Summary ~~of the invention~~

It has been found that compound (I) can exist in one or more crystalline salt forms that have necessary properties, including stability and processability, that allow their use in large scale manufacture of pharmaceutical products such as tablets or capsules.

~~In one aspect, the~~The present disclosure provides a salt of compound (I) with *p*-toluenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalenedisulfonic acid, hydrobromic acid, nitric acid, benzenesulfonic acid, hydrochloric acid, maleic acid, 1,2-ethanedisulfonic acid, oxalic acid, ethanesulfonic acid, sulfuric acid and methanesulfonic acid.

In one aspect, the present disclosure provides a salt of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (I) with an acid selected from the group consisting of

- *p*-toluenesulfonic acid,
- 2-naphthalenesulfonic acid,
- 1,5-naphthalenedisulfonic acid,
- hydrobromic acid,
- nitric acid,
- benzenesulfonic acid,
- hydrochloride acid,
- maleic acid,
- 1,2-ethanedisulfonic acid,
- oxalic acid,
- ethanesulfonic acid,
- sulfuric acid and
- methanesulfonic acid.

In ~~another aspect~~one example, the present disclosure provides the above salts in crystalline form.

In particular, the present disclosure provides *p*-toluenesulfonic acid salt, 2-naphthalenesulfonic acid salt, 1,5-naphthalenedisulfonic acid salt and hydrobromic acid salt of compound (I). These salts are crystalline and exhibit particularly high melting point, lack of polymorphism, low weight loss during heating and excellent sold-state stability in pharmaceutical dosage forms such as tablets.

In another aspect, the present disclosure provides a method of preparing a crystalline salt as described herein, comprising dissolving compound (I) and *p*-toluenesulfonic acid in a mixture of acetonitrile and water, cooling the mixture and isolating the crystalline product.

In another aspect, the present disclosure provides a method of preparing a crystalline salt as described herein, comprising dissolving compound (I) and 2-naphthalenesulfonic acid in ethanol or a mixture of ethanol and water, cooling the mixture and isolating the crystalline product.

In another aspect, the present disclosure provides a method of preparing a crystalline salt as described herein, comprising dissolving compound (I) and 1,5-naphthalenedisulfonic acid in ethanol, a mixture of ethanol and water or a mixture of acetonitrile and water, cooling the mixture and isolating the crystalline product.

In another aspect, the present disclosure provides a method of preparing a crystalline salt as described herein, comprising dissolving compound (I) and hydrobromic acid in ethanol, or a mixture of water with ethanol or isopropanol, cooling the mixture and isolating the crystalline product.

~~In another aspect, the~~The present disclosure provides a method for the treatment of diseases where CYP11A1 inhibition is desired, particularly in the treatment of hormonally regulated cancers, such as prostate cancer and breast cancer, comprising administering to a subject in need thereof a therapeutically effective amount of any of the above salts of compound (I) or a crystalline form thereof.

~~In yet another aspect, the~~The present disclosure provides pharmaceutical compositions, particularly in the form of a tablet or a capsule, comprising any of the above salts of compound (I) or a crystalline for thereof together with one or more excipients. In another aspect, the present disclosure provides a pharmaceutical composition comprising a salt as described herein as an active ingredient together with with one or more excipients. ~~In yet another aspect, the~~The present disclosure provides such compositions for use in the treatment of hormonally regulated cancers, such as prostate cancer and breast cancer.

In another aspect, the present disclosure provides a salt as described herein for use in the treatment of hormonally regulated cancers, such as prostate cancer and breast cancer.

In another aspect, the present disclosure provides use of a salt as described herein in the manufacture of a medicament for the treatment of hormonally regulated cancers, such as prostate cancer and breast cancer.

Claims

1. A salt of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (I) with an acid selected from the group consisting of

- *p*-toluenesulfonic acid,
- 2-naphthalenesulfonic acid,
- 1,5-naphthalenedisulfonic acid,
- hydrobromic acid,
- nitric acid,
- benzenesulfonic acid,
- hydrochloride acid,
- maleic acid,
- 1,2-ethanedisulfonic acid,
- oxalic acid,
- ethanesulfonic acid,
- sulfuric acid and
- methanesulfonic acid.

2. A salt according to claim 1, which is a salt of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (I) with an acid selected from the group consisting of

- *p*-toluenesulfonic acid,
- 2-naphthalenesulfonic acid,
- 1,5-naphthalenedisulfonic acid and
- hydrobromic acid.

3. A salt according to claim 1 or 2 which is crystalline.

4. A salt according to claim 2 or 3, which is a crystalline *p*-toluenesulfonic acid salt of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (I).

5. A salt according to claim 4, which is of crystalline form 1 having an X-ray powder diffraction pattern characterized by peaks, expressed in degrees 2-theta (± 0.2), at 4.4, 15.2, 18.4, 19.1, 20.8 and 22.4.

6. A salt according to claim 5, wherein the crystalline form 1 has an X-ray powder diffraction pattern characterized by peaks, expressed in degrees 2-theta (± 0.2), at 4.4, 8.8, 11.4, 15.2, 16.5, 17.1, 18.4, 19.1, 20.8 and 22.4.

7. A salt according to any one of claims 4 to 6, wherein the crystalline form 1 has the following unit cell parameters at T=293(2) K:

Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.02369(10) Å	α = 90°
	b = 12.21533(19) Å	β = 92.5099(16)°
	c = 20.1514(4) Å	γ = 90°
Volume	V = 1481.35(4) $Å^3$	
Z	2	
Goodness-of-fit	1.030	
R factor	0.0657	
Morphology	Prismatic	

8. A salt according to claim 2 or 3, which is a crystalline 2-naphthalenesulfonic acid salt of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (I).

9. A salt according to claim 8, which is of crystalline form 1 having an X-ray powder diffraction pattern characterized by peaks, expressed in degrees 2-theta (± 0.2), at 4.3, 8.7, 13.0, 18.8 and 27.1.

10. A salt according to claim 9, wherein the crystalline form 1 has an X-ray powder diffraction pattern characterized by peaks, expressed in degrees 2-theta (± 0.2), at 4.3, 8.7, 13.0, 18.8, 21.7, 27.1 and 35.8.

11. A salt according to claim 2 or 3, which is a crystalline 1,5-naphthalene-disulfonic acid salt of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (I).

12. A salt according to claim 11, which is of crystalline form 1 having an X-ray powder diffraction pattern characterized by peaks, expressed in degrees 2-theta (± 0.2), at 10.6, 17.6, 20.2, 20.4, 22.8 and 24.8.

13. A salt according to claim 12, wherein the crystalline form 1 has an X-ray powder diffraction pattern characterized by peaks, expressed in degrees 2-theta (± 0.2), at 5.9, 9.2, 10.6, 15.5, 17.1, 17.6, 20.2, 20.4, 22.8 and 24.8.

14. A salt according to claim 2 or 3, which is a crystalline hydrobromic acid salt of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (I).

15. A salt according to claim 14, which is of crystalline form 1 having an X-ray powder diffraction pattern characterized by peaks, expressed in degrees 2-theta (± 0.2), at 5.3, 10.5, 13.6, 18.3, 21.4 and 26.9.

16. A salt according to claim 15, wherein the crystalline form 1 has an X-ray powder diffraction pattern characterized by peaks, expressed in degrees 2-theta (± 0.2), at about 5.3, 10.5, 13.6, 16.9, 18.3, 18.8, 21.4, 22.6 and 26.9.

17. A method of preparing a crystalline salt according to any of claims 4 to 7, comprising dissolving compound (I) and *p*-toluenesulfonic acid in a mixture of acetonitrile and water, cooling the mixture and isolating the crystalline product.

18. A method of preparing a crystalline salt according to any of claims 8 to 10, comprising dissolving compound (I) and 2-naphthalenesulfonic acid in ethanol or a mixture of ethanol and water, cooling the mixture and isolating the crystalline product.

19. A method of preparing a crystalline salt according to any of claims 11 to 13, comprising dissolving compound (I) and 1,5-naphthalenedisulfonic acid in ethanol, a mixture of ethanol and water or a mixture of acetonitrile and water, cooling the mixture and isolating the crystalline product.

20. A method of preparing a crystalline salt according to any of claims 14 to 16, comprising dissolving compound (I) and hydrobromic acid in ethanol, or a mixture of water with ethanol or isopropanol, cooling the mixture and isolating the crystalline product.

21. A pharmaceutical composition comprising a salt according to any one of claims 1 to 16 as an active ingredient together with with one or more excipients.

22. A pharmaceutical composition according to claim 21, which is in the form of a tablet, capsule, granule, powder or suspension.

23. A pharmaceutical composition according to claim 22, which is in the form of a tablet or capsule.

24. A pharmaceutical composition according to claim 23, which is in the form of a tablet.

25. A salt according to any of claims 1 to 16 for use in the treatment of hormonally regulated cancers, such as prostate cancer and breast cancer.

26. Use of a salt according to any of claims 1 to 16 in the manufacture of a medicament for the treatment of hormonally regulated cancers, such as prostate cancer and breast cancer.