CRYSTALLINE FORMS OF A BRUTON'S TYROSINE KINASE INHIBITOR

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/655,381 entitled "CRYSTALLINE FORMS OF A BRUTON'S TYROSINE KINASE INHIBITOR" filed on June 4, 2012, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein is the Bruton's tyrosine kinase (Btk) inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including crystalline forms, solvates and pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions that include the Btk inhibitor and methods of using the Btk inhibitor in the treatment of diseases or conditions that would benefit from inhibition of Btk activity.

BACKGROUND OF THE INVENTION

[0003] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[0004] Btk is a key regulator of B-cell development, activation, signaling, and survival. In addition, Btk plays a role in a number of other hematopoetic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor–mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation.

[0005] 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is also known by its IUPAC name as 1-{(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one or 2-Propen-1-one, 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinyl-, and has been given the USAN name, ibrutinib. The various names given for ibrutinib are used interchangeably herein.

SUMMARY ~~OF THE INVENTION~~

[0006] Described herein is the Btk inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including pharmaceutically acceptable solvates (including hydrates), polymorphs, and amorphous phases, and methods of uses thereof. Also described are pharmaceutically acceptable salts of the Btk inhibitor, including pharmaceutically acceptable solvates (including hydrates), polymorphs, and

amorphous phases, and methods of uses thereof. 1-((R)-3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, as well as the pharmaceutically acceptable salts thereof, are used in the manufacture of medicaments for the treatment of diseases or conditions that are associated with Btk activity. 1-((R)-3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is an irreversible Btk inhibitor.

[0007] Also described herein are methods for preparing crystalline forms of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. Further described are pharmaceutical compositions that include the crystalline forms and methods of using the Btk inhibitor in the treatment of diseases or conditions (including diseases or conditions wherein irreversible inhibition of Btk provides therapeutic benefit to a mammal having the disease or condition).

[0008] In one ~~embodiment~~example there is provided anhydrous 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

[0009] In another ~~embodiment~~example there is provided crystalline anhydrous 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

[0010] In a further ~~embodiment~~example there is provided amorphous anhydrous 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

[0011] ~~In one aspect~~There is provided a solvate of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

[0012] In one ~~embodiment~~example there is provided a solvate, wherein 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is solvated with methyl isobutyl ketone (MIBK), toluene or methanol. In one ~~embodiment~~example is a solvate, wherein 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is solvated with methyl isobutyl ketone (MIBK) or toluene. In one ~~embodiment~~example there is provided a solvate, wherein 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is solvated with methanol.

[0013] In a further ~~embodiment~~example, the solvate is anhydrous.

[0014] In another ~~embodiment~~example the solvate is crystalline.

[0015] In yet another ~~embodiment~~example the solvate is amorphous.

[0016] ~~In one aspect, described~~Described herein is a crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one that has at least one of the following properties:

(a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 1**;

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 5.7±0.1° 2-Theta, 13.6±0.1° 2-Theta, 16.1±0.1° 2-Theta, 18.9±0.1° 2-Theta, 21.3±0.1° 2-Theta, and 21.6±0.1° 2-Theta;

(c) substantially the same X-ray powder diffraction (XRPD) pattern post storage at 40°C and 75% RH for at least a week;

(d) substantially the same X-ray powder diffraction (XRPD) pattern post storage at 25°C and 97% RH for at least a week;

(e) Infrared (IR) spectrum substantially similar to the one set forth in **Fig. 2**;

(f) Infrared (IR) spectrum weak peaks at about 1584 cm^{-1}, about 1240 cm^{-1}, about 1147 cm^{-1}, about 1134 cm^{-1}, about 1099 cm^{-1}, and about 1067cm^{-1};

(g) a DSC thermogram substantially similar to the one set forth in **Fig. 3**;

(h) a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 4**;

(i) a DSC thermogram with an endotherm having an onset at about 154°C and a peak at about 157°C and an exotherm at about 159°C;

(j) non-hygroscopicity;

(k) an observed aqueous solubility of about 0.013 mg/mL at about pH 8;

or

(l) combinations thereof.

[0017] In some ~~embodiments~~examples, the crystalline Form A has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 1**. In some ~~embodiments~~examples, the crystalline Form A has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 5.7±0.1° 2-Theta, 13.6±0.1° 2-Theta, 16.1±0.1° 2-Theta, 18.9±0.1° 2-Theta, 21.3±0.1° 2-Theta, and 21.6±0.1° 2-Theta. In some ~~embodiments~~examples, the crystalline Form A has substantially the same X-ray powder diffraction (XRPD) pattern post storage at 40°C and 75% RH for at least a week. In some ~~embodiments~~examples, the crystalline Form A has substantially the same X-ray powder diffraction (XRPD) pattern post storage at 25°C and 97% RH for at least a week. In some ~~embodiments~~examples, the crystalline Form A has an Infrared (IR) spectrum substantially similar to the one set forth in **Fig. 2**. In some ~~embodiments~~examples, the crystalline Form A has an Infrared (IR) spectrum weak peaks at about 1584 cm^{-1}, about 1240 cm^{-1}, about 1147 cm^{-1}, about 1134 cm^{-1}, about 1099 cm^{-1}, and about 1067cm^{-1}. In some ~~embodiments~~examples, the crystalline Form A has a melting temperature of about 155-156°C. In some ~~embodiments~~examples, the crystalline Form A has a DSC thermogram substantially similar to the one set forth in **Fig. 3**. In some ~~embodiments~~examples, the crystalline Form A has a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 4**. In some ~~embodiments~~examples, the crystalline Form A has a DSC thermogram with an

endotherm having an onset at about 154°C and a peak at about 157°C and an exotherm at about 159°C. In some ~~embodiments~~examples, the crystalline Form A is non-hygroscopic. In some ~~embodiments~~examples, the crystalline Form A has an observed aqueous solubility of about 0.013 mg/mL at about pH 8. In some ~~embodiments~~examples, the crystalline Form A that is characterized as having properties (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), and (k). In some ~~embodiments~~examples, the crystalline Form A was obtained from ethyl acetate, isopropyl acetate, tetrahydrofuran, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), nitromethane, methanol, ethanol, acetonitrile, dioxane, methyl tert-butyl ether (MTBE), anisole, acetone, heptanes, a methanol/water mixture or an acetone/heptane mixture. In some ~~embodiments~~examples, the crystalline Form A was obtained from a methanol/water mixture. In some ~~embodiments~~examples, the crystalline Form A is unsolvated. In some ~~embodiments~~examples, the crystalline Form A is anhydrous.

