CLAIMS

1. A crystalline form of (2S)-3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl]amino]propane-1,2-diol (Compound 1).

2. The crystalline form of claim 1, which is crystalline Form A.

3. The crystalline form of claim 1, which has an X-ray powder diffraction pattern (Cu K_α radiation) with at least five specific peaks at about 2-theta = 13.0, 19.3, 19.8, 22.7 and 24.1°.

4. The crystalline form of claim 1, which has an X-ray powder diffraction pattern (Cu K_α radiation) with at least five specific peaks at 2-theta = 13.0, 19.3, 19.8, 22.7 and 24.1°, wherein said values are each ± 0.2° 2-theta.

5. The crystalline form of claim 1, which has an X-ray powder diffraction pattern (Cu K_α radiation) substantially the same as the X-ray powder diffraction pattern shown in Figure 1.

6. A crystalline form of 2-(4-(((1R,2R)-2-hydroxycyclohexyl)amino)pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (Compound 2), hydrochloride salt.

7. A pharmaceutical composition comprising the crystalline form of any one of the preceding claims, and a pharmaceutically acceptable excipient.

8. The crystalline form or the pharmaceutical composition of any one of claims 1-7 for use in therapy.

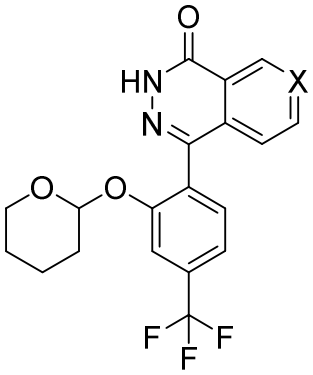
9. The crystalline form or the pharmaceutical composition of any one of claims 1-7 for use in the treatment of a subject with a disease or condition in which NLRP3 inflammasome activity is implicated.

10. The crystalline form or the pharmaceutical composition of any one of claims 1-7 for use in the treatment of a subject with a disease or condition selected from the group consisting of kidney diseases such as acute kidney injury, chronic kidney disease, and diabetic kidney disease; cardiovascular diseases such as coronary atherosclerotic heart disease, cardiomyopathy, myocardial infarction, cardiac hypertrophy, and ischaemia-reperfusion injury; liver diseases such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, alcoholic steatohepatitis, chronic hepatitis C virus infection, and

paracetamol-induced liver injury; inflammatory diseases such as autoinflammatory disorders, Cryopyrin-associated periodic syndromes, familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), chronic infantile neurologic cutaneous articular (CINCA) syndrome, and neonatal onset multi-system inflammatory disease (NOMID); inflammatory skin diseases such as acne vulgaris, and hidradenitis suppurativa; inflammatory bowel diseases such as ulcerative colitis (UC), and Crohn's disease; autoimmune diseases such as gout, pseudo gout, rheumatoid arthritis (RA), multiple sclerosis (MS), Addison's disease, celiac disease, systemic lupus erythematous (SLE), and vitiligo; and respiratory diseases such as chronic pulmonary diseases, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and asthma.

11. Use of the crystalline form or the pharmaceutical composition of any one of claims 1-7 in the manufacture of a medicament for inhibiting NLRP3 inflammasome activity in a subject in need thereof, wherein the crystalline form or the pharmaceutical composition is to be administered to the subject.

12. A process for the preparation of a compound of Formula (Ic), or a salt thereof,



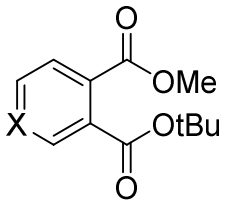
Formula (Ic)

comprising the steps:

(a) reacting 2-(3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran with an alkyl lithium, optionally n-BuLi, to form (2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)lithium;

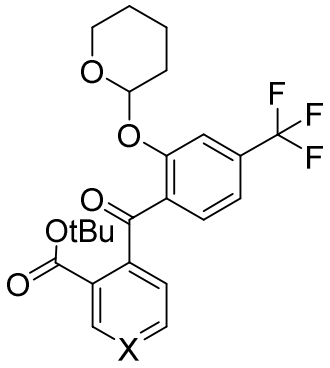
(b) optionally adding magnesium chloride or magnesium bromide to the reaction product of (a);

(c) reacting the product of (a) or (b) with a compound of Formula (Ia)



Formula (Ia)

to form a compound of Formula (Ib), or a salt thereof



Formula (Ib) ;

(d) reacting the compound of Formula (Ib), or a salt thereof, with hydrazine, optionally in the presence of an acid such as acetic acid, to form a compound of Formula (Ic), or a salt thereof; and

(e) isolating the compound of Formula (Ic), or a salt thereof;

and wherein X = CH or N in Formula (Ia), Formula (Ib) and Formula (Ic).

