position in which it is contained.

[0030]

A “perimenopausal woman” refers to a woman within the interval in which the woman’s body makes a shift from more-or-less regular cycles of ovulation and menstruation toward permanent infertility or menopause. The interval may be a period of a few months, to several years, to 15 years or more before menopause. “Perimenopause” is also known as the menopausal transition. A “postmenopausal woman” refers to a woman who has undergone menopause, i.e., experienced twelve consecutive months without menstruation. A “menopausal woman” as used herein includes both a perimenopausal woman and a postmenopausal woman as defined herein. The menopause in these women may be either natural (such as with age), surgical (such as by removal of both ovaries), or induced by chemical treatment (such as by treatment with estrogen antagonists, e.g. fulvestrant, raloxifene, tamoxifen, or toremifene).

[0031]

The present inventors discovered a new treatment for vasomotor symptoms by administering an active agent that is a TRPM8 antagonist. Without wishing to be bound by any particular theory, the present inventors believe that TRPM8 antagonists utilize the body’s methods of passive cooling to prospectively reduce core body temperature. In use, the present inventors believe that TRPM8 antagonists will rebalance sensory input, allowing a new equilibration to a slightly lower, and newly stabilized, but still normal, core body temperature. The body’s need for excessive thermoregulatory shifts will be prevented and heat that would otherwise have been shifted to the skin surface in a hot flash will tend to be made unnecessary.

[0032]

The present disclosure is directed to a method for treating or preventing vasomotor symptoms in a subject in need thereof, comprising administering to the subject an effective amount of a TRPM8 antagonist. In some embodiments, the vasomotor symptom is hot flashes. In some embodiments, the subject is a human. The subject may be male or female. It is envisioned that the methods will be used for subjects that are prone to having, are having, or are expected to have vasomotor symptoms, such as hot flashes. The subject in need thereof may suffer from or anticipate suffering from vasomotor symptoms associated with menopause, with the symptoms or effects of a medical condition, with the side effects of a treatment for a medical condition, or with any other trigger or cause of vasomotor symptoms.

[0033]

Subjects include, but are not limited to, menopausal women, subjects who are taking or anticipate taking anti-estrogen drugs (such as tamoxifen or aromatase inhibitors), subjects who are anticipating or have gone through surgery, or subjects having or anticipating having any other condition or undergoing or anticipating undergoing any other treatment that results in changes in hormone levels.

[0034]

Subjects further include, but are not limited to, oncology patients. For example, subjects may include those who are anticipating, are undergoing, or have undergone

R^4 is independently, at each instance, H, C_{1-6}alk, -C_{1-3}haloalk, -OC_{1-6}alk, -OC_{1-3}haloalk, -$N(C_{1-6}alk)C_{1-6}$alk, -NHC_{1-6}alk, -$NC(=O)C_{1-6}$alk, -$N(C_{1-6}alk)C_{1-6}$alk, F, Cl, Br, CN, OH or NH_2; or R^3 and R^4 together form a four-atom unsaturated bridge containing 0 or 1 N atoms, wherein the bridge is substituted by 0, 1 or 2 R^5 substituents;
R^5 is independently, in each instance, halo, OR^a, CH_3 or CF_3;
R^6 is F, C_{1-6}alk, or OR^a;
R^a is independently, at each instance, H or R^b; and
R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alk, the phenyl, benzyl and C_{1-6} alk being substituted by 0, 1, 2 or 3 substituents selected from halo, oxo, C_{1-4}alk, C_{1-3}haloalk, -OC_{1-4}alk, -OH, -NH_2, -OC_{1-4}alk, -OC_{1-4}haloalk, -NHC_{1-4}alk, and -$N(C_{1-4}alk)C_{1-4}$alk.

[0046]

In certain embodiments, the amide compound is selected from the group consisting of:
(S)-N-((3-fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide;
(S)-N-((3-fluoro-4-(trifluoromethoxy)phenyl)(3-(trifluoromethyl)pyridin-2-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide;
(S)-N-((2-fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide;
(S)-5-fluoro-N-((3-fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide;
(S)-N-((3-fluoro-4-(trifluoromethyl)phenyl)(3-fluoropyridin-2-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide;
(S)-6-(((3-fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methyl)carbamoyl)nicotinic acid;
a pharmaceutically-acceptable salt thereof, a tautomer thereof, a pharmaceutically-acceptable salt of the tautomer, and a mixture thereof.

