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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 February 2014 (13.02.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/025978 A1

(51) International Patent Classification:
C07D 401/04 (2006.01)

(21) International Application Number:
PCT/US2013/054099

(22) International Filing Date:
8 August 2013 (08.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/681,477 9 August 2012 (09.08.2012) US

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

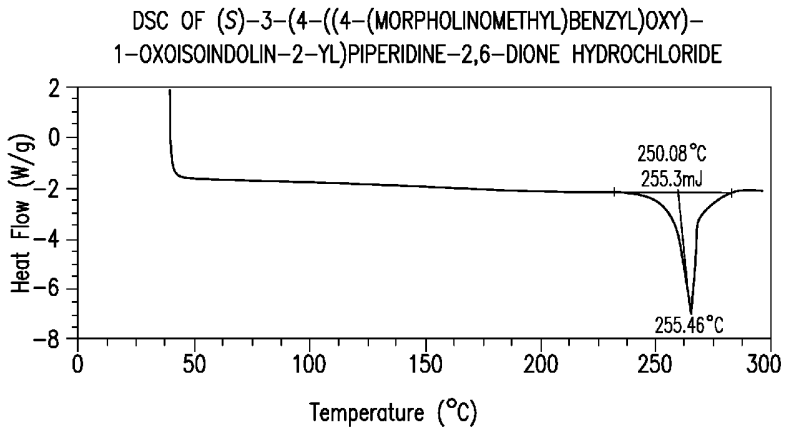
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,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

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: PROCESSES FOR THE PREPARATION OF (S)-3-4-((4-(MORPHOLINOMETHYL) BENZYL)OXY)-1-OXOISOINDOLIN-2-YL) PIPERIDINE-2,6-DIONE AND PHARMACEUTICALLY ACCEPTABLE FORMS THEREOF



(57) Abstract: Provided are processes for the preparation of enantiomerically enriched or enantiomerically pure 3-(4-((4-(morpholinomethyl)benzyl)oxy)- 1 -oxoisoindolin-2-yl)piperidine- 2,6-dione, or a pharmaceutically acceptable form thereof.

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PROCESSES FOR THE PREPARATION OF (S)-3-(4-((4-(MORPHOLINOMETHYL)BENZYL)OXY)-1-OXOISOINDOLIN-2-YL)PIPERIDINE-2,6-DIONE AND PHARMACEUTICALLY ACCEPTABLE FORMS THEREOF

1. CLAIM OF PRIORITY

[0001] Priority is claimed herein to U.S. Provisional Application No. 61/681,477, entitled "Processes for the Preparation of (S)-3-(4-((4-(Morpholinomethyl)Benzyl)Oxy)-1-Oxoisoindolin-2-Yl)Piperidine-2,6-Dione and Pharmaceutically Acceptable Forms Thereof," filed August 9, 2012. The above-referenced application is incorporated by reference herein in its entirety.

2. FIELD

[0002] Provided herein are processes for the preparation of enantiomerically enriched or enantiomerically pure 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable form thereof, which is useful for treating, preventing and managing various disorders.

3. BACKGROUND

[0003] Many types of cancers are associated with new blood vessel formation, a process known as angiogenesis. Several of the mechanisms involved in tumor-induced angiogenesis have been elucidated. The most direct of these mechanisms is the secretion by the tumor cells of cytokines with angiogenic properties, including tumor necrosis factor α (TNF-α).

[0004] A variety of other diseases and disorders are also associated with, or characterized by, undesired angiogenesis. For example, enhanced or unregulated angiogenesis has been implicated in a number of diseases and medical conditions including, but not limited to, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, rubeosis (neovascularization of the angle), viral diseases, genetic diseases, inflammatory diseases, allergic diseases, and autoimmune diseases. Examples of such diseases and conditions include, but are not limited to: diabetic retinopathy; retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasia; arthritis; and proliferative vitreoretinopathy.

[0005] Certain 4'-arylmethoxy isoindoline compounds, including 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, have been reported to be capable of controlling angiogenesis or inhibiting the production of certain cytokines, including TNF-α, and useful in the treatment and prevention of various diseases and conditions. *See* U.S. Patent Publication No. 2011/0196150, which is incorporated herein by reference in its entirety.

[0006] Methods for synthesizing racemic 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione have been previously described in U.S. Patent Publication No. 2011/0196150. A need still exists for efficient and scalable processes for the preparation of enantiomerically enriched or enantiomerically pure 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable form thereof.

[0007] Among general approaches for providing enantiomerically enriched or enantiomerically pure compounds, utilizing naturally or commercially available enantiopure starting materials is the most straightforward approach and is often preferred for processes of industrial scale. One of the challenges often encountered by this approach is full or partial racemization during the synthetic process, which leads to decrease of the enantiomeric excess (ee) of the material. In order to minimize the chance of racemization, harsh reaction conditions are often avoided wherever possible.

[0008] In addition to the need for synthetic processes for the preparation of an enantiomerically enriched or enantiomerically pure compound, a need for a method that can increase the enantiopurity of a compound still exists, because process deviations can result in lower ee even if the process is capable of providing the compound with a high ee. Further, developing a method that can increase the product ee may allow for alternative synthetic routes to the enantiomerically enriched or enantiomerically pure compound, resulting in lower cost of goods and a more streamlined manufacturing process.

[0009] General methods for ee enhancement by crystallization based on the thermodynamic relationship between racemic mixture and enantiopure species have been reported (Wang *et al.*, *Org. Proc. Res. Dev.*, 2005, 9, 670; Wang *et al.*, *Org. Proc. Res. Dev.*,

2008, 12, 282; Jacques, J.; Collet, A.; Wilen, S.H. *Enatniomers, Racemates and Resolution*; John Wiley & Sons: New York, 1981). Development of a crystallization method for a direct ee enhancement typically includes three steps: (1) determining the thermodynamically stable phase of the racemate (conglomerate, racemic compound, or pseudoracemate) at the temperature of interest, (2) obtaining the key solubility data, and (3) designing the crystallization process.

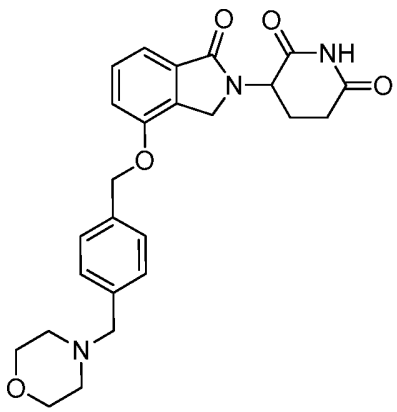
[0010] The majority of racemic mixtures preferentially form racemic compounds (reference Jacques book). The saturation solubility of a racemic compound and the pure enantiomer in the presence of a solvent is known as the eutectic point. The ratio of the solubility, i.e., the "eutectic enantioexcess" (ee_{eu}), is a useful parameter to assess the chiral upgrade capability for a given system. The ee_{eu} is calculated from the relative solubility of the R- and S-enantiomers: $ee_{eu} = ([major] - [minor]) / ([major] + [minor])$, where *[major]* is the solubility of the major enantiomer at the eutectic, and *[minor]* is the solubility of the minor enantiomer at the eutectic. Provided that the most stable crystalline forms of the racemic compound and single enantiomer are used, in dilute solutions, the ee_{eu} should be independent of solvent selection, unless one or both of the forms are solvates and/or the solvent under study is chiral. The ee_{eu} can be dependent on temperature in all cases.

[0011] In the case of racemic compound, low ee_{eu} is desired to increase ee of a compound in the solids. This occurs when the racemic compound has relatively high solubility compared to the single enantiomer. In the case of a low ee_{eu}, facile purification can occur by a trituration or recrystallization of the crude mixture in a specified solvent, followed by filtration, which will afford enantiomerically enriched or enantiomerically pure solids with a mixture of both enantiomers dissolved in the filtrate.

[0012] Identifying a low ee_{eu} condition often requires extensive solubility screening of a range of crystalline forms, solvents and conditions, and in many cases still cannot be achieved.

4. SUMMARY

[0013] Provided herein are processes for the preparation of an enantiomerically enriched or enantiomerically pure compound of Formula (I):

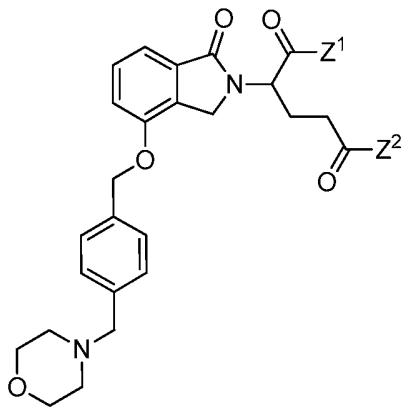


(I)

or a pharmaceutically acceptable form thereof. A compound of Formula (I) has the chemical name of 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. In one embodiment, the compound is (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable form thereof. In one embodiment, the compound is (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride, which is also known as (3*S*)-3-(4-{[4-(morpholin-4-ylmethyl)benzyl]oxy}-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione hydrochloride (1:1), or 2,6-piperidinedione, 3-[1,3-dihydro-4-[[4-(4-morpholinylmethyl)phenyl]methoxy]-1-oxo-2*H*-isoindol-2-yl]-, (3*S*)-, hydrochloride (1:1).

[0014] In one embodiment, provided herein are processes for the preparation of an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a pharmaceutically acceptable form thereof, comprising:

(step 1.1) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II):



(II)

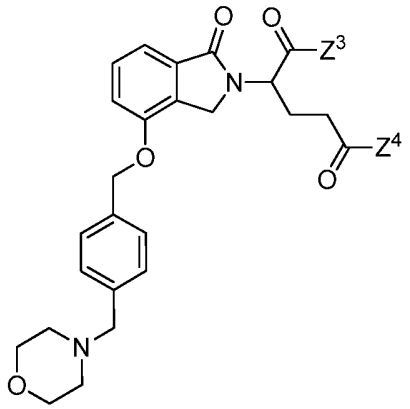
or a salt thereof, wherein

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY;

wherein R and Y are defined herein elsewhere;

to an enantiomerically enriched or enantiomerically pure compound of Formula (III):



(III),

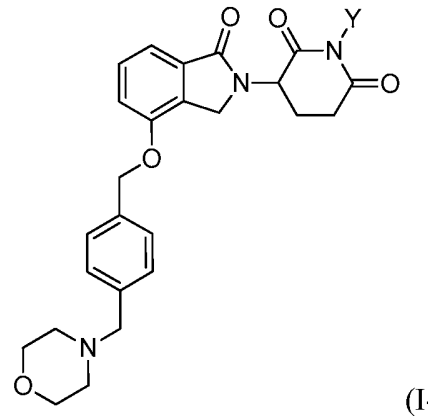
or a salt thereof, wherein

(i) Z^3 is NHY, and Z^4 is OH; or

(ii) Z^3 is OH, and Z^4 is NHY;

under conditions suitable for ester to acid transformation;

(step 1.2) cyclizing the enantiomerically enriched or enantiomerically pure compound of Formula (III) to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a):



(I-a),

under conditions suitable for cyclization;

(step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I) under conditions suitable for deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation.

[0015] Also provided herein are methods for increasing the enantiopurity of a compound of Formula (I), or a salt and/or solvate thereof. In one embodiment, without being limited by any particular theory, such methods are based on thermodynamic relationship between (*S*)- and racemic 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a salt and/or solvate thereof.

5. BRIEF DESCRIPTION OF THE FIGURES

[0016] **FIG. 1** depicts a differential scanning calorimetric (DSC) thermogram of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride.

[0017] **FIG. 2** depicts an X-ray powder diffractogram (XRD) of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride.

[0018] **FIG. 3** depicts a thermogravimetric (TGA) thermogram of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride.

[0019] **FIG. 4** depicts the eutectic solubility of the HCl salt of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione in IPA/water.

[0020] **FIG. 5** depicts the eutectic solubility of the HCl salt of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione as a function of temperature in various solvent systems.

6. DETAILED DESCRIPTION

6.1 Definition

[0021] As used herein and unless otherwise indicated, the term "process(es)" provided herein refers to the methods disclosed herein which are useful for preparing a compound provided herein. Modifications to the methods disclosed herein (*e.g.*, starting materials,

reagents, protecting groups, solvents, temperatures, reaction times, purification) are also encompassed by the present disclosure.

[0022] As used herein, and unless otherwise indicated, the term "adding," "reacting," "treating," or the like means contacting one reactant, reagent, solvent, catalyst, reactive group or the like with another reactant, reagent, solvent, catalyst, reactive group or the like. Reactants, reagents, solvents, catalysts, reactive group or the like can be added individually, simultaneously or separately and can be added in any order. They can be added in the presence or absence of heat and can optionally be added under an inert atmosphere. "Reacting" can refer to *in situ* formation or intramolecular reaction where the reactive groups are in the same molecule.

[0023] As used herein, and unless otherwise indicated, the term "transforming" refers to subjecting the compound at hand to reaction conditions suitable to effect the formation of the desired compound at hand.

[0024] As used herein, and unless otherwise specified, a "one-pot" process refers to a process of preparing a desired product, wherein all reactants are added simultaneously or successively, and wherein no separation, isolation, and/or purification of any intermediate formed is conducted before the formation of the desired product is substantially complete. A "one-pot" process is preferably conducted in a single container, but may be conducted in more than one container.

[0025] As used herein, and unless otherwise indicated, a reaction that is "substantially complete" or is driven to "substantial completion" means that the reaction contains more than about 50% by percent yield, in one embodiment more than about 60% by percent yield, in one embodiment more than about 70% by percent yield, in one embodiment more than about 80% by percent yield, in one embodiment more than about 90% by percent yield, in another embodiment more than about 95% by percent yield, and in another embodiment more than about 97% by percent yield of the desired product.

[0026] As used herein, and unless otherwise specified, a "pharmaceutically acceptable form" includes any pharmaceutically acceptable salts, solvates, stereoisomers, polymorphs, or prodrugs of a compound.

[0027] As used herein, and unless otherwise indicated, the term "salt" includes, but is not limited to, salts of acidic or basic groups that may be present in the compounds disclosed herein. Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare salts of such basic compounds are those that form salts comprising anions including, but not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, bromide, iodide, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydroxynaphthoate, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, muscate, napsylate, nitrate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, succinate, sulfate, tannate, tartrate, teoclate, triethiodide, and pamoate. Compounds that include an amino group also can form salts with various amino acids, in addition to the acids mentioned above. Compounds that are acidic in nature are capable of forming base salts with various cations. Non-limiting examples of such salts include alkali metal or alkaline earth metal salts and, in some embodiments, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds that are acidic in nature are also capable of forming base salts with compounds that include an amino group.

[0028] As used herein, and unless otherwise specified, the term "solvate" means a compound that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

[0029] As used herein, and unless otherwise specified, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide the compound. Examples of prodrugs include, but are not limited to, compounds that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include compounds that comprise -NO, $-NO_2$, -ONO, or $-ONO_2$ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed. 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elselvier, New York 1985).

