



(51) International Patent Classification:

C07D 403/12 (2006.01) A61P 35/00 (2006.01)
A61K 31/407 (2006.01)

(21) International Application Number:

PCT/CN2020/133636

(22) International Filing Date:

03 December 2020 (03.12.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PCT/CN2019/122380
02 December 2019 (02.12.2019) CN
PCT/CN2020/072803
17 January 2020 (17.01.2020) CN
PCT/CN2020/088323
30 April 2020 (30.04.2020) CN

(71) Applicant: **BEIGENE, LTD.**; c/o Maurant Governance Services (Cayman) Limited, 94 Solaris Avenue, Camana Bay, Grand Cayman, KY1-1108 (KY).

(72) Inventor; and

(71) Applicant (for SC only): **HU, Nan** [CN/CN]; No. 30 Science Park Road, Zhongguancun Life Science Park, Changping, Beijing 102206 (CN).

(72) Inventors: **GUO, Yin**; No. 30 Science Park Road, Zhongguancun Life Science Park, Changping, Beijing 102206 (CN). **GUO, Yunhang**; No. 30 Science Park Road, Zhongguancun Life Science Park, Changping, Beijing 102206 (CN). **WANG, Zhiwei**; No. 30 Science Park Road, Zhongguancun Life Science Park, Changping, Beijing 102206 (CN).

(74) Agent: **WU, FENG & ZHANG**; 3 FL, Building 2, Yard 3, FengXiuZhongLu Road, Haidian District, Beijing 100094 (CN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- with information concerning request for restoration of the right of priority in respect of one or more priority claims (Rules 26bis.3 and 48.2(b)(vii))

(54) Title: METHODS OF CANCER TREATMENT USING BCL-2 INHIBITOR

(57) Abstract: Provided herein are methods of treating cancer in a subject with a Bcl-2 inhibitor, in particular-ly 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-(((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl) pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide or a pharmaceutically acceptable salt thereof.

WO 2021/110102 A1

METHODS OF CANCER TREATMENT USING BCL-2 INHIBITOR

FIELD OF THE DISCLOSURE

[0001] Disclosed herein are methods of treating cancer with a Bcl-2 inhibitor, in particularly 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide or a pharmaceutically acceptable salt thereof.

BACKGROUND OF THE DISCLOSURE

[0002] Impaired apoptosis plays a central role in tumor development, tumor maintenance, and therapeutic resistance. Apoptosis can be triggered via two main pathways: the extrinsic or death-receptor-mediated pathway, and the intrinsic or mitochondrial pathway (Czabotar et al 2014). It is the intrinsic pathway that is more commonly perturbed in lymphoid malignancies. Cell death mediated through this pathway is regulated by members of a family of proteins related to B-cell lymphoma-2 (Bcl-2), which is considered to contain three subfamilies. The pro-survival subgroup (Bcl-2, Bcl-xL, Bcl-W, Mcl-1, A1/Bfl-1, and possibly Bcl-B) promotes cell survival by inhibiting their pro-apoptotic relatives. The pro-apoptotic BAX/BAK-like proteins, including BOK, are the essential effectors of apoptosis, and the BH3-only proteins (BIM, PUMA, BID, NOXA, BMF, BIK, and HRK) are the initiators of apoptosis (Anderson et al 2014). In healthy cells, the pro-survival Bcl-2 proteins bind and inhibit BAX and BAK after they have been partially activated, impairing the ability of BAX/BAK to oligomerize and form pores to induce mitochondrial outer membrane permeabilization. The BH3-only proteins are induced transcriptionally or post-transcriptionally in response to diverse stresses and initiate apoptosis by either binding the pro-survival Bcl-2 proteins, thereby unleashing BAX/BAK, or by directly activating these effectors of apoptosis. The various Bcl-2 family proteins have differential specificity of binding to one another, resulting in a complex but ordered network of interactions governing cell fate (Roberts 2016).

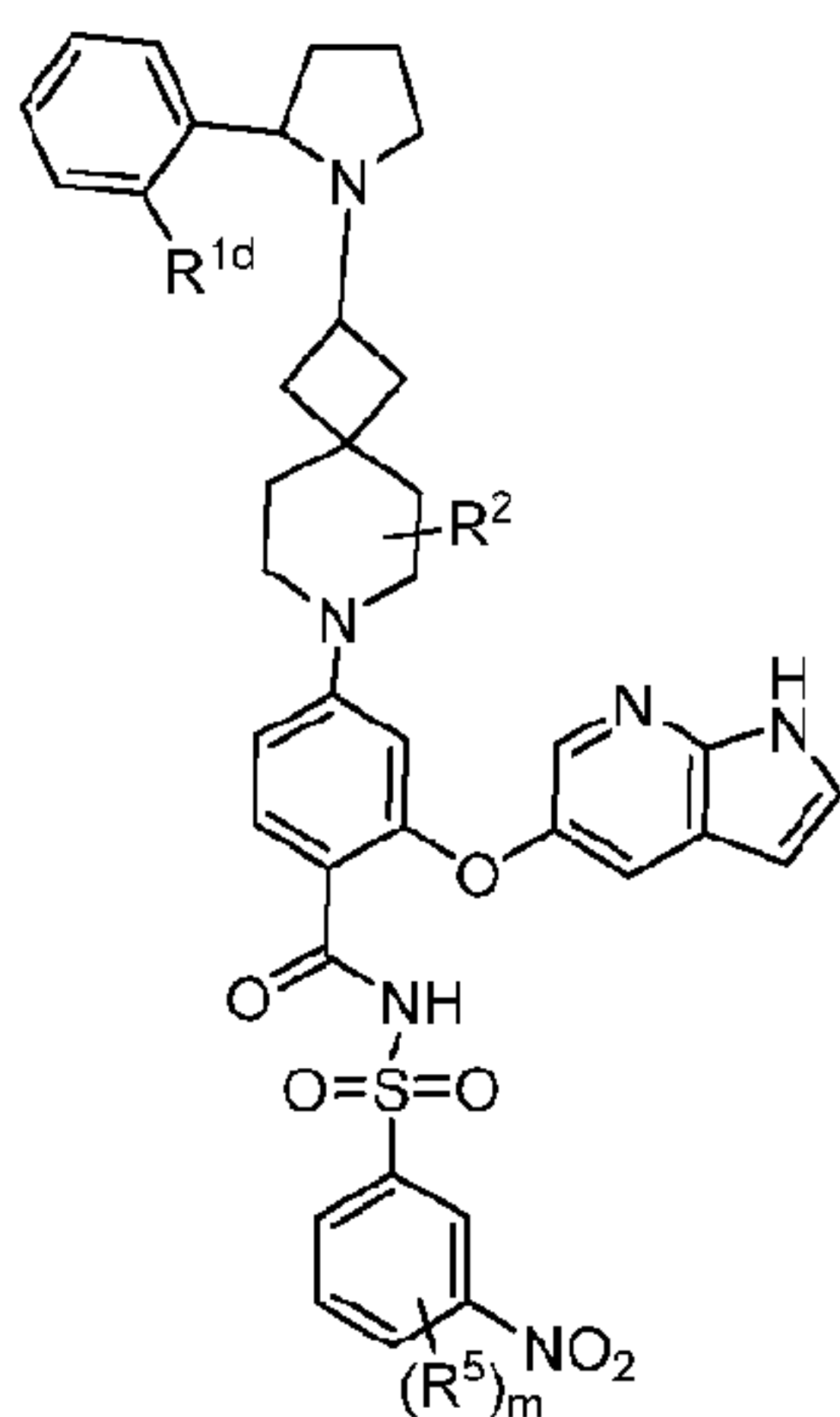
[0003] Bcl-2 was the first anti-apoptotic protein discovered in 1980s as a consequence of t(14;18) chromosomal translocation and the hallmark of FL. BCL-2 gene resides on chromosome 18q21.33. The Bcl-2 protein has 239 amino acids and a molecular weight of 26 kDA (Schenk et al 2017). Bcl-2 is widely expressed during development and becomes restricted upon maturation in many tissues (Kondo et al 2008). Mice lacking Bcl-2 succumb to polycystic kidney disease early in life because Bcl-2 is critical for the survival of renal epithelial progenitor cells during embryogenesis (Veis et al 1993). The Bcl-2-deficient mice

also have abnormally reduced numbers of mature, resting B and T lymphocytes, and gray prematurely because of the aberrant death of melanocytes (Veis et al 1993, Yamamura et al 1996). Although originally believed to act as a classical growth-driving oncogene, it was later shown that Bcl-2 instead promotes malignant cell survival by attenuating apoptosis. Transgenic mice with pan-hematopoietic Bcl-2 expression (VavP-*BCL-2*) preferentially develop follicular lymphoma, preceded by florid germinal center hyperplasia (Egle et al 2004). Mice co-expressing *BCL-2* and *MYC* transgenes developed lymphomas markedly faster than littermates expressing either transgene alone, validating *BCL-2* as an oncogene (Adams and Cory 2007).

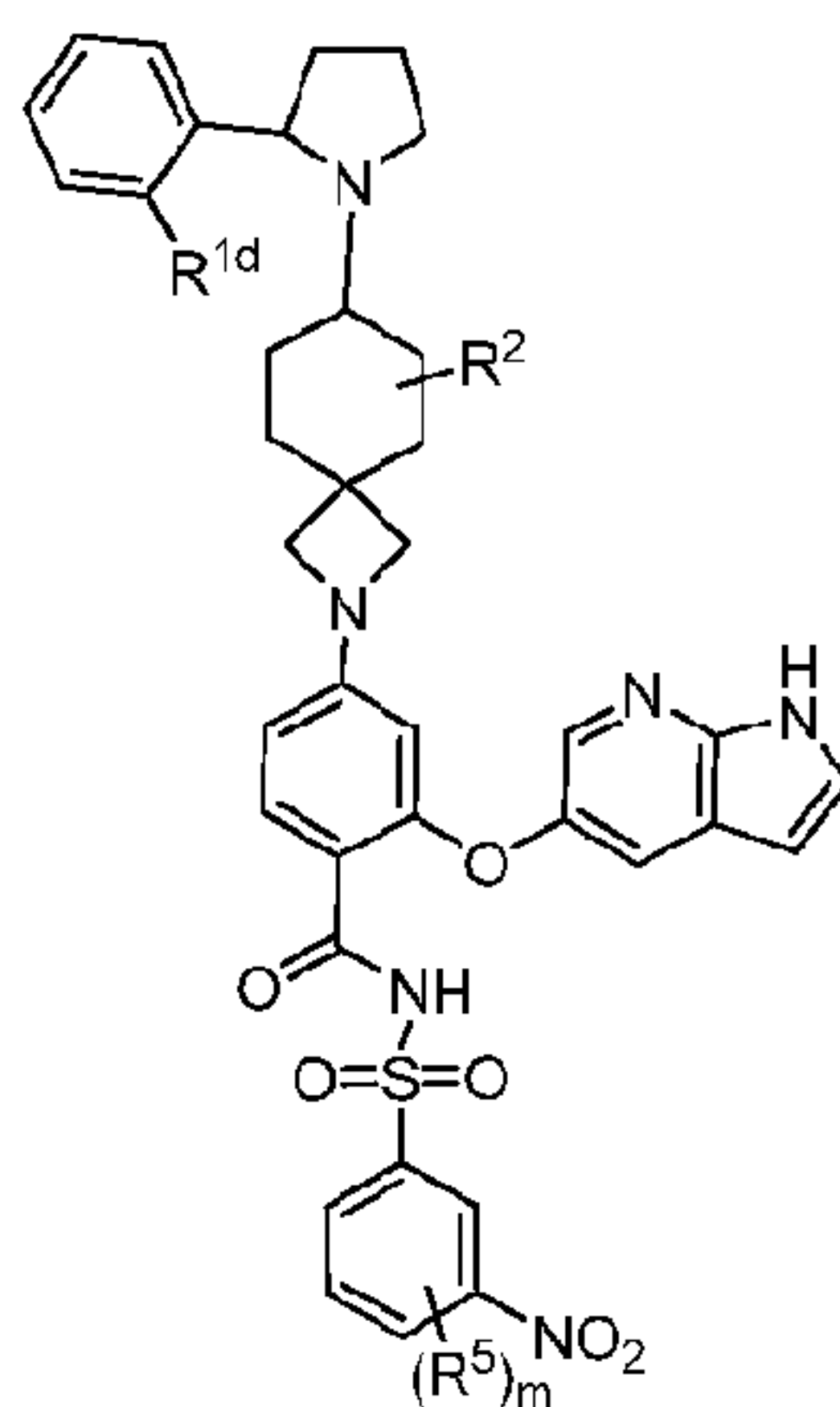
[0004] High Bcl-2 expression is almost universal in CLL, FL, MCL, and Waldenstrom macroglobulinemia (WM); in contrast, the levels of Bcl-2 expression are somewhat more variable among multiple myeloma (MM) and substantially more variable among DLBCL and B-lineage acute lymphoblastic leukemia (Roberts and Huang 2017). When Bcl-2 is overexpressed, the ratio of pro- and anti-apoptotic Bcl-2 family members is disturbed and apoptotic cell death can be prevented. Moreover, Bcl-2 protein is closely related to chemoresistance in hematological tumors. As Bcl-2-mediated resistance to intrinsic apoptosis is considered as a key to pathogenesis, targeting Bcl-2 can improve apoptosis and overcome drug resistance to cancer therapy. Thus, Bcl-2 has become an attractive target for therapeutic strategy in cancer.

[0005] Venetoclax (ABT-199) was approved for treating patients with chronic lymphocytic leukemia (CLL) and acute myeloblastic leukemia (AML). However, despite this high clinical activity and favorable safety profile, patients can develop acquired resistance to venetoclax over time with continuous treatment. Blombery et al demonstrated that the Gly101Val mutation (G101V mutation) in *BCL-2* confers acquired refractoriness by reducing the binding affinity of venetoclax without disrupting the binding of pro-apoptotic proteins to Bcl-2. The novel Gly101Val mutation in *Bcl-2* was identified at progression in 7 of 15 patients. This mutation is mainly found in patients after long-term exposure to venetoclax monotherapy (Tausch et al 2019).

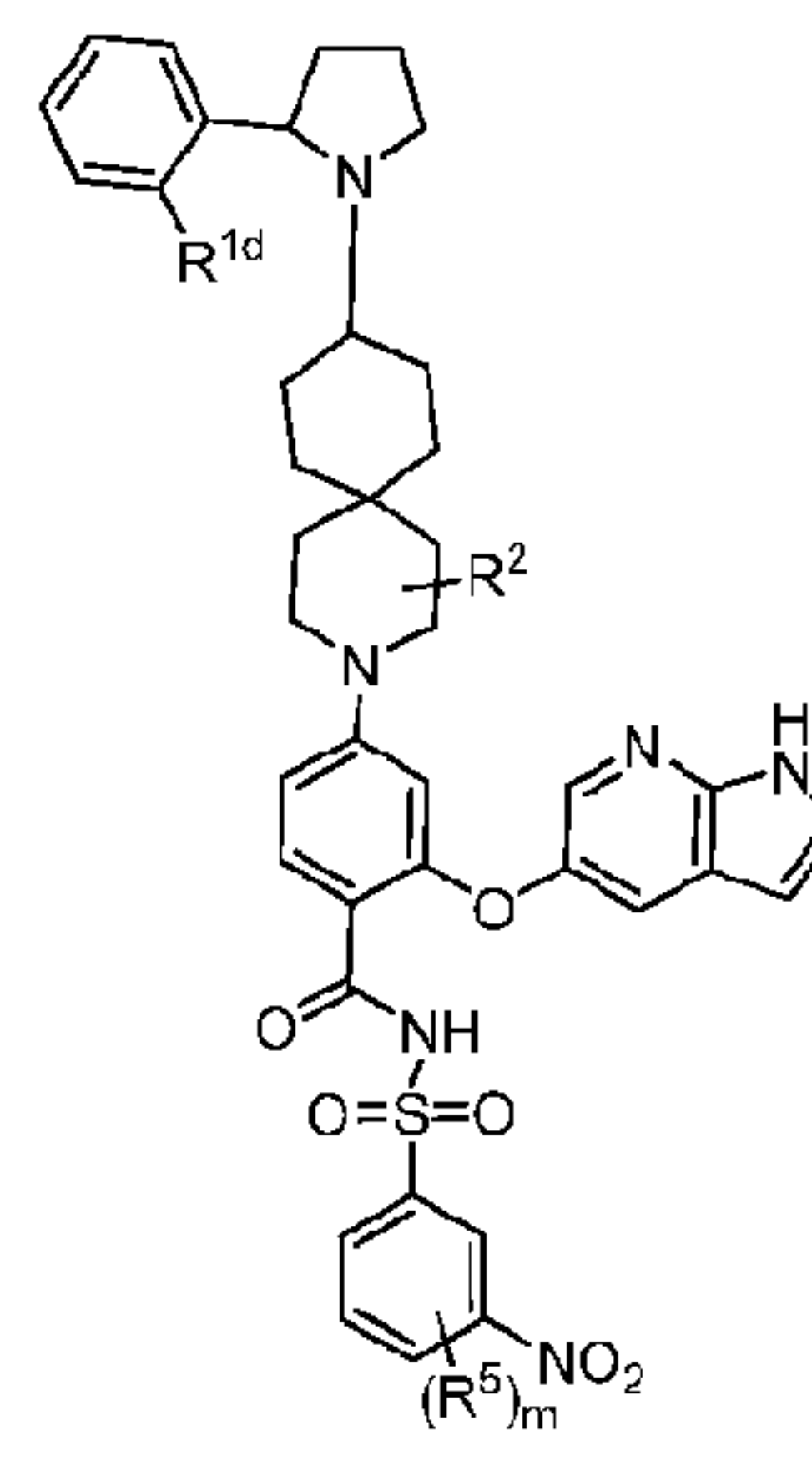
[0006] WO2019/210828A disclosed a series of compounds having following Formulas (III-B), (III-C), (III-D) or (III-E), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as Bcl-2 inhibitors,



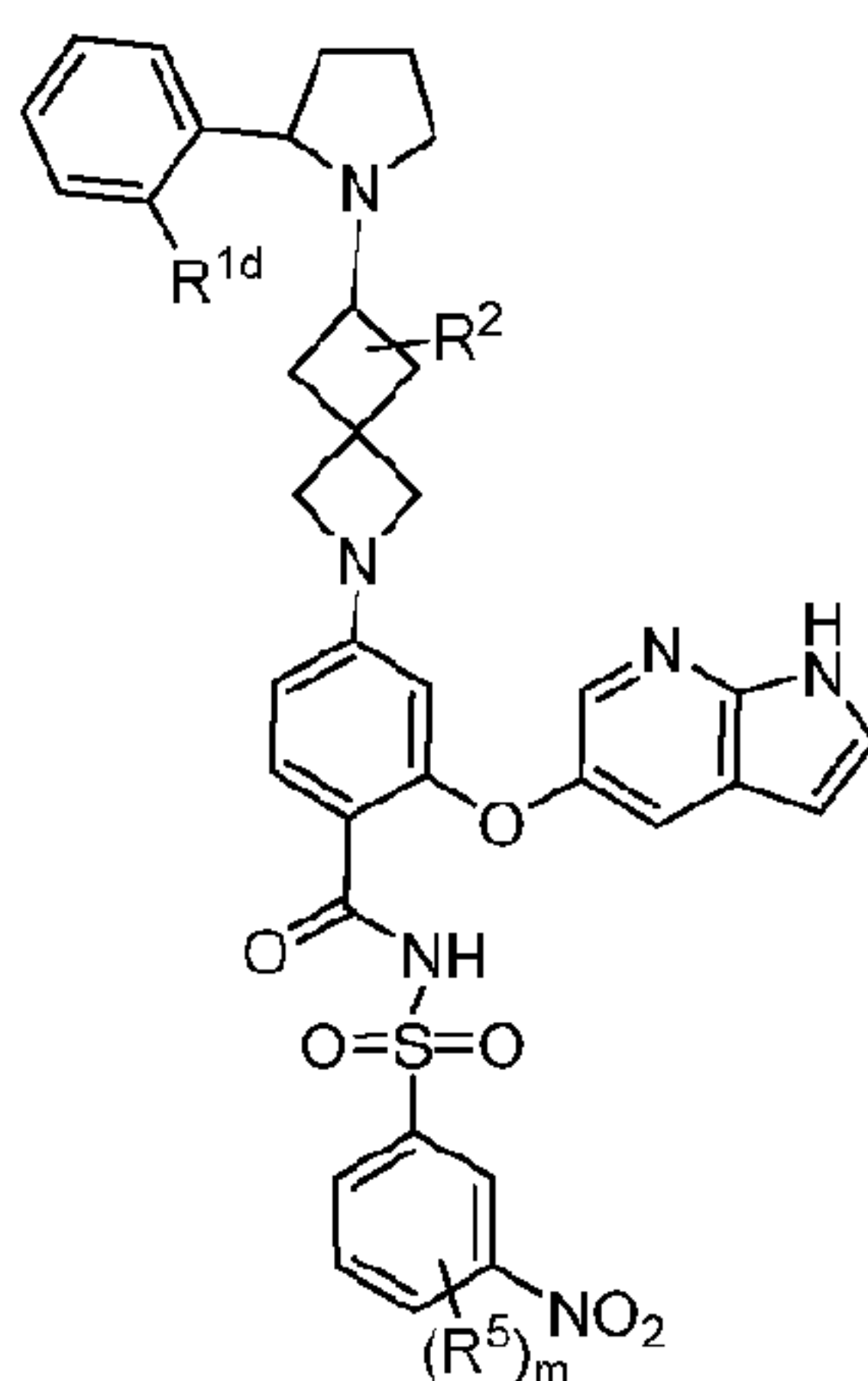
(III-B),



(III-C),



(III-D),



(III-E),

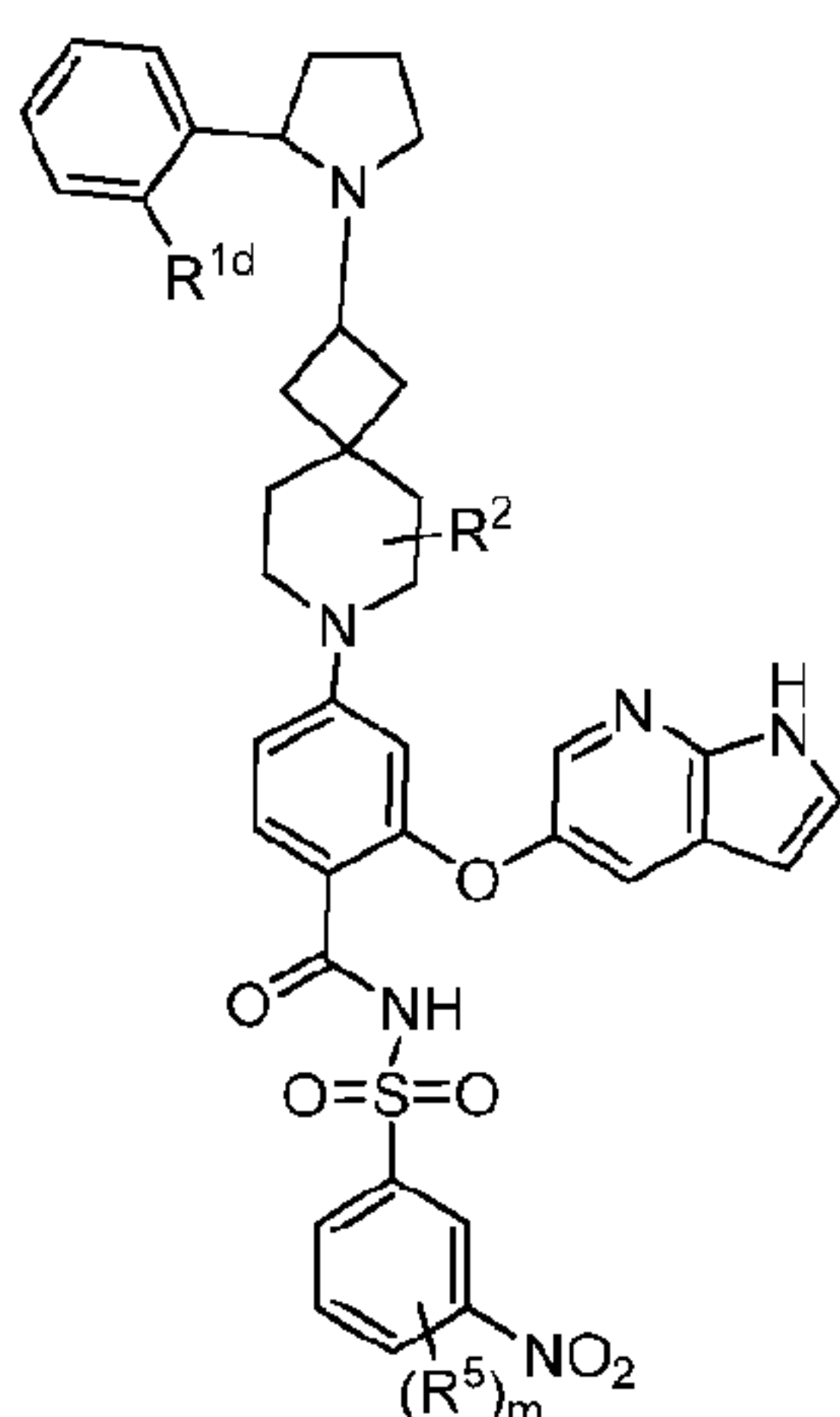
[0007] The compounds disclosed in WO2019/210828A are potent and selective Bcl-2 protein inhibitor.

SUMMARY OF THE DISCLOSURE

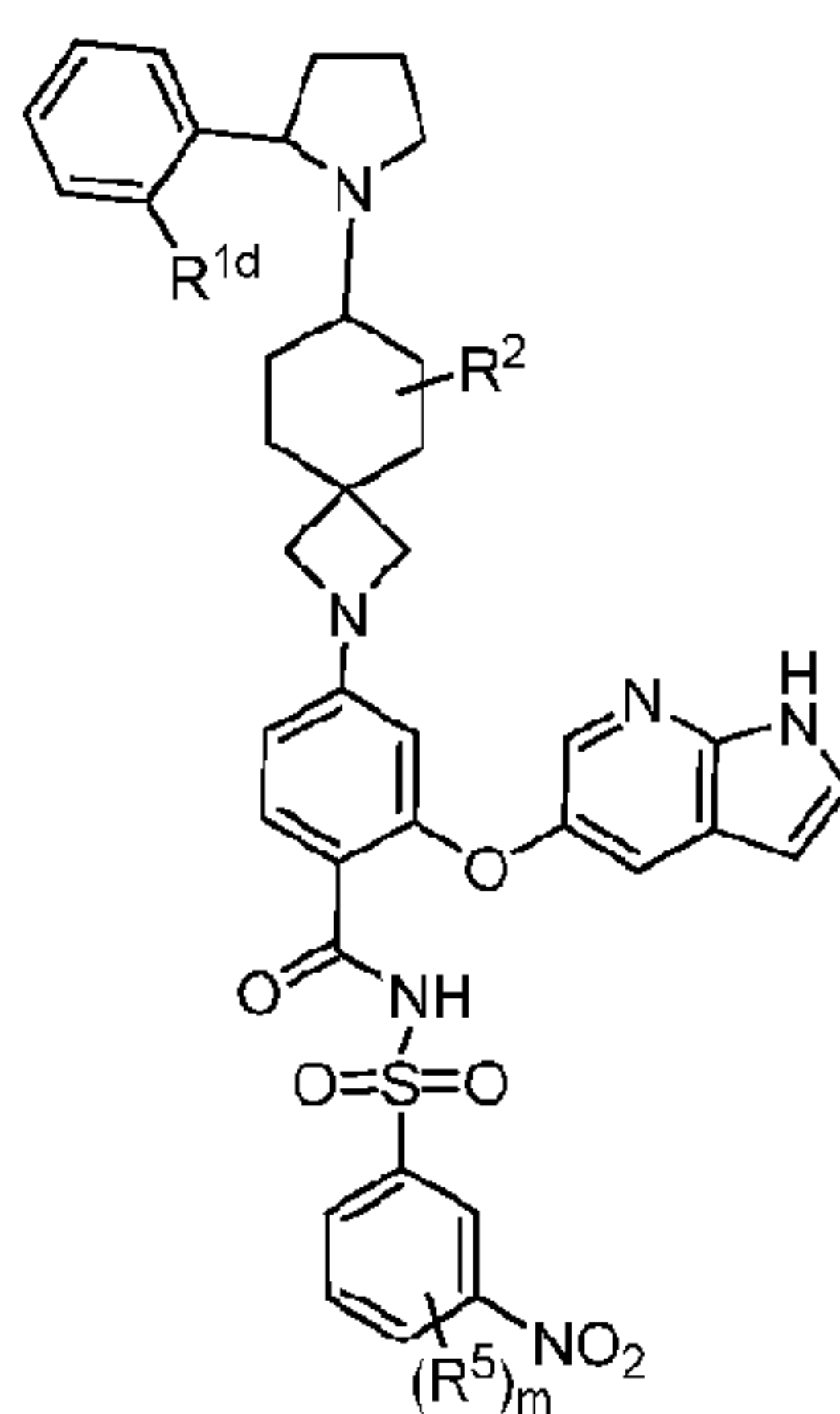
[0008] The inventors of the present disclosure have found that a Bcl2 inhibitor having Formulas (III-B), (III-C), (III-D) or (III-E), in particularly 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1R,4R)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide (**Compound 1**) or a pharmaceutically acceptable salt thereof, exhibited potent cell killing activity against a variety of lymphoma and leukemia cell lines, including MV4-11 (acute myeloid leukemias, AML), OCI-LY10 (B-cell non-Hodgkin's lymphoma, B-NHL), Toledo (diffuse large B-cell lymphomas, DLBCL), DOHH2 (follicular lymphomas, FL), DHL-4 (Germinal center B-cell like diffuse large B-cell lymphomas, GCB-DLBCL) and MAVER-1 (mantle cell lymphomas, MCL). And, the IC₅₀ values were found ranging from 0.6 nM to 13 nM.

[0009] The inventors of the present disclosure have also found that a Bcl2 inhibitor having Formulas (III-B), (III-C), (III-D) or (III-E), in particularly **Compound 1** or a pharmaceutically acceptable salt thereof, demonstrated significant inhibition of tumor growth in cancer with high safety, including B-cell malignancies selected from acute lymphoblastic leukemia (ALL), mantle cell lymphomas (MCL) and diffuse large B-cell lymphomas (DLBCL). The inventors have found that said B-cell malignancies has Bcl-2 expression and / or Bcl-2 G101V mutation expression.

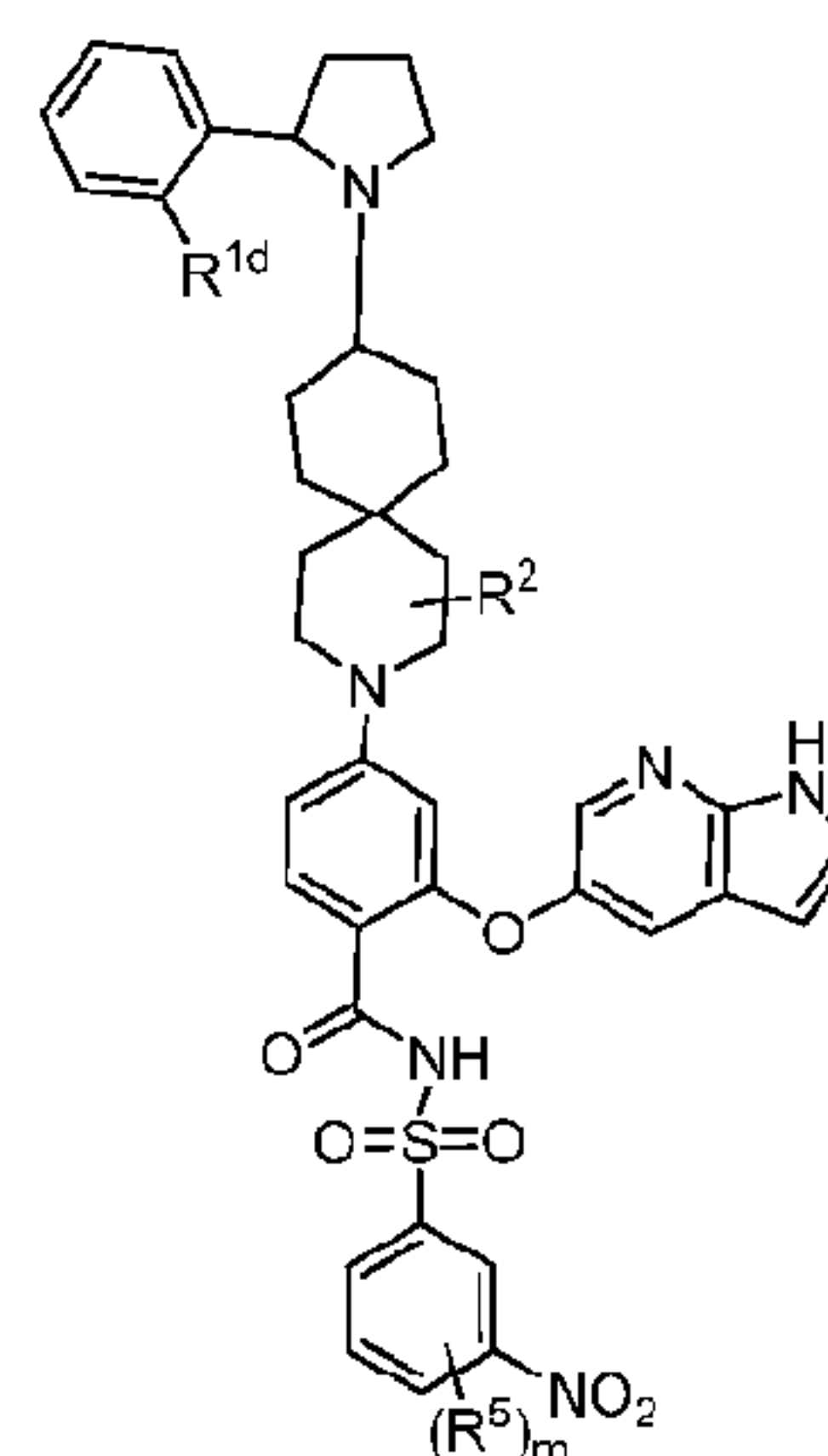
[0010] In a first aspect, disclosed herein is a method of treating cancer with a Bcl-2 inhibitor, wherein the Bcl-2 inhibitor is a compound represented by the following Formulas (III-B), (III-C), (III-D) or (III-E),



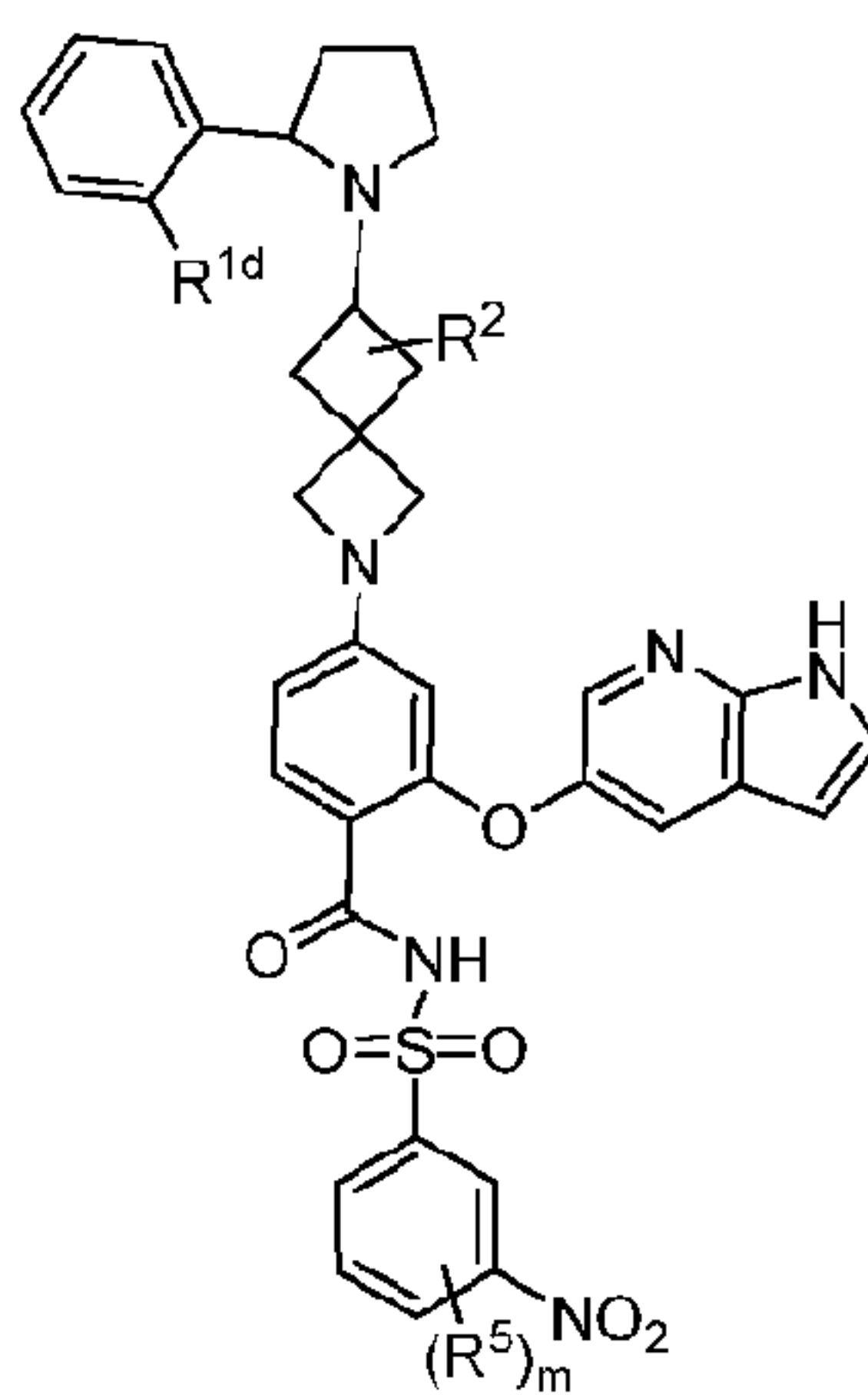
(III-B),



(III-C),



(III-D),



(III-E),

or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, wherein,

R², at each occurrence, is independently selected from the group consisting of hydrogen, halogen, or -C₁₋₈alkyl optionally substituted with halogen;

R^{1d} , at each occurrence, is independently halogen, $-C_{1-8}alkyl$, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, $-CN$, $-NO_2$, $-OR^{Ba}$, $-SO_2R^{Ba}$, $-COR^{Ba}$, $-CO_2R^{Ba}$, $-CONR^{Ba}R^{Bb}$, $-C(=NR^{Ba})NR^{Bb}R^{Bc}$, $-NR^{Ba}R^{Bb}$, $-NR^{Ba}COR^{Bb}$, $-NR^{Ba}CONR^{Bb}R^{Bc}$, $-NR^{Ba}CO_2R^{Bb}$, $-NR^{Ba}SONR^{Bb}R^{Bc}$, $-NR^{Ba}SO_2NR^{Bb}R^{Bc}$, or $-NR^{Ba}SO_2R^{Bb}$; wherein said $-C_{1-8}alkyl$, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cycloalkyl, heterocyclyl, aryl or heteroaryl are each independently optionally substituted with 1 to 4 substituents R^{Bd} ;

R^{Ba} , R^{Bb} , and R^{Bc} , are each independently hydrogen, $-C_{1-8}alkyl$, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said $-C_{1-8}alkyl$, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with halogen, hydroxy, $-NH_2$ or $-N(C_{1-6}alkyl)_2$, $-C_{1-8}alkyloxy$, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^{Bd} , at each occurrence, is independently hydrogen, halogen, oxo, $-CN$, $-NO_2$, $-C_{1-8}alkyl$, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said $-C_{1-8}alkyl$, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with halogen, hydroxy, $-C_{1-8}alkyloxy$, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

m is an integer of 1-4;

R^5 is $-L^5-CyC$,

Wherein L^5 is a direct bond, $-(CR^aR^b)_t-$, $-(CR^aR^b)_{t-1}-(CR^c=CR^d)-(CR^aR^b)_{v-1}-$, $-(CR^aR^b)_{t-1}-(C\equiv C)-(CR^aR^b)_{v-1}-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-C(O)-$, $C(O)O-$, $-OC(O)-$, $-NR^a-$, $-C(O)NR^a-$, $-NR^aC(O)-$, $-NR^aC(O)O-$, $-NR^aC(O)NR^b-$, $-SO_2NR^a-$, $-NR^aSO_2-$, $-NR^aS(O)_2NR^b-$, $-NR^aS(O)NR^b-$, $-C(O)NR^aSO_2-$, $-C(O)NR^aSO-$, or $-C(=NR^a)NR^b-$, wherein t and v , at each occurrence, are independently a number of 1 to 7, and one or two CR^aR^b moieties in $-(CR^aR^b)_t-$, $-(CR^aR^b)_{t-1}-(CR^c=CR^d)-(CR^aR^b)_{v-1}-$, $-(CR^aR^b)_{t-1}-(C\equiv C)-(CR^aR^b)_{v-1}-$ are un-replaced or replaced with one or more moieties selected from O, S, SO, SO_2 , C(O) and NR^a ;

CyC is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or two substituents R^{5a} ;

R^{5a} , at each occurrence, is independently selected from hydrogen, halogen, cyano, oxo, $-NO_2$, $-OR^{5b}$, $-SR^{5b}$, $-NR^{5b}R^{5c}$, $-COR^{5b}$, $-SO_2R^{5b}$, $-C(=O)OR^{5b}$, $-C(=O)NR^{5b}R^{5c}$, $-C(=NR^{5b})NR^{5c}R^{5d}$, $-N(R^{5b})C(=O)R^{5c}$, $-N(R^{5b})C(=O)OR^{5c}$, $-N(R^{5b})C(O)NR^{5c}R^{5d}$, $-N(R^{5b})S(O)NR^{5c}R^{5d}$, $-N(R^{5b})S(O)_2NR^{5c}R^{5d}$, $-NR^{5b}SO_2R^{5c}$, $-C_{1-8}alkyl$, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, $-cycloalkyl$, heterocyclyl, aryl, or heteroaryl, each of said $-C_{1-8}alkyl$, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, $-cycloalkyl$, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or two substituents R^{5e} ;

wherein R^{5b} , R^{5c} , and R^{5d} are each independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or two substituents R^{5e} ;

R^{5e} , at each occurrence, is independently selected from hydrogen, halogen, cyano, oxo, -NO₂, -OR^{5f}, -SR^{5f}, -NR^{5f}R^{5g}, -COR^{5f}, -SO₂R^{5f}, -C(=O)OR^{5f}, -C(=O)NR^{5f}R^{5g}, -C(=NR^{5f})NR^{5g}R^{5h}, -N(R^{5f})C(=O)R^{5g}, -N(R^{5f})C(=O)OR^{5g}, -N(R^{5f})C(O)NR^{5g}R^{5h}, -N(R^{5f})S(O)NR^{5g}R^{5h}, -N(R^{5f})S(O)₂NR^{5g}R^{5h}, -NR^{5f}SO₂R^{5g}, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -cycloalkyl, heterocyclyl, aryl, or heteroaryl; R^{5f} , R^{5g} , and R^{5h} are each independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

or, two adjacent R^5 on the phenyl ring together with the phenyl ring form a benzo ring, said ring is optionally substituted with halogen, oxo, cyano, -NO₂, -OR⁵ⁱ, -SR⁵ⁱ, -NR⁵ⁱR^{5j}, -COR⁵ⁱ, -SO₂R⁵ⁱ, -C(=O)OR⁵ⁱ, -C(=O)NR⁵ⁱR^{5j}, -C(=NR⁵ⁱ)NR^{5j}R^{5k}, -N(R⁵ⁱ)C(=O)R^{5j}, -N(R⁵ⁱ)C(=O)OR^{5j}, -N(R⁵ⁱ)C(O)NR^{5j}R^{5k}, -N(R⁵ⁱ)S(O)NR^{5j}R^{5k}, -N(R⁵ⁱ)S(O)₂NR^{5j}R^{5k}, -NR⁵ⁱSO₂R^{5k}, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^{5i} , R^{5j} , and R^{5k} are independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with halogen, hydroxy or -C₁₋₈alkoxy;

R^a , R^b , R^c , and R^d at each occurrence, are independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl are each independently substituted with -CN, halogen, -NO₂, -NR^eR^f, oxo, -OR^e, or -SR^e; and

wherein R^e and R^f are each independently hydrogen, C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkyl-, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl.

[0010] In a second aspect, disclosed herein is a Bcl-2 inhibitor of Formulas (III-B), (III-C), (III-D) or (III-E) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

[0011] In a third aspect, disclosed herein is a method of treating cancer in a subject, said

method comprising administering to the subject a therapeutically effective amount of a Bcl-2 inhibitor of Formulas (III-B), (III-C), (III-D) or (III-E) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[0012] In a fourth aspect, disclosed herein is a use of a pharmaceutical composition in the manufacture of a medicament for use in the treatment of cancer, said pharmaceutical combination comprising a Bcl-2 inhibitor of Formulas (III-B), (III-C), (III-D) or (III-E) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[0013] In an embodiment of each of the above aspects, the Bcl-2 inhibitor is 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide (**Compound 1**) or a pharmaceutically acceptable salt thereof.

[0014] In an embodiment of each of the above aspects, the cancer is B-cell malignancies.

[0015] In an embodiment of each of the above aspects, the cancer is lymphoma or leukemia.

[0016] In one embodiment of each of the above aspects, the cancer is selected from the group consisting of acute myeloid leukemias (AML), B-cell non-Hodgkin's lymphoma (B-NHL), indolent B-cell Non-Hodgkin Lymphoma (NHL), diffuse large B-cell lymphomas (DLBCL), Germinal center B-cell like diffuse large B-cell lymphomas (GCB-DLBCL), follicular lymphomas (FL), mantle cell lymphomas (MCL), acute lymphoblastic leukemia (ALL) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and marginal zone lymphoma (MZL).

[0017] In one embodiment of each of the above aspects, the cancer is relapsed/refractory, or transformed.

[0018] In one embodiment of each of the above aspects, the Bcl-2 inhibitor is orally administrated at a dose of 20 mg/per day to 700 mg/per day.

[0019] In one embodiment of each of the above aspects, the cancer has Bcl-2 expression.

[0020] In one embodiment of each of the above aspects, the cancer has Bcl-2 Gly101Val mutation expression.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] **Figure 1** shows efficacy of Bcl-2 inhibitors in RS4;11 acute lymphoblastic leukemia (ALL) subcutaneous xenograft model.

$p < 0.0001$ versus vehicle by one-way ANOVA (Dunnett's multiple comparisons test)

* $p < 0.05$, **** $p < 0.0001$ versus venetoclax by one-way ANOVA (Tukey's multiple comparisons test).

Abbreviation: ANOVA, analysis of variance; SEM, standard error of the mean; QD, once daily; BID, twice daily; p.o., oral gavage.

[0022] Figure 2 shows efficacy of Bcl-2 inhibitors in MAVER-1 mantle cell lymphoma (MCL) subcutaneous xenograft model.

$p < 0.01$, ##### $p < 0.0001$ versus vehicle by one-way ANOVA (Dunnett's multiple comparisons test).

**** $p < 0.0001$ versus venetoclax by one-way ANOVA (Tukey's multiple comparisons test).

Abbreviation: ANOVA, analysis of variance; SEM, standard error of the mean; QD, once daily; BID, twice daily; p.o., oral gavage.

[0023] Figure 3 shows efficacy of Bcl-2 inhibitors in Toledo diffuse large B cell lymphoma (DLBCL) subcutaneous xenograft model.

$p < 0.001$, ##### $p < 0.0001$ versus vehicle by one-way ANOVA (Dunnett's multiple comparisons test).

** $p < 0.01$, **** $p < 0.0001$ versus venetoclax by one-way ANOVA (Tukey's multiple comparisons test).

Abbreviation: ANOVA, analysis of variance; SEM, standard error of the mean; QD, once daily; BID, twice daily; p.o., oral gavage.

[0024] Figure 4 shows efficacy of Bcl-2 inhibitors in RS4;11 Bcl-2G101V KI acute lymphoblastic leukemia (ALL) subcutaneous xenograft model.

$p < 0.01$, ##### $p < 0.0001$ versus vehicle by one-way ANOVA; **** $p < 0.0001$ versus venetoclax by one-way ANOVA.

Definitions

[0025] Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art.

[0026] As used herein, including the appended claims, the singular forms of words such as “a,” “an,” and “the,” include their corresponding plural references unless the context clearly dictates otherwise.

[0027] The term “or” is used to mean, and is used interchangeably with, the term “and/or” unless the context clearly dictates otherwise.

[0028] The term “anti-cancer agent” as used herein refers to any agent that can be used to treat a cell proliferative disorder such as cancer, including but not limited to, cytotoxic agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents,

and immunotherapeutic agents.

[0029] The terms “**administration**,” “**administering**,” “**treating**,” and “**treatment**” herein, when applied to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, means contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell. The term “administration” and “treatment” also means *in vitro* and *ex vivo* treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell. The term “subject” herein includes any organism, preferably an animal, more preferably a mammal (e.g., rat, mouse, dog, cat, rabbit) and most preferably a human. Treating any disease or disorder refer in one aspect, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another aspect, “treat,” “treating,” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another aspect, “treat,” “treating,” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another aspect, “treat,” “treating,” or “treatment” refers to preventing or delaying the onset or development or progression of the disease or disorder.

[0030] The term “**subject**” in the context of the present disclosure is a mammal, e.g., a primate, preferably a higher primate, e.g., a human (e.g., a patient having, or at risk of having, a disorder described herein). In some embodiments, the subject is a human or a patient.

[0031] The terms “**cancer**” or “**tumor**” herein has the broadest meaning as understood in the art and refers to the physiological condition in mammals that is typically characterized by unregulated cell growth. In the context of the present disclosure, the cancer is not limited to certain type or location.

[0032] The term “**therapeutically effective amount**” as herein used, refers to the amount of a Bcl-2 inhibitor that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to effect such treatment for the disease, disorder, or symptom. The “**therapeutically effective amount**” can vary with the agent, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be apparent to those skilled in the art or can be determined by routine experiments. In the case of combination therapy, the “**therapeutically effective amount**” refers to the total amount of the

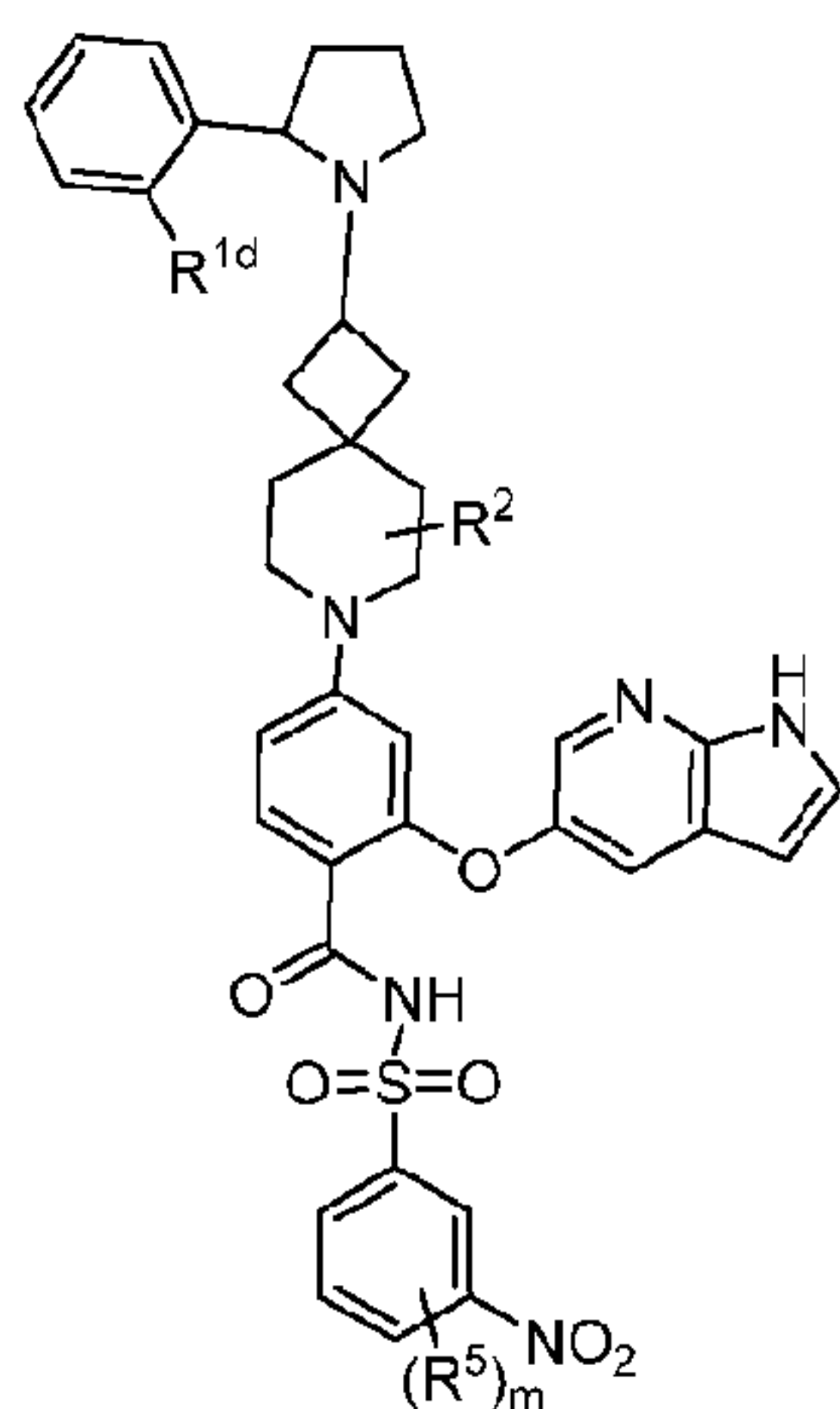
combination objects for the effective treatment of a disease, a disorder or a condition.

DETAILED DESCRIPTION OF THE DISCLOSURE

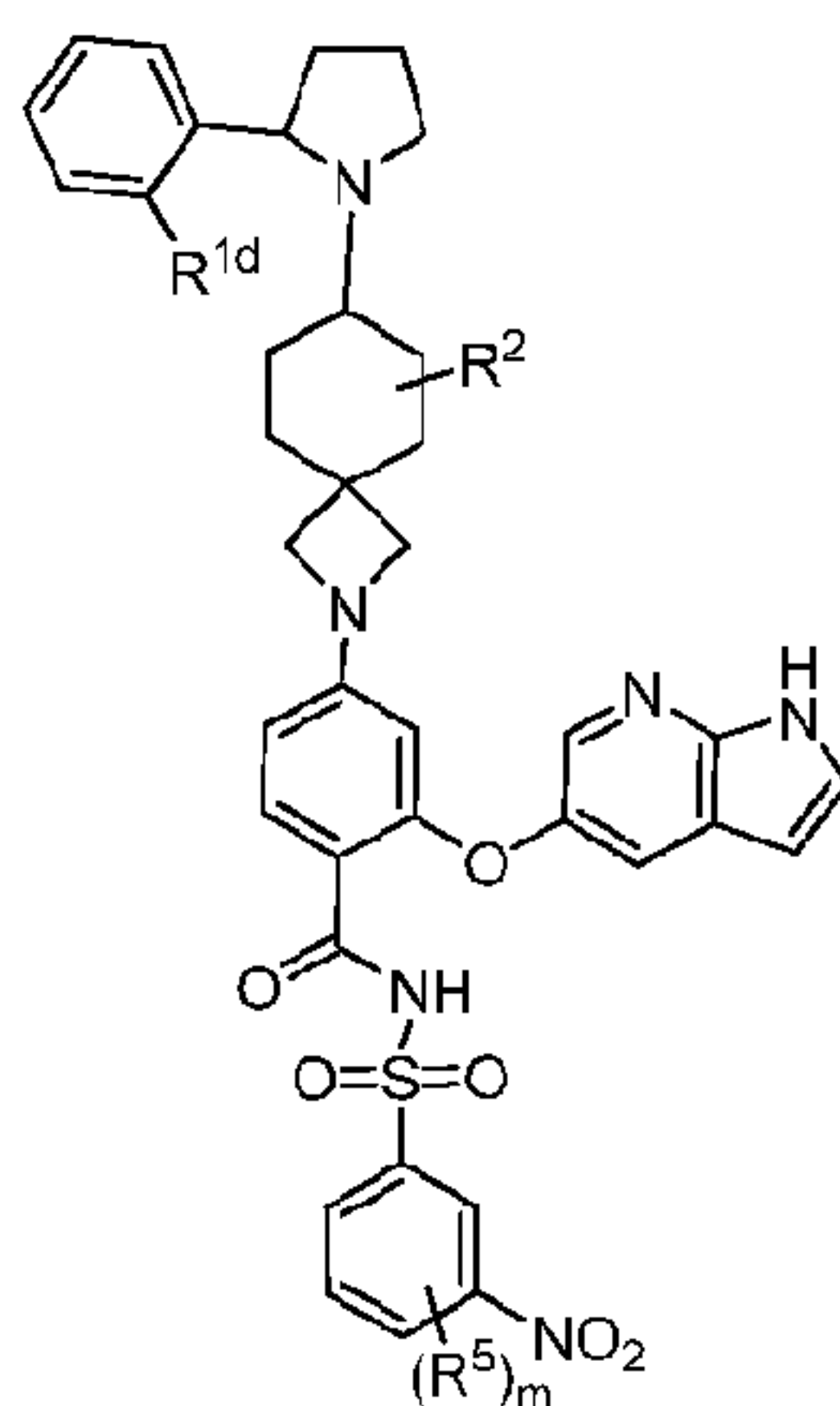
[0033] The present disclosure provides a method of treating cancer in a subject with Bcl-2 inhibitor, in particularly 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide (**Compound 1**) or a pharmaceutically acceptable salt thereof.

Bcl-2 inhibitor

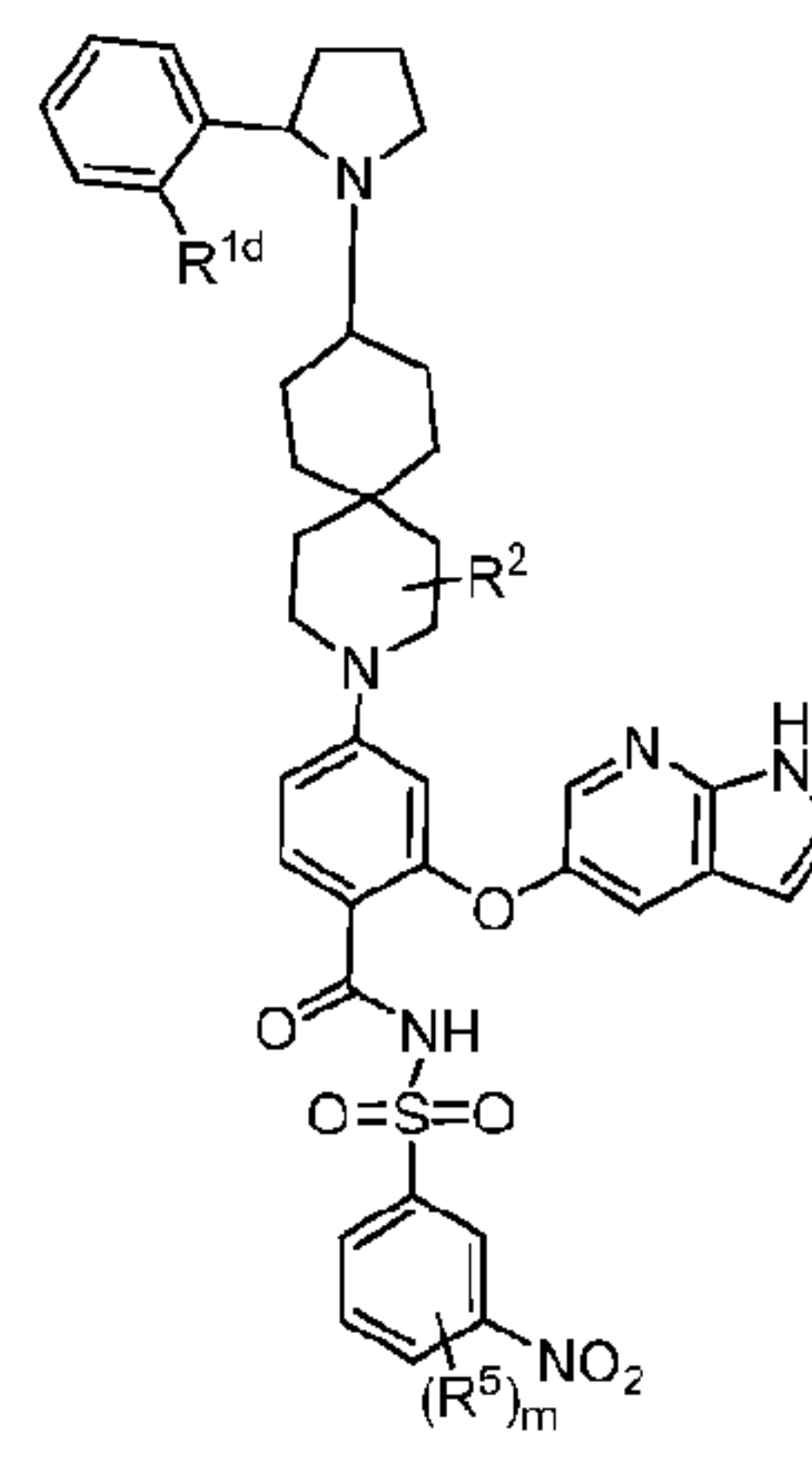
[0034] The Bcl-2 inhibitor in present disclosure is a compound represented by the following Formulas (III-B), (III-C), (III-D) or (III-E),



