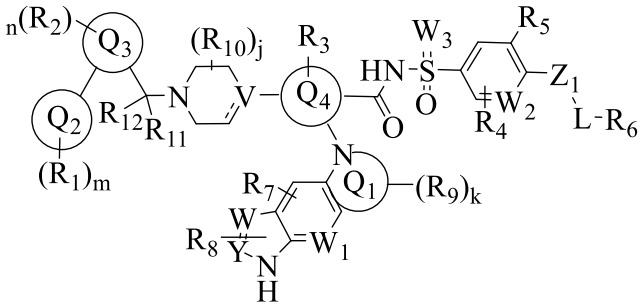
observed with 80% TGI and 20% of treated tumors indicating at least a 50% reduction in tumor volume. Oral administration of ABT-263 alone causes complete tumor regressions in xenograft models of small-cell lung cancer and acute lymphoblastic leukemia [Tse C, et al. Cancer Res. 2008, 68(9), 3421-3428]. In the clinical trial, however, the inhibition of BCL-XL by ABT-263 (navitoclax) induces a rapid, concentration-dependent decrease in the number of circulating platelets. This mechanism-based thrombocytopenia is the dose-limiting toxicity of single-agent navitoclax treatment in patients and limits the ability to drive drug concentrations into a highly efficacious range.

Thus, a BCL-2 selective (BCL-XL sparing) inhibitor would culminate in substantially reduced thrombocytopenia while maintaining efficacy in lymphoid malignancies. The resulting increase in the therapeutic window should allow for greater BCL-2 suppression and clinical efficacy in BCL-2–dependent tumor types. After extensive MedChem, ABT-199 (GDC-0199) has been successfully developed [Andrew J Souers, et al, Nature Medicine, Volume 19, 22, p202, 2013]. ABT-199 is a Bcl-2-selective inhibitor with Ki of <0.01 nM, >4800-fold more selective versus Bcl-xL and Bcl-w, and no activity to Mcl-1. ABT-199 potently inhibits RS4;11 cells with EC_{50} of 8 nM. In addition, ABT-199 induces a rapid apoptosis in RS4;11 cells with cytochrome c release, caspase activation, and the accumulation of sub-G0/G1 DNA. Quantitative immunoblotting reveals that sensitivity to ABT-199 correlated strongly with the expression of Bcl-2, including NHL, DLBCL, MCL, AML and ALL cell lines. ABT-199 also induces apoptosis in CLL with an average EC_{50} of 3.0 nM. A single dose of 100 mg/kg of ABT-199 causes a maximal tumor growth inhibition of 95% and tumor growth delay of 152% in RS4;11 xenografts. ABT-199 also inhibits xenograft growth (DoHH2, Granta-519) as a single agent or in combination with Bendamustine and other agents. Human Phase I and II data showed that ABT-199 is highly efficacious for CLL who have 17p deletion, and was approved by FDA in 2016.

WO/2017/132474 discloses a novel class of BCL-2 inhibitors. However, there is still a strong need for continuing search in this field of art for more potent BCL-2 inhibitor.

SUMMARY

In a first aspect, the present disclosure refers to a compound of Formula (A), or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form, of said compound of Formula (A) or N-oxide thereof:



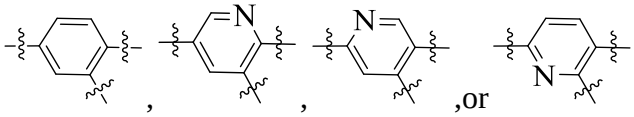
Formula (A) ,

wherein

Q_1 is 7-membered heterocycloalkyl, 7-membered heterocycloalkenyl, or 7-membered heteroaryl;

Q_2 is aryl or heteroaryl;

Q_3 is cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

Q_4 is  ;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12}, independently, is H, D, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, halo, nitro, oxo, cyano, OR_a, SR_a, alkyl-R_a, $NH(CH_2)_pR_a$, $C(O)R_a$, $S(O)R_a$, SO_2R_a, $C(O)OR_a$, $OC(O)R_a$, NR_bR_c, $P(O)R_bR_c$, alkyl-$P(O)R_bR_c$, $C(O)N(R_b)R_c$, $N(R_b)C(O)R_c$, $S(O)(=N(R_b))R_c$, $-N=S(O)R_bR_c$, $SO_2N(R_b)R_c$, or $N(R_b)SO_2R_c$, in which said cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl is optionally subsitiuted with one or more R_d;

R_a, R_b, R_c and R_d, independently, is H, D, alkyl, alkenyl, alkynyl, halo, cyano, amine, nitro, hydroxy, =O, C(O)NHOH, C(O)OH, $C(O)NH_2$, alkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkylamino, oxo, halo-alkylamino, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl, in which said alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl is optionally subsitiuted with one or more R_e;