[0030] As used herein, and unless otherwise specified, the terms "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide" and "biohydrolyzable phosphate " mean a carbamate, carbonate, ureide and phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties *in vivo*, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted *in vivo* to the biologically active compound. Examples of biohydrolyzable carbamates include, but are not limited to, carbamates that include lower alkylamine, substituted ethylenediamine, aminoacid, hydroxyalkylamine, heterocyclic and heteroaromatic amine, and polyether amine moieties.

[0031] As used herein, and unless otherwise specified, the term "stereoisomer" encompasses all enantiomerically/stereomerically pure and enantiomerically/stereomerically enriched compounds provided herein.

[0032] If the stereochemistry of a structure or a portion thereof is not indicated, *e.g.*, with bold or dashed lines, the structure or portion thereof is to be interpreted as encompassing all enantiomerically pure, enantiomerically enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures of the compounds.

[0033] Unless otherwise indicated, the terms "enantiomerically enriched" and "enantiomerically pure," as used interchangeably herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (*e.g.,* greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (*S*)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (*S*)-enantiomer relative to the (*R*)-enantiomer, such as at least 75% by weight, and even such as at least 80% by weight. In some embodiments, the enrichment can be much greater than 80% by weight, providing a "substantially optically enriched," "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, such as at least 90% by weight, and such as at least 95% by weight. In some embodiments, the enantiomerically enriched composition has a higher potency with respect to

therapeutic utility per unit mass than does the racemic mixture of that composition.

[0034] As used herein, and unless otherwise specified, "polymorph" refers to a crystalline compound existing in more than one crystalline form/structure. When polymorphism exists as a result of difference in crystal packing it is called packing polymorphism. Polymorphism can also result from the existence of different conformers of the same molecule in conformational polymorphism. In pseudopolymorphism, the different crystal types are the result of hydration or solvation.

[0035] As used herein, and unless otherwise indicated, the term "halo", "halogen", or the like means -F, -Cl, -Br, or -I.

[0036] As used herein, and unless otherwise specified, the term "alkyl" refers to a saturated straight chain or branched hydrocarbon having a number of carbon atoms as specified herein. In some embodiments, alkyl groups have 1 to 15, 1 to 10, 1 to 6, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The term "alkyl" also encompasses cycloalkyl.

[0037] As used herein, and unless otherwise specified, the term "heteroalkyl" refers to an alkyl in which one or more, in some embodiments, 1 to 3, carbon atoms are replaced by heteroatoms such as, but not limited to, N, S, O and Si, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atom may optionally be quaternized. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)_2$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-Si(CH_3)_3$, and $-CH_2-CH=N-OCH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. When a prefix such as C_{2-6} is used to refer to a heteroalkyl group, the number of carbons (2-6, in this example) is meant to include the heteroatoms as well. For example, a C_{2-6} heteroalkyl group is meant to include, for example, $-CH_2OH$ (one carbon atom and one heteroatom replacing a carbon atom) and $-CH_2SH$. In some embodiments, heteroalkyl groups have 2 to 15, 2 to 10, 2 to 6, or 2 to 3 carbon and hetero atoms

[0038] As used herein, and unless otherwise specified, the term "cycloalkyl" means a species of alkyl, which is cyclic and contains from 3 to 15, 3 to 9, 3 to 6, or 3 to 5 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Examples of unsubstituted cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and adamantyl. A cycloalkyl may be substituted with one or more substituents. In some embodiments, a cycloalkyl may be a cycloalkyl fused with aryl or heteroaryl groups.

[0039] As used herein, and unless otherwise specified, the term "heterocycloalkyl" means a cycloalkyl in which one or more, in some embodiments, 1 to 3, carbon atoms are replaced by heteroatoms such as, but not limited to, N, S, and O. In some embodiments, a heterocycloalkyl group contains from 3 to 15, 3 to 9, 3 to 6, or 3 to 5 carbon and hetero atoms. In some embodiments, a heterocycloalkyl may be a heterocycloalkyl fused with aryl or heteroaryl groups. When a prefix such as C_{3-6} is used to refer to a heterocycloalkyl group, the number of carbons (3-6, in this example) is meant to include the heteroatoms as well. For example, a C_{3-6} heterocycloalkyl group is meant to include, for example, tetrahydropyranyl (five carbon atoms and one heteroatom replacing a carbon atom).

[0040] As used herein, and unless otherwise specified, the term "aryl" means a carbocyclic aromatic ring containing from 5 to 14 ring atoms. The ring atoms of a carbocyclic aryl group are all carbon atoms. Aryl ring structures include compounds having one or more ring structures such as mono-, bi-, or tricyclic compounds as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl and the like. Specifically, the aryl group may be a mono- , bi-, or tricyclic ring. Representative aryl groups include phenyl, anthracenyl, fluorenyl, indenyl, azulenyl, phenanthrenyl and naphthyl.

[0041] As used herein, and unless otherwise specified, the term "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in some embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, N, O or S. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, indolinyl, pyrrolidinyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl,

pyrrolyl, N-methylpyrrolyl, quinolinyl and isoquinolinyl.

[0042] As used herein, and unless otherwise specified, the term "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

[0043] Where the number of any given substituent is not specified (*e.g.*, "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens.

[0044] As used herein, and unless otherwise indicated, the term "alcohol" means any compound substituted with an -OH group.

[0045] As used herein, and unless otherwise indicated, the term "amino" or "amino group" means a monovalent group of the formula $-NH_2$, -NH(alkyl), -NH(aryl), $-N(alkyl)_2$, $-N(aryl)_2$ or -N(alkyl)(aryl).

[0046] Unless otherwise indicated, the compounds provided herein, including intermediates useful for the preparation of the compounds provided herein, which contain reactive functional groups (such as, without limitation, carboxy, hydroxy, and amino moieties) also include protected derivatives thereof. "Protected derivatives" are those compounds in which a reactive site or sites are blocked with one or more protecting groups (also known as blocking groups). Suitable protecting groups are well known to those of ordinary skill in the art. The choice and use of protecting groups and the reaction conditions to install and remove protecting groups are described in *T. W. Green*, *Protective Groups in Organic Synthesis* (Third Ed., Wiley, New York, 1999), which is incorporated herein by reference in its entirety.

[0047] Amino protecting groups are well known in the art and include those described in detail in *T. W. Green*, *Protective Groups in Organic Synthesis*. Amino protecting groups include, but are not limited to, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl *(e.g.,* aralkyl groups), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups.

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups.

each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3{}^+X^-$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$,$–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S.

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups attached to an N atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1-6}$ alkyl, $–ON(C_{1-6}$ alkyl$)_2$, $–N(C_{1-6}$ alkyl$)_2$, $–N(C_{1-6}$ alkyl$)_3X$, $–NH(C_{1-6}$ alkyl$)_2X$, $–NH_2(C_{1-6}$ alkyl$)X$, $–NH_3X$, $–N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl), –N(OH)(C_{1-6} alkyl), –NH(OH), –SH, $–SC_{1-6}$ alkyl, $–SS(C_{1-6}$ alkyl), $–C(=O)(C_{1-6}$ alkyl), $–CO_2H$, $–CO_2(C_{1-6}$ alkyl), $–OC(=O)(C_{1-6}$ alkyl), $–OCO_2(C_{1-6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1-6}$ alkyl$)_2$, $–OC(=O)NH(C_{1-6}$ alkyl), $–NHC(=O)(C_{1-6}$ alkyl), $–N(C_{1-6}$ alkyl$)C(=O)(C_{1-6}$ alkyl), $–NHCO_2(C_{1-6}$ alkyl), $–NHC(=O)N(C_{1-6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1-6}$ alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1-6}$ alkyl),$–OC(=NH)(C_{1-6}$ alkyl), $–OC(=NH)OC_{1-6}$ alkyl, $–C(=NH)N(C_{1-6}$ alkyl$)_2$, $–C(=NH)NH(C_{1-6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1-6}$ alkyl$)_2$, $–OC(NH)NH(C_{1-6}$ alkyl), $–OC(NH)NH_2$, $–NHC(NH)N(C_{1-6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1-6}$ alkyl), $–SO_2N(C_{1-6}$ alkyl$)_2$, $–SO_2NH(C_{1-6}$ alkyl), $–SO_2NH_2$,$–SO_2C_{1-6}$ alkyl, $–SO_2OC_{1-6}$ alkyl, $–OSO_2C_{1-6}$ alkyl, $–SOC_{1-6}$ alkyl, $–Si(C_{1-6}$ alkyl$)_3$, $–OSi(C_{1-6}$ alkyl$)_3$ $–C(=S)N(C_{1-6}$ alkyl$)_2$, C(=S)NH(C_{1-6} alkyl), $C(=S)NH_2$, $–C(=O)S(C_{1-6}$ alkyl), $–C(=S)SC_{1-6}$ alkyl, $–SC(=S)SC_{1-6}$ alkyl, $–P(=O)_2(C_{1-6}$ alkyl), $–P(=O)(C_{1-6}$ alkyl$)_2$, $–OP(=O)(C_{1-6}$ alkyl$)_2$, $–OP(=O)(OC_{1-6}$ alkyl$)_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, , C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S;

wherein X^- is a counterion.

[0048] As used herein, a “counterion” is a negatively charged group associated with a positively charged quarternary amine in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.,* F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (*e.g.,* methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic

acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like) and carboxylate ions (*e.g.,* acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0049] For example, amino protecting groups such as amide groups *(e.g.,* –C(=O)R^{aa}) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxycarbonylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 3–(*o*–nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2–methyl–2–(*o*–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*–acetylmethionine derivative, *o*–nitrobenzamide and *o*–(benzoyloxymethyl)benzamide.

[0050] Amino protecting groups such as carbamate groups (*e.g.,* –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–*t*–butylphenyl)–1–methylethyl carbamate (*t*–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(*N,N*–dicyclohexylcarboxamido)ethyl carbamate, *t*–butyl carbamate (BOC), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, *N*–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–methoxybenzyl carbamate (Moz), *p*–nitobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–

dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), *m*–nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, *o*–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(*o*–nitrophenyl)methyl carbamate, *t*–amyl carbamate, *S*–benzyl thiocarbamate, *p*–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*–decyloxybenzyl carbamate, 2,2–dimethoxycarbonylvinyl carbamate, *o*–(*N,N*–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(*N,N*–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*–(*p'*–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(*p*–phenylazophenyl)ethyl carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, *p*–(phenylazo)benzyl carbamate, 2,4,6–tri–*t*–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, and 2,4,6–trimethylbenzyl carbamate.

[0051] Amino protecting groups such as sulfonamide groups (*e.g.*, $–S(=O)_2R^{aa}$) include, but are not limited to, *p*–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0052] Other amino protecting groups include, but are not limited to, phenothiazinyl–(10)–carbonyl derivative, *N'*–*p*–toluenesulfonylaminocarbonyl derivative, *N'*–

phenylaminothiocarbonyl derivative, *N*–benzoylphenylalanyl derivative, *N*–acetylmethionine derivative, 4,5–diphenyl–3–oxazolin–2–one, *N*–phthalimide, *N*–dithiasuccinimide (Dts), *N*–2,3–diphenylmaleimide, *N*–2,5–dimethylpyrrole, *N*–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, *N*–methylamine, *N*–allylamine, *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentacarbonylchromium– or tungsten)carbonyl]amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide and 3–nitropyridinesulfenamide (Npys).

[0053] As used herein, and unless otherwise indicated, acronyms or symbols for groups or reagents have the following definition: HPLC = high performance liquid chromatography; TFA = trifluoroacetic acid; TFE = 2,2,2-trifluoroethanol, THF = tetrahydrofuran; CH_3CN = acetonitrile; HOAc = acetic acid; DCM = dichloromethane.

[0054] As used herein, and unless otherwise indicated, the term “substituted” or

"substitution," when used to describe a chemical structure or moiety, refers to a derivative of that structure or moiety wherein one or more of its hydrogen atoms is replaced with a substituent such as, but not limited to: alkyl, alkenyl, alkynyl, and cycloalkyl; alkoxyalkyl; aroyl; halo; haloalkyl (*e.g.*, trifluoromethyl); heterocycloalkyl; haloalkoxy (*e.g.*, trifluoromethoxy); hydroxy; alkoxy; cycloalkyloxy; heterocylooxy; oxo; alkanoyl; aryl; heteroaryl (*e.g.* , indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, and pyrimidyl); arylalkyl; alkylaryl; heteroaryl; heteroarylalkyl; alkylheteroaryl; heterocyclo; heterocycloalkyl-alkyl; aryloxy, alkanoyloxy; amino; alkylamino; arylamino; arylalkylamino; cycloalkylamino; heterocycloamino; mono- and di-substituted amino; alkanoylamino; aroylamino; aralkanoylamino; aminoalkyl; carbamyl (*e.g.*, $CONH_2$); substituted carbamyl (*e.g.*, CONH-alkyl, CONH-aryl, CONH-arylalkyl or instances where there are two substituents on the nitrogen); carbonyl; alkoxycarbonyl; carboxy; cyano; ester; ether; guanidino; nitro; sulfonyl; alkylsulfonyl; arylsulfonyl; arylalkylsulfonyl; sulfonamido (*e.g.*, SO_2NH_2); substituted sulfonamido; thiol; alkylthio; arylthio; arylalkylthio; cycloalkylthio; heterocyclothio; alkylthiono; arylthiono; and arylalkylthiono. In some embodiments, a substituent itself may be substituted with one or more chemical moieties such as, but not limited to, those described herein.

[0055] As used herein, and unless otherwise indicated, the term "about" is used to specify that the values given are approximate. For example, the term "about," where it is used in connection with reaction temperatures, denotes that the temperature deviations within 30%, 25%, 20%, 15%, 10%, or 5% are encompassed by the temperature indicated. Similarly, the term "about," where it is used in connection with reaction time, denotes that the time period deviations within 30%, 25%, 20%, 15%, 10%, or 5% are encompassed by the time period indicated.

[0056] As used herein, and unless otherwise specified, a "suitable leaving group" refers to any atom or group of atoms that can leave the carbon atom to which it is attached. Specifically, a suitable leaving group is one that can be displaced by an approaching nucleophile. Those of ordinary skill in the art can determine what atom or group of atoms can serve as a suitable leaving group. In addition, routine experimentation can identify whether any specific atom or group of atoms can serve as a suitable leaving group. Preferred suitable leaving groups include those that are primary (*e.g.*, a primary halo), although leaving groups that are secondary

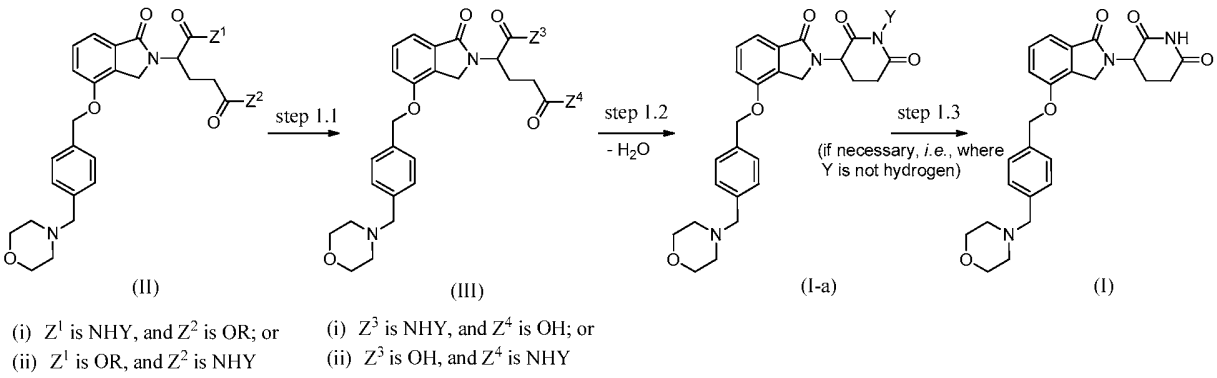
may also be used. Examples of suitable leaving groups include halogens and sulfonate esters. Among the halogens, bromo, chloro, iodo, and fluoro are preferred, with bromo and chloro being particularly preferred halogen-type leaving groups. With respect to sulfonate esters, methanesulfonate, trifluoromethanesulfonate, trichloromethanesulfonate, 2,2,2-trifluoroethanesulfonate, 2,2,2-trichloroethanesulfonate, and para-toluenesulfonate are particularly preferred, although other sulfonate esters and similarly constituted leaving groups known to those of ordinary skill in the art can be used as well.

