heterocyclyl), and each R^a, R^b and R^c is independently optionally further substituted by 1-3 groups selected from halide, hydroxyl,-CN, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxyl and C_1-C_6 alkylamino; or, when connected to the same nitrogen, R^a and R^b may together optionally form a 3-7 membered heterocyclyl, which may optionally be further substituted by 0-3 groups selected from halide, hydroxyl, -CN, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, C_1-C_6 alkoxyl or C_1-C_6 alkylamino;

each R^d and R^e is independently-(C_1-C_3 alkylene)-,-(C_2-C_5 alkenylene)-,or-(C_2-C_5 alkynylene)-; and each m is independently 0 or 1, or a pharmaceutically acceptable salt thereof.

[00124] Another embodiment provides a method of treating a hematological malignancy, wherein for the compound of Formula (B), A is N and B is C. Another embodiment provides a method of treating a hematological malignancy, wherein for the compound of Formula (B), R^9 and R^{10} are both methyl. Another embodiment provides a method of treating a hematological malignancy, wherein for the compound of Formula (B), R^4 is-$(R^d)_m$-OR^a, C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl. Another embodiment provides a method of treating a hematological malignancy, wherein for the compound of Formula (B), R^4 is methyl. Another embodiment provides a method of treating a hematological malignancy, wherein for the compound of Formula (B), R^1 is –$(R^d)_m$-OR^a, C_1-C_8 alkyl, or-$(R^d)_m$-NR^aR^b. Another embodiment provides a method of treating a hematological malignancy, wherein for the compound of Formula (B), each R^d and R^e is independently an-(C_1-C_3 alkylene)-.

[00125] One embodiment provides a method of treating a hematological malignancy in an individual in need thereof, comprising administering to the individual 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. Another embodiment provides the method wherein the hematological malignancy is a lymphoma or leukemia.

[00125a] One embodiment provides 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.

[00126] Another embodiment provides the method 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). Another embodiment provides the method 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.

[00127] Another embodiment provides the method 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.

[00128] Another embodiment provides the method wherein the hematological malignancy is a relapsed or refractory hematological malignancy. Another embodiment provides the method wherein the relapsed or refractory hematological malignancy is a relapsed or refractory lymphoma or leukemia. Another embodiment provides the method 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).

[00129] One embodiment provides a method of treating a hematological malignancy in an individual in need thereof, comprising administering to the individual 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, wherein the use of ibritinub is unsuitable or otherwise contraindicated.

[00130] One embodiment provides a method of treating a diffuse large B-cell lymphoma (DLBCL) in an individual in need thereof, comprising administering to the individual 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. Another

embodiment provides the method wherein the DLBCL is ABC- DLBCL.

[00130a] One embodiment provides 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.

[00131] One embodiment provides a method of treating a relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in an individual in need thereof, comprising administering to the individual 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. Another embodiment provides the method wherein the relapsed or refractory diffuse large B-cell lymphoma (DLBCL) is refractory to a BTK inhibitor. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib. Another embodiment provides the method wherein the DLBCL is ABC- DLBCL.

[00131a] One embodiment provides 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.

[00132] One embodiment provides a method of treating a chronic lymphocytic leukemia (CLL) in an individual in need thereof, comprising administering to the individual 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. Another embodiment provides the method further comprising administration of selinexor.

[00132a] One embodiment provides 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.

[00133] One embodiment provides a method of treating a relapsed or refractory chronic lymphocytic leukemia (CLL) in an individual in need thereof, comprising administering to the individual 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. Another embodiment provides the method wherein the relapsed or refractory chronic lymphocytic leukemia (CLL) is refractory to a BTK inhibitor. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib. Another embodiment provides the method further comprising administration of selinexor.

[0133a] One embodiment provides 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.

[00134] One embodiment provides a method of treating a chronic lymphocytic leukemia (CLL) in an individual in need thereof, comprising administering to the individual: (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; (b) a BTK inhibitor; and (c) a composition comprising selinexor. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib.

[00135] One embodiment provides a method of treating a relapsed or refractory chronic lymphocytic leukemia (CLL) in an individual in need thereof, comprising administering to the individual: (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 composition comprising selinexor. Another embodiment provides the method wherein the relapsed or refractory chronic lymphocytic leukemia (CLL) is refractory to a BTK inhibitor. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib.

[00136] One embodiment provides a method of treating a diffuse large B-cell lymphoma (DLBCL) in an individual in need thereof, comprising administering to the individual: (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. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib. Another embodiment provides the method wherein the DLBCL is ABC- DLBCL.

[00136a] One embodiment provides 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.

[00137] One embodiment provides a method of treating a chronic lymphocytic leukemia (CLL) in an individual in need thereof, comprising administering to the individual: (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. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib.

[00137a] One embodiment provides 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.

[00138] One embodiment provides a method of treating an acute myeloid leukemia (AML) in an individual in need thereof, comprising administering to the individual 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.

[00138a] One embodiment provides 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.

[00139] One embodiment provides a method of treating a relapsed or refractory acute myeloid leukemia (AML) in an individual in need thereof, comprising administering to the

individual 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.

[00139a] One embodiment provides 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.

[00140] One embodiment provides a method of treating a acute myeloid leukemia (AML) in an individual in need thereof, comprising administering to the individual: (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. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib.

[00140a] One embodiment provides 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.

[00141] One embodiment provides a method of treating multiple myeloma in an individual in need thereof, comprising administering to the individual 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. Another embodiment provides the method wherein the multiple myeloma is relapsed or refractory multiple myeloma. Another embodiment provides the method wherein the relapsed or refractory multiple myeloma is refractory to a BTK inhibitor. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib.

[00141a] One embodiment provides 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.

[00142] One embodiment provides a method of treating a multiple myeloma in an individual in need thereof, comprising administering to the individual: (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. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib.

[00142a] One embodiment provides 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.

[00143] One embodiment provides a method of treating a Ewing's sarcoma in an individual in need thereof, comprising administering to the individual 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.

[00143a] One embodiment provides 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 Ewing's sarcoma in an individual in need thereof, wherein the medicament is to be administered to the individual.

[00144] One embodiment provides a method of treating a small lymphocytic lymphoma (SLL) in an individual in need thereof, comprising administering to the individual 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. Another embodiment provides the method further comprising administration of selinexor.

[00145] One embodiment provides a method of treating a relapsed or refractory small lymphocytic lymphoma (SLL) in an individual in need thereof, comprising administering to the individual 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. Another embodiment provides the method wherein the relapsed or refractory small lymphocytic lymphoma (SLL) is refractory to a BTK inhibitor. Another embodiment provides the method wherein the BTK inhibitor is ibrutinib. Another embodiment provides the method further comprising administration of selinexor.

[00146] One embodiment provides a method of treating a small lymphocytic lymphoma (SLL) in an individual in need thereof, comprising administering to the individual: (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-

composition. In some instances, the lymphocyte count is increased by at least 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 99%, relative to a second individual without the administration of the pharmaceutical composition. In some instances, the lymphocyte count is higher than 3000 lymphocytes per microliter of blood in the first individual after administration of the pharmaceutical composition.

[00157] One embodiment provides a method of inducing lymphocytosis in a first individual, comprising administering to the first individual: (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; (b) ibrutinib; and (c) a composition comprising selinexor; wherein the lymphocyte count is increased in the first individual relative to a second individual without the administration of the compositions of (a), (b), and (c). In some instances, the lymphocyte count is increased by at least 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 99%, relative to the second individual. In some instances, the lymphocyte count is higher than 3000 lymphocytes per microliter of blood in the first individual post-administration.

[00158] One embodiment provides a method for inducing apoptosis in a cell comprising administering to the cell an effective amount of 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.

[00158a] One embodiment provides a use of 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 in the manufacture of a medicament for inducing apoptosis in a cell, wherein an effective amount of the medicament is to be administered to the cell.

[00159] One embodiment provides a method for decreasing cell proliferation in a cell comprising administering to the cell an effective amount of 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.

[00159a] One embodiment provides a use of 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 in the manufacture of a medicament for decreasing cell

proliferation in a cell, wherein an effective amount of the medicament is to be administered to the cell.

Combination Therapy

[00160] In some instances, the methods described herein further comprise combination therapy with at least one additional oncology therapeutic agent. One embodiment provides a method of treating a hematological malignancy in an individual in need thereof, comprising administering to the individual: (a) a composition comprising a compound of formula (I), formula (A) or formula (B), 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 coojugate, 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.

[00161] One embodiment provides a method of treating a hematological malignancy in an individual in need thereof, comprising administering to the individual: (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 coojugate, 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.

[00161a] One embodiment provides 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 coojugate, 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.

[00162] Another embodiment provides the method wherein the hematological malignancy is a lymphoma or leukemia. Another embodiment provides the method 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). Another embodiment provides the method wherein the hematological malignancy is a relapsed or refractory hematological malignancy. Another embodiment provides the method wherein the relapsed or refractory hematological malignancy is a relapsed or refractory lymphoma or leukemia.

Pharmaceutical compositions and dosage forms

[00163] The pyrrolo-pyrazole compounds used in the methods described herein are, in some instances, administered orally as tablets or capsules, as oily or aqueous suspensions, lozenges, troches, powders, granules, emulsions, syrups or elixirs. The compositions for oral use may include one or more agents for flavoring, sweetening, coloring and preserving in order to produce pharmaceutically elegant and palatable preparations. Tablets may contain pharmaceutically acceptable excipients as an aid in the manufacture of such tablets. As is conventional in the art these tablets may be coated with a pharmaceutically acceptable enteric coating, such as glyceryl monostearate or glyceryl distearate, to delay disintegration and absorption in the gastrointestinal tract to provide a sustained action over a longer period.

[00164] Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium

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 ibritinub 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 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 Ewing's sarcoma in an individual in need thereof, wherein the medicament is to be administered to the individual.

34. Use of 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 in the manufacture of a medicament for inducing apoptosis in a cell, wherein an effective amount of the medicament is to be administered to the cell.

35. Use of 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 in the manufacture of a medicament for decreasing cell proliferation in a cell, wherein an effective amount of the medicament is to be administered to the cell.

36. 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 coojugate, 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.

37. The use of claim 36, wherein the hematological malignancy is a lymphoma or leukemia.

38. The use of claim 37, 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).

39. The use of claim 36, wherein the hematological malignancy is a relapsed or refractory hematological malignancy.

40. The use of claim 39, wherein the relapsed or refractory hematological malignancy is a relapsed or refractory lymphoma or leukemia.