

HETEROBIFUNCTIONAL COMPOUNDS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/511,374, filed on June 30, 2023, which is incorporated herein by reference in its entirety.

5 STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with Government support under contracts CA163915, CA276167, and MH126720 awarded by the National Institutes of Health. The Government has certain rights in the invention.

SEQUENCE LISTING STATEMENT

10 The contents of the electronic sequence listing titled
STDU2_42137_601_SequenceListing.xml (Size: 2,854 bytes; and Date of Creation: June 28,
2024) is incorporated herein by reference in its entirety.

TECHNICAL FIELD

Disclosed herein are heterobifunctional compounds that include a BCL6-binding moiety
15 and a moiety that binds to a bromodomain of a histone acetyltransferase (HAT), with the two
moieties connected via a linker. Also disclosed herein are pharmaceutical compositions
comprising the compounds, and methods of using the compounds, e.g., to treat proliferative
diseases such as cancers.

BACKGROUND

20 One of the major accomplishments of cancer biology within the last 40 years has been the
identification of cancer drivers that, when mutated or otherwise misregulated, drive the
proliferation, spread, or survival of cancer cells (Weinberg, *Science* 230(4727), 770-776 (1985);
Davoli *et al. Cell* 155, 948-962 (2013); Sanchez-Vega *et al. Cell* 173, 321-337 e310 (2018);
Denny *et al. Cell* 166, 328-342 (2016)). The cancer drivers have been largely recognized from
25 human genetic studies of specific tumors, and can be grouped into tumor suppressors that
prevent cancer from developing, or oncogenes that contribute directly to the proliferation or
spread of the cancer at the expense of the organism.

During the past forty years, parallel studies conducted largely in the laboratories of developmental biologists have identified pathways of programmed cell death that kill specific populations of cells that have made mistakes in developmental programs or have errors in DNA replication or repair (Hengartner *et al. Cell* 76, 665-676 (1994); Strasser *et al. Annu. Rev.*

- 5 *Biochem.* 69, 217-245 (2000)). These pathways of cell death have been evolutionarily perfected for over 100 million years and are remarkably effective. Indeed, about 60 billion of our cells are killed every day by these mechanisms (Alberts *et al. in Molecular Biology of the Cell* (2002)). The genes, proteins, and biochemical pathways inducing (pro-apoptotic) and preventing (anti-apoptotic) programmed cell death are well-known and reasonably well-understood.

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SUMMARY

Disclosed herein is a compound of formula (I)

A-L-B (I)

or a pharmaceutically acceptable salt thereof, wherein:

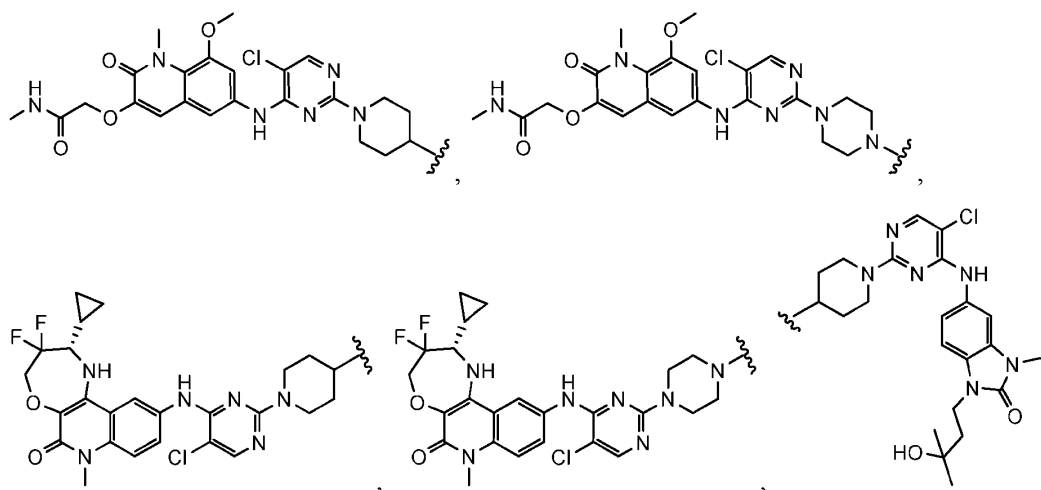
A is a BCL6-binding moiety;

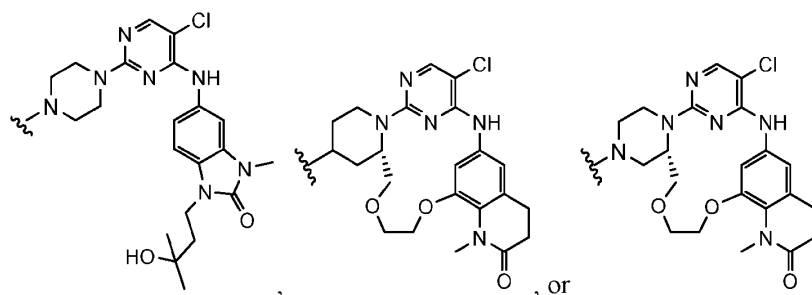
15

L is a linker; and

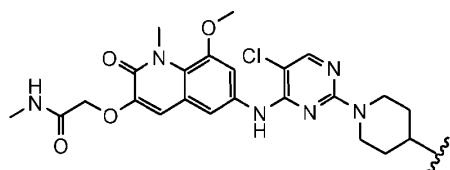
B is a moiety that binds to the bromodomain of a histone acetyltransferase.

In some embodiments, A is a moiety of formula:

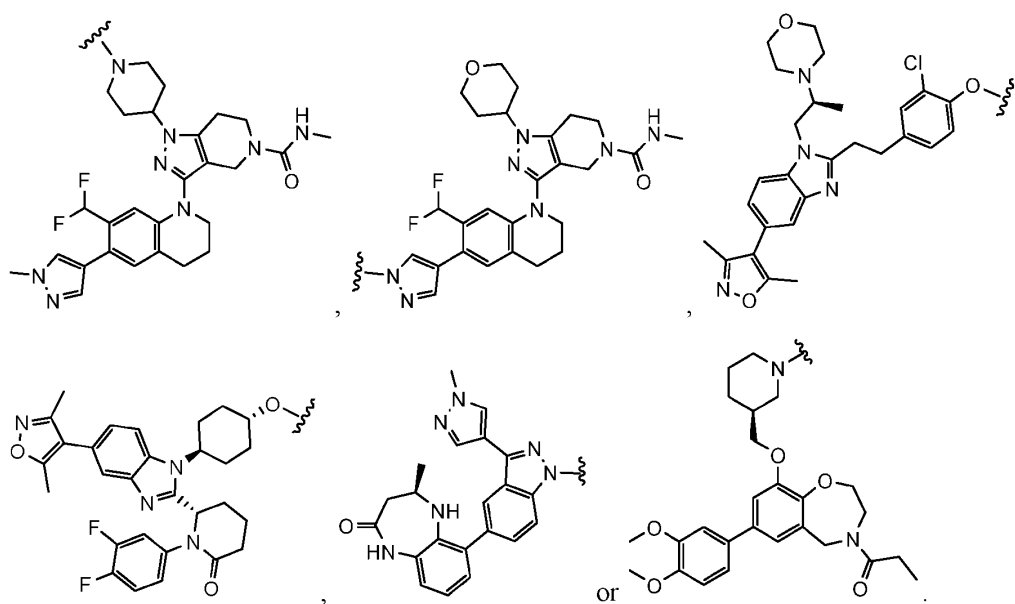




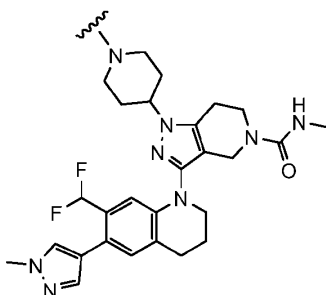
In some embodiments, A is a moiety of formula:



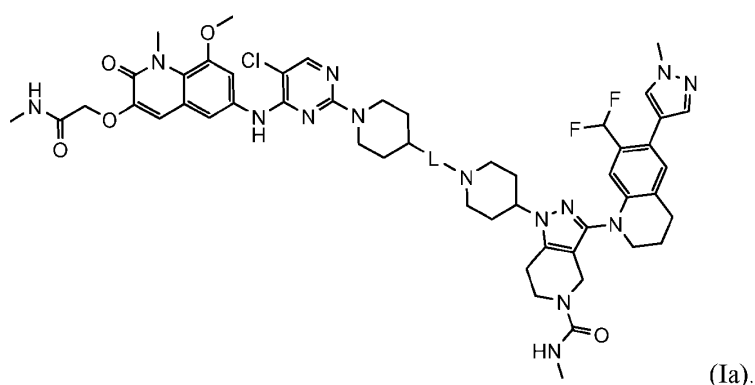
In some embodiments, B is a moiety that binds to the bromodomain of p300 or CBP. In
5 some embodiments, B is a moiety of formula:



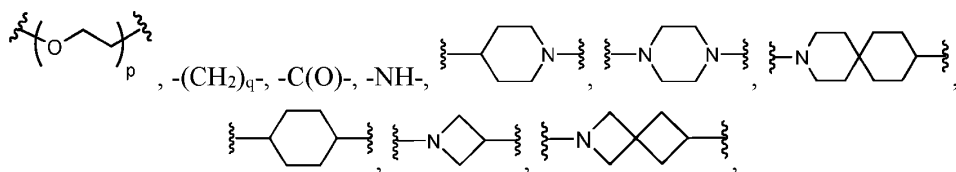
In some embodiments, B is a moiety of formula:



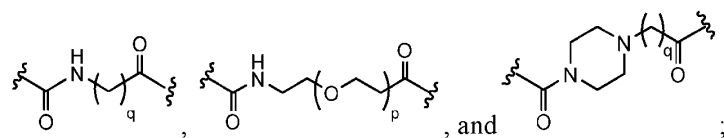
In some embodiments, the compound is a compound of formula (Ia):



- In some embodiments, L is a direct bond or comprises any combination of -CH₂-, -CH=CH-, -C≡C-, -O-, -NR'-, -BR'-, -S-, -C(O)-, -C(NR')-, -S(O)-, -S(O)₂-, arylene, heteroarylene, cycloalkylene, and heterocyclylene moieties, wherein the arylene, heteroarylene, cycloalkylene, and heterocyclylene moieties are independently unsubstituted or substituted with 1, 2, or 3 substituents. In some embodiments, L is a direct bond or comprises any combination of -CH₂-, -O-, -C(O)-, -NH-, -N(CH₃)-, cycloalkylene, and heterocyclylene moieties. In some
- embodiments, L comprises any combination of the following moieties:

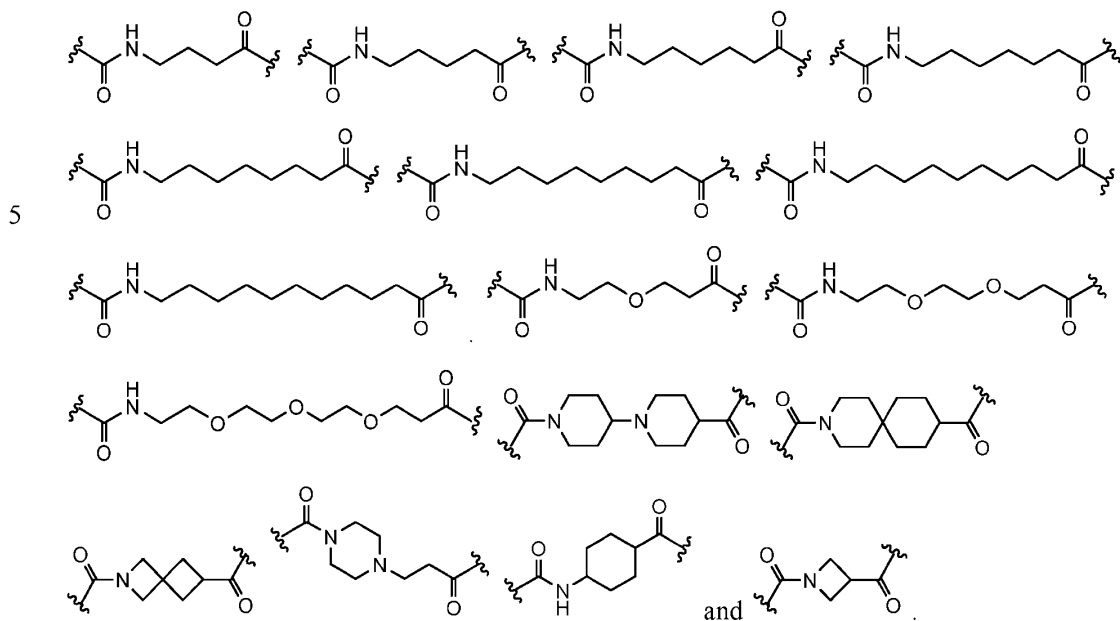


wherein p is 1, 2, 3, 4, 5, or 6; and q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16. In some embodiments, L has a formula selected from:

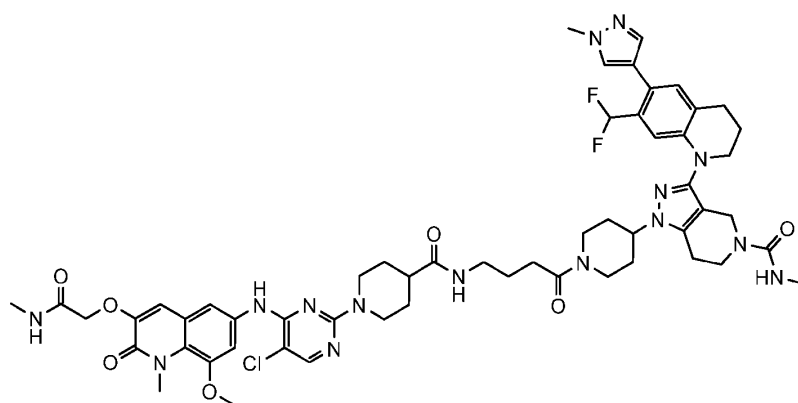


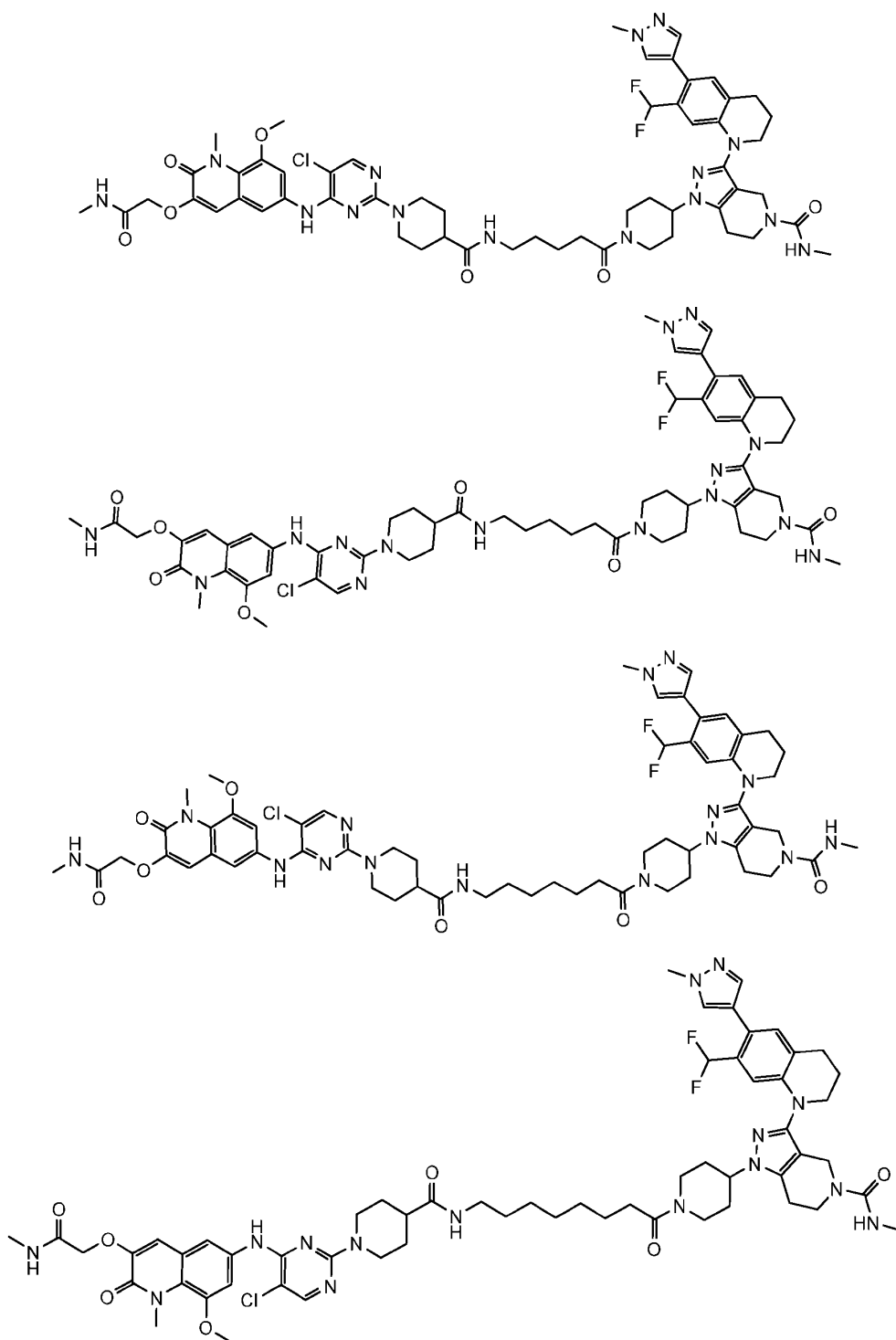
wherein p is 1, 2, 3, 4, 5, or 6; and q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

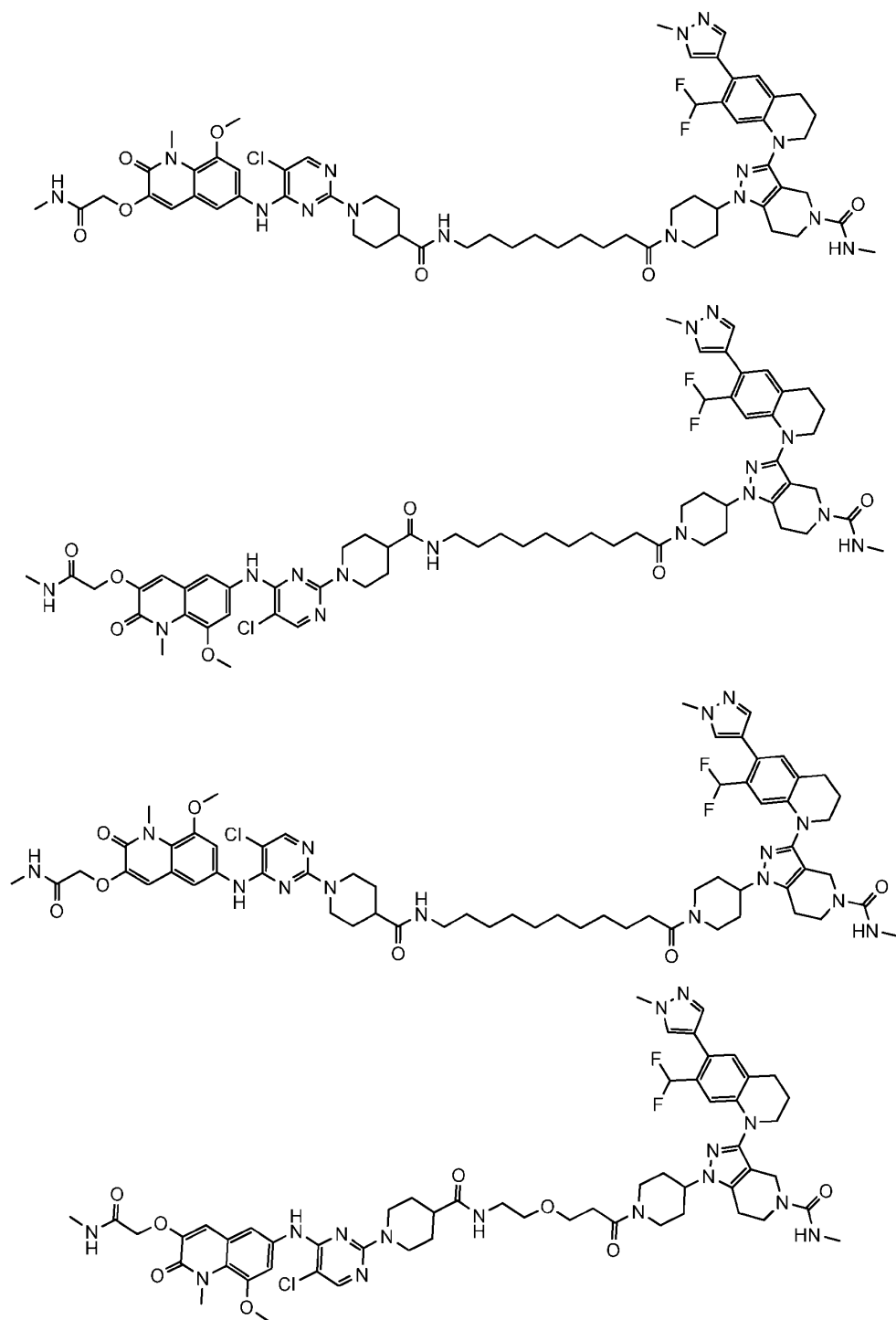
In some embodiments, L has a formula selected from:

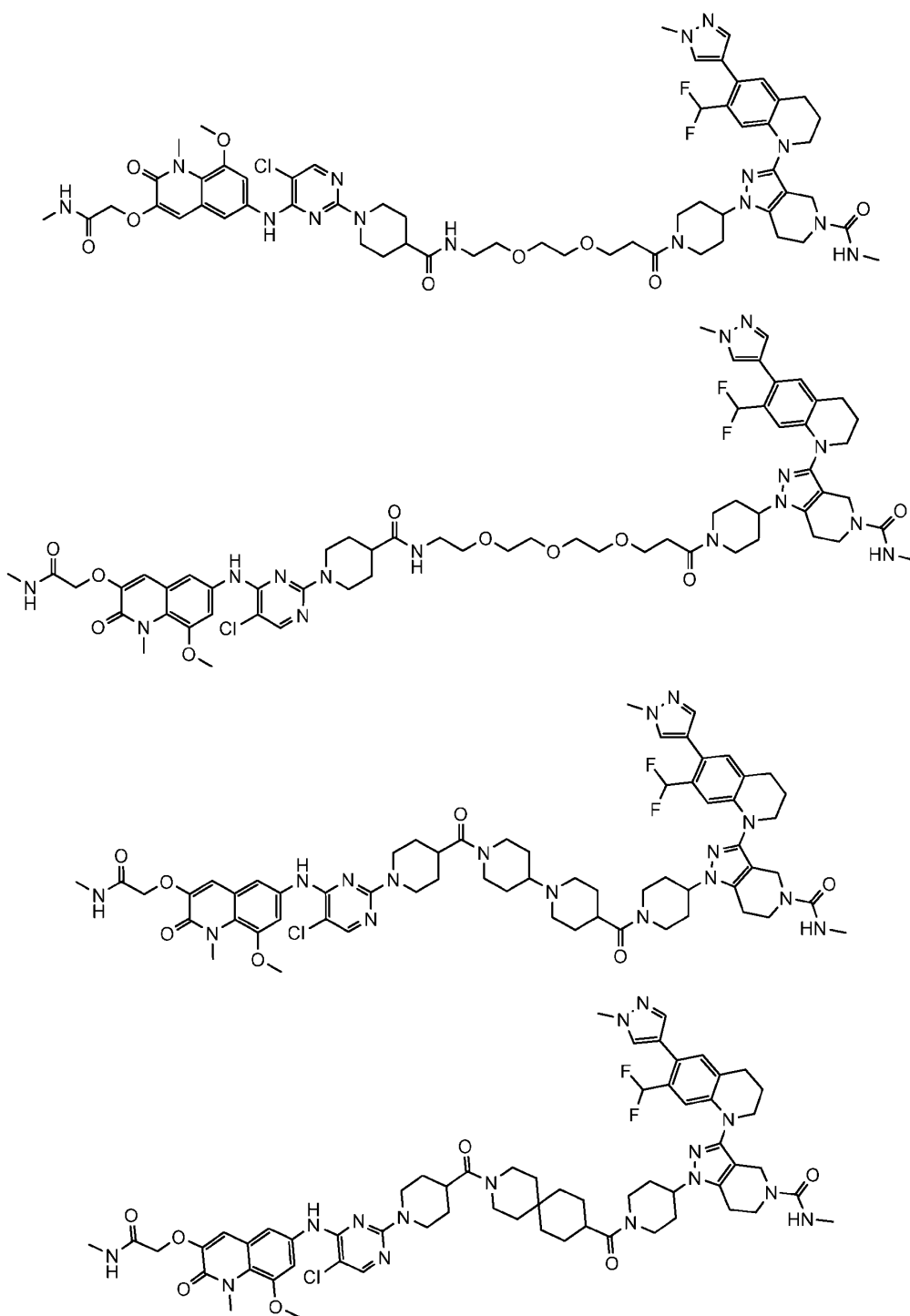


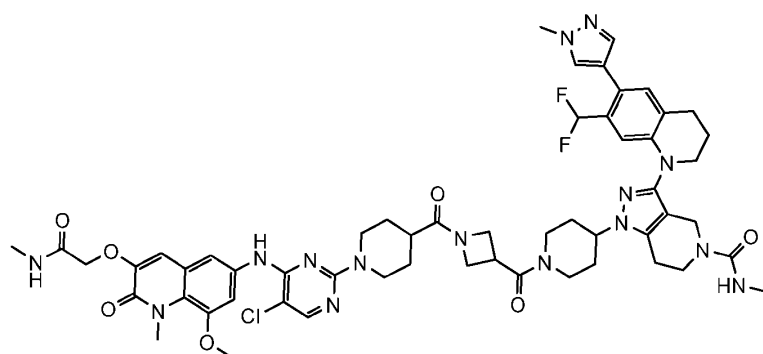
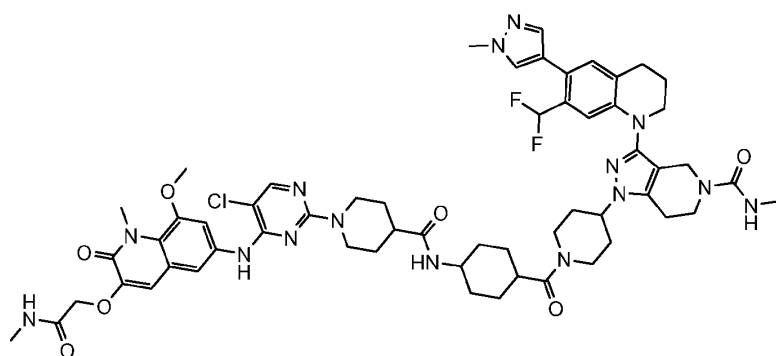
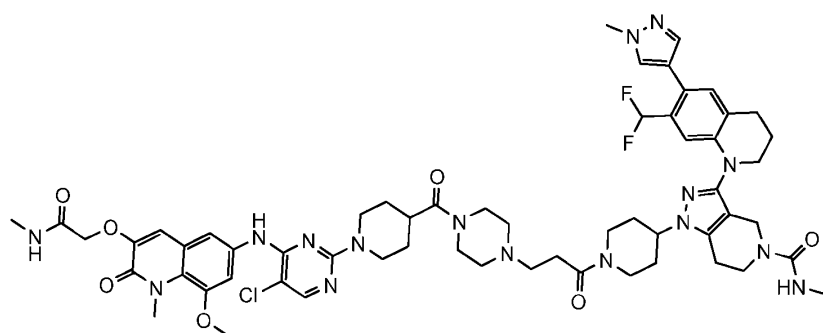
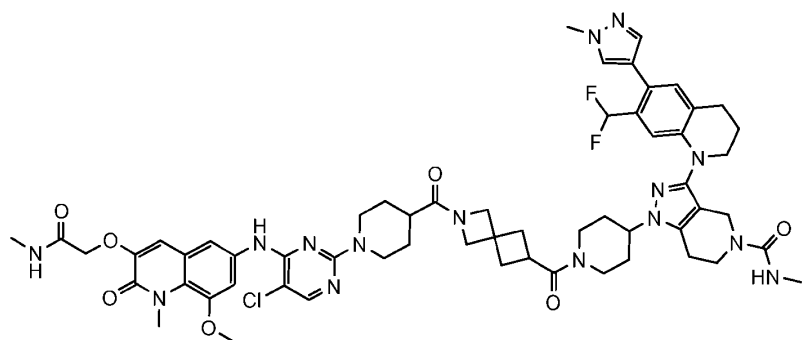
In some embodiments, the compound is selected from:

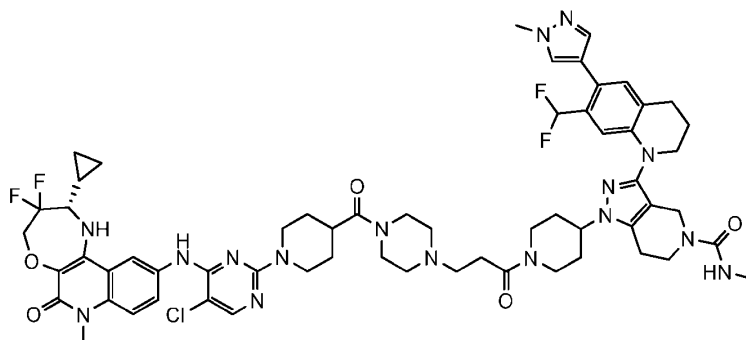












and pharmaceutically acceptable salts thereof.

Also disclosed herein is a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Also disclosed herein is a method of treating a proliferative disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the proliferative disease is a cancer selected from a carcinoma, a sarcoma, and a hematologic malignancy. In some embodiments, the cancer is a lymphoma. In some embodiments, a diffuse large B-cell lymphoma.

Also disclosed herein is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

Also disclosed herein is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in treating a proliferative disease. In some embodiments, the proliferative disease is a cancer selected from a carcinoma, a sarcoma, and a hematologic malignancy. In some embodiments, the cancer is a lymphoma. In some embodiments, the cancer is a diffuse large B-cell lymphoma.

Also disclosed herein is a kit comprising a compound of formula (I), or a
20 pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a general strategy to activate cell death pathways with cancer drivers. On the left are shown major cancer driver pathways. On the right, proapoptotic or cell death pathways are shown. The TCIP engages the cancer driver pathway with one chemical entity and

the engages the cell death pathway with a second chemical entity. In the case of this application, histone acetyl transferases contribute a driving mechanism to certain cancers such as Diffuse Large Cell B Cell lymphoma (DLBCL) and BCL6 is a powerful regulator of programmed cell death or apoptosis.

5 FIG. 2 is an illustration of a Transcriptional/Epigenetic Chemical Inducer of Proximity (TCIP) that binds a histone acetyl transferase on one side and BCL6 on the other side. The combination of the two proteins and the TCIP is termed a ternary complex.

 FIG. 3 is an illustration showing that TCIPs borrow only a small fraction of the total target and rewire it to produce new connections. This gain-of-function strategy underlies their
10 remarkable potency and their lack of toxicity.

 FIG. 4 shows activation of a reporter gene, green fluorescent protein (GFP), that is under transcriptional control by endogenous BCL6 in the diffuse large B cell lymphoma (DLBCL) cell line KARPAS422. Cells were treated with drug for 24 hours with the HAT-BCL6 TCIPs. Mean $\pm$ s.e., n=1-3 independent replicates.

15 FIGS. 5A-5B show the effects of HAT-BCL6 TCIPs on viability in the DLBCL lines SUDHL5 (FIG. 5A) and KARPAS422 (FIG. 5B). Cells were treated with compounds for 72 hours. Mean $\pm$ s.d., 1-3 biological replicates

 FIGS. 6A-6B show results assaying cell viability after competitive titration of monovalent inhibitors to BCL6 or p300/CBP in SUDHL5 (FIG. 6A) or KARPAS422 (FIG. 6B)
20 cell lines against 1 nM of the most potent HAT-BCL6 TCIP, MNN-03-038. Cells were treated with compounds for 72 hours.

 FIGS. 7A-7G show results assaying repression of the oncoprotein c-MYC, by: (FIG. 7A) Western blot measuring protein levels of c-MYC, BCL6, CBP, and p300 after 4 hours of MNN-03-038 (TCIP3) treatment in SUDHL5 cells. Representative of 3 biological replicates. (FIG. 7B) Quantification of Western blot in FIG. 7A, mean $\pm$ s.d., n=3 biological replicates. (FIG. 7C) Western blot of time-dependent change in c-MYC protein after 1 nM of MNN-03-038 (TCIP3) in SUDHL5 cells; representative of 3 biological replicates. (FIG. 7D) Quantification of Western blot in FIG. 7C overlaid with RT-qPCR measurement of c-MYC mRNA time-dependent changes after 1 nM of MNN-03-038 (TCIP3) in SUDHL5 cells; half-life of repression calculated by fit to
25 a one-phase exponential decay; mean $\pm$ s.d., n=3 biological replicates. (FIG. 7E) All differential transcripts quantified by RNA-seq after 1 nM TCIP3 treatment in SUDHL5 cells; 3 biological
30

replicates; P-values computed by two-sided Wald test and adjusted for multiple comparisons by Benjamini-Hochberg. (FIG. 7F) RT-qPCR quantification of c-MYC mRNA comparing 1 nM MNN-03-038 (TCIP3) treatment with 1 nM GNE-781 and 1 nM BI-3812 treatment in SUDHL5 cells. mean $\pm$ s.d., n=3 biological replicates. (FIG. 7G) RT-qPCR quantification of c-MYC mRNA comparing 1 nM MNN-03-038 (TCIP3) treatment in lymphoma cell lines with increasing amounts of BCL6. mean $\pm$ s.d., n=3 biological replicates.

FIGS. 8A-8F show cytotoxicity and ternary complex formation activity by: (FIG. 8A) 72-hour viability curves of MNN-03-038 (TCIP3) and inhibitors in SUDHL5 cells; mean $\pm$ s.d.; n = 3 biological replicates. (FIG. 8B) IC₅₀ values of a 72-hour viability assay in SUDHL5 cells for all synthesized TCIPs. (FIG. 8C) Activation of BCL6 reporter upon treatment with MNN-03-038 (TCIP3) and inhibitors; mean $\pm$ s.d.; n=3 biological replicates. (FIG. 8D) TR-FRET assay depicting ternary complex formation between recombinant p300-Bromodomain-His and BCL6-BTB-domain proteins after 1 hour co-incubation with TCIP molecules. (FIG. 8E) Competitive titration of p300/CBP inhibitors (GNE-781 or SGC-CBP-30) or BCL6 inhibitors (BI-3812, GSK 137, or CCT373566) against MNN-03-038 (TCIP3) (1 nM) in SUDHL5 cells for 72 hours; mean $\pm$ s.d.; n = 2-3 biological replicates. (FIG. 8F) 72-hour viability curves of MNN-03-038 (TCIP3) or GNE-781 + BI-3812 treatment in four DLBCL cell lines in order of decreasing BCL6 levels.

DETAILED DESCRIPTION

The fact that the biochemical pathways used to drive cancer co-exist in the same cell with the programmed cell death pathways that efficiently kill cells raises the possibility that one could rewire the cellular biochemical circuitry such that the cancer cell kills itself using the biochemical pathway initiated by the cancer driver. Disclosed herein is a class of small molecules (Transcriptional/Epigenetic Chemical Inducers of Proximity, or TCIPs) that rewire the biochemical circuitry of the cell to activate pathways not normally under the control of the first pathway, in this case the cancer driver. The operation of these molecules is shown in FIG. 1 by the gray arrow linking the cancer driver and its dependent biochemical pathways to the cell death pathways initiated, in this case by DNA replication damage or developmental errors. The general structure of a TCIP that recruits the transcriptional activator, histone acetyl transferase to the promoters of cell death genes bound by BCL6 is shown in FIG. 2.

TCIPs borrow only a fraction of the target protein and use it to activate the transcription. For example, as shown in FIG. 3, only a fraction of the total HAT is used. By borrowing only a small amount of the target protein rather than inhibiting it all, TCIPs can avoid mechanism-based toxicity associated with complete inhibition or removal of the target. This is generally illustrated in FIG. 3.

Disclosed herein are highly potent TCIPs for the treatment of cancers, such as human Diffuse Large Cell B Cell Lymphoma (DLCL). BCL6 represses pro-apoptotic genes by binding histone deacetylase. Recruitment of a histone acetyl transferase might therefore activate these repressed genes. Compounds such as B-I3812 bind to the BTB-domain of BCL6 and prevent binding of histone deacetylase. Thus, compounds disclosed herein were designed to bind the BTB-domain of BCL6, and are linked chemically to an entity that bind the histone acetyl transferases (HATs) Ep300 and CBP.

Definitions

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. In case of conflict, the present document, including definitions, will control.

Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Sorrell, Organic Chemistry, 2nd edition, University Science Books, Sausalito, 2006; Smith, March's Advanced Organic Chemistry: Reactions, Mechanism, and Structure, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Larock, Comprehensive Organic Transformations, 3rd Edition, John Wiley & Sons, Inc., New York, 2018; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987.

As used herein, the modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (for example, it includes at least the degree of error associated with the measurement of the particular quantity). The modifier "about" should also be considered as disclosing the range defined by the absolute values of the two

endpoints. For example, the expression “from about 2 to about 4” also discloses the range “from 2 to 4.” The term “about” may refer to $\pm 10\%$ of the indicated number. For example, “about 10%” may indicate a range of 9% to 11%, and “about 1” may mean from 0.9 - 1.1. Other meanings of “about” may be apparent from the context, such as rounding off; for example, “about 1” may
5 also mean from 0.5 to 1.4.

As used herein, the term “alkyl” refers to a radical of a straight or branched saturated hydrocarbon chain. The alkyl chain can include, e.g., from 1 to 24 carbon atoms (C₁-C₂₄ alkyl), 1 to 16 carbon atoms (C₁-C₁₆ alkyl), 1 to 14 carbon atoms (C₁-C₁₄ alkyl), 1 to 12 carbon atoms (C₁-C₁₂ alkyl), 1 to 10 carbon atoms (C₁-C₁₀ alkyl), 1 to 8 carbon atoms (C₁-C₈ alkyl), 1 to 6 carbon
10 atoms (C₁-C₆ alkyl), 1 to 4 carbon atoms (C₁-C₄ alkyl), 1 to 3 carbon atoms (C₁-C₃ alkyl), or 1 to 2 carbon atoms (C₁-C₂ alkyl). Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, and n-dodecyl.

As used herein, the term “alkenyl” refers to a radical of a straight or branched hydrocarbon chain containing at least one carbon-carbon double bond and no triple bonds. The double bond(s) may be located at any position(s) with the hydrocarbon chain. The alkenyl chain can include, e.g., from 2 to 24 carbon atoms (C₂-C₂₄ alkenyl), 2 to 16 carbon atoms (C₂-C₁₆ alkenyl), 2 to 14 carbon atoms (C₂-C₁₄ alkenyl), 2 to 12 carbon atoms (C₂-C₁₂ alkenyl), 2 to 10
20 carbon atoms (C₂-C₁₀ alkenyl), 2 to 8 carbon atoms (C₂-C₈ alkenyl), 2 to 6 carbon atoms (C₂-C₆ alkenyl), 2 to 4 carbon atoms (C₂-C₄ alkenyl), 2 to 3 carbon atoms (C₂-C₃ alkenyl), or 2 carbon atoms (C₂ alkenyl). Representative examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, butadienyl, 2-methyl-2-propenyl, 3-butenyl, pentenyl, pentadienyl, hexenyl, heptenyl, octenyl, octatrienyl, and the like.

As used herein, the term “alkynyl” means a radical of a straight or branched hydrocarbon chain containing at least one carbon-carbon triple bond. The alkynyl chain can include, e.g., from 2 to 24 carbon atoms (C₂-C₂₄ alkynyl), 2 to 16 carbon atoms (C₂-C₁₆ alkynyl), 2 to 14 carbon atoms (C₂-C₁₄ alkynyl), 2 to 12 carbon atoms (C₂-C₁₂ alkynyl), 2 to 10 carbon atoms (C₂-C₁₀ alkynyl), 2 to 8 carbon atoms (C₂-C₈ alkynyl), 2 to 6 carbon atoms (C₂-C₆ alkynyl), 2 to 4 carbon
30 atoms (C₂-C₄ alkynyl), 2 to 3 carbon atoms (C₂-C₃ alkynyl), or 2 carbon atoms (C₂ alkynyl). The triple bond(s) may be located at any position(s) with the hydrocarbon chain. Representative

examples of alkynyl include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, and the like.

As used herein, the term “alkoxy” refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy
5 include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, and tert-butoxy.

As used herein, the term “amino” refers to a group $-NR_xR_y$, wherein R_x and R_y are selected from hydrogen and alkyl (e.g., C_1 - C_4 alkyl). A group $-NH(\text{alkyl})$ may be referred to herein as “alkylamino” and a group $-N(\text{alkyl})_2$ may be referred to herein as “dialkylamino.”

As used herein, the term “aryl” refers to a radical of a monocyclic, bicyclic, or tricyclic
10 $4n+2$ aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms (“ C_6 - C_{14} aryl”). In some embodiments, an aryl group has six ring carbon atoms (“ C_6 aryl,” i.e., phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“ C_{10} aryl,” e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some
15 embodiments, an aryl group has fourteen ring carbon atoms (“ C_{14} aryl,” e.g., anthracenyl and phenanthrenyl).

As used herein, the term “arylene” refers to a divalent aryl radical.

As used herein, the term “cycloalkyl” refers to a radical of a saturated carbocyclic ring system containing three to ten carbon atoms and zero heteroatoms. The cycloalkyl may be monocyclic, bicyclic, bridged, fused, or spirocyclic. Representative examples of cycloalkyl
20 include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl, and bicyclo[5.2.0]nonanyl.

As used herein, the term “cycloalkylene” refers to a divalent cycloalkyl radical.

As used herein, the term “cyano” refers to a $-CN$ group.

25 As used herein, the term “halogen” or “halo” refers to F, Cl, Br, or I.

As used herein, the term “haloalkyl” refers to an alkyl group, as defined herein, in which at least one hydrogen atom (e.g., one, two, three, four, five, six, seven or eight hydrogen atoms) is replaced with a halogen. In some embodiments, each hydrogen atom of the alkyl group is replaced with a halogen (“perhaloalkyl”). Representative examples of haloalkyl include, but are
30 not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, and 3,3,3-trifluoropropyl.

As used herein, the term “haloalkoxy” refers to a haloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of haloalkoxy include, but are not limited to, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

5 As used herein, the term “heteroalkyl” refers to an alkyl group, as defined herein, in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with a heteroatom group such as -NH-, -O-, -S-, -S(O)-, -S(O)₂-, -OP(O)(O⁺)O-, or the like. By way of example, 1, 2, 3, 4, 5, 6, or more carbon atoms may be independently replaced with the same or different heteroatom group. A heteroalkyl group can
10 also include one or more carbonyl moieties (i.e., wherein a carbon atom of the alkyl group is oxidized to a -C(O)- group).

As used herein, the term “heteroaryl” refers to a radical of a 5-10 membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently
15 selected from nitrogen, oxygen and sulfur (“5-10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on
20 the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolyl, carbazolyl, and the like) the point of attachment can be on either ring, i.e., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl). Exemplary 5-
25 membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl
30 groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl.

Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indoliziny, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

As used herein, the term “heteroarylene” refers to a divalent heteroaryl radical.

As used herein, the term “heterocyclyl” refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3-10 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups wherein the point of attachment is either on the cycloalkyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. A heterocyclyl group may be described as, e.g., a 3-7-membered heterocyclyl, wherein the term “membered” refers to the non-hydrogen ring atoms, i.e., carbon, nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, within the moiety. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, and thiorenyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without

limitation, azetidiny, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without

5 limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl (e.g., 2,2,6,6-tetramethylpiperidinyl), tetrahydropyranyl, dihydropyridinyl, pyridinonyl (e.g., 1-methylpyridin-

10 2-onyl), and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, pyridazinonyl (2-methylpyridazin-3-onyl), pyrimidinonyl (e.g., 1-methylpyrimidin-2-onyl, 3-methylpyrimidin-4-onyl), dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without

15 limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclyl ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 5-

20 membered heterocyclyl groups fused to a heterocyclyl ring (also referred to herein as a 5,5-bicyclic heterocyclyl ring) include, without limitation, octahydropyrrolopyrrolyl (e.g., octahydropyrrolo[3,4-c]pyrrolyl), and the like. Exemplary 6-membered heterocyclyl groups fused to a heterocyclyl ring (also referred to as a 4,6-membered heterocyclyl ring) include, without limitation, diazaspiro[3.5]nonanyl (e.g., 2,7-diazaspiro[3.5]nonanyl). Exemplary 6-membered

25 heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclyl ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like. Exemplary 6-membered heterocyclyl groups fused to a cycloalkyl ring (also referred to herein as a 6,7-bicyclic heterocyclyl ring) include, without limitation, azabicyclooctanyl (e.g., (1,5)-8-azabicyclo[3.2.1]octanyl). Exemplary 6-membered heterocyclyl groups fused to a cycloalkyl ring

30 (also referred to herein as a 6,8-bicyclic heterocyclyl ring) include, without limitation, azabicyclononanyl (e.g., 9-azabicyclo[3.3.1]nonanyl).

