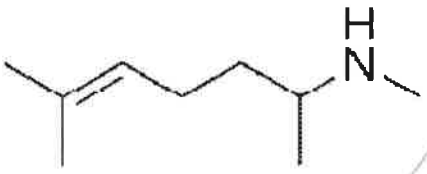
CLAIMS

What is claimed is:

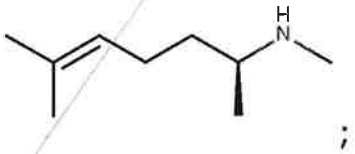
1. A purified racemic Isometheptene compound comprising the structure according to Formula (I),



(6-methylamino-2-methylheptene)

a hydrochloride, or a pharmaceutically acceptable addition salt thereof.

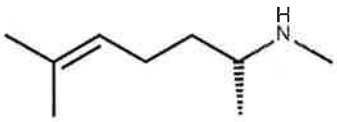
2. An isolated (S)-enantiomer of the Isometheptene compound according to claim 1, comprising the structure according to Formula (Ia),



(S)-Isometheptene

or a hydrochloride, or a pharmaceutically acceptable addition salt thereof.

3. An isolated (R)-enantiomer of the Isometheptene compound according to claim 1, comprising the structure according to Formula (Ib),



(R)-Isometheptene

or a hydrochloride, or a pharmaceutically acceptable addition salt thereof.

4. The compound of claim 2, wherein the pharmaceutically acceptable addition salt is selected from mucate and bitartrate.

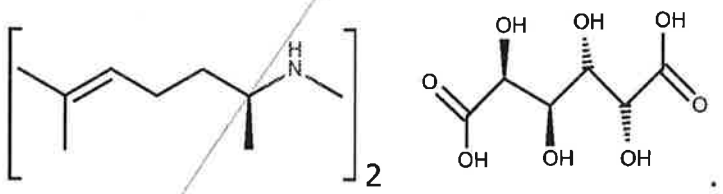
5. The compound of claim 2, wherein the pharmaceutically acceptable addition salt is selected from mucate and bitartrate.

6. The compound of claim 3, wherein the pharmaceutically acceptable addition salt is selected from mucate and bitartrate.

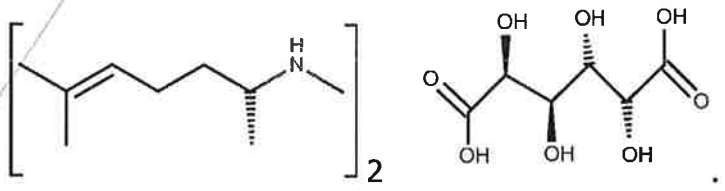
7. The (R)-enantiomeric Isometheptene compound of claim 3, capable of selectively or specifically binding to Imidazoline receptor type 1 (I_1).

8. The (S)-enantiomeric Isometheptene compound of claim 3, relatively free of binding to Imidazoline receptor type 1 (I_1).

9. An (S)-Isometheptene mucate salt comprising the structure according to Formula (II):



10. An (R)-Isometheptene mucate salt comprising the structure according to Formula (III):



11. A pure (R)-enantiomeric Isometheptene mucate salt according to claim 9 in crystal form.

12. A composition comprising a purified Isometheptene enantiomer or pharmaceutically acceptable addition salt or hydrochloride thereof; and a nontoxic carrier.

13. The composition of claim 10, comprising a purified (S)-Isometheptene enantiomer or hydrochloride or pharmaceutically acceptable addition salt thereof; and a nontoxic carrier.

14. The composition of claim 10, comprising a purified (R)-Isometheptene enantiomer or a hydrochloride or pharmaceutically acceptable addition salt thereof; and a nontoxic carrier.

15. A composition comprising a therapeutic amount of the (S)-Isometheptene enantiomer compound of claim 2, or a pharmaceutically acceptable addition salt thereof; and a nontoxic carrier.

16. A composition comprising a therapeutic amount of the (R)-Isometheptene enantiomer compound of claim 3, or a pharmaceutically acceptable addition salt thereof; and a nontoxic carrier.

