HDAC INHIBITOR SOLID STATE FORMS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims benefit of U.S. Patent Application No. 62/944,246, filed on December 5, 2019 which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The present disclosure relates to a HDAC inhibitor compound used as viral inducing agent and pharmaceutical compositions of said compound, as well as the use of said compound in pharmaceutical compositions and medicine.

SUMMARY ~~OF THE INVENTION~~

[0003] The present disclosure relates to various solid-state forms of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide and methods of making the same. Such forms of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide are useful in the treatment of cancer, immune disorders and inflammation.

[0003a] In an aspect of the present disclosure, there is provided a crystalline hydrate Form A of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0003b] In another aspect of the present disclosure, there is provided a crystalline hydrate Form A 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 15.9.

[0003c] In a further aspect of the present disclosure, there is provided a crystalline hydrate Form A as further characterized by X-ray diffraction pattern reflections at 2 theta values of 21.7, 29.1, and 23.2.

[0003d] In another aspect of the present disclosure, there is provided a crystalline hydrate Form A as further characterized by X-ray diffraction pattern reflections at 2 theta values of 21.7, 29.1, 23.2, 24.1, and 26.7.

[0003e] In a further aspect of the present disclosure, there is provided a crystalline hydrate Form A 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 hydrate Form A is characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 15.9, 21.7, 29.1, 23.2, 24.1, and 26.7.

[0003f] In another aspect of the present disclosure, there is provided a crystalline hydrate Form A 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.

[0003g] In a further aspect of the present disclosure, there is provided a crystalline hydrate Form A 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 differential scanning calorimetry pattern as shown in Figure 2.

[0003h] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising any one of the crystalline forms as disclosed herein, and one or more pharmaceutically acceptable excipients or carriers.

[0003i] In a further aspect of the present disclosure, there is provided a crystalline Form B of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0003j] In another aspect of the present disclosure, there is provided a crystalline Form B 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 19.9.

[0003k] In a further aspect of the present disclosure, there is provided a crystalline Form B as further characterized by X-ray diffraction pattern reflections at 2 theta values of 21.1, 17.3, 22.4, and 26.0.

[0003l] In another aspect of the present disclosure, there is provided a crystalline Form B as further characterized by X-ray diffraction pattern reflections at 2 theta values of 21.1, 17.3, 22.4, 26.0, 25.5, and 28.3.

[0003m] In a further aspect of the present disclosure, there is provided a crystalline Form B 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 Form B is characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 19.9, 21.1, 17.3, 22.4, 26.0, 25.5, 28.3, and 24.6.

[0003n] In another aspect of the present disclosure, there is provided a crystalline Form B 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. 4.

[0003o] In a further aspect of the present disclosure, there is provided a crystalline Form B 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 differential scanning calorimetry pattern as shown in Figure 5.

[0003p] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising any one of the crystalline forms as disclosed herein, and one or more pharmaceutically acceptable excipients or carriers.

[0004] Provided herein is a composition comprising crystalline hydrate Form A of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0005] Provided herein is a composition comprising crystalline hydrate Form A 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 15.9.

[0006] Provided herein is a pharmaceutical composition comprising crystalline hydrate Form A of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide and at least one pharmaceutically acceptable excipient.

[0007] Provided herein is a composition comprising crystalline Form B of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

[0008] Provided herein is a composition comprising crystalline Form B 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 19.9.

[0009] Provided herein is a pharmaceutical composition comprising crystalline Form B of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide and at least one pharmaceutically acceptable excipient.

CLAIMS

We claim:

1. Crystalline hydrate Form A of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

2. Crystalline hydrate Form A 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 15.9.

3. Crystalline hydrate Form A ~~is~~ as further characterized by X-ray diffraction pattern reflections at 2 theta values of 21.7, 29.1, and 23.2.

4. Crystalline hydrate Form A ~~is~~ as further characterized by X-ray diffraction pattern reflections at 2 theta values of 21.7, 29.1, 23.2, 24.1, and 26.7.

5. Crystalline hydrate Form A 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 hydrate Form A is characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 15.9, 21.7, 29.1, 23.2, 24.1, and 26.7.

6. The ~~Crystalline~~ crystalline form of claim 5 further characterized by at least two X-ray diffraction pattern reflections selected from a 2 theta value of 15.9, 21.7, 29.1, 23.2, 24.1, and 26.7.

7. The ~~Crystalline~~ crystalline form of claim 5 further characterized by at least three X-ray diffraction pattern reflections selected from a 2 theta value of 15.9, 21.7, 29.1, 23.2, 24.1, and 26.7.

8. The ~~Crystalline~~ crystalline form of claim 5 further characterized by at least four X-ray diffraction pattern reflections selected from a 2 theta value of 15.9, 21.7, 29.1, 23.2, 24.1, and 26.7.

9. The ~~Crystalline~~ crystalline form of claim 5 further characterized by at least five X-ray diffraction pattern reflections selected from a 2 theta value of 15.9, 21.7, 29.1, 23.2, 24.1, and 26.7.

10. Crystalline hydrate Form A 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.

11. Crystalline hydrate Form A 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 differential scanning calorimetry pattern as shown in Figure 2.

12. A pharmaceutical composition comprising any one of the crystalline forms ~~compositions~~ of claims 1-11, and one or more pharmaceutically acceptable excipients or carriers.

13. Crystalline Form B of N-hydroxy 2-{6-[(6-fluoro-quinolin-2-ylmethyl)-amino]-3-aza-bicyclo[3.1.0]hex-3-yl}pyrimidine-5-carboxamide.

14. Crystalline Form B 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 19.9.

15.Crystalline Form B ~~is~~ as further characterized by X-ray diffraction pattern reflections at 2 theta values of 21.1, 17.3, 22.4, and 26.0.

16. Crystalline Form B ~~is~~ as further characterized by X-ray diffraction pattern reflections at 2 theta values of 21.1, 17.3, 22.4, 26.0, 25.5, and 28.3.

17. Crystalline Form B 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 Form B is characterized by at least one X-ray diffraction pattern reflection selected from a 2 theta value of 19.9, 21.1, 17.3, 22.4, 26.0, 25.5, 28.3, and 24.6.

18. The crystalline form of claim 17, wherein the crystalline Form B is further characterized by at least two X-ray diffraction pattern reflections selected from a 2 theta value of 19.9, 21.1, 17.3, 22.4, 26.0, 25.5, 28.3, and 24.6.

19. The crystalline form ~~composition~~ of claim 17, wherein the crystalline Form B is further

characterized by at least three X-ray diffraction pattern reflections selected from a 2 theta value of 19.9, 21.1, 17.3, 22.4, 26.0, 25.5, 28.3, and 24.6.

20. The crystalline form ~~composition~~ of claim 17, wherein the crystalline Form B is further characterized by at least four X-ray diffraction pattern reflections selected from a 2 theta value of 19.9, 21.1, 17.3, 22.4, 26.0, 25.5, 28.3, and 24.6.

21. The crystalline form ~~composition~~ of claim 17, wherein the crystalline Form B is further characterized by at least five X-ray diffraction pattern reflections selected from a 2 theta value of 19.9, 21.1, 17.3, 22.4, 26.0, 25.5, 28.3, and 24.6.

22. The crystalline form ~~composition~~ of claim 17, wherein the crystalline Form B is further characterized by at least six X-ray diffraction pattern reflections selected from a 2 theta value of 19.9, 21.1, 17.3, 22.4, 26.0, 25.5, 28.3, and 24.6.

23. Crystalline Form B 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. 4.

24. Crystalline Form B 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 differential scanning calorimetry pattern as shown in Figure 5.

25. A pharmaceutical composition comprising any one of the crystalline forms ~~compositions~~ of claims 13-24, and one or more pharmaceutically acceptable excipients or carriers.