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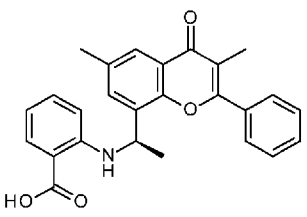
(54) Title: ALLOSTERIC CHROMENONE INHIBITORS OF PHOSPHOINOSITIDE 3-KINASE (PI3K) FOR THE TREATMENT OF DISEASE

(57) Abstract: The present invention relates to Compound (A), pharmaceutically acceptable salts thereof, methods of making, and use thereof for the treatment of disease.



(A)

WO 2024/097205 A1

ALLOSTERIC CHROMENONE INHIBITORS OF PHOSPHOINOSITIDE 3-KINASE (PI3K) FOR THE TREATMENT OF DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[1] This application claims priority to U.S. Provisional Applications 63/421,636, filed November 02, 2022 (Attorney Docket 30219_US_PRI); and 63/423,879, filed November 9, 2022 (Attorney Docket 30219A_US_PRI); the content of each of which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[2] The present invention is directed to 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid ("Compound A"), pharmaceutically acceptable salts thereof, and use thereof for the treatment of disease.

BACKGROUND

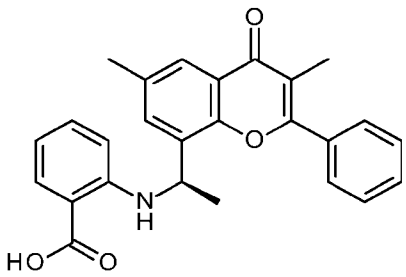
[3] The PIK3CA gene encoding the PI3K catalytic isoform p110α is the most frequently mutated gene in solid tumors and is also the most frequent site of genetic alteration within the PI3K pathway. PIK3CA mutations are most frequently found in endometrial, breast, and head and neck cancers. Approximately 40% of patients with HR+/HER2- breast cancer harbor activating mutations in PIK3CA, which activates p110α and the PI3K/AKT/mTOR signaling network. H1047R is the most common missense mutation in PIK3CA.

[4] Several PI3K-targeting agents have been tested in breast cancer patients. In a randomized Phase 3 study (SOLAR-1; NCT02437318), the PI3Kα specific inhibitor alpelisib in combination with fulvestrant increased progression-free survival to 11.0 months compared to 5.7 months with fulvestrant alone, leading to FDA approval of alpelisib in combination with fulvestrant for the treatment of HR+/HER2- PIK3CA-mutant advanced or metastatic breast cancer patients. While this approval represented a significant therapeutic advancement for PIK3CA-mutant breast cancer, alpelisib along with other investigational PI3Kα inhibitors in the clinic, inhibit both wild-type (WT) and mutated PI3Kα with approximately equal potency. As a result, their efficacy is potentially limited by on-target WT PI3Kα mediated toxicity including dose-limiting hyperglycemia as well as cutaneous and GI toxicity, that has somewhat limited the broad clinical utility of PI3Kα inhibitors.

[5] There is a need for PI3Kα inhibitors with improved therapeutic indices for the treatment of diseases associated with mutant PI3K, including PIK3CA-mutant cancers. There is also a need for solid forms of PI3Kα inhibitors having advantageous physical stability, chemical stability, solubility, or pharmacokinetic properties.

SUMMARY

[6] In one aspect, provided are solid forms of Compound A,



[7] The chemical name for Compound A can be written as 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid.

[8] In another aspect, provided are pharmaceutically acceptable salts of Compound A, and solid forms thereof. Examples of pharmaceutically acceptable salts of Compound A include a tromethamine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid and an erbumine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid.

[9] In another aspect, provided are therapies including Compound A, or a pharmaceutically acceptable salt thereof, for the treatment of disease, such as PIK3CA-mutated cancer.

BRIEF DESCRIPTION OF THE FIGURES

[10] FIG. 1 is an XRPD pattern of crystalline Compound A Form A.

[11] FIG. 2 is an XRPD pattern of crystalline Compound A Form B.

[12] FIG. 3 is an XRPD pattern of crystalline Compound A Form C.

[13] FIG. 4 is an XRPD pattern of crystalline Compound A Tromethamine Salt Form A.

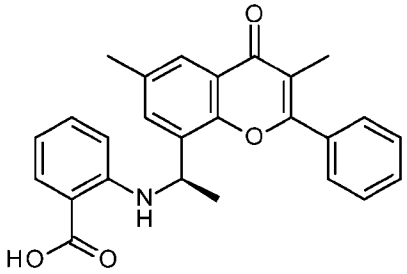
[14] FIG. 5 is an XRPD pattern of crystalline Compound A Tromethamine Salt Form C.

[15] FIG. 6 is an XRPD pattern of crystalline Compound A Tromethamine Salt Form D.

[16] FIG. 7 is an XRPD pattern of a crystalline Compound A Erbumine Salt.

DETAILED DESCRIPTION

[17] The compound 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid ("Compound A") is a potent and mutant-selective inhibitor of PI3Kα H1047R.



Compound A

[18] In one aspect, provided herein are solid forms of Compound A.

Compound A Form A

[19] In one aspect, provided is crystalline 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid Form A, also referred to as Compound A Form A. In an embodiment, Compound A Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 7.8° ± 0.2°, 12.1° ± 0.2°, 13.7° ± 0.2°, 14.1° ± 0.2°, 16.8° ± 0.2°, 17.5° ± 0.2°, 18.2° ± 0.2°, 18.9° ± 0.2°, 19.5° ± 0.2°, 20.7° ± 0.2°, 21.2° ± 0.2°, and 24.1° ± 0.2°. In another embodiment, Compound A Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 12.1° ± 0.2° in combination with at least one peak selected from 14.1° ± 0.2°, 16.8° ± 0.2°, 18.9° ± 0.2°, and 20.7° ± 0.2°. In another embodiment, Compound A Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 12.1° ± 0.2° in combination with at least two peaks selected from 14.1° ± 0.2°, 16.8° ± 0.2°, 18.9° ± 0.2°, and 20.7° ± 0.2°. In another embodiment, Compound A Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 12.1° ± 0.2° in combination with at least three peaks selected from 14.1° ± 0.2°, 16.8° ± 0.2°, 18.9° ± 0.2°, and 20.7° ± 0.2°. In another embodiment, Compound A Form A is

characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 12.1° ± 0.2° in combination with the peaks 14.1° ± 0.2°, 16.8° ± 0.2°, 18.9° ± 0.2°, and 20.7° ± 0.2°. In another embodiment, Compound A Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 7.8° ± 0.2°, 12.1° ± 0.2°, 13.7° ± 0.2°, 14.1° ± 0.2°, 16.8° ± 0.2°, 17.5° ± 0.2°, 18.2° ± 0.2°, 18.9° ± 0.2°, 19.5° ± 0.2°, 20.7° ± 0.2°, 21.2° ± 0.2°, and 24.1° ± 0.2°.

Compound A Form B

[20] In another aspect, provided is crystalline 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid Form B, also referred to as Compound A Form B. In an embodiment, Compound A Form B is characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 7.0° ± 0.2°, 9.7° ± 0.2°, 11.9° ± 0.2°, 14.9° ± 0.2°, and 17.4° ± 0.2°. In another embodiment, Compound A Form B is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 9.7° ± 0.2° in combination with at least one peak selected from 14.9° ± 0.2°, 11.9° ± 0.2°, 17.4° ± 0.2°, and 7.0° ± 0.2°. In another embodiment, Compound A Form B is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 9.7° ± 0.2° in combination with at least two peaks selected from 14.9° ± 0.2°, 11.9° ± 0.2°, 17.4° ± 0.2°, and 7.0° ± 0.2°. In another embodiment, Compound A Form B is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 9.7° ± 0.2° in combination with at least three peaks selected from 14.9° ± 0.2°, 11.9° ± 0.2°, 17.4° ± 0.2°, and 7.0° ± 0.2°. In another embodiment, Compound A Form B is characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 7.0° ± 0.2°, 9.7° ± 0.2°, 11.9° ± 0.2°, 14.9° ± 0.2°, and 17.4° ± 0.2°.

Compound A Form C

[21] In another aspect, provided is crystalline 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid Form C, also referred to as Compound A Form C. In an embodiment, Compound A Form C is characterized by an X-ray powder diffraction

pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 7.4° ± 0.2°, 8.5° ± 0.2°, 10.6° ± 0.2°, 13.4° ± 0.2°, and 15.7° ± 0.2°. In another embodiment, Compound A Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 13.4° ± 0.2° in combination with at least one peak selected from 8.5° ± 0.2°, 15.7° ± 0.2°, 10.6° ± 0.2°, and 7.4° ± 0.2°. In another embodiment, Compound A Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 13.4° ± 0.2° in combination with at least two peaks selected from 8.5° ± 0.2°, 15.7° ± 0.2°, 10.6° ± 0.2°, and 7.4° ± 0.2°. In another embodiment, Compound A Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 13.4° ± 0.2° in combination with at least three peaks selected from 8.5° ± 0.2°, 15.7° ± 0.2°, 10.6° ± 0.2°, and 7.4° ± 0.2°. In another embodiment, Compound A Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 7.4° ± 0.2°, 8.5° ± 0.2°, 10.6° ± 0.2°, 13.4° ± 0.2°, and 15.7° ± 0.2°.

[22] In another aspect, provided herein is a tromethamine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid. Certain tromethamine salts of Compound A may have advantageous physical stability, chemical stability, solubility, or pharmacokinetic properties. Certain tromethamine salts of Compound A may have processability or other manufacturing advantages. Certain tromethamine salts of Compound A may provide a chiral enhancement of Compound A upon crystallization of the tromethamine salt.

Compound A Tromethamine Salt Form A

[23] In another aspect, provided is a crystalline tromethamine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid, referred to as Compound A Tromethamine Salt Form A. In an embodiment, Compound A Tromethamine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.4° ± 0.2°, 8.4° ± 0.2°, 10.9° ± 0.2°, 11.8° ± 0.2°, 13.0° ± 0.2°, 16.5° ± 0.2°, 16.9° ± 0.2°, 22.1° ± 0.2°, 23.0° ± 0.2°, and 24.9° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form A is characterized by an X-

ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with at least one peak selected from 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with at least two peaks selected from 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with at least three peaks selected from 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with the peaks 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 6.4° ± 0.2°, 8.4° ± 0.2°, 10.9° ± 0.2°, 11.8° ± 0.2°, 13.0° ± 0.2°, 16.5° ± 0.2°, 16.9° ± 0.2°, 22.1° ± 0.2°, 23.0° ± 0.2°, and 24.9° ± 0.2°.

[24] In another embodiment, Compound A Tromethamine Salt Form A is characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 179.0, 158.7, 151.7, 149.7, 136.3, 134.7, 132.9, 129.3, 127.4, 125.2, 121.7, 117.0, 115.5, 115.2, 110.4, 64.1, 63.2, 45.3, 22.6, 20.3, and 11.6 ppm (± 0.2 ppm, respectively). In another embodiment, Compound A Tromethamine Salt Form A is characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 179.0, 129.3, 63.2, 20.3, and 11.6 ppm (± 0.2 ppm, respectively). In another embodiment, Compound A Tromethamine Salt Form A is characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises peaks referenced to glycine (external reference at 176.5 ppm) at: 179.0, 158.7, 151.7, 149.7, 136.3, 134.7, 132.9, 129.3, 127.4, 125.2, 121.7, 117.0, 115.5, 115.2, 110.4, 64.1, 63.2, 45.3, 22.6, 20.3, and 11.6 ppm (± 0.2 ppm, respectively).

Compound A Tromethamine Salt Form C

[25] In another aspect, provided is a crystalline tromethamine salt of 2-[[(1R)-1-(3,6-

dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid, referred to as Compound A Tromethamine Salt Form C. In an embodiment, Compound A Tromethamine Salt Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 10.6° ± 0.2°, 13.2° ± 0.2°, 14.5° ± 0.2°, 15.9° ± 0.2°, and 17.4° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 15.9° ± 0.2° in combination with at least one peak selected from 10.6° ± 0.2°, 17.4° ± 0.2°, 13.2° ± 0.2°, and 14.5° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 15.9° ± 0.2° in combination with at least two peaks selected from 10.6° ± 0.2°, 17.4° ± 0.2°, 13.2° ± 0.2°, and 14.5° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 15.9° ± 0.2° in combination with at least three peaks selected from 10.6° ± 0.2°, 17.4° ± 0.2°, 13.2° ± 0.2°, and 14.5° ± 0.2°. In an embodiment, Compound A Tromethamine Salt Form C is characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 10.6° ± 0.2°, 13.2° ± 0.2°, 14.5° ± 0.2°, 15.9° ± 0.2°, and 17.4° ± 0.2°.

Compound A Tromethamine Salt Form D

[26] In another aspect, provided is a crystalline tromethamine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid, referred to as Compound A Tromethamine Salt Form D. In an embodiment, Compound A Tromethamine Salt Form D is characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.3° ± 0.2°, 11.1° ± 0.2°, 12.6° ± 0.2°, 17.1° ± 0.2°, and 18.9° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form D is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least one peak selected from 12.6° ± 0.2°, 17.1° ± 0.2°, 6.3° ± 0.2°, and 18.9° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form D is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least two peaks selected from 12.6° ± 0.2°, 17.1° ± 0.2°, 6.3° ±

0.2°, and 18.9° ± 0.2°. In another embodiment, Compound A Tromethamine Salt Form D is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least three peaks selected from 12.6° ± 0.2°, 17.1° ± 0.2°, 6.3° ± 0.2°, and 18.9° ± 0.2°. In an embodiment, Compound A Tromethamine Salt Form D is characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 6.3° ± 0.2°, 11.1° ± 0.2°, 12.6° ± 0.2°, 17.1° ± 0.2°, and 18.9° ± 0.2°.

[27] In another aspect, provided herein is an erbumine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid. Certain erbumine salts of Compound A may have advantageous physical stability, chemical stability, solubility, or pharmacokinetic properties. Certain erbumine salts of Compound A may have processability or other manufacturing advantages.

Compound A Erbumine Salt Form A

[28] In another aspect, provided is a crystalline erbumine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid, referred to as Compound A Erbumine Salt Form A. In an embodiment, Compound A Erbumine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.5° ± 0.2°, 10.5° ± 0.2°, 11.1° ± 0.2°, 15.2° ± 0.2°, 15.9° ± 0.2°, 17.6° ± 0.2°, 18.0° ± 0.2°, 19.3° ± 0.2°, 21.5° ± 0.2°, 22.2° ± 0.2°, 22.7° ± 0.2°, and 26.3° ± 0.2°. In another embodiment, Compound A Erbumine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least one peak selected from 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°. In another embodiment, Compound A Erbumine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least two peaks selected from 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°. In another embodiment, Compound A Erbumine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least three peaks selected from 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°. In another embodiment, Compound A Erbumine Salt Form A is characterized by an X-ray

powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with the peaks 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°. In an embodiment, Compound A Erbumine Salt Form A is characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 66.5° ± 0.2°, 10.5° ± 0.2°, 11.1° ± 0.2°, 15.2° ± 0.2°, 15.9° ± 0.2°, 17.6° ± 0.2°, 18.0° ± 0.2°, 19.3° ± 0.2°, 21.5° ± 0.2°, 22.2° ± 0.2°, 22.7° ± 0.2°, and 26.3° ± 0.2°.

[29] In another embodiment, Compound A Erbumine Salt Form A is characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 177.4, 174.8, 159.8, 151.7, 149.5, 134.0, 132.6, 130.7, 130.3, 129.0, 128.1, 123.1, 122.4, 119.4, 116.8, 115.9, 112.3, 53.0, 47.5, 27.4, 23.3, 21.3, and 11.3 ppm (± 0.2 ppm, respectively). In another embodiment, Compound A Erbumine Salt Form A is characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 177.4, 132.6, 27.4, 21.3, and 11.3 ppm (± 0.2 ppm, respectively). In another embodiment, Compound A Erbumine Salt Form A is characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises peaks referenced to glycine (external reference at 176.5 ppm) at: 177.4, 174.8, 159.8, 151.7, 149.5, 134.0, 132.6, 130.7, 130.3, 129.0, 128.1, 123.1, 122.4, 119.4, 116.8, 115.9, 112.3, 53.0, 47.5, 27.4, 23.3, 21.3, and 11.3 ppm (± 0.2 ppm, respectively).

Therapeutic Uses

[30] Also provided herein are therapies including Compound A, or a pharmaceutically acceptable salt thereof, for the treatment of patients with a disease, including PIK3CA-mutated cancer, such as PIK3CA-mutated advanced or metastatic breast cancer, or other solid tumors with a PIK3CA mutation. Compound A, or a pharmaceutically acceptable salt thereof, may be used in monotherapy or in combination with one or more additional therapeutic agents. The therapies may provide new treatment options for patients, and may provide an enhanced and/or unexpected beneficial therapeutic effect in some patients over known therapies.

[31] The efficacy of a cancer treatment can be measured by various endpoints commonly used in evaluating cancer treatments, including but not limited to, tumor regression, tumor weight or size shrinkage, time to progression, overall survival, progression free survival,

overall response rate, duration of response, best overall response, disease control rate, clinical benefit rate, time to response, and quality of life. Therapeutic agents may cause inhibition of metastatic spread without shrinkage of the primary tumor, may induce shrinkage of the primary tumor, or may simply exert a tumoristatic effect. Novel approaches to determining efficacy of any particular mono- or combination therapy of the present invention can be optionally employed, including, for example, measurement of plasma or urinary markers of angiogenesis and/or cell cycle activity, tissue-based biomarkers for angiogenesis and/or cell cycle activity, and measurement of response through radiological imaging.

[32] In one aspect, provided is a method of treating a patient with a disease associated with mutant phosphoinositide 3-kinase (PI3K), comprising administering to the patient an effective amount of Compound A, or a pharmaceutically acceptable salt thereof.

[33] In another aspect, provided is a method of treating a patient with PIK3CA-mutated cancer, comprising administering to the patient an effective amount of Compound A, or a pharmaceutically acceptable salt thereof.

[34] In another aspect, provided is a method of treating a patient with a PIK3CA-mutated solid tumor, comprising administering to the patient an effective amount of Compound A, or a pharmaceutically acceptable salt thereof.

[35] In another aspect, provided is a method of treating a patient with PIK3CA-mutated breast cancer, comprising administering to the patient an effective amount of Compound A, or a pharmaceutically acceptable salt thereof.

[36] In another aspect, provided is a method of treating a patient with PIK3CA-mutated, advanced or metastatic breast cancer, comprising administering to the patient an effective amount of Compound A, or a pharmaceutically acceptable salt thereof.

[37] In another aspect, provided is a method of treating a patient with CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal, and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS), comprising administering to the patient an effective amount of Compound A, or a pharmaceutically acceptable salt thereof.

[38] In another aspect, provided is Compound A, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease associated with mutant phosphoinositide 3-kinase (PI3K).

[39] In another aspect, provided is Compound A, or a pharmaceutically acceptable salt

thereof, for use in the treatment of PIK3CA-mutated cancer.

[40] In another aspect, provided is Compound A, or a pharmaceutically acceptable salt thereof, for use in the treatment of a PIK3CA-mutated solid tumor.

[41] In another aspect, provided is Compound A, or a pharmaceutically acceptable salt thereof, for use in the treatment of PIK3CA-mutated breast cancer.

[42] In another aspect, provided is Compound A, or a pharmaceutically acceptable salt thereof, for use in the treatment of PIK3CA-mutated, advanced or metastatic breast cancer.

[43] In another aspect, provided is Compound A, or a pharmaceutically acceptable salt thereof, for use in the treatment of CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal, and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS).

[44] In another aspect, provided is the use of Compound A, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease associated with mutant phosphoinositide 3-kinase (PI3K).

[45] In another aspect, provided is the use of Compound A, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of PIK3CA-mutated cancer.

[46] In another aspect, provided is the use of Compound A, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a PIK3CA-mutated solid tumor.

[47] In another aspect, provided is the use of Compound A, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of PIK3CA-mutated breast cancer.

[48] In another aspect, provided is the use of Compound A, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of PIK3CA-mutated, advanced or metastatic breast cancer.

[49] In another aspect, provided is the use of Compound A, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal, and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS).

[50] In an embodiment, the PIK3CA-mutated cancer is selected from acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, aids-related

cancers, aids-related lymphoma, anal cancer, astrocytoma, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, malignant fibrous histiocytoma, brain tumors, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, cancer of unknown primary, cardiac (heart) tumors, atypical teratoid/rhabdoid tumor, primary CNS lymphoma, cervical cancer, cholangiocarcinoma, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colorectal cancer, craniopharyngioma, cutaneous t-cell lymphoma, mycosis fungoides, Sézary syndrome, ductal carcinoma in situ (DCIS), embryonal tumors, medulloblastoma, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, fallopian tube cancer, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, malignant gastrointestinal stromal tumors (GIST), germ cell tumors, gestational trophoblastic disease, hairy cell leukemia, head and neck cancer, hepatocellular cancer, Langerhans cell histiocytosis, Hodgkin lymphoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, laryngeal cancer, leukemia, liver cancer, lung cancer, lymphoma, male breast cancer, intraocular melanoma, Merkel cell carcinoma, malignant mesothelioma, metastatic cancer, metastatic squamous neck cancer, midline tract carcinoma with nut gene changes, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasms, myelodysplastic syndromes, myelodysplastic neoplasms, myeloproliferative neoplasms, chronic myeloproliferative neoplasm, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, lip and oral cavity cancer, oropharyngeal cancer, malignant fibrous histiocytoma of bone, ovarian cancer, pancreatic cancer, pancreatic neuroendocrine tumors (islet cell tumors), papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pituitary tumor, plasma cell neoplasm, multiple myeloma, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, recurrent cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, childhood vascular tumors, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma of the skin, testicular cancer, oropharyngeal cancer, hypopharyngeal cancer, thymoma, thymic carcinoma, thyroid cancer, tracheobronchial tumors, transitional cell cancer of the renal pelvis and ureter, urethral cancer, uterine

sarcoma, vaginal cancer, vascular tumors, vulvar cancer, and Wilms tumor.

[51] In an embodiment, the PIK3CA-mutated cancer is endometrial cancer, breast cancer, oesophageal squamous-cell cancer, cervical squamous-cell carcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, glioblastoma, ovarian cancer, non-small-cell lung cancer, esophagogastric cancer, nerve-sheath tumor, head and neck squamous-cell carcinoma, melanoma, esophagogastric adenocarcinoma, soft-tissue sarcoma, prostate cancer, fibrolamellar carcinoma, hepatocellular carcinoma, diffuse glioma, colorectal cancer, pancreatic cancer, cholangiocarcinoma, B-cell lymphoma, mesothelioma, adrenocortical carcinoma, renal non-clear-cell carcinoma, renal clear-cell carcinoma, germ-cell carcinoma, thymic tumor, pheochromocytoma, miscellaneous neuroepithelial tumor, thyroid cancer, leukemia, or encapsulated glioma.

[52] In an embodiment, the PIK3CA-mutated cancer is breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer.

[53] In an embodiment, the PIK3CA-mutated cancer is breast cancer, prostate cancer, or brain cancer. In an embodiment, the PIK3CA-mutated cancer is breast cancer. In an embodiment, the PIK3CA-mutated cancer is prostate cancer. In an embodiment, the PIK3CA-mutated cancer is brain cancer.

[54] In an embodiment, the PIK3CA-mutated cancer is a breast neoplasm, a thyroid neoplasm, an ovarian neoplasm, non-small-cell lung carcinoma, an endometrial neoplasm, or a pancreatic neoplasm. In an embodiment, the PIK3CA-mutated cancer is a breast neoplasm. In an embodiment, the PIK3CA-mutated cancer is a thyroid neoplasm. In an embodiment, the PIK3CA-mutated cancer is an ovarian neoplasm. In an embodiment, the PIK3CA-mutated cancer is non-small-cell lung carcinoma. In an embodiment, the PIK3CA-mutated cancer is an endometrial neoplasm. In an embodiment, the PIK3CA-mutated cancer is a pancreatic neoplasm.

[55] In an embodiment, the PIK3CA-mutated, advanced or metastatic breast cancer is PIK3CA H1047R-mutant advanced or metastatic breast cancer. In an embodiment, the PIK3CA-mutated, advanced or metastatic breast cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA-mutated, advanced or metastatic breast cancer. In an embodiment, the PIK3CA-mutated, advanced or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-

negative (HER2-), PIK3CA-mutated, advanced or metastatic breast cancer. In an embodiment, the PIK3CA-mutated, advanced or metastatic breast cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA H1047R-mutant, advanced or metastatic breast cancer. In an embodiment, the PIK3CA-mutated, advanced or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA H1047R-mutant, advanced or metastatic breast cancer.

[56] In an embodiment, the PIK3CA-mutated solid tumor is a PIK3CA-mutated advanced solid tumor. In an embodiment, the PIK3CA-mutated advanced solid tumor is selected from gynecological cancer, head and neck cancer, and triple negative breast cancer. In an embodiment, the PIK3CA-mutated advanced solid tumor is gynecological cancer. In an embodiment, the PIK3CA-mutated advanced solid tumor is head and neck cancer. In an embodiment, the PIK3CA-mutated advanced solid tumor is triple negative breast cancer.

Pharmaceutical Compositions

[57] Compound A, or a pharmaceutically salt thereof, can be formulated for oral administration in forms such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Compound A, or a pharmaceutically salt thereof can also be formulated for intravenous (bolus or in-fusion), intraperitoneal, topical, subcutaneous, intramuscular or transdermal (*e.g.*, patch) administration, all using forms well known to those of ordinary skill in the pharmaceutical arts.

[58] Compound A, or a pharmaceutically salt thereof, or a pharmaceutical composition thereof, may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

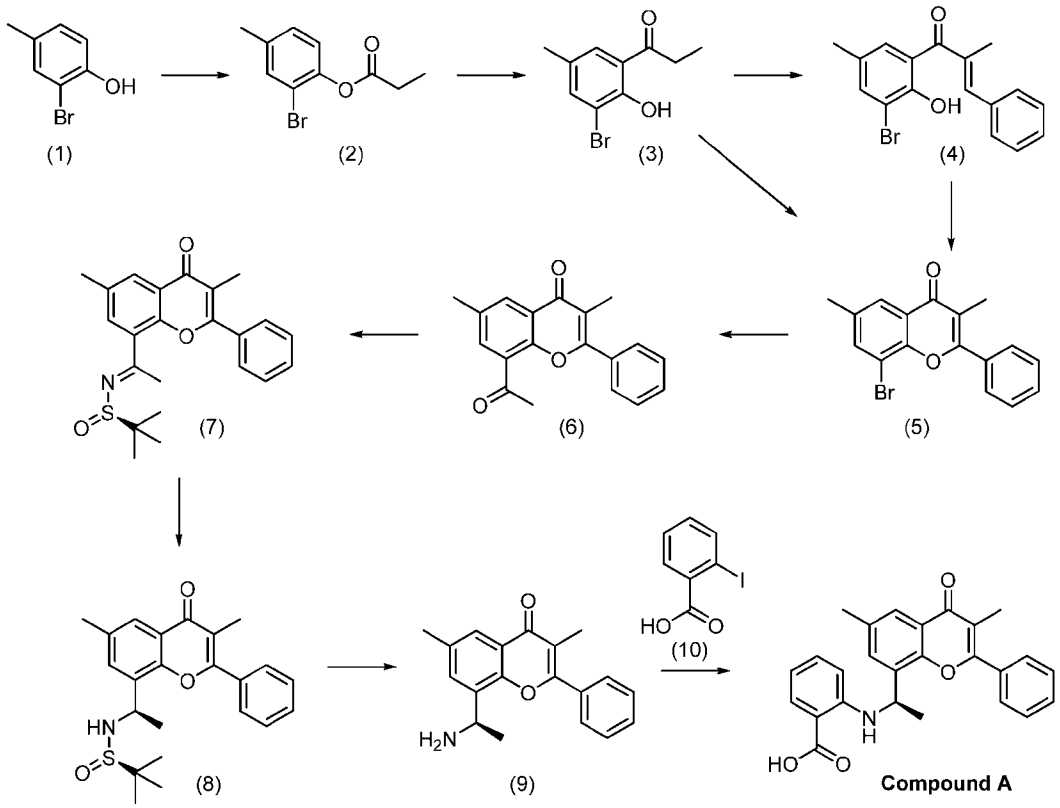
[59] Routes of administration include, but are not limited to, oral (e.g. by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular,

intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

Synthetic Methods

[60] Compound A can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Compound A can be synthesized by following the steps outlined in General Schemes 1 and 2. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated below.

Scheme 1

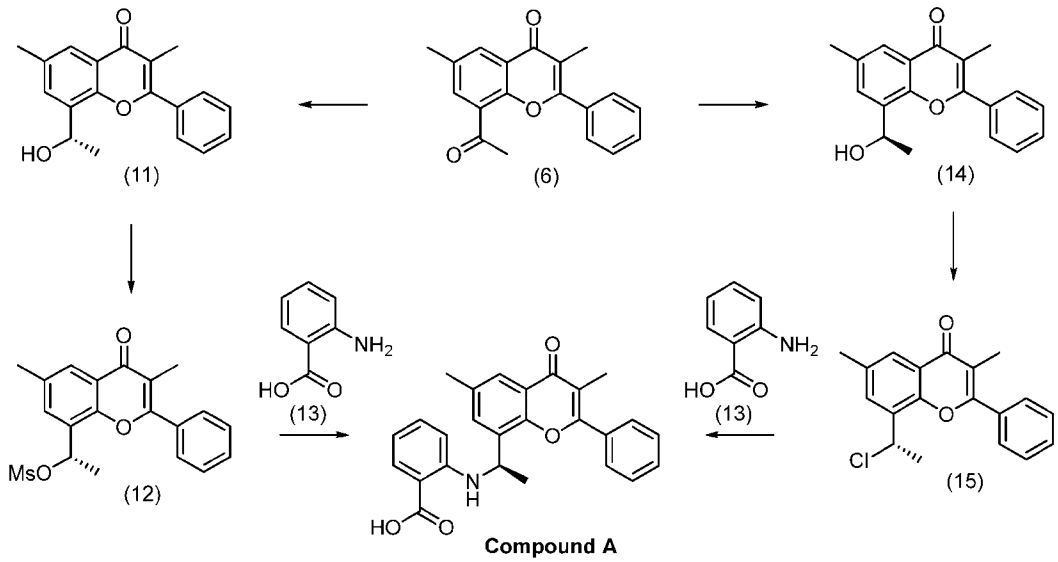


[61] Scheme 1 depicts an exemplary preparation of Compund A. Acylation of substituted

phenol (1) can provide ester (2). Ester (2) can undergo rearrangement under Lewis acid (e.g., $AlCl_3$) or Bronsted acid (e.g., triflic acid) conditions to the hydroxy aryl ketone (3). Acidic condensation of an aryl aldehyde with hydroxy aryl ketone (3) can provide keto-alkene (4) which can cyclize to the 2-substituted chromen-4-one (5). Alternatively, alkylation of hydroxy aryl ketone (3) with an aryl halide in the presence of a base (e.g., pyridine or lithium bis(trimethylsilyl)amide), followed by acidic conditions (e.g., HCl) can affect cyclization to 2-substituted chromen-4-one (5).

[62] Phenyl bromide (5) can be acylated via palladium catalysis to produce acyl chromen-4-one (6). Exemplary palladium catalysis conditions include phenyl bromide (5), about 5-10 mol% $PdCl_2(Ph_3)_2$ and about 1.2 mol% tributyl(1-ethoxyvinyl)stannane in about 30-35 equivalents dioxane at 95°C for about 16 hours; or phenyl bromide (5), about 1 mol% $Pd(OAc)_2$, about 2 mol% 1,3-bis(diphenylphosphino)propane, about 5 equivalents butyl vinyl ether, about 3 equivalents triethylamine, and about 10 volumes of ethylene glycol at about 100°C for about 16 hours. Condensation of ketone (6) with tert-butanesulfinamide using a Lewis acidic dehydrating agent such as a titanium(IV) alkoxide can afford ketimine (7). Asymmetric reduction of sulfinimine (7) can be affected with a borohydride reagent in the presence of a transition metal catalyst such as cerium (III) chloride to yield chirally enriched sulfinamide (8). Removal of the sulfinyl group under acidic conditions may be used to transform sulfinamide (8) to benzylamine (9) which can be alkylated with aryl halide (10) under Finkelstein or Ullmann-type conditions to give Compound A.

Scheme 2



[63] Scheme 2 depicts another exemplary preparation of Compound A. Ketone (6) can be reduced to hydroxy compound (11) with a chiral catalyst such as the Noyori catalyst. The hydroxyl group can be converted into a leaving group with methanesulfonic anhydride or methanesulfonyl chloride to give mesylate (12). Mesylate (12) can be used to alkylate arylamine (13) to give Compound A. Alternatively, ketone (6) can be reduced to hydroxy compound (14) with a chiral catalyst such as the Noyori catalyst. The hydroxyl group can be converted to chloride (15) with a chlorinating agent such as 2,4,6-trichloro-1,3,5-triazine. Chloride (15) can then be used to alkylate arylamine (13) to give Compound A.

Definitions

[64] As used herein, the terms "treating", "to treat", or "treatment" refer to restraining, slowing, stopping, reducing, shrinking, maintaining stable disease, or reversing the progression or severity of an existing symptom, disorder, condition, or disease.

[65] As used herein, the term "patient" refers to a mammal, preferably, a human.

[66] As used herein, the terms "cancer" and "cancerous" refer to or describe the physiological condition in patients that is typically characterized by unregulated cell proliferation. Included in this definition are benign and malignant cancers.

[67] As used herein, the term "advanced" or "metastatic" means cancers that have spread to

one or more parts of the body that were not the site of the original cancerous tissue.

[68] As used herein, the term "effective amount" refers to the amount or dose of a therapeutic agent, or a pharmaceutically acceptable salt thereof, for example Compound A or a pharmaceutically acceptable salt thereof, optionally in combination with one or more additional agents, or a pharmaceutically acceptable salt thereof, which provides an effective response in the patient under diagnosis or treatment.

[69] As used herein, the term "effective response" of a patient or a patient's "responsiveness" to treatment with a therapeutic agent, or a pharmaceutically acceptable salt thereof, refers to the clinical or therapeutic benefit imparted to a patient upon administration of the therapeutic agent, or pharmaceutically acceptable salt thereof, optionally in combination with one or more additional agents, or a pharmaceutically acceptable salt thereof.

[70] As used herein, the term "in combination with" refers to the administration of a therapeutic agent, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents, or a pharmaceutically acceptable salt thereof, either separately, simultaneously or sequentially in any order, such as for example, at repeated intervals as during a standard course of treatment for a single cycle or more than one cycle, such that one agent can be administered prior to, at the same time, or subsequent to the administration of the other agent, or any combination thereof.

[71] As used herein, the term "tromethamine" may otherwise be referred to as tris(hydroxymethyl)aminomethane or tris.

[72] As used herein, the term "erbumine" may otherwise be referred to as *tert*-butylamine.

Exemplary Aspects

[73] Various aspects of the invention are set forth in the following numbered clauses.

[74] Clause 1. A compound that is 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid; or a pharmaceutically acceptable salt thereof.

[75] Clause 2. A compound that is 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid.

[76] Clause 3. A compound that is crystalline 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid.

[77] Clause 4. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta

selected from 7.8° ± 0.2°, 12.1° ± 0.2°, 13.7° ± 0.2°, 14.1° ± 0.2°, 16.8° ± 0.2°, 17.5° ± 0.2°, 18.2° ± 0.2°, 18.9° ± 0.2°, 19.5° ± 0.2°, 20.7° ± 0.2°, 21.2° ± 0.2°, and 24.1° ± 0.2°.

[78] Clause 5. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 12.1° ± 0.2° in combination with at least one peak selected from 14.1° ± 0.2°, 16.8° ± 0.2°, 18.9° ± 0.2°, and 20.7° ± 0.2°.

[79] Clause 6. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 12.1° ± 0.2° in combination with at least two peaks selected from 14.1° ± 0.2°, 16.8° ± 0.2°, 18.9° ± 0.2°, and 20.7° ± 0.2°.

[80] Clause 7. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 12.1° ± 0.2° in combination with at least three peaks selected from 14.1° ± 0.2°, 16.8° ± 0.2°, 18.9° ± 0.2°, and 20.7° ± 0.2°.

[81] Clause 8. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 12.1° ± 0.2° in combination with the peaks 14.1° ± 0.2°, 16.8° ± 0.2°, 18.9° ± 0.2°, and 20.7° ± 0.2°.

[82] Clause 9. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 7.8° ± 0.2°, 12.1° ± 0.2°, 13.7° ± 0.2°, 14.1° ± 0.2°, 16.8° ± 0.2°, 17.5° ± 0.2°, 18.2° ± 0.2°, 18.9° ± 0.2°, 19.5° ± 0.2°, 20.7° ± 0.2°, 21.2° ± 0.2°, and 24.1° ± 0.2°.

[83] Clause 10. The compound of any one of clauses 1-3, having an X-ray powder diffraction pattern substantially as shown in FIG. 1.

[84] Clause 11. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 7.0° ± 0.2°, 9.7° ± 0.2°, 11.9° ± 0.2°, 14.9° ± 0.2°, and 17.4° ± 0.2°.

[85] Clause 12. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 9.7° ± 0.2° in combination with at least one peak selected from 14.9° ± 0.2°, 11.9° ± 0.2°, 17.4° ± 0.2°, and 7.0° ± 0.2°.

[86] Clause 13. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 9.7° ±

0.2° in combination with at least two peaks selected from 14.9° ± 0.2°, 11.9° ± 0.2°, 17.4° ± 0.2°, and 7.0° ± 0.2°.

[87] Clause 14. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 9.7° ± 0.2° in combination with at least three peaks selected from 14.9° ± 0.2°, 11.9° ± 0.2°, 17.4° ± 0.2°, and 7.0° ± 0.2°.

[88] Clause 15. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 7.0° ± 0.2°, 9.7° ± 0.2°, 11.9° ± 0.2°, 14.9° ± 0.2°, and 17.4° ± 0.2°.

[89] Clause 16. The compound of any one of clauses 1-3, having an X-ray powder diffraction pattern substantially as shown in FIG. 2.

[90] Clause 17. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 7.4° ± 0.2°, 8.5° ± 0.2°, 10.6° ± 0.2°, 13.4° ± 0.2°, and 15.7° ± 0.2°.

[91] Clause 18. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 13.4° ± 0.2° in combination with at least one peak selected from 8.5° ± 0.2°, 15.7° ± 0.2°, 10.6° ± 0.2°, and 7.4° ± 0.2°.

[92] Clause 19. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 13.4° ± 0.2° in combination with at least two peaks selected from 8.5° ± 0.2°, 15.7° ± 0.2°, 10.6° ± 0.2°, and 7.4° ± 0.2°.

[93] Clause 20. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 13.4° ± 0.2° in combination with at least three peaks selected from 8.5° ± 0.2°, 15.7° ± 0.2°, 10.6° ± 0.2°, and 7.4° ± 0.2°.

[94] Clause 21. The compound of any one of clauses 1-3, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 7.4° ± 0.2°, 8.5° ± 0.2°, 10.6° ± 0.2°, 13.4° ± 0.2°, and 15.7° ± 0.2°.

[95] Clause 22. The compound of any one of clauses 1-3, having an X-ray powder diffraction pattern substantially as shown in FIG. 3.

[96] Clause 23. A tromethamine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-

yl)ethyl]amino]benzoic acid.

[97] Clause 24. The tromethamine salt of clause 23, that is crystalline.

[98] Clause 25. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.4° ± 0.2°, 8.4° ± 0.2°, 10.9° ± 0.2°, 11.8° ± 0.2°, 13.0° ± 0.2°, 16.5° ± 0.2°, 16.9° ± 0.2°, 22.1° ± 0.2°, 23.0° ± 0.2°, and 24.9° ± 0.2°.

[99] Clause 26. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with at least one peak selected from 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°.

[100] Clause 27. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with at least two peaks selected from 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°.

[101] Clause 28. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with at least three peaks selected from 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°.

[102] Clause 29. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with the peaks 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°.

[103] Clause 30. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 6.4° ± 0.2°, 8.4° ± 0.2°, 10.9° ± 0.2°, 11.8° ± 0.2°, 13.0° ± 0.2°, 16.5° ± 0.2°, 16.9° ± 0.2°, 22.1° ± 0.2°, 23.0° ± 0.2°, and 24.9° ± 0.2°.

[104] Clause 31. The tromethamine salt of clause 23 or clause 24, having an X-ray powder diffraction pattern substantially as shown in FIG. 4.

[105] Clause 32. The tromethamine salt of any one of clauses 23-31, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 179.0, 158.7, 151.7, 149.7, 136.3, 134.7, 132.9, 129.3, 127.4, 125.2, 121.7, 117.0, 115.5, 115.2, 110.4, 64.1, 63.2, 45.3, 22.6,

20.3, and 11.6 ppm (± 0.2 ppm, respectively).

[106] Clause 33. The tromethamine salt of any one of clauses 23-31, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 179.0, 129.3, 63.2, 20.3, and 11.6 ppm (± 0.2 ppm, respectively).

[107] Clause 34. The tromethamine salt of any one of clauses 23-31, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises peaks referenced to glycine (external reference at 176.5 ppm) at: 179.0, 129.3, 63.2, 20.3, and 11.6 ppm (± 0.2 ppm, respectively).

[108] Clause 35. The tromethamine salt of any one of clauses 23-31, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises peaks referenced to glycine (external reference at 176.5 ppm) at: 179.0, 158.7, 151.7, 149.7, 136.3, 134.7, 132.9, 129.3, 127.4, 125.2, 121.7, 117.0, 115.5, 115.2, 110.4, 64.1, 63.2, 45.3, 22.6, 20.3, and 11.6 ppm (± 0.2 ppm, respectively).

[109] Clause 36. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 10.6° ± 0.2°, 13.2° ± 0.2°, 14.5° ± 0.2°, 15.9° ± 0.2°, and 17.4° ± 0.2°.

[110] Clause 37. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 15.9° ± 0.2° in combination with at least one peak selected from 10.6° ± 0.2°, 17.4° ± 0.2°, 13.2° ± 0.2°, and 14.5° ± 0.2°.

[111] Clause 38. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 15.9° ± 0.2° in combination with at least two peaks selected from 10.6° ± 0.2°, 17.4° ± 0.2°, 13.2° ± 0.2°, and 14.5° ± 0.2°.

[112] Clause 39. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 15.9° ± 0.2° in combination with at least three peaks selected from 10.6° ± 0.2°, 17.4° ± 0.2°, 13.2° ± 0.2°, and 14.5° ± 0.2°.

[113] Clause 40. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of

10.6° ± 0.2°, 13.2° ± 0.2°, 14.5° ± 0.2°, 15.9° ± 0.2°, and 17.4° ± 0.2°.

[114] Clause 41. The tromethamine salt of clause 23 or clause 24, having an X-ray powder diffraction pattern substantially as shown in FIG. 5.

[115] Clause 42. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.3° ± 0.2°, 11.1° ± 0.2°, 12.6° ± 0.2°, 17.1° ± 0.2°, and 18.9° ± 0.2°.

[116] Clause 43. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least one peak selected from 12.6° ± 0.2°, 17.1° ± 0.2°, 6.3° ± 0.2°, and 18.9° ± 0.2°.

[117] Clause 44. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least two peaks selected from 12.6° ± 0.2°, 17.1° ± 0.2°, 6.3° ± 0.2°, and 18.9° ± 0.2°.

[118] Clause 45. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least three peaks selected from 12.6° ± 0.2°, 17.1° ± 0.2°, 6.3° ± 0.2°, and 18.9° ± 0.2°.

[119] Clause 46. The tromethamine salt of clause 23 or clause 24, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 6.3° ± 0.2°, 11.1° ± 0.2°, 12.6° ± 0.2°, 17.1° ± 0.2°, and 18.9° ± 0.2°.

[120] Clause 47. The tromethamine salt of clause 23 or clause 24, having an X-ray powder diffraction pattern substantially as shown in FIG. 6.

[121] Clause 48. An erbumine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid.

[122] Clause 49. The erbumine salt of clause 48, that is crystalline.

[123] Clause 50. The erbumine salt of clause 48 or clause 49, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.5° ± 0.2°, 10.5° ± 0.2°, 11.1° ± 0.2°, 15.2° ± 0.2°, 15.9° ± 0.2°, 17.6° ± 0.2°, 18.0° ± 0.2°, 19.3° ± 0.2°, 21.5° ± 0.2°, 22.2° ± 0.2°, 22.7° ± 0.2°, and 26.3° ± 0.2°.

[124] Clause 51. The erbumine salt of clause 48 or clause 49, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of

11.1 ° ± 0.2° in combination with at least one peak selected from 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°.

[125] Clause 52. The erbumine salt of clause 48 or clause 49, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1 ° ± 0.2° in combination with at least two peaks selected from 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°.

[126] Clause 53. The erbumine salt of clause 48 or clause 49, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1 ° ± 0.2° in combination with at least three peaks selected from 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°.

[127] Clause 54. The erbumine salt of clause 48 or clause 49, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1 ° ± 0.2° in combination with the peaks 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°.

[128] Clause 55. The erbumine salt of clause 48 or clause 49, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 66.5° ± 0.2°, 10.5° ± 0.2°, 11.1° ± 0.2°, 15.2° ± 0.2°, 15.9° ± 0.2°, 17.6° ± 0.2°, 18.0° ± 0.2°, 19.3° ± 0.2°, 21.5° ± 0.2°, 22.2° ± 0.2°, 22.7° ± 0.2°, and 26.3° ± 0.2°.

[129] Clause 56. The erbumine salt of clause 48 or clause 49, having an X-ray powder diffraction pattern substantially as shown in FIG. 7.

[130] Clause 57. The erbumine salt of any one of clauses 48-56, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 177.4, 174.8, 159.8, 151.7, 149.5, 134.0, 132.6, 130.7, 130.3, 129.0, 128.1, 123.1, 122.4, 119.4, 116.8, 115.9, 112.3, 53.0, 47.5, 27.4, 23.3, 21.3, and 11.3 ppm (± 0.2 ppm, respectively).

[131] Clause 58. The erbumine salt of any one of clauses 48-56, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 177.4, 132.6, 27.4, 21.3, and 11.3 ppm (± 0.2 ppm, respectively).

[132] Clause 59. The erbumine salt of any one of clauses 48-56, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises peaks referenced to glycine (external

reference at 176.5 ppm) at: 177.4, 132.6, 27.4, 21.3, and 11.3 ppm (± 0.2 ppm, respectively).

[133] Clause 60. The erbumine salt of any one of clauses 48-56, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises peaks referenced to glycine (external reference at 176.5 ppm) at: 177.4, 174.8, 159.8, 151.7, 149.5, 134.0, 132.6, 130.7, 130.3, 129.0, 128.1, 123.1, 122.4, 119.4, 116.8, 115.9, 112.3, 53.0, 47.5, 27.4, 23.3, 21.3, and 11.3 ppm (± 0.2 ppm, respectively).

[134] Clause 61. A pharmaceutical composition comprising a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, or an erbumine salt of any one of clauses 48-60, and a pharmaceutically acceptable carrier.

[135] Clause 62. A method of inhibiting phosphoinositide 3-kinase (PI3K), comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61.

[136] Clause 63. A method of treating a patient with a disease associated with mutant phosphoinositide 3-kinase (PI3K), comprising administering to the patient a therapeutically effective amount of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61.

[137] Clause 64. The method of clause 62 or clause 63, wherein the PI3K is PI3Kα.

[138] Clause 65. The method of any one of clauses 62-64, wherein the PI3K has a H1047R mutation.

[139] Clause 66. The method of any one of clauses 63-65, wherein the disease is a cancer.

[140] Clause 67. The method of clause 66, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

[141] Clause 68. The method of clause 66, wherein the cancer is breast cancer.

[142] Clause 69. The method of clause 66, wherein the cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.

[143] Clause 70. The method of any one of clauses 63-65, wherein the disease is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi,

scoliosis/skeletal, and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS).

[144] Clause 71. A method of treating a patient with PIK3CA-mutated cancer, comprising administering to the patient an effective amount of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61.

[145] Clause 72. A method of treating a patient with a PIK3CA-mutated solid tumor, comprising administering to the patient an effective amount of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61.

[146] Clause 73. A method of treating a patient with PIK3CA-mutated breast cancer, comprising administering to the patient an effective amount of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61.

[147] Clause 74. A method of treating a patient with PIK3CA-mutated, advanced or metastatic breast cancer, comprising administering to the patient an effective amount of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61.

[148] Clause 75. The method of clause 71, wherein the PIK3CA-mutated cancer is PIK3CA H1047R-mutant cancer.

[149] Clause 76. The method of clause 72, wherein the PIK3CA-mutated solid tumor is a PIK3CA H1047R-mutant solid tumor.

[150] Clause 77. The method of clause 72, wherein the PIK3CA-mutated solid tumor is selected from gynecological cancer, head and neck cancer, and triple negative breast cancer.

[151] Clause 78. The method of clause 77, wherein the PIK3CA-mutated solid tumor is gynecological cancer.

[152] Clause 79. The method of clause 77, wherein the PIK3CA-mutated solid tumor is head and neck cancer.

[153] Clause 80. The method of clause 77, wherein the PIK3CA-mutated solid tumor is triple negative breast cancer.

[154] Clause 81. The method according to clause 73, wherein the PIK3CA-mutated breast cancer is PIK3CA H1047R-mutant breast cancer.

[155] Clause 82. The method according to clause 74, wherein the PIK3CA-mutated,

advanced or metastatic breast cancer is PIK3CA H1047R-mutant advanced or metastatic breast cancer.

[156] Clause 83. The method according to clause 74, wherein the PIK3CA-mutated, advanced or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA-mutated, advanced or metastatic breast cancer.

[157] Clause 84. The method according to clause 74, wherein the PIK3CA-mutated, advanced or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA H1047R-mutant, advanced or metastatic breast cancer.

[158] Clause 85. A compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, for use in therapy.

[159] Clause 86. A compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, for use in treating a disease associated with mutant phosphoinositide 3-kinase (PI3K).

[160] Clause 87. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to clause 86, wherein the PI3K is PI3Kα.

[161] Clause 88. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to clause 86 or 87, wherein the PI3K has a H1047R mutation.

[162] Clause 89. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to any one of clauses 86-88, wherein the disease is a cancer.

[163] Clause 90. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to clause 89, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

[164] Clause 91. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to clause 89, wherein the cancer is breast cancer.

[165] Clause 92. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to clause 89, wherein the cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic

breast cancer.

[166] Clause 93. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to any one of clauses 86-88, wherein the disease is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal, and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS).

[167] Clause 94. A compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, for use in the treatment of PIK3CA-mutated cancer.

[168] Clause 95. A compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, for use in the treatment of a PIK3CA-mutated solid tumor.

[169] Clause 96. A compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, for use in the treatment of PIK3CA-mutated breast cancer.

[170] Clause 97. A compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, for use in the treatment of PIK3CA-mutated, advanced or metastatic breast cancer.

[171] Clause 98. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 94, wherein the PIK3CA-mutated cancer is PIK3CA H1047R-mutant cancer.

[172] Clause 99. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 95, wherein the PIK3CA-mutated solid tumor is a PIK3CA H1047R-mutant solid tumor.

[173] Clause 100. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 95, wherein the PIK3CA-mutated solid tumor is selected from gynecological cancer, head and neck cancer, and triple negative breast cancer.

[174] Clause 101. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 100, wherein the PIK3CA-mutated solid tumor is gynecological cancer.

[175] Clause 102. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 100, wherein the PIK3CA-mutated solid tumor is

head and neck cancer.

[176] Clause 103. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 100, wherein the PIK3CA-mutated solid tumor is triple negative breast cancer.

[177] Clause 104. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 96, wherein the PIK3CA-mutated breast cancer is PIK3CA H1047R-mutant breast cancer.

[178] Clause 105. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 97, wherein the PIK3CA-mutated, advanced or metastatic breast cancer is PIK3CA H1047R-mutant advanced or metastatic breast cancer.

[179] Clause 106. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 97, wherein the PIK3CA-mutated, advanced or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA-mutated, advanced or metastatic breast cancer.

[180] Clause 107. The compound, tromethamine salt, erbumine salt, or pharmaceutical composition for use according to clause 97, wherein the PIK3CA-mutated, advanced or metastatic breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA H1047R-mutant, advanced or metastatic breast cancer.

[181] Clause 108. The use of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, in the manufacture of a medicament for the treatment of PIK3CA-mutated cancer.

[182] Clause 109. The use of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, in the manufacture of a medicament for the treatment of a PIK3CA-mutated solid tumor.

[183] Clause 110. The use of a compound of any one of clauses 1-22, a tromethamine salt of any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, in the manufacture of a medicament for the treatment of PIK3CA-mutated breast cancer.

[184] Clause 111. The use of a compound of any one of clauses 1-22, a tromethamine salt of

any one of clauses 23-47, an erbumine salt of any one of clauses 48-60, or a pharmaceutical composition of clause 61, in the manufacture of a medicament for the treatment of PIK3CA-mutated, advanced or metastatic breast cancer.

Examples

[185] Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz or 300 MHz as stated and at 300.3 K unless otherwise stated; the chemical shifts (δ) are reported in parts per million (ppm). Spectra were recorded using a Bruker or Varian instrument with 8, 16 or 32 scans.

[186] LC-MS chromatograms and spectra were recorded using an Agilent 1200 or Shimadzu LC-20 AD&MS 2020 instrument using a C-18 column such as a Luna-C18 2.0x30 mm or Xbridge Shield RPC18 2.1x50 mm. Injection volumes were 0.7 – 8.0 µl and the flow rates were typically 0.8 or 1.2 ml/min. Detection methods were diode array (DAD) or evaporative light scattering (ELSD) as well as positive ion electrospray ionization. MS range was 100 - 1000 Da. Solvents were gradients of water and acetonitrile both containing a modifier (typically 0.01 – 0.04 %) such as trifluoroacetic acid or ammonium carbonate.

[187] The XRPD patterns of crystalline solids were obtained on a Bruker D8 Endeavor X-ray powder diffractometer, equipped with a CuKα (1.5418Å) source and a Linxeye detector, operating at 40 kV and 40 mA. The samples were scanned between 4 and 42 2θ°, with a step size of 0.009 2θ° and a scan rate of 0.5 seconds/step, and using 0.3° primary slit opening, and 3.9° PSD opening; or were scanned between 4 and 30 2θ°, with a step size of 0.009 2θ° and a scan rate of 0.25 seconds/step, and using 0.3° primary slit opening, and 3.9° PSD opening. The dry powder was packed on a quartz sample holder and a smooth surface was obtained using a glass slide. The crystal form diffraction patterns were collected at ambient temperature and relative humidity. Crystal peak positions were determined in MDI-Jade after whole pattern shifting based on an internal NIST 675 standard with peaks at 8.853 and 26.774 2θ°. It is well known in the crystallographic art that, for any given crystal form, the relative intensities of the diffraction peaks may vary due to preferred orientation resulting from factors such as crystal morphology and habit. Where the effects of preferred orientation are present, peak intensities are altered, but the characteristic peak positions of the polymorph are unchanged. See, *e.g.* The United States Pharmacopeia #23, National Formulary #18, pages 1843-1844, 1995. Furthermore, it is also well known in the crystallography art that for

any given crystal form the angular peak positions may vary slightly. For example, peak positions can shift due to a variation in the temperature at which a sample is analyzed, sample displacement, or the presence or absence of an internal standard. In the present case, a peak position variability of ± 0.2 20° is presumed to take into account these potential variations without hindering the unequivocal identification of the indicated crystal form. Confirmation of a crystal form may be made based on any unique combination of distinguishing peaks.

[188] Single Crystal X-ray Diffraction. Preliminary examination and data collection were performed on a Rigaku SuperNova diffractometer, equipped with a copper anode microfocus sealed X-ray tube (Cu Kα λ = 1.54184 Å) and a Dectris Pilatus3 R 200K hybrid pixel array detector. Cell refinement and data reduction were accomplished using CRYSALISPRO (CrysAlisPro 1.171.38.41r (Rigaku Oxford Diffraction, 2015)). The data were collected to a maximum diffraction angle (2θ) of 151.16° or 151.992° at room temperature. The structures were solved by direct methods using SHELXT (Sheldrick, G.M. *Acta Cryst.* 2015, A71, 3-8). The structures were refined using SHELXL-2014 (Sheldrick, G.M. *Acta Cryst.* 2008, A64, 112-122). Hydrogen atoms residing on nitrogen were refined independently. All other hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. The structures were refined in full-matrix least-squares. The simulated XRPD pattern was generated using the unit cell parameters and atomic coordinates from the single crystal structures in MERCURY crystal modeling software.

[189] Differential scanning calorimetry (DSC) analysis was conducted using a TA Q2000 DSC run by TA Thermal Advantage Software v5.2.6 and data analyzed by Universal Analysis 2000 v4.5a. Samples were equilibrated at 25 °C in crimped aluminum pans, then pierced prior to being heated to 300 °C at 10 °C/min with a 50 mL/min nitrogen purge. The temperature and heat flow were calibrated against indium melting.

[190] Thermogravimetric analysis was collected using a TA Instruments Q5000 TGA (run by TA Thermal Advantage Software v5.2.6 and data analyzed by Universal Analysis 2000 v4.5a. Samples (3-10 mg) were heated from ambient temperature (approximately 25 °C) to 200 °C at a rate of 10 °C/min. N_2 was the carrier (10 mL/min) and purge (50 mL/min) gas. Temperature was calibrated by Curie temperature determination with nickel and alumel standards. The weight calibration was performed with manufacturer-supplied standards.

[191] Solid state NMR (ssNMR) was obtained on an Agilent DD2-400 NMR spectrometer and processed with VnmrJ v3.2A. The data were externally referenced to glycine at 176.5

ppm.

ssNMR Parameters

Probe 4mm_NBT3-2
Ambient temperature
Pulse sequence: tancpx
Relax. Delay: 10.000 sec
Pulse width: 2.6 μsec
Acquisition time: 0.030 sec
Spectral width: 44642.9 Hz (443.991 ppm)
1600 scans
2 dummy scans
Acquired points: 2678
Observed Nucleus: C13 (100.5489521 MHz)
Decouple Nucleus: H1 (399.8166525 MHz)
SPINAL-64 decoupling
Cross Polarization
linear RAMP-CP on H1
Contact time: 5.0 ms
Spinning rate: 12.0 kHz
Data Processing
Backward linear prediction: 3 points
Line broadening: 10.0 Hz
FT size: 65536

[192] Abbreviations:

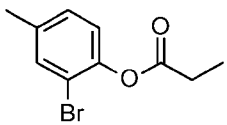
ACN	Acetonitrile
AcOH	Acetic Acid
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
$CDCl_3$	Chloroform-*d*
DCM	Dichloromethane
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Hexadeuterodimethylsulfoxide
DSC	Differential Scanning Calorimetry

eq	equivalents
EtOAc	Ethyl Acetate
EtOH	Ethanol
h	hour(s)
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
IPA	Isopropanol
Kg	Kilograms
L	Liters
LC-MS	Liquid Chromatography – Mass Spectrometry
MeOH	Methanol
MPa	Megapascal
2-MeTHF	2-Methyltetrahydrfuran
min	minute(s)
MS ES	Mass Spectroscopy Electro Spray
ppm	parts per million
rt	room temperature
SFC	Supercritical Fluid Chromatography
THF	Tetrahydrofuran
TGA	Thermogravimetric Analysis
XRD	X-ray Diffraction
XRPD	X-ray Powder Diffraction

Example 1

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid ("Compound A")

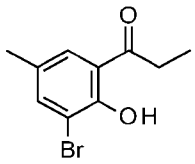
Intermediate 1: (2-Bromo-4-methyl-phenyl) propanoate



[193] A mixture of 2-bromo-4-methyl-phenol (10.0 g, 53.5 mmol) and pyridine (6.34 g, 80.2 mmol) in DCM (100 mL) was treated with propanoyl chloride (5.44 g, 58.8 mmol) at 0°C

and stirred at 25°C for 16 h. The mixture was diluted with water (100 mL), the pH adjusted to 5 with HCl (2 M), and extracted with DCM (2 x 100 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give the product as an oil (13 g, crude). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.17 (t, J=7.6 Hz, 3H), 2.30 (s, 3H), 2.62 (q, J=7.6 Hz, 2H), 7.11-7.18 (m, 1H), 7.19-7.26 (m, 1H), 7.50-7.55 (m, 1H).

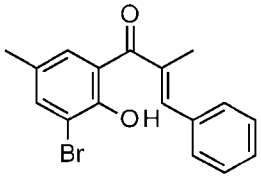
Intermediate 2: 1-(3-Bromo-2-hydroxy-5-methyl-phenyl)propan-1-one



[194] Route 1: A mixture of (2-bromo-4-methyl-phenyl) propanoate (12.5 g, 51.4 mmol) and $AlCl_3$ (24.0 g, 180 mmol) was stirred at 140°C for 1 h. When cooled to rt, the mixture was quenched with water (80 mL) dropwise and stirred for 30 min. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated and triturated with petroleum ether (20 mL) to give the product as a solid (9.82 g, 79%). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.10 (t, J=7.2 Hz, 3H), 2.28 (s, 3H), 3.15 (q, J=7.2 Hz, 2H), 7.66-7.73 (m, 1H), 7.77-7.83 (m, 1H), 12.66 (s, 1H).

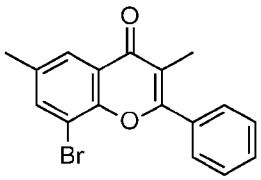
[195] Route 2: (2-Bromo-4-methyl-phenyl) propanoate (120 g, 496 mmol) was transferred to a reactor, cooled to -20°C, and treated with trifluoromethanesulfonic acid (216 mL). After addition was complete, the reaction was stirred at 60°C for 1 h. The reaction was cooled to rt and poured into icy water (600 mL). The product was removed by filtration (114 g, 95%) as a yellow solid. MS ES- *m/z* 241, 243 $[M-H]^-$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.26 (t, 3H), 2.33 (s, 3H), 3.06 (q, 2H), 7.55 (m, 2H), 12.87 (s, 1H).

Intermediate 3: (E)-1-(3-Bromo-2-hydroxy-5-methyl-phenyl)-2-methyl-3-phenyl-prop-2-en-1-one



[196] A mixture of 1-(3-bromo-2-hydroxy-5-methyl-phenyl)propan-1-one (200 g, 822.72 mmol), benzaldehyde (96.04 g, 904.99 mmol), AcOH (105.23 g, 1.75 mol), and piperidine (172.33 g, 2.02 mol) in EtOH (1600 mL) was stirred at 70°C for 16 h. The resulting dark solution was poured into water (3 L), filtered, and the solid dissolved in 6 L of DCM. The organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated to give the product as a dark gum. MS ES+ *m/z* 331, 333 $[M+H]^+$.

Intermediate 4: 8-Bromo-3,6-dimethyl-2-phenyl-chromen-4-one

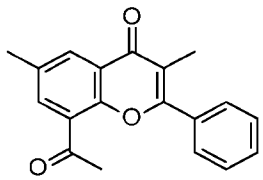


[197] Route 1: A mixture of (E)-1-(3-bromo-2-hydroxy-5-methyl-phenyl)-2-methyl-3-phenyl-prop-2-en-1-one (284 g, 857.48 mmol) and iodine (21.76 g, 85.75 mmol, 17.27 mL, 0.1 eq) in DMSO (1200 mL) was stirred at 140°C for 2 h to give a black-brown solution. Cooled to rt, poured the reaction into 3 L of water, filtered, dissolved the solid product in DCM (4 L), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was triturated with petroleum ether/EtOAc (1:1, 1 L) to give the product as a light yellow solid (195 g, 69%). MS ES+ *m/z* 329, 331 $[M+H]^+$.

[198] Route 2: A solution of 1-(3-bromo-2-hydroxy-5-methyl-phenyl)propan-1-one (50.0 g, 205.7 mmol) in THF (100 mL) was cooled to -80°C and treated with lithium bis(trimethylsilyl)amide (1M in THF, 617 mmol). After stirring at -80°C for 1 h, the mixture was warmed to 0°C and stirred for 1 h. The mixture was cooled to -80°C and treated dropwise with benzoyl chloride (37.6 g, 267.4 mmol). After addition was complete, the reaction was allowed to stir at 25°C for 16 h. The reaction was cooled to -20°C and the pH adjusted to 4 with 50% aqueous acetic acid. The THF was removed under vacuum and the precipitate removed by filtration. The solid was dissolved in acetic acid and aqueous HCl (250 mL / 10 mL) and the resulting solution stirred at 100°C for 1 h. The mixture was cooled

to 20°C and diluted with water (100 mL). A solid was removed by filtration and washed with water (50 mL) and triturated with 200 mL of EtOAc at rt for 30 min. The product was collected by filtration (170.7 g, 83%) as an off-white solid. MS ES+ *m/z* 329, 331 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.24 (s, 3H), 2.48 (s, 3H), 7.55-7.57 (m, 3H), 7.75-7.78 (m, 3H), 8.00 (s, 1H).

Intermediate 5: 8-Acetyl-3,6-dimethyl-2-phenyl-chromen-4-one

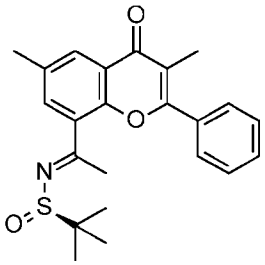


[199] Route 1: A mixture of 8-bromo-3,6-dimethyl-2-phenyl-chromen-4-one (195 g, 592.37 mmol), bis(triphenylphosphine)palladium(II) dichloride (20.79 g, 29.62 mmol), and tributyl(1-ethoxyvinyl)stannane (256.72 g, 710.84 mmol, 239.92 mL) in dioxane (1600 mL) was stirred under N_2 at 95°C for 16 h to give a black-brown solution. After cooling to rt, treated the reaction with 1M aqueous HCl (100 mL) and stirred at 20°C for 30 min. The mixture was quenched with saturated aqueous KF (2000 mL), stirred for 30 min, and filtered. The filter cake was washed with 10% MeOH in DCM (5 x 5000 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was triturated with petroleum ether/EtOAc (5/1, 1000 mL) to give a crude product which was triturated with DCM/MeOH (10/1, 500 mL) to give the product as a light yellow solid (180 g, 96%, 92% purity). MS ES+ *m/z* 293 $[M+H]^+$.

[200] Route 2: A mixture of 8-bromo-3,6-dimethyl-2-phenyl-chromen-4-one (50.0 g, 151.9 mmol), palladium acetate (0.34 g, 1.52 mmol), 1,3-bis(diphenylphosphino)propane (1.25 g, 3.04 mmol), triethylamine (46.17 g, 455.7 mmol), n-butyl vinyl ether (76 g, 759.5 mmol) and ethylene glycol (400 mL) was stirred at 100°C for 7 h under a nitrogen atmosphere. The reaction was cooled to 30°C and treated with 3 g of active carbon and stirred. The suspension was filtered through celite and the pH of the filtrate adjusted to 3-4 with HCl and stirred at 60°C for 12 h. The reaction was cooled to 40°C and a solid removed by filtration. The solids were slurred in 250 mL of THF and stirred at 60°C for 5 h. The reaction was cooled to 30°C and the product (40 g, 90%) removed by filtration and dried at 50°C giving an off-white solid. MS ES+ *m/z* 293 $[M+H]^+$. 1H NMR (400 mHz, $CDCl_3$) δ ppm 2.21 (s, 3H), 2.52 (s,

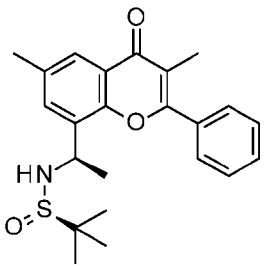
3H), 2.73 (s, 3H), 7.55-7.58 (m, 3H), 7.67-7.70 (m, 2H), 7.97 (s, 1H), 8.26-8.27 (m, 1H).

Intermediate 6: (NE,R)-N-[1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethylidene]-2-methyl-propane-2-sulfinamide



[201] To a mixture of 8-acetyl-3,6-dimethyl-2-phenyl-chromen-4-one (180 g, 615.75 mmol) and (R)-2-methylpropane-2-sulfinamide (149.26 g, 1.23 mol) in THF (1500 mL) was added tetraisopropoxytitanium (700.01 g, 2.46 mol, 726.90 mL). The mixture was stirred at 80°C for 56 h to give a black-brown solution. After cooling to rt, quenched the reaction with brine (2000 mL) and stirred for 30 min and filtered. The filter cake was washed with EtOAc (4000 mL). After separating the organic layer, the aqueous layer was extracted with EtOAc (1000 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was triturated with petroleum ether/EtOAc (1/1, 600 mL) to give the product as a white solid (186 g, 76%). MS ES+ *m/z* 396 $[M+H]^+$.

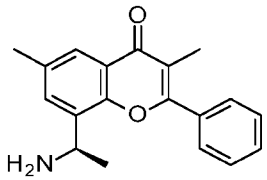
Intermediate 7: (R)-N-[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]-2-methyl-propane-2-sulfinamide



[202] To a mixture of (NE,R)-N-[1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethylidene]-2-methyl-propane-2-sulfinamide (186 g, 470.27 mmol) and $CeCl_3{\cdot}7H_2O$ (87.61 g, 235.14 mmol, 22.35 mL) in MeOH (1600 mL) was added $NaBH_4$ (26.69 g, 705.41 mmol) at 15°C. The mixture was stirred at 15°C for 1 h to give a dark suspension. The reaction was quenched with saturated aqueous NH_4Cl (1500 mL) at 15°C. Extracted with DCM (2 x 1500 mL),

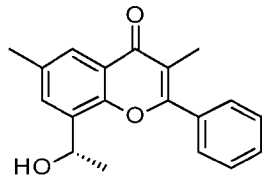
washed the combined organic phases with brine (1500 mL), dried the organic phase over anhydrous Na_2SO_4, filtered, and concentrated to give the product as a yellow solid (180 g, 96%). MS ES+ *m/z* 398 $[M+H]^+$.

Intermediate 8: 8-[(1R)-1-Aminoethyl]-3,6-dimethyl-2-phenyl-chromen-4-one



[203] A mixture of (R)-N-[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]-2-methyl-propane-2-sulfinamide (180 g, 452.80 mmol) in MeOH (1500 mL) was treated with HCl/MeOH (4 M, 300 mL) and the mixture was stirred at 15°C for 1 h to give a white suspension. Concentrated the reaction, poured the residue into water (1000 mL) and DCM (2000 mL), adjusted the pH to 12 with NH_3 in H_2O (25%), and extracted with DCM (2 x 1000 mL). The combined organic phases were washed with brine (1000 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was triturated with DCM (200 mL) to give the product as a white solid (122 g, 89%). MS ES+ *m/z* 294 $[M+H]^+$.

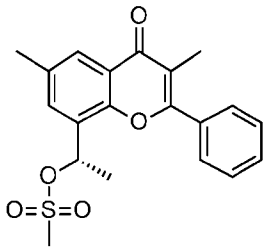
Intermediate 9: 8-[(1S)-1-Hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one



[204] A flask equipped with overhead stirring and a temperature probe was charged with 8-acetyl-3,6-dimethyl-2-phenyl-chromen-4-one (11.0 g, 37.25 mmol) and chloroform (200 mL). The stirring slurry was treated with formic acid (5.14 g, 111.76 mmol) and cooled to ~10 °C in an ice bath. The cold solution was slowly treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (17.01 g, 111.76 mmol) maintaining the temperature below 25 °C. The reaction was removed from the cooling bath and treated with RuCl(p-cymene)[(S,S)-Ts-DPEN] (CAS 192139-90-5, 0.66 g, 1.12 mmol). The reaction was stirred at 45 °C for 16 h. The reaction was transferred to a separatory funnel and washed with 2M

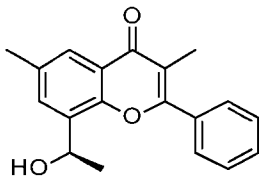
aqueous HCl (2 x 50 mL). The organic layer was concentrated under vacuum at 45 – 50 °C to 50 to 100 mL. Diluted with ACN (150 mL) and concentrated under vacuum at 45 – 50 °C to 50 mL. The solvent swap was done again until the amount of solvent was 50 mL. The material was cooled to rt over 1-2 h and the slurry aged for 4 h. The product (10.10 g, 92%) was collected by filtration, washed with ACN (25 mL), washed with heptane (50 mL), and dried under vacuum at 45 °C.

Intermediate 10: [(1S)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl] methanesulfonate



[205] A flask was charged with 8-[(1S)-1-hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one (2.0 g, 6.79 mmol), methanesulfonic anhydride (1.42 g, 8.15 mmol), and DCM (20 mL). The solution was cooled to <10 °C in an ice bath. Slowly treated the reaction with triethylamine (1.38 g, 13.59 mmol) over 5 min. Removed from the ice bath and stirred at rt for 1 h. This reaction mixture was used as is.

Intermediate 11: 8-[(1R)-1-Hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one



[206] A flask equipped with overhead stirring, condenser, and temperature probe was charged with 8-acetyl-3,6-dimethyl-2-phenyl-chromen-4-one (10 g, 34.2 mmol) and RuCl(p-cymene)[(R,R)-TsDPEN] (CAS 192139-92-7, 0.65 g, 1.03 mmol). Added 50 mL of methanol and started stirring. The reaction was cooled to 10 °C and treated slowly with 1,8-diazabicyclo[5.4.0]undec-7-ene (15.62 g, 102.62 mmol) keeping the temperature below 25 °C. After addition was complete, cooled the reaction back down to 10 °C and treated the

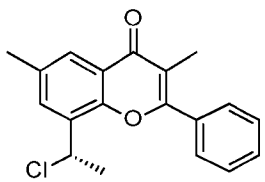
reaction in portions with formic acid (4.72 g, 102.62 mmol) maintaining the temperature below 15 °C. After addition, the reaction was stirred at 55 °C for about 3 h. The reaction was cooled to 20 °C and treated with 4 M aqueous HCl (50 mL) over 1 h and the resulting slurry stirred overnight at rt. The product (9.35 g, 95%) was isolated by filtration, washed with water, and dried under vacuum at 45 °C.

Alternate Sythesis of Intermediate 11: 8-[(1R)-1-Hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one

[207] Charged a reactor with THF (3 L/kg, 360 L), 8-acetyl-3,6-dimethyl-2-phenyl-chromen-4-one (120 kg, 410 mol), and sodium methoxide (2.2 kg, 41 mol, 0.10 eq). Evacuated the reactor and refilled with nitrogen three times. Charged the reactor with (S)-RUCY-XylBINAP [CAS# 1312713-89-5] (364 g, 0.31 mol, 0.00075 eq) and washed the reactor with THF (2 L/kg, 240 L). Evacuated and refilled with nitrogen three times. Pressurized the reactor to 1 MPa hydrogen and stirred the reaction at 40 °C for 18 h. After cooling to 25 °C, pulled a sample for analysis. If reaction was not complete, refilled reactor with 1 MPa hydrogen and stirred at 40 °C another 6 h.

[208] Upon reaction completion, charged the reactor with 2-MeTHF (5 L/kg, 600 L) and purified water (5 L/kg, 600 L) and stirred at 25 °C for 30 min. Filtered the reaction and washed the solids with 2-MeTHF (1L/kg, 120 L). Let stand for 30 min. Remove the aqueous layer and solvent exchanged the organic layer into ACN (4 L/kg, 480 L). Cooled to 5 °C over 10 h and stirred the mixture at 5 °C for 6 h. Filtered the mixture, washed the solids with ACN (1.52 L/kg, 182 L) and n-heptane (5.0 L/kg, 600 L), and dried under vacuum at 45 °C for 12 h to give the title compound (102.7 kg, 85%). ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 1.40 (d, 3H, J = 6.5 Hz), 2.03 (s, 3H), 2.41 (s, 3H), 5.24 (dq, 1H, J = 4.2, 6.5 Hz), 5.38 (d, 1H, J = 4.2 Hz), 7.58 (m, 3H), 7.73 (m, 4H).

Intermediate 12: 8-[(1S)-1-Chloroethyl]-3,6-dimethyl-2-phenyl-chromen-4-one

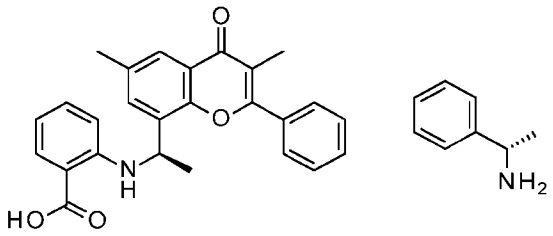


[209] A flask equipped with overhead stirring was charged with 8-[(1R)-1-hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one (20.0 g, 68.0 mmol) and cyclopentyl methyl ether (200 mL). Added 2,4,6-trichloro[1,3,5]triazine (12.5 g, 23.8 mmol) followed by DMF (7.9 mL, 102 mmol) and stirred overnight at rt. The reaction was treated slowly with 2M aqueous NaOH (100 mL) and allowed to stir for 10 min. The reaction was transferred to a separatory funnel and the organic layer removed. The organic layer was diluted with water (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). After removal of the aqueous layer, the organic layer was washed with 5% aqueous LiCl. The organic layer was transferred to a flask and solvent swapped with IPA by charging the flask with 200 mL of IPA and concentrating down to 100 mL three times. The slurry was then warmed to 45 °C and stirred at that temperature for 2 h and allowed to cool to rt. The material was treated with 80 mL of water via syringe pump over 4 h and the reaction aged overnight. The product (18.4 g, 87%) was collected by filtration, washed with 40 mL of 1:1 IPA/water and dried at 45 °C.

Alternate Synthesis of Intermediate 12: 8-[(1S)-1-Chloroethyl]-3,6-dimethyl-2-phenyl-chromen-4-one

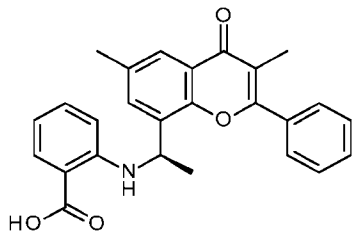
[210] Charged a reactor with 2-MeTHF (5 L/kg, 480 L) and 8-[(1R)-1-hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one (96 kg, 326.5 mol) and cooled to 10 °C. Charged the reactor with 1-formylpyrrolidine (32.4 kg, 326.5 mol, 1 eq) and then added benzoyl chloride (91.8 kg, 653 mol, 2 eq) over 2 h. The reaction was warmed to 25 °C and stirred for 18 h. After reaction completion, the reaction was diluted with 2-MeTHF (5 L/kg, 480 L) and cooled to 15 °C. Aqueous 3M NaOH (5 L/kg, 480 L) was slowly added, the mixture warmed to 25 °C, and the mixture stirred for 45 min. After standing for 30 min, the aqueous layer was removed. Charged the reactor with water (5 L/kg, 480 L) and stirred for 15 min. After standing for 30 min, the aqueous layer was removed and the resulting organic layer filtered. The filtrate was allowed to stand for 30 min and the aqueous layer removed again. The resulting organic solution was solvent exchanged into isopropanol (5 L/kg, 480 L) and used in the next step without further purification.

Intermediate 13: 2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid; (1S)-1-phenylethanamine



[211] A DCM solution (20 mL) of [(1S)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl] methanesulfonate was treated with anthranilic acid (2.79 g, 20.38 mmol) and triethylamine (1.38 g, 13.59 mmol) dropwise. The reaction was allowed to stir overnight at rt. The reaction was washed with 1M aqueous HCl (3 x 10 mL) and brine. The organic layer was collected, dried over $MgSO_4$, and concentrated to 10 mL. Charged with 20 mL of 2-methyltetrahydrofuran and concentrated to 10 mL. Solvent swapped with 2-methyltetrafuran again, concentrated to 70 to 80 mL and heated to 45 – 50 °C. Added (S)-α-methylbenzylamine (0.91 g, 7.48 mmol) over 3 h. Cooled to rt and let age overnight. The title compound (2.13 g, 59%) was collected by filtration, washed with 2-methyltetrahydrofuran (2 x 10 mL), and dried under vacuum at 45 °C.

Compound A: 2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid



[212] Route 1: A mixture of 8-[(1R)-1-aminoethyl]-3,6-dimethyl-2-phenyl-chromen-4-one (30 g, 102.3 mmol), 2-iodobenzoic acid (25.36 g, 102.26 mmol), copper (13.00 g, 204.5 mmol), and potassium carbonate (21.20 g, 153.4 mmol) was suspended in DMF (300 mL) and stirred at 100°C for 3 h. The reaction was combined with another reaction of the same amounts, the pH adjusted to pH 3 with 2M aqueous HCl, diluted with 1000 mL of DCM and 500 mL of water, filtered, and the layers separated. The organic layer was washed with 3 x 1000 mL of brine, collected, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography eluted with 5% ethyl acetate in petroleum ether to 50% EtOAc

in petroleum ether. The resulting solid was triturated with 300 mL of EtOAc and collected by filtration. The resulting solid was suspended in 500 mL of boiling acetonitrile and collected by filtration to give the product (33 g; 39%) as a white solid. MS ES+ *m/z* 414 $[M+H]^+$.

[213] Route 2: 2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid; (1S)-1-phenylethanamine (15 g) was mixed with DCM (150 mL). 1M aqueous HCl (75 mL) was added and the mixture was stirred for 5 min. 1M aqueous HCl (75 mL) was added and the mixture was again stirred for 5 min. The reaction was concentrated to ~45 mL. DCM (30 mL) and ACN (150 mL) were added and the mixture was concentrated to ~75 mL. ACN (150 mL) was added and the mixture was concentrated to ~120 mL. Heated to 80 °C for a short time. Cooled to 65 °C and stirred for 2 h. Cooled to 25 °C over 4 h and stirred for an additional 4 h. The product (7.50 g, 65%) was collected by filtration and washed with 5 mL of ACN, washed with 75 mL of heptane, and dried in a vac oven at 45 °C. MS ES+ *m/z* 414 $[M+H]^+$.

[214] Route 3: A flask was charged with 8-[(1S)-1-chloroethyl]-3,6-dimethyl-2-phenyl-chromen-4-one (5.0 g, 16.0 mmol) and IPA (50 mL). The reaction was then treated with anthranilic acid (6.58 g, 48.0 mmol) and dropwise with triethylamine (6.7 mL, 48.0 mmol). The reaction was stirred at 60 °C overnight. The reaction was cooled to rt and 50 mL of 2-methyltetrahydrofuran added and the reaction concentrated to ~50 mL. This solvent swap was done 3 more times with 25 mL of 2-methyltetrahydrofuran. Added 25 mL of 2M aqueous HCl and allowed to stir. Transferred to a separatory funnel and removed the aqueous layer. The remaining organic layer was washed with 2M aqueous HCl (2 x 25 mL) and then diluted with 50 mL of ACN and concentrated to ~50 mL three times leaving a thick slurry. The slurry was warmed to 80 °C for 1 h and then at 65 °C for 2 h. The reaction was cooled to rt over ~5 h and stirred overnight. The product (5.19 g, 79%) was collected by filtration and washed with 5 mL of ACN, washed with 25 mL of heptane, and dried in a vac oven at 45 °C.

[215] Route 4: Charged a solution of 8-[(1S)-1-chloroethyl]-3,6-dimethyl-2-phenyl-chromen-4-one in isopropanol prepared according to the Alternate Synthesis of Intermediate 12 to a reactor and added anthranilic acid (111.9 kg, 816.3 mol, 2.5 eq) and sodium bicarbonate (41.1 kg, 489.4 mol, 1.5 eq). Isopropanol (2 L/kg, 192 L) was added and the reaction stirred at 65 °C for 24 h. Upon completion, the reaction was solvent exchanged into 2-MeTHF (15 L/kg, 1400 L). At 20 °C, added 4M aqueous HCl (5 L/kg, 480 L) and stirred for 30 min. After standing for 30 min, the aqueous layer was removed. Added 2-MeTHF (2 L/kg, 192 L) and

2M aqueous HCl (3 L/kg, 288 L) to the organic layer and stirred for 30 min at 20 °C. After standing for 30 min, the aqueous layer was removed. Added 2-MeTHF (3 L/Kg, 288 L) and water (5 L/kg, 480 L) and stirred for 30 min. After standing for 30 min, the aqueous layer was removed. The resulting solution was used without purification in the next step. [Note: Amounts are relative to 8-[(1R)-1-hydroxyethyl]-3,6-dimethyl-2-phenyl-chromen-4-one.]

Alternate Synthesis of Intermediate 13: 2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid; (1S)-1-phenylethanamine

[216] Charged a solution of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid in 2-MeTHF according to the Route 4 step above to a reactor and concentrated to 10 L/kg (960 L). Heated the mixture to 50 °C and added (S)-methylbenzylamine (6.72 kg, 55.5 mol, 0.17 eq) over 1 h. The resulting slurry was stirred at 50 °C for 45 min and additional (S)-methylbenzylamine (303.6 mol, 0.93 equiv) was added over 2 h. The slurry was stirred at 65 °C for 2 h before being cooled to 20 °C over 12 h. After stirring at 20 °C for 4 h, the slurry was filtered and the wet cake washed with 1:1 2-MeTHF/n-heptane (3 L/kg, 288 L) and n-heptane (3 L/kg, 288 L) and then dried under vacuum at 45 °C for 16 h to afford the title compound in 77% yield over 3 steps.

Example 2

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid Form A ("Compound A Form A")

[217] Compound A Form A was obtained following a procedure according to Example 1.

[218] The XRPD pattern of Compound A Form A, shown in FIG. 1, was successfully indexed, confirming that the experimental pattern represents that of a single crystalline phase and the unit cell volume is consistent with an anhydrous crystal form.

XRPD

[219] A prepared sample of Form A was characterized by an XRD pattern using CuKα radiation as having diffraction peaks (2-theta values) as described in Table 1 below, and in particular having a peak at 12.1° in combination with one or more of the peaks selected from the group consisting of 14.1°, 16.8°, 18.9°, and 20.7°; with a tolerance for the diffraction angles of 0.2 degrees.

Table 1. XRPD peaks

Peak	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	7.8	34.7%
2	12.1	100%
3	13.7	10.2%
4	14.1	54.8%
5	16.8	14.2%
6	17.5	40.1%
7	18.2	9.8%
8	18.9	11.9%
9	19.5	20.2%
10	20.7	59.1%
11	21.2	14.1%
12	24.1	37.4%

Thermal Analysis

[220] Form A was confirmed to be anhydrous based on the lack of mass loss detected on heating from 25 °C to 200 °C. The sharp endothermic peak at 185 °C was attributed to Form A melting. An exothermic transition was observed at 192 °C followed by an endothermic event at 211 °C, consistent with Form C crystallization and melting, respectively.

Example 3

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid Form B ("Compound A Form B")

[221] A THF solvate was produced by slow evaporation of a saturated solution of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid in THF at ambient temperature. The XRPD pattern of the THF solvate filtrate shown in FIG. 2 was successfully indexed confirming that the material is a single crystalline phase, designated as Form B. The unit cell volume is consistent with a mono-THF solvate.

XRPD

[222] A prepared sample of Form B was characterized by an XRD pattern using CuKα radiation as having diffraction peaks (2-theta values) as described in Table 2 below, and in particular having a peak at 9.7° in combination with one or more of the peaks selected from the group consisting of 14.9°, 11.9°, 17.4°, and 7.0°; with a tolerance for the diffraction angles of 0.2 degrees.

Table 2. XRPD peaks

Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
7.0	6.9%
9.7	57.6%
11.9	20.4%
14.9	46.0%
17.4	30.4%

Thermal Analysis

[223] On heating at a rate of 10 °C/min, a low-temperature endothermic event was attributed to desolvation, followed by, likely, a Compound A Form C melt at 213 °C. On TGA, the mass loss observed on heating was consistent with 0.8 molar equivalent of THF.

Example 4

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid Form C ("Compound A Form C")

[224] Form C was produced by annealing Compound A Form A at 194 °C for 30 min. From XRPD indexing (FIG. 3), the phase purity of Form C was confirmed, and the unit cell volume is consistent with an anhydrous material.

XRPD

[225] A prepared sample of Form C was characterized by an XRD pattern using CuKα radiation as having diffraction peaks (2-theta values) as described in Table 3 below, and in particular having a peak at 13.4° in combination with one or more of the peaks selected from the group consisting of 8.5°, 15.7°, 10.6°, and 7.4°; with a tolerance for the diffraction angles of 0.2 degrees.

Table 3. XRPD peaks

Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
7.4	3.8%
8.5	100%
10.6	2.9%
13.4	7.1%
15.7	29.0%

Thermal Analysis

[226] DSC of isolated Compound A Form C showed an endothermic event at 209 °C, attributed to melting.

Example 5

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid tromethamine salt Form A ("Compound A Tromethamine Salt Form A")

[227] Preparation of Compound A Tromethamine Salt Form A was performed by dissolving 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid (2.4 g, 5.80 mmol) and tris(hydroxymethyl)aminomethane (714.5 mg, 5.90 mmol) in 4:1 THF:MeOH (15.9 mL), while stirring at 850 rpm at 60°C. While stirring, heptane (15.8 mL) was added over 12 hours at 60°C. The slurry was cooled to 10°C over 4 hours, then stirred overnight at 10°C. The solid product was isolated on Whatman paper under vacuum to yield the title compound (1.72 g, 88% yield).

Chiral Enhancement

[228] Generation and isolation of Compound A Tromethamine Salt Form A provided a chiral enhancement of the (R)-enantiomer relative to the free acid (R)-enantiomer content. HPLC of the free acid starting material showed 96.6% (R)-enantiomer and 3.4% (S)-enantiomer. HPLC of the crystalline tromethamine salt showed > 99.9% (R)-enantiomer.

XRPD

[229] A prepared sample of the crystalline tromethamine salt was characterized by an XRD pattern (FIG. 4) using CuKα radiation as having diffraction peaks (2-theta values) as described in Table 4 below, and in particular having a peak at 6.4° in combination with one or more of the peaks selected from the group consisting of 8.4°, 10.9°, 16.9°, and 22.1°; with a tolerance for the diffraction angles of 0.2 degrees.

Table 4. XRPD peaks

Peak	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	6.4	100%
2	8.4	15.3%
3	10.9	23.7%
4	11.8	8.6%
5	13.0	8.2%

6	16.5	9.4%
7	16.9	13.2%
8	22.1	22.4%
9	23.0	11.3%
10	24.9	11.2%

Thermal Analysis

[230] Compound A Tromethamine Salt Form A was confirmed to be anhydrous based on the negligible weight loss detected on heating to 200 °C. DSC analysis showed a small endothermic event at 68 °C (onset) attributed to conversion of Form A to Form D. With continuous heating an endothermic event was observed at 203 °C (onset) which is consistent with melting of Form D.

Single Crystal Structure Analysis

[231] A suitable single crystal was selected and analyzed by single-crystal X-ray diffractometry. The single crystal structure of Compound A Tromethamine Salt Form A was determined to confirm the molecular structure and absolute configuration. The structure was determined to be an anhydrous crystal form, composed of one Compound A anion and one tromethamine cation in the asymmetric unit. The absolute structure was determined from the crystal structure and the molecule was found to bond in the R configuration.

Solid State NMR

[232] A prepared sample of Compound A Tromethamine Salt Form A was characterized by solid state NMR. ^{13}C Solid state NMR (100.6 MHz) δ 179.0, 158.7, 151.7, 149.7, 136.3, 134.7, 132.9, 129.3, 127.4, 125.2, 121.7, 117.0, 115.5, 115.2, 110.4, 64.1, 63.2, 45.3, 22.6, 20.3, 11.6 ppm.

Alternate Example 5

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid tromethamine salt Form A ("Compound A Tromethamine Salt Form A")

[233] Charged a reactor with 2-MeTHF (10 L/kg), 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid; (1S)-1-phenylethanamine, and 2N aqueous HCl (4 L/kg) at 25 °C. The resulting biphasic mixture was stirred for 30 min, allowed to stand for 30 min, and then the aqueous layer was removed. Aqueous 2N HCl (4 L/kg) was added to the organic layer, stirred for 30 min, and then allowed to stand for 30 min. The aqueous layer was removed and water (4 L/kg) was added to the organic layer. After stirring for 30 min, the

mixture was allowed to stand for 30 min and the aqueous layer removed. The resulting organic layer was solvent exchanged into THF (1.93 L/kg). MeOH (1.93 L/kg) was added followed by aminotris(hydroxymethyl)methane (0.95 equiv). The solution was heated to 40 °C, polish filtered (0.22 μm filter), and aged for 30 min. n-Heptane (1.29 L/kg) was added and the crystallization was seeded (2.5 wt%) and aged for 30 min. At 40 °C, n-heptane (3.24 L/kg) was added over 8 h. Additional n-heptane (3.24 L/kg) was added over 4 h. The resulting slurry was cooled to 10 °C over 5 h and stirred at 10 °C for 4 h. The slurry was filtered and the wet cake washed with 1:2 (1:1 THF/MeOH):n-heptane (3.8 L/kg) and then n-heptane (3.8 L/kg). The wet cake was dried under vacuum at 50 °C to afford the title compound in 87% yield. The solid was pin milled in a Hosokawa Alpine 160 UPZ pin mill to obtain material with a particle size below 20 micrometers. See Table 8 for a record of particle size analysis for 4 lots of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid tromethamine salt Form A.

Table 8. D90 Measurements

Material Lot	D90 Measure (micrometers)
A	18
B	19
C	19
D	22

Example 6

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid tromethamine salt Form C ("Compound A Tromethamine Salt Form C")

[234] Preparation of seed material was performed by dissolving tris(hydroxymethyl)aminomethane (>1 eq) in either water (0.5 – 1.7 mL) and acetone (0.1 - 0.2 mL) or ~3:1 water:acetone (0.6 mL), followed by addition of Compound A Form A (30 – 100 mg). Additional acetone was added if the resulting slurry was difficult to stir. Samples were stirred at rt for a couple hours or overnight. Suspensions were centrifuged at rt for 5 min and dried overnight at rt to give solids consistent with Compound A Tromethamine Salt Form

C as a monohydrate.

[235] Preparation of Compound A Tromethamine Salt Form C was performed by combining ~3:1 acetone:water (16.5 mL) and Compound A Tromethamine Salt Form A (4.93 g, milled). The mixture was stirred (750 rpm) at rt for 5 min. Seed material (monohydrate Compound A Tromethamine Salt Form C, 45 mg) was added to the suspension the mixture was stirred (750 rpm) at rt overnight and sample was stirred overnight under the same previous conditions. The suspension was centrifuged at rt for 5 min to give solids consistent with Compound A Tromethamine Salt Form C as a monohydrate.

XRPD

[236] A prepared sample of Compound A Tromethamine Salt Form C was characterized by an XRD pattern (FIG. 5) using CuKα radiation as having diffraction peaks (2-theta values) as described in Table 5 below, and in particular having a peak at 15.9° in combination with one or more of the peaks selected from the group consisting of 10.6°, 17.4°, 13.2°, and 14.5°; with a tolerance for the diffraction angles of 0.2 degrees.

Table 5. XRPD peaks

Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
10.6	98.2%
13.2	29.6%
14.5	41.8%
15.9	29.6%
17.4	50.0%

Thermal Analysis

[237] On thermal analysis, Form C desolvation was indicated by a weight loss of 3.1% which is consistent with the theoretical value of 3.4% for a monohydrate form.

Example 7

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid tromethamine salt Form D ("Compound A Tromethamine Salt Form D")

[238] Preparation of Compound A Tromethamine Salt Form D was performed by dispensing Compound A Tromethamine Salt Form A onto a flat plate XRPD sample holder and heating to 150°C. The conversion from Form A to Form D occurred during heating.

XRPD

[239] Form D has only been observed *in situ* (VT-XRPD). Attempts to produce Form D via high temperature annealing have resulted in Form A via XRPD, suggesting conversion to Form A occurs within minutes at RT.

[240] The XRPD pattern of Form D (FIG. 6) collected on VT-XRPD at 150 °C was successfully indexed, confirming that the experimental pattern represents that of a single crystalline phase. Compound A Tromethamine Salt Form D was characterized by an XRD pattern using CuKα radiation as having diffraction peaks (2-theta values) as described in Table 6 below, and in particular having a peak at 11.1° in combination with one or more of the peaks selected from the group consisting of 12.6°, 17.1°, 6.3°, and 18.9°; with a tolerance for the diffraction angles of 0.2 degrees.

Table 6. XRPD peaks

Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
6.3	100%
11.1	43.3%
12.6	13.1%
17.1	39.6%
18.9	6.1%

Example 8

2-[[(1R)-1-(3,6-Dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid erbumine salt form A ("Compound A Erbumine Salt Form A")

[241] 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid (0.752 g, 1.82 mmol) was suspended in acetone (30 mL), while stirring at 500 rpm at 55°C. *tert*-Butylamine (0.220 mL, 2.09 mmol) was added. Acetone (5 mL) was added to thin the resulting slurry. The slurry was stirred for 45 minutes at 450 rpm at 55°C, cooled to room temperature, and isolated on Whatman paper under vacuum to yield the title compound (0.849 g, 96% yield).

XRPD

[242] A prepared sample of the crystalline erbumine salt was characterized by an XRD pattern (FIG. 7) using CuKα radiation as having diffraction peaks (2-theta values) as described in Table 7 below, and in particular having a peak at 11.1 in combination with one

or more of the peaks selected from the group consisting of 10.5, 15.2, 18.0, and 19.3; with a tolerance for the diffraction angles of 0.2 degrees.

Table 7. XRPD peaks

Peak	Angle (°2-Theta) +/- 0.2°	Relative Intensity (% of most intense peak)
1	6.5	6.9%
2	10.5	39.9%
3	11.1	100%
4	15.2	14.4%
5	15.9	61.8%
6	17.6	15.8%
7	18.0	33.1%
8	19.3	19.5%
9	21.5	28.0%
10	22.2	11.2%
11	22.7	22.5%
12	26.3	19.7%

Solid State NMR

[243] A prepared sample of Compound A Erbumine Salt Form A was characterized by solid state NMR. ^{13}C Solid state NMR (100.6 MHz) δ 177.4, 174.8, 159.8, 151.7, 149.5, 134.0, 132.6, 130.7, 130.3, 129.0, 128.1, 123.1, 122.4, 119.4, 116.8, 115.9, 112.3, 53.0, 47.5, 27.4, 23.3, 21.3, 11.3 ppm.

Example 9

PI3K-Alpha kinase (PIK3CA) activity in vitro cell based assay

[244] To measure the inhibitory effect of Compound A on PI3Kα H1047R signaling in cancer cells in-vitro, MDA-MB-453 cells without added serum were dosed with increasing concentrations of inhibitor. After 3 hours of treatment, the cells were lysed and phospho-AKT Ser473 was monitored using the SureFire® Ultra® assay (PerkinElmer, catalog number ALSU-PAKT-B50K).

[245] The MDA-MB-453 (ATCC-HTB-131) cell line was obtained from the American Type Culture Collection (Manassas, VA). Cells were maintained in Dulbecco's Modified Eagle Media (DMEM, Gibco 11965-092) supplemented with 10% Fetal Bovine Serum, heat inactivated (FBS HI, Gibco 10082-147), 1X non-essential amino acids (NEAA, Gibco 11140-

050), and 1 mM sodium pyruvate (Gibco 11360-070). Cultures were maintained in a humidified incubator at 37°C under 5% CO_2/95% air.

[246] For compound testing in 0% FBS, MDA-MB-453 cells were seeded at a density of 1.5×10^4 cells per well in white 384-well plates in 20 µl of Minimum Essential Media (MEM) assay media with 1X NEAA, 1 mM sodium pyruvate, and 1 µg/mL human insulin (Sigma I9278). Compounds dissolved in 10 mM stock solutions in DMSO were serially diluted 1:3 in DMSO to generate a 10-point dilution series and plated using an acoustic liquid handler system (Echo 550 Series Liquid Handler, Labcyte). A 5X intermediate compound dilution plate in MEM with 1X NEAA and 1 mM sodium pyruvate (150 µM starting compound concentration in 1.5% DMSO) was then prepared. Five µl of the intermediate serially diluted compounds were added to the cell plate to final concentrations ranging from 30 mM to 0.0015 mM in 0.3% DMSO. 0.3% DMSO alone was used to establish the maximum (MAX) signal and GDC-0032 at a final concentration of 1 µM was used as a reference compound for the minimum (MIN) signal. After 3 hours treatment, the medium was removed, and the cells lysed in 10 µL of 1X SureFire Lysis buffer with shaking for 10 minutes at room temperature. The Acceptor Mix (Reaction Buffer 1 + Reaction Buffer 2 + Activation Buffer + SureFire Ultra Acceptor Beads) was prepared by diluting Activation buffer 25-fold in combined Reaction Buffer 1 and Reaction Buffer 2. The Acceptor beads were diluted 50-fold in the combined Reaction Buffers. Five µL of Acceptor Mix was added to each well, the plate was sealed and covered with foil and incubated for 1 hour at room temperature. The Donor Mix (dilution buffer + SureFire Ultra Donor Beads) was prepared by diluting Donor Beads 50-fold in dilution buffer. Five µL of the Donor Mix was added to each well and the plate sealed and covered with foil and incubated for 1 hour at room temperature in the dark. The plates were read on a Neo2 plate reader instrument from Biotek using standard AlphaLisa settings.

[247] Compounds were tested in duplicate and the average % inhibition at each compound concentration was used to generate a single dose response curve. The data were processed using the Genedata-Screener tool. Relative IC_{50} values were determined using luminescence units by calculating percent inhibition with respect to the in-plate "MIN" (GDC-0032 reference control) and "MAX" (DMSO) controls. The data was analyzed using a 4-parameter nonlinear logistic equation (four-parameter logistic concentration-response curve):

$$Y = \text{bottom} + [(\text{top} - \text{bottom})/1+(X / IC50)^{\text{slope}}]$$

where Y = % inhibition, X = concentration of inhibitor, bottom = minimum value of y

attained by curve-fit, top = maximum value of y attained by curve-fit and slope = steepness of curve at the IC_{50}.

%Inhibition = [(signal at X – median Min)/ (median Max – median Min)] x 100

IC_{50}: concentration of compound that reduces a given response (ligand binding, enzyme response) by 50%. Relative IC_{50}: concentration giving half the compound's maximum response.

[248] Compound A was determined to have an IC_{50} value of 6.83 nanomolar.

WE CLAIM:

1. A tromethamine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid.

2. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.4° ± 0.2°, 8.4° ± 0.2°, 10.9° ± 0.2°, 11.8° ± 0.2°, 13.0° ± 0.2°, 16.5° ± 0.2°, 16.9° ± 0.2°, 22.1° ± 0.2°, 23.0° ± 0.2°, and 24.9° ± 0.2°.

3. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with at least one peak selected from 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°.

4. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 6.4° ± 0.2° in combination with the peaks 8.4° ± 0.2°, 10.9° ± 0.2°, 16.9° ± 0.2°, and 22.1° ± 0.2°.

5. The tromethamine salt of any one of claims 1-4, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 179.0, 158.7, 151.7, 149.7, 136.3, 134.7, 132.9, 129.3, 127.4, 125.2, 121.7, 117.0, 115.5, 115.2, 110.4, 64.1, 63.2, 45.3, 22.6, 20.3, and 11.6 ppm (± 0.2 ppm, respectively).

6. The tromethamine salt of any one of claims 1-4, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises peaks referenced to glycine (external reference at 176.5 ppm) at: 179.0, 129.3, 63.2, 20.3, and 11.6 ppm (± 0.2 ppm, respectively).

7. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected

from 10.6° ± 0.2°, 13.2° ± 0.2°, 14.5° ± 0.2°, 15.9° ± 0.2°, and 17.4° ± 0.2°.

8. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 15.9° ± 0.2° in combination with at least one peak selected from 10.6° ± 0.2°, 17.4° ± 0.2°, 13.2° ± 0.2°, and 14.5° ± 0.2°.

9. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 10.6° ± 0.2°, 13.2° ± 0.2°, 14.5° ± 0.2°, 15.9° ± 0.2°, and 17.4° ± 0.2°.

10. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.3° ± 0.2°, 11.1° ± 0.2°, 12.6° ± 0.2°, 17.1° ± 0.2°, and 18.9° ± 0.2°.

11. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1° ± 0.2° in combination with at least one peak selected from 12.6° ± 0.2°, 17.1° ± 0.2°, 6.3° ± 0.2°, and 18.9° ± 0.2°.

12. The tromethamine salt of claim 1, characterized by an X-ray powder diffraction pattern using CuKa radiation having peaks at diffraction angle 2-theta of 6.3° ± 0.2°, 11.1° ± 0.2°, 12.6° ± 0.2°, 17.1° ± 0.2°, and 18.9° ± 0.2°.

13. An erbumine salt of 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid.

14. The erbumine salt of claim 13, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 6.5° ± 0.2°, 10.5° ± 0.2°, 11.1° ± 0.2°, 15.2° ± 0.2°, 15.9° ± 0.2°, 17.6° ± 0.2°, 18.0° ±

0.2°, 19.3° ± 0.2°, 21.5° ± 0.2°, 22.2° ± 0.2°, 22.7° ± 0.2°, and 26.3° ± 0.2°.

15. The erbumine salt of claim 13, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1 ° ± 0.2° in combination with at least one peak selected from 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°.

16. The erbumine salt of claim 13, characterized by an X-ray powder diffraction pattern using CuKa radiation having a peak at diffraction angle 2-theta of 11.1 ° ± 0.2° in combination with the peaks 10.5° ± 0.2°, 15.2° ± 0.2°, 18.0° ± 0.2°, and 19.3° ± 0.2°.

17. The erbumine salt of any one of claims 13-16, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises at least one peak referenced to glycine (external reference at 176.5 ppm) selected from: 177.4, 174.8, 159.8, 151.7, 149.5, 134.0, 132.6, 130.7, 130.3, 129.0, 128.1, 123.1, 122.4, 119.4, 116.8, 115.9, 112.3, 53.0, 47.5, 27.4, 23.3, 21.3, and 11.3 ppm (± 0.2 ppm, respectively).

18. The erbumine salt of any one of claims 13-16, characterized by a ^{13}C solid state NMR (100.6 MHz) spectrum which comprises peaks referenced to glycine (external reference at 176.5 ppm) at: 177.4, 132.6, 27.4, 21.3, and 11.3 ppm (± 0.2 ppm, respectively).

19. A pharmaceutical composition comprising a tromethamine salt of any one of claims 1-12, or an erbumine salt of any one of claims 13-18, and a pharmaceutically acceptable carrier.

20. A method of inhibiting phosphoinositide 3-kinase (PI3K), comprising administering to a patient in need thereof a therapeutically effective amount of a tromethamine salt of any one of claims 1-12, an erbumine salt of any one of claims 13-18, or a pharmaceutical composition of claim 19.

21. A method of treating a patient with a disease associated with mutant phosphoinositide 3-kinase (PI3K), comprising administering to the patient a therapeutically

effective amount of a tromethamine salt of any one of claims 1-12, an erbumine salt of any one of claims 13-18, or a pharmaceutical composition of claim 19.

22. The method of claim 20 or claim 21, wherein the PI3K is PI3Kα.

23. The method of any one of claims 20-22, wherein the PI3K has a H1047R mutation.

24. The method of any one of claims 21-23, wherein the disease is a cancer.

25. The method of claim 24, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

26. The method of claim 24, wherein the cancer is breast cancer.

27. The method of claim 24, wherein the cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.

28. The method of any one of claims 21-23, wherein the disease is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal, and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS).

29. A tromethamine salt of any one of claims 1-12, an erbumine salt of any one of claims 13-18, or a pharmaceutical composition of claim 19, for use in treating a disease associated with mutant phosphoinositide 3-kinase (PI3K).

30. The tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to claim 29, wherein the PI3K is PI3Kα.

31. The tromethamine salt, erbumine salt, or pharmaceutical composition, for use

according to claim 29 or 30, wherein the PI3K has a H1047R mutation.

32. The tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to any one of claims 29-31, wherein the disease is a cancer.

33. The tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to claim 32, wherein the cancer is endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, breast cancer, brain cancer, or prostate cancer.

34. The tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to claim 32, wherein the cancer is breast cancer.

35. The tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to claim 32, wherein the cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.

36. The tromethamine salt, erbumine salt, or pharmaceutical composition, for use according to any one of claims 29-31, wherein the disease is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal, and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS).

37. Crystalline 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 7.0° ± 0.2°, 9.7° ± 0.2°, 11.9° ± 0.2°, 14.9° ± 0.2°, and 17.4° ± 0.2°.

38. Crystalline 2-[[(1R)-1-(3,6-dimethyl-4-oxo-2-phenyl-chromen-8-yl)ethyl]amino]benzoic acid, characterized by an X-ray powder diffraction pattern using CuKa radiation having at least one peak at diffraction angle 2-theta selected from 7.4° ± 0.2°,

8.5° ± 0.2°, 10.6° ± 0.2°, 13.4° ± 0.2°, and 15.7° ± 0.2.

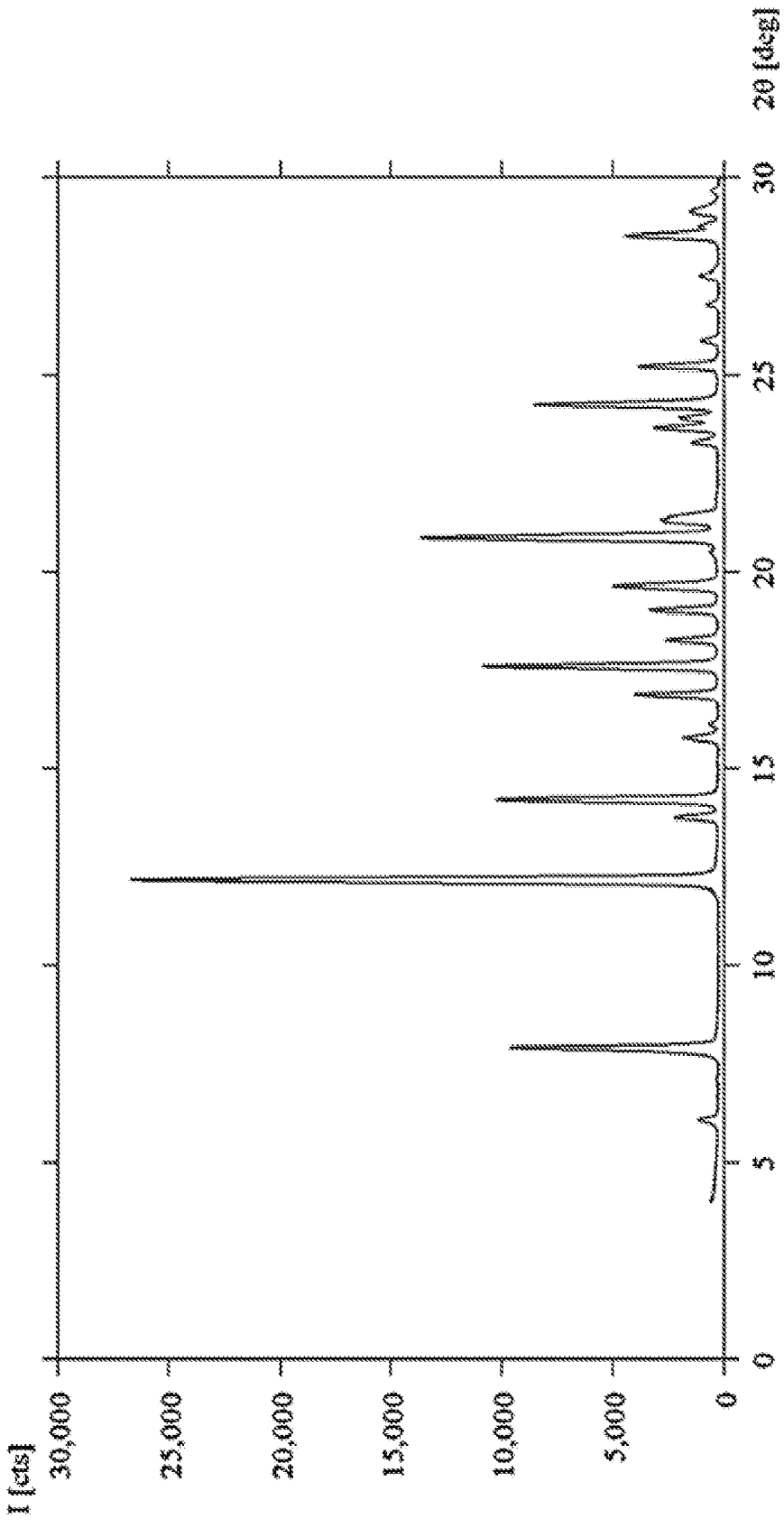
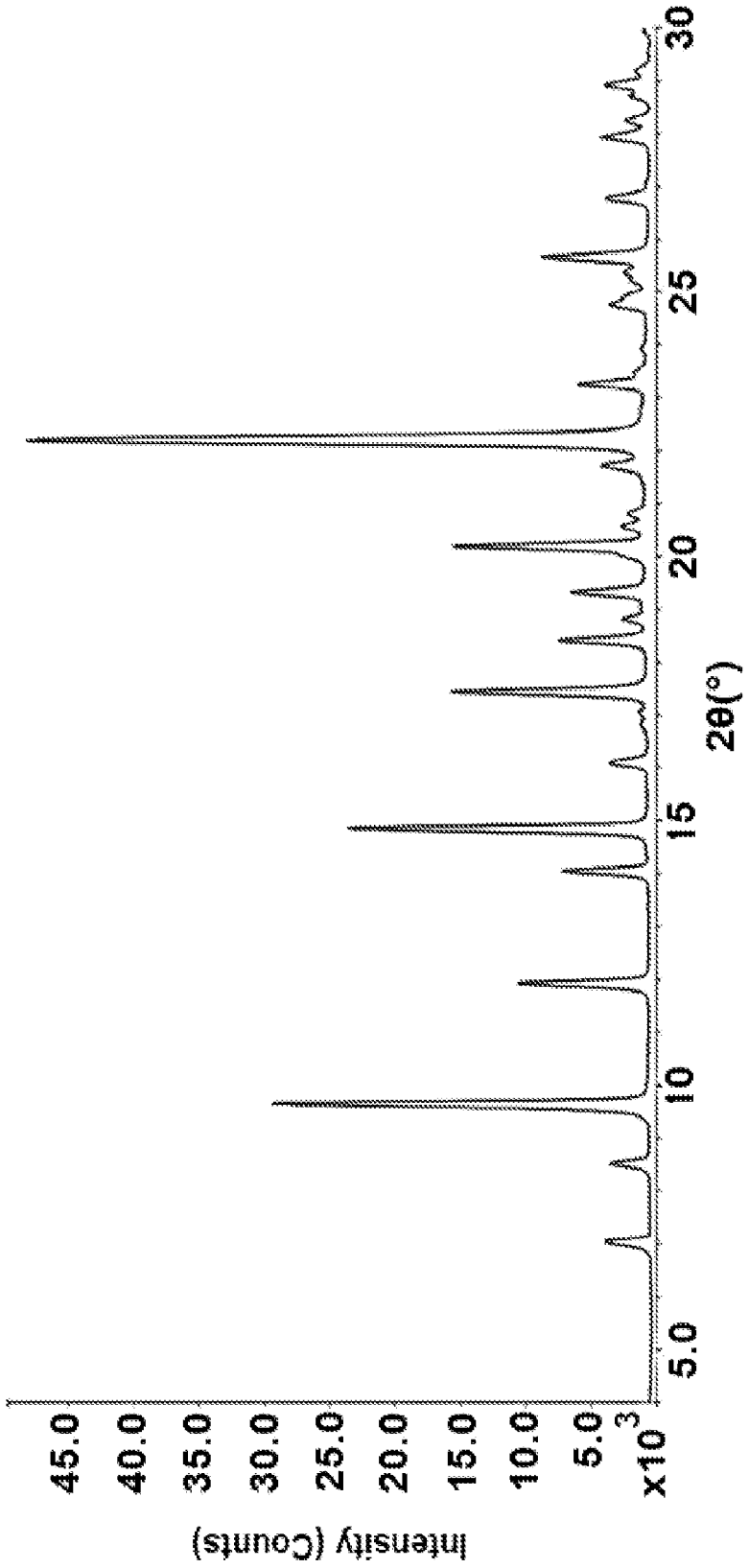

I [cts]
30,000
25,000
20,000
15,000
10,000
5,000
0
0
5
10
15
20
25
30
2θ [deg]

FIG. 1


Intensity (Counts)
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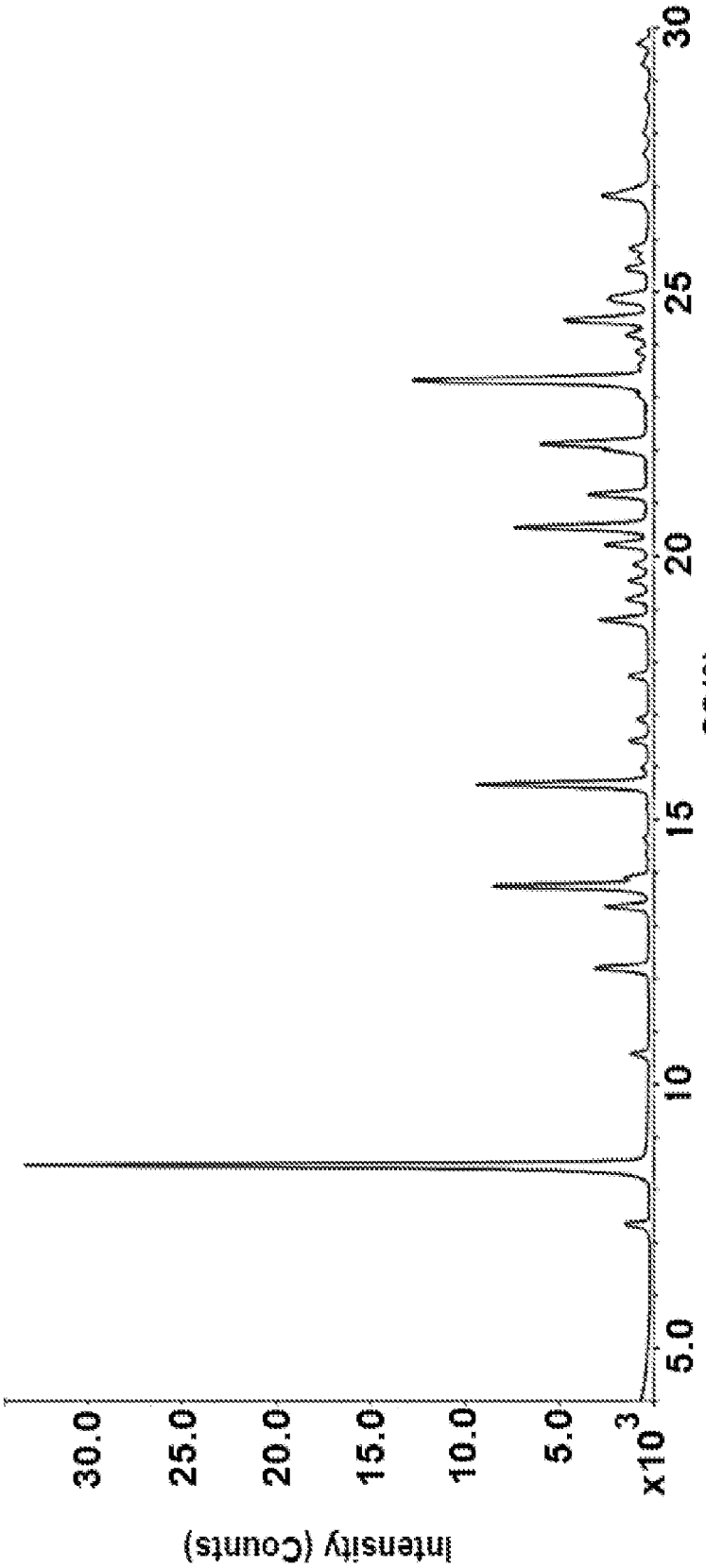
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
5.0
10
15
20
25
30
2θ(°)

FIG. 2


Intensity (Counts)
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10.0
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x10^3
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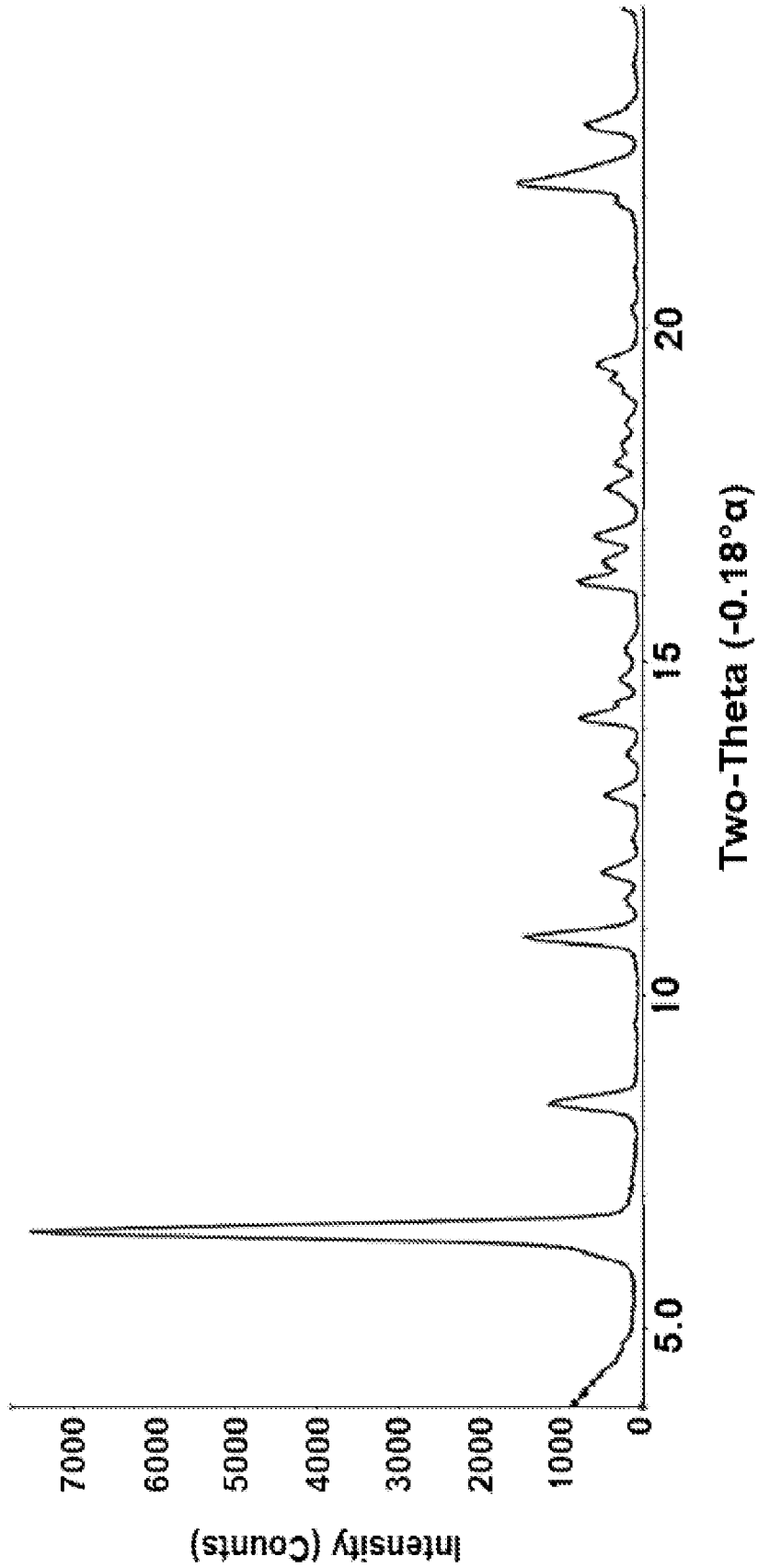
20
25
30
2θ(°)

FIG. 3


Intensity (Counts)
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4000
3000
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1000
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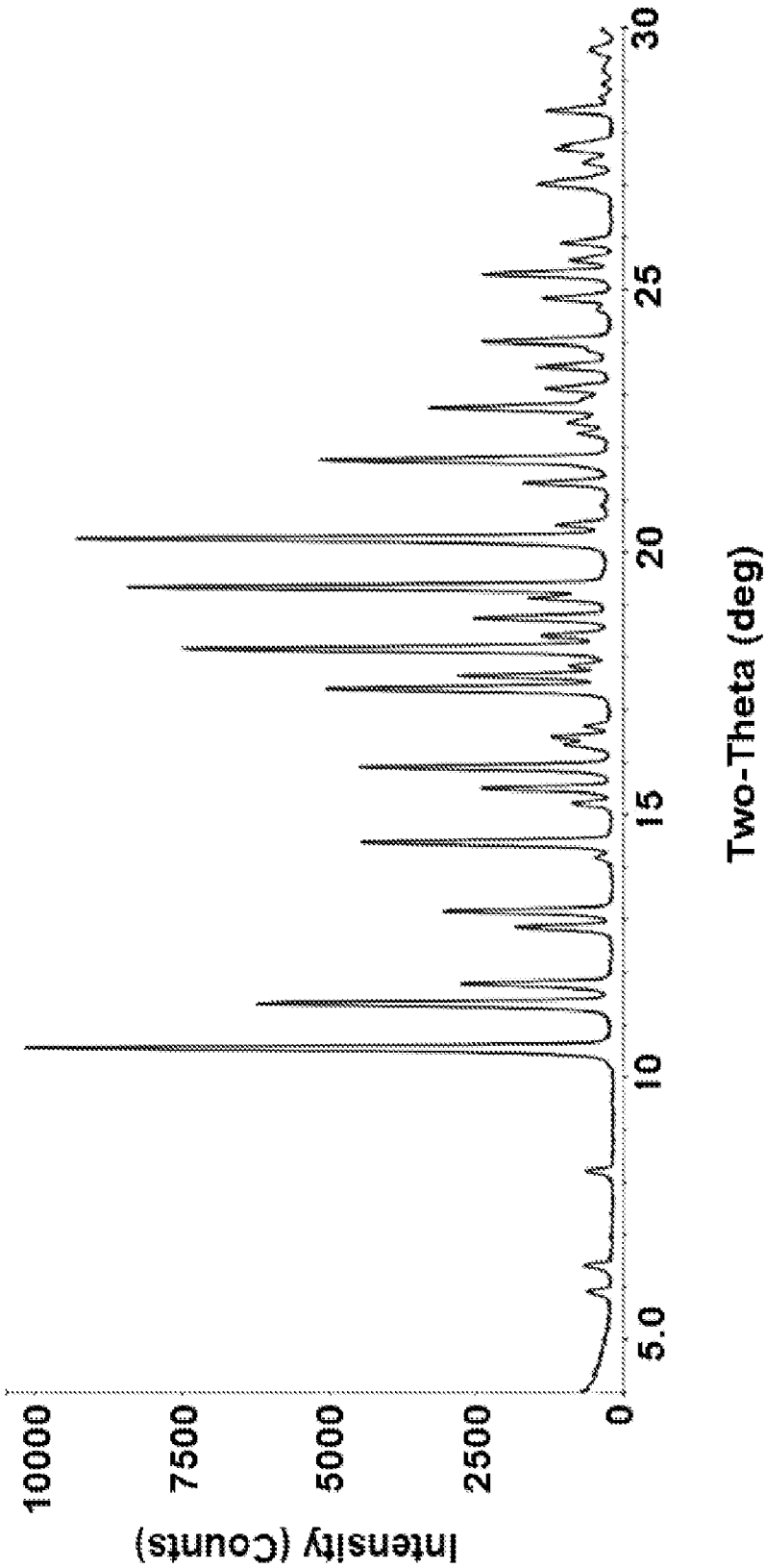
10
15
20
Two-Theta (-0.18°α)

FIG. 4


Intensity (Counts)
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2500
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5.0
10
15
20
25
30
Two-Theta (deg)

FIG. 5

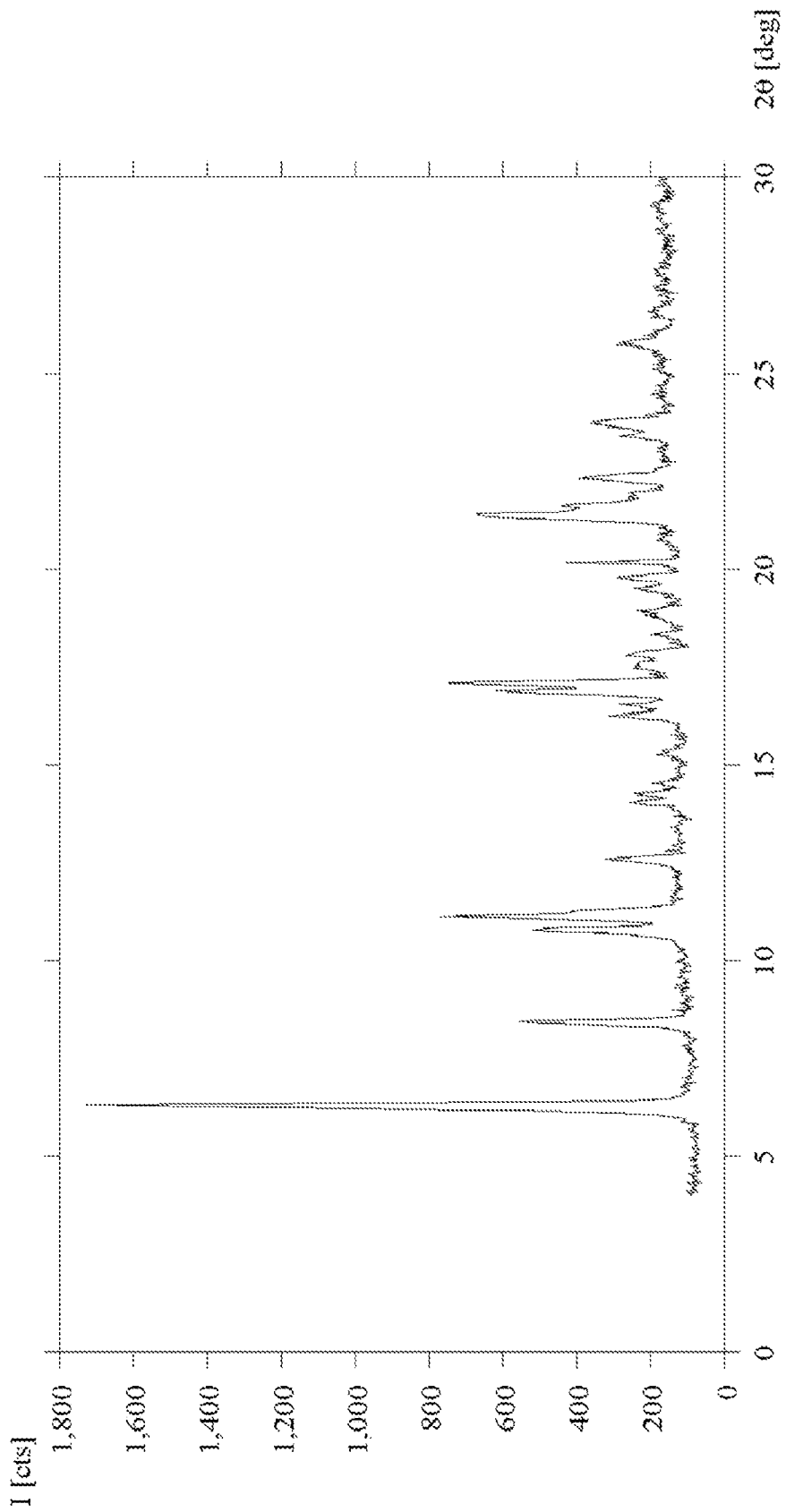
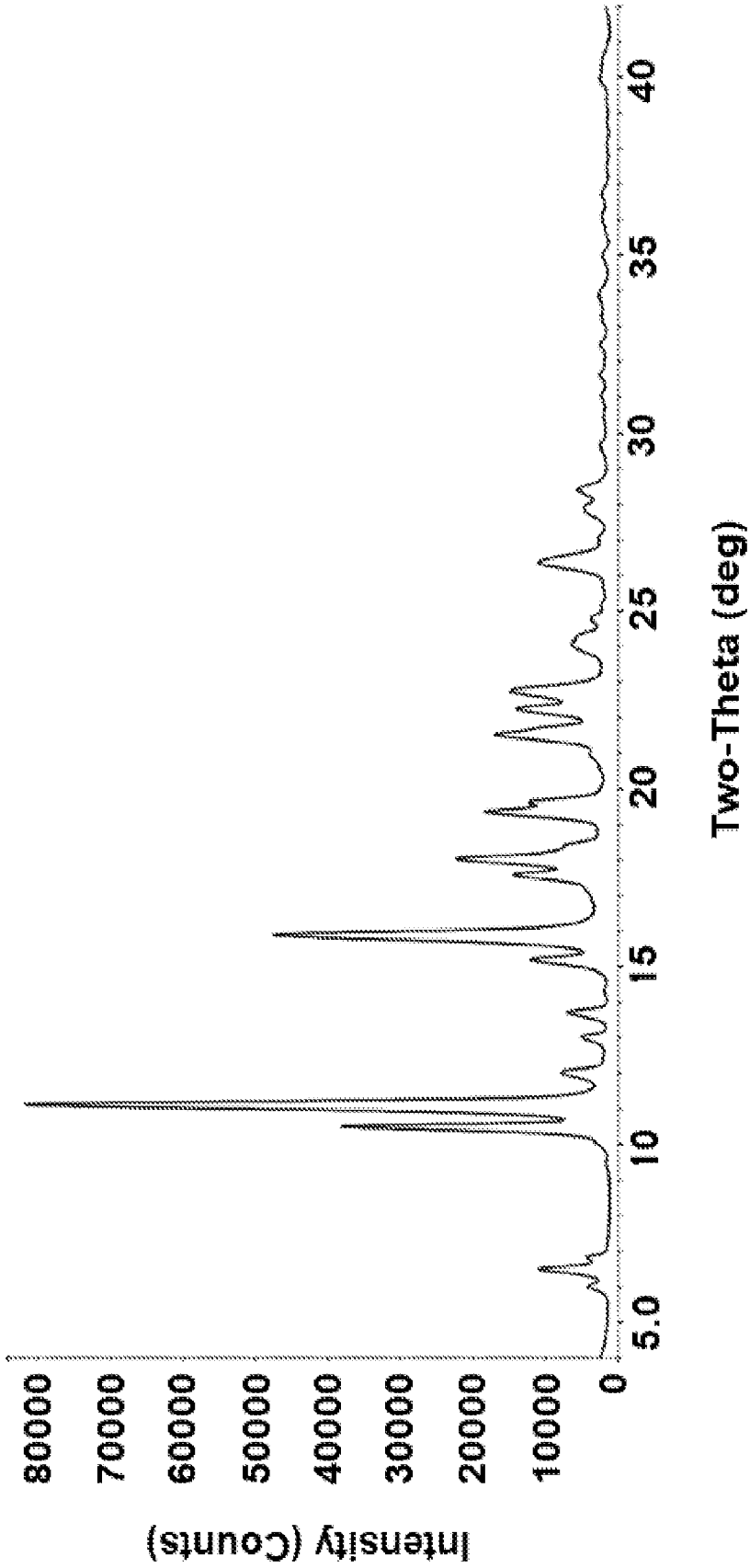

I [cts]
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
0
5
10
15
20
25
30
2θ [deg]

FIG. 6


Intensity (Counts)
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70000
60000
50000
40000
30000
20000
10000
0
5.0
10
15
20
25
30
35
40
Two-Theta (deg)

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/036445

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/30 A61P35/00 A61K31/352
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/202964 A1 (PETRA PHARMA CORP [US]) 7 October 2021 (2021-10-07) abstract page 367 - page 415; compounds 1-447 claim 1	1-38
A	WO 2004/016607 A1 (KINACIA PTY LTD [AU]; JACKSON SHAUN P [AU] ET AL.) 26 February 2004 (2004-02-26) abstract page 29 - page 49; compounds TGX195-TGX295 claim 1	1-38
X,P	WO 2022/235574 A1 (PETRA PHARMA CORP [US]) 10 November 2022 (2022-11-10) abstract page 224; example 21 claim 1	1-38

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2024	05/02/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/036445

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