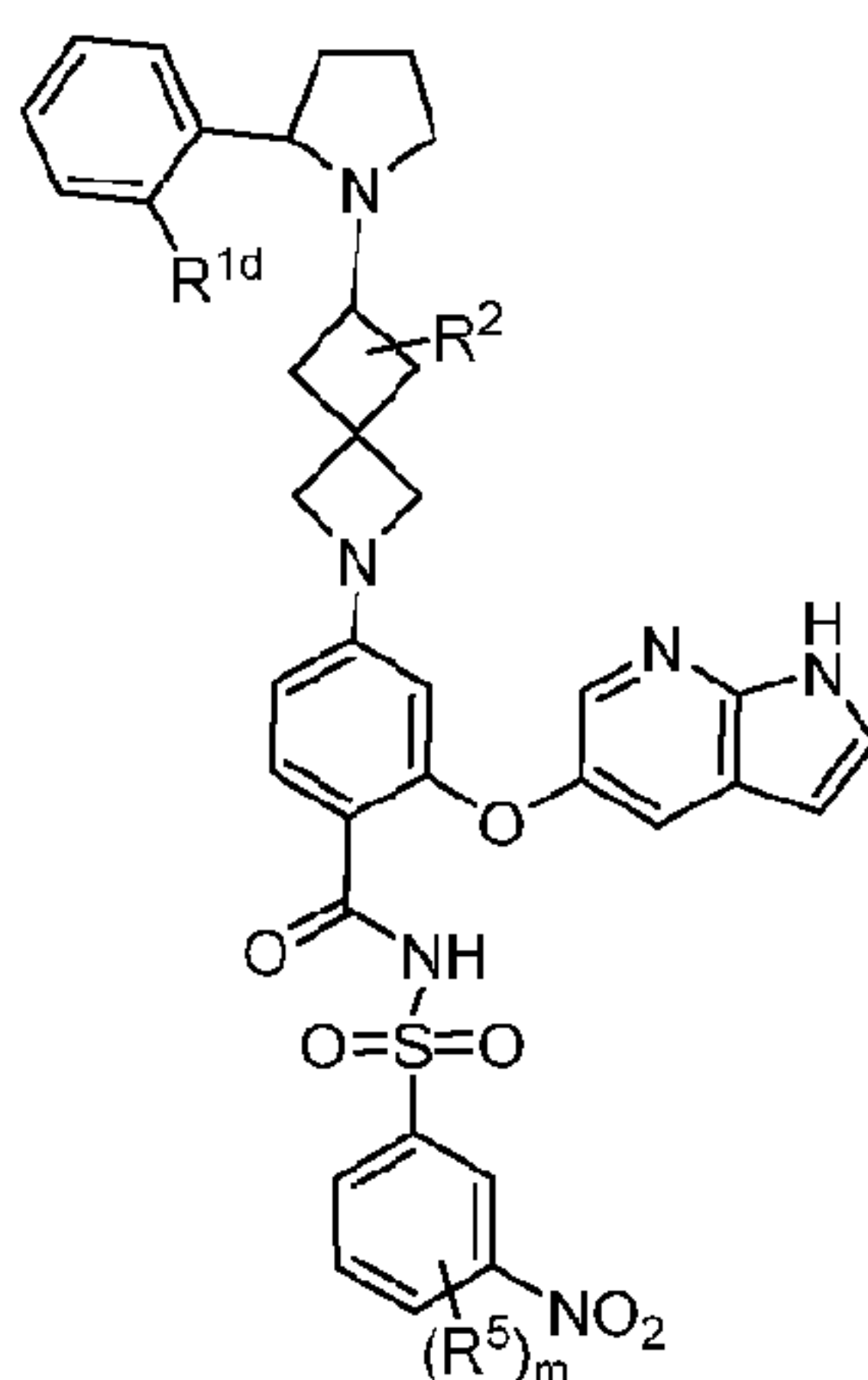
(III-B),



(III-C),



(III-D),



(III-E),

or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof,

wherein,

R^2 , at each occurrence, is independently selected from the group consisting of hydrogen, halogen, or -C₁₋₈alkyl optionally substituted with halogen;

R^{1d} , at each occurrence, is independently halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO₂, -OR^{Ba}, -SO₂R^{Ba}, -COR^{Ba}, -CO₂R^{Ba}, -CONR^{Ba}R^{Bb}, -C(=NR^{Ba})NR^{Bb}R^{Bc}, -NR^{Ba}R^{Bb}, -NR^{Ba}COR^{Bb}, -NR^{Ba}CONR^{Bb}R^{Bc}, -NR^{Ba}CO₂R^{Bb}, -NR^{Ba}SONR^{Bb}R^{Bc}, -NR^{Ba}SO₂NR^{Bb}R^{Bc}, or -NR^{Ba}SO₂R^{Bb}; wherein said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl are each independently optionally substituted with 1 to 4 substituents R^{Bd};

R^{Ba}, R^{Bb}, and R^{Bc}, are each independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with halogen, hydroxy, -NH₂ or -N(C₁₋₆alkyl)₂, -C₁₋₈alkyloxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^{Bd}, at each occurrence, is independently hydrogen, halogen, oxo, -CN, -NO₂, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with halogen, hydroxy, -C₁₋₈alkyloxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

m is an integer of 1-4;

R⁵ is -L⁵-CyC,

Wherein L⁵ is a direct bond, -(CR^aR^b)_t-, -(CR^aR^b)_{t-1}-(CR^c=CR^d)-(CR^aR^b)_{v-1}-, -(CR^aR^b)_{t-1}-(C≡C)-(CR^aR^b)_{v-1}-, -O-, -S-, -S(O)-, -SO₂-, -C(O)-, C(O)O-, -OC(O)-, -NR^a-, -C(O)NR^a-, -NR^aC(O)-, -NR^aC(O)O-, -NR^aC(O)NR^b-, -SO₂NR^a-, -NR^aSO₂-, -NR^aS(O)₂NR^b-, -NR^aS(O)NR^b-, -C(O)NR^aSO₂-, -C(O)NR^aSO-, or -C(=NR^a)NR^b-, wherein t and v, at each occurrence, are independently a number of 1 to 7, and one or two CR^aR^b moieties in -(CR^aR^b)_t-, -(CR^aR^b)_{t-1}-(CR^c=CR^d)-(CR^aR^b)_{v-1}-, -(CR^aR^b)_{t-1}-(C≡C)-(CR^aR^b)_{v-1}- are un-replaced or replaced with one or more moieties selected from O, S, SO, SO₂, C(O) and NR^a;

CyC is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or two substituents R^{5a};

R^{5a}, at each occurrence, is independently selected from hydrogen, halogen, cyano, oxo, -NO₂, -OR^{5b}, -SR^{5b}, -NR^{5b}R^{5c}, -COR^{5b}, -SO₂R^{5b}, -C(=O)OR^{5b}, -C(=O)NR^{5b}R^{5c}, -C(=NR^{5b})NR^{5c}R^{5d}, -N(R^{5b})C(=O)R^{5c}, -N(R^{5b})C(=O)OR^{5c}, -N(R^{5b})C(O)NR^{5c}R^{5d}, -N(R^{5b})S(O)NR^{5c}R^{5d}, -N(R^{5b})S(O)₂NR^{5c}R^{5d}, -NR^{5b}SO₂R^{5c}, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or two substituents R^{5e};

wherein R^{5b} , R^{5c} , and R^{5d} are each independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or two substituents R^{5e} ;

R^{5e} , at each occurrence, is independently selected from hydrogen, halogen, cyano, oxo, -NO₂, -OR^{5f}, -SR^{5f}, -NR^{5f}R^{5g}, -COR^{5f}, -SO₂R^{5f}, -C(=O)OR^{5f}, -C(=O)NR^{5f}R^{5g}, -C(=NR^{5f})NR^{5g}R^{5h}, -N(R^{5f})C(=O)R^{5g}, -N(R^{5f})C(=O)OR^{5g}, -N(R^{5f})C(O)NR^{5g}R^{5h}, -N(R^{5f})S(O)NR^{5g}R^{5h}, -N(R^{5f})S(O)₂NR^{5g}R^{5h}, -NR^{5f}SO₂R^{5g}, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -cycloalkyl, heterocyclyl, aryl, or heteroaryl; R^{5f} , R^{5g} , and R^{5h} are each independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

or, two adjacent R^5 on the phenyl ring together with the phenyl ring form a benzo ring, said ring is optionally substituted with halogen, oxo, cyano, -NO₂, -OR⁵ⁱ, -SR⁵ⁱ, -NR⁵ⁱR^{5j}, -COR⁵ⁱ, -SO₂R⁵ⁱ, -C(=O)OR⁵ⁱ, -C(=O)NR⁵ⁱR^{5j}, -C(=NR⁵ⁱ)NR^{5j}R^{5k}, -N(R⁵ⁱ)C(=O)R^{5j}, -N(R⁵ⁱ)C(=O)OR^{5j}, -N(R⁵ⁱ)C(O)NR^{5j}R^{5k}, -N(R⁵ⁱ)S(O)NR^{5j}R^{5k}, -N(R⁵ⁱ)S(O)₂NR^{5j}R^{5k}, -NR⁵ⁱSO₂R^{5k}, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^{5i} , R^{5j} , and R^{5k} are independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with halogen, hydroxy or -C₁₋₈alkoxy;

R^a , R^b , R^c , and R^d at each occurrence, are independently hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl are each independently substituted with -CN, halogen, -NO₂, -NR^eR^f, oxo, -OR^e, or -SR^e; and

wherein R^e and R^f are each independently hydrogen, C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkyl-, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl.

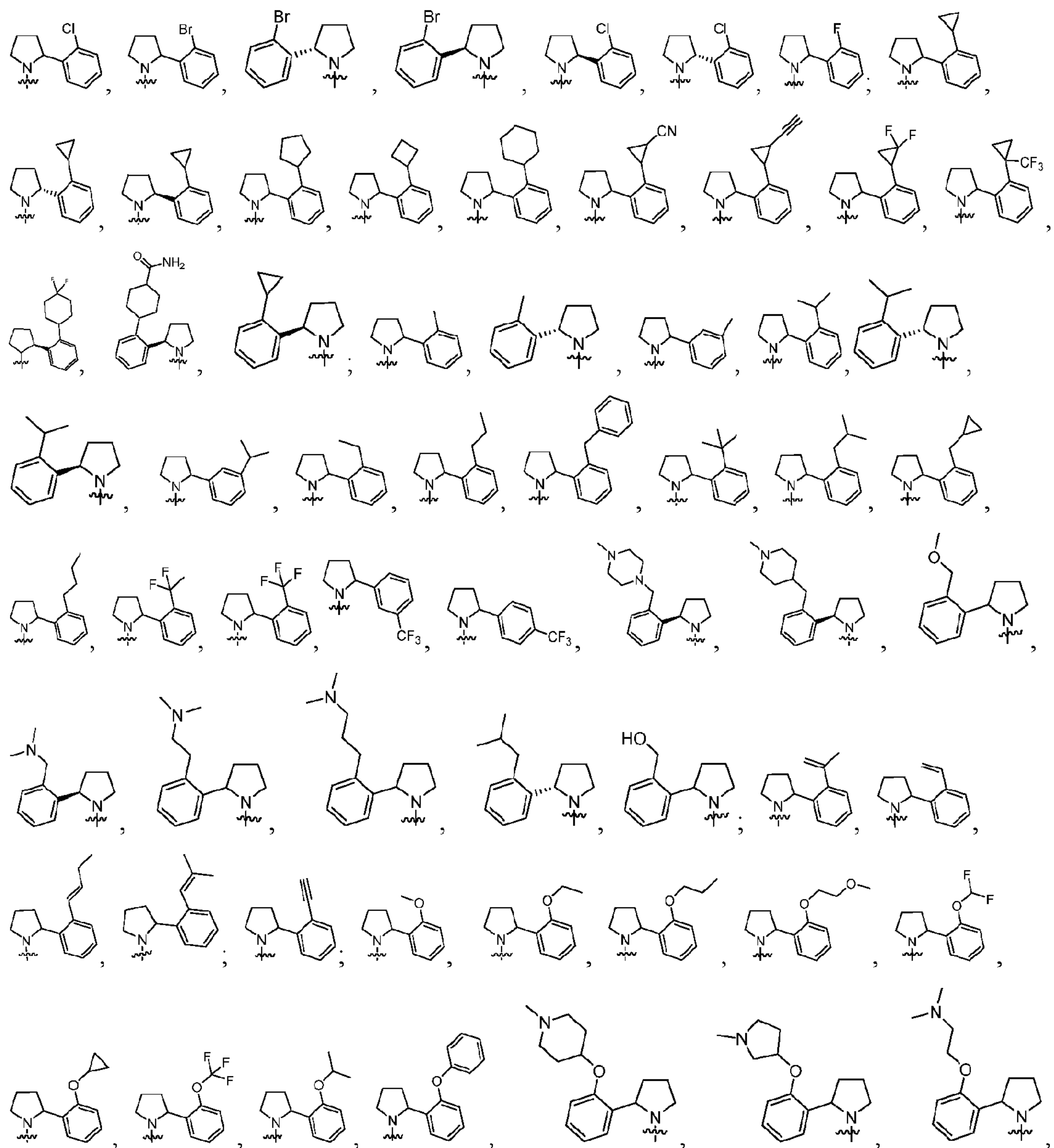
[0035] In some embodiments, R^2 is hydrogen.

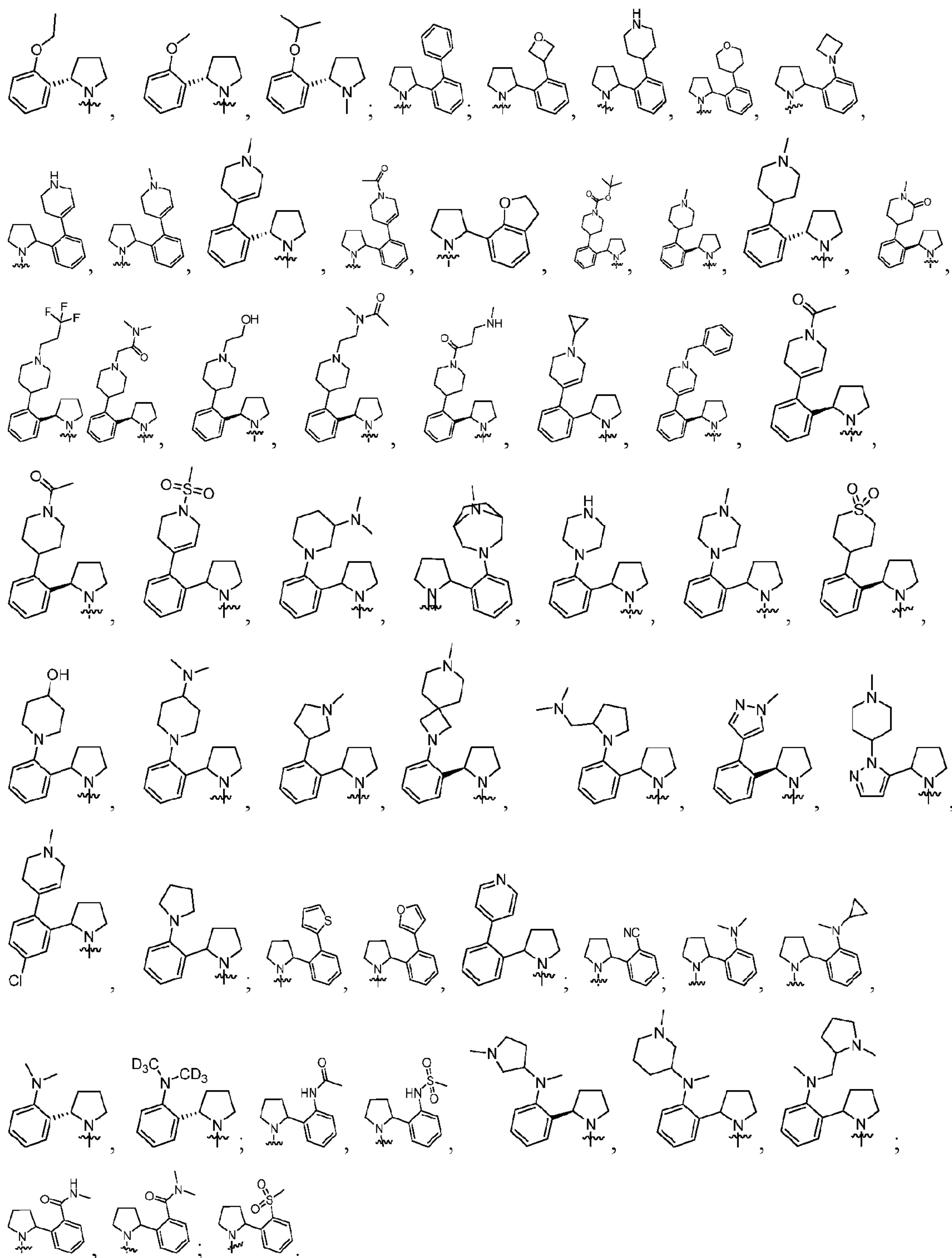
[0036] In some embodiments, R^{1d} , when substituted on the phenyl group at position 2 of ring B (including the aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, piperidin-1-yl, azepan-1-yl, or azocan-1-yl, preferably the pyrrolidin-1-yl group), is independently halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CN, -OR^{Ba}, -

SO₂R^{Ba}, -CONR^{Ba}R^{Bb}, -NO₂, -NR^{Ba}R^{Bb}, -NR^{Ba}COR^{Bb}, or -NR^{Ba}SO₂R^{Bb}; wherein said -C₁-8alkyl, -C₂-8alkenyl, -C₂-8alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl are each independently optionally substituted with 1 to 4 substituents R^{Bd} as defined as with Formulas (III-B), (III-C), (III-D) or (III-E)., preferably 1 or 2 substituents R^{Bd} as defined as with Formulas (III-B), (III-C), (III-D) or (III-E). In another aspect, one R^{1d} is at position 2 of the phenyl ring at position 2 of ring B.

[0037] In some embodiments, R^{1d} is methyl, ethyl, isopropyl, propyl or methoxymethyl, or two methyl at position of the phenyl ring; or propenyl; or cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; or ethoxy or isopropoxy; or amino or dimethylamino.

[0038] In some embodiments, the 2-(2-substituted phenyl)pyrrolidin-1-yl moiety in Formulas (III-B), (III-C), (III-D) or (III-E), is selected from the group consisting of:





[0039] In some embodiments, m is 1; and L^5 is a direct bond, $-(CR^aR^b)_t-$ or $-NR^a-$, wherein t is a number of 1 to 7, and one or two CR^aR^b moieties in $-(CR^aR^b)_t-$ are un-replaced or replaced with one or more moieties selected from O and NR^a , wherein R^a and R^b are defined with Formulas (III-B), (III-C), (III-D) or (III-E).

[0040] In some embodiments, L^5 is a direct bond, $-(CR^aR^b)_{1-4}-$, $-O-(CR^aR^b)_{1-3}-$, $-NH-(CR^aR^b)_1-$.

3, or -NH-, wherein R^a and R^b are defined as with Formulas (III-B), (III-C), (III-D) or (III-E), so that the $-L^5\text{-CyC}$ moiety is CyC , $-(\text{CR}^a\text{R}^b)_{1-4}\text{-CyC}$, $-\text{O}-(\text{CR}^a\text{R}^b)_{1-3}\text{-CyC}$, $-\text{NH}-(\text{CR}^a\text{R}^b)_{1-3}\text{-CyC}$, or $-\text{NH-CyC}$, respectively. More preferably, L^5 is a direct bond, $-(\text{CH}_2)_{1-4}-$, $-\text{O}-(\text{CH}_2)_{1-3}-$, $-\text{NH}-(\text{CR}^a\text{R}^b)-(\text{CH}_2)_2-$, or $-\text{NH}-$, wherein R^a is hydrogen and R^b is C_{1-8} alkyl optionally substituted with phenyl-S- so that the $-L^5\text{-CyC}$ moiety is CyC , $-(\text{CH}_2)_{1-4}\text{-CyC}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{-CyC}$, $-\text{NH}-(\text{CR}^a\text{R}^b)-(\text{CH}_2)_2\text{-CyC}$, or $-\text{NH-CyC}$, respectively. More preferably, L^5 is a direct bond, $-\text{CH}_2-$, $-\text{O-CH}_2-$, $-\text{NH-CH}_2-$, or $-\text{NH}-$ so that the $-L^5\text{-CyC}$ moiety is CyC , $-\text{CH}_2\text{-CyC}$, $-\text{O-CH}_2\text{-CyC}$, $-\text{NH-CH}_2\text{-CyC}$, or $-\text{NH-CyC}$, respectively.

[0041] In some embodiments, CyC is cycloalkyl, or heterocyclyl, each of which is optionally substituted with one or two substituents R^{5a} ;

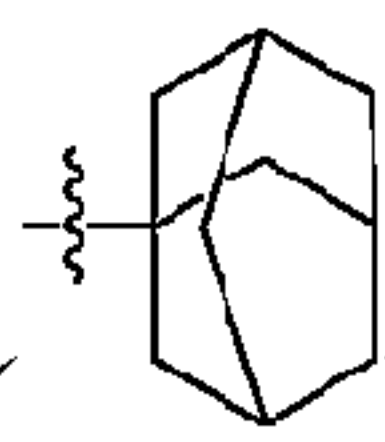
R^{5a} is independently selected from hydrogen, halogen, cyano, oxo, $-\text{OR}^{5b}$, $-\text{NR}^{5b}\text{R}^{5c}$, $-\text{COR}^{5b}$, $-\text{SO}_2\text{R}^{5b}$, $-\text{C}_{1-8}$ alkyl, $-\text{C}_{2-8}$ alkynyl, -cycloalkyl, or heterocyclyl, each of said $-\text{C}_{1-8}$ alkyl, and heterocyclyl is optionally substituted with one or two substituents R^{5e} which is selected from hydrogen, halogen, cyano, $-\text{OR}^{5f}$, $-\text{C}_{1-8}$ alkyl, -cycloalkyl, or heterocyclyl;

wherein R^{5b} , and R^{5c} are each independently hydrogen, $-\text{C}_{1-8}$ alkyl or heterocyclyl, said $-\text{C}_{1-8}$ alkyl is optionally substituted with one or two substituents R^{5e} which is hydrogen, $-\text{NR}^{5f}\text{R}^{5g}$, or -cycloalkyl;

R^{5f} and R^{5g} are each independently hydrogen or $-\text{C}_{1-8}$ alkyl;

or, two adjacent R^5 on the phenyl ring together with the phenyl ring form a benzo ring, said ring is optionally substituted with heteroaryl.

