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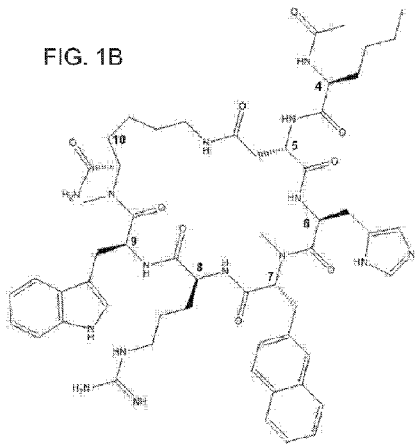
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(54) Title: COMPOSITIONS AND METHODS FOR TREATING CENTRAL NERVOUS SYSTEM (CNS) DISORDERS AND MOOD DISORDERS

FIG. 1B



(57) Abstract: Compositions and methods of treating a central nervous system (CNS) disorder or mood disorder in a subject in need of such treatment are described. A therapeutically effective amount of a composition comprising a melanocortsn 5 receptor (MC5R) peptide ligand in a pharmaceutically acceptable carrier is administered to the subject. The MCSR peptide ligand is a selective MCSR antagonist, in which administration thereof to the subject can treat the CNS disorder or mood disorder with clinical improvement ob - served in a relatively short time.

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COMPOSITIONS AND METHODS FOR TREATING CENTRAL NERVOUS SYSTEM (CNS) DISORDERS AND MOOD DISORDERS

CROSS REFERENCE

[0001] This application claims benefit of U.S. Patent Application No. 14/943,606 filed November 17, 2015, which is a non-provisional and claims benefit of U.S. Provisional Patent Application No. 62/242,874, filed October 16, 2015, the specification(s) of which is/are incorporated herein in their entirety by reference.

[0002] This application claims benefit of U.S. Patent Application No. 14/943,885 filed November 17, 2015, which is a non-provisional and claims benefit of U.S. Provisional Patent Application No. 62/242,907, filed October 16, 2015, the specification(s) of which is/are incorporated herein in their entirety by reference.

[0003] This application claims benefit of U.S. Patent Application No. 14/943,936 filed November 17, 2015, which is a non-provisional and claims benefit of U.S. Provisional Patent Application No. 62/242,850, filed October 16, 2015, the specification(s) of which is/are incorporated herein in their entirety by reference.

REFERENCE TO SEQUENCE LISTING

[0004] Applicant asserts that the information recorded in the form of an Annex C/ST.25 text file submitted under Rule 13*ter*.1(a), entitled UNIA_15_38_PCT_Sequence_Listing_ ST25, is identical to that forming part of the international application as filed. The content of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0005] The present invention relates to N-methylated variations of a cyclic peptide and analogues thereof that are modulators for MC5R.

[0006] The present invention relates to compositions and methods of treating central nervous system (CNS) disorders and mood disorders with selective melanocortin 5 receptor (MC5R) antagonists.

BACKGROUND OF THE INVENTION

[0007] Central nervous system (CNS) disorders are diseases that can affect the brain or spinal cord. The CNS disorders may be caused by trauma, infections, degeneration,

structural defects, tumors, blood flow disruption, autoimmunity, or strokes. There exists a wide range of treatments for these disorders, such as surgery, rehabilitation, and medications. Examples of CNS medications include analgesics, anticonvulsants, antipsychotics, sedatives, and tranquilizers. Despite their beneficial effects, CNS medications have the potential for developing tolerance, dependence, or addiction.

[0008] Mood disorders, such as depression and anxiety disorders, are some of the most common mental illnesses. Although the two are different, depression and anxiety can occur together and can have similar treatments. These disorders can be treated through psychotherapy and medications, such as anti-depressants. Unfortunately, current medications may take weeks to months to achieve their full effects and in the meantime, patients continue to suffer from their symptoms and continue to be at risk. Moreover, side effects from these medications can range from unpleasant to life-threatening; for instance, there can be an increased risk of suicide, hostility, and even homicidal behavior. Pharmacological treatments that have a rapid onset of antidepressant or anti-anxiety effects within hours or a few days and that are sustained are therefore desired.

[0009] Hence, there remains a need for improved treatments of CNS disorders, mood disorders, and/or other related diseases that provide increased efficacy and reduces or eliminates any potential side effects.

[0010] Melanocortin receptors, MC1-5R are a family of five receptor compounds of the melanocortin receptor system. Prior to the invention, it has been difficult to target the receptors independently of one another. The key difference between the present invention and similar compounds is that the present invention is specific to individual types of melanocortin receptors, specifically to MC5R. An N-methylated form of a cyclic peptide, Ac-Nle^4-c[Asp^5, D-Nal(2')^7, Lys^{10}]α-MSH(4-10)-NH_2 (SHU9119) and analogues thereof can antagonize MC5R. This could potentially reduce the side effects incurred by treatments using these MC5R peptide ligands.

[0011] Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art. Additional advantages and aspects of the present invention are apparent in the following detailed

description and claims.

SUMMARY OF THE INVENTION

[0012] According to one embodiment, the subject disclosure relates to compositions for use and methods of treating a central nervous system (CNS) disorder or a mood disorder. The composition may comprise a melanocortin 5 receptor (MC5R) peptide ligand in a pharmaceutically acceptable carrier. The composition is administered in a subject in need of such treatment. In one embodiment, the MC5R peptide ligand is according to Formula 1:

$$R_1\text{-Nle}^4\text{-c[Xaa}^5\text{-Yaa}^6\text{-}(NMe)\text{D-Nal(2')}^7\text{-Arg}^8\text{-Trp}^9\text{-}(NMe)\text{Zaa}^{10}\text{]-}R_2 \qquad \text{(SEQ NO. 1)}$$

[0013] In some embodiments, R_1 may be an acetyl, a glycosylated amino acid, –CO-$(CH_2)_nCH_3$, or –CO-$(CH_2)_nCF_3$, wherein n ranges from 1 to 6. In other embodiments, R_2 may be an amide (e.g. $–CONH_2$), –COOH, or $–CH_2OH$. In preferred embodiments, Xaa is a natural amino acid or an unnatural amino acid, Yaa is a natural amino acid or an unnatural amino acid, and Zaa is a natural amino acid or an unnatural amino acid. According to one embodiment, the MC5R peptide ligand is an antagonist of MC5R.

[0014] The MC5R may be present in the central nervous system (CNS), but its function in this location is not completely understood. Without wishing to limit the invention to a particular theory or mechanism, since the MC5R peptide ligand is a selective MC5R antagonist, then the MC5R peptide ligand may be potentially therapeutic for treating the CNS disorder or mood disorder. None of the presently known prior references or work has the unique inventive technical feature of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The features and advantages of the present invention will become apparent from a consideration of the following detailed description presented in connection with the accompanying drawings in which:

[0016] FIG. 1A shows a structure of SHU 9119. The two arrows indicate the sites of N-methylation of the backbone NHs to form one embodiment of a MC5R modulator.

[0017] FIG. 1B shows a non-limiting example of a structure of an analogue that has been *N*-methylated at the sites shown in FIG. 1A.

DESCRIPTION OF PREFERRED EMBODIMENTS

[0018] Before the present compounds, compositions, and/or methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods or to specific compositions, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[0019] Following is a list of abbreviations referred to herein:

[0020] Abu 2-aminobutyric acid

[0021] Acpc 1-aminocyclopropane carboxylic acid

[0022] Aic 2-aminoindane-2-carboxylic acid

[0023] Che 1-amino-1-cyclohexane carboxylic acid

[0024] Cpe 1-amino-1-cyclopentane carboxylic acid

[0025] Dab diaminobutyric acid

[0026] Ioc indoline-2-carboxylic acid

[0027] Nle norleucine

[0028] Oic octahydroindole-2-carboxylic acid

[0029] Orn ornithine

[0030] Tic tetrahydro-isoquinoline-3-carboxylic Acid

[0031] As used herein, the term “natural amino acids” refers to the twenty amino acids that are found in nature, i.e. occur naturally. The natural amino acids are as follows: alanine, arginine, glycine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, serine, threonine, histidine, lysine, methionine, proline, valine, isoleucine, leucine, tyrosine, tryptophan, and phenylalanine. This application adheres to the IUPAC rules of standard abbreviations for amino acids.

[0032] As used herein, the term “unnatural amino acids” refers to amino acids that are not naturally encoded or found in the genetic code of any organisms. Typically, the unnatural amino acids are different from the twenty naturally occurring amino acids in their side chain functionality.

[0033] As defined herein, the term “antagonist” refers to compound that diminishes a response. The antagonist binds to the same site as the endogenous compound and diminishes or blocks the signal generated by the endogenous agent.

[0034] As defined herein, the term "N-methylation" refers to a form of alkylation wherein a methyl group, CH_3, replaces the hydrogen atom of the NH moiety in the backbone amide NHs of peptides. As used herein, the term "*NMe*" preceding any three-letter abbreviation for an amino acid, i.e. (*NMe*)Lys, denotes the N-methylated form of the amino acid. As used herein, the term "c" or "cyclo" means cyclic, i.e. a cyclic peptide.

[0035] As used herein, "glycosylated" is defined as a saccharide (or sugar) covalently attached, i.e. linked, to an amino acid. Specifically, the saccharide is linked to the side-chain of the amino acid. In one aspect, the glycosylated amino acid may comprise a saccharide O-linked to a natural amino acid. For instance, the saccharide is attached to the hydroxyl group of the side-chain of the amino acid, such as Ser, Thr, or Tyr. Examples of glycosylated peptides include, but are not limited to, glucosylated Serine, glucosylated Threonine, and lactosylated Serine. In another aspect, the glycosylated amino acid may comprise a saccharide N-linked to a natural amino. For example, the saccharide is attached to the amine group of the side-chain of the amino acid, such as Asn or Lys. In some embodiments, the saccharide may be a mono-, di-, tri- and poly-saccharides. Examples of saccharides include, but are not limited to, glucose, fructose, galactose, cellobiose, and lactose. Without wishing to limit the invention to a particular theory or mechanism, glycosylation may increase the ability of the peptide to cross a blood brain barrier (BBB) as compared to a peptide lacking the glycosylation.

