

TREATMENT FOR THE SYMPTOMS OF MENOPAUSE AND PERIMENOPAUSE

BACKGROUND

[0001] Menopause is defined as the permanent cessation of menstrual activity
5 resulting from the loss of follicular function. In general, menopause occurs when estrogen
and progesterone levels are low. During the menopausal transition (also referred to as
perimenopause), the ovaries begin to work less effectively and the production of
hormones like estrogen and progesterone declines over time. Such changes can cause an
extended period (often years) during which a woman's the body's thermal regulation
10 mechanism can be, relatively, severely dysregulated during the perimenopausal period of
transition. These changes in thermal regulation lead to hot flashes and other menopausal
symptoms that can be extremely disruptive daily, often striking unexpectedly and
impacting both daily and nighttime activities, such as sleep. Up to 80% of women
experience significant perimenopause symptoms and it is estimated that by 2030 the
15 number of peri- and post- menopausal women will reach 1.2 billion globally.

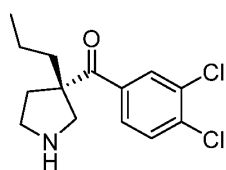
[0002] Menopause symptoms have historically been treated primarily by hormone
replacement therapy (HRT). Historically, HRT using estrogen and estrogen/progestin
drug products (e.g., conjugated equine estrogens, estradiols, and estropipates) have been
provided to women for controlling symptoms of menopause including hot flashes;
20 however, multiple side effects were found, including nausea, headaches, and mood
changes. More recently, care providers are reluctant to prescribe and women have become
reluctant to undertake the HRT therapy due to data indicating a significant correlation
between HRT and an increased incidence of heart disease, stroke, blood clots, and breast
cancer. For this reason, many women are left with few effective alternatives to HRT for
25 controlling their hot flashes.

[0003] Given that the natural progression of menopause occurs for nearly all healthy
women between the ages of 40 and 65, with some experiencing extreme symptoms, and
the contraindication and/or serious side effects of HRT, a safe non-hormonal treatment
for the symptoms of perimenopause and menopause presents a large and unmet medical
30 need.

SUMMARY

[0004] We have discovered a non-hormonal therapeutic compound, Compound 1, that relieves the symptoms of perimenopausal syndrome (PMPS). Treatments of the invention alleviate symptoms that occur in perimenopause, menopause, and post menopause, including hot flashes and night sweats experienced by about 80% of women, many of whom are not considered good candidates for HRT. In addition, the methods of the invention provide for treatment in subjects having VMS, for reasons other than age-related PMPS.

[0005] The present invention presents methods of treating subjects manifesting at least one symptom associated with menopause or post-menopause, wherein the symptom is a vasomotor symptom, a cognitive symptom, a nervous system symptom, an emotional symptom, or a physical symptom, and the method includes administering a composition comprising Compound 1 to the subject,

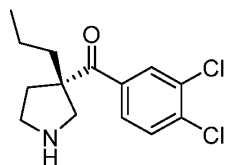


(Compound 1), or a pharmaceutically acceptable salt thereof,

sufficient to improve at least one symptom associated with menopause or post-menopause in the subject. In certain aspects, the subject is about 40 to about 65 years of age. In certain aspects, the subject experiences age related menopause or natural menopause from the natural aging process. In certain aspects the subject experiences a symptom (a vasomotor symptom, a cognitive symptom, a nervous system symptom, an emotional symptom, or a physical symptom), leading up to menopause. In other aspects, the subject experiences a symptom (a vasomotor symptom, a cognitive symptom, a nervous system symptom, an emotional symptom, or a physical symptom) after menopause, for example in post-menopause. The subject may experience at least one symptom weeks, months, or even years after menopause or the cessation of menstrual periods. In certain aspects, the subject has a low estrogen level. In certain embodiments, the treatment also suppresses appetite in the subject.

[0006] The disclosure also provides for methods of treating subjects manifesting at least one symptom associated with perimenopause, wherein the symptom is a vasomotor symptom, a cognitive symptom, a nervous system symptom, an emotional symptom, or a

physical symptom, and the method includes administering a composition comprising Compound 1 to the subject,



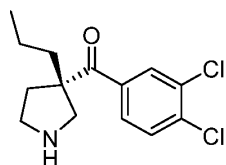
(Compound 1), or a pharmaceutically acceptable salt thereof,

sufficient to improve at least one symptom associated with perimenopause in the subject.

- 5 In certain aspects, the subject is about 40 to about 65 years of age. In certain aspects, the subject experiences age related perimenopause, or natural perimenopause from the natural aging process. In certain aspects, the subject has a low estrogen level. In certain aspects, the subject experiences a symptom associated with perimenopause several years before menopause. In certain aspects, the subject experiences a symptom associated with
- 10 perimenopause three to five years before menopause.

[0007] In addition, the disclosure also provides methods of treating subjects manifesting at least one symptom associated with induced-menopause, wherein the symptom is a vasomotor symptom, a cognitive symptom, a nervous system symptom, an emotional symptom, or a physical symptom, and the method includes administering a

15 composition comprising Compound 1 to the subject,



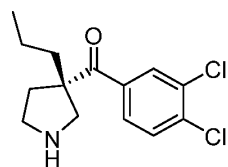
(Compound 1), or a pharmaceutically acceptable salt thereof,

sufficient to improve at least one symptom associated with induced-menopause in the subject. In certain aspects, induced menopause occurs or results from the subject having chemotherapy. In other aspects, induced menopause occurs or results from the subject

20 having surgical removal of one or both ovaries. In other aspects, induced menopause occurs or results from the subject having a surgery that impairs the function of one or both ovaries. In certain aspects, induced menopause occurs or results from the subject having radiotherapy. In some embodiments, induced menopause occurs or results from the subject taking or being administered a drug or medication.

- 25 [0008] The disclosure provides methods of treating subjects manifesting at least one symptom associated with early onset menopause or early onset perimenopause, wherein

the symptom is a vasomotor symptom, a cognitive symptom, a nervous system symptom, an emotional symptom, or a physical symptom, and the method includes administering a composition comprising Compound 1 to the subject,



(Compound 1), or a pharmaceutically acceptable salt thereof,

- 5 sufficient to improve at least one symptom associated with early onset menopause or early onset perimenopause in the subject. In certain aspects, the early onset menopause or early onset perimenopause results from the subject smoking or having a weight loss. In other aspects, the early onset menopause or early onset perimenopause results from the subject having a chromosomal defect, an autoimmune disease, or a thyroid disease. In some
10 embodiments, the early onset menopause or early onset perimenopause results from the subject having a low estrogen level. In other aspects, the early onset menopause or early onset perimenopause results from the subject have damage to one or both ovaries. In some aspects, the subject is younger than age 40.

[0009] In certain aspects, the vasomotor symptom is hot flashes, night sweats, and
15 heart palpitations, or a combination thereof.

[0010] In other aspects, the cognitive symptom is a cognitive executive dysfunction, and hypomnesia, or a combination thereof; wherein the cognitive executive dysfunction is selected from the group consisting of an impairment of working memory, an impairment of cognitive flexibility, and an impairment of inhibition control. In some
20 embodiments, the cognitive symptom is brain fog.

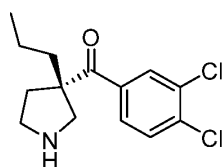
[0011] The disclosure provides methods of treating subjects suffering from brain fog. In some embodiments, the subject is suffering from brain fog over a period of 1, 2, 3, 4, or 5 minutes. In some embodiments, the subject is suffering from brain fog over a period of 1, 2, 3, 4, or 5 hours. In some embodiments, the subject is suffering from brain fog
25 over a period of 1, 2, 3, 4, or 5 days. In some embodiments, the subject is suffering from brain fog over a period of 1, 2, 3, 4, or 5 weeks. In some embodiments, the subject is suffering from brain fog over a period of 1, 2, 3, 4, or 5 months. In some embodiments, the subject is suffering from brain fog over a period of time until medical intervention.

[0012] In some embodiments, the nervous system symptom is fatigue, dizziness, a sleep-wake disorder, and appetite changes, or a combination thereof; wherein the sleep-wake disorder is selected from the group consisting of insomnia, somniphobia, and excessive daytime sleepiness.

5 [0013] In certain aspects, the emotional symptom is irritability, anxiety, depression, low mood, lack of motivation, mood swings, and panic disorder, or a combination thereof; wherein low mood is selected from the group consisting of sadness, feeling anxious or panicky, worry, tiredness, low self-esteem, frustration, and anger.

[0014] In other aspects the physical symptom is vulvar and vaginal atrophy, bleeding
10 associated with sexual activity, symptoms resulting from musculoskeletal changes, symptoms caused by urogenital changes, irregular periods, weight gain, bloating, sore breasts, headaches, electric shock sensations, burning tongue, gum problems, dry and itchy skin, loss of hair, brittle nails, changes in body odor, and allergies, or combinations thereof; wherein the symptoms associated with vulvar and vaginal atrophy is selected
15 from the group consisting of vaginitis, vaginal dryness, loss of libido, and vaginal pain associated with sexual activity; wherein the bleeding associated with sexual activity is selected from the group consisting of dyspareunia, dysuria, vaginal infections, pruritus, and dryness, irritation, itching, and/or burning in and around the vaginal area; wherein the symptoms resulting from musculoskeletal changes is selected from the group
20 consisting of myalgia, muscle pain, joint pain, arthralgia, and back pain; wherein the symptoms caused by urogenital changes is changes in urinary frequency or urinary incontinence.

[0015] The disclosure provides methods of treating subjects manifesting a vasomotor symptom, where the method includes administering a composition comprising
25 Compound 1 to the subject, wherein Compound 1 has the structure:

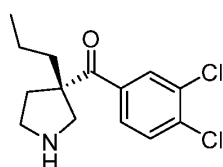


(Compound 1), or a pharmaceutically acceptable salt thereof,

sufficient to reduce at least one of symptom associated with vasomotor symptoms in the subject, wherein a vasomotor symptom is hot flashes, night sweats, and heart palpitations. In certain aspects, the vasomotor symptom is hot flashes. In other aspects, the vasomotor

symptom is night sweats. In other aspects, the symptoms are hot flashes and night sweats. In other aspects, the symptoms are heart palpitations. In some embodiments, the subject manifests hot flashes, night sweats, and heart palpitations. In some aspects, the subject has a low estrogen level.

- 5 [0016] The disclosure provides methods of treating subjects manifesting a vasomotor symptom and also having weight gain, where the method includes administering a composition comprising Compound 1 to the subject, wherein Compound 1 has the structure:



(Compound 1), or a pharmaceutically acceptable salt thereof,

- 10 sufficient to reduce at least one of symptom associated with vasomotor symptoms in the subject and also reduce the subject's weight, wherein a vasomotor symptom is hot flashes, night sweats, and heart palpitation. In certain aspects, the vasomotor symptom is hot flashes. In other aspects, the vasomotor symptom is night sweats. In other aspects, the symptoms are hot flashes and night sweats. In other aspects, the symptoms are heart
15 palpitations. In some embodiments, the subject manifests hot flashes, night sweats, and heart palpitations. In some aspects, the subject has a low estrogen level.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0017] FIG. 1 depicts an exemplary X-ray powder diffraction pattern of a
20 hydrochloride quarterhydrate of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone.

[0018] FIG. 2 depicts an exemplary X-ray powder diffraction pattern of a hydrochloride of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone.

- [0019] FIG. 3 depicts a mean ($\pm$ SEM) of chow intake (in grams) by adult male
25 Sprague Dawley rats (n=31) during a 30-minute session, where $^{***}p<0.001$: significant between groups effect of treatment on chow consumption between Compound 1 and vehicle (VEH).

- [0020] FIG. 4 depicts a mean ($\pm$ SEM) of total lever presses by adult male Sprague Dawley rats ($n = 31$) during a 30-minute session, where $^{***}p < 0.001$: significant difference between Compound 1 treatments and vehicle (VEH) on lever presses.
- [0021] FIG. 5 depicts a mean ($\pm$ SEM) of total lever presses by adult male Sprague Dawley rats ($n = 31$) during a 30-minute operant session, where $^{***}p < 0.001$: significant difference between Compound 1 treatments ($n=16$) and vehicle (VEH) ($n=15$) on lever presses.
- [0022] FIG. 6. depicts a mean ($\pm$ SEM) of latency to the first 6 continuous epochs of nonrapid eye movement sleep (NR).
- 10 [0023] FIG. 7. depicts a mean ($\pm$ SEM) of latency to the first 3 continuous epochs of rapid eye movement sleep (REM).
- [0024] FIG. 8 and FIG. 9 depict effect of Compound 1 on chocolate intake. FIGS 8 and 9 illustrate that Compound 1 is effective in controlling binge eating in animal model.
- [0025] FIG. 10A and FIG. 10B depict the five-choice serial-reaction time task (5CSRTT) test in rats to study impulsive behaviors in rats. FIGS 10A and 10B illustrate that Compound 1 reduces impulsive behaviors in rats and that Compound 1 dose-dependently reduced premature and perseverative responses with no adverse effects on accuracy or speed of responding.
- 15 [0026] FIG. 11 depicts an SRTM model of Compound 1 plasma concentration versus SERT occupancy in Raphe Nuclei as a result of a PET study in HVs. FIG. 11 illustrates that there is 70% to 90% SERT occupancy at 30 mg to 60 mg of Compound 1.
- [0027] FIG. 12 depicts a 2TCM model of Compound 1 plasma concentration versus DAT occupancy in the striatum. FIG. 12 illustrates that there is 25% to 40% DAT occupancy at 30 mg to 60 mg of Compound 1.
- 25 [0028] FIG. 13 depicts mean ($\pm$ SEM) intake of chocolate over the 12 1-hour training sessions during the chocolate intake experiment described in Example 7.
- [0029] FIG. 14 and FIG. 15 depict effects of Compound 1 on lever pressing and chow consumption of high ($n=15$) and low ($n=16$) responder groups in PROG/Chow feeding choice task. FIG. 14 depicts a mean ($\pm$ SEM) number of total lever presses during a 30-minute session, where $^{***}p < 0.001$: significant difference between Compound 1 dose treatments and VEH on lever presses. FIG. 15 depicts a mean ($\pm$ SEM) of chow intake (in grams) during a 30-minute session, where $^{***}p < 0.001$, $^{*}p < 0.01$: significant difference
- 30

between groups effect of treatment on chow consumption between dose Compound 1 and VEH.

DETAILED DESCRIPTION

[0030] Disclosed herein is a non-hormonal compound, Compound 1, that relieves,
5 improves, alleviates, lessens, or prevents at least one symptom of natural menopause, post-menopause or perimenopause, and also early onset menopause, post-menopause, or perimenopause, and also induced-menopause or induced-perimenopause.

I. Definitions

[0031] To facilitate an understanding of the present disclosure, a number of terms
10 and phrases are defined below.

[0032] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth
15 herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0033] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that,
20 additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0034] The articles “a” and “an” are used in this disclosure to mean one or more than one (i.e., at least one) of the grammatical object of the article, unless the context is
25 inappropriate. By way of example, “an element” means one element or more than one element.

[0035] The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

[0036] The expression “and/or” in connection with three or more recited objects should be understood to have the same meaning unless otherwise understood from the context.

[0037] Where the use of the term “about” is before a quantitative value, the present invention also includes the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term “about” refers to a $\pm 10\%$ variation from the nominal value unless otherwise indicated or inferred from the context.

[0038] The use of the term “comprise,” “comprises,” “comprising,” “include,” “includes,” “including,” “have,” “has,” “having,” “contain,” “contains,” or “containing,” including grammatical equivalents thereof, should be understood generally as open-ended and non-limiting, for example, not excluding additional unrecited elements or steps, unless otherwise specifically stated or understood from the context.

[0039] In the present invention, variable or parameters are disclosed in groups or in ranges. It is specifically intended that the description include each and every individual subcombination of the members of such groups and ranges. For example, an integer in the range of 0 to 40 is specifically intended to individually disclose 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, and 40, and an integer in the range of 1 to 20 is specifically intended to individually disclose 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20.

[0040] As used herein, “administering” means oral administration, administration as a suppository, topical contact, intravenous administration, parenteral administration, intraperitoneal administration, intramuscular administration, intralesional administration, intrathecal administration, intracranial administration, intranasal administration, transmucosal administration (e.g., buccal, sublingual, nasal, or transdermal), or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Parenteral administration includes, e.g., intravenous, intramuscular, intra-arterial, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc.

[0041] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

[0042] As used herein, “composition” or “pharmaceutical composition” or
5 “pharmaceutical formulation” means a combination of an active agent with an excipient or a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0043] “Pharmaceutically acceptable” mean compounds, molecular entities,
compositions, materials and/or dosage forms that do not produce an adverse, allergic or
10 other untoward reaction when administered to an animal, or a human, as appropriate, and/or that are approved or approvable by a regulatory agency of the federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0044] As used herein, “pharmaceutically acceptable salt” mean any salt of an acidic
or a basic group that may be present in a compound of the present invention (e.g.,
Compound 1), which salt is compatible with pharmaceutical administration.

[0045] As used herein, “Acids” means hydrochloric, hydrobromic, sulfuric, nitric,
perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-
20 sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic,
malonic, naphthalene-2-sulfonic and benzenesulfonic acid. Other acids, such as oxalic,
while not in themselves pharmaceutically acceptable, may be employed in the preparation
of salts useful as intermediates in obtaining the compounds described herein and their
pharmaceutically acceptable acid addition salts.

