

CLAIMS

1. A compound, N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate dihydrate, wherein the compound is at least 98% pure and comprises less than 1% of 4-N-butyl-6-[(3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine.
2. The compound of claim 1, wherein the 4-N-butyl-6-[(3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine is 4-N-butyl-6-[(3R)-3-methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine.
3. The compound of claim 1, wherein the compound comprises less than 0.95%, 0.90%, 0.85%, 0.80%, 0.75%, 0.70%, 0.65%, 0.60%, 0.55%, 0.50%, 0.45%, 0.40%, 0.35%, 0.30%, 0.29%, 0.28%, 0.27%, 0.26%, 0.25%, 0.24%, 0.23%, 0.22%, 0.21%, 0.20%, 0.15%, 0.10%, or 0.05% of 4-N-butyl-6-[(3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine.
4. The compound of claim 1, wherein the compound comprises less than 0.26% of 4-N-butyl-6-[(3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine.
5. The compound of claim 1, wherein the compound further comprises less than 0.5% methanol.
6. The compound of claim 5, wherein the compound comprises less than 0.45%, 0.4%, 0.35%, 0.3%, 0.25%, 0.2%, 0.15%, 0.1%, or 0.05% methanol.
7. The compound of claim 1, wherein the compound comprises between about 0.1% to about 0.5% methanol.
8. The compound of claim 7, wherein the compound comprises between 0.1-0.2%, 0.1-0.3%, 0.1-0.4%, 0.2-0.3%, 0.2-0.4%, 0.2-0.5%, 0.3-0.4%, 0.3-0.5%, or 0.4-0.5% methanol.
9. The compound of any one of claims 1-8, wherein the compound comprises a polymorph of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate dihydrate distinguished by PXRD peaks at about 6.7, 9.2, 22.4, and 24.4 degrees 2-theta.
10. The compound of claim 9, wherein the polymorph comprises two additional peaks at about 13.5 and 18.7 degrees 2-theta.

11. The compound of claim 9 or claim 10, wherein the polymorph comprises four additional peaks at about 20.9, 21.4, 26.8, and 30.0 degrees 2-theta.
12. The compound of any one of claims 9-11, wherein the polymorph comprises four additional peaks at about 11.4, 15.6, 25.0, and 26.1 degrees 2-theta.
13. The compound of any one of claims 9-12, wherein the polymorph comprises three additional peaks at about 17.0, 21.8, and 22.0 degrees 2-theta.
14. The compound of any one of claims 1-8, wherein the composition comprises a polymorph of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate dihydrate distinguished by PXRD peaks at about 17.0, 21.8, and 26.1 degrees 2-theta.
15. A pharmaceutical composition comprising the compound of any one of claims 1-14 and one or more pharmaceutically acceptable carrier(s) or diluent(s).
16. A dosage form comprising an effective amount of the compound of any one of claims 1-14 or the pharmaceutical composition of claim 15, wherein the dosage form is selected from the group consisting of powder-in-capsule forms, capsules, tablets, liquids, powders, lozenges, chews, multi- and nano-particulates, gels, solid solutions, liposomes, nanoparticles, films, ovules, sprays, injectables, and liquid formulations.
17. The dosage form of claim 16, wherein the dosage form is a powder-in-capsule form.
18. The dosage form of claim 16, wherein the dosage form is a tablet.
19. Use of a compound of any one of claims 1-14 in the manufacture of a medicament for the treatment of a H₄ mediated disease or condition, wherein the H₄ mediated disease or condition is selected from the group consisting of inflammatory skin diseases, pruritic diseases, respiratory diseases, cardiac diseases, inflammatory diseases of the gastrointestinal tract, cancer, joint diseases, kidney diseases, pain disorders, overactive bladder conditions, vestibular disorders, macular degenerative disorders, inflammatory eye diseases, and other diseases involving immune and inflammatory disorders.
20. A compound according to any one of claims 1-14, pharmaceutical composition according to claim 15, or dosage form according to any one of claims 16-18 for use in the treatment of an H₄ mediated disease or condition, wherein the treatment comprises administering an effective

amount of the compound according to any one of claims 1-14, the pharmaceutical composition according to claim 15, or the dosage form according to any one of claims 16-18 to a patient in need thereof.

21. The compound, pharmaceutical composition or dosage form of claim 20, wherein the H₄ mediated disease or condition is selected from the group consisting of inflammatory skin diseases, pruritic diseases, respiratory diseases, cardiac diseases, inflammatory diseases of the gastrointestinal tract, cancer, joint diseases, kidney diseases, pain disorders, overactive bladder conditions, vestibular disorders, macular degenerative disorders, inflammatory eye diseases, and other diseases involving immune and inflammatory disorders.

