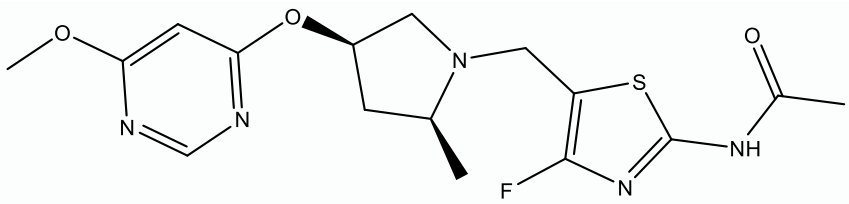
functionally related enzymes. In the case of β-N-acetylglucosaminidases, existing compounds that act to block O-GlcNAcase (OGA) function are non-specific and act potently to inhibit the lysosomal β-hexosaminidases.

[0010] Orally active OGA inhibitors have been previously described in PCT/US2019/051661. However, after a specific compound is identified as a promising candidate for use in a pharmaceutical composition, it is still necessary to fine-tune its properties with respect to a number of critical parameters, such as stability in solid state and/or liquid formulations, hygroscopicity, crystallinity, toxicological considerations, melting point, or solubility in water and aqueous media.

[0011] In view of foregoing technical challenge and given the potential for regulation of O-GlcNAcase for treatment of AD, tauopathies and other neurological diseases, there remains a need for discovery of potent solid forms of O-GlcNAcase inhibitors.

SUMMARY

[0011a] In one aspect of the present disclosure, there is provided a crystalline form of formula (I), wherein the compound is N-(4-fluoro-5-(((2S,4R)-4-((6-methoxypyrimidin-4-yl)oxy)-2-methylpyrrolidin-1-yl)methyl)thiazol-2-yl)acetamide



(I) .

[0011b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the crystalline form disclosed herein and a pharmaceutically acceptable carrier or diluent.

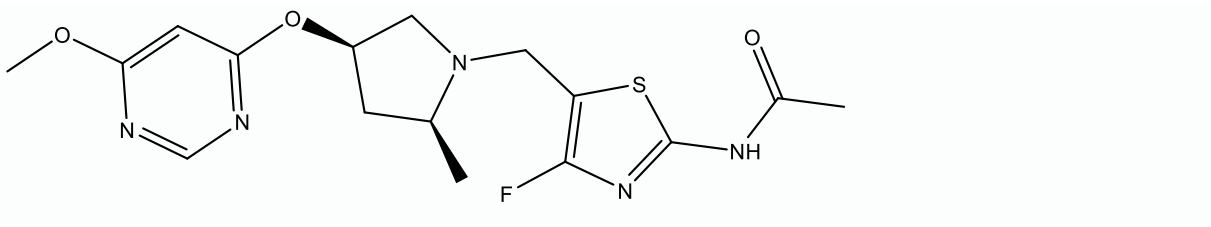
[0011c] In a further aspect of the present disclosure, there is provided a use of a crystalline form of N-(4-fluoro-5-(((2S,4R)-4-((6-methoxypyrimidin-4-yl)oxy)-2-methylpyrrolidin-1-yl)methyl)thiazol-2-yl)acetamide disclosed herein, in the manufacture of a medicament for the treatment of a disease in a subject in need thereof, wherein the disease is Alzheimer's disease or progressive supranuclear palsy.

[0011d] In another aspect of the present disclosure, there is provided a use of a crystalline form of N-(4-fluoro-5-(((2S,4R)-4-((6-methoxypyrimidin-4-yl)oxy)-2-methylpyrrolidin-1-yl)methyl)thiazol-2-yl)acetamide disclosed herein, in the manufacture of a medicament for preventing the progression of mild cognitive impairment to Alzheimer's disease in a subject in need thereof.

[0011e] In a further aspect of the present disclosure, there is provided a composition comprising at least 90 weight % of crystalline form disclosed herein, based upon the weight of the composition.

[0011f] In another aspect of the present disclosure, there is provided a crystalline form of N-(4-fluoro-5-(((2S,4R)-4-((6-methoxypyrimidin-4-yl)oxy)-2-methylpyrrolidin-1-yl)methyl)thiazol-2-yl)acetamide disclosed herein for use in therapy.

[0012] The present disclosure provides different forms of the Compound (I)



(I) .

[0013] Examples of these crystalline forms include those characterized forms A and B. The names used herein to characterize a specific form, e.g. Form A and Form B should not be considered limiting with respect to any other substance possessing similar or identical physical and chemical characteristics, but rather it should be understood that these designations are mere identifiers that should be interpreted according to the characterization information also presented herein.

[0014] In another example, provided herein is a pharmaceutical composition comprising the crystalline Form A of Compound (I) and at least one pharmaceutically acceptable carrier or diluent.

[0015] In another example, provided herein is the crystalline Form A of the Compound (I) for use as a medicament.

