

RADIOLABELED MELANOCORTIN 1 RECEPTOR-SPECIFIC ALPHA-MELANOCYTE-STIMULATING HORMONE ANALOGUES FOR IMAGING OR THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/539,948, filed on September 22, 2023, the contents of which is hereby incorporated by reference in its entirety for all purposes.

FIELD OF INVENTION

[0002] The present invention relates to alpha-melanocyte-stimulating hormone analogues which target melanocortin 1 receptor.

BACKGROUND OF THE INVENTION

[0003] Current imaging technologies for metastatic melanomas, e.g. including cutaneous, amelanotic and uveal melanomas, have limited sensitivity for detecting small metastatic lesions, early nodal metastases, and liver metastases. In addition, current treatments for metastatic melanomas have limited success at later stages.

[0004] The melanocortin 1 receptor (MC1R) is specifically expressed in cutaneous, amelanotic and uveal melanomas. The low level of MC1R expression in normal tissues makes this protein an attractive target for radionuclide imaging and therapy. The endogenous ligand of MC1R is alpha-melanocyte-stimulating hormone (α MSH), which binds MC1R with sub-nanomolar binding affinity. However, α MSH also binds to other melanocortin receptors, including MC3R, MC4R and MC5R. α MSH does not bind to MC2R, which is selectively activated by adrenocorticotrophic hormone.

[0005] While peptide analogues of α MSH have been developed for imaging applications (e.g. ^{68}Ga -labeled CCZ01048 having sequence DOTA-Pip-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-NH₂; *see* Zhang et al., 2017 *Theranostics* 7(4):805-813)), there remains a need for higher selectivity for MC1R over the other melanocortin receptors to reduce off-target accumulation of MC1R targeting radiolabeled peptides *in vivo*. The metabolic stability of the peptide analogues is also important to achieve high tumour accumulation and long term retention of the radiolabeled peptide analogues for *in vivo* for imaging of MC1R-expressing tissues and/or

therapy of MC1R-related conditions or diseases (e.g. melanoma, non-melanoma skin cancers and others).

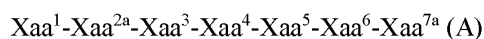
[0006] No admission is necessarily intended, nor should it be construed, that any of the preceding information constitutes prior art against the present invention.

SUMMARY OF THE INVENTION

[0007] Various embodiments in this disclosure relate to a compound comprising a melanocortin 1 receptor (MC1R) targeting peptide (MC1RTP), a radiolabeling group, and a linker joining the MC1RTP to the radiolabeling group.

[0008] The present disclosure further relates to a compound, or a salt thereof, comprising an MC1RTP linked to a CROWN chelator by a linker, wherein:

[0009] the MC1RTP is cyclized and comprises a sequence of Formula A:



[0010] Xaa¹ is selected from the group consisting of norleucine (Nle), D-Nle, Ala, D-Ala, Leu, D-Leu, Ile, D-Ile, Cys, D-Cys, Met, D-Met, Phe, D-Phe, Trp, D-Trp, Val, D-Val, 3-(1-naphthyl)alanine (Nal), D-Nal, 3-(2-naphthyl)alanine (2-Nal), D-2-Nal, Gly, α -aminobutyric acid, norvaline, D-norvaline, homonorleucine, and D-homonorleucine;

[0011] Xaa^{2a} is selected from the group consisting of Cys, D-Cys, Asp, D-Asp, Glu, D-Glu, 2-aminoadipic acid (2-Aad), D-2-Aad, 3-aminoadipic acid (3-Aad), D-3-Aad, propargylglycine (Pra), D-Pra, homopropargylglycine (Hpg), D-Hpg, beta-homopropargylglycine (Bpg), and D-Bpg;

[0012] Xaa³ is His;

[0013] Xaa⁴ is D-Phe;

[0014] Xaa⁵ is Arg;

[0015] Xaa⁶ is Trp;

[0016] Xaa^{7a} is selected from the group consisting of Cys, D-Cys, Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, D-Dap, Lys(N₃), D-Lys(N₃), Orn(N₃), D-Orn(N₃), Dab(N₃), D-Dab(N₃), Dap(N₃), D-Dap(N₃), 2-(5'-azidopentyl)alanine, D-2-(5'-azidopentyl)alanine, 2-(6'-azidoheptyl)alanine, and D-2-(6'-azidoheptyl)alanine;

[0017] one or more amino acid residues of the MC1RTP is alpha N-methylated; and

[0018] the MC1RTP is optionally C-terminally amidated.

[0019] The present disclosure further relates to pharmaceutical compositions comprising the compounds as disclosed herein.

[0020] The present disclosure further relates to methods of treating cancer with the compounds and compositions as disclosed herein.

[0021] The present disclosure further relates to methods of treating melanoma with the compounds and compositions as disclosed herein.

[0022] This summary of the invention does not necessarily describe all features of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

[0024] **FIG. 1** shows change in tumor volume in a dose escalation study between ^{225}Ac -labeled CCZ01178 (at 15 kBq and 30 kBq) and ^{177}Lu -labeled CCZ01158 (at 20 MBq and 40 MBq) in SK-MEL-1 tumour-bearing NRG mice.

[0025] **FIG. 2** shows probability of survival of SK-MEL-1 tumour-bearing NRG mice injected with ^{225}Ac -labeled CCZ01178 (at 15 kBq and 30 kBq) or ^{177}Lu -labeled CCZ01158 (at 20 MBq and 40 MBq).

DETAILED DESCRIPTION

[0026] GENERAL DEFINITIONS

[0027] As used herein, the terms “comprising,” “having,” “including” and “containing,” and grammatical variations thereof, are inclusive or open-ended and do not exclude additional, non-recited elements and/or method steps. The term “consisting essentially of” if used herein in connection with a compound, composition, use or method, denotes that additional elements and/or method steps may be present, but that these additions do not materially affect the manner in which the recited compound, composition, method or use functions. The term “consisting of” when used herein in connection with a composition, use or method, excludes the presence of additional elements and/or method steps. A compound, composition, use or method described herein as comprising certain elements and/or steps may also, in certain embodiments, consist essentially of those elements and/or steps, and in other embodiments consist of those elements and/or steps, whether or not these embodiments are specifically referred to. A use or method described herein as comprising certain elements and/or steps may also, in certain embodiments, consist essentially of those elements and/or steps, and in other embodiments,

consist of those elements and/or steps, whether or not these embodiments are specifically referred to.

[0028] A reference to an element by the indefinite article “a” does not exclude the possibility that more than one of the elements is present, unless the context clearly requires that there be one and only one of the elements. The singular forms “a”, “an”, and “the” include plural referents unless the content clearly dictates otherwise. The use of the word “a” or “an” when used herein in conjunction with the term “comprising” may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one” and “one or more than one.” The term “plurality” if used herein means more than one, for example, two or more, three or more, four or more, and the like.

[0029] In this disclosure, the recitation of numerical ranges by endpoints includes all numbers subsumed within that range including all whole numbers, all integers and, where suitable, all fractional intermediates (e.g., 1 to 5 may include 1, 1.5, 2, 2.75, 3, 3.80, 4, and 5 etc.).

[0030] Unless otherwise specified, “certain embodiments”, “various embodiments”, “an embodiment” and similar terms includes the particular feature(s) described for that embodiment either alone or in combination with any other embodiment or embodiments described herein, whether or not the other embodiments are directly or indirectly referenced and regardless of whether the feature or embodiment is described in the context of a compound, method, product, use, composition, *et cetera*.

[0031] The term “subject” refers to an animal (e.g. a mammal or a non-mammal animal). The subject may be a human or a non-human primate. The subject may be a laboratory mammal (e.g., mouse, rat, rabbit, hamster and the like). The subject may be an agricultural animal (e.g., equine, ovine, bovine, porcine, camelid and the like) or a domestic animal (e.g., canine, feline and the like). In some embodiments, the subject is a human.

[0032] The compounds disclosed herein may also include base-free forms, prodrugs, salts or pharmaceutically acceptable salts thereof. Unless otherwise specified, the compounds claimed and described herein are meant to include all racemic mixtures and all individual enantiomers or combinations thereof, whether or not they are explicitly represented herein.

[0033] The compounds disclosed herein may be shown as having one or more charged groups, may be shown with ionizable groups in an uncharged (e.g. protonated) state or may be shown without specifying formal charges. As will be appreciated by the person of skill in the art, the ionization state of certain groups within a compound (e.g. without limitation, CO₂H, PO₃H₂, SO₂H, SO₃H, SO₄H, OPO₃H₂ and the like) is dependent, *inter alia*, on the pKa of that group and the pH at that location. For example, but without limitation, a carboxylic acid group (i.e.

COOH) would be understood to usually be deprotonated (and negatively charged) at neutral pH and at most physiological pH values, unless the protonated state is stabilized (e.g. due to intramolecular H-bonding). Likewise, OSO₃H (i.e. SO₄H) groups, SO₂H groups, SO₃H groups, OPO₃H₂ (i.e. PO₄H₂) groups and PO₃H groups would generally be deprotonated (and negatively charged) at neutral and physiological pH values.

[0034] As used herein, the terms “salt” and “solvate” have their usual meaning in chemistry. As such, when the compound is a salt or solvate, it is associated with a suitable counter-ion. It is well known in the art how to prepare salts or to exchange counter-ions. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of a suitable base (e.g. without limitation, Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of a suitable acid. Such reactions are generally carried out in water or in an organic solvent, or in a mixture of the two. Counter-ions may be changed, for example, by ion-exchange techniques such as ion-exchange chromatography. All zwitterions, salts, solvates and counter-ions are intended, unless a particular form is specifically indicated.

[0035] In certain embodiments, the salt or counter-ion may be pharmaceutically acceptable, e.g. for administration to a subject. More generally, with respect to any pharmaceutical composition disclosed herein, non-limiting examples of suitable excipients include any suitable buffers, stabilizing agents, salts, antioxidants, complexing agents, tonicity agents, cryoprotectants, lyoprotectants, suspending agents, emulsifying agents, antimicrobial agents, preservatives, chelating agents, binding agents, surfactants, wetting agents, non-aqueous vehicles such as fixed oils, or polymers for sustained or controlled release. See, for example, Berge et al. 1977. (J. Pharm Sci. 66:1-19), or Remington— The Science and Practice of Pharmacy, 21st edition (Gennaro et al editors. Lippincott Williams & Wilkins Philadelphia).

[0036] As used herein, the expression “X_y-X_z”, where y and z are integers (e.g. X₁-X₁₅, X₁-X₃₀, X₁-X₁₀₀, and the like), refers to the number of carbons (for alkyls and aryls, whether saturated or unsaturated) in a compound, R-group or substituent, or refers to the number of carbons and heteroatoms (for heteroalkyls and heteroaryl, whether saturated or unsaturated) in a compound, R-group or substituent. Heteroatoms may include any, some or all possible heteroatoms. For example, in some embodiments, the heteroatoms are selected from N, O, S, P and Se. In some embodiments, the heteroatoms are selected from N, O, S and P. Such embodiments are non-limiting. Alkyls and aryls may alternatively be referred to using the expression “C_y-C_z”, where y and z are integers (e.g. C₃-C₁₅ and the like).

[0037] Unless explicitly stated otherwise, the terms “alkyl” and “heteroalkyl” each includes any reasonable combination of the following: (1) saturated alkyls as well as unsaturated alkyls (e.g. alkenyls and alkynyls); (2) linear or branched; (3) acyclic or cyclic (aromatic or nonaromatic), the latter of which may include multi-cyclic (fused rings, multiple non-fused rings or a combination thereof); and (4) unsubstituted or substituted. For example, an alkyl or heteroalkyl (i.e. “alkyl/heteroalkyl”) may be saturated, branched and cyclic, or unsaturated, branched and cyclic, or linear and unsaturated, or any other reasonable combination according to the skill of the person of skill in the art. If unspecified, the size of the alkyl/heteroalkyl is what would be considered reasonable to the person of skill in the art. For example, but without limitation, if unspecified, the size of an alkyl may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more than 100 carbons in length, subject to the common general knowledge of the person of skill in the art. Further, but without limitation, if unspecified, the size of a heteroalkyl may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more than 100 carbons and heteroatoms in length, subject to the common general knowledge of the person of skill in the art.

[0038] As used herein, in the context of an alkyl/heteroalkyl group of a compound, the term “linear” may be used as it is normally understood to a person of skill in the art and generally refers to a chemical entity that comprises a skeleton or main chain that does not split off into more than one contiguous chain. Non-limiting examples of linear alkyls include methyl, ethyl, n-propyl, and n-butyl.

[0039] As used herein, a “cyclic” peptide/polypeptide may be used as it is normally understood to a person of skill in the art and generally refers to the peptide or polypeptide having a covalent bond between two amino acids within the peptide or polypeptide to form a ring structure, e.g. between carboxyl and amino termini, between carboxyl terminus and side chain amino, between amino terminus and side chain carboxyl, or between side chains. For example, but without limitation, a peptide may be cyclized by forming a lactam bridge (i.e., an amide bond) between the side-chain carboxylate of one amino acid residue in the peptide (e.g. Asp, Glu) and the amine of another amino acid residue in the peptide (e.g. Dap, Dab, Orn, Lys). In

embodiments, a lactam bridge is formed between the side-chain carboxylate of Asp and the side chain amine of Lys. Further details are provided herein.