[0042] In some embodiments, CyC is cycloalkyl selected from monocyclic C_{3-8} cycloalkyl or



bridged cycloalkyl (), each of which is optionally substituted with one or two substituents R^{5a} . preferably, CyC is cyclopentyl or cyclohexyl, each of which is optionally substituted with one or two substituents R^{5a} .

[0043] In some embodiments, CyC is heterocyclyl selected from:

- monocyclic 4 to 9-membered heterocyclyl groups containing one nitrogen or oxygen or sulfur heteroatom as ring member;
 - monocyclic 4 to 9-membered heterocyclyl groups containing two heteroatoms selected from oxygen, sulfur and nitrogen as ring members; and
 - 5 to 20-membered spiro heterocyclyl comprising one or two heteroatoms selected from nitrogen, sulfur and oxygen as ring members,
- each of which is optionally substituted with one or two R^{5a} .

[0044] In some embodiments, CyC is monocyclic 4 to 6-membered heterocyclyl groups

containing one nitrogen or oxygen or sulfur heteroatom as ring member. More preferably, Cyc is selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, and piperdiny. Even more preferably, CyC is selected from oxetan-2-yl, Oxetan-3-yl, tetrahydrofuran-4-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, azetidin-3-yl, azetidin-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperdin-4-yl, piperdin-2-yl, and piperdin-3-yl.

[0045] In some embodiments, CyC is monocyclic 6-membered heterocyclyl group containing two heteroatoms selected from oxygen and nitrogen as ring members. More preferably, CyC is dioxanyl, morpholino, morpholinyl, or piperziny. Even more preferably 1,3-dioxan-2-yl, 1,3-dioxan-4-yl, 1,4-dioxan-2-yl, morpholin-1-yl, morpholin-2-yl, or morpholin-3-yl.

[0046] In some embodiments, R^{5a} is independently selected from hydrogen, halogen, cyano, oxo, $-OR^{5b}$, $-NR^{5b}R^{5c}$, $-COR^{5b}$, $-SO_2R^{5b}$, $-C_{1-8}alkyl$, $-C_{2-8}alkynyl$, monocyclic $C_{3-8}cycloalkyl$, or monocyclic 4 to 9-membered heterocyclyl group containing one or two heteroatoms selected from nitrogen or oxygen or sulfur heteroatom as ring members, each of said $-C_{1-8}alkyl$ and monocyclic 4 to 9-membered heterocyclyl group is optionally substituted with one or two substituents R^{5e} ; preferably, cycloalkyl as R^{5a} is $C_{3-6}cycloalkyl$; more preferably cyclopropyl; preferably, heterocyclyl as R^{5a} is 4 to 6-membered heterocyclyl groups containing one or two heteroatoms selected from nitrogen or oxygen or sulfur heteroatom as ring members; more preferably, heterocyclyl as R^{5a} is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperziny, or morpholinyl; even more preferably, heterocyclyl as R^{5a} is oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydro-2H-pyran-4-yl, or morphin-4-yl.

[0047] In some embodiments, heterocyclyl as R^{5e} is monocyclic 4 to 9-membered heterocyclyl group containing one or two heteroatoms selected from nitrogen or oxygen or sulfur heteroatom as ring members.

[0048] In some embodiments, heterocyclyl as R^{5e} is tetrahydro-pyran-4-yl.

[0049] In some embodiments, R^{5a} is $-NR^{5b}R^{5c}$, wherein R^{5b} is hydrogen, and R^{5c} is heterocyclyl.

[0050] In some embodiments, R^{5a} is $-NR^{5b}R^{5c}$, wherein R^{5b} is hydrogen, and R^{5c} is tetrahydro-pyran-4-yl.

[0051] In some embodiments, R^{5a} is $-NR^{5b}R^{5c}$, wherein R^{5b} and R^{5c} are each independently hydrogen or $-C_{1-6}alkyl$ substituted with cycloalkyl, preferably $-C_{1-6}alkyl$ substituted with monocyclic $C_{3-8}cycloalkyl$.

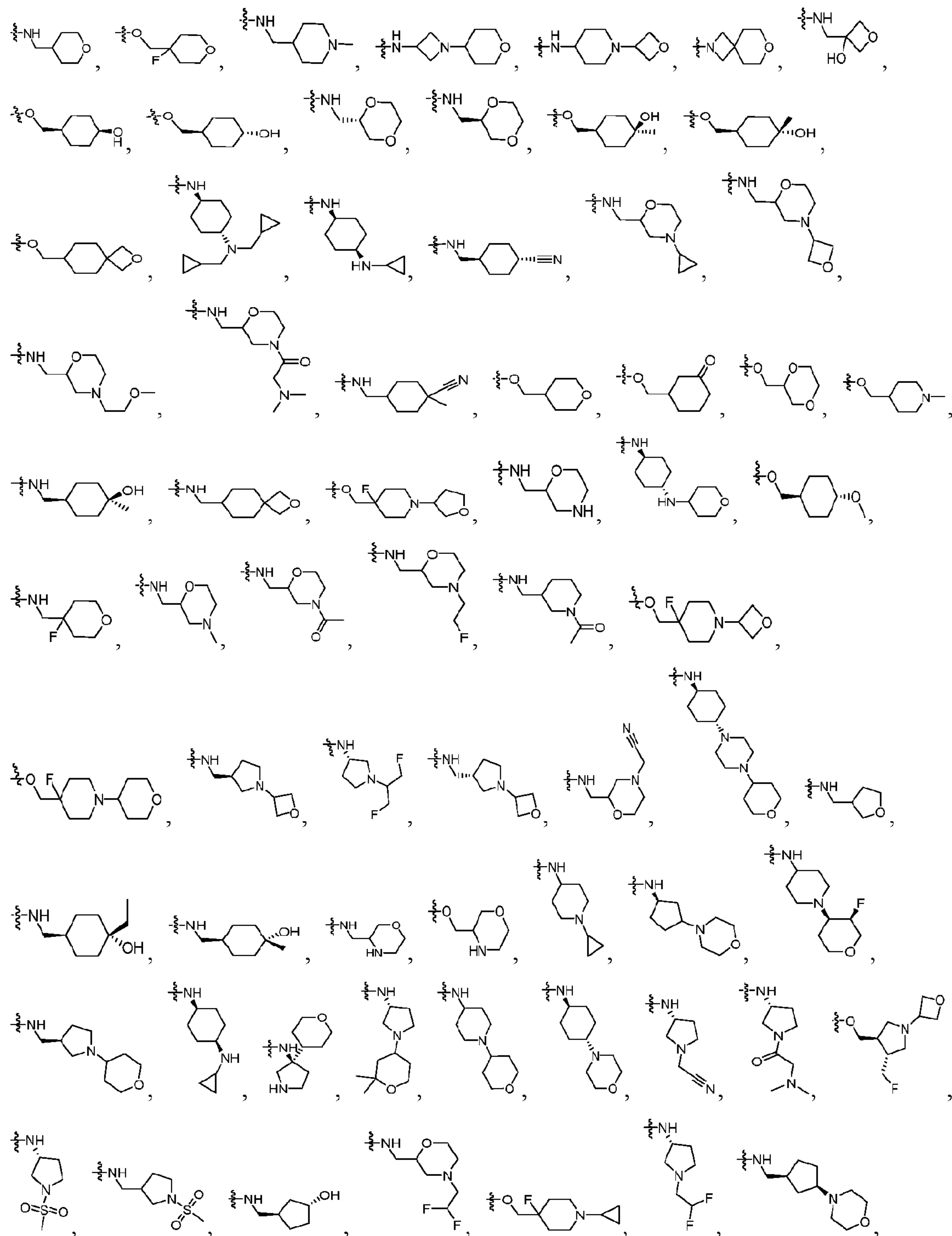
[0052] In some embodiments, R^{5a} is $-OR^{5b}$ or $-SO_2R^{5b}$, wherein R^{5b} is hydrogen or $C_{1-8}alkyl$, preferably methyl.

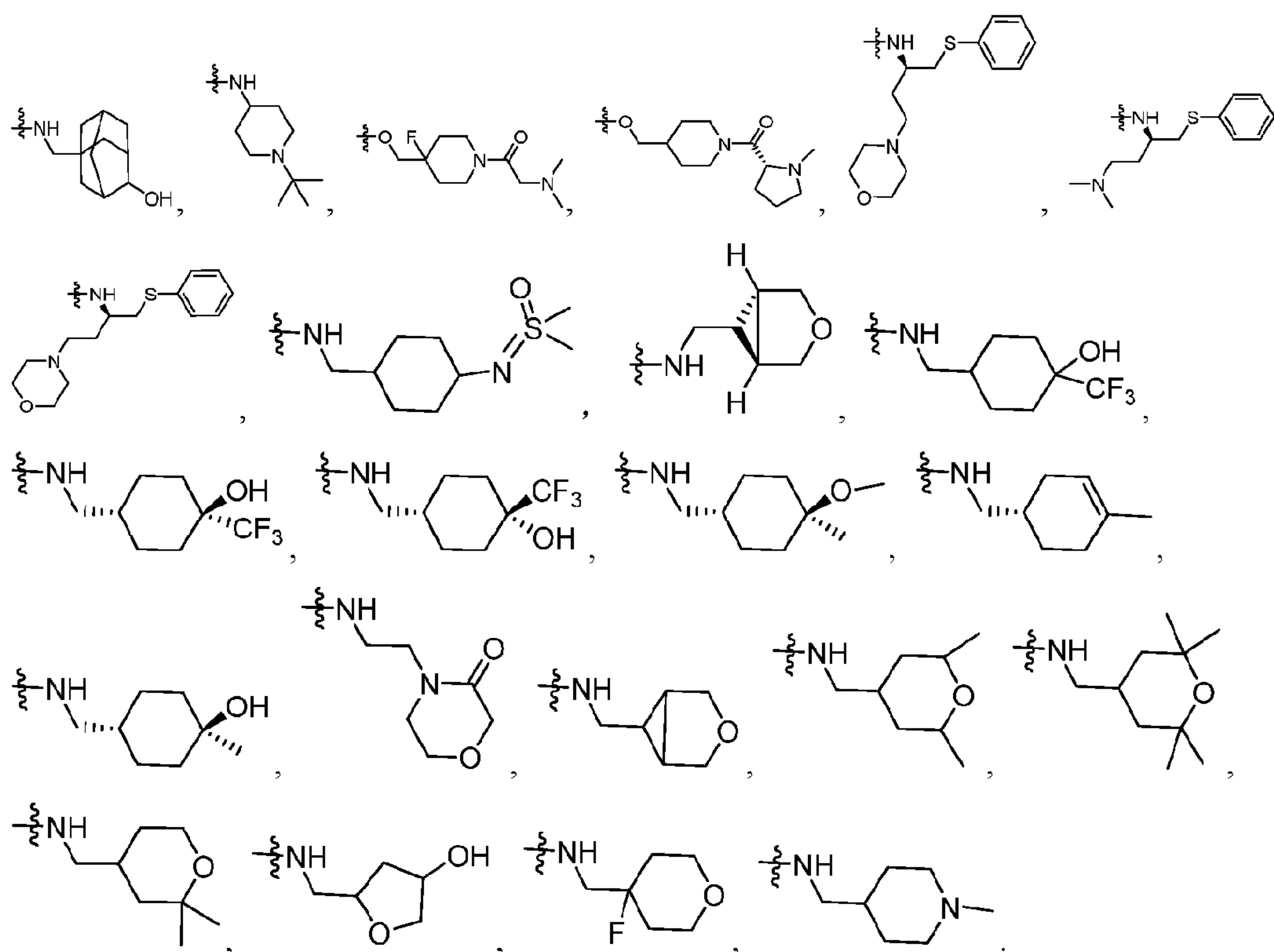
[0053] In some embodiments, R^{5a} is $-COR^{5b}$, wherein R^{5b} is hydrogen or $C^{1-8}alkyl$ optionally

substituted with $-\text{NR}^{5f}\text{R}^{5g}$, wherein R^{5f} and R^{5g} are each independently hydrogen or C_{1-8} alkyl, preferably methyl.

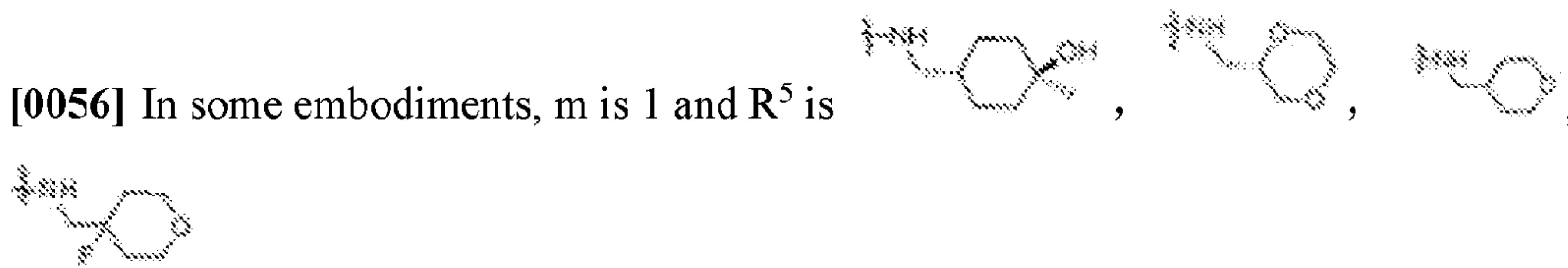
[0054] In some embodiments, two adjacent R^5 on the phenyl ring together with the phenyl ring form indazolyl which is substituted with tetrahydropyranyl.

[0055] In some embodiments, m is 1, and R^5 is $-\text{L}^5\text{-CyC}$ selected from the group consisting of:





[0056] In some embodiments, m is 1 and R⁵ is



[0057] In some embodiments, the Bcl-2 inhibitor in present disclosure is selected from the group consist of:

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-(((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-(((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-ethylphenyl)pyrrolidin-1-yl)-7-

azaspiro[3.5]nonan-7-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((R)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(7-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.5]nonan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(7-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.5]nonan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(9-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(9-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-(dimethylamino)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

N-((4-(((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-8-azaspiro[4.5]decan-8-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-8-azaspiro[4.5]decan-8-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

N-((4-(((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(8-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[4.5]decan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

N-((4-(((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-

yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((R)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((R)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclobutylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isobutylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)-4-(2-(2-(o-tolyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-bromophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chlorophenyl)pyrrolidin-1-yl)-7-

azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(4-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-ethoxyphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(dimethylamino)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-(dimethylamino)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-(bis(methyl-d3)amino)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)-4-(2-(2-(2-(pyrrolidin-1-yl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(1-methylpiperidin-4-yl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-methoxyphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropoxyphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(methoxymethyl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(hydroxymethyl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(5-chloro-2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S or R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2,4-dicyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2,5-dicyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-(2-chlorophenyl)thiophen-2-yl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-methylpyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(4-cyclopropyl-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-phenyl-2,5-dihydro-1H-pyrrol-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-

yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4,4-dimethylpyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4,4-difluoropyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-(trifluoromethyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-(dimethylamino)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-(2-(dimethylamino)ethoxy)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-3,3-dimethylpyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-((((1s,4s) or (1r,4r))-4-((dimethyl(oxo)-16-sulfaneylidene)amino)cyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-(methyl(3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)(oxo)-16-sulfaneylidene)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((3-oxabicyclo[3.1.0]hexan-6-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((4-hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide; ;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-((((1s,4s)-4-hydroxy-4-

(trifluoromethyl)cyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-methoxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((S)-4-methylcyclohex-3-en-1-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-(prop-1-en-2-yl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-propylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

N-((4-(((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(6-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-((2-(tetrahydro-2H-pyran-4-yl)ethyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-((2-morpholinoethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-((2-(3-oxomorpholino)ethyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((3-oxabicyclo[3.1.0]hexan-6-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((2,6-dimethyltetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-6-azaspiro[3.4]octan-6-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.4]octan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-((7R or 7S)-7-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[4.4]nonan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide ;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-((7S or 7R)-7-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[4.4]nonan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((2,2-dimethyltetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(3-methyl-3-((tetrahydro-2H-pyran-4-yl)methyl)ureido)-3-

nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-phenylpyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((cis or trans)-4-hydroxytetrahydrofuran-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((trans or cis)-4-hydroxytetrahydrofuran-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

[0058] In some embodiments, the Bcl-2 inhibitor in present disclosure is 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide (**Compound 1**) or a pharmaceutically acceptable salt thereof.

Preparation of Bcl-2 inhibitors

[0059] All the Bcl-2 inhibitors having Formulas (III-B), (III-C), (III-D) or (III-E), including 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide (**Compound 1**), can be prepared by the method disclosed in international publication WO2019/210828A1.

Preparation of Compound 1

[0060] Step 1: 2,2-dimethoxy-7-azaspiro[3.5]nonane hydrochloride

[0061] To the solution of tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (500 g, 2.09 mol) in MeOH (750 mL) and EA (750 mL) was added conc. HCl acid (350 mL, 4.18 mol) at room temperature and stirred for 4 hours. After concentrated in vacuum, MeOH (750 mL) was added into the residue and then the resulting mixture was concentrated in vacuum (repeated this work-up twice). The brown residue was suspended in EA (1250 mL) and stirred for 1 hour. The solid precipitation was filtered and dried in vacuum to afford the title product as an off-white powder (350 g, yield: 76.0%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 3.03 (s, 6 H), 2.96-2.89 (m, 4 H), 1.93 (s, 4 H), 1.74-1.67 (m, 4 H). MS (ESI, m/e) [M+1]⁺ 186.0.

[0062] Step 2: methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2,2-dimethoxy-7-azaspiro[3.5]nonan-7-yl)benzoate

[0063] The mixture of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-fluorobenzoate (100 g), 2,2-dimethoxy-7-azaspiro[3.5]nonane hydrochloride (116 g, 1.5 eq.) and DBU (160 g, 3.0

eq.) in NMP (500 mL) was stirred for 16 hours at 85 °C. After the reaction was completed, the mixture was cooled to $50 \pm 5^\circ\text{C}$ and citric acid in water (2%, 5 L) was added drop-wise into the system under stirring. After filtered, the cake was collected and dissolved with DCM (1.5 L). The solution of crude product was washed with citric acid in water (2%, 1.5 L), saturated aq. NaHCO_3 (1.5 L) and 15% aq. NaCl (1.5 L), and then dried over anhydrous Na_2SO_4 . Silica gel (100 g) was added into the solution of crude product under stirring and then filtered. The filtrate was concentrated to 300 mL. MTBE (500mL) was poured into the system. After stirred for 2 hours, the cake was collected after filtration and was dried in vacuum to give an off-white solid (192 g, yield: 72.1%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 11.63 (s, 1H), 8.00 (d, $J = 2.4$ Hz, 1H), 7.76 (d, $J = 9.2$ Hz, 1H), 7.47 (t, $J = 3.2$ Hz, 1H), 7.42 (d, $J = 2.4$ Hz, 1H), 6.79 (dd, $J = 2.4$ Hz, $J = 9.2$ Hz, 1H), 6.39-6.36 (m, 2H), 3.64 (s, 3H), 3.17-3.12 (m, 4H), 3.01 (s, 6H), 1.86 (s, 4H), 1.54-1.50 (m, 4H). MS (ESI, m/e) $[\text{M}+1]^+$ 451.9.

[0064] Step 3: methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-oxo-7-azaspiro[3.5]nonan-7-yl)benzoate

[0065] To the solution of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2,2-dimethoxy-7-azaspiro[3.5]nonan-7-yl)benzoate (176 g, 0.39 mol) in DCM (2 L) was added diluted HCl acid (1M, 1.5 L) and stirred for overnight. After the reaction was completed, the mixture was cooled to 10°C and was adjusted to pH = 8-9 with aqueous NaOH solution (4 M) under stirring. The organic phase was separated and washed with 15% aq. NaCl (1 L), then washed with H_2O (1 L). After the organic phase was concentrated to 500 mL, MTBE (1 L) was poured into the solution and then the system was concentrated to 500 mL (repeated this work-up 3 times). The resulting system was stirred for 0.5 hour. After filtration, the cake was collected and then dried in vacuum to obtain the tittle product as a white solid (152 g, yield: 96.23%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 11.64 (s, 1H), 8.02 (d, $J = 2.4$ Hz, 1H), 7.78 (d, $J = 9.2$ Hz, 1H), 7.47 (t, $J = 3.2$ Hz, 1H), 7.44 (d, $J = 2.4$ Hz, 1H), 6.83 (dd, $J = 2.4$ Hz, $J = 9.2$ Hz, 1H), 6.43 (d, $J = 2.4$ Hz, 1H), 6.38-6.36 (m, 1H), 3.65 (s, 3H), 3.24-3.21 (m, 4H), 2.80 (s, 4H), 1.70-1.67 (m, 4H). MS (ESI, m/e) $[\text{M}+1]^+$ 405.9.