[0036] As used herein, "clinical improvement" may refer to a noticeable reduction or cessation of the symptoms of a disorder. The term "antidepressant effect" is used in the conventional sense. It is associated with a reversal of or a reduction in the severity of a depressed mood or state of mind. The term "anxiolytic effect" is used in the conventional sense. It is associated with an inhibition, a reversal of, a reduction in the severity of symptoms of anxiety.

[0037] The term "psychostimulating effect", as the term implies, is associated in an increase or improvement in the overall level of mental activity. It is related to patients exhibiting nervous behavior, or having unpleasant feelings of dread, or lacking energy, drive and desire, or lacking concentration and memory. Common psychostimulating effects may include, but are not limited to, enhanced alertness, awareness, wakefulness, endurance, productivity, motivation, increased arousal, and locomotion

(i.e. movement or increased energy). The psychostimulants may also be capable of improving mood and relieving anxiety, and can even induce feelings of euphoria.

[0038] Referring now to FIG. 1A and 1B, the present invention features a composition for use in treating a central nervous system (CNS) disorder or a mood disorder. The composition may comprise a melanocortin 5 receptor (MC5R) peptide ligand in a pharmaceutically acceptable carrier. In one embodiment, the MC5R peptide ligand is according to Formula 1:

R_1-Nle^4-c[Xaa^5-Yaa^6-(NMe)D-Nal(2')^7-Arg^8-Trp^9-(NMe)Zaa^{10}]-R_2 (SEQ NO. 1)

[0039] In some embodiments, R_1 may be an acetyl, a glycosylated amino acid,–CO-$(CH_2)_nCH_3$, or –CO-$(CH_2)_nCF_3$, wherein n ranges from 1 to 6. In other embodiments, R_2 may be an amide (e.g. $–CONH_2$), –COOH, or $–CH_2OH$. In preferred embodiments, Xaa is a natural amino acid or an unnatural amino acid, Yaa is a natural amino acid or an unnatural amino acid, and Zaa is a natural amino acid or an unnatural amino acid. According to one embodiment, the MC5R peptide ligand is an antagonist of MC5R.

[0040] In one embodiment, Xaa may be Asp, Glu or 2-aminobutyric acid. In another embodiment, Yaa may be selected from a group consisting of His, Pro, octahydroindole-2-carboxylic acid, indoline-2-carboxylic acid, tetrahydro-isoquinoline-3-carboxylic acid, 1-amino-1-cyclohexane carboxylic acid, 1-amino-1-cyclopentane carboxylic acid, 2-aminoindane-2-carboxylic acid, and 1-aminocyclopropane carboxylic acid. In yet another embodiment, Zaa may be Lys, ornithine or diaminobutyric acid.

[0041] For example, in one embodiment, the composition for use in treating a central nervous system (CNS) disorder or a mood disorder may comprise the following melanocortin 5 receptor (MC5R) peptide ligand:

Ac-Nle^4-c[Asp^5-His^6-(NMe)D-Nal(2')^7-Arg^8-Trp^9-(NMe)Lys^{10}]-NH_2 (SEQ NO. 9)

in a pharmaceutically acceptable carrier. As used herein, one of ordinary skill in the art will understand that the use of "NH_2" in a sequence refers to $–CONH_2$.

[0042] In some embodiments, the glycosylated amino acid may comprise a saccharide linked to a natural amino acid, such as Ser, Thr, Tyr, Asn or Gln. The saccharide may be a monosaccharide, a disaccharide, or an oligosaccharide. For example, the saccharide may be glucose, fructose, or lactose. In one embodiment, the glycosylated

amino acid may comprise a saccharide O-linked to a natural amino acid, such as Ser, Thr, or Tyr. In another embodiment, the glycosylated amino acid may comprise a saccharide N-linked to a natural amino acid, such Asn or Lys.

[0043] In preferred embodiments, Xaa may be linked to Zaa via a carba, lactam, disulfide, thioether, or succinic linker, thereby forming a cyclic peptide. In some embodiments, the MC5R peptide ligand may comprise a 23- to 27-membered ring.

[0044] In a preferred embodiment, the composition for use is administered to a subject who has been diagnosed with the CNS disorder or mood disorder. In some embodiments, the disorder is a CNS disorder. In other embodiments, the disorder is a mood disorder, such as a depressive disorder or an anxiety disorder. In further embodiments, the disorder may be a combination of CNS and mood disorders. For example, a mood disorder may arise from or be symptom of the CNS disorder.

[0045] According to one embodiment, the composition can be administered once daily or twice daily. According to another embodiment, the composition can be administered at least once daily, at least once every other day, or at least once weekly. In some embodiments, the composition is administered at a daily dose ranging from about 0.001 mg/kg to 100 mg/kg of body weight. In other embodiments, the composition is administered intranasally, intravenously, transdermally, or orally.

[0046] Without wishing to limit the invention to a particular theory or mechanism, the composition can treat the CNS disorder or the mood disorder such that clinical improvement is observed in about 1 to 14 days, for instance, in 1-7 says, or 7-14 days. Further still, the composition may be effective to evoke at least one of a psychostimulating effect, an anxiolytic effect, or an antidepressant effect.

[0047] In yet a further embodiment, the present invention features a composition for use in treating a CNS disorder or a mood disorder in a subject, comprising determining if the subject has the CNS disorder or a mood disorder, and administering a therapeutically effective amount of the composition to the subject if it is determined that the subject has the CNS disorder or a mood disorder. The composition for use may comprise a melanocortin 5 receptor (MC5R) peptide ligand in a pharmaceutically acceptable carrier. The MC5R peptide ligand may be according to Formula 1:

R_1-Nle^4-c[Xaa^5-Yaa^6-(NMe)D-Nal(2')^7-Arg^8-Trp^9-(NMe)Zaa^{10}]-R_2 (SEQ NO. 1)

[0048] In one embodiment, R_1 may be an acetyl, a glycosylated amino acid,–CO-$(CH_2)_nCH_3$, or –CO-$(CH_2)_nCF_3$, wherein n ranges from 1 to 6. In another embodiment, R_2 may be an amide (e.g. –$CONH_2$), –COOH, or –CH_2OH. In a preferred embodiment, Xaa is a natural amino acid or an unnatural amino acid, Yaa is a natural amino acid or an unnatural amino acid, and Zaa is a natural amino acid or an unnatural amino acid. In some embodiments, the MC5R peptide ligand is an antagonist of MC5R.

[0049] In one embodiment, Xaa may be Asp, Glu or 2-aminobutyric acid. In another embodiment, Yaa may be selected from a group consisting of His, Pro, octahydroindole-2-carboxylic acid, indoline-2-carboxylic acid, tetrahydro-isoquinoline-3-carboxylic acid, 1-amino-1-cyclohexane carboxylic acid, 1-amino-1-cyclopentane carboxylic acid, 2-aminoindane-2-carboxylic acid, and 1-aminocyclopropane carboxylic acid. In yet another embodiment, Zaa may be Lys, ornithine or diaminobutyric acid.

[0050] For example, in one embodiment, the composition for use in treating a CNS disorder or a mood disorder in a subject may comprise the following melanocortin 5 receptor (MC5R) peptide ligand:

Ac-Nle^4-c[Asp^5-His^6-(NMe)D-Nal(2')^7-Arg^8-Trp^9-(NMe)Lys^{10}]-NH_2 (SEQ NO. 9)

in a pharmaceutically acceptable carrier.

[0051] In some embodiments, the glycosylated amino acid may comprise a saccharide linked to a natural amino acid, such as Ser, Thr, Tyr, Asn or Gln. The saccharide may be a monosaccharide, a disaccharide, or an oligosaccharide. For example, the saccharide may be glucose, fructose, or lactose. In one embodiment, the glycosylated amino acid may comprise a saccharide O-linked to a natural amino acid, such as Ser, Thr, or Tyr. In another embodiment, the glycosylated amino acid may comprise a saccharide *N*-linked to a natural amino acid, such Asn or Lys.

[0052] In preferred embodiments, Xaa may be linked to Zaa via a carba, lactam, disulfide, thioether, or succinic linker, thereby forming a cyclic peptide. In some embodiments, the MC5R peptide ligand may comprise a 23- to 27-membered ring.

[0053] According to one embodiment, the composition can be administered once daily or twice daily. According to another embodiment, the composition can be administered at

least once daily, at least once every other day, or at least once weekly. In some embodiments, the composition is administered at a daily dose ranging from about 0.001 mg/kg to 100 mg/kg of body weight. In other embodiments, the composition is administered intranasally, intravenously, transdermally, or orally. In preferred embodiments, the composition for use in the treatment resulted in clinical improvement of the depressive disorder or anxiety disorder that is observed in about 1 to 14 days, such as, for example, about 1 to 7 days or about 7 to 14 days.