[0040] As used herein, the term “branched” may be used as it is normally understood to a person of skill in the art and generally refers to a chemical entity that comprises a skeleton or main chain that splits off into more than one contiguous chain. The portions of the skeleton or main chain that split off in more than one direction may be linear, cyclic or any combination thereof. Non-limiting examples of a branched alkyl group include tert-butyl and isopropyl.

[0041] As used herein, the term “saturated” when referring to a chemical entity may be used as it is normally understood to a person of skill in the art and generally refers to a chemical entity that comprises only single bonds. Non-limiting examples of a saturated C₁-C₁₅ alkyl group may include methyl, ethyl, n-propyl, i-propyl, sec-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, i-pentyl, sec-pentyl, t-pentyl, n-hexyl, i-hexyl, 1,2-dimethylpropyl, 2-ethylpropyl, 1-methyl-2-ethylpropyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1,2-triethylpropyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-ethylbutyl, 1,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, sec-hexyl, t-hexyl, n-heptyl, i-heptyl, sec-heptyl, t-heptyl, n-octyl, i-octyl, sec-octyl, t-octyl, n-nonyl, i-nonyl, sec-nonyl, t-nonyl, n-decyl, i-decyl, sec-decyl and t-decyl. Non-limiting examples of C₂-C₁₅ alkenyl group may include vinyl, allyl, isopropenyl, 1-propene-2-yl, 1-butene-1-yl, 1-butene-2-yl, 1-butene-3-yl, 2-butene-1-yl, 2-butene-2-yl, octenyl and decenyl. Non-limiting examples of C₂-C₁₅ alkynyl group may include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl and decynyl. Without limitation, the above-defined saturated C₁-C₁₅ alkyls, C₂-C₁₅ alkenyls and C₂-C₁₅ alkynyls are all encompassed within the term “X₁-X₁₅ alkyl”, as used herein. Without limitation, the term “X₁-X₁₅ heteroalkyl” would encompass each of the above-defined saturated C₁-C₁₅ alkyls, C₂-C₁₅ alkenyls and C₂-C₁₅ alkynyls, where one or more of the carbon atoms is independently replaced with a heteroatom. The person of skill in the art would understand that various combinations of different heteroatoms may be used.

[0042] Unless explicitly stated otherwise, the terms “aryl” and “heteroaryl” each includes any reasonable combination of the following: (1) cyclic or multi-cyclic (fused rings, multiple non-fused rings or a combination thereof); (2) aromatic (i.e. unsaturated rings) or nonaromatic (i.e. saturated rings); and (3) unsubstituted or substituted. Non-limiting examples of aryls or heteroaryl (i.e. “aryl/heteroaryl”) include: phenyl, naphthyl, thienyl, indolyl, pyridyl and the like. If unspecified, the size of the aryl/heteroaryl is what would be considered reasonable to the person of skill in the art. For example, but without limitation, if unspecified, the size of an aryl may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26,

27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more than 100 carbons in length, subject to the common general knowledge of the person of skill in the art. Further, but without limitation, if unspecified, the size of a heteroaryl may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more than 100 carbons and heteroatoms in length, subject to the common general knowledge of the person of skill in the art. It is noted that an aryl or heteroaryl may have all or only a portion of its skeleton or main chain bonded in such a way so as to form a 'loop', circle or ring of atoms bonded together. That is, the aryl/heteroaryl may comprise linear or branched chains of carbons/heteroatoms that are not part of a ring or loop.

[0043] For example, a X_3-X_{18} aryl/heteroaryl may include, without limitation, a saturated C_3-C_{18} cycloalkyl group, a C_3-C_{18} cycloalkenyl group, a C_3-C_{18} cycloalkynyl group, a C_3-C_{18} aromatic aryl group, a X_3-X_{18} non-aromatic heterocyclic group where each X may independently be C, N, S, P, O or Se, and a X_3-X_{18} aromatic heterocyclic group where each X may independently be C, N, S, P, O or Se. Non-limiting examples of the saturated C_3-C_{18} cycloalkyl group may include cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, cyclooctanyl, cyclononanyl and cyclodecanyl. Non-limiting examples of the C_3-C_{18} cycloalkenyl group may include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononanenyl and cyclodecanenyl. Non-limiting examples of the C_3-C_{18} aromatic aryl group may include phenyl (Ph), pentalenyl, indenyl, naphthyl and azulenyl. Non-limiting examples of the X_3-X_{18} non-aromatic heterocyclic group may include aziridinyl, azetidiny, diazetidinyl, pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, imidazoliny, pyrazolidinyl, imidazolydinyl, phthalimidyl, succinimidyl, oxiranyl, tetrahydropyranyl, oxetanyl, dioxanyl, thietanyl, thiepinyl, morpholinyl, and oxathiolanyl. Non-limiting examples of the X_3-X_{18} aromatic heterocyclic group may include pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pirazinyl, quinolinyl, isoquinolinyl, acridinyl, indolyl, isoindolyl, indoliziny, purinyl, carbazolyl, indazolyl, phthalazinyl, naphthyridinyl, quinoxaliny, quinazoliny, cinnoliny, pteridinyl, phenanthridinyl, phenazinyl, phenanthrolinyl, perimidiny, furyl, dibenzofuryl, xanthenyl, benzofuryl, thiophenyl, thianthrenyl, benzothiophenyl, phosphorinyl, phosphinolinyl, phosphindolyl, thiazolyl,

oxazolyl, and isoxazolyl. Unless otherwise specified, X₁-X₁₈ alkyl/heteroalkyl would encompass, among others, X₃-X₁₈ aryl/heteroaryl, including the groups defined above.

[0044] As used herein, the term “substituted” is used as it would normally be understood to a person of skill in the art and generally refers to a compound or chemical entity that has one chemical group replaced with a different chemical group. Unless otherwise specified, a substituted alkyl is an alkyl in which one or more hydrogen atom(s) are independently each replaced with an atom that is not hydrogen. For example, chloromethyl is a non-limiting example of a substituted alkyl, more particularly an example of a substituted methyl. Aminoethyl is another non-limiting example of a substituted alkyl, more particularly an example of a substituted ethyl. Unless otherwise specified, a substituted compound or group (e.g. alkyl, heteroalkyl, aryl, heteroaryl and the like) may be substituted with any chemical group reasonable to the person of skill in the art. For example, but without limitation, a hydrogen bonded to a carbon or heteroatom (e.g. N) may be substituted with halide (e.g. F, I, Br, Cl), amine, amide, oxo, hydroxyl, thiol, phosphate, phosphonate, sulfate, SO₂H, SO₃H, alkyls, heteroalkyls, aryl, heteroaryl, ketones, carboxaldehyde, carboxylates, carboxamides, nitriles, monohalomethyl, dihalomethyl or trihalomethyl.

[0045] As used herein, the term “unsubstituted” is used as it would normally be understood to a person of skill in the art. Non-limiting examples of unsubstituted alkyls include methyl, ethyl, tert-butyl, pentyl and the like. The expression “optionally substituted” is used interchangeably with the expression “unsubstituted or substituted”.

[0046] In the structures provided herein, hydrogen may or may not be shown. In some embodiments, hydrogens (whether shown or implicit) may be protium (i.e. ¹H), deuterium (i.e. ²H) or combinations of ¹H and ²H. Methods for exchanging ¹H with ²H are well known in the art. For solvent-exchangeable hydrogens, the exchange of ¹H with ²H occurs readily in the presence of a suitable deuterium source, without any catalyst. The use of acid, base or metal catalysts, coupled with conditions of increased temperature and pressure, can facilitate the exchange of non-exchangeable hydrogen atoms, generally resulting in the exchange of all ¹H to ²H in a molecule.

[0047] Unless otherwise specified a “peptide” as referred to herein may comprise proteinogenic and/or non-proteinogenic amino acid residues. Non-limiting examples of nonproteinogenic amino acids include: D-amino acids (including without limitation any D-form of the following amino acids), ornithine (Orn), 3-(1-naphtyl)alanine (Nal), 3-(2-naphtyl)alanine (2-Nal), α-aminobutyric acid, norvaline, norleucine (Nle), homonorleucine,

beta-(1,2,3-triazol-4-yl)-L-alanine, 1,2,4-triazole-3-alanine, Phe(4-F), Phe(4-Cl), Phe(4-Br), Phe(4-I), Phe(4-NH₂), Phe(4-NO₂), homoarginine (hArg), 2-amino-4-guanidinobutyric acid (Agb), 2-amino-3-guanidinopropionic acid (Agp), Trp(5-Br), Trp(5-OCH₃), Trp(6-F), Trp(5-OH) or Trp(CHO), 2-aminoadipic acid (2-Aad), 3-aminoadipic acid (3-Aad), propargylglycine (Pra), homopropargylglycine (Hpg), beta-homopropargylglycine (Bpg), 2,3-diaminopropionic acid (Dap), 2,4-diaminobutyric acid (Dab), azidolysine (Lys(N₃)), azido-ornithine (Orn(N₃)), 2-amino-4-azidobutanoic acid Dab(N₃), Dap(N₃), 2-(5'-azidopentyl)alanine, 2-(6'-azidohexyl)alanine, 4-amino-1-carboxymethyl-piperidine (Pip), 4-(2-aminoethyl)-1-carboxymethyl-piperazine (Acp).

[0048] If not specified as an L- or D-amino acid, an amino acid shall be understood to be an L-amino acid.

[0049] Unless otherwise specified, amino acids may be modified by any modifications known in the art subject to the common general knowledge of the person of skill in the art. For example, but without limitation, a C-terminal amino acid residue may be amidated, which refers to replacement of the C-terminal carboxylate with an amide, i.e. -C(O)NH₂ instead of -C(O)OH. Amidated residues are identified with -NH₂ (e.g. Lys-NH₂, Trp-NH₂ and the like). As a further non-limiting example, amino acids may be methylated, e.g. N-methylated or alpha N-methylated.

[0050] The term “Xaa” refers to any amino acid. The term “-Xaa⁸-Xaa⁹-Xaa¹⁰-” refers to three amino acids, Xaa⁸, Xaa⁹, and Xaa¹⁰ chained together with peptide bonds. The term “-Xaa⁹(Xaa⁸)-Xaa¹⁰-” refers to the same three amino acids, but chained together with an amide bond between the C-terminus of Xaa⁹ and the N-terminus of Xaa¹⁰ with a further amide bond formed between the C-terminus of Xaa⁸ and the side chain amine of Xaa⁹. Unless otherwise indicated, “Xaa” may be any amino acid commonly known to the person of skill in the art, including proteinogenic and nonproteinogenic amino acids (e.g. but not limited to the nonproteinogenic amino acids listed above).

[0051] For cyclized peptides, the formula Xaa¹-cyclo(Xaa²-Xaa³-Xaa⁴)-Xaa⁵ and the like, refers to a covalent linkage between the side chains of Xaa² and Xaa⁴ (i.e. between the first and last amino acids in the parentheses). Similarly, the formula Xaa¹-cyclo(Xaa²-Xaa³-Xaa⁴-Xaa⁵) refers to a cyclized peptide having a covalent linkage between the side chains of Xaa² and Xaa⁵.

[0052] COMPOUNDS

[0053] The compounds presented herein incorporate peptides, which may be synthesized by any of a variety of methods established in the art. This includes but is not limited to liquid-phase as well as solid-phase peptide synthesis using methods employing 9-fluorenylmethoxycarbonyl (Fmoc) and/or t-butyloxycarbonyl (Boc) chemistries, and other synthetic approaches.

[0054] Solid-phase peptide synthesis methods and technology are well-established in the art. For example, peptides may be synthesized by sequential incorporation of the amino acid residues of interest one at a time. In such methods, peptide synthesis is typically initiated by attaching the C-terminal amino acid of the peptide of interest to a suitable resin. Prior to this, reactive side chain and alpha amino groups of the amino acids are protected from reaction by suitable protecting groups, allowing only the alpha carboxyl group to react with a functional group such as an amine group, a hydroxyl group, or an alkyl halide group on the solid support. Following coupling of the C-terminal amino acid to the support, the protecting group on the side chain and/or the alpha amino group of the amino acid is selectively removed, allowing the coupling of the next amino acid of interest. This process is repeated until the desired peptide is fully synthesized, at which point the peptide can be cleaved from the support and purified. A non-limiting example of an instrument for solid-phase peptide synthesis is the Aapptec Endeavor 90 peptide synthesizer.

[0055] The choice of resin determines whether the peptide will have either a C-terminal carboxylate or a C-terminal amide (i.e. whether or not the C-terminus of the peptide is amidated). For example, but without limitation, 4-(2',4'-Dimethoxyphenyl-Fmoc-aminomethyl)phenoxy resin (Rink Amide Resin) or 9-Fmoc-aminoxanthen-3-yloxy-Merrifield resin (Sieber Amide resin) may be used for a C-terminal amide once the peptide is cleaved. Without limitation, p-benzyloxybenzyl alcohol resin (Wang resin) or 2-chlorotrityl chloride resin may be used for a C-terminal carboxylate once the peptide is cleaved. During use, the resin is swelled in solvents, such as N,N-dimethylformamide (DMF), dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP), and the like.

[0056] To allow coupling of additional amino acids, Fmoc protecting groups may be removed from the amino acid on the solid support, e.g. under mild basic conditions, such as piperidine (20-50% v/v) in DMF. The amino acid to be added must also have been activated for coupling (e.g. at the alpha carboxylate). Non-limiting examples of activating reagents include without limitation 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-

1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP). Racemization is minimized by using triazoles, such as 1-hydroxy-benzotriazole (HOBt) and 1-hydroxy-7-aza-benzotriazole (HOAt). Coupling may be performed in the presence of a suitable base, such as N,N-diisopropylethylamine (DIPEA/DIEA) and the like. For long peptides, peptide synthesis and ligation may be used.