R_e is H, D, alkyl, alkenyl, alkynyl, halo, cyano, amine, nitro, hydroxy, =O, C(O)NHOH, alkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkylamino, oxo, halo-alkylamino, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

Z_1 is a bond, $(CH_2)_p$, N(H), O, S, C(O), $S(O_2)$, OC(O), C(O)O, OSO_2, $S(O_2)O$,

C(O)S, SC(O), C(O)C(O), C(O)N(H), N(H)C(O), $S(O_2)N(H)$, $N(H)S(O_2)$, OC(O)O, OC(O)S, OC(O)N(H), N(H)C(O)O, N(H)C(O)S, N(H)C(O)N(H), $(CH_2)_pN(H)(CH_2)_q$, $(CH_2)_pN(H)C(O)(CH_2)_q$, $(CH_2)_pC(O)N(H)(CH_2)_q$, $OC(O)N(H)(CH_2)_{p+1}N(H)(CH_2)_q$, a bivalent alkenyl group, or a bivalent alkynyl group;

L is a bond, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl, in which said alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl is optionally subsitiuted with one or more R_d;

each of Y, W, W_1, and W_2, independently, is CH or N;

W_3 is O or $N(R_a)$;

V is N, C, or CH;

two of R_9 group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_9, is optionally subsitiuted with one or more R_d;

two of R_2 group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_2, is optionally subsitiuted with one or more R_d;

two of R_{10} group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_{10}, is optionally subsitiuted with one or more R_d;

R_{11} and R_{12} group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_{11} or R_{12}, is optionally subsitiuted with one or more R_d;

R_{10} and R_2 group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_{10} or R_2, is optionally subsitiuted with one or more R_d;

R_4 and $-Z_1$-L-R_6 group, taken together with the atom to which they are attached, may optionally form a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl, in which said cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl of R_4, is optionally subsitiuted with one or more R_d;

R_b and R_c group, taken together with the atom to which they are attached, may optionally form a cycloalkyl, or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_b and R_c, is optionally subsitiuted with one or more R_e;

two of R_d group, taken together with the atom to which they are attached, may

optionally form a cycloalkyl, or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_d, is optionally subsitiuted with one or more R_e;

two of R_e group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_e is optionally subsitiuted with one or more groups selected from H, D, alkyl, alkenyl, alkynyl, halo, cyano, amine, nitro, hydroxy, C(O)NHOH, alkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkylamino, oxo, halo-alkylamino, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

each of j and k, independently, is 0, 1, 2, 3, 4, 5, 6, 7, or 8; and

each of m, n, p, q, and r, independently, is 0, 1, 2, 3, or 4.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula (A) or an N-oxide thereof disclosed herein, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, and a pharmaceutically acceptable diluent or carrier.

In yet another aspect, the present disclosure refers to a compound of Formula (A) or an N-oxide thereof disclosed herein, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, for use in treating a neoplastic disease, an autoimmune disease, or a neorodegenerative disease.

In a further aspect, the present disclosure refers to a use of a compound of Formula (A) or an N-oxide thereof disclosed herein, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, in the manufacture of a medicament for treating a neoplastic disease, an autoimmune disease, or a neorodegenerative disease.

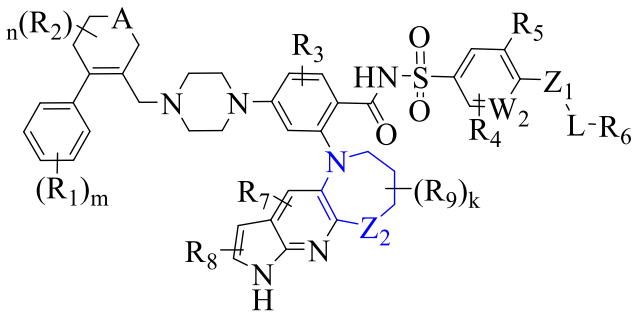
In a first example, this present disclosure provides compounds of the Formula (A) or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula (A) or N-oxide thereof:

optionally subsitiuted with one or more groups selected from H, D, alkyl, alkenyl, alkynyl, halo, cyano, amine, nitro, hydroxy, C(O)NHOH, alkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkylamino, oxo, halo-alkylamino, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

each of j and k, independently, is 0, 1, 2, 3, 4, 5, 6, 7, or 8; and

each of m, n, p, q, and r, independently, is 0, 1, 2, 3, or 4.

