Claims

[Claim 1] A method for treating or preventing vasomotor symptoms in a subject in need thereof, comprising:
administering to the subject an effective amount of a Transient Receptor Potential Melastatin 8 (TRPM8) antagonist.

[Claim 2] The method of claim 1, wherein the subject is a human subject.

[Claim 3] The method of claim 2, wherein the TRPM8 antagonist is administered as a composition comprising the TRPM8 antagonist and a pharmaceutically acceptable carrier.

[Claim 4] The method of claim 2, wherein the human subject is a menopausal woman.

[Claim 5] The method of claim 4, wherein the human subject is a perimenopausal woman.

[Claim 6] The method of claim 4, wherein the human subject is a postmenopausal woman.

[Claim 7] The method of claim 2, wherein the human subject is a cancer patient.

[Claim 8] The method of claim 2, wherein the human subject is undergoing or has undergone treatment for cancer.

[Claim 9] The method of claim 8, wherein the treatment for cancer is gonadal ablative therapy or gonadal hormonal suppressive therapies.

[Claim 10] The method of claim 2, wherein the human subject has undergone surgery.

[Claim 11] The method of claim 10, wherein the surgery is hysterectomy, oophorectomy, or orchiectomy.

[Claim 12] The method of claim 2, wherein the vasomotor symptoms are hot flashes.

[Claim 13] The method of claim 2, wherein the vasomotor symptoms are night sweats.

[Claim 14] The method of claim 2, wherein the TRPM8 antagonist is administered immediately upon sensing the onset of a vasomotor symptom.

[Claim 15] The method of claim 2, wherein the TRPM8 antagonist is administered daily.

[Claim 16] The method of claim 15, wherein the TRPM8 antagonist is administered once daily.

[Claim 17] The method of claim 15, wherein the TRPM8 antagonist is administered twice daily.

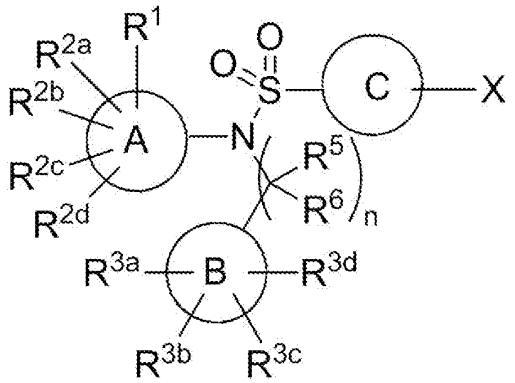
[Claim 18] The method of any one of claims 2 and 3, wherein the TRPM8 an-

tagonist comprises a compound chosen from sulfonamides, sulfamides, amides, 2-aryl oxazoles, 2-aryl thiazoles, spirocyclic piperidines, naphthyl derivatives, and benzimidazole derivatives.

[Claim 19] The method of claim 18, wherein the TRPM8 antagonist is a compound chosen from sulfonamides.

[Claim 20] The method of claim 19, wherein the sulfonamide compound 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 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 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 halogenocy-

cloalkyl, 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.

[Claim 21] The method of claim 20, 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 22] The method of claim 20, wherein the sulfonamide compound 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 23] The method of claim 18, wherein the TRPM8 antagonist is a compound chosen from amides.

[Claim 24] The method of claim 18, wherein the TRPM8 antagonist is administered daily.

[Claim 25] The method of claim 24, wherein the TRPM8 antagonist is administered once daily.

[Claim 26] The method of claim 24, wherein the TRPM8 antagonist is administered twice daily.

[Claim 27] The method of any one of claims 2 and 3, wherein the TRPM8 antagonist is administered with an additional active agent.

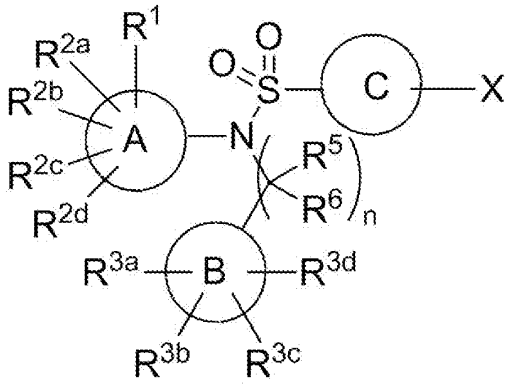
[Claim 28] The method of claim 3, wherein the composition is a pharmaceutical composition.

[Claim 29] A composition comprising
an effective amount of a TRPM8 antagonist for treating or preventing vasomotor symptoms and a pharmaceutically acceptable carrier.

[Claim 30] The composition of claim 29, wherein the TRPM8 antagonist comprises a compound chosen from sulfonamides, sulfamides, amides, 2-aryl oxazoles, 2-aryl thiazoles, spirocyclic piperidines, naphthyl derivatives, and benzimidazole derivatives.

[Claim 31] The composition of claim 29, wherein the TRPM8 antagonist is a compound chosen from sulfonamides.

[Claim 32] The composition of claim 31, wherein the sulfonamide compound 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 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 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.

[Claim 33] The composition of claim 32, wherein the sulfonamide compound 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 34] The composition of claim 30, wherein the TRPM8 antagonist is a compound chosen from amides.

[Claim 35] The composition of claim 29, further comprising an additional active agent.

[Claim 36] Use of a TRPM8 antagonist or a composition comprising the same as an active ingredient for treating or preventing vasomotor symptoms in a subject in need thereof.