[0057] It should be noted that if there is a discrepancy between a depicted structure and a name given to that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

6.2 Processes

6.2.1 Preparation of compound (I)

[0058] As depicted in Scheme 1 below, provided herein are processes for the preparation of an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a pharmaceutically acceptable form thereof, comprising: (step 1.1) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II), or a salt thereof, to an enantiomerically enriched or enantiomerically pure compound of Formula (III), or a salt thereof; (step 1.2) cyclizing the enantiomerically enriched or enantiomerically pure compound of Formula (III) to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a); (step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I); and (step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt. In one embodiment, the formation of the glutarimide ring in the compound of Formula (I) occurs with high preservation of the configuration of the chiral center. In one embodiment, the process is efficient and scalable.



Scheme 1

[0059] R may be a suitable carboxy protecting group, including methyl, *tert*-butyl, benzyl, and the like. Other suitable protecting groups are well known to those of ordinary skill in the art. Y may be any suitable amino protecting group. The choice and use of protecting groups and the reaction conditions to install and remove protecting groups are described in *T. W. Green*, *Protective Groups in Organic Synthesis* (Third Ed., Wiley, New York, 1999), which is incorporated herein by reference in its entirety.

[0060] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a pharmaceutically acceptable form thereof, comprising:

(step 1.1) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II), or a salt thereof, wherein

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY; wherein

R is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or a suitable protecting group of a carboxy group; and

Y is hydrogen, or a suitable amino protecting group;

to an enantiomerically enriched or enantiomerically pure compound of Formula (III), or a salt thereof, wherein

(i) Z^3 is NHY, and Z^4 is OH; or

(ii) Z^3 is OH, and Z^4 is NHY;

under conditions suitable for ester to acid transformation;

(step 1.2) cyclizing the enantiomerically enriched or enantiomerically pure compound of Formula (III) to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a) under conditions suitable for cyclization;

(step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I) under conditions suitable for deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation.

[0061] In one embodiment, the compound of Formula (I) is (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, which is also known as (3*S*)-3-(4-{[4-(morpholin-4-ylmethyl)benzyl]oxy}-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione, or 2,6-piperidinedione, 3-[1,3-dihydro-4-[[4-(4-morpholinylmethyl)phenyl]methoxy]-1-oxo-2*H*-isoindol-2-yl]-, (3*S*)-.

[0062] In one embodiment, R is C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-6} haloalkyl; C_{2-10} heteroalkyl; C_{3-6} heterocycloalkyl; C_{1-6} alkyl or C_{2-10} heteroalkyl substituted with 1 to 3 aryl; or $-SiR^a_3$ wherein each R^a is independently C_{1-6} alkyl or C_{5-14} aryl.

[0063] In one embodiment, R is methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, *tert*-butyl, methoxymethyl (MOM), methylthiomethyl (MTM), tetrahydropyranyl (THP), methoxyethoxymethyl (MEM), 2-(trimethylsilyl)ethoxymethylamine (SEM), benzyloxymethyl (BOM), 2-(trimethylsilyl)ethyl (TMSE), 2,2,2-trichloroethyl, benzyl, triphenylmethyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), *t*-butyldimethylsilyl (TBDMS), or *t*-butyldiphenylsilyl (TBDPS). In one embodiment, R is methyl, *tert*-butyl, or benzyl. In one embodiment, R is methyl. In another embodiment, R is *tert*-butyl. In yet another embodiment, R is benzyl.

[0064] In one embodiment, Y is hydrogen.

[0065] In one embodiment, Y is a suitable amino protecting group. In one embodiment, Y is allyl, *t*-butyl, methoxymethyl (MOM), methylthiomethyl (MTM), benzyloxymethyl (BOM), 2,2,2-trichloroethoxymethyl, *t*-butyldimethylsiloxymethyl, pivaloyloxymethyl, cyanomethyl, pyrrolidinomethyl, methoxy, benzyloxy, methylthio, triphenylmethylthio, *t*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), 4-methoxyphenyl, 4-(methyoxymethoxy)phenyl, 2-methoxy-1-naphthyl, benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 2-acetoxy-4-methoxybenzyl, 2-nitrobenzyl, bis(4-methoxyphenyl)methyl (DAM), bis(4-methoxyphenyl)phenylmethyl, bis(4-methylsulfinylphenyl)methyl, triphenylmethyl (Tr), 9-phenylfluorenyl (Pf), bis(trimethylsilyl)methyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), methoxycarbonyl, ethoxycarbonyl, *p*-toluenesulfonyl (Ts), butenyl, (*E*)-2-(methoxycarbonyl)vinyl, diethoxymethyl, 1-methoxy-2,2-dimethylpropyl, or 2-(4-methylphenylsulfonyl)ethyl. In one embodiment, Y is benzyl, 4-methoxybenzyl, *t*-butyldimethylsilyl, *t*-butoxycarbonyl, or benzyloxycarbonyl. In one embodiment, Y is benzyl.

[0066] Methods for transforming an ester to an acid (step 1.1) are well known to those of ordinary skill in the art. *See generally*, *T. W. Green*, *Protective Groups in Organic Synthesis* (Third Ed., Wiley, New York, 1999).

[0067] In one embodiment, step 1.1 occurs in the presence of an acid. In some embodiments, the acid is generated in situ. In one embodiment, step 1.1 occurs in the presence of an organic acid. In one embodiment, step 1.1 occurs in the presence of R^bCOOH wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl. In one embodiment, step 1.1 occurs in the presence of formic acid, acetic acid, trifluoroacetic acid, or benzoic acid.

[0068] In one embodiment, step 1.1 occurs in the presence of R^bSO_3H wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl. In one embodiment, step 1.1 occurs in the presence of sulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, methanesulfonic acid, or trifluoromethanesulfonic acid. In one embodiment, step 1.1 occurs in the presence of benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, or methanesulfonic acid. In one embodiment, step 1.1 occurs in the presence of benzenesulfonic

acid. In another embodiment, step 1.1 occurs in the presence of *p*-toluenesulfonic acid. In yet another embodiment, step 1.1 occurs in the presence of camphorsulfonic acid. In yet another embodiment, step 1.1 occurs in the presence of methanesulfonic acid.

[0069] In one embodiment, step 1.1 occurs in the presence of an inorganic acid. In one embodiment, step 1.1 occurs in the presence of hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid. In one embodiment, step 1.1 occurs in the presence of hydrochloric acid.

[0070] In one embodiment, step 1.1 occurs in the presence of a base. In some embodiments, the base is generated in situ. In one embodiment, step 1.1 occurs in the presence of an alkali metal base. In one embodiment, step 1.1 occurs in the presence of an alkali metal hydroxide, carbonate, hydrogencarbonate, phosphate, hydrogenphosphate, or dihydrogenphosphate. In one embodiment, step 1.1 occurs in the presence of LiOH, NaOH, KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $KHCO_3$, Na_3PO_4, K_3PO_4, Na_2HPO_4, K_2HPO_4, NaH_2PO_4, or KH_2PO_4.

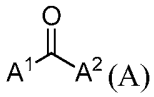
[0071] In one embodiment, step 1.1 occurs in the presence of M-R^c or M-OR^c, wherein M is alkali metal; and R^c is substituted or unsubstituted C_{1-10} alkyl. In one embodiment, step 1.1 occurs in the presence of sodium methoxide, sodium ethoxide, sodium *t*-butoxide, potassium methoxide, potassium ethoxide, or potassium *t*-butoxide. In one embodiment, step 1.1 occurs in the presence of sodium *t*-butoxide, or potassium *t*-butoxide.

[0072] In one embodiment, step 1.1 occurs in the presence of a nitrogen containing base. In one embodiment, step 1.1 occurs in the presence of NH_4OH, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, imidazole, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

[0073] In one embodiment, step 1.1 occurs by hydrogenation.

[0074] The cyclization of a compound of Formula (III) (step 1.2) may occur with any dehydrating agent or any combination of dehydrating agents according to a person of ordinary skill in the art. In some embodiments, the dehydrating agent is (or the combination of dehydrating agents are) generated in situ. In some embodiments, the dehydrating agent is (or the combination of dehydrating agents contains) thionyl chloride, sulfuryl chloride, 4-

dimethylaminopyridine, phosgene, diphosgene, triphosgene, oxalyl chloride, a carbodiimide, an anhydride or a mixed anhydride, a phenol, or a compound of Formula (A):



(A)

wherein each of A^1 and A^2 is independently an unsubstituted or substituted heteroaryl group. In some embodiments, the dehydrating agent is (or combination of dehydrating agents contains) benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), N,N'-carbonyldiimidazole (CDI), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT), 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide (EDCI), 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 1-hydroxybenzotriazole (HOBt), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), O-(3,4-dihydro-4-oxo-1,2,3-benzotriazine-3-yl)-N,N,N,N-tetramethyluronium tetrafluoroborate (TDBTU), 3-(diethyloxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT), dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC), or 1-hydroxy-7-azabenzotriazole (HOAt). In some embodiments, the dehydrating agent is 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide (EDCI) or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU). In another embodiment, the dehydrating agent is molecular sieve.

[0075] The cyclization of a compound of Formula (III) (step 1.2) may occur when water is removed from the reaction mixture. In one embodiment of step 1.2, water is removed by azeotropic distillation. Other techniques to remove water from a reaction mixture are well known to those of ordinary skill in the art.

[0076] The cyclization of a compound of Formula (III) (step 1.2) may also occur in the absence of dehydrating agent or without removal of water.

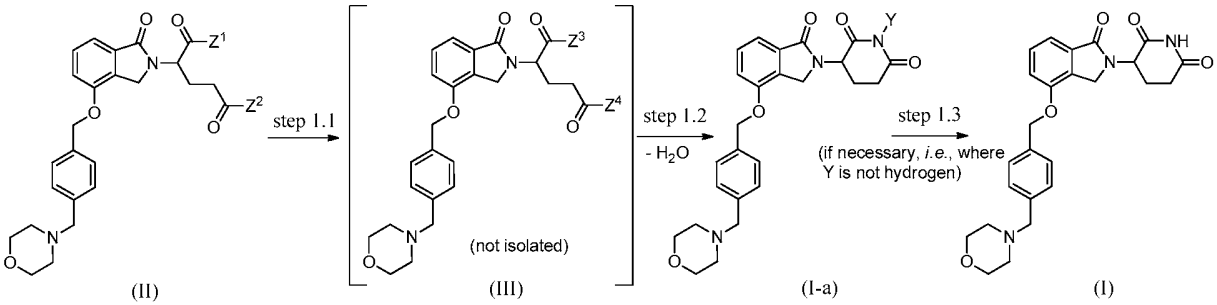
[0077] In one embodiment, wherein Y is hydrogen, a compound of Formula (I-a) is a compound of Formula (I), and step 1.3 is not necessary.

[0078] In one embodiment, wherein Y is not a hydrogen, a compound of Formula (I-a) is not a compound of Formula (I), and step 1.3 is necessary. The reaction conditions to install and

remove suitable amino protecting groups are well known to those of ordinary skill in the art, including those described in *T. W. Green*, *Protective Groups in Organic Synthesis* (Third Ed., Wiley, New York, 1999). In one embodiments, Y is benzyl, and step 1.3 occurs by hydrogenation.

[0079] Optionally, the compound of Formula (I), or a salt thereof, may be transformed to a different pharmaceutically acceptable salt by reacting with an acid (step 1.4). In one embodiment, step 1.4 comprises transforming a free base of a compound of Formula (I) to a pharmaceutically acceptable salt thereof. In another embodiment, step 1.4 comprises transforming a salt of a compound of Formula (I) to a free base, and transforming the free base to a pharmaceutically acceptable salt thereof. In yet another embodiments, step 1.4 comprises directly transforming a salt of a compound of Formula (I) to a different pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutically acceptable salt is hydrochloride.

[0080] In one embodiment, as depicted in Scheme 1a below, step 1.1 and step 1.2 occur in one-pot, without isolation of the compound of Formula (III).



Scheme 1a

[0081] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a pharmaceutically acceptable form thereof, comprising:

(step 1.1) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II), or a salt thereof, wherein

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY; wherein

R is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or a suitable protecting group of a carboxy group; and

Y is hydrogen, or a suitable amino protecting group;

to an enantiomerically enriched or enantiomerically pure compound of Formula (III), or a salt thereof, wherein

(i) Z^3 is NHY, and Z^4 is OH; or

(ii) Z^3 is OH, and Z^4 is NHY;

under conditions suitable for ester to acid transformation;

(step 1.2) cyclizing the enantiomerically enriched or enantiomerically pure compound of Formula (III) to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a) under conditions suitable for cyclization;

(step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I) under conditions suitable for deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation;

wherein step 1.1 and step 1.2 occur in one-pot.

[0082] In one embodiment, the compound of Formula (I) is (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione.

[0083] In one embodiment, step 1.1 and step 1.2 occur in one-pot; and R is C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-6} haloalkyl; C_{2-10} heteroalkyl; C_{3-6} heterocycloalkyl; C_{1-6} alkyl or C_{2-10} heteroalkyl substituted with 1 to 3 aryl; or $-SiR^a_3$ wherein each R^a is independently C_{1-6} alkyl or C_{5-14} aryl.

[0084] In one embodiment, step 1.1 and step 1.2 occur in one-pot; and R is methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methoxymethyl (MOM),

methylthiomethyl (MTM), tetrahydropyranyl (THP), methoxyethoxymethyl (MEM), 2-(trimethylsilyl)ethoxymethylamine (SEM), benzyloxymethyl (BOM), 2-(trimethylsilyl)ethyl (TMSE), 2,2,2-trichloroethyl, benzyl, triphenylmethyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), *t*-butyldimethylsilyl (TBDMS), or *t*-butyldiphenylsilyl (TBDPS). In one embodiment, step 1.1 and step 1.2 occur in one-pot; and R is methyl, *tert*-butyl, or benzyl. In one embodiment, step 1.1 and step 1.2 occur in one-pot; and R is methyl. In another embodiment, step 1.1 and step 1.2 occur in one-pot; and R is *tert*-butyl. In yet another embodiment, step 1.1 and step 1.2 occur in one-pot; and R is benzyl.