[0054] Another embodiment of the present invention features a melanocortin 5 receptor (MC5R) peptide ligand according to Formula 1:

$$R_1\text{-Nle}^4\text{-c[Xaa}^5\text{-Yaa}^6\text{-}(NMe)\text{D-Nal(2')}^7\text{-Arg}^8\text{-Trp}^9\text{-}(NMe)\text{Zaa}^{10}\text{]-}R_2 \quad \text{(SEQ NO. 1)}$$

[0055] In one embodiment, R_1 is an acetyl, a glycosylated amino acid, $–CO-(CH_2)_nCH_3$, or $–CO-(CH_2)_nCF_3$, with n ranging from 1 to 6. In another embodiment, R_2 is an amide (e.g. $–CONH_2$), –COOH, or $–CH_2OH$. In a preferred embodiment, Xaa is a natural amino acid or an unnatural amino acid, Yaa is a natural amino acid or an unnatural amino acid, and Zaa is a natural amino acid or an unnatural amino acid, with the proviso that Xaa is not Asp, Yaa is not His, and Zaa is not Lys concurrently.

[0056] In some embodiments, the glycosylated amino acid may comrpise a saccharide *O*-linked to a natural amino acid, such as Ser, Thr, or Tyr. In other embodiments, the glycosylated amino acid may comprise a saccharide *N*-linked to a natural amino acid, such as Asn or Lys. In still other embodiments, the saccharide is a monosaccharide, a disaccharide, or an oligosaccharide, such as, for example, glucose, fructose, or lactose.

[0057] In one embodiment, Xaa may be Glu or 2-aminobutyric acid. In another embodiment, Yaa may be selected from a group consisting of Pro, octahydroindole-2-carboxylic acid, indoline-2-carboxylic acid, tetrahydro-isoquinoline-3-carboxylic acid, 1-amino-1-cyclohexane carboxylic acid, 1-amino-1-cyclopentane carboxylic acid, 2-aminoindane-2-carboxylic acid, and 1-aminocyclopropane carboxylic acid. In yet another embodiment, Zaa may be ornithine or diaminobutyric acid.

[0058] In some embodiments, the MC5R peptide ligand is a cyclised peptide formed when Xaa is linked to Zaa via a carba, lactam, disulfide, thioether, or succinic linker. In other embodiments, the MC5R peptide ligand comprises a 23 to 27-membered ring.

[0059] According to yet another embodiment, the present invention features a method of treating a central nervous system (CNS) disorder or a mood disorder in a subject in need thereof. In one embodiment, the method may comprise administering to the subject a therapeutically effective amount of a composition comprising a melanocortin 5 receptor (MC5R) peptide ligand in a pharmaceutically acceptable carrier. The MC5R peptide ligand may be according to Formula 1:

$$R_1\text{-Nle}^4\text{-c[Xaa}^5\text{-Yaa}^6\text{-}(NMe)\text{D-Nal(2')}^7\text{-Arg}^8\text{-Trp}^9\text{-}(NMe)\text{Zaa}^{10}\text{]-}R_2 \quad \text{(SEQ NO. 1)}$$

[0060] In some embodiments, R_1 is an acetyl, a glycosylated amino acid, $–CO-(CH_2)_nCH_3$, or $–CO-(CH_2)_nCF_3$, with n ranging from 1 to 6. In other embodiments, R_2 is an amide (e.g. $–CONH_2$), –COOH, or $–CH_2OH$. In further embodiments, Xaa can be a natural amino acid or an unnatural amino acid, Yaa can be a natural amino acid or an unnatural amino acid, and Zaa can be a natural amino acid or an unnatural amino acid. Without wishing to limit the invention to a particular theory or mechanism, it is believed that the MC5R peptide ligand is an antagonist of MC5R.

[0061] In one embodiment, Xaa may be Asp, Glu or 2-aminobutyric acid. In another embodiment, Yaa may be selected from a group consisting of His, Pro, octahydroindole-2-carboxylic acid, indoline-2-carboxylic acid, tetrahydro-isoquinoline-3-carboxylic acid, 1-amino-1-cyclohexane carboxylic acid, 1-amino-1-cyclopentane carboxylic acid, 2-aminoindane-2-carboxylic acid, and 1-aminocyclopropane carboxylic acid. In still another embodiment, Zaa may be Lys, ornithine or diaminobutyric acid.

[0062] In some embodiments, the glycosylated amino acid may comprise a saccharide linked to a natural amino acid, such as Ser, Thr, Tyr, Asn or Gln. The saccharide may be a monosaccharide, a disaccharide, or an oligosaccharide. For example, the saccharide may be glucose, fructose, or lactose. In one embodiment, the glycosylated amino acid may comprise a saccharide *O*-linked to a natural amino acid, such as Ser, Thr, or Tyr. In another embodiment, the glycosylated amino acid may comprise a saccharide *N*-linked to a natural amino acid, such Asn or Lys.

[0063] In preferred embodiments, Xaa may be linked to Zaa via a carba, lactam, disulfide, thioether, or succinic linker, thereby forming a cyclic peptide. In some embodiments, the MC5R peptide ligand may comprise a 23- to 27-membered ring.

[0064] For example, in an exemplary embodiment, the method of treating a CNS disorder or a mood disorder in a subject in need of such treatment may comprise administering to the subject a therapeutically effective amount of a composition comprising:

Ac-Nle^4-c[Asp^5-His^6-(*NMe*)D-Nal(2')^7-Arg^8-Trp^9-(*NMe*)Lys^{10}]-NH_2 (SEQ NO. 9)

in a pharmaceutically acceptable carrier.

[0065] In some embodiments, the subject is a mammal, such as a human. In other embodiments, the composition may be administered at a daily dose ranging from about 0.001 mg/kg to 100 mg/kg of body weight. In one embodiment, the composition may be administered once daily or twice daily. In another embodiment, the composition may be administered at least once daily, at least once every other day, or at least once weekly. The composition may be administered intranasally, intravenously, transdermally, or orally.

[0066] Without wishing to limit the invention to a particular theory or mechanism, since the MC5R peptide ligand is a selective MC5R antagonist, then the MC5R peptide ligand may be potentially therapeutic for treating the CNS disorder or mood disorder. Preferably, when the composition is administered to the subject, the disorder is treated such that clinical improvement may be observed in about 1 to 14 days, for instance, in about 1 to 7 days or about 1 to 14 days. Moreover, administration of the composition may be effective to evoke at least one of a psychostimulating effect, an anxiolytic effect, or an antidepressant effect.

[0067] Examples of mood disorder include, but are not limited to, depressive disorders such as major depressive disorders or persistent depressive disorders; and anxiety disorders such as generalized anxiety disorders or panic disorders.

[0068] In any of the aforementioned embodiments of the present invention, the composition may be administered in a dosage of about 0.001 mg/kg to 100 mg/kg of body weight. For example, the dosage may range from about 0.001 mg/kg to 1 mg/kg of body weight, or about 1 mg/kg to 10 mg/kg of body weight, or about 10 mg/kg to 20 mg/kg of body weight, or about 20 mg/kg to 30 mg/kg of body weight, or about 30 mg/kg to 40 mg/kg of body weight, or about 50 mg/kg to 60 mg/kg of body weight, or about 60 mg/kg to 70 mg/kg of body weight, or about 70 mg/kg to 80 mg/kg of body weight, or

about 80 mg/kg to 90 mg/kg of body weight, or about 90 mg/kg to 100 mg/kg of body weight.

[0069] Alternative embodiments for treating the CNS disorder or mood disorder in the subject, according to any of the aforementioned methods, may include administering the composition is combination with a non-pharmacological treatment. Examples of non-pharmacological treatments may include, but are not limited to, is psychotherapy, electroconvulsive therapy, transcranial magnetic stimulation, vagus nerve stimulation, acupuncture, hypnosis, meditation, an exercise regimen, and administration of naturopathic herbs and supplements.

[0070] ***N-Terminal Modification***

[0071] As used herein, the N-terminal modification refers to the modification of the NH_2 at the N-terminus, resulting in R_1 being linked to the NH moiety. N-terminal modifications are known to one of ordinary skill in the art.

[0072] For example, in some embodiments, acetylation of the N-terminal results in R_1 being an acetyl.

[0073] In other embodiments, R_1 may be a glycosylated amino acid. In one aspect, the glycosylated amino acid may comprise a saccharide *O*-linked to a natural amino acid. For instance, the saccharide is attached to the hydroxyl group of the side-chain of the amino acid, such as Ser, Thr, or Tyr. In another aspect, the glycosylated amino acid may comprise a saccharide *N*-linked to a natural amino. For example, the saccharide is attached to the amine group of the side-chain of the amino acid, such as Asn or Lys. Examples of saccharides include, but are not limited to, glucose, fructose, and lactose.

[0074] In further embodiments, R_1 may be $-CO-(CH_2)_nCH_3$ or $-CO-(CH_2)_nCF_3$. Preferably, "n" can range from 1 to 6.

[0075] Without wishing to limit the invention to a particular theory or mechanism, N-terminal modifications may play a role in stability, protein folding, cellular attachment, and function modulation of the MC5R peptide ligand.

[0076] ***C-Terminal Modification***

[0077] As used herein, the C-terminal modification refers to the modification of the

carboxyl moiety at the C-terminus. C-terminal modifications are known to one of ordinary skill in the art.

[0078] Conventionally, the C-terminal of a peptide chain is –COOH. In some embodiments of C-terminal modification, R_2 can be an amide (e.g. $–CONH_2$) or $–CH_2OH$. Without wishing to limit the invention to a particular theory or mechanism, C-terminal modifications, such as amidation, can enhance the biological activity of the peptide ligand, increase the ligand's stability, efficacy, and ability to enter cells, as well as increase its ability to resist enzymatic degradation.

[0079] ***Amino Acid Modifications***

[0080] In one embodiment, Xaa may be a natural amino acid or an unnatural amino acid. For example, Xaa may be the natural amino acid Asp or Glu, or the unnatural amino acid Abu. In another embodiment, Yaa may be a natural amino acid such as His or Pro, or an unnatural amino acid such as Oic, Ioc, Tic, Cpe, Che, Aic, and Acpc. Without wishing to limit the invention to a particular theory or mechanism, the Yaa modification can provide for a stable β turn-like structure and improved potency of the MC5R peptide ligand. In a further embodiment, Zaa may be a natural amino acid such as Lys, or an unnatural amino acid such as Orn, and Dab.

