(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
03 October 2024 (03.10.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/206100 A2

(51) International Patent Classification:
Not classified

(21) International Application Number:
PCT/US2024/021053

(22) International Filing Date:
22 March 2024 (22.03.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/492,013 24 March 2023 (24.03.2023) US

(71) Applicant: **OHIO STATE INNOVATION FOUNDATION** [US/US]; Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US).

(72) Inventors: **CHENG, Xiaolin**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). **YANG, Rui**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). **ALINARI, Lapo**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). **LI, Pui-Kai**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US).

(74) Agent: **CUTCHINS, William W.** et al.; MEUNIER CARLIN & CURFMAN LLC, 999 Peachtree St. NE, Suite 1300, Atlanta, Georgia 30309 (US).

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

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

**Declarations under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

**Published:**
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: TRANSDUCIN BETA-LIKE PROTEIN 1 DEGRADERS

(57) Abstract: Disclosed herein are transducin β-like protein 1 X-linked targeting compounds covalently linked to an E3 ligase ligand. The compounds are useful for the treatment of cancer.

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# TRANSDUCIN BETA-LIKE PROTEIN 1 DEGRADERS

## CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application 63/492,013, filed March 24, 2023, the contents of which are hereby incorporated in its entirety.

## FIELD OF THE INVENTION

The invention relates to PROTAC compounds and their use for the treatment of proliferative disorders, including cancer. In some implementations, the PROTAC compounds include a tegavivint warhead.

## BACKGROUND

Proteolysis Targeting Chimeras (PROTACs) are heterobifunctional molecules composed of two warheads and a linker. The two covalently linked warheads can engage both the protein of interest (POI) and the E3 ligase simultaneously, which results in POI ubiquitination and subsequent proteasomal degradation.

Transducin β-like protein 1 X-linked (TBL1X) is an essential scaffold protein that engages in the formation of key protein complexes and regulates multiple critical signaling pathways such as the Wnt/β-catenin pathway. It functions as an exchange factor of corepressors SMRT/NCoR for coactivators to modulate the transcriptional activity of nuclear hormone receptors (NHRs). It plays an indispensable role in protecting β-catenin from proteasomal degradation in the Wnt/β-catenin pathway. To date, only one compound, tegavivint (BC-2059), has been reported to promote apoptosis by disrupting TBL1X/β-catenin interactions, thus showing promising therapeutic effects both in vitro and in vivo in Wnt-driven cancers, such as breast cancer, desmoid tumor and lymphomas.

There remains a need for improved PROTAC agents. There remains a need for improved systems and methods for targeting TBL1X. There remains a need for improved systems and methods for treating cancer.

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the synthesis of a series of PROTAC compounds.

Figure 2 depicts the synthesis of a series of PROTAC compounds.

## DETAILED DESCRIPTION

Before the present methods and systems are disclosed and described, it is to be understood that the methods and systems are not limited to specific synthetic methods, specific components, or to particular compositions. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes¬ from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps. "Exemplary" means "an example of" and is not intended to convey an indication of a preferred or ideal embodiment. "Such as" is not used in a restrictive sense, but for explanatory purposes.

Disclosed are components that can be used to perform the disclosed methods and systems. These and other components are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these components are disclosed that while

specific reference of each various individual and collective combinations and permutation of these may not be explicitly disclosed, each is specifically contemplated and described herein, for all methods and systems. This applies to all aspects of this application including, but not limited to, steps in disclosed methods. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the disclosed methods.

Compounds disclosed herein may be provided in the form of pharmaceutically acceptable salts. Examples of such salts are acid addition salts formed with inorganic acids, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids and the like; salts formed with organic acids such as acetic, oxalic, tartaric, succinic, maleic, fumaric, gluconic, citric, malic, methanesulfonic, p-toluenesulfonic, napthalenesulfonic, and polygalacturonic acids, and the like; salts formed from elemental anions such as chloride, bromide, and iodide; salts formed from metal hydroxides, for example, sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, and magnesium hydroxide; salts formed from metal carbonates, for example, sodium carbonate, potassium carbonate, calcium carbonate, and magnesium carbonate; salts formed from metal bicarbonates, for example, sodium bicarbonate and potassium bicarbonate; salts formed from metal sulfates, for example, sodium sulfate and potassium sulfate; and salts formed from metal nitrates, for example, sodium nitrate and potassium nitrate.

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions*, Wiley Interscience, New York, 1981; Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds,* McGraw-Hill, NY, 1962; and Wilen, S.H., *Tables of Resolving Agents and Optical Resolutions* p. 268, E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972. The invention additionally encompasses

compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "$C_{1-6}$ alkyl" is intended to encompass $C_1$, $C_2$, $C_3$, $C_4$, $C_5$, $C_6$, $C_{1-6}$, $C_{1-5}$, $C_{1-4}$, $C_{1-3}$, $C_{1-2}$, $C_{2-6}$, $C_{2-5}$, $C_{2-4}$, $C_{2-3}$, $C_{3-6}$, $C_{3-5}$, $C_{3-4}$, $C_{4-6}$, $C_{4-5}$, and $C_{5-6}$ alkyl.

The term "alkyl" refers to a radical of a straight-chain or branched hydrocarbon group having a specified range of carbon atoms (e.g., a "$C_{1-16}$ alkyl" can have from 1 to 16 carbon atoms). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("$C_{1-9}$ alkyl"). An alkyl group can be saturated or unsaturated, i.e., an alkenyl or alkynyl group as defined herein. Unless specified to the contrary, an "alkyl" group includes both saturated alkyl groups and unsaturated alkyl groups.

In some embodiments, an alkyl group has 1 to 8 carbon atoms ("$C_{1-8}$ alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("$C_{1-7}$ alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("$C_{1-6}$ alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("$C_{1-5}$ alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("$C_{1-4}$ alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("$C_{1-3}$ alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("$C_{1-2}$ alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("$C_1$ alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("$C_{2-6}$ alkyl"). Examples of $C_{1-6}$ alkyl groups include methyl ($C_1$), ethyl ($C_2$), propyl ($C_3$) (*e.g.*, n-propyl, isopropyl), butyl ($C_4$) (*e.g.*, n-butyl, tert-butyl, sec-butyl, iso-butyl), pentyl ($C_5$) (*e.g.*, n-pentyl, 3-pentanyl, amyl, neopentyl, 3- methyl-2-butanyl, tertiary amyl), and hexyl ($C_6$) (*e.g.*, n-hexyl). Additional examples of alkyl groups include n-heptyl ($C_7$), n-octyl ($C_8$), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents (*e.g.*, halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted $C_{1-10}$ alkyl (such as unsubstituted $C_{1-6}$ alkyl, *e.g.*, $-CH_3$ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted n-propyl (n-Pr), unsubstituted isopropyl (i-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted n-butyl (n-Bu), unsubstituted tert-butyl (tert-Bu or t-Bu), unsubstituted sec-butyl (sec-Bu), unsubstituted isobutyl (i-Bu)). In certain embodiments, the alkyl group is a substituted $C_{1-10}$ alkyl (such as substituted $C_{1-6}$ alkyl, *e.g.*, $-CF_3$, Bn).

The term "haloalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("$C_{1-8}$ haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("$C_{1-6}$ haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("$C_{1-4}$ haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("$C_{1-3}$ haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("$C_{1-2}$ haloalkyl"). Examples of haloalkyl groups include $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

The term "hydroxyalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a hydroxyl. In some embodiments, the hydroxyalkyl moiety has 1 to 8 carbon atoms ("$C_{1-8}$ hydroxyalkyl"). In some embodiments, the hydroxyalkyl moiety has 1 to 6 carbon atoms ("$C_{1-6}$ hydroxyalkyl"). In some embodiments, the hydroxyalkyl moiety has 1 to 4 carbon atoms ("$C_{1-4}$ hydroxyalkyl"). In some embodiments, the hydroxyalkyl moiety has 1 to 3 carbon atoms ("$C_{1-3}$ hydroxyalkyl"). In some embodiments, the hydroxyalkyl moiety has 1 to 2 carbon atoms ("$C_{1-2}$ hydroxyalkyl").

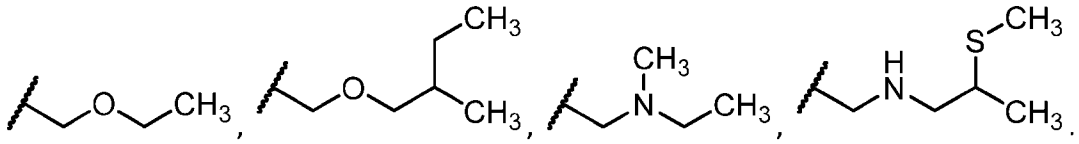
The term "alkoxy" refers to an alkyl group, as defined herein, appended through an oxygen atom. In some embodiments, the alkoxy moiety has 1 to 8 carbon atoms ("$C_{1-8}$ alkoxy"). In some embodiments, the alkoxy moiety has 1 to 6 carbon atoms ("$C_{1-6}$ alkoxy"). In some embodiments, the alkoxy moiety has 1 to 4 carbon atoms ("$C_{1-4}$ alkoxy"). In some embodiments, the alkoxy moiety has 1 to 3 carbon atoms ("$C_{1-3}$ alkoxy"). In some embodiments, the alkoxy moiety has 1 to 2 carbon atoms ("$C_{1-2}$ alkoxy"). Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

The term "haloalkoxy" refers to a haloalkyl group, as defined herein, appended through an oxygen atom. In some embodiments, the alkoxy moiety has 1 to 8 carbon atoms ("$C_{1-8}$ haloalkoxy"). In some embodiments, the alkoxy moiety has 1 to 6 carbon atoms ("$C_{1-6}$ haloalkoxy"). In some embodiments, the alkoxy moiety has 1 to 4 carbon atoms ("$C_{1-4}$ haloalkoxy"). In some embodiments, the alkoxy moiety has 1 to 3 carbon atoms ("$C_{1-3}$ haloalkoxy"). In some embodiments, the alkoxy moiety has 1 to 2 carbon atoms ("$C_{1-2}$ haloalkoxy"). Representative examples of haloalkoxy include, but are not limited to, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

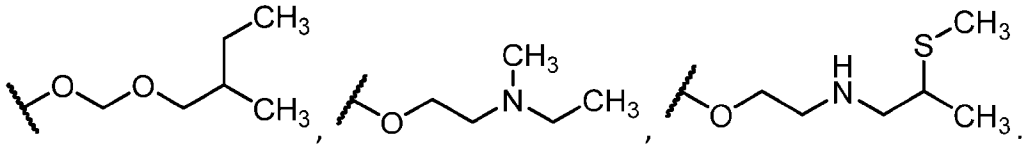
The term "alkoxyalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by an alkoxy group, as defined herein. In some embodiments, the alkoxyalkyl moiety has 1 to 8 carbon atoms ("$C_{1-8}$ alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 6 carbon atoms ("$C_{1-6}$ alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 4 carbon atoms ("$C_{1-4}$ alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 3 carbon atoms ("$C_{1-3}$ alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 2 carbon atoms ("$C_{1-2}$ alkoxyalkyl"). By way of example, a $C_3$alkoxy$C_3$alkyl group includes, but is not limited to, the groups having the formula:

$–CH_2CH_2CH_2OCH_2CH_2CH_3$, $–CH_2CH_2CH_2OCH(CH_3)_2$, $– CH(CH_3)CH_2OCH(CH_3)_2$,

The term "heteroalkyl" refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (i.e., inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. By way of example, a hetero$C_{1-6}$alkyl (which may also be designated a $C_{1-6}$heteroalkyl) group includes, but is not limited to, the following structures:



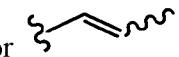
The term "heteroalkyl" preceded by a separate heteroatom refers to a heteroalkyl group bonded through the specified heteroatom. By way of example, a O$C_{1-6}$heteroalkyl group includes, but it not limited to, the following structures:



In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 20 carbon atoms and 1 or more heteroatoms within the parent chain ("hetero$C_{1-20}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 18 carbon atoms and 1or more heteroatoms within the parent chain ("hetero$C_{1-18}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 16 carbon atoms and1or more heteroatoms within the parent chain ("hetero$C_{1-16}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 14 carbon atoms and 1 or more heteroatoms within the parent chain ("hetero$C_{1-14}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to

12 carbon atoms and 1 or more heteroatoms within the parent chain ("hetero$C_{1-12}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1to 10 carbon atoms and 1or more heteroatoms within the parent chain ("hetero$C_{1-10}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("hetero$C_{1-8}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("hetero$C_{1-6}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms within the parent chain ("hetero$C_{1-4}$ alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("hetero$C_{1-3}$alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("hetero$C_{1-2}$alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("hetero$C_1$alkyl"). In some embodiments, the heteroalkyl group defined herein is a partially unsaturated group having 1 or more heteroatoms within the parent chain and at least one unsaturated carbon, such as a carbonyl group. For example, a heteroalkyl group may comprise an amide or ester functionality in its parent chain such that one or more carbon atoms are unsaturated carbonyl groups. Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted hetero$C_{1-20}$alkyl. In certain embodiments, the heteroalkyl group is an unsubstituted hetero$C_{1-10}$alkyl. In certain embodiments, the heteroalkyl group is a substituted hetero$C_{1-20}$alkyl. In certain embodiments, the heteroalkyl group is an unsubstituted hetero$C_{1-10}$alkyl.