[0085] In one embodiment, step 1.1 and step 1.2 occur in one-pot; and Y is hydrogen.

[0086] In one embodiment, step 1.1 and step 1.2 occur in one-pot; and Y is a suitable amino protecting group. In one embodiment, step 1.1 and step 1.2 occur in one-pot; and Y is allyl, *t*-butyl, methoxymethyl (MOM), methylthiomethyl (MTM), benzyloxymethyl (BOM), 2,2,2-trichloroethoxymethyl, *t*-butyldimethylsiloxymethyl, pivaloyloxymethyl, cyanomethyl, pyrrolidinomethyl, methoxy, benzyloxy, methylthio, triphenylmethylthio, *t*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), 4-methoxyphenyl, 4-(methyoxymethoxy)phenyl, 2-methoxy-1-naphthyl, benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 2-acetoxy-4-methoxybenzyl, 2-nitrobenzyl, bis(4-methoxyphenyl)methyl (DAM), bis(4-methoxyphenyl)phenylmethyl, bis(4-methylsulfinylphenyl)methyl, triphenylmethyl (Tr), 9-phenylfluorenyl (Pf), bis(trimethylsilyl)methyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), methoxycarbonyl, ethoxycarbonyl, *p*-toluenesulfonyl (Ts), butenyl, (*E*)-2-(methoxycarbonyl)vinyl, diethoxymethyl, 1-methoxy-2,2-dimethylpropyl, or 2-(4-methylphenylsulfonyl)ethyl. In one embodiment, step 1.1 and step 1.2 occur in one-pot; and Y is benzyl, 4-methoxybenzyl, *t*-butyldimethylsilyl, *t*-butoxycarbonyl, or benzyloxycarbonyl. In one embodiment, step 1.1 and step 1.2 occur in one-pot; and Y is benzyl.

[0087] In one embodiment, step 1.1 and step 1.2 occur in one-pot by hydrogenation. In one embodiment, R is benzyl, and step 1.1 and step 1.2 occur in one-pot by hydrogenation.

[0088] In one embodiment, step 1.1 and step 1.2 occur in one-pot by hydrogenation/cyclization, wherein the cyclization is promoted by an acid or base.

[0089] In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of a base. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of an alkali metal hydroxide, carbonate, hydrogencarbonate, phosphate, hydrogenphosphate, or dihydrogenphosphate. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of LiOH, NaOH, KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $KHCO_3$, Na_3PO_4, K_3PO_4, Na_2HPO_4, K_2HPO_4, NaH_2PO_4, or KH_2PO_4. In one embodiment, R is methyl, and step 1.1 and step 1.2 occur in one-pot in the presence of NaOH or KOH.

[0090] In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of M-R^c or M-OR^c, wherein M is alkali metal; and R^c is substituted or unsubstituted C_{1-10} alkyl. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of sodium methoxide, sodium ethoxide, sodium *t*-butoxide, potassium methoxide, potassium ethoxide, or potassium *t*-butoxide. In one embodiment, R is methyl, and step 1.1 and step 1.2 occur in one-pot in the presence of sodium *tert*-butoxide, or potassium *tert*-butoxide.

[0091] In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of an acid. In some embodiments, the acid is generated in situ. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of an organic acid. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of R^bCOOH wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of formic acid, acetic acid, trifluoroacetic acid, or benzoic acid. In one embodiment, R is *tert*-butyl, and step 1.1 and step 1.2 occur in one-pot in the presence of trifluoroacetic acid.

[0092] In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of a Brønsted or Lewis acid. In some embodiments, the acid is generated in situ.

[0093] In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of R^bSO_3H wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of sulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, methanesulfonic acid, or trifluoromethanesulfonic acid. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of

benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, or methanesulfonic acid. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of benzenesulfonic acid. In another embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of *p*-toluenesulfonic acid. In yet another embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of camphorsulfonic acid. In yet another embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of methanesulfonic acid. In one embodiment, R is *tert*-butyl, and step 1.1 and step 1.2 occur in one-pot in the presence of benzenesulfonic acid.

[0094] In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of an inorganic acid. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid. In one embodiment, step 1.1 and step 1.2 occur in one-pot in the presence of hydrochloric acid. In one embodiment, R is *tert*-butyl, and step 1.1 and step 1.2 occur in one-pot in the presence of hydrochloric acid.

[0095] Step 1.1 and step 1.2, separately or in one-pot, may occur in any solvent or any combination of solvents. In some embodiments, the solvent is, or the combination of solvents contains, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone. In some embodiments, the solvent is acetonitrile.

[0096] Step 1.1 and step 1.2, separately or in one-pot, may occur at any reaction temperature. In some embodiments, the reaction temperature is from about -100 °C to about 200 °C. In some embodiments, the reaction temperature is from about -50 °C to about 150 °C. In some embodiments, the reaction temperature is from about 0 °C to about 100 °C. In some embodiments, the reaction temperature is from about 85 °C to about 95 °C. In some embodiments, the reaction temperature is about 90 °C.

[0097] Step 1.1 and step 1.2, separately or in one-pot, may occur at any reaction time. In some embodiments, the reaction time is from about 1 minute to about 14 days. In some embodiments, the reaction time is from about 5 minute to about 48 hours. In some embodiments, the reaction time is from about 1 hour to about 24 hours. In some embodiments, the reaction time is from about 3 hours to about 12 hours. In some embodiments, the reaction

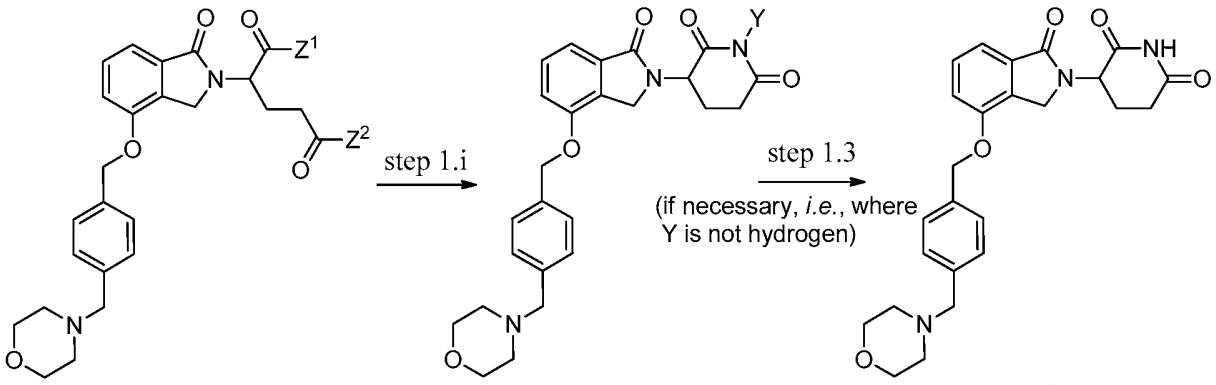
time is from about 8 hours to about 9 hours.

[0098] In one exemplary embodiment, Y is hydrogen, R is *tert*-butyl, and step 1.1 and step 1.2 occur in one-pot in the presence of benzenesulfonic acid, wherein the solvent is acetonitrile, the reaction temperature is about 90 °C, and the reaction time is from about 8 hours to about 9 hours.

[0099] In one exemplary embodiment, Y is hydrogen, R is *tert*-butyl, and step 1.1 and step 1.2 occur in one-pot in the presence of benzenesulfonic acid, wherein the solvent is acetonitrile, the reaction temperature is about 90 °C, the reaction time is from about 8 hours to about 9 hours, and water is removed by azeotropic distillation.

[00100] Steps 1.3 and 1.4 are as described above and herein.

[00101] In another embodiment, as depicted in Scheme 1b below, without being limited to any intermediate or any theory, a compound of Formula (I-a) can be prepared from a compound of Formula (II) in one step.



(II) (I-a) (I)

(i) Z^1 is NHY, and Z^2 is OR; or
(ii) Z^1 is OR, and Z^2 is NHY

Scheme 1b

[00102] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a pharmaceutically acceptable form thereof, comprising:

(step 1.i) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II), or a salt thereof, wherein

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY; wherein

R is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or a suitable protecting group of a carboxy group; and

Y is hydrogen, or a suitable amino protecting group;

to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a), or a salt thereof, under conditions suitable for cyclization;

(step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I) under conditions suitable for deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation.

[00103] In one embodiment, the compound of Formula (I) is (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione.

[00104] In one embodiment, R is C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-6} haloalkyl; C_{2-10} heteroalkyl; C_{3-6} heterocycloalkyl; C_{1-6} alkyl or C_{2-10} heteroalkyl substituted with 1 to 3 aryl; or $-SiR^a_3$ wherein each R^a is independently C_{1-6} alkyl or C_{5-14} aryl.

[00105] In one embodiment, R is methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methoxymethyl (MOM), methylthiomethyl (MTM), tetrahydropyranyl (THP), methoxyethoxymethyl (MEM), 2-(trimethylsilyl)ethoxymethylamine (SEM), benzyloxymethyl (BOM), 2-(trimethylsilyl)ethyl (TMSE), 2,2,2-trichloroethyl, benzyl, triphenylmethyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), *t*-butyldimethylsilyl (TBDMS), or *t*-butyldiphenylsilyl (TBDPS). In one embodiment, R is

methyl, *tert*-butyl, or benzyl. In one embodiment, R is methyl. In another embodiment, R is *tert*-butyl. In yet another embodiment, R is benzyl.

[00106] In one embodiment, Y is hydrogen.

[00107] In one embodiment, Y is a suitable amino protecting group. In one embodiment, Y is allyl, *t*-butyl, methoxymethyl (MOM), methylthiomethyl (MTM), benzyloxymethyl (BOM), 2,2,2-trichloroethoxymethyl, *t*-butyldimethylsiloxymethyl, pivaloyloxymethyl, cyanomethyl, pyrrolidinomethyl, methoxy, benzyloxy, methylthio, triphenylmethylthio, *t*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), 4-methoxyphenyl, 4-(methyoxymethoxy)phenyl, 2-methoxy-1-naphthyl, benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 2-acetoxy-4-methoxybenzyl, 2-nitrobenzyl, bis(4-methoxyphenyl)methyl (DAM), bis(4-methoxyphenyl)phenylmethyl, bis(4-methylsulfinylphenyl)methyl, triphenylmethyl (Tr), 9-phenylfluorenyl (Pf), bis(trimethylsilyl)methyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), methoxycarbonyl, ethoxycarbonyl, *p*-toluenesulfonyl (Ts), butenyl, (*E*)-2-(methoxycarbonyl)vinyl, diethoxymethyl, 1-methoxy-2,2-dimethylpropyl, or 2-(4-methylphenylsulfonyl)ethyl. In one embodiment, Y is benzyl, 4-methoxybenzyl, *t*-butyldimethylsilyl, *t*-butoxycarbonyl, or benzyloxycarbonyl. In one embodiment, Y is benzyl.

[00108] In one embodiment, step 1.i occurs by hydrogenation. In one embodiment, R is benzyl, and step 1.i occurs by hydrogenation.

[00109] In one embodiment, step 1.i occurs in the presence of a base. In one embodiment, step 1.i occurs in the presence of an alkali metal hydroxide, carbonate, hydrogencarbonate, phosphate, hydrogenphosphate, or dihydrogenphosphate. In one embodiment, step 1.i occurs in the presence of LiOH, NaOH, KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $KHCO_3$, Na_3PO_4, K_3PO_4, Na_2HPO_4, K_2HPO_4, NaH_2PO_4, or KH_2PO_4. In one embodiment, R is methyl, and step 1.i occurs in the presence of NaOH or KOH.

[00110] In one embodiment, step 1.i occurs in the presence of M-R^c or M-OR^c, wherein M is alkali metal; and R^c is substituted or unsubstituted C_{1-10} alkyl. In one embodiment, step 1.i occurs in the presence of sodium methoxide, sodium ethoxide, sodium *t*-butoxide, potassium methoxide, potassium ethoxide, or potassium *t*-butoxide. In one embodiment, R is methyl, and

step 1.i occurs in the presence of sodium *tert*-butoxide, or potassium *tert*-butoxide.

[00111] In one embodiment, step 1.i occurs in the presence of an acid. In some embodiments, the acid is generated in situ. In one embodiment, step 1.i occurs in the presence of an organic acid. In one embodiment, step 1.i occurs in the presence of R^bCOOH wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl. In one embodiment, step 1.i occurs in the presence of formic acid, acetic acid, trifluoroacetic acid, or benzoic acid. In one embodiment, R is *tert*-butyl, and step 1.i occurs in the presence of trifluoroacetic acid.

[00112] In one embodiment, step 1.i occurs in the presence of a Brønsted or Lewis acid. In some embodiments, the acid is generated in situ.

[00113] In one embodiment, step 1.i occurs in the presence of R^bSO_3H wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl. In one embodiment, step 1.i occurs in the presence of sulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, methanesulfonic acid, or trifluoromethanesulfonic acid. In one embodiment, step 1.i occurs in the presence of benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, or methanesulfonic acid. In one embodiment, step 1.i occurs in the presence of benzenesulfonic acid. In another embodiment, step 1.i occurs in the presence of *p*-toluenesulfonic acid. In yet another embodiment, step 1.i occurs in the presence of camphorsulfonic acid. In yet another embodiment, step 1.i occurs in the presence of methanesulfonic acid. In one embodiment, R is *tert*-butyl, and step 1.i occurs in the presence of benzenesulfonic acid.

[00114] In one embodiment, step 1.i occurs in the presence of an inorganic acid. In one embodiment, step 1.i occurs in the presence of hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid. In one embodiment, step 1.i occurs in the presence of hydrochloric acid. In one embodiment, R is *tert*-butyl, and step 1.i occurs in the presence of hydrochloric acid.

[00115] Step 1.i may occur in any solvent or any combination of solvents. In some embodiments, the solvent is, or the combination of solvents contains, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-

methyl-2-pyrrolidone. In some embodiments, the solvent is acetonitrile.

[00116] Step 1.i may occur at any reaction temperature. In some embodiments, the reaction temperature is from about -100 °C to about 200 °C. In some embodiments, the reaction temperature is from about -50 °C to about 150 °C. In some embodiments, the reaction temperature is from about 0 °C to about 100 °C. In some embodiments, the reaction temperature is from about 85 °C to about 95 °C. In some embodiments, the reaction temperature is about 90 °C.

[00117] Step 1.i may occur at any reaction time. In some embodiments, the reaction time is from about 1 minute to about 14 days. In some embodiments, the reaction time is from about 5 minute to about 48 hours. In some embodiments, the reaction time is from about 1 hour to about 24 hours. In some embodiments, the reaction time is from about 3 hours to about 12 hours. In some embodiments, the reaction time is from about 8 hours to about 9 hours.

[00118] In one exemplary embodiment, Y is hydrogen, R is *tert*-butyl, and step 1.i occurs in the presence of benzenesulfonic acid, wherein the solvent is acetonitrile, the reaction temperature is about 90 °C, and the reaction time is from about 8 hours to about 9 hours.

