

compounds of the present invention can be prepared according to the methods illustrated in the following examples.

The description of this invention utilizes a variety of abbreviations well known to those skilled in the art, including the following:

- 5 aq.: aqueous
 CH₃CN: Acetonitrile
 DCM: Dichloromethane
 DMF: N,N-Dimethylformamide
 DMSO: Dimethylsulfoxide
10 EtOAc: Ethyl acetate
 EtOH: Ethanol
 FT-IR: Fourier Transform-Infrared
 HOAc: Acetic acid
 MeOH: Methanol
15 PXRD: powder X-ray diffraction
 ss ¹³C NMR: solid state ¹³C nuclear magnetic resonance
 THF: Tetrahydrofuran
 TLC: Thin Layer Chromatography

20 **EXAMPLES**

The following non-limiting example is presented merely to illustrate the present invention. The skilled person will understand that there are numerous equivalents and variations not exemplified but which still form part of the present teachings.

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Example 1

Preparation of ((S)-2,2-difluorocyclopropyl)-((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone

30 The Title compound was prepared according to Example 7 of US Patent No. 9,663,526. The crude material is warmed in 10 vol (100mg/ml) 2:1 EtOH/water to 80°C (until entirely dissolved), and then filtered, and slowly cooled until the product crystallizes. After filtration, the material is dried under vacuum at 45-55°C.

Example 2

35 Preparation of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone Form I

One Molar aqueous sodium hydroxide solution (1.2 equiv) and *p*-Toluenesulfonic acid salt of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)-pyrimidin-4-yl)-3,8-

diazabicyclo[3.2.1]octan-8-yl)methanone (1.0 equiv) were combined in methyl isobutyl ketone (MIBK) (8mL/g). After the solids dissolve and the salt is neutralized, the two liquid layers are allowed to separate. The aqueous layer is back-extracted with MIBK (5 mL/g) and the combined organic layers are washed with water (3 mL/g). The washed organic solution is speck free filtered and concentrated to remove water. The concentrate is diluted with MIBK (total volume = 6.8 mL/g with respect to free base ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone), heated to 75°C, then further diluted with n-heptane (3.2 mL/g with respect to (S)-2,2-difluorocyclopropyl)-((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]-octan-8-yl)methanone to give an approximate 2:1 v/v MIBK:n-heptane solution of the free base. The solution is cooled slightly to 65°C and seeded with 0.02 mol% free base ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone) Form 1 (0.02 equiv) while warm. The free base API is allowed to crystallize at 65C for ~ 1 hour and the resulting slurry is cooled to ambient temperature (~20°C at 0.1°C/min) and held at that temperature for 14 hours to complete the crystallization. Free base ((S)-2,2-difluorocyclopropyl)-((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-methanone) is collected by filtration, washed with 3:7 v/v MIBK/n-heptane (0.7 mL/g) and dried in the filter, or optionally in a vacuum oven at 45°C.

Example 3

Preparation of free base ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone:

Amorphous free base ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone) (100 mg) and ethyl acetate (EtOAc) (1mL) were added to a vial to form a solution, and heated to 60°C. Heptane was added until a precipitate appeared, then EtOAc was added back in until the precipitate dissolved again. The solution was cooled to room temperature (RT) and stirred at RT overnight. Clear oil droplets were on the bottom of vial, so the mixture was heated to 60°C then allowed to cool at ambient conditions. Racemate seed prepared in accordance with US Patent No. 9,663,526 was added, and the mixture was stirred at RT overnight. The mixture (seed from racemate was still undissolved, but no other precipitation had occurred) was heated at 35°C for ~64 hrs. The resulting precipitate was filtered as crystalline free base ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-methanone) Form 1.

Example 4

Preparation of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone, Form 1

5 One and 0.72 mmol of racemate ((2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone), 1 mol of (S)-2,2-difluorocyclopropane-1-carboxylic acid, 2.06 mol HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxido hexafluoro-phosphate, N-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide)

10 and 8 mL dichloromethane were added to a flask at RT, followed by addition of 6.88 mmol of DIEA (N,N-Diisopropylethylamine). The reaction was stirred at RT for 6 hrs. Solvent was removed and the resulting reaction crude material was purified using silica gel chromatography and eluted with 30% ethyl acetate 70% heptane to 100% ethyl acetate. It was further purified by silica gel chromatography with 8% methanol (MeOH) and 92% dichloromethane (DCM). The sample was

15 dissolved in DCM and washed with water saturated with ammonium chloride (NH₄Cl) three times. The organic layer was concentrated to a gum. The residue was placed in a flask and 3 mL of EtOAc was added and heated to 60°C, then heptane was added until a precipitate appeared, then EtOAc was added back in until the precipitate dissolved again. The solution was cooled to RT and stirred overnight at RT. The resulting precipitate was temperature cycled twice with the

20 following parameters: hold at 60°C for 2 h then cool to 20°C and hold for an additional 18 hrs. The solid was filtered and dried under vacuum. PXRD showed that this solid was crystalline.