[0066] Step 4: (S)-tert-butyl 2-(2-(prop-1-en-2-yl)phenyl)pyrrolidine-1-carboxylate

[0067] To a mixture of (S)-tert-butyl 2-(2-bromophenyl)pyrrolidine-1-carboxylate (50 g, 153.3 mmol) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (38.6 g, 229.9 mmol) in dioxane (500 mL) and H_2O (50 mL) was added Cs_2CO_3 (100 g, 305 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (6.6 g, 7.5 mmol). The mixture was stirred at 100°C for 8 hours. TLC showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluent: PE/EA (v/v) = 100/1 to 10/1) to obtain (S)-tert-butyl 2-(2-(prop-1-en-2-yl)phenyl)pyrrolidine-1-carboxylate (65 g, crude). The crude product was used

directly in next step.

[0068] Step 5: (S)-tert-butyl 2-(2-isopropylphenyl)pyrrolidine-1-carboxylate

[0069] To a solution of (S)-tert-butyl 2-(2-(prop-1-en-2-yl)phenyl)pyrrolidine-1-carboxylate (30 g, 104.39 mmol) in MeOH (500 mL) was added Pd/C (10 g, 10%) and the mixture was stirred at 20 °C under H₂ (15 Psi) for 12 hours. TLC showed the reaction was completed. The mixture was filtered and the filtrate was concentrated in vacuum to give (S)-tert-butyl 2-(2-isopropylphenyl)pyrrolidine-1-carboxylate (60 g, crude), which was used in next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.39-6.90 (m, 4H), 5.36-5.04 (m, 1H), 3.77-3.52 (m, 2H), 3.20-3.17 (m, 1H), 2.47-2.24 (m, 1H), 1.96-1.65 (m, 3H), 1.54-1.38 (m, 2H), 1.31-1.22 (m, 8H), 1.17 (s, 7H).

[0070] Step 6: (S)-2-(2-isopropylphenyl)pyrrolidine hydrochloride

[0071] To a solution of tert-butyl 2-(2-isopropylphenyl)pyrrolidine-1-carboxylate (55 g, 190 mmol) in DCM (50 mL) was added HCl in 1,4-dioxane (4 M, 142 mL, 570 mmol) dropwise at room temperature. The mixture was stirred at room temperature for overnight. The mixture was concentrated in vacuum. The resulting residue was slurried with EA (100 mL) and then filtered, dried in vacuum to give (S)-2-(2-isopropylphenyl)pyrrolidine hydrochloride 26 g (yield: 60.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.93 (s, 1H), 8.81 (s, 1H), 7.63-7.57 (m, 1H), 7.41-7.34 (m, 2H), 7.32-7.24 (m, 1H), 4.91-4.75 (m, 1H), 3.47-3.35 (m, 1H), 3.31-3.25 (m, 1H), 2.40-2.21 (m, 1H), 2.19-1.86 (m, 3H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.17 (d, *J* = 6.7 Hz, 3H). MS (ESI, *m/e*) [M+1]⁺ 190.0.

[0072] Step 7: methyl (S)-2-((1H-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzoate

[0073] A mixture of (S)-2-(2-isopropylphenyl)pyrrolidine hydrochloride (120 g, 0.535 mole) and methyl 2-((1H-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(2-oxo-7-azaspiro[3.5]nonan-7-yl)benzoate (218 g, 0.509 mole) in DCM (2.2L) was charged into a reactor. The temperature was controlled below 30 °C and NaBH(OAc)₃ (216 g, 1.018 mole) was added into the reactor in 5-6 portions. Then the reaction mixture was stirred at room temperature and monitored by TLC. After the starting material ketone was consumed completely, the mixture was adjusted to pH = 4~5 with diluted HCl acid (0.5 M). The separated organic phase was washed with H₂O (600 mL × 2) and then washed with aq. NaHCO₃ (600 mL × 2), saturated aq. NaCl (600 mL). The organic phase was collected, then dried over anhydrous Na₂SO₄ and concentrated. 256 g off-white solid was obtained as crude product, which was used in next step directly. MS (ESI, *m/e*) [M+1]⁺ 579.0.

[0074] Step 8: (S)-2-((1H-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzoic acid

[0075] To a solution of methyl (S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzoate (105 g, 181.7 mmol) in THF (525 mL) and MeOH (525 mL) was added aq. NaOH (3.5 M). It was stirred at room temperature overnight. After THF and MeOH were removed in vacuum, 3.5 L of water was added into the residue. The resulting mixture was adjusted to pH = 5~6 with 3 N HCl acid at room temperature with stirring. The precipitate was filtered and dried in vacuum to give the product as a white solid (102.4 g, yield: 99%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 12.13 (s, 1H), 11.58 (s, 1H), 7.95 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.56 - 7.40 (m, 2H), 7.35 (s, 1H), 7.27 - 7.04 (m, 3H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.32 (s, 2H), 3.62 (s, 1H), 3.32 - 3.26 (m, 1H), 3.10 - 3.04 (m, 4H), 2.35-2.30 (m, 1 H), 2.9-2.15 (m, 1 H), 1.74 -1.64 (m, 4H), 1.52-1.37 (m, 6H), 1.28 - 1.06 (m, 6H). MS (ESI, *m/e*) [M+1]⁺ 564.9.

[0076] Step 9: 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1*r*,4*r*)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide

[0077] A mixture of (S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzoic acid (44 g, 78 mmol), 4-(((1*r*,4*r*)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrobenzenesulfonamide (26.8 g, 78 mmol), TEA (15.7 g, 156 mmol), EDCI (19.4 g, 101 mmol) and DMAP (19 g, 156 mmol) in anhydrous DCM (880 mL) was stirred overnight at room temperature. The reaction was monitored by HPLC. After starting material of (S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzoic acid was consumed completely, the reaction mixture was heated to ~35 °C and N¹,N¹-dimethylethane-1,2-diamine (17.2 g, 195 mmol) was added in one portion. The reaction was stirred for another 12 hours. The mixture was washed twice with 10 wt % aq. AcOH solution (300 mL × 2) and then washed with saturated aq. NaHCO₃ (300 mL × 2). The organic layer was collected and concentrated to about 90 mL. 22 g of silica gel was added and stirred for 2 hours. After filtration, 180 mL EA was added into the filtrate at reflux and further stirred for 5 hours. After the mixture was cooled to room temperature, the precipitate was filtered and then the wet cake was washed twice with EA (180 mL). After drying in vacuum at 80-90 °C, the desired compound was obtained (48 g, yield: 69.5%). ¹H NMR (DMSO-*d*₆) δ ppm: 11.65 (s, 1H), 11.11 (br, 1H), 8.58-8.39 (m, 2H), 8.00 (d, *J* = 2.8 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.57-7.37 (m, 4H), 7.30-7.10 (m, 3H), 7.00 (d, *J* = 9.2 Hz, 1H), 6.65 (d, *J* = 1.2 Hz, 1H), 6.35 (s, 1H), 6.17 (s, 1H), 4.24 (s, 1H), 3.39-3.20 (m, 5H), 3.04-2.88 (m, 4H), 2.23 (s, 1H), 1.94-1.47 (m, 11H), 1.44-1.26 (m, 7H), 1.19 (d, *J* = 8.0 Hz, 3H), 1.14 (d, *J* = 8.0 Hz, 3H), 1.10 (s, 4H). MS (ESI, *m/e*) [M+1]⁺ 889.9.

Methods of Treatment

[0078] In one aspect, the present disclosure provides a method of treating cancer. In certain aspects, the method comprises administering to a patient in need an effective amount of **Compound 1**. The cancer can include, without limitation, B-cell malignancies, lymphoma or leukemia, selected from the group consisting of acute myeloid leukemias (AML), B-cell non-Hodgkin's lymphoma (B-NHL)), indolent B-cell Non-Hodgkin Lymphoma (NHL), diffuse large B-cell lymphomas (DLBCL), Germinal center B-cell like diffuse large B-cell lymphomas (GCB-DLBCL), follicular lymphomas (FL), mantle cell lymphomas (MCL), acute lymphoblastic leukemia (ALL) , chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and marginal zone lymphoma (MZL). In some embodiments, the cancer is relapsed/refractory, or transformed.

[0079] **Compound 1** can be administered by any suitable means, including oral, parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Dosing can be by any suitable route. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

[0080] **Compound 1** would be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. **Compound 1** is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of **Compound 1** in the formulation, the type of disorder or treatment, and other factors discussed above.

[0081] For the prevention or treatment of disease, the appropriate dosage of **Compound 1** will depend on the type of disease to be treated, the severity and course of the disease, whether **Compound 1** is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to **Compound 1**, and the discretion of the attending physician. **Compound 1** is suitably administered to the patient at one time or over a series of treatments.

EXAMPLES

[0082] The present invention is further exemplified, but not limited to, by the following examples that illustrate the invention.

Example 1: Efficacy study of Bcl-2 inhibitors in RS4;11 acute lymphoblastic leukemia (ALL) subcutaneous xenograft model

[0083] The RS4;11 cells are of acute lymphoblastic leukemia (ALL) origin and were obtained from American Type Culture Collection (ATCC CRL-1873, Manassas, VA, DC, USA). Cells were grown in RPMI 1640 medium (Corning, Cat# 10-040-CVR), supplemented with 10% (v/v) fetal bovine serum (Gibco, Cat# 10099-141C), and 100 µg/mL of penicillin and streptomycin (Gibco, Cat# 15140-122). RS4;11 cells were maintained as suspension cell cultures at 37 °C in a 5% CO₂ atmosphere. Five to six-week-old female NCG mice were purchased from Gempharmatech of Information Technology Center. All animals were maintained under specific pathogen free (SPF) “full barrier” condition with free access to food and water. Mice were group-housed under a 12 h light: dark cycle (lights on at 08:00 h), at a temperature of 20-26 °C and 37-62% humidity in IVC cages (Lingyunboji (Beijing) Technology Co., Ltd.). Mice were fed with complete granulated feed with Co60 radiosterilization (Beijing Ke Ao Xie Li Feed Co., Ltd.).

[0084] On the day of implantation, RS4;11 cells were harvested and re-suspended with appropriate volume of ice cold DPBS and same volume of Matrigel (Corning, Cat# 356237) to give a final concentration of 5×10^7 cells/mL. Re-suspended cells were placed on ice prior to inoculation. The right front flank region of each mouse was cleaned with 75% ethanol prior to cell inoculation. Each animal was injected subcutaneously with 1×10^7 cells in 200 µL of cell suspension in the right front flank via a 26-gauge needle. After implantation, primary tumor volume was measured in two dimensions using a caliper.

[0085] Animals were randomly assigned into 10 groups with 10 mice per group according to body weight and tumor volume (100 mm^3 - 200 mm^3). The groups consisted of vehicle group, 5, 15, 50 mg/kg of venetoclax with QD dosing, 5, 15, 50 mg/kg of **Compound 1** with QD dosing, and 2.5, 7.5, 25 mg/kg of **Compound 1** with BID dosing. Treatments were administered by oral gavage (p.o.) in a volume of 10 mL/kg body weight. Body weight was assessed immediately before dosing and volume dosed was adjusted accordingly.

[0086] Individual body weight was recorded twice weekly, with mice being monitored daily for clinical signs of toxicity for the duration of the study. Mice were euthanized using carbon dioxide when their tumor volume reached $2,000 \text{ mm}^3$, the tumor was ulcerated, or body weight loss exceeded 20%.

[0087] Tumor volume was calculated using the formula: $V = 0.5 \times (a \times b^2)$ where a and b are the long and short diameters of the tumor, respectively.

[0088] *In vivo* efficacy of **Compound 1** was examined and compared to venetoclax in RS4;11

ALL xenografts grown subcutaneously in NCG mice. Following oral administration at well tolerated doses, **Compound 1** potently and dose-dependently inhibited tumor growth (**Figure 1** and **Table 1**). At the same total daily doses of 5 and 15 mg/kg, **Compound 1** demonstrated significantly better efficacy when compared with venetoclax. Venetoclax was dosed at 400 mg daily in clinic. Its clinically relevant dose in mice is around 15 mg/kg QD based on free AUC. **Compound 1** 2.5 mg/kg BID was more active than venetoclax at 15 mg/kg QD. Furthermore, at the same total daily doses of 15 and 50 mg/kg, **Compound 1** QD and BID dosing schedule showed equivalent anti-tumor activities. These results are shown in **Figure 1**.

[0089] All treatment groups had no significant impact on animal body weight throughout the study.

Table 1

Agent	Dose (mg/kg)	Schedule	Route	Mean Tumor volume (Day 42) (mm ³ ±SEM)
Vehicle	Vehicle	BID × 21	p.o.	>2000
Compound 1	2.5	BID × 42	p.o.	512.5±115.9
Compound 1	7.5	BID × 42	p.o.	252.8±48.3
Compound 1	25	BID × 42	p.o.	136.6±2.2
Compound 1	5	QD × 42	p.o.	820.9±140.2
Compound 1	15	QD × 42	p.o.	312.6±57.9
Compound 1	50	QD × 42	p.o.	141.8±5.1
Venetoclax	5	QD × 35	p.o.	>2000
Venetoclax	15	QD × 42	p.o.	1070.6±181.1
Venetoclax	50	QD × 42	p.o.	288.4±37.8

Example 2: Efficacy study of Bcl-2 inhibitors in MAVER-1 mantle cell lymphoma (MCL) subcutaneous xenograft model

[0090] MAVER-1 cells are of mantle cell lymphoma (MCL) origin and were obtained from American Type Culture Collection (ATCC CRL-3008, Manassas, VA, DC, USA). Cells were grown in RPMI 1640 medium (Corning, Cat# 10-040-CVR), supplemented with 10% (v/v) fetal bovine serum (Gibco, Cat# 10099-141C), and 100 µg/mL of penicillin and streptomycin (Gibco, Cat# 15140-122). MAVER-1 cells were maintained as suspension cell cultures at 37 °C in a 5% CO₂ atmosphere. Five to six-week-old female NCG mice were purchased from Gempharmatech of Information Technology Center. All animals were maintained under specific pathogen free (SPF) “full barrier” condition with free access to food and water. Mice were group-housed under a 12 h light: dark cycle (lights on at 08:00 h), at a temperature of 21-26 °C and 44-61% humidity in IVC cages (Lingyunboji (Beijing) Technology Co., Ltd.). Mice

were fed with complete granulated feed with Co60 radiosterilization (Beijing Ke Ao Xie Li Feed Co., Ltd.).

[0091] On the day of implantation, MAVER-1 cells were harvested and re-suspended with appropriate volume of ice cold DPBS and same volume of Matrigel (Corning, Cat# 356237) to give a final concentration of 1.5×10^7 cells/mL. Re-suspended cells were placed on ice prior to inoculation. The right front flank region of each mouse was cleaned with 75% ethanol prior to cell inoculation. Each animal was injected subcutaneously with 3×10^6 cells in 200 μ L of cell suspension in the right front flank via a 26-gauge needle. After implantation, primary tumor volume was measured in two dimensions using a caliper.

[0092] Animals were randomly assigned into 7 groups with 10 mice per group according to body weight and tumor volume (100 mm^3 - 200 mm^3). The groups consisted of vehicle group, 5, 15 mg/kg of venetoclax with QD dosing, 5, 15 mg/kg of **Compound 1** with QD dosing, and 2.5, 7.5 mg/kg of **Compound 1** with BID dosing. Treatments were administered by oral gavage (p.o.) in a volume of 10 mL/kg body weight. Body weight was assessed immediately before dosing and volume dosed was adjusted accordingly.

[0093] Individual body weight was recorded twice weekly, with mice being monitored daily for clinical signs of toxicity for the duration of the study. Mice were euthanized using carbon dioxide when their tumor volume reached $2,000 \text{ mm}^3$, the tumor was ulcerated, or body weight loss exceeded 20%.

[0094] Tumor volume was calculated using the formula: $V = 0.5 \times (a \times b^2)$ where a and b are the long and short diameters of the tumor, respectively. Tumor growth inhibition (TGI) was calculated using the following formula: $\% \text{ TGI} = 100 \times [1 - (\text{treated } t - \text{treated } t_0) / (\text{vehicle } t - \text{vehicle } t_0)]$ (treated t = treated tumor volume at time t, treated t₀ = treated tumor volume at time 0, vehicle t = vehicle tumor volume at time t and vehicle t₀ = vehicle tumor volume at time 0)

[0095] *In vivo* efficacy of **Compound 1** was also examined and compared to venetoclax in MAVER-1 MCL xenografts grown subcutaneously in NCG mice. **Compound 1** potently suppressed tumor growth in a dose-dependent manner. The tumor growth inhibition (TGI) on day 14 for 2.5, 7.5 mg/kg BID and 5, 15 mg/kg QD of **Compound 1** were 77%, 103% and 86%, 103%, respectively. Venetoclax at 5 and 15 mg/kg QD achieved 38% and 91% TGI, respectively. At the same total daily doses of 5 and 15 mg/kg, **Compound 1** showed more anti-tumor activities relative to venetoclax. **Compound 1** 15 mg/kg QD and 7.5 mg/kg BID were similarly active. These results are shown in **Figure 2** and **Table 2**.

[0096] All treatment groups had no significant impact on animal body weight throughout the study.

Table 2

Agent	Dose (mg/kg)	Schedule	Route	Mean Tumor volume (Day 14) (mm ³ ±SEM)	TGI (Day 14)
Vehicle	Vehicle	BID × 17	p.o.	1637.7±143.0	-
Compound 1	2.5	BID × 17	p.o.	511.5±49.9	77%
Compound 1	7.5	BID × 17	p.o.	136.2±2.6	103%
Compound 1	5	QD × 17	p.o.	383.5±29.6	86%
Compound 1	15	QD × 17	p.o.	140.5±5.3	103%
Venetoclax	5	QD × 17	p.o.	1082.1±109.4	38%
Venetoclax	15	QD × 17	p.o.	315.4±23.1	91%

Example 3: Efficacy study of Bcl-2 inhibitors in Toledo diffuse large B cell lymphoma (DLBCL) subcutaneous xenograft model

[0097] Toledo cells are of diffuse large B cell lymphoma (DLBCL) origin and were obtained from American Type Culture Collection (ATCC CRL-2631, Manassas, VA, DC, USA). Cells were grown in RPMI 1640 medium (Corning, Cat# 10-040-CVR), supplemented with 10% (v/v) fetal bovine serum (Gibco, Cat# 10099-141C), and 100 µg/mL of penicillin and streptomycin (Gibco, Cat# 15140-122). Toledo cells were maintained as suspension cell cultures at 37 °C in a 5% CO₂ atmosphere. Five to six-week-old female NCG mice were purchased from Gempharmatech of Information Technology Center. All animals were maintained under specific pathogen free (SPF) “full barrier” condition with free access to food and water. Mice were group-housed under a 12 h light: dark cycle (lights on at 08:00 h), at a temperature of 21-26 °C and 35-61% humidity in IVC cages (Lingyunboji (Beijing) Technology Co., Ltd.). Mice were fed with complete granulated feed with Co60 radiosterilization (Beijing Ke Ao Xie Li Feed Co., Ltd.).

[0098] On the day of implantation, Toledo cells were harvested and re-suspended with appropriate volume of ice cold DPBS and same volume of Matrigel (Corning, Cat# 356237) to give a final concentration of 1.5×10^7 cells/mL. Re-suspended cells were placed on ice prior to inoculation. The right front flank region of each mouse was cleaned with 75% ethanol prior to cell inoculation. Each animal was injected subcutaneously with 3×10^6 cells in 200 µL of cell suspension in the right front flank via a 26-gauge needle. After implantation, primary tumor volume was measured in two dimensions using a caliper.

[0099] Transplanted animals were randomized into 10 groups with 10 mice per group on day 0 according to transplantation sequence and body weight. The groups consisted of vehicle group, 5, 15, 50 mg/kg of venetoclax with QD dosing, 5, 15, 50 mg/kg of **Compound 1** with QD dosing, and 2.5, 7.5, 25 mg/kg of **Compound 1** with BID dosing. Treatments were

administered by oral gavage (p.o.) in a volume of 10 mL/kg body weight. Body weight was assessed immediately before dosing and volume dosed was adjusted accordingly.

[0100] Individual body weight was recorded twice weekly, with mice being monitored daily for clinical signs of toxicity for the duration of the study. Mice were euthanized using carbon dioxide when their tumor volume reached 2,000 mm³, the tumor was ulcerated, or body weight loss exceeded 20%.

