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 embodiments 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 embodiment provides a pharmaceutical composition comprising crystalline form of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one.

[0005] At least one embodiment provides a pharmaceutical composition comprising crystalline Form A of 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methyliso-quinolin-1-one. In particular embodiments, 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 2θ.

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

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

[0006b] At least one embodiment provides a pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one characterized as exhibiting XRPD pattern in FIG. 2 and at least one solid matrix polymer.

[0007] In at least one embodiment, the pharmaceutical composition comprises 4-[2-(cycloropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one and at least one solid matrix polymer. A related embodiment 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 embodiment 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 embodiment 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 embodiment provides the pharmaceutical composition wherein the

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

[0011] At least one embodiment 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 embodiment 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 embodiment 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 embodiment 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 embodiment 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 embodiment 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 embodiment 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 embodiment 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 embodiment 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 embodiments, the cancer is NMC, prostate cancer, breast cancer, bladder cancer, lung cancer, or melanoma. In another embodiment the cancer is Burkitts lymphoma. In other embodiments, the cancer is GBM, basal cell carcinoma, pancreatic, multiple myeloma, or AML.

[0016a] At least one embodiment 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 embodiment provides 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.

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.

[0024] FIG. 8a illustrates a rat PK study using a SDD comprising Compound 1, showing AUC 0-24hr (hr*ng/mL); dosing by oral administration (PO) at 10 mg/kg, 30 mg/kg, 100 mg/kg, or 300 mg/kg. FIG. 8b illustrates a dog PK study using a SDD comprising Compound 1, showing AUC 0-24hr (hr*ng/mL); dosing PO at 1 mg/kg, 3 mg/kg, or10 mg/kg.

DETAILED DESCRIPTION

[0025] It should be understood that this invention is not limited to the particular methodology, protocols, and reagents, etc., described herein and as such may vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims.

CLAIMS

We claim:

1. A pharmaceutical composition comprising crystalline 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 solid 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. A pharmaceutical composition comprising 4-[2-(cyclopropylmethoxy)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one characterized as exhibiting XRPD pattern in FIG. 2 and 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 any one of the preceding claims, 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 10, 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.