

## COMBINATIONS OF A POTASSIUM CHANNEL ACTIVATOR AND AN MC4R AGONIST AND RELATED METHODS OF USE

### CLAIM OF PRIORITY

The present application claims priority to U.S. Application No. 63/548,506, filed on November 14, 2023, the entire contents of which is hereby incorporated by reference.

### BACKGROUND

The melanocortin 4 receptor (MC4R) is a heterotrimeric G-protein-coupled receptor that transduces signals by activating adenylate cyclase. MC4R is primarily expressed in neuronal tissue and plays a role in controlling feeding behavior and energy homeostasis by, for example, integrating an agonist signal provided by the  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH), and an antagonist signal provided by the agouti-related peptide (AGRP). MC4R is a part of the leptin-melanocortin pathway, also known as the POMC-MC4R pathway, which includes a number of proteins such as leptin, leptin receptors, pro-opiomelanocortin (POMC), and prohormone convertases including PCSK1,  $\alpha$ -MSH, and others. In mammals, the hypothalamic POMC-MC4R pathway is part of the regulatory network of appetite and body. While agonism of the MC4R pathway has shown to be an effective treatment for weight loss in certain contexts, there is a desire for enhancement of this treatment and thus interest in exploring certain combination therapies.

### SUMMARY

The present disclosure features methods of treating and/or preventing a disease or disorder in a subject comprising administering a combination of a potassium channel activator (e.g., SURx/Kirx channel activator compound, e.g., a SUR1/Kir6.1 or SUR1/Kir6.2 channel activator compound), or a pharmaceutically acceptable salt thereof and an MC4R agonist, or a pharmaceutically acceptable salt thereof, to the subject. In an embodiment, the SURx/Kirx channel activator compound is a compound having the structure of Formula (XIV), or a pharmaceutically acceptable salt thereof, e.g., as described herein. In an embodiment, the MC4R agonist is a peptide or a small molecule. In an embodiment, the MC4R agonist is a small molecule, e.g., a peptidomimetic small molecule. In an embodiment, the MC4R agonist is a

peptide. In an embodiment, the MC4R agonist is selected from a structure of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII) or a pharmaceutically acceptable salt thereof, e.g., as described herein.

In one aspect, the method comprises administering the combination such that the SURx/Kirx channel activator compound is between about 1 mg/kg to about 200 mg/kg, and the dosage of the MC4R agonist is between about 0.5 mg/kg to about 20 mg/kg. In an embodiment, the SURx/Kirx channel activator compound and the MC4R agonist are administered as a single formulation. In an embodiment, the SURx/Kirx channel activator compound and the MC4R agonist are administered as separate formulations. In an embodiment, the SURx/Kirx channel activator compound is formulated for oral administration. In an embodiment, the SURx/Kirx channel activator compound is formulated for parenteral administration. In an embodiment, the SURx/Kirx channel activator compound is formulated for subcutaneous administration. In an embodiment, the MC4R agonist is formulated for parenteral administration. In an embodiment, the MC4R agonist is formulated for subcutaneous administration. In an embodiment, the MC4R agonist is formulated for oral administration. In an embodiment, the ratio of the amount of the SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 200:1 to 1:1.

In another aspect, the method comprises treating and/or preventing a disease or disorder, e.g., obesity or an obesity-related disorder, such as hyperphagia or hypothalamic obesity, with a combination of a potassium channel activator (e.g., SURx/Kirx channel activator compound, e.g., a SUR1/Kir6.1 or SUR1/Kir6.2 channel activator compound), or a pharmaceutically acceptable salt thereof and an MC4R agonist, or a pharmaceutically acceptable salt thereof. In an embodiment, the disease or disorder is a metabolic syndrome. In some embodiments, the metabolic disorder is a genetic or epigenetic disorder, e.g., Prader-Willi syndrome, Alström syndrome, Bardet-Biedl syndrome, or Smith-Magenis syndrome. In an embodiment, the disease or disorder is Prader Willi syndrome or congenital hyperinsulinism (CHI). In an embodiment, the disease or disorder is a behavioural disorder or a psychological disorder. In an embodiment, the disease or disorder is obesity (e.g., a genetic obesity or a non-genetic obesity, e.g., an acquired obesity).



The present disclosure further contemplates compositions, e.g., pharmaceutical compositions, as well related methods of making. Further embodiments of the present disclosure are provided herein in the **Description, Drawings, Examples, and Claims**.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**FIGS. 1A-B** demonstrate the synergistic effects of an exemplary MC4R agonist (MC4R Agonist I) and an exemplary SURx/Kirx channel activator compound I (SURx/Kirx channel activator compound I) on body weight in obese Zucker rats over a 21-day period. **FIG. 1A** is a plot of the body weight (grams) of Zucker rats administered placebo (5 mg/kg), SURx/Kirx channel activator compound I (150, 50, 80 and 100 mg/kg/day from day 1-6, 7-13, 13-17, 17-22 respectively), and SURx/Kirx channel activator compound I (150, 50, 80 and 100 mg/kg/day from day 1-6, 7-13, 13-17, 17-22 respectively) + MC4R Agonist I (5 mg/kg/week) over 21 days. **FIG. 1B** is a plot of the body weight of Zucker rats administered placebo depot injection (5 mg/kg, subcutaneous (SC), once per week), a second exemplary MC4R agonist (MC4R Agonist II) depot injection (30 mg/mL, 5 mg/kg, SC, once per week), MC4R Agonist I depot injection (30 mg/mL, 5 mg/kg, SC, once per week) and MC4R Agonist I depot injection (30 mg/mL, 10 mg/kg, SC, once per week).

**FIGS. 2A-B** are graphs of the cumulative food intake of Zucker rats administered placebo, SURx/Kirx channel activator compound I alone, or a combination of SURx/Kirx channel activator compound + MC4R agonist compound. **FIG. 2A** is a graph of the cumulative food intake of Zucker rats over the 21-day period administered placebo, SURx/Kirx channel activator compound I (150, 50, 80 and 100 mg/kg/day from day 1-6, 7-13, 13-17, 17-22 respectively) and SURx/Kirx channel activator compound I (150, 50, 80 and 100 mg/kg/day from day 1-6, 7-13, 13-17, 17-22 respectively) + MC4R Agonist I (5 mg/kg/weekly) in the Experiment 1 study. **FIG. 2B** is a plot of the cumulative food intake (g) of male Zucker rats over the 21 days in all 3 groups of male Zucker rats in Experiment 2 over 21 days that were treated with placebo (5 mg/kg), SURx/Kirx channel activator compound I (50, 80 and 100 mg/kg/day from day 1-6, 6-10, 10-21 respectively) and SURx/Kirx channel activator compound I (50, 80 and 100 mg/kg/day from day 1-6, 6-10, 10-21 respectively) + MC4R Agonist I (5 mg/kg/week).

**FIGS. 3A-C** are plots of the plasma glucose, insulin, and leptin in obese Zucker rats in the fed state in the Experiment 1 over 17 days. Zucker rats were administered placebo,

SURx/Kirx channel activator compound I and SURx/Kirx channel activator compound I + MC4R Activator Is (5mg/kg/week). **FIG. 3A** is a plot of the plasma glucose concentration (mM) in the Zucker rats during Experiment 1. **FIG. 3B** is a plot of the plasma insulin concentration (ng/mL) in the Zucker rats during the experiment. **FIG. 3C** is a plot of the plasma leptin concentration (ng/mL) in the Zucker rats during the experiment.

**FIGS. 4A-B** show the results of the oral glucose tolerance test (2g/kg glucose given after overnight fast) at the end of the 21-day in Experiment 1 in Zucker rats administered placebo, SURx/Kirx channel activator compound I (100 mg/kg/day), and SURx/Kirx channel activator compound I (100mg/kg/day) + MC4R Agonist I (5 mg/kg/week). **FIG. 4A** is a plot of the plasma glucose concentration (mg/dL) in the Zucker rats over 120 min. **FIG. 4B** is a plot of the plasma insulin (ng/mL) concentration over 120 min.

**FIG. 5** is a graph of the body weight changes of male Zucker rats in the Experiment 2 during 21-day administration of placebo (5 mg/kg), SURx/Kirx channel activator compound I 50, 80 and 100 mg/kg/day from day (1-6, 6-10, 10-21 respectively) and SURx/Kirx channel activator compound I (50, 80 and 100 mg/kg/day from day 1-6, 6-10, 10-21 respectively) + MC4R Agonist I (5 mg/kg/week).

**FIG. 6** is a bar graph of the weekly body weight gain for the male obese Zucker rats for Days 1-7, Days 7-14, Days 14-20, and overall from Days 1-20.

**FIGS. 7A-7B** are plots of the plasma glucose and insulin in fed Zucker rats in Experiment 2. **FIG. 7A** shows plasma glucose concentration (mM) in the Zucker rats over the course of Experiment 2. **FIG. 7B** is a graph of plasma insulin concentration (ng/mL) in the Zucker rats through Experiment 2. All data presents mean (sem).

**FIGS. 8A-8D** show the results of the oral glucose tolerance test (2g/kg glucose given after overnight fast) for the both the combined and main study in Zucker rats administered placebo (5 mg/kg), SURx/Kirx channel activator compound I (100 mg/kg/day) and SURx/Kirx channel activator compound I (100mg/kg/day) + MC4R Agonist I (5 mg/kg). **FIG. 8A** is a plot of the plasma glucose concentration (mg/dL) in the Zucker rats over the course of 120 min. **FIG. 8B** is a bar graph showing the plasma glucose (mg/dL) for the Placebo, SURx/Kirx Channel Activator I, and SURx/Kirx Channel Activator I + MC4R Agonist I groups for the combined pilot and main study. **FIG. 8C** is a plot of the plasma insulin concentration (ng/mL) in the Zucker rats over for 120 min. **FIG. 8D** is a bar graph showing the plasma insulin (ng/mL) for the

Placebo, SURx/Kirx Channel Activator I, and SURx/Kirx Channel Activator I + MC4R Agonist I groups for the combined pilot and main study.

**FIGS. 9A-9D** show the calculated areas under the curve (AUC) for plasma insulin and glucose for the OGTT measurements in **FIGS. 8A-D**. Shown is the mean (SEM) n=4. **FIG. 9A** are plots of the glucose AUC (0-60 min) and glucose (0-120 min) for the treatment groups: placebo, SURx/Kirx channel activator compound I (100 mg/kg) and SURx/Kirx channel activator compound I (100mg/kg)+ MC4R Agonist I (5 mg/kg). **FIG. 9B** is a bar graph of the glucose AUC (0-60 min) for the Placebo, SURx/Kirx Channel Activator I, and SURx/Kirx Channel Activator I + MC4R Agonist I groups for the combined pilot and main study. **FIG. 9C** are plots of the insulin AUC (0-60 min) and insulin AUC (0-120 min) for the three treatment groups: placebo, SURx/Kirx channel activator compound I (100 mg/kg) and SURx/Kirx channel activator compound I (100mg/kg)+ MC4R Agonist I (5 mg/kg/week). All data present means (sem). **FIG. 9D** is a bar graph of the insulin AUC (0-60 min) for the Placebo, SURx/Kirx Channel Activator I, and SURx/Kirx Channel Activator I + MC4R Agonist I groups for the combined pilot and main study.

**FIGS. 10A-10D** are bar graphs of plasma fat and inflammatory hepatic biomarkers in samples collected on day 17 (fed state) in Experiment 2. All data presents mean (sem). **FIG. 10A-B** are bar graphs of plasma cholesterol concentration (mg/dL) and total triglycerides (mmol/L) for placebo, SURx/Kirx channel activator compound I (100 mg/kg/day) and SURx/Kirx channel activator compound I (100 mg/kg/day) + MC4R Agonist I (5 mg/kg/week). **FIG. 10C** is a bar graph of plasma aspartate aminotransferase (AST, U/L) for placebo, SURx/Kirx channel activator compound I (100 mg/kg/day) and SURx/Kirx channel activator compound I(100 mg/kg/day) + MC4R Agonist I (5 mg/kg/week). **FIG. 10D** is a bar graphs for plasma alanine transaminase (ALT, U/L) for placebo, channel activator compound I (100 mg/kg/day) and SURx/Kirx channel activator compound I(100 mg/kg/day) + MC4R Agonist I (5 mg/kg/week).

**FIGS. 11A-11D** are bar graphs of hepatic parameters, i.e., liver cholesterol (mg/g), liver triglycerides (mg/g), liver nonesterified fatty acids (NEFA, mg/g) and liver glycogen (µg/g) for placebo, SURx/Kirx channel activator compound I (100 mg/kg/day) and SURx/Kirx channel activator compound I(100 mg/kg/day) + MC4R Agonist I (5 mg/kg/week) in Experiment 2.

**FIG. 12A-B** are plots demonstrating the effect of SURx/Kirx channel activator compound I and MC4R Agonist I on body weight reduction over MC4R Agonist I alone or SURx/Kirx channel activator compound I, in which the obese Zucker rats were administered an initially high dose of SURx/Kirx channel activator compound I, which was subsequently reduced. The three treatment groups were SURx/Kirx channel activator compound I (150, 50, 80 and 100 mg/kg/day from day 1-6, 7-13, 13-17, 17-22 respectively), SURx/Kirx channel activator compound I (150, 50, 80 and 100 mg/kg/day from day 1-6, 7-13, 13-17, 17-22 respectively) + MC4R Agonist I (5 mg/kg/week), and MC4R Agonist I (5 mg/kg/week). All data are shown mean (sem), SURx/Kirx channel activator compound I + MC4R Agonist I vs MC4R Agonist I:  $p < 0.05$  from day 3 up to day 21.

**FIG. 13** is a plot demonstrating the effect of SURx/Kirx channel activator compound I and MC4R Agonist I on body weight reduction compared to MC4R agonist I alone or SURx/Kirx channel activator I alone, in which the obese Zucker rats were administered an initially low dose of SURx/Kirx channel activator compound I, which was subsequently increased as part of Experiment 2. The three treatment groups were SURx/Kirx channel activator compound I (50, 80 and 100 mg/kg/day from day 1-6, 6-10, 10-21 respectively), SURx/Kirx channel activator compound I (50, 80 and 100 mg/kg/day from day 1-6, 6-10, 10-21 respectively) + MC4R Agonist I (5 mg/kg/weekly), and MC4R Agonist I (5 mg/kg/weekly). All data are shown mean (sem), SURx/Kirx channel activator compound I + MC4R Agonist I (5 mg/kg/week) vs + MC4R Agonist I (5 mg/kg/week):  $p < 0.05$  from day 3 till the end of the study.

**FIGS. 14A-E** are plots demonstrating the effect of the once-weekly MC4 agonist I and SURx/Kirx channel activator compound I (100 mg/kg/day) vs SURx/Kirx channel activator compound I (100 mg/kg/day) alone or Placebo on liver histology in obese male Zucker rats in the pilot study, including steatosis, hepatocellular ballooning, lobular inflammation, lipid deposition and total NAS in Experiment 1.

**FIGS. 15A-E** are plots demonstrating the effect of the once-weekly MC4 agonist I and SURx/Kirx channel activator compound I (100 mg/kg/day) vs SURx/Kirx channel activator compound I (100 mg/kg/day) alone or Placebo on liver histology in obese male Zucker rats in the pilot study, including steatosis, hepatocellular ballooning, lobular inflammation, lipid deposition and total NAS in Experiment 2. The significant reduction ( $p < 0.05$ ) in measured steatosis,

hepatocellular ballooning, lobular inflammation, lipid deposition and total NAS from placebo is shown [mean (sem)].

**FIGS. 16A-B** are graphs showing the percent change in body weight compared to Placebo for the repeat study for various doses of SURx/Kirx Channel Activator I dose regimes, comparing the Placebo, SURx/Kirx Channel Activator I, and SURx/Kirx Channel Activator I + MC4R Agonist I, and MC4R Agonist I (Original).

**FIGS. 17A-B** are graphs showing the percent change cumulative food intake compared to Placebo for the repeat study for various doses of SURx/Kirx Channel Activator I dose regimes, comparing the Placebo, SURx/Kirx Channel Activator I, and SURx/Kirx Channel Activator I + MC4R Agonist I, and MC4R Agonist I (Original).

**FIG. 18** is a table showing the SURx/Kirx Channel Activator I and MC4R Agonist concentrations in liver, CSF, and plasma at a dose for the SURx/Kirx Channel Activator I (100 mg/kg/d) + MC4 Activator I ( 5 mg/kg) combo arm.

**FIGS. 19A-D** are graphs showing the percentage changes in carcass weight (**FIG. 19A**), fat (**FIG. 19B**), protein (**FIG. 19C**), and water (**FIG. 19D**) for the SURx/Kirx Channel Activator I alone (repeat), SURx/Kirx Channel Activator I + MC4R Agonist I 5 mg/kg (repeat), MC4R Agonist II 5 mg/kg (original), and MC4R Agonist I 5 mg/kg (original) groups.

#### DETAILED DESCRIPTION

Described herein are combinations of a potassium channel activator compound (i.e., a SURx/Kirx channel activator compound) and MC4R agonist, as well as compositions thereof and related methods of use. In an embodiment, the SURx/Kirx channel activator compound and the MC4R agonist are administered to a subject in combination in order to treat and/or prevent a disease, disorder, or condition, for example, an obesity or obesity-related condition. In an embodiment, the subject is diagnosed with obesity or an obesity-related condition.

#### Definitions

As used herein “about” and “approximately” generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

“Acquire” or “acquiring” as the terms are used herein, refer to obtaining possession of a physical entity, or a value, *e.g.*, a numerical value, or knowledge of (*e.g.*, knowledge of the sequence or mutational state of) a genotype or a nucleic acid or polypeptide, by “directly acquiring” or “indirectly acquiring” the physical entity, value, or knowledge. “Directly acquiring” means performing a physical process (*e.g.*, performing a synthetic or analytical method) to obtain the physical entity, value, or knowledge. “Indirectly acquiring” refers to receiving the physical entity, value, or knowledge from another party or source (*e.g.*, a third-party laboratory that directly acquired the physical entity, value, or knowledge). Directly acquiring a physical entity includes performing a process that includes a physical change in a physical substance, *e.g.*, a starting material. Exemplary changes include making a physical entity from two or more starting materials, shearing or fragmenting a substance, separating or purifying a substance, combining two or more separate entities into a mixture, performing a chemical reaction that includes breaking or forming a covalent or non-covalent bond. Directly acquiring a value or knowledge includes performing a process that includes a physical change in a sample or another substance. Examples include performing an analytical process which includes a physical change in a substance, *e.g.*, a sample, analyte, or reagent (sometimes referred to herein as “physical analysis”), performing an analytical method, *e.g.*, a method which includes one or more of the following: separating or purifying a substance, *e.g.*, an analyte, or a fragment or other derivative thereof, from another substance; combining an analyte, or fragment or other derivative thereof, with another substance, *e.g.*, a buffer, solvent, or reactant; or changing the structure of an analyte, or a fragment or other derivative thereof, *e.g.*, by breaking or forming a covalent or non-covalent bond, between a first and a second atom of the analyte; or by changing the structure of a reagent, or a fragment or other derivative thereof, *e.g.*, by breaking or forming a covalent or non-covalent bond, between a first and a second atom of the reagent.

As used herein, the term “obese” refers to a subject having a body mass index (BMI) within the ranges defined as “obese” by the Center for Disease Control (*see, e.g.*, URL.cdc.gov/obesity/defining.html and www.cdc.gov/obesity/childhood-/defining.html, last accessed on August 26, 2012) or as defined by “Clinical Guidelines on the

Identification, Evaluation, and Treatment of Overweight and Obesity in Adults” from the National Institutes of Health. BMI is obtained by dividing a subject’s weight, e.g., in kilograms (kg) by the square of the subject’s height, e.g., in meter (m). For example, an adult who has a BMI of 30 kg/m<sup>2</sup> or higher is considered obese. For example, an adult with a BMI of 25.0 to 29.9 kg/m<sup>2</sup> is considered overweight; an adult with a BMI of 18.5 to 24.9 kg/m<sup>2</sup> is considered to have a normal or healthy weight range; and an adult with a BMI of less than 18.5 kg/m<sup>2</sup> is considered to be underweight. For example, an adult having a height of 5 feet, 9 inches with a body weight of 203 pounds or more is considered obese. For pediatric subject, e.g., children and teens, obese refers to a subject having a BMI at or above the 85<sup>th</sup> to 95<sup>th</sup> percentile for pediatric subjects, e.g., children and teens, of the same age and sex.

As used herein, a “weekly average of daily most hunger score” refers to the average or mean of the daily most score hunger score of a subject for a period of week or seven days.

A “severely obese” subject or a subject having “severe obesity” refers to a subject having a BMI of 35 kg/m<sup>2</sup> or higher, e.g., 40 kg/m<sup>2</sup> or higher. For example, a severely obese subject is over 100% over the ideal (normal, healthy) body weight.

As used herein “early onset”, e.g., as in early onset obesity, refers to an onset (e.g., first occurrence of one or more symptoms of a disorder, e.g., a disorder described herein, e.g., obesity) that occurs in a subject before adulthood, e.g., during childhood, e.g., when the subject is less 18 years of age or younger (e.g., 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 year of age or younger, or during adolescence, e.g., when the child is younger than 12 years of age or when the child is younger than 6 years of age).

As used herein, the term “metabolic syndrome” refers to a group of symptoms that occur together and increase the risk for coronary artery disease, stroke, and type 2 diabetes. In an embodiment, e.g., according to the American Heart Association and the National Heart, Lung, and Blood Institute, metabolic syndrome (also referred to as Syndrome X) is present if a subject has three or more of the following signs: 1) Blood pressure equal to or higher than 130/85 mmHg; 2) Fasting blood sugar (glucose) equal to or higher than 100 mg/dL; 3) Large waist circumference (length around the waist): - Men - 40 inches or more; - Women - 35 inches or more; 4) Low HDL cholesterol: - Men - under 40 mg/dL; - Women - under 50 mg/dL; 5) Triglycerides equal to or higher than 150 mg/dL. Metabolic syndrome can be diagnosed by

testing subject's blood pressure, blood glucose level, HDL cholesterol level, LDL cholesterol level, total cholesterol level, and triglyceride level.

As used herein, the term “agonist” refers to any chemical compound, either naturally occurring or synthetic, that, upon interacting with (*e.g.*, binding to) its target, *e.g.*, MC4R, raises the signaling activity of MC4R above its basal level. An agonist can be a superagonist (*i.e.*, a compound that is capable of producing a greater maximal response than the endogenous agonist for the target receptor, and thus has an efficacy of more than 100%), a full agonist (*i.e.*, a compound that elicits a maximal response following receptor occupation and activation) or a partial agonist (*i.e.*, a compounds that can activate receptors but are unable to elicit the maximal response of the receptor system).

As used herein “treating” includes achieving one or more of the following results: reducing the body weight (as measured, for example, by a body mass index (BMI) and/or body weight), *e.g.*, compared to a control (*e.g.*, body weight before treatment or a predetermined body weight); reducing the waist circumference, *e.g.*, compared to a control (*e.g.*, waist circumference before treatment or a predetermined waist circumference); reducing the hunger level, *e.g.*, compared to a control (*e.g.*, hunger level before treatment or a predetermined hunger level); increasing the resting energy expenditure (REE), *e.g.*, compared to a control (*e.g.*, REE before treatment or a predetermined REE); decreasing the food intake, *e.g.*, compared to a control level (*e.g.*, before treatment or a predetermined food intake); ameliorating or improving a clinical symptom or indicators associated with a disorder described herein such as obesity, Prader Willi Syndrome, Smith-Magenis syndrome, *e.g.*, type-II diabetes, pre-diabetic condition, blood level of hemoglobin A1C (Hb1Ac) above 6%, hyperinsulinemia, hyperlipidemia, insulin insensitivity, or glucose intolerance; delaying, inhibiting or preventing the progression of obesity and/or obesity related indications; or partially or totally delaying, inhibiting or preventing the onset or development of obesity or a obesity related indication. Delaying, inhibiting or preventing the progression of the obesity includes for example, delaying, inhibiting or preventing the progression of a subject having normal weight to obesity. In embodiments, a control is a value of a parameter measured before treatment by a MC4R agonist described herein or a predetermined value. The term “treating” further includes partially or totally reducing the risk for coronary artery disease, stroke, and type 2 diabetes associated with the metabolic syndrome as well as ameliorating or improving a clinical symptom or signs of metabolic syndrome



associated with metabolic syndrome, such as any one or more of the five indicators listed above. For example, the term “treating” includes delaying, inhibiting or preventing the progression of parameters associated with the metabolic syndrome, including insulin resistance, glucose clearance and parameters of cardiovascular disease including heart rate and blood pressure.

As used herein “inhibition” or “inhibits” can include a reduction in a certain parameter, such as a parameter described herein. For example, inhibition of a parameter, e.g., activity, can be at least 5%, 10%, 20%, 30%, 40%, or more is included by this term. Thus, inhibition need not be 100%.

As used herein, the term “prophylactic treatment” refers to treatment before onset of obesity to prevent, inhibit or reduce its occurrence.

As used herein, the term “potassium channel activator compound” is a compound that binds to and/or activates (e.g., induces the opening of or prolongs the open state of) a potassium channel. In an embodiment, a potassium channel activator compound hyperpolarizes the cell membrane and/or promotes potassium efflux. In an embodiment, a potassium channel activator compound enhances cell membrane permeability to potassium ions. In an embodiment, a potassium channel activator prevents intracellular penetration of calcium. In an embodiment, the potassium channel activator compound is a SURx or Kirx channel activator compound (e.g., a SURx/Kirx channel activator compound, e.g., a SUR1/Kir6.2 channel activator compound). Exemplary potassium channel activator compounds include aprikalim, bimakalim, cromakalim, emakalim, levromakalim, diazoxide, nicorandil, pinacidil, retigabine, minoxidil, and tifenazoxide (NN414), NNC 55-0118, as well as pharmaceutically acceptable salts thereof.

As used herein, the term “subject” refers to a mammal, e.g., a human. Subject can also refer to an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like). In an embodiment, the subject is a pediatric subject (e.g., a subject under 21 or 18 years of age). In an embodiment, the subject is an adult subject (e.g., a subject over 18 or 21 years of age).

As used herein “unit dosage form” refers to a physically discrete unit suited as unitary doses for a subject to be treated. Each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

As used herein “dosage” refers to a quantity or amount of a therapeutic agent. In some embodiments, a dosage is the amount administered to the subject in a single administration, e.g., in a single injection, a single infusion, or single administration of one or more unit dosages. In embodiments, a dosage is the amount administered to the subject in multiple administrations, e.g., multiple injections, multiple infusions, or multiple administrations of one or more unit dosages. In other embodiments, a dosage can refer to the total amount administered to the subject in a certain time period, e.g., per day. In such examples, the dosage is typically referred to as “daily dosage” or dosage in terms of quantity per day.

As used herein “hunger” or “hunger level” refers to a subject’s appetite, desire to consume food, or perceived need for food. In an embodiment, hunger comprises an inability to recognize that one is full (satiety), a constant preoccupation with food, persistent food-seeking behaviors, abnormal behaviors (e.g., emotional outbursts or violence), or an inability to concentrate, e.g., in the presence or absence of food. In embodiments, the hunger or hunger level of a subject can be quantified by using a scale to obtain a hunger score. In embodiments, the scale for hunger assigns a higher score for a subject that more frequently (e.g., often or always) feels unbearable hunger and a lower score for a subject that less frequently (e.g., sometimes or never) feels unbearable hunger. See, e.g., Sibilia. *Psychological Topics* 19 (2010), 2, 341-354. For example, a Likert scale for hunger can be used that assigns scores from 0 to 10 points (0=no hunger; 10=severe hunger). In other examples, a Likert scale for hunger can be used that assigns scores from 1 to 4 points, where a subject who never feels unbearable hunger is assigned a score of 1, where a subject who sometimes feels unbearable hunger is assigned a score of 2, where a subject who often feels unbearable hunger is assigned a score of 3, and where a subject who always feels unbearable hunger is assigned a score of 4. See *Id.*

#### *Selected Chemical Definitions*

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75<sup>th</sup> Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of

organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5<sup>th</sup> Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3<sup>rd</sup> Edition, Cambridge University Press, Cambridge, 1987.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used to define the peptides is that typically used in the art wherein the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. Where the amino acid has D and L isomeric forms, it is the L form of the amino acid that is represented unless otherwise explicitly indicated.

When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C<sub>1</sub>-C<sub>6</sub> alkyl" is intended to encompass, C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>1</sub>-C<sub>6</sub>, C<sub>1</sub>-C<sub>5</sub>, C<sub>1</sub>-C<sub>4</sub>, C<sub>1</sub>-C<sub>3</sub>, C<sub>1</sub>-C<sub>2</sub>, C<sub>2</sub>-C<sub>6</sub>, C<sub>2</sub>-C<sub>5</sub>, C<sub>2</sub>-C<sub>4</sub>, C<sub>2</sub>-C<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub>, C<sub>3</sub>-C<sub>5</sub>, C<sub>3</sub>-C<sub>4</sub>, C<sub>4</sub>-C<sub>6</sub>, C<sub>4</sub>-C<sub>5</sub>, and C<sub>5</sub>-C<sub>6</sub> alkyl.

The compounds useful for practicing the methods described herein may possess one or more chiral centers and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present disclosure. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilizing methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of the disclosure.

The compounds useful for practicing the methods described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including <sup>1</sup>H, <sup>2</sup>H (D or deuterium), and <sup>3</sup>H (T or tritium); C may be in any isotopic form, including <sup>12</sup>C, <sup>13</sup>C, and <sup>14</sup>C; O may be in any isotopic form, including <sup>16</sup>O and <sup>18</sup>O; and the like.

The term "pharmaceutically acceptable salt" as used herein is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds used in the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds used in the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, e.g., Berge et al, *Journal of Pharmaceutical Science* 66: 1-19 (1977)). Certain specific compounds used in the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. These salts may be prepared by methods known to those skilled in the art. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for use in the present disclosure.

The compounds useful for practicing the methods described herein can also exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. The compounds useful for practicing the methods described herein may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

The term “solvate” refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates.

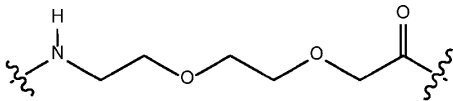
The term “hydrate” refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula  $R \cdot x H_2O$ , wherein R is the compound and wherein x is a number greater than 0.

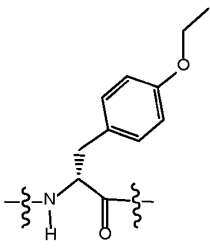
The term “tautomer” as used herein refers to compounds that are interchangeable forms of a compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of  $\pi$  electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest. Table 1 provides definition for chemical abbreviations used herein.

**Table 1.** Definitions of chemical abbreviations.

| Symbol | Meaning                                                               |
|--------|-----------------------------------------------------------------------|
| Abu    | $\alpha$ -aminobutyric acid                                           |
| Ac     | acyl group                                                            |
| Acc    | 1-amino-1-cyclo(C <sub>3</sub> -C <sub>9</sub> )alkyl carboxylic acid |
| A3c    | 1-amino-1-cyclopropanecarboxylic acid                                 |
| A4c    | 1-amino-1-cyclobutanecarboxylic acid                                  |
| A5c    | 1-amino-1-cyclopentanecarboxylic acid                                 |
| A6c    | 1-amino-1-cyclohexanecarboxylic acid                                  |
| Aha    | 7-aminoheptanoic acid                                                 |
| Ahx    | 6-aminohexanoic acid                                                  |

|              |                                                                          |
|--------------|--------------------------------------------------------------------------|
| Aib          | $\alpha$ -aminoisobutyric acid                                           |
| Aic          | 2-aminoindan-2-carboxylic acid                                           |
| Ala or A     | Alanine                                                                  |
| $\beta$ -Ala | $\beta$ -alanine                                                         |
| Apc          | denotes the structure:<br>                                               |
| Apn          | 5-aminopentanoic acid ( $\text{HN}-(\text{CH}_2)_4-\text{C}(\text{O})$ ) |
| Arg or R     | Arginine                                                                 |
| hArg         | Homoarginine                                                             |
| Asn or N     | Asparagine                                                               |
| Asp or D     | aspartic acid                                                            |
| Bal          | 3-benzothierylalanine                                                    |
| Bip          | 4,4'-biphenylalanine, represented by the structure<br>                   |
| Bpa          | 4-benzoylphenylalanine                                                   |
| 4-Br-Phe     | 4-bromo-phenylalanine                                                    |
| Cha          | $\beta$ -cyclohexylalanine                                               |
| hCha         | homo-cyclohexylalanine                                                   |
| Chg          | Cyclohexylglycine                                                        |
| Cys or C     | Cysteine                                                                 |
| hCys         | Homocysteine                                                             |

|               |                                                                                                                                            |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Dab           | 2,4-diaminobutyric acid                                                                                                                    |
| Dap           | 2,3-diaminopropionic acid                                                                                                                  |
| Dip           | $\beta,\beta$ -diphenylalanine                                                                                                             |
| Doc           | 8-amino-3,6-dioxaoctanoic acid with the structure of:<br> |
| 2-Fua         | $\beta$ -(2-furyl)-alanine                                                                                                                 |
| Gaba          | 4-aminobutyric acid                                                                                                                        |
| Gln or Q      | Glutamine                                                                                                                                  |
| Glu or E      | glutamic acid                                                                                                                              |
| Gly or G      | Glycine                                                                                                                                    |
| His or H      | Histidine                                                                                                                                  |
| 3-Hyp         | trans-3-hydroxy-L-proline, i.e., (2S,3S)-3-hydroxy-pyrrolidine-2-carboxylic acid                                                           |
| 4-Hyp         | 4-hydroxyproline, i.e., (2S,4R)-4-hydroxypyrrolidine-2-carboxylic acid                                                                     |
| Ile or I      | Isoleucine                                                                                                                                 |
| Leu or L      | Leucine                                                                                                                                    |
| hLeu          | Homoleucine                                                                                                                                |
| Lys or K      | Lysine                                                                                                                                     |
| Met or M      | Methionine                                                                                                                                 |
| $\beta$ -hMet | $\beta$ -homomethionine                                                                                                                    |
| 1-Nal         | $\beta$ -(1-naphthyl)alanine                                                                                                               |
| 2-Nal         | $\beta$ -(2-naphthyl)alanine                                                                                                               |
| Nip           | nipecotic acid                                                                                                                             |
| Nle           | Norleucine                                                                                                                                 |
| Ole           | octahydroindole-2-carboxylic acid                                                                                                          |
| Orn           | Ornithine                                                                                                                                  |
| 2-Pal         | $\beta$ -(2-pyridyl)alanine                                                                                                                |
| 3-Pal         | $\beta$ -(3-pyridyl)alanine                                                                                                                |
| 4-Pal         | $\beta$ -(4-pyridyl)alanine                                                                                                                |

|            |                                                                                                           |
|------------|-----------------------------------------------------------------------------------------------------------|
| Pen        | Penicillamine                                                                                             |
| Pff        | (S)-pentafluorophenylalanine                                                                              |
| Phe or F   | Phenylalanine                                                                                             |
| hPhe       | homophenylalanine                                                                                         |
| Pro or P   | Proline                                                                                                   |
| hProP      | Homoproline                                                                                               |
| Ser or S   | Serine                                                                                                    |
| Tle        | tert-Leucine                                                                                              |
| Taz        | $\beta$ -(4-thiazolyl)alanine                                                                             |
| 2-Thi      | $\beta$ -(2-thienyl)alanine                                                                               |
| 3-Thi      | $\beta$ -(3-thienyl)alanine                                                                               |
| Thr or T   | Threonine                                                                                                 |
| Trp or W   | Tryptophan                                                                                                |
| Tyr or Y   | Tyrosine                                                                                                  |
| D-(Et) Tyr | has a structure of<br> |
| Val or V   | Valine                                                                                                    |
|            | Certain other abbreviations used herein are defined as follows:                                           |
| Boc:       | tert-butyloxycarbonyl                                                                                     |
| Bzl:       | Benzyl                                                                                                    |
| DCM:       | Dichloromethane                                                                                           |
| DIC:       | N,N-diisopropylcarbodiimide                                                                               |
| DIEA:      | diisopropylethyl amine                                                                                    |
| Dmab:      | 4-{N-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-amino}benzyl                               |



|        |                                                                           |
|--------|---------------------------------------------------------------------------|
| DMAP:  | 4-(dimethylamino)pyridine                                                 |
| DMF:   | Dimethylformamide                                                         |
| DNP:   | 2,4-dinitrophenyl                                                         |
| Fm:    | Fluorenylmethyl                                                           |
| Fmoc:  | fluorenylmethyloxycarbonyl                                                |
| For:   | Formyl                                                                    |
| HBTU:  | 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate  |
| cHex   | Cyclohexyl                                                                |
| HOAT:  | O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HOBt:  | 1-hydroxy-benzotriazole                                                   |
| MBNA   | 4-methylbenzhydramine                                                     |
| Mmt:   | 4-methoxytrityl                                                           |
| NMP:   | N-methylpyrrolidone                                                       |
| O-tBu  | oxy-tert-butyl                                                            |
| Pbf:   | 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl                         |
| PyBroP | bromo-tris-pyrrolidino-phosphonium hexafluorophosphate                    |
| tBu:   | tert-butyl                                                                |
| TIS:   | triisopropylsilane                                                        |
| TOS:   | Tosyl                                                                     |
| Trt    | Trityl                                                                    |
| TFA:   | trifluoro acetic acid                                                     |
| TFFH:  | tetramethylfluoroformidinium hexafluorophosphate                          |
| Z:     | benzyloxycarbonyl                                                         |

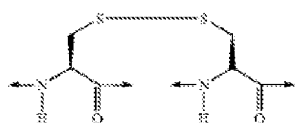
Unless otherwise indicated, with the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-C(R)(R')-CO-, wherein R and R' each is, independently, hydrogen or the side chain of an amino acid (e.g., R=CH<sub>3</sub> and R'=H for Ala), or R and R' may be joined to form a ring system.



