[((1*R*,2*S*,5*R*)-2-ISOPROPYL-5-METHYL-CYCLOHEXANECARBONYL) -AMINO]-ACETIC ACID ISOPROPYL ESTER AND RELATED COMPOUNDS AND THEIR USE IN THERAPY

RELATED APPLICATION

This application is related to United States patent application number 12/928,184 filed 06 December 2010~~, the contents of which are incorporated herein by reference in their entirety~~.

TECHNICAL FIELD

The present invention pertains generally to the field of coolants and medical therapy. More particularly, the present invention relates to certain anti-nociceptive agents, such as [((*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester, that are potent and long-acting and selectively cooling for non-keratinized epithelial tissues as compared to keratinized epithelial tissues, and are useful, for example, for the treatment of (e.g., the alleviation of symptoms of; the amelioration of) sensory discomfort of non-keratinized stratified epithelial (NKSE) tissue; and so for treatment of: sensory discomfort of an ocular surface, an eyelid, a margin of an eyelid, an anterior part of an eyeball, a conjunctiva, a lachrymal system, a pre-corneal film, or a cornea, a lining of the oral cavity, an internal portion of the lips, a pharyngeal surface, an esophageal surface, or an anogenital surface; eye discomfort, e.g., caused by extended wear of contact lenses, by eye strain and/or fatigue, by air pollutants, by excessive exposure to the sun, by conjunctivitis, by dry eye syndrome; sensory discomfort associated with oral mucositis; airway (e.g., larynx, trachea, and/or bronchi) tightness, discomfort in the airways (e.g., larynx, trachea, and/or bronchi), choking, cough, and/or dyspnea, e.g., associated with asthma and/or chronic obstructive pulmonary diseases (COPD).

BACKGROUND

A number of publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. ~~Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.~~

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group

REFERENCES

A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. ~~Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.~~

Dhaka *et al.*, 2008, "Visualizing cold spots: TRPM8-expressing sensory neurons and their projections", J. Neuroscience, Vol. 28, pp. 566-575.

Morice *et al.*, 2001, "Cough Challenge in the Assessment of Cough Reflex", Brit. J. Clin. Pharmacol., Vol. 52, pp. 365-375.

Watson *et al.*, 1978, "Compounds with the Menthol Cooling Effect", J. Soc. Cosmet. Chem., Vol. 29, pp. 185-200.

Watson *et al.*, 1979, "*N*-Substituted paramenthane carboxamides", US Patent No 4,178,459 granted 11 December 1979.

CLAIMS

1. A compound which is:
[((1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic cid isopropyl ester; or
[((1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-methyl-amino]-acetic acid isopropyl ester;
or a pharmaceutically acceptable salt, hydrate, or solvate of the foregoing.

2. A compound according to claim 1, which is [((1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

3. A compound according to claim 1, which is [((1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, which is [((1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester.

5. A composition comprising a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier, diluent, or excipient.

6. A composition according to claim 5, in the form of a liquid.

7. A composition according to claim 6, wherein the compound is present in the composition at a concentration of 0.01 to 5 % w/v.

8. A composition according to claim 5, in the form of eye drop solution.

9. A composition according to claim 8, wherein the compound is present in the composition at a concentration of 0.01 to 1 % w/v.

10. A composition according to claim 5, in the form of an ointment or cream.

11. A composition according to claim 10, wherein the compound is present in the composition at a concentration of 0.5 to 5 mg/mL.

12. A composition according to claim 5, in the form of a powder, a tablet, a lozenge, a pastille, a film, a paste, or a gum.

13. A composition according to claim 5, in the form of a tablet.

14. A composition according to claim 5, in the form of an orally disintegrating tablet (ODT).

15. A composition according to claim 5, in the form of a sugar candy.

16. A composition according to claim 5, the form of a gum.

17. A composition according to claim 5, in the form of chewing gum.

18. A composition according to any one of claims 12 to 17, wherein the compound is present in the composition at a concentration of 0.5 to 5% by weight.

19. A composition according to any one of claims 5 to 18, which is suitable for topical administration to a human.

20. A composition according to any one of claims 5 to 11, which is suitable for topical ocular administration to a human.

