NON-NATURALLY OCCURRING MELANOCORTIN ANALOGS AND ASSOCIATED METHODS

CROSS-REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/607,500, filed December 7, 2023, U.S. Provisional Patent Application No. 63/618,843, filed January 8, 2024, U.S. Provisional Patent Application No. 63/557,385, filed February 23, 2024, U.S. Provisional Patent Application No. 63/573,429, filed April 2, 2024, of U.S. Provisional Patent Application No. 63/650,705, filed May 22, 2024, U.S. Provisional Patent Application No. 63/656,583, filed June 5, 2025, and U.S. Provisional Patent Application No. 63/663,648, filed June 24, 2024, all of which applications are incorporated herein by reference in their entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0002] This application contains an ST.26 compliant Sequence Listing, which is submitted concurrently in xml format and hereby incorporated by reference in its entirety. The .xml copy, created on December 9, 2024, is titled "146316_8017_WO03_SL.xml" and is 667,080 bytes in size.

BACKGROUND

[0003] Melanocortins are a group of small peptides that bind to a family of five known melanocortin receptors (MC1R through MC5R). They are derived from a common precursor protein, pro-opiomelanocortin (POMC), which is expressed in the neurons of the central and peripheral nervous system, and in the pituitary gland. The proteolytic cleavage of POMC results in α-, β- and γ-melanocortin and adrenocorticotrophic hormone (ACTH), in addition to several other biologically important peptides.

[0004] Melanocortin analogs have been synthesized for the potential regulation and treatment of many conditions, including weight regulation (e.g., obesity, anorexia, and cachexia), hormonal secretion, and hyposecretion of many exocrine glands. However, in regulating these physiological effects, melanocortin analogs have also been shown to cause certain side effects, such as, for example hypertension and cardiac arrhythmias.

[0005] Despite recent attempts to reduce melanocortin peptide side effects or enhance melanocortin in vivo activity, there still exists a need for highly stable and selective melanocortin analogs in the treatment and prevention of various melanocortin-related diseases.

SUMMARY

[0006] The present technology comprises non-naturally occurring melanocortin analogs including a sequence of Formula (I): X1-X2-R1-R2-R3-R4-R5-R6-R7-R8-Y1-Y2-Y3 (I), wherein: X1 is absent, norleucine (Nle), or D-valine (dVal); X2 is absent or D-proline (dPro); R1 is absent or is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen); R2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys); R3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, Trp, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), indoline-2-carboxylic acid (Ioc), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip); R4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe); R5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn); R6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic); R7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen; R8 is absent or Lys; Y1 is selected from the group consisting of Trp, Nle and dVal; Y2 is absent or is selected from the group consisting of Nle, dVal, and dPro; Y3 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R1 or R2 and R7 when each of R1 or R2 and R7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp and R7 or R8 is Lys; and a lactam bridge between R1 and R7 when

R1 is Lys and R7 is Asp; provided that: when R4 is p(I)dPhe, then the non-naturally occurring melanocortin analog is cyclized between R1 and R7; when R4 is p(F)dPhe and the non-naturally occurring melanocortin analog is cyclized between R2 and R7, then R3 is not Pro, His, dGln, or Trp; when R4 is p(Cl)dPhe, and the non-naturally occurring melanocortin analog is cyclized between R2 and R7, then R3 is not Pro, His, dPhe, or Trp; when R4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then (i) R5 and R6 are absent or (ii) R3 is absent and R2 is not Cys; when R4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R2 and R7 or R8, then R3 is selected from dIle, dVal, and dAla, R5 is Pro, or R6 is Nal(1'); when R4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R1 and R7, then (i) R2 is Trp, and (a) R3 is dVal or dLeu, (b) R5 is His, or (c) R6 is dNal(1'), Phe, or dPhe, or (ii) R2 is Pro and R3 is Pro; when R4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then the disulfide bond is not formed between Pen at R2 and dCys at R7 and R3 is not Pro; when R4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R2 and R7 or R8, then (i) R3 is selected from dPro, dTrp, His, and Ioc, or (ii) R3 is Pro and either R5 is selected from dLys, dArg, dOrn, Gly, Asp, dHis, dAla, dAsp, dGlu, and Pro or R6 is absent selected from His, dHis, Ala, and dAla; and when R4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R1 and R7, then one or both of R5 and R6 is absent.

[0007] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein: X2 is absent or D-proline (dPro); R1 is absent or is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen); R2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys); R3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, Trp, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), indoline-2-carboxylic acid (Ioc), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip); R4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine

(p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe); R5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn); R6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic); R7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen; R8 is absent or Lys; Y1 is selected from the group consisting of Trp, Nle and dVal; Y2 is absent or is selected from the group consisting of Nle, dVal, and dPro; Y3 is absent or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R1 or R2 and R7 when each of R1 or R2 and R7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp and R7 or R8 is Lys; and a lactam bridge between R1 and R7 when R1 is Lys and R7 is Asp; provided that the non-naturally occurring melanocortin analog does not include a sequence selected from the group consisting of: Ac--Nle-c[Asp-Pro-p(I)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 216); Ac--Nle-c[Asp-His-p(I)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 221); Ac--Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 223); Ac--Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 460); Ac--Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 464); Ac--Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 465); Ac--Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 469); Ac--Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 470); Ac--Nle-c[Cys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 459); Ac--Nle-c[dCys-His-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 461); Ac--Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 218); Ac--Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 433); Ac--Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 434); Ac--dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 436); Ac--Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 437); Ac--Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 438); Ac--Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 442); Ac--Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 443); Ac--Nle-c[Asp-dGln-p(F)dPhe-

Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 492); Ac--dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 463); Ac--Nle-c[Cys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 432); Ac--Nle-c[Asp-Trp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 493); Ac--Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 499); Ac--dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 501); Ac--Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 502); Ac--Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 503); Ac--Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 215); Ac--Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 220); Ac--Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 498); Ac--Nle-c[Cys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 497); Ac--Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 508); Ac--Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 507); Ac--Nle-c[Asp-Trp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 531); Ac--Nle-c[Asp-dPhe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 526); Ac--Nle-c[Cys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 318); Ac--Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 319); Ac--Nle-c[dPen-Pro-dPhe-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 320); Ac--Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 321); Ac--Nle-c[Cys-dPhe-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 324); Ac--Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 363); Ac--dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 302); Ac--Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 311); Ac--Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 313); Ac--Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 295); Ac--Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro--NH2 (SEQ ID NO: 351); Ac--Nle-c[Asp-dBip-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 369); Ac--Nle-c[Asp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 354); Ac--Nle-c[Asp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 355); Ac--Nle-c[Asp-Ioc-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 361); Ac--Nle-c[Asp-dPhe-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 367); Ac--Nle-c[Asp-dGln-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 371); Ac--Nle-c[Asp-Trp-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 372); Ac--Nle-c[Asp-dTrp-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 373); Ac--Nle-c[Asp-Pro-dPhe-His-Trp-

Lys]-dVal-dPro--NH2 (SEQ ID NO: 425); Ac--Nle-c[Asp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro--NH2 (SEQ ID NO: 429); Ac--Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 628); Ac--Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-Trp--NH2 (SEQ ID NO: 600); Ac--Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro--NH2 (SEQ ID NO: 595); Ac--Nle-c[Asp-Trp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 394); Ac--Nle-c[Asp-Trp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 395); Ac--Nle-c[Asp-Trp-Pro-dPhe-Arg-Nal(1')-Lys]-dVal-dPro--NH2 (SEQ ID NO: 399); Ac--Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 226); Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 297); Ac--Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 413); Ac--Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 40); Ac--Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 41); Ac--Nle-c[Cys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 42); Ac--Nle-c[dCys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 43); Ac--Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 48); Ac--Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 49); Ac--Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 50); Ac--Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 51); Ac--Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 52); Ac--Nle-c[dPen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 53); Ac--Nle-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 54); Ac--Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 55); Ac--dArg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 329); Ac--Arg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 330); Ac--Lys-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 337); Ac--Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 59); Ac--Nle-c[Asp-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 68); Ac--Nle-c[Asp-Ala-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 69); Ac--Nle-c[Asp-dAla-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 71); Ac--Nle-c[Asp-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 75); Ac--Nle-c[Asp-Leu-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 76); Ac--Nle-c[Asp-dLeu-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 79); Ac--Nle-c[Asp-dIle-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 80); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 3); Ac--dArg-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-

dVal-dPro--NH2 (SEQ ID NO: 15); Ac--dVal-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 19); Ac--dPro-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 27); Ac--Nle-c[Asp-Trp-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 82); Ac--Nle-c[Asp-Pro-dNal(2')-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 86); Ac--Nle-c[Asp-Pro-dNal(2')-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 92); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Phe-Lys]-dVal-dPro--NH2 (SEQ ID NO: 104); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-dNal(1')-Lys]-dVal-dPro--NH2 (SEQ ID NO: 108); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-dPhe-Lys]-dVal-dPro--NH2 (SEQ ID NO: 109); Ac--Nle-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 184); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal--NH2 (SEQ ID NO: 128); Ac--Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 255); Ac--Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro--NH2 (SEQ ID NO: 256); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro--NH2 (SEQ ID NO: 259); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal-dPro--NH2 (SEQ ID NO: 179); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal--NH2 (SEQ ID NO: 126); Ac--Nle-c[Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 73); Ac--Nle-c[Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 74); Ac--Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 257); Ac--Nle-c[Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 194); Ac--Nle-c[Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 195); and Ac--Nle-c[Asp-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 5).

[0008] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, including a sequence according to Formula (IA): X1-X2-R1-R2-R3-R4-R5-R6-R7-R8-Y1-Y2 (IA), wherein: X1 is absent, norleucine (Nle), or D-valine (dVal); X2 is absent or D-proline (dPro); R1 is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen); R2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys); R3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip); R4 is selected from the group consisting

of dPhe, dBip, biphenylalanine (Bip), and 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe); R5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn); R6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic); R7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen; R8 is absent or Lys; Y1 is Nle or dVal; Y2 is absent, Nle, or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R1 or R2 and R7 when each of R1 or R2 and R7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp and R7 or R8 is Lys; and a lactam bridge between R1 and R7 when R1 is Lys and R7 is Asp; provided that: when R4 is p(F)dPhe and the non-naturally occurring melanocortin analog is cyclized between R2 and R7, then R3 is not Pro, His, or dGln; when R4 is p(Cl)dPhe, and the non-naturally occurring melanocortin analog is cyclized between R2 and R7, then R3 is not Pro, His, or dPhe; when R4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then (i) R5 and R6 are absent or (ii) R3 is absent and R2 is not Cys; when R4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R2 and R7 or R8, then (i) R3 is selected from dIle, dVal, and dAla, (ii) R5 is Pro, or (iii) R6 is Nal(1'); when R4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R1 and R7, then (i) R2 is Trp, and (a) R3 is dVal or dLeu, (b) R5 is His, or (c) R6 is dNal(1'), Phe, or dPhe, or (ii) R2 is Pro and R3 is Pro; when R4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then the disulfide bond is not formed between Pen at R2 and dCys at R7 and R3 is not Pro; when R4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R2 and R7 or R8, then (i) R3 is selected from dPro, dTrp, His, and Ioc, , or (ii) R3 is Pro and either R5 is selected from dLys, dArg, dOrn, Gly, Asp, dHis, dAla, dAsp, dGlu, and Pro or R6 is absent or selected from His, dHis, Ala, and dAla; and when R4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R1 and R7, then one or both of R5 and R6 is absent.

[0009] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, including a sequence according to Formula (IA), wherein: X1 is absent, norleucine (Nle), or D-valine (dVal); X2 is absent or D-proline (dPro); R1 is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen); R2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys); R3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip); R4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), and 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe); R5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn); R6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic); R7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen; R8 is absent or Lys; Y1 is Nle or dVal; Y2 is absent, Nle, or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a disulfide bond between R1 or R2 and R7 when each of R1 or R2 and R7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen; a lactam bridge between R1 or R2 and R7 or R8 when R1 or R2 is Asp and R7 or R8 is Lys; and a lactam bridge between R1 and R7 when R1 is Lys and R7 is Asp; provided that the non-naturally occurring melanocortin analog does not include a sequence selected from the group consisting of: Ac--Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 223); Ac--Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 460); Ac--Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 464); Ac--Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 465); Ac--Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 469); Ac--Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 470); Ac--Nle-c[Cys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 459); Ac--Nle-c[dCys-His-p(F)dPhe-

Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 461); Ac--Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 218); Ac--Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 433); Ac--Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 434); Ac--dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 436); Ac--Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 437); Ac--Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 438); Ac--Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 442); Ac--Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 443); Ac--Nle-c[Asp-dGln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 492); Ac--dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 463); Ac--Nle-c[Cys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 432); Ac--Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 499); Ac--dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 501); Ac--Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 502); Ac--Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 503); Ac--Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 215); Ac--Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 220); Ac--Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 498); Ac--Nle-c[Cys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 497); Ac--Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 508); Ac--Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 507); Ac--Nle-c[Asp-dPhe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 526); Ac--Nle-c[Cys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 318); Ac--Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 319); Ac--Nle-c[dPen-Pro-dPhe-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 320); Ac--Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 321); Ac--Nle-c[Cys-dPhe-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 324); Ac--Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 363); Ac--dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 302); Ac--Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 311); Ac--Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 313); Ac--Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291); Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 295); Ac--Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro--NH2 (SEQ ID NO: 351); Ac--Nle-c[Asp-dBip-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID

NO: 369); Ac--Nle-c[Asp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 354); Ac--Nle-c[Asp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 355); Ac--Nle-c[Asp-dPhe-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 367); Ac--Nle-c[Asp-dGln-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 371); Ac--Nle-c[Asp-dTrp-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 373); Ac--Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 425); Ac--Nle-c[Asp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro--NH2 (SEQ ID NO: 429); Ac--Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 628); Ac--Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-Trp--NH2 (SEQ ID NO: 600); Ac--Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro--NH2 (SEQ ID NO: 595); Ac--Nle-c[Asp-Trp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 394); Ac--Nle-c[Asp-Trp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 395); Ac--Nle-c[Asp-Trp-Pro-dPhe-Arg-Nal(1')-Lys]-dVal-dPro--NH2 (SEQ ID NO: 399); Ac--Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 226); Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 297); Ac--Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 413); Ac--Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 40); Ac--Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 41); Ac--Nle-c[Cys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 42); Ac--Nle-c[dCys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 43); Ac--Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 48); Ac--Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 49); Ac--Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro--NH2 (SEQ ID NO: 50); Ac--Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 51); Ac--Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 52); Ac--Nle-c[dPen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro--NH2 (SEQ ID NO: 53); Ac--Nle-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 54); Ac--Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 55); Ac--dArg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 329); Ac--Arg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 330); Ac--Lys-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro--NH2 (SEQ ID NO: 337); Ac--Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 59); Ac--Nle-c[Asp-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 68); Ac--Nle-c[Asp-Ala-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 69); Ac--Nle-c[Asp-dAla-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 71); Ac--Nle-c[Asp-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 75); Ac--

Nle-c[Asp-Leu-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 76); Ac--Nle-c[Asp-dLeu-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 79); Ac--Nle-c[Asp-dIle-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 80); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 3); Ac--dArg-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 15); Ac--Nle-c[Asp-Pro-dNal(2')-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 86); Ac--Nle-c[Asp-Pro-dNal(2')-His-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 92); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Phe-Lys]-dVal-dPro--NH2 (SEQ ID NO: 104); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-dNal(1')-Lys]-dVal-dPro--NH2 (SEQ ID NO: 108); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-dPhe-Lys]-dVal-dPro--NH2 (SEQ ID NO: 109); Ac--Nle-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 184); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal--NH2 (SEQ ID NO: 128); Ac--Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 255); Ac--Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro--NH2 (SEQ ID NO: 256); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro--NH2 (SEQ ID NO: 259); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal-dPro--NH2 (SEQ ID NO: 179); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal--NH2 (SEQ ID NO: 126); Ac--Nle-c[Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 73); Ac--Nle-c[Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 74); Ac--Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 257); Ac--Nle-c[Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 194); Ac--Nle-c[Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 195); and Ac--Nle-c[Asp-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 5).

[0010] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, including a sequence according to Formula (IB): R1-R2-R3-dNal(2')-R5-R6-R7-Y1-Y2 (IB), wherein: R1 is norleucine (Nle); R2 is selected from the group consisting of penicillamine (Pen), D-penicillamine (dPen), cysteine (Cys), and D-cysteine (dCys); R3 is absent or is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly R5 is Arg; R6 is Trp; R7 is selected from the group consisting of Cys, dCys, Pen, dPen; Y1 is dVal; Y2 is dPro; and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R2 and R7 when R2 and R7 are each independently selected from the group consisting of Cys, dCys, Pen, and dPen, provided

that: when R3 is absent, then the disulfide bond is not formed between Pen at R2 and dCys at R7.

[0011] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, including a sequence of Formula (IB), wherein: R1 is norleucine (Nle); R2 is selected from the group consisting of penicillamine (Pen), D-penicillamine (dPen), cysteine (Cys), and D-cysteine (dCys); R3 is absent or is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly R5 is Arg; R6 is Trp; R7 is selected from the group consisting of Cys, dCys, Pen, dPen; Y1 is dVal; Y2 is dPro; and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R2 and R7 when R2 and R7 are each independently selected from the group consisting of Cys, dCys, Pen, and dPen, provided that the non-naturally occurring melanocortin analog does not include a sequence of: Ac--Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro--NH2 (SEQ ID NO: 59).

[0012] In some embodiments, the present technology comprises a the non-naturally occurring melanocortin analog, including a sequence of Formula (IC): R1-Asp-R3-dNal(2')-R5-R6-Lys-Y1-Y2 (IC), wherein: R1 is norleucine (Nle); R3 is selected from the group consisting of histidine (His), proline (Pro), D-proline (dPro), D-tryptophan (dTrp), and indoline-2-carboxylic acid (Ioc); R5 is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn); R6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, and dAla; Y1 is dVal; Y2 is dPro; and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R2 and Lys at R7; provided that: when R3 is Pro, then either R5 is not Arg or R6 is not Trp.

[0013] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, including a sequence of Formula (IC), wherein: R1 is norleucine (Nle); R3 is selected from the group consisting of histidine (His), proline (Pro), D-proline (dPro), D-tryptophan (dTrp), and indoline-2-carboxylic acid (Ioc); R5 is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn); R6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, and dAla; Y1 is dVal; Y2 is dPro;

and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R2 and Lys at R7; provided that the non-naturally occurring melanocortin analog does not include a sequence selected from the group consisting of: Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2); Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro--NH2 (SEQ ID NO: 3); and Ac--Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116).

[0014] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, including a sequence of Formula (ID): X1-X2-R1-R2-Arg-R4-R5-R6-R7-Y1-Y2 (ID), wherein: X1 is norleucine (Nle) or D-valine (dVal); X2 is absent or D-proline (dPro); R1 is aspartic acid (Asp) or lysine (Lys); R2 is selected from the group consisting of tryptophan (Trp), proline (Pro), and histidine (His); R4 is selected from the group consisting of D-biphenylalanine (dBip), 2'-D-naphthylalanine (dNal(2')), and para-iodo-D-phenylalanine (p(I)dPhe); R5 is arginine (Arg) or Pro; R6 is absent or tetrahydro-isoquinoline-3-carboxylic acid (Tic); R7 is Asp or Lys; Y1 is Nle or dVal; Y2 is absent, Nle, or dPro; and the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of: a lactam bridge between R1 and R7 when R1 is Asp and R7 is Lys; and a lactam bridge between R1 and R7 when R1 is Lys and R7 is Asp.

[0015] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, including a sequence of Formula (IE): X1-R1-R2-R3-R4-Arg-R6-Lys-Y1-Y2 (IE), wherein: X1 is absent or norleucine (Nle); R1 is Nle or aspartic acid (Asp); R2 is selected from the group consisting of Asp, histidine (His), and proline (Pro); R3 is arginine (Arg) or indoline-2-carboxylic acid (Ioc); R4 is 2'-D-naphthylalanine (dNal(2')) or para-iodo-D-phenylalanine (p(I)dPhe); R6 is Trp or tetrahydro-isoquinoline-3-carboxylic acid (Tic); Y1 is dVal; Y2 is dPro; and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between the Asp at R1 or R2 and the Lys at R7.

[0016] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the N-terminus of the non-naturally occurring melanocortin analog is modified by an acyl group.

[0017] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the acyl group is an acetyl group.

[0018] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the N-terminus of the non-naturally occurring melanocortin analog is not modified.

[0019] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the C-terminus of the non-naturally occurring melanocortin analog is modified by an amide group.

[0020] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the C-terminus of the non-naturally occurring melanocortin analog is not modified.

[0021] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein Y1-Y2 are present and Y3 is absent.

[0022] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein Y1 is D-valine and Y2 is D-proline.

[0023] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond.

[0024] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond between R1 or R2 and R7.

[0025] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is dNal(2').

[0026] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R3 is absent.

[0027] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH2 (SEQ ID NO: 44); Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH2 (SEQ ID NO: 45); Ac-Nle-c[Cys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH2 (SEQ ID NO: 46); Ac-Nle-c[dCys-

dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH2 (SEQ ID NO: 47); Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH2 (SEQ ID NO: 56); Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH2 (SEQ ID NO: 57); Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH2 (SEQ ID NO: 58); Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH2 (SEQ ID NO: 60); Ac-Nle-c[dPen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH2 (SEQ ID NO: 61); Ac-Nle-c[dPen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 62); and Ac-Nle-c[Pen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 63), wherein c represents cyclization through R2 and R7 via a disulfide bond.

[0028] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R3 is present and is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly.

[0029] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[dPen-Ala-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 338); Ac-Nle-c[dPen-Leu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 339); Ac-Nle-c[dPen-dLeu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 340); Ac-Nle-c[dPen-dVal-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 341); Ac-Nle-c[dPen-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 342); and Ac-Nle-c[dPen-Gly-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 343), wherein c represents cyclization through R1 or R2 and R7 via a disulfide bond.

[0030] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is dPhe.

[0031] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein at least one of R1, R3, R5, and R6 is absent.

[0032] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-c[Cys-Arg-dPhe-Cys]-Trp-dVal-dPro-NH2 (SEQ ID NO: 202); Ac-Nle-c[Pen-dPhe-Arg-Trp-Cys]-dVal-dPro-NH2 (SEQ ID NO: 325); and Ac-

Nle-c[dPen-dPhe-Arg-Trp-dPen]-dVal-dPro-NH2 (SEQ ID NO: 326), wherein c represents cyclization through R2 and R7 via a disulfide bond.

[0033] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond.

[0034] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R1 and R7.

[0035] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is dBip or p(I)dPhe.

[0036] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein one of R2 and R3 is Arg.

[0037] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH2 (SEQ ID NO: 188); Ac-Nle-c[Asp-His-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH2 (SEQ ID NO: 189); Ac-Nle-c[Asp-Pro-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH2 (SEQ ID NO: 190); Ac-Nle-c[Asp-Pro-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH2 (SEQ ID NO: 191); Ac-Nle-c[Asp-Arg-Pro-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH2 (SEQ ID NO: 192); and Ac-Nle-c[Asp-Arg-Pro-dBip-Arg-Tic-Lys]-dVal-dPro-NH2 (SEQ ID NO: 193), wherein c represents cyclization through R1 and R7 via a lactam bond.

[0038] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is dPhe.

[0039] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R2 is Trp and/or R3 is Pro.

[0040] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-

NH2 (SEQ ID NO: 225); Ac-Nle-c[Asp-Trp-dLeu-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 396); Ac-Nle-c[Asp-Trp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 397); Ac-Nle-c[Asp-Trp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 398); Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH2 (SEQ ID NO: 400); Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro-NH2 (SEQ ID NO: 401); and Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dPhe-Lys]-dVal-dPro-NH2 (SEQ ID NO: 402), wherein c represents cyclization through R1 and R7 via a lactam bond.

[0041] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is dNal(2').

[0042] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein (i) R2 is Pro and R3 is Trp or Trp-Arg or (ii) R2 is Trp and R3 is Arg.

[0043] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein (i) R5 is Pro or absent.

[0044] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH2 (SEQ ID NO: 276); Ac-Nle-c[Asp-Pro-Trp-dNal(2')-Lys]-dVal-dPro-NH2 (SEQ ID NO: 277); Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH2 (SEQ ID NO: 278); Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Lys]-dVal-dPro-NH2 (SEQ ID NO: 279); Ac-Nle-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-dVal-dPro-NH2 (SEQ ID NO: 280); Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-NH2 (SEQ ID NO: 284); Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-Nle-NH2 (SEQ ID NO: 285); Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-Nle-NH2 (SEQ ID NO: 286); Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-Nle-Nle-NH2 (SEQ ID NO: 287); Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH2 (SEQ ID NO: 288); and Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-dVal-dPro-NH2 (SEQ ID NO: 289), wherein c represents cyclization through R1 and R7 via a lactam bond.

[0045] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R2 and R7.

[0046] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is Bip.

[0047] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is: Ac-Nle-c[Asp-Pro-Bip-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 114), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0048] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is dPhe.

[0049] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R3 is not Pro, R5 is not Arg, and/or R6 is not Trp.

[0050] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-dIle-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 356); Ac-Nle-c[Asp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 357); Ac-Arg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 376); Ac-dArg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 377); Ac-Nle-c[Asp-His-dPhe-Pro-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 227); Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 230); and Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH2 (SEQ ID NO: 428), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0051] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is p(Cl)dPhe.

[0052] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R3 is selected from the group consisting of dBip, dGln, and dTrp.

[0053] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-dBip-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 528); Ac-Nle-c[Asp-dGln-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 530); and Ac-Nle-c[Asp-dTrp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 532), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0054] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is p(F)dPhe.

[0055] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R3 is selected from the group consisting of dBip, dPhe, and dTrp.

[0056] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-dPhe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 488); Ac-Nle-c[Asp-dBip-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 490); and Ac-Nle-c[Asp-dTrp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 494), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0057] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R4 is dNal(2').

[0058] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R3 is selected from the group consisting of dPro, dTrp, and Ioc.

[0059] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-dPro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 70); Ac-Nle-c[Asp-dTrp-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 83); and Ac-Nle-c[Asp-Ioc-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 243), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0060] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R5 is selected from the group consisting of dLys, dArg, dOrn, Gly, Asp, dHis, dAsp, dGlu and Pro.

[0061] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-Pro-dNal(2')-dLys-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 88); Ac-Nle-c[Asp-Pro-dNal(2')-dArg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 89); Ac-Nle-c[Asp-Pro-dNal(2')-dOrn-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 91); Ac-Nle-c[Asp-Pro-dNal(2')-Gly-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 94); Ac-Nle-c[Asp-Pro-dNal(2')-Asp-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 95); Ac-Nle-c[Asp-Pro-dNal(2')-dHis-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 97); Ac-Nle-c[Asp-Pro-dNal(2')-dAla-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 98); Ac-Nle-c[Asp-Pro-dNal(2')-dAsp-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 99); Ac-Nle-c[Asp-Pro-dNal(2')-dGlu-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 100); Ac-Nle-c[Asp-His-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 246); and Ac-Nle-c[Asp-Pro-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 249), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0062] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R6 is absent or selected from the group consisting of His, dHis, Ala, and dAla.

[0063] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of: Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Lys]-dVal-dPro-NH2 (SEQ ID NO: 101); Ac-Nle-c[Asp-Pro-dNal(2')-Arg-His-Lys]-dVal-dPro-NH2 (SEQ ID NO: 106); Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Ala-Lys]-dVal-dPro-NH2 (SEQ ID NO: 107); Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dHis-Lys]-dVal-dPro-NH2 (SEQ ID NO: 112); and Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dAla-Lys]-dVal-dPro-NH2 (SEQ ID NO: 113), wherein c represents cyclization through R1 and R7 via a lactam bond.

[0064] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R1 and R8.

[0065] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein R2 is Pro, R3 is Glu, R4 is dNal(2'), and R7 is Gly.

[0066] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the sequence of any one of Formulae (I)-(IE) is: Ac-Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro-NH2 (SEQ ID NO: 258), wherein c represents cyclization through R1 and R8 via a lactam bond.

[0067] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog includes any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

[0068] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

[0069] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342.

[0070] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249.

[0071] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289.

[0072] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 188, 190, and 243.

[0073] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is present in a pharmaceutical composition.

[0074] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the pharmaceutical composition includes one or more pharmaceutically acceptable excipients and/or carriers.

[0075] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the one or more pharmaceutically acceptable excipients and/or carriers of the pharmaceutical composition include water.

[0076] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg to about 20 mg/kg administered once a day for about 5 days to about 10 days; (ii) at a second dose of about 10 mg/kg to about 40 mg/kg administered once a day after administration of the first dose for about 5 days to about 10 days; (iii) at a third dose of about 5 mg/kg to about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days to about 10 days.

[0077] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 15 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 10 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

[0078] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 10 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 20 mg/kg administered once a day after administration of the

first dose for about 7 days; (iii) at a third dose of about 15 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

[0079] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 15 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 25 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 20 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

[0080] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.5 mg/kg to about 10 mg/kg per body weight of the subject once daily.

[0081] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 1 mg/kg or 3 mg/kg per body weight of the subject once daily.

[0082] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

[0083] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

[0084] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

[0085] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog crosses a blood-brain-barrier of a subject.