[0047]

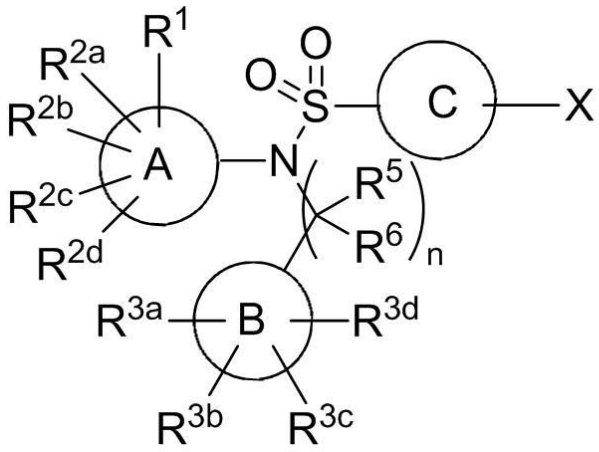
In some embodiments, the TRPM8 antagonist is chosen from sulfonamide compounds, such as those of formula (I), such as Compound A or a pharmaceutically acceptable salt thereof, and the effective amount for oral administration is chosen from about 0.01 to about 100 mg/kg per day, such as from about 0.1 to about 10 mg/kg per day or any amount in between. In some embodiments, the TRPM8 antagonist is chosen from sulfonamide compounds, such as those of formula (I), such as Compound A, and the effective amount for oral administration is from about 10 mg to about 400 mg, for example, from about 10 mg to about 400 mg per day. The effective amount of the TRPM8 antagonist can vary and may depend on a number of factors, such as the specific active agent, the type of composition or dosage form, the selected route of administration, and the subject under treatment, including factors such as age, weight,

CLAIMS

[Claim 1]

A Transient Receptor Potential Melastatin 8 (TRPM8) antagonist for use in a method for treating or preventing vasomotor symptoms in a subject in need thereof, wherein the TRPM8 antagonist is represented by the following formula (I):

[Chem. 1]



(I)

,

wherein:

Ring A is bicyclic aromatic heterocycle comprised of (a) pyridine condensed with benzene; or (b) pyridine condensed with 5 to 6-membered monocyclic aromatic heterocycle containing carbon atoms and 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom, and Ring A binds to a sulfonylamino moiety on a carbon atom adjacent to a nitrogen atom of pyridine ring constituting Ring A,

Ring B is (a) monocyclic or bicyclic aromatic hydrocarbon with 6 to 11 carbons as a ring atom; (b) monocyclic or bicyclic alicyclic hydrocarbon with 3 to 12 carbons as a ring atom; (c) 5 to 11-membered monocyclic or bicyclic aromatic heterocycle containing carbon atoms and 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom; or (d) 4 to 12-membered monocyclic or bicyclic non-aromatic

heterocycle containing carbon atoms and 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom,

Ring C is (a) benzene; or (b) 5 to 6-membered monocyclic aromatic heterocycle containing carbon atoms and 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom,

R^1 is (a) hydrogen; (b) C_1-C_6 alkyl which may be optionally substituted by 1 to 7 groups selected from C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen, oxo and hydroxy; (c) C_3-C_7 cycloalkyl which may be optionally substituted by 1 to 7 groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; (d) C_1-C_6 alkoxy which may be optionally substituted by 1 to 7 groups selected from C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, halogen and hydroxy; (e) phenyl which may be optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen; (f) halogen; or (g) nitrile,

R^{2a}, R^{2b}, R^{2c} and R^{2d} are each independently (a) hydrogen; (b) C_1-C_6 alkyl which may be optionally substituted by 1 to 7 groups selected from C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, halogen, oxo and hydroxy; (c) C_3-C_7 cycloalkyl which may be optionally substituted by 1 to 7 groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; (d) C_1-C_6 alkoxy which may be optionally substituted by 1 to 7 groups selected from C_1-C_6 alkoxy, C_3-C_7 cycloalkyl and halogen; (e) phenyl which may be optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen; (f) 5 to 6-membered monocyclic aromatic heterocyclic group which may be optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen; (g) 4 to 7-membered monocyclic non-aromatic heterocyclic group which may be optionally

substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen; (h) halogen; or (i) nitrile,

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently (a) hydrogen; (b) C_1-C_6 alkyl which may be optionally substituted by 1 to 7 groups selected from C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl (in which the cycloalkyl and halogenocycloalkyl may be each independently optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl and C_1-C_6 halogenoalkyl), C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy, phenyl, 5 to 6-membered monocyclic aromatic heterocyclic group, 4 to 7-membered monocyclic non-aromatic heterocyclic group (in which the phenyl, aromatic heterocyclic group and non-aromatic heterocyclic group may be each independently optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen), halogen, oxo and hydroxy; (c) C_3-C_7 cycloalkyl which may be optionally substituted by 1 to 7 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy, halogen and hydroxy; (d) C_1-C_6 alkoxy which may be optionally substituted by 1 to 7 groups selected from C3-C7 cycloalkyl, C_3-C_7 halogenocycloalkyl (in which the cycloalkyl and halogenocycloalkyl may be each independently optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl and C_1-C_6 halogenoalkyl), C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy, phenyl, 5 to 6-membered monocyclic aromatic heterocyclic group, 4 to 7-membered monocyclic non-aromatic heterocyclic group (in which the phenyl, aromatic heterocyclic group and non-aromatic heterocyclic group may be each independently optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen), halogen and hydroxy; (e) C_3-C_7 cycloalkoxy which may

be optionally substituted by 1 to 7 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy, halogen and hydroxy; (f) phenyl which may be optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen; (g) 5 to 6-membered monocyclic aromatic heterocyclic group which may be optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen; (h) 4 to 7-membered monocyclic non-aromatic heterocyclic group which may be optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen; (i) phenoxy which may be optionally substituted by 1 to 3 groups selected from C_1-C_6 alkyl, C_1-C_6 halogenoalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halogenocycloalkyl, C_1-C_6 alkoxy, C_1-C_6 halogenoalkoxy and halogen; (j) halogen; or (k) hydroxy, or

two substituent groups selected from R^{3a}, R^{3b}, R^{3c} and R^{3d} combine each other to form oxo,