13. A process for the preparation of 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof, comprising the steps:

(a) reacting 2-(3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran with an alkyl lithium, optionally n-BuLi, to form (2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)lithium;

(b) optionally adding magnesium chloride or magnesium bromide to the reaction product of (a);

(c) reacting the product of (a) or (b) with phthalic anhydride to form 2-[2-(tetrahydro-2H-pyran-2-yloxy)-4-(trifluoromethyl)benzoyl]benzoic acid or a salt thereof;

(d) reacting 2-[2-(tetrahydro-2H-pyran-2-yloxy)-4-(trifluoromethyl)benzoyl]benzoic acid, or a salt thereof, with aqueous acid to form 2-[2-hydroxy-4-(trifluoromethyl)benzoyl]benzoic acid, or a salt thereof;

(e) reacting 2-[2-hydroxy-4-(trifluoromethyl)benzoyl]benzoic acid, or a salt thereof, with hydrazine to form 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof; and

(f) isolating 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof.

14. A process for the preparation of 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof, comprising the steps:

(a) reacting 2-(3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran with an alkyl lithium, optionally n-BuLi, to form (2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)lithium;

(b) optionally adding magnesium chloride or magnesium bromide to the reaction product of (a);

(c) reacting the product of (a) or (b) with phthalic anhydride to form 2-[2-(tetrahydro-2H-pyran-2-yloxy)-4-(trifluoromethyl)benzoyl]benzoic acid or a salt thereof;

(d) reacting 2-[2-(tetrahydro-2H-pyran-2-yloxy)-4-(trifluoromethyl)benzoyl]benzoic acid, or a salt thereof, with hydrazine to form 4-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof;

(e) reacting 4-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)phthalazine-1(2H)-one, or a salt thereof, with an acid to form 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof; and

(f) isolating 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof.

15. A process for the preparation of 2-(4-chlorophthalazin-1-yl)-5-(trifluoromethyl)phenol, or a salt thereof, comprising the steps:

(a) reacting 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof, with a chlorinating agent such as $POCl_3$ to form 2-(4-chlorophthalazin-1-yl)-5-(trifluoromethyl)phenol, or a salt thereof; and

(b) isolating 2-(4-chlorophthalazin-1-yl)-5-(trifluoromethyl)phenol, or a salt thereof.

16. The process of claim 15, wherein the 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof, used in step (a) is prepared by the process of claim 13.

17. The process of claim 15, wherein the 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof, used in step (a) is prepared by the process of claim 14.

18. A process for the preparation of Compound 1, or a salt thereof, comprising the steps:

(a) reacting 2-(3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran with an alkyl lithium, optionally n-BuLi, to form (2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)lithium;

(b) optionally adding magnesium chloride or magnesium bromide to the reaction product of (a);

(c) reacting the product of (a) or (b) with phthalic anhydride to form 2-[2-(tetrahydro-2H-pyran-2-yloxy)-4-(trifluoromethyl)benzoyl]benzoic acid or a salt thereof;

(d) reacting 2-[2-(tetrahydro-2H-pyran-2-yloxy)-4-(trifluoromethyl)benzoyl]benzoic acid, or a salt thereof, with aqueous acid to form 2-[2-hydroxy-4-(trifluoromethyl)benzoyl]benzoic acid, or a salt thereof;

(e) reacting 2-[2-hydroxy-4-(trifluoromethyl)benzoyl]benzoic acid, or a salt thereof, with hydrazine to form 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof;

(f) reacting 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof, with a chlorinating agent such as $POCl_3$ to form 2-(4-chlorophthalazin-1-yl)-5-(trifluoromethyl)phenol, or a salt thereof;

(g) reacting 2-(4-chlorophthalazin-1-yl)-5-(trifluoromethyl)phenol, or a salt thereof, with (1) (2S)-3-amino-1,2-propanediol, or a salt thereof, to form Compound 1, or a salt thereof, or (2) diol-protected (2S)-3-amino-1,2-propanediol, or a salt thereof, followed by deprotection of the resulting product to form Compound 1, or a salt thereof; and

(h) isolation of Compound 1, or a salt thereof.