[0086] In some embodiments, the present technology comprises a method or the use, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[0087] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog includes any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

[0088] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered to a subject for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years.

[0089] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog is administered to a subject for 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days.

[0090] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog, wherein the non-naturally occurring melanocortin analog elicits a reduction, prevention, or amelioration in a melanocortin system disease, disorder, or condition, or a symptom thereof.

[0091] In some embodiments, the melanocortin system disease, disorder, or condition, or the symptom thereof is selected from the group consisting of cachexia, lethargy, appetite, sleep, arousal, libido, locomotion, cardiovascular anomalies, vasodilatation, hypertension,

hypotension, sodium regulation, pain, pain perception, homeostasis, endocrine and exocrine gland secretion, inflammation, addictive behavior, increasing endogenous opioid activity, obesity, anorexia, and sexual dysfunction.

DETAILED DESCRIPTION

[0092] The present technology comprises non-naturally occurring melanocortin analogs useful in treating, preventing, reducing, or otherwise ameliorating one or more symptoms, conditions, diseases, or disorders associated with the melanocortin system. In some embodiments, the non-naturally occurring melanocortin analog is administered orally. In some embodiments, the non-naturally occurring melanocortin analog is a melanocortin receptor agonist and/or an opioid receptor agonist.

[0093] The following description is merely exemplary in nature and is not intended to limit the present technology, its applications, or its uses. It should be understood that throughout the drawings, corresponding reference numerals indicate like or corresponding parts and features. The description of specific examples indicated in various embodiments of the present technology are intended for purposes of illustration only and are not intended to limit the scope of the present technology disclosed herein. Moreover, recitation of multiple embodiments having stated features is not intended to exclude other embodiments having additional features or other embodiments incorporating different combinations of the stated features.

[0094] The following description is merely exemplary in nature and is not intended to limit the present technology, its applications, or its uses. It should be understood that throughout the drawings, corresponding reference numerals indicate like or corresponding parts and features. The description of specific examples indicated in various embodiments of the present technology are intended for purposes of illustration only and are not intended to limit the scope of the present technology disclosed herein. Moreover, recitation of multiple embodiments having stated features is not intended to exclude other embodiments having additional features or other embodiments incorporating different combinations of the stated features.

[0095] While the embodiments are described in sufficient detail to enable those skilled in the art to practice the present technology, it should be understood that other embodiments may be realized, and that logical changes may be made without departing from the spirit and scope of the present technology. Thus, the detailed description herein is presented for purposes of illustration only and not of limitation. For example, steps recited in any method or process, may be executed in any order and are not limited to the order presented. Moreover, any of the steps thereof may be outsourced to or performed by one or more third parties.

Definitions

[0096] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the present technology belongs. For the purposes of the present technology, the following terms are defined below.

[0097] The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element. Likewise, any reference to singular includes plural embodiments, and any reference to more than one component may include a singular embodiment.

[0098] The term "about" means a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by acceptable levels in the art. Typically, such variation may be as much 10% above and below a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length and such variation may be influenced by standard applicable measurement practices. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth.

[0099] The terms "administering" or "administer" include delivery of therapies (e.g., non-naturally occurring melanocortin analogs (also referred to herein as peptides)) of the present technology to a subject either by local or systemic administration. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal

delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer), intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration.

[0100] The terms "active ingredient" and "active compound" refer to a biologically active substance, whether naturally or non-naturally occurring, that is the main component of the pharmaceutical composition which elicits the intended effect of an administered therapeutic. This may be any component that drives the pharmacological activity or direct effect in the diagnosis, cure, mitigation, treatment, or prevention of the conditions associated with the present technology, such as conditions associated with the melanocortin system.

[0101] As used herein, a "composition" or a "pharmaceutical composition" refers to a mixture of the active ingredient with other chemical components, such as pharmaceutically acceptable carriers and/or excipients.

[0102] As used herein, a "pharmaceutically acceptable carrier" of the pharmaceutical composition refers to a carrier or diluent that does not cause significant irritation to an organism, does not abrogate the biological activity and properties of the administered active ingredient, and/or does not interact in a deleterious manner with the other components of the composition in which it is contained. The term "carrier" encompasses any excipient, binder, diluent, filler, salt, buffer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will depend upon the intended route of administration for the composition. The preparation of pharmaceutically acceptable carriers and formulations containing these materials is described in, e.g., Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005, which is incorporated herein by reference in its entirety). Some examples of physiologically acceptable carriers include antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides,

disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN® (ICI, Inc.; Bridgewater, N.J.), polyethylene glycol (PEG), and PLURONICS™ (BASF; Florham Park, N.J.). An "excipient" of the first or the pharmaceutical composition refers to an inert substance added to a composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

[0103] The terms "treat," "treatment," and "treating" refer to a manner of providing a pharmaceutical composition and/or melanocortin analog to alleviate disease outcomes. This includes utilizing administration techniques as described in the context of the present technology. Efficacy of treatment may be determined by various assessment methods as described in the context of the present technology (e.g., assessment of appetite, food consumption, body weight, muscle mass, fat mass, and measurement of biomarkers). The term "biomarker" refers to a biological output that is used as a measure of cellular response, whether that be to assess response to therapeutics, disease status, such as cachexia, or as a predictor of clinical outcomes. Biomarkers evaluated in the context of cells, tissue, or whole organisms. The term "disease" herein refers to any disorder adversely affecting biological status. This includes weight-related disorders, such as cachexia. Disease also may be in the context of human and animal health.

[0104] The terms "treat", "treatment", and "treating" may also refer to the reduction or inhibition of the progression and/or duration of a disease or a condition (e.g., a disease associated with the melanocortin system), the reduction or amelioration of the severity of the disease or the condition, and/or the amelioration of one or more symptoms thereof resulting from the administration of one or more therapies. Specifically, these terms may refer to: (1) a stabilization or reduction (e.g. by more than 10%, 20%, 30%, 40%, 50%, or more than 60% of the baseline of the symptom, condition, disease, or disorder before administration) in a disease or condition, (2) a stabilization or reduction (e.g. by more than 10%, 20%, 30%, 40%, 50%, or more than 60% of the baseline of symptom before administration) in a symptom associated with the disease or the condition, (3) inhibiting or reducing rate of the disease/condition or a symptom thereof increase, (4) relieving to some

extent (or, preferably, eliminating) one or more symptoms associated with a pathology related to or caused in part by the disease or the condition, (5) an increase in disease-free, relapse-free, progression-free, and/or overall survival, duration, or rate, (6) a decrease in hospitalization rate, (7) a decrease in hospitalization length, or (8) an increase in the response rate, the durability of response, or number of patients who respond. The terms "treat", "treatment", and "treating" include prophylactic and/or therapeutic treatments. If it is administered prior to clinical manifestation of a condition, the treatment is considered prophylactic. Therapeutic treatment includes, e.g., ameliorating or reducing the severity of a disease, or shortening the length or frequency of the disease.

[0105] As used herein, the terms "effective amount" or "therapeutically effective amount," refer to that amount of the active ingredient being administered which will relieve to some extent one or more of the symptoms of the disease or disorder being treated. The result may be a reduction and/or alleviation of the signs, symptoms, or causes of a disease or disorder, or any other desired alteration of a biological system. An appropriate "effective amount" may differ from one individual to another. An appropriate "effective amount" in any individual case may be determined using techniques, such as a dose escalation study.

[0106] The term "after administration" refers to any duration of time after the non-naturally occurring melanocortin analog or pharmaceutical composition thereof has been administered to a subject. "After administration" may also refer to the duration of time after one dose has been completed or after more than one dose has been completed, such as two doses, three doses, four doses, and the like. In some embodiments, "after administration" refers to completion of dosing regimen that includes one or more doses. Likewise, the term "prior to" refers to any duration of time before the non-naturally occurring melanocortin analog or pharmaceutical composition thereof has been administered to a subject. Unless otherwise specified, durations of time encompassed by "after administration" or "prior to administration" may include seconds, minutes, hours, days, weeks, months, and years.

[0107] The terms "subject" and "patient" refer to anyone being evaluated for disease, disorder, or condition or being administered a therapeutic or pharmaceutical composition. This includes people without diagnosed or confirmed disease or condition. This also includes

people with diagnosed or confirmed disease or condition, such as an alcohol use disorder or an opioid use disorder.

[0108] The term "control subject," as used herein, refers to any subject used as a basis for comparison to the subject (e.g., test subject). A control subject includes, but is not limited to, any subject who has not been administered the therapeutic or pharmaceutical composition (e.g., the non-naturally occurring melanocortin analog, a therapeutically effective amount of the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof) or administered a placebo.

[0109] "Melanocortin analogs," "non-naturally occurring melanocortin analogs," "melanocortin peptides," "melanocortin receptor peptides," or "melanocortins," are used interchangeably and refer to melanocortin-receptor ligands, which are macromolecules containing at least one melanocortin pharmacophore. Melanocortin analogs are typically peptides that bind melanocortin receptors under physiological conditions. Melanocortin analogs include naturally occurring non-naturally occurring melanocortin analogs (i.e., "synthetic peptides" or "synthetic analogs") and truncated and/or modified versions of melanocortin full-length protein or peptides. For example, the full-length pro-opiomelanocortin protein (POMC), prior to proteolytic cleavage of "sub-peptides," consists of 241 amino acids. Tissue-specific proteolytic cleavage of POMC yields peptides ranging in size from 13 amino acids to 76 amino acids. See Bicknell and Lawry, Encyclopedia of Stress, vol. 3, 257-265, Academic Press (2000). Synthesized, non-naturally occurring melanocortin analogs having increased melanocortin receptor activity as discussed herein are approximately 7-12 amino acids in size. Melanocortin analogs exhibit binding functionality with melanocortin receptors. The binding to the melanocortin receptor is inhibitory (antagonist). In addition to peptides, the non-naturally occurring melanocortin analogs include small molecule analogs of melanocortin or portions thereof comprised of organic compounds, inorganic compounds, or combinations of peptide and small molecule—i.e., peptide mimetics, or various combinations thereof. "Non-naturally occurring melanocortin analogs" may be structurally similar and/or functionally similar to biological melanocortin proteins in their ability to bind melanocortin receptors. Further, the

melanocortin analogs generally contain the pharmacophore: His-Phe-Arg-Trp (SEQ ID NO: 1) or a modified version thereof, or a structural or functional peptide mimetic thereof.

[0110] A "pharmacophore" is the minimum set of amino acid residues necessary to achieve a physiological effect; or a small molecule that is (with respect to a receptor) a structural mimic of the amino acid residues required for binding to and activation of a receptor. His-Phe-Arg-Trp (SEQ ID NO: 1) and their analogs are the pharmacophore of melanocortin for the regulated physiological effect. Therefore, non-naturally occurring melanocortin pharmacophore analogs may be small peptides or organic molecules designed to mimic the appearance or function (including activation or deactivation of receptor activity) of the melanocortin pharmacophore core sequence peptide.

[0111] A melanocortin receptor "agonist" is a naturally occurring substance or manufactured drug substance or composition that may interact with a melanocortin receptor and initiate a pharmacological response characteristic of the melanocortin receptor.

[0112] A melanocortin receptor "antagonist" is a naturally occurring substance or manufactured drug substance or composition that opposes the melanocortin receptor-associated responses normally induced by a melanocortin receptor agonist agent.

[0113] "Potentiated therapeutic activity" refers to an increase in melanocortin activity in a non-naturally occurring melanocortin analog that has undergone derivatization at the N- and/or C-terminus. Such derivatizations do not necessarily involve the pharmacophore, but do imply a relative increase in in vivo biological half-life.

[0114] The terms "bind," "binding," "complex," and "complexing," refer to all types of physical and chemical binding, reactions, complexing, attraction, chelating and the like.

[0115] The "peptides" of the present technology may be (a) naturally-occurring, (b) produced by chemical synthesis, (c) produced by recombinant DNA technology, (d) produced by biochemical or enzymatic fragmentation of larger molecules, (e) produced by methods resulting from a combination of methods (a) through (d) listed above, or (f) produced by any other means for producing peptides.

[0116] The term "peptide" as used herein includes any structure comprised of two or more amino acids, including chemical modifications and derivatives of amino acids. The

amino acids forming all or a part of a peptide may be naturally occurring amino acids, stereoisomers and modifications of such amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically modified amino acids, constructs or structures designed to mimic amino acids, and the like, so that the term "peptide" includes pseudopeptides and peptidomimetics, including structures which have a non-peptidic backbone. The term "peptide" also includes dimers or multimers of peptides. A "manufactured" peptide includes a peptide produced by chemical synthesis, recombinant DNA technology, biochemical, or enzymatic fragmentation of larger molecules, combinations of the foregoing or, in general, made by any other method. The term "peptide" includes peptides containing a variable number of amino acid residues, optionally with non-amino acid residue groups at the N- and C-termini, such groups including acyl, acetyl, alkenyl, alkyl, N-alkyl, amine, or amide groups, among others.

[0117] By employing chemical synthesis, a useful means of production, it is possible to introduce various amino acids which do not naturally occur along the chain, modify the N- or C-terminus, and the like, thereby providing for improved stability and formulation, resistance to protease degradation, and the like.

[0118] "Amino acids" are molecules containing an amine group, a carboxylic acid group, and a side-chain that is specific to each amino acid. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen and have the generic formula H_2N—CHR—COOH, wherein R represents a side chain group. The various α-amino acids differ in the side-chain moiety that is attached to the α-carbon. The "amino acids" of the present technology include the known naturally occurring protein amino acids, which are referred to by both their common three letter abbreviation and single letter abbreviation. See generally *Synthetic Peptides: A User's Guide*, G. A. Grant, editor, W.H. Freeman & Co., New York (1992), the teachings of which are incorporated herein by reference, including the text and table set forth at pages 11 through 24. As set forth above, the term "amino acid" also includes stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, and the like. Modified and unusual amino acids are described generally in *Synthetic Peptides: A*

User's Guide, supra; Hruby et al., *Biochem. J.* 268:249-262 (1990); and Toniolo, *Int. J. Peptide Protein Res.* 35:287-300 (1990); the teachings of all of which are incorporated herein by reference.

[0119] The phrase "amino acid side chain moiety" used herein, including as used in the specification and claims, includes any side chain of any amino acid, as the term "amino acid" is defined herein. This thus includes the side chain moiety present in naturally occurring amino acids. It further includes side chain moieties in modified naturally occurring amino acids, such as glycosylated amino acids. It further includes side chain moieties in stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs, or structures designed to mimic amino acids, and the like. For example, the side chain moiety of any amino acid of the present technology is included within the definition. A "derivative" of an amino acid side chain moiety is included within the definition of an amino acid side chain moiety.

[0120] The "derivative" of an amino acid side chain moiety includes any modification to or variation in any amino acid side chain moieties, including a modification of naturally occurring amino acid side chain moieties. By way of example, derivatives of amino acid side chain moieties include straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated, alkyl, aryl or aralkyl moieties.

[0121] In the peptides of the present technology, conventional amino acid residues have their conventional meaning as given in Chapter 2400, of the *Manual of Patent Examining Procedure,* 8th Ed. Thus, "Ala" is alanine; "Arg" is arginine; "Asn" is asparagine; "Asp" is aspartic acid; "Cys" is cysteine; "Gln" is glutamine; "Glu" is glutamic acid; "His" is histidine; "Ile" is isoleucine; "Leu" is leucine; "Lys" is lysine; "Met" is methionine; "Phe" is phenylalanine; "Pro" is proline; "Ser" is serine; "Thr" is threonine; "Trp" is tryptophan; "Tyr" is tryosine; and "Val" is valine. Unless otherwise indicated, all amino acids abbreviations represent either isomer, i.e., the L-isomer, the D-isomer, or combinations thereof may be used. Thus, for example, "L-Phe" is L-phenylalanine; "D-Phe" is D-phenylalanine; "D-/L-Phe" is D-phenylalanine, L-phenylalanine, or combinations thereof; "Phe" is also D-phenylalanine, L-phenylalanine, or combinations thereof, and so on. Non-standard amino acids are "Nle" is

norleucine; "Nal" is naphthylalanine; "D-Nal" is D-naphthylalanine; D-Nal(2') is D-2′-naphthylalanine; L-Nal(2') is L-2′-naphthylalanine; L-Nal(1') is L-1′-naphthylalanine; D-Nal(1') is D-1′-naphthylalanine; Tle is tert-Leucine; Nva is norvaline; Orn is ornithine; Bip is biphenylalanine; and so on.

[0122] An alpha (α)-amino acid has the generic formula $H_2N—C_\alpha HR—COOH$, where R is a side chain moiety and the amino group is attached to the carbon atom immediately adjacent to the carboxylate group (i.e., the α-carbon). Other types of amino acids exist when the amino group is attached to a different carbon atom. For example, beta (β)-amino acids, the carbon atom to which the amino group is attached is separated from the carboxylate group by one carbon atom, C_β.

[0123] When β-amino acids are incorporated into peptides, two main types of β-peptides exist: those with the side chain residue, R, on the carbon next to the amine are called β^3 peptides and those with the side chain residue on the carbon next to the carbonyl group are called β^2 amino acids.

[0124] Gamma (γ)-amino acids are amino acids with the carbon atom to which the amino group attaches is separated from the carboxylate moiety by two carbon atoms.

[0125] For additional modified and unusual amino acids, see §2422 of the MPEP, particularly Table 4 at 2400-24. Additionally, "Ac" indicates N-acetyl and "cyclo" refers to a cyclic structure, which is also shown as "c." "NH_2" indicates an amine group, typically added on the C-terminus of a polypeptide. Accordingly, as used herein, an $—NH_2$ moiety on the C-terminus of a peptide indicates an amide, i.e., $—CO—NH_2$.

[0126] Additional abbreviations are used as follows: Nle is norleucine; Nal(2') is 2′-naphthylalanine; Nal(1') is 1′-naphthylalanine; Tle is tert-leucine; Nva is norvaline; Orn is ornithine; Bip is biphenylalanine; Hyp is hydroxyproline; Mamb is 3-aminomethyl-benzoic acid; Pen is Penicillamine; Tic is 1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid; Aba is 4-amino-1,2,4,5-tetra-hydro-2-benzazepin-3-one; Oic is octohydroindole-2-carboxylic acid; Atc is 2-aminotetraline-2-carboxylic acid; APC is 1-amino-4-phenylcyclohexane-carboxylic acid; APPC is 4-aminophenylpiperidine-4-carboxylic acid; Acpc is 1-aminocyclo-propane-1-carboxylic acid; Aic is 2-aminoindone-2-carboxylic acid; Ata is 7-amino-7,8-dihydro-4H-

[1,2,3]triazolo-[1,5-a][1,4]diazepin-6(5H)-one; Aia is 4-amino-1,4,5,6-tetrahydroazepino[4,3-*b*]indol-3(*2H*)-one; Che is 1-amino-1-cyclohexanecarboxylic acid Ioc is indoline-2-carboxylic acid, Aic is 2-aminoindone-2-carboxylic acid; Cpe is 1-amino-1-cyclopentane carboxylic; and p(Cl)dPhe is para-chloro-phenylalanine (I – iodo, F – fluoro, Br – bromo, CF_3 – trifluoromethyl).

[0127] The term "acyl" includes a group RCO—, where R is an organic group. An example is the acetyl group CH_3CO—, referred to herein as "Ac."

[0128] A peptide or aliphatic moiety is "acylated" when an alkyl or substituted alkyl group as defined above is bonded through one or more carbonyl {—(C=O)—} groups. A peptide is most usually acylated at the N-terminus.

[0129] An "amine" includes compounds that contain an amine group (—NH_2).

[0130] An "amide" includes compounds that have a trivalent nitrogen attached to a carbonyl group (i.e., —CO—NH_2), such as for example methylamide, ethylamide, propylamide, and the like. A peptide is most usually amidated at the C-terminus by the addition of an amine (—NH_2) moiety to the C-terminal carboxyl group.

[0131] Amino acids, including stereoisomers and modifications of naturally occurring amino acids, protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs, or structures designed to mimic amino acids (peptide mimetics), and the like, including all of the foregoing, are sometimes referred to herein as "residues."

[0132] "Substantial degradation" refers to the degradation of the N-terminal extension, the C-terminal extension, both N- and C-terminal degradation or degradation to other regions of the non-naturally occurring melanocortin analog by physiological enzymes and other factors, in such a manner or to a degree that side effects appear. According to one aspect, a non-naturally occurring melanocortin analog having a C-terminal extension that resists substantial degradation is one where no more than 50% of the administered peptide causes side effects and/or displays a low half-life. In some aspects, no more than 25% of the administered peptide causes side effects and/or displays a low half-life. More preferably, in some aspects, less than 10% of the administered peptide causes side effects and/or

displays a low half-life, as compared to a non-naturally occurring melanocortin analog that lacks a C-terminal extension.

[0133] The disclosure of all publications, patents, and published patent applications listed herein are hereby incorporated by reference in their entireties, including but not limited to U.S. Patent Nos. 8,541,545 and 9,534,018.

Non-naturally Occurring Melanocortin Analogs

[0134] The non-naturally occurring melanocortin analogs of the present technology may comprise a non-naturally occurring melanocortin analog or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. Non-naturally occurring melanocortin analogs of the present technology may be selective for the melanocortin 3 receptor (MC3R) over other melanocortin receptors, i.e., the melanocortin 1 receptor (MC1R), the melanocortin 2 receptor (MC2R), the melanocortin 1 receptor (MC4R), and the melanocortin 5 receptor (MC5R). Some of the non-naturally occurring melanocortin analogs may bind only the MC3R.

[0135] Alternatively, the non-naturally occurring melanocortin analogs of the present technology may be selective for the MC1R and/or MC5R over other melanocortin receptors, i.e., the MC2R, MC3R, and MC4R. Some of the non-naturally occurring melanocortin analogs may bind only the MC1R or the MC5R. Alternatively, some of the non-naturally occurring melanocortin analogs may bind the MC1R with greater affinity than the MC5R, whereas other melanocortin analogs may bind the MC5R with greater affinity than the MC1R. Certain melanocortin analogs may bind the MC1R with the same or generally similar affinity as the MC5R.

[0136] The non-naturally occurring melanocortin analogs of the present technology may be full agonists or full antagonists for one or more melanocortin receptors. A full agonist may comprise a non-naturally occurring melanocortin analog having a maximum effect (E_{max}) agonist value of greater than or equal to 85%. Similarly, a full antagonist may comprise a non-naturally occurring melanocortin analog having an E_{max} antagonist value of greater than or equal to 85%.

[0137] The non-naturally occurring melanocortin analogs of the present technology may be partial agonists or partial antagonists A partial agonist may comprise a non-naturally occurring melanocortin analog having a maximum effect E_{max} agonist value of less than 85%. Similarly, a partial antagonist may comprise a non-naturally occurring melanocortin analog having an E_{max} antagonist value of less than 85%.

[0138] If a non-naturally occurring melanocortin analog's E_{max} agonist value is greater than it's E_{max} antagonist value, then the non-naturally occurring melanocortin analog may be classified as an agonist (e.g., a full agonist or a partial agonist).

[0139] If a non-naturally occurring melanocortin analog's E_{max} antagonist value is greater than it's E_{max} agonist value, then the non-naturally occurring melanocortin analog may be classified as an antagonist (e.g., a full antagonist or a partial antagonist).

[0140] The non-naturally occurring melanocortin analogs of the present technology may be one or more of (i) a full MC3R antagonist having no MC4R activity; (ii) a partial MC3R antagonist having no MC4R activity; (iii) a full MC3R agonist having no MC4R activity, (iv) a partial MC3R agonist having no MC4R activity; (v) a full MC1R agonist and a partial MC5R agonist; (vi) a full MC1R agonist and a full MC5R agonist; (vii) a full MC5R agonist having no MC1R activity; (viii) a partial MC5R agonist having no MC1R activity); (ix) a full MC1R agonist having no MC5R activity; (x) a partial MC1R agonist having no MC5R activity; and (xi) a partial MC1R agonist and a full MC5R agonist.

[0141] The non-naturally occurring melanocortin analogs of the present technology may avoid cardiac activation typically seen in conventional melanocortin peptide and small molecule agonists. For example, a subject may maintain a stable heart rate, systolic blood pressure, and/or diastolic blood pressure following administration of a melanocortin analog of the present technology.

[0142] The non-naturally occurring melanocortin analogs in accordance with the present technology may have certain structural features that impart specific properties on the analogs, such as, for example, degradation resistance, enhanced epithelial, gastrointestinal, and/or blood brain barrier transport, and binding affinity for the melanocortin 4 receptor and/or melanocortin 3 receptor. Accordingly, in some embodiments, the non-

naturally occurring melanocortin analogs have one or more beta hairpin (β-hairpin) and/or beta turn (β-turn) structures. The presence of amino acids that are structurally rigid, such as, for example, Pro and dPro, may lead to formation of β-hairpin and/or β-turn structures in the non-naturally occurring melanocortin analog. Additionally, dMet and disulfide bridges (e.g., cyclization via disulfide bond), as well as Pro-Gly and Gly-Gly moieties may induce and/or stabilize beta-turn structures of the non-naturally occurring melanocortin analogs. In general, cyclization may stabilize beta-turns, and D-amino acids may induce and/or stabilize beta-turns. Further, in some embodiments, melanocortin analogs include D-valine-D-proline (dVal-dPro) chain as their C-terminus, which may provide enhanced transport and resistance to degradation.

[0143] In some embodiments, the non-naturally occurring melanocortin analog has activity on one or more of MC1R, MC3R, and MC5R. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I),

$$X^1\text{-}X^2\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3 \quad (I),$$

wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is absent or is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, Trp, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), indoline-2-carboxylic acid (Ioc), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of Trp, Nle and dVal;

Y^2 is absent or is selected from the group consisting of Nle, dVal, and dPro;

Y^3 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that:

when R^4 is p(I)dPhe, then the non-naturally occurring melanocortin analog is cyclized between R^1 and R^7;

when R^4 is p(F)dPhe and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, dGln, or Trp;

when R^4 is p(Cl)dPhe, and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, dPhe, or Trp;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then (i) R^5 and R^6 are absent or (ii) R^3 is absent and R^2 is not Cys; when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then R^3 is selected from dIle, dVal, and dAla, R^5 is Pro, or R^6 is Nal(1');

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then (i) R^2 is Trp, and (a) R^3 is dVal or dLeu, (b) R^5 is His, or (c) R^6 is dNal(1'), Phe, or dPhe, or (ii) R^2 is Pro and R^3 is Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7 and R^3 is not Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dPro, dTrp, His, and Ioc, , or (ii) R^3 is Pro and either R^5 is selected from dLys, dArg, dOrn, Gly, Asp, dHis, dAla, dAsp, dGlu, and Pro or R^6 is absent selected from His, dHis, Ala, and dAla; and

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then one or both of R^5 and R^6 is absent.

[0144] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I), wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is absent or is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, Trp, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), indoline-2-carboxylic acid (Ioc), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of Trp, Nle and dVal;

Y^2 is absent or is selected from the group consisting of Nle, dVal, and dPro;

Y^3 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac—Nle-c[Asp-Pro-p(I)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 216);

Ac—Nle-c[Asp-His-p(I)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 221);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 223);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 460);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 464);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 465);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 469);

Ac—Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 470);

Ac—Nle-c[Cys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 459);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 461);

Ac—Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 218);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 433);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 434);

Ac—dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 436);

Ac—Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 437);

Ac—Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 438);

Ac—Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 442);

Ac—Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 443);

Ac—Nle-c[Asp-dGln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 492);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 463);

Ac—Nle-c[Cys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 432);

Ac—Nle-c[Asp-Trp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 493);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 499);

Ac—dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 501);

Ac—Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 502);

Ac—Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 503);

Ac—Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 215);

Ac—Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 220);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 498);

Ac—Nle-c[Cys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 497);

Ac—Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 508);

Ac—Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 507);

Ac—Nle-c[Asp-Trp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 531);

Ac—Nle-c[Asp-dPhe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 526);

Ac—Nle-c[Cys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 318);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 319);

Ac—Nle-c[dPen-Pro-dPhe-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 320);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 321);

Ac—Nle-c[Cys-dPhe-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 324);

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 363);

Ac—dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 302);

Ac—Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 311);

Ac—Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 313);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 295);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 351);

Ac—Nle-c[Asp-dBip-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 369);

Ac—Nle-c[Asp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 354);

Ac—Nle-c[Asp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 355);

Ac—Nle-c[Asp-Ioc-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 361);

Ac—Nle-c[Asp-dPhe-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 367);

Ac—Nle-c[Asp-dGln-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 371);

Ac—Nle-c[Asp-Trp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 372);

Ac—Nle-c[Asp-dTrp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 373);

Ac—Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 425);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 429);

Ac—Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 628);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-Trp—NH2 (SEQ ID NO: 600);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 595);

Ac—Nle-c[Asp-Trp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 394);

Ac—Nle-c[Asp-Trp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 395);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Nal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 399);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 226);

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 297);

Ac—Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 413);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 40);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 41);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 42);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 43);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 48);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 49);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 50);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 51);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 52);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 53);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 54);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 55);

Ac—dArg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 329);

Ac—Arg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 330);

Ac—Lys-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 337);

Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59);

Ac—Nle-c[Asp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 68);

Ac—Nle-c[Asp-Ala-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 69);

Ac—Nle-c[Asp-dAla-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 71);

Ac—Nle-c[Asp-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 75);

Ac—Nle-c[Asp-Leu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 76);

Ac—Nle-c[Asp-dLeu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 79);

Ac—Nle-c[Asp-dIle-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 80);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3);

Ac—dArg-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 15);

Ac—dVal-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 19);

Ac—dPro-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 27);

Ac—Nle-c[Asp-Trp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 82);

Ac—Nle-c[Asp-Pro-dNal(2')-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 86);

Ac—Nle-c[Asp-Pro-dNal(2')-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 92);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 104);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dNal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 108);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dPhe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 109);

Ac—Nle-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 184);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal—NH2 (SEQ ID NO: 128);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 255);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 256);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 259);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 179);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal—NH2 (SEQ ID NO: 126);

Ac—Nle-c[Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 73);

Ac—Nle-c[Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 74);

Ac—Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 257);

Ac—Nle-c[Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 194);

Ac—Nle-c[Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 195); and

Ac—Nle-c[Asp-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 5).

