

PROCESSES FOR MAKING ARYL COMPOUNDS THAT MODULATE IKZF2

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of United States Provisional Application Serial Number 63/516,061, filed July 27, 2023, the contents of which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present disclosure relates generally to processes for preparing compounds that bind to cereblon, thereby modulating cereblon activity, and the synthetic intermediates prepared thereby.

BACKGROUND

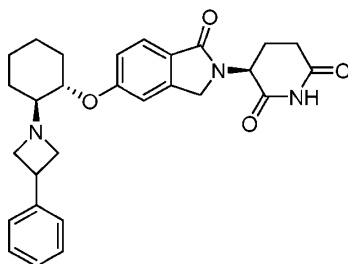
[0003] IKAROS Family Zinc Finger 2 (IKZF2) (also known as Helios) is one of the five members of the Ikaros family of transcription factors found in mammals. IKZF2 is a critical regulator of T cell activity and function. IKZF2 is believed to have an important role in the function and stability of regulatory T cells (Tregs), a subpopulation of T cells that restricts the activity of effector T cells. Currently, anti-CTLA4 antibodies are used in the clinic to target Tregs in tumors. However, targeting CTLA4 often causes systemic activation of T-effector cells, resulting in excessive toxicity and limiting therapeutic utility.

[0004] There is a need for therapies that can target Tregs in tumors without causing systemic activation of T-effector cells. Accordingly, an IKZF2-specific modulator or degrader would have the potential to focus an enhanced immune response to areas within or near tumors providing a potentially more tolerable and less toxic therapy for the treatment of diseases mediated by IKZF2.

SUMMARY

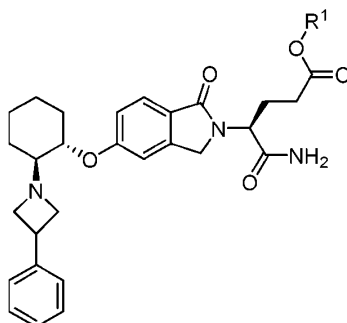
[0005] An improved process is provided herein for the synthesis of compounds that are IKZF2-specific modulator or degraders and the useful intermediates obtained therein. The synthesis of these compounds have been previously described in WO2023283425. The improved process provided here allows for more efficient preparation of optically pure compounds requiring fewer synthetic steps, reduced waste of undesirable and/or inactive intermediates, and reduced chromatographic purification steps.

[0006] Provided herein is a process for preparing Compound I, or a salt thereof:



I,

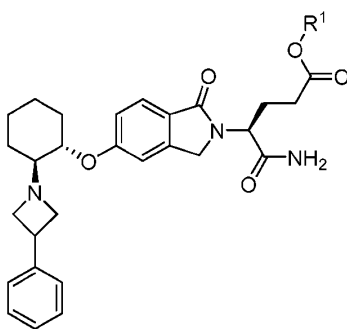
comprising contacting Compound II, or a salt thereof;



II,

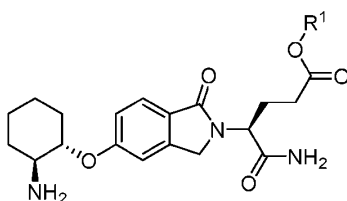
under conditions suitable to provide Compound I, wherein R^1 is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl.

[0007] Also provided herein is a process for preparing Compound II, or a salt thereof:



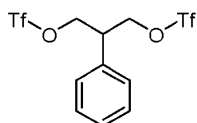
II

comprising contacting a compound of formula III, or a salt thereof:



III,

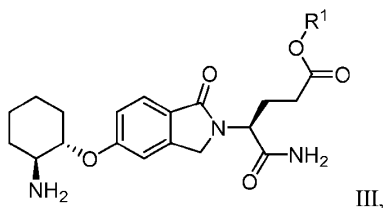
with a compound of formula IV, or a salt thereof:



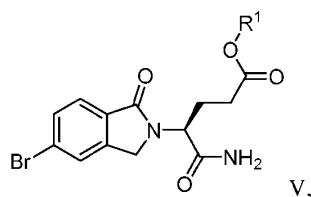
IV,

under conditions suitable to provide Compound II, wherein R^1 is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl.

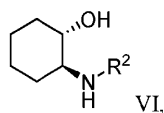
[0008] Also provided herein is a process for preparing a compound of formula III, or a salt thereof:



comprising contacting a compound of formula V, or a salt thereof:

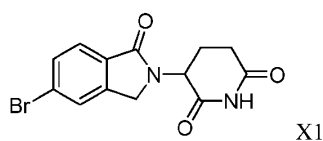


with a compound of formula VI, or a salt thereof:

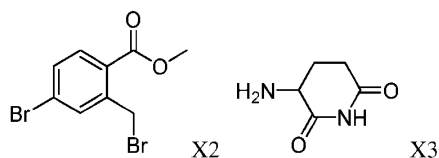


under conditions suitable to provide Compound III; wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl; and R² is a protecting group.

[0009] Also provided is a process for preparing Compound X1, or a salt thereof:

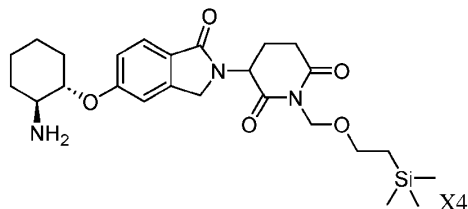


comprising contacting Compound X2 with Compound X3, or a salt thereof;

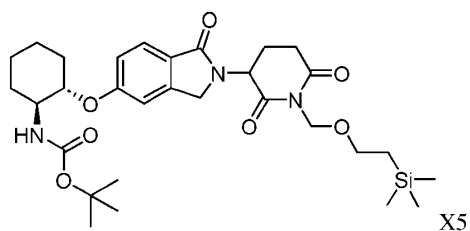


wherein the contacting comprises a first stage having a reaction temperature of about 45-55 °C and a second stage having a reaction temperature of from about 85-95 °C, under conditions suitable to provide Compound X1.

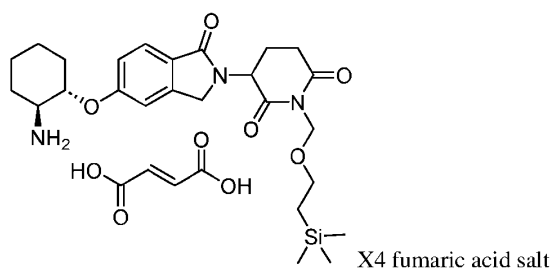
[0010] Also provided is a process for preparing Compound X4, or a salt thereof:



comprising deprotecting Compound X5:

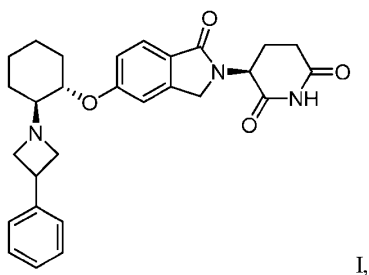


in the presence of fumaric acid, under conditions suitable to provide Compound X4 fumaric acid salt:

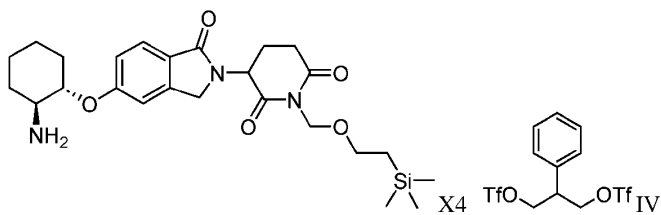


and contacting Compound X4 fumaric acid salt with a base in a solvent under conditions suitable to provide Compound X4.

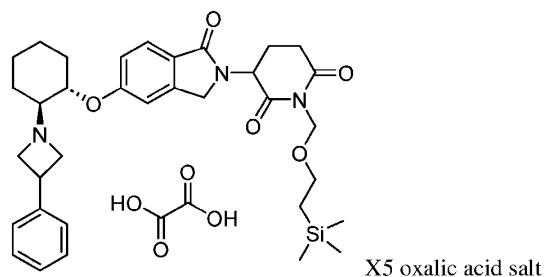
[0011] Also provided is a process for preparing Compound I, or a salt thereof:



comprising contacting Compound X4, or a salt thereof with Compound IV:

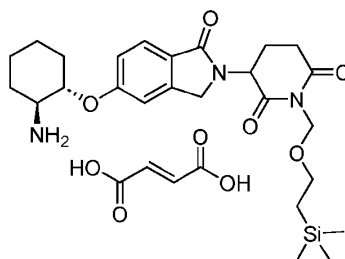


in the presence of oxalic acid, under conditions suitable to provide Compound X5 oxalic acid salt:

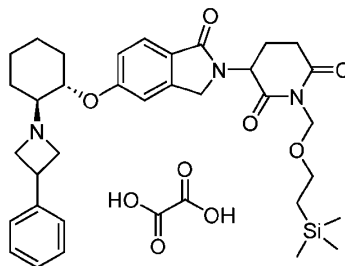


and contacting Compound X5 oxalic acid salt with a base in a solvent, under conditions suitable to provide Compound I; or dissociating the Compound X5 oxalic acid salt to provide Compound X5, and contacting the Compound X5 with a base in a solvent.

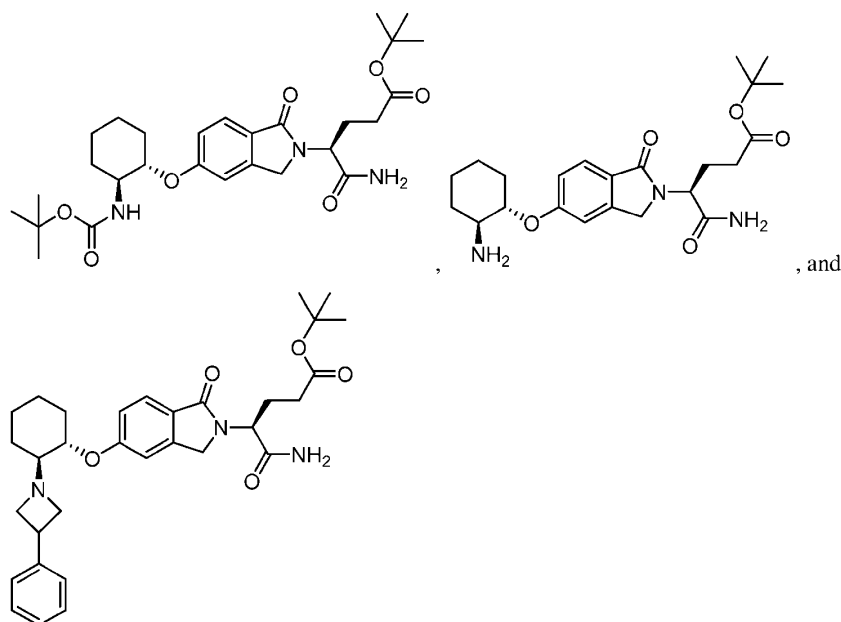
[0012] Also provided is 3-(5-(((1S,2S)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione fumaric acid salt (Compound X4 fumaric acid salt), having the structure:



[0013] Also provided is 3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione oxalic acid salt (Compound X5 oxalic acid salt), having the structure:



[0014] Also provided is a compound or a salt thereof, selected from:



DESCRIPTION

Definitions

[0015] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0016] The term “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, the singular forms “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. Thus, reference to “the compound” includes a plurality of such compounds, and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0017] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term “about” includes the indicated amount $\pm 10\%$. In other embodiments, the term “about” includes the indicated amount $\pm 5\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 2.5\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 1\%$. Also, to the term “about X” includes description of “X”.

[0018] Recitation of numeric ranges of values throughout the disclosure is intended to serve as a shorthand notation of referring individually to each separate value falling within the range inclusive of the values defining the range, and each separate value is incorporated in the specification as it were individually recited herein.

[0019] As used herein, the term “contacting” refers to the process of bringing into contact at least two distinct species such that they can react. It should be appreciated, however, that the resulting reaction

product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0020] The term “reaction conditions” is intended to refer to the physical and/or environmental conditions under which a chemical reaction proceeds. Examples of reaction conditions include, but are not limited to, one or more of following: reaction temperature, solvent, pH, pressure, reaction time, mole ratio of reactants, the presence of a base or acid, one or more protecting groups, or catalyst, radiation, etc. Reaction conditions may be named after the particular chemical reaction in which the conditions are employed, such as, coupling conditions, hydrogenation conditions, acylation conditions, reduction conditions, etc. Reaction conditions for most reactions are generally known to those skilled in the art or can be readily obtained from the literature. Exemplary reaction conditions sufficient for performing the chemical transformations provided herein can be found throughout, and in particular, the examples below. It is also contemplated that the reaction conditions can include reagents in addition to those listed in the specific reaction.

[0021] “Protecting group” refers to a moiety of a compound that masks or alters the properties of a functional moiety. “Deprotecting” or “deprotection” refers to a step removing the protecting group so as to restore the functional moiety to its original state. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See also Protective Groups in Organic Chemistry*, Peter G. M. Wuts and Theodora W. Greene, 4th Ed., 2006. Protecting groups are often utilized to mask the reactivity of certain functional moieties, to assist in the efficiency of desired chemical reactions, e.g., making and breaking chemical bonds in an ordered and planned fashion. For example, a “carboxylic acid protecting group” refers to a protecting group useful for masking the carboxylic acid moiety, e.g., to render the carboxylic acid group unreactive during intermediate steps of a synthetic process. Exemplary carboxylic acid protecting groups include alkyl or benzyl protecting groups, such as methyl, ethyl, benzyl, or *tert*-butyl; silyl groups such as 2-(trimethylsilyl)ethyl; and thioesters such as *tert*-butyl thioester. In some embodiments, the protecting group is *tert*-butyl. Exemplary amine protecting groups include carbamate protecting groups, such as *tert*-butyl carbamate (Boc), 9-fluorenylmethyl carbamate (Fmoc), or benzyl carbamate. In some embodiments, the protecting group is *tert*-butyl carbamate (Boc).

[0022] “Catalyst” refers to a chemical reactant that increases the rate of a reaction without itself being consumed. Similarly, a “precatalyst” refers to a compound that is converted to a catalyst during the course of the catalyzed reaction.

[0023] A “photocatalyst” refers to a type of catalyst used in photocatalytic reactions. “Photocatalysis” refers to a reaction that is irradiated with UV or visible light to accelerate the rate of reaction in the presence of a photocatalyst. Photocatalysts may be homogeneous or heterogeneous, and may or may not include metals. Exemplary metal-based photocatalysts include iridium, ruthenium, or nickel-based compounds.

[0024] An “activating agent” as defined herein refers to a chemical reactant that is capable of modifying an ester or carboxylic acid functional group to render it susceptible towards nucleophilic attack. Several

types of activating agents are known in the art and include, for example, carbonyl diimidazole (e.g., N,N'-dicyclohexylcarbodiimide (DCC), N,N'-dicyclopentylcarbodiimide, N,N'-diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), N-t-butyl-N-methylcarbodiimide (BMC), N-t-butyl-N-ethylcarbodiimide (BEC), 1,3-bis(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)carbodiimide (BDDC), etc.), anhydrides (e.g., symmetric, mixed, or cyclic anhydrides), activated ester forming agents (e.g., phenyl activated ester derivatives, p-hydroxamic activated ester, hexafluoroacetone (HFA), etc.), acylazole forming agents (acylimidazoles using CDI, acylbenzotriazoles, etc.), acyl azide forming agents, acid halide forming agents, phosphonium salts (HOBt, PyBOP, HOAt, etc.), aminium/uronium salts (e.g., tetramethyl aminium salts, bispyrrolidino aminium salts, bispiperidino aminium salts, imidazolium uronium salts, pyrimidinium uronium salts, uronium salts derived from N,N,N'-trimethyl-N'-phenylurea, morpholino-based aminium/uronium coupling reagents, antimoniate uronium salts, etc.), organophosphorus reagents (e.g., phosphinic and phosphoric acid derivatives), organosulfur reagents (e.g., sulfonic acid derivatives), triazine coupling reagents (e.g., 2-chloro-4,6-dimethoxy-1,3,5-triazine, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4 methylmorpholinium chloride, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4 methylmorpholinium tetrafluoroborate, etc.), pyridinium coupling reagents (e.g., Mukaiyama's reagent, pyridinium tetrafluoroborate coupling reagents, etc.), polymer-supported reagents (e.g., polymer-bound carbodiimide, polymer-bound TBTU, polymer-bound 2,4,6-trichloro-1,3,5-triazine, polymer-bound HOBt, polymer-bound HOSu, polymer-bound IIDQ, polymer-bound EEDQ, etc.), and the like.

[0025] As used herein, the term "salt" refers to a compound formed by the reaction of an acid and a base, resulting in the formation of a positively charged cation and a negatively charged anion. In general, a salt is defined as a compound that is formed by the combination of positively and negatively charged ions, where the charges of the ions result in a neutral compound. Salts can be either inorganic or organic. As used herein, the term "salt" includes partially or fully ionized salt forms. In some embodiments, the salt is fully ionized. The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids, and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic or organic acids. Salts derived from inorganic acids include, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include, e.g., acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic

acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic or organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, such as alkyl amines (i.e., $\text{NH}_2(\text{alkyl})$), dialkyl amines (i.e., $\text{HN}(\text{alkyl})_2$), trialkyl amines (i.e., $\text{N}(\text{alkyl})_3$), substituted alkyl amines (i.e., $\text{NH}_2(\text{substituted alkyl})$), di(substituted alkyl) amines (i.e., $\text{HN}(\text{substituted alkyl})_2$), tri(substituted alkyl) amines (i.e., $\text{N}(\text{substituted alkyl})_3$), alkenyl amines (i.e., $\text{NH}_2(\text{alkenyl})$), dialkenyl amines (i.e., $\text{HN}(\text{alkenyl})_2$), trialkenyl amines (i.e., $\text{N}(\text{alkenyl})_3$), substituted alkenyl amines (i.e., $\text{NH}_2(\text{substituted alkenyl})$), di(substituted alkenyl) amines (i.e., $\text{HN}(\text{substituted alkenyl})_2$), tri(substituted alkenyl) amines (i.e., $\text{N}(\text{substituted alkenyl})_3$), mono-, di- or tri- cycloalkyl amines (i.e., $\text{NH}_2(\text{cycloalkyl})$, $\text{HN}(\text{cycloalkyl})_2$, $\text{N}(\text{cycloalkyl})_3$), mono-, di- or tri- arylamines (i.e., $\text{NH}_2(\text{aryl})$, $\text{HN}(\text{aryl})_2$, $\text{N}(\text{aryl})_3$), or mixed amines, etc. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0026] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

[0027] The term “alkyl” as used herein, means a straight or branched, saturated hydrocarbon chain containing from 1 to 30 carbon atoms. The term “lower alkyl” or “C₁-C₆-alkyl” means a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. The term “C₁-C₃- alkyl” means a straight or branched chain hydrocarbon containing from 1 to 3 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*- propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3- methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-decyl.

[0028] “Alkenyl” refers to an alkyl group containing at least one (e.g., 1-3, or 1) carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C₂₋₂₀ alkenyl), 2 to 12 carbon atoms (i.e., C₂₋₁₂ alkenyl), 2 to 8 carbon atoms (i.e., C₂₋₈ alkenyl), 2 to 6 carbon atoms (i.e., C₂₋₆ alkenyl), or 2 to 4 carbon atoms

(i.e., C₂₋₄ alkenyl). Examples of alkenyl groups include, e.g., ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0029] “Alkynyl” refers to an alkyl group containing at least one (e.g., 1-3, or 1) carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C₂₋₂₀ alkynyl), 2 to 12 carbon atoms (i.e., C₂₋₁₂ alkynyl), 2 to 8 carbon atoms (i.e., C₂₋₈ alkynyl), 2 to 6 carbon atoms (i.e., C₂₋₆ alkynyl), or 2 to 4 carbon atoms (i.e., C₂₋₄ alkynyl). The term “alkynyl” also includes those groups having one triple bond and one double bond.

[0030] “Alkoxy” refers to the group “alkyl-O-”. Examples of alkoxy groups include, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

[0031] “Alkylthio” refers to the group “alkyl-S-”. “Alkylsulfinyl” refers to the group “alkyl-S(O)-”. “Alkylsulfonyl” refers to the group “alkyl-S(O)₂-”. “Alkylsulfonylalkyl” refers to -alkyl-S(O)₂-alkyl.

[0032] “Acyl” refers to a group -C(O)R^y, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include, e.g., formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0033] “Amido” refers to both a “C-amido” group which refers to the group -C(O)NR^yR^z and an “N-amido” group which refers to the group -NR^yC(O)R^z, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocyclyl; each of which may be optionally substituted, as defined herein.

[0034] “Amino” refers to the group -NR^yR^z wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0035] “Amidino” refers to -C(NR^y)(NR^z)₂, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0036] The term “aryl” as used herein, refers to a phenyl group, or bicyclic aryl or tricyclic aryl fused ring systems. Bicyclic fused ring systems are exemplified by a phenyl group appended to the parent molecular moiety and fused to a phenyl group. Tricyclic fused ring systems are exemplified by a phenyl group appended to the parent molecular moiety and fused to two other phenyl groups. Representative examples of bicyclic aryls include, but are not limited to, naphthyl. Representative examples of tricyclic aryls include, but are not limited to, anthracenyl. The monocyclic, bicyclic, and tricyclic aryls are connected to the parent molecular moiety through any carbon atom contained within the rings, and can be unsubstituted or substituted.

[0037] The term “benzyl” as used herein refers to -CH₂-phenyl, which may be unsubstituted or substituted, as defined herein.

[0038] “Arylalkyl” or “Aralkyl” refers to the group “aryl-alkyl”.

[0039] “Carbamoyl” refers to both an “O-carbamoyl” group which refers to the group $-O-C(O)NR^yR^z$ and an “N-carbamoyl” group which refers to the group $-NR^yC(O)OR^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0040] “Carboxyl ester” or “ester” refer to both $-OC(O)R^x$ and $-C(O)OR^x$, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0041] “Cyanoalkyl” refers to refers to an alkyl group as defined above, wherein one or more (e.g., 1 or 2) hydrogen atoms are replaced by a cyano ($-CN$) group.

[0042] “Cycloalkyl” refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term “cycloalkyl” includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 14 ring carbon atoms (i.e., C_{3-14} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbornyl, decalanyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Further, the term cycloalkyl is intended to encompass any non-aromatic ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also includes “spirocycloalkyl” when there are two positions for substitution on the same carbon atom, for example spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl.

[0043] “Cycloalkylalkyl” refers to the group “cycloalkyl-alkyl”.

[0044] The term “halogen” or “halo” as used herein, means Cl, Br, I, or F.

[0045] “Haloalkyl” refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0046] “Haloalkoxy” refers to an alkoxy group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen.

[0047] “Haloalkoxyalkyl” refers to an alkoxyalkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen.

[0048] “Hydroxyalkyl” refers to an alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a hydroxy group.

[0049] “Heteroalkyl” refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms), excluding any terminal carbon atom(s), are each independently replaced with the same or different heteroatomic group, provided the point of attachment to the remainder of the molecule is through a carbon atom. The term “heteroalkyl” includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR^y-, -O-, -S-, -S(O)-, -S(O)₂-, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkyl groups include, e.g., ethers (e.g., -CH₂OCH₃, -CH(CH₃)OCH₃, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OCH₃, etc.), thioethers (e.g., -CH₂SCH₃, -CH(CH₃)SCH₃, -CH₂CH₂SCH₃, -CH₂CH₂SCH₂CH₂SCH₃, etc.), sulfones (e.g., -CH₂S(O)₂CH₃, -CH(CH₃)S(O)₂CH₃, -CH₂CH₂S(O)₂CH₃, -CH₂CH₂S(O)₂CH₂CH₂OCH₃, etc.), and amines (e.g., -CH₂NR^yCH₃, -CH(CH₃)NR^yCH₃, -CH₂CH₂NR^yCH₃, -CH₂CH₂NR^yCH₂CH₂NR^yCH₃, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkyl includes 2 to 10 carbon atoms, 2 to 8 carbon atoms, or 2 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0050] “Heteroaryl” refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C₁₋₂₀ heteroaryl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heteroaryl), or 3 to 8 carbon ring atoms (i.e., C₃₋₈ heteroaryl), and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinoxalinyl, quinoxalinyl, quinolyl, quinuclidinyl, isoquinolyl, thiazolyl, thiadiazolyl, thiophenyl (i.e., thienyl), triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolyl, isoquinolyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the

heteroaryl can be bound *via* either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0051] “Heteroarylalkyl” refers to the group “heteroaryl-alkyl-”.

[0052] The term “heterocyclyl” refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. The term “heterocyclyl” includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups, and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro, and may comprise one or more (e.g., 1 to 3) oxo (=O) or N-oxide (-O-) moieties. Any non-aromatic ring or fused ring system containing at least one heteroatom and one non-aromatic ring is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to a cycloalkyl, an aryl, or heteroaryl ring, regardless of the attachment to the remainder of the molecule. For example, fused ring systems such as decahydroquinazolinyl, 1,2,3,4-tetrahydroquinazolinyl, and 5,6,7,8-tetrahydroquinazolinyl are heterocyclyl, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (i.e., C2-20 heterocyclyl), 2 to 12 ring carbon atoms (i.e., C2-12 heterocyclyl), 2 to 10 ring carbon atoms (i.e., C2-10 heterocyclyl), 2 to 8 ring carbon atoms (i.e., C2-8 heterocyclyl), 3 to 12 ring carbon atoms (i.e., C3-12 heterocyclyl), 3 to 8 ring carbon atoms (i.e., C3-8 heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C3-6 heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur, or oxygen. Examples of heterocyclyl groups include, e.g., azetidiny, azepiny, benzodioxoly, benzo[b][1,4]dioxepiny, 1,4-benzodioxany, benzopyrany, benzodioxiny, benzopyranony, benzofuranony, dioxolany, dihydropyrany, hydropyrany, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanony, imidazoliny, imidazolidiny, indoliny, indoliziny, isoindoliny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2 oxopiperaziny, 2 oxopiperidiny, 2 oxopyrrolidiny, oxazolidiny, oxirany, oxetany, phenothiaziny, phenoxaziny, piperidiny, piperaziny, 4 piperidony, pyrrolidiny, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, tetrahydropyrany, trithianyl, tetrahydroquinoliny, thiomorpholiny, thiamorpholiny, 1 oxo thiomorpholiny, and 1,1 dioxo thiomorpholiny. The term “heterocyclyl” also includes “spiroheterocyclyl” when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocyclyl rings include, e.g., bicyclic and tricyclic ring systems, such as oxabicyclo[2.2.2]octany, 2-oxa-7-azaspiro[3.5]nonany, 2-oxa-6-azaspiro[3.4]octany, and 6-oxa-1-azaspiro[3.3]heptany. Examples of the fused-heterocyclyl rings include, but are not limited to, 1,2,3,4-

tetrahydroisoquinoliny, 4,5,6,7-tetrahydrothieno[2,3-c]pyridiny, indoliny, and isoindoliny, where the heterocyclyl can be bound via either ring of the fused system.

[0053] “Heterocyclylalkyl” refers to the group “heterocyclyl-alkyl-.”

[0054] “Imino” refers to a group $-C(NR^y)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0055] “Imido” refers to a group $-C(O)NR^yC(O)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0056] “Oxime” refers to the group $-CR^y(=NOH)$ wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0057] “Oxo” refers to the moiety $=O$.

[0058] “Sulfonyl” refers to the group $-S(O)_2R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0059] “Sulfinyl” refers to the group $-S(O)R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfinyl are methylsulfinyl, ethylsulfinyl, phenylsulfinyl, and toluenesulfinyl.

[0060] “Sulfonamido” refers to the groups $-SO_2NR^yR^z$ and $-NR^ySO_2R^z$, where R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0061] The terms “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term “optionally substituted” refers to any one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0062] The term “substituted” used herein means any of the above groups (i.e., alkyl, alkoxy, aryl, benzyl, heterocyclyl, and heteroaryl) wherein at least one (e.g., 1 to 5 or 1 to 3) hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $-NHNH_2$, $=NNH_2$, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, thiocyanate, $-S(O)OH$, $-S(O)_2OH$, sulfonamido, thiol, thioxo, N-oxide, or $-Si(R_y)_3$, wherein each R_y is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl.

[0063] The term “acid” refers to a chemical species that donate protons. Acidic compounds may be organic compounds such as carboxylic acids and sulfonic acids, inorganic compounds such as sulfuric acid, hydrochloric acid, nitric acids, and phosphoric acid, and may be classified as strong or weak.

[0064] The term “base” refers to a chemical species that can accept protons. Basic compounds may be organic compounds such as basic amines, inorganic compounds such as metal hydroxides and carbonates, and may be classified as strong or weak.

[0065] The term “amine base” as used herein generally refers to a primary, secondary, or tertiary amine, such as a alkyl amine, dialkyl amine, trialkyl amine, nitrogen-containing heterocycle, or nitrogen-containing heteroaryl, wherein each of which is optionally substituted, e.g., by alkyl.

[0066] The term “nitrogen-containing heterocyclic base” as used herein, refers to a saturated or partially unsaturated cyclic alkyl group, with at least one ring nitrogen atom, and optionally one or more additional ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. The term “heterocyclic” includes heterocycloalkenyl rings (i.e., a heterocyclic ring having at least one double bond), bridged-heterocyclic rings, fused-heterocyclic rings, and spiro-heterocyclic rings. A heterocycle may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro, and may comprise one or more (e.g., one to three or one or two) oxo (=O) or N-oxide (-O-) moieties. Any non-aromatic ring containing at least one nitrogen atom capable of accepting a proton is considered a nitrogen-containing heterocyclic base. Further, the term heterocyclic is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to a cycloalkyl, aryl or heteroaryl ring, regardless of the position of the heteroatom. As used herein, a nitrogen-containing heterocyclic has 2 to 20 ring carbon atoms (i.e., C₂₋₂₀ heterocycle), 2 to 12 ring carbon atoms (i.e., C₂₋₁₂ heterocycle), 2 to 10 ring carbon atoms (i.e., C₂₋₁₀ heterocycle), 2 to 8 ring carbon atoms (i.e., C₂₋₈ heterocycle), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heterocycle), 3 to 8 ring carbon atoms (i.e., C₃₋₈ heterocycle), or 3 to 6 ring carbon atoms (i.e., C₃₋₆ heterocycle); having at least 1 nitrogen atom capable of accepting a proton, and optionally an additional 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen.

[0067] The term “nitrogen-containing heteroaryl base” refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with at least one nitrogen atom capable of accepting a proton, and optionally one or more additional ring heteroatoms independently selected from nitrogen, oxygen and sulfur. As used herein, nitrogen-containing heteroaryl includes 1 to 20 ring carbon atoms (i.e., C₁₋₂₀ heteroaryl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heteroaryl), or 3 to 8 carbon ring atoms (i.e., C₃₋₈ heteroaryl); and having at least 1 nitrogen atom, and optionally an additional 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4

ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur.

[0068] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

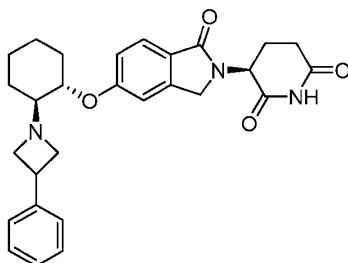
[0069] For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the number 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

[0070] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub- combination. All combinations of the embodiments pertaining to the disclosure are embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace subject matter that are, for example, compounds that are stable compounds (i.e., compounds that can be made, isolated, characterized, and tested for biological activity). In addition, all sub- combinations of the various embodiments and elements thereof (e.g., elements of the chemical groups listed in the embodiments describing such variables) are also embraced by the present disclosure and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

Processes

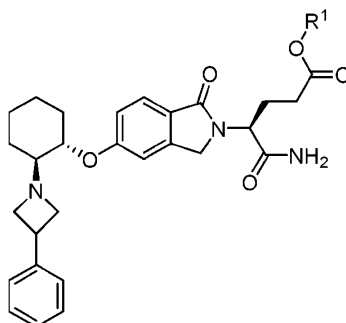
[0071] The processes described herein provide compounds that bind to cereblon, thereby modulating cereblon activity.

[0072] Provided herein is a process for preparing Compound I, or a salt thereof:



I.

comprising contacting Compound II, or a salt thereof;



II,

under conditions suitable to provide Compound I, wherein R^1 is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl.

[0073] In some embodiments, R^1 is an optionally substituted alkyl group. In some embodiments, R^1 is a C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy, cyano, or $-Si(C_{1-6} \text{ alkyl})_3$. In some embodiments, R^1 is an optionally substituted benzyl group.

[0074] In some embodiments, R^1 is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, methoxymethyl, *t*-butoxymethyl, benzyl, *p*-methoxybenzyl, or *p*-nitrobenzyl. In some embodiments, R^1 is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, or benzyl. In some embodiments, R^1 is *tert*-butyl.

[0075] In some embodiments, R^1 is hydrogen.

[0076] In some embodiments, the conditions comprise an acid or an activating agent.

[0077] In some embodiments, the conditions comprise an acid. In some embodiments, the acid is an inorganic acid, a carboxylic acid or a sulfonic acid. In some embodiments, the acid is hydrochloric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, citric acid, 2,2-dimethylbutyric acid, isobutyric acid, pivalic acid, oxalic acid, methanesulfonic acid, benzenesulfonic acid, or *p*-toluenesulfonic acid.

[0078] In some embodiments, the acid is an inorganic acid. In some embodiments, the inorganic acid is hydrochloric acid or phosphoric acid.

[0079] In some embodiments, the acid is a carboxylic acid. In some embodiments, the carboxylic acid is formic acid, acetic acid, trifluoroacetic acid, citric acid, 2,2-dimethylbutyric acid, isobutyric acid, pivalic acid, or oxalic acid.

[0080] In some embodiments, the organic acid is a sulfonic acid. In some embodiments, the sulfonic acid is methanesulfonic acid, benzenesulfonic acid, or *p*-toluenesulfonic acid.

[0081] In some embodiments, the acid is benzenesulfonic acid.

[0082] In some embodiments, the conditions comprise an activating agent. In some embodiments, the activating agent is an acid halide forming agent, a carbodiimide, a phosphonium salt, or a uronium salt. In some embodiments, the activating agent is thionyl chloride, oxalyl chloride, phosphorus pentachloride, *N,N*-dicyclohexylcarbodiimide (DCC), *N,N*-diisopropylcarbodiimide (DIC), *N*-*t*-butyl-*N*-methylcarbodiimide (BMC), *N*-*t*-butyl-*N*-ethylcarbodiimide (BEC), 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide (EDC), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), or O-(1H-6-chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HCTU).

[0083] In some embodiments, the activating agent is an acid halide forming agent. In some embodiments, the acid halide forming agent is thionyl chloride, oxalyl chloride, or phosphorus pentachloride.

[0084] In some embodiments, the activating agent is a carbodiimide. In some embodiments, the carbodiimide is *N,N'*-dicyclohexylcarbodiimide (DCC), *N,N'*-diisopropylcarbodiimide (DIC), *N*-*t*-butyl-*N*-methylcarbodiimide (BMC), *N*-*t*-butyl-*N*-ethylcarbodiimide (BEC), or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).

[0085] In some embodiments, the activating agent is a phosphonium salt. In some embodiments, the phosphonium salt is benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP).

[0086] In some embodiments, the activating agent is a uronium salt. In some embodiments, the uronium salt is 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), or O-(1H-6-chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HCTU).

[0087] In some embodiments, the conditions further comprise a solvent. In some embodiments, the conditions further comprise a solvent at a temperature of about 40 °C to about 120 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about 60 °C to about 100 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about 70 °C to about 90 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about 80 °C.

[0088] In some embodiments, the solvent is a polar aprotic solvent, an ether, an ester, or a combination thereof. In some embodiments, the solvent is dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, or a combination thereof.

[0089] In some embodiments, the solvent is a polar aprotic solvent. In some embodiments, the polar aprotic solvent is dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide, or a combination thereof.

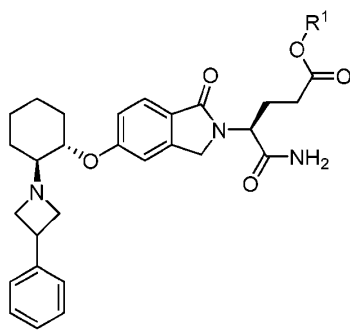
[0090] In some embodiments, the solvent is an ether. In some embodiments, the ether is methyl *tert*-butyl ether, 1,4-dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, or a combination thereof.

[0091] In some embodiments, the solvent is an ester. In some embodiments, the ester is ethyl acetate, isopropyl acetate, or a combination thereof.

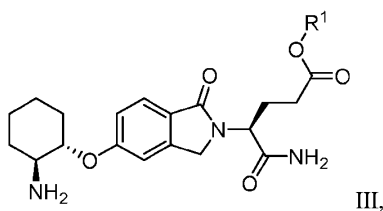
[0092] In some embodiments, the solvent is acetonitrile.

[0093] In some embodiments, the conditions comprise an acid and a solvent. In some embodiments, the conditions comprise benzenesulfonic acid and acetonitrile. In some embodiments, the conditions comprise benzenesulfonic acid and acetonitrile at a temperature of about 70 °C to about 90 °C. In some embodiments, the conditions comprise benzenesulfonic acid and acetonitrile at a temperature of about 80 °C.

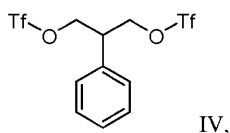
[0094] Also provided herein is a process for preparing Compound II, or a salt thereof:



comprising contacting a compound of formula III, or a salt thereof:



with a compound of formula IV, or a salt thereof:



under conditions suitable to provide Compound II, wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl.

[0095] In some embodiments, R¹ is an optionally substituted alkyl group. In some embodiments, R¹ is a C₁₋₆ alkyl optionally substituted with C₁₋₆ alkoxy, cyano, or -Si(C₁₋₆ alkyl)₃. In some embodiments, R¹ is an optionally substituted benzyl group.

[0096] In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, methoxymethyl, *t*-butoxymethyl, benzyl, *p*-methoxybenzyl, or *p*-nitrobenzyl. In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, or benzyl. In some embodiments, R¹ is *tert*-butyl.

[0097] In some embodiments, R¹ is hydrogen.

[0098] In some embodiments, the conditions comprise a base.

[0099] In some embodiments, the base is an amine base. In some embodiments, the amine base is a tertiary amine. In some embodiments, the amine base is a nitrogen-containing heterocyclic or nitrogen-containing heteroaryl base. In some embodiments, the amine base is *N,N*-diisopropylmethylamine, *N,N*-diisopropylethylamine, triethylamine, tributylamine, *N*-methylmorpholine, pyridine, *N*-methylimidazole, *N*-methylmorpholine, 2,2,6,6,-tetramethylpiperidine, quinuclidine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, or a combination thereof.

[0100] In some embodiments, the base is a tertiary amine. In some embodiments, the tertiary amine is *N,N*-diisopropylmethylamine, *N,N*-diisopropylethylamine, triethylamine, tributylamine, *N*-methylmorpholine, or a combination thereof.

[0101] In some embodiments, the base is a nitrogen-containing heterocyclic or nitrogen-containing heteroaryl base. In some embodiments, the nitrogen-containing heterocyclic or nitrogen-containing heteroaryl base is pyridine, *N*-methylimidazole, *N*-methylmorpholine, 2,2,6,6,-tetramethylpiperidine, quinuclidine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, or a combination thereof.

[0102] In some embodiments, the base is *N,N*-diisopropylethylamine.

[0103] In some embodiments, the conditions further comprise a solvent.

[0104] In some embodiments, the conditions further comprise a solvent at a temperature of about -40 °C to about 40 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about -30 °C to about 30 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about -20 °C to about 20 °C.

[0105] In some embodiments, the solvent is a polar aprotic solvent, an ether, an ester, or a combination thereof. In some embodiments, the solvent is dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide, methyl *tert*-butyl ether, 1,4-dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, or a combination thereof.

[0106] In some embodiments, the solvent is a polar aprotic solvent. In some embodiments, the polar aprotic solvent is dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide, or a combination thereof.

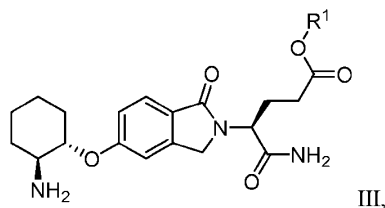
[0107] In some embodiments, the solvent is an ether. In some embodiments, the ether is methyl *tert*-butyl ether, 1,4-dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, or a combination thereof.

[0108] In some embodiments, the solvent is an ester. In some embodiments, the ester is ethyl acetate, isopropyl acetate, or a combination thereof.

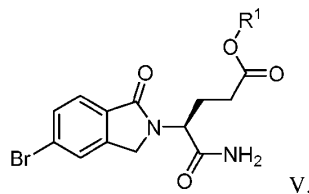
[0109] In some embodiments, the solvent is acetonitrile.

[0110] In some embodiments, the conditions comprise a base and a solvent. In some embodiments, the conditions comprise *N,N*-diisopropylethylamine and acetonitrile. In some embodiments, the conditions comprise *N,N*-diisopropylethylamine and acetonitrile at a temperature of about -20 °C to about 20 °C.

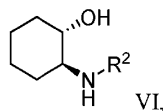
[0111] Also provided herein is a process for preparing Compound III, or a salt thereof:



comprising contacting a compound of formula V, or a salt thereof:



with a compound of formula VI, or a salt thereof:



under conditions suitable to provide Compound III; wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl; and R² is a protecting group.

[0112] In some embodiments, R¹ is an optionally substituted alkyl group. In some embodiments, R¹ is a C₁₋₆ alkyl optionally substituted with C₁₋₆ alkoxy, cyano, or -Si(C₁₋₆ alkyl)₃. In some embodiments, R¹ is an optionally substituted benzyl group.

[0113] In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, methoxymethyl, *t*-butoxymethyl, benzyl, *p*-methoxybenzyl, or *p*-nitrobenzyl. In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, or benzyl. In some embodiments, R¹ is *tert*-butyl.

[0114] In some embodiments, R¹ is hydrogen.

[0115] In some embodiments, R² is an amine protecting group. In some embodiments, R² is -C(O)OR, wherein R is 9-fluorenylmethyl, *tert*-butyl, or benzyl.

[0116] In some embodiments, R² is -C(O)O-*tert*-butyl.

[0117] In some embodiments, the conditions further comprise irradiation under visible light. In some embodiments, the conditions comprise irradiation under visible light having a wavelength of about 300 to about 600 nanometers. In some embodiments, the conditions comprise irradiation under visible light having a wavelength of about 400 to about 500 nanometers.

[0118] In some embodiments, the conditions further comprise a catalyst. In some embodiments, the conditions further comprise a photocatalyst. In some embodiments, the conditions further comprise a metal-based photocatalyst.

[0119] In some embodiments, the catalyst an iridium, ruthenium, or nickel-based photocatalyst, or a combination thereof. In some embodiments, the catalyst is [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-

N1,N1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate, [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N1,N1'*]bis[2-(2-pyridinyl-*N*)phenyl-C]Iridium(III) hexafluorophosphate, tris(4,4'-di-*tert*-butyl-2,2'-bipyridine)ruthenium bis(hexafluorophosphate), [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride, or a combination thereof.

[0120] In some embodiments, the catalyst is a combination of [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N1,N1'*]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate and [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride.

[0121] In some embodiments, the conditions further comprise a base.

[0122] In some embodiments, the base is an amine base. In some embodiments, the amine base is a tertiary amine. In some embodiments, the amine base is a nitrogen-containing heterocyclic or nitrogen-containing heteroaryl base. In some embodiments, the amine base is *N,N*-diisopropylmethylamine, *N,N*-diisopropylethylamine, triethylamine, tributylamine, *N*-methylmorpholine, pyridine, *N*-methylimidazole, *N*-methylmorpholine, 2,2,6,6,-tetramethylpiperidine, quinuclidine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, or a combination thereof.

[0123] In some embodiments, the base is a tertiary amine. In some embodiments, the tertiary amine is *N,N*-diisopropylmethylamine, *N,N*-diisopropylethylamine, triethylamine, tributylamine, *N*-methylmorpholine, or a combination thereof.

[0124] In some embodiments, the base is a nitrogen-containing heterocyclic or nitrogen-containing heteroaryl base. In some embodiments, the nitrogen-containing heterocyclic or nitrogen-containing heteroaryl base is pyridine, *N*-methylimidazole, *N*-methylmorpholine, 2,2,6,6,-tetramethylpiperidine, quinuclidine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, or a combination thereof.

[0125] In some embodiments, the base is a combination of 2,2,6,6,-tetramethylpiperidine and quinuclidine.

[0126] In some embodiments, the conditions further comprise a solvent.

[0127] In some embodiments, the conditions further comprise a solvent at a temperature of about -40 °C to about 40 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about -30 °C to about 30 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about -20 °C to about 20 °C.

[0128] In some embodiments, the solvent is a polar aprotic solvent, an ether, an ester, or a combination thereof. In some embodiments, the solvent is dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide, methyl *tert*-butyl ether, 1,4-dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, or a combination thereof.

[0129] In some embodiments, the solvent is a polar aprotic solvent. In some embodiments, the polar aprotic solvent is dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide, or a combination thereof.

[0130] In some embodiments, the solvent is an ether. In some embodiments, the ether is methyl *tert*-butyl ether, 1,4-dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, or a combination thereof.

[0131] In some embodiments, the solvent is an ester. In some embodiments, the ester is ethyl acetate, isopropyl acetate, or a combination thereof.

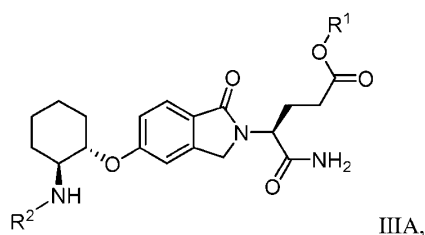
[0132] In some embodiments, the solvent is acetonitrile.

[0133] In some embodiments, the conditions comprise irradiation under visible light and a catalyst. In some embodiments, the conditions comprise irradiation under visible light in the presence of a combination of [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate and [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride.

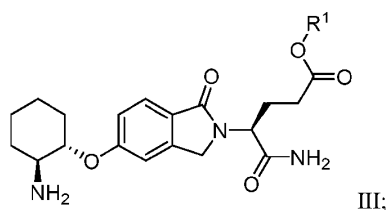
[0134] In some embodiments, the conditions comprise irradiation under visible light, a catalyst, and a base. In some embodiments, the conditions comprise irradiation under visible light in the presence of a combination of [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate and [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride and a combination of 2,2,6,6-tetramethylpiperidine and quinuclidine.

[0135] In some embodiments, the conditions comprise irradiation under visible light, a catalyst, a base, and a solvent. In some embodiments, the conditions comprise irradiation under visible light in the presence of a combination of [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate and [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride and a combination of 2,2,6,6-tetramethylpiperidine and quinuclidine, in acetonitrile at a temperature of about -20 °C to about 20 °C.

[0136] In some embodiments, the conditions further comprise a deprotection step comprising converting a compound of formula IIIA, or a salt thereof:



to compound III under conditions suitable to provide compound III:



wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl; and R² is a protecting group.

[0137] In some embodiments, R¹ is an optionally substituted alkyl group. In some embodiments, R¹ is a C₁₋₆ alkyl optionally substituted with C₁₋₆ alkoxy, cyano, or -Si(C₁₋₆ alkyl)₃. In some embodiments, R¹ is an optionally substituted benzyl group.

[0138] In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, methoxymethyl, *t*-butoxymethyl, benzyl, *p*-methoxybenzyl, or *p*-nitrobenzyl. In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, or benzyl. In some embodiments, R¹ is *tert*-butyl.

[0139] In some embodiments, R¹ is hydrogen.

[0140] In some embodiments, R² is an amine protecting group. In some embodiments, R² is -C(O)OR, wherein R is 9-fluorenylmethyl, *tert*-butyl, or benzyl. In some embodiments, R² is -C(O)O-*tert*-butyl.

[0141] In some embodiments, the conditions comprise an acid.

[0142] In some embodiments, the acid is an inorganic acid, a carboxylic acid, or a sulfonic acid. In some embodiments, the acid is hydrochloric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, citric acid, 2,2-dimethylbutyric acid, isobutyric acid, pivalic acid, oxalic acid, methanesulfonic acid, benzenesulfonic acid, or *p*-toluenesulfonic acid.

[0143] In some embodiments, the acid is an inorganic acid. In some embodiments, the inorganic acid is hydrochloric acid or phosphoric acid.

[0144] In some embodiments, the acid is a carboxylic acid. In some embodiments, the organic acid is formic acid, acetic acid, trifluoroacetic acid, citric acid, 2,2-dimethylbutyric acid, isobutyric acid, pivalic acid, or oxalic acid.

[0145] In some embodiments, the organic acid is a sulfonic acid. In some embodiments, the sulfonic acid is methanesulfonic acid, benzenesulfonic acid, or *p*-toluenesulfonic acid.

[0146] In some embodiments, the acid is *p*-toluenesulfonic acid.

[0147] In some embodiments, the conditions further comprise a solvent. In some embodiments, the conditions further comprise a solvent at a temperature of about 0 °C to about 40 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about 10 °C to about 30 °C. In some embodiments, the conditions further comprise a solvent at a temperature of about 20 °C.

[0148] In some embodiments, the solvent is a polar aprotic solvent, an ether, an ester, or a combination thereof. In some embodiments, the solvent is dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide, methyl *tert*-butyl ether, 1,4-dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, or a combination thereof.

[0149] In some embodiments, the solvent is a polar aprotic solvent. In some embodiments, the polar aprotic solvent is dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide, or a combination thereof.

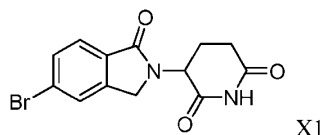
[0150] In some embodiments, the solvent is an ether. In some embodiments, the ether is methyl *tert*-butyl ether, 1,4-dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, or a combination thereof.

[0151] In some embodiments, the solvent is an ester. In some embodiments, the ester is ethyl acetate, isopropyl acetate, or a combination thereof.

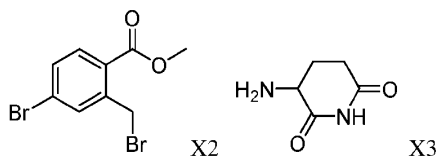
[0152] In some embodiments, the solvent is acetonitrile.

[0153] In some embodiments, the conditions comprise an acid and a solvent. In some embodiments, the conditions comprise *p*-toluenesulfonic acid and acetonitrile. In some embodiments, the conditions comprise *p*-toluenesulfonic acid and acetonitrile at a temperature of about 10 °C to about 30 °C. In some embodiments, the conditions comprise *p*-toluenesulfonic acid and acetonitrile at a temperature of about 20 °C.

[0154] Also provided herein is a process for preparing Compound X1, or a salt thereof:



comprising contacting Compound X2 with Compound X3, or a salt thereof;



wherein the contacting comprises a first stage having a reaction temperature of about 45-55 °C and a second stage having a reaction temperature of from about 85-95 °C, under conditions suitable to provide Compound X1.

[0155] In some embodiments, the conditions comprise DMF.

[0156] In some embodiments, the conditions comprise a base. In some embodiments, the conditions comprise DIEA.

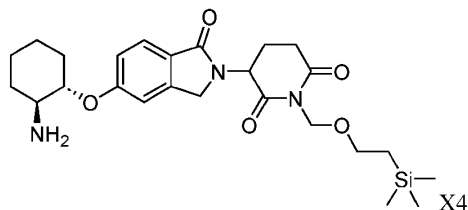
[0157] In some embodiments, the conditions comprise a first stage having a reaction temperature of about 45 °C, about 50 °C, or about 55 °C.

[0158] In some embodiments, the first stage is from about 12-24 hours, or from about 18-24 hours, or from about 18-22 hours, or about 22 hours.

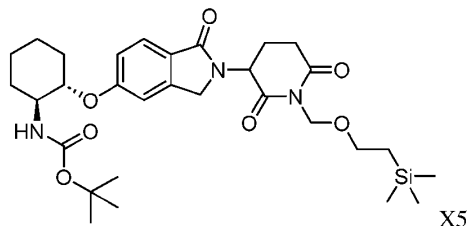
[0159] In some embodiments, the conditions comprise a second stage having a reaction temperature of from about 85 °C, about 90 °C, or about 95 °C.

[0160] In some embodiments, the second stage is from about 12-24 hours, or from about 18-24 hours, or from about 18-22 hours, or about 21 hours.

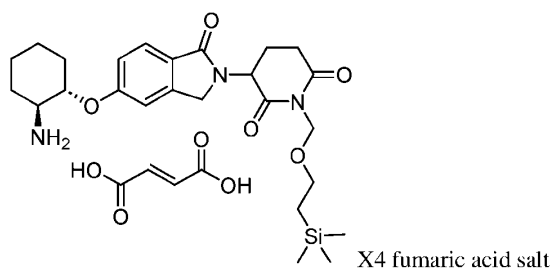
[0161] In certain embodiments, provided is a process for preparing Compound X4, or a salt thereof:



comprising deprotecting Compound X5:



in the presence of fumaric acid, under conditions suitable to provide Compound X4 fumaric acid salt:



and contacting Compound X4 fumaric acid salt with a base in a solvent under conditions suitable to provide Compound X4.

[0162] In certain embodiments, the process is performed in the absence of DCM.

[0163] In certain embodiments, the process comprises TMSOTf.

[0164] In certain embodiments, the solvent comprises THF. In certain embodiments, the solvent is THF.

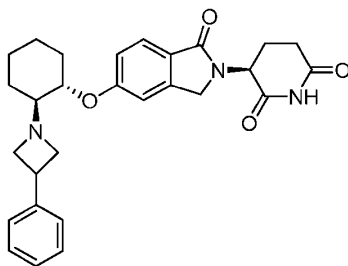
[0165] In certain embodiments, the conditions comprise a temperature of about 25 °C.

[0166] In certain embodiments, the base is sodium bicarbonate.

[0167] In certain embodiments, the conditions comprise adding fumaric acid in ACN.

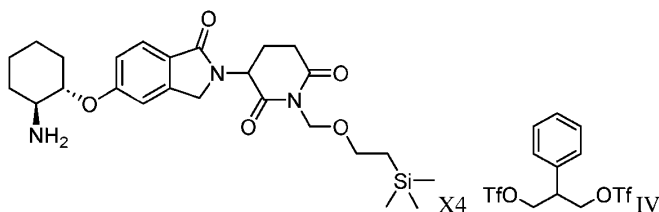
[0168] In certain embodiments, the Compound X4 fumaric acid salt is not isolated. In certain embodiments, the Compound X4 fumaric acid salt is isolated.

[0169] Also provided herein is a process for preparing Compound I, or a salt thereof:

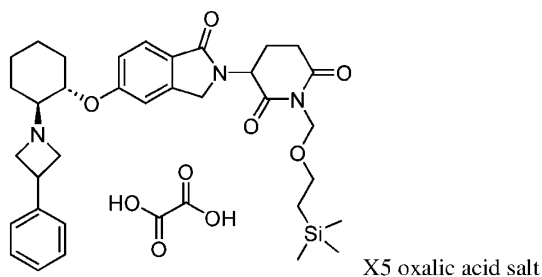


I,

comprising contacting Compound X4, or a salt thereof with Compound IV:



in the presence of oxalic acid, under conditions suitable to provide Compound X5 oxalic acid salt:



X5 oxalic acid salt

and contacting Compound X5 oxalic acid salt with a base in a solvent, under conditions suitable to provide Compound I; or dissociating the Compound X5 oxalic acid salt to provide Compound X5, and contacting the Compound X5 with a base in a solvent.

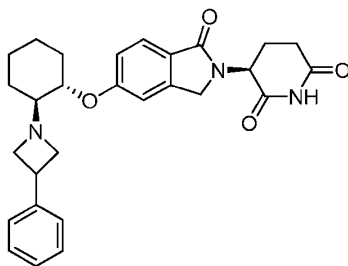
[0170] In certain embodiments, the solvent comprises ACN.

[0171] In certain embodiments, the process comprises a base. In certain embodiments, the process comprises DIEA.

[0172] In certain embodiments, the process comprises dissociating the Compound X5 oxalic acid salt prior to contacting with a base.

[0173] In certain embodiments, the process comprises isolating the Compound X5 oxalic acid salt.

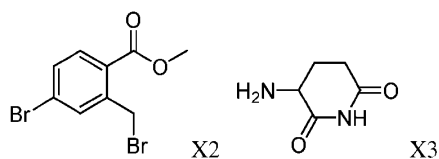
[0174] Also provided herein is a process for preparing Compound I:



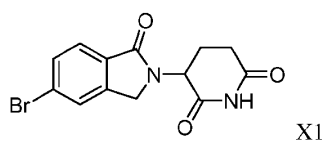
I,

comprising:

contacting Compound X2 with Compound X3, or a salt thereof;

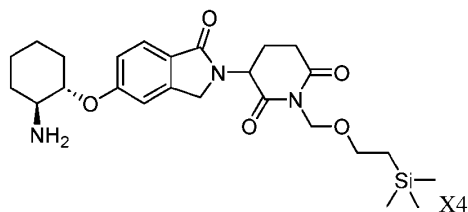


wherein the contacting comprises a first stage having a reaction temperature of about 45-55 °C and a second stage having a reaction temperature of from about 85-95 °C, under conditions suitable to provide Compound X1



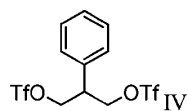
X1

contacting Compound X1 with to provide Compound X4



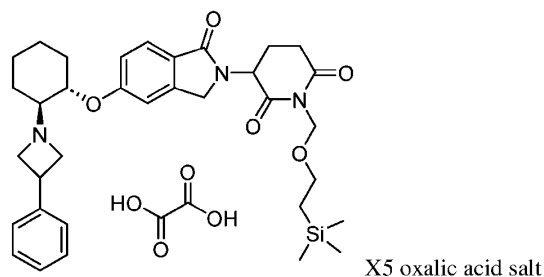
X4

contacting Compound X4, or a salt thereof with Compound IV:



IV

in the presence of oxalic acid, under conditions suitable to provide Compound X5 oxalic acid salt:



and contacting Compound X5 oxalic acid salt with a base in a solvent, under conditions suitable to provide Compound I; or dissociating the Compound X5 oxalic acid salt to provide Compound X5, and contacting the Compound X5 with a base in a solvent; to provide Compound I.

[0175] In some embodiments, the process further comprises isolating Compound I.

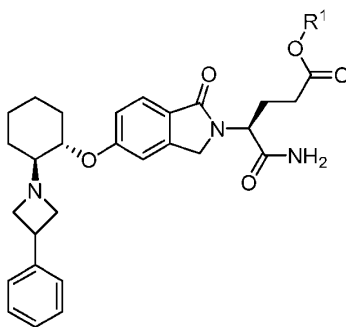
[0176] In some embodiments, the process comprises crystallizing Compound I to provide crystalline Compound I. In some embodiments, the crystallizing comprises a 10% Na₂SO₄ solution. In some embodiments, the crystallizing comprises a DCM/IPA/IPAc system.

Compounds

[0177] In certain embodiments, the disclosure provides for intermediate compounds that are useful in the processes described herein.

[0178] It can be appreciated that the straight bolded or dashed bond is used to indicate relative stereochemistry, and the wedged bolded or dashed bond is used to indicate absolute stereochemistry. Where the composition is identified as enantiomerically enriched, it is intended that the composition comprises more than 50% of a single enantiomer, or at least about 55%, or at least about 60%, or at least about 65%, or at least about 70%, or at least about 75%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 97%, or about 99% ee.

[0179] Provided herein is a compound, or a salt thereof, of formula II:



II,

wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl.

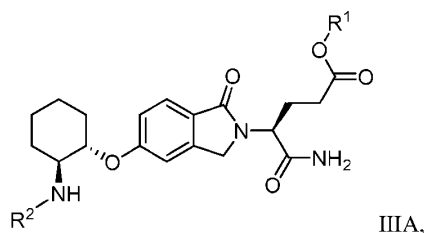
[0180] In some embodiments, R¹ is an optionally substituted alkyl group. In some embodiments, R¹ is a C₁₋₆ alkyl optionally substituted with C₁₋₆ alkoxy, cyano, or -Si(C₁₋₆ alkyl)₃. In some embodiments, R¹ is an optionally substituted benzyl group.

[0181] In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, methoxymethyl, *t*-butoxymethyl, benzyl, *p*-methoxybenzyl, or *p*-nitrobenzyl. In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, or benzyl. I

[0182] In some embodiments, R¹ is *tert*-butyl.

[0183] In some embodiments, R¹ is hydrogen.

[0184] Also provided herein is a compound, or a salt thereof, of formula IIIA:



wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl; and R² is a protecting group.

[0185] In some embodiments, R¹ is an optionally substituted alkyl group. In some embodiments, R¹ is a C₁₋₆ alkyl optionally substituted with C₁₋₆ alkoxy, cyano, or -Si(C₁₋₆ alkyl)₃. In some embodiments, R¹ is an optionally substituted benzyl group.

[0186] In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, methoxymethyl, *t*-butoxymethyl, benzyl, *p*-methoxybenzyl, or *p*-nitrobenzyl. In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, or benzyl. In some embodiments, R¹ is *tert*-butyl.

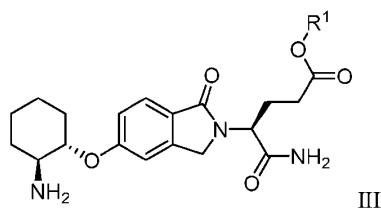
[0187] In some embodiments, R¹ is hydrogen.

[0188] In some embodiments, R² is an amine protecting group. In some embodiments, R² is -C(O)OR, wherein R is 9-fluorenylmethyl, *tert*-butyl, or benzyl.

[0189] In some embodiments, R² is -C(O)O-*tert*-butyl.

[0190] In some embodiments, R¹ is *tert*-butyl and R² is -C(O)O-*tert*-butyl.

[0191] Also provided herein is a compound of formula III, or a salt thereof:



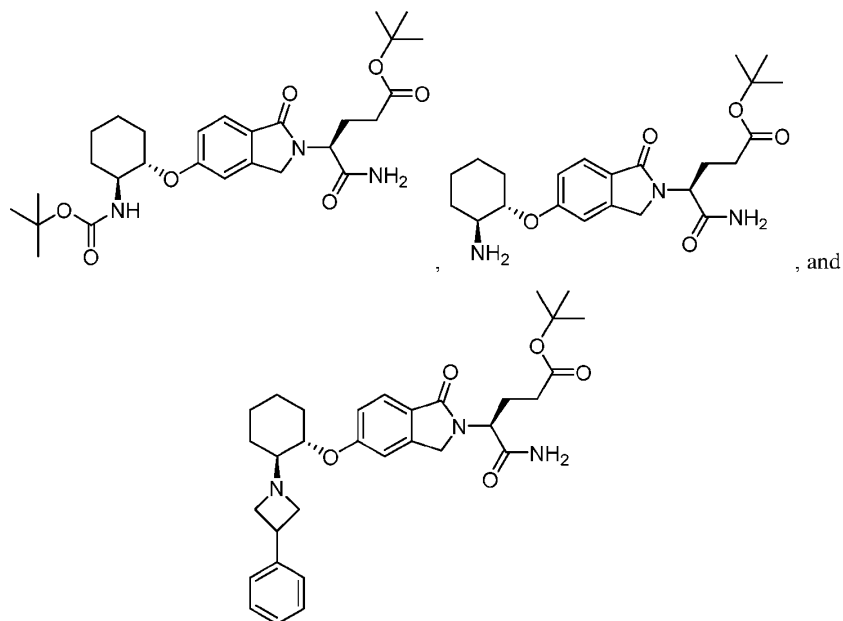
wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl; and R² is a protecting group.

[0192] In some embodiments, R¹ is an optionally substituted alkyl group. In some embodiments, R¹ is a C₁₋₆ alkyl optionally substituted with C₁₋₆ alkoxy, cyano, or -Si(C₁₋₆ alkyl)₃. In some embodiments, R¹ is an optionally substituted benzyl group.

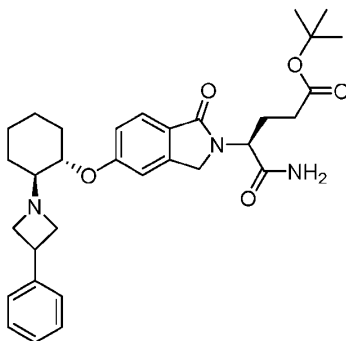
[0193] In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, methoxymethyl, *t*-butoxymethyl, benzyl, *p*-methoxybenzyl, or *p*-nitrobenzyl. In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, or benzyl. In some embodiments, R¹ is *tert*-butyl.

[0194] In some embodiments, R¹ is hydrogen.

[0195] Also provided herein is a compound, or a salt thereof, selected from:

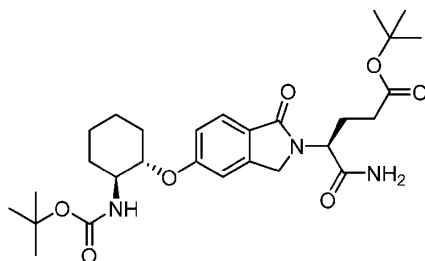


[0196] Also provided herein is a compound having the structure:



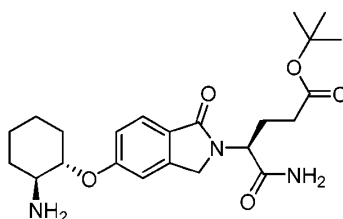
or a salt thereof.

[0197] Also provided herein is a compound having the structure:



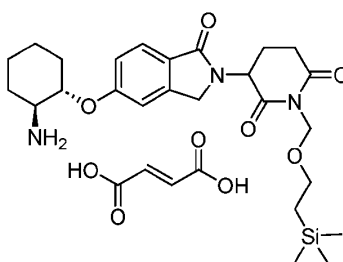
or a salt thereof.

[0198] Also provided herein is a compound having the structure:

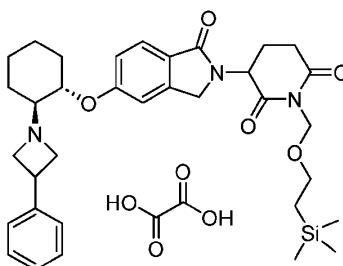


or a salt thereof.

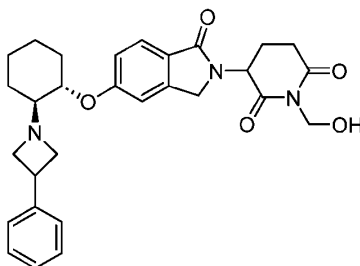
[0199] Also provided herein is 3-(5-(((1S,2S)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione fumaric acid salt (Compound X4 fumaric acid salt), having the structure:



[0200] Also provided herein is 3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione oxalic acid salt (Compound X5 oxalic acid salt), having the structure:



[0201] Also provided herein is a compound having the structure:



or a salt thereof.

[0202] It is appreciated that certain features described herein, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features described herein, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

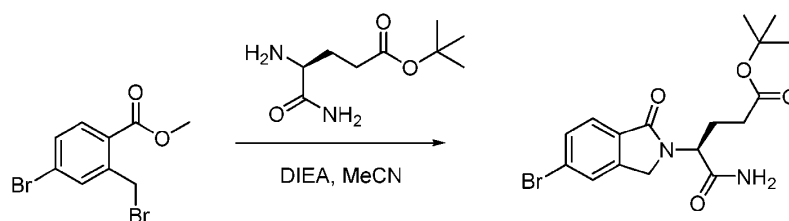
EXAMPLES

[0203] The compounds of the disclosure may be prepared using methods disclosed herein and routine modifications thereof which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of compounds described herein, may be accomplished as described in the following examples. If available, reagents may be purchased commercially, e.g. from Sigma Aldrich or other chemical suppliers. Unless otherwise noted, the starting materials for the following reactions may be obtained from commercial sources.

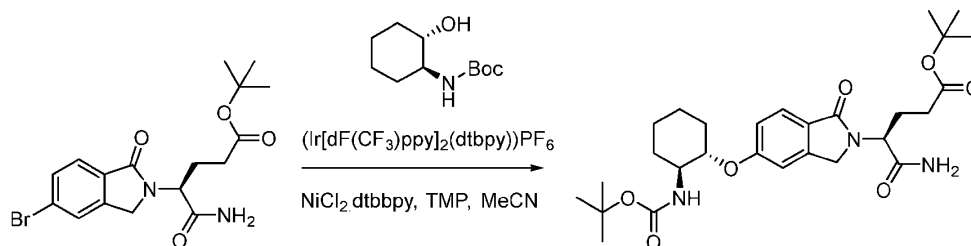
[0204] List of abbreviations and acronyms

Abbreviation	Meaning
° C	degrees Celsius
ACN/MeCN	acetonitrile
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
IPA	isopropyl alcohol

Abbreviation	Meaning
IPAC/IPAc	Isopropyl acetate
Ir[dF(CF ₃)ppy] ₂ (dtbpy))PF ₆	[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine- <i>N</i> 1, <i>N</i> 1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl- <i>N</i>]phenyl- <i>C</i>]Iridium(III) hexafluorophosphate
LCMS	Liquid chromatography–mass spectrometry
Me	methyl
MsCl	methanesulfonyl chloride
MsOH	methanesulfonic acid
MTBE	methyl <i>tert</i> -butyl ether
Na ₂ SO ₄	sodium sulfate
NiCl ₂ dtbbpy	[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride
NMR abbreviations	br = broad d = doublet dd = doublet of doublets ddd = doublet of doublet of doublets dt = doublet of triplets m = multiplet q = quartet s = singlet t = triplet
SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
<i>t</i> -Bu	<i>tert</i> -butyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TsCl	4-toluenesulfonyl chloride
TsOH	<i>p</i> -toluenesulfonic acid
V	volumes

Procedure A: Synthesis of *tert*-butyl (*S*)-5-amino-4-(5-bromo-1-oxoisindolin-2-yl)-5-oxopentanoate

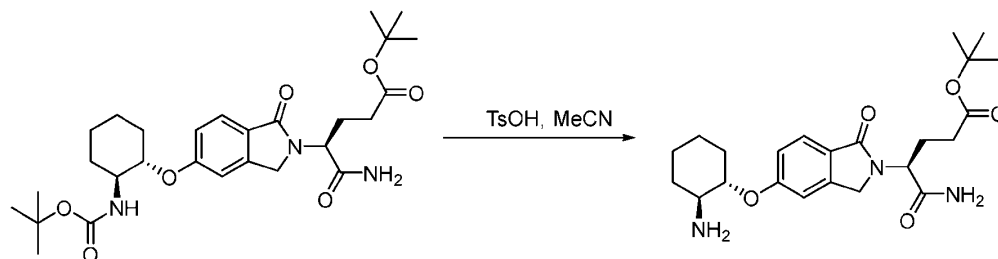
[0205] To a solution of methyl 4-bromo-2-(bromomethyl)benzoate (4.00 g, 12.99 mmol, 1 eq) and *tert*-butyl (*S*)-4,5-diamino-5-oxopentanoate (3.10 g, 12.99 mmol, 1 eq, HCl) in MeCN (40 mL) was added DIEA (6.71 g, 51.95 mmol, 9.05 mL, 4 eq). The mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (3 × 30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with MTBE (20 mL). The precipitate was collected by filtration and dried *in vacuo* to give *tert*-butyl (*S*)-5-amino-4-(5-bromo-1-oxoisindolin-2-yl)-5-oxopentanoate. ¹H NMR (400 MHz, d₆-DMSO) δ 1.33 (s, 9H), 1.90-2.04 (m, 1H), 2.07-2.27 (m, 3H), 4.44-4.51 (m, 1H), 4.57-4.65 (m, 1H), 4.70-4.76 (m, 1H), 6.93-7.41 (m, 1H), 7.61 (br d, *J*=12.38 Hz, 1H), 7.65 (s, 1H), 7.66-7.71 (m, 1H), 7.88 (s, 1H).

Procedure B: Synthesis of *tert*-butyl (*S*)-5-amino-4-(5-(((1*S*,2*S*)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-5-oxopentanoate**Step 1:**

[0206] A solution of *tert*-butyl (*S*)-5-amino-4-(5-bromo-1-oxoisindolin-2-yl)-5-oxopentanoate (2.00 g, 5.03 mmol, 1 eq), *tert*-butyl ((1*S*,2*S*)-2-hydroxycyclohexyl)carbamate (2.17 g, 10.07 mmol, 2 eq), quinuclidine (55.98 mg, 503.45 μmol, 0.1 eq), (Ir[dF(CF₃)ppy]₂(dtbbpy))PF₆ (56.48 mg, 50.34 μmol, 0.01 eq), NiCl₂ dtbbpy (100.18 mg, 251.72 μmol, 0.05 eq) and TMP (1.42 g, 10.07 mmol, 1.71 mL, 2 eq) in MeCN (10 mL) was degassed three times with nitrogen. The reaction vial was sealed with parafilm, placed 2 cm away from one blue LED, and irradiated at 25 °C for 14 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, 10 to 20% ethyl acetate in petroleum ether). The residue was purified by prep-HPLC (Column: Agela DuraShell C₁₈ 250 mm × 50 mm × 10 μm; mobile phase: [water (+ 1% formic acid)-ACN]; B%: 25%-55%, 25 minute gradient) to give *tert*-butyl (*S*)-5-amino-4-(5-(((1*S*,2*S*)-2-((*tert*-

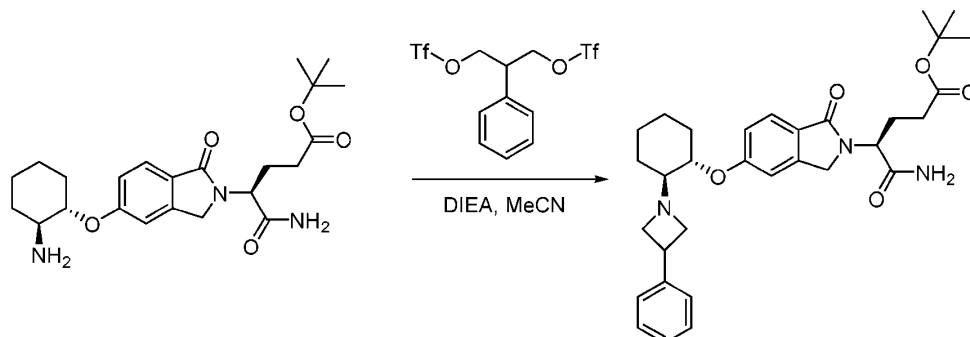
butoxycarbonyl)amino)cyclohexyl)oxy)-1-oxoisindolin-2-yl)-5-oxopentanoate. ^1H NMR (400 MHz, d_6 -DMSO) δ 1.29 (br s, 9 H) 1.33 (s, 9 H) 1.66 (br s, 2 H) 1.80 (br d, $J=9.88$ Hz, 1 H) 1.90 - 2.02 (m, 1 H) 2.04 - 2.20 (m, 4 H) 3.49 (br d, $J=8.51$ Hz, 1 H) 4.20 (br t, $J=8.88$ Hz, 1 H) 4.32 - 4.40 (m, 1 H) 4.49 - 4.58 (m, 1 H) 4.69 (br dd, $J=10.38, 3.75$ Hz, 1 H) 6.80 (br d, $J=8.75$ Hz, 1 H) 6.99 (br d, $J=8.25$ Hz, 1 H) 7.15 (br s, 2 H) 7.47 - 7.60 (m, 2 H).

Step 2:



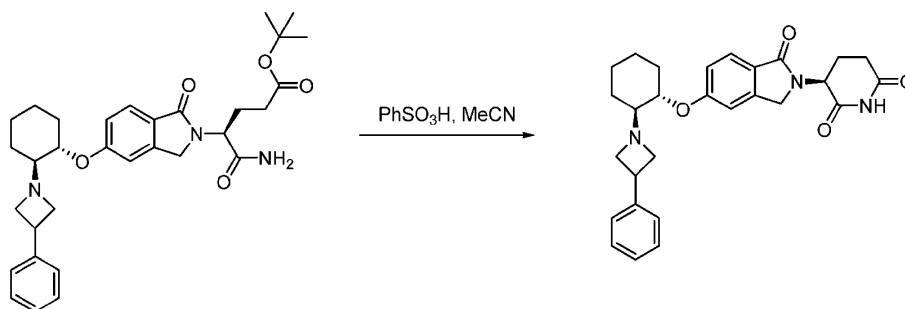
[0207] To a solution of tert-butyl (*S*)-5-amino-4-(5-(((1*S*,2*S*)-2-((*tert*-butoxycarbonyl)amino)cyclohexyl)oxy)-1-oxoisindolin-2-yl)-5-oxopentanoate (400.00 mg, 752.39 μmol , 1 *eq*) in MeCN (4 mL), was added TsOH (129.56 mg, 752.39 μmol , 1 *eq*) at 0 °C. The mixture was stirred at 20 °C for 16 hours. Additional TsOH (64.78 mg, 376.19 μmol , 0.5 *eq*) was added to the mixture. The mixture was stirred at 20 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give a residue. Water (150 mL) was added to the residue and the aqueous layer was extracted with EtOAc (3 $\times$ 50 mL). Saturated aqueous sodium bicarbonate solution was added to aqueous phase until the pH = 9. The aqueous layer was extracted with EtOAc (3 $\times$ 50 mL). The combined organic phases were washed with brine (3 $\times$ 30 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give *tert*-butyl (*S*)-5-amino-4-(5-(((1*S*,2*S*)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-5-oxopentanoate which was used in the following step without further purification. ^1H NMR (400 MHz, d_6 -DMSO) δ 1.21-1.29 (m, 4H), 1.31-1.35 (m, 9H), 1.59-1.72 (m, 2H), 1.85 (br d, $J=11.38$ Hz, 1H), 1.91-1.98 (m, 1H), 2.03-2.19 (m, 4H), 2.73-2.82 (m, 1H), 3.96-4.03 (m, 1H), 4.34-4.59 (m, 2H), 4.65-4.74 (m, 1H), 7.05 (br d, $J=8.50$ Hz, 1H), 7.12-7.24 (m, 2H), 7.49-7.64 (m, 2H).

Procedure C: Synthesis of (*S*)-5-amino-5-oxo-4-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)pentanoate



[0208] To a solution of *tert*-butyl (*S*)-5-amino-4-(5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)-1-oxoisindolin-2-yl)-5-oxopentanoate (231.54 mg, 556.17 μ mol, 1 *eq*) in MeCN (3 mL) was added DIEA (251.62 mg, 1.95 mmol, 339.11 μ L, 3.50 *eq*) and 2-phenylpropane-1,3-diyl bis(trifluoromethanesulfonate) (240.00 mg, 556.17 μ mol, 1 *eq*) at -20 °C. The mixture was stirred at 20 °C for 20 min. The mixture was purified directly by prep-HPLC (Column: Phenomenex C₁₈ 150 mm $\times$ 25 mm $\times$ 10 μ m; mobile phase: [water (+ NH₄HCO₃)-ACN]; B%: 45%-75%, 8 minute gradient) and lyophilized to give *tert*-butyl (*S*)-5-amino-5-oxo-4-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)pentanoate. ¹H NMR (400 MHz, d₆-DMSO) δ 1.06-1.18 (m, 1H), 1.25-1.34 (m, 9H), 1.38 (br t, *J*=9.07 Hz, 2H), 1.65 (br s, 2H), 1.79-1.87 (m, 1H), 1.89-2.04 (m, 2H), 2.06-2.20 (m, 3H), 2.39-2.46 (m, 2H), 3.12 (t, *J*=6.75 Hz, 1H), 3.22-3.28 (m, 1H), 3.49 (quin, *J*=7.13 Hz, 1H), 3.62 (dt, *J*=19.82, 6.91 Hz, 2H), 4.24-4.31 (m, 1H), 4.32-4.54 (m, 2H), 4.65-4.71 (m, 1H), 5.22-5.25 (m, 1H), 5.39 (d, *J*=1.50 Hz, 1H), 7.01 (dd, *J*=8.44, 2.19 Hz, 1H), 7.13-7.21 (m, 2H), 7.26-7.33 (m, 3H), 7.49-7.53 (m, 1H), 7.56 (d, *J*=8.38 Hz, 1H).

Procedure D: Synthesis of (*S*)-3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione

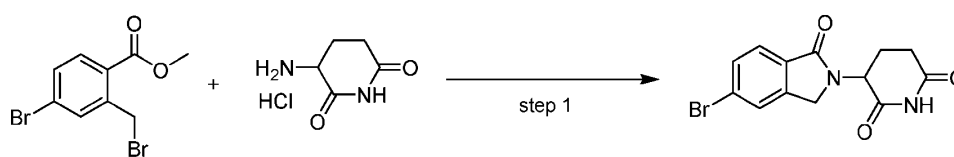


[0209] To a solution of *tert*-butyl (*S*)-5-amino-5-oxo-4-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)pentanoate (40 mg, 73.03 μ mol, 1 *eq*) in MeCN (0.5 mL) was added benzenesulfonic acid (34.66 mg, 219.10 μ mol, 3 *eq*). The reaction vessel was purged with N₂. The mixture was stirred at 80 °C for 3 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: Welch Xtimate

C₁₈ 150 mm × 25 mm × 5 μm; mobile phase: [water (+ 1% TFA)-ACN]; B%: 18%-38%, 10 minute gradient) and lyophilized to give (S)-3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione. ¹H NMR (400 MHz, d₆-DMSO) δ 1.11-1.53 (m, 4H), 1.70-1.86 (m, 2H), 1.94-2.04 (m, 1H), 2.12-2.27 (m, 2H), 2.35-2.43 (m, 1H), 2.56-2.65 (m, 1H), 2.84-2.98 (m, 1H), 3.64-3.82 (m, 2H), 3.95-4.08 (m, 1H), 4.21-4.48 (m, 5H), 4.49-4.59 (m, 1H), 5.09 (dd, *J*=13.32, 5.07 Hz, 1H), 7.17 (dd, *J*=8.44, 2.06 Hz, 1H), 7.27-7.36 (m, 2H), 7.41 (t, *J*=7.44 Hz, 2H), 7.44-7.50 (m, 2H), 7.67 (d, *J*=8.50 Hz, 1H), 10.97 (s, 1H).

Procedure E: Synthesis of 3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione

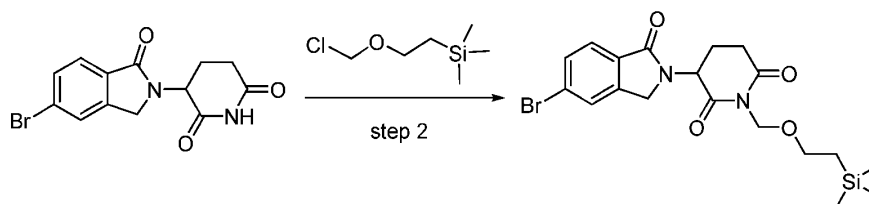
Step 1:



[0210] 3-(5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione: To a solution of methyl 4-bromo-2-(bromomethyl)benzoate (50 g, 162.36 mmol, 1 eq) and 3-aminopiperidine-2,6-dione hydrochloride (32.07 g, 194.83 mmol, 1.2 eq) in DMF (500 mL) was added DIEA (83.93 g, 649.42 mmol, 113.12 mL, 4 eq) at 20 °C. The mixture was stirred 120 °C for 12 hr. LCMS showed the starting material was consumed completely. The mixture was filtered and the filtrate was concentrated under vacuum to give the title compound (42 g, 80% yield) as a pink solid, which was used in the next step without further purification.

[0211] ¹H NMR (400 MHz, DMSO-d₆) δ = 11.00 (s, 1H), 7.89 (s, 1H), 7.74 - 7.63 (m, 2H), 5.10 (dd, *J* = 5.1, 13.3 Hz, 1H), 4.52 - 4.28 (m, 2H), 2.96 - 2.85 (m, 1H), 2.59 (br d, *J* = 17.4 Hz, 1H), 2.38 (dq, *J* = 4.4, 13.2 Hz, 1H), 2.08 - 1.92 (m, 1H).

Step 2:

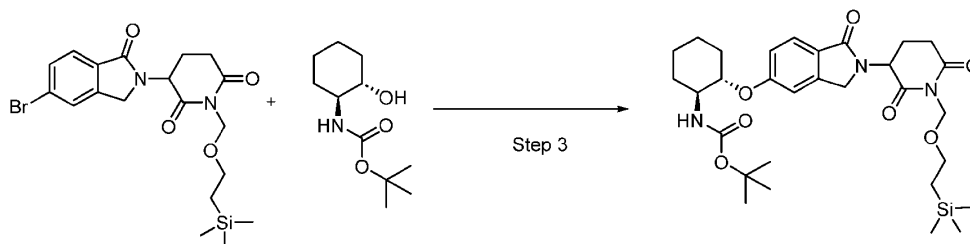


[0212] 3-(5-bromo-1-oxoisoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione: To a solution of 3-(5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (80 g, 247.57 mmol, 1 eq) and DBU (75.38 g, 495.14 mmol, 2 eq) in DMF (800 mL) was added SEM-Cl (61.91 g, 371.35 mmol, 1.5 eq) dropwise at 0 °C. The mixture was stirred at 20 °C for 5 h. TLC showed the reaction was complete. The mixture was poured into water (1 L) and extracted with MTBE (3 x 500 mL). The combined organic phases were washed with brine (3 x 200 mL), dried over Na₂SO₄ and concentrated under vacuum. The

residue was purified by column chromatography on silica gel, eluted with (petroleum ether: ethyl acetate = 10:1 to 1:1) to give the title compound (75 g, yield 66.8%) as a white solid.

[0213] ¹H NMR (400 MHz, CDCl₃) δ = 7.76 (d, *J* = 8.6 Hz, 1H), 7.68 - 7.60 (m, 2H), 5.28 - 5.16 (m, 3H), 4.52 - 4.28 (m, 2H), 3.68 - 3.56 (m, 2H), 3.08 - 3.00 (m, 1H), 2.96 - 2.84 (m, 1H), 2.40 - 2.28 (m, 1H), 2.24 - 2.16 (m, 1H), 0.96 - 0.92 (m, 2H), 0.01 (s, 9H).

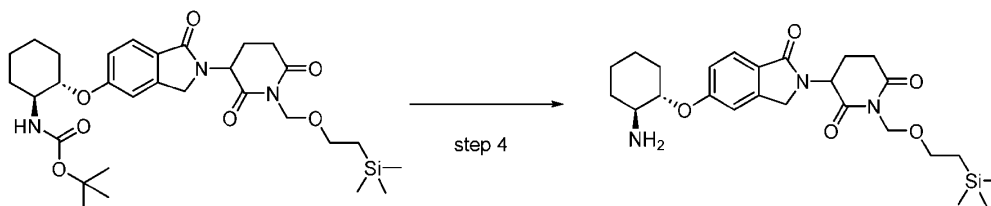
Step 3:



[0214] ***tert*-butyl ((1*S*,2*S*)-2-((2-(2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-1-oxoisindolin-5-yl)oxy)cyclohexyl)carbamate**: To a mixture of 3-(5-bromo-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione (2 g, 4.41 mmol, 1 *eq*), *tert*-butyl ((1*S*,2*S*)-2-hydroxycyclohexyl)carbamate (1.42 g, 6.62 mmol, 1.5 *eq*), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (59 mg, 0.22 mmol, 0.05 *eq*), Ir[(dF(CF₃)ppy)₂dtbbpy]PF₆ (49 mg, 44.1 μmol, 0.01 *eq*) and NiCl₂(glyme) (49 mg, 0.22 mmol, 0.05 *eq*) in MeCN (15 mL) was added 2,2,6,6-tetramethylpiperidine (623 mg, 4.41 mmol, 1 *eq*). The mixture was stirred for 12 h under irradiation of blue LED light at 20°C. LCMS showed the reaction was completed. The mixture was filtered and filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel eluted with petroleum ether: ethyl acetate (10:1 to 1:3) to provide the title compound (1.94 g, yield 75%) as a yellow solid.

[0215] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.60 (dd, *J* = 1.9, 8.4 Hz, 1H), 7.19 - 7.11 (m, 1H), 7.07 - 6.99 (m, 1H), 6.87 - 6.79 (m, 1H), 5.26 - 5.14 (m, 1H), 5.04 (q, *J* = 10.0 Hz, 2H), 4.46 - 4.38 (m, 1H), 4.24 - 4.17 (m, 2H), 3.56 - 3.49 (m, 2H), 3.16 - 3.03 (m, 2H), 2.82 - 2.73 (m, 1H), 2.44 - 2.34 (m, 1H), 2.16 - 2.01 (m, 2H), 1.85 - 1.76 (m, 2H), 1.69 - 1.54 (m, 3H), 1.30 (s, 9H), 1.14 - 1.08 (m, 2H), 0.89 - 0.79 (m, 2H), -0.02 (d, *J* = 0.9 Hz, 9H).

Step 4:

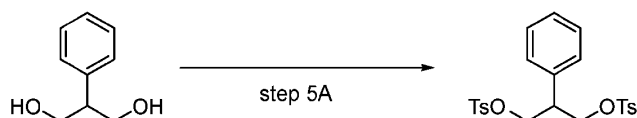


[0216] **3-(5-(((1*S*,2*S*)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione**: To a solution of *tert*-butyl ((1*S*,2*S*)-2-((2-(2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-1-oxoisindolin-5-

yl)oxy)cyclohexyl)carbamate (2 g, 3.4 mmol, 1 *eq*) in DCM (15 mL) was added 2,6-lutidine (911 mg, 8.51 mmol, 2.5 *eq*) and TMSOTf (1.51 g, 6.81 mmol, 2 *eq*). The resulting mixture was stirred at 25°C for 24 h. LCMS showed the reaction was completed. The reaction mixture was concentrated under vacuum. The residue was purified by reversed phase column (0.1% TFA) to give the title compound (1.08 g, yield 65%) as yellow solid.

[0217] ¹H NMR (400 MHz, DMSO-d₆) δ = 8.04 (br s, 3H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.27 (dd, *J* = 1.7, 5.9 Hz, 1H), 7.15 (td, *J* = 2.7, 8.3 Hz, 1H), 5.19 (dd, *J* = 4.6, 13.2 Hz, 1H), 5.05 (q, *J* = 9.7 Hz, 2H), 4.50 - 4.20 (m, 3H), 3.58 - 3.46 (m, 2H), 3.29 (br d, *J* = 9.0 Hz, 2H), 3.14 - 2.97 (m, 1H), 2.84 - 2.71 (m, 1H), 2.45 - 2.31 (m, 1H), 2.25 - 2.14 (m, 1H), 2.05 (br dd, *J* = 2.4, 5.4 Hz, 1H), 1.72 (br d, *J* = 11.0 Hz, 2H), 1.44 - 1.29 (m, 4H), 0.90 - 0.78 (m, 2H), 0.05 - 0.08 (m, 9H).

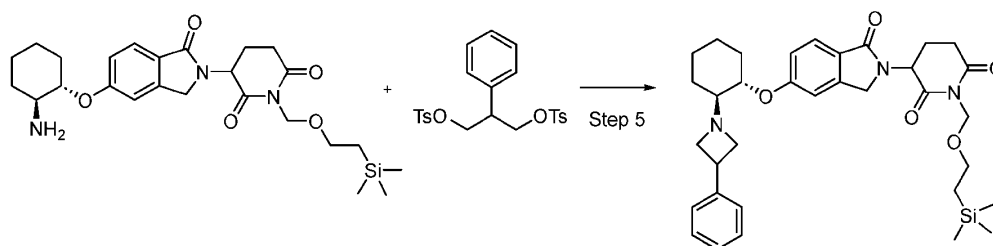
Step 5A:



[0218] **2-phenylpropane-1,3-diyl bis(4-methylbenzenesulfonate):** To a solution of 2-phenylpropane-1,3-diol (5 g, 32.85 mmol, 1 *eq*) in DCM (100 mL) was added TsCl (21.92 g, 114.99 mmol, 3.5 *eq*), DMAP (401.37 mg, 3.29 mmol, 0.1 *eq*) and Et₃N (13.30 g, 131.41 mmol, 18.29 mL, 4 *eq*), the mixture was stirred at 20°C for 16 hr. TLC showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate=100:1, 50:1) to afford 2-phenylpropane-1,3-diyl bis(4-methylbenzenesulfonate) (6.5 g, 12.70 mmol, 38.66% yield, 90% purity) as white solid.

[0219] ¹H NMR (400 MHz, chloroform-*d*) δ ppm 2.45 (s, 6 H) 3.27 (m, 1 H) 4.21 (d, *J*=6.02 Hz, 4 H) 7.01 - 7.07 (m, 2 H) 7.21 - 7.27 (m, 3 H) 7.30 (d, *J*=8.03 Hz, 4 H) 7.67 (d, *J*=8.53 Hz, 4 H).

Step 5:

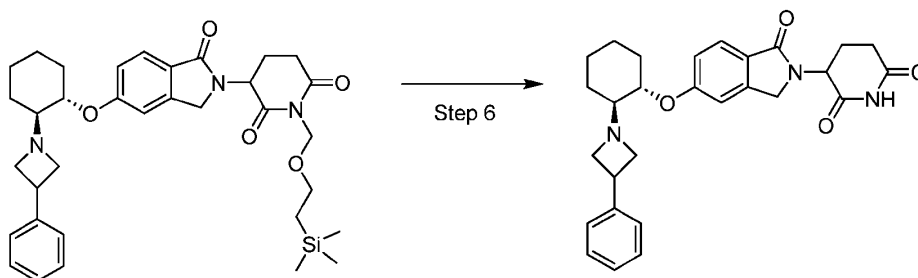


[0220] **3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione:** 3-(5-(((1*S*,2*S*)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione (2 g, 4.1 mmol, 1 *eq*), 2-phenylpropane-1,3-diyl bis(4-methylbenzenesulfonate) (2.27 g, 4.92 mmol, 1.2 *eq*) and DIEA (2.12 g, 16.4 mmol, 4 *eq*) were taken up into a microwave tube in MeCN (10 mL). The sealed tube was heated at 120°C and stirred for 16 h. LCMS showed the reaction was completed. The reaction mixture was

concentrated under vacuum. The residue was purified by reversed phase column (0.5% TFA) and SFC separation to give the title compound (0.9 g, 36% yield) as a white solid.

[0221] ¹H NMR (400 MHz, DMSO-d₆) δ = 7.61 (d, *J* = 8.4 Hz, 1H), 7.34 - 7.26 (m, 4H), 7.22 - 7.16 (m, 2H), 7.05 (dd, *J* = 2.1, 8.5 Hz, 1H), 5.17 (dd, *J* = 5.1, 13.4 Hz, 1H), 5.10 - 4.99 (m, 2H), 4.44 - 4.15 (m, 3H), 3.75 - 3.59 (m, 2H), 3.55 - 3.46 (m, 3H), 3.27 (br d, *J* = 8.2 Hz, 2H), 3.18 - 2.98 (m, 2H), 2.83 - 2.73 (m, 1H), 2.43 - 2.36 (m, 1H), 2.04 - 2.00 (m, 1H), 1.84 (br dd, *J* = 2.3, 10.2 Hz, 1H), 1.65 (br d, *J* = 5.0 Hz, 2H), 1.39 (br t, *J* = 8.5 Hz, 2H), 1.30 - 1.22 (m, 2H), 1.17 - 1.10 (m, 1H), 0.89 - 0.77 (m, 3H), -0.03 (d, *J* = 3.8 Hz, 8H).

Step 6:



[0222] **3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione:** To a solution of 3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione (22 g, 36.5 mmol, 1 *eq*) in DCM (200 mL) was added MsOH (14.01 g, 145.82 mmol, 10.38 mL, 4 *eq*) at 20°C. The mixture was stirred for 2 h at 20°C. N1,N2-dimethylethane-1,2-diamine (3.85 g, 43.69 mmol, 2.31 mL, 1.2 *eq*) and TEA (29.49 g, 291.34 mmol, 40.54 mL, 8 *eq*) was added to above mixture at 20°C. The mixture was stirred at 20°C for 2 h. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC (neutral) to give the title compound (10.02 g, 58.07% yield) as a white solid.

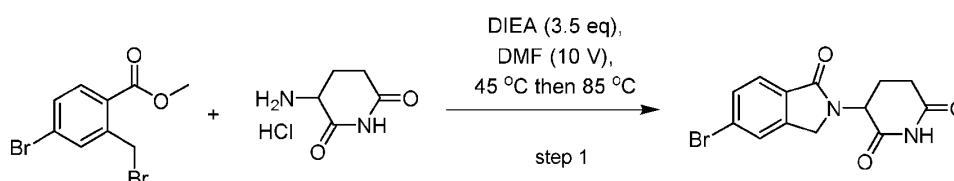
[0223] ¹H NMR (400 MHz, DMSO-d₆) δ = 10.96 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.38 - 7.25 (m, 4H), 7.23 - 7.14 (m, 2H), 7.04 (br d, *J* = 8.4 Hz, 1H), 5.06 (dd, *J* = 4.9, 13.3 Hz, 1H), 4.45 - 4.17 (m, 3H), 3.82 - 3.46 (m, 3H), 3.30 - 3.04 (m, 2H), 2.96 - 2.82 (m, 1H), 2.59 (br d, *J* = 17.0 Hz, 1H), 2.48 - 2.27 (m, 2H), 2.09 - 1.92 (m, 2H), 1.92 - 1.80 (m, 1H), 1.66 (br s, 2H), 1.45 - 1.33 (m, 2H), 1.32 - 1.21 (m, 1H), 1.20 - 1.07 (m, 1H).

[0224] The two isomers ((*S*)-3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione and (*R*)-3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione) from Procedure E can be separated as described herein or according to the literature to yield Compound I, (*S*)-3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione, as a single stereoisomer.

[0225] Alternatively, Compound I was provided without the need for a final separation step using Procedure F. In Procedure F, each of the intermediates was confirmed using standard characterization techniques (e.g., HPLC) as compared to a reference standard (e.g., the compounds produced in the reactions described herein or the literature).

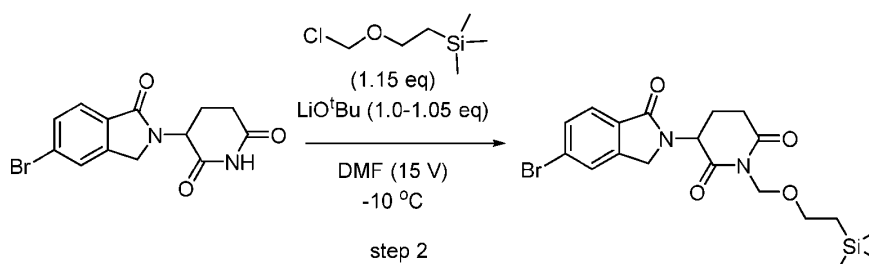
Procedure F: Synthesis of (S)-3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione

Step 1:



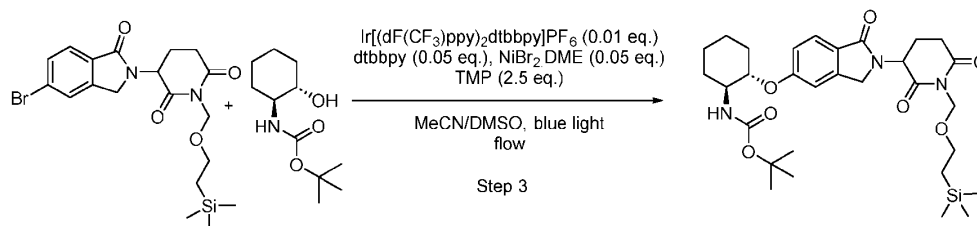
[0226] **3-(5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione:** To a solution of methyl 4-bromo-2-(bromomethyl)benzoate and 3-aminopiperidine-2,6-dione hydrochloride in DMF (10 V) was added DIEA (3.5 eq). The reaction mixture was heated to 45 °C for 22 hours and then the temperature increased to 85 °C for an additional 21 hours. After the reaction was determined complete (LCMS showed the starting material was consumed), water was added and the precipitate was isolated. After crystallization, the resulting product was isolated with 99.6% purity in 84% isolated yield.

Step 2:



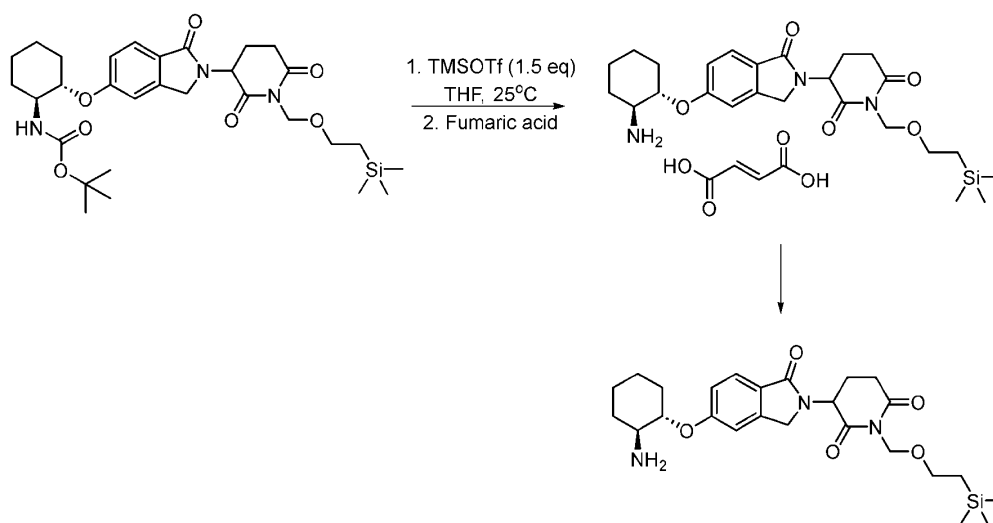
[0227] **3-(5-bromo-1-oxoisoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione:** To a solution of 3-(5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione in DMF (15V) at -10 °C was added t-BuOLi (1-1.5 eq) , and the mixture was stirred for 6 hours at -10 °C. SEM-Cl (1.15 eq) was added at -10 °C and the mixture was stirred while allowing to warm to 25 °C until reaction completion, approx. 1-3 hours. After reaction completion, water was added and mixture cooled to 10 °C and stirred for approximately 10-20 hours the desired product was obtained via filtration in 97.6% purity and 88% isolated yield.

Step 3:



[0228] *tert*-butyl ((1*S*,2*S*)-2-((2-(2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-1-oxoisindolin-5-yl)oxy)cyclohexyl)carbamate: A mixture of 3-(5-bromo-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione, *tert*-butyl ((1*S*,2*S*)-2-hydroxycyclohexyl)carbamate (1.5 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (0.05 eq), Ir[(dF(CF₃)ppy)₂dtbbpy]PF₆ (0.01 eq) and NiCl₂·DME (0.05 eq) in MeCN (20V) / DMSO (4.5V) was reacted at 40 °C using a flow mode photochemical reaction under blue light at 40 °C for 120 min of the residence time in the single-layer reactor of 1/4inch FEP fluid tube. A telescoped work-up approach was used to obtain a THF solution of the desired product, which was directly carried forward for the next step. After reaction completion, the THF solution containing the desired product was obtained in two batches in 58% assay yield (61% assay yield for the first batch and 53% assay yield for the second batch). After purification, a THF solution of *tert*-butyl ((1*S*,2*S*)-2-((2-(2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-1-oxoisindolin-5-yl)oxy)cyclohexyl)carbamate was obtained with 72.8% purity in about 61% yield.

Step 4:

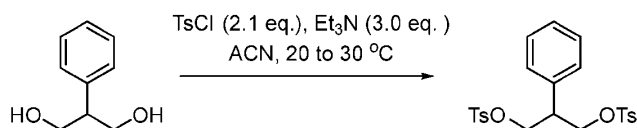


3-(5-(((1*S*,2*S*)-2-aminocyclohexyl)oxy))-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione:

[0229] To a solution of *tert*-butyl ((1*S*,2*S*)-2-((2-(2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-1-oxoisindolin-5-yl)oxy)cyclohexyl)carbamate in THF (10V) was added TMSOTf (1.2 eq) and the reaction was stirred at 25 °C for an hour, and an additional

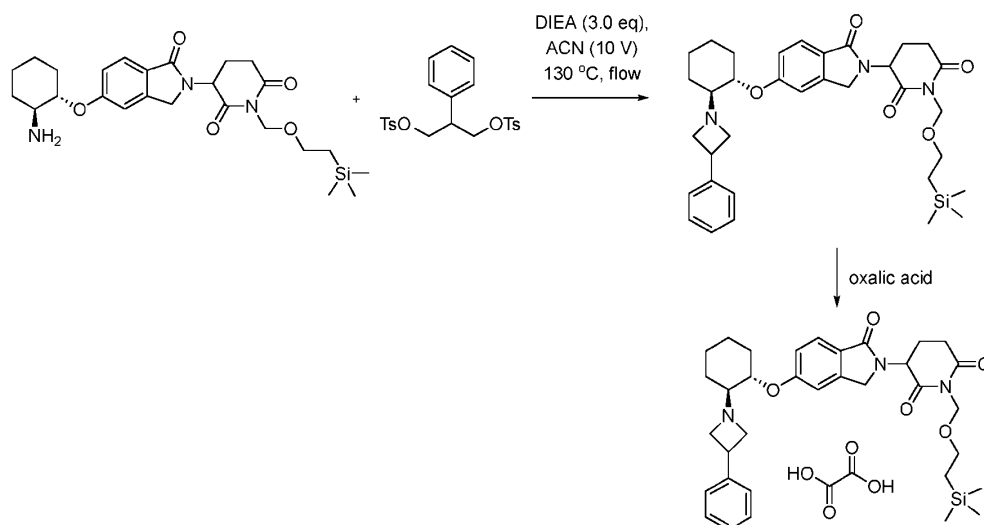
0.3 eq of TMSOTf was added, and the reaction was stirred an additional 16 hours. The crude reaction was extracted with ethyl acetate and washed with water. The crude product in ethyl acetate was stirred at 50 °C and was treated with 1 eq. fumaric acid and stirred for 7 hr at 50 °C. The mixture was cooled to RT and n-heptane was added to produce a slurry which was filtered to provide 3-(5-(((1S,2S)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione fumarate. The resulting 3-(5-(((1S,2S)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione fumarate was resuspended in EtOAc and stirred for 1 hour at 25 °C. After 1 hour, 7% aq NaHCO₃ was added, and the resulting aq phase pH was 7.5. Water was added and the organic phase was separated. ACN was added to the resulting ethyl acetate solution, and the organic solvents were removed under vacuum and mild heat, this was repeated several times to ultimately provide 3-(5-(((1S,2S)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione a solution in ACN in 96.8% purity and 74% yield.

Step 5A:



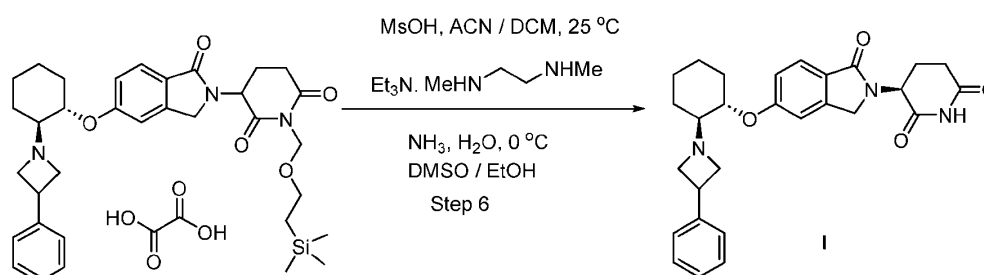
[0230] 2-phenylpropane-1,3-diyl bis(4-methylbenzenesulfonate): 2-phenylpropane-1,3-diol was reacted with tosyl-chloride (2.1 eq) and triethyl amine (3 eq) in acetonitrile at 20-30 °C to provide the desired product. Utilizing acetonitrile allowed for lower reagent ratios and improved scaled purification as compared to literature procedure. Direct crystallization with the addition of water into the reaction mixture afforded 2-phenylpropane-1,3-diyl bis(4-methylbenzenesulfonate). After work up and isolation, 2-phenylpropane-1,3-diyl bis(4-methylbenzenesulfonate) was obtained in 99.9% purity and 92% isolated yield.

Step 5:



[0231] 3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione oxalate: 3-(5-(((1*S*,2*S*)-2-aminocyclohexyl)oxy)-1-oxoisoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione, 2-phenylpropane-1,3-diyl bis(4-methylbenzenesulfonate), and DIEA (3 eq) were combined in ACN (10 V) at 130 °C under flow chemistry conditions for a residence time of 2 hours. The crude mixture was cooled to 25 °C and 0.6 equivalents of di-*tert*-butyl-dicarbonate was added and the mixture was stirred for 16 hours. The mixture was then charged with 10 vol. 10% KH_2PO_4 , the wet cake was filtered and rinsed with acetonitrile and water and extracted into isopropyl acetate. To this solution of 3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione in isopropylacetate was added 1.05 eq oxalic acid to the solution, which provided the desired product in 98.7% purity and 26% isolated yield.

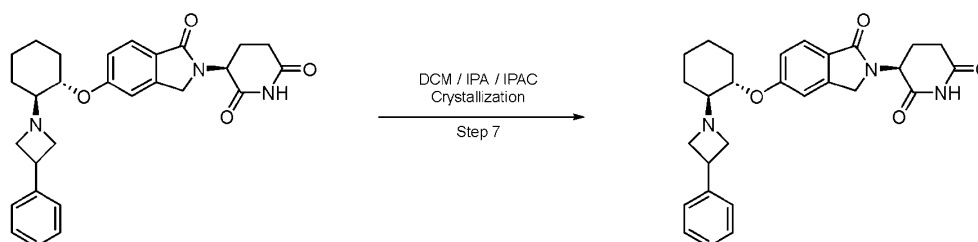
Step 6:



[0232] (*S*)-3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione: To a solution of 3-(1-oxo-5-(((1*S*,2*S*)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione oxalate in 10 V ACN/DCM (1:2 ratio) at 25 °C was added 4.7 eq. MsOH and the mixture was stirred at 25 °C. After 24 hours, N1,N2-dimethylethane-1,2-diamine (1.5 eq) and TEA (10 eq) were added, NH_3 in water was added and the

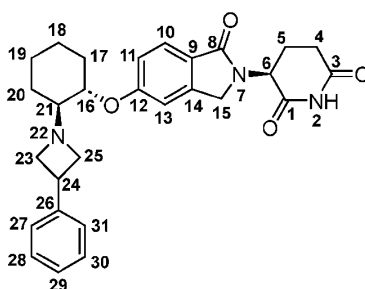
mixture was stirred at 40 °C for 30 hours. After aqueous quenching and work-up with 10 % KH_2PO_4 solution and adjustment of the pH to pH=6. Crude product was extracted the aqueous with DCM, and then solvent was evaporated and replaced with EtOH and this process was repeated to provide a crude slurry in EtOH. The slurry was further dried and filtered, and rinsed with DMSO to provide enrichment of the desired isomer of (S)-3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione in 99.8% purity and R_sSS/S_sSS = 5.0%/95.0% in 69% isolated yield.

Step 7:



[0233] Recrystallized (S)-3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione (Compound I) was obtained from the crude (S)-3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione from Step 6 by washing with a 10% Na_2SO_4 solution, concentrating with DCM, and crystallization in a DCM (6.6 V) / IPA (3.3 V) / IPAc (20 V) system to yield the desired product with 99.9% purity, R_sSS/S_sSS=3.9%/96%, in 84% isolated yield.

[0234] ^1H and ^{13}C NMR data provided was generated in $\text{MeOD}-d_4$ at 27 °C using a Bruker AVANCE III 400 MHz NMR spectrometer equipped with a Bruker 5 mm PABBO BB-400 MHz Z-gradient high resolution probe, and supported by TOPSPIN software. The atom numbers referred to in the table are as shown below.



Atom Number	Type	δ_{H} (ppm) (mult, J in Hz)	δ_{C} (ppm) (mult, J in Hz)	Relative Intensity
1	C=O	N/A	172.30	N/A
2	NH	N/A	N/A	N/A
3	C=O	N/A	174.71	N/A
4a	CH_2	2.90 (m)	32.39	1H

Atom Number	Type	δ_H (ppm) (mult, J in Hz)	δ_C (ppm) (mult, J in Hz)	Relative Intensity
4b		2.77 (m)		1H
5a	CH ₂	2.47 (ddd, J = 18.0, 13.3, 4.8 Hz)	24.14	1H
5b		2.15 (ov)		1H
6	CH	5.11 (dd, J = 13.3, 5.2 Hz)	53.60	1H
7	N	N/A	N/A	N/A
8	C=O	N/A	171.45	N/A
9	C	N/A	125.10	N/A
10	CH	7.71 (d, J =8.4 Hz)	125.99	1H
11	CH	7.06 (dd, J =8.4, 2.1 Hz)	117.57	1H
12	C	N/A	162.64	N/A
13	CH	7.14 (d, J =1.7 Hz)	110.32	1H
14	C	N/A	146.31	N/A
15a	CH ₂	4.46 (d, J =17.0 Hz)	48.79	1H
15b		4.40 (d, J =17.0 Hz)		1H
16	CH	4.32 (m)	82.62	1H
17a	CH ₂	2.17 (ov)	30.85	1H
17b		1.41 (ov)		1H
18a	CH ₂	1.78 (ov)	25.02 or 24.87	1H
18b		1.46 (ov)		1H
19a	CH ₂	1.78 (ov)	25.02 or 24.87	1H
19b		1.46 (ov)		1H
20a	CH ₂	2.01 (m)	28.63	1H
20b		1.15 (m)		1H
21	CH	2.58 (m)	69.95	1H
22	N	N/A	N/A	N/A
23a/25a		3.80 (t, J =7.8 Hz)		2H
23b/25b	CH ₂	3.53 (t, J =8.0 Hz) 3.33 (ov)	63.95, 60.73	1H 1H
24	CH	3.67 (m)	37.46	1H
26	C	N/A	142.85	N/A
27/31	CH	7.27 (ov)	127.92	2H

Atom Number	Type	δ_{H} (ppm) (mult, <i>J</i> in Hz)	δ_{C} (ppm) (mult, <i>J</i> in Hz)	Relative Intensity
28/30	CH	7.30 (ov)	129.50	2H
29	CH	7.19 (m)	127.60	1H

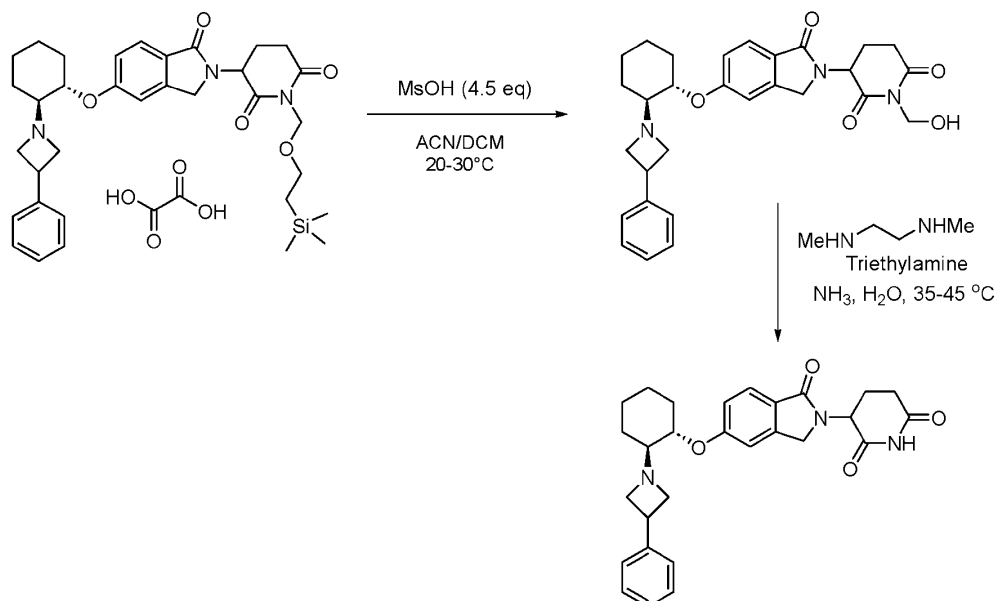
[0001] *HRMS*: High resolution mass spectrometric analysis was performed on an Agilent G6224A TOF LC/MS using high performance liquid chromatography with electrospray ionization time of flight mass spectrometry (HPLC-ESI-TOF/MS). Electrospray ionization was performed in positive ion mode. The solution for analysis was prepared by dissolving 2.633 mg of Compound I in 30 mL of ACN. The sample yielded a characteristic positive ion with $[\text{M}+\text{H}]^+$ observed at 474.2399 *m/z* corresponding to protonated Compound I $\text{C}_{28}\text{H}_{32}\text{N}_3\text{O}_4^+$ (calculated 474.2387 *m/z*).

[0002] *Elemental Analysis*: Carbon, hydrogen, nitrogen analysis of Compound I was performed on a Thermo Flashsmart Elemental Analyzer. The sample was analyzed in duplicate. Anal. Calcd for $\text{C}_{28}\text{H}_{31}\text{N}_3\text{O}_4$: C, 71.02; H, 6.60; N, 8.87. Found: C, 71.28; H, 6.63; N, 8.86.

[0003] *Optical Rotation*: The optical rotation analysis for Compound I was performed using Rudolph Autopol V Automatic Polarimeter instrument under 25 °C. A 99.20 mg sample of Compound I was weighed and added into a 10 mL volumetric flask, dissolved in pyridine, and diluted to volume with pyridine. The solvent blank was measured followed by the sample solution, providing a $[\alpha]_{\text{D}}^{25}$ of +17.3° (calculated on the basis). Analysis parameters are as below.

Item	Parameters
Temperature (°C)	25°C
Wavelength (nm)	589
Solvent	pyridine
Length of polarimeter tube (dm)	1

Procedure G: Synthesis of 3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione as a 1:1 mixture of mixed isomers



[0235] 3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione as a 1:1 mixture of mixed isomers: To a solution of 3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione oxalate was added MsOH (4.5 eq) in ACN/DCM at 20-30 °C to provide 1-(hydroxymethyl)-3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione which is typically not isolated from the reaction mixture but observed as an intermediate. To the resulting 1-(hydroxymethyl)-3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione was added N1,N2-dimethylethane-1,2-diamine (1.5 eq) and TEA (10 eq), followed by NH₃, H₂O in DCM/ACN and the mixture was stirred at 35 to 45 °C for 30 hours. After aqueous quenching and work-up with 10 % KH₂PO₄ solution and adjustment of the pH to pH=6. Crude product was extracted the aqueous with DCM, and then solvent was evaporated and replaced with EtOH and this process was repeated to provide a crude slurry in EtOH. Crystallization from EtOH as solvent provided 3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isoindolin-2-yl)piperidine-2,6-dione in 99.1% purity in 58% isolated yield.

[0236] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0237] The embodiments illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising,” “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not

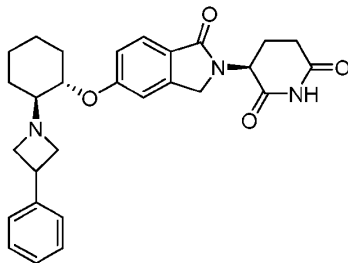
of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the embodiments claimed.

[0238] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

[0239] It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

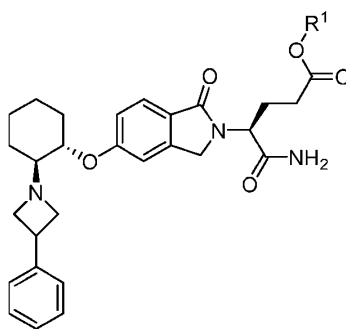
What is Claimed is:

1. A process for preparing Compound I, or a salt thereof:



I,

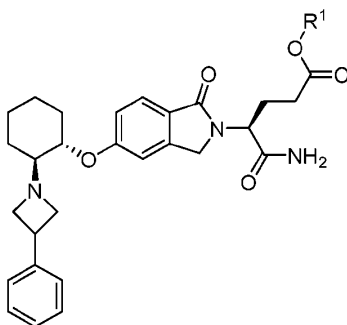
comprising contacting Compound II, or a salt thereof;



II,

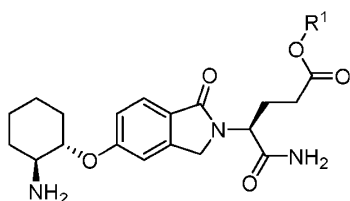
under conditions suitable to provide Compound I, wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl.

2. The process of claim 1, wherein the conditions comprise an acid or an activating agent.
3. The process of claim 2, wherein the activating agent is thionyl chloride, oxalyl chloride, phosphorus pentachloride, *N,N*-dicyclohexylcarbodiimide (DCC), *N,N*-diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), or O-(1H-6-chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HCTU).
4. The process of claim 2, wherein the acid is hydrochloric acid, phosphoric acid, benzenesulfonic acid, *p*-toluenesulfonic acid, or trifluoroacetic acid.
5. The process of claim 4, wherein the acid is benzenesulfonic acid.
6. A process for preparing Compound II, or a salt thereof:



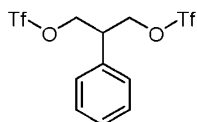
II

comprising contacting a compound of formula III, or a salt thereof:



III,

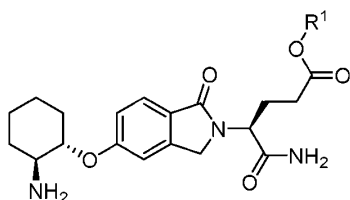
with a compound of formula IV, or a salt thereof:



IV,

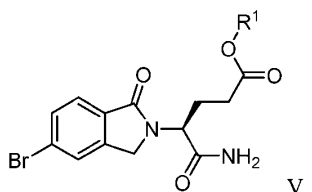
under conditions suitable to provide Compound II, wherein R¹ is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl.

7. A process for preparing a compound of formula III, or a salt thereof:



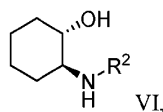
III,

comprising contacting a compound of formula V, or a salt thereof:



V,

with a compound of formula VI, or a salt thereof:



under conditions suitable to provide Compound III; wherein R^1 is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl; and R^2 is a protecting group.

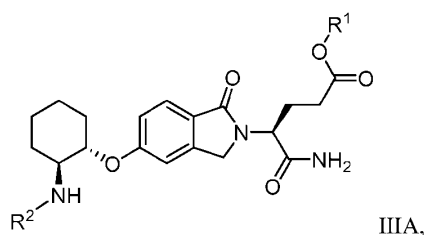
8. The process of claim 7, wherein the conditions further comprise irradiation under visible light.
9. The process of claim 7 or claim 8, wherein the conditions further comprise a catalyst.
10. The process of claim 9, wherein the catalyst is a metal-based photocatalyst.
11. The process of claim 9, wherein the catalyst is:

[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine- $N1,N1'$]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl- N]phenyl-C]Iridium(III) hexafluorophosphate;

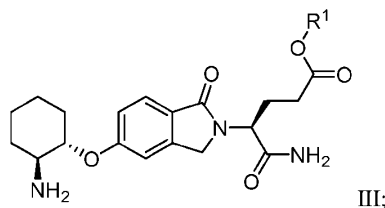
[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine- $N1,N1'$]bis[2-(2-pyridinyl- N)phenyl-C]Iridium(III) hexafluorophosphate;

tris(4,4'-di-*tert*-butyl-2,2'-bipyridine)ruthenium bis(hexafluorophosphate);

[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride; or a combination thereof.
12. The process of claim 9, wherein the catalyst is a combination of [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine- $N1,N1'$]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl- N]phenyl-C]Iridium(III) hexafluorophosphate and [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride.
13. The process of any one of claims 6-12, wherein the conditions further comprise a base.
14. The process of claim 13, wherein the base is *N,N*-diisopropylethylamine, *N,N*-diisopropylethylamine, triethylamine, tributylamine, *N*-methylimidazole, *N*-methylmorpholine, 2,2,6,6-tetramethylpiperidine, quinuclidine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, or a combination thereof.
15. The process of claim 13, wherein the base is diisopropylethylamine.
16. The process of claim 13, wherein the base is a combination of 2,2,6,6-tetramethylpiperidine and quinuclidine.
17. The process of claim 7, wherein the conditions further comprise a deprotection step comprising converting a compound of formula IIIA, or salt thereof:

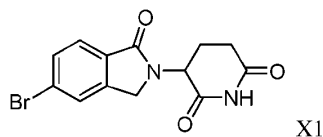


to compound III under conditions suitable to provide compound III:

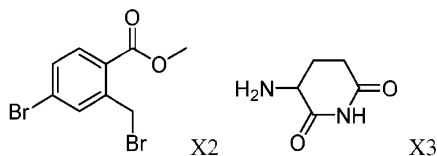


wherein R^1 is hydrogen, an optionally substituted alkyl, or an optionally substituted benzyl; and R^2 is a protecting group.

18. The process of claim 17, wherein the conditions further comprise an acid.
19. The process of claim 18, wherein the acid is hydrochloric acid, phosphoric acid, benzenesulfonic acid, *p*-toluenesulfonic acid, or trifluoroacetic acid.
20. The process of claim 18, wherein the acid is *p*-toluenesulfonic acid.
21. The process of any one of claim 7-20, wherein R^2 is $-C(O)OR$; wherein R is 9-fluorenylmethyl, *tert*-butyl, or benzyl.
22. The process of claim 21, wherein R^2 is $-C(O)O$ -*tert*-butyl.
23. The process of any one of claims 1-22, wherein R^1 is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, or benzyl.
24. The process of claim 23, wherein R^1 is *tert*-butyl.
25. The process of any one of claims 1-22, wherein R^1 is hydrogen.
26. The process of any one of the preceding claims, wherein the conditions further comprise a solvent.
27. The process of claim 26, wherein the solvent is acetonitrile, 1,4-dioxane, dichloromethane, tetrahydrofuran, dimethylsulfoxide, or *N,N*-dimethylformamide.
28. The process of claim 26, wherein the solvent is acetonitrile.
29. A process for preparing Compound X1, or a salt thereof:

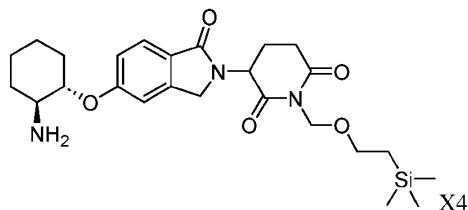


comprising contacting Compound X2 with Compound X3, or a salt thereof;

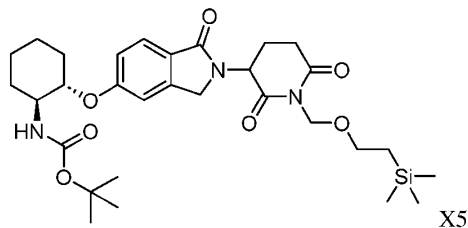


wherein the contacting comprises a first stage having a reaction temperature of about 45-55 °C and a second stage having a reaction temperature of from about 85-95 °C, under conditions suitable to provide Compound X1.

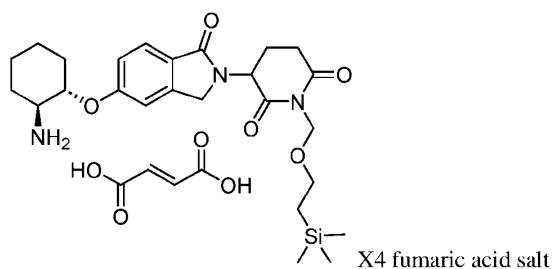
30. A process for preparing Compound X4, or a salt thereof:



comprising deprotecting Compound X5:

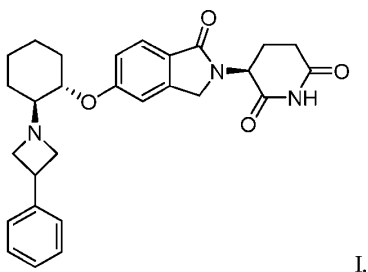


in the presence of fumaric acid, under conditions suitable to provide Compound X4 fumaric acid salt:

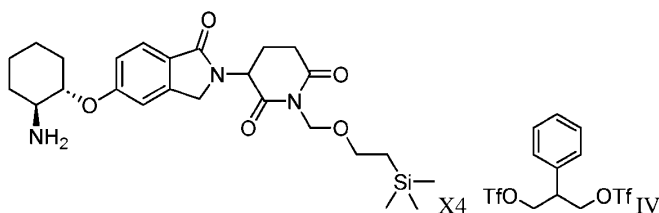


and contacting Compound X4 fumaric acid salt with a base in a solvent under conditions suitable to provide Compound X4.

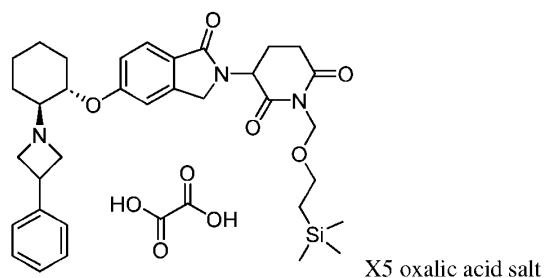
31. The process of claim 30, wherein the process is performed in the absence of DCM.
32. The process of claim 30 or 31, wherein the solvent comprises THF.
33. The process of any one of claims 30-32, wherein the base is sodium bicarbonate.
34. The process of any one of claims 30-33, wherein the Compound X4 fumaric acid salt is not isolated.
35. A process for preparing Compound I, or a salt thereof:



comprising contacting Compound X4, or a salt thereof with Compound IV:

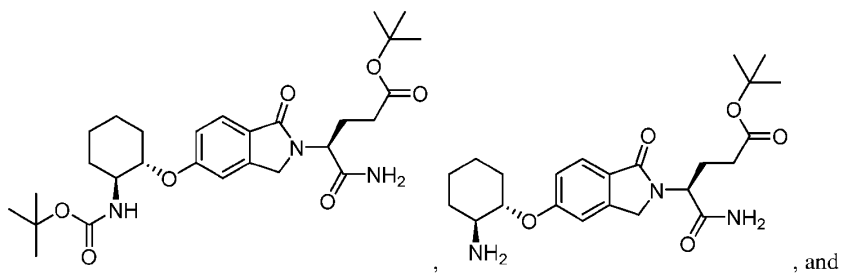


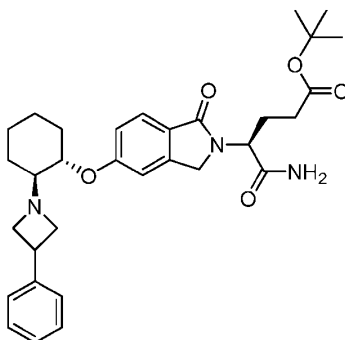
in the presence of oxalic acid, under conditions suitable to provide Compound X5 oxalic acid salt:



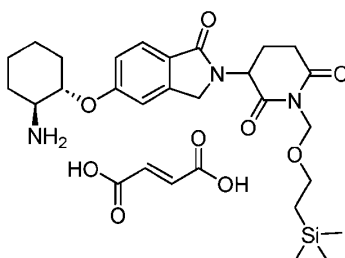
and contacting Compound X5 oxalic acid salt with a base in a solvent, under conditions suitable to provide Compound I; or dissociating the Compound X5 oxalic acid salt to provide Compound X5, and contacting the Compound X5 with a base in a solvent.

36. The process of claim 35, wherein the solvent comprises ACN.
37. The process of claim 35 or 36, wherein the process comprises dissociating the Compound X5 oxalic acid salt prior to contacting with a base.
38. The process of any one of claims 35-37, wherein the process comprises isolating the Compound X5 oxalic acid salt.
39. A compound, or a salt thereof, selected from:





40. 3-(5-(((1S,2S)-2-aminocyclohexyl)oxy)-1-oxoisindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione fumaric acid salt (Compound X4 fumaric acid salt):



41. 3-(1-oxo-5-(((1S,2S)-2-(3-phenylazetidin-1-yl)cyclohexyl)oxy)isindolin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione oxalic acid salt (Compound X5 oxalic acid salt):

