

arrangements and/or conformations of the molecules in the crystal lattices giving the crystals different physicochemical properties. The ability to be able to manufacture the selected polymorphic form reliably is a key factor in determining the success of the drug product.

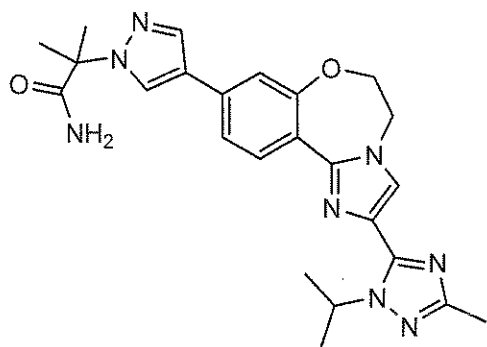
Regulatory agencies worldwide require a reasonable effort to identify the polymorphs of the drug substance and check for polymorph interconversions. Due to the often unpredictable behavior of polymorphs and their respective differences in physicochemical properties, consistency in manufacturing between batches of the same product must be demonstrated. Proper understanding of the polymorph landscape and nature of the polymorphs of a pharmaceutical will contribute to manufacturing consistency.

Knowledge of crystal structure at the atomic level and intermolecular interactions offer important information to establish absolute configuration (enantiomers), phase identification, quality control, and process development control and optimization. X-ray Diffraction is widely recognized as a reliable tool for the crystal structure analysis of pharmaceutical solids and crystal form identification.

Availability of a single crystal of the drug substance is preferred due to the speed and accuracy of the structure determination. However, it is not always possible to obtain a crystal of suitable size for data collection. In those cases the crystal structure can be solved from X-ray powder diffraction data obtained by measurements at ambient conditions and/or at variable temperature or humidity.

SUMMARY OF THE INVENTION

The ~~invention~~ disclosure relates to polymorph forms of the PI3K inhibitor **I** (taselisib, GDC-0032, RG7604, CAS Reg. No. 1282512-48-4, Genentech, Inc.), named as 2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide, having the structure:



I (GDC-0032)

and stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof.

In one aspect, there is provided a crystalline, mono-methanolate polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form A polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 10.1, 11.2, 14.0, 18.3, 20.2, and 22.0.

In another aspect, there is provided a crystalline, isoamyl alcohol polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form C polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.2, 14.1, 17.2, 18.3, 21.9, and 26.7.

In another aspect, there is provided a crystalline, mono-hydrate polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form D polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 12.2, 17.5, 17.7, 18.3, 20.1, 21.3, 22.8, and 26.0.

~~An aspect of the invention is~~ The disclosure provides a pharmaceutical composition of a polymorph form of taselisib. In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of the crystalline, isoamyl alcohol polymorph as defined herein and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

~~An aspect of the invention is~~ The disclosure provides a method of treating a hyperproliferative disorder in a mammal with a polymorph form of taselisib. In another aspect, there is provided a pharmaceutical composition as defined herein for use in the treatment of a

hyperproliferative disorder selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.

In another aspect, there is provided use of the pharmaceutical composition as defined herein in the manufacture of a medicament for treating a hyperproliferative disorder in a mammal, wherein the hyperproliferative disorder is selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.

An aspect of the invention is ~~The disclosure provides~~ a process for preparing a crystalline polymorph of taselesib. In another aspect, there is provided a process for preparing a crystalline polymorph comprising heating a slurry of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide in isoamyl alcohol and then cooling the mixture whereby a Form B crystalline polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 10.7, 14.0, 16.4, 18.6, 22.1, and 26.4 is formed.

In another aspect, there is provided a process for preparing a crystalline polymorph comprising mixing (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide with an aqueous alcohol solvent comprising water and alcohol selected from the group consisting of n-butanol and n-propanol, whereby a crystalline, mono-hydrate polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form D polymorph is formed that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 12.2, 17.5, 17.7, 18.3, 20.1, 21.3, 22.8, and 26.0.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an ORTEP drawing of GDC-0032 Form A - mono-methanolate solvate. Atoms are represented by 50% probability anisotropic thermal ellipsoids.

Figure 2 shows XRPD of GDC-0032 Form A, mono-methanolate.

Figure 3 shows ORTEP drawing of GDC-0032 Form B - non-solvate. Atoms are represented by 50% probability anisotropic thermal ellipsoids.

Figure 4 shows a Packing diagram of GDC-0032 viewed down the crystallographic a axis.

Figure 5 shows a Packing diagram of GDC-0032 viewed down the crystallographic b axis.

5 Figure 6 shows a Packing diagram of GDC-0032 viewed down the crystallographic c axis.

Figure 7 shows Hydrogen bonding in GDC-0032 as viewed down the crystallographic c axis.

Figure 8 shows Apparent π -Stacking Interaction in GDC-0032.

Figure 9 shows Calculated X-ray powder pattern of GDC-0032.

Claims

1. ~~A crystalline, non-solvated polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 10.7, 14.0, 16.4, 18.6, 22.1, and 26.4.~~

2. ~~The Form B polymorph of claim 1 characterized by the X-ray powder diffraction pattern shown in Figure 10.~~

31. A crystalline, mono-methanolate polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form A polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 10.1, 11.2, 14.0, 18.3, 20.2, and 22.0.

42. The Form A polymorph of claim 31 characterized by the X-ray powder diffraction pattern shown in Figure 2.

53. A crystalline, isoamyl alcohol polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form C polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.2, 14.1, 17.2, 18.3, 21.9, and 26.7.

64. The Form C polymorph of claim 53 characterized by the X-ray powder diffraction pattern shown in Figure 13.

75. A crystalline, mono-hydrate polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form D polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 12.2, 17.5, 17.7, 18.3, 20.1, 21.3, 22.8, and 26.0.

86. The Form D polymorph of claim 75 characterized by the X-ray powder diffraction pattern shown in Figure 14.

97. A pharmaceutical composition comprising a therapeutically effective amount of a the crystalline, isoamyl alcohol polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide) claim 3, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

~~108.~~ The pharmaceutical composition of claim 97 in the form of a tablet.

~~119.~~ The pharmaceutical composition of claim 97 wherein the therapeutically effective amount is from 1 to 100 mg.

~~12.~~ The pharmaceutical composition of claim 9 wherein the crystalline polymorph is a Form-B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 10.7, 14.0, 16.4, 18.6, 22.1, and 26.4.

10. A pharmaceutical composition of claim 7 for use in the treatment of a hyperproliferative disorder selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.

~~1311.~~ A method of Use of the pharmaceutical composition of claim 7 in the manufacture of a medicament for treating a hyperproliferative disorder in a mammal comprising administering the pharmaceutical composition of claim 9, wherein the hyperproliferative disorder is selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.

~~1412.~~ The ~~method-use~~ of claim 13-11 wherein the therapeutically effective amount is from 1 mg to 100 mg.

~~15.~~ The method of claim 13 wherein the pharmaceutical composition comprises a Form-B crystalline polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 10.7, 14.0, 16.4, 18.6, 22.1, and 26.4.

~~1613.~~ The ~~method-use~~ of claim 12-11 further comprising administering a chemotherapeutic agent selected from 5-FUfluorouracil, docetaxel, eribulin, gemcitabine, cobimetinib, 5-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)imidazole[1,5-a]pyridine-6-

carboxamide GDC-0973, GDC-0623, paclitaxel, tamoxifen, fulvestrant, dexamethasone, pertuzumab, trastuzumab emtansine, trastuzumab and letrozole.

1714. A process for preparing a crystalline polymorph comprising heating a slurry of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide comprising recrystallizing (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide in isoamyl alcohol and then cooling

the mixture whereby a Form B crystalline polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 10.7, 14.0, 16.4, 18.6, 22.1, and 26.4 is formed.

15. The process of claim 14 wherein the Form B polymorph is characterized by the X-ray powder diffraction pattern shown in Figure 10.

16. A process for preparing a crystalline polymorph comprising mixing (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide with an aqueous alcohol solvent comprising water and alcohol selected from the group consisting of n-butanol and n-propanol, whereby a crystalline, mono-hydrate polymorph of (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide designated the Form D polymorph is formed that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 12.2, 17.5, 17.7, 18.3, 20.1, 21.3, 22.8, and 26.0.

17. The process of claim 16 wherein the Form D polymorph is characterized by the X-ray powder diffraction pattern shown in Figure 14.

~~18. The pharmaceutical composition of claim 9 for use in the treatment of a hyperproliferative disorder selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.~~

~~19. The use of a pharmaceutical composition of claim 9 for treating a hyperproliferative disorder selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.~~

~~20. The use of a crystalline polymorph of any one of claims 1-8 as therapeutically active substance.~~

~~21. The crystalline polymorphs of any one of claims 1-8 for use in the treatment of a hyperproliferative disorder selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.~~

~~22. The use of the crystalline polymorphs of any one of claims 1-8 in the treatment of a hyperproliferative disorder selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.~~

5 ~~23. The crystalline polymorphs of any one of claims 1-8 for use in the manufacture of a medicament for the treatment of a hyperproliferative disorder selected from multiple myeloma, lymphoma, leukemias, prostate cancer, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colorectal cancer.~~