POLYMORPHIC FORMS OF 2-(5-BROMO-4-(4-CYCLOPROPYLNAPHTHALEN-1-YL)-4*H*-1,2,4-TRIAZOL-3-YLTHIO)ACETIC ACID AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Application No. 61/428,660, filed December 30, 2010, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

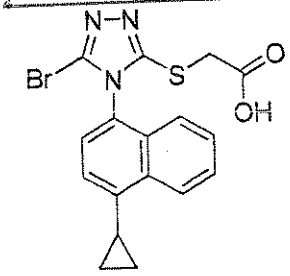
[0002] Described herein are polymorphic forms of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid, which is known to decrease uric acid levels.

BACKGROUND OF THE INVENTION

[0003] Gout is associated with elevated levels of uric acid that crystallize and deposit in joints, tendons, and surrounding tissues. Gout is marked by recurrent attacks of red, tender, hot, and/or swollen joints.

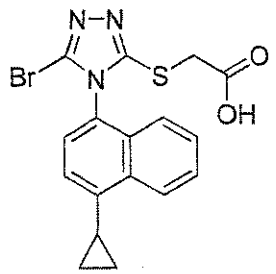
SUMMARY OF THE INVENTION

[0003a] In a first aspect, there is provided a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid:



characterized by peaks at 10.32, 18.84 and 20.75 °2θ ± 0.1°2θ.

[0003b] In a second aspect, there is provided a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid:



characterized by peaks at 10.46, 18.76, and 19.83 °2θ±0.1°2θ.

[0003c] In a third aspect, there is provided a crystalline polymorphic form of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid as defined above prepared by a method comprising the step of crystallizing 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid from a mixture of water and ethyl acetate.

[0003d] In a fourth aspect, there is provided a solid pharmaceutical composition comprising:

an effective amount of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid, the 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid comprising the crystalline polymorph as defined in the second aspect as an active ingredient; and at least one excipient or carrier.

[0003e] In a fifth aspect, there is provided a process for the preparation of a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid, the process comprising:

dissolving sodium 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetate in water resulting in a solution;

adding a mineral acid;

adding ethylacetate;

separating an organic layer;

precipitating the crystalline polymorph from the organic layer;

wherein the crystalline polymorph is characterized by peaks at 10.46, 18.76, and 19.83 °2θ ± 0.1°2θ.

[0003f] In a sixth aspect, there is provided a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid as defined above, comprising:

(a) contacting sodium 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetate with aqueous hydrogen bromide solution and an organic solvent to form an aqueous phase and an organic phase;

(b) isolating the organic phase from the mixture of step (a); and

(c) crystallizing 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid from the organic phase.

[0003g] In a seventh aspect, there is provided a process for the preparation of a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid as defined above, comprising crystallizing 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid from a mixture of water and ethyl acetate.

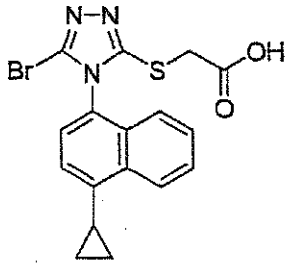
[0003h] In an eighth aspect, there is provided a solid pharmaceutical composition comprising:

2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid form 1 as defined in the first aspect as an active ingredient; and

2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid form 2 as defined in the second aspect as an active ingredient; and

and at least one excipient or carrier.

