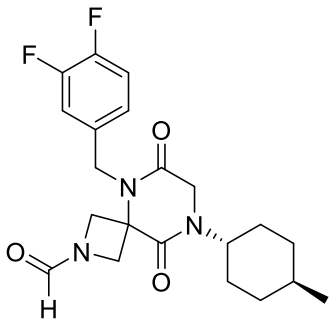
CLAIMS

1. A crystalline form of the compound of Formula 1:



1.

2. The crystalline form of claim 1, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 5.9±0.2, 11.5±0.2, 11.7±0.2, 17.9±0.2, and 19.1±0.2 degrees.

3. The crystalline form of claim 2, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 7.8±0.2, and 16.2±0.2 degrees.

4. The crystalline form of any one of claims 2 or 3, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 13.1±0.2, and 19.8±0.2 degrees.

5. The crystalline form of any one of claims 1-4, characterized by having an XRPD pattern substantially as shown in FIG. 2A.

6. The crystalline form of any one of claims 1-5, characterized by having a DSC graph substantially as shown in FIG. 2B.

7. The crystalline form of any one of claims 1-6, characterized by having an endotherm onset at 154.9±2 °C as determined by DSC.

8. The crystalline form of any one of claims 1-7, characterized by having an endotherm peak at 155.8±2 °C as determined by DSC.

9. The crystalline form of any one of claims 1-8, characterized by having a TGA graph substantially as shown in FIG. 2B.

10. The crystalline form of any one of claims 1-9, characterized by having less than 0.1% weight loss prior to degradation as determined by TGA.

11. The crystalline form of any one of claims 1-10, characterized by having a GVS graph substantially as shown in FIG. 2C.

12. The crystalline form of claim 1, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 6.0±0.2, 10.2±0.2, 21.6±0.2, and 22.1±0.2 degrees.

13. The crystalline form of claim 12, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 17.9±0.2, and 24.1±0.2 degrees.

14. The crystalline form of any one of claims 12 or 13, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 16.0±0.2, 16.6±0.2, 17.3±0.2, 17.6±0.2, and 20.5±0.2 degrees.

15. The crystalline form of any one of claims 1 and 12-14, characterized by having an XRPD pattern substantially as shown in FIG. 1A.

16. The crystalline form of any one of claims 1 and 12-15, characterized by having a DSC graph substantially a shown in FIG. 1B.

17. The crystalline form of any one of claims 1 and 12-16, characterized by having an endotherm onset at 125.6±2 °C as determined by DSC.

18. The crystalline form of any one of claim 1 and 12-17, characterized by having an endotherm peak at 130.2±2 °C as determined by DSC.

19. The crystalline form of any one of claims 1 and 12-18, characterized by having a TGA graph substantially as shown in FIG. 1B.

20. The crystalline form of any one of claims 1 and 12-19, characterized by having a weight loss of 0.35%±0.05% between 105 °C and 145 °C, as determined by TGA.

21. The crystalline form of any one of claims 1 and 12-20, characterized by having a GVS graph substantially as shown in FIG. 1C.

22. A method of preparing the crystalline form of any one of claims 2-11, comprising (1) forming a mixture of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde and a solvent selected from the group consisting of an alcohol, water and mixtures thereof, and (2) cooling the mixture of step (1).

23. The method of claim 22, wherein the solvent comprises ethanol and water.

24. The method of claim 22 or 23, wherein step (1) comprises stirring the mixture at a temperature of 40 °C to 60 °C.

25. The method of any one of claims 22-24, wherein the step (2) comprises cooling the mixture of step (1) to a temperature of 0 °C to 10 °C.

26. A method of preparing the crystalline form of any one of claims 2-11, comprising (1) forming a mixture of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde and a first solvent; (2) heating the mixture of step (1) to a first temperature between 75 °C and 95 °C; (3) adding a second solvent to the mixture of step (2); (4) cooling the mixture of step (3) to a second temperature between 10 °C and 30 °C; and (5) filtering the mixture of step (4) to obtain the crystalline form.

27. The method of claim 26, wherein step (4) further comprises cooling the mixture of step (3) to an intermediate temperature between 50 °C and 75 °C, adding seed crystals of the crystalline form, and further cooling the mixture to the second temperature.

28. The method of claim 26 or 27, wherein the first solvent is ethanol or a mixture of ethanol and water.

29. The method of any one of the claims 26-28, wherein the second solvent is water.

30. A pharmaceutical composition comprising the crystalline form of any one of claims 1-21, and a pharmaceutically acceptable excipient.

31. Use of the crystalline form of any one of claims 1-21, or the pharmaceutical composition of claim 30 in the manufacture of a medicament for the treatment of heart disease in a subject in need thereof.

32. The use of claim 31, wherein the heart disease is hypertrophic cardiomyopathy or heart failure with preserved ejection fraction.

33. The use of claim 32, wherein the hypertrophic cardiomyopathy is obstructive or nonobstructive or is caused by (i) sarcomeric mutations, (ii) non-sarcomeric mutations, or (iii) both sarcomeric mutations and non-sarcomeric mutations.

34. The use of claim 31, wherein the heart disease is selected from the group consisting of diastolic dysfunction, primary or secondary restrictive cardiomyopathy, myocardial infarction and angina pectoris, left ventricular outflow tract obstruction, hypertensive heart disease, congenital heart disease, cardiac ischemia, coronary heart disease, diabetic heart disease, congestive heart failure, right heart failure, cardiorenal syndrome, and infiltrative cardiomyopathy; or wherein the heart disease is or is related to one or more conditions selected from the group consisting of cardiac senescence, diastolic dysfunction due to aging, left ventricular hypertrophy, and concentric left ventricular remodeling.

35. Use of the crystalline form of any one of claims 1-21, or the pharmaceutical composition of claim 30 in the manufacture of a medicament for the treatment of a disease or condition associated with hypertrophic cardiomyopathy, secondary left ventricular wall thickening, small left ventricular cavity and cavity obliteration, hyperdynamic left ventricular contraction, myocardial ischemia, or cardiac fibrosis, or a disease or condition selected from muscular dystrophies and glycogen storage diseases in a subject in need thereof.

36. The use of claim 35, wherein the disease or condition is selected from the group consisting of Fabry's Disease, Danon Disease, mitochondrial cardiomyopathies, Noonan Syndrome, hypertension, valvular heart diseases, aortic stenosis, Mitral valve regurgitation, metabolic syndromes, diabetes, obesity, end stage renal disease, scleroderma, sleep apnea, amyloidosis, Friedreich Ataxia, and Pompe disease.

37. Use of the crystalline form of any one of claims 1-21, or the pharmaceutical composition of claim 30 in the manufacture of a medicament for the inhibition of cardiac sarcomere.