[0101] Tumor volume was calculated using the formula: $V = 0.5 \times (a \times b^2)$ where a and b are the long and short diameters of the tumor, respectively. Tumor growth inhibition (TGI) was calculated using the following formula: $\% \text{ TGI} = 100 \times [1 - (\text{treated}_t - \text{treated}_{t_0}) / (\text{vehicle}_t - \text{vehicle}_{t_0})]$ (treated t = treated tumor volume at time t, treated t₀ = treated tumor volume at time 0, vehicle t = vehicle tumor volume at time t and vehicle t₀ = vehicle tumor volume at time 0)

[0102] *In vivo* efficacy of **Compound 1** was further examined and compared to venetoclax in Toledo DLBCL subcutaneous xenograft model. Following daily oral administration at well tolerated doses at 2.5, 7.5, 25 mg/kg BID or 5, 15, 50 mg/kg QD, **Compound 1** induced dose-dependent anti-tumor effects. At the same total daily doses of 5 and 15 mg/kg, **Compound 1** demonstrated significantly better efficacy when compared with venetoclax. These results are shown in **Figure 3** and **Table 3**.

[0103] All treatment groups had no significant impact on animal body weight throughout the study.

Table 3

Agent	Dose (mg/kg)	Schedule	Route	Mean Tumor volume (Day 31) (mm ³ ±SEM)	TGI (Day 31)
Vehicle	Vehicle	BID × 31	p.o.	1703.1±190.9	-
Compound 1	2.5	BID × 31	p.o.	515.7±79.1	70%
Compound 1	7.5	BID × 31	p.o.	230.5±25.9	86%
Compound 1	25	BID × 31	p.o.	182.5±15.9	89%
Compound 1	5	QD × 31	p.o.	679.3±63.2	60%
Compound 1	15	QD × 31	p.o.	267.4±30.4	84%
Compound 1	50	QD × 31	p.o.	214.8±19.4	87%
Venetoclax	5	QD × 31	p.o.	1256.5±136.5	26%
Venetoclax	15	QD × 31	p.o.	847.8±109.4	50%
Venetoclax	50	QD × 31	p.o.	258.3±22.6	85%

Example 4: Efficacy study of Bcl-2 inhibitors in RS4;11 Bcl-2G101V KI acute lymphoblastic leukemia (ALL) subcutaneous xenograft model

[0001] The RS4;11 Bcl-2G101V KI cells are of acute lymphoblastic leukemia (ALL) origin and were screened in house. Cells were grown in RPMI 1640 medium (Corning, Cat# 10-040-CVR), supplemented with 10% (v/v) fetal bovine serum (Gibco, Cat# 10099-141C), and 100 µg/mL of penicillin and streptomycin (Gibco, Cat# 15140-122). RS4;11 Bcl-2G101V KI cells were maintained as suspension cell cultures at 37 °C in a 5% CO₂ atmosphere. Five to six-week-old female NCG mice were supplied by GemPharmatech Co., Ltd, Jiangsu, China. All animals were maintained under specific pathogen free (SPF) “full barrier” condition with free access to food and water. Mice were group-housed under a 12 h light: dark cycle (lights on at 08:00 h), at a temperature of 20-26 °C and 37-62% humidity in IVC cages (Lingyunboji (Beijing) Technology Co., Ltd.). Mice were fed with complete granulated feed with Co60 radio sterilization (Beijing Ke Ao Xie Li Feed Co., Ltd.).

[0002] On the day of implantation, RS4;11 Bcl-2G101V KI cells were harvested and re-suspended with appropriate volume of ice cold DPBS and same volume of Matrigel (Corning, Cat# 356237) to give a final concentration of 5×10^7 cells/mL. Re-suspended cells were placed on ice prior to inoculation. The right front flank region of each mouse was cleaned with 75% ethanol prior to cell inoculation. Each animal was injected subcutaneously with 1×10^7 cells in 200 µL of cell suspension in the right front flank via a 26-gauge needle. After implantation, primary tumor volume was measured in two dimensions using a caliper.

[0003] Animals were randomly assigned into 7 groups with 8 mice per group according to body weight and tumor volume (around 300 mm³). The groups consisted of vehicle group, 15, 50 and 100 mg/kg of venetoclax with QD dosing, 15, 50 and 100 mg/kg of **Compound 1** with QD dosing. Treatments were administered by oral gavage (p.o.) in a volume of 10 mL/kg body weight. Body weight was assessed immediately before dosing and volume dosed was adjusted accordingly.

[0004] Individual body weight was recorded twice weekly, with mice being monitored daily for clinical signs of toxicity for the duration of the study. Mice were euthanized using carbon dioxide when their tumor volume reached 2,000 mm³, the tumor was ulcerated, or body weight loss exceeded 20%.

[0005] Tumor volume was calculated using the formula: $V = 0.5 \times (a \times b^2)$ where a and b are the long and short diameters of the tumor, respectively.

[0006] *In vivo* efficacy of **Compound 1** was examined and compared to venetoclax in RS4;11 Bcl-2G101V KI xenografts grown subcutaneously in NCG mice. venetoclax showed marginal efficacy even at higher dose level, whereas **Compound 1** potently and dose-dependently

inhibited tumor growth. These results are shown in **Figure 4** and **Table 4**. The curves for **Compound 1** at 50 mg/kg p.o. QD and 100 mg/kg p.o. QD merged.

[0007] All treatment groups had no significant impact on animal body weight throughout the study.

Table 4

Agent	Dose (mg/kg)	Schedule	Route	Mean Tumor Volume (Day 10) (mm ³ ±SEM)	TGI (Day 10)
Vehicle	N/A	QD × 10	p.o.	1515.4±84.2	N/A
Compound 1	15	QD × 10	p.o.	554.2±70.3	78%
Compound 1	50	QD × 10	p.o.	155.1±4.3	110%
Compound 1	100	QD × 10	p.o.	144.5±3.5	111%
Venetoclax	15	QD × 10	p.o.	976.6±64.0	44%
Venetoclax	50	QD × 10	p.o.	711.8±49.7	65%
Venetoclax	100	QD × 10	p.o.	530.4±75.4	80%

[0104] The foregoing examples and description of certain embodiments should be taken as illustrating, rather than as limiting the present invention as defined by the claims. As will be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. All such variations are intended to be included within the scope of the present invention. All references cited are incorporated herein by reference in their entireties.

REFERENCES

- Adams, J. M., and Cory, S. (2007) The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene* 26, 1324-1337
- Anderson, M. A., Huang, D., and Roberts, A. (2014) Targeting BCL2 for the treatment of lymphoid malignancies. *Semin Hematol* 51, 219-227
- Czabotar, P. E., Lessene, G., Strasser, A., and Adams, J. M. (2014) Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. *Nat Rev Mol Cell Biol* 15, 49-63
- Egle, A., Harris, A. W., Bath, M. L., O'Reilly, L., and Cory, S. (2004) VavP-Bcl2 transgenic mice develop follicular lymphoma preceded by germinal center hyperplasia. *Blood* 103, 2276-2283
- Kondo, S., Oakes, M. G., and Sorenson, C. M. (2008) Rescue of renal hypoplasia and cystic dysplasia in Bcl-2 ^{-/-} mice expressing Bcl-2 in ureteric bud derived epithelia. *Dev Dyn* 237, 2450-2459

- Roberts, A. W. (2016) Targeting apoptotic pathways to treat lymphoid malignancies. *Rinsho Ketsueki* 57, 2054-2058
- Roberts, A. W., and Huang, D. (2017) Targeting BCL2 With BH3 Mimetics: Basic Science and Clinical Application of Venetoclax in Chronic Lymphocytic Leukemia and Related B Cell Malignancies. *Clin Pharmacol Ther* 101, 89-98
- Schenk, R. L., Strasser, A., and Dewson, G. (2017) BCL-2: Long and winding path from discovery to therapeutic target. *Biochem Biophys Res Commun* 482, 459-469
- Tausch, E., Close, W., Dolnik, A., Bloehdorn, J., Chyla, B., Bullinger, L., Dohner, H., Mertens, D., and Stilgenbauer, S. (2019) Venetoclax resistance and acquired BCL2 mutations in chronic lymphocytic leukemia. *Haematologica* 104, e434-e437.
- Veis, D.J., Sorenson, C.M., Shutter, J.R. and Korsmeyer, S.J. (1993) Bcl-2-deficient mice demonstrate fulminant lymphoid apoptosis, polycystic kidneys, and hypopigmented hair. *Cell*, 75, 229–240.
- Yamamura, K., Kamada, S., Ito, S., Nakagawa, K., Ichihashi, M., and Tsujimoto, Y. (1996) Accelerated disappearance of melanocytes in bcl-2-deficient mice. *Cancer Res* 56, 3546-3550

CLAIMS

1. A method of cancer treatment, the method comprising administering to a subject an effective amount of a Bcl-2 inhibitor,

wherein the Bcl-2 inhibitor is selected from the group consisting of:

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((R)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(7-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.5]nonan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(7-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-

2-azaspiro[3.5]nonan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(9-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(9-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-(dimethylamino)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

N-((4-(((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-8-azaspiro[4.5]decan-8-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-8-azaspiro[4.5]decan-8-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

N-((4-(((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(8-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[4.5]decan-2-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-(2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

N-((4-(((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((R)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((R)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclobutylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isobutylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-

yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)-4-(2-(2-(o-tolyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-bromophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(4-chlorophenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-ethoxyphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(dimethylamino)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-(dimethylamino)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-(bis(methyl-d3)amino)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-

yl)methyl)amino)phenyl)sulfonyl)-4-(2-(2-(2-(pyrrolidin-1-yl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(1-methylpiperidin-4-yl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-methoxyphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-isopropoxyphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(methoxymethyl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-(hydroxymethyl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(5-chloro-2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

(S or R)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-chloro-2-ethylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2,4-dicyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2,5-dicyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(3-(2-chlorophenyl)thiophen-2-yl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-methylpyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(4-cyclopropyl-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-phenyl-2,5-dihydro-1H-pyrrol-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4,4-dimethylpyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4,4-difluoropyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-(trifluoromethyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-(dimethylamino)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-4-(2-(dimethylamino)ethoxy)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)-3,3-dimethylpyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-

yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-((((1s,4s) or (1r,4r))-4-((dimethyl(oxo)-16-sulfaneylidene)amino)cyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-(methyl(3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)(oxo)-16-sulfaneylidene)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((3-oxabicyclo[3.1.0]hexan-6-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((4-hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-((((1r,4r)-4-hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide; ;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-((((1s,4s)-4-hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-((((1r,4r)-4-methoxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((S)-4-methylcyclohex-3-en-1-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-((((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-(prop-1-en-2-yl)phenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-((((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-propylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)-N-((4-((((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-

b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

N-((4-(((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(6-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

N-((4-(((S)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-ethylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.3]heptan-2-yl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-((2-(tetrahydro-2H-pyran-4-yl)ethyl)amino)phenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-((2-morpholinoethyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-((2-(3-oxomorpholino)ethyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((3-oxabicyclo[3.1.0]hexan-6-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((2,6-dimethyltetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((3-nitro-4-(((2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-6-azaspiro[3.4]octan-6-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(6-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[3.4]octan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-((7R or 7S)-7-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[4.4]nonan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide; ;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-((7S or 7R)-7-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-2-azaspiro[4.4]nonan-2-yl)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((2,2-dimethyltetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

(S)-2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-(2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(3-methyl-3-((tetrahydro-2H-pyran-4-yl)methyl)ureido)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-phenylpyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((cis or trans)-4-hydroxytetrahydrofuran-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(2-((S)-2-(2-cyclopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)-N-((4-(((trans or cis)-4-hydroxytetrahydrofuran-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide;

or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

2. The method of claim 1, wherein the Bcl-2 inhibitor is 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-N-((4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(2-((S)-2-(2-isopropylphenyl)pyrrolidin-1-yl)-7-azaspiro[3.5]nonan-7-yl)benzamide or a pharmaceutically acceptable salt thereof.

3. The method of claim 1, wherein the cancer is B-cell malignancies.

4. The method of claim 1, wherein the cancer is lymphoma or leukemia.
5. The method of claims 3 or 4, wherein the cancer is selected from the group consisting of acute myeloid leukemias (AML), B-cell non-Hodgkin's lymphoma (B-NHL), indolent B-cell Non-Hodgkin Lymphoma (NHL), diffuse large B-cell lymphomas (DLBCL), Germinal center B-cell like diffuse large B-cell lymphomas (GCB-DLBCL), follicular lymphomas (FL), mantle cell lymphomas (MCL), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and marginal zone lymphoma (MZL).
6. The method of claim 1, wherein the cancer is relapsed/refractory, or transformed.
7. The method of claim 1, wherein the Bcl-2 inhibitor is orally administered.
8. The method of claim 1, wherein the Bcl-2 inhibitor is orally administered at a dose of 20 mg/per day to 700 mg/per day.
9. The method of claim 1, wherein the cancer has Bcl-2 expression.
10. The method of claim, wherein the cancer has Bcl-2 Gly101 Val mutation expression.

Figure 1 A
1/8

Study ID	Cell Line	Mouse Strain	Animal No./group	Agent	Dose (mg/kg)	Schedule	Route	Mean Tumor volume (Day 42) (mm ³ ±SEM)
EPC- RS4;11- 1905	RS4;11- (ALL)	NCG	10	Vehicle	Vehicle	BID × 21	p.o.	>2000
			10	Compound 1	2.5	BID × 42	p.o.	512.5±115.9
			10	Compound 1	7.5	BID × 42	p.o.	252.8±48.3
			10	Compound 1	25	BID × 42	p.o.	136.6±2.2
			10	Compound 1	5	QD × 42	p.o.	820.9±140.2
			10	Compound 1	15	QD × 42	p.o.	312.6±57.9
			10	Compound 1	50	QD × 42	p.o.	141.8±5.1
			10	Venetoclax	5	QD × 35	p.o.	>2000
			10	Venetoclax	15	QD × 42	p.o.	1070.6±181.1
			10	Venetoclax	50	QD × 42	p.o.	288.4±37.8

Figure 1 B

2/8

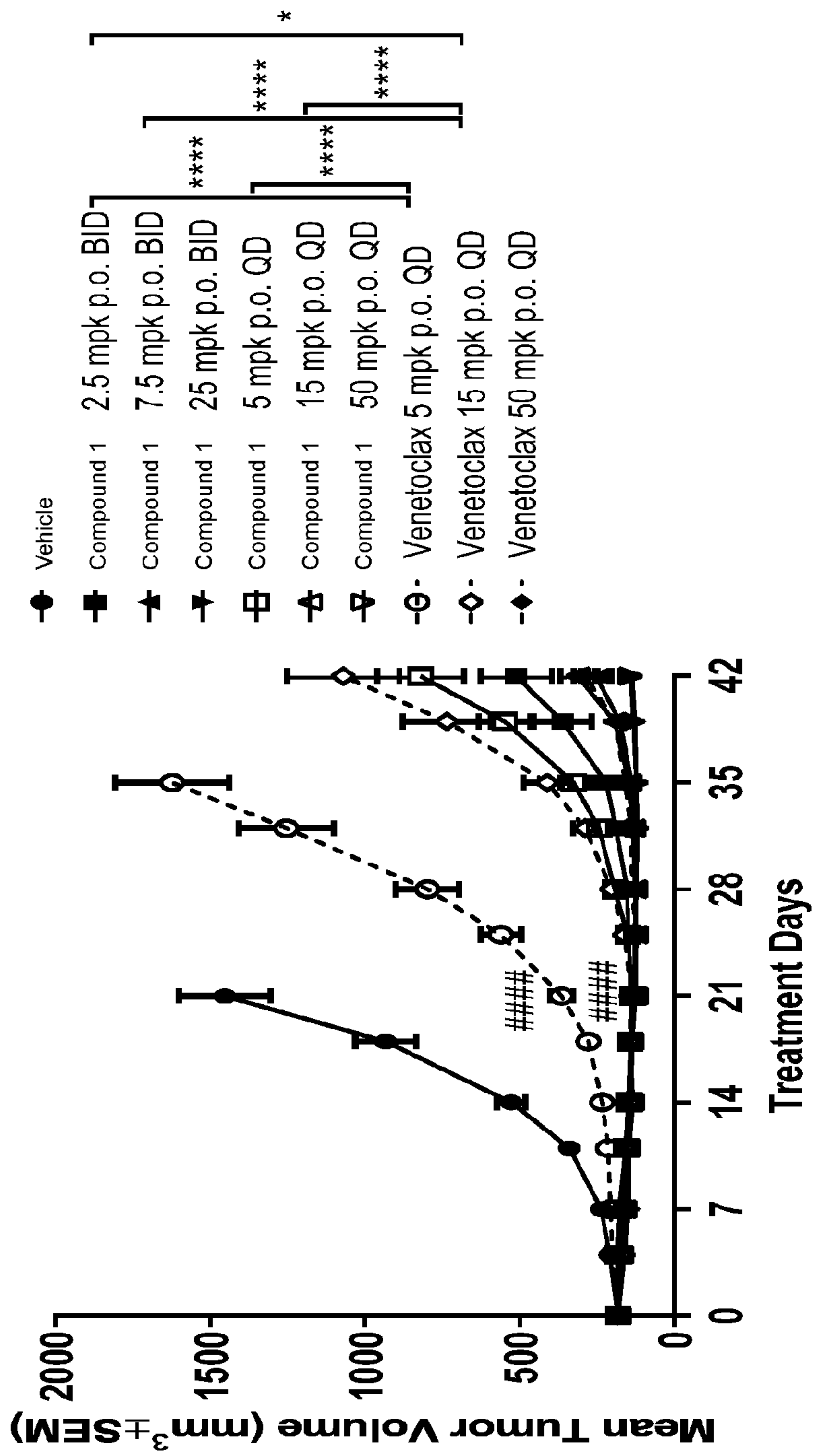


Figure 2 A
3/8

Study ID	Cell Line	Mouse Strain	Animal No./group	Agent	Dose (mg/kg)	Schedule	Route	Mean Tumor volume (Day 14) (mm ³ ±SEM)	TGI (Day 14)
EPC-MAVER-1-1902	MAVER-1 (MCL)	NCG	10	Vehicle	Vehicle	BID × 17	p.o.	1657.7±143.0	-
			10	Compound 1	2.5	BID × 17	p.o.	511.5±49.9	77%
			10	Compound 1	7.5	BID × 17	p.o.	136.2±2.6	103%
			10	Compound 1	5	QD × 17	p.o.	383.5±29.6	86%
			10	Compound 1	15	QD × 17	p.o.	140.3±5.3	103%
			10	Venetoclax	5	QD × 17	p.o.	1082.1±100.4	38%
			10	Venetoclax	15	QD × 17	p.o.	315.4±23.1	91%