21. A composition according to any one of claims 7 to 11, which is suitable for topical ocular administration to the eyelid, the margin of the eyelid, the anterior part of the eyeball, the conjunctiva, the lachrymal system, the pre-corneal film or the cornea of a human.

22. A composition according to any one of claims 5 to 7 and 12 to 18, which is suitable for topical oral administration to a human.

23. A composition according to any one of claims 5 to 7 and 12 to 18, which is suitable for topical administration to the lining of the oral cavity of a human.

24. A composition according to any one of claims 5 to 7 and 12 to 18, which is suitable for topical administration to the internal portion of the lips of a human.

25. A composition according to any one of claims 5 to 7 and 12 to 18, which is suitable for topical pharyngeal administration to a human.

26. A composition according to any one of claims 5 to 7 and 12 to 18, which is suitable for topical administration to the pharyngeal surface of a human.

27. A composition according to any one of claims 5 to 7 and 12 to 18, which is suitable for topical esophageal administration to a human.

28. A composition according to any one of claims 5 to 7 and 12 to 18, which is suitable for topical administration to the esophageal surface of a human.

29. A composition according to any one of claims 5 to 7, 10, and 11, which is suitable for topical anogenital administration to a human.

30. A composition according to any one of claims 5 to 7, 10, and 11, which is suitable for topical administration to the anogenital surface of a human.

31. A wipe, pad, or towelette carrying an aqueous composition comprising a compound according to any one of claims 1 to 4.

32. A wipe, pad, or towelette according to claim 31, wherein the aqueous composition is water further comprising the compound.

33. A wipe, pad, or towelette according to claim 31, wherein the aqueous composition is an isotonic saline solution further comprising the compound.

34. A wipe, pad, or towelette according to any one of claims 31 to 33, wherein the compound is present in the aqueous composition at a concentration of 0.01 to 1 % w/v.

35. A wipe, pad, or towelette according to any one of claims 31 to 34, wherein the aqueous composition further comprises an adjunctive ocular drug.

36. A wipe, pad, or towelette according to claim 35, wherein the adjunctive ocular drug is a polymer lubricant, hypromellose, polyethylene glycol 400, hyaluronan, or propanediol.

37. A wipe, pad, or towelette according to any one of claims 31 to 36, which is suitable for use in the topical administration of the compound to a human.

38. A wipe, pad, or towelette according to any one of claims 31 to 36, which is suitable for use in the topical ocular administration of the compound to a human.

39. A wipe, pad, or towelette according to any one of claims 31 to 36, which is suitable for use in the topical ocular administration of the compound to the eyelid, the margin of the eyelid, the anterior part of the eyeball, the conjunctiva, the lachrymal system, the pre-corneal film or the cornea of a human.

40. A compound according to any one of claims 1 to 4, for treatment of the human or animal body by therapy.

41. A compound according to any one of claims 1 to 4, for treatment of sensory discomfort of non-keratinized stratified epithelial (NKSE) tissue of a human.

42. A compound according to any one of claims 1 to 4, for treatment of sensory discomfort of an ocular surface, a lining of the oral cavity, an internal portion of the lips, a pharyngeal surface, an esophageal surface, or an anogenital surface of a human.

43. A compound according to any one of claims 1 to 4, for treatment of sensory discomfort of an eyelid, a margin of an eyelid, an anterior part of an eyeball, a conjunctiva, a lachrymal system, a pre-corneal film, or a cornea of a human.

44. A compound according to any one of claims 1 to 4, for treatment of sensory discomfort of a lining of the oral cavity, an internal portion of the lips, a pharyngeal surface, or an esophageal surface of a human.

45. A compound according to any one of claims 1 to 4, for treatment of sensory discomfort of an anogenital surface of a human.

46. A compound according to any one of claims 1 to 4, for treatment of eye discomfort in a human.

47. A compound for use according to claim 46, wherein the eye discomfort is eye discomfort caused by extended wear of contact lenses, eye discomfort caused by eye strain and/or fatigue, eye discomfort caused by air pollutants, or eye discomfort caused by excessive exposure to the sun.