R^5 and R^6 are each independently (a) hydrogen; (b) C_1-C_6 alkyl; (c) C_1-C_6 halogenoalkyl; (d) C_3-C_7 cycloalkyl; or (e) C_3-C_7 halogenocycloalkyl, or R^5 and R^6 combine each other at their terminals together with the adjacent carbon atom to form 3 to 7-membered monocyclic alicyclic hydrocarbon,

n is 0, 1 or 2;

X is (a) carboxy; (b) C_1-C_6 alkoxycarbonyl; (c) hydroxy-C_1-C_6 alkyl; (d) aminocarbonyl wherein a nitrogen atom may be optionally substituted by one group selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and nitrile; or (e) C_2-C_7 alkanoyl which may be optionally substituted by 1 to 3 halogens;

or a pharmaceutically acceptable salt thereof,

wherein the subject is a human subject.

[Claim 2]

The TRPM8 antagonist of claim 1, wherein the TRPM8 antagonist is administered as a composition comprising the TRPM8 antagonist and a pharmaceutically acceptable carrier.

[Claim 3]

The TRPM8 antagonist of claim 1, wherein the administration to the human subject of an effective amount of the TRPM8 antagonist decreases the human subject's core body temperature by about 0.5°C to about 2°C.

[Claim 4]

The TRPM8 antagonist of claim 1, wherein the TRPM8 antagonist is selected from the group consisting of:

4-({(1-cyclopropyl-4-methylisoquinolin-3-yl)[4-(trifluoromethoxy)benzyl]amino}-sulfonyl)-benzoic acid,

4-({(1-isopropyl-4-methylisoquinolin-3-yl)[4-(trifluoromethoxy)benzyl]amino}-sulfonyl)-benzoic acid,

4-{[{3-chloro-4-[cyclopropyl(difluoro)methyl]benzyl}(4-methylisoquinolin-3-yl)amino]-sulfonyl}-benzoic acid,

4-({(4-cyclopropylisoquinolin-3-yl)[4-(trifluoromethoxy)benzyl]amino}sulfonyl) benzoic acid,

4-{[{3-chloro-4-[cyclopropyl(difluoro)methyl]benzyl}(1-cyclopropyl-4-methylisoquinolin-3-yl)amino]-sulfonyl}-benzoic acid,
4-{[{4-[cyclopropyl(difluoro)methyl]-3-fluorobenzyl}(4-methylisoquinolin-3-yl)amino]sulfonyl}benzoic acid,
4-({[4-(trifluoromethoxy)benzyl][4-(trifluoromethyl)isoquinolin-3-yl]amino}sulfonyl)-benzoic acid,
4-[((4-cyclopropylisoquinolin-3-yl){[5-(trifluoromethyl)pyridin-2-yl]methyl}amino)-sulfonyl]benzoic acid,
4-{[{4-[cyclopropyl(difluoro)methyl]-3-fluorobenzyl}(4-cyclopropylisoquinolin-3-yl)amino]sulfonyl}benzoic acid, and
a pharmaceutically acceptable salt thereof.

[Claim 5]
The TRPM8 antagonist of claim 1, wherein the TRPM8 antagonist is administered daily.

[Claim 6]
The TRPM8 antagonist of claim 1, wherein the TRPM8 antagonist is administered once daily or wherein the TRPM8 antagonist is administered twice daily.

[Claim 7]
The TRPM8 antagonist of claim 1, wherein the TRPM8 antagonist is administered with an additional active agent.

[Claim 8]

The TRPM8 antagonist of claim 1, wherein the composition is a pharmaceutical composition.

[Claim 9]

The TRPM8 antagonist of claim 1, wherein the human subject is a menopausal woman, a perimenopausal woman, or a postmenopausal woman.

[Claim 10]

The TRPM8 antagonist of claim 1, wherein the human subject is undergoing or has undergone treatment for cancer.

[Claim 11]

The TRPM8 antagonist of claim 1, wherein the treatment for cancer is gonadal ablative therapy or gonadal hormonal suppressive therapies.

[Claim 12]

The TRPM8 antagonist of claim 1, wherein the human subject has undergone surgery, that is hysterectomy, oophorectomy, or orchiectomy.

[Claim 13]

The TRPM8 antagonist of claim 1, wherein the vasomotor symptoms are hot flashes or are night sweats.

[Claim 14]

The TRPM8 antagonist of claim 1, wherein the TRPM8 antagonist is administered

immediately upon sensing the onset of a vasomotor symptom.