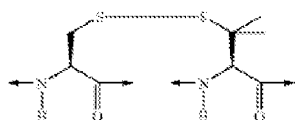
For the N-terminal amino acid, the abbreviation stands for the structure of:

The designation “NH<sub>2</sub>” in e.g., as in Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO:13), indicates that the C-terminus of the peptide is amidated. Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys) (SEQ ID NO:107), or alternatively Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH (SEQ ID NO:107), indicates that the C-terminus is the free acid.

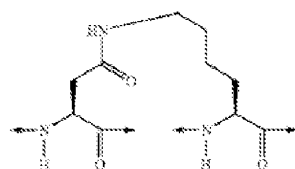
“-c(Cys-Cys)-” or “-cyclo(Cys-Cys)-” denotes the structure:



“-c(Cys-Pen)-” or “-cyclo(Cys-Pen)-” denotes the structure:

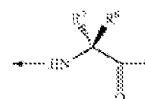
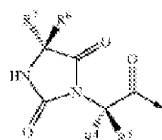


“-c(Asp-Lys)-” or “-cyclo(Asp-Lys)-” denotes the structure:

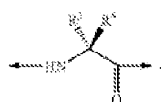


The following abbreviations are used throughout the disclosure:

“Hydantoin-(C(O)-(A<sup>a</sup>-A<sup>b</sup>))” denotes the structure:

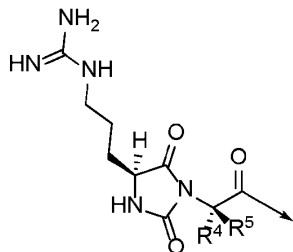


, wherein amino acid “A<sup>a</sup>” has the structure:

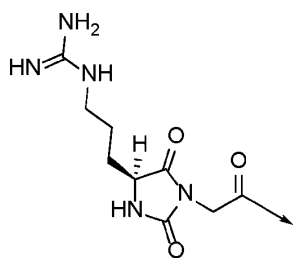


and amino acid “A<sup>b</sup>” the structure:

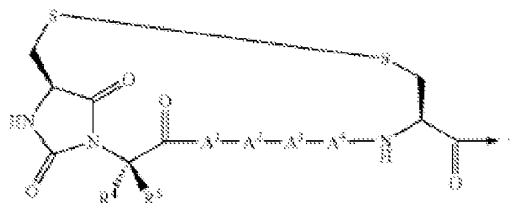
For example, “Hydantoin-(C(O)-Arg-A<sup>b</sup>)” would have the following structure:



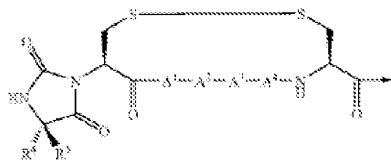
For example, “Hydantoin-(C(O)-(Arg-Gly))” would have the following structure:



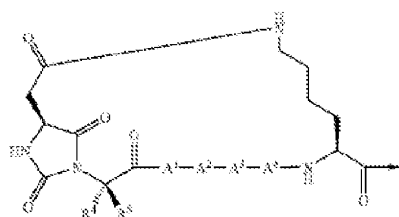
For example, a compound represented as “c[Hydantoin(C(O)-(Cys-A<sup>b</sup>))-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-Cys]-” would have the following the structure:



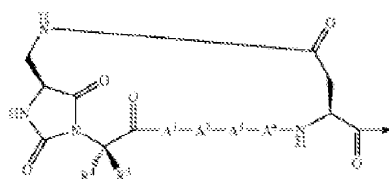
whereas a compound represented as “c[Hydantoin(C(O)-(A<sup>b</sup>-Cys))-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-Cys]-” would have the structure:



For further guidance, “c[Hydantoin(C(O)-(Asp-A<sup>b</sup>))-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-Lys]-” represents the following compound:



whereas “c[Hydantoin(C(O)-(Dap-A<sup>b</sup>))-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-Asp]-” has the following formula:



“Acyl” refers to R<sup>''</sup>-C(O)-, where R<sup>''</sup> is H, alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, alkenyl, substituted alkenyl, aryl, alkylaryl, or substituted alkylaryl, and is indicated in the general formula of a particular embodiment as “Ac”.

“Alkyl” refers to a hydrocarbon group containing one or more carbon atoms, where multiple carbon atoms if present are joined by single bonds. The alkyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups.

“Hydroxyalkyl” refers to an alkyl group wherein one or more hydrogen atoms of the hydrocarbon group are substituted with one or more hydroxy radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like.

“Substituted alkyl” refers to an alkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, amine (e.g., -NH<sub>2</sub>, -NHCH<sub>3</sub>), -NO<sub>2</sub>, guanidine, urea, amidine, and -(C<sub>1</sub>-C<sub>20</sub>) alkyl, wherein said -(C<sub>1</sub>-C<sub>20</sub>) alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens, —CF<sub>3</sub>, —OCH<sub>3</sub>, —OCF<sub>3</sub>, and -(CH<sub>2</sub>)<sub>0-20</sub>-COOH. In different embodiments 1, 2, 3 or 4 substituents are present. The presence of -(CH<sub>2</sub>)<sub>0-20</sub>-COOH results in the production of an alkyl acid. Non-limiting examples of alkyl acids containing, or consisting of, -(CH<sub>2</sub>)<sub>0-20</sub>-COOH include 2-norbornane acetic acid, tert-butyric acid, 3-cyclopentyl propionic acid, and the like.

The term “halo” encompasses fluoro, chloro, bromo and iodo.

Guanidines are a group of organic compounds that share a common functional group with the general structure  $(R^1R^2N)(R^3R^4N)C=N-R^5$ . The central bond within this group is an imine, and the group is related structurally to amidines and ureas.

“Heteroalkyl” refers to an alkyl wherein one or more of the carbon atoms in the hydrocarbon group is replaced with one or more of the following groups: amino, amido,  $—O—$ ,  $—S—$  or carbonyl. In different embodiments 1 or 2 heteroatoms are present.

“Substituted heteroalkyl” refers to a heteroalkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine),  $—OH$ ,  $—CN$ ,  $—SH$ ,  $—NH_2$ ,  $—NHCH_3$ ,  $—NO_2$ , and  $-(C_1-C_{20})$  alkyl, wherein said  $-(C_1-C_{20})$  alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens,  $—CF_3$ ,  $—OCH_3$ ,  $—OCF_3$ , and  $-(CH_2)_{0-20}-COOH$ . In different embodiments 1, 2, 3 or 4 substituents are present.

“Alkenyl” refers to a hydrocarbon group made up of two or more carbons where one or more carbon-carbon double bonds are present. The alkenyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups.

“Substituted alkenyl” refers to an alkenyl wherein one or more hydrogens are replaced with one or more substituents selected from the group consisting of halogen (i.e., fluorine, chlorine, bromine, and iodine),  $—OH$ ,  $—CN$ ,  $—SH$ ,  $—NH_2$ ,  $—NHCH_3$ ,  $—NO_2$ , and  $-(C_1-C_{20})$  alkyl, wherein said  $-(C_1-C_{20})$  alkyl optionally may be substituted with one or more substituents selected, independently for each occurrence, from the group consisting of halogens,  $—CF_3$ ,  $—OCH_3$ ,  $—OCF_3$ , and  $-(CH_2)_{0-20}-COOH$ . In different embodiments 1, 2, 3 or 4 substituents are present.

“Aryl” refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to three conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups. Preferably, the aryl is a 5- or 6-membered ring. Preferred atoms for a heterocyclic aryl are one or more sulfur, oxygen, and/or nitrogen. Non-limiting examples of aryl include phenyl, 1-naphthyl, 2-naphthyl, indole, quinoline, 2-imidazole, 9-anthracene, and the like. Aryl substituents are selected from the group consisting of  $-(C_1-C_{20})$  alkyl,  $-(C_1-C_{20})$  alkoxy, halogen (i.e., fluorine, chlorine, bromine, and iodine),  $—OH$ ,  $—CN$ ,  $—SH$ ,  $—NH_2$ ,  $—NO_2$ ,  $-(C_1-C_{20})$  alkyl substituted with halogens,  $—CF_3$ ,  $—$

OCF<sub>3</sub>, and —(CH<sub>2</sub>)<sub>0-20</sub>—COOH. In different embodiments the aryl contains 0, 1, 2, 3, or 4 substituents.

“Alkylaryl” refers to an “alkyl” joined to an “aryl”.

The term “(C<sub>1-12</sub>)hydrocarbon moiety” encompasses alkyl, alkenyl and alkynyl and in the case of alkenyl and alkynyl there is C<sub>2</sub>-C<sub>12</sub>.

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different. For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

Designation “(amino acid)<sub>n</sub>” means that an amino acid is repeated *n* times. For example, designation “(Pro)<sub>2</sub>” or “(Arg)<sub>3</sub>” mean that proline or arginine residues are repeated, respectively, two or three times.

#### **MC4R agonists**

Described herein are methods for treating and/or preventing a disease, disorder, or condition, such as obesity or an obesity-related disorder (e.g., a metabolic disorder) in a subject, comprising administering a combination therapy to a subject comprising a melanocortin 4 receptor (MC4R) agonist and a SURx/Kirxchannel activator compound. Examples of naturally occurring MC4R agonists include α-MSH, β-MSH, γ-MSH and adrenocorticotrophic hormone (ACTH) or a functional fragment thereof. Examples of synthetic MC4R agonists are described in detail below.

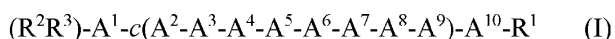
In some embodiments, an MC4R agonist can be any known agonist of MC4R. In some example embodiment, the MC4R agonist is not an adrenocorticotrophic hormone (ACTH) or a fragment thereof. Exemplary MC4R agonists include those described in WO2011104378; WO2011104379; WO201060901; WO200887189, WO200887188, WO200887187, WO200887186; US20110065652; WO2010144341; WO2010144344; WO201065799; WO201065800; WO201065801; WO201065802; WO201037081; WO2009152079; WO2009151383; US20100311648; US20100280079; WO201081666; WO201034500; WO200910299; WO2008116665; WO201052256; WO201052255; WO201126015; US20100120783; WO201096854; US20100190793; WO201025142; WO2014144260;

WO2017059075; and WO201015972. Further examples of MC4R agonists are found in U.S. Pat. No. 8,263,608; U.S. Pat. No. 8,247,530; U.S. Pat. No. 8,114,844; and U.S. Pat. No. 7,968,548. The entire teachings of these publications are incorporated herein by reference.

In some embodiments, the MC4R agonist is a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a pharmaceutically acceptable salt thereof as described herein. In some embodiments, the MC4R agonist is a compound of any one of Formulas (I) or (II), or a pharmaceutically acceptable salt thereof as described herein. In one embodiment, the MC4R agonist is a compound of Formula (I). In one embodiment, the MC4R agonist is a compound of Formula (II).

In one example embodiment, the agonist of MC4R is a tripeptide D-Phe-Arg-Trp (SEQ ID NO: 560) or a pharmaceutical salt thereof. In another example, the agonist is any peptide that includes SEQ ID NO: 560 or a pharmaceutical salt thereof. In yet another example, the MC4R agonist is an acetylated tripeptide Ac-D-Phe-Arg-Trp-NH<sub>2</sub> (SEQ ID NO: 561) or a pharmaceutical salt thereof.

In some embodiments, the MC4R agonist is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein A<sup>1</sup> is Acc, HN—(CH<sub>2</sub>)<sub>m</sub>—C(O), L- or D-amino acid, or deleted; A<sup>2</sup> is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu; A<sup>3</sup> is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted; A<sup>4</sup> is His, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe; A<sup>5</sup> is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe, L-Phe or D-(Et)Tyr; A<sup>6</sup> is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH((CH<sub>2</sub>)<sub>n</sub>-N(R<sup>4</sup>R<sup>5</sup>))-C(O); A<sup>7</sup> is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip; A<sup>8</sup> is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-(CH<sub>2</sub>)<sub>s</sub>-C(O), or deleted; A<sup>9</sup> is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys; A<sup>10</sup> is Acc, HN-(CH<sub>2</sub>)<sub>r</sub>-C(O), L- or D-amino acid, or deleted; R<sup>1</sup> is OH or NH<sub>2</sub>; each of R<sup>2</sup> and R<sup>3</sup> is, independently for each occurrence, selected from the group consisting of H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, (C<sub>1</sub>-C<sub>30</sub>)acyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, (C<sub>2</sub>-C<sub>30</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkynyl, substituted aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl, and substituted aryl(C<sub>1</sub>-C<sub>30</sub>)acyl; each of R<sup>4</sup> and R<sup>5</sup> is, independently for each occurrence, H, (C<sub>1</sub>-C<sub>40</sub>)alkyl, (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, (C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>2</sub>-C<sub>40</sub>)alkenyl, (C<sub>2</sub>-C<sub>40</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>1</sub>-C<sub>40</sub>)alkyl,

substituted (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkynyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>1</sub>-C<sub>40</sub>)alkylsulfonyl, or -C(NH)-NH<sub>2</sub>; m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; n is, independently for each occurrence, 1, 2, 3, 4 or 5; s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7; t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7; X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, and X<sup>5</sup> each is, independently for each occurrence, H, F, Cl, Br, I, -(C<sub>1</sub>-C<sub>10</sub>) alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>2</sub>-C<sub>10</sub>) alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>) alkenyl, (C<sub>2</sub>-C<sub>10</sub>) alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>) alkynyl, aryl, substituted aryl, OH, NH<sub>2</sub>, NO<sub>2</sub>, or CN.

In some embodiments, for Formula (I), when R<sup>4</sup> is (C<sub>1</sub>-C<sub>40</sub>)acyl, aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>1</sub>-C<sub>40</sub>)acyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>1</sub>-C<sub>40</sub>)alkylsulfonyl, or -C(NH)-NH<sub>2</sub>, then R<sup>5</sup> is H or (C<sub>1</sub>-C<sub>40</sub>)alkyl, (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>40</sub>)alkenyl, (C<sub>2</sub>-C<sub>40</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkynyl, or substituted aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl.

In some embodiments, for Formula (I), when R<sup>2</sup> is (C<sub>1</sub>-C<sub>30</sub>)acyl, aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>1</sub>-C<sub>30</sub>)acyl, or substituted aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, then R<sup>3</sup> is H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, (C<sub>2</sub>-C<sub>30</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkynyl, or substituted aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl;

In some embodiments, for Formula (I), either A<sup>3</sup> or A<sup>8</sup> or both must be present in said compound.

In some embodiments, for Formula (I) when A<sup>2</sup> is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen, then A<sup>9</sup> is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen.

In some embodiments, for Formula (I), when A<sup>2</sup> is Asp or Glu, then A<sup>9</sup> is Dab, Dap, Orn, or Lys.

In some embodiments, for Formula (I), when A<sup>8</sup> is Ala or Gly, then A<sup>1</sup> is not Nle.

In some embodiments, for Formula (I), when A<sup>1</sup> is deleted, then R<sup>2</sup> and R<sup>3</sup> cannot both be H.

In some embodiments, for Formula (I): A<sup>1</sup> is A6c, Arg, D-Arg, Cha, D-Cha, hCha, Chg, D-Chg, Gaba, Ile, Leu, hLeu, Met, β-hMet, 2-Nal, D-2-Nal, Nip, Nle, Oic, Phe, D-Phe, hPhe, hPro, Val, or deleted; A<sup>2</sup> is Asp, Cys, D-Cys, hCys, D-hCys, Glu, Pen, or D-Pen; A<sup>3</sup> is D-Abu, Aib, Ala, β-Ala, D-Ala, D-Cha, Gaba, D-Glu, Gly, D-Ile, D-Leu, D-Tle, D-Val, or deleted; A<sup>4</sup> is



His or 3-Pal; A<sup>5</sup> is D-Bal, D-1-Nal, D-2-Nal, D-Phe, D-Trp, or D-(Et)Tyr; A<sup>6</sup> is Arg, or hArg; A<sup>7</sup> is Bal, Bip, 1-Nal, 2-Nal, Trp, D-Trp; A<sup>8</sup> is A6c, D-Ala, Aha, Ahx, Ala,  $\beta$ -Ala, Apn, Gaba, Gly or deleted; A<sup>9</sup> is Cys, D-Cys, hCys, D-hCys, Lys, Pen, or D-Pen; and A<sup>10</sup> is Thr, or deleted, wherein at least one of A<sup>3</sup> or A<sup>8</sup> is deleted, but not both.

In some embodiments, the compound of Formula (I) is a compound disclosed in International Patent Application Publication Number WO 2007/008704, which is incorporated herein by reference in its entirety.

In some embodiments, the compound of Formula (I) is selected from:

- (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp- $\beta$ -Ala-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp- $\beta$ -Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 14) Ac-Nle-c(Cys- $\beta$ -Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 20) Ac-Nle-c(D-Cys- $\beta$ -Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

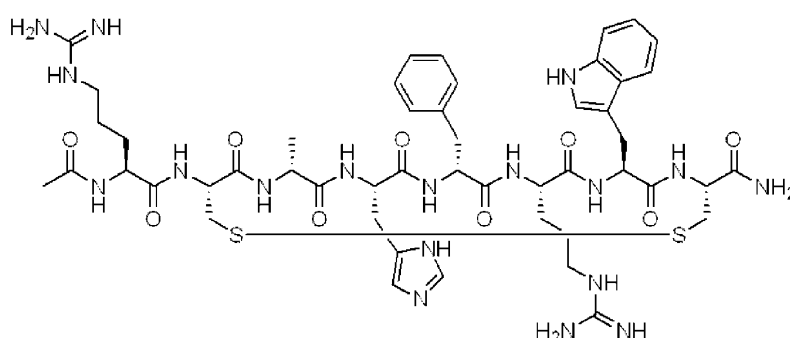
(SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 45) n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 46) n-butyryl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 68) n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 69) n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;

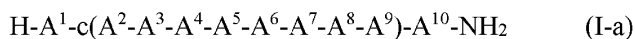
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 88) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 104) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 107) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;  
(SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 115) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH;  
(SEQ ID NO: 116) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH;

(SEQ ID NO: 117) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH;  
(SEQ ID NO: 118) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH;  
(SEQ ID NO: 119) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH;  
(SEQ ID NO: 120) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH;  
(SEQ ID NO: 121) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH;  
(SEQ ID NO: 122) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 123) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 124) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 125) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 126) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 127) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 128) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 129) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH;  
(SEQ ID NO: 130) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH;  
(SEQ ID NO: 131) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH;  
(SEQ ID NO: 132) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH;  
(SEQ ID NO: 133) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH;  
(SEQ ID NO: 134) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH;  
(SEQ ID NO: 135) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH;  
(SEQ ID NO: 136) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH;  
(SEQ ID NO: 137) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;  
(SEQ ID NO: 138) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH;  
(SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH<sub>2</sub>; and  
(SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof. In embodiments, the compound of Formula (I) is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof. Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 140), also known as RM-493 and setmelanotide, is a peptide that retains the specificity and functionality of the naturally occurring hormone that activates MC4R and has not been shown to adversely affect blood pressure in clinical trials (see, e.g., Chen et al. *J. Clin. Endocrinol. Metab.* 2015;100(4):1639-45. The structure of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 140) is shown below:



In some embodiments, the MC4R agonist is a compound of Formula (I-a):



or a pharmaceutically acceptable salt thereof, wherein A<sup>1</sup> is Phe, D-Phe, or Nle; A<sup>2</sup> is Cys; A<sup>3</sup> is deleted; A<sup>4</sup> is His; A<sup>5</sup> is D-Phe or D-(Et)Tyr; A<sup>6</sup> is Arg or hArg; A<sup>7</sup> is Trp or Bip; A<sup>8</sup> is Ala, β-Ala, Gaba, or Apn; A<sup>9</sup> is D-Cys; and A<sup>10</sup> is Thr or deleted.

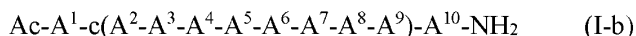
In some embodiments, the compound of Formula (I-a) is selected from:

- (SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;
- (SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;

(SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>; and

(SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>.

In some embodiments, the MC4R agonist is a compound of Formula (I-b):



or a pharmaceutically acceptable salt thereof, wherein:

A<sup>1</sup> is Nle, A6c, D-2-Nal, Cha, Oic, Chg, hCha, D-Cha, D-hCha, Nip, hPro, hLeu, Phe, D-Phe, D-Chg, hPhe, β-hMet, Gaba, Leu, Ile, Val, 2-Nal, Arg or D-Arg; A<sup>2</sup> is Asp, Cys, D-Cys, or Pen; A<sup>3</sup> is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, D-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha, deleted; A<sup>4</sup> His or 3-Pal; A<sup>5</sup> is Phe, D-Phe, or D-2-Nal; A<sup>6</sup> is Arg; A<sup>7</sup> is Trp, 1-Nal, 2-Nal, Bal, or D-Trp; A<sup>8</sup> is β-Ala, A6c, Ahx, Apn, Gaba, Ala, Aha, D-Ala or deleted; A<sup>9</sup> is Lys, Cys, D-Cys, or Pen; A<sup>10</sup> is deleted, wherein A<sup>2</sup> and A<sup>9</sup> are pairwise selected to form a disulfide or lactam bridge.

In some embodiments, the compound of Formula (I-b) is selected from:

(SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 14) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 20) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

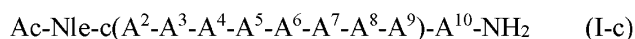
(SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH<sub>2</sub>;



(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH<sub>2</sub>.

In some embodiments, the MC4R agonist is a compound of Formula (I-c):



or a pharmaceutically acceptable salt thereof, wherein: A<sup>2</sup> is Asp, Cys, D-Cys, or Pen; A<sup>3</sup> is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, Aib, DI-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha, or deleted; A<sup>4</sup> is His or 3-Pal; A<sup>5</sup> is D-Phe, D-2-Nal, or Phe; A<sup>6</sup> is Arg; A<sup>7</sup> is Trp, D-Trp, 2-Nal, 1-Nal, Bal; A<sup>8</sup> is β-Ala, A6c, Ahx, Apn, Gaba, D-Ala, Aha, Ala or deleted; A<sup>9</sup> is Lys, Cys, D-Cys or

Pen; and A<sup>10</sup> is deleted, wherein A<sup>2</sup> and A<sup>9</sup> are pairwise selected to form a disulfide or lactam bridge.

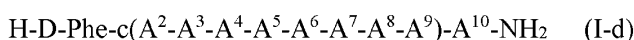
In some embodiments, the compound of Formula (I-c) is selected from:

- (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 14) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 20) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>.

In some embodiments, the MC4R agonist is a compound of Formula (I-d):

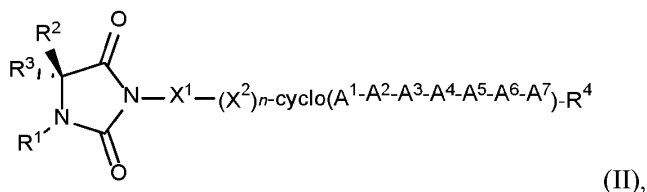


or a pharmaceutically acceptable salt thereof, wherein A<sup>2</sup> is Cys; A<sup>3</sup> is deleted; A<sup>4</sup> is His; A<sup>5</sup> is D-Phe or D-(Et)Tyr; A<sup>6</sup> is Arg or hArg; A<sup>7</sup> is Trp or Bip; A<sup>8</sup> is Ala, β-Ala, or Gaba; A<sup>9</sup> is D-Cys; and A<sup>10</sup> is Thr.

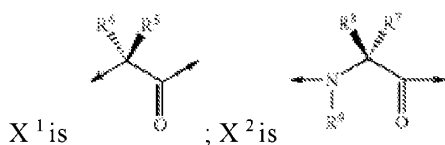
In some embodiments, the compound of Formula (I-d) is selected from:

(SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>; and  
 (SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>.

In some embodiments, the MC4R agonist is a compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:



; A<sup>1</sup> is Asp, Cys, D-Cys, Dab, Dap, Glu, Lys, Orn, Pen or D-Pen; A<sup>2</sup> is an L- or D-amino acid; A<sup>3</sup> is H is, 2-Pal, 3-Pal, 4-Pal, (X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe, Taz, 2-Thi or 3-Thi; A<sup>4</sup> is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D-(X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe; A<sup>5</sup> is Arg, hArg, Dab, Dap, Lys or Orn; A<sup>6</sup> is Bal, 1-Nal, 2-Nal, (X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe or Trp; A<sup>7</sup> is Asp, Cys, D-Cys, Dab, Dap, Glu, Lys, Orn, Pen or D-Pen; R<sup>1</sup> is H, (C<sub>1</sub>-C<sub>10</sub>)alkyl or substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl; R<sup>2</sup> and R<sup>3</sup> each is, independently, H, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl, aryl(C<sub>1</sub>-C<sub>5</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl or substituted aryl(C<sub>1</sub>-C<sub>5</sub>)alkyl or R<sup>2</sup> and R<sup>3</sup> may be fused together form a cyclic moiety; R<sup>4</sup> is OH, NH<sub>2</sub>, CO<sub>2</sub>H or C(O)NH<sub>2</sub>; R<sup>5</sup> and R<sup>6</sup> each is, independently, H, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl, aryl(C<sub>1</sub>-C<sub>5</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl or substituted aryl(C<sub>1</sub>-C<sub>5</sub>)alkyl or R<sup>5</sup> and R<sup>6</sup> may be fused together form a cyclic moiety; R<sup>7</sup> and R<sup>8</sup> each is, independently, H, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl, aryl(C<sub>1</sub>-C<sub>5</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl or substituted aryl(C<sub>1</sub>-C<sub>5</sub>)alkyl; or R<sup>7</sup> and R<sup>8</sup> may be fused together form a cyclic moiety; R<sup>9</sup> is H, (C<sub>1</sub>-C<sub>10</sub>)alkyl or substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl; and n is, independently for each occurrence thereof, 0, 1, 2, 3, 4, 5, 6 or 7; or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula (II), A<sup>1</sup> is Cys; A<sup>2</sup> is D-Ala, Asn, Asp, Gln, Glu or D-Phe; A<sup>3</sup> is H is; A<sup>4</sup> is D-2-Nal or D-Phe; A<sup>5</sup> is Arg; A<sup>6</sup> is Trp; and A<sup>7</sup> is Cys or Pen; each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>9</sup> is, independently, H; R<sup>4</sup> is C(O)NH<sub>2</sub>; each of R<sup>5</sup> and R<sup>6</sup> is, independently, H, (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl or substituted (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl or R<sup>5</sup> and R<sup>6</sup> may be fused together form a cyclic moiety; and each of R<sup>7</sup> and R<sup>8</sup> is, independently, H, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl or substituted (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl; or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula (II) is selected from:

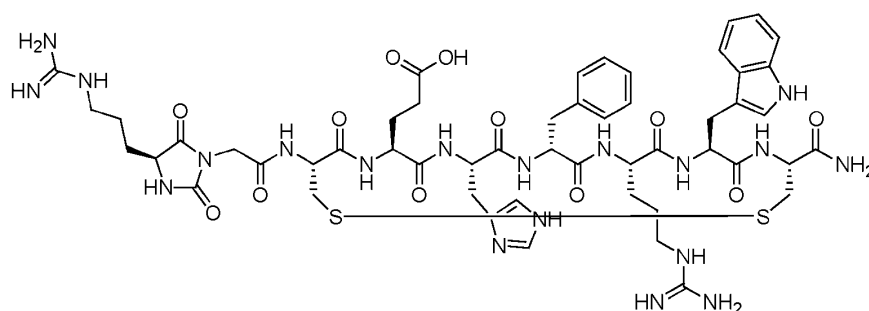
- (SEQ ID NO: 148) Hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 149) Hydantoin(C(O)-(Nle-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 150) Hydantoin(C(O)-(Gly-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 151) Hydantoin(C(O)-(Nle-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 152) Hydantoin(C(O)-(Gly-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 153) Hydantoin(C(O)-(Nle-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 154) Hydantoin(C(O)-(Gly-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 155) Hydantoin(C(O)-(Ala-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 156) Hydantoin(C(O)-(D-Ala-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 157) Hydantoin(C(O)-(Aib-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 158) Hydantoin(C(O)-(Val-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 159) Hydantoin(C(O)-(Ile-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 160) Hydantoin(C(O)-(Leu-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 161) Hydantoin(C(O)-(Gly-Gly))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 162) Hydantoin(C(O)-(Nle-Gly))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 163) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 164) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 165) Hydantoin(C(O)-(Arg-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 166) Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 167) Hydantoin(C(O)-(Arg-Gly))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 168) Hydantoin(C(O)-(Ala-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 169) Hydantoin(C(O)-(Val-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 170) Hydantoin(C(O)-(Gly-Nle))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 171) Hydantoin(C(O)-(A6c-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 172) Hydantoin(C(O)-(Gly-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 173) Hydantoin(C(O)-(Ala-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 174) Hydantoin(C(O)-(D-Ala-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 175) Hydantoin(C(O)-(Val-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 176) Hydantoin(C(O)-(Leu-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 177) Hydantoin(C(O)-(Cha-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 178) Hydantoin(C(O)-(Aib-Nle))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 179) Hydantoin(C(O)-(Gly-Arg))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 180) Hydantoin(C(O)-(Gly-Arg))-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 181) Hydantoin(C(O)-(Gly-Arg))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 182) Hydantoin(C(O)-(Gly-Arg))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;

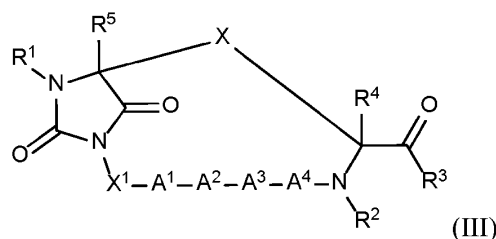
(SEQ ID NO: 183) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 184) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 185) Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 186) Hydantoin(C(O)-(Nle-Ala))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,  
 or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (II) is described in WO2008/147556 or International Patent Application Number PCT/US08/06675, each of which is incorporated herein by reference in its entirety.

In embodiments, the compound of Formula (II) is hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 148) or a pharmaceutically acceptable salt thereof, also known as RM-511. The structure of hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 148) is shown below:



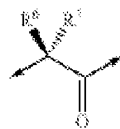
In some embodiments, the MC4R agonist is a compound of Formula (III):



or a pharmaceutically acceptable salt thereof, wherein X is selected from the group consisting of -CH<sub>2</sub>-S-S-CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-S-S-CH<sub>2</sub>-, -CH<sub>2</sub>-S-S-C(CH<sub>3</sub>)<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-S-S-C(CH<sub>3</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-S-S-CH<sub>2</sub>-, -CH<sub>2</sub>-S-S-(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-S-S-(CH<sub>2</sub>)<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-S-S-(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-S-S-C(CH<sub>3</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>r</sub>-C(O)-NR<sup>8</sup>-(CH<sub>2</sub>)<sub>r</sub>- and -(CH<sub>2</sub>)<sub>r</sub>-NR<sup>8</sup>-C(O)-(CH<sub>2</sub>)<sub>r</sub>-; R<sup>2</sup> each is, independently, H, (C<sub>1</sub>-



C<sub>10</sub>)alkyl or substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl; R<sup>3</sup> is -OH or -NH<sub>2</sub>; R<sup>4</sup> and R<sup>5</sup> each is, independently, H,



(C<sub>1</sub>-C<sub>10</sub>)alkyl or substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl; X<sup>1</sup> is ; A<sup>1</sup> is H is, 2-Pal, 3-Pal, 4-Pal, (X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe, Taz, 2-Thi, 3-Thi or is deleted;

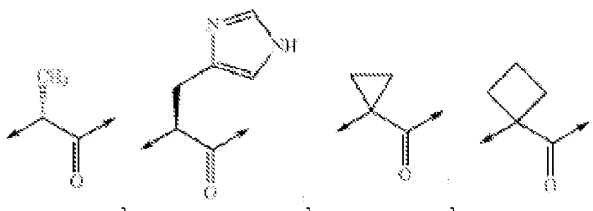
A<sup>2</sup> is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D-(X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe; A<sup>3</sup> is Arg, hArg, Dab, Dap, Lys or Orn; A<sup>4</sup> is Bal, 1-Nal, 2-Nal, (X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe or Trp; R<sup>6</sup> and R<sup>7</sup> each is,

independently for each occurrence thereof, H, (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl, aryl(C<sub>1</sub>-C<sub>5</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)heteroalkyl or substituted aryl(C<sub>1</sub>-C<sub>5</sub>)alkyl provided that R<sup>6</sup>

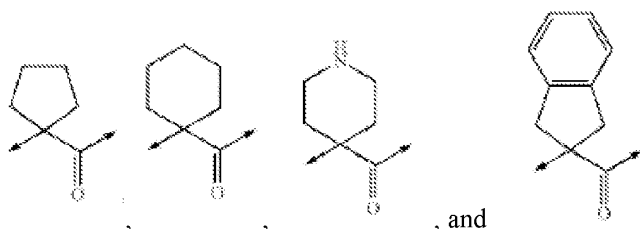
and R<sup>7</sup> may be joined together to form a ring; R<sup>8</sup> is H, (C<sub>1</sub>-C<sub>10</sub>)alkyl or substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl;

r is, independently for each occurrence thereof, 1, 2, 3, 4 or 5; and t is, independently for each occurrence thereof, 1 or 2.

Compounds according to the foregoing formula can include compounds wherein X<sup>1</sup> is



selected from the group consisting of:



Compounds of Formula (III) are disclosed in International Patent Publication WO 2008/147556 or International Patent Application Number PCT/US08/06675, each of which is incorporated herein by reference in its entirety.

In some embodiments, the compound of Formula (III) is selected from:

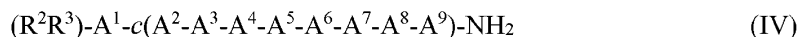
(SEQ ID NO: 187) c[Hydantoin(C(O)-(Cys-D-Ala))-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;

(SEQ ID NO: 188) c[Hydantoin(C(O)-(hCys-D-Ala))-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;

(SEQ ID NO: 189) c[Hydantoin(C(O)-(Cys-D-Ala))-His-D-2-Nal-Arg-Trp-Cys]-NH<sub>2</sub>;

(SEQ ID NO: 190) c[Hydantoin(C(O)-(hCys-D-Ala))-His-D-2-Nal-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 191) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 192) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Orn]-NH<sub>2</sub>;  
 (SEQ ID NO: 193) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Dab]-NH<sub>2</sub>;  
 (SEQ ID NO: 194) c[Hydantoin(C(O)-(Asp-D-Ala))-His-D-Phe-Arg-Trp-Dap]-NH<sub>2</sub>;  
 (SEQ ID NO: 195) c[Hydantoin(C(O)-(Asp-His))-D-2-Nal-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 196) c[Hydantoin(C(O)-(Asp-His))-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 197) c[Hydantoin(C(O)-(Asp-A3c))-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 198) c[Hydantoin(C(O)-(Asp-A5c))-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 199) c[Hydantoin(C(O)-(Asp-A6c))-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 200) c[Hydantoin(C(O)-(Asp-A3c))-D-2-Nal-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 201) c[Hydantoin(C(O)-(Asp-A5c))-D-2-Nal-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 202) c[Hydantoin(C(O)-(Asp-A6c))-D-2-Nal-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 203) c[Hydantoin(C(O)-(Asp-Aic))-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 204) c[Hydantoin(C(O)-(Asp-Apc))-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 205) c[Hydantoin(C(O)-(Asp-Aic))-D-2-Nal-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 206) c[Hydantoin(C(O)-(Asp-Apc))-D-2-Nal-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 207) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Orn]-NH<sub>2</sub>;  
 (SEQ ID NO: 208) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Dab]-NH<sub>2</sub>;  
 (SEQ ID NO: 209) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Dap]-NH<sub>2</sub>;  
 (SEQ ID NO: 210) c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>;  
 (SEQ ID NO: 211) c[Hydantoin(C(O)-(Glu-His))-D-Phe-Arg-Trp-Dap]-NH<sub>2</sub>; and  
 (SEQ ID NO: 212) c[Hydantoin(C(O)-(Glu-His))-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>,  
 or a pharmaceutically acceptable salt thereof.

In some embodiments, the MC4R agonist is a compound of Formula (IV):



or a pharmaceutically acceptable salt thereof, wherein A<sup>1</sup> is Nle or deleted; A<sup>2</sup> is Cys or Asp; A<sup>3</sup> is Glu or D-Ala; A<sup>4</sup> is His; A<sup>5</sup> is D-Phe; A<sup>6</sup> is Arg; A<sup>7</sup> is Trp, 2-Nal or Bal; A<sup>8</sup> is Gly, Ala, D-Ala, 3-Ala, Gaba or Apn; A<sup>9</sup> is Cys or Lys; each of R<sup>2</sup> and R<sup>3</sup> is independently selected from the group consisting of H or (C<sub>1</sub>-C<sub>6</sub>)acyl.

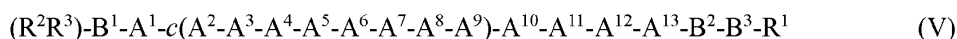
In exemplary embodiments of Formula (IV): (I) when  $R^2$  is (C<sub>1</sub>-C<sub>6</sub>)acyl, then  $R^3$  is H; and (II) when  $A^2$  is Cys, then  $A^9$  is Cys.

Exemplary MC4R agonists of Formula (IV) are disclosed in International Patent Application Publication Number WO 2007/008704, which is incorporated herein by reference in its entirety.

In some embodiments, the compound of Formula (IV) is selected from:

(SEQ ID NO: 213) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 214) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Ala-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 215) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-β-Ala-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 216) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 217) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 218) Ac-c(Cys-Glu-His-D-Phe-Arg-Trp-Ala-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 219) Ac-c(Cys-Glu-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 220) Ac-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 221) Ac-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Ala-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 222) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Ala-Cys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 223) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Ala-Lys)-NH<sub>2</sub>,  
 or a pharmaceutically acceptable salt thereof.

In some embodiments, the MC4R agonist is a compound of Formula (V):



or a pharmaceutically acceptable salt thereof:  $B^1$  is a peptide moiety which contains 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids, wherein at least 5 amino acids are independently selected from the group consisting of L-Arg, D-Arg, L-hArg and D-hArg, or  $B^1$  is optionally deleted;  $A^1$  is Acc, HN-(CH<sub>2</sub>)<sub>m</sub>-C(O), L- or D-amino acid or deleted;  $A^2$  is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp or Glu;  $A^3$  is Gly, Glu, Ala, β-Ala, Gaba, Aib, D-amino acid or deleted;  $A^4$  is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi or (X', X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe;  $A^5$  is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe, D-(Et)Tyr, D-Dip, D-Bip or D-Bpa;  $A^6$  is Arg, hArg, Dab, Dap, Lys, Orn or HN-CH((CH<sub>2</sub>)<sub>n</sub>-N(R<sup>4</sup>R<sup>5</sup>))-C(O);  $A^7$  is Trp, 1-Nal, 2-Nal, Bal, Bip, Dip, Bpa, D-Trp, D-1-Nal, D-2-Nal, D-Bal, D-Bip, D-Dip or D-Bpa;  $A^8$  is Gly, D-Ala, Acc, Ala, β-Ala, Gaba, Apn, Ahx, Aha, HN-(CH<sub>2</sub>)<sub>s</sub>-C(O) or deleted;  $A^9$  is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn or Lys;  $A^{10}$  is Acc, HN-(CH<sub>2</sub>)<sub>r</sub>-C(O), Pro, hPro, 3-Hyp, 4-Hyp, Thr, an L- or D-amino

acid or deleted; A<sup>11</sup> is Pro, hPro, 3-Hyp, 4-Hyp or deleted; A<sup>12</sup> is Lys, Dab, Dap, Arg, hArg or deleted; A<sup>13</sup> is Asp, Glu or deleted; B<sup>2</sup> is a peptide moiety containing 1, 2, 3, 4, or 5 amino acids or deleted, B<sup>3</sup> is a peptide moiety which contains 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids wherein at least 5 amino acids are independently selected from the group consisting of L-Arg, D-Arg, L-hArg and D-hArg, or is deleted; R<sup>1</sup> is OH or NH<sub>2</sub>; R<sup>2</sup> and R<sup>3</sup> each is, independently for each occurrence, selected from the group consisting of H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, (C<sub>1</sub>-C<sub>30</sub>)acyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, (C<sub>2</sub>-C<sub>30</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkynyl, substituted aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl and substituted aryl(C<sub>1</sub>-C<sub>30</sub>)acyl; R<sup>4</sup> and R<sup>5</sup> each is, independently for each occurrence, H, (C<sub>1</sub>-C<sub>40</sub>)alkyl, (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, (C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>2</sub>-C<sub>40</sub>)alkenyl, (C<sub>2</sub>-C<sub>40</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkynyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>1</sub>-C<sub>40</sub>)alkylsulfonyl or C(NH)-NH<sub>2</sub>; n is, independently for each occurrence, 1, 2, 3, 4 or 5; m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; s is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; t is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup> and X<sup>5</sup> each is, independently for each occurrence, H, F, Cl, Br, I, -(C<sub>1</sub>-C<sub>10</sub>) alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>2</sub>-C<sub>10</sub>) alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>) alkenyl, (C<sub>2</sub>-C<sub>10</sub>) alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>) alkynyl, aryl, substituted aryl, OH, NH<sub>2</sub>, NO<sub>2</sub> or CN.

In some embodiments of Formula (V):

(I) when R<sup>4</sup> is (C<sub>1</sub>-C<sub>40</sub>)acyl, aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>1</sub>-C<sub>40</sub>)acyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>1</sub>-C<sub>40</sub>)alkylsulfonyl or C(NH)—NH<sub>2</sub>, then R<sup>5</sup> is H, (C<sub>1</sub>-C<sub>40</sub>)alkyl, (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>40</sub>)alkenyl, (C<sub>2</sub>-C<sub>40</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkynyl or substituted aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl;

(II) when R<sup>2</sup> is (C<sub>1</sub>-C<sub>30</sub>)acyl, aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>1</sub>-C<sub>30</sub>)acyl or substituted aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, then R<sup>3</sup> is H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, (C<sub>2</sub>-C<sub>30</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkynyl or substituted aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl;

(III) neither B<sup>1</sup> nor B<sup>2</sup> contains one or more of the following amino acid sequences: Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>, Tyr-Ala-Arg-Lys-Ala-(Arg)<sub>2</sub>-Gln-Ala-(Arg)<sub>2</sub>, Tyr-Ala-Arg-(Ala)<sub>2</sub>-

(Arg)<sub>2</sub>-(Ala)<sub>2</sub>-(Arg)<sub>2</sub>, Tyr-Ala-(Arg)<sub>9</sub>, Tyr-(Ala)<sub>3</sub>-(Arg)<sub>7</sub>, Tyr-Ala-Arg-Ala-Pro-(Arg)<sub>2</sub>-Ala-(Arg)<sub>3</sub> or Tyr-Ala-Arg-Ala-Pro-(Arg)<sub>2</sub>-Pro-(Arg)<sub>2</sub>;

(IV) either B<sup>1</sup> or B<sup>2</sup> or both must be present in said compound;

(V) when A<sup>2</sup> is Cys, D-Cys, hCys, D-hCys, Pen or D-Pen, then A<sup>9</sup> is Cys, D-Cys, hCys, D-hCys, Pen or D-Pen; and

(VI) when A<sup>2</sup> is Asp or Glu, then A<sup>9</sup> is Dab, Dap, Orn or Lys.

In some embodiments of Formula (V):

B<sup>1</sup> is Arg-Lys-Gln-Lys-(Arg)<sub>5</sub>, Arg-(Lys)<sub>2</sub>-Arg-Gln-(Arg)<sub>4</sub>, Arg-(Lys)<sub>2</sub>-(Arg)<sub>3</sub>-Gln-(Arg)<sub>2</sub>, Arg-(Lys)<sub>2</sub>-(Arg)<sub>4</sub>-Gln-Arg, Arg-(Lys)<sub>2</sub>-(Arg)<sub>5</sub>-Gln, Arg-(Lys)<sub>2</sub>-Gln-(Arg)<sub>5</sub>, Arg-Gln-(Lys)<sub>2</sub>-(Arg)<sub>5</sub>, Arg-Gln-(Arg)<sub>7</sub>, Arg-Gln-(Arg)<sub>8</sub>, (Arg)<sub>2</sub>-Gln-(Arg)<sub>6</sub>, (Arg)<sub>2</sub>-Gln-(Arg)<sub>7</sub>, (Arg)<sub>3</sub>-Gln-(Arg)<sub>5</sub>, (Arg)<sub>3</sub>-Gln-(Arg)<sub>6</sub>, (Arg)<sub>4</sub>-Gln-(Arg)<sub>4</sub>, (Arg)<sub>4</sub>-Gln-(Arg)<sub>5</sub>, (Arg)<sub>5</sub>, (Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>, (Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>, (Arg)<sub>6</sub>, (Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>, (Arg)<sub>7</sub>, (Arg)<sub>7</sub>-Gln-(Arg)<sub>2</sub>, (Arg)<sub>8</sub>, (Arg)<sub>8</sub>-Gln-Arg, (Arg)<sub>9</sub>, (Arg)<sub>9</sub>-Gln, (D-Arg)<sub>5</sub>, (D-Arg)<sub>6</sub>, (D-Arg)<sub>7</sub>, (D-Arg)<sub>8</sub>, (D-Arg)<sub>9</sub>, Gln-Arg-(Lys)<sub>2</sub>-(Arg)<sub>5</sub>, Gln-(Arg)<sub>8</sub>, Gln-(Arg)<sub>9</sub>, Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>, Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-Doc; or deleted;

B<sup>2</sup> is β-Ala, β-Ala-Gly, β-Ala-Tyr, β-Ala-Tyr-Gly, (β-Ala)<sub>2</sub>, (β-Ala)<sub>2</sub>-Gly, (β-Ala)<sub>2</sub>-Tyr, (β-Ala)<sub>2</sub>-Tyr-Gly, Doc, Doc-Gly, Doc-Tyr, Doc-Tyr-Gly, (Doc)<sub>2</sub>, (Doc)<sub>2</sub>-Gly, (Doc)<sub>2</sub>-Tyr, (Doc)<sub>2</sub>-Tyr-Gly, or deleted;

B<sup>3</sup> is Arg-Lys-Gln-Lys-(Arg)<sub>5</sub>, Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>, Arg-(Lys)<sub>2</sub>-Arg-Gln-(Arg)<sub>4</sub>, Arg-(Lys)<sub>2</sub>-Gln-(Arg)<sub>5</sub>, Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>, Arg-(Lys)<sub>2</sub>-(Arg)<sub>3</sub>-Gln-(Arg)<sub>2</sub>, Arg-(Lys)<sub>2</sub>-(Arg)<sub>4</sub>-Gln-Arg, Arg-(Lys)<sub>2</sub>-(Arg)<sub>5</sub>-Gln, Arg-Gln-(Lys)<sub>2</sub>-(Arg)<sub>5</sub>, Arg-Gln-(Arg)<sub>7</sub>, Arg-Gln-(Arg)<sub>8</sub>, (Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>, (Arg)<sub>2</sub>-Gln-(Arg)<sub>6</sub>, (Arg)<sub>2</sub>-Gln-(Arg)<sub>7</sub>, (Arg)<sub>3</sub>-Gln-(Arg)<sub>5</sub>, (Arg)<sub>3</sub>-Gln-(Arg)<sub>6</sub>, (Arg)<sub>4</sub>-Gln-(Arg)<sub>4</sub>, (Arg)<sub>4</sub>-Gln-(Arg)<sub>5</sub>, (Arg)<sub>5</sub>, (Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>, (Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>, (Arg)<sub>6</sub>, (Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>, (Arg)<sub>7</sub>, (Arg)<sub>7</sub>-Gln-(Arg)<sub>2</sub>, (Arg)<sub>8</sub>, (Arg)<sub>8</sub>-Gln-Arg, (Arg)<sub>9</sub>, (Arg)<sub>9</sub>-Gln, (D-Arg)<sub>5</sub>, (D-Arg)<sub>6</sub>, (D-Arg)<sub>7</sub>, (D-Arg)<sub>8</sub>, (D-Arg)<sub>9</sub>, Gln-Arg-(Lys)<sub>2</sub>-(Arg)<sub>5</sub>, Gln-(Arg)<sub>8</sub>, Gln-(Arg)<sub>9</sub>, or deleted;

A<sup>1</sup> is A6c, Cha, hCha, Chg, D-Chg, hChg, Gaba, hLeu, Met, β-hMet, D-2-Nal, Nip, Nle, Oic, Phe, D-Phe, hPhe, hPro, or deleted;

A<sup>2</sup> is Cys;

A<sup>3</sup> is D-Abu, Aib, Ala, β-Ala, D-Ala, D-Cha, Gaba, Glu, Gly, D-Ile, D-Leu, D-Met, D-Nle, D-Phe, D-Tle, D-Trp, D-Tyr, D-Val, or deleted;

A<sup>4</sup> is H;

A<sup>5</sup> is D-Bal, D-1-Nal, D-2-Nal, D-Phe, D-(X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe, D-Trp, or D-(Et)Tyr;

A<sup>6</sup> is Arg or hArg;

A<sup>7</sup> is Bal, Bip, 1-Nal, 2-Nal, Trp, or D-Trp;

A<sup>8</sup> is A5c, A6c, Aha, Ahx, Ala, β-Ala, Apn, Gaba, Gly, or deleted;

A<sup>9</sup> is Cys, D-Cys, hCys, D-hCys, Lys, Pen, or D-Pen;

A<sup>10</sup> is Pro, Thr or deleted;

A<sup>11</sup> is Pro or deleted;

A<sup>12</sup> is Arg, Lys, or deleted;

A<sup>13</sup> is Asp or deleted;

each of R<sup>2</sup> and R<sup>3</sup> is, independently, H or acyl;

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound of Formula (V) is selected from:

(SEQ ID NO: 224) Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 225) Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-Doc-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 226) Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 227) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 228) Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Doc)<sub>2</sub>-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 229) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Pro)<sub>2</sub>-Lys-Asp-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 230) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Gly-Cys)-(Pro)<sub>2</sub>-Lys-Asp-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 231) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(β-Ala)<sub>2</sub>-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 232) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Pro)<sub>2</sub>-Lys-Asp-Doc-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 233) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Gly-Cys)-(Pro)<sub>2</sub>-Lys-Asp-Doc-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 234) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 235) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-Doc-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 236) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Lys)-(Doc)<sub>2</sub>-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 237) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 238) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 239) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 240) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 241) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-Arg-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 242) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-Gln-(Arg)<sub>5</sub>-NH<sub>2</sub>;

(SEQ ID NO: 243) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-Gln-Lys-(Arg)<sub>5</sub>-NH<sub>2</sub>;

(SEQ ID NO: 244) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>4</sub>-Gln-Arg-NH<sub>2</sub>;

(SEQ ID NO: 245) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Aib-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 246) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 247) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 248) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 249) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 250) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 251) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 252) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 253) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 254) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 255) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>3</sub>-Gln-(Arg)<sub>2</sub>-NH<sub>2</sub>;

(SEQ ID NO: 256) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-Gln-(Lys)<sub>2</sub>-(Arg)<sub>5</sub>-NH<sub>2</sub>;

(SEQ ID NO: 257) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-NH<sub>2</sub>;

(SEQ ID NO: 258) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 259) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 260) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 261) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 262) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;



(SEQ ID NO: 263) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 264) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Gly-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 265) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Gly-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 266) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 267) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 268) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Gly-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 269) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Gly-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 270) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 271) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 272) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 273) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 274) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 275) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 276) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 277) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Gly-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 278) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Gly-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 279) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 280) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 281) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 282) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 283) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 284) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 285) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 286) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 287) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 288) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 289) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 290) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 291) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 292) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 293) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 294) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 295) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 296) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 297) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 298) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 299) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 300) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 301) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 302) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 303) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 304) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 305) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 306) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 307) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 308) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 309) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 310) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-β-Ala-Tyr-Gly-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 311) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Arg-Asp-β-Ala-Tyr-Gly-(Arg)<sub>6</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 312) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 313) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-Arg-(Lys)<sub>2</sub>-Arg-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 314) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-Arg-(Lys)<sub>2</sub>-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 315) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 316) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 317) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 318) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 319) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 320) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 321) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 322) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-β-Ala-Gly-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 323) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- $\beta$ -Ala-(Arg)<sub>2</sub>-Lys-(Arg)<sub>2</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 324) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- $\beta$ -Ala-Arg-Lys-(Arg)<sub>3</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 325) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-( $\beta$ -Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 326) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-( $\beta$ -Ala)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 327) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-( $\beta$ -Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 328) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 329) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 330) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 331) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 332) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 333) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 334) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- $\beta$ -Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 335) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)- $\beta$ -Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 336) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-( $\beta$ -Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 337) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-( $\beta$ -Ala)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 338) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-( $\beta$ -Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 339) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 340) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 341) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 342) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 343) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 344) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 345) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 346) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 347) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 348) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 349) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 350) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 351) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 352) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 353) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 354) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 355) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 356) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 357) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 358) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 359) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 360) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 361) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 362) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 363) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 364) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 365) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 366) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 367) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 368) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 369) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 370) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 371) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 372) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Lys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 373) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 374) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 375) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 376) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 377) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)<sub>5</sub> - Gln-(Arg)<sub>3</sub> - NH<sub>2</sub>;
- (SEQ ID NO: 378) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 379) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 380) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 381) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly- (Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 382) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 383) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 384) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 385) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 386) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 387) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub>- NH<sub>2</sub>;
- (SEQ ID NO: 388) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;
- (SEQ ID NO: 389) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)<sub>2</sub> -Tyr-Gly-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub> - NH<sub>2</sub>;
- (SEQ ID NO: 390) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 391) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-Tyr-Gly-(Arg)<sub>5</sub> -Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 392) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub> -NH<sub>2</sub>;



- (SEQ ID NO: 393) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 394) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 395) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 396) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 397) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 398) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 399) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 400) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 401) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 402) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 403) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 404) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 405) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 406) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 407) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 408) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)- $\beta$ -Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 409) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)- $\beta$ -Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 410) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)- $\beta$ -Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 411) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp- $\beta$ -Ala-Cys)- $\beta$ -Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 412) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp- $\beta$ -Ala-Cys)- $\beta$ -Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 413) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- $\beta$ -Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 414) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- $\beta$ -Ala-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 415) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)- $\beta$ -Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 416) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-( $\beta$ -Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 417) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-( $\beta$ -Ala)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 418) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-( $\beta$ -Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 419) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 420) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 421) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 422) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 423) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 424) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 425) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 426) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 427) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 428) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 429) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 430) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 431) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 432) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 433) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 434) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 435) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 436) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 437) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 438) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 439) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)<sub>2</sub>-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 440) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 441) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 442) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 443) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 444) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 445) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 446) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 447) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 448) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 449) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 450) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 451) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 452) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 453) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 454) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 455) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 456) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 457) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 458) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 459) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 460) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 461) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 462) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 463) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 464) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 465) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 466) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 467) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Gly-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 468) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 469) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 470) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 471) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 472) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 473) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 474) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 475) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 476) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 477) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 478) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 479) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 480) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 481) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 482) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 483) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 484) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 485) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 486) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 487) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 488) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

- (SEQ ID NO: 489) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 490) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 491) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 492) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 493) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 494) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 495) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 496) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 497) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 498) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 499) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 500) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 501) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 502) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 503) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 504) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;
- (SEQ ID NO: 505) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 506) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 507) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 508) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 509) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 510) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 511) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 512) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 513) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 514) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 515) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 516) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 517) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 518) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 519) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;

(SEQ ID NO: 520) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 521) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-β-Ala-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

(SEQ ID NO: 522) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;

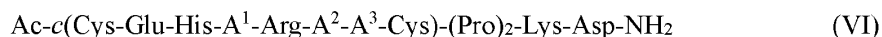
(SEQ ID NO: 523) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(β-Ala)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;



(SEQ ID NO: 524) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;  
 (SEQ ID NO: 525) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;  
 (SEQ ID NO: 526) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;  
 (SEQ ID NO: 527) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>3</sub>-NH<sub>2</sub>;  
 (SEQ ID NO: 528) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;  
 (SEQ ID NO: 529) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-Doc-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>;  
 (SEQ ID NO: 530) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)<sub>2</sub>-Tyr-Gly-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>; and  
 (SEQ ID NO: 531) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-(Doc)<sub>2</sub>-(Arg)<sub>5</sub>-Gln-(Arg)<sub>4</sub>-NH<sub>2</sub>,  
 or pharmaceutically acceptable salts thereof.

In some embodiments, a compound of Formula (V) is disclosed in International Application Publication Number WO 2007/008684, which is incorporated herein by reference in its entirety.

In some embodiments, the MC4R agonist is a compound of Formula (VI):



or pharmaceutically acceptable salts thereof. In Formula (VI):

A<sup>1</sup> is the D-isomer of X-Phe or 2-Nal where X is halogen;

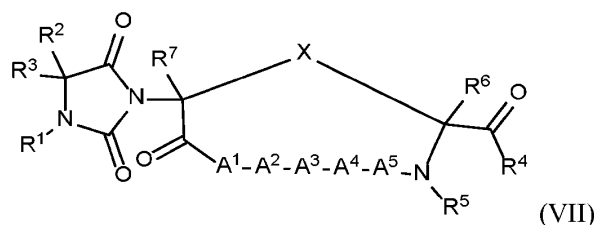
A<sup>2</sup> is Bal, 1-Nal, 2-Nal, or Trp; and

A<sup>3</sup> is Aib, Ala, β-Ala or Gly,

In some embodiments, the compound of Formula (VI) is selected from:

(SEQ ID NO: 532) Ac-c(Cys-Glu-His-D-4-Br-Phe-Arg-Trp-Gly-Cys)-(Pro)<sub>2</sub>-Lys-Asp-NH<sub>2</sub>;  
 (SEQ ID NO: 533) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-NH<sub>2</sub>;  
 (SEQ ID NO: 534) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-NH<sub>2</sub>;  
 (SEQ ID NO: 535) Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-NH<sub>2</sub>;  
 (SEQ ID NO: 536) Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-NH<sub>2</sub>;  
 (SEQ ID NO: 537) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-β-Ala-Cys)-(Pro)<sub>2</sub>-Lys-Asp-NH<sub>2</sub>; and  
 (SEQ ID NO: 538) Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Aib-Cys)-(Pro)<sub>2</sub>-Lys-Asp-NH<sub>2</sub>,  
 or pharmaceutically acceptable salts thereof.

In an example embodiment, the MC4R agonist is a compound of Formula (VII):



or a pharmaceutically acceptable salt thereof wherein:

X is selected from the group consisting of  $-\text{CH}_2-\text{S}-\text{S}-\text{CH}_2-$ ,  $-\text{C}(\text{CH}_3)_2-\text{S}-\text{S}-\text{CH}_2-$ ,  $-\text{CH}_2-\text{S}-\text{S}-\text{C}(\text{CH}_3)_2-$ ,  $-\text{C}(\text{CH}_3)_2-\text{S}-\text{S}-\text{C}(\text{CH}_3)_2-$ ,  $-(\text{CH}_2)_2-\text{S}-\text{S}-\text{CH}_2-$ ,  $-\text{CH}_2-\text{S}-\text{S}-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_2-\text{S}-\text{S}-(\text{CH}_2)_2-$ ,  $-\text{C}(\text{CH}_3)_2-\text{S}-\text{S}-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_2-\text{S}-\text{S}-\text{C}(\text{CH}_3)_2-$ ,  $-(\text{CH}_2)_r-\text{C}(\text{O})-\text{NR}^8-(\text{CH}_2)_t-$  and  $-(\text{CH}_2)_r-\text{NR}^8-\text{C}(\text{O})-(\text{CH}_2)_t-$ ;

each of  $\text{R}^1$  and  $\text{R}^5$  is, independently, H,  $(\text{C}_1-\text{C}_{10})$ alkyl or substituted  $(\text{C}_1-\text{C}_{10})$ alkyl;

each of  $\text{R}^2$  and  $\text{R}^3$  is, independently, H,  $(\text{C}_1-\text{C}_{10})$ alkyl,  $(\text{C}_1-\text{C}_{10})$ heteroalkyl, aryl $(\text{C}_1-\text{C}_5)$ alkyl, substituted  $(\text{C}_1-\text{C}_{10})$ alkyl, substituted  $(\text{C}_1-\text{C}_{10})$ heteroalkyl or substituted aryl $(\text{C}_1-\text{C}_5)$ alkyl or  $\text{R}^2$  and  $\text{R}^3$  may be fused together to form a ring;

$\text{R}^4$  is OH or  $\text{NH}_2$ ;

each of  $\text{R}^6$  and  $\text{R}^7$  is, independently, H,  $(\text{C}_1-\text{C}_{10})$ alkyl or substituted  $(\text{C}_1-\text{C}_{10})$ alkyl;

$\text{A}^1$  is an L- or D-amino acid or deleted;

$\text{A}^2$  is H is, 2-Pal, 3-Pal, 4-Pal,  $(\text{X}^1, \text{X}^2, \text{X}^3, \text{X}^4, \text{X}^5)$ Phe, Taz, 2-Thi or 3-Thi;

$\text{A}^3$  is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D- $(\text{X}^1, \text{X}^2, \text{X}^3, \text{X}^4, \text{X}^5)$ Phe;

$\text{A}^4$  is Arg, hArg, Dab, Dap, Lys or Orn;

$\text{A}^5$  is Bal, 1-Nal, 2-Nal,  $(\text{X}^1, \text{X}^2, \text{X}^3, \text{X}^4, \text{X}^5)$ Phe or Trp;

r is, independently for each occurrence thereof, 1, 2, 3, 4 or 5; and

t is, independently for each occurrence thereof, 1 or 2;

or pharmaceutically acceptable salts thereof.

In an example embodiment of the compounds of Formula (VII),

$\text{A}^1$  is Ala, D-Ala, Asn, Asp, Gln, Glu or Gly.

Example compounds according to Formula (VII) include:

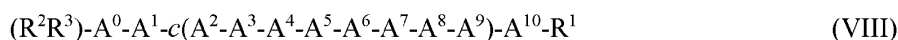
(SEQ ID NO: 539) c[Hydantoin(C(O)-(Nle-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]- $\text{NH}_2$ ;

(SEQ ID NO: 540) c[Hydantoin(C(O)-(Ala-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]- $\text{NH}_2$ ;

(SEQ ID NO: 541) c[Hydantoin(C(O)-(D-Ala-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 542) c[Hydantoin(C(O)-(Aib-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 543) c[Hydantoin(C(O)-(Val-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 544) c[Hydantoin(C(O)-(Abu-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 545) c[Hydantoin(C(O)-(Leu-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 546) c[Hydantoin(C(O)-(Ile-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 547) c[Hydantoin(C(O)-(Cha-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 548) c[Hydantoin(C(O)-(A6c-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 549) c[Hydantoin(C(O)-(Phe-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>;  
 (SEQ ID NO: 550) c[Hydantoin(C(O)-(Gly-Cys))-D-Ala-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>; and  
 (SEQ ID NO: 551) c[Hydantoin(C(O)-(Gly-Cys))-Glu-His-D-Phe-Arg-Trp-Cys]-NH<sub>2</sub>,  
 or pharmaceutically acceptable salts thereof.

In some embodiments, a compound of Formula (VII) is disclosed in International Application Publication Number WO2008/147556, which is incorporated herein by reference in its entirety.

In some embodiments, the MC4R agonist is a compound of Formula (VIII):



or a pharmaceutically acceptable salt thereof wherein:

A<sup>0</sup> is an aromatic amino acid

A<sup>1</sup> is Acc, HN-(CH<sub>2</sub>)<sub>m</sub>-C(O), an L- or D-amino acid;

A<sup>2</sup> is Asp, Cys, D-Cys, hCys, D-hCys, Glu, Pen, or D-Pen;

A<sup>3</sup> is Aib, Ala, β-Ala, Gaba, Gly or a D-amino acid;

A<sup>4</sup> is H is, 2-Pal, 3-Pal, 4-Pal, (X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe, Taz, 2-Thi, or 3-Thi;

A<sup>5</sup> is D-Bal, D-1-Nal, D-2-Nal, D-Phe, L-Phe, D-(X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe, L-Phe, D-Trp

or D-(Et)Tyr;

A<sup>6</sup> is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH((CH<sub>2</sub>)<sub>n</sub>-N(R<sup>4</sup>R<sup>5</sup>))-C(O);

A<sup>7</sup> is Bal, D-Bal, Bip, D-Bip, 1-Nal, D-1-Nal, 2-Nal, D-2-Nal, or D-Trp;

A<sup>8</sup> is Acc, Aha, Ahx, Ala, D-Ala, β-Ala, Apn, Gaba, Gly, HN-(CH<sub>2</sub>)<sub>s</sub>-C(O), or deleted;

A<sup>9</sup> is Cys, D-Cys, hCys, D-hCys, Dab, Dap, Lys, Orn, Pen, or D-Pen;

A<sup>10</sup> is Acc, HN-(CH<sub>2</sub>)<sub>r</sub>-C(O), L- or D-amino acid, or deleted;

R<sup>1</sup> is OH, or NH<sub>2</sub>;

each of R<sup>2</sup> and R<sup>3</sup> is, independently for each occurrence selected from the group consisting of H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, (C<sub>1</sub>-C<sub>30</sub>)acyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, (C<sub>2</sub>-C<sub>30</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkynyl, substituted aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl, and substituted aryl(C<sub>1</sub>-C<sub>30</sub>)acyl;

each of R<sup>4</sup> and R<sup>5</sup> is, independently for each occurrence, H, (C<sub>1</sub>-C<sub>40</sub>)alkyl, (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, (C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>2</sub>-C<sub>40</sub>)alkenyl, (C<sub>2</sub>-C<sub>40</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkynyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>1</sub>-C<sub>40</sub>)alkylsulfonyl, or -C(NH)-NH<sub>2</sub>;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, and X<sup>5</sup> each is, independently for each occurrence, H, F, Cl, Br, I, (C<sub>1</sub>-C<sub>10</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>2</sub>-C<sub>10</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)alkenyl, (C<sub>2</sub>-C<sub>10</sub>)alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>)alkynyl, aryl, substituted aryl, OH, NH<sub>2</sub>, NO<sub>2</sub>, or CN.

In example embodiments of Formula (VIII)

(I) when R<sup>4</sup> is (C<sub>1</sub>-C<sub>40</sub>)acyl, aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, substituted (C<sub>1</sub>-C<sub>40</sub>)acyl, substituted aryl(C<sub>1</sub>-C<sub>40</sub>)acyl, (C<sub>1</sub>-C<sub>40</sub>)alkylsulfonyl, or -C(NH)-NH<sub>2</sub>, then R<sup>5</sup> is H or (C<sub>1</sub>-C<sub>40</sub>)alkyl, (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>40</sub>)alkenyl, (C<sub>2</sub>-C<sub>40</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>40</sub>)heteroalkyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>40</sub>)alkynyl, or substituted aryl(C<sub>1</sub>-C<sub>40</sub>)alkyl;

(II) when R<sup>2</sup> is (C<sub>1</sub>-C<sub>30</sub>)acyl, aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, substituted (C<sub>1</sub>-C<sub>30</sub>)acyl, or substituted aryl(C<sub>1</sub>-C<sub>30</sub>)acyl, then R<sup>3</sup> is H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, (C<sub>2</sub>-C<sub>30</sub>)alkynyl, aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)alkyl, substituted (C<sub>1</sub>-C<sub>30</sub>)heteroalkyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkenyl, substituted (C<sub>2</sub>-C<sub>30</sub>)alkynyl, or substituted aryl(C<sub>1</sub>-C<sub>30</sub>)alkyl;

(III) when A<sup>2</sup> is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen, then A<sup>9</sup> is Cys, D-Cys, hCys, D-hCys, Pen, or D-Pen;

(IV) when A<sup>2</sup> is Asp or Glu, then A<sup>9</sup> is Dab, Dap, Orn, or Lys;

(V) when A<sup>8</sup> is Ala or Gly, then A<sup>1</sup> is not Nle; or pharmaceutically acceptable salts thereof.

In example embodiments of compounds of Formula (VIII):

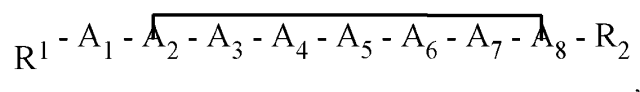
A<sup>0</sup> is 1-Nal, 2-Nal, H is, Pff, Phe, Trp, or Tyr; A<sup>1</sup> is Arg; A<sup>2</sup> is Cys; A<sup>3</sup> is D-Ala; A<sup>4</sup> is H; A<sup>5</sup> is D-Phe; A<sup>6</sup> is Arg; A<sup>7</sup> is Trp; A<sup>8</sup> is deleted; A<sup>9</sup> is Cys; and A<sup>10</sup> is deleted; or pharmaceutically acceptable salts thereof.

Particular compounds of the immediately foregoing group of Formula (VIII) compounds include:

(SEQ ID NO: 552) Ac-Tyr-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 553) Ac-2-Nal-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 554) Ac-1-Nal-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 555) Ac-Phe-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 556) Ac-Trp-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 557) Ac-Pff-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 558) H-His-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 559) Ac-His-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,  
 or a pharmaceutically acceptable salt thereof.

In some embodiments, the MC4R agonist is an agonist described in WO2014/144260 A1, incorporated herein by reference.

In one example embodiment, an MC4R agonist is a compound represented by formula (IX):



or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup> is H, or a (C<sub>1</sub>-C<sub>6</sub>)acyl;

R<sup>2</sup> is, -NR<sup>3</sup>R<sup>4</sup>, or -OR<sup>5</sup> wherein R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are each independently is H or a (C<sub>1</sub>-C<sub>6</sub>)alkyl;

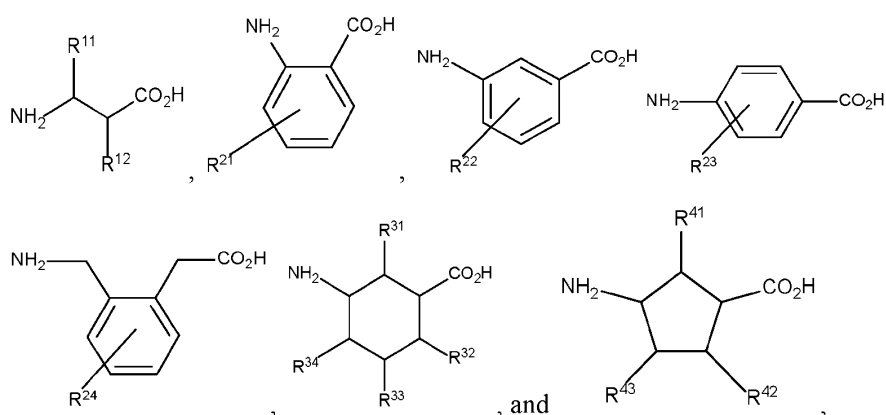
A<sup>1</sup> is an amino acid residue selected from Arg, Lys, Orn, His, Nle, Phe, Val, Leu, Trp, Tyr, Ala, Ser, Thr, Gln, Asn, Asp, Glu, or TzAla; or

A<sup>1</sup> is a moiety selected from an optionally substituted -(C<sub>1</sub>-C<sub>12</sub>)-alkyl, an optionally substituted -(C<sub>6</sub>-C<sub>18</sub>)-aryl, an optionally substituted -(C<sub>5</sub>-C<sub>18</sub>)-heteroaryl, an alkyl wherein the

aryl portion is an optionally substituted (C<sub>6</sub>-C<sub>18</sub>)aryl, and the alkyl portion is an optionally substituted (C<sub>1</sub>-C<sub>12</sub>)alkyl, or a heteroaralkyl, wherein the heteroaryl portion is an optionally substituted (C<sub>5</sub>-C<sub>18</sub>)heteroaryl, and the alkyl portion is an optionally substituted (C<sub>1</sub>-C<sub>12</sub>)alkyl;

A<sup>2</sup> and A<sup>8</sup> is each independently an amino acid residue selected from Cys, hCys, Pen, Asp, Glu, Lys, Orn, Dbu, or Dpr, wherein A<sup>2</sup> and A<sup>8</sup> are pairwise selected so as to be able to form covalent bond between their respective side chains;

A<sup>3</sup> is absent or is an amino acid residue selected from Ala, Tle, Val, Leu, Ile, Cha, Pro, Ser, Thr, Lys, Arg, His, Phe, Gln, Sar, Gly, Asn, Aib, or residue Y, wherein Y is an amino acid selected from amino acids represented by the following structural formulas



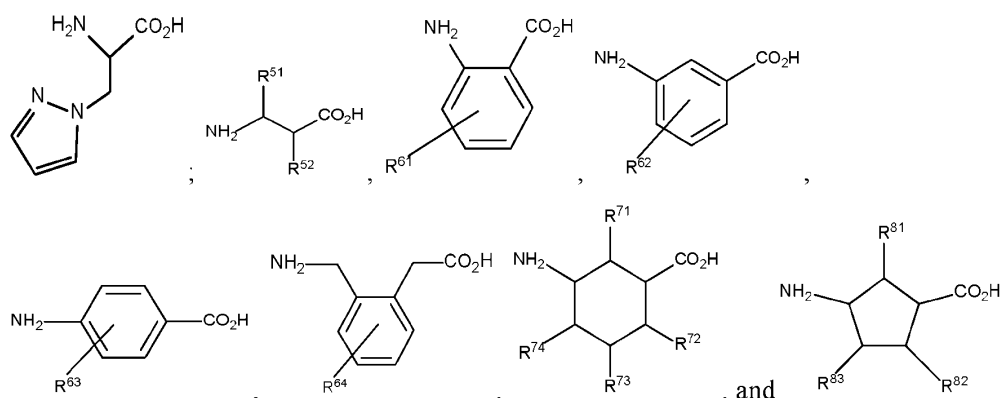
wherein:

R<sup>11</sup> and R<sup>12</sup>, each independently, is H, -CH<sub>3</sub>, phenyl, or benzyl;

R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, and R<sup>24</sup>, each independently is H, -CH<sub>3</sub>, -CF<sub>3</sub>, phenyl, benzyl, F, Cl, Br, I, -OCH<sub>3</sub>, or -OH;

R<sup>31</sup>, R<sup>32</sup>, R<sup>33</sup>, R<sup>34</sup>, R<sup>41</sup>, R<sup>42</sup>, and R<sup>43</sup>, each independently is H, -CH<sub>3</sub>, -CF<sub>3</sub>, phenyl, benzyl, F, Cl, Br, I, -OCH<sub>3</sub>, or -OH;

A<sup>4</sup> is absent or is an amino acid residue selected from Atc, Ala, QAla, Aib, Sar, Ser, Thr, Pro, Hyp, Asn, Gln, an optionally substituted His, Trp, Tyr, Lys, Arg, sChp, or residue X, where the X is an amino acid selected from amino acids represented by the following formulas:



wherein:

R<sup>51</sup> and R<sup>52</sup>, each independently, is H, -CH<sub>3</sub>, phenyl, or benzyl;

R<sup>61</sup>, R<sup>62</sup>, R<sup>63</sup>, and R<sup>64</sup>, each independently is H, -CH<sub>3</sub>, -CF<sub>3</sub>, phenyl, benzyl, F, Cl, Br, I, -OCH<sub>3</sub>, or -OH;

R<sup>71</sup>, R<sup>72</sup>, R<sup>73</sup>, R<sup>74</sup>, R<sup>81</sup>, R<sup>82</sup>, and R<sup>83</sup>, each independently is H, -CH<sub>3</sub>, -CF<sub>3</sub>, phenyl, benzyl, F, Cl, Br, I, -OCH<sub>3</sub>, or -OH;

A<sup>5</sup> is an optionally substituted Phe, an optionally substituted 1-Nal, or an optionally substituted 2-Nal;

A<sup>6</sup> is Arg; and

A<sup>7</sup> is Trp,

wherein any amino acid residue is either in L- or in D-configuration.

Exemplary compound of Formula (IX) include:

(SEQ ID NO: 560) Ac-Arg-c(Cys-D-Ala-His-D-Phe(p-F)-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 561) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 562) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe(p-F)-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 563) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe(p-F)-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 564) Ac-Arg-c(Cys-D-Ala-Ser-D-Phe(p-F)-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 565) Ac-Arg-c(Cys-D-Ala-Thr-D-Phe(p-CN)-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 566) Ac-Arg-c(Cys-D-Ala-Asn-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 567) Ac-Arg-c(Cys-D-Ala-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 568) Ac-Arg-c(Cys-D-Ala-Trp-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 569) Ac-Arg-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 570) Ac-Arg-c(Cys-D-Val-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 571) Ac-Arg-c(Cys-D-Val-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 572) Ac-Arg-c(Cys-D-Ser-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,  
 or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the polypeptides of the present invention include any one of the following structural formulas:

(SEQ ID NO: 573) Ac-Arg-c(hCys-D-Ala-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 574) Ac-Arg-c(hCys-Ala-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 575) Ac-Arg-c(hCys-Ala-D-Phe-Arg-Trp-Cys)-OH;  
 (SEQ ID NO: 576) Ac-Arg-c(Cys-D-Ala-D-Phe-Arg-Trp-hCys)-NH<sub>2</sub>;  
 (SEQ ID NO: 577) Ac-Arg-c(Pen-D-Ala-D-Phe-Arg-Trp-hCys)-NH<sub>2</sub>;  
 (SEQ ID NO: 578) Ac-Arg-c(hCys-D-Ala-D-Phe(p-F)-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 579) Ac-Arg-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 580) Ac-Nle-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 581) Arg-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 582) CH<sub>3</sub>-(CH<sub>2</sub>)<sub>4</sub>-CO-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 583) Benzyl-CO-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the polypeptides of the present invention include the polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 584) Ac-Arg-c(Asp-D-Ala-D-Phe-Arg-Trp-Dbu)-NH<sub>2</sub>;  
 (SEQ ID NO: 585) Ac-Arg-c(Glu-D-Ala-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;  
 (SEQ ID NO: 586) Ac-Arg-c(Glu-Ala-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;  
 (SEQ ID NO: 587) Ac-Arg-c(Dpr-D-Ala-D-Phe-Arg-Trp-Glu)-NH<sub>2</sub>;  
 (SEQ ID NO: 588) Ac-Arg-c(Dpr-D-Ala-D-Phe(4-F)-Arg-Trp-Glu)-NH<sub>2</sub>;  
 (SEQ ID NO: 589) Ac-Arg-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH<sub>2</sub>;  
 (SEQ ID NO: 590) Ac-Arg-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-OH;  
 (SEQ ID NO: 591) Ac-Nle-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH<sub>2</sub>;  
 (SEQ ID NO: 592) Arg-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH<sub>2</sub>;  
 (SEQ ID NO: 593) CH<sub>3</sub>-(CH<sub>2</sub>)<sub>4</sub>-CO-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH<sub>2</sub>; or



(SEQ ID NO: 594) Benzyl-CO-c(Dpr-Ala-D-Phe-Arg-Trp-Glu)-NH<sub>2</sub>,  
or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the polypeptides of the present invention include a polypeptide represented by Formula (IV), wherein A<sup>4</sup> is an amino acid residue selected from Atc, Ala, QAla, Aib, Sar, Ser, Thr, Pro, Hyp, Asn, Gln, a substituted His, Trp, Tyr, Lys, Arg, sChp, or residue X. Examples of such peptides include peptides represented by any one of the following structural formulas:

(SEQ ID NO: 595) Ac-Arg-c(Cys-D-Ala-His(3-Me)-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 596) Ac-Arg-c(Cys-D-Ala-His(1-Me)-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 568) Ac-Arg-c(Cys-D-Ala-Trp-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 567) Ac-Arg-c(Cys-D-Ala-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 566) Ac-Arg-c(Cys-D-Ala-Asn-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 597) Ac-Arg-c(Cys-D-Ala-Arg-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 598) Ac-Arg-c(Cys-D-Ala-Tyr-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 599) Ac-Arg- c(Cys-D-Ala-D-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 561) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 563) Ac-Arg-c(Cys-D-Ala-Pro-D-Phe(p-F)-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 600) Ac-Arg- c(Cys-D-Ala-Atc-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 601) Ac-Arg- c(Cys-D-Ala-QAla-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 602) Ac-Arg- c(Cys-D-Ala-sChp-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; or  
(SEQ ID NO: 603) Ac-Arg- c(Cys-D-Ala-X-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof.

In example embodiments, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 574) Ac-Arg-c(hCys-Ala-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 573) Ac-Arg-c(hCys-D-Ala-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 604) Ac-Arg-c(hCys-D-Ala-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 585) Ac-Arg-c(Glu-D-Ala-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;  
(SEQ ID NO: 586) Ac-Arg-c(Glu-Ala-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;

(SEQ ID NO: 605) Ac-Arg-c(hCys-Aib-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 606) Ac-Arg-c(hCys-Sar-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 607) Ac-Arg-c(hCys-Val-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 608) Ac-Arg-c(hCys-D-Val-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 609) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 610) Ac-Arg-c(hCys-D-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 611) Ac-Arg-c(hCys-Ala-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 612) Ac-Arg-c(D-Pen-D-Ala-D-Phe-Arg-Trp-hCys)-NH<sub>2</sub>;  
 (SEQ ID NO: 576) Ac-Arg-c(Cys-D-Ala-D-Phe-Arg-Trp-hCys)-NH<sub>2</sub>;  
 (SEQ ID NO: 613) Ac-Arg-c(Pen-D-Ala-D-Phe-Arg-Trp-hCys)-NH<sub>2</sub>;  
 (SEQ ID NO: 614) Ac-Arg-c(D-hCys-D-Ala-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 579) Ac-Arg-c(hCys-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; or  
 (SEQ ID NO: 615) Ac-Arg-c(hCys-D-Pro-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof.

In another embodiment, the polypeptides of the present invention include polypeptides represented by Formula (IV), wherein A<sup>3</sup> is an amino acid residue selected from Tle, Val, Leu, Ile, Cha, Pro, Ser, Thr, Lys, Arg, His, Phe, Gln, Sar, Gly, Asn, or Aib; and A<sup>4</sup> is an amino acid residue selected from Ate, Ala, QAla, Aib, Sar, Ser, Thr, Pro, Hyp, Asn, Gln, a substituted His, Trp, Tyr, Lys, Arg, sChp, or residue X. Examples of such polypeptides are polypeptides represented by any one of the following structural formulas:

(SEQ ID NO: 616) Ac-Arg-c(Cys-Val-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 570) Ac-Arg-c(Cys-D-Val-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; or  
 (SEQ ID NO: 617) Ac-Arg-c(Cys-D-Val-His(1-Me)-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 618) Ac-TzAla-c(Cys-Ala-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; or  
 (SEQ ID NO: 619) Ac-Glu-c(Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 596) Ac-Arg-c(Cys-D-Ala-His(1-Me)-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 567) Ac-Arg-c(Cys-D-Ala-Gln-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; or

(SEQ ID NO: 566) Ac-Arg-c(Cys-D-Ala-Asn-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 620) Ac-Arg-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 621) Ac-Arg-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 622) Ac-Arg-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>; or

(SEQ ID NO: 569) Ac-Arg-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

(SEQ ID NO: 623) Ac-Arg-c(Cys-D-Ala-His(1-Me)-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 624) Ac-Arg-c(Cys-D-Ala-Gln-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>; or

(SEQ ID NO: 625) Ac-Arg-c(Cys-D-Ala-Asn-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>,

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the polypeptides of the present invention include a polypeptide represented by any one of the following structural formulas:

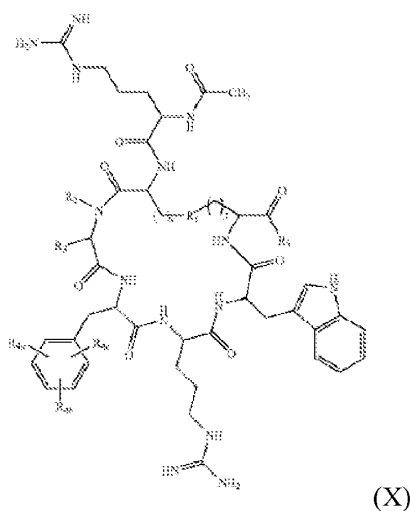
(SEQ ID NO: 626) Ac-Arg-c(Cys-D-Ala-His(1-Me)-D-Phe-Arg-Trp-Cys)-OH;

(SEQ ID NO: 627) Ac-Arg-c(Cys-D-Ala-Gln-D-Phe-Arg-Trp-Cys)-OH; or

(SEQ ID NO: 628) Ac-Arg-c(Cys-D-Ala-Asn-D-Phe-Arg-Trp-Cys)-OH,

or a pharmaceutically acceptable salt thereof.

In one example embodiment, an MC4R agonist is a compound represented by Formula (X):

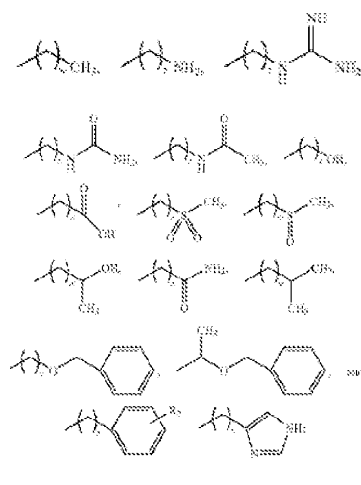


or a pharmaceutically acceptable salt thereof. In Formula (X), the chemical substituents are defined as follows:

$R_1$  is  $-\text{NH}-\text{C}(\text{O})-$  or  $-\text{C}(\text{O})-\text{NH}-$ ;

$R_2$  is  $-\text{H}$ ,  $-\text{CH}_2-$ , or  $R_2$ , together with  $R_3$ , forms a pyrrolidine ring optionally substituted with  $-\text{OH}$ ;

$R_3$  is  $-(\text{CH}_2)_2-$  if  $R_2$  is  $-\text{CH}_2-$ , and otherwise  $R_3$  is selected from



$R^{4a}$ ,  $R^{4b}$ , and  $R^{4c}$  are each independently selected from hydrogen, halo,  $(\text{C}_1-\text{C}_{10})$ alkyl-halo,  $(\text{C}_1-\text{C}_{10})$ alkyl-dihalo,  $(\text{C}_1-\text{C}_{10})$ alkyl-trihalo,  $(\text{C}_1-\text{C}_{10})$ alkyl,  $(\text{C}_1-\text{C}_{10})$ alkoxy,  $(\text{C}_1-$

C<sub>10</sub>)alkylthio, aryl, aryloxy, nitro, nitrile, sulfonamide, amino, hydroxyl, carboxy, and alkoxy-carbonyl. In one example embodiment, R<sup>4a</sup>, R<sup>4b</sup>, and R<sup>4c</sup> is not hydrogen.

R<sup>5</sup> is -OH or -N(R<sup>6a</sup>)(R<sup>6b</sup>);

R<sup>6a</sup> and R<sup>6b</sup> are each independently H or C<sub>1</sub> to C<sub>4</sub> linear, branched or cyclic alkyl chain;

R<sup>7</sup> is -H or -C(O)-NH<sub>2</sub>;

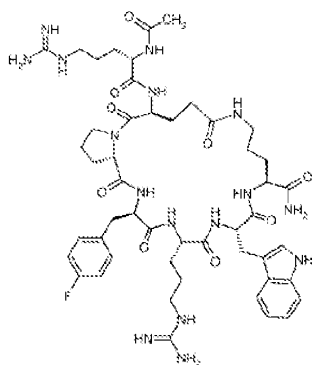
w is in each instance independently 0 to 5;

x is 1 to 5;

y is 1 to 5;

z is in each instance independently 1 to 5.

An example of a compound of Formula (X) is a cyclic peptide defined by Formula (XI):

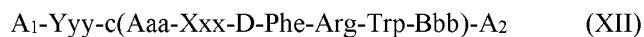


(XI), or a pharmaceutically acceptable salt thereof.

In one example embodiment, the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof. In another example embodiment, the MC4R agonist is Hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 148) or a pharmaceutically acceptable salt thereof.

In some embodiments, the MC4R agonist is an agonist described in WO2014/144260 A1, incorporated herein by reference.

In one example embodiment, the MC4 agonist is a compound represented by Formula (XII):



Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

Xxx is Asn, Gln, Ser, Thr;

Yyy is Lys, Arg, D-Lys, D-Arg;

A1 is H, Ac;

A2 is OH, NH<sub>2</sub>;

In embodiments, the MC4R agonist is chosen from one or more of the following compounds, (or pharmaceutically acceptable salt thereof):

(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;

(SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

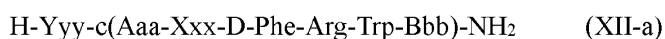
(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>, or  
 (SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>.

In some embodiments, the MC4R agonist is a compound of Formula (XII-a):



or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

In some embodiments, the compound of Formula (XII-a) is selected from:

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;



(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; and

(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>.

In some embodiments, the MC4R agonist is a compound of Formula (XII-b):



or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

In some embodiments, the compound of Formula (XII-b) is selected from:

(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;

(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; and

(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>.

In some embodiments, the MC4R agonist is a compound of Formula (XII-c):



or a pharmaceutically acceptable salt thereof, wherein:

A<sub>1</sub> is H or Ac;

A<sub>2</sub> is OH or NH<sub>2</sub>;

Yyy is L-Arg or D-Arg;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and

Xxx is Asn, Gln, Ser, or Thr.

In some embodiments, the compound of Formula (XII-c) is selected from:

(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;

(SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH; and  
 (SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH.

In some embodiments, the MC4R agonist is a compound of Formula (XII-d):



or a pharmaceutically acceptable salt thereof, wherein:

A<sub>1</sub> is H or Ac;

A<sub>2</sub> is OH or NH<sub>2</sub>;

Yyy is L-Lys or D-Lys;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or  
 Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and  
 Xxx is Asn, Gln, Ser, or Thr.

In some embodiments, the compound of Formula (XII-d) is selected from:

(SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>, and  
(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>.

In some embodiments, the MC4R agonist is an agonist described in WO2014/144260 or WO2017/059075, each of which is incorporated herein by reference. Administration of a compound or pharmaceutically acceptable salt thereof or a composition comprising a compound or pharmaceutical salt of a compound of the disclosure useful to practice the methods described herein, can be continuous, hourly, four times daily, three time daily, twice daily, once daily, once every other day, twice weekly, once weekly, once every two weeks, once a month, or once every two months, or longer or some other intermittent dosing regimen.

Examples of administration of a compound or composition comprising a compound or pharmaceutical salt of a compound of the disclosure include peripheral

administration. Examples of peripheral administration include oral, subcutaneous, intraperitoneal, intramuscular, intravenous, rectal, transdermal or intranasal forms of administration.

As used herein, peripheral administration can include all forms of administration of a compound or a composition comprising a compound of the instant disclosure which excludes intracranial administration. Examples of peripheral administration include, but are not limited to, oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, extended release, slow release implant, depot and the like), nasal, vaginal, rectal, sublingual or topical routes of administration, including transdermal patch applications and the like.

The nomenclature used to define the peptides is that typically used in the art wherein the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. Where the amino acid has D and L isomeric forms, it is the L form of the amino acid that is represented unless otherwise explicitly indicated.

The compounds of the disclosure useful for practicing the methods described herein may possess one or more chiral centers and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present disclosure. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilizing methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of the disclosure.

The compounds described herein may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present disclosure. For example, a claim to 2-hydroxypyridinyl would also cover its tautomeric form,  $\alpha$ -pyridonyl.

The present disclosure further features providing an MC4R agonist in combination with an additional agent. Exemplary agents include a second MC4R agonist (e.g., an agent described herein or elsewhere), or an agent aimed to treat a symptom of obesity or a co-morbidity. For example, the additional agent may be an anti-hypertensive drug, a pain medication, an anti-inflammatory, a lipid-lowering agent, a cardiovascular drug, or a diuretic. The combination therapy may be administered as a single formulation or as separate formulations. In an embodiment, the MC4R agonist and the additional agent are administered as a single pharmaceutical composition. In an embodiment, the MC4R agonist and the additional agent are

administered as separate pharmaceutical compositions. In the case of separate formulations, the MC4R agonist and the additional agent may be administered concomitantly or sequentially. In an embodiment, the MC4R agonist and the additional agent are administered concomitantly. In an embodiment, the MC4R agonist and the additional agent are administered sequentially. For example, the MC4R agonist may be administered prior to the additional agent or subsequent to the additional agent.

In some embodiments, the administration of the MC4R agonist and the additional agent has a synergistic or additive effect. For example, the administration of the MC4R agonist and the additional agent may have an additive effect, in which the therapeutic effect of the MC4R agonist and the additional agent is the total sum of the effects of each of the components individually. In contrast, the administration of the MC4R agonist and the additional agent may have a synergistic effect, in which the therapeutic effect of the MC4R agonist and the additional agent is greater than the sum of the individual components. The synergistic effect of the combination of the MC4R agonist and the additional agent may be 0.1%, 0.25%, 0.5%, 0.75%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than the total sum of the effects of the MC4R agonist and the additional agent administered individually. In an embodiment, the synergistic effect of the combination of the MC4R agonist and the additional agent is greater than between 5% and 75% of the total sum of the effects of the MC4R agonist and the additional agent administered individually.

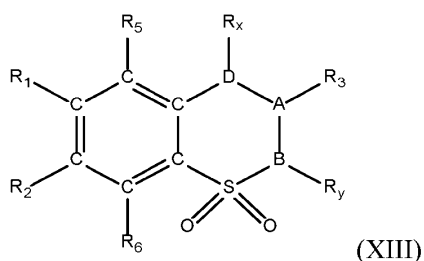
Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

### **Potassium Channel Activator Compounds**

The present disclosure further features combinations of an MC4R agonist with a potassium channel activator compound (e.g., a SURx/Kirxchannel activator compound) an aspect, the present disclosure relates to methods of treatment comprising a SURx/Kirx channel activator.

The  $K_{ATP}$  channel Kir.6/SUR1 is a multimeric ATP-driven ion channel which mediates cell membrane potential in pancreatic  $\beta$ -cells. The ATP-driven ion channel comprises a sulphonyl urea receptor SUR1 capable of binding to glucose, sulphonyl urea, diazoxide and other SURx/Kirxchannel activator compounds, initiating a depolarization of the cell membrane,  $Ca^{2+}$  transport, and ultimately exocytosis of secretory vesicles containing insulin, thereby modulating blood glucose levels. See Reimann, F. *Br. J. Pharmacol.* 2001: 132, 1542-1548.

In an embodiment, the SURx/Kirxchannel activator compound has the structure of Formula (XIII):



or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein A is C(R<sup>1</sup>); each of B and D are independently N; wherein A and B or A and D are connected via a double or single bond; each of R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano; wherein A and B form a double bond and R<sub>x</sub> is hydrogen or wherein A and D form a double bond and R<sub>y</sub> is hydrogen; R<sub>3</sub> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, or N(R<sup>B</sup>)(R<sup>C</sup>), wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>4</sub>; R<sup>1</sup> is absent, hydrogen, or C1-C6 alkyl; each R<sub>4</sub> is independently C1-C6 alkyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, fluorine, chlorine, bromine, or iodine; R<sup>A</sup> is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, or heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>; each of R<sup>B</sup> and R<sup>C</sup> is independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>; or wherein R<sup>B</sup> and R<sup>C</sup> are taken together to form heterocyclyl

optionally substituted with one or more  $R^7$ ; each  $R^7$  is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl,  $-OR^A$ , fluorine, chlorine, bromine, iodine, nitro, or cyano.

In an embodiment, B is N. In an embodiment, D is N. In an embodiment, A is C. In an embodiment,  $R_5$  is hydrogen. In an embodiment,  $R_6$  is hydrogen. In an embodiment, each of  $R_1$  and  $R_2$  is independently hydrogen, fluorine, chlorine, bromine, iodine, nitro, or cyano. In an embodiment,  $R_1$  is hydrogen, fluorine, chlorine, bromine, iodine, nitro, or cyano. In an embodiment,  $R_1$  is hydrogen, fluorine, chlorine, bromine, iodine, cyano. In an embodiment,  $R_1$  is hydrogen, fluorine or chlorine. In an embodiment,  $R_1$  is hydrogen. In an embodiment,  $R_1$  is fluorine. In an embodiment,  $R_1$  is chlorine. In an embodiment,  $R_1$  is bromine. In an embodiment,  $R_1$  is iodine. In an embodiment,  $R_1$  is cyano. In an embodiment,  $R_2$  is hydrogen, fluorine, chlorine, bromine, iodine, nitro, or cyano. In an embodiment,  $R_2$  is hydrogen, fluorine, chlorine, bromine, iodine, cyano. In an embodiment,  $R_2$  is hydrogen, fluorine or chlorine. In an embodiment,  $R_2$  is hydrogen. In an embodiment,  $R_2$  is fluorine. In an embodiment,  $R_2$  is chlorine. In an embodiment,  $R_2$  is bromine. In an embodiment,  $R_1$  is iodine. In an embodiment,  $R_2$  is cyano.

In an embodiment,  $R_3$  is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, or  $N(R^B)(R^C)$ , each of which is optionally substituted with optionally substituted with one or more  $R_7$ . In an embodiment,  $R_3$  is C1-C6 heteroalkyl optionally substituted with optionally substituted with one or more  $R_7$ . In an embodiment,  $R_3$  is C1-C6 haloalkyl, optionally substituted with optionally substituted with one or more  $R_7$ . In an embodiment,  $R_3$  is cycloalkyl, optionally substituted with optionally substituted with one or more  $R_7$ . In an embodiment,  $R_3$  heterocyclyl, optionally substituted with optionally substituted with one or more  $R_7$ .

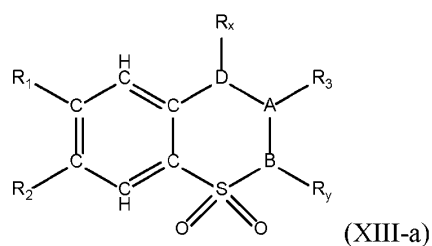
In an embodiment,  $R_3$  is  $N(R^B)(R^C)$ . In an embodiment,  $R^B$  and  $R^C$  are taken together to form heterocyclyl optionally substituted with one or more  $R^7$  (e.g., a 4-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, or a bridged heterocyclyl). In an embodiment,  $R^B$  is hydrogen. In an embodiment,  $R^C$  is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, each optionally substituted with one or more  $R_7$ . In an embodiment,  $R^C$  is C1-C6 alkyl optionally substituted with one or more  $R_7$ . In an embodiment,  $R^C$  is C1-C6 heteroalkyl optionally substituted with one



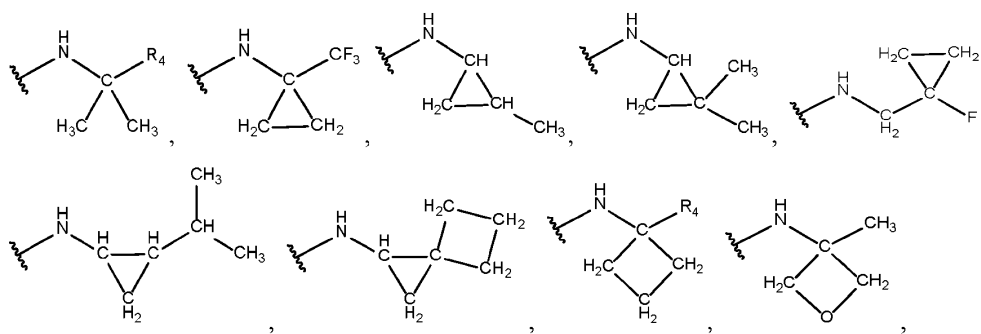
or more R<sub>7</sub>. In an embodiment, R<sup>C</sup> is C1-C6 haloalkyl optionally substituted with one or more R<sub>7</sub>. In an embodiment, R<sup>C</sup> is cycloalkyl optionally substituted with one or more R<sub>7</sub> (e.g., monocyclic cycloalkyl, bicyclic cycloalkyl). In an embodiment, R<sup>C</sup> is cycloalkyl substituted with one or more R<sub>7</sub>, wherein R<sub>7</sub> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano. In an embodiment, R<sup>C</sup> is heterocyclyl optionally substituted with one or more R<sub>7</sub>.

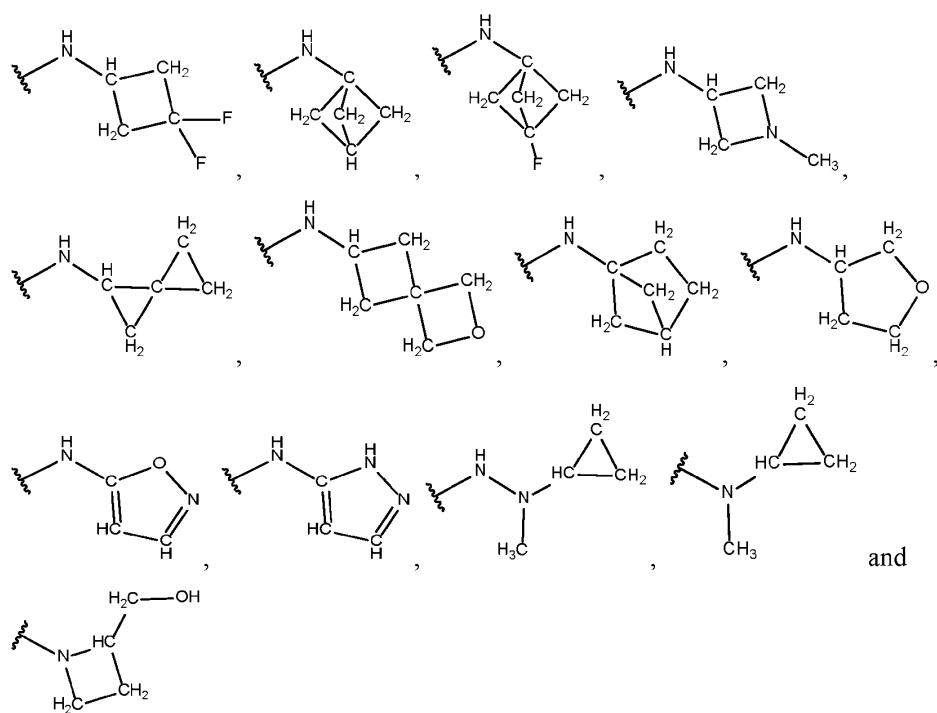
In an embodiment, the compound of Formula (XIII) is not 3-(tert-butylamino)-7-chloro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide or a pharmaceutically acceptable salt thereof. In an embodiment, the compound of Formula (XIII) is 3-(tert-butylamino)-7-chloro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide or a pharmaceutically acceptable salt thereof. In an embodiment, the compound of Formula (XIII) is diazoxide.

In an embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-a):



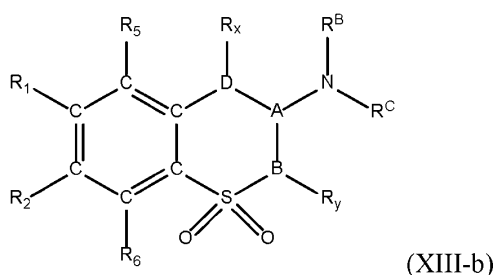
or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein A is C; each of B and D are independently N; wherein A and B or A and D are connected via a double or single bond; R<sub>1</sub> and R<sub>2</sub> are hydrogen, fluorine, chlorine, bromine and iodine; and wherein A and B form a double bond and R<sub>x</sub> is H or wherein A and D form a double bond and R<sub>y</sub> is H; R<sub>3</sub> is independently selected from the group consisting of:





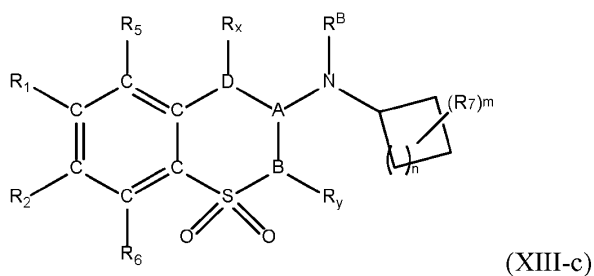
R<sub>4</sub> is selected from the group consisting of C1-C3 alkyl optionally substituted with one to two substituents selected from the group consisting of fluoro and hydroxy, ethynyl, C1-C2 alkoxy, (methoxy)-C1-C2 alkyl, cyano, fluoro, (methylsulfonyl)-C1-C2 alkyl, (dimethylamino)-C1-C2 alkyl and n-methyl carbamoyl, under the proviso that said compound is not 3-(tert-butylamino)-7-chloro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide. In relation to these compounds the present inventors have surprisingly found that these compounds exhibit remarkable potency for binding selectively to SURx/Kirx and inhibiting glucose stimulated insulin secretion. In view of the fact that the binding of these compounds to the target is so specific, reduced off target effects are observed. Moreover, the compounds according to the present invention exhibit excellent bioavailability, stability and safety and can be administered orally.

In another embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-b):



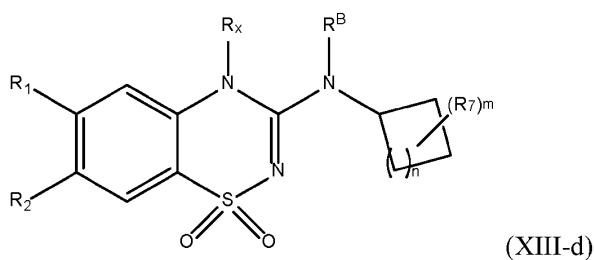
or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein A, B, D, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>x</sub>, R<sub>y</sub>, R<sup>A</sup>, R<sup>B</sup>, R<sup>C</sup>, and R<sup>7</sup> are defined as provided for Formula (XIII).

In another embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-c):



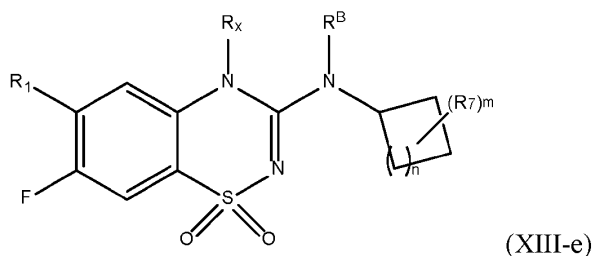
or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein A, B, D, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>x</sub>, R<sub>y</sub>, R<sup>A</sup>, R<sup>B</sup>, R<sup>C</sup>, and R<sup>7</sup> are defined as provided for Formula (XIII), m is an integer between 0 and 12; and n is an integer between 0 and 4.

In another embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-d):



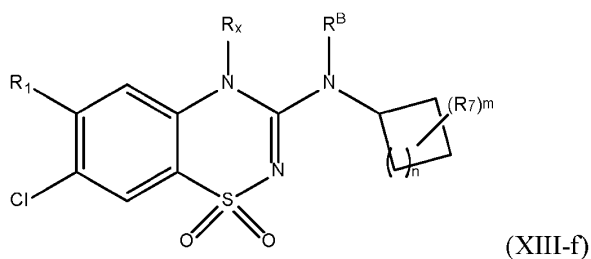
or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>x</sub>, and R<sup>7</sup> are defined as provided for Formula (XIII), m is an integer between 0 and 12; and n is an integer between 0 and 4.

In another embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-e):



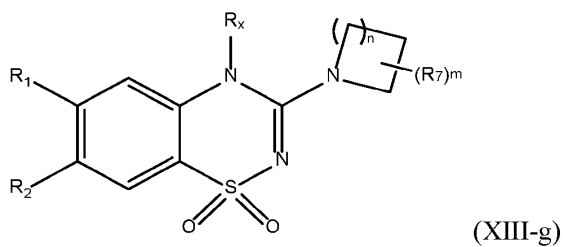
or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein  $R_1$ ,  $R_5$ ,  $R_x$ , and  $R^7$  are defined as provided for Formula (XIII),  $m$  is an integer between 0 and 12; and  $n$  is an integer between 0 and 4.

In another embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-f):



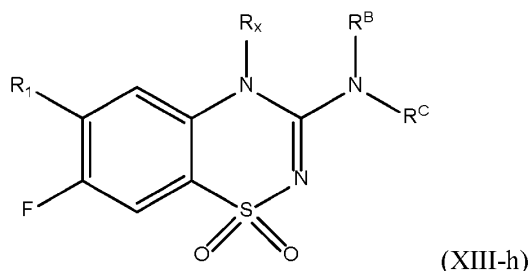
or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein  $R_1$ ,  $R_5$ ,  $R_x$ , and  $R^7$  are defined as provided for Formula (XIII),  $m$  is an integer between 0 and 12; and  $n$  is an integer between 0 and 4.

In another embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-g):



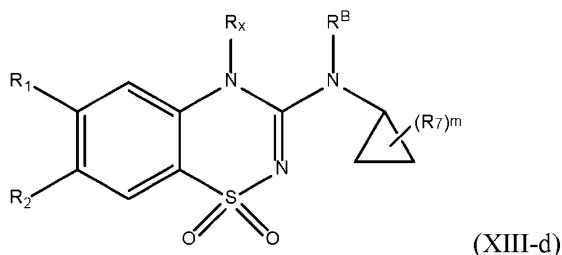
or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein  $R_1$ ,  $R_2$ ,  $R_5$ ,  $R_x$ , and  $R^7$  are defined as provided for Formula (XIII),  $m$  is an integer between 0 and 12; and  $n$  is an integer between 0 and 4.

In another embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-h):



or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein  $R_1$ ,  $R_5$ ,  $R_x$ ,  $R^B$ ,  $R^C$ , and  $R^7$  are defined as provided for Formula (XIII).

In another embodiment, the compound of Formula (XIII) is a compound of Formula (XIII-d):



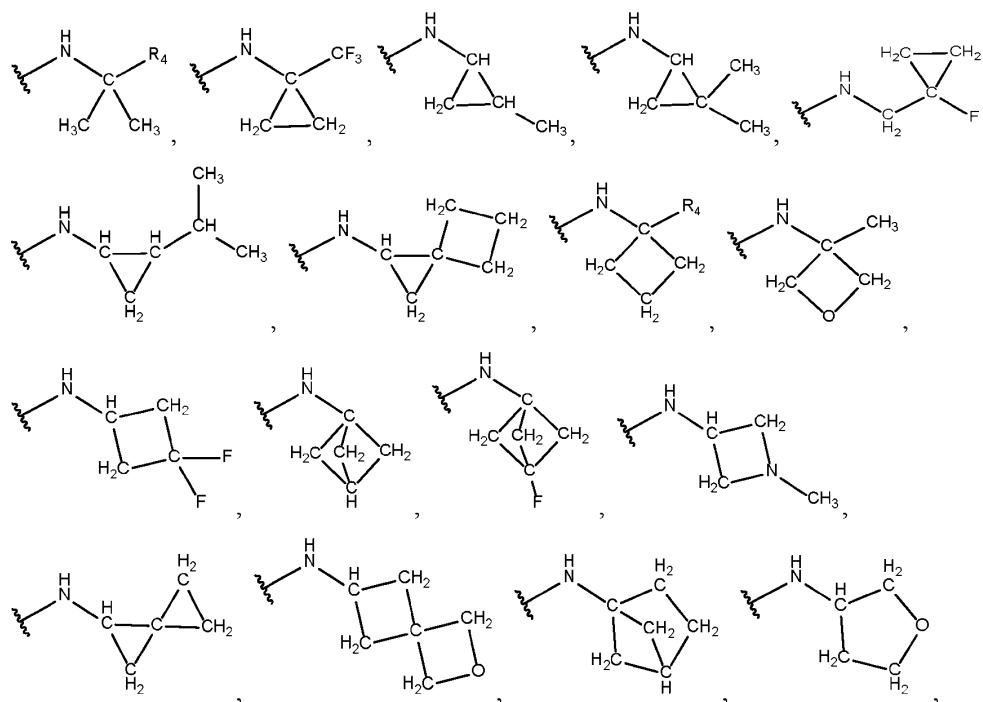
or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein  $R_1$ ,  $R_2$ ,  $R_5$ ,  $R^B$ ,  $R_x$ , and  $R^7$  are defined as provided for Formula (XIII),  $m$  is an integer between 0 and 12; and  $n$  is an integer between 0 and 4.

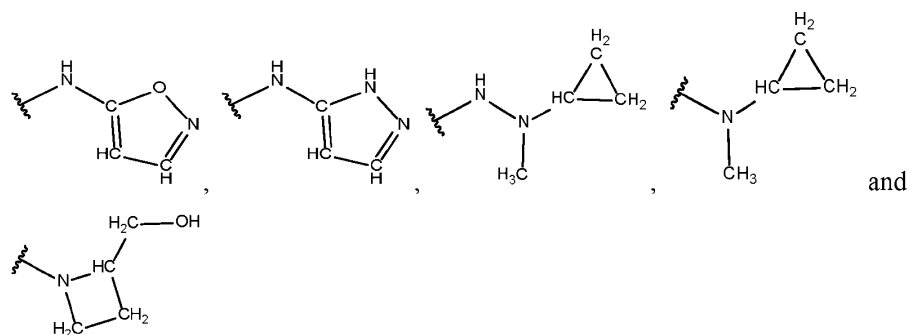
In an embodiment, the compounds of Formula (XIII) described herein exhibit improved properties over the compounds in the art. The known compounds cause serious side effects due to lack of channel specificity. Moreover, the benefit for the patient group at large of compounds already known in the prior art is modest as the responsiveness of patients suffering from HI, in particular CHI varies considerably within patients. It is assumed that this is due to their low specificity. In view of the high specificity of the compounds of the present invention responsiveness of patients suffering from HI, in particular CHI will be considerably better.

With respect to the compounds according to the present invention it is noted that they include all their acid addition and base salts, tautomeric forms, metabolites or prodrugs. The present invention further includes unsolvated forms, solvated forms including hydrated forms of the compounds of the present invention.

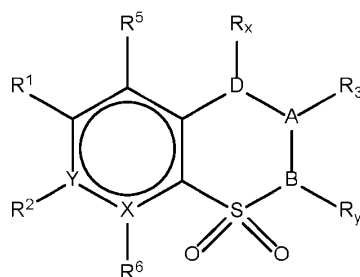
Preferred compounds according to the present invention are wherein said compounds are according to general formula (XIII) such that:

- A is carbon (C);
- B and D are Nitrogen (N); and
- wherein A and B or A and D are connected via a double or single bond; and
- wherein R<sub>1</sub> and R<sub>2</sub> are independently selected from the group consisting of hydrogen, fluorine, chlorine, bromine and iodine; and
- wherein A and B form a double bond and R<sub>x</sub> is H or wherein A and D form a double bond and R<sub>y</sub> is H; and
- wherein R<sub>3</sub> is independently selected from the group consisting of:





In another aspect, the SURx/Kirx channel activator compound is a compound having the structure of Formula (XIV):



or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein:

$A$  is  $C(R')$ ;

each of  $B$  and  $D$  are independently  $N$ ; wherein  $A$  and  $B$  or  $A$  and  $D$  are connected via a double or single bond;

$X$  is  $C(R')$  or  $S$ ;

when  $X$  is  $C(R')$  then  $Y$  is  $C(R')$ ; or,

when  $X$  is  $S$ , then  $Y$  is absent;

each of  $R_1$ ,  $R_2$ ,  $R_5$ , and  $R_6$  are independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl,  $-OR^A$ , fluorine, chlorine, bromine, iodine, nitro, or cyano; wherein  $A$  and  $B$  form a double bond and  $R_x$  is hydrogen or wherein  $A$  and  $D$  form a double bond and  $R_y$  is hydrogen;

$R_3$  is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, or  $N(R^B)(R^C)$ , wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more  $R_4$ ;

R' is absent, hydrogen, or C1-C6 alkyl;

each R<sub>4</sub> is independently C1-C6 alkyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, fluorine, chlorine, bromine, or iodine;

R<sup>A</sup> is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, or heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>;

each of R<sup>B</sup> and R<sup>C</sup> is independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>; or

wherein R<sup>B</sup> and R<sup>C</sup> are taken together to form heterocyclyl optionally substituted with one or more R<sub>7</sub>;

each R<sup>7</sup> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano.

In some embodiments, the SURx/Kirx channel activator compound is a compound disclosed in WO1997049692A1, WO2002074945A1, WO2003087089A1, WO2003091245A1, WO2005063742A2, WO2006045799A2, WO2007125048A1, WO2010093243A1, WO2013130411A1, WO2014046172A1, WO2019084271A1, WO2021236818A1, WO2004087053A2, WO2005058348A1, WO2007053514A2, WO2007081521A2, WO2007136125A1, WO2009006483A1, WO2017098421A1, US20100226943A1, WO2000037474A1, WO2001002410A1, WO2002000222A1, WO2002000665A1, WO2002050085A1, WO2003045954A1, WO2003045955A1, WO2003105896A1, WO2004005299A1, WO2005013962A1, WO2006045799A2, WO2006088798A2, WO2007020286A2, WO2007125048A1, WO2009000038A1, WO2022125784A1, WO1997026265A1, WO2003087089A1, WO1999003861A1, or WO1999032494A1, the contents of which are hereby incorporated by reference in their entirety.

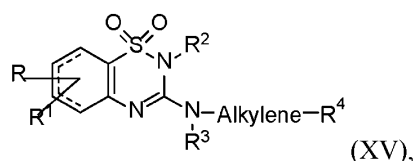
In some embodiments, the SURx/Kirx channel activator compound is a compound disclosed in US4035374A, US20070254862A1, DE2757922A1, DE2757999A1, EP105732A2, EP112142A2, EP172968A1, EP355612A2, JP6284823B2, JP51054576A, JP60072868A, EP386931A1, JP2015214525A, JP2016011275A, JP3254698A,



JP60112781A, DK200400395A, or EP1676573A1, the contents which are hereby incorporated by reference in their entirety.

In an aspect, the SURx/Kirx channel activator compound is diazoxide, which is disclosed in US2986573A, the contents of which is hereby incorporated by reference in its entirety.

In an aspect, the SURx/Kirx channel activator compound is a compound disclosed in DE2757999A1, e.g., the SURx/Kirx channel activator compound is a compound of formula (XV):



wherein:

R represents hydrogen, halogen, trifluoromethyl, alkyl, alkoxy, alkoxyalkyl, alkylthio, alkylcarbonyl, phenylcarbonyl, phenylsulfonyl, phenylsulfinyl, phenyloxy, phenylthio, where the phenyl radicals can be substituted by alkyl, alkoxy, halogen, nitro or amino, or for thenoyl or pyridylcarbonyl, which can be substituted by alkyl;

R<sup>1</sup> is hydrogen, halogen, trifluoromethyl, alkyl, alkoxy, alkoxyalkyl, alkylthio, alkylcarbonyl, phenylcarbonyl, phenylsulfonyl, phenylsulfinyl, phenyloxy or phenylthio, the phenyl radicals being represented by alkyl, alkoxy, halogen, nitro or amino can be substituted, or stands for thenoyl or pyridylcarbonyl, whereby these can be substituted by alkyl;

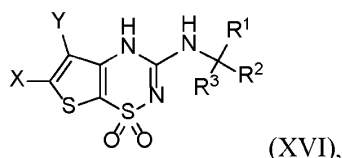
R<sup>2</sup> stands for hydrogen or alkyl;

R<sup>3</sup> stands for hydrogen or alkyl;

R<sup>4</sup> stands for the NH<sub>2</sub>, NHR<sup>5</sup> or the NR<sup>5</sup>R<sup>6</sup>- Group, where the radicals R<sup>5</sup> and R<sup>6</sup> can be identical or different and are alkyl or phenyl or phenylalkyl, and in the case of v on R<sup>5</sup> - alkyl this group can be connected to a carbon atom of the alkylene group to form a 5- or 6-membered ring, or where the radicals R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom can form an optionally substituted azabicycloalkyl radical with 6 to 10 ring members or R represents a cycloalkyleneimino group optionally interrupted by O, S, NH or NR<sup>5</sup> and/or substituted by one or two alkyl groups with a total of 5 to 7 ring members and in which the ring can optionally contain one, two or three double bonds, and alkylene represents a divalent

alkylene group, which can optionally be substituted by alkyl and/or by a hydroxy, acyloxy or alkoxy group, and their physiologically compatible salts.

In an aspect, the SURx/Kirx channel activator compound is a compound disclosed in WO2000037474A1, e.g., the SURx/Kirx channel activator compound is a compound of formula (XVI):



wherein

X and Y independently are hydrogen, halogen, perhalomethyl, C1-6-alkyl or C1-6-alkoxy; R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> independently are C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C3-6-cycloalkyl, carboxy, C1-6-alkoxycarbonyl or aryl, all of which are optionally being mono- or polysubstituted with halogen, hydroxy, oxo, or aryl; or

R<sup>1</sup> is as defined above and R<sup>2</sup>-C-R<sup>3</sup> form a C3-6 -cycloalkyl group, optionally being mono- or polysubstituted with C1-6-alkyl, perhalomethyl, halogen, hydroxy or aryl; or

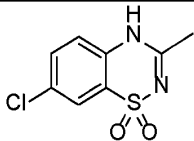
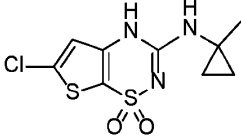
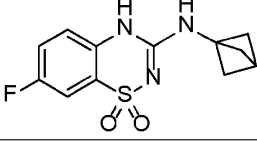
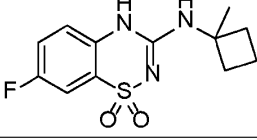
-CR<sup>1</sup>R<sup>2</sup>R<sup>3</sup> form a 4- to 12-membered bicyclic or tricyclic carbocyclic system, optionally being mono- or polysubstituted with C-6-alkyl, perhalomethyl, halogen, hydroxy or aryl; or a salt thereof with a pharmaceutically acceptable acid or base including all optical isomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixtures, or any tautomeric form thereof.

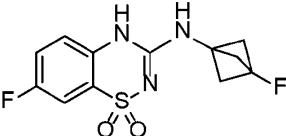
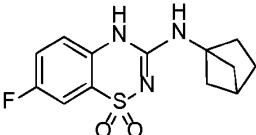
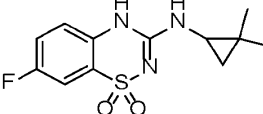
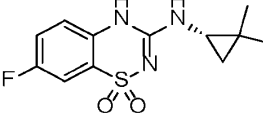
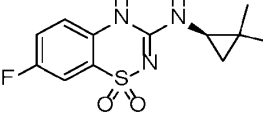
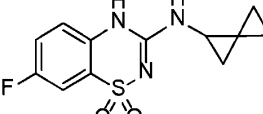
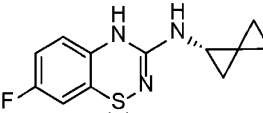
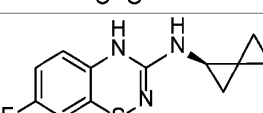
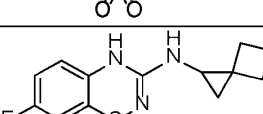
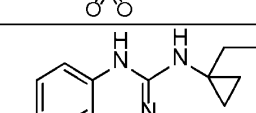
In some embodiments, the SURx/Kirx channel activator compound is a compound as shown in the Table 2 below:

| Compound No. | Name                                                                                         |
|--------------|----------------------------------------------------------------------------------------------|
| 77           | 3-tert-butylamino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide                    |
| 78           | 6-Chloro-3-(1,1-dimethylpropylamino)-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide          |
| 79           | 6-Chloro-3-(1-methylcyclopropyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide         |
| 80           | 6-Chloro-3-(2-hydroxy-1,1-dimethylethylamino)-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide |
| 81           | 6-Chloro-3-(1,1,3,3-tetramethylbutylamino)-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide    |
| 82           | 3-(1-adamantyl)amino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide                 |

|    |                                                                                                                                  |
|----|----------------------------------------------------------------------------------------------------------------------------------|
| 83 | 1-(6-Chloro-1,4-dihydro-1,1-dioxo-thieno[3,2-e]-1 $\lambda^6$ ,2,4-thiadiazin-3-ylamino)-cyclopropanecarboxylic acid ethyl ester |
| 84 | 6-Chloro-3-(1-methyl-1-phenylethyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide                                          |
| 85 | 6-Chloro-3-(1-hydroxymethylcyclopentyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide                                      |
| 86 | 1-(6-Chloro-1,4-dihydro-1,1-dioxo-thieno[3,2-e]-1 $\lambda^6$ ,2,4-thiadiazin-3-ylamino)-cyclopropanecarboxylic acid             |
| 87 | 6-Chloro-3-(1-methylcyclobutyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide                                              |
| 88 | 6-Chloro-3-(1-methylcyclohexyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide                                              |
| 89 | 6-Chloro-3-(1-methylcyclopentyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide                                             |
| 90 | 6-Chloro-3-(1-ethylcyclobutyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide                                               |

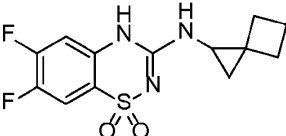
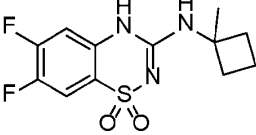
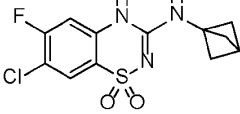
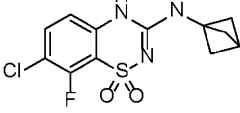
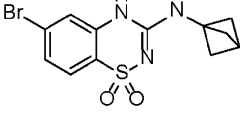
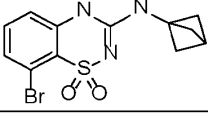
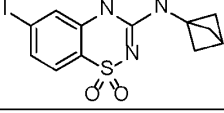
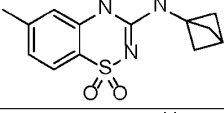
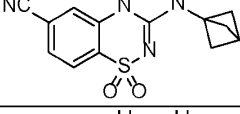
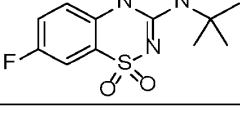
Exemplary SURx/Kirx channel activator compound compounds of the present disclosure are shown in **Table 3** below:

| Compound No.                            | Structure                                                                           | Name                                                                                   |
|-----------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| SURx/Kirx channel activator compound I  |  | 7-chloro-3-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide                                |
| SURx/Kirx channel activator compound II |  | 6-chloro-3-[(1-methylcyclopropyl)amino]-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide |
| 1                                       |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide  |
| 2                                       |  | 7-fluoro-3-((1-methylcyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide       |

|    |                                                                                     |                                                                                                                 |
|----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| 3  |    | 7-fluoro-3-((3-fluorobicyclo[1.1.1]pentan-1-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                 |
| 4  |    | 3-(bicyclo[2.1.1]hexan-1-ylamino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                            |
| 5  |    | 3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                           |
| 6  |    | ( <i>S</i> <sup>*</sup> )-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 7  |   | ( <i>R</i> <sup>*</sup> )-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 8  |  | 7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                               |
| 9  |  | ( <i>S</i> <sup>*</sup> )-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide     |
| 10 |  | ( <i>R</i> <sup>*</sup> )-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide     |
| 11 |  | 7-fluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                |
| 12 |  | 3-((1-ethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                |

|    |  |                                                                                                                          |
|----|--|--------------------------------------------------------------------------------------------------------------------------|
| 13 |  | 3-([1,1'-bi(cyclopropan)]-1-ylamino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                  |
| 14 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6-chloro-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide)                          |
| 15 |  | 6-chloro-7-fluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                |
| 16 |  | ( <i>S</i> <sup>*</sup> )-6-chloro-7-fluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide      |
| 17 |  | ( <i>R</i> <sup>*</sup> )-6-chloro-7-fluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide      |
| 18 |  | 6-chloro-7-fluoro-3-((3-methylbicyclo[1.1.1]pentan-1-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                 |
| 19 |  | 6-chloro-7-fluoro-3-((3-fluorobicyclo[1.1.1]pentan-1-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                 |
| 20 |  | 6-chloro-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                           |
| 21 |  | ( <i>S</i> <sup>*</sup> )-6-chloro-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 22 |  | ( <i>R</i> <sup>*</sup> )-6-chloro-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |

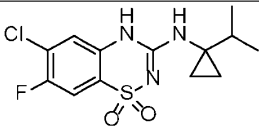
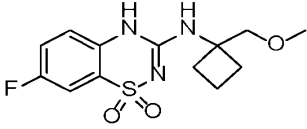
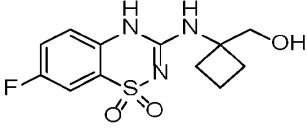
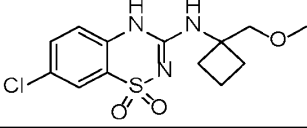
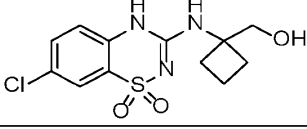
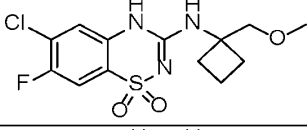
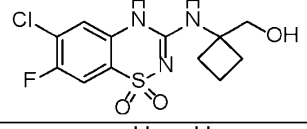
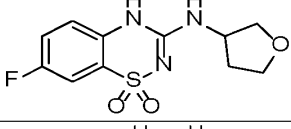
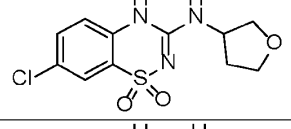
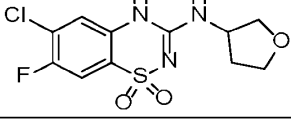
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|----|--|--------------------------------------------------------------------------------------------------------|
| 23 |  | 6-chloro-7-fluoro-3-((1-(trifluoromethyl)cyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide  |
| 24 |  | 6-chloro-7-fluoro-3-((1-methylcyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide              |
| 25 |  | (rac)-trans-6-chloro-7-fluoro-3-((2-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 26 |  | 6-chloro-7-fluoro-3-(((1S*,2S*)-2-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide   |
| 27 |  | 6-chloro-7-fluoro-3-(((1R*,2R*)-2-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide   |
| 28 |  | 6-chloro-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide             |
| 29 |  | (S*)-6-chloro-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide        |
| 30 |  | (R*)-6-chloro-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide        |
| 31 |  | 3-(bicyclo[2.1.1]hexan-1-ylamino)-6-chloro-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 32 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6,7-difluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide              |

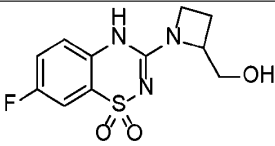
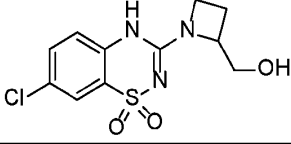
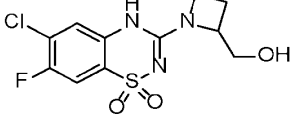
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|----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 33 |    | 6,7-difluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 34 |    | 6,7-difluoro-3-((1-methylcyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 35 |    | 3-(bicyclo[1.1.1]pentan-1-ylamino)-7-chloro-6-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 36 |    | 3-(bicyclo[1.1.1]pentan-1-ylamino)-7-chloro-8-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 37 |   | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6-bromo-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 38 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-8-bromo-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 39 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6-iodo-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide            |
| 40 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6-methyl-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 41 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine-6-carbonitrile 1,1-dioxide    |
| 42 |  | 3-(tert-butylamino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                         |

|    |  |                                                                                                     |
|----|--|-----------------------------------------------------------------------------------------------------|
| 43 |  | 3-((1,3-difluoropropan-2-yl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide               |
| 44 |  | 7-fluoro-3-((1-(dimethylamino)-2-methylpropan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 45 |  | 7-fluoro-3-((4-methoxy-2-methylbutan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 46 |  | 7-fluoro-3-((1-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                   |
| 47 |  | 7-fluoro-3-((1-(fluoromethyl)cyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 48 |  | 7-chloro-3-((4-methoxy-2-methylbutan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 49 |  | 7-chloro-3-((1,3-difluoropropan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide               |
| 50 |  | 7-chloro-3-((1-(dimethylamino)-2-methylpropan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 51 |  | 7-chloro-3-((1-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                   |
| 52 |  | 7-chloro-3-((1-(fluoromethyl)cyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 53 |  | 7-chloro-3-((3,3-difluorocyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                |



|    |  |                                                                                                              |
|----|--|--------------------------------------------------------------------------------------------------------------|
| 54 |  | 3-(tert-butylamino)-6-chloro-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                              |
| 55 |  | 6-chloro-3-((1,3-difluoropropan-2-yl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide               |
| 56 |  | 6-chloro-3-((1-(dimethylamino)-2-methylpropan-2-yl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 57 |  | 6-chloro-7-fluoro-3-((4-methoxy-2-methylbutan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 58 |  | 6-chloro-7-fluoro-3-((1-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                   |
| 59 |  | 6-chloro-3-((1-ethynylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                  |
| 60 |  | 6-chloro-7-fluoro-3-((1-(fluoromethyl)cyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 61 |  | 6-chloro-3-((3,3-difluorocyclobutyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                |
| 62 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-7-chloro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                        |
| 63 |  | 7-fluoro-3-((1-isopropylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                         |

|    |                                                                                     |                                                                                                    |
|----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| 64 |    | 6-chloro-7-fluoro-3-((1-isopropylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide      |
| 65 |    | 7-fluoro-3-((1-(methoxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 66 |    | 7-fluoro-3-((1-(hydroxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 67 |    | 7-chloro-3-((1-(methoxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 68 |   | 7-chloro-3-((1-(hydroxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 69 |  | 6-chloro-7-fluoro-3-((1-(methoxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 70 |  | 6-chloro-7-fluoro-3-((1-(hydroxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 71 |  | (R)-7-fluoro-3-((tetrahydrofuran-3-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide             |
| 72 |  | (R)-7-chloro-3-((tetrahydrofuran-3-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide             |
| 73 |  | (R)-6-chloro-7-fluoro-3-((tetrahydrofuran-3-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide    |

|    |                                                                                   |                                                                                                    |
|----|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| 74 |  | (R)-7-fluoro-3-(2-(hydroxymethyl)azetidin-1-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 75 |  | (R)-7-chloro-3-(2-(hydroxymethyl)azetidin-1-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 76 |  | (R)-6-chloro-7-fluoro-3-(2-(hydroxymethyl)azetidin-1-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |

### Methods of Use

Disclosed herein are methods for treating and/or preventing a disease, disorder or condition with a combination of a potassium channel activator (e.g., a SURx/Kirx channel activator compound) and an MC4R agonist. Exemplary diseases or disorders may include obesity or an obesity-related disorder, a metabolic disorder (e.g., hyperphagia, congenital hyperinsulinism), cancer, a neurological disorder, a cardiovascular disorder, a pulmonary disorder, an integumentary disorder, a sexual disorder, a urinary disorder, or a symptom thereof.

In some embodiments, the disease, disorder or condition is a metabolic disorder. In some embodiments, the metabolic disorder is hyperinsulinism (HI), congenital hyperinsulinism (CHI), persistent hyperinsulinism, or transient hyperinsulinism. In some embodiments, the metabolic disorder is a hyperinsulinism-related syndrome, e.g., Beckwith-Wiedemann syndrome, hyperinsulinism-hyperammonaemia (HIHA) syndrome, Sotos syndrome, Turner syndrome, Costello syndrome, Kabuki syndrome, and the like. Glucose is an important source of energy for mammals, as it is transported from the intestines or liver to body cells via the bloodstream and is made available for cellular metabolism by secretion of the hormone insulin. By means of a delicate mechanism, referred to as glucose homeostasis, the body in healthy human subjects is able to maintain the glucose concentration within a preferred range of around 3.5 to 5.5 mmol/L. Blood glucose levels outside this normal range may be an indicator of a medical condition.

The major hormones involved in regulation of glucose metabolism over the time scale of hours are insulin and glucagon. Insulin and glucagon are secreted by the pancreatic islets and are both secreted in response to blood glucose levels, but in opposite fashion.

Insulin is an important peptide hormone involved in nutrient homeostasis which is produced by the  $\beta$ -cells in the pancreatic islets. It regulates the metabolism of carbohydrates and fats by promoting the transport of glucose from the blood to skeletal muscles and fat tissue. The general stimulus for insulin secretion is a high blood glucose. Although there is always a low level of insulin secreted by the pancreas, the amount secreted into the blood increases as the blood glucose rises.

On the other hand, when glucose levels are low, glucagon secretion increases and insulin secretion decreases. The most important effect of the glucagon increase is that it triggers the liver to release the glucose it has stored in its cells (as the polymer glycogen) into the bloodstream. The net effect of this release of glucose is the raising of the blood glucose concentration. Moreover, glucagon also induces the liver and other cells to make glucose out of building blocks obtained from other nutrients found in the body (e.g., protein).

Blood glucose levels outside the normal range may be an indicator of a medical condition. A persistently high level is referred to as hyperglycaemia and low levels are referred to as hypoglycaemia. One particular condition associated with a dysfunctional glucose homeostasis is hyperinsulinism.

Hyperinsulinism (HI) is defined as the elevated insulin levels in blood due to dysregulated release of the insulin from  $\beta$ -cells and causes hypoglycaemia. It can be genetic or acquired and transient or permanent. Hyperinsulinaemic hypoglycaemia (HH) is described as a clinically, genetically, and morphologically heterozygous conditions where the insulin secretion is persistent despite low blood glucose levels. The most severe and permanent forms of HH is due to congenital hyperinsulinism.

Congenital hyperinsulinism (CHI) is an inherited form of hyperinsulinaemic hypoglycaemia (HH) due to mutations in genes involved in the regulation of insulin secretion. CHI is a permanent form of hypoglycaemia in neonates, infants and children which causes irreversible brain damage due to the secondary metabolic actions of insulin. The excessive release of insulin causes suppression of lipolysis and reduction in ketones which are alternative energy sources for the brain. The rise of the insulin levels also inhibits secretion of glucagon

which hinders the fat breakdown causing again direct damage of the brain. Therefore, up to 48% of children having recurrent hypoglycaemia suffer from brain damage.

The genetic basis of CHI has been related to 23 mutations in essential genes controlling insulin secretion and two of these genes, namely ABCC8 and KCNJ11, are genes encoding K<sub>ATP</sub> channel proteins SUR1 and Kir6.2, regulating the insulin release from the pancreatic  $\beta$ -cell among other proteins.

In some embodiments, the metabolic disorder is obesity, e.g., hypothalamic obesity. In some embodiments, the metabolic disorder is diabetes, e.g., Type 1 or Type 2 diabetes, or first-phase diabetes or a pre-diabetes syndrome. In some embodiments, the metabolic disorder is a genetic or epigenetic disorder, e.g., Prader-Willi syndrome, Alström syndrome, Bardet-Biedl syndrome, or Smith-Magenis syndrome. In some embodiments, the metabolic disorder is Prader-Willi syndrome. In some embodiments, the metabolic disorder is Alström syndrome. In some embodiments, the metabolic disorder is Bardet-Biedl syndrome. In some embodiments, the metabolic disorder is Smith-Magenis syndrome. In an embodiment, the disease or disorder is ischemia.

In some embodiments, the disease or disorder is alopecia or baldness. In an embodiment, the disease or disorder is a behavioral disorder or a psychological disorder.

In some embodiments, the methods described herein directly or indirectly reduce or alleviate at least one symptom of a disease or disorder (e.g., a disease or disorder described herein).

In some embodiments, the methods described herein may treat or alleviate at least one symptom of the metabolic disorder, e.g., an increase in waist circumference of at least 2 cm relative to a reference (e.g., the waist circumference of a subject before onset of the metabolic disorder); an increase in blood pressure relative to a reference (e.g., the blood pressure of a subject before onset of the metabolic disorder); hyperglycemia or an increase in fasting blood sugar relative to a reference (e.g., the fasting blood sugar of a subject before the onset of the metabolic disorder); an increase in thirst (e.g., an increase in thirst relative to a reference, e.g., the level of thirst of a subject before the onset the metabolic disorder); an increase in fatigue (e.g., an increase in fatigue relative to a reference, e.g., the level of fatigue of a subject before the onset of a metabolic disorder); or an increase in urination (e.g., an increase in urination relative

to a reference, e.g., the frequency or amount of urination of a subject before the onset of a metabolic disorder).

In some embodiments, the methods described herein prevents or slows the onset of a disease or disorder, e.g., a metabolic disorder.

In some embodiments, the subject has a comorbidity, e.g., obesity, hyperphagia or hyperphagia-related syndromes, unwanted appetite, hypoglycemia, hyperglycemia, hyperlipidemia, hypercholesterolemia, or hypertriglyceridemia. In some embodiments, the metabolic disorder is hyperinsulinemia, e.g., chronic hyperinsulinemia (CHI). In some embodiments, the metabolic disorder is pre-diabetes, type I diabetes, or type II diabetes. In some embodiments, the metabolic disorder is a diabetological condition.

In some embodiments, the subject has had interventional surgery, e.g., bariatric surgery. In some embodiments, the subject has had brain surgery, e.g., a hypothalamic surgery. In some embodiments, the subject has a brain tumor, e.g., a craniopharyngioma, germinoma, glioma, hamartoma, pituitary adenoma.

In some embodiments, the methods described herein may treat a metabolic disorder. In some embodiments, the methods described herein may provide a counterregulatory response to hypoglycemia in subject with diabetes, e.g., type I or type II diabetes. In some embodiments, the methods described herein may be useful in combination with a second agent, e.g., a sulfonylurea prior to a bolus to restore normal insulin levels in a subject, e.g., a subject with diabetes, e.g., type I or type II diabetes.

In some embodiments, the disease or disorder is a cancer. In some embodiments, the cancer is a gastrointestinal cancer, e.g., oesophageal cancer, gastric cancer, pancreatic cancer, liver cancer, gallbladder cancer, colorectal cancer, anal cancer, or a gastrointestinal carcinoid tumour. In some embodiments, the gastrointestinal cancer is oesophageal cancer. In some embodiments, the gastrointestinal cancer is gastric cancer. In some embodiments, the gastrointestinal cancer is pancreatic cancer. In some embodiments, the gastrointestinal cancer is a pancreatic cancer, wherein the pancreatic cancer is an insulinoma. In some embodiments, the gastrointestinal cancer is liver cancer. In some embodiments, the gastrointestinal cancer is gallbladder cancer. In some embodiments, the gastrointestinal cancer is colorectal cancer. In some embodiments, the gastrointestinal cancer is anal cancer. In some embodiments, the gastrointestinal cancer is a gastrointestinal cancer.

In some embodiments, the disease or disorder is a neurological disorder, e.g., Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, migraine (e.g., chronic migraine), epilepsy and epilepsy-related syndromes.

In some embodiments, the methods as described herein directly or indirectly reduce or alleviate at least one symptom of a disease or disorder, e.g., a neurological disease or disorder described herein. In some embodiments, the methods directly or indirectly reduce or alleviate pain or aid in pain management, i.e., the methods as described herein directly or indirectly function in analgesia of a disease or a disorder, e.g., a neurological disorder.

In some embodiments, the methods as described herein directly or indirectly alleviate a symptom of a disease or disorder, e.g., a neurological disorder. In some embodiments, the methods as described herein provide neuroprotection in a subject in need thereof, e.g., in a subject with a neurological disorder, e.g., Alzheimer's Disease, Parkinson's Disease, or Multiple Sclerosis.

In some embodiments, the disease or disorder is a cardiovascular disorder, e.g., ischemia, ischemia-reperfusion injury, hypertension, coronary spasm, ocular pressure, peripheral vascular disease. In some embodiments, the cardiovascular disorder is angina, cardioplegia, a ventricular septal defect, atrial fibrillation, arrhythmia, coronary artery disease, or myocardial stunning.

In some embodiments, the methods as described herein provide cardioprotection in a subject in need thereof, e.g., in a subject with a cardiovascular disorder, e.g., angina, cardioplegia, a ventricular septal defect, atrial fibrillation, arrhythmia, coronary artery disease, or myocardial stunning.

In some embodiments, the disease or disorder is a pulmonary disorder, e.g., pulmonary hypertension or asthma.

In some embodiments, the disease or disorder is an integumentary disorder, e.g., a disorder of the hair, skin, and nails, inter alia. In some embodiments, the disease or disorder is alopecia, baldness, e.g., male-pattern baldness, or disorders of hair follicular growth.

In some embodiments, the disease or disorder is a sexual disorder, e.g., male impotence.

In some embodiments, the disease or disorder is a urinary disorder, e.g., detrusor hyperreactivity.

In an embodiment, the subject is a mammal, e.g., a human. In an embodiment, the subject is an adult (e.g., over the age of 18 years old) or a child (e.g., under the age of 18, 12, 10, 8, 6, 4,

or 2 years old). In an embodiment, the subject has been treated for a metabolic disorder previously. For example, the subject may be a bariatric surgery patient.

### **Combination Therapies**

Described herein are combination therapies comprising a potassium channel activator compound (i.e., a SURx/Kirx channel activator compound) and an MC4R agonist, useful for treating and/or preventing a disease, disorder, or condition, such as obesity or an obesity-related disorder. The combination therapy may be administered as a single formulation or as separate formulations. In an embodiment, the SURx/Kirx channel activator compound and the MC4R agonist are administered as a single pharmaceutical composition. In an embodiment, the SURx/Kirx channel activator compound and the MC4R agonist are administered as separate pharmaceutical compositions. In the case of separate formulations, the SURx/Kirx channel activator compound and the MC4R agonist may be administered concomitantly or sequentially. In an embodiment, the SURx/Kirx channel activator compound and the MC4R agonist are administered concomitantly. In an embodiment, the SURx/Kirx channel activator compound and the MC4R agonist are administered sequentially. For example, the SURx/Kirx channel activator compound may be administered prior to the MC4R agonist or subsequent to the MC4R agonist.

In some embodiments, the administration of the SURx/Kirx channel activator compound and the MC4R agonist has a synergistic or additive effect. For example, the SURx/Kirx channel activator compound and the MC4R agonist may have an additive effect, in which the therapeutic effect of the SURx/Kirx channel activator compound and the MC4R agonist is the total sum of the effects of each of the components individually. In contrast, the administration of the SURx/Kirx channel activator compound and the MC4R agonist may have a synergistic effect, in which the therapeutic effect of the SURx/Kirx channel activator compound and the MC4R agonist is greater than the sum of the individual components. The synergistic effect of the combination of the SURx/Kirx channel activator compound and the MC4R agonist may be 0.1%, 0.25%, 0.5%, 0.75%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than the total sum of the effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually. In an embodiment, the synergistic effect of the combination of the SURx/Kirx channel activator compound and the MC4R agonist is greater than between 5% and 75% of the total sum of the



effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually.

In an embodiment, the synergistic effect of the combination of the SURx/Kirx channel activator compound and the MC4R agonist is greater than 10% of the total sum of the effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually. In an embodiment, the synergistic effect of the combination of the SURx/Kirx channel activator compound and the MC4R agonist is greater than 25% of the total sum of the effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually. In an embodiment, the synergistic effect of the combination the SURx/Kirx channel activator compound and the MC4R agonist is greater than 50% of the total sum of the effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually. In an embodiment, the synergistic effect of the combination of the SURx/Kirx channel activator compound and the MC4R agonist is greater than 75% of the total sum of the effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually.

The synergistic effect of the combination of the SURx/Kirx channel activator compound and the MC4R agonist may be 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 40-fold, 50-fold, 75-fold, 100-fold, 200-fold, 500-fold greater or more than the total sum of the effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually. In an embodiment, the synergistic effect of the combination of the SURx/Kirx channel activator compound and the MC4R agonist is greater than between 2-fold and 100-fold of the total sum of the effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually. In an embodiment, the synergistic effect of the combination of the SURx/Kirx channel activator compound and the MC4R agonist is greater than between 5-fold and 50-fold of the total sum of the effects of the SURx/Kirx channel activator compound and the MC4R agonist administered individually.

In one aspect, the amount of the SURx/Kirx channel activator compound and the MC4R agonist are selected such that the molar concentration of the SURx/Kirx channel activator compound is greater than the molar concentration of the MC4R agonist. For example, the molar concentration of the SURx/Kirx channel activator compound is greater than 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 40-

fold, 50-fold, 75-fold, 100-fold, 200-fold, or 500-fold greater than the molar concentration of the MC4R agonist. In an embodiment, the molar concentration of the SURx/Kirx channel activator compound is greater than 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, or 10-fold greater than the molar concentration of the MC4R agonist. In an embodiment, the molar concentration of the SURx/Kirx channel activator compound is between 2-fold and 20-fold greater than the molar concentration of the MC4R agonist. In an embodiment, the molar concentration of the SURx/Kirx channel activator compound is between 5-fold and 10-fold greater than the molar concentration of the MC4R agonist. In an embodiment, the molar concentration of the SURx/Kirx channel activator compound is about 5-fold greater than the molar concentration of the MC4R agonist. In an embodiment, the molar concentration of the SURx/Kirx channel activator compound is about 10-fold greater than the molar concentration of the MC4R agonist. In an embodiment, the molar concentration of the SURx/Kirx channel activator compound is about 15-fold greater than the molar concentration of the MC4R agonist.

In another aspect, the combination of the SURx/Kirx channel activator compound and the MC4R agonist results in reducing the toxicity one or more of the SURx/Kirx channel activator compound and the MC4R agonist in a subject or cell when administered individually. For example, administration of a combination of the SURx/Kirx channel activator compound and the MC4R agonist may result in reducing the toxicity of the SURx/Kirx channel activator compound in a subject or cell, compared with the toxicity of the SURx/Kirx channel activator compound when administered to the subject or cell individually. In an embodiment, the toxicity of the SURx/Kirx channel activator compound in a subject or cell is reduced upon administration of SURx/Kirx channel activator compound in combination with an MC4R agonist, e.g., by about 0.1%, 0.25%, 0.5%, 0.75%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared with the toxicity of the SURx/Kirx channel activator compound when administered individually.

In another aspect, the combination of the SURx/Kirx channel activator compound and the MC4R agonist results in reducing the toxicity of the MC4R agonist in a subject or cell. For example, administration of a combination of the SURx/Kirx channel activator compound may result in reducing the toxicity of the MC4R agonist in a subject or cell, compared with the toxicity of the MC4R agonist when administered to the subject or cell individually. In an embodiment, the toxicity of the SURx/Kirx channel activator compound in a subject or cell is

reduced upon administration of an MC4R agonist in combination with a SURx/Kirx channel activator compound, e.g., by about 0.1%, 0.25%, 0.5%, 0.75%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared with the toxicity of the SURx/Kirx channel activator compound when administered individually.

In an embodiment, the SURx/Kirx channel activator compound is administered at a dosage to provide a concentration of between 0.1  $\mu\text{M}$  and 500  $\mu\text{M}$  in a subject or cell. In an embodiment, the SURx/Kirx channel activator compound is administered at a dosage to provide a concentration of between 0.5  $\mu\text{M}$  and 100  $\mu\text{M}$  in a subject or cell. In an embodiment, the SURx/Kirx channel activator compound is administered at a dosage to provide a concentration of between 1  $\mu\text{M}$  and 100  $\mu\text{M}$  in a subject or cell. In an embodiment, the SURx/Kirx channel activator compound is administered at a dosage to provide a concentration of between 1  $\mu\text{M}$  and 50  $\mu\text{M}$  in a subject or cell. In an embodiment, the SURx/Kirx channel activator compound is administered at a dosage to provide a concentration of between 1  $\mu\text{M}$  and 25  $\mu\text{M}$  in a subject or cell. In an embodiment, the MC4R agonist is administered at a dosage to provide a concentration of between 0.01  $\mu\text{M}$  and 50  $\mu\text{M}$  in a subject or cell. In an embodiment, the MC4R agonist is administered at a dosage to provide a concentration of between 0.1  $\mu\text{M}$  and 25  $\mu\text{M}$  in a subject or cell. In an embodiment, the MC4R agonist is administered at a dosage to provide a concentration of between 0.1  $\mu\text{M}$  and 10  $\mu\text{M}$  in a subject or cell. In an embodiment, the MC4R agonist is administered at a dosage to provide a concentration of between 0.1  $\mu\text{M}$  and 5  $\mu\text{M}$  in a subject or cell. In an embodiment, the MC4R agonist is administered at a dosage to provide a concentration of between 0.1  $\mu\text{M}$  and 2.5  $\mu\text{M}$  in a subject or cell.

In an embodiment, the SURx/Kirx channel activator compound is administered at a dosage to provide a concentration of between 0.1  $\mu\text{M}$  and 500  $\mu\text{M}$  and the MC4R agonist is administered at a dosage to provide a concentration of between 0.01  $\mu\text{M}$  and 50  $\mu\text{M}$  in a subject or cell. In an embodiment, the SURx/Kirx channel activator compound is administered at a dosage to provide a concentration of between 1  $\mu\text{M}$  and 100  $\mu\text{M}$  and the MC4R agonist is administered at a dosage to provide a concentration of between 0.1  $\mu\text{M}$  and 25  $\mu\text{M}$  in a subject or cell. In an embodiment, the SURx/Kirx channel activator compound is administered at a dosage to provide a concentration of between 1  $\mu\text{M}$  and 25  $\mu\text{M}$  and the MC4R agonist is administered at a dosage to provide a concentration of between 0.1  $\mu\text{M}$  and 2.5  $\mu\text{M}$  in a subject or cell.

In an embodiment, the combination of the SURx/Kirx channel activator compound and the MC4R agonist administered to the subject allows for a reduction in the dosage of the SURx/Kirx channel activator compound needed to achieve a therapeutic effect, e.g., allows for a subefficacious dosage of the SURx/Kirx channel activator compound, relative to the treatment of a disease or disorder or a symptom of a disease or disorder, for example, a (i) reduction in body weight, (ii) reduction in food intake, (iii) reduction in plasma blood glucose, (iv) reduction in plasma insulin, (v) reduction in plasma insulin, (vi) reduction in plasma leptin, (vii) reduction in a liver marker, such as steatosis, hepatocellular ballooning, lobular inflammation, lipid deposition, or total NAS.

In an embodiment, the combination of the SURx/Kirx channel activator compound and the MC4R agonist administered to the subject allows for a reduction in the dosage of the SURx/Kirx channel activator compound needed to achieve a reduction in body weight. In an embodiment, the combination of the SURx/Kirx channel activator compound and the MC4R agonist administered to the subject allows for a reduction in the dosage of the SURx/Kirx channel activator compound needed to achieve a reduction in food intake. In an embodiment, the combination of the SURx/Kirx channel activator compound and the MC4R agonist administered to the subject allows for a reduction in the dosage of the SURx/Kirx channel activator compound needed to achieve a reduction in plasma blood glucose. In an embodiment, the combination of the SURx/Kirx channel activator compound and the MC4R agonist administered to the subject allows for a reduction in the dosage of the SURx/Kirx channel activator compound needed to achieve a reduction in plasma insulin. In an embodiment, the combination of the SURx/Kirx channel activator compound and the MC4R agonist administered to the subject allows for a reduction in the dosage of the SURx/Kirx channel activator compound needed to achieve a reduction in plasma leptin. In an embodiment, the combination of the SURx/Kirx channel activator compound and the MC4R agonist administered to the subject allows for a reduction in the dosage of the SURx/Kirx channel activator compound needed to achieve a reduction in a liver marker, such as steatosis, hepatocellular ballooning, lobular inflammation, lipid deposition, or total NAS.

In another aspect, the combination of the SURx/Kirx channel activator compound with an MC4R agonist results in reducing a symptom of a disease, disorder or condition in a subject.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and has substantially no reduction in body weight, e.g., relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in body weight of between 1% and 40%, e.g., 5% and 30%, e.g., relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in body weight of between 18-20%, e.g., relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 1**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in body weight of between 20-25% after 22 days, e.g., relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 12A**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in body weight of between 18-20% after 22 days relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 13**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in body weight of between 15-20% after 22 days relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 12B**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in body weight of between 18-20% after 22 days relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 16A**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in body weight of between 18-20% after 22 days relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 16B**.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and provides a reduction in plasma glucose relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in plasma glucose between about 1% and 50% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to subject and provides a reduction in plasma glucose of between 30-40%

relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 3A**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in plasma glucose between about 25% -45% relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 7A**.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and provides a reduction in plasma insulin relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in plasma insulin between about 1% and 90% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to subject and provides a reduction in plasma insulin of between 70-90% relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 3B**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to subject and provides a reduction in plasma insulin of between 65-75% relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 7B**.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and provides a reduction in plasma leptin relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in plasma leptin between about 1% and 50% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to subject and provides a reduction in plasma leptin of between 30-50% relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 3C**.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and provides a reduction in plasma glucose relative to a reference standard, e.g., a placebo,. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in plasma glucose of about 100-400mg/dL relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered with an MC4R agonist and provides a reduction in plasma glucose of about 300-400 mg/dL relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 4A**. In some embodiments, the

SURx/Kirx channel activator compound is administered with an MC4R agonist and provides a reduction in plasma glucose of about 100-200 mg/dL relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 8A**. In some embodiments, the SURx/Kirx channel activator compound is administered with an MC4R agonist and provides a reduction in plasma glucose of about 100-200 mg/dL relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 8B**.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and provides a reduction in plasma insulin relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in plasma insulin of about 1-10 ng/mL relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered with an MC4R agonist and provides a reduction in plasma insulin of about 4-8 ng/dL relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 4B**. In some embodiments, the SURx/Kirx channel activator compound is administered with an MC4R agonist and provides a reduction in plasma insulin of about 5-10 ng/dL relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 8C**. In some embodiments, the SURx/Kirx channel activator compound is administered with an MC4R agonist and provides a reduction in plasma insulin of about 5-10 ng/dL relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 8D**.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and provides no substantial reduction in body weight relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered with an MC4R agonist to a subject and provides a reduction in body weight of about 1-30% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered with an MC4R agonist and provides a reduction of 10-20% relative to a reference standard, e.g., a placebo, as shown in **FIG. 5**.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and provides no substantial reduction in body weight relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered with an MC4R agonist to a subject and provides a reduction in body weight of about 1-40 g relative to a reference standard, e.g., a placebo. In some embodiments, the

SURx/Kirx channel activator compound is administered with an MC4R agonist and provides a reduction of 20-40 g relative to a reference standard, e.g., a placebo, as shown in **FIG. 6**.

In some embodiments, the SURx/Kirx channel activator compound is administered to a subject as a single therapy and provides no substantial reduction in cumulative food intake relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in cumulative food intake of about 10-500 g after 22 days relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction of 200-400 g after 22 days relative to a reference standard, e.g., a placebo, as shown in **FIG. 2**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction of 200-400 g after 22 days relative to a reference standard, e.g., a placebo, as shown in **FIG. 2B**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction of 200-400 g after 22 days relative to a reference standard, e.g., a placebo, as shown in **FIG. 17A**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction of 200-400 g after 22 days relative to a reference standard, e.g., a placebo, as shown in **FIG. 17B**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in glucose area-under-the-curve (AUC) relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in glucose area-under-the-curve (AUC) of about 10-200 mg/(dL·h) after 120 min relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in glucose area-under-the-curve (AUC) of 100-200 mg/(dL·h) after 120 min relative to a reference standard, e.g., a placebo, as shown in **FIG. 9A**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in glucose area-under-the-curve (AUC) of 100-200 mg/(dL·h) after 120 min relative to a reference standard, e.g., a placebo, as shown in **FIG. 9B**.



In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in insulin area-under-the-curve (AUC) relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in insulin area-under-the-curve (AUC) of about 1-15 ng/(mL·h) after 120 min relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in glucose area-under-the-curve (AUC) of 5-10 ng/(mL·h) after 120 min relative to a reference standard, e.g., a placebo, as shown in **FIG. 9C**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides a reduction in glucose area-under-the-curve (AUC) of 5-10 ng/(mL·h) after 120 min relative to a reference standard, e.g., a placebo, as shown in **FIG. 9D**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has no substantial change in plasma cholesterol relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides no substantial change in plasma cholesterol relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist to a subject and provides no substantial change in plasma cholesterol relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 10A**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in plasma triglycerides relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in plasma triglycerides of about 1-10 mmol/L relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in plasma triglycerides of about 5-10 mmol/L relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 10A**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in plasma NEFA relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is

administered in combination with an MC4R agonist and provides a reduction in plasma NEFA of about 100-1000  $\mu$ M relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in plasma NEFA of about 400-800  $\mu$ M relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 10B** or in **FIG. 10D**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in plasma AST relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in plasma AST of about 1-20 U/L relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in plasma AST of about 10-20 U/L relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 10C**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has no substantial reduction in plasma ALT relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in plasma ALT of about 1-20 U/L relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in plasma ALT of about 10-20 U/L relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 10D**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has no substantial reduction in liver cholesterol relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist a provides a reduction in liver cholesterol of about 0.1-0.5 mg/g relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist a provides a reduction in liver cholesterol of about 0.1-0.3 mg/g relative to a reference standard, e.g., a placebo, e.g. as shown in **FIG. 11**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has no substantial reduction in liver NEFA relative to a reference

standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist a provides a reduction in liver NEFA of about 0.1-0.5 mg/g relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist a provides a reduction in liver NEFA of about 0.1-0.3 mg/g relative to a reference standard, e.g., a placebo, e.g. as shown in **FIG. 11**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has no substantial reduction in liver triglycerides relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in liver triglycerides of about 10-100 mg/g relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in liver triglycerides of about 30-60 mg/g relative to a reference standard, e.g., a placebo, e.g. as shown in **FIG. 11**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has no substantial reduction in liver glycogen relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides no substantial reduction in liver glycogen relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides no substantial reduction in liver glycogen relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 11**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in steatosis score relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in steatosis score of about 0.1 to 2 relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in steatosis score of about 1 to 2 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 14**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in

steatosis score of about 1 to 2 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 15**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in vacuolation score relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in vacuolation score of about 0.1 to 2 relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in vacuolation score of about 1 to 2 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 14**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in vacuolation score of about 1 to 2 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 15**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in inflammatory infiltration score relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in inflammatory infiltration score of about 0.1 to 3 relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in vacuolation score of about 2 to 3 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 14**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in vacuolation score of about 1 to 2 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 15**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in lipid deposition score relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in lipid deposition score of about 0.1 to 4 relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in lipid deposition score of about 2 to 4 relative to a reference standard,

e.g., a placebo, e.g., as shown in **FIG. 14**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in lipid deposition score of about 2 to 4 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 15**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has a reduction in total NAS score relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in total NAS score of about 0.1 to 8 relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in lipid deposition score of about 4 to 8 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 14**. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in lipid deposition score of about 4 to 8 relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 15**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has no substantial change in carcass weight relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in carcass weight of between about 1-25% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in carcass weight of 15-20% relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 19A**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has no substantial change in fat relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in fat of between about 10-40% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in fat of 20-30% relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 19B**.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has an increase in protein of about 10-30% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in protein of between about 0-10% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides no change in protein relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in protein of 5% relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 19C**. In some embodiments, the SURx/Kirx channel activator compound administered in combination with an MC4R agonist reduces fat tissue in a subject has a lower (e.g., substantially lower) reduction in lean muscle mass, e.g., protein.

In some embodiments, the SURx/Kirx channel activator compound is administered as a single therapy and the subject has an increase in water of about 1-20% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in water of between about 5-15% relative to a reference standard, e.g., a placebo. In some embodiments, the SURx/Kirx channel activator compound is administered in combination with an MC4R agonist and provides a reduction in water of 10% relative to a reference standard, e.g., a placebo, e.g., as shown in **FIG. 19D**.

In some embodiments, the SURx/Kirx channel activator concentration in the CSF is between about 100-1000 ng/mL when administered as a monotherapy. In some embodiments, the SURx/Kirx channel activator concentration in the liver is between about 10,000-100,000 ng/mL when administered as a monotherapy. In some embodiments, the SURx/Kirx channel activator plasma concentration is between about 10,000-100,000 ng/mL when administered as a monotherapy. In some embodiments, the SURx/Kirx channel activator concentration in the CSF is between about 606 ng/mL when administered as a monotherapy, e.g., as shown in **FIG. 18**. In some embodiments, the SURx/Kirx channel activator concentration in the liver is between about 25,133 ng/mL when administered as a monotherapy, e.g., as shown in **FIG. 18**. In some embodiments, the SURx/Kirx channel activator plasma concentration is between about 27,600 ng/mL, when administered as a monotherapy, e.g., as shown in **FIG. 18**.

In some embodiments, the SURx/Kirx channel activator concentration in the CSF is between about 100-1000 ng/mL when administered as a combination therapy with an MC4R agonist. In some embodiments, the SURx/Kirx channel activator concentration in the liver is between about 10,000-100,000 ng/mL when administered as a combination therapy with an MC4R agonist. In some embodiments, the SURx/Kirx channel activator plasma concentration is between about 10,000-100,000 ng/mL when administered as a combination therapy with an MC4R agonist. In some embodiments, the SURx/Kirx channel activator concentration in the CSF is between about 429 ng/mL when administered as a combination therapy with an MC4R agonist, e.g., as shown in **FIG. 18**. In some embodiments, the SURx/Kirx channel activator concentration in the liver is between about 23,714 ng/mL when administered as a combination therapy with an MC4R agonist, e.g., as shown in **FIG. 18**. In some embodiments, the SURx/Kirx channel activator plasma concentration is between about 31,371 ng/mL when administered as a combination therapy with an MC4R agonist, e.g., as shown in **FIG. 18**.

In some embodiments, the MC4R concentration in the CSF is between about 0.01-1 ng/mL when administered as a combination therapy with an SURx/Kirx channel activator compound. In some embodiments, the SURx/Kirx channel activator concentration in the liver is between about 1-100 ng/mL when administered as a combination therapy with an SURx/Kirx channel activator compound. In some embodiments, the SURx/Kirx channel activator plasma concentration is between about 1-100 ng/mL when administered as a combination therapy with an MC4R agonist. In some embodiments, the MC4R concentration in the CSF is between about 0.59 ng/mL when administered as a combination therapy with an SURx/Kirx channel activator compound, e.g., as shown in **FIG. 18**. In some embodiments, the SURx/Kirx channel activator concentration in the liver is between about 12.7 ng/mL when administered as a combination therapy with an SURx/Kirx channel activator compound, e.g., as shown in **FIG. 18**. In some embodiments, the SURx/Kirx channel activator plasma concentration is between about 27.6 ng/mL when administered as a combination therapy with an MC4R agonist, e.g., as shown in **FIG. 18**.

#### **Routes of Administration and Dosages**

The compounds and compositions, according to the method of the present invention, are administered using any amount and any route of administration effective for treating or lessening

the severity of a disorder provided above. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and 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.

Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention are administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 100 mg/kg and preferably from about 1 mg/kg to about 50 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms optionally contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures



thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions are formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation are also a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables. In some embodiments, a triglyceride or a plurality of triglycerides (e.g., medium chain triglycerides or long chain triglycerides) are used in the preparation of the injectable. In other embodiments, a phospholipid or a plurality of phospholipids are used in the preparation of the injectable.

Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This is accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, acetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form also optionally comprises buffering agents.

Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and

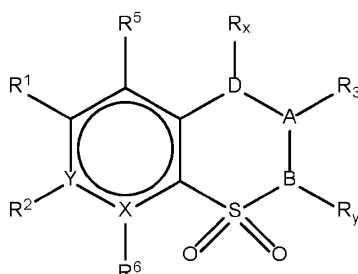
granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms optionally also comprise buffering agents. They optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

#### ENUMERATED EMBODIMENTS

1. A method of treating a disease or disorder in a subject, the method comprising administering a combination of:
  - (i) a potassium channel activator (e.g., SURx/Kirx channel activator compound) or a pharmaceutically acceptable salt thereof; and
  - (ii) an MC4R agonist,to the subject, thereby treating the disease or disorder in the subject.

2. The method of embodiment 1, wherein the SURx/Kirx channel activator compound is a compound having the structure of Formula (XIV):



or a pharmaceutically acceptable salt thereof, wherein:

A is C(R<sup>'</sup>);

each of B and D are independently N; wherein A and B or A and D are connected via a double or single bond;

X is C(R<sup>'</sup>) or S;

when X is C(R<sup>'</sup>) then Y is C(R<sup>'</sup>); or,

when X is S, then Y is absent;

each of R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano; wherein A and B form a double bond and R<sub>x</sub> is hydrogen or wherein A and D form a double bond and R<sub>y</sub> is hydrogen;

R<sub>3</sub> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, or N(R<sup>B</sup>)(R<sup>C</sup>), wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>4</sub>;

R<sup>'</sup> is absent, hydrogen, or C1-C6 alkyl;

each R<sub>4</sub> is independently C1-C6 alkyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, fluorine, chlorine, bromine, or iodine;

R<sup>A</sup> is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, or heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>;

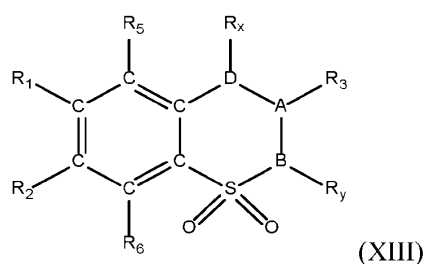
each of R<sup>B</sup> and R<sup>C</sup> is independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, wherein alkyl,

alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sup>7</sup>; or

wherein R<sup>B</sup> and R<sup>C</sup> are taken together to form heterocyclyl optionally substituted with one or more R<sup>7</sup>;

each R<sup>7</sup> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano.

3. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is diazoxide or a pharmaceutically acceptable salt thereof.
4. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is 3-(1-methylcyclopropyl)amino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide or a pharmaceutically acceptable salt thereof.
5. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is a compound having the structure of Formula (XIII):



or a pharmaceutically acceptable salt thereof, wherein:

A is C(R<sup>7</sup>);

each of B and D are independently N; wherein A and B or A and D are connected via a double or single bond;

each of R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano; wherein A and B form a double bond and R<sub>x</sub> is hydrogen or wherein A and D form a double bond and R<sub>y</sub> is hydrogen;

$R_3$  is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, or  $N(R^B)(R^C)$ , wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more  $R_4$ ;

$R'$  is absent, hydrogen, or C1-C6 alkyl;

each  $R_4$  is independently C1-C6 alkyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, fluorine, chlorine, bromine, or iodine;

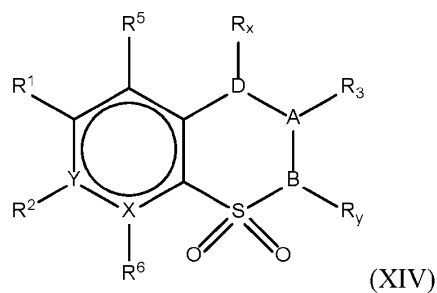
$R^A$  is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, or heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more  $R_7$ ;

each of  $R^B$  and  $R^C$  is independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more  $R_7$ ; or

wherein  $R^B$  and  $R^C$  are taken together to form heterocyclyl optionally substituted with one or more  $R_7$ ;

each  $R^7$  is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl,  $-OR^A$ , fluorine, chlorine, bromine, iodine, nitro, or cyano.

6. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is a compound having the structure of Formula (XIV):



or a pharmaceutically acceptable salt, tautomer, stereoisomer, hydrate, or isotope thereof, wherein:

A is  $C(R')$ ;

each of B and D are independently N; wherein A and B or A and D are connected via a double or single bond;

X is C(R') or S;

when X is C(R') then Y is C(R'); or,

when X is S, then Y is absent;

each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>6</sub> are independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano; wherein A and B form a double bond and R<sub>x</sub> is hydrogen or wherein A and D form a double bond and R<sub>y</sub> is hydrogen;

R<sub>3</sub> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, or N(R<sup>B</sup>)(R<sup>C</sup>), wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>4</sub>;

R' is absent, hydrogen, or C1-C6 alkyl;

each R<sub>4</sub> is independently C1-C6 alkyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, fluorine, chlorine, bromine, or iodine;

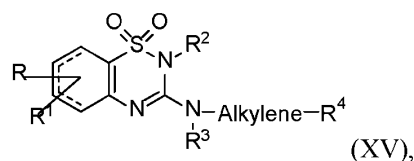
R<sup>A</sup> is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, or heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>;

each of R<sup>B</sup> and R<sup>C</sup> is independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>; or

wherein R<sup>B</sup> and R<sup>C</sup> are taken together to form heterocyclyl optionally substituted with one or more R<sub>7</sub>;

each R<sup>7</sup> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano.

7. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is a compound having the structure of Formula (XV):



wherein:

R represents hydrogen, halogen, trifluoromethyl, alkyl, alkoxy, alkoxyalkyl, alkylthio, alkylcarbonyl, phenylcarbonyl, phenylsulfonyl, phenylsulfinyl, phenyloxy, phenylthio, where the phenyl radicals can be substituted by alkyl, alkoxy, halogen, nitro or amino, or for thenoyl or pyridylcarbonyl, which can be substituted by alkyl;

R<sup>1</sup> is hydrogen, halogen, trifluoromethyl, alkyl, alkoxy, alkoxyalkyl, alkylthio, alkylcarbonyl, phenylcarbonyl, phenylsulfonyl, phenylsulfinyl, phenyloxy or phenylthio, the phenyl radicals being represented by alkyl, alkoxy, halogen, nitro or amino can be substituted, or stands for thenoyl or pyridylcarbonyl, whereby these can be substituted by alkyl;

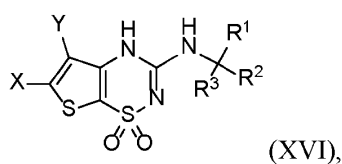
R<sup>2</sup> stands for hydrogen or alkyl;

R<sup>3</sup> stands for hydrogen or alkyl;

R<sup>4</sup> stands for the NH<sub>2</sub>, NHR<sup>5</sup> or the NR<sup>5</sup>R<sup>6</sup>- Group, where the radicals R<sup>5</sup> and R<sup>6</sup> can be identical or different and are alkyl or phenyl or phenylalkyl, and in the case of v on R<sup>5</sup> - alkyl this group can be connected to a carbon atom of the alkylene group to form a 5- or 6-membered ring, or where the radicals R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom can form an optionally substituted azabicycloalkyl radical with 6 to 10 ring members or R represents a cycloalkyleneimino group optionally interrupted by O, S, NH or NR<sup>5</sup> and/or substituted by one or two alkyl groups with a total of 5 to 7 ring members and in which the ring can optionally contain one, two or three double bonds, and alkylene represents a divalent alkylene group, which can optionally be substituted by alkyl and/or by a hydroxy, acyloxy or alkoxy group, and their physiologically compatible salts.

8. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is a compound having the structure of Formula (XVI):





wherein

X and Y independently are hydrogen, halogen, perhalomethyl, C1-6-alkyl or C1-6-alkoxy;

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> independently are C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C3-6-cycloalkyl, carboxy, C1-6-alkoxycarbonyl or aryl, all of which are optionally being mono- or polysubstituted with halogen, hydroxy, oxo, or aryl; or

R<sup>1</sup> is as defined above and R<sup>2</sup>-C-R<sup>3</sup> form a C3-6 -cycloalkyl group, optionally being mono- or polysubstituted with C1-6-alkyl, perhalomethyl, halogen, hydroxy or aryl; or

-CR<sup>1</sup>R<sup>2</sup>R<sup>3</sup> form a 4- to 12-membered bicyclic or tricyclic carbocyclic system, optionally being mono- or polysubstituted with C<sub>n</sub>-alkyl, perhalomethyl, halogen, hydroxy or aryl; or

a salt thereof with a pharmaceutically acceptable acid or base including all optical isomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixtures, or any tautomeric form thereof.

9. The method of any of the preceding embodiments, SURx/Kirx channel activator compound is selected from:

- 3-tert-butylamino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;
- 6-Chloro-3-(1,1-dimethylpropylamino)-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;
- 6-Chloro-3-(1-methylcyclopropyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;
- 6-Chloro-3-(2-hydroxy-1,1-dimethylethylamino)-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;
- 6-Chloro-3-(1,1,3,3-tetramethylbutylamino)-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(1-adamantyl)amino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;
- 1-(6-Chloro-1,4-dihydro-1,1-dioxo-thieno[3,2-e]-1λ<sup>6</sup>,2,4-thiadiazin-3-ylamino)-cyclopropanecarboxylic acid ethyl ester;
- 6-Chloro-3-(1-methyl-1-phenylethyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;

6-Chloro-3-(1-hydroxymethylcyclopentyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;

1-(6-Chloro-1,4-dihydro-1,1-dioxo-thieno[3,2-e]-1 $\lambda^6$ ,2,4-thiadiazin-3-ylamino)-cyclopropanecarboxylic acid;

6-Chloro-3-(1-methylcyclobutyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;

6-Chloro-3-(1-methylcyclohexyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;

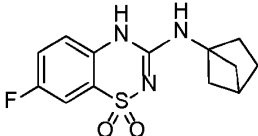
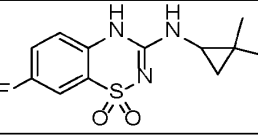
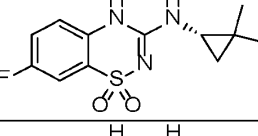
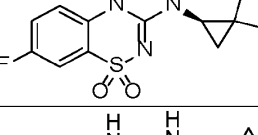
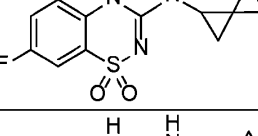
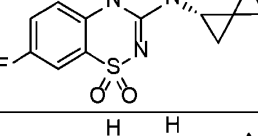
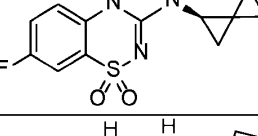
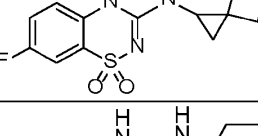
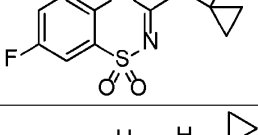
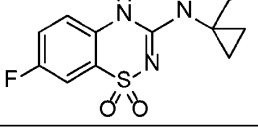
6-Chloro-3-(1-methylcyclopentyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide;

and

6-Chloro-3-(1-ethylcyclobutyl)amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide.

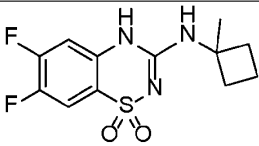
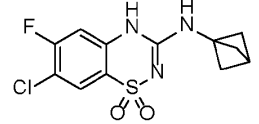
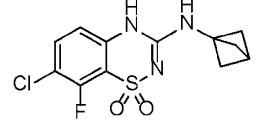
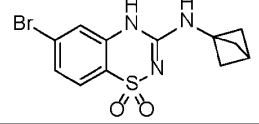
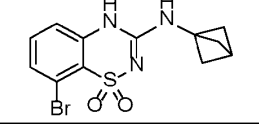
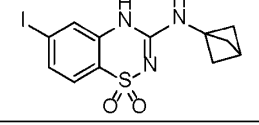
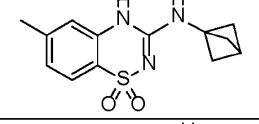
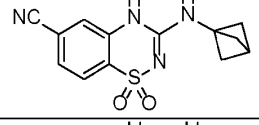
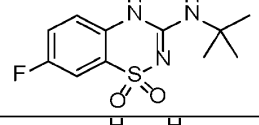
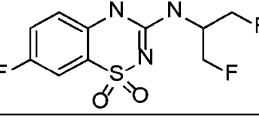
10. The method of any of the preceding embodiments, SURx/Kirx channel activator compound is selected from a compound in the Table below:

| Compound No.                            | Structure | Name                                                                                            |
|-----------------------------------------|-----------|-------------------------------------------------------------------------------------------------|
| SURx/Kirx channel activator compound I  |           | 7-chloro-3-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide                                         |
| SURx/Kirx channel activator compound II |           | 6-chloro-3-[[11-methylcyclopropyl]amino]-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide         |
| 1                                       |           | 3-(bicyclo[1.1.1]pentan-1-ylamino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 2                                       |           | 7-fluoro-3-((1-methylcyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                |
| 3                                       |           | 7-fluoro-3-((3-fluorobicyclo[1.1.1]pentan-1-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |

|    |                                                                                     |                                                                                                                 |
|----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| 4  |    | 3-(bicyclo[2.1.1]hexan-1-ylamino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                            |
| 5  |    | 3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                           |
| 6  |    | ( <i>S</i> <sup>*</sup> )-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 7  |    | ( <i>R</i> <sup>*</sup> )-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 8  |   | 7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                               |
| 9  |  | ( <i>S</i> <sup>*</sup> )-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide     |
| 10 |  | ( <i>R</i> <sup>*</sup> )-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide     |
| 11 |  | 7-fluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                |
| 12 |  | 3-((1-ethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                |
| 13 |  | 3-([1,1'-bi(cyclopropan)]-1-ylamino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                         |

|    |  |                                                                                                              |
|----|--|--------------------------------------------------------------------------------------------------------------|
| 14 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6-chloro-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide)              |
| 15 |  | 6-chloro-7-fluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                    |
| 16 |  | ( <i>S*</i> )-6-chloro-7-fluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide      |
| 17 |  | ( <i>R*</i> )-6-chloro-7-fluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide      |
| 18 |  | 6-chloro-7-fluoro-3-((3-methylbicyclo[1.1.1]pentan-1-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide     |
| 19 |  | 6-chloro-7-fluoro-3-((3-fluorobicyclo[1.1.1]pentan-1-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide     |
| 20 |  | 6-chloro-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide               |
| 21 |  | ( <i>S*</i> )-6-chloro-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 22 |  | ( <i>R*</i> )-6-chloro-3-((2,2-dimethylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 23 |  | 6-chloro-7-fluoro-3-((1-(trifluoromethyl)cyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide        |

|    |  |                                                                                                                          |
|----|--|--------------------------------------------------------------------------------------------------------------------------|
| 24 |  | 6-chloro-7-fluoro-3-((1-methylcyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                |
| 25 |  | ( <i>rac</i> )- <i>trans</i> -6-chloro-7-fluoro-3-((2-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 26 |  | 6-chloro-7-fluoro-3-(((1 <i>S</i> *,2 <i>S</i> *)-2-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide   |
| 27 |  | 6-chloro-7-fluoro-3-(((1 <i>R</i> *,2 <i>R</i> *)-2-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide   |
| 28 |  | 6-chloro-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                               |
| 29 |  | ( <i>S</i> *)-6-chloro-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                 |
| 30 |  | ( <i>R</i> *)-6-chloro-7-fluoro-3-(spiro[2.2]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                 |
| 31 |  | 3-(bicyclo[2.1.1]hexan-1-ylamino)-6-chloro-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                            |
| 32 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6,7-difluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                |
| 33 |  | 6,7-difluoro-3-(spiro[2.3]hexan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                                     |

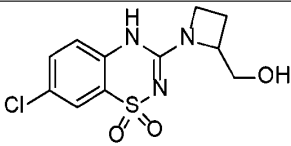
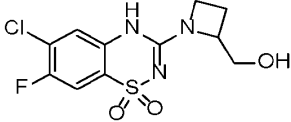
|    |                                                                                     |                                                                                                |
|----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 34 |    | 6,7-difluoro-3-((1-methylcyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 35 |    | 3-(bicyclo[1.1.1]pentan-1-ylamino)-7-chloro-6-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 36 |    | 3-(bicyclo[1.1.1]pentan-1-ylamino)-7-chloro-8-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 37 |    | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6-bromo-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 38 |   | 3-(bicyclo[1.1.1]pentan-1-ylamino)-8-bromo-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 39 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6-iodo-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide            |
| 40 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-6-methyl-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 41 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-4H-benzo[e][1,2,4]thiadiazine-6-carbonitrile 1,1-dioxide    |
| 42 |  | 3-(tert-butylamino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                         |
| 43 |  | 3-((1,3-difluoropropan-2-yl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |

|    |  |                                                                                                     |
|----|--|-----------------------------------------------------------------------------------------------------|
| 44 |  | 7-fluoro-3-((1-(dimethylamino)-2-methylpropan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 45 |  | 7-fluoro-3-((4-methoxy-2-methylbutan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 46 |  | 7-fluoro-3-((1-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                   |
| 47 |  | 7-fluoro-3-((1-(fluoromethyl)cyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 48 |  | 7-chloro-3-((4-methoxy-2-methylbutan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 49 |  | 7-chloro-3-((1,3-difluoropropan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide               |
| 50 |  | 7-chloro-3-((1-(dimethylamino)-2-methylpropan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 51 |  | 7-chloro-3-((1-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                   |
| 52 |  | 7-chloro-3-((1-(fluoromethyl)cyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 53 |  | 7-chloro-3-((3,3-difluorocyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                |
| 54 |  | 3-(tert-butylamino)-6-chloro-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                     |

|    |  |                                                                                                              |
|----|--|--------------------------------------------------------------------------------------------------------------|
| 55 |  | 6-chloro-3-((1,3-difluoropropan-2-yl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide               |
| 56 |  | 6-chloro-3-((1-(dimethylamino)-2-methylpropan-2-yl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 57 |  | 6-chloro-7-fluoro-3-((4-methoxy-2-methylbutan-2-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 58 |  | 6-chloro-7-fluoro-3-((1-methylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                   |
| 59 |  | 6-chloro-3-((1-ethynylcyclopropyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                  |
| 60 |  | 6-chloro-7-fluoro-3-((1-(fluoromethyl)cyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide           |
| 61 |  | 6-chloro-3-((3,3-difluorocyclobutyl)amino)-7-fluoro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                |
| 62 |  | 3-(bicyclo[1.1.1]pentan-1-ylamino)-7-chloro-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                        |
| 63 |  | 7-fluoro-3-((1-isopropylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                         |
| 64 |  | 6-chloro-7-fluoro-3-((1-isopropylcyclopropyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide                |



|    |  |                                                                                                    |
|----|--|----------------------------------------------------------------------------------------------------|
| 65 |  | 7-fluoro-3-((1-(methoxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 66 |  | 7-fluoro-3-((1-(hydroxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 67 |  | 7-chloro-3-((1-(methoxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 68 |  | 7-chloro-3-((1-(hydroxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 69 |  | 6-chloro-7-fluoro-3-((1-(methoxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 70 |  | 6-chloro-7-fluoro-3-((1-(hydroxymethyl)cyclobutyl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |
| 71 |  | (R)-7-fluoro-3-((tetrahydrofuran-3-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide             |
| 72 |  | (R)-7-chloro-3-((tetrahydrofuran-3-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide             |
| 73 |  | (R)-6-chloro-7-fluoro-3-((tetrahydrofuran-3-yl)amino)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide    |
| 74 |  | (R)-7-fluoro-3-(2-(hydroxymethyl)azetidin-1-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |

|    |                                                                                   |                                                                                                    |
|----|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| 75 |  | (R)-7-chloro-3-(2-(hydroxymethyl)azetidin-1-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide          |
| 76 |  | (R)-6-chloro-7-fluoro-3-(2-(hydroxymethyl)azetidin-1-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide |

11. The method of any one of the preceding embodiments, wherein the MC4R agonist is a peptide or a small molecule.
12. The method of any one of the preceding embodiments, wherein the MC4R agonist is a peptide.
13. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII) or a pharmaceutically acceptable salt thereof, e.g., as described herein.
14. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (I), or a pharmaceutically acceptable salt thereof, e.g., as described herein.
15. The method of embodiment 14, wherein R<sup>2</sup> is Ac.
16. The method of embodiment 14, wherein R<sup>3</sup> is H.
17. The method of embodiment 14, wherein R<sup>1</sup> is NH<sub>2</sub>.
18. The method of embodiment 14, wherein A<sup>1</sup> is Arg.
19. The method of embodiment 14, wherein A<sup>2</sup> is Cys.

20. The method of embodiment 14, wherein A<sup>9</sup> is Cys.
21. The method of embodiment 14, wherein A<sup>3</sup> is deleted.
22. The method of embodiment 14, wherein A<sup>4</sup> is His.
23. The method of embodiment 14, wherein A<sup>5</sup> is D-(X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>)Phe.
24. The method of embodiment 14, wherein A<sup>5</sup> is D-Phe.
25. The method of embodiment 14, wherein A<sup>6</sup> is Arg.
26. The method of embodiment 14, wherein A<sup>7</sup> is Trp.
27. The method of embodiment 14, wherein A<sup>8</sup> is deleted.
28. The method of any one of the preceding embodiments, wherein the MC4R agonist is selected from:
  - (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;
  - (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH<sub>2</sub>;
  - (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;
  - (SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH<sub>2</sub>;
  - (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;
  - (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH<sub>2</sub>;
  - (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;
  - (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH<sub>2</sub>;
  - (SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
  - (SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
  - (SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
  - (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 14) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 20) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;

(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 45) n-butanoyl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 46) n-butyryl-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 68) n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 69) n-butanoyl-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH<sub>2</sub>;

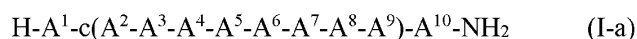
- (SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 88) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 104) Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 107) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;  
(SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 115) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-OH;  
(SEQ ID NO: 116) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-OH;  
(SEQ ID NO: 117) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-OH;  
(SEQ ID NO: 118) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-OH;  
(SEQ ID NO: 119) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-OH;  
(SEQ ID NO: 120) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-OH;  
(SEQ ID NO: 121) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-OH;  
(SEQ ID NO: 122) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 123) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 124) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 125) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 126) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 127) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 128) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-OH;  
(SEQ ID NO: 129) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-OH;  
(SEQ ID NO: 130) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-OH;  
(SEQ ID NO: 131) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-OH;  
(SEQ ID NO: 132) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-OH;  
(SEQ ID NO: 133) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-OH;  
(SEQ ID NO: 134) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-OH;  
(SEQ ID NO: 135) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-OH;  
(SEQ ID NO: 136) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-OH;

(SEQ ID NO: 137) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-OH;  
 (SEQ ID NO: 138) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-OH;  
 (SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH<sub>2</sub>,  
 or a pharmaceutically acceptable salt thereof.

29. The method of any one of the preceding embodiments, wherein the MC4R agonist is:  
 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 140), or a pharmaceutically  
 acceptable salt thereof.

30. The method of any of the preceding embodiments, wherein the MC4R agonist compound is a  
 compound of Formula (I-a):



or a pharmaceutically acceptable salt thereof, wherein:

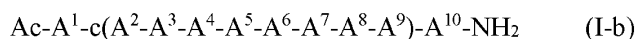
A<sup>1</sup> is Phe, D-Phe, or Nle;  
 A<sup>2</sup> is Cys;  
 A<sup>3</sup> is deleted;  
 A<sup>4</sup> is His;  
 A<sup>5</sup> is D-Phe or D-(Et)Tyr;  
 A<sup>6</sup> is Arg or hArg;  
 A<sup>7</sup> is Trp or Bip;  
 A<sup>8</sup> is Ala, β-Ala, Gaba, or Apn;  
 A<sup>9</sup> is D-Cys; and  
 A<sup>10</sup> is Thr or deleted.



31. The method of any of the preceding embodiments, wherein the compound is a compound of Formula (I-a) is selected from:

SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>.

32. The method of any of the preceding embodiments, wherein the MC4R agonist compound is a compound of Formula (I-b):



or a pharmaceutically acceptable salt thereof, wherein:

A<sup>1</sup> is Nle, A6c, D-2-Nal, Cha, Oic, Chg, hCha, D-Cha, D-hCha, Nip, hPro, hLeu, Phe, D-Phe, D-Chg, hPhe, β-hMet, Gaba, Leu, Ile, Val, 2-Nal, Arg or D-Arg;

A<sup>2</sup> is Asp, Cys, D-Cys, or Pen;

A<sup>3</sup> is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, D-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha, deleted;

A<sup>4</sup> His or 3-Pal;

A<sup>5</sup> is Phe, D-Phe, or D-2-Nal;

A<sup>6</sup> is Arg;

A<sup>7</sup> is Trp, 1-Nal, 2-Nal, Bal, or D-Trp;

A<sup>8</sup> is β-Ala, A6c, Ahx, Apn, Gaba, Ala, Aha, D-Ala or deleted;

A<sup>9</sup> is Lys, Cys, D-Cys, or Pen;

A<sup>10</sup> is deleted.

wherein A<sup>2</sup> and A<sup>9</sup> are pairwise selected to form a disulfide or lactam bridge.

33. The method of any one of the preceding embodiments, wherein the compound of Formula (I-b) is:

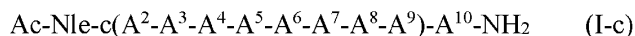
- (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 14) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 20) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH<sub>2</sub>.

34. The method of any of the preceding embodiments, wherein the MC4R agonist compound is a compound of Formula (I-c):



or a pharmaceutically acceptable salt thereof, wherein:

A<sup>2</sup> is Asp, Cys, D-Cys, or Pen;

A<sup>3</sup> is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, Aib, Dl-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha, or deleted;

A<sup>4</sup> is His or 3-Pal;

A<sup>5</sup> is D-Phe, D-2-Nal, or Phe;

A<sup>6</sup> is Arg;

A<sup>7</sup> is Trp, D-Trp, 2-Nal, 1-Nal, Bal;

A<sup>8</sup> is β-Ala, A6c, Ahx, Apn, Gaba, D-Ala, Aha, Ala or deleted;

A<sup>9</sup> is Lys, Cys, D-Cys or Pen; and

A<sup>10</sup> is deleted,

wherein A<sup>2</sup> and A<sup>9</sup> are pairwise selected to form a disulfide or lactam bridge.

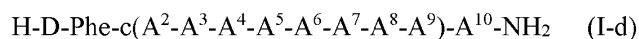
35. The method of any one of the preceding embodiments, wherein the compound of Formula (I-c) is:

- (SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH<sub>2</sub>;
- (SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 14) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 20) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;
- (SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH<sub>2</sub>;  
(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub>;  
(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;

(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)-NH<sub>2</sub>;  
 (SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH<sub>2</sub>;  
 (SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH<sub>2</sub>; and  
 (SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH<sub>2</sub>.

36. The method of any of the preceding embodiments, wherein the MC4R agonist compound is a compound of Formula (I-d):



or a pharmaceutically acceptable salt thereof, wherein:

A<sup>2</sup> is Cys;  
 A<sup>3</sup> is deleted;  
 A<sup>4</sup> is His;  
 A<sup>5</sup> is D-Phe or D-(Et)Tyr;  
 A<sup>6</sup> is Arg or hArg;  
 A<sup>7</sup> is Trp or Bip;  
 A<sup>8</sup> is Ala, β-Ala, or Gaba;  
 A<sup>9</sup> is D-Cys; and  
 A<sup>10</sup> is Thr.

37. The method of any one of the preceding embodiments, wherein the compound of Formula (I-d) is:

(SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;  
 (SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH<sub>2</sub>;



(SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp- $\beta$ -Ala-D-Cys)-Thr-NH<sub>2</sub>;  
(SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip- $\beta$ -Ala-D-Cys)-Thr-NH<sub>2</sub>; and  
(SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip- $\beta$ -Ala-D-Cys)-Thr-NH<sub>2</sub>.

38. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (II), or a pharmaceutically acceptable salt thereof, e.g., as described herein.

39. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (III), or a pharmaceutically acceptable salt thereof, e.g., as described herein.

40. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (IV), or a pharmaceutically acceptable salt thereof, e.g., as described herein.

41. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (V), or a pharmaceutically acceptable salt thereof, e.g., as described herein.

42. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (VI), or a pharmaceutically acceptable salt thereof, e.g., as described herein.

43. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (VII), or a pharmaceutically acceptable salt thereof, e.g., as described herein.

44. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (VIII), or a pharmaceutically acceptable salt thereof, e.g., as described herein.

45. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (IX), or a pharmaceutically acceptable salt thereof, e.g., as described herein.
46. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (X), or a pharmaceutically acceptable salt thereof, e.g., as described herein.
47. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (XI), or a pharmaceutically acceptable salt thereof, e.g., as described herein.
48. The method of any one of the preceding embodiments, wherein the MC4R agonist has the structure of Formula (XII), or a pharmaceutically acceptable salt thereof, e.g., as described herein.
49. The method of embodiment 48, wherein A<sup>1</sup> is Ac.
50. The method of embodiment 48, wherein Yyy is Arg.
51. The method of embodiment 48, wherein Aaa is hCys.
52. The method of embodiment 48, wherein Xxx is selected from Asn, Gln, Ser, and Thr.
53. The method of embodiment 48, wherein Xxx is Asn.
54. The method of embodiment 48, wherein Xxx is Gln.
55. The method of embodiment 48, wherein Xxx is Ser.

56. The method of embodiment 48, wherein Xxx is Thr.
57. The method of embodiment 48, wherein Bbb is Pen.
58. The method of embodiment 48, wherein A<sup>2</sup> is NH<sub>2</sub>.
59. The method of any one of the embodiments, wherein the MC4R agonist is selected from the following structural formulas:  
Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 629)  
Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 630)  
Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 631); and  
Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 632),  
or a pharmaceutically acceptable salt thereof.
60. The method of any one of the preceding embodiments, wherein the MC4R agonist is:  
Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 629), or a pharmaceutically acceptable salt thereof.
61. The method of any one of the preceding embodiments, wherein the MC4R agonist is:  
Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 630), or a pharmaceutically acceptable salt thereof.
62. The method of any one of the embodiments, wherein the MC4R agonist is:  
Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 631), or a pharmaceutically acceptable salt thereof.
63. The method of any one of the preceding embodiments, wherein the MC4R agonist is:  
Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 632), or a pharmaceutically acceptable salt thereof.

64. The method of any one of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (XII-a):



or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

65. The method of any one of the preceding embodiments, wherein the of Formula (XII-a) is selected from:

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; and

(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>.

66. The method of any one of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (XII-b):



or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge;

or

Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

67. The method of any one of the preceding embodiments, wherein the of Formula (XII-b) is selected from:

(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;

(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; and

(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>.

68. The method of any one of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (XII-c):



or a pharmaceutically acceptable salt thereof, wherein:

A<sub>1</sub> is H or Ac;

A<sub>2</sub> is OH or NH<sub>2</sub>;

Yyy is L-Arg or D-Arg;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and  
Xxx is Asn, Gln, Ser, or Thr.

69. The method of any one of the preceding embodiments, wherein the compound of Formula (XII-c) is selected from:

- (SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;
- (SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;
- (SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;
- (SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;
- (SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH<sub>2</sub>;
- (SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
- (SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;
- (SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
- (SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;
- (SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;
- (SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
- (SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
- (SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
- (SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;
- (SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
- (SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;

(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
 (SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
 (SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH; and  
 (SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH.

70. The method of any one of the preceding embodiments, wherein the MC4R agonist is a compound of Formula (XII-d):



or a pharmaceutically acceptable salt thereof, wherein:

A<sub>1</sub> is H or Ac;

A<sub>2</sub> is OH or NH<sub>2</sub>;

Yyy is L-Lys or D-Lys;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or

Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and

Xxx is Asn, Gln, Ser, or Thr.

71. The method of any one of the preceding embodiments, wherein the compound of Formula (XII-d) is selected from:

SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;  
(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;



(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>;  
(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>, and  
(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>.

72. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is administered at a dosage of between about 1 mg/kg to about 200 mg/kg.
73. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is administered at a dosage of between about 25 mg/kg to about 125 mg/kg.
74. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is administered at a dosage of between about 75 mg/kg.
75. The method of any one of the preceding embodiments, wherein the MC4R agonist is administered at a dosage of between about 0.5 mg/kg to about 20 mg/kg.
76. The method of any one of the preceding embodiments, wherein the MC4R agonist is administered at a dosage of between about 2.5 mg/kg to about 15 mg/kg.
77. The method of any one of the preceding embodiments, wherein the MC4R agonist is administered at a dosage of about 5 mg/kg.
78. The method of any one of the preceding embodiments, wherein the MC4R agonist is administered at a dosage of about 10 mg/kg.
79. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is formulated for oral administration.
80. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is formulated for parenteral administration.

81. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound is formulated for subcutaneous administration.
82. The method of any one of the preceding embodiments, wherein the MC4R agonist is administered parenterally.
83. The method of any one of the preceding embodiments, wherein the MC4R agonist is administered subcutaneously.
84. The method of any one of the preceding embodiments, wherein the MC4R agonist is dosed with a needle (e.g., a 20-25 gauge needle).
85. The method of any one of the preceding embodiments, wherein (i) the SURx/Kirx channel activator compound and (ii) the MC4R agonist are administered as a single formulation.
86. The method of any one of the preceding embodiments, wherein (i) the SURx/Kirx channel activator compound and (ii) the MC4R agonist are administered as separate formulations.
87. The method of any one of the preceding embodiments, wherein (i) the SURx/Kirx channel activator compound is administered orally; and (ii) the MC4R agonist is administered parenterally, e.g., subcutaneously.
88. The method of any one of the preceding embodiments, wherein (i) the SURx/Kirx channel activator compound is administered orally once per day; and (ii) the MC4R agonist is administered parenterally, e.g., subcutaneously, once per week.
89. The method of any one of the preceding embodiments, wherein the efficacy of the combination is at least  $X_1$ -fold greater than the efficacy of the SURx/Kirx channel activator compound alone at the molar amount used in the combination, wherein  $X_1$  is 1, 1.25, 1.5, 1.75, 2, 2.5, or greater.

90. The method of embodiment 89, wherein  $X_1$  is 1.
91. The method of embodiment 89, wherein  $X_1$  is 1.25.
92. The method of embodiment 89, wherein  $X_1$  is 1.5.
93. The method of embodiment 89, wherein  $X_1$  is 1.75.
94. The method of embodiment 89, wherein  $X_1$  is 2.
95. The method of embodiment 89, wherein  $X_1$  is 2.5.
96. The method of any one of the preceding embodiments, wherein the efficacy of the combination is at least  $X_1$ -fold greater than the efficacy of the MC4R agonist alone at the molar amount used in the combination, wherein  $X_1$  is 1, 1.25, 1.5, 1.75, 2, 2.5, or greater.
97. The method of embodiment 96, wherein  $X_1$  is 1.
98. The method of embodiment 96, wherein  $X_1$  is 1.25.
99. The method of embodiment 96, wherein  $X_1$  is 1.5.
100. The method of embodiment 96, wherein  $X_1$  is 1.75.
101. The method of embodiment 96, wherein  $X_1$  is 2.
102. The method of embodiment 96, wherein  $X_1$  is 2.5.
103. The method of any one of the preceding embodiments, wherein the efficacy of the combination is at least  $X_1$ -fold greater than the efficacy of the SURx/Kirx channel activator

compound alone or the MC4R agonist alone at the molar amount used in the combination, wherein  $X_1$  is 1, 1.25, 1.5, 1.75, 2, 2.5, or greater.

104. The method of embodiment 103, wherein  $X_1$  is 1.

105. The method of embodiment 103, wherein  $X_1$  is 1.25.

106. The method of embodiment 103, wherein  $X_1$  is 1.5.

107. The method of embodiment 103, wherein  $X_1$  is 1.75.

108. The method of embodiment 103, wherein  $X_1$  is 2.

109. The method of embodiment 103, wherein  $X_1$  is 2.5.

110. The method of any one of the preceding embodiments, wherein the molar amount of the SURx/Kirx channel activator compound in the combination comprises the molar concentration of the SURx/Kirx channel activator compound in the combination.

111. The method of any one of the preceding embodiments, wherein the molar amount of the MC4R agonist in the combination comprises the molar concentration of the MC4R agonist in the combination.

112. The method of any one of the preceding embodiments, wherein each of the SURx/Kirx channel activator compound and the MC4R agonist is independently formulated as a pharmaceutical composition.

113. The method of any one of the preceding embodiments, wherein the SURx/Kirx channel activator compound and the MC4R agonist are formulated together as a pharmaceutical composition.

114. The method any one of the preceding embodiments, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 200:1 to 1:1.

115. The method of embodiment 114, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 100:1 to 1:1.

116. The method of any one of embodiments 114-115, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 50:1 to 1:1.

117. The method of any one of embodiments 114-116, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 50:1 to 2:1.

118. The method of any one of embodiments 114-117, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 25:1 to 2:1.

#### EXAMPLES

The following examples are provided to further illustrate some embodiments of the present invention, but are not intended to limit the scope of the invention; it will be understood by their exemplary nature that other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

##### **Example 1. Effects of a Once Weekly Formulation of MC4R Agonist I Depot and SURx/Kirx channel activator compound I on Metabolic Phenotype in Obese Male Zucker Rats**

The example set forth below describes an investigation of a once weekly formulation of MC4R Agonist I depot and SURx/Kirx channel activator compound I in obese male Zucker rats and an analysis of various metabolic parameters. These data demonstrate that co-administration

of once-weekly SURx/Kirx channel activator compound I + MC4R Agonist I depot weekly formulation has a synergistically positive effect on metabolic parameters, e.g., reduction in body weight, reduction in cumulative food intake, plasma glucose, insulin, leptin, and certain hepatic parameters (reduction in inflammatory biomarkers associated with the liver)

### **Purpose**

Zucker fatty rats (*ZUC-Lepr<sup>fa</sup>*) are hyperphagic due to a mutated leptin receptor and have been established as a model for obesity, impaired glucose tolerance, and hyperlipidemia. A 3-week parallel study of 3 groups was designed to investigate the effects of SURx/Kirx channel activator compound I given twice daily by oral gavage (n=7), or given together with a once-weekly sustained release formulation of MC4R Agonist I; (n = 7) administered as a subcutaneous injection (sc), on body weight (**FIGS. 1A-B, 5, 6**) food intake (**FIGS. 2A-B**), water intake, and lean mass. A placebo depot formulation was used as vehicle control (Group A, n=7). Changes in insulin sensitivity, glycemic control, and lipid profile were also characterized. As a control, a group of seven (n=7) obese Zucker rats was given Placebo (SC injection of PG Depot, MC4R agonist I weekly formulation without test article and oral gavage of carboxymethyl cellulose, vehicle for SURx/Kirx channel activator compound I).

During the study period, rats were maintained on a regular maintenance diet. To test the insulin sensitivity upon 3 weeks of treatment with SURx/Kirx channel activator compound I or SURx/Kirx channel activator compound I + MC4R Agonist I depot, an oral glucose tolerance test (OGTT) was performed on Day 21, the last day of study, as shown in **FIGS. 4A-B, 8A-8D, and 9A-D**. Plasma parameters such as glucose, insulin and leptin were determined in fed state prior to treatments on day 1, 7, 14 and 17. To address the impact of SURx/Kirx channel activator compound I and MC4R agonist I on the fat and liver biomarkers, plasma parameters such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), triglyceride, cholesterol, NEFA, and leptin were measured. Also, hepatic tissue parameters such as triglyceride, cholesterol, NEFA together with estimation of changes in the nonalcoholic fatty liver disease (NAFLD) activity score (NAS) were determined at end of the study (cf. **FIGS. 10A-C and 11, 12A-B**).

### **Materials and Methods**

#### **Animals**

The study comprised 21 male Zucker obese rats (Obese; *ZUC-Lepr<sup>fa</sup>*, CRL strain code: 185, USA) at 8-10 weeks of age. Rats were singly housed in individually ventilated cages (IVC) at an ambient

temperature of  $22\pm 2^{\circ}\text{C}$ . Each cage contained sawdust, red house, red tunnel, sizzle-nest and nestlet so that the rats could make nests and facilitate warmth. Rats were housed on a normal phase 12 h light-dark cycle (lights on 07:00). Room relative humidity was typically  $55\pm 15\%$  with prolonged periods below 40% RH or above 70% RH avoided according to the UK Code of Practice. Animals had free access to a standard maintenance diet (Envigo Teklad 2018) and tap water *ad libitum* for the duration of the study. Animals were accustomed to animal facility conditions for one week before start of the experiment.

### Experimental Design

Experiment 1: was performed to assess the tolerability and efficacy of SURx/Kirx channel activator compound I (decreasing doses over 20 days) alone, or in combination with fixed dose of MC4R Agonist I. As a control a Placebo was used (daily dose of SURx/Kirx channel activator compound I vehicle and weekly SC injection of MC4R agonist vehicle PG Depot),  $n=3/\text{group}$

Experiment 2. was performed to assess the tolerability and efficacy of SURx/Kirx channel activator compound I alone (increasing doses over 20 days) or in combination with the fixed dose of MC4R Agonist I. As a control a Placebo was used (daily dose of SURx/Kirx channel activator compound I vehicle and weekly SC injection of MC4R agonist vehicle PG Depot),  $n=4/\text{group}$

Experiment 3 (MC4R agonist experiment): was performed to assess the tolerability and efficacy of sc weekly injection of MC4R Agonist I (increasing doses) and MC4R Agonist II. As a control sc weekly injection of MC4R agonist vehicle PG Depot was used,  $n=8/\text{group}$

Table below:

| Treatment schedule-Experiment 1                                        |                                                                                                                         |                                                             |   |
|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|---|
| Treatment 1 to be administered on Day 1-20 (09:00)/<br>Day 1, 7 and 14 |                                                                                                                         | Treatment 2 on Day 1-20<br>(17:00)                          | n |
| Placebo                                                                | Vehicle (0.5% CMC, 5 mL/kg, po, bid)<br>followed by Placebo<br>(5 mg/kg, sc, once a week)                               | Vehicle (0.5% CMC, po,<br>5 ml/kg, bid)                     | 3 |
| SURx/Kirx channel<br>activator I                                       | SURx/Kirx channel activator I<br>(75/25/40/50 mg/kg bid po) followed by<br>Placebo (5 mg/kg, sc, once a week)           | SURx/Kirx channel activator I<br>(75/25/40/50 mg/kg bid po) | 3 |
| SURx/Kirx channel<br>activator I + MC4R<br>Agonist I                   | SURx/Kirx channel activator I<br>(75/25/40/50 mg/kg bid po) followed by<br>MC4R Agonist I<br>(5 mg/kg, sc, once a week) | SURx/Kirx channel activator I<br>(75/25/40/50 mg/kg bid po) | 3 |
| Treatment schedule-Experiment 2                                        |                                                                                                                         |                                                             |   |

| Treatment 1 on Day 1-20 (09:00)<br>/Day 1, 7 and 14                                |                                                                                                             | Treatment 2 on Day 1-20<br>(17:00)                                                       | n |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---|
| Placebo                                                                            | Vehicle (0.5% CMC, 5 ml/kg, po, bid) followed by Placebo (5 mg/kg, sc, once a week)                         | Vehicle (0.5% CMC, 5 ml/kg, po, bid)                                                     | 4 |
| SURx/Kirx channel activator I                                                      | SURx/Kirx channel activator I (25/40/50 mg/kg bid po) followed by Placebo (5 mg/kg, sc, once a week)        | SURx/Kirx channel activator I (25/40/50 mg/kg bid po)                                    | 4 |
| SURx/Kirx channel activator I + MC4R Agonist I                                     | SURx/Kirx channel activator I (25/40/50 mg/kg bid po) followed by MC4R Agonist I (5 mg/kg, sc, once a week) | SURx/Kirx channel activator I (25/40/50 mg/kg bid po)                                    | 4 |
| PG Depot Placebo:<br>Vehicle control for MC4R Agonist I                            |                                                                                                             | 0.5% Carboxy methylcellulose (CMC):<br>Vehicle control for SURx/Kirx channel activator I |   |
| Treatment schedule: Experiment 3 (MC4R agonist experiment, treatment day 1, 7, 14) |                                                                                                             |                                                                                          |   |
| Placebo                                                                            | Placebo (5 mg/kg, sc, once a week)                                                                          |                                                                                          | 8 |
| MC4R Agonist I                                                                     | MC4R Agonist I (5mg/kg.sc once a week)                                                                      |                                                                                          | 8 |
| MC4R Agonist I                                                                     | MC4R Agonist I (10 mg/kg.sc once a week)                                                                    |                                                                                          | 8 |
| MC4R Agonist II                                                                    | MC4R Agonist II (5mg/kg.sc once a week)                                                                     |                                                                                          | 8 |
| PG Depot Placebo: Vehicle control for MC4R Agonist I and MC4R agonist II           |                                                                                                             |                                                                                          |   |

CMC =carboxymethyl cellulose

Subcutaneous (sc) injection procedure: Formulations were drawn from the sample vials by 18-gauge needle and dosed with 25 gauge with long 5/8" inch needle. The animals were temporarily restrained for dose administration and were not sedated.

#### **Blood sample collection for plasma parameters estimation**

Glucose/insulin/leptin/cholesterol, TG, NEFA, ALT, and AST analysis: Blood samples were drawn into a lithium heparin tube (e.g., Sarstedt CB300LH) and analyzed according standard procedures. Plasma glucose, insulin and leptin concentration in the Zucker rats during the Experiment 1 and Experiment 2 are shown in **FIGS. 3A-C** and **7A-B**, respectively. Cholesterol, triglyceride, ALT, AST and NEFA for the Zucker rats are shown in **FIGS. 10A-C** and **11**. Cholesterol, triglyceride, ALT, AST and NEFA for the Zucker rats are shown in **FIGS. 10A-D** and **11**.

#### **Oral glucose tolerance test-OGTT**

An OGTT was performed on Day 21 for Experiments 1 and Experiments 2. The day prior to the OGTT (Day 20), rats were deprived of food (but not water) to a timed schedule (beginning



approximately ~17 hours). The following morning, the rats (approximately 16 hours later) underwent an OGTT. The tail vein of the animals was temporarily cannulated. Each animal was dosed with D-glucose (2 g/kg po). Blood samples were taken immediately prior to glucose administration at baseline (B), and 15, 30, 60, and 120 min after glucose administration. 75 µl blood samples were taken from the tail vein cannula. Between blood sampling, animals were returned to the home cage with free access to water (but not food). All blood samples were collected into lithium heparinized tubes (Sarstedt Microvette CB300LH) and plasma was separated by centrifugation to produce a single aliquot of plasma, which was frozen (-80°C) and subsequently assayed for glucose (Thermoelectron infinity glucose reagent, TR15421) and insulin (Alpco mouse ultrasensitive insulin kit 80 INSMU-E10). After 120 min rats were sacrificed as described below. OGTT test results are shown in **FIGS. 4A-B, 8A-D, and 9A-D** (AUCs).

#### **Termination**

**2.5.1. Tail vein blood sampling for plasma parameters:** On Day 21 following the OGTT, rats (overnight fasted and glucose treated) underwent blood sampling from the tail vein and blood was collected in a lithium heparin-containing tube (e.g., Sarstedt CB300LH) and stored at -20°C.

**2.5.2. Termination:** Rats were humanely sacrificed (exposure to an increasing concentration of CO<sub>2</sub> with confirmation by cessation of circulation) and ~50 µl cerebrospinal fluid (CSF) was taken from the cisterna magna region using a winged infusion set attached to a syringe (e.g., 25G Terumo Europe) and placed in a screwcap microtube (CP5915, Alpha Laboratories). All CSF samples were frozen and stored at -80°C.

**2.5.4. Liver collection and carcass weight:** right lobe of the liver was collected and frozen using liquid nitrogen and then stored at -80°C for the TG, cholesterol, NEFA and glycogen analyses (**FIGS. 10A-D and 11**). Also, from the left lobe of the liver, a horizontal section of approx. 2 cm wide was cut and fixed in 10% NBF to be processed into Formalin-Fixed Paraffin-Embedded (FFPE) blocks. An additional 1-2 cm<sup>2</sup> section was placed on tin foil and frozen on dry ice (-20°C) and preserved for histological analysis (**FIGS. 14 and 15**)

#### **Test Articles**

Placebo (PG Depot) formulation and MC4R Agonist I PG Depot, (30 mg/mL) were allowed to equilibrate to room temperature for up to 30 minutes on Days 1, 7, and 14. Placebo was dosed at a volume matching the dose of MC4R Agonist I (5 mg/kg/weekly). Dosing volume was calculated

based on the body weight on the injection day. SURx/Kirx channel activator compound I was purchased from a commercial supplier (MedChemExpress, Cat. No.: HY-B1140). SURx/Kirx channel activator compound I was formulated in 0.5% sodium carboxymethylcellulose (Sigma, Cat# C4888) as is known in the art. Rats were dosed orally using a dosing volume of 5 ml/kg po. SURx/Kirx channel activator compound I formulation (75, 50, 40, 25 mg/day, po, bid) was freshly prepared in the morning before the first dosing and stored at 2-4°C until the second dosing on the same day. D-Glucose was purchased from Fischer Scientific and dissolved in de-ionized water. D-Glucose was administered at a volume of 5 ml/kg po at a concentration of 400 mg/ml (*i.e.*, a dose of 2.0 g/kg).

#### **Data and statistical analysis**

Daily body weight and body weight gain were analyzed by two-way analysis of covariance with treatment and cohort as factors, with Day 1 body weight as the covariate. Daily food and water intake, cumulative food intake and average food and water intake were analyzed by two-way analysis of covariance with treatment and cohort as factors and average food and water intake during the baseline period as the covariate. Plasma glucose was analyzed by linear mixed effects model with cohort and the group by day interaction as fixed effects and animal as the random effect. Comparisons between groups at the same time point were performed.

Liver weights were analyzed by two-way analysis of covariance with treatment and cohort as factors and Day 1 body weight as the covariate. To determine effects on liver weight in addition to those that may be expected given treatment effects on body weight, liver weights were also analyzed by two-way analysis of covariance with treatment and cohort as factors and final carcass weight as the covariate.

Terminal plasma data was analyzed by a general linear model with treatment and cohort as factors and Day 1 body weight and bleeding order as covariates. A log transformation and/or robust regression was used, as appropriate.

Analysis of body composition parameters was performed by a general linear model with treatment and cohort as factors and Day 1 body weight as a covariate. A log transformation and/or robust regression was used, as appropriate.

Plasma glucose and insulin data from the OGTT was analyzed by a general linear model with treatment and cohort as factors and Day 1 body weight and baseline fasted glucose or insulin as covariates. A separate model was fitted for each timepoint. In addition to the baseline (B), 15-,

30-, 60-, and 120-minutes time points, AUC 0 to 60 and 0 to 120 minutes was calculated for the glucose and insulin data (as total AUC and AUC from baseline) by the trapezoidal rule and analyzed by the same methodology. A log transformation and/or robust regression was used, as appropriate. Please refer to **FIGS. 9A-9D** for calculated AUCs.

Appropriate comparisons (two-tailed) were performed to compare each group to the placebo group and to compare the two treatment groups. In all analyses, a p value of less than 0.05 was considered to be statistically significant.

### **Example 2. Investigating the Effects of a Once Weekly Formulation of MC4R Agonist I Depot and SURx/Kirx channel activator compound I on Metabolic Phenotype in Obese Male Zucker Rats**

The example set forth below describes a repeat investigation concerning the metabolic effects of a once weekly formulation of MC4R agonist I and SURx/Kirx Channel Activator I on in obese male Zucker rats. The results presented below underscore the synergistic effect on metabolic parameters, including a reduction in body weight and cumulative food intake; plasma glucose, insulin and leptin; and hepatic biomarkers.

#### **Overview.**

The aim of this investigation was to determine any synergistic effect of variable doses of SURx/Kirx Channel Activator I and a fixed dose of once weekly MC4R Agonist I formulation (5mg/kg, sc injection) over a period of three weeks on body weight and cumulative food intake in obese Zucker rats.

We repeat a proof-of-concept exploratory investigation consisting of a parallel study of 3 groups with a 3-week duration in which the effect on body weight and food intake with SURx/Kirx Channel Activator I (variable doses) and a fixed dose of MC4R Agonist I (5 mg/kg, sc, once, per week) alone or in combination. The study comprises three groups: Group A (Placebo), Group B (SURx/Kirx Channel Activator I alone), and Group C (SURx/Kirx Channel Activator I and MC4R Agonist I combined) with two phases (Pilot and Main) that were staggered by one week. Each arm had 3-4 rats in both the Pilot and Main studies.

Both body weight and cumulative food intake were characterized by a larger decrease with the SURx/Kirx Channel Activator I and MC4R Agonist I combination compared to the Placebo

and SURx/Kirx Channel Activator I alone, with the Group C (combination) having a 19% reduction in body weight compared to Placebo (**FIGS. 16A-B**).

Hyperphagia was diminished and overall daily food intake was normalized in Group C (SURx/Kirx Channel Activator I + MC4R Agonist I combination) to the range typically seen in normal, healthy rats. The food intake in Group C was normalized in both the Pilot and Main parts. Overall average food intake in the Pilot part was  $18.9 \pm 1.0$  g/day, compared to  $32.9 \pm 0.6$  g/day and  $33.4 \pm 1.3$  g/day in the Placebo and SURx/Kirx Channel Activator I groups, respectively. Overall average food intake in the Main part was  $17.6 \pm 0.6$  g/day, compared to  $33.6 \pm 0.8$  g/day and  $31.2 \pm 0.2$  g/day in the Placebo and SURx/Kirx Channel Activator I groups, respectively.

Overall insulin resistance was improved with both SURx/Kirx Channel Activator I and SURx/Kirx Channel Activator I + MC4R Agonist I treatments versus Placebo, but the effect was significantly greater in the SURx/Kirx Channel Activator I + MC4R Agonist I combination group relative to SURx/Kirx Channel Activator I alone and Placebo (**FIG. 8C-D, and 9C-D**).

Fatty liver phenotype expressed as NAS score was reversed with SURx/Kirx Channel Activator I + MC4R Agonist I treatment, but not completely with SURx/Kirx Channel Activator I alone (SURx/Kirx Channel Activator I + MC4R Agonist I: NAS score 0.6; SURx/Kirx Channel Activator I: NAS score 2.7, Placebo: NAS score 5.7) indicating the synergistic effect of SURx/Kirx Channel Activator I and MC4R Agonist I on reduction of liver steatosis, inflammation, and lipid deposits.

The reduced carcass weight was associated with a statistically significant ( $p < 0.001$ ) reduction in fat mass (g) in SURx/Kirx Channel Activator I + MC4R Agonist I (-25.4 %) without changes in the protein content (**FIGS. 19A-B**). SURx/Kirx Channel Activator I treatment alone did not change the carcass weight and fat mass, but significantly increased water (+8.23%) and protein (+21.33%) content compared to placebo treated rats (**FIGS. 19C-D**).

Collectively, these results confirm the synergistic positive effects of SURx/Kirx Channel Activator I and MC4R I agonist combination administration on metabolic parameters including reduction in body weight and cumulative food intake; plasma glucose, insulin and leptin; and hepatic biomarkers.

## **Materials and Methods**

### Animals and Environment

21 male Zucker obese rats (Obese; ZUC-Lepr<sup>fa</sup>; Charles River Laboratories USA; CRL strain code-185; 8-10 weeks of age) were singly housed in individually ventilated cages at an ambient temperature of 21±2°C. Each cage contained sawdust with environment enrichment to facilitate warmth and so that the rats could make nests. Rats were housed on a normal light: dark cycle of 12h:12h (lights on 7:00). Room relative humidity was maintained at 55±20% with prolonged periods below 40% RH or above 70% RH avoided as provided for in the UK Code of Practice. The rats had free access to a standard maintenance diet (Envigo Teklad 2018) for one week before handling.

#### Experimental Design

| Treatment schedule-PILOT Study                                         |                                                                                                         |                                                                                                 |          |
|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------|
| Treatment 1 to be administered on Day 1-20 (09:00)/<br>Day 1, 7 and 14 |                                                                                                         | Treatment 2 on Day 1-20<br>(17:00)                                                              | n        |
| <b>A</b>                                                               | Vehicle (0.5% CMC, 5 mL/kg, po, bid) followed by Placebo (5 mg/kg, sc, once a week)                     | Vehicle (0.5% CMC, po, 5 ml/kg, bid)                                                            | <b>3</b> |
| <b>B</b>                                                               | SURx/Kirx channel activator I (75 mg/kg po) followed by Placebo (5 mg/kg, sc, once a week)              | SURx/Kirx channel activator I (75 mg/kg, po, bid)                                               | <b>3</b> |
| <b>C</b>                                                               | SURx/Kirx channel activator I (75 mg/kg po) followed by MC4R agonist I (5 mg/kg, sc, once a week)       | SURx/Kirx channel activator I (75 mg/kg, po, bid)                                               | <b>3</b> |
| Treatment schedule-MAIN study                                          |                                                                                                         |                                                                                                 |          |
| Treatment 1 on Day 1-20 (09:00)<br>/Day 1, 7 and 14                    |                                                                                                         | Treatment 2 on Day 1-20<br>(17:00)                                                              | n        |
| <b>A</b>                                                               | Vehicle (0.5% CMC, 5 mL/kg, po, bid) followed by Placebo                                                | Vehicle (0.5% CMC, 5 mL/kg, po, bid)                                                            | <b>4</b> |
| <b>B</b>                                                               | SURx/Kirx channel activator I (25 mg/kg, po, bid) followed by Placebo (5 mg/kg, sc, once a week)        | SURx/Kirx channel activator I (25 mg/kg, po, bid)                                               | <b>4</b> |
| <b>B</b>                                                               | SURx/Kirx channel activator I (25 mg/kg, po, bid) followed by Placebo (5 mg/kg, sc, once a week)        | SURx/Kirx channel activator I (25 mg/kg, po, bid)                                               | <b>4</b> |
| <b>C</b>                                                               | SURx/Kirx channel activator I (25 mg/kg, po, bid) followed by MC4R agonist I (5 mg/kg, sc, once a week) | SURx/Kirx channel activator I (25 mg/kg, po, bid)                                               | <b>4</b> |
| <b>PG Depot Placebo:</b><br>Vehicle control for MC4R Agonist I         |                                                                                                         | <b>0.5% Carboxy methylcellulose (CMC):</b><br>Vehicle control for SURx/Kirx channel activator I |          |

Subcutaneous (sc) injection procedure: Formulations were drawn from the sample vials by 18-gauge needle and dosed with 25 gauge with long 5/8" inch needle. The animals were temporarily restrained for dose administration and were not sedated.

Blood Sampling for Pharmacokinetic (PK) Analysis and Plasma Glucose

*PK Analysis*

Non-fasted blood samples were collected via tail vein cannulation on Days 1, 4, 7, 11 and 14 before dosing. ~70µl was collected into K2-EDTA coated tubes (Sarstedt Multivette® CB 300 K2 EDTA). All samples were stored on ice. Plasma was separated by cooled centrifugation (yielding ~35 µl) and collected in polypropylene tubes and labeled. Samples were then immediately frozen on dry ice and stored at -80°C until PK analysis.

*Glucose/Insulin/Leptin Analysis*

A second aliquot of blood was collected into lithium heparinized tubes for glucose, insulin and leptin analysis according to the following schedule: on Day 1 ~150µl of blood was collected for measurement of glucose, insulin, and leptin; on Days 7 and 14, ~100µl of blood was collected for measurement of glucose and insulin; and on Day 11, ~70µl of blood was collected for measurement of leptin.

*Non-Fasted Blood Sample Collection for Plasma Lipid and Inflammatory Biomarkers*

~600µl of blood was collected into lithium heparinized tubes (Sarstedt CH300LH). Plasma was separated by centrifugation and the ~250-300µl into three aliquots: (1) ~110µl for measurement of plasma ALT/AST/triglyceride/cholesterol; (2) ~50µl for measurement of plasma insulin and leptin; and (3) ~100µl for measurement of glucose/NEFA.

Oral Glucose Tolerance Test-OGTT

OGTT was conducted on Day 21. On Day 20 (one day prior to the OGTT), rats were deprived of food (but not water) on a timed schedule beginning at approximately 16:45. The OGTT was performed 16 hours latter the following morning. The animals were moved to a separate room and underwent temporary cannulation of the tail vein. D-Glucose was dosed at 2 g/kg po to each animal on a timed schedule. Blood samples were taken immediately prior to glucose administration at baseline, and 15, 30, 60, and 120 minutes after glucose administration. 75 µl blood samples were taken from the tail vein cannula and collected in lithium heparinized tubes (Sarstedt Microvette CB300LH). Plasma separated by centrifugation were frozen at -80°C and assayed for glucose (Thermoelectron infinity glucose reagent, TR15421) and insulin (Alpco mouse ultrasensitive

insulin kit 80 INSMSU-E10). Between each sampling, the rats were returned to their home cages with free access to water (but not food). After the 120-minute time point, rats were humanely terminated as described below.

#### Termination

Rats were humanely terminated after the OGTT.

#### *Tail Vein Blood Sampling for Pharmacokinetic (PK) and Plasma Parameters*

Blood sampling from the overnight-fasted and glucose-treated rats after OGTT is delineated below:

Aliquot 1: ~70 µl blood was collected in K2-ETDA-coated tubes (Sarstedt Multivette® CB 300 K2 EDTA for pharmacokinetic analysis as described above.

Aliquot 2: ~50 µl blood was collected in lithium heparinized tubes (Sarstedt CB300LH). ~20 µl plasma was separated by centrifugation and stored at -80°C.

Plasma samples for pharmacokinetic analysis were from fasted rats as opposed to samples from freely fed rats collected on Day 1, 7, 11, and 14. Following tail vein bleeding, rats were humanely killed by a Schedule 1 method (exposure to an increasing amount of CO<sub>2</sub> with mortality confirm by cessation of circulation). Cerebrospinal fluid (CSF) was collected immediately after termination.

#### *CSF Collection*

Following termination, ~50µl CSF was collected from the cisterna magna region employing a winged infusion set attached to a syringe (25G Terumo Europe) and disposed in a screwcap microtube (CP5915, Alpha Laboratories). All CSF samples were subsequently stored at -80°C within 2 hours.

#### *Liver Collection and Carcass Weight*

300 mg of the right lobe of the liver was removed immediately after termination, frozen with liquid nitrogen, and then stored at -80°C for measurement of hepatic glycogen content. Approximately the same weight was removed from each rat.

An additional 300 mg of the right lobe of the liver was isolated, weighed, and stored at -80°C for measurement of hepatic triglyceride (assayed by Cobas c111 analyzer), cholesterol (assayed by Cobas c111 analyzer), and NEFA (assayed by plate assay). Approximately the same weight was removed from each rat.

A horizontal section approximately 2 cm wide from the left lobe of the liver was cut and fixed in 10% NBF and processed into Formalin-Fixed Paraffin-Embedded (FFPE) blocks. A second piece approximately 1-2 cm<sup>2</sup> was removed, placed on tin foil, and frozen with dry ice for storage at -20°C. Approximately the same weight was removed from each rat.

The carcass of each rat was further weighed, frozen and stored frozen.

#### Test Articles

In **Example 1**, MC4R agonist I (30 mg/mL) or Placebo doses of 5 and 10 mg/kg/weekly were administered and minor redness was observed at the injection site which resolved within a few days after sc injection. However, no other adverse effects were observed.

MC4R agonist I was provided in prefilled glass vials at a concentration of 32.5 mg/L and stored at a refrigerated temperature of 4°C. The MC4R agonist I was allowed to equilibrate at room temperature for a period up to 30 minutes prior to administration on Days 1, 7, and 14.

Placebo (Group A) dose matched the dose volume of MC4R Agonist I (5 mg/mL; Group C) and was calculated to be 0.3077 mL/kg. Dosing volume was calculated based on the body weight on injection day.

The effects of SURx/Kirx channel activators in a Zucker obese rat model is well-known in the art. In order to assess the tolerability of SURx/Kirx Channel Activator I alone or in combination with MC4R Agonist I, 3 rats from each group were allocated to a Pilot Study (n=3/group). The remaining rats were allocated to the Main Study (n=4/group) that started 7 days later. SURx/Kirx Channel Activator I was purchased from a commercial supplier (MedChemExpress, Cat No.: HY-B1140, Batch # 266971) and was formulated in 0.5% sodium carboxymethyl cellulose (Sigma, Cat# C4888) as is known in the art. Rats were dosed orally using a dosing volume of 5 mL/kg po. The SURx/Kirx formulation (all doses) was prepared freshly each morning before the first dosing and was stored at 4°C until the second dosing on the same day.

D-Glucose (Fisher Scientific) for OGTT was supplied by Sygnature Discovery and dissolved in de-ionized water. D-Glucose was administered at a concentration of 400 mg/mL (i.e., a dose of 2.0g/kg) at a volume of 400 mg/mL.

#### 2.12 Statistical Analysis

##### *Statistical methods*

Body weights, body weight gain, daily and average weekly food/water intakes and cumulative food intakes were analyzed by one-way ANCOVA with treatment as a factor and



baseline values (Day 1 body weight or average food/water intake from Days -6 to 0) as the covariate.

Liver weights, terminal plasma and liver lipid data were analyzed by one-way ANCOVA with Day 1 body weight as the covariate. Liver weights were also analyzed with terminal (Day 21) body weight as the covariate. Liver glycogen data were analyzed by one-way ANOVA. Pilot and main study liver analysis results were combined and run with study as a blocking factor.

Plasma glucose, insulin, and leptin data were log transformed and analyzed by linear mixed effects model with treatment by day as a fixed factor and animal as the random factor. Analysis was run on the OGTT data by a general linear model with treatment as a factor, and baseline 9Day 1) body weight and pre-dose (Day -10) glucose and insulin as covariates. Areas under the curve were calculated as follows:  $AUC_{120min} = (t_{0min} + 2t_{15min} + 3t_{30min} + 6t_{60min} + 4t_{120min})/8$ ;  $AUC_{60min} = AUC_{120min} - (t_{60min} + t_{120min})/2$ . The areas under the curve above baseline were calculated as follows:  $AUC_{120min} - 2t_{0min}$ ; and  $AUC_{60min} - t_{0min}$ . Combined pilot and main study results were analyzed with study added as a blocking factor.

In order to calculate percent (%) change in body composition, several comparisons were conducted by multiple t-tests to compare treatment to Placebo. SURx/Kirx Channel Activator I and MC4R Agonist I were each compared to the combination of SURx/Kirx Channel Activator I + MC4R Agonist I by multiple t-test.

Liver histopathology data were analyzed by exact Wilcoxon Rank Sum tests in order to compare SURx/Kirx Channel Activator I + MC4R Agonist I to Placebo, and SURx/Kirx Channel Activator I + MC4R Agonist to SURx/Kirx Channel Activator I alone. Multiple comparisons between SURx/Kirx Channel Activator I alone and SURx/Kirx Channel Activator I + MC4R Agonist I to Placebo, and SURx/Kirx Channel Activator I + MC4R Agonist were conducted by multiple t-tests.  $P < 0.05$  was considered statistically significant. All tests were carried out as two-sided tests.

#### EQUIVALENTS AND SCOPE

This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because

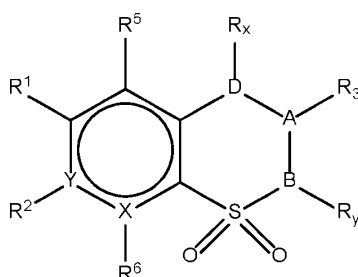
such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, Figures, or Examples but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

\*\*\*\*\*

## CLAIMS

1. A method of treating a disease or disorder in a subject, the method comprising administering a combination of:
  - (iii) a potassium channel activator (e.g., SURx/Kirx channel activator compound) or a pharmaceutically acceptable salt thereof; and
  - (iv) an MC4R agonist,
 to the subject, thereby treating the disease or disorder in the subject.
2. The method of claim 1, wherein the SURx/Kirx channel activator compound is a compound having the structure of Formula (XIV):



or a pharmaceutically acceptable salt thereof, wherein:

A is C(R<sup>1</sup>);

each of B and D are independently N; wherein A and B or A and D are connected via a double or single bond;

X is C(R<sup>2</sup>) or S;

when X is C(R<sup>2</sup>) then Y is C(R<sup>3</sup>); or,

when X is S, then Y is absent;

each of R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano; wherein A and B form a double bond and R<sub>x</sub> is hydrogen or wherein A and D form a double bond and R<sub>y</sub> is hydrogen;

R<sub>3</sub> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, or N(R<sup>B</sup>)(R<sup>C</sup>), wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>4</sub>;

R' is absent, hydrogen, or C1-C6 alkyl;

each R<sub>4</sub> is independently C1-C6 alkyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, fluorine, chlorine, bromine, or iodine;

R<sup>A</sup> is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, or heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>;

each of R<sup>B</sup> and R<sup>C</sup> is independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>; or

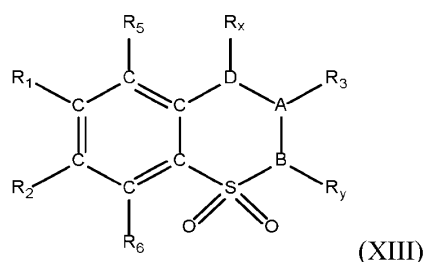
wherein R<sup>B</sup> and R<sup>C</sup> are taken together to form heterocyclyl optionally substituted with one or more R<sub>7</sub>;

each R<sup>7</sup> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano.

3. The method of claim 1, wherein the SURx/Kirx channel activator compound is diazoxide or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein the SURx/Kirx channel activator compound is 3-(1-methylcyclopropyl)amino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide or a pharmaceutically acceptable salt thereof.

5. The method of claim 1, wherein the SURx/Kirx channel activator compound is a compound having the structure of Formula (XIII):



or a pharmaceutically acceptable salt thereof, wherein:

A is C(R<sup>7</sup>);

each of B and D are independently N; wherein A and B or A and D are connected via a double or single bond;

each of R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano; wherein A and B form a double bond and R<sub>x</sub> is hydrogen or wherein A and D form a double bond and R<sub>y</sub> is hydrogen;

R<sub>3</sub> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, or N(R<sup>B</sup>)(R<sup>C</sup>), wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>4</sub>;

R<sup>7</sup> is absent, hydrogen, or C1-C6 alkyl;

each R<sub>4</sub> is independently C1-C6 alkyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, fluorine, chlorine, bromine, or iodine;

R<sup>A</sup> is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, or heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>;

each of R<sup>B</sup> and R<sup>C</sup> is independently hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, cycloalkyl, heterocyclyl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl are each optionally substituted with one or more R<sub>7</sub>; or

wherein R<sup>B</sup> and R<sup>C</sup> are taken together to form heterocyclyl optionally substituted with one or more R<sub>7</sub>;

each R<sup>7</sup> is C1-C6 alkyl, C2-C6 alkenyl, C1-C6 alkynyl, C1-C6 heteroalkyl, C1-C6 haloalkyl, -OR<sup>A</sup>, fluorine, chlorine, bromine, iodine, nitro, or cyano.

6. The method of claim 1, wherein the MC4R agonist is a peptide or a small molecule.
7. The method of claim 1, wherein the MC4R agonist is a peptide.

8. The method of claim 1, wherein the MC4R agonist has the structure of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII) or a pharmaceutically acceptable salt thereof, e.g., as described herein.
9. The method of claim 1, wherein the MC4R agonist has the structure of Formula (I), or a pharmaceutically acceptable salt thereof, e.g., as described herein.
10. The method of claim 9, wherein  $R^2$  is Ac.
11. The method of claim 9, wherein  $R^3$  is H.
12. The method of claim 9, wherein  $R^1$  is  $NH_2$ .
13. The method of claim 9, wherein  $A^1$  is Arg.
14. The method of claim 9, wherein  $A^2$  is Cys.
15. The method of claim 9, wherein  $A^9$  is Cys.
16. The method of claim 9, wherein  $A^3$  is deleted.
17. The method of claim 9, wherein  $A^4$  is His.
18. The method of claim 9, wherein  $A^5$  is D-( $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$ )Phe.
19. The method of claim 9, wherein  $A^5$  is D-Phe.
20. The method of claim 9, wherein  $A^6$  is Arg.
21. The method of claim 9, wherein  $A^7$  is Trp.

22. The method of claim 9, wherein A<sup>8</sup> is deleted.
23. The method of claim 1, wherein the MC4R agonist is:  
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH<sub>2</sub> (SEQ ID NO: 140), or a pharmaceutically acceptable salt thereof.
24. The method of claim 1, wherein the MC4R agonist has the structure of Formula (XII), or a pharmaceutically acceptable salt thereof, e.g., as described herein.
25. The method of claim 24, wherein A<sup>1</sup> is Ac.
26. The method of claim 24, wherein Yyy is Arg.
27. The method of claim 24, wherein Aaa is hCys.
28. The method of claim 24, wherein Xxx is selected from Asn, Gln, Ser, and Thr.
29. The method of claim 24, wherein Bbb is Pen.
30. The method of claim 24, wherein A<sup>2</sup> is NH<sub>2</sub>.
31. The method of claim 1, wherein the MC4R agonist is selected from the following structural formulas:  
Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 629)  
Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 630)  
Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 631); and  
Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 632),  
or a pharmaceutically acceptable salt thereof.
32. The method of claim 1, wherein the MC4R agonist is:

Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 629), or a pharmaceutically acceptable salt thereof.

33. The method of claim 1, wherein the MC4R agonist is:

Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 630), or a pharmaceutically acceptable salt thereof.

34. The method of claim 1, wherein the MC4R agonist is:

Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 631), or a pharmaceutically acceptable salt thereof.

35. The method of claim 1, wherein the MC4R agonist is:

Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH<sub>2</sub>; (SEQ ID NO: 632), or a pharmaceutically acceptable salt thereof.

36. The method of claim 1, wherein the SURx/Kirx channel activator compound is administered at a dosage of between about 1 mg/kg to about 200 mg/kg.

37. The method of claim 1, wherein the SURx/Kirx channel activator compound is administered at a dosage of between about 25 mg/kg to about 125 mg/kg.

38. The method of claim 1, wherein the SURx/Kirx channel activator compound is administered at a dosage of between about 75 mg/kg.

39. The method of claim 1, wherein the MC4R agonist is administered at a dosage of between about 0.5 mg/kg to about 20 mg/kg.

40. The method of claim 1, wherein the MC4R agonist is administered at a dosage of between about 2.5 mg/kg to about 15 mg/kg.



41. The method of claim 1, wherein the MC4R agonist is administered at a dosage of about 5 mg/kg.
42. The method of claim 1, wherein the MC4R agonist is administered at a dosage of about 10 mg/kg.
43. The method of claim 1, wherein the SURx/Kirx channel activator compound is formulated for oral administration.
44. The method of claim 1, wherein the SURx/Kirx channel activator compound is formulated for parenteral administration.
45. The method of claim 1, wherein the SURx/Kirx channel activator compound is formulated for subcutaneous administration.
46. The method of claim 1, wherein the MC4R agonist is administered parenterally.
47. The method of claim 1, wherein the MC4R agonist is administered subcutaneously.
48. The method of claim 1, wherein the MC4R agonist is dosed with a needle (e.g., a 20-25 gauge needle).
49. The method of claim 1, wherein (i) the SURx/Kirx channel activator compound and (ii) the MC4R agonist are administered as a single formulation.
50. The method of claim 1, wherein (i) the SURx/Kirx channel activator compound and (ii) the MC4R agonist are administered as separate formulations.
51. The method of claim 1, wherein (i) the SURx/Kirx channel activator compound is administered orally; and (ii) the MC4R agonist is administered parenterally, e.g., subcutaneously.

52. The method of claim 1, wherein (i) the SURx/Kirx channel activator compound is administered orally once per day; and (ii) the MC4R agonist is administered parenterally, e.g., subcutaneously, once per week.
53. The method of claim 1, wherein the efficacy of the combination is at least  $X_1$ -fold greater than the efficacy of the SURx/Kirx channel activator compound alone at the molar amount used in the combination, wherein  $X_1$  is 1, 1.25, 1.5, 1.75, 2, 2.5, or greater.
54. The method of claim 1, wherein the efficacy of the combination is at least  $X_1$ -fold greater than the efficacy of the MC4R agonist alone at the molar amount used in the combination, wherein  $X_1$  is 1, 1.25, 1.5, 1.75, 2, 2.5, or greater.
55. The method of claim 1, wherein the efficacy of the combination is at least  $X_1$ -fold greater than the efficacy of the SURx/Kirx channel activator compound alone or the MC4R agonist alone at the molar amount used in the combination, wherein  $X_1$  is 1, 1.25, 1.5, 1.75, 2, 2.5, or greater.
56. The method of claim 1, wherein the molar amount of the SURx/Kirx channel activator compound in the combination comprises the molar concentration of the SURx/Kirx channel activator compound in the combination.
57. The method of claim 1, wherein the molar amount of the MC4R agonist in the combination comprises the molar concentration of the MC4R agonist in the combination.
58. The method of claim 1, wherein each of the SURx/Kirx channel activator compound and the MC4R agonist is independently formulated as a pharmaceutical composition.
59. The method of claim 1, wherein the SURx/Kirx channel activator compound and the MC4R agonist are formulated together as a pharmaceutical composition.

60. The method of claim 1, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 200:1 to 1:1.
61. The method of claim 60, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 50:1 to 1:1.
62. The method of claim 60, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 50:1 to 2:1.
63. The method of claim 60, wherein the ratio of the amount of SURx/Kirx channel activator compound to the MC4R agonist in the combination is between 25:1 to 2:1.
64. The method of claim 1, wherein the disease or disorder is obesity.
65. The method of claim 1, wherein the disease or disorder is hypothalamic obesity.
66. The method of claim 1, wherein the disease or disorder is a metabolic syndrome.
67. The method of claim 1, wherein the disease or disorder is Prader-Willi syndrome.
68. The method of claim 1, wherein the disease or disorder is Bardet-Biedl syndrome.
69. The method of claim 1, wherein the disease or disorder is congenital hyperinsulinism (CHI).
70. The method of claim 1, wherein the disease or disorder is a hyperinsulism-related syndrome.
71. The method of claim 1, wherein the disease or disorder is a behavioral disorder or a psychological disorder.