48. A compound for use according to claim 46, wherein the eye discomfort is eye discomfort caused by conjunctivitis.

49. A compound for use according to claim 46, wherein the eye discomfort is eye discomfort caused by dry eye syndrome.

50. A compound according to any one of claims 1 to 4, for treatment of sensory discomfort associated with oral mucositis in a human.

51. A compound according to any one of claims 1 to 4, for treatment of airway (e.g., larynx, trachea, and/or bronchi) tightness, discomfort in the airways (e.g., larynx, trachea, and/or bronchi), choking, cough, and/or dyspnea in a human.

52. A compound according to any one of claims 1 to 4, for treatment of airway (e.g., larynx, trachea, and/or bronchi) tightness and/or discomfort in the airways (e.g., larynx, trachea, and/or bronchi) in a human.

53. A compound according to any one of claims 1 to 4, for treatment of cough in a human.

54. A compound according to any one of claims 1 to 4, for treatment of airway (e.g., larynx, trachea, and/or bronchi) tightness, discomfort in the airways (e.g., larynx, trachea, and/or bronchi), choking, cough, and/or dyspnea associated with asthma in a human.

55. A compound according to any one of claims 1 to 4, for treatment of airway (e.g., larynx, trachea, and/or bronchi) tightness, discomfort in the airways (e.g., larynx, trachea, and/or bronchi), choking, cough, and/or dyspnea associated with chronic obstructive pulmonary diseases (COPD) in a human.

56. A compound for use according to any one of claims 40 to 55, wherein the treatment is by topical administration.

57. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of sensory discomfort of non-keratinized stratified epithelial (NKSE) tissue of a human.

58. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of sensory discomfort of an ocular surface, a lining of the oral cavity, an internal portion of the lips, a pharyngeal surface, an esophageal surface, or an anogenital surface of a human.

59. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of sensory discomfort of an eyelid, a margin of an eyelid, an anterior part of an eyeball, a conjunctiva, a lachrymal system, a pre-corneal film, or a cornea of a human.

60. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of sensory discomfort of a lining of the oral cavity, an internal portion of the lips, a pharyngeal surface, or an esophageal surface of a human.

61. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of sensory discomfort of an anogenital surface of a human.

62. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of eye discomfort in a human.

63. The use according to claim 62, wherein the eye discomfort is eye discomfort caused by extended wear of contact lenses, eye discomfort caused by eye strain and/or fatigue, eye discomfort caused by air pollutants, or eye discomfort caused by excessive exposure to the sun.

64. The use according to claim 62, wherein the eye discomfort is eye discomfort caused by conjunctivitis.

65. The use according to claim 62, wherein the eye discomfort is eye discomfort caused by dry eye syndrome.

66. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of sensory discomfort associated with oral mucositis in a human.

67. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of airway (e.g., larynx, trachea, and/or bronchi) tightness, discomfort in the airways (e.g., larynx, trachea, and/or bronchi), choking, cough, and/or dyspnea in a human.

68. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of airway (e.g., larynx, trachea, and/or bronchi) tightness and/or discomfort in the airways (e.g., larynx, trachea, and/or bronchi) in a human.

69. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of cough in a human.

70. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of airway (e.g., larynx, trachea, and/or bronchi) tightness, discomfort in the airways (e.g., larynx, trachea, and/or bronchi), choking, cough, and/or dyspnea associated with asthma in a human.

71. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for treatment of airway (e.g., larynx, trachea, and/or bronchi) tightness, discomfort in the airways (e.g., larynx, trachea, and/or bronchi), choking, cough, and/or dyspnea associated with chronic obstructive pulmonary diseases (COPD) in a human.

72. The use according to any one of claims 57 to 71, wherein the medicament is for topical administration.

CLAIMS

1. A compound which is [((1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester.

2. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, diluent, or excipient.

3. A composition according to claim 2, in the form of a liquid.

4. A composition according to claim 3, wherein the compound is present in the composition at a concentration of 0.01 to 5 % w/v.

5. A composition according to claim 2, in the form of a powder, a tablet, a lozenge, a pastille, a film, a paste, or a gum.

6. A composition according to claim 2, in the form of a tablet.

7. A composition according to claim 2, in the form of an orally disintegrating tablet (ODT).

8. A composition according to claim 2, in the form of a sugar candy.

9. A composition according to claim 2, in the form of a gum.

10. A composition according to claim 2, in the form of chewing gum.

11. A composition according to any one of claims 5 to 10, wherein the compound is present in the composition at a concentration of 0.5 to 5% by weight.

12. A composition according to claim 2, in the form of an aerosol.

13. A composition according to any one of claims 2 to 12, which is suitable for topical administration to a human.

14. A composition according to any one of claims 2 to 12, which is suitable for topical oral administration to a human.

15. A composition according to any one of claims 2 to 12, which is suitable for topical administration to the pharyngeal surface of a human.

16. A composition according to any one of claims 2 to 12, which is suitable for topical administration to the esophageal surface of a human.

17. A compound according to claim 1, for treatment of the human or animal body by therapy.

18. A compound according to claim 1, for treatment of sensory discomfort of non-keratinized stratified epithelial (NKSE) tissue of a human.

19. A compound according to claim 1, for treatment of sensory discomfort of a lining of the oral cavity, an internal portion of the lips, a pharyngeal surface, or an esophageal surface of a human.

20. A compound according to claim 1, for treatment of sensory discomfort associated with oral mucositis in a human.

21. A compound according to claim 1, for treatment of airway tightness in a human.

22. A compound according to claim 1, for treatment of larynx tightness, trachea tightness, and/or bronchi tightness in a human.

23. A compound according to claim 1, for treatment of discomfort in the airways in a human.

24. A compound according to claim 1, for treatment of discomfort in the larynx, discomfort in the trachea, and/or discomfort in the bronchi in a human.

25. A compound according to claim 1, for treatment of choking in a human.

26. A compound according to claim 1, for treatment of cough in a human.

27. A compound according to claim 1, for treatment of dyspnea in a human.

28. A compound for use according to any one of claims 21 to 27, wherein the airway tightness, larynx tightness, trachea tightness, bronchi tightness, discomfort in the airways, discomfort in the larynx, discomfort in the trachea, discomfort in the bronchi, choking, cough, and/or dyspnea is associated with asthma.

29. A compound for use according to any one of claims 21 to 27, wherein the airway tightness, larynx tightness, trachea tightness, bronchi tightness, discomfort in the airways, discomfort in the larynx, discomfort in the trachea, discomfort in the bronchi, choking, cough, and/or dyspnea is associated with chronic obstructive pulmonary diseases (COPD).

30. A compound for use according to any one of claims 17 to 29, wherein the treatment is by topical administration.

31. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of sensory discomfort of non-keratinized stratified epithelial (NKSE) tissue of a human.

32. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of sensory discomfort of a lining of the oral cavity, an internal portion of the lips, a pharyngeal surface, or an esophageal surface of a human.

33. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of sensory discomfort associated with oral mucositis in a human.

34. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of airway tightness in a human.

35. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of larynx tightness, trachea tightness, and/or bronchi tightness in a human.

36. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of discomfort in the airways in a human.

37. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of discomfort in the larynx, discomfort in the trachea, and/or discomfort in the bronchi in a human.

38. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of choking in a human.

39. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of cough in a human.

40. Use of a compound according to claim 1, in the manufacture of a medicament for treatment of dyspnea in a human.

41. Use according to any one of claims 31 to 40, wherein the airway tightness, larynx tightness, trachea tightness, bronchi tightness, discomfort in the airways, discomfort in the larynx, discomfort in the trachea, discomfort in the bronchi, choking, cough, and/or dyspnea is associated with asthma.

42. Use according to any one of claims 31 to 40, wherein the airway tightness, larynx tightness, trachea tightness, bronchi tightness, discomfort in the airways, discomfort in the larynx, discomfort in the trachea, discomfort in the bronchi, choking, cough, and/or dyspnea is associated with chronic obstructive pulmonary diseases (COPD).

43. Use according to any one of claims 31 to 42, wherein the treatment is by topical administration.