

MODULATORS OF BCL6 PROTEOLYSIS AND ASSOCIATED METHODS OF USE**RELATED APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Application No. 63/559,779, filed on February 29, 2024. The entire contents of the foregoing application are expressly incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The description provides compounds comprising a target protein binding moiety and a E3 ubiquitin ligase binding moiety, and associated methods of using those compounds. The compounds are useful as modulators of targeted ubiquitination, such as B-cell lymphoma 6 protein (BCL6), which is degraded by the compounds of the present disclosure.

BACKGROUND

[0003] Most small molecule drugs bind enzymes or receptors in tight and well-defined pockets. On the other hand, protein-protein interactions are notoriously difficult to target using small molecules due to their large contact surfaces and the shallow grooves or flat interfaces involved. E3 ubiquitin ligases (of which hundreds are known in humans) confer substrate specificity for ubiquitination, and therefore, are more attractive therapeutic targets than general proteasome inhibitors due to their specificity for certain protein substrates. The development of ligands of E3 ligases has proven challenging, in part due to the fact that they must disrupt protein-protein interactions. However, recent developments have provided specific ligands which bind to these ligases. For example, since the discovery of nutlins, the first small molecule E3 ligase inhibitors, additional compounds have been reported that target E3 ligases but the field remains underdeveloped.

[0004] Cereblon is a protein that in humans is encoded by the *CRBN* gene. *CRBN* orthologs are highly conserved from plants to humans, which underscores its physiological importance. Cereblon forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1), Cullin-4A (CUL4A), and regulator of cullins 1 (ROC1). This complex ubiquitinates a number of other proteins. Through a mechanism which has not been completely elucidated, cereblon ubiquitination of target proteins results in increased levels of fibroblast growth factor 8 (FGF8) and fibroblast growth factor 10 (FGF10). FGF8 in turn regulates a number of developmental processes, such as limb and auditory vesicle formation. The net result is that this ubiquitin

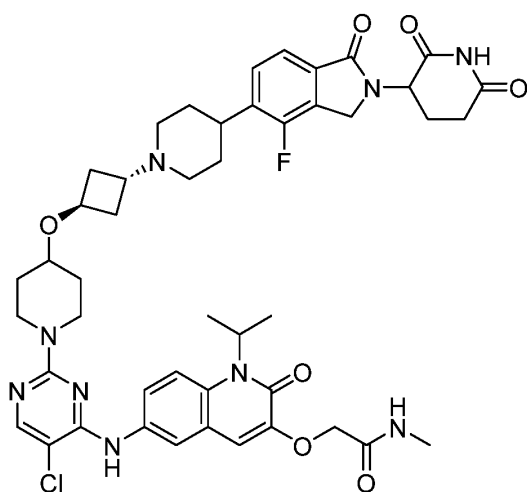
ligase complex is important for limb outgrowth in embryos. In the absence of cereblon, DDB1 forms a complex with DDB2 that functions as a DNA damage-binding protein.

[0005] Bifunctional compounds such as those that are described in U.S. Patent Application Publications 2015-0291562 and 2014-0356322 (incorporated herein by reference), function to recruit endogenous proteins to an E3 ubiquitin ligase for degradation. In particular, the publications describe bifunctional or proteolysis targeting chimeric (PROTAC) compounds, which find utility as modulators of targeted ubiquitination of a variety of polypeptides and other proteins, which are then degraded and/or otherwise inhibited by the bifunctional compounds.

[0006] An ongoing need exists in the art for effective treatments for disease associated with (i) aberrant BCL6 expression and/or activity and/or (ii) overexpression or aggregation of B-cell lymphoma 6 protein (BCL6). However, non-specific effects, and the inability to target and modulate BCL6, remain as obstacles to the development of effective treatments. As such, small-molecule therapeutic agents that target BCL6 and that leverage or potentiate E3 ubiquitin ligase (e.g., cereblon's) substrate specificity would be very useful.

SUMMARY

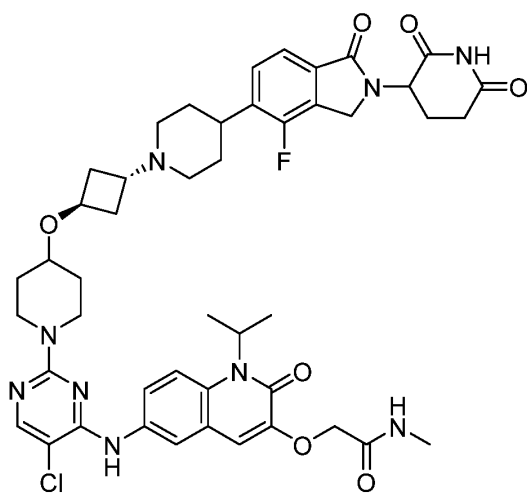
[0007] In one aspect, this application pertains to a method of treating or ameliorating advanced cancer, relapsed/refractory (R/R) cancer, advanced lymphoma, relapsed/refractory (R/R) lymphoma, advanced non-Hodgkin lymphoma (NHL), relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL), advanced B-Cell non-Hodgkin lymphoma (NHL), relapsed/refractory (R/R) B-Cell non-Hodgkin lymphoma (NHL), transformed follicular lymphoma, nodal T-follicular helper cell lymphoma (nTFHL), nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / advanced angioimmunoblastic T-cell lymphoma (AITL), or relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A),

or a pharmaceutically acceptable salt thereof.

[0008] In one aspect, this application pertains to a method of treating or ameliorating advanced non-Hodgkin lymphoma (NHL), relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL), transformed follicular lymphoma, nodal T-follicular helper cell lymphoma (nTFHL), relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma, nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / advanced angioimmunoblastic T-cell lymphoma (AITL), or relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A).

[0009] In some embodiments, the method is for treating advanced non-Hodgkin lymphoma (NHL).

[0010] In some embodiments, the method is for treating relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL).

[0011] In some embodiment, the method is for treating nodal T-follicular helper cell lymphoma (nTFHL).

[0012] In some embodiments the method is for treating relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma (nTFHL).

[0013] In some embodiments, the method is for treating nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / advanced angioimmunoblastic T-cell lymphoma (AITL).

[0014] In some embodiments, the method is for treating relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL).

[0015] In some embodiments, the method is for treating transformed follicular lymphoma.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present disclosure and, together with the description, serve to explain the principles of the disclosure. The drawings are only for the purpose of illustrating an embodiment of the disclosure and are not to be construed as limiting the disclosure. Further objects, features and advantages of the disclosure will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the disclosure, in which:

[0017] **FIG. 1A** Exemplary heterobifunctional degradative Compound A comprises a protein targeting moiety (PTM; *rectangle*), a ubiquitin ligase binding moiety (ULM; *triangle*), and optionally a linker moiety (L; *bold black line*) coupling or tethering the PTM to the ULM.