[0046] As used herein, “Bases” means alkali metal (e.g., sodium and potassium)
hydroxides, alkaline earth metal (e.g., magnesium and calcium) hydroxides, ammonia,
and compounds of formula NW_4^+ , wherein W is C_{1-4} alkyl, and the like.

[0047] As used herein, “Salts” means acetate, adipate, alginate, aspartate, benzoate,
benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate,
30 cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate,
flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride,
hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate,

methanesulfonate, monosulfate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as

5 Na⁺, K⁺, Ca²⁺, NH₄⁺, and NW₄⁺ (where W can be a C₁₋₄ alkyl group), and the like.

[0048] For therapeutic use, salts of the compounds of the present invention are pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

10 **[0049]** As used herein, “pharmaceutically acceptable excipient” means a substance that aids the administration of an active agent to and/or absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, such as a phosphate

15 buffered saline solution, emulsions (e.g., such as an oil/water or water/oil emulsions), lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations

20 can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. For examples of excipients, *see* Martin, Remington’s Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA

25 (1975).

[0050] A “subject” to which administration is contemplated includes, but is not limited to, humans (i.e., a patient of any age group) and/or a non-human animal, e.g., a mammal such as primates (e.g., cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments of the present

30 invention, the subject is a human. In certain embodiments of the present invention, the subject is a non-human animal. In certain embodiments of the present invention, the subject is a female.

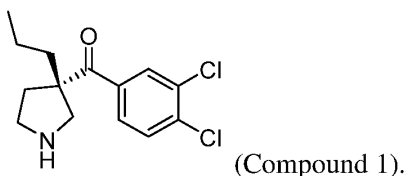
[0051] As used herein, and unless otherwise specified, the terms “treat,” “treating” and “treatment” include an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition (e.g., “therapeutic treatment”). “Treat,” “treating” and “treatment”, as used
5 herein, can include any effect, for example, lessening, reducing, modulating, ameliorating, or eliminating, that results in the improvement of the symptoms, including one or more symptoms thereof. Treating can be improving or partially ameliorating the disorder. In some embodiments, the methods of the present disclosure treat a subject
10 manifesting severe vasomotor symptoms, wherein the severe vasomotor symptoms is a sensation of heat with sweating, causing cessation of activity.

[0052] As used herein, “improve,” “improving,” or “improvement” mean the reduction of the severity or frequency, or both, of the symptoms a subject is suffering from.

[0053] As used herein, “therapeutically effective amount” means the amount of a compound (e.g., Compound 1), or a pharmaceutically acceptable salt thereof, that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compound, or a pharmaceutically acceptable salt thereof, described in the present disclosure can be
20 administered in therapeutically effective amounts to treat a disease. A therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, can be the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in lessening of a symptom of a disorder such as hot flashes.

[0054] As used herein, “age-related condition” means a condition associated with
25 increased age of an individual. In various embodiments, “age-related condition” means perimenopause, menopause, or post-menopause in women as a result of increased age.

[0055] As used herein, a “Compound” refers to the pharmaceutically acceptable form of Compound 1, which can be represented by:



[0056] As used herein, a “co-therapeutic” means a second compound administered
5 in addition to the compound of the invention to a patient to treat at least one or more of the symptoms. One example of a co-therapeutic is hormone replacement therapy (HRT).

[0057] As used herein, “hormone replacement therapy,” or HRT, means administering of medications such as estrogen receptor blockers, aromatase inhibitors, luteinizing hormone-releasing hormone agonists, estrogen modulators, or estrogen
10 receptor blockers.

[0058] “Menopause,” as used herein, means a permanent cessation of menstrual periods (one year after the last menstrual period).

[0059] Natural menopause, or age related menopause means menopause that occurs naturally in subjects between the ages of 40 to 65. Menopause includes the period of time
15 in a subject’s life after menopause (one year after the last menstrual period), or post-menopause.

[0060] “Perimenopause,” or “menopausal transition,” as used herein, means the period of time prior to menopause (*e.g.*, approximately three to four years prior) and ends after the final menstrual period (*e.g.*, one year after) when hormonal and biological
20 changes and physical symptoms begin to occur in subjects. During perimenopause, estrogen levels may start to decrease and the body’s production of estrogen and progesterone may vary greatly. Perimenopause can be characterized by persistent irregular menstrual cycles, extreme fluctuations in hormonal levels, frequent anovulation and the appearance of vasomotor symptoms (VMS).

[0061] “Induced menopause,” as used herein, means menopause in a subject that is distinct from natural menopause and occurs as a result of surgically-induced menopause
25 (*e.g.*, bilateral oophorectomy, oophorectomy), chemotherapy, radiotherapy, drugs (anti-cancer, immunotherapeutic, hormonotherapeutic or endocrine therapeutic agents), cancer

treatments, chemically-induced menopause, drug-induced ovariectomy, iatrogenic-induced menopause, cancer treatment, or sex-change treatments, for example.

[0062] “Early onset menopause,” or “premature menopause,” as used herein means a permanent cessation of menstrual periods (one year after the last menstrual period) that occurs in subjects before the age of 40, that is not caused by induced menopause.

[0063] The term “vasomotor symptoms” or “VMS,” as used herein, means hot flashes, night sweats, and/or heart palpitations, or a combination thereof. The vasomotor symptoms can be categorized into mild vasomotor symptoms, moderate vasomotor symptoms, and severe vasomotor symptoms. Vasomotor symptoms severity has been defined based on the 2003 US Food and Drug Administration Guidance for Industry; the same definition used by the European Medicines Agency: (1) mild vasomotor symptoms is a sensation of heat without sweating; (2) moderate vasomotor symptoms is a sensation of heat with sweating, able to continue activity; and (3) severe vasomotor symptoms is a sensation of heat with sweating, causing cessation of activity. Vasomotor symptoms can be diagnosed or identified using one or more of the following assays: the Hot Flash Patient Diary, the Greene Climacteric Scale (GCS), the Hot Flash Related Daily Interference Scale (HFRDIS), and the MENopause-Specific Quality of Life (MENQOL).

[0064] The term “Hot Flash,” as used herein, means a core symptom of vasomotor symptoms. Hot flashes typically begin as the sudden sensation of heat centered on the upper chest and face. Hot flashes can be diagnosed or identified using the Hot Flash Patient Diary. When mild, the hot flashes are characterized by a sudden sensation of heat centered on the upper chest and face. When moderate or severe, the hot flashes rapidly become generalized, lasts from 2 to 4 minutes, and can be associated with profuse perspiration, palpitations, or anxiety – here, the physical generalizability delineates mild from moderate and severe VMS due to menopause.

[0065] The term “Cognitive Symptoms,” as used herein, means symptoms related to, being, or involving conscious intellectual activity (such as thinking, reasoning, or remembering). In embodiments, cognitive symptoms are selected from the group consisting of a brain fog, cognitive executive dysfunction, and hypomnesia, or a combination thereof; wherein the cognitive executive dysfunction is selected from the group consisting of an impairment of working memory, an impairment of cognitive flexibility, and an impairment of inhibition control. Cognitive symptoms can be

diagnosed or identified using one or more of the following assays: the Clinical Global Impression of Severity (CGI-S) and the Patient Global Impression of Change (PGI-C).

[0066] The term “Nervous System Symptoms,” as used herein, means symptoms related to, being, or involving a nervous system’s main function that connects the brain and body. In embodiments, nervous system symptoms are fatigue, dizziness, a sleep-wake disorder, and appetite changes, or a combination thereof; wherein the sleep-wake disorder includes insomnia, somniphobia, and excessive daytime sleepiness. Nervous system symptoms can be diagnosed or identified using one or more of the following assays: the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS), the Digit Symbol Substitution Test (DSST), and the Epworth Sleepiness Scale (ESS).

[0067] The term “Emotional Symptoms,” as used herein, means symptoms related to, being, or involving a feeling that arise from your mood, temperament, and reactions to situations. In embodiments, emotional symptoms are selected from the group consisting of irritability, anxiety, depression, low mood, lack of motivation, mood swings, and panic disorder, or a combination thereof; wherein low mood is selected from the group consisting of sadness, feeling anxious or panicky, worry, tiredness, low self-esteem, frustration, and anger. Emotional symptoms can be diagnosed or identified using one or more of the following assays: the Clinical Global Impression of Severity (CGI-S) and the Patient Global Impression of Change (PGI-C).

[0068] The term “Physical Symptoms,” as used herein, means symptoms related to, being, or involving a painful or uncomfortable feelings in the body. In embodiments, physical symptoms are selected from the group consisting of symptoms associated with vulvar and vaginal atrophy, bleeding associated with sexual activity, symptoms resulting from musculoskeletal changes, symptoms caused by urogenital changes, irregular periods, weight gain, bloating, sore breasts, headaches, electric shock sensations, burning tongue, gum problems, dry and itchy skin, loss of hair, brittle nails, changes in body odor, and allergies, or combinations thereof.

[0069] The term “Vulvar and Vaginal Atrophy,” as used herein, means vaginitis, vaginal dryness, loss of libido, and vaginal pain associated with sexual activity; wherein the bleeding associated with sexual activity is selected from the group consisting of

dyspareunia, dysuria, vaginal infections, pruritus, and dryness, irritation, itching, and/or burning in and around the vaginal area.

[0070] The term “Musculoskeletal Changes,” as used herein, means myalgia, muscle pain, joint pain, arthralgia, and back pain.

5 **[0071]** The term “Urogenital Changes,” as used herein, means changes in urinary frequency or urinary incontinence.

[0072] The term “weight gain,” or “gained weight,” as used herein, means an increase in body weight due to changes in body composition, such as fat, muscle, or fluids. The hormonal changes of menopause tend to make it more likely that women will gain
10 weight around the abdomen, rather than the hips and thighs. However, hormonal changes alone may not necessarily cause the weight gain. The weight gain could be related to aging, as well as lifestyle and genetic factors. In some embodiments, the method is treats subjects who have experienced any one of above symptoms (a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical
15 symptom) and has experienced a weight gain.

[0073] The term “brain fog,” as used herein, means a symptom related to mental fatigue associated with cognitive impairment. Brain fog can be described as slow thinking, difficulty focusing, confusion, lack of concentration, forgetfulness, or a haziness in thought processes. A subject with brain fog would have difficulty with learning new
20 skills, recalling information and words, handling periods of multitasking, thinking and responding quickly, focusing and maintaining clear thought, and following conversations and paying attention.

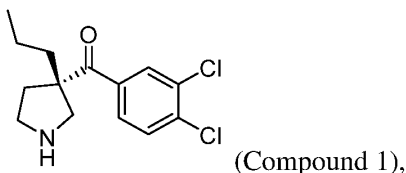
[0074] In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that
25 the element or component can be any one of the recited elements or components, or the element or component can be selected from the group consisting of two or more of the recited elements or components.

[0075] Further, it should be understood that elements and/or features of a composition or a method described herein can be combined in a variety of ways without
30 departing from the spirit and scope of the present invention, whether explicit or implicit herein. For example, where a reference is made to a particular compound, that compound can be used in various embodiments of methods of the present invention, unless otherwise

understood from the context. In other words, within this application, embodiments have been described and depicted in a way that enables a clear and concise application to be written and drawn, but it is intended and will be appreciated that embodiments may be variously combined or separated without parting from the present teachings and invention(s). For example, it will be appreciated that all features described and depicted herein can be applicable to all aspects of the invention(s) described and depicted herein. The use of any and all examples, or exemplary language herein, for example, “such as” or “including,” is intended merely to illustrate better the present invention and does not pose a limitation on the scope of the invention unless claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the present invention.

II. Methods of Use and Treatment

[0076] The disclosure is generally directed to methods of treating a subject manifesting at least one symptom associated with menopause (natural menopause, induced-menopause, and early onset menopause, including perimenopause and post-menopause) by administering Compound 1 to the subject,



or a pharmaceutically acceptable salt thereof.

[0077] Disclosed methods herein may be used to treat subjects manifesting at least one symptom associated with perimenopause, menopause and/or post-menopause, induced menopause, early onset menopause, or subjects unable to take a hormone replacement therapy.

[0078] It will be understood by those skilled in the art, based on the present disclosure, that compositions of the invention can suitably prevent, suppress, lessen, and/or treat symptoms of the subjects.

Menopause and induced-menopause

[0079] An aspect of the disclosure is to treat subjects manifesting various symptoms associated with menopause. Menopause is the permanent ending of menstrual periods in a subject, and this is considered to occur once a subject has gone one year or 12 months without a period. Post-menopause is considered the period of time after a subject reaches menopause (12 months from their last period) until the end of their life. Perimenopause means the period of time prior to reaching menopause, where hormonal and biological changes and physical symptoms begin to occur in subjects. This can take several months to several years, where subjects may be in the perimenopause phase for 3 to 5 years. During perimenopause, estrogen levels start to decrease and the body's production of estrogen and progesterone varies greatly. Perimenopause can be characterized by persistent irregular menstrual cycles, extreme fluctuations in hormonal levels, frequent anovulation and the appearance of vasomotor symptoms (VMS). Even after menopause, or post-menopause, subjects may experience at least one symptom associated with menopause for months, years, or until the end of their life.

[0080] Menopause is considered a natural aging process that occurs in subjects between the ages of 40 to 65. Perimenopause can begin several years before, usually 3 to 4 years before menopause.

[0081] Methods disclosed herein may be used to treat symptoms associated with natural menopause and/or post-menopause, or treat subjects who are at menopause (ceasing of menstrual periods) or who are in the post-menopause phase of life and who are experiencing or manifesting at least one symptoms associated with menopause. Methods disclosed herein may be used to treat symptoms associated with perimenopause, or treat subjects who are in perimenopause, or in the perimenopause phase of life and who are experiencing or manifesting at least one symptoms associated with menopause.

[0082] Subjects may experience menopause earlier in life. Early onset menopause, or premature menopause, means a permanent cessation of menstrual periods (one year after the last menstrual period) that occurs in subjects before the age of 40, that is not caused by induced menopause. Early onset menopause may be preceded by early onset perimenopause.

[0083] Besides the natural process of menopause that occurs from aging, early onset menopause may result from smoking, weight loss, chromosomal defects, autoimmune

diseases, thyroid diseases, low estrogen levels, diseases that interfere with ovarian function or hormone levels, or unknown factors that may be related to genetics, lifestyle or environmental exposure.

[0084] Methods disclosed herein may be used to treat symptoms associated with
5 early onset menopause and/or early onset post-menopause, or treat subjects who are at early onset menopause (ceasing of menstrual periods) or who are in the early onset post-menopause phase of life and who are experiencing or manifesting at least one symptoms associated with early onset menopause. Methods disclosed herein may be used to treat symptoms associated with early onset perimenopause, or treat subjects who are in early
10 onset perimenopause, or in the early onset perimenopause phase of life and who are experiencing or manifesting at least one symptom associated with menopause.

[0085] Subject treated by the disclosed methods herein may have induced menopause. Induced menopause is distinct from natural menopause and occurs from a type of medical intervention, medical treatment, or medical process. Induced menopause
15 may result from surgically-induced menopause (e.g., bilateral oophorectomy, single oophorectomy, or a surgery that affects ovarian hormone production), chemotherapy, radiotherapy, drugs (anti-cancer, immunotherapeutic, hormonotherapeutic or endocrine therapeutic agents, estrogen blockers such as tamoxifen), cancer treatments, chemically-induced menopause, drug-induced ovariectomy, iatrogenic-induced menopause, cancer
20 treatment, or sex-change treatments, for example.

[0086] In certain embodiments, the drug inducing menopause may be an estrogen receptor blocker. The list of medication includes, but not limited to, aromatase inhibitors, luteinizing hormone-releasing hormones (LHRH), and estrogen modulators. In some
25 embodiments, the aromatase inhibitors are selected from the group consisting of anastrozole, letrozole, and exemestane. In embodiments, the estrogen modulators are selected from tamoxifen and evista. Tamoxifen and evista are both used in cancer treatment, functioning by blocking estrogen receptors in vaginal tissue, causing lower levels of lubrication.

[0087] In some aspects, subjects treated by the disclosed methods may include
30 subjects that are unable to take Hormone Replacement Therapy. This may include subjects with an increased risk of gynecological or breast cancer onset or relapse. This

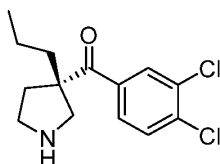
may include subjects that have transgender gender affirming care, and/or undergone a sex change.

[0088] In some aspects, subjects treated by the disclosed methods may include subjects that have low estrogen levels or a low estrogen level. In certain embodiments, a
5 low estrogen level is below about 30 pg/mL.

[0089] In some aspects, subjects treated by the disclosed methods may include subjects with damaged ovaries.

Symptoms associated with menopause and induced menopause

[0090] The disclosure is generally directed to methods of treating a subject
10 manifesting at least one symptom associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by administering Compound 1 to the subject,



(Compound 1),

or a pharmaceutically acceptable salt thereof. In one aspect, the methods of the present
15 disclosure contemplate that Compound 1 may be useful in methods of treating subjects manifesting at least one symptom associated with low estrogen level. In one aspect, the methods of the present disclosure contemplate that Compound 1 is useful in methods of treating subjects manifesting at least one symptom associated with low estrogen level.

[0091] In various embodiments, the disclosure provides methods of treating a subject
20 manifesting at least two symptoms associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by administering Compound 1 to the subject or a pharmaceutically acceptable salt thereof.