In a second example, the present disclosure provides a compound represented by Formula (B):



Formula (B)

,

or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula (B) or N-oxide thereof, wherein

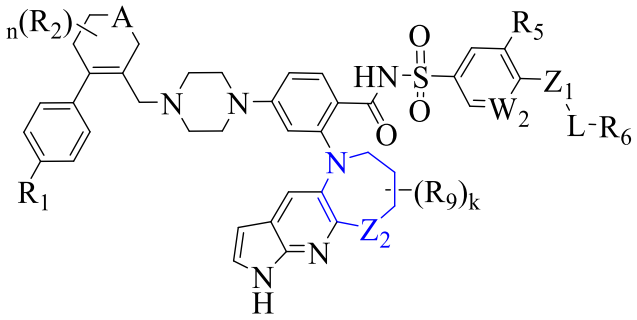
Z_2 is -O-, -CH_2-, -C(O)-, -N(R_a)-, -S-, -S(O)-, -S(O_2)-, -S(O)(=N(R_a))-, -P(O)(R_a)-; wherein R_a of Z_2, independently, is H, D, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_6cycloalkyl, 5-8 membered monocyclic heterocycloalkyl, C_6-C_{14}aryl, or 5-8 membered monocyclic heteroaryl, in which said C_1-C_6alkyl, C_3-C_6cycloalkyl, 5-8 membered monocyclic heterocycloalkyl, C_6-C_{14}aryl, 5-8 membered monocyclic heteroaryl is optionally subsitiuted with one or more Re, and

A is -(CR_2R_2)$_r$- or -O-; wherein r is 0, 1, 2, or 3;

each R_2 independently is H, -(C_1-C_4)alkoxy, -(C_1-C_4)alkyl optionally susbtituted with -(C_1-C_4)alkoxy, or

two of R_2 groups, taken together with the same carbon atom to which they are attached, form -(C_3-C_6)cycloalkyl or 4-6 membered heterocyclic ring, wherein the -(C_3-C_6)cycloalkyl or 4-6 membered heterocyclic ring is optionally substituted with one or more groups selected from -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl or oxetanyl; and the remaining variables are as defined in the first example.

In a third example, the present disclosure provides a compound represented by Formula (C):

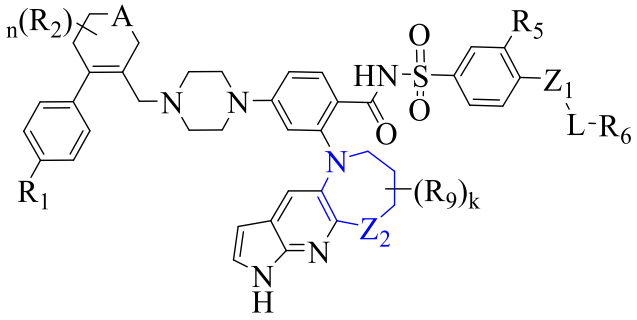


Formula (C)

,

or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula (C) or N-oxide thereof, wherein R_1 is H, D, halo or -(C_1-C_4)alkyl, and the remaining variables are as defined in the first and/or second examples.

In a fourth example, the present disclosure provides a compound represented by Formula (D):



Formula (D)

,

or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula (D) or N-oxide thereof, wherein

R_5 independently, is nitro, halo, or -SO_2R_a, wherein R_a of R_5 is -(C_1-C_4)alkyl or -(C_1-C_4)haloalkyl (e.g., -CF_3); and

Z_1 is bond, NH, N(H)(CH_2)$_q$, O, S, or -(C_1-C_4)alkylene, wherein q is 1, 2, or 3;

L is absent or -(C_1-C_4)alkylene optionally substituted with -(C_3-C_6)cycloalkyl; and

R_6 is H, D, -N(CH_3)-(C_1-C_4)alkylene-P(O)((C_1-C_4)alkoxy)$_2$, -P(O)(N(CH_3)$_2$)(OEt), -P(O)(O-(C_1-C_4)alkylene-O-CO-(C_1-C_4)alkyl)$_2$, -(C_3-C_6)cycloalkyl, phenyl, 5-7 membered heterocyclyl, 8-10 membered bicyclic ring, wherein the -(C_3-C_6)cycloalkyl, phenyl, 5-7 membered heterocyclyl, or 7-10 membered bicyclic ring is optionally substituted with one or more groups selected from halo, -OH, =O, -CN, -COOH, -NH_2, -N(CH_3)$_2$, -NS(=O)(CH_3)$_2$, -SO_2(C_1-C_4)alkyl, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, cyclopropyl, 4-6 membered heterocyclyl, -CH_2P(O)(OH)$_2$, -CH_2P(O)((C_1-C_4)alkoxy)$_2$, -P(O)((C_1-C_4)alkyl)$_2$, or -N=S(O)((C_1-C_4)alkyl)$_2$, and the remaining variables are as defined in the first, second, and/or third examples.

In a fifth example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula or N-oxide thereof, wherein R_9 independently, is D, halo, -OH, CN, -NH_2, =O, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkyl, -(C_1-C_4)hydroxyalkyl, -(C_3-C_6)cycloalkyl, or 1,3-dithiolanyl; and k is 0, 1, 2, 3, or 4; and the remaining variables are as defined in the first, second, third, and/or fourth examples.