[0018] **FIG. 1B.** Illustration of the functional use of the heterobifunctional degradative Compound A as described herein. Briefly, the ULM recognizes and binds to a specific E3 ubiquitin ligase, and the PTM binds and recruits a target protein bringing it into close proximity to the E3 ubiquitin ligase. Typically, the E3 ubiquitin ligase is complexed with an E2 ubiquitin-conjugating protein, and either alone or via the E2 protein catalyzes attachment of ubiquitin (*small filled ovals*) to a lysine on the target protein via an isopeptide bond. The poly-ubiquitinated protein (*far right*) is then targeted for degradation by the proteasomal machinery of the cell.

- [0019] **FIG. 2A.** Compound A degradation of BCL6 protein in OCI-Ly1 cell line. OCI-Ly1 was treated with Compound A and its E3-binding deficient analogue for 24-hours.
- [0020] **FIG. 2B.** Compound A degradation of BCL6 protein in germinal center B-cell (GCB) DLBCL cell lines. GCB DLBCL cell lines Farage, SU-DHL-4, SU-DHL-6 and OCI-Ly7
- [0021] **FIG. 2C.** Compound A degradation of BCL6 protein in activated B-cell (ABC) DLBCL cell lines. ABC DLBCL lines SU-DHL-2 and OCI-Ly10, were treated for 24 hours with Compound A.
- [0022] **FIG. 3A.** Antiproliferative effects of Compound A on DLBCL-derived cell lines in 9-day cell growth inhibition assays. GCB lines OCI-Ly1, OCI-Ly7, SU-DHL-4, and SU-DHL-6.
- [0023] **FIG. 3B.** Antiproliferative effects of Compound A on DLBCL-derived cell lines in 9-day cell growth inhibition assays. ABC lines SU-DHL-2 and OCI-Ly10 were dosed with a 7-point 3-fold serial dilution of Compound A at a top dose of 30 nM.
- [0024] **FIG. 4A.** Average tumor growth of DLBCL (GCB) cell line derived xenograft model OCI-Ly1 with a treatment of Compound A.
- [0025] **FIG. 4B.** Average body weights of treated mice.
- [0026] **FIG. 5.** Tumor lysate BCL6 protein levels in OCI-Ly1 cell line xenograft tumor tissue following a treatment time-course with Compound A.
- [0027] **FIG. 6.** Total Compound A plasma and tumor levels (related to **FIG. 5**).
- [0028] **FIG. 7A.** Average tumor growth of DLBCL (GCB) cell line derived xenograft model OCI-Ly1 with a treatment of Compound A.
- [0029] **FIG. 7B** Average body weights of treated mice.
- [0030] **FIG. 7C** Tumor lysate BCL6 protein levels 16-hours post-last dose analyzed by western blotting.
- [0031] **FIG. 8A.** Average tumor growth of DLBCL (GCB) cell line derived xenograft model OCI-Ly7 with a treatment of Compound A.
- [0032] **FIG. 8B.** Average body weights of treated mice.
- [0033] **FIG. 8C.** Tumor lysate BCL6 protein levels 16-hours post-last dose analyzed by western blotting.
- [0034] **FIG. 9A.** Average tumor growth of DLBCL (ABC) cell line derived xenograft model SU-DHL-2 with a treatment of Compound A.
- [0035] **FIG. 9B.** Average body weights of treated mice.

[0036] **FIG. 9C.** Tumor lysate BCL6 protein levels 16-hours post-last dose analyzed by western blotting.

[0037] **FIG. 10A.** Average tumor growth of DLBCL (ABC) cell line derived xenograft model OCI-Ly10 with a treatment of Compound A.

[0038] **FIG. 10B.** Average body weights of treated mice.

[0039] **FIG. 10C.** Tumor lysate BCL6 protein levels 16-hours post-last dose analyzed by western blotting.

[0040] **FIG. 11A.** Mean tumor volumes of patient-derived xenograft (PDX) tumors in a mouse model of Double Hit/ diffuse large B-cell lymphoma (DLBCL) treated with Compound A or vehicle as described in Example 10. Data points represent the mean per group and error bars the standard error of the mean.

[0041] **FIG. 11B.** Mean tumor volumes of patient-derived xenograft (PDX) tumors in a mouse model of unclassified DLBCL treated with Compound A or vehicle as described in Example 10. Data points represent the mean per group and error bars the standard error of the mean.

[0042] **FIG. 11C.** Mean tumor volumes of patient-derived xenograft (PDX) mouse model of Burkitt's lymphoma treated with Compound A or vehicle as described in Example 10. Data points represent the mean per group and error bars the standard error of the mean.

[0043] **FIG. 11D.** Mean tumor volumes of (PDX) mouse model of GCB DLBCL treated with Compound A or vehicle as described in Example 10. Data points represent the mean per group and error bars the standard error of the mean.

[0044] **FIG. 12A.** Peripheral blood tumor burden of a patient-derived xenograft (PDX) preclinical model of nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) treated with Compound A, romidepsin or vehicle.

[0045] **FIG. 12B.** Bone marrow tumor burden in a patient-derived xenograft (PDX) preclinical model of nodal T-follicular helper cell lymphoma angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) treated with Compound A, romidepsin or vehicle.

[0046] **FIG. 12C.** Splenic tumor burden by weight of a patient-derived xenograft (PDX) preclinical model of nodal T-follicular helper cell lymphoma angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) treated with Compound A, romidepsin or vehicle.

[0047] **FIG. 13A.** Mean tumor volumes of a patient-derived xenograft (PDX) model of transformed follicular lymphoma (tFL) treated with Compound A or vehicle.

[0048] **FIG. 13B.** Mean tumor volumes of a patient-derived xenograft (PDX) model of transformed follicular lymphoma (tFL) treated with Compound A or vehicle.

DETAILED DESCRIPTION

[0049] The following is a detailed description provided to aid those skilled in the art in practicing the present disclosure. Those of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present disclosure. All publications, patent applications, patents, figures and other references mentioned herein are expressly incorporated by reference in their entirety.

[0050] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The terminology used in the description is for describing particular embodiments only, and is not intended to be limiting of the disclosure.

[0051] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms in which case each carbon atom number falling within the range is provided), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0052] The following terms are used to describe the present disclosure. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present disclosure.

[0053] The articles “a” and “an” as used herein and in the appended claims are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article unless the context clearly indicates otherwise. By way of example, “an element” means one element or more than one element.

[0054] The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements

listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B”, when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[0055] As used herein in the specification and in the claims, “or” should be understood to have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” will refer to the inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (i.e., “one or the other but not both”) when preceded by terms of exclusivity, such as “either,” “one of,” “only one of,” or “exactly one of.”

[0056] In the claims, as well as in the specification above, all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” “holding,” “composed of,” and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of” shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

[0057] It should also be understood that, in certain methods described herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited unless the context indicates otherwise.

