

USE OF MELANOCORTIN-4 RECEPTOR AGONISTS FOR THE TREATMENT OF A LEPR AND/OR SH2B1 DEFICIENCY

CLAIM OF PRIORITY

This application claims priority to KR Patent Application No. 10-2023-0191648, filed on December 26, 2023; and KR Patent Application No. 10-2024-0003091, filed on January 8, 2024. The contents of the foregoing applications are hereby incorporated by reference in their entirety.

BACKGROUND

The melanocortin receptors (MCR) are a type of G-protein coupled receptor (GPCR). A total of five types of melanocortin receptors have been identified to date: MC1R, MC2R, MC3R, MC4R, and MC5R. MC1R is expressed in melanocytes and macrophages, and plays a role in determining skin and hair color through regulation melanin pigment in melanocytes. MC2R is expressed in the adrenal gland and adipose tissue, and has a part in the regulation of adrenal hormone secretion by adrenocorticotrophic hormone in the adrenal gland. MC3R, MC4R, and MC5R are expressed not only in nerve terminals but also in the brain and are thought to mediate central nervous system actions by melanocortin peptides that result in effects on behavior, learning, memory, appetite, and neurogenesis and regeneration. Research on these melanocortins is actively being conducted to better understand their individual roles; however, the connection between the MC4R and regulating weight in a subject is well established. Genetic studies in humans with obesity have shown that MC4R is deeply involved, and knockout mice with MC4R deletions have shown that they develop obesity due to overeating, underscoring that this receptor plays an important role in appetite control. As such, there is a need to develop new treatments for the treatment of subjects with deficiencies in certain genes, such as those in the MC4R pathway, like SH2B1 and LEPR.

SUMMARY

The present disclosure features, *inter alia*, methods and compositions for use in treating a disease or disorder, e.g., a disease or disorder associated with a sarcoma (Src) homology 2 B adaptor protein 1 (SH2B1) deficiency or a leptin receptor (LEPR) deficiency, such as a heterozygous LEPR deficiency, in a subject with a compound of Formula 1, or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure features a method of treating a disease or disorder associated with a SH2B1 deficiency in a subject, e.g., the subject is homozygous (SH2B1^{-/-}) or heterozygous (SH2B1^{+/-}), with a compound of Formula 1 or a

pharmaceutically acceptable salt thereof. In some embodiments, the subject is homozygous (SH2B1^{-/-}). In some embodiments, the subject is heterozygous (SH2B1^{+/-}). In another aspect, the present disclosure features a method of treating a disease or disorder associated with a LEPR deficiency in a subject, e.g., the subject has a disease or disorder associated with a LEPR deficiency, with a compound of Formula 1 or a pharmaceutically acceptable salt thereof. For example, the subject may have a disease or disorder associated with a heterozygous LEPR deficiency. In some embodiments, the subject is heterozygous (LEPR^{+/-}). The disease or disorder can comprise obesity or metabolic syndrome. In some embodiments, the disease or disorder comprises obesity. In some embodiments, the disease or disorder comprises metabolic syndrome. The subject may have been identified with having either a SH2B1 deficiency or a LEPR deficiency.

In an aspect, the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is formulated as a pharmaceutical composition, together with a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated as a dosage form. The dosage form can be a unit dosage form. In some embodiments, the dosage form is a solid dosage form. The solid dosage form can be an oral dosage form. In some embodiments, the oral dosage form comprises a capsule, a tablet, a pill, a powder or a granule. The oral dosage form can be a capsule. The oral dosage form can be a tablet. The oral dosage form can be a pill. The oral dosage form can be a powder. The oral dosage form can be a granule. The solid dosage form can be formulated as a transdermal dosage form. For example, the dosage form can be a lotion, ointment, gel, cream, patch, or spray.

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, can be administered to the subject at a dosage between about 0.1 mg to 1000 mg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject, can be about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 mg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg to about 500 mg, e.g., 1 to 250 mg, 1 to 100 mg, 10 to 100 mg, 10 to 250 mg, 10 to 500 mg, 10 to 1000 mg, 100 to 1000 mg, 100 to 500 mg, 100 to 250 mg, 250 to 1000 mg, 250 to 750 mg, 250 to 500 mg, or 500 to 1000 mg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 10 mg to about 500 mg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg to about 50 mg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg to about 30 mg. In some embodiments, the

dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg to about 10 mg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 10 mg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 30 mg.

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, can be administered to the subject at a dosage between about 0.1 mg/kg to 500 mg/kg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject, can be about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg/kg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg/kg to about 50 mg/kg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg/kg to about 30 mg/kg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg/kg to about 10 mg/kg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 10 mg/kg. In some embodiments, the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 30 mg/kg.

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, can be administered at various schedules. In some embodiments, the administration occurs daily, weekly, or monthly. In some embodiments, the administration occurs once daily or twice daily. In some embodiments, the administration occurs once daily. In some embodiments, the administration occurs twice daily. In some embodiments, the administration occurs once weekly, twice weekly, or three times weekly. In some embodiments, the administration occurs once weekly. In some embodiments, the administration occurs twice weekly. In some embodiments, the administration occurs three times weekly.

The subject can be obese, e.g., severely obese. In some embodiments, the subject is hyperphagic. In some embodiments, the subject has a body mass index greater than 35 kg/m² (e.g., 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration. In some embodiments, the subject has a body mass index greater than 40 kg/m² (e.g., ≥ 41 , 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration. In some embodiments, subject has a body mass index greater than 45 kg/m² (e.g., ≥ 46 , 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m² or greater), prior to administration of the compound

of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.

The subject can have an additional genetic deficiency, e.g., an additional genetic metabolic deficiency. In some embodiments, the subject has diabetes or a diabetological condition, e.g., pre-diabetes, diabetes mellitus type 1, diabetes mellitus type 2, hyperglycemia, hypoglycemia, hyperinsulinemia, hyperleptinemia. In some embodiments, the subject has high blood pressure, e.g., the subject has high diastolic and/or systolic blood pressure. In some embodiments, the subject has failed one or more previous therapies comprising exercise, diet or behavior modification therapies prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of administration.

The subject can exhibit weight loss prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dose of 10 mg/kg after 28 days or longer. In some embodiments, the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dose of 30 mg/kg after 28 days or longer.

The subject can exhibit an appetite suppressing upon administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, compared to a reference standard, e.g., the solvent administered control group (Vehicle). In some embodiments, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle). In some embodiments, the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 28 days or longer.

In some embodiments, the subject exhibits loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a

pharmaceutically acceptable salt thereof, at an oral daily dose of 30 mg/kg after 28 days or longer.

The subject can exhibit a decrease in food intake upon administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, compared to a reference standard, e.g., the solvent administered control group (Vehicle). In some embodiments, the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle). In some embodiments, the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose an oral daily dose of 10 mg/kg after 28 days or longer. In some embodiments, subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose an oral daily dose of 30 mg/kg after 28 days or longer.

In an aspect, the compound of Formula 1 is selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-

N-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide, or a pharmaceutically acceptable salt thereof.

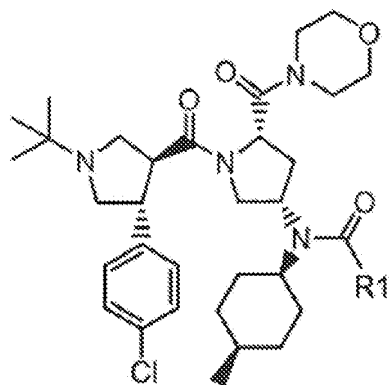
In an aspect, the compound of Formula 1 is selected from a compound as described herein, e.g., in Table 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula 1 is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof: *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide.

In some embodiments, the compound of Formula 1 is selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide hydrochloride.

In an aspect, the present invention is intended to provide a compound of chemical formula 1 below or a pharmaceutically acceptable salt thereof for use in the prevention, improvement or treatment of SH2B1 deficiency genetic obesity (e.g., a rare genetic obesity):

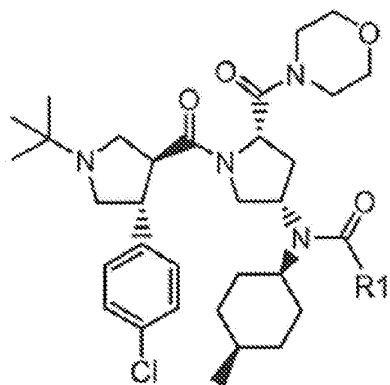
[Formula 1]



In Formula 1 above, R1 is C₂-C₅ alkyl.

In an aspect, the present invention is intended to provide a use of a compound of the following Formula 1 or a pharmaceutically acceptable salt thereof in the prevention, improvement, or treatment of LEPR deficient obesity (e.g., a heterozygous LEPR genetic obesity):

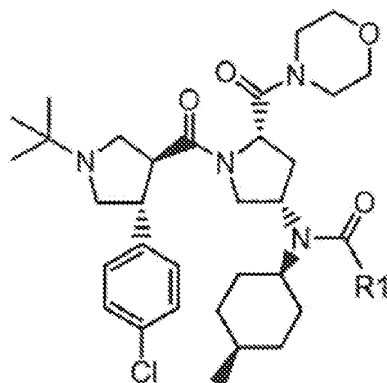
[Formula 1]



In Formula 1 above, R1 is C₂-C₅ alkyl.

The present invention provides a medicament for the prevention, improvement or treatment of LEPR Heterozygous deficient rare genetic obesity disease which comprises a therapeutically effective amount of a compound of Formula 1 below, or a pharmaceutically acceptable salt thereof:

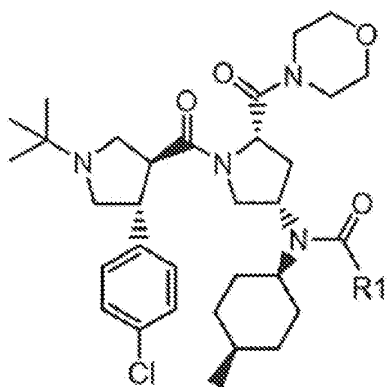
[Formula 1]



In Formula 1 above, R1 is C₂-C₅ alkyl.

In an aspect, the present invention provides a drug for preventing, improving or treating SH2B1 (sarcoma (Src) homology 2 B adaptor protein 1) deficiency rare genetic obesity disease, comprising a therapeutically effective amount of a compound of the following chemical formula 1 or a pharmaceutically acceptable salt thereof:

[Formula 1]



In Formula 1 above, R1 is C₂-C₅ alkyl.

In addition, the present invention provides a pharmaceutical composition for preventing, improving, or treating a rare genetic obesity disease associated with SH2B1 deficiency, comprising a therapeutically effective amount of a compound of chemical formula 1 above or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier. The present invention also provides a pharmaceutical composition for the prevention, improvement or treatment of rare genetic obesity diseases associated with LEPR Heterozygous deficiency, which comprises a therapeutically effective amount of the compound of Formula 1 above or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

In addition, the present invention provides a method for preventing, improving or treating a rare genetic obesity disease associated with SH2B1 deficiency, by including

administering to a subject a therapeutically effective amount of a compound of chemical formula 1 above or a pharmaceutically acceptable salt thereof. In addition, the present invention provides a use of the compound of chemical formula 1 above or a pharmaceutically acceptable salt thereof for preventing, improving or treating a rare genetic obesity disease associated with SH2B1 deficiency.

Furthermore, the present invention provides methods of preventing, improving, or treating rare genetic obesity diseases associated with LEPR Heterozygous deficiency, including administering to a subject of treatment a therapeutically effective amount of the compound of Formula 1 above or a pharmaceutically acceptable salt thereof. The present invention also provides a use for preventing, improving, or treating rare genetic obesity diseases associated with LEPR Heterozygous deficiency of the compound of Formula 1 above or a pharmaceutically acceptable salt thereof. Hereinafter, the present invention will be described in more detail.

According to one aspect of the present invention, a drug for preventing, improving or treating rare genetic obesities associated with SH2B1 deficiency is provided, comprising a therapeutically effective amount of a compound of chemical formula 1 above or a pharmaceutically acceptable salt thereof.