[0057] Cyclization of the peptide may be performed by any known method. Cyclization may be performed on-resin or off-resin. Non-limiting examples of peptide cyclization include: forming a lactam bridge between an amino acid side chain containing a carboxyl group (e.g. Asp, D-Asp, Glu, D-Glu, and the like) and an amino acid side chain containing an amino group (e.g. Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, D-Dap, and the like); forming a 1, 2, 3-triazole via click chemistry between an amino acid side chain containing an azide group (e.g. Lys(N₃), D-Lys(N₃), and the like) and an alkyne group (e.g. Pra, D-Pra, and the like); and forming a disulfide bridge between side chains of Cys residues. Since cyclization occurs between amino acid side chains, the protecting groups on these amino acids must be selectively removed before cyclization except the reaction between an alkyne and an azido groups via the click reaction to form an 1,2,3-triazole. Non-limiting examples of selectively removable protecting groups include acetaminomethyl (Acm) (e.g. on Cys), 2-phenylisopropyl esters (O-2-PhiPr) (e.g. on Asp/Glu) as well as 4-methyltrityl (Mtt), allyloxycarbonyl (alloc), 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl (Dde), and 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl (ivDde) (e.g. on Lys/Orn/Dab/Dap). The Acm group on Cys can be selectively removed by 2 eq. of thallium (III) trifluoroacetate in DMF, which simultaneously induces cyclization via the formation of the disulfide bridge. O-2-PhiPr and Mtt protecting groups can be selectively deprotected under mild acidic conditions, such as 2.5% trifluoroacetic acid (TFA) in DCM. Alloc protecting groups can be selectively deprotected using tetrakis(triphenylphosphine)palladium(0) and phenyl silane in DCM. Dde and ivDde protecting groups can be selectively deprotected using 2-5% of hydrazine in DMF. Deprotected side chains of Asp/Glu (L- or D-forms) and Lys/Orn/Dab/Dap (L- or D-forms) can then be cyclized, e.g. by using the coupling reaction conditions described above.

[0058] Peptide backbone amides may be N-methylated (i.e. alpha amino methylated). This may be achieved by directly using Fmoc-N-methylated amino acids during peptide synthesis. Alternatively, N-methylation under Mitsunobu conditions may be performed. First, a free

primary amine group is protected using a solution of 4-nitrobenzenesulfonyl chloride (Ns-Cl) and 2,4,6-trimethylpyridine (collidine) in NMP. N-methylation may then be achieved in the presence of triphenylphosphine, diisopropyl azodicarboxylate (DIAD) and methanol. Subsequently, N-deprotection may be performed using mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in NMP. For coupling protected amino acids to N-methylated alpha amino groups, HATU, HOAt and DIEA may be used.

[0059] As described further below, chelators, linkers (peptide or non-peptide linkers) and/or albumin-binding groups may be coupled to the peptide N-terminus while the peptide is attached to the solid support. This is facile when the chelator, linker and/or albumin-binding groups comprise an activated carboxylate (and protected groups if necessary) so that coupling can be performed on resin.

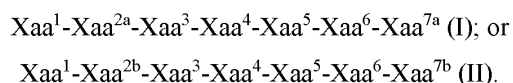
[0060] When the peptide has been fully synthesized on the solid support, the desired peptide may be cleaved from the solid support using suitable reagents, such as TFA, tri-isopropylsilane (TIS) and water. Side chain protecting groups, such as Boc, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf), trityl (Trt) and tert-butyl (tBu) are simultaneously removed (i.e. deprotection). The crude peptide may be precipitated and collected from the solution by adding cold ether followed by centrifugation. Purification and characterization of the peptides may be performed by standard separation techniques, such as high performance liquid chromatography (HPLC) based on the size, charge and polarity of the peptides. The identity of the purified peptides may be confirmed by mass spectrometry or other similar approaches.

[0061] The present disclosure provides a compound comprising a melanocortin 1 receptor (MC1R) targeting peptide (MC1RTP), a radiolabeling group, and a linker joining the MC1RTP to the radiolabeling group. In some embodiments, the radiolabeling group is a CROWN chelator.

[0062] In some embodiments, the MC1RTP is alpha N-methylated.

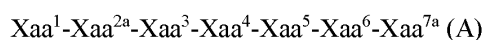
[0063] The MC1RTP binds MC1R under physiological conditions (e.g. *in vivo*), and in some embodiments is selective for MC1R over at least one other member of melanocortin receptor (i.e. MC3R, MC4R and/or MC5R). The MC1RTP may be selective for MC1R over MC3R. The MC1RTP may be selective for MC1R over MC4R. The MC1RTP may be selective for MC1R over MC5R. The MC1RTP may be selective for MC1R over any combination of MC3R, MC4R and/or MC5R. The MC1RTP may be selective for MC1R over MC3R, MC4R and MC5R.

[0064] In some embodiments of the present disclosure, MC1RTP comprises an amino acid sequence defined by Formula I or Formula II:



[0065] In some embodiments, the disclosure provides a compound comprising a melanocortin 1 receptor (MC1R) targeting peptide (MC1RTP) linked to a CROWN chelator by a linker, or a salt thereof, wherein:

[0066] the MC1RTP is cyclized and comprises a sequence of Formula A:



[0067] Xaa¹ is selected from the group consisting of norleucine (Nle), D-Nle, Ala, D-Ala, Leu, D-Leu, Ile, D-Ile, Cys, D-Cys, Met, D-Met, Phe, D-Phe, Trp, D-Trp, Val, D-Val, 3-(1-naphthyl)alanine (Nal), D-Nal, 3-(2-naphthyl)alanine (2-Nal), D-2-Nal, Gly, α -aminobutyric acid, norvaline, D-norvaline, homonorleucine, and D-homonorleucine;

[0068] Xaa^{2a} is selected from the group consisting of Cys, D-Cys, Asp, D-Asp, Glu, D-Glu, 2-aminoadipic acid (2-Aad), D-2-Aad, 3-aminoadipic acid (3-Aad), D-3-Aad, propargylglycine (Pra), D-Pra, homopropargylglycine (Hpg), D-Hpg, beta-homopropargylglycine (Bpg), and D-Bpg;

[0069] Xaa³ is His;

[0070] Xaa⁴ is D-Phe;

[0071] Xaa⁵ is Arg;

[0072] Xaa⁶ is Trp;

[0073] Xaa^{7a} is selected from the group consisting of Cys, D-Cys, Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, D-Dap, Lys(N₃), D-Lys(N₃), Orn(N₃), D-Orn(N₃), Dab(N₃), D-Dab(N₃), Dap(N₃), D-Dap(N₃), 2-(5'-azidopentyl)alanine, D-2-(5'-azidopentyl)alanine, 2-(6'-azidoheptyl)alanine, and D-2-(6'-azidoheptyl)alanine;

[0074] one or more amino acid residues of the MC1RTP is alpha N-methylated; and

[0075] the MC1RTP is optionally C-terminally amidated.

[0076] In some embodiments, Xaa¹ is norleucine (Nle), D-Nle, Ala, D-Ala, Leu, D-Leu, Ile, D-Ile, Cys, D-Cys, Met, D-Met, Phe, D-Phe, Trp, D-Trp, Val, D-Val, 3-(1-naphthyl)alanine (Nal), D-Nal, 3-(2-naphthyl)alanine (2-Nal), D-2-Nal, Gly, α -aminobutyric acid, D- α -aminobutyric acid, norvaline, D-norvaline, homonorleucine, or D-homonorleucine. In some embodiments, Xaa¹ is Nle, Ala, Leu, Ile, Cys, Met, Phe, Trp, Val, Nal, 2-Nal, Gly, α -

aminobutyric acid, norvaline or homonorleucine. In some embodiments, Xaa¹ is Nle, Ala, Leu, Ile, Cys, Met, Phe, Trp, Val, Nal, 2-Nal, α -aminobutyric acid, norvaline or homonorleucine. In some embodiments, Xaa¹ is Nle.

[0077] In some embodiments, Xaa^{2a} is Cys, D-Cys, Asp, D-Asp, Glu, D-Glu, 2-aminoadipic acid (2-Aad), D-2-Aad, 3-aminoadipic acid (3-Aad), D-3-Aad, propargylglycine (Pra), D-Pra, homopropargylglycine (Hpg), D-Hpg, beta-homopropargylglycine (Bpg) or D-Bpg. In some embodiments, Xaa^{7b} is Cys, Asp, Glu, 2-Aad, 3-Aad, Pra, Hpg, or Bpg. In some embodiments, Xaa^{2a} is Asp, Glu, Pra or D-Pra. In some embodiments, Xaa^{2a} is Asp, Glu, or Pra. In some embodiments, Xaa^{2a} is Asp.

[0078] In some embodiments, Xaa^{2b} is Cys, D-Cys, Lys, D-Lys, Ornithine (Orn), D-Orn, 2,4-diaminobutyric acid (Dab), D-Dab, 2,3-diaminopropionic acid (Dap), D-Dap, Lys(N₃), D-Lys(N₃), Orn(N₃), D-Orn(N₃), Dab(N₃), D-Dab(N₃), Dap(N₃), D-Dap(N₃), 2-(5'-azidopentyl)alanine, D-2-(5'-azidopentyl)alanine, 2-(6'-azidohexyl)alanine or D-2-(6'-azidohexyl)alanine. In some embodiments, Xaa^{2b} is Cys, Lys, Orn, Dab, Dap, Lys(N₃), Orn(N₃), Dab(N₃), Dap(N₃), or 2-(5'-azidopentyl)alanine, 2-(6'-azidohexyl)alanine. In some embodiments, Xaa^{2b} is Lys Orn, Dab, Dap, Lys(N₃), Orn(N₃), Dab(N₃), Dap(N₃), 2-(5'-azidopentyl)alanine, or 2-(6'-azidohexyl)alanine. In some embodiments, Xaa^{2b} is Lys.

[0079] In some embodiments, Xaa³ is His, D-His, Pro, beta-(1,2,3-triazol-4-yl)-DL-alanine, beta-(1,2,3-triazol-4-yl)-L-alanine, beta-(1,2,3-triazol-4-yl)-D-alanine, 1,2,4-triazole-3-alanine, or 1,2,4-triazole-3-D-alanine. In some embodiments, Xaa³ is His, Pro, beta-(1,2,3-triazol-4-yl)-L-alanine, or 1,2,4-triazole-3-alanine. In some embodiments, Xaa³ is His, beta-(1,2,3-triazol-4-yl)-DL-alanine, or 1,2,4-triazole-3-alanine. In some embodiments, Xaa³ is His.

[0080] In some embodiments, Xaa⁴ is Phe, D-Phe, 2-Nal, D-2-Nal, Phe(4-F), D-Phe(4-F), Phe(4-Cl), D-Phe(4-Cl), Phe(4-Br), D-Phe(4-Br), Phe(4-I), D-Phe(4-I), Phe(4-NH₂), D-Phe(4-NH₂), Phe(4-NO₂), or D-Phe(4-NO₂). In some embodiments, Xaa⁴ is D-Phe, D-2-Nal, D-Phe(4-F), D-Phe(4-Cl), D-Phe(4-Br), D-Phe(4-I), D-Phe(4-NH₂), or D-Phe(4-NO₂). In some embodiments, Xaa⁴ is Phe, D-Phe, 2-Nal or D-2-Nal. In some embodiments, Xaa⁴ is D-Phe or D-2-Nal. In some embodiments, Xaa⁴ is D-Phe.

[0081] In some embodiments, Xaa⁵ is Arg, D-Arg, homoarginine (hArg), D-hArg, Leu, D-Leu, 2-amino-4-guanidinobutyric acid (Agb), D-Agb, 2-amino-3-guanidinopropionic acid (Agp), or D-Agp. In some embodiments, Xaa⁵ is Arg, D-Arg, hArg, Leu, D-hArg, Agb, D-Agb, Agp or D-Agp. In some embodiments, Xaa⁵ is Arg, hArg, Leu, Agb, or Agp. In some embodiments, Xaa⁵ is Arg.

[0082] In some embodiments, Xaa⁶ is Phe, D-Phe, Trp, D-Trp, Trp(5-Br), D-Trp(5-Br), Trp(5-OCH₃), D-Trp(5-OCH₃), Trp(6-F), D-Trp(6-F), Trp(5-OH), D-Trp(5-OH), Trp(CHO), or D-Trp(CHO). In some embodiments, Xaa⁶ is Phe, Trp, Trp(5-Br), Trp(5-OCH₃), Trp(6-F), Trp(5-OH), or Trp(CHO). In some embodiments, Xaa⁶ is Trp or D-Trp. In some embodiments, Xaa⁶ is Trp.

[0083] In some embodiments, Xaa^{7a} is Cys, D-Cys, Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, D-Dap, Lys(N₃), D-Lys(N₃), Orn(N₃), D-Orn(N₃), Dab(N₃), D-Dab(N₃), Dap(N₃), D-Dap(N₃), 2-(5'-azidopentyl)alanine, D-2-(5'-azidopentyl)alanine, 2-(6'-azidoheptyl)alanine or D-2-(6'-azidoheptyl)alanine. In some embodiments, Xaa^{7a} is Cys, Lys, Orn, Dab, Dap, Lys(N₃), Orn(N₃), Dab(N₃), Dap(N₃), 2-(5'-azidopentyl)alanine, or 2-(6'-azidoheptyl)alanine. In some embodiments, Xaa^{7a} is Lys Orn, Dab, Dap, Lys(N₃), Orn(N₃), Dab(N₃), Dap(N₃), 2-(5'-azidopentyl)alanine, or 2-(6'-azidoheptyl)alanine. In some embodiments, Xaa^{7a} is Lys.