[0058] The term “ubiquitin ligase” refers to a family of proteins that facilitate the transfer of ubiquitin to a specific substrate protein, targeting the substrate protein for degradation. For example, cereblon an E3 ubiquitin ligase protein that alone or in combination with an E2 ubiquitin-conjugating enzyme causes the attachment of ubiquitin to a lysine on a target protein, and subsequently targets the specific protein substrates for degradation by the proteasome. Thus, E3 ubiquitin ligase alone or in complex with an E2 ubiquitin conjugating enzyme is responsible for the transfer of ubiquitin to targeted proteins. In general, the ubiquitin ligase is

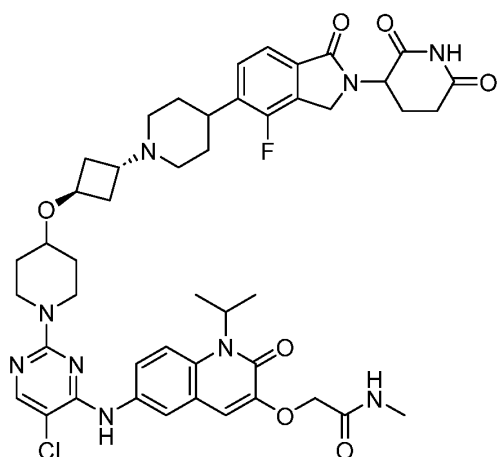
involved in polyubiquitination such that a second ubiquitin is attached to the first; a third is attached to the second, and so forth. Polyubiquitination marks proteins for degradation by the proteasome. However, there are some ubiquitination events that are limited to mono-ubiquitination, in which only a single ubiquitin is added by the ubiquitin ligase to a substrate molecule. Mono-ubiquitinated proteins are not targeted to the proteasome for degradation, but may instead be altered in their cellular location or function, for example, via binding other proteins that have domains capable of binding ubiquitin. Further complicating matters, different lysines on ubiquitin can be targeted by an E3 to make chains. The most common lysine is Lys48 on the ubiquitin chain. This is the lysine used to make polyubiquitin, which is recognized by the proteasome.

[0059] The term “patient” or “subject” is used throughout the specification to describe an animal, preferably a human or a domesticated animal, to whom treatment, including prophylactic treatment, with the compositions according to the present disclosure is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human patient, the term patient refers to that specific animal, including a domesticated animal such as a dog or cat or a farm animal such as a horse, cow, sheep, etc. In general, in the present disclosure, the term patient refers to a human patient unless otherwise stated or implied from the context of the use of the term.

[0060] The term “effective” is used to describe an amount of a compound, composition or component which, when used within the context of its intended use, effects an intended result. The term effective subsumes all other effective amount or effective concentration terms, which are otherwise described or used in the present application.

Compounds of the Disclosure

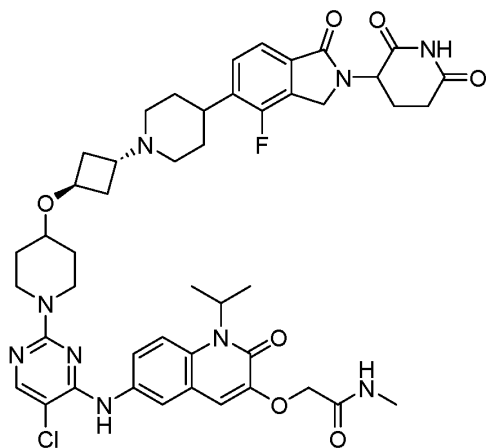
[0061] In some embodiments, the compound of the disclosure is Compound A:



(Compound A),

or a pharmaceutically acceptable salt thereof.

[0062] In some embodiments, the compound of the disclosure is Compound A:



(Compound A).

[0063] A compound of the disclosure may be synthesized using standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations, including the use of protective groups, as can be obtained from the relevant scientific literature or from standard reference textbooks in the field in view of this disclosure. Although not limited to any one or several sources, recognized reference textbooks of organic synthesis include: Smith, M.B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons: New York, 2001; and Greene, T.W.; Wuts, P.G. M. *Protective Groups in Organic Synthesis*, 3rd; John Wiley & Sons: New York, 1999. The synthetic methods described in U.S. Patent Application Publication No. 2022/0395576 and International Publication No. 2022/221673 are incorporated herein by reference in their entireties.

[0064] The term “independently” is used herein to indicate that the variable, which is independently applied, varies independently from application to application.

[0065] As used herein, the term “advanced” as applied to cancer, e.g., lymphoma, e.g., non-Hodgkin lymphoma (NHL) (including, but not limited to, B-Cell non-Hodgkin lymphoma (NHL), transformed follicular lymphoma, nodal T-follicular helper cell lymphoma (nTFHL), and/or nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL)) may refer to a cancer that has spread to one or more areas of the body. Cancers which are advanced may be identified according to methods known to those skilled in the art. In some embodiments, for example, advanced lymphomas (e.g., advanced B-Cell non-Hodgkin lymphoma (NHL), transformed follicular lymphoma, nodal T-follicular helper cell lymphoma (nTFHL), and/or advanced nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL)) may refer to lymphomas at a later stage according to a known staging system, such as the Lugano Classification (see, e.g., Hodgkin and Non-Hodgkin Lymphomas. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 937–58).

[0066] As used herein, the term “relapsed” as applied to cancer, e.g., lymphoma, e.g., non-Hodgkin lymphoma (NHL) (including, but not limited to, B-Cell non-Hodgkin lymphoma (NHL), nodal T-follicular helper cell lymphoma (nTFHL), and/or nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL)) may refer to cancer that has reappeared or grown following a period of remission.

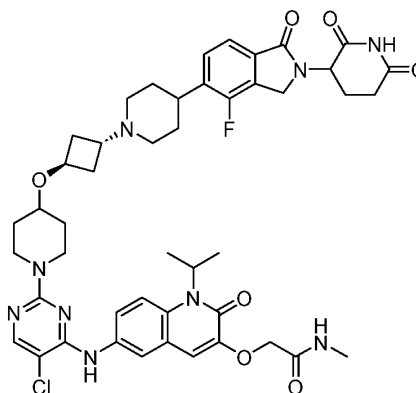
[0067] As used herein, the term “relapsed” as applied to cancer, e.g., lymphoma, e.g., non-Hodgkin lymphoma (NHL) (including, but not limited to, B-Cell non-Hodgkin lymphoma (NHL), nodal T-follicular helper cell lymphoma (nTFHL), and/or nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL)) may refer to cancer that does not respond to treatment.

[0068] As used herein, the term “Relapsed/Refractory” (often abbreviated “R/R”) can refer to cancer that is relapsed and/or refractory. In some embodiments, “Relapsed/Refractory” or “R/R” can refer to cancer in patients with disease progression who have failed at least one line of therapy.

