METHODS OF TREATMENT OF TUBEROUS SCLEROSIS COMPLEX

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims priority to U.S.S.N. 63/035,313 filed on June 5, 2020, the contents of which is incorporated herein by reference in its entirety.

FIELD

[002] The present disclosure relates to the field of medicine and the treatment of medical conditions associated with tuberous sclerosis complex. More specifically, the present disclosure relates to use of compositions comprising 2-chloro-4-[1-(4-fluorophenyl)-2,5-dimethyl-1*H*-imidazol-4-ylethynyl]pyridine, or a pharmaceutically acceptable salt thereof, in the treatment or amelioration of medical conditions associated with tuberous sclerosis complex.

BACKGROUND

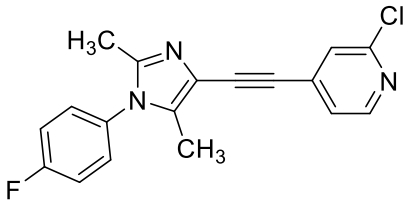
[003] Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the growth of numerous noncancerous tumors in many parts of the body such as the skin, brain, kidneys, and other organs. TSC can cause developmental issues and in some cases lead to significant health problems. Typically, TSC results from mutations in the TSC1 or TSC2 gene, which codes for the proteins hamartin and tuberin, respectively, with TSC2 mutations accounting for the majority and tending to cause more severe symptoms.

[004] There is currently no cure for TSC. While medications such as antiepileptics can help treat certain types of disorders associated with TSC (e.g., seizures), some of these medications have significant side effects, thereby limiting their medical use.

[005] Therefore, there is an unmet medical need to develop new methods for treating TSC without significant side effects.

SUMMARY

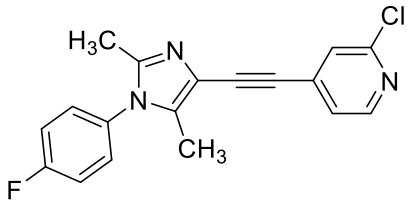
[005a] In one aspect of the present disclosure, there is provided a use of a composition comprising a therapeutically effective amount of a therapeutic agent, in the manufacture of a medicament for treating tuberous sclerosis complex (TSC) in a subject in need thereof, wherein the therapeutic agent is a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof.

[006] In one example, provided herein are methods of treating medical conditions associated with tuberous sclerosis complex (TSC), comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula I:



(I).

[007] In some examples, treating uses a composition comprising a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, wherein Form A has an X-ray powder diffraction (XRPD) pattern as substantially shown in FIG. 1. Specifically, Form A is characterized by the following X-ray powder diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8±0.2°, 13.4±0.2°, 14.2±0.2°, 18.1±0.2°, 18.9±0.2°, 19.6±0.2°, 22.6±0.2°, 22.9±0.2°, 25.7±0.2°, 27.1±0.2°, and 29.9±0.2°. The crystalline Form A typically has a T_m of about 180-190 °C by differential scanning calorimetry (DSC) analysis.

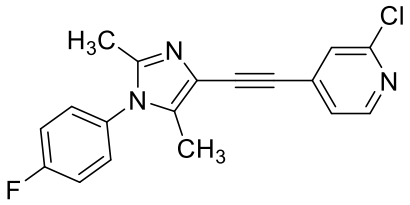
[008] In some examples, treating uses a composition comprising a crystalline monohydrate form (Form B) of a monosulfate salt of the compound of Formula I, wherein Form B has an XRPD pattern as substantially shown in FIG. 2. The crystalline Form B typically has a T_m of about 60-70 °C by DSC analysis.

[009] In some examples, treating uses a composition comprising a crystalline hemihydrate form (Form C) of a hemisulfate salt of the compound of Formula I, wherein Form C has an XRPD pattern as substantially shown in FIG. 3. The crystalline Form C typically has a T_m of about 90-100 °C by DSC analysis.

