

CLAIMS

1. A method of preparing a solid crystalline form of a N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide monohydrochloride, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 8.438, 10.083, 10.18, 10.74, 10.940, 11.22, 12.0, 13.116, 13.318, 13.418, 13.541, 13.762, 13.899, 16.443, 16.583, 17.026, 17.124, 17.219, 17.53, 17.78, 18.032, 18.32, 18.340, 18.419, 18.66, 19.399, 20.182, 20.199, 20.421, 20.500, 20.839, 21.14, 21.84, 21.917, 21.958, 22.22, 22.499, 23.238, 23.46, 23.725, 24.159, 24.363, 24.7, 24.958, 25.498, 26.222, 26.596, 26.863, 27.72, 30.30, 30.557, and 30.879, comprising the step of combining N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide with hydrochloric acid.
2. The method of claim 1, comprising the steps of:
 - a) Dissolving N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide in a first solvent to obtain a solution;
 - b) Combining hydrochloric acid with the solution;
 - c) Combining a second solvent with the solution;
 - d) Precipitating or crystallizing the solid crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide monohydrochloride from the solution; and
 - e) Collecting the solid crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide monohydrochloride.
3. The method of claim 2, wherein the first solvent comprises ethanol.

4. The method of claim 3, wherein the hydrochloric acid is in a concentrated aqueous solution.
5. The method of claim 4, wherein the second solvent comprises ethyl acetate.
6. The method of claim 5, wherein one or more of the solutions of steps a), b) or c) is heated.
7. A method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a solid crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, or a salt thereof, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (± 0.2), selected from the group consisting of 8.438, 10.083, 10.18, 10.74, 10.940, 11.22, 12.0, 13.116, 13.318, 13.418, 13.541, 13.762, 13.899, 16.443, 16.583, 17.026, 17.124, 17.219, 17.53, 17.78, 18.032, 18.32, 18.340, 18.419, 18.66, 19.399, 20.182, 20.199, 20.421, 20.500, 20.839, 21.14, 21.84, 21.917, 21.958, 22.22, 22.499, 23.238, 23.46, 23.725, 24.159, 24.363, 24.7, 24.958, 25.498, 26.222, 26.596, 26.863, 27.72, 30.30, 30.557, and 30.879, wherein the cancer is B cell lymphoma, non-Hodgkin's lymphoma, or breast cancer.
8. The method of claim 7, wherein the cancer is non-Hodgkin's lymphoma.
9. The method of claim 7, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having three or more characteristic peaks expressed in degrees 2-theta (± 0.2), selected from the group consisting of 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.
10. A method of inhibiting the histone methyltransferase activity of EZH2 in a subject in need thereof or in vitro, comprising administering to the subject an effective amount of a solid crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-

2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, or a salt thereof, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (± 0.2), selected from the group consisting of 8.438, 10.083, 10.18, 10.74, 10.940, 11.22, 12.0, 13.116, 13.318, 13.418, 13.541, 13.762, 13.899, 16.443, 16.583, 17.026, 17.124, 17.219, 17.53, 17.78, 18.032, 18.32, 18.340, 18.419, 18.66, 19.399, 20.182, 20.199, 20.421, 20.500, 20.839, 21.14, 21.84, 21.917, 21.958, 22.22, 22.499, 23.238, 23.46, 23.725, 24.159, 24.363, 24.7, 24.958, 25.498, 26.222, 26.596, 26.863, 27.72, 30.30, 30.557, and 30.879.

11. The method of claim 10, wherein the histone methyltransferase activity of EZH2 is inhibited in a subject.

12. The method of claim 10, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having three or more characteristic peaks expressed in degrees 2-theta (± 0.2), selected from the group consisting of 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.

13. The method of claim 1, wherein the solid crystalline form is Polymorph A of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph A exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (± 0.2), selected from the group consisting of 11.22, 12.0, 13.116, 13.418, 13.899, 17.026, 18.032, 18.32, 19.399, 20.199, 21.84, 22.499, 23.238, 24.363, 24.7, 24.958, 30.557, and 30.879.

14. The method of claim 1, wherein the solid crystalline form is Polymorph B of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph B exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (± 0.2), selected from the group consisting of 8.438, 10.18, 10.74, 13.318, 13.541, 13.762, 16.443, 17.219, 17.78, 18.419, 20.182, 20.421, 20.839, 21.958, 23.725, 24.159, 25.498, and 26.863.

15. The method of claim 1, wherein the solid crystalline form is Polymorph C of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph C exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta ($\pm$ 0.2), selected from the group consisting of 10.083, 10.940, 16.583, 17.124, 17.534, 18.340, 18.662, 20.500, 21.143, 21.917, 22.219, 23.460, 26.222, 26.596, 27.722, and 30.299.
16. The method of claim 15, wherein the solid crystalline form exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of $^{\circ}\text{C}$ at a temperature of $228 \pm 5^{\circ}\text{C}$.
17. The method of claim 1, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having three or more characteristic peaks expressed in degrees 2-theta ($\pm$ 0.2) at 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.
18. The method of claim 7, wherein the solid crystalline form is Polymorph A of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph A exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta ($\pm$ 0.2), selected from the group consisting of 11.22, 12.0, 13.116, 13.418, 13.899, 17.026, 18.032, 18.32, 19.399, 20.199, 21.84, 22.499, 23.238, 24.363, 24.7, 24.958, 30.557, and 30.879.
19. The method of claim 7, wherein the solid crystalline form is Polymorph B of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph B exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta ($\pm$ 0.2), selected from the group consisting of 8.438, 10.18, 10.74, 13.318, 13.541, 13.762, 16.443, 17.219, 17.78, 18.419, 20.182, 20.421, 20.839, 21.958, 23.725, 24.159, 25.498, and 26.863.

20. The method of claim 7, wherein the solid crystalline form is Polymorph C of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph C exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 10.083, 10.940, 16.583, 17.124, 17.534, 18.340, 18.662, 20.500, 21.143, 21.917, 22.219, 23.460, 26.222, 26.596, 27.722, and 30.299.

21. The method of claim 20, wherein the solid crystalline form exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 228 +/- 5 °C.

22. The method of claim 10, wherein the solid crystalline form is Polymorph A of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph A exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 11.22, 12.0, 13.116, 13.418, 13.899, 17.026, 18.032, 18.32, 19.399, 20.199, 21.84, 22.499, 23.238, 24.363, 24.7, 24.958, 30.557, and 30.879.

23. The method of claim 10, wherein the solid crystalline form is Polymorph B of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph B exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 8.438, 10.18, 10.74, 13.318, 13.541, 13.762, 16.443, 17.219, 17.78, 18.419, 20.182, 20.421, 20.839, 21.958, 23.725, 24.159, 25.498, and 26.863.

24. The method of claim 10, wherein the solid crystalline form is Polymorph C of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph C exhibits an

X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta ($\pm$ 0.2), selected from the group consisting of 10.083, 10.940, 16.583, 17.124, 17.534, 18.340, 18.662, 20.500, 21.143, 21.917, 22.219, 23.460, 26.222, 26.596, 27.722, and 30.299.

25. The method of claim 24, wherein the solid crystalline form exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of $^{\circ}\text{C}$ at a temperature of 228 ± 5 $^{\circ}\text{C}$.