

SMALL MOLECULE DEGRADERS OF HELIOS AND METHODS OF USE**RELATED APPLICATIONS**

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No: 62/928,139, filed October 30, 2019, U.S. Provisional Application No: 63/035,272, filed June 5, 2020, and U.S. Provisional Application No: 63/047,411, filed July 2, 2020, each of which are incorporated herein by reference in their entireties.

GOVERNMENT LICENSE RIGHTS

[0002] This invention was made with government support under grant numbers R01 CA21460803 awarded by the National Institute of Health (NIH). The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

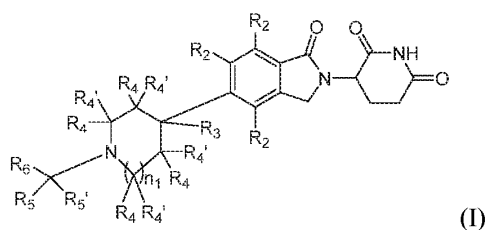
[0003] Imide molecules, such as thalidomide and its analogs, bind to Cereblon (CRBN), a substrate adaptor for the ubiquitously expressed cullin ring ligase 4 (CUL4)-RBX1-DDB1-CRBN (CUL4CRBN) E3 ligase (Kronke *et al.*, Science 343:301-305 (2014); Ito *et al.*, Science 327:1345-1350 (2010)). This results in the recruitment, ubiquitination, and the subsequent proteasomal degradation of neo-substrates, namely Ikaros (IKZF1) and Aiolos (IKZF3), but not any other members of the IKZF zinc finger transcription factor family. CC-885, an imide analog, is predicted to have some activity in inducing Helios degradation, but also induces degradation of GSPT1, a key translation termination factor (Matyskiela *et al.*, Nature 535:252-257 (2016)).

[0004] Helios (IKZF2), a member of the IKZF family, is a critical regulator of T cell activity and function. Genetic deletion of Helios resulted in an enhanced anti-tumor immune response (Kim *et al.*, Science 350:334-339 (2015)). Notably, Helios is highly expressed in regulatory T cells (Elkord *et al.*, Expert Opin. Biol. Ther. 12:1423-1425 (2012)), a subpopulation of T cells that restricts the activity of effector T cells. Selective deletion of Helios in regulatory T cells resulted in both loss of suppressive activity and acquisition of effector T cell functions (Najagawa *et al.*, Proc. Natl. Acad. Sci. USA 113:6248-6253 (2016); Yates *et al.*, Proc. Natl. Acad. Sci. USA 115:2162-2167 (2018)). Therefore, Helios is a critical factor in restricting T cell effector function in Tregs.

[0005] Helios expression has also been reported to be upregulated in ‘exhausted’ T cells, in the settings of both chronic viral infections (Crawford *et al.*, *Immunity* 40:289-302 (2014), Doering *et al.*, *Immunity* 37:1130-1144 (2012); Scott-Browne *et al.*, *Immunity* 45:1327-1340 (2016)) and tumors (Martinez *et al.*, *Immunity* 42:265-278 (2015); Mognol *et al.*, *Proc. Natl. Acad. Sci. USA* 114:E2776-E2785 (2017); Pereira *et al.*, *J. Leukoc. Biol.* 102:601-615 (2017); Singer *et al.*, *Cell* 166:1500-1511 (2016); Schietinger *et al.*, *Immunity* 45:389-401 (2016)), as well as in dysfunctional chimeric antigen receptor (CAR) T cells (Long *et al.*, *Nat. Med.* 21:581-590 (2015)) 16). Overexpression or aberrant expression of Helios and various splice isoforms have been reported in several hematological malignancies, including T cell leukemias and lymphomas (Nakase *et al.*, *Exp. Hematol.* 30:313-317 (2002); Tabayashi *et al.*, *Cancer Sci.* 98:182-188 (2007); Asanuma *et al.*, *Cancer Sci.* 104:1097-1106 (2013)). Moreover, knockdown of Helios in a model of mixed lineage leukemia (MLL)-driven myeloid leukemia potently suppressed proliferation and increased cell death (Park *et al.*, *J. Clin. Invest.* 125:1286-1298 (2015); Park *et al.*, *Cell Stem Cell* 24:153-165 (2019)).

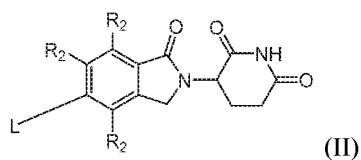
SUMMARY OF THE INVENTION

[0006] A first aspect of the present invention is directed to a compound having a structure represented by formula (I):



wherein R₂, R₃, R₄, R₄', R₅, R₅', R₆, and n₁ are as defined herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0007] A second aspect of the present invention is directed to a compound having a structure represented by formula (II):



wherein L and R₂ are as defined herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0008] Another aspect of the present invention is directed to a pharmaceutical composition that includes a therapeutically effective amount of a compound of formula (I) or (II) or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises a co-crystal of the compound.

[0009] A further aspect of the present invention is directed to methods of treating diseases or disorders that would benefit from IKZF2 (Helios) degradation.

[0010] In some embodiments, the disease or disorder is cancer. In some embodiments, the cancer is T cell leukemia, T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloid leukemia, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, or carcinoid.

[0011] As demonstrated in the working examples, compounds of the present invention exhibit potent degradation of IKZF2 (Helios).

[0012] Although not intending to be bound by any particular theory of operation, it is believed that inventive compounds may enhance an anti-tumor immune response by enabling regulatory T cells to assume functions of effector T cells, and by rescuing effector T cell function in exhausted T cells or CAR-T cells.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1A-FIG. 1C are plots of the cellular IKZF2-degradation green fluorescent protein (GFP) assay for inventive compounds 36, 72, and 79, where IC₅₀ values show the combinatorial effect of cell permeability and compounds' ability to degrade IKZF2 in the cell.

DETAILED DESCRIPTION OF THE INVENTION

[0014] 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 invention.

[0015] 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.

[0016] 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.”

[0017] 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 claimed invention.

[0018] With respect to compounds of the present invention, and to the extent the following terms are used herein to further describe them, the following definitions apply.

[0019] As used herein, the term “alkyl” refers to a saturated linear or branched-chain monovalent hydrocarbon radical. In one embodiment, the alkyl radical is a C₁-C₁₈ group. In other embodiments, the alkyl radical is a C₀-C₆, C₀-C₅, C₀-C₃, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₅, C₁-C₄ or C₁-C₃ group (wherein C₀ 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, 3,3-dimethyl-2-butyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl. In some embodiments, an alkyl group is a C₁-C₃ alkyl group. In some embodiments, an alkyl group is a C₁-C₂ alkyl group, or a methyl group.

[0020] 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 12 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 8 carbon atoms (C₁-C₈

alkylene). In other embodiments, an alkylene group contains one to 5 carbon atoms (C₁-C₅ alkylene). In other embodiments, an alkylene group contains one to 4 carbon atoms (C₁-C₄ alkylene). In other embodiments, an alkylene contains one to three carbon atoms (C₁-C₃ alkylene). In other embodiments, an alkylene group contains one to two carbon atoms (C₁-C₂ alkylene). In other embodiments, an alkylene group contains one carbon atom (C₁ alkylene).

[0021] 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 one example, the alkenyl radical is a C₂-C₁₈ group. In other embodiments, the alkenyl radical is a C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃ 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.

[0022] As used herein, the term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical with at least one carbon-carbon triple bond. In one example, the alkynyl radical is a C₂-C₁₈ group. In other examples, the alkynyl radical is C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃. Examples include ethynyl prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl and but-3-ynyl.

[0023] 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. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbyl groups covalently linked by an oxygen. 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.

[0024] As used herein, the term "halogen" (or "halo" or "halide") refers to fluorine, chlorine, bromine, or iodine.

[0025] 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.

[0026] 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 20 carbon atoms, that is alone or part of a larger moiety (*e.g.*, an alkylcarbocyclic group). The term carbocyclyl includes mono-, bi-, tri-, fused, bridged, and spiro-ring systems, and combinations thereof. In one embodiment, carbocyclyl includes 3 to 15 carbon atoms (C₃-C₁₅). In one embodiment, carbocyclyl includes 3 to 12 carbon atoms (C₃-C₁₂). In another embodiment, carbocyclyl includes C₃-C₈, C₃-C₁₀ or C₅-C₁₀. In another embodiment, carbocyclyl, as a monocycle, includes C₃-C₈, C₃-C₆ or C₅-C₆. In some embodiments, carbocyclyl, as a bicycle, includes C₇-C₁₂. In another embodiment, carbocyclyl, as a spiro system, includes C₅-C₁₂. Representative examples of monocyclic carbocyclyls include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, perdeuteriocyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, phenyl, and cyclododecyl; bicyclic carbocyclyls having 7 to 12 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 carbocyclyl 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.

[0027] 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.

[0028] 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 6-18 carbon atoms. In another embodiment, aryl includes groups having 6-10 carbon atoms. Examples of aryl groups include phenyl, naphthyl, anthracyl, biphenyl, phenanthrenyl, naphthacenyl, 1,2,3,4-tetrahydronaphthalenyl, 1H-indenyl, 2,3-dihydro-1H-indenyl, naphthyridinyl, 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.

[0029] 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.

[0030] 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, or 4) carbon atoms have been replaced with a heteroatom (*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 15 membered heterocyclyl ring system. 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 14 membered heteroaryl ring system. The term heterocyclyl also includes C₃-C₈ heterocycloalkyl, which is a saturated or partially unsaturated mono-, bi-, or spiro-ring system containing 3-8 carbons and one or more (1, 2, 3 or 4) heteroatoms.

[0031] 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 nitrogen, sulfur or oxygen. In some embodiments, heterocyclyl includes 4- to 6-membered monocycles having one or more heteroatoms selected from nitrogen, sulfur or oxygen. In some embodiments, heterocyclyl includes 3-membered monocycles. In some embodiments, heterocyclyl includes 4-membered monocycles. In some embodiments, heterocyclyl includes 5-6 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, SO₂), and any nitrogen heteroatom may optionally be quaternized (*e.g.*, [NR₄]⁺Cl⁻, [NR₄]⁺OH⁻). Representative examples of heterocyclyls include oxiranyl, aziridinyl, thiiranyl, azetidiny, 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, tetrahydrobenzimidazolyl, 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, thiatiazinyl, oxatriazinyl, dithiadiazinyl, imidazoliny, 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, pyrazolidinylimidazoliny, 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-onyl, azaspiro[5.5]undecanyl, tetrahydroindolyl, octahydroindolyl, tetrahydroisindolyl, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl. Examples of 5-membered heterocyclyls containing a sulfur or oxygen atom and one to three nitrogen atoms

are thiazolyl, including thiazol-2-yl and thiazol-2-yl N-oxide, thiadiazolyl, including 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl, oxazolyl, for example oxazol-2-yl, and oxadiazolyl, such as 1,3,4-oxadiazol-5-yl, and 1,2,4-oxadiazol-5-yl. Example 5-membered ring heterocyclyls containing 2 to 4 nitrogen atoms include imidazolyl, such as imidazol-2-yl; triazolyl, such as 1,3,4-triazol-5-yl; 1,2,3-triazol-5-yl, 1,2,4-triazol-5-yl, and tetrazolyl, such as 1H-tetrazol-5-yl. Representative examples of benzo-fused 5-membered heterocyclyls are benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl. Example 6-membered heterocyclyls contain one to three nitrogen atoms and optionally a sulfur or oxygen atom, for example pyridyl, such as pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl; pyrimidyl, such as pyrimid-2-yl and pyrimid-4-yl; triazinyl, such as 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl; pyridazinyl, in particular pyridazin-3-yl, and pyrazinyl. The pyridine N-oxides and pyridazine N-oxides and the pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyridazinyl and the 1,3,4-triazin-2-yl groups, are yet other examples of heterocyclyl groups. In some embodiments, a heterocyclic group includes a heterocyclic 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 heterocyclic ring, and in some embodiments wherein the point of attachment is a heteroatom contained in the heterocyclic ring.

[0032] Therefore, the term heterocyclic embraces N-heterocyclyl groups which as used herein refer to a heterocyclyl group containing at least one nitrogen 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, pyrazolidinyl, imidazolinyl and 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-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.

[0033] 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 14 ring atoms, wherein at least one ring is aromatic and contains at least one heteroatom. In one embodiment, heteroaryl includes 5-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. 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, 1,2,3-triazol-5-yl, and pyrid-2-yl N-oxide. 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, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl 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, 2 or 3) 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.

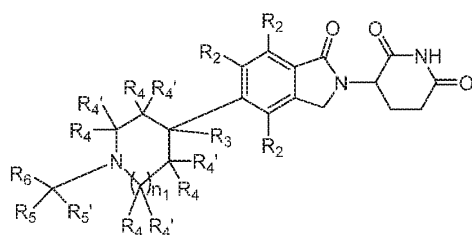
[0034] Therefore, the term heteroaryl embraces N-heteroaryl groups which as used herein refer to a heteroaryl group as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl group to the rest of the molecule is through a nitrogen atom in the heteroaryl group. 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^c-heteroaryl, wherein R^c 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^c-heteroaryl, where R^c is an alkylene group as defined above.

[0035] Unless stated otherwise, and to the extent not further defined for any particular group(s), any of the groups described herein may be substituted or unsubstituted. As used herein, the term “substituted” broadly refers to all permissible substituents with the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.* a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. Representative substituents include halogens, hydroxyl groups, and any other organic groupings containing any number of carbon atoms, *e.g.*, 1-14 carbon atoms, and which may include one or more (*e.g.*, 1, 2, 3, or 4) heteroatoms such as oxygen, sulfur, and nitrogen grouped in a linear, branched, or cyclic structural format.

[0036] To the extent not disclosed otherwise for any particular group(s), representative examples of substituents may include alkyl, substituted alkyl (*e.g.*, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₁), alkoxy (*e.g.*, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₁), substituted alkoxy (*e.g.*, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₁), haloalkyl (*e.g.*, CF₃), alkenyl (*e.g.*, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₂), substituted alkenyl (*e.g.*, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₂), alkynyl (*e.g.*, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₂), substituted alkynyl (*e.g.*, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₂), cyclic (*e.g.*, C₃-C₁₂, C₅-C₆), substituted cyclic (*e.g.*, C₃-C₁₂, C₅-C₆), carbocyclic (*e.g.*, C₃-C₁₂, C₅-C₆), substituted carbocyclic (*e.g.*, C₃-C₁₂, C₅-C₆), heterocyclic (*e.g.*, C₃-C₁₂, C₅-C₆), substituted heterocyclic (*e.g.*, C₃-C₁₂, C₅-C₆), aryl (*e.g.*, benzyl and phenyl), substituted aryl (*e.g.*, substituted benzyl or phenyl), heteroaryl (*e.g.*, pyridyl or pyrimidyl), substituted heteroaryl (*e.g.*, substituted pyridyl or pyrimidyl), aralkyl (*e.g.*, benzyl), substituted aralkyl (*e.g.*, substituted benzyl), halo, hydroxyl, aryloxy (*e.g.*, C₆-C₁₂, C₆), substituted aryloxy (*e.g.*, C₆-C₁₂, C₆), alkylthio (*e.g.*, C₁-C₆), substituted alkylthio (*e.g.*, C₁-C₆), arylthio (*e.g.*, C₆-C₁₂, C₆), substituted arylthio (*e.g.*, C₆-C₁₂, C₆), cyano, carbonyl, substituted carbonyl, carboxyl, substituted carboxyl, amino, substituted amino, amido, substituted amido, thio, substituted thio, sulfinyl, substituted sulfinyl, sulfonyl, substituted sulfonyl, sulfonamide, substituted sulfonamide, sulfonamide, substituted sulfonamide, urea, substituted urea, carbamate, substituted carbamate, amino acid, and peptide groups.

[0037] In one aspect, compounds of the invention are represented by formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,

wherein:

each R_2 is independently selected from the group consisting of hydrogen, amino, cyano, halo, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl;

R_3 is selected from the group consisting of hydrogen, amino, hydroxyl, cyano, halogen, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl, or

R_2 and R_3 , together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, wherein said cycloalkyl, heterocycloalkyl is further optionally and independently substituted by one or more identical or different R_{15} groups;

each R_4 and R_4' are independently selected from the group consisting of hydrogen, hydroxyl, amino, amido, carbonyl, cyano, halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)hydroxyalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl; wherein said alkyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups, or

R_3 and R_4 , together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R_4 and R_4' , together with the same carbon atom to which they are attached, form a spiro (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R_4 and R_4' , when on different carbon atoms, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

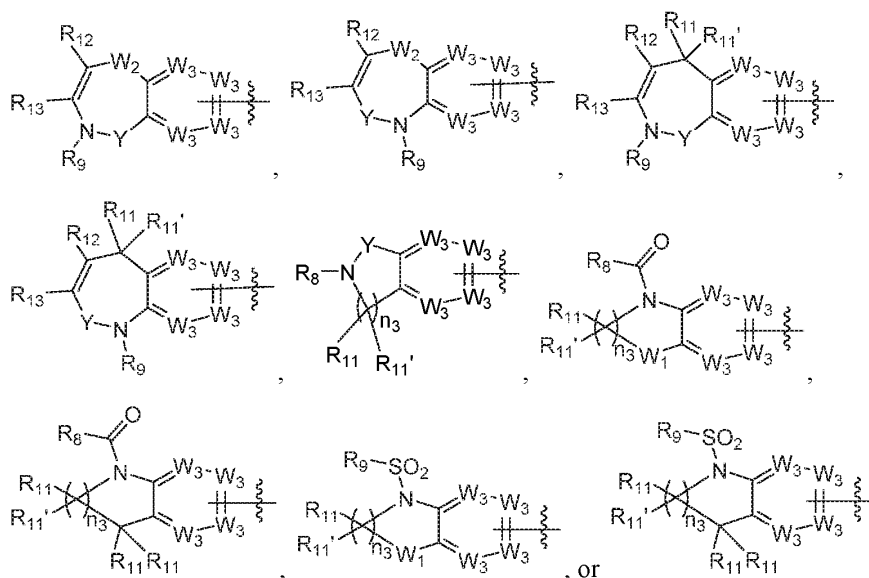
R_4 and R_4' , when on adjacent atoms, together with the atoms to which they are attached, form a (C₆-C₁₀)aryl or a 5- or 6-membered heteroaryl; wherein said cycloalkyl, heterocycloalkyl,

aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups;

R_5 and R_5' are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₁-C₆)hydroxyalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups;

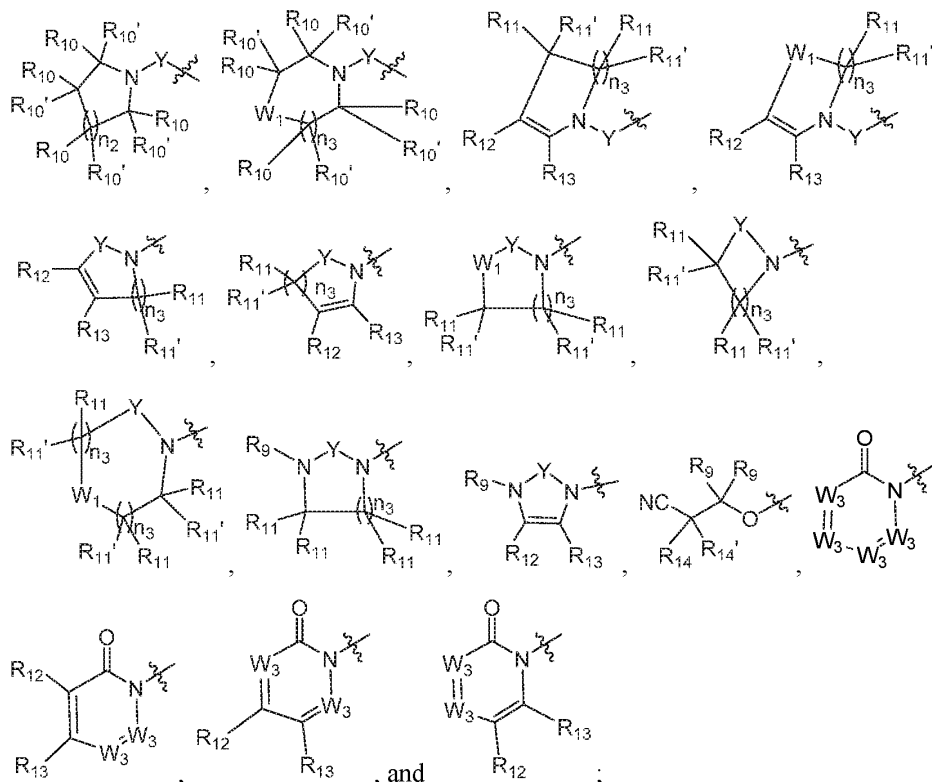
R_6 is optionally substituted aryl or heteroaryl, or an R_7 -substituted aryl or a R_7 -substituted heteroaryl; wherein said R_7 -substituted aryl or R_7 -substituted heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups,

or R_6 is:



provided that when R_6 is optionally substituted aryl or heteroaryl, at least one of R_4 and R_4' is independently selected from the group consisting of alkynyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkynyl, aryl, or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups;

R₇ is selected from the group consisting of -C(O)NR₈R₉, -SO₂NR₈R₉, -S(O)(=NH)R₉, -OR₈, -N(R₈R₉), -N(R₉)C(O)R₈, -N(R₉)SO₂R₉, -N(R₉)C(O)N(R₉)₂, -P(O)(R₉)₂, -N(R₉)S(O)₂N(R₉)₂,



R₈ is selected from the group consisting of (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₉ is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₁₀ and R_{10'} are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, halo, cyano, -N(R₉)₂, -OR₉, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl, provided at least one R₁₀ and one R_{10'}, when attached to the same carbon atom, form a spiro 4- to 7-membered

heterocycle or a 3- to 7-membered carbocycle, or when attached to different carbon atoms, form a heterocycle or carbocycle, and wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups;

each R_{11} and R_{11}' are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, halo, cyano, -N(R₉)₂, -OR₉, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups, or

R_{11} and R_{11}' , together with the same carbon atom to which they are attached, form a spiro (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R_{11} and R_{11}' , when on different carbon atoms, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group; wherein said cycloalkyl, or heterocycloalkyl is further optionally and independently substituted by one or more identical or different R_{15} groups;

R_{12} and R_{13} , together with the carbon atoms to which they are attached, form a (C₆-C₁₀)aryl, or a monocyclic or bicyclic 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups;

R_{14} and R_{14}' , together with the same carbon atom to which they are attached, form a spiro 4- to 7-membered heterocycloalkyl, or a (C₃-C₇)cycloalkyl; wherein said cycloalkyl or heterocycloalkyl is further optionally and independently substituted by one or more identical or different R_{15} groups;

R_{15} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, cycloalkyl, heterocycloalkyl, hydroxy, alkoxy, cycloalkoxy, heterocycloalkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyloxy, alkyenyloxy, alkynyloxy, amino, alkylamino, cycloalkylamino, heterocycloalkylamino, arylamino, heteroarylamino, aralkylamino, N-alkyl-N-aryl amino, N-alkyl-N-heteroaryl amino, N-alkyl-N-aralkyl amino, hydroxyalkyl, aminoalkyl, alkylthio, haloalkylthio, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocycloalkylsulfonyl, arylsulfonyl, heteroaryl sulfonyl, aminosulfonyl, alkylaminosulfonyl, cycloalkylaminosulfonyl, heterocycloalkylaminosulfonyl,

arylaminosulfonyl, heteroarylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, N-alkyl-N-heteroarylaminosulfonyl, formyl, alkylcarbonyl, haloalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylsulfonylamino, haloalkylsulfonylamino, cycloalkylsulfonylamino, heterocycloalkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, aralkylsulfonylamino, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylsulfonylamino, aminocarbonyl, alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, N-alkyl-N-heteroarylaminocarbonyl, cyano, nitro, azido, phosphinyl, phosphoryl including phosphine oxide and phosphonate, cyclic acetal, 4- to 7-membered heterocycloalkyl which contains at least one nitrogen atom and is linked via the nitrogen atom, aryl, heteroaryl, and where two adjacent R₁₅ taken together with the respective atoms to which each is attached form an aryl, a heteroaryl, a 5- to 8-membered cycloalkyl or a 5- to 8-membered heterocycloalkyl;

W₁ is selected from the group consisting of -O-, -S- and -NR₉-;

W₂ is selected from the group consisting of -O-, -S-, -SO₂-, -C(O)- and -NR₉-;

each W₃ is independently selected from the group consisting of nitrogen, CR₁₁, and a carbon atom that is the point of attachment;

Y is selected from the group consisting of -SO₂- and -C(O)-;

n₁ is 0, 1 or 2;

n₂ is 0, 1, 2 or 3; and

n₃ is independently 1, 2 or 3.

[0038] In some embodiments, compounds are represented by formula I or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R₂ is hydrogen, halo or (C₁-C₆)alkyl;

R₃ is selected from the group consisting of hydrogen, halogen, (C₁-C₆)alkyl and (C₁-C₆)haloalkyl;

each R₄ and R₄' are independently selected from the group consisting of hydrogen, amido, halogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl and (C₂-C₆)alkynyl; wherein said alkyl, alkynyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups, or

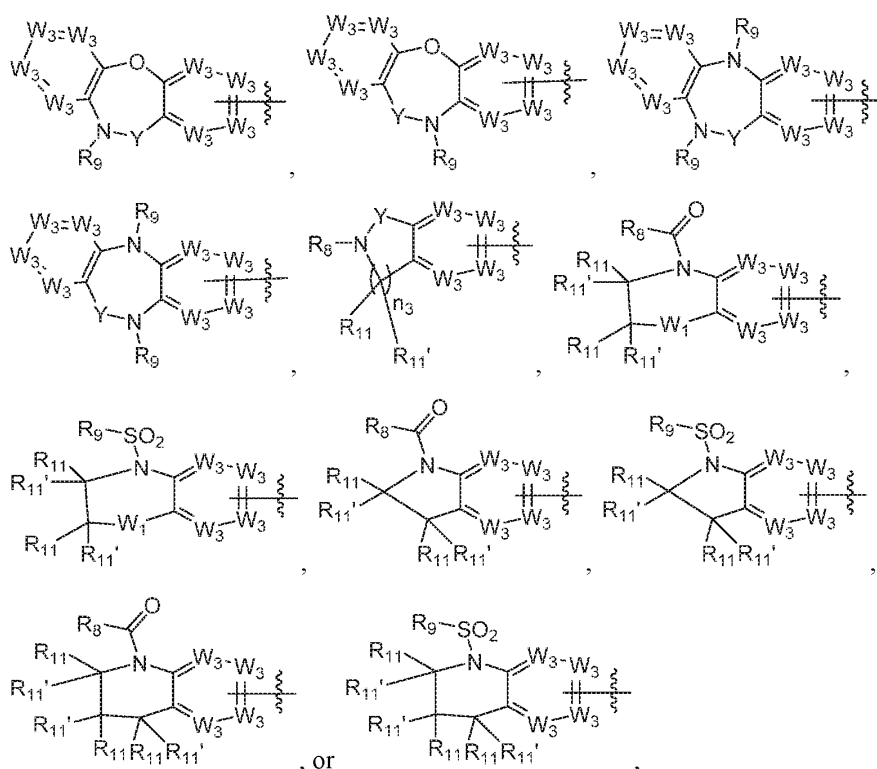
R₄ and R₄', together with the same carbon atom to which they are attached, form a spiro (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R₄ and R₄', when on different carbon atoms, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group; wherein said cycloalkyl or heterocycloalkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₅ and R₅' are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl and (C₁-C₆)hydroxyalkyl; wherein said alkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₆ is optionally substituted aryl or heteroaryl, or R₆ is a R₇-substituted aryl or a R₇-substituted heteroaryl; wherein said R₇-substituted aryl or R₇-substituted heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

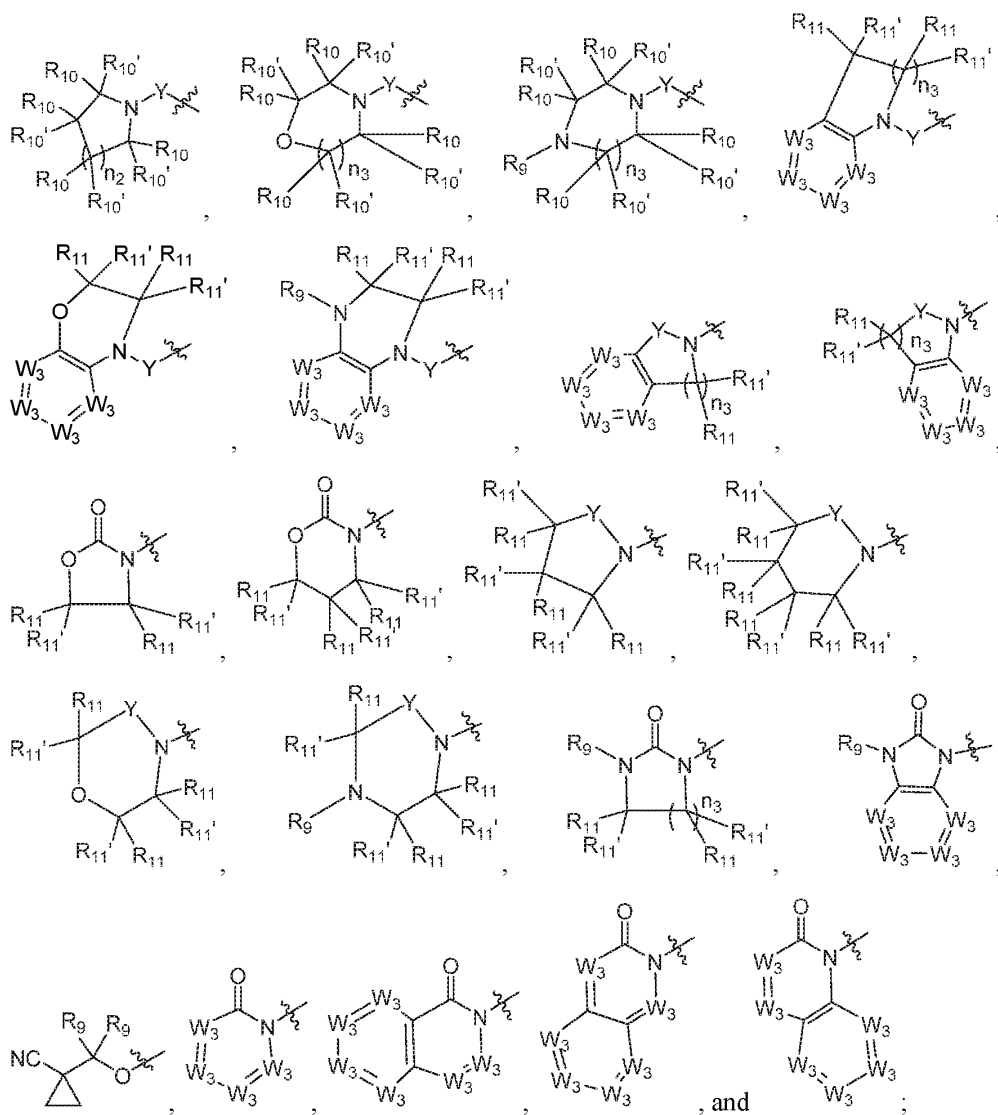
or R₆ is:



provided that when R₆ is optionally substituted aryl or heteroaryl, at least one of R₄ or R₄' is independently selected from the group consisting of alkynyl, (C₆-C₁₀)aryl, and monocyclic

and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkynyl, aryl, or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups;

R_7 is selected from the group consisting of $-C(O)NR_8R_9$, $-SO_2NR_8R_9$, $-S(O)(=NH)R_9$, $-OR_8$, $-N(R_8R_9)$, $-N(R_9)C(O)R_8$, $-N(R_9)SO_2R_9$, $-N(R_9)C(O)N(R_9)_2$, $-P(O)(R_9)_2$, $-N(R_9)S(O)_2N(R_9)_2$,



R₈ is selected from the group consisting of (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₉ is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₁₀ and R_{10'} are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl and halo, provided at least one R₁₀ and one R_{10'} when attached to the same carbon atom forms a spiro 4- to 7-membered heterocycle or a 3- to 7-membered carbocycle, or when attached to different carbon atoms, forms a 4- to 7-membered heterocycle or a 3- to 7-membered carbocycle, wherein said alkyl, heterocycle, or carbocycle is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₁₁ and R_{11'} are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, and halo; wherein said alkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups; or

R₁₁ and R_{11'}, together with the same carbon atom to which they are attached, form a spiro (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R₁₁ and R_{11'}, when on different carbon atoms, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group; wherein said cycloalkyl, or heterocycloalkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₁₂ and R₁₃, together with the carbon atoms to which they are attached, form a (C₆-C₁₀)aryl or a monocyclic or bicyclic 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₁₄ and R_{14'}, together with the same carbon atom to which they are attached, form a spiro 4- to 7-membered heterocycloalkyl, or a (C₃-C₇)cycloalkyl; wherein said cycloalkyl or

heterocycloalkyl is further optionally and independently substituted by one or more identical or different R_{15} groups;

W_1 is selected from the group consisting of -O-, -S- and -NR₉-;

W_2 is selected from the group consisting of -O-, -S- and -NR₉-;

each W_3 is independently selected from the group consisting of nitrogen, CR₁₁, and a carbon atom that is the point of attachment;

Y is selected from the group consisting of -SO₂- and -C(O)-;

n_1 is 0, 1 or 2;

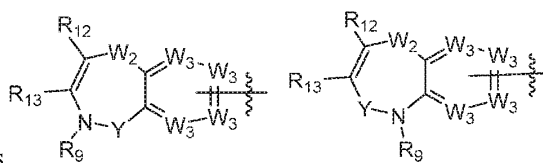
n_2 is 0, 1, 2 or 3; and

n_3 is independently 1, 2 or 3.

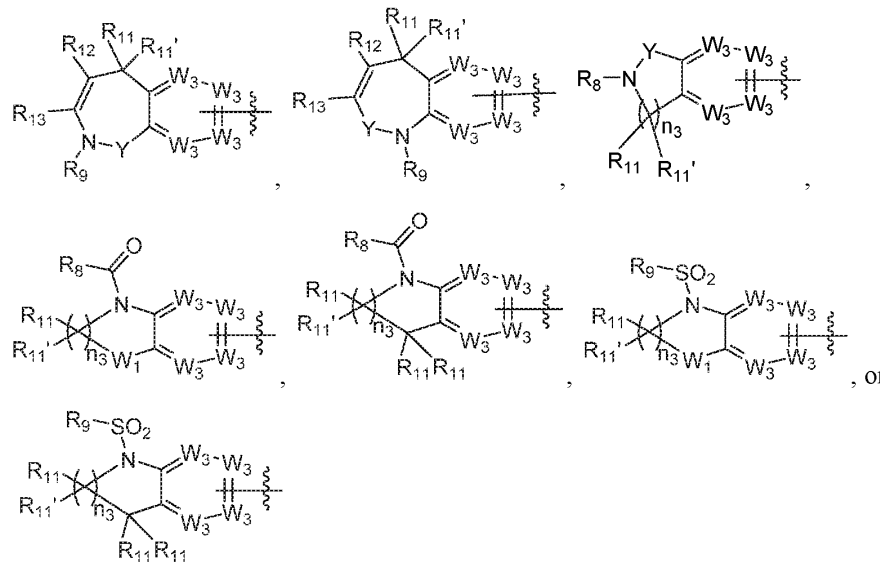
[0039] In some embodiments, R_2 is hydrogen.

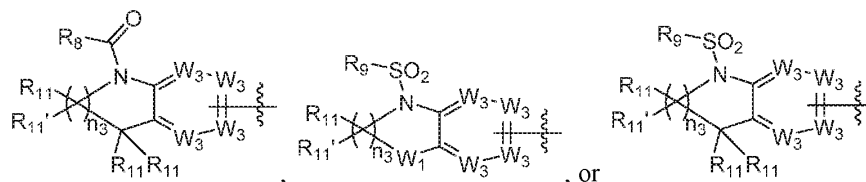
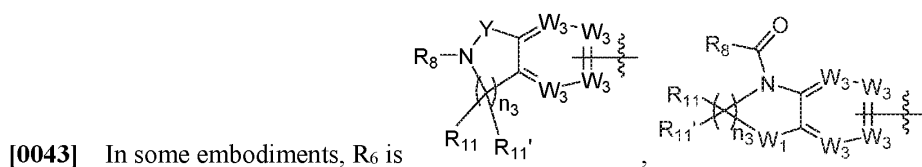
[0040] In some embodiments, R_3 is independently selected from the group consisting of amino, hydroxyl, cyano, halogen, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl.

[0041] In some embodiments, R_5 and R_5' are independently hydrogen or methyl.



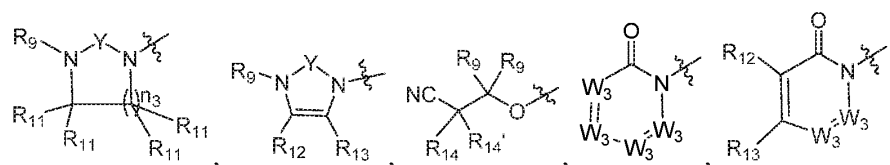
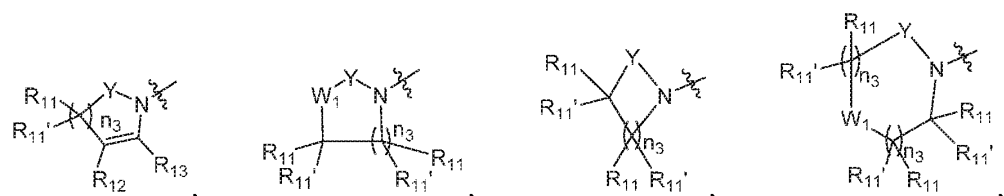
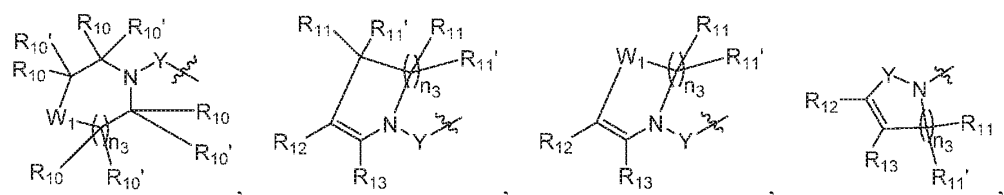
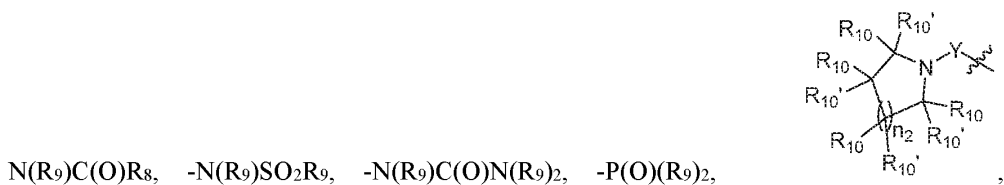
[0042] In some embodiments, R_6 is

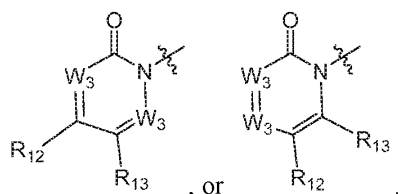




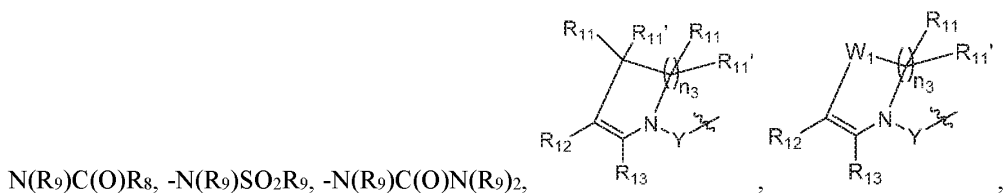
[0044] In some embodiments, R_6 is a R_7 -substituted aryl or a R_7 -substituted heteroaryl; wherein said R_7 -substituted aryl or R_7 -substituted heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups.

[0045] In some embodiments, R_7 is $-C(O)NR_8R_9$, $-SO_2NR_8R_9$, $-OR_8$, $-N(R_8R_9)$, $-$

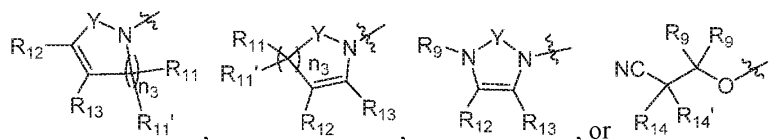




[0046] In some embodiments, R₇ is -C(O)NR₈R₉, -SO₂NR₈R₉, -OR₈, -N(R₈R₉), -



N(R₉)C(O)R₈, -N(R₉)SO₂R₉, -N(R₉)C(O)N(R₉)₂,



[0047] In some embodiments, W₁ is -O-.

[0048] In some embodiments, W₁ -NR₉-.

[0049] In some embodiments, W₃ is nitrogen

[0050] In some embodiments, W₃ is CR₁₁.

[0051] In some embodiments, W₃ is a carbon atom that is the point of attachment.

[0052] In some embodiments, Y is -SO₂-.

[0053] In some embodiments, Y is -C(O)-.

[0054] In some embodiments, n₁ is 0.

[0055] In some embodiments, n₁ is 1.

[0056] In some embodiments, n₁ is 2.

[0057] In some embodiments, n₂ is 0.

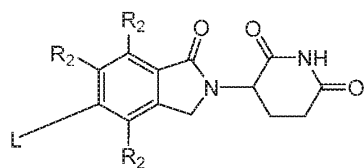
[0058] In some embodiments, n₂ is 1.

[0059] In some embodiments, n₂ is 2.

[0060] In some embodiments, n₂ is 3.

[0061] In some embodiments, each R₂ is hydrogen, R₃ is hydrogen or hydroxyl, R₄ and R₄' are each hydrogen, halo, or (C₁-C₆)alkyl, R₅ and R₅' are each hydrogen, and n₁ is 1.

[0062] In a second aspect, compounds of the invention are represented by formula (II):

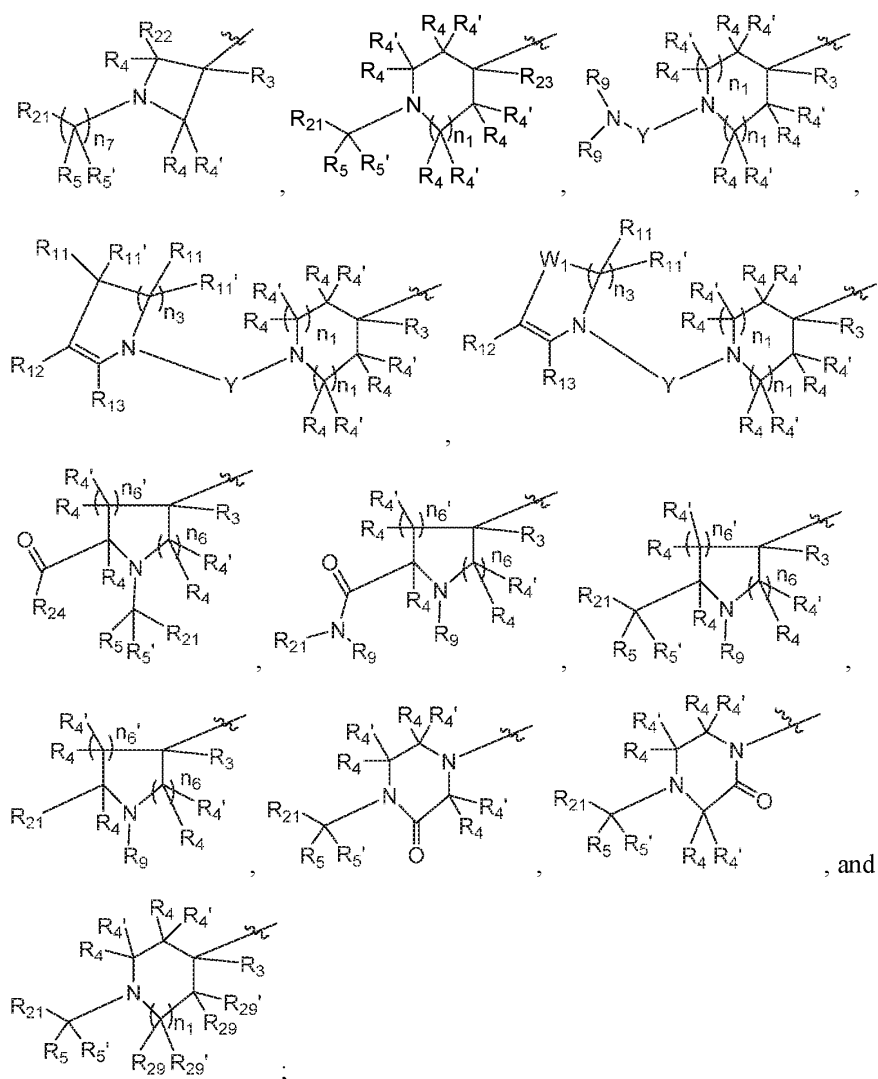


(II),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,

wherein:

L is selected from the group consisting of:



each R₂ is independently selected from the group consisting of hydrogen, amino, cyano, halo, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl;

R₃ is selected from the group consisting of hydrogen, amino, hydroxyl, cyano, halogen, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl, or

R₃ and R₄, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R₂ and R₃, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, wherein said cycloalkyl, heterocycloalkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₄ and R₄' are independently selected from the group consisting of hydrogen, hydroxyl, amino, amido, carbonyl, cyano, halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)hydroxyalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl; wherein said alkyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups, or

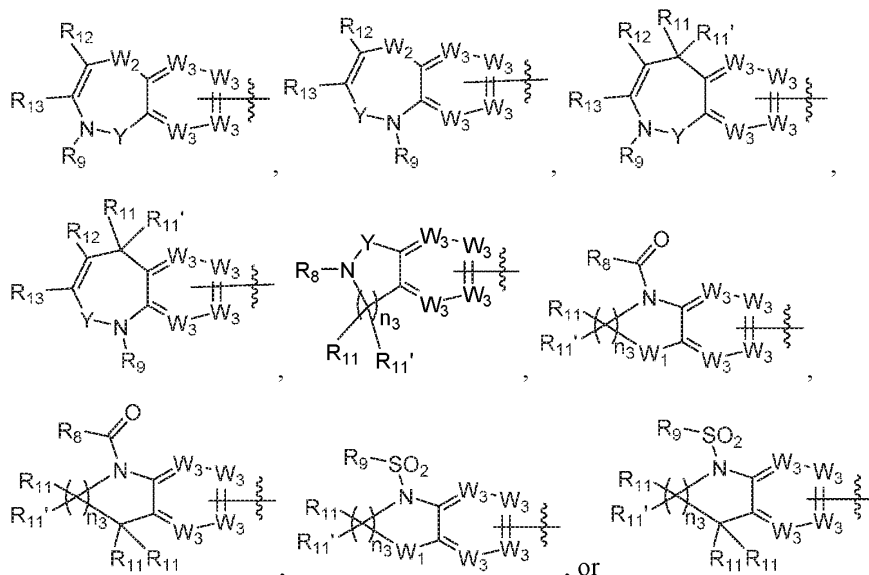
R₄ and R₄', together with the same carbon atom to which they are attached, form a spiro (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R₄ and R₄', when on different carbon atoms, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R₄ and R₄', when on adjacent atoms, together with the atoms to which they are attached, form a (C₆-C₁₀)aryl or a 5- or 6-membered heteroaryl; wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

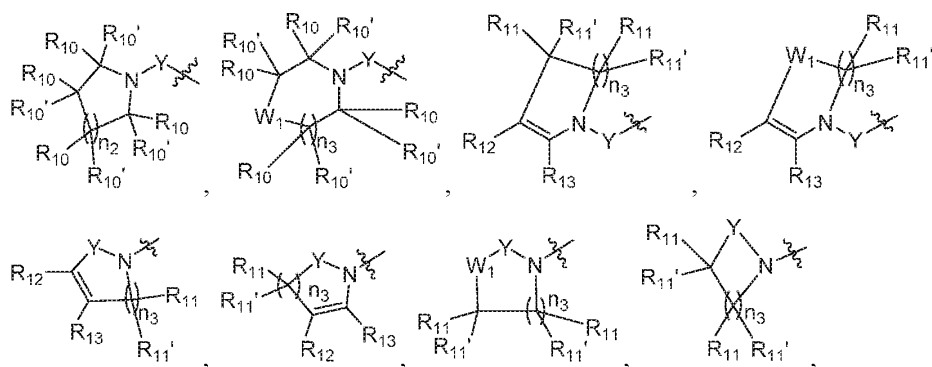
R₅ and R₅' are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₁-C₆)hydroxyalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

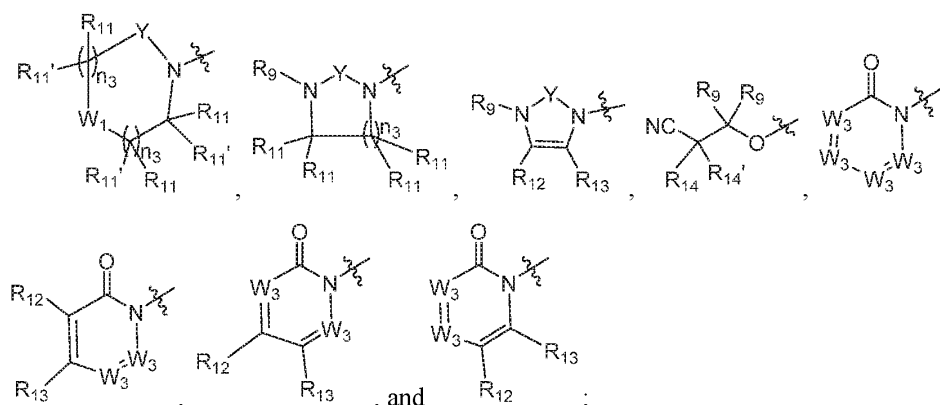
R₆ is optionally substituted aryl or heteroaryl, or R₆ is a R₇-substituted aryl or a R₇-substituted heteroaryl; wherein said R₇-substituted aryl or R₇-substituted heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups; or R₆ is:



provided that when R₆ is optionally substituted aryl or heteroaryl, at least one of R₄ or R₄' is independently selected from the group consisting of alkynyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkynyl, aryl, or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₇ is selected from the group consisting of -C(O)NR₈R₉, -SO₂NR₈R₉, -S(O)(=NH)R₉, -OR₈, -N(R₈R₉), -N(R₉)C(O)R₈, -N(R₉)SO₂R₉, -N(R₉)C(O)N(R₉)₂, -P(O)(R₉)₂, -N(R₉)S(O)₂N(R₉)₂,





R₈ is selected from the group consisting of (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₉ is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₁₀ and R₁₀' are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, halo, cyano, -N(R)₂, -OR₉, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl, provided at least one R₁₀ and one R₁₀' when attached to the same carbon atom form a spiro 4- to 7-membered heterocycle or a 3- to 7-membered carbocycle, or when attached to different carbon atoms, form a heterocycle or carbocycle, and wherein said alkyl, cycloalkyl, heterocycle, or carbocycle is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₁₁ and R₁₁' are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, halo, cyano, -N(R₉)₂, -OR₉, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups; or

R₁₁ and R_{11'}, together with the same carbon atom to which they are attached, form a spiro (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R₁₁ and R_{11'}, when on different carbon atoms, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group; wherein said cycloalkyl, or heterocycloalkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₁₂ and R₁₃, together with the carbon atoms they are attached, form a (C₆-C₁₀)aryl, or a monocyclic or bicyclic 5- to 10-membered heteroaryl, wherein said aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₁₄ and R_{14'}, together with the same carbon atom they are attached, form a spiro 4- to 7-membered heterocycloalkyl, or a (C₃-C₇)cycloalkyl; wherein said cycloalkyl or heterocycloalkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₁₅ is independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, cycloalkyl, heterocycloalkyl, hydroxy, alkoxy, cycloalkoxy, heterocycloalkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyloxy, alkyenyloxy, alkynyloxy, amino, alkylamino, cycloalkylamino, heterocycloalkylamino, arylamino, heteroarylamino, aralkylamino, N-alkyl-N-arylamine, N-alkyl-N-heteroarylamine, N-alkyl-N-aralkylamine, hydroxyalkyl, aminoalkyl, alkylthio, haloalkylthio, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocycloalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aminosulfonyl, alkylaminosulfonyl, cycloalkylaminosulfonyl, heterocycloalkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, N-alkyl-N-heteroarylaminosulfonyl, formyl, alkylcarbonyl, haloalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxy carbonyl, alkylcarbonyloxy, amino, alkylsulfonylamino, haloalkylsulfonylamino, cycloalkylsulfonylamino, heterocycloalkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, aralkylsulfonylamino, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylsulfonylamino, aminocarbonyl, alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, N-alkyl-N-heteroarylaminocarbonyl, cyano, nitro, azido, phosphinyl, phosphoryl including phosphine oxide and phosphonate, cyclic acetal, 4- to 7-membered heterocycloalkyl which contains at

least one nitrogen atom and is linked via the nitrogen atom, aryl, heteroaryl, and where two adjacent R₁₅ taken together with the respective atoms to which each is bonded form an aryl, or a heteroaryl, or a 5- to 8-membered cycloalkyl or 5- to 8-membered heterocycloalkyl;

R₂₁ is selected from the group consisting of R₆, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said aryl or heteroaryl is optionally and independently substituted by one or more identical or different R₂₅ groups;

R₂₂ is selected from the group consisting alkyl, haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7- membered heterocycloalkyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₂₃ is selected from the group consisting amino, hydroxyl, cyano, halogen, (C₁-C₆)alkyl and (C₁-C₆)haloalkyl, or

R₂₃ and R₄, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7- membered heterocycloalkyl group, or

R₂₃ and R₂, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, wherein said cycloalkyl, heterocycloalkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₂₄ is selected from the group consisting of -N(R₉)₂, and 4- to 7-membered heterocyclalkyl, wherein said heterocyclalkyl contains at least one nitrogen atom and is linked via the nitrogen atom;

R₂₅ is independently selected from the group consisting of (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, -C(O)R₂₆, -(CH₂)₀₋₃C(O)OR₂₆, -C(O)NR₂₆R₂₇, -NR₂₆C(O)R₂₇, -NR₂₆C(O)OR₂₇, -S(O)pNR₂₆R₂₇, -S(O)pR₂₈, (C₁-C₆)hydroxyalkyl, halogen, -OH, -O(CH₂)₁₋₃CN, -(CH₂)₁₋₃CN, -(CR₂₉R_{29'})CN, -NH₂, CN, -O(CH₂)₀₋₃(C₆-C₁₀)aryl, adamantyl, -O(CH₂)₀₋₃-5- or 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, (C₃-C₇)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups; or

wherein two R₂₅ groups when on adjacent atoms, together with the atoms to which they are attached, form an aryl or a 5- or 6-membered heteroaryl, optionally substituted with one or more R₁₅ groups; or

wherein two R₂₅ groups, together with the atoms to which they are attached, form a (C₅-C₇) cycloalkyl ring, or a 5- to 7-membered heterocycloalkyl ring, optionally substituted with one or more R₁₅;

R₂₆ and R₂₇ are independently selected from the group consisting of hydrogen and alkyl;

R₂₈ is selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₂₉ and R_{29'} are independently selected from the group consisting of R₄, provided at least one of R₂₉ and R_{29'}, together with the same carbon atom to which they are attached, form a spiro (C₃-C₇)cycloalkyl; or

R₂₉ and R_{29'}, when on adjacent carbon atoms, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl; wherein said cycloalkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

W₁ is selected from the group consisting of -O-, -S- and -NR₉-;

W₂ is selected from the group consisting of -O-, -S-, -SO₂-, -C(O)- and -NR₉-;

each W₃ is independently selected from the group consisting of nitrogen, CR₁₁, and a carbon atom that is the point of attachment;

Y is selected from the group consisting of -SO₂- and -C(O)-;

n₁ is independently 0, 1 or 2;

n₂ is 0, 1, 2 or 3;

n₃ is independently 1, 2 or 3;

n₆ and n_{6'} are independently 0, 1, 2, 3, 4 or 5, provided n₆ and n_{6'} cannot both be 0;

n₇ is 1 or 2; and

p is 0, 1 or 2.

[0063] In some embodiments, compounds are represented by formula II or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each R₂ is hydrogen, halo or (C₁-C₆)alkyl;

R₃ is selected from the group consisting of hydrogen, halogen, (C₁-C₆)alkyl and (C₁-C₆)haloalkyl;

each R₄ and R₄' are independently selected from the group consisting of hydrogen, amido, halogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl and (C₂-C₆)alkynyl; wherein said alkyl, alkynyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups, or

R₄ and R₄', together with the same carbon atom to which they are attached, form a spiro (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group, or

R₄ and R₄', when on different carbon atoms, together with the atoms to which they are attached, form a (C₃-C₇)cycloalkyl group or a 4- to 7-membered heterocycloalkyl group; wherein said cycloalkyl, heterocycloalkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₅ and R₅' are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl and (C₁-C₆)hydroxyalkyl; wherein said alkyl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₉ is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C₆-C₁₀)aryl, and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₂₁ is selected from the group consisting of R₆, (C₆-C₁₀)aryl and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

R₂₂ is selected from the group consisting of alkyl, (C₆-C₁₀)aryl and monocyclic and/or bicyclic 5- to 10-membered heteroaryl; wherein said alkyl, aryl or heteroaryl is further optionally and independently substituted by one or more, identical or different R₁₅ groups;

R₂₃ is selected from the group consisting of halogen, (C₁-C₆)alkyl and (C₁-C₆)haloalkyl;

R₂₄ is selected from the group consisting of -N(R₉)₂ and 4- to 12-membered heterocyclalkyl, wherein said heterocyclalkyl contains at least one nitrogen atom and is linked via the nitrogen atom;

R₂₅ is independently selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, -C(O)NR₂₆R₂₇, -NR₂₆C(O)R₂₇, -S(O)pNR₂₆R₂₇, -

S(O)pR₂₈, halogen, -O(CH₂)₁₋₃CN, -NH₂, CN, -(CR₂₉R_{29'})CN, -O(CH₂)₀₋₃₋₅₋ or 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, (C₆-C₁₀)aryl, monocyclic and/or bicyclic 5- to 10-membered heteroaryl, (C₃-C₇)cycloalkyl, and 4- to 7-membered heterocycloalkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R₁₅ groups, or two R₂₅ groups when on adjacent atoms, together with the atoms to which they are attached, form an aryl, or a 5- or 6-membered heteroaryl, optionally substituted with one or more R₁₅ groups or

two R₂₅ groups, together with the atoms to which they are attached, form a (C₅-C₇)cycloalkyl or a 5- to 7- membered heterocycloalkyl optionally substituted with one or more R₁₅ groups;

R₂₆ and R₂₇ are independently selected from the group consisting of hydrogen and alkyl;

R₂₈ is selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl and (C₆-C₁₀)aryl; wherein said alkyl, cycloalkyl or aryl is further optionally and independently substituted by one or more identical or different R₁₅ groups;

each R₂₉ and R_{29'} are independently selected from the group consisting of R₄, provided at least one R₂₉ and one R_{29'}, together with the same carbon atom to which they are attached, form a spiro (C₃-C₅)cycloalkyl, or

R₂₉ and R_{29'}, when on adjacent carbon atoms, together with the atoms to which they are attached, form a (C₃-C₅)cycloalkyl that is further optionally and independently substituted by one or more identical or different R₁₅ groups;

n₁ is independently 0, 1 or 2;

n₆ and n_{6'} are independently 0, 1, 2, 3, 4 or 5, provided n₆ and n_{6'} cannot both be 0;

n₇ is 1 or 2;

p is 0, 1 or 2; and

W₁ is selected from the group consisting of -O- and -NR₉-.

[0064] In some embodiments, R₃ is independently selected from the group consisting of amino, hydroxyl, cyano, halogen, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl.

[0065] In some embodiments, R₂₃ is selected from the group consisting of amino, hydroxyl, cyano, halogen, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl.

[0066] In certain embodiments, n₁ is 1.

[0067] In certain embodiments, n₂ is 0, 1 or 2.

[0068] In certain embodiments, n₃ is 1 or 2.

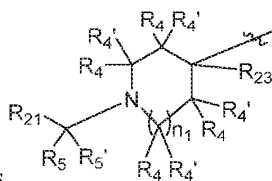
[0069] In certain embodiments, p is 2.

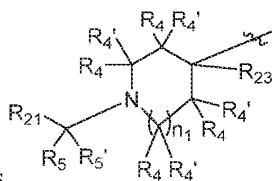
[0070] In some embodiments, each R₂ is hydrogen.

[0071] In some embodiments, R₂₁ is a substituted C₆-aryl, provided said aryl is substituted with at least two R₂₅, and provided two of the R₂₅, when on adjacent atoms, form a 5- or 6-membered heterocyclyl that is substituted with at least one (C₆-C₁₀)aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl that is optionally and independently substituted with one or more R₁₅, or

R₂₁ is a substituted 5- or 6-membered heteroaryl, provided said heteroaryl is substituted with at least two R₂₅, and provided two of the R₂₅, when on adjacent atoms, form a C₆-aryl, or 5- or 6-membered heteroaryl that is substituted with at least one (C₆-C₁₀)aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl that is optionally and independently substituted with one or more R₁₅.

[0072] In some embodiments, R₂ is hydrogen, R₃ is hydrogen or hydroxyl, R₄ and R₄' are each hydrogen, halo, or C(1-6) alkyl, R₅ and R₅' are each hydrogen, and n₁ is 1.



[0073] In some embodiments, L is , R₂ is hydrogen, R₄ and R₄' are each hydrogen, halo, or (C₁-C₆)alkyl, and R₅ and R₅' are each hydrogen.

[0074] In some embodiments, R₂₃ is hydroxyl and n₁ is 1 or 2.

[0075] In some embodiments, R₂₁ is a substituted C₆-aryl, provided said aryl is substituted with at least two R₂₅, and provided two of the R₂₅, when on adjacent atoms, form a 5- or 6-membered heteroaryl that is substituted with at least one (C₆-C₁₀)aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl that is optionally and independently substituted with one or more R₁₅, or

R₂₁ is a substituted 5- or 6-membered heteroaryl, provided said heteroaryl is substituted with at least two R₂₅, and provided two of the R₂₅, when on adjacent atoms, form a C₆-aryl, or 5- or 6-membered heteroaryl that is substituted with at least one (C₆-C₁₀)aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl that is optionally and independently substituted with one or more R₁₅; and

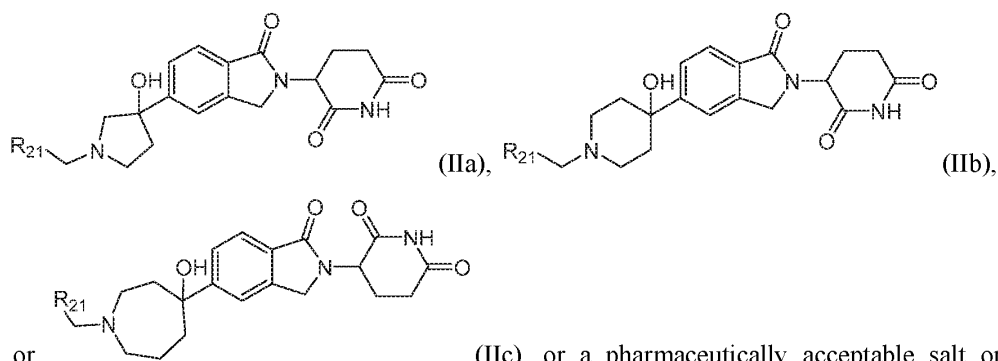
n₁ is 1.

[0076] In some embodiments, R_{21} is a (C₆-C₁₀)aryl, or a monocyclic or bicyclic 5- to 10-membered heteroaryl; wherein said aryl or heteroaryl is optionally and independently substituted by one or more identical or different R_{25} groups;

R_{25} is independently selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, halogen, CN, -O(CH₂)(C₆-C₁₀)aryl, -O(CH₂)-5- or 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from O, N, and S, (C₆-C₁₀)aryl, monocyclic or bicyclic 5- to 10-membered heteroaryl, (C₃-C₇)cycloalkyl, and 4- to 7-membered heterocycloalkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is further optionally and independently substituted by one or more identical or different R_{15} groups; and

n_1 is 1.

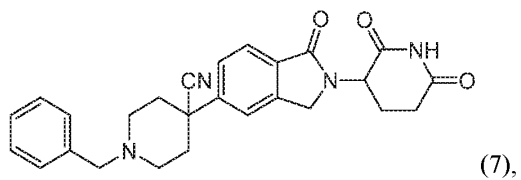
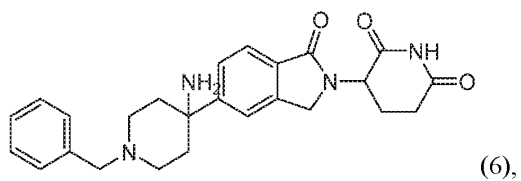
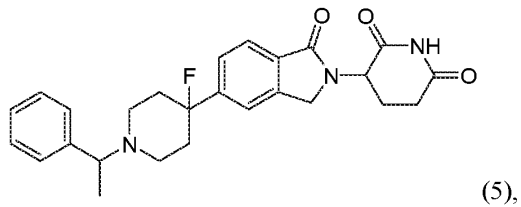
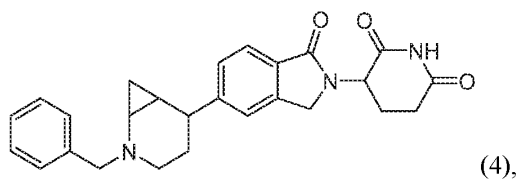
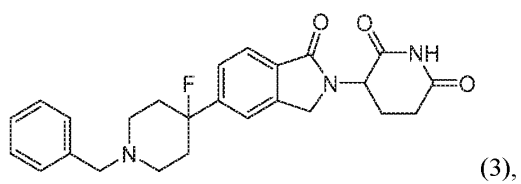
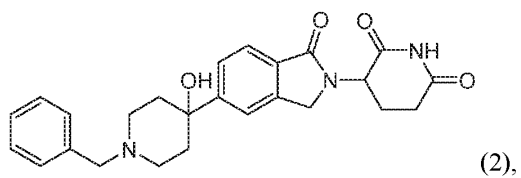
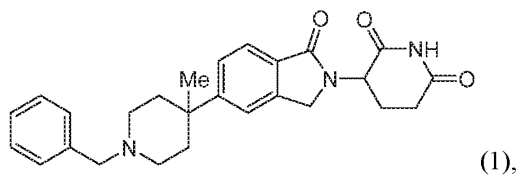
[0077] In some embodiments, compounds of formula II are represented by formula IIa, IIb, or IIc:

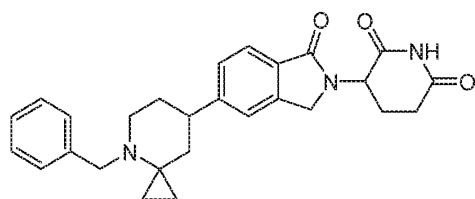


[0078] In some embodiments, R_{21} is a substituted C₆-aryl, provided said aryl is substituted with at least two R_{25} , and provided that two of the R_{25} , when on adjacent atoms, form a 5- or 6-membered heteroaryl that is substituted with at least one (C₆-C₁₀)aryl, or monocyclic or bicyclic 5- to 10-membered heteroaryl that is optionally and independently substituted with one or more R_{15} , or

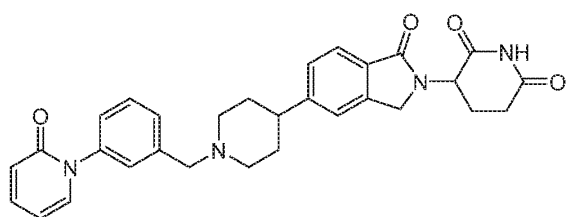
R_{21} is a substituted 5- or 6-membered heteroaryl, provided said heteroaryl is substituted with at least two R_{25} , and provided that two of the R_{25} , when on adjacent atoms, form a C₆-aryl, or 5- or 6-membered heteroaryl that is substituted with at least one (C₆-C₁₀)aryl or monocyclic or bicyclic 5- to 10-membered heteroaryl that is optionally and independently substituted with one or more R_{15} .

[0079] Representative compounds of the invention have the following structures:

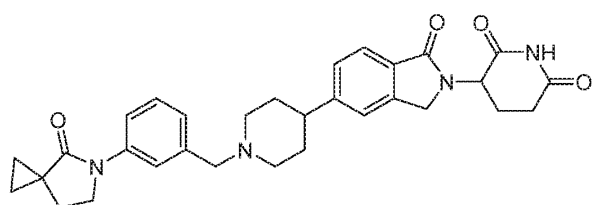




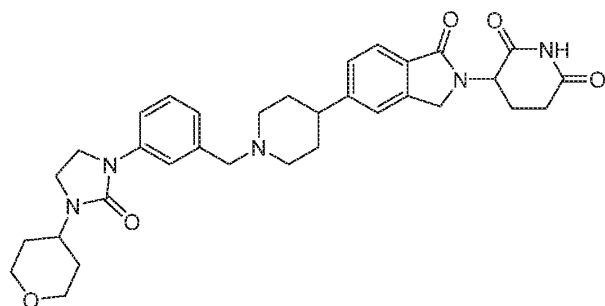
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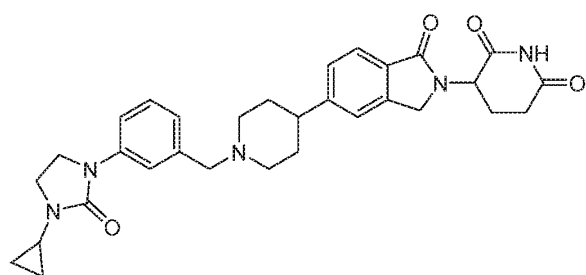
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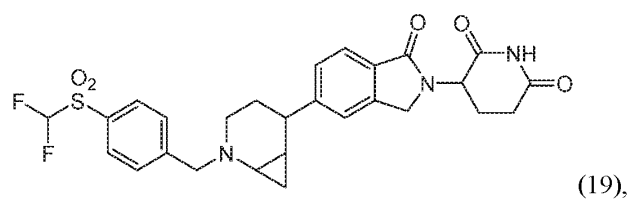
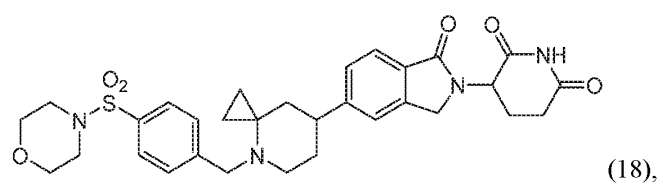
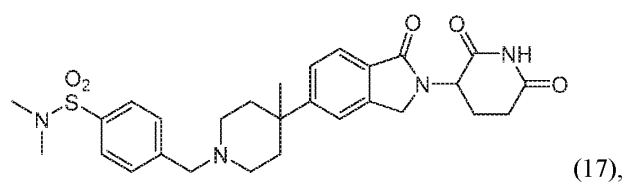
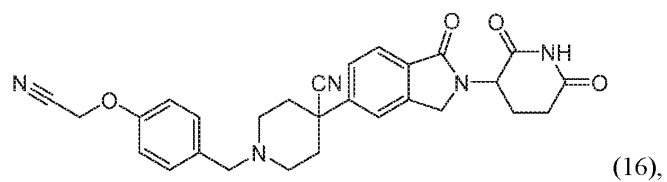
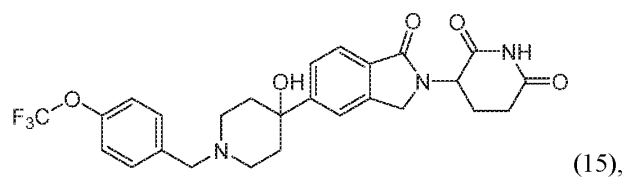
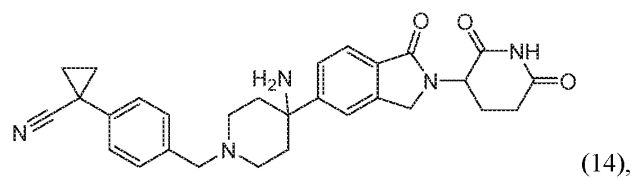
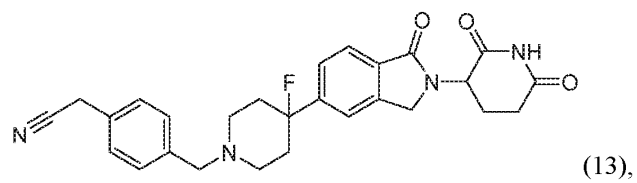
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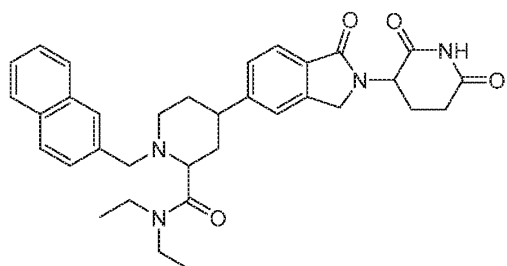


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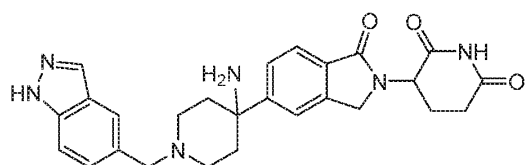


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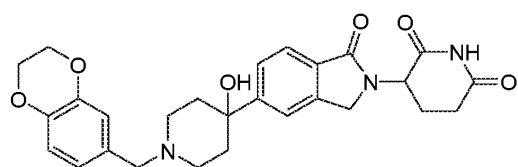




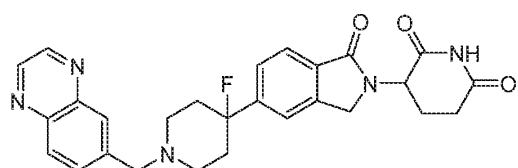
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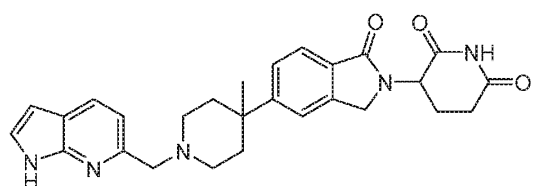
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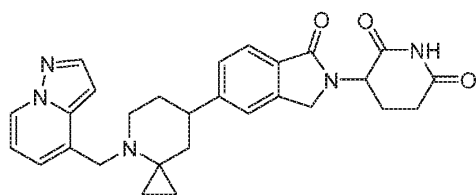
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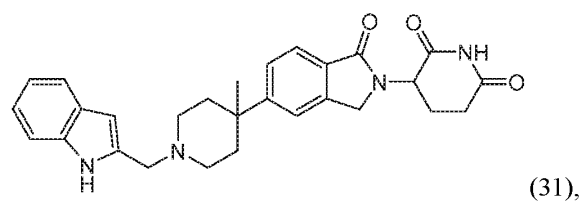
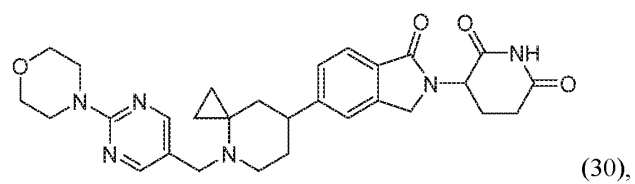
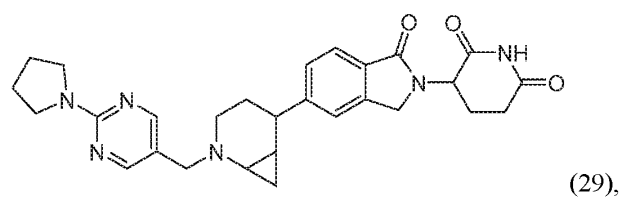
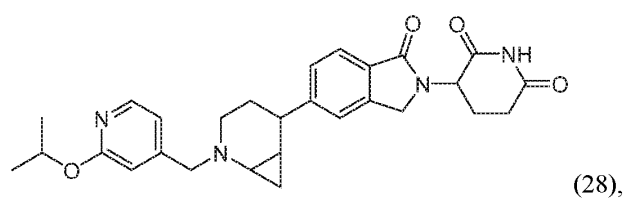
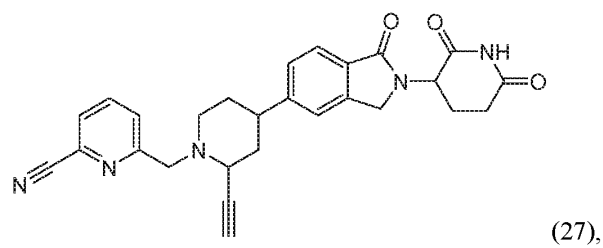
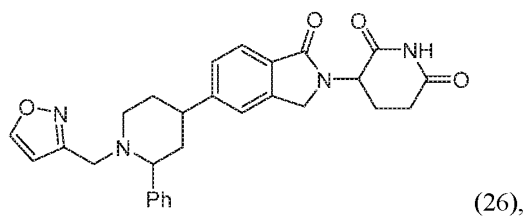
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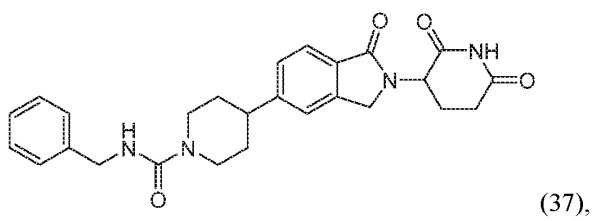
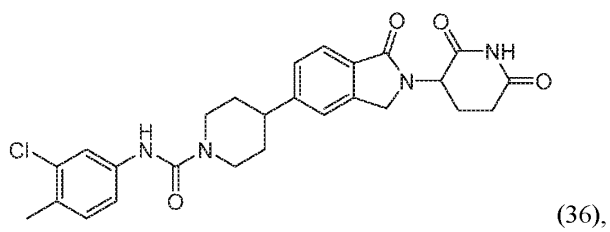
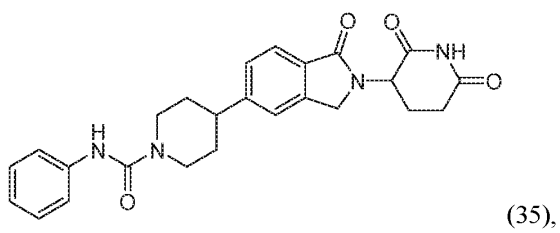
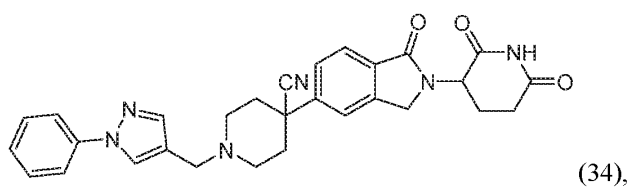
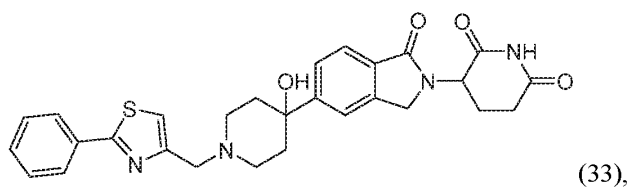
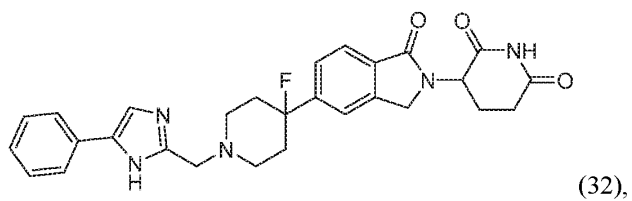


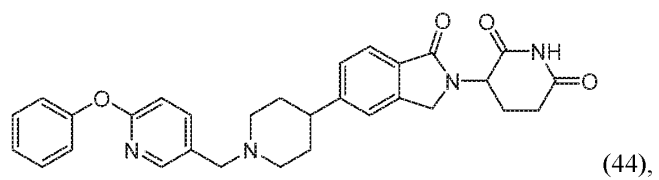
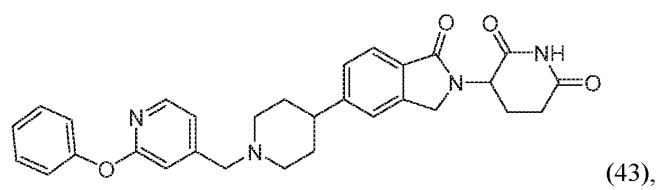
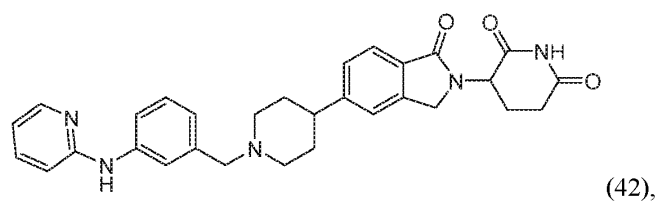
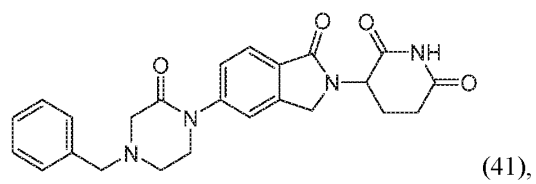
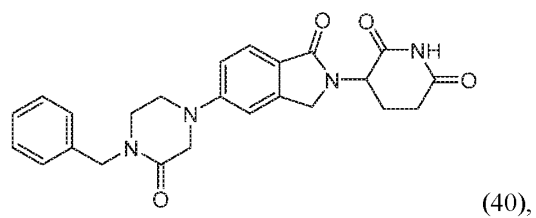
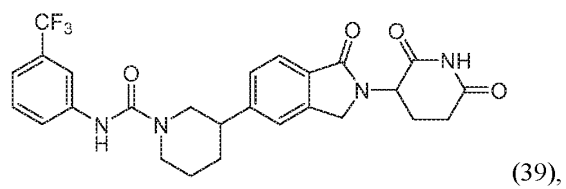
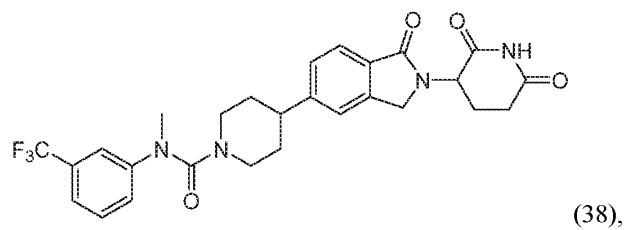
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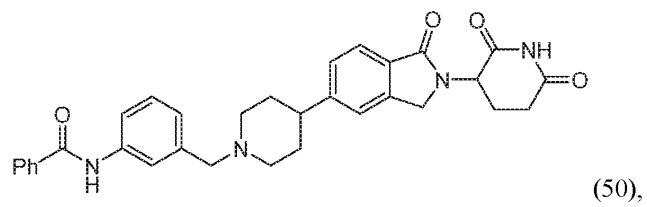
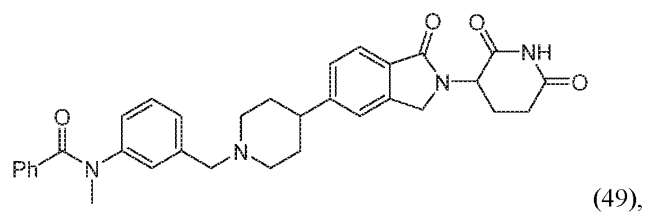
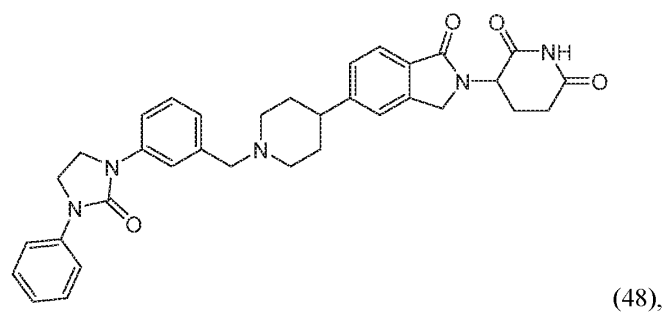
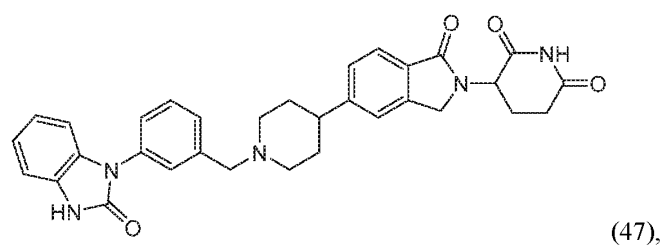
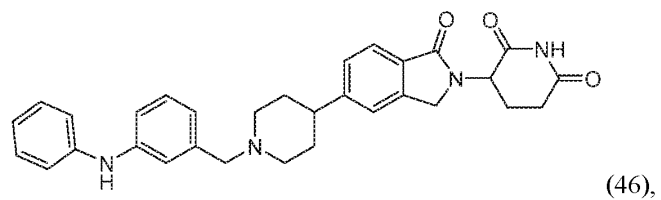
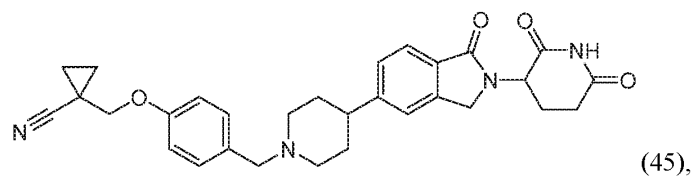


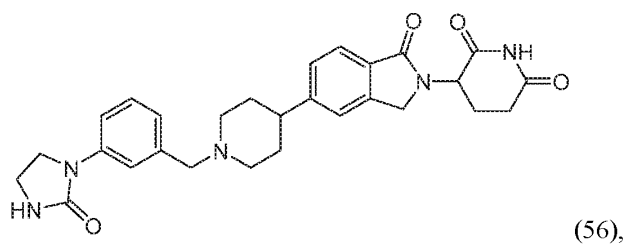
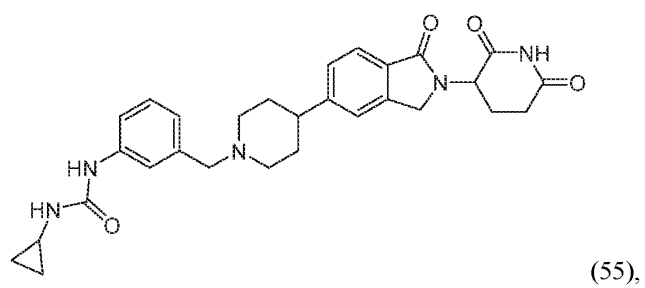
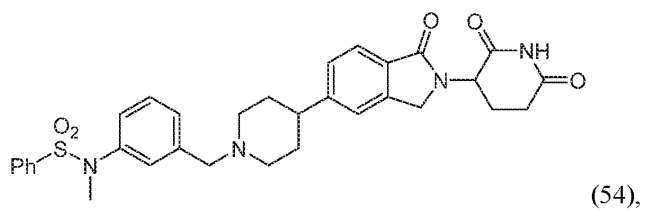
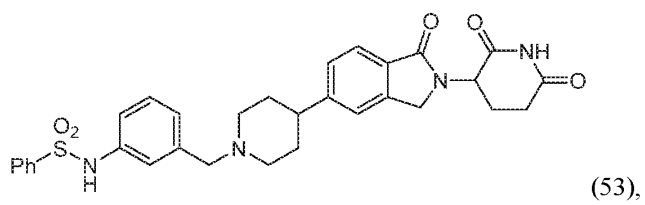
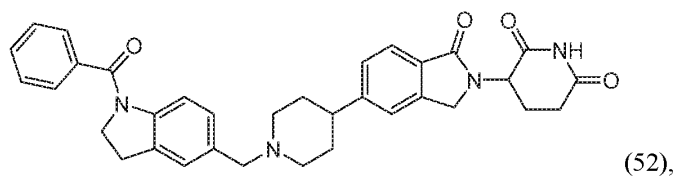
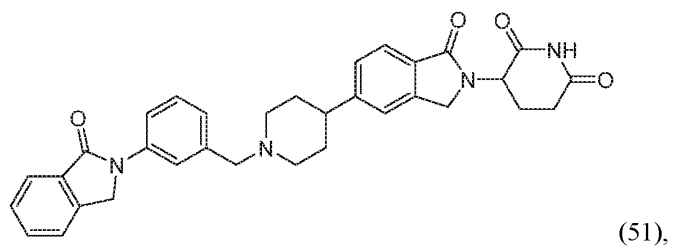
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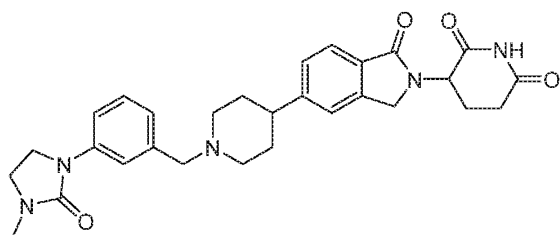




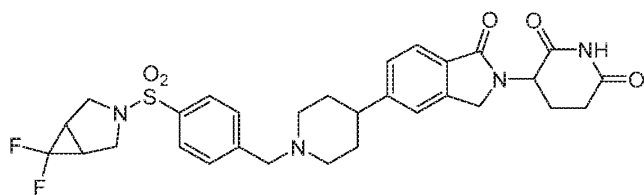




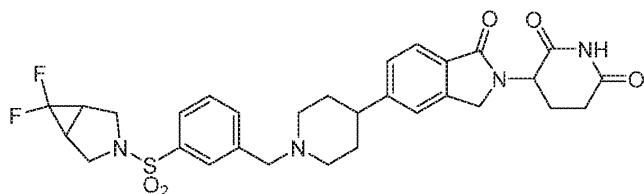




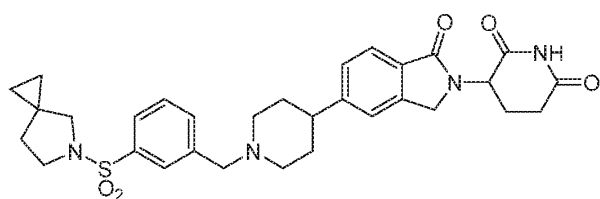
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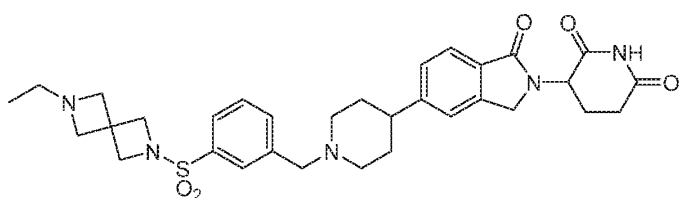
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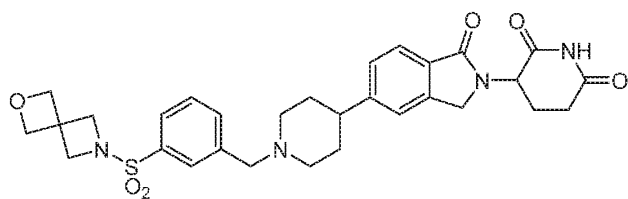
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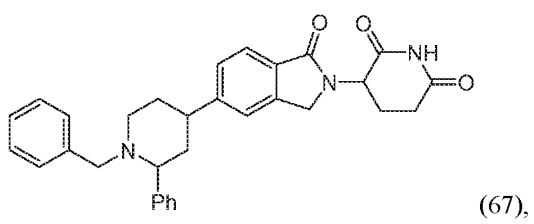
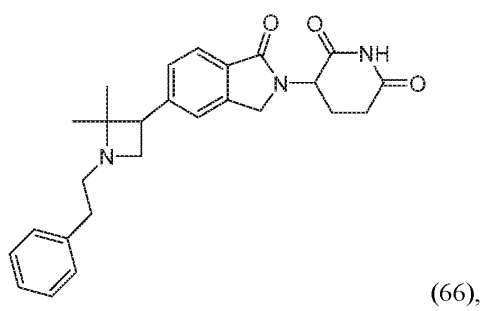
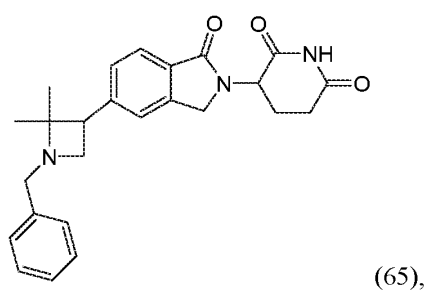
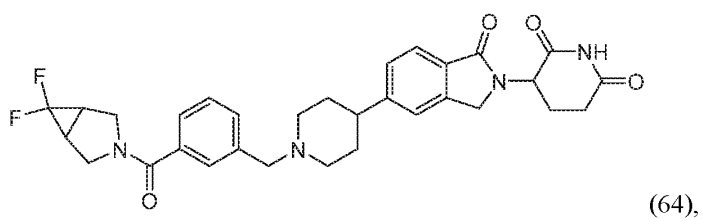
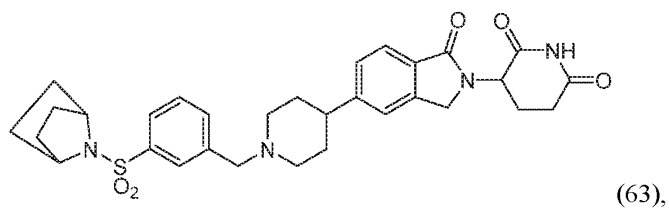
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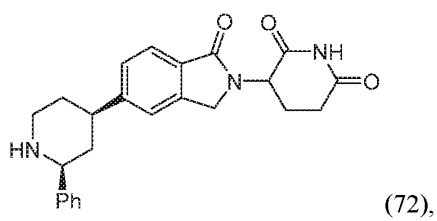
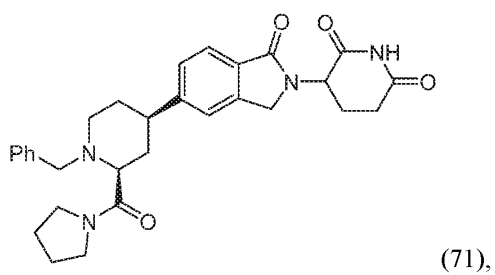
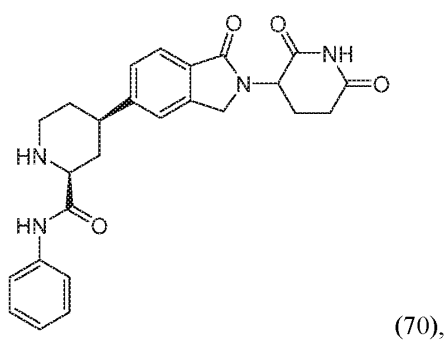
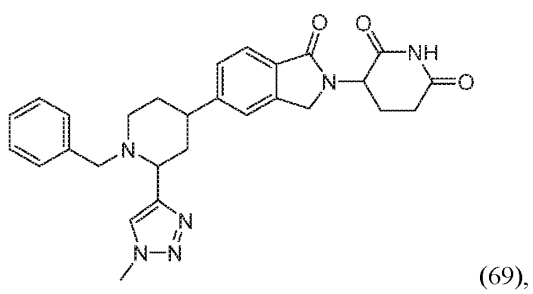
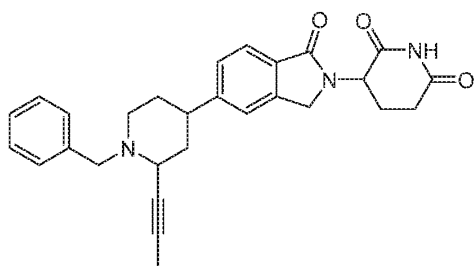


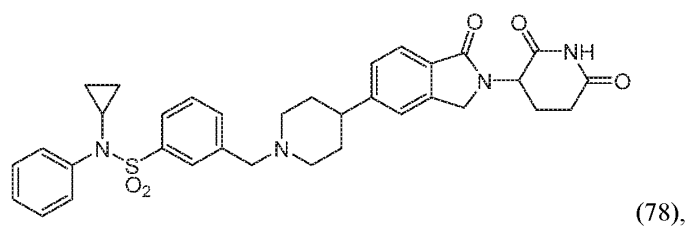
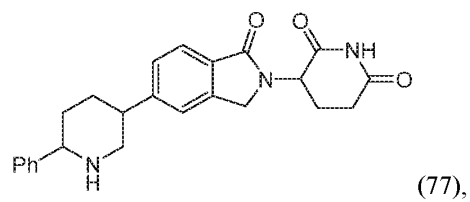
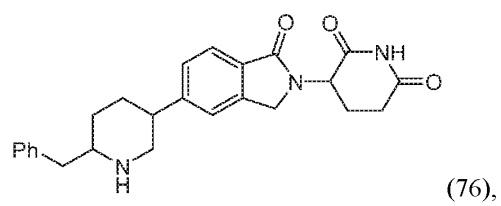
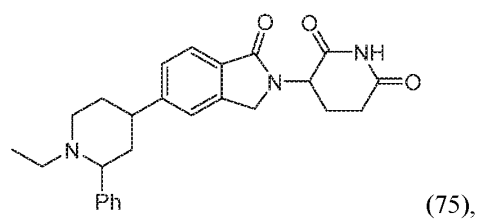
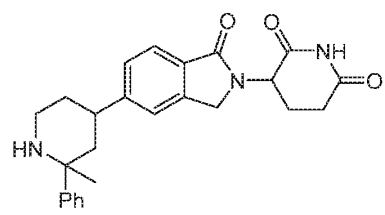
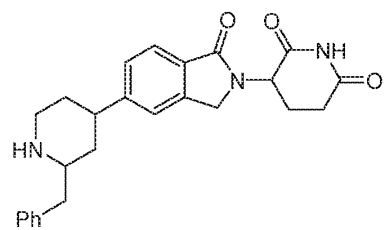
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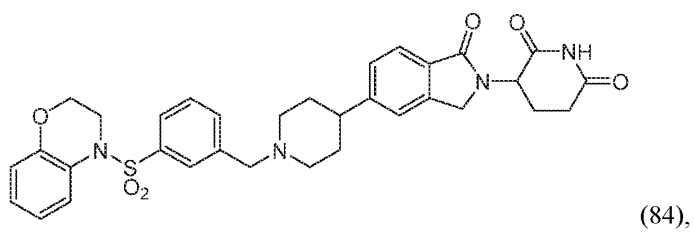
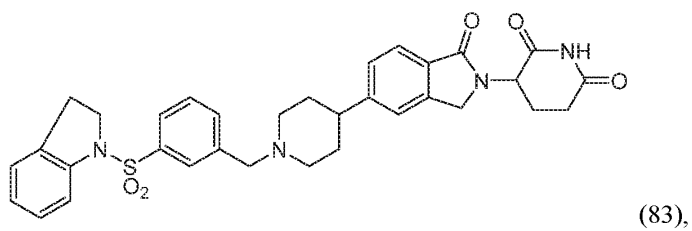
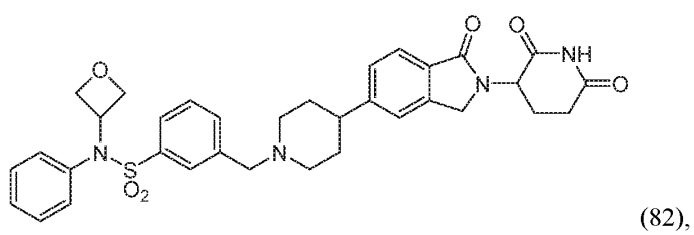
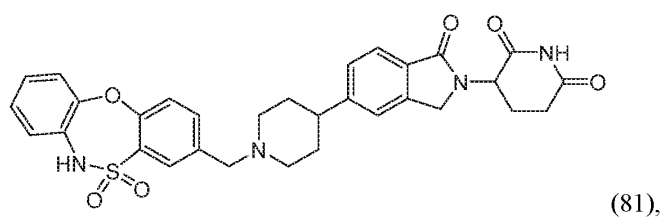
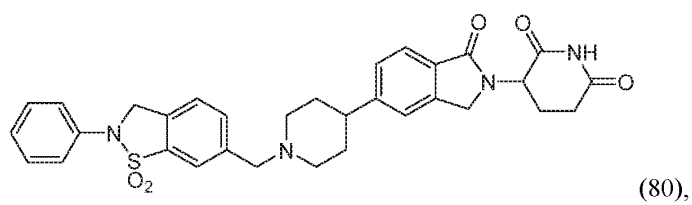
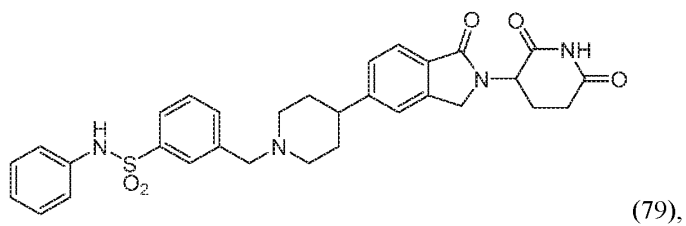


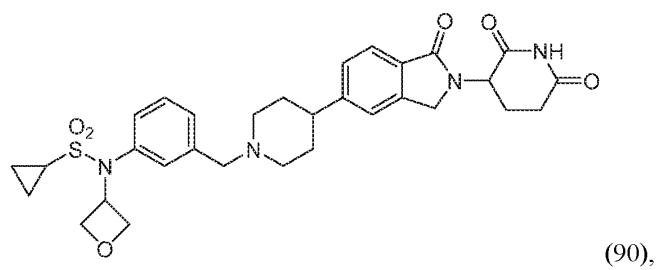
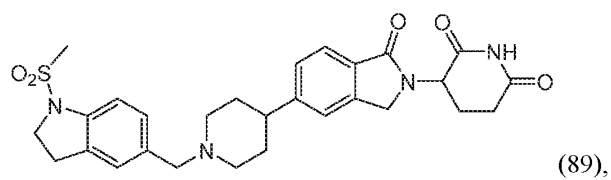
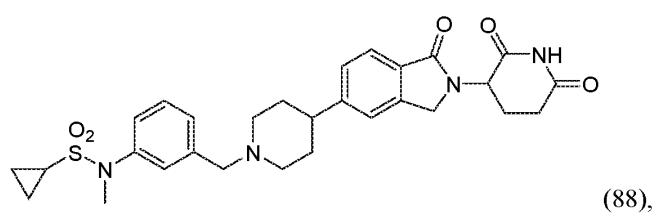
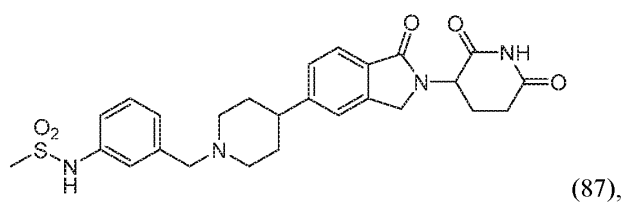
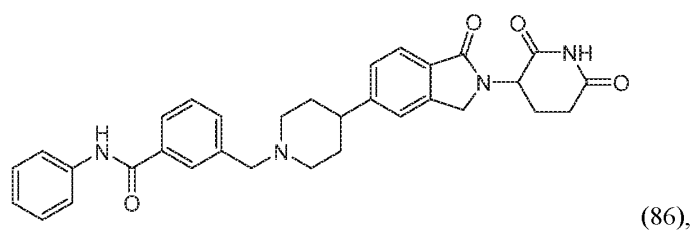
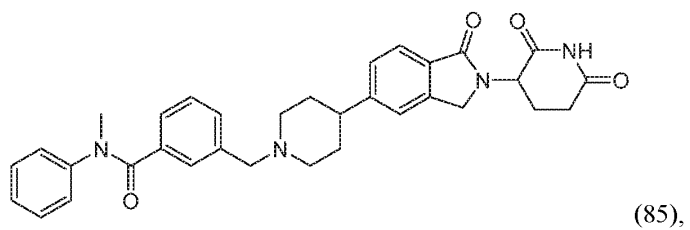
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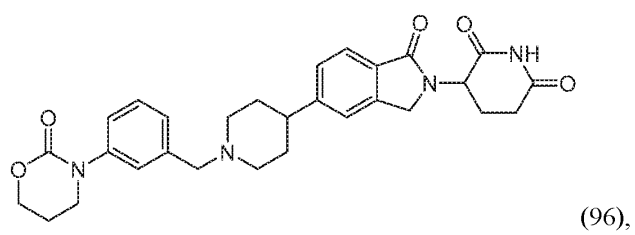
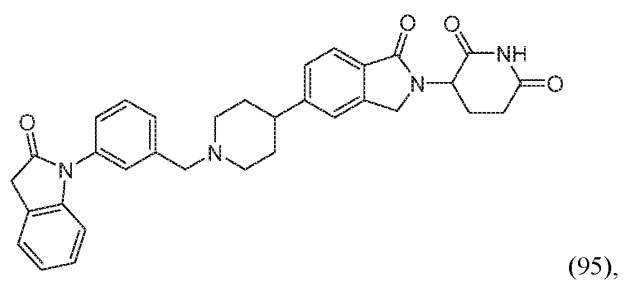
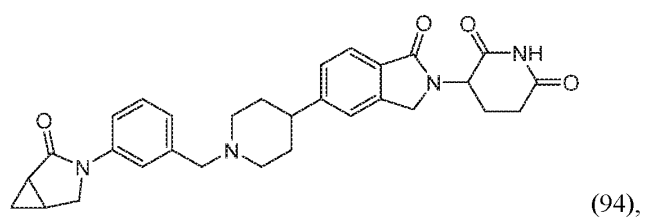
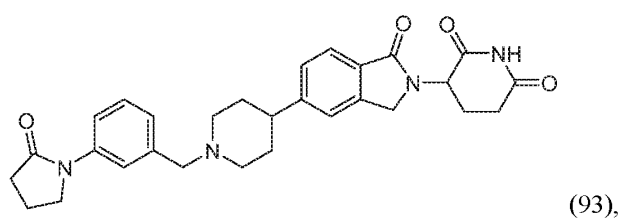
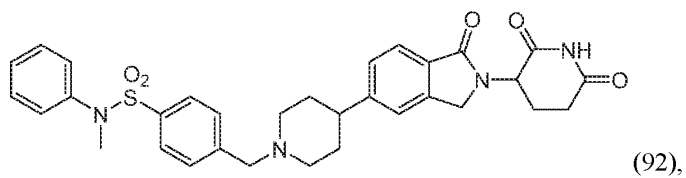
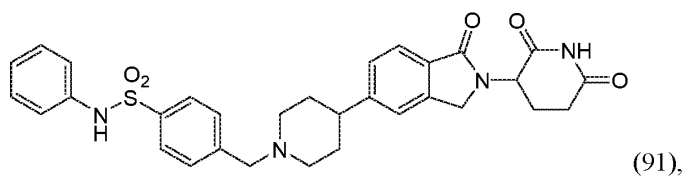


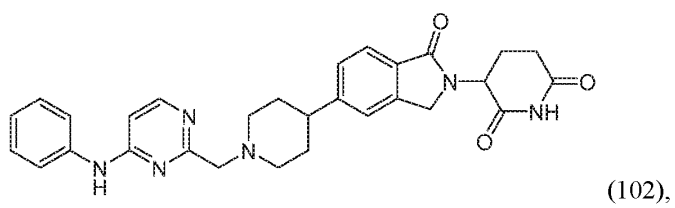
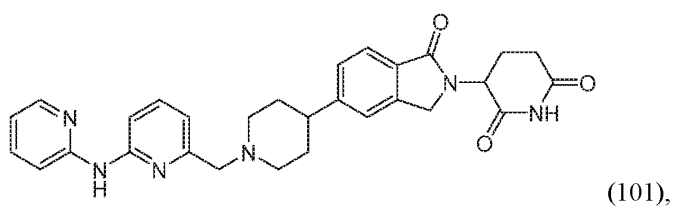
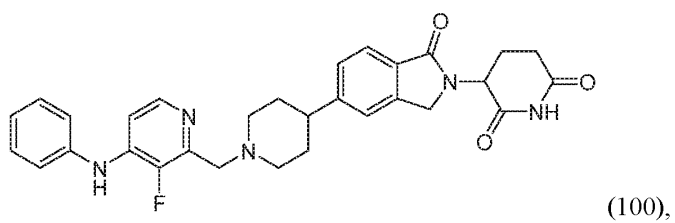
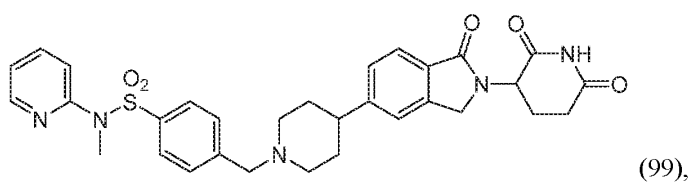
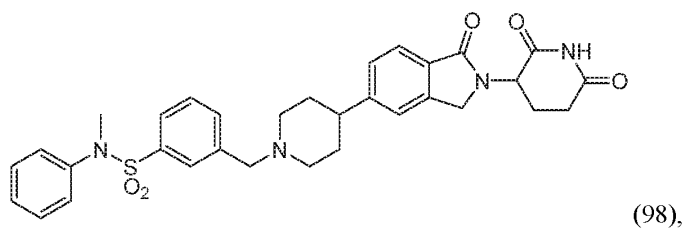
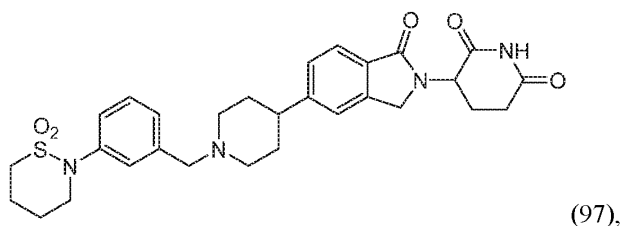


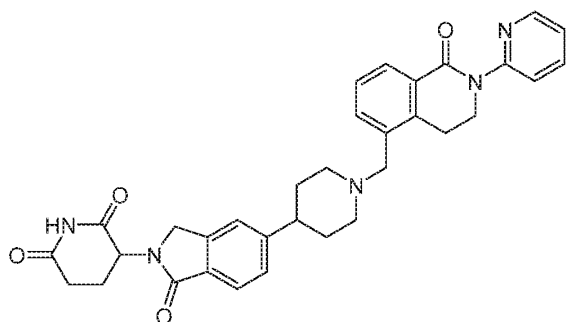




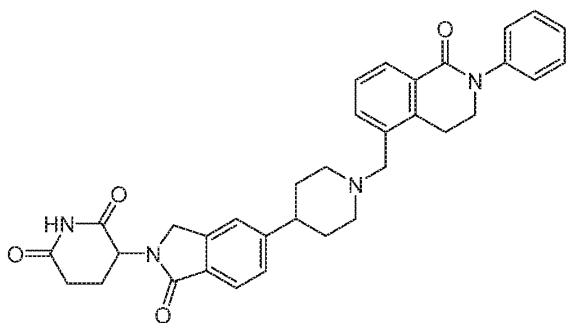




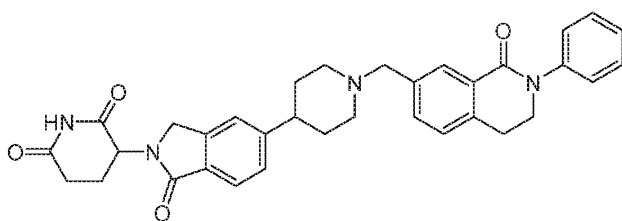




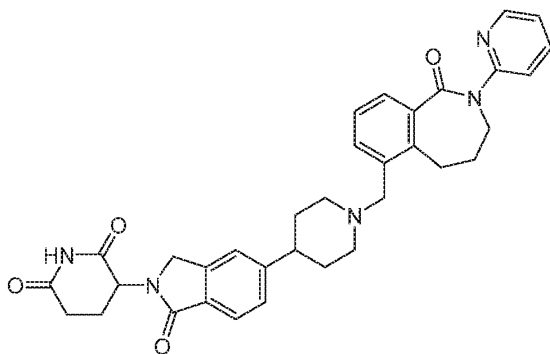
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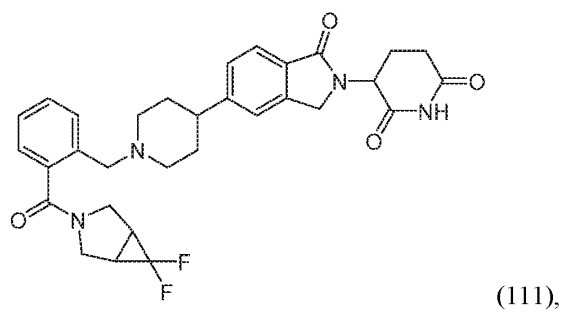
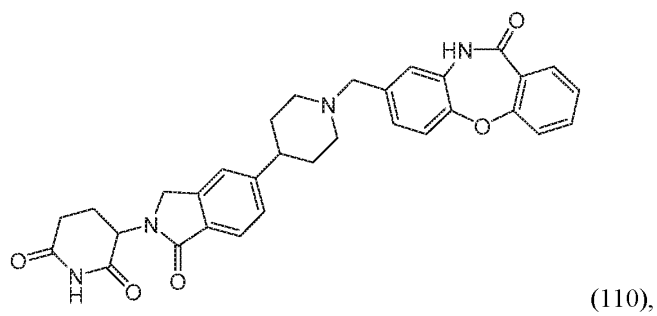
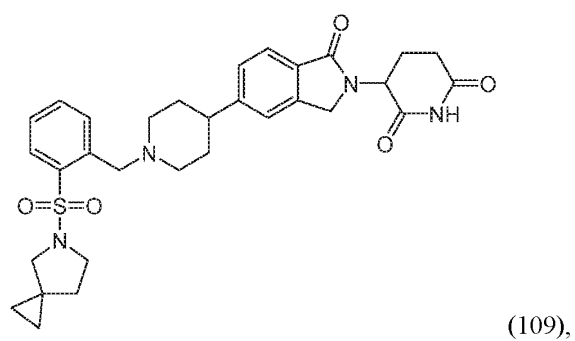
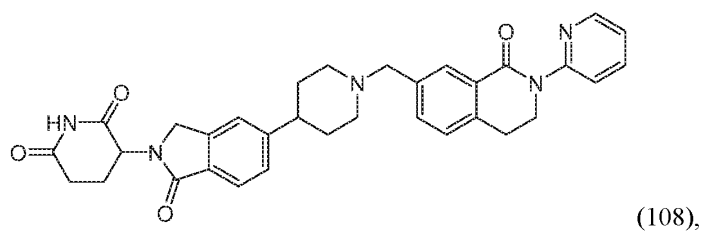
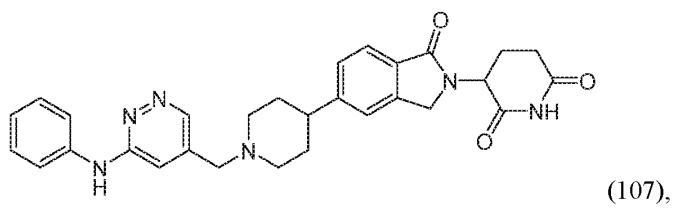
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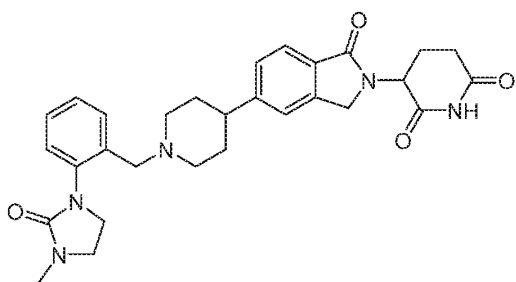


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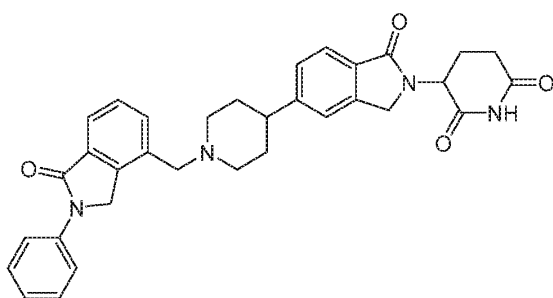


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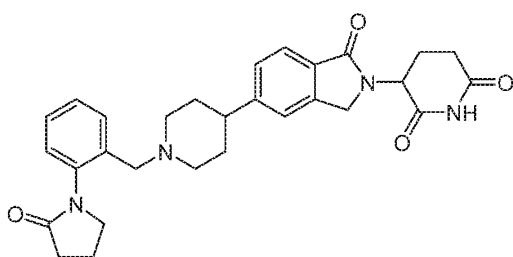




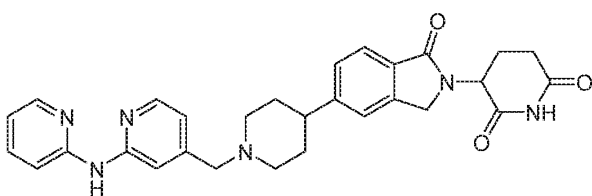
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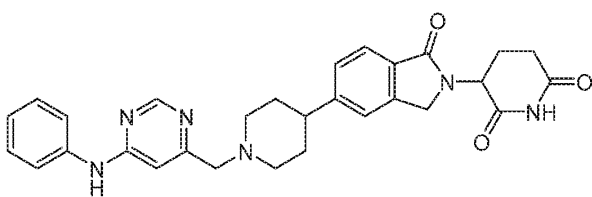
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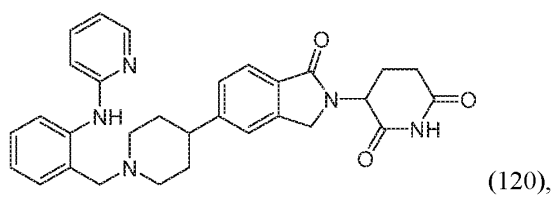
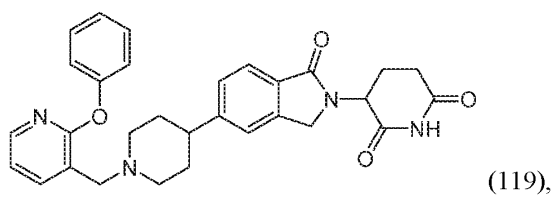
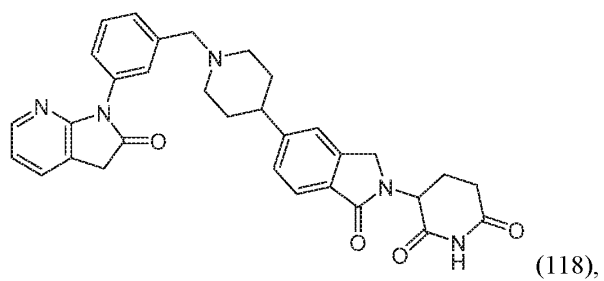
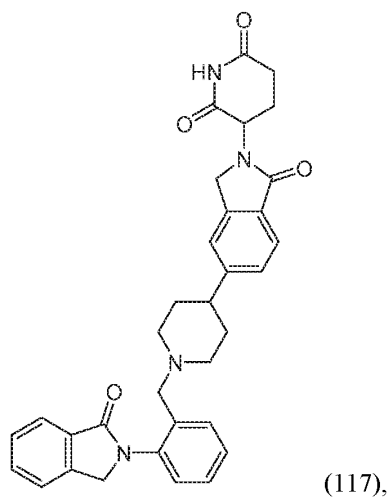
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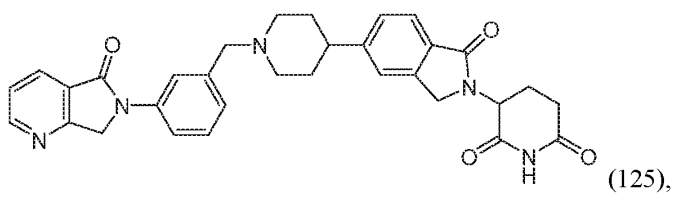
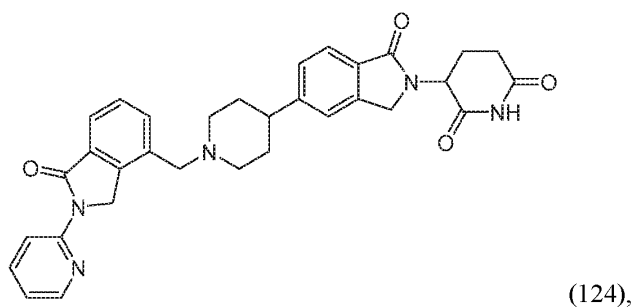
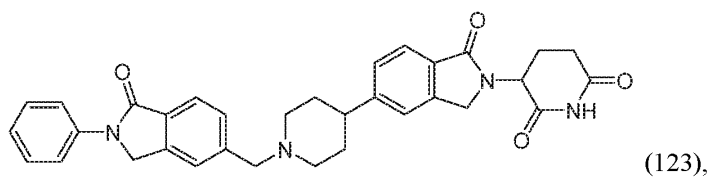
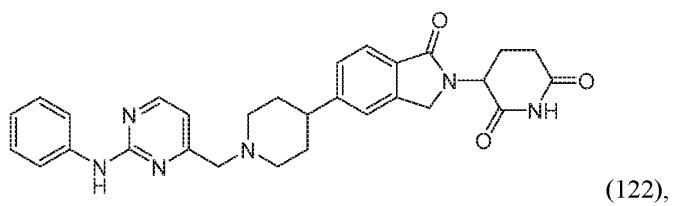
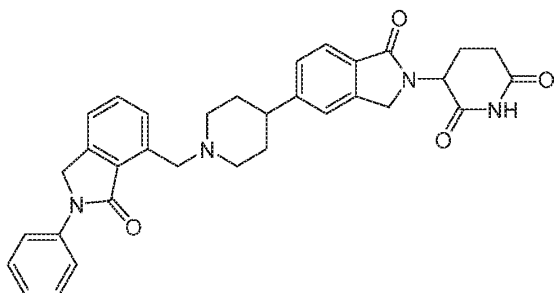


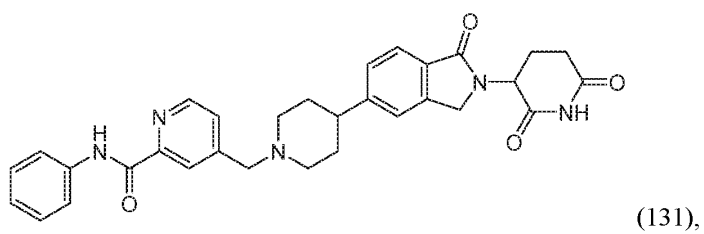
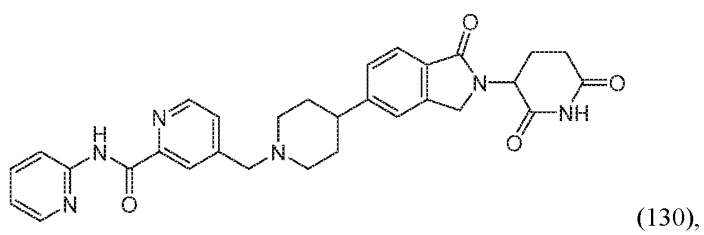
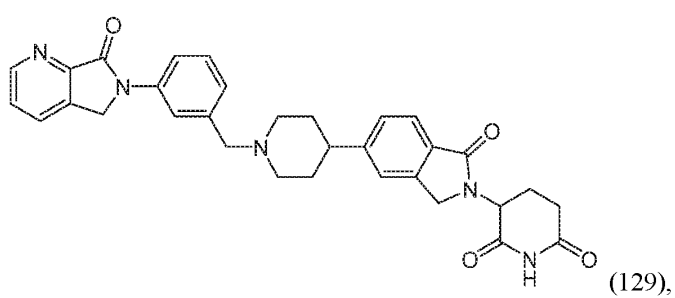
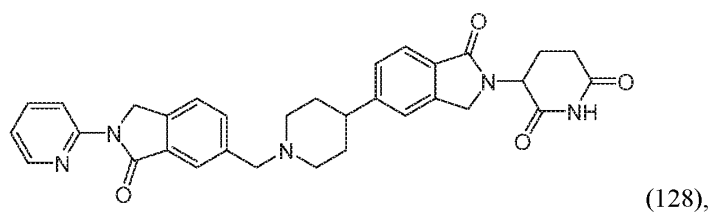
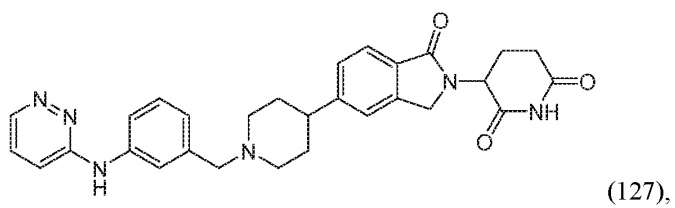
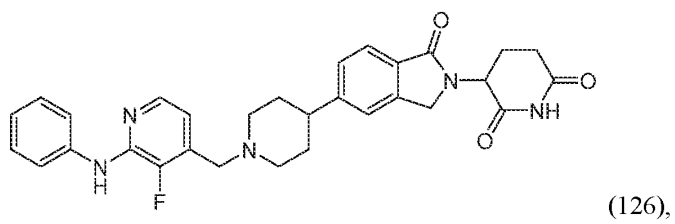
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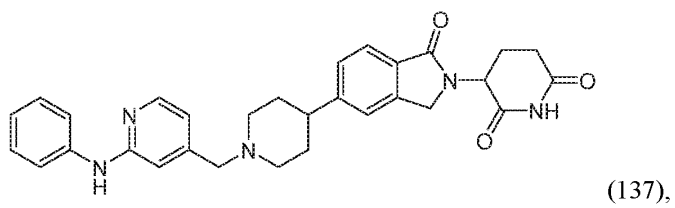
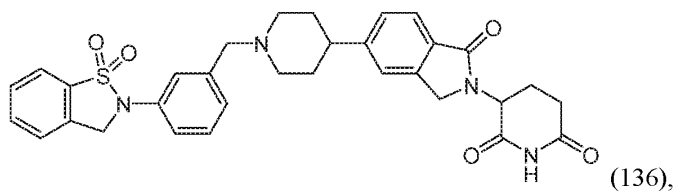
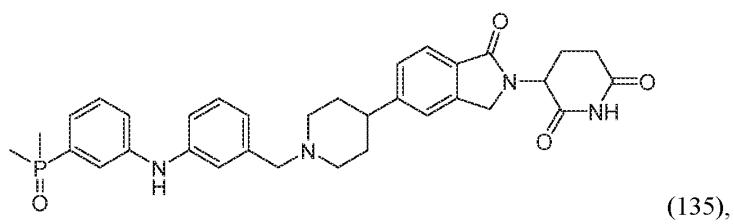
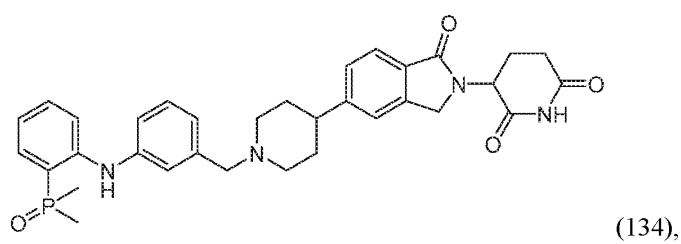
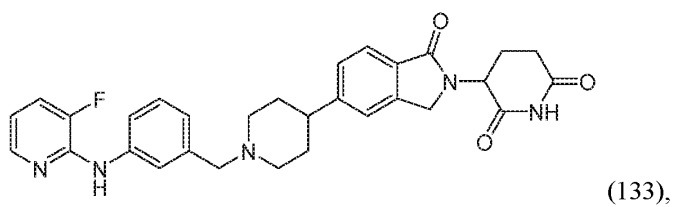
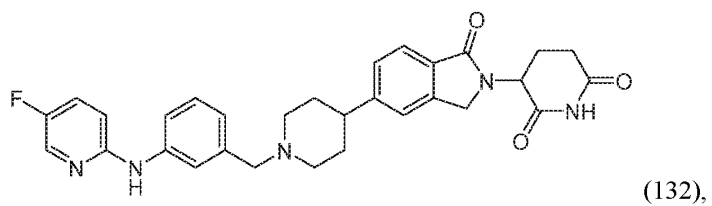


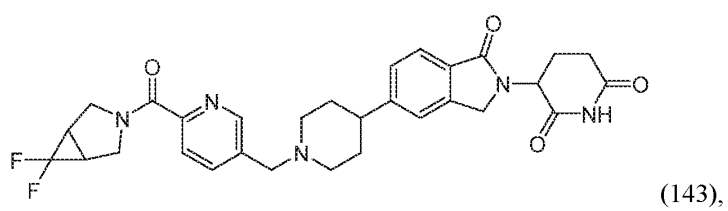
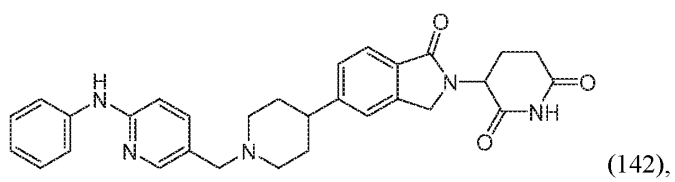
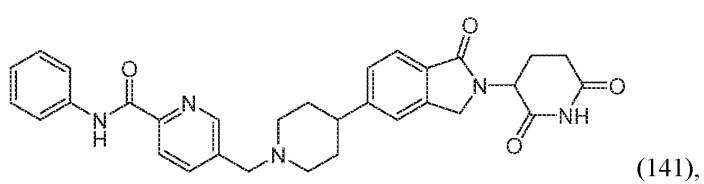
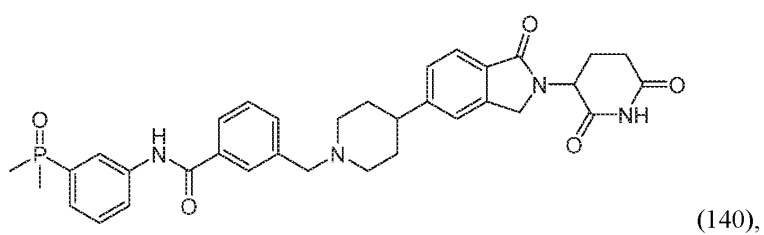
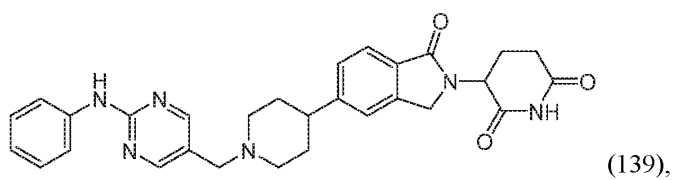
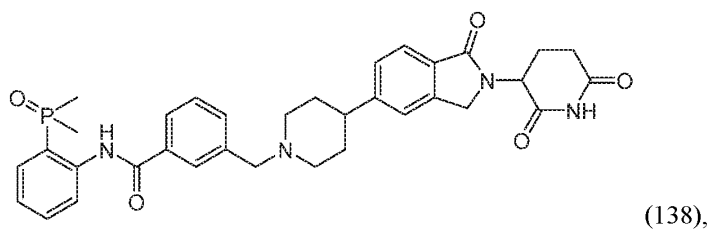
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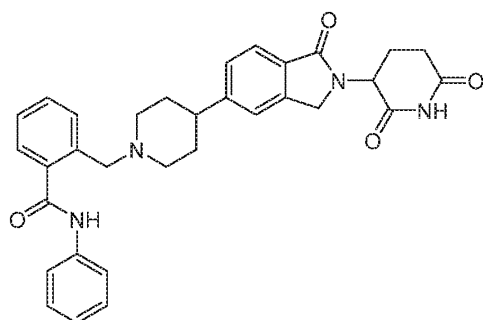




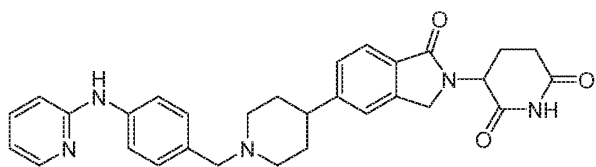




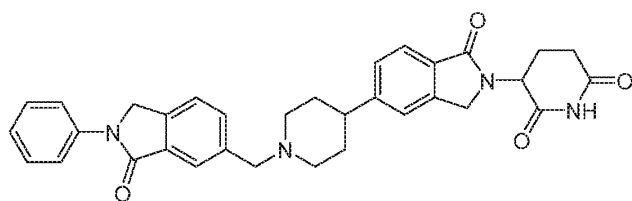




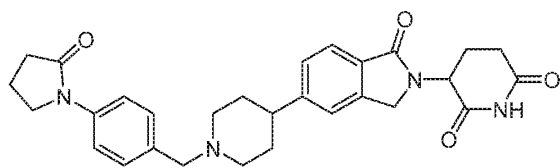
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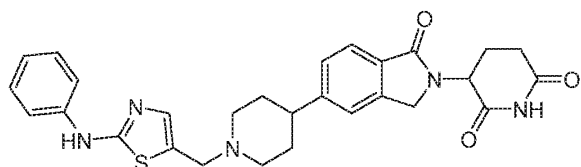
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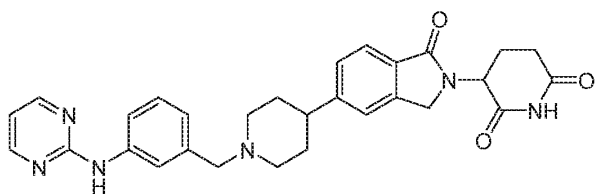
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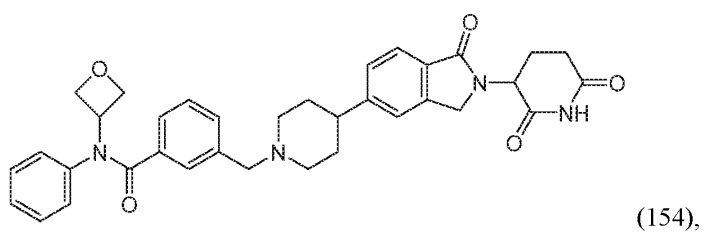
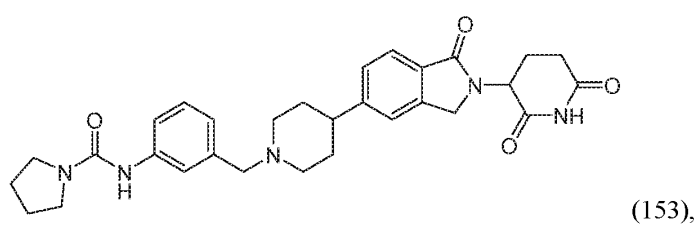
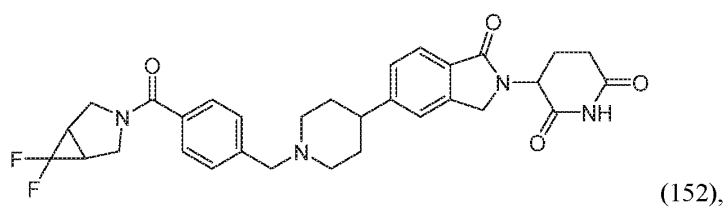
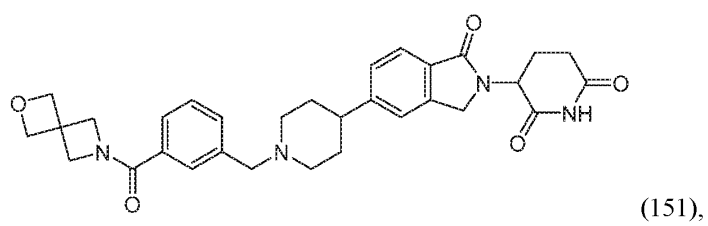
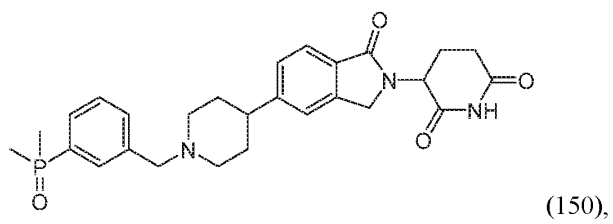
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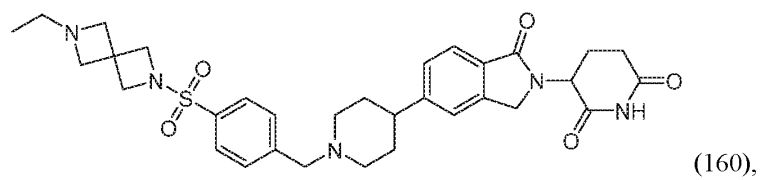
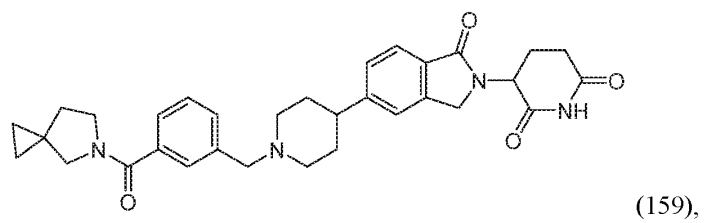
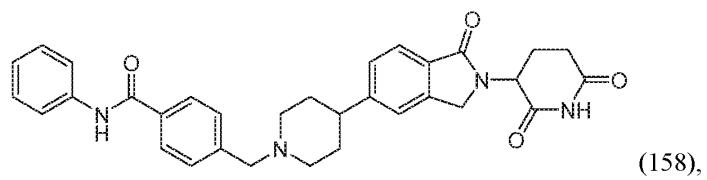
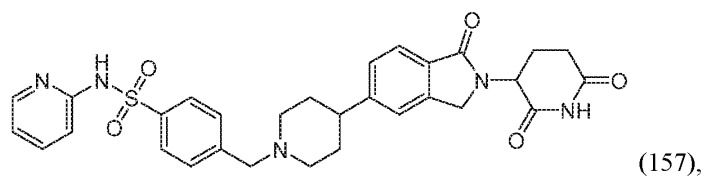
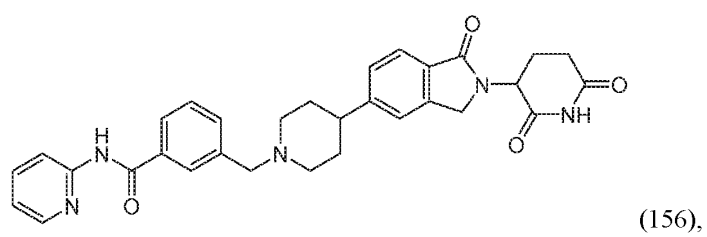
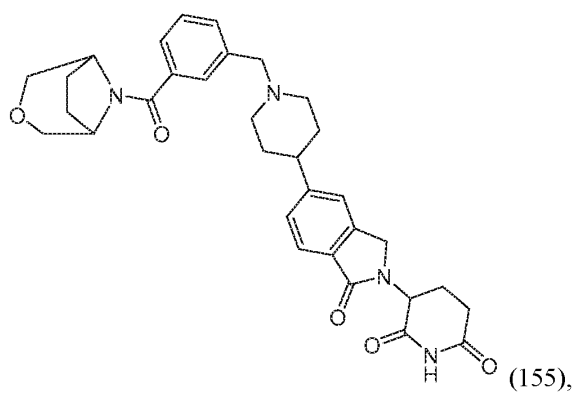


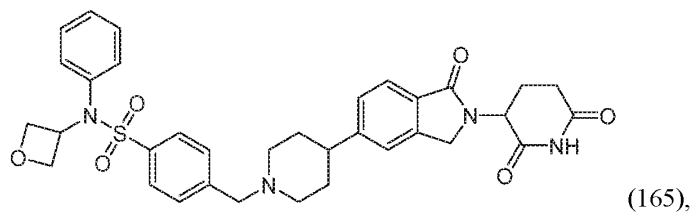
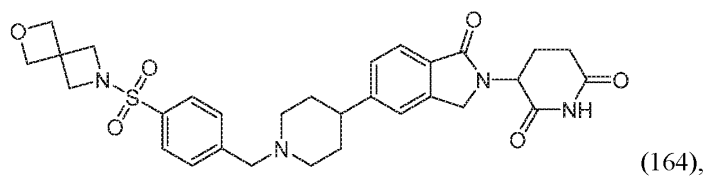
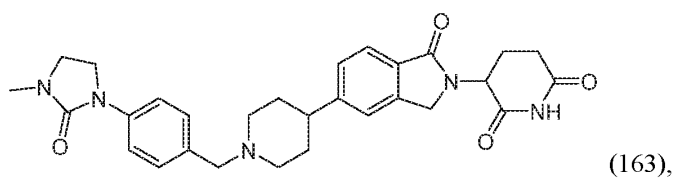
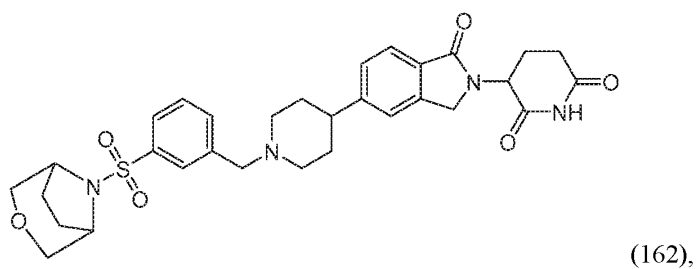
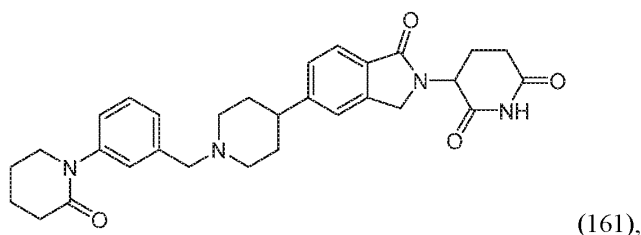
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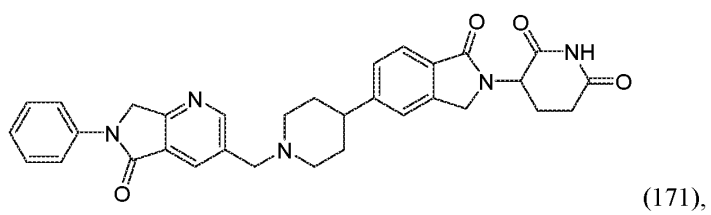
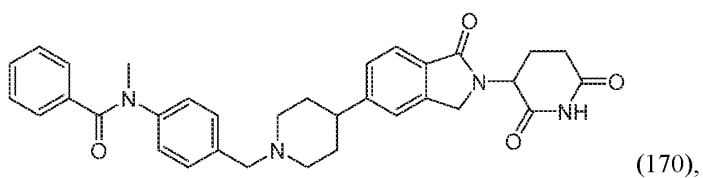
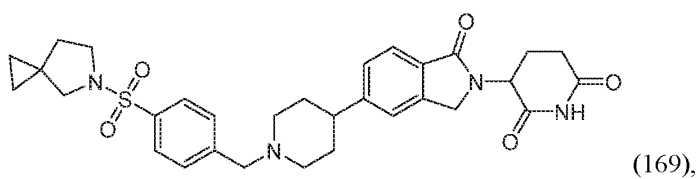
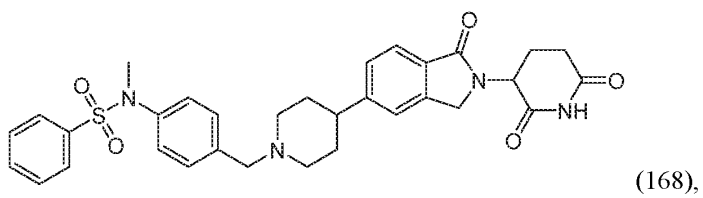
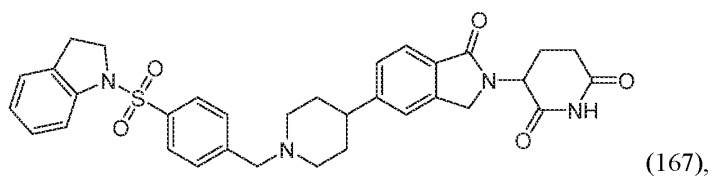
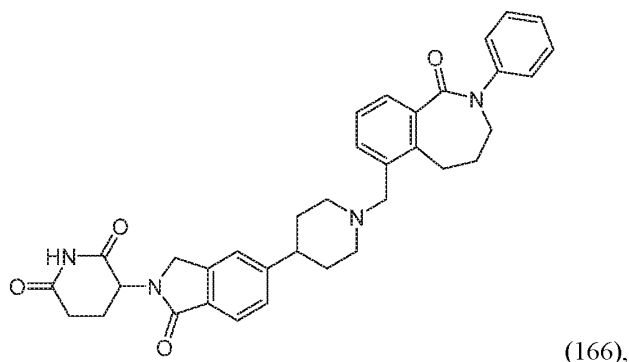


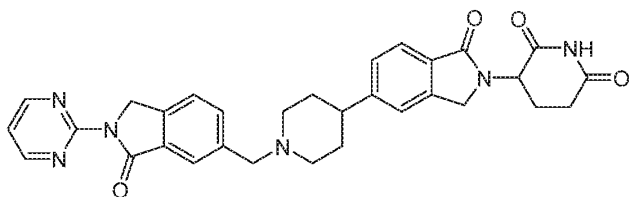
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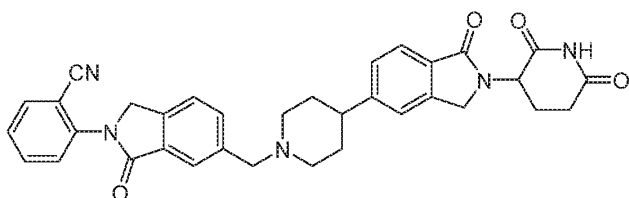




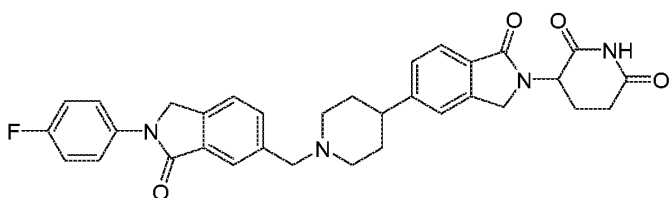




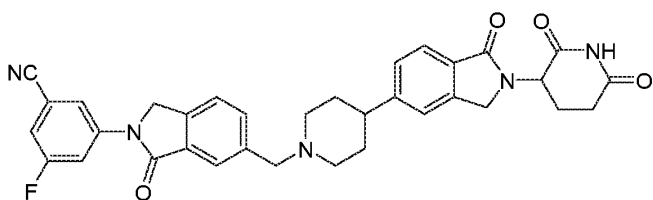
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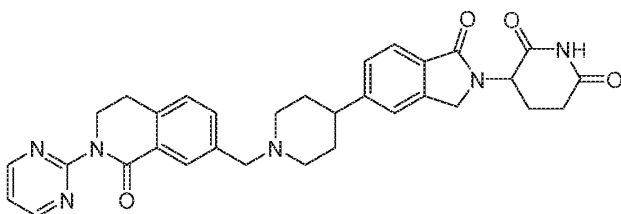
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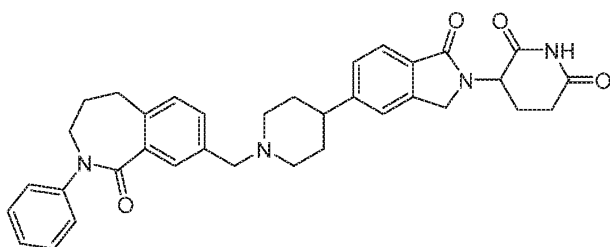
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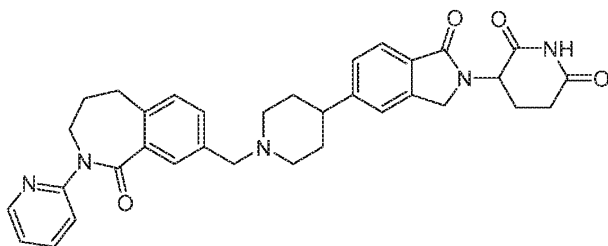
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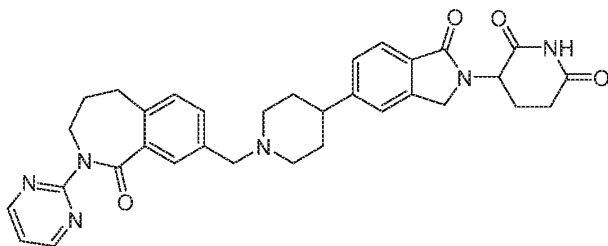
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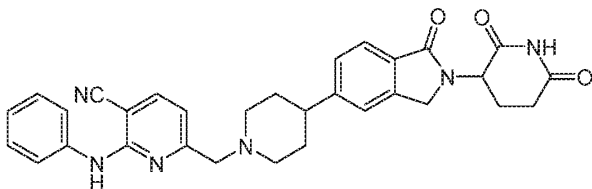
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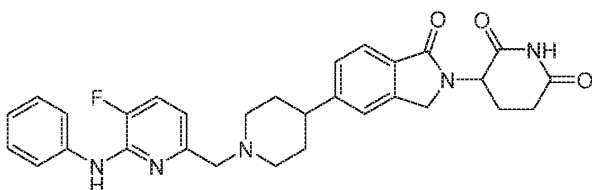
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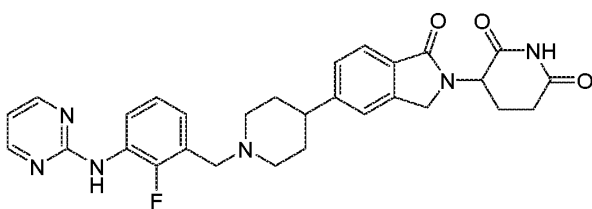
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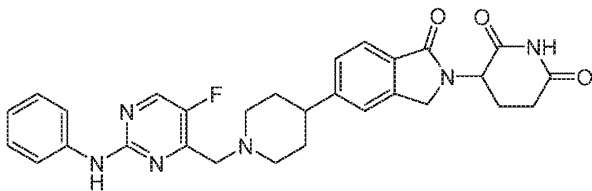
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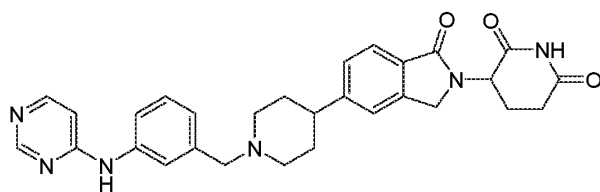
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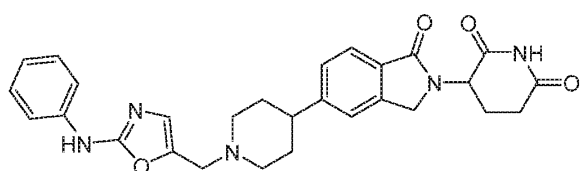
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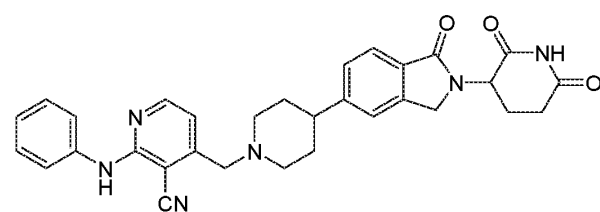
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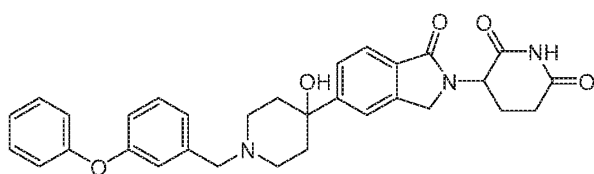
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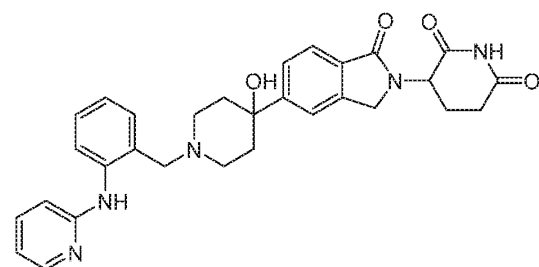
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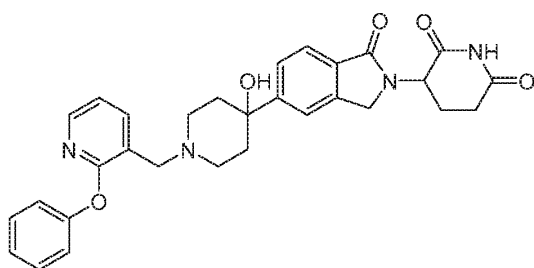
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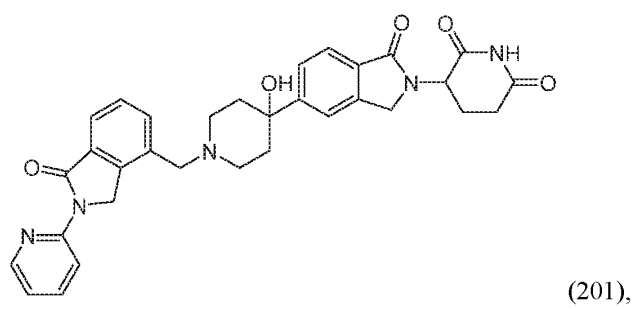
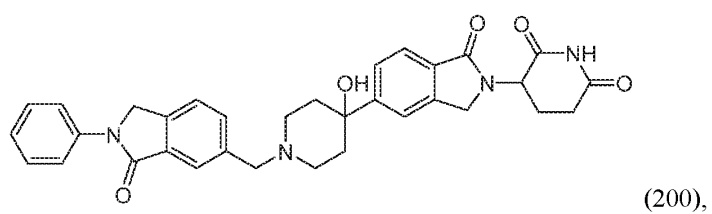
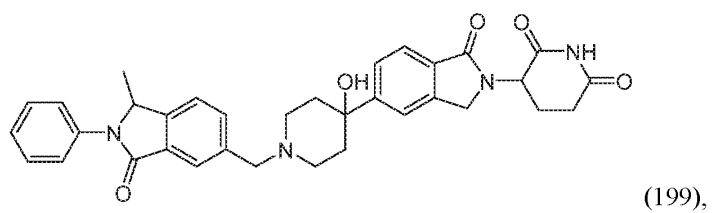
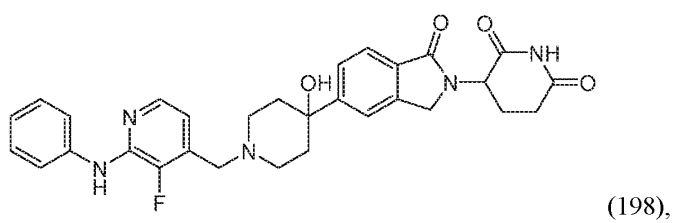
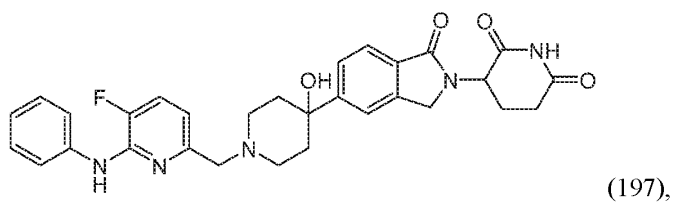
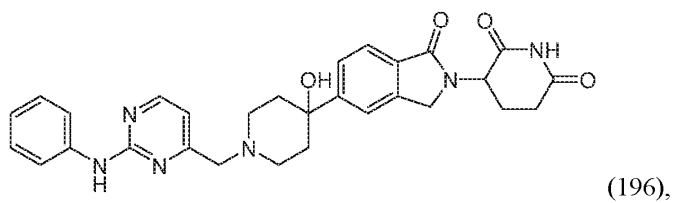
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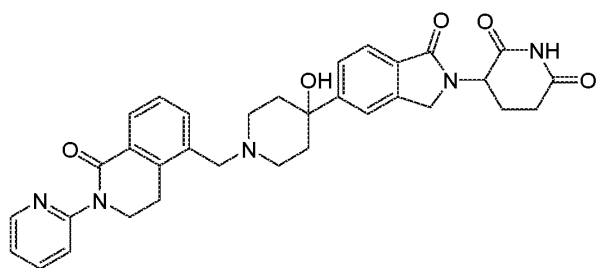


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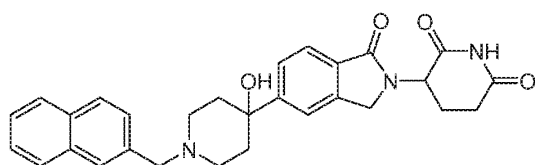


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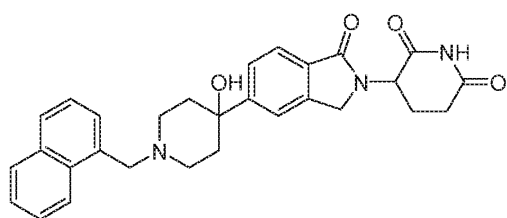




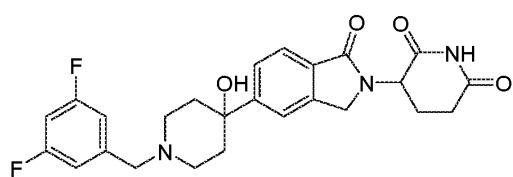
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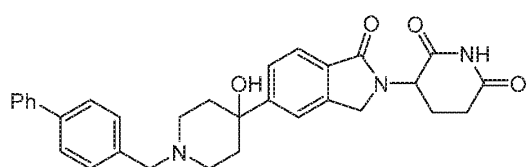
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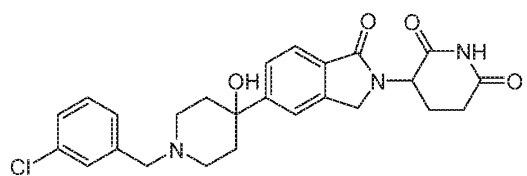
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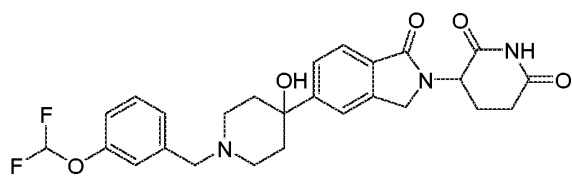
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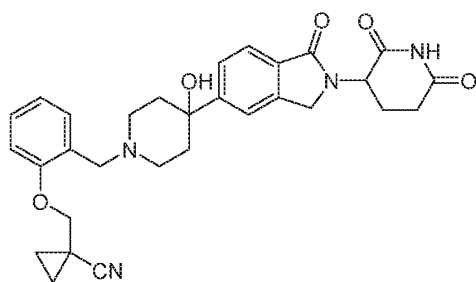
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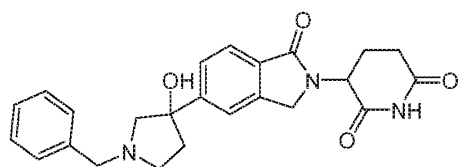
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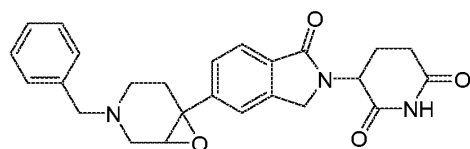
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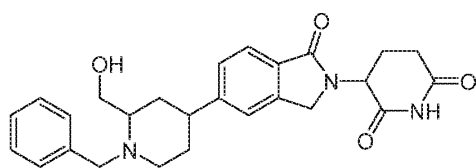
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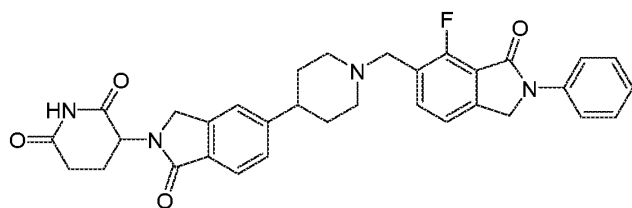
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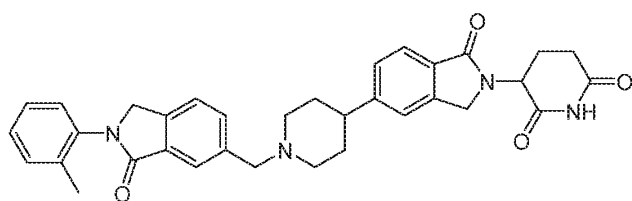
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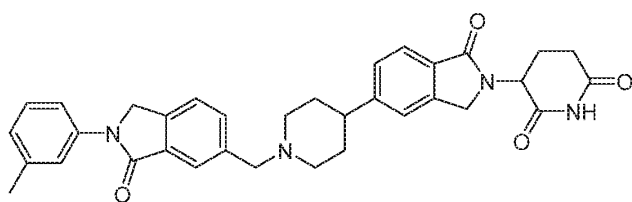
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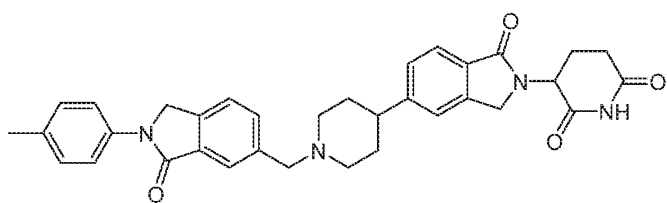
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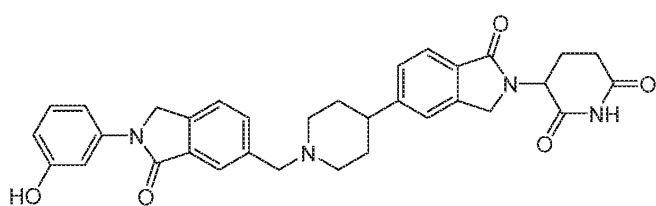
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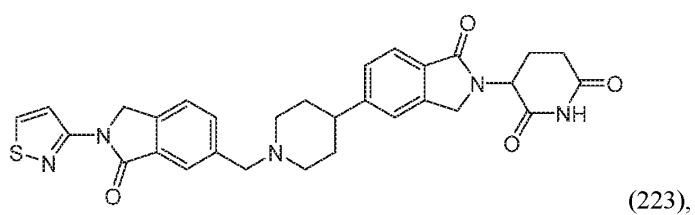
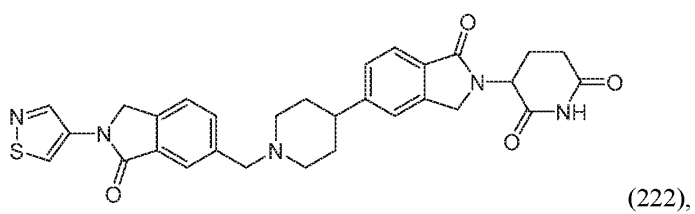
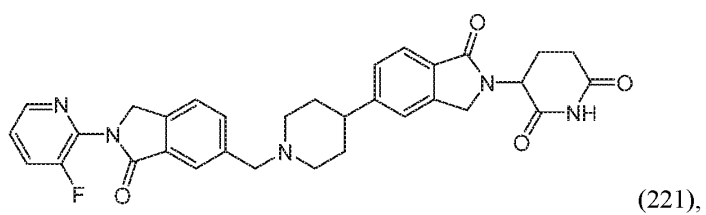
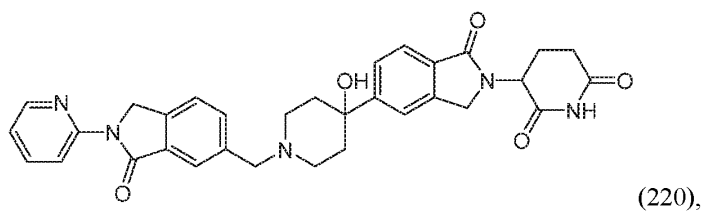
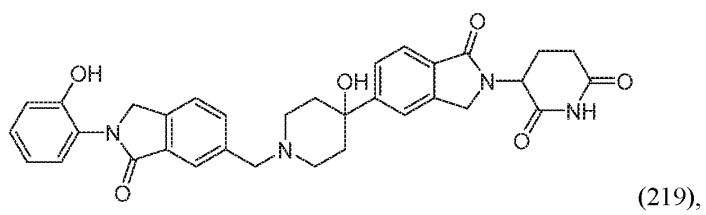
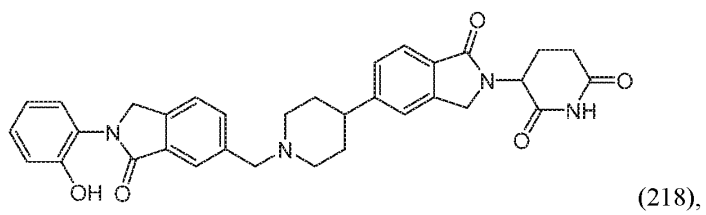
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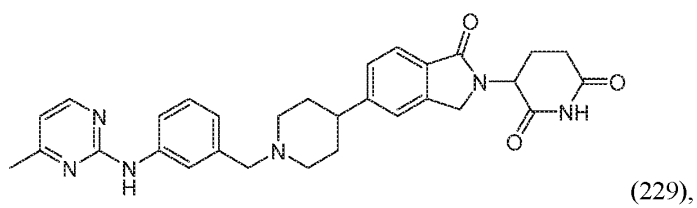
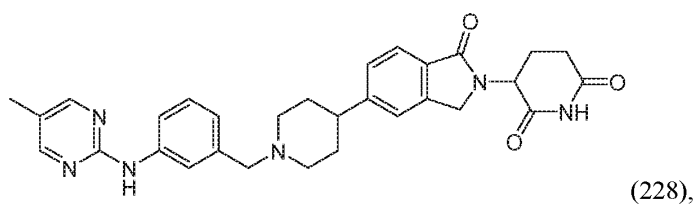
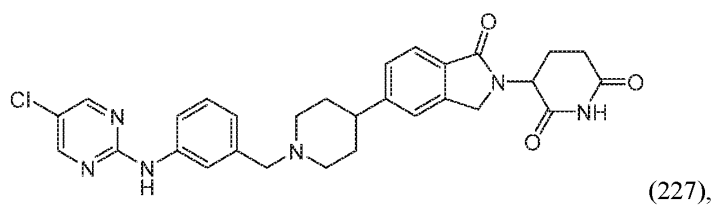
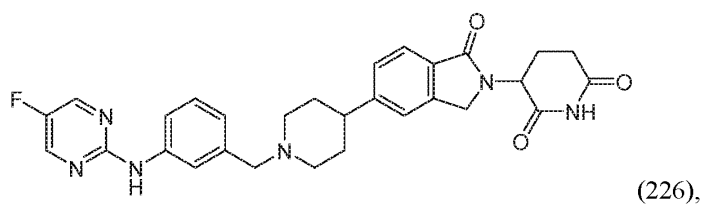
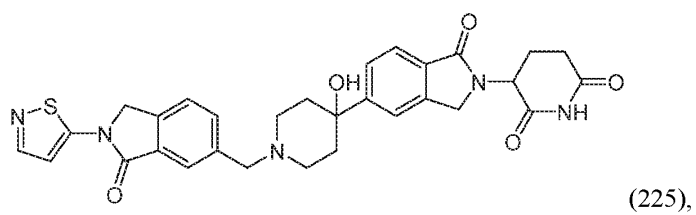
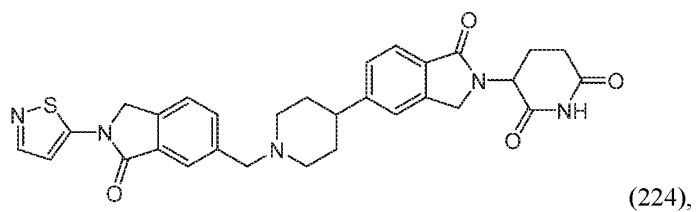


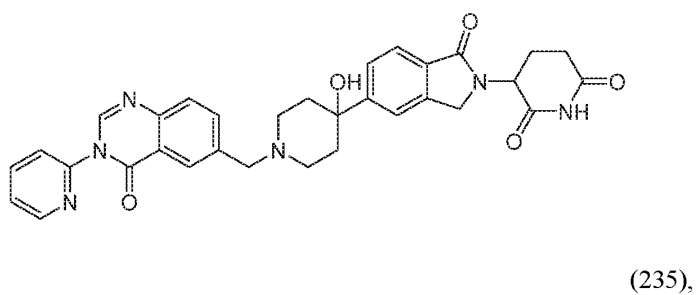
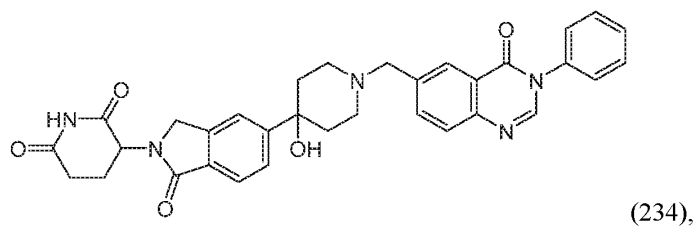
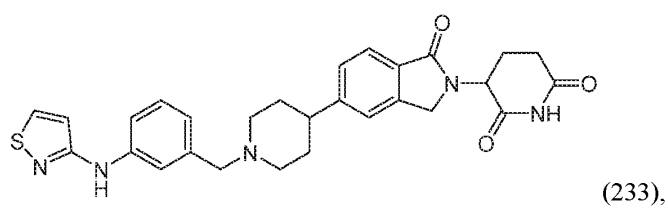
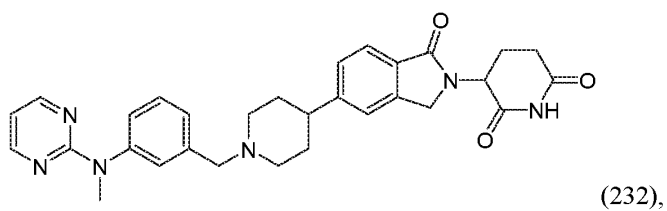
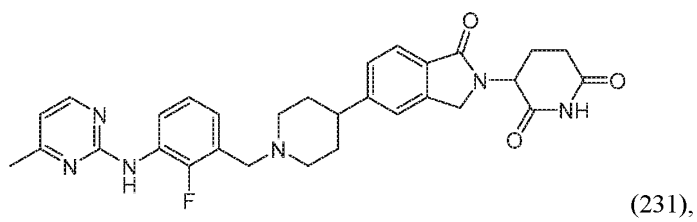
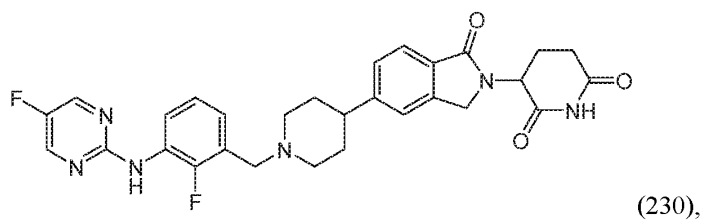
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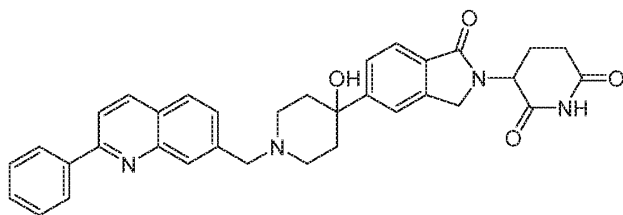


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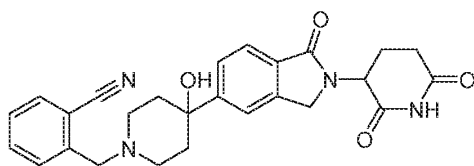




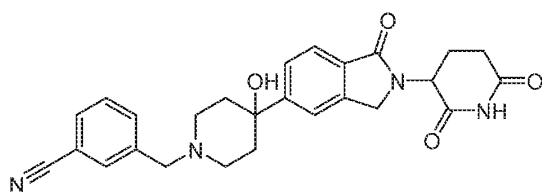




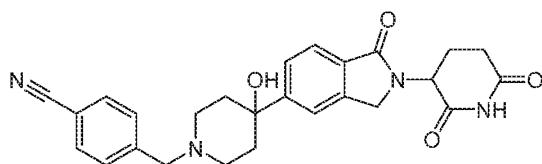
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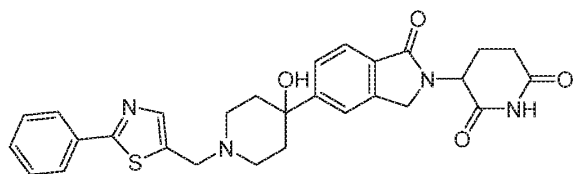
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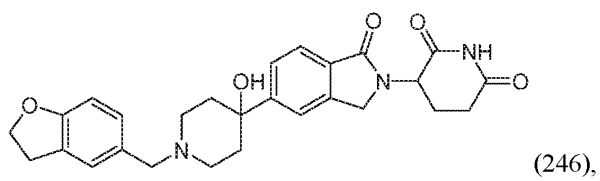
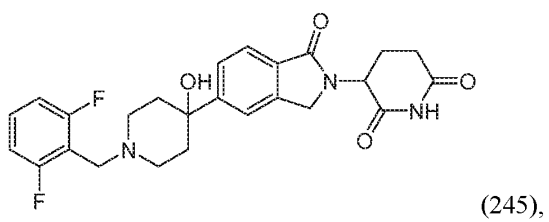
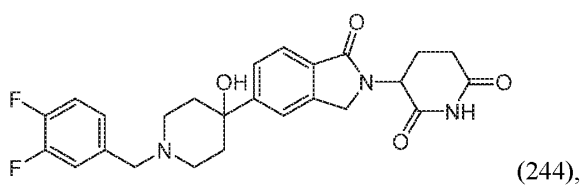
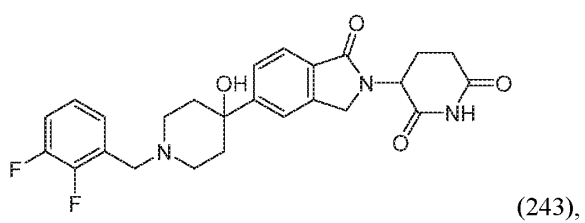
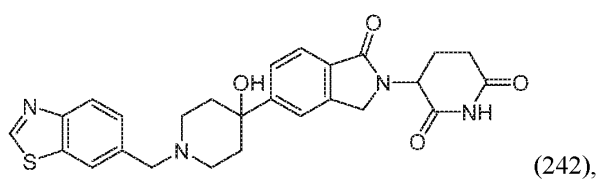
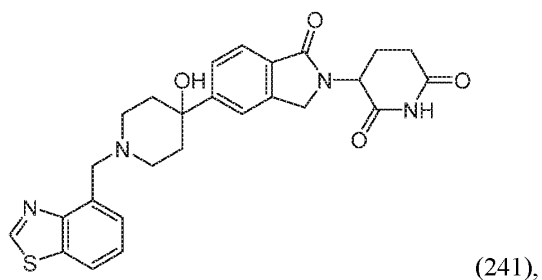
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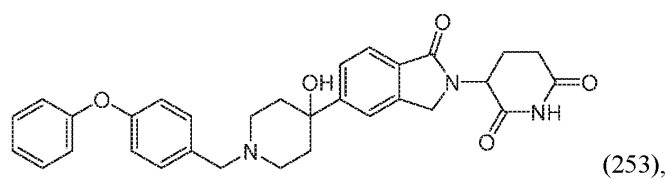
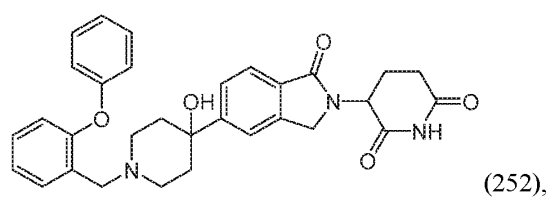
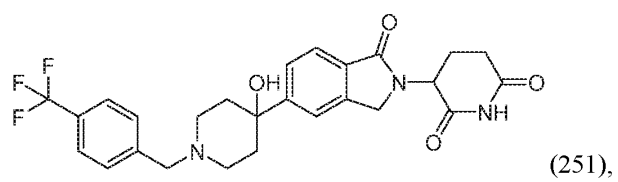
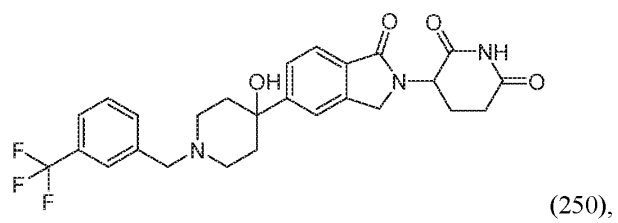
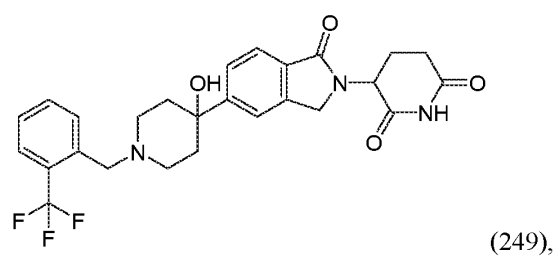
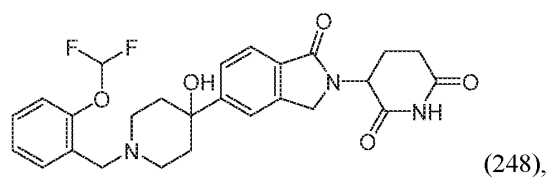
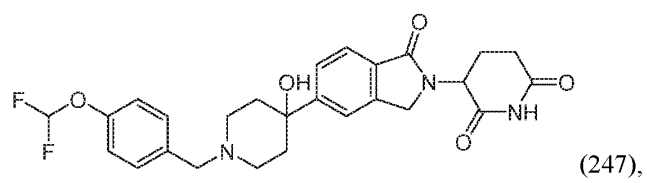


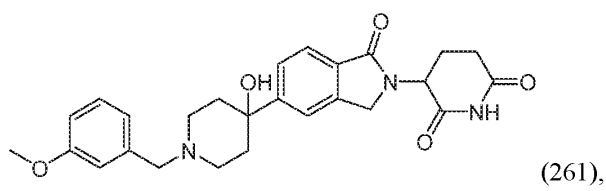
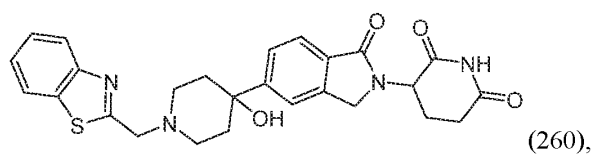
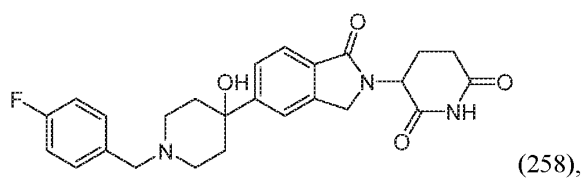
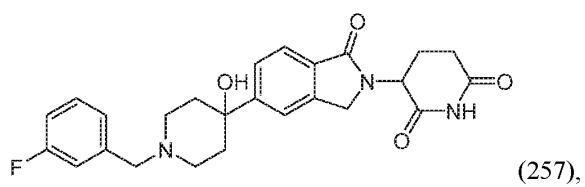
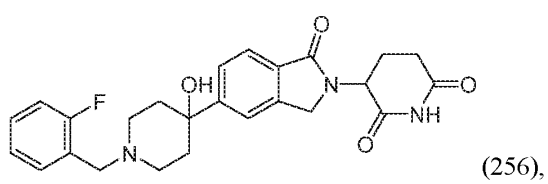
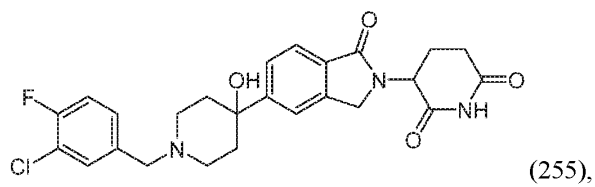
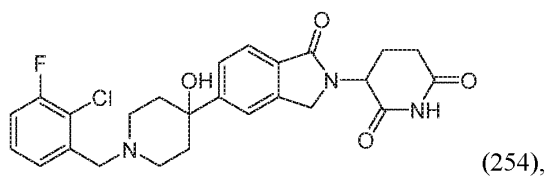
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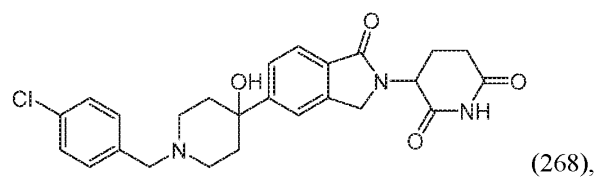
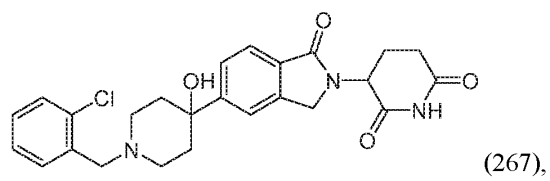
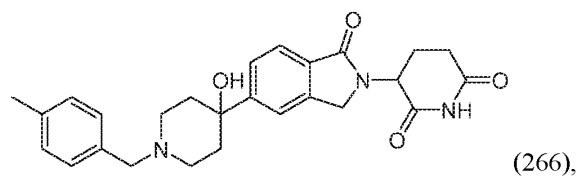
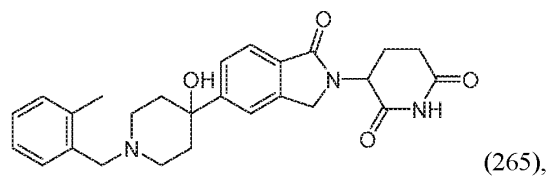
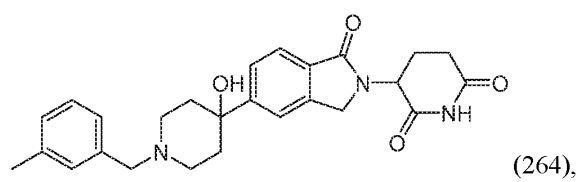
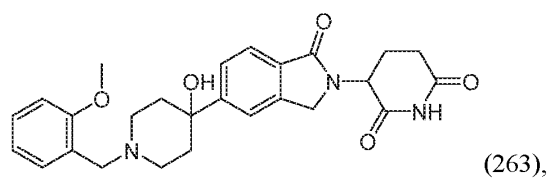
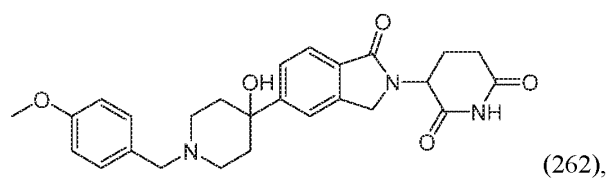


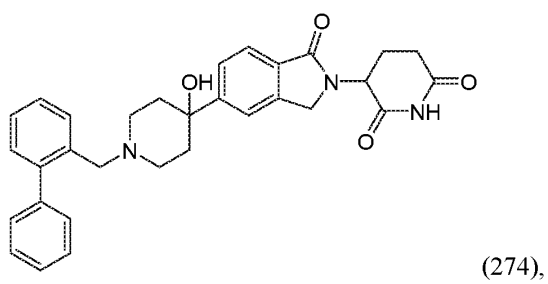
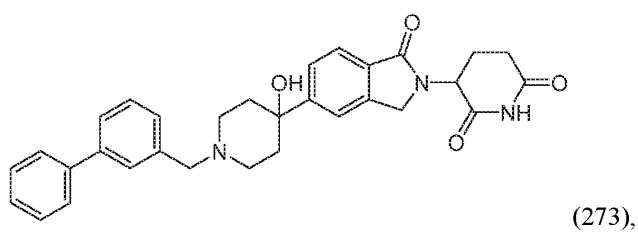
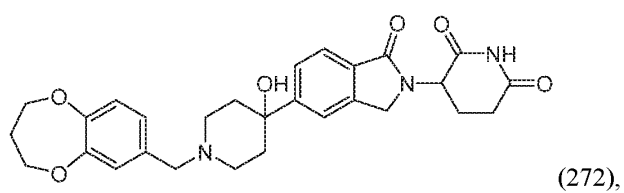
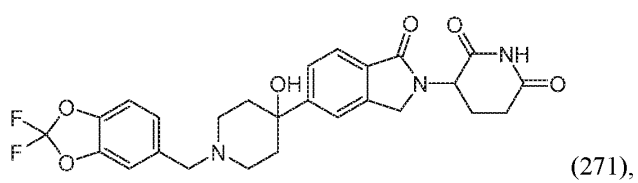
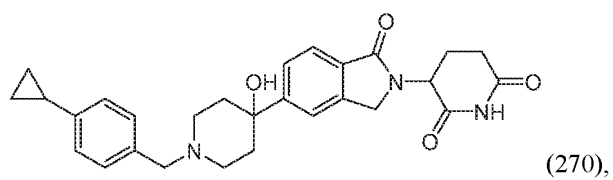
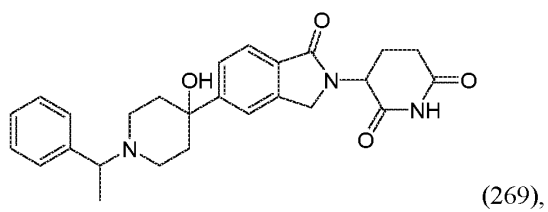
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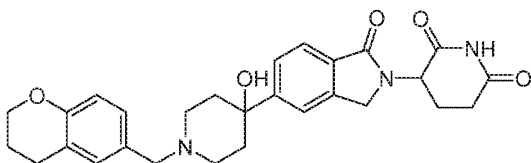




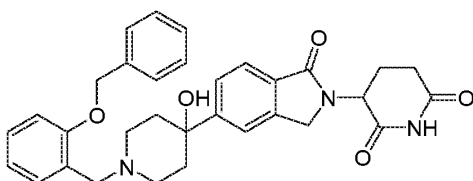




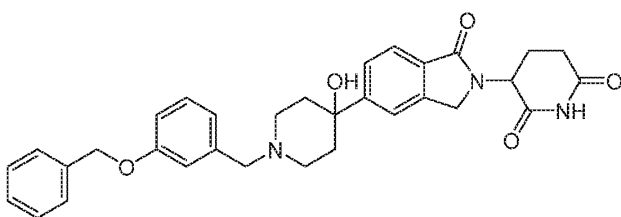




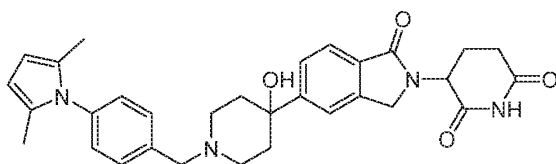
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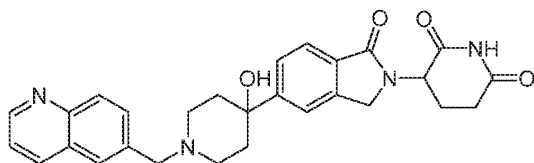
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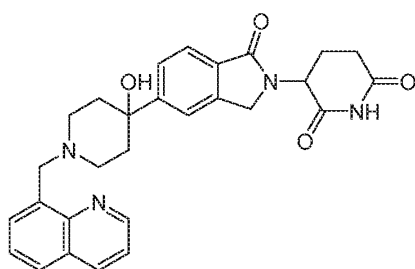
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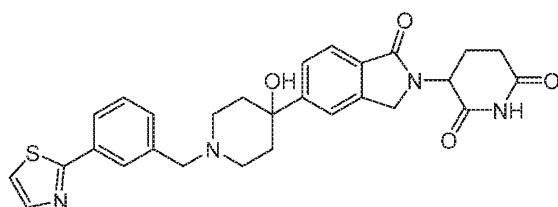
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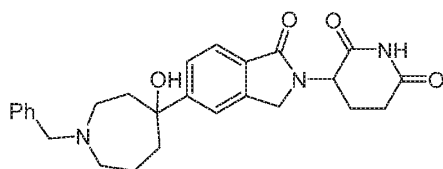
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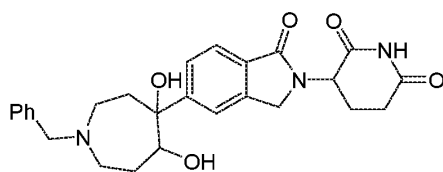
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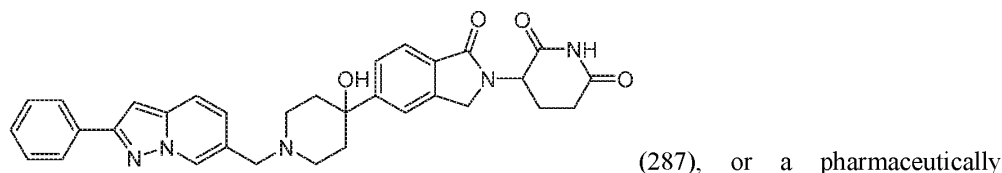
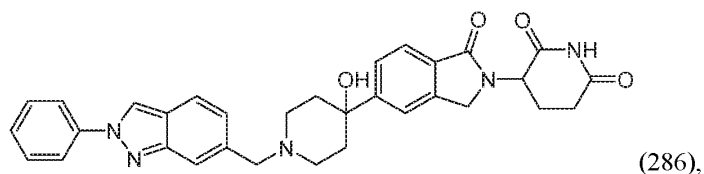
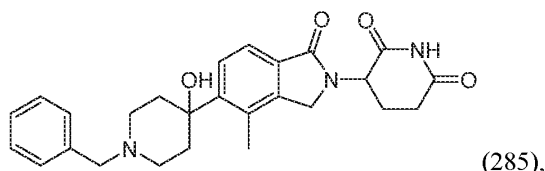
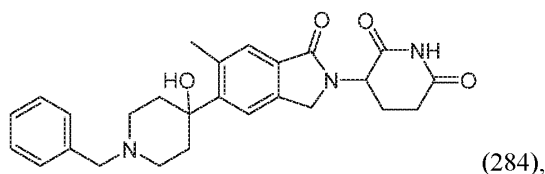
(281),



(282),



(283),



acceptable salt or stereoisomer thereof.

[0080] Compounds 9-12, 18, 26-27, 42-64, 67-69, 78-202, 209, 213-218, 221-224, and 226-233 are embraced by formula I. Compounds 1-8, 13-17, 19-25, 28-41, 65-66, 70-77, 203-208, 210-212, 219-220, 225, 234-258, and 260-287 are embraced by formula II.

[0081] Compounds of the present invention may be in the form of a free acid or free base, or a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable" in the context of a salt refers to a salt of the compound that does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, *i.e.*, the compound in salt form may be administered to a subject without causing undesirable biological effects (such as dizziness or gastric upset) or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The term "pharmaceutically acceptable salt" refers to a product obtained by reaction of the compound of the present invention with a suitable acid or a base. Examples of pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Al, Zn and Mn salts. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloride, hydrobromide,

hydroiodide, nitrate, sulfate, bisulfate, phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, 4-methylbenzenesulfonate or p-toluenesulfonate salts and the like. Certain compounds of the invention can form pharmaceutically acceptable salts with various organic bases such as lysine, arginine, guanidine, diethanolamine or metformin. Suitable base salts include aluminum, calcium, lithium, magnesium, potassium, sodium, or zinc salts.

[0082] Compounds of the present invention may have at least one chiral center and therefore 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*; therefore, 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 invention 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.

[0083] In some embodiments, the compound 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. Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and therefore may be advantageous in some circumstances.

[0084] Compounds of formulas (I) and (II) may also be in the form of N-oxides, crystalline forms (also known as polymorphs), 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.

[0085] The compounds of the present invention 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.

[0086] In some embodiments, the pharmaceutical composition comprises a co-crystal of an inventive compound. The term “co-crystal”, as used herein, refers to a stoichiometric multi-component system comprising a compound of the invention and a co-crystal former wherein the compound of the invention 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 the invention 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

[0087] In another aspect, the present invention is directed to a method for making an inventive compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. Broadly, the inventive compounds or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof may be prepared by any process known to be applicable to the preparation of chemically related compounds. The compounds of the present invention will be better understood in connection with the synthetic schemes that described in various working examples and which illustrate non-limiting methods by which the compounds of the invention may be prepared.

Pharmaceutical Compositions

[0088] Another aspect of the present invention is directed to a pharmaceutical composition that includes a therapeutically effective amount of an inventive compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer 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 invention 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.

[0089] Broadly, compounds of the invention and their pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers 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). 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). 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.

[0090] In some embodiments, the compounds are formulated for oral or intravenous administration (*e.g.*, systemic intravenous injection).

[0091] Accordingly, compounds of the invention 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.

[0092] 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.

[0093] In some embodiments, compounds of the invention 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.

[0094] 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.

[0095] 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.

[0096] In certain embodiments, compounds of the invention 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.

[0097] The compositions may be formulated for buccal or sublingual administration, examples of which include tablets, lozenges and gels.

[0098] The compounds of the invention 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.

[0099] Compounds of the invention may be formulated for topical administration which as used herein, refers to administration intradermally by invention of the formulation to the epidermis. These types of compositions are typically in the form of ointments, pastes, creams, lotions, gels, solutions and sprays.

[00100] 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.

[00101] 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). Representative examples of penetration enhancing agents include triglycerides (*e.g.*, soybean oil), aloe compositions (*e.g.*, aloe-vera gel), ethyl alcohol, isopropyl alcohol, octyloxyphenylpolyethylene 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.

[00102] 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, allantoin, dimethicone, glycerin, petrolatum, and zinc oxide.

[00103] 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.

[00104] Ophthalmic formulations include eye drops.

[00105] 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

[00106] As used herein, the term, "therapeutically effective amount" refers to an amount of an inventive compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof that is effective in producing the desired therapeutic response in a patient suffering from a disease or disorder involving IKZF2 (Helios) and would benefit from IKZF2 degradation. The term "therapeutically effective amount" therefore includes the amount of the inventive compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer 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 cells, or reduces the amounts of IKZF2 in diseased cells.

[00107] 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 will depend upon a variety of factors, including the following: the disease or disorder being treated and the severity thereof (*e.g.*, its present status); the activity of the compound employed; the specific composition employed; 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 compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts (*see, for example, Hardman et al., eds., Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th Edition, McGraw-Hill Press, 155-173, 2001).

[00108] Compounds of the invention may be effective over a wide dosage range. In some embodiments, the total daily dosage (*e.g.*, for adult humans) may range from about 0.001 to about 1600 mg, from 0.01 to about 1000 mg, from 0.01 to about 500 mg, from about 0.01 to about 100 mg, from about 0.5 to about 100 mg, from 1 to about 100-400 mg per day, from about 1 to about 50 mg per day, from about 5 to about 40 mg per day, and in yet other embodiments from about 10 to about 30 mg per day. Individual dosages may be formulated to contain the desired dosage amount depending upon the number of times the compound is administered per day. By way of example, capsules may be formulated with from about 1 to about 200 mg of compound (*e.g.*, 1, 2, 2.5, 3, 4, 5, 10, 15, 20, 25, 50, 100, 150, and 200 mg). In some embodiments, the compound may be administered at a dose in range from about 0.01 mg to about 200 mg/kg of body weight per day. In some embodiments, a dose of from 0.1 to 100, *e.g.*, from 1 to 30 mg/kg per day in one or more dosages per day may be effective. By way of example, a suitable dose for oral administration may be in the range of 1-30 mg/kg of body weight per day, and a suitable dose for intravenous administration may be in the range of 1-10 mg/kg of body weight per day.

Methods of Use

[00109] In some aspects, the present invention is directed to methods of treating diseases or disorders involving IKZF2, that entails administration of a therapeutically effective amount of a compound of formula (I) and/or (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, to a subject in need thereof.

[00110] Broadly, the diseases or disorders that may be amenable to treatment with compounds of the present invention involve IKZF2 or otherwise functionally abnormal IKZF2 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 subject's state of health. In some embodiments, compounds of formula (I) and (II) may be useful in the treatment of cell proliferative diseases and disorders (*e.g.*, cancer or benign neoplasms). 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.

[00111] 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 as well as livestock such as cows, horses, sheep, goats, pigs, and other domesticated and wild animals. A subject "in need of" treatment according to the present invention 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. Therefore, subjects suffering from, and suspected of suffering from, a specific disease or disorder are not necessarily two distinct groups.

[00112] Exemplary types of non-cancerous (*e.g.*, cell proliferative) diseases or disorders that may be amenable to treatment with the compounds of the present invention include inflammatory diseases and conditions, autoimmune diseases, neurodegenerative diseases, heart diseases, viral diseases, chronic and acute kidney diseases or injuries, metabolic diseases, and allergic and genetic diseases.

[00113] Representative examples of specific non-cancerous diseases and disorders include rheumatoid arthritis, alopecia areata, lymphoproliferative conditions, autoimmune hematological disorders (*e.g.* hemolytic anemia, aplastic anemia, anhidrotic ectodermal dysplasia, pure red cell anemia and idiopathic thrombocytopenia), cholecystitis, acromegaly, rheumatoid spondylitis, osteoarthritis, gout, scleroderma, sepsis, septic shock, dacryoadenitis, cryopyrin associated periodic syndrome (CAPS), endotoxic shock, endometritis, gram-negative sepsis, keratoconjunctivitis sicca, toxic shock syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, chronic pulmonary inflammation, chronic graft rejection, hidradenitis suppurativa, inflammatory bowel disease, Crohn's disease, Behcet's syndrome, systemic lupus erythematosus, glomerulonephritis, multiple sclerosis,

juvenile-onset diabetes, autoimmune uveoretinitis, autoimmune vasculitis, thyroiditis, Addison's disease, lichen planus, appendicitis, bullous pemphigus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, myasthenia gravis, immunoglobulin A nephropathy, Hashimoto's disease, Sjogren's syndrome, vitiligo, Wegener granulomatosis, granulomatous orchitis, autoimmune oophoritis, sarcoidosis, rheumatic carditis, ankylosing spondylitis, Grave's disease, autoimmune thrombocytopenic purpura, psoriasis, psoriatic arthritis, eczema, dermatitis herpetiformis, ulcerative colitis, pancreatic fibrosis, hepatitis, hepatic fibrosis, CD14 mediated sepsis, non-CD14 mediated sepsis, acute and chronic renal disease, irritable bowel syndrome, pyresis, restenosis, cervicitis, stroke and ischemic injury, neural trauma, acute and chronic pain, allergic rhinitis, allergic conjunctivitis, chronic heart failure, congestive heart failure, acute coronary syndrome, cachexia, malaria, leprosy, leishmaniasis, Lyme disease, Reiter's syndrome, acute synovitis, muscle degeneration, bursitis, tendonitis, tenosynovitis, herniated, ruptured, or prolapsed intervertebral disk syndrome, osteopetrosis, rhinosinusitis, thrombosis, silicosis, pulmonary sarcosis, bone resorption diseases, such as osteoporosis, fibromyalgia, AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus and cytomegalovirus, diabetes Type I and II, obesity, insulin resistance and diabetic retinopathy, 22q11.2 deletion syndrome, Angelman syndrome, Canavan disease, celiac disease, Charcot-Marie-Tooth disease, color blindness, Cri du chat, Down syndrome, cystic fibrosis, Duchenne muscular dystrophy, haemophilia, Klinefelter's syndrome, neurofibromatosis, phenylketonuria, Prader-Willi syndrome, sickle cell disease, Tay-Sachs disease, Turner syndrome, urea cycle disorders, thalassemia, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, uveitis, polymyositis, proctitis, interstitial lung fibrosis, dermatomyositis, atherosclerosis, arteriosclerosis, amyotrophic lateral sclerosis, asociality, varicosis, vaginitis, depression, and Sudden Infant Death Syndrome.

[00114] In other embodiments, the methods are directed to treating subjects having cancer. Broadly, the compounds of the present invention may be effective in the treatment of carcinomas (solid tumors including both primary and metastatic tumors), sarcomas, melanomas, and hematological cancers (cancers affecting blood including lymphocytes, bone marrow and/or lymph nodes) such as leukemia, lymphoma and multiple myeloma. Adult tumors/cancers and pediatric tumors/cancers are included. The cancers may be vascularized, or not yet substantially vascularized, or non-vascularized tumors.

[00115] Representative examples of cancers includes adrenocortical carcinoma, AIDS-related cancers (*e.g.*, Kaposi's and AIDS-related lymphoma), appendix cancer, childhood cancers (*e.g.*, childhood cerebellar astrocytoma, childhood cerebral astrocytoma), basal cell carcinoma, skin cancer (non-melanoma), biliary cancer, extrahepatic bile duct cancer, intrahepatic bile duct cancer, bladder cancer, urinary bladder cancer, brain cancer (*e.g.*, gliomas and glioblastomas such as brain stem glioma, gestational trophoblastic tumor glioma, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma), breast cancer, bronchial adenomas/carcinoids, carcinoid tumor, nervous system cancer (*e.g.*, central nervous system cancer, central nervous system lymphoma), cervical cancer, chronic myeloproliferative disorders, colorectal cancer (*e.g.*, colon cancer, rectal cancer), polycythemia vera, lymphoid neoplasm, mycosis fungoides, Sezary Syndrome, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastrointestinal cancer (*e.g.*, stomach cancer, small intestine cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST)), germ cell tumor, ovarian germ cell tumor, head and neck cancer, Hodgkin's lymphoma, leukemia, lymphoma, multiple myeloma, hepatocellular carcinoma, hypopharyngeal cancer, intraocular melanoma, ocular cancer, islet cell tumors (endocrine pancreas), renal cancer (*e.g.*, Wilm's Tumor, clear cell renal cell carcinoma), liver cancer, lung cancer (*e.g.*, non-small cell lung cancer and small cell lung cancer), Waldenstrom's macroglobulinemia, melanoma, intraocular (eye) melanoma, merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer with occult primary, multiple endocrine neoplasia (MEN), myelodysplastic syndromes, essential thrombocythemia, myelodysplastic/myeloproliferative diseases, nasopharyngeal cancer, neuroblastoma, oral cancer (*e.g.*, mouth cancer, lip cancer, oral cavity cancer, tongue cancer, oropharyngeal cancer, throat cancer, laryngeal cancer), ovarian cancer (*e.g.*, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor), pancreatic cancer, islet cell pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineoblastoma, pituitary tumor, plasma cell neoplasm, pleuropulmonary blastoma, prostate cancer, retinoblastoma rhabdomyosarcoma, salivary gland cancer, uterine cancer (*e.g.*, endometrial uterine cancer, uterine sarcoma, uterine corpus cancer), squamous cell carcinoma, testicular cancer, thymoma, thymic carcinoma, thyroid

cancer, transitional cell cancer of the renal pelvis and ureter and other urinary organs, urethral cancer, gestational trophoblastic tumor, vaginal cancer and vulvar cancer.

[00116] Sarcomas that may be treatable with compounds of the present invention include both soft tissue and bone cancers alike, representative examples of which include osteosarcoma or osteogenic sarcoma (bone) (*e.g.*, Ewing's sarcoma), chondrosarcoma (cartilage), leiomyosarcoma (smooth muscle), rhabdomyosarcoma (skeletal muscle), mesothelial sarcoma or mesothelioma (membranous lining of body cavities), fibrosarcoma (fibrous tissue), angiosarcoma or hemangioendothelioma (blood vessels), liposarcoma (adipose tissue), glioma or astrocytoma (neurogenic connective tissue found in the brain), myxosarcoma (primitive embryonic connective tissue) and mesenchymous or mixed mesodermal tumor (mixed connective tissue types).

[00117] In some embodiments, methods of the present invention entail treatment of subjects having cell proliferative diseases or disorders of the hematological system, liver, brain, lung, colon, pancreas, prostate, ovary, breast, skin, and endometrium.

[00118] As used herein, "cell proliferative diseases or disorders of the hematologic 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 multiple myeloma, lymphoma (including T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma (diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and ALK+ anaplastic large cell lymphoma (*e.g.*, B-cell non-Hodgkin's lymphoma selected from diffuse large B-cell lymphoma (*e.g.*, germinal center B-cell-like diffuse large B-cell lymphoma or 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, metastatic pancreatic adenocarcinoma, refractory B-cell non-Hodgkin's lymphoma, and relapsed B-cell non-Hodgkin's lymphoma, childhood lymphomas, and lymphomas of lymphocytic and cutaneous origin, *e.g.*, small lymphocytic lymphoma, leukemia, including childhood leukemia, hairy-cell leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloid leukemia (*e.g.*, acute monocytic leukemia), chronic

lymphocytic leukemia, small lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, and mast cell leukemia, myeloid neoplasms and mast cell neoplasms.

[00119] 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 brain may include hyperplasia, metaplasia, dysplasia of the liver, hepatocellular carcinoma, intrahepatic cholangiocarcinoma (bile duct cancer), angiosarcoma, hemangiosarcoma, hepatoblastoma, and secondary liver cancer (metastatic liver cancer).

[00120] 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.

[00121] As used herein, “cell proliferative diseases or disorders of the lung” include all forms of cell proliferative disorders affecting lung cells. Cell proliferative disorders of the lung include lung cancer, precancer and precancerous conditions of the lung, benign growths or lesions of the lung, hyperplasia, metaplasia, and dysplasia of the lung, and metastatic lesions in the tissue and organs in the body other than the lung. Lung cancer includes all forms of cancer of the lung, *e.g.*, malignant lung neoplasms, carcinoma *in situ*, typical carcinoid tumors, and atypical carcinoid tumors. Lung cancer includes small cell lung cancer (“SLCL”), non-small cell lung cancer (“NSCLC”), squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, squamous cell carcinoma, and mesothelioma. Lung cancer can include “scar carcinoma”, bronchioveolar carcinoma, giant cell carcinoma, spindle cell carcinoma, and large cell neuroendocrine carcinoma. Lung cancer also includes lung neoplasms having histologic and ultrastructural heterogeneity (*e.g.*, mixed cell types). In some embodiments, a compound of the present invention may be used to treat non-metastatic or

metastatic lung cancer (*e.g.*, NSCLC, ALK-positive NSCLC, NSCLC harboring ROS1 Rearrangement, Lung Adenocarcinoma, and Squamous Cell Lung Carcinoma).

[00122] 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, familial 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.

[00123] As used herein, “cell proliferative diseases or disorders of the pancreas” include all forms of cell proliferative disorders affecting pancreatic cells. Cell proliferative disorders of the pancreas may include pancreatic cancer, a precancer or precancerous condition of the pancreas, hyperplasia of the pancreas, dysplasia of the pancreas, benign growths or lesions of the pancreas, and malignant growths or lesions of the pancreas, and metastatic lesions in tissue and organs in the body other than the pancreas. Pancreatic cancer includes all forms of cancer of the pancreas, including ductal adenocarcinoma, adenosquamous carcinoma, pleomorphic giant cell carcinoma, mucinous adenocarcinoma, osteoclast-like giant cell carcinoma, mucinous cystadenocarcinoma, acinar carcinoma, unclassified large cell carcinoma, small cell carcinoma, pancreatoblastoma, papillary neoplasm, mucinous cystadenoma, papillary cystic neoplasm, and serous cystadenoma, and pancreatic neoplasms having histologic and ultrastructural heterogeneity (*e.g.*, mixed cell types).

[00124] 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.

[00125] As used herein, “cell proliferative diseases or disorders of the ovary” include all forms of cell proliferative disorders affecting cells of the ovary. Cell proliferative disorders of

the ovary may include a precancer or precancerous condition of the ovary, benign growths or lesions of the ovary, ovarian cancer, and metastatic lesions in tissue and organs in the body other than the ovary. Cell proliferative disorders of the ovary may include hyperplasia, metaplasia, and dysplasia of the ovary.

[00126] 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.

[00127] As used herein, “cell proliferative diseases or disorders of the skin” include all forms of cell proliferative disorders affecting skin cells. Cell proliferative disorders of the skin may include a precancer or precancerous condition of the skin, benign growths or lesions of the skin, melanoma, malignant melanoma or other malignant growths or lesions of the skin, and metastatic lesions in tissue and organs in the body other than the skin. Cell proliferative disorders of the skin may include hyperplasia, metaplasia, and dysplasia of the skin.

[00128] As used herein, “cell proliferative diseases or disorders of the endometrium” include all forms of cell proliferative disorders affecting cells of the endometrium. Cell proliferative disorders of the endometrium may include a precancer or precancerous condition of the endometrium, benign growths or lesions of the endometrium, endometrial cancer, and metastatic lesions in tissue and organs in the body other than the endometrium. Cell proliferative disorders of the endometrium may include hyperplasia, metaplasia, and dysplasia of the endometrium.

[00129] In some embodiments, compounds of the present invention may be used to treat T cell leukemia or T cell lymphoma.

[00130] In some embodiments, compounds of the present invention may be used to treat Hodgkin’s lymphoma or non-Hodgkin’s lymphoma.

[00131] In some embodiments, compounds of the present invention may be used to treat myeloid leukemia.

[00132] In some embodiments, compounds of the present invention may be used to treat non-small cell lung cancer (NSCLC).

[00133] In some embodiments, compounds of the present invention may be used to treat melanoma.

[00134] In some embodiments, compounds of the present invention may be used to treat triple-negative breast cancer (TNBC).

[00135] In some embodiments, compounds of the present invention may be used to treat nasopharyngeal cancer (NPC).

[00136] In some embodiments, compounds of the present invention may be used to treat microsatellite stable colorectal cancer (mssCRC).

[00137] In some embodiments, compounds of the present invention may be used to treat thymoma.

[00138] In some embodiments, compounds of the present invention may be used to treat carcinoid.

[00139] In some embodiments, compounds of the present invention may be used to treat gastrointestinal stromal tumor (GIST).

[00140] The compounds of the present invention and their pharmaceutically acceptable salts and stereoisomers may be administered to a patient, *e.g.*, a cancer patient, as a monotherapy or by way of combination therapy. Therapy may be "front/first-line", *i.e.*, as an initial treatment in patients who have undergone no prior anti-cancer treatment regimens, either alone or in combination with other treatments; or "second-line", as a treatment in patients who have undergone a prior anti-cancer treatment regimen, either alone or in combination with other treatments; or as "third-line", "fourth-line", etc. treatments, either alone or in combination with other treatments. Therapy may also be given to patients who have had previous treatments which have been unsuccessful, or partially successful but who became non-responsive or intolerant to the particular treatment. Therapy may also be given as an adjuvant treatment, *i.e.*, to prevent reoccurrence of cancer in patients with no currently detectable disease or after surgical removal of a tumor. Therefore, in some embodiments, the compound may be administered to a patient who has received prior therapy, such as chemotherapy, radioimmunotherapy, surgical therapy, immunotherapy, radiation therapy, targeted therapy or any combination thereof.

[00141] The methods of the present invention may entail administration of an inventive compound or a pharmaceutical composition thereof to the patient in a single dose or in multiple doses (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 10, 15, 20, or more doses). For example, the frequency of

administration may range from once a day up to about once every eight weeks. In some embodiments, the frequency of administration ranges from about once a day for 1, 2, 3, 4, 5, or 6 weeks, and in other embodiments entails at least one 28-day cycle which includes daily administration for 3 weeks (21 days) followed by a 7-day off period. In other embodiments, the compound may be dosed twice a day (BID) over the course of two and a half days (for a total of 5 doses) or once a day (QD) over the course of two days (for a total of 2 doses). In other embodiments, the compound may be dosed once a day (QD) over the course of five days.

Combination Therapy

[00142] The compounds of the present invention and their pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers may be used in combination or concurrently with at least one other active agent *e.g.*, anti-cancer agent or regimen, in treating diseases and disorders. The terms “in combination” and “concurrently” in this context mean that the agents are co-administered, which includes substantially contemporaneous administration, by way of the same or separate dosage forms, and by the same or different modes of administration, or sequentially, *e.g.*, as part of the same treatment regimen, or by way of successive treatment regimens. Therefore, if given sequentially, at the onset of administration of the second agent, the first of the two agents is in some cases still detectable at effective concentrations at the site of treatment. The sequence and time interval may be determined such that they can act together (*e.g.*, synergistically to provide an increased benefit than if they were administered otherwise). For example, the agents may be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they may be administered sufficiently close in time so as to provide the desired therapeutic effect, which may be in a synergistic fashion. Therefore, the terms are not limited to the administration of the active agents at exactly the same time.

[00143] In some embodiments, the treatment regimen may include administration of a compound of the present invention or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof in combination with one or more additional therapeutic agents known for use in treating the disease or disorder (*e.g.*, cancer). The dosage of the additional anticancer therapeutic may be the same or even lower than known or recommended doses. *See, Hardman et al.*, eds., *Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics*, 10th ed., McGraw-Hill, New York, 2001; *Physician's Desk Reference* 60th ed., 2006. For example, anti-cancer agents that may be used in combination

with the inventive compounds are known in the art. *See, e.g.*, U.S. Patent 9,101,622 (Section 5.2 thereof) and U.S. Patent 9,345,705 B2 (Columns 12-18 thereof). Representative examples of additional anti-cancer agents and treatment regimens include radiation therapy, chemotherapeutics (*e.g.*, mitotic inhibitors, angiogenesis inhibitors, anti-hormones, autophagy inhibitors, alkylating agents, intercalating antibiotics, growth factor inhibitors, anti-androgens, signal transduction pathway inhibitors, anti-microtubule agents, platinum coordination complexes, HDAC inhibitors, proteasome inhibitors, and topoisomerase inhibitors), immune-modulators, therapeutic antibodies (*e.g.*, mono-specific and bispecific antibodies) and CAR-T therapy.

[00144] In some embodiments, the compound of the invention and the additional anticancer therapeutic agent may be administered less than 5 minutes apart, less than 30 minutes apart, less than 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart. The two or more anticancer therapeutics may be administered within the same patient visit.

[00145] In some embodiments, the compound of the present invention and the additional therapeutic agent (*e.g.*, an anti-cancer therapeutic) are cyclically administered. By way of example in the context of cancer treatment, cycling therapy involves the administration of one anticancer therapeutic for a period of time, followed by the administration of a second anticancer therapeutic for a period of time and repeating this sequential administration, *i.e.*, the cycle, in order to reduce the development of resistance to one or both of the anticancer therapeutics, to avoid or reduce the side effects of one or both of the anticancer therapeutics, and/or to improve the efficacy of the therapies. In one example, cycling therapy involves the administration of a first anticancer therapeutic for a period of time, followed by the administration of a second anticancer therapeutic for a period of time, optionally, followed by the administration of a third anticancer therapeutic for a period of time and so forth, and

repeating this sequential administration, *i.e.*, the cycle in order to reduce the development of resistance to one of the anticancer therapeutics, to avoid or reduce the side effects of one of the anticancer therapeutics, and/or to improve the efficacy of the anticancer therapeutics.

[00146] In some embodiments, and depending on the particular cancer being treated, the compound of the present invention may be used in combination with at least one other anti-cancer agent such as Paclitaxel (*e.g.*, ovarian cancer, breast cancer, lung cancer, Kaposi sarcoma, cervical cancer, and pancreatic cancer), Topotecan (*e.g.*, ovarian cancer and lung cancer), Irinotecan (*e.g.*, colon cancer, and small cell lung cancer), Etoposide (*e.g.*, testicular cancer, lung cancer, lymphomas, and non-lymphocytic leukemia), Vincristine (*e.g.*, leukemia), Leucovorin (*e.g.*, colon cancer), Altretamine (*e.g.*, ovarian cancer), Daunorubicin (*e.g.*, acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), and Kaposi's sarcoma), Trastuzumab (*e.g.*, breast cancer, stomach cancer, and esophageal cancer), Rituximab (*e.g.*, non-Hodgkin's lymphoma), Cetuximab (*e.g.*, colorectal cancer, metastatic non-small cell lung cancer and head and neck cancer), Pertuzumab (*e.g.*, metastatic HER2-positive breast cancer), Alemtuzumab (*e.g.*, chronic lymphocytic leukemia (CLL), cutaneous T-cell lymphoma (CTCL) and T-cell lymphoma), Panitumumab (*e.g.*, colon and rectum cancer), Tamoxifen (*e.g.*, breast cancer), Fulvestrant (*e.g.*, breast cancer), Letrozole (*e.g.*, breast cancer), Exemestane (*e.g.*, breast cancer), Azacytidine (*e.g.*, myelodysplastic syndromes), Mitomycin C (*e.g.*, gastro-intestinal cancers, anal cancers, and breast cancers), Dactinomycin (*e.g.*, Wilms tumor, rhabdomyosarcoma, Ewing's sarcoma, trophoblastic neoplasm, testicular cancer, and ovarian cancer), Erlotinib (*e.g.*, non-small cell lung cancer and pancreatic cancer), Sorafenib (*e.g.*, kidney cancer and liver cancer), Temsirolimus (*e.g.*, kidney cancer), Bortezomib (*e.g.*, multiple myeloma and mantle cell lymphoma), Pegaspargase (*e.g.*, acute lymphoblastic leukemia), Cabometyx (*e.g.*, hepatocellular carcinoma, medullary thyroid cancer, and renal cell carcinoma), Keytruda (*e.g.*, cervical cancer, gastric cancer, hepatocellular carcinoma, Hodgkin's lymphoma, melanoma, Merkel cell carcinoma, non-small cell lung cancer, urothelial carcinoma, and squamous cell carcinoma of the head and neck), Nivolumab (*e.g.*, colorectal cancer, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, small cell lung cancer, and urothelial carcinoma), and Regorafenib (*e.g.*, colorectal cancer, gastrointestinal stromal tumor, and hepatocellular carcinoma).

Pharmaceutical Kits

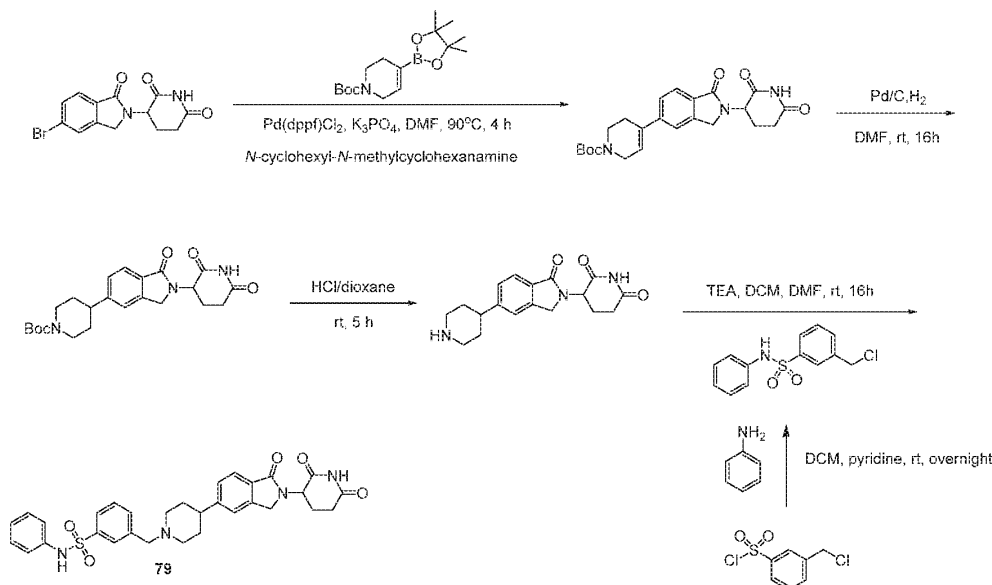
[00147] The present compositions may be assembled into kits or pharmaceutical systems. Kits or pharmaceutical systems according to this aspect of the invention include a carrier or package such as a box, carton, tube or the like, having in close confinement therein one or more containers, such as vials, tubes, ampoules, or bottles, which contain a compound of the present invention or a pharmaceutical composition which contains the compound and a pharmaceutically acceptable carrier wherein the compound and the carrier may be disposed in the same or separate containers. The kits or pharmaceutical systems of the invention may also include printed instructions for using the compounds and compositions.

[00148] These and other aspects of the present invention will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the invention but are not intended to limit its scope, as defined by the claims.

EXAMPLES

[00149] These and other aspects of the present invention will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the invention but are not intended to limit its scope, as defined by the claims.

[00150] Example 1: Synthesis of 3-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-yl)methyl)-N-phenylbenzenesulfonamide (79) - General Method A



tert-Butyl-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate

[00151] A mixture of 3-(6-bromo-3-oxo-1H-isindol-2-yl)piperidine-2,6-dione (3.0 g, 9.3 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (11.5 g, 37.3 mmol), potassium phosphate (2.0 g, 9.3 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.7 g, 1.9 mmol) in *N,N*-dimethylformamide (DMF) (20 mL) stirred at 90°C for 4 h. The reaction mixture was then concentrated to afford a residue, which was then dissolved in ethyl acetate (EtOAc) (500 mL). Water (500 mL) was added and the layers were separated. To the aqueous phase was added solid sodium chloride under vigorous stirring until saturation of NaCl was reached (solid NaCl was visible and not dissolved). The undissolved NaCl was removed, and the aqueous phase was further extracted with tetrahydrofuran (THF) (500 mL x 2). The combined organic layers were dried and concentrated to afford a crude product, which was purified using silica gel column chromatography (petroleum ether/EtOAc = 1:1 to 100% EtOAc) to afford the title compound as a yellow solid (1.1 g, 36%). ESI-MS (EI^+ , m/z): 426.3.

tert-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidine-1-carboxylate

[00152] To a mixture of *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.0 g, 2.4 mmol) and 10% Pd/C (400 mg) was added DMF (10 mL). The suspension stirred at room temperature (rt) for 16 h under hydrogen atmosphere. The reaction mixture was then diluted with dichloromethane (DCM), filtered and concentrated to afford the title compound as a yellow solid (1.0 g, 91%), which was used without further purification. ESI-MS (EI⁺, m/z): 428.3.

3-(1-Oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione

[00153] To *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidine-1-carboxylate (1.0 g, 2.3 mmol) was added 4.0 M HCl/dioxane (6 mL), and the reaction vessel was closed and the reaction stirred at rt for 2 h. The reaction mixture was concentrated under vacuum to afford the title compound as a yellow solid (1.0 g, 100%), which was used without further purification. ESI-MS (EI⁺, m/z): 328.3.

3-(Chloromethyl)-N-phenylbenzenesulfonamide

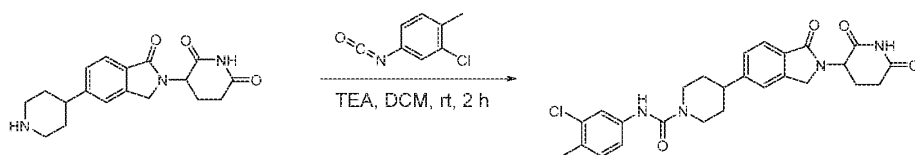
[00154] To a rt solution of aniline (46 mg, 0.491 mmol) in DCM (4 mL) was added pyridine (35.3 mg), and the reaction mixture was cooled to 0°C. Then a solution of 3-(chloromethyl)benzenesulfonyl chloride (100 mg, 0.447 mmol) in DCM (2 mL) was added, and the reaction stirred for 4 h at 0°C. The reaction mixture was then partitioned between EtOAc and water, and the pH was adjusted to 4-5 by adding citric acid. The combined organic phases were washed with water and brine, dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (Petroleum ether/EtOAc = 3/1) to afford the title compound as a yellow oil (110 mg). LC-MS (EI⁺, m/z): 280.

3-((4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-yl)methyl)-N-phenylbenzenesulfonamide (79)

[00155] To a solution of 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (117 mg, 0.36 mmol), triethylamine (TEA) (360 mg, 3.6 mmol) in DMF (2 mL) was added the 3-(chloromethyl)-N-phenylbenzenesulfonamide (100 mg, 0.36 mmol) in DCM (1 mL), and the reaction mixture stirred at rt for 16 h. The reaction was then concentrated and the residue was

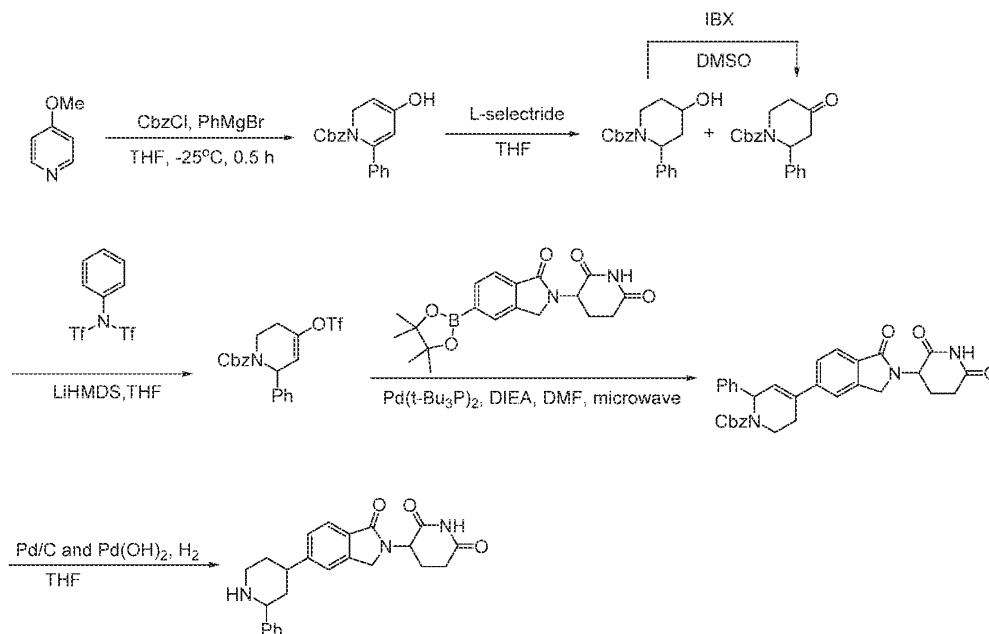
purified with prep-HPLC to afford the title compound as a yellow solid (56.1 mg, 32%). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.9 (s, 1H), 10.24 (br, 1H), 8.16 (d, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.54-7.48 (m, 3H), 7.41 (t, $J = 8.0$ Hz, 1H), 7.20 (t, $J = 8.0$ Hz, 1H), 7.08 (d, $J = 8.0$ Hz, 2H), 7.00 (t, $J = 4.0$ Hz, 1H), 5.0 (dd, $J = 12.0, 4.0$ Hz, 1H), 4.46-4.28 (m, 2H), 3.55 (d, $J = 8.0$ Hz, 2H), 2.91-2.87 (m, 1H), 2.78 (d, $J = 12.0$ Hz, 2H), 2.64-2.58 (m, 2H), 2.45-2.34 (m, 1H), 2.05-1.98 (m, 3H), 1.77-1.63 (m, 4H). ESI-MS (EI^+ , m/z): 573.3.

[00156] Example 2: Synthesis of N-(3-chloro-4-methylphenyl)-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidine-1-carboxamide (36)



[00157] To a solution of 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (80 mg, 0.25 mmol), TEA (252 mg, 10.0 mmol) in DCM (5 mL) was added 2-chloro-4-isocyanato-1-methylbenzene (41 mg, 0.25 mmol) in DCM (1 mL), and the reaction mixture stirred at rt for 2 h. The mixture was then concentrated and the crude product was purified with prep-HPLC to afford the title compound as a yellow solid (17.1 mg, 13%). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 11.97 (s, 1H), 8.58 (s, 1H), 7.66 (s, 1H), 7.55 (s, 1H), 7.51 (d, $J = 4.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.38 (dd, $J = 12.0, 8.0$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 1H), 5.12-5.07 (m, 1H), 4.43 (d, $J = 2.0$ Hz, 1H), 4.30 (t, $J = 4.0$ Hz, 3H), 2.96-2.90 (m, 4H), 2.63 (d, $J = 12.0$ Hz, 1H), 2.48-2.37 (m, 1H), 2.31 (s, 3H), 2.04-2.00 (m, 1H), 1.85 (d, $J = 12.0$ Hz, 2H), 1.69-1.60 (m, 2H). ESI-MS (EI^+ , m/z): 495.2.

[00158] Example 3: Synthesis of 3-(1-oxo-5-(2-phenylpiperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (72) - General method B



Benzyl 4-hydroxy-6-phenylpyridine-1(2H)-carboxylate

[00159] To anhydrous THF (400 mL) in a round bottomed flask under nitrogen was added PhMgBr (91.63 mL, 91.63 mmol) and the resulting solution was cooled to -25°C. 4-Methoxypyridine (10.00 g, 91.63 mmol) was added followed by CbzCl (15.58 g, 91.32 mmol). The mixture stirred at -25°C for 1.5 h under N₂. The mixture was quenched with aq. HCl (2 M, 60 mL) slowly at -25°C. After stirring for 15 min, the mixture was diluted with H₂O (80 mL) and extracted with EtOAc (240 mL). The combined organic layers were concentrated and the residue was purified by silica gel chromatography (Petroleum Ether: EtOAc = 5:1) to afford the title compound as a white solid (25 g, 89%). ESI-MS (EI⁺, m/z): 308.10.

Benzyl 4-hydroxy-2-phenylpiperidine-1-carboxylate and benzyl 4-oxo-2-phenylpiperidine-1-carboxylate

[00160] To a solution of benzyl 4-hydroxy-6-phenylpyridine-1(2H)-carboxylate (20.0 g, 65.15 mmol) in THF (400 mL) was added L-selectride (162.87 mL, 162.87 mmol) dropwise at -25°C under N₂. The mixture stirred at -25°C for 3 h under N₂. The mixture was quenched with

aq. NaHCO₃ (3%, 400 mL) at -25°C, and then further diluted with H₂O (100 mL). The aqueous phase was extracted with EtOAc (1.2 L). The combined organic layers were concentrated and the residue was purified by silica gel chromatography to afford benzyl 4-hydroxy-2-phenylpiperidine-1-carboxylate as a yellow oil (15.6 g, 74%) and benzyl 4-oxo-2-phenylpiperidine-1-carboxylate as a yellow oil (4 g, 20%). ESI-MS (EI⁺, m/z): 312.20.

[00161] To a solution of 4-hydroxy-2-phenylpiperidine-1-carboxylate (15.6 g, 50.16 mmol) in DMSO (90 mL) was added IBX (42.14 g, 150.50 mmol). The mixture stirred at 60°C for 16 h. The mixture was filtered and the filtrate was diluted with H₂O (450 mL) and extracted with EtOAc (800 mL). The combined organic layers were concentrated and the residue was purified by silica gel chromatography to afford benzyl 4-oxo-2-phenylpiperidine-1-carboxylate as a yellow oil (10.5 g, 68%). ESI-MS (EI⁺, m/z): 310.15.

Benzyl 6-phenyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate

[00162] To a solution of benzyl 4-oxo-2-phenylpiperidine-1-carboxylate (1.0 g, 3.24 mmol) in THF (45 mL) was added dropwise LiHMDS (9.27 mL, 9.27 mmol) at -78°C under N₂. The mixture was warmed to 0°C and stirred for 1 h and then cooled to -78°C. To the mixture was added *N,N*-bis(trifluoromethylsulfonyl)aniline (1.72 g, 3.55 mmol) in THF (45 mL). The reaction mixture was allowed to slowly warm to rt and stirred for 16 h under N₂. The mixture was quenched with aq. NH₄Cl (sat. 40 mL) at 0°C, diluted with H₂O (20 mL) and extracted with EtOAc (80 mL). The combined organic layers were concentrated and the residue was purified by silica gel chromatography (Petroleum Ether:EtOAc = 20:1) to afford the title compound as a yellow oil (0.5 g, 35%). ESI-MS (EI⁺, m/z): 442.15.

Benzyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-6-phenyl-3,6-dihydropyridine-1(2H)-carboxylate

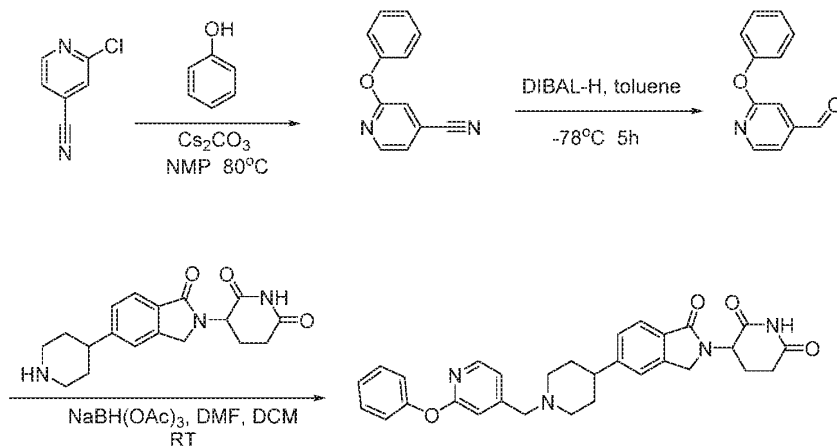
[00163] To a solution of compound benzyl 6-phenyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (340 mg, 0.77 mmol) and 3-[3-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isindol-2-yl]piperidine-2,6-dione (238 mg, 0.64 mmol) in DMF (4 mL) was added Pd(t-Bu₃P)₂ (65 mg, 0.13 mmol) and EtNi-Pr₂ (165 mg, 1.28 mmol). The reaction mixture was heated at 110°C and stirred for 16 h in a microwave reactor. The reaction mixture was then concentrated. The residue was suspended in DCM (30 mL), and then filtered. The filtrate was concentrated and the residue was first purified by silica gel column

chromatography (DCM:MeOH = 99:1), then by prep-thin layer chromatography (DCM:MeOH = 30:1) to afford the title compound as a yellow solid (90 mg). ESI-MS (EI^+ , m/z): 536.30.

3-(1-Oxo-5-(2-phenylpiperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (72)

[00164] To a solution of benzyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-6-phenyl-3,6-dihydropyridine-1(2H)-carboxylate (80 mg, 0.15 mmol) in THF (7 mL) was added 10% Pd/C (40 mg), and 10% Pd(OH)₂/C (40 mg). The reaction mixture stirred at rt for 16 h under hydrogen atmosphere. The reaction mixture was then filtered and the filtrate was concentrated to give the crude product as yellow solid, which was purified by prep-HPLC to afford the title compound as a white solid (4.3 mg, 7%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.99 (s, 1H), 9.12 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 12.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 4.0 Hz, 1H), 7.43-7.50 (m, 3H), 5.13-5.09 (m, 1H), 4.48-4.39 (m, 3H), 3.52 (d, J = 8.0 Hz, 1H), 3.24-3.20 (m, 1H), 2.96-2.87 (m, 1H), 2.67-2.58 (m, 1H), 2.45-2.32 (m, 1H), 2.18-1.96 (m, 5H). ESI-MS (EI^+ , m/z): 404.25.

[00165] Example 4: Synthesis of 3-(1-oxo-5-(1-((2-phenoxyphenyl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (43)



2-Phenoxyisonicotinonitrile

[00166] Phenol (6.8 g, 72.2 mmol) and Cs₂CO₃ (35.3 g, 108.3 mmol) were added to a solution of 2-chloroisonicotinonitrile (10 g, 72.2 mmol) in NMP (50 mL) and the reaction mixture stirred at 80°C for 16 h. The reaction was then partitioned with EtOAc (100 mL) and H₂O (100

mL). The layers were separated and the aq. phase extracted with EtOAc (2 x 100 mL). The combined organic phases were concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluted with DCM/MeOH = 50/1) to afford the title compound as a white solid (8.2 g, 57.95%).

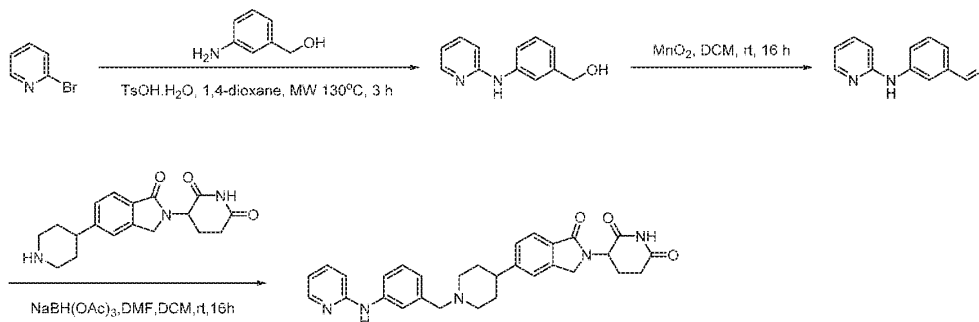
2-Phenoxyisonicotinaldehyde

[00167] A solution of 2-phenoxyisonicotinonitrile (500 mg, 2.55 mmol) in toluene (10 mL) stirred at -70°C for 0.5 h and then DIBAL-H (5 mL) was slowly added. The mixture was warmed to rt and stirred for 2 h. The reaction was quenched with NH₄Cl (aq.), and water (50 mL) was added. The aq. phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluted with DCM/MeOH = 30/1) to afford the title compound as a white solid (220 mg, 43.4%).

3-(1-Oxo-5-(1-((2-phenoxy)pyridin-4-yl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (43)

[00168] A suspension of 2-phenoxyisonicotinaldehyde (50 mg, 0.25 mmol), 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (82 mg, 0.25 mmol) and NaBH(OAc)₃ (159 mg, 0.75 mmol) in a 1:1 (v:v) solution of DMF (3 mL) and DCM (3 mL) stirred at rt for 16 h. The reaction mixture was diluted with EtOAc (50 mL) and water (25 mL), and the aq. phase extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with water (25 mL), brine (25 mL), dried over Na₂SO₄ and then concentrated under reduced pressure to afford a crude product, which was purified by prep-HPLC to afford the title compound as a white solid (3.0 mg, 2.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.98 (s, 1H), 8.34 (s, 1H), 8.08 (d, *J* = 5.2 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.51 (s, 1H), 7.46 – 7.36 (m, 3H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.14 – 7.10 (m, 2H), 6.98 (s, 1H), 5.10 (dd, *J* = 13.4, 4.8 Hz, 1H), 4.42 (d, *J* = 17.2 Hz, 1H), 4.29 (d, *J* = 17.2 Hz, 1H), 3.57 (s, 2H), 2.68 – 2.56 (m, 3H), 2.42 – 2.30 (m, 2H), 2.18 – 2.09 (m, 2H), 2.04 – 1.95 (m, 2H), 1.82 – 1.67 (m, 4H). ESI-MS (EI⁺, *m/z*): 511.23.

[00169] Example 5: Synthesis of 3-(1-oxo-5-(1-(3-(pyridin-2-ylamino)benzyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (42) - General method C



3-(Pyridin-2-ylamino)phenyl)methanol

[00170] A solution of 2-bromopyridine (1.0 g, 6.3 mmol), (3-aminophenyl)methanol (0.8 g, 6.3 mmol) and 4-methylbenzenesulfonic acid hydrate (0.1 g, 0.6 mmol) in dioxane (5 mL) was heated at 130°C for 5 min in a microwave reactor. The reaction was diluted with H₂O (50 mL) and extracted with EtOAc (100 mL). The phases were separated and the organic phase was removed under reduced pressure; then the residue was purified by silica gel column chromatography (eluted with DCM /MeOH =20/1) to afford the title compound as a yellow oil (300 mg, 23.6%).

3-(Pyridin-2-ylamino)benzaldehyde

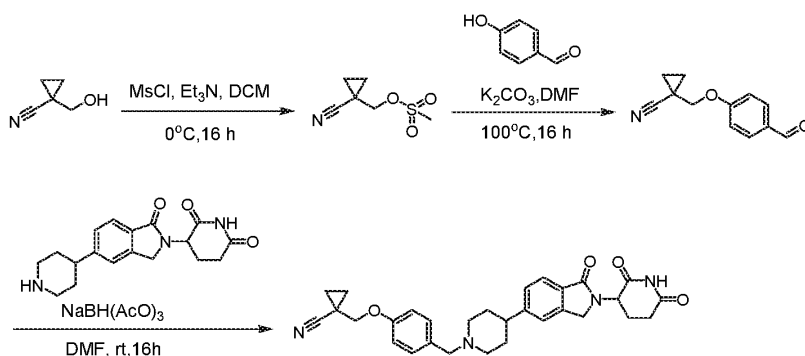
[00171] Manganese(IV) oxide (208 mg, 24.4 mmol) was added to a solution of (3-(pyridin-2-ylamino)phenyl)methanol (240 mg, 1.2 mmol) in DCM (10 mL) and the reaction stirred at rt for 16 hours. The reaction was diluted with H₂O (50 mL) and extracted with EtOAc (2 x 50 mL). The organic phase was concentrated under reduced pressure and the residue that was purified by silica gel column chromatography (eluted with DCM/MeOH = 20/1) to afford the title compound as a yellow oil (180 mg, 75.6%). ESI-MS (EI⁺, m/z) :199.09.

3-(1-Oxo-5-(1-(3-(pyridin-2-ylamino)benzyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (42)

[00172] 3-(Pyridin-2-ylamino)benzaldehyde was converted to compound 42 using a similar procedure as described for compound 43 (Example 5). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.97 (s, 1H), 8.99 (s, 1H), 8.21 – 8.11 (m, 2H), 7.72 – 7.67 (m, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.55-7.52 (m, 2H), 7.49 (s, 1H), 7.40 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.87 – 6.80

(m, 2H), 6.74-6.71 (m, 1H), 5.10 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.42 (d, $J = 17.2$ Hz, 1H), 4.28 (d, $J = 17.2$ Hz, 1H), 2.98 (d, $J = 11.5$ Hz, 2H), 2.94 – 2.84 (m, 1H), 2.59 (d, $J = 18.1$ Hz, 2H), 2.39 (dd, $J = 13.1, 4.5$ Hz, 1H), 2.09 (t, $J = 11.3$ Hz, 2H), 2.03 – 1.93 (m, 1H), 1.80-1.67 (m, 4H). ESI-MS(EI^+ , m/z): 510.35.

[00173] Example 6: Synthesis of 1-((4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-yl)methyl)phenoxy)methyl)cyclopropane-1-carbonitrile (45) - General method D



(1-Cyanocyclopropyl)methyl methanesulfonate

[00174] A solution of 1-(hydroxymethyl)cyclopropane-1-carbonitrile (680 mg, 5.15 mmol) in DCM (10 mL) was cooled to 0°C and stirred for 10 min. TEA (1.56 g, 15.45 mmol) was added and the reaction was then kept at 0°C for 1 h. MsCl (1.18 g, 10.3 mmol) was slowly added and the reaction stirred for 16 h. The reaction mixture was diluted with DCM (20 mL) and water (20 mL), and the organic phase was separated and washed with water (20 mL) and brine (20 mL). The organic phase was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluted with EtOAc/petroleum ether = 1/5) to afford the title compound as a white solid (420 mg, 46.6%).

1-((4-Formylphenoxy)methyl)cyclopropane-1-carbonitrile

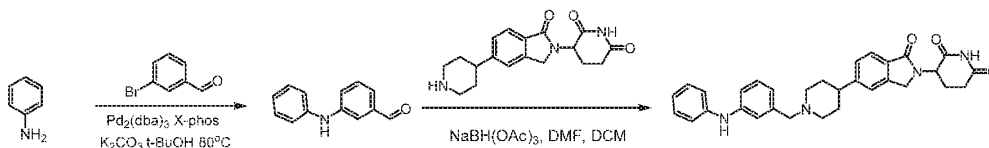
[00175] To a solution of phenol (474 mg, 3.89 mmol), (1-cyanocyclopropyl)methyl methanesulfonate (680 mg, 3.89 mmol) in DMF (20 mL), was added K_2CO_3 (1074 mg, 7.78 mmol), and the reaction stirred at 100°C for 16 h. The reaction was then concentrated and then the residue was diluted with EtOAc (50 mL), and the organic phase washed with water (20 mL) and brine (20 mL). The organic phase was then concentrated under reduced pressure, and the

residue was purified by silica gel column chromatography (eluted with EtOAc/petroleum ether = 1/3) to afford the title compound as a yellow solid (300 mg, 38.4%).

1-((4-((4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-yl)methyl)phenoxy)methyl)cyclopropane-1-carbonitrile (45)

[00176] 1-((4-formylphenoxy)methyl)cyclopropane-1-carbonitrile was converted to compound 45 using a similar procedure as described for compound 43 (Example 5). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.98 (s, 1H), 8.13 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.38 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.97 – 6.87 (m, 2H), 5.09 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.45 – 4.20 (m, 2H), 4.00 (s, 2H), 3.57 (s, 2H), 3.07 – 2.82 (m, 3H), 2.62 (dd, *J* = 28.5, 14.3 Hz, 3H), 2.37 (qd, *J* = 13.4, 4.6 Hz, 1H), 2.18 (t, *J* = 11.5 Hz, 2H), 2.03 – 1.91 (m, 1H), 1.84 – 1.64 (m, 4H), 1.40 – 1.33 (m, 2H), 1.20 – 1.10 (m, 2H). ESI-MS (EI⁺, *m/z*): 513.15.

[00177] Example 7: Synthesis of 3-(1-oxo-5-(1-(3-(phenylamino)benzyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (46) - General method E



3-(Phenylamino)benzaldehyde

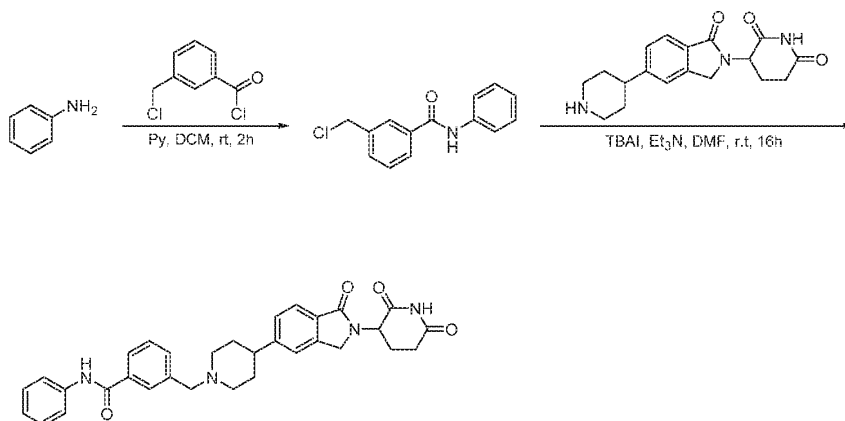
[00178] A solution of aniline (1.0 g, 10.7 mmol), 3-bromobenzaldehyde (2.0 g, 10.7 mmol), Pd₂(dba)₃ (600 mg, 0.64 mmol), x-phos (600 mg, 1.2 mmol), and K₂CO₃ (3.0 g, 21.4 mmol) in *t*-BuOH (50 mL) stirred at 80°C for overnight. The reaction was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluted with petroleum ether/EtOAc = 5/1) to afford the title compound as a yellow solid (400 mg, 10%).

3-(1-Oxo-5-(1-(3-(phenylamino)benzyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (46)

[00179] 3-(Phenylamino)benzaldehyde was converted to compound 46 using similar a procedure as described for compound 43 (Example 5). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.98 (s, 1H), 8.15 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.49 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.20 (dt, *J* = 20.1, 7.9 Hz, 3H), 7.07 (d, *J* = 7.9 Hz, 3H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.85 – 6.74 (m, 2H),

5.10 (dd, $J = 13.3, 5.0$ Hz, 1H), 4.42 (d, $J = 17.2$ Hz, 1H), 4.28 (d, $J = 17.3$ Hz, 1H), 3.46 (s, 2H), 2.96 (d, $J = 11.3$ Hz, 2H), 2.92 – 2.85 (m, 1H), 2.69 – 2.55 (m, 2H), 2.45 – 2.34 (m, 1H), 2.08 (t, $J = 12.0$ Hz, 2H), 2.02 – 1.94 (m, 1H), 1.84 – 1.64 (m, 4H). ESI-MS (EI⁺, m/z): 509.25.

[00180] Example 8: Synthesis of 3-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-yl)methyl)-N-phenylbenzamide (86) - General method F



3-(Chloromethyl)-N-phenylbenzamide

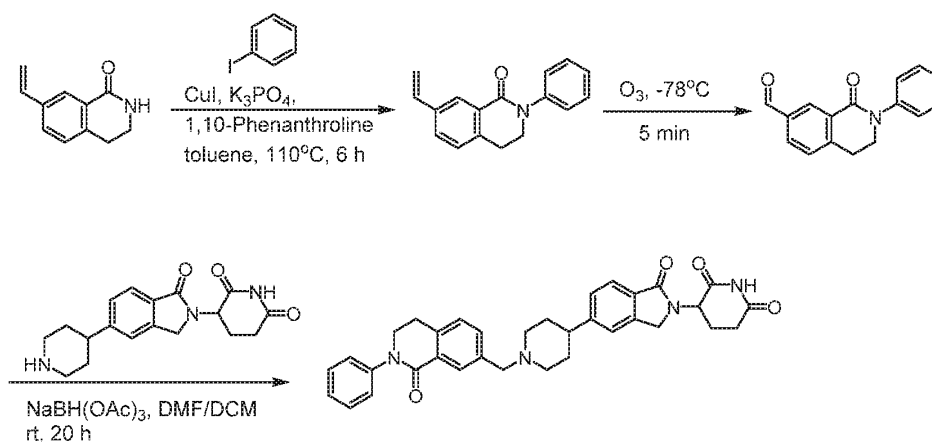
[00181] Pyridine (261 mg, 3.3 mmol) was added to a solution of aniline (100 mg, 1.1 mmol) and 3-(chloromethyl)benzoyl chloride (203 mg, 1.1 mmol) in DCM (2 mL), and the reaction mixture stirred at rt for 2 h. The reaction was concentrated under reduced pressure and the crude mixture was purified by silica gel column chromatography (eluting petroleum ether/EtOAc = 10/1) to give the title compound as a white solid (111 mg, 53.4%).

3-((4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-yl)methyl)-N-phenylbenzamide (86)

[00182] A suspension of the 3-(chloromethyl)-N-phenylbenzamide (100 mg, 0.41 mmol), 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (133 mg, 0.41 mmol), NaI (149 mg, 0.41 mmol) and Et₃N (414 mg, 4.1 mmol) in DMF (2 mL) stirred at rt for 16 h. The reaction mixture was filtered through diatomite and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC to afford the title compound as a white solid (25 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.97 (s, 1H), 10.28 (s, 1H), 8.01 – 7.86

(m, 2H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.64 (t, $J = 8.2$ Hz, 1H), 7.59 – 7.48 (m, 2H), 7.38 (dt, $J = 15.6, 7.9$ Hz, 3H), 7.11 (t, $J = 7.4$ Hz, 1H), 5.09 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.42 (d, $J = 17.3$ Hz, 1H), 4.29 (d, $J = 17.2$ Hz, 1H), 3.86 (s, 1H), 3.12 (s, 2H), 2.88 (d, $J = 12.8$ Hz, 2H), 2.76 (s, 1H), 2.59 (d, $J = 18.2$ Hz, 1H), 2.44 – 2.33 (m, 2H), 2.02 – 1.92 (m, 1H), 1.82 (d, $J = 14.9$ Hz, 3H). ESI-MS (EI^+ , m/z): 537.24.

[00183] Example 9: Synthesis of 3-(1-oxo-5-(1-((1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (105) - General method G



2-Phenyl-7-vinyl-3,4-dihydroisoquinolin-1(2H)-one

[00184] A solution of 7-vinyl-3,4-dihydroisoquinolin-1(2H)-one (800 mg, 4.62 mmol), iodobenzene (1886 mg, 9.25 mmol), CuI (351 mg, 1.85 mmol), 1,10-phenanthroline (333 mg, 1.85 mmol), and K_3PO_4 (2450 mg, 11.56 mmol) in toluene (20 mL) stirred at 110°C overnight under nitrogen. The reaction mixture was partitioned between EtOAc (50 mL) and water (20 mL), and the organic phase was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluted with hexanes/EtOAc = 10/1) to afford the title compound as a yellow solid (400 mg, 34.7%).

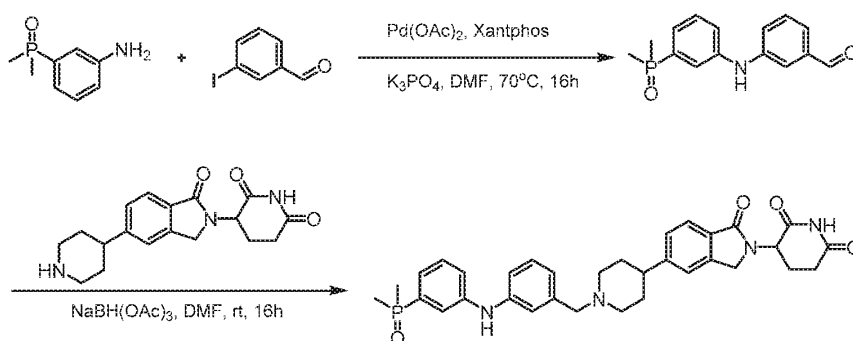
1-Oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-7-carbaldehyde

[00185] A solution of 2-phenyl-7-vinyl-3,4-dihydroisoquinolin-1(2H)-one (400 mg, 1.60 mmol) in a mixture of DCM (4 mL) and MeOH (10 mL) stirred at -78°C for 5 minutes, with ozone bubbled through the reaction. The reaction mixture was then concentrated *in-vacuo*, and the residue was purified by prep silica gel TLC to afford the title compound as a yellow oil (240 mg, 24.8%).

3-(1-oxo-5-(1-((1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (105)

[00186] A solution of 1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-7-carbaldehyde (100 mg, 0.39 mmol), 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (174 mg, 0.48 mmol), and NaBH(OAc)₃ (169 mg, 0.79 mmol) in a mixture of DMF (2 mL) and DCM (2 mL) stirred at rt overnight. The reaction mixture was then concentrated to about 2 mL (with most DCM removed) and filtered. The filtrate was purified by prep HPLC to afford the title compound as a white solid (30 mg, 13.3%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.96 (s, 1H), 7.91 (s, 1H), 7.65 – 7.61 (m, 1H), 7.51 – 7.47 (m, 2H), 7.41 (q, *J* = 6.3, 4.8 Hz, 6H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.26 (tt, *J* = 5.8, 2.4 Hz, 1H), 5.09 (dd, *J* = 13.3, 5.0 Hz, 1H), 4.45 – 4.23 (m, 2H), 3.95 (t, *J* = 6.4 Hz, 2H), 3.56 (s, 2H), 3.11 (t, *J* = 6.1 Hz, 2H), 2.91 (dd, *J* = 21.5, 11.2 Hz, 3H), 2.70 – 2.55 (m, 2H), 2.38 (qd, *J* = 13.1, 4.3 Hz, 1H), 2.10 (t, *J* = 11.3 Hz, 2H), 2.03 – 1.94 (m, 1H), 1.82 – 1.65 (m, 4H). ESI-MS(EI⁺, *m/z*): 549.28.

[00187] Example 10: Synthesis of 3-(5-(1-(3-((3-(dimethylphosphoryl)phenyl)amino)benzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (135) - General method H



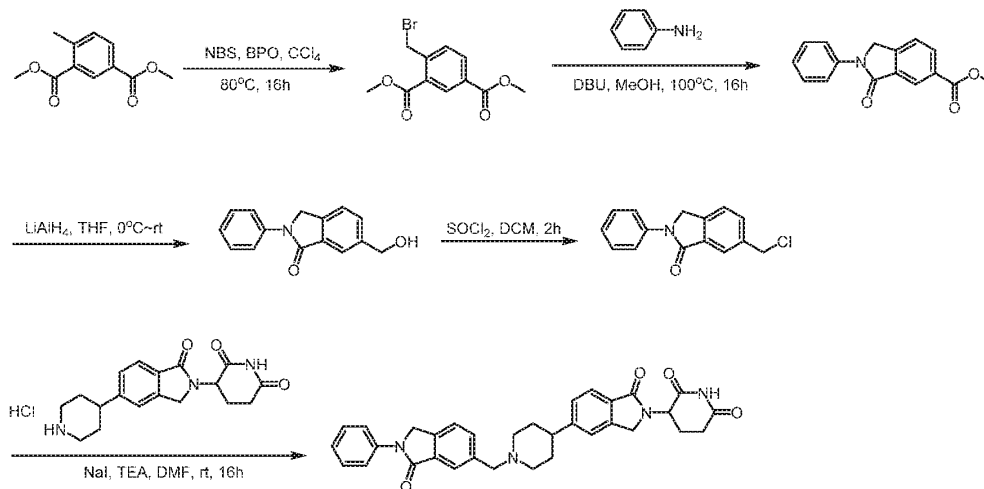
3-((3-(Dimethylphosphoryl)phenyl)amino)benzaldehyde

[00188] A solution of (3-aminophenyl)dimethylphosphine oxide (100 mg, 0.59 mmol), 3-iodobenzaldehyde (165 mg, 0.71 mmol), Pd(OAc)₂ (6.6 mg, 0.03 mmol), Xantphos (17 mg, 0.03 mmol), and K₃PO₄ (150 mg, 0.71 mmol) in DMF (2 mL) stirred at 70°C for 16 h. The reaction mixture was then concentrated under reduced pressure, and purified by silica gel column chromatography (eluting petroleum ether/EtOAc = 4/1) to give the title compound as a white solid (50 mg, 26.4%).

3-(5-(1-(3-((3-Ddimethylphosphoryl)phenyl)amino)benzyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (135)

[00189] 3-((3-(Dimethylphosphoryl)phenyl)amino)benzaldehyde was converted to compound 135 using a similar procedure as described for compound 43 (Example 5). ¹H NMR: (400 MHz, DMSO-*d*₆) δ 10.99 (s, 1H), 8.39 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.49 (s, 1H), 7.48 – 7.42 (m, 1H), 7.40 (m, 1H), 7.34 (m, 1H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.17 – 7.10 (m, 2H), 6.99 (m, 1H), 6.84 (m, 1H), 5.10 (m, 1H), 4.42 (d, *J* = 17.2 Hz, 1H), 4.28 (d, *J* = 17.2 Hz, 1H), 3.47 (s, 2H), 2.96 (d, *J* = 10.7 Hz, 2H), 2.92 – 2.85 (m, 1H), 2.61 (t, *J* = 16.2 Hz, 2H), 2.39 (m, 1H), 2.13 – 2.05 (m, 2H), 2.02 – 1.95 (m, 1H), 1.74 (d, *J* = 16.2 Hz, 4H), 1.63 (s, 3H), 1.60 (s, 3H). ESI-MS (EI⁺, *m/z*): 585.26.

[00190] Example 11: Synthesis of 3-(1-oxo-5-(1-((3-oxo-2-phenylisoindolin-5-yl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (146) - General method I



Dimethyl 4-(bromomethyl)isophthalate

[00191] A solution of dimethyl 4-methylisophthalate (15.3 g, 73.48 mmol), NBS (15.69 g, 88.18 mmol) and BPO (1.78 g, 7.35 mmol) in CCl_4 (210 mL) stirred at 85°C for 16 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluted with petroleum ether/EtOAc = 80/1) to afford the title compound as a yellow solid (10 g, 48%).

Methyl 3-oxo-2-phenylisoindoline-5-carboxylate

[00192] A solution of dimethyl 4-(bromomethyl)isophthalate (10 g, 34.71 mmol), aniline (3.23 g, 34.71 mmol), and DBU (10.57 g, 69.42 mmol) in MeOH (200 mL) stirred at 70°C for 16 h. The solvent was removed under reduced pressure to afford the crude title compound as a yellow solid (5.07 g, 54.5%), which was used without further purification.

6-(Hydroxymethyl)-2-phenylisoindolin-1-one

[00193] A solution of methyl 3-oxo-2-phenylisoindoline-5-carboxylate (5.07 g, 18.98 mmol) in THF (40 mL) stirred at 0°C and then LiBH_4 (37.96 mL, 75.92 mmol, 2 M) was slowly added. After stirring for 5 minutes at 0°C, the reaction was warmed to rt and stirred overnight. The reaction mixture was partitioned with DCM/MeOH (200 mL, v:v, 20:1) and water (50 mL), and the organic phase was separated and washed with brine (40 mL). The organic phase was

concentrated and the residue was purified by silica gel column chromatography (eluted with DCM/MeOH = 40/1) to afford the title compound as a white solid (3 g, 66.6%).

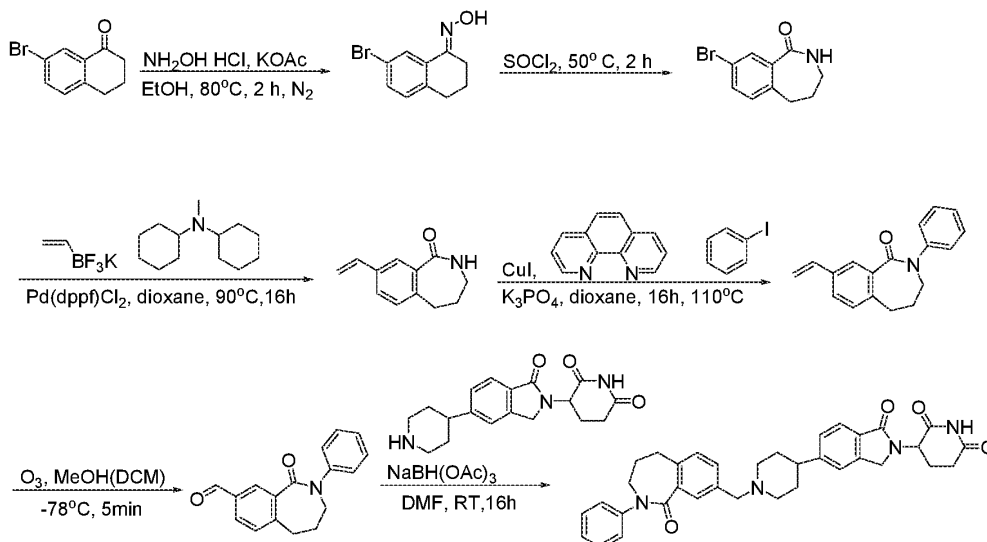
6-(Chloromethyl)-2-phenylisoindolin-1-one

[00194] Thionyl chloride (198.87 mg, 1.67 mmol) was added to a solution of 6-(hydroxymethyl)-2-phenylisoindolin-1-one (100 mg, 0.42 mmol) in DCM (2 mL). The mixture stirred at rt for 2 h. The reaction mixture was then concentrated to give the crude title compound as a white solid (100 mg), which was used without further purification.

3-(1-Oxo-5-(1-((3-oxo-2-phenylisoindolin-5-yl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (146)

[00195] A solution of 6-(chloromethyl)-2-phenylisoindolin-1-one (80 mg, 0.31 mmol), 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (112.9 mg, 0.31 mmol), NaI (46.53 mg, 0.31 mmol) and TEA (314.12 mg, 3.1 mmol) in DMF (2 mL) stirred at rt for 16 h. The reaction mixture was then purified by prep-HPLC to give the title compound as a white solid (16.6 mg, 9.7%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.76 (s, 1H), 7.69 – 7.63 (m, 3H), 7.54 (s, 1H), 7.49 – 7.43 (m, 3H), 7.20 (t, *J* = 7.4 Hz, 1H), 5.15 – 5.10 (m, 1H), 5.04 (s, 2H), 4.44 (d, *J* = 17.4 Hz, 1H), 4.30 (d, *J* = 17.2 Hz, 1H), 3.67 (s, 2H), 2.98 (d, *J* = 11.6 Hz, 2H), 2.75 – 2.61 (m, 2H), 2.58 (d, *J* = 11.8 Hz, 1H), 2.41 (dd, *J* = 11.4, 5.1 Hz, 1H), 2.15 (t, *J* = 11.0 Hz, 2H), 2.05 – 1.97 (m, 1H), 1.80 (s, 4H).

[00196] Example 12: Synthesis of 3-(1-oxo-5-(1-((1-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (183) - General method J



7-Bromo-3,4-dihydronaphthalen-1(2H)-one oxime

[00197] A solution of 7-bromo-3,4-dihydronaphthalen-1(2H)-one (10.0 g, 44.43 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (3.4 g, 48.87 mmol) and KOAc (6.54 g, 66.64 mmol) in EtOH (200 mL) stirred at 80°C for 2 h under N_2 . The solution was concentrated, and the solid residue was filtered, washed with water, and dried to afford the crude title compound (14.3 g), which was used without further purification.

8-Bromo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one

[00198] A solution of 7-bromo-3,4-dihydronaphthalen-1(2H)-one oxime (5.00 g, 20.83 mmol) in SOCl_2 (37.5 mL) stirred at 50°C for 2 h. The reaction was concentrated and the residue was cooled to 0°C. Sat. aq. NaHCO_3 was added slowly and the aq. suspension was then extracted with EtOAc (200 mL). The layers were separated, and the organic phase dried, and concentrated under reduced pressure. Purification by silica gel column chromatography afford the title compound (3.6 g).

8-Vinyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one

[00199] A solution of 8-bromo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (2.60 g, 10.9 mmol), trifluoro(vinyl)-borane-potassium salt (2.93 g, 21.8 mmol), *N*-cyclohexyl-*N*-methylcyclohexanamine (4.26 g, 21.8 mmol) and Pd(dppf)Cl₂ (798.6 mg, 1.09 mmol) in 1,4-dioxane (50 mL) stirred at 90°C for 16 h under N₂. The solution was partitioned by EtOAc (100 mL) and H₂O (30 mL). The organic phase separated and washed with water (2 x 30 mL), dried over Na₂SO₄, and concentrated to afford the crude product. Purification by silica gel column chromatography afforded the title compound (2.8 g).

2-Phenyl-8-vinyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one

[00200] A solution of 8-vinyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (800.0 mg, 4.28 mmol), iodobenzene (4.36 g, 21.40 mmol), CuI (325.1 mg, 1.71 mmol), 1,10-phenanthroline (308.0 mg, 1.71 mmol) and K₃PO₄ (2.72 g, 12.83 mmol) in 1,4-dioxane (16 mL) stirred at 110°C for 16 h under N₂. The solution was partitioned by EtOAc (100 mL) and H₂O (30 mL). The organic phase was separated and washed with water (2 x 30 mL), dried over Na₂SO₄, and concentrated to afford the crude product. Purification by silica gel column chromatography afforded the title compound (600 mg).

1-Oxo-2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine-8-carbaldehyde

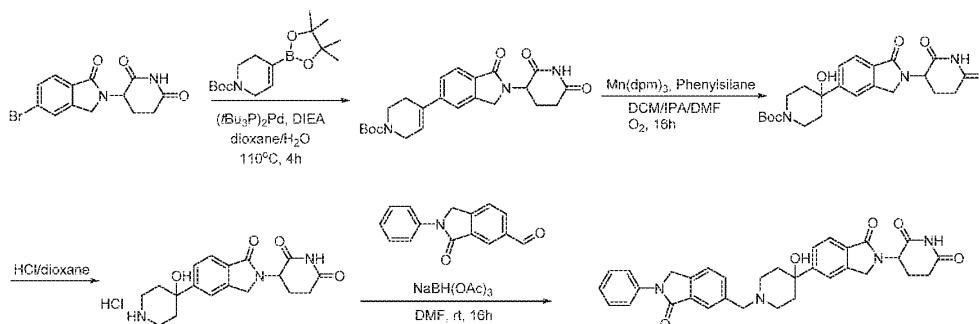
[00201] A solution of 2-phenyl-8-vinyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (300 mg, 1.14 mmol) in MeOH (5 mL) stirred at -78°C, and ozone gas was bubbled into the reaction mixture for 10 min. The reaction was then warmed to rt, concentrated under reduced pressure to afford a residue. Purification by silica gel prep. TLC (petroleum ether:EtOAc = 1:1), afforded the title compound (100 mg).

3-(1-Oxo-5-(1-((1-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (183)

[00202] 1-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine-8-carbaldehyde was converted to compound 183 using similar a procedure as described for compound 43 (Example 5). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.96 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.52 (s, 1H), 7.46–7.40 (m, 6H), 7.30–7.26 (m, 2H), 5.08 (m, *J* = 13.4, 5.1 Hz, 1H), 4.42 (d, *J* = 17.3 Hz, 1H), 4.28 (d, *J* = 17.3 Hz, 1H), 3.56 (s, 2H), 2.98–2.86 (m, 6H), 2.68–

2.58 (m, 2H), 2.38 (m, $J = 13.1, 4.6$ Hz, 1H), 2.16 – 1.92 (m, 6H), 1.82– 1.68 (m, 4H). ESI-MS (EI^+ , m/z): 577.35.

[00203] Example 13: Synthesis of 3-(5-(4-hydroxy-1-((3-oxo-2-phenylisoindolin-5-yl)methyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (200) - General method K



tert-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate

[00204] DIEA (4.8 g, 37.2 mmol) and bis(tri-*t*-butylphosphine)palladium (1.9 g, 3.72 mmol) were added to a solution of 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione (6 g, 18.6 mmol) and *N*-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (22.92 g, 74.4 mmol) in 1,4-dioxane/ H_2O (120 mL, v:v, 20/1). The reaction mixture stirred at 110°C for 4 h under N_2 atmosphere. The reaction mixture was filtered to obtain a clear organic solution. The solution was concentrated to give a crude residue that was titrated with DCM/petroleum ether (1:1) to give a solid, which was filtered and dried to give the crude title compound (7.2 g, 91.1%), which was used without further purification.

tert-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-4-hydroxypiperidine-1-carboxylate

[00205] Phenylsilane (2.0 g, 18.3 mmol) was added to a solution of *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3.9 g, 9.2 mmol) and $\text{Mn}(\text{dpm})_3$ (2.8 g, 4.6 mmol) in DCM/*i*PrOH/DMF (60 mL, v:v:v, 5/5/1). The reaction mixture stirred at 0°C for 16 h under O_2 atmosphere. A sat. aq. solution of $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) was then added and the mixture stirred at rt for 2 h. Brine (60 mL) was added and the organic phase was separated. The aq. phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude product

that was purified by silica gel column chromatography to give the title compound as a yellow solid (1.5 g, 36.9%).

3-(5-(4-Hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione hydrochloride

[00206] In a sealed flask was placed *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (500 mg, 1.1 mmol) and HCl (4.0 M in 1,4-dioxane, 5 mL). The suspension stirred at rt for 2 h. The reaction mixture was then concentrated to give the crude title compound as a yellow solid (480 mg, quant.), which was used without further purification.

3-(5-(4-Hydroxy-1-((3-oxo-2-phenylisindolin-5-yl)methyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (200)

[00207] A suspension of *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-4-hydroxypiperidine-1-carboxylate (20.00 mg, 0.084 mmol), 3-(5-(4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione hydrochloride (32.02 mg, 0.084 mmol) and sodium triacetoxyborohydride (53.60 mg 0.25 mmol) in DMF (1 mL) stirred at rt for 16 h. Reaction monitoring by LC-MS showed 40% conversion. The suspension was filtered to give a clear organic phase which was purified by prep-HPLC to give the title compound as a white solid (4.4 mg, 9.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.98 (s, 1H), 7.92 (s, 2H), 7.75 (s, 2H), 7.66 (s, 4H), 7.44 (s, 2H), 7.18 (s, 1H), 5.14 – 5.00 (m, 4H), 4.44 (d, *J* = 20.8 Hz, 1H), 4.29 (d, *J* = 18.9 Hz, 1H), 3.66 (s, 2H), 3.03 – 2.80 (m, 2H), 2.66 (s, 2H), 2.42 – 2.29 (m, 2H), 2.00 (d, *J* = 4.5 Hz, 4H), 1.61 (d, *J* = 11.5 Hz, 2H). ESI-MS (EI⁺, *m/z*): 565.3.

[00208] Example 14: Liquid Chromatography Mass Spectrometry (LCMS) Data

[00209] Reaction monitoring and final compound characterization were done using Shimadzu LC-20AD series (binary pump and diode array detector) with Agilent Poroshell 120 EC-C18 column (2.7 μm, 4.6×50 mm). Mobile phase: A: 0.05% Formate in water (v/v), B: 0.05% Formate in MeCN (v/v). Flow Rate: 1 mL/min at 25°C. MS: 2020, Quadrupole LC/MS, Ion Source: API-ESI, TIC: 100~900 *m/z*; Drying gas flow: 15 L/min; Nebulizer pressure: 1.5L/min; Drying gas temperature: 250°C, Vcap: 4500V.

Table 1. LCMS data of inventive compounds

<u>Compound #</u>	<u>Calculated Mass</u>	<u>Observed Mass (M+H)</u>	<u>Compound #</u>	<u>Calculated Mass</u>	<u>Observed Mass (M+H)</u>
2	433.2	434.2	99	587.2	588.3
9	510.2	511.4	100	527.2	528.3
10	526.3	527.4	101	510.2	511.3
33	516.2	517.2	102	510.2	511.3
35	446.2	447.2	103	563.3	564.3
36	494.2	495.3	104	562.3	563.3
37	460.2	461.2	105	562.3	563.4
38	528.2	529.2	106	577.3	578.4
40	432.2	433.2	107	510.2	511.3
41	432.2	433.3	108	563.3	564.5
42	509.2	510.3	109	576.2	577.4
43	510.2	511.3	110	550.6	551.3
45	512.2	513.2	111	562.6	563.4
46	508.3	509.2	112	515.3	516.3
48	577.3	578.4	113	548.2	549.4
50	536.2	537.2	114	500.2	501.2
51	548.2	549.4	115	510.2	511.3
53	572.2	573.3	116	510.2	511.2
56	501.2	502.3	117	548.2	549.3
57	515.3	516.3	118	549.2	550.5
58	598.2	599.2	119	510.2	511.3
59	598.2	599.4	120	509.2	510.4
60	576.2	577.4	121	548.2	549.2
62	578.2	579.4	122	510.2	511.4
64	562.2	563.3	123	548.2	549.3
67	493.2	494.3	124	549.2	550.3
72	403.2	404.2	125	549.2	550.4
73	417.2	418.1	126	527.2	528.1
79	572.2	573.4	127	510.2	511.1
80	584.2	583.15 (M-H)	128	549.2	550.3
81	586.2	587.4	129	549.2	550.3
84	614.2	615.4	130	538.2	539.4
85	550.3	551.3	131	537.2	538.4
86	536.2	537.3	132	527.2	528.1
87	510.2	511.2	133	527.2	528.3
91	572.2	573.3	134	584.3	585.2
92	586.2	587.4	135	584.3	585.4
93	500.2	501.2	136	584.2	585.3
94	512.2	513.4	137	509.2	510.3
95	548.2	549.4	138	612.3	613.3
96	516.2	517.4	139	510.2	511.3
97	550.2	551.4	140	612.3	613.4
98	586.2	587.5	141	537.2	538.4

Table 1. Continued

<u>Compound #</u>	<u>Calculated Mass</u>	<u>Observed Mass (M+H)</u>	<u>Compound #</u>	<u>Calculated Mass</u>	<u>Observed Mass (M+H)</u>
142	509.2	510.3	187	527.2	528.3
143	563.2	564.4	188	528.2	529.4
144	536.2	537.4	190	510.2	511.3
145	509.2	510.4	191	499.2	500.4
146	548.2	549.4	193	525.2	526.2
147	500.2	501.4	195	526.2	527.4
148	515.2	516.3	196	526.2	527.2
149	510.2	511.2	197	543.2	544.3
150	493.2	494.4	198	543.2	544.2
151	542.3	543.4	200	564.2	565.4
152	562.2	563.4	202	579.2	580.2
153	529.3	530.4	203	483.2	484.2
154	592.3	593.4	204	483.2	484.2
155	556.3	557.8	205	469.2	470.2
156	537.2	536.30 (M-H)	206	509.2	510.1
157	573.2	574.2	207	467.2	468.2
158	536.2	537.4	208	498.2	500.2
159	540.3	541.5	209	528.2	529.4
160	605.3	606.8	210	419.2	420.5
161	514.3	515.2	211	431.2	432.2
162	592.2	593.4	212	447.2	448.3
163	515.3	516.4	213	566.2	567.4
164	578.2	579.4	214	562.3	563.5
165	628.2	629.4	215	562.3	563.4
166	576.3	577.5	216	562.3	563.4
167	598.2	599.3	217	564.2	656.3
168	586.7	587.2	218	564.2	565.4
169	576.7	577.2	219	580.2	581.2
170	550.3	551.2	220	565.2	566.3
172	549.2	550.3	221	567.2	568.3
173	549.2	550.3	222	555.2	556.3
174	566.2	567.3	223	555.2	556.2
175	566.2	567.4	224	555.2	556.2
176	582.2	583.3	225	571.2	572.3
177	591.2	592.4	226	528.2	529.3
178	550.2	551.4	227	544.2	545.3
179	573.2	574.3	228	524.3	525.4
180	566.2	567.4	229	524.3	525.4
182	564.3	565.4	230	546.2	547.3
183	576.3	577.4	231	542.2	543.4
184	577.3	578.4	232	524.3	525.5
185	578.3	579.3	233	515.2	516.2
186	534.2	535.4	234	577.2	578.2

Table 1. Continued

Compound #	Calculated Mass	Observed Mass (M+H)	Compound #	Calculated Mass	Observed Mass (M+H)
235	578.2	579.2	258	451.2	452.2
236	560.2	561.2	260	490.2	491.2
237	458.2	459.2	261	463.2	464.3
238	458.2	459.1	262	463.2	464.1
239	458.2	459.2	263	463.2	464.1
240	516.2	517.2	264	447.2	448.2
241	490.2	491.1	265	447.2	448.2
242	490.2	491.1	266	447.2	448.2
243	469.2	470.1	267	467.2	468.0
244	469.2	470.1	268	467.2	468.1
245	469.2	470.2	269	447.2	448.2
246	475.2	476.2	270	473.2	474.2
247	498.2	500.1	271	513.2	514.2
248	498.2	500.2	272	505.2	506.2
249	501.2	502.2	273	509.2	510.2
250	501.2	502.1	274	509.2	510.1
251	501.2	502.1	275	489.2	490.1
252	525.2	526.2	276	539.2	540.2
253	525.2	526.1	277	539.2	540.2
254	485.2	486.2	278	526.3	527.2
255	485.2	486.2	279	484.2	485.2
256	451.2	452.1	280	484.2	485.2
257	451.2	452.2	281	516.2	517.2

[00210] Example 15: Cellular Degradation GFP Assays

[00211] IKZF1, IKZF2, GSPT1 were sub-cloned into mammalian pcDNA5/FRT Vector (Ampicillin and Hygromycin B resistant) modified to contain MCS-eGFP-P2A-mCherry. Stable cell lines expressing eGFP-protein fusion and mCherry reporter were generated using Flip-In 293 system. Plasmid (0.3 µg) and pOG44 (4.7 µg) DNA were preincubated in 100 µL of Opti-MEM I (Gibco®, Life Technologies™) media containing 0.05 mg/mL Lipofectamine 2000 (Invitrogen™) for 20 min and added to Flip-In 293 cells containing 1.9 mL of DMEM media (Gibco®, Life Technologies™) per well in a 6-well plate format (Falcon®, 353046). Cells were propagated after 48 h and transferred into a 10 cm² plate (Corning, 430165) in DMEM media containing 50 µg/mL of Hygromycin B (REF 10687010, Invitrogen™) as a selection marker. Following 2-3 passages, cycle FACS (FACSAria™ II, BD) was used to enrich for cells expressing eGFP and mCherry.

[00212] Cells stably expressing the IKZF1, IKZF2 or GSPT1 GFP fusions with mCherry reporter were seeded at 30-50% confluency in 384-well plates with 50 μ L FluoroBrite™ DMEM media (Thermo Fisher Scientific A18967) containing 10% FBS per well a day before compound treatment. Compound titrations were dispensed using a D300e Digital Dispenser® (HP), normalized to 0.5% DMSO, and incubated with cells for 5 hours.

[00213] The assay plate was imaged immediately using an Acumen® High Content Imager (TTP Labtech) with 488 nm and 561 nm lasers in 2 μ m x 1 μ m grid per well format. The resulting images were analyzed using CellProfiler™. A series of image analysis steps ('image analysis pipeline') was constructed. First, the red and green channels were aligned and cropped to target the middle of each well (to avoid analysis of heavily clumped cells at the edges). A background illumination function was calculated for both red and green channels of each well individually and subtracted to correct for illumination variations across the 384-well plate from various sources of error. An additional step was then applied to the green channel to suppress the analysis of large auto fluorescent artifacts and enhance the analysis of cell specific fluorescence by way of selecting for objects under a given size, 30 A.U., and with a given speckle shape. mCherry-positive cells were then identified in the red channel filtering for objects between 8-60 pixels in diameter and using intensity to distinguish between clumped objects. The green channel was then segmented into GFP positive and negative areas and objects were labeled as GFP positive if at least 40% of it overlapped with a GFP positive area. The fraction of GFP-positive cells/mCherry-positive cells in each well was then calculated, and the green and red images were rescaled for visualization. The concentrations that lead to half degradation at 5h (DC₅₀, 5h) were calculated using the nonlinear fit variable slope model (GraphPad Software).

[00214] The results are shown in FIG. 1A-FIG. 1C. They show that compounds of the invention that were tested potently degraded IKZF2 in cells.

[00215] Example 16: HiBit-IKZF2 Assay

[00216] The HiBiT protein tagging system was applied to MOLT4 cells via a CRISPR/Cas9 – mediated insertion of the HiBiT peptide tag (Promega™) to the N-terminus of the IKZF2 gene locus (Neon™ Transfection System). The resulting HiBiT-Helios stable cell line was treated with the following compounds in triplicates following a 13-point concentration scheme ranging from 10 μ M to 0.00026 μ M. At the indicated timepoints, the Nano-Glo® HiBiT Lytic

Detection System (Promega™) was utilized for detecting bioluminescence of the HiBiT tag in treated cells: abundance of the tag is proportionate to the level of luminescence. Following normalization to DMSO, dose-response curves were plotted (GraphPad Prism) to determine the concentration points at which 50% of HiBiT-Helios degradation was achieved by each compound. The extent of degradation (range of luminescence) from the highest to lowest concentration points was calculated to determine the $D_{\max}$.

Table 2. IKZF2 Degradation for Inventive Compounds

Compound #	D _{max}	DC ₅₀	Compound #	D _{max}	DC ₅₀
2	+++	+++	122	+	++
10	+	++	123	++	++
33	+++	+++	124	++	++
42	++	+++	125	++	+++
43	++	+	126	++	++
45	++	++	127	++	++
46	++	+++	128	++	++
48	++	+	129	++	++
50	++	++	130	++	++
51	++	+++	131	++	+
58	+	++	132	++	+++
59	++	+++	133	++	+++
60	++	++	134	++	+++
62	++	+	135	++	++
80	+	+	136	++	+++
84	++	+	137	++	+++
86	++	+++	138	++	+++
91	++	+++	139	++	+
92	++	+++	141	++	+
93	++	++	142	++	++
94	++	++	144	++	++
95	++	+++	145	++	+
97	+	++	146	+++	++
98	++	+++	147	++	+
99	+	+	148	++	++
100	++	++	149	++	+++
101	+	++	156	++	+++
102	++	++	157	++	+
103	++	++	158	++	+
104	++	++	161	+	++
105	++	+++	162	++	+++
106	+	++	165	++	+++
108	++	+++	166	++	++
109	+	+	167	++	+++
110	++	++	169	++	+++
111	+	+	170	++	++
113	+	+++	172	+	++
115	++	+++	173	++	++
116	+	+	174	++	+++
117	+	+	175	++	+++
118	+	+	176	+++	+
119	+	+	177	++	+++
120	++	++	178	+	++
121	+	+	179	++	+++

Table 2. Continued

Compound #	D _{max}	DC ₅₀	Compound #	D _{max}	DC ₅₀
180	++	++	231	++	+++
182	++	+	232	++	++
183	++	+++	233	++	++
184	++	++	234	+++	+++
185	++	+	235	+++	+++
186	++	+	236	+++	+++
187	++	++	237	++	+++
188	++	+++	238	+++	+++
190	+	+	239	+++	+++
191	++	++	240	+++	+++
193	+++	+++	241	+++	+++
195	++	+++	242	+++	+++
196	+++	+++	243	+++	+++
197	++	+++	244	+++	+++
198	+++	+++	245	++	+++
200	+++	+++	246	+++	+++
202	++	+++	247	+++	+++
203	+++	+++	248	+++	+++
204	+++	+++	249	+++	+++
205	+++	+++	250	+++	+++
206	+++	+++	251	+++	+++
207	+++	+++	252	+++	+++
208	+++	+++	253	++	+++
209	++	++	254	+++	+++
210	+	+	255	+++	+++
212	++	+	256	+++	+++
213	++	++	257	+++	+++
214	++	++	258	+++	+++
215	+++	++	260	++	++
216	++	+++	261	+++	+++
217	+++	+++	262	++	++
218	+++	++	263	+++	+++
219	+++	+++	264	+++	+++
220	+++	+++	265	+++	+++
221	++	+++	266	+++	+++
222	++	+++	267	+++	+++
223	++	++	268	+++	+++
224	+++	+++	269	+++	+++
225	+++	+++	270	+++	+++
226	+	++	271	+++	+++
227	++	+++	272	+++	+++
228	++	++	273	+++	+++
229	++	+++	274	++	+++
230	++	+	275	+++	+++

Table 2. Continued

Compound #	D _{max}	DC ₅₀	Compound #	D _{max}	DC ₅₀
276	++	+++	279	+++	+++
277	+++	+++	280	+++	++
278	+++	++	281	+++	+++

D_{max}: “+” is from > 30% to < 50%; “++” is from > 50% to < 70%; “+++” is > 70%.

DC₅₀: “+” is from > 30 x10⁻⁹ M to < 150 x10⁻⁹ M; “++” is from > 10 x10⁻⁹ M to < 30 x10⁻⁹ M; “+++” is < 10 x10⁻⁹ M.

[00217] All patent publications and non-patent publications are indicative of the level of skill of those skilled in the art to which this invention 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.

[00218] Although the invention 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 invention. 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 invention as defined by the appended claims.