19. A process for the preparation of Compound 1, or a salt thereof, comprising the steps:

(a) reacting 2-(3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran with an alkyl lithium, optionally n-BuLi, to form (2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)lithium;

(b) optionally adding magnesium chloride or magnesium bromide to the reaction product of (a);

(c) reacting the product of (a) or (b) with phthalic anhydride to form 2-[2-(tetrahydro-2H-pyran-2-yloxy)-4-(trifluoromethyl)benzoyl]benzoic acid or a salt thereof;

(d) reacting 2-[2-(tetrahydro-2H-pyran-2-yloxy)-4-(trifluoromethyl)benzoyl]benzoic acid, or a salt thereof, with hydrazine to form 4-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof;

(e) reacting 4-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)phthalazine-1(2H)-one, or a salt thereof, with an aqueous acid to form 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof;

(f) reacting 4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof, with a chlorinating agent such as $POCl_3$ to form 2-(4-chlorophthalazin-1-yl)-5-(trifluoromethyl)phenol, or a salt thereof;

(g) reacting 2-(4-chlorophthalazin-1-yl)-5-(trifluoromethyl)phenol, or a salt thereof, with (1) (2S)-3-amino-1,2-propanediol, or a salt thereof, to form Compound 1, or a salt thereof, or (2) diol-protected (2S)-3-amino-1,2-propanediol, or a salt thereof, followed by deprotection of the resulting product to form Compound 1, or a salt thereof; and

(h) isolation of Compound 1, or a salt thereof.

20. A process for the preparation of Compound 1, or a salt thereof, comprising the steps:

(a) reacting 2-(3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran with an alkyl lithium, optionally n-BuLi, to form (2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)lithium;

(b) optionally adding magnesium chloride or magnesium bromide to the reaction product of (a);

(c) reacting the product of (a) or (b) with tert-butyl methyl phthalate to form tert-butyl 2-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)benzoyl)benzoate;

(d) reacting tert-butyl 2-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)benzoyl)benzoate with hydrazine, optionally in the presence of an acid such as acetic acid, to form 4-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof; and

(e) reacting 4-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)phthalazin-1(2H)-one, or a salt thereof, with diol-protected (2S)-3-amino-1,2-propanediol, or a salt thereof, in the presence of a coupling reagent, followed by removal of the THP

protecting group and diol protecting group from the resulting product by reaction with an acid, to form Compound 1, or a salt thereof; and

(f) isolation of Compound 1, or a salt thereof.

21. A process for the preparation of Compound 2, or a salt thereof, comprising the steps:

(a) reacting 2-(3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran with an alkyl lithium, optionally n-BuLi, to form (2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)lithium;

(b) optionally adding magnesium chloride or magnesium bromide to the reaction product of (a);

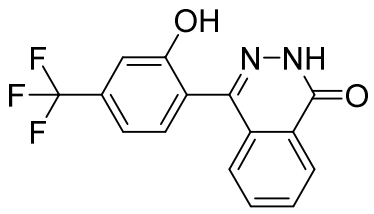
(c) reacting the product of (a) or (b) with 3-(tert-butyl) 4-methyl pyridine-3,4-dicarboxylate to form tert-butyl 4-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)benzoyl)nicotinate, or a salt thereof;

(d) reacting tert-butyl 4-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)benzoyl)nicotinate, or a salt thereof, with hydrazine, optionally in the presence of an acid such as acetic acid, to form 1-[2-tetrahydropyran-2-yloxy-4-(trifluoromethyl)phenyl]-3H-pyrido[3,4-d]pyridazin-4-one, or a salt thereof;

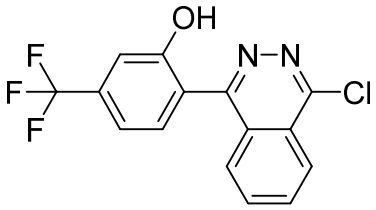
(e) reacting 1-[2-tetrahydropyran-2-yloxy-4-(trifluoromethyl)phenyl]-3H-pyrido[3,4-d]pyridazin-4-one with (1R,2R)-2-aminocyclohexan-1-ol, or a salt thereof, in the presence of a coupling reagent, to form (1R,2R)-2-((1-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4-yl)amino)cyclohexan-1-ol, or a salt thereof;

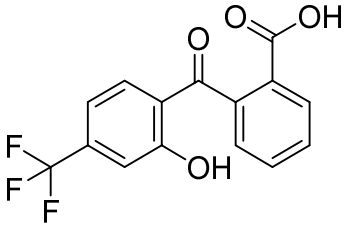
(f) removal of the THP protecting group from (1R,2R)-2-((1-(2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4-yl)amino)cyclohexan-1-ol, or a salt thereof, by reaction with an acid to form Compound 2, or a salt thereof; and

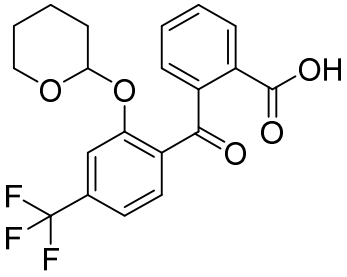
(g) isolation of Compound 2, or a salt thereof.