[0018] ~~In one aspect, described~~Described herein is a crystalline Form B of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one that has at least one of the following properties:

(a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 5**;

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 5.2±0.1° 2-Theta, 10.2±0.1° 2-Theta, 16.5±0.1° 2-Theta, 18.5±0.1° 2-Theta, and 20.8±0.1° 2-Theta;

(c) substantially the same X-ray powder diffraction (XRPD) pattern post storage at 40°C and 75% RH for at least a week;

(d) substantially the same X-ray powder diffraction (XRPD) pattern post storage at 25°C and 97% RH for at least a week;

(e) Infrared (IR) spectrum substantially similar to the one set forth in **Fig. 6**;

(f) Infrared (IR) spectrum weak peaks at about about 1586 cm^{-1}, about 1573 cm^{-1}, about 1562 cm^{-1}, about 1229 cm^{-1}, about 1141 cm^{-1}, about 1103 cm^{-1}, about 1056 cm^{-1}, and about 1033 cm^{-1};

(g) a DSC thermogram substantially similar to the one set forth in **Fig. 7**;

(h) a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 8**;

(i) a DSC thermogram with an endotherm having an onset at about 99-106 °C and a peak at about 115-118 °C;

(j) an observed aqueous solubility of about 0.0096 mg/mL at a pH of about 7.42;

or

(k) combinations thereof.

[0019] In some ~~embodiments~~examples, the crystalline Form B has an an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 5**. In some ~~embodiments~~examples, the crystalline Form B has an an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 5.2±0.1° 2-Theta, 10.2±0.1° 2-Theta, 16.5±0.1° 2-Theta, 18.5±0.1° 2-Theta, and 20.8±0.1° 2-Theta. In some ~~embodiments~~examples, the crystalline Form B has an substantially the same X-ray powder diffraction (XRPD) pattern post storage at 40°C and 75% RH for at least a week. In some ~~embodiments~~examples, the crystalline Form B has an substantially the same X-ray powder diffraction (XRPD) pattern post storage at 25°C and 97% RH for at least a week. In some ~~embodiments~~examples, the crystalline Form B has an Infrared (IR) spectrum substantially similar to the one set forth in **Fig. 6**. In some ~~embodiments~~examples, the crystalline Form B has an Infrared (IR) spectrum weak peaks at about 1586 cm^{-1}, about 1573 cm^{-1}, about 1562 cm^{-1}, about 1229 cm^{-1}, about 1141 cm^{-1}, about 1103 cm^{-1}, about 1056 cm^{-1}, and about 1033 cm^{-1}. In some ~~embodiments~~examples, the crystalline Form B has a DSC thermogram substantially similar to the one set forth in **Fig. 7**. In some ~~embodiments~~examples, the crystalline Form B has a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 8**. In some ~~embodiments~~examples, the crystalline Form B has a DSC thermogram with an endotherm having an onset at about 99-106 °C and a peak at about 115-118 °C. In some ~~embodiments~~examples, the crystalline Form B has an observed aqueous solubility of about 0.0096 mg/mL at a pH of about 7.42. In some ~~embodiments~~examples, the crystalline Form B that is characterized as having properties (a), (b), (c), (d), (e), (f), (g), (h), (i), and (j). In some ~~embodiments~~examples, the crystalline Form B was obtained from a mixture of methanol and water. In some ~~embodiments~~examples, the crystalline Form B is unsolvated. In some ~~embodiments~~examples, the crystalline Form B is anhydrous.

[0020] ~~In one aspect, described~~Described herein is a crystalline Form C of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one that has at least one of the following properties:

(a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 9**;

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 7.0±0.1° 2-Theta, 14.0±0.1° 2-Theta, 15.7±0.1° 2-Theta, 18.2±0.1° 2-Theta, 19.1±0.1° 2-Theta, 19.5±0.1° 2-Theta, 20.3±0.1° 2-Theta, 22.1±0.1° 2-Theta, and 22.9±0.1° 2-Theta;

(c) a DSC thermogram substantially similar to the one set forth in **Fig. 10**;

(d) a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 11**;

(e) a DSC thermogram with an endotherm having an onset at about 134-135 °C and a peak at about 137-139 °C;

or

(f) combinations thereof.

[0021] In some ~~embodiments~~examples, the crystalline Form C has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 9**. In some ~~embodiments~~examples, the crystalline Form C has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 7.0±0.1° 2-Theta, 14.0±0.1° 2-Theta, 15.7±0.1° 2-Theta, 18.2±0.1° 2-Theta, 19.1±0.1° 2-Theta, 19.5±0.1° 2-Theta, 20.3±0.1° 2-Theta, 22.1±0.1° 2-Theta, and 22.9±0.1° 2-Theta. In some ~~embodiments~~examples, the crystalline Form C has a DSC thermogram substantially similar to the one set forth in **Fig. 10**. In some ~~embodiments~~examples, the crystalline Form C has a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 11**. In some ~~embodiments~~examples, the crystalline Form C has a DSC thermogram with an endotherm having an onset at about 134-135 °C and a peak at about 137-139 °C. In some ~~embodiments~~examples, the crystalline Form C that is characterized as having properties (a), (b), (c), (d), and (e). In some ~~embodiments~~examples, the crystalline Form C was obtained from a mixture of methanol and water. In some ~~embodiments~~examples, the crystalline Form C is unsolvated. In some ~~embodiments~~examples, the crystalline Form C is anhydrous.

[0022] ~~In one aspect, described~~Described herein is a crystalline Form D of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one that has at least one of the following properties:

(a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 12**;

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 7.2±0.1° 2-Theta, 8.0±0.1° 2-Theta, 9.2±0.1° 2-Theta, 14.5±0.1° 2-Theta, 18.5±0.1° 2-Theta, 19.5±0.1° 2-Theta, 20.7±0.1° 2-Theta, 21.0±0.1° 2-Theta, 21.9±0.1° 2-Theta, and 22.4±0.1° 2-Theta;

(c) a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 13**;

or

(d) combinations thereof.

[0023] In some ~~embodiments~~examples, the crystalline Form D has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 12**. In some ~~embodiments~~examples, the crystalline Form D has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 7.2±0.1° 2-Theta, 8.0±0.1° 2-Theta, 9.2±0.1° 2-Theta, 14.5±0.1° 2-Theta, 18.5±0.1° 2-Theta, 19.5±0.1° 2-Theta, 20.7±0.1° 2-Theta, 21.0±0.1° 2-Theta, 21.9±0.1° 2-Theta, and 22.4±0.1° 2-Theta. In some ~~embodiments~~examples, the crystalline Form D has a thermo-gravimetric analysis (TGA)

thermogram substantially similar to the one set forth in **Fig. 13**. In some ~~embodiments~~examples, the crystalline Form D that is characterized as having properties (a), (b), and (c). In some ~~embodiments~~examples, the crystalline Form D was obtained from methyl isobutyl ketone (MIBK). In some ~~embodiments~~examples, the crystalline Form D is solvated. In some ~~embodiments~~examples, the crystalline Form D is solvated with methyl isobutyl ketone (MIBK).