In a sixth example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D, or N-oxide thereof, wherein A is -CH_2- or -O-; and the remaining variables are as defined in the first, second, third, fourth, and/or fifth examples.

In a seventh example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D or N-oxide thereof, wherein each R_2 independently is –CH_3; and n is 0 or 2; and the remaining variables are as defined in the first, second, third, fourth, fifth and/or sixth examples.

In an eighth example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D, or N-oxide thereof, wherein Z_2 is -O-; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth and/or seventh examples.

In a ninth example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D, or N-oxide thereof, wherein R_1 is halo, such as Cl; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, and/or eighth examples.

In a tenth example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D or N-oxide thereof, wherein R_5 is nitro; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, and/or ninth examples.

In an eleventh example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate,

polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D or N-oxide thereof, wherein Z_1 is absent, NH or O; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, and/or tenth examples.

In a twelfth example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D or N-oxide thereof, wherein Z_2 is -O-, -CH_2-, -C(O)-, -NH-, -N-(oxetanyl)-, -S-, -S(O)-, -S(O_2)-, -S(O)(=NH)-, -S(O)(=NCH_3)-, or -P(O)(CH_3)-; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, and/or eleventh examples.

In a thirteenth example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D or N-oxide thereof, wherein R_6 is H, D, -(C_3-C_6)cycloalkyl, phenyl, tetrahydro-2H-pyranyl, or 1,4-dioxanyl, wherein the -(C_3-C_6)cycloalkyl, phenyl, tetrahydro-2H-pyranyl or 1,4-dioxanyl is optionally substituted with 1 or 2 groups selected from halogen, -OH, =O, -(C_1-C_4)alkyl, or -(C_1-C_4)alkoxy; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, and/or twelfth examples.

In a fourteenth example, the present disclosure provides a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D or N-oxide thereof, wherein R_6 is tetrahydro-2H-pyranyl or 1,4-dioxanyl, wherein the tetrahydro-2H-pyranyl or 1,4-dioxanyl is optionally substituted with 1 or 2 halogen; and the remaining variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, and/or thirteenth examples.

For example, in a compound according to Structural Formula A, B, C, or D, or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug of said compound of Formula A, B, C, or D or N-oxide thereof, Z_1 is -NH-, L is -CH_2-, R_6 is tetrahydro-2H-pyranyl or 1,4-dioxanyl optionally substituted with 1 or 2 groups of halogen, and, preferably A is -CH_2- or -O-, R_1 is Cl, R_5 is nitro, Z_2 is -O-, each R_2 independently is -CH_3 and n is 0 or 2, and R_9 is methyl (and k is 1) or halo (and k is 2, such as di-fluoro).

A modified compound of any one of such compounds including a modification having an improved (*e.g.*, enhanced, greater) pharmaceutical solubility, stability, bioavailability, and/or

therapeutic index as compared to the unmodified compound is also contemplated. Exemplary modifications include (but are not limited to) applicable prodrug derivatives, and deuterium-enriched compounds.

Also within the scope of this present disclosure is a pharmaceutical composition containing one or more of the compounds (such as any one of those in Formulae (A)-(D), or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug thereof or an N-oxide thereof), modifications, and/or salts thereof described herein, and a pharmaceutically acceptable diluent or carrier, for use in treating a neoplastic disease, therapeutic uses thereof, and use of the compounds for the manufacture of a medicament for treating the disease / disorder.

This present disclosure also relates to a method of treating a neoplastic disease, an autoimmune disease, or a neorodegenerative disease, comprising administering to a subject in need thereof an effective amount of one or more compounds of the present disclosure (such as any one of those in Formulae (A)-(D), or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, an isotopic form, or a prodrug thereof or an N-oxide thereof), modifications, and/or salts thereof described herein, or a pharmaceutical composition comprising the compound(s) of the present disclosure.

In certain examples, the neoplastic disease, autoimmune disease, or neorodegenerative disease is characterized by abnormal (*e.g.*, enhanced or increased) Bcl-2 activity. For example, the neoplastic disease can be a hematological malignancy or cancer including solid tumor; the autoimmune disease can be type I diabetes; and the neorodegenerative disease can be schizophrenia.

In certain examples, the neoplastic disease is myeloma, multiple myeloma, lymphoma, follicular lymphoma (FL), non-Hodgkin's lymphoma, leukemia, acute leukemia, acute lymphoblastic leukemia (ALL) (such as BCL-2–dependent ALL and pediatric ALL), chronic lymphoblastic leukemia (CLL) (such as relapsed/refractory CLL, del(17p) CLL), chronic myeloid leukemia (CML) (such as blast-crisis CML), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma, lung cancer such as small cell lung cancer (SCLC), melanoma, breast cancer, or prostate cancer, including drug-resistant cancer thereof.