The term "alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("$C_{2-9}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("$C_{2-8}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("$C_{2-7}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("$C_{2-6}$alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("$C_{2-5}$alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("$C_{2-4}$alkenyl"). In some embodiments, an alkenyl group has 2 to 3

carbon atoms ("$C_{2-3}$alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("$C_2$ alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2- butenyl) or terminal (such as in 1-butenyl). Examples of $C_{2-4}$ alkenyl groups include ethenyl ($C_2$), 1-propenyl ($C_3$), 2-propenyl ($C_3$), 1-butenyl ($C_4$), 2-butenyl ($C_4$), butadienyl ($C_4$), and the like. Examples of $C_{2-6}$ alkenyl groups include the aforementioned $C_{2-4}$ alkenyl groups as well as pentenyl ($C_5$), pentadienyl ($C_5$), hexenyl ($C_6$), and the like. Additional examples of alkenyl include heptenyl ($C_7$), octenyl ($C_8$), octatrienyl ($C_8$), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted $C_{2-10}$ alkenyl. In certain embodiments, the alkenyl group is a substituted $C_{2-10}$ alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, -CH=CHCH$_3$ or  ) may be an (E)- or (Z)-double bond.

The term "heteroalkenyl" refers to an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (i.e., inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2-10}$alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2-9}$alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2-8}$alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2-7}$alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2-6}$alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("hetero$C_{2-5}$alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("hetero$C_{2-4}$ alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("hetero$C_{2-3}$alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or

2 heteroatoms within the parent chain ("hetero$C_{2-6}$alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted hetero$C_{2-10}$alkenyl. In certain embodiments, the heteroalkenyl group is a substituted hetero$C_{2-10}$alkenyl.

The term "alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) ("$C_{2-10}$alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("$C_{2-9}$alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("$C_{2-8}$alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("$C_{2-7}$alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("$C_{2-6}$alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("$C_{2-5}$alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("$C_{2-4}$alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("$C_{2-3}$alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("$C_2$ alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of $C_{2\_4}$ alkynyl groups include, without limitation, ethynyl ($C_2$), 1-propynyl ($C_3$), 2-propynyl ($C_3$), 1-butynyl ($C_4$), 2-butynyl ($C_4$), and the like. Examples of $C_{2-6}$ alkenyl groups include the aforementioned $C_{2-4}$ alkynyl groups as well as pentynyl ($C_5$), hexynyl ($C_6$), and the like. Additional examples of alkynyl include heptynyl ($C_7$), octynyl ($C_8$), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted $C_{2-10}$ alkynyl. In certain embodiments, the alkynyl group is a substituted $C_{2-10}$ alkynyl.

The term "heteroalkynyl" refers to an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (i.e., inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2-10}$alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1or more heteroatoms within the parent chain ("hetero$C_{2-9}$alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and

1or more heteroatoms within the parent chain ("hetero$C_{2-8}$alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2-7}$alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2-6}$alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("hetero$C_{2-5}$alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("hetero$C_{2-4}$alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("hetero$C_{2-3}$alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("hetero$C_{2-6}$alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted hetero$C_{2-10}$alkynyl. In certain embodiments, the heteroalkynyl group is a substituted hetero$C_{2-10}$alkynyl.

The term "carbocyclyl," “cycloalkyl,” or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("$C_{3-14}$carbocyclyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("$C_{3-10}$carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("$C_{3-8}$carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("$C_{3-7}$carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("$C_{3-6}$carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("$C_{4-6}$carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("$C_{5-6}$carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("$C_{5-10}$carbocyclyl"). Exemplary $C_{3-6}$ carbocyclyl groups include, without limitation, cyclopropyl ($C_3$), cyclopropenyl ($C_3$), cyclobutyl ($C_4$), cyclobutenyl ($C_4$), cyclopentyl ($C_5$), cyclopentenyl ($C_5$), cyclohexyl ($C_6$), cyclohexenyl ($C_6$), cyclohexadienyl ($C_6$), and the like.

Exemplary $C_{3-8}$carbocyclyl groups include, without limitation, the aforementioned $C_{3-6}$ carbocyclyl groups as well as cycloheptyl ($C_7$), cycloheptenyl ($C_7$), cycloheptadienyl ($C_7$),

cycloheptatrienyl ($C_7$), cyclooctyl ($C_8$), cyclooctenyl ($C_8$), bicyclo[2.2.1]heptanyl ($C_7$), bicyclo[2.2.2]octanyl ($C_8$), and the like. Exemplary $C_{3-10}$ carbocyclyl groups include, without limitation, the aforementioned $C_{3-8}$ carbocyclyl groups as well as cyclononyl ($C_9$), cyclononenyl ($C_9$), cyclodecyl ($C_{10}$), cyclodecenyl ($C_{10}$), octahydro-1H-indenyl ($C_9$), decahydronaphthalenyl ($C_{10}$), spiro[4.5]decanyl ($C_{10}$), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted $C_{3-14}$ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted $C_{3-14}$ carbocyclyl.

In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("$C_{3-14}$cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("$C_{3-10}$cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("$C_{3-8}$cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("$C_{3-6}$cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("$C_{4-6}$cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("$C_{5-6}$cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("$C_{5-10}$cycloalkyl"). Examples of $C_{5-6}$ cycloalkyl groups include cyclopentyl ($C_5$) and cyclohexyl ($C_6$). Examples of $C_{3-6}$ cycloalkyl groups include the aforementioned $C_{5-6}$ cycloalkyl groups as well as cyclopropyl ($C_3$) and cyclobutyl ($C_4$). Examples of $C_{3-8}$ cycloalkyl groups include the aforementioned $C_{3-6}$ cycloalkyl groups as well as cycloheptyl ($C_7$) and cyclooctyl ($C_8$). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted $C_{3-14}$ cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted $C_{3-14}$ cycloalkyl.

As used herein, the term “heterocyclyl” refers to an aromatic (also referred to as a heteroaryl), unsaturated, or saturated cyclic hydrocarbon that includes at least one heteroatom in the cycle. For example, the term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3-14 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 polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic 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 carbocyclyl groups wherein the point of attachment is either on the carbocyclyl 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. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3-14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3-14 membered heterocyclyl.

In some embodiments, a heterocyclyl group is a 5-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heterocyclyl"). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some

embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include, without limitation, aziridinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazinyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7 -tetrahydro-1H-pyrrolo[2,3-b ]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

The term "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 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 provided in the aromatic ring system ("$C_{6-14}$aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("$C_6$aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("$C_{10}$aryl"; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("$C_{14}$aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted $C_{6-14}$aryl. In certain embodiments, the aryl group is a substituted $C_{6-14}$ aryl.

The term "heteroaryl" refers to a radical of a 5-14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-14 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 polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "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 the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, 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).

In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

Exemplary 5-membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 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, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

In general, the inclusion of the prefix "alk" in front of a substituent name indicates there is an alkyl group (as defined herein) connecting the named substitutent with the rest of the compound. For example, "alkaryl" (which is a subset of alkyl) refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety and "alkheteroaryl" (which is a subset of "alkyl") refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety. The number of carbons atoms may be specified in the alkyl chain, the named substituent, or both. For example, $C_{1\text{-}2}$alk$C_6$aryl refers to a phenyl ring (which may be substituted) connected via a 1-2 carbon alkylene group.

Affixing the suffix "-ene" to a group indicates the group is a polyvalent moiety, *e.g.*, boned to two or more groups. Alkylene is the polyvalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

A group is optionally substituted unless expressly provided otherwise. The term "optionally substituted" refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. "Optionally substituted" refers to a group which may be substituted or unsubstituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted"

heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds and includes any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. The invention is not intended to be limited in any manner by the exemplary substituents described herein.

Exemplary carbon atom substituents include, but are not limited to, halogen, -CN, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, -OH, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, -SH, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, -CHO, $-C(OR^{cc})_3$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$, $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)(N(R^{bb})_2)_2$,$-OP(=O)(N(R^{bb})_2)_2$, $-NR^{bb}P(=O)(R^{aa})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, $-P(R^{cc})_2$, $-P(OR^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_3^+X^-$, $-P(R^{cc})_4$, $-P(OR^{cc})_2$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3^+X^-$, $-OP(R^{cc})_4$, $-OP(OR^{cc})_4$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, $C_{1-10}$alkyl, $C_{1-10}$perhaloalkyl, $C_{2-10}$ alkenyl, $C_{2-10}$alkynyl, hetero$C_{1-10}$alkyl, hetero$C_{2-10}$ alkenyl, hetero$C_{2-10}$alkynyl, $C_{3-10}$ carbocyclyl, 3-14 membered heterocyclyl, $C_{6-14}$ aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 $R^{dd}$ groups; wherein $X^-$ is a

counterion; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$ or $=NOR^{cc}$; each instance of $R^{aa}$ is, independently, selected from $C_{1-10}$alkyl, $C_{1-10}$perhaloalkyl, $C_{2-10}$alkenyl, $C_{2-10}$ alkynyl, hetero$C_{1-10}$alkyl, hetero$C_{2-10}$ alkenyl, hetero$C_{2-10}$alkynyl, $C_{3-10}$ carbocyclyl, 3-14 membered heterocyclyl, $C_{6-14}$aryl, and 5-14 membered heteroaryl, or two $R^{aa}$ groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 $R^{dd}$ groups; each instance of $R^{bb}$ is, independently, selected from hydrogen, -OH, $-OR^{aa}$, $-N(R^{cc})_2$, -CN, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)(N(R^{cc})_2)_2$, $C_{1-10}$ alkyl, $C_{1-10}$perhaloalkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, hetero$C_{1-10}$alkyl, hetero$C_{2-10}$alkenyl, hetero$C_{2-10}$alkynyl, $C_{3-10}$carbocyclyl, 3-14 membered heterocyclyl, $C_{6-14}$aryl, and 5-14 membered heteroaryl, or two $R^{bb}$ groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 $R^{dd}$ groups; wherein $X^-$ is a counterion; each instance of $R^{cc}$ is, independently, selected from hydrogen, $C_{1-10}$alkyl, $C_{1-10}$perhaloalkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, hetero$C_{1-10}$ alkyl, hetero$C_{2-10}$alkenyl, hetero$C_{2-10}$alkynyl, $C_{3-10}$carbocyclyl, 3-14 membered heterocyclyl, $C_{6-14}$aryl, and 5-14 membered heteroaryl, or two $R^{cc}$ groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 $R^{dd}$ groups; each instance of $R^{dd}$ is, independently, selected from halogen, -CN, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, -OH, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, -SH, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, $C_{1-6}$ alkyl, $C_{1-6}$ perhaloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, hetero$C_{1-6}$ alkyl, hetero$C_{2-6}$ alkenyl, hetero$C_{2-6}$ alkynyl, $C_{3-10}$ carbocyclyl, 3-10