[0024] ~~In one aspect, described~~Described herein is a crystalline Form E of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one that has at least one of the following properties:

(a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 14**;

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 7.8±0.1° 2-Theta, 8.8±0.1° 2-Theta, 16.1±0.1° 2-Theta, 18.1±0.1° 2-Theta, 19.3±0.1° 2-Theta, 19.5±0.1° 2-Theta, 20.5±0.1° 2-Theta, 21.6±0.1° 2-Theta, and 25.2±0.1° 2-Theta;

(c) a DSC thermogram substantially similar to the one set forth in **Fig. 15**;

(d) a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 15**;

or

(e) combinations thereof.

[0025] In some ~~embodiments~~examples, the crystalline Form E has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 14**. In some ~~embodiments~~examples, the crystalline Form E has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 7.8±0.1° 2-Theta, 8.8±0.1° 2-Theta, 16.1±0.1° 2-Theta, 18.1±0.1° 2-Theta, 19.3±0.1° 2-Theta, 19.5±0.1° 2-Theta, 20.5±0.1° 2-Theta, 21.6±0.1° 2-Theta, and 25.2±0.1° 2-Theta. In some ~~embodiments~~examples, the crystalline Form E has a DSC thermogram substantially similar to the one set forth in **Fig. 15**. In some ~~embodiments~~examples, the crystalline Form E has a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 15**. In some ~~embodiments~~examples, the crystalline Form E that is characterized as having properties (a), (b), (c), and (d). In some ~~embodiments~~examples, the crystalline Form E was obtained from toluene. In some ~~embodiments~~examples, the crystalline Form E is solvated. In some ~~embodiments~~examples, the crystalline Form E is solvated with toluene.

[0026] ~~In one aspect, described~~Described herein is a crystalline Form F of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one that has at least one of the following properties:

(a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 16**;

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 6.2±0.1° 2-Theta, 10.1±0.1° 2-Theta, 17.6±0.1° 2-Theta, 18.6±0.1° 2-Theta, 20.0±0.1° 2-Theta, 20.4±0.1° 2-Theta, 20.7±0.1° 2-Theta, 22.4±0.1° 2-Theta, 23.0±0.1° 2-Theta, 23.2±0.1° 2-Theta, 24.4±0.1° 2-Theta, 25.1±0.1° 2-Theta, 27.6±0.1° 2-Theta, 29.3±0.1° 2-Theta, and 29.7±0.1° 2-Theta;

(c) unit cell parameters substantially equal to the following at 100(2) K:

Crystal system	Triclinic				
Space group	*P1*	*a*	9.6332(3) Å	α	105.762(3)°
		b	9.7536(4) Å	β	95.132(2)°
		c	15.0592(4) Å	γ	111.332(3)°
V	1240.15(7) Å^3				
Z	1				
Density (calculated)	1.308 Mg/m^3				
Absorption coefficient	0.726 mm^{-1}				
Wavelength	1.54178 Å				
F(000)	518				

or

(d) combinations thereof.

[0027] In some ~~embodiments~~examples, crystalline Form F has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 16**. In some ~~embodiments~~examples, crystalline Form F has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 6.2±0.1° 2-Theta, 10.1±0.1° 2-Theta, 17.6±0.1° 2-Theta, 18.6±0.1° 2-Theta, 20.0±0.1° 2-Theta, 20.4±0.1° 2-Theta, 20.7±0.1° 2-Theta, 22.4±0.1° 2-Theta, 23.0±0.1° 2-Theta, 23.2±0.1° 2-Theta, 24.4±0.1° 2-Theta, 25.1±0.1° 2-Theta, 27.6±0.1° 2-Theta, 29.3±0.1° 2-Theta, and 29.7±0.1° 2-Theta.

[0028] In some ~~embodiments~~examples, crystalline Form F has unit cell parameters substantially equal to the following at 100(2) K:

Crystal system	Triclinic				
Space group	*P1*	*a*	9.6332(3) Å	α	105.762(3)°
		b	9.7536(4) Å	β	95.132(2)°
		c	15.0592(4) Å	γ	111.332(3)°
V	1240.15(7) Å^3				
Z	1				
Density (calculated)	1.308 Mg/m^3				
Absorption coefficient	0.726 mm^{-1}				
Wavelength	1.54178 Å				
F(000)	518				

[0029] In some ~~embodiments~~examples, crystalline Form F was obtained from methanol.

[0030] In some ~~embodiments~~examples, crystalline Form F is solvated. In some ~~embodiments~~examples, crystalline Form F is solvated with methanol.

[0031] ~~In one aspect, described~~Described herein is a pharmaceutically acceptable salt of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, wherein the pharmaceutically acceptable salt is an acid addition salt. In some ~~embodiments~~examples, the pharmaceutically acceptable salt is amorphous. In some ~~embodiments~~examples, the pharmaceutically acceptable salt is crystalline.

[0032] ~~In a further aspect~~There are further provided pharmaceutical compositions, which include 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one as described herein, and at least one additional ingredient selected from pharmaceutically acceptable carriers, diluents and excipients. In some ~~embodiments~~examples, the pharmaceutical composition comprises Form A. In some ~~embodiments~~examples, the pharmaceutical composition comprises Form B. In some ~~embodiments~~examples, the pharmaceutical composition comprises Form C. In some ~~embodiments~~examples, the pharmaceutical composition comprises Form D. In some ~~embodiments~~examples, the pharmaceutical composition comprises Form E. In some ~~embodiments~~examples, the pharmaceutical composition comprises Form F. In some ~~embodiments~~examples, the pharmaceutical composition is in a form suitable for oral administration to a mammal. In some ~~embodiments~~examples, the pharmaceutical composition is an oral solid dosage form. In some ~~embodiments~~examples, the pharmaceutical composition comprises about 0.5mg to about 1000mg of crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

[0033] ~~In another aspect, provided~~Provided herein is a pharmaceutical formulation for oral administration comprising:

[0034] (a) about 40 mgs to about 200 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0035] (b) about 40 wt% to about 50 wt% of a diluent;

[0036] (c) about 3 wt% to about 10 wt% of a disintegrating agent;

[0037] (d) about 2 wt% to about 7 wt% of a surfactant; and

[0038] (e) about 0.2 wt% to about 1.0 wt% of a lubricant.

[0038a] In one aspect, there is provided a pharmaceutical formulation for oral administration comprising:

(a) about 40 mg to about 200 mg of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

(b) about 40 wt% to about 50 wt% of one or more diluents;

(c) one or more disintegrating agents; and

(d) about 0.2 wt% to about 1.0 wt% of one or more lubricants.

[0039] In some ~~embodiments~~examples, the diluent is selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, microcellulose, and talc. In some ~~embodiments~~examples the diluent is microcrystalline cellulose. In some ~~embodiments~~examples, the disintegrating agent is selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-

linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch such as sodium starch glycolate, cross-linked polymer such as crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, or a gum. In some ~~embodiments~~examples, the disintegrating agent is croscarmellose sodium. In some ~~embodiments~~examples, the surfactant is selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide. In some ~~embodiments~~examples, the surfactant is sodium lauryl sulfate. In some ~~embodiments~~examples, the lubricant is selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, stearic acid, sodium stearates, magnesium stearate, zinc stearate, and waxes. In some ~~embodiments~~examples, the lubricant is magnesium stearate.