22. The use of claim 19, or the compound, pharmaceutical composition or dosage form of claim 21, wherein:

- a) the inflammatory skin disease is atopic dermatitis or psoriasis;
- b) the pruritic disease is urticaria or uraemic pruritus;
- c) the respiratory disease is asthma, chronic obstructive airway disease, or allergic rhinitis;
- d) the cardiac disease is myocardial ischaemia;
- e) the inflammatory disease of the gastrointestinal tract is Crohn's disease or colitis ulcerosa;
- f) the joint disease is rheumatoid arthritis or psoriatic arthritis;
- g) the kidney disease is diabetic nephropathy;
- h) the pain disorder is inflammatory pain or neuropathic pain;
- i) the vestibular disorder is vertigo or tinnitus;
- j) the inflammatory eye disease is conjunctivitis or uveitis; or
- k) the other disease involving immune and inflammatory disorders is multiple sclerosis, mastocytosis, or inflammatory or systemic lupus erythematosus.

23. The use of claim 19, or the compound, pharmaceutical composition or dosage form of claim 20, wherein the H₄ mediated disease or condition is selected from the group consisting of

atopic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, seborrheic dermatitis or contact dermatitis, eczema, urticaria, pruritus, uraemic pruritus, rosacea, prurigo nodularis, hypertrophic scarring, keloid scar formation, scleroderma, Folliculitis keloidalis nuchae, Kawasaki Disease, Sjögren-Larsson Syndrome, Grover's disease, a first degree burn, a second degree burn, a third degree burn, a fourth degree burn, cutaneous mucinosis, solar keratosis, squamous cell carcinoma or melanoma.

24. The use of claim 19, or the compound, pharmaceutical composition or dosage form of claim 20, wherein the disease or condition is psoriasis, atopic dermatitis, or other pruritic conditions.

25. The use of claim 19, or the compound, pharmaceutical composition or dosage form of any one of claims 20-24, wherein the composition, pharmaceutical composition, or dosage form is to be administered to the patient via an oral, topical, intravenous, intraarterial, intraocular, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, or subcutaneous route of administration.

26. The use of claim 19, or the compound, pharmaceutical composition or dosage form of any one of claims 20-25, wherein the composition, pharmaceutical composition, or dosage form is to be administered to the patient once daily.

27. The use of claim 19, or the compound, pharmaceutical composition or dosage form of any one of claims 20-26, wherein the composition, pharmaceutical composition, or dosage form is to be administered at a dose of from about 1 mg to about 60 mg.

28. The use of claim 19, or the compound, pharmaceutical composition or dosage form of any one of claims 20-27, wherein the composition, pharmaceutical composition, or dosage form is to be administered at a dose of from about 10 to about 60 mg, about 5 mg to about 50 mg, about 1 mg to about 10 mg, about 3 mg to about 15 mg, about 5 mg to about 20 mg, or about 10 mg to about 30 mg.

29. The use of claim 19, or the compound, pharmaceutical composition or dosage form of any one of claims 20-25, wherein the composition, pharmaceutical composition, or dosage form is to be administered intravenously, subcutaneously, or intraocularly, at a dosage of from about 0.005 to about 100 mg/ml.

30. The use, compound, pharmaceutical composition or dosage form of claim 29, wherein the composition, pharmaceutical composition, or dosage form is to be administered at a dose of from about 0.05 to about 100 mg/ml, about 0.01 to about 90 mg/ml, about 0.005 to about 10 mg/ml, about 0.05 to about 15 mg/ml, about 0.5 to about 20 mg/ml, or about 10 to about 30 mg/ml.

31. The use of claim 19, or the compound, pharmaceutical composition or dosage form of any one of claims 20-30, wherein the composition, pharmaceutical composition or dosage form is to be administered to the patient with one or more additional therapeutic agents.

32. The use, compound, pharmaceutical composition or dosage form of claim 31, wherein the one or more additional therapeutic agents are selected from the group consisting of Histamine H₁ receptor antagonists; Histamine H₃ receptor antagonists; Histamine H₂ receptor antagonists; leukotriene antagonists; phosphodiesterase inhibitors; neurotransmitter re-uptake inhibitors; 5-lipoxygenase (5-LO) inhibitors; 5-lipoxygenase activating protein (FLAP) inhibitors; α_1 - and α_2 -adrenoceptor agonist vasoconstrictor sympathomimetic agents; muscarinic M₃ receptor antagonists or anticholinergic agents; β_2 -adrenoceptor agonists; dual acting β_2 /M₃ agents; xanthines; non-steroidal anti-inflammatories; ketotifen; COX-1 inhibitors (NSAIDs) and COX-2 selective inhibitors; oral, inhaled intranasal and topical glucocorticosteroids; monoclonal antibodies active against endogenous inflammatory entities; anti-tumor necrosis factor (anti-TNF- α) agents; adhesion molecule inhibitors including VLA-4 antagonists; kinin- B₁ - and B₂ - receptor antagonists; immunosuppressive agents; inhibitors of matrix metalloproteases (MMPs); tachykinin NK₁, NK₂ and NK₃ receptor antagonists; elastase inhibitors; adenosine A_{2a} receptor agonists; inhibitors of urokinase; compounds that act on dopamine receptors; modulators of the NF κ b pathway; agents that can be classed as mucolytics or anti-tussive agents; antibiotics; modulators of cytokine signaling pathways; modulators of the prostaglandin pathways; antagonists of chemokine receptors CXCR1 and CXCR2; antagonists of chemokine receptors CCR3, CCR4 and CCR5; inhibitors of cytosolic and soluble phospholipase A₂ (cPLA₂ and sPLA₂); inhibitors of phosphoinositide-3-kinase; HDAC inhibitors; p38 inhibitors; CXCR2 antagonists; calcineurin inhibitors; anti-interleukin 17 (anti-IL-17) agents; anti-interleukin 4 receptor (anti-IL4R) agents; anti-interleukin 31 (anti-IL-31) agents; CRTH2 antagonists; and combinations thereof.

33. The use, compound, pharmaceutical composition or dosage form of claim 31 or claim 32,

wherein the one or more additional therapeutic agents are Histamine H₁ receptor antagonists selected from the group consisting of fexofenadine, cetirizine, levocetirizine, loratadine, desloratadine, mepyramine, and diphenhydramine.

34. The use, compound, pharmaceutical composition or dosage form of claim 31 or claim 32, wherein the one or more additional therapeutic agents are leukotriene antagonists selected from the group consisting of montelukast, zafirlukast, and pranlukast.

35. The use, compound, pharmaceutical composition or dosage form of claim 31 or claim 32, wherein the one or more additional therapeutic agents are CRTH2 antagonists selected from the group consisting of ADC3680, NVP-QAV680, and OC459.

36. The use, compound, pharmaceutical composition or dosage form of claim 31 or claim 32, wherein the one or more additional therapeutic agents are PDE4 phosphodiesterase inhibitors selected from the group consisting of apremilast and roflumilast.

37. A method of producing N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate dihydrate, the method comprising:

a) crystallizing N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine 2,4-diamine tartrate from an aqueous solution of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate,

b) isolating the crystallized material,

c) drying the isolated material under wet inert gas flow until such time that the water content of the isolated material is between 6 and 10% and any organic solvent present comprises <0.5% of the isolated material;

wherein the isolated material comprises N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate dihydrate.

38. The method of claim 37, wherein the isolated material comprises a polymorph of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate dihydrate.

39. The method of claim 38, wherein the polymorph is distinguished by PXRD peaks at about 6.7, 9.2, 22.4, and 24.4 degrees 2-theta.

40. The method of claim 39, wherein the polymorph comprises two additional peaks at about 13.5 and 18.7 degrees 2-theta.
41. The method of claim 40, wherein the polymorph comprises four additional peaks at about 20.9, 21.4, 26.8, and 30.0 degrees 2-theta.
42. The method of claim 41, wherein the aqueous solution is treated with an organic solvent.
43. The method of claim 42, wherein the organic solvent is an alcohol.
44. The method of claim 43, wherein the organic solvent is an alcohol that is methanol.
45. The method of any one of claims 37-44, wherein the inert gas is nitrogen.
46. The method of any one of claims 37-45, wherein the relative water humidity in the drying chamber is more than about 40% RH.
47. The method of any one of claims 37-46, wherein the relative water humidity in the drying chamber is between about 50 and 99% RH, about 60 and about 80% RH, or about 69 and 99% RH.
48. The method of any one of claims 37-47, wherein N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate is crystallized by progressively cooling the aqueous solution of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate.
49. The method of claim 48, wherein a polymorph of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate is crystallized by progressively cooling the aqueous solution of polymorph of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate.
50. The method of any one of claims 37-49, wherein the method comprises:
- a) adding an amount of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine (2R,3R)-tartrate to a volume of purified water to produce a first solution and warming to a temperature above 50 °C;
 - b) charging the first solution with an organic solvent to produce a second solution;
 - c) cooling the second solution to 40-60 °C to produce a slurry;

d) progressively cooling the slurry to 20-35 °C;

e) isolating the slurry;

f) washing the isolated material; and

g) drying the isolated material under wet inert gas flow until such time that the water content of the isolated material is between 6 and 10% and any organic solvent present comprises <0.5% of the isolated material;

wherein the isolated material comprises a polymorph of N⁴-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate dihydrate.

51. The method of claim 50, wherein step a) is performed at a temperature range of about 55 °C to about 65 °C.

52. The method of claim 50, wherein in step c), the solution is cooled to about 50 °C over a period of about 20 to about 60 minutes.

53. The method of claim 52, wherein the solution is subsequently cooled to about 40 °C over a period of about 20 to about 60 minutes.

54. The method of claim 53, wherein the solution is subsequently cooled to about 30 °C over a period of 20 to 60 minutes.

55. The method of any one of claims 37-54, wherein the organic solvent content of the isolated material was determined using nuclear magnetic resonance (NMR) or gas chromatography (GC).

56. The method of any one of claims 50-55, wherein the organic solvent is an alcohol.

57. The method of claim 56, wherein the alcohol is methanol.

58. The method of any one of claims 50-57, wherein the inert gas is nitrogen.

59. The method of any one of claims 50-58, wherein the relative water humidity in the drying chamber is more than about >40% RH, between about 50 and 99% RH, or between about 60 and about 80% RH.