[0145] In some embodiments, the non-naturally occurring melanocortin analog does not have activity on MC3R. Accordingly, in some embodiments, the non-naturally occurring melanocortin analog has activity on MC1R and/or MC5R. In some embodiments, R^4 is not p(I)dPhe. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA):

$$X^1\text{-}X^2\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2 \text{ (IA)},$$

wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), and 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that:

when R^4 is p(F)dPhe and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, or dGln;

when R^4 is p(Cl)dPhe, and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, or dPhe;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then (i) R^5 and R^6 are absent or (ii) R^3 is absent and R^2 is not Cys;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dIle, dVal, and dAla, (ii) R^5 is Pro, or (iii) R^6 is Nal(1');

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then (i) R^2 is Trp, and (a) R^3 is dVal or dLeu, (b) R^5 is His, or (c) R^6 is dNal(1'), Phe, or dPhe, or (ii) R^2 is Pro and R^3 is Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7 and R^3 is not Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dPro, dTrp, His, and Ioc, , or (ii) R^3 is Pro and either R^5 is selected from dLys, dArg, dOrn, Gly, Asp, dHis, dAla, dAsp, dGlu, and Pro or R^6 is absent or selected from His, dHis, Ala, and dAla; and

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then one or both of R^5 and R^6 is absent.

[0146] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA), wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), and 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 223);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 460);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 464);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 465);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 469);

Ac—Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 470);

Ac—Nle-c[Cys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 459);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 461);

Ac—Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 218);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 433);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 434);

Ac—dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 436);

Ac—Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 437);

Ac—Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 438);

Ac—Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 442);

Ac—Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 443);

Ac—Nle-c[Asp-dGln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 492);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 463);

Ac—Nle-c[Cys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 432);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 499);

Ac—dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 501);

Ac—Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 502);

Ac—Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 503);

Ac—Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 215);

Ac—Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 220);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 498);

Ac—Nle-c[Cys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 497);

Ac—Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 508);

Ac—Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 507);

Ac—Nle-c[Asp-dPhe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 526);

Ac—Nle-c[Cys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 318);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 319);

Ac—Nle-c[dPen-Pro-dPhe-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 320);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 321);

Ac—Nle-c[Cys-dPhe-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 324);

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 363);

Ac—dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 302);

Ac—Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 311);

Ac—Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 313);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 295);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 351);

Ac—Nle-c[Asp-dBip-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 369);

Ac—Nle-c[Asp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 354);

Ac—Nle-c[Asp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 355);

Ac—Nle-c[Asp-dPhe-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 367);

Ac—Nle-c[Asp-dGln-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 371);

Ac—Nle-c[Asp-dTrp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 373);

Ac—Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 425);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 429);

Ac—Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 628);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-Trp—NH2 (SEQ ID NO: 600);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 595);

Ac—Nle-c[Asp-Trp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 394);

Ac—Nle-c[Asp-Trp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 395);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Nal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 399);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 226);

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 297);

Ac—Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 413);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 40);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 41);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 42);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 43);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 48);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 49);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 50);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 51);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 52);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 53);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 54);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 55);

Ac—dArg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 329);

Ac—Arg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 330);

Ac—Lys-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 337);

Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59);

Ac—Nle-c[Asp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 68);

Ac—Nle-c[Asp-Ala-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 69);

Ac—Nle-c[Asp-dAla-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 71);

Ac—Nle-c[Asp-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 75);

Ac—Nle-c[Asp-Leu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 76);

Ac—Nle-c[Asp-dLeu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 79);

Ac—Nle-c[Asp-dIle-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 80);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3);

Ac—dArg-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 15);

Ac—Nle-c[Asp-Pro-dNal(2')-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 86);

Ac—Nle-c[Asp-Pro-dNal(2')-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 92);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 104);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dNal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 108);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dPhe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 109);

Ac—Nle-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 184);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal—NH2 (SEQ ID NO: 128);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 255);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 256);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 259);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 179);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal—NH2 (SEQ ID NO: 126);

Ac—Nle-c[Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 73);

Ac—Nle-c[Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 74);

Ac—Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 257);

Ac—Nle-c[Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 194);

Ac—Nle-c[Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 195); and

Ac—Nle-c[Asp-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 5).

[0147] In some embodiments, R^4 is dNal(2'). In further embodiments, the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R^2 and R^7. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB):

$$R^1\text{-}R^2\text{-}R^3\text{-dNal(2')-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IB)},$$

wherein:

R^1 is norleucine (Nle);

R^2 is selected from the group consisting of penicillamine (Pen), D-penicillamine (dPen), cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly

R^5 is Arg;

R^6 is Trp;

R^7 is selected from the group consisting of Cys, dCys, Pen, dPen;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R^2 and R^7 when R^2 and R^7 are each independently selected from the group consisting of Cys, dCys, Pen, and dPen;

provided that:

when R^3 is absent, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7.

[0148] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB), wherein:

R^1 is norleucine (Nle);

R^2 is selected from the group consisting of penicillamine (Pen), D-penicillamine (dPen), cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly

R^5 is Arg;

R^6 is Trp;

R^7 is selected from the group consisting of Cys, dCys, Pen, dPen;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R^2 and R^7 when R^2 and R^7 are each independently selected from the group consisting of Cys, dCys, Pen, and dPen;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence of: Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59).

[0149] Alternatively, in some embodiments, when R^4 is dNal(2'), the non-naturally occurring melanocortin analog is cyclized throughout a lactam bond between R^2 and R^7. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IC):

$$R^1\text{-Asp-}R^3\text{-dNal(2')-}R^5\text{-}R^6\text{-Lys-}Y^1\text{-}Y^2 \text{ (IC)},$$

wherein:

R^1 is norleucine (Nle);

R^3 is selected from the group consisting of histidine (His), proline (Pro), D-proline (dPro), D-tryptophan (dTrp), and indoline-2-carboxylic acid (Ioc);

R^5 is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, and dAla;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^7;

provided that:

when R^3 is Pro, then either R^5 is not Arg or R^6 is not Trp.

[0150] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IC), wherein:

R^1 is norleucine (Nle);

R^3 is selected from the group consisting of histidine (His), proline (Pro), D-proline (dPro), D-tryptophan (dTrp), and indoline-2-carboxylic acid (Ioc);

R^5 is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, and dAla;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^7;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:
Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3); and

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116).

[0151] In some embodiments, R^3 is Arg. In further embodiments, R^2 is Trp, His, or Pro, and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7. In still further embodiments, R^4 is dNal(2'), dBip, or p(I)dPhe. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (ID):

$$X^1\text{-}X^2\text{-}R^1\text{-}R^2\text{-Arg-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (ID)},$$

wherein:

X^1 is norleucine (Nle) or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is aspartic acid (Asp) or lysine (Lys);

R^2 is selected from the group consisting of tryptophan (Trp), proline (Pro), and histidine (His);

R^4 is selected from the group consisting of D-biphenylalanine (dBip), 2'-D-naphthylalanine (dNal(2')), and para-iodo-D-phenylalanine (p(I)dPhe);

R^5 is arginine (Arg) or Pro;

R^6 is absent or tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is Asp or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a lactam bridge between R^1 and R^7 when R^1 is Asp and R^7 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp.

[0152] In some embodiments, the non-naturally occurring melanocortin analog has no activity on MC1R or MC5R. Accordingly, in some embodiments, the non-naturally occurring melanocortin analog has activity on MC3R. In further embodiments, R^4 is p(I)dPhe or dNal(2'). In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IE):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-Arg-}R^6\text{-Lys-}Y^1\text{-}Y^2 \text{ (IE)},$$

wherein:

X^1 is absent or norleucine (Nle);

R^1 is Nle or aspartic acid (Asp);

R^2 is selected from the group consisting of Asp, histidine (His), and proline (Pro);

R^3 is arginine (Arg) or indoline-2-carboxylic acid (Ioc);

R^4 is 2'-D-naphthylalanine (dNal(2')) or para-iodo-D-phenylalanine (p(I)dPhe);

R^6 is Trp or tetrahydro-isoquinoline-3-carboxylic acid (Tic);

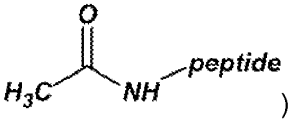
Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between the Asp at R^1 or R^2 and the Lys at R^7.

[0153] In some embodiments, the non-naturally occurring melanocortin analog has one or more beta hairpin (β-hairpin) and/or beta turn (β-turn) structures. In some embodiments, the presence of Pro, dPro, Hyp, dHyp, *trans*Pro(guan), and/or *cis*Pro(guan), provides the β-hairpin and/or β-turn structures of the non-naturally occurring melanocortin analog. In some embodiments, the disulfide bond of the sequence according to Formula (I), if present, provides the β-hairpin and/or β-turn structures of the non-naturally occurring melanocortin analog.

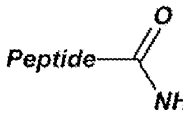
[0154] As will be appreciated by the skilled artisan, non-naturally occurring melanocortin analogs comprising a sequence of any one of Formulae (I)-(IE), have an N-terminus and a C-terminus. The melanocortin analogs of the present technology are written beginning with the N-terminus at the left-most amino acid residue and ending with the C-terminus at the right most residue. Accordingly, the N-terminus of a non-naturally melanocortin analog comprising a sequence of any one of Formulae (I)-(IE) may be at any of X^1, X^2, and R^1. Analogously, the C-terminus of a non-naturally occurring melanocortin analog comprising a sequence of any one of Formulae (I)-(IE) may be at any of R^7, R^8, Y^1, Y^2, and Y^3.

[0155] In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog is modified by an acyl group. In some embodiments, the acyl group is acetyl group (e.g., 

).

[0156] In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog is not modified.

[0157] As discussed above, $Y^1Y^2Y^3$ represents a C-terminus of the non-naturally occurring melanocortin analog. In some embodiments, Y^1 is present and Y^2 and Y^3 are absent. In some embodiments, Y^1 and Y^2 are present and Y^3 is absent. In some embodiments, Y^1-Y^3 are present.

[0158] In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is modified by an amide group (e.g., ). In the sequence of any one of Formulae (I)-(IE), a non-naturally occurring melanocortin analog with a C-terminus modified by an amide may be represented by a terminal -NH_2.

[0159] In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is not modified. In the sequence of any one of Formulae (I)-(IE), a non-naturally occurring melanocortin analog with an unmodified C-terminus may be represented by -OH.

[0160] Non-naturally occurring melanocortin analogs comprising a sequence of any one of Formulae (I)-(IE) are cyclized. For example, the non-naturally occurring melanocortin analog may be cyclized through a moiety selected from the group consisting of: a disulfide bond between a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen; a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp.

[0161] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence cyclized through a disulfide bond. In some embodiments, the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond between R^1 or R^2 and R^7. In further embodiments, R^4 is dNal(2'). In still further embodiments, R^3 is absent. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 44);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 45);

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 46);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 47);

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 60);

Ac-Nle-c[dPen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[dPen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 62); and

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 63),

wherein c represents cyclization through R^2 and R^7 via a disulfide bond.

[0162] Alternatively, in some embodiments, when the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond between R^1 or R^2 and R^7 and R^4 is dNal(2'), then R^3 is present. In further embodiments, R^3 is Ala, Leu, dLeu, dVal, or Gly. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[dPen-Ala-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 338);

Ac-Nle-c[dPen-Leu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 339);

Ac-Nle-c[dPen-dLeu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 340);

Ac-Nle-c[dPen-dVal-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 341);

Ac-Nle-c[dPen-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 342); and

Ac-Nle-c[dPen-Gly-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 343),

wherein c represents cyclization through R^1 or R^2 and R^7 via a disulfide bond.

[0163] In some embodiments, the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond between R^2 and R^7 and R^4 is dPhe. In further embodiments, at least one of R^1, R^3, R^5, and R^6 is absent. In some embodiments, R^1 and R^3 are absent. In other embodiments, R^5 and R^6 are absent. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-c[Cys-Arg-dPhe-Cys]-Trp-dVal-dPro-NH_2 (SEQ ID NO: 202);

Ac-Nle-c[Pen-dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 325); and

Ac-Nle-c[dPen-dPhe-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 326),

wherein c represents cyclization through R^2 and R^7 via a disulfide bond.

[0164] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence cyclized through a lactam bond. In some embodiments, the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^1 and R^7. In some embodiments, R^4 is not dNal(2'). In further embodiments, R^4 is dBip or p(I)dPhe. In still further embodiments, one of R^2 and R^3 is Arg and R^6 is Tic. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:
Ac-Nle-c[Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 188);
Ac-Nle-c[Asp-His-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 189);
Ac-Nle-c[Asp-Pro-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 190);
Ac-Nle-c[Asp-Pro-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 191);
Ac-Nle-c[Asp-Arg-Pro-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 192); and
Ac-Nle-c[Asp-Arg-Pro-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 193),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0165] In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:
Ac-Nle-c[Asp-His-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 189);
Ac-Nle-c[Asp-Pro-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 191);
Ac-Nle-c[Asp-Arg-Pro-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 192); and
Ac-Nle-c[Asp-Arg-Pro-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 193),
wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0166] In some embodiments, the sequence of any one of Formulae (I)-(IE) is:
Ac-Nle-c[Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 188); or
Ac-Nle-c[Asp-Pro-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 190),
wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0167] Alternatively, in some embodiments, when the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^1 and R^7 and R^4 is not dNal(2'), then R^4 is dPhe. In further embodiments, R^2 is Trp and/or R^3 is Pro, R^5 is Arg, and R^6 is Trp.

In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 225);

Ac-Nle-c[Asp-Trp-dLeu-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 396);

Ac-Nle-c[Asp-Trp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 397);

Ac-Nle-c[Asp-Trp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 398);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 400);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 401); and

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dPhe-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 402),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0168] In some embodiments, the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^1 and R^7 and R^4 is dNal(2'). In some embodiments, R^2 is Pro and R^3 is Trp or Trp-Arg. In other embodiments, R^2 is Trp and R^3 is Arg. In further embodiments, R^5 is Pro or absent and R^6 is absent. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 276);

Ac-Nle-c[Asp-Pro-Trp-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 277);

Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 278);

Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 279);

Ac-Nle-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-dVal-dPro-NH_2 (SEQ ID NO: 280);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-NH_2 (SEQ ID NO: 284);

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-Nle-NH_2 (SEQ ID NO: 285);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-Nle-NH_2 (SEQ ID NO: 286);

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-Nle-Nle-NH_2 (SEQ ID NO: 287);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 288); and

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-dVal-dPro-NH_2 (SEQ ID NO: 289),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0169] In some embodiments, the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^2 and R^7. In some embodiments, R^4 is not dNal(2'). In some embodiments, R^4 is Bip. In some embodiments, the sequence of any one of Formulae (I)-(IE) is: Ac-Nle-c[Asp-Pro-Bip-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 114), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0170] In other embodiments, when the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^2 and R^7 and R^4 is not dNal(2'), then R^4 is dPhe. In some embodiments, R^3 is not Pro, R^5 is not Arg, and/or R^6 is not Trp. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dIle-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 356);

Ac-Nle-c[Asp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 357);

Ac-Arg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 376);

Ac-dArg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 377);

Ac-Nle-c[Asp-His-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 227);

Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 230); and

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 428),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0171] In other embodiments, when the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^2 and R^7 and R^4 is not dNal(2'), then R^4 is p(Cl)dPhe. In some embodiments, R^3 is not Pro. In further embodiments, R^3 is dBip, dGln, or dTrp. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dBip-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 528);

Ac-Nle-c[Asp-dGln-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 530); and

Ac-Nle-c[Asp-dTrp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 532),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0172] In still other embodiments, when the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^2 and R^7 and R^4 is not dNal(2'), then R^4 is p(F)dPhe. In some embodiments, R^3 is not Pro. In further embodiments, R^3 is dBip, dPhe, or dTrp. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dPhe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 488);

Ac-Nle-c[Asp-dBip-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 490); and

Ac-Nle-c[Asp-dTrp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 494),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0173] In some embodiments the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^2 and R^7 and R^4 is dNal(2'). In some embodiments, R^3 is Pro. Alternatively, in some embodiments, R^3 is not Pro. In further embodiments, R^3 is dPro, dTrp, or Ioc. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dPro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 70);

Ac-Nle-c[Asp-dTrp-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 83); and

Ac-Nle-c[Asp-Ioc-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 243),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0174] In some embodiments, the sequence of any one of Formulae (I)-(IE) is:

Ac-Nle-c[Asp-dPro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 70); or

Ac-Nle-c[Asp-dTrp-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 83),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0175] In some embodiments, the sequence of any one of Formulae (I)-(IE) is: Ac-Nle-c[Asp-Ioc-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 243), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0176] In some embodiments, R^5 is Arg. Alternatively, in some embodiments, R^5 is not Arg. In further embodiments, R^5 is dLys, dArg, dOrn, Gly, Asp, dHis, dAsp, dGlu or Pro. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-dNal(2')-dLys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 88);

Ac-Nle-c[Asp-Pro-dNal(2')-dArg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 89);

Ac-Nle-c[Asp-Pro-dNal(2')-dOrn-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 91);

Ac-Nle-c[Asp-Pro-dNal(2')-Gly-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dNal(2')-Asp-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 95);

Ac-Nle-c[Asp-Pro-dNal(2')-dHis-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c[Asp-Pro-dNal(2')-dAla-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 98);

Ac-Nle-c[Asp-Pro-dNal(2')-dAsp-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c[Asp-Pro-dNal(2')-dGlu-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-His-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 246); and

Ac-Nle-c[Asp-Pro-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 249),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0177] In some embodiments, R^6 is Trp. Alternatively, in some embodiments, R^6 is not Trp. In further embodiments, R^6 is absent, His, dHis, Ala, or dAla. In some embodiments, the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Lys]-dVal-dPro-NH2 (SEQ ID NO: 101);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-His-Lys]-dVal-dPro-NH2 (SEQ ID NO: 106);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Ala-Lys]-dVal-dPro-NH2 (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dHis-Lys]-dVal-dPro-NH2 (SEQ ID NO: 112); and

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dAla-Lys]-dVal-dPro-NH2 (SEQ ID NO: 113),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0178] In some embodiments, the sequence of any one of Formulae (I)-(IE) is cyclized through R^1 and R^8 via a lactam bond. In further embodiments, R^2 is Pro, R^3 is Glu, R^4 is dNal(2'), and R^7 is Gly. In some embodiments, the sequence of any one of Formulae (I)-(ID) is: Ac-Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 258), wherein c represents cyclization through R^1 and R^8 via a lactam bond.

[0179] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

[0180] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

[0181] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342.

[0182] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IC). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249.

[0183] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (ID). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289.

[0184] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IE). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 188, 190, and 243.

[0185] Melanocortin analogs comprising a sequence of any one of Formulae (I)-(ID), may be an agonist and/or antagonist on one or more of MC1R, MC3R and MC5R. In some embodiments, the melanocortin analog is an antagonist on MC3R. In some embodiments, when the non-naturally occurring melanocortin analog is an antagonist on the MC3R, the melanocortin analog comprises a sequence of Formula (IE). In further embodiments, the non-naturally occurring melanocortin analog comprises any one of SEQ ID NOs: 188, 190, and 243.

[0186] In some embodiments, the melanocortin analog is an agonist on the MC1R and/or MC5R. In some embodiments, the melanocortin analog is an agonist on the MC1R In some embodiments, the melanocortin analog is an agonist on the MC5R. In some embodiments, the melanocortin analog is an agonist on the MC1R and MC5R. In some embodiments, when the non-naturally occurring melanocortin analog is an agonist on the MC1R and/or MC5R, then the melanocortin analog comprises a sequence of Formula (IA). In further embodiments, the non-naturally occurring melanocortin analog comprises any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

Non-Naturally Occurring Melanocortin Analog Synthesis

[0187] The non-naturally occurring melanocortin analogs of the present technology may be readily synthesized by any known conventional procedure for the formation of a peptide linkage between amino acids. Such conventional procedures include, for example, any solution phase procedure permitting a condensation between the free alpha amino group of an amino acid or residue thereof having the carboxyl group or other reactive groups protected and the free primary carboxyl group of another amino acid or residue thereof having the amino group or other reactive groups protected. In an exemplary procedure, the peptides of the present technology may be synthesized by solid-phase synthesis and

purified according to methods known in the art. Any of a number of well-known procedures utilizing a variety of resins and reagents may be used to prepare the peptides of the present technology.

[0188] The process for synthesizing the peptides may be carried out by a procedure whereby each amino acid in the desired sequence is added one at a time in succession to another amino acid or residue thereof or by a procedure whereby peptide fragments with the desired amino acid sequence are first synthesized conventionally and then condensed to provide the desired peptide. The resulting peptide is then cyclized to yield a cyclic peptide.

[0189] Solid phase peptide synthesis methods are well known and practiced in the art. In such methods, the synthesis of peptides may be carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods. These methods are disclosed in numerous references, including Merrifield, Angew Chem. 24:799-810 (1985) and Barany et al., The Peptides, Analysis, Synthesis and Biology, Vol. 2, Gross E. and Meienhofer J., Eds. Academic Press 1-284 (1980).

[0190] In chemical syntheses of peptides, reactive side chain groups of the various amino acid residues are protected with suitable protecting groups, which prevent a chemical reaction from occurring at that site until the protecting group is removed. Also common is the protection of the alpha amino group of an amino acid residue or fragment while that entity reacts at the carboxyl group, followed by the selective removal of the alpha amino protecting group to allow a subsequent reaction to take place at that site. Specific protecting for solid phase synthesis methods and solution phase synthesis methods groups are known to those having ordinary skill in the art.

[0191] Alpha amino groups may be protected by a suitable protecting group, including a urethane-type protecting group, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl. Fmoc is useful for alpha amino protection.

[0192] Guanidino groups may be protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tosyl), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pmc is a useful protecting group for Arg.

[0193] Solid phase synthesis is commenced from the C-terminal end of the peptide by coupling a protected alpha amino acid to a suitable resin. Such starting material is prepared by attaching an alpha amino-protected amino acid by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin or a 2-chlorotrityl chloride resin, by an amide bond between an Fmoc-Linker, such as p-[(R,S)-α-[1-(9H-fluor-en-9-yl)-methoxyformamido]-2,4-dimethyloxybenzyl]-phenoxyacetic acid (Rink linker) to a benzhydrylamine (BHA) resin, or by other means well known in the art. Fmoc-Linker-BHA resin supports are commercially available and generally used when feasible. The resins are carried through repetitive cycles as necessary to add amino acids sequentially. The alpha amino Fmoc protecting groups are removed under basic conditions. Piperidine, piperazine, diethylamine, or morpholine (20-40% v/v) in N,N-dimethylformamide (DMF) may be used for this purpose.

[0194] Following removal of the alpha amino protecting group, the subsequent protected amino acids are coupled stepwise in the desired order to obtain an intermediate, protected peptide-resin. The activating reagents used for coupling of the amino acids in the solid phase synthesis of the peptides are well known in the art. After the peptide is synthesized, if desired, the orthogonally protected side chain protecting groups may be removed using methods well known in the art for further derivatization of the peptide.

[0195] Reactive groups in a peptide may be selectively modified, either during solid phase synthesis or after removal from the resin. For example, peptides may be modified to obtain N-terminus modifications, such as acetylation, while on resin, or may be removed from the resin by use of a cleaving reagent and then modified. Methods for N-terminus modification, such as acetylation, and for C-terminus modification, such as amidation, are known in the art. Similarly, methods for modifying side chains of amino acids are well known to those skilled in the art of peptide synthesis. The choice of modifications made to reactive groups present on the peptide will be determined, in part, by the characteristics that are desired in the peptide.

[0196] The peptide may be cyclized prior to cleavage from the peptide resin. For cyclization through reactive side chain moieties, the desired side chains are deprotected, and the peptide suspended in a suitable solvent and a cyclic coupling agent added. Suitable solvents include, for example DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP). Suitable cyclic coupling reagents include, for example, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1 (2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or N,N′-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt). Coupling is convention initiated by use of a suitable base, such as N,N-diispropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM).

[0197] Following cleavage of peptides from the solid phase following their synthesis, the peptide may be purified by any number of methods, such as reverse phase high performance liquid chromatography (RP-HPLC), using a suitable column, such as a C18 column. Other methods of separation or purification, such as methods based on the size or charge of the peptide, may also be employed. Once purified, the peptide may be characterized by any number of methods, such as high-performance liquid chromatograph (HPLC), amino acid analysis, mass spectrometry, and the like.

Salt Forms of Non-Naturally Occurring Melanocortin Analogs

[0198] The non-naturally occurring melanocortin analog peptides of the present technology may be in the form of any salt. The term “pharmaceutically acceptable salts” refers to salts prepared from non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Exemplary salts are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines

including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N′-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

[0199] When the peptides of the present technology are basic, acid addition salts may be prepared from non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, carboxylic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Acid addition salts of the peptides of the present technology are prepared in a suitable solvent from the peptide and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, citric, tartaric, maleic, succinic or methanesulfonic acid. The acetate salt form is especially useful. Where the peptides of the present technology include an acidic moiety, suitable salts may include alkali metal salts, such as sodium or potassium salts, or alkaline earth metal salts, such as calcium or magnesium salts.

Pharmaceutical Compositions, Formulations, and Administration

[0200] The non-naturally occurring melanocortin analogs of the present technology may be present in a pharmaceutical composition.

[0201] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally

occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 10 mg/mL, relative to a total volume of the pharmaceutical composition.

[0202] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, about 0.5 mg/mL to about 40 mg/mL, about 1 mg/mL to about 30 mg/mL, about 2.5 mg/mL to about 20 mg/mL, about 5 mg/mL to about 15 mg/mL, or about 5 mg/mL to about 10 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 10 mg/mL, relative to a total volume of the pharmaceutical composition.

[0203] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least 0.1 mg/mL to at least 50 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least 0.1 mg/mL to at least 50 mg/mL, at least 0.5 mg/mL to at least 40 mg/mL, at least 1 mg/mL to at least 30 mg/mL, at least 2.5 mg/mL to at least 20 mg/mL, at least 5 mg/mL to at least 15 mg/mL, or at least 5 mg/mL to at least 10 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least 10 mg/mL, relative to a total volume of the pharmaceutical composition.

[0204] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least about 0.1 mg/mL to at least about 50 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least about 0.1 mg/mL to at least about 50 mg/mL, at least about 0.5 mg/mL to at least about 40 mg/mL, at least about 1 mg/mL to

at least about 30 mg/mL, at least about 2.5 mg/mL to at least about 20 mg/mL, at least about 5 mg/mL to at least about 15 mg/mL, or at least about 5 mg/mL to at least about 10 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of at least about 10 mg/mL, relative to a total volume of the pharmaceutical composition.

Formulations

[0205] The pharmaceutical composition comprising the non-naturally occurring melanocortin analog may be formulated for intraperitoneal, intravenous, parenteral, depot, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration. In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is formulated for subcutaneous administration. In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is formulated for oral administration. In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is formulated for depot administration.

[0206] In some embodiments, the pharmaceutical composition further comprises a pharmaceutical salt. Any pharmaceutical salt known in the art may be included in the pharmaceutical composition.

[0207] Pharmaceutical compositions comprising the non-naturally occurring melanocortin analog may be administered using any means known in the art, including orally, rectally, vaginally, ocularly, intranasally, topically, parenterally, or by injection. If administered by injection, the injection may be intravenous (IV), subcutaneous (SC), intramuscular (IM), intraperitoneal (IP), intracerebroventricular (ICV), or other means known in the art. Compositions administered by injection may be formulated for depot injection. Pharmaceutical compositions may be formulated by any means known in the art, including but not limited to formulation as tablets, capsules, caplets, suspensions, powders, lyophilized preparations, suppositories, pessaries, ocular drops, skin patches, orally soluble formulations, enteric formulations, solutions sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants,

antioxidants and other agents known in the art. In general, any route of administration by which the compositions are introduced across an epidermal layer of cells may be employed. Administration includes topical delivery. Administration includes delivery across the epithelium. Administration includes delivery through the gastrointestinal tract. Administration includes delivery across the blood brain barrier. Administration includes delivery through mucous membranes, buccal administration, ophthalmic administration, oral administration, dermal administration, inhalation administration, nasal administration, urethral administration, vaginal administration, rectal administration, and the like.

[0208] In order to facilitate delivery of the active ingredients, to enhance dispersion, solubility, and stability of the active ingredients, and/or to reduce adverse injection site reactions, the pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers and/or excipients.

[0209] The pharmaceutical composition may comprise one or more pharmaceutically acceptable carriers and/or excipients such as, for example, buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants, and antioxidants. For example, when the pharmaceutical composition is formulated for subcutaneous administration, the one or more pharmaceutically acceptable carriers and/or excipients may comprise water.

[0210] In some embodiments, the pharmaceutical composition contains 0.1 to 99.9999 wt.%, 1 to 99.999 wt.%, 5 to 99.99 wt.%, 10 to 99.9 wt.%, 15 to 99 wt.%, 20 to 90 wt.%, 30 to 85 wt.%, 40 to 80 wt.%, 50 to 75 wt.%, or 60 to 70 wt.% of the one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the pharmaceutical composition.

[0211] In some embodiments, the pharmaceutical composition contains 0.1 to 99.9999 wt.%, 1 to 99.999 wt.%, 5 to 99.99 wt.%, 10 to 99.9 wt.%, 15 to 99 wt.%, 20 to 90 wt.%, 30 to 85 wt.%, 40 to 80 wt.%, 50 to 75 wt.%, or 60 to 70 wt.% of the one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the pharmaceutical composition.

[0212] In some embodiments, the pharmaceutical composition contains at least 0.1 to at least 99.9999 wt.%, at least 1 to at least 99.999 wt.%, at least 5 to at least 99.99 wt.%, at

least 10 to at least 99.9 wt.%, at least 15 to at least 99 wt.%, at least 20 to at least 90 wt.%, at least 30 to at least 85 wt.%, at least 40 to at least 80 wt.%, at least 50 to at least 75 wt.%, or at least 60 to at least 70 wt.% of the one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the pharmaceutical composition.

[0213] In some embodiments, the pharmaceutical composition contains at least about 0.1 to at least about 99.9999 wt.%, at least about 1 to at least about 99.999 wt.%, at least about 5 to at least about 99.99 wt.%, at least about 10 to at least about 99.9 wt.%, at least about 15 to at least about 99 wt.%, at least about 20 to at least about 90 wt.%, at least about 30 to at least about 85 wt.%, at least about 40 to at least about 80 wt.%, at least about 50 to at least about 75 wt.%, or at least about 60 to at least about 70 wt.% of the one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the pharmaceutical composition.

[0214] Any pharmaceutically acceptable carriers and/or excipients known in the art may be included in the pharmaceutical composition. Non-limiting examples of pharmaceutically acceptable carriers and/or excipients include buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants, preservatives, lipids, and antioxidants. The pharmaceutical composition may comprise any combination of the one or more pharmaceutically acceptable carriers and/or excipients previously described in relation to the first and pharmaceutical compositions. In some embodiments, the one or more pharmaceutically acceptable carriers and/or excipients comprise water.

[0215] To facilitate delivery of the non-naturally occurring melanocortin analog, the pharmaceutical composition may comprise one or more pharmaceutically acceptable carriers and/or excipients. Other pharmaceutically acceptable carriers and/or excipients may be included in the pharmaceutical composition to enhance dispersion, solubility, and stability of the non-naturally occurring melanocortin analog, and to reduce adverse injection site reactions.

[0216] In some embodiments, the one or more pharmaceutically acceptable carriers and/or excipients are isotonic.

[0217] In some embodiments, the salt is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, about 1 mg/mL to about 25 mg/mL, or about 5 mg/mL to about 10 mg/mL, relative to a total volume of the composition.

[0218] In some embodiments, the salt is present in the pharmaceutical composition in a concentration of at least 0.1 mg/mL to at least 50 mg/mL, at least 1 mg/mL to at least 25 mg/mL, or at least 5 mg/mL to at least 10 mg/mL, relative to a total volume of the composition

[0219] In order to achieve a desirable tonicity, the pharmaceutical composition may further include a salt such as sodium chloride, sodium succinate, sodium sulfate, potassium chloride, magnesium chloride, magnesium sulfate, and calcium chloride.

[0220] In some embodiments, the salt is present in the pharmaceutical composition in a concentration of at least about 0.1 mg/mL to at least about 50 mg/mL, at least about 1 mg/mL to at least about 25 mg/mL, or at least about 5 mg/mL to at least about 10 mg/mL, relative to a total volume of the composition.

[0221] Pharmaceutically acceptable carriers and/or excipients that may be included in the pharmaceutical composition generally include a pH buffered aqueous solution comprising one or more of the following components: (a) sodium acetate, (b) Tris, and (c) water. In some embodiments, all components are compatible with the non-naturally occurring melanocortin analog (i.e., do not react or cause the non-naturally occurring melanocortin analog to react) and are homogeneously dispersed or dissolved uniformly in the composition.

[0222] In the pH buffered solution of the pharmaceutical composition, the water may act as a diluent and include, without limitation, water for injection (WFI), sterile water, bacteriostatic water for injection (BWFI), distilled water, bidistilled water, deionized water, deionized distilled water, and reverse osmosis water. In some embodiments, the water present in the pH buffered aqueous solution is water for injection.

[0223] In some embodiments, the pharmaceutical composition includes water in an amount of about 1 wt% to about 90 wt%, about 10 wt% to about 75 wt%, or about 25 wt% to about 50 wt%, relative to a total weight of the composition.

[0224] In some embodiments, the pharmaceutical composition includes water in an amount of at least 1 wt% to at least 90 wt%, at least 10 wt% to at least 75 wt%, or at least 25 wt% to at least 50 wt%, relative to a total weight of the composition.

[0225] In some embodiments, the pharmaceutical composition includes water in an amount of at least about 1 wt% to at least about 90 wt%, at least about 10 wt% to at least about 75 wt%, or at least about 25 wt% to at least about 50 wt%, relative to a total weight of the composition. In some embodiments, sodium acetate is present in the pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, sodium acetate may be present in the pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, 1 mg/mL to 40 mg/mL, 2 mg/mL to 30 mg/mL, 4 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, 6 mg/mL to 12 mg/mL, or 8 mg/mL to 10 mg/mL, relative to a total volume of the composition.

[0226] In some embodiments, sodium acetate is present in the pharmaceutical composition in a concentration of about 6 mg/mL to about 8 mg/mL, relative to a total volume of the composition. For example, sodium acetate may be present in the pharmaceutical composition in a concentration of 6 mg/mL, 6.5 mg/mL, 7 mg/mL, 7.1 mg/mL, 7.5 mg/mL, or 8 mg/mL, relative to a total volume of the composition.

[0227] In some embodiments, sodium acetate is present in the pharmaceutical composition in a molar concentration of 5 mM to 700 mM, relative to a total volume of the composition. For example, sodium acetate may be present in the pharmaceutical composition in a molar concentration of 5 mM to 700 mM, 10 mM to 600 mM, 20 mM to 500 mM, 30 mM to 400 mM, 40 mM to 300 mM, 50 mM to 200 mM, 60 mM to 100 mM, or 70 mM to 80 mM, relative to a total volume of the composition.

[0228] In some embodiments, sodium acetate is present in the pharmaceutical composition in a molar concentration of about 80 mM to about 100 mM, relative to a total volume of the composition. For example, sodium acetate may be present in the pharmaceutical composition in a molar concentration of 80 mM, 85 mM, 87 mM, 90 mM, 95 mM, or 100 mM, relative to a total volume of the composition.

[0229] The term "Tris" refers to tris(hydroxymethyl)aminomethane, which is also known as Tris buffer, Tris base, TRIS, tromethamine, tromethamine buffer, Trizma®, Trisamine, Trometamol, Tromethane, Trisaminol, or THAM. In some embodiments, Tris is present in the pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, 1 mg/mL to 40 mg/mL, 2 mg/mL to 30 mg/mL, 4 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, 6 mg/mL to 12 mg/mL, or 8 mg/mL to 10 mg/mL, relative to a total volume of the composition.

[0230] In some embodiments, Tris is present in the pharmaceutical composition in a concentration of about 6 mg/mL to about 8 mg/mL, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical composition in a concentration of 6 mg/mL, 6.5 mg/mL, 7 mg/mL, 7.3 mg/mL, 7.6 mg/mL, or 8 mg/mL, relative to a total volume of the composition.

[0231] In some embodiments, Tris is present in the pharmaceutical composition in a molar concentration of 2 mM to 500 mM, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical composition in a molar concentration of 2 mM to 500 mM, 5 mM to 400 mM, 10 mM to 300 mM, 20 mM to 200 mM, 30 mM to 150 mM, 40 mM to 100 mM, 50 mM to 80 mM, or 60 mM to 70 mM, relative to a total volume of the composition.

[0232] In some embodiments, Tris is present in the pharmaceutical composition in a molar concentration of about 50 mM to about 70 mM, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical composition in a molar concentration of 50 mM, 55 mM, 60 mM, 65 mM, or 70 mM, relative to a total volume of the composition.

[0233] In some embodiments, the pH buffered aqueous solution provides the pharmaceutical composition with a pH equivalent or close to the physiological pH levels. This may reduce adverse injection site reactions and also provide the non-naturally occurring melanocortin analog with enhanced stability and resistance to aggregation and degradation.

[0234] In some embodiments, a weight ratio of sodium acetate to Tris is about 1:4 to about 4:1, about 2:7 to about 7:2, about 1:3 to about 3:1, about 2:5 to about 5:2, about 1:2 to about 2:1, about 2:3 to about 3:2, or about 1:1. In some embodiments, the weight ratio of sodium acetate to Tris is about 1:1.

[0235] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is about 1:1 to about 20:1, about 3:2 to about 15:1, about 2:1 to about 12:1, about 3:1 to about 10:1, about 4:1 to about 9:1, about 5:1 to about 8:1, or about 6:1 to about 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is about 7:1.

[0236] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to Tris is about 1:1 to about 20:1, about 3:2 to about 15:1, about 2:1 to about 12:1, about 3:1 to about 10:1, about 4:1 to about 9:1, about 5:1 to about 8:1, or about 6:1 to about 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to Tris is about 7:1.

[0237] In addition to sodium acetate and Tris, the pharmaceutical composition may include other buffering agents. Non-limiting examples of additional buffering agents include saline, phosphate, phosphoric acid, citrate, succinate, gluconate, histidine, acetic acid, ascorbate, tartartic acid, maleic acid, glycine, lactate, lactic acid, ascorbic acid, imidazole, bicarbonate, carbonic acid, succinic acid, sodium benzoate, benzoic acid, gluconate, edetate, malate, imidazole, and mixtures thereof. In some embodiments, the pharmaceutical composition comprises acetic acid as an additional buffering agent.

[0238] The pharmaceutical composition may further comprise one or more chelating agents. Suitable chelating agents include, but are not limited to edetate disodium dihydrate, calcium disodium edetate, sodium edetate, calcium versetamide sodium, calteridol, and diethylenetriaminepentaacetic acid. In some embodiments, the pharmaceutical composition further comprises edetate disodium dihydrate.

[0239] The pharmaceutical composition may further comprise a preservative agent. Exemplary preservative agents include, but are not limited to, ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, ascorbyl palmitate,

butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, phenol, m-cresol, benzyl alcohol, alpha-tocopherol, citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, benzalkonium chloride, phenoxyethanol, and methyl paraben. In some embodiments, when the pharmaceutical composition comprises a preservative agent, the preservative agent is phenol, benzyl alcohol, or a combination thereof.

[0240] If present in the pharmaceutical composition, the concentration of the preservative agent may range from 0.001 mg/mL to 50 mg/mL, 0.01 mg/mL to 25 mg/mL, 0.1 mg/mL to 10 mg/mL, or 1 mg/mL to 5 mg/mL, relative to a total volume of the composition.

[0241] The pharmaceutical composition may further comprise an emulsifier. Non-limiting examples of emulsifiers that may be included in the pharmaceutical composition include sodium carboxymethylcellulose, cetyl alcohol, glycerol monostearate, methylcellulose, and stearic acid. In some embodiments, when the pharmaceutical composition comprises an emulsifier, the emulsifier is sodium carboxymethylcellulose.

[0242] The pharmaceutical composition may further comprise a lipid. Lipids may enhance solubility and/or improve permeability of the non-naturally occurring melanocortin analog. In some embodiments, the lipid is a phospholipid. Non-limiting examples of phospholipids that may be included in the pharmaceutical composition include egg phosphatidylcholine, hydrogenated soybean phoshphaditylcholine, glycerophosphocholine, lecithin, and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt. In some embodiments, when the pharmaceutical composition comprises a lipid, the lipid is N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt.

[0243] The pharmaceutical composition may further comprise a bulking agent. Inclusion of a bulking agent may increase the stability of the pharmaceutical composition. Non-limiting examples of bulking agents that may be included in the pharmaceutical composition include sucrose, lactose, trehalose, mannitol, sorbitol, glucose, raffinose, glycine, histidine, and polyvinyl pyrrolidone. In some embodiments, when the pharmaceutical composition comprises a bulking agent, the bulking agent is mannitol.

[0244] In some embodiments, the pharmaceutical composition is in the form of an aqueous solution or a suspension. In some embodiments, the pharmaceutical composition is in the form of an emulsion. In some embodiments, the pharmaceutical composition is in the form of an aqueous solution. In some embodiments, the pharmaceutical composition is in the form of an aqueous solution which is clear, colorless, and/or free of visible foreign matter.

[0245] In some embodiments, the pharmaceutical composition has a pH ranging from about 6.5 to about 8.5. In some embodiments, the pharmaceutical composition has a pH of about 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, or 8.5.

[0246] In some embodiments, the pharmaceutical composition is basic and has a pH of about 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, or 8.5. In some embodiments, the pharmaceutical composition has a pH ranging from about 7.3 to about 7.4. In some embodiments, the pharmaceutical composition has a pH of 7.3 or 7.4.

[0247] In some embodiments, the pharmaceutical composition has an osmolality ranging from 250 mOsm/kg to 350 mOsm/kg. For example, the pharmaceutical composition may have an osmolality ranging from 250 mOsm/kg to 360 mOsm/kg, 260 mOsm/kg to 340 mOsm/kg, 270 mOsm/kg to 330 mOsm/kg, 280 mOsm/kg to 320 mOsm/kg, 290 mOsm/kg to 310 mOsm/kg, or about 300 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolarity of about 250 mOsm/kg, about 260 mOsm/kg, about 270 mOsm/kg, about 280 mOsm/kg, about 290 mOsm/kg, about 300 mOsm/kg, about 310 mOsm/kg, about 320 mOsm/kg, about 330 mOsm/kg, about 340 mOsm/kg, about 350 mOsm/kg, or about 360 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality ranging from about 275 mOsm/kg to about 330 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality of about 279 mOsm/kg, about 314 mOsm/kg, or about 329 mOsm/kg.

[0248] In some embodiments, the pharmaceutical composition has a viscosity ranging from about 0.5 cP to about 5 cP. For example, the pharmaceutical composition may have a viscosity ranging from about 0.5 cP to about 5 cP, about 0.75 cP to about 4.5 cP, about 1.0 cP to about 4 cP, about 1.2 cP to about 3.5 cP, about 1.3 cP to about 3 cP, about 1.4 cP to

about 2.5 cP, about 1.5 cP to about 2 cP, or about 1.6 cP to about 1.8 cP. In some embodiments, the pharmaceutical composition has a viscosity of about 0.5 cP, 0.6 cP, 0.7 cP, 0.8 cP, 0.9 cP, 1.0 cP, 1.1 cP, 1.2 cP, 1.3 cP, 1.4 cP, 1.5 cP, 1.6 cP, 1.7 cP, 1.8 cP, 1.9 cP, or 2.0 cP. In some embodiments, the pharmaceutical composition has a viscosity of about 1.4 cP or about 1.6 cP.

[0249] In some embodiments, the pharmaceutical composition disclosed is formulated for parenteral administration, such as, for example, in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. The term "parenteral," as used herein, includes subcutaneous, intravenous, intraperitoneal, intramuscular, and intralesional, or infusion techniques.

[0250] When the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration), the active ingredient(s) (e.g., the non-naturally occurring melanocortin analog) may be dissolved or suspended in the aforementioned carrier and/or excipient. Additional aqueous or non-aqueous carriers that may facilitate dissolution of the active ingredient include, but are not limited to, ethanol, benzyl alcohol, DMSO, polyethylene glycol, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, and/or various buffers.

[0251] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises a non-naturally occurring melanocortin analog in a concentration of about 0.001 nmol, 0.005 nmol, 0.01 nmol, 0.02 nmol, 0.05 nmol, 0.1 nmol, 0.25 nmol, 0.5 nmol, 1 nmol, 2.5 nmol, 5 nmol, 10 nmol, 20 nmol, 25 nmol, 50 nmol, 100 nmol, 250 nmol, 500 nmol, or 1000 nmol, or even more, depending on the specific peptide selected, the desired therapeutic response, the route of administration, the formulation and other factors known to those of skill in the art.

[0252] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises sodium acetate in a concentration of about 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 76 mM, 77 mM, 78 mM, 79 mM, 80 mM, 81 mM, 82 mM, 83 mM, 84 mM, 85 mM, 86 mM, 87 mM, 88 mM, 89 mM, 90 mM, 91 mM, 92 mM, 93 mM, 94 mM, 95 mM, 96 mM, 97 mM, 98 mM, 99 mM, 100 mM, 105 mM,

110 mM, 120 mM, 130 mM, 140 mM, 150 mM, 160 mM, 170 mM, 180 mM, 190 mM, or 200 mM.

[0253] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises Tris in a concentration of about 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 3 5mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, 85 mM, 90 mM, 95 mM, 100 mM, 105 mM, 110 mM, or 120 mM.

[0254] Alternatively, in some embodiments, the pharmaceutical composition is formulated for intranasal administration. When the pharmaceutical composition is formulated for intranasal administration, the composition may comprise one or more pharmaceutically acceptable carriers and/or excipients to facilitate delivery and enhance dispersion, solubility, and stability of the non-naturally occurring melanocortin analog.

[0255] The pharmaceutical composition may be formulated to be delivered by nose drop, spray device, or topical solution. In some embodiments, the pharmaceutical composition may be formulated as an aerosol, atomizer, inhalation, insufflation, metered-dose inhaler, or nebulizer. In some embodiments, the composition includes a propellant, such as hydrofluoroalkane.

[0256] When the pharmaceutical composition is formulated for intranasal administration, the active ingredient(s) (e.g., the non-naturally occurring melanocortin analog) may be dissolved or suspended in the one or more pharmaceutically acceptable carriers and/or excipients. Additional aqueous or non-aqueous carriers that may facilitate dissolution of the active ingredient include, but are not limited to, ethanol, benzyl alcohol, DMSO, polyethylene glycol, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, and/or various buffers.

[0257] In some embodiments, the pharmaceutical composition is formulated for intranasal administration and comprises the non-naturally occurring melanocortin analog in a concentration of about 0.001 nmol, 0.005 nmol, 0.01 nmol, 0.02 nmol, 0.05 nmol, 0.1 nmol, 0.25 nmol, 0.5 nmol, 1 nmol, 2.5 nmol, 5 nmol, 10 nmol, 20 nmol, 25 nmol, 50 nmol, 100 nmol, 250 nmol, 500 nmol, or 1000 nmol, or even more, depending on the specific peptide

selected, the desired therapeutic response, the route of administration, the formulation and other factors known to those of skill in the art.

[0258] In some embodiments, the pharmaceutical composition is formulated for intranasal administration and is configured to be administered using a spray device or nasal inhaler. The spray device or nasal inhaler may be configured to deliver about 1mg to about 100mg per spray. In some embodiments, the spray device or nasal inhaler is configured to deliver 1mg to 100mg, 5mg to 90mg, 10mg to 80mg, 15mg to 70mg, 20mg to 60mg, 25mg, to 50mg, or 30mg to 40mg per spray.

[0259] In some embodiments, the pharmaceutical composition is formulated for intranasal administration and has a pH approximating the normal pH range of the nasal fluid. Accordingly, in some embodiments, the pharmaceutical composition has a pH ranging from about 5.5 to about 6.5. In some embodiments, the pharmaceutical composition has a pH of about 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, or 6.5.

[0260] Pharmaceutically acceptable carriers and/or excipients that may be included in the pharmaceutical composition formulated for intranasal administration may generally include (i) one or more antioxidants, (ii) one or more preservatives, (iii) one or more buffers, (iv) one or more tonicity adjustors, (v) one or more surfactants, (vi) flavor, (vii) propellants, and/or (viii) a vehicle or solvent. In some embodiments, all components are compatible with the non-naturally occurring melanocortin analog (i.e., do not react or cause the non-naturally occurring melanocortin analog to react) and are homogeneously dispersed or dissolved uniformly in the composition.

[0261] In some embodiments, the pharmaceutically acceptable carriers and/or excipients are isotonic to nasal fluids.

[0262] In order to achieve a desirable tonicity, the pharmaceutical composition formulated for intranasal administration may further include a salt such as sodium chloride, sodium succinate, sodium sulfate, potassium chloride, magnesium chloride, magnesium sulfate, and calcium chloride. In some embodiments, the salt is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 1 mg/mL to 25 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the composition. In some

embodiments, the salt is sodium chloride and is present in a concentration of 0.9% by weight.

[0263] When the pharmaceutical composition is formulated for intranasal administration, the composition may comprise a pH buffered aqueous solution as previously described.

[0264] In some embodiments, the pharmaceutical composition is formulated for intranasal administration and comprises sodium acetate in a concentration of about 80 mM to about 100 mM. For example, sodium acetate may be present in the pharmaceutical composition in a molar concentration of 80 mM, 81 mM, 82 mM, 83 mM, 84 mM, 85 mM, 86 mM, 87 mM, 88 mM, 89 mM, 90 mM, 91 mM, 92 mM, 93 mM, 94 mM, 95 mM, 96 mM, 97 mM, 98 mM, 99 mM, or 100 mM.

[0265] In some embodiments, the pharmaceutical composition is formulated for intranasal administration and comprises Tris in a concentration of about 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 3 5mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, 85 mM, 90 mM, 95 mM, 100 mM, 105 mM, 110 mM, or 120 mM.

[0266] Additionally, when the pharmaceutical composition is formulated for intranasal administration, the composition may further comprise a phosphate, e.g., sodium phosphate. In some embodiments, the pharmaceutical composition is formulated for intranasal administration and comprises sodium phosphate in a molar concentration of about 5 mM to about 700 mM, relative to a total volume of the composition. For example, sodium phosphate may be present in the pharmaceutical composition in a molar concentration of 5 mM to 700 mM, 10 mM to 600 mM, 20 mM to 500 mM, 30 mM to 400 mM, 40 mM to 300 mM, 50 mM to 200 mM, 60 mM to 100 mM, or 70 mM to 80 mM, relative to a total volume of the composition.

[0267] In some embodiments, the pharmaceutical composition comprises one or more antioxidants. For example, the pharmaceutical composition may comprise ascorbic acid, cysteine, sodium metabisulfite, propyl gallate, butylated hydroxytoluene, and/or butylated hydroxyanisole.

[0268] In some embodiments, the pharmaceutical composition comprises a surfactant, such as a sorbitan ester.

[0269] In some embodiments, the pharmaceutical composition comprises a flavoring or scent, such as an aromatic oil.

[0270] In some embodiments, the non-naturally occurring melanocortin analog is solubilized or suspended in a solvent or vehicle. The solvent or vehicle may be purified water, ethyl alcohol, and/or propylene glycol. In some embodiments, the pharmaceutical composition comprises between 0.03 wt% and 1 wt% melanocortin analog solubilized or suspended in a solvent or vehicle. For example, the pharmaceutical composition may comprise the non-naturally occurring melanocortin analog in an amount of about 0.03 wt%, about 0.05 wt%, about 0.1 wt%, about 0.15 wt%, about 0.2 wt%, about 0.25 wt%, about 0.3 wt%, about 0.35 wt%, about 0.4 wt%, about 0.45 wt%, about 0.5 wt%, about 0.55 wt%, about 0.6 wt%, about 0.65 wt%, about 0.7 wt%, about 0.75 wt%, about 0.8 wt%, about 0.85 wt%, about 0.9 wt%, about 0.95 wt%, or about 1 wt%.

[0271] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, relative to a total volume of the composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, 5 g/mL to 15 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the pharmaceutical composition. Any of the non-naturally occurring melanocortin analogs and corresponding concentrations described previously with reference to the pharmaceutical composition may be present in the pharmaceutical composition at the same or substantially similar concentrations.

Administration

[0272] The pharmaceutical compositions of the present technology may be administered once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

[0273] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once about monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

[0274] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 50 mg to at about100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed about once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

[0275] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. I

[0276] n some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In some embodiments, the administration is performed once monthly.

[0277] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is

present in the pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

[0278] In some embodiments, any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 is present in the pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

[0279] In some embodiments, any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 is present in the pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

[0280] In some embodiments, any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 is present in the pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the

administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

[0281] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532and is present in the pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day.

[0282] In some embodiments, any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 is present in the pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 is present in the pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398,

400-402, 428, 488, 490, 494, 528, 530, and 532 is present in the pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

[0283] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342and is present in the pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342is present in the pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342 is present in the pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342 is present in the pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per

week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

[0284] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 and is present in the pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 is present in the pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 is present in the pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 is present in the pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other

embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

[0285] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289 and is present in the pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289 is present in the pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289 is present in the pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289 is present in the pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

[0286] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 188, 190, and 243 and is present in the pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NO: 188, 190, and 243 is present in the pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NO: 188, 190, and 243 is present in the pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, any one of SEQ ID NO: 188, 190, and 243 is present in the pharmaceutical composition at a dose of about 10 mg in a dose volume of about 1 mL, and wherein the administration is performed once monthly, once every three weeks, once every two weeks, once per week, twice per week, 3 times per week, 4 times per week, 5 times per week, once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, or 10 times per day. In some embodiments, the administration is performed once per day. In other embodiments, the administration is performed once weekly. In still other embodiments, the administration is performed once monthly.

[0287] In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof is administered hourly (such as every hour, every 2 hours, every 4 hours, every 8 hours, etc.), once a day, or twice a day. In some embodiments, the non-naturally occurring melanocortin analog is administered every morning, every evening, or every afternoon. In some embodiments, the non-naturally occurring melanocortin analog is administered before a meal, after a meal, or with a meal.

[0288] In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof may be administered as a dosing regimen comprising once, twice, or three times daily administration on a (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off; (iv) two weeks of therapy followed by one, two, three or four weeks off; (v) three weeks of therapy followed by one, two, three, four or five week off; (vi) four weeks of therapy followed by one, two, three, four or five week off; (vii) five weeks of therapy followed by one, two, three, four or five week off; or (viii) monthly schedule. The (i)-(viii) schedules may be repeated 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times or more. In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is administered at various dosages during the dosing regimen (e.g., a first dose with an effective amount of 10 mg/kg and a second dose with an effective amount of 5 mg/kg).

[0289] In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is administered once every other day, once every 2 or 3 days, once every third day, once per week, once every other week, once every third week, once every month, once every six weeks, once every other month, once every three months, once every six months, or once per year. Administration of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof at any of the dosing frequencies of the present technology may be repeated for a total of at least 2 dosages, at least 3 dosages, at least 4 dosages, at least 5 dosages, at least 10 dosages, at least 15 dosages, at least 20 dosages, at least 30 dosages, at least 40 dosages, at least 50 dosages or more. In some embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is the same during a treatment regimen. In other embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is different during a treatment regimen. The non-naturally occurring melanocortin analog or the pharmaceutical composition thereof may be administered even less frequently. Alternatively, the dosage regimen may be decreased or increased from an initial dosing regimen for days, weeks, months, or years. In some embodiments, the dosing regimen is repeated at other intervals.

Dosing

[0290] In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the non-naturally occurring melanocortin analog to the subject in need thereof.

[0291] In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of at least 1 mg, at least 2 mg, at least 3 mg, at least 5 mg, at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 40 mg, at least 50 mg, at least 60 mg, at least 75 mg, at least 100 mg, at least 125 mg, at least 150 mg, at least 175 mg, at least 200 mg, at least 225 mg, at least 250 mg, at least 275 mg, at least 300 mg, at least 325 mg, at least 350 mg, at least 375 mg, at least 400 mg, at least 425 mg, at least 450 mg, at least 475 mg, or at least 500 mg of the non-naturally occurring melanocortin analog to the subject in need thereof.

[0292] In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of at least about 1 mg, at least about 2 mg, at least about 3 mg, at least about 5 mg, at least about 10 mg, at least about 15 mg, at least about 20 mg, at least about 25 mg, at least about 30 mg, at least about 40 mg, at least about 50 mg, at least about 60 mg, at least about 75 mg, at least about 100 mg, at least about 125 mg, at least about 150 mg, at least about 175 mg, at least about 200 mg, at least about 225 mg, at least about 250 mg, at least about 275 mg, at least about 300 mg, at least about 325 mg, at least about 350 mg, at least about 375 mg, at least about 400 mg, at least about 425 mg, at least about 450 mg, at least about 475 mg, or at least about 500 mg of the non-naturally occurring melanocortin analog to the subject in need thereof.

[0293] In some embodiments, the compositions of the present technology are administered to the subject at a dose that is based on the subject's BMI. In some embodiments, two or more doses of the compositions of the present technology are

administered to the subject, wherein the two or more doses are titrated (e.g., inversely titrated) based on the subject's BMI at the time of each administration.

[0294] In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of about 0.001 mg/kg, about 0.005 mg/kg, about 0.01 mg/kg, about 0.05 mg/kg, about 0.10 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 75 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 225 mg/kg, about 250 mg/kg, about 275 mg/kg, about 300 mg/kg, about 325 mg/kg, about 350 mg/kg, about 375 mg/kg, about 400 mg/kg, about 425 mg/kg, about 450 mg/kg, about 475 mg/kg, or about 500 mg/kg of the non-naturally occurring melanocortin analog to the subject in need thereof.

[0295] In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of at least 0.001 mg/kg, at least 0.005 mg/kg, at least 0.01 mg/kg, at least 0.05 mg/kg, at least 0.10 mg/kg, at least 0.5 mg/kg, at least 1 mg/kg, at least 2 mg/kg, at least 3 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 15 mg/kg, at least 20 mg/kg, at least 25 mg/kg, at least 30 mg/kg, at least 40 mg/kg, at least 50 mg/kg, at least 60 mg/kg, at least 75 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, at least 175 mg/kg, at least 200 mg/kg, at least 225 mg/kg, at least 250 mg/kg, at least 275 mg/kg, at least 300 mg/kg, at least 325 mg/kg, at least 350 mg/kg, at least 375 mg/kg, at least 400 mg/kg, at least 425 mg/kg, at least 450 mg/kg, at least 475 mg/kg, or at least 500 mg/kg of the non-naturally occurring melanocortin analog to the subject in need thereof.

In some embodiments, the pharmaceutical compositions of the present technology are formulated to provide a dose of at least about 0.001 mg/kg, at least about 0.005 mg/kg, at least about 0.01 mg/kg, at least about 0.05 mg/kg, at least about 0.10 mg/kg, at least about 0.5 mg/kg, at least about 1 mg/kg, at least about 2 mg/kg, at least about 3 mg/kg, at least about 5 mg/kg, at least about 10 mg/kg, at least about 15 mg/kg, at least about 20 mg/kg, at least about 25 mg/kg, at least about 30 mg/kg, at least about 40 mg/kg, at least about 50 mg/kg, at least about 60 mg/kg, at least about 75 mg/kg, at least about 100 mg/kg, at least

about 125 mg/kg, at least about 150 mg/kg, at least about 175 mg/kg, at least about 200 mg/kg, at least about 225 mg/kg, at least about 250 mg/kg, at least about 275 mg/kg, at least about 300 mg/kg, at least about 325 mg/kg, at least about 350 mg/kg, at least about 375 mg/kg, at least about 400 mg/kg, at least about 425 mg/kg, at least about 450 mg/kg, at least about 475 mg/kg, or at least about 500 mg/kg of the non-naturally occurring melanocortin analog to the subject in need thereof.

[0296] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg to about 500 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg to about 250 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg to about 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0297] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg to at least 500 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 10 mg/kg to at least 250 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of at least 15 mg/kg to at least 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 20 mg/kg to at least 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0298] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg to at least about 500 mg/kg per body weight

of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 10 mg/kg to at least about 250 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of at least about 15 mg/kg to at least about 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 20 mg/kg to at least about 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0299] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject.

[0300] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0301] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from at least 0.5 mg/kg to at least 10 mg/kg, at least 1 mg/kg to at least 7.5 mg/kg, or at least 2.5 mg/kg to at least 5 mg/kg per body weight of the subject.

[0302] In some embodiments, the non-naturally occurring melanocortin analog is administered about once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0303] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg , about 40 mg/kg, about 50 mg/kg, about

65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 250 mg/kg, about 300 mg/kg, about 350 mg/kg, about 400 mg/kg, about 450 mg/kg, or about 500 mg/kg per body weight of the subject once daily.

[0304] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg, at least 10 mg/kg, at least 15 mg/kg, at least 20 mg/kg, at least 25 mg/kg, at least 30 mg/kg, at least 35 mg/kg , at least 40 mg/kg, at least 50 mg/kg, at least 65 mg/kg, at least 70 mg/kg, at least 75 mg/kg, at least 80 mg/kg, at least 85 mg/kg, at least 90 mg/kg, at least 95 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, at least 175 mg/kg, at least 200 mg/kg, at least 250 mg/kg, at least 300 mg/kg, at least 350 mg/kg, at least 400 mg/kg, at least 450 mg/kg, or at least 500 mg/kg per body weight of the subject once daily.

[0305] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg, at least about 10 mg/kg, at least about 15 mg/kg, at least about 20 mg/kg, at least about 25 mg/kg, at least about 30 mg/kg, at least about 35 mg/kg , at least about 40 mg/kg, at least about 50 mg/kg, at least about 65 mg/kg, at least about 70 mg/kg, at least about 75 mg/kg, at least about 80 mg/kg, at least about 85 mg/kg, at least about 90 mg/kg, at least about 95 mg/kg, at least about 100 mg/kg, at least about 125 mg/kg, at least about 150 mg/kg, at least about 175 mg/kg, at least about 200 mg/kg, at least about 250 mg/kg, at least about 300 mg/kg, at least about 350 mg/kg, at least about 400 mg/kg, at least about 450 mg/kg, or at least about 500 mg/kg per body weight of the subject once daily.

[0306] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg per body weight of the subject once daily.

[0307] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg per body weight of the subject once daily.

[0308] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg per body weight of the subject once daily.

[0309] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg per body weight of the subject once daily.

[0310] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 10 mg/kg per body weight of the subject once daily.

[0311] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 10 mg/kg per body weight of the subject once daily.

[0312] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg per body weight of the subject once daily.

[0313] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 15 mg/kg per body weight of the subject once daily.

[0314] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 15 mg/kg per body weight of the subject once daily.

[0315] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg per body weight of the subject once daily.

[0316] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 20 mg/kg per body weight of the subject once daily.

[0317] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 20 mg/kg per body weight of the subject once daily.

[0318] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 25 mg/kg per body weight of the subject once daily.

[0319] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 25 mg/kg per body weight of the subject once daily.

[0320] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 25 mg/kg per body weight of the subject once daily.

[0321] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg per body weight of the subject once daily.

[0322] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 30 mg/kg per body weight of the subject once daily.

[0323] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 30 mg/kg per body weight of the subject once daily.

[0324] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 35 mg/kg per body weight of the subject once daily.

[0325] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 35 mg/kg per body weight of the subject once daily.

[0326] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 35 mg/kg per body weight of the subject once daily.

[0327] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 40 mg/kg per body weight of the subject once daily.

[0328] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 40 mg/kg per body weight of the subject once daily.

In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 40 mg/kg per body weight of the subject once daily.

[0329] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 50 mg/kg per body weight of the subject once daily.

[0330] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 50 mg/kg per body weight of the subject once daily.

[0331] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 50 mg/kg per body weight of the subject once daily.

[0332] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg , about 40 mg/kg, about 50 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175

mg/kg, about 200 mg/kg, about 250 mg/kg, about 300 mg/kg, about 350 mg/kg, about 400 mg/kg, about 450 mg/kg, or about 500 mg/kg per body weight of the subject twice daily.

[0333] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg, at least 10 mg/kg, at least 15 mg/kg, at least 20 mg/kg, at least 25 mg/kg, at least 30 mg/kg, at least 35 mg/kg , at least 40 mg/kg, at least 50 mg/kg, at least 65 mg/kg, at least 70 mg/kg, at least 75 mg/kg, at least 80 mg/kg, at least 85 mg/kg, at least 90 mg/kg, at least 95 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, at least 175 mg/kg, at least 200 mg/kg, at least 250 mg/kg, at least 300 mg/kg, at least 350 mg/kg, at least 400 mg/kg, at least 450 mg/kg, or at least 500 mg/kg per body weight of the subject twice daily.

[0334] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg, at least about 10 mg/kg, at least about 15 mg/kg, at least about 20 mg/kg, at least about 25 mg/kg, at least about 30 mg/kg, at least about 35 mg/kg , at least about 40 mg/kg, at least about 50 mg/kg, at least about 65 mg/kg, at least about 70 mg/kg, at least about 75 mg/kg, at least about 80 mg/kg, at least about 85 mg/kg, at least about 90 mg/kg, at least about 95 mg/kg, at least about 100 mg/kg, at least about 125 mg/kg, at least about 150 mg/kg, at least about 175 mg/kg, at least about 200 mg/kg, at least about 250 mg/kg, at least about 300 mg/kg, at least about 350 mg/kg, at least about 400 mg/kg, at least about 450 mg/kg, or at least about 500 mg/kg per body weight of the subject twice daily.

[0335] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg per body weight of the subject twice daily.

[0336] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg per body weight of the subject twice daily.

[0337] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg per body weight of the subject twice daily.

[0338] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg per body weight of the subject twice daily.

[0339] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 25 mg/kg per body weight of the subject twice daily.

[0340] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg per body weight of the subject twice daily.

[0341] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 35 mg/kg per body weight of the subject twice daily.

[0342] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 40 mg/kg per body weight of the subject twice daily.

[0343] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 50 mg/kg per body weight of the subject twice daily.

[0344] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg per body weight of the subject twice daily.

[0345] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg per body weight of the subject twice daily.

[0346] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg per body weight of the subject twice daily.

[0347] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg per body weight of the subject twice daily.

[0348] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 25 mg/kg per body weight of the subject twice daily.

[0349] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg per body weight of the subject twice daily.

[0350] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 35 mg/kg per body weight of the subject twice daily.

[0351] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 40 mg/kg per body weight of the subject twice daily.

[0352] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 50 mg/kg per body weight of the subject twice daily.

[0353] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg per body weight of the subject twice daily.

[0354] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 10 mg/kg per body weight of the subject twice daily.

[0355] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 15 mg/kg per body weight of the subject twice daily.

[0356] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 20 mg/kg per body weight of the subject twice daily.

[0357] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 25 mg/kg per body weight of the subject twice daily.

[0358] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 30 mg/kg per body weight of the subject twice daily.

[0359] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 35 mg/kg per body weight of the subject twice daily.

[0360] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 40 mg/kg per body weight of the subject twice daily.

[0361] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 50 mg/kg per body weight of the subject twice daily.

[0362] In some embodiments, the non-naturally occurring melanocortin analog is administered at one or more doses. In some embodiments, the non-naturally occurring melanocortin analog is administered at two or more doses.

[0363] In some embodiments, the non-naturally occurring melanocortin analog is administered at a first dose once daily or twice daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a second dose once daily or twice daily.

[0364] In some embodiments, the non-naturally occurring melanocortin analog is administered at a first dose once daily for about 5 days to about 10 days. In some embodiments, the non-naturally occurring melanocortin analog is administered at a second dose once daily for about 5 days to about 10 days, after administration of the first dose. In some embodiments, the non-naturally occurring melanocortin analog is administered at a third dose twice daily for about 7 days to about 21 days, after administration of the second dose. In some embodiments, the second dose is greater than the first dose. In some embodiments, the third dose comprises a cumulative dose that is greater than the second dose.

[0365] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg to about 20 mg/kg administered once a day for about 5 days to about 10 days; (ii) at a second dose of about 10 mg/kg to about 40 mg/kg administered once a day after administration of the first dose for about 5 days to about 10 days; (iii) at a third dose of about 5 mg/kg to about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days to about 10 days. In some embodiments, the third dose is administered twice a day for at least about 7 days or more.

[0366] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, or about 20 mg/kg administered once a day for about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or about 10 days; (ii) at a second dose of about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, or about 40 mg/kg administered once a day after administration of the first dose about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or about 10 days; (iii) at a third dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, or about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days, about, 6 days, about 7 days, about 8 days, about 9 days, or about 10 days. In some embodiments, the third dose is administered twice a day for at least about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, or about 14 days or more.

[0367] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 15 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 10 mg/kg administered twice a day after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

[0368] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 10 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 20 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 15 mg/kg administered twice a day after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

[0369] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 15 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 25 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 20 mg/kg administered twice a day after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

[0370] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from about 0.5

mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0371] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0372] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0373] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10

mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0374] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0375] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 188, 190, and 243 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 188, 190, and 243 and is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0376] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring

melanocortin analog is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount of about 50 mg.

[0377] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount of about 50 mg.

[0378] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount of about 50 mg.

[0379] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ

ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342 and is administered at least once daily in an amount of about 50 mg.

[0380] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249 and is administered at least once daily in an amount of about 50 mg.

[0381] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring

melanocortin analog is any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289 and is administered at least once daily in an amount of about 50 mg.

[0382] In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 188, 190, and 243 and is administered at least once daily in an amount of about 0.1 mg to about 100 mg, 0.5 mg to about 50 mg, about 1 mg to about 40 mg, about 2.5 mg to about 30 mg, about 5 to about 20 mg, or about 7.5 to about 15 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 188, 190, and 243 and is administered once daily in an amount of about 10 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 188, 190, and 243 and is administered at least once daily in an amount of about 1 mg to about 100 mg, about 5 mg to about 95 mg, about 10 mg to about 90 mg, about 15 mg to about 85 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 30 mg to about 70 mg, about 35 mg to about 65 mg, about 40 to about 60 mg, or about 45 to about 55 mg. In some embodiments, the non-naturally occurring melanocortin analog is any one of SEQ ID NO: 188, 190, and 243 and is administered at least once daily in an amount of about 50 mg.

[0383] In some embodiments, administration of the non-naturally occurring melanocortin analog comprises delivery across the blood brain barrier. In some embodiments, administration of the non-naturally occurring melanocortin analog comprises delivery across the epithelium. In some embodiments, administration of the non-naturally occurring melanocortin analog comprises delivery across the epithelium and the blood brain

barrier. In some embodiments, administration of the non-naturally occurring melanocortin analog comprises delivery through the gastrointestinal tract.

Methods

[0384] The present technology comprises methods of treating, preventing, reducing, or otherwise ameliorating one or more symptoms or conditions associated with the melanocortin system. In some embodiments, the methods treat, prevent, or otherwise reduce a disease, a condition, or a disorder associated with the melanocortin system or a symptom thereof. The melanocortin system of the present technology may comprise regulatory pathways exerted through melanocortin receptor signaling (e.g., activation or inhibition of a melanocortin receptor or a signal transduction therefrom).

[0385] In some embodiments, the present technology comprises treating, preventing, reducing, or otherwise ameliorating one or more symptoms, conditions, diseases, or disorders associated with melanocortin system dysfunction (e.g., dysfunction in energy balance regulation, appetite, and/or energy expenditure). Nonlimiting examples of such symptoms, conditions, diseases, or disorders include cachexia, lethargy, appetite, sleep, arousal, libido, locomotion, cardiovascular anomalies, vasodilatation, hypertension, hypotension, sodium regulation, pain, pain perception, homeostasis, endocrine and exocrine gland secretion, inflammation, addictive behavior, increasing endogenous opioid activity, or decreasing opioid tolerance.

[0386] In some embodiments, the present technology is useful in treating, preventing, reducing, or otherwise ameliorating bodily conditions such as weight regulation (e.g., obesity, anorexia, and cachexia), hormonal secretion (e.g., dry eye and/or dry mouth syndrome), immuno-relevant conditions, or sexual dysfunction.

[0387] In some embodiments, the subject of the present technology is administered a non-naturally occurring melanocortin analog at least about 30 seconds, 1 minute, 5 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 36 hours, 2 days, 3 days, 4 days, 5 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 15 weeks, 20 weeks, 30 weeks, 40 weeks, 1 year, or 2 years after diagnosis or identification of the disease, condition, disorder, or the symptom thereof.

[0388] In some embodiments, the methods comprise administering a non-naturally occurring melanocortin analog at a first dose and a second to a subject in need thereof, wherein the second dose is greater than the first dose. In some embodiments, the subject is administered a third dose that is greater than the first and the second dose.

[0389] In some embodiments, the methods comprise administered the non-naturally occurring melanocortin analog to the subject in increase doses or increased dosages, relative to the first dose.

Maintenance Doses

[0390] In some embodiments, a maintenance dose of the non-naturally occurring melanocortin agonist is administered to the subject to maintain or enhance one or more outcomes of the methods of the present technology.

Subjects

[0391] In some embodiments, the subject is a mammal, including but not limited to a human, a non-human primate such as a chimpanzee, a domestic livestock or a farm animal such as a cow, a bison, sheep, a pig, a goat, a horse, a chicken, and a rooster, a domestic pet animal such as a dog, a cat, a rat, a mouse, and a rabbit, and a laboratory subject such as a rodent, including a rat, a mouse, and a guinea pig. In some embodiments, the subject is a human. In some embodiments, the subject is an animal such as a rat or a dog.

Controls

[0392] The controls of the present technology may comprise the subject at baseline. In some embodiments, the controls of the methods of the present technology comprise a subject that is not administered a non-naturally occurring melanocortin analog of the present technology or a subject subjected to a method lacking one or more steps of the methods of the present technology.

EXAMPLES

[0393] The following examples are intended to illustrate various embodiments of the present technology. As such, the specific embodiments discussed are not to be construed as limitations on the scope of the present technology. It will be apparent to one skilled in the

art that various equivalents, changes, and modifications may be made without departing from the scope of present technology, and it is understood that such equivalent embodiments, are to be included herein. Further, all references cited herein are hereby incorporated by reference in their entirety, as if fully set forth herein.

Example 1: Peptide Synthesis-Generic

[0394] The non-naturally occurring melanocortin analogs of the present technology were synthesized by conventional procedures (e.g., solution-phase procedure, solid-phase synthesis) for the formation of a peptide linkage between amino acids. The solution-phase procedure involved a condensation between the free alpha amino group of an amino acid or derivative thereof having the carboxyl group or other reactive groups protected and the free primary carboxyl group of another amino acid or derivative thereof having the amino group or other reactive groups protected. The solid-phase synthesis utilized a variety of resins and reagents and may involve additional purification steps.

[0395] The process for synthesizing the non-naturally occurring melanocortin analogs was generally performed by a procedure as follows. Each amino acid in the desired sequence of the non-naturally occurring melanocortin analogs was added one at a time in succession to another amino acid or derivative thereof or by a procedure whereby peptide fragments with the desired amino acid sequence were first synthesized conventionally and then condensed to provide the desired peptide. In most cases, the resulting peptide was then cyclized to yield a cyclic peptide.

[0396] Solid-phase peptide synthesis was carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain coupled to a solid-phase support according to the general principles of solid phase methods (see Merrifield, Angew Chem. 24:799-810 (1985) and Barany et al., The Peptides, Analysis, Synthesis and Biology, Vol. 2, Gross E. and Meienhofer J., Eds. Academic Press 1-284 (1980)). An exemplary solid-phase synthesis of non-naturally occurring melanocortin analogs is provided below.

[0397] Initially, the C-terminal amino acid residue of the non-naturally occurring melanocortin analog was coupled to a solid-phase support, e.g., a solid-phase resin.

Coupling of the C-terminal amino acid residue and the solid-phase support may be carried out according to any method know in the art. Depending on the coupling method, the alpha-amine of the C-terminal amino acid residue may or may not be protected with an amine protecting group, as described below. Likewise, the carboxyl group of the amino acid residue may or may not be activated prior to coupling to the solid-phase support in order to increase its electrophilicity. Some methods of coupling rely on the formation of an ester bond between the carboxyl group of the amino acid and a reactive handle on the solid-phase resin. For example, an amino acid residue may be coupled to a p-benzyloxybenzyl alcohol resin (Wang) or a 2-chlorotrityl chloride resin via an ester linkage. Some methods of coupling rely on the formation of an amide bond between the carboxyl group of the amino acid and a reactive handle on the solid-phase resin For example, an amino acid residue may be coupled to a benzhydrylamine (BHA) resin through an Fmoc-linker such as, for example, p-[(R,S)-α-[1-(9H-fluor-en-9-yl)-methoxyformamido]-2,4-dimethyloxybenzyl]-phenoxyacetic acid (Rink linker) via an amide linkage.

[0398] The non-naturally occurring melanocortin analog was then synthesized by sequential amino acid addition or combination of peptide fragments. Subsequently, the peptide was cleaved from the solid-phase support and purified by methods known in the art, such as, for example, reverse phase high performance liquid chromatography (RP-HPLC) using a suitable column, such as a C18 column. Additionally, or alternatively, other methods of separation or purification were employed, including, but not limited to, methods based on the size or charge of the peptide. Once purified, the peptide was characterized by methods such as high-performance liquid chromatograph (HPLC), amino acid analysis, mass spectrometry, and the like.

Example 2: Peptide Synthesis-Protecting Groups

[0399] During synthesis of the non-naturally occurring melanocortin analogs, reactive side chain groups of the various amino acid residues were protected with suitable protecting groups, which prevented undesirable chemical reaction from occurring at that site until the protecting group was removed.

[0400] Additionally, protection of the alpha amino group of an amino acid residue or fragment was performed while that entity reacting with the carboxyl group, followed by the

selective removal of the alpha amino protecting group to allow a subsequent reaction to take place at that site. Specific protecting groups for solid phase synthesis methods and solution phase synthesis methods are known to those having ordinary skill in the art. Alpha amino groups were protected by a suitable protecting group, including a urethane-type protecting group, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl. Fmoc was also used for alpha amino protection. Guanidino groups, if present, were protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tos), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pmc was used as a protecting group for Arg.

[0401] Alpha aminoprotecting groups may be removed under basic conditions, such as, for example, using a solution of piperidine, piperazine, diethylamine, or morpholine (20-40% v/v) in N,N-dimethylformamide (DMF). In synthesis methods in which alpha amino protecting groups were used, protecting groups were removed after synthesis of the peptide and before or after cleavage of the solid-phase support.

Example 3: Peptide Synthesis-Additional Modifications

[0402] If necessary, the peptides were further modified to obtain N-terminus modifications, such as acetylation, while on resin, or were removed from the resin by use of a cleaving reagent and then modified. Likewise, C-terminus modification (e.g., amidation), was performed if needed.

[0403] Additionally, the cyclized peptide structures were obtained prior to cleavage from the peptide resin. For cyclization through reactive side chain moieties, the desired side chains were deprotected, and the peptide suspended in a suitable solvent and a cyclic coupling agent added. Suitable solvents, for example DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP), were used for the cyclization. Suitable cyclic coupling reagents (e.g., 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(1H-

benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1 (2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), N,N′-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt)) were also used for the cyclization. Coupling was initiated by a suitable base, such as N,N-diispropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM).

Example 4: Biological Data

[0404] The agonist and antagonist activity of exemplary non-naturally occurring melanocortin analogs at the melanocortin receptors (e.g., MC1R, MC3R, MC4R, and MC5R) were measured via cAMP accumulation assay, according to the following procedure. Experimental design and execution were conducted by Epics Therapeutics S.A. EuroscreenFast (Bruxelles, Belgium).

Compound Handing

[0405] Compounds were delivered as powder (1 mg) or 10 mM solutions (100 µl) in 100% DMSO. Powders were solubilized in 100% DMSO at a concentration of 10 mM (master solution) in a solvent volume defined. Serial dilutions were performed from master solution in 100% DMSO to obtain intermediate concentrations 200-, 300- or 400-fold higher than the concentrations to be tested, depending on the assay. Each sample was diluted 100-fold in the assay buffer and dispensed in a test plate. Amounts, solvents, and dilutions were estimated based on standard small-molecule drugs. Cell lines used for functional assays are shown in Table 1.

Table 1. Cell lines

Receptor	Accession Number	Cell Line	Reference agonist	Reference antagonist
MC1R	NP_002377.4	CHO-K1	NDP-α-MSH	N/A
MC3R	AAC13541.1 I81V	CHO-K1	NDP-α-MSH	SHU9119
MC4R	NP_005903.2	CHO-K1	NDP-α-MSH	SHU9119

MC5R	NP_005904.1	CHO-K1	NDP-α-MSH	N/A

Compound Testing

[0406] Compounds were tested for (i) agonist and/or antagonist activity at the human MC3 (FAST-0232C) and MC4 (FAST-0233C) receptors, (ii) agonist activity at the human MC1 (FAST-0232C) receptor, and/or (iii) agonist activity at the human MC5 (FAST-0233C) receptor at the following nanomolar concentrations, in duplicate: 0.0001, 0.001, 0.01, 0.03, 0.1, 0.3, 1, 10, 100, and 1,000.

Testing Protocol

[0407] Cyclic AMP (cAMP) Homogenous Time-Resolved Fluorescence (HTRF) assay for Gs coupled receptor:

[0408] CHO-K1 cells expressing recombinant human receptor grown prior to the test in media without antibiotic were detached by gentle flushing with PBS-EDTA (5 mM EDTA), recovered by centrifugation and resuspended in assay buffer (KRH: 5 mM KCl, 1.25 mM MgSO4, 124 mM NaCl, 25 mM HEPES, 13.3 mM Glucose, 1.25 mM KH2PO4, 1.45 mM CaCl2, 0.5 g/l BSA, supplemented with 1mM IBMX or 25µM Rolipram).

[0409] Dose response curves were performed in parallel with the reference compounds.

[0410] For agonist test (384well): 5 µl of cells were mixed with 5 µl of the test compound at increasing concentrations and then incubated 30 min at room temperature. After addition of the lysis buffer containing cAMP-d2 and anti-cAMP cryptate detection reagents, plates were incubated 1-hour at room temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

[0411] For antagonist test (384well): 5 µl of cells were mixed in the wells of an assay plate with 5 µl of a mix of test compound at increasing concentrations and reference agonist for a final concentration corresponding to the historical EC80. The plates were then incubated 30 min at room temperature. After addition of the lysis buffer containing cAMP-d2 and anti-cAMP cryptate detection reagents, plates were incubated 1-hour at room

temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

Quality Control for Compound Testing

[0412] On each day of experimentation and prior to the testing of compounds, reference compounds were tested at several concentrations in duplicate (n=2) to obtain a dose-response curve and an estimated EC50 and/or IC50 values.

[0413] Reference values thus obtained for the test were compared to historical values obtained from the same receptor and used to validate the experimental session.

[0414] A session was considered as valid only if the reference value was found to be within a 0.5 logs interval from the historical value.

[0415] For replicate determinations, the maximum variability tolerated in the test was of +/-20% around the average of the replicates.

Non-naturally occurring melanocortin analog grouping

[0416] Non-naturally occurring melanocortin analogs were grouped based on structural similarities. Group A included non-naturally occurring melanocortin analogs A1 and A2, both of which are cyclic peptides comprising the motif Arg-p(I)dPhe-Arg-Trp. Group A peptides are provided in Table 2.

[0417] **Table 2.** Group A non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
188	A1	Ac-Nle-c[Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2
190	A2	Ac-Nle-c[Asp-Pro-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2

[0418] Group B included non-naturally occurring melanocortin analog B1, which is a cyclic peptide comprising the motif Ioc-dNal(2')-Arg-Trp. The group B peptide is provided in Table 3.

[0419] **Table 3.** Group B non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
243	B1	Ac-Nle-c[Asp-Ioc-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2

[0420] Group C included non-naturally occurring melanocortin analog C1 to C11, all of which are cyclic peptides comprising the motif R^3-dNal(2')-Arg-Trp, where R^3 is not Pro. Group C peptides are provided in Table 4.

[0421] **Table 4.** Group B non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
44	C1	Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2
45	C2	Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2
46	C3	Ac-Nle-c[Cys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH_2
47	C4	Ac-Nle-c[dCys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH_2
56	C5	Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2
57	C6	Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2
58	C7	Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2

60	C8	Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2
61	C9	Ac-Nle-c[dPen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2
62	C10	Ac-Nle-c[dPen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2
63	C11	Ac-Nle-c[Pen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2
338	C12	Ac-Nle-c[dPen-Ala-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2
339	C13	Ac-Nle-c[dPen-Leu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2
340	C14	Ac-Nle-c[dPen-dLeu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2
341	C15	Ac-Nle-c[dPen-dVal-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2
342	C16	Ac-Nle-c[dPen-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2
343	C17	Ac-Nle-c[dPen-Gly-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2

[0422] Group D included non-naturally occurring melanocortin analog D1 to D16, all of which are cyclic peptides comprising the motif Pro-dNal(2')-Arg-Trp, or a derivative thereof. Derivatives of the motif Pro-dNal(2')-Arg-Trp, include no more than one substitution at Pro, Arg, or Trp. Group D peptides are provided in Table 5.

[0423] **Table 5.** Group D non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
70	D1	Ac-Nle-c[Asp-dPro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2

83	D2	Ac-Nle-c[Asp-dTrp-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2
88	D3	Ac-Nle-c[Asp-Pro-dNal(2')-dLys-Trp-Lys]-dVal-dPro-NH_2
89	D4	Ac-Nle-c[Asp-Pro-dNal(2')-dArg-Trp-Lys]-dVal-dPro-NH_2
91	D5	Ac-Nle-c[Asp-Pro-dNal(2')-dOrn-Trp-Lys]-dVal-dPro-NH_2
94	D6	Ac-Nle-c[Asp-Pro-dNal(2')-Gly-Trp-Lys]-dVal-dPro-NH_2
95	D7	Ac-Nle-c[Asp-Pro-dNal(2')-Asp-Trp-Lys]-dVal-dPro-NH_2
97	D8	Ac-Nle-c[Asp-Pro-dNal(2')-dHis-Trp-Lys]-dVal-dPro-NH_2
98	D9	Ac-Nle-c[Asp-Pro-dNal(2')-dAla-Trp-Lys]-dVal-dPro-NH_2
99	D10	Ac-Nle-c[Asp-Pro-dNal(2')-dAsp-Trp-Lys]-dVal-dPro-NH_2
100	D11	Ac-Nle-c[Asp-Pro-dNal(2')-dGlu-Trp-Lys]-dVal-dPro-NH_2
101	D12	Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Lys]-dVal-dPro-NH_2 (no Trp)
106	D13	Ac-Nle-c[Asp-Pro-dNal(2')-Arg-His-Lys]-dVal-dPro-NH_2
107	D14	Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Ala-Lys]-dVal-dPro-NH_2
112	D15	Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dHis-Lys]-dVal-dPro-NH_2
113	D16	Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dAla-Lys]-dVal-dPro-NH_2

[0424] Group E included non-naturally occurring melanocortin analog E1 to E5, all of which are cyclic peptides comprising the motif Pro-dBip-Arg-Trp, or a derivative thereof. Group E peptides are provided in Table 6.

[0425] **Table 6.** Group E non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
114	E1	Ac-Nle-c[Asp-Pro-Bip-Arg-Trp-Lys]-dVal-dPro-NH_2
189	E2	Ac-Nle-c[Asp-His-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2
191	E3	Ac-Nle-c[Asp-Pro-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2
192	E4	Ac-Nle-c[Asp-Arg-Pro-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2
193	E5	Ac-Nle-c[Asp-Arg-Pro-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2

[0426] Group F included non-naturally occurring melanocortin analog F1 to F4, all of which are cyclic peptides comprising the motif Pro-dNal(2')-Arg-Trp, or a derivative thereof. Group F peptides are provided in Table 7.

[0427] **Table 7.** Group F non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
227	F1	Ac-Nle-c[Asp-His-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2
230	F2	Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2

246	F3	Ac-Nle-c[Asp-His-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH_2
249	F4	Ac-Nle-c[Asp-Pro-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH_2

[0428] Group G included non-naturally occurring melanocortin analog G1 to G11, all of which are cyclic peptides comprising the motif Trp-Arg-dNal(2')-Pro, or a derivative thereof. Group G peptides are provided in Table 8.

[0429] **Table 8.** Group G non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
276	G1	Ac-Nle-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2
277	G2	Ac-Nle-c[Asp-Pro-Trp-dNal(2')-Lys]-dVal-dPro-NH_2
278	G3	Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2
279	G4	Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Lys]-dVal-dPro-NH_2
280	G5	Ac-Nle-c[Lys-Trp-Arg-dNal(2')-Pro-Asp)-dVal-dPro-NH_2
284	G6	Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-NH_2
285	G7	Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp)-Nle-NH_2
286	G8	Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-Nle-NH_2
287	G9	Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp)-Nle-Nle-NH_2

288	G10	Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2
289	G11	Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp)-dVal-dPro-NH_2

[0430] Group H included non-naturally occurring melanocortin analog H1 to H5, all of which are cyclic peptides comprising a derivative of the motif Pro-dPhe-Arg-Trp, where the derivative may have one substitution at Pro or Trp. Group H peptides are provided in Table 9.

[0431] **Table 9.** Group H non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
356	H1	Ac-Nle-c[Asp-dIle-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
357	H2	Ac-Nle-c[Asp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
376	H3	Ac-Arg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
377	H4	Ac-dArg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
428	H5	Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH_2

[0432] Group I included non-naturally occurring melanocortin analog I1 to I3, all of which are cyclic peptides comprising the motif dPhe-Arg-Trp, or a derivative thereof, cyclized by a disulfide bond. Group I peptides are provided in Table 10.

[0433] **Table 10.** Group I non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring	Formula

	melanocortin analog	
202	I1	Ac-c[Cys-Arg-dPhe-Cys]-Trp-dVal-dPro-NH_2
325	I2	Ac-Nle-c[Pen-dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2
326	I3	Ac-Nle-c[dPen-dPhe-Arg-Trp-dPen]-dVal-dPro-NH_2

[0434] Group J included non-naturally occurring melanocortin analog J1 to J8, all of which are cyclic peptide comprising the motif Trp-Pro-dPhe-Arg, or a derivative thereof. Group J peptides are provided in Table 11.

Table 11. Group J non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
225	J1	Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
258	J2	Ac-Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2
396	J3	Ac-Nle-c[Asp-Trp-dLeu-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
397	J4	Ac-Nle-c[Asp-Trp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
398	J5	Ac-Nle-c[Asp-Trp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2
400	J6	Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH_2
401	J7	Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro-NH_2
402	J8	Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dPhe-Lys]-dVal-dPro-NH_2

[0435] Group K included non-naturally occurring melanocortin analog K1 to K6, all of which are cyclic peptide comprising the motif dTrp-p(X)dPhe-Arg-Trp, where X is Cl or F, or a derivative thereof. Group K peptides are provided in Table 12.

[0436] **Table 11.** Group K non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
488	K1	Ac-Nle-c[Asp-dPhe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
490	K2	Ac-Nle-c[Asp-dBip-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
494	K3	Ac-Nle-c[Asp-dTrp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
528	K4	Ac-Nle-c[Asp-dBip-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
530	K5	Ac-Nle-c[Asp-dGln-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
532	K6	Ac-Nle-c[Asp-dTrp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2

Agonist activity of melanocortin analogs on melanocortin 1 receptor and melanocortin 5 receptor

[0437] Administration of some non-naturally occurring melanocortin analogs activated melanocortin 1 receptor (MC1R) activity and/or melanocortin 5 receptor (MC5R) activity, as measured by cAMP levels (Table 12).

Table 12. Dose-response results of melanocortin agonist analogs and control against the melanocortin 1 receptor (MC1R) and melanocortin 5 receptor (MC5R)

SEQ ID NO		MC1R	MC5R

	Compound ID	EC50 (nM)	Max Activation (Emax)	EC50 (nM)	Max Activation (Emax)
	NDP-a-MSH	0.039	101.06	0.12	101.44
188	A1	0.48	94.13	518.20	42.07
190	A2	1.49	89.90	-	-
243	B1	1.02	89.18	2.93	99.87
44	C1	69.20	85.26	54.96	82.09
45	C2	66.28	97.89	438.94	100.00
46	C3	-	-	1558.35	100.00
47	C4	495.18	100.00	625.46	100.00
56	C5	405.42	100.00	1667.41	100.00
57	C6	392.95	100.00	163.91	87.14
58	C7	-	-	936.09	102.53
60	C8	-	-	2673.78	100.00
61	C9	-	-	1791.98	100.00
62	C10	-	-	1983.65	100.00
63	C11	-	-	2720.74	100.00
70	D1	5.35	93.25	226.58	100.00
83	D2	24.06	83.90	66.21	99.92
88	D3	-	-	374.57	100.00
89	D4	870.62	100.00	213.72	100.00
91	D5	-	-	240.14	91.55
94	D6	3001.10	100.00	4.00	103.86
95	D7	-	-	55.13	108.70
97	D8	-	-	74.81	81.21
98	D9	-	-	82.30	99.27
99	D10	-	-	1103.70	100.00
100	D11	413.76	100.00	893.09	100.00

101	D12	311.10	100.00	28.81	100.72
106	D13	39.88	98.00	14.07	101.51
107	D14	504.22	100.00	36.76	99.80
112	D15	430.12	100.00	18.97	109.10
113	D16	107.90	86.89	38.32	102.24
114	E1	6.42	102.57	5.92	61.29
189	E2	1.82	93.44	2123.94	100.00
191	E3	3.39	93.67	1738.92	100.00
192	E4	4.34	100.55	15.89	85.11
193	E5	3.60	97.47	23.09	75.05
202	I1	-	-	5390.72	100.00
225	J1	670.87	100.00	2856.44	100.00
227	F1	11.32	101.04	1517.07	100.00
230	F2	-	-	586.96	100.00
246	F3	3.69	100.31	11.61	101.31
249	F4	454.94	100.00	10.74	102.30
258	J2	-	-	205.87	100.00
276	G1	501.31	110.13	1986.84	100.00
277	G2	-	-	108.65	32.93
278	G3	698.94	100.00	965.55	100.00
279	G4	833.29	100.00	361.07	100.00
280	G5	201.85	91.65	2211.96	100.00
284	G6	163.23	87.31	906.87	100.00
285	G7	428.95	100.00	1791.42	100.00
286	G8	293.93	100.00	356.92	86.44
287	G9	50.63	95.02	1594.80	100.00
288	G10	418.16	100.00	628.75	100.00
289	G11	250.44	118.57	-	-
325	I2	1047.72	100.00	-	-
326	I3	96.74	101.42	48.42	100.93

338	C12	-	-	3146.86	100.00
339	C13	-	-	987.85	100.00
340	C14	2271.77	100.00	-	-
341	C15	3090.13	100.00	2738.55	100.00
342	C16	-	-	2076.43	100.00
343	C17	-	-	2883.30	100.00
356	H1	2.97	100.93	-	-
357	H2	0.87	100.90	2083.21	100.00
376	H3	1968.22	100.00	-	-
377	H4	23.69	89.27	-	-
396	J3	76.34	96.85	-	-
397	J4	3.41	100.67	646.00	100.00
398	J5	-	-	653.14	100.00
400	J6	46.56	80.81	-	-
401	J7	98.36	79.39	2485.38	100.00
402	J8	10.98	88.41	1455.80	100.00
428	H5	7.36	100.94	50.04	97.05
488	K1	10.28	92.83	17.73	95.08
490	K2	39.81	81.88	146.68	100.00
494	K3	35.70	95.22	118.52	97.61
528	K4	27.20	75.00	518.09	100.00
530	K5	43.96	101.41	21.03	95.75
532	K5	33.53	88.03	8.10	91.98

Antagonist activity of melanocortin analogs on melanocortin 3 receptor

[0438] Administration of some non-naturally occurring melanocortin analogs inhibited melanocortin 3 receptor (MC4R) activity, as measured by cAMP levels (Table 13).

Table 13. Dose-response results of melanocortin analogs and control against the melanocortin 3 receptor (MC3R)

SEQ ID NO	Compound ID	EC50 (nM)	Max Activation (Emax)

	SHU9119	2.34	97.24
188	A1	186.88	97.40
190	A2	165.25	90.14
243	B1	176.11	94.69

Example 5: Cardiac Activation of Melanocortin Agonists

[0439] The effect of the melanocortin agonists on cardiac activation in rats was tested using E2 (SEQ ID NO:295) according to the following procedure. Baseline measurements of heart rate, systolic blood pressure, and diastolic blood pressure of rats were taken 15 minutes prior to administration of E2. The rats were then administered saline, 3 mg/kg E2, or 6 mg/kg E2 via subcutaneous injection and the heart rate, systolic blood pressure, and diastolic blood pressure were measure at the following time points post injection: 5 minutes, 15 minutes, 30 minutes, 60 minutes, 120 minutes, and 180 minutes.

[0440] FIGS. 1A-1C show the cardiac activation data from 15 minutes before subcutaneous injection of E2 to 180 minutes after injection of E2. As shown in FIG. 1A, the heart rate of rats administered 3 mg/kg E2 (G1) decreased directly after injection, increased steadily from 30 minutes to 120 minutes, and then decreased again at 180 minutes to just slightly above the starting heart rate (i.e., at -15 min). Rats administered 6 mg/kg E2 (G2) maintained a steady heart rate until 120 minutes after injection when an increase in heart rate may be seen, however, the final heart rate of G2 rats was similar to that of G1 and control (G3) rats.

[0441] As may be seen in FIG. 1B the systolic blood pressure (SBP) of the rats in each group was similar for all time points, with a slight increase overall after injection for all three groups. The diastolic blood pressure (DBP) of rats administered 3 mg/kg E2 and 6 mg/kg E2 was higher than the diastolic blood pressure of the control rats at all time points post injection, however, no group of rats had a diastolic blood pressure above 100 at any time point (FIG. 1C).

[0442] This data suggests that melanocortin agonists in accordance with the present technology such as E2 avoid cardiac activation, which has been seen in earlier peptide and small molecule agonists of the melanocortin receptors.

Example 6: Pharmacokinetic Assessment of Non-Naturally Occurring Melanocortin Analogs Following Subcutaneous Administration to Rats

Study Objective

[0443] The objective of this study is to determine the pharmacokinetics of non-naturally occurring melanocortin analogs of the present technology following subcutaneous administration in male rats. In rats, the test article will be monitored in plasma for up to 24 hours post each dose. Study design and sample collection will be conducted as outlined in Table 14 and 15.

Table 14. Study Design

Animal	N	Compound	Target Dose Level (mg/kg)	Target Dose Volume (mL/kg)	Target Dose Concen-tration (mg/mL)	Vehicle	Dose Route
Rat	3	A07D	1	1	1	physiological saline	SC
Rat	3	A07D	3	1	3	physiological saline	SC
Rat	3	A07D	10	1	10	physiological saline	SC

Table 15. Sample Collections

Group	Dosage	Sampling time points (hr.)								
	(mg/kg)	0.083	0.25	0.5	1	2	4	6	8	24
Rat	1	P	P	P	P	P	P	P	P	P
Rat	3	P	P	P	P	P	P	P	P	P
Rat	10	P	P	P	P	P/C	P/C	P	P	P

E: Anticoagulant: Potassium (K_2) EDTA;

P: plasma

C: cerebrospinal fluid (CSF)

[0444] Dose Solution Analysis Samples: After each dose preparation, remove approximately 0.5 mL aliquots from the formulations, transfer the aliquots into amber HPLC vials and stored at -60°C or lower until assayed in duplicate for dose validation.

[0445] Disposition of Remaining Test Article Formulations: Remaining formulations will be stored at -60°C or lower.

[0446] Disposition of Remaining Test Article (dry powder or solid): Remaining test article will be stored at room temperature desiccated, and protected from light until shipment or discard.

[0447] Animals will be fasted overnight through 4 hours post dosing.

Vehicle and Formulation Preparation:

[0448] Appropriate amount of test article will be accurately weighed and mixed with appropriate volume of vehicle to get a clear solution or suspension.

[0449] Formulation samples will be removed from each of the formulation solutions, transferred into 1.5 mL of polypropylene microcentrifuge tubes and run dose validation by LC/UV or LC-MS/MS.

Animal Specifications: Rats

[0450] Rat specifications are outlined in Table 16.

Table 16. Rat Specifications

Species	Rat
Strain	SD
Source	Approved Vendor.
Gender	Male
Body weight	＞200g
Age	7-10 W
Total number of animals	9 male rats

Justification	The SD rat is a standard species used in pharmacokinetic evaluations and is acceptable to regulatory agencies. The number of animals used in this study is, in the judgment of the investigator involved, the minimum necessary to properly perform this plasma pharmacokinetic evaluation.

Observations and Examinations

[0451] Clinical Observations: All animals will be observed at dosing and each scheduled collection. All abnormalities will be recorded.

[0452] Body Weight: All animals will be weighed on the dosing day prior to dosing to determine the dose volume to be administered.

Sample Collection and Processing

[0453] Blood Sample Collection and Process: At least 0.1 mL blood will be collected at each time point. All blood samples will be collected via jugular vein. All blood samples will be transferred into low binding EP tube with anticoagulant (0.5 M Potassium (K2) EDTA will be pre-added as a ratio of 50:1 for blood: anticoagulant), 0.05% Triton X-100 (e.g., 100uL Blood+2uL 2.5% Triton X-100) will be used for desorption the blood samples will be placed on wet ice.

[0454] Blood samples will be centrifuged within 1hr of collection at 3,200 g 4°C for 10 minutes. Following centrifugation, plasma samples will be transferred into their respective pre-labeled low binding EP tube and immediately frozen over dry ice. The plasma samples will be stored lower than -60°C until bioanalysis.

[0455] LC-MS/MS method development:

[0456] A LC-MS/MS method for the quantitative determination of test compound in biological matrix will be developed.

[0457] N in 1 cassette LC-MS/MS method can be developed for samples coming from different studies as long as these studies belong to the same sponsor.

[0458] Cassette administration assay could be performed if the mass difference (ΔMass) among different analytes is ≥4 Da. In this case, interference evaluation is not necessary.

[0459] If ΔMass among different analytes is less than 4 Da, there is a potential risk that interference would occur during LC-MS/MS analysis. If such kind of cassette assay is still requested by client, interference among analytes will not be evaluated but the LC separation of those analytes by using a generic method will be attempted.

[0460] Sample analysis:

[0461] A calibration curve with at least 6 non-zero calibration standards will be applied for each batch including LLOQ.

[0462] If sample number within a batch is ≤ 12, at least one set of standard curves separated with two parts through begin and end of the sequence should be included in the run and QCs are not required. The recommended injection order is C8, C6, C4, C2, study samples, C7, C5, C3, C1.

[0463] If sample number within a batch is > 12, one standard curve and two sets of QCs with low, middle and high concentrations will be applied for bioanalysis. Meanwhile, QCs number should be more than 5% of study sample number.

[0464] Samples, coming from one client with the same type of matrix in different studies, are allowed to be quantified in one analysis run by using the developed N in 1 cassette LC-MS/MS method.

[0465] Acceptance criteria:

[0466] (1) Linearity: At least 75% of the calibration standards should fall within ±20% of their nominal values for biofluid and within ±25% of their nominal values for tissue and feces samples. If the endpoints, such as LLOQ and ULOQ, on the calibration curve are eliminated, the calibration curve will be truncated. The truncated calibration curve should consist of at least 75% of the initial STDs.

[0467] (2) Accuracy: At least 67% of QCs should fall within ±20% of their nominal values for biofluid and within ±25% of their nominal values for tissue and feces samples. At least half of QCs at each concentration should be passed.

[0468] (3) Specificity: The mass response of analyte in the double blank and blank should be ≤ 50% LLOQ.

[0469] (4) Sensitivity: The LLOQ will be tried to target ≤ 3 ng/mL. Any adjustment of LLOQ will be informed to client in advance.

[0470] (5) Carryover: The mean calculated carryover peak area in the double blanks or blanks immediately after the highest standard injection should be less than that of LLOQ. If the carryover couldn't meet the criteria, the impact of the carryover on unknown samples should be re-evaluated according to the below procedure:

[0471] Carryover should be re-evaluated based on absolute carryover. Absolute carryover is calculated by carryover contribution multiplies carryover impact, where the carryover contribution is calculated by the area ratio of the double blank or blank with the highest carryover (Area max of carryover blank) to the ULOQ with the minimum calculated value (Area min of ULOQ), and the carryover impact is calculated by the area ratio of one injection (Area of one injection) to the following injection (Area of the following injection). The absolute carryover should be below the acceptable accuracy of the studies (e.g., 20% or 25%).

[0472] Carryover contribution = $Area_{max}$ of carryover blank / $Area_{min}$ of ULOQ Carryover impact = Area of one injection / Area of the following injection Absolute carryover = Carryover contribution * Carryover impact

Data Analysis

[0473] Preliminary plasma and cerebrospinal fluid (CSF) results after 24 hours of subcutaneous (SC) administration of A07D in Rats are shown in Table 17 and Table 18. Graphs of plasma concentration and CSF concentration in Rats are shown in FIGS 2A-2D.

Table 17. Concentration of A07D in plasma and CSF of Rats over time

Comp. Name	Dose (mg/kg)	Plasma Concentration (ng/mL) over Time								CSF Concentration (ng/mL) over Time		Plasma/CSF ratio	
		0.25h	0.5 h	1 h	2 h	4 h	6 h	8 h	24 h	2 h	4 h	2h	4 h
A07D	1	228	253	319	249	122	17.1	1.47	ND	-	-	-	-
A07D	3	303	369	570	620	431	267	93.9	ND	-	-	-	-
A07D	10	274	364	747	1169	1139	844	575	7.23	8.60	15.9	0.00749	0.0141

ND = not determined

Table 18. Plasma Pharmacokinetic Results of A07D in Rats after 24 hours

Comp. Name	Dose (mg/kg)	Cmax (ng/mL)	Tmax (h)	Tfinal	T1/2 (h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ (ng.h/mL)	$MRT_{0\text{-last}}$ (h)	$MRT_{0\text{-inf}}$ (h)	AUC_{EX} (%)	$AUMC_{EX}$ (%)	Bioavailability (%)
A07D	1	319	1.00	8h-24h	2.58	1066	1106	3.02	3.87	3.02	14.0	95.1
A07D	3	647	1.67	8h	1.85	2986	3305	3.23	3.94	8.97	22.3	94.7
A07D	10	1324	2.67	24h	2.50	9002	9032	5.65	5.72	0.319	1.50	77.7

[0474] Dose proportionality of A07D in male rats following a single subcutaneous administration in Rats is shown in Table 19.

Table 19. Dose Proportionality of A07D in Rats after a single SC administration

Compound Name	Compare Doses (mg/kg)			Dose Ratio	Cmax Values	Cmax Ratio	$AUC_{0\text{-last}}$ Values	$AUC_{0\text{-last}}$ Ratio
D	3.00	Over	1.00	3.00	647/319	2.03	2986/1066	2.80
D	10.0	Over	1.00	3.33	1324/647	2.05	9002/298	3.01
D	10.0	Over	3.00	10.0	13824/319	4.15	9002/1066	8.44

Example 7: Residue Impact on Bioavailability

[0475] To assess the impact of non-naturally occurring melanocortin analogs on bioavailability, various pharmacokinetic parameters were assessed in the plasma of male cynomolgus monkeys fasted prior to dosing A07D at 1 mg/kg intravenously, 10 mg/kg orally, or 30 mg/kg orally. Results are shown in Table 20 and FIG 3.

Table 20: A07D Results

IV bolus1 (1 mg/kg)							
Time (h)	C1001	C1002	C1003	Mean		SD	CV (%)
--	Plasma Concentration (ng/mL)						
0.083	9594	5458	5566	6873	±	2357	34.3
0.25	6334	3905	3783	4674	±	1439	30.8
0.5	5668	3474	3125	4089	±	1379	33.7

1	4917	2312	2499	3243	±	1453	44.8
2	3191	1673	1687	2184	±	872	40.0
4	1869	868	830	1189	±	589	49.6
6	1249	602	465	772	±	419	54.2
8	871	324	238	478	±	343	71.9
24	82.4	17.3	12.6	37.4	±	39.0	104
PK Parameters	C1001	C1002	C1003	Mean		SD	CV (%)
Rsq_adj	0.999	0.995	0.989	--	±	--	--
No. points used for $T_{1/2}$	3.00	4.00	3.00	ND	±	--	--
C_0 (ng/mL)	11793	6446	6744	8328	±	3005	36.1
$T_{1/2}$ (h)	4.63	3.57	3.57	3.92	±	0.612	15.6
Vd_{ss} (L/kg)	0.201	0.328	0.313	0.281	±	0.0694	24.7
Cl(mL/min/kg)	0.633	1.37	1.48	1.16	±	0.461	39.7
T_{last} (h)	24.0	24.0	24.0	24.0	±	--	--
$AUC_{0\text{-}last}$ (ng.h/mL)	25795	12071	11189	16352	±	8190	50.1
$AUC_{0\text{-}inf}$ (ng.h/mL)	26346	12160	11254	16587	±	8464	51.0
$MRT_{0\text{-}last}$ (h)	4.76	3.81	3.37	3.98	±	0.710	17.8
$MRT_{0\text{-}inf}$ (h)	5.31	3.99	3.52	4.27	±	0.928	21.7
AUC_{Extra} (%)	2.09	0.733	0.577	1.13	±	0.832	73.4
$AUMC_{Extra}$ (%)	12.1	5.35	4.78	7.41	±	4.07	54.9

PO2 (10 mg/kg)							
Time (h)	C2001	C2002	C2003	Mean		SD	CV (%)
--	Plasma Concentration (ng/mL)						
0.083	2.85	3.83	8.58	5.09	±	3.06	60.3
0.25	20.2	101	23.2	48.1	±	45.8	95.2
0.5	67.0	418	74.9	187	±	200	107
1	85.1	450	111	215	±	204	94.5
2	174	408	79.6	221	±	169	76.7
4	136	240	59.8	145	±	90.5	62.3
6	90.9	171	45.3	102	±	63.6	62.1
8	53.7	71.5	23.2	49.5	±	24.4	49.4
24	8.75	7.42	2.45	6.21	±	3.32	53.5
PK Parameters	C2001	C2002	C2003	Mean		SD	CV (%)
Rsq_adj	0.974	0.963	0.987	--	±	--	--
No. points used for $T_{1/2}$	3.00	5.00	5.00	ND	±	--	--
C_{max} (ng/mL)	174	450	111	245	±	180	73.6
T_{max} (h)	2.00	1.00	1.00	1.33	±	0.577	43.3
$T_{1/2}$ (h)	5.61	3.93	4.37	4.64	±	0.871	18.8
T_{last} (h)	24.0	24.0	24.0	24.0	±	--	--
$AUC_{0\text{-}last}$ (ng.h/mL)	1251	2441	613	1435	±	928	64.7
$AUC_{0\text{-}inf}$ (ng.h/mL)	1321	2483	628	1477	±	937	63.4

$MRT_{0\text{-last}}$ (h)	6.94	5.01	5.74	5.90	±	0.974	16.5
$MRT_{0\text{-inf}}$ (h)	8.29	5.43	6.34	6.69	±	1.46	21.9
AUC_{Extra} (%)	5.36	1.69	2.46	3.17	±	1.94	61.0
$AUMC_{Extra}$ (%)	20.7	9.24	11.7	13.9	±	6.03	43.5
Bioavailability (%)[a]	-	-	-	0.890	--	--	--

PO3 (30 mg/kg)							
Time (h)	C3001	C3002	C3003	Mean		SD	CV (%)
--	Plasma Concentration (ng/mL)						
0.083	17.0	10.4	33.8	20.4	±	12.1	59.1
0.25	108	24.0	97.6	76.5	±	45.8	59.8
0.5	431	37.3	171	213	±	200	93.9
1	504	122	236	287	±	196	68.3
2	502	427	326	418	±	88.3	21.1
4	332	320	244	299	±	47.7	16.0
6	220	190	180	197	±	20.8	10.6
8	120	124	163	136	±	23.8	17.5
24	57.7	19.1	39.6	38.8	±	19.3	49.8
PK Parameters	C3001	C3002	C3003	Mean		SD	CV (%)
Rsq_adj	0.785	0.989	0.996	--	±	--	--
No. points used for $T_{1/2}$	5.00	3.00	3.00	ND	±	--	--
C_{max} (ng/mL)	504	427	326	419	±	89.3	21.3
T_{max} (h)	1.00	2.00	2.00	1.67	±	0.577	34.6
$T_{1/2}$ (h)	7.80	5.61	8.08	7.16	±	1.35	18.9
T_{last} (h)	24.0	24.0	24.0	24.0	±	--	--
$AUC_{0\text{-last}}$ (ng.h/mL)	3873	2772	3154	3266	±	559	17.1
$AUC_{0\text{-inf}}$ (ng.h/mL)	4522	2927	3615	3688	±	800	21.7
$MRT_{0\text{-last}}$ (h)	7.44	7.05	8.39	7.63	±	0.689	9.04
$MRT_{0\text{-inf}}$ (h)	11.4	8.37	11.9	10.6	±	1.91	18.1
AUC_{Extra} (%)	14.4	5.28	12.8	10.8	±	4.87	45.0
$AUMC_{Extra}$ (%)	44.3	20.2	38.4	34.3	±	12.6	36.6
Bioavailability (%)[a]	-	-	-	0.741	--	--	--

[0476] ND = Not determined (Parameters not determined due to inadequately defined terminal elimination phase).

[0477] BQL = Below the lower limit of quantitation (LLOQ).

[0478] If the adjusted rsq (linear regression coefficient of the concentration value on the terminal phase) is less than 0.9, $T_{1/2}$ might not be accurately estimated.

[0479] If the % AUC_{Extra} > 20%, $AUC_{0\text{-}inf}$, Cl, $MRT_{0\text{-}inf}$ and Vd_{ss} might not be accurately estimated.

[0480] If the % $AUMC_{Extra}$ > 20%, $MRT_{0\text{-}inf}$ and Vd_{ss} might not be accurately estimated.

[0481] The adjusted linear regression coefficient of the concentration value on the terminal phase is less than 0.9, $T_{1/2}$ might not be accurately estimated.

[0482] a: Bioavailability (%) was calculated using $AUC_{0\text{-}inf}$ (if all $AUC_{Extra} \leq 20\%$) or $AUC_{0\text{-}last}$ (if one or more AUC_{Extra} > 20%) with Nominal Dose.

Additional Embodiments

[0483] Various embodiments of the present technology are set forth below in paragraphs [0484] to [0543]:

[0484] 1. A non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

X^1-X^2-R^1-R^2-R^3-R^4-R^5-R^6-R^7-R^8-Y^1-Y^2-Y^3 (I),

wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is absent or is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, Trp, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), indoline-2-carboxylic acid (Ioc), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of Trp, Nle and dVal;

Y^2 is absent or is selected from the group consisting of Nle, dVal, and dPro;

Y^3 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that:

when R^4 is p(I)dPhe, then the non-naturally occurring melanocortin analog is cyclized between R^1 and R^7;

when R^4 is p(F)dPhe and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, dGln, or Trp;

when R^4 is p(Cl)dPhe, and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, dPhe, or Trp;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then (i) R^5 and R^6 are absent or (ii) R^3 is absent and R^2 is not Cys; when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then R^3 is selected from dIle, dVal, and dAla, R^5 is Pro, or R^6 is Nal(1');

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then (i) R^2 is Trp, and (a) R^3 is dVal or dLeu, (b) R^5 is His, or (c) R^6 is dNal(1'), Phe, or dPhe, or (ii) R^2 is Pro and R^3 is Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7 and R^3 is not Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dPro, dTrp, His, and Ioc, or (ii) R^3 is Pro and either R^5 is selected from dLys, dArg, dOrn, Gly, Asp, dHis, dAla, dAsp, dGlu, and Pro or R^6 is absent selected from His, dHis, Ala, and dAla; and

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then one or both of R^5 and R^6 is absent.

[0485] 2. The non-naturally occurring melanocortin analog of embodiment 1, wherein:

X^2 is absent or D-proline (dPro);

R^1 is absent or is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, Trp, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), indoline-2-carboxylic acid (Ioc), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of Trp, Nle and dVal;

Y^2 is absent or is selected from the group consisting of Nle, dVal, and dPro;

Y^3 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac—Nle-c[Asp-Pro-p(I)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 216);

Ac—Nle-c[Asp-His-p(I)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 221);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 223);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 460);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 464);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 465);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 469);

Ac—Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 470);

Ac—Nle-c[Cys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 459);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 461);

Ac—Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 218);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 433);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 434);

Ac—dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 436);

Ac—Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 437);

Ac—Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 438);

Ac—Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 442);

Ac—Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 443);

Ac—Nle-c[Asp-dGln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 492);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 463);

Ac—Nle-c[Cys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 432);

Ac—Nle-c[Asp-Trp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 493);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 499);

Ac—dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 501);

Ac—Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 502);

Ac—Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 503);

Ac—Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 215);

Ac—Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 220);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 498);

Ac—Nle-c[Cys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 497);

Ac—Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 508);

Ac—Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 507);

Ac—Nle-c[Asp-Trp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 531);

Ac—Nle-c[Asp-dPhe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 526);

Ac—Nle-c[Cys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 318);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 319);

Ac—Nle-c[dPen-Pro-dPhe-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 320);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 321);

Ac—Nle-c[Cys-dPhe-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 324);

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 363);

Ac—dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 302);

Ac—Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 311);

Ac—Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 313);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 295);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 351);

Ac—Nle-c[Asp-dBip-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 369);

Ac—Nle-c[Asp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 354);

Ac—Nle-c[Asp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 355);

Ac—Nle-c[Asp-Ioc-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 361);

Ac—Nle-c[Asp-dPhe-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 367);

Ac—Nle-c[Asp-dGln-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 371);

Ac—Nle-c[Asp-Trp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 372);

Ac—Nle-c[Asp-dTrp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 373);

Ac—Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 425);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 429);

Ac—Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 628);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-Trp—NH2 (SEQ ID NO: 600);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 595);

Ac—Nle-c[Asp-Trp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 394);

Ac—Nle-c[Asp-Trp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 395);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Nal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 399);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 226);

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 297);

Ac—Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 413);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 40);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 41);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 42);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 43);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 48);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 49);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 50);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 51);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 52);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 53);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 54);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 55);

Ac—dArg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 329);

Ac—Arg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 330);

Ac—Lys-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 337);

Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59);

Ac—Nle-c[Asp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 68);

Ac—Nle-c[Asp-Ala-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 69);

Ac—Nle-c[Asp-dAla-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 71);

Ac—Nle-c[Asp-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 75);

Ac—Nle-c[Asp-Leu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 76);

Ac—Nle-c[Asp-dLeu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 79);

Ac—Nle-c[Asp-dIle-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 80);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3);

Ac—dArg-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 15);

Ac—dVal-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 19);

Ac—dPro-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 27);

Ac—Nle-c[Asp-Trp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 82);

Ac—Nle-c[Asp-Pro-dNal(2')-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 86);

Ac—Nle-c[Asp-Pro-dNal(2')-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 92);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 104);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dNal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 108);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dPhe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 109);

Ac—Nle-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 184);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal—NH2 (SEQ ID NO: 128);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 255);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 256);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 259);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 179);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal—NH2 (SEQ ID NO: 126);

Ac—Nle-c[Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 73);

Ac—Nle-c[Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 74);

Ac—Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 257);

Ac—Nle-c[Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 194); Ac—Nle-c[Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 195); and Ac—Nle-c[Asp-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 5).

[0486] 3. The non-naturally occurring melanocortin analog of embodiment 1 or 2, comprising a sequence according to Formula (IA):

X^1-X^2-R^1-R^2-R^3-R^4-R^5-R^6-R^7-R^8-Y^1-Y^2 (IA),

wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), and 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that:

when R^4 is p(F)dPhe and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, or dGln;

when R^4 is p(Cl)dPhe, and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, or dPhe;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then (i) R^5 and R^6 are absent or (ii) R^3 is absent and R^2 is not Cys;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dIle, dVal, and dAla, (ii) R^5 is Pro, or (iii) R^6 is Nal(1');

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then (i) R^2 is Trp, and (a) R^3 is dVal or dLeu, (b) R^5 is His, or (c) R^6 is dNal(1'), Phe, or dPhe, or (ii) R^2 is Pro and R^3 is Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7 and R^3 is not Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dPro, dTrp, His, and Ioc, , or (ii) R^3 is Pro and either R^5 is selected from dLys, dArg, dOrn, Gly, Asp, dHis, dAla, dAsp, dGlu, and Pro or R^6 is absent or selected from His, dHis, Ala, and dAla; and

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then one or both of R^5 and R^6 is absent.

[0461] 4. The non-naturally occurring melanocortin analog of embodiment 1 or 2, comprising a sequence according to Formula (IA), wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), and 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 223);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 460);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 464);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 465);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 469);

Ac—Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 470);

Ac—Nle-c[Cys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 459);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 461);

Ac—Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 218);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 433);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 434);

Ac—dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 436);

Ac—Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 437);

Ac—Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 438);

Ac—Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 442);

Ac—Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 443);

Ac—Nle-c[Asp-dGln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 492);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 463);

Ac—Nle-c[Cys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 432);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 499);

Ac—dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 501);

Ac—Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 502);

Ac—Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 503);

Ac—Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 215);

Ac—Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 220);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 498);

Ac—Nle-c[Cys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 497);

Ac—Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 508);

Ac—Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 507);

Ac—Nle-c[Asp-dPhe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 526);

Ac—Nle-c[Cys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 318);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 319);

Ac—Nle-c[dPen-Pro-dPhe-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 320);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 321);

Ac—Nle-c[Cys-dPhe-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 324);

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 363);

Ac—dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 302);

Ac—Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 311);

Ac—Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 313);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 295);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 351);

Ac—Nle-c[Asp-dBip-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 369);

Ac—Nle-c[Asp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 354);

Ac—Nle-c[Asp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 355);

Ac—Nle-c[Asp-dPhe-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 367);

Ac—Nle-c[Asp-dGln-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 371);

Ac—Nle-c[Asp-dTrp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 373);

Ac—Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 425);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 429);

Ac—Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 628);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-Trp—NH2 (SEQ ID NO: 600);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 595);

Ac—Nle-c[Asp-Trp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 394);

Ac—Nle-c[Asp-Trp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 395);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Nal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 399);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 226);

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 297);

Ac—Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 413);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 40);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 41);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 42);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 43);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 48);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 49);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 50);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 51);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 52);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 53);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 54);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 55);

Ac—dArg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 329);

Ac—Arg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 330);

Ac—Lys-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 337);

Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59);

Ac—Nle-c[Asp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 68);

Ac—Nle-c[Asp-Ala-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 69);

Ac—Nle-c[Asp-dAla-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 71);

Ac—Nle-c[Asp-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 75);

Ac—Nle-c[Asp-Leu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 76);

Ac—Nle-c[Asp-dLeu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 79);

Ac—Nle-c[Asp-dIle-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 80);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3);

Ac—dArg-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 15);

Ac—Nle-c[Asp-Pro-dNal(2')-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 86);

Ac—Nle-c[Asp-Pro-dNal(2')-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 92);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 104);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dNal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 108);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dPhe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 109);

Ac—Nle-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 184);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal—NH2 (SEQ ID NO: 128);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 255);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 256);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 259);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 179);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal—NH2 (SEQ ID NO: 126);

Ac—Nle-c[Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 73);

Ac—Nle-c[Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 74);

Ac—Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 257);

Ac—Nle-c[Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 194);

Ac—Nle-c[Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 195); and

Ac—Nle-c[Asp-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 5).

[0462] 5. The non-naturally occurring melanocortin analog of embodiment 1 or 2, comprising a sequence according to Formula (IB):

R^1-R^2-R^3-dNal(2')-R^5-R^6-R^7-Y^1-Y^2 (IB),

wherein:

R^1 is norleucine (Nle);

R^2 is selected from the group consisting of penicillamine (Pen), D-penicillamine (dPen), cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly

R^5 is Arg;

R^6 is Trp;

R^7 is selected from the group consisting of Cys, dCys, Pen, dPen;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R^2 and R^7 when R^2 and R^7 are each independently selected from the group consisting of Cys, dCys, Pen, and dPen,

provided that:

when R^3 is absent, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7.

[0463] 6. The non-naturally occurring melanocortin analog of embodiment 1 or 2, comprising a sequence of Formula (IB), wherein:

R^1 is norleucine (Nle);

R^2 is selected from the group consisting of penicillamine (Pen), D-penicillamine (dPen), cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly

R^5 is Arg;

R^6 is Trp;

R^7 is selected from the group consisting of Cys, dCys, Pen, dPen;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R^2 and R^7 when R^2 and R^7 are each independently selected from the group consisting of Cys, dCys, Pen, and dPen,

provided that the non-naturally occurring melanocortin analog does not comprise a sequence of: Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59).

[0464] 7. The non-naturally occurring melanocortin analog of embodiment 1 or 2, comprising a sequence of Formula (IC):

R^1-Asp-R^3-dNal(2')-R^5-R^6-Lys-Y^1-Y^2 (IC),

wherein:

R^1 is norleucine (Nle);

R^3 is selected from the group consisting of histidine (His), proline (Pro), D-proline (dPro), D-tryptophan (dTrp), and indoline-2-carboxylic acid (Ioc);

R^5 is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, and dAla;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^7;

provided that:

when R^3 is Pro, then either R^5 is not Arg or R^6 is not Trp.

[0465] 8. The non-naturally occurring melanocortin analog of embodiment 1 or 2, comprising a sequence of Formula (IC), wherein:

R^1 is norleucine (Nle);

R^3 is selected from the group consisting of histidine (His), proline (Pro), D-proline (dPro), D-tryptophan (dTrp), and indoline-2-carboxylic acid (Ioc);

R^5 is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, and dAla;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^7;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3); and

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116).

[0466] 9. The non-naturally occurring melanocortin analog of embodiment 1 or 2, comprising a sequence of Formula (ID):

X^1-X^2-R^1-R^2-Arg-R^4-R^5-R^6-R^7-Y^1-Y^2 (ID),

wherein:

X^1 is norleucine (Nle) or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is aspartic acid (Asp) or lysine (Lys);

R^2 is selected from the group consisting of tryptophan (Trp), proline (Pro), and histidine (His);

R^4 is selected from the group consisting of D-biphenylalanine (dBip), 2'-D-naphthylalanine (dNal(2')), and para-iodo-D-phenylalanine (p(I)dPhe);

R^5 is arginine (Arg) or Pro;

R^6 is absent or tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is Asp or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a lactam bridge between R^1 and R^7 when R^1 is Asp and R^7 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp.

[0467] 10. The non-naturally occurring melanocortin analog of embodiment 1 or 2, comprising a sequence of Formula (IE):

X^1-R^1-R^2-R^3-R^4-Arg-R^6-Lys-Y^1-Y^2 (IE),

wherein:

X^1 is absent or norleucine (Nle);

R^1 is Nle or aspartic acid (Asp);

R^2 is selected from the group consisting of Asp, histidine (His), and proline (Pro);

R^3 is arginine (Arg) or indoline-2-carboxylic acid (Ioc);

R^4 is 2'-D-naphthylalanine (dNal(2')) or para-iodo-D-phenylalanine (p(I)dPhe);

R^6 is Trp or tetrahydro-isoquinoline-3-carboxylic acid (Tic);

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between the Asp at R^1 or R^2 and the Lys at R^7.

[0468] 11. The non-naturally occurring melanocortin analog of any one of embodiments 1-10, wherein the N-terminus of the non-naturally occurring melanocortin analog is modified by an acyl group.

[0469] 12. The non-naturally occurring melanocortin analog of embodiment 11, wherein the acyl group is an acetyl group.

[0470] 13. The non-naturally occurring melanocortin analog of any one of embodiments 1-10, wherein the N-terminus of the non-naturally occurring melanocortin analog is not modified.

[0471] 14. The non-naturally occurring melanocortin analog of any one of embodiments 1-13, wherein the C-terminus of the non-naturally occurring melanocortin analog is modified by an amide group.

[0472] 15. The non-naturally occurring melanocortin analog of any one of embodiments 1-13, wherein the C-terminus of the non-naturally occurring melanocortin analog is not modified.

[0473] 16. The non-naturally occurring melanocortin analog of any one of embodiments 1-15, wherein Y^1-Y^2 are present and Y^3 is absent.

[0474] 17. The non-naturally occurring melanocortin analog of any one of embodiments 1-16, wherein Y^1 is D-valine and Y^2 is D-proline.

[0475] 18. The non-naturally occurring melanocortin analog of any one of embodiments 1-17, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond.

[0476] 19. The non-naturally occurring melanocortin analog of any one of embodiments 1-18, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond between R^1 or R^2 and R^7.

[0477] 20. The non-naturally occurring melanocortin analog of any one of embodiments 1-19, wherein R^4 is dNal(2').

[0478] 21. The non-naturally occurring melanocortin analog of any one of embodiments 1-20, wherein R^3 is absent.

[0479] 22. The non-naturally occurring melanocortin analog of any one of embodiments 1-21, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 44);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 45);

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 46);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 47);

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 60);

Ac-Nle-c[dPen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[dPen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 62); and

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 63),

wherein c represents cyclization through R^2 and R^7 via a disulfide bond.

[0480] 23. The non-naturally occurring melanocortin analog of any one of embodiments 1-20, wherein R^3 is present and is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly.

[0481] 24. The non-naturally occurring melanocortin analog of any one of embodiments 1-23, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[dPen-Ala-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 338);

Ac-Nle-c[dPen-Leu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 339);

Ac-Nle-c[dPen-dLeu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 340);

Ac-Nle-c[dPen-dVal-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 341);

Ac-Nle-c[dPen-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 342); and

Ac-Nle-c[dPen-Gly-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 343),

wherein c represents cyclization through R^1 or R^2 and R^7 via a disulfide bond.

[0482] 25. The non-naturally occurring melanocortin analog of any one of embodiments 1-19, wherein R^4 is dPhe.

[0483] 26. The non-naturally occurring melanocortin analog of any one of embodiments 1-25, wherein at least one of R^1, R^3 , R^5, and R^6 is absent.

[0484] 27. The non-naturally occurring melanocortin analog of any one of embodiments 1-26, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-c[Cys-Arg-dPhe-Cys]-Trp-dVal-dPro-NH_2 (SEQ ID NO: 202);

Ac-Nle-c[Pen-dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 325); and

Ac-Nle-c[dPen-dPhe-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 326),

wherein c represents cyclization through R^2 and R^7 via a disulfide bond.

[0485] 28. The non-naturally occurring melanocortin analog of any one of embodiments 1-17, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond.

[0486] 29. The non-naturally occurring melanocortin analog of embodiment 18, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^1 and R^7.

[0487] 30. The non-naturally occurring melanocortin analog of embodiment 28 or 29, wherein R^4 is dBip or p(I)dPhe.

[0488] 31. The non-naturally occurring melanocortin analog of any one of embodiments 28-30, wherein one of R^2 and R^3 is Arg.

[0489] 32. The non-naturally occurring melanocortin analog of any one of embodiments 28-31, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 188);

Ac-Nle-c[Asp-His-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 189);

Ac-Nle-c[Asp-Pro-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 190);

Ac-Nle-c[Asp-Pro-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 191);

Ac-Nle-c[Asp-Arg-Pro-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 192); and

Ac-Nle-c[Asp-Arg-Pro-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 193),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0490] 33. The non-naturally occurring melanocortin analog of embodiment 28 or 29, wherein R^4 is dPhe.

[0491] 34. The non-naturally occurring melanocortin analog of embodiment 33, wherein R^2 is Trp and/or R^3 is Pro.

[0492] 35. The non-naturally occurring melanocortin analog of embodiment 33 or 34, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 225);

Ac-Nle-c[Asp-Trp-dLeu-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 396);

Ac-Nle-c[Asp-Trp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 397);

Ac-Nle-c[Asp-Trp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 398);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 400);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 401); and

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dPhe-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 402),
wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0493] 36. The non-naturally occurring melanocortin analog of embodiment 28 or 29, wherein R^4 is dNal(2').

[0494] 37. The non-naturally occurring melanocortin analog of embodiment 36, wherein (i) R^2 is Pro and R^3 is Trp or Trp-Arg or (ii) R^2 is Trp and R^3 is Arg.

[0495] 38. The non-naturally occurring melanocortin analog of embodiment 36 or 37, wherein (i) R^5 is Pro or absent.

[0496] 39. The non-naturally occurring melanocortin analog of any one of embodiments 36-38, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 276);

Ac-Nle-c[Asp-Pro-Trp-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 277);

Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 278);

Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 279);

Ac-Nle-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-dVal-dPro-NH_2 (SEQ ID NO: 280);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-NH_2 (SEQ ID NO: 284);

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-Nle-NH_2 (SEQ ID NO: 285);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-Nle-NH_2 (SEQ ID NO: 286);

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-Nle-Nle-NH_2 (SEQ ID NO: 287);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 288); and

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-dVal-dPro-NH_2 (SEQ ID NO: 289),
wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0497] 40. The non-naturally occurring melanocortin analog of embodiment 18, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^2 and R^7.

[0498] 41. The non-naturally occurring melanocortin analog of embodiment 40, wherein R^4 is Bip.

[0499] 42. The non-naturally occurring melanocortin analog of embodiment 40 or 41, wherein the sequence of any one of Formulae (I)-(IE) is: Ac-Nle-c[Asp-Pro-Bip-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 114), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0500] 43. The non-naturally occurring melanocortin analog of embodiment 40, wherein R^4 is dPhe.

[0501] 44. The non-naturally occurring melanocortin analog of embodiment 40 or 43, wherein R^3 is not Pro, R^5 is not Arg, and/or R^6 is not Trp.

[0502] 45. The non-naturally occurring melanocortin analog of any one of embodiments 40, 43, and 44, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dIle-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 356);

Ac-Nle-c[Asp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 357);

Ac-Arg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 376);

Ac-dArg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 377);

Ac-Nle-c[Asp-His-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 227);

Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 230); and

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 428),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0503] 46. The non-naturally occurring melanocortin analog of embodiment 40, wherein R^4 is p(Cl)dPhe.

[0504] 47. The non-naturally occurring melanocortin analog of embodiment 40 or 43, wherein R^3 is selected from the group consisting of dBip, dGln, and dTrp.

[0505] 48. The non-naturally occurring melanocortin analog of any one of embodiments 40, 46, and 47, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dBip-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 528);

Ac-Nle-c[Asp-dGln-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 530); and

Ac-Nle-c[Asp-dTrp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 532),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0506] 49. The non-naturally occurring melanocortin analog of embodiment 40, wherein R^4 is p(F)dPhe.

[0507] 50. The non-naturally occurring melanocortin analog of embodiment 40 or 49, wherein R^3 is selected from the group consisting of dBip, dPhe, and dTrp.

[0508] 51. The non-naturally occurring melanocortin analog of any one of embodiments 40, 49, and 50, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dPhe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 488);

Ac-Nle-c[Asp-dBip-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 490); and

Ac-Nle-c[Asp-dTrp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 494),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0509] 52. The non-naturally occurring melanocortin analog of embodiment 40, wherein R^4 is dNal(2').

[0510] 53. The non-naturally occurring melanocortin analog of embodiment 40 or 52, wherein R^3 is selected from the group consisting of dPro, dTrp, and Ioc.

[0511] 54. The non-naturally occurring melanocortin analog of any one of embodiments 40, 52, and 53, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dPro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 70);

Ac-Nle-c[Asp-dTrp-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 83); and Ac-Nle-c[Asp-Ioc-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 243),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0512] 55. The non-naturally occurring melanocortin analog of embodiment 40 or 52, wherein R^5 is selected from the group consisting of dLys, dArg, dOrn, Gly, Asp, dHis, dAsp, dGlu and Pro.

[0513] 56. The non-naturally occurring melanocortin analog of any one of embodiments 40, 52, and 55, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-dNal(2')-dLys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 88);

Ac-Nle-c[Asp-Pro-dNal(2')-dArg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 89);

Ac-Nle-c[Asp-Pro-dNal(2')-dOrn-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 91);

Ac-Nle-c[Asp-Pro-dNal(2')-Gly-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dNal(2')-Asp-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 95);

Ac-Nle-c[Asp-Pro-dNal(2')-dHis-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c[Asp-Pro-dNal(2')-dAla-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 98);

Ac-Nle-c[Asp-Pro-dNal(2')-dAsp-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c[Asp-Pro-dNal(2')-dGlu-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-His-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 246); and

Ac-Nle-c[Asp-Pro-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 249),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0514] 57. The non-naturally occurring melanocortin analog of embodiment 40 or 52, wherein R^6 is absent or selected from the group consisting of His, dHis, Ala, and dAla.

[0515] 58. The non-naturally occurring melanocortin analog of any one of embodiments 40, 52, and 57, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Lys]-dVal-dPro-NH2 (SEQ ID NO: 101);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-His-Lys]-dVal-dPro-NH2 (SEQ ID NO: 106);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Ala-Lys]-dVal-dPro-NH2 (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dHis-Lys]-dVal-dPro-NH2 (SEQ ID NO: 112); and

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dAla-Lys]-dVal-dPro-NH2 (SEQ ID NO: 113),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0516] 59. The non-naturally occurring melanocortin analog of embodiment 18, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^1 and R^8.

[0517] 60. The non-naturally occurring melanocortin analog of embodiment 59, wherein R^2 is Pro, R^3 is Glu, R^4 is dNal(2'), and R^7 is Gly.

[0518] 61. The non-naturally occurring melanocortin analog of embodiment 59 or 60, wherein the sequence of any one of Formulae (I)-(IE) is: Ac-Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 258), wherein c represents cyclization through R^1 and R^8 via a lactam bond.

[0519] 62. The non-naturally occurring melanocortin analog of any one of embodiments 1-61, wherein the non-naturally occurring melanocortin analog comprises any one of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

[0520] 63. The non-naturally occurring melanocortin analog of embodiment 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

[0521] 64. The non-naturally occurring melanocortin analog of embodiment 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342.

[0522] 65. The non-naturally occurring melanocortin analog of embodiment 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249.

[0523] 66. The non-naturally occurring melanocortin analog of embodiment 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289.

[0524] 67. The non-naturally occurring melanocortin analog of embodiment 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 188, 190, and 243.

[0525] 68. The non-naturally occurring melanocortin analog of any one of embodiments 1-67, wherein the non-naturally occurring melanocortin analog is present in a pharmaceutical composition.

[0526] 69. The non-naturally occurring melanocortin analog of embodiment 68, wherein the pharmaceutical composition comprises one or more pharmaceutically acceptable excipients and/or carriers.

[0527] 70. The non-naturally occurring melanocortin analog of embodiment 69, wherein the one or more pharmaceutically acceptable excipients and/or carriers of the pharmaceutical composition comprise water.

[0528] 71. The non-naturally occurring melanocortin analog of any one of embodiments 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg to about 20 mg/kg administered once a day for about 5

days to about 10 days; (ii) at a second dose of about 10 mg/kg to about 40 mg/kg administered once a day after administration of the first dose for about 5 days to about 10 days; (iii) at a third dose of about 5 mg/kg to about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days to about 10 days.

[0529] 72. The non-naturally occurring melanocortin analog of any one of embodiments 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 15 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 10 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

[0530] 73. The non-naturally occurring melanocortin analog of any one of embodiments 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 10 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 20 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 15 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

[0531] 74. The non-naturally occurring melanocortin analog of any one of embodiments 1-70 wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 15 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 25 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 20 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

[0532] 75. The non-naturally occurring melanocortin analog of any one of embodiments 1-70, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.5 mg/kg to about 10 mg/kg per body weight of the subject once daily.

[0533] 76. The non-naturally occurring melanocortin analog of embodiment 75, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 1 mg/kg or 3 mg/kg per body weight of the subject once daily.

[0534] 77. The non-naturally occurring melanocortin analog of any one of embodiments 1-70, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

[0535] 78. The non-naturally occurring melanocortin analog of any one of embodiments 1-70, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

[0536] 79. The non-naturally occurring melanocortin analog of any one of embodiments 1-78, wherein the non-naturally occurring melanocortin analog is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

[0537] 80. The non-naturally occurring melanocortin analog of any one of embodiments 1-79, wherein the non-naturally occurring melanocortin analog crosses a blood-brain-barrier of a subject.

[0538] 81. The method or the use of any one of embodiments 79 or 80, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[0539] 82. The non-naturally occurring melanocortin analog of embodiment 81, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

[0540] 83. The non-naturally occurring melanocortin analog of any one of embodiments 1-70, wherein the non-naturally occurring melanocortin analog is administered to a subject for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years.

[0541] 84. The non-naturally occurring melanocortin analog of any one of embodiments 1-82, wherein the non-naturally occurring melanocortin analog is administered to a subject for 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days.

[0542] 85. The non-naturally occurring melanocortin analog of any one of embodiments 1-84, wherein the non-naturally occurring melanocortin analog elicits a reduction, prevention, or amelioration in a melanocortin system disease, disorder, or condition, or a symptom thereof.

[0543] 86. The non-naturally occurring melanocortin analog of embodiment 85, wherein the melanocortin system disease, disorder, or condition, or the symptom thereof is selected from the group consisting of cachexia, lethargy, appetite, sleep, arousal, libido, locomotion, cardiovascular anomalies, vasodilatation, hypertension, hypotension, sodium regulation, pain, pain perception, homeostasis, endocrine and exocrine gland secretion, inflammation, addictive behavior, increasing endogenous opioid activity, obesity, anorexia, and sexual dysfunction.

CLAIMS

I/We claim:

1. A non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

$$X^1\text{-}X^2\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3 \text{ (I)},$$

wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is absent or is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, Trp, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), indoline-2-carboxylic acid (Ioc), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of Trp, Nle and dVal;

Y^2 is absent or is selected from the group consisting of Nle, dVal, and dPro;

Y^3 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that:

when R^4 is p(I)dPhe, then the non-naturally occurring melanocortin analog is cyclized between R^1 and R^7;

when R^4 is p(F)dPhe and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, dGln, or Trp;

when R^4 is p(Cl)dPhe, and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, dPhe, or Trp;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then (i) R^5 and R^6 are absent or (ii) R^3 is absent and R^2 is not Cys; when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then R^3 is selected from dIle, dVal, and dAla, R^5 is Pro, or R^6 is Nal(1');

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then (i) R^2 is Trp, and (a) R^3 is dVal or dLeu, (b) R^5 is His, or (c) R^6 is dNal(1'), Phe, or dPhe, or (ii) R^2 is Pro and R^3 is Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7 and R^3 is not Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dPro, dTrp, His, and Ioc, or (ii) R^3 is Pro and either R^5 is selected from dLys, dArg, dOrn, Gly, Asp, dHis, dAla, dAsp, dGlu, and Pro or R^6 is absent selected from His, dHis, Ala, and dAla; and

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then one or both of R^5 and R^6 is absent.

2. The non-naturally occurring melanocortin analog of claim 1, wherein:

X^2 is absent or D-proline (dPro);

R^1 is absent or is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, Trp, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), indoline-2-carboxylic acid (Ioc), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of Trp, Nle and dVal;

Y^2 is absent or is selected from the group consisting of Nle, dVal, and dPro;

Y^3 is absent or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac—Nle-c[Asp-Pro-p(I)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 216);

Ac—Nle-c[Asp-His-p(I)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 221);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 223);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 460);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 464);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 465);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 469);

Ac—Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 470);

Ac—Nle-c[Cys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 459);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 461);

Ac—Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 218);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 433);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 434);

Ac—dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 436);

Ac—Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 437);

Ac—Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 438);

Ac—Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 442);

Ac—Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 443);

Ac—Nle-c[Asp-dGln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 492);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 463);

Ac—Nle-c[Cys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 432);

Ac—Nle-c[Asp-Trp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 493);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 499);

Ac—dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 501);

Ac—Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 502);

Ac—Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 503);

Ac—Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 215);

Ac—Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 220);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 498);

Ac—Nle-c[Cys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 497);

Ac—Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 508);

Ac—Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 507);

Ac—Nle-c[Asp-Trp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 531);

Ac—Nle-c[Asp-dPhe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 526);

Ac—Nle-c[Cys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 318);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 319);

Ac—Nle-c[dPen-Pro-dPhe-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 320);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 321);

Ac—Nle-c[Cys-dPhe-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 324);

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 363);

Ac—dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 302);

Ac—Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 311);

Ac—Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 313);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 295);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 351);

Ac—Nle-c[Asp-dBip-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 369);

Ac—Nle-c[Asp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 354);

Ac—Nle-c[Asp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 355);

Ac—Nle-c[Asp-Ioc-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 361);

Ac—Nle-c[Asp-dPhe-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 367);

Ac—Nle-c[Asp-dGln-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 371);

Ac—Nle-c[Asp-Trp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 372);

Ac—Nle-c[Asp-dTrp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 373);

Ac—Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 425);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 429);

Ac—Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 628);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-Trp—NH2 (SEQ ID NO: 600);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 595);

Ac—Nle-c[Asp-Trp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 394);

Ac—Nle-c[Asp-Trp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 395);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Nal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 399);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 226);

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 297);

Ac—Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 413);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 40);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 41);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 42);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 43);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 48);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 49);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 50);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 51);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 52);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 53);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 54);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 55);

Ac—dArg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 329);

Ac—Arg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 330);

Ac—Lys-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 337);

Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59);

Ac—Nle-c[Asp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 68);

Ac—Nle-c[Asp-Ala-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 69);

Ac—Nle-c[Asp-dAla-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 71);

Ac—Nle-c[Asp-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 75);

Ac—Nle-c[Asp-Leu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 76);

Ac—Nle-c[Asp-dLeu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 79);

Ac—Nle-c[Asp-dIle-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 80);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3);

Ac—dArg-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 15);

Ac—dVal-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 19);

Ac—dPro-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 27);

Ac—Nle-c[Asp-Trp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 82);

Ac—Nle-c[Asp-Pro-dNal(2')-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 86);

Ac—Nle-c[Asp-Pro-dNal(2')-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 92);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 104);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dNal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 108);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dPhe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 109);

Ac—Nle-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 184);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal—NH2 (SEQ ID NO: 128);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 255);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 256);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 259);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 179);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal—NH2 (SEQ ID NO: 126);

Ac—Nle-c[Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 73);

Ac—Nle-c[Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 74);

Ac—Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 257);

Ac—Nle-c[Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 194);

Ac—Nle-c[Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 195); and

Ac—Nle-c[Asp-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 5).

3. The non-naturally occurring melanocortin analog of claim 1 or 2, comprising a sequence according to Formula (IA):

$$X^1\text{-}X^2\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2 \text{ (IA)},$$

wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), alanine (Ala), D-alanine

(dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), and 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that:

when R^4 is p(F)dPhe and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, or dGln;

when R^4 is p(Cl)dPhe, and the non-naturally occurring melanocortin analog is cyclized between R^2 and R^7, then R^3 is not Pro, His, or dPhe;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then (i) R^5 and R^6 are absent or (ii) R^3 is absent and R^2 is not Cys;

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dIle, dVal, and dAla, (ii) R^5 is Pro, or (iii) R^6 is Nal(1');

when R^4 is dPhe and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then (i) R^2 is Trp, and (a) R^3 is dVal or dLeu, (b) R^5 is His, or (c) R^6 is dNal(1'), Phe, or dPhe, or (ii) R^2 is Pro and R^3 is Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a disulfide bond, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7 and R^3 is not Pro;

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^2 and R^7 or R^8, then (i) R^3 is selected from dPro, dTrp, His, and Ioc, , or (ii) R^3 is Pro and either R^5 is selected from dLys, dArg, dOrn, Gly, Asp, dHis, dAla, dAsp, dGlu, and Pro or R^6 is absent or selected from His, dHis, Ala, and dAla; and

when R^4 is dNal(2') and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between R^1 and R^7, then one or both of R^5 and R^6 is absent.

4. The non-naturally occurring melanocortin analog of claim 1 or 2, comprising a sequence according to Formula (IA), wherein:

X^1 is absent, norleucine (Nle), or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is selected from the group consisting of Nle, arginine (Arg), D-arginine (dArg), aspartic acid (Asp), lysine (Lys), and D-penicillamine (dPen);

R^2 is selected from the group consisting of Asp, Arg, tryptophan (Trp), proline (Pro), histidine (His), glycine (Gly), penicillamine (Pen), dPen, cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of His, Pro, dPro, Arg, dVal, Gly, D-tryptophan (dTrp), tryptyl-arginine (Trp-Arg), glutamic acid (Glu), alanine (Ala), D-alanine (dAla), leucine (Leu), D-leucine (dLeu), D-isoleucine (dIle), D-phenylalanine (dPhe), D-glutamine (dGln), and D-biphenylalanine (dBip);

R^4 is selected from the group consisting of dPhe, dBip, biphenylalanine (Bip), and 2'-D-naphthylalanine (dNal(2')), para-chloro-D-phenylalanine (p(Cl)dPhe), and para-fluoro-D-phenylalanine (p(F)dPhe);

R^5 is absent or is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), His, D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, dAla, phenylalanine (Phe), dPhe, 1'-D-naphthylalanine (dNal(1')), tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is selected from the group consisting of Gly, Asp, Lys, Cys, dCys, Pen, dPen;

R^8 is absent or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 when each of R^1 or R^2 and R^7 are independently selected from the group consisting of Cys, dCys, Pen, and dPen;

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 223);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 460);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 464);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 465);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 469);

Ac—Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 470);

Ac—Nle-c[Cys-His-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 459);

Ac—Nle-c[dCys-His-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 461);

Ac—Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 218);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 433);

Ac—Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 434);

Ac—dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 436);

Ac—Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 437);

Ac—Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 438);

Ac—Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 442);

Ac—Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 443);

Ac—Nle-c[Asp-dGln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 492);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 463);

Ac—Nle-c[Cys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 432);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 499);

Ac—dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 501);

Ac—Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 502);

Ac—Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 503);

Ac—Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 215);

Ac—Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 220);

Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 498);

Ac—Nle-c[Cys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 497);

Ac—Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 508);

Ac—Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 507);

Ac—Nle-c[Asp-dPhe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 526);

Ac—Nle-c[Cys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 318);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 319);

Ac—Nle-c[dPen-Pro-dPhe-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 320);

Ac—Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 321);

Ac—Nle-c[Cys-dPhe-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 324);

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 363);

Ac—dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 302);

Ac—Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 311);

Ac—Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 313);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 291);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 295);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 351);

Ac—Nle-c[Asp-dBip-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 369);

Ac—Nle-c[Asp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 354);

Ac—Nle-c[Asp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 355);

Ac—Nle-c[Asp-dPhe-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 367);

Ac—Nle-c[Asp-dGln-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 371);

Ac—Nle-c[Asp-dTrp-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 373);

Ac—Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 425);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 429);

Ac—Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 628);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-Trp—NH2 (SEQ ID NO: 600);

Ac—Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 595);

Ac—Nle-c[Asp-Trp-Ala-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 394);

Ac—Nle-c[Asp-Trp-Leu-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 395);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Nal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 399);

Ac—Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 226);

Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 297);

Ac—Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 413);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 40);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 41);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 42);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 43);

Ac—Nle-c[Cys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 48);

Ac—Nle-c[dCys-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 49);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 50);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 51);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 52);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-Pen]-dVal-dPro—NH2 (SEQ ID NO: 53);

Ac—Nle-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 54);

Ac—Nle-c[Pen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 55);

Ac—dArg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 329);

Ac—Arg-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 330);

Ac—Lys-c[dPen-Pro-dNal(2')-Arg-Trp-dPen]-dVal-dPro—NH2 (SEQ ID NO: 337);

Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59);

Ac—Nle-c[Asp-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 68);

Ac—Nle-c[Asp-Ala-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 69);

Ac—Nle-c[Asp-dAla-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 71);

Ac—Nle-c[Asp-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 75);

Ac—Nle-c[Asp-Leu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 76);

Ac—Nle-c[Asp-dLeu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 79);

Ac—Nle-c[Asp-dIle-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 80);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3);

Ac—dArg-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 15);

Ac—Nle-c[Asp-Pro-dNal(2')-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 86);

Ac—Nle-c[Asp-Pro-dNal(2')-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 92);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Phe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 104);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dNal(1')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 108);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-dPhe-Lys]-dVal-dPro—NH2 (SEQ ID NO: 109);

Ac—Nle-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 184);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal—NH2 (SEQ ID NO: 128);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 255);

Ac—Nle-c[Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 256);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro—NH2 (SEQ ID NO: 259);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal-dPro—NH2 (SEQ ID NO: 179);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dVal—NH2 (SEQ ID NO: 126);

Ac—Nle-c[Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 73);

Ac—Nle-c[Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 74);

Ac—Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 257);

Ac—Nle-c[Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 194);

Ac—Nle-c[Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 195); and

Ac—Nle-c[Asp-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 5).

5. The non-naturally occurring melanocortin analog of claim 1 or 2, comprising a sequence according to Formula (IB):

$$R^1\text{-}R^2\text{-}R^3\text{-dNal(2')-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IB)},$$

wherein:

R^1 is norleucine (Nle);

R^2 is selected from the group consisting of penicillamine (Pen), D-penicillamine (dPen), cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly

R^5 is Arg;

R^6 is Trp;

R^7 is selected from the group consisting of Cys, dCys, Pen, dPen;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R^2 and R^7 when R^2 and R^7 are each independently selected from the group consisting of Cys, dCys, Pen, and dPen,

provided that:

when R^3 is absent, then the disulfide bond is not formed between Pen at R^2 and dCys at R^7.

6. The non-naturally occurring melanocortin analog of claim 1 or 2, comprising a sequence of Formula (IB), wherein:

R^1 is norleucine (Nle);

R^2 is selected from the group consisting of penicillamine (Pen), D-penicillamine (dPen), cysteine (Cys), and D-cysteine (dCys);

R^3 is absent or is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly

R^5 is Arg;

R^6 is Trp;

R^7 is selected from the group consisting of Cys, dCys, Pen, dPen;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between R^2 and R^7 when R^2 and R^7 are each independently selected from the group consisting of Cys, dCys, Pen, and dPen,

provided that the non-naturally occurring melanocortin analog does not comprise a sequence of: Ac—Nle-c[Pen-dNal(2')-Arg-Trp-dCys]-dVal-dPro—NH2 (SEQ ID NO: 59).

7. The non-naturally occurring melanocortin analog of claim 1 or 2, comprising a sequence of Formula (IC):

$$R^1\text{-Asp-}R^3\text{-dNal(2')-}R^5\text{-}R^6\text{-Lys-}Y^1\text{-}Y^2 \text{ (IC)},$$

wherein:

R^1 is norleucine (Nle);

R^3 is selected from the group consisting of histidine (His), proline (Pro), D-proline (dPro), D-tryptophan (dTrp), and indoline-2-carboxylic acid (Ioc);

R^5 is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, and dAla;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^7;

provided that:

when R^3 is Pro, then either R^5 is not Arg or R^6 is not Trp.

8. The non-naturally occurring melanocortin analog of claim 1 or 2, comprising a sequence of Formula (IC), wherein:

R^1 is norleucine (Nle);

R^3 is selected from the group consisting of histidine (His), proline (Pro), D-proline (dPro), D-tryptophan (dTrp), and indoline-2-carboxylic acid (Ioc);

R^5 is selected from the group consisting of Arg, dArg, Pro, Gly, dAla, Asp, D-aspartic acid (dAsp), D-histidine (dHis), D-glutamic acid (dGlu), D-lysine (dLys), and D-ornithine (dOrn);

R^6 is absent or is selected from the group consisting of Trp, His, dHis, Ala, and dAla;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^7;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:
Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro (SEQ ID NO: 2);

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3); and

Ac—Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 116).

9. The non-naturally occurring melanocortin analog of claim 1 or 2, comprising a sequence of Formula (ID):

X^1-X^2-R^1-R^2-Arg-R^4-R^5-R^6-R^7-Y^1-Y^2 (ID),

wherein:

X^1 is norleucine (Nle) or D-valine (dVal);

X^2 is absent or D-proline (dPro);

R^1 is aspartic acid (Asp) or lysine (Lys);

R^2 is selected from the group consisting of tryptophan (Trp), proline (Pro), and histidine (His);

R^4 is selected from the group consisting of D-biphenylalanine (dBip), 2'-D-naphthylalanine (dNal(2')), and para-iodo-D-phenylalanine (p(I)dPhe);

R^5 is arginine (Arg) or Pro;

R^6 is absent or tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^7 is Asp or Lys;

Y^1 is Nle or dVal;

Y^2 is absent, Nle, or dPro; and

the non-naturally occurring melanocortin analog is cyclized through a moiety selected from the group consisting of:

a lactam bridge between R^1 and R^7 when R^1 is Asp and R^7 is Lys; and

a lactam bridge between R^1 and R^7 when R^1 is Lys and R^7 is Asp.

10. The non-naturally occurring melanocortin analog of claim 1 or 2, comprising a sequence of Formula (IE):

X^1-R^1-R^2-R^3-R^4-Arg-R^6-Lys-Y^1-Y^2 (IE),

wherein:

X^1 is absent or norleucine (Nle);

R^1 is Nle or aspartic acid (Asp);

R^2 is selected from the group consisting of Asp, histidine (His), and proline (Pro);

R^3 is arginine (Arg) or indoline-2-carboxylic acid (Ioc);

R^4 is 2'-D-naphthylalanine (dNal(2')) or para-iodo-D-phenylalanine (p(I)dPhe);

R^6 is Trp or tetrahydro-isoquinoline-3-carboxylic acid (Tic);

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bond between the Asp at R^1 or R^2 and the Lys at R^7.

11. The non-naturally occurring melanocortin analog of any one of claims 1-10, wherein the N-terminus of the non-naturally occurring melanocortin analog is modified by an acyl group.

12. The non-naturally occurring melanocortin analog of claim 11, wherein the acyl group is an acetyl group.

13. The non-naturally occurring melanocortin analog of any one of claims 1-10, wherein the N-terminus of the non-naturally occurring melanocortin analog is not modified.

14. The non-naturally occurring melanocortin analog of any one of claims 1-13, wherein the C-terminus of the non-naturally occurring melanocortin analog is modified by an amide group.

15. The non-naturally occurring melanocortin analog of any one of claims 1-13, wherein the C-terminus of the non-naturally occurring melanocortin analog is not modified.

16. The non-naturally occurring melanocortin analog of any one of claims 1-15, wherein Y^1-Y^2 are present and Y^3 is absent.

17. The non-naturally occurring melanocortin analog of any one of claims 1-16, wherein Y^1 is D-valine and Y^2 is D-proline.

18. The non-naturally occurring melanocortin analog of any one of claims 1-17, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond.

19. The non-naturally occurring melanocortin analog of any one of claims 1-18, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a disulfide bond between R^1 or R^2 and R^7.

20. The non-naturally occurring melanocortin analog of any one of claims 1-19, wherein R^4 is dNal(2').

21. The non-naturally occurring melanocortin analog of any one of claims 1-20, wherein R^3 is absent.

22. The non-naturally occurring melanocortin analog of any one of claims 1-21, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 44);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 45);

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 46);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 47);

Ac-Nle-c[Cys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-Nle-c[dCys-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 60);

Ac-Nle-c[dPen-dNal(2')-Arg-Trp-Pen]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[dPen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 62); and

Ac-Nle-c[Pen-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 63),

wherein c represents cyclization through R^2 and R^7 via a disulfide bond.

23. The non-naturally occurring melanocortin analog of any one of claims 1-20, wherein R^3 is present and is selected from the group consisting of Ala, Leu, dLeu, dVal, and Gly.

24. The non-naturally occurring melanocortin analog of any one of claims 1-23, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[dPen-Ala-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 338);

Ac-Nle-c[dPen-Leu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 339);

Ac-Nle-c[dPen-dLeu-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 340);

Ac-Nle-c[dPen-dVal-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 341);

Ac-Nle-c[dPen-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 342); and

Ac-Nle-c[dPen-Gly-Gly-dNal(2')-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 343),

wherein c represents cyclization through R^1 or R^2 and R^7 via a disulfide bond.

25. The non-naturally occurring melanocortin analog of any one of claims 1-19, wherein R^4 is dPhe.

26. The non-naturally occurring melanocortin analog of any one of claims 1-25, wherein at least one of R^1, R^3 , R^5, and R^6 is absent.

27. The non-naturally occurring melanocortin analog of any one of claims 1-26, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-c[Cys-Arg-dPhe-Cys]-Trp-dVal-dPro-NH_2 (SEQ ID NO: 202);

Ac-Nle-c[Pen-dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 325); and

Ac-Nle-c[dPen-dPhe-Arg-Trp-dPen]-dVal-dPro-NH_2 (SEQ ID NO: 326),

wherein c represents cyclization through R^2 and R^7 via a disulfide bond.

28. The non-naturally occurring melanocortin analog of any one of claims 1-17, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond.

29. The non-naturally occurring melanocortin analog of claim 18, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^1 and R^7.

30. The non-naturally occurring melanocortin analog of claim 28 or 29, wherein R^4 is dBip or p(I)dPhe.

31. The non-naturally occurring melanocortin analog of any one of claims 28-30, wherein one of R^2 and R^3 is Arg.

32. The non-naturally occurring melanocortin analog of any one of claims 28-31, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 188);

Ac-Nle-c[Asp-His-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 189);
Ac-Nle-c[Asp-Pro-Arg-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 190);
Ac-Nle-c[Asp-Pro-Arg-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 191);
Ac-Nle-c[Asp-Arg-Pro-p(I)dPhe-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 192); and
Ac-Nle-c[Asp-Arg-Pro-dBip-Arg-Tic-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 193),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

33. The non-naturally occurring melanocortin analog of claim 28 or 29, wherein R^4 is dPhe.

34. The non-naturally occurring melanocortin analog of claim 33, wherein R^2 is Trp and/or R^3 is Pro.

35. The non-naturally occurring melanocortin analog of claim 33 or 34, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:
Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 225);

Ac-Nle-c[Asp-Trp-dLeu-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 396);

Ac-Nle-c[Asp-Trp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 397);

Ac-Nle-c[Asp-Trp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 398);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 400);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-Phe-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 401); and

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-dPhe-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 402),
wherein c represents cyclization through R^1 and R^7 via a lactam bond.

36. The non-naturally occurring melanocortin analog of claim 28 or 29, wherein R^4 is dNal(2').

37. The non-naturally occurring melanocortin analog of claim 36, wherein (i) R^2 is Pro and R^3 is Trp or Trp-Arg or (ii) R^2 is Trp and R^3 is Arg.

38. The non-naturally occurring melanocortin analog of claim 36 or 37, wherein (i) R^5 is Pro or absent.

39. The non-naturally occurring melanocortin analog of any one of claims 36-38, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 276);

Ac-Nle-c[Asp-Pro-Trp-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 277);

Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 278);

Ac-Nle-c[Asp-Pro-Trp-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 279);

Ac-Nle-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-dVal-dPro-NH_2 (SEQ ID NO: 280);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-NH_2 (SEQ ID NO: 284);

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-Nle-NH_2 (SEQ ID NO: 285);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-Nle-Nle-NH_2 (SEQ ID NO: 286);

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-Nle-Nle-NH_2 (SEQ ID NO: 287);

Ac-dVal-dPro-c[Asp-Trp-Arg-dNal(2')-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 288); and

Ac-dVal-dPro-c[Lys-Trp-Arg-dNal(2')-Pro-Asp]-dVal-dPro-NH_2 (SEQ ID NO: 289),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

40. The non-naturally occurring melanocortin analog of claim 18, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^2 and R^7.

41. The non-naturally occurring melanocortin analog of claim 40, wherein R^4 is Bip.

42. The non-naturally occurring melanocortin analog of claim 40 or 41, wherein the sequence of any one of Formulae (I)-(IE) is: Ac-Nle-c[Asp-Pro-Bip-Arg-Trp-Lys]-dVal-

dPro-NH_2 (SEQ ID NO: 114), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

43. The non-naturally occurring melanocortin analog of claim 40, wherein R^4 is dPhe.

44. The non-naturally occurring melanocortin analog of claim 40 or 43, wherein R^3 is not Pro, R^5 is not Arg, and/or R^6 is not Trp.

45. The non-naturally occurring melanocortin analog of any one of claims 40, 43, and 44, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dIle-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 356);

Ac-Nle-c[Asp-dVal-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 357);

Ac-Arg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 376);

Ac-dArg-c[Asp-dAla-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 377);

Ac-Nle-c[Asp-His-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 227);

Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 230); and

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(1')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 428),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

46. The non-naturally occurring melanocortin analog of claim 40, wherein R^4 is p(Cl)dPhe.

47. The non-naturally occurring melanocortin analog of claim 40 or 43, wherein R^3 is selected from the group consisting of dBip, dGln, and dTrp.

48. The non-naturally occurring melanocortin analog of any one of claims 40, 46, and 47, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dBip-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 528);

Ac-Nle-c[Asp-dGln-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 530); and

Ac-Nle-c[Asp-dTrp-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 532),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

49. The non-naturally occurring melanocortin analog of claim 40, wherein R^4 is p(F)dPhe.

50. The non-naturally occurring melanocortin analog of claim 40 or 49, wherein R^3 is selected from the group consisting of dBip, dPhe, and dTrp.

51. The non-naturally occurring melanocortin analog of any one of claims 40, 49, and 50, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dPhe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 488);

Ac-Nle-c[Asp-dBip-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 490); and

Ac-Nle-c[Asp-dTrp-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 494),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

52. The non-naturally occurring melanocortin analog of claim 40, wherein R^4 is dNal(2').

53. The non-naturally occurring melanocortin analog of claim 40 or 52, wherein R^3 is selected from the group consisting of dPro, dTrp, and Ioc.

54. The non-naturally occurring melanocortin analog of any one of claims 40, 52, and 53, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-dPro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 70);

Ac-Nle-c[Asp-dTrp-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 83); and

Ac-Nle-c[Asp-Ioc-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 243),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

55. The non-naturally occurring melanocortin analog of claim 40 or 52, wherein R^5 is selected from the group consisting of dLys, dArg, dOrn, Gly, Asp, dHis, dAsp, dGlu and Pro.

56. The non-naturally occurring melanocortin analog of any one of claims 40, 52, and 55, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-dNal(2')-dLys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 88);

Ac-Nle-c[Asp-Pro-dNal(2')-dArg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 89);

Ac-Nle-c[Asp-Pro-dNal(2')-dOrn-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 91);

Ac-Nle-c[Asp-Pro-dNal(2')-Gly-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dNal(2')-Asp-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 95);

Ac-Nle-c[Asp-Pro-dNal(2')-dHis-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c[Asp-Pro-dNal(2')-dAla-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 98);

Ac-Nle-c[Asp-Pro-dNal(2')-dAsp-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c[Asp-Pro-dNal(2')-dGlu-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-His-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 246); and

Ac-Nle-c[Asp-Pro-dNal(2')-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 249),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

57. The non-naturally occurring melanocortin analog of claim 40 or 52, wherein R^6 is absent or selected from the group consisting of His, dHis, Ala, and dAla.

58. The non-naturally occurring melanocortin analog of any one of claims 40, 52, and 57, wherein the sequence of any one of Formulae (I)-(IE) is selected from the group consisting of:

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Lys]-dVal-dPro-NH2 (SEQ ID NO: 101);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-His-Lys]-dVal-dPro-NH2 (SEQ ID NO: 106);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Ala-Lys]-dVal-dPro-NH2 (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dHis-Lys]-dVal-dPro-NH2 (SEQ ID NO: 112); and

Ac-Nle-c[Asp-Pro-dNal(2')-Arg-dAla-Lys]-dVal-dPro-NH2 (SEQ ID NO: 113),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

59. The non-naturally occurring melanocortin analog of claim 18, wherein the sequence of any one of Formulae (I)-(IE) is cyclized through a lactam bond between R^1 and R^8.

60. The non-naturally occurring melanocortin analog of claim 59, wherein R^2 is Pro, R^3 is Glu, R^4 is dNal(2'), and R^7 is Gly.

61. The non-naturally occurring melanocortin analog of claim 59 or 60, wherein the sequence of any one of Formulae (I)-(IE) is: Ac-Nle-c[Asp-Pro-Glu-dNal(2')-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 258), wherein c represents cyclization through R^1 and R^8 via a lactam bond.

62. The non-naturally occurring melanocortin analog of any one of claims 1-61, wherein the non-naturally occurring melanocortin analog comprises any one of SEQ ID NOs:

44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

63. The non-naturally occurring melanocortin analog of claim 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-191, 193, 225, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532.

64. The non-naturally occurring melanocortin analog of claim 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44, 45, 46, 47, 56, 57, 58, 60, 61, 62, 63, 338, 339, 340, 341, and 342.

65. The non-naturally occurring melanocortin analog of claim 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 70, 83, 88, 89, 91, 94, 95, 97, 98, 99, 100, 101, 106, 107, 112, 113, 243, 246, and 249.

66. The non-naturally occurring melanocortin analog of claim 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 188, 189, 190, 191, 276, 280, 284, 285, 286, 287, 288, and 289.

67. The non-naturally occurring melanocortin analog of claim 62, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 188, 190, and 243.

68. The non-naturally occurring melanocortin analog of any one of claims 1-67, wherein the non-naturally occurring melanocortin analog is present in a pharmaceutical composition.

69. The non-naturally occurring melanocortin analog of claim 68, wherein the

pharmaceutical composition comprises one or more pharmaceutically acceptable excipients and/or carriers.

70. The non-naturally occurring melanocortin analog of claim 69, wherein the one or more pharmaceutically acceptable excipients and/or carriers of the pharmaceutical composition comprise water.

71. The non-naturally occurring melanocortin analog of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg to about 20 mg/kg administered once a day for about 5 days to about 10 days; (ii) at a second dose of about 10 mg/kg to about 40 mg/kg administered once a day after administration of the first dose for about 5 days to about 10 days; (iii) at a third dose of about 5 mg/kg to about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days to about 10 days.

72. The non-naturally occurring melanocortin analog of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 15 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 10 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

73. The non-naturally occurring melanocortin analog of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 10 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 20 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 15 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

74. The non-naturally occurring melanocortin analog of any one of claims 1-70 wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of

about 15 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 25 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 20 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

75. The non-naturally occurring melanocortin analog of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.5 mg/kg to about 10 mg/kg per body weight of the subject once daily.

76. The non-naturally occurring melanocortin analog of claim 75, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 1 mg/kg or 3 mg/kg per body weight of the subject once daily.

77. The non-naturally occurring melanocortin analog of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

78. The non-naturally occurring melanocortin analog of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

79. The non-naturally occurring melanocortin analog of any one of claims 1-78, wherein the non-naturally occurring melanocortin analog is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

80. The non-naturally occurring melanocortin analog of any one of claims 1-79, wherein the non-naturally occurring melanocortin analog crosses a blood-brain-barrier of a subject.

81. The method or the use of any one of claims 79 or 80, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

82. The non-naturally occurring melanocortin analog of claim 81, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 44-47, 56-58, 60-63, 70, 83, 88-89, 91, 94-95, 97-101, 106-107, 112-114, 188-193, 202, 225, 227, 230, 243, 246, 249, 258, 276-280, 284-289, 325-326, 338-343, 356-357, 376-377, 396-398, 400-402, 428, 488, 490, 494, 528, 530, and 532 and is administered at least once daily in an amount ranging from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

83. The non-naturally occurring melanocortin analog of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered to a subject for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years.

84. The non-naturally occurring melanocortin analog of any one of claims 1-82, wherein the non-naturally occurring melanocortin analog is administered to a subject for 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days.

85. The non-naturally occurring melanocortin analog of any one of claims 1-84, wherein the non-naturally occurring melanocortin analog elicits a reduction, prevention, or amelioration in a melanocortin system disease, disorder, or condition, or a symptom thereof.

86. The non-naturally occurring melanocortin analog of claim 85, wherein the melanocortin system disease, disorder, or condition, or the symptom thereof is selected from the group consisting of cachexia, lethargy, appetite, sleep, arousal, libido, locomotion, cardiovascular anomalies, vasodilatation, hypertension, hypotension, sodium regulation,

pain, pain perception, homeostasis, endocrine and exocrine gland secretion, inflammation, addictive behavior, increasing endogenous opioid activity, obesity, anorexia, and sexual dysfunction.