[0092] In various embodiments, the disclosure provides methods of treating a subject
25 manifesting at least three symptoms associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by administering Compound 1 to the subject or a pharmaceutically acceptable salt thereof.

[0093] In various embodiments, the disclosure provides methods of treating a subject manifesting at least four symptoms associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by administering Compound 1 to the subject or a pharmaceutically acceptable salt thereof.

[0094] It will be appreciated from one of skill in the art that the phrase “manifesting at least one symptom” means that the subject manifests one or more symptoms (e.g., one symptom, two symptoms, three symptoms, four symptoms, five symptoms, six symptoms, seven symptoms, eight symptoms, nine symptoms, and ten symptoms) selected from the group consisting of a vasomotor symptom, a cognitive symptom (e.g., brain fog), a nervous system symptom, an emotional symptom, and a physical symptom, including the symptoms as defined therein. For example, the subject manifesting at least one symptom may manifest two symptoms, wherein the symptoms are two vasomotor symptoms, two cognitive symptoms, two nervous system symptoms, two emotional symptoms, or two physical symptoms. In another example, the subject manifesting at least one symptom may manifest three symptoms, wherein the symptoms are two vasomotor symptoms and one cognitive symptom, or two cognitive symptoms and one vasomotor symptom. Yet in another example, the subject manifesting at least one symptom may manifest two symptoms, wherein the symptoms are hot flashes and night sweats, which are both vasomotor symptoms.

[0095] In another aspect, the methods of the present disclosure contemplate that Compound 1 is useful in methods of treating subjects manifesting at least one symptom associated with menopause and/or post-menopause. In some aspects, the subject manifests one symptom, two symptoms, three symptoms, four symptoms, five symptoms, or six symptoms.

[0096] In one aspect, the methods of the present disclosure contemplate that Compound 1 is useful in methods of treating subjects manifesting at least one symptom associated with perimenopause. In some aspects, the subject manifests one symptom, two symptoms, three symptoms, four symptoms, five symptoms, or six symptoms.

[0097] In certain aspects, the methods of the present disclosure contemplate that Compound 1 is useful in methods of treating subjects manifesting at least one symptom

associated with induced-menopause. In some aspects, the subject manifests one symptom, two symptoms, three symptoms, four symptoms, five symptoms, or six symptoms.

[0098] In certain aspects, the methods of the present disclosure contemplate that Compound 1 is useful in methods of treating subjects manifesting at least one symptom
5 associated with early onset menopause and/or early onset perimenopause. In some aspects, the subject manifests one symptom, two symptoms, three symptoms, four symptoms, five symptoms, or six symptoms.

[0099] A symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset perimenopause,
10 or low estrogen levels include a symptom such as a vasomotor symptom; a cognitive symptom (e.g., brain fog); a nervous system symptom; an emotional symptom; or a physical symptom, or any combination thereof.

[0100] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where
15 the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom.

[0101] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; a
20 nervous system symptom; an emotional symptom; and a physical symptom.

[0102] In another aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom.

25 [0103] In another aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause or early onset post-menopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom.

30 [0104] In another aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset perimenopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a

cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom. In some embodiments, the vasomotor symptom is selected from the group consisting of hot flashes, night sweats, and heart palpitations, or a combination thereof.

5 [0105] In some embodiments, the cognitive symptom is selected from the group consisting of a cognitive executive dysfunction, and hypomnesia, or a combination thereof; wherein the cognitive executive dysfunction is selected from the group consisting of an impairment of working memory, an impairment of cognitive flexibility, and an impairment of inhibition control.

10 [0106] In some embodiments, the nervous system symptom is selected from the group consisting of fatigue, dizziness, a sleep-wake disorder, and appetite changes, or a combination thereof; wherein the sleep-wake disorder is selected from the group consisting of insomnia, somnipathy, and excessive daytime sleepiness.

15 [0107] In some embodiments, the emotional symptom is selected from the group consisting of irritability, anxiety, depression, low mood, lack of motivation, mood swings, and panic disorder, or a combination thereof; wherein low mood is selected from the group consisting of sadness, feeling anxious or panicky, worry, tiredness, low self-esteem, frustration, and anger.

20 [0108] In some embodiments, the physical symptom is selected from the group consisting of symptoms associated with vulvar and vaginal atrophy, bleeding associated with sexual activity, symptoms resulting from musculoskeletal changes, symptoms caused by urogenital changes, irregular periods, weight gain, bloating, sore breasts, headaches, electric shock sensations, burning tongue, gum problems, dry and itchy skin, loss of hair, brittle nails, changes in body odor, and allergies, or combinations thereof; wherein the symptoms associated with vulvar and vaginal atrophy is selected from the group consisting of vaginitis, vaginal dryness, loss of libido, and vaginal pain associated with sexual activity; wherein the bleeding associated with sexual activity is selected from the group consisting of dyspareunia, dysuria, vaginal infections, pruritus, and dryness, irritation, itching, and/or burning in and around the vaginal area; wherein the symptoms resulting from musculoskeletal changes is selected from the group consisting of myalgia, muscle pain, joint pain, arthralgia, and back pain; wherein the symptoms caused by
30 urogenital changes is changes in urinary frequency or urinary incontinence.

[0109] In another aspect, the disclosure is directed to methods of treating a subject manifesting at least one vasomotor symptom by administering Compound 1 to the subject, wherein the vasomotor symptom is hot flashes, night sweats, and heart palpitations.

5 [0110] In one other aspect, provided herein are methods of treating a subject manifesting a vasomotor symptom and weight gain, by administering Compound 1 to the subject, wherein the vasomotor symptom is selected from the group consisting of hot flashes, night sweats, and heart palpitations.

[0111] In one aspect, the present disclosure includes methods of treating a subject
10 manifesting at least one symptom associated with menopause or post-menopause, where the symptom is a vasomotor symptom.

[0112] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where the symptom is a vasomotor symptom or a cognitive symptom.

15 [0113] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; and a nervous system symptom.

[0114] In one aspect, the present disclosure includes methods of treating a subject
20 manifesting at least one symptom associated with menopause or post-menopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; a nervous system symptom; and an emotional symptom.

[0115] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where
25 the symptom is a cognitive symptom.

[0116] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where the symptom is selected from the group consisting of: a cognitive symptom and a nervous system symptom.

30 [0117] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where

the symptom is selected from the group consisting of: a cognitive symptom; a nervous system symptom; and an emotional symptom.

[0118] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where
5 the symptom is selected from the group consisting of: a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom.

[0119] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where the symptom is a nervous system symptom.

10 [0120] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where the symptom is selected from the group consisting of: a nervous system symptom and an emotional symptom.

[0121] In one aspect, the present disclosure includes methods of treating a subject
15 manifesting at least one symptom associated with menopause or post-menopause, where the symptom is selected from the group consisting of: a nervous system symptom and a physical symptom.

[0122] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where
20 the symptom is selected from the group consisting of: a nervous system symptom; an emotional symptom; and a physical symptom.

[0123] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where the symptom is an emotional symptom.

25 [0124] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where the symptom is a physical symptom.

[0125] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with menopause or post-menopause, where
30 the symptom is selected from the group consisting of: an emotional symptom; and a physical symptom.

[0126] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is a vasomotor symptom.

5 [0127] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is a vasomotor symptom or a cognitive symptom.

[0128] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; and
10 a nervous system symptom.

[0129] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; a nervous system symptom; and an emotional symptom.

15 [0130] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is a cognitive symptom.

[0131] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is
20 selected from the group consisting of: a cognitive symptom and a nervous system symptom.

[0132] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: a cognitive symptom; a nervous system symptom;
25 and an emotional symptom.

[0133] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom.

30 [0134] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is a nervous system symptom.

[0135] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: a nervous system symptom and an emotional symptom.

5 [0136] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: a nervous system symptom and an physical symptom.

[0137] In one aspect, the present disclosure includes methods of treating a subject
10 manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: a nervous system symptom; an emotional symptom; and a physical symptom.

[0138] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause where the symptom is
15 an emotional symptom.

[0139] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with perimenopause, where the symptom is a physical symptom.

[0140] In one aspect, the present disclosure includes methods of treating a subject
20 manifesting at least one symptom associated with perimenopause, where the symptom is selected from the group consisting of: an emotional symptom; and a physical symptom.

[0141] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is a vasomotor symptom.

25 [0142] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is a vasomotor symptom or a cognitive symptom.

[0143] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the
30 symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; and a nervous system symptom.

[0144] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; a nervous system symptom; and an emotional symptom.

5 [0145] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is a cognitive symptom.

[0146] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the
10 symptom is selected from the group consisting of: a cognitive symptom and a nervous system symptom.

[0147] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is selected from the group consisting of: a cognitive symptom; a nervous system
15 symptom; and an emotional symptom.

[0148] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is selected from the group consisting of: a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom.

20 [0149] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is a nervous system symptom.

[0150] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the
25 symptom is selected from the group consisting of: a nervous system symptom and an emotional symptom.

[0151] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is selected from the group consisting of: a nervous system symptom and an
30 physical symptom.

[0152] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the

symptom is selected from the group consisting of: a nervous system symptom; an emotional symptom; and a physical symptom.

5 [0153] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause where the symptom is an emotional symptom.

[0154] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is a physical symptom.

10 [0155] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is selected from the group consisting of: an emotional symptom; and a physical symptom.

[0156] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is a vasomotor symptom.

[0157] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is a vasomotor symptom or a cognitive symptom.

20 [0158] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; and a nervous system symptom.

25 [0159] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with induced-menopause, where the symptom is selected from the group consisting of: a vasomotor symptom; a cognitive symptom; a nervous system symptom; and an emotional symptom.

[0160] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is a cognitive symptom.

30 [0161] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early

onset perimenopause, where the symptom is selected from the group consisting of: a cognitive symptom and a nervous system symptom.

[0162] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is selected from the group consisting of: a
5 cognitive symptom; a nervous system symptom; and an emotional symptom.

[0163] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is selected from the group consisting of: a
10 cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom.

[0164] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is a nervous system symptom.

15 [0165] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is selected from the group consisting of: a nervous system symptom and an emotional symptom.

[0166] In one aspect, the present disclosure includes methods of treating a subject
20 manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is selected from the group consisting of: a nervous system symptom and a physical symptom.

[0167] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is selected from the group consisting of: a
25 nervous system symptom; an emotional symptom; and a physical symptom.

[0168] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause where the symptom is an emotional symptom.

30 [0169] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is a physical symptom.

- [0170] In one aspect, the present disclosure includes methods of treating a subject manifesting at least one symptom associated with early onset menopause and/or early onset perimenopause, where the symptom is selected from the group consisting of: an emotional symptom; and a physical symptom.
- 5 [0171] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, occurs daily.
- 10 [0172] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, occurs twice daily.
- 15 [0173] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, occurs weekly.
- 20 [0174] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, occurs 2-3 times a week.
- 25 [0175] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, occurs 4-6 times a week.
- 30 [0176] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive

symptom; a nervous system symptom; an emotional symptom; and a physical symptom, occurs 7-10 times a week.

[0177] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset
5 perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, occurs 2-3 times a month.

[0178] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset
10 perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, occurs 4-8 times a month.

[0179] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset
15 perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, persists for several hours.

[0180] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset
20 perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, persists for several days.

[0181] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset
25 perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, persists for several weeks.

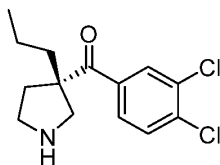
[0182] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset
30 perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, persists for several months.

[0183] In some aspects, a symptom associated with menopause and/or post menopause, perimenopause, induced-menopause, early onset menopause, early onset perimenopause, or low estrogen levels, such as a vasomotor symptom; a cognitive symptom; a nervous system symptom; an emotional symptom; and a physical symptom, persists for several years.

[0184] In some aspects, the disclosed methods are for treating perimenopausal syndrome. In certain aspects, the subject with perimenopausal syndrome has a vasomotor symptom. Methods of treatment include administering a composition comprising Compound 1 to the subject, sufficient to reduce at least one of symptom associated with vasomotor symptoms in the subject. In other aspects, the subject also has a cognitive symptom (e.g., brain fog). In other aspects, the subject also has a sleep-wake disorder. In other embodiments, the subject also has a change in appetite, which could include an increase in appetite. In some embodiments the increase in appetite could include a weight gain in the subject. In other aspects, the subject also has an emotional symptom. In some aspects, a subject with perimenopausal syndrome has a vasomotor symptom, a cognitive symptom, a sleep-wake disorder, a change in appetite, and an emotional symptom. In some aspects, a subject with perimenopausal syndrome has a vasomotor symptom, a cognitive symptom, a sleep-wake disorder, a change in appetite, or an emotional symptom, or any combination thereof.

20 Treatment

[0185] The present disclosure is generally directed to methods of treating a subject manifesting at least one symptom associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by administering Compound 1 to the subject,



(Compound 1),

or a pharmaceutically acceptable salt thereof, sufficient to improve at least one symptom associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause in the subject.

[0186] In certain aspects, methods disclosed herein may be used in combination with another therapeutic, or a co-therapeutic. One example of a co-therapeutic is the use of HRT. In some embodiments, when used in combination (for example, administering Compound 1 and HRT), the dose of Compound 1 or HRT is reduced (as compared to dosing as a monotherapy). In some embodiments, when administered as co-therapeutics, the dose of Compound 1 and HRT are both reduced (as compared to dosing as a monotherapy).

[0187] In certain embodiment, the methods disclosed herein improve at least one symptom associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by lessening the severity of the symptom.

[0188] In certain embodiment, the methods disclosed herein improve at least one symptom associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by reducing the frequency of the symptom.

[0189] In certain embodiment, the methods disclosed herein improve at least one symptom associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by lessening the severity of the symptom and reducing the frequency of the symptom.

[0190] In certain embodiment, the methods disclosed herein improve at least one symptom associated with menopause, perimenopause, post-menopause, induced-menopause or early onset menopause and early onset perimenopause by eliminating the symptom.

[0191] The present disclosure provides methods of treating a subject In an aspect of the disclosure, the method results in a decrease in the symptoms described herein. In an embodiment of the disclosure, the method results in a decrease in the frequency of the symptoms.

[0192] In certain embodiments of the disclosure, the method results in an improvement of the subjects' vasomotor symptoms based on a Greene Climacteric Scale (GCS) total score. In certain embodiments of the disclosure, the method results in an improvement of the subjects' vasomotor symptoms based on a Hot Flash Related Daily Interference Scale (HFRDIS). In certain embodiments of the disclosure, the method

results in an improvement of the subjects' vasomotor symptoms based on a Menopause-Specific Quality of Life (MENQOL) questionnaire. In certain embodiments, the Greene Climacteric Scale (GCS) total score is ≥ 12 , or the Greene Climacteric Scale (GCS) total score is ≥ 2 at screening and baseline. In certain embodiments, the score range of Hot Flash Related Daily Interference Scale (HFRDIS) ranges from 0 to 10, with higher scores indicating greater interference with daily life. In certain embodiments, the Menopause-Specific Quality of Life (MENQOL) questionnaire measures the impact of menopause on quality of life, including the severity of VMS. Treatment is typically guided by how bothersome the subject finds VMS symptoms, with the expected relationship between increased frequency and severity of VMS and greater impact on VMS on daily functioning.

[0193] In other embodiments of the disclosure, the method results in an improvement of the subjects' overall perception of physiological and/or mental well-being.

[0194] In certain embodiments of the disclosure, the method results in an improvement of the subjects' perception of one or more menopause-related symptoms, as determined using a specific questionnaire, such as a Hot Flash patient diary. In embodiments, the Hot Flash patient diary summarizes in multiple ways in order to characterize vasomotor symptoms. Summaries include: a weekly mean change in the frequency of moderate or severe VMS from baseline to Week 4, a weekly mean change in the severity of moderate or severe hot flashes from baseline to Week 4, and a weekly mean change in the frequency of hot flashes (of any severity) from baseline to Week 4. The Hot Flash patient diary documents the number of moderate to severe hot flashes and the overall severity over the day of hot flashes.

[0195] In certain embodiments of the disclosure, the method results in an improvement of the subjects' symptoms, as determined using a scale selected from the group consisting of clinical global impression of severity (CGI-S), structured interview guide for the Hamilton depression rating scale with Atypical Depression Supplement (SIGH-ADS), patient global impression of change (PGI-C), food craving questionnaire-trait-reduced (FCQ-T-R), digit symbol substitution test (DSST), Epworth Sleepiness Scale (ESS), behavior rating inventory of executive function—adult version (BRIEF-A), and MENO-D.

[0196] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on a Hot Flash patient diary. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on a Hot Flash patient diary, where the subject shows a change from baseline.

[0197] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on mean change in daily frequency of moderate or severe VMS. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on mean change in daily frequency of moderate or severe VMS, where the subject shows a change from baseline.

[0198] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on mean change in daily severity of VMS. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on mean change in daily severity of VMS, where the subject shows a change from baseline.

[0199] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based CGI-S. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based CGI-S, where the subject shows a change from baseline.

[0200] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing mean change in frequency of VMS. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing mean change in frequency of VMS, where the subject shows a change from baseline.

[0201] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing a response defined as a reduction from baseline in mean frequency of VMS. In some embodiments, therapeutic efficacy of the treatment is determined by assessing a response defined as a 50%, 75% or 100% reduction from baseline in mean frequency of VMS, as recorded in the Hot Flash patient diary.