[0010] In some examples, the composition used is a tablet formulation such as a modified release tablet formulation, or a matrix pellet formulation such as a modified release matrix pellet formulation, which can be encapsulated in a capsule, as defined herein.

[0011] In some examples, treating uses a composition comprising a pharmaceutically acceptable salt of the compound of Formula I, wherein said salt is 90% by weight or more (e.g., 95% by weight or more, or 99% by weight or more) in crystalline Form A based on the total weight of the salt present in the composition.

[0012] The present disclosure also includes a solid pharmaceutical composition comprising a solid form of a compound of Formula I:



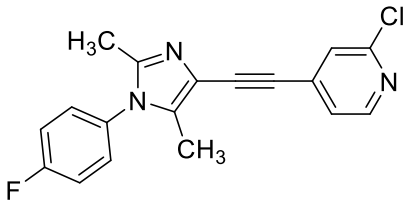
(I),

wherein the solid form is a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, characterized by at least three peaks selected from the following XRPD peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8±0.2°, 13.4±0.2°, 14.2±0.2°, 18.1±0.2°, 18.9±0.2°, 19.6±0.2°, 22.6±0.2°, 22.9±0.2°, 25.7±0.2°, 27.1±0.2°, and 29.9±0.2°; and has a median particle size (Dv50) of less than or equal to about 100 μm, wherein the solid pharmaceutical composition is the form of a matrix pellet. In some examples, the solid form has a particle size of less than 47 μm (e.g., about 25 μm or less, or about 10 μm or less).

[0013] In some examples, the pharmaceutical composition comprises the Form A monosulfate salt characterized by the following XRPD peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8±0.2°, 13.4±0.2°, 14.2±0.2°, 18.1±0.2°, 18.9±0.2°, 19.6±0.2°, 22.6±0.2°, 22.9±0.2°, 25.7±0.2°, 27.1±0.2°, and 29.9±0.2°.

[0014] In some examples, the pharmaceutical composition comprises the Form A monosulfate salt characterized by an XRPD pattern as substantially shown in FIG. 1.

[0015] The present disclosure also includes a method of preparing a matrix pellet comprising a crystalline anhydrate form (Form A) of a monosulfate salt of a compound of Formula I:



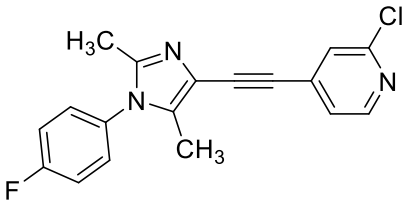
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wherein the method comprises: granulating the Form A monosulfate salt and one or more polymers with purified water to form a mixture; extruding, spheronizing, drying, and sieving the mixture to afford a solid material; and blending the solid material with another pharmaceutical excipient to afford a matrix pellet.

[0016] In some examples, the method of preparation further comprises filling the matrix pellet into a capsule to form a matrix pellet capsule. In some examples, the one or more

polymers are selected from the group consisting of a cellulose such as microcrystalline cellulose, methacrylic acid copolymer, and hypromellose. In some examples, the other pharmaceutical excipient is talc.

[0017] In another example, provided herein are methods of treating TSC, comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of an mGlu5 negative allosteric modulator (NAM) or a pharmaceutically acceptable salt thereof, wherein the mGlu5 NAM is a compound of Formula I:



(I).

[0018] The details of one or more examples of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the below drawings, description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIG. 1 depicts an exemplary XRPD pattern of a crystalline anhydrate form (Form A) of a monosulfate of the compound of Formula I.

[0020] FIG. 2 depicts an exemplary XRPD pattern of a crystalline monohydrate form (Form B) of a monosulfate of the compound of Formula I.