[0081] In one alternate embodiment, a side-chain of the amino acid in the MC5R peptide ligand may be halogenated. For example, if the MC5R peptide ligand contains a Phe, then the side-chain of Phe can be halogenated. However, in embodiments where the MC5R peptide ligand contains a His, then His cannot be halogenated. As another example, the side-chain of *(NMe)*D-Nal(2') or Trp in the cyclic peptide may be para-, meta-, or ortho- halogenated or di-halogenated. In another alternate embodiment, a side-chain of the amino acid may be glycosylated. For example, the side-chain of Lys in the cyclic peptide may be glycosylated.

[0082] It is understood that the aforementioned examples of R_1, R_2, Xaa, Yaa, and Zaa are non-limiting. For instance, Xaa, Yaa, and Zaa can be any natural amino acid or unnatural amino acid. Preferably, R_1, R_2, Xaa, Yaa, and Zaa are each selected to produce a specific MC5R peptide ligand having desired properties.

[0083] Without wishing to limit the present invention to a particular theory or mechanism,

N-methylation of the backbone NHs as indicated in FIG. 1A can provide for an increase in blood-brain barrier penetration, selectivity, and stability of the MC5R peptide ligand. A non-limiting example of an MC5R peptide ligand resulting from the N-methylation of sites indicated in FIG. 1A is the following peptide, also shown in FIG. 1B, that may be used for treating CNS disorders or mood disorders:

Ac-Nle^4-c[Asp^5-His^6-(*NMe*)D-Nal(2')^7-Arg^8-Trp^9-(*NMe*)Lys^{10}]-NH_2 (SEQ NO. 9)

[0084] For instance, R_1 is an acetyl ("Ac"), R_2 is $-CONH_2$, Xaa is the natural amino acid "Asp", Yaa is the natural amino acid "His", and Zaa is the natural amino acid "Lys".

[0085] ***Cyclic Modifications***

[0086] The MC5R peptide ligand is preferably a cyclic peptide formed by the bridging of Xaa to Zaa via ring closing reactions. In particular, the side chain of the Xaa residue is linked to the side chain of the Zaa residue via a linker L_1. In some embodiments, the linker L_1 is a carba, lactam, disulfide, thioether, or succinic linker. As understood by one of ordinary skill in the art, the linker is not limited to the aforementioned examples, and may depend upon the specific cyclization chemistry used to produce the cyclic peptide.

[0087] As a non-limiting example, Xaa can be linked to Zaa via an amide bond formation reaction, which may form a $-(CH_2)-CO-NH-(CH_2)_n-$ bridge, where n=1,2,3,4. In addition, carbon-carbon bonds, lactone, thioether, ether, disulfide and other covalent bonds can be used as a part of the ring closing reactions.

[0088] Without wishing to limit the invention to a particular theory or mechanism, the type of linker can affect the structural, chemical, and biological activities of the peptide ligand.

[0089] ***Ring Size Modification***

[0090] Selection of Xaa and Zaa can affect the ring size of the MC5R peptide ligand. Ideally, the MC5R peptide ligand may be a 23-membered ring. For instance, as shown in FIG. 2, the MC5R peptide ligand is a 23-membered ring. In another preferred embodiment, the MC5R peptide ligand may be a 23 to 29-membered ring. As another example, if Zaa is Orn and Xaa is Glu, the MC5R peptide ligand is a 23-membered ring. As a further example, if Zaa is Lys and Xaa is Glu, the MC5R peptide ligand is a 24-membered ring.

[0091] Without wishing to limit the invention to a particular theory or mechanism, the ring size of the MC5R peptide ligand can affect the selectivity of the peptide ligand. For example, a 23-membered ring may provide a universal peptide ligand for MC1R, MC3R, MC4R, and MC5R. For a ring-size greater than 26 members, the peptide ligand may be selective for a particular melanocortin receptor, such as MC1R and MC5R.

[0092] Table 1 summarizes the modifications on the MC5R peptide ligand.

Modification	Variable	Variable Examples
N-Terminal	R_1	Acetyl, glycosylated amino acids, $–CO-(CH_2)_nCH_3$, or $–CO-(CH_2)_nCF_3$, n is 1 to 6
C-Terminal	R_2	$–CONH_2$, –COOH, or $–CH_2OH$
Amino Acid	Xaa	Asp, Glu, or Abu
	Yaa	His, Pro, Oic, Ioc, Tic, Cpe, Che, Aic, or Acpc
	Zaa Amino acid in the cyclic peptide	Lys, Orn, or Dab Glycosylated amino acid, p-, m-, o- halogen or di-halogen substitution of a side-chain of the amino acid
Cyclic Linker	L_1	carba, lactam, disulfide, thioether, or succinic linker
Ring Size	Xaa, Zaa	23, 24, 25, 26, 27, 28, or 29-membered ring

[0093] TABLE 2 shows non-limiting examples of the MC5R peptide ligand of the present invention, wherein Xaa is Asp, Zaa is Lys, R_1 is Ac, and R_2 is $–CONH_2$. As used herein, one of ordinary skill in the art will understand that the use of "NH_2" in a sequence refers to $–CONH_2$.

SEQ. NO.	Cyclo	R_1	4	5	6	7	8	9	10	R_2
2	Cyclo5,10	Ac	Nle	Asp	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2
3	Cyclo5,10	Ac	Nle	Asp	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2
4	Cyclo5,10	Ac	Nle	Asp	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2
5	Cyclo5,10	Ac	Nle	Asp	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2
6	Cyclo5,10	Ac	Nle	Asp	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2
7	Cyclo5,10	Ac	Nle	Asp	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2
8	Cyclo5,10	Ac	Nle	Asp	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2
9	Cyclo5,10	Ac	Nle	Asp	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2
10	Cyclo5,10	Ac	Nle	Asp	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	NH_2

[0094] TABLE 3 shows non-limiting examples of the MC5R peptide ligand of the present invention. In said examples, R_1 can be an acetyl, a glycosylated amino acid, –CO-$(CH_2)_nCH_3$, or –CO-$(CH_2)_nCF_3$, wherein 'n' ranges from 1 to 6, and R_2 can be –$CONH_2$, –COOH, or –CH_2OH.

SEQ. NO.	Cyclo	R_1	4	5	6	7	8	9	10	R_2
11	Cyclo5,10	R_1	Nle	Asp	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
12	Cyclo5,10	R_1	Nle	Asp	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
13	Cyclo5,10	R_1	Nle	Asp	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
14	Cyclo5,10	R_1	Nle	Asp	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
15	Cyclo5,10	R_1	Nle	Asp	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
16	Cyclo5,10	R_1	Nle	Asp	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
17	Cyclo5,10	R_1	Nle	Asp	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
18	Cyclo5,10	R_1	Nle	Asp	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
19	Cyclo5,10	R_1	Nle	Asp	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
20	Cyclo5,10	R_1	Nle	Asp	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
21	Cyclo5,10	R_1	Nle	Asp	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
22	Cyclo5,10	R_1	Nle	Asp	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
23	Cyclo5,10	R_1	Nle	Asp	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
24	Cyclo5,10	R_1	Nle	Asp	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
25	Cyclo5,10	R_1	Nle	Asp	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
26	Cyclo5,10	R_1	Nle	Asp	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
27	Cyclo5,10	R_1	Nle	Asp	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
28	Cyclo5,10	R_1	Nle	Asp	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
29	Cyclo5,10	R_1	Nle	Asp	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
30	Cyclo5,10	R_1	Nle	Asp	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
31	Cyclo5,10	R_1	Nle	Asp	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
32	Cyclo5,10	R_1	Nle	Asp	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
33	Cyclo5,10	R_1	Nle	Asp	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
34	Cyclo5,10	R_1	Nle	Asp	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
35	Cyclo5,10	R_1	Nle	Asp	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
36	Cyclo5,10	R_1	Nle	Asp	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
37	Cyclo5,10	R_1	Nle	Asp	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
38	Cyclo5,10	R_1	Nle	Glu	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
39	Cyclo5,10	R_1	Nle	Glu	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
40	Cyclo5,10	R_1	Nle	Glu	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
41	Cyclo5,10	R_1	Nle	Glu	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
42	Cyclo5,10	R_1	Nle	Glu	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
43	Cyclo5,10	R_1	Nle	Glu	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
44	Cyclo5,10	R_1	Nle	Glu	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2

45	Cyclo5,10	R_1	Nle	Glu	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
46	Cyclo5,10	R_1	Nle	Glu	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
47	Cyclo5,10	R_1	Nle	Glu	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
48	Cyclo5,10	R_1	Nle	Glu	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
49	Cyclo5,10	R_1	Nle	Glu	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
50	Cyclo5,10	R_1	Nle	Glu	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
51	Cyclo5,10	R_1	Nle	Glu	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
52	Cyclo5,10	R_1	Nle	Glu	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
53	Cyclo5,10	R_1	Nle	Glu	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
54	Cyclo5,10	R_1	Nle	Glu	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
55	Cyclo5,10	R_1	Nle	Glu	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
56	Cyclo5,10	R_1	Nle	Glu	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
57	Cyclo5,10	R_1	Nle	Glu	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
58	Cyclo5,10	R_1	Nle	Glu	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
59	Cyclo5,10	R_1	Nle	Glu	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
60	Cyclo5,10	R_1	Nle	Glu	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
61	Cyclo5,10	R_1	Nle	Glu	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
62	Cyclo5,10	R_1	Nle	Glu	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
63	Cyclo5,10	R_1	Nle	Glu	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
64	Cyclo5,10	R_1	Nle	Glu	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
65	Cyclo5,10	R_1	Nle	Abu	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
66	Cyclo5,10	R_1	Nle	Abu	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
67	Cyclo5,10	R_1	Nle	Abu	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
68	Cyclo5,10	R_1	Nle	Abu	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
69	Cyclo5,10	R_1	Nle	Abu	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
70	Cyclo5,10	R_1	Nle	Abu	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
71	Cyclo5,10	R_1	Nle	Abu	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
72	Cyclo5,10	R_1	Nle	Abu	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
73	Cyclo5,10	R_1	Nle	Abu	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	R_2
74	Cyclo5,10	R_1	Nle	Abu	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
75	Cyclo5,10	R_1	Nle	Abu	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
76	Cyclo5,10	R_1	Nle	Abu	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
77	Cyclo5,10	R_1	Nle	Abu	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
78	Cyclo5,10	R_1	Nle	Abu	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
79	Cyclo5,10	R_1	Nle	Abu	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
80	Cyclo5,10	R_1	Nle	Abu	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
81	Cyclo5,10	R_1	Nle	Abu	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
82	Cyclo5,10	R_1	Nle	Abu	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	R_2
83	Cyclo5,10	R_1	Nle	Abu	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
84	Cyclo5,10	R_1	Nle	Abu	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2

85	Cyclo5,10	R_1	Nle	Abu	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
86	Cyclo5,10	R_1	Nle	Abu	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
87	Cyclo5,10	R_1	Nle	Abu	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
88	Cyclo5,10	R_1	Nle	Abu	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
89	Cyclo5,10	R_1	Nle	Abu	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
90	Cyclo5,10	R_1	Nle	Abu	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2
91	Cyclo5,10	R_1	Nle	Abu	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Dab	R_2

[0095] TABLE 4 shows non-limiting examples of the MC5R peptide ligand of the present invention. In the following examples, Xaa is Glu, Zaa is Orn, R_1 is $-CO-(CH_2)CH_3$, and R_2 is $-CONH_2$.

SEQ. NO.	Cyclo	R_1	4	5	6	7	8	9	10	R_2
92	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2
93	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2
94	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2
95	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2
96	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2
97	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2
98	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2
99	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2
100	Cyclo5,10	$CO-(CH_2)CH_3$	Nle	Glu	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Orn	NH_2

[0096] TABLE 5 shows non-limiting examples of the MC5R peptide ligand of the present invention. In the following examples, Xaa is Glu, Zaa is Lys, R_1 is glucosylated Ser (Ser-*O*-Glc), and R_2 is –COOH. As used herein, one of ordinary skill in the art will understand that the use of "OH" in a sequence refers to –COOH.

SEQ. NO.	Cyclo	R_1	4	5	6	7	8	9	10	R_2
101	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	Acpc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH
102	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	Aic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH
103	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	Cpe	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH
104	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	Che	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH
105	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	Tic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH
106	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	Ioc	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH
107	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	Oic	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH
108	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	His	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH
109	Cyclo5,10	Ser-*O*-Glc	Nle	Glu	Pro	*(NMe)*D-Nal(2')	Arg	Trp	*(NMe)*Lys	OH

[0097] Disclosed are the various compounds, solvents, solutions, carriers, and/or components to be used to prepare the compositions to be used within the methods disclosed herein. Also disclosed are the various steps, elements, amounts, routes of administration, symptoms, and/or treatments that are used or observed when performing the disclosed methods, as well as the methods themselves. These and other materials, steps, and/or elements are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed, that while specific reference of each various individual and collective combination and permutation of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein.

[0098] As used herein, a central nervous system (CNS) disorder may include, but are not limited to, stress, Tourette syndrome (TS), attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), an ascular disorder, such as stroke, transient ischemic attack (TIA), subarachnoid hemorrhage, subdural hemorrhage and hematoma, and extradural hemorrhage; an infection, such as meningitis, encephalitis, polio, and epidural abscess; a structural disorder, such as brain or spinal cord injury, Bell's palsy, cervical spondylosis, carpal tunnel syndrome, brain or spinal cord tumors, peripheral neuropathy, and Guillain-Barré syndrome; a functional disorder, such as headache, epilepsy, dizziness, and neuralgia; or degeneration, such as Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Huntington's chorea, dementia and Alzheimer's disease.

[0099] Symptoms of CNS disorders may include, but are not limited to, headaches, loss of feeling or tingling, muscle weakness or loss of muscle strength, sudden loss of sight or double vision, memory loss, impaired mental ability, lack of coordination, muscle rigidity, tremors and seizures, back pain, muscle wasting, slurred speech, and motor and vocal tics.

[00100] Stress may be defined as the brain's response to any demand, or any uncomfortable emotional experience accompanied by predictable biochemical, physiological and behavioral changes. Stress is often described as a feeling of being overwhelmed, worried or run-down, which can lead to both physical and psychological health issues. Excessive chronic stress, which is constant and persists over an

extended period of time, can have health consequences and adversely affect the immune, cardiovascular, neuroendocrine and central nervous systems. Chronic stress can occur in response to everyday stressors that are ignored or poorly managed, as well as to exposure to traumatic events, such as acute stress disorder (ASD) or post-traumatic stress disorder (PTSD). Furthermore, chronic stress can cause or exacerbate health problems such as anxiety, depression, high blood pressure, a weakened immune system, heart disease, digestive problems such as ulcers, weight problems such as obesity, skin conditions, such as eczema, reproductive issues, pain of any kind, sleep problems such as insomnia, cognitive and memory problems.

[00101] As used herein, a major depressive disorder (MDD) is a common disorder of mood and affect characterized by one or more major depressive episodes. These episodes are defined diagnostically using a criteria-based syndrome listed and described in literature as would be known to one of ordinary skill in the art. These episodes are diagnosed in a human patient if the patient has experienced 5 symptoms from a list of 9 symptom categories every day, or nearly every day, for a period lasting at least 2 weeks. At least one symptom must be present from either category 1 (having a sad, depressed, empty, or irritable mood, or appearing sad to others), or category 2 (experiencing loss of interest in or pleasure from activities). The other symptom categories include: 3) change in weight and/or appetite, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue and/or loss of energy, 7) feelings of worthlessness and/or excessive or inappropriate guilt, 8) diminished ability to think or of concentrate and/or indecisiveness, and 9) recurrent thoughts of death or suicide.

[00102] Persistent depressive disorder, also known as dysthymia, is a chronic (ongoing) type of depression in which a person's moods are regularly low. However, the symptoms are not as severe as with major depression.

[00103] Bipolar Disorder (also known as “manic-depressive illness”) is a mood disorder arising in a human patient who experiences major depressive episodes which alternate with episodes of mania (in the case of type I) or hypomania (in the case of type II). Mania is a syndrome characterized by a euphoric, expansive, or irritable mood lasting at least one week. In addition, at least three of the following symptoms persisted during the same time period: inflated self esteem and/or grandiosity, decreased need for sleep,

increased volume or rate of speech, flight of ideas and/or racing thoughts, distractibility, increased goal-directed activity and/or psychomotor agitation, excessive involvement in pleasurable activities that have a high potential for painful consequences. Mania and hypomania have similar signs and symptoms but are distinguished by the degree to which they result in impaired social and occupational functioning.

[00104] Bipolar affective disorder is characterized by two or more episodes in which the patient's mood and activity levels are significantly disturbed, this disturbance consisting on some occasions of an elevation of mood and increased energy and activity (hypomania or mania) and on others of a lowering of mood and decreased energy and activity (depression). Repeated episodes of hypomania or mania only are classified as bipolar. This includes manic depressive illness, psychosis, and reaction. This excludes bipolar disorder, single manic episode and cyclothymia.

[00105] In Bipolar affective disorder, current episode mild or moderate depression, the patient is currently depressed, as in a depressive episode of either mild or moderate severity, and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.

[00106] In Bipolar affective disorder, current episode severe depression without psychotic symptoms, the patient is currently depressed, as in severe depressive episode without psychotic symptoms, and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.

[00107] Treatment-resistant depression is exemplified by a case in which a human patient with either major depressive disorder or bipolar disorder continues to meet criteria for a major depressive episode in spite of treatment with conventional antidepressant drugs at adequate doses and treatment durations (at least 4 to 8 weeks).

[00108] Panic Disorder is an episodic paroxysmal anxiety syndrome characterized by recurrent attacks of severe anxiety (panic) which are not restricted to any particular situation or set of circumstances and are therefore unpredictable. The symptoms include sudden onset of palpitations, chest pain, dyspnea, dizziness, and feelings of unreality (depersonalization or derealization). There is often also a secondary fear of dying, losing control, or going insane. Panic disorder may be seen with or without agoraphobia, which

is characterized by a cluster of phobias embracing fears of leaving home, entering shops, crowds and public places, or traveling alone in trains, buses or planes. Avoidance of the phobic situation is prominent, to an extent that agoraphobics alter their lifestyles to avoid their relevant phobic situations.

[00109] Social phobia (also called Social Anxiety Disorder) is characterized by a marked and persistent fear of one or more social or performance settings in which the patient is exposed to unfamiliar people or to possible scrutiny by other people. The patient fears that in such situation they will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. Exposure to the feared social situation almost invariably provokes anxiety, and this response may progress to panic attacks. The feared social or performance situations are avoided, or else are endured with intense anxiety and distress.

[00110] Post-traumatic stress disorder arises as a delayed or protracted response to a stressful event or situation (of either brief or long duration) of an exceptionally threatening or catastrophic nature which is likely to cause pervasive distress in almost anyone. Predisposing factors, such as personality traits or previous history of mood or anxiety disorders, may lower the threshold for the development of the syndrome or aggravate its course, but they are neither necessary nor sufficient to explain its occurrence. Typical features include episodes of repeated reliving of the trauma in intrusive memories ("flashbacks"), dreams or nightmares occurring against the persisting background of a sense of "numbness" and emotional blunting, detachment from other people, unresponsiveness to surroundings, anhedonia, and avoidance of activities and situations reminiscent of the trauma. There often is a state of autonomic hyperarousal with hypervigilance, an enhanced startle reaction, and insomnia. Anxiety and depression commonly are associated with these symptoms and signs. The onset follows the trauma with a latency period that may range from a few weeks to months.

[00111] Generalized anxiety disorder is a chronic anxiety syndrome characterized by excessive worry or anxiety over a period lasting at least 6 months. These symptoms are associated with at least 3 of the following 6 symptoms: 1) restlessness or feeling on edge, 2) feeling easily fatigued, 3) impaired concentration, 4) irritability, 5) muscle tension, and 6) sleep disturbance. These anxiety symptoms are generalized and

persistent but not restricted to, or even strongly predominating in, any particular environmental circumstances. The anxiety syndrome is sufficiently severe to cause clinically significant distress or to impair social or occupational functioning.

[00112] A "subject" is an individual and includes, but is not limited to, a mammal (e.g., a human, horse, pig, rabbit, dog, sheep, goat, non-human primate, cow, cat, guinea pig, or rodent), a fish, a bird, a reptile or an amphibian. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be included. A "patient" is a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects.

[00113] The terms "administering" and "administration" refer to methods of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, administering the compositions orally, parenterally (e.g., intravenously and subcutaneously), by intramuscular injection, by intraperitoneal injection, intrathecally, transdermally, extracorporeally, topically or the like.

[00114] A composition can also be administered by topical intranasal administration (intranasally) or administration by inhalant. As used herein, "topical intranasal administration" means delivery of the compositions into the nose and nasal passages through one or both of the nares and can comprise delivery by a spraying mechanism (device) or droplet mechanism (device), or through aerosolization of the composition. Administration of the compositions by inhalant can be through the nose or mouth via delivery by a spraying or droplet mechanism. As used herein, "an inhaler" can be a spraying device or a droplet device for delivering a composition comprising MC5R peptide ligand, in a pharmaceutically acceptable carrier, to the nasal passages and the upper and/or lower respiratory tracts of a subject. Delivery can also be directly to any area of the respiratory system (e.g., lungs) via intratracheal intubation. The exact amount of the compositions required will vary from subject to subject, depending on the species, age, weight and general condition of the subject, the severity of the disorder being treated, the particular composition used, its mode of administration and the like. Thus, it is not possible to specify an exact amount for every composition. However, an

appropriate amount can be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein.

[00115] Parenteral administration of the composition, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution of suspension in liquid prior to injection, or as emulsions. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system such that a constant dosage is maintained. See, for example, U.S. Pat. No. 3,610,795, which is incorporated by reference herein.

[00116] A "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products.

[00117] As described above, the compositions can be administered to a subject in a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be

administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art.

[00118] Pharmaceutical carriers are known to those skilled in the art. These most typically would be standard carriers for administration of drugs to humans, including solutions such as sterile water, saline, and buffered solutions at physiological pH. Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically-acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. The pH of the solution is preferably from about 5 to about 8, and more preferably from about 7 to about 7.5. Further carriers include sustained release preparations such as semi-permeable matrices of solid hydrophobic polymers containing the disclosed compounds, which matrices are in the form of shaped articles, e.g., films, liposomes, microparticles, or microcapsules. It will be apparent to those persons skilled in the art that certain carriers can be more preferable depending upon, for instance, the route of administration and concentration of composition being administered. Other compounds can be administered according to standard procedures used by those skilled in the art.

[00119] Pharmaceutical formulations can include additional carriers, as well as thickeners, diluents, buffers, preservatives, surface active agents and the like in addition to the compounds disclosed herein. Pharmaceutical formulations can also include one or more additional active ingredients such as antimicrobial agents, anti-inflammatory agents, anesthetics, and the like.

[00120] The pharmaceutical formulation can be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated. Administration may be topically (including ophthahnically, vaginally, rectally, intranasally), orally, by inhalation, or parenterally, for example by intravenous drip, subcutaneous, intraperitoneal or intramuscular injection. The disclosed compounds can

be administered intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally.

[00121] Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, fish oils, and injectable organic-esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like.

[00122] Pharmaceutical formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

[00123] Pharmaceutical formulations for oral administration include, but are not limited to, powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable.

[00124] In one aspect, the MC5R peptide ligand can be administered in an intravenous dosage. This dosage can be administered to a subject once daily or in divided dosages throughout a day, as determined by methods known in the art. This dosage can be administered to a subject for one day and then stopped if the subject responds immediately, or the dosage can be administered on a daily basis until a clinical response is noted. It is contemplated that the dosage of the MC5R peptide ligand can be administered as infrequently as once every month or every two months, or at any interval in between, depending on a subject's clinical response to the medication. Thus, if a subject responds to one dosage of the MC5R peptide ligand, a person of skill may determine that further dosages of the medication can be withheld. Moreover, if a subject does not respond to the initial dosage and administration of the MC5R peptide ligand, a

person of skill can administer the medication daily for several days until such response occurs. A person of skill can monitor a subject's clinical response to the administration of the MC5R peptide ligand, and administer additional dosages if the subject's mood disorder symptoms reappear after a period of remission. It is contemplated that the MC5R peptide ligand, can be administered to a subject with, for example, major mood disorder on a daily basis, on an alternating daily basis, on a weekly basis, on a monthly basis, or at any interval in between.

[00125] In another aspect, the MC5R peptide ligand can be administered to a subject transdermally, by using an adherent patch, by using iontophoresis, or by using any other method known to a person of skill. The dosage of the MC5R peptide ligand, administered transdermally, can be given daily or infrequently as once every 1 to 4 weeks. A person of skill, monitoring a subject's clinical response and improvement, can determine the frequency of administration by methods known in the art.

[00126] In another aspect, the MC5R peptide ligand can be administered to a subject intranasally in a dosage taken once daily or in divided doses. The medication can be administered for one day and then stopped if clinical improvement occurs rapidly. Further, the medication can be administered as infrequently as once every 1 to 4 weeks. A person of skill, monitoring a subject's clinical response to the administration of the medication, can adjust the frequency of administration according to methods known in the art.

[00127] In another aspect, the MC5R peptide ligand can be administered to a subject intramuscularly in a dosage taken once daily or in divided doses. The medication can be administered for one day and then stopped if clinical improvement occurs rapidly. Furthermore, the medication can be administered as infrequently as once every 1 to 4 weeks. A person of skill, monitoring a subject's clinical response, can adjust the frequency of administration of the medication according to methods known in the art.

[00128] In still another aspect, the MC5R peptide ligand can be administered to a subject orally in a dosage taken once daily or in divided doses. The medication can be administered for one day and then stopped if clinical improvement occurs rapidly. Furthermore, the medication can be administered as infrequently as once every 1 to 4

weeks. A person of skill, monitoring a subject's clinical response, can adjust the frequency of administration of the medication according to methods known in the art.

[00129] EXAMPLES

[00130] The following examples are included to demonstrate certain embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventors to function well in the practice of the invention, and thus are considered to constitute certain aspects for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

[00131] EXAMPLE 1 - Transdermal Administration of the MC5R peptide ligand

[00132] The following example describes treatment strategies for depression involving transdermal administration of the MC5R peptide ligand.

[00133] Six weeks after a 30 year old female gives birth to her first child, a follow up appointment with her obstetrician reveals that she is suffering from post-partum depression. The patient is experiencing excessive crying, difficulty bonding with her baby, excess sleeping, overwhelming fatigue, intense anger and sadness, and severe anxiety and panic attacks. She further reports that in some instances, she has thoughts of suicide and harm coming to her baby. The female takes the Edinburgh Post Natal Depression Scale (EPDS) test, in which she scores a 25. A score of 10 or greater indicates possible perinatal mood or anxiety disorder. Her obstetrician refers her to a psychiatrist, who officially diagnoses her with postpartum depression. The psychiatrist recommends a trial of the MC5R peptide ligand administered using a transdermal patch. The patient is given a patch comprising the MC5R peptide ligand dose of 20 mg for transdermal delivery over a period 24 hours. A patch is to be administered every day for two weeks, followed by a visit with her psychiatrist. During her follow up visit with her psychiatrist, the patient retakes the EPDS test and scores a 12. She reports that her symptoms have drastically lessened in the past two weeks. Her psychiatrist prescribes another treatment of a transdermal patch comprising the MC5R peptide ligand dose of 10 mg for transdermal delivery over a period 24 hours. The patch is to be administered every other day for two weeks, followed by a visit with her psychiatrist. The patient

continues to improve and is no longer suffering from post-partum depression 6 months later. No side effects are reported.

[00134] EXAMPLE 2 - Oral Administration of the MC5R peptide ligand

[00135] The following example describes treatment strategies for Bell's Palsy involving oral administration of the MC5R peptide ligand.

[00136] A 40 year old male is experiencing sudden paralysis on the left side of his face, causing it to droop. He is also drooling and is unable to close his left eye. His doctor performs physical and neurological exams to check his facial nerve function. The patient is diagnosed with Bell's Palsy. His doctor prescribes an oral medication of a formulation comprising the MC5R peptide ligand in a dose of 20 mg per tablet. The patient is to take the tablet twice a day for one week. The patient is highly responsive and experiences a reduction in his symptoms during the initial treatment period. After the initial treatment, the patient is prescribed to take a tablet of 10 mg of the MC5R peptide ligand once a day for another week. The patient continues to improve and completely recovers after the second treatment. No side effects are reported.