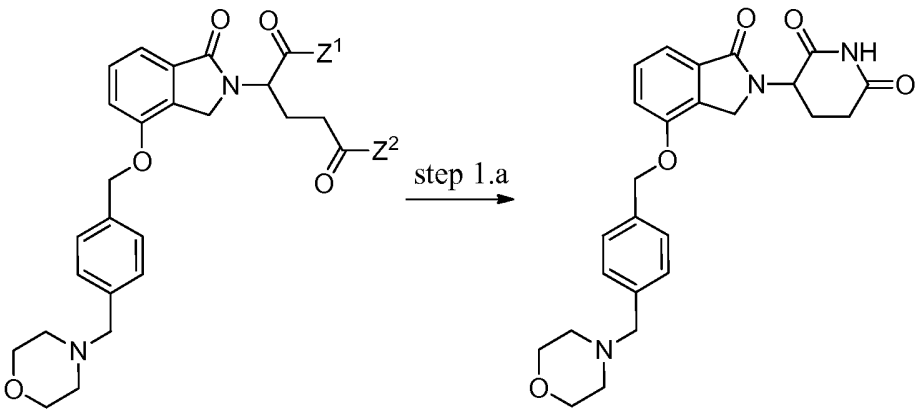
[00119] In one exemplary embodiment, Y is hydrogen, R is *tert*-butyl, and step 1.i occurs in the presence of benzenesulfonic acid, wherein the solvent is acetonitrile, the reaction temperature is about 90 °C, the reaction time is from about 8 hours to about 9 hours, and water is removed by azeotropic distillation.

[00120] In one exemplary embodiment, Y is benzyl, R is methyl, and step 1.i occurs in the presence of *p*-toluenesulfonic acid. In one exemplary embodiment, Y is benzyl, R is methyl, and step 1.i occurs in the presence of *p*-toluenesulfonic acid, wherein the solvent is acetic acid, the reaction temperature is about 100 °C, the reaction time is about 8 hours.

[00121] Steps 1.3 and 1.4 are as described above and herein.

[00122] In another embodiment, deprotection of Y may occur concurrently with formation of the glutarimide ring. As depicted in Scheme 1c below, without being limited to any intermediate or any theory, a compound of Formula (I) can be prepared from a compound of

Formula (II) in one step.



(II) (I)

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY

Scheme 1c

[00123] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a pharmaceutically acceptable form thereof, comprising:

(step 1.a) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II), or a salt thereof, wherein

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY; wherein

R is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or a suitable protecting group of a carboxy group; and

Y is hydrogen, or a suitable amino protecting group;

to an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a salt thereof, under conditions suitable for cyclization and deprotection;

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation.

[00124] In one embodiment, the compound of Formula (I) is (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione.

[00125] In one embodiment, R is C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-6} haloalkyl; C_{2-10} heteroalkyl; C_{3-6} heterocycloalkyl; C_{1-6} alkyl or C_{2-10} heteroalkyl substituted with 1 to 3 aryl; or $-SiR^a_3$ wherein each R^a is independently C_{1-6} alkyl or C_{5-14} aryl.

[00126] In one embodiment, R is methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methoxymethyl (MOM), methylthiomethyl (MTM), tetrahydropyranyl (THP), methoxyethoxymethyl (MEM), 2-(trimethylsilyl)ethoxymethylamine (SEM), benzyloxymethyl (BOM), 2-(trimethylsilyl)ethyl (TMSE), 2,2,2-trichloroethyl, benzyl, triphenylmethyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), *t*-butyldimethylsilyl (TBDMS), or *t*-butyldiphenylsilyl (TBDPS). In one embodiment, R is methyl, *tert*-butyl, or benzyl. In one embodiment, R is methyl. In another embodiment, R is *tert*-butyl. In yet another embodiment, R is benzyl.

[00127] In one embodiment, Y is hydrogen.

[00128] In one embodiment, Y is a suitable amino protecting group. In one embodiment, Y is allyl, *t*-butyl, methoxymethyl (MOM), methylthiomethyl (MTM), benzyloxymethyl (BOM), 2,2,2-trichloroethoxymethyl, *t*-butyldimethylsiloxymethyl, pivaloyloxymethyl, cyanomethyl, pyrrolidinomethyl, methoxy, benzyloxy, methylthio, triphenylmethylthio, *t*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), 4-methoxyphenyl, 4-(methyoxymethoxy)phenyl, 2-methoxy-1-naphthyl, benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 2-acetoxy-4-methoxybenzyl, 2-nitrobenzyl, bis(4-methoxyphenyl)methyl (DAM), bis(4-methoxyphenyl)phenylmethyl, bis(4-methylsulfinylphenyl)methyl, triphenylmethyl (Tr), 9-phenylfluorenyl (Pf), bis(trimethylsilyl)methyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), methoxycarbonyl, ethoxycarbonyl, *p*-toluenesulfonyl (Ts), butenyl, (*E*)-2-(methoxycarbonyl)vinyl, diethoxymethyl, 1-methoxy-2,2-dimethylpropyl, or 2-(4-methylphenylsulfonyl)ethyl. In one embodiment, Y is benzyl, 4-methoxybenzyl, *t*-butyldimethylsilyl, *t*-butoxycarbonyl, or benzyloxycarbonyl. In one embodiment, Y is benzyl.

[00129] In one embodiment, step 1.a occurs by hydrogenation. In one embodiment, R is benzyl, and step 1.a occurs by hydrogenation.

[00130] In one embodiment, step 1.a occurs in the presence of a base. In one embodiment, step 1.a occurs in the presence of an alkali metal hydroxide, carbonate, hydrogencarbonate, phosphate, hydrogenphosphate, or dihydrogenphosphate. In one embodiment, step 1.a occurs in the presence of LiOH, NaOH, KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $KHCO_3$, Na_3PO_4, K_3PO_4, Na_2HPO_4, K_2HPO_4, NaH_2PO_4, or KH_2PO_4. In one embodiment, R is methyl, and step 1.a occurs in the presence of NaOH or KOH.

[00131] In one embodiment, step 1.a occurs in the presence of M-R^c or M-OR^c, wherein M is alkali metal; and R^c is substituted or unsubstituted C_{1-10} alkyl. In one embodiment, step 1.a occurs in the presence of sodium methoxide, sodium ethoxide, sodium *t*-butoxide, potassium methoxide, potassium ethoxide, or potassium *t*-butoxide. In one embodiment, R is methyl, and step 1.a occurs in the presence of sodium *tert*-butoxide, or potassium *tert*-butoxide.

[00132] In one embodiment, step 1.a occurs in the presence of an acid. In some embodiments, the acid is generated in situ. In one embodiment, step 1.a occurs in the presence of an organic acid. In one embodiment, step 1.a occurs in the presence of R^bCOOH wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl. In one embodiment, step 1.a occurs in the presence of formic acid, acetic acid, trifluoroacetic acid, or benzoic acid. In one embodiment, R is *tert*-butyl, and step 1.a occurs in the presence of trifluoroacetic acid.

[00133] In one embodiment, step 1.a occurs in the presence of R^bSO_3H wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl. In one embodiment, step 1.a occurs in the presence of sulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, methanesulfonic acid, or trifluoromethanesulfonic acid. In one embodiment, step 1.a occurs in the presence of benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, or methanesulfonic acid. In one embodiment, step 1.a occurs in the presence of benzenesulfonic acid. In another embodiment, step 1.a occurs in the presence of *p*-toluenesulfonic acid. In yet another embodiment, step 1.a occurs in the presence of camphorsulfonic acid. In yet another

embodiment, step 1.a occurs in the presence of methanesulfonic acid. In one embodiment, R is *tert*-butyl, and step 1.a occurs in the presence of benzenesulfonic acid.

[00134] In one embodiment, step 1.a occurs in the presence of an inorganic acid. In one embodiment, step 1.a occurs in the presence of hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid. In one embodiment, step 1.a occurs in the presence of hydrochloric acid. In one embodiment, R is *tert*-butyl, and step 1.a occurs in the presence of hydrochloric acid.

[00135] Step 1.a may occur in any solvent or any combination of solvents. In some embodiments, the solvent is, or the combination of solvents contains, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone. In some embodiments, the solvent is acetonitrile.

[00136] Step 1.a may occur at any reaction temperature. In some embodiments, the reaction temperature is from about -100 °C to about 200 °C. In some embodiments, the reaction temperature is from about -50 °C to about 150 °C. In some embodiments, the reaction temperature is from about 0 °C to about 100 °C. In some embodiments, the reaction temperature is from about 85 °C to about 95 °C. In some embodiments, the reaction temperature is about 90 °C.

[00137] Step 1.a may occur at any reaction time. In some embodiments, the reaction time is from about 1 minute to about 14 days. In some embodiments, the reaction time is from about 5 minute to about 48 hours. In some embodiments, the reaction time is from about 1 hour to about 24 hours. In some embodiments, the reaction time is from about 3 hours to about 12 hours. In some embodiments, the reaction time is from about 8 hours to about 9 hours.

[00138] Step 1.4 is as described above and herein.

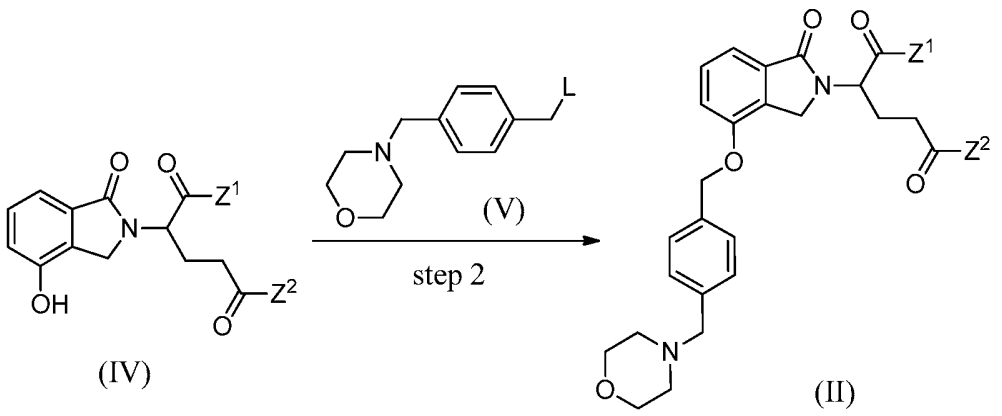
6.2.2 Preparation of compound (II)

[00139] In one embodiment, as depicted in Scheme 2 below, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (II), or a salt thereof, comprising:

(step 2) contacting an enantiomerically enriched or enantiomerically pure compound of Formula (IV) with a compound with Formula (V), or a salt thereof, wherein

Z^1 and Z^2 are as defined above and herein; and

L is halogen, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, $-OSO_2C_6H_4$-*p*-Me (*para*-toluenesulfonate), or a suitable leaving group; under conditions suitable for displacement.



(i) Z^1 is NHY, and Z^2 is OR; or
(ii) Z^1 is OR, and Z^2 is NHY

(i) Z^1 is NHY, and Z^2 is OR; or
(ii) Z^1 is OR, and Z^2 is NHY

Scheme 2

[00140] L may be any suitable leaving group known to those of ordinary skill in the art. In one embodiment, L is halogen, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, or $-OSO_2C_6H_4$-*p*-Me (*para*-toluenesulfonate). In one embodiment, L is halogen. In one embodiment, L is fluoro. In another embodiment, L is chloro. In yet another embodiment, L is bromo. In yet another embodiment, L is iodo.

[00141] Z^1, Z^2, R, and Y are as defined above and herein. The selection of R group is important for step 2. A sterically hindered R group, such as *tert*-butyl, generally results in higher conversion of a compound of Formula (IV) to a compound of Formula (II), than a non-sterically hindered R group, such as methyl, does.

[00142] The displacement of the leaving group L with the phenol group in a compound of Formula (IV) (step 2) may occur in the presence of a base. In some embodiments, the base is generated in situ. In one embodiment, step 2 occurs in the presence of an alkali metal base. In

one embodiment, step 2 occurs in the presence of an alkali metal hydroxide, carbonate, hydrogencarbonate, phosphate, hydrogenphosphate, or dihydrogenphosphate. In one embodiment, step 2 occurs in the presence of LiOH, NaOH, KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $KHCO_3$, Na_3PO_4, K_3PO_4, Na_2HPO_4, K_2HPO_4, NaH_2PO_4, or KH_2PO_4. In one embodiment, step 2 occurs in the presence of K_2CO_3.

[00143] In one embodiment, step 2 occurs in the presence of M-R^c or M-OR^c, wherein M is alkali metal; and R^c is substituted or unsubstituted C_{1-10} alkyl. In one embodiment, step 2 occurs in the presence of sodium methoxide, sodium ethoxide, sodium *t*-butoxide, potassium methoxide, potassium ethoxide, or potassium *t*-butoxide.

[00144] In one embodiment, step 2 occurs in the presence of a nitrogen containing base. In one embodiment, step 2 occurs in the presence of triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

[00145] Step 2 may occur in any solvent or any combination of solvents. In some embodiments, the solvent is, or the combination of solvents contains, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone. In one embodiment, the solvent is acetonitrile. In another embodiments, the solvent is dimethylformamide.

[00146] Step 2 may occur at any reaction temperature. In some embodiments, the reaction temperature is from about -100 °C to about 200 °C. In some embodiments, the reaction temperature is from about -50 °C to about 150 °C. In some embodiments, the reaction temperature is from about 0 °C to about 100 °C. In some embodiments, the reaction temperature is from about 40 °C to about 50 °C.

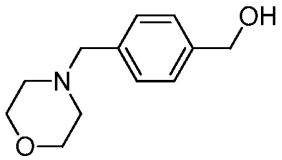
[00147] Step 2 may occur at any reaction time. In some embodiments, the reaction time is from about 1 minute to about 14 days. In some embodiments, the reaction time is from about 5 minute to about 48 hours. In some embodiments, the reaction time is from about 1 hour to about 24 hours. In some embodiments, the reaction time is from about 12 hours to about 24 hours.

[00148] Step 2 may occur at any molar ratio of the compound of Formula (IV) to the

compound of Formula (V). In some embodiments, the molar ratio of the compound of Formula (IV) to the compound of Formula (V) is from about 10:1 to about 1:10. In some embodiments, the molar ratio of the compound of Formula (IV) to the compound of Formula (V) is from about 5:1 to about 1:5. In some embodiments, the molar ratio of the compound of Formula (IV) to the compound of Formula (V) is from about 3:1 to about 1:3. In some embodiments, the molar ratio of the compound of Formula (IV) to the compound of Formula (V) is from about 1.5:1 to about 1:1.5. In some embodiments, the molar ratio of the compound of Formula (IV) to the compound of Formula (V) is from about 1.1:1 to about 1:1.1. In some embodiments, the molar ratio of the compound of Formula (IV) to the compound of Formula (V) is about 1:1.

[00149] In one embodiment, Y is hydrogen, R is *tert*-butyl and L is chloro. In one embodiment, Y is hydrogen, R is *tert*-butyl and L is chloro, wherein step 2 occurs in the presence of K_2CO_3. In one exemplary embodiment, Y is hydrogen, R is *tert*-butyl and L is chloro, wherein step 2 occurs in the presence of K_2CO_3, the solvent is dimethylformamide, the reaction temperature is from about 40 °C to about 50 °C, the reaction time is from about 12 hours to about 24 hours, and the molar ratio of the compound of Formula (IV) to the compound of Formula (V) is about 1:1.