[0084] In some embodiments, Xaa^{7b} is Cys, D-Cys, Asp, D-Asp, Glu, D-Glu, 2-Aad, D-2-Aad, 3-Aad, D-3-Aad, Pra, D-Pra, Hpg, D-Hpg, Bpg or D-Bpg. In some embodiments, Xaa^{7b} is Cys, Asp, Glu, 2-Aad, 3-Aad, Pra, Hpg, or Bpg. In some embodiments, Xaa^{7b} is Asp, Glu, Pra or D-Pra. In some embodiments, Xaa^{7b} is Asp.

[0085] In some embodiments, each of Xaa¹, Xaa^{2a}, Xaa^{2b}, Xaa³, Xaa⁵, Xaa⁶, Xaa^{7a}, and Xaa^{7b} are L-amino acids and Xaa⁴ is a D-amino acid.

[0086] In some embodiments, the sequence of the MC1RTP consists essentially of the sequence defined by Formula A, I or II, wherein Xaa¹, Xaa^{2a}, Xaa^{2b}, Xaa³, Xaa⁴, Xaa⁵, Xaa⁶, Xaa^{7a}, and Xaa^{7b} are as defined for any combination of embodiments defined in this disclosure. In some embodiments, the sequence of the MC1RTP consists of the sequence defined by Formula A, I or II, wherein Xaa¹, Xaa^{2a}, Xaa^{2b}, Xaa³, Xaa⁴, Xaa⁵, Xaa⁶, Xaa^{7a}, and Xaa^{7b} are as defined for any combination of embodiments defined in this disclosure. In some embodiments, the sequence of the MC1RTP comprises, consists or consists essentially of the sequence defined by Formula A or Formula I, wherein Xaa¹, Xaa^{2a}, Xaa³, Xaa⁴, Xaa⁵, Xaa⁶, and Xaa^{7a} are as defined for any combination of embodiments defined in this disclosure. In some embodiments, the sequence of the MC1RTP comprises, consists or consists essentially of the sequence defined by Formula II, wherein Xaa¹, Xaa^{2b}, Xaa³, Xaa⁴, Xaa⁵, Xaa⁶, and Xaa^{7b} are as defined for any combination of embodiments defined in this disclosure.

[0087] In some embodiments, the sequence of MC1RTP comprises, consists or consists essentially of the sequence defined by Formula A or Formula I, wherein: Xaa¹ is Nle, Ala, Leu, Ile, Cys, Met, Phe, Trp, Val, Nal, 2-Nal, α -aminobutyric acid, norvaline or homonorleucine; Xaa^{2a} is Asp, Glu, Pra or D-Pra; Xaa³ is His, beta-(1,2,3-triazol-4-yl)-DL-alanine, or 1,2,4-

triazole-3-alanine; Xaa⁴ is Phe, D-Phe, 2-Nal or D-2-Nal; Xaa⁵ is Arg, D-Arg, hArg, Leu, D-hArg, Agb, D-Agb, Agp or D-Agp; Xaa⁶ is Trp or D-Trp; and Xaa^{7a} is Lys Orn, Dab, Dap, Lys(N₃), Orn(N₃), Dab(N₃), Dap(N₃), 2-(5'-azidopentyl)alanine, or 2-(6'-azidohexyl)alanine.

[0088] In some embodiments, Xaa¹ is Nle, Xaa^{2a} is Asp, Xaa³ is His, Xaa⁴ is D-Phe, Xaa⁵ is Arg, Xaa⁶ is Trp and Xaa⁷ is Lys. The sequence of MC1RTP may consist essentially of Nle-Asp-His-(D-Phe)-Arg-Trp-Lys, linear or cyclic, optionally C-terminally amidated, and alpha N-methylated as elsewhere defined in this disclosure. The sequence of MC1RTP may consist of Nle-Asp-His-(D-Phe)-Arg-Trp-Lys, linear or cyclic, optionally C-terminally amidated, and alpha N-methylated as elsewhere defined in this disclosure.

[0089] The MC1RTP may or may not be C-terminally amidated (e.g. at Xaa^{7a} or Xaa^{7b}). In some embodiments, the MC1RTP is C-terminally amidated. In some embodiments, the MC1RTP has a C-terminal carboxylate.

[0090] One or more amino acid residues of the MC1RTP is alpha N-methylated, including N-methylation of 1, 2, 3 or 4 of Xaa³, Xaa⁵, Xaa⁶ and Xaa^{7a} in the sequence defined by Formula A or Formula I and/or 1, 2, 3 or 4 of Xaa³, Xaa⁵, Xaa⁶ and Xaa^{7b} in the sequence defined by Formula II. In some embodiments, the MC1RTP has only 1, only 2, only 3 or only 4 alpha N-methylations. In some embodiments, one or more of Xaa³, Xaa⁵, Xaa⁶, and Xaa^{7a} in the sequence defined by Formula A or Formula I is alpha N-methylated. In some embodiments, Xaa⁵ and Xaa^{7a} in the sequence defined by Formula A or Formula I are alpha N-methylated. In some embodiments, Xaa⁵ and Xaa^{7b} in the sequence defined by Formula II are alpha N-methylated. In some embodiments, the N-methylations are (N-Me-Xaa³), (N-Me-Xaa⁵), (N-Me-Xaa⁶) and (N-Me-Xaa^{7a}). In some embodiments, the N-methylations are (N-Me-Xaa³), (N-Me-Xaa⁵), (N-Me-Xaa⁶) and (N-Me-Xaa^{7b}). In some embodiments, the N-methylations are (N-Me-Xaa⁵), (N-Me-Xaa⁶) and (N-Me-Xaa^{7a}). In some embodiments, the N-methylations are (N-Me-Xaa⁵), (N-Me-Xaa⁶) and (N-Me-Xaa^{7b}). In some embodiments, the N-methylations are (N-Me-Xaa⁵) and (N-Me-Xaa⁶). In some embodiments, the N-methylations are (N-Me-Xaa⁶) and (N-Me-Xaa^{7a}). In some embodiments, the N-methylations are (N-Me-Xaa⁶) and (N-Me-Xaa^{7b}). In some embodiments, the N-methylations are (N-Me-Xaa⁵) and (N-Me-Xaa^{7a}). In some embodiments, the N-methylations are (N-Me-Xaa⁵) and (N-Me-Xaa^{7b}). In some embodiments, the only N-methylation is (N-Me-Xaa⁶).

[0091] In some embodiments, the MC1RTP is linear. In some embodiments, the MC1RTP is cyclized. In some embodiments, the MC1RTP comprises, consists or consists essentially of Xaa¹-cyclo[Xaa^{2a}-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa^{7a}]. In some embodiments, the MC1RTP comprises, consists or consists essentially of cyclo[Xaa¹-Xaa^{2a}-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa^{7a}].

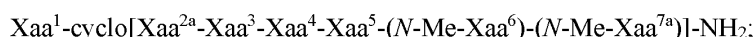
In some embodiments, the MC1RTP comprises, consists or consists essentially of Xaa¹-cyclo[Xaa^{2b}-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa^{7b}]. In some embodiments, the MC1RTP comprises, consists or consists essentially of cyclo[Xaa¹-Xaa^{2a}-Xaa³-Xaa⁴-Xaa⁵-Xaa⁶-Xaa^{7b}]. In the foregoing sequences, Xaa¹, Xaa^{2a}, Xaa^{2b}, Xaa³, Xaa⁴, Xaa⁵, Xaa⁶, Xaa^{7a}, Xaa^{7b} may have any of the alternative definitions presented in the paragraphs above or elsewhere in this disclosure.

[0092] The MC1RTP may be cyclized by a lactam bridge connecting Xaa^{2a} to Xaa^{7a} in the sequence defined by Formula A or Formula I, formed by connecting the side chain of Asp, D-Asp, Glu, D-Glu, 2-Aad, or D-2-Aad with the side chain of Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, or D-Dap. The MC1RTP may be cyclized by a lactam bridge connecting Xaa^{2b} to Xaa^{7b} in the sequence defined by Formula II, formed by connecting the side chain of Asp, D-Asp, Glu, D-Glu, 2-Aad, or D-2-Aad with the side chain of Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, or D-Dap.

[0093] The MC1RTP may be cyclized by a 1,2,3-triazole connecting Xaa^{2a} to Xaa^{7a} in the sequence defined by Formula A or Formula I, formed by connecting the side chains of Pra, D-Pra, Hpg, D-Hpg, Bpg or D-Bpg with Lys(N₃), D-Lys(N₃), Orn(N₃), D-Orn(N₃), Dab(N₃), D-Dab(N₃), Dap(N₃), D-Dap(N₃), 2-(5'-azidopentyl)alanine, D-2-(5'-azidopentyl)alanine, 2-(6'-azidohexyl)alanine or D-2-(6'-azidohexyl)alanine. The MC1RTP may be cyclized by a 1,2,3-triazole connecting Xaa^{2b} to Xaa^{7b} in the sequence defined by Formula II, formed by connecting the side chains of Pra, D-Pra, Hpg, D-Hpg, Bpg or D-Bpg with Lys(N₃), D-Lys(N₃), Orn(N₃), D-Orn(N₃), Dab(N₃), D-Dab(N₃), Dap(N₃), D-Dap(N₃), 2-(5'-azidopentyl)alanine, D-2-(5'-azidopentyl)alanine, 2-(6'-azidohexyl)alanine or D-2-(6'-azidohexyl)alanine.

[0094] The MC1RTP may be cyclized by a disulfide bridge connecting Xaa¹ to Xaa^{7a} in the sequence defined by Formula A or Formula I when both Xaa¹ and Xaa^{7a} are Cys (D- and/or L-form). The MC1RTP may be cyclized by a disulfide bridge connecting Xaa^{2a} to Xaa^{7a} in the sequence defined by Formula A or Formula I when both Xaa^{2a} and Xaa^{7a} are Cys (D- and/or L-form). The MC1RTP may be cyclized by a disulfide bridge connecting Xaa¹ to Xaa^{7b} in the sequence defined by Formula II when both Xaa¹ and Xaa^{7b} are Cys (D- or L-form). The MC1RTP may be cyclized by a disulfide bridge connecting Xaa^{2b} to Xaa^{7b} in the sequence defined by Formula II when both Xaa^{2b} and Xaa^{7b} are Cys (D- or L-form).

[0095] In some embodiments, the MC1RTP may comprise, consist or consist essentially of:



$\text{Xaa}^1\text{-cyclo}[\text{Xaa}^{2a}\text{-Xaa}^3\text{-Xaa}^4\text{-(N-Me-Xaa}^5\text{)-Xaa}^6\text{-Xaa}^{7a}]\text{-NH}_2$;
 $\text{Xaa}^1\text{-cyclo}[\text{Xaa}^{2b}\text{-Xaa}^3\text{-Xaa}^4\text{-(N-Me-Xaa}^5\text{)-(N-Me-Xaa}^6\text{)-(N-Me-Xaa}^{7b})]\text{-NH}_2$;
 $\text{Xaa}^1\text{-cyclo}[\text{Xaa}^{2b}\text{-Xaa}^3\text{-Xaa}^4\text{-(N-Me-Xaa}^5\text{)-(N-Me-Xaa}^6\text{)-Xaa}^{7b}]\text{-NH}_2$;
 $\text{Xaa}^1\text{-cyclo}[\text{Xaa}^{2b}\text{-Xaa}^3\text{-Xaa}^4\text{-Xaa}^5\text{-(N-Me-Xaa}^6\text{)-(N-Me-Xaa}^{7b})]\text{-NH}_2$;
 $\text{Xaa}^1\text{-cyclo}[\text{Xaa}^{2b}\text{-Xaa}^3\text{-Xaa}^4\text{-(N-Me-Xaa}^5\text{)-Xaa}^6\text{-(N-Me-Xaa}^{7b})]\text{-NH}_2$; or
 $\text{Xaa}^1\text{-cyclo}[\text{Xaa}^{2b}\text{-Xaa}^3\text{-Xaa}^4\text{-(N-Me-Xaa}^5\text{)-Xaa}^6\text{-Xaa}^{7b}]\text{-NH}_2$;

wherein Xaa^1 , Xaa^{2a} , Xaa^{2b} , Xaa^3 , Xaa^4 , Xaa^5 , Xaa^6 , Xaa^{7a} and Xaa^{7b} may be any of the alternative definitions provided above. The MC1RTP may be cyclized by the formation of a lactam bridge, a 1,2,3-triazole, or a disulfide bridge. In some such embodiments, Xaa^{2a} is Asp and Xaa^{7a} is Lys, and a lactam bridge is formed between Xaa^{2a} and Xaa^{7a} . In some such embodiments, Xaa^{2b} is Lys and Xaa^{7b} is Asp, and a lactam bridge is formed between Xaa^{2b} and Xaa^{7b} . In some such embodiments, Xaa^{2a} is Glu and Xaa^{7a} is Orn, and a lactam bridge is formed between Xaa^{2a} and Xaa^{7a} . In some such embodiments, Xaa^{2b} is Orn and Xaa^{7b} is Glu, and a lactam bridge is formed between Xaa^{2b} and Xaa^{7b} .