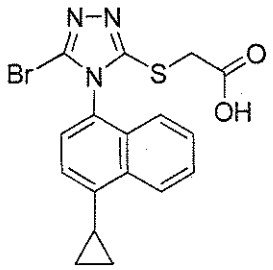
[0004] Described herein are crystalline polymorphs of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid:



[0005] In one aspect described herein are crystalline polymorphs of 2-(5-bromo-4-(4-cyclopropyl naphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid characterized by peaks at 10.32, 18.84 and 20.75 °2θ±0.1°2θ. In further embodiments, such a crystalline polymorph is further characterized by at least two further peaks at 6.80, 21.54, 24.97, 25.53, 27.28 and 27.60 °2θ ± 0.1°2θ. In yet further embodiments, the crystalline polymorph exhibits an x-ray powder diffraction pattern substantially the same as the x-ray powder diffraction pattern shown in FIGURE 1. In yet further embodiments, the crystalline polymorph exhibits an x-ray powder diffraction pattern substantially the same as the x-ray powder diffraction pattern shown in FIGURE 2. In a related aspect described herein are crystalline polymorphs of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid, characterized by an endothermic point onset at about 151 °C, as determined by differential scanning calorimetry. In a further embodiment, the crystalline polymorph is characterized by a differential scanning

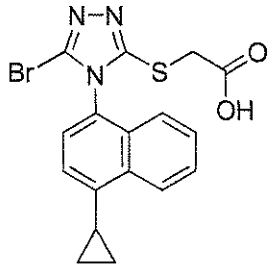
CLAIMS:

1. A crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid:



characterized by peaks at 10.32, 18.84 and 20.75 °2θ ± 0.1°2θ.

2. A crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid:



characterized by peaks at 10.46, 18.76, and 19.83 °2θ±0.1°2θ.

3. The crystalline polymorph of claim 2, further characterized by at least one further peak at 18.21 or 23.08 °2θ±0.1°2θ.

4. The crystalline polymorph of claim 2 that exhibits an x-ray powder diffraction pattern substantially the same as the x-ray powder diffraction pattern shown in FIGURE 5.

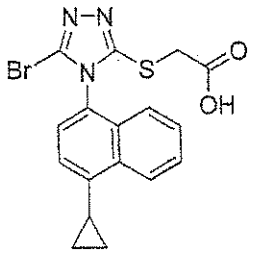
5. A crystalline polymorphic form of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid of claim 2 prepared by a method comprising the step of crystallizing 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid from a mixture of water and ethyl acetate.

6. A solid pharmaceutical composition comprising:

   an effective amount of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid, the 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid comprising the crystalline polymorph of claim 2 as an active ingredient; and

CLAIMS:

1. A crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid:

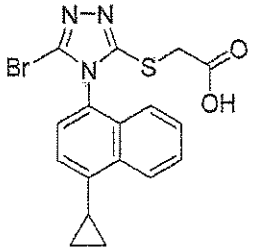


characterized by peaks at 10.46, 18.76, and 19.83 °2θ±0.1°2θ.

2. The crystalline polymorph of claim **1**, further characterized by at least one further peak at 18.21 or 23.08 °2θ±0.1°2θ.
3. The crystalline polymorph of claim **1** that exhibits an x-ray powder diffraction pattern substantially the same as the x-ray powder diffraction pattern shown in FIGURE 5.
4. The crystalline polymorph form 2 of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid.
5. A crystalline polymorphic form of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid prepared by a method comprising the step of crystallizing 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid from a mixture of water and ethyl acetate.
6. A solid pharmaceutical composition comprising:

   an effective amount of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid, the 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid comprising the crystalline polymorph of claim **1**, claim **4**, or claim **5** as an active ingredient; and

   at least one excipient or carrier.
7. The compound of claim **1**, claim **4**, or claim **5** for use in treating or preventing hyperuricemia, or a disease caused by elevated uric acid levels.
8. The compound of claim **1**, claim **4**, or claim **5** for use in treating or preventing gout.
9. A crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid:



characterized by peaks at 10.32, 18.84 and 20.75 °2θ ± 0.1°2θ.

10. The crystalline polymorph of claim **9**, further characterized by at least two further peaks at 6.80, 21.54, 24.97, 25.53, 27.28 and 27.60 °2θ ± 0.1°2θ.

11. The crystalline polymorph of claim **9**, that exhibits an x-ray powder diffraction pattern substantially the same as the x-ray powder diffraction pattern shown in FIGURE 1.