In certain examples, the method further comprises administering one or more further treatment(s) effective to treat the neoplastic disease, such as surgery, radiation therapy, a chemotherapeutic agent (such as bendamustine, NL-101 (7-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-N-hydroxyheptanamide), cisplatin, carboplatin, etoposide, topotecan), a target thearpy (*e.g.*, an anti-CD20 antibody such as rituximab, a Bruton's tyrosine kinase inhibitor such as ibrutinib and acalabrutinib (ACP-196), a PI3Kδ inhibitor such as

idelalisib); an antibody-drug conjugate or ADC (such as anti-CD30 ADC brentuximab vedotin), an immunotherapy (such as an anti-PD-1 antibody including pembrolizumab and nivolumab, or an anti-PD-L1 antibody including atezolizumab, durvalumab, and avelumab), or a CAR-T thearpy (such as tisagenlecleucel, axicabtagene ciloleucel).

Also provided herein is the use of one or more compounds of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or more compounds of the present disclosure, for the preparation of a medicament for the treatment of the above-referenced diseases or conditions.

In another example, provided herein the compounds of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or more of the disclosed compounds are for use in treating the above-referenced diseases or conditions.

The details of one or more examplesof the present disclosure are set forth in the description below. Other features, objects, and advantages of the present disclosure will be apparent from the description and from the claims. It should be understood that all mebodiments / features of the present disclosure (compounds, pharmaceutical compositions, methods of make / use, *etc*) described herein, including any specific features described in the examples and original claims, can combine with one another unless not applicable or explicitly disclaimed.

DETAILED DESCRIPTION OF THE INVENTION

Exemplary compounds described herein include, but are not limited to, the following:

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide,

(R)-N-((4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

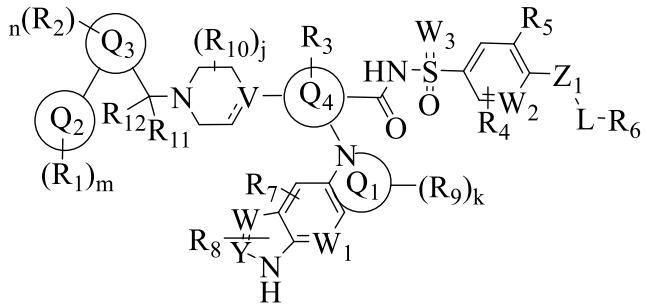
(S)-N-((4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

(S)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-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)-4-(4-((4'-chloro-

WHAT IS CLAIMED IS:

1. A compound of Formula (A), or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form, of said compound of Formula (A) or N-oxide thereof:



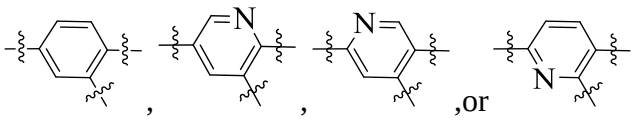
Formula (A) ,

wherein

Q_1 is 7-membered heterocycloalkyl, 7-membered heterocycloalkenyl, or 7-membered heteroaryl;

Q_2 is aryl or heteroaryl;

Q_3 is cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

Q_4 is  ;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12}, independently, is H, D, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, halo, nitro, oxo, cyano, OR_a, SR_a, alkyl-R_a, $NH(CH_2)_pR_a$, $C(O)R_a$, $S(O)R_a$, SO_2R_a, $C(O)OR_a$, $OC(O)R_a$, NR_bR_c, $P(O)R_bR_c$, alkyl-$P(O)R_bR_c$, $C(O)N(R_b)R_c$, $N(R_b)C(O)R_c$, $S(O)(=N(R_b))R_c$, $-N=S(O)R_bR_c$, $SO_2N(R_b)R_c$, or $N(R_b)SO_2R_c$, in which said cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl is optionally subsitiuted with one or more R_d;

R_a, R_b, R_c and R_d, independently, is H, D, alkyl, alkenyl, alkynyl, halo, cyano, amine, nitro, hydroxy, =O, C(O)NHOH, C(O)OH, $C(O)NH_2$, alkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkylamino, oxo, halo-alkylamino, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl, in which said alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl is optionally subsitiuted with one or more R_e;

R_e is H, D, alkyl, alkenyl, alkynyl, halo, cyano, amine, nitro, hydroxy, =O,

C(O)NHOH, alkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkylamino, oxo, halo-alkylamino, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