17. A composition comprising the (S)-Isometheptene enantiomer mucate salt of claim 8; and a nontoxic carrier.

18. A composition comprising the (R)-Isometheptene enantiomer mucate salt of claim 9; and a nontoxic carrier.

19. The composition according to claim 10, wherein the Isometheptene enantiomer compound or hydrochloride or addition salt thereof, comprises therapeutic efficacy for treating, reducing the severity of, inhibiting, eliminating, or preventing symptoms of a

disease or condition associated with one or more of inflammatory diseases or disorders, allergic diseases or disorders, metabolic diseases, cardiovascular disease or disorders, or a neurogenic vascular disease or painful condition associated therewith.

20. The composition according to claim 10, wherein the Isometheptene enantiomer hydrochloride or addition salt thereof, comprises therapeutic efficacy for treating, reducing the severity of, inhibiting, eliminating, or preventing symptoms of a disease or condition associated with one or more of inflammatory diseases or disorders, allergic diseases or disorders, metabolic diseases, cardiovascular disease or disorders, or a neurogenic vascular disease or painful condition associated therewith.

21. The composition according to claim 12 wherein a single dosage of (R)-Isometheptene enantiomer hydrochloride or addition salt thereof is administered to a patient, optionally twice, three times or four times in a day, in capsules containing increasing amounts of 15 mg, 30 mg, 32.5 mg, 50 mg, 65 mg, 100 mg, 130 mg, 150 mg, 300 mg or 500mg.

22. The composition according to claim 12 (R)-Isometheptene enantiomer hydrochloride or addition salt thereof is administered to a patient, acutely for one day or less.

23. The composition according to claim 12 wherein (R)-Isometheptene enantiomer hydrochloride or addition salt thereof is administered to a patient chronically every day for a period of time greater than one day.

24. The composition according to claim 20, comprising a therapeutic effect on an episodic tension-type headache.

25. The composition according to claim 20, comprising a therapeutic effect on a migraine headache.

26. The composition according to claim 20, comprising a therapeutic effect on headaches, cramping, or cognitive disorders.

27. A therapeutic amount of the (R)-Isometheptene enantiomer according to claim 3 for ameliorating or alleviating headaches.

28. The composition according to claim 20, comprising a prophylactic effect to prevent an episodic tension-type headache.

29. The composition according to claim 20, comprising a prophylactic effect to prevent a migraine headache.

30. The composition according to claim 20, comprising a prophylactic effect to prevent headaches, cramping, or cognitive disorders.

31. A therapeutic amount of the (R)-Isometheptene enantiomer according to claim 3 for ameliorating or alleviating headaches.

32. The composition according to claim 15, comprising an ameliorative or extinguishing effect on symptoms of tension or migraine headaches due to a vascular, neurovascular or neurogenic disorder or dysfunction during migraine episodes.

33. The composition according to claim 15, comprising an ameliorative or extinguishing effect on symptoms of tension or migraine headaches due to a vascular, neurovascular or neurogenic disorder or dysfunction during menstrual cycle episodes.

34. The composition according to claim 15, comprising an ameliorative or extinguishing effect on symptoms of headaches from mild to moderate hypertension.

35. The composition according to claim 15, further comprising a therapeutic effect on mild to moderate essential hypertension.

36. The composition according to claim 15, further comprising a therapeutic effect in treating or reducing the severity of organ transplantation rejection.

37. A composition, comprising a (R)-Isometheptene enantiomer or hydrochloride or pharmaceutically acceptable addition salt thereof, and one or more pharmaceutical substances selected from the group consisting of acetaminophen, ibuprofen, aspirin, caffeine, dichloralphenazone, naproxen, and sumatriptan succinate; and a nontoxic carrier.

