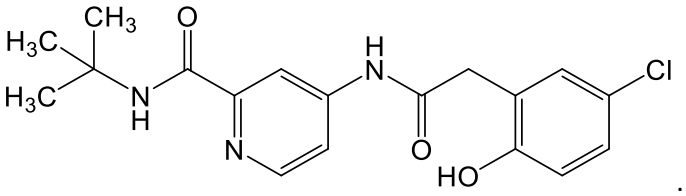
activity is independent of CFTR function, TMEM16A positive modulators have the potential to deliver clinical benefit to all CF patients and non-CF respiratory diseases characterised by mucus congestion including chronic bronchitis and severe asthma.

TMEM16A modulation has been implicated as a therapy for dry mouth (xerostomia), resultant from salivary gland dysfunction in Sjorgen's syndrome and radiation therapy, dry eye, cholestasis and gastrointestinal motility disorders.

The present inventors have developed novel compounds, and novel forms of these compounds, which are positive modulators of TMEM16A and which are therefore of use in the treatment of diseases and conditions in which TMEM16A plays a role, particularly respiratory diseases and conditions. These compounds were described for the first time in our earlier application WO2019/145726, the contents of which are hereby incorporated by reference in their entirety. In particular, WO2019/145726 discloses N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 1), which has the following structural formula:

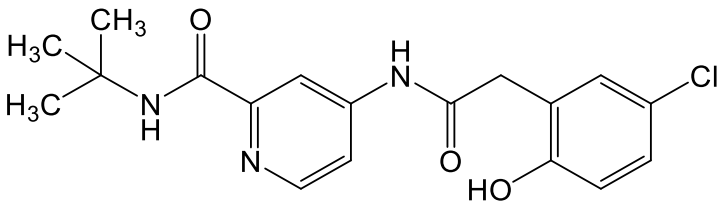


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Summary

The inventors have now developed novel forms of Compound 1.

In an aspect, there is provided a polymorph form of N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 1), having the following structural formula:



,

wherein the polymorph form is:

(a) anhydrous solid crystalline polymorph Form A which exhibits an XRPD diffractogram with a characteristic major peak expressed in values of degrees 2Θ at 7.25± 0.2 and at least three characteristic peaks at 14.44±0.2, 20.42± 0.2, 21.68±0.2, 24.38±0.2, 27.21±0.2, 29.01± 0.2, 30.82±0.2, 36.46±0.2 and 41.49±0.2;

(b) solid crystalline polymorph Form B hydrate which exhibits an XRPD diffractogram with a characteristic major peak expressed in values of degrees 2Θ at 11.03± 0.2 and at least three characteristic peaks at 5.56± 0.2, 14.04± 0.2, 17.28± 0.2, 18.03± 0.2, 18.86± 0.2, 22.08±0.2, 23.69± 0.2, 24.12± 0.2 and 24.93± 0.2; or

(c) an anhydrous amorphous form.

In another aspect, there is provided a process for the preparation of anhydrous solid crystalline polymorph Form A as defined above comprising crystallising Compound 1 from a solvent selected from acetone, butanol, ethanol, ethyl formate, isopropyl acetate, methyl acetate, nitromethane, 2-propanol, propionitrile and acetonitrile.

In another aspect, there is provided a process for the preparation of solid crystalline polymorph Form B hydrate as defined above, comprising crystallising Compound 1 from an aqueous solvent such as water or water mixed with acetonitrile.

In a first example of the disclosure there is provided Compound 1 in the form of its Form A anhydrous solid crystalline polymorph.

In a second example of the disclosure there is provided Compound 1 in the form of its Form B hydrate solid crystalline polymorph, in particular the Form B(I) hydrate solid crystalline pseudopolymorph or the Form B(II) hydrate solid crystalline pseudopolymorph.

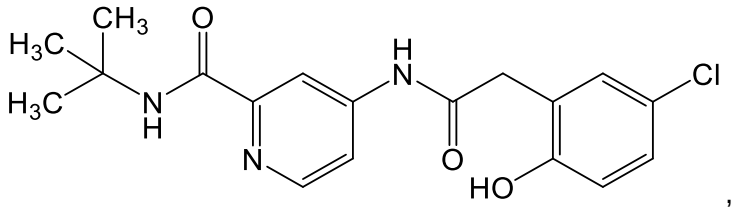
In a third example of the disclosure there is provided anhydrous solid amorphous Compound 1.

Brief description of the figures

Figure 1a is an XRPD diffractogram of solid crystalline polymorphic form A of Compound 1 in the range of 5 to 60 2-theta, step size 0.02 s (reflection mode, offset 500 counts).

CLAIMS

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



,

wherein the polymorph form is:

(a) anhydrous solid crystalline polymorph Form A which exhibits an XRPD diffractogram with a characteristic major peak expressed in values of degrees 2Θ at 7.25± 0.2 and at least three characteristic peaks at 14.44±0.2, 20.42± 0.2, 21.68±0.2, 24.38±0.2, 27.21±0.2, 29.01± 0.2, 30.82±0.2, 36.46±0.2 and 41.49±0.2;

(b) solid crystalline polymorph Form B hydrate which exhibits an XRPD diffractogram with a characteristic major peak expressed in values of degrees 2Θ at 11.03± 0.2 and at least three characteristic peaks at 5.56± 0.2, 14.04± 0.2, 17.28± 0.2, 18.03± 0.2, 18.86± 0.2, 22.08±0.2, 23.69± 0.2, 24.12± 0.2 and 24.93± 0.2; or

(c) an anhydrous amorphous form.