membered heterocyclyl, $C_{6-10}$ aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 $R^{gg}$ groups, or two geminal $R^{dd}$ substituents can be joined to form =O or =S; wherein $X^-$ is a counterion; each instance of $R^{ee}$ is, independently, selected from $C_{1-6}$alkyl, $C_{1-6}$perhaloalkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, hetero$C_{1-6}$ alkyl, hetero$C_{2-6}$alkenyl, hetero$C_{2-6}$alkynyl, $C_{3-10}$carbocyclyl, $C_{6-10}$aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 $R^{gg}$ groups; each instance of $R^{ff}$ is, independently, selected from hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ perhaloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, hetero$C_{1-6}$ alkyl, hetero$C_{2-6}$ alkenyl, hetero$C_{2-6}$ alkynyl, $C_{3-10}$ carbocyclyl, 3-10 membered heterocyclyl, $C_{6-10}$ aryl and 5-10 membered heteroaryl, or two $R^{ff}$ groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 $R^{gg}$ groups; and each instance of $R^{gg}$ is, independently, halogen, -CN, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, -OH, $-OC_{1-6}$ alkyl, $-ON(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_3^+X^-$, $-NH(C_{1-6}$ alkyl$)2^+$ $X^-$, $-NH_2(C_{1-6}$ alkyl$)^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl), -N(OH)($C_{1-6}$ alkyl), -NH(OH), -SH, $-SC_{1-6}$ alkyl, $-SS(C_{1-6}$ alkyl), $-C(=O)(C_{1-6}$ alkyl), $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), $-OC(=O)(C_{1-6}$ alkyl), $-OCO_2(C_{1-6}$ alkyl), $-C(=O)NH_2$, $-C(=O)N(C_{1-6}$ alkyl$)_2$, -OC(=O)NH($C_{1-6}$ alkyl), -NHC(=O)($C_{1-6}$ alkyl), -N($C_{1-6}$ alkyl)C(=O)( $C_{1-6}$ alkyl), $-NHCO_2(C_{1-6}$ alkyl), -NHC(=O)N($C_{1-6}$ alkyl$)_2$, -NHC(=O)NH($C_{1-6}$ alkyl), $-NHC(=O)NH_2$, -C(=NH)O($C_{1-6}$ alkyl), -OC(=NH)($C_{1-6}$ alkyl), -OC(=NH)O$C_{1-6}$ alkyl, $-C(=NH)N(C_{1-6}$ alkyl$)_2$, -C(=NH)NH($C_{1-6}$ alkyl), $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6}$ alkyl$)_2$, -OC(=NH)NH($C_{1-6}$ alkyl), $-OC(=NH)NH_2$, -NHC(=NH)N($C_{1-6}$ alkyl$)_2$, $-NHC(=NH)NH_2$, $-NHSO_2(C_{1-6}$ alkyl), $-SO_2N(C_{1-6}$ alkyl$)_2$, $-SO_2NH(C_{1-6}$ alkyl), $-SO_2NH_2$, $-SO_2(C_{1-6}$ alkyl), $-SO_2O(C_{1-6}$ alkyl), $-OSO_2(C_{1-6}$ alkyl), -SO($C_{1-6}$ alkyl), $-Si(C_{1-6}$ alkyl$)_3$, $-OSi(C_{1-6}$ alkyl$)_3$, $-C(=S)N(C_{1-6}$ alkyl$)_2$, -C(=S)NH($C_{1-6}$ alkyl), $-C(=S)NH_2$, -C(=O)S($C_{1-6}$ alkyl), -C(=S)S$C_{1-6}$ alkyl, -SC(=S)S$C_{1-6}$ alkyl, $-P(=O)(OC_{1-6}$ alkyl$)_2$, $-P(=O)(C_{1-6}$ alkyl$)_2$, $-OP(=O)(C_{1-6}$ alkyl$)_2$, $-OP(=O)(OC_{1-6}$ alkyl$)_2$, $C_{1-6}$alkyl, $C_{1-6}$perhaloalkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, hetero$C_{1-6}$alkyl, hetero$C_{2-6}$alkenyl, hetero$C_{2-6}$alkynyl, $C_{3-10}$carbocyclyl, $C_{6-10}$aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal $R^{gg}$ substituents can be joined to form =O or =S; wherein $X^-$ is a counterion.

The term "halo" or "halogen" refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

The term "acyl" refers to a group having the general formula -C(=O)$R^{X1}$, -C(=O)O$R^{X1}$, -C(=O)-O-C(=O)$R^{X1}$, -C(=O)S$R^{X1}$, -C(=O)N($R^{X1}$)$_2$, -C(=S)$R^{X1}$, -C(=S)N($R^{X1}$)2, -C(=S)O($R^{X1}$), -C(=S)S($R^{X1}$), -C(=N$R^{X1}$)$R^{X1}$, -C(=N$R^{X1}$)O$R^{X1}$, -C(=N$R^{X1}$)S$R^{X1}$, and -C(=N$R^{X1}$)N($R^{X1}$)$_2$, wherein $R^{X1}$ is hydrogen; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, mono- or di- aliphaticamino, mono- or di- heteroaliphaticamino, mono- or dialkylamino, mono- or di-heteroalkylamino, mono- or di-arylamino, or mono- or diheteroarylamino; or two $R^{X1}$ groups taken together form a 5- to 6-membered heterocyclic ring.

Exemplary acyl groups include aldehydes (-CHO), carboxylic acids (-$CO_2$H), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents include, butare not limited to, any of the substituents described herein, that result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

The term "carbonyl" refers a group wherein the carbon directly attached to the parent molecule is $sp^2$ hybridized, and is substituted with an oxygen, nitrogen or sulfur atom, *e.g.*, a group selected from ketones (*e.g.*, -C(=O)$R^{aa}$), carboxylic acids (*e.g.*, -$CO_2$H), aldehydes( CHO), esters (*e.g.*, -$CO_2R^{aa}$, -C(=O)S$R^{aa}$, -C(=S)S$R^{aa}$), amides (*e.g.*, -C(=O)N($R^{bb}$)$_2$, C(=O)N$R^{bb}$S$O_2R^{aa}$,

-C(=S)N($R^{bb}$)$_2$, and imines (*e.g.*, -C(=N$R^{bb}$)$R^{aa}$, -C(=N$R^{bb}$)O$R^{aa}$), C(=N$R^{bb}$)N($R^{bb}$)$_2$, wherein $R^{aa}$ and $R^{bb}$ are as defined herein.

The term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

The term "cyano" refers to the group –CN.

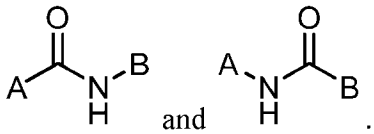
The term "azide" and "azido" refers to the group $-N_3$.

Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -O$R^{aa}$, -N($R^{cc}$)$_2$, -CN, -C(=O)$R^{aa}$, -C(=O)N($R^{cc}$)$_2$, -$CO_2R^{aa}$, -$SO_2R^{aa}$, -C(=N$R^{bb}$)$R^{aa}$, -C(=N$R^{cc}$)O$R^{aa}$, -C(=N$R^{cc}$)N($R^{cc}$)$_2$, -$SO_2$N($R^{cc}$)$_2$, -$SO_2R^{cc}$, -$SO_2OR^{cc}$, -$SOR^{aa}$, -C(=S)N($R^{cc}$)$_2$, -C(=O)S$R^{cc}$, -C(=S)S$R^{cc}$, -P(=O)(O$R^{cc}$)$_2$, -P(=O)($R^{aa}$)$_2$, -P(=O)(N($R^{cc}$)$_2$)$_2$, $C_{1-10}$ alkyl, $C_{1-10}$ perhaloalkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, hetero$C_{1-10}$ alkyl, hetero$C_{2-10}$ alkenyl, hetero$C_{2-10}$ alkynyl, $C_{3-10}$ carbocyclyl, 3-14 membered heterocyclyl, $C_{6-14}$ aryl, and 5-14 membered heteroaryl, or two $R^{cc}$ groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or a 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 $R^{dd}$ groups, and wherein $R^{aa}$, $R^{bb}$, $R^{cc}$, and $R^{dd}$ are as defined herein.

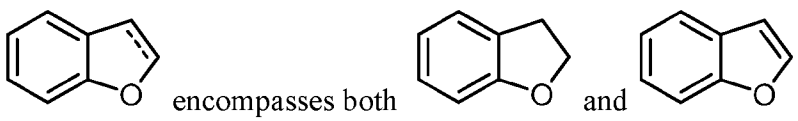
As used herein, the designation of a polyvalent moiety without specifying the specific order of attachment is intended to cover all possible arrangements. By way of example, a compound represented by the formula:

A-X-B,

wherein X is NHC(=O) embraces both:



As used herein, a chemical bond depicted: ⫶ represents either a single, double, or triple bond, valency permitting. By way of example,

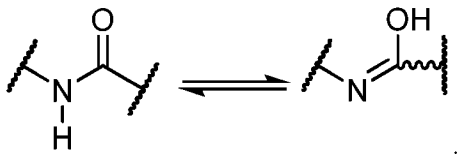


An electron-withdrawing group is a functional group or atom that pulls electron density towards itself, away from other portions of the molecule, e.g., through resonance and/or inductive effects. Exemplary electron-withdrawing groups include F, Cl, Br, I, $NO_2$, CN, $SO_2R$, $SO_3R$, $SO_2NR_2$, $C(O)R^{1a}$; C(O)OR, and $C(O)NR_2$ (wherein R is H or an alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl group) as well as alkyl group substituted with one or more of those group

An electron-donating group is a functional group or atom that pushes electron density away from itself, towards other portions of the molecule, e.g., through resonance and/or inductive effects. Exemplary electron-donating groups include unsubstituted alkyl or aryl groups, OR and $N(R)_2$ and alkyl groups substituted with one or more OR and $N(R)_2$ groups.

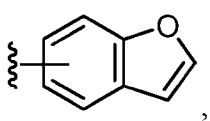
Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer, diastereomer, and meso compound, and a mixture of isomers, such as a racemic or scalemic mixture. Unless stated to the contrary, a formula depicting one or more stereochemical features does not exclude the presence of other isomers.

Some compounds disclosed herein may exist as one or more tautomers. Tautomers are interconvertible structural isomers that differ in the position of one or more protons or other labile atom. By way of example:




The prevalence of one tautomeric form over another will depend on the specific chemical compound as well as its local chemical environment. Unless specified to the contrary, the depiction of one tautomeric form is inclusive of all possible tautomeric forms.

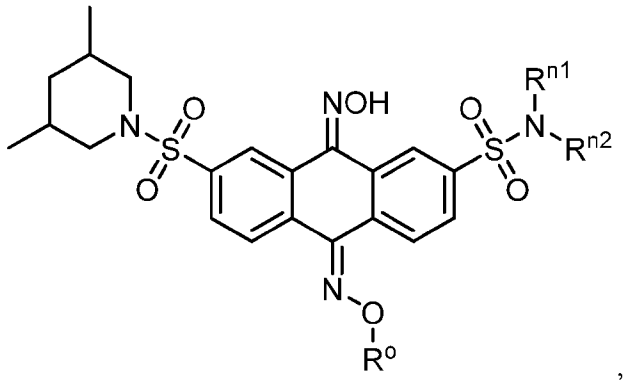
Unless stated to the contrary, a substituent drawn without explicitly specifying the point of attachment indicates that the substituent may be attached at any possible atom. For example, in a benzofuran depicted as:




the substituent may be present at any one of the six possible carbon atoms.

As used herein, the term "null," when referring to a possible identity of a chemical moiety, indicates that the group is absent, and the two adjacent groups are directly bonded to one another. By way of example, for a genus of compounds having the formula $CH_3$-X-$CH_3$, if X is null, then the resulting compound has the formula $CH_3$-$CH_3$.