[00150] The formation of the ether linkage in a compound of Formula (II) may be achieved by other chemical transformations known to those of ordinary skill in the art. For example, a Mitsunobu reaction between a compound of Formula (IV), in its racemic form, and an alcohol of Formula (B), in the presence of diisopropyl azodicarboxylate (DIAD) and PPh_3, has been reported in U.S. Patent Publication No. 2011/0196150.



(B)

Silica gel chromatography is often required for the purification of coupling product of a Mitsunobu reaction. The basic displacement process as depicted in Scheme 2 has the following advantages over the reported Mitsunobu reaction: (1) efficient and scalable; (2) high conversion; and (3) simple purification without the need of silica gel chromatography.

6.2.3 Preparation of compound (V)

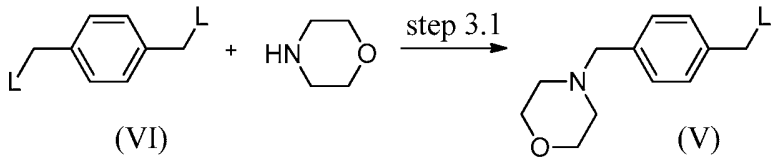
[00151] In one embodiment, as depicted in Scheme 3 below, provided herein is a process for preparing a compound of Formula (V), or a salt thereof, comprising:

(step 3.1) contacting a compound of Formula (VI), wherein

each L is independently halogen, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, $-OSO_2C_6H_4$-*p*-Me (*para*-toluenesulfonate), or a suitable leaving group;

with morpholine, or a salt thereof, under conditions suitable for displacement; and

(step 3.2) optionally purifying the compound of Formula (V) by selective extraction.



(VI) (V)

Scheme 3

[00152] Each L independently may be any suitable leaving group known to those of ordinary skill in the art. In one embodiment, each L is independently halogen, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, or $-OSO_2C_6H_4$-*p*-Me (*para*-toluenesulfonate). In one embodiment, each L is independently halogen. In one embodiment, both L are chloro. In another embodiment, one L is chloro and the other L is $-OSO_2Me$.

[00153] The displacement of the leaving group L with morpholine (step 3.1) may occur in the presence of a base. In some embodiments, the base is generated in situ. In one embodiment, step 3.1 occurs in the presence of an alkali metal base. In one embodiment, step 3.1 occurs in the presence of an alkali metal hydroxide, carbonate, hydrogencarbonate, phosphate, hydrogenphosphate, or dihydrogenphosphate. In one embodiment, step 3.1 occurs in the presence of LiOH, NaOH, KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $KHCO_3$, Na_3PO_4, K_3PO_4, Na_2HPO_4, K_2HPO_4, NaH_2PO_4, or KH_2PO_4.

[00154] In one embodiment, step 3.1 occurs in the presence of M-R^c or M-OR^c, wherein M is alkali metal; and R^c is substituted or unsubstituted C_{1-10} alkyl. In one embodiment, step 3.1 occurs in the presence of sodium methoxide, sodium ethoxide, sodium *t*-butoxide, potassium methoxide, potassium ethoxide, or potassium *t*-butoxide.

[00155] In one embodiment, step 3.1 occurs in the presence of a nitrogen containing base. In one embodiment, step 3.1 occurs in the presence of triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In one embodiment, step 3.1 occurs in the presence of diisoproprylethylamine. In another embodiment, morpholine itself serves as the base.

[00156] Step 3.1 may occur in any solvent or any combination of solvents. In some embodiments, the solvent is, or the combination of solvents contains, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone. In one embodiment, the solvent is acetonitrile. In another embodiment, the solvent is tetrahydrofuran. In yet another embodiment, the solvent is isopropyl acetate.

[00157] The reaction temperature, reaction time and molar ratio of the compound of Formula (VI) to morpholine are important to achieve the optimal conversion of the compound of Formula (V). In certain cases, elevated reaction temperature, prolonged reaction time, and/or large excess of morpholine may result in the formation of a large amount of by-product 1,4-bis(morpholinomethyl)benzene or a salt thereof.

[00158] Step 3.1 may occur at any reaction temperature. In some embodiments, the reaction temperature is from about -100 °C to about 200 °C. In some embodiments, the reaction temperature is from about -50 °C to about 150 °C. In some embodiments, the reaction temperature is from about 0 °C to about 100 °C. In some embodiments, the reaction temperature is about room temperature.

[00159] Step 3.1 may occur at any reaction time. In some embodiments, the reaction time is from about 1 minute to about 14 days. In some embodiments, the reaction time is from about 5 minute to about 48 hours. In some embodiments, the reaction time is from about 1 hour to about 24 hours. In some embodiments, the reaction time is from about 20 hours to no more than 24 hours.

[00160] Step 3.1 may occur at any molar ratio of the compound of Formula (VI) to morpholine. In some embodiments, the molar ratio of the compound of Formula (VI) to

morpholine is from about 10:1 to about 1:10. In some embodiments, the molar ratio of the compound of Formula (VI) to morpholine is from about 5:1 to about 1:5. In some embodiments, the molar ratio of the compound of Formula (VI) to morpholine is from about 3:1 to about 1:3. In some embodiments, the molar ratio of the compound of Formula (VI) to morpholine is from about 1.5:1 to about 1:1.5. In one embodiment, the molar ratio of the compound of Formula (VI) to morpholine is about 1:1.5. In another embodiment, the molar ratio of the compound of Formula (VI) to morpholine is about 1:1.

[00161] Step 3.1 usually results in a mixture of the compound of Formula (V), or a salt thereof, and by-product 1,4-bis(morpholinomethyl)benzene, or a salt thereof. The mixture may be optionally separated by selective extraction in a suitable solvent or a combination of suitable solvents (step 3.2). In some embodiments, the solvent is, or the combination of solvents contains, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone. In one embodiment, the solvent is methanol.

[00162] In one exemplary embodiment, both L are chloro, wherein step 3.1 occurs in a solvent of isopropyl acetate, the reaction temperature is about room temperature, the reaction time is from about 20 hours to no more than 24 hours, and the molar ratio of the compound of Formula (VI) to morpholine is about 1:1.5; and the compound of Formula (V) is optionally purified by selective extraction in methanol.

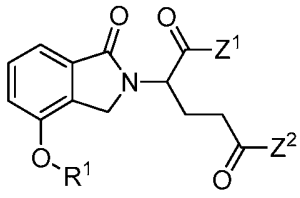
[00163] In another exemplary embodiment, one L is chloro, and the other L is $-OSO_2CH_3$, wherein step 3.1 occurs in the presence of diisopropylethylamine and the solvent is acetonitrile.

6.2.4 Preparation of compound (IV)

[00164] The compound of Formula (IV) may be prepared using methods known to those of ordinary skill in the art. For example, the preparation of a compound of Formula (IV), wherein R is methyl and the compound is in its racemic form, has been reported in U.S. Patent Publication No. 2011/0196150.

[00165] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (IV), comprising

(step 4) deprotecting an enantiomerically enriched or enantiomerically pure compound of Formula (VII):



(VII), wherein

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY; and

R^1 is a suitable phenol protecting group;

under conditions suitable for deprotection.

[00166] Suitable phenol protecting groups are well known to those of ordinary skill in the art. The choice and use of protecting groups and the reaction conditions to install and remove protecting groups are described in *T. W. Green*, *Protective Groups in Organic Synthesis* (Third Ed., Wiley, New York, 1999). In one embodiments, R^1 is methyl, isopropyl, cyclopropylmethyl, *tert*-butyl, cyclohexyl, allyl, propargyl, cyanomethyl, 2-bromoethyl, methoxymethyl (MOM), methylthiomethyl (MTM), methoxyethoxymethyl (MEM), 2-(trimethylsilyl)ethoxymethylamine (SEM), tetrahydropyranyl (THP), benzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), *t*-butyldimethylsilyl (TBDMS), or *t*-butyldiphenylsilyl (TBDPS), formate, acetate, benzoate, methyl carbonate, *t*-butyl carbonate (BOC), benzyl carbonate, dimethylphosphinyl, methanesulfonate, or toluenesulfonate.

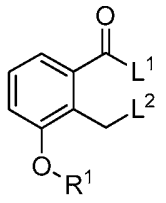
[00167] In one exemplary embodiment, Y is hydrogen, R is *tert*-butyl and R^1 is *t*-butyldimethylsilyl (TBDMS), wherein the reaction occurs in methanol in the presence of tetrabutylammonium fluoride (TBAF).

6.2.5 Preparation of compound (VII)

[00168] The compound of Formula (VII) may be prepared using methods known to those of ordinary skill in the art. For example, the preparation of a compound of Formula (VII), wherein R is methyl, R^1 is *t*-butyldimethylsilyl (TBDMS), and the compound is in its racemic form, has been reported in U.S. Patent Publication No. 2011/0196150.

[00169] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (VII), comprising

(step 5) contacting a compound of Formula (VIII):

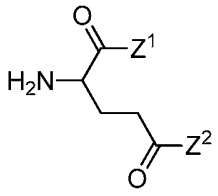


(VIII), wherein

R^1 is a suitable phenol protecting group; L^1 and L^2 are, independently, halogen, OR^2, $OCOR^2$, OSO_2R^2, OPO_3R^2, or a suitable leaving group;

wherein R^2 is saturated, partially saturated, or unsaturated $C_{1\text{-}10}$ alkyl, optionally substituted with one or more halogen; or 5 to 10 membered aryl or heteroaryl, optionally substituted with one or more halogen;

with an enantiomerically enriched or enantiomerically pure compound of Formula (IX), or a salt thereof:



(IX), wherein

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY;

under conditions suitable for cyclization.

[00170] L^1 and L^2 may be, independently, any suitable leaving group known to those of ordinary skill in the art. In one embodiment, L^1 and L^2 are, independently, halogen, methoxy, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, or $-OSO_2C_6H_4$-*p*-Me (*para*-toluenesulfonate). In one embodiment, L^1 is methoxy, and L^2 is bromo.

[00171] In one exemplary embodiment, Y is hydrogen, R is *tert*-butyl, R^1 is *t*-butyldimethylsilyl (TBDMS), L^1 is methoxy, and L^2 is bromo, wherein the reaction occurs in acetonitrile in the presence of KH_2PO_4.

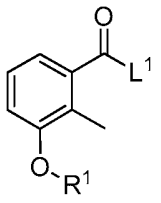
[00172] In another exemplary embodiment, Y is hydrogen, R is methyl, R^1 is *t*-butyldimethylsilyl (TBDMS), L^1 is methoxy, and L^2 is bromo, wherein the reaction occurs in acetonitrile in the presence of diisopropylethylamine.

6.2.6 Preparation of compound (VIII)

[00173] The compound of Formula (VIII) may be prepared using methods known to those of ordinary skill in the art. For example, the preparation of a compound of Formula (VIII), wherein R^1 is *t*-butyldimethylsilyl, L^1 is methoxy, and L^2 is bromo, has been reported in U.S. Patent Publication No. 2011/0196150.

[00174] In one embodiment, provided herein is a process for preparing a compound of Formula (VIII), comprising

(step 6) halogenating a compound of Formula (X) at its benzylic position:



(X);

under conditions suitable for halogenations.

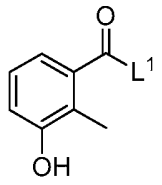
[00175] In one embodiment, the halogenation reaction is free radical bromination. The free radical bromination may be initiated by ultraviolet radiation, sunlight, or heating in the presence of a radical initiator. The bromination reagents and conditions for free radical bromination are well known to those of ordinary skill in the art. In one exemplary embodiment, the bromination reagent is 1-bromopyrrolidine-2,5-dione (NBS), the radical initiator is 2,2'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (AIBN), and the solvent is isopropyl acetate.

6.2.7 Preparation of compound (X)

[00176] The compound of Formula (X) may be prepared using methods known to those of ordinary skill in the art. For example, the preparation of a compound of Formula (X), wherein R^1 is *t*-butyldimethylsilyl, and L^1 is methoxy, has been reported in U.S. Patent Publication No. 2011/0196150.

[00177] In one embodiment, provided herein is a process for preparing a compound of Formula (X), comprising

(step 7) reacting a compound of Formula (XI):



(XI);

with a protecting group under conditions suitable for protection.

[00178] In one exemplary embodiment, L^1 is methoxy, wherein the protection occurs in a solvent of N,N-diemethylformamide, and in the presence of *tert*-butyldimethylsilyl chloride and imidazole.

6.2.8 Preparation of compound (XI)

[00179] The compound of Formula (XI) may be prepared using methods known to those of ordinary skill in the art. For example, the preparation of a compound of Formula (XI), wherein L^1 is methoxy, has been reported in U.S. Patent Publication No. 2011/0196150.

[00180] In one embodiment, provided herein is a process for preparing a compound of Formula (XI), comprising

(step 8) reacting 3-hydroxy-2-methylbenzoic acid with an alcohol under conditions suitable for esterification.

[00181] The methods for preparing an ester from an acid are well known to those of ordinary skill in the art. In some embodiments, the esterification occurs by reacting the acid with an alcohol under an acidic condition. In one exemplary embodiment, the alcohol is methanol and the reaction occurs in the presence of sulfuric acid.

6.2.9 Additional embodiments

[00182] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure (*S*)- 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, wherein Y is

hydrogen, R is *tert*-butyl, and step 1.1 and step 1.2 occur in one-pot in the presence of benzenesulfonic acid; wherein L is chloro, and step 2 occurs in the presence of K_2CO_3.

[00183] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure (*S*)- 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, wherein Y is hydrogen, R is *tert*-butyl, and step 1.1 and step 1.2 occur in one-pot in the presence of benzenesulfonic acid; wherein L is chloro, and step 2 occurs in the presence of K_2CO_3; wherein step 3.1 occurs in a solvent of isopropyl acetate, the reaction temperature is about room temperature, the reaction time is from about 20 hours to no more than 24 hours, and the molar ratio of the compound of Formula (VI) to morpholine is about 1:1.5; and the compound of Formula (V) is optionally purified by selective extraction in methanol.

[00184] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure (*S*)- 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, wherein Y is hydrogen, R is *tert*-butyl, and step 1.1 and step 1.2 occur in one-pot in the presence of benzenesulfonic acid; wherein L is chloro, and step 2 occurs in the presence of K_2CO_3; wherein R^1 is *t*-butyldimethylsilyl (TBDMS), step 4 occurs in methanol in the presence of tetrabutylammonium fluoride (TBAF).

[00185] In one embodiment, provided herein is a process for preparing an enantiomerically enriched or enantiomerically pure (*S*)- 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable form thereof, comprising:

(step 1.1) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II), or a salt thereof, to an enantiomerically enriched or enantiomerically pure compound of Formula (III), or a salt thereof, under conditions suitable for ester to acid transformation;

(step 1.2) cyclizing the enantiomerically enriched or enantiomerically pure compound of Formula (III) to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a) under conditions suitable for cyclization;

(step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I) under conditions suitable for deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation;

wherein step 1.1 and step 1.2 occur in one-pot; and

wherein the enantiomerically enriched or enantiomerically pure compound of Formula (II) is prepared by a process comprising:

(step 2) contacting an enantiomerically enriched or enantiomerically pure compound of Formula (IV) with a compound with Formula (V), or a salt thereof, under conditions suitable for displacement;

wherein the compound of Formula (V) is prepared by a process comprising:

(step 3.1) contacting a compound of Formula (VI) with morpholine, or a salt thereof, under conditions suitable for displacement; and

(step 3.2) optionally purifying the compound of Formula (V) by selective extraction;

wherein the enantiomerically enriched or enantiomerically pure compound of Formula (IV) is prepared by a process comprising:

(step 4) deprotecting an enantiomerically enriched or enantiomerically pure compound of Formula (VII) under conditions suitable for deprotection;

wherein the enantiomerically enriched or enantiomerically pure compound of Formula (VII) is prepared by a process comprising:

(step 5) contacting a compound of Formula (VIII) with an enantiomerically enriched or enantiomerically pure compound of Formula (IX), or a salt thereof, under conditions suitable for cyclization;

wherein the compound of Formula (VIII) is prepared by a process comprising:

(step 6) halogenating a compound of Formula (X) at its benzylic position under conditions suitable for halogenation;

wherein the compound of Formula (X) is prepared by a process comprising:

(step 7) reacting a compound of Formula (XI) with a protecting group under conditions suitable for protection;

wherein the compound of Formula (XI) is prepared by a process comprising:

(step 8) reacting 3-hydroxy-2-methylbenzoic acid with an alcohol under conditions suitable for esterification;

wherein R, R^1, R^2, Y, L, L^1, and L^2 are as defined above and herein.

[00186] All of the combinations of the above embodiments are encompassed by this invention.

[00187] It is to be understood that the processes of the present invention are also suitable for the preparation of the R-enantiomer or racemate of 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, via replacing the compound of Formula (IX) with its corresponding R-enantiomer or racemate. Additionally, the racemate of 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione may be synthesized by the racemization of any enantiomerically enriched or pure compounds on the synthetic route according to methods known in the art and provided herein.

6.3 Enhancement of Enantiopurity

[00188] In one embodiment, provided herein are methods of increasing the enantiopurity of a compound of Formula (I), or a salt and/or solvate thereof. Generally, enantiopurity can be increased by recrystallization or trituration under conditions that lead to optimal ee_{eu}.

[00189] In one embodiment, provided herein is a process for increasing or enhancing the enantiopurity of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a salt and/or solvate thereof, comprising recrystallization or trituration of a first sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a salt and/or solvate thereof, in a solvent or a mixture of solvents, resulting in a second sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a salt and/or solvate thereof, wherein the second sample has a higher ee than the first sample.

[00190] In one embodiment, the enantiopurity is increased by recrystallization. In another embodiment, the enantiopurity is increased by trituration.

[00191] In one embodiment, the enantiopurity may increase by 1%, 5%, 10%, 15%, 20%, 25%, 30% or more after the recrystallization or trituration as compared to the enantiopurity before the recrystallization or trituration.

[00192] The first sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (*i.e.*, the sample whose enantiopurity is to be increased) may be in anhydrous form, freebase form, hydrate form, solvate form, salt form, or any combination thereof. In one embodiment, the first sample is in the anhydrous freebase form. In another embodiment, the first sample is in the freebase hydrate form. In another embodiment, the first sample is in the freebase THF solvate form. In yet another embodiment, the first sample is in the HCl salt form. In yet another preferred embodiment, the first sample is in the anhydrous HCl salt form.

[00193] The ee of the first sample may be from 0% to about 95%. In one embodiment, the ee of the first sample is from about 25% to about 90%. In one embodiment, the ee of the first sample is from about 50% to about 80%. In one embodiment, the ee of the first sample is about 75%.

[00194] The recrystallization or trituration may occur in any solvent or any combination of solvents. In some embodiments, the solvent is, or the combination of solvents contains, water, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone. In one embodiment, the solvent is acetonitrile. In another embodiment, the solvent is tetrahydrofuran.

[00195] In one embodiment, the solvent is an alcohol. In one embodiment, the solvent is methanol.

[00196] In one embodiment, the solvent is a mixture of alcohol and water. In one embodiment, the solvent is a mixture of isopropyl alcohol and water. In one embodiment, the solvent is a 90:10 mixture of isopropyl alcohol and water. In another embodiment, the solvent is a 95:5 mixture of isopropyl alcohol and water.

[00197] The recrystallization or trituration may occur at any temperature. In some

embodiments, the temperature is from about 0 °C to about 100 °C. In some embodiments, the temperature is from about 10 °C to about 80 °C. In one embodiment, the temperature is about 22 °C. In another embodiment, the temperature is about 55 °C.

[00198] The second sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (*i.e.*, the compound after increase of enantiopurity) may be in a same or different form as that of the first sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. In one embodiment, the second sample is in a different form as that of the first sample. In another embodiment, the second sample is in a same form as that of the first sample. In one embodiment, both the first and the second samples are in the HCl salt form.

[00199] The ee of the second sample is higher than the ee of the first sample. In one embodiment, the ee of the second sample is no less than about 50%, no less than about 60%, no less than about 70%, no less than about 80%, no less than about 85%, no less than about 90%, no less than about 91%, no less than about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, no less than about 99.9%, no less than about 99.95%, no less than about 99.99%, or about 100%.

[00200] In one embodiment, the first sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione is in the HCl salt form having an ee of 75%, the trituration occurs in methanol at 55 °C, resulting in a second sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione in the HCl salt form having an ee of 97.5%.

[00201] All of the combinations of the above embodiments are encompassed by this invention.

7. EXAMPLES

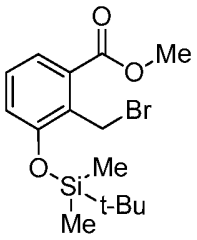
[00202] As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of

the American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μL (microliters); M (molar); mM (millimolar); μM (micromolar); eq. (equivalent); mmol (millimoles); Hz (Hertz); MHz (megahertz); hr or hrs (hour or hours); min (minutes); and MS (mass spectrometry). Unless otherwise specified, the water content in a compound provided herein is determined by Karl Fisher (KF) method.

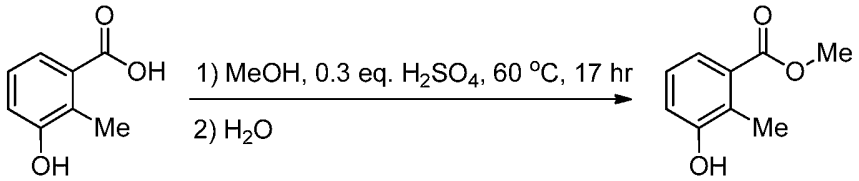
[00203] For all of the following examples, unless otherwise specified, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise specified, all temperatures are expressed in °C (degrees Centigrade). All reactions were conducted at room temperature unless otherwise noted. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

Example 1

Synthesis of methyl 2-(bromomethyl)-3-((*tert*-butyldimethylsilyl)oxy)benzoate



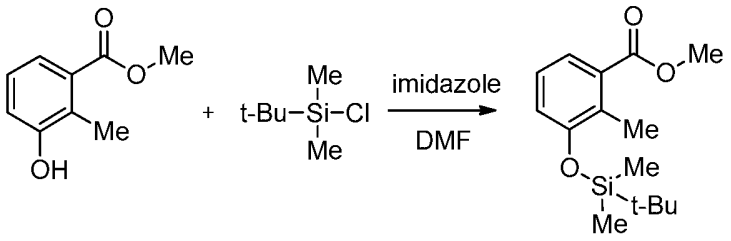
Step 1:



[00204] 3-Hydroxy-2-methylbenzoic acid (250 g, 1.32 mole) was added to methanol (2500 mL, 10X) in a jacketed bottom drop three neck flask under nitrogen. Sulfuric acid (48.3 g, 0.49 mole) was added to the above solution. The mixture was heated to 60 °C and stirred for 8

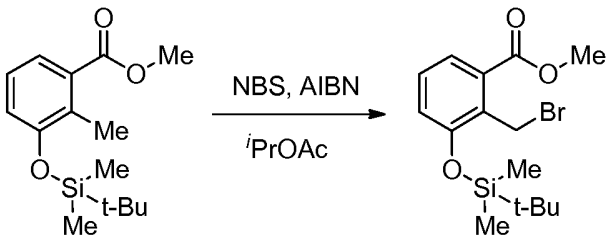
to 17 hours. Once conversion was >98%, the mixture was atmospherically distilled to 3X volume. The residue was cooled to 20 °C and slowly added to water (500 mL, 2X) over at least 30 minutes. Seeds (2 g, 0.01X) were added and the mixture was agitated at 20 °C for at least 1 hour. Water (1500 mL, 6X) was added at 20 °C over at least 3 hours and the mixture was agitated at 20 °C for at least one additional hour. The solid was filtered, and washed three times with 9:1 water: methanol (500 mL, 2X each) until pH ≥ 3. The solid was dried under vacuum at 35 to 45°C until KF ≤ 0.1% to give methyl 3-hydroxy-2-methylbenzoate (235.3 g, 86% yield); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.68 (s, 1H), 7.18 (dd, J = 7.5, 1.2 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.00 (dd, J = 8.1, 1.2 Hz, 1H), 3.80 (s, 3H), 2.29 (s, 3H) ppm.

Step 2:



[00205] Methyl 3-hydroxy-2-methylbenzoate (110 g, 662 mmol) was added to DMF (660 mL, 6X) in a 3 liter jacketed bottom drop reactor. The mixture was cooled to 5 °C, and imidazole (113 g, 1655 mmol, 1.03X) was added to the solution. *tert*-Butyldimethylsilyl chloride (110 g, 728 mmol, 1X) was added, and the mixture was agitated at 5 °C for 1 hour. The mixture was warmed up to 20 °C and agitated for at least 2 hours until no more than 0.2% of the starting phenol was left. Isopropyl acetate (770 mL, 7X) was added, then water (1100 mL, 10X) was slowly added, keeping temperature below 30 °C. The mixture was agitated, settled, and split. The organic layer was washed three additional times with water (770 mL, 7X each), and distilled under vacuum at 40 to 55 °C to 6X volume and until KF was no more than 0.05%. The methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-methylbenzoate product was stored as isopropyl acetate solution, which was used in the next step without further purification (expected 168 g, 90% yield); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.15 (dd, J = 7.8, 1.2 Hz, 1H), 6.97 (t, J = 7.8 Hz, 1H), 6.82 (dd, J = 8.1, 1.2 Hz, 1H), 3.60 (s, 3H), 2.29 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H) ppm.

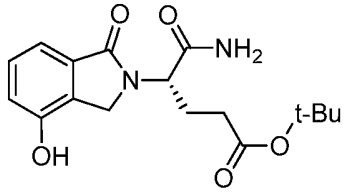
Step 3:



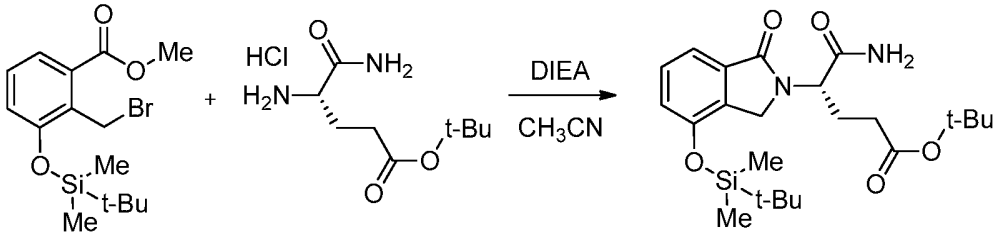
[00206] The isopropyl acetate solution of methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-methylbenzoate (157 g, 560 mmol, from step 2, with an amount of residue free phenol ≤ 0.2%) was added to a 3 liter jacketed bottom drop reactor. Additional isopropyl acetate was added and the mixture was distilled under vacuum at 40 to 55 °C, if necessary, to bring total volume to about 9X (1410 mL, KF ≤ 0.05%). 1-Bromopyrrolidine-2,5-dione (NBS, 103.6 g, 580 mmol, 0.66X) and 2,2'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (AIBN, 1.9 g, 11 mmol, 0.012X) were added to the solution. The reaction mixture was heated to 70 °C over at least 2 hours and stirred at 70 °C for 2 hours. The color changed from orange to yellow. If conversion was less than 95%, additional 0.05 molar equiv. of NBS was added and the mixture was stirred at 70 °C for 1 hour. The process was repeated, in necessary, until conversion reached 95%. The mixture was cooled to 20 °C and held at 20 °C for at least 1 hour. The solid (succinimide) was filtered and washed with isopropyl acetate (75 mL, 0.5X). The filtrate was washed with solution of sodium sulfite (157 g, 1X) in water (1413 mL, 9X), followed by water (315 mL, 2X). The organic layer was distilled under vacuum at 30 to 40 °C to ~2X volume. Additional isopropyl acetate (315 mL, 2X) was added and distilled back to 2X volume, if necessary, until KF was no more than 0.1%. Then the organic layer was distilled at 30 to 40 °C to give methyl 2-(bromomethyl)-3-((*tert*-butyldimethylsilyl)oxy)benzoate as an oil (expected 180 g, 90% yield); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.47 (dd, J = 7.8, 1.2 Hz, 1H), 7.37 (t, J = 8.1 Hz, 1H), 7.15 (dd, J = 8.1, 1.2 Hz, 1H), 4.96 (s, 2H), 3.86 (s, 3H), 1.03 (s, 9H), 0.30 (s, 6H) ppm.

Example 2

Synthesis of (*S*)-*tert*-butyl 5-amino-4-(4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate

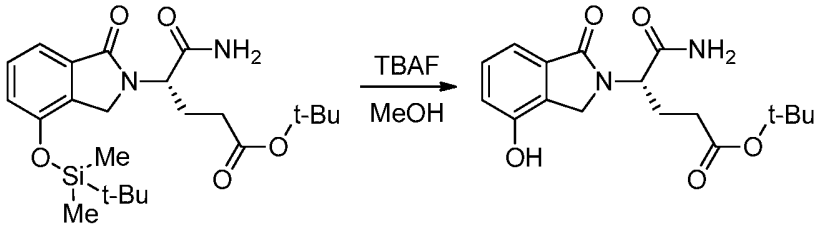


Step 1:



[00207] Methyl 2-(bromomethyl)-3-((*tert*-butyldimethylsilyl)oxy)benzoate (250 g, 696 mmol) and (*S*)-*tert*-butyl 4,5-diamino-5-oxopentanoate hydrochloride (183 g, 765 mmol) were added to acetonitrile (2150 mL, 8.6X) in a 5 liter jacketed bottom drop vessel with overhead agitation under nitrogen. Diisopropylethylamine (DIEA, 303 mL, 1.74 mmol, 1.2X) was added, and the mixture was heated at 45 to 50 °C for 24 to 45 hours. Once conversion was ≥ 97%, the mixture was distilled under vacuum below 50 °C to 4X volume. An aqueous wash solution of KH_2PO_4 (190 g, 1.32 mmol, 0.75X) in water (2500 mL, 10X) was prepared in a separate vessel. The reaction mixture was cooled to 20 to 25 °C, and methyl *tert*-butyl ether (MTBE, 1500 mL, 6X) was added. The mixture was washed twice with half of the phosphate solution and twice with water (500 mL, 2X). The mixture was atmospherically distilled to 4X volume (1000 mL). Additional MTBE was added and the mixture was distilled back to 4X volume, if necessary, until KF was ≤ 0.2%. Methanol (1500 mL, 6X) was then added, and the mixture was distilled under vacuum at 25 to 35 °C to 4X volume. Additional methanol was added and the mixture was distilled back to 4X volume, if necessary, until MTBE was no more than 5% with respect to methanol by mole). The crude (*S*)-*tert*-butyl 5-amino-4-(4-((*tert*-butyldimethylsilyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate was used in the next step without further purification.