[0040] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[0041] (a) about 40 mgs to about 200 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0042] (b) about 40 wt% to about 50 wt% of microcrystalline cellulose;

[0043] (c) about 3 wt% to about 10 wt% of croscarmellose sodium;

[0044] (d) about 2 wt% to about 7 wt% of sodium lauryl sulfate; and

[0045] (e) about 0.2 wt% to about 1.0 wt% of magnesium stearate.

[0046] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[0047] (a) about 40 wt% to about 50 wt% of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0048] (b) about 40 wt% to about 50 wt% of microcrystalline cellulose;

[0049] (c) about 3 wt% to about 10 wt% of croscarmellose sodium;

[0050] (d) about 2 wt% to about 7 wt% of sodium lauryl sulfate; and

[0051] (e) about 0.2 wt% to about 1.0 wt% of magnesium stearate.

[0052] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[0053] (a) 140 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0054] (b) 45.9 wt% of microcrystalline cellulose;

[0055] (c) 7.0 wt% of croscarmellose sodium;

[0056] (d) 4.2 wt% of sodium lauryl sulfate; and

[0057] (e) 0.5 wt% of magnesium stearate.

[0058] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[0059] (a) 140 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0060] (b) 151.4 mgs of microcrystalline cellulose;

[0061] (c) 23.0 mgs of croscarmellose sodium;

[0062] (d) 14.0 mgs of sodium lauryl sulfate; and

[0063] (e) 1.6 mgs of magnesium stearate.

[0064] In another ~~aspect~~example, provided herein is a pharmaceutical formulation for oral administration comprising:

[0065] (a) about 40 mgs to about 200 mgs of crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0066] (b) about 40 wt% to about 50 wt% of a diluent;

[0067] (c) about 3 wt% to about 10 wt% of a disintegrating agent;

[0068] (d) about 2 wt% to about 7 wt% of a surfactant; and

[0069] (e) about 0.2 wt% to about 1.0 wt% of a lubricant.

[0070] In some ~~embodiments~~examples, the diluent is selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, microcellulose, and talc. In some ~~embodiments~~examples the diluent is microcrystalline cellulose. In some ~~embodiments~~examples, the disintegrating agent is selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch such as sodium starch glycolate, cross-linked polymer such as crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, or a gum. In some ~~embodiments~~examples, the disintegrating agent is croscarmellose sodium. In some ~~embodiments~~examples, the surfactant is selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide. In some ~~embodiments~~examples, the surfactant is sodium lauryl sulfate. In some ~~embodiments~~examples, the lubricant is selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, stearic acid, sodium stearates, magnesium stearate, zinc stearate, and waxes. In some ~~embodiments~~examples, the lubricant is magnesium stearate.

[0071] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[0072] (a) about 40 mgs to about 200 mgs of crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0073] (b) about 40 wt% to about 50 wt% of microcrystalline cellulose;

[0074] (c) about 3 wt% to about 10 wt% of croscarmellose sodium;

[0075] (d) about 2 wt% to about 7 wt% of sodium lauryl sulfate; and

[0076] (e) about 0.2 wt% to about 1.0 wt% of magnesium stearate.

[0077] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[0078] (a) about 40 wt% to about 50 wt% of crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0079] (b) about 40 wt% to about 50 wt% of microcrystalline cellulose;

[0080] (c) about 3 wt% to about 10 wt% of croscarmellose sodium;

[0081] (d) about 2 wt% to about 7 wt% of sodium lauryl sulfate; and

[0082] (e) about 0.2 wt% to about 1.0 wt% of magnesium stearate.

[0083] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[0084] (a) 140 mgs of crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0085] (b) 45.9 wt% of microcrystalline cellulose;

[0086] (c) 7.0 wt% of croscarmellose sodium;

[0087] (d) 4.2 wt% of sodium lauryl sulfate; and

[0088] (e) 0.5 wt% of magnesium stearate.

[0089] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[0090] (a) 140 mgs of crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0091] (b) 151.4 mgs of microcrystalline cellulose;

[0092] (c) 23.0 mgs of croscarmellose sodium;

[0093] (d) 14.0 mgs of sodium lauryl sulfate; and

[0094] (e) 1.6 mgs of magnesium stearate.

[0095] In some ~~embodiments~~examples of the aforementioned pharmaceutical formulation ~~embodiments~~examples, crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is crystalline Form A. In some ~~embodiments~~examples of the aforementioned pharmaceutical formulation ~~embodiments~~examples, crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is crystalline

Form B. In some ~~embodiments~~examples of the aforementioned pharmaceutical formulation ~~embodiments~~examples, crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is crystalline Form C. In some ~~embodiments~~examples of the aforementioned pharmaceutical formulation ~~embodiments~~examples, crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is crystalline Form D. In some ~~embodiments~~examples of the aforementioned pharmaceutical formulation ~~embodiments~~examples, crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is crystalline Form E. In some ~~embodiments~~examples of the aforementioned pharmaceutical formulation ~~embodiments~~examples, crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is crystalline Form F. In some ~~embodiments~~examples of the aforementioned pharmaceutical formulation ~~embodiments~~examples, crystalline 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is a mixture of two or more crystalline forms selected from the group consisting of Form A, Form B, Form C, Form D, Form E, and Form F. In another ~~embodiment~~example of the aforementioned pharmaceutical formulation ~~embodiments~~examples provided herein, is a pharmaceutical formulation wherein the dosage form is a hard gelatin capsule.

[0096] In another ~~aspect~~example, provided herein is a pharmaceutical formulation for oral administration comprising:

[0097] (a) about 40 mgs to about 200 mgs of crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[0098] (b) about 40 wt% to about 50 wt% of a diluent;

[0099] (c) about 3 wt% to about 10 wt% of a disintegrating agent;

[00100] (d) about 2 wt% to about 7 wt% of a surfactant; and

[00101] (e) about 0.2 wt% to about 1.0 wt% of a lubricant.

[00102] In some ~~embodiments~~examples, the diluent is selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, microcellulose, and talc. In some ~~embodiments~~examples the diluent is microcrystalline cellulose. In some ~~embodiments~~examples, the disintegrating agent is selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch such as sodium starch glycolate, cross-linked polymer such as crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, or a gum. In some ~~embodiments~~examples, the disintegrating agent is

croscarmellose sodium. In some ~~embodiments~~examples, the surfactant is selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide. In some ~~embodiments~~examples, the surfactant is sodium lauryl sulfate. In some ~~embodiments~~examples, the lubricant is selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, stearic acid, sodium stearates, magnesium stearate, zinc stearate, and waxes. In some ~~embodiments~~examples, the lubricant is magnesium stearate.

[00103] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[00104] (a) about 40 mgs to about 200 mgs of crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[00105] (b) about 40 wt% to about 50 wt% of microcrystalline cellulose;

[00106] (c) about 3 wt% to about 10 wt% of croscarmellose sodium;

[00107] (d) about 2 wt% to about 7 wt% of sodium lauryl sulfate; and

[00108] (e) about 0.2 wt% to about 1.0 wt% of magnesium stearate.

[00109] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[00110] (a) about 40 wt% to about 50 wt% of crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[00111] (b) about 40 wt% to about 50 wt% of microcrystalline cellulose;

[00112] (c) about 3 wt% to about 10 wt% of croscarmellose sodium;

[00113] (d) about 2 wt% to about 7 wt% of sodium lauryl sulfate; and

[00114] (e) about 0.2 wt% to about 1.0 wt% of magnesium stearate.

[00115] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[00116] (a) 140 mgs of crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[00117] (b) 45.9 wt% of microcrystalline cellulose;

[00118] (c) 7.0 wt% of croscarmellose sodium;

[00119] (d) 4.2 wt% of sodium lauryl sulfate; and

[00120] (e) 0.5 wt% of magnesium stearate.

[00121] In some ~~embodiments~~examples, provided herein is a pharmaceutical formulation for oral administration comprising:

[00122] (a) 140 mgs of crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

[00123] (b) 151.4 mgs of microcrystalline cellulose;

[00124] (c) 23.0 mgs of croscarmellose sodium;

[00125] (d) 14.0 mgs of sodium lauryl sulfate; and

(e) 1.6 mgs of magnesium stearate.

[00126] In another ~~aspect~~ example, provided herein~~,~~ is a pharmaceutical formulation comprising: a) about 40 mgs to about 200 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one; b) about 40 wt% to about 50 wt% of a diluent; c) about 3 wt% to about 10 wt% of a disintegrating agent; d) about 2 wt% to about 7 wt% of a surfactant; and e) about 0.2 wt% to about 1.0 wt% of a lubricant; wherein the formulation is in a unit dosage form in a blister pack, and said blister pack comprises metal or plastic foil. In some ~~embobodiments~~examples, there is provided a pharmaceutical formulation comprising: a) 140 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one; b) 45.9 wt% of microcrystalline cellulose; c) 7.0 wt% of croscarmellose sodium; d) 4.2 wt% of sodium lauryl sulfate; and e) 0.5 wt% of magnesium stearate wherein the formulation is in a unit dosage form in a blister pack, and said blister pack comprises metal or plastic foil.

[00127] ~~In another embodiment~~There is provided a package comprising one or more discrete blister pockets, wherein each blister pocket comprises a unit dosage form comprising:
a) about 40 mgs to about 200 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;
b) about 40 wt% to about 50 wt% of a diluent; c) about 3 wt% to about 10 wt% of a disintegrating agent; d) about 2 wt% to about 7 wt% of a surfactant; and
e) about 0.2 wt% to about 1.0 wt% of a lubricant;
wherein each blister pocket comprises metal or plastic foil.

[00128] In another ~~aspect~~ example, provided herein~~,~~ is a pharmaceutical formulation comprising: a) about 40 mgs to about 200 mgs of crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one; b) about 40 wt% to about 50 wt% of a diluent; c) about 3 wt% to about 10 wt% of a disintegrating agent; d) about 2 wt% to about 7 wt% of a surfactant; and e) about 0.2 wt% to about 1.0 wt% of a lubricant; wherein the formulation is in a unit dosage form in a blister pack, and said blister pack comprises metal or plastic foil. In some ~~embobodiments~~examples, there is provided a pharmaceutical formulation comprising: a) 140 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one; b) 45.9 wt% of microcrystalline cellulose; c) 7.0 wt% of croscarmellose sodium; d) 4.2 wt% of sodium lauryl sulfate; and e) 0.5 wt% of magnesium stearate wherein the formulation is in a unit dosage form in a blister pack, and said blister pack comprises metal or plastic foil.

[00129] In another ~~embodiment~~ example, there is provided a package comprising one or more discrete blister pockets, wherein each blister pocket comprises a unit dosage form comprising:

a) about 40 mgs to about 200 mgs of crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

b) about 40 wt% to about 50 wt% of a diluent; c) about 3 wt% to about 10 wt% of a disintegrating agent; d) about 2 wt% to about 7 wt% of a surfactant; and

e) about 0.2 wt% to about 1.0 wt% of a lubricant;

wherein each blister pocket comprises metal or plastic foil.

[00130] ~~In one embodiment, a~~A kit is provided which contains a multiplicity of oral dosage forms, such as tablets or capsules, packaging such as a jar containing the oral dosage forms, and instructions for use to administer the oral dosage forms in accordance with the method described herein. Unit dose packaging such as blister packs provide a useful way of packaging the oral dosage form of the formulations described herein, and in other ~~embodiments~~examples embody a kit when combined with instructions for use. In other ~~embodiments~~examples, detailed product information are included with the instructions for use in the kit. Blister packaging is particularly useful with solid oral dosage forms and are in further ~~embodiments~~examples useful for alternate day dosing schedules for example. In one ~~embodiment~~example, solid unit dosage forms of the formulations described herein included in a blister pack with instructions to administer one or more tablets or capsules on a daily basis so that the dosage of the formulations described herein are sufficiently administered. In another ~~embodiment~~example, solid unit dosage forms are included in a blister pack with instructions to administer one or more tablets or capsules on an alternate day basis so that the dosage per day is sufficiently administered.

[00131] ~~In one aspect, provided~~Provided herein are methods for treating a patient by administering Compound 1. In some ~~embodiments~~examples, provided herein is a method of inhibiting the activity of tyrsoine kinase(s), such as Btk, or of treating a disease, disorder, or condition, which would benefit from inhibition of tyrosine kinase(s), such as Btk, in a mammal, which includes administering to the mammal a therapeutically effective amount of Compound 1, or pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate.

[00132] ~~In another aspect, provided~~Provided herein is the use of Compound 1 for inhibiting Bruton's tyrosine kinase (Btk) activity or for the treatment of a disease, disorder, or condition, which would benefit from inhibition of Bruton's tyrosine kinase (Btk) activity.

[00133] In some ~~embodiments~~examples, crystalline Compound 1 is administered to a human.

[00134] In some ~~embodiments~~examples, crystalline Compound 1 is orally administered.

[00135] In other ~~embodiments~~examples, crystalline Compound 1 is used for the formulation of a medicament for the inhibition of tyrosine kinase activity. In some other ~~embodiments~~examples, crystalline Compound 1 is used for the formulation of a medicament for the inhibition of Bruton's tyrosine kinase (Btk) activity.

