HDAC INHIBITOR SOLID STATE FORMS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims benefit of U.S. Patent Application No. 63/106,811 filed on October 28, 2020 which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The present disclosure relates to pharmaceutically acceptable salt forms of a histone deacetylase inhibitor compound and pharmaceutical compositions of said salt form, as well as the use of said compound in pharmaceutical compositions and medicine.

SUMMARY ~~OF THE INVENTION~~

[0002a] In an aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0002b] In another aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide as characterized by an X-ray diffraction pattern reflection at a 2 theta value of 3.7°±0.3.

[0002c] In a further aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide as characterized by an X-ray diffraction pattern reflection at a 2 theta value of 3.7°±0.3, and 14.9°±0.3.

[0002d] In another aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide as characterized by an X-ray diffraction pattern reflection at a 2 theta value of 3.7°±0.3, 7.5°±0.3, and 14.9°±0.3.

[0002e] In a further aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide, wherein the crystalline mesylate form 1 salt is characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 3.7°±0.3, 7.5°±0.3, 14.9°±0.3, 17.3°±0.3, 19.7°±0.3, 22.5°±0.3, 22.9°±0.3, or 30.1°±0.3.

[0002f] In another aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide exhibiting the X-ray powder diffraction pattern as shown in Fig. 1.

[0002g] In a further aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide exhibiting the TGA pattern as shown in Fig. 3.

[0002h] In another aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide wherein the DSC is characterized by a single exothermic event with an onset temperature at about 222.1 °C±5.0 (433 J/g) or an exothermic peak at 225.8 °C ±5.0.

[0002i] In a further aspect of the present disclosure, there is provided a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide exhibiting the DSC pattern as shown in Fig. 3.

[0002j] In another aspect of the present disclosure, there is provided an amorphous mesylate salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0002k] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising any one of the compositions disclosed herein, and one or more pharmaceutically acceptable excipients or carriers.

[0003] One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0004] One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide as characterized by an X-ray diffraction pattern reflection at a 2 theta value of 3.7°±0.3. One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide as characterized by an X-ray diffraction pattern reflection at a 2 theta value of 3.7°±0.3, and 14.9°±0.3. One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide as characterized by an X-ray diffraction pattern reflection at a 2 theta value of 3.7°±0.3, 7.5°±0.3, and 14.9°±0.3.

[0005] One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide, wherein the crystalline mesylate form 1 salt is characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 3.7°±0.3, 7.5°±0.3, 14.9°±0.3, 17.3°±0.3, 19.7°±0.3, 22.5°±0.3, 22.9°±0.3, or 30.1°±0.3. One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide, wherein the crystalline mesylate form 1 salt is characterized by at least two X-ray diffraction pattern reflections selected from a 2 theta value of 3.7°±0.3, 7.5°±0.3, 14.9°±0.3, 17.3°±0.3, 19.7°±0.3, 22.5°±0.3, 22.9°±0.3, or 30.1°±0.3. One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide, wherein the crystalline mesylate form 1 salt is characterized by at least three X-ray diffraction pattern reflections

selected from a 2 theta value of 3.7°±0.3, 7.5°±0.3, 14.9°±0.3, 17.3°±0.3, 19.7°±0.3, 22.5°±0.3, 22.9°±0.3, or 30.1°±0.3. One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide, wherein the crystalline mesylate form 1 salt is characterized by at least four X-ray diffraction pattern reflections selected from a 2 theta value of 3.7°±0.3, 7.5°±0.3, 14.9°±0.3, 17.3°±0.3, 19.7°±0.3, 22.5°±0.3, 22.9°±0.3, or 30.1°±0.3. One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide, wherein the crystalline mesylate form 1 salt is characterized by at least five X-ray diffraction pattern reflections selected from a 2 theta value of 3.7°±0.3, 7.5°±0.3, 14.9°±0.3, 17.3°±0.3, 19.7°±0.3, 22.5°±0.3, 22.9°±0.3, or 30.1°±0.3.

[0006] One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide exhibiting the X-ray powder diffraction pattern as shown in Fig. 1.

[0007] One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide exhibiting the TGA pattern as shown in Fig. 3.

[0008] One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide wherein the DSC is characterized by a single exothermic event with an onset temperature at about 222.1 °C±5.0 (433 J/g) or an exothermic peak at 225.8 °C ±5.0.

[0009] One ~~embodiment~~example provides a crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide exhibiting the DSC pattern as shown in Fig. 3.

[0010] One ~~embodiment~~example provides an amorphous mesylate salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0011] One ~~embodiment~~example provides a solid form of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide wherein the amount of other crystalline or amorphous forms is 5 % (w/w) or less.

[0012] One ~~embodiment~~example provides a solid form of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide, wherein the solid form is substantially free of impurities.

[0013] One ~~embodiment~~example provides a solid form of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide, wherein the amount of impurities is 3% or less.

[0014] One ~~embodiment~~example provides a pharmaceutical composition comprising any one of the compositions described herein, and one or more pharmaceutically acceptable excipients or carriers. One ~~embodiment~~example provides a pharmaceutical composition further comprising one or more additional active pharmaceutical ingredient (API). One ~~embodiment~~example provides a pharmaceutical composition, wherein the additional API is valganciclovir.

INCORPORATION BY REFERENCE

[0015] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The features of the invention are set forth with particularity in the appended claims. A better understanding of the features of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0017] Fig. 1 shows the X-ray powder diffractogram of crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0018] Fig. 2 shows the ^{1}H NMR spectra of crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0019] Fig. 3 shows the thermal gravimetric analysis pattern of crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0020] Fig. 4 shows the HPLC analysis of crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0021] Fig. 5 shows the microscope image of crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0022] Fig. 6 shows the GVS kinetic plot of crystalline mesylate Form 1 salt of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.