2. The anhydrous solid crystalline polymorph Form A according to claim 1, wherein the XRPD diffractogram comprises a characteristic major peak expressed in values of degrees 2Θ at 7.25±0.2 and at least three characteristic peaks at 10.20±0.2, 14.44±0.2, 17.79±0.2, 20.42±0.2, 20.69±0.2, 21.68±0.2, 24.22±0.2, 24.38±0.2, 26.13±0.2, 27.21±0.2, 29.01±0.2, 30.82±0.2, 36.46±0.2 and 41.49±0.2.

3. The anhydrous solid crystalline polymorph Form A according to claim 1, wherein the XRPD diffractogram comprises a characteristic major peak expressed in values of degrees 2Θ at 7.25±0.2 and at least three characteristic peaks at 10.20±0.2, 14.44±0.2, 16.13±0.2, 17.79±0.2, 20.42±0.2, 20.69±0.2, 21.07±0.2, 21.68±0.2, 24.09±0.2, 24.22±0.2, 24.38±0.2, 26.13±0.2, 27.21±0.2, 29.01±0.2, 29,30±0.2, 30.82±0.2, 32.50±0.2, 36.46±0.2 and 41.49±0.2.

4. The anhydrous solid crystalline polymorph Form A according to any one of claims 2 to 3, wherein the XRPD diffractogram further comprises characteristic peaks expressed in values of degrees 2Θ at 21.68±0.2 and 29.01±0.2 and a cluster of characteristic peaks at 24.09±0.2, 24.22±0.2 and 24.3801±0.2.

5. The anhydrous solid crystalline polymorph Form A according to any one of claims 2 to 4, wherein the anhydrous solid crystalline polymorph Form A is free of other forms of Compound 1 such that at least 97% by weight of Compound 1 is present as the anhydrous solid crystalline polymorph Form A.

6. The anhydrous solid crystalline polymorph Form A according to any one of claims 2 to 5, wherein the form is micronised.

7. A process for the preparation of anhydrous solid crystalline polymorph Form A according to any one of claims 2 to 6 comprising crystallising Compound 1 from a solvent selected from acetone, butanol, ethanol, ethyl formate, isopropyl acetate, methyl acetate, nitromethane, 2-propanol, propionitrile and acetonitrile.

8. The process according to claim 7 comprising the steps of:

i. preparing a saturated solution of Compound 1 in a solvent at a temperature of 50 to 70°C;

ii. cooling the solution to a temperature of 5 to 20°C;

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.

9. The process according to claim 7 or claim 8, wherein the solvent is selected from acetonitrile, ethanol, ethyl acetate, methyl acetate, butanol, 2-propanol and isopropyl acetate.

10. The solid crystalline polymorph Form B hydrate according to claim 1, wherein the XRPD diffractogram comprises a characteristic major peak expressed in values of degrees 2Θ at 11.03±0.2 and at least three characteristic peaks at 5.56±0.2, 14.04±0.2, 17.28±0.2, 18.03±0.2, 18.86±0.2, 19.34±0.2, 22.08±0.2, 23.69±0.2, 24.12±0.2, 24.93±0.2, 25.98±0.2, 26.53±0.2, 27.28±0.2 and 28.79±0.2.

11. The solid crystalline polymorph Form B hydrate according to claim claim 10, wherein the XRPD diffractogram further comprises characteristic peaks expressed in values of degrees 2Θ at 5.36±0.2 and 22.08±0.2.

12. The solid crystalline polymorph Form B hydrate according to claim 10 or 11, wherein the Form B polymorph is free of other forms of Compound 1 such that at least 97% by weight of Compound 1 is present as the solid crystalline polymorph Form B hydrate.

13. The solid crystalline polymorph Form B hydrate according to any one of claims 10 to 13, wherein the solid crystalline polymorph Form B hydrate is Form B(I) pseudopolymorph and is characterised in that it undergoes unimodal dehydration.

14. A process for the preparation of solid crystalline polymorph Form B hydrate according to any one of claims 10 to 14 comprising crystallising Compound 1 from an aqueous solvent such as water or water mixed with acetonitrile.

15. The process according to claim 14 comprising the steps of:

i. preparing a saturated solution of Compound 1 in a solvent at a temperature of 60 to 80°C;

ii. cooling the solution to a temperature of 5 to 20°C;

iii. allowing the cooled solution to stand until crystals of Compound 1 form; and

iv. isolating the crystallised product;

wherein the solvent is an aqueous solvent such as water or water mixed with acetonitrile, preferably wherein the solvent is acetonitrile/water in a ratio of from 5:1 to 1:5 v/v.

16. The polymorph form according to claim 1, wherein Compound 1 is in the solid anhydrous amorphous form.