Disclosed herein a PROTAC compounds including a tegavivint warhead, covalently linked to a E3 ligase ligand. In some implementations, the compound has the formula:



,

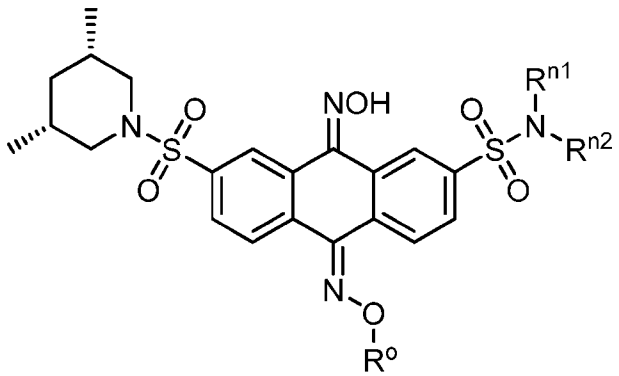
or a pharmaceutically acceptable salt thereof, wherein

$R^0$ is H and $R^{n1}$ and $R^{n2}$ form a heterocycle substituted by $X^e$, or

$R^o$ is $X^e$ and $R^{n1}$ and $R^{n2}$ form a heterocycle,

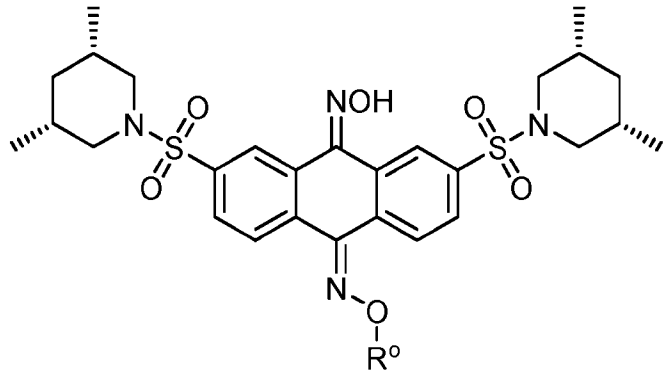
wherein $X^e$ represents a covalently linked E3 ligand.

In certain implementations the compound has the formula:

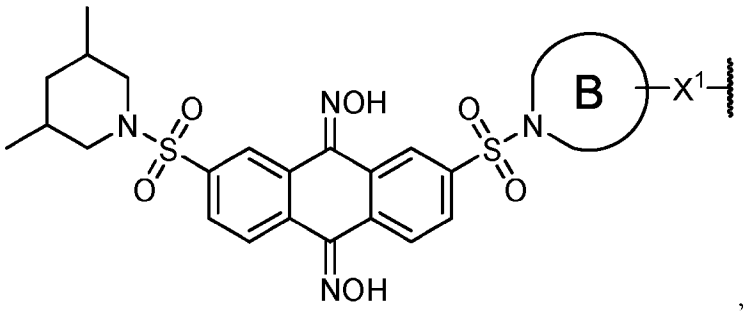


.

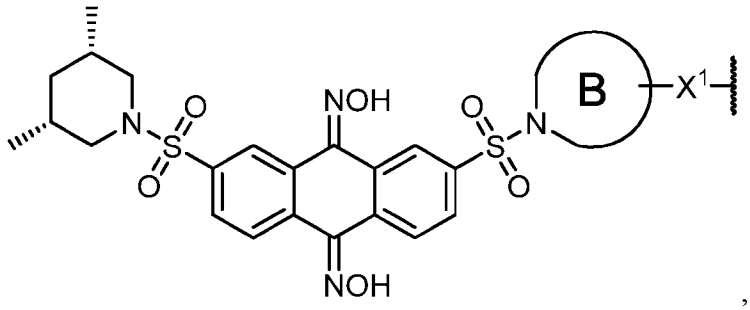
In certain implementations the PROTAC compound has the formula:



In certain implementations the PROTAC compound has the formula:



, or



,

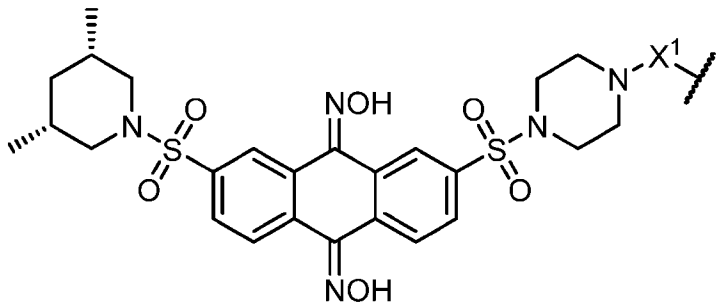
wherein

B represents a monocyclic heterocyclic system;

$X^1$ is selected from null, -C≡C-, NH, O, C(=O), OC(=O), or NHC(=O); and

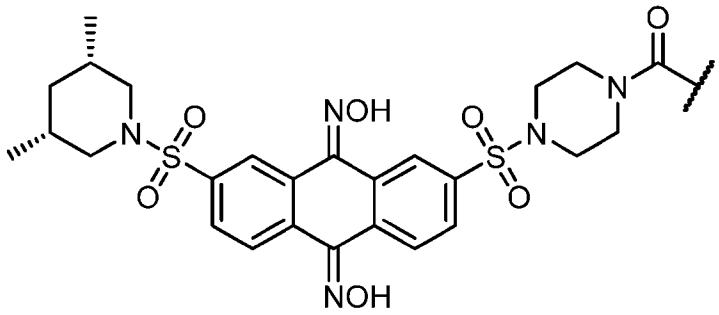
the wavy line represents the bond to $X^e$.

In certain implementations B is a piperazine ring, for example:

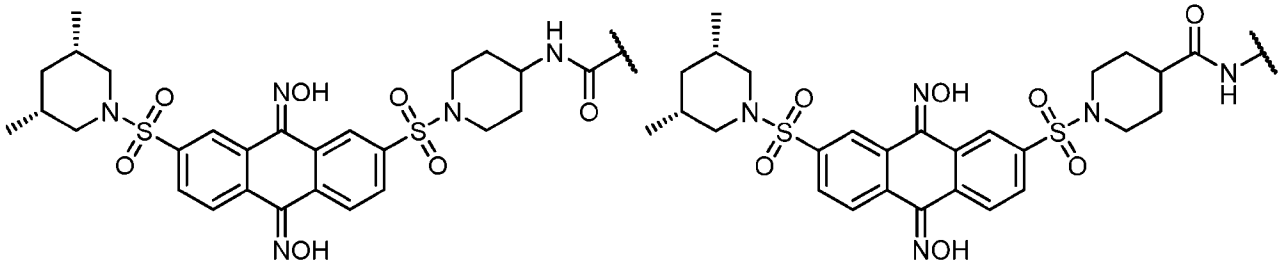


.

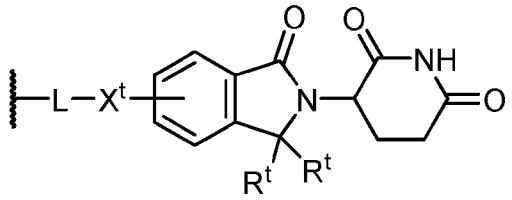
In certain implementations B is a piperazine ring and $X^1$ is carbonyl:



In certain embodiments, B is a piperidine, and $X^1$ is NHC(=O):



A variety of E3 ligase ligands may be deployed in the PROTAC compound. In some implementations, $X^e$ can have the formula:



,

wherein

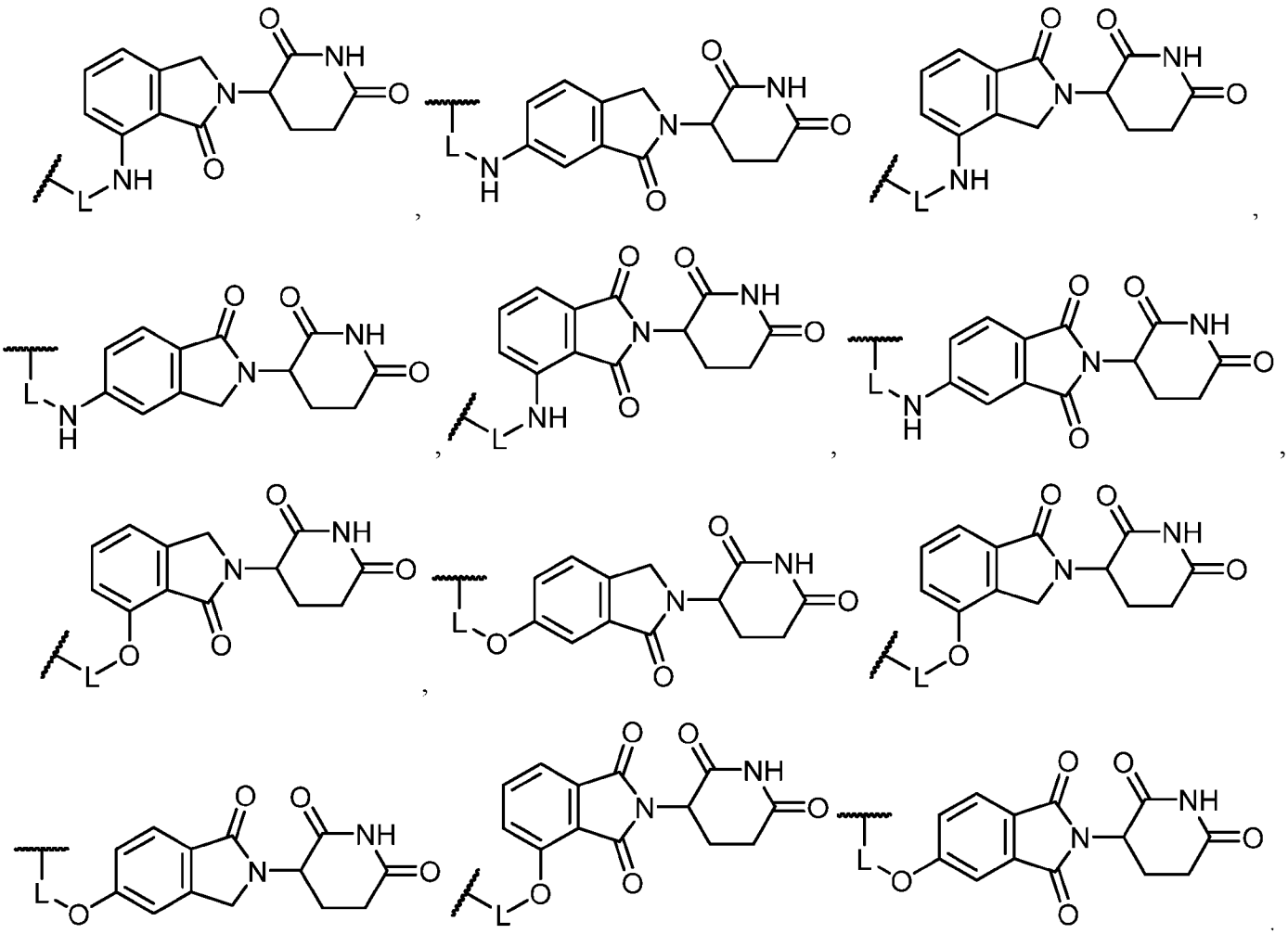
L is a linker

$R^t$ is in each case hydrogen, or both of $R^t$ together form an oxo; and

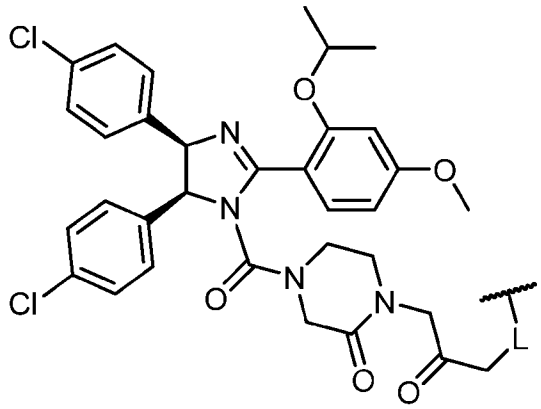
$X^t$ is null, NH, O, -C≡C-, or NHC(=O).

In certain implementations, $X^t$ is NH, O, or -C≡C-.