12. The crystalline polymorph form 1 of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid.

13. A crystalline polymorphic form of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid prepared by a method comprising the step of crystallizing 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid from a mixture of water and acetic acid.

14. A solid pharmaceutical composition comprising:

an effective amount of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid, the 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid comprising the crystalline polymorph of claim **9**, claim **12**, or claim **13** as an active ingredient; and

at least one excipient or carrier.

15. The compound of claim **9**, claim **12**, or claim **13** for use in treating or preventing hyperuricemia, or a disease caused by elevated uric acid levels.

16. The compound of claim **9**, claim **12**, or claim **13** for use in treating or preventing gout.

17. A solid pharmaceutical composition comprising:

2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid form 1 as an active ingredient; and

2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid form 2 as an active ingredient;

and at least one excipient or carrier.

18. A process for the preparation of a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid, the process comprising:

dissolving sodium 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetate in water resulting in a solution;

adding a mineral acid (e.g., about 1 equivalent);

adding ethyl acetate;

separating an organic layer;

precipitating the crystalline polymorph from the organic layer (e.g,. by cooling and/or reducing the volume of the organic layer);

wherein the crystalline polymorph is characterized by peaks at 10.46, 18.76, and 19.83 °2θ ± 0.1°2θ.

19. The process of claim **18**, wherein the process in characterized by one or more of the following:

the mineral acid comprises hydrobromic acid;

the mineral acid is added at about 1.05 equivalents;

the volume of the organic layer is reduced to precipitate the crystalline polymorph;

the organic layer is cooled to precipitate the crystalline polymorph;

the crystalline polymorph is filtered and washed; and/or

the crystalline polymorph is further characterized by at least one further peak at 18.21 or 23.08 °2θ ± 0.1°2θ.

20. A process for the preparation of a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid, comprising:

(a) contacting sodium 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetate with aqueous hydrogen bromide solution and an organic solvent to form an aqueous phase and an organic phase;

(b) isolating the organic phase from the mixture of step (a); and

(c) crystallizing 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid from the organic phase.

21. A process for the preparation of a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid, comprising crystallizing 2-(5-bromo-4-(4-cyclopropyl naphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid from a mixture of water and ethyl acetate.

at least one excipient or carrier.

7. A process for the preparation of a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid, the process comprising:

dissolving sodium 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetate in water resulting in a solution;

adding a mineral acid;

adding ethylacetate;

separating an organic layer;

precipitating the crystalline polymorph from the organic layer;

wherein the crystalline polymorph is characterized by peaks at 10.46, 18.76, and 19.83 °2θ ± 0.1°2θ.

8. The process of claim 7, wherein the process in characterized by one or more of the following:

the mineral acid comprises hydrobromic acid;

the mineral acid is added at about 1.05 equivalents;

the volume of the organic layer is reduced to precipitate the crystalline polymorph;

the organic layer is cooled to precipitate the crystalline polymorph;

the crystalline polymorph is filtered and washed; and/or

the crystalline polymorph is further characterized by at least one further peak at 18.21 or 23.08 °2θ ± 0.1°2θ.

9. A process for the preparation of a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid of claim 2, comprising:

(a) contacting sodium 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetate with aqueous hydrogen bromide solution and an organic solvent to form an aqueous phase and an organic phase;

(b) isolating the organic phase from the mixture of step (a); and

(c) crystallizing 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid from the organic phase.

10. A process for the preparation of a crystalline polymorph of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid of claim 2, comprising crystallizing 2-(5-bromo-4-(4-cyclopropyl naphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid from a mixture of water and ethyl acetate.

11. A solid pharmaceutical composition comprising:

2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid form 1 of claim 1 as an active ingredient; and

2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4,-triazol-3-ylthio)acetic acid form 2 of claim 2 as an active ingredient;

and at least one excipient or carrier.