Variations, modifications, and other implementations of what is described herein will occur to those skilled in the art without departing from the spirit and the essential characteristics of the

25 present teachings. Accordingly, the scope of the present teachings is to be defined not by the preceding illustrative description but instead by the following claims, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Each of the printed publications, including but not limited to patents, patent applications, books, technical papers, trade publications and journal articles described or referenced in this

30 specification are herein incorporated by reference in their entirety and for all purposes.

CLAIMS:

1. A method for preparing a crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone, characterized by a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at 5.0, 9.9, and $15.3^\circ \pm 0.2^\circ 2\theta$, comprising the steps of:

- (i) combining ((2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone racemate with (S)-2,2-difluorocyclopropane-1-carboxylic acid and solvent in a mixture at room temperature with stirring;
- (ii) removing the solvent to obtain a crude material;
- (iii) purifying the crude material using chromatography to obtain a purified material;
- (iv) dissolving the purified material in dichloromethane and washing same with an ammonium chloride solution;
- (v) collecting the organic layer and concentrating same into a gum;
- (vi) dissolving the gum in ethyl acetate at an elevated temperature;
- (vii) adding heptane to the ethyl acetate-containing solution until a first precipitate appears;
- (viii) adding additional ethyl acetate to dissolve the first precipitate in a solution;
- (ix) cooling the solution to room temperature to obtain a second precipitate;
- (x) temperature cycling the second precipitate between an elevated temperature and room temperature to obtain a solid, wherein the solid is the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone.

2. A method for preparing a crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone, characterized by a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at 5.0, 9.9, and $15.3^\circ \pm 0.2^\circ 2\theta$, comprising the steps of:

- (i) combining amorphous ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone with ethyl acetate to form an ethyl acetate-containing solution;
- (ii) adding heptane to the ethyl acetate-containing solution to form a precipitate;
- (iii) adding additional ethyl acetate to the solution to dissolve the precipitate;
- (iv) cooling the solution to room temperature;
- (v) seeding the cooled solution with racemate seed to form a mixture; and

(vi) heating the mixture to precipitate crystalline free base ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone Form 1 in the mixture, wherein the racemate seed comprises (2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone.

3. A method for preparing a crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone, characterized by a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at 5.0, 9.9, and $15.3^\circ \pm 0.2^\circ 2\theta$, comprising the steps of:

- (i) dissolving a salt of amorphous ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone in a mixture of methyl isobutyl ketone and sodium hydroxide;
- (ii) collecting an organic layer comprising free base ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone (free base) and concentrating to remove water;
- (iii) diluting the concentrate in methyl isobutyl ketone (MIBK) to form a MIBK-containing solution;
- (iv) heating the MIBK-containing solution and further diluting same with heptane to form a MIBK/heptane solution of the free base;
- (v) cooling the MIBK/heptane solution of the free base to 65°C and seeding same with crystalline free base ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone Form 1 while warm; and
- (vi) crystallizing the free base at 65°C to form a slurry followed by cooling the slurry to ambient temperature to complete crystallization.

4. The method of claim 1, further comprising drying the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone.

5. The method of claim 1, wherein the mixture further comprises 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxidohexafluorophosphate (HATU), dichloromethane and N,N-diisopropylethylamine.

6. The method of claim 1, wherein purified material was washed with the ammonium chloride solution three times.

7. The method of claim 1, wherein the temperature is cycled twice.
8. The method of claim 1, wherein the elevated temperature is 60°C.
9. The method of claim 2, further comprising separating the crystalline ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone Form 1 from the mixture.
10. The method of claim 3, further comprising separating the free base from the slurry to obtain the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone.
11. The method of any of claims 1-10, wherein the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone is characterized by a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at 5.0, 9.9, 15.3, and $19.7^\circ \pm 0.2^\circ 2\theta$.
12. The method of any of claims 1-10, wherein the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone is characterized by a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at 5.0, 9.9, 15.3, 16.8 and $19.7^\circ \pm 0.2^\circ 2\theta$.
13. The method of any of claims 1-10, wherein the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone is characterized by solid state ^{13}C nuclear magnetic resonance chemical shifts selected from the group consisting of 54.6, 129.8, and 124.9 $\text{ppm} \pm 0.2 \text{ ppm}$.
14. The method of any of claims 1-10, wherein the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone is characterized by a set of Raman bands at 1578, 1605, and $1566 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$.
15. The method of any of claims 1-10, wherein the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone is characterized by a powder X-ray diffraction

pattern comprising peaks, in terms of 2θ , at 5.0, 9.9, and $15.3^\circ \pm 0.2^\circ$ 2θ and solid state ^{13}C nuclear magnetic resonance chemical shifts selected from the group consisting of 54.6 and $129.8 \text{ ppm} \pm 0.2 \text{ ppm}$.

16. The method of any of claims 1-10, wherein the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone is characterized by a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at 5.0, 9.9, and $15.3^\circ \pm 0.2^\circ$ 2θ and a Raman band at $1578 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$.

17. The method of any of claims 1-10, wherein the crystalline form of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone is characterized by a Raman band at $1578 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$ and solid state ^{13}C nuclear magnetic resonance chemical shifts selected from the group consisting of 54.6 and $129.8 \text{ ppm} \pm 0.2 \text{ ppm}$.