[00136] ~~In one aspect, provided~~Provided herein is a method of treating cancer in a mammal comprising administering to the mammal a pharmaceutical composition described herein comprising Compound 1. In some ~~embodiments~~examples, the cancer is a B cell malignancy. In some ~~embodiments~~examples, the cancer is a B cell malignancy selected from chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B Cell lymphoma (DLBCL), and multiple myeloma. In some ~~embodiments~~examples, the cancer is a lymphoma, leukemia or a solid tumor. In some ~~embodiments~~examples, the cancer is diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis. In some ~~embodiments~~examples, where the subject is suffering from a cancer, an anti-cancer agent is administered to the subject in addition to one of the above-mentioned compounds. In one ~~embodiment~~example, the anti-cancer agent is an inhibitor of mitogen-activated protein kinase signaling

[00137] ~~In one aspect, provided~~Provided herein is a method of treating an inflammatory or an autoimmune disease in a mammal comprising administering to the mammal a pharmaceutical composition described herein comprising Compound 1. In some ~~embodiments~~examples, the inflammatory disease is asthma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, or vulvitis. In some ~~embodiments~~examples, the autoimmune disease is inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjögren's syndrome, multiple sclerosis, Guillain-Barré syndrome, acute disseminated encephalomyelitis,

Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylitisis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behçet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, or vulvodynia

[00138] Articles of manufacture including packaging material, Compound 1 within the packaging material, and a label that indicates that Compound 1 is used for inhibiting the activity of tyrosine kinase(s), such as Btk, are provided.

[00139] ~~In a further aspect, provided~~Provided herein is a method of treating an autoimmune disease in a mammal, comprising administering Compound 1 to the mammal.

[00140] ~~In a further aspect, provided~~Provided herein is a method of treating a heteroimmune disease or condition in a mammal, comprising administering Compound 1 to the mammal.

[00141] ~~In a further aspect, provided~~Provided herein is a method of treating an inflammatory disease in a mammal, comprising administering Compound 1 to the mammal.

[00142] ~~In a further aspect, provided~~Provided herein is a method of treating cancer in a mammal, comprising administering Compound 1 to the mammal.

[00143] ~~In a further aspect, provided~~Provided herein is a method of treating a thromboembolic disorder in a mammal, comprising administering Compound 1 to the mammal. Thromboembolic disorders include, but are not limited to, myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, or deep venous thrombosis.

[00144] ~~In another aspect~~There are provided methods for modulating, including irreversibly inhibiting the activity of Btk or other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with Compound 1, in a mammal comprising administering to the mammal at least once an effective amount of Compound 1. ~~In another aspect~~There are provided methods for modulating, including including irreversibly inhibiting, the activity of Btk in a mammal comprising administering to the mammal at least once an effective amount of Compound 1. ~~In another aspect~~There are provided methods for treating Btk-dependent or Btk mediated conditions or diseases, comprising administering to the mammal at least once an effective amount of Compound 1.

[00145] ~~In another aspect~~There are provided methods for treating inflammation comprising administering to the mammal at least once an effective amount of Compound 1.

[00146] ~~A further aspect~~There are provided methods for the treatment of cancer comprising administering to the mammal at least once an effective amount of Compound 1. The type of cancer may include, but is not limited to, pancreatic cancer and other solid or hematological tumors.

[00147] ~~In another aspect~~There are provided methods for treating respiratory diseases comprising administering to the mammal at least once an effective amount of Compound 1. In a further ~~embodiment~~example ~~of this aspect~~, the respiratory disease is asthma. In a further ~~embodiment~~example ~~of this aspect~~, the respiratory disease includes, but is not limited to, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma.

[00148] ~~In another aspect~~There are provided methods for preventing rheumatoid arthritis and/or osteoarthritis comprising administering to the mammal at least once an effective amount of Compound 1.

[00149] ~~In another aspect~~There are provided methods for treating inflammatory responses of the skin comprising administering to the mammal at least once an effective amount of Compound 1. Such inflammatory responses of the skin include, by way of example, dermatitis, contact dermatitis, eczema, urticaria, rosacea, and scarring. ~~In another aspect~~There are provided methods for reducing psoriatic lesions in the skin, joints, or other tissues or organs, comprising administering to the mammal an effective amount of Compound 1.

[00150] ~~In another aspect~~There is provided the use of Compound 1 in the manufacture of a medicament for treating an inflammatory disease or condition in an animal in which the activity of Btk or other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with at least one irreversible inhibitor described herein, contributes to the pathology and/or symptoms of the disease or condition. In one ~~embodiment~~example ~~of this aspect~~, the tyrosine kinase protein is Btk. In another or further ~~embodiment~~example ~~of this aspect~~, the inflammatory disease or conditions are respiratory, cardiovascular, or proliferative diseases.

[00151] ~~In any of the aforementioned aspects are~~Where mentioned above, further ~~embodiments~~examples are provided in which Compound 1 is (a) systemically administered to the mammal; (b) administered orally to the mammal; (c) intravenously administered to the mammal; (d) administered by inhalation; (e) administered by nasal administration; or (f) administered by injection to the mammal; (g) administered topically (dermal) to the mammal; (h) administered by ophthalmic administration; or (i) administered rectally to the mammal.

[00152] ~~In any of the aforementioned aspects are~~Where mentioned above, further ~~embodiments~~examples are provided comprising single administration of Compound 1, including further ~~embodiments~~examples in which Compound 1 is

administered (i) once; (ii) multiple times over the span of one day; (iii) continually; or (iv) continuously.

[00153] ~~In any of the aforementioned aspects are~~Where mentioned above, further ~~embodiments~~examples are provided comprising multiple administrations of Compound 1, including further ~~embodiments~~examples in which (i) Compound 1 is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) Compound 1 is administered to the mammal every 8 hours. In further or alternative ~~embodiments~~examples, the method comprises a drug holiday, wherein the administration of Compound 1is temporarily suspended or the dose of Compound 1 being administered is temporarily reduced; at the end of the drug holiday, dosing of Compound 1 is resumed. The length of the drug holiday can vary from 2 days to 1 year.

[00154] In some ~~embodiments~~examples, in any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is: optically pure (i.e. greater than 99% chiral purity by HPLC). In some ~~embodiments~~examples, in any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is replaced with: a) Compound 1, or a pharmaceutically acceptable salt or solvate thereof, of lower chiral purity; b) 1-((S)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, or a pharmaceutically acceptable salt or solvate thereof of any optical purity; or c) racemic 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, or a pharmaceutically acceptable salt or solvate thereof.

[00155] In any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), amorphous Compound 1 is used. In any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 is used. In any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 (Form A) is used. In any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 (Form B) is used. In any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 (Form C) is used. In any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 (Form D) is used. In any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 (Form E) is used. In any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 (Form F) is used.

[00156] In some ~~embodiments~~examples, in any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically acceptable salt thereof, is replaced with an active metabolite of Compound 1. In some ~~embodiments~~examples, the active metabolite is in a crystalline form. In some ~~embodiments~~examples, the active metabolite is in an amorphous phase. In further ~~embodiments~~examples the metabolite is isolated. In some ~~embodiments~~examples, in any of the ~~embodiments~~examples disclosed herein (including methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically acceptable salt thereof, is replaced with a prodrug of Compound 1, or a deuterated analog of Compound 1, or a pharmaceutically acceptable salt thereof.

[00157] Other objects, features and advantages of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific ~~embodiments~~examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present disclosure will become apparent to those skilled in the art from this detailed description. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

INCORPORATION BY REFERENCE

[00158] All publications and patent applications mentioned in this specification are herein incorporated by reference to the extent applicable and relevant.

BRIEF DESCRIPTION OF THE FIGURES

[00159] **Fig. 1**. Illustrates an X-Ray powder diffraction (XRPD) pattern of Form A.

[00160] **Fig. 2**. Illustrates an an Infrared (IR) spectrum of Form A.

[00161] **Fig. 3**. Illustrates DSC thermograms of Form A.

[00162] **Fig. 4**. Illustrates a thermo-gravimetric analysis (TGA) thermogram of Form A.

[00163] **Fig. 5**. Illustrates an X-Ray powder diffraction (XRPD) pattern of Form B.

[00164] **Fig. 6**. Illustrates an an Infrared (IR) spectrum of Form B.

[00165] **Fig. 7**. Illustrates DSC thermograms of Form B.

[00166] **Fig. 8**. Illustrates a thermo-gravimetric analysis (TGA) thermogram of Form B.

[00167] **Fig. 9**. Illustrates an X-Ray powder diffraction (XRPD) pattern of Form C.

[00168] **Fig. 10**. Illustrates DSC thermograms of Form C.

[00169] **Fig. 11**. Illustrates a thermo-gravimetric analysis (TGA) thermogram of Form C.

[00170] **Fig. 12**. Illustrates an X-Ray powder diffraction (XRPD) pattern of Form D.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation for oral administration comprising:

(a) about 40 mg~~s~~ to about 200 mg~~s~~ of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

(b) about 40 wt% to about 50 wt% of ~~a~~ one or more diluents;

(c) ~~about 3 wt% to about 10 wt% of a~~one or more disintegrating agents; and

~~(d) about 2 wt% to about 7 wt% of a surfactant; and~~

(~~e~~d) about 0.2 wt% to about 1.0 wt% of ~~a~~one or more lubricants.

2. The pharmaceutical formulation of claim 1, wherein the formulation is in the form of a capsule comprising about 140 mg of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

~~2.~~3. The pharmaceutical formulation of claim 1, wherein the one or more diluents ~~is~~ are selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, microcellulose, and talc.

4. The pharmaceutical formulation of claim 1, wherein the one or more diluents are selected from the group consisting of lactose, sucrose, dextrose, mannitol, xylitol, sorbitol, calcium phosphate, starches, modified starches, microcrystalline cellulose, and microcellulose.

5. The pharmaceutical formulation of claim 1, wherein the one or more diluents are selected from the group consisting of lactose, sucrose, mannitol, calcium phosphate, starches, modified starches, and microcrystalline cellulose.

~~3.~~6. The pharmaceutical formulation of claim ~~2~~1, wherein the one or more diluent is microcrystalline cellulose.

7. The pharmaceutical formulation of claim 1, wherein the one or more lubricants are selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumarate, sodium stearate, magnesium stearate, zinc stearate, and waxes.

8. The pharmaceutical formulation of claim 1, wherein the one or more lubricants are selected from the group consisting of stearic acid, talc, sodium stearyl fumarate, magnesium stearate, and zinc stearate.

9. The pharmaceutical formulation of claim 1, wherein the one or more lubricants are selected from the group consisting of stearic acid, talc, sodium stearyl fumarate, and magnesium stearate.

10. The pharmaceutical formulation of claim 1, wherein the one or more lubricant is magnesium stearate.

~~4.~~11. The pharmaceutical formulation of claim 1, wherein the one or more disintegrating agents ~~is~~ are selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch ~~such as sodium starch glycolate~~, cross-linked polymer ~~such as crospovidone~~, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, ~~or~~ and a gum.

12. The pharmaceutical formulation of claim 1, wherein the one or more disintegrating agents are selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, sodium starch glycolate, crospovidone, sodium alginate, a clay, and a gum.

13. The pharmaceutical formulation of claim 1, wherein the one or more disintegrating agents are selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, croscarmellose, croscarmellose sodium, sodium starch glycolate, and crospovidone.

14. The pharmaceutical formulation of claim 1, wherein the one or more disintegrating agents are selected from the group consisting of croscarmellose sodium, sodium starch glycolate, and crospovidone.

~~5.~~15. The pharmaceutical formulation of claim ~~4~~1, wherein the one or more disintegrating agent is croscarmellose sodium.

16. The pharmaceutical formulation of claim 1, wherein the formulation further comprises one or more surfactants.

~~6.~~17. The pharmaceutical formulation of claim ~~1~~16, wherein the one or more surfactants ~~is~~ are selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, ~~polaxomers~~poloxamers, bile salts, glyceryl monostearate, and copolymers of ethylene oxide and propylene oxide.

18. The pharmaceutical formulation of claim 16, wherein the one or more surfactants are selected from the group consisting of sodium lauryl sulfate, polyoxyethylene sorbitan monooleate, polysorbates, poloxamers, and copolymers of ethylene oxide and propylene oxide.

19. The pharmaceutical formulation of claim 16, wherein the one or more surfactants are selected from the group consisting of sodium lauryl sulfate, poloxamers, and copolymers of ethylene oxide and propylene oxide.

~~7.~~20. The pharmaceutical formulation of claim ~~6~~16, wherein the one or more surfactant is sodium lauryl sulfate.

21. The pharmaceutical formulation of claim 1, wherein:

i. the one or more diluents are selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, microcellulose, and talc; and

ii. the one of more lubricants are selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumarate, sodium stearate, magnesium stearate, zinc stearate, and waxes.

~~8. The pharmaceutical formulation of claim 1, wherein the lubricant is selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, stearic acid, sodium stearates, magnesium stearate, zinc stearate, and waxes.~~

~~9. The pharmaceutical formulation of claim 8, wherein the lubricant is magnesium stearate.~~

~~10. The pharmaceutical formulation of claim 1 comprising:~~

~~(a) 140 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;~~

~~(b) 45.9 wt% of microcrystalline cellulose;~~

~~(c) 7.0 wt% of croscarmellose sodium;~~

~~(d) 4.2 wt% of sodium lauryl sulfate; and~~

~~(e) 0.5 wt% of magnesium stearate.~~

~~11.~~22. The pharmaceutical formulation of ~~any one of claims 1-10~~claim 21, wherein the dosage form is a hard gelatin capsule.

23. The pharmaceutical formulation of claim 1, wherein:

i. the one or more diluents are selected from the group consisting of lactose, sucrose, dextrose, mannitol, xylitol, sorbitol, calcium phosphate, starches, modified starches, microcrystalline cellulose, and microcellulose; and

ii. the one of more lubricants are selected from the group consisting of stearic acid, talc, sodium stearyl fumarate, magnesium stearate, and zinc stearate.