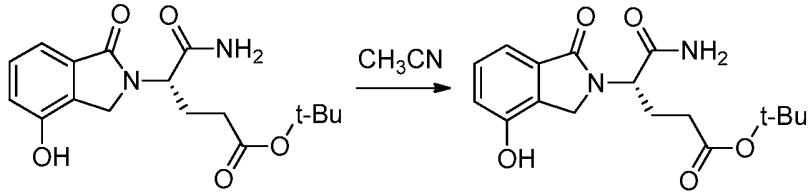
Step 2:



[00208] Methanol (1500 mL, 6X) was added to the crude (*S*)-*tert*-butyl 5-amino-4-(4-

((*tert*-butyldimethylsilyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate from step 1. Tetrabutylammonium fluoride trihydrate (35 g, 0.14X) was added. The mixture was agitated at 15 to 25 °C for 12 to 24 hours. The agitation was prolonged, if necessary, until conversion reached 99.5%. The mixture was distilled under vacuum below 45 °C to 3.5 to 4X volume (875 to 1000 mL). Baffle was inserted into the reactor, the temperature was adjusted to 15 to 25 °C, and seeds (1.25 g, 0.005X) were added. Water (1750 mL, 7X) was added over 7 hours. The mixture was agitated for 12 to 24 hours. The solid was filtered, washed with water (500 mL, 2X), and dried under reduced pressure with nitrogen bleed at 40 °C until KF ≤ 0.5%. The crude (*S*)-*tert*-butyl 5-amino-4-(4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate was used in the next step without further purification.

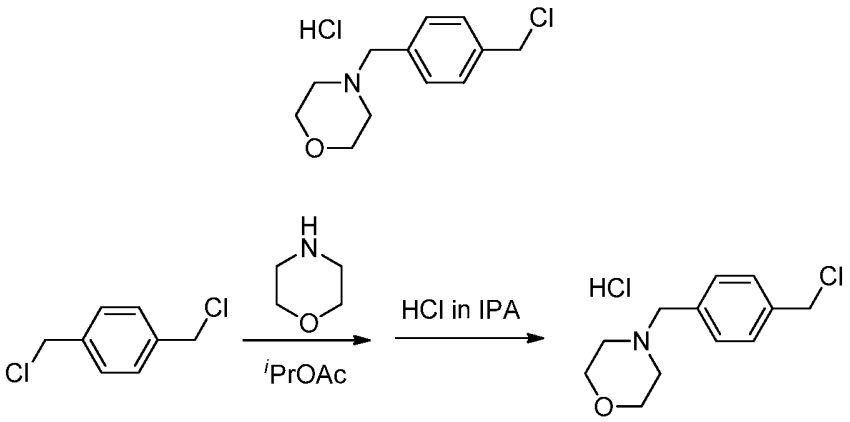
Step 3:



[00209] The crude (*S*)-*tert*-butyl 5-amino-4-(4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate from step 2 was added to acetonitrile (750 mL, 3X) in a 2 liter flask with overhead agitation, thermocouple and nitrogen atmosphere. The mixture was heated to 60 to 70 °C and agitated in this range for 4 to 5 hours. The mixture was cooled to 15 to 25 °C over 4 to 5 hours and agitated in this range for 12 to 24 hours. The solid was filtered, washed with acetonitrile (250 mL, 1X), and dried under reduced pressure with nitrogen sweep at 35 to 45 °C until Loss On Drying (LOD) ≤ 1% to give (*S*)-*tert*-butyl 5-amino-4-(4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate (182 g, 78% yield); MS *m/z*: 335.1 (M+1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.03 (s, 1H), 7.56 (br s, 1H), 7.31 (dd, J = 7.8, 7.8 Hz, 1H), 7.18 (br s, 1H), 7.15 (dd, J = 7.5, 0.6 Hz, 1H), 6.98 (dd, J = 7.8, 0.6 Hz, 1H), 4.71 (dd, J = 10.2, 4.2 Hz, 1H), 4.49 (d, J = 17.7 Hz, 1H), 4.32 (d, J = 17.4 Hz, 1H), 2.21 – 1.93 (m, 4H), 1.34 (s, 9H) ppm.

Example 3

Synthesis of 4-(4-(chloromethyl)benzyl)morpholine hydrochloride



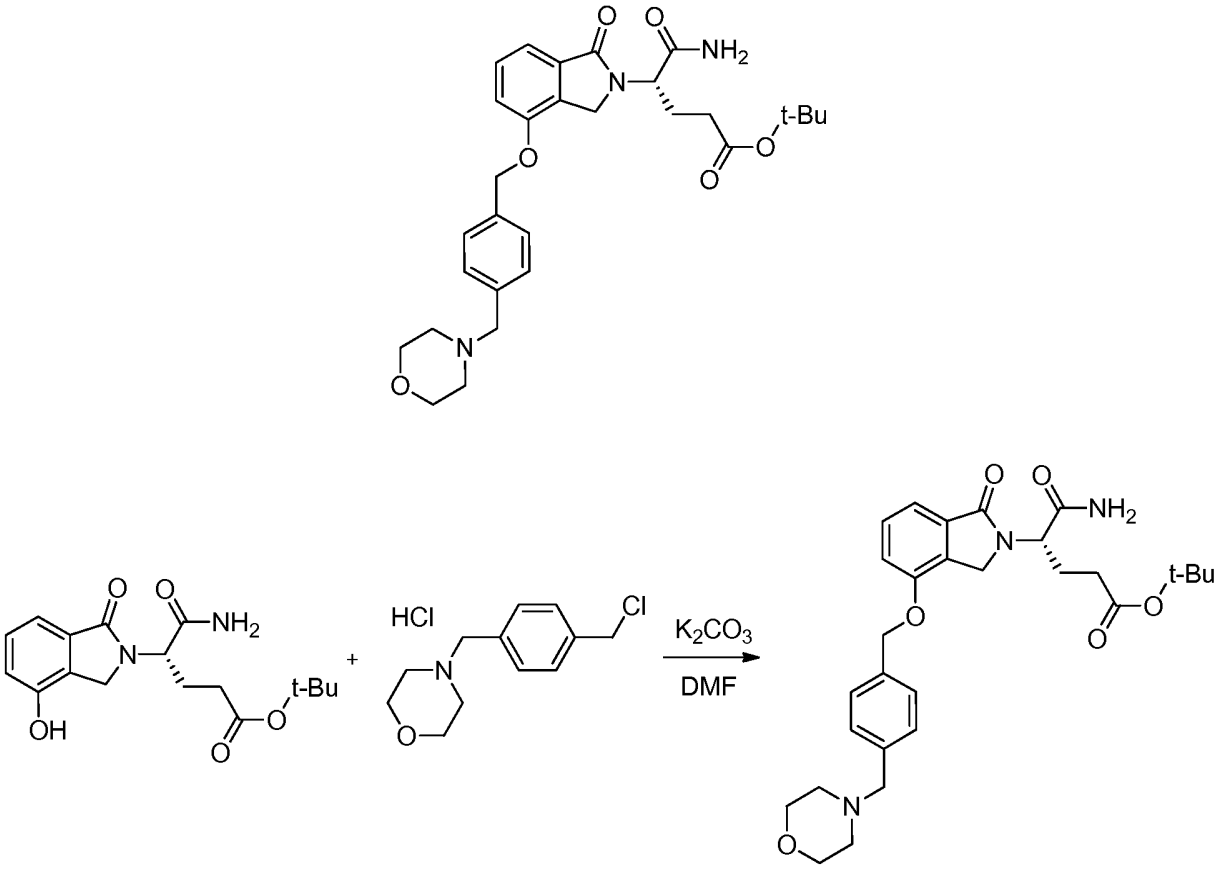
[00210] 1,4-Bis(chloromethyl)benzene (50 g, 286 mmol) was added to isopropyl acetate (500 mL, 10X) in a reaction vessel. Once the solid dissolved, morpholine (37.5 mL, 428 mmol) was added in a single portion. The mixture was stirred at room temperature for 20 to no more than 24 hours. The solid (morpholine-HCl and bis-morpholine by-product) was filtered and washed with isopropyl acetate (50 mL). The filtrate was washed twice with water (125 mL) and once with 5% brine (100 mL). The organic phase was dried azeotropically or with $MgSO_4$. HCl in 2-propanol (IPA, 50 mL, 5 – 6 N) was added to the dried organic phase. The first 20 mL was added slowly to establish a good seed bed. The resulting white solid was filtered, washed with isopropyl acetate (100 mL), dried on the filter to constant weight to give crude product (39.4 g, including 80.3% strength product and 19.7% bis-morpholine by-product, 56.4% yield).

[00211] The crude product (2.0 g, 80.3% strength, 48.8 mmol) was added to methanol (20 mL, 10X), and the mixture was stirred at room temperature for 3 hours. The solid (bis-morpholine by-product) was filtered and NOT rinsed. Isopropyl acetate (20 mL) was added to the filtrate, and methanol was removed by distillation at atmospheric pressure. Methanol removal was considered sufficiently complete when the head temperature dropped rapidly from the boiling temperature of methanol (64 – 65 °C). The mixture was cooled to room temperature and stirred overnight. The resulting solid was filtered by rapid vacuum filtration, washed with isopropyl acetate (1 – 2 mL), dried on funnel over vacuum to constant weight, to give 4-(4-(chloromethyl)benzyl)morpholine hydrochloride as a white crystal product (1.3 g, 81% yield);

MS *m/z*: 226.1, 228.0 (M+1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.56 (br s, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 4.79 (s, 2H), 4.32 (d, J = 5.4 Hz, 2H), 3.94 – 3.78 (m, 4H), 3.20 – 3.00 (m, 4H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 138.9, 131.8, 129.3, 129.1, 63.0, 58.4, 50.6, 45.5 ppm.

Example 4

Synthesis of (*S*)-*tert*-butyl 5-amino-4-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate

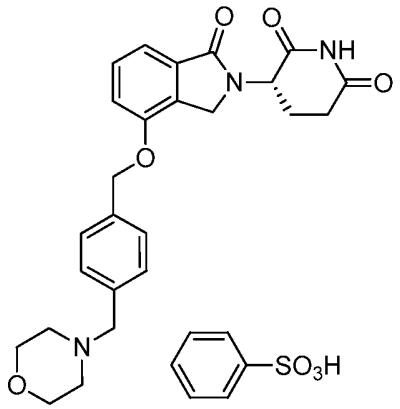


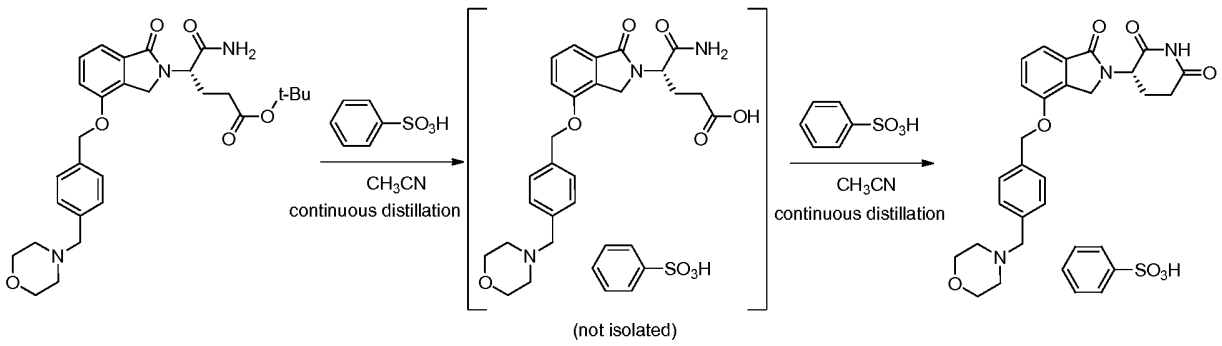
[00212] (*S*)-*tert*-Butyl 5-amino-4-(4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate (160 g), 4-(4-(chloromethyl)benzyl)morpholine hydrochloride (138 g, 0.87X) and potassium carbonate (165 g, 1.04X) were added to DMF (960 mL, 6X) in a 5 liter jacketed vessel. The mixture was heated to 40 to 50 °C and agitated for 12 to 24 hours. The mixture was cooled to 25 to 35 °C, then ethyl acetate (1600 mL, 10X) and water (1600 mL, 10X) were added. The

mixture was agitated at 25 to 35 °C, settled, and split. Additional ethyl acetate (800 mL, 5X) and water (800 mL, 5X) were added. The mixture was agitated at 25 to 35 °C, settled, and split. The combined organic phase was washed four times with water (400 mL, 2.5X). The organic phase was distilled under vacuum below 50 °C to 6X volume. Additional ethyl acetate (2880 mL, 18X) was continuously added, and the distillation was continued to maintain about 6X volume. The temperature was adjusted to 40 to 45 °C, then seeds (0.8 g, 0.005X) were added. The mixture was held for about 30 minutes to build seed bed, then heptane (960 mL, 6X) was added over about 1.5 hours. The mixture was cooled to 15 to 25 °C over about 1 to 1.5 hours, agitated at 15 to 25 °C for at least one hour, and held for 16 hours. The solid was filtered, washed with heptane: ethyl acetate (5X total, 2.5X heptane, 2.5X ethyl acetate), and dried under reduced pressure with nitrogen sweep at 35 to 45 °C until LOD ≤ 1%, to give (*S*)-*tert*-butyl 5-amino-4-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate as a white solid (215.3 g, 86% yield); MS *m/z*: 524.3 (M+1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.57 (br s, 1H), 7.48 – 7.43 (m, 3H), 7.34 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.19 (br s, 1H), 5.21 (s, 2H), 4.71 (dd, J = 10.2, 4.2 Hz, 1H), 4.54 (d, J = 17.4 Hz, 1H), 4.40 (d, J = 17.7 Hz, 1H), 3.56 (dd, J = 4.5, 4.5 Hz, 4H), 3.45 (s, 2H), 2.34 (dd, J = 4.5, 4.5 Hz, 4H), 2.15 – 1.99 (m, 4H), 1.32 (s, 9H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.8, 171.3, 167.8, 153.4, 137.7, 135.3, 133.3, 130.2, 129.5, 129.0, 127.6, 115.1, 114.6, 79.7, 69.4, 66.2, 62.1, 53.5, 53.1, 44.8, 31.8, 27.6, 24.8 ppm.

Example 5

Synthesis of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione besylate