[0016] In a further example, provided herein is the crystalline Form A of the Compound (I) for use in the treatment or prevention of Alzheimer's disease or a related neurological disease.

[0017] In a further example, provided herein is a process of manufacturing the crystalline Form A of the Compound (I).

[0018] In another example, provided herein is a pharmaceutical composition comprising the crystalline Form B of the Compound (I) and at least one pharmaceutically acceptable carrier or diluent.

[0019] In another example, provided herein is the crystalline Form B of the Compound (I) for use as a medicament.

[0020] In a further example, provided herein is the crystalline Form B of the Compound (I) for use in the treatment or prevention of Alzheimer's disease or a related neurological disease.

[0021] In a further example, provided herein is a process of manufacturing the crystalline Form A of the Compound (I).

[0022]

Brief Description of the Drawings

Brief Description of the Drawings

Figure 1: shows the X-ray powder diffraction pattern for freeform Type A of Compound (I).

Figure 1B: shows the TGA/DSC curves of freeform Type A of Compound (I).

Figure 2: shows the X-ray powder diffraction pattern for Freeform type B of Compound (I).

Figure 2B: shows the TGA/DSC curves for Freeform Type B of Compound (I).

Figure 3: shows the X-ray powder diffraction pattern for Amorphous Freeform of Compound (I).

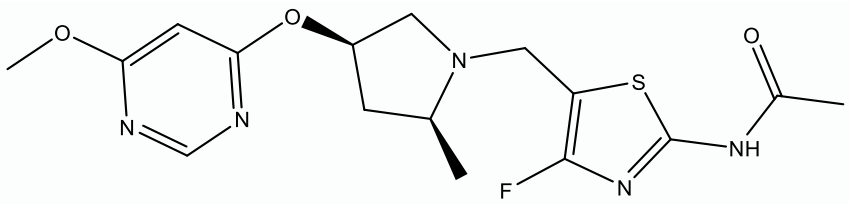
Figure 4: shows the X-ray powder diffraction pattern for HCl salt Form A of Compound (I).

Figure 4B: shows the TGA/DSC curves for HCl salt Form A of Compound (I).

Figure 5: shows the X-ray powder diffraction pattern for phosphate salt Form A of Compound (I).

CLAIMS

1. A crystalline form of formula (I), wherein the compound is N-(4-fluoro-5-(((2S,4R)-4-((6-methoxypyrimidin-4-yl)oxy)-2-methylpyrrolidin-1-yl)methyl)thiazol-2-yl)acetamide



(I) .

2. The crystalline form according to claim 1, wherein
   i) the crystalline form comprises Form A; or
   ii) the crystalline form consisting essentially of Form A.

3. The crystalline form according to claim 2, wherein
   i) said Form A is in substantially pure form;
   ii) said Form A is anhydrate Free Form;
   iii) said Form A is anhydrate hydrochloric salt Form; or
   iv) said Form A is anhydrate Phosphate salt Form.

4. The crystalline form according to claim 1, wherein
   i) the crystalline form comprises Form B; or
   ii) the crystalline form consisting essentially of Form B.

5. The crystalline form according to claim 4, wherein
   i) said Form B is in substantially pure form; or
   ii) said Form B is anhydrate Tartrate salt Form.

6. The crystalline form according to claim 3, wherein said anhydrate Free Form A of the compound has an X-ray powder diffraction pattern with at least one, two, or three peaks having an angle of refraction 2 theta (Θ) values selected from 4.3, 8.6 and 12.0° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ.

7. The crystalline anhydrate Free Form A of the compound according to claim 3, wherein

i) said anhydrate Free Form A has an X-ray powder diffraction pattern with at least four peaks having an angle of refraction 2 theta (Θ) values selected from 13.5, 14.9, 21.1, 24.4 and 27.2° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ;

ii) said anhydrate Free Form A has an X-ray powder diffraction pattern with at least five peaks having an angle of refraction 2 theta (Θ) values selected from 4.3, 8.6, 10, 11, 12, 13.5, 14.9, 19.9, 21.1, 24.4° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ;

iii) said anhydrate Free Form A has an X-ray powder diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in Figure 1; or

iv) said anhydrate Free Form A has a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in figure 1B.

8. The crystalline form according to claim 3, wherein said anhydrate Hydrochloric acid Form A has an X-ray powder diffraction pattern with at least one, two, or three peaks having an angle of refraction 2 theta (Θ) values selected from 9.6, 15.6, 21.5, 23.6° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ.