[0096] In some embodiments, the MC1RTP comprises Nle-cyclo[Asp-His-(D-Phe)-Arg-Trp-Lys], wherein the MC1RTP is optionally C-terminally amidated, and wherein 1, 2, 3 or 4 of Xaa^3 , Xaa^5 , Xaa^6 and Xaa^{7a} in the sequence defined by Formula A or Formula I is alpha N-methylated. In some embodiments, the MC1RTP comprises, consists or consists essentially of:

$\text{Nle-cyclo}[\text{Asp-(N-Me-His)-(D-Phe)-(N-Me-Arg)-(N-Me-Trp)-(N-Me-Lys)}]$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-(N-Me-Arg)-(N-Me-Trp)-(N-Me-Lys)}]$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-(N-Me-Arg)-(N-Me-Trp)-Lys}]$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-Arg-(N-Me-Trp)-(N-Me-Lys)}]$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-(N-Me-Arg)-Trp-(N-Me-Lys)}]$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-(N-Me-Arg)-Trp-Lys}]$;
 $\text{Nle-cyclo}[\text{Asp-(N-Me-His)-(D-Phe)-(N-Me-Arg)-(N-Me-Trp)-(N-Me-Lys)}]\text{-NH}_2$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-(N-Me-Arg)-(N-Me-Trp)-(N-Me-Lys)}]\text{-NH}_2$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-(N-Me-Arg)-(N-Me-Trp)-Lys}]\text{-NH}_2$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-Arg-(N-Me-Trp)-(N-Me-Lys)}]\text{-NH}_2$;
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-(N-Me-Arg)-Trp-(N-Me-Lys)}]\text{-NH}_2$; or
 $\text{Nle-cyclo}[\text{Asp-His-(D-Phe)-(N-Me-Arg)-Trp-Lys}]\text{-NH}_2$.

In some such embodiments, the MC1RTP is cyclized by a lactam bridge.

[0097] The linker may attach to the N-terminus of the MC1RTP. The linker may be any linker, e.g. but without limitation, ether, ester, thioether, disulfide, thioester, amide, carbamate, ureido, phosphodiester, polyethylene glycol (PEG), peptide, polypeptide, alkyl (e.g. $\text{C}_1\text{-C}_{10}$, $\text{C}_1\text{-C}_{15}$,

C₁-C₂₀, C₁-C₃₀, C₁-C₅₀, C₁-C₇₅, C₁-C₁₀₀, C₁-C₁₂₀ and the like), heteroalkyl (e.g. X₁-X₁₀, X₁-X₁₅, X₁-X₂₀, X₁-X₃₀, X₁-X₅₀, X₁-X₇₅, X₁-X₁₀₀ and the like), aryl (e.g. C₃-C₁₀, C₃-C₁₅, C₃-C₂₀, C₃-C₃₀, C₃-C₅₀, C₃-C₇₅, C₃-C₁₀₀, C₃-C₁₂₀ and the like) or heteroaryl (e.g. X₃-X₁₀, X₃-X₁₅, X₃-X₂₀, X₃-X₃₀, X₃-X₅₀, X₃-X₇₅, X₃-X₁₀₀, X₃-X₁₂₀ and the like). The alkyl or heteroalkyl may be one or more of: branched or linear; acyclic, cyclic or multi-cyclic; saturated or unsaturated; and unsubstituted or substituted. The aryl or heteroaryl may be one or more of: cyclic or multi-cyclic; aromatic or nonaromatic; and unsubstituted or substituted. Without limitation, in substituted embodiments, the alkyl, heteroalkyl, aryl or heteroaryl may be substituted with one or more of halide, amide, oxo, hydroxyl, thiol, phosphate and sulfate. In certain embodiments, each X is independently C, N, O, P, Se or S. The halide may be -F, -Br, -I or -Cl. In certain embodiments, the halide is -Br, -I or -Cl. In some embodiments, the linker is cationic. In some embodiments, the linker has net neutral charge.

[0098] In some embodiments, the linker consists or consists essentially of a C₁-C₁₂₀ alkylene which is: linear or branched; saturated or unsaturated; and acyclic or cyclic (including multi-cyclic). In some embodiments, the linker consists or consists essentially of a X₁-X₁₂₀ heteroalkylene, which is: linear or branched; saturated or unsaturated; and acyclic or cyclic (including multi-cyclic). In some such embodiments, the linker comprises a peptide. In some such embodiments, the linker consists or consists essentially of a peptide attached to the N-terminus of the MC1RTP. For example, the peptide may be 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 amino acid residues long. The peptide may comprise proteinogenic and/or non-proteinogenic amino acids.

[0099] In some embodiments, the linker is a linear peptide of 3 to 6 amino acid residues, -Xaa⁸-Xaa⁹-(Xaa¹⁰)₁₋₄-, attached to the N-terminus of the MC1RTP and the radiolabeling group (e.g., the CROWN chelator), wherein Xaa⁸, Xaa⁹, and Xaa¹⁰ are each independently an amino acid. In one embodiment, the linker Xaa⁸-Xaa⁹-(Xaa¹⁰)₁₋₄- is attached to the N-terminus of the MC1RTP by forming a bond with the free C-terminus of Xaa¹⁰.

[0100] In some embodiments, the linker comprises an albumin binding-group. In some embodiments, the linker is a linear peptide of 3 to 6 amino acid residues, -Xaa⁸-Xaa⁹-(Xaa¹⁰)₁₋₄-, wherein Xaa⁸, Xaa⁹, and Xaa¹⁰ are each independently an amino acid. In these embodiments, the radiolabeling group (e.g., the CROWN chelator) and the albumin-binding group are bonded to the free N-terminus of Xaa⁸ and the side chain of Xaa⁹, respectively, or the radiolabeling group (e.g., the CROWN chelator) and the albumin-binding group are bonded to the side chain of Xaa⁹ and the free N-terminus of Xaa⁸, respectively. In one embodiment, the N-terminus of the MC1RTP is bonded to the C-terminus of Xaa¹⁰ in the linker -Xaa⁸-Xaa⁹-

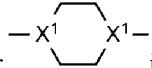
(Xaa¹⁰)₁₋₄-. In one embodiment, the linker -Xaa⁸-Xaa⁹-(Xaa¹⁰)₁₋₄- is attached to the N-terminus of the MC1RTP by forming an amide bond with the free C-terminus of Xaa¹⁰. Xaa⁸, Xaa⁹ and each Xaa¹⁰ may independently be any amino acid, including proteinogenic and/or non-proteinogenic amino acids (including D-amino acids). In some embodiments, Xaa⁸ is Gly, Glu, D-Glu, Asp, D-Asp, 2-Aad, D-2-Aad, 3-Aad, or D-3-Aad. In some embodiments, Xaa⁹ is Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap or D-Dap, any of which can form an amide bond with a carboxylate of a radiolabeling group or an albumin binding group. In some embodiments, Xaa⁸ is Gly, Glu or D-Glu. In some embodiments, Xaa⁹ is Lys or D-Lys. In some such embodiments, (Xaa¹⁰)₁₋₄ is diglycine. In some embodiments, (Xaa¹⁰)₁₋₄ is p-aminomethylaniline-diglycolic acid (pABzA-DIG), a 4-amino-(1-carboxymethyl)piperidine (Pip), a 9-amino-4,7-dioxanonanoic acid (dPEG2), or a 4-(2-aminoethyl)-1-carboxymethyl-piperazine (Acp). In some embodiments, (Xaa¹⁰)₁₋₄ is Pip.

[10101] In some embodiments, the linker is a branched peptide of 3 to 6 amino acid residues, -Xaa⁹(Xaa⁸)-(Xaa¹⁰)₁₋₄-, attached to the N-terminus of the MC1RTP and the radiolabeling group (e.g., the CROWN chelator), wherein Xaa⁸, Xaa⁹, and Xaa¹⁰ are each independently an amino acid. In one embodiment, the linker -Xaa⁹(Xaa⁸)-(Xaa¹⁰)₁₋₄- is attached to the N-terminus of the MC1RTP by forming a bond with the free C-terminus of Xaa¹⁰.

[10102] In some embodiments, the linker comprises an albumin binding-group. In some embodiments, the linker is a branched peptide of 3 to 6 amino acid residues, -Xaa⁹(Xaa⁸)-(Xaa¹⁰)₁₋₄-, wherein Xaa⁸, Xaa⁹, and Xaa¹⁰ are each independently an amino acid. In these embodiments, the C-terminus of Xaa⁸ forms an amide with the side chain of Xaa⁹, and the radiolabeling group (e.g., the CROWN chelator) and the albumin-binding group are bonded to the free N-termini of Xaa⁸ and Xaa⁹, respectively, or the radiolabeling group (e.g., the CROWN chelator) and the albumin-binding group are bonded to the free N-termini of Xaa⁹ and Xaa⁸, respectively. In these embodiments, Xaa⁹ is Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap or D-Dap, the C-terminus of Xaa⁸ forms an amide with the side chain of Xaa⁹, and the radiolabeling group and the albumin-binding group are bonded to the free N-termini of Xaa⁸ and Xaa⁹, respectively, or are bonded to the free N-termini of Xaa⁹ and Xaa⁸, respectively. Xaa⁸ and each Xaa¹⁰ may independently be any amino acid, including proteinogenic and/or non-proteinogenic amino acids (including D-amino acids). In some embodiments, Xaa⁸ is Gly, Glu, D-Glu, Asp, D-Asp, 2-Aad, D-2-Aad, 3-Aad, or D-3-Aad. In some embodiments, Xaa⁸ is Gly, Glu or D-Glu. In some embodiments, Xaa⁹ is Lys or D-Lys. In some such embodiments, (Xaa¹⁰)₁₋₄ is diglycine. In some embodiments, (Xaa¹⁰)₁₋₄ is p-aminomethylaniline-diglycolic acid (pABzA-DIG), a 4-amino-(1-carboxymethyl)piperidine (Pip), a 9-amino-4,7-dioxanonanoic acid

(dPEG2), or a 4-(2-aminoethyl)-1-carboxymethyl-piperazine (Acp). In some embodiments, (Xaa¹⁰)₁₋₄ is Pip.

[0103] In some embodiments, the linker comprises a linear peptide, -Xaa⁸-Xaa⁹-Xaa¹⁰-, wherein Xaa⁸, Xaa⁹, and Xaa¹⁰ are each independently an amino acid, and wherein the radiolabeling group (e.g., the CROWN chelator) and the albumin-binding group are bonded to the free N-terminus of Xaa⁸ and the side chain of Xaa⁹, respectively, or the radiolabeling group (e.g., the CROWN chelator) and the albumin-binding group are bonded to the side chain of Xaa⁹ and the free N-terminus of Xaa⁸, respectively. In one embodiment, the N-terminus of the MC1RTP is bonded to the C-terminus of Xaa¹⁰. In one embodiment, the linker -Xaa⁸-Xaa⁹-Xaa¹⁰- is attached to the N-terminus of the MC1RTP by forming an amide bond with the free C-terminus of Xaa¹⁰. In such embodiments, Xaa¹⁰ is -N(H)R²R³R²C(O)-, in which each R² is

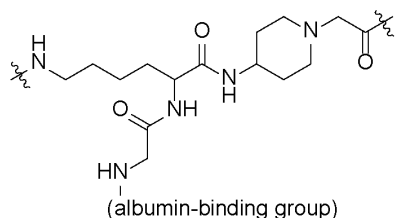
independently absent, methylene or ethylene, and R³ is -(CH₂)_n- or  in which each X¹ is independently carbon or nitrogen, and n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11. In some embodiments, n is 6-8. In some embodiments, n is 7. In some embodiments, one X¹ is nitrogen. In other embodiments, both X¹ are nitrogen. In some embodiments, at least one nitrogen of X¹ is protonated, resulting in a cationic peptide. In some embodiments, Xaa¹⁰ is 4-amino-1-carboxymethyl-piperidine (Pip), 4-(2-aminoethyl)-1-carboxymethyl-piperazine (Acp), or -N(H)-(CH₂)₂₋₁₅C(O)- (e.g. 8-aminooctanoic acid (Aoc) and the like). In some embodiments, Xaa¹⁰ is Pip. Xaa⁸ and Xaa⁹ may independently be any amino acid, including proteinogenic or non-proteinogenic amino acids (including D-amino acids). In some embodiments, Xaa⁸ is Gly, Glu, D-Glu, Asp, D-Asp, 2-Aad, D-2-Aad, 3-Aad, or D-3-Aad. In some embodiments, Xaa⁹ is Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap or D-Dap, any of which can form an amide bond with a carboxylate of a radiolabeling group or an albumin binding group. In some embodiments, Xaa⁸ is Gly, Glu or D-Glu. In some embodiments, Xaa⁹ is Lys or D-Lys.