[00137] EXAMPLE 3 - Oral Administration of the MC5R peptide ligand

[00138] The following example describes treatment strategies for depression and anxiety involving oral administration of the MC5R peptide ligand.

[00139] A 50-year-old Caucasian male reports to his psychiatrist that he is feeling depressed and having panic attacks. He reveals that these symptoms began after his divorce. His psychiatrist prescribes an oral medication of a formulation comprising the MC5R peptide ligand in a dose of 10 mg per tablet. The patient is to take the tablet twice a day for one month. The patient is highly responsive and experiences a reduction in his symptoms during the initial treatment period. After the initial treatment, the patient is prescribed to take a tablet of 5 mg of the MC5R peptide ligand once a day for another month. The patient continues to improve and is functioning normally at three months. No side effects are reported.

[00140] EXAMPLE 4 - Repeated Administration of a Fixed Dose IV

[00141] The following example describes a treatment strategy for depression involving the repeated administration of the MC5R peptide ligand.

[00142] A 52 year old female has a strong family history of depression and has had disabling depression since her teens. She has been tried on numerous oral medications without benefit. At times she is agitated and has panic attacks, which fluctuates with lethargy and insomnia. She is referred to a neurologist, who rules out any secondary causes for her symptoms. Her brain MRI scan and routine lab testing is within normal limits. Her psychiatrist recommends a trial of the MC5R peptide ligand administered intravenously. A fixed IV of the MC5R peptide ligand dose (1 mg/kg infusion over 30 minutes) is repeated administered every two days over a two to three week period in hospital. A follow up visit with her psychiatrist reveals improving depression symptoms with less agitation, improved energy levels and sleep patterns. A second treatment of the fixed IV of the MC5R peptide ligand is given two months later. The patient continues to improve and is functioning normally at 6 months. No side effects are reported.

[00143] As used herein, the term "about" refers to plus or minus 10% of the referenced number.

[00144] Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference cited in the present application is incorporated herein by reference in its entirety.

[00145] Although there has been shown and described the preferred embodiment of the present invention, it will be readily apparent to those skilled in the art that modifications may be made thereto which do not exceed the scope of the appended claims. Therefore, the scope of the invention is only to be limited by the following claims. In some embodiments, the figures presented in this patent application are drawn to scale, including the angles, ratios of dimensions, etc. In some embodiments, the figures are representative only and the claims are not limited by the dimensions of the figures. In some embodiments, descriptions of the inventions described herein using the phrase "comprising" includes embodiments that could be described as "consisting of", and as such the written description requirement for claiming one or more embodiments of the present invention using the phrase "consisting of" is met.

WHAT IS CLAIMED IS:

1. A composition for use in treating a central nervous system (CNS) disorder or a mood disorder, comprising a melanocortin 5 receptor (MC5R) peptide ligand in a pharmaceutically acceptable carrier, wherein the MC5R peptide ligand is according to Formula 1:

R_1-Nle^4-c[Xaa^5-Yaa^6-*(NMe)*D-Nal(2')^7-Arg^8-Trp^9-*(NMe)*Zaa^{10}]-R_2

wherein R_1 is an acetyl, a glycosylated amino acid,–CO-$(CH_2)_nCH_3$, or –CO-$(CH_2)_nCF_3$, wherein n ranges from 1 to 6,

wherein R_2 is an amide, –COOH, or –CH_2OH,

wherein Xaa is a natural amino acid or an unnatural amino acid, wherein Yaa is a natural amino acid or an unnatural amino acid, and wherein Zaa is a natural amino acid or an unnatural amino acid.

2. The composition for use according to claim 1, wherein Xaa is Asp, Glu or 2-aminobutyric acid.

3. The composition for use according to claim 1 or 2, wherein Yaa is selected from a group consisting of His, Pro, octahydroindole-2-carboxylic acid, indoline-2-carboxylic acid, tetrahydro-isoquinoline-3-carboxylic acid, 1-amino-1-cyclohexane carboxylic acid, 1-amino-1-cyclopentane carboxylic acid, 2-aminoindane-2-carboxylic acid, and 1-aminocyclopropane carboxylic acid.

4. The composition for use according to any of claims 1-3, wherein Zaa is Lys, ornithine or diaminobutyric acid.

5. The composition for use according to any of claims 1-4, wherein the glycosylated amino acid comprises a saccharide linked to a natural amino acid, wherein the natural amino acid is Ser, Thr, Tyr, Asn or Gln, wherein the saccharide is a monosaccharide, a disaccharide, or an oligosaccharide.

6. The composition for use according to claim 5, wherein the glycosylated amino acid comprises a saccharide O-linked to a natural amino acid, wherein the O-linked natural amino acid is Ser, Thr, or Tyr.

7. The composition for use according to claim 5, wherein the glycosylated amino acid

comprises a saccharide *N*-linked to a natural amino acid, wherein the *N*-linked natural amino acid is Asn or Lys.

8. The composition for use according to any of claims 1-7, wherein Xaa is linked to Zaa via a carba, lactam, disulfide, thioether, or succinic linker, thereby forming a cyclic peptide.

9. The composition for use according to any of claims 1-8, wherein the MC5R peptide ligand is an antagonist of MC5R.

10. The composition for use according to any of claims 1-9, wherein the mood disorder is a depressive disorder or an anxiety disorder.

11. The composition for use according to any of claims 1-10, wherein the composition is administered once daily or twice daily.

12. The composition for use according to any of claims 1-10, wherein the composition is administered at least once daily, at least once every other day, or at least once weekly.

13. The composition for use according to any of claims 1-12, wherein the composition is administered at a daily dose ranging from about 0.001 mg/kg to 100 mg/kg of body weight.

14. The composition for use according to any of claims 1-14, wherein the composition is administered intranasally, intravenously, transdermally, or orally.

15. The composition for use according to any of claims 1-14, wherein the composition treats the CNS disorder or the mood disorder such that clinical improvement is observed in about 1 to 14 days.

16. The composition for use according to any of claims 1-15, wherein the composition is effective to evoke at least one of a psychostimulating effect, an anxiolytic effect, or an antidepressant effect.

17. A melanocortin 5 receptor (MC5R) peptide ligand according to Formula 1:

$$R_1\text{-Nle}^4\text{-c[Xaa}^5\text{-Yaa}^6\text{-}(NMe)\text{D-Nal(2')}^7\text{-Arg}^8\text{-Trp}^9\text{-}(NMe)\text{Zaa}^{10}\text{]-}R_2$$

wherein R_1 is an acetyl, a glycosylated amino acid,–CO-$(CH_2)_nCH_3$, or –CO-$(CH_2)_nCF_3$, wherein n ranges from 1 to 6,

wherein R_2 is an amide, –COOH, or –CH_2OH, and

wherein Xaa is a natural amino acid or an unnatural amino acid, wherein Yaa is a natural amino acid or an unnatural amino acid, and wherein Zaa is a natural amino acid or an unnatural amino acid, with a proviso that the Xaa is not Asp, Yaa is not His, and Zaa is not Lys concurrently.

18. The MC5R peptide ligand of claim 17, wherein the glycosylated amino acid comprises a saccharide *O*-linked to a natural amino acid, wherein the *O*-linked natural amino acid is Ser, Thr, or Tyr, wherein the saccharide is a monosaccharide, a disaccharide, or an oligosaccharide.

19. The MC5R peptide ligand of claim 17, wherein the glycosylated amino acid comprises a saccharide *N*-linked to a natural amino acid, wherein the *N*-linked natural amino acid is Asn or Lys, wherein the saccharide is a monosaccharide, a disaccharide, or an oligosaccharide.

20. The MC5R peptide ligand of any of claims 17-19, wherein Xaa is Glu or 2-aminobutyric acid.

21. The MC5R peptide ligand of any of claims 17-20, wherein Yaa is selected from a group consisting of Pro, octahydroindole-2-carboxylic acid, indoline-2-carboxylic acid, tetrahydro-isoquinoline-3-carboxylic acid, 1-amino-1-cyclohexane carboxylic acid, 1-amino-1-cyclopentane carboxylic acid, 2-aminoindane-2-carboxylic acid, and 1-aminocyclopropane carboxylic acid.

22. The MC5R peptide ligand of any of claims 17-21, wherein Zaa is ornithine or diaminobutyric acid.

23. The MC5R peptide ligand of any of claims 17-22, wherein Xaa is linked to Zaa via a carba, lactam, disulfide, thioether, or succinic linker.

24. The MC5R peptide ligand of any of claims 17-23, wherein the MC5R peptide ligand is a 23 to 27-membered ring.

25. A method of treating a central nervous system (CNS) disorder or a mood

disorder in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a composition comprising a melanocortin 5 receptor (MC5R) peptide ligand in a pharmaceutically acceptable carrier, wherein the MC5R peptide ligand is according to Formula 1:

R_1-Nle^4-c[Xaa^5-Yaa^6-*(NMe)*D-Nal(2')^7-Arg^8-Trp^9-*(NMe)*Zaa^{10}]-R_2

wherein R_1 is an acetyl, a glycosylated amino acid,–CO-$(CH_2)_nCH_3$, or –CO-$(CH_2)_nCF_3$, wherein n ranges from 1 to 6,

wherein R_2 is an amide, –COOH, or –CH_2OH,

wherein Xaa is a natural amino acid or an unnatural amino acid, wherein Yaa is a natural amino acid or an unnatural amino acid, and wherein Zaa is a natural amino acid or an unnatural amino acid.