[0202] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on depression. In certain

embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on depression, where the subject shows a change from baseline.

5 **[0203]** In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on SIGH-ADS. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on SIGH-ADS, where the subject shows a change from baseline.

10 **[0204]** In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on clinical global impression of severity (CGI-S). In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on clinical global impression of severity (CGI-S), where the subject shows a change from baseline.

15 **[0205]** In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on patient global impression of change (PGI-C). In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on patient global impression of change (PGI-C), where the subject shows a change from baseline.

20 **[0206]** In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on food craving questionnaire-trait-reduced (FCQ-T-R). In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on food craving questionnaire-trait-reduced (FCQ-T-R), where the subject shows a change from baseline.

25 **[0207]** In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on digit symbol substitution test (DSST). In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on digit symbol substitution test (DSST), where the subject shows a change from baseline.

30 **[0208]** In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on Epworth Sleepiness Scale (ESS). In certain embodiments of the disclosure, therapeutic efficacy of the treatment is

determined by assessing an improvement based on Epworth Sleepiness Scale (ESS), where the subject shows a change from baseline.

[0209] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on behavior rating inventory of executive function–adult version (BRIEF-A). In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on behavior rating inventory of executive function–adult version (BRIEF-A), where the subject shows a change from baseline.

[0210] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on MENO-D. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on MENO-D, where the subject shows a change from baseline.

[0211] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on global impression. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on global impression, where the subject shows a change from baseline.

[0212] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on PGI-C. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on PGI-C, where the subject shows a change from baseline.

[0213] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on neuroinflammatory biomarkers (e.g., CRP, IL-6, TNF α). In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on neuroinflammatory biomarkers (e.g., CRP, IL-6, TNF α), where the subject shows a change from baseline.

[0214] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on food cravings. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by

assessing an improvement based on food cravings, where the subject shows a change from baseline.

[0215] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on FCQ-T-R. In certain
5 embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on FCQ-T-R, where the subject shows a change from baseline.

[0216] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on cognition. In certain
10 embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on cognition, where the subject shows a change from baseline.

[0217] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on DSST. In certain
15 embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on DSST, where the subject shows a change from baseline.

[0218] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on daytime sleepiness. In
20 certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on daytime sleepiness, where the subject shows a change from baseline.

[0219] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on ESS. In certain
25 embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on ESS, where the subject shows a change from baseline.

[0220] In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based on change in body weight,
30 BMI, cholesterol, triglycerides, and glucose. In certain embodiments of the disclosure, therapeutic efficacy of the treatment is determined by assessing an improvement based

on change in body weight, BMI, cholesterol, triglycerides, and glucose, where the subject shows a change from baseline.

[0221] In certain embodiments of the disclosure, the method results in one or more of the effects defined here above within at least 12, 10, 8, 6, 4 or 2 weeks of treatment, based on the compositions and treatment regimens as defined herein.

[0222] In certain embodiments, the subject is a female. The subject can be of any age, e.g. the human subject can be a juvenile, an adolescent, an adult or an elderly subject.

[0223] In preferred embodiments of the invention the subject suffers from and/or is at risk of suffering from menopause-associated symptoms or from menopausal syndrome, due to the normal aging process. For example, the subject may be 40 to 110 years of age; may be 40 to 100 years of age; may be 40 to 90 years of age; may be 40 to 80 years of age; may be 40 to 70 years of age; may be 40 to 60 years of age; may be 40 to 50 years of age; or may be 40 to 45 years of age. The subject may be 40 to 65 years of age; may be 45 to 60 years of age; may be 45 to 55 years of age, or may be 45 to 65 years of age. Hence, in preferred embodiments the subject is at least 40 years of age, at least 45 years of age, at least 48 years of age, at least 49 years of age, at least 50 years of age, at least 51 years of age, at least 52 years of age, at least 53 years of age, at least 54 years of age, at least 55 years of age, at least 56 years of age, at least 57 years of age, at least 58 years of age, at least 59 years of age, or at least 60 years of age.

[0224] In preferred embodiments of the invention the subject suffers from and/or is at risk of suffering from early onset menopause-associated symptoms or from menopausal syndrome. Subjects may be 39 years of age or younger. Subjects may be 35 years of age or younger. Subjects may be 30 years of age or younger. Subjects may be 25 years of age or younger. Subjects may be 20 years of age or younger. Subjects may be 35 to 39 years of age. Subjects may be 30 to 39 years of age. Subjects may be 25 to 39 years of age. Subjects may be 20 to 39 years of age. Subjects may be 20 to 30 years of age. Subjects may be 20 to 25 years of age. Subjects may be 25 to 35 years of age. Subjects may be 18 to 39 years of age.

[0225] In accordance with other embodiments of the disclosure, the subject suffers from and/or is at risk of suffering from menopause-associated symptoms due to a medical condition or pathology. Hence, in certain embodiments, the subject is a subject suffering from pre-mature ovarian failure.

[0226] In accordance with other embodiments of the disclosure, the subject suffers from and/or is at risk of suffering from menopause-associated symptoms as a consequence of surgical intervention. Hence, in preferred embodiments, the subject is a subject that has undergone oophorectomy.

5 [0227] In accordance with other embodiments of the disclosure, the subject suffers from and/or is at risk of suffering from menopause-associated symptoms as a consequence of other medical treatments. Hence, in embodiments, the subject is a subject that has undergone and/or is undergoing therapeutic treatments resulting in suppression of circulating estrogen levels, such as a subject that has undergone and/or is undergoing
10 chemotherapy and/or radiotherapy.

[0228] In embodiments of the invention, the methods as described herein comprise the step of identifying a subject that is in need of receiving treatment with the compositions of the invention and/or identifying a subject suffering from or at risk of suffering from any of the conditions as described here above and/or a subject meeting any
15 of the above-described physiological characteristics.

[0229] In one embodiment such method of treatment is carried out for non-medical or non-therapeutic reasons. Hence, in an embodiment of the invention, the subject is a healthy subject.

[0230] In certain embodiments, Compound 1 or a pharmaceutically acceptable salt thereof is administered in an amount of from about 1 mg to about 85 mg per day, from
20 about 1 mg to about 60 mg per day, from about 1 mg to about 30 mg per day, from about 1 mg to about 25 mg per day, from about 1 mg to about 20 mg, from about 5 mg to about 85 mg per day, from about 5 mg to about 60 mg per day, from about 5 mg to about 30 mg per day, from about 5 mg to about 25 mg per day, from about 5 mg to about 25 mg per
25 day, from about 5 mg to about 20 mg per day, from about 10 mg to about 85 mg per day, from about 10 mg to about 60 mg per day, from about 10 mg to about 30 mg per day, from about 10 mg to about 25 mg per day, or from about 10 mg to about 20 mg per day.

[0231] In certain embodiments, Compound 1 or a pharmaceutically acceptable salt thereof is administered in a first amount (e.g., from about 1 mg to about 30 mg per day, for example 15 mg per day) for about 1 week, a second amount (e.g., from about 15 mg.
30 to about 45 mg per day, for example, about 30 mg per day) for about 1 week, and a third

amount (e.g., about 45 mg to about 75 mg per day, for example, about 60 mg day) continuously as needed.

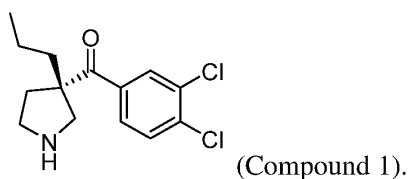
III. Compound

[0232] The methods described herein comprise administering to a subject in need thereof a composition comprising a therapeutically effective amount of a triple reuptake inhibitor, or a pharmaceutically acceptable salt thereof. In certain embodiments, the triple reuptake inhibitor is Compound 1. Thus, in various embodiments, the methods comprise administering to a subject in need thereof a composition comprising a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

Compound 1

[0233] Compound 1 is a triple reuptake inhibitor (TRI). Specifically, Compound 1 is a monoaminergic reuptake inhibitor of serotonin (also referred to as 5-HT), norepinephrine, and dopamine, which also maintains anti-inflammatory activity. Monoaminergic reuptake inhibitors have the potential to treat disorders associated with an imbalance of monoamine neurotransmitters, and potentially with a relatively fast onset of action. Compound 1 adds dopamine transporter blockade to the dual (serotonin and norepinephrine) reuptake inhibition which make them more favorable than various antidepressant drugs for treating methods described herein, including alleviating symptoms related to reward/motivation, wakefulness, attention/executive functioning, and appetite changes.

[0234] Compound 1 can be referred to as (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone. Compound 1 can be represented by:



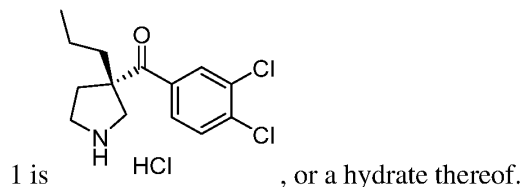
[0235] A method of chemically synthesizing Compound 1 is described in U.S. Patent No. 8,084,623 and U.S. Patent No. 9,527,810 which are incorporated by reference in their entirety.

[0236] Compound 1 is a potent TRI that blocks the reuptake of serotonin, norepinephrine, and dopamine. The compound is highly potent on serotonin reuptake transporter (SERT) ($K_i = 0.4$ nM) while 30 and 65-fold less potent on norepinephrine transporter (NET) and dopamine transporter (DAT), respectively. The differences in binding affinity are also reflected in transporter occupancy. Typically, a concentration inhibiting 80% SERT only occupied 10 to 38% of DAT. Compound 1 demonstrated antidepressant-like activity in animal models in mouse, rat, and cynomolgus monkey and did not induce nor reduce anxiety-like activity. The compound was wake-promoting, reduced impulsive/compulsive behavior, and showed an effect on appetite and binge-like eating in rats. In dietary-induced obese rats, Compound 1 reduced weight and body fat mass. Further, Compound 1 showed an 'anti-impulsive' effect in a 5-Choice Serial Reaction Time test and reduced food intake in an Effort-Expenditure for Reward Task test as well as reduced binge-like eating of chocolate in a rodent binge eating model. Further, Compound 1 may have anti-inflammatory properties as it reduced lipopolysaccharide-induced TNF- α release.

[0237] In various embodiments, methods described herein comprise administering Compound 1 or a pharmaceutically acceptable salt thereof. In various embodiments, the pharmaceutically acceptable salt of Compound 1 can be a salt of Compound 1 with physiologically compatible mineral acids, such as hydrochloric acid, sulfuric acid, sulfurous acid or phosphoric acid; or with organic acids, such as methanesulfonic acid, p-toluenesulfonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid.

[0238] In certain embodiments, the pharmaceutically acceptable salt of Compound 1 is a hydrochloride salt, being in a hydrate or an anhydrate form (e.g., anhydrate, hemihydrate, monohydrate, or quarterhydrate). In certain embodiments, the pharmaceutically acceptable salt of Compound 1 is a hydrochloride salt, being in a quarterhydrate form.

[0239] In various embodiments, the pharmaceutically acceptable salt of Compound



Crystalline Form 1 of Compound 1

[0240] In some embodiments, the compound is in a crystalline quarterhydrate form (Form 1) of a hydrochloride salt of Compound 1, wherein Form 1 has an X-ray powder diffraction (XRPD) pattern as substantially shown in **FIG. 1**. In some embodiments, Form 1 is characterized by at least three peaks selected from the following X-ray powder diffraction peaks obtained with a $\text{CuK}\alpha$ radiation at 2θ (2 Theta): $5.5\pm0.20^\circ$, $9.4\pm0.20^\circ$, $10.6\pm0.20^\circ$, $12.5\pm0.20^\circ$, $14.6\pm0.20^\circ$, $16.2\pm0.20^\circ$, $16.6\pm0.20^\circ$, $17.3\pm0.20^\circ$, $18.6\pm0.20^\circ$, $19.6\pm0.20^\circ$, $22.2\pm0.20^\circ$, $22.7\pm0.20^\circ$, $23.1\pm0.20^\circ$, $23.7\pm0.20^\circ$ and $25.3\pm0.20^\circ$.

Crystalline Form 2 of Compound 1

[0241] In some embodiments, the compound is in a crystalline form (Form 2) of a hydrochloride salt of Compound 1, wherein Form 2 has an X-ray powder diffraction (XRPD) pattern as substantially shown in **FIG. 2**. In some embodiments, Form 2 is characterized by at least three peaks selected from the following X-ray powder diffraction peaks obtained with a $\text{CuK}\alpha$ radiation at 2θ (2 Theta): $5.2\pm0.20^\circ$, $10.5\pm0.20^\circ$, $12.3\pm0.20^\circ$, $15.3\pm0.20^\circ$, $15.6\pm0.20^\circ$, $16.0\pm0.20^\circ$, $17.1\pm0.20^\circ$, $18.8\pm0.20^\circ$, $23.0\pm0.20^\circ$, $23.9\pm0.20^\circ$, $27.2\pm0.20^\circ$, $28.2\pm0.20^\circ$ and $30.5\pm0.20^\circ$.

Pharmaceutical compositions

[0242] In one aspect, the present disclosure relates to a composition such as a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, for the treatment of disorders and symptoms described herein.

[0243] In various embodiments, the amount of the Compound 1, or a pharmaceutically acceptable salt thereof, in the pharmaceutical compositions described herein can be from about 1 mg to about 85 mg, from about 1 mg to about 60 mg, from about 1 mg to about 30 mg, from about 1 mg to about 25 mg, from about 1 mg to about

20 mg, from about 5 mg to about 85 mg, from about 5 mg to about 60 mg, from about 5 mg to about 30 mg, from about 5 mg to about 25 mg, from about 5 mg to about 25 mg, from about 5 mg to about 20 mg, from about 10 mg to about 85 mg, from about 10 mg to about 60 mg, from about 10 mg to about 30 mg, from about 10 mg to about 25 mg, or
5 from about 10 mg to about 20 mg. In certain embodiments, the amount of the Compound 1, or a pharmaceutically acceptable salt thereof, in the pharmaceutical compositions described herein is about 15 mg.

[0244] In certain embodiments, the pharmaceutically acceptable salt of Compound 1 is a monosulfate salt or a hemisulfate salt, each being in hydrate or anhydrate form (e.g.,
10 anhydrate, hemihydrate, or monohydrate).

[0245] The pharmaceutical compositions provided herein may be presented in unit dosage forms to facilitate accurate dosing. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to
15 produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. In various embodiments, the pharmaceutical dosage forms described herein can be administered as a unit dose. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions.

20 [0246] In various embodiments, the subject may receive multiple “unit dosage forms,” amounting to a total administration of about 15 mg, about 30 mg, or about 60 mg of Compound 1 once daily. For example, in the case that the unit dosage form is a table, the subject may be administered 1 capsule for 15 mg/day, 2 capsules for 30 mg/day, or 4 capsules for 60 mg/day.

25 [0247] In certain embodiments, the pharmaceutical compositions provided herein are administered to the patient as a solid dosage form. In certain embodiments, the solid dosage form is a capsule (e.g., a modified release pellet formulation encapsulated in a capsule). In certain embodiments, the solid dosage form is a tablet (e.g., a modified release tablet formulation). In certain embodiments, the pharmaceutical compositions
30 provided herein are administered with food. In certain embodiments, the pharmaceutical compositions provided herein are administered without food.

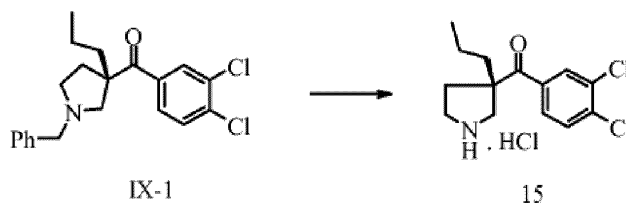
[0248] In certain embodiments, the pharmaceutical compositions provided herein comprise the Compound 1 as the sole active agent.

EXAMPLES

[0249] In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

[0250] In the Examples provided below, the following abbreviations are used: “PROG” refers to progressive ratio; “FR1” refers to fixed ratio of one or fixed ratio 1; “SEM” refers to standard error of mean; “VEH” refers to vehicle; “ANOVA” refers to analysis of variance test; “NR” refers to non-rapid eye movement sleep; “REM” refers to rapid eye movement sleep; “p.o.” or “*per os*” refers to by mouth; “CAF” refers to caffeine; “DAT” refers to dopamine transporters; “SERT” refers to serotonin transporters; “TRI” refers to triple reuptake inhibitor; “NR” refers to non-rapid eye movement sleep; “REM” refers to rapid eye movement sleep; “AE(s)” refers to adverse event(s), “AESI(s)” refers to adverse events of special interest; “BMI” refers to body mass index; “CGI-S” refers to clinical global impression of severity; “CRP” refers to C-reactive protein; “DSST” refers to digit symbol substitution test; “ESS” refers to Epworth Sleepiness Scale, “FCQ-T-R” refers to food craving questionnaire-trait-reduced; “PGI-C” refers to patient global impression of change; “PK” refers to pharmacokinetic; “IL-6” refers to interleukin 6; “PENN PWC” refers to PENN physician withdrawal checklist; “SIGH-ADS” refers to structured interview guide for the Hamilton depression rating scale with Atypical Depression Supplement; “SAE” refers to serious adverse event; “S-STs” refers to Sheehan suicidality tracking scale; “TEAE(s)” refers to treatment-emergent adverse event(s); “TNF α ” refers to tumor necrosis factor alpha; “VMS” refers to vasomotor symptoms; “qd” refers to once daily; “BRIEF-A” refers to behavior rating inventory of executive function–adult version; “MENO-D” is a rating scale for perimenopausal depression.