As used herein, the term “heterocyclylene” refers to a divalent heterocyclyl radical.

As used herein, the term “hydroxy” or “hydroxyl” refers to an -OH group.

As used herein, the term “nitro” refers to an -NO₂ group.

When a group or moiety can be substituted, the term “substituted” indicates that one or
5 more (e.g., 1, 2, 3, 4, 5, or 6; in some embodiments 1, 2, or 3; and in other embodiments 1 or 2)
hydrogens on the group indicated in the expression using “substituted” can be replaced with a
selection of recited indicated groups or with a suitable substituent group known to those of skill
in the art (e.g., one or more of the groups recited below), provided that the designated atom’s
normal valence is not exceeded. Substituent groups include, but are not limited to, alkyl, alkenyl,
10 alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester,
cyano, cycloalkyl, cycloalkenyl, guanidino, halo, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl,
heterocyclyl, hydroxy, hydrazino, imino, oxo, nitro, phosphate, phosphonate, sulfonic acid, thiol,
thione, or combinations thereof.

As used herein, in chemical structures the indication:

15 

represents a point of attachment of one moiety to another moiety (e.g., a substituent group to the
rest of the compound).

For compounds described herein, groups and substituents thereof may be selected in
accordance with permitted valence of the atoms and the substituents, such that the selections and
20 substitutions result in a stable compound, e.g., which does not spontaneously undergo
transformation such as by rearrangement, cyclization, elimination, etc.

When substituent groups are specified by their conventional chemical formulae, written
from left to right, such indication also encompass substituent groups resulting from writing the
structure from right to left. For example, if a bivalent group is shown as -CH₂O-, such indication
25 also encompasses -OCH₂-; similarly, -OC(O)NH- also encompasses -NHC(O)O-. When linker
moieties are shown, the linkers can be attached to other moieties of the compound in either
direction.

The terms “administer,” “administering,” or “administration,” as used herein refer to
implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound or a
30 pharmaceutical composition.

As used herein, the terms “condition,” “disease,” and “disorder” are used interchangeably.

An “effective amount” of a compound or composition refers to an amount sufficient to elicit a desired biological response (e.g., treating a condition). As will be appreciated by those skilled in the art, the effective amount of a compound may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. For example, in treating cancer, an effective amount of a compound or composition may reduce tumor burden or stop the growth or spread of a tumor.

A “therapeutically effective amount” of a compound or composition is an amount sufficient to provide a therapeutic benefit in the treatment of a condition, or to delay or minimize one or more symptoms associated with the condition. In some embodiments, a therapeutically effective amount is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, that provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

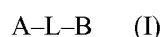
A “subject” to which administration is contemplated includes, but is not limited to, a human (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult, or senior adult)) and/or other non-human animals, for example, mammals (e.g., primates (e.g., cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (e.g., commercially relevant birds such as chickens, ducks, geese, and/or turkeys).

As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or condition, or one or more signs or symptoms thereof. In some embodiments, “treatment,” “treat,” and “treating” require that signs or symptoms of the disease disorder or condition have developed or have been

observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

Compounds

Disclosed herein is a compound of formula (I):



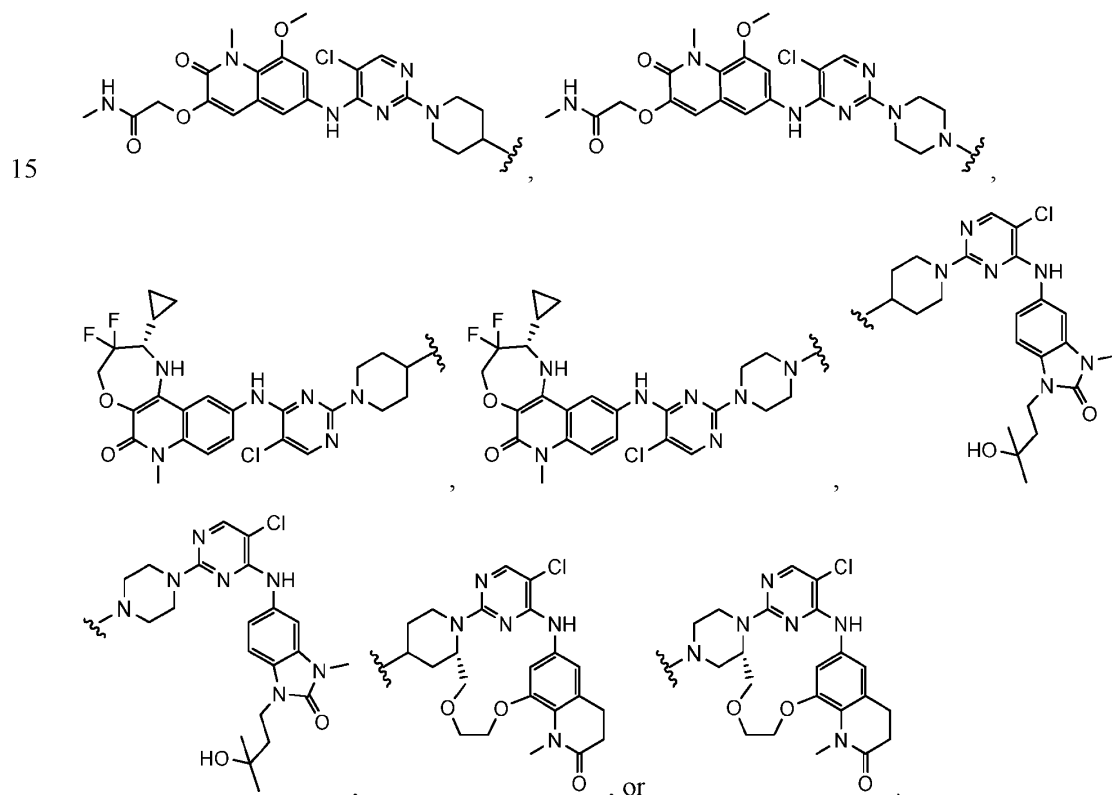
or a pharmaceutically acceptable salt thereof, wherein:

10 A is a BCL6-binding moiety;

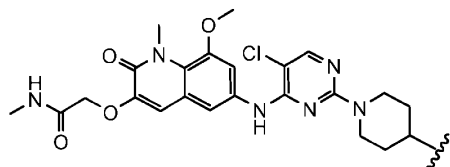
L is a linker; and

B is a moiety that binds to the bromodomain of a histone acetyltransferase.

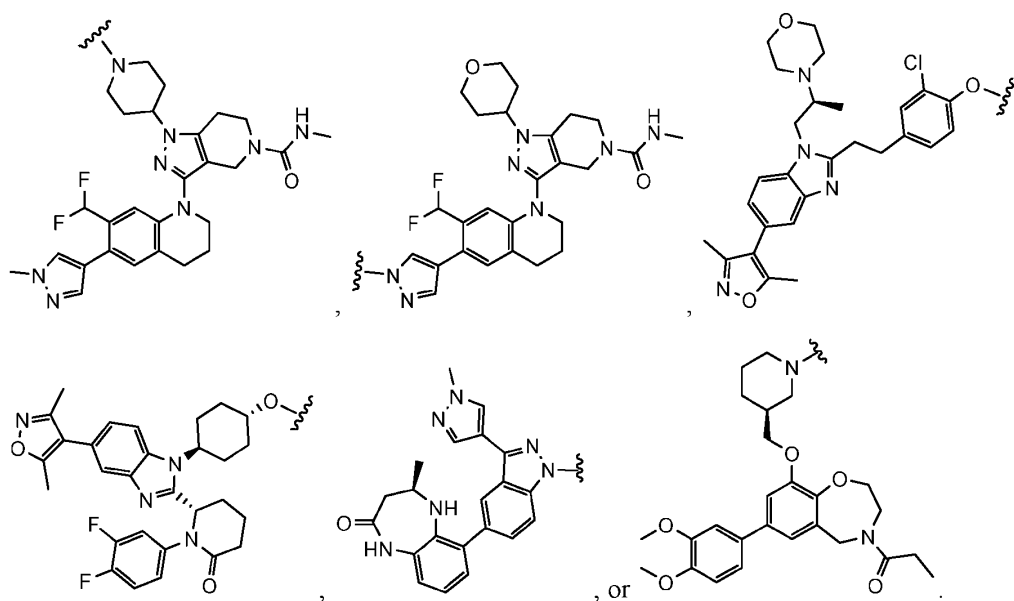
The moiety A is a BCL6-binding moiety. In some embodiments, A is a moiety of formula:



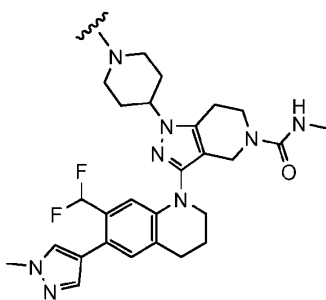
In some embodiments, A is a moiety of formula:



The moiety B is a moiety that binds to the bromodomain of a histone acetyltransferase. In some embodiments, B is a moiety that binds to the bromodomain of p300 or CBP. In some
5 embodiments, B is a moiety of formula:

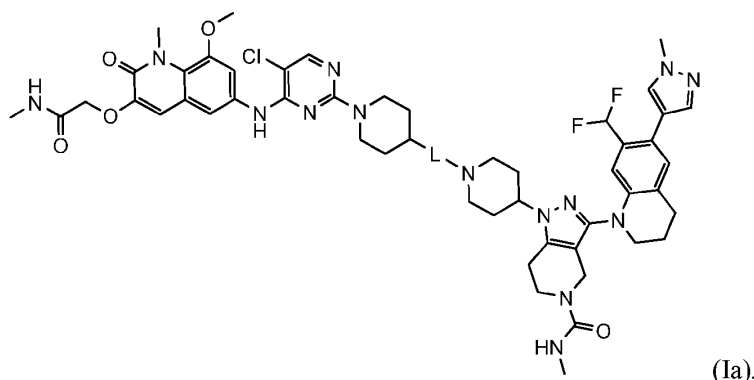


In some embodiments, B is a moiety of formula:



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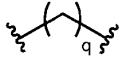
In some embodiments, the compound of formula (I) is a compound of formula (Ia):

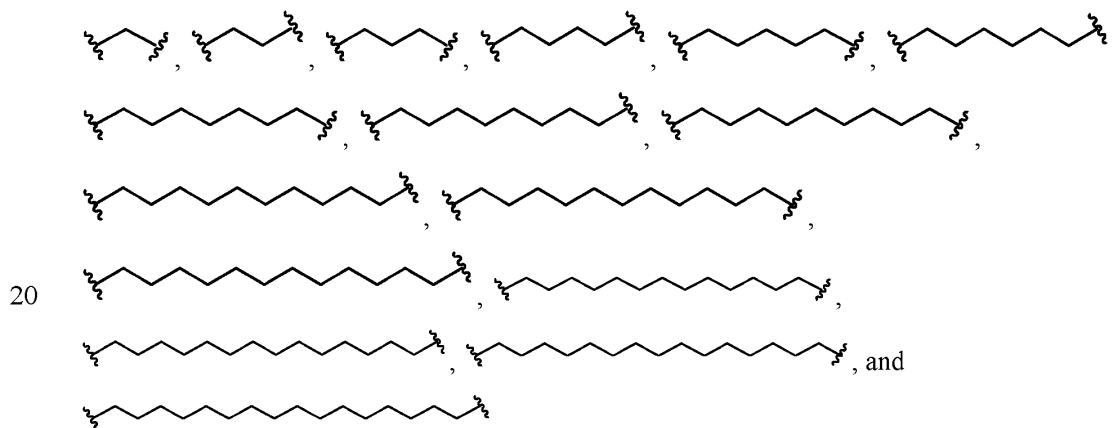


or a pharmaceutically acceptable salt thereof.

L is a linker, which provides a covalent attachment between the A and B moieties. The exact structure of linker may not be critical in some embodiments, provided it is substantially non-interfering with the activities of the BCL6-binding moiety or the moiety that binds to the bromodomain of the HAT. In some embodiments, L is a direct bond. In other embodiments, L comprises any combination of -CH₂-, -CH=CH-, -C≡C-, -O-, -NR'-, -BR'-, -S-, -C(O)-, -C(NR')-, -S(O)-, -S(O)₂-, arylene, heteroarylene, cycloalkylene, and heterocyclylene moieties, wherein R' is selected from hydrogen and C₁-C₆ alkyl, and wherein the arylene, heteroarylene, cycloalkylene, and heterocyclylene moieties are independently unsubstituted or substituted with 1, 2, or 3 substituents.

In some embodiments, the linker comprises an alkylene chain (e.g., having 2-20 -CH₂- units). In other embodiments, the linker comprises an alkylene chain that is interrupted by, and/or terminated by (at either or both termini), at least one group selected from -O-, -S-, -N(R')-, -CH=CH-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(CH₃)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, C₃-C₁₂ cycloalkylene, 3- to 12-membered heterocyclylene, 5- to 10-membered arylene, 5- to 12-membered heteroarylene, or any combination thereof, wherein each R' is independently selected from hydrogen and C₁-C₆ alkyl, and wherein the interrupting and terminating groups may be the same or different.

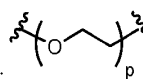
In some embodiments, L comprises an alkylene chain: , wherein q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16. In some embodiments, q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12. For example in some embodiments, q is 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 2-16, 2-15, 2-14, 2-13, 2-12, 2-11, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-16, 3-15, 3-14, 3-13, 3-12, 3-11, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-16, 4-15, 4-14, 4-13, 4-12, 4-11, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-16, 5-15, 5-14, 5-13, 5-12, 5-11, 5-10, 5-9, 5-8, 5-7, 5-6, 6-16, 6-15, 6-14, 6-13, 6-12, 6-11, 6-10, 6-9, 6-8, 6-7, 7-16, 7-15, 7-14, 7-13, 7-12, 7-11, 7-10, 7-9, 7-8, 8-16, 8-15, 8-14, 8-13, 8-12, 8-11, 8-10, 8-9, or 9-16, 9-15, 9-14, 9-13, 9-12, 9-11, 9-10, 10-16, 10-15, 10-14, 10-13, 10-12, 10-11, 11-16, 11-15, 11-14, 11-13, 11-12, 12-16, 12-15, 12-14, 12-13, 13-16, 13-15, 13-14, 14-16, 14-15, and 15-16. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4. In some embodiments, q is 5. In some embodiments, q is 6. In some embodiments, q is 7. In some embodiments, q is 8. In some embodiments, q is 9. In some embodiments, q is 10. In some embodiments, q is 11. In some embodiments, q is 12. In some embodiments, q is 13. In some embodiments, q is 14. In some embodiments, q is 15. In some embodiments, q is 16. Specific examples of alkylene chains, include:

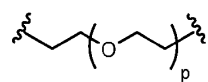


In some embodiments, L comprises an alkylene chain interrupted by a functional group, such as -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(CH₃)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -

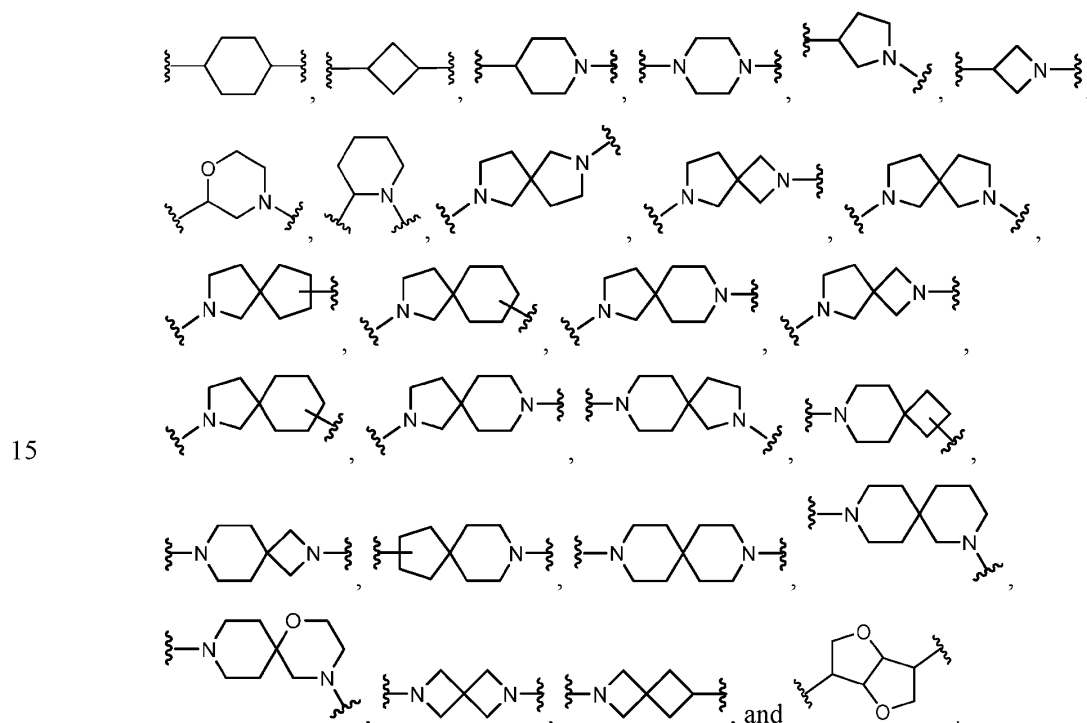
S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, or -N(R')S(O)N(R')-.

In some embodiments, L comprises one or more alkylene glycol repeat units, such as ethylene glycol or propylene glycol repeat units. For example, in some embodiments, L

5 comprises a poly- or oligo-ethylene glycol chain:  , wherein p is 1, 2, 3, 4, 5, or 6. In

some embodiments, L comprises a group of formula:  , wherein p is 1, 2, 3, 4, 5, or 6. In some embodiments, p is 1-6, 1-5, 1-4, 1-3, 1-2, 2-6, 2-5, 2-4, 2-3, 3-6, 3-5, 3-4, 4-6, 4-6, or 5-6. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6.

10 In some embodiments, L comprises one or more cycloalkylene or heterocyclylene groups, non-limiting examples of which include:



In some embodiments, L comprises a cycloalkylene or heterocyclylene group, such as one of the above-illustrated cycloalkylene and heterocyclylene groups, with one or more

additional groups on one or both termini, wherein the additional groups are independently selected from -CH₂-, -O-, -S-, -N(R')-, -CH=CH-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(CH₃)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, and -N(R')S(O)N(R')-, or any combination thereof, wherein each R' is independently selected from hydrogen and C₁-C₆ alkyl. In some embodiments, L comprises a cycloalkylene or heterocyclylene group, such as one of the above-illustrated cycloalkylene and heterocyclylene groups, with one or more additional groups on one or both termini, wherein the additional groups are independently selected from -CH₂-, -C(O)-, -NH-, and -O-.

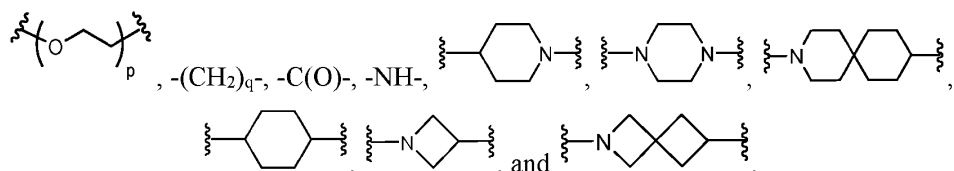
In some embodiments, L comprises two or more cycloalkylene or heterocyclylene groups, such as two or three cycloalkylene or heterocyclylene groups independently selected from those illustrated above, connected to each other via covalent bonds or one or linking groups, optionally with one or more additional linking group son one or both termini, wherein the linking groups are independently selected from -O-, -S-, -N(R')-, -CH₂-, -CH=CH-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(CH₃)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, and -N(R')S(O)N(R')-, or any combination thereof, wherein each R' is independently selected from hydrogen and C₁-C₆ alkyl. In some embodiments, L comprises two or more cycloalkylene or heterocyclylene groups, such as two or three cycloalkylene or heterocyclylene groups independently selected from those illustrated above, connected to each other via covalent bonds or one or linking groups, optionally with one or more additional linking group son one or both termini, wherein the linking groups are independently selected from -O- and -CH₂-.

In some embodiments, L comprises one or more cycloalkylene or heterocyclylene groups that are substituted with 1, 2, or 3 substituents, e.g., substituents independently selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, halo, hydroxy, and the like. In some embodiments, L comprises one or more cycloalkylene or heterocyclylene groups that are substituted with 1, 2, or

3 substituents independently selected from C₁-C₄ alkyl and halo. In some embodiments, L comprises one or more cycloalkylene or heterocyclylene groups that are substituted with 1, 2, or 3 substituents independently selected from methyl and fluoro.

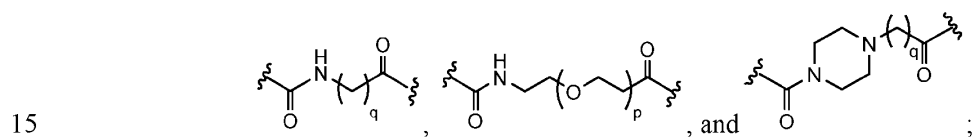
In some embodiments, L is a direct bond or comprises any combination of -CH₂-, -CH=CH-, -C≡C-, -O-, -NR'-, -BR'-, -S-, -C(O)-, -C(NR')-, -S(O)-, -S(O)₂-, arylene, heteroarylene, cycloalkylene, and heterocyclylene moieties, wherein the arylene, heteroarylene, cycloalkylene, and heterocyclylene moieties are independently unsubstituted or substituted with 1, 2, or 3 substituents. In some embodiments, L is a direct bond or comprises any combination of -CH₂-, -O-, -C(O)-, -NH-, -N(CH₃)-, cycloalkylene, and heterocyclylene moieties.