26. The method of claim 25, wherein the subject is a mammal.

27. The method of claim 26, wherein the mammal is a human.

28. The method of any of claims 25-27, wherein Xaa is Asp, Glu or 2-aminobutyric acid.

29. The method of any of claims 25-28, wherein Yaa is selected from a group consisting of His, Pro, octahydroindole-2-carboxylic acid, indoline-2-carboxylic acid, tetrahydro-isoquinoline-3-carboxylic acid, 1-amino-1-cyclohexane carboxylic acid, 1-amino-1-cyclopentane carboxylic acid, 2-aminoindane-2-carboxylic acid, and 1-aminocyclopropane carboxylic acid.

30. The method of any of claims 25-29, wherein Zaa is Lys, ornithine or diaminobutyric acid.

31. The method of any of claims 25-30, wherein the glycosylated amino acid comprises a saccharide linked to a natural amino acid, wherein the natural amino acid is Ser, Thr, Tyr, Asn or Gln, wherein the saccharide is a monosaccharide, a disaccharide, or an oligosaccharide.

32. The method of claim 31, wherein the glycosylated amino acid comprises a saccharide *O*-linked to a natural amino acid, wherein the *O*-linked natural amino acid is Ser, Thr, or Tyr.

33. The method of claim 31, wherein the glycosylated amino acid comprises a saccharide *N*-linked to a natural amino acid, wherein the *N*-linked natural amino acid is Asn or Lys.

34. The method of any of claims 25-33, wherein Xaa is linked to Zaa via a carba, lactam, disulfide, thioether, or succinic linker, thereby forming a cyclic peptide.

35. The method of any of claims 25-34, wherein the MC5R peptide ligand is an antagonist of MC5R.

36. The method of any of claims 25-35, wherein the composition is administered once daily or twice daily.

37. The method of any of claims 25-35, wherein the composition is administered at least once daily, at least once every other day, or at least once weekly.

38. The method of any of claims 25-37, wherein the composition is administered at a daily dose ranging from about 0.001 mg/kg to 100 mg/kg of body weight.

39. The method of any of claims 25-38, wherein the composition is administered intranasally, intravenously, transdermally, or orally.

40. The method of any of claims 25-39, wherein clinical improvement of the CNS disorder or mood disorder is observed in about 1 to 14 days.

41. The method of any of claims 25-40, wherein the mood disorder is a depressive disorder or an anxiety disorder.

42. The method of any of claims 25-41, wherein the composition is effective to evoke at least one of a psychostimulating effect, an anxiolytic effect, or an antidepressant effect.

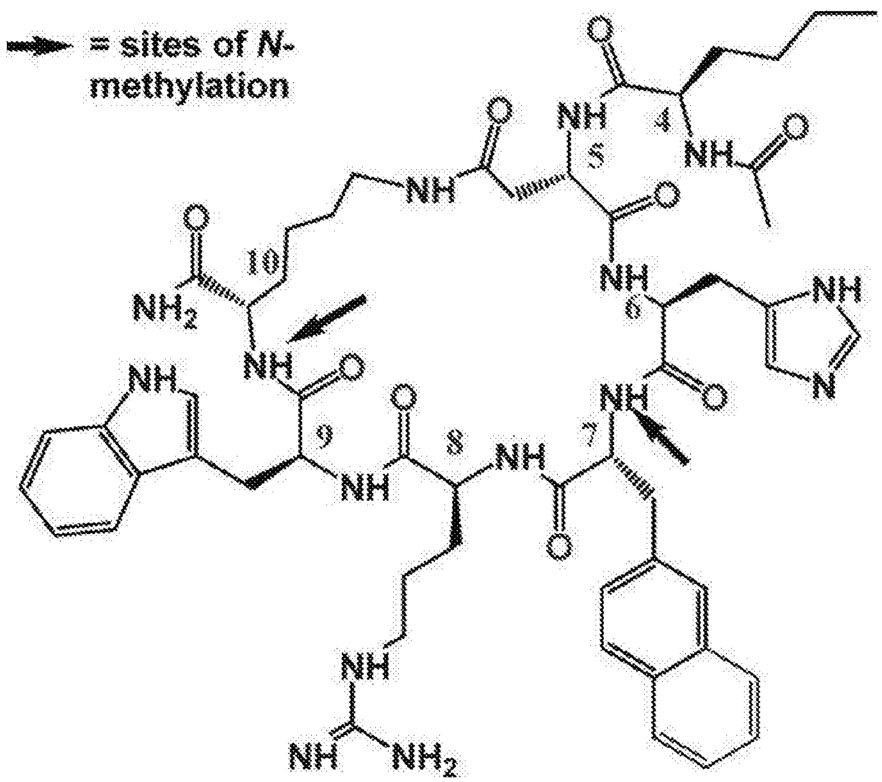


FIG. 1A

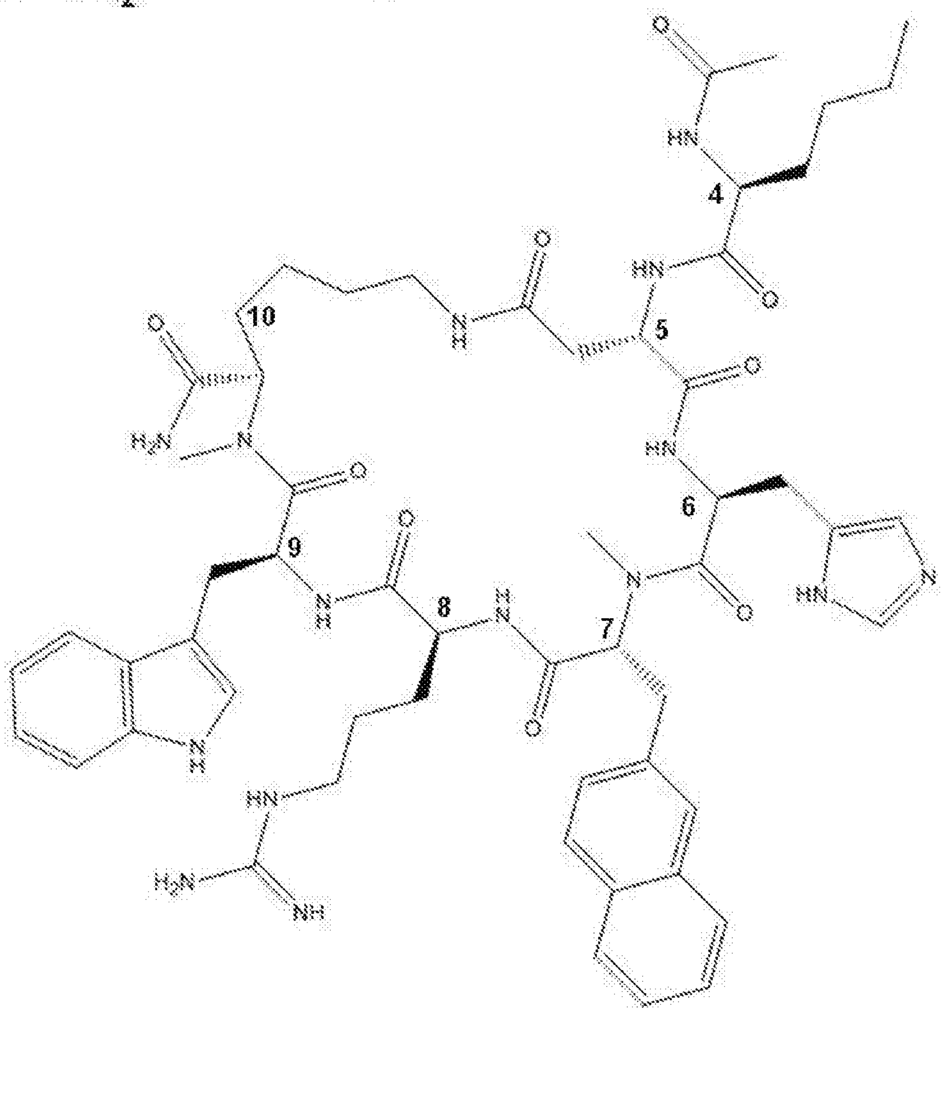


FIG. 1B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/057364

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/00; A61K 31/4985; A61K 31/519; A61K 31/53 (2016.01)
CPC - A61K 31/00; A61K 31/519; A61K 38/00; A61K 38/06 (2016.11)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC - A61K 31/00; A61K 31/4985; A61K 31/519; A61K 31/53
CPC - A61K 31/00; A61K 31/519; A61K 38/00; A61K 38/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/12; 514/16; 514/17; 514/12.2 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patents, PubMed, Google

Search terms used: MC5R melanocortin receptor antagonist inhibitor nervous system administer SHU9119 modified peptide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/0037951 A1 (BLOOD et al) 17 February 2005 (17.02.2005) entire document	1-3, 17-20, 25-28
A	LEE et al. "Solution Structures and Molecular Interactions of Selective Melanocortin Receptor Antagonists," Mol. Cells, 31 December 2010 (31.12.2010), Vol. 30, Pgs. 551-556. entire document	1-3, 17-20, 25-28
A	US 2010/0129319 A1 (LINDQUIST et al) 27 May 2010 (27.05.2010) entire document	1-3, 17-20, 25-28
A	WO 2005/079574 A1 (PALATIN TECHNOLOGIES INC.) 01 September 2005 (01.09.2005)	1-3, 17-20, 25-28
A	US 2015/0037376 A1 (XION PHARMACEUTICAL CORPORATION) 05 February 2015 (05.02.2015) entire document	1-3, 17-20, 25-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 2016	09 JAN 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/057364

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NOs: 1-8 were searched.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/057364

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-16, 21-24, 29-42
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.