Therapeutic Methods

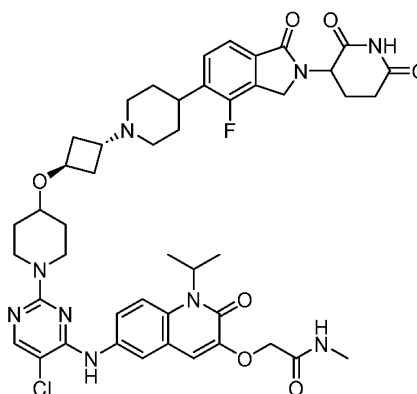
[0069] In some embodiments, the present disclosure provides a method of treating or ameliorating a disease or disorder disclosed herein in a subject in need thereof, comprising

administering to the subject an effective amount of Compound A or a pharmaceutically acceptable salt thereof.



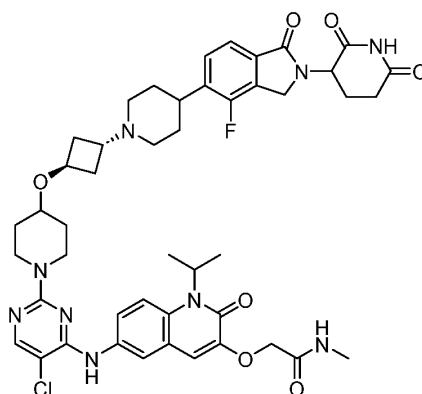
[0070] In some embodiments, the compound is (Compound A), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is Compound A.

[0071] In some embodiments, the present disclosure provides a method of treating or ameliorating a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure. In



some embodiments, the compound is (Compound A).

[0072] In some embodiments, the present disclosure provides a method of treating or ameliorating a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure. In



some embodiments, the compound is  (Compound A), or a pharmaceutically acceptable salt thereof.

[0073] The terms “treat”, “treating”, and “treatment”, etc., as used herein, refer to any action providing a benefit to a patient for which the present compounds may be administered, including the treatment of any disease state or condition which is modulated through the protein to which the present compounds bind. Disease states or conditions, including cancer, which may be treated using compounds according to the present disclosure are set forth hereinabove.

[0074] In some embodiments, the disease or disorder is associated with aberrant BCL6 expression and/or activity.

[0075] In some embodiments, the disease or disorder is a cancer associated with aberrant BCL6 expression and/or activity.

[0076] In some embodiments, the disease or disorder is associated with BCL6 accumulation and aggregation.

[0077] In some embodiments, the disease or disorder is a cancer associated with BCL6 accumulation and aggregation.

[0078] In some embodiments, the disease or disorder is cancer.

[0079] In some embodiments, the cancer is angioimmunoblastic T-cell lymphoma, large B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), mature B-cell neoplasm, transformed follicular lymphoma, high grade B-cell lymphoma, germinal center B-cell (GCB) DLBCL, activated B-cell (ABC) DLBCL, non-Hodgkin lymphoma not otherwise specified, or solid tumors.

[0080] In some embodiments, the cancer is angioimmunoblastic T-cell lymphoma, large B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma, high grade B-cell lymphoma, germinal center B-cell (GCB) DLBCL, activated B-cell (ABC) DLBCL, and non-Hodgkin lymphoma not otherwise specified, or solid tumors.

[0081] In some embodiments, the cancer is advanced cancer, relapsed/refractory (R/R) cancer, advanced lymphoma, relapsed/refractory (R/R) lymphoma, advanced non-Hodgkin lymphoma (NHL), relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL), advanced B-Cell non-Hodgkin lymphoma (NHL), relapsed/refractory (R/R) B-Cell non-Hodgkin lymphoma (NHL), transformed follicular lymphoma, nodal T-follicular helper cell lymphoma (nTFHL), relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma, nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / advanced angioimmunoblastic T-cell lymphoma (AITL), or relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL).

[0082] In some embodiments, the cancer is advanced non-Hodgkin lymphoma (NHL), relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL), transformed follicular lymphoma, nodal T-follicular helper cell lymphoma (nTFHL), relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma, advanced nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL), or relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL).

[0083] As used herein, “angioimmunoblastic T-cell lymphoma” is also known as “AITL”, “Nodal T-follicular helper (TFH) cell lymphoma, angioimmunoblastic-type”, or “nTFHL-AL”.

[0084] As used herein “nodal T-follicular helper cell lymphoma” is also known as “nTFHL”.

[0085] In some embodiments, the cancer is angioimmunoblastic T-cell lymphoma, large B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma, germinal center B-cell (GCB) DLBCL, activated B-cell (ABC) DLBCL, non-Hodgkin lymphoma not otherwise specified, or solid tumors.

[0086] In some embodiments, the cancer is angioimmunoblastic T-cell lymphoma, large B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma, high grade B-cell lymphoma, non-Hodgkin lymphoma not otherwise specified, or solid tumors.

[0087] In some embodiments, the cancer is angioimmunoblastic T-cell lymphoma, large B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), or solid tumors.

[0088] In some embodiments, the cancer is angioimmunoblastic T-cell lymphoma.

[0089] In some embodiments, the cancer is large B-cell lymphoma.

[0090] In some embodiments, the cancer is diffuse large B-cell lymphoma (DLBCL).

[0091] In some embodiments, the cancer is transformed follicular lymphoma.

[0092] In some embodiments, the cancer is high grade B-cell lymphoma.

[0093] In some embodiments, the cancer is diffuse large B-cell lymphoma (DLBCL), wherein the diffuse large B-cell lymphoma (DLBCL) is selected from germinal center B-cell (GCB) DLBCL and activated B-cell (ABC) DLBCL.

[0094] In some embodiments, the cancer is germinal center B-cell (GCB) DLBCL.

[0095] In some embodiments, the cancer is activated B-cell (ABC) DLBCL.

[0096] In some embodiments, the cancer is non-Hodgkin lymphoma not otherwise specified.

[0097] In some embodiments, the cancer is mature B-cell neoplasm.

[0098] In some embodiments, the cancer is solid tumors.

[0099] In some embodiments, the cancer is solid tumors, wherein the solid tumors are selected from breast cancer, lung cancer, ovarian cancer, blastoma, neuroblastoma, and glioblastoma.

[00100] In some embodiments, the cancer is breast cancer.

[00101] In some embodiments, the cancer is lung cancer.

[00102] In some embodiments, the cancer is ovarian cancer.

[00103] In some embodiments, the cancer is blastoma.

[00104] In some embodiments, the cancer is neuroblastoma.

[00105] In some embodiments, the cancer is glioblastoma.

[00106] In some embodiments, the cancer is advanced cancer.

[00107] In some embodiments, the cancer is relapsed/refractory (R/R) cancer.

[00108] In some embodiments, the cancer is advanced lymphoma.

[00109] In some embodiments, the cancer is relapsed/refractory (R/R) lymphoma.