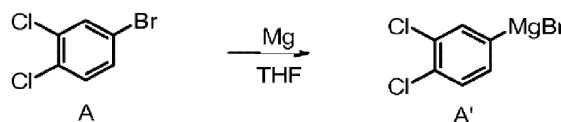
30 **Example 1.** Synthesis of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride (15) quarterhydrate [See U.S. Patent No. 9,527,810]



[0251] (S)-(1-benzyl-3-propylpyrrolidin-3-yl)(3,4-dichlorophenyl)methanone (IX-1) (5 g, 13.3 mmol, Eq: 1.00, see U.S. Patent No. 9,527,810 for synthesis) was dissolved in dichloromethane (30 mL). The light yellow solution was cooled to 0-5 °C and *N*-ethyl-diisopropylamine (172 mg, 226 µL, 1.33 mmol, Eq: 0.1) was added. 1-Chloroethyl chloroformate (2.28 g, 1.74 mL, 15.9 mmol, Eq: 1.2) was added dropwise while the temperature was maintained in between 0-5 °C. The reaction was warmed to room temperature over 30 min and was stirred 1 h at room temperature. Methanol (25 mL) was added and the light yellow solution was heated to 40 °C for 40 min. The reaction mixture was concentrated under reduced pressure (40 °C, 600-15 mbar) to give 5.48 g of crude product. Ethyl acetate (30.0 mL) was added and the suspension was heated to 50 °C. A solution of water (239 mg, 239 µL, 13.3 mmol, Eq: 1.0) in ethyl acetate (35 mL) was added over 10 min. The white suspension was stirred for 1 h at 50 °C and cooled to room temperature over 1.5 h. The suspension was filtered, and the filter cake was washed twice with ethyl acetate (10 mL) and dried under reduced pressure (40 °C, 15 mbar) to give 4.02 g of (15) as quarterhydrate (93% yield).

Example 2. Synthesis of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride (15) quarterhydrate [See U.S. Patent No. 9,527,810]

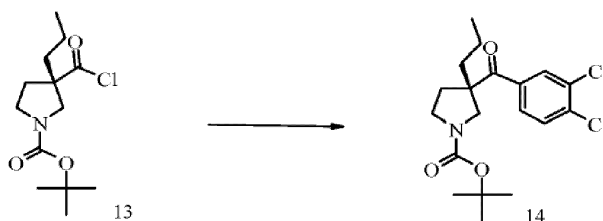
1. Grignard formation (A')



[0252] 6.8 g of Magnesium (279 mmol, 1.3 equiv.) was suspended in 60 mL tetrahydrofuran. The suspension was heated to 40 °C, and 2% of a solution of 70.5 g 3,4-dichlorobromobenzene (A) in 200 mL tetrahydrofuran was added (the Grignard started within a few minutes). After the exotherm ceased, the remaining aryl bromide solution

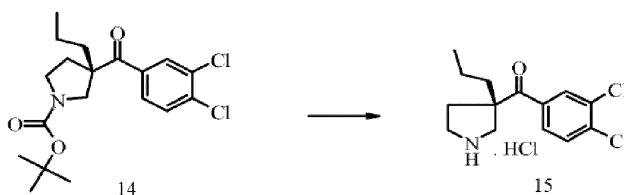
was added over 2 h. The reaction mixture was stirred for 1 h at 40 °C, and then the mixture was cooled to room temperature.

2. Grignard addition



- 5 [0253] A solution of the acid chloride (13) (see U.S. Patent No. 9,527,810 for synthesis) was degassed 3 times and 55.8 g of N,N,N',N',N''-pentamethyldiethylenetriamine (PMDTA) (322 mmol, 1.5 equiv.) was added. The light suspension was heated to 40-45 °C, and the Grignard solution (A') was added dropwise over 1.5 h. After 1 h of additional reaction time, the reaction mixture was cooled to room
- 10 temperature. 500 mL of 2 M HCl (aq), 300 mL saturated NaCl (aq) and 300 mL ethanol were added. The organic phase was separated and washed with a mixture consisting of 500 mL 2 M HCl (aq), 300 mL saturated NaCl (aq) and 300 mL ethanol. The organic phase was washed with 400 mL of 1M NaOH (aq) and twice with 150 mL 10% NaCl (aq). The organic phase was concentrated under reduced pressure to an oil, taken up in
- 15 100 mL toluene and concentrated again to give 87 g of crude (14) with 80 % purity.

3. (3,4-Dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride (15) as quarterhydrate



- [0254] The crude (14) was dissolved in 130 mL of toluene and the solution was
- 20 added dropwise to a mixture of 140 mL toluene and 70 mL 37% HCl (aq) at 60-70 °C. After 1 h, the reaction mixture was azeotroped with toluene (Tr max=70 °C, Tj max=120 °C, reduced pressure) and adjusted to a volume of 350-400 mL. A mixture consisting of 700 mL ethyl acetate and 3.6 mL water was added at 65 °C. The solution was cooled to

room temperature over 1 h, during which crystallization started (around 45 °C). After stirring overnight, the suspension was cooled to 0-5 °C for 2 h, filtered and washed twice with 200 mL ethyl acetate. The crystals were re-suspended in 250 mL of ethyl acetate, digested at 55 °C for 2 h, and then cooled to room temperature. The suspension was
5 filtered, and the filter cake was washed with 200 mL ethyl acetate. The crystals were dried at 50 °C under reduced pressure to give 54.4 g of the (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate as a powder with 99 % purity.

An alternative route for (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride (15) as quarterhydrate

10 **[0255]** The crude (14) was dissolved in 63 mL toluene and deprotected at 60 °C with 24 mL 37% HCl (aq). After completion of the reaction, the reaction mixture was dried azeotropically with toluene at 50-60 °C. The solution was cooled to room temperature, and 100 mL water was added. The aqueous phase was separated and washed with 50 mL toluene. The aqueous phase was dried azeotropically with toluene and concentrated to
15 dryness to give 22.5 g of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate (90% yield). (3,4-Dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate can be obtained by digestion or recrystallization, for example, by processes described below.

Transformation of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride anhydrate to the quarterhydrate form:

20 **[0256]** (3,4-Dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride anhydrate (40 g, 124 mmol, Eq: 1.00, see Example 3 or U.S. Patent No. 9,527,810 for synthesis) was suspended in a mixture of ethyl acetate (340 mL), ethanol (36 mL) and water (0.6 mL) at room temperature. The suspension was heated to 40 °C
25 and a mixture consisting of ethyl acetate (20 mL), ethanol (0.5 mL) and water (0.6 mL) was added over 1 h. The suspension was cooled to room temperature over 1 h. After stirring overnight at room temperature, the suspension was cooled over 2-3 h at 0-5 °C, filtered and washed with a cold (0-5 °C) mixture of ethyl acetate (55 mL), ethanol (5 mL) and water (0.5 mL). The filter cake was dried at 50 °C under reduced pressure to give 38

g of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate (1.5% water).

Recrystallization of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate:

- 5 [0257] 54.4 g of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate was dissolved at room temperature in 550 mL ethanol. The solution was filtered and concentrated under reduce pressure at 60 °C to a volume of 140 mL. The volume was adjusted to 550 mL by the addition of ethyl acetate. The remaining ethanol was solvent exchanged to ethyl acetate (60 °C, reduced pressure), and 55 mL
- 10 ethanol was added to the resulting suspension at 60 °C. 1.5 mL water was then added and the solution was slowly cooled to room temperature, during which the crystallization occurred. After stirring at room temperature overnight, the suspension was cooled to 0-5 °C for 1 h and was filtered. The filter cake was washed with a mixture of 50 mL ethyl acetate and 5 mL ethanol, followed by two more washes with 50 mL ethyl acetate. The
- 15 crystals were dried at 50 °C overnight under reduced pressure to give 48.9 g of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate as a powder with 99 % purity.

Example 3. Synthesis of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride (15) anhydrate [See U.S. Patent No. 9,527,810]

- 20 [0258] 50 g of Sodium salt was transformed into the corresponding acid chloride (13) (see U.S. Patent No. 9,527,810 for synthesis). The acid chloride (13) was reacted with 3,4-dichlorophenyl-MgBr (A'), and then deprotected. After azeotrope drying, an orange turbid toluene solution (300 g, water content <0.1%) was obtained by Karl Fischer titration of the crude (15).
- 25 [0259] (i) 1/5 of the crude (15) solution (max theoretical content: 11.3 g of (15)) was cooled to room temperature. After storing for overnight at room temperature, the resulting suspension was filtered. The filter cake was washed with ethyl acetate (Karl Fischer titration of wet filter cake 0.2%) and dried at 50-60 °C under reduced pressure to give 5.9 g of (15) crystals.

[0260] (ii) 1/5 of the crude (15) solution (max theoretical content: 11.3 g of (15)) was cooled to room temperature. After storing for 4 days at room temperature, the resulting suspension was stirred at 0-2 °C for 4 h. The resulting suspension was filtered, the filter cake was washed with ethylacetate (Karl Fischer titration of wet filter cake 0.2%) and dried at 50-60 °C under reduced pressure to give 8.8 g of (15) crystals.

Example 4. Crystalline Forms of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride and (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate [See U.S. Patent No. 9,527,810]

[0261] Characterization methods and data of crystalline forms of Compound 1 are described in U.S. Patent No. 9,527,810, which is incorporated by reference in its entirety.

X-ray Powder Diffraction (XRPD)

[0262] X-ray diffraction powder patterns were recorded at ambient conditions in transmission geometry with a STOE STADI P diffractometer ($\text{CuK}\alpha$ radiation, primary monochromator, position sensitive detector, angular range 3° to 42° (2 Theta), approximately 60 minutes total measurement time). The samples were prepared and analyzed without further processing (e.g. grinding or sieving) of the substance.

XRPD Pattern of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate (Form 1)

[0263] The hydrochloride quarterhydrate of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone solid (Form 1) can be identified by as few as one characteristic peak in its powder X-ray diffraction patterns as shown in **FIG. 1**. Exemplary X-ray powder diffraction patterns of hydrochloride quarterhydrate of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone (Form 1) in terms of 2 θ (2 Theta) are: 5.5±0.20°, 9.4±0.20°, 10.6±0.20°, 12.5±0.20°, 14.6±0.20°, 16.2±0.20°, 16.6±0.20°, 17.3±0.20°, 18.6±0.20°, 19.6±0.20°, 22.2±0.20°, 22.7±0.20°, 23.1±0.20°, 23.7±0.20° and 25.3±0.20°; in particular characteristic peaks are 9.4±0.20°, 14.6±0.20°, 16.6±0.20°, 19.6±0.20° and 22.2±0.20°.

XRPD Pattern of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride (Form 2)

[0264] The hydrochloride of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone solid (Form 2) can be identified by as few as one characteristic peak in its powder X-ray diffraction patterns as shown in **FIG. 2**. Exemplary X-ray powder diffraction patterns of hydrochloride of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone solid (Form 2) in terms of 2θ (2 Theta) are: 5.2±0.20°, 10.5±0.20°, 12.3±0.20°, 15.3±0.20°, 15.6±0.20°, 16.0±0.20°, 17.1±0.20°, 18.8±0.20°, 23.0±0.20°, 23.9±0.20°, 27.2±0.20°, 28.2±0.20° and 30.5±0.20°.

10 *Crystal Structure Analysis*

[0265] For single crystal structure analysis, a single crystal was mounted in a loop on a goniometer and measured at ambient conditions. Data were collected on a GEMINI R Ultra diffractometer from Oxford Diffraction (Oxford). Cu-radiation of 1.54 Å wavelength was used for data collection. Data was processed with the software CRYVALIS. The crystal structure was solved and refined with standard crystallographic software. In this case, the program ShelXTL from Bruker AXS (Karlsruhe) was used.

Preparation of single crystals of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone monohydrochloride quarterhydrate

[0266] 10 mg of (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride were dissolved in 0.226 mL of nitromethane at 60 °C. The solution was allowed to reach the ambient temperature without agitation. After 24 h, single crystals were harvested and subjected to X-ray crystal structure analysis.

[0267] Structural data derived from (3,4-dichloro-phenyl)-((S)-3-propyl-pyrrolidin-3-yl)-methanone hydrochloride quarterhydrate single crystal X-ray analysis are the following unit cell parameters:

a	6.14 Å
b	16.70 Å
c	17.43 Å
alpha	66.73°

beta	81.47°
gamma	86.51°

wherein a, b and c are each a representative length of the crystal lattice, and alpha, beta and gamma are unit cell angles. The salt crystallizes in the space group P1, affording a cell volume of 1623.82 Å³.

5 *Differential Scanning Calorimetry (DSC)*

[0268] Differential Scanning Calorimetry curves were recorded using a Mettler-Toledo™ differential scanning calorimeter DSC820, DSC821 or DSC1 with a FRS05 sensor. System suitability tests were performed with Indium as reference substance and calibrations were carried out using Indium, Benzoic acid, Biphenyl and Zinc as reference
10 substances.

[0269] For the measurements, approximately 2-6 mg of sample were placed in aluminum pans, accurately weighed and hermetically closed with perforation lids. Prior to measurement, the lids were automatically pierced resulting in approximately 1.5 mm pin holes. The samples were then heated under a flow of nitrogen of about 100 mL/min
15 using heating rates of usually 10 K/min.

Thermal Gravimetric Analysis (TGA)

[0270] Thermal Gravimetric Analysis was performed on a Mettler-Toledo™ thermogravimetric analyzer (TGA850 or TGA851). System suitability tests were performed with Hydranal as reference substance and calibrations using Aluminum and
20 Indium as reference substances.

[0271] For the thermogravimetric analyses, approximately 5-10 mg of sample were placed in aluminum pans, accurately weighed and hermetically closed with perforation lids. Prior to the measurement, the lids were automatically pierced resulting in approximately 1.5 mm pin holes. The samples were then heated under a flow of nitrogen
25 of about 50 mL/min using a heating rate of 5 K/min.

Example 5. Assessment of Compound 1 for appetite suppressant effects using progressive ratio/chow feeding choice task in rats

[0272] A study to evaluate Compound 1 for appetite suppressant effects were conducted. The PROG/Chow feeding choice procedure was used as a test designed to
5 evaluate the effort a rat is willing to make to eat a palatable food by pressing a lever instead of eating freely available standard food.

[0273] *Methods.* Thirty-one ($n = 31$) adult male Sprague Dawley rats were used in this study. The animals were restricted to 85% of their free-feeding weight, with modest growth allowed throughout the study period. Animals were assessed using operant
10 conditioning chambers. Animals were first introduced to the high carbohydrate pellets (“palatable food”) and trained to lever press using a continuous reinforcement schedule with a fixed ratio of one (FR1 = one active lever press triggered the delivery of the palatable food) for one week. After this, the rats were trained on the progressive ratio (progressively more lever pressures were needed to trigger the delivery of the palatable
15 food) schedule alone for nine weeks at which point chow (“standard food”) was introduced (=PROG/Chow feeding choice procedure), and animals trained for another 5 weeks to acquire a steady baseline. Each session lasted 30 minutes and rats ran in the operant chambers once a day, five days a week (Monday-Friday). Vehicle (VEH), or Compound 1 doses of 5.0, 10.0, and 20.0 mg/kg were administered via oral gavage once
20 a week (Thursday or Friday) after the training period. Treatment conditions were selected randomly. Lever presses and chow consumption (including spillage) were recorded after each operant session.

[0274] *Statistical analyses.* Repeated measures analysis of variance test (ANOVA) and planned comparisons were used to assess the data overall. Factorial ANOVA was
25 used to assess group x treatment interaction. If significant interactions were found, planned comparisons (using the overall error term) were used to assess the groups individually. Dunnett’s tests were also used to analyze differences between drug treatments and VEH. A p value of <0.05 was considered statistically significant for all analyses.

