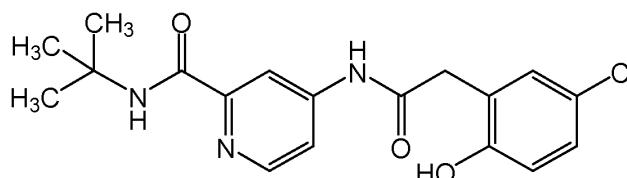


CLAIMS

1. A compound which is N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 1), having the following
5 structural formula:



in the form of its Form A anhydrous solid crystalline polymorph, for example a form having
10 an XRPD diffractogram substantially as shown in Figure 1; or in the form of its Form B
hydrate solid crystalline polymorph, for example a form having an XRPD diffractogram
substantially as shown in Figure 4; or in amorphous form.

2. A compound according to claim 1, which is Compound 1 in the form of its Form A
15 crystalline polymorph characterised by an XRPD diffractogram comprising a major peak
at 7.25 (± 0.2 degrees, 2-theta value) and at least three (for example three, four, five, six,
seven, eight or all nine) of the peaks at positions 14.44, 20.42, 21.68, 24.38, 27.21, 29.01,
30.82, 36.46 and 41.49 (± 0.2 degrees, 2-theta values).

- 20 3. A compound according to claim 2 characterised by an XRPD diffractogram
comprising a major peak at 7.25 (± 0.2 degrees, 2-theta value) and at least three (for
example three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen or all fourteen)
of the peaks at positions 10.20, 14.44, 17.79, 20.42, 20.69, 21.68, 24.22, 24.38, 26.13,
27.21, 29.01, 30.82, 36.46 and 41.49 (± 0.2 degrees, 2-theta values).

- 25 4. A compound according to claim 2 or claim 3 characterised by an XRPD
diffractogram comprising a major peak at 7.25 (± 0.2 degrees, 2-theta value) and at least
three (for example three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen,
fourteen, fifteen, sixteen, seventeen, eighteen or all nineteen) of the peaks at positions
30 10.20, 14.44, 16.13, 17.79, 20.42, 20.69, 21.07, 21.68, 24.09, 24.22, 24.38, 26.13, 27.21,
29.01, 29.30, 30.82, 32.50, 36.46 and 41.49 (± 0.2 degrees, 2-theta values).

5. A compound according to any one of claims 2 to 4, wherein the XRPD diffractogram comprises peaks at positions 21.68 and 29.01 (± 0.2 degrees, 2-theta values) and a cluster of peaks at 24.09, 24.22 and 24.3801 (± 0.2 degrees, 2-theta values).
- 5 6. A compound according to any one of claims 2 to 5, wherein the Form A polymorph is substantially free of other forms of Compound 1 such that at least 97% by weight of Compound 1 is present as the Form A polymorph.
7. A compound according to any one of claims 2 to 6 which is micronised.
- 10 8. A process for the preparation of a compound according to any one of claims 2 to 7 comprising crystallising Compound 1 from a solvent selected from acetone, butanol, ethanol, ethyl formate, isopropyl acetate, methyl acetate, nitromethane, 2-propanol, propionitrile and acetonitrile.
- 15 9. A process according to claim 8, wherein the process comprises the steps of:
- i. preparing a saturated solution of Compound 1 in a solvent at a temperature of about 50 to 70°C;
- ii. cooling the solution to a temperature of about 5 to 20°C;
- 20 iii. allowing the cooled solution to stand until crystals of Compound 1 form; and
- iv. isolating the crystallised product;
- wherein the solvent is selected from acetone, butanol, ethanol, ethyl formate, isopropyl acetate, methyl acetate, nitromethane, 2-propanol, propionitrile and acetonitrile.
- 25 10. A process according to claim 8 or claim 9 wherein the solvent is selected from acetonitrile, ethanol, ethyl acetate, methyl acetate, butanol, 2-propanol or isopropyl acetate.
- 30 11. A compound according to claim 1, which is Compound 1 in the form of its Form B hydrate solid crystalline polymorph characterised by an XRPD diffractogram comprising a major peak at position 11.03 (± 0.4 degrees, more suitably ± 0.3 degrees or ± 0.2 degrees, 2-theta value) and at least three (for example three, four, five, six, seven, eight or all nine) of the peaks at positions 5.56, 14.04, 17.28, 18.03, 18.86, 22.08, 23.69, 24.12 and 24.93 (± 0.4 degrees, more suitably ± 0.3 degrees or ± 0.2 degrees, 2-theta values).