[00110] In some embodiments, the cancer is advanced non-Hodgkin lymphoma (NHL).

[00111] In some embodiments, the cancer is relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL).

[00112] In some embodiments, the cancer is advanced B-Cell non-Hodgkin lymphoma (NHL).

[00113] In some embodiments, the cancer is relapsed/refractory (R/R) B-Cell non-Hodgkin lymphoma (NHL).

[00114] In some embodiment, the cancer is nodal T-follicular helper cell lymphoma (nTFHL).

[00115] In some embodiments, the cancer is relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma.

[00116] In some embodiments, the cancer is advanced nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL).

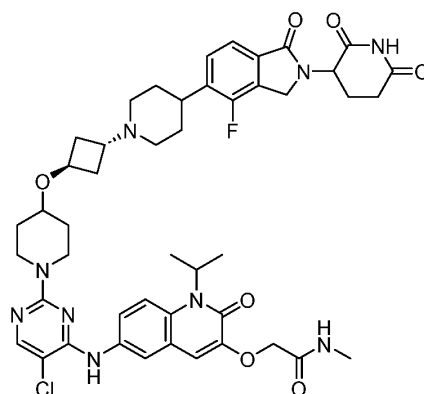
[00117] In some embodiments, the cancer is relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL).

[00118] In some embodiments, the cancer is nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) that has recurred or progressed following institutional standard-of-care therapy.

[00119] In some embodiments, the cancer is transformed follicular lymphoma.

[00120] The term “neoplasia” or “cancer” is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal tissue that grows by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, metastasize to several sites, and are likely to recur after attempted removal and to cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and solid tumors. Exemplary cancers which may be treated by the present compounds either alone or in combination with at least one additional anti-cancer agent include non-Hodgkin lymphoma (NHL) including advanced NHL and relapsed/refractory (R/R) NHL, B-cell non-Hodgkin lymphoma (NHL) including advanced B-cell NHL and relapsed/refractory B-cell (R/R) NHL, transformed follicular lymphoma, nodal T-follicular helper cell lymphoma (nTFHL), relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma, nodal T-follicular helper cell lymphoma (nTFHL), relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma, nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) including advanced nTFHL-AI / AITL and relapsed/refractory nTFHL-AI / AITL, large B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), angioimmunoblastic T-cell lymphoma, mature B-cell neoplasm, transformed follicular lymphoma, high grade B-cell lymphoma, germinal center B-cell (GCB) DLBCL, activated B-cell (ABC) DLBCL, non-Hodgkin lymphoma not otherwise specified, or solid tumors, including, but not limited to, breast, lung and ovarian cancers, and neuroblastoma and glioblastoma.

[00121] In some embodiments, the present disclosure provides a method of treating or ameliorating diffuse large B-cell lymphoma (DLBCL) in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure. In



some embodiments, the compound is (Compound A), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is Compound A.

EXAMPLES

Example 1. Compound A degrades BCL6 protein in GCB and ABC DLBCL cell lines.

[00122] Degradation of BCL6 protein in DLBCL cell lines were measured by ELISA. OCI-Ly1 cell line was treated with Compound A and its E3-binding deficient analogue for 24-hours (FIG. 2A). GCB DLBCL cell lines Farage, SU-DHL-4, SU-DHL-6 and OCI-Ly7 (FIG. 2B) and ABC DLBCL cell lines SU-DHL-2 and OCI-Ly10 (FIG. 2C) were treated for 24 hours with Compound A. FIG. 2A showed that Compound A treatment demonstrated potent BCL6 protein degradation in OCI-Ly1 cell line compared to its E3-binding deficient analogue. FIG. 2B and FIG. 2C showed that Compound A treatment demonstrated potent BCL6 protein degradation in GCB and ABC DLBCL cell lines.

Example 2. Compound A inhibits the proliferation of DLBCL cell lines.

[00123] Antiproliferative effects of Compound A on DLBCL-derived cell lines were tested. Nine-day cell growth inhibition assays were conducted using GCB lines OCI-Ly1, OCI-Ly7, SU-DHL-4 and SU-DHL-6 (FIG. 3A), and ABC lines SU-DHL-2 and OCI-Ly10 (FIG. 3B) dosed with a 7-point 3-fold serial dilution of Compound A at a top dose of 30 nM. On days 3 and 6-7, samples were split to new 48-well plates for re-treatment, and 20% to a 96-well plate to measure cell viability using CellTiter-Glo (CTG). Split cells in the 48-well plates were retreated and cultured out to day 9, when 20% of each sample was analyzed by CTG. Dose response was plotted as a percentage of vehicle (DMSO) control (FIG. 3A and FIG. 3B). Graphs are representative of at least two independent proliferation assays per cell line. Each

Compound A treatment demonstrated a significant decrease on DLBCL cells growth, the effect was concentration dependent.

Example 3. Compound A inhibits the tumor growth of DLBCL (GCB) cell line derived xenograft model OCI-Ly1.

[00124] Mice bearing subcutaneous tumors were orally (po) administered vehicle or Compound A at 1, 3, 10, or 30 mg/kg daily for 22 days (qdx22). Dosing began with tumors at an average of 140 mm³. FIG. 4A shows average OCI-Ly1 tumor growth. FIG. 4B shows average body weights of treated mice. Statistical analyses were performed using 2-way ANOVA: $p < 0.0001$ (****). Error bars represent standard error of the mean ($\pm$ SEM). The data indicate that the treatment with compound A inhibits the tumor growth of DLBCL cell line derived xenograft model OCI-Ly1, the effect was dosing dependent.

Example 4. Tumor lysate BCL6 protein levels in OCI-Ly1 (GCB) cell line xenograft tumor tissue following a treatment time-course with Compound A.

[00125] Tumor lysate BCL6 protein levels in OCI-Ly1 cell line xenograft tumor tissue was measured following a treatment time-course with Compound A. A single dose of Compound A was orally administered in a vehicle of 40% hydroxypropyl- β -cyclodextrin in pH 3.0 citrate buffer when tumors reached 200-400 mm³. Tumors were harvested at the indicated timepoints. Tumor tissue lysates were analyzed using western immunoblotting procedures and densitometry. BCL6 levels are normalized to a GAPDH loading control and presented as a percentage (%) of the average of BCL6 levels in the vehicle control group. Percent BCL6 degradation (%) relative to vehicle is shown above each arm. Cells (1×10^7 cells in 50% matrigel+50% RMPI-1640 (phenol red-free)/100 μ l/mouse) were implanted on the right flank subcutaneously. FIG. 5 showed that Compound A treatment degraded BCL6 protein rapidly and kept them down for up to 36 hours in the OCI-Ly1 model.