24. The pharmaceutical formulation of claim 23, wherein the dosage form is a hard gelatin capsule.

25. The pharmaceutical formulation of claim 1, wherein:

i. the one or more diluents are selected from the group consisting of lactose, sucrose, mannitol, calcium phosphate, starches, modified starches, and microcrystalline cellulose; and

ii. the one of more lubricants are selected from the group consisting of stearic acid, talc, sodium stearyl fumarate, and magnesium stearate.

26. The pharmaceutical formulation of claim 25, wherein the dosage form is a hard gelatin capsule.

27. The pharmaceutical formulation of claim 1, wherein:

i. the one or more diluent is microcrystalline cellulose; and

ii. the one or more lubricant is magnesium stearate.

28. The pharmaceutical formulation of claim 1 comprising:

(a) about 40 wt% to about 50 wt% of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

(b) microcrystalline cellulose; and

(c) magnesium stearate.

29. The pharmaceutical formulation of claim 28, wherein the dosage form is a hard gelatin capsule.

~~12. A package comprising one or more discrete blister pockets, wherein each blister pocket comprises a unit dosage form comprising:~~

~~a) about 40 mgs to about 200 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;~~

~~b) about 40 wt% to about 50 wt% of a diluent; c) about 3 wt% to about 10 wt% of a disintegrating agent; d) about 2 wt% to about 7 wt% of a surfactant; and~~

~~e) about 0.2 wt% to about 1.0 wt% of a lubricant;~~

~~wherein each blister pocket comprises metal or plastic foil.~~

~~13. The package of claim 12 wherein each unit dosage comprises:~~

~~a) 140 mgs of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;~~

~~b) 45.9 wt% of microcrystalline cellulose;~~

~~c) 7.0 wt% of croscarmellose sodium; and~~

~~d) 4.2 wt% of sodium lauryl sulfate; and e) 0.5 wt% of magnesium stearate.~~

~~14. A crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one that has at least one of the following properties:~~

~~(a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 1**;~~

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 5.7±0.1° 2-Theta, 13.6±0.1° 2-Theta, 16.1±0.1° 2-Theta, 18.9±0.1° 2-Theta, 21.3±0.1° 2-Theta, and 21.6±0.1° 2-Theta;

(c) substantially the same X-ray powder diffraction (XRPD) pattern post storage at 40°C and 75% RH for at least a week;

(d) substantially the same X-ray powder diffraction (XRPD) pattern post storage at 25°C and 97% RH for at least a week;

(e) Infrared (IR) spectrum substantially similar to the one set forth in **Fig. 2**;

(f) Infrared (IR) spectrum weak peaks at about 1584 cm^{-1}, about 1240 cm^{-1}, about 1147 cm^{-1}, about 1134 cm^{-1}, about 1099 cm^{-1}, and about 1067cm^{-1};

(g) a DSC thermogram substantially similar to the one set forth in **Fig. 3**;

(h) a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 4**;

(i) a DSC thermogram with an endotherm having an onset at about 154°C and a peak at about 157°C and an exotherm at about 159°C;

(j) non-hygroscopicity;

(k) an observed aqueous solubility of about 0.013 mg/mL at about pH 8;

or

(l) combinations thereof.

15. The crystalline form of claim 14, wherein the crystalline form has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 1**.

16. The crystalline form of claim 14, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 5.7±0.1° 2-Theta, 13.6±0.1° 2-Theta, 16.1±0.1° 2-Theta, 18.9±0.1° 2-Theta, 21.3±0.1° 2-Theta, and 21.6±0.1° 2-Theta.

17. The crystalline form of claim 14, wherein the crystalline form has substantially the same X-ray powder diffraction (XRPD) pattern post storage at 40°C and 75% RH for at least a week.

18. The crystalline form of claim 14, wherein the crystalline form has substantially the same X-ray powder diffraction (XRPD) pattern post storage at 25°C and 97% RH for at least a week.

19. The crystalline form of claim 14, wherein the crystalline form has an Infrared (IR) spectrum substantially similar to the one set forth in **Fig. 2**.

20. The crystalline form of claim 14, wherein the crystalline form has an Infrared (IR) spectrum weak peaks at about 1584 cm^{-1}, about 1240 cm^{-1}, about 1147 cm^{-1}, about 1134 cm^{-1}, about 1099 cm^{-1}, and about 1067cm^{-1}.

21. The crystalline form of claim 14, wherein the crystalline form has a melting temperature of about 155-156°C.

22. The crystalline form of claim 14, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Fig. 3**.

23. The crystalline form of claim 14, wherein the crystalline form has a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 4**.

24. The crystalline form of claim 14, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 154°C and a peak at about 157°C and an exotherm at about 159°C.

25. The crystalline form of claim 14, wherein the crystalline form is non-hygroscopic.

26. The crystalline form of claim 14, wherein the crystalline form has an observed aqueous solubility of about 0.013 mg/mL at about pH 8.

27. The crystalline form of claim 14, wherein the crystalline form that is characterized as having properties (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), and (k).

28. The crystalline form of any one of claims 14-27, wherein the crystalline form was obtained from ethyl acetate, isopropyl acetate, tetrahydrofuran, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), nitromethane, methanol, ethanol, acetonitrile, dioxane, methyl tert-butyl ether (MTBE), anisole, acetone, heptanes, a methanol/water or an acetone/heptane mixture.

29. The crystalline form of any one of claims 14-28, wherein the crystalline form is unsolvated.

30. The crystalline form of any one of claims 14-29, wherein the crystalline form is anhydrous.

31. The pharmaceutical formulation of any one of claims 1-11, wherein 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is crystalline Form A.

32. A pharmaceutical formulation for oral administration comprising:

(a) 140 mgs of crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one;

(b) 45.9 wt% of microcrystalline cellulose;

(c) 7.0 wt% of croscarmellose sodium;

(d) 4.2 wt% of sodium lauryl sulfate; and

(e) 0.5 wt% of magnesium stearate.

33. The package of claim 12 or claim 13, wherein 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is crystalline Form A.

34. A method of treating cancer in a mammal comprising administering to the mammal a pharmaceutical formulation according to any one of claims 1-11, 31 or 32.

35. The method of claim 34, wherein the cancer is a B-cell malignancy.

36. The method of claim 34, wherein the cancer is a B-cell malignancy selected from chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B-Cell lymphoma (DLBCL), and multiple myeloma.

37. The method of claim 34, wherein the cancer is a lymphoma, leukemia or a solid tumor.

38. The method of claim 34, wherein the cancer is diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis. In some embodiments, where the subject is suffering from a cancer, an anti-cancer agent is administered to the subject in addition to one of the above-mentioned compounds. In one embodiment, the anti-cancer agent is an inhibitor of mitogen-activated protein kinase signaling