Z_1 is a bond, $(CH_2)_p$, N(H), O, S, C(O), $S(O_2)$, OC(O), C(O)O, OSO_2, $S(O_2)O$, C(O)S, SC(O), C(O)C(O), C(O)N(H), N(H)C(O), $S(O_2)N(H)$, $N(H)S(O_2)$, OC(O)O, OC(O)S, OC(O)N(H), N(H)C(O)O, N(H)C(O)S, N(H)C(O)N(H), $(CH_2)_pN(H)(CH_2)_q$, $(CH_2)_pN(H)C(O)(CH_2)_q$, $(CH_2)_pC(O)N(H)(CH_2)_q$, $OC(O)N(H)(CH_2)_{p+1}N(H)(CH_2)_q$, a bivalent alkenyl group, or a bivalent alkynyl group;

L is a bond, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl, in which said alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl is optionally subsitiuted with one or more R_d;

each of Y, W, W_1, and W_2, independently, is CH or N;

W_3 is O or $N(R_a)$;

V is N, C, or CH;

two of R_9 group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_9, is optionally subsitiuted with one or more R_d;

two of R_2 group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_2, is optionally subsitiuted with one or more R_d;

two of R_{10} group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_{10}, is optionally subsitiuted with one or more R_d;

R_{11} and R_{12} group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_{11} or R_{12}, is optionally subsitiuted with one or more R_d;

R_{10} and R_2 group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_{10} or R_2, is optionally subsitiuted with one or more R_d;

R_4 and $-Z_1$-L-R_6 group, taken together with the atom to which they are attached, may optionally form a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl, in which said cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl of R_4, is optionally subsitiuted with one or more R_d;

R_b and R_c group, taken together with the atom to which they are attached, may optionally form a cycloalkyl, or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_b and R_c, is optionally subsitiuted with one or more R_e;

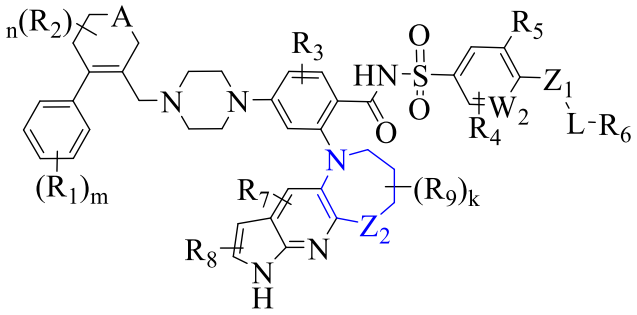
two of R_d group, taken together with the atom to which they are attached, may optionally form a cycloalkyl, or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_d, is optionally subsitiuted with one or more R_e;

two of R_e group, taken together with the atom to which they are attached, may optionally form a cycloalkyl or heterocycloalkyl, in which said cycloalkyl or heterocycloalkyl of R_e is optionally subsitiuted with one or more groups selected from H, D, alkyl, alkenyl, alkynyl, halo, cyano, amine, nitro, hydroxy, C(O)NHOH, alkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, alkylamino, oxo, halo-alkylamino, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

each of j and k, independently, is 0, 1, 2, 3, 4, 5, 6, 7, or 8; and

each of m, n, p, q, and r, independently, is 0, 1, 2, 3, or 4.

2. The compound according to claim 1 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein the compound is represented by Formula (B):



Formula (B) ,

wherein

Z_2 is -O-, -CH_2-, -C(O)-, -N(R_a)-, -S-, -S(O)-, -S(O_2)-, -S(O)(=N(R_a))-, -P(O)(R_a)-; wherein R_a of Z_2, independently, is H, D, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_6cycloalkyl, 5-8 membered monocyclic heterocycloalkyl, C_6-C_{14}aryl, or 5-8 membered monocyclic heteroaryl, in which said C_1-C_6alkyl, C_3-C_6cycloalkyl, 5-8 membered monocyclic heterocycloalkyl, C_6-C_{14}aryl, 5-8 membered monocyclic heteroaryl is optionally subsitiuted with one or more Re, and

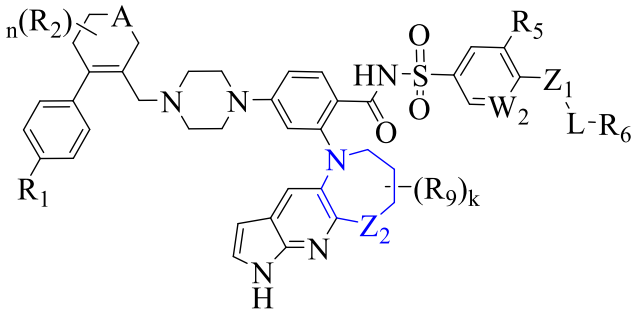
A is -(CR_2R_2)$_r$- or -O-; wherein r is 0, 1, 2, or 3;

each R_2 independently is H, -(C_1-C_4)alkoxy, -(C_1-C_4)alkyl optionally susbtituted

with -(C_1-C_4)alkoxy, or

two of R_2 groups, taken together with the same carbon atom to which they are attached, form -(C_3-C_6)cycloalkyl or 4-6 membered heterocyclic ring, wherein the -(C_3-C_6)cycloalkyl or 4-6 membered heterocyclic ring is optionally substituted with one or more groups selected from -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl or oxetanyl.

3. The compound according to claim 2 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein the compound is represented by Formula (C):

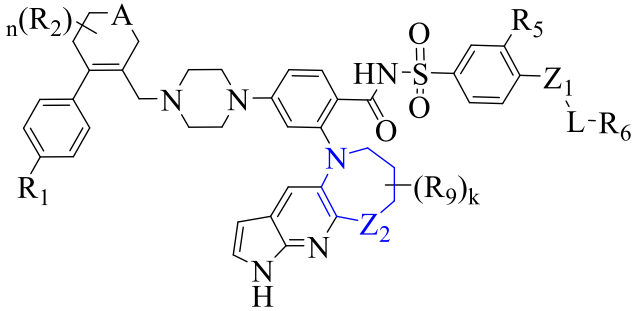


Formula (C)

,

wherein R_1 is H, D, halo or -(C_1-C_4)alkyl.

4. The compound according to claim 3 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein the compound is represented by Formula (D):



Formula (D)

,

wherein

R_5 independently, is nitro, halo, or -SO_2R_a, wherein R_a of R_5 is -(C_1-C_4)alkyl or -(C_1-C_4)haloalkyl; and

Z_1 is bond, NH, N(H)(CH_2)$_q$, O, S, or -(C_1-C_4)alkylene, wherein q is 1, 2, or 3;

L is absent or -(C_1-C_4)alkylene optionally substituted with -(C_3-C_6)cycloalkyl; and

R_6 is H, D, -N(CH_3)-(C_1-C_4)alkylene-P(O)((C_1-C_4)alkoxy)$_2$,

-P(O)(N(CH_3)$_2$)(OEt), -P(O)(O-(C_1-C_4)alkylene-O-CO-(C_1-C_4)alkyl)$_2$, -(C_3-C_6)cycloalkyl, phenyl, 5-7 membered heterocyclyl, 8-10 membered bicyclic ring, wherein the -(C_3-C_6)cycloalkyl, phenyl, 5-7 membered heterocyclyl, or 7-10 membered bicyclic ring is optionally substituted with one or more groups selected from halo, -OH, =O, -CN, -COOH, -NH_2, -N(CH_3)$_2$, -NS(=O)(CH_3)$_2$, -SO_2(C_1-C_4)alkyl, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, cyclopropyl, 4-6 membered heterocyclyl, -CH_2P(O)(OH)$_2$, -CH_2P(O)((C_1-C_4)alkoxy)$_2$, -P(O)((C_1-C_4)alkyl)$_2$, or -N=S(O)((C_1-C_4)alkyl)$_2$.

5. The compound according to claim 4 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein R_9 independently, is D, halo, -OH, CN, -NH_2, =O, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkyl, -(C_1-C_4)hydroxyalkyl, -(C_3-C_6)cycloalkyl, or 1,3-dithiolanyl; and k is 0, 1, 2, 3, or 4.

6. The compound according to claim 4 or 5 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein A is -CH_2- or -O-.

7. The compound according to any one of claims 4-6 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein each R_2 independently is –CH_3; and n is 0 or 2.

8. The compound according to any one of claims 4-7 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein Z_2 is -O-.

9. The compound according to any one of claims 4-8 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein R_1 is Cl.

10. The compound according to any one of claims 4-9 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein R_5 is nitro.

11. The compound according to any one of claims 4-10 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein Z_1 is absent, NH or O.

12. The compound according to any one of claims 4-11 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein Z_2 is -O-, -CH_2-, -C(O)-, -NH-, -N-(oxetanyl)-, -S-, -S(O)-, -$S(O_2)$-, -S(O)(=NH)-, -S(O)(=NCH_3)-, or -P(O)(CH_3)-.

13. The compound according to any one of claims 4-12 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein R_6 is H, D, -(C_3-C_6)cycloalkyl, phenyl, tetrahydro-2H-pyranyl, or 1,4-dioxanyl, wherein the -(C_3-C_6)cycloalkyl, phenyl, tetrahydro-2H-pyranyl or 1,4-dioxanyl is optionally substituted with 1 or 2 groups selected from halogen, -OH, =O, -(C_1-C_4)alkyl, or -(C_1-C_4)alkoxy.

14. The compound according to any one of claims 4-13 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein R_6 is tetrahydro-2H-pyranyl or 1,4-dioxanyl, wherein the tetrahydro-2H-pyranyl or 1,4-dioxanyl is optionally substituted with 1 or 2 groups selected from halogen.

15. The compound according to claim 1 or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form thereof, wherein the compound is

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide,

(R)-N-((4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

(S)-N-((4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

(S)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-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)-4-(4-((4'-

chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-((S)-4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

N-((4-((((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-((S)-4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

(R)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-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)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-((R)-4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

N-((4-((((R)-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-((R)-4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4,4-difluoro-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide,

(R)-N-((4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4,4-difluoro-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

(S)-N-((4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4,4-difluoro-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide,

(S)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((4-(((2-fluoro-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide,

(R)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((4-(((2-fluoro-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide,

(S)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-(4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-((((R)-2-fluoro-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((S)-4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-((((S)-2-fluoro-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((S)-4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

(R)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-(4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-((((R)-2-fluoro-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((R)-4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-((((S)-2-fluoro-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-((R)-4-methyl-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)benzamide,

4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4,4-difluoro-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-3-

nitrophenyl)sulfonyl)benzamide,

(S)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4,4-difluoro-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((4-(((2-fluoro-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide, or

(R)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-2-(4,4-difluoro-3,4-dihydro-2H-pyrrolo[3',2':5,6]pyrido[2,3-b][1,4]oxazepin-1(7H)-yl)-N-((4-(((2-fluoro-1,4-dioxan-2-yl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide.

16. A pharmaceutical composition comprising a compound of Formula (A) or an N-oxide thereof as defined in claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, and a pharmaceutically acceptable diluent or carrier.

17. A compound of Formula (A) or an N-oxide thereof as defined in claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, for use in treating a neoplastic disease, an autoimmune disease, or a neorodegenerative disease.

18. The compound of Formula (A) or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, for use of claim 17, wherein the neoplastic disease, the autoimmune disease, or the neorodegenerative disease is characterized by abnormal (*e.g.*, enhanced or increased) Bcl-2 activity, such as a hematological malignancy / cancer, type I diabetes, or schizophrenia.

19. The compound of Formula (A) or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, for use of claim 17, wherein the neoplastic disease is myeloma, multiple myeloma, lymphoma, follicular lymphoma (FL), non-Hodgkin’s lymphoma, leukemia, acute leukemia, acute lymphoblastic leukemia (ALL) (such as BCL-2–dependent ALL and pediatric ALL), chronic lymphoblastic leukemia (CLL) (such as relapsed/refractory CLL, del(17p) CLL), chronic myeloid leukemia (CML) (such as blast-crisis CML), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma, lung cancer such as small cell lung cancer (SCLC), melanoma, breast cancer,

or prostate cancer, including drug-resistant cancer thereof.

20. The compound of Formula (A) or an N-oxide thereof, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, for use of any one of claims 17-19, wherein one or more further treatment(s) effective to treat the neoplastic disease, such as surgery, radiation therapy, a chemotherapeutic agent (such as bendamustine, NL-101, cisplatin, carboplatin, etoposide, topotecan), a target therapy (such as rituximab, ibrutinib, ACP-196, idelalisib); an antibody-drug conjugate or ADC (such as brentuximab vedotin), an immunotherapy (such as pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab), or a CAR-T therapy (such as tisagenlecleucel, axicabtagene ciloleucel) are to be further administered.

21. Use of a compound of Formula (A) or an N-oxide thereof as defined in claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, tautomer, stereoisomer, or an isotopic form of said compound of Formula (A) or an N-oxide thereof, in the manufacture of a medicament for treating a neoplastic disease, an autoimmune disease, or a neorodegenerative disease.

22. The use of claim 21, wherein the neoplastic disease, the autoimmune disease, or the neorodegenerative disease is characterized by abnormal (*e.g.*, enhanced or increased) Bcl-2 activity, such as a hematological malignancy / cancer, type I diabetes, or schizophrenia.

23. The use of claim 21, wherein the neoplastic disease is myeloma, multiple myeloma, lymphoma, follicular lymphoma (FL), non-Hodgkin's lymphoma, leukemia, acute leukemia, acute lymphoblastic leukemia (ALL) (such as BCL-2–dependent ALL and pediatric ALL), chronic lymphoblastic leukemia (CLL) (such as relapsed/refractory CLL, del(17p) CLL), chronic myeloid leukemia (CML) (such as blast-crisis CML), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma, lung cancer such as small cell lung cancer (SCLC), melanoma, breast cancer, or prostate cancer, including drug-resistant cancer thereof.

24. The use of any one of claims 21-23, wherein one or more further treatment effective to treat the neoplastic disease, such as surgery, radiation therapy, a chemotherapeutic agent (such as bendamustine, NL-101, cisplatin, carboplatin, etoposide, topotecan), a target therapy (such as rituximab, ibrutinib, ACP-196, idelalisib); an antibody-drug conjugate or

ADC (such as brentuximab vedotin), an immunotherapy (such as pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab), or a CAR-T therapy (such as tisagenlecleucel, axicabtagene ciloleucel) are to be further administered.