30 [0275] *Results.* All treatment conditions showed significant decreases in standard chow intake when compared to VEH (5.0 mg/kg: $[F(1,90)=15.589, p<0.001]$, 10.0 mg/kg $[F(1,90)=159.881, p<0.001]$, and 20.0 mg/kg: $[F(1,90)=236.567, p<0.001]$), as shown in

FIG. 3. No significant difference between VEH and the 5.0 mg/kg dose [$F(1,90)=0.391$, $p = \text{n.s.}$], significant decreases in lever pressing were seen at both the 10.0 mg/kg dose [$F(1,90)=13.534$, $p<0.001$] and the 20.0 mg/kg dose [$F(1,90)=38.407$, $p<0.001$], as shown in **FIG. 4.**

- 5 **[0276]** The study reveals that Compound 1 demonstrates appetite suppressant effects. The pattern of decreased lever pressing and chow intake as shown in this study of PROG/Chow feeding choice task is also shown in other studies with drugs and conditions known for suppressing appetite. Examples of the drugs include fenfluramine, pre-feeding, cannabinoid antagonists and inverse agonists, and fluoxetine.
- 10 **[0277]** *High vs. Low Responders.* Factorial ANOVA on lever pressing revealed a significant group x treatment interaction [$F(3,90)=13.824$, $p<0.001$; $\eta^2 = 0.323$] and a significant interaction of the linear trend ($p < 0.001$). Due to this significant interaction, the high and low responder level pressing was analyzed separately. Significant treatment effects were found in both groups (high: $p<0.001$; low: $p=0.01$). High responder lever presses showed a significant linear trend ($p<0.001$). Planned comparisons revealed significant decreases in lever pressing at both the 10.0 mg/kg [$F(1,42)=26.735$, $p<0.001$] and 20.0 mg/kg [$F(1,42)=55.797$, $p<0.001$] doses when compared to VEH. There were no significant difference found when comparing the 5.0 mg/kg dose to VEH conditions [$F(1,42)=3.372$, $p=\text{n.s.}$] (**FIG. 14**). Planned comparisons showed no significant differences when comparing any of the drug conditions to VEH (5.0 mg/kg: [$F(1,45)=0.319$, $p=\text{n.s.}$], 10.0 mg/kg: [$F(1,45)=0.079$, $p=\text{n.s.}$], 20.0g mg/kg: [$F(1,45)=3.157$, $p=\text{n.s.}$]). However, a significant quadratic trend ($p=0.01$) was found in the low responder group, as shown in **FIG. 14**. A factorial ANOVA was also used to assess the concurrent chow Intake. A significant group x treatment interaction [$F(3,90)=3.191$, $p<0.05$; $\eta^2 = 0.099$] was found, as well as an interaction of linear trend ($p<0.05$). This significant interaction allowed for separate analysis of the high and low responders. Significant treatment effects ($p<0.001$) and significant linear trend ($p<0.001$) were found in both high and low responders. In the high responder group, significant decreases in chow intake were found at the 5.0 mg/kg [$F(1,42)=13.450$, $p<0.010$], 10.0 mg/kg [$F(1,42)=70.714$, $p<0.001$], and 20.0g mg/kg [$F(1,42)=100.204$, $p<0.001$] groups when compared to VEH through planned comparisons. Low responders also showed significant decreases in lever presses at all dose treatments (5.0 mg/kg [$F(1,45)=16.976$,
- 15
- 20
- 25
- 30

$p < 0.001$], 10.0 mg/kg [$F(1,45)=156.918$, $p < 0.001$], 20.0 mg/kg [$F(1,45)=226.122$, $p < 0.001$]) as determined by Dunnett's test (**FIG. 15**).

Example 6. Assessment of Compound 1 for appetite suppressant effects using a fixed ratio schedule in rats

5 [0278] Another study to evaluate Compound 1 for appetite suppressant effects were conducted. A fixed ratio 1 (FR1) schedule was used, and this task is the most food dense and appetite dependent operant schedule, with high sensitivity to appetite-related manipulations such as pre-feeding and appetite suppressant drugs.

[0279] *Methods.* The same adult male Sprague Dawley rats ($n = 31$) as in Example 10 5 were used in this study. Animals trained once daily on the PROG/Chow feeding choice procedure from Monday through Thursday. On Friday, the testing day, the animals were switched from the PROG/Chow feeding choice procedure to FR1 with no prior training. Each operant session lasted 30 minutes and lever presses were recorded at the end of the run. Drug treatment and the FR1 probe occurred on the Friday after two weeks of washout 15 period from Example 5. A dose of 20.0 mg/kg of Compound 1 or vehicle was administered via oral gavage on the testing day. Only the highest dose was tested in this study because, in Example 5, it produced the most robust decrease in lever pressing and chow intake compared to VEH. Treatment conditions were assigned randomly. Treatment group difference was assessed by unpaired t-test. A p value of < 0.05 was considered 20 statistically significant.

[0280] *Results.* Compound 1 caused a significant decrease in lever pressing in the FR1 probe study, as measured by an unpaired t-test ($t = 9.74$; $p < 0.001$). As shown in **FIG. 5**, there is a significant decrease at the 20.0 mg/kg dose when compared to the vehicle (VEH). Importantly, 6 of the 16 rats that received the high drug dose pressed the lever 25 but refrained from eating some of the pellets. After the completion of the 30-minute operant session, approximately 5-10 uneaten pellets were left in the food dishes of these animals which is an additional marker of appetite suppression. Accordingly, together with the results in the study of Example 5, the study highlights that Compound 1 demonstrates appetite suppressant effects.

Example 7. Assessment of Compound 1 for appetite suppressant effects using binge-like eating of chocolate

[0281] Another study to evaluate Compound 1 for appetite suppressant effects was conducted, on binge-like eating of chocolate.

5 [0282] *Methods.* A new group of male Sprague-Dawley rats (n=8; initial weight 300-325 g) was used for the binge-like eating experiment. They were pair-housed under the same conditions described above, however, they were not food restricted, and in the home cage were allowed *ad libitum* access to food (laboratory chow) and water. Acquisition of the binge-like eating took place over the course of 12 exposure sessions. A 3-day, 1-hr
10 habituation exposure to an empty feeding cage with a ceramic dish took place before chocolate exposure. With chocolate exposure, rats received chocolate (0.3 g fat, 0.57 g carbohydrate, and 0.073 g protein with a total of 5.34 kcal/g) on days 1, 2, 4, 6, 7, 9, 12, 14, 15, 18, 23, and 28. On exposure days, rats were placed in an empty feeding cage with a ceramic dish containing ground chocolate for 1 hr. Weight of chocolate was taken before
15 and after each session to determine intake. These acquisition procedures led to gradually increased levels of chocolate intake across sessions (from 0.9 ± 0.3 g chocolate on the first session to 5.5 ± 0.5 g on the 12th session (see **FIG. 13**)

[0283] *Drug Administration.* Upon completion of the 12 acquisition sessions of binge-like eating rats continued to be exposed to chocolate sessions twice a week for 1-
20 hr in empty feeding cages with a ceramic dish containing chocolate. One session was for maintenance of the binge-like behavior, and then the second was for drug treatment. These sessions took place randomly throughout the week with the maintenance session always occurring prior to the drug treatment session. Compound 1 was dissolved in 0.3 % Tween 80 in dH₂O. Vehicle (VEH), or doses of 5.0, 10.0, and 20.0 mg/kg were
25 administered via oral gavage once a week for testing. A pre-treatment lead time of four hours was used. A within-subjects design was used in this study, with each rat receiving one treatment per week for a total of four weeks. Treatment conditions were selected randomly.

[0284] *Data Analysis.* Repeated measures ANOVA and planned comparisons were
30 used to assess the effect of Compound 1 on binge-like eating of chocolate.

[0285] *Results.* The results of the binge-like eating experiment are shown in **FIG. 8**, **FIG. 9**, and **FIG. 13**. **FIG. 13** depicts the acquisition of binge-like chocolate intake over

the 12 training sessions. **FIG. 8** shows the suppressive effects of Compound 1 administration of binge-like eating. There was an overall significant effect of Compound 1 treatment [$F(3,21) = 17.3$, $p < 0.001$]. Planned comparisons revealed that the 5.0 mg/kg dose of Compound 1 did not significantly suppress chocolate intake [$F(1,21) = 1.5$, n.s.],
5 but there were significant reductions in chocolate intake at the 10.0 [$F(1,21) = 20.4$, $p < 0.001$] and 20.0 [$F(1,21) = 4.09$, $p < 0.001$] mg/kg doses.

Example 8. Assessment of Compound 1 on sleep using repeated measures in rats

[0286] Using a counter-balanced, repeated measures design, three doses of Compound 1 (1-10 mg/kg, p.o.) were tested for their effects on sleep/wake parameters in
10 adult male Sprague-Dawley rats ($n=8$). The results were compared with the effects on caffeine (10 mg/kg).

[0287] *Methods.* Eight ($n = 8$) adult male Sprague Dawley rats were used in this study. Each rat received Compound 1 at 3 doses (1, 3 and 10 mg/kg), vehicle (purified H_2O - negative control) and caffeine (10 mg/kg - positive control). Dosings were
15 administered orally during the middle of the rats' normal inactive period on occurrences separated by a minimum of 3 days. Sleep parameters (non-rapid eye movement sleep, NR; rapid eye movement sleep, REM) were recorded and the first 6 hours post-dosing records were analyzed. Results were compared to vehicle, as shown in **FIG. 6** and **FIG. 7**.

20 [0288] *Results.* Compound 1 has wake-promoting effects at 10 mg/kg p.o. in rats with a complete suppression of REM sleep. 3 mg/kg p.o. also significantly increased wake and reduced REM sleep, but to a lesser extent.

Example 9. Assessment of Compound 1 in the rat 5-choice serial reaction time task (5-CSRTT)

25 [0289] The 5-choice serial reaction time task (5-CSRTT) is widely used to measure attentional performance and response control (motor impulsivity) in rodents. A strength of the test is its adaptability to task modification. Variations to stimulus duration and frequency of stimulus presentation, amongst others, have become commonly used to challenge performance in the context of attention and response control. The primary
30 objective of these studies was to examine the effect of Compound 1 on attentional

performance and on aspects of response control, defined as premature responses (PREM) and perseverative responses (PSV), measures of impulsive action, and compulsive action respectively. Two experimental manipulations were undertaken to differentially challenge performance. Specifically, (1) test Compound 1 (1, 3, 10 mg/kg) under standard
5 test conditions of 0.75s SD, 5s ITI, 100 trials, and (2) test Compound 1 (1, 3 mg/kg) against a long ITI challenge. The long ITI challenge is designed to elevate PREM and PSV responses and so provide a means to examine the effect of both test articles on measures of impulsive and compulsive action.

Materials

10 [0290] Vehicle Control

Dosage form: 0.3% Tween80 in 0.9% Saline

Pretreatment time: 180 minutes

[0291] Compound 1

15 Dosage form: Compound 1 was suspended in 0.3% Tween80 in 0.9% Saline and sonicated. Drug was administered at a volume of 5 mL/kg, oral (PO) route.

Pretreatment time: 180 minutes

Doses tested: Phase 1: 1, 3, 10 mg/kg; Phase 2: 1, 3 mg/kg

[0292] Subjects: 24 male Long Evans rats

[0293] Housing and Management of Test System: Following a one-week period of
20 familiarization to the test facility, animals were placed on a restricted diet regimen, in which they were fed approximately 20g of standard laboratory chow once per day (corresponding to ~80% of normal food consumption) following the completion of study procedures (between 16:00h and 18:00h). Overall food intakes were therefore based on food earned during 5-choice training/testing and chow at the end of each study day. On
25 days where no training/testing occurred, the daily allotted lab chow was increased to approximately 24g per animal. Water was available ad-libitum except during 5-choice training/testing sessions. Animals were maintained on a 12h/12h light/dark cycle with all testing conducted during the animals' light cycle.

[0294] 5-choice serial reaction time task: 5-choice operant chambers were housed in
30 sound-insulated and ventilated enclosures. Chambers consisted of an aluminum enclosure (25 x 30 cm), containing a reward magazine attached to a food pellet dispenser and house

light on one wall, and on the opposite wall an array of 5 square niches (2.5 x 2.5 x 2.5 cm) arranged on a curved panel and raised 2.5 cm from the grid floor. An LED was positioned at the rear of each niche. Each niche, and the reward magazine, also contained a photocell to detect head entry. Test chambers were controlled by Med PC software.

5 **[0295]** The 5-CSRTT schedule began with the illumination of the house light and delivery of a food pellet. A nose-poke into the magazine tray initiated the first trial which consisted of an inter-trial interval (ITI, 5s) followed by the random illumination of one of the 5 lights for a fixed interval (stimulus duration, SD). If a nose-poke was registered in the illuminated niche before the end of either the SD, or a fixed interval after this period
10 (limited hold, LH) a further pellet was dispensed and a Correct Trial registered. An incorrect nose poke (Incorrect Trial) or failure to respond within the allotted time (Missed Trial) resulted in a Time Out (TO) period in which the house light was extinguished for 5s. Responding into one of the five niches during the ITI (PREM response), resulted in a further TO. PSV responses were not punished by a TO.

15 **[0296]** Each session ran for either 100 trials or 60 min, depending on which session endpoint was achieved first. Animals were trained via a series of steps to final test conditions of 0.75s SD, 5s ITI, 5s limited hold. Target performance was stable performance around a threshold of 80% correct ($[\text{correct}/(\text{correct} + \text{incorrect})] * 100$) and <20% omissions for at least a two week period. At this point drug testing began according
20 to a repeated measures design with animals receiving treatment over repeated test sessions. Test sessions were run twice weekly under the standard (5s ITI) and long ITI schedule to allow drug washout and to re-baseline subjects between cycles.

[0297] Phase 1: The effect of Compound 1 (1, 3, 10 mg/kg) or vehicle control was investigated on test performance under standard test conditions of: 0.75s SD, 5s ITI, 5s
25 LH, 100 trials total. Treatments were administered in a randomized sequence.

[0298] Phase 2: The effect of Compound 1 (1 and 3 mg/kg) or vehicle control was investigated in a 10s ITI 5-choice schedule (10s ITI, 0.3s SD, 5s LH, 100 trials). Treatments were administered in a randomized sequence.

[0299] Statistical Analyses: Primary measures of performance from the 5-CSRTT,
30 i.e. accuracy measured either as % correct ($[\text{\# correct}/\text{\# correct} + \text{\# incorrect}] * 100$) or % hit ($[\text{\# correct}/\text{\# correct} + \text{\# incorrect} + \text{\# omissions}] * 100$), speed of responding (correct latency), incomplete trials (omissions) and total # trials are expressed as means and SEM.

Results

- [0300] Phase 1: Effect of Compound 1 on 5-choice task performance: Standard Conditions: Compound 1 was tested at doses 1, 3, and 10 mg/kg in all rats at each dose according to a repeated measures design. A vehicle pretreated group served as control.
- 5 Main effects of treatment were found for total trials ($F_{3,69}=4.4$; $P<0.01$), PREM responses ($F_{3,69}=5.1$; $P<0.01$) and PSV responses ($F_{3,69}=4.6$; $P<0.01$). These main effects reflected a dose-related decrease in PREM and PSV responses following Compound 1 pretreatment relative to vehicle control. Additionally, trial number was decreased at the 10 mg/kg dose. There were no main effects of treatment on any other
- 10 task measure including accuracy. 5-CSRTT results obtained under standard test conditions (0.75 sec. stimulus duration, 5 sec. ITI, 100 trials) are shown in **FIG. 10A** and **FIG. 10B**.
- [0301] Phase 2: Effect of Compound 1 on 5-choice task performance: 10s ITI: Compound 1 was tested at doses 1, and 3 mg/kg in all rats at each dose according to a
- 15 repeated measures design under the 10s ITI schedule. A vehicle pretreated group served as control. Increasing the ITI from 5s to 10s, and duration of the visual stimulus from 0.75s to 0.3s, reduced accuracy (% correct; 5s ITI: $83.9\pm1.5\%$; 10s ITI: $68.5\pm2.4\%$; $P<0.01$) and increased both PREM (5s ITI: 6.0 ± 1.2 ; 10s ITI: 46.7 ± 10.2 ; $P<0.01$) and PSV (5s ITI: 20.9 ± 3.4 ; 10s ITI: 33.8 ± 7.4 ; $P<0.05$) responses. The effect of Compound 1 on
- 20 task performance under the 10s ITI schedule was evaluated against vehicle pretreatment under the same condition. There were no main effects of treatment on any measure ($F_{2,40}\leq2.5$; NS), i.e., no effects of treatment on accuracy (% correct, % hit) or on PREM/PSV responses when all $N=21$ rats were included in the analysis. Subsequently the rats were sub-grouped into low impulsive (LI) and high impulsive (HI) based on the
- 25 level of PREM responses made following vehicle pretreatment under the 10s ITI schedule, (i.e., PREM: LI: 16.7 ± 2.4 ; HI: 93.9 ± 21.6 ; $P<0.01$). This subgrouping resulted in main effects of subgroup on PREM ($F_{1,12}=8.0$; $P=0.02$), and PSV responses ($F_{1,12}=8.3$; $P=0.01$), reflecting the HI rats to have significantly higher PREM and PSV responses relative to their LI counterparts. In terms of the effect of Compound 1 on task
- 30 performance in these subgroups, main effects of treatment and subgroup x treatment interactions were noted for both PREM (treatment: $F_{2,24}=6.7$; $P<0.01$; subgroup x

treatment: $F_{2,24}=10.2$; $P<0.01$) and PSV responses (treatment: $F_{2,24}=4.2$; $P=0.02$; subgroup x treatment: $F_{2,24}=7.7$; $P<0.01$).

Example 10. A Phase 2a, 4-Week, Single Arm, Open-label, Multi-center Study to Assess Safety, Tolerability, and Preliminary Efficacy of Compound 1 in Women with Vasomotor Symptoms Due to Menopause

[0302] A multi-center study was conducted to evaluate the effect of Compound 1 in patients with VMS due to menopause. Approximately 24 participants with VMS due to menopause are examined. This study consists of a Screening Period, a Treatment Period, and a Follow-up Period. The study is designed with a maximum duration of up to 12 weeks (4 weeks screening, 4 weeks treatment, 4 weeks follow up). In this single-arm, open-label study, all participants receive Compound 1. Compound 1 is administered at a starting dose of 15 mg qd for 1 week, increasing to 30 mg qd for a further 1 week, followed by 60 mg for a further 2 weeks of administration for patients who tolerate the previous dose level.

[0303] Severity and frequency of VMS are assessed by use of a Hot Flash patient diary which participants complete on a daily basis to document the number of moderate to severe hot flashes and the overall severity over the day of hot flashes. Other scales e.g., SIGH-ADS CGI scale, PGI, ESS, FCQ-T-R, DSST are used to measure other common symptoms of menopause.

I. Dosing Information

Compound	Compound 1
Dose formulation	Powder in (Hard-Gelatin) Capsule
Unit dose strength(s)	15 mg
Dosage level(s)	1 capsule for 15 mg/day, 2 capsules for 30 mg/day, 4 capsules for 60 mg/day
Route of administration	Oral

II. Inclusion and Exclusion Criteria

[0304] Inclusion:

- **Age:** Female 45 years to 60 years of age inclusive
- **Type of Participant and Disease Characteristics:** Women who are
5 perimenopausal or early postmenopausal (within 5 years of last menstrual period)
with significant menopause-related symptoms, as indicated by the following
criteria:
 - Capable of giving signed informed consent
 - Women who have experienced changes in menstrual cycle frequency or
10 duration, and/or symptoms that are indicative of menopausal transition, as
determined by the investigator.
 - GCS total score > 20, and
 - GCS subscore for vasomotor symptoms ≥ 3 , and
 - Over the 10 days prior to enrollment (during the Screening Period), subject
15 has a minimum of 7 to 8 moderate to severe hot flashes (VMS) per day, or
50 to 60 per week.
 - Five or more moderate or severe hot flashes per week (self- reported at
screening)
 - For women who are using a hormonal IUD, a FSH level will be required
20 to be > 20 mIU/ml because menstrual periods are irregular with IUDs that
use hormones making assessment of menopausal transition difficult.
 - Willingness to discontinue SSRIs, SNRIs, or bupropion, if applicable, at
least 4 weeks before Study Day 1
- **Weight:** Body weight > 50 kg; BMI within the range 17.5 to 40.0 kg/m²
25 (inclusive).
- **Sex:** Female participants not of childbearing potential or are of childbearing
potential and willing to use an acceptable contraceptive method as described in
Clinical Trial Facilitation Group recommendations related to contraception and
pregnancy testing in clinical trials (2014).

30

[0305] Exclusion:

- **Medical Conditions:**

- 1 Participants with clinically overt alcohol or drug use disorder (including use of cannabis/cannabinoids within 4 weeks prior to screening).
- 5 • 2 Participants with a history of psychiatric diagnoses (schizophrenia, schizoaffective, obsessive-compulsive disorder, bipolar disorder, or ADHD).
- 3 Participants with a history of seizures (except for childhood febrile convulsions).
- 4 Participants with current episode of major depression with HAM-D-17
10 score > 17 [to be calculated as a subscore of the SIGH-ADS].
- 5 Participants with prior or current history of a malignant tumor, except for basal cell carcinoma in remission.
- 6 Participants with a current history of significant cardiovascular, pulmonary, gastrointestinal, renal, hepatic, metabolic, hematological,
15 immunological, or neurological (excluding focal onset epilepsy) disease that, in the opinion of the investigator or medical monitor, could compromise either the patient's safety or the results of the study.
- 7 Participants with a history of cardiovascular disease including:
 - a) Uncontrolled hypertension (systolic BP > 165 mmHg or diastolic
20 BP > 100 mm Hg) (average of 3 measurements at least 5 minutes apart)
 - b) History of myocardial infarction, cardiac arrhythmia (other than sinus arrhythmia)
 - c) Patients with a 12-lead ECG demonstrating either of the following:
 - QTcF > 450 msec for males and > 470 msec for females (average
25 of 3 ECGs obtained at the Screening Visit and assessed by central reader)
 - QRS interval > 120 msec at the Screening Visit
 - Arrhythmia (other than sinus arrhythmia), conduction abnormalities (Atrioventricular block Grade 1 is allowed)
- 8 Patients who express suicidal ideation or have recent history of suicidal
30 behavior and who, in the opinion of the investigator, are at risk of harming themselves.

- 9 Participants who have abnormal findings identified during the Screening Period assessments, including neurological and physical examinations, hematology and biochemistry parameters, pulse rate and/or blood pressure and ECG, as compared with the appropriate reference ranges.
- 5 • 10 Participants with a history of unexplained uterine bleeding or endometrial hyperplasia.
- 11 Participants with a history of acute angle closure glaucoma.
- 12 Participants with medication for VMS taken during the 12 months prior to Screening visit, hormone therapies in prior 6 months to Screening visit, and other
10 medication taken 90 days prior to the Screening visit and up to the first dose of study medication (Treatment period) will be as prior medication.
- 13 Participants not to take any new concomitant medication without first consulting investigator.
- 14 Participants taking any medication or vaccine (including OTC or
15 prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:
 - Reason for use
 - Dates of administration including start and end dates
 - 20 ○ Dosage information including dose and frequency
- **Prior/Concomitant Therapy:**
- 15 Participants currently receiving sleep medication at screening, with the exception of melatonin or diphenhydramine or other OTC sleep medications up to 3 times per week.
- 25 • 16 Participants currently taking prohibited medications: SSRIs, SNRIs, bupropion, MAO inhibitors, BCRP substrates (ozanimod, rosuvastatin, simvastatin, sofosbuvir, sulfasalazine, sunitinib, teriflunomide), stimulants, or non-stimulants used in the treatment of cognitive disorders, excessive daytime sleepiness, narcolepsy, stimulants and non-stimulant ADHD medications, and
30 more than one antidepressant given at a therapeutic dose.
- 17 Participants taking other treatments (RX, OTC, or herbal) for VMS.

- 18 Participants using oral HRT within the last 2 months or long-acting HRT within the last 6 months prior to screening.
- 19 Participants taking prohibited hormonal medications or any treatment for VMS (prescription, OTC or herbal) or is not willing to wash out and discontinue use of these medications for the full duration of study conduct (Section 6.5 and 6.5.1). Prior or current history of a malignant tumor, except for basal cell carcinoma in remission.
- **Prior Hormone Therapy:**
- 20 For women who recently discontinued hormone therapy, the therapy must have been discontinued for at least the following durations prior to the Screening visit:
 - 1 week or longer for prior vaginal hormonal products (rings, creams, gels and inserts);
 - 4 weeks or longer for prior transdermal estrogen alone or estrogen/progestin products;
 - 8 weeks or longer for prior oral estrogen and/or progestin therapy;
 - 8 weeks or longer for prior intrauterine progestin therapy;
 - 3 months or longer for prior progestin implants and estrogen alone injectable drug therapy; or
 - 6 months or longer for prior estrogen pellet therapy or progestin injectable drug therapy.
- **Prior/Concurrent Clinical Study Experience:**
- 21 Participation in another clinical study with an Investigational IMP administered in the last 30 days or 5 half-lives, whichever is longer.
- 22 Positive test for drugs of abuse (amphetamines, methamphetamines, barbiturates, cocaine, opiates, methadone and benzodiazepines, phencyclidine, 3,4methylenedioxymethamphetamine, tetrahydrocannabinol). A positive test that can be explained by use of a prescription medicine is not exclusionary.
- **Other Exclusions:**
- 23 Involvement in the planning and/or conduct of the study (applies to both Noema staff and/or staff at the study site).

- 24 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.
- 25 Previous enrollment in the present study.
- 5 • 26 Currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

III. Objectives and Endpoints

Objectives	Endpoints
Primary	
To examine the safety and tolerability of Compound 1 in participants with VMS due to menopause	Withdrawals due to AEs
Secondary / Safety	
To examine the safety and tolerability of Compound 1 in participants with VMS due to menopause	- SAEs - AESIs (euphoria, hypertension) - Suicidal ideation and behavior assessed using the S-STS - Withdrawal symptoms assessed using the PENN PWC - Nature, frequency, and temporality of TEAEs (nonserious and serious) including abuse-related AEs and AEs related to Medication Handling Irregularities

Secondary / Efficacy	
To examine the effect of Compound 1 on the frequency and severity of VMS due to menopause	- Mean change in daily frequency of moderate or severe VMS from baseline at Week 4 as recorded in the Hot Flash patient diary - Mean change in daily severity of VMS from baseline at Week 4 as recorded in the Hot Flash patient diary
To examine the effect of Compound 1 on CGI-S	Change in CGI-S from baseline at Week 4
Exploratory	
To examine the temporal effect of Compound 1 on VMS due to menopause	- Mean change in frequency of VMS from baseline at Weeks 1, 2 and 3 as recorded in the Hot Flash patient diary - Mean change in severity of VMS from baseline at Weeks 1, 2 and 3 as recorded in the Hot Flash patient diary
To examine response rate of Compound 1	- Response defined as 50%, 75% and 100% reduction from baseline in mean frequency of VMS at Week 4 as recorded in the Hot Flash patient diary - Response defined as 50%, 75% and 100% reduction from baseline in mean severity of VMS at Week 4 as recorded in the Hot Flash patient diary
To examine the effect of Compound 1 on global VMS using GCS scale	GCS score from baseline at Week 4

To examine the effect of Compound 1 on depression as measured by the SIGH-ADS	Change in SIGH-ADS total score from baseline at Week 4
To examine the effect of Compound 1 on PGIC	PGI-C score from baseline at Week 4
To examine the effect of Compound 1 on plasma biomarkers of inflammation	Change in neuroinflammatory biomarkers (e.g., CRP, IL-6, TNFα) from baseline at Week 4
To examine the effect of Compound 1 on food craving as measured by the FCQ-T-R	Change in FCQ-T-R total score from baseline at Week 4
To examine the effect of Compound 1 on cognitive endpoints using the DSST	Change in DSST total score from baseline at Week 4
To examine the effect of Compound 1 on an executive function as measured by the BRIEF-A	Change in BRIEF-A total score and individual items from baseline at Week 4
To examine the effect of Compound 1 on menopausal symptoms as measured by the MENO-D	Change in MENO-D total score and individual items from baseline at Week 4
To examine the effect of Compound 1 on daytime sleepiness	Change in sleepiness as measured by the ESS from baseline at Week 4
To examine the effect of Compound 1 on body weight, BMI, and metabolic biomarkers	Change in body weight, BMI, cholesterol, triglycerides, and glucose from baseline at Week 4
Exploratory - PK	
To examine exposure of Compound 1	Plasma concentration of Compound 1

IV. Analysis of Secondary Efficacy Endpoints

- [0306] The data from the Hot Flash patient diary is summarized in multiple ways in order to characterize vasomotor symptoms. Such summaries include:
- Weekly mean change in the frequency of moderate or severe VMS from baseline to Week 4
 - Weekly mean change in the severity of moderate or severe hot flashes from baseline to Week 4
 - Weekly mean change in the frequency of hot flashes (of any severity) from baseline to Week 4
- [0307] Similar summaries are provided for each week (i.e., Baseline, Week 1, 2, 3 and 4 and Follow-up). The severity score for a specific week is derived for each patient. For categorical endpoints (e.g., change in CGI-S score from baseline to Week 4), frequency counts and percentages are calculated.

V. Study Assessments and Procedures

A. Efficacy Assessments

[0308] The following assessments are completed in the following order.

Assessment Order	Assessment
VMS	Hot Flash Diary; frequency and severity of VMS episodes
Global VMS	Patient: PGI-C Physician: CGI-S, CGO-S
Daytime sleepiness	ESS
Food craving	FCQ-T-R
Cognitive dysfunction	Computerized DSST
Mood/Anxiety	SIGH-ADS

B. Vasomotor Symptoms Due to Menopause

- [0309] The effect of Compound 1 on VMS due to menopause will be measured using the Hot Flash patient diary. Patients will complete the Hot Flash patient diary starting after the screening visit and then daily until the follow up visit. This diary is designed to document the frequency of moderate to severe hot flashes, and the severity

of hot flashes using an 11-point numerical rating scale (0 for no, 10 for as severe as you can imagine).

- [0310] The CGI-S rating is based upon observed and reported symptoms, behavior, and function in the past seven days and asks the clinician one question: “Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?” which is rated on the following seven-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients.

C. Other Symptoms of Menopause

- 10 [0311] **Global Impression:** The self-report measure PGI-C reflects a patient's belief about the efficacy of treatment. PGI-C is a 7-point scale depicting a patient's rating of overall improvement.
- [0312] **Depression:** The SIGH-ADS contains 29 items of which 21 HAM-D, and 8 atypical symptom components related to social withdrawal, weight gain, appetite increase, increased eating, carbohydrate craving/eating, hypersomnia, fatigability, and diurnal variation (in mood or energy).
- 15 [0313] **Daytime Sleepiness:** Daytime sleepiness will be assessed using the ESS which is a scale intended to measure daytime sleepiness by use of a very short questionnaire. The ESS is a self-administered questionnaire with 8 questions.
- 20 Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life (ASP), or their 'daytime sleepiness'.
- 25 [0314] **Food Cravings:** The effect of Compound 1 on food cravings will be assessed using the FCQ-T-R total score. The 15-item FCQ-T-R measures the frequency and intensity of food craving experiences in general. Items are scored on a 6-point scale from never/not applicable (1) to always (6).
- 30 [0315] **Cognition:** The effect of Compound 1 on cognitive endpoints will be assessed using the DSST. The DSST is a neuropsychological test sensitive to brain damage, dementia, age, and depression. The test is not sensitive to the location of brain-

damage (except for damage comprising part of the visual field). It consists of (e.g., nine) digit-symbol pairs (e.g. 1/-, 2/ $\perp$, ... 7/ Δ , 8/X, 9/=) followed by a list of digits. Under each digit the patient should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (e.g., 90 or 120 sec) is measured.

5 **VI. Participant Withdrawal – Treatment Discontinuation Criteria**

<u>Criteria</u>	<u>Threshold</u>
Change from baseline blood pressure	Increase of ≥ 30 mmHg systolic or ≥ 20 mmHg diastolic (as measured by the average of 3 pre-dose readings, with 1-hour persistence)
Change from baseline pulse	Increase of >30 bpm (as measured by the average of 3 pre-dose readings, with 1-hour persistence)
Adverse Events	Participant experiences severe signs or symptoms of poor tolerability Participant experiences suspected treatment-related rash
Suicidal Ideation	Participant demonstrates clinically significant potential suicidal ideation or behavior per investigator judgement using the S-STS
Abnormal Liver Function - Liver Function Testing	Serum ALT or AST level $\geq 5x$ ULN Serum ALT or AST level $\geq 3x$ ULN and serum total bilirubin level $\geq 2x$ ULN. NOTE: Serum bilirubin fractionation should be performed if the serum total bilirubin level is $\geq 2x$ ULN.) Serum ALT or AST level $\geq 3 \times$ ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia).
Abnormalities in ECG - Central ECG read (average measurement over 3 ECGs)	QTcF value ≥ 500 msec Increase of ≥ 60 msec from baseline in QTcF with an absolute QTcF value ≥ 470 msec Following manual recheck, and central reader confirms clinically significant abnormality with increase from baseline of >60 msec, participant to be discontinued

VII. Protocol Deviations

- All deviations must be addressed in subject source documentation; subject specific deviations should also be captured within CTMS.
- 5 • Should include the root cause of deviation, corrective and preventive actions.
- Report to IRB when applicable as per IRB guidelines.
- Should the site become aware of any deviations, the site should notify the CRA (and/or Sponsor) as soon as possible.
- 10 • Protocol deviation logs will be provided following each monitoring visit (as applicable) for PI review and filing.
- Final protocol deviation log will be sent to the site before database lock for PI review and filing at final monitoring visit.

Example 11. Interim results from Phase 2a, 4-Week, Single Arm, Open-label, Multi-center Study to Assess Safety, Tolerability, and Preliminary Efficacy of Compound 1 in Women with Vasomotor Symptoms Due to Menopause

[0316] As described in **Example 10** above, the present study was conducted to evaluate safety, tolerability, and efficacy of Compound 1 in women with vasomotor and other symptoms due to menopause. The data provided below summarize preliminary findings for the effects of Compound 1 in 17 women with VMS due to menopause. An initial sentinel cohort (Cohort 1; n =5) was treated for 4 weeks with Compound 1 at 15 mg, and another set of participants were included in Cohort 2 (n = 15) for treatment over the full-dose range (up to 60 mg) for 12 weeks. Daily assessments were performed for VMS symptoms using a validated diary, and weekly to monthly assessments were performed across other symptom domains. The demographics and disposition of the study participants is summarized in the table below.

Variable	Cohort 1 n (%)	Cohort 2 n (%)
Age mean years (SD)	53.2 (4.7)	53.5 (5.3)
Race		
Asian	0	1 (8.3)
Black/AA	3 (60)	7 (58.3)
Native H/PI	0	1 (8.3)
White	2 (40)	3 (25)
Other	0	0
Hispanic/Latino	1 (20)	0
Weight mean kg (SD)	87.9 (16.4)	78.7 (16.3)
BMI kg/m ² (SD)	33.4 (6.2)	28.7 (5.4)

“AA” = African American
“H/PI” = Hawaiian/Pacific Islander
“SD” = standard deviation
“BMI” = body mass index

5

[0317] A summary of the present status of the study participants is summarized in the table below.

	n (%)
Enrolled	17
Cohort 1 (15 mg x 4-week exposure)	5
Completed Cohort 1	5 (100)
Cohort 2 (up to 60 mg x 12-week exposure)	12
Completed /Ongoing Cohort 2	8
Discontinued	7
Adverse event	5
Withdrawal of consent	2
Lost to follow-up	0
Protocol deviation	0

10 [0318] Results from the 4-week sentinel cohort (Cohort 1) and preliminary 8 week results from the 12-week exposure group (Cohort 2) indicate a robust reduction in the mean number of moderate-to-severe hot flashes per day.

	Cohort 1 (n=5) n (%)		Cohort 2 (n=12) n (%)		All patients (n=17)	
Mean number of moderate/severe hot flashes/day (SD)	14.6 (10)		11.5 (6.3)		12.4 (7.4)	
Week 4	n=5 HF count (SE)	n=5 HF % change (SD)	n=4 HF count (SE)	n=4 HF % change (SD)	n=9 HF count (SE)	n=9 HF % change (SD)
	-8.2 (2.3)*	-32.1 (52.9)	-6.6 (1.5)**	-38.8 (15.6)	-7.4 (1.3)**	-35.1 (38.8)
LS mean change from baseline in Mod/severe HF/day: count (SE) and % change from baseline (SD)						
Week 8	n=4	n=4	n=3	n=3	n=7	n=7
	-11 (4.1)	-81.7 (25.6)	-5.4 (1.8)*	-33.6 (25)	-6.5 (2)*	-61.1 (34.6)
LS mean for change from baseline in Mod/severe HF/day: count (SE) and % change from baseline (SD)						
Week 12		ongoing		ongoing		ongoing

From baseline *p<0.01 **p<0.001
“SD” = standard deviation”
“LS” = least squares
“HF” = hot flashes
“SE” = standard error

[0319] A summary of other physiological effects resulting from treatment with Compound 1 is provided in the table below.

	Baseline (SD)	Week 8 Avg change $\pm$ SD (n=17)
Systolic BP (mm Hg)	118 $\pm$ 9.4	4.5 $\pm$ 13
Diastolic BP (mm Hg)	78.4 $\pm$ 9.2	1.6 $\pm$ 8.6
Heart rate (bpm)	68 $\pm$ 8.9	3.6 $\pm$ 6.5
Weight (kg)	82.7 $\pm$ 16.3	-1.4 $\pm$ 2.2
BMI (kg/m ²)	30.62 $\pm$ 6	-0.59 $\pm$ 0.86

- 5 “SD” = standard deviation
 “BP” = blood pressure”
 “BMI” = body mass index

[0320] The above data suggests that treatment with Compound 1 resulted in a moderate weight loss and reduction in body mass index in treated patients.

- 10 [0321] A summary of the safety profile, as indexed by prevalence of adverse effects (“AE”) is provided in the tables below.

Period 1	n (%)	AE	n (%)
Enrolled	17	Constipation	3 (17.6)
Any AE	8 (47.1)	Odynophagia	2 (11.8)
Mild		Headache	2 (11.8)
Moderate			
Severe			
AE leading to study discontinuation	2 (11.8)		
Serious AE	0		
Deaths	0		

- [0322] Combined, the above preliminary results demonstrate preliminary efficacy of Compound 1 in reducing VMS symptoms (hot flashes) in menopausal women, with the added benefit of producing a moderate reduction in weight and body mass index and an overall favorable safety and tolerability profile.
- 15

EQUIVALENTS AND SCOPE

[0323] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered
5 satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all
10 of the group members are present in, employed in, or otherwise relevant to a given product or process.

[0324] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any
15 claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are
20 referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or
25 steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

30 [0325] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the

instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

5 [0326] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

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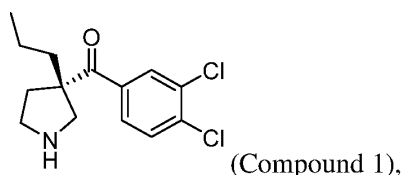
CLAIMS

What is claimed:

1. A method of treating a subject manifesting at least one symptom associated with menopause or post-menopause, wherein the symptom is selected from the group
5 consisting of:

- a vasomotor symptom;
- a cognitive symptom;
- a nervous system symptom;
- an emotional symptom; and
- 10 a physical symptom;

wherein said method comprises administering a composition comprising Compound 1 to the subject, wherein Compound 1 has the structure:

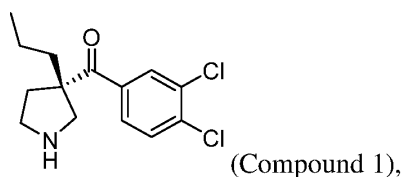


- or a pharmaceutically acceptable salt thereof,
15 sufficient to improve at least one symptom associated with menopause or post-menopause in the subject.

2. The method of claim 1, wherein the subject is about 40 to about 65 years of age.
- 20 3. A method of treating a subject manifesting at least one symptom associated with perimenopause, wherein the symptom is selected from the group consisting of:

- a vasomotor symptom;
- a cognitive symptom;
- a nervous system symptom;
- 25 an emotional symptom; and
- a physical symptom;

wherein said method comprises administering a composition comprising Compound 1 to the subject, wherein Compound 1 has the structure:



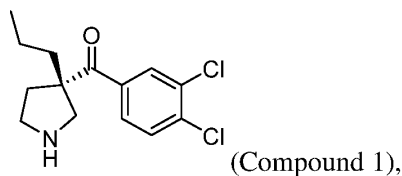
or a pharmaceutically acceptable salt thereof,
sufficient to improve at least one of the symptoms in the subject.

5 **4.** The method of any one of claims **1-3**, wherein the subject has a low estrogen level.

5. A method of treating a subject manifesting at least one symptom associated with induced-menopause, wherein the symptom is selected from the group consisting of:

- 10 a vasomotor symptom;
 a cognitive symptom;
 a nervous system symptom;
 an emotional symptom; and
 a physical symptom;

wherein said method comprises administering a composition comprising Compound 1 to
15 the subject, wherein Compound 1 has the structure:



or a pharmaceutically acceptable salt thereof,
sufficient to improve at least one of the symptoms in the subject.

20 **6.** The method of claim **5**, wherein the induced-menopause results from chemotherapy.

7. The method of claim **5**, wherein the induced-menopause results from surgical removal of one or both ovaries.

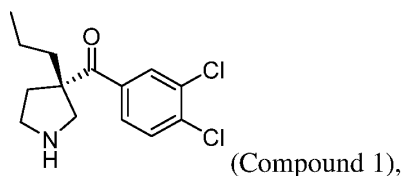
8. The method of claim 5, wherein the induced-menopause results from radiotherapy.

9. The method of claim 5, wherein the induced-menopause results from a drug or
5 medication.

10. A method of treating a subject manifesting at least one symptom associated with early onset menopause or early onset perimenopause, wherein the symptom is selected from the group consisting of:

- 10 a vasomotor symptom;
a cognitive symptom;
a nervous system symptom;
an emotional symptom; and
a physical symptom;

15 wherein said method comprises administering a composition comprising Compound 1 to the subject, wherein Compound 1 has the structure:



or a pharmaceutically acceptable salt thereof,
sufficient to improve at least one of the symptoms in the subject.

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11. The method of claim 10, wherein the early onset menopause or early onset perimenopause results from smoking or weight loss.

12. The method of claim 10, wherein the early onset menopause or early onset
25 perimenopause results from a chromosomal defect, an autoimmune disease, or a thyroid disease.

13. The method of claim 10, wherein the early onset menopause or early onset perimenopause results from low estrogen levels.

14. The method of any one of claims **1-13**, wherein the vasomotor symptom is selected from the group consisting of hot flashes, night sweats, and heart palpitations, or a combination thereof.

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15. The method of any one of claims **1-14**, wherein the cognitive symptom is selected from the group consisting of a cognitive executive dysfunction, and hypomnesia, or a combination thereof;

wherein the cognitive executive dysfunction is selected from the group consisting of an impairment of working memory, an impairment of cognitive flexibility, and an impairment of inhibition control.

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16. The method of any one of claims **1-15**, wherein the nervous system symptom is selected from the group consisting of fatigue, dizziness, a sleep-wake disorder, and appetite changes, or a combination thereof;

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wherein the sleep-wake disorder is selected from the group consisting of insomnia, somniphobia, and excessive daytime sleepiness.

17. The method of any one of claims **1-16**, wherein the emotional symptom is selected from the group consisting of irritability, anxiety, depression, low mood, lack of motivation, mood swings, and panic disorder, or a combination thereof;

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wherein low mood is selected from the group consisting of sadness, feeling anxious or panicky, worry, tiredness, low self-esteem, frustration, and anger.

18. The method of any one of claims **1-17**, wherein the physical symptom is selected from the group consisting of symptoms associated with vulvar and vaginal atrophy, bleeding associated with sexual activity, symptoms resulting from musculoskeletal changes, symptoms caused by urogenital changes, irregular periods, weight gain, bloating, sore breasts, headaches, electric shock sensations, burning tongue, gum problems, dry and itchy skin, loss of hair, brittle nails, changes in body odor, and allergies, or combinations thereof;

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wherein the symptoms associated with vulvar and vaginal atrophy is selected from the group consisting of vaginitis, vaginal dryness, loss of libido, and vaginal pain associated with sexual activity;

wherein the bleeding associated with sexual activity is selected from the group consisting of dyspareunia, dysuria, vaginal infections, pruritus, and dryness, irritation, itching, and/or burning in and around the vaginal area;

wherein the symptoms resulting from musculoskeletal changes is selected from the group consisting of myalgia, muscle pain, joint pain, arthralgia, and back pain;

wherein the symptoms caused by urogenital changes is changes in urinary frequency or urinary incontinence.

19. The method of any one of claims **1-18**, wherein the subject is manifesting a vasomotor symptom.

20. The method of any one of claims **1-18**, wherein the subject is manifesting a vasomotor symptom and a cognitive symptom.

21. The method of any one of claims **1-18**, wherein the subject is manifesting a vasomotor symptom and a nervous system symptom.

22. The method of any one of claims **1-18**, wherein the subject is manifesting a vasomotor symptom and an emotional symptom.

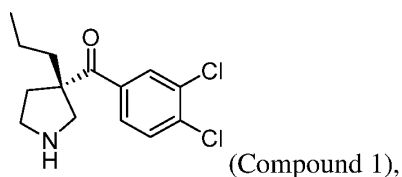
23. The method of any one of claims **1-18**, wherein the subject is manifesting a vasomotor symptom and a physical symptom.

24. The method of any one of claims **1-18**, wherein the subject is manifesting a vasomotor symptom, a cognitive symptom, and a nervous system symptom.

25. The method of any one of claims **1-18**, wherein the subject is manifesting a vasomotor symptom, a cognitive symptom, and an emotional symptom.

26. The method of any one of claims **1-18**, wherein the subject is manifesting a vasomotor symptom, a cognitive symptom, and a physical symptom.
27. The method of any one of claims **1-18**, wherein the subject is manifesting a
5 vasomotor symptom, a cognitive symptom, a nervous system symptom, and an emotional symptom.
28. The method of any one of claims **1-18**, wherein the subject is manifesting a
10 vasomotor symptom, a cognitive symptom, a nervous system symptom, and a physical symptom.
29. The method of any one of claims **1-18**, wherein the subject is manifesting a
15 vasomotor symptom, a cognitive symptom, a nervous system symptom, an emotional symptom, and a physical symptom.
30. The method of any one of claims **1-18**, wherein the subject is manifesting a
cognitive symptom.
31. The method of claim 30, wherein the cognitive symptom is brain fog.
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32. The method of any one of claims **1-18**, wherein the subject is manifesting a
cognitive symptom and a nervous system symptom.
33. The method of any one of claims **1-18**, wherein the subject is manifesting a
25 cognitive symptom and an emotional symptom.
34. The method of any one of claims **1-18**, wherein the subject is manifesting a
cognitive symptom and a physical symptom.
- 30 35. The method of any one of claims **1-18**, wherein the subject is manifesting a
cognitive symptom, a nervous system symptom, and an emotional symptom.

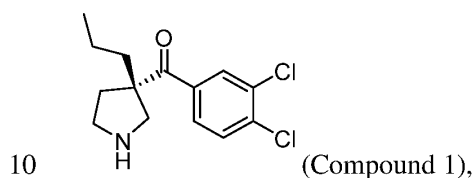
36. The method of any one of claims **1-18**, wherein the subject is manifesting a cognitive symptom, a nervous system symptom, and a physical symptom.
37. The method of any one of claims **1-18**, wherein the subject is manifesting a cognitive symptom, a nervous system symptom, an emotional symptom, and a physical symptom.
38. The method of any one of claims **1-18**, wherein the subject is manifesting a nervous system symptom.
39. The method of any one of claims **1-18**, wherein the subject is manifesting a nervous system symptom and an emotional symptom.
40. The method of any one of claims **1-18**, wherein the subject is manifesting a nervous system symptom and a physical symptom.
41. The method of any one of claims **1-8**, wherein the subject is manifesting a nervous system symptom, an emotional symptom, and a physical symptom.
42. The method of any one of claims **1-18**, wherein the subject is manifesting an emotional symptom.
43. The method of any one of claims **1-18**, wherein the subject is manifesting an emotional symptom, and a physical symptom.
44. The method of any one of claims **1-18**, wherein the subject is manifesting a physical symptom.
45. A method of treating a subject manifesting a vasomotor symptom, said method comprising administering a composition comprising Compound 1 to the subject, wherein Compound 1 has the structure:



or a pharmaceutically acceptable salt thereof, sufficient to reduce at least one of symptom associated with vasomotor symptoms in the subject,

wherein the vasomotor symptoms are selected from the group consisting of hot
5 flashes, night sweats, and heart palpitations.

46. A method of treating a subject manifesting a vasomotor symptom, said method comprising administering a composition comprising Compound 1 to the subject, wherein Compound 1 has the structure:



or a pharmaceutically acceptable salt thereof, sufficient to reduce at least one vasomotor symptoms and to reduce the weight of the subject,

wherein the vasomotor symptoms are selected from the group consisting of hot
15 flashes, night sweats, and heart palpitations.

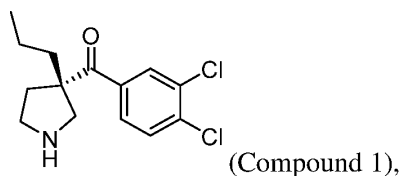
47. The method of any one of claim **45** or **46**, wherein the treatment suppresses appetite in the subject.

48. The method of any one of claims **45** or **46**, wherein the subject manifests hot
20 flashes or night sweats, or both hot flashes and night sweats.

49. The method of any one of claims **45** or **46**, wherein the subject manifests hot flash.

50. The method of any one of claims **45** or **46**, wherein the subject has a low estrogen
25 level.

51. A method of treating perimenopausal syndrome in a subject having a vasomotor symptom, said method comprising administering a composition comprising Compound 1 to the subject, wherein Compound 1 has the structure:



5 or a pharmaceutically acceptable salt thereof, sufficient to reduce at least one of symptom associated with vasomotor symptoms in the subject,

wherein the vasomotor symptoms are selected from the group consisting of hot flashes, night sweats, and heart palpitations.

10 **52.** The method of claim **51**, wherein the subject also has a cognitive symptom.

53. The method of claim **51** or **52**, wherein the subject also has a sleep-wake disorder.

15 **54.** The method of any one of claims **51-53**, wherein the subject also has a change in appetite.

55. The method of any one of claims **51-54**, wherein the subject also has an emotional symptom.

20 **56.** The method of any one of claims **1-55**, wherein the manifestation of the symptom occurs at least once daily.

57. The method of any one of claims **1-55**, wherein the manifestation of the symptom persists for at least a week, persists for at least two weeks, persists for at least a month,
25 persists for at least six months, persists for at least one year, or persists for at least two years.

58. The method of any one of claims **1-55**, wherein the manifestation of symptoms occurs periodically.

- 59.** The method of any one of claims **1-57**, wherein the composition is a pharmaceutical composition.
- 5 **60.** The method of any one of claims **1-57**, wherein the composition is administered orally.
- 61.** The method of any one of claims **1-57**, wherein the composition is administered once daily.
- 10 **62.** The method of any one of claims **1-57**, wherein Compound 1 is a free base form.
- 63.** The method of any one of claims **1-57**, wherein the composition comprises a pharmaceutically acceptable salt form of Compound 1.
- 15 **64.** The method of any one of claims **1-57**, wherein the composition comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount of about 1 mg to about 30 mg.
- 20 **65.** The method of any one of claims **1-57**, wherein the composition comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount of about 5 mg to about 25 mg.
- 66.** The method of any one of claims **1-57**, wherein the composition comprises
25 Compound 1, or a pharmaceutically acceptable salt thereof, in an amount of about 10 mg to about 20 mg.
- 67.** The method of any one of claims **1-57**, wherein the composition comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount of about 15 mg.
- 30 **68.** The method of any one of claims **1-57**, wherein therapeutic efficacy of the treatment is determined by assessing an improvement based on a Hot Flash patient diary.

69. The method of any one of claims **1-57**, wherein therapeutic efficacy of the treatment is determined by assessing an improvement based on a Hot Flash patient diary, where the subject shows a change from baseline.

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70. The method of claims **1-57**, wherein therapeutic efficacy of the treatment is determined by assessing an improvement based on a scale, wherein the scale is selected from the group consisting of clinical global impression of severity (CGI-S), structured interview guide for the Hamilton depression rating scale with Atypical Depression Supplement (SIGH-ADS), patient global impression of change (PGI-C), food craving questionnaire-trait-reduced (FCQ-T-R), digit symbol substitution test (DSST), Epworth Sleepiness Scale (ESS), behavior rating inventory of executive function—adult version (BRIEF-A), and MENO-D.

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