38. The composition according to claim 15, further comprising a therapeutic effect on cognitive disorders

39. The composition according to claim 27, wherein the routes of administration comprise, without limitation, parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

40. A method of treating, reducing the severity of, inhibiting, eliminating, or preventing a disease or condition associated with an activation, in a patient, comprising administering to the subject an effective amount of the composition according to claim

27, so as to treat, reduce the severity of, inhibit, eliminate, or prevent a disease or a condition; wherein the painful condition is related to one or more of inflammatory diseases or disorders, allergic diseases or disorders, metabolic diseases, cardiovascular disease or disorders, or a neurogenic vascular disease or painful condition associated therewith.

41. A method of treating, reducing the severity of, inhibiting, eliminating, or preventing a disease or condition associated with an activation, in a patient, comprising administering to the subject an amount of the composition of claim 27, effective against suffering of cramps, hot and cold flushes, cognitive disorders, TBI, neurotoxicity, depression, schizophrenia, anxiety, epilepsy, stress disorders, excess sweating, or symptoms related to drug withdrawal.

42. The method according to claim 30, wherein the composition is administered in combination with one or more additional therapeutics, chemotherapeutic drugs, anti-proliferative agents, anti-inflammatory agents, anti-asthmatic agents, anti-allergic agents, immunosuppressive agents, immunomodulatory agents, cardiovascular disease treatment agents, anti-diabetics agents, or blood disorder treatment agents.

43. The method of treatment of migraine comprising administering to a human in need of such treatment a therapeutic composition according to claim 14.

44. A method of treatment of hypertension comprising administering a therapeutic amount of a composition comprising Isometheptene (R)-enantiomer mucate salt, and a pharmaceutically acceptable carrier, to a patient in need of such treatment.

45. The method of administering to a patient in need of such treatment, a therapeutic amount of a composition against hypertension comprising Isometheptene (R)-isomer mucate salt of claim 9 combined with an active ingredient selected from

acetaminophen, ibuprofen, aspirin, caffeine, dichloralphenazone, naproxen, and sumatriptan succinate; and a pharmaceutically acceptable carrier.

46. A method of treatment of migraine comprising administering to a patient in need of such treatment, a therapeutic amount of a composition comprising (R)-Isometheptene enantiomer mucate salt combined with an active ingredient selected from acetaminophen, ibuprofen, aspirin, caffeine, dichloralphenazone, naproxen, and sumatriptan succinate; and a pharmaceutically acceptable carrier.

47. A method for nitric oxidase inhibition comprising administering to a patient in need of such treatment, a therapeutic amount of a composition comprising Isometheptene (R)-enantiomer mucate salt combined with an active ingredient selected from acetaminophen, ibuprofen, aspirin, caffeine, dichloralphenazone, naproxen, and sumatriptan succinate; and a pharmaceutically acceptable carrier.

48. The method of treatment according to claim 22, wherein the therapeutic composition comprises:
a tablet formulation comprising about 50 mg to about 100 mg, or about 30 mg to about 40 mg, or about 10 mg to about 30 mg of Isometheptene (R)-enantiomer, 20 mg of caffeine, and 500 mg of acetaminophen, or about 200 mg to about 800 mg ibuprofen, wherein the treatment is applied once or up to 4 times in one day.

49. The method of treatment of claim 22, wherein the therapeutic composition comprises: an injectable solution comprising 50 mg to about 100 mg, or about 30 mg to about 40 mg, or about 10 mg to about 30 mg of Isometheptene (R)-enantiomer, 20 mg of caffeine, and 150 mg of acetaminophen, or about 200 mg to about 800 mg ibuprofen, and a physiological saline solution.

50. A method of making the compound of claim 4, comprising the steps of:

(a) combining (S)-methyloxirane with 3-methyl-2-buten-1-ylmagnesium chloride in THF in the presence of Copper iodide;

(b) neutralizing, extracting with ether, drying with magnesium sulfate, removing solvent, and distilling the (S)-6-Methyl-hept-5-en-2-ol;

(c) reacting (S)-6-Methyl-hept-5-en-2-ol with methanesulfonyl chloride and DIEA in anhydrous DCM;

(d) cooling the reaction mixture to about 5° C.;

(e) adding mesyl chloride dropwise;

