# BROMODOMAIN INHIBITOR

## RELATED APPLICATION

[0001] This application claims priority benefit of U.S. Provisional Patent Application No. 62/151,205, filed April 22, 2015, incorporated fully herein by reference for all purposes.

## FIELD

[0002] The present embodiments provide compounds and pharmaceutical compositions useful for the treatment of cancer, such as, for example, 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one.

## BACKGROUND

[0003] A need exists in the art for effective treatments of cancer and neoplastic disease.

## SUMMARY

[0004] The present examples provide a bromodomain inhibitor, the compound 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one ("Compound 1"), which compound includes crystalline forms, amorphous forms, solvates, and hydrates thereof; as well as pharmaceutical compositions that include this compound.

[0004a] At least one aspect provides a pharmaceutical composition comprising a spray dried dispersion or a micronized form of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one.

[0005] At least one example provides a pharmaceutical composition comprising crystalline Form A of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methyliso-quinolin-1-one. In particular examples, the crystalline Form A of 4-[2-(cyclopropyl-methoxy)-5-methylsulfonylphenyl]-2-methyliso-quinolin-1-one exhibits X-ray powder diffraction (XRPD) 2theta reflection peaks at 7.8, 9.0, 15.7, 18.0, 21.1, 22.0, 23.6, and 24.5 2$\theta$.

[0005a] At least one aspect provides a pharmaceutical composition comprising crystalline Form A of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, characterized as exhibiting XRPD reflection peaks at 7.8, 9.0, 15.7, 18.0, 21.1, 22.0, 23.6 and 24.5 2-theta (2θ).

[0006] At least one example provides a pharmaceutical composition comprising amorphous 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one.

[0006a] At least one aspect provides a pharmaceutical composition comprising a spray dried dispersion or a micronized form of amorphous 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, characterized as exhibiting XRPD pattern in FIG. 2.

[0007] In at least one example, the pharmaceutical composition comprises 4-[2-(cycloropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one and at least one solid matrix polymer. A related example provides a pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmeth-oxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is from about 1:1 to about 1:9. Another example provides the pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is 1:1. Another example provides the pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is 1:2. Another example provides the pharmaceutical composition wherein the

ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is 1:3. Another example provides the pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methyliso-quinolin-1-one to solid matrix polymer is 1:4. Another example provides the pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is 1:5. Another example provides the pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is 1:6. Another example provides the pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is 1:7. Another example provides the pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is 1:8. Another example provides the pharmaceutical composition wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is 1:9.

[0008] At least one example provides a solid matrix comprising a polyvinyl-pyrrolididone derivative At least one embododiment provides a solid matrix comprising a cellulose derivative. The cellulose derivative may be at least one of hydroxypropylmethycellulose, hydroxypropylmethy-cellulose phthalate, hydroxypropylmethylcellulose acetate stearate, or hydroxypropylmethylcellulose acetate succinate. Another example provides the pharmaceutical composition wherein the cellulose derivative is hydroxypropylmethycellulose. Another example provides the pharmaceutical composition wherein the cellulose derivative is hydroxypropylmethy-cellulose phthalate. Another example provides the pharmaceutical composition wherein the cellulose derivative is hydroxypropylmethylcellulose acetate stearate. Another example provides the pharmaceutical composition wherein the cellulose derivative is hydroxypropylmethylcellulose acetate succinate.

[0009] In at least one example, the pharmaceutical composition comprises amorphous the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one and a solid polymer matrix.

[0010] In some examples, the pharmaceutical composition comprises a spray dried dispersion of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, and, optionally, further comprises a solid polymer matrix. In some examples, the pharmaceutical composition comprises micronized 4-[2-(cyclopropylmethoxy)-5-methyl-

sulfonylphenyl]-2-methylisoquinolin-1-one, and, optionally, further comprises a solid polymer matrix.

[0011] At least one example provides a pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one has been prepared by a process comprising spray drying.

[0011a] At least one aspect provides a pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one is processed by spray drying.

[0012] At least one example provides a pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one has been prepared by a process comprising rapid expansion of supercritical $CO_2$ solution (RESS) micronization.

[0012a] At least one aspect provides a pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one is micronized by rapid expansion of supercritical $CO_2$ solution (RESS) process.

[0013] At least one example provides a pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one and a solid matrix polymer, wherein the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methyl-isoquinolin-1-one has been processed by spray drying, and the solid matrix polymer is a polyvinylpyrrolididone derivative.

[0014] At least one example provides a pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one and a solid matrix polymer, wherein the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one is processed by spray drying, and the solid matrix polymer is a cellulose derivative.

[0015] At least one example provides a medicament for the treatment of cancer, wherein the medicament comprises a pharmaceutical composition comprising 4-[2-(cyclo-propyl-methoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the pharmaceutical composition includes a spray dried dispersion of the 4-[2-(cyclopropylmeth-oxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, optionally with a solid matrix polymer. At least one example provides a medicament for the treatement of

cancer, wherein the medicament comprises a pharmaceutical composition comprising 4-[2-(cyclopropylmeth-oxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the pharmaceutical composition is prepared by a process that includes spray dried dispersion, optionally with a solid matrix polymer. The cancer may be nuclear protein in testis (NUT) midline carcinoma (NMC), prostate cancer, breast cancer, bladder cancer, lung cancer, or melanoma. The cancer may be Burkitts lymphoma. The cancer may be gliobastoma (GBM), basal cell carcinoma, pancreatic, multiple myeloma, or acute myeloid leukemia (AML).

[0016] At least one example provides a method of treating cancer in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising 4-[2-(cyclopropyl-methoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the pharmaceutical composition is prepared by a process that includes spray dried dispersion. In certain examples, the cancer is NMC, prostate cancer, breast cancer, bladder cancer, lung cancer, or melanoma. In another example the cancer is Burkitts lymphoma. In other examples, the cancer is GBM, basal cell carcinoma, pancreatic, multiple myeloma, or AML.

[0016a] At least one aspect provides a pharmaceutical composition comprising a solid polymer matrix comprising: (a) an amorphous form of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one; and (b) a polymer selected from polyvinylpyrrolidone or hydroxypropyl methylcellulose; wherein the solid polymer matrix is a spray dried dispersion.

[0016b] At least one aspect provides the use of the pharmaceutical composition as described herein for preparation of a medicament for the treatment of cancer or other neoplastic disease.

## BRIEF DESCRIPTION OF THE FIGURES

[0017] FIG. 1 shows an X-ray powder diffraction (XRPD) pattern of crystalline Form A of Compound 1.

[0018] FIG. 2 shows an XRPD pattern of amorphous Compound 1.

[0019] FIG. 3 presents data from a differential scanning calorimetry (DSC) experiment for crystalline form A of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one (Compound 1).

[0020] FIG. 4 shows data from a gravimetric vapour sorption (GVS)/(DVS) isotherm plot experiment for crystalline form A of Compound 1. ♦ Cycle 1 Sorp; ■ Cycle 1 Desorp; ▲ Cycle 2 Sorp; □ Cycle 2 Desorp; ■ Cycle 3 Sorp.

[0021] FIG. 5 is a bar graph of AUG 0-20hr (hr ng/mL) from a full rat pharmacokinetic (PK) study of crystalline form A of Compound 1. Dosing was PO at 10 mg/kg, 30 mg/kg, 100 mg/kg, or 300 mg/kg.

[0022] FIG. 6 shows data from a 6 hr mouse PK study in which Compound 1 was processed as a spray dried dispersion (SDD) in four different formulations comprising Compound 1 and polymer.

[0023] FIG. 7 illustrates an XRPD pattern of amorphous Compound 1 in a SDD.

## CLAIMS

We claim:

1. A pharmaceutical composition comprising a spray dried dispersion or a micronized form of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one.

2. A pharmaceutical composition comprising crystalline Form A of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, characterized as exhibiting XRPD reflection peaks at 7.8, 9.0, 15.7, 18.0, 21.1, 22.0, 23.6 and 24.5 2-theta (2θ).

3. A pharmaceutical composition comprising a spray dried dispersion or a micronized form of amorphous 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, characterized as exhibiting XRPD pattern in FIG. 2.

4. A pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one is processed by spray drying.

5. A pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, wherein the 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one is micronized by rapid expansion of supercritical $CO_2$ solution (RESS) process.

6. The pharmaceutical composition of any one of claims 1-5, wherein the composition comprises at least one solid matrix polymer.

7. The pharmaceutical composition of claim 6, wherein the solid matrix polymer is polyvinylpyrrolidone or a polyvinylpyrrolidone derivative.

8. The pharmaceutical composition of claim 6, wherein the solid matrix polymer is a cellulose derivative.

9. The pharmaceutical composition of claim 8, wherein the cellulose derivative is hydroxypropylmethycellulose.

10. The pharmaceutical composition of claim 8, wherein the cellulose derivative is hydroxypropylmethycellulose phthalate.

11. The pharmaceutical composition of claim 8, wherein the cellulose derivative is hydroxypropylmethylcellulose acetate stearate.

12. The pharmaceutical composition of claim 8, wherein the cellulose derivative is hydroxypropylmethylcellulose acetate succinate.

13. The pharmaceutical composition of any one of the preceding claims, wherein the pharmaceutical composition is processed by spray drying.

14. The pharmaceutical composition of claim 6, wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is from about 1:1 to about 1:9.

15. The pharmaceutical composition of claim 6, wherein the ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one to solid matrix polymer is selected from 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, or 1:9.

16. A pharmaceutical composition comprising a solid polymer matrix comprising: (a) an amorphous form of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one; and (b) a polymer selected from polyvinylpyrrolidone or hydroxypropyl methylcellulose; wherein the solid polymer matrix is a spray dried dispersion.

17. The pharmaceutical composition of claim 16, wherein the polymer is hydroxypropyl methylcellulose present in a ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one:polymer of about 1:3.

18. The pharmaceutical composition of claim 16, wherein the polymer is hydroxypropyl methylcellulose present in ratio of 1:1 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one:polymer of about 1:1

19. The pharmaceutical composition of claim 16, wherein the polymer is polyvinylpyrrolidone in a ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one:polymer of about 1:3.

20. The pharmaceutical composition of claim 16, wherein the polymer is polyvinylpyrrolidone in a ratio of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one:polymer of about 1:1.

21. The use of the pharmaceutical composition of any one of the preceding claims for preparation of a medicament for the treatment of cancer or other neoplastic disease.

22. The use of claim 21, wherein the pharmaceutical composition comprises a solid polymer matrix comprising (a) an amorphous form of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one; and (b) a polymer selected from polyvinylpyrrolidone or hydroxypropyl methylcellulose; wherein the solid polymer matrix is a spray dried dispersion.

23. The use of claim 21, wherein the cancer is nuclear protein in testis (NUT) midline carcinoma (NMC), prostate cancer, breast cancer, bladder cancer, lung cancer, or melanoma.

24. The use of claim 21, wherein the cancer is Burkitts lymphoma.

25. The use of claim 21, wherein the cancer is gliobastoma (GBM), basal cell carcinoma, pancreatic, multiple myeloma, or acute myeloid leukemia (AML).