10 In some embodiments, L comprises any combination of the following moieties:



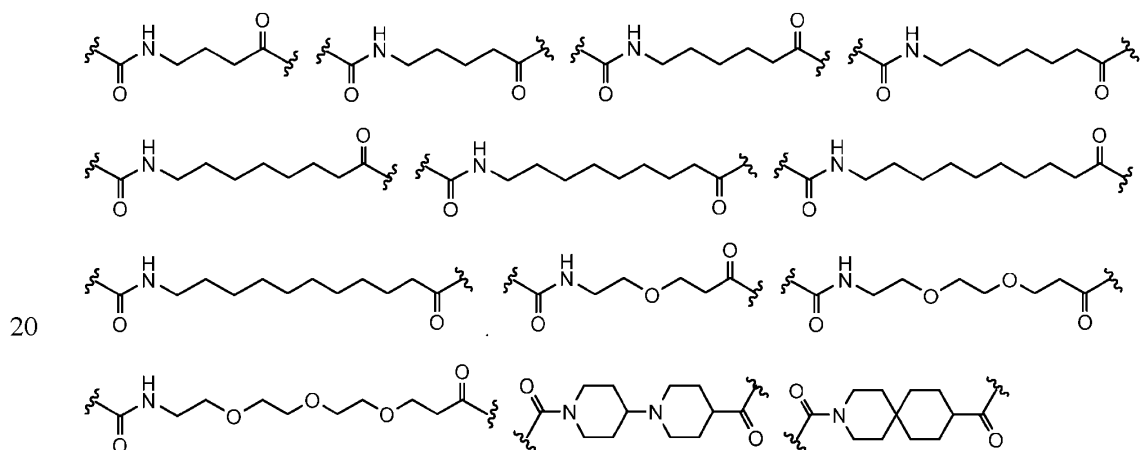
wherein p is 1, 2, 3, 4, 5, or 6; and q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

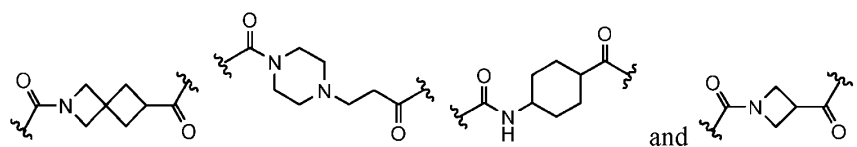
In some embodiments, L has a formula selected from:



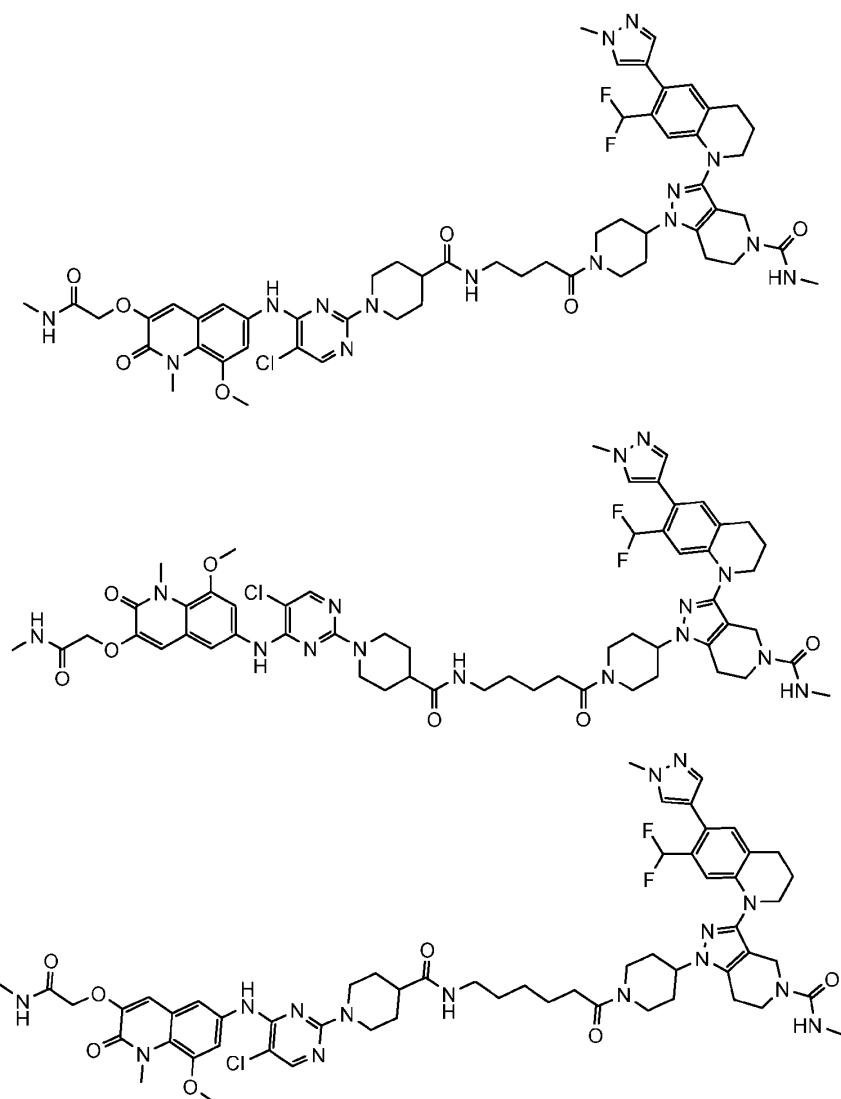
wherein p is 1, 2, 3, 4, 5, or 6; and q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

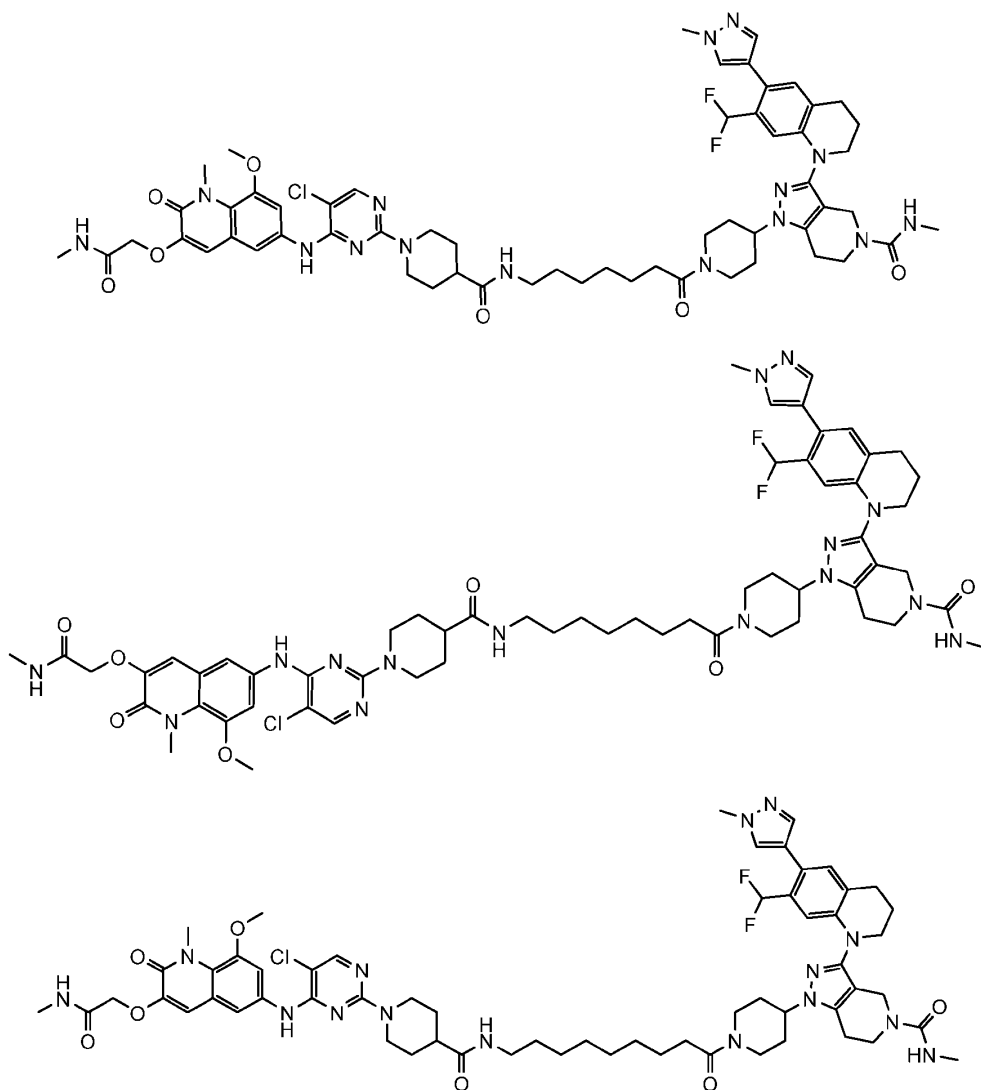
In some embodiments, L has a formula selected from:

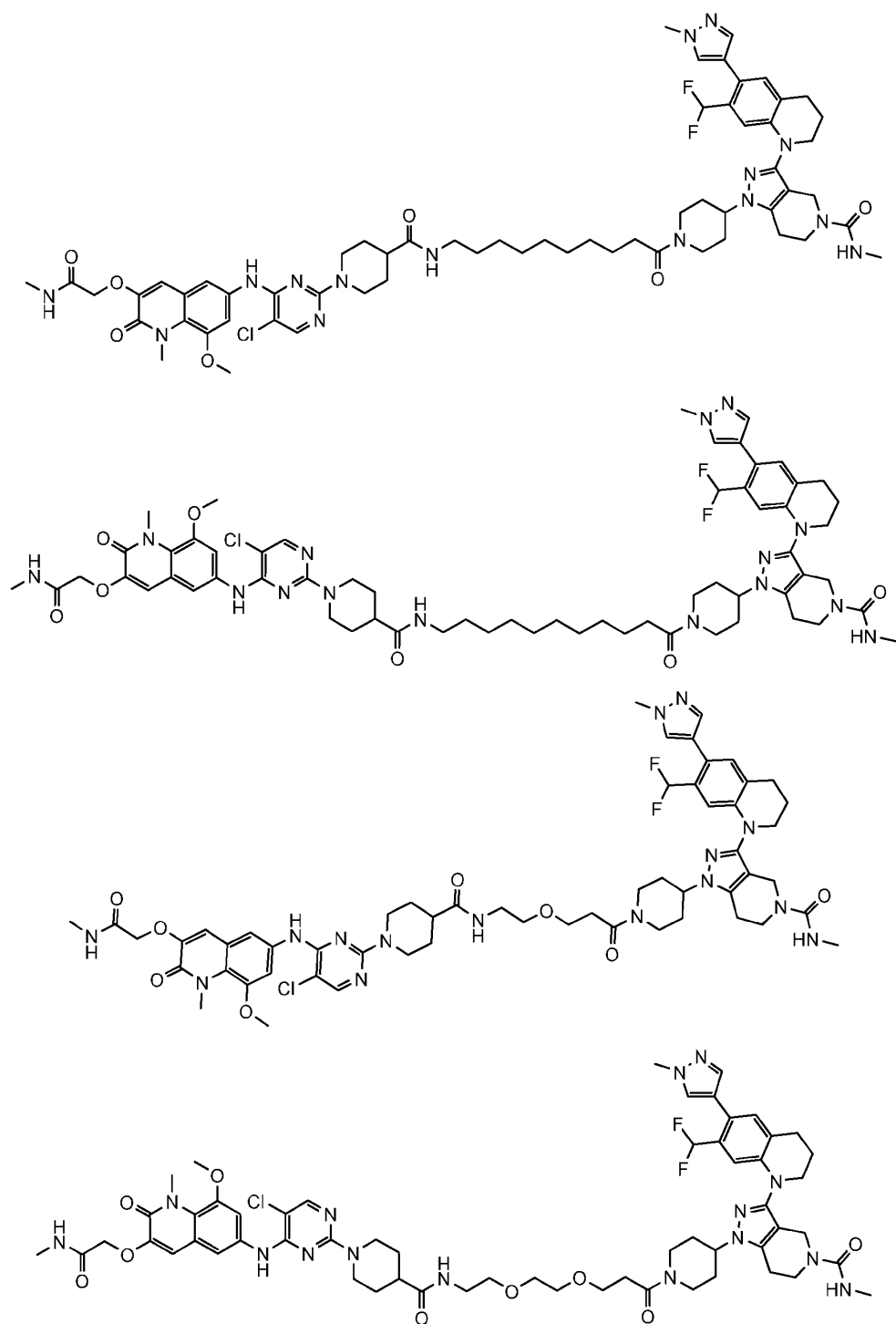


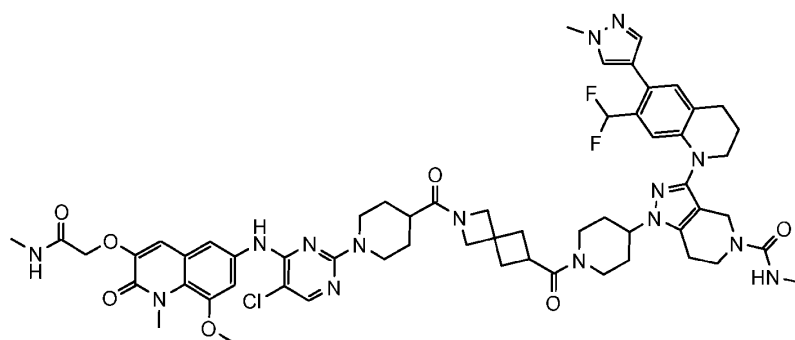


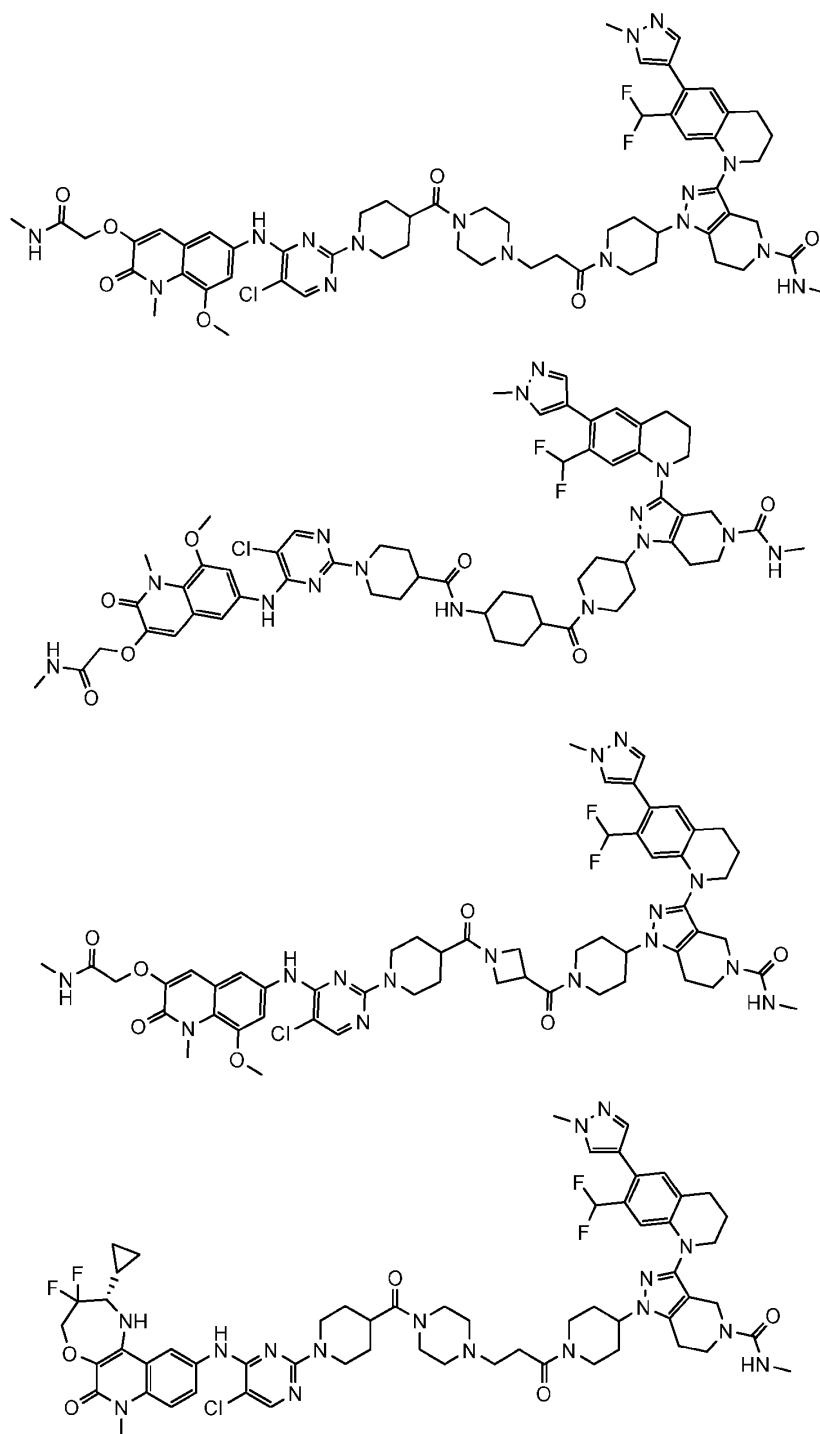
In some embodiments, the compound of formula (I) is selected from:











and pharmaceutically acceptable salts thereof.

When discussing certain features or properties of compounds of formula (I) herein, or compositions, methods, or kits comprising compounds of formula (I), it is understood that such reference also includes compounds of formula (Ia), and to specific exemplary compounds disclosed herein.

The compound may exist as a stereoisomer wherein asymmetric or chiral centers are present. The stereoisomer is “R” or “S” depending on the configuration of substituents around the chiral carbon atom. The terms “R” and “S” used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, in *Pure Appl. Chem.* 1976, 45: 13-30. Various stereoisomers and mixtures thereof are specifically included within the scope of this disclosure. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of the compounds may be prepared synthetically from commercially available starting materials, which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by methods of resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by: (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and optional liberation of the optically pure product from the auxiliary as described in Furniss, Hannaford, Smith, and Tatchell, “Vogel's Textbook of Practical Organic Chemistry,” 5th edition (1989), Longman Scientific & Technical, Essex CM202JE, England; (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns; or (3) fractional recrystallization methods.

It should be understood that the compounds may exist in different tautomeric forms, and all such forms are included within the scope of the disclosure.

The present disclosure also includes an isotopically-labeled compound, which is identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Substitution with heavier isotopes such as deuterium (^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage

requirements and, hence, may be preferred in some circumstances. The compound may incorporate positron-emitting isotopes for medical imaging and positron-emitting tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of formula (I) are ^{11}C , ^{13}N , ^{15}O , and ^{18}F . Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using appropriate isotopically-labeled reagent in place of non-isotopically-labeled reagent.

Compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure encompass both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

a. Pharmaceutically Acceptable Salts

The disclosed compounds may exist as pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to salts or zwitterions of the compounds which are water or oil-soluble or dispersible, suitable for treatment of disorders without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit/risk ratio and effective for their intended use. The salts may be prepared during the final isolation and purification of the compounds or separately by reacting an amino group of the compounds with a suitable acid. For example, a compound may be dissolved in a suitable solvent, such as but not limited to methanol and water and treated with at least one equivalent of an acid, like hydrochloric acid. The resulting salt may precipitate out and be isolated by filtration and dried under reduced pressure. Alternatively, the solvent and excess acid may be removed under reduced pressure to provide a salt. Representative salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, isethionate, fumarate, lactate, maleate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, oxalate, maleate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, glutamate, para-toluenesulfonate, undecanoate, hydrochloric,

hydrobromic, sulfuric, phosphoric, and the like. Amino groups of the compounds may also be quaternized with alkyl chlorides, bromides and iodides such as methyl, ethyl, propyl, isopropyl, butyl, lauryl, myristyl, stearyl and the like.

Basic addition salts may be prepared during the final isolation and purification of the disclosed compounds by reaction of a carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation such as lithium, sodium, potassium, calcium, magnesium, or aluminum, or an organic primary, secondary, or tertiary amine. Quaternary amine salts can be prepared, such as those derived from methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine and N,N'-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like.

b. Methods of Synthesis

In another aspect, disclosed herein are methods for making compounds of formula (I), or a pharmaceutically acceptable salt thereof. Broadly, the compounds of formula (I) and pharmaceutically acceptable salts thereof can be prepared by any process known to be applicable to the preparation of chemically related compounds. Exemplary suitable synthetic schemes are provided in the Examples section.

The compounds and intermediates may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for example in "Vogel's Textbook of Practical Organic Chemistry," 5th edition (1989), by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

Reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the reactants used. Reactions can be worked up in a conventional manner, e.g., by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to,

crystallization, distillation, extraction, trituration and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature.

5 Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that cannot be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method, are included in the scope of the disclosure. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable
10 protecting groups are well known to those skilled in the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book titled Protective Groups in Organic Synthesis (4th ed.), John Wiley & Sons, NY (2006).

 When an optically active form of a disclosed compound is required, it can be obtained by carrying out one of the procedures described herein using an optically active starting material
15 (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

 Similarly, when a pure geometric isomer of a compound is required, it can be obtained by carrying out one of the procedures described herein using a pure geometric isomer as a starting
20 material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

 The synthetic schemes and specific examples as described are illustrative and are not to be read as limiting the scope of the disclosure or the claims. Alternatives, modifications, and equivalents of the synthetic methods and specific examples are contemplated.

25 Pharmaceutical Compositions

 The disclosed compounds may be incorporated into pharmaceutical compositions suitable for administration to a subject (such as a patient, which may be a human or non-human). The pharmaceutical compositions may include a "therapeutically effective amount" or a
30 "prophylactically effective amount" of the agent. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the composition may be determined by a

person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of a compound of the disclosure are outweighed by the therapeutically beneficial effects.

- 5 A “prophylactically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease or condition, the prophylactically effective amount will be less than the therapeutically effective amount.

The pharmaceutical compositions may include pharmaceutically acceptable carriers. The
10 term “pharmaceutically acceptable carrier,” as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium
15 carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such as propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and
20 aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

- 25 Thus, the compounds and their pharmaceutically acceptable salts may be formulated for administration by, for example, solid dosing, eye drop, in a topical oil-based formulation, injection, inhalation (either through the mouth or the nose), implants, or oral, buccal, parenteral, or rectal administration. Techniques and formulations may generally be found in “Remington’s Pharmaceutical Sciences,” (Meade Publishing Co., Easton, Pa.). Therapeutic compositions must
30 typically be sterile and stable under the conditions of manufacture and storage.

The route by which the disclosed compounds are administered and the form of the composition will dictate the type of carrier to be used. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, implants, or parenteral) or topical administration (e.g., dermal, pulmonary, nasal, aural, ocular, liposome delivery systems, or iontophoresis).

Carriers for systemic administration typically include at least one of diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, antioxidants, preservatives, glidants, solvents, suspending agents, wetting agents, surfactants, combinations thereof, and others. All carriers are optional in the compositions.

Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of diluent(s) in a systemic or topical composition is typically about 50 to about 90% by weight of the composition.

Suitable lubricants include silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of lubricant(s) in a systemic or topical composition is typically about 5 to about 10% by weight of the composition.

Suitable binders include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of binder(s) in a systemic composition is typically about 5 to about 50% by weight of the composition.

Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of disintegrant(s) in a systemic or topical composition is typically about 0.1 to about 10% by weight of the composition.