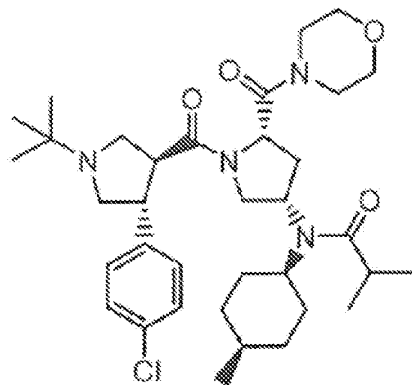
According to one aspect of the present invention, a medicament is provided for the prevention, improvement or treatment of rare genetic obesity disease associated with LEPR Heterozygous deficiency, which comprises a therapeutically effective amount of the compound of Formula 1 above or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, a pharmaceutical composition for preventing, improving, or treating a rare genetic obesity disease associated with SH2B1 deficiency is provided, comprising a therapeutically effective amount of a compound of chemical formula 1 above or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

According to another aspect of the present invention, a pharmaceutical composition is provided for the prevention, improvement or treatment of rare genetic obesity diseases associated with LEPR Heterozygous deficiency, which comprises a therapeutically effective amount of the compound of Formula 1 above, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

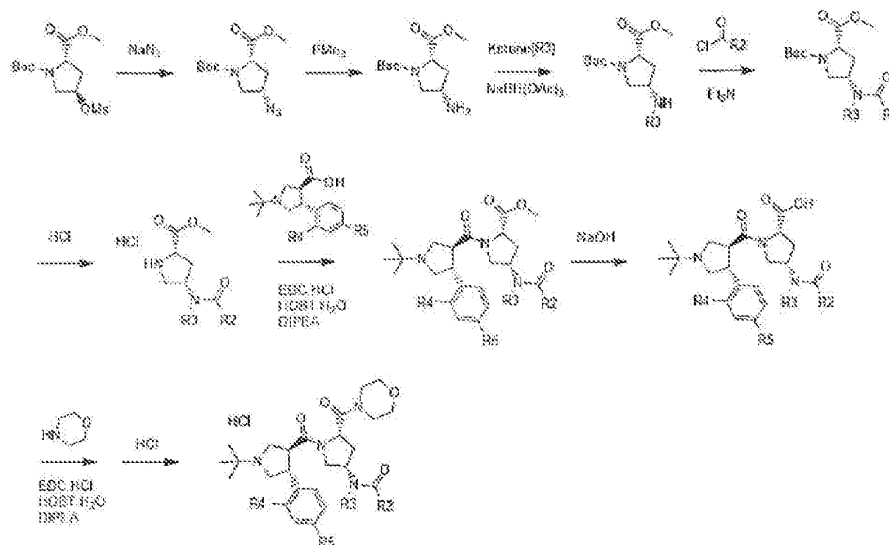
In one embodiment according to the present invention, the compound of chemical formula 1 above is *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidin-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyrylamide represented by the structure of chemical formula 2 below:

[Formula 2] (Compound 100)



In one specific embodiment according to the present invention, the pharmaceutically acceptable salts above include, but are not limited to acid addition salts formed by inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, and hydroiodic acid or the like, organic carboxylic acids, such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, and maleic acid or the like, sulfonic acids, such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and naphthalenesulfonic acid, or the like. In one specific embodiment according to the present invention, the pharmaceutically acceptable salts above may be selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, and hydroiodic acid. In another specific embodiment according to the present invention, the pharmaceutically acceptable salt is hydrochloride. In one specific embodiment according to the present invention, the hydrochloride salt of the compound of chemical formula 1 above can be prepared according to Reaction Scheme 1 below. However, a person of ordinary skill in the art to which the present invention belongs would be able to prepare the compounds of chemical formula 1 by various methods based on the structure of chemical formula 1.

[Reaction Scheme 1]



In Reaction Scheme 1 above, R2 is C₁-C₅ alkyl; R3 is C₃-C₈ cycloalkyl unsubstituted or substituted with 1 or 2 C₁-C₅ alkyls; R4 and R5 are each independently hydrogen or halogen.

In another specific embodiment according to the present invention, the rare genetic obesity disease above may be SH2B1 deficiency, which is a rare genetic obesity disease associated with a damaged melanocortin-4 receptor (MC4R) pathway. In another embodiment according to the present invention, the above rare genetic obesity disease, i.e., the rare genetic obesity disease associated with the damaged melanocortin-4 receptor (MC4R) pathway may be leptin receptor (LEPR) heterozygous deficiency. Leptin is a hormone produced by fat cells, and leptin receptors play an important role in the body's ability to regulate weight because the hormone acts on leptin receptors in the hypothalamus to maintain homeostasis of metabolism and appetite at the top of the melanocortin-4 receptor (MC4R) pathway. Therefore, leptin receptor deficiency can lead to severe obesity. In another specific embodiment according to the present invention, the "therapeutically effective amount" for individual subject means an amount sufficient to achieve the above pharmacological effect, that is, a therapeutic effect, and the amount of the compound will vary depending on the condition of the subject and the severity thereof, the mode of administration, and the age of the subject to be treated, can be determined by those skilled in the art based on the own knowledge thereof. In another specific embodiment according to the present invention, a therapeutically effective dose of the compound of chemical formula 1 above, for example, a dose required to treat adults, typically ranges from approximately 0.1 to 500 mg per day depending on the frequency and intensity of administration. When administered intramuscularly or intravenously to adults, a total dose of approximately 0.1 to 300 mg per day, divided into single doses, will usually be sufficient, but higher daily doses may be desirable for some patients. In the present invention, the "pharmaceutical composition"

may comprise other chemical components such as carriers, diluents, excipients, and the like in addition to the active compound according to the present invention. Accordingly, the pharmaceutical composition may include, as necessary, a pharmaceutically acceptable carrier, diluent, excipient, or a combination thereof. Pharmaceutical compositions facilitate the administration of active compounds into a living organism. There are a variety of techniques for administering compounds, including but not limited to oral, injection, aerosol, parenteral, and topical administration. As used herein, the “carrier” refers to a compound that facilitates introduction of a compound into cells or tissues. For example, dimethyl sulfoxide (DMSO) is a common carrier that facilitates the introduction of many organic compounds into the cells or tissues of an organism. The “diluent” in the present specification is defined as a compound that is diluted in water to not only stabilize the biologically active form of the subject compound, but also to dissolve the compound. Salts dissolved in buffer solutions are used as diluents in the field of art. A commonly used buffer solution is phosphate buffered saline, which mimics the salt form of human body fluids. Buffer salts can control the pH of a solution at low concentrations, and thus it is rare for buffer diluents to modify the biological activity of a compound.

The “pharmaceutically acceptable” in the present specification refers to a property that does not impair the biological activity and physical properties of a compound. In the present invention, the compound can be formulated into various pharmaceutical dosage forms depending on the purpose. When preparing a pharmaceutical composition according to the present invention, an active ingredient, specifically the compound of Formula 1 or a pharmaceutically acceptable salt thereof, is mixed with various pharmaceutically acceptable carriers that can be selected depending on the formulation to be prepared. For example, a pharmaceutical composition according to the present invention may be formulated as an injectable formulation, an oral formulation, or the like, depending on the intended purpose. The compound of the present invention can be formulated by well-known methods using well-known pharmaceutical carriers and excipients and placed in unit dosage form or multi-dose containers. The form of the formulation may be in the form of a solution, suspension or emulsion in an oil or aqueous medium and may contain conventional dispersing, suspending or stabilizing agents. Additionally, for example, it may be in the form of a dry powder that is dissolved in sterile, pyrogen-free water before use. The compounds of the present invention may also be formulated in suppository form using conventional suppository bases such as cocoa butter or other glycerides. Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules, and capsules and tablets are particularly useful. Tablets and pills are preferably manufactured as enteric coating agents. Solid dosage forms can be prepared by mixing the compound of the present invention with one or more inert diluents such as sucrose, lactose, starch, and the like and carriers

such as lubricants such as magnesium stearate, disintegrants, binders, and the like. Additionally, it may be formulated in a transdermal dosage form, for example, as a lotion, ointment, gel, cream, patch, or spray. In another specific embodiment according to the present invention, the medicament or pharmaceutical composition may be in an oral dosage form. The “prevention” in the present specification is reducing or eliminating the possibility of contracting a disease. The “treatment” in the present specification, when used on a subject showing symptoms of disease, refers to stopping, delaying, or alleviating the progression of a disease.

A pharmaceutical composition comprising a compound according to the present invention can effectively prevent, improve or treat a SH2B1 deficiency rare genetic obesity disease. A pharmaceutical composition comprising a compound according to the invention is capable of efficiently preventing, improving or treating LEPR heterozygous deficiency related rare genetic obesity disease.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a graph showing the effect on body weight loss and 1-week cumulative food intake measured in a SH2B1 heterozygous deficiency mouse model. **FIG. 1A** is a graph of body weight (g) in the SH2B1 heterozygous deficiency mouse model at oral doses of 10 mg/kg and 30 mg/kg LB54640. **FIG. 1B** is a graph of weight gain or loss (%) in the SH2B1 heterozygous deficiency mouse model at oral doses of 10 mg/kg and 30 mg/kg LB54640. **FIG. 1C** is a bar graph of weight (g) on day 28 in the SH2B1 heterozygous deficiency mouse model for Vehicle and at oral doses of 10 mg/kg and 30 mg/kg LB54640. **FIG. 1D** is a bar graph of food intake (g) at 1 week in the SH2B1 heterozygous deficiency mouse model for Vehicle at oral doses of 10 mg/kg and 30 mg/kg LB54640.

FIG. 2 is a graph showing the effect on body weight loss and 1-week cumulative food intake measured in a SH2B1 homozygous deficiency mouse model. **FIG. 2A** is a graph of body weight (g) in the SH2B1 homozygous deficiency mouse model at oral doses of 10 mg/kg and 30 mg/kg LB54640. **FIG. 2B** is a graph of weight gain or loss (%) in the SH2B1 homozygous deficiency mouse model at oral doses of 10 mg/kg and 30 mg/kg LB54640. **FIG. 2C** is a bar graph of weight (g) on day 28 in the SH2B1 homozygous deficiency mouse model for Vehicle and at oral doses of 10 mg/kg and 30 mg/kg LB54640. **FIG. 2D** is a bar graph of food intake (g) at 1 week in the SH2B1 homozygous deficiency mouse model for Vehicle at oral doses of 10 mg/kg and 30 mg/kg LB54640.

FIG. 3 is a graph showing the weight loss effect measured in a leptin receptor heterozygous mouse model. **FIG. 3A** is a graph of body weight (g) in the LEPR heterozygous deficiency mouse model at oral doses of 10 mg/kg and 30 mg/kg LB54640. **FIG. 3B** is a graph of weight

gain or loss (%) in the LEPR heterozygous deficiency mouse model at oral doses of 10 mg/kg and 30 mg/kg LB54640. **FIG. 3C** is a bar graph of weight (g) on day 28 in the SH2B1 homozygous deficiency mouse model for Vehicle and at oral doses of 10 mg/kg and 30 mg/kg LB54640.

FIG. 4 is a graph showing the results of measuring the effect of decrease in 1-week cumulative food intake in a leptin receptor heterozygous mouse model.

DETAILED DESCRIPTION

Hereinafter, the present disclosure will be described in more detail through preparation examples, examples, and experimental examples. However, these examples are only intended to illustrate one or more specific examples and the scope of the invention is not limited thereby.

The present disclosure provides methods for treating a genetic obesity comprising administering a compound of Formula 1, or a pharmaceutically acceptable salt thereof, to a subject. In some embodiments, the subject has a genetic obesity characterized by either a LEPR deficiency or an SH2B1 deficiency. In an embodiment, the subject has a genetic obesity characterized by an SH2B1 deficiency. In some embodiments, the SH2B1 deficiency is homozygous (SH2B1^{-/-}). In some embodiments, the SH2B1 deficiency is heterozygous (SH2B1^{+/-}). In some embodiments, the subject has a genetic obesity characterized by a heterozygous LEPR mutation. In some embodiments, the subject is a mammal, e.g., a mouse or a human. In some embodiments, the subject is a mouse, e.g., a SH2B1-deficient mouse, e.g., a SH2B1^{+/-}-deficient mouse or a SH2B1^{-/-} deficient mouse. In some embodiments, the subject is a human, e.g., a human with a SH2B1 deficiency. In some embodiments, the human has a SH2B1^{-/-} genotype or a SH2B1^{+/-} genotype.

In an aspect, upon administering the compound of Formula 1, or a pharmaceutically acceptable salt thereof, the subject can be obese, e.g., severely obese. In some embodiments, the subject is hyperphagic. In some embodiments, the subject has a body mass index greater than 35 kg/m² (e.g., $\geq 36, 37, 38, 39, 40, 41, 42, 43, 44, 45$ kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration. In some embodiments, the subject has a body mass index greater than 40 kg/m² (e.g., $\geq 41, 42, 43, 44, 45, 46, 47, 48, 49, 50$ kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration. In some embodiments, the subject has a body mass index greater than 45 kg/m² (e.g., $\geq 46, 47, 48, 49, 50, 51, 52, 53, 54, 55$ kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.

In an aspect, the subject has, or has been diagnosed with having, an additional genetic metabolic deficiency. In some embodiments, the subject has diabetes or a diabetological condition, e.g., pre-diabetes, diabetes mellitus type 1, diabetes mellitus type 2, hyperglycemia, hypoglycemia, hyperinsulinemia, hyperleptinemia, *inter alia*. In some embodiments, the subject has high blood pressure, e.g., the subject has high diastolic and/or systolic blood pressure. In some embodiments, the subject has failed one or more previous therapies comprising exercise, diet or behavior modification therapies prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of administration.

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, can be administered orally. In some embodiments, the administration occurs daily, weekly, or monthly. In some embodiments, the administration occurs once weekly, twice weekly, three times weekly, or more. In some embodiments, the administration is repeated daily, twice daily, or three times daily. In some embodiments, the administration, e.g., the oral administration, is repeated daily for the duration of treatment.

In an aspect, the methods described herein comprise administering the compound of Formula 1, or a pharmaceutically acceptable salt thereof, for 7 days, 14 days, 21 days, 28 days, or longer. In some embodiments, the duration of administration is 7 days. In some embodiments, the duration of administration is 14 days. In some embodiments, the duration of administration is 21 days. In some embodiments, the duration of administration is 28 days.

In an aspect, the methods described herein comprise administering the compound of Formula 1, or a pharmaceutically acceptable salt thereof, for 7 days or less, e.g., 1, 2, 3, 4, 5, 6 or 7 days. In an aspect, the methods described herein comprise administering the compound of Formula 1, or a pharmaceutically acceptable salt thereof, for 14 days or less, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days. In an aspect, the methods described herein comprise administering the compound of Formula 1, or a pharmaceutically acceptable salt thereof, for 21 days or less, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days. In an aspect, the methods described herein comprise administering the compound of Formula 1, or a pharmaceutically acceptable salt thereof, for 28 days or less, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 days.

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, can be administered at a dose between about 0.1 mg to about 500 mg. In some embodiments, the dose is about 1 mg to about 400 mg. In some embodiments, the dose is about 1 mg to about 300 mg. In some embodiments, the dose is about 1 mg to about 200 mg. In some embodiments, the dose is about 1 mg to about 100 mg. In some embodiments, the dose is about 1 mg to about 90 mg. In some embodiments, the dose is about 1 mg to about 80 mg. In some embodiments, the dose is

about 1 mg to about 70 mg. In some embodiments, the dose is about 1 mg to about 60 mg. In some embodiments, the dose is about 1 mg to about 50 mg. In some embodiments, the dose is about 1 mg to about 30 mg. In some embodiments, the dose is about 10 mg to about 30 mg. In some embodiments, the compound of Formula 1, or a pharmaceutically acceptable salt there, is provided as an oral dosage form.

The compound of Formula 1 can be administered at a dose of about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg. In some embodiments, the dose is about 0.1 mg. In some embodiments, the dose is about 1 mg. In some embodiments, the dose is about 2 mg. In some embodiments, the dose is about 3 mg. In some embodiments, the dose is about 4 mg. In some embodiments, the dose is about 5 mg. In some embodiments, the dose is about 6 mg. In some embodiments, the dose is about 7 mg. In some embodiments, the dose is about 8 mg. In some embodiments, the dose is about 9 mg. In some embodiments, the dose is about 10 mg. In some embodiments, the dose is about 15 mg. In some embodiments, the dose is about 20 mg. In some embodiments, the dose is about 30 mg. In some embodiments, the dose is about 40 mg. In some embodiments, the dose is about 50 mg. In some embodiments, the dose is about 60 mg. In some embodiments, the dose is about 70 mg. In some embodiments, the dose is about 80 mg. In some embodiments, the dose is about 90 mg. In some embodiments, the dose is about 100 mg. In some embodiments, the dose is about 200 mg. In some embodiments, the dose is about 300 mg. In some embodiments, the dose is about 400 mg. In some embodiments, the dose is about 500 mg.

The compound of Formula 1, or a pharmaceutically acceptable salt thereof, can be administered at a dose between about 0.1 mg/kg to about 500 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 400 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 300 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 200 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 100 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 90 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 80 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 70 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 60 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 50 mg/kg. In some embodiments, the dose is about 1 mg/kg to about 30 mg/kg. In some embodiments, the dose is about 10 mg/kg to about 30 mg/kg. In some embodiments, the compound of Formula 1, or a pharmaceutically acceptable salt there, is provided as an oral dosage form.

The compound of Formula 1 can be administered at a dose of about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg/kg. In some embodiments, the dose is about 0.1 mg/kg. In some embodiments, the dose is about 1 mg/kg. In

some embodiments, the dose is about 2 mg/kg. In some embodiments, the dose is about 3 mg/kg. In some embodiments, the dose is about 4 mg/kg. In some embodiments, the dose is about 5 mg/kg. In some embodiments, the dose is about 6 mg/kg. In some embodiments, the dose is about 7 mg/kg. In some embodiments, the dose is about 8 mg/kg. In some embodiments, the dose is about 9 mg/kg. In some embodiments, the dose is about 10 mg/kg. In some embodiments, the dose is about 15 mg/kg. In some embodiments, the dose is about 20 mg/kg. In some embodiments, the dose is about 30 mg/kg. In some embodiments, the dose is about 40 mg/kg. In some embodiments, the dose is about 50 mg/kg. In some embodiments, the dose is about 60 mg/kg. In some embodiments, the dose is about 70 mg/kg. In some embodiments, the dose is about 80 mg/kg. In some embodiments, the dose is about 90 mg/kg. In some embodiments, the dose is about 100 mg/kg. In some embodiments, the dose is about 200 mg/kg. In some embodiments, the dose is about 300 mg/kg. In some embodiments, the dose is about 400 mg/kg. In some embodiments, the dose is about 500 mg/kg.

Upon administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, the subject can exhibit a weight loss effect. In some embodiments, the weight loss is equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the weight loss is equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) relative to prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dosage of 10 mg/kg for 28 days or longer. In some embodiments, the weight loss is equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) relative to prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dosage of 30 mg/kg for 28 days or longer. In some embodiments, the weight loss is equal to about -3.19% of the subject's body weight prior to the administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof at an oral daily dose of 10 mg/kg after 28 days or longer. In some embodiments, the weight loss is equal to about -2.4% of the subject's body weight prior to the administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof at an oral daily dose of 10 mg/kg after 28 days or longer.

In some embodiments, the weight loss is equal to about -5.31% of the subject's body weight prior to the administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof at an oral daily dose of 30 mg/kg after 28 days or longer. In some embodiments, the weight loss is equal to about -3.94% of the subject's body weight prior to the

administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof at an oral daily dose of 10 mg/kg after 28 days or longer. In some embodiments, the weight loss is equal to about -7.83% of the subject's body weight prior to the administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof at an oral daily dose of 30 mg/kg after 28 days or longer.

In some embodiments, the weight loss is equal to about -12.2% of the subject's body weight prior to the administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof at an oral daily dose of 30 mg/kg after 28 days or longer.

In some embodiments, the subject is administered a high fat diet (e.g., a diet with 60% kcal% fat). In some embodiments, the subject is a mouse, e.g., a SH2B1 knock-out mouse. In some embodiments, the mouse is aa SH2B1 homozygous(-/-) knock-out mouse. In some embodiments, the mouse is a SHB21 heterozygous (+/-) knock-out mouse.

Upon administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, the subject can exhibit an appetite suppressing effect. In some embodiments, the appetite suppressing effect is 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle). In some embodiments, the appetite suppressing effect is 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle) at an oral daily dose of 10 mg/kg after 28 days or longer. In some embodiments, the appetite suppressing effect is 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle) at an oral daily dose of 30 mg/kg after 28 days or longer. In some embodiments, the subject is administered a high fat diet (e.g., a diet with 60% kcal% fat). In some embodiments, the subject is a mouse, e.g., a SH2B1 knock-out mouse. In some embodiments, the mouse is aa SH2B1 homozygous(-/-) knock-out mouse. In some embodiments, the mouse is a SHB21 heterozygous (+/-) knock-out mouse.

Upon administration of the Compound of Formula 1, or a pharmaceutically acceptable salt thereof, the subject can exhibit a decrease in food intake. In some embodiments, the decrease in food intake is about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle). In some embodiments, the decrease in food intake is about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 28 days or longer. In some embodiments, the

decrease in food intake is about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 28 days or longer.

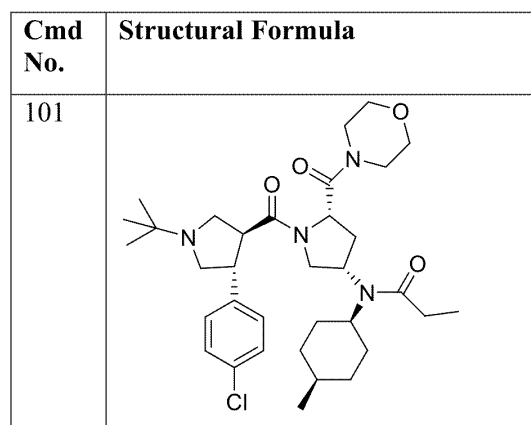
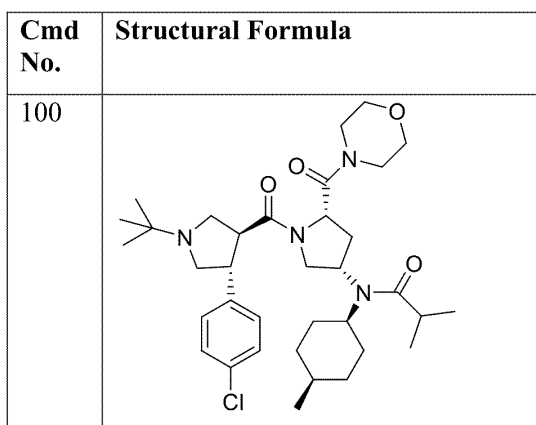
In some embodiments, is about 1% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 2% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 3% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 4% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 5% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 6% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 7% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 8% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 9% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 10% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 11% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 12% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 13% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 14% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days. In some embodiments, is about 15% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 7 days.

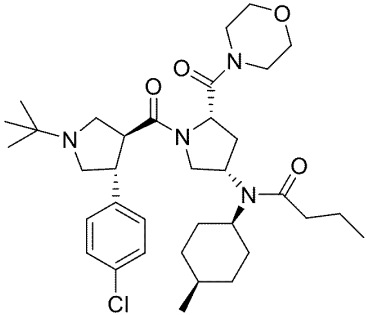
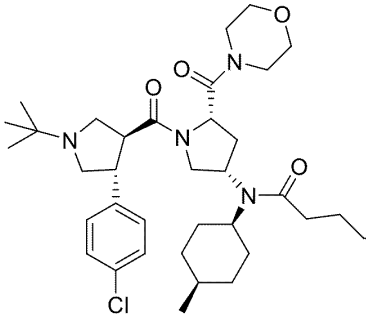
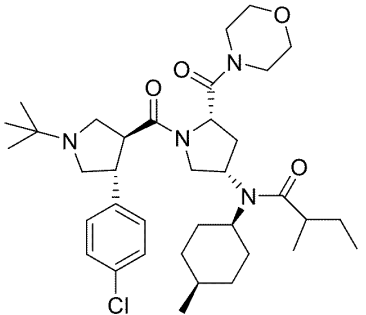
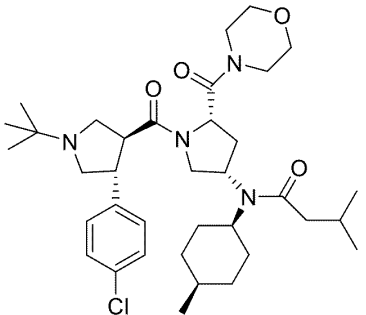
In some embodiments, is about 1% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 2% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 3% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 4% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 5% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 6% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 7% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 8% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 9% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 10% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 11% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 12% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 13% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 14% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days. In some embodiments, is about 15% or greater compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 7 days.

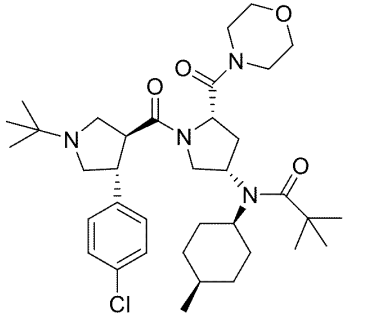
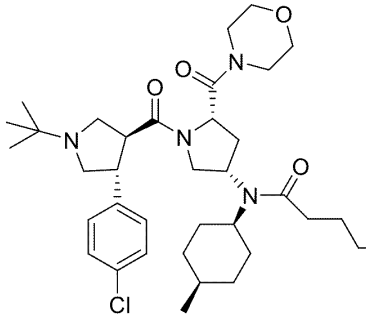
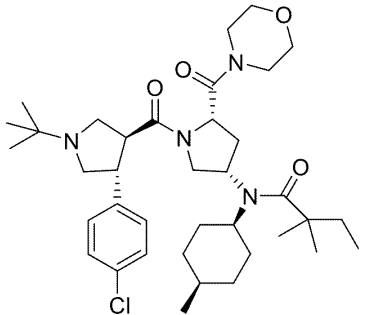
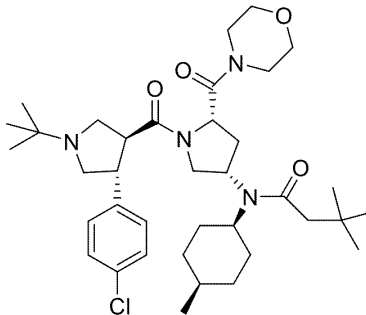
The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-

chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula 1 is selected from a compound or a pharmaceutically acceptable salt thereof, having one of the following structural formulas:



Cmd No.	Structural Formula
102	
103	
104	
105	

Cmd No.	Structural Formula
106	
107	
108	
109	

Cmd No.	Structural Formula
110	
111	

Cmd No.	Structural Formula
112	

The compound of Formula 1 may be selected from the pharmaceutically acceptable salt of any of the following compounds: *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-

N-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide, wherein the pharmaceutically acceptable salt is an acid addition salt formed by an inorganic acid selected from hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, and hydroiodic acid.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydrochloride; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-

yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydrochloride; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrochloride. The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide sulfate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide sulfate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide sulfate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-

chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide nitrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide nitrate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide nitrate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-

chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide phosphate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide phosphate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide phosphate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-

(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydrobromide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydrobromide; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydrobromide.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydroiodide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide hydroiodide; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide hydroiodide.

The compound of Formula 1 may be selected from the pharmaceutically acceptable salt of any of the following compounds: *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-

chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide, wherein the pharmaceutically acceptable salt is an acid addition salt formed by a carboxylic acid selected from tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, and maleic acid.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-

methylcyclohexyl)butyramide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pivalamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)hexanamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide tartrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide tartrate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide tartrate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)isobutyramide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)propionamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butyramide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-

methylcyclohexyl)pivalamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)hexanamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide formate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide formate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide formate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)isobutyramide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)propionamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butyramide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pivalamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)hexanamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-

((1*S*,4*R*)-4-methylcyclohexyl)pentanamide citrate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide citrate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide citrate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide acetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide acetate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide acetate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-

butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide trichloroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide trichloroacetate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trichloroacetate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-

((1*S*,4*R*)-4-methylcyclohexyl)butanamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide trifluoroacetate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide trifluoroacetate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide trifluoroacetate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-

chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide gluconate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide gluconate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide gluconate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide benzoate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide benzoate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-

(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzoate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide lactate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide lactate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide lactate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-

methylcyclohexyl)butyramide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pivalamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)hexanamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide fumarate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide fumarate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide fumarate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)isobutyramide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)propionamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butyramide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-

methylcyclohexyl)pivalamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)hexanamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide maleate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide maleate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide maleate.

The compound of Formula 1 may be selected from the pharmaceutically acceptable salt of any of the following compounds: *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)isobutyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)propionamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butyramide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pivalamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)hexanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-

chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide, wherein the pharmaceutically acceptable salt is an acid addition salt formed by a sulfonic acid selected from methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, and naphthalenesulfonic acid.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)isobutyramide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)propionamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butyramide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pivalamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)hexanamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)butanamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide methanesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pentanamide methanesulfonate; and *N*-((3*S*,5*S*)-1-

((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide methanesulfonate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide benzenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide benzenesulfonate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide benzenesulfonate.

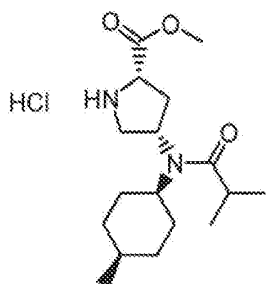
The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-

chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide tosylate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide tosylate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide tosylate.

The compound of Formula 1 may be selected from *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-

((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide naphthalenesulfonate; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide naphthalenesulfonate; and *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide naphthalenesulfonate.

Preparation Example 1: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate hydrochloride



The title compound was obtained using the method described in International Publication No. WO 2009/007930. Specifically, the title compound was obtained through the following steps A, B, C, D, and E.

Step A: Preparation of 1-(*tert*-butyl)-2-methyl (2*S*,4*S*)-4-azidopyrrolidine-1,2-dicarboxylate

1-(*tert*-butyl)-2-methyl (2*S*,4*R*)-4-((methylsulfonyl)oxy)pyrrolidine-1,2-dicarboxylate (48.5 g, 150 mmol) was dissolved in *N,N*-dimethylformamide (250 ml) under a nitrogen atmosphere, and sodium azide (19.5 g, 300 ml) was added. After stirring at 80°C for 16 hours and concentrating the reaction solvent under reduced pressure, water was added and extraction was performed twice using ethyl acetate. The organic layer was washed with aqueous sodium chloride solution and water, then dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated

under reduced pressure to obtain a crude (39.59 g, 98%), which was used in the next step without purification.

MS [M+H] = 271 (M+1)

¹H NMR (400 MHz, CD₃OD) δ 4.43-4.37 (m, 1H), 4.35-4.27 (br, 1H), 3.77 (s, 1.8H), 3.76 (s, 1.2H), 3.73-3.66 (m, 1H), 3.44-3.38 (m, 1H), 2.63-2.49 (m, 1H), 2.19-2.11 (m, 1H), 1.50 (s, 4.5H), 1.44 (s, 4.5H)

Step B: Preparation of 1-(*tert*-butyl)2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate

After 1-(*tert*-butyl) 2-methyl (2*S*, 4*S*)-4-azidopyrrolidine-1,2-dicarboxylate (24.59 g, 91.0 mmol) obtained in step A above was dissolved in tetrahydrofuran (180 ml), 1M trimethylphosphine tetrahydro solution (109.2 ml, 109.2 mmol) was slowly added at 0°C. Stirring was performed at the same temperature for 1 hour, then at room temperature for 3 hours. After concentrating the reaction solvent under reduced pressure, dichloromethane (100 ml) and water (150 ml) were added and stirred for about 30 minutes. After separating the layers and extracting once more using dichloromethane, the organic layer was dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure to obtain a crude (20.62 g, 93%), which was used in the next step without purification.

MS [M+H] = 245 (M+1)

¹H NMR (400 MHz, CD₃OD) δ 4.27 (m, 1H), 3.77 (s, 1.8H), 3.76 (s, 1.2H), 3.75-3.67 (m, 1H), 3.50-3.42 (m, 1H), 3.22-3.17 (m, 1H), 2.58-2.47 (m, 1H), 1.82-1.71 (m, 1H), 1.48 (s, 4.5H), 1.42 (s, 4.5H)

Step C: Preparation of 1-(*tert*-butyl)2-methyl (2*S*,4*S*)-4-(((1*S*,4*R*)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate

1-(*tert*-butyl)2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (20.62 g, 84.4 mmol) obtained in step B above was dissolved in dichloroethane (150 ml) and 4-methylcyclohexanone (9.5 ml, 101.3 mmol) was added. Sodium triacetoxyborohydride (26.8 g, 126.6 mmol) was added at 0°C, and stirred at room temperature for 16 hours. The reaction solvent was concentrated under reduced pressure, water was added, and extraction was performed twice using ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, then dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (22.9 g, 80%).

MS [M+H] = 341 (M+1)

¹H NMR (400 MHz, CD₃OD) δ 4.26 (m, 1H), 3.76 (s, 1.8H), 3.75 (s, 1.2H), 3.78-3.71 (m, 1H), 3.49-3.40 (m, 1H), 3.22-3.16 (m, 1H), 2.69-2.60 (br, 1H), 2.58-2.46 (m, 1H), 1.87-1.77 (m, 1H), 1.73-1.63 (m, 1H), 1.62-1.35 (m, 8H), 1.48 (s, 4.5H), 1.42 (s, 4.5H), 0.96 (d, 3H)

Step D: Preparation of 1-(*tert*-butyl)2-methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-1,2-dicarboxylate

1-(*tert*-butyl)2-methyl (2*S*,4*S*)-4-(((1*S*,4*R*)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate (37.29 g, 109.5 mmol) obtained in step C above was dissolved in dichloromethane (500 ml), triethyl amine (61.1 ml, 438.1 mmol) was added, and then isobutyryl chloride (11.7 ml, 219 mmol) was slowly added at 0°C. After stirring at room temperature for 16 hours, the reaction solvent was concentrated under reduced pressure, then sodium bicarbonate aqueous solution was added and extracted twice using ethyl acetate. The organic layer was washed with aqueous sodium chloride solution and water, then dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (38.79 g, 86%).

MS [M+H] = 411 (M+1)

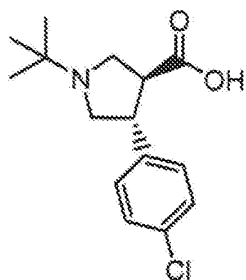
¹H NMR (400 MHz, CD₃OD) δ 4.27 (m, 1H), 3.76 (s, 1.8H), 3.75 (s, 1.2H), 3.78-3.72 (m, 1H), 3.50-3.41 (m, 1H), 3.33-3.14 (m, 1H), 2.69-2.60 (m, 2H), 2.57-2.43 (m, 1H), 1.87-1.79 (m, 1H), 1.70-1.61 (m, 1H), 1.60-1.32 (m, 8H), 1.47 (s, 4.5H), 1.41 (s, 4.5H), 1.10 (dd, 6H), 0.99 (d, 3H)

Step E: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate hydrochloride

After 1-(*tert*-butyl)2-methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-1,2-dicarboxylate (34.0 g, 82.8 mmol) obtained in step D above was dissolved in dichloromethane (200 ml), 4N hydrochloric acid 1,4-dioxane solution (82.8 ml, 331.3 mmol) was added at 0°C. After stirring at room temperature for 6 hours, the reaction solvent was concentrated under reduced pressure to obtain a crude (28.7 g, 99%), which was used in the next step without purification.

MS [M+H] = 311 (M+1)

Preparation Example 2: Preparation of (3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid

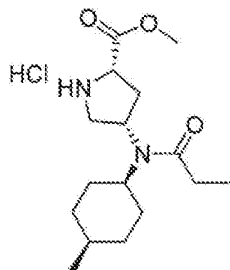


The title compound was obtained using the method described in International Publication No. WO 2004/092126.

MS [M+H] = 282 (M+1)

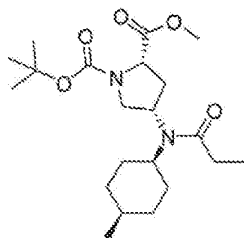
^1H NMR (400 MHz, CD_3OD) δ 7.43-7.33 (m, 4H), 3.90-3.69 (m, 3H), 3.59 (dd, $J = 11.2, 10.0$ Hz, 1H), 3.29 (dd, $J = 11.2, 11.2$ Hz, 1H), 3.18-3.09 (m, 1H), 1.44 (s, 9H)

Preparation Example 3: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate hydrochloride



The title compound was obtained through the following steps A and B.

Step A: Preparation of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-1,2-dicarboxylate

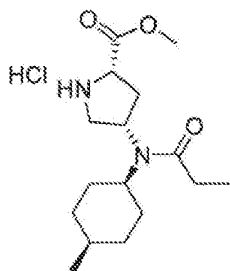


The title compound (0.98 g, 84%) was obtained using the same method as in Step D of Preparation Example 1, using 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-((1*S*,4*R*)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate (1.0 g, 2.9 mmol) obtained in Step C of Preparation Example 1 and propionyl chloride (0.33 g, 3.5 mmol).

MS $[\text{M}+\text{Na}] = 419.5$ ($\text{M}+23$)

^1H NMR (400 MHz, CD_3OD) δ 4.33 (m, 1H), 4.00-3.80 (m, 2H), 3.75 (m, 3H), 3.58 (m, 1H), 3.47 (m, 1H), 2.85-2.68 (m, 1H), 2.38 (q, 2H), 2.31 (m, 1H), 1.93 (m, 1H), 1.80 (m, 2H), 1.72-1.55 (m, 4H), 1.45 (m, 2H), 1.45-1.41 (m, 9H), 1.07 (m, 6H)

Step B: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate hydrochloride

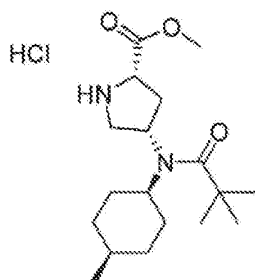


The title compound (0.76 g, 93%) was obtained using the same method as in Step E of Preparation Example 1, using 1-(*tert*-butyl)2-methyl(2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-1,2-dicarboxylate (0.98 g, 2.4 mmol) obtained in step A above.

MS [M+H] = 297.4 (M+1)

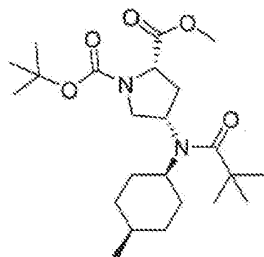
¹H NMR (400 MHz, DMSO-*d*₆) δ 9.95 (brs, 1H), 8.63 (brs, 1H), 4.38 (m, 1H), 4.21 (m, 1H), 3.77 (s, 3H), 3.53 (m, 1H), 3.40 (m, 2H), 2.53 (m, 1H), 2.37 (q, 2H), 2.24 (m, 1H), 1.88 (m, 1H), 1.68-1.55 (m, 4H), 1.52 (m, 2H), 1.40 (m, 2H), 0.97 (m, 6H)

Preparation Example 4: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate hydrochloride



The title compound was obtained through the following steps A and B.

Step A: Preparation of 1-(*tert*-butyl)2-methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-1,2-dicarboxylate

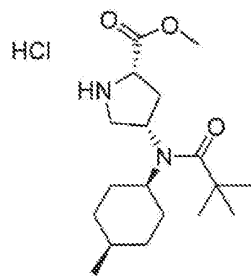


The title compound was obtained using the method described in International Publication No. WO 2008/007930.

MS [M+Na] = 447.5 (M+23)

¹H NMR (400 MHz, CD₃OD) δ 4.34 (m, 1H), 3.90-3.75 (m, 2H), 3.73 (m, 3H), 3.45 (m, 2H), 2.75-2.60 (m, 1H), 2.30 (m, 1H), 1.95 (m, 1H), 1.85 (m, 2H), 1.66 (m, 4H), 1.50 (m, 2H), 1.45-1.41 (m, 9H), 1.25-1.20 (m, 9H), 1.05 (d, 3H)

Step B: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate hydrochloride

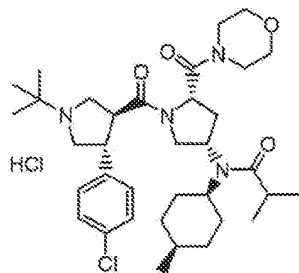


The title compound (0.68 g, 99%) was obtained using the same method as in Step E of Preparation Example 1, using 1-(*tert*-butyl)2-methyl(2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-1,2-dicarboxylate (0.80 g, 1.88 mmol) obtained in Step A above.

MS [M+H] = 325.4 (M+1)

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.24 (brs, 1H), 8.60 (brs, 1H), 4.41 (m, 1H), 4.22 (m, 1H), 3.77 (m, 3H), 3.40-3.28 (m, 3H), 2.55 (m, 1H), 2.20 (m, 1H), 1.87 (m, 1H), 1.70-1.50 (m, 6H), 1.40 (m, 2H), 1.21-1.10 (m, 9H), 1.00 (m, 3H)

Example 1: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride



The title compound was obtained through the following steps A, B, C, and D.

Step A: Preparation of methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate

Methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate hydrochloride (28.7 g, 82.73 mmol) obtained in Preparation Example 1, (3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid (24.5 g, 86.87 mmol) obtained in Preparation Example 2, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (22.2 g, 115.83 mmol), and 1-hydroxybenzotriazole hydrate (15.7 g, 115.83 mmol) were dissolved in *N,N*-dimethylformamide (400ml) and *N,N*-diisopropylethylamine (72.0 ml, 413.66 mmol) was slowly added. After stirring at room temperature for 16 hours and concentrating the reaction solvent under reduced pressure, 0.5N aqueous sodium hydroxide solution was added and extraction was performed twice using ethyl acetate. The organic layer was washed twice with aqueous sodium

chloride solution and water, then dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (41.19 g, 87%).

MS [M+H] = 575 (M+1)

Step B: Preparation of (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylic acid

After methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate (39.4 g, 68.62 mmol) obtained in step A above was dissolved in methanol (450 ml), 6N aqueous sodium hydroxide solution (57.2 ml, 343.09 mmol) was added. After stirring at room temperature for 16 hours and adjusting the pH to about 5 using a 6N aqueous hydrochloric acid solution, the reaction solution was concentrated under reduced pressure. After dissolving the concentrate in dichloromethane, the insoluble solid was filtered through a paper filter. The filtrate was concentrated under reduced pressure to obtain a crude (38.4 g, 99%), which was used in the next step without purification.

MS [M+H] = 561 (M+1)

Step C: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide

(2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylic acid (38.4 g, 68.60 mmol) obtained in step B above, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (18.4 g, 96.04 mmol), and 1-hydroxybenzotriazole hydrate (13.0 g, 96.04 mmol) were dissolved in *N,N*-dimethylformamide (200 ml) and then sequentially morpholine (5.9 ml, 68.80 mmol) and *N,N*-diisopropylethylamine (59.7 ml, 343.02 mmol) were slowly added. After stirring at room temperature for 16 hours, the reaction solution was concentrated under reduced pressure, 0.5 N sodium hydroxide aqueous solution was added, and extraction was performed twice using ethyl acetate. The organic layer was washed twice with aqueous sodium chloride solution and water, then dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (37.05 g, 86%).

MS [M+H] = 630 (M+1)

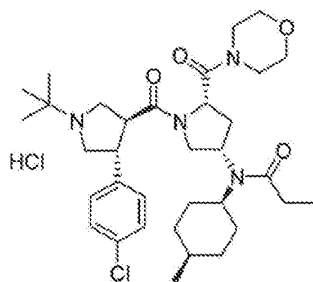
Step D: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride

After *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide (5.0 g, 7.95 mmol) obtained in step C above was dissolved in ethyl acetate (50 ml), 2N hydrochloric acid ethyl acetate solution (3.97 ml, 15.89 mmol) was slowly added. After stirring at room temperature for 30 minutes, the reaction solvent was concentrated under reduced pressure. The resulting crude solid was purified by trituration using hexane and diethyl ether to obtain the title compound (5.23 g, 99%).

MS [M+H] = 630 (M+1)

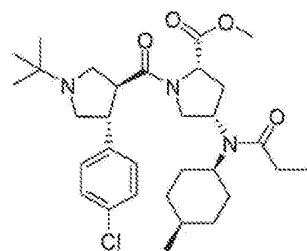
¹H NMR (500 MHz, CD₃OD) δ 7.49-7.44 (m, 4H), 4.83 (m, 1H), 4.23-4.20 (m, 1H), 3.95-3.91 (m, 2H), 3.79-3.47 (m, 14H), 3.03-3.00 (m, 1H), 2.86-2.82 (m, 1H), 2.73-2.67 (m, 1H), 2.20-2.14 (m, 1H), 1.97 (m, 1H), 1.80-1.62 (m, 5H), 1.50 (s, 9H), 1.44-1.27 (m, 3H), 1.06-1.04 (m, 9H)

Example 2: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide hydrochloride



The title compound was obtained through the following steps A, B, C, and D.

Step A: Preparation of methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate

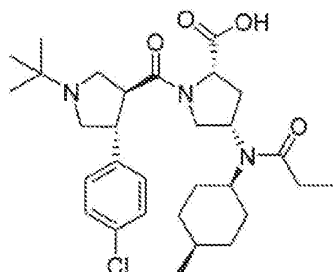


The title compound (0.45 g, 35%) was obtained using the same method as in Step A of Example 1, using methyl (2*S*, 4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate hydrochloride (0.76 g, 2.28 mmol) obtained in Preparation Example 3 and (3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid (0.64 g, 2.28 mmol) obtained in Preparation Example 2.

MS [M+H] = 560.4 (M+1)

¹H NMR (400 MHz, CD₃OD) δ 7.39-7.30 (m, 4H), 4.45 (m, 1H), 4.04 (m, 1H), 3.71 (s, 3H), 3.65-3.35 (m, 6H), 3.13 (m, 2H), 2.99 (m, 1H), 2.71 (m, 1H), 2.34 (q, 2H), 2.20 (m, 1H), 1.92 (m, 1H), 1.75-1.55 (m, 6H), 1.42 (m, 2H), 1.22 (m, 9H), 1.03 (m, 6H)

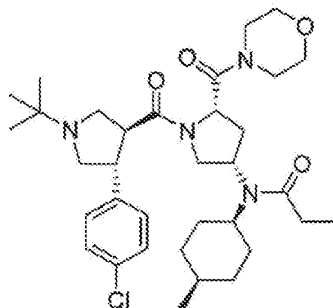
Step B: Preparation of (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylic acid



The title compound (0.44 g, 99%) was obtained using the same method as in Step B of Example 1 using methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate (0.45 g, 0.80 mmol) obtained in step A above.

MS [M+H] = 546.4 (M+1)

Step C: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide

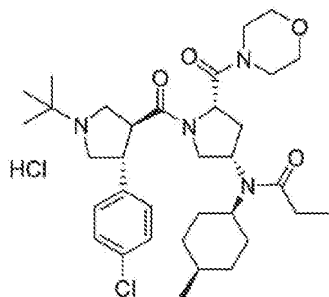


The title compound (0.28g, 53%) was obtained using the same method as in Step C of Example 1 using (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylic acid (0.44 g, 0.80 mmol) obtained in Step B above.

MS [M+H] = 615.5 (M+1)

¹H NMR (400 MHz, CD₃OD) δ 7.36 (m, 4H), 4.79 (m, 1H), 4.18 (m, 1H), 3.80-3.40 (m, 15H), 3.20 (m, 1H), 3.03 (m, 1H), 2.70 (m, 1H), 2.33 (q, 2H), 2.15 (m, 1H), 1.93 (m, 1H), 1.71-1.56 (m, 6H), 1.40-1.20 (m, 11H), 1.00 (m, 6H)

Step D: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide hydrochloride

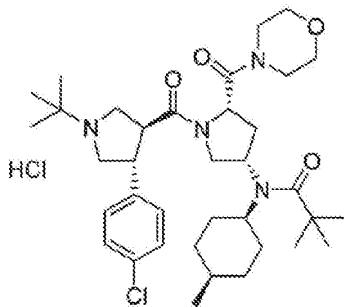


The title compound (0.08 g, 94%) was obtained using the same method as in Step D of Example 1 using *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide (0.08 g, 0.13 mmol) obtained in step C above.

MS [M+H] = 615.5 (M+1)

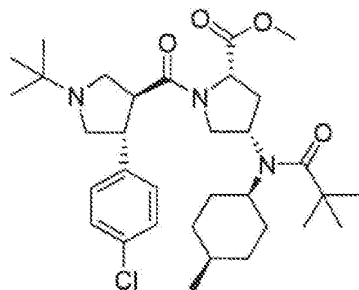
¹H NMR (400 MHz, CD₃OD) δ 7.43 (m, 4H), 4.82 (t, 1H), 4.20 (m, 1H), 4.06-3.40 (m, 15H), 2.97 (m, 1H), 2.69 (m, 1H), 2.33 (m, 2H), 2.15 (m, 1H), 1.93 (m, 1H), 1.80-1.53 (m, 5H), 1.47 (s, 9H), 1.50-1.25 (m, 4H), 1.01 (m, 6H)

Example 3: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide hydrochloride



The title compound was obtained through the following steps A, B, C, and D.

Step A: Preparation of methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate

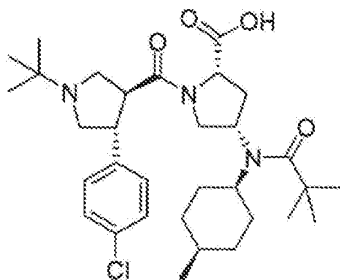


The title compound (0.70 g, 66%) was obtained using the same method as in Step A of Example 1, using methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate hydrochloride (0.65 g, 1.8 mmol) obtained in Preparation Example 4 and (3*S*, 4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid (0.50 g, 1.8 mmol) obtained in Preparation Example 2.

MS [M+H] = 588.5 (M+1)

¹H NMR (400 MHz, CD₃OD) δ 7.40-7.30 (m, 4H), 4.49 (m, 1H), 4.00-3.50 (m, 4H), 3.71 (s, 3H), 3.40 (m, 3H), 3.20-3.05 (m, 2H), 3.00 (m, 1H), 2.70 (m, 1H), 2.27 (m, 1H), 1.90 (m, 1H), 1.73-1.60 (m, 6H), 1.60-1.35 (m, 2H), 1.25-1.17 (m, 18H), 1.01 (m, 3H)

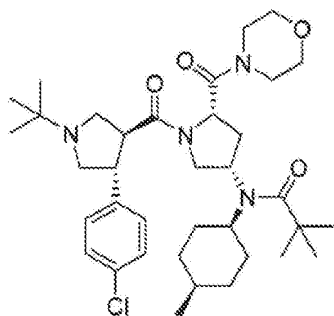
Step B: Preparation of (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylic acid



The title compound (0.10 g, 99%) was obtained using the same method as in Step B of Example 1 using methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate (0.10 g, 0.18 mmol) obtained in step A above.

MS [M+H] = 574.4 (M+1)

Step C: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide

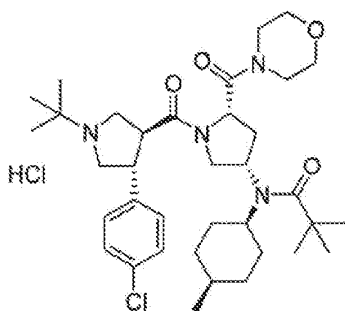


The title compound (0.020 g, 17%) was obtained using the same method as in Step C of Example 1 using (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylic acid (0.10 g, 0.18 mmol) obtained in step B above.

MS [M+H] = 643.5 (M+1)

¹H NMR (400 MHz, CD₃OD) δ 7.40-7.30 (m, 4H), 4.79 (m, 1H), 4.17 (m, 1H), 3.80-3.40 (m, 15H), 3.10 (m, 1H), 2.96 (m, 1H), 2.71 (m, 1H), 2.15 (m, 1H), 1.90 (m, 1H), 1.80-1.35 (m, 8H), 1.21-1.15 (m, 18H), 1.02 (m, 3H)

Step D: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide hydrochloride



The title compound (0.29 g, 83%) was obtained using the same method as in Step D of Example 1 using *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide (0.33 g, 0.51 mmol) obtained in step C above.

MS [M+H] = 643.5 (M+1)

¹H NMR (400 MHz, CD₃OD) δ 7.41 (m, 4H), 4.80 (m, 1H), 4.13 (m, 1H), 3.90 (m, 2H), 3.80-3.40 (m, 13H), 2.94 (m, 1H), 2.63 (m, 1H), 2.11 (m, 1H), 1.93 (m, 1H), 1.75 (m, 2H), 1.60 (m, 4H), 1.46 (s, 9H), 1.15 (s, 9H), 1.45-1.30 (m, 3H), 1.01 (m, 3H)

Experimental example 1: SH2B1 knock-out mouse model experiment

SH2B Adaptor protein 1 (SH2B1) deficiency is a disease caused by mutations in the SH2B1 gene, which plays a role in the MC4R pathway. Because impaired SH2B1 activity/expression

leads to insufficient LEPR activity, disruption of SH2B1 is associated with the development of severe obesity and metabolic syndrome. The SH2B1 knockout mouse model may be an important example of human SH2B1 deficiency, as it can exhibit obesity and glucose intolerance. The in vivo effect of the compound of chemical formula 1 according to the present invention was evaluated in a SH2B1 knockout mouse model.

Specifically, sh2b1 heterozygous knock-out mice, in which the sh2b1 gene encoding SH2B1 is not normally expressed, were fed a 60 kcal% high-fat diet (diet with 60 kcal% fat) while administering *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride (compound of chemical formula 2, also referred to as "LB54640" hereinafter) obtained in the example at daily doses of 10 mg/kg and 30 mg/kg for 4 weeks to confirm the anti-obesity efficacy. The results are shown in FIG. 1. In addition, the anti-obesity efficacy was confirmed by administering LB54640 at daily doses of 10 mg/kg and 30 mg/kg for 4 weeks to sh2b1 homozygous knock-out mouse, in which the sh2b1 gene encoding SH2B1 is not expressed, while feeding a 60 kcal% high-fat diet (diet with 60 kcal% fat). The results are shown in FIG. 2.

As shown in FIG. 1, compared to the vehicle-administered control group in sh2b1 heterozygous knock-out mice, administration of 10 mg/kg and 30 mg/kg of LB54640 according to the present invention resulted in significant weight loss of -3.19% and -5.31% on the last day of treatment, respectively ($p < 0.001$) (**FIG. 1B**). In addition, it was confirmed that LB54640 exhibited a significant appetite suppression effect. Based on 1-week cumulative feed intake, LB54640 showed a dose-related decrease in food intake when administered at doses of 10 mg/kg and 30 mg/kg, and the 30 mg/kg administration group showed a statistically significant appetite suppression effect compared to the vehicle administration control group (**FIG. 1D**).

As shown in FIG. 2, compared to the vehicle administration control group, the administration of 10 mg/kg and 30 mg/kg of LB54640 according to the present invention in sh2b1 homozygous knock-out mice caused a significant weight loss of -3.94% and -7.83% ($p < 0.05$) on the last day of treatment (**FIG. 2B**), respectively. In addition, it was confirmed that LB54640 exhibited a significant appetite suppression effect. Based on 1-week cumulative feed intake, LB54640 showed a dose-related decrease in food intake when administered at doses of 10 mg/kg and 30 mg/kg, and all showed a statistically significant appetite suppression effect compared to the vehicle administration control group (**FIG 2D**).

Experimental example 2: LEPR heterozygous deficiency mouse model experiment

Leptin receptor (LEPR) is important for energy homeostasis and metabolism. Since the LEPR heterozygous mouse model can exhibit leptin deficiency conditions, the possible therapeutic

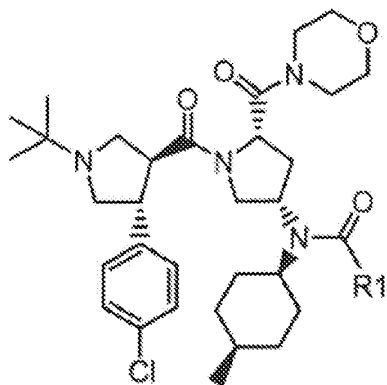
potential of the compounds according to the present invention can be identified in LEPR heterozygous which exhibits overweight or obesity.

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1- (*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin- 3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride (a compound of Formula 2, also referred to as “LB54640” below) obtained in Embodiment 1 was administered daily at 10 mg/kg and 30 mg/kg to LEPR heterozygous deficiency mice, while feeding them with 60 kcal% high-fat feed (diet with 60 kcal% fat), for 4 weeks to confirm antiobesity effect. The weight gain inhibition effect was checked by measuring the weight during the administration period, and the results are shown in **FIGS. 3** and **4**. As shown in FIG. 1, it was found that the compound of the present invention, LB54640, exhibited a significant weight loss effect. As of the last day of treatment (day 28), the LB54640 30 mg/kg dose group showed a significant weight loss of -12.2% (**FIG 3B**).

In addition, as shown in FIG. 4, cumulative food intake over 7 days of treatment also showed significant loss in both 10 mg/kg and 30 mg/kg compared to the solvent-administered control group ($p < 0.01$, $p < 0.001$).

ENUMERATED EMBODIMENTS

1. A method of treating a disease or disorder in a subject, wherein the disease or disorder is associated with a SH2B1 deficiency or a leptin receptor (LEPR) deficiency, the method comprising administering to the subject a compound of Formula 1 or a pharmaceutically acceptable salt thereof:



wherein R1 is C₂-C₅ alkyl,
thereby treating a disease or disorder in the subject.

2. The method of the preceding embodiment, wherein the subject has a disease or disorder associated with SH2B1 deficiency.

3. The method of any of the preceding embodiments, wherein the subject having the SH2B1 deficiency is homozygous (SH2B1^{-/-}) or heterozygous (SH2B1^{+/-}).
4. The method of any of the preceding embodiments, wherein the subject having SH2B1 deficiency is homozygous (SH2B1^{-/-}).
5. The method of any of the preceding embodiments, wherein subject having the SH2B1 deficiency is heterozygous (SH2B1^{+/-}).
6. The method of any of the preceding embodiments, wherein the subject has a disease or disorder associated with a LEPR deficiency.
7. The method of any of the preceding embodiments, wherein the subject having the heterozygous LEPR deficiency is heterozygous (LEPR^{+/-}).
8. The method of any of the preceding embodiments, wherein the disease or disorder comprises obesity or metabolic syndrome.
9. The method of any of the preceding embodiments, wherein the disease or disorder comprises obesity.
10. The method of any of the preceding embodiments, wherein the disease or disorder comprises metabolic syndrome.
11. The method of any of the preceding embodiments, wherein the subject has been identified as having either a SH2B1 deficiency or a leptin receptor (LEPR) deficiency.
12. The method of any of the preceding embodiments, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is formulated as a pharmaceutical composition, together with a pharmaceutically acceptable carrier.
13. The method of any of the preceding embodiments, wherein the pharmaceutical composition is formulated as a dosage form, e.g., a unit dosage form.

14. The method of any of the preceding embodiments, wherein the dosage form is a solid dosage form.
15. The method of any of the preceding embodiments, wherein the pharmaceutical composition is formulated as an oral dosage form.
16. The method of any of the preceding embodiments, wherein the oral dosage form comprises a capsule, a tablet, a pill, a powder, or a granule.
17. The method of any of the preceding embodiments, wherein the oral dosage form comprises a capsule.
18. The method of any of the preceding embodiments, wherein the oral dosage form comprises a tablet.
19. The method of any of the preceding embodiments, wherein the dosage form is formulated as a transdermal dosage form.
20. The method of any of the preceding embodiments, wherein the transdermal dosage form comprises a lotion, ointment, gel, cream, patch or spray.
21. The method of any of the preceding embodiments, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is administered to the subject at a dosage between about 0.1 mg to about 500 mg.
22. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg.
23. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg to about 50 mg.

24. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 10 mg to about 30 mg.
25. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 10 mg.
26. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 30 mg.
27. The method of any of the preceding embodiments, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is administered to the subject at a dosage between about 0.1 mg/kg to about 500 mg/kg.
28. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg/kg.
29. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg/kg to about 50 mg/kg.
30. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 10 mg/kg to about 30 mg/kg.
31. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 10 mg/kg.
32. The method of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 30 mg/kg.
33. The method of any of the preceding embodiments, wherein administration occurs daily, weekly, or monthly.

34. The method of any of the preceding embodiments, wherein administration occurs once daily or twice daily.
35. The method of any of the preceding embodiments, wherein administration occurs once daily.
36. The method of any of the preceding embodiments, wherein administration occurs twice daily.
37. The method of any of the preceding embodiments, wherein administration occurs once weekly, twice weekly, or three times weekly.
38. The method of any of the preceding embodiments, wherein administration occurs once weekly.
39. The method of any of the preceding embodiments, wherein administration occurs twice weekly.
40. The method of any of the preceding embodiments, wherein administration occurs three times weekly.
41. The method of any of the preceding embodiments, wherein the subject is obese, e.g., severely obese.
42. The method of any of the preceding embodiments, wherein the subject is hyperphagic.
43. The method of any of the preceding embodiments, wherein the subject has a body mass index greater than 35 kg/m^2 (e.g., 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 kg/m^2 or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.
44. The method of any of the preceding embodiments, wherein the subject has a body mass index greater than 40 kg/m^2 (e.g., ≥ 41 , 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.

45. The method of any of the preceding embodiments, wherein the subject has a body mass index greater than 45 kg/m² (e.g., $\geq$ 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.
46. The method of any of the preceding embodiments, wherein the subject has an additional genetic deficiency, e.g., an additional genetic metabolic deficiency.
47. The method of any of the preceding embodiments, wherein the subject has diabetes or a diabetological condition, e.g., pre-diabetes, diabetes mellitus type 1, diabetes mellitus type 2, hyperglycemia, hypoglycemia, hyperinsulinemia, hyperleptinemia.
48. The method of any of the preceding embodiments, wherein the subject has high blood pressure, e.g., the subject has high diastolic and/or systolic blood pressure.
49. The method of any of the preceding embodiments, wherein the subject has failed one or more previous therapies comprising exercise, diet or behavior modification therapies prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of administration.
50. The method of any of the preceding embodiments, wherein the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq$ 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof.
51. The method of any of the preceding embodiments, wherein the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq$ 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dose of 10 mg/kg after 28 days or longer.
52. The method of any of the preceding embodiments, wherein the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq$ 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the

compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dose of 30 mg/kg after 28 days or longer.

53. The method of any of the preceding embodiments, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle).

54. The method of any of the preceding embodiments, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 28 days or longer.

55. The method of any of the preceding embodiments, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 28 days or longer.

56. The method of any of the preceding embodiments, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle).

57. The method of any of the preceding embodiments, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose an oral daily dose of 10 mg/kg after 28 days or longer.

58. The method of any of the preceding embodiments, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose an oral daily dose of 30 mg/kg after 28 days or longer.

59. The method of any of the preceding embodiments, wherein the compound of Formula 1 is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;

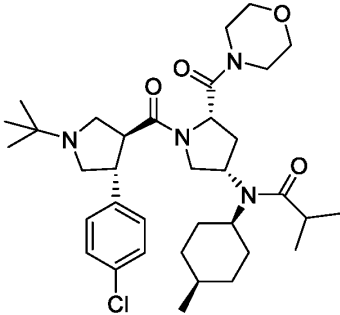
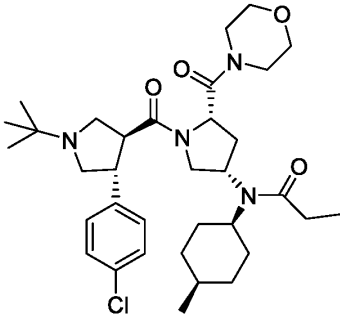
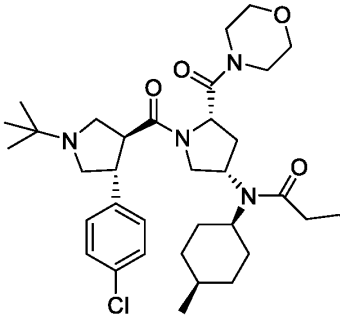
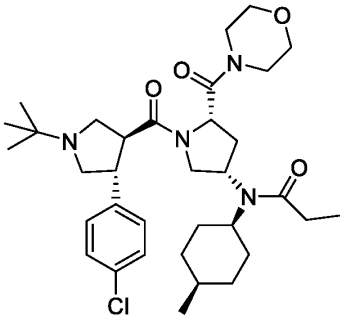
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;

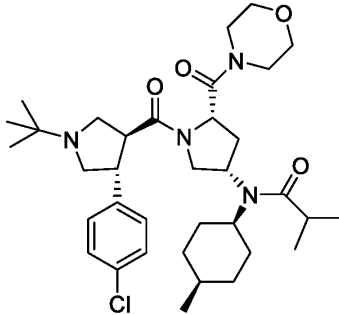
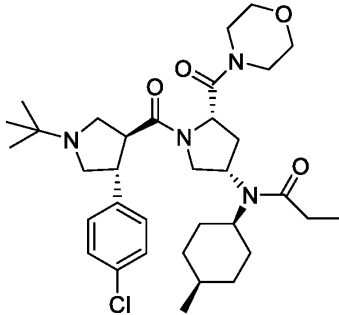
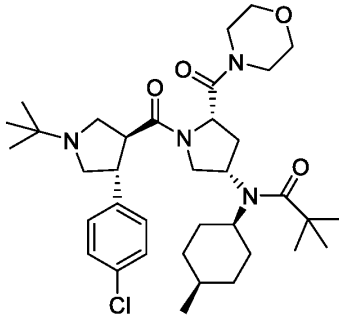
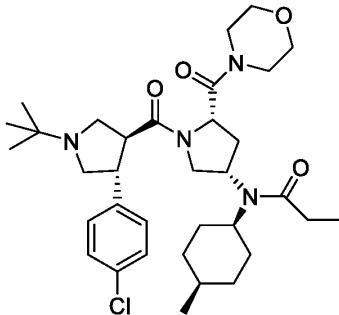
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; and

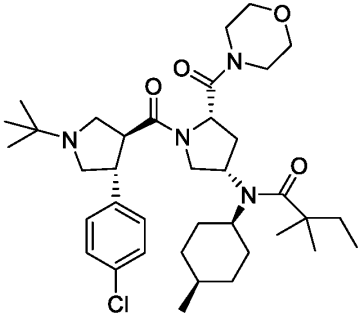
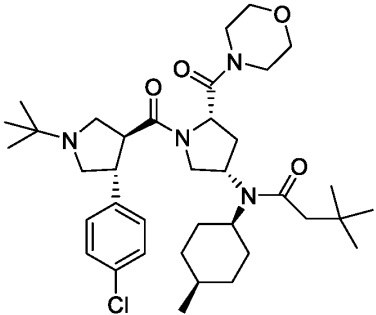
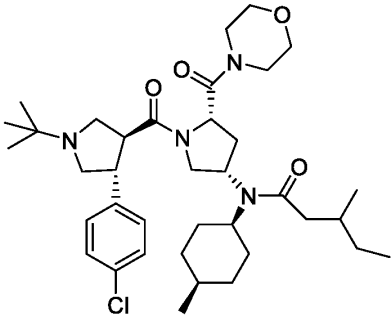
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide,

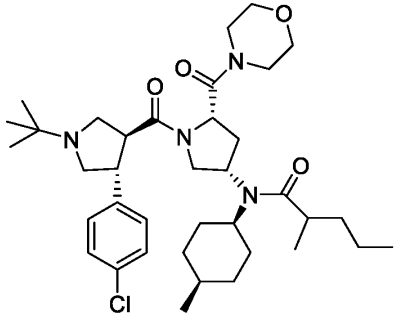
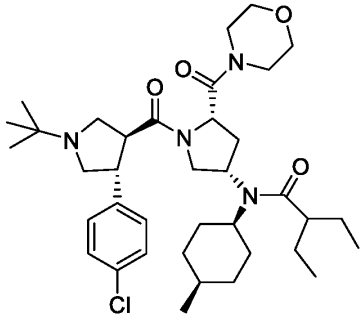
or a pharmaceutically acceptable salt thereof.

60. The method of any of the preceding embodiments, wherein the compound of Formula 1 is selected from a compound having one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

Cmd No.	Structural Formula
100	
101	
102	
103	

Cmd No.	Structural Formula
104	
105	
106	
107	

Cmd No.	Structural Formula
108	
109	
110	

Cmd No.	Structural Formula
111	
112	

61. The method of any of the preceding embodiments, wherein the compound of Formula 1 is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)propionamide;

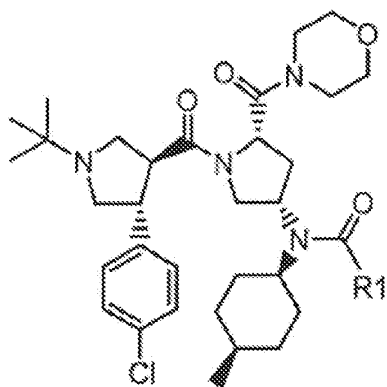
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)isobutyramide; and

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pivalamide.

62. The method of any of the preceding embodiments, wherein the compound of Formula 1 is selected from one of the following compounds:

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide hydrochloride;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride; and
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide hydrochloride.

63. A composition for use in treating a disease or disorder in a subject, wherein the disease or disorder is associated with a SH2B1 deficiency or a heterozygous leptin receptor (LEPR) deficiency, the composition comprising a therapeutically effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof:



wherein R1 is C₂-C₅ alkyl.

64. The composition for use of embodiment 1, wherein the subject has a disease or disorder associated with SH2B1 deficiency.

65. The composition for use of any of the preceding embodiments, wherein the subject having the SH2B1 deficiency is homozygous (SH2B1^{-/-}) or heterozygous (SH2B1^{+/-}).

66. The composition for use of any of the preceding embodiments, wherein the subject having SH2B1 deficiency is homozygous (SH2B1^{-/-}).

67. The composition for use of any of the preceding embodiments, wherein the subject having the SH2B1 deficiency is heterozygous (SH2B1^{+/-}).

68. The composition for use of any of the preceding embodiments, wherein the subject has a disease or disorder associated with a heterozygous LEPR deficiency.
69. The composition for use of any of the preceding embodiments, wherein the subject having the heterozygous LEPR deficiency is heterozygous (LEPR+/-).
70. The composition for use of any of the preceding embodiments, wherein the disease or disorder comprises obesity or metabolic syndrome.
71. The composition for use of any of the preceding embodiments, wherein the disease or disorder comprises obesity.
72. The composition for use of any of the preceding embodiments, wherein the disease or disorder comprises metabolic syndrome.
73. The composition for use of any of the preceding embodiments, wherein the subject has been identified as having either a SH2B1 deficiency or a leptin receptor (LEPR) deficiency.
74. The composition for use of any of the preceding embodiments, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is formulated as a pharmaceutical composition, together with a pharmaceutically acceptable carrier.
75. The composition for use of any of the preceding embodiments, wherein the pharmaceutical composition is formulated as a dosage form, e.g., a unit dosage form.
76. The composition for use of any of the preceding embodiments, wherein the dosage form is a solid dosage form.
77. The composition for use of any of the preceding embodiments, wherein the pharmaceutical composition is formulated as an oral dosage form.
78. The composition for use of any of the preceding embodiments, wherein the oral dosage form comprises a capsule, a tablet, a pill, a powder, or a granule.

79. The composition for use of any of the preceding embodiments, wherein the oral dosage form comprises a capsule.
80. The composition for use of any of the preceding embodiments, wherein the oral dosage form comprises a tablet.
81. The composition for use of any of the preceding embodiments, wherein the dosage form is formulated as a transdermal dosage form.
82. The composition for use of any of the preceding embodiments, wherein the transdermal dosage form comprises a lotion, ointment, gel, cream, patch or spray.
83. The composition for use of any of the preceding embodiments, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is administered to the subject at a dosage between about 0.1 mg to about 500 mg.
84. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg.
85. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg to about 50 mg.
86. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 10 mg to about 30 mg.
87. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 10 mg.
88. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 30 mg.

89. The composition for use of any of the preceding embodiments, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is administered to the subject at a dosage between about 0.1 mg/kg to about 500 mg/kg.

90. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg/kg.

91. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg/kg to about 50 mg/kg.

92. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 10 mg/kg to about 30 mg/kg.

93. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 10 mg/kg.

94. The composition for use of any of the preceding embodiments, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 30 mg/kg.

95. The composition for use of any of the preceding embodiments, wherein administration occurs daily, weekly, or monthly.

96. The composition for use of any of the preceding embodiments, wherein administration occurs once daily or twice daily.

97. The composition for use of any of the preceding embodiments, wherein administration occurs once daily.

98. The composition for use of any of the preceding embodiments, wherein administration occurs twice daily.

99. The composition for use of any of the preceding embodiments, wherein administration occurs once weekly, twice weekly, or three times weekly.
100. The composition for use of any of the preceding embodiments, wherein administration occurs once weekly.
101. The composition for use of any of the preceding embodiments, wherein administration occurs twice weekly.
102. The composition for use of any of the preceding embodiments, wherein administration occurs three times weekly.
103. The composition for use of any of the preceding embodiments, wherein the subject is obese, e.g., severely obese.
104. The composition for use of any of the preceding embodiments, wherein the subject is hyperphagic.
105. The composition for use of any of the preceding embodiments, wherein the subject has a body mass index greater than 35 kg/m^2 (e.g., 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 kg/m^2 or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.
106. The composition for use of any of the preceding embodiments, wherein the subject has a body mass index greater than 40 kg/m^2 (e.g., ≥ 41 , 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.
107. The composition for use of any of the preceding embodiments, wherein the subject has a body mass index greater than 45 kg/m^2 (e.g., ≥ 46 , 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.
108. The composition for use of any of the preceding embodiments, wherein the subject has an additional genetic deficiency, e.g., an additional genetic metabolic deficiency.

109. The composition for use of any of the preceding embodiments, wherein the subject has diabetes or a diabetological condition, e.g., pre-diabetes, diabetes mellitus type 1, diabetes mellitus type 2, hyperglycemia, hypoglycemia, hyperinsulinemia, hyperleptinemia.

110. The composition for use of any of the preceding embodiments, wherein the subject has high blood pressure, e.g., the subject has high diastolic and/or systolic blood pressure.

111. The composition for use of any of the preceding embodiments, wherein the subject has failed one or more previous therapies comprising exercise, diet or behavior modification therapies prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of administration.

112. The composition for use of any of the preceding embodiments, wherein the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof.

113. The composition for use of any of the preceding embodiments, wherein the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dose of 10 mg/kg after 28 days or longer.

114. The composition for use of any of the preceding embodiments, wherein the subject exhibits weight loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dose of 30 mg/kg after 28 days or longer.

115. The composition for use of any of the preceding embodiments, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle).

116. The composition for use of any of the preceding embodiments, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 28 days or longer.

117. The composition for use of any of the preceding embodiments, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 28 days or longer.

118. The composition for use of any of the preceding embodiments, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle).

119. The composition for use of any of the preceding embodiments, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose an oral daily dose of 10 mg/kg after 28 days or longer.

120. The composition for use of any of the preceding embodiments, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose an oral daily dose of 30 mg/kg after 28 days or longer.

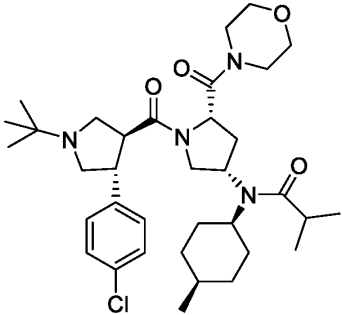
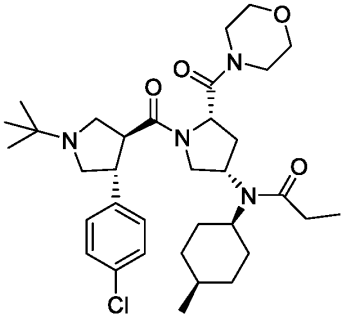
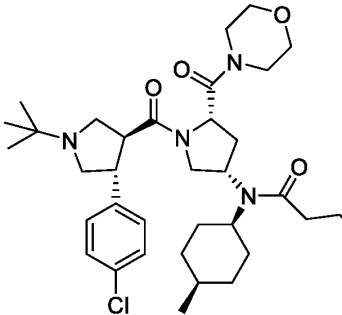
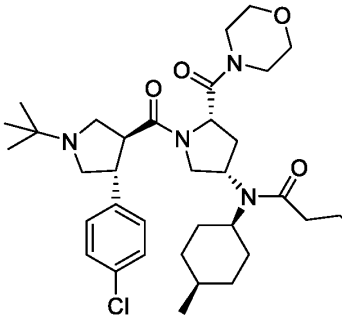
121. The composition for use of any of the preceding embodiments, wherein the compound of Formula 1 is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

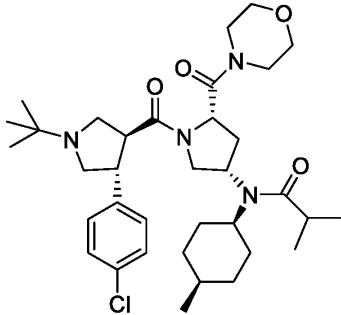
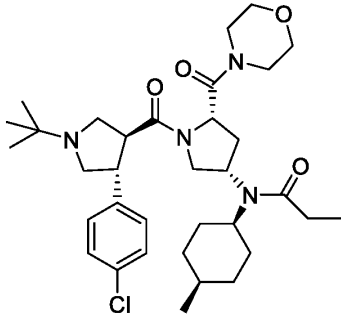
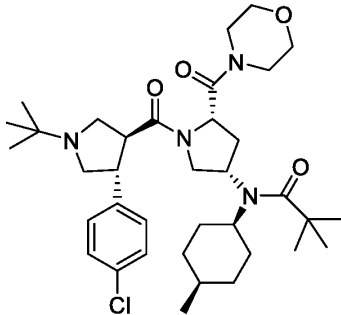
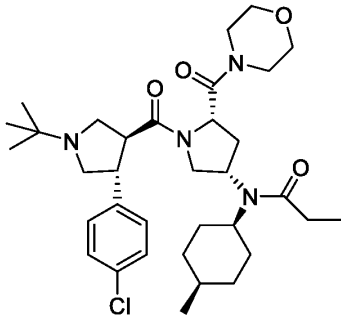
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide;

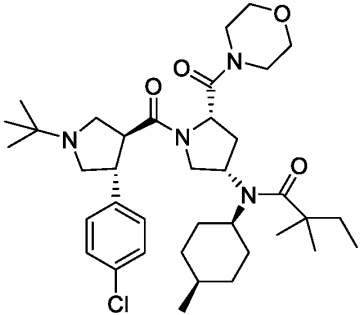
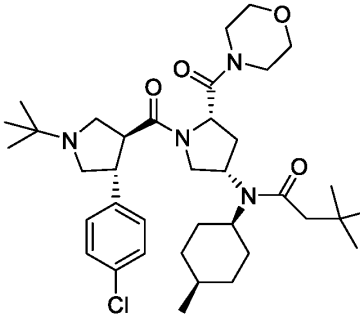
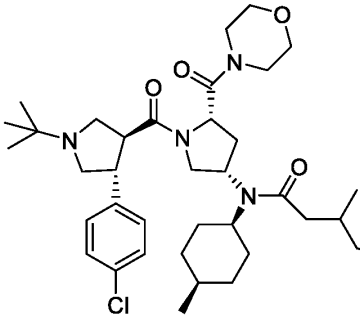
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; and
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide,
 or a pharmaceutically acceptable salt thereof.

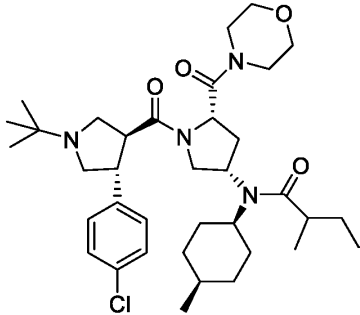
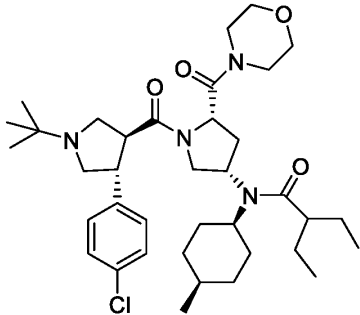
122. The composition for use of any of the preceding embodiments, wherein the compound of Formula 1 is selected from a compound having one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

Cmd No.	Structural Formula
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Cmd No.	Structural Formula
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101	
102	
103	

Cmd No.	Structural Formula
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Cmd No.	Structural Formula
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109	
110	

Cmd No.	Structural Formula
111	
112	

123. The composition for use of any of the preceding embodiments, wherein the compound of Formula 1 is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide; and

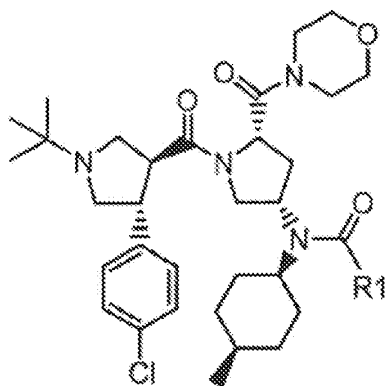
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide.

124. The composition for use of any of the preceding embodiments, wherein the compound of Formula 1 is selected from one of the following compounds:

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)propionamide hydrochloride;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride; and
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*s*,4*R*)-4-methylcyclohexyl)pivalamide hydrochloride.

CLAIMS

1. A method of treating a disease or disorder in a subject, wherein the disease or disorder is associated with a SH2B1 deficiency or a heterozygous leptin receptor (LEPR) deficiency, the method comprising administering to the subject a compound of Formula 1 or a pharmaceutically acceptable salt thereof:



wherein R1 is C₂-C₅ alkyl,
thereby treating a disease or disorder in the subject.

2. The method of claim 1, wherein the subject has a disease or disorder associated with SH2B1 deficiency.
3. The method of claim 2, wherein the subject having the SH2B1 deficiency is homozygous (SH2B1^{-/-}) or heterozygous (SH2B1^{+/-}).
4. The method of claim 3, wherein the subject having SH2B1 deficiency is homozygous (SH2B1^{-/-}).
5. The method of claim 3, wherein subject having the SH2B1 deficiency is heterozygous (SH2B1^{+/-}).
6. The method of claim 1, wherein the subject has a disease or disorder associated with a heterozygous LEPR deficiency.

7. The method of claim 6, wherein the subject having the heterozygous LEPR deficiency is heterozygous (LEPR+/-).
8. The method of claim 1, wherein the disease or disorder comprises obesity or metabolic syndrome.
9. The method of claim 8, wherein the disease or disorder comprises obesity.
10. The method of claim 8, wherein the disease or disorder comprises metabolic syndrome.
11. The method of claim 1, wherein the subject has been identified as having either a SH2B1 deficiency or a leptin receptor (LEPR) deficiency.
12. The method of claim 1, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is formulated as a pharmaceutical composition, together with a pharmaceutically acceptable carrier.
13. The method of claim 12, wherein the pharmaceutical composition is formulated as a dosage form, e.g., a unit dosage form.
14. The method of claim 13, wherein the dosage form is a solid dosage form.
15. The method of claim 12, wherein the pharmaceutical composition is formulated as an oral dosage form.
16. The method of claim 15, wherein the oral dosage form comprises a capsule, a tablet, a pill, a powder, or a granule.
17. The method of claim 16, wherein the oral dosage form comprises a capsule.
18. The method of claim 16, wherein the oral dosage form comprises a tablet.
19. The method of claim 13, wherein the dosage form is formulated as a transdermal dosage form.

20. The method of claim 19, wherein the transdermal dosage form comprises a lotion, ointment, gel, cream, patch or spray.
21. The method of claim 1, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is administered to the subject at a dosage between about 0.1 mg to about 500 mg.
22. The method of claim 21, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg.
23. The method of claim 21, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg to about 50 mg.
24. The method of claim 23, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 10 mg to about 30 mg.
25. The method of claim 24, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 10 mg.
26. The method of claim 24, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 30 mg.
27. The method of claim 1, wherein the compound of Formula 1, or a pharmaceutically acceptable salt thereof, is administered to the subject at a dosage between about 0.1 mg/kg to about 500 mg/kg.
28. The method of claim 27, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or 500 mg/kg.
29. The method of claim 27, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 1 mg/kg to about 50 mg/kg.

30. The method of claim 29, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is between about 10 mg/kg to about 30 mg/kg.
31. The method of claim 30, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 10 mg/kg.
32. The method of claim 30, wherein the dosage of Formula 1, or a pharmaceutically acceptable salt thereof, administered to the subject is 30 mg/kg.
33. The method of claim 1, wherein administration occurs daily, weekly, or monthly.
34. The method of claim 1, wherein administration occurs once daily or twice daily.
35. The method of claim 34, wherein administration occurs once daily.
36. The method of claim 34, wherein administration occurs twice daily.
37. The method of claim 1, wherein administration occurs once weekly, twice weekly, or three times weekly.
38. The method of claim 37, wherein administration occurs once weekly.
39. The method of claim 37, wherein administration occurs twice weekly.
40. The method of claim 37, wherein administration occurs three times weekly.
41. The method of claim 1, wherein the subject is obese, e.g., severely obese.
42. The method of claim 1, wherein the subject is hyperphagic.
43. The method of claim 1, wherein the subject has a body mass index greater than 35 kg/m² (e.g., 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.

44. The method of claim 1, wherein the subject has a body mass index greater than 40 kg/m² (e.g., $\geq 41, 42, 43, 44, 45, 46, 47, 48, 49, 50$ kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.
45. The method of claim 1, wherein the subject has a body mass index greater than 45 kg/m² (e.g., $\geq 46, 47, 48, 49, 50, 51, 52, 53, 54, 55$ kg/m² or greater), prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of the first administration.
46. The method of claim 1, wherein the subject has an additional genetic deficiency, e.g., an additional genetic metabolic deficiency.
47. The method of claim 1, wherein the subject has diabetes or a diabetological condition, e.g., pre-diabetes, diabetes mellitus type 1, diabetes mellitus type 2, hyperglycemia, hypoglycemia, hyperinsulinemia, hyperleptinemia.
48. The method of claim 1, wherein the subject has high blood pressure, e.g., the subject has high diastolic and/or systolic blood pressure.
49. The method of claim 1, wherein the subject has failed one or more previous therapies comprising exercise, diet or behavior modification therapies prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, or at the time of administration.
50. The method of claim 1, wherein the subject exhibits loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%, 2\%, 3\%, 4\%, 5\%, 6\%, 7\%, 8\%, 9\%, 10\%, 11\%, 12\%, 13\%, 14\%, 15\%$ or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof.
51. The method of claim 50, wherein the subject exhibits loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%, 2\%, 3\%, 4\%, 5\%, 6\%, 7\%, 8\%, 9\%, 10\%, 11\%, 12\%, 13\%, 14\%, 15\%$ or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dose of 10 mg/kg after 28 days or longer.

52. The method of claim 50, wherein the subject exhibits loss equal to or greater than 1% of the subject's body weight (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% or greater) prior to administration of the compound of Formula 1, or a pharmaceutically acceptable salt thereof, at an oral daily dose of 30 mg/kg after 28 days or longer.

53. The method of claim 1, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle).

54. The method of claim 53, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle), at an oral daily dose of 10 mg/kg after 28 days or longer.

55. The method of claim 53, wherein the subject exhibits an appetite suppressing effect of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%), compared to a reference standard, e.g., the solvent administered control group (Vehicle), at an oral daily dose of 30 mg/kg after 28 days or longer.

56. The method of claim 1, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle).

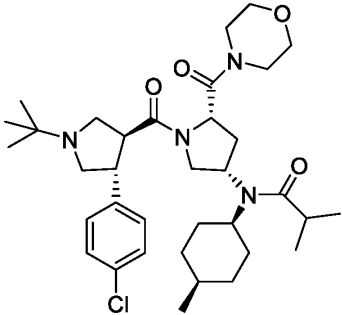
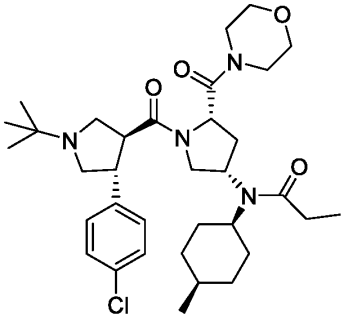
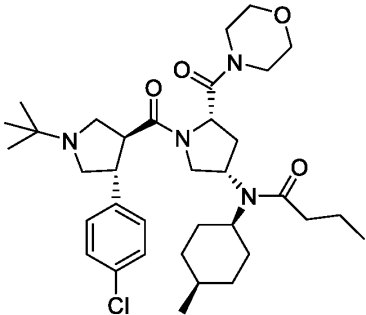
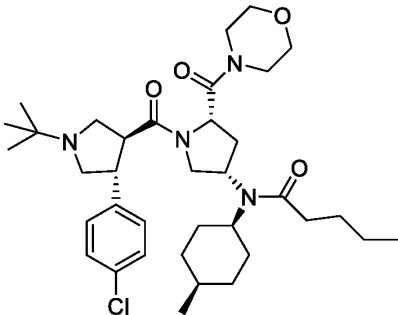
57. The method of claim 56, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose an oral daily dose of 10 mg/kg after 28 days or longer.

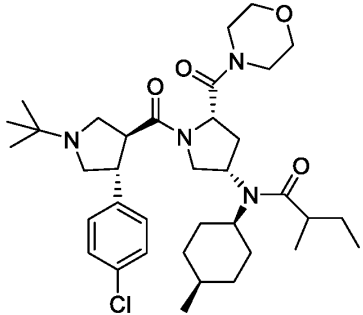
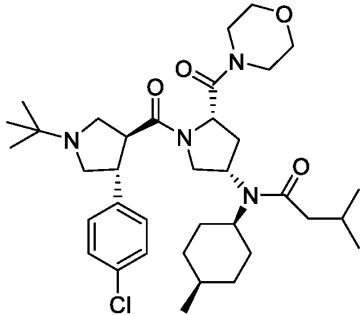
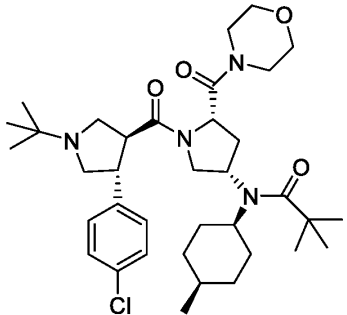
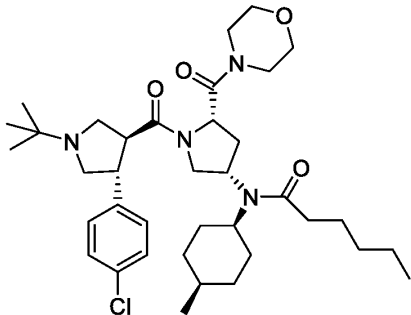
58. The method of claim 56, wherein the subject exhibits a decrease in food intake of about 1% or greater (e.g., $\geq 1\%$, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, or greater), compared to a reference standard, e.g., the solvent-administered control group (Vehicle), at an oral daily dose an oral daily dose of 30 mg/kg after 28 days or longer.

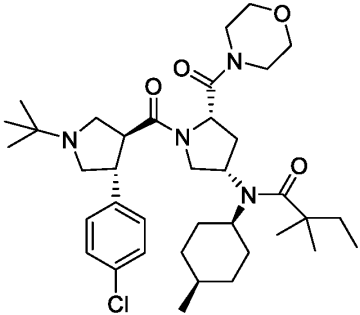
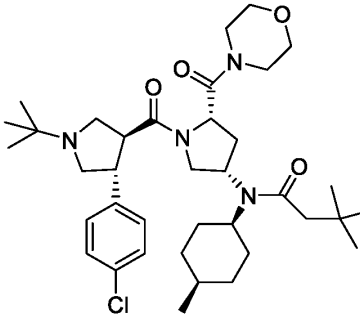
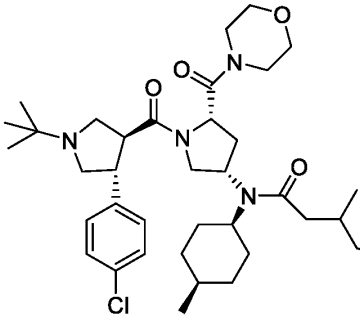
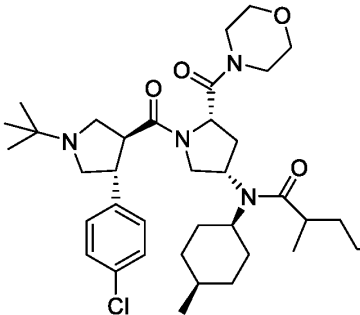
59. The method of claim 1, wherein the compound of Formula 1 is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

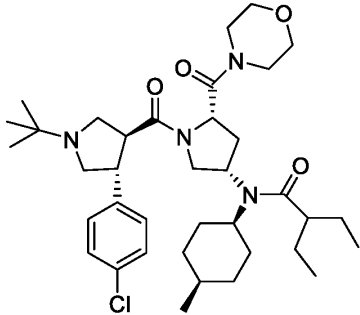
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butyramide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)hexanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2,2-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3,3-dimethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide;
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-3-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-methyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pentanamide; and
N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-2-ethyl-*N*-((1*S*,4*R*)-4-methylcyclohexyl)butanamide,
or a pharmaceutically acceptable salt thereof.

60. The method of claim 1, wherein the compound of Formula 1 is selected from a compound having one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

Cmd No.	Structural Formula
100	
101	
102	
103	

Cmd No.	Structural Formula
104	
105	
106	
107	

Cmd No.	Structural Formula
108	
109	
110	
111	

Cmd No.	Structural Formula
112	

61. The method of claim 1, wherein the compound of Formula 1 is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide; and

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide.

62. The method of claim 61, wherein the compound of Formula 1 is selected from one of the following compounds:

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide hydrochloride;

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride; and

N-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide hydrochloride.