[00126] Additionally, FIG. 6 showed the total Compound A plasma and tumor levels following a treatment time-course with Compound A. Curves represented average drug levels within each dose group for each tissue type over time. Individual data points were shown to demonstrate spread of the data within each group of seven mice per condition assayed. Compound A achieved maximum concentration (C_{max}) at 4-hours in plasma and at 8-hours in tumor tissues.

Example 5. Compound A inhibits the tumor growth of DLBCL (GCB) cell line derived xenograft model OCI-Ly1.

[00127] Mice bearing subcutaneous tumors were orally (po) administered vehicle or Compound A at 1, 3, or 10 mg/kg bi-daily for 23 days (bidx23). Dosing began with tumors at an average of 170 mm³. FIG. 7A and FIG. 7B indicate that the treatment with compound A inhibits the tumor growth of DLBCL cell line derived xenograft model OCI-Ly1, the effect was dosing dependent. FIG. 7C depicts tumor lysate BCL6 protein levels 16-hours post-last dose analyzed by western blotting. Individual tumor BCL6 levels are shown in a scatter plot, mean is represented by the bar, determined by densitometry, normalized to GAPDH loading controls, and shown as a percentage of vehicle. Percent BCL6 degradation (%) relative to vehicle is shown above each arm. Statistical analyses were performed using 2-way ANOVA: $p < 0.0001$ (****). Error bars represent standard error of the mean ($\pm$ SEM). FIG. 7C showed that tumor growth inhibition by Compound A treatment was associated with a dose-dependent degradation of BCL6 protein in the OCI-Ly1 model.

Example 6. Compound A inhibits the tumor growth of DLBCL (GCB) cell line derived xenograft model OCI-Ly7.

[00128] Mice bearing subcutaneous tumors were orally (po) administered vehicle or Compound A at 1, 3, 10, or 30 mg/kg daily for 13 days (qdx13). Dosing began with tumors at an average of 130 mm³. FIG. 8A and FIG. 8B indicate that the treatment with compound A inhibits the tumor growth of DLBCL cell line derived xenograft model OCI-Ly7, the effect was dosing dependent. FIG. 8C depicts tumor lysate BCL6 protein levels 16-hours post-last dose analyzed by western blotting. Individual tumor BCL6 levels are shown in a scatter plot, mean is represented by the bar, determined by densitometry, normalized to GAPDH loading controls, and shown as a percentage of vehicle. Percent BCL6 degradation (%) relative to vehicle is shown above each arm. Statistical analyses were performed using 2-way ANOVA: $p < 0.0001$ (****). Error bars represent standard error of the mean ($\pm$ SEM). FIG. 8C showed that tumor growth inhibition by Compound A treatment was associated with a dose-dependent degradation of BCL6 protein in the OCI-Ly7 model.

Example 7. Compound A inhibits the tumor growth of DLBCL (ABC) cell line derived xenograft model SU-DHL-2.

[00129] Mice bearing subcutaneous tumors were orally (po) administered vehicle or Compound A at 3, 10, or 30 mg/kg bi-daily for 27 days (bidx27) or 30 mg/kg daily for 27 days

(qdx27). Dosing began with tumors at an average of 180 mm³. FIG. 9A and FIG. 9B indicate that the treatment with compound A inhibits the tumor growth of DLBCL cell line derived xenograft model SU-DHL-2, the effect was dosing dependent. FIG. 9C depicts tumor lysate BCL6 protein levels 16-hours post-last dose analyzed by western blotting. Individual tumor BCL6 levels are shown in a scatter plot, mean is represented by the bar, determined by densitometry, normalized to GAPDH loading controls, and shown as a percentage of vehicle. Percent BCL6 degradation (%) relative to vehicle is shown above each arm. Statistical analyses were performed using 2-way ANOVA: $p < 0.0001$ (****). Error bars represent standard error of the mean ($\pm$ SEM). FIG. 8C showed that tumor growth inhibition by Compound A treatment was associated with a dose-dependent degradation of BCL6 protein in the SU-DHL-2 model.

Example 8. Compound A inhibits the tumor growth of DLBCL(ABC) cell line derived xenograft model OCI-Ly10.

[00130] Mice bearing subcutaneous tumors were orally (po) administered vehicle or Compound A at 3, 10, or 30 mg/kg bi-daily for 28 days (bidx28) or 30 mg/kg daily for 28 days (qdx28). Dosing began with tumors at an average of 190 mm³. FIG. 10A and FIG. 10B indicate that the treatment with compound A inhibits the tumor growth of DLBCL cell line derived xenograft model OCI-Ly10, the effect was dosing dependent. FIG. 10C depicts tumor lysate BCL6 protein levels 16-hours post-last dose analyzed by western blotting. Individual tumor BCL6 levels are shown in a scatter plot, mean is represented by the bar, determined by densitometry, normalized to GAPDH loading controls, and shown as a percentage of vehicle. Percent BCL6 degradation (%) relative to vehicle is shown above each arm. Statistical analyses were performed using 2-way ANOVA: $p < 0.05$ (*), $p < 0.0001$ (****). Error bars represent standard error of the mean ($\pm$ SEM). FIG. 10C showed that Compound A treatment at all dose levels degraded BCL6 protein in the OCI-Ly10 model.

Example 9: Tumor growth inhibition.

Compound A displays 100% TGI in a BCL6 sensitive tumor xenograft model (OCI-Ly1) when dosed at 10 mg/kg (BID).

Example 10: Mean tumor volumes of PDX mouse models of DLBCL and Burkitt's lymphoma, treated with Compound A or vehicle.

[00506] Compound A orally dosed at 30 mg/kg induces in-vivo tumor regressions in patient derived xenograft (PDX) models of DLBCL and Burkitt's lymphoma. The results are shown

in FIGs. 11A-11D. The DLBCL models representing 1) Double hit DLBCL(LY2214), 2) Unclassified DLBCL (LY6934) subtypes, show sensitivity to Compound A resulting in tumor regression compared to vehicle dosed controls. Compound A also induces tumor regressions in models of Burkitt's lymphoma (LY3148) and GCB DLBCL (LY12962). HuPrime® Lymphoma Xenograft Models in NOD/SCID or BALB/c Nude Mice, 4/group, were dosed orally (*per os*, PO) daily for 21 days (QDx21) and tumor measurements were acquired twice per week. No significant body weight loss was observed (not shown). Data points represent the mean per group and error bars the standard error of the mean.

Example 11: Preclinical model of nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) is sensitive to Compound A *in vivo*

[00507] Compound A was tested in a systemic cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-refractory patient derived xenograft (PDX) preclinical model of nTFHL-AI / AITL. After systemic tumor engraftment was confirmed (as determined by flow cytometry quantification of hCD2), Compound A (30 mpk) was administered orally (po), once daily (qd) for 23 days. At the terminal time point (Day 23), tumor burden in peripheral blood, bone marrow and spleen were measured. As a positive control for the PDX model (based on published literature), the histone deacetylase (HDAC) inhibitor, romidespin which is commonly used to treat nTFHL-AI patients, was administered (1 mpk) via intraperitoneal injection once every three days (q3d) for 23 days. The data is shown in FIGs. 12A-12C. The percentCD2+ /hCD45+ cells (FIGs. 12A-12B) or spleen weight (FIG 12C) is reported $\pm$ SEM. Compound A significantly decreased tumor cell infiltration in the peripheral blood, bone marrow and spleen as compared to the vehicle control. One-way ANOVA, Tukey's multiple comparison's test, ** $p < .01$, *** $p < 0.001$, **** $p < 0.0001$.

Example 12: Compound A demonstrates efficacy in transformed follicular lymphoma

[00508] An in-vivo efficacy study was performed in two different patient derived xenografts (PDX) preclinical models of transformed follicular lymphoma (tFL). Mice bearing subcutaneous tumors were orally (po) administered vehicle or Compound A at 30 mg/kg once daily for 25 days (qdx25). The data is shown in FIGs. 13A-13B. Fig 13A shows 95% tumor growth inhibition (TGI) and Fig 13B shows 99% TGI. Mean tumor volume is reported $\pm$ SEM. One-way ANOVA, Student's t test, **** $p < 0.0001$.

Example 13: Synthesis of Compound A.

[00509] Compound A can be prepared, according to methods known to those skilled in the art, for example, as described in Example 25 of U.S. Patent Application Publication No. 2022/0395576 and International Publication No. 2022/221673, the contents of which are incorporated by reference in their entirety for all purposes.

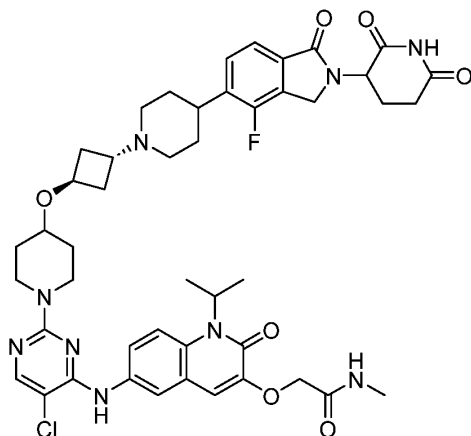
[00510] The contents of all references, patents, pending patent applications and published patents, cited throughout this application are hereby expressly incorporated by reference.

[00511] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims. It is understood that the detailed examples and embodiments described herein are given by way of example for illustrative purposes only, and are in no way considered to be limiting to the disclosure. Various modifications or changes in light thereof will be suggested to persons skilled in the art and are included within the spirit and purview of this application and are considered within the scope of the appended claims. For example, the relative quantities of the ingredients may be varied to optimize the desired effects, additional ingredients may be added, and/or similar ingredients may be substituted for one or more of the ingredients described. Additional advantageous features and functionalities associated with the systems, methods, and processes of the present disclosure will be apparent from the appended claims. Moreover, those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What Is Claimed Is:

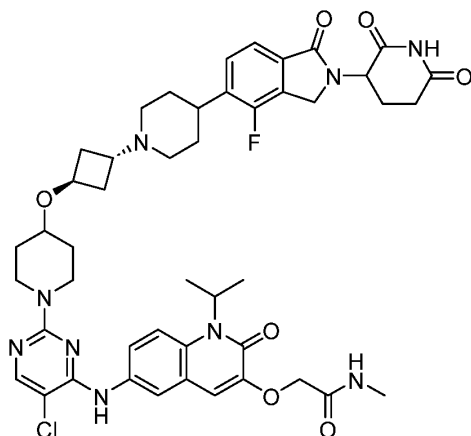
1. A method of treating or ameliorating advanced non-Hodgkin lymphoma (NHL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A),

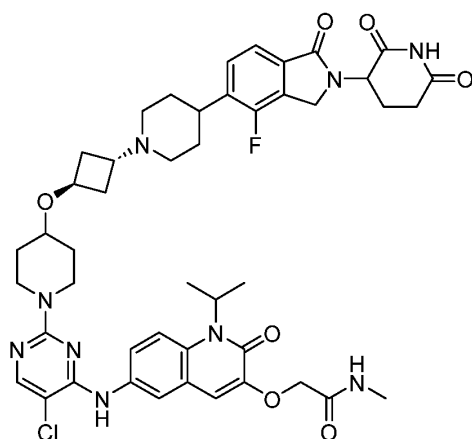
or a pharmaceutically acceptable salt thereof.

2. A method of treating or ameliorating advanced non-Hodgkin lymphoma (NHL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A).

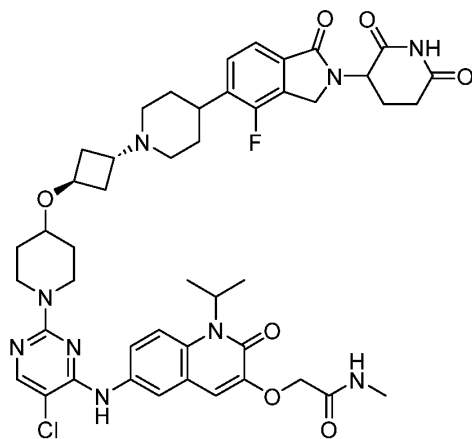
3. A method of treating or ameliorating relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A),

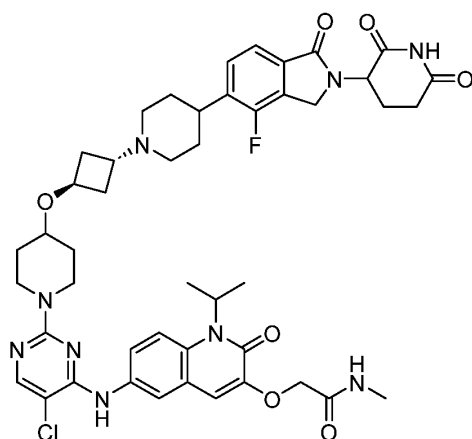
or a pharmaceutically acceptable salt thereof.

4. A method of treating or ameliorating relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A).

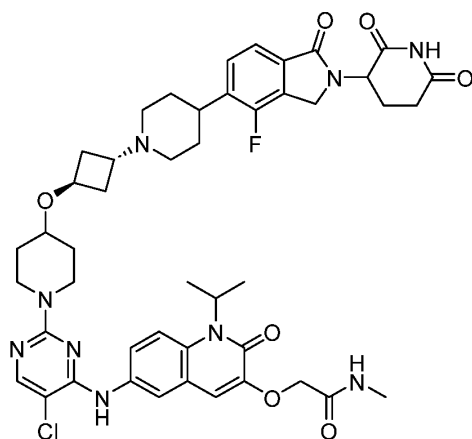
5. A method of treating or ameliorating advanced nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A),

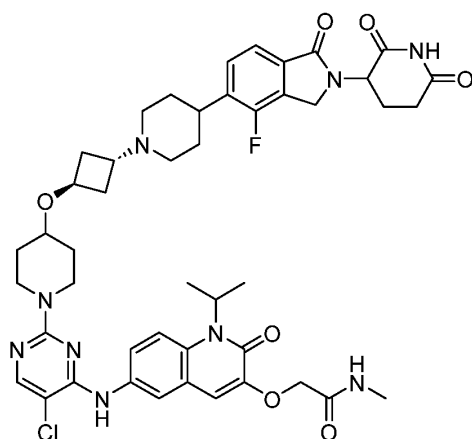
or a pharmaceutically acceptable salt thereof.

6. A method of treating or ameliorating advanced nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A).

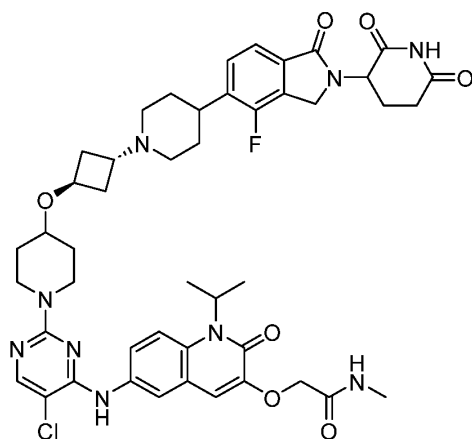
7. A method of treating or ameliorating relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A),

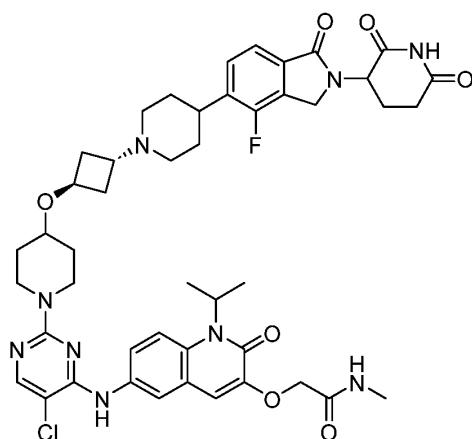
or a pharmaceutically acceptable salt thereof.

8. A method of treating or ameliorating relapsed/refractory (R/R) nodal T-follicular helper cell lymphoma - angioimmunoblastic type (nTFHL-AI) / angioimmunoblastic T-cell lymphoma (AITL) in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A).

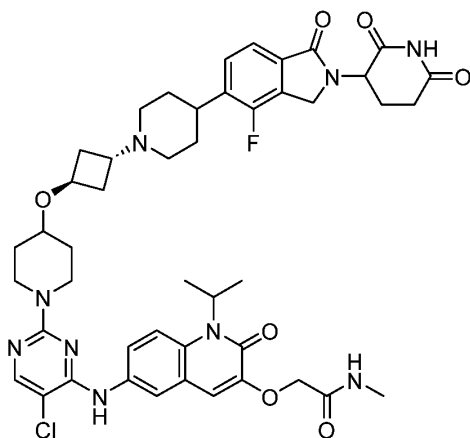
9. A method of treating or ameliorating transformed follicular lymphoma in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



(Compound A),

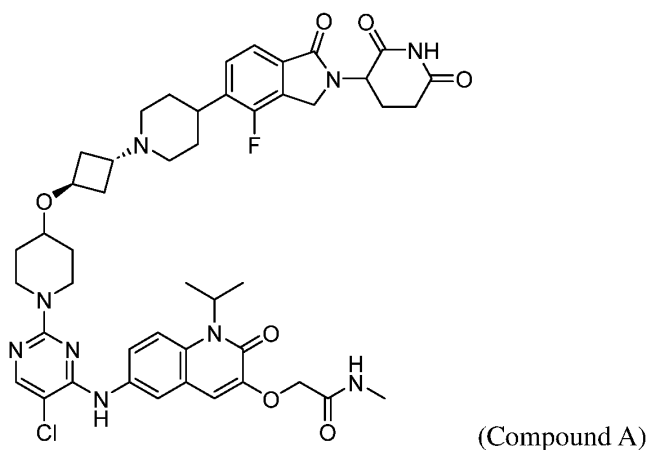
or a pharmaceutically acceptable salt thereof.

10. A method of treating or ameliorating transformed follicular lymphoma in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



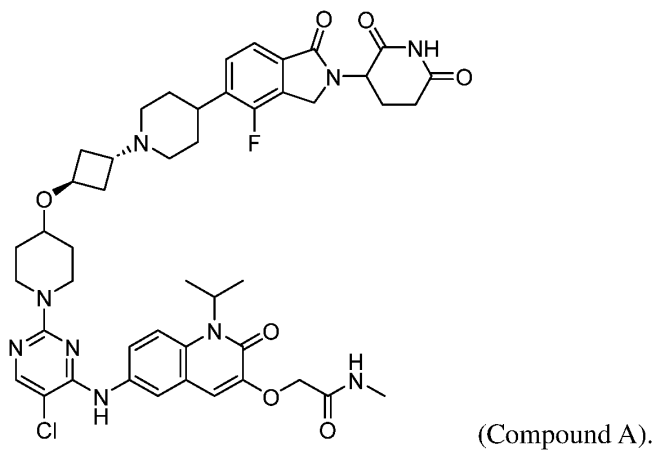
(Compound A).

11. A method of treating or ameliorating transformed follicular lymphoma in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:

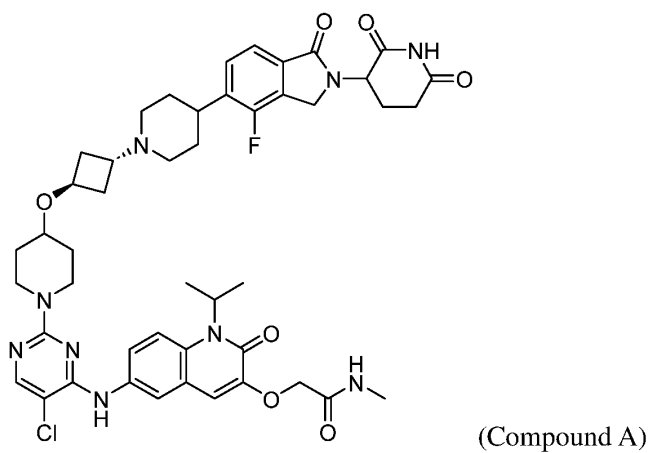


or a pharmaceutically acceptable salt thereof.

12. A method of treating or ameliorating transformed follicular lymphoma in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



13. A method of treating or ameliorating relapsed/refractory (R/R) transformed follicular lymphoma in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:



or a pharmaceutically acceptable salt thereof.

14. A method of treating or ameliorating relapsed/refractory (R/R) transformed follicular lymphoma in a subject in need thereof, comprising administering to the subject an effective amount of Compound A:

