

TREATMENT OF CANCER

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. provisional patent application number 62/362,369 filed on July 14, 2016 which is incorporated herein by reference in its entirety.

BRIEF SUMMARY OF THE DISCLOSURE

[0002] Provided herein are compositions and methods for the treatment of cancer. The types of cancer suitable for the methods disclosed herein include, but are not limited to, hematological malignancy and Ewing's Sarcoma. The compositions useful for the methods of treating cancer disclosed herein comprise pyrrolo-pyrazole PKC inhibitors.

[0002a] In one aspect, provided herein is a use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a hematological malignancy in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002b] In one aspect, provided herein is a use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a diffuse large B-cell lymphoma (DLBCL) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002c] In one aspect, provided herein is a use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002d] In one aspect, provided herein is a use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-

tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a chronic lymphocytic leukemia (CLL) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002e] In one aspect, provided herein is a use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a relapsed or refractory chronic lymphocytic leukemia (CLL) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002f] In one aspect, provided herein is a use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an acute myeloid leukemia (AML) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002g] In one aspect, provided herein is a use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a relapsed or refractory acute myeloid leukemia (AML) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002h] In one aspect, provided herein is a use of (a) a composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) a BTK inhibitor in the manufacture of a medicament for treating a diffuse large B-cell lymphoma (DLBCL) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002i] In one aspect, provided herein is a use of (a) a composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) a BTK inhibitor in the

manufacture of a medicament for treating a chronic lymphocytic leukemia (CLL) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002j] In one aspect, provided herein is a use of (a) a composition comprising 5-
{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) a BTK inhibitor in the manufacture of a medicament for treating a acute myeloid leukemia (AML) in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002k] In one aspect, provided herein is a use of a pharmaceutical composition comprising 5-
{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a multiple myeloma in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002l] In one aspect, provided herein is a use of (a) a composition comprising 5-
{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) a BTK inhibitor in the manufacture of a medicament for treating a multiple myeloma in an individual in need thereof, wherein the medicament is to be administered to the individual.

[0002m] In one aspect, provided herein is a use of (a) a composition comprising 5-
{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) at least one oncology therapeutic selected from a SYK inhibitor, a dual SYK-JAK inhibitor, a PI3K inhibitor, a JAK-STAT inhibitor, a BCL2 inhibitor, an immunomodulatory agent, an antibody-drug conjugate, an immune checkpoint inhibitor, a PD-1 inhibitor, a TIM-3 inhibitor, a CTLA-4 inhibitor, a bromodomain inhibitor, an EZH2 inhibitor, an HDAC inhibitor, or an IDH2 inhibitor in the manufacture of a medicament for treating a hematological malignancy in an individual in need thereof, wherein the medicament is to be administered to the individual

[0003] One example provides a method of treating a hematological malignancy in a subject in need thereof comprising administering to the subject a composition comprising a compound having the formula 5-
{[(2S,5R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-

4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] **FIGS. 1A-B** shows the dose dependent inhibition of IL-6 production in TMD8 and OCI-Ly3 cells exposed to Compound A (**FIG. 1B**) or sotrastaurin (**FIG. 1A**).

[0005] **FIGS. 2A-B** shows the dose dependent inhibition of cell proliferation and survival in TMD8 and OCI-Ly3 cells exposed to Compound A (**FIG. 2B**) or sotrastaurin (**FIG. 2A**).

[0006] **FIGS. 3A-C** shows single agent treatment of TMD8 cells with either Compound A (**FIG. 3A**), ibrutinib (**FIG. 3B**), or combination treatment with Compound A and ibrutinib (**FIG. 3C**).

[0007] **FIG. 4** shows the effect of Compound A treatment on body weight in a TMD8 cell mouse xenograph model of DLBCL.

[0008] **FIG. 5** shows the effect of Compound A treatment on tumor volume in a TMD8 cell mouse xenograph model of DLBCL.

[0009] **FIG. 6** shows the lymphocyte count in a human subject treated with Compound A in a multiple ascending dose study.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a hematological malignancy in an individual in need thereof, wherein the medicament is to be administered to the individual.
2. The use of claim 1, wherein the hematological malignancy is a lymphoma or leukemia.
3. The use of claim 2, wherein the lymphoma or leukemia is a classical Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL), mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt's lymphoma, lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia), hairy cell leukemia, primary central nervous system (CNS) lymphoma, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), or chronic myelomonocytic leukemia (CMML).
4. The use of claim 3, wherein the diffuse large B-cell lymphoma (DLBCL) is activated B cell-like diffuse large B-cell lymphoma (ABC-DLBCL), germinal center B-cell-like diffuse large B-cell lymphoma (GCB-DLBC), primary mediastinal B-cell lymphoma, or intravascular large B-cell lymphoma.
5. The use of claim 3, wherein the marginal zone B-cell lymphoma is extranodal marginal zone lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, nodal marginal zone lymphoma, or splenic marginal zone lymphoma.
6. The use of claim 1, wherein the hematological malignancy is a relapsed or refractory hematological malignancy.