Suitable colorants include a colorant such as an FD&C dye. When used, the amount of colorant in a systemic or topical composition is typically about 0.005 to about 0.1% by weight of the composition.

Suitable flavors include menthol, peppermint, and fruit flavors. The amount of flavor(s), when used, in a systemic or topical composition is typically about 0.1 to about 1.0%.

Suitable sweeteners include aspartame and saccharin. The amount of sweetener(s), when used, in a systemic or topical composition is typically about 0.001 to about 1% by weight of the composition.

Suitable antioxidants include butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of antioxidant(s) in a systemic or topical composition is typically about 0.1 to about 5% by weight of the composition.

Suitable preservatives include benzalkonium chloride, methyl paraben, and sodium benzoate. The amount of preservative(s) in a systemic or topical composition is typically about 0.01 to about 5% by weight of the composition.

Suitable glidants include silicon dioxide. The amount of glidant(s) in a systemic or topical composition is typically about 1 to about 5% by weight of the composition.

Suitable solvents include water, isotonic saline, ethyl oleate, glycerin, hydroxylated castor oils, alcohols such as ethanol, and phosphate buffer solutions. The amount of solvent(s) in a systemic or topical composition is typically from about 0 to about 100% by weight of the composition.

Suitable suspending agents include AVICEL RC-591 (from FMC Corporation of Philadelphia, PA) and sodium alginate. The amount of suspending agent(s) in a systemic or topical composition is typically about 1 to about 8% by weight of the composition.

Suitable surfactants include lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS from Atlas Powder Company of Wilmington, Delaware. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of surfactant(s) in the systemic or topical composition is typically about 0.1% to about 5% by weight of the composition.

Although the amounts of components in the systemic compositions may vary depending on the type of systemic composition prepared, in general, systemic compositions include 0.01% to 50% by weight of an active compound and 50% to 99.99% by weight of one or more carriers.

Compositions for parenteral administration typically include 0.1% to 10% by weight of actives and 90% to 99.9% by weight of a carrier including a diluent and a solvent.

Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms include a safe and effective amount, usually at least about 5% by weight, and more particularly from about 25% to about 50% by weight of actives. The oral dosage compositions include about 50% to about 95% by weight of carriers, and more particularly, from about 50% to about 75% by weight.

Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically include an active component, and a carrier comprising ingredients selected from diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, glidants, and combinations thereof. Specific diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmellose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain sweeteners such as aspartame and saccharin, or flavors such as menthol, peppermint, fruit flavors, or a combination thereof.

Capsules (including implants, time release and sustained release formulations) typically include an active compound (e.g., a compound of formula (I)), and a carrier including one or more diluents disclosed above in a capsule comprising gelatin. Granules typically comprise a disclosed compound, and preferably glidants such as silicon dioxide to improve flow characteristics. Implants can be of the biodegradable or the non-biodegradable type.

The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this disclosure.

Solid compositions may be coated by conventional methods, typically with pH or time-dependent coatings, such that a disclosed compound is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically include one or more components selected from the group consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose

phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Evonik Industries of Essen, Germany), waxes and shellac.

Compositions for oral administration can have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically include a disclosed compound and a carrier, namely, a carrier selected from diluents, colorants, flavors, sweeteners, preservatives, solvents, suspending agents, and surfactants. Peroral liquid compositions preferably include one or more ingredients selected from colorants, flavors, and sweeteners.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically include one or more of soluble filler substances such as diluents including sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Such compositions may further include lubricants, colorants, flavors, sweeteners, antioxidants, and glidants.

The disclosed compounds can be topically administered. Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions include: a disclosed compound (e.g., a compound of formula (I)), or a pharmaceutically acceptable salt thereof, and a carrier. The carrier of the topical composition preferably aids penetration of the compounds into the skin. The carrier may further include one or more optional components.

The amount of the carrier employed in conjunction with a disclosed compound is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this disclosure are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

A carrier may include a single ingredient or a combination of two or more ingredients. In the topical compositions, the carrier includes a topical carrier. Suitable topical carriers include

one or more ingredients selected from phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include

5 propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, and symmetrical alcohols.

The carrier of a topical composition may further include one or more ingredients selected from emollients, propellants, solvents, humectants, thickeners, powders, fragrances, pigments,

10 and preservatives, all of which are optional.

Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl

15 myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane. The amount of emollient(s)

20 in a skin-based topical composition is typically about 5% to about 95% by weight of the composition.

Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof. The amount of propellant(s) in a topical composition is typically about 0% to about 95% by weight of the composition.

Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Specific solvents include ethyl alcohol and homotopic alcohols. The amount of solvent(s) in a topical composition is typically about 0% to about 95% by weight of the

30 composition.

Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants include glycerin. The amount of humectant(s) in a topical composition is typically 0% to 95% by weight of the composition.

- 5 The amount of thickener(s) in a topical composition is typically about 0% to about 95% by weight of the composition.

Suitable powders include beta-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium
10 aluminum silicate, organically-modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. The amount of powder(s) in a topical composition is typically 0% to 95% by weight of the composition.

- 15 The amount of fragrance in a topical composition is typically about 0% to about 0.5%, particularly, about 0.001% to about 0.1% by weight of the composition.

Suitable pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of a topical pharmaceutical composition.

Methods of Use

- 20 The disclosed compounds and pharmaceutical compositions may be used in methods for treatment of disorders, including proliferative disorders such as cancers. In some embodiments, the cancer is characterized or mediated by the activity of BCL6. In some embodiments, the cancer is a cancer in which BCL6 and p300/CBP are expressed.

- 25 Accordingly, in some embodiments, disclosed herein is a method of treating a disorder in a subject in need thereof, wherein the disorder is characterized or mediated by activity of BCL6, or a cancer in which BCL6 and p300/CBP are expressed, the method comprising: administering to the subject a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (I) or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of formula (I) or a pharmaceutically acceptable salt thereof). In some embodiments, the disorder is a proliferative
30 disease, i.e., a disease that occurs due to abnormal growth or extension by the multiplication of cells. In some embodiments, the proliferative disease is cancer. The term “cancer” refers to a

class of diseases characterized by development of abnormal cells that proliferate uncontrollably and have the ability to infiltrate and destroy normal body tissues. *See, e.g.*, Stedman's Medical Dictionary, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990.

In some embodiments, the compounds and pharmaceutical compositions disclosed herein are used for treating cancer in a subject in need thereof. In some embodiments, the cancer is a cancer in which BCL6 is mutated. In some embodiments, the cancer is a cancer in which BCL6 is highly expressed, or is overexpressed relative to non-cancerous cells.

In some embodiments, the cancer is a solid tumor, such as a sarcoma or a carcinoma. In some embodiments, the cancer is a hematologic malignancy.

Exemplary sarcomas include, but are not limited to, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastoma, angiosarcoma, chondrosarcoma, chordoma, clear cell sarcoma of soft tissue, dedifferentiated liposarcoma, desmoid, desmoplastic small round cell tumor, embryonal rhabdomyosarcoma, epithelioid fibrosarcoma, epithelioid hemangioendothelioma, epithelioid sarcoma, esthesioneuroblastoma, Ewing sarcoma, extrarenal rhabdoid tumor, extraskeletal myxoid chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, giant cell tumor, hemangiopericytoma, infantile fibrosarcoma, inflammatory myofibroblastic tumor, Kaposi sarcoma, leiomyosarcoma of bone, liposarcoma, liposarcoma of bone, malignant fibrous histiocytoma (MFH), malignant fibrous histiocytoma (MFH) of bone, malignant mesenchymoma, malignant peripheral nerve sheath tumor, mesenchymal chondrosarcoma, myxofibrosarcoma, myxoid liposarcoma, myxoinflammatory fibroblastic sarcoma, neoplasms with perivascular epithelioid cell differentiation, osteosarcoma, parosteal osteosarcoma, neoplasm with perivascular epithelioid cell differentiation, periosteal osteosarcoma, pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, PNET/extraskeletal Ewing tumor, rhabdomyosarcoma, round cell liposarcoma, small cell osteosarcoma, solitary fibrous tumor, synovial sarcoma, and telangiectatic osteosarcoma.

Exemplary carcinomas include, but are not limited to, adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of unknown primary (CUP), esophageal cancer (e.g., esophageal squamous cell carcinoma), eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer (e.g., hepatocellular carcinoma),

lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

- 5 Exemplary hematologic malignancies include, but are not limited to, leukemias, lymphomas, myelomas, non-Hodgkin's lymphomas, Hodgkin's lymphomas, T-cell malignancies, and B-cell malignancies. Exemplary T-cell malignancies include anaplastic large cell lymphoma, angioimmunoblastic lymphoma, adult T-cell leukemia/lymphoma (ATLL), blastic NK-cell lymphoma, cutaneous T-cell lymphoma, enteropathy-type T-cell lymphoma,
- 10 hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma, nasal NK/T-cell lymphomas, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), and treatment-related T-cell lymphomas. Exemplary B-cell malignancies include chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, and a non-CLL/SLL lymphoma. In some embodiments, the cancer is selected from B cell prolymphocytic leukemia, Burkitt's
- 15 lymphoma, diffuse large B-cell lymphoma (DLBCL), extranodal marginal zone B cell lymphoma, follicular lymphoma (FL), immunoblastic large cell lymphoma, intravascular large B cell lymphoma, lymphomatoid granulomatosis, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), mediastinal (thymic) large B cell lymphoma, multiple myeloma, nodal marginal zone B cell lymphoma, non-Burkitt high grade B cell lymphoma, plasma cell myeloma,
- 20 plasmacytoma, precursor B-lymphoblastic lymphoma, primary effusion lymphoma, primary mediastinal B-cell lymphoma (PMBL), splenic marginal zone lymphoma, or Waldenstrom's macroglobulinemia. In some embodiments, the cancer is diffuse large B-cell lymphoma (DLBCL).

- In some embodiments, the cancer is a relapsed or refractory cancer, such as a cancer
- 25 described herein. In some embodiments, the cancer is a metastasized cancer, such as a cancer described herein.

- In the methods of treatment disclosed herein, a compound or pharmaceutical composition may be administered to the subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to, oral (e.g.,
- 30 by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., an aerosol, e.g., through mouth

or nose); rectal; vaginal; parenteral (e.g., by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal injection); or by implant of a depot, for example, subcutaneously or intramuscularly. In some embodiments, the administration comprises oral administration. In some embodiments, the administration comprises parenteral administration. Additional modes of administration may include adding the compound and/or a composition comprising the compound to a food or beverage, including a water supply for an animal, to supply the compound as part of the animal's diet.

It will be appreciated that appropriate dosages of the compounds, and compositions comprising the compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present disclosure. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration in vivo can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician. In general, a suitable dose of the compound is in the range of about 100 µg to about 250 mg per kilogram body weight of the subject per day.

The compound or composition may be administered once, on a continuous basis (e.g. by an intravenous drip), or on a periodic/intermittent basis, including about once per hour, about

once per two hours, about once per four hours, about once per eight hours, about once per twelve hours, about once per day, about once per two days, about once per three days, about twice per week, about once per week, and about once per month. The composition may be administered until a desired reduction of symptoms is achieved.

5 A compound described herein may be used in combination with other known therapies. Administered “in combination,” as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, e.g., the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In
10 some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as “simultaneous” or “concurrent delivery.” In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the
15 second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be
20 observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

 A compound or composition described herein and the at least one additional therapeutic
25 agent can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the compound described herein can be administered first, and the additional agent can be administered subsequently, or the order of administration can be reversed.

 In some embodiments, a compound described herein is administered in combination with
30 other therapeutic treatment modalities, including surgery, radiation, transplantation (e.g., stem cell transplantation, bone marrow transplantation), cryotherapy, and/or thermotherapy. Such

combination therapies may allow for lower dosages of the administered agent and/or other chemotherapeutic agent, thus avoiding possible toxicities or complications associated with the various therapies.

In some embodiments, the compound described herein is administered with at least one additional therapeutic agent, such as a chemotherapeutic agent. In certain embodiments, the compound described herein is administered in combination with one or more additional chemotherapeutic agents. The chemotherapeutic agent may be a chemotherapeutic agent identified on the “A to Z List of Cancer Drugs” published by the National Cancer Institute.

Also disclosed herein are methods of reducing proliferation of cancer cells in a sample, comprising contacting the sample with a compound described herein (e.g., a compound of formula (I) or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition described herein.

Kits

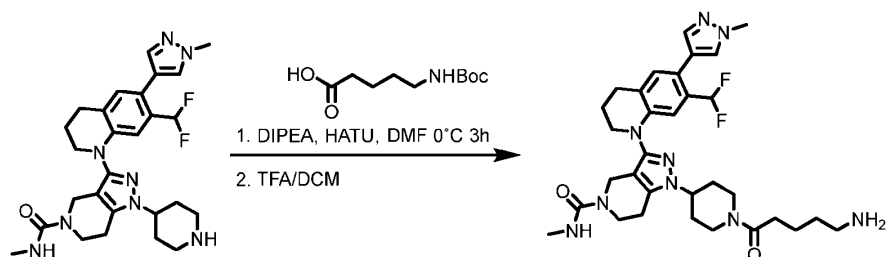
Compounds and/or compositions disclosed herein may be assembled into kits or pharmaceutical systems. Kits or pharmaceutical systems according may include a carrier or package such as a box, carton, tube or the like, having in close confinement therein one or more containers, such as vials, tubes, ampoules, or bottles, which contain a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof. Kits or pharmaceutical systems may also include printed instructions for using the compounds and/or compositions.

The following examples further illustrate aspects of the disclosure, but should not be construed as in any way limiting its scope.

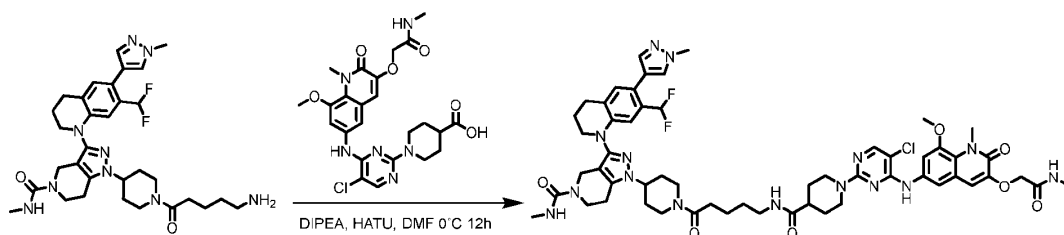
EXAMPLES

The following abbreviations are used in the Examples: DIPEA is *N,N*-diisopropylethylamine; DMF is *N,N*-dimethylformamide; DMSO is dimethylsulfoxide; HATU is 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate; HPLC is high performance liquid chromatography; TFA is trifluoroacetic acid; and UP-LC is ultra performance liquid chromatography.

Example 1: Compound Syntheses



Procedure A (MNN-02-155): To a solution of 5-((tert-butoxycarbonyl)amino)pentanoic acid (4.35 mg, 0.0200 mmol, 1.50 equiv) in anhydrous DMF (300 μ L, 0.05 M) and DIPEA (6.97 μ L, 0.0400 mmol, 3.00 equiv) under nitrogen at 0°C was added HATU (7.61 mg, mmol, 1.50 equiv). The reaction was stirred for 15 minutes at 0°C, and then 3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1-(piperidin-4-yl)-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide (7.00 mg, 0.0133 mmol, 1.00 equiv) dissolved in DMSO (1 mg/ 10 μ L) was added dropwise. The reaction was allowed to stir for 3 hours, at which point the product mass was observed by UP-LC in an acceptable purity (MS m/z 724.62 $[M+H]^+$). The reaction was diluted in water and the product was extracted 3x into ethyl acetate, dried over Na_2SO_4 , and concentrated in-vacuo. The crude product was then dissolved in 500 μ L of dichloromethane and 100 μ L of TFA and stirred at room temperature for 1 hour, at which point the solution was concentrated in-vacuo, azeotroped 3x with dichloromethane, and placed under vacuum for 12 hours.



Procedure B (MNN-02-155): To a solution of 1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxylic acid (7.66 mg, 0.0144 mmol, 1.50 equiv) in DMF (200 μ L, 0.05 M) was added DIPEA (11.7 μ L, 0.0673 mmol, 7.00 equiv) and HATU (5.49 mg, 0.0144 mmol, 1.50 equiv) and the mixture was stirred at 0°C for 15 minutes under nitrogen. Then the product of Procedure A (6.00 mg, 0.00962 mmol, 1.00 equiv) dissolved in 200 μ L of DMF was added dropwise and the

mixture was stirred for 12 hours. The reaction mixture was purified directly by prep-HPLC 85%-20% water (0.05% TFA)/methanol. The product 1-(1-(5-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)pentanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide was obtained as a white solid (4.28 mg, 40%, MS m/z 1136.52 [M+H]⁺). ¹H NMR (500 MHz, DMSO-*d*⁶) δ = 9.03 (s, 1H), 8.10 (d, *J* = 6.0 Hz, 1H), 7.95 (q, *J* = 4.5 Hz, 1H), 7.79 (t, *J* = 5.6 Hz, 1H), 7.73 (s, 1H), 7.51 (s, 2H), 7.48 (s, 1H), 7.08 (s, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 6.77 (t, *J* = 55.3 Hz, 1H), 6.54 (s, 1H), 4.55 (s, 2H), 4.49 – 4.43 (m, 3H), 4.31 (td, *J* = 10.6, 5.4 Hz, 1H), 4.01 (s, 2H), 3.95 (d, *J* = 13.7 Hz, 1H), 3.87 (d, *J* = 3.4 Hz, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.60 (q, *J* = 6.1 Hz, 2H), 3.56 (t, *J* = 5.6 Hz, 2H), 3.21 – 3.09 (m, 1H), 3.03 (q, *J* = 7.0 Hz, 2H), 2.95 – 2.87 (m, 2H), 2.82 (t, *J* = 6.3 Hz, 2H), 2.76 – 2.71 (m, 2H), 2.68 (d, *J* = 12.5 Hz, 1H), 2.64 (d, *J* = 4.7 Hz, 3H), 2.54 (s, 3H), 2.42 – 2.35 (m, 1H), 2.33 (t, *J* = 7.3 Hz, 2H), 1.96 (q, *J* = 5.9 Hz, 2H), 1.91 – 1.82 (m, 3H), 1.70 (d, *J* = 13.1 Hz, 3H), 1.58-1.43 (m, 4H), 1.40 (t, *J* = 7.4 Hz, 2H).

MNN-03-037: (1-(1-(4-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)butanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide). Compound MNN-03-037 was synthesized according to Procedure A using the linker 4-((tert-butoxycarbonyl)amino)butanoic acid, and subsequently through Procedure B to afford the title compound (1.95 mg, 18%, MS m/z 1122.51 [M+H]⁺). ¹H NMR (500 MHz, DMSO-*d*⁶) δ = 9.03 (s, 1H), 8.09 (s, 1H), 7.97 – 7.91 (m, 1H), 7.81 (t, *J* = 5.7 Hz, 1H), 7.74 (d, *J* = 2.6 Hz, 1H), 7.51 (d, *J* = 2.7 Hz, 2H), 7.49 (s, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 6.78 (s, 1H), 6.77 (t, *J* = 55.3 Hz, 1H), 6.54 (s, 1H), 4.55 (s, 2H), 4.46 (d, *J* = 12.9 Hz, 3H), 4.35 – 4.26 (m, 1H), 4.01 (s, 2H), 3.93 (d, *J* = 13.4 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.66-3.58 (m, 2H), 3.56 (t, *J* = 5.7 Hz, 2H), 3.14 (d, *J* = 12.3 Hz, 1H), 3.05 (q, *J* = 6.6 Hz, 2H), 2.96 – 2.87 (m, 2H), 2.81 (d, *J* = 6.5 Hz, 2H), 2.73 (d, *J* = 5.5 Hz, 2H), 2.69 (d, *J* = 12.7 Hz, 1H), 2.64 (d, *J* = 4.7 Hz, 3H), 2.54 (s, 3H), 2.42 – 2.36 (m, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.95 (p, *J* = 6.3 Hz, 2H), 1.87 (d, *J* = 17.1 Hz, 3H), 1.75 – 1.68 (m, 3H), 1.62 (p, *J* = 7.2 Hz, 2H), 1.50 (td, *J* = 12.2, 8.6 Hz, 2H).

MNN-02-195: 1-(1-(6-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)hexanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-02-195 was synthesized according to Procedure A using the linker 6-((tert-butoxycarbonyl)amino)hexanoic acid, and subsequently through Procedure B to afford the title compound (3.52 mg, 20%, MS m/z 1150.53 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 9.12 (s, 1H), 8.12 (d, J = 5.5 Hz, 1H), 7.95 (q, J = 4.5 Hz, 1H), 7.77 (t, J = 5.6 Hz, 1H), 7.73 (s, 1H), 7.51 (s, 2H), 7.48 (s, 1H), 7.08 (s, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 6.77 (t, J = 55.2 Hz, 1H), 6.54 (s, 1H), 4.55 (s, 2H), 4.44 (d, J = 13.2 Hz, 3H), 4.36 – 4.26 (m, 1H), 4.01 (s, 2H), 3.95 (d, J = 13.2 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.60 (q, J = 5.8 Hz, 2H), 3.56 (t, J = 5.6 Hz, 2H), 3.15 (t, J = 12.0 Hz, 1H), 3.01 (q, J = 6.8 Hz, 2H), 2.93 (t, J = 12.5 Hz, 2H), 2.82 (t, J = 6.5 Hz, 2H), 2.73 (t, J = 5.9 Hz, 2H), 2.71 – 2.66 (m, 1H), 2.64 (d, J = 4.6 Hz, 3H), 2.54 (s, 3H), 2.41 – 2.34 (m, 1H), 2.31 (t, J = 7.5 Hz, 2H), 1.95 (t, J = 5.8 Hz, 2H), 1.91 – 1.83 (m, 3H), 1.71 (dd, J = 13.2, 3.7 Hz, 3H), 1.49 (dt, J = 14.5, 5.6 Hz, 4H), 1.39 (p, J = 7.1 Hz, 2H), 1.25 (qd, J = 8.5, 5.8 Hz, 2H).

RCS-SBM-IJD-001: 1-(1-(7-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)heptanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound RCS-SBM-IJD-001 was synthesized according to Procedure A using the linker 8-((tert-butoxycarbonyl)amino)octanoic acid, and subsequently through Procedure B to afford the title compound (3.92 mg, 18%, MS m/z 1165.48 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 9.16 (s, 1H), 8.12 (s, 1H), 7.95 (q, J = 4.6 Hz, 1H), 7.76 (t, J = 5.6 Hz, 1H), 7.73 (s, 1H), 7.50 (s, 2H), 7.48 (d, J = 0.8 Hz, 1H), 7.08 (s, 1H), 7.01 (s, 1H), 6.79 (s, 1H), 6.77 (t, J = 55.2 Hz, 1H), 6.53 (s, 1H), 4.55 (s, 2H, assigned by HSQC), 4.46 – 4.40 (3H, assigned by HSQC), 4.35 – 4.27 (m, 1H, assigned by HSQC), 4.01 (s, 2H), 3.95 (d, J = 13.6 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.60 (q, J = 5.8 Hz, 2H), 3.56 (t, J = 5.7 Hz, 2H), 3.15 (t, J = 12.5 Hz, 1H), 3.00 (q, J = 6.6 Hz, 2H), 2.97 – 2.89 (m, 2H), 2.82 (t, J = 6.3 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.68 (d, J = 12.1 Hz, 1H), 2.64 (d, J = 4.6 Hz, 3H), 2.54 (s, 3H), 2.42 – 2.34 (m, 1H),

2.31 (t, $J = 7.5$ Hz, 2H), 1.96 (p, $J = 6.3$ Hz, 2H), 1.88 (dd, $J = 18.7, 8.7$ Hz, 3H), 1.74 – 1.68 (m, 3H), 1.56 – 1.42 (m, 4H), 1.36 (q, $J = 7.0$ Hz, 2H), 1.25 (d, $J = 5.4$ Hz, 4H).

MNN-02-196: 1-(1-(8-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)octanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-02-196 was synthesized according to Procedure A using the linker 8-((tert-butoxycarbonyl)amino)octanoic acid, and subsequently through Procedure B to afford the title compound (1.43 mg, 8%, MS m/z 1180.09 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 8.86 (d, $J = 8.5$ Hz, 1H), 8.06 (d, $J = 8.2$ Hz, 1H), 8.02 – 7.97 (m, 1H), 7.74 (q, $J = 7.3$ Hz, 2H), 7.52 (d, $J = 8.9$ Hz, 2H), 7.47 (d, $J = 8.9$ Hz, 1H), 7.08 (d, $J = 8.8$ Hz, 1H), 7.00 (d, $J = 8.6$ Hz, 1H), 6.79 (s, 1H), 6.76 (t, 1H), 6.53 (s, 1H), 4.54 (s, 2H), 4.50 (d, $J = 21.7$ Hz, 3H), 4.35 – 4.26 (m, 1H), 4.00 (d, $J = 8.7$ Hz, 2H), 3.94 (d, $J = 13.2$ Hz, 1H), 3.87 (d, $J = 2.2$ Hz, 3H), 3.86 – 3.82 (m, 6H), 3.68-3.34 (4H, assigned by HSQC), 3.14 (q, $J = 10.1$ Hz, 1H), 3.00 (q, $J = 6.7$ Hz, 2H), 2.88 (t, $J = 12.1$ Hz, 2H), 2.82 (t, $J = 6.5$ Hz, 2H), 2.73 (t, $J = 6.1$ Hz, 2H), 2.68 (d, $J = 12.1$ Hz, 1H), 2.64 (dd, $J = 9.2, 4.6$ Hz, 3H), 2.54 (s, 3H), 2.36 (q, $J = 5.2$ Hz, 1H), 2.30 (t, $J = 7.5$ Hz, 2H), 1.95 (q, $J = 6.2$ Hz, 2H), 1.86 (d, $J = 10.5$ Hz, 3H), 1.69 (d, $J = 12.3$ Hz, 3H), 1.47 (t, $J = 11.0$ Hz, 4H), 1.35 (d, $J = 8.0$ Hz, 2H), 1.29 – 1.14 (m, 6H).

MNN-02-187: 1-(1-(9-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)nonanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-02-187 was synthesized according to Procedure A using the linker 9-((tert-butoxycarbonyl)amino)nonanoic acid, and subsequently through Procedure B to afford the title compound (1.41 mg, 8%, MS m/z 1193.80 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 8.10 (d, $J = 3.5$ Hz, 1H), 7.95 (q, $J = 4.6$ Hz, 1H), 7.79 – 7.72 (m, 2H), 7.51 (s, 2H), 7.48 (s, 1H), 7.08 (s, 1H), 7.01 (d, $J = 2.6$ Hz, 1H), 6.79 (s, 1H), 6.76 (t, $J = 55.2$ Hz, 1H), 6.54 (s, 1H), 4.54 (s, 2H), 4.46 (d, $J = 13.1$ Hz, 3H), 4.31 (s, 1H), 4.01 (s, 2H), 3.95 (d, $J = 13.7$ Hz, 1H), 3.88 – 3.83 (m, 9H), 3.58 (dt, $J = 22.9, 5.6$ Hz, 4H), 3.19 – 3.11 (m, 1H), 3.09 – 2.97 (m, 2H), 2.97 – 2.87 (m, 2H), 2.82 (t, $J = 6.4$ Hz, 2H), 2.79 – 2.71 (m, 2H), 2.69 (s, 1H), 2.64 (d, $J = 4.7$ Hz, 3H), 2.53 (s, 3H), 2.38 (d, $J = 11.7$ Hz, 2H), 2.30 (t, $J = 7.4$ Hz, 2H), 1.95 (p, $J = 6.0$

Hz, 3H), 1.89 (s, 3H), 1.70 (d, $J = 13.2$ Hz, 3H), 1.56 – 1.42 (m, 4H), 1.38 – 1.28 (m, 2H), 1.28 – 1.20 (m, 6H).

MNN-02-197: 1-(1-(10-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)decanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-02-197 was synthesized according to Procedure A using the linker 10-((tert-butoxycarbonyl)amino)decanoic acid, and subsequently through Procedure B to afford the title compound (1.41 mg, 8%, MS m/z 1207.76 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 9.10 (s, 1H), 8.11 (s, 1H), 7.95 (q, $J = 4.6$ Hz, 1H), 7.75 (t, $J = 5.6$ Hz, 1H), 7.74 (s, 1H), 7.51 (s, 2H), 7.48 (d, $J = 0.9$ Hz, 1H), 7.08 (s, 1H), 7.01 (d, $J = 1.8$ Hz, 1H), 6.79 (s, 1H), 6.77 (t, $J = 55.3$ Hz, 1H), 6.54 (s, 1H), 4.55 (s, 2H), 4.45 (d, $J = 12.9$ Hz, 3H), 4.30 (m, $J = 10.4$, 5.3 Hz, 1H), 4.01 (s, 2H), 3.95 (d, $J = 13.6$ Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.65 – 3.53 (m, 4H), 3.18 – 3.09 (m, 1H), 2.99 (q, $J = 6.6$ Hz, 2H), 2.97 – 2.89 (m, 2H), 2.82 (t, $J = 6.4$ Hz, 2H), 2.73 (t, $J = 5.9$ Hz, 2H), 2.68 (d, $J = 12.0$ Hz, 1H), 2.64 (d, $J = 4.7$ Hz, 3H), 2.54 (d, $J = 1.2$ Hz, 3H), 2.43 – 2.35 (m, 2H), 2.33 – 2.27 (m, 2H), 1.96 (p, $J = 6.3$ Hz, 3H), 1.91 – 1.80 (m, 3H), 1.71 (d, $J = 13.3$ Hz, 3H), 1.56 – 1.43 (m, 4H), 1.35 (t, $J = 6.8$ Hz, 2H), 1.29 – 1.20 (m, 8H).

MNN-02-160: 1-(1-(11-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)undecanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-02-160 was synthesized according to Procedure A using the linker 11-((tert-butoxycarbonyl)amino)undecanoic acid, and subsequently through Procedure B to afford the title compound (0.89 mg, 7%, MS m/z 1221.82 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 9.07 (s, 1H), 8.10 (s, 1H), 7.96 (q, $J = 4.8$ Hz, 1H), 7.77 (t, $J = 5.6$ Hz, 1H), 7.74 (d, $J = 0.9$ Hz, 1H), 7.52 (s, 2H), 7.48 (d, $J = 0.8$ Hz, 1H), 7.08 (s, 1H), 7.01 (s, 1H), 6.79 (s, 1H), 6.76 (t, $J = 55.3$ Hz, 1H), 6.55 (s, 1H), 4.55 (s, 2H), 4.47 (m, $J = 13.0$ Hz, 3H), 4.31 (tt, $J = 10.6$, 4.5 Hz, 1H), 4.01 (s, 2H), 3.98 – 3.91 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.58 (m, $J = 17.8$, 5.3 Hz, 4H), 3.15 (t, $J = 12.4$ Hz, 1H), 2.99 (q, $J = 6.6$ Hz, 2H), 2.97 – 2.88 (m, 2H), 2.82 (t, $J = 6.5$ Hz, 2H), 2.73 (t, $J = 6.0$ Hz, 2H), 2.68 (d, $J = 11.7$ Hz, 1H), 2.64 (d, $J = 4.6$ Hz, 3H),

2.54 (d, $J = 1.7$ Hz, 3H), 2.42 – 2.34 (m, 1H), 2.33 – 2.27 (m, 2H), 1.96 (dt, $J = 10.0, 6.3$ Hz, 2H), 1.91 – 1.83 (m, 3H), 1.71 (d, $J = 13.2$ Hz, 3H), 1.49 (dq, $J = 22.0, 8.1$ Hz, 4H), 1.38 – 1.32 (m, 2H), 1.27 – 1.15 (m, 12H).

MNN-02-161: 1-(1-(3-(2-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)ethoxy)propanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-02-161 was synthesized according to Procedure A using the linker 3-(2-((tert-butoxycarbonyl)amino)ethoxy)propanoic acid, and subsequently through
10 Procedure B to afford the title compound (2.52 mg, 20%, MS m/z 1152.48 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 8.83 (s, 1H), 8.05 (s, 1H), 7.96 (q, $J = 4.6$ Hz, 1H), 7.84 (t, $J = 5.6$ Hz, 1H), 7.73 (s, 1H), 7.53 (q, $J = 2.3$ Hz, 2H), 7.48 (s, 1H), 7.08 (s, 1H), 6.99 (s, 1H), 6.76 (t, 2H), 6.54 (d, $J = 4.7$ Hz, 1H), 4.54 (s, 2H), 4.47 (t, $J = 18.1$ Hz, 3H), 4.31 (d, $J = 10.2$ Hz, 1H), 3.98 (d, $J = 18.1$ Hz, 2H), 3.96 (s, 1H), 3.91 – 3.81 (m, 9H), 3.64 – 3.52 (m, 4H), 3.38 (t, $J = 5.9$ Hz, 2H), 3.17 (dt, $J = 5.9, 2.8$ Hz, 1H), 2.87 (s, 1H), 2.81 (d, 2H), 2.73 (t, $J = 5.8$ Hz, 2H), 2.72 – 2.68 (m, 1H), 2.64 (d, $J = 4.7$ Hz, 3H), 2.59 (dt, $J = 12.3, 6.6$ Hz, 1H), 2.54 (s, 3H), 2.44 – 2.36 (m, 2H), 1.95 (p, $J = 6.3$ Hz, 2H), 1.87 (d, $J = 22.9$ Hz, 3H), 1.69 (d, $J = 9.7$ Hz, 4H), 1.53 – 1.43 (m, 2H), 1.29 – 1.21 (m, 2H).

MNN-02-162: 1-(1-(3-(2-(2-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)ethoxy)ethoxy)propanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-02-162 was synthesized according to Procedure A using the linker 2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatetradecan-14-oic acid, and subsequently
25 through Procedure B to afford the title compound (2.91 mg, 20%, MS m/z 1196.40 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 8.85 (s, 1H), 8.06 (s, 1H), 7.95 (q, $J = 4.6$ Hz, 1H), 7.84 (t, $J = 5.8$ Hz, 1H), 7.73 (s, 1H), 7.53 (s, 2H), 7.48 (s, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 6.77 (t, 1H), 6.53 (d, $J = 5.1$ Hz, 1H), 4.54 (s, 2H), 4.47 (dd, $J = 26.3, 12.9$ Hz, 3H), 4.35 – 4.27 (m, 1H), 4.00 (d, $J = 5.1$ Hz, 2H), 3.96 (d, $J = 5.9$ Hz, 1H), 3.90 – 3.82 (m, 9H), 3.60-3.56 (4H, assigned by
30 HSQC), 3.48 (s, 2H), 3.37 (t, $J = 5.9$ Hz, 2H), 3.16 (q, $J = 6.0$ Hz, 3H), 2.88 (td, $J = 13.0, 2.7$ Hz, 2H), 2.82 (t, $J = 6.4$ Hz, 2H), 2.73 (q, $J = 5.7$ Hz, 2H), 2.69 (s, 1H), 2.64 (d, $J = 4.7$ Hz, 3H),

2.59 (q, $J = 6.5$ Hz, 2H), 2.54 (s, 3H), 2.40 (dh, $J = 11.4, 3.7$ Hz, 2H), 1.99 – 1.92 (m, 2H), 1.87 (d, $J = 18.6$ Hz, 3H), 1.77 – 1.66 (m, 3H), 1.48 (qd, $J = 12.5, 4.1$ Hz, 2H), 1.29 – 1.21 (m, 2H), 1.13 – 1.08 (m, 1H).

MNN-02-156: 1-(1-(1-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidin-4-yl)-1-oxo-5,8,11-trioxa-2-azatetradecan-14-oyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-02-156 was synthesized according to Procedure A using the linker 2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azaheptadecan-17-oic acid, and subsequently through Procedure B to afford the title compound. (2.00 mg, 20%, MS m/z 1241.04 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d^6) δ = 8.83 (s, 1H), 8.06 (d, $J = 1.4$ Hz, 1H), 7.96 (d, $J = 4.9$ Hz, 1H), 7.85 (q, $J = 6.2$ Hz, 1H), 7.74 (d, $J = 1.7$ Hz, 1H), 7.53 (s, 2H), 7.48 (s, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 6.91 – 6.63 (m, 2H), 6.53 (d, $J = 4.7$ Hz, 1H), 4.54 (s, 2H), 4.47 (dd, $J = 27.5, 12.8$ Hz, 3H), 4.31 (s, 1H), 4.00 (s, 2H), 3.97 (s, 1H), 3.89 – 3.83 (m, 9H), 3.61 (dt, $J = 6.6, 3.4$ Hz, 4H), 3.50 – 3.36 (m, 2H), 3.17 (p, $J = 5.8$ Hz, 3H), 2.88 (td, $J = 12.8, 2.7$ Hz, 1H), 2.82 (t, $J = 6.1$ Hz, 2H), 2.76 – 2.72 (m, 2H), 2.70 (d, $J = 12.8$ Hz, 1H), 2.65 (d, $J = 4.7$ Hz, 3H), 2.62 – 2.56 (m, 1H), 2.53 (d, $J = 3.3$ Hz, 3H), 2.45 – 2.33 (m, 1H), 2.30 (dd, $J = 7.8, 5.2$ Hz, 1H), 1.99 – 1.92 (m, 2H), 1.91 – 1.84 (m, 3H), 1.75 – 1.66 (m, 3H), 1.54 – 1.43 (m, 2H).

MNN-03-039: 1-(1-(1'-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carbonyl)-[1,4'-bipiperidine]-4-carbonyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-03-039 was synthesized according to Procedure A using the linker 1'-(tert-butoxycarbonyl)-[1,4'-bipiperidine]-4-carboxylic acid, and subsequently through Procedure B to afford the title compound (0.88 mg, 10%, MS m/z 1232.68 $[M+H]^+$).

MNN-03-049: 1-(1-(3-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carbonyl)-3-azaspiro[5.5]undecane-9-carbonyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-03-049 was synthesized according to Procedure A using the linker 3-(tert-butoxycarbonyl)-3-azaspiro[5.5]undecane-9-carboxylic acid, and

subsequently through Procedure B to afford the title compound. (2.65 mg, 30%, MS m/z 1216.57 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d_6) δ = 9.11 (s, 1H), 8.11 (s, 1H), 7.94 (q, J = 4.6 Hz, 1H), 7.74 (s, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.09 (s, 1H), 7.01 (s, 1H), 6.81 (s, 1H), 6.77 (t, J = 55.2 Hz, 1H), 6.54 (s, 1H), 4.55 (s, 2H), 4.45 (d, J = 12.7 Hz, 3H), 4.40 – 4.28 (m, 1H), 4.02 (s, 3H), 3.89 – 3.84 (m, 9H), 3.71 – 3.58 (m, 4H), 3.56 (t, J = 5.6 Hz, 2H), 3.47 (s, 2H), 3.41 (s, 2H), 3.18 (t, J = 12.7 Hz, 1H), 3.00 (s, 2H), 2.93 (d, J = 10.5 Hz, 1H), 2.83 (t, J = 6.4 Hz, 2H), 2.74 (t, J = 5.7 Hz, 2H), 2.69 (s, 1H), 2.64 (d, J = 4.7 Hz, 3H), 2.60 (s, 1H), 2.54 (s, 3H), 1.96 (h, J = 6.8 Hz, 2H), 1.85 (d, J = 16.9 Hz, 2H), 1.73 – 1.63 (m, 4H), 1.50 (d, J = 16.4 Hz, 6H), 1.38 (s, 1H), 1.30 (s, 1H), 1.16 (dd, J = 24.9, 9.9 Hz, 3H).

MNN-03-050: 1-(1-(2-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carbonyl)-2-azaspiro[3.3]heptane-6-carbonyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-03-050 was synthesized according to Procedure 1 using the linker 2-(tert-butoxycarbonyl)-2-azaspiro[3.3]heptane-6-carboxylic acid, and subsequently through Procedure 2 to afford the title compound (4.72 mg, 40%, MS m/z 1160.73 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d_6) δ = 9.17 (s, 1H), 8.12 (s, 1H), 7.94 (q, J = 4.7 Hz, 1H), 7.74 (s, 1H), 7.52 (dd, J = 7.1, 2.3 Hz, 1H), 7.48 (d, J = 2.6 Hz, 2H), 7.09 (s, 1H), 7.00 (s, 1H), 6.81 (d, J = 2.2 Hz, 1H), 6.77 (t, 1H), 6.54 (s, 1H), 4.55 (s, 2H), 4.42 (d, J = 12.8 Hz, 3H), 4.32 (dq, J = 11.2, 5.3 Hz, 1H), 4.24 (s, 1H), 4.22 (s, 1H), 4.08 (s, 1H), 4.06 (s, 2H), 4.02 (s, 2H), 3.86 (dd, J = 4.5, 1.7 Hz, 9H), 3.80 (d, J = 13.9 Hz, 1H), 3.70 (s, 1H), 3.58 (dt, J = 18.3, 6.3 Hz, 4H), 3.26 (td, J = 8.4, 2.7 Hz, 1H), 3.11 (s, 1H), 2.97 (s, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.73 (h, J = 6.2 Hz, 3H), 2.64 (d, J = 4.7 Hz, 3H), 2.54 (s, 3H), 2.34 (td, J = 8.1, 4.0 Hz, 2H), 2.25 (d, J = 8.2 Hz, 1H), 1.97 (p, J = 6.1 Hz, 2H), 1.87 (d, J = 13.2 Hz, 2H), 1.81 (s, 1H), 1.69 (d, J = 31.1 Hz, 3H), 1.44 (t, J = 12.0 Hz, 2H).

MNN-03-038: 1-(1-(3-(4-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carbonyl)piperazin-1-yl)propanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-03-038 was synthesized according to Procedure 1 using the linker 3-(4-(tert-butoxycarbonyl)piperazin-1-yl)propanoic acid, and subsequently

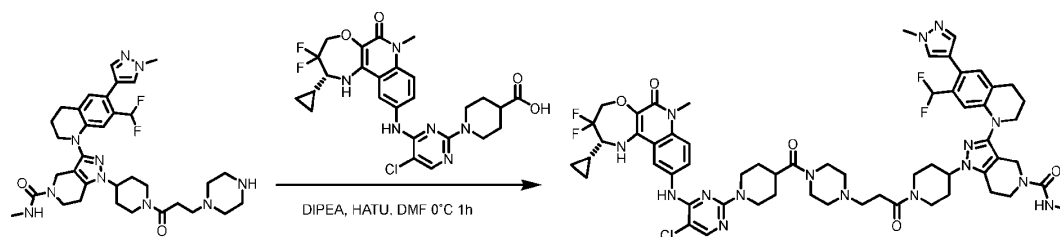
through Procedure 2 to afford the title compound (3.33 mg, 30% yield, MS m/z 1177.74 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d_6) δ = 9.57 (s, 1H), 8.94 (s, 1H), 8.09 (s, 1H), 7.98 (d, J = 4.7 Hz, 1H), 7.74 (s, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.49 (d, J = 0.8 Hz, 1H), 7.09 (s, 1H), 6.99 (s, 1H), 6.77 (t, J = 55.2 Hz, 1H), 6.76 (s, 1H), 6.55 (s, 1H), 4.55 (s, 2H), 4.48 (m, J = 15.8 Hz, 4H), 4.41 – 4.32 (m, 1H), 4.23 (s, 1H), 4.02 (s, 2H), 3.95 (d, J = 13.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 6H), 3.80-3.50 (7H, as assigned by HSQC), 3.36 (s, 2H), 3.26 – 3.17 (m, 1H), 3.10 (s, 1H), 3.04 – 2.94 (m, 5H), 2.91 (q, J = 6.8 Hz, 2H), 2.83 (q, J = 8.5 Hz, 3H), 2.76 (q, J = 8.1 Hz, 2H), 2.64 (d, J = 4.7 Hz, 3H), 2.54 (s, 3H), 1.94 (m, J = 13.2, 4.8 Hz, 5H), 1.84 – 1.63 (m, 3H), 1.50 (s, 2H).

10 **MNN-03-041**: 1-(1-(4-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carboxamido)cyclohexane-1-carbonyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-03-041 was synthesized according to Procedure 1
15 using the linker 4-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid, and subsequently through Procedure 2 to afford the title compound (4.73 mg, 40%, MS m/z 1162.38 $[M+H]^+$). 1H NMR (500 MHz, DMSO- d_6) δ = 8.96 (s, 1H), 8.09 (s, 1H), 7.94 (q, J = 4.8 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.55 – 7.49 (m, 2H), 7.48 (t, J = 1.4 Hz, 1H), 7.08 (s, 1H), 7.04 – 6.98 (m, 1H), 6.81 (s, 1H), 6.76 (t, J = 55.3 Hz, 1H), 6.54 (s, 1H), 4.55 (d, J = 2.3 Hz, 2H), 4.50 (d, J = 13.2 Hz, 3H),
20 4.32 (dq, J = 10.8, 5.4 Hz, 1H), 4.02 (s, 3H), 3.90 – 3.80 (m, 9H), 3.77 (s, 1H), 3.60 (t, J = 5.7 Hz, 2H), 3.56 (t, J = 5.6 Hz, 2H), 3.43 (s, 1H), 3.18 (t, J = 12.7 Hz, 1H), 3.07 (t, J = 11.4 Hz, 1H), 2.98 (t, J = 12.4 Hz, 1H), 2.92 – 2.85 (m, 2H), 2.85 – 2.79 (m, 2H), 2.74 (t, J = 6.0 Hz, 2H), 2.69 (d, J = 3.3 Hz, 1H), 2.67 – 2.59 (m, 3H), 2.54 (s, 3H), 1.96 (q, J = 5.9 Hz, 2H), 1.88 (s, 3H), 1.68 (d, J = 12.7 Hz, 6H), 1.48 (d, J = 29.4 Hz, 4H).

25 **MNN-03-040**: 1-(1-(1-(1-(5-chloro-4-((8-methoxy-1-methyl-3-(2-(methylamino)-2-oxoethoxy)-2-oxo-1,2-dihydroquinolin-6-yl)amino)pyrimidin-2-yl)piperidine-4-carbonyl)azetidine-3-carbonyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-03-040 was synthesized according to Procedure 1 using the
30 linker 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid, and subsequently through Procedure 2 to afford the title compound (0.82 mg, 6%, MS m/z 1120.61 $[M+H]^+$). 1H NMR (500 MHz,

DMSO-*d*₆) δ = 8.89 (s, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.97 – 7.92 (m, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.54 (t, J = 2.8 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.48 (d, J = 4.7 Hz, 1H), 7.08 (s, 1H), 6.98 (d, J = 5.2 Hz, 1H), 6.79 (d, J = 3.1 Hz, 1H), 6.78 (td, J = 55.2, 3.1 Hz, 1H), 6.54 (s, 1H), 4.55 (d, J = 3.4 Hz, 2H), 4.48 (d, J = 13.8 Hz, 3H), 4.31 (dt, J = 14.3, 6.9 Hz, 1H), 4.01 (d, J = 5.2 Hz, 2H), 3.99 (s, 1H), 3.94 – 3.88 (m, 1H), 3.88 – 3.81 (m, 9H), 3.74 (ddd, J = 15.0, 8.5, 6.0 Hz, 1H), 3.67 (d, J = 13.5 Hz, 1H), 3.60 (s, 2H), 3.56 (t, J = 5.7 Hz, 2H), 3.21 – 3.12 (m, 2H), 3.09 (td, J = 7.3, 4.8 Hz, 2H), 2.94 (t, J = 13.0 Hz, 2H), 2.83 (t, J = 6.5 Hz, 2H), 2.79 (s, 1H), 2.74 (t, J = 5.9 Hz, 2H), 2.64 (dd, J = 4.7, 2.2 Hz, 3H), 2.58 – 2.52 (m, 3H), 1.96 (t, J = 5.8 Hz, 2H), 1.90 (s, 3H), 1.76 (d, J = 7.3 Hz, 1H), 1.66 (t, J = 14.3 Hz, 2H), 1.43 (d, J = 13.7 Hz, 2H).

MNN-04-022: (S)-1-(1-(3-(4-(1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbonyl)piperazin-1-yl)propanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide. Compound MNN-04-022 was synthesized according to Procedure 1 using the linker 3-(4-(tert-butoxycarbonyl)piperazin-1-yl)propanoic acid to afford 3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1-(1-(3-(piperazin-1-yl)propanoyl)piperidin-4-yl)-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide as a white solid (9.90 mg, 97%).



To a solution of (S)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carboxylic acid (11.1 mg, 0.0199 mmol, 1.20 equiv) in DMF (330 μ L, 0.05 M) was added DIPEA (20.2 μ L, 0.0116 mmol, 7.00 equiv) and HATU (8.18 mg, 0.0215 mmol, 1.30 equiv) and the mixture was stirred at 0°C for 15 minutes under nitrogen. After 15 minutes of stirring, the crude mixture of 3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1-(1-(3-(piperazin-1-yl)propanoyl)piperidin-4-yl)-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide dissolved in DMF was added dropwise and the reaction

was left to stir for 1 hour to afford (S)-1-(1-(3-(4-(1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbonyl)piperazin-1-yl)propanoyl)piperidin-4-yl)-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide (1.88 mg, 9%, MS m/z 1207.86 [M+H]⁺).

Example 2: Reporter Gene Activation

The compounds shown above were tested for their ability to activate a BCL6 reporter gene, GFP, integrated into the KARPAS lymphoma cell line. The reporter construct contains 8 high-confidence BCL6 binding sites and flanking base pairs identified from chromatin immunoprecipitation sequencing (ChIP-seq) and functional genomic data at validated cell death genes, upstream of a minimal promoter driving green fluorescent protein (GFP) described in Gourisankar *et al. Nature* 620, 417–425 (2023). It was integrated into the genome of otherwise genetically unmodified KARPAS422 DLBCL cells, and GFP is normally not transcribed due to the repressive function of endogenous BCL6. As shown in FIG. 4 and in FIG. 8C, several of the compounds activated the reporter at even the lowest concentration.

Example 3: Cell Viability Assays

The HAT-BCL6 TCIPs were tested for their ability to kill lymphoma cells after 72 hours of treatment. 30,000 cells were plated in 100 μ L media per well of a 96 well plate and treated with drug for indicated times and doses. A resazurin-based indicator of cell was added for 1.5 hours after which the fluorescence ratio at 560/590nm was recorded. The background fluorescence was subtracted and the signal was normalized to DMSO-treated cells. DMSO content was normalized to 0.1%. EC50 values were calculated using a standard 4-parameter log-logistic function. Data are shown in FIG. 5A and FIG. 8A (SUDHL5 cells) and FIG. 5B (KARPAS422 cells), with EC50 values in FIG. 8A and FIG. 8B and Table 1. dCBP-1 is a degrader of p300/CBP (CAS No. 2484739-25-3), A485 is a catalytic-site p300/CBP inhibitor (CAS No. 1889279-16-6), and GNE-781 is a p300/CBP bromodomain inhibitor (CAS No. 1936422-33-1). Negative 1 is the negative control of MNN-02-155 in which BCL6 binding is abrogated; the compound has a structure:

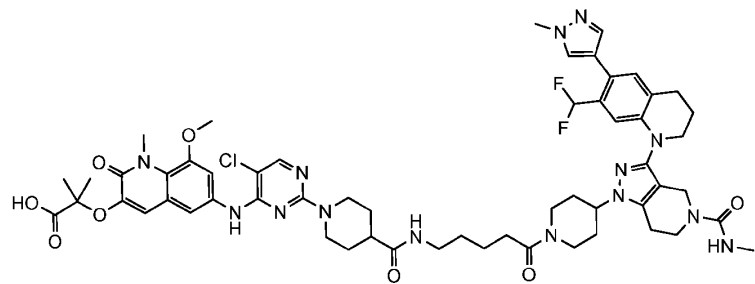


Table 1. EC₅₀ values in KARPAS422 cells

Compound	EC ₅₀ (nM)
A-485	62.29
dCBP-1	6.088
GNE-781	2.405
MNN-02-155	2.907
MNN-03-037	1.254
MNN-03-038	0.6346
Negative 1	244.9

5

Example 4: Ternary Complex Formation

To determine if the HAT-BCL6 TCIPs function by inducing formation of a ternary complex between p300/CBP and BCL6 each compound was assayed for its ability to rescue the loss of cell viability produced with a constant 1 nM amount of one of the most potent HAT-BCL6 TCIP, MNN-03-038 (TCIP3), against excess p300/CBP inhibitors including SGC-CBP-30, GNE-781, or A-485, and against excess BCL6 inhibitors including BI-3812, GSK137 (CAS 2728727-91-9), or CCT373567 (CAS 2378853-67-7) added at the time of the initiation of the experiment. Data is shown in FIG. 6A (KARPAS422 cells) and FIG. 6B and FIG. 8E (SUDHL5 cells). Ternary complex formation is reflected in the rescue of viability as excess monomeric drug competes away the biologically active ternary complexes.

15

Example 5: Half-Life and Internal Clearance

Table 3 shows the *in vitro* half-life and internal clearance of p300/CBP TCIPs in mouse liver microsomal stability analysis relative to the reference kinase inhibitor sunitinib.

Table 3.

Compound	T _{1/2} (min)	(Cl _{int} - µl/min/mg)
Sunitinib	13.9	50
MNN-03-038	52.9	13
MNN-03-037	148.4	5
MNN-02-155	166.9	4

Example 6: Oncogene Repression Studies

Methods

5 **Cell Culture.** Lymphoma and leukemia cells were cultured in RPMI-1640 (ATCC 30-2001) + 10% FBS with antibiotics (100X PenStrep GIBCO #15140122) and incubated at 37 °C and 5% CO₂. Cells were routinely checked for mycoplasma and immediately checked upon suspicion. No cultures tested positive.

10 **Western Blots.** Cells were plated at 1million/milliliter (mL) and treated with drug at indicated timepoints and doses. Cells were harvested on ice in RIPA buffer (50mM Tris-HCl pH 8, 150mM NaCl, 1% NP-40, 0.1% DOC, 1% SDS, protease inhibitor cocktail (~20 mg/ml pepstatin, aprotinin, and leupeptin), 1mM DTT) and 1:200 benzonase (Sigma #E1014) was added and incubated for 20 mins. After 10 min centrifugation at 14,000g and 4 °C, the supernatant was collected and protein concentration was measured by Bradford. Antibodies used
15 for immunoblots are: BCL6 (Cell Signaling D65C10), p300 (Santa Cruz F-4), CBP (Cell Signaling D6C5), c-MYC (Cell Signaling D84C12), and GAPDH (Santa Cruz 6C5). All antibodies were used at 1:1000 v/v dilutions except GAPDH (1:2000). ImageStudio (Licor) was used for blot imaging and quantification.

20 **RNA Extraction, qPCR, and Sequencing Library Preparation.** Cells were plated at 1million/milliliter and harvested in TRIsure (Bioline #38033). RNA was extracted using Direct-zol RNA MicroPrep columns (Zymo #R2062) treated with DNaseI. cDNA was prepared for RT-qPCR using the SensiFAST cDNA preparation kit according to manufacturer instructions (Bioline #65054). 1µL of cDNA was used per RT-qPCR reaction prepared with SYBR Lo-ROX (Bioline #94020). For sequencing library preparation, polyA-containing transcripts were

enriched for (NEB #E7490S), prepared into paired-end libraries (NEB #E7760S), and sequenced on an Illumina NovaSeq using paired-end 150-bp read length by Novogene.

RNA-seq Analysis. Raw reads were checked for quality using fastqc (www.bioinformatics.babraham.ac.uk/projects/fastqc/) and trimmed from adapters using cutadapt (Martin, *EMBnet.journal* **17**, 10 (2011)) using parameters cutadapt -a AGATCGGAAGAGCACACGTCTGAACTCCAGTCA (SEQ ID NO: 1) -b AGATCGGAAGAGCGTCGTGTAGGGAAAGAGTGT (SEQ ID NO: 2) --nextseq-trim=20 --minimum-length 1. Transcripts were quantified using kallisto (Bray *et al. Nature Biotechnology* **34**, 525-527 (2016)) against the human Gencode v33 indexed transcriptome and annotations. Differential gene analysis was performed using DESeq2 (Love *et al. Genome Biol* **15**, 550 (2014)) using apegglm (Zhu *et al. Bioinformatics* **35**, 2084-2092 (2019)) to shrink log₂FoldChanges.

Results

Results are shown in FIGS. 7A-7G. Data in FIGS. 7A-7F show reduction in c-MYC compared to controls such as BCL6 inhibition via BI-3812 (a nanomolar inhibitor of BCL6) (or a related compound) or p300/CBP bromodomain inhibition via GNE-781 (a nanomolar inhibitor of p300/CBP) (or a related compound). Data in FIG. 7E shows that in an unbiased analysis of all transcripts altered by TCIP3, $\neg$ c-MYC is the most significantly repressed gene at 1 hour of 1 nM treatment. Data in FIG. 7G shows this reduction is dependent on BCL6 levels of cell lines. Data in FIG. 7A shows that repression of MYC does not occur via target (p300, CBP, BCL6) protein degradation or loss but by a new signaling event. Data in FIG. 7D shows that the repression c-MYC is temporally at first at the level of transcription of the c-MYC gene as expected for the TCIP which acts via modulation of transcription.

Example 7: Ternary Complex Dependence, BCL6-regulated Intracellular Gene Expression, and Cytotoxicity Assays

Methods

Cell Viability Measurements. 30,000 cells in 100 μ L of media were seeded into 96-well plates and treated with drug for 72 hours at the indicated doses. A resazurin-based indicator of cell health (PrestoBlue, ThermoFisher #P50200) was added, at which point the plate was allowed to

incubate for 1.5 hours at 37°C. The fluorescence ratio at 560/590nm was then recorded. The background fluorescence was subtracted and the signal was normalized to DMSO-treated cells. Fit of dose-response curves to data and statistical analysis was performed using drc package in R using the four-parameter log-logistic function.

5 **Reporter Assay.** KARPAS422 cells were lenti-virally transduced with a previously reported GFP-reporter construct (Gourisankar *et al. Nature* 620, 417–425 (2023)). After selection, cells were plated and treated with the indicated amount of each compound for 8 hours. Cells were washed in 2.5% FBS/PBS, administered a 1:250 v/v of 7-AAD to distinguish live from dead cells, and harvested for flow cytometry on a BD Accuri. Given the polyclonal population after
10 transduction, the area under the curve of the histogram representing FITC signal across all live cells was calculated as an integrative measure of total GFP signal. A GFP-positive gate was drawn off non-transduced cells and the area past the threshold for each sample was calculated and normalized to cells treated with DMSO.

TR-FRET. A mixture of 10 nM p300-Bromodomain (purified from Addgene construct #
15 39018, a gift from Nicola Burgess-Brown), 200 nM biotinylated BCL6-BTB, 20 nM Streptavidin-FITC (Thermo #SA1001), and 1:400 anti-6xHis terbium antibody (PerkinElmer #61HI2TLF) in 10 µL buffer (20 mM HEPES, 150 mM NaCl, 0.1% BSA, 0.1% NP-40, and 1 mM TCIP) was added to a low-volume 384-well plate. Each protein mixture was incubated with drug digitally dispensed (Tecan D300e) for 1 hour in the dark at room temperature before excitation at 337 nM
20 and measurement of emission at 520 nM (FITC) and 490 nM (terbium) with a PHERAstar FS plate reader (BMG Labtech). The ratio of signal at 520 nm to 490 nm was calculated and normalized to DMSO-treated conditions and plotted.

Results

Results are shown in FIGS. 8A-8F, and show that MNN-03-038 (TCIP3) exhibits greater
25 cell killing than inhibitors alone and that cell killing is dependent on a ternary complex formation between p300 and BCL6. FIG. 8A shows increased cell killing induced by TCIP3 compared to known p300/CBP inhibitors (A-485), degraders (dCBP-1), or the combination of BCL6 and p300/CBP inhibitors (BI-3812 and GNE-781, respectively). FIG. 8B shows the IC₅₀ values of and structure-activity relationship with all the p300/CBP TCIP molecules synthesized in a 72-
30 hour viability assay in SUDHL5 cells. FIG. 8C shows that treatment with TCIP3 relative to BI-3812 or GNE-781 induces transcriptional activation at BCL6 promoters. FIG. 8D shows that all

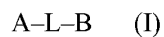
TCIPs are capable of inducing a ternary complex between p300 and BCL6 biochemically in a TR-FRET assay relative to BI-3812 and GNE-781 for both linear and rigid linkers. FIG. 8E shows that titration of BI-3812 or GNE-781 in a dose-dependent manner was able to rescue cell killing by TCIP3 in a 72-hour viability assay. FIG. 8F shows that TCIP3 killing is more effective
5 in DLBCL cell lines with high levels of BCL6 protein.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

10

CLAIMS:

1. A compound of formula (I)



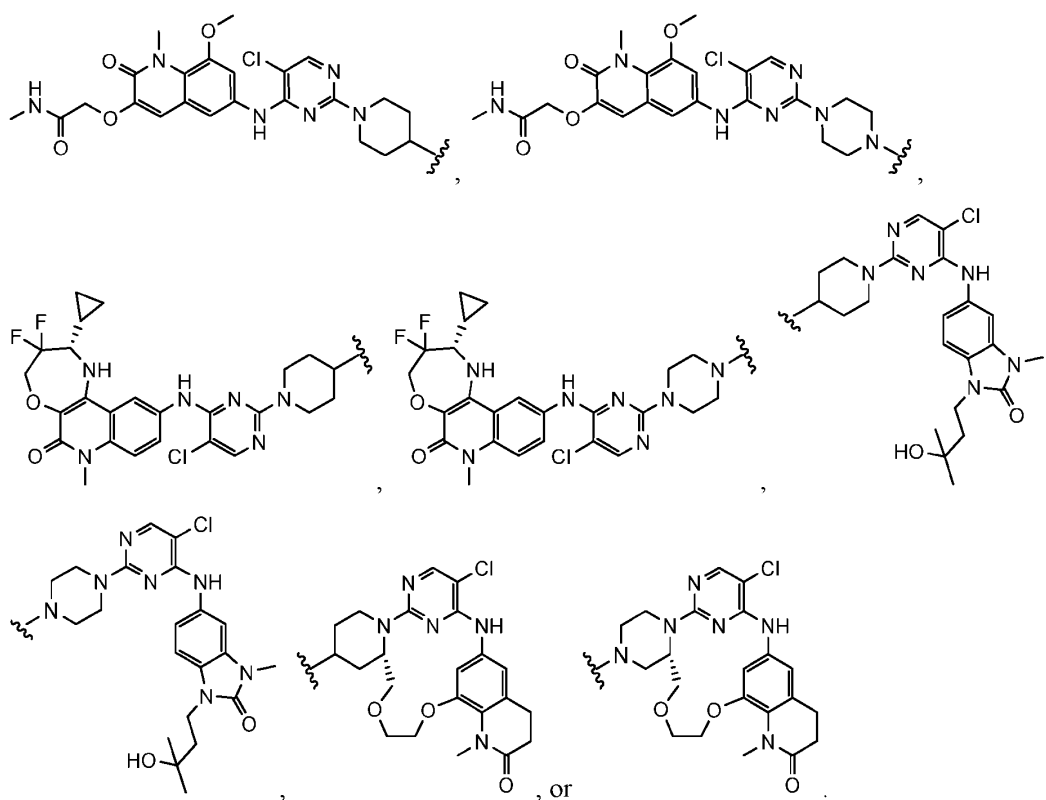
or a pharmaceutically acceptable salt thereof, wherein:

- 5 A is a BCL6-binding moiety;

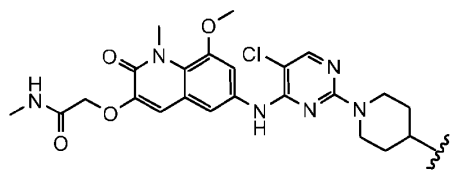
L is a linker; and

B is a moiety that binds to the bromodomain of a histone acetyltransferase.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is a moiety of formula:



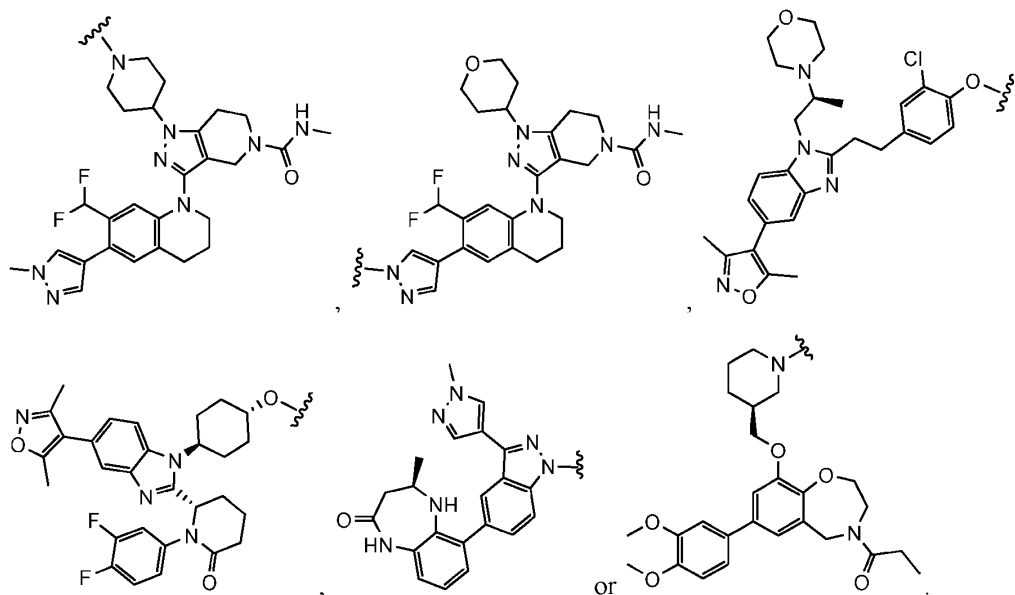
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is a moiety of formula:



4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein B is a moiety that binds to the bromodomain of p300 or CBP.

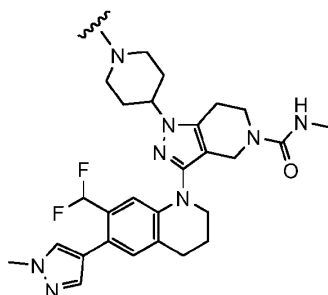
5

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein B is a moiety of formula:

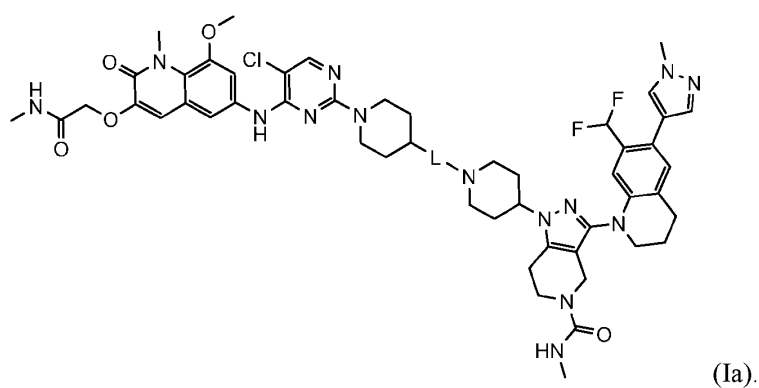


10

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein B is a moiety of formula:



7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (Ia):

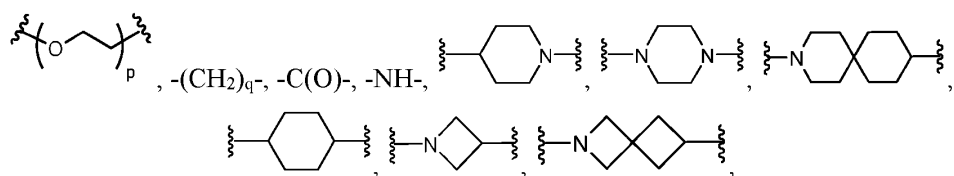


5

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein L is a direct bond or comprises any combination of -CH₂-, -CH=CH-, -C≡C-, -O-, -NR'-, -BR'-, -S-, -C(O)-, -C(NR')-, -S(O)-, -S(O)₂-, arylene, heteroarylene, cycloalkylene, and heterocyclylene moieties, wherein the arylene, heteroarylene, cycloalkylene, and heterocyclylene moieties are independently unsubstituted or substituted with 1, 2, or 3 substituents.

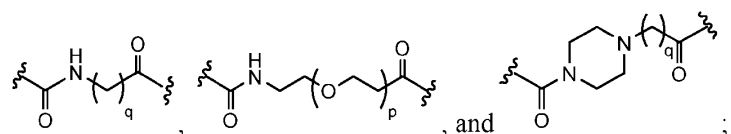
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein L is a direct bond or comprises any combination of -CH₂-, -O-, -C(O)-, -NH-, -N(CH₃)-, cycloalkylene, and heterocyclylene moieties.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein L comprises any combination of the following moieties:



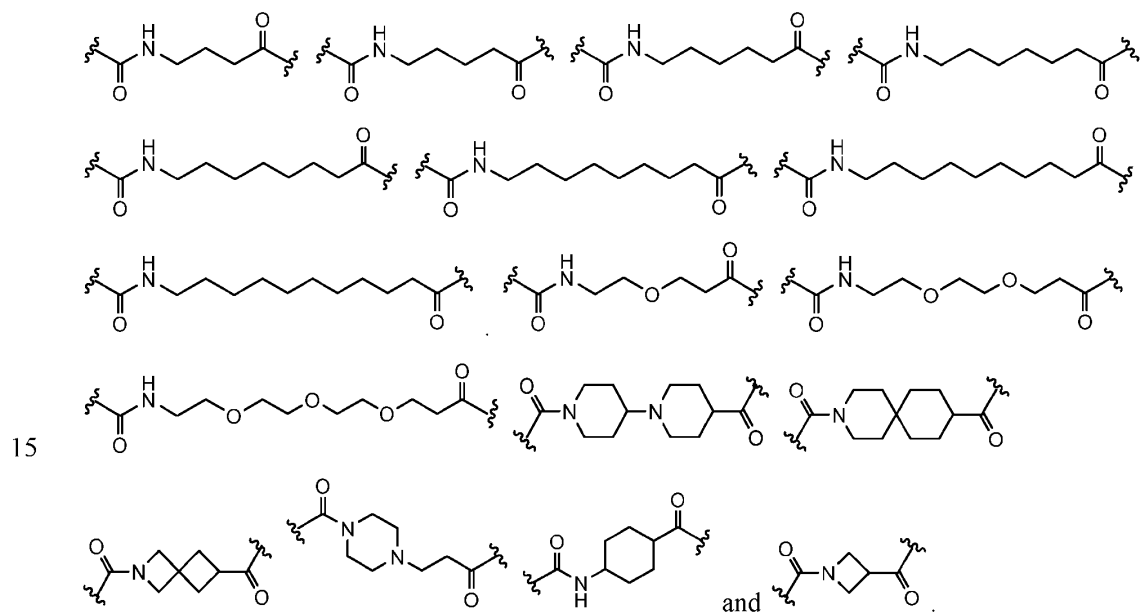
wherein p is 1, 2, 3, 4, 5, or 6; and q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

- 5 11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein L has a formula selected from:

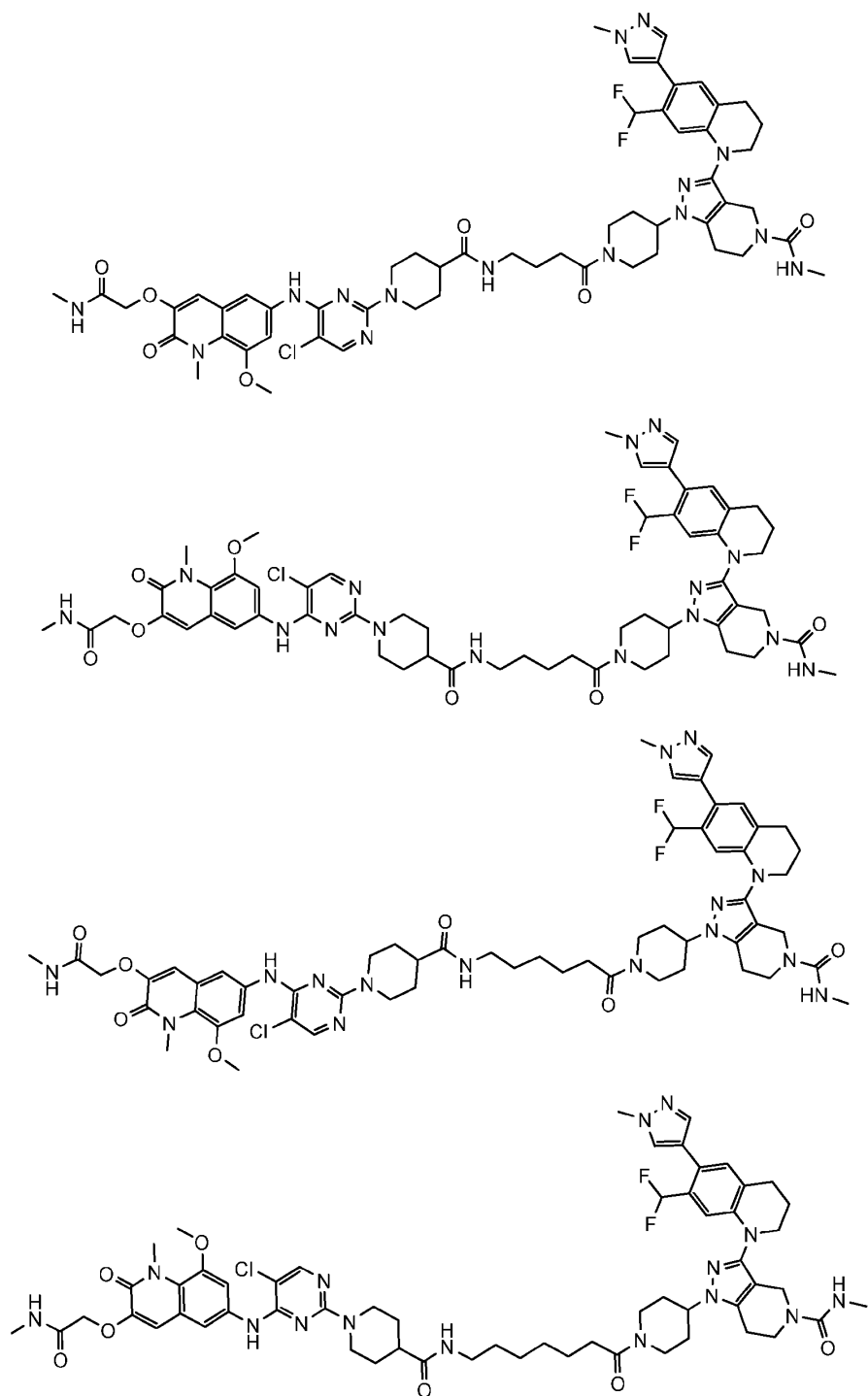


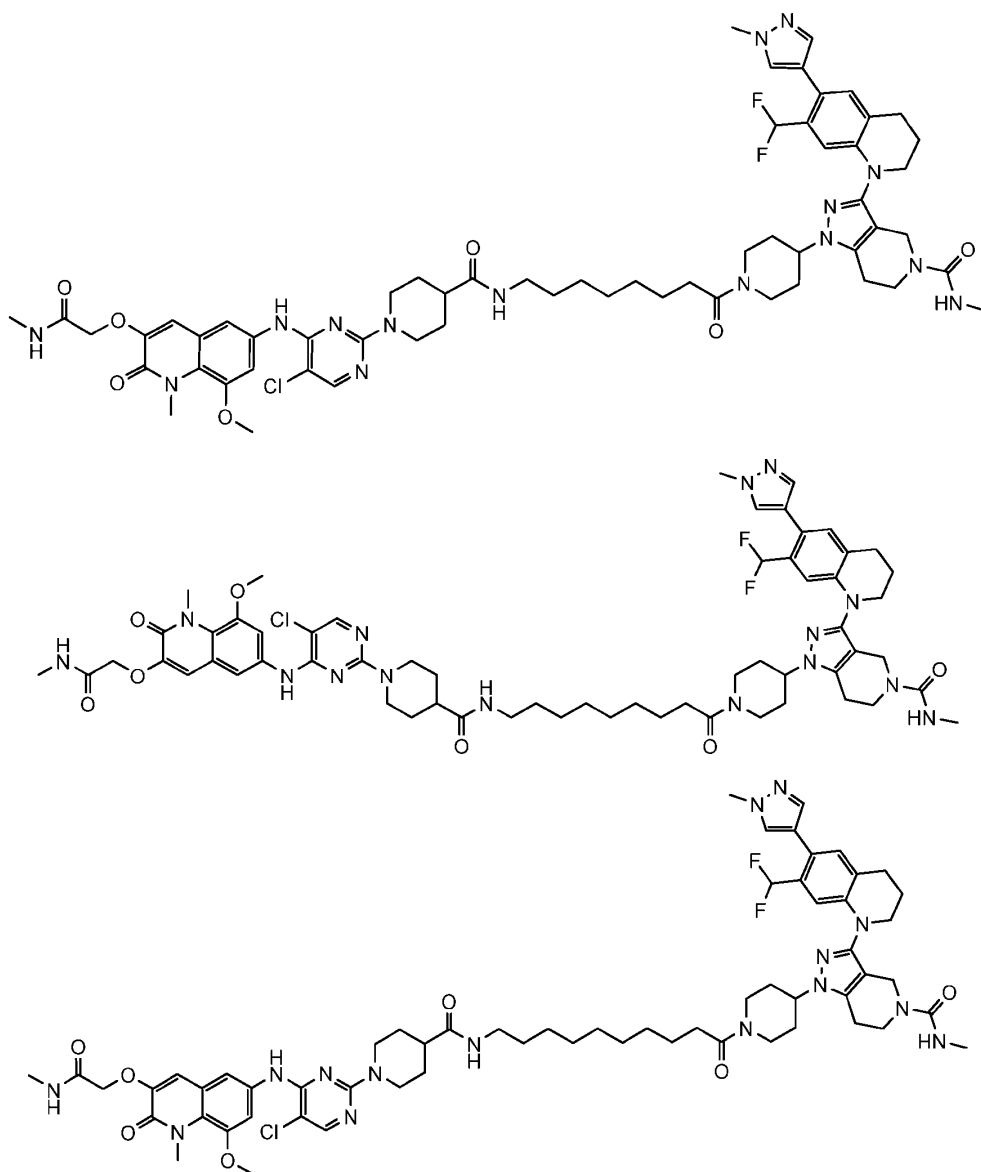
wherein p is 1, 2, 3, 4, 5, or 6; and q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

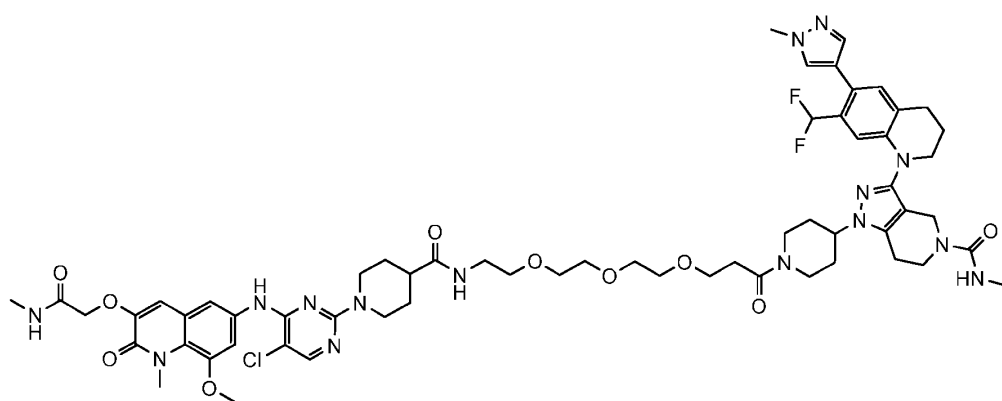
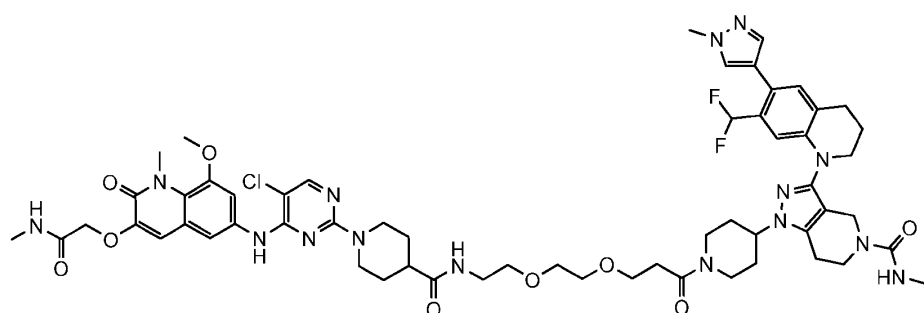
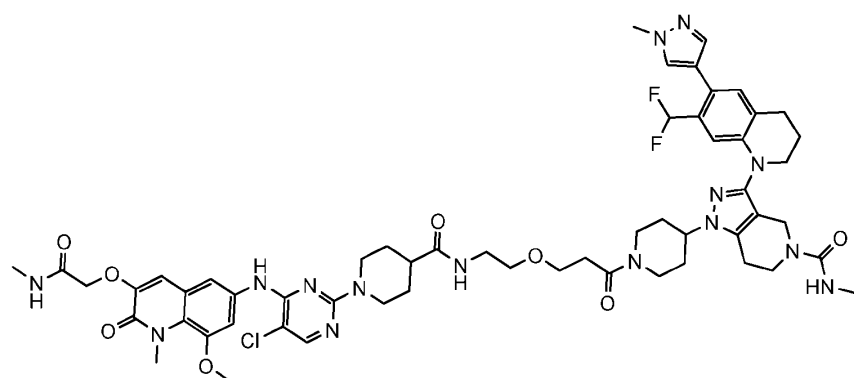
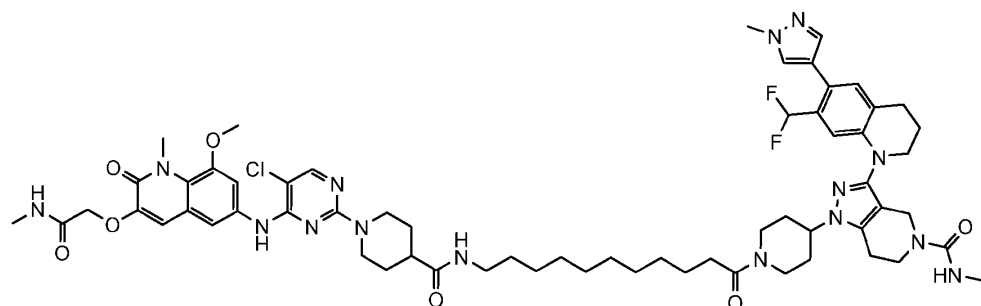
- 10 12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof,
wherein L has a formula selected from:

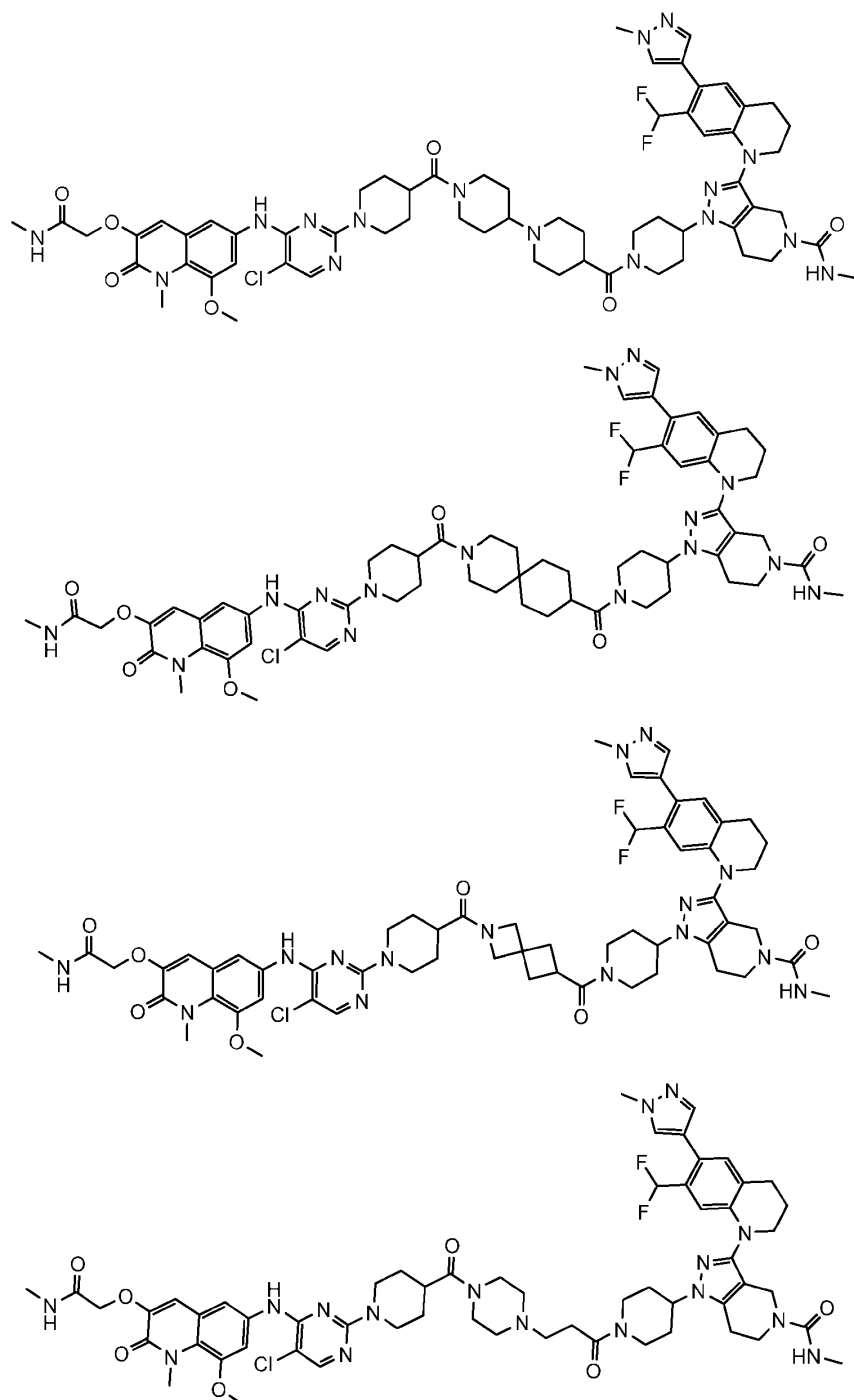


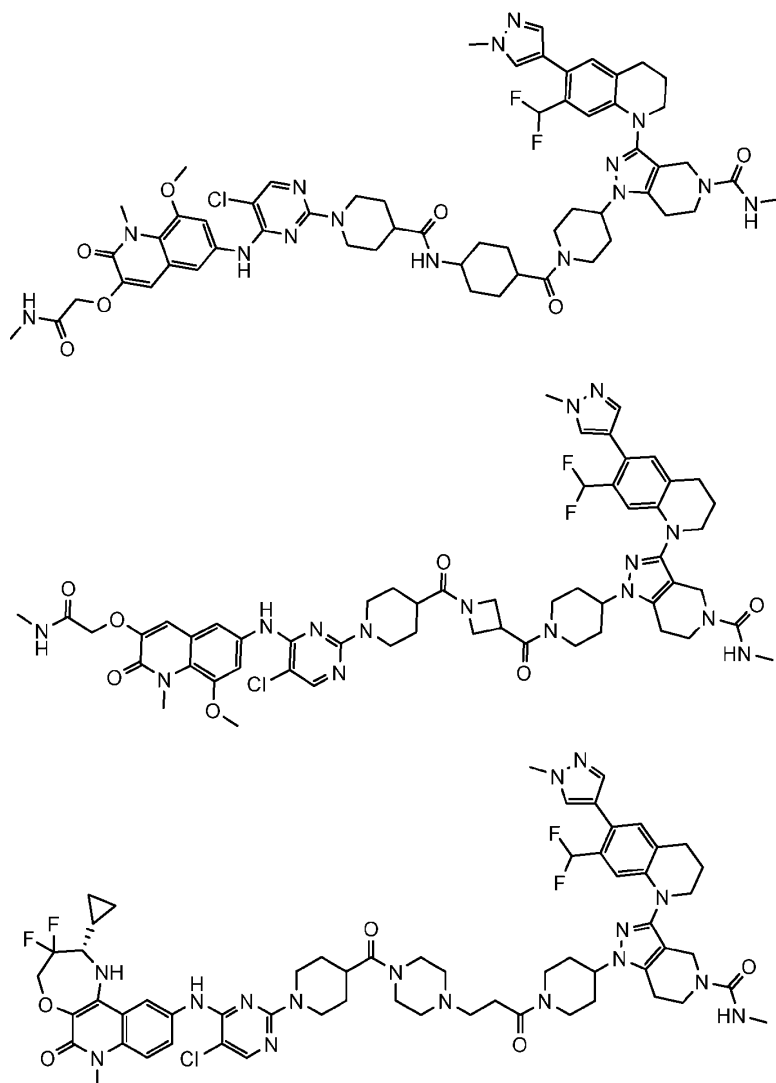
13. The compound of claim 1, wherein the compound is selected from:











and pharmaceutically acceptable salts thereof.

5

14. A pharmaceutical composition comprising a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. A method of treating a proliferative disease in a subject in need thereof, comprising
 10 administering to the subject a therapeutically effective amount of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof.

16. The method of claim 14, wherein the proliferative disease is a cancer selected from a carcinoma, a sarcoma, and a hematologic malignancy.
- 5 17. The method of claim 15, wherein the cancer is a lymphoma.
18. The method of claim 16, wherein the cancer is a diffuse large B-cell lymphoma.
19. A compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, for
10 use as a medicament.
20. A compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, for use in treating a proliferative disease.
- 15 21. The compound of claim 20, wherein the proliferative disease is a cancer selected from a carcinoma, a sarcoma, and a hematologic malignancy.
22. The compound of claim 21, wherein the cancer is a lymphoma.
- 20 23. The compound of claim 22, wherein the cancer is a diffuse large B-cell lymphoma.
24. A kit comprising a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof.