3,4-DI-SUBSTITUTED PYRIDINE COMPOUND, METHODS OF USING AND COMPOSITIONS COMPRISING THE SAME

CROSS-REFERENCE

This application claims the benefit of U.S. Application Serial No. 61/555,450, filed November 3, 2011, and U.S. Application Serial No. 61/616,363, filed March 27, 2012, which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Uric acid is the result of the oxidation of xanthine. Disorders of uric acid metabolism include, but are not limited to, polycythemia, myeloid metaplasia, gout, a recurrent gout attack, gouty arthritis, hyperuricaemia, hypertension, a cardiovascular disease, coronary heart disease, Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, kidney disease, kidney stones, kidney failure, joint inflammation, arthritis, urolithiasis, plumbism, hyperparathyroidism, psoriasis or sarcoidosis.

SUMMARY OF THE INVENTION

[003] In one embodiment, there is provided use of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for reducing serum uric levels in a human, wherein the medicament is adapted for administration of less than 40 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid.

[003a] In certain embodiments, provided herein is a compound for use in reducing serum uric acid levels in a human, wherein the compound is 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.

[004] In some embodiments of the compound for use, less than 100 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human. In certain embodiments, less than 50 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human. In some embodiments, about 40 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human. In certain embodiments, about 20 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human. In some embodiments, less than 20 mg per day of 2-((3-(4-

WHAT IS CLAIMED IS:

1. Use of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for reducing serum uric levels in a human, wherein the medicament is adapted for administration of less than 40 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid.
2. The use of claim 1 for the manufacture of a medicament, wherein the medicament is adapted for administration of about 10 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.
3. The use of claim 1 for the manufacture of a medicament, wherein the medicament is adapted for administration of about 20 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
4. The use of claim 1 for the manufacture of a medicament, wherein the medicament is adapted for administration of less than 20 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
5. The use of claim 1 for the manufacture of a medicament, wherein the medicament is adapted for administration of about 5 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
6. The use of claim 1 for the manufacture of a medicament, wherein the medicament is adapted for administration of less than 5 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
7. The use of claim 1 for the manufacture of a medicament, wherein the medicament is adapted for administration of about 2 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
8. The use of claim 1 for the manufacture of a medicament , wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 1 mg/dL.

9. The use according to any one of claims 1-7, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, serum uric acid levels are reduced by at least 15% from baseline.
10. The use according to any one of claims 1-7, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, serum uric acid levels are reduced by at least 20% from baseline.

11. The use according to any one of the preceding claims, for treating or preventing a condition characterized by abnormal tissue or organ levels of uric acid.
12. The use of claim 11, wherein the condition is gout, a recurrent gout attack, gouty arthritis, hyperuricaemia, hypertension, a cardiovascular disease, coronary heart disease, Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, kidney disease, kidney stones, kidney failure, joint inflammation, arthritis, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency or a combination thereof.
13. The use of claim 12, wherein the condition is gout.
14. The use of claim 1, wherein the medicament is adapted for administration with a second agent effective for the treatment of the gout is administered to the human.
15. The use of claim 14, wherein the second agent is a URAT 1 inhibitor, a xanthine oxidase inhibitor, a xanthine dehydrogenase, a xanthine oxidoreductase inhibitor, or combinations thereof.
16. The use of claim 15, wherein the URAT 1 inhibitor is 2-((5-bromo-4-(4-cyclopropyl-1-naphthalenyl)-4H-1,2,4-triazol-3-yl)thio)acetic acid, or a pharmaceutically acceptable salt thereof.
17. The use of claim 16, wherein the xanthine oxidase inhibitor is allopurinol or febuxostat.
18. A pharmaceutical composition comprising less than 40mg of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
19. The pharmaceutical composition of claim 18, comprising less than 20mg of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.

20. The pharmaceutical composition of claim 18, comprising about 20mg of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
21. The pharmaceutical composition of claim 18, comprising about 10mg of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
22. The pharmaceutical composition of claim 18, comprising less than 5mg of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.
23. The pharmaceutical composition of claim 18, comprising about 5mg of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.

WHAT IS CLAIMED IS:

1. A compound for use in reducing serum uric acid levels in a human, wherein the compound is 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.

2. The compound for use of claim 1, wherein less than 100 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.

3. The compound for use of claim 1, wherein less than 50 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.

4. The compound for use of claim 1, wherein about 40 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.

5. The compound for use of claim 1, wherein about 20 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.

6. The compound for use of claim 1, wherein less than 20 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.

7. The compound for use of claim 1, wherein about 5 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.

8. The compound for use of claim 1, wherein less than 5 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid is administered to the human.

9. The compound for use of claim 1, wherein about 2 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.

10. The compound for use of claim 1, wherein less than 2 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, is administered to the human.

11. The compound for use of claim 1, wherein about 1 mg per day of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid is administered to the human.

12. The compound for use according to any one of the preceding claims, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 0.5 mg/dL.

13. The compound for use according to any one of the preceding claims, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 0.8 mg/dL.

14. The compound for use according to any one of the preceding claims, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 1 mg/dL.

15. The compound for use according to any one of the preceding claims, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acids levels are reduced by at least 2 mg/dL.

16. The compound for use according to any one of the preceding claims, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acids levels are reduced by at least 3 mg/dL.

17. The compound for use according to any one of the preceding claims, wherein 48 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 0.5 mg/dL.

18. The compound for use according to any one of the preceding claims, wherein 48 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 1 mg/dL.

19. The compound for use according to any one of the preceding claims, wherein 48 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 3 mg/dL.

20. The compound for use according to any one of the preceding claims, wherein 72 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 0.5 mg/dL.

21. The compound for use according to any one of the preceding claims, wherein 72 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 1 mg/dL.

22. The compound for use according to any one of the preceding claims, wherein 72 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 2 mg/dL.

23. The compound for use according to any one of claims 1-11, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, the serum uric acid levels are reduced by at least 15% from baseline.

24. The compound for use according to any one of claims 1-11, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 20% from baseline.

25. The compound for use according to any one of claims 1-11, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid,

or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 30% from baseline.

26. The compound for use according to any one of claims 1-11, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 40% from baseline.

27. The compound for use according to any one of claims 1-11, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 20% from baseline.

28. The compound for use according to any one of claims 1-11, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 40% from baseline.

29. The compound for use according to any one of claims 1-11, wherein 24 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 60% from baseline.

30. The compound for use according to any one of claims 1-11 or 23-29, wherein 48 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 10% from baseline.

31. The compound for use according to any one of claims 1-11 or 23-29, wherein 48 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 20% from baseline.

32. The compound for use according to any one of claims 1-11 or 23-29, wherein 48 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 30% from baseline.

33. The compound for use according to any one of claims 1-11 or 23-29, wherein 48 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 40% from baseline.

34. The compound for use according to any one of claims 1-11 or 23-29, wherein 48 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 50% from baseline.

35. The compound for use according to any one of claims 1-11 or 23-34, wherein 72 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 15% from baseline.

36. The compound for use according to any one of claims 1-11 or 23-34, wherein 72 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by at least 20% from baseline.

37. The compound for use according to any one of claims 1-11 or 23-34, wherein 72 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 20% from baseline.

38. The compound for use according to any one of claims 1-11 or 23-34, wherein 72 hours after administration of 2-((3-(4-cyanonaphthalen-1-yl)pyridin-4-yl)thio)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof, the serum uric acid levels are reduced by about 30% from baseline.

39. The compound for use according to any one of the preceding claims, wherein the compound is for use in treating or preventing a condition characterized by abnormal tissue or organ levels of uric acid.

40. The compound for use of claim 39, wherein the condition is gout, a recurrent gout attack, gouty arthritis, hyperuricaemia, hypertension, a cardiovascular disease, coronary heart disease, Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, kidney disease, kidney

stones, kidney failure, joint inflammation, arthritis, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency or a combination thereof.

41. The compound for use of claim 40, wherein the condition is gout.

42. The compound for use according to any one of the preceding claims, wherein a second agent effective for the treatment of the gout is administered to the human.

43. The compound for use of claim 42, wherein the second agent is a URAT 1 inhibitor, a xanthine oxidase inhibitor, a xanthine dehydrogenase, a xanthine oxidoreductase inhibitor, or combinations thereof.

44. The compound for use of claim 43, wherein the URAT 1 inhibitor is 2-((5-bromo-4-(4-cyclopropyl-1-naphthalenyl)-4H-1,2,4-triazol-3-yl)thio)acetic acid, or a pharmaceutically acceptable salt thereof.

45. The compound for use of claim 43, wherein the xanthine oxidase inhibitor is allopurinol or febuxostat.