Figure 2 B

4/8

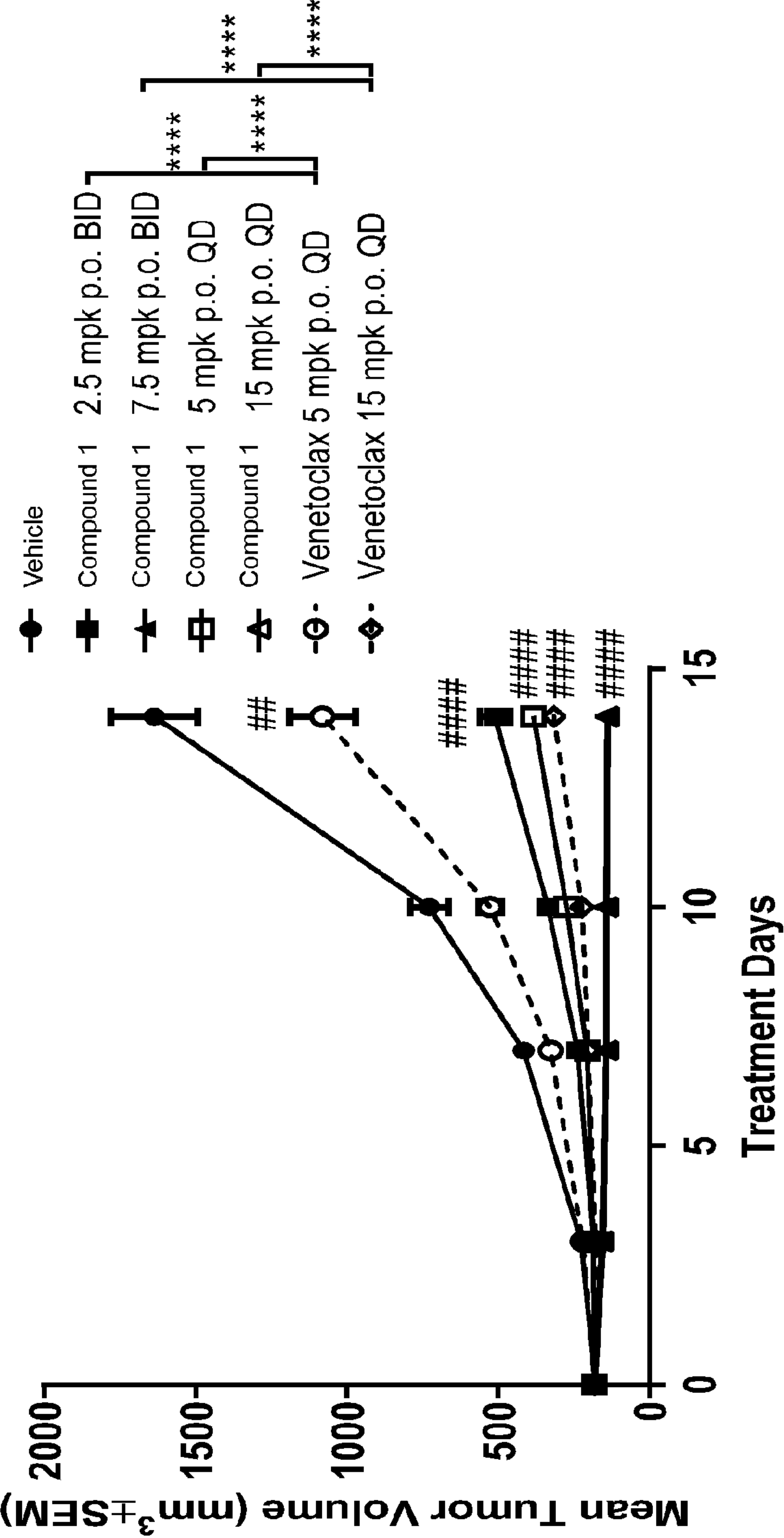


Figure 3 A
5/8

Study ID	Cell Line	Mouse Strain	Animal No./group	Agent	Dose (mg/kg)	Schedule	Route	Mean Tumor volume (Day 31) (mm ³ ±SEM)	TGI (Day 31)
EFC-Toledo-1901	Toledo (DLBCL)	NCG	10	Vehicle	Vehicle	BID × 31	p.o.	1703.1±190.9	-
			10	Compound 1	2.5	BID × 31	p.o.	515.7±79.1	70%
			10	Compound 1	7.5	BID × 31	p.o.	230.5±25.9	86%
			10	Compound 1	25	BID × 31	p.o.	162.5±15.9	89%
			10	Compound 1	5	QD × 31	p.o.	679.3±63.2	60%
			10	Compound 1	15	QD × 31	p.o.	267.4±30.4	84%
			10	Compound 1	50	QD × 31	p.o.	214.8±19.4	87%
			10	Venetoclax	5	QD × 31	p.o.	1256.5±136.5	26%
			10	Venetoclax	15	QD × 31	p.o.	847.8±109.4	50%
			10	Venetoclax	50	QD × 31	p.o.	258.3±22.6	85%

Figure 3 B
6/8

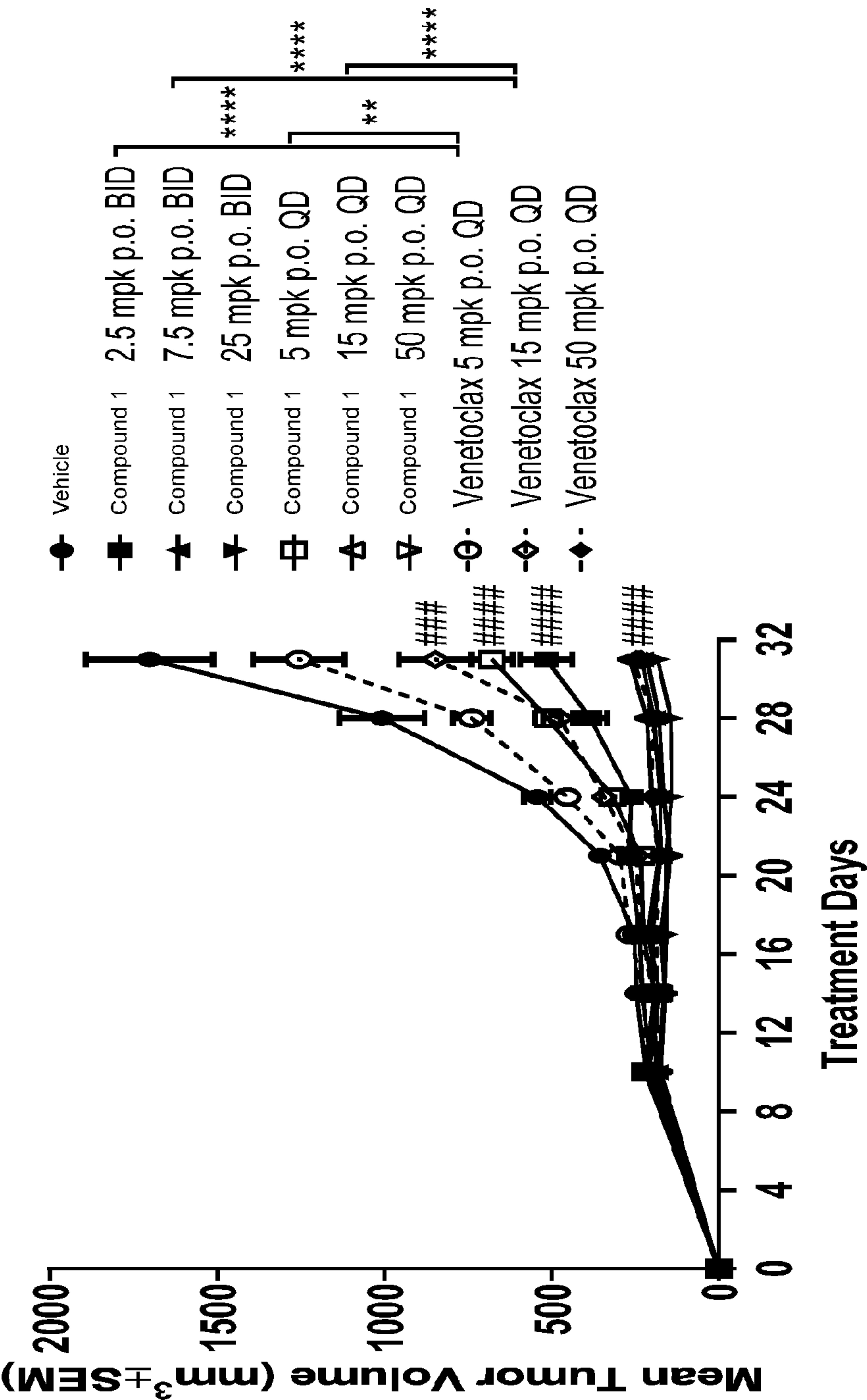


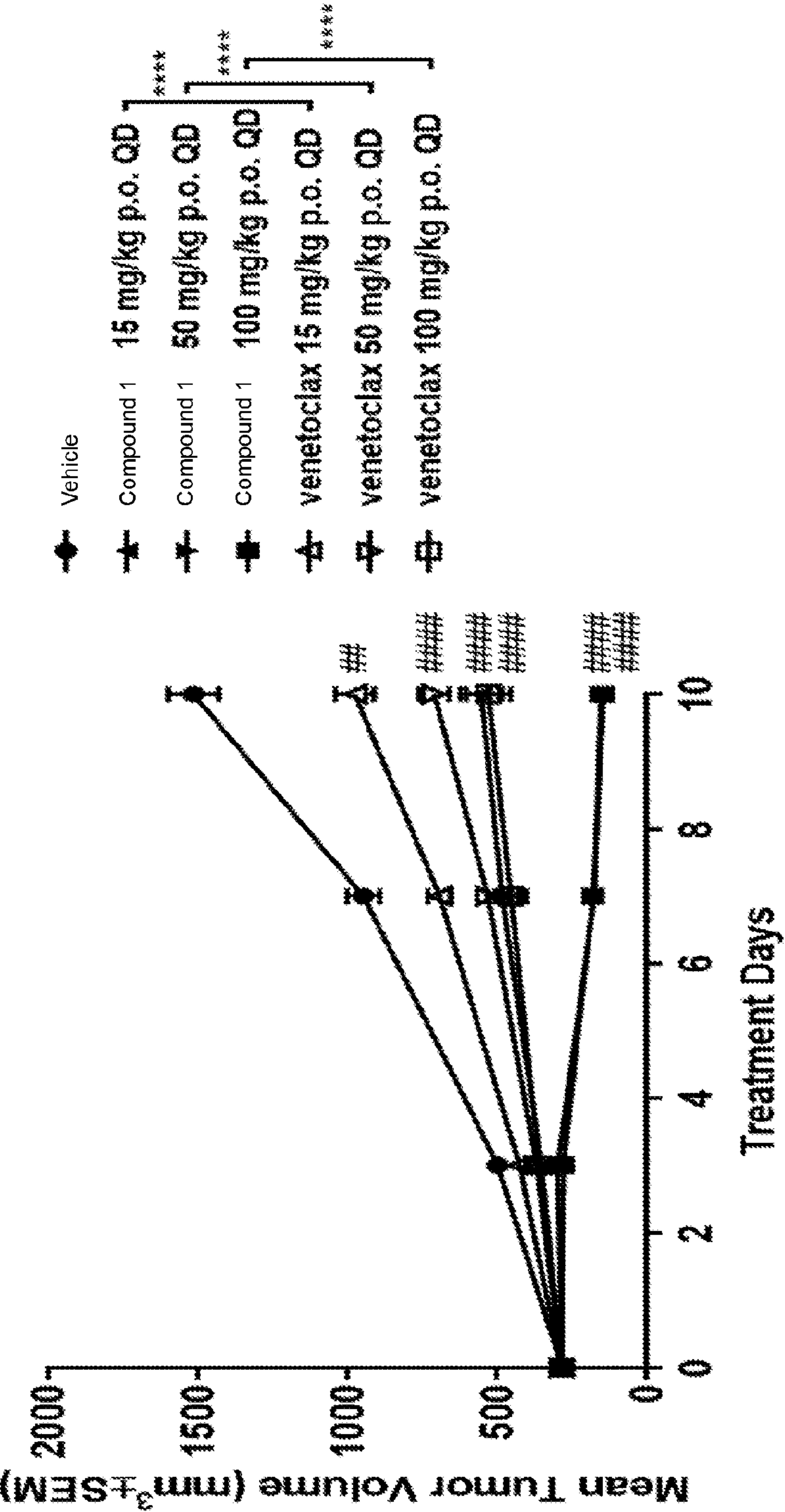
Figure 4 A

7/8

Study ID	Cell Line	Release Strain	Animal No./ Group	Agent	Dose (mg/kg)	Schedule	Route	Mean Tumor Volume (mm ³ ±SEM)	IC ₅₀ (Day 10)
EPC- RS4.11- 1915	RS4.11 Bel- 2G101V K1	NCG	6	Vehicle	N/A	QD × 10	p.o.	1515.4±94.2	N/A
			8	Compound I	15	QD × 10	p.o.	534.2±70.3	78%
			8	Compound I	50	QD × 10	p.o.	155.1±4.3	110%
			8	Compound I	100	QD × 10	p.o.	144.5±3.5	113%
			6	Venutochax	15	QD × 10	p.o.	976.6±64.0	44%
			6	Venutochax	50	QD × 10	p.o.	711.3±49.7	65%
			8	Venutochax	100	QD × 10	p.o.	330.4±75.4	80%

Figure 4 B

8/8



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2020/133636

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/12(2006.01)i; A61K 31/407(2006.01)i; A61P 35/00(2006.01)i

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; A61K; A61P

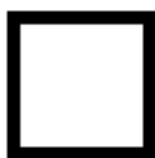
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI; SIPOABS; CNKI; CNABS; STNext; Web of Science: BEIGENE, cancer, tumor, Bcl-2, inhibit+, lymphomas, leukemia, lymphocytic, AML, NHL, DLBCL, MCL, Gly101Val

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019210828 A1 (BEIGENE LTD. et al.) 07 November 2019 (2019-11-07) the abstract, claims 1-139, description paragraphs [0005], [0006], [0103], [0150], [1153], [2006]	1-10
X	WO 2010138588 A2 (ABBOTT LAB. et al.) 02 December 2010 (2010-12-02) example compound 23, claims 1-32	1-10
X	WO 2012103059 A2 (UNIV. MICHIGAN et al.) 02 August 2012 (2012-08-02) the abstract, claims 1-33	1-10
A	WO 2011150016 A1 (ABBOTT LAB. et al.) 01 December 2011 (2011-12-01) the abstract, claims 1-11	1-10
A	CN 102947283 A (ABBOTT LAB.) 27 February 2013 (2013-02-27) the abstract, claims 1-4	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“A” document defining the general state of the art which is not considered to be of particular relevance	“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
“E” earlier application or patent but published on or after the international filing date	“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
“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	“&” document member of the same patent family
“O” document referring to an oral disclosure, use, exhibition or other means	
“P” document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

09 February 2021

Date of mailing of the international search report

26 February 2021

Name and mailing address of the ISA/CN

National Intellectual Property Administration, PRC
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088
China

Facsimile No. (86-10)62019451

Authorized officer

CUI,Chuanming

Telephone No. (86-10)53961869

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **1-10**
because they relate to subject matter not required to be searched by this Authority, namely:
[1] Claims 1-10 relate to a method of cancer treatment. These claims relate to a subject defined in PCT Rule 39.1(iv) that does not require search by the International Searching Authority. The search has been carried out and based on the use of the Bcl-2 inhibitor for the manufacturing of a medicament for cancer treatment.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2020/133636

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2019210828	A1	07 November 2019	AU	2019264475	A1	12 November 2020
WO	2010138588	A2	02 December 2010	HK	1163099	A1	07 September 2012
				CN	102448959	A	09 May 2012
				RU	2573832	C2	27 January 2016
				CA	2759182	A1	02 December 2010
				CN	104876927	A	02 September 2015
				TW	I537269	B	11 June 2016
				JP	2012528178	A	12 November 2012
				EP	2435432	A2	04 April 2012
				RU	2015154494	A	22 June 2017
				CN	102448959	B	17 June 2015
				CN	104906100	A	16 September 2015
				CA	3052016	A1	02 December 2010
				HU	S1700021	I1	28 June 2017
				JP	2018138577	A	06 September 2018
				BR	PI1014359	A2	05 April 2016
				JP	2017048219	A	09 March 2017
				KR	20180124164	A	20 November 2018
				KR	102001418	B1	19 July 2019
				KR	20150065947	A	15 June 2015
				SI	EP2435432	T1	30 October 2015
				HU	E027698	T2	28 October 2016
				JP	2020023545	A	13 February 2020
				TW	I561523	B	11 December 2016
				JP	6353506	B2	04 July 2018
				AR	109974	A2	13 February 2019
				PH	12015500297	A1	07 December 2015
				UY	33047	A	30 September 2011
				RS	54234	B1	31 December 2015
				UA	106079	C2	25 July 2014
				AU	2010254160	B2	12 February 2015
				HR	P20151001	T1	23 October 2015
				TW	201506025	A	16 February 2015
				IL	215644	D0	31 January 2012
				US	8580794	B2	12 November 2013
				NZ	595708	A	28 March 2014
				SG	175253	A1	28 November 2011
				PE	20120345	A1	17 May 2012
				KR	101659583	B1	29 September 2016
				JP	5747025	B2	08 July 2015
				JP	6038195	B2	07 December 2016
				UY	32668	A	31 December 2010
				ZA	201108616	B	23 December 2015
				WO	2010138588	A9	05 May 2011
				IL	269092	D0	28 November 2019
				KR	20180049164	A	10 May 2018
				LT	C2435432	I2	11 June 2018
				CA	2759182	C	07 June 2016
				US	2011124628	A1	26 May 2011
				JP	2015110605	A	18 June 2015

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2020/133636

Patent document cited in search report				Publication date (day/month/year)			Patent family member(s)			Publication date (day/month/year)		
							AR	076705	A1	29 June 2011		
WO 2012103059 A2				02 August 2012			NZ	613504	A	27 March 2015		
							ZA	201305571	B	29 October 2014		
							JP	2014507421	A	27 March 2014		
							US	8691184	B2	08 April 2014		
							JP	5998152	B2	28 September 2016		
							CA	2825306	A1	02 August 2012		
							AU	2012209295	B2	30 June 2016		
							ES	2693107	T3	07 December 2018		
							EP	2668180	B1	01 August 2018		
							EP	3459945	A1	27 March 2019		
							CN	103562202	B	14 September 2016		
							CN	103562202	A	05 February 2014		
							CA	2825306	C	26 February 2019		
							WO	2012103059	A3	18 October 2012		
							SG	192126	A1	30 September 2013		
							KR	101762724	B1	28 July 2017		
							EP	2668180	A4	13 August 2014		
							US	2012189539	A1	26 July 2012		
							KR	20140005984	A	15 January 2014		
							EP	2668180	A2	04 December 2013		
WO 2011150016 A1				01 December 2011			PE	20170465	A1	18 May 2017		
							CN	102939009	B	25 March 2015		
							DK	2575463	T3	25 July 2016		
							US	9403822	B2	02 August 2016		
							RU	2012156940	A	10 July 2014		
							RS	54892	B1	31 October 2016		
							PH	12018501264	A1	01 July 2019		
							MY	165427	A	22 March 2018		
							DO	P2013000242	A	31 March 2014		
							ES	2666181	T3	03 May 2018		
							EC	SP12012348	A	30 April 2013		
							ME	02452	B	20 September 2016		
							CA	2798765	C	23 October 2018		
							AU	2011258350	B2	09 April 2015		
							US	2017096424	A1	06 April 2017		
							CR	20120648	A	03 April 2013		
							US	2012028925	A1	02 February 2012		
							IL	222831	A	31 August 2014		
							RU	2567857	C2	10 November 2015		
							US	9006247	B2	14 April 2015		
							GT	201200315	A	11 July 2014		
							EP	3312178	A1	25 April 2018		
							SG	10201700112V	A	30 March 2017		
							SG	10201700115R	A	27 February 2017		
							DO	P2017000186	A	15 September 2017		
							PH	12016501126	A1	14 June 2017		
							PL	2575463	T3	31 October 2016		
							US	2015246914	A1	03 September 2015		
							BR	112012029733	A2	13 June 2017		

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2020/133636

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)		Publication date (day/month/year)
				EP	2575463 B1	30 March 2016
				PT	2575463 T	13 July 2016
				DO	P2016000100 A	31 May 2016
				CL	2012003285 A1	04 October 2013
				CA	2798765 A1	01 December 2011
				HR	P20160714 T1	15 July 2016
				NZ	603284 A	30 January 2015
				UA	109278 C2	10 August 2015
				KR	101800167 B1	22 November 2017
				SI	EP2575463 T1	30 November 2016
				IL	222831 D0	31 December 2012
				CY	1117655 T1	17 May 2017
				MX	337104 B	09 February 2016
				EP	3091017 A1	09 November 2016
				US	2020277291 A1	03 September 2020
				ES	2574855 T3	22 June 2016
				JP	5782508 B2	24 September 2015
				CR	20180222 A	05 June 2018
				ZA	201208727 B	31 July 2013
				DO	P2012000298 A	30 April 2018
				HK	1179614 A1	04 October 2013
				SG	10201406608Y A	30 December 2014
				AU	2011229862 A1	20 September 2012
				CA	2792276 A1	29 September 2011
				EP	2550258 A2	30 January 2013
				SI	EP2550258 T1	29 January 2016
				ZA	201206837 B	29 May 2013
CN	102947283	A	27 February 2013	PL	2550258 T3	29 January 2016
				SM	T201600016 B	25 February 2016
				TW	201623291 A	01 July 2016
				KR	20130040834 A	24 April 2013
				TW	201139418 A	16 November 2011
				JP	5959501 B2	02 August 2016
				NZ	628298 A	27 November 2015
				CN	105218483 A	06 January 2016
				MX	2012011086 A	21 March 2013
				NZ	602055 A	29 August 2014
				DK	2550258 T3	07 December 2015
				IL	221771 A	30 November 2015
				PT	2550258 E	30 November 2015
				RU	2015141713 A3	28 December 2018
				US	8343967 B2	01 January 2013
				SG	184094 A1	30 October 2012
				RS	54388 B1	28 April 2016
				SI	2550258 T1	29 January 2016
				WO	2011119345 A2	29 September 2011
				US	8188077 B2	29 May 2012
				RU	2568611 C2	20 November 2015
				EP	2550258 B1	19 August 2015
				WO	2011119345 A3	22 December 2011

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2020/133636

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		EP 2757105 A1	23 July 2014
		US 2012214796 A1	23 August 2012
		HK 1200444 A1	07 August 2015
		IL 231702 D0	30 April 2014
		RU 2012145298 A	27 April 2014
		ES 2553143 T3	04 December 2015
		JP 2013523636 A	17 June 2013
		CN 102947283 B	07 October 2015
		US 2011237553 A1	29 September 2011
		RU 2015141713 A	28 December 2018
		HU E026241 T2	28 June 2016
		AU 2011229862 B2	24 July 2014
		IL 221771 D0	02 December 2012
		EP 2957558 A3	02 March 2016
		TW I535713 B	01 June 2016
		HR P20151218 T1	01 January 2016
		BR 112012024382 A2	08 August 2017
		HK 1219092 A1	24 March 2017
		EP 2957558 A2	23 December 2015