[0104] In some embodiments, the linker comprises a branched peptide, -Xaa⁹(Xaa⁸)-Xaa¹⁰-, wherein Xaa⁸, Xaa⁹, and Xaa¹⁰ are each independently an amino acid, the C-terminus of Xaa⁸ forms an amide with the side chain of Xaa⁹, and the radiolabeling group (e.g., the CROWN chelator) and the albumin-binding group are bonded to the free N-termini of Xaa⁸ and Xaa⁹, respectively, or the radiolabeling group (e.g., the CROWN chelator) and the albumin-binding group are bonded to the free N-termini of Xaa⁹ and Xaa⁸, respectively. In one embodiment, the N-terminus of the MC1RTP is bonded to the C-terminus of Xaa¹⁰. In one embodiment, the

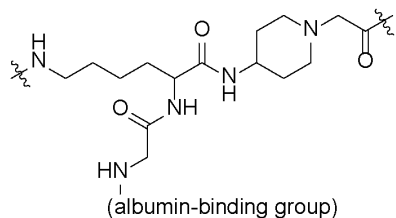
linker $-Xaa^9(Xaa^8)-Xaa^{10}-$ is attached to the N-terminus of the MC1RTP by forming a bond with the free C-terminus of Xaa^{10} . In some embodiments, the linker comprises a branched peptide, $-Xaa^9(Xaa^8)-Xaa^{10}-$, wherein Xaa^9 is Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap or D-Dap and the C-terminus of Xaa^8 forms an amide with the side chain of Xaa^9 , and wherein the radiolabeling group and the albumin-binding group are bonded to the free N-termini of Xaa^8 and Xaa^9 , respectively, or are bonded to the free N-termini of Xaa^9 and Xaa^8 , respectively. Xaa^{10} is $-N(H)R^2R^3R^2C(O)-$, in which each R^2 is independently absent, methylene or ethylene,

and R^3 is $-(CH_2)_n-$ or $-X^1\text{---}X^1-$ in which each X^1 is independently carbon or nitrogen, and n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11. In some embodiments, n is 6-8. In some embodiments, n is 7. In some embodiments, one X^1 is nitrogen. In other embodiments, both X^1 are nitrogen. In some embodiments, at least one nitrogen of X^1 is protonated, resulting in a cationic peptide. In some embodiments, Xaa^{10} is 4-amino-1-carboxymethyl-piperidine (Pip), 4-(2-aminoethyl)-1-carboxymethyl-piperazine (Acp), or $-N(H)-(CH_2)_{2-15}C(O)-$ (e.g. 8-aminooctanoic acid (Aoc) and the like). In some embodiments, Xaa^{10} is Pip. Xaa^8 may be any amino acid, including proteinogenic or non-proteinogenic amino acids (including D-amino acids). In some embodiments, Xaa^8 is Gly, Glu, D-Glu, Asp, D-Asp, 2-Aad, D-2-Aad, 3-Aad, or D-3-Aad. In some embodiments, Xaa^8 is Gly, Glu or D-Glu. In some embodiments, Xaa^9 is Lys or D-Lys.

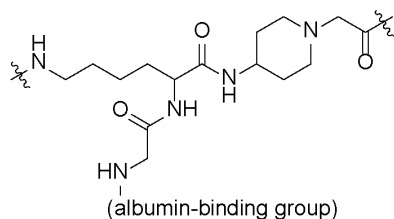
[0105] In some embodiment, the linker is



. In some embodiment, the linker is

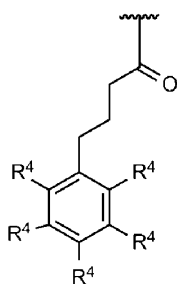


. In some embodiment, the linker is



and the albumin-binding group is *N*-[4-(*p*-tolyl)butanoyl].

[0106] The albumin-binding group may have the following structure, wherein each R^4 is independently H, halogen, C_{1-5} alkyl, C_{1-5} alkoxy or nitro group:



[0107] In some embodiments, three R^4 groups are H and two R^4 group are independently I, F, Br, Cl or methyl in meta/meta, ortho/ortho, para/meta, meta/para, para/ortho, ortho/para, meta/ortho or ortho/meta. In some embodiments, four R^4 groups are H and one R^4 group is I, F, Br, Cl or methyl in para, meta or ortho position. In some embodiments, the albumin-binding group is *N*-[4-(iodophenyl)butanoyl], *N*-[4-(fluorophenyl)butanoyl], *N*-[4-(bromophenyl)butanoyl], *N*-[4-(chlorophenyl)butanoyl], or *N*-[4-(tolyl)butanoyl]. In some embodiments, the albumin-binding group is *N*-[4-(*p*-tolyl)butanoyl]. In some embodiments, the albumin-binding group is *N*-[4-(*p*-iodophenyl)butanoyl], *N*-[4-(*p*-fluorophenyl)butanoyl], *N*-[4-(*p*-bromophenyl)butanoyl], *N*-[4-(*p*-chlorophenyl)butanoyl], or *N*-[4-(*p*-tolyl)butanoyl]. In some embodiments, the albumin-binding group is *N*-[4-(*p*-tolyl)butanoyl].

[0108] In embodiments where the linker comprises the linear peptide, the albumin-binding group may be coupled to the α -amino group of Xaa⁸ and the radiolabeling group may be coupled to the side chain of Xaa⁹. In other such embodiments, the radiolabeling group may be coupled to the α -amino group of Xaa⁸ and the albumin-binding group may be coupled to the side chain of Xaa⁹.

[0109] In embodiments where the linker comprises the branched peptide, the albumin-binding group may be coupled to the α -amino group of Xaa⁸ and the radiolabeling group may be coupled to the α -amino group of Xaa⁹. In other such embodiments, the radiolabeling group may

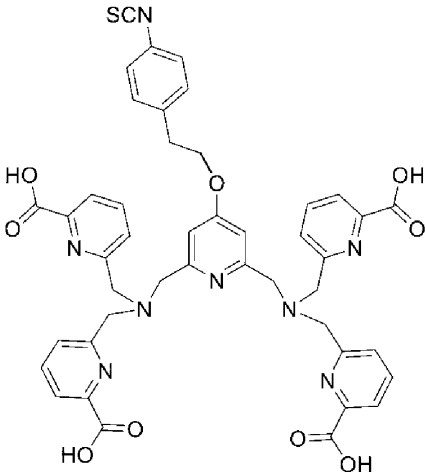
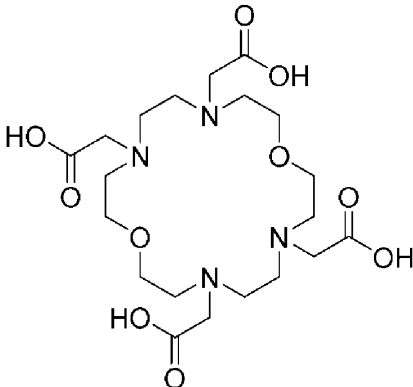
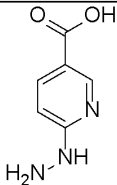
be coupled to the α -amino group of Xaa⁸ and the albumin-binding group may be coupled to the α -amino group of Xaa⁹.

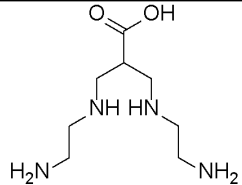
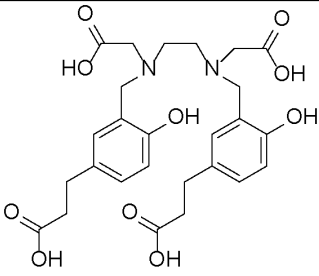
[0110] The radiolabeling group may be a radioisotope chelator. Chelators may be incorporated into the compound by coupling to a peptide portion of the compound.

[0111] Non-limiting examples of radioisotope chelators include chelators selected from H4py4pa-phenyl-NCS, CROWN, HYNIC, N4, or HBED-CC. Exemplary non-limiting examples of radioisotope chelators and radioisotopes chelated by the chelators are shown in Table 1. In alternative embodiments, the radioisotope chelator in the compound is one of those listed above or in Table 1, or is any other radioisotope chelator. One skilled in the art could replace any of the chelators listed herein with another chelator.

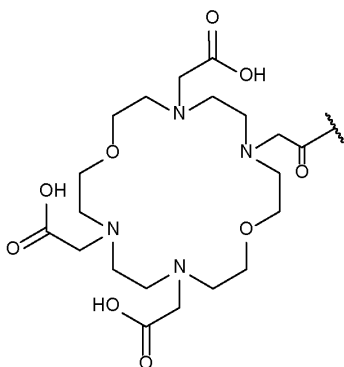
[0112] In one embodiment, the radioisotope chelator is CROWN.

[0113] **TABLE 1:** Exemplary chelators and exemplary isotopes which bind said chelators

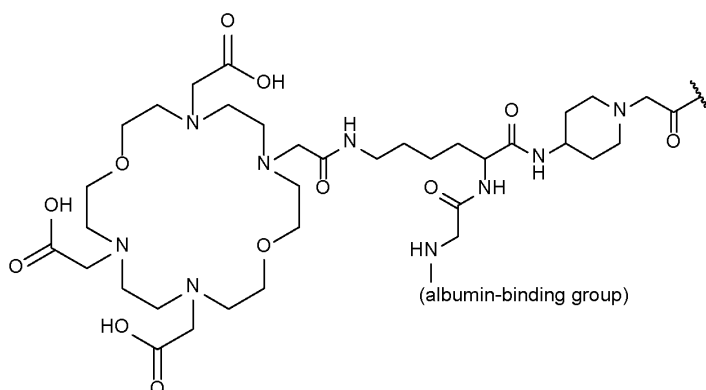
Chelator	Radionuclide
 H4py4pa-phenyl-NCS	Ac-225
 CROWN (2,2',2'',2'''-(1,10-dioxa-4,7,13,16-tetraazacyclooctadecane-4,7,13,16-tetrayl)tetraacetic acid)	Bis-213 Lu-177 Ac-225 Tb-149 Tb-152 Tb-155 Tb-161 Th-227
 HYNIC	Tc-99m Tc-94m

Chelator	Radionuclide
 N4 (6-carboxy-1,4,7,11-tetraazaundecane)	Tc-99m Tc-94m
 HBED-CC	Ga-68

[0114] In some embodiments, the CROWN chelator has the following connectivity to the linker (— shows the connectivity to the linker):



[0115] In some embodiments, the CROWN chelator connected to a linker has the following structure (— shows the connectivity to MC1RTP):



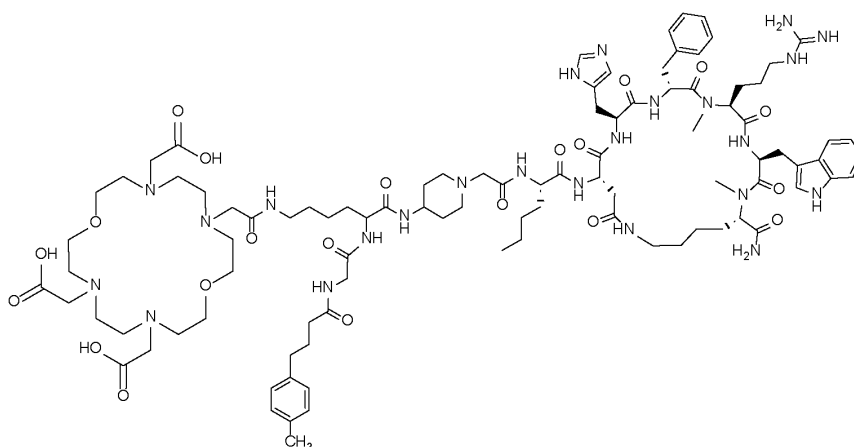
[0116] In some embodiments, the radioisotope chelator is conjugated with a radioisotope. The conjugated radioisotope may be, without limitation, ^{68}Ga , ^{61}Cu , ^{64}Cu , ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , $^{114\text{m}}\text{In}$, ^{44}Sc , ^{47}Sc , ^{86}Y , ^{90}Y , ^{89}Zr , ^{90}Nb , ^{177}Lu , $^{117\text{m}}\text{Sn}$, ^{165}Er , ^{227}Th , ^{225}Ac , ^{213}Bi , ^{212}Bi , ^{211}As , ^{203}Pb , ^{212}Pb , ^{166}Ho , ^{188}Re , ^{186}Re , ^{149}Pm , ^{159}Gd , ^{105}Rh , ^{109}Pd , ^{198}Au , ^{199}Au , ^{175}Yb , ^{142}Pr , ^{149}Tb , ^{152}Tb , ^{155}Tb , ^{161}Tb , and the like. In some embodiments, the chelator is a chelator from Table 1 and the conjugated radioisotope is a radioisotope indicated in Table 1 as a binder of the chelator.

[0117] In some embodiments, the conjugated radioisotope is a therapeutic radioisotope (e.g. a beta emitter or an alpha emitter). Non-limiting examples of therapeutic radioisotopes include, ^{165}Er , ^{212}Bi , ^{213}Bi , ^{211}At , ^{166}Ho , ^{149}Pm , ^{159}Gd , ^{105}Rh , ^{109}Pd , ^{198}Au , ^{199}Au , ^{175}Yb , ^{142}Pr , ^{177}Lu , ^{111}In , ^{203}Pb , ^{212}Pb , ^{47}Sc , ^{90}Y , $^{117\text{m}}\text{Sn}$, ^{153}Sm , ^{149}Tb , ^{152}Tb , ^{155}Tb , ^{161}Tb , ^{224}Ra , ^{225}Ac , ^{227}Th , ^{223}Ra , ^{77}As , ^{131}I , ^{64}Cu , ^{67}Cu , and the like. In some embodiments, the radioisotope is ^{225}Ac .

[0118] In some embodiments, the conjugated radioisotope is suitable for PET or SPECT imaging (e.g. a positron emitter or a gamma emitter). Non-limiting examples of positron or gamma emitting radioisotopes include ^{68}Ga , ^{67}Ga , ^{61}Cu , ^{64}Cu , $^{99\text{m}}\text{Tc}$, $^{110\text{m}}\text{In}$, ^{111}In , ^{44}Sc , ^{86}Y , ^{89}Zr , ^{90}Nb , ^{18}F , ^{131}I , ^{123}I , ^{124}I or ^{72}As .

[0119] In some embodiments, the conjugated radioisotope is ^{213}Bi , ^{177}Lu , ^{225}Ac , ^{149}Tb , ^{152}Tb , ^{155}Tb , ^{161}Tb , or ^{227}Th .

[0120] There is also provided a compound having the following structure or a salt thereof,



(CCZ01178),

wherein the compound is optionally conjugated with a radioisotope. In some embodiments, the compound is conjugated with ^{213}Bi , ^{177}Lu , ^{225}Ac , ^{149}Tb , ^{152}Tb , ^{155}Tb , ^{161}Tb , or ^{227}Th . In some embodiments, the compound is conjugated with ^{225}Ac . In some embodiment, the compound is ^{225}Ac -labeled CCZ01178.

[0121] In some embodiments, the MC1RTP are those disclosed in WO2019/222851, which is hereby incorporated by reference in its entirety for all purposes.

[0122] USES/METHODS

[0123] This section incorporates all embodiments and combinations of features of the compounds described in the previous section.

[0124] There is also disclosed a pharmaceutical composition comprising a compound as defined in Section II and a pharmaceutically acceptable excipient, carrier or diluent. The compound may be any of the embodiments (or combination of features thereof) defined in the previous section. The compound may be conjugated with a therapeutic radioisotope (as defined in the previous section) or may be conjugated with a radioisotope that is suitable for PET or SPECT imaging (as defined in the previous section).

[0125] The compounds may be useful in preparing a radioisotope-conjugated compound. There is therefore provided a method of preparing a radioisotope-conjugated compound comprising conjugating a radioisotope as defined in the previous section to the radioisotope chelator of a compound as defined in the previous section. The compound may be any of the embodiments (or combination of features thereof) defined in the previous section. The

radioisotope may be a therapeutic radioisotope (as defined in the previous section) or may be a radioisotope that is suitable for PET or SPECT imaging (as defined in the previous section).

[0126] In some embodiments, the present disclosure provides a method of treating cancer.

[0127] In some embodiments, the present disclosure provides a method of treating melanoma.

[0128] In some embodiments, the present disclosure provides a method of treating an MC1R-related disease, comprising administering any one of the compounds as disclosed herein to a subject. In some embodiments, the present disclosure provides a use of any one of the compounds disclosed herein in manufacture of a medicament for treatment of an MC1R-related disease or condition.

[0129] In some embodiments, the MC1R-related disease or condition is an MC1R-expressing cancer. In some embodiment, cancer is melanoma or non-melanoma skin cancer. For example, but without limitation, MC1R is specifically expressed in cutaneous, amelanotic and uveal melanomas. In some embodiments, the MC1R-expressing cancer is melanoma or non-melanoma skin cancer. In some embodiments, the MC1R-expressing cancer is primary melanoma or metastatic melanoma. In some embodiments, the MC1R-expressing cancer is uveal melanoma. In some embodiments, the MC1R-expressing cancer is melanoma.

[0130] In some embodiment of the methods of treating cancer, administering the compound of the present disclosure with a CROWN chelator extends the survival of the subject when compared to administering a compound with a DOTA chelator (instead of the CROWN chelator) where the rest of the compound is the same (i.e., same linker and same MC1RTP). In some embodiment, the survival is extended by at least 3 months, at least 6 months, at least 9 months, or at least 12 months. In some embodiment, the survival is extended by at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years.

[0131] In some embodiment of the methods of treating cancer, administering the compound of the present disclosure with a ²²⁵Ac labeled CROWN chelator extends the survival of the subject when compared to administering a compound with a ¹⁷⁷Lu labeled DOTA chelator (instead of the CROWN chelator) where the rest of the compound is the same (i.e., same linker and same MC1RTP). In some embodiment, the survival is extended by at least 3 months, at least 6 months, at least 9 months, or at least 12 months. In some embodiment, the survival is extended by at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years.

[0132] In some embodiment of the methods of treating cancer, administering the compound of the present disclosure with a CROWN chelator is more effective at reducing the size of a tumor or slowing the progression of cancer when compared to administering a compound with a

DOTA chelator (instead of the CROWN chelator) where the rest of the compound is the same (i.e., same linker and same MC1RTP).

[0133] In some embodiment of the methods of treating cancer, administering the compound of the present disclosure with a ^{225}Ac labeled CROWN chelator is more effective at reducing the size of a tumor or slowing the progression of cancer when compared to administering a compound with a ^{177}Lu DOTA chelator (instead of the CROWN chelator) where the rest of the compound is the same (i.e., same linker and same MC1RTP).

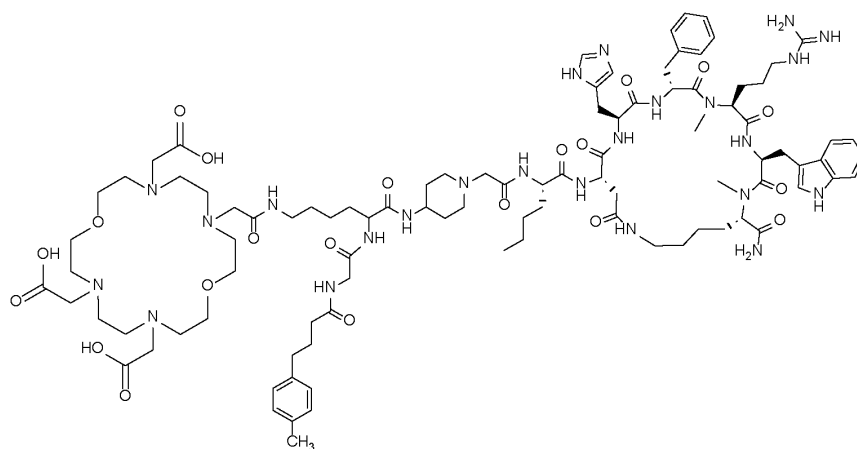
[0134] In some embodiments, the present disclosure provides a method of imaging MC1R-expressing tissues in a subject, in which the method comprises: administering to the subject any one of the compounds as described herein; and imaging tissue of the subject using PET or SPECT. When the tissue is a diseased tissue (e.g. an MC1R-expressing cancer), MC1R-targeted treatment may then be selected for treating the subject. In some embodiment of any one of the methods as disclosed herein, the compound is administered as a pharmaceutical composition. In some embodiments, the MC1R-expressing tissues are cancer tissues. In some embodiments, cancer is melanoma or non-melanoma skin cancer. In some embodiments, cancer is primary melanoma or metastatic melanoma. In some embodiments, cancer is uveal melanoma.

[0135] Without limitation, the compound of the disclosure or a pharmaceutical composition comprising the compound may be administered to the subject intravenously, or as a subcutaneous or intradermal injection surrounding the site of the initial tumour (e.g. to detect lymphatic spread).

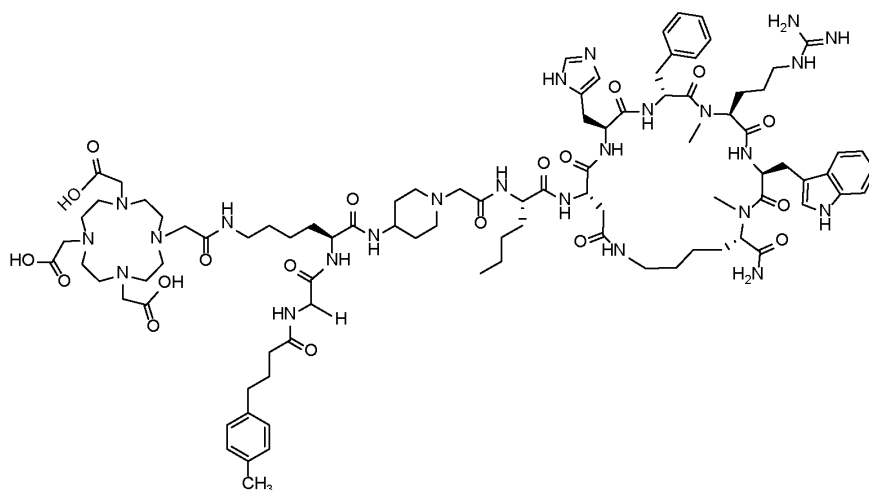
EXAMPLES

[0136] The present invention is further illustrated in the following examples.

[0137] Example 1: Synthesis and radiolabelling of CCZ01178 ([4-(*p*-tolylphenyl)butanoyl]-Gly-Lys(CROWN)-Pip-Nle-cyclo[Asp-His-D-Phe-*N*-Me-Arg-Trp-*N*-Me-Lys]-NH₂) and CCZ01158 ([4-(*p*-tolylphenyl)butanoyl]-Gly-Lys(DOTA)-Pip-Nle-cyclo[Asp-His-D-Phe-*N*-Me-Arg-Trp-*N*-Me-Lys]-NH₂)



CCZ01178



CCZ01158

[0138] CCZ01178 was synthesized according to a modified procedure disclosed in WO2019/222851 and WO2021/168567, the disclosure of each of which is hereby incorporated by reference in its entirety for all purposes. CCZ01158 was synthesized according to WO2019/222851.

[0139] Radiolabelling of [^{225}Ac]Ac-CCZ01178 and [^{225}Ac]Ac-CCZ01158

[0140] CCZ01178 and CCZ01158 were radiolabelled with $^{225}\text{AcCl}_3$. *See* WO2021/168567. For example, an aliquot of CCZ01178 precursor (1 mM, 1 nmol, 0.9 μL) was dissolved in 0.2 M NaOAc (pH 5.5, 223 μL) and EtOH (10%, 34 μL), followed by 0.86 MBq of $^{225}\text{AcCl}_3$ (85 μL). The mixture reacted at room temperature for 20 minutes. The reaction mixture was further diluted in formulation buffer.

[0141] [^{225}Ac]Ac-CCZ01158 was prepared in a similar manner as described above, with heating up to 95 °C during the reaction.

[0142] Radiolabelling of [^{177}Lu]Lu-CCZ01158

[0143] CCZ01158 was radiolabelled with $^{177}\text{LuCl}_3$. See Bratanovic et al. *J. Nucl. Med.* **2022**, 63, 424-430, which is incorporated by reference in its entirety for all purposes. For example, an aliquot of CCZ01158 precursor (1 mM, 0.7 nmol, 0.7 μL) was dissolved in 0.2 M NaOAc (pH 5.5, 114 μL) and ethanol (10%, 13 μL), followed by 62.2 MBq of $^{177}\text{LuCl}_3$ (2.3 μL), then heated up to 95°C for 15 minutes. The reaction mixture was further diluted in formulation buffer.

[0144] Example 2: Biodistribution

[0145] NRG mice bearing SK-MEL-1 human melanoma were injected with 15-30 kBq of [^{225}Ac]Ac-CCZ01178 or ^{225}Ac -labeled CCZ01158 via tail vein under anesthesia. At various time points, such as 1, 3, 4, 20, 24, 70, 119 and/or 120 h p.i., the mice were anesthetized again, and euthanized by CO_2 inhalation. Blood was promptly withdrawn, and the organs of interest were harvested, rinsed with 1 $\times$ PBS (pH 7.4), and blotted dry. Each organ was then weighed and the radioactivity of the collected tissue was measured using a Wallac WIZARD2 gamma counter (Perkin Elmer), normalized to the injected dose using a standard curve and expressed as the percentage of the injected dose per gram of tissue (%ID/g). **Table 2** summarizes the biodistribution data of [^{225}Ac]Ac-CCZ01178 at 1, 3, 20, 70 and 119 h p.i.

[0146] **Table 2.** Biodistribution of [^{225}Ac]Ac-CCZ01178 in NRG mice bearing SK-MEL-1 human melanoma at 1, 3, 20, 70 and 119 h p.i. Values are in %ID/g (mean $\pm$ standard deviation), n = 4.

	1 h		3 h		20 h		70 h		119 h	
	Avg	Std	Avg	Std	Avg	Std	Avg	Std	Avg	Std
Blood	14.21	2.76	10.83	2.79	0.46	0.15	0.10	0.04	0.03	0.01
Urine	173.49	97.25	105.63	21.50	5.61	4.40	0.24	0.13	0.06	0.11
Fat	2.10	0.76	1.60	0.28	0.27	0.18	0.27	0.06	0.28	0.09
seminal	0.82	0.07	0.63	0.24	0.12	0.06	0.17	0.05	0.04	0.04
Testes	2.40	0.19	2.86	1.43	0.80	0.26	0.79	0.05	0.79	0.31
Intestine	1.81	0.44	1.36	0.31	0.28	0.07	0.35	0.10	0.14	0.04
Spleen	3.57	0.39	2.85	0.49	1.84	0.75	1.82	0.50	1.61	1.19
Pancreas	1.89	0.29	1.56	0.31	0.22	0.06	0.25	0.13	0.17	0.06
Stomach	0.81	0.18	0.73	0.17	0.34	0.10	0.66	0.34	0.23	0.06

	1 h		3 h		20 h		70 h		119 h	
	Avg	Std	Avg	Std	Avg	Std	Avg	Std	Avg	Std
Liver	5.44	0.95	4.34	1.59	3.81	0.93	5.03	1.10	4.25	3.35
Adrenal	5.24	0.90	4.05	1.21	0.98	0.20	1.17	0.50	0.47	0.33
Kidney	9.37	5.78	11.76	3.47	9.63	2.47	5.78	0.85	3.76	1.37
Heart	3.77	0.23	2.72	0.46	0.56	0.10	0.54	0.16	0.45	0.19
Lungs	8.79	1.44	6.78	0.42	1.03	0.35	0.69	0.18	0.64	0.29
SK-MEL-1 tumor	6.70	1.00	10.45	0.42	12.07	3.60	10.70	2.06	8.62	3.49
Thyroid	4.01	0.62	3.58	0.82	2.74	0.74	3.16	0.54	3.06	1.05
Bone	1.02	0.18	1.20	0.27	0.63	0.26	1.06	0.15	0.45	0.33
Muscle	1.22	0.23	1.01	0.25	0.12	0.05	0.13	0.05	0.09	0.05
Brain	0.26	0.07	0.22	0.05	0.03	0.01	0.03	0.02	0.04	0.03

[0147] Example 3. Dose Escalation Study

[0148] Dose escalation study was conducted with [²²⁵Ac]Ac-CCZ01178 (at 15 kBq and 30 kBq) and [¹⁷⁷Lu]Lu-CCZ01158 (at 20 MBq and 40 MBq) in SK-MEL-1 bearing mice.