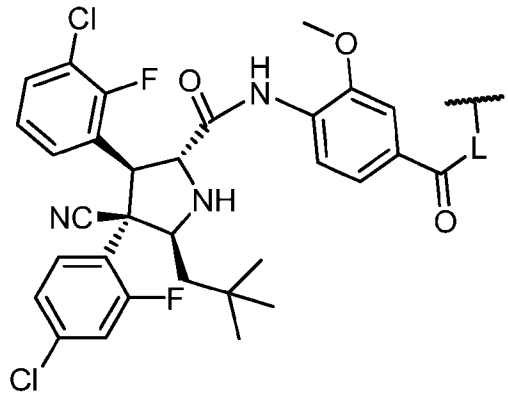
In some implementations, $X^e$ has the formula:

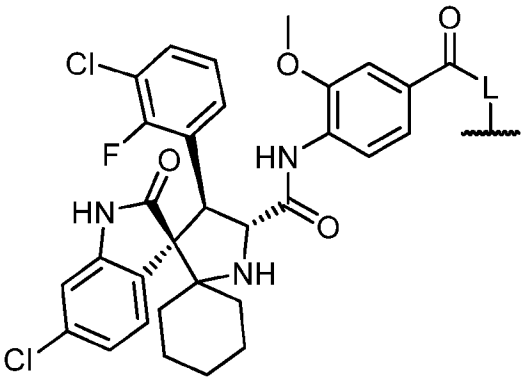


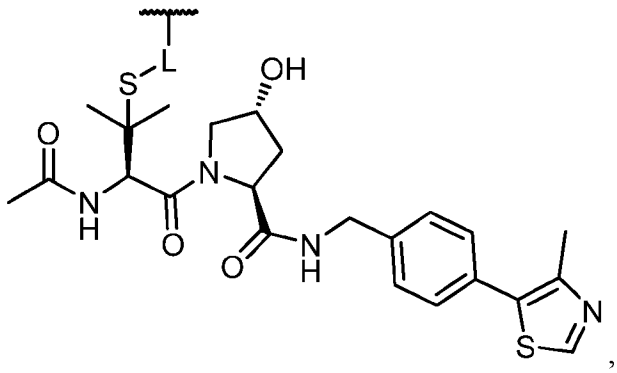
In some embodiments, $X^e$ has the formula:



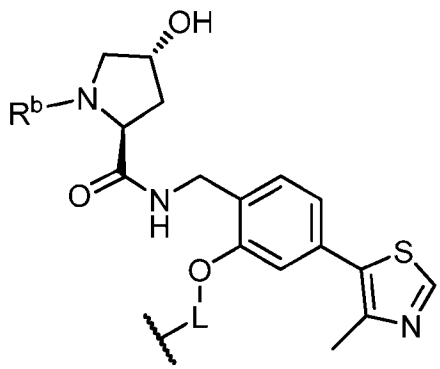
,

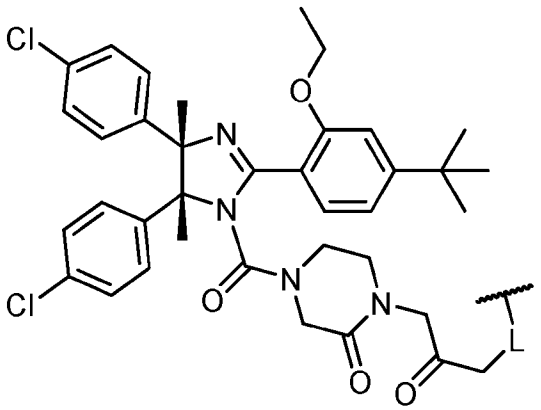


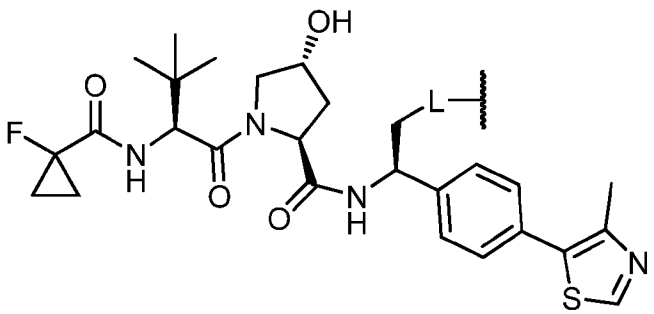


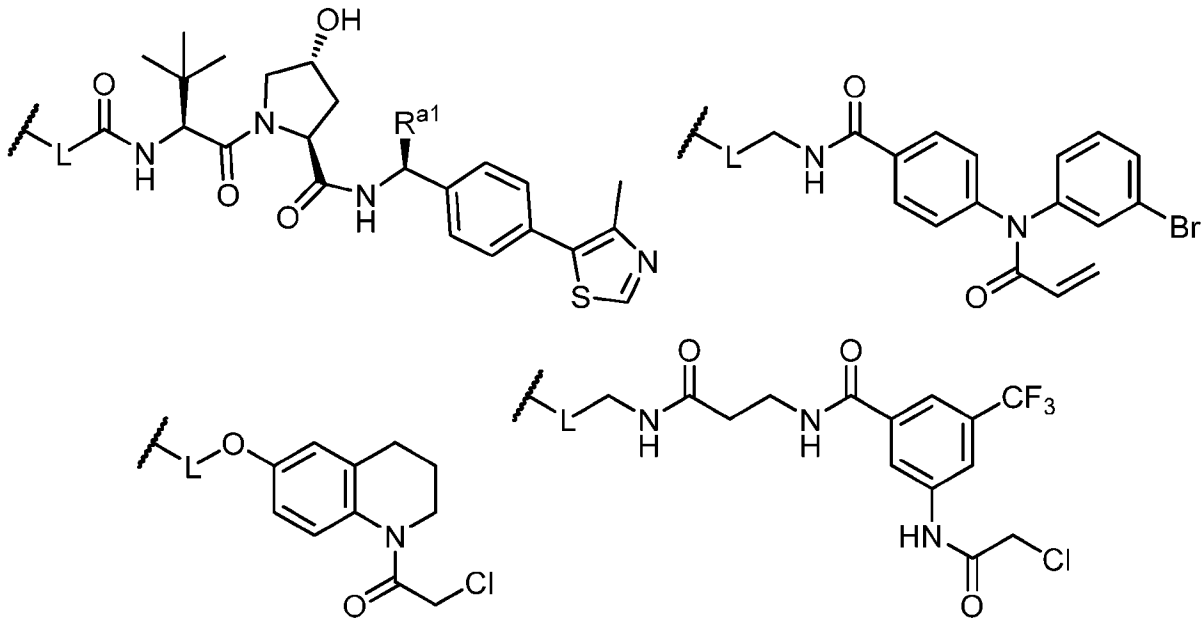


,





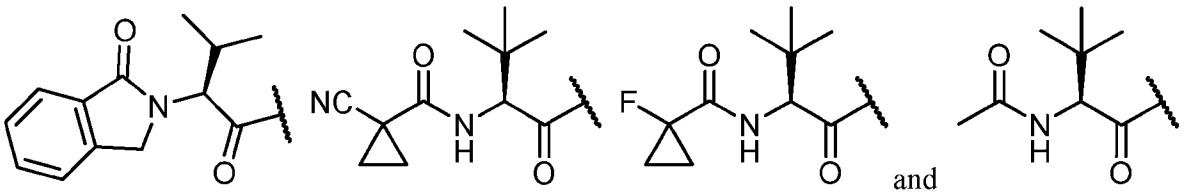




wherein L is a linker;

$R^{a1}$ is H or $CH_3$; and

$R^b$ is selected from:



and .

In certain implementation the linker may be represented by the formula:

$$L^1\text{-}X^2\text{-}L^2,$$

wherein

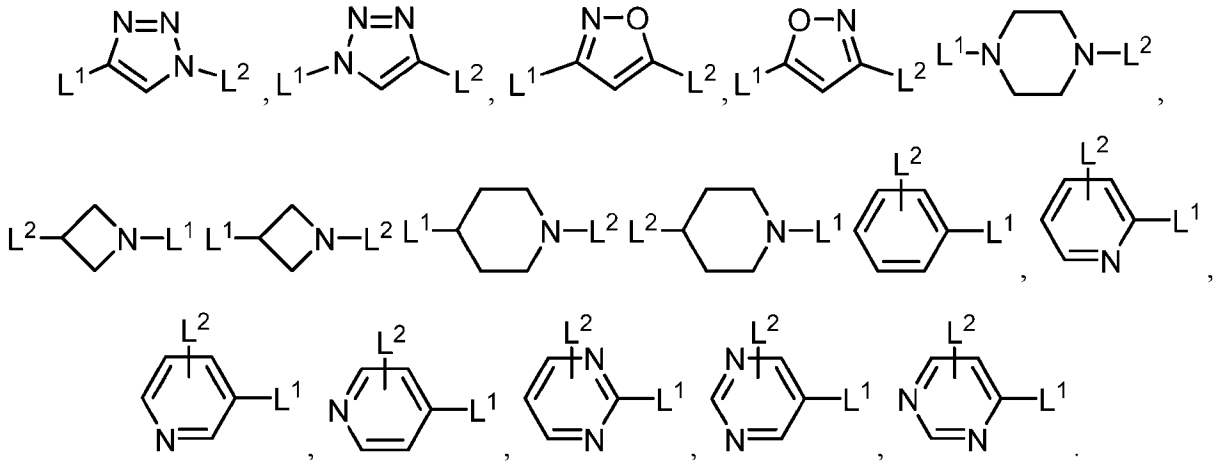
$X^2$ is null, heteroaryl, heterocyclyl, carbocyclyl, aryl, NH, O, C(=O), OC(=O), NHC(=O), NHC(=O)NH, or NHC(=O)O;

$L^1$ is null, $C_{1\text{-}20}$alkylene, or $(CH_2CH_2O)_n$, wherein n is from 1-20; and $L^1$ is bonded to $R^o$ or $X^1$ ,and

$L^2$ is null, $C_{1\text{-}20}$alkylene, or $(CH_2CH_2O)_m$, wherein m is from 1-20, and $L^2$ is bonded to the E3 ligand.

In certain implementations, $X^2$ includes a heterocycle or heteroaryl formed from a cycloaddition reaction, for example a click 1,3 dipole cycloaddition reaction or inverse demand Diels Alder reaction. Such coupling protocols are well established to covalently link two compounds having a wide variety of functional groups under mild conditions. In some implementations, $X^2$ a 1,2,3 triazole ring. In other implementations, the coupling is carried out under copper-free conditions using a azide and cyclooctyne, which results in a triazole fused to a cyclooctyl ring.

In some implementations, L has the formula:



When $X^2$ is an aromatic or heteroaromatic ring, the $L^1$ and $L^2$ groups may be 1,2 substituted, 1,3 substituted, or 1,4 substituted.

$X^2$ may be further substituted with groups to increase water solubility, for example by hydroxyalkyls, carboxylic acids, sulfonic acids, and/or ammonium salts.

The overall length of the linker may be controlled by selection of the particular $L^1$ and $L^2$ groups. In certain implementations, $L^1$ is $(CH_2CH_2O)_n$, wherein n is from 1-10, and $L^2$ is $C_{1-8}$alkylene.

In some implementations, $L^2$ is $(CH_2CH_2O)_n$, wherein n is from 1-10, and $L^1$ is $C_{1-8}$alkylene.

In further implementations, both $L^1$ and $L^2$ are ethylene glycol chains, e.g., $L^1$ is $(CH_2CH_2O)_n$, wherein n is from 1-10, and $L^2$ is $(CH_2CH_2O)_n$, wherein n is from 1-10. In some implementations, both $L^1$ and $L^2$ are both alkylene chains, e.g., $L^1$ is $C_{2-8}$alkylene and $L^1$ is $C_{2-8}$alkylene.

In some implementations, one or both of $L^1$ and $L^2$ are absent (i.e., null). For example, in certain implementations $L^1$ is absent and in other implementations $L^2$ is absent. In yet further implementations, both of $L^1$ and $L^2$ are absent. In certain implementations, $L^1$ is $C_{2\text{-}12}$alkylene, $C_{2\text{-}6}$alkylene, $C_{4\text{-}8}$alkylene, $C_{6\text{-}12}$alkylene, or $C_{8\text{-}12}$alkylene, and $X^2$ and $L^2$ are null.

In other implementations $L^2$ is $(CH_2CH_2O)_n$, wherein n is 1 to 5, $X^2$ is null or NHC(=O), and $L^2$ is ethylene.

In some implementations $L^1$ is $(CH_2CH_2O)_n$, wherein n is 1 to 5, $X^2$ is null or NHC(=O), and $L^2$ is ethylene.

Also provided herein are methods of treating cancer in a subject in need thereof, by administering to the subject one or more of the compounds disclosed herein. In certain embodiments the cancer is breast cancer, leukemia, or lymphoma, for example diffuse large B-cell lymphoma.

## EXAMPLES

The following examples are for the purpose of illustration of the invention only and are not intended to limit the scope of the present invention in any manner whatsoever.

**Example 1:**

A library of PROTAC compounds was prepared according to the sequences depicted in Figures 1 and 2. These compounds were evaluated against three different lymphoma cell lines (Riva, Pfeiffer, and Granta-519):

| Compound | Series | Linker | $IC_{50}$/nM | | |
|---|---|---|---|---|---|
| | | | Riva | Pfeiffer | Granta-519 |
| RY-3-119 | N-linked | Alkyl/3 | 796.9 | 564.5 | 398.6 |
| RY-3-120 | N-linked | Alkyl/5 | 560.3 | 646.6 | 495.6 |
| RY-3-108 | N-linked | Alkyl/7 | 604.6 | 343.4 | 439.2 |
| RY-3-121 | N-linked | Alkyl/11 | 1162 | 2500 | 1157 |
| RY-3-122 | N-linked | PEG/6 | > 20,000 | > 20,000 | > 20,000 |
| RY-3-113 | N-linked | PEG/9 | > 20,000 | > 20,000 | > 20,000 |
| RY-3-123 | N-linked | PEG/12 | > 20,000 | > 20,000 | > 20,000 |

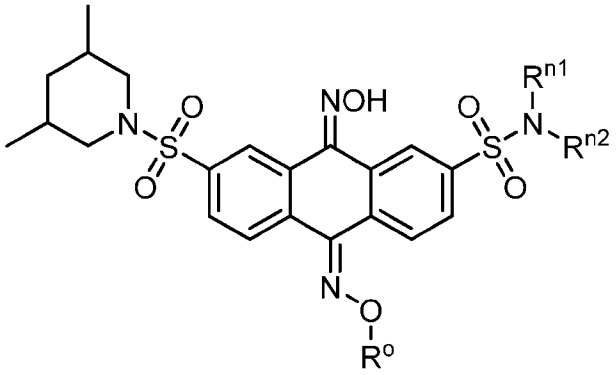
| | | | | | |
|---|---|---|---|---|---|
| RY-3-127 | O-linked | Alkyl/7 | 650.9 | 188.9 | 323.4 |
| RY-3-128 | O-linked | Alkyl/9 | 795.0 | 397.6 | 522.6 |
| RY-3-130 | O-linked | Alkyl/11 | 928.9 | 354.6 | 529.7 |
| RY-3-124 | O-linked | Alkyl/15 | > 20,000 | > 20,000 | > 20,000 |
| RY-3-129 | O-linked | PEG/10 | 1353 | 553.7 | 1041 |
| RY-3-131 | O-linked | PEG/13 | > 20,000 | 1878 | > 20,000 |
| RY-3-132 | O-linked | PEG/16 | > 20,000 | > 20,000 | > 20,000 |
| Tegavivint | - | - | 86 | 175.4 | 94 |

The compositions and methods of the appended claims are not limited in scope by the specific compositions and methods described herein, which are intended as illustrations of a few aspects of the claims and any compositions and methods that are functionally equivalent are intended to fall within the scope of the claims. Various modifications of the compositions and methods in addition to those shown and described herein are intended to fall within the scope of the appended claims. Further, while only certain representative compositions and method steps disclosed herein are specifically described, other combinations of the compositions and method steps also are intended to fall within the scope of the appended claims, even if not specifically recited. Thus, a combination of steps, elements, components, or constituents may be explicitly mentioned herein or less, however, other combinations of steps, elements, components, and constituents are included, even though not explicitly stated. The term "comprising" and variations thereof as used herein is used synonymously with the term "including" and variations thereof and are open, non-limiting terms. Although the terms "comprising" and "including" have been used herein to describe various embodiments, the terms "consisting essentially of" and "consisting of" can be used in place of "comprising" and "including" to provide for more specific embodiments of the invention and are also disclosed. Other than in the examples, or where otherwise noted, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood at the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, to be construed in light of the number of significant digits and ordinary rounding approaches.

## CLAIMS

What is claimed is:

1. A compound having the formula:



,

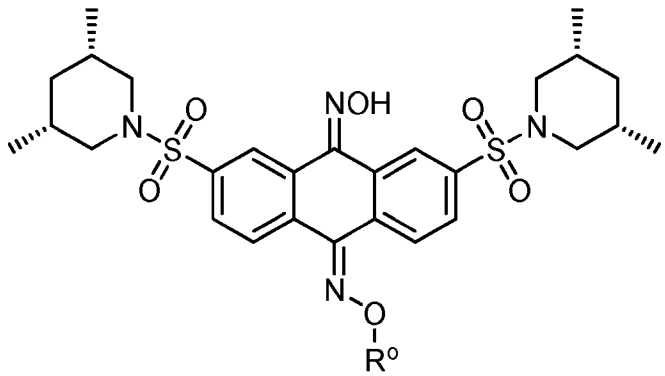
or a pharmaceutically acceptable salt thereof, wherein

$R^0$ is H and $R^{n1}$ and $R^{n2}$ form a heterocycle substituted by $X^e$, or

$R^o$ is $X^e$ and $R^{n1}$ and $R^{n2}$ form a heterocycle; and

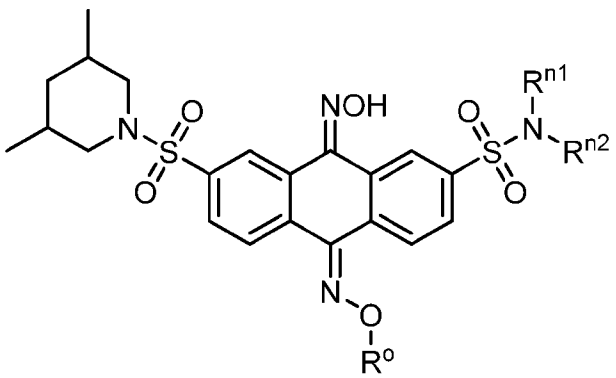
$X^e$ represents a covalently linked E3 ligand.

2. The compound according to claim 1, wherein the compound has the formula:



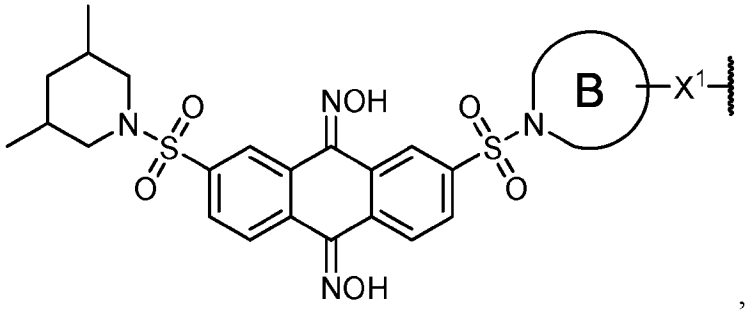
,

3. The compound according to claim 1, wherein the compound has the formula:



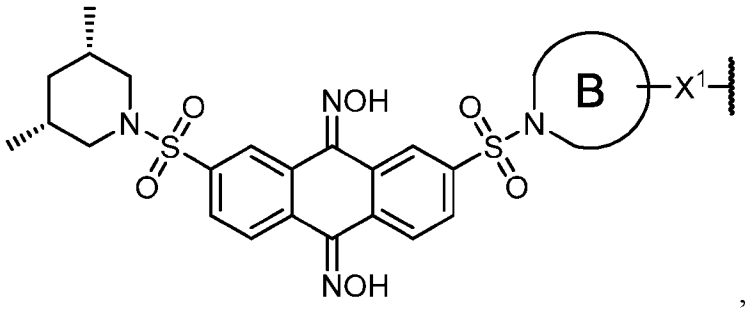
,

4. The compound according to claim 1, wherein the compound has the formula:



,

5. The compound according to claim 1, wherein the compound has the formula:



,

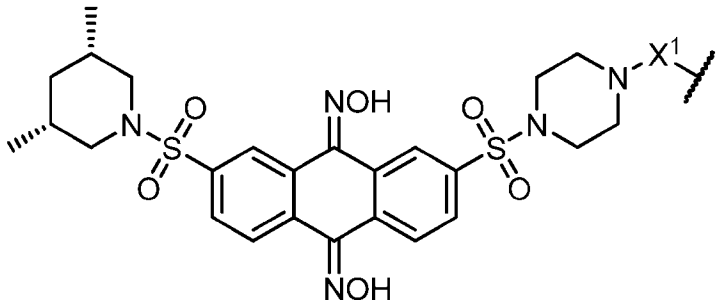
wherein

B represents a monocyclic heterocyclic system;

$X^1$ is selected from null, -C≡C-, NH, O, C(=O), OC(=O), or NHC(=O); and

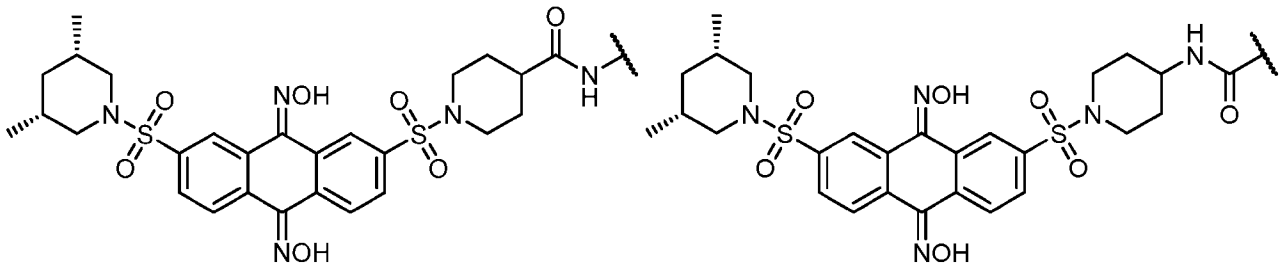
the wavy line represents the bond to $X^e$.

6. The compound according to claim 5, wherein the compound has the formula:

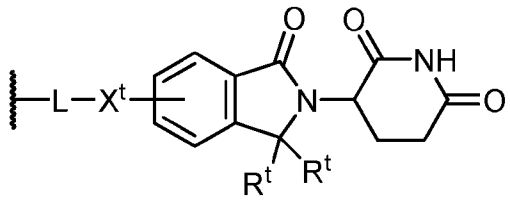


7. The compound according to claim 4, wherein $X^1$ is carbonyl or NHC(=O).

8. The compound according to claim 1, having the formula:



9. The compound according to any of claims 1-8, wherein $X^e$ has the formula:



,

wherein

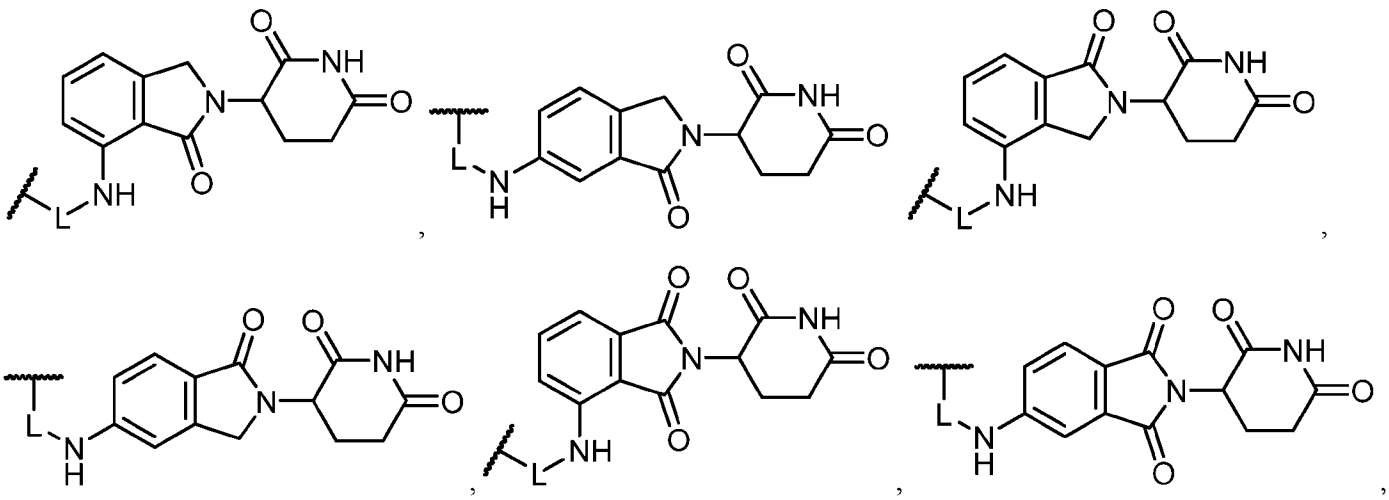
L is a linker

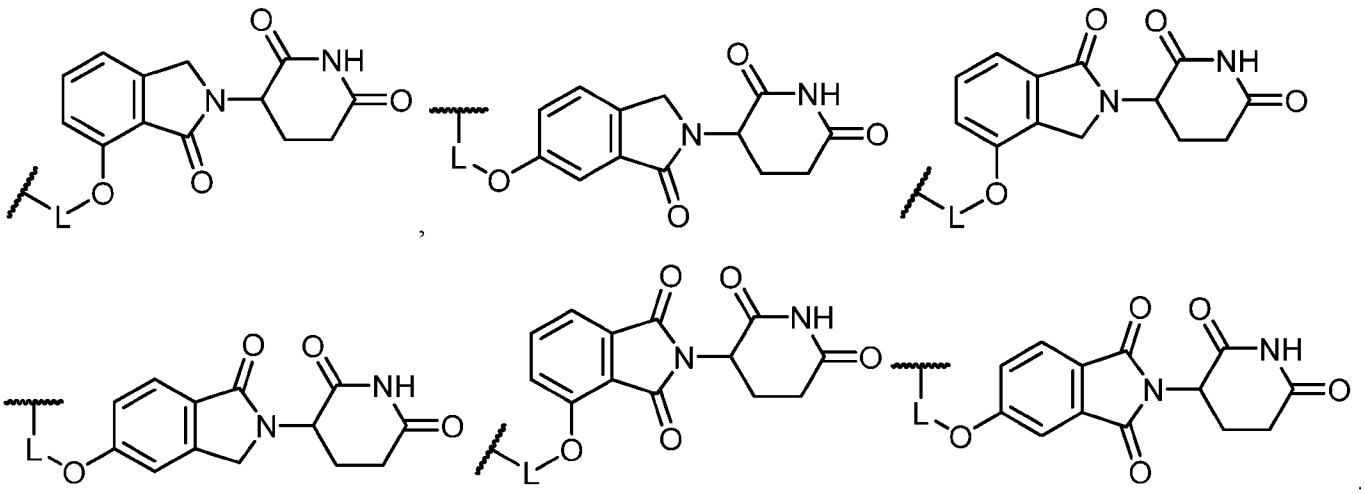
$R^t$ is in each case hydrogen, or both of $R^t$ together form an oxo; and

$X^t$ is null, NH, O, -C≡C-, or NHC(=O).

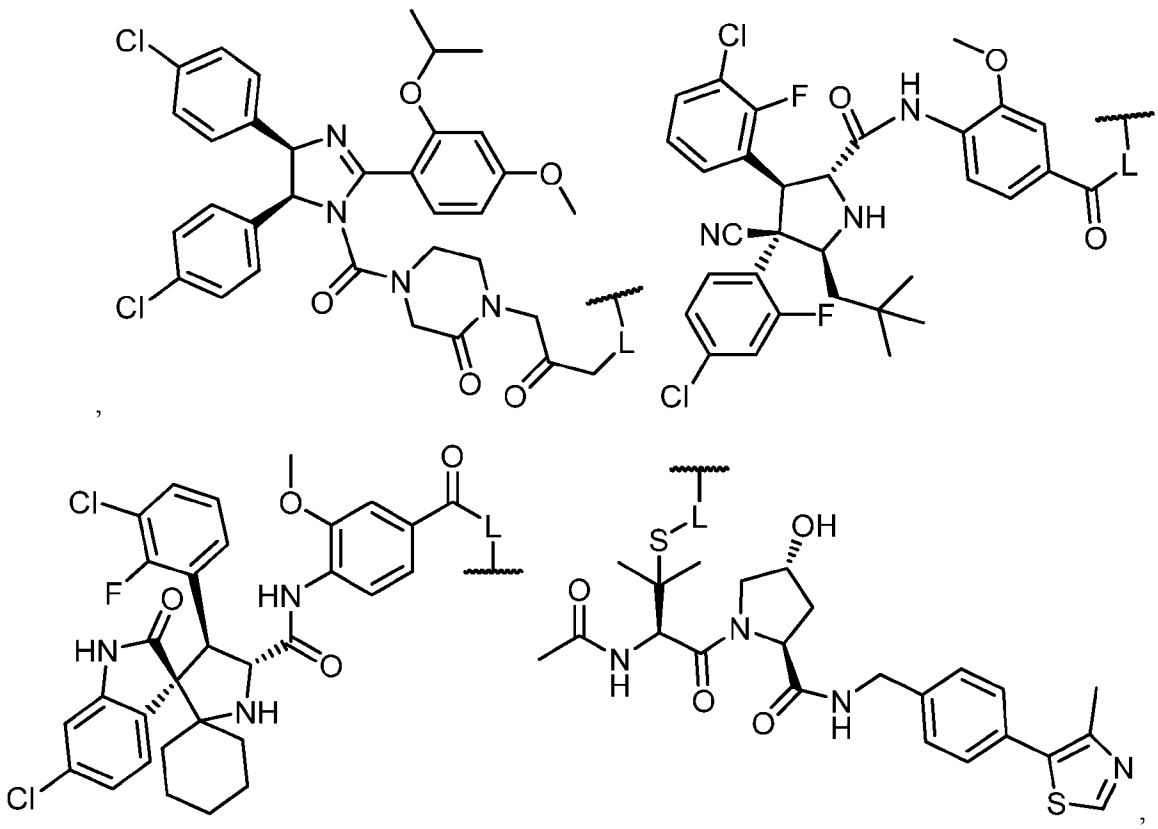
10. The compound according to claim 9, wherein $X^t$ is NH, O, or -C≡C-.

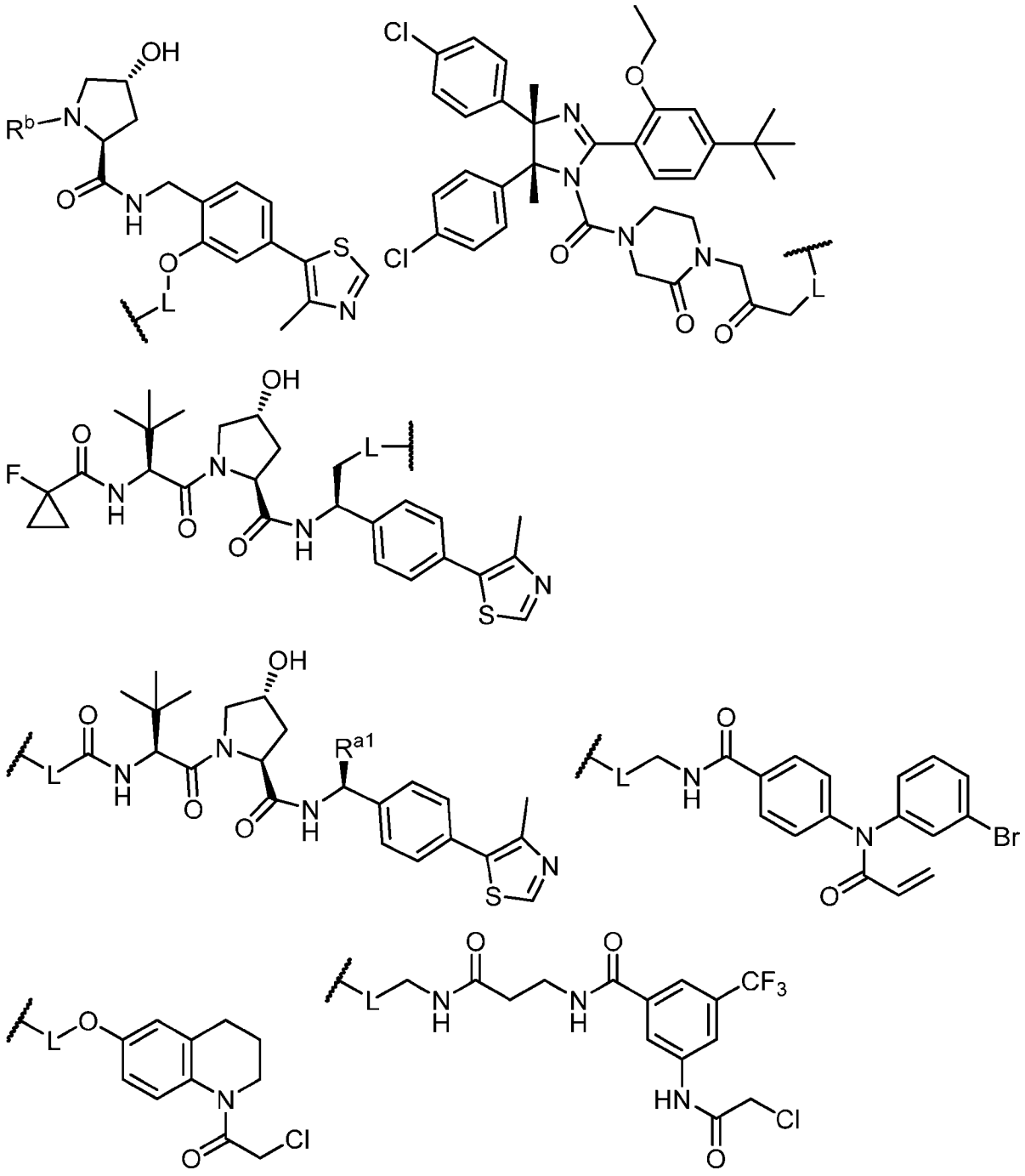
11. The compound according to claim 9, wherein $X^e$ has the formula:





12. The compound according to any of claims 1-8, wherein $X^e$ has the formula:





wherein

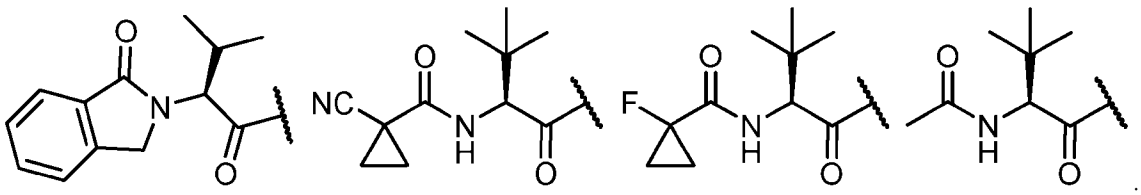
L is a linker

$R^t$ is in each case hydrogen, or both of $R^t$ together form an oxo;

$X^t$ is null, NH, O, -C≡C-, or NHC(=O);

$R^{a1}$ is H or $CH_3$; and

$R^b$ is selected from



13. The compound according to any of claims 9-12, wherein L has the formula:

$$L^1\text{-}X^2\text{-}L^2,$$

wherein

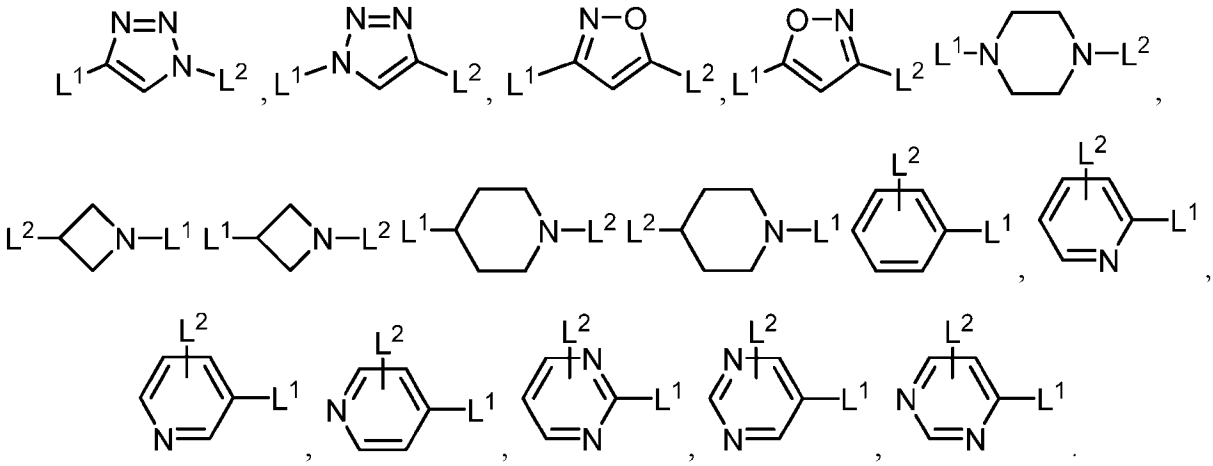
$X^2$ is null, heteroaryl, heterocyclyl, carbocyclyl, aryl, NH, O, C(=O), OC(=O), NHC(=O), NHC(=O)NH, or NHC(=O)O;

$L^1$ is null, $C_{1\text{-}20}$alkylene, or $(CH_2CH_2O)_n$, wherein n is from 1-20; and $L^1$ is bonded to $R^o$ or $X^1$ ,and

$L^2$ is null, $C_{1\text{-}20}$alkylene, or $(CH_2CH_2O)_m$, wherein m is from 1-20, and $L^2$ is bonded to the E3 ligand.

14. The compound according to claim 13, wherein $X^2$ comprises a 1,2,3 triazole ring.

15. The compound according to claim 13, wherein L has the formula:



16. The compound according to any of claims 13-15, wherein $L^1$ is $(CH_2CH_2O)_n$, wherein n is from 1-10, and $L^2$ is $C_{1\text{-}8}$alkylene.

17. The compound according to any of claims 13-15, wherein $L^2$ is $(CH_2CH_2O)_n$, wherein n is from 1-10, and $L^1$ is $C_{1\text{-}8}$alkylene.

18. The compound according to any of claims 13-15, wherein $L^1$ is $C_{2-8}$alkylene and $L^1$ is $C_{2-8}$alkylene.
19. The compound according to any of claims 13-15, wherein $L^1$ is $C_{2-12}$alkylene, and $X^2$ and $L^2$ are null.
20. The compound according to any of claims 13-15, wherein $L^1$ is $C_{2-6}$alkylene, and $X^2$ and $L^2$ are null.
21. The compound according to any of claims 13-15, wherein $L^1$ is $C_{4-8}$alkylene, and $X^2$ and $L^2$ are null.
22. The compound according to any of claims 13-15, wherein $L^1$ is $C_{6-12}$alkylene, and $X^2$ and $L^2$ are null.
23. The compound according to any of claims 13-15, wherein $L^1$ is $C_{8-12}$alkylene, and $X^2$ and $L^2$ are null.
24. The compound according to any of claims 13-15, wherein $L^2$ is $(CH_2CH_2O)_n$, wherein n is 1 to 5, $X^2$ is null, and $L^2$ is ethylene.
25. The compound according to any of claims 13-15, wherein $L^1$ is $(CH_2CH_2O)_n$, wherein n is 1 to 5, $X^2$ is null, and $L^2$ is ethylene.
26. The compound according to any of claims 13-15, wherein $L^1$ is $(CH_2CH_2O)_n$, wherein n is 1 to 5, $X^2$ is NHC(=O), and $L^2$ is $C_{1-6}$alkylene.
27. The compound according to any of claims 13-15, wherein $L^2$ is $(CH_2CH_2O)_n$, wherein n is 1 to 5, $X^2$ is NHC(=O), and $L^1$ is $C_{1-6}$alkylene.
28. A method of treating cancer in a subject in need thereof, comprising administering to the subject a compound according to any of claims 1-27.
29. The method according to claim 28, wherein the cancer is breast cancer, leukemia, or lymphoma.
30. The method according to claim 28, wherein the cancer is diffuse large B-cell lymphoma.

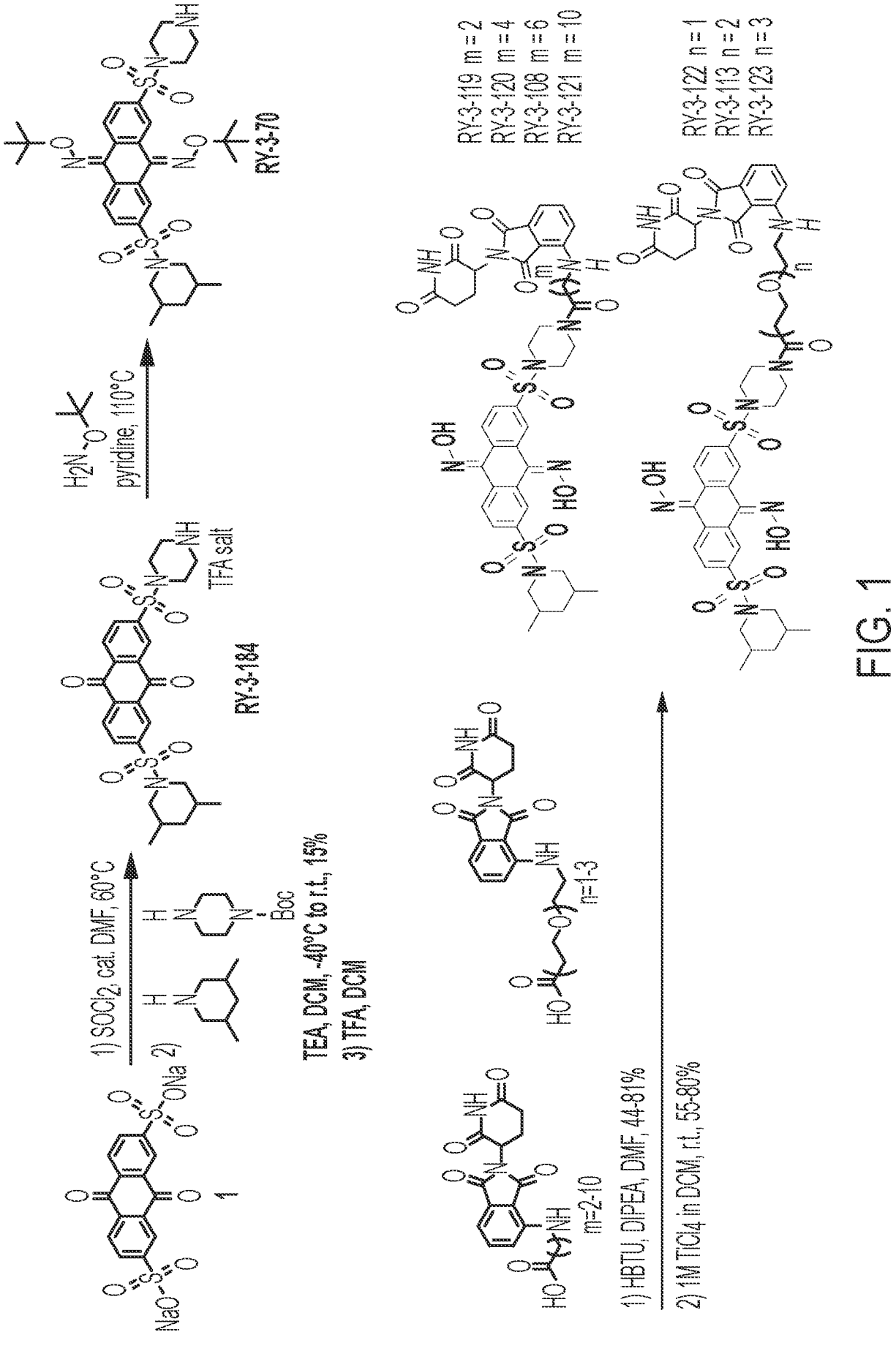

1) SOCl2, cat. DMF, 60°C
2)
1
TEA, DCM, -40°C to r.t., 15%
3) TFA, DCM
RY-3-184
TFA salt
H2N-O
pyridine, 110°C
RY-3-70
1) HBTU, DIPEA, DMF, 44-81%
2) 1M TiCl4 in DCM, r.t., 55-80%
m=2-10
n=1-3
RY-3-119 m = 2
RY-3-120 m = 4
RY-3-108 m = 6
RY-3-121 m = 10
RY-3-122 n = 1
RY-3-113 n = 2
RY-3-123 n = 3

FIG. 1

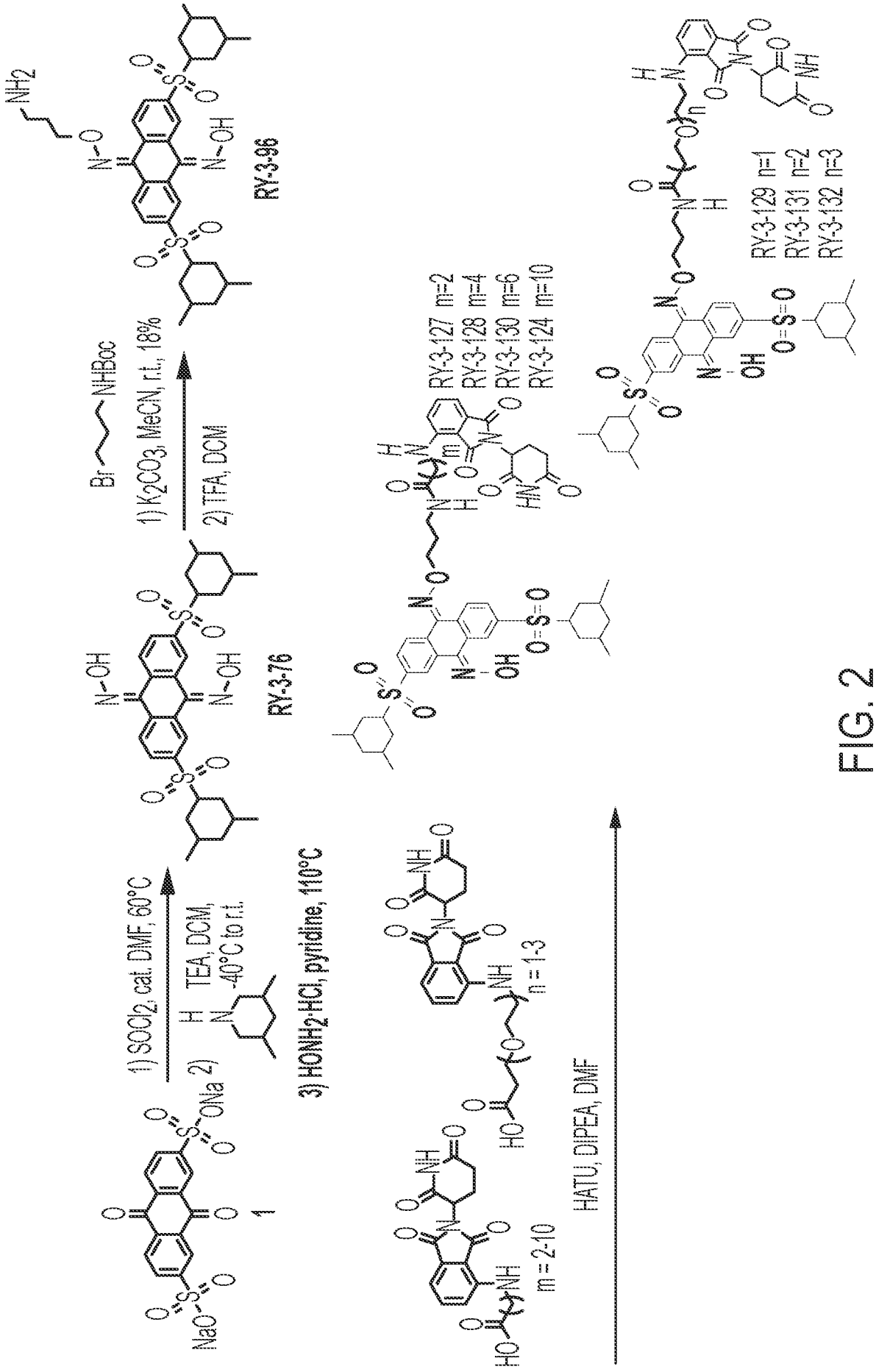

1) SOCl2, cat. DMF, 60°C
2)
TEA, DCM, -40°C to r.t.
3) HONH2·HCl, pyridine, 110°C
1
RY-3-76
1) K2CO3, MeCN, r.t., 18%
2) TFA, DCM
RY-3-96
HATU, DIPEA, DMF
m = 2-10
n = 1-3
RY-3-127 m=2
RY-3-128 m=4
RY-3-130 m=6
RY-3-124 m=10
RY-3-129 n=1
RY-3-131 n=2
RY-3-132 n=3

FIG. 2