12. A compound according to claim 11 characterised by an XRPD diffractogram comprising a major peak at position 11.03 (± 0.4 degrees, more suitably ± 0.3 degrees or ± 0.2 degrees, 2-theta value) and at least three (for example three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen or all fourteen) of the peaks at positions 5.56, 14.04, 17.28, 18.03, 18.86, 19.34, 22.08, 23.69, 24.12, 24.93, 25.98, 26.53, 27.28 and 28.79 (± 0.4 degrees, more suitably ± 0.3 degrees or ± 0.2 degrees, 2-theta values).
13. A compound according to claim 11 or claim 12 which has an XRPD diffractogram comprising peaks at positions 5.36 and 22.08 (± 0.4 degrees, more suitably ± 0.3 degrees or ± 0.2 degrees, 2-theta values).
14. A compound according to any one of claims 11 to 13, which is micronised.
15. A compound according to any one of claims 11 to 14, wherein the Form B polymorph is substantially free of other forms of Compound 1 such that at least 97% by weight of Compound 1 is present as the Form B polymorph.
16. A compound according to any one of claims 11 to 15 wherein the Form B polymorph is the Form B(I) pseudopolymorph and is characterised in that it undergoes unimodal dehydration
17. A process for the preparation of a compound according to any one of claims 11 to 16, comprising crystallising Compound 1 from an aqueous solvent such as water or water mixed with acetonitrile.
18. A process according to claim 17 comprising the steps of:
- preparing a saturated solution of Compound 1 in a solvent at a temperature of about 60 to 80°C;
 - cooling the solution to a temperature of about 5 to 20°C;
 - allowing the cooled solution to stand until crystals of Compound 1 form; and
 - isolating the crystallised product;
- wherein the solvent is an aqueous solvent such as water or water mixed with acetonitrile, for example acetonitrile/water in a ratio of from 5:1 to 1:5 v/v.
19. A compound according to claim 1, which is Compound 1 in solid anhydrous amorphous form.

20. A compound according to any one of claims 1 to 7, 11 to 16 or 19 for use in medicine.
- 5 21. A compound for use according to claim 20 in the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.
22. Use of a compound according to any one of claims 1 to 7, 11 to 16 or 19 in the manufacture of a medicament for the treatment or prophylaxis of diseases and conditions
10 affected by modulation of TMEM16A.
23. A method for the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A, the method comprising administering to a patient in need of such treatment an effective amount of a compound according to any one of claims 1 to 7, 11 to
15 16 or 19.
24. A compound for use, a use or a method according to any one of claims 21 to 23, wherein the disease or condition affected by modulation of TMEM16A is selected from respiratory diseases and conditions, dry mouth (xerostomia), intestinal hypermobility, cholestasis and ocular conditions.
20
25. A compound for use, a use or a method according to claim 24, wherein the respiratory diseases and conditions are selected from cystic fibrosis, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, bronchiectasis, including non-cystic fibrosis bronchiectasis, asthma and primary ciliary dyskinesia.
25
26. A compound for use, a use or a method according to claim 24, wherein the dry mouth (xerostomia) results from Sjorgens syndrome, radiotherapy treatment or xerogenic drugs.
30
27. A compound for use, a use or a method according to claim 24, wherein the intestinal hypermobility is associated with gastric dyspepsia, gastroparesis, chronic constipation or irritable bowel syndrome.
- 35 28. A compound for use, a use or a method according to claim 24, wherein the ocular disease is dry eye disease.

29. A compound for use, a use or a method according to any one of claims 21 to 28 wherein the compound is used in combination with an additional agent useful in the treatment or prevention of respiratory conditions as a combined preparation for simultaneous, sequential or separate use in the treatment of a disease or condition affected by modulation of TMEM16A.

30. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7, 11 to 16 or 19 together with a pharmaceutically acceptable excipient.

31. A pharmaceutical composition according to claim 30 formulated for oral, rectal, nasal, topical (including topical administration to the lung, dermal, transdermal, eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration.

32. A pharmaceutical composition according to claim 30 or claim 31 which is adapted for oral administration or for topical administration to the lung and which comprises an aqueous suspension of a compound according to any one of claims 2 to 7 or 16.

33. A pharmaceutical composition according to any one of claims 30 to 32 further including an additional active agent useful in the treatment or prevention of respiratory conditions.

34. a product comprising a compound according to any one of claims 1 to 7, 11 to 16 or 19 and an additional agent useful in the treatment or prevention of respiratory conditions as a combined preparation for simultaneous, sequential or separate use in the treatment of a disease or condition affected by modulation of TMEM16A.

35. A compound for use, a use or a method according to claim 29, a pharmaceutical composition according to claim 33 or a product according to claim 34, wherein the additional agent useful in the treatment or prevention of respiratory conditions is selected from:

β 2 adrenoreceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, indacaterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol, olodaterol, vilanterol and abediterol;

- antihistamines, for example histamine H₁ receptor antagonists such as loratadine, cetirizine, desloratadine, levocetirizine, fexofenadine, astemizole, azelastine and chlorpheniramine or H₄ receptor antagonists;
- dornase alpha;
- 5 corticosteroids such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate mometasone furoate and fluticasone furoate;
- Leukotriene antagonists such as montelukast and zafirlukast;
- anticholinergic compounds, particularly muscarinic antagonists such as ipratropium,
- 10 tiotropium, glycopyrrolate, aclidinium and umeclidinium;
- CFTR repair therapies (e.g. CFTR potentiators, correctors or amplifiers) such as Ivacaftor, QBW251, Bamacaftor (VX659), Elexacaftor (VX445), VX561/CPT-656, VX152, VX440, GLP2737, GLP2222, GLP2451, PTI438, PTI801, PTI808, FDL-169 and FDL-176 and CFTR correctors such as Lumacaftor and Tezacaftor or combinations thereof (for example
- 15 a combination of Ivacaftor, Tezacaftor and Elexacaftor);
- Antibiotics;
- Antivirals such as ribavirin and neuraminidase inhibitors such as zanamivir;
- Antifungals such as PUR1900;
- Airway hydrating agents (osmoloytes) such as hypertonic saline and mannitol
- 20 (Bronchitol®); and
- Mucolytic agents such as N-acetyl cysteine;
- ENaC modulators, particularly ENaC inhibitors such as:
- amiloride, VX-371, AZD5634, QBW276, SPX-101, BI443651, BI1265162, ETD001 and compounds having a cation selected from:
- 25 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido) ethyl]-6-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidine-1-carbonyl)-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
- 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido) methyl]-6-{[2-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidin-1-yl)ethyl]carbamoyl]-
- 30 1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
- 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-5-[4-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}methyl)piperidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
- 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-6-[(3*R*)-3-
- 35 {bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-6-[(3*S*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-1,3-diethyl-6-[(1*r*,4*r*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl]-1*H*-1,3-benzodiazol-3-ium;

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-1,3-diethyl-6-[(1*s*,4*s*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl]-1*H*-1,3-benzodiazol-3-ium;

10 and a suitable anion, for example halide, sulfate, nitrate, phosphate, formate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methane sulfonate or p-toluene sulfonate.

36. A process for the preparation of a pharmaceutical composition according to any one of claims 30 to 32 comprising bringing a compound according to any one of claims 1 to 7, 11 to 16 or 19 into association with the excipient.