[0149] SK-MEL-1 human melanoma-bearing mice were injected with saline (control), [²²⁵Ac]Ac-CCZ01178 (about 15 or 30 kBq/mouse), or [¹⁷⁷Lu]Lu-CCZ01158 (about 20 or 40 MBq/mouse). Tumour size and body weight were measured every 2-4 days from the date of injection. Endpoint was defined as > 15% weight loss, ulceration of tumours, or tumour volume > 1000 mm³ (Volume = width × width × length / 2, measured with calliper).

[0150] Fig. 1. Shows the change in tumor volume over time and **Fig. 2** shows survival curve of different treatment groups.

[0151] Example 4: Biodistribution Comparison at 24 h post injection

[0152] NRG mice bearing SK-MEL-1 human melanoma were injected with 15-30 kBq of [²²⁵Ac]Ac-CCZ01178 or [²²⁵Ac]Ac-CCZ01158 via tail vein under anesthesia. At 24 h p.i., the mice were anesthetized again, and euthanized by CO₂ inhalation. Blood was promptly withdrawn, and the organs of interest were harvested, rinsed with 1× PBS (pH 7.4), and blotted dry. Each organ was then weighed and the radioactivity of the collected tissue was measured using a Wallac WIZARD2 gamma counter (Perkin Elmer), normalized to the injected dose using a standard curve and expressed as the percentage of the injected dose per gram of tissue (%ID/g). **Table 3** summarizes the biodistribution data of [²²⁵Ac]Ac-CCZ01178 and [²²⁵Ac]Ac-CCZ01158 at 24 h p.i.

[0153] **Table 3.** Biodistribution of [^{225}Ac]Ac-CCZ01178 and [^{225}Ac]Ac-CCZ01158 in NRG mice bearing SK-MEL-1 human melanoma at 24 h p.i. Values are in %ID/g (mean $\pm$ standard deviation), n = 3 or 4.

Organs	[^{225}Ac]Ac-CCZ01178			[^{225}Ac]Ac-CCZ01158		
	Mean	SD	n	Mean	SD	n
Blood	0.27	0.02	3	0.24	0.06	4
Fat	0.08	0.03	3	0.12	0.05	4
Seminal Glands	0.10	0.02	3	0.07	0.08	4
Testes	0.38	0.01	3	0.48	0.16	4
Intestines	0.34	0.11	3	0.19	0.03	4
Spleen	1.42	0.20	3	4.09	0.97	4
Pancreas	0.14	0.03	3	0.15	0.07	4
Stomach	0.97	0.40	3	0.23	0.15	4
Liver	4.52	0.23	3	13.05	1.94	4
Adrenals	0.49	0.43	3	0.36	0.50	4
Kidney	4.66	0.34	3	3.23	0.74	4
Heart	0.39	0.03	3	0.41	0.05	4
Lungs	0.77	0.19	3	1.05	0.28	4
Bone	0.43	0.08	3	0.78	0.29	4
Muscle	0.06	a.as	3	0.39	0.60	4
Brain	0.03	0.01	3	0.02	0.02	4
SK-MEL-1 tumor	10.58	0.76	3	3.39	0.24	4
Tumor-to-Blood	39.68	2.62	3	14.53	2.86	4
Tumor-to-Muscle	124.93	19.74	3	28.57	18.35	4
Tumor-to-Bone	25.67	7.02	3	5.39	1.60	4
Tumor-to-Kidney	2.28	0.23	3	1.08	0.19	4

[0154] All citations are hereby incorporated by reference.

[0155] The present invention has been described with regard to one or more embodiments. However, it will be apparent to persons skilled in the art that a number of variations and

modifications can be made without departing from the scope of the invention as defined in the claims.

WHAT IS CLAIMED IS:

1. A compound or a salt thereof, wherein the compound comprises a melanocortin 1 receptor (MC1R) targeting peptide (MC1RTP) linked to a CROWN chelator by a linker, wherein:

the MC1RTP is cyclized and comprises a sequence of Formula A:

$$\text{Xaa}^1\text{-Xaa}^{2a}\text{-Xaa}^3\text{-Xaa}^4\text{-Xaa}^5\text{-Xaa}^6\text{-Xaa}^{7a} \text{ (A)}$$

Xaa¹ is selected from the group consisting of norleucine (Nle), D-Nle, Ala, D-Ala, Leu, D-Leu, Ile, D-Ile, Cys, D-Cys, Met, D-Met, Phe, D-Phe, Trp, D-Trp, Val, D-Val, 3-(1-naphthyl)alanine (Nal), D-Nal, 3-(2-naphthyl)alanine (2-Nal), D-2-Nal, Gly, α -aminobutyric acid, norvaline, D-norvaline, homonorleucine, and D-homonorleucine;

Xaa^{2a} is selected from the group consisting of Cys, D-Cys, Asp, D-Asp, Glu, D-Glu, 2-aminoadipic acid (2-Aad), D-2-Aad, 3-aminoadipic acid (3-Aad), D-3-Aad, propargylglycine (Pra), D-Pra, homopropargylglycine (Hpg), D-Hpg, beta-homopropargylglycine (Bpg), and D-Bpg;

Xaa³ is His;

Xaa⁴ is D-Phe;

Xaa⁵ is Arg;

Xaa⁶ is Trp;

Xaa^{7a} is selected from the group consisting of Cys, D-Cys, Lys, D-Lys, Orn, D-Orn, Dab, D-Dab, Dap, D-Dap, Lys(N₃), D-Lys(N₃), Orn(N₃), D-Orn(N₃), Dab(N₃), D-Dab(N₃), Dap(N₃), D-Dap(N₃), 2-(5'-azidopentyl)alanine, D-2-(5'-azidopentyl)alanine, 2-(6'-azidoheptyl)alanine, and D-2-(6'-azidoheptyl)alanine;

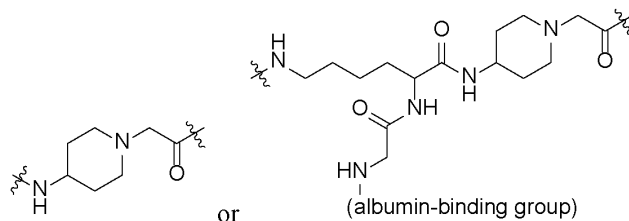
one or more amino acid residues of the MC1RTP is alpha N-methylated; and

the MC1RTP is optionally C-terminally amidated.
2. The compound of claim 1, wherein the MC1RTP is cyclized by a lactam bridge connecting Xaa^{2a} to Xaa^{7a}.
3. The compound of claim 2, wherein Xaa^{2a} is Asp and Xaa^{7a} is Lys; and the lactam bridge connects the side chains of Asp and Lys.
4. The compound of any one of claims 1-3, wherein Xaa¹ is norleucine (Nle), Xaa^{2a} is Asp, Xaa³ is His, Xaa⁴ is D-Phe, Xaa⁵ is Arg, Xaa⁶ is Trp, and Xaa^{7a} is Lys.

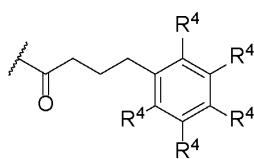
5. The compound of any one of claims 1-4, wherein one or more of Xaa³, Xaa⁵, Xaa⁶, and Xaa^{7a} is alpha N-methylated.
6. The compound of any one of claims 1-5, wherein only Xaa⁵ and Xaa^{7a} are alpha N-methylated.
7. The compound of any one of claims 1-6, wherein the linker comprises an albumin binding group.
8. The compound of claim 7, wherein the linker is a linear peptide of 3 to 6 amino acid residues, $-Xaa^8-Xaa^9-(Xaa^{10})_{1-4}-$, wherein Xaa⁸, Xaa⁹, and Xaa¹⁰ are each independently an amino acid and wherein:
 - the N-terminus of the MC1RTP is bonded to the free C-terminus of Xaa¹⁰; and
 - the CROWN chelator and the albumin-binding group are bonded to the free N-terminus of Xaa⁸ and the side chain of Xaa⁹, respectively, or
 - the CROWN chelator and the albumin-binding group are bonded to the side chain of Xaa⁹ and the free N-terminus of Xaa⁸, respectively.
9. The compound of claim 8, wherein the CROWN chelator and the albumin-binding group are bonded to the side chain of Xaa⁹ and the free N-terminus of Xaa⁸, respectively
10. The compound of claim 8 or 9, wherein:
 - Xaa⁸ is Gly, Glu or D-Glu; and
 - Xaa⁹ is Lys or D-Lys.
11. The compound of any one of claims 8-10, wherein (Xaa¹⁰)₁₋₄ is p-aminomethylaniline-diglycolic acid (pABzA-DIG), a 4-amino-(1-carboxymethyl)piperidine (Pip), a 9-amino-4,7-dioxanonanoic acid (dPEG2), or a 4-(2-aminoethyl)-1-carboxymethyl-piperazine (Acp).
12. The compound of any one of claims 8-11, wherein (Xaa¹⁰)₁₋₄ is Pip.

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13. The compound of any one of claims 1-6, wherein the linker is:

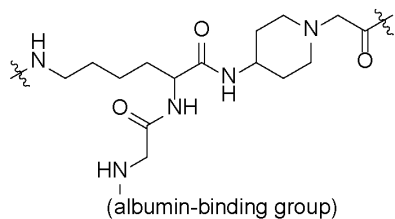


14. The compound of any one of claims 7-13, wherein the albumin-binding group has the following structure:

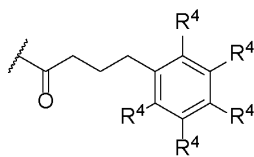


wherein each R⁴ is independently H, halogen, C₁₋₅ alkyl, C₁₋₅ alkoxy, or nitro.

15. The compound of any one of claims 1-13, wherein the linker is:



and the albumin-binding group has the following structure:



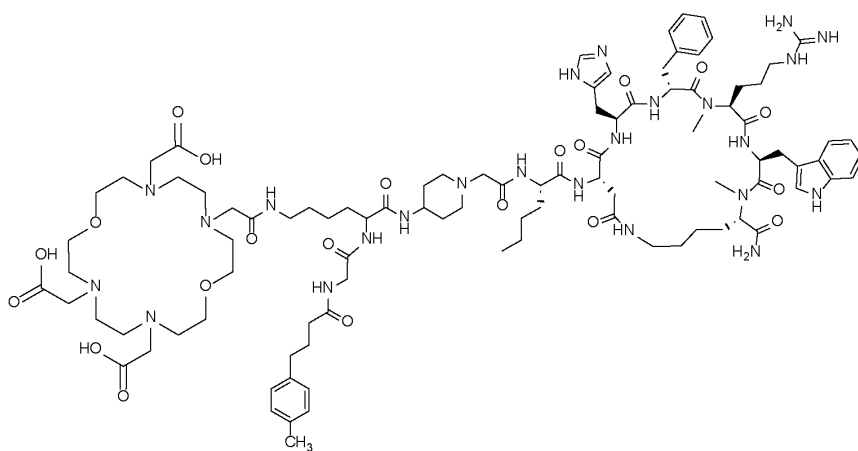
wherein each R⁴ is independently H, I, Br, F, Cl, -OH, -OCH₃, -NH₂, -NO₂ or -C₁-C₆ alkyl.

16. The compound of any one of claims 7-15 wherein the albumin-binding group is *N*-[4-(*p*-tolyl)butanoyl].

17. The compound of any one of claims 1-16, wherein the CROWN chelator is

conjugated to a radioisotope.

18. The compound of any one of claims 1-17, wherein the CROWN chelator is conjugated to ^{213}Bi , ^{177}Lu , ^{225}Ac , ^{149}Tb , ^{152}Tb , ^{155}Tb , ^{161}Tb , or ^{227}Th .
19. The compound of any one of claims 1-18, wherein the CROWN chelator is conjugated to ^{225}Ac .
20. A compound having the structure:



, or a salt

thereof.

21. The compound of claim 20, conjugated to ^{213}Bi , ^{177}Lu , ^{225}Ac , ^{149}Tb , ^{152}Tb , ^{155}Tb , ^{161}Tb , or ^{227}Th .
22. The compound of claim 20 or 21, conjugated to ^{225}Ac .
23. A method of treating melanoma, comprising administering a compound of any one of claims 1-22.
24. The method of claim 23, wherein the melanoma is metastatic cutaneous melanoma or metastatic uveal melanoma.