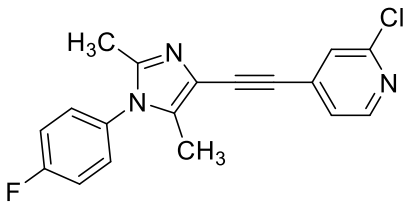
[0021] FIG. 3 depicts an exemplary XRPD pattern of a crystalline hemihydrate form (Form C) of a hemisulfate of the compound of Formula I.

DETAILED DESCRIPTION

[0022] As generally described herein, the present disclosure provides methods of treating medical conditions associated with tuberous sclerosis complex (TSC) in a subject in need thereof. The present disclosure also describes treating medical conditions associated with TSC by using certain crystalline forms of pharmaceutically acceptable salts of the compound of Formula I. In addition, the present disclosure provides a solid form of a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, wherein the solid form has a

CLAIMS

1. Use of a composition comprising a therapeutically effective amount of a therapeutic agent, in the manufacture of a medicament for treating tuberous sclerosis complex (TSC) in a subject in need thereof, wherein the therapeutic agent is a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof.

2. The use of claim 1, wherein therapeutic efficacy of the treatment is determined by assessing improvement based on the Sheehan Disability Scale (SDS).

3. The use of claim 1, wherein therapeutic efficacy of the treatment is determined by assessing improvement based on the Sheehan Disability Scale (SDS), where the subject shows a change from baseline.

4. The use of claim 1, wherein therapeutic efficacy of the treatment is determined by assessing improvement based on the Caregiver Global Impression of Change (CGIC) score.

5. The use of claim 1, wherein therapeutic efficacy of the treatment is determined by assessing improvement based on the Caregiver Global Impression of Change (CGIC) score, where the subject shows a change from baseline.

6. The use of claim 1, wherein therapeutic efficacy of the treatment is determined by an increase in the number of seizure free days within a four week period.

7. The use of of claim 1, wherein therapeutic efficacy of the treatment is determined by a greater than or equal to 25% reduction in seizures from baseline within a four week period.

8. The use of of claim 1, wherein therapeutic efficacy of the treatment is determined by a greater than or equal to 50% reduction in seizures from baseline within a four week period.

9. The use of of claim 1, wherein therapeutic efficacy of the treatment is determined by a greater than or equal to 75% reduction in seizures from baseline within a four week period.

10. The use of of claim 1, wherein therapeutic efficacy of the treatment is determined by a 100% reduction in seizures from baseline within a four week period.

11. The use of claim 1, wherein the therapeutic agent is in its free base form.

12. The use of claim 1, wherein the therapeutic agent is a pharmaceutically acceptable salt.

13. The use of claim 1, wherein the pharmaceutically acceptable salt is a monosulfate salt or a hemisulfate salt.

14. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 0.1 mg to about 3.5 mg once daily.

15. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 0.1 mg to about 3 mg once daily.

16. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 1.5 mg to about 3.5 mg once daily.

17. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 1 mg to about 3 mg once daily.

18. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 3.5 mg, about 3.0 mg, about 2.5 mg, about 2.0 mg, about 1.5 mg, or about 1.0 mg once daily.

19. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 3.5 mg once daily.

20. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 3 mg once daily.

21. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 0.1 mg to about 3 mg once daily, or about 3.5 mg to about 5 mg.

22. The use of claim 1, wherein the therapeutic agent is to be administered orally.

23. The use of claim 1, wherein the therapeutic agent is to be administered as a unit dose.

24. The use of claim 1, wherein the therapeutic effect of the treatment is determined by a reduction of seizure occurrence or frequency.

25. The use of claim 1, wherein the therapeutic effect of the treatment is determined by reduction of the size of a tumor in the brain, eyes, heart, kidney, skin, or lungs.

26. The use of claim 1, wherein the therapeutic effect of the treatment is determined by suppression of tumor growth in the brain, eyes, heart, kidney, skin, or lungs.

27. The use of claim 1, wherein the therapeutic effect of the treatment is determined by improvement of cognitive function.