9. The crystalline anhydrate Hydrochloric acid Form A of the compound according to claim 3, wherein

i) said anhydrate hydrochloric acid Form A has an X-ray powder diffraction pattern with at least four peaks having an angle of refraction 2 theta (Θ) values selected from 9.6, 15.6, 17.1, 20.4, 21.5, 23.6, 26.5° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ;

ii) said anhydrate hydrochloric acid Form A has an X-ray powder diffraction pattern with at least five peaks having an angle of refraction 2 theta (Θ) values selected from 9.6, 10.2, 12.2, 15.2, 15.6, 17.1, 20.4, 21.5, 23.6, 26.5° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ;

iii) said anhydrate hydrochloric acid Form A has an X-ray powder diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in Figure 4; or

iv) said anhydrate hydrochloric acid Form A has a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in figure 4B.

10. The crystalline form according to claim 3, wherein said anhydrate Phosphate Form A has an X-ray powder diffraction pattern with at least one, two, or three peaks having an angle of refraction 2 theta (Θ) values selected from 7.3, 14.8, 22.5, 24.1, 26.3° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ.

11. The crystalline anhydrate Phosphate Form A of the compound according to claim 3, wherein
i) said anhydrate phosphate Form A has an X-ray powder diffraction pattern with at least four peaks having an angle of refraction 2 theta (Θ) values selected from 7.3, 14.8, 17.1, 18.6, 22.5, 24.1, 26.3, 27.6° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ;
ii) said anhydrate phosphate Form A has an X-ray powder diffraction pattern with at least four peaks having an angle of refraction 2 theta (Θ) values selected from 7.3, 14.8, 17.1, 17.6, 18.6, 22.5, 24.1, 26.3, 27.6, 28.4° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ;
iii) said anhydrate phosphate Form A has an X-ray powder diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in Figure 5; or
iv) said anhydrate phosphate Form A has a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in figure 5B.

12. The crystalline form according to claim 5, wherein said anhydrate Tartrate Form B has an X-ray powder diffraction pattern with at least one, two, or three peaks having an angle of refraction 2 theta (Θ) values selected from 12.7, 13.2, 14.6, 17.3, 20.9°, when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ.

13. The crystalline anhydrate Tartrate Form B of the compound according to claim 5, wherein
i) said anhydrate Tartrate Form B has an X-ray powder diffraction pattern with at least four peaks having an angle of refraction 2 theta (Θ) values selected from 12.7, 13.2, 14.6, 17.3, 20.9, 21.8, 24.4° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ;
ii) said anhydrate Tartrate Form B has an X-ray powder diffraction pattern with at least five peaks having an angle of refraction 2 theta (Θ) values selected from 12.7, 13.2, 14.6, 16.5,

17.3, 20.9, 21.8, 24.4, 25.7, 26.9, 28.8° when measured using CuKa radiation, wherein said values are plus or minus 0.2° 2Θ;
iii) said anhydrate Tartrate Form B has an X-ray powder diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in Figure 6; or
iv) said anhydrate Tartrate Form B has a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in figure 6B.

14. A pharmaceutical composition comprising the crystalline form according to claim 1 and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition according to claim 14, wherein

i) the crystalline form is anhydrate Free Form A;

ii) the crystalline form is anhydrate Hydrochloric acid Form A that is in substantially pure form; or

iii) the crystalline form is anhydrate Phosphate Form A that is in substantially pure form.

16. The pharmaceutical composition according to claim 15 wherein anhydrate Free Form A is in substantially pure form.

17. The pharmaceutical composition according to claim 14, wherein the crystalline form is anhydrate Tartrate Form B that is in substantially pure form.

18. Use of a crystalline form of N-(4-fluoro-5-(((2S,4R)-4-((6-methoxypyrimidin-4-yl)oxy)-2-methylpyrrolidin-1-yl)methyl)thiazol-2-yl)acetamide according to claim 1, in the manufacture of a medicament for the treatment of a disease in a subject in need thereof, wherein the disease is Alzheimer's disease or progressive supranuclear palsy.

19. Use of a crystalline form of N-(4-fluoro-5-(((2S,4R)-4-((6-methoxypyrimidin-4-yl)oxy)-2-methylpyrrolidin-1-yl)methyl)thiazol-2-yl)acetamide according to claim 1, in the manufacture of a medicament for preventing the progression of mild cognitive impairment to Alzheimer’s disease in a subject in need thereof.

20. The use according to claim 18 or 19, wherein

i) said crystalline form is anhydrate Free Form A;

ii) said crystalline form is anhydrate hydrochloric acid Form A;

iii) said crystalline form is anhydrate Phosphate Form A; or

iv) said crystalline form is anhydrate Tartrate Form B.

21. A composition comprising at least 90 weight % of crystalline form according to claim 1, based upon the weight of the composition.

22. The composition of claim 21, wherein

i) the crystalline form is anhydrate Free Form A; or

ii) the crystalline form is anhydrate Free Form B.

23. The crystalline form of N-(4-fluoro-5-(((2S,4R)-4-((6-methoxypyrimidin-4-yl)oxy)-2-methylpyrrolidin-1-yl)methyl)thiazol-2-yl)acetamide according to claim 1 for use in therapy.