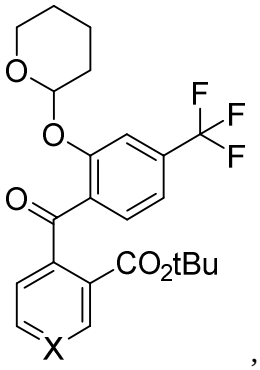
22. A compound that is 

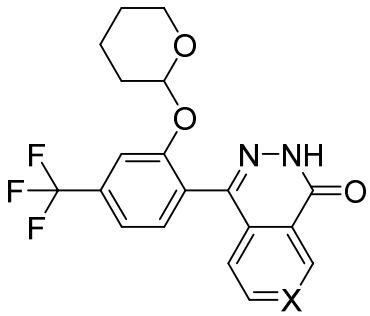
, or a salt thereof.

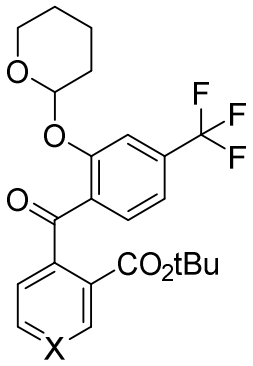
23. A compound that is , or a salt thereof.

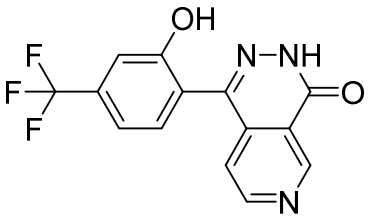
24. A compound that is , or a salt thereof.

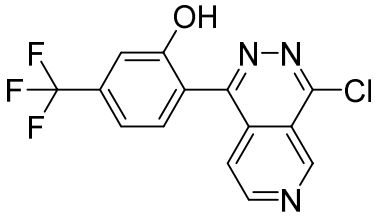
25. A compound that is , or a salt thereof.

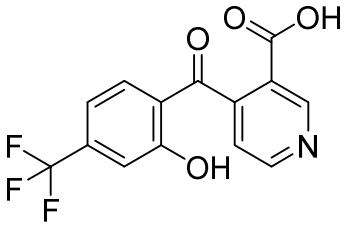
26. A compound that is , or a salt thereof, wherein X is CH or N.

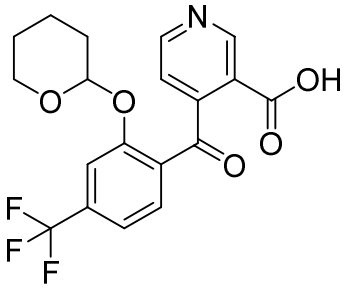
27. A compound that is , or a salt thereof, wherein X is CH or N.

28. A compound that is , or a salt thereof, wherein X is CH or N.

29. A compound that is , or a salt thereof.

30. A compound that is , or a salt thereof.

31. A compound that is , or a salt thereof.

32. A compound that is , or a salt thereof.

33. Use of the crystalline form or the pharmaceutical composition of any one of claims 1-7 in the manufacture of a medicament for the treatment of a disease or condition in which NLRP3 inflammasome activity is implicated.

34. Use of the crystalline form or the pharmaceutical composition of any one of claims 1-7 in the manufacture of a medicament for the treatment of a disease or condition selected from the group consisting of kidney diseases such as acute kidney injury, chronic kidney disease, and diabetic kidney disease; cardiovascular diseases such as coronary atherosclerotic heart disease, cardiomyopathy, myocardial infarction, cardiac hypertrophy, and ischaemia-reperfusion injury; liver diseases such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, alcoholic steatohepatitis, chronic hepatitis C virus infection, and paracetamol-induced liver injury; inflammatory diseases such as autoinflammatory disorders, Cryopyrin-associated periodic syndromes, familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), chronic infantile neurologic cutaneous articular (CINCA) syndrome, and neonatal onset multi-system inflammatory disease (NOMID); inflammatory skin diseases such as acne vulgaris, and hidradenitis suppurativa; inflammatory bowel diseases such as ulcerative colitis (UC), and Crohn’s disease; autoimmune diseases such as gout, pseudo gout, rheumatoid arthritis (RA), multiple sclerosis (MS), Addison’s disease, celiac disease, systemic lupus erythematous (SLE), and vitiligo; and respiratory diseases such as chronic pulmonary diseases, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and asthma.