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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 January 2025 (02.01.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/006902 A2

(51) International Patent Classification:
Not classified

(21) International Application Number:
PCT/US2024/036042

(22) International Filing Date:
28 June 2024 (28.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/523,993 29 June 2023 (29.06.2023) US

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(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))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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

(54) **Title:** SYNTHESIS AND IN VITRO CHARACTERIZATION OF PROTEOLYSIS TARGETING CHIMERAS (PROTACS) FOR DEGRADATION OF DNA METHYLTRANSFERASE 1 (DNMT1)

(57) **Abstract:** Disclosed are compounds (degraders) that target DNMT1 for degradation. Also disclosed are pharmaceutical compositions containing the compounds and methods of using the compounds to treat diseases and disorders characterized or mediated by aberrant DNMT1 activity.

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SYNTHESIS AND IN VITRO CHARACTERIZATION OF PROTEOLYSIS TARGETING CHIMERAS (PROTACS) FOR DEGRADATION OF DNA METHYLTRANSFERASE 1 (DNMT1)

RELATED APPLICATIONS

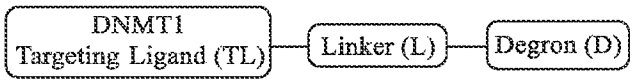
[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No: 63/523,993, filed June 29, 2023, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] Deoxyribonucleic acid methyltransferase 1 (DNMT1) is an epigenetic writer protein which is responsible for the maintenance of DNA methylation during cell proliferation. DNA methylation is a well-studied mechanism of epigenetic regulation, affecting the transcription of crucial genes, and DNA hyper- or hypo-methylation has been found to be associated with a number of human diseases including cancer. As such, abnormal DNMT1 activity plays an important role in cancer development. Existing drugs for DNMT1 dysregulation, such as decitabine and 5-azacytidine, are highly toxic, and cancer cells often develop drug resistance.

SUMMARY OF THE INVENTION

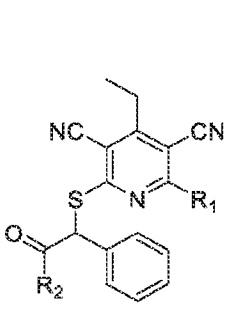
[0003] A first aspect of the present disclosure is directed to a compound of formula I,



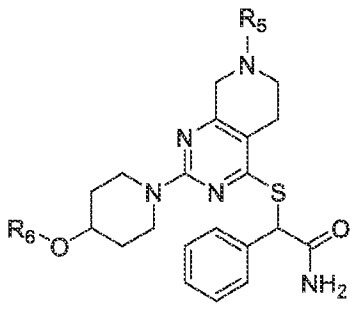
(I), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

DNMT1 Targeting Ligand is of Formula TL-1 or TL-2:



(TL-1) or



(TL-2),

wherein:

R_1 is NR_3R_4;

R_3 is H or methyl and R_4 is $-\!\!\S\!\!-$, or

R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl, or

R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl which is also bound to the linker;

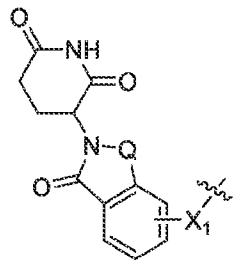
R_2 is NH_2 or $-\!\!\S\!\!-NH$; and

R_5 and R_6 are independently H, optionally substituted alkyl, or $-\!\!\S\!\!-$;

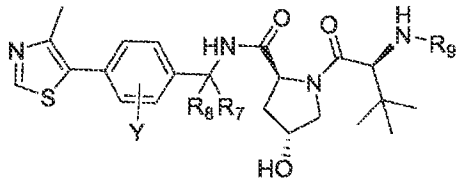
wherein $-\!\!\S\!\!-$ is a bond between the DNMT1 Targeting Ligand and the Linker, provided that there is only one bond between the DNMT1 Targeting Ligand and the Linker;

the linker represents a moiety that connects covalently the degron and the targeting ligand; and

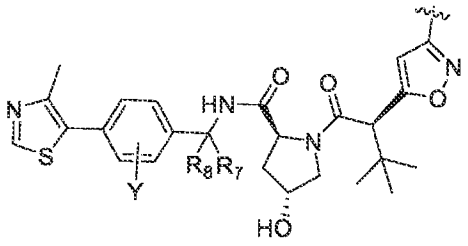
the Degron is of Formula D1, D2, or D3:



(D1),



(D2) or



(D3),

wherein

Q is CH_2 or C(O); and

X_1 is O, NH, CH_2, or C≡C;

R_7 is H or optionally substituted C_1-C_3 alkyl, or

R_7 and R_8, together with the carbon atom to which they are attached, form cyclopropyl;

R_8 is H, methyl, or $-\!\!\S\!\!-$;

R_9 is $C(O)CR_{10}R_{11}R_{12}$,  or $-\!\!\S\!\!-$;

R_{10} and R_{11} are both H, or

R_{10} and R_{11}, together with the carbon atom to which they are attached, form cyclopropyl;

R_{12} is H, fluoro, cyano, or NMe_2; and

Y is H,  ,  ,  , or  ;

wherein  is a bond between the Degron and the Linker, provided that there is only one bond between the Degron and the Linker.

[0004] Another aspect of the present disclosure is directed to a pharmaceutical composition containing a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[0005] In another aspect of the present disclosure, methods of making the compounds are provided.

[0006] A further aspect of the present disclosure is directed to a method of treating a disease or disorder involving (characterized or mediated by) aberrant DNMT1 activity, that includes administering a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt or stereoisomer thereof, to a subject in need thereof.

[0007] Without intending to be bound by any particular theory of operation, compounds of formula I (also referred to herein as PROTACs or degraders) are believed to promote the degradation of DNMT1 via cells' Ubiquitin/Proteasome System, whose function is to routinely identify and remove damaged proteins. After destruction of an DNMT1 protein molecule, the degrader is released and continues to be active. Therefore, by engaging and exploiting the body's own natural protein disposal system, compounds of the present disclosure may represent a potential improvement over current small molecule inhibitors of DNMT1. Therefore, effective intracellular concentrations of the degraders may be significantly lower than for small molecule DNMT1 inhibitors.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIG. 1 is a Western Blot showing that compounds 1-4 degraded DNMT1 in HL60 cells at indicated concentrations.

[0009] FIG. 2 is a Western Blot showing that compounds 5-8 degraded DNMT1 in HL60 cells at indicated concentrations.

[0010] FIG. 3 is a Western Blot showing that compounds 9-12 degraded DNMT1 in HL60 cells at indicated concentrations.

[0011] FIG. 4 is a Western Blot showing that compounds 13-16 degraded DNMT1 in HL60 cells at indicated concentrations.

[0012] FIG. 5 is a Western Blot showing that compounds 17-19 degraded DNMT1 in HL60 cells at indicated concentrations.

[0013] FIG. 6 is a Western Blot showing that compounds 20-23 degraded DNMT1 in HL60 cells at indicated concentrations.

[0014] FIG. 7 is a Western Blot showing that compound 20 degraded DNMT1 in HL60 cells at indicated concentrations.

[0015] FIG. 8 is a Western Blot showing that compound 20 degraded DNMT1 in Jurkat cells at indicated concentrations.

[0016] FIG. 9 is a Western Blot showing that compound 20 degraded DNMT1 in A172 cells at indicated concentrations.

[0017] FIG. 10 is a Western Blot showing that compound 20 (that contains a cereblon (CRBN)-targeted degron) degraded DNMT1 in MOLM13 ch2.2 (left). The extent of degradation of DNMT1 relative to MOLM13 CRBN KO (right) cells illustrates that the degradation is CRBN-dependent.

[0018] FIG. 11 is a Western Blot showing that compound 20 (3 μM) degraded DNMT1 in HL60 cells at indicated time points.

[0019] FIG. 12 is a Western Blot showing that compounds 26 and 27 degraded DNMT1 in HL60 cells at indicated concentrations.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0020] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present disclosure.

[0021] As used in the description and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Therefore, for example, reference to "a composition" includes mixtures of two or more such compositions, reference to "an inhibitor" includes mixtures of two or more such inhibitors, and the like.

[0022] Unless stated otherwise, the term "about" means within 10% (*e.g.*, within 5%, 2%, or 1%) of the particular value modified by the term "about."

[0023] The transitional term "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. When used in the context of the number of heteroatoms in a heterocyclic structure, it means that the heterocyclic group that that minimum number of heteroatoms. By contrast, the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the disclosure.

[0024] With respect to compounds of the present disclosure, and to the extent the following terms are used herein to further describe them, the following definitions apply.

[0025] As used herein, the term "alkyl" refers to a saturated linear or branched-chain monovalent hydrocarbon radical. In some embodiments, the alkyl radical is a C_1-C_6 group. In some embodiments, and to the extent not disclosed otherwise for any one or more groups of the compounds of formula (I), the alkyl radical is a C_0-C_6, C_0-C_5, C_0-C_3, C_1-C_6, C_1-C_5, C_1-C_4 or C_1-C_3 group (wherein C_0 alkyl refers to a bond). Examples of alkyl groups include methyl, ethyl, 1-propyl, 2-propyl, i-propyl, 1-butyl, 2-methyl-1-propyl, 2-butyl, 2-methyl-2-propyl, 1-pentyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, and 3,3-dimethyl-2-butyl. In some embodiments, an alkyl group is a C_1-C_3 alkyl group. In some embodiments, an alkyl group is a C_1-C_2 alkyl group. In some embodiments, an alkyl group is a methyl group.

[0026] As used herein, the term "alkylene" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to 18 carbon atoms, for example, methylene, ethylene, propylene, n-butylene, and the like. The alkylene chain may be attached to the rest of the molecule through a single bond and to the radical group through a single bond. In some embodiments, the alkylene group contains one to 15 carbon atoms (C_1-C_{15} alkylene). In some embodiments, the alkylene group contains one to 12 carbon atoms (C_1-C_{12} alkylene). In some embodiments, the alkylene group contains one to 10 carbon atoms (C_1-C_{10} alkylene). In some embodiments, the alkylene group contains one to 8 carbon atoms (C_1-C_8 alkylene). In other embodiments, an alkylene group contains one to 5 carbon atoms (C_1-C_5

alkylene). In other embodiments, an alkylene group contains one to 4 carbon atoms (C_1-C_4 alkylene). In other embodiments, an alkylene contains one to three carbon atoms (C_1-C_3 alkylene). In other embodiments, an alkylene group contains one to two carbon atoms (C_1-C_2 alkylene). In other embodiments, an alkylene group contains one carbon atom (C_1 alkylene).

[0027] As used herein, the term "alkenyl" refers to a linear or branched-chain monovalent hydrocarbon radical with at least one carbon-carbon double bond. An alkenyl includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. In some embodiments, the alkenyl radical is a C_2-C_{18} group. In some embodiments, and to the extent not disclosed otherwise for any one or more groups of the compounds of formula (I), the alkenyl radical is a C_2-C_{15}, C_2-C_{12}, C_2-C_{10}, C_2-C_8, C_2-C_6 or C_2-C_3 group. Examples include ethenyl or vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl and hexa-1,3-dienyl.

[0028] As used herein, the term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical with at least one carbon-carbon triple bond. In some embodiments, the alkynyl radical is a C_2-C_{18} group. In some embodiments, and to the extent not disclosed otherwise for any one or more groups of the compounds of formula (I), the alkynyl radical is C_2-C_{15}, C_2-C_{12}, C_2-C_{10}, C_2-C_8, C_2-C_6 or C_2-C_3. Examples include ethynyl prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl and but-3-ynyl.

[0029] The terms "alkoxyl" or "alkoxy" as used herein refer to an alkyl group, as defined above, having an oxygen radical attached thereto, and which is the point of attachment. In some embodiments, the alkoxyl group is methoxy, ethoxy, propyloxy, or tert-butoxy. An "ether" is two hydrocarbyl groups covalently linked by an oxygen atom. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, and -O-alkynyl.

[0030] As used herein, the term "halogen" (or "halo" or "halide") refers to fluorine, chlorine, bromine, or iodine.

[0031] As used herein, the term "cyclic group" broadly refers to any group that used alone or as part of a larger moiety, contains a saturated, partially saturated or aromatic ring system *e.g.*, carbocyclic (cycloalkyl, cycloalkenyl), heterocyclic (heterocycloalkyl, heterocycloalkenyl), aryl and heteroaryl groups. Cyclic groups may have one or more (*e.g.*, fused) ring systems. Therefore, for example, a cyclic group can contain one or more carbocyclic, heterocyclic, aryl or heteroaryl groups.

[0032] As used herein, the term "carbocyclic" (also "carbocyclyl") refers to a group that used alone or as part of a larger moiety, contains a saturated, partially unsaturated, or aromatic ring system having 3 to 12 carbon atoms, that is alone or part of a larger moiety (*e.g.*, an alkcarbocyclic group). The term carbocyclyl includes mono-, bi-, tri-, fused, bridged, and spiro-ring systems, and combinations thereof. In one embodiment, carbocyclyl includes 3 to 10 carbon atoms (C_3-C_{10}). In one embodiment, carbocyclyl includes 3 to 6 carbon atoms (C_3-C_6). In one embodiment, carbocyclyl includes 5 to 6 carbon atoms (C_5-C_6). In some embodiments, carbocyclyl, as a bicycle, includes C_6-C_{10}. In another embodiment, carbocyclyl, as a spiro system, includes C_5-C_{11}. Representative examples of monocyclic carbocyclyls include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and phenyl; bicyclic carbocyclyls having 7 to 11 ring atoms include [4,3], [4,4], [4.5], [5,5], [5,6] or [6,6] ring systems, such as for example bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, naphthalene, and bicyclo[3.2.2]nonane. Representative examples of spiro carbocyclyls include spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane and spiro[4.5]decane. The term carbocyclyl includes aryl ring systems as defined herein. The term carbocycyl also includes cycloalkyl rings (*e.g.*, saturated or partially unsaturated mono-, bi-, or spiro-carbocycles). The term carbocyclic group also includes a carbocyclic ring fused to one or more (*e.g.*, 1, 2 or 3) different cyclic groups (*e.g.*, aryl or heterocyclic rings), where the radical or point of attachment is on the carbocyclic ring.

[0033] Therefore, the term carbocyclic also embraces carbocyclylalkyl groups which as used herein refer to a group of the formula --R^c-carbocyclyl where R^c is an alkylene chain. The term carbocyclic also embraces carbocyclylalkoxy groups which as used herein refer to a group bonded through an oxygen atom of the formula --O--R^c-carbocyclyl where R^c is an alkylene chain.

[0034] As used herein, the term "aryl" used alone or as part of a larger moiety (*e.g.*, "aralkyl", wherein the terminal carbon atom on the alkyl group is the point of attachment, *e.g.*, a benzyl group),"aralkoxy" wherein the oxygen atom is the point of attachment, or "aroxyalkyl" wherein the point of attachment is on the aryl group) refers to a group that includes monocyclic, bicyclic or tricyclic, carbon ring system, that includes fused rings, wherein at least one ring in the system is aromatic. In some embodiments, the aralkoxy group is a benzoxy group. The term "aryl" may be used interchangeably with the term "aryl ring". In one embodiment, aryl includes

groups having 6-12 carbon atoms. In another embodiment, aryl includes groups having 6-10 carbon atoms. Examples of aryl groups include phenyl, naphthyl, biphenyl, 1,2,3,4-tetrahydronaphthalenyl, and the like, which may be substituted or independently substituted by one or more substituents described herein. A particular aryl is phenyl. In some embodiments, an aryl group includes an aryl ring fused to one or more (*e.g.*, 1, 2 or 3) different cyclic groups (*e.g.*, carbocyclic rings or heterocyclic rings), where the radical or point of attachment is on the aryl ring.

[0035] Therefore, the term aryl embraces aralkyl groups (*e.g.*, benzyl) which as disclosed above refer to a group of the formula --R^c-aryl where R^c is an alkylene chain such as methylene or ethylene. In some embodiments, the aralkyl group is an optionally substituted benzyl group. The term aryl also embraces aralkoxy groups which as used herein refer to a group bonded through an oxygen atom of the formula --O—R^c--aryl where R^c is an alkylene chain such as methylene or ethylene.

[0036] As used herein, the term "heterocyclyl" refers to a "carbocyclyl" that used alone or as part of a larger moiety, contains a saturated, partially unsaturated or aromatic ring system, wherein one or more (*e.g.*, 1, 2, 3, 4, or 5) carbon atoms have been replaced with a heteroatom or heteroatom-containing group (*e.g.*, O, N, N(O), S, S(O), or $S(O)_2$). The term heterocyclyl includes mono-, bi-, tri-, fused, bridged, and spiro-ring systems, and combinations thereof. In some embodiments, a heterocyclyl refers to a 3- to 12-membered heterocyclyl ring system. In some embodiments, a heterocyclyl refers to a saturated ring system, such as a 3- to 12-membered saturated heterocyclyl ring system. In some embodiments, a heterocyclyl refers to a heteroaryl ring system, such as a 5- to 12-membered heteroaryl ring system. The term heterocyclyl also includes C_2-C_8 heterocycloalkyl, which is a saturated or partially unsaturated mono-, bi-, or spiro-ring system containing 2-8 carbons and one or more (*e.g.*, 1, 2, or 3) heteroatoms.

[0037] In some embodiments, a heterocyclyl group includes 3-12 ring atoms and includes monocycles, bicycles, tricycles and spiro ring systems, wherein the ring atoms are carbon, and one to 5 ring atoms is a heteroatom such as nitrogen, sulfur or oxygen. In some embodiments, heterocyclyl includes 3- to 7-membered monocycles having one or more heteroatoms selected from O, N, and S. In some embodiments, heterocyclyl includes 4- to 6-membered monocycles having one or more heteroatoms selected from O, N, and S. In some embodiments, heterocyclyl includes 3-membered monocycles. In some embodiments, heterocyclyl includes 4-membered monocycles. In some embodiments, heterocyclyl includes 5- to 6-membered monocycles. In

some embodiments, the heterocyclyl group includes 0 to 3 double bonds. In any of the foregoing embodiments, heterocyclyl includes 1, 2, 3 or 4 heteroatoms. Any nitrogen or sulfur heteroatom may optionally be oxidized (*e.g.*, NO, SO, SO_2), and any nitrogen heteroatom may optionally be substituted (*e.g.*, methyl, isopropyl) and/or quaternized (*e.g.*, $[NR_4]^+Cl^-$, $[NR_4]^+OH^-$). Representative examples of heterocyclyls include oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, dihydro-1H-pyrrolyl, dihydrofuranyl, tetrahydropyranyl, dihydrothienyl, tetrahydrothienyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, hexahydrothiopyranyl, hexahydropyrimidinyl, oxazinanyl, thiazinanyl, thioxanyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, tetrahydrothiopyranyl, oxazolidinyl, thiazolidinyl, isothiazolidinyl, 1,1-dioxoisothiazolidinonyl, oxazolidinonyl, imidazolidinonyl, 4,5,6,7-tetrahydro[2H]indazolyl, tetrahydrobenzoimidazolyl, 4,5,6,7-tetrahydrobenzo[d]imidazolyl, 1,6-dihydroimidazol[4,5-d]pyrrolo[2,3-b]pyridinyl, thiazinyl, thiophenyl, oxazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, thiapyranyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrimidinonyl, pyrimidindionyl, pyrimidin-2,4-dionyl, piperazinonyl, piperazindionyl, pyrazolidinylimidazolinyl, 3-azabicyclo[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 2-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 8-azabicyclo[2.2.2]octanyl, 7-oxabicyclo[2.2.1]heptane, azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, azaspiro[4.5]decanyl, 1-azaspiro[4.5]decan-2-only, azaspiro[5.5]undecanyl, tetrahydroindolyl, octahydroindolyl, tetrahydroisoindolyl, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl. Examples of 5-membered heterocyclyls containing a sulfur or oxygen atom and one to three nitrogen atoms are thiazolyl (*e.g.*, thiazol-2-yl), thiadiazolyl (*e.g.*, 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl), oxazolyl (*e.g.*, oxazol-2-yl), and oxadiazolyl (*e.g.*, 1,3,4-oxadiazol-5-yl and 1,2,4-oxadiazol-5-yl). Example of 5-membered heterocyclyls containing 2 to 4 nitrogen atoms include imidazolyl (*e.g.*, imidazol-2-yl), triazolyl (*e.g.*, 1,3,4-triazol-5-yl, 1,2,3-triazol-5-yl, and 1,2,4-triazol-5-yl), and tetrazolyl (*e.g.*, 1H-tetrazol-5-yl). Representative examples of benzo-fused 5-membered heterocyclyls include benzoxazol-2-yl, benzthiazol-2-yl and

benzimidazol-2-yl. Example of 6-membered heterocyclyls containing one to three nitrogen atoms and optionally a sulfur or oxygen atom are pyridyl (*e.g.*, pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl), pyrimidyl (*e.g.*, pyrimid-2-yl and pyrimid-4-yl), triazinyl (*e.g.*, 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl), pyridazinyl (*e.g.*, pyridazin-3-yl), and pyrazinyl. In some embodiments, a heterocyclic group includes a heterocyclic ring fused to one or more (*e.g.*, 1 or 2) different cyclic groups (*e.g.*, carbocyclic rings or heterocyclic rings), where the radical or point of attachment is on the heterocyclic ring, and in some embodiments wherein the point of attachment is a heteroatom contained in the heterocyclic ring.

[0038] Therefore, the term heterocyclic embraces N-heterocyclyl groups which as used herein refer to a heterocyclyl group containing at least one nitrogen atom and where the point of attachment of the heterocyclyl group to the rest of the molecule is through a nitrogen atom in the heterocyclyl group. Representative examples of N-heterocyclyl groups include 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl, 1-pyrazolidinyl, 1-imidazolinyl and 1-imidazolidinyl. The term heterocyclic also embraces C-heterocyclyl groups which as used herein refer to a heterocyclyl group containing at least one heteroatom and where the point of attachment of the heterocyclyl group to the rest of the molecule is through a carbon atom in the heterocyclyl group. Representative examples of C-heterocyclyl radicals include 2- or 3-morpholinyl, 2- or 3- or 4-piperidinyl, 2-piperazinyl, and 2- or 3-pyrrolidinyl. The term heterocyclic also embraces heterocyclylalkyl groups which as disclosed above refer to a group of the formula --R^c-heterocyclyl where R^c is an alkylene chain. The term heterocyclic also embraces heterocyclylalkoxy groups which as used herein refer to a radical bonded through an oxygen atom of the formula --O--R^c-heterocyclyl where R^c is an alkylene chain.

[0039] As used herein, the term "heteroaryl" used alone or as part of a larger moiety (*e.g.*, "heteroarylalkyl" (also "heteroaralkyl"), or "heteroarylalkoxy" (also "heteroaralkoxy")) refers to a monocyclic, bicyclic or tricyclic ring system having 5 to 12 ring atoms, wherein at least one ring is aromatic and contains at least one heteroatom. In one embodiment, heteroaryl includes 5- to 6- membered monocyclic aromatic groups where one or more ring atoms is O, N, or S. Representative examples of heteroaryl groups include thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, imidazopyridyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, tetrazolo[1,5-b]pyridazinyl, purinyl, deazapurinyl, benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl,

indolyl, 1,3-thiazol-2-yl, 1,3,4-triazol-5-yl, 1,3-oxazol-2-yl, 1,3,4-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 1H-tetrazol-5-yl, and 1,2,3-triazol-5-yl. The term "heteroaryl" also includes groups in which a heteroaryl is fused to one or more cyclic (*e.g.*, carbocyclyl, or heterocyclyl) rings, where the radical or point of attachment is on the heteroaryl ring. Nonlimiting examples include indolyl, indolizinyl, isoindolyl, benzothienyl, benzothiophenyl, methylenedioxyphenyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzodioxazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. A heteroaryl group may be mono-, bi- or tri-cyclic. In some embodiments, a heteroaryl group includes a heteroaryl ring fused to one or more (*e.g.*, 1 or 2) different cyclic groups (*e.g.*, carbocyclic rings or heterocyclic rings), where the radical or point of attachment is on the heteroaryl ring, and in some embodiments wherein the point of attachment is a heteroatom contained in the heterocyclic ring.

[0040] Therefore, the term heteroaryl embraces N-heteroaryl groups which as used herein refer to a heteroaryl group as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl group to the rest of the molecule is through a nitrogen atom in the heteroaryl group. The term heteroaryl also embraces C-heteroaryl groups which as used herein refer to a heteroaryl group as defined above and where the point of attachment of the heteroaryl group to the rest of the molecule is through a carbon atom in the heteroaryl group. The term heteroaryl also embraces heteroarylalkyl groups which as disclosed above refer to a group of the formula --R^e-heteroaryl, wherein R^e is an alkylene chain as defined above. The term heteroaryl also embraces heteroaralkoxy (or heteroarylalkoxy) groups which as used herein refer to a group bonded through an oxygen atom of the formula --O--R^e-heteroaryl, where R^e is an alkylene group as defined above.

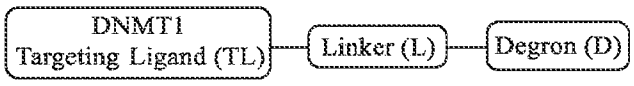
[0041] Unless stated otherwise, and to the extent not further defined for any particular group(s) in the compound of formula (I), any of the groups described herein may be substituted or unsubstituted. To the extent not disclosed otherwise for any particular group(s), representative examples of substituents may include alkyl (*e.g.*, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_1), substituted alkyl (*e.g.*, substituted C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_1), alkoxy (*e.g.*, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_1), substituted alkoxy (*e.g.*, substituted C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_1), haloalkyl (*e.g.*, CF_3), alkenyl (*e.g.*, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_2), substituted alkenyl (*e.g.*, substituted C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_2), alkynyl (*e.g.*, C_2-C_6,

C_2-C_5, C_2-C_4, C_2-C_3, C_2), substituted alkynyl (*e.g.*, substituted C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_2), cyclic (*e.g.*, C_3-C_{12}, C_5-C_6), substituted cyclic (*e.g.*, substituted C_3-C_{12}, C_5-C_6), carbocyclic (*e.g.*, C_3-C_{12}, C_5-C_6), substituted carbocyclic (*e.g.*, substituted C_3-C_{12}, C_5-C_6), heterocyclic (*e.g.*, 3- to 12-membered, 5-to 6-membered), substituted heterocyclic (*e.g.*, substituted 3- to 12-membered, 5-to 6-membered), aryl (*e.g.*, benzyl and phenyl), substituted aryl (*e.g.*, substituted benzyl or substituted phenyl), heteroaryl (*e.g.*, pyridyl or pyrimidyl), substituted heteroaryl (*e.g.*, substituted pyridyl or substituted pyrimidyl), aralkyl (*e.g.*, benzyl), substituted aralkyl (*e.g.*, substituted benzyl), halo, hydroxyl, aryloxy (*e.g.*, C_6-C_{12}, C_6), substituted aryloxy (*e.g.*, substituted C_6-C_{12}, C_6), alkylthio (*e.g.*, C_1-C_6), substituted alkylthio (*e.g.*, substituted C_1-C_6), arylthio (*e.g.*, C_6-C_{12}, C_6), substituted arylthio (*e.g.*, substituted C_6-C_{12}, C_6), cyano, carbonyl, substituted carbonyl, carboxyl, substituted carboxyl, amino, substituted amino, amido, substituted amido, thio, substituted thio, sulfinyl, substituted sulfinyl, sulfonyl, substituted sulfonyl, sulfinamide, substituted sulfinamide, sulfonamide, substituted sulfonamide, urea, substituted urea, carbamate, substituted carbamate, amino acid, and peptide groups. Terminal substituents may include C_1-C_6 alkyl, halo, hydroxyl, cyano, amino, or amido groups.

[0042] The term "binding" as it relates to interaction between the compound of formula (I) and the targeted protein, which in this disclosure is DNMT1, via the DNMT1 targeting ligand, typically refers to an inter-molecular interaction that may be preferential (also referred to herein as "selective") in that binding of the compounds of formula (I) with other proteins present in the cell is substantially less and may be functionally insignificant. Present compounds preferentially bind and recruit DNMT1 for targeted degradation.

[0043] The term "binding" as it relates to interaction between the degron and the E3 ubiquitin ligase, typically refers to an inter-molecular interaction that may or may not exhibit an affinity level that equals or exceeds that affinity between the compound and DNMT1, but is nonetheless sufficient to achieve recruitment of the E3 ubiquitin ligase to DNMT1.

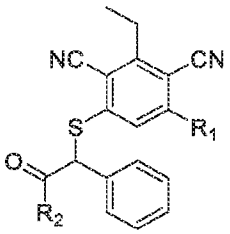
[0044] Broadly, the compounds of the present disclosure have a structure represented by formula (I):



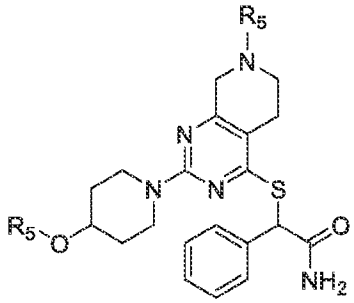
(I),

wherein:

DNMT1 Targeting Ligand is of Formula TL-1 or TL-2:



(TL-1) or



(TL-2),

wherein:

R_1 is NR_3R_4;

R_3 is H or methyl and R_4 is $-\!\!\!\sim\!\!\!-$, or

R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl, or

R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl which is also bound to the linker;

R_2 is NH_2 or $-\!\!\!\sim\!\!\!-NH$;

each R_5 is independently H, optionally substituted alkyl, or $-\!\!\!\sim\!\!\!-$;

wherein $-\!\!\!\sim\!\!\!-$ is a bond between the DNMT1 Targeting Ligand and the Linker, provided that there is only one bond between the DNMT1 Targeting Ligand and the Linker;

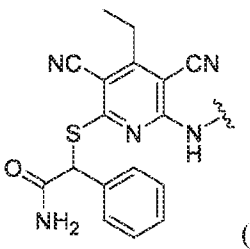
the linker represents a moiety that connects covalently the degron and the targeting ligand; and

the degron represents a moiety that binds an E3 ubiquitin ligase, or a pharmaceutically acceptable salt or stereoisomer thereof.

Targeting Ligands

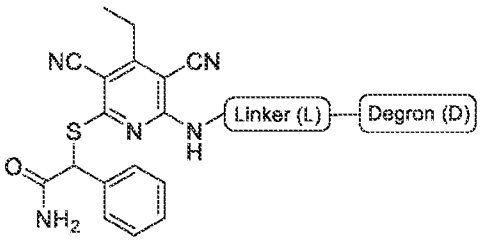
[0045] In some embodiments, the DNMT1 Targeting Ligand is of Formula TL-1 and R_2 is NH_2.

[0046] In some embodiments, R_1 is NR_3R_4, wherein R_3 is H and R_4 is $-\!\!\!\sim\!\!\!-$, R_2 is NH_2, and Formula TL-1 is of TL-1a:



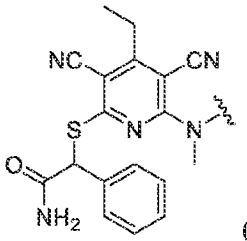
(TL-1a).

[0047] Therefore, in some embodiments, the compounds have a structure represented by formula I-1a:



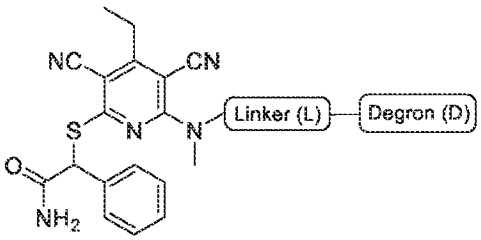
(I-1a), or a pharmaceutically acceptable salt or stereoisomer thereof.

[0048] In some embodiments, R_1 is NR_3R_4, wherein R_3 is Me and R_4 is  , R_2 is NH_2, and Formula TL-1 is of TL-1b:



(TL-1b).

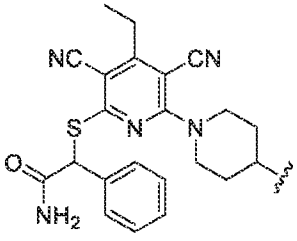
[0049] Therefore, in some embodiments, the compounds have a structure represented by formula I-1b:



(I-1b), or a pharmaceutically acceptable salt or stereoisomer thereof.

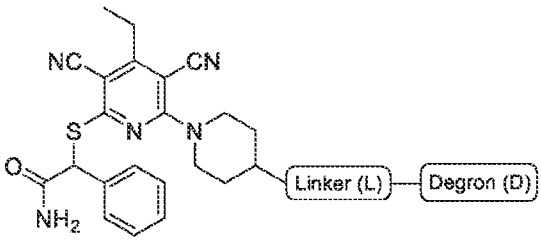
[0050] In some embodiments, R_1 is NR_3R_4, wherein R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl which is also bound to the linker, and R_2 is NH_2.

[0051] In some embodiments, R_1 is NR_3R_4, wherein R_3 and R_4, together with the nitrogen atom to which they are attached, form piperidyl, and Formula TL-1 is of TL-1c:



(TL-1c).

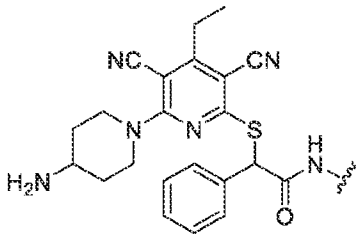
[0052] Therefore, in some embodiments, the compounds have a structure represented by formula I-1c:



(I-1c), or a pharmaceutically acceptable salt or stereoisomer thereof.

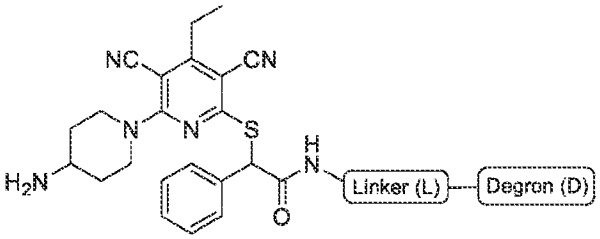
[0053] In some embodiments, R_1 is NR_3R_4, wherein R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl. In some embodiments, R_3 and R_4, together with the nitrogen atom to which they are attached, form optionally substituted piperidyl. In some embodiments, piperidyl is substituted with an amino group.

[0054] In some embodiments, R_1 is NR_3R_4, wherein R_3 and R_4, together with the nitrogen atom to which they are attached, form piperidyl substituted with an amino group, R_2 is



, and Formula TL-1 is of TL-1d: (TL-1d).

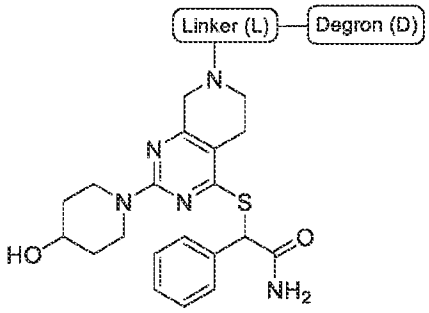
[0055] Therefore, in some embodiments, the compounds have a structure represented by formula I-1d:



(I-1d), or a pharmaceutically acceptable salt or stereoisomer thereof.

[0056] In some embodiments, the DNMT1 Targeting Ligand is of Formula TL-2, R_5 is  , and R_6 is H.

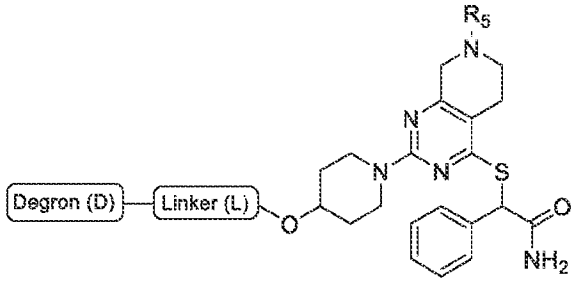
[0057] Therefore, in some embodiments, the compounds have a structure represented by formula I-2a:



(I-2a), or a pharmaceutically acceptable salt or stereoisomer thereof.

[0058] In some embodiments, the DNMT1 Targeting Ligand is of Formula TL-2, R_5 is H or optionally substituted alkyl, and R_6 is  .

[0059] Therefore, in some embodiments, the compounds have a structure represented by formula I-2b:

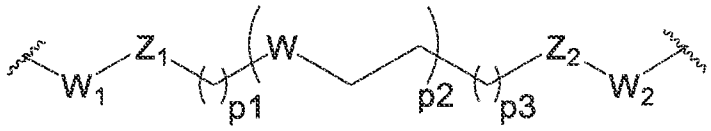


(I-2b), or a pharmaceutically acceptable salt or stereoisomer thereof.

Linkers

[0060] The linker ("L") provides a covalent attachment between the targeting ligand and the degron.

[0061] In some embodiments, the linker is of Formula L0:



(L0),

or stereoisomer thereof, wherein

p1 is an integer selected from 0 to 6;

p2 is an integer selected from 0 to 12;

p3 is an integer selected from 0 to 12;

each W is independently absent, CH_2, O, S, NR_{13}, or $C(O)NR_{13}$;

each R_{13} is independently hydrogen or C_1-C_6 alkyl;

W_1 and W_2 are independently absent, $(CH_2)_{1-3}$, O, NH, or $C(O)NR_{13}$; and

Z_1 and Z_2 are independently absent, –O–, –S–, –N(R_{13})–, –C≡C–, –C(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(NOR_{13})–, –C(O)N(R_{13})–, –C(O)N(R_{13})C(O)–, –C(O)N(R_{13})C(O)N(R_{13})–, –N(R_{13})C(O)–, –N(R_{13})C(O)N(R_{13})–, –N(R_{13})C(O)O–, –OC(O)N(R_{13})–, –C(NR_{13})–, –N(R_{13})C(NR_{13})–, –C(NR_{13})N(R_{13})–, –N(R_{13})C(NR_{13})N(R_{13})–, –OB(Me)O–, –S(O)$_2$–, –OS(O)–, –S(O)O–, –S(O)–, –OS(O)$_2$–, –S(O)$_2$O–, –N(R_{13})S(O)$_2$–, –S(O)$_2$N(R_{13})–, –N(R_{13})S(O)–, –S(O)N(R_{13})–, –N(R_{13})S(O)$_2$N(R_{13})–, –N(R_{13})S(O)N(R_{13})–, C_3-C_{12} carbocyclene, 3- to 12-membered heterocyclene, or 5- to 12-membered heteroarylene;

wherein the Linker is covalently bonded to a Degron via the next to W_2, and covalently bonded to a Targeting Ligand via the  next to W_1, or the Linker is covalently bonded to a Degron via the  next to W_1, and covalently bonded to a Targeting Ligand via the  next to W_2.

[0062] In some embodiments, p1 is an integer selected from 0 to 4. In some embodiments, p1 is an integer selected from 0 to 2. In some embodiments, p1 is an integer selected from 1 to 3.

[0063] In some embodiments, p2 is an integer selected from 0 to 8. In some embodiments, p2 is an integer selected from 0 to 6. In some embodiments, p2 is an integer selected from 0 to 4. In some embodiments, p2 is an integer selected from 1 to 4.

[0064] In some embodiments, p3 is an integer selected from 0 to 10. In some embodiments, p3 is an integer selected from 0 to 8. In some embodiments, p3 is an integer selected from 0 to 6. In some embodiments, p3 is an integer selected from 0 to 4. In some embodiments, p3 is an integer selected from 1 to 8. In some embodiments, p3 is an integer selected from 1 to 6. In some embodiments, p3 is an integer selected from 1 to 4.

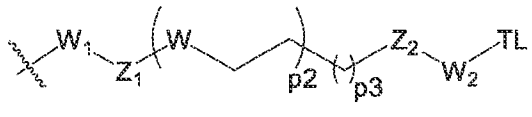
[0065] In some embodiments, each W is CH_2. In some embodiments, each W is O.

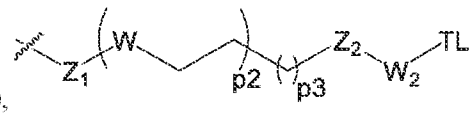
[0066] In some embodiments, each R_{10} is independently hydrogen or methyl.

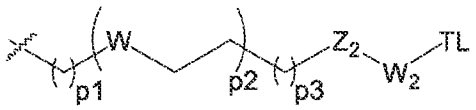
[0067] In some embodiments, W_1 and W_2 are independently absent, CH_2, $(CH_2)_2$, $(CH_2)_3$, NH, C(O)NH, or C(O)NMe.

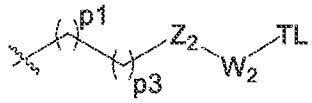
[0068] In some embodiments, Z_1 and Z_2 are independently absent, –O–, –N(R_{13})–, –C(O)–, –C(O)N(R_{13})–, –N(R_{13})C(O)–, C_5-C_6 carbocyclene, 5- to 6-membered heterocyclene, or 5- to 6-membered heteroarylene.

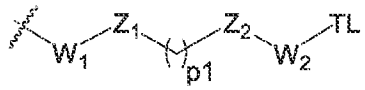
[0069] In some embodiments, Formula L0 is of Formula L0a-L0j:

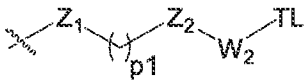


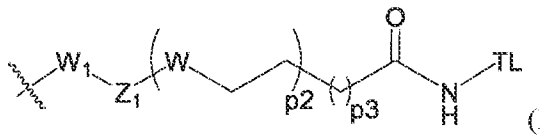
(L0a),


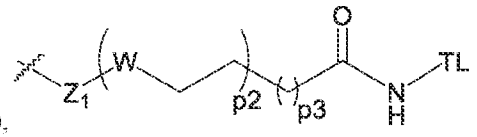


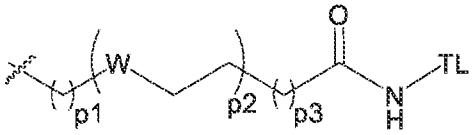
(L0b),


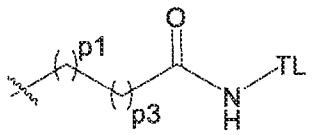
(L0c), (L0d),


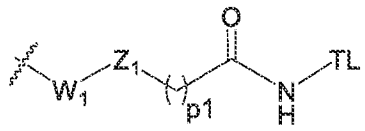
(L0e),


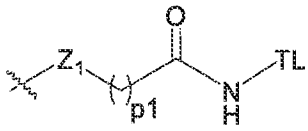
(L0f),


(L0g),




(L0h),


(L0i), (L0j),


(L0k), or


(L0l), wherein TL represents targeting ligand.

[0070] In some embodiments, the linker includes an alkylene chain (*e.g.*, having 1-18 alkylene units). In other embodiments, the linker may include an alkylene chain or a bivalent alkylene chain, either of which may be interrupted by, and/or terminate (at either or both termini) at least one of –O–, –S–, –N(R')–, –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(Me)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')–, C_3-C_{12} carbocyclene, 3- to 12-membered heterocyclene, 5- to 12-membered heteroarylene or any combination thereof, wherein R' is H or C_1-C_6 alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

[0071] In some embodiments, the linker includes an alkylene chain having 1-18 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-12 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered

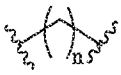
heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-6 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-3 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-18 alkylene units. In some embodiments, the linker includes an alkylene chain having 1-12 alkylene units. In some embodiments, the linker includes an alkylene chain having 1-6 alkylene units. In some embodiments, the linker includes an alkylene chain having 1-3 alkylene units.

[0072] "Carbocyclene" refers to a bivalent carbocycle radical, which is optionally substituted.

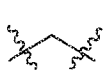
[0073] "Heterocyclene" refers to a bivalent heterocyclyl radical which may be optionally substituted.

[0074] "Heteroarylene" refers to a bivalent heteroaryl radical which may be optionally substituted.

[0075] Representative examples of linkers that may be suitable for use in the present disclosure include alkylene chains:



(L1), wherein n is an integer of 1-12 ("of" meaning inclusive), *e.g.*, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9, 9-10 and 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, examples of which include:


(L1-a);

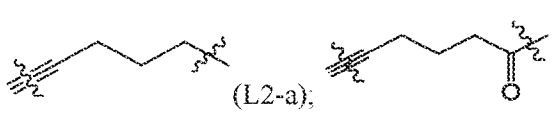
(L1-b);

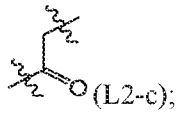
(L1-c);

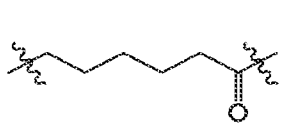
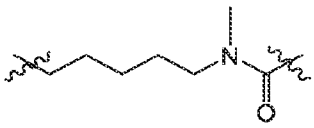

(L1-d); and

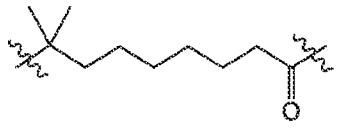
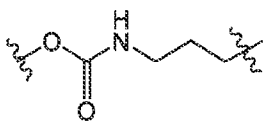

(L1-e);

alkylene chains terminating in various functional groups (as described above), examples of which are as follows:

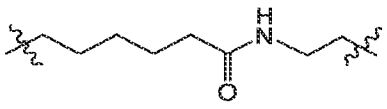
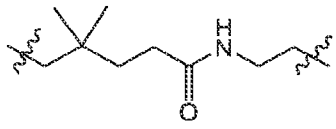

(L2-a);

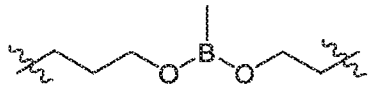
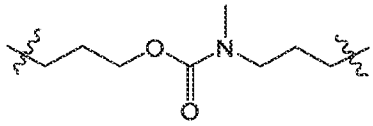
(L2-b);

(L2-c);


(L2-d);

(L2-e);

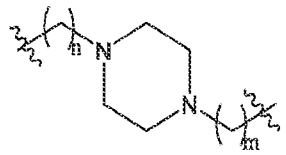

(L2-f); and

(L2-g);

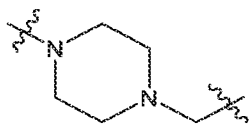
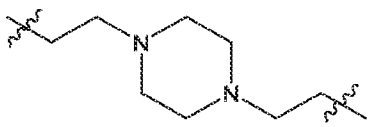
alkylene chains interrupted by various functional groups (as described above), examples of which are as follows:

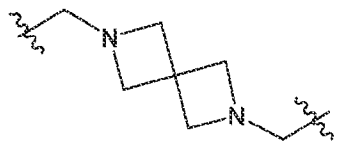
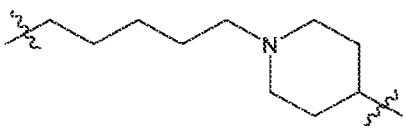

(L3-a);

(L3-b);

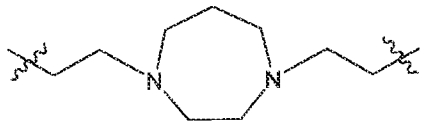

(L3-c); and

(L3-d);

alkylene chains interrupted by or terminating with heterocyclene groups, *e.g.*,


(L4), wherein m and n are independently an integer from 0-10, examples of which include:

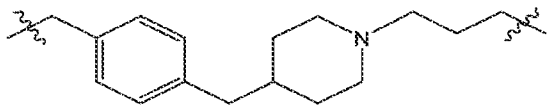

(L4-a);

(L4-b);


(L4-c);

(L4-d); and

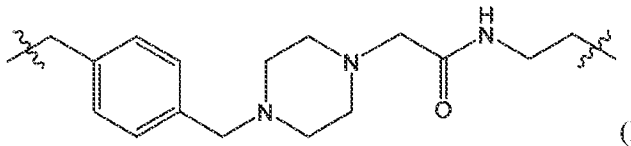


(L4-e);

alkylene chains interrupted by amide, heterocyclene and/or aryl groups, examples of which include:

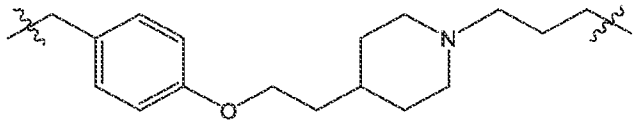


(L5-a); and

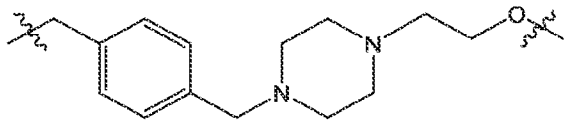


(L5-b);

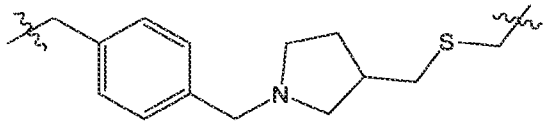
alkylene chains interrupted by heterocyclene and aryl groups, and a heteroatom, examples of which include:



(L6-a);



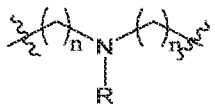
(L6-b); and



(L6-c);

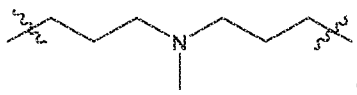
and

alkylene chains interrupted by and/or terminating in a heteroatom such as N, O or B, *e.g.*,



(L7), wherein each n is independently an integer of 1-10, *e.g.*, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10,

8-9, 9-10, and 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and R is H or C1 to C4 alkyl, an example of which is

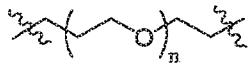


(L7-a).

[0076] In some embodiments, the linker may include a polyethylene glycol (PEG) chain which may terminate at either or both termini with at least one of –S–, –N(R')–, –C≡C–, –C(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(NOR')–, –C(O)N(R')–, –C(O)N(R')C(O)–, –R'C(O)N(R')R'–, –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(Me)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')–, C_{3-12} carbocyclene, 3- to 12-membered heterocyclene, 5- to 12-membered heteroarylene or any combination thereof, wherein R' is H or C_1-C_6 alkyl, wherein the one or both terminating groups may be the same or different.

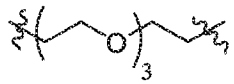
[0077] In some embodiments, the linker includes a polyethylene glycol chain having 1-10 PEG units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, or any combination thereof. In some embodiments, the linker includes a polyethylene glycol chain having 1-6 PEG units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, or any combination thereof. In some embodiments, the linker includes a polyethylene glycol chain having 1-2 PEG units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, or any combination thereof. In some embodiments, the linker includes a polyethylene glycol chain having 1-10 PEG. In some embodiments, the linker includes a polyethylene glycol chain having 1-6 PEG units. In some embodiments, the linker includes a polyethylene glycol chain having 1-2 PEG units.

[0078] Examples of linkers that include a polyethylene glycol chain include:

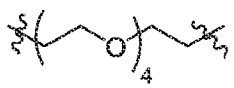


(L8), wherein n is an integer of 2-10, examples of which include:

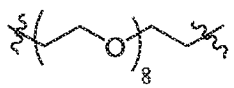
(L8-a);



(L8-b);

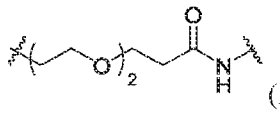
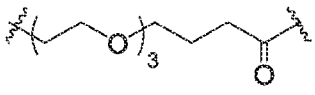
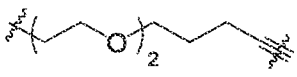
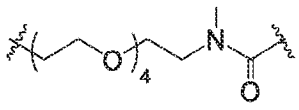
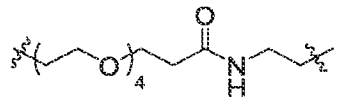


(L8-c); and

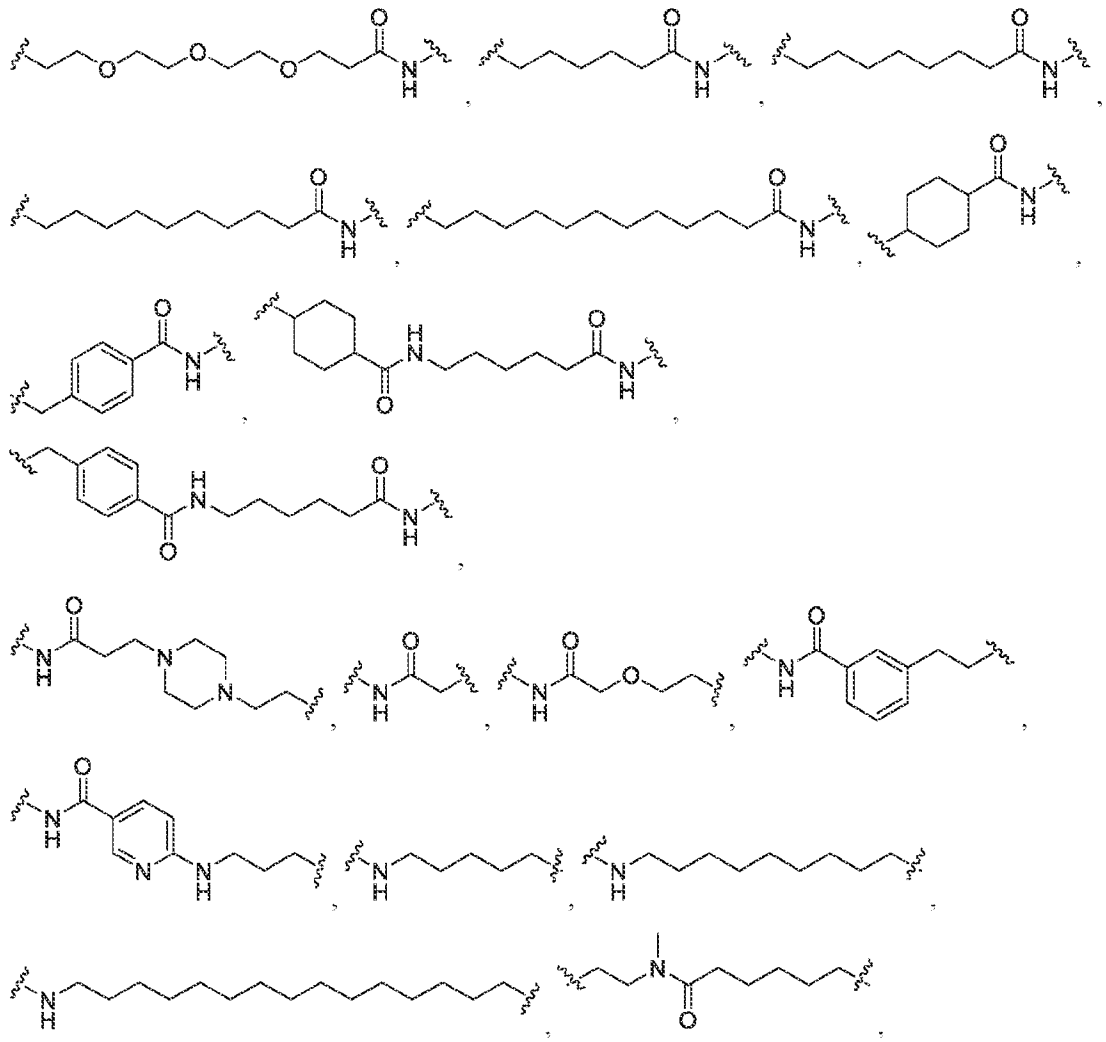


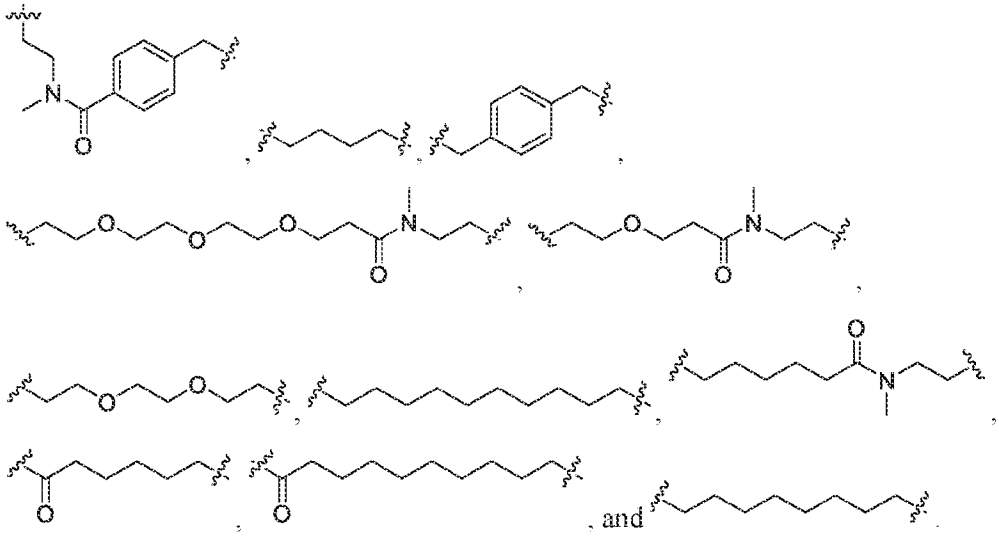
(L8-d).

[0079] In some embodiments, the linker containing a polyethylene glycol chain may terminate in a functional group, examples of which are as follows:

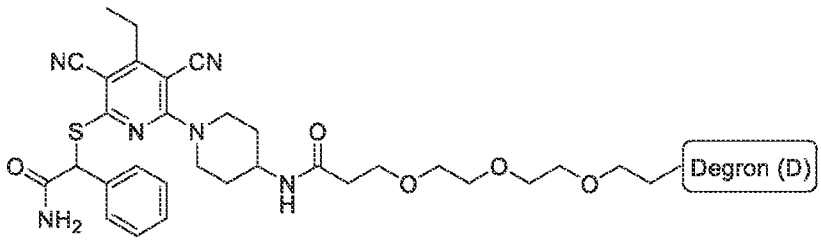

(L9-a);

(L9-b);

(L9-c);

(L9-d); and

(L9-e).

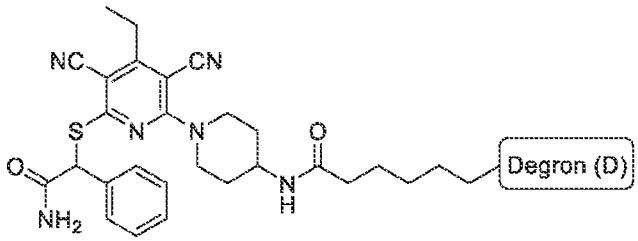
[0080] In some embodiments, the linker is represented by any one of structures:

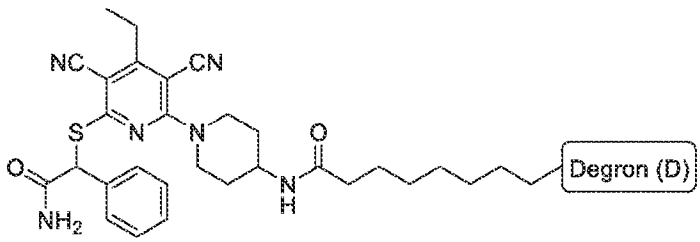


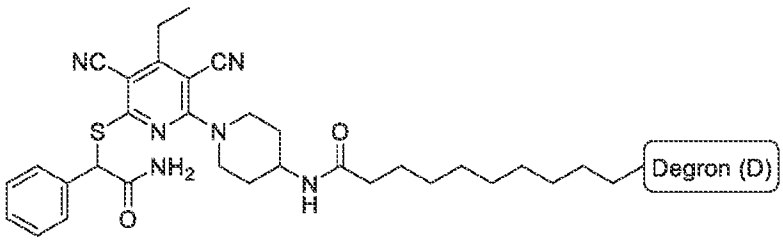


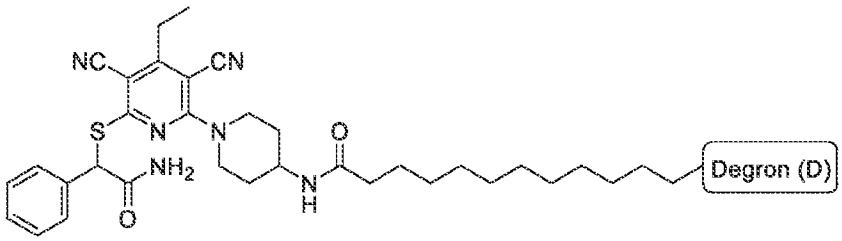
[0081] In some embodiments, compounds of the present disclosure may be represented by any one of the following structures:

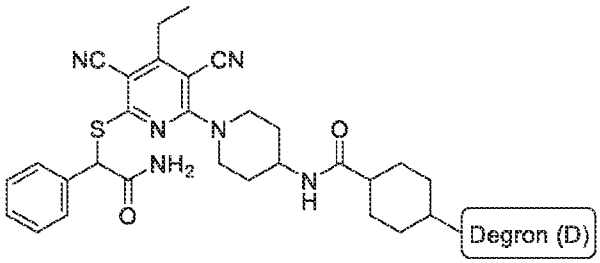









NC
CN
S
N
N
O
NH2
O
N
H
Degron (D)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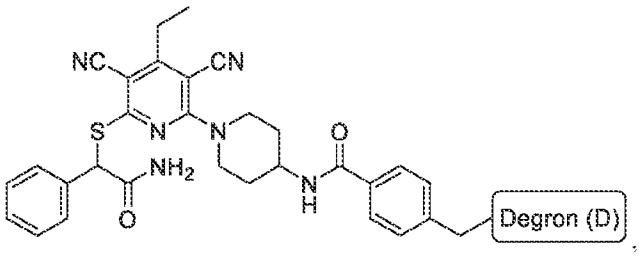
O
NH2
O
N
H
Degron (D)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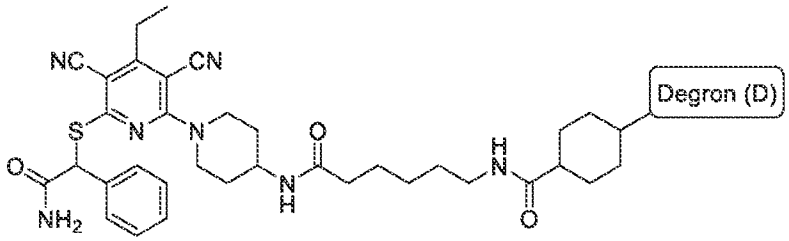
NH2
O
N
H
Degron (D)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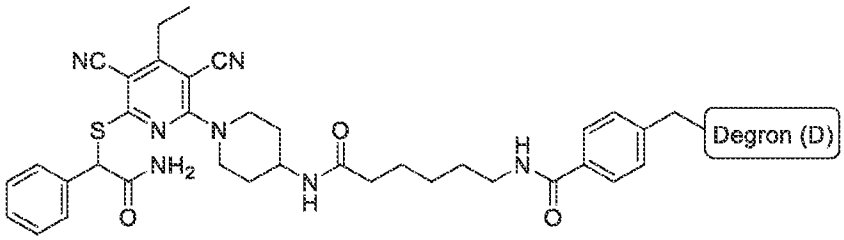
Degron (D)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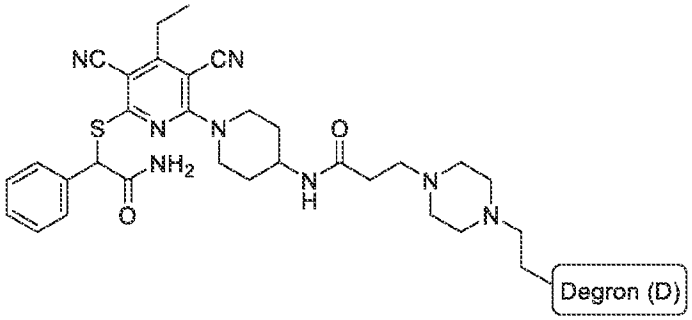
Degron (D)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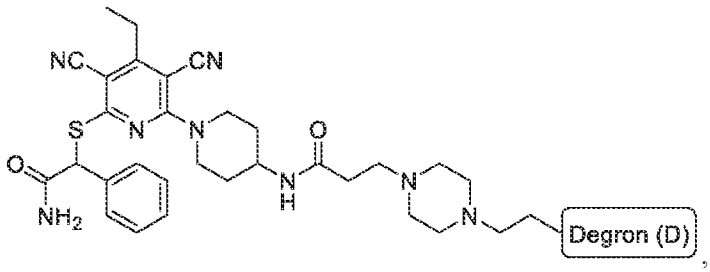
Degron (D)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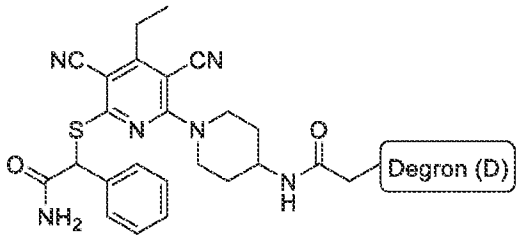
Degron (D)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NH2
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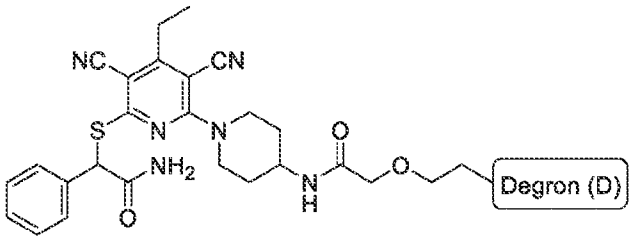
Degron (D)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NH2
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N
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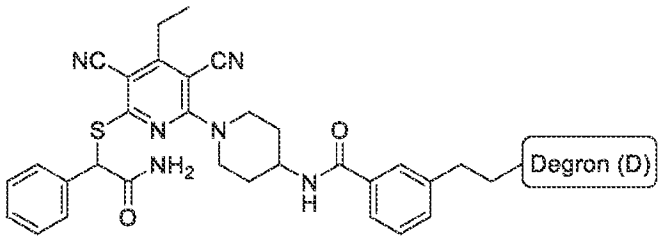
O
Degron (D)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O
NH2
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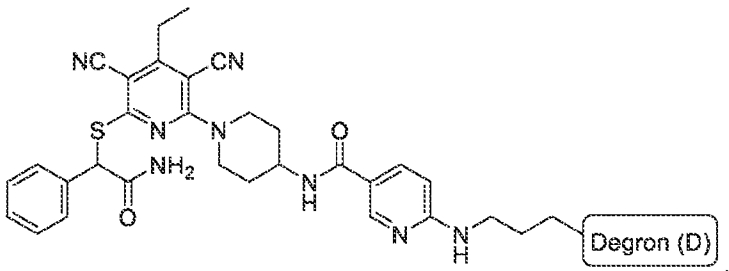
N
H
Degron (D)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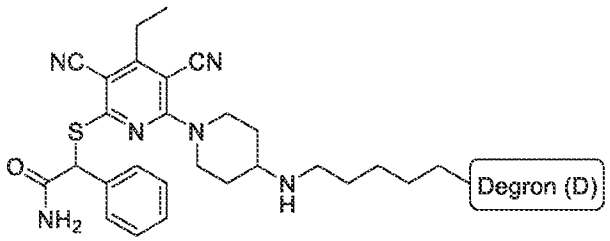
O
NH2
O
N
H
N
N
H
Degron (D)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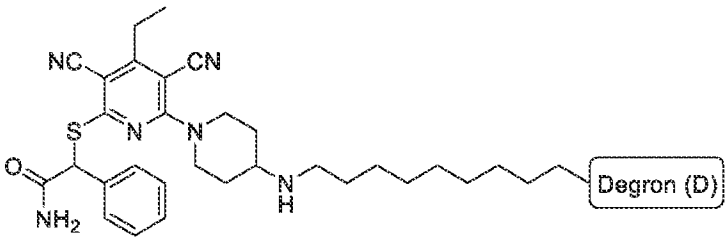
O
NH2
N
H
Degron (D)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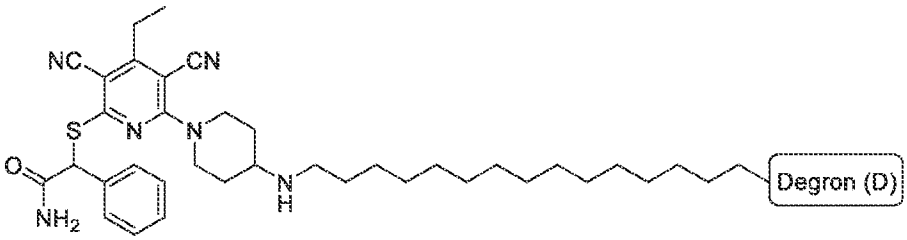
O
NH2
N
H
Degron (D)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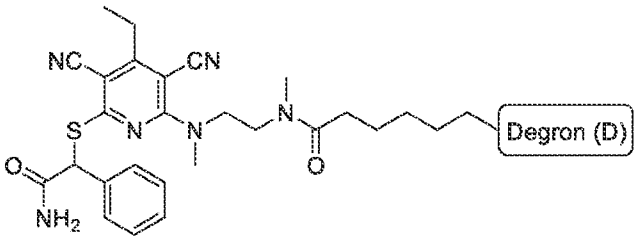
CN
S
N
N
O
NH2
N
H
Degron (D)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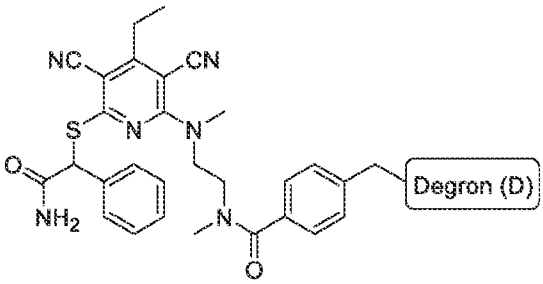
CN
S
N
N
N
O
NH2
O
Degron (D)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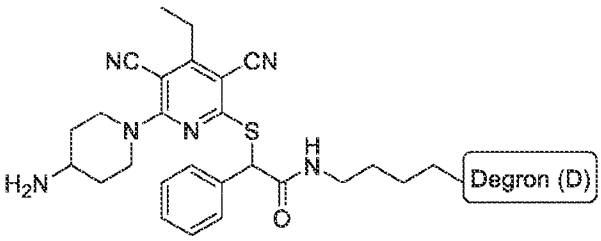
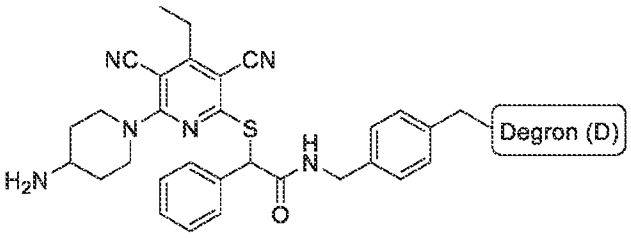
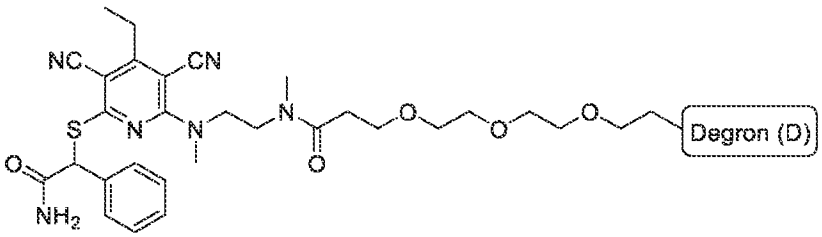
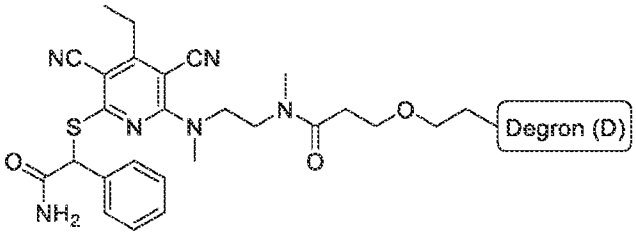
CN
S
N
N
O
NH2
N
O
Degron (D)


NC
CN
N
N
S
H2N
HN
O
Degron (D)


NC
CN
N
N
S
H2N
HN
O
Degron (D)


NC
CN
S
N
N
N
O
O
O
O
O
NH2
Degron (D)


NC
CN
S
N
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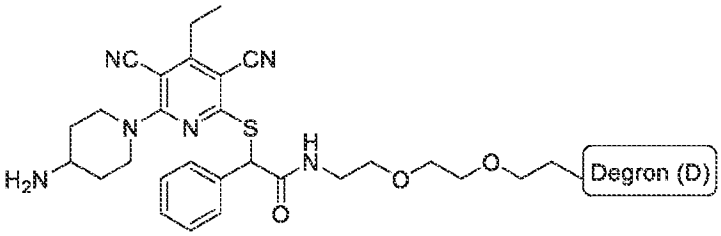
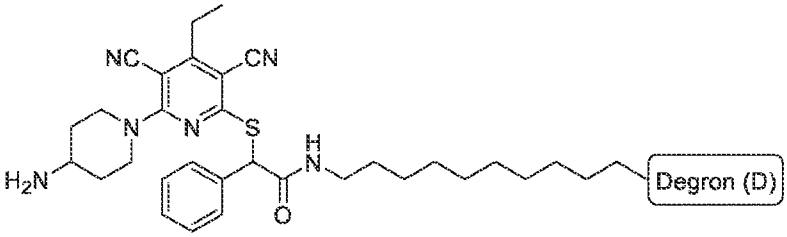
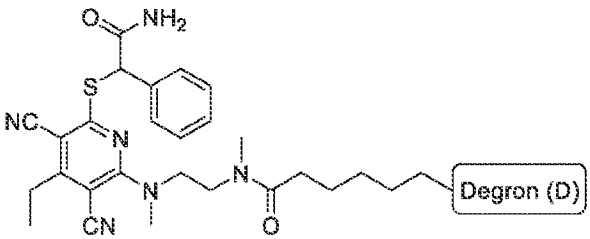
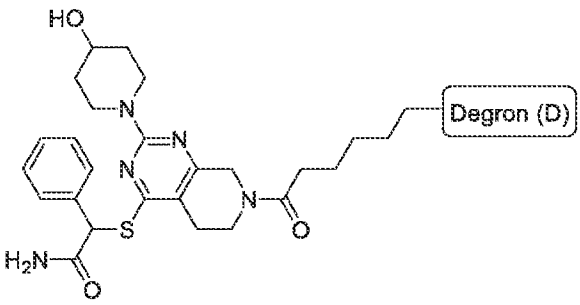
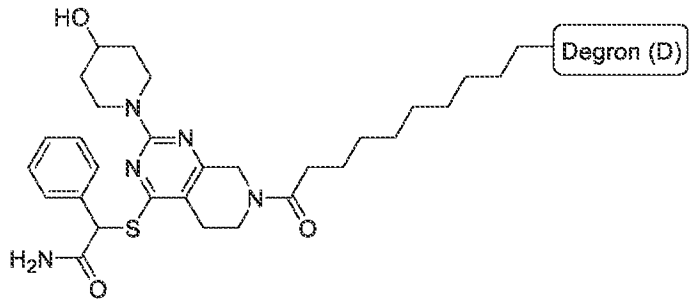
N
O
O
NH2
Degron (D)

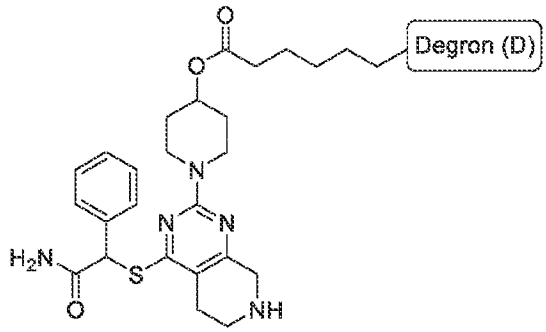

NC
CN
N
N
S
H2N
H
N
O
O
O
Degron (D)

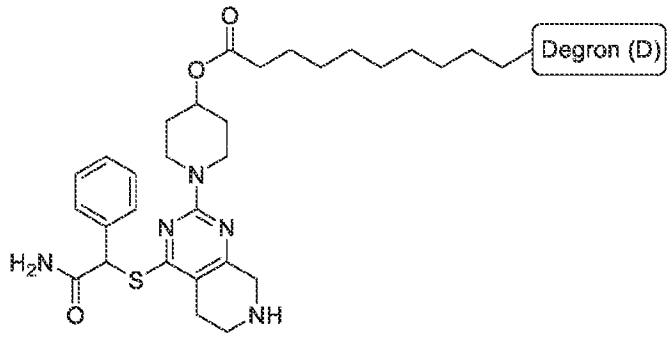

NC
CN
N
N
S
H2N
H
N
O
Degron (D)

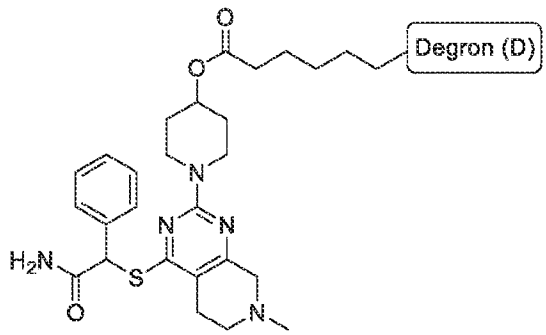

O
NH2
S
NC
N
N
N
O
CN
Degron (D)

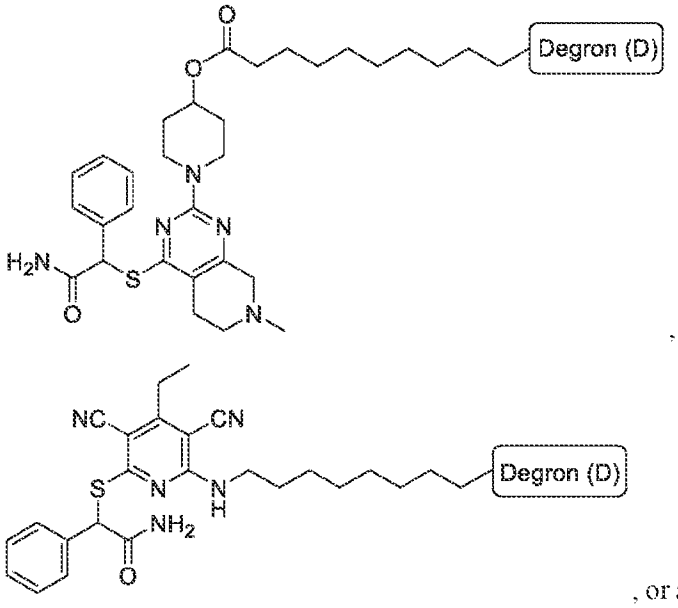

HO
N
N
N
S
N
O
H2N
O
Degron (D)


HO
N
N
N
S
N
O
H2N
O
Degron (D)


O
O
Degron (D)
N
N
N
H2N
S
O
NH


O
O
Degron (D)
N
N
N
H2N
S
O
NH


O
O
Degron (D)
N
N
N
H2N
S
O
N



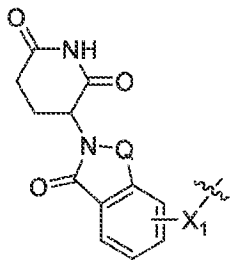
, or a pharmaceutically acceptable salt or stereoisomer thereof.

Degrons

[0082] The Ubiquitin-Proteasome Pathway (UPP) is a critical cellular pathway that regulates key regulator proteins and degrades misfolded or abnormal proteins. UPP is central to multiple cellular processes. The covalent attachment of ubiquitin to specific protein substrates is achieved through the action of E3 ubiquitin ligases. These ligases include over 500 different proteins and are categorized into multiple classes defined by the structural element of their E3 functional activity.

[0083] The degron may bind the E3 ligase which is cereblon (CRBN) or von Hippel Lindau (VHL) tumor suppressor.

[0084] In some embodiments, the degron that binds cereblon is represented by D1:



(D1), or a stereoisomer thereof;

wherein,

Q is CH_2 or C(O); and

X_1 is O or NH.

[0085] In some embodiments, Q is CH_2.

[0086] In some embodiments, Q is C=O.

[0087] In some embodiments, X_1 is O.

[0088] In some embodiments, X_1 is NH.

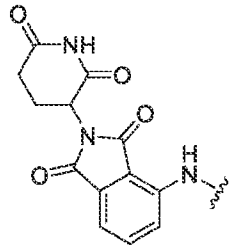
[0089] In some embodiments, X_1 is CH_2.

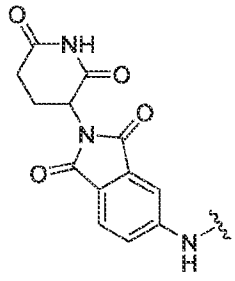
[0090] In some embodiments, X_1 is C≡C.

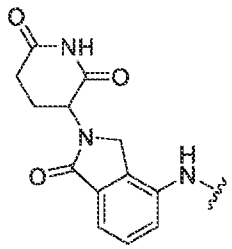
[0091] In some embodiments, Q is CH_2 and X_1 is O. In some embodiments, Q is CH_2 and X_1 is NH. In some embodiments, Q is CH_2 and X_1 is CH_2. In some embodiments, Q is CH_2 and X_1 is C≡C.

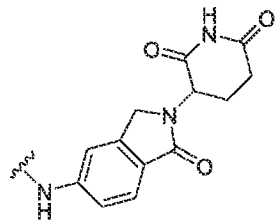
[0092] In some embodiments, Q is C(O) and X_1 is O. In some embodiments, Q is C(O) and X_1 is NH. In some embodiments, Q is C(O) and X_1 is CH_2. In some embodiments, Q is C(O) and X_1 is C≡C.

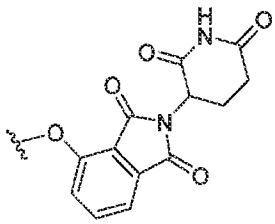
[0093] In some embodiments, formula D1 is of formula D1a-D1p:


(D1a),


(D1b),


(D1c),


(D1d),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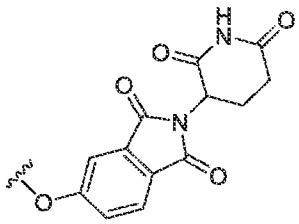
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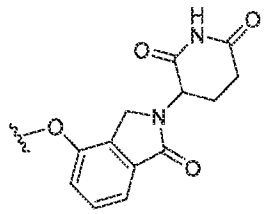
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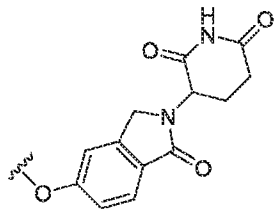
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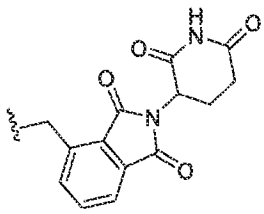
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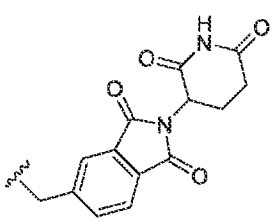
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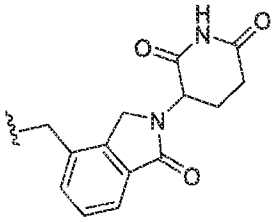
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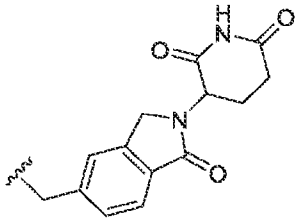
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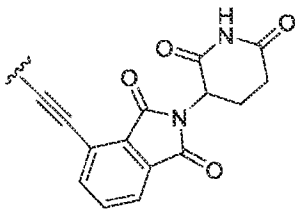
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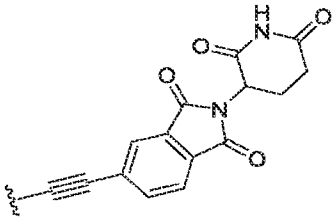
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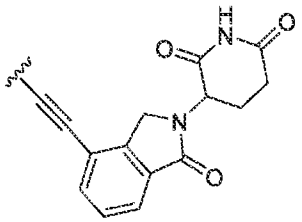
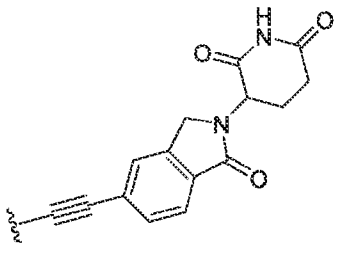
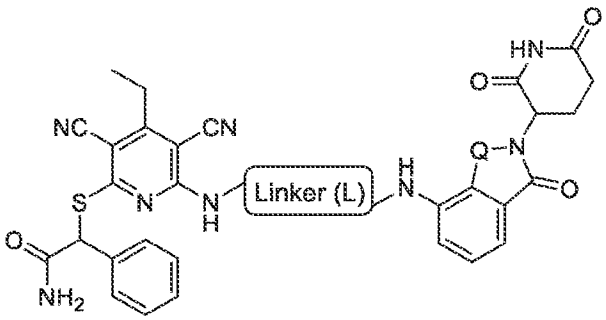

(D1o), or

(D1p).

[0094] Therefore, in some embodiments, the compounds of the present disclosure may be represented by any of the following structures:



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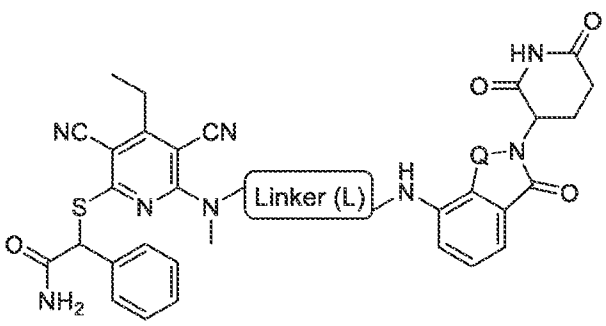

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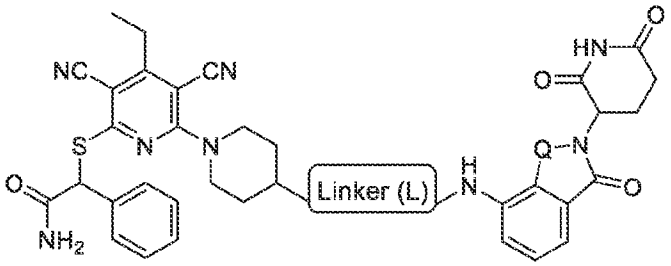
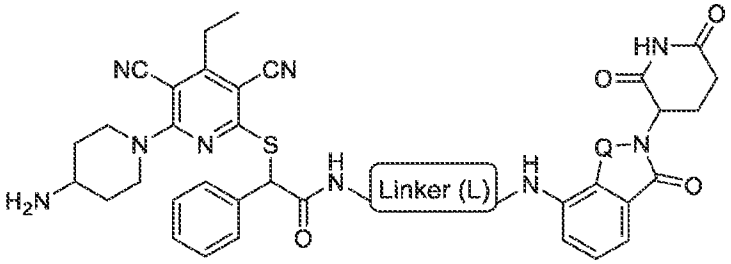
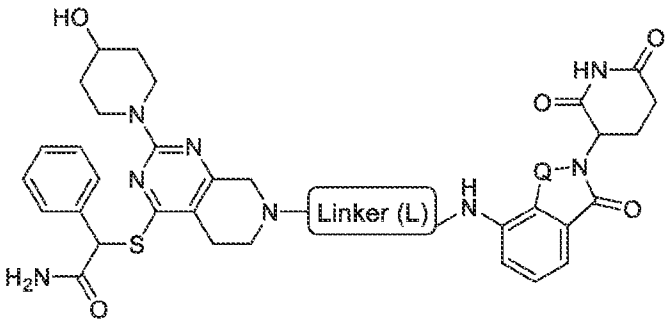
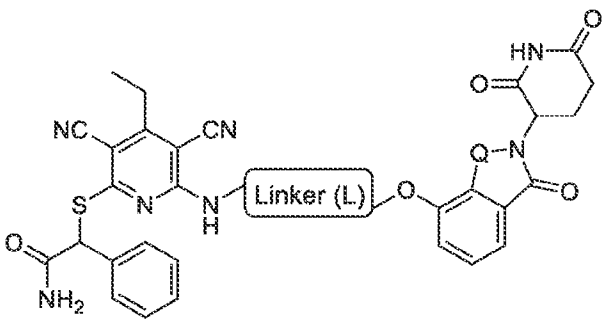

NC
CN
S
N
N
Linker (L)
H
N
HN
O
O
Q
N
O
O
O
NH2


NC
CN
N
N
S
H2N
H
N
Linker (L)
H
N
HN
O
O
Q
N
O
O


HO
N
N
N
N
Linker (L)
H
N
HN
O
O
Q
N
O
O
S
H2N
O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Linker (L)
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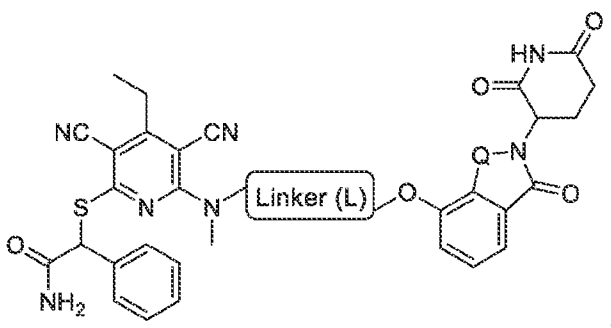
NH2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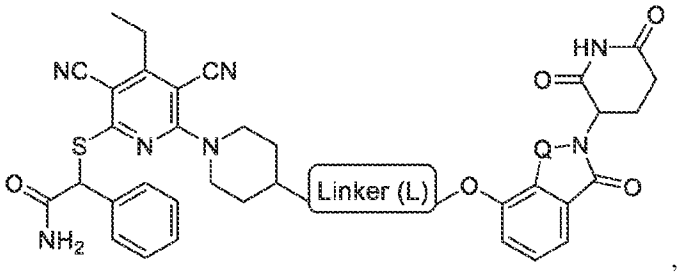
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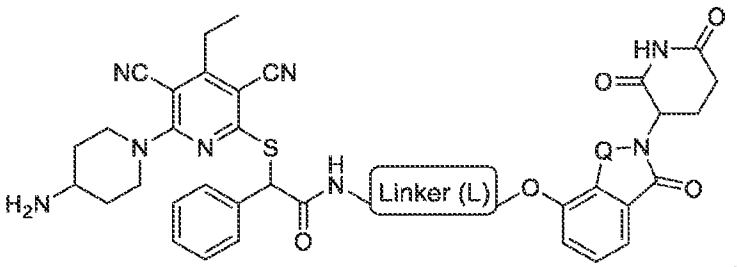
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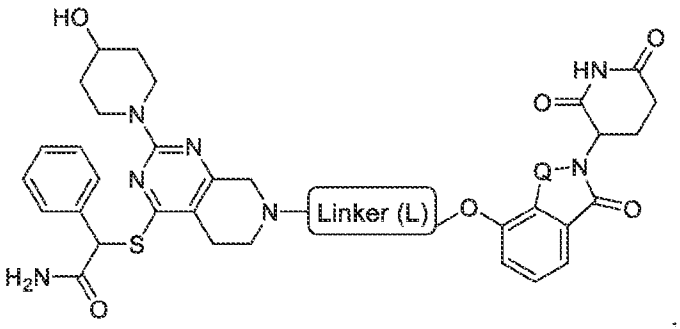
HO
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Linker (L)
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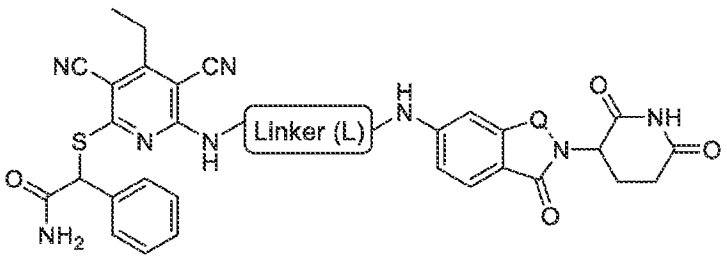
NC
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Linker (L)
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NH
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NH2

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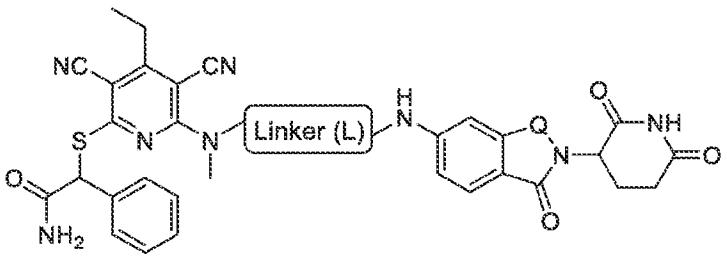
NC
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Linker (L)
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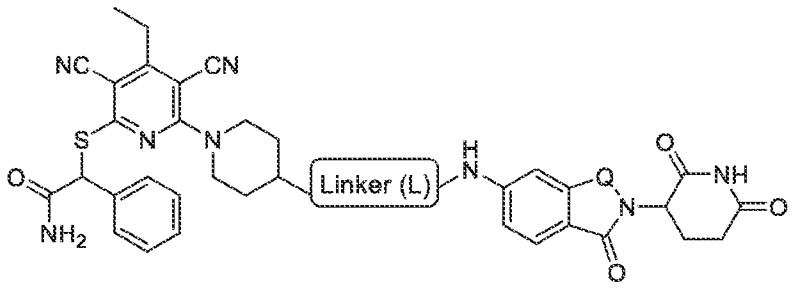

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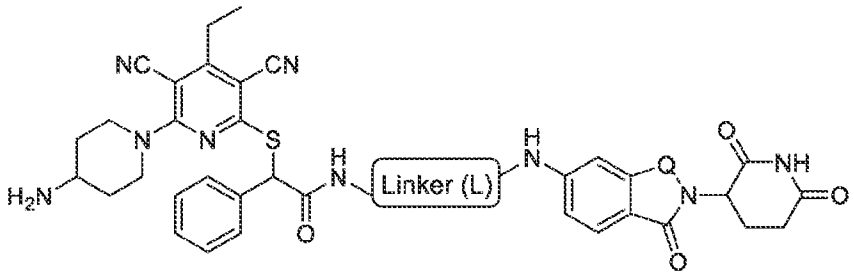

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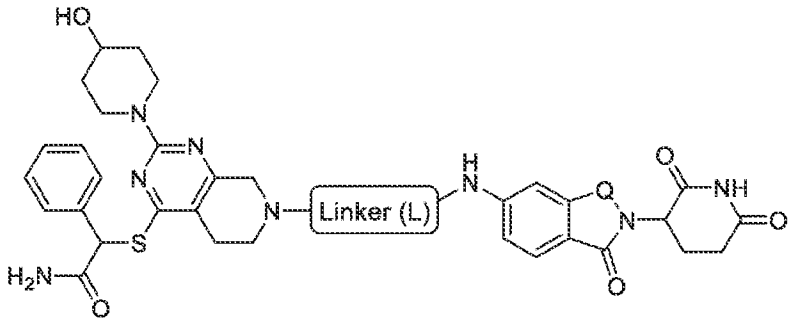
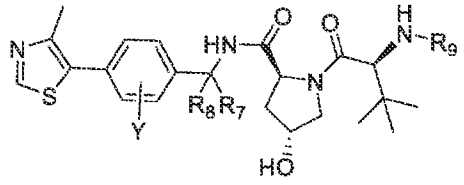


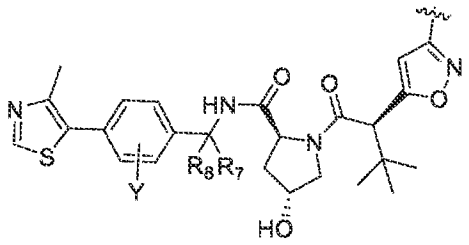
, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Q is CH_2 or C(O). In some embodiments, the linker includes an alkylene chain having 1-12 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-6 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-3 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-12 alkylene units. In some embodiments, the linker includes an alkylene chain having 1-6 alkylene units. In some embodiments, the linker includes an alkylene chain having 1-3 alkylene units. In some embodiments, the linker includes a polyethylene glycol chain having 1-6 PEG units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, or any

combination thereof. In some embodiments, the linker includes a polyethylene glycol chain having 1-2 PEG units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, or any combination thereof. In some embodiments, the linker includes a polyethylene glycol chain having 1-6 PEG units. In some embodiments, the linker includes a polyethylene glycol chain having 1-2 PEG units.

[0095] In some embodiments, the degron may bind the E3 ligase which is von Hippel-Lindau (VHL) tumor suppressor, and is represented by D2 or D3:



(D2) or



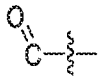
(D3), or stereoisomer thereof,

wherein:

R_7 is H or optionally substituted C_1-C_3 alkyl, or

R_8 and R_9, together with the carbon atom to which they are attached, form cyclopropyl;

R_8 is H, methyl, or  ;

R_9 is $C(O)CR_{10}R_{11}R_{12}$,  or  ;

R_{10} and R_{11} are both H, or

R_{10} and R_{11}, together with the carbon atom to which they are attached, form cyclopropyl;

R_{12} is H, fluoro, cyano, or NMe_2; and

Y is H,  ,  ,  , or  ;

wherein  is a bond between the Degron and the Linker, provided that there is only one bond between the Degron and the Linker.

[0096] In some embodiments, the degron is of formula D2.

[0097] In some embodiments, R_7 is H and R_8 is  .

[0098] In some embodiments, R_7 and R_8 are both H.

[0099] In some embodiments, R_7 is H and R_8 is methyl.

[00100] In some embodiments, R_7 is optionally substituted C_1-C_3 alkyl and R_8 is H.

[00101] In some embodiments, R_7 is optionally substituted C_1-C_3 alkyl and R_8 is methyl.

[00102] In some embodiments, R_7 and R_8, together with the carbon atom to which they are attached, form cyclopropyl.

[00103] In some embodiments, Y is H.

[00104] In some embodiments, Y is  ,  ,  , or  .

[00105] In some embodiments R_9 is  .

[00106] In some embodiments, R_9 is $C(O)CR_{10}R_{11}R_{12}$. In some embodiments, R_{10}, R_{11}, and R_{12} are H. In some embodiments, R_6 and R_7, together with the carbon atom to which they are attached, form cyclopropyl and R_8 is H, fluoro, cyano, or NMe_2. In some embodiments, R_8 is fluoro, cyano, or NMe_2.

[00107] In some embodiments, R_7 is H, R_8 is  , and Y is H.

[00108] In some embodiments, R_7 is H, R_8 is  , Y is H, and R_9 is $C(O)CR_{10}R_{11}R_{12}$, wherein R_{10} and R_{11}, together with the carbon atom to which they are attached, form cyclopropyl and R_{12} is fluoro, cyano, or NMe_2.

[00109] In some embodiments, Y is  ,  ,  , or  and R_7 and R_8 are H.

[00110] In some embodiments, Y is  ,  ,  , or  , R_7 and R_8 are H, and R_9 is $C(O)CR_{10}R_{11}R_{12}$, wherein R_{10} and R_{11}, together with the carbon atom to which they are attached, form cyclopropyl and R_{12} is fluoro, cyano, or NMe_2.

[00111] In some embodiments R_9 is  , Y is H, and R_7 and R_8 are H.

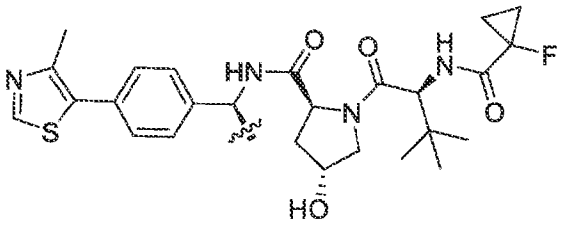
[00112] In some embodiments R_9 is  , Y is H, R_7 is H, and R_8 is methyl.

[00113] In some embodiments R_9 is  , Y is H, R_7 is optionally substituted C_1-C_3 alkyl, and R_8 is H.

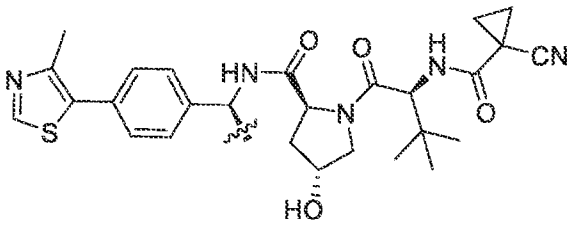
[00114] In some embodiments R_9 is  , Y is H, R_7 is optionally substituted C_1-C_3 alkyl, and R_8 is H.

[00115] In some embodiments R_9 is  , Y is H, and R_7 and R_8, together with the carbon atom to which they are attached, form cyclopropyl.

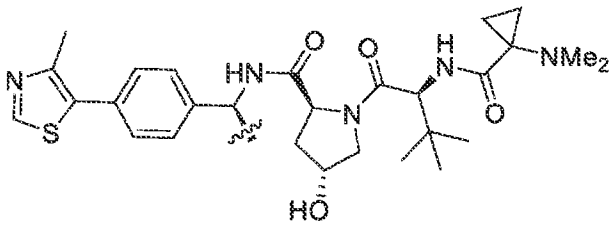
[00116] In some embodiments, formula D2 is of formula D2a-D2o:



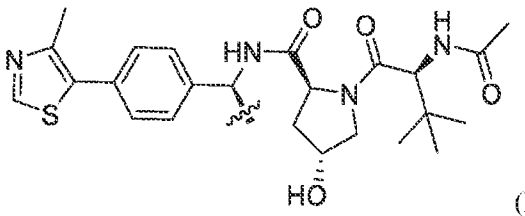
(D2a),



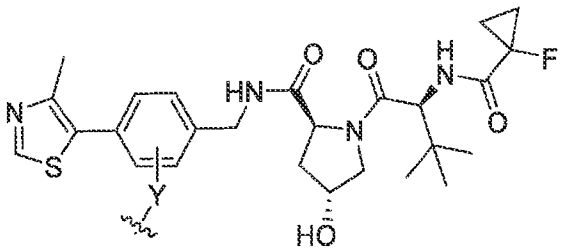
(D2b),



(D2c),



(D2d),



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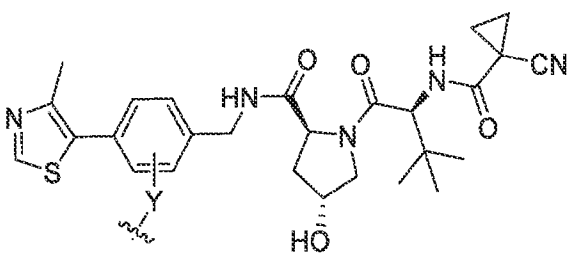

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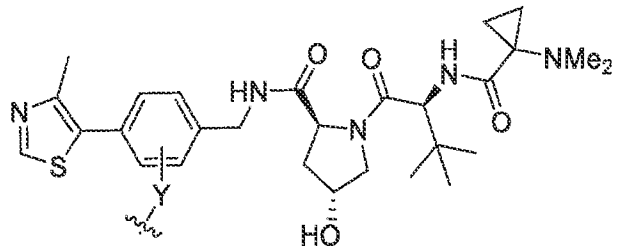
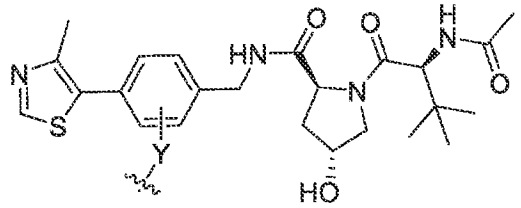
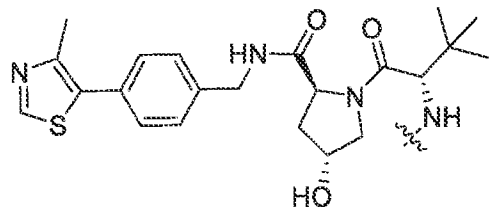


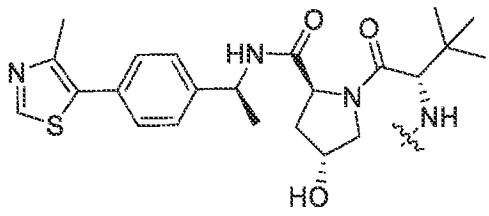
(D2g),



(D2h),



(D2i),



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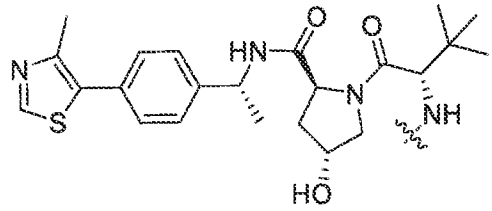
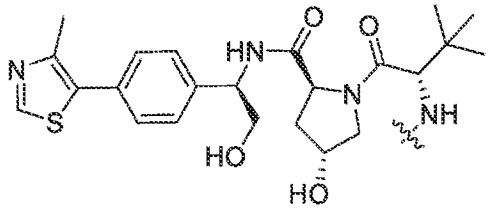
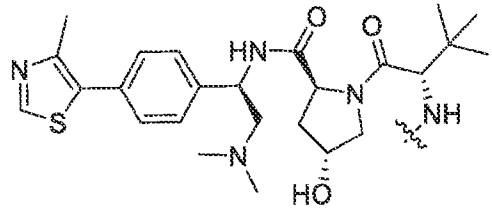


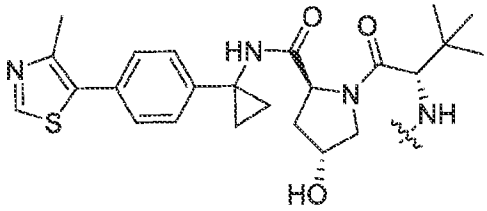
(D2k),

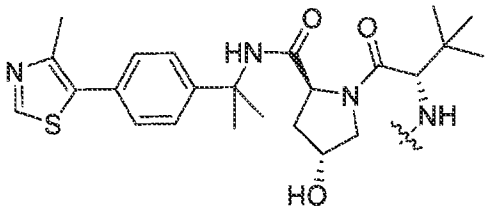


(D2l),



(D2m),

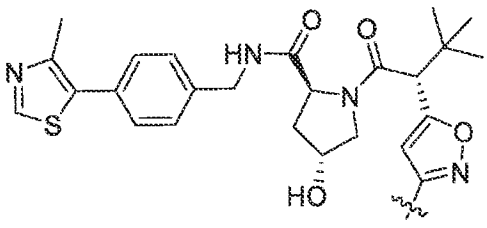


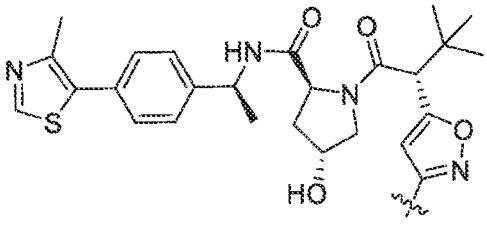


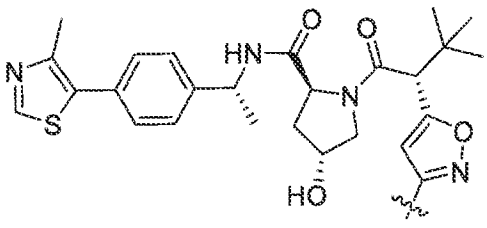
(D2n), or (D2o), or a stereoisomer thereof.

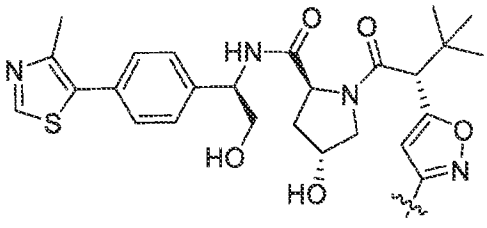
[00117] In some embodiments, the degron is of formula D3.

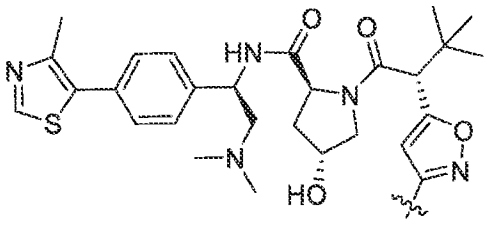
[00118] In some embodiments, the degron of formula D3 is of formula D3a-D3g:

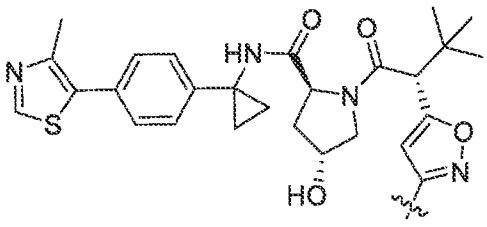

(D3a),

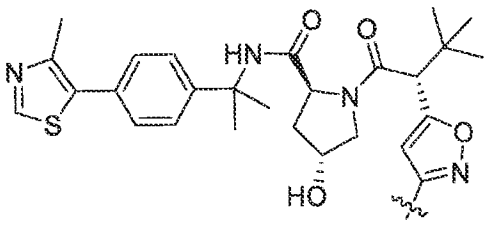

(D3b),


(D3c),


(D3d),

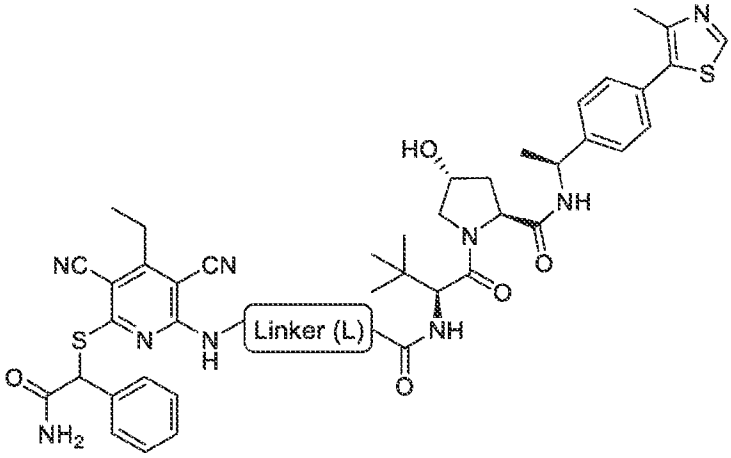

(D3e),


(D3f), or



(D3g), or stereoisomer thereof.

[00119] Therefore, in some embodiments, the compounds of the present disclosure may be represented by any of the following structures:



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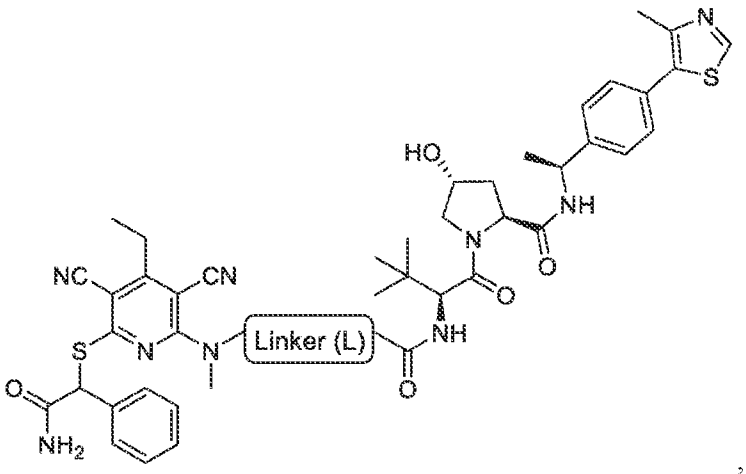

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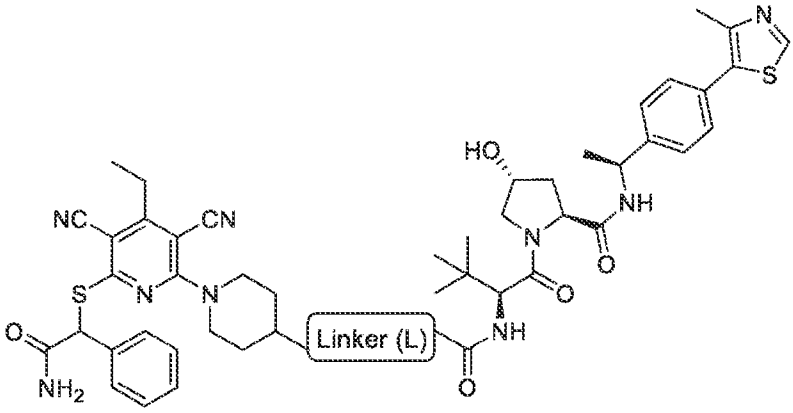
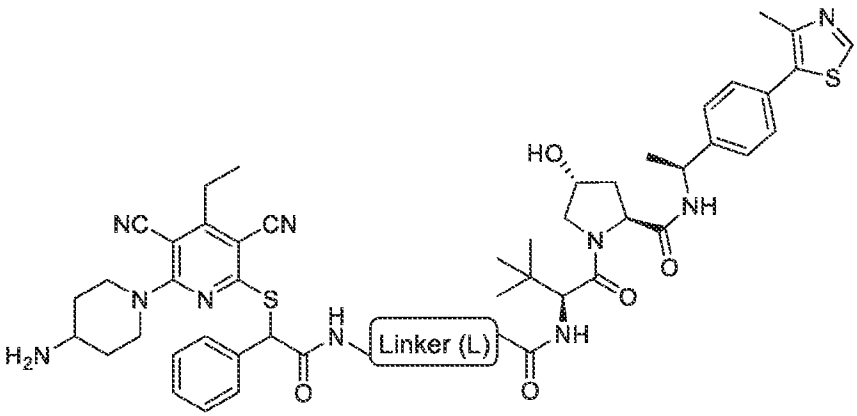
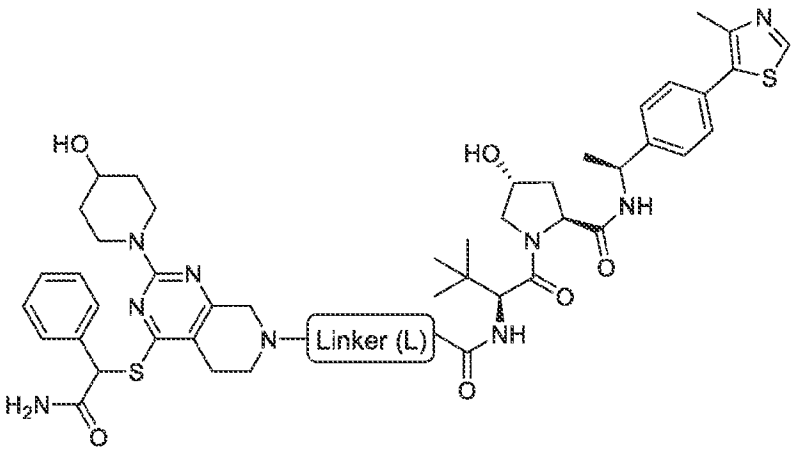
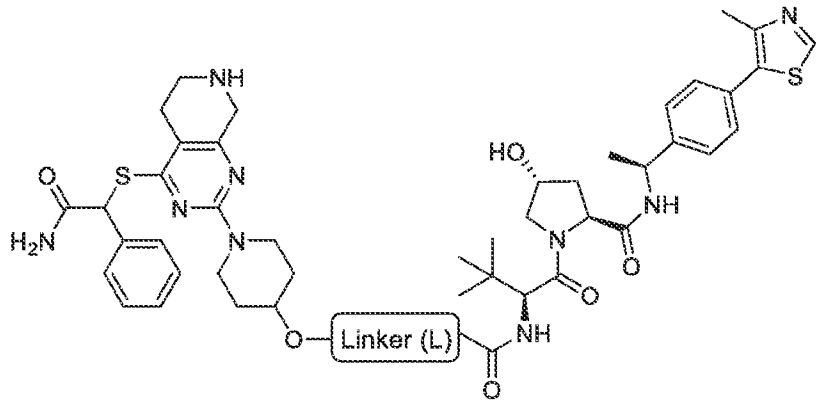

NC
CN
S
N
N
O
NH2
Linker (L)
HO
N
O
NH
O
N
S

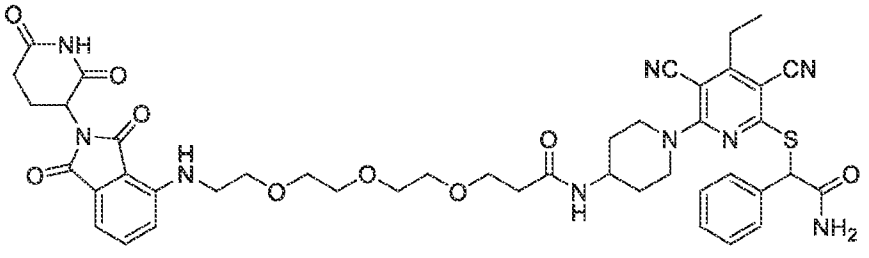

NC
CN
N
N
S
H2N
O
H
N
Linker (L)
HO
N
O
NH
O
NH
O
N
S


HO
N
N
N
S
H2N
O
N
Linker (L)
HO
N
O
NH
O
NH
O
N
S



, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, the linker includes an alkylene chain having 1-12 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-6 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-3 alkylene units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, C_6 carbocyclene, 6-membered heteroarylene or any combination thereof. In some embodiments, the linker includes an alkylene chain having 1-12 alkylene units. In some embodiments, the linker includes an alkylene chain having 1-6 alkylene units. In some embodiments, the linker includes an alkylene chain having 1-3 alkylene units. In some embodiments, the linker includes a polyethylene glycol chain having 1-6 PEG units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, or any combination thereof. In some embodiments, the linker includes a polyethylene glycol chain having 1-2 PEG units and is interrupted by and/or terminates in –C(O)–, –NH–, –C(O)NH–, –C(O)N(Me)–, or any combination thereof. In some embodiments, the linker includes a polyethylene glycol chain having 1-6 PEG units. In some embodiments, the linker includes a polyethylene glycol chain having 1-2 PEG units.

[00120] In some embodiments, compounds of the present disclosure are represented by any one of the following structures: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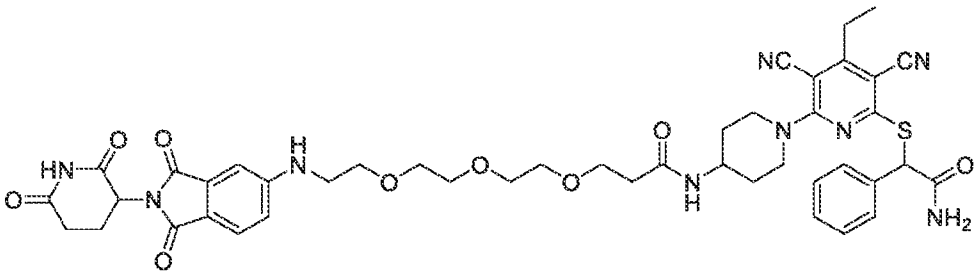
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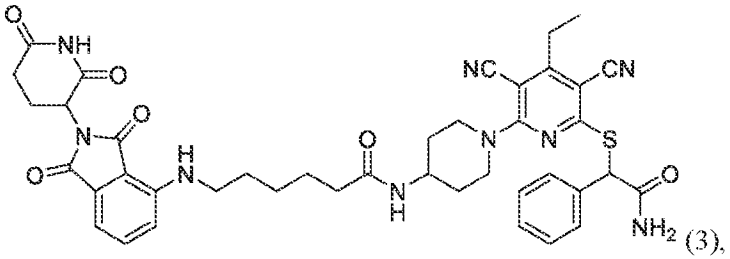
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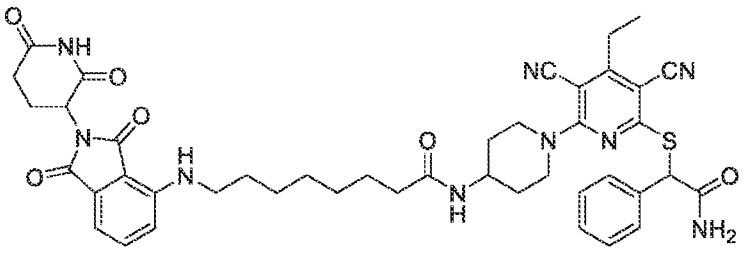
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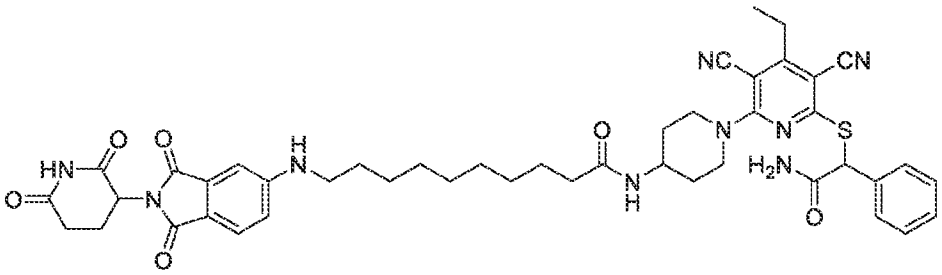
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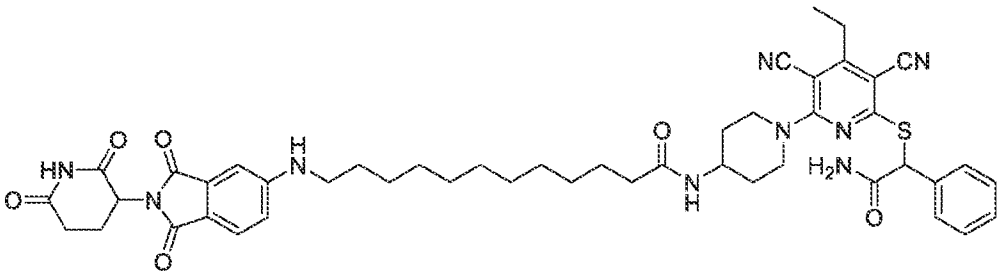

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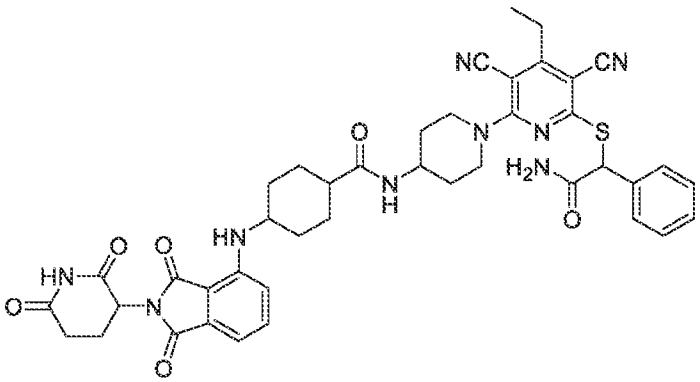

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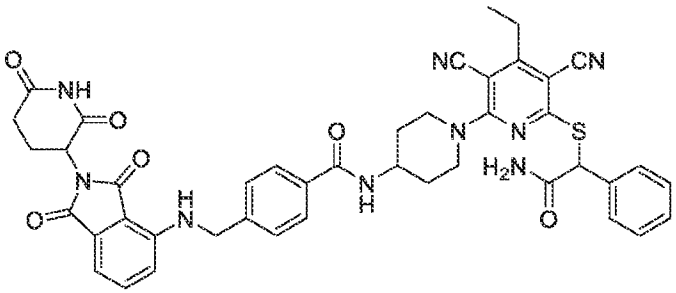

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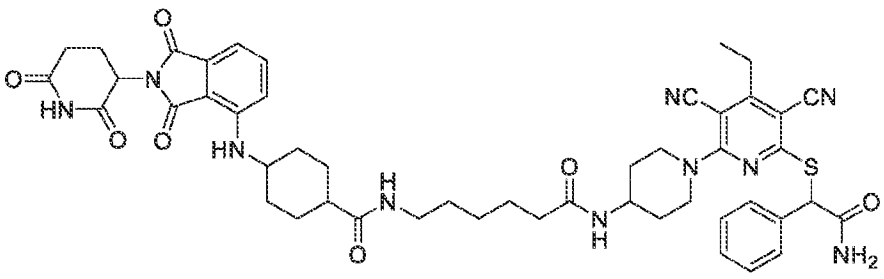

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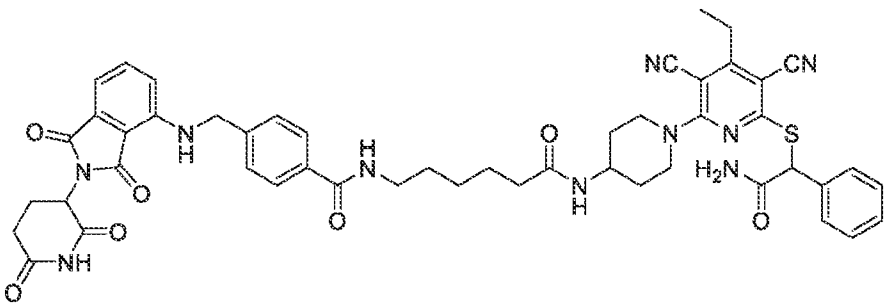

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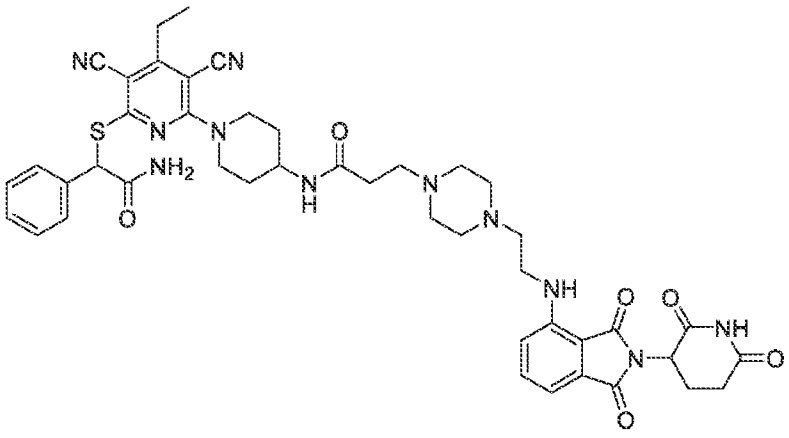

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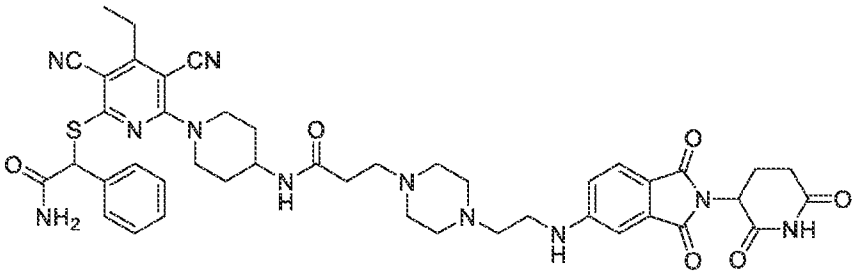

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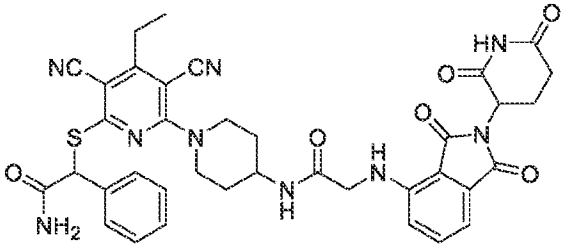

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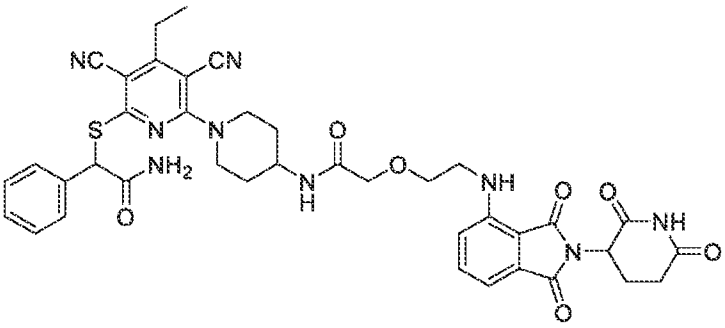

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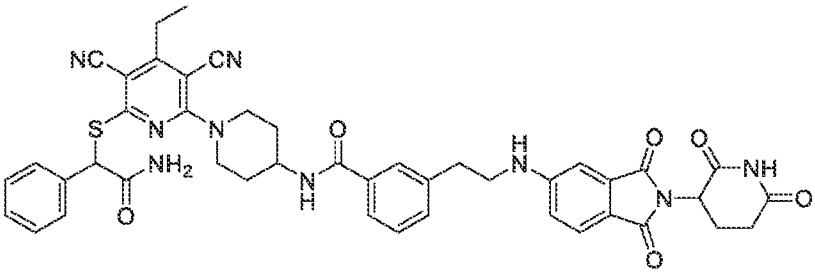

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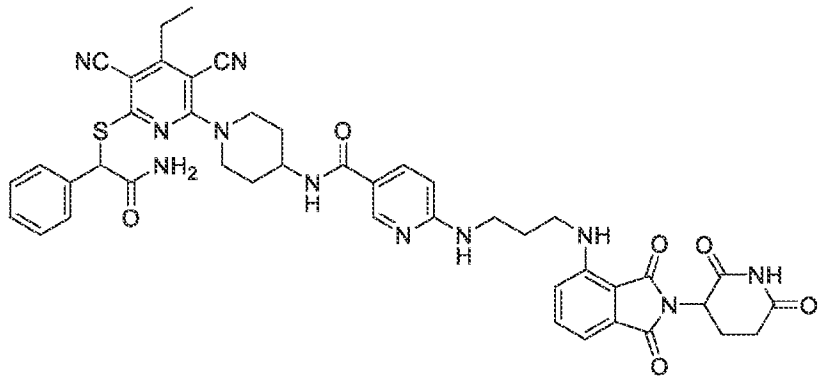

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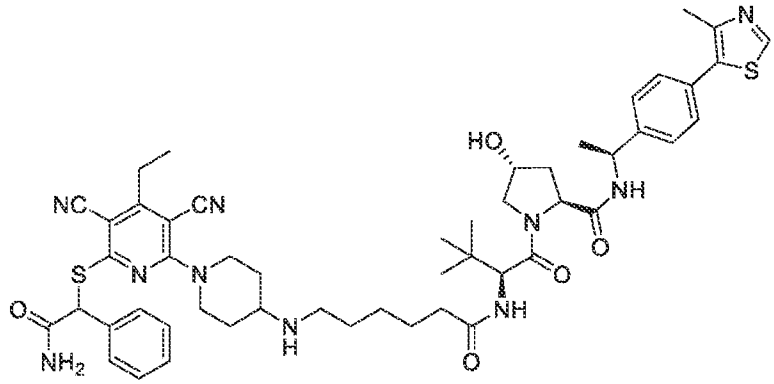

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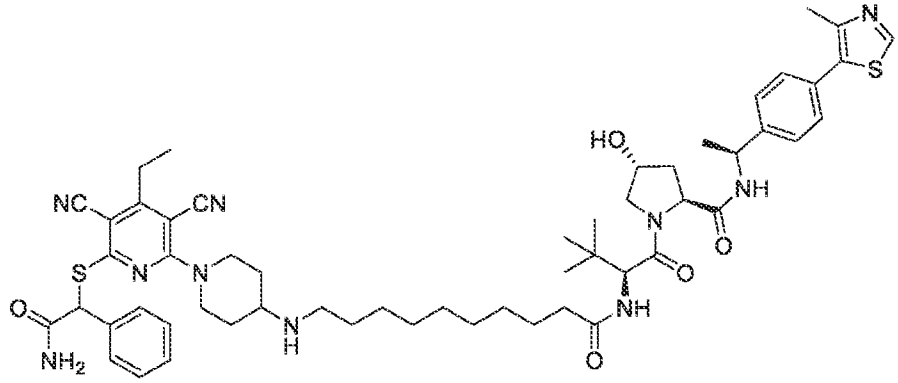

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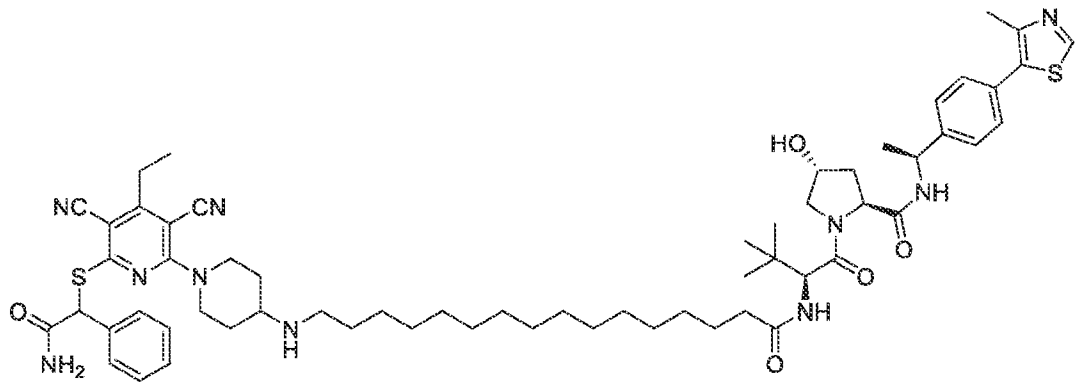

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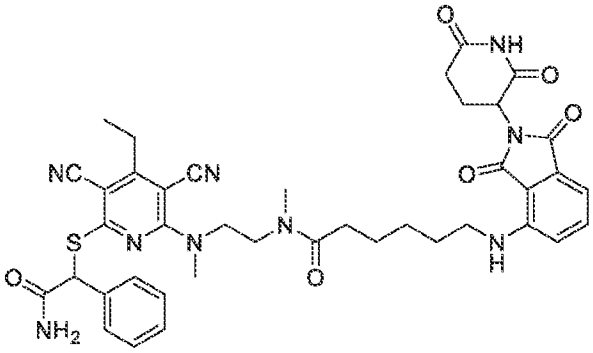

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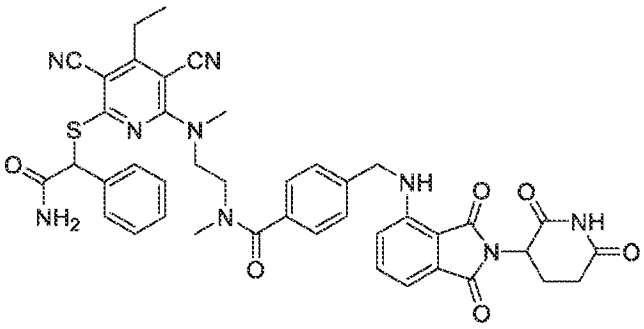

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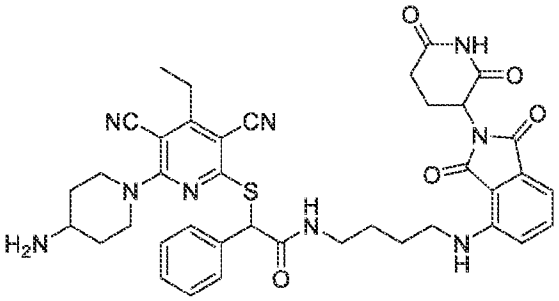

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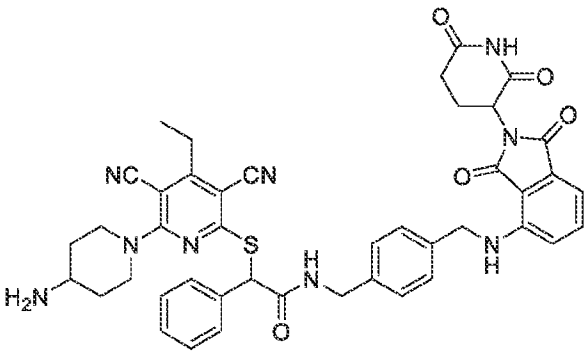

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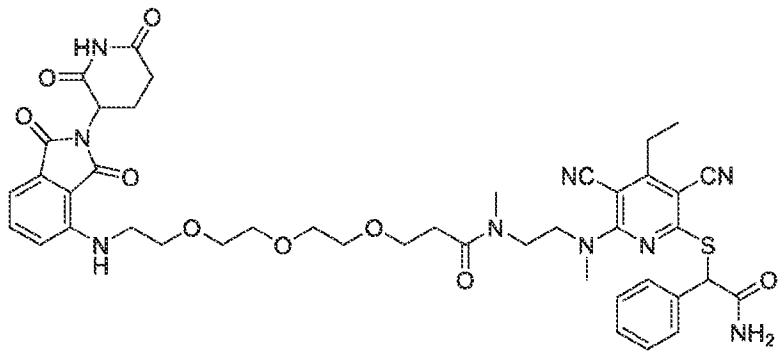

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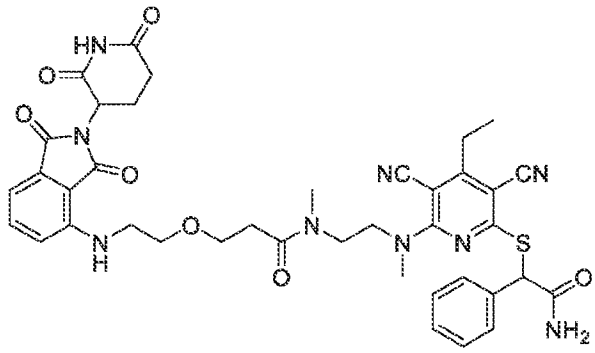

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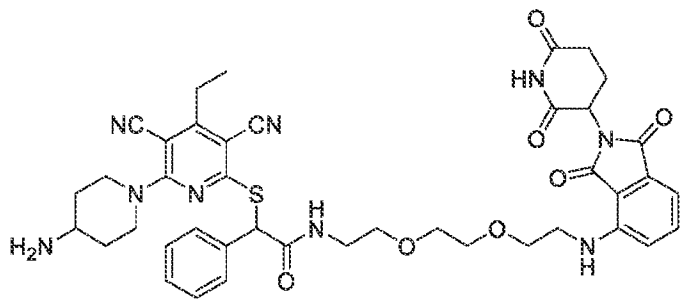

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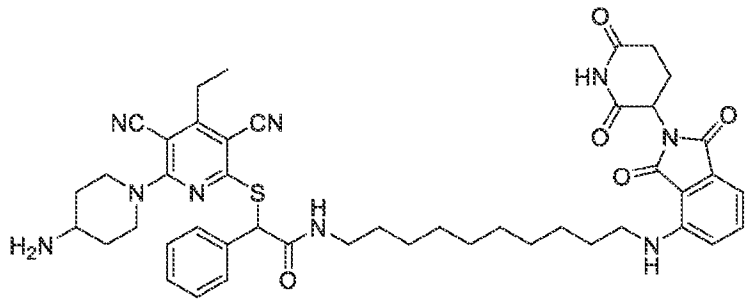

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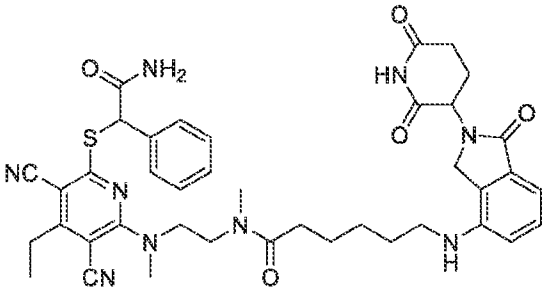

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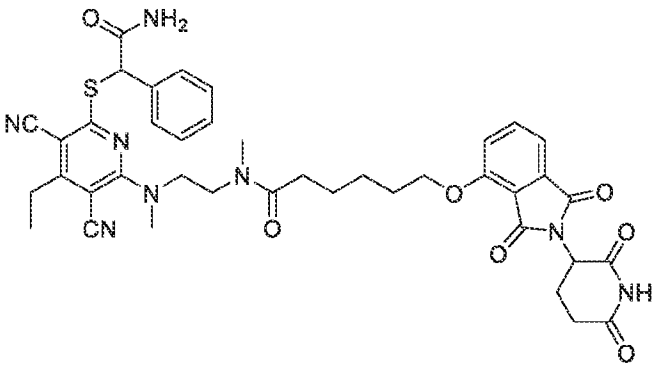

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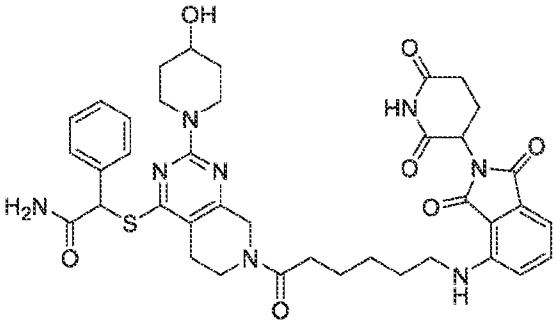

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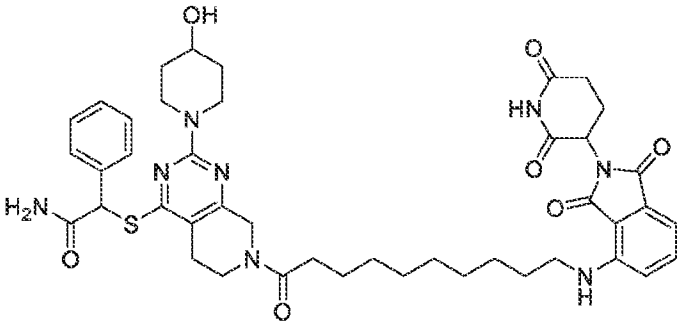

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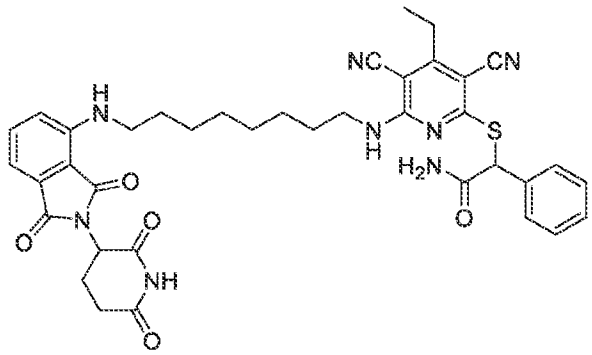


(32), or a pharmaceutically acceptable salt or stereoisomer thereof.

[00121] Compounds of the present disclosure may be in the form of a free acid or free base, or a pharmaceutically acceptable salt. A pharmaceutically acceptable salt of the compounds of this disclosure can be formed, for example, by reaction of an appropriate free base of a compound of the disclosure and an appropriate pharmaceutically acceptable acid in a suitable solvent under standard conditions well known in the art. *See*, for example, Gould, P. L., "Salt selection for basic drugs," International Journal of Pharmaceutics, *33*: 201-217 (1986); Bastin, R. J., et al., "Salt Selection and Optimization Procedures for Pharmaceutical New Chemical Entities," Organic Process Research and Development, *4*:427-435 (2000); and Berge, S. M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Sciences, *66*:1-19, (1977).

[00122] Compounds of the present disclosure may have at least one chiral center and thus may be in the form of a stereoisomer, which as used herein, embraces all isomers of individual compounds that differ only in the orientation of their atoms in space. The term stereoisomer includes mirror image isomers (enantiomers which include the (R-) or (S-) configurations of the compounds), mixtures of mirror image isomers (physical mixtures of the enantiomers, and racemates or racemic mixtures) of compounds, geometric (cis/trans or E/Z, R/S) isomers of compounds and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers). The chiral centers of the compounds may undergo epimerization *in vivo*; thus, for these compounds, administration of the compound in its (R-) form is considered equivalent to administration of the compound in its (S-) form. Accordingly, the compounds of the present disclosure may be made and used in the form of individual isomers and substantially free of other isomers, or in the form of a mixture of various isomers, *e.g.*, racemic mixtures of stereoisomers.

[00123] In some embodiments, the compound of formula (I) is an isotopic derivative in that it has at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, *i.e.*, enriched. In one embodiment, the compound includes deuterium

or multiple deuterium atoms. As used herein, the term "compound" embraces isotopic derivatives.

[00124] Compounds of formula (I) may also be in the form of N-oxides, crystalline forms (also known as polymorphs), co-crystals, active metabolites of the compounds having the same type of activity, prodrugs, tautomers, and unsolvated as well as solvated (*e.g.*, hydrated) forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, of the compounds. As used herein, the term "compound" embraces all these forms.

[00125] The compounds of formula (I) may be prepared by crystallization under different conditions and may exist as one or a combination of polymorphs of the compound. For example, different polymorphs may be identified and/or prepared using different solvents, or different mixtures of solvents for recrystallization, by performing crystallizations at different temperatures, or by using various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffractogram and/or other known techniques.

[00126] In some embodiments, the pharmaceutical composition comprises a co-crystal of a compound of formula (I). The term "co-crystal", as used herein, refers to a stoichiometric multi-component system comprising a compound of formula (I) and a co-crystal former wherein the compound of formula (I) and the co-crystal former are connected by non-covalent interactions. The term "co-crystal former", as used herein, refers to compounds which can form intermolecular interactions with a compound of formula (I) and co-crystallize with it. Representative examples of co-crystal formers include benzoic acid, succinic acid, fumaric acid, glutaric acid, *trans*-cinnamic acid, 2,5-dihydroxybenzoic acid, glycolic acid, *trans*-2-hexanoic acid, 2-hydroxycaproic acid, lactic acid, sorbic acid, tartaric acid, ferulic acid, suberic acid, picolinic acid, salicylic acid, maleic acid, saccharin, 4,4'-bipyridine *p*-aminosalicylic acid, nicotinamide, urea, isonicotinamide, methyl-4-hydroxybenzoate, adipic acid, terephthalic acid, resorcinol, pyrogallol, phloroglucinol, hydroxyquinol, isoniazid, theophylline, adenine, theobromine, phenacetin, phenazone, etofylline, and phenobarbital.

Methods of Synthesis

[00127] In some embodiments, the present disclosure is directed to a method for making a compound of formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof. Broadly, the compounds or pharmaceutically acceptable salts or stereoisomers thereof, may be

prepared by any process known to be applicable to the preparation of chemically related compounds. The compounds of the present disclosure will be better understood in connection with the synthetic schemes that described in various working examples that illustrate non-limiting methods by which the compounds of the disclosure may be prepared.

Pharmaceutical Compositions

[00128] Another aspect of the present disclosure is directed to a pharmaceutical composition that includes a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier," as known in the art, refers to a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present disclosure to mammals. Suitable carriers may include, for example, liquids (both aqueous and non-aqueous alike, and combinations thereof), solids, encapsulating materials, gases, and combinations thereof (*e.g.*, semi-solids), and gases, that function to carry or transport the compound from one organ, or portion of the body, to another organ, or portion of the body. A carrier is "acceptable" in the sense of being physiologically inert to and compatible with the other ingredients of the formulation and not injurious to the subject or patient. Depending on the type of formulation, the composition may also include one or more pharmaceutically acceptable excipients.

[00129] Broadly, compounds of formula (I) and their pharmaceutically acceptable salts and stereoisomers may be formulated into a given type of composition in accordance with conventional pharmaceutical practice such as conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping and compression processes (*see, e.g.*, Remington: *The Science and Practice of Pharmacy* (20th ed.), ed. A. R. Gennaro, Lippincott Williams & Wilkins, 2000 and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York), each of which is incorporated herein by reference in its entirety. The type of formulation depends on the mode of administration which may include enteral (*e.g.*, oral, buccal, sublingual and rectal), parenteral (*e.g.*, subcutaneous (*s.c.*), intravenous (*i.v.*), intramuscular (*i.m.*), and intrasternal injection, or infusion techniques, intra-ocular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, interdermal, intravaginal, intraperitoneal, mucosal, nasal, intratracheal instillation, bronchial instillation, and inhalation) and topical (*e.g.*, transdermal).

[00130] In general, the most appropriate route of administration will depend upon a variety of factors including, for example, the nature of the agent (*e.g.*, its stability in the environment

of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration). For example, parenteral (*e.g.*, intravenous) administration may also be advantageous in that the compound may be administered relatively quickly such as in the case of a single-dose treatment and/or an acute condition.

[00131] In some embodiments, the compounds are formulated for oral or intravenous administration (*e.g.*, systemic intravenous injection).

[00132] Accordingly, compounds of formula (I) may be formulated into solid compositions (*e.g.*, powders, tablets, dispersible granules, capsules, cachets, and suppositories), liquid compositions (*e.g.*, solutions in which the compound is dissolved, suspensions in which solid particles of the compound are dispersed, emulsions, and solutions containing liposomes, micelles, or nanoparticles, syrups and elixirs); semi-solid compositions (*e.g.*, gels, suspensions and creams); and gases (*e.g.*, propellants for aerosol compositions). Compounds may also be formulated for rapid, intermediate or extended release.

[00133] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with a carrier such as sodium citrate or dicalcium phosphate and an additional carrier or excipient such as a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as crosslinked polymers (*e.g.*, crosslinked polyvinylpyrrolidone (crospovidone), crosslinked sodium carboxymethyl cellulose (croscarmellose sodium), sodium starch glycolate, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also include buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings. They may further contain an opacifying agent.

[00134] In some embodiments, compounds of formula (I) may be formulated in a hard or soft gelatin capsule. Representative excipients that may be used include pregelatinized starch, magnesium stearate, mannitol, sodium stearyl fumarate, lactose anhydrous, microcrystalline cellulose and croscarmellose sodium. Gelatin shells may include gelatin, titanium dioxide, iron oxides and colorants.

[00135] Liquid dosage forms for oral administration include solutions, suspensions, emulsions, micro-emulsions, syrups and elixirs. In addition to the compound, the liquid dosage forms may contain an aqueous or non-aqueous carrier (depending upon the solubility of the compounds) commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Oral compositions may also include an excipients such as wetting agents, suspending agents, coloring, sweetening, flavoring, and perfuming agents.

[00136] Injectable preparations for parenteral administration may include sterile aqueous solutions or oleaginous suspensions. They may be formulated according to standard techniques using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. The effect of the compound may be prolonged by slowing its absorption, which may be accomplished by the use of a liquid suspension or crystalline or amorphous material with poor water solubility. Prolonged absorption of the compound from a parenterally administered formulation may also be accomplished by suspending the compound in an oily vehicle.

[00137] In certain embodiments, compounds of formula (I) may be administered in a local rather than systemic manner, for example, via injection of the conjugate directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Injectable depot forms are made by forming microencapsule matrices of the compound in a biodegradable polymer, *e.g.*, polylactide-polyglycolides, poly(orthoesters) and poly(anhydrides). The rate of release of the compound may be controlled by varying the ratio of compound to polymer and the nature of the particular polymer employed. Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues. Furthermore, in other embodiments, the compound is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ.

[00138] The compositions may be formulated for buccal or sublingual administration, examples of which include tablets, lozenges and gels.

[00139] The compounds of formula (I) may be formulated for administration by inhalation. Various forms suitable for administration by inhalation include aerosols, mists or powders. Pharmaceutical compositions may be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In some embodiments, the dosage unit of a pressurized aerosol may be determined by providing a valve to deliver a metered amount. In some embodiments, capsules and cartridges including gelatin, for example, for use in an inhaler or insufflator, may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00140] Compounds of formula (I) may be formulated for topical administration which as used herein, refers to administration intradermally by injection of the formulation to the epidermis. These types of compositions are typically in the form of ointments, pastes, creams, lotions, gels, solutions and sprays.

[00141] Representative examples of carriers useful in formulating compounds for topical application include solvents (*e.g.*, alcohols, poly alcohols, water), creams, lotions, ointments, oils, plasters, liposomes, powders, emulsions, microemulsions, and buffered solutions (*e.g.*, hypotonic or buffered saline). Creams, for example, may be formulated using saturated or

unsaturated fatty acids such as stearic acid, palmitic acid, oleic acid, palmito-oleic acid, cetyl, or oleyl alcohols. Creams may also contain a non-ionic surfactant such as polyoxy-40-stearate.

[00142] In some embodiments, the topical formulations may also include an excipient, an example of which is a penetration enhancing agent. These agents are capable of transporting a pharmacologically active compound through the *stratum corneum* and into the epidermis or dermis, preferably, with little or no systemic absorption. A wide variety of compounds have been evaluated as to their effectiveness in enhancing the rate of penetration of drugs through the skin. *See*, for example, *Percutaneous Penetration Enhancers*, Maibach H. I. and Smith H. E. (eds.), CRC Press, Inc., Boca Raton, Fla. (1995), which surveys the use and testing of various skin penetration enhancers, and Buyuktimkin *et al.*, *Chemical Means of Transdermal Drug Permeation Enhancement in Transdermal and Topical Drug Delivery Systems*, Gosh T. K., Pfister W. R., Yum S. I. (Eds.), Interpharm Press Inc., Buffalo Grove, Ill. (1997), each of which is incorporated herein by reference in its entirety. Representative examples of penetration enhancing agents include triglycerides (*e.g.*, soybean oil), aloe compositions (*e.g.*, aloe-vera gel), ethyl alcohol, isopropyl alcohol, octolyphenylpolyethylene glycol, oleic acid, polyethylene glycol 400, propylene glycol, N-decylmethylsulfoxide, fatty acid esters (*e.g.*, isopropyl myristate, methyl laurate, glycerol monooleate, and propylene glycol monooleate), and N-methylpyrrolidone.

[00143] Representative examples of yet other excipients that may be included in topical as well as in other types of formulations (to the extent they are compatible), include preservatives, antioxidants, moisturizers, emollients, buffering agents, solubilizing agents, skin protectants, and surfactants. Suitable preservatives include alcohols, quaternary amines, organic acids, parabens, and phenols. Suitable antioxidants include ascorbic acid and its esters, sodium bisulfite, butylated hydroxytoluene, butylated hydroxyanisole, tocopherols, and chelating agents like EDTA and citric acid. Suitable moisturizers include glycerin, sorbitol, polyethylene glycols, urea, and propylene glycol. Suitable buffering agents include citric, hydrochloric, and lactic acid buffers. Suitable solubilizing agents include quaternary ammonium chlorides, cyclodextrins, benzyl benzoate, lecithin, and polysorbates. Suitable skin protectants include vitamin E oil, allatoin, dimethicone, glycerin, petrolatum, and zinc oxide.

[00144] Transdermal formulations typically employ transdermal delivery devices and transdermal delivery patches wherein the compound is formulated in lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Transdermal delivery of the compounds may be accomplished by means of an iontophoretic patch. Transdermal patches may provide controlled delivery of the compounds wherein the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Absorption enhancers may be used to increase absorption, examples of which include absorbable pharmaceutically acceptable solvents that assist passage through the skin.

[00145] Ophthalmic formulations include eye drops.

[00146] Formulations for rectal administration include enemas, rectal gels, rectal foams, rectal aerosols, and retention enemas, which may contain conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. Compositions for rectal or vaginal administration may also be formulated as suppositories which can be prepared by mixing the compound with suitable non-irritating carriers and excipients such as cocoa butter, mixtures of fatty acid glycerides, polyethylene glycol, suppository waxes, and combinations thereof, all of which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the compound.

Dosage Amounts

[00147] As used herein, the term, "therapeutically effective amount" refers to an amount of a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof; or a composition including a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, effective in producing the desired therapeutic response in a particular patient in need thereof. Therefore, the term "therapeutically effective amount" includes the amount of a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, that when administered, induces a positive modification in the disease or disorder to be treated, or is sufficient to prevent development or progression of the disease or disorder, or alleviate to some extent, one or more of the symptoms of the disease or disorder being treated in a subject, or which simply kills or inhibits the growth of diseased (*e.g.*, cancer, autophagy-dependent disease (*e.g.*, neurodegenerative disorder)) cells, or reduces the amount of DNMT1 in diseased cells.

[00148] The total daily dosage of the compounds and usage thereof may be decided in accordance with standard medical practice, *e.g.*, by the attending physician using sound medical judgment. The specific therapeutically effective dose for any particular subject may depend upon a variety of factors including the disease or disorder being treated and the severity

thereof (*e.g.*, its present status); the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the compound; and like factors well known in the medical arts (*see*, for example, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th Edition, A. Gilman, J. Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001), which is incorporated herein by reference in its entirety.

Methods of Use

[00149] In some aspects, the present disclosure is directed to methods of treating diseases or disorders by reducing the level or activity of DNMT1. The methods entail administration of a therapeutically effective amount of a compound formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof, to a subject in need thereof.

[00150] The diseases or disorders are characterized or mediated by aberrant DNMT1 activity (*e.g.*, elevated levels of DNMT1 or otherwise functionally abnormal DNMT1, e.g., mutant DNMT1 activity, relative to a non-pathological state). A "disease" is generally regarded as a state of health of a subject wherein the subject cannot maintain homeostasis, and wherein if the disease is not ameliorated then the subject's health continues to deteriorate. In contrast, a "disorder" in a subject is a state of health in which the subject is able to maintain homeostasis, but in which the subject's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal's state of health.

[00151] The term "subject" (or "patient") as used herein includes all members of the animal kingdom prone to or suffering from the indicated disease or disorder. In some embodiments, the subject is a mammal, *e.g.*, a human or a non-human mammal. The methods are also applicable to companion animals such as dogs and cats. A subject "in need of" treatment according to the present disclosure may be "suffering from or suspected of suffering from" a specific disease or disorder may have been positively diagnosed or otherwise presents with a sufficient number of risk factors or a sufficient number or combination of signs or symptoms such that a medical professional could diagnose or suspect that the subject was suffering from the disease or disorder. Thus, subjects suffering from, and suspected of suffering from, a specific disease or disorder are not necessarily two distinct groups.

[00152] In some embodiments, compounds of formula (I) may be useful in the treatment of cell proliferative diseases and disorders. As used herein, the term "cell proliferative disease or

disorder" refers to the conditions characterized by deregulated or abnormal cell growth, or both, including noncancerous conditions such as neoplasms, precancerous conditions, benign tumors, and cancer.

[00153] In some embodiments, methods of the present disclosure entail treatment of subjects having cell proliferative diseases or disorders of the hematological system, liver, brain, colon, prostate, breast, and head and neck.

[00154] As used herein, "cell proliferative diseases or disorders of the hematological system" include lymphoma, leukemia, myeloid neoplasms, mast cell neoplasms, myelodysplasia, benign monoclonal gammopathy, lymphomatoid papulosis, polycythemia vera, chronic myelocytic leukemia, agnogenic myeloid metaplasia, and essential thrombocythemia. Representative examples of hematologic cancers may therefore include leukemia, multiple myeloma, and lymphoma (including T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL). Examples of NHL include diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), cutaneous T-cell lymphoma (CTCL) (including mycosis fungoides and Sezary syndrome), peripheral T-cell lymphoma (PTCL) (including anaplastic large-cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma, hepatosplenic T-cell lymphoma, epithelial T-cell lymphoma, and gamma-delta T-cell lymphoma), germinal center B-cell-like diffuse large B-cell lymphoma, activated B-cell-like diffuse large B-cell lymphoma, Burkitt's lymphoma/leukemia, mantle cell lymphoma, mediastinal (thymic) large B-cell lymphoma, follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, refractory NHL, relapsed NHL, childhood lymphomas, and small lymphocytic lymphoma. Examples of leukemia include childhood leukemia, hairy-cell leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloid leukemia (*e.g.*, acute monocytic leukemia), chronic lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, mast cell leukemia, myeloid neoplasms and mast cell neoplasms.

[00155] As used herein, "cell proliferative diseases or disorders of the liver" include all forms of cell proliferative disorders affecting the liver. Cell proliferative disorders of the liver may include liver cancer (*e.g.*, hepatocellular carcinoma, intrahepatic cholangiocarcinoma and hepatoblastoma), a precancer or precancerous condition of the liver, benign growths or lesions of the liver, and malignant growths or lesions of the liver, and metastatic lesions in tissue and organs in the body other than the liver. Cell proliferative disorders of the liver may include hyperplasia, metaplasia, and dysplasia of the liver.

[00156] As used herein, "cell proliferative diseases or disorders of the brain" include all forms of cell proliferative disorders affecting the brain. Cell proliferative disorders of the brain may include brain cancer (*e.g.*, gliomas, glioblastomas, meningiomas, pituitary adenomas, vestibular schwannomas, and primitive neuroectodermal tumors (medulloblastomas)), a precancer or precancerous condition of the brain, benign growths or lesions of the brain, and malignant growths or lesions of the brain, and metastatic lesions in tissue and organs in the body other than the brain. Cell proliferative disorders of the brain may include hyperplasia, metaplasia, and dysplasia of the brain.

[00157] As used herein, "cell proliferative diseases or disorders of the colon" include all forms of cell proliferative disorders affecting colon cells, including colon cancer, a precancer or precancerous conditions of the colon, adenomatous polyps of the colon and metachronous lesions of the colon. Colon cancer includes sporadic and hereditary colon cancer, malignant colon neoplasms, carcinoma *in situ*, typical carcinoid tumors, and atypical carcinoid tumors, adenocarcinoma, squamous cell carcinoma, and squamous cell carcinoma. Colon cancer can be associated with a hereditary syndrome such as hereditary nonpolyposis colorectal cancer, familiar adenomatous polyposis, MYH associated polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, Turcot's syndrome and juvenile polyposis. Cell proliferative disorders of the colon may also be characterized by hyperplasia, metaplasia, or dysplasia of the colon.

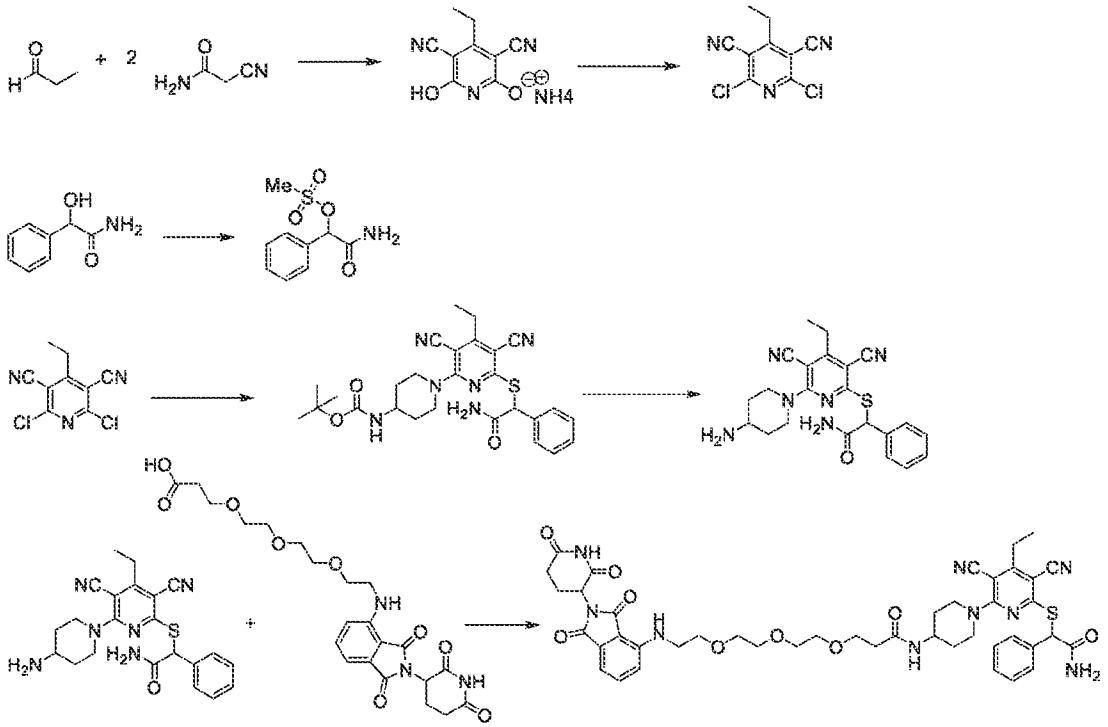
[00158] As used herein, "cell proliferative diseases or disorders of the prostate" include all forms of cell proliferative disorders affecting the prostate. Cell proliferative disorders of the prostate may include prostate cancer, a precancer or precancerous condition of the prostate, benign growths or lesions of the prostate, and malignant growths or lesions of the prostate, and metastatic lesions in tissue and organs in the body other than the prostate. Cell proliferative disorders of the prostate may include hyperplasia, metaplasia, and dysplasia of the prostate.

[00159] As used herein, "cell proliferative diseases or disorders of the breast" include all forms of cell proliferative disorders affecting breast cells. Cell proliferative disorders of the breast may include breast cancer, a precancer or precancerous condition of the breast, benign growths or lesions of the breast, and metastatic lesions in tissue and organs in the body other than the breast. Cell proliferative disorders of the breast may include hyperplasia, metaplasia, and dysplasia of the breast.

[00160] These and other aspects of the present disclosure will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the disclosure but are not intended to limit its scope, as defined by the claims.

EXAMPLES

[00161] Example 1: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanamide (1)



[00162] *Ammonium 3,5-dicyano-4-ethyl-6-hydroxypyridin-2-olate*

[00163] To a solution of 2-cyanoacetamide (28.6 g, 0.34 mol) in water (190 mL) were added ammonium hydroxide (25% aqueous solution, 10 mL) and propionaldehyde (10 g, 0.17 mol). The mixture was stirred at room temperature (rt) for 16 hours, then filtered. The filter cake was washed with cold methanol and dried under reduced pressure to give the title compound (12 g, 34.3%).

[00164] *2,6-Dichloro-4-ethylpyridine-3,5-dicarbonitrile*

[00165] A thick-walled 75 mL reaction tube with magnetic stir bar was charged with $POCl_3$ (10 mL). Ammonium 3,5-dicyano-4-ethyl-6-hydroxypyridin-2-olate (1.26 g, 5.82 mmol) was cautiously added while stirring. The tube was capped and heated at 150°C for 30 hours. The

reaction mixture was cooled to rt, and $POCl_3$ was evaporated under a stream of nitrogen gas. The residue was poured into 150 mL of ice water. The resulting suspension was filtered, and the filter cake was washed with water and dried under reduced pressure to give the title compound as a grey solid (1.03 g, 78.2%). LCMS m/z = 206.31, 208.32, 226.38.

2-Amino-2-oxo-1-phenylethyl methanesulfonate

[00166] To a solution of 2-hydroxy-2-phenylacetamide (0.90 g, 5.95 mmol) in acetonitrile (18 mL) was added triethylamine (1.20 g, 1.65 mL, 2 eq) and methanesulfonyl chloride (0.84 g, 0.52 mL, 1.23 eq). The reaction mixture was stirred at 40°C for 5.5 hours. The solvent was removed by rotary evaporation and the residue was dissolved in DCM (100 mL). The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (1.1 g, 80 %). LCMS m/z = 230.22.

[00167] *tert-Butyl (1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate*

[00168] A suspension of 2,6-dichloro-4-ethylpyridine-3,5-dicarbonitrile (300 mg, 1.33 mmol) in EtOH (2 mL) was cooled to -20°C. A solution of *tert*-butyl piperidin-4-ylcarbonate (292 mg, 1.1 eq) in EtOH (2.5 mL) was added and the mixture was stirred at -20°C for 30 minutes. Potassium thioacetate (227 mg, 1.5 eq), triethylamine (0.46 mL), and ethanol (5 mL) were then added and the mixture was stirred at rt for 17 hours. 2-amino-2-oxo-1-phenylethyl methanesulfonate (608 mg, 2 eq) was added and the mixture was stirred at 40°C for 3 hours, then cooled to rt. The mixture was filtered, and the filter cake was washed with EtOH, water, and ether, then dried under reduced pressure to give the title compound (0.283 g, 41.0%). LCMS m/z = 521.55 $[M+H]^+$.

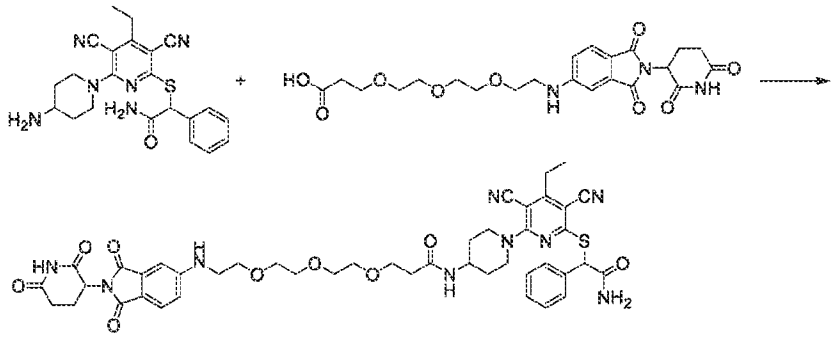
[00169] *2-((6-(4-Aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide*

[00170] Dioxane (0.3 mL) and 4M HCl solution in dioxane (0.3 mL) were added to *tert*-butyl 4-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperazine-1-carboxylate (51.96 mg, 0.1 mmol). The mixture was stirred for 6 hours at rt and the solvent was removed under reduced pressure to give the title compound (45.1 mg, 100%). LCMS m/z = 422.48 $[M+H]^+$.

[00171] *N-(1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propenamide*

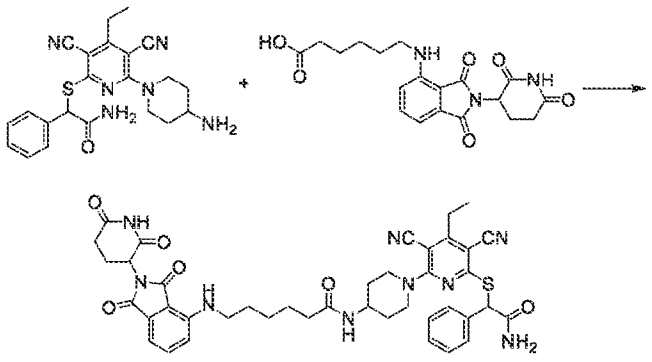
[00172] 2-((6-(4-Aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide (3.85 mg, 0.00915 mmol), 3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoic acid (4.37 mg, 1.0 eq), and triethylamine (4.62 mg, 5.0 eq) were dissolved in DMF (0.2 mL). HATU (5.22 mg, 1.5 eq) was added and the solution was stirred at rt for 15 minutes. The reaction mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 5% MeOH in DCM, to give the title compound (3.18 mg, 39.5%). LCMS m/z = 880.78 $[M+H]^+$.

[00173] Example 2: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethoxy)ethoxy)ethoxy)propanamide (2)



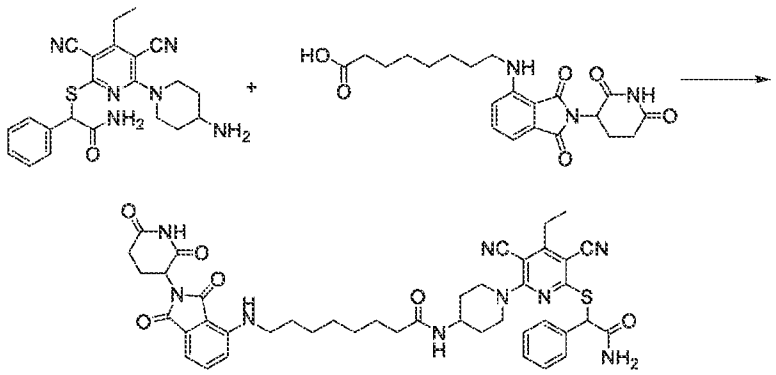
[00174] Compound 2 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethoxy)ethoxy)ethoxy)propanoic acid using a procedure similar to that used in Example 1. LCMS m/z = 880.82 $[M+H]^+$.

[00175] Example 3: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanamide (3)



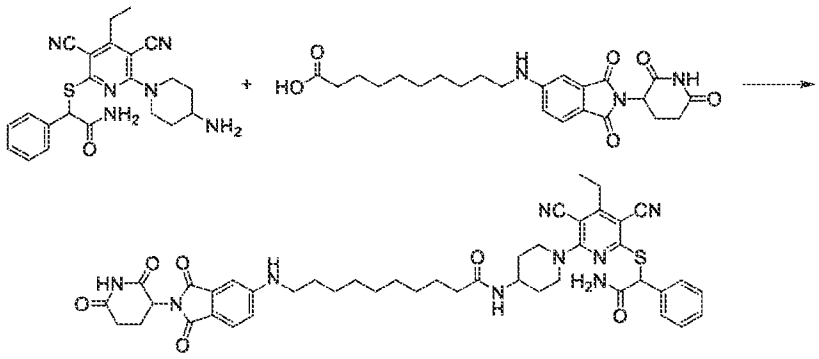
[00176] Compound 3 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoic acid using a procedure similar to that used in Example 1. LCMS m/z = 790.72 $[M+H]^+$.

[00177] Example 4: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanamide (4)



[00178] Compound 4 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanoic acid using a procedure similar to that used in Example 1. LCMS m/z = 818.77 $[M+H]^+$.

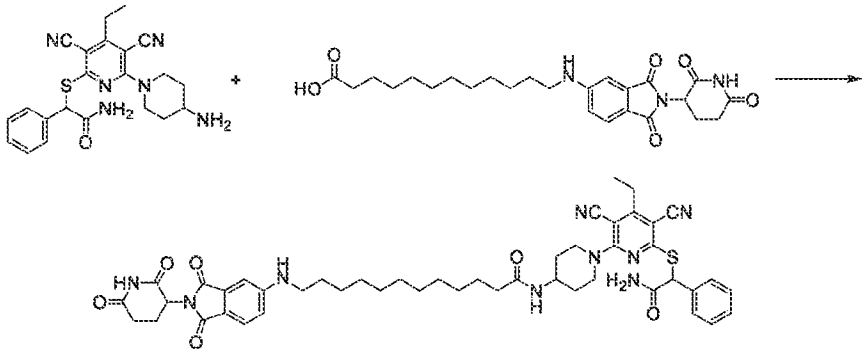
[00179] Example 5: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)decanamide (5)



[00180] Compound 5 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 10-((2-(2,6-dioxopiperidin-3-yl)-1,3-

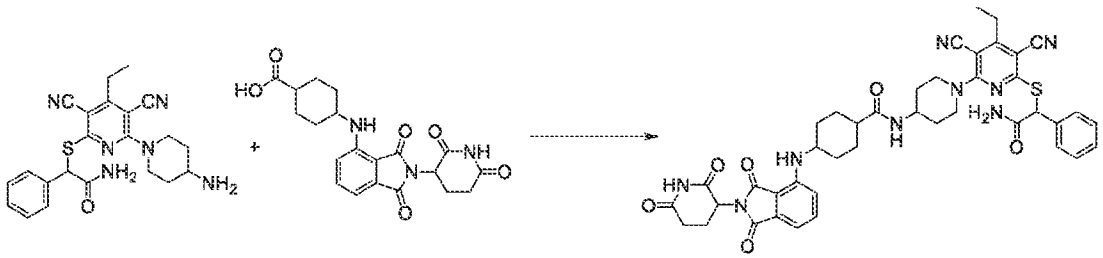
dioxoisoindolin-5-yl)amino)decanoic acid using a procedure similar to that used in Example 1. LCMS m/z = 846.77 $[M+H]^+$.

[00181] Example 6: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-12-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)dodecanamide (6)



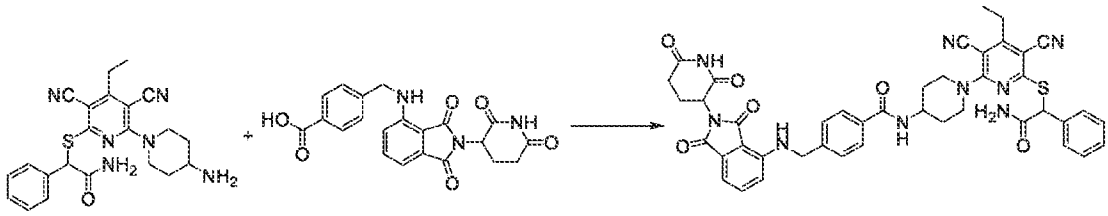
[00182] Compound 6 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 12-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)dodecanoic acid using a procedure similar to that used in Example 1. LCMS m/z = 874.85 $[M+H]^+$.

[00183] Example 7: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)cyclohexane-1-carboxamide (7)



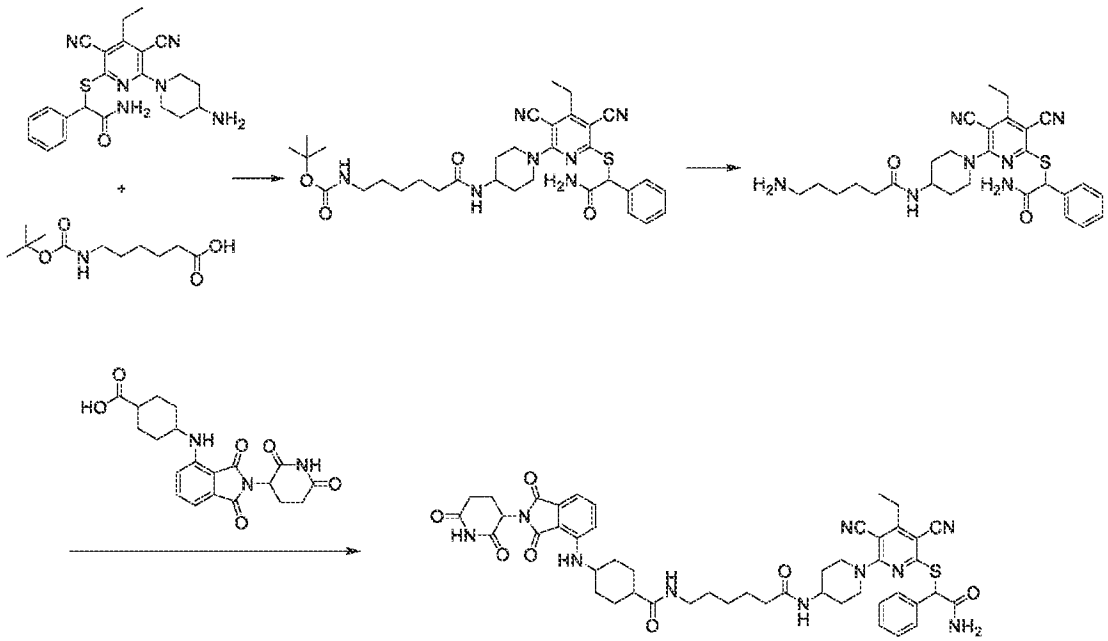
[00184] Compound 7 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)cyclohexane-1-carboxylic acid using a procedure similar to that used in Example 1. LCMS m/z = 802.77 $[M+H]^+$.

[00185] Example 8: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzamide (8)



[00186] Compound 8 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzoic acid using a procedure similar to that used in Example 1. LCMS m/z = 810.71 $[M+H]^+$.

[00187] Example 9: Synthesis of N-(6-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)-6-oxohexyl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)cyclohexane-1-carboxamide (9)



[00188] *tert-Butyl (6-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)-6-oxohexyl)carbamate*

[00189] 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide (20.7 mg, 0.0492 mmol), 6-((*tert*-butoxycarbonyl)amino)hexanoic acid (11.4 mg, 0.0492 mmol), and triethylamine (34.4 µL, 0.245 mmol) were dissolved in DMF (0.25

mL). HATU (28.1 mg, 0.0738 mmol) was added and the mixture was stirred at rt for 15 minutes. The solvent was removed under a stream of nitrogen and the residue was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with 0 to 4% MeOH/DCM, to give the title compound (26.7 mg, 85.6%). LCMS m/z = 634.67 $[M+H]^+$.

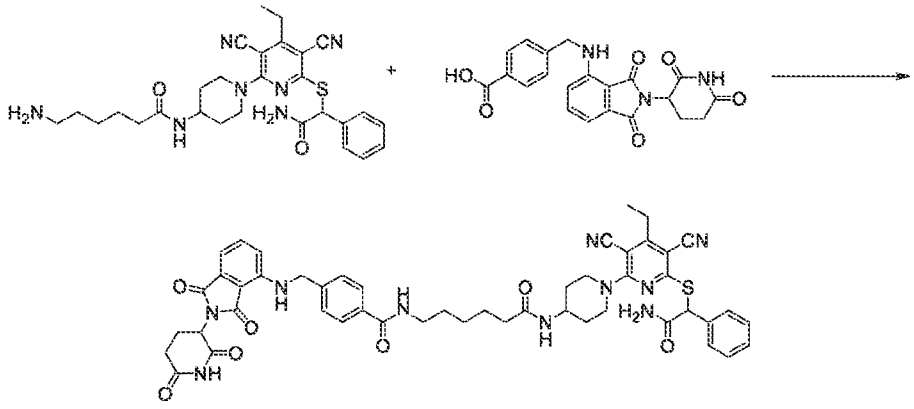
[00190] *6-Amino-N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)hexanamide*

[00191] THF (0.2 mL) and 4 M HCl solution in dioxane (0.4 mL, 1.6 mmol) were added to *tert*-butyl (6-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)-6-oxohexyl)carbamate (11.9 mg, 0.0188 mmol). The mixture was stirred at rt for 13 hours. The solvent was removed under reduced pressure to give the title compound (9.84 mg, 98%). LCMS m/z = 535.53 $[M+H]^+$.

[00192] *N-(6-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)-6-oxohexyl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)cyclohexane-1-carboxamide*

[00193] The title compound was prepared from 6-amino-*N*-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)hexanamide and 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)cyclohexane-1-carboxylic acid using a procedure similar to that used in Example 1. LCMS m/z = 915.74 $[M+H]^+$.

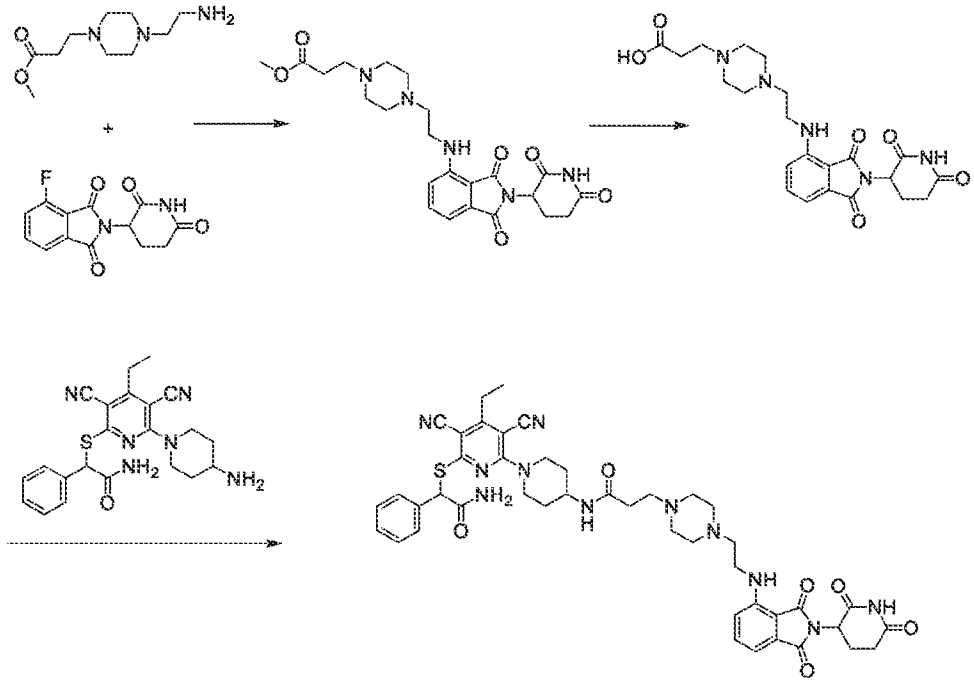
[00194] Example 10: Synthesis of N-(6-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)-6-oxohexyl)-4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzamide (10)



[00195] Compound 10 was prepared from 6-amino-*N*-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)hexanamide and 4-(((2-(2,6-

dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzoic acid using a procedure similar to that used in Example 1. LCMS m/z = 923.79 $[M+H]^+$.

[00196] Example 11: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)piperazin-1-yl)propanamide (11)



[00197] *Methyl 3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)piperazin-1-yl)propanoate*

[00198] Methyl 3-(4-(2-aminoethyl)piperazin-1-yl)propanoate (100 mg, 0.464 mmol), 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (128.3 mg, 0.464 mmol), diisopropylethylamine (405 µL, 2.32 mmol), and *N*-methylpyrrolidine (2.3 mL) were added to a microwave reaction tube. The tube was capped and microwaved at 100°C for 1 hour. The mixture was cooled to rt and purified by column chromatography (Teledyne ISCO, 40 g silica column) eluting with a gradient of 0 to 5% MeOH/DCM, to give the title compound (44.16 mg, 20.1%). LCMS m/z = 472.45 $[M+H]^+$.

[00199] *3-(4-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)piperazin-1-yl)propanoic acid*

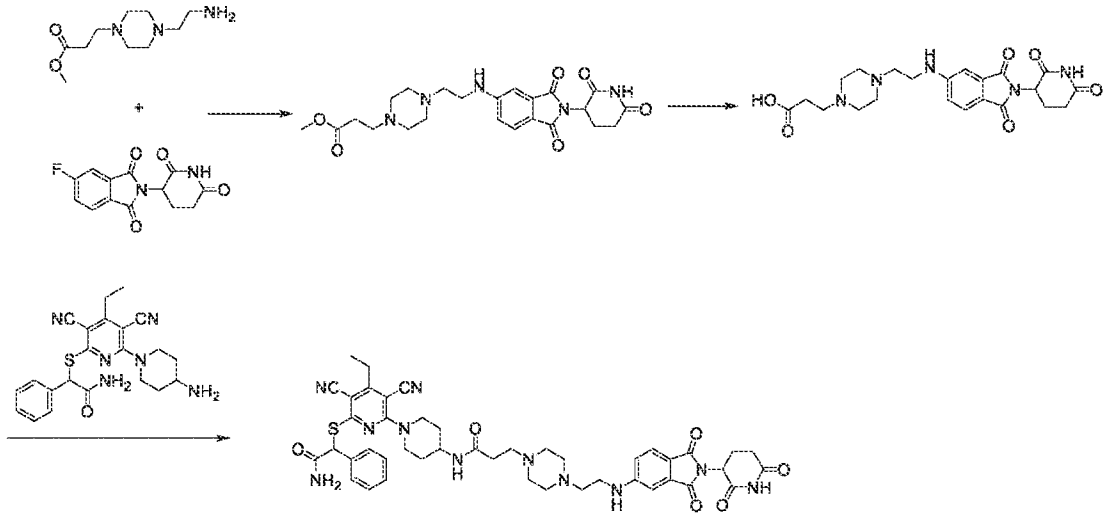
[00200] A mixture of methyl 3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)piperazin-1-yl)propanoate (44.16 mg, 0.0937 mmol), 4 M HCl solution in

dioxane (1.6 mL), and water (0.5 mL) was heated at 100°C for 30 minutes. The solvent was removed by lyophilization to give the title compound. LCMS m/z = 458.69 $[M+H]^+$.

[00201] *N-(1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)piperazin-1-yl)propenamide*

[00202] The title compound was prepared from 6-amino-*N*-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)hexanamide and 3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)piperazin-1-yl)propanoic acid using a procedure similar to that used in Example 1. LCMS m/z = 860.64 $[M+H]^+$.

[00203] Example 12: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethyl)piperazin-1-yl)propanamide (12)



[00204] *Methyl 3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethyl)piperazin-1-yl)propanoate*

[00205] Methyl 3-(4-(2-aminoethyl)piperazin-1-yl)propanoate (91.3 mg, 0.424 mmol), 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (117.1 mg, 0.424 mmol), diisopropylethylamine (370 µL, 2.12 mmol), and *N*-methylpyrrolidine (2.0 mL) were added to a microwave reaction tube. The tube was capped and microwaved at 100°C for 1 hour. The mixture was cooled to rt and purified by column chromatography (Teledyne ISCO, 40 g silica column) eluting with a gradient of 0 to 15% MeOH/DCM, to give the title compound (25.0 mg, 12.5%). LCMS m/z = 473.33 $[M+H]^+$.

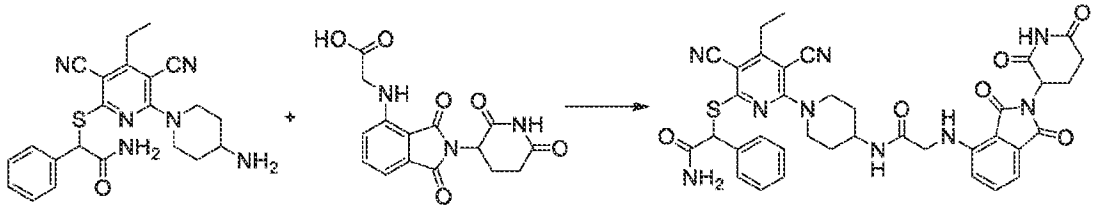
[00206] *3-(4-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethyl)piperazin-1-yl)propanoic acid*

[00207] A mixture of methyl 3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethyl)piperazin-1-yl)propanoate(25.0 mg, 0.0531 mmol), 4 M HCl solution in dioxane (1.0 mL), and water (0.25 mL) was heated at 100°C for 30 minutes. The solvent was removed by lyophilization to give the title compound. LCMS m/z = 458.43 $[M+H]^+$.

[00208] *N-(1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethyl)piperazin-1-yl)propenamide*

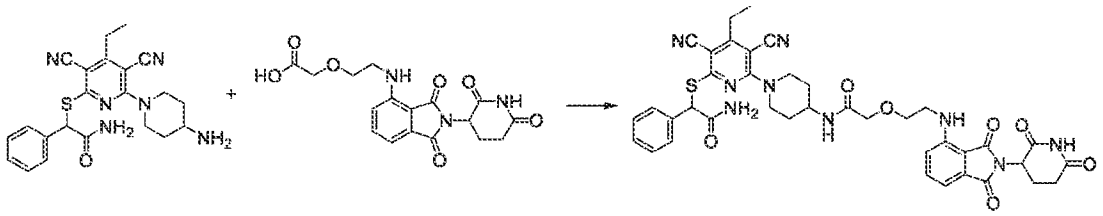
[00209] The title compound was prepared from 6-amino-*N*-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)hexanamide and 3-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethyl)piperazin-1-yl)propanoic acid using a procedure similar to that used in Example 1. LCMS m/z = 860.60 $[M+H]^+$.

[00210] Example 13: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamide (13)



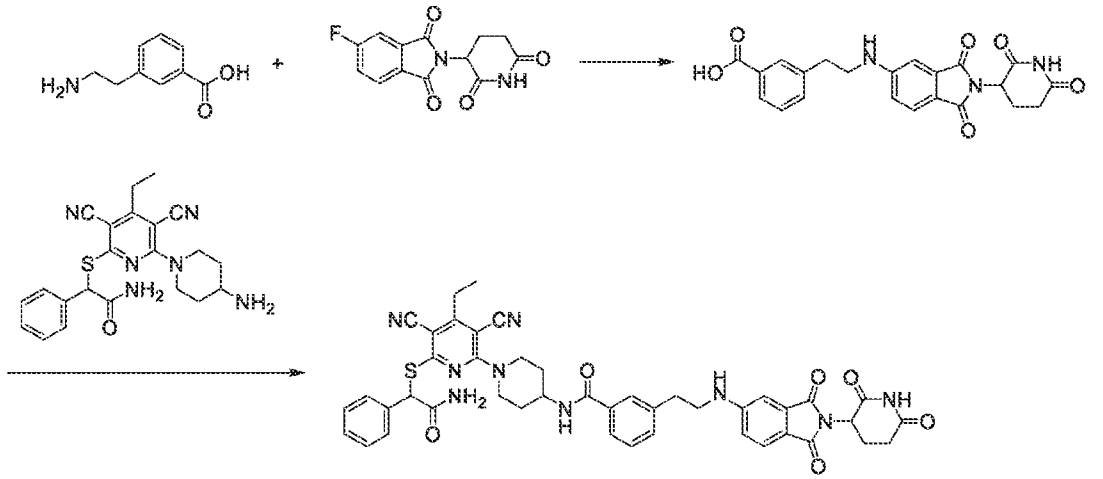
[00211] Compound 13 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycine using a procedure similar to that used in Example 1. LCMS m/z = 734.49 $[M+H]^+$.

[00212] Example 14: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)acetamide (14)



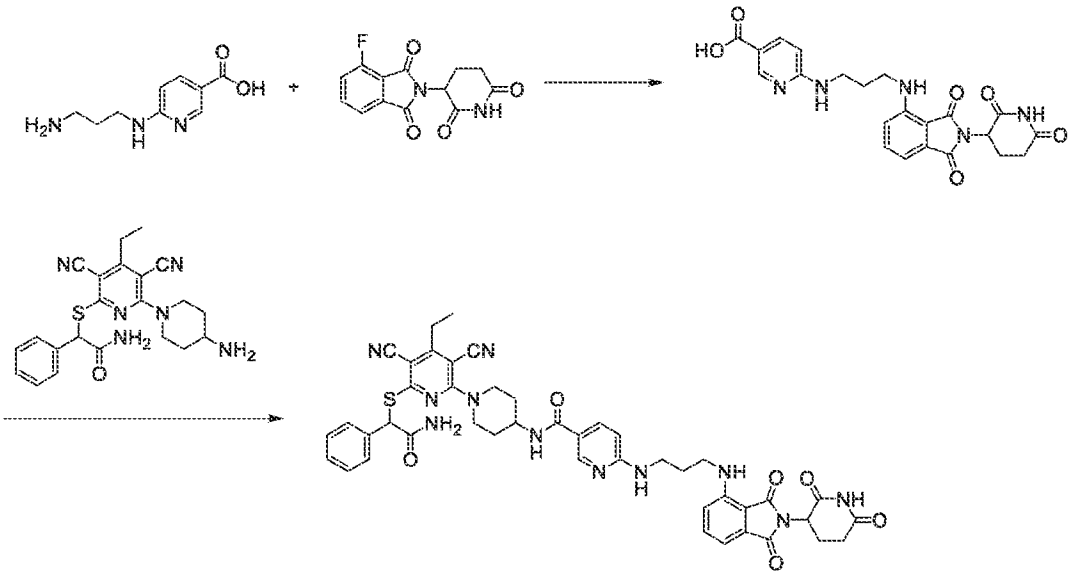
[00213] Compound 14 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)acetic acid using a procedure similar to that used in Example 1. LCMS m/z = 778.57 $[M+H]^+$.

[00214] Example 15: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethyl)benzamide (15)



[00215] Compound 15 was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethyl)benzoic acid using a procedure similar to that used in Example 1. LCMS m/z = 824.50 $[M+H]^+$.

[00216] Example 16: Synthesis of N-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-6-((3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)amino)nicotinamide (16)



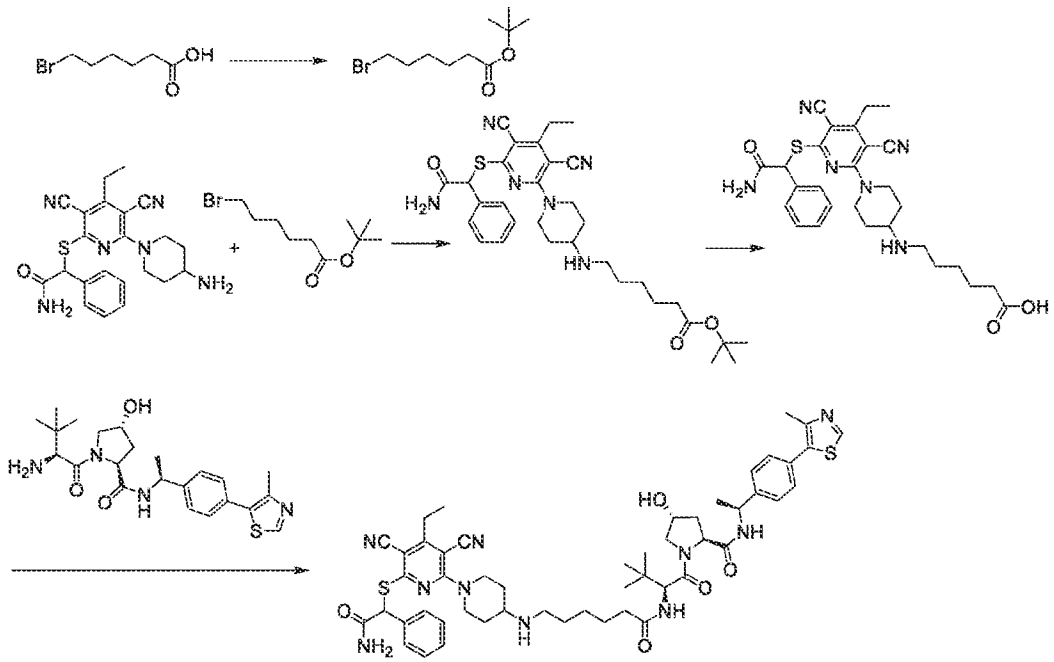
[00217] *6-((3-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)amino)nicotinic acid*

[00218] A mixture of 6-((3-aminopropyl)amino)nicotinic acid (2.8 mg, 0.0143 mmol), 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (4.3 mg, 0.0155 mmol), diisopropylethylamine (10.8 µL, 0.062 mmol), and *N*-methylpyrrolidone (0.1 mL) was stirred at 90°C for 20 hours. The mixture was cooled to rt and purified by column chromatography (Teledyne ISCO, 12 g silica column) eluting with a gradient of 0 to 12% MeOH/DCM, to give the title compound (1.0 mg, 14.3%). LCMS m/z = 452.34 $[M+H]^+$.

[00219] *N-(1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)-6-((3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)amino)nicotinamide*

[00220] The title compound was prepared from 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetamide and 6-((3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)amino)nicotinic acid using a procedure similar to that used in Example 1. LCMS m/z = 854.57 $[M+H]^+$.

[00221] Example 17: Synthesis of (2S,4R)-1-((2S)-2-(6-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (17)



[00222] *tert-Butyl 6-bromohexanoate*

[00223] 6-Bromohexanoic acid (390 mg, 2.0 mmol) and trifluoroacetic acid anhydride (1.11 mL, 8.0 mmol) were dissolved in THF (4 mL). The solution was stirred at rt for 1.5 hours, then *tert*-butanol (2 mL, 34.5 mmol) was added. The solution was stirred at rt for 16 hours, then quenched by slowly adding saturated aqueous $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc (3 x 20 mL, and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was filtered through a silica plug, washing with 50% EtOAc/hexanes (20 mL). The filtrate was concentrated *in vacuo* to give the title compound as a colorless oil (357.05 mg, 71.1%).

[00224] *tert-Butyl 6-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexanoate*

[00225] 6-Amino-*N*-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)hexanamide (5.0 mg, 0.0119 mmol) and DIPEA (10.4 µL, 0.0594 mmol) were dissolved in DMF (60 µL) and the solution was stirred at rt for 4 hours. A solution of *tert*-butyl 6-bromohexanoate (2.2 mg, 0.00893 mmol) in DMF (50 µL) was added and the mixture was stirred at rt for 16 hours. An additional portion of *tert*-butyl 6-

bromohexanoate (0.88 mg, 0.0035 mmol) was added and the mixture was stirred for a further 6 hours. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 6% MeOH/DCM, to give the title compound (2.0 mg, 28.6%). LCMS m/z = 591.54 $[M+H]^+$.

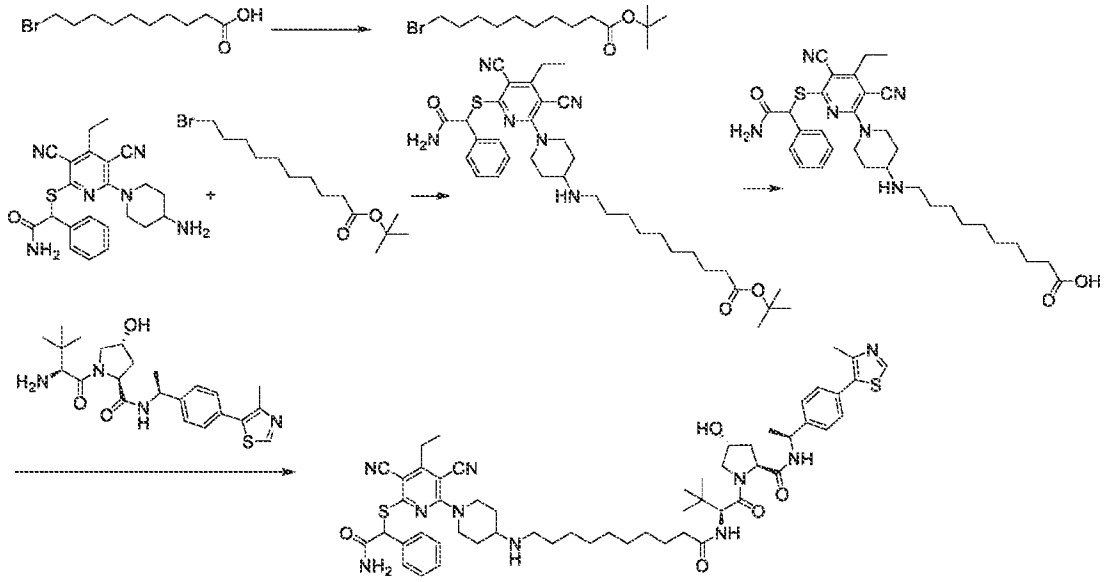
[00226] *6-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexanoic acid*

[00227] *tert*-Butyl 6-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexanoate (2.0 mg, 0.00339 mmol) and TFA (5 µL, 0.0653 mmol) were dissolved in DCM (20 µL). The mixture was stirred at rt for 2 h, then concentrated *in vacuo* to give the title compound. LCMS m/z = 535.45 $[M+H]^+$.

[00228] *(2S,4R)-1-((2S)-2-(6-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide*

[00229] 6-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexanoic acid (2.0 mg, 0.00374 mmol) and (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (1.8 mg, 0.00374 mmol), and triethylamine (2.62 µL, 0.0187 mmol) were dissolved in DMF (100 µL). HATU (2.1 mg, 0.00561 mmol) was added to the solution and the mixture was stirred for 15 minutes at rt, then purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0% to 20% MeOH in DCM, to give the title compound (0.62 mg, 17.2%). LCMS m/z = 961.80 $[M+H]^+$.

[00230] Example 18: Synthesis of (2S,4R)-1-((2S)-2-(10-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (18)



[00231] *tert-Butyl 10-bromodecanoate*

[00232] 10-Bromodecanoic acid (251.2 mg, 1 mmol) and trifluoroacetic anhydride (556 µL, 4.00 mmol) were dissolved in THF (2 mL) and the solution was stirred at rt for 2 hours. *tert*-Butanol (1 mL) was added and the mixture was stirred for 16 hours. The reaction was quenched slowly by adding saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to the title compound (0.28 g, 92.6%).

[00233] *tert-Butyl 10-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)decanoate*

[00234] 6-Amino-*N*-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)hexanamide (10.0 mg, 0.0238 mmol) and DIPEA (20.8 µL, 0.119 mmol) were dissolved in DMF (50 µL) and the solution was stirred at rt for 2 hours. A solution of *tert*-butyl 10-bromodecanoate (7.3 mg, 0.0238 mmol) in DMF (50 µL) was added and the mixture was stirred at rt for 16 hours. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 5% MeOH/DCM, to give the title compound (4.51 mg, 29.3%). LCMS m/z = 647.62 $[M+H]^+$.

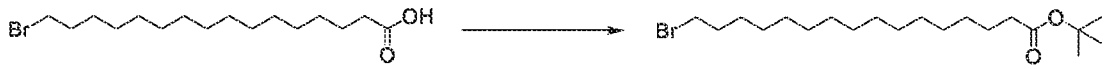
[00235] *10-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)decanoic acid*

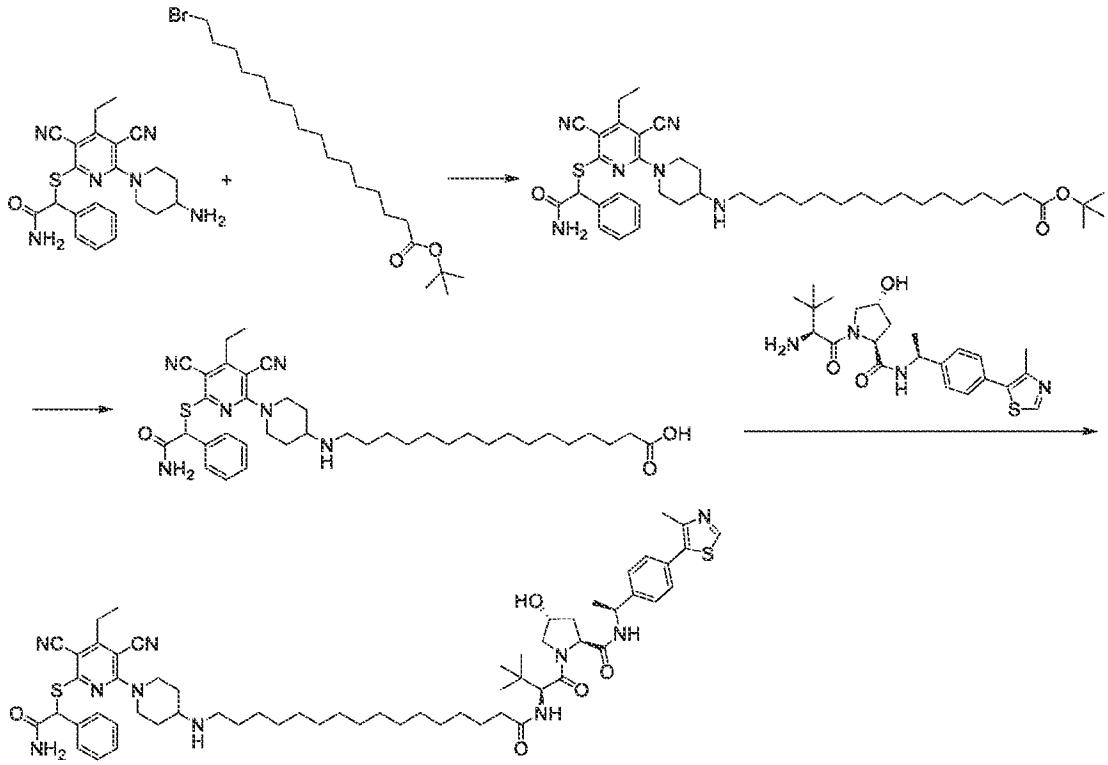
[00236] *tert*-Butyl 10-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)decanoate (4.51 mg, 0.00697 mmol) and TFA (5 µL) were dissolved in DCM (50 µL) and the solution was stirred at rt for 18 hours, then concentrated *in vacuo* to give the title compound. LCMS m/z = 592.52 $[M+H]^+$.

[00237] *(2S,4R)-1-((2S)-2-(10-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide*

[00238] 10-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)decanoic acid (4.1 mg, 0.00697 mmol), (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (3.4 mg, 0.00697 mmol), and TEA (4.9 µL, 0.0349 mmol) were dissolved in DMF (50 µL). HATU (4.0 mg, 0.0105 mmol) was added and the mixture was stirred at rt for 1 hour, then purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 15% MeOH/DCM, to give the title compound (3.73 mg, 52.6%). LCMS m/z = 1017.85 $[M+H]^+$.

[00239] Example 19: Synthesis of (2S,4R)-1-((2S)-2-(16-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexadecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (19)





[00240] *tert-Butyl 16-bromodecanoate*

[00241] 16-Bromohexadecanoic acid (335.3 mg, 1 mmol) and trifluoroacetic anhydride (556 µL, 4.00 mmol) were dissolved in THF (2 mL) and the solution was stirred at rt 2 hours, then *tert*-butanol (1 mL) was added and the mixture was stirred for 16 hours. The reaction was quenched by slowly adding saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (0.39 g, 100%).

[00242] *tert-Butyl 16-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexadecanoate*

[00243] 6-Amino-*N*-(1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)hexanamide (10.0 mg, 0.0238 mmol) and DIPEA (20.8 µL, 0.119 mmol) were dissolved in DMF (50 µL) and the solution was stirred at rt for 2 hours. A solution of *tert*-butyl 10-bromohexadecanoate (9.3 mg, 0.0238 mmol) in DMF (50 µL) was added and the mixture was stirred at rt for 16 hours. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 4% MeOH/DCM, to give the title compound (3.92 mg, 22.5%). LCMS m/z = 731.79 $[M+H]^+$.

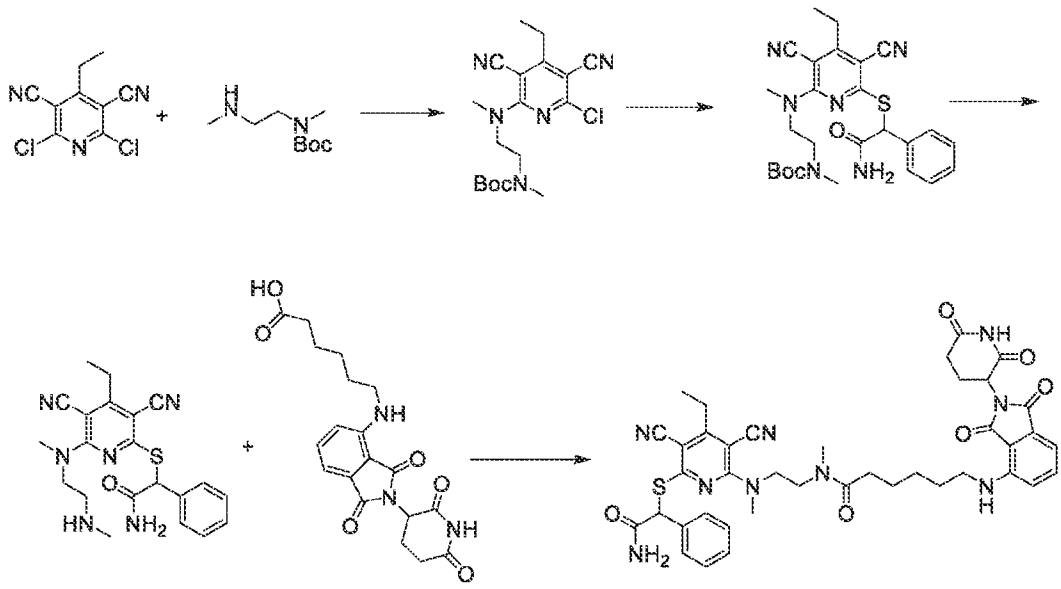
[00244] *16-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexadecanoic acid*

[00245] *tert*-Butyl 16-((1-(6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexadecanoate (3.92 mg, 0.00536 mmol) and TFA (5 µL) were dissolved in DCM (50 µL) and the solution was stirred at rt for 18 hours, then concentrated *in vacuo* to give the title compound. LCMS m/z = 675.67 $[M+H]^+$.

[00246] *(2S,4R)-1-((2S)-2-(16-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexadecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide*

[00247] 16-((1-(6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)amino)hexadecanoic acid (3.6 mg, 0.00536 mmol), (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (2.6 mg, 0.00536 mmol), and TEA (3.8 µL, 0.0268 mmol) were dissolved in DMF (50 µL). HATU (3.1 mg, 0.00804 mmol) was added and the solution was stirred at rt for 1 hour, then purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 15% MeOH/DCM, to give the title compound (3.89 mg, 65.9%). LCMS m/z = 1101.99 $[M+H]^+$.

[00248] Example 20: Synthesis of N-(2-((6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-N-methylhexanamide (20)



[00249] *tert-Butyl (2-((6-chloro-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)(methyl)carbamate*

[00250] 2,6-Dichloro-4-ethylpyridine-3,5-dicarbonitrile (113 mg, 0.500 mmol) was dissolved in DMF (3 mL) and a solution of *tert*-butyl methyl(2-(methylamino)ethyl)carbamate (112 mg, 0.595 mmol) in DMF (2 mL) was added, followed by triethylamine (70.1 µL, 0.500 mmol). The mixture was stirred at rt for 5 minutes, then diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water and brine, then dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Teledyne ISCO, 12 g silica column) eluting with a gradient of 0 to 28% EtOAc/hexanes, to give the title compound (152.43 mg, 80.7 %). LCMS m/z = 378.31 $[M+H]^+$.

[00251] *tert-Butyl (2-((6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)(methyl)carbamate*

[00252] A mixture of *tert*-butyl (2-((6-chloro-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)(methyl)carbamate (69.79 mg, 0.184 mmol), potassium thioacetate (25.2 mg, 0.221 mmol), and DMF (0.9 mL) was stirred at rt for 30 minutes. 2-amino-2-oxo-1-phenylethyl methanesulfonate (50.7 mg, 0.221 mmol) and triethylamine (51.6 µL, 0.368 mmol) were added and the mixture was stirred at rt for 15 hours. Water (2 mL) was added to the reaction mixture and the mixture was filtered and the filtered solids were redissolved in DCM. The solution was purified by column chromatography (Teledyne ISCO, 4g silica column) eluting with DCM, to give the title compound (20.24 mg, 21.6%). LCMS m/z = 509.42 $[M+H]^+$.

[00253] *2-((3,5-Dicyano-4-ethyl-6-(methyl(2-(methylamino)ethyl)amino)pyridin-2-yl)thio)-2-phenylacetamide*

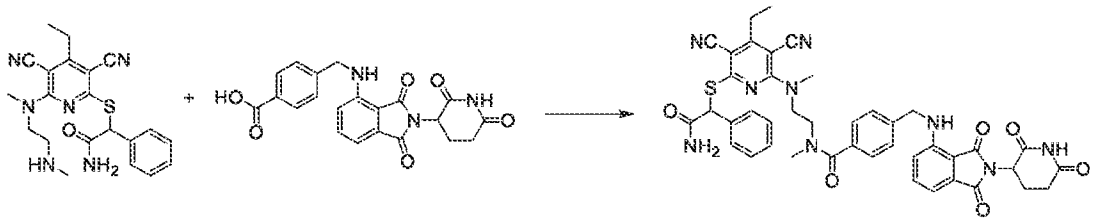
[00254] THF (0.1 mL) and 4 M solution of HCl in dioxane (0.1 mL) were added to *tert*-butyl (2-((6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)(methyl)carbamate (20.24 mg, 0.0398 mmol) and the mixture was stirred at rt for 16 hours, then concentrated *in vacuo* to give the title compound. LCMS m/z = 410.39 $[M+H]^+$.

[00255] *N-(2-((6-((2-Amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-N-methylhexanamide*

[00256] 2-((3,5-Dicyano-4-ethyl-6-(methyl(2-(methylamino)ethyl)amino)pyridin-2-yl)thio)-2-phenylacetamide (5.0 mg, 0.0123 mmol), 6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoic acid (4.7 mg, 0.0123 mmol), and TEA (8.6 µL, 0.0615

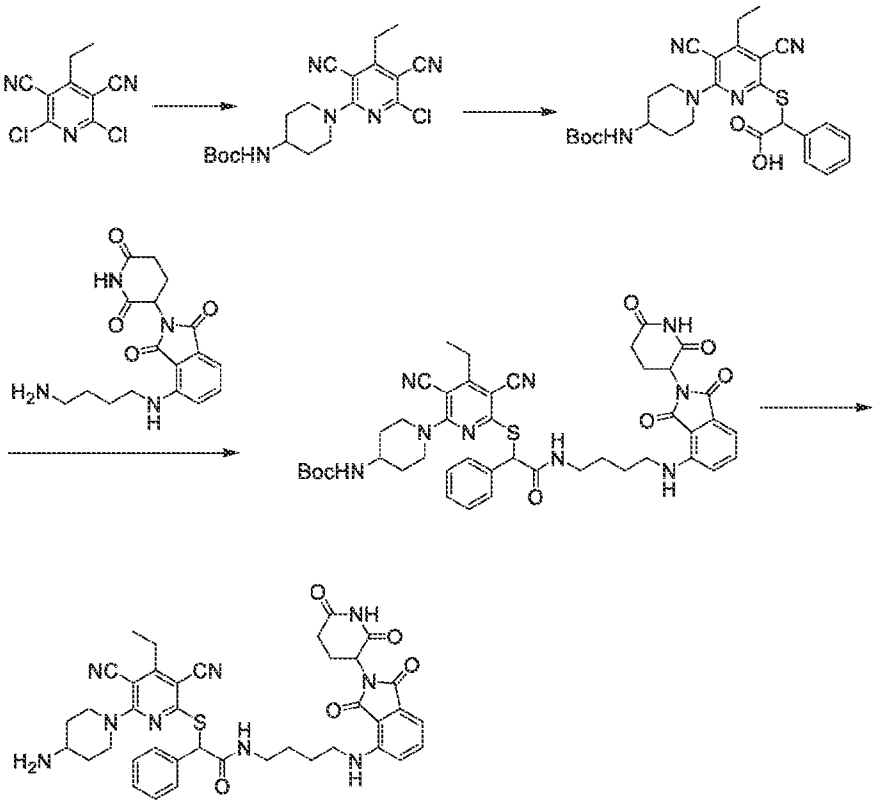
mmol) were dissolved in DMF (50 µL) and DCM (50 µL). HATU (7.0 mg, 0.0185 mmol) was added and the mixture was stirred for 15 minutes at rt, then purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 2.5% MeOH in DCM, to give the title compound (8.27 mg, 86.4%). LCMS m/z = 778.61 $[M+H]^+$.

[00257] Example 21: Synthesis of N-(2-((6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)-4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-N-methylbenzamide (21)



[00258] 2-((3,5-dicyano-4-ethyl-6-(methyl(2-(methylamino)ethyl)amino)pyridin-2-yl)thio)-2-phenylacetamide (5.0 mg, 0.0123 mmol), 4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzoic acid (5.0 mg, 0.0123 mmol), and triethylamine (8.6 µL, 0.0615 mmol) were dissolved in DMF (50 µL) and DCM (50 µL). HATU (7.0 mg, 0.0185 mmol) was added and the mixture was stirred at rt for 15 minutes. The mixture was purified by column chromatography (Teledyne ISCO, 4 g) eluting with a gradient of 50 to 100% EtOAc/hexanes, to give the title compound (4.36 mg, 44.4%). LCMS m/z = 798.56 $[M+H]^+$.

[00259] Example 22: Synthesis of 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-N-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)-2-phenylacetamide (22)



[00260] *2-Bromo-2-phenylacetic acid*

[00261] 2-Hydroxy-2-phenylacetic acid (3.00 g, 19.7 mmol) was carefully added to a mixture of 48% HBr solution (5.6 mL) and concentrated H_2SO_4 (2.2 mL) and the mixture was refluxed at 105°C for 3 hours, then cooled to rt and poured into 25 mL of ice water. This mixture was extracted ether (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound.

[00262] *2-((6-(4-((tert-Butoxycarbonyl)amino)piperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetic acid*

[00263] *tert*-Butyl (1-(6-chloro-3,5-dicyano-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate (39.0 mg, 0.100 mmol) and potassium thioacetate (13.7 mg, 0.120 mmol) were dissolved in DMF (200 µL) and the solution was stirred at rt for 30 minutes, then 2-bromo-2-phenylacetic acid (25.7 mg, 0.120 mmol) and triethylamine (42.1 µL, 0.300 mmol) were added. The mixture was stirred at rt for 16 hours, then purified by column chromatography (Teledyne ISCO, 12 g silica column) eluting with a gradient of 0 to 100% EtOAc/hexanes, to give the title compound (16.4 mg, 31.4%). LCMS m/z = 522.49 $[M+H]^+$.

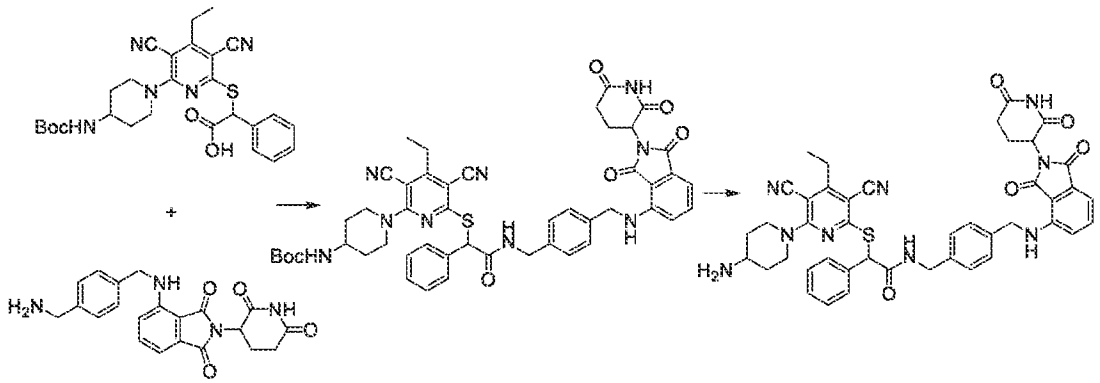
[00264] *tert-Butyl (1-(3,5-dicyano-6-((2-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)amino)-2-oxo-1-phenylethyl)thio)-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate*

[00265] 2-((6-(4-((*tert*-Butoxycarbonyl)amino)piperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetic acid (2.2 mg, 0.00425 mmol) was dissolved in DMF (100 µL) and cooled to 0°C. *N,N'*-dicyclohexylcarbodiimide (0.9 mg, 0.00425 mmol) and hydroxybenzotriazole (0.6 mg, 0.00425 mmol) were added and the mixture was stirred at 0°C for 10 minutes. 4-((4-aminobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (1.5 mg, 0.00425 mmol) and *N*-methylmorpholine (0.47 µL, 0.00425 mmol) were added and the mixture was allowed to warm to rt. After 16 hours, the mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 5% MeOH/DCM, to give the title compound (4.83 mg, 100%). LCMS m/z = 848.71 $[M+H]^+$.

[00266] *2-((6-(4-Aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-N-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)-2-phenylacetamide*

[00267] *tert*-Butyl (1-(3,5-dicyano-6-((2-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)amino)-2-oxo-1-phenylethyl)thio)-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate (4.83 mg, 0.00570 mmol) and 4 M HCl solution in dioxane (0.1 mL) were stirred at rt for 3 hours. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 10% MeOH/DCM, to give the title compound (0.40 mg, 9.4%). LCMS m/z = 748.62 $[M+H]^+$.

[00268] Example 23: Synthesis of 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-N-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzyl)-2-phenylacetamide (23)



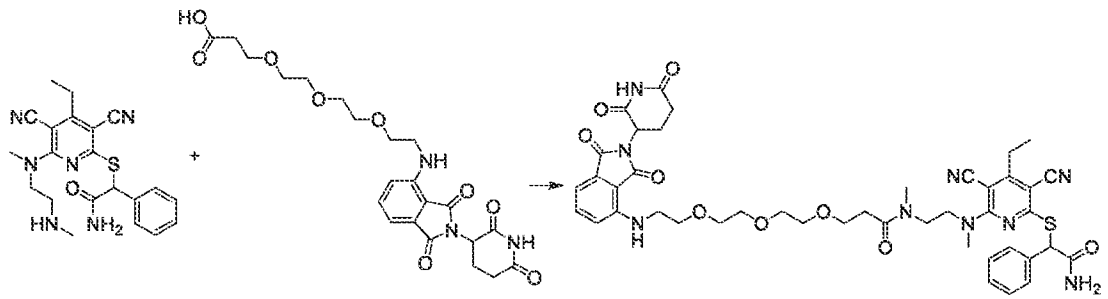
[00269] *tert-Butyl (1-(3,5-dicyano-6-((2-((4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzyl)amino)-2-oxo-1-phenylethyl)thio)-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate*

[00270] 2-((6-(4-((*tert*-Butoxycarbonyl)amino)piperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetic acid (5.22 mg, 0.01 mmol) was dissolved in DMF (50 µL) and cooled to 0°C. *N,N'*-dicyclohexylcarbodiimide (2.1 mg, 0.01 mmol) and hydroxybenzotriazole (1.4 mg, 0.01 mmol) were added and the mixture was stirred at 0°C for 15 minutes. 4-((4-(aminomethyl)benzyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (3.9 mg, 0.01 mmol) and *N*-methylmorpholine (1.1 µL, 0.01 mmol) were added and the mixture was allowed to warm to rt. After 3 hours, the mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with DCM, to give the title compound (2.47 mg, 27.6%). LCMS m/z = 897.66 $[M+H]^+$.

[00271] *2-((6-(4-Aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-N-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzyl)-2-phenylacetamide*

[00272] *tert*-Butyl (1-(3,5-dicyano-6-((2-((4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzyl)amino)-2-oxo-1-phenylethyl)thio)-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate) (2.47 mg, 0.00276 mmol) and 4 M HCl solution in dioxane (0.1 mL) were stirred at rt for 1 hour. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 8% MeOH/DCM, to give the title compound (0.57 mg, 26.0%). LCMS m/z = 796.66 $[M+H]^+$.

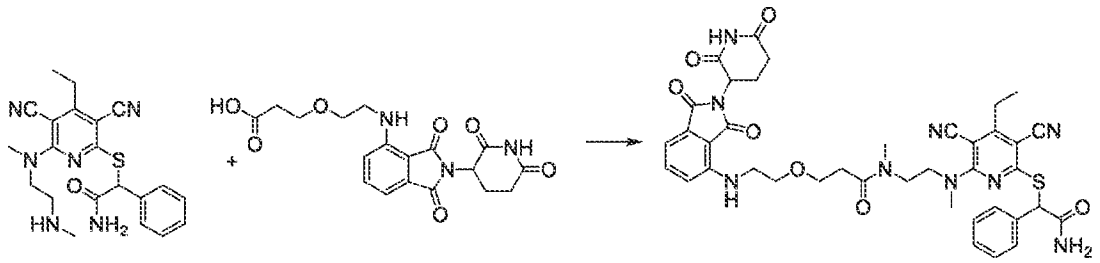
[00273] Example 24: Synthesis of N-(2-((6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)-N-methylpropanamide (24)



[00274] 2-((3,5-Dicyano-4-ethyl-6-(methyl(2-(methylamino)ethyl)amino)pyridin-2-yl)thio)-2-phenylacetamide (2.1 mg, 0.0511 mmol), 3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoic acid (2.4 mg, 0.00511

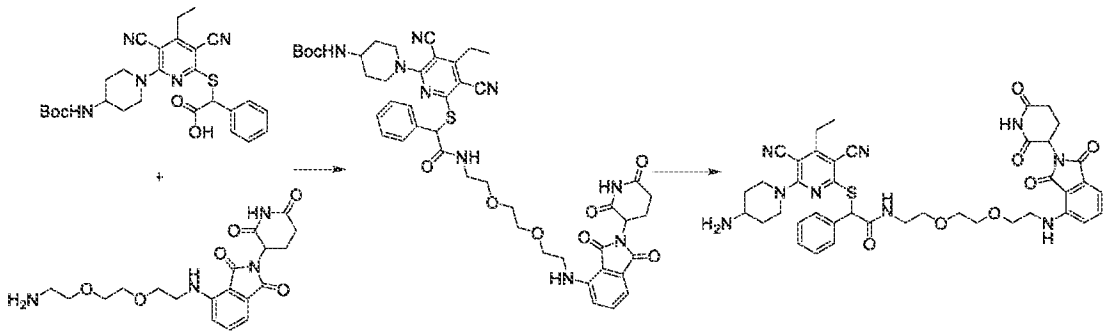
mmol), and triethylamine (3.6 µL, 0.0256 mmol) were dissolved in DMF (50 µL). HATU (2.9 mg, 0.00767 mmol) was added and the mixture was stirred at rt for 15 minutes. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 15% MeOH/DCM, to give the title compound (1.97 mg, 44.5%). LCMS m/z = 868.82 $[M+H]^+$.

[00275] Example 25: Synthesis of N-(2-((6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)-3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)-N-methylpropanamide (25)



[00276] 2-((3,5-Dicyano-4-ethyl-6-(methyl(2-(methylamino)ethyl)amino)pyridin-2-yl)thio)-2-phenylacetamide (2.1 mg, 0.00511 mmol), 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanoic acid (2.0 mg, 0.0511 mmol), and triethylamine (3.6 µL, 0.0256 mmol) were dissolved in DMF (50 µL). HATU (2.9 mg, 0.00767 mmol) was added and the mixture was stirred at rt for 15 minutes. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 3% MeOH/DCM, to give the title compound (0.81 mg, 20.4%). LCMS m/z = 780.73 $[M+H]^+$.

[00277] Example 26: Synthesis of 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-N-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)-2-phenylacetamide (26)



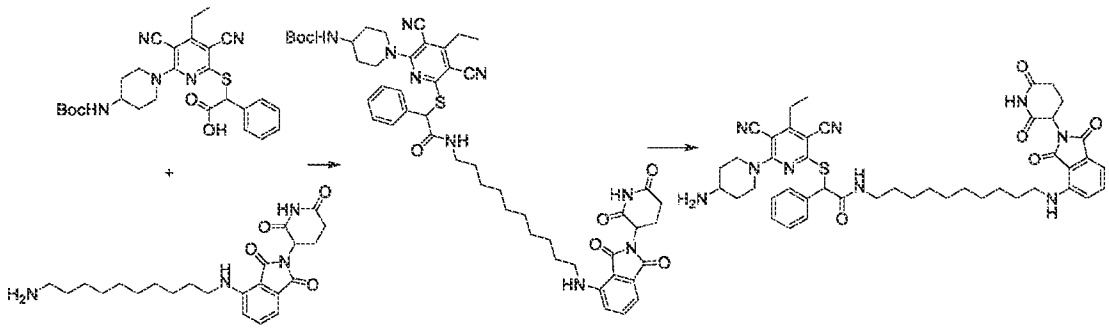
[00278] *tert-Butyl (1-(3,5-dicyano-6-((2-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)-2-oxo-1-phenylethyl)thio)-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate*

[00279] 2-((6-(4-((*tert*-Butoxycarbonyl)amino)piperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetic acid (2.6 mg, 0.00500 mmol), 4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2.0 mg, 0.00500 mmol), and triethylamine (3.5 µL, 0.025 mmol) were dissolved in DMF (50 µL). HATU (2.9 mg, 0.0075 mmol) was added and the mixture was stirred at rt for 15 minutes. The mixture was diluted with EtOAc (5 mL), washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (4.97 mg, 100%). LCMS m/z = 908.75 $[M+H]^+$.

[00280] *2-((6-(4-Aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-N-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)-2-phenylacetamide*

[00281] A mixture of *tert*-Butyl (1-(3,5-dicyano-6-((2-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)-2-oxo-1-phenylethyl)thio)-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate (4.97 mg, 0.00547 mmol) and 4 M HCl solution in dioxane (0.1 mL) was stirred at rt for 19 hours. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 10% MeOH/DCM, to give the title compound (0.77 mg, 17.4%). LCMS m/z = 808.74 $[M+H]^+$.

[00282] Example 27: Synthesis of 2-((6-(4-aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-N-(10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)-2-phenylacetamide (27)



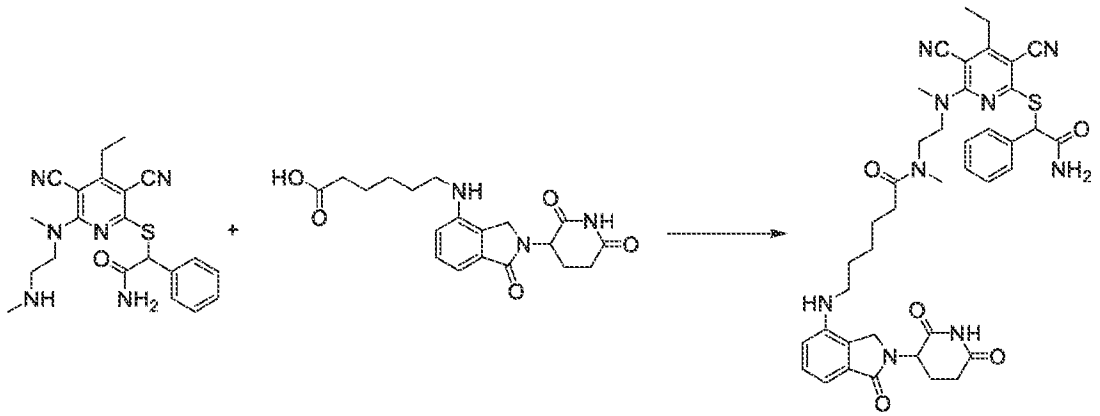
[00283] *tert-Butyl (1-(3,5-dicyano-6-((2-((10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)amino)-2-oxo-1-phenylethyl)thio)-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate*

[00284] 2-((6-(4-((*tert*-Butoxycarbonyl)amino)piperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-2-phenylacetic acid (2.6 mg, 0.005 mmol), 4-((10-aminodecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2.2 mg, 0.005 mmol), and triethylamine (3.5 µL, 0.025 mmol) were dissolved in DMF (50 µL). HATU (2.9 mg, 0.0075 mmol) was added and the mixture was stirred at rt for 15 minutes. The mixture was diluted with EtOAc (5 mL), washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (4.05 mg, 86.9%).

[00285] *2-((6-(4-Aminopiperidin-1-yl)-3,5-dicyano-4-ethylpyridin-2-yl)thio)-N-(10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)-2-phenylacetamide*

[00286] A mixture of *tert*-Butyl (1-(3,5-dicyano-6-((2-((10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)amino)-2-oxo-1-phenylethyl)thio)-4-ethylpyridin-2-yl)piperidin-4-yl)carbamate (4.05 mg, 0.00434 mmol) and 4 M HCl solution in dioxane (0.1 mL) was stirred at rt for 19 hours. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 8% MeOH/DCM, to give the title compound (0.87 mg, 24.1%). LCMS m/z = 832.79 $[M+H]^+$.

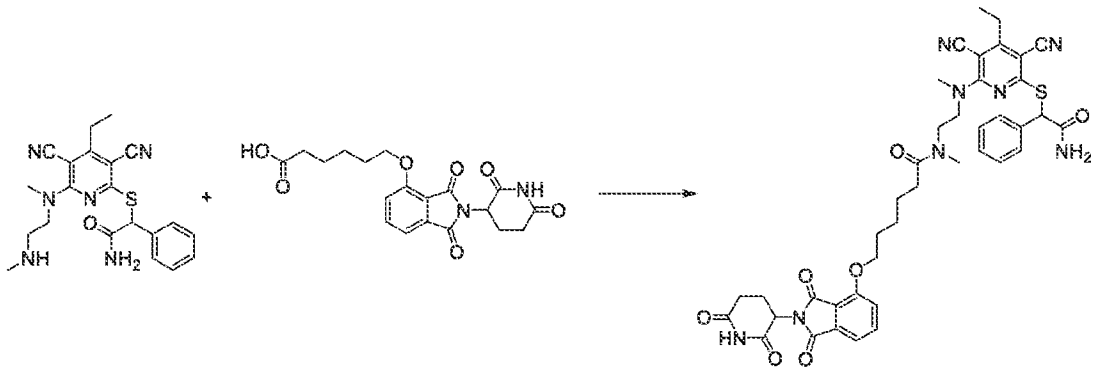
[00287] Example 28: Synthesis of N-(2-((6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)-6-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-N-methylhexanamide (28)



[00288] 2-((3,5-Dicyano-4-ethyl-6-(methyl(2-(methylamino)ethyl)amino)pyridin-2-yl)thio)-2-phenylacetamide (6.0 mg, 0.0161 mmol), 6-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)hexanoic acid (6.6 mg, 0.0161 mmol), and triethylamine (11.3 µL, 0.0805 mmol) were dissolved in DMF (80 µL). HATU (9.2 mg, 0.0242 mmol) was added and the mixture was stirred at rt for 15 minutes. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 15%

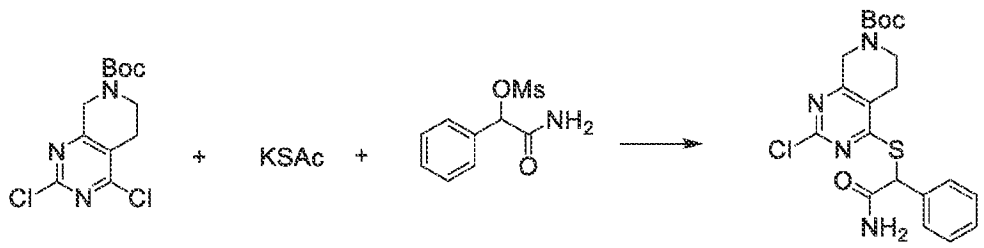
MeOH/EtOAc. Product fractions were collected and concentrated *in vacuo*, then repurified by preparative HPLC, to give the title compound (0.34 mg, 2.8%). LCMS m/z = 764.70 $[M+H]^+$.

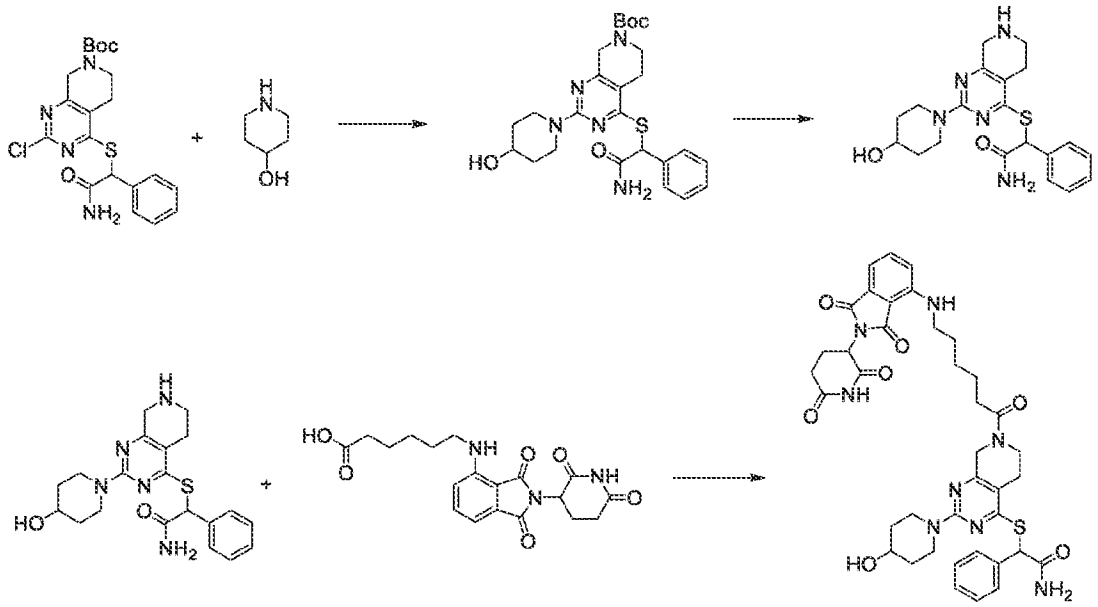
[00289] Example 29: Synthesis of N-(2-((6-((2-amino-2-oxo-1-phenylethyl)thio)-3,5-dicyano-4-ethylpyridin-2-yl)(methyl)amino)ethyl)-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)-N-methylhexanamide (29)



[00290] 2-((3,5-Dicyano-4-ethyl-6-(methyl(2-(methylamino)ethyl)amino)pyridin-2-yl)thio)-2-phenylacetamide (3.9 mg, 0.0100 mmol), 6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)hexanoic acid (4.1 mg, 0.0100 mmol), and triethylamine (7.0 µL, 0.0500 mmol) were dissolved in DMF (50 µL). HATU (5.7 mg, 0.0150 mmol) was added, and the mixture was stirred at rt for 4 hours. The mixture was purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 5% MeOH/DCM, to give the title compound (0.32 mg, 4.1%). LCMS m/z = 779.67 $[M+H]^+$.

[00291] Example 30: Synthesis of 2-((7-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoyl)-2-(4-hydroxypiperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)thio)-2-phenylacetamide (30)





[00292] *tert-Butyl 4-((2-amino-2-oxo-1-phenylethyl)thio)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate*

[00293] *tert*-Butyl 2,4-dichloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (30.4 mg, 0.100 mmol) and potassium ethanethioate (13.7 mg, 0.120 mmol) were dissolved in DMF (300 µL) and the mixture was stirred at rt for 2 hours. 2-Amino-2-oxo-1-phenylethyl methanesulfonate (27.5 mg, 0.120 mmol), triethylamine (28.0 µL), and DMF (300 µL) were added and the mixture was stirred at rt for 15 hours. The mixture was purified by column chromatography (Teledyne ISCO, 12 g silica column) eluting with a gradient of 20 to 50% EtOAc/hexanes, to give the title compound (27.6 mg, 63.5%). LCMS m/z = 435.35 $[M+H]^+$.

[00294] *tert-Butyl 4-((2-amino-2-oxo-1-phenylethyl)thio)-2-(4-hydroxypiperidin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate*

[00295] *tert*-Butyl 4-((2-amino-2-oxo-1-phenylethyl)thio)-2-chloro-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (9.3 mg, 0.0214 mmol), piperidin-4-ol (6.5 mg, 0.0642 mmol), and diisopropylethylamine (18.7 µL, 0.107 mmol) were dissolved in 2-butanol (200 µL) and 2-propanol (50 µL). The mixture was heated in a sealed reaction tube at 130°C for 3 hours. The mixture was cooled to rt, diluted with EtOAc, and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (6.35 mg, 59.4%).

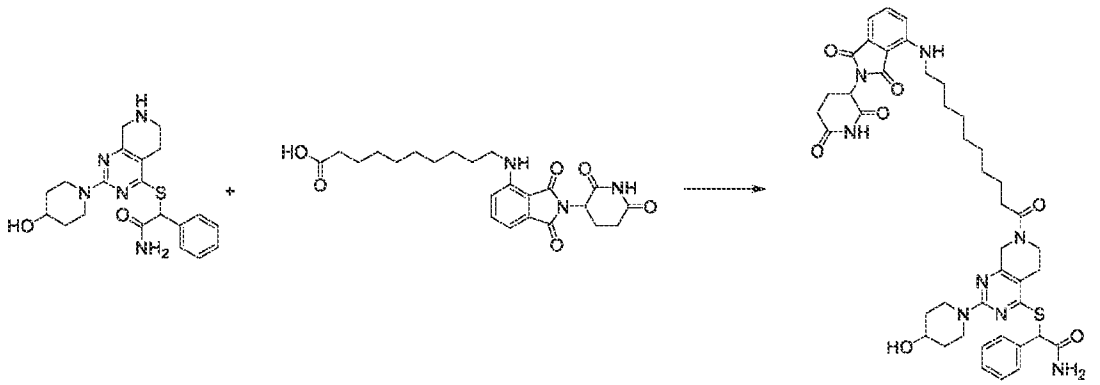
[00296] *2-((2-(4-Hydroxypiperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)thio)-2-phenylacetamide*

[00297] *tert*-Butyl 4-((2-amino-2-oxo-1-phenylethyl)thio)-2-(4-hydroxypiperidin-1-yl)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (6.4 mg, 0.0127 mmol) was dissolved in 4 M HCl solution in dioxane (0.1 mL) and THF (0.1 mL). The mixture was stirred at rt for 2 hours, then concentrated *in vacuo* to give the title compound (5.1 mg, 100%). LCMS m/z = 400.39 $[M+H]^+$.

[00298] *2-((7-(6-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoyl)-2-(4-hydroxypiperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)thio)-2-phenylacetamide*

[00299] 2-((2-(4-Hydroxypiperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)thio)-2-phenylacetamide (2.5 mg, 0.00635 mmol), 6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoic acid (2.5 mg, 0.000635 mmol), and triethylamine (4.5 µL, 0.0318 mmol) were dissolved in DMF (90 µL). HATU (3.6 mg, 0.00953 mmol) was added and the mixture was stirred at rt for 2 hours, then purified by column chromatography (Teledyne ISCO, 4 g silica column) eluting with a gradient of 0 to 7% MeOH/DCM, to give the title compound (3.35 mg, 68.6%). LCMS m/z = 769.64 $[M+H]^+$.

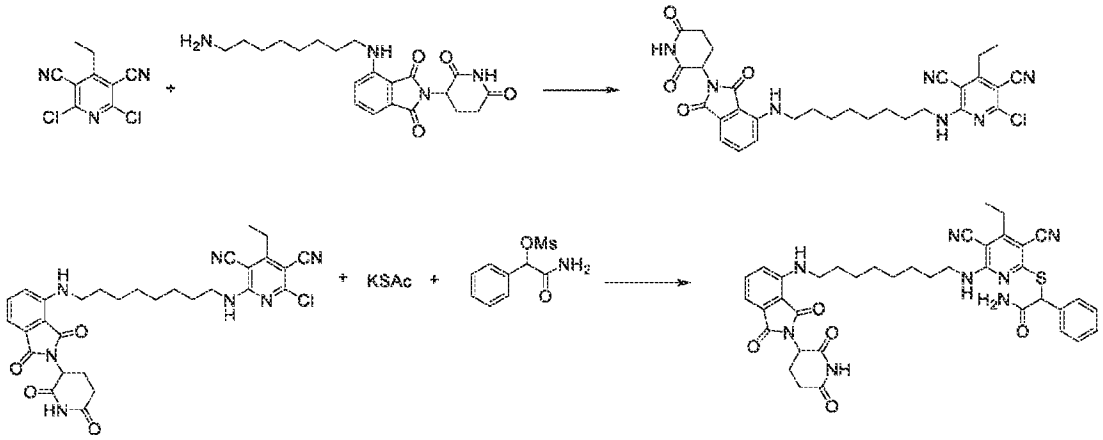
[00300] Example 31: Synthesis of 2-((7-(10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decanoyl)-2-(4-hydroxypiperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)thio)-2-phenylacetamide (31)



[00301] 2-((2-(4-Hydroxypiperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)thio)-2-phenylacetamide (2.5 mg, 0.00635 mmol), 10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decanoic acid (2.8 mg, 0.00635 mmol), and triethylamine (4.5 µL, 0.0318 mmol) were dissolved in DMF (90 µL). HATU (3.6 mg, 0.00953 mmol) was added and the mixture was stirred at rt for 30 minutes, then purified by column chromatography (Teledyne

ISCO, 4 g silica column) eluting with a gradient of 0 to 7% MeOH/DCM, to give the title compound (2.88 mg, 55.0%). LCMS m/z = 825.72 $[M+H]^+$.

[00302] Example 32: Synthesis of 2-((3,5-dicyano-6-((8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)amino)-4-ethylpyridin-2-yl)thio)-2-phenylacetamide (32)



[00303] *2-Chloro-6-((8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)amino)-4-ethylpyridine-3,5-dicarbonitrile*

[00304] 2,6-Dichloro-4-ethylpyridine-3,5-dicarbonitrile (11.3 mg, 0.050 mmol), 4-((8-aminooctyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (24.0 mg, 0.060 mmol), and triethylamine (7.0 µL, 0.050 mmol) were dissolved in DMF (300 µL) and the mixture was stirred at rt for 3 hours. Then triethylamine (21 µL, 0.150 mmol) was added and mixture was stirred at rt for 24 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (26.2 mg, 88.8%). LCMS m/z = 590.51 $[M+H]^+$.

[00305] *2-((3,5-Dicyano-6-((8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)amino)-4-ethylpyridin-2-yl)thio)-2-phenylacetamide*

[00306] 2-Chloro-6-((8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)amino)-4-ethylpyridine-3,5-dicarbonitrile (11.8 mg, 0.020 mmol) and potassium ethanethioate (2.7 mg, 0.024 mmol) were dissolved in DMF (100 µL) and the mixture was stirred at rt for 1 hour. 2-Amino-2-oxo-1-phenylethyl methanesulfonate (5.5 mg, 0.024 mmol), triethylamine (5.6 µL, 0.040 mmol), and DMF (50 µL) were added, and the mixture was stirred at rt for 16 hours. The mixture was purified by column chromatography

(Teledyne ISCO, 12 g silica column) eluting with a gradient of 20 to 100% EtOAc/hexanes, to give the title compound (3.35 mg, 23.2%). LCMS m/z = 721.76 $[M+H]^+$.

[00307] Example 33: Degradation Activity – Western Blot

[00308] HL60 cells were seeded in 6-well plates at $1*10^6$ cells/well and treated with the compound at the indicated concentrations and time. Total protein was extracted from cells using the RIPA buffer (Abcam) supplemented with the Halt Protease Inhibitor Cocktail (Millipore®-Sigma). Samples were loaded to Invitrogen Bolt™ Bis-Tris Plus gels (ThermoFisher® Scientific) and transferred to Invitrolon™ PVDF membranes (ThermoFisher® Scientific) using the Invitrogen Bolt™ wet-gel Transfer Device. Immunodetection was performed with standard techniques. The following primary and secondary antibodies were used: anti-DNMT1, CRBN and β-actin (Cell Signaling Technology®). and IRDye secondary antibodies at the concentration recommended by the manufacturer.

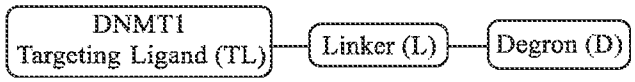
[00309] Compounds showed down regulation of DNMT1 (FIG. 1-FIG. 12).

[00310] All patent publications and non-patent publications are indicative of the level of skill of those skilled in the art to which this disclosure pertains. All these publications are herein incorporated by reference to the same extent as if each individual publication were specifically and individually indicated as being incorporated by reference.

[00311] Although the disclosure herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present disclosure. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present disclosure as defined by the appended claims.

What is claimed is:

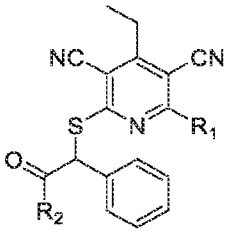
1. A compound of formula (I):



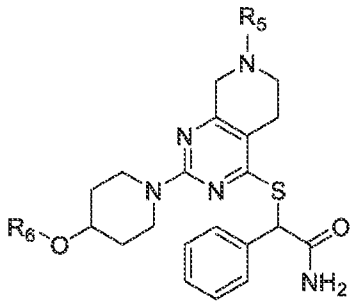
(I), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

DNMT1 Targeting Ligand is of Formula TL-1 or TL-2:



(TL-1) or



(TL-2),

wherein:

R_1 is NR_3R_4;

R_3 is H or methyl and R_4 is $-\!\!\!\!\!\!\sim$, or

R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl, or

R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl which is also bound to the linker;

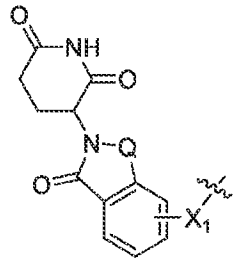
R_2 is NH_2 or $-\!\!\!\!\!\!\sim\!\!-NH$;

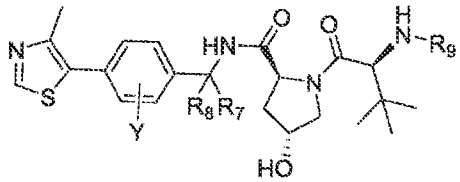
R_5 and R_6 are independently H, optionally substituted alkyl, or $-\!\!\!\!\!\!\sim$;

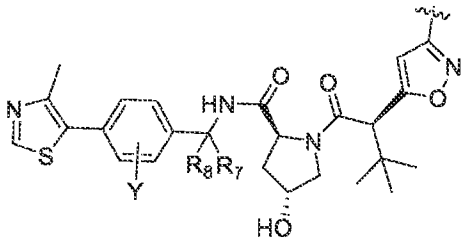
wherein $-\!\!\!\!\!\!\sim$ is a bond between the DNMT1 Targeting Ligand and the Linker, provided that there is only one bond between the DNMT1 Targeting Ligand and the Linker;

the linker represents a moiety that connects covalently the degron and the targeting ligand; and

the Degron is of Formula D1, D2, or D3:


(D1),


(D2), or


(D3),

wherein:

Q is CH_2 or C(O); and

X_1 is O, NH, CH_2, or C≡C,

R_7 is H or optionally substituted C_1-C_3 alkyl, or

R_7 and R_8, together with the carbon atom to which they are attached, form cyclopropyl;

R_8 is H, methyl, or  ;

R_9 is $C(O)CR_{10}R_{11}R_{12}$,  or  ;

R_{10} and R_{11} are both H, or

R_{10} and R_{11}, together with the carbon atom to which they are attached, form cyclopropyl;

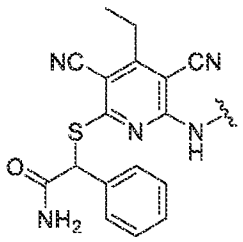
R_{12} is H, fluoro, cyano, or NMe_2; and

Y is H,  , , , or ;

wherein  is a bond between the Degron and the Linker, provided that there is only one bond between the Degron and the Linker.

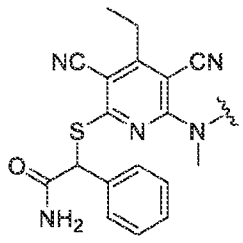
2. The compound of claim 1, wherein R_2 is NH_2.

3. The compound of claim 1 or 2, wherein R_3 is H and R_4 is $-\!\!\!\sim\!\!\!-$, and Formula TL-1 is of TL-1a:



(TL-1a).

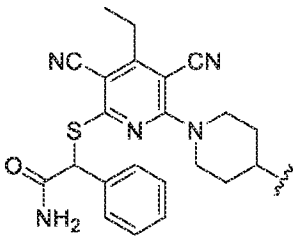
4. The compound of claim 1 or 2, wherein R_3 is Me and R_4 is $-\!\!\!\sim\!\!\!-$, and Formula TL-1 is of TL-1b:



(TL-1b).

5. The compound of claim 1 or 2, wherein R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl which is also bound to the linker.

6. The compound of claim 5, wherein R_3 and R_4, together with the nitrogen atom to which they are attached, form piperidyl, the Formula TL-1 is of TL-1c:



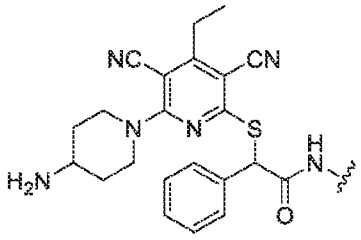
(TL-1c).

7. The compound of claim 1, wherein R_3 and R_4, together with the nitrogen atom to which they are attached, form an optionally substituted 6-membered heterocyclyl.

8. The compound of claim 7, wherein R_3 and R_4, together with the nitrogen atom to which they are attached, form optionally substituted piperidyl.

9. The compound of claim 8, wherein piperidyl is substituted with an amino group.

10. The compound of any one of claims 7-9, wherein R_2 is $-\!\!\!\!\!\!\sim\!\!\!\!\!\!-NH$ and Formula TL-1 is of TL-1d:

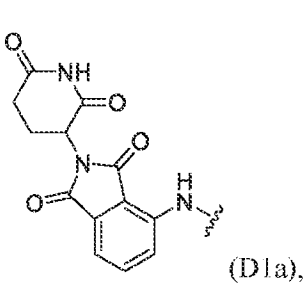


(TL-1d).

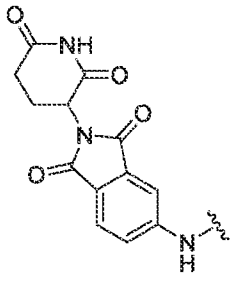
11. The compound of claim 1, wherein the DNMT1 Targeting Ligand is of Formula TL-2 and R_5 is $-\!\!\!\!\!\!\sim\!\!\!\!\!\!-$ and R_6 is H, or R_5 is H or optionally substituted alkyl and R_6 is $-\!\!\!\!\!\!\sim\!\!\!\!\!\!-$.

12. The compound of any one of claims 1-11, wherein the Degron is of Formula D1.

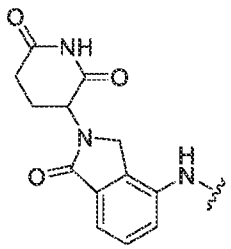
13. The compound of claim 12, wherein Formula D1 is of Formula D1a-D1p:



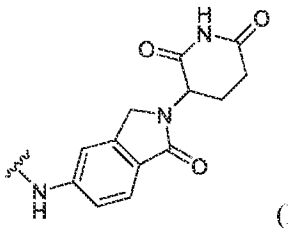
(D1a),



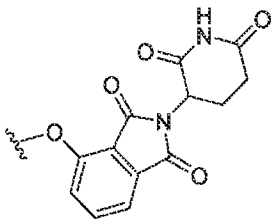
(D1b),



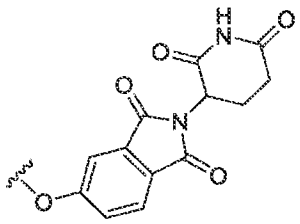
(D1c),



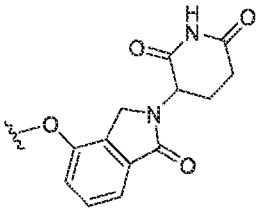
(D1d),



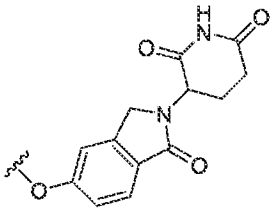
(D1e),



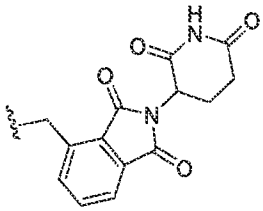
(D1f),



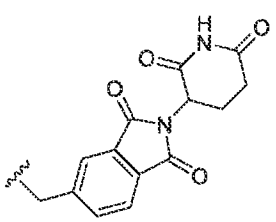
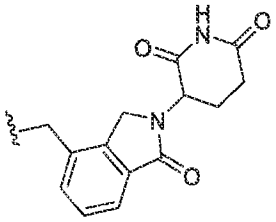
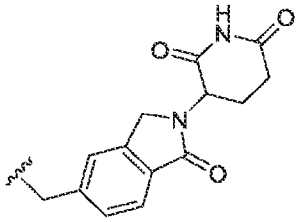
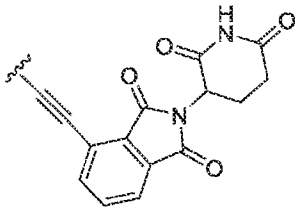
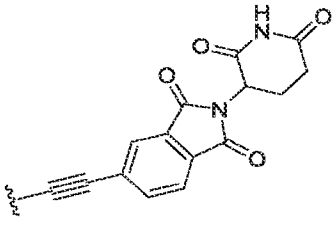
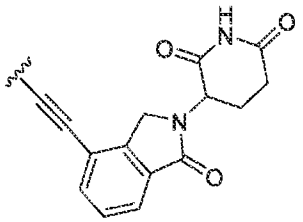
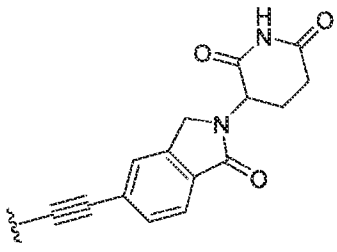
(D1g),



(D1h),

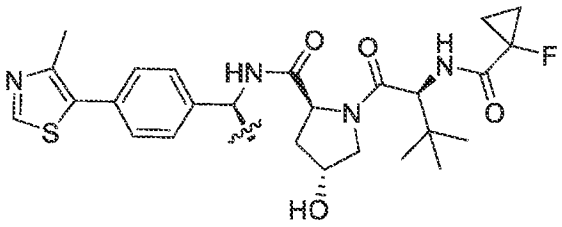
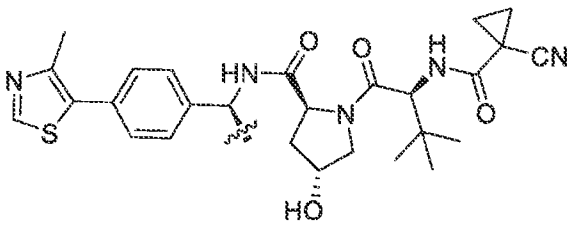


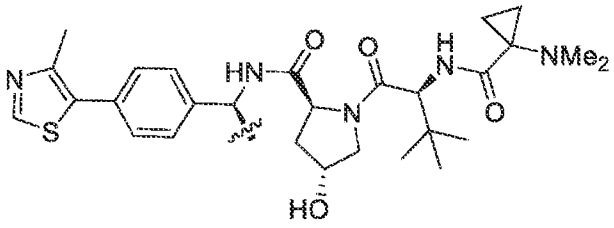
(D1i),


(D1j),

(D1k),

(D1l),

(D1m),

(D1n),

(D1o), or

(D1p).

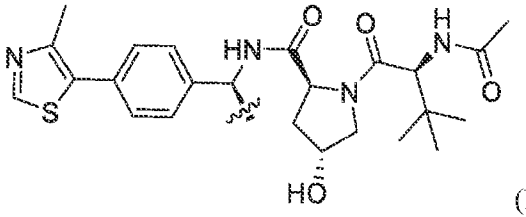
14. The compound of any one of claims 1-11, wherein the Degron is of Formula D2 or D3.

15. The compound of claim 14, wherein the Degron is of Formula D2a-D2o or D3a-D3g:

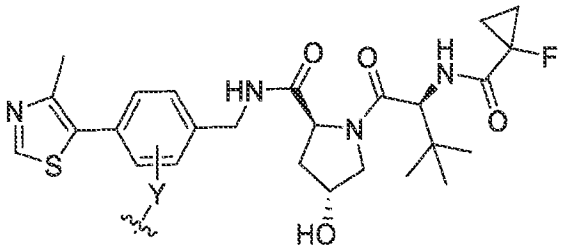

(D2a),

(D2b),



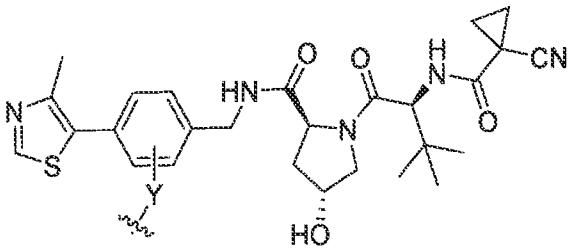
(D2c),



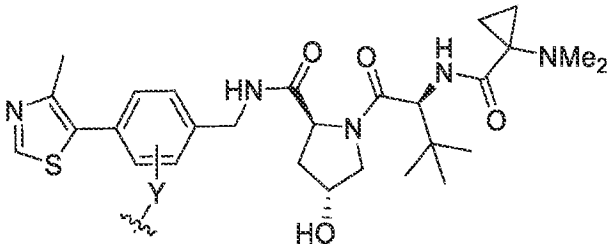
(D2d),



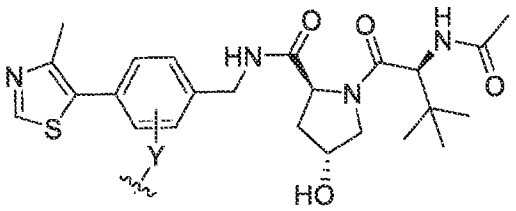
(D2e),



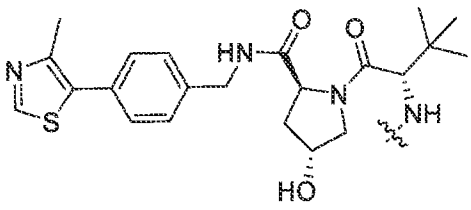
(D2f),

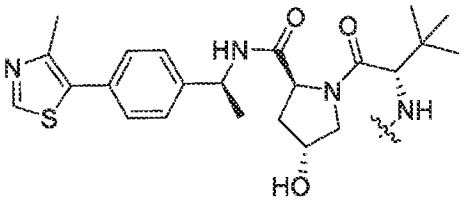


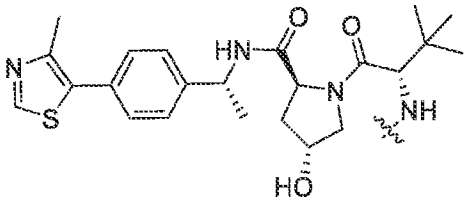
(D2g),

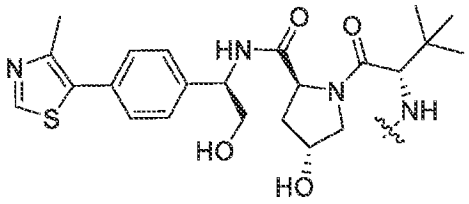


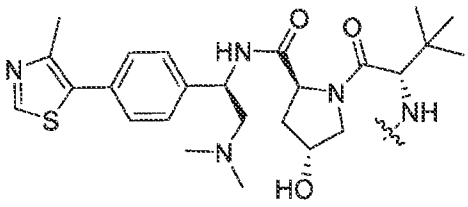
(D2h),

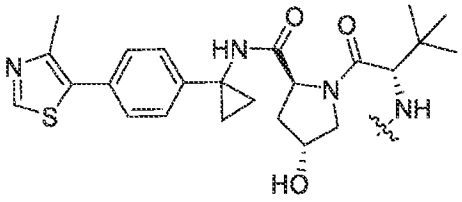

(D2i),

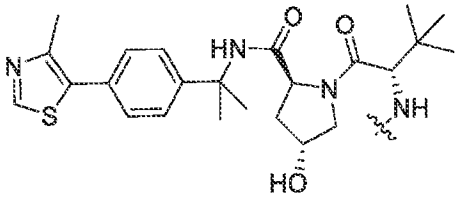

(D2j),

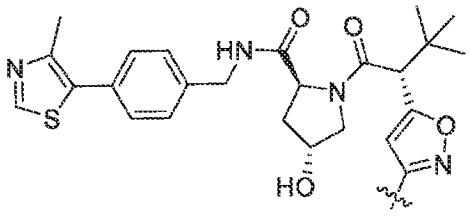

(D2k),

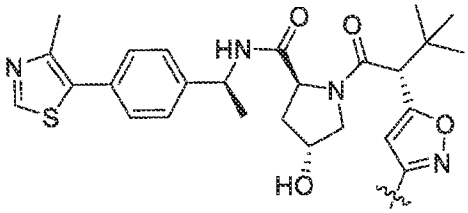

(D2l),

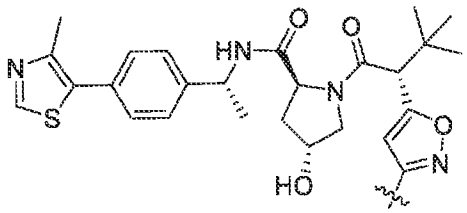

(D2m),

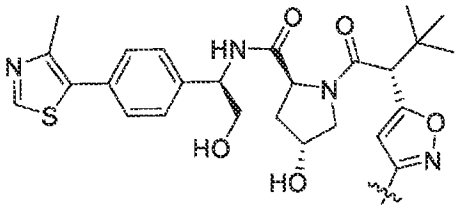

(D2n),

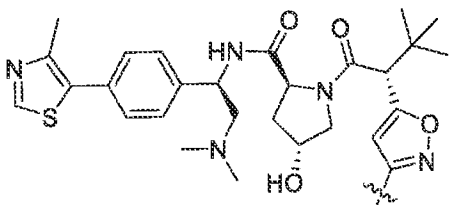

(D2o),

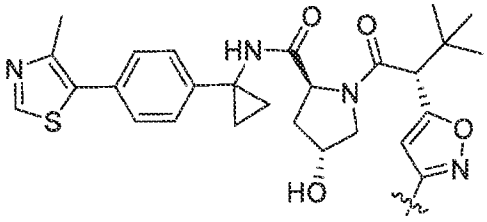

(D3a),

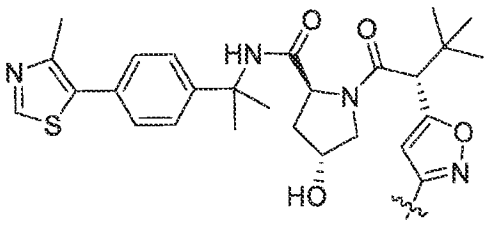

(D3b),


(D3c),


(D3d),

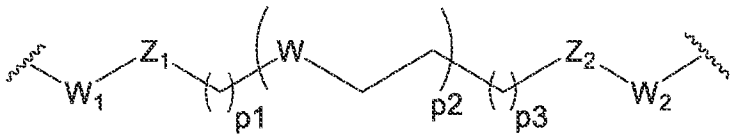

(D3e),


(D3f), or



(D3g), or stereoisomer thereof.

16. The compound of any one of claims 1-15, wherein the Linker is of Formula L0:



(L0),

or stereoisomer thereof, wherein

p1 is an integer selected from 0 to 6;

p2 is an integer selected from 0 to 12;

p3 is an integer selected from 0 to 12;

each W is independently absent, CH_2, O, S, NR_{13}, or C(O)NH;

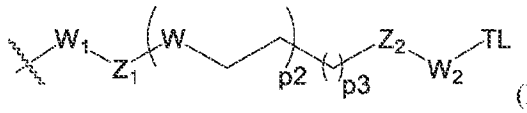
each R_{13} is independently hydrogen or C_1-C_6 alkyl;

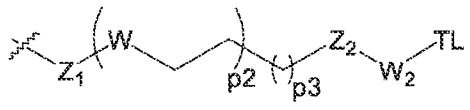
W_1 and W_2 are independently absent, $(CH_2)_{1-3}$, O, NH, or $C(O)NR_{13}$; and

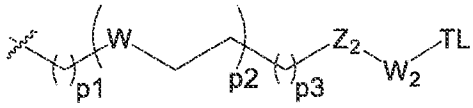
Z_1 and Z_2 are independently absent, –O–, –S–, $-N(R_{13})-$, –C≡C–, –C(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, $-C(NOR_{13})-$, $-C(O)N(R_{13})-$, $-C(O)N(R_{13})C(O)-$, $-C(O)N(R_{13})C(O)N(R_{13})-$, $-N(R_{13})C(O)-$, $-N(R_{13})C(O)N(R_{13})-$, $-N(R_{13})C(O)O-$, $-OC(O)N(R_{13})-$, $-C(NR_{13})-$, $-N(R_{13})C(NR_{13})-$, $-C(NR_{13})N(R_{13})-$, $-N(R_{13})C(NR_{13})N(R_{13})-$, –OB(Me)O–, $-S(O)_2-$, –OS(O)–, –S(O)O–, –S(O)–, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R_{13})S(O)_2-$, $-S(O)_2N(R_{13})-$, $-N(R_{13})S(O)-$, $-S(O)N(R_{13})-$, $-N(R_{13})S(O)_2N(R_{13})-$, $-N(R_{13})S(O)N(R_{13})-$, C_3-C_{12} carbocyclyl, or 3- to 12-membered heterocyclyl;

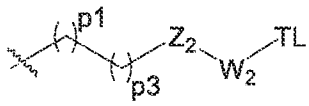
wherein the Linker is covalently bonded to a Degron via the  next to W_2, and covalently bonded to a Targeting Ligand via the  next to W_1, or the Linker is covalently bonded to a Degron via the  next to W_1, and covalently bonded to a Targeting Ligand via the  next to W_2.

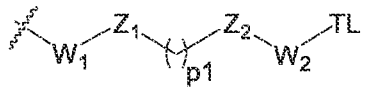
17. The compound of claim 16, wherein Formula L0 is of Formula L0a-L0j:

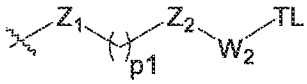

(L0a),

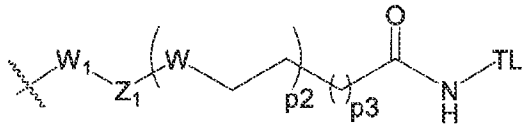

(L0b),

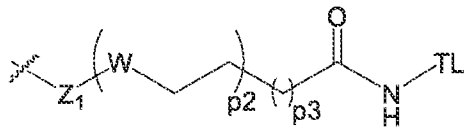

(L0c),

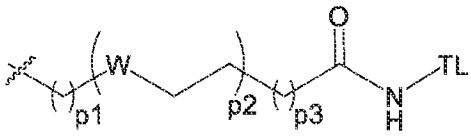

(L0d),

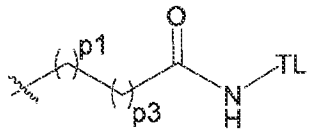

(L0e),

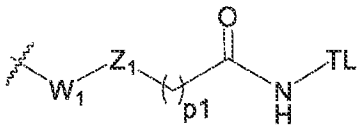

(L0f),

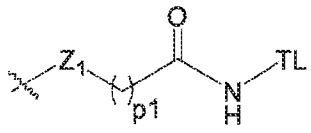

(L0g),


(L0h),


(L0i),


(L0j),


(L0k), or

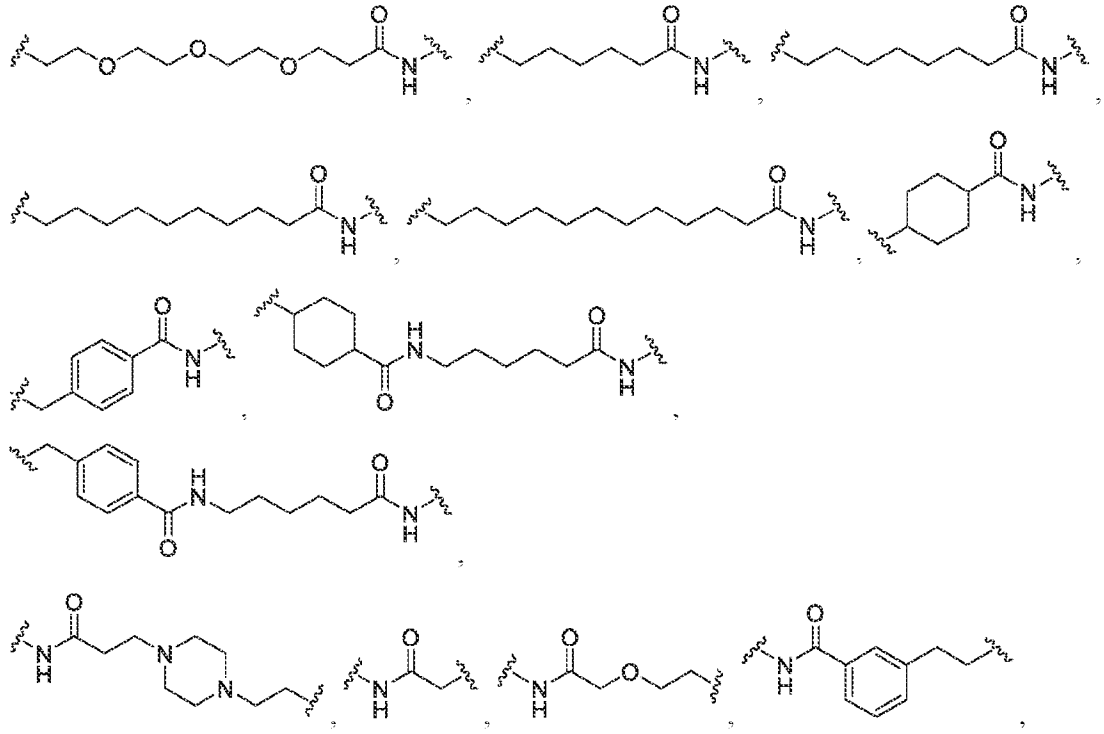

(L0l), wherein TL represents targeting ligand.

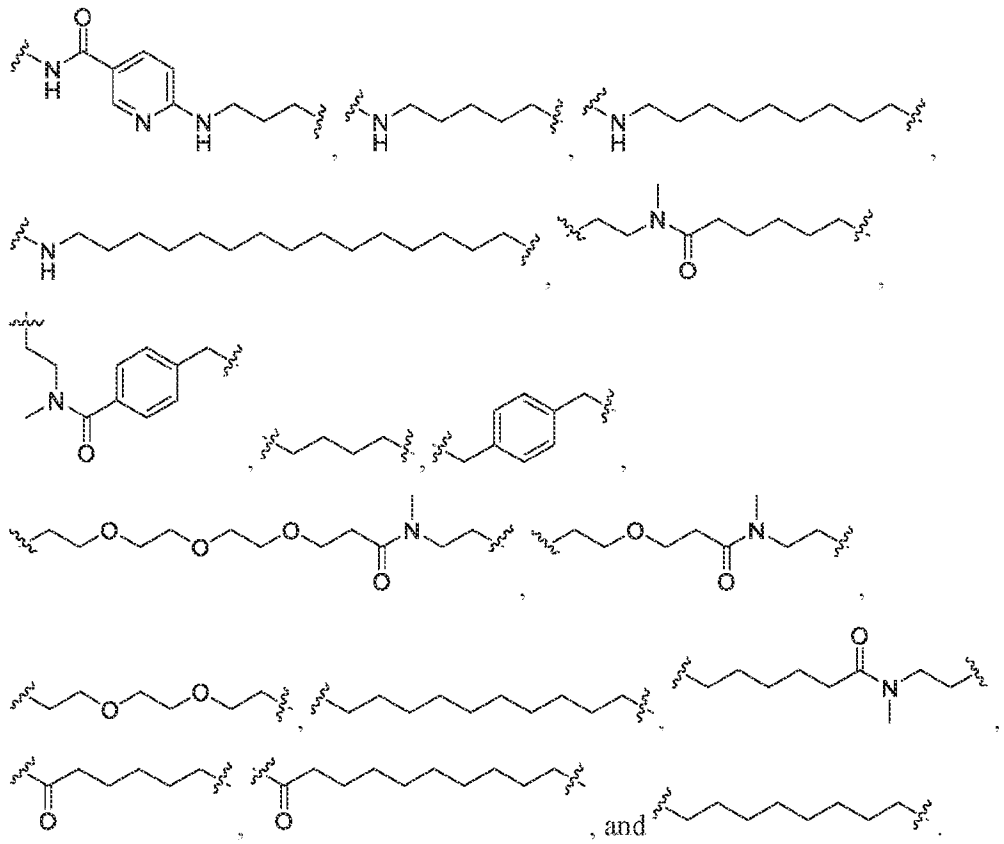
18. The compound of any one of claims 1-15, wherein the Linker is a bond or comprises an alkylene chain or a bivalent alkylene chain, either of which may be interrupted by, and/or terminates at either or both termini with at least one of –O–, –S–, –N(R')–, –C≡C–, –C(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(NOR')–, –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(Me)O–, –S(O)$_2$–, –OS(O)–, –S(O)O–, –S(O)–, –OS(O)$_2$–, –S(O)$_2$O–, –N(R')S(O)$_2$–, –S(O)$_2$N(R')–, –N(R')S(O)–, –S(O)N(R')–, –N(R')S(O)$_2$N(R')–, –N(R')S(O)N(R')–, C$_3$-C$_{12}$ carbocyclene, 3- to 12-membered heterocyclene, 5- to 12-membered heteroarylene or any combination thereof,

wherein R' is H or C_1-C_6 alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

19. The compound of any one of claims 1-15, wherein the Linker is a polyethylene glycol (PEG) chain which may be interrupted by, and/or terminates at either or both termini with at least one of –O–, –S–, –N(R')–, –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(Me)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')–, C_3-C_{12} carbocyclene, 3- to 12-membered heterocyclene, 5- to 12-membered heteroarylene or any combination thereof, wherein R' is H or C_1-C_6 alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

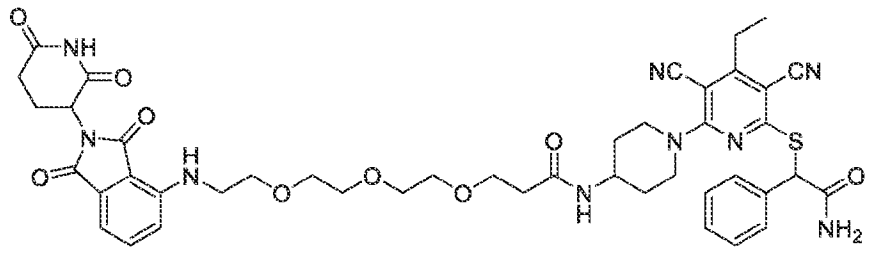
20. The compound of any one of claims 1-15, wherein the Linker is represented by any one of structures:



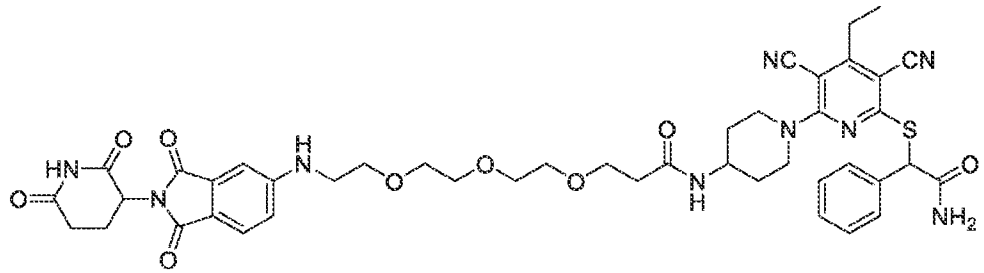


, and

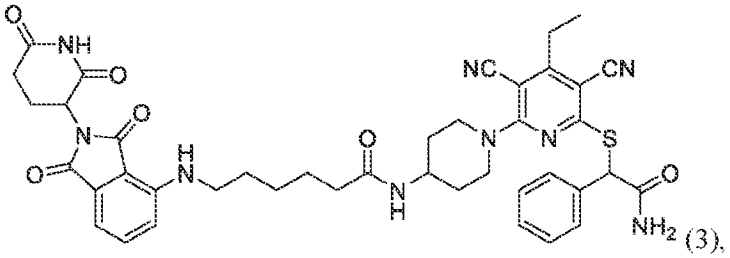
21. The compound of claim 1, which is:



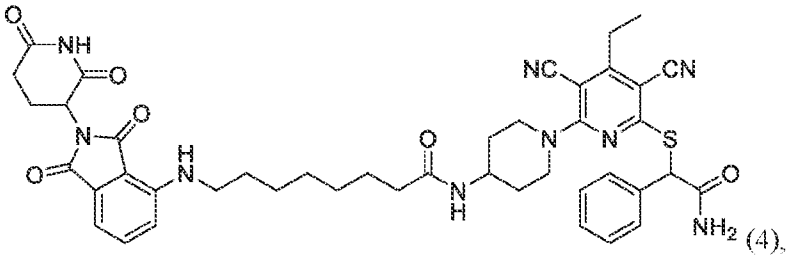
(1),



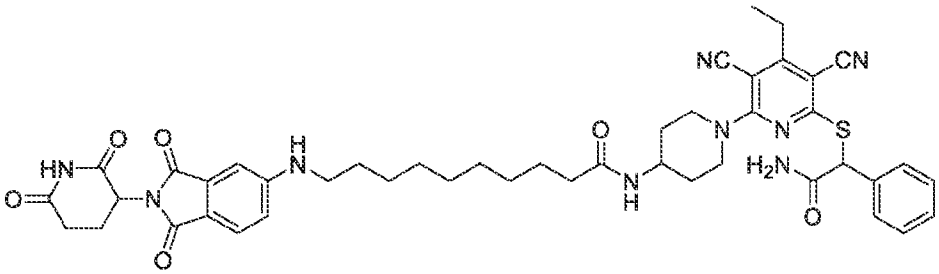
(2),



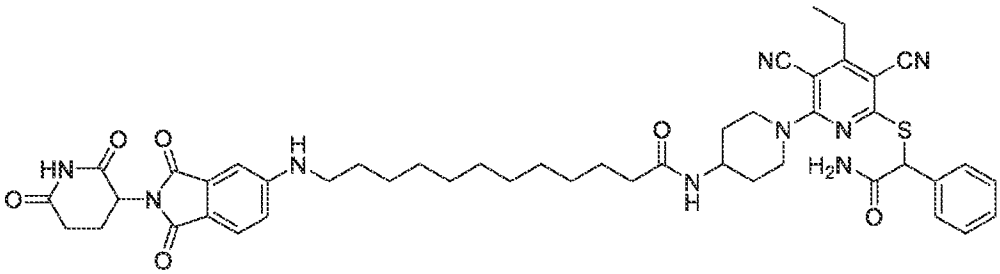
(3),



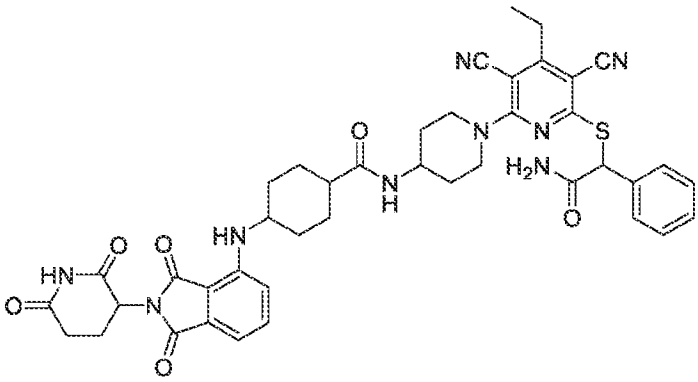
(4),



(5),



(6),



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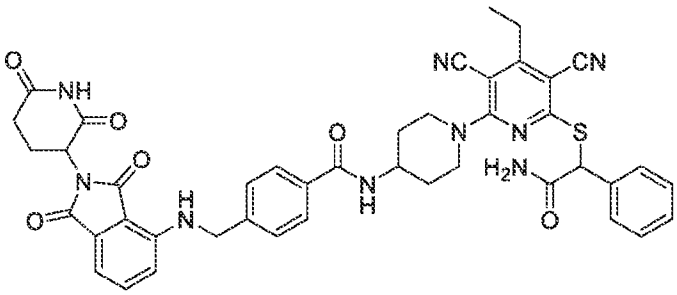

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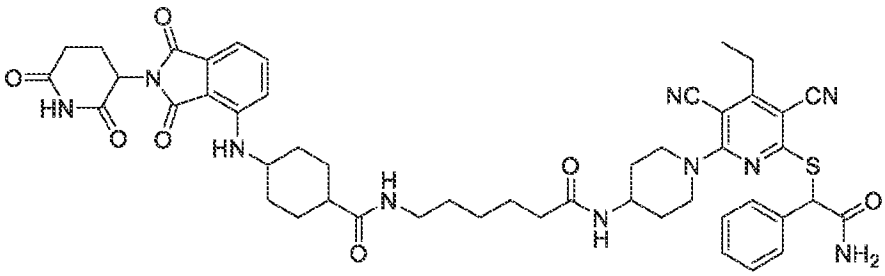

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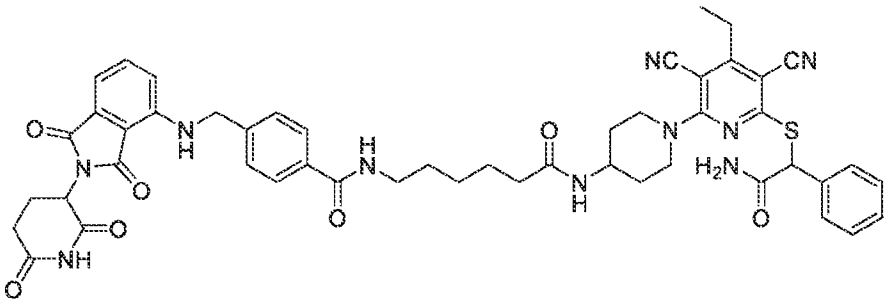
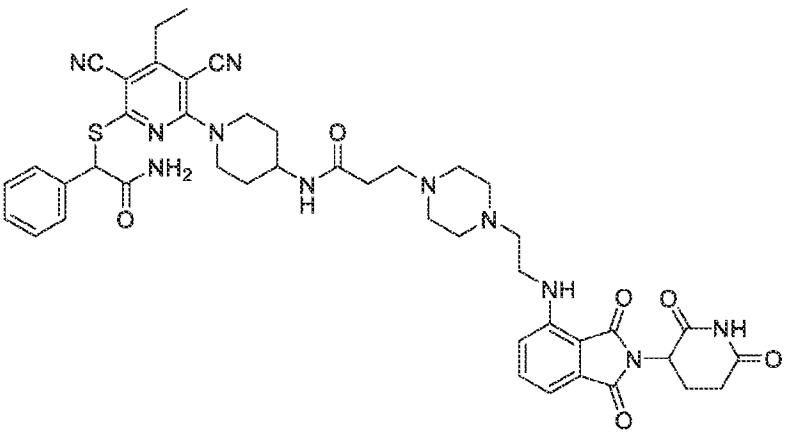
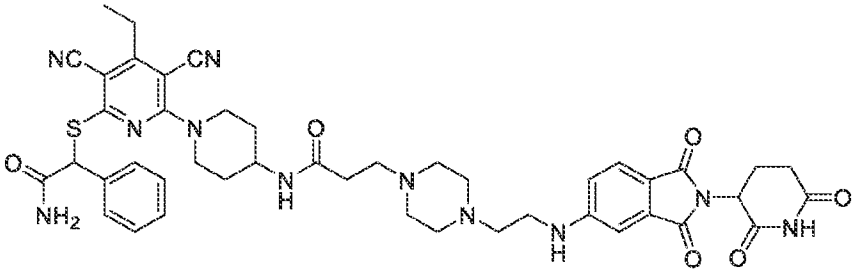


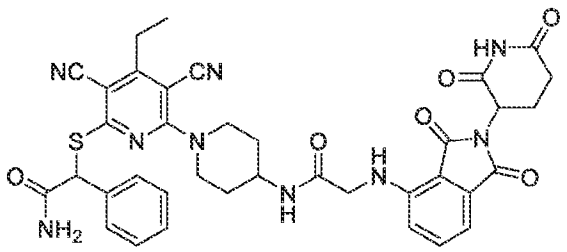
(10),



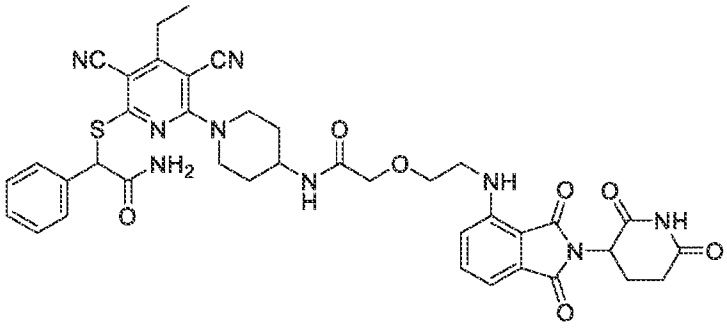
(11),



(12),



(13),



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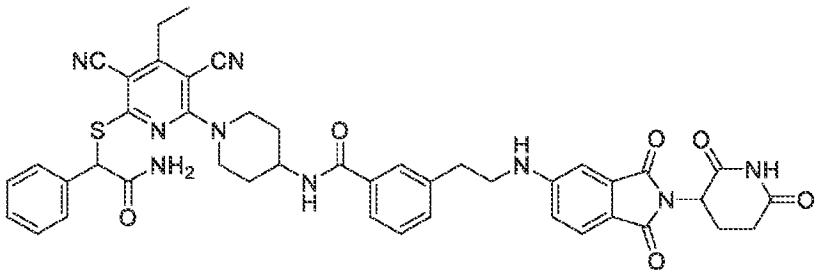

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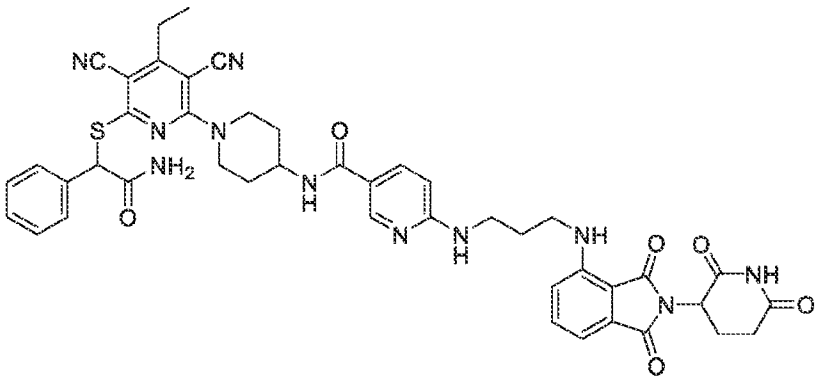

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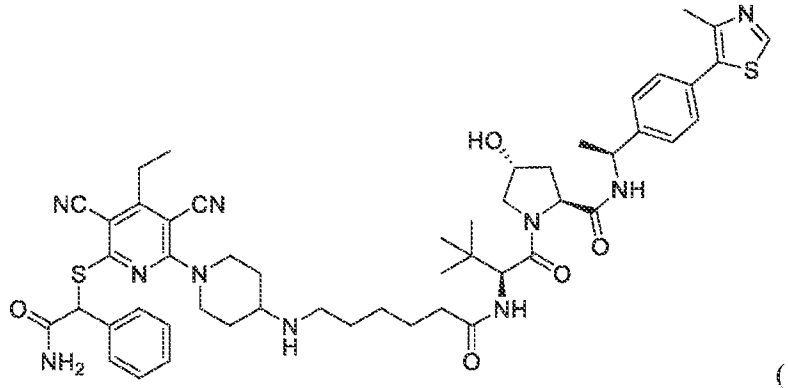

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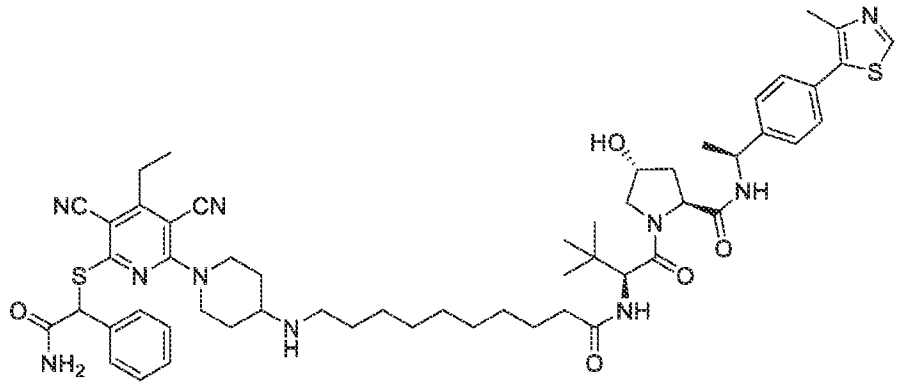

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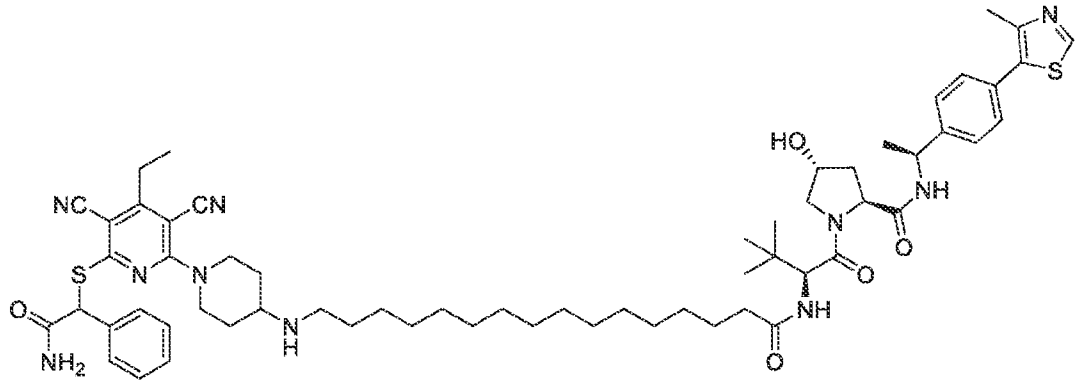

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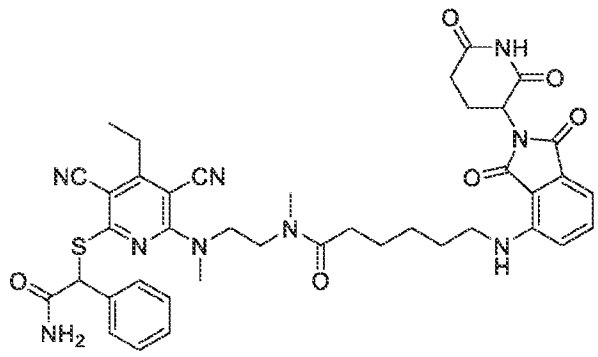

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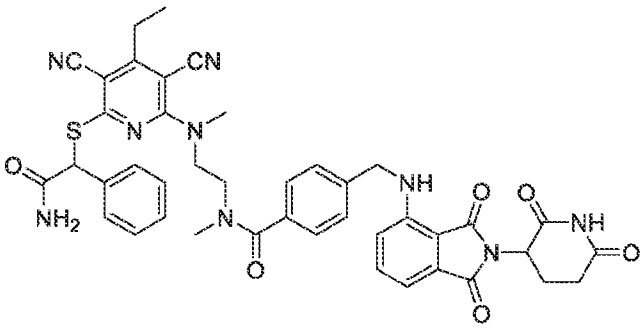

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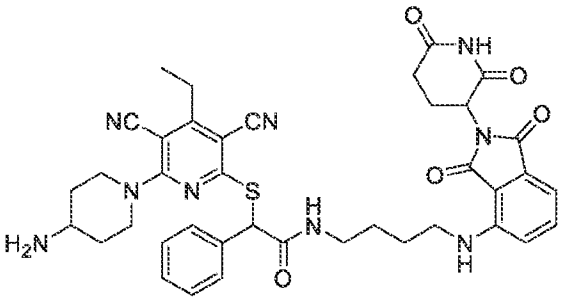

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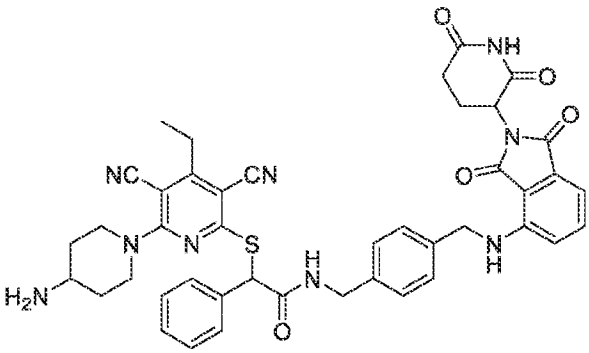

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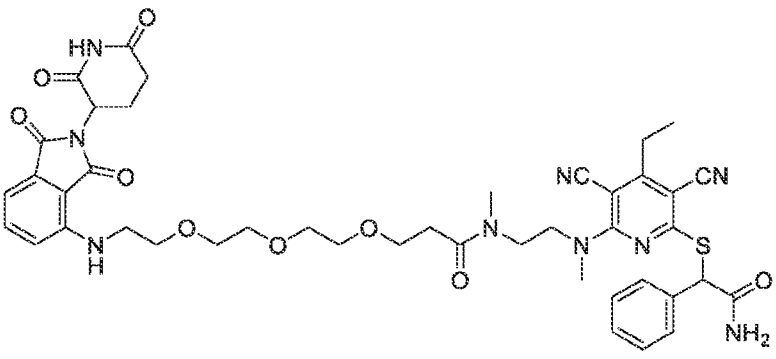

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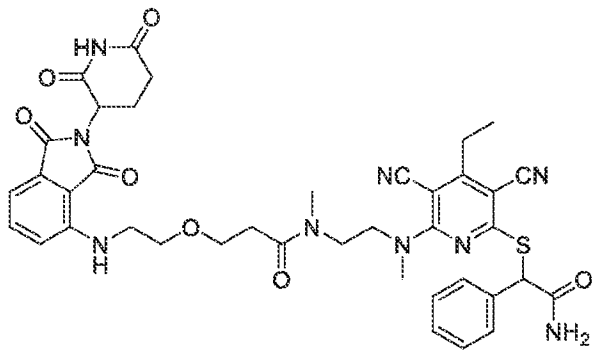

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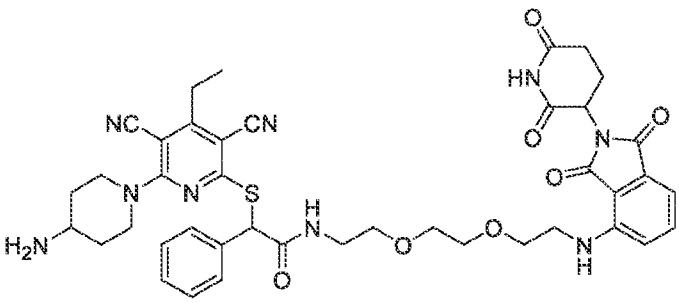

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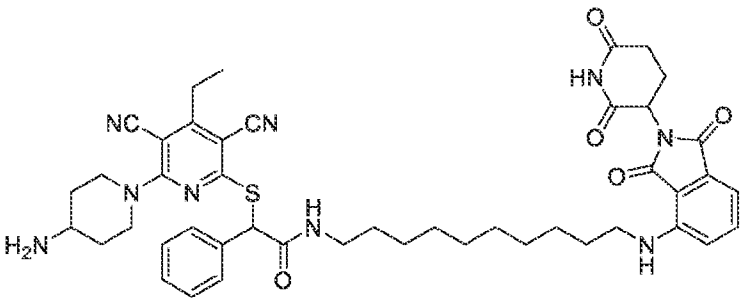

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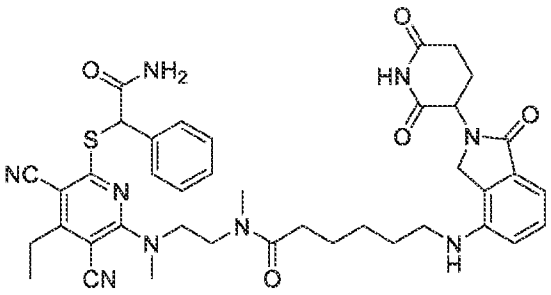

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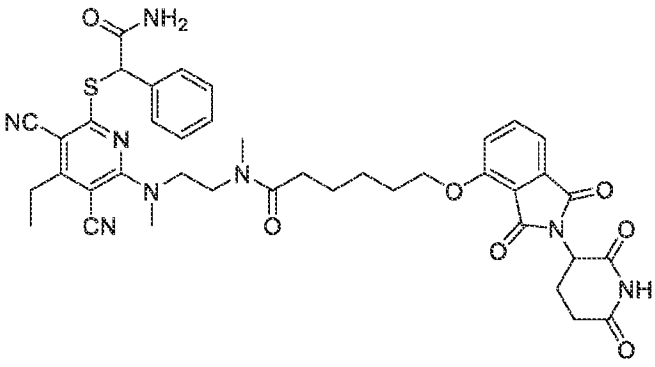

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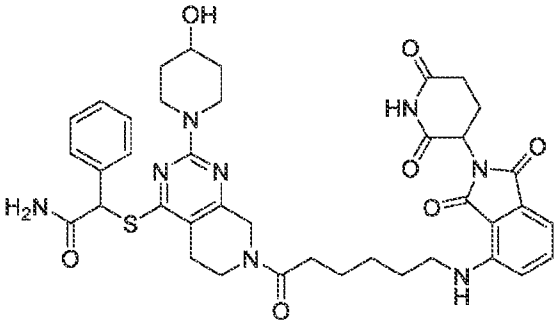

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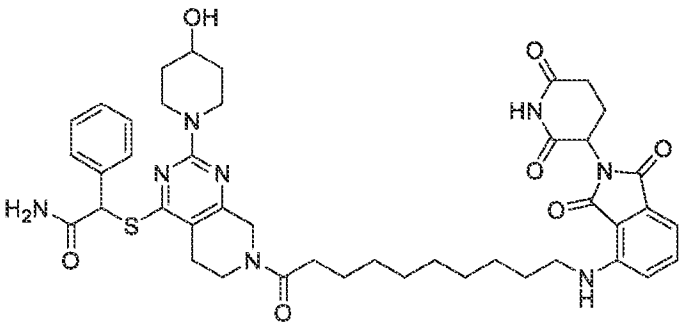

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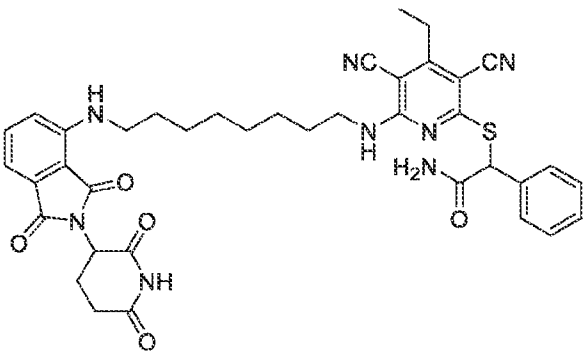

(32), or a pharmaceutically acceptable salt or stereoisomer thereof.

22. A pharmaceutical composition, comprising a therapeutically effective amount of the compound or pharmaceutically acceptable salt or stereoisomer thereof of any one of claims 1-21, and a pharmaceutically acceptable carrier.

23. A method of treating a disease or disorder characterized or mediated by aberrant DNMT1 activity, comprising administering a therapeutically effective amount of the compound of any one of claims 1-21 or a pharmaceutically acceptable salt or stereoisomer thereof, to a subject in need thereof.

24. The method of claim 23, wherein the disease or disorder is cancer.

25. The method of claim 24, wherein the cancer is breast, colon, or prostate cancer.

FIG. 1

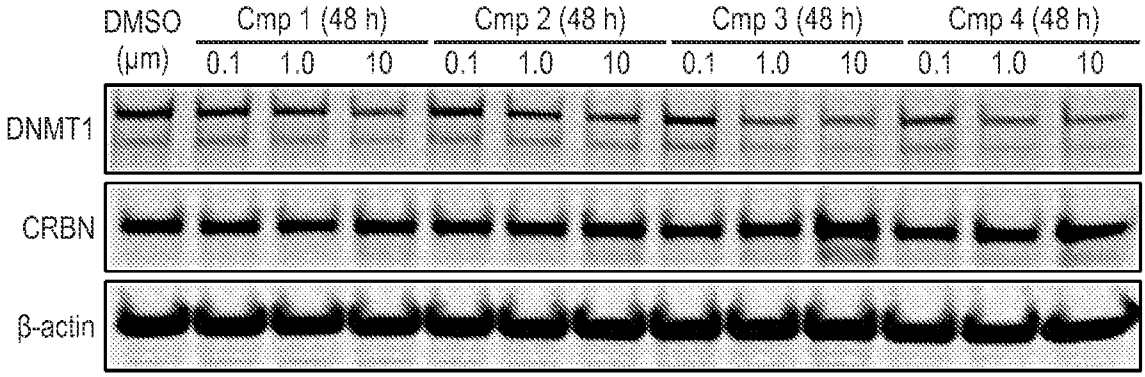

FIG. 2

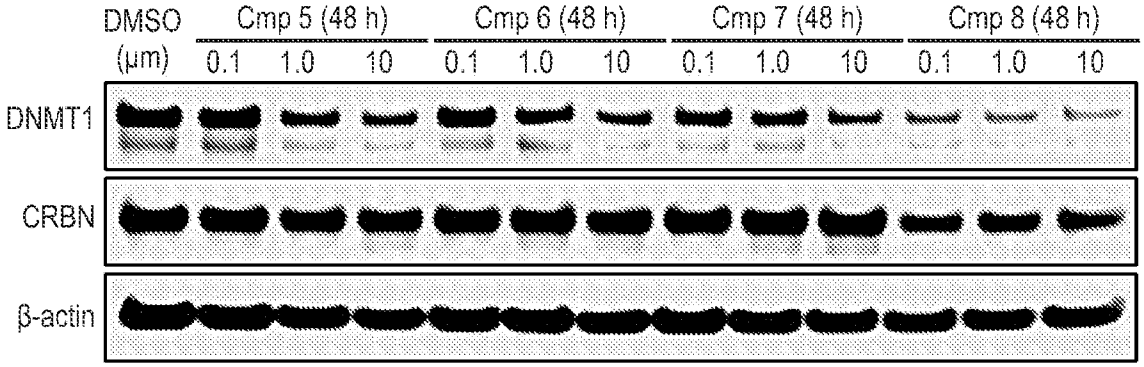

FIG. 3

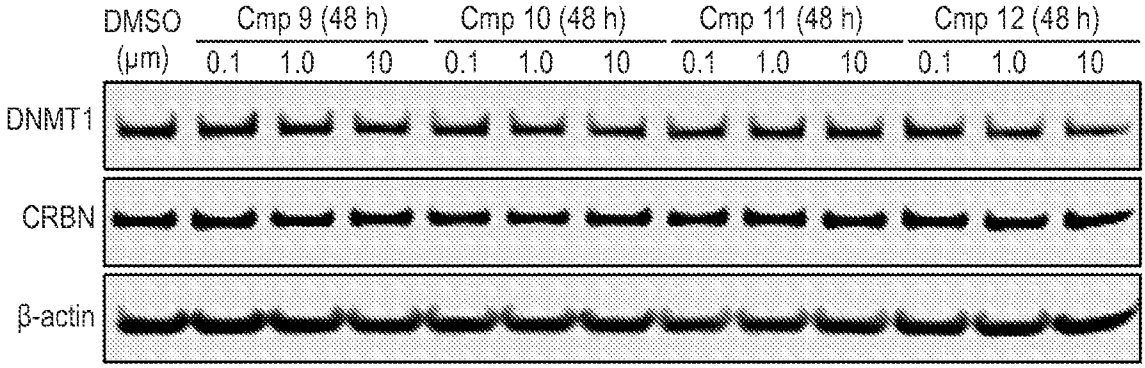

FIG. 4

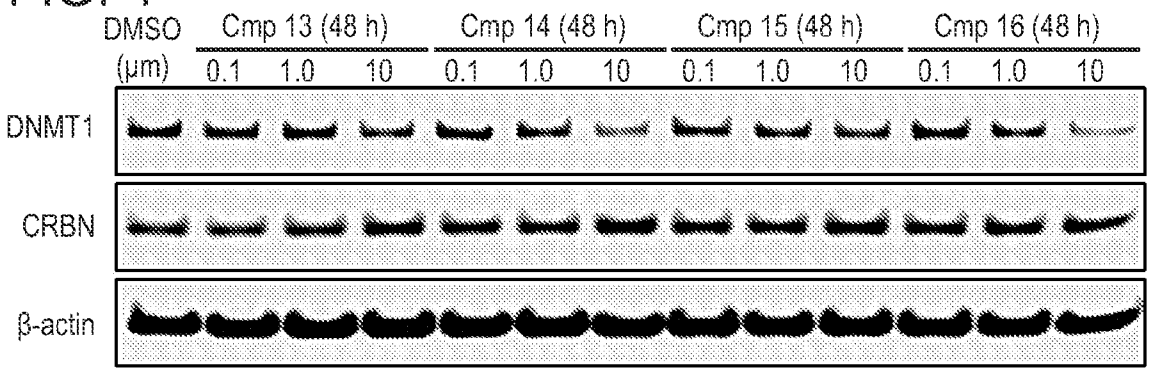

FIG. 5

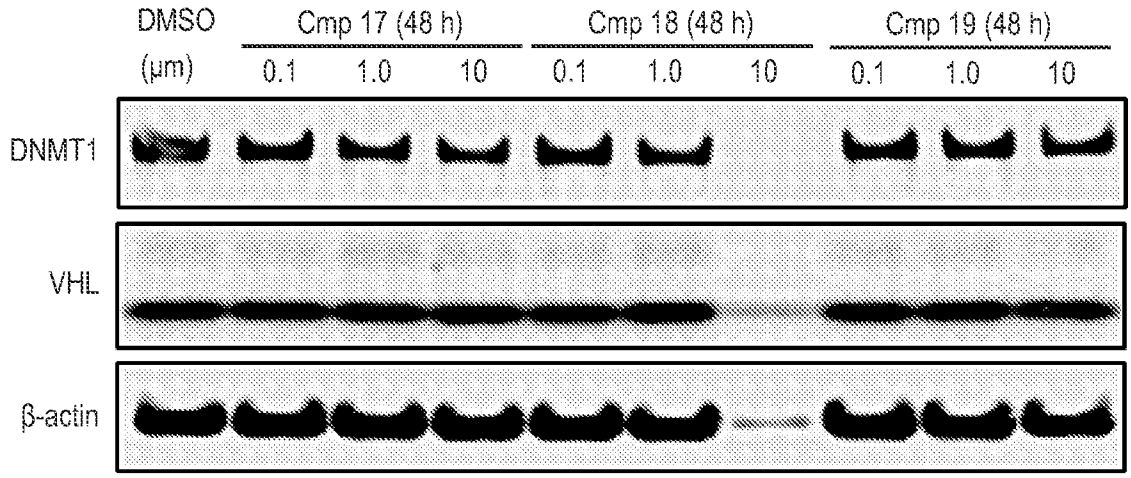

FIG. 6

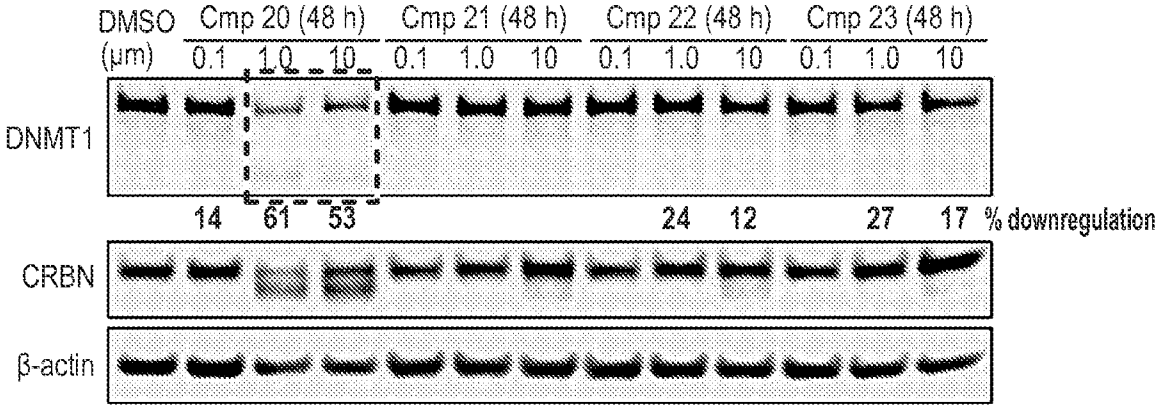

FIG. 7

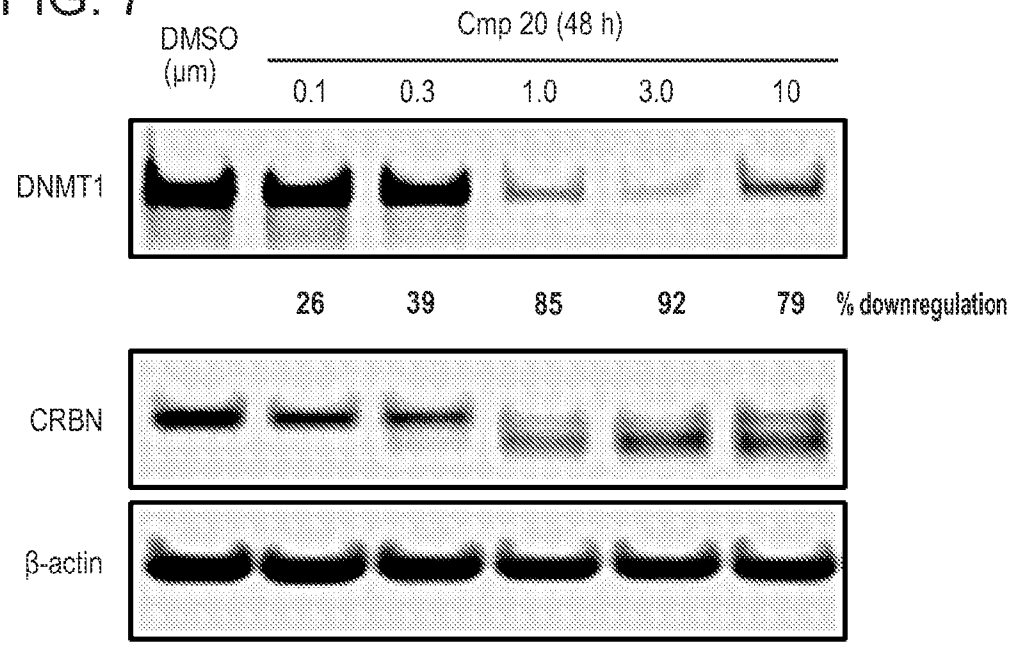

FIG. 8

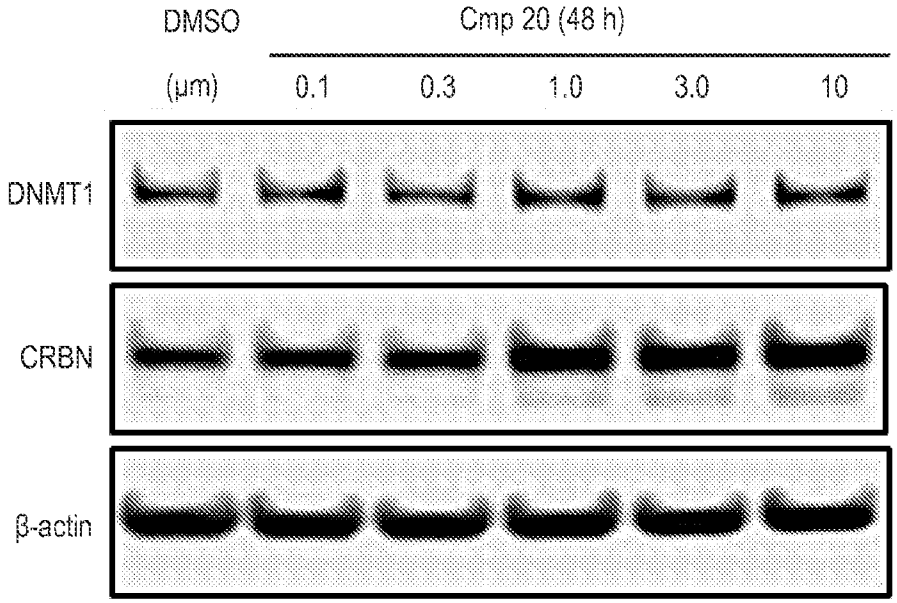
DMSO
Cmp 20 (48 h)
(μm)
0.1
0.3
1.0
3.0
10
DNMT1
CRBN
β-actin

FIG. 9

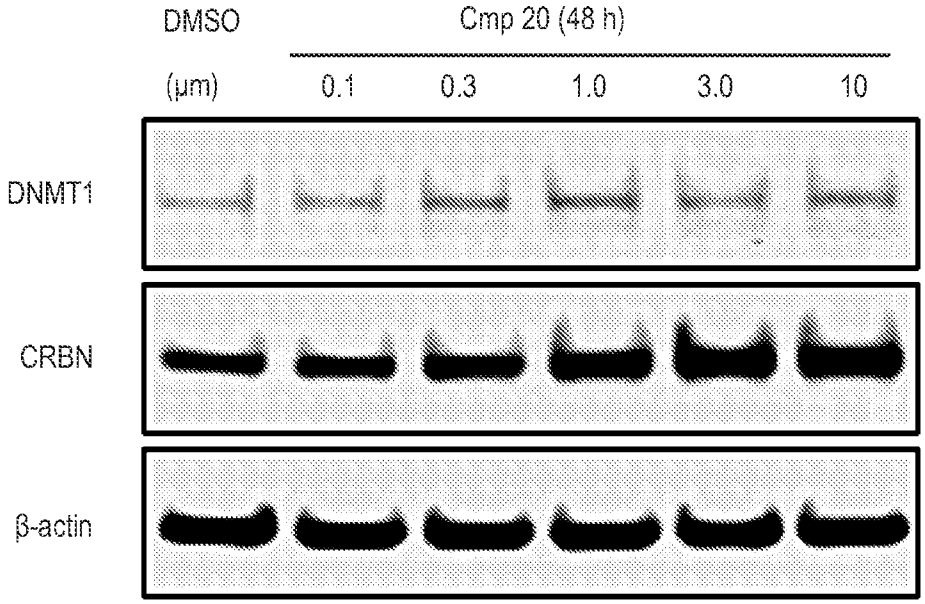
DMSO
Cmp 20 (48 h)
(μm)
0.1
0.3
1.0
3.0
10
DNMT1
CRBN
β-actin

FIG. 10

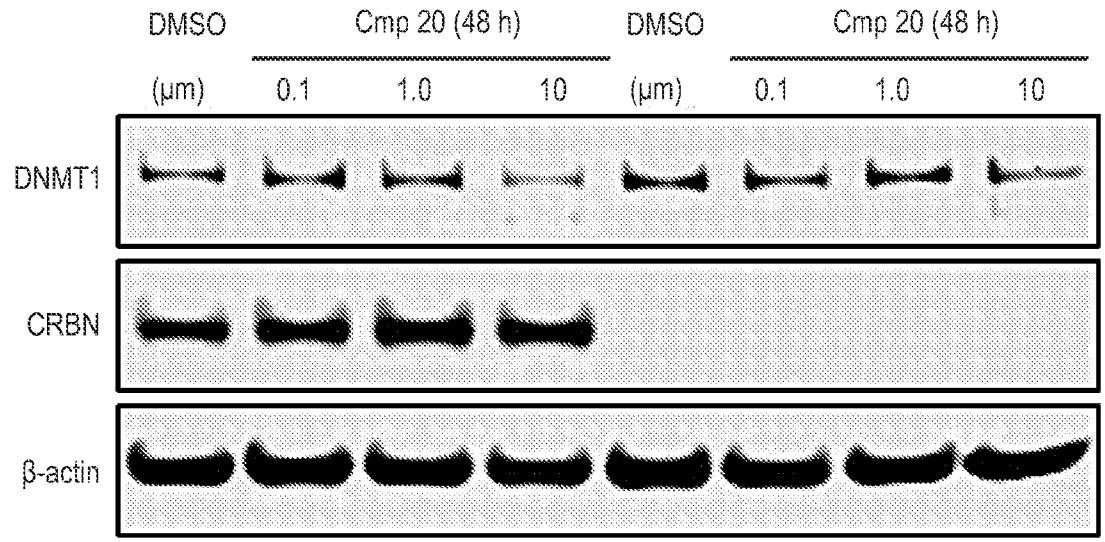

FIG. 11

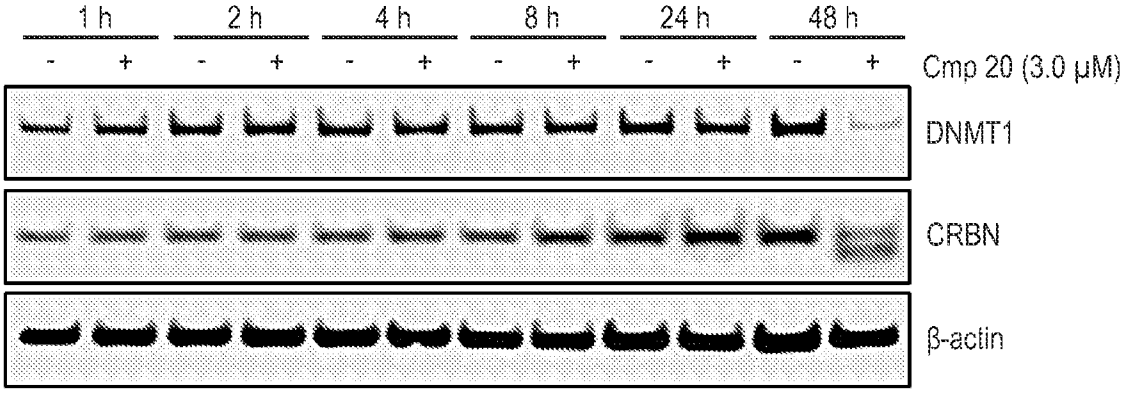

FIG. 12