7. The use of claim 6, wherein the relapsed or refractory hematological malignancy is a relapsed or refractory lymphoma or leukemia.
8. The use of claim 7, wherein the relapsed or refractory lymphoma or leukemia is relapsed or refractory classical Hodgkin lymphoma, relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory follicular lymphoma, relapsed or refractory small lymphocytic lymphoma (SLL), relapsed or refractory chronic lymphocytic leukemia (CLL), relapsed or refractory mantle cell lymphoma, relapsed or refractory marginal zone B-cell lymphoma, relapsed or refractory Burkitt's lymphoma, relapsed or refractory lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia), relapsed or refractory hairy cell leukemia, relapsed or refractory primary central nervous system (CNS) lymphoma, relapsed or refractory acute lymphocytic leukemia (ALL), relapsed or refractory acute myeloid leukemia (AML), relapsed or refractory chronic myeloid leukemia (CML), or relapsed or refractory chronic myelomonocytic leukemia (CMML).
9. The use of claim 1, wherein use of ibrutinib is unsuitable or otherwise contraindicated in the individual.
10. Use of a pharmaceutical composition comprising 5-([(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl)-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a diffuse large B-cell lymphoma (DLBCL) in an individual in need thereof, wherein the medicament is to be administered to the individual.
11. The use of claim 10, wherein the DLBCL is ABC- DLBCL.
12. Use of a pharmaceutical composition comprising 5-([(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl)-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in an

individual in need thereof, wherein the medicament is to be administered to the individual.

13. The use of claim 12, wherein the DLBCL is ABC- DLBCL.
14. Use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a chronic lymphocytic leukemia (CLL) in an individual in need thereof, wherein the medicament is to be administered to the individual.
15. Use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a relapsed or refractory chronic lymphocytic leukemia (CLL) in an individual in need thereof, wherein the medicament is to be administered to the individual.
16. Use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an acute myeloid leukemia (AML) in an individual in need thereof, wherein the medicament is to be administered to the individual.
17. Use of a pharmaceutical composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a relapsed or refractory acute myeloid leukemia (AML) in an individual in need thereof, wherein the medicament is to be administered to the individual.

18. The use of any one of claims 8, 12, 13, 15 or 17, wherein the relapsed or refractory diffuse large B-cell lymphoma or leukemia is refractory to a BTK inhibitor.
19. The use of claim 18, wherein the BTK inhibitor is ibrutinib.
20. Use of (a) a composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) a BTK inhibitor in the manufacture of a medicament for treating a diffuse large B-cell lymphoma (DLBCL) in an individual in need thereof, wherein the medicament is to be administered to the individual.
21. The use of claim 20, wherein the BTK inhibitor is ibrutinib.
22. The use of claim 20, wherein the DLBCL is ABC-DLBCL.
23. Use of (a) a composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) a BTK inhibitor in the manufacture of a medicament for treating a chronic lymphocytic leukemia (CLL) in an individual in need thereof, wherein the medicament is to be administered to the individual.
24. The use of claim 23, wherein the BTK inhibitor is ibrutinib.
25. Use of (a) a composition comprising 5-{[(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl}-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) a BTK inhibitor in the manufacture of a medicament for treating a acute myeloid leukemia (AML) in an individual in need thereof, wherein the medicament is to be administered to the individual.
26. The use of claim 25, wherein the BTK inhibitor is ibrutinib.

27. Use of a pharmaceutical composition comprising 5-([(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl)-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a multiple myeloma in an individual in need thereof, wherein the medicament is to be administered to the individual.
28. The use of claim 27, wherein the multiple myeloma is relapsed or refractory multiple myeloma.
29. The use of claim 28, wherein the relapsed or refractory multiple myeloma is refractory to a BTK inhibitor.
30. The use of claim 29, wherein the BTK inhibitor is ibrutinib.
31. Use of (a) a composition comprising 5-([(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl)-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) a BTK inhibitor in the manufacture of a medicament for treating a multiple myeloma in an individual in need thereof, wherein the medicament is to be administered to the individual.
32. The use of claim 31, wherein the BTK inhibitor is ibrutinib.
33. Use of (a) a composition comprising 5-([(2S,5R)-2,5-Dimethyl-4-(tetrahydro-2H-pyran-4-ylmethyl)piperazin-1-yl]carbonyl)-N-(5-fluoro-2-methylpyrimidin-4-yl)-6,6-dimethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-amine, or a pharmaceutically acceptable salt thereof; and (b) at least one oncology therapeutic selected from a SYK inhibitor, a dual SYK-JAK inhibitor, a PI3K inhibitor, a JAK-STAT inhibitor, a BCL2 inhibitor, an immunomodulatory agent, an antibody-drug conjugate, an immune checkpoint inhibitor, a PD-1 inhibitor, a TIM-3 inhibitor, a CTLA-4 inhibitor, a bromodomain inhibitor, an EZH2 inhibitor, an HDAC inhibitor, or an IDH2 inhibitor in

the manufacture of a medicament for treating a hematological malignancy in an individual in need thereof, wherein the medicament is to be administered to the individual.

34. The use of claim 33, wherein the hematological malignancy is a lymphoma or leukemia.
35. The use of claim 34, wherein the lymphoma or leukemia is a classical Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL), mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt's lymphoma, lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia), hairy cell leukemia, primary central nervous system (CNS) lymphoma, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), or chronic myelomonocytic leukemia (CMML).
36. The use of claim 33, wherein the hematological malignancy is a relapsed or refractory hematological malignancy.
37. The use of claim 36, wherein the relapsed or refractory hematological malignancy is a relapsed or refractory lymphoma or leukemia.