(f) diluting the reaction mixture after 18 hours at RT;

(g) washing said mixture with water, brine and drying over $MgSO_4$;

(h) concentrate to oily product, (S)-Methanesulfonic acid 1,5-dimethyl-hex-4-enyl ester, wherein the 1H NMR in $CDCl_3$ at 500 MHz identifies the parameters: 5.08ppm 1Hm, 4.80ppm 1Hm, 2.99ppm 3Hs, 2.08ppm 2Hm, 1.75ppm 1Hm, 1.69ppm 3Hs, 1.624 1Hm, 1.61 3Hs, 1.43ppm 3Hd.;

(i) reacting (S)-Methanesulfonic acid 1,5-dimethyl-hex-4-enyl ester with N,N-dimethyl-acetamide (170 mL), and 40% methylamine in water in a sealed, heavy-walled reaction vessel at 50° C.;

(k) adding diethyl ether and washing said mixture with water and brine, drying over $MgSO_4$; and filtering to remove the solvent;

(l) removing the ether in vacuo (~25mmHg) to yield (R)–Isometheptene in the free base form; and

(m) adding a pharmacologically acceptable acid, comprising hydrochloric, mucic, or tartaric, to form a pharmacologicaly acceptable salt.

51. A method for producing a composition comprising the steps of mixing a therapeutically effective amount of (R)-Isometheptene mucate salt with an anti-inflammatory substance selected from the group consisting of acetaminophen, ibuprofen, aspirin, dichloralphenazone, naproxen, and sumatriptan succinate; and a nontoxic carrier.

52. The (R)-enantiomeric Isometheptene mucate salt according to claim 9, wherein an X-ray analysis showed a substantially disordered (poor overlap) hydrophobic dimethylalkene part of the molecule but highly ordered (good overlap) near the cation where the mucate anion appears to dock.

53. An oral dosage comprising the composition comprising a therapeutic amount of (R)-Isometheptene in a controlled release formulation comprising coated or uncoated capsules.

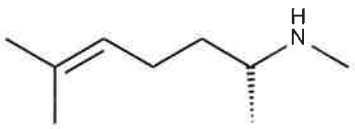
53. A therapeutic controlled release formulation comprising a drug selected from pure (R)-Isometheptene within or on a core coated with a biodegradable material.

54. The formulation of claim 53 wherein the drug is coated with a delayed release material, or the drug is interspersed throughout a material, or the drug is adsorbed into a material.

CLAIMS

What is claimed is:

1. An isolated (R)-enantiomer of an isometheptene compound of formula (Ib)



(1b)

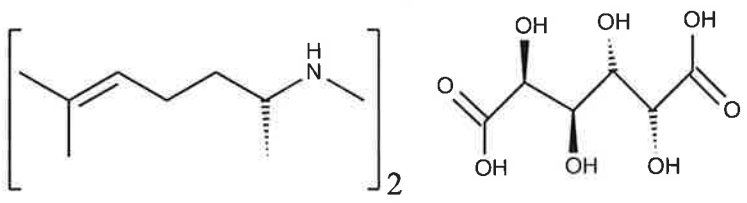
(R)-Isometheptene

a hydrochloride or other pharmaceutically acceptable addition salt thereof.

2. The compound of claim 1, wherein the pharmaceutically acceptable addition salt is bitartrate.

3. The compound of claim 1, wherein the pharmaceutically acceptable addition salt is mucate.

4. An (R)-Isometheptene mucate salt of formula (III):



(III).

5. The salt of claim 4 in pure crystalline form.

6. The (R)-enantiomeric isometheptene mucate salt of claim 4 or 5, which on X-ray analysis shows a substantially disordered (poor overlap) hydrophobic dimethylalkene part of the molecule but highly ordered (good overlap) part of the molecule near the cation where the mucate anion appears to dock.

7. A method of making the compound of any of claims 1-6, which comprises:

(a) converting 6-methylhept-5-en-2-one to the Mosher's amide of 6-methylhept-5-en-2-imine;

(b) separating the R isomer of the Mosher's amide; and

(c) either removing the Mosher's acid residue and methylating the resulting amine or methylating the Mosher's amide and removing the Mosher's acid residue.

8. A method of making the compound of any of claims 1-6, which comprises:

(a) combining (S)-2-methyloxirane with 3-methylbut-2-enyl magnesium chloride to give (S)-6-methylhept-5-en-2-ol;

(b) combining the (S)-6-methylhept-5-en-2-ol with methanesulfonyl chloride to give (S)-6-methylhept-5-en-2-yl methanesulfonate;

(c) combining the (S)-6-methylhept-5-en-2-yl methanesulfonate with methylamine to give (R)-*N*,6-dimethylhept-5-en-2-amine.

9. The method of claim 7 or 8, further comprising reacting the (R)-N,6-dimethylhept-5-en-2-amine with mucic acid to form a mucate salt.

10. Use of a compound according to any of claims 1-6 for the manufacture of a single agent medicament for administration to a human in need thereof for treating, reducing the severity of, inhibiting, eliminating, or preventing episodic tension-type headache.

11. Use of a compound according to any of claims 1-6 for the manufacture of a medicament for administration to a human in need thereof for any of:

(a) treating, reducing the severity of, inhibiting, eliminating, or preventing symptoms of a disease or condition associated with one or more of inflammatory diseases or disorders, allergic diseases or disorders, metabolic diseases, cardiovascular disease or disorders, or a neurogenic vascular disease or painful condition associated therewith;

(b) treating, reducing the severity of, inhibiting, eliminating, or preventing symptoms of a disease or condition associated with one or more of inflammatory diseases or disorders, allergic diseases or disorders, metabolic diseases, cardiovascular disease or disorders, or a neurogenic vascular disease or painful condition associated therewith;

(c) cramps, hot and cold flushes, cognitive disorders, TBI, neurotoxicity, depression, schizophrenia, anxiety, epilepsy, stress disorders, excess sweating, or symptoms related to drug withdrawal.

(d) treating or preventing an episodic tension-type headache;

(e) treating or preventing a migraine headache;

(f) treating or reducing the severity of a cognitive disorder;

(g) treating or preventing cramping;

(h) producing an ameliorative or extinguishing effect on symptoms of tension or migraine headaches due to a vascular, neurovascular or neurogenic disorder or dysfunction during migraine episodes;

(i) producing an ameliorative or extinguishing effect on symptoms of tension or migraine headaches due to a vascular, neurovascular or neurogenic disorder or dysfunction during menstrual cycle episodes

(j) producing an ameliorative or extinguishing effect on symptoms of headaches from mild to moderate hypertension;

(k) producing a therapeutic effect on mild to moderate essential hypertension;

(l) treating or reducing the severity of organ transplantation rejection; and/or

(m) treating or reducing the severity of hypertension.

12. The use of claim 11 wherein the medicament is for administration by any of:

(a) as a single dosage of (R)-Isometheptene enantiomer hydrochloride or addition salt thereof administered to a patient, optionally twice, three times or four times in a day, in capsules containing increasing amounts of 15 mg, 30 mg, 32.5 mg, 50 mg, 65 mg, 100 mg, 130 mg, 150 mg, 300 mg or 500mg;

(b) to a patient, acutely for one day or less;

(c) chronically every day for a period of time greater than one day.

13. The use of claim 11 or 12 wherein the medicament is for parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal administration.

14. A pharmaceutical composition comprising the compound of any of claims 1-6 or a compound made by the method of any of claims 7-9 and a pharmaceutically acceptable carrier.

15. The composition of claim 14, further comprising one or more additional therapeutics, chemotherapeutic drugs, anti-proliferative agents, anti-inflammatory agents, anti-asthmatic agents, anti-allergic agents, immunosuppressive agents, immunomodulatory agents, cardiovascular disease treatment agents, anti-diabetics agents, or blood disorder treatment agents.

16. The composition of claim 14 or 15, further comprising one or more pharmaceutical substances selected from the group consisting of acetaminophen, ibuprofen, aspirin, caffeine, dichloralphenazone, naproxen, and sumatriptan succinate; and a nontoxic carrier.

17. The composition of claim 14, which is a tablet formulation comprising about 50 mg to about 100 mg, or about 30 mg to about 40 mg, or about 10 mg to about 30 mg of Isometheptene (R)-enantiomer, 20 mg of caffeine, and 500 mg of acetaminophen, or about 200 mg to about 800 mg ibuprofen, for treatment is applied once or up to 4 times in one day.

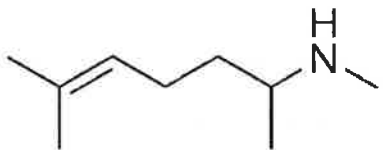
18. The composition of claim 14, which is an injectable solution comprising 50 mg to about 100 mg, or about 30 mg to about 40 mg, or about 10 mg to about 30 mg of Isometheptene (R)-enantiomer, 20 mg of caffeine, and 150 mg of acetaminophen, or about 200 mg to about 800 mg ibuprofen, and a physiological saline solution.

19. The composition of claim 14, which is an oral dosage composition ition comprising a therapeutic amount of (R)-Isometheptene in a controlled release formulation comprising coated or uncoated capsules.

20. The composition of claim 14, which is a controlled release formulation comprising a drug selected from pure (R)-Isometheptene within or on a core coated with a biodegradable material.

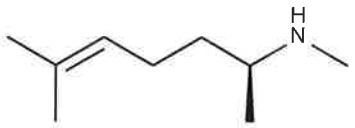
21. The composition of claim 20, wherein the drug is coated with a delayed release material, or the drug is interspersed throughout a material, or the drug is adsorbed into a material.

22. A purified racemic Isometheptene compound comprising the structure according to Formula (I),



(6-methylamino-2-methylheptene), a hydrochloride, or a pharmaceutically acceptable addition salt thereof.

23. An isolated (S)-enantiomer of the Isometheptene compound according to claim 1, comprising the structure according to Formula (Ia),



;

(S)-Isometheptene or a hydrochloride, a mucate or another pharmaceutically acceptable addition salt thereof.

24. Use of the compound of claim 22 or 23 in the manufacture of a medicament for administering to a human in need thereof for any of:

(a) treating, reducing the severity of, inhibiting, eliminating, or preventing symptoms of a disease or condition associated with one or more of inflammatory diseases or disorders, allergic diseases or disorders, metabolic diseases, cardiovascular disease or disorders, or a neurogenic vascular disease or painful condition associated therewith;

(b) treating, reducing the severity of, inhibiting, eliminating, or preventing symptoms of a disease or condition associated with one or more of inflammatory diseases or disorders, allergic diseases or disorders, metabolic diseases, cardiovascular disease or disorders, or a neurogenic vascular disease or painful condition associated therewith;

(c) cramps, hot and cold flushes, cognitive disorders, TBI, neurotoxicity, depression, schizophrenia, anxiety, epilepsy, stress disorders, excess sweating, or symptoms related to drug withdrawal.

(d) treating or preventing an episodic tension-type headache;

(e) treating or preventing a migraine headache;

(f) treating or reducing the severity of a cognitive disorder;

(g) treating or preventing cramping;

(h) producing an ameliorative or extinguishing effect on symptoms of tension or migraine headaches due to a vascular, neurovascular or neurogenic disorder or dysfunction during migraine episodes;

(i) producing an ameliorative or extinguishing effect on symptoms of tension or migraine headaches due to a vascular, neurovascular or neurogenic disorder or dysfunction during menstrual cycle episodes

(j) producing an ameliorative or extinguishing effect on symptoms of headaches from mild to moderate hypertension;

(k) producing a therapeutic effect on mild to moderate essential hypertension;

(l) treating or reducing the severity of organ transplantation rejection; and/or

(m) treating or reducing the severity of hypertension.

25. A pharmaceutical composition comprising a compound according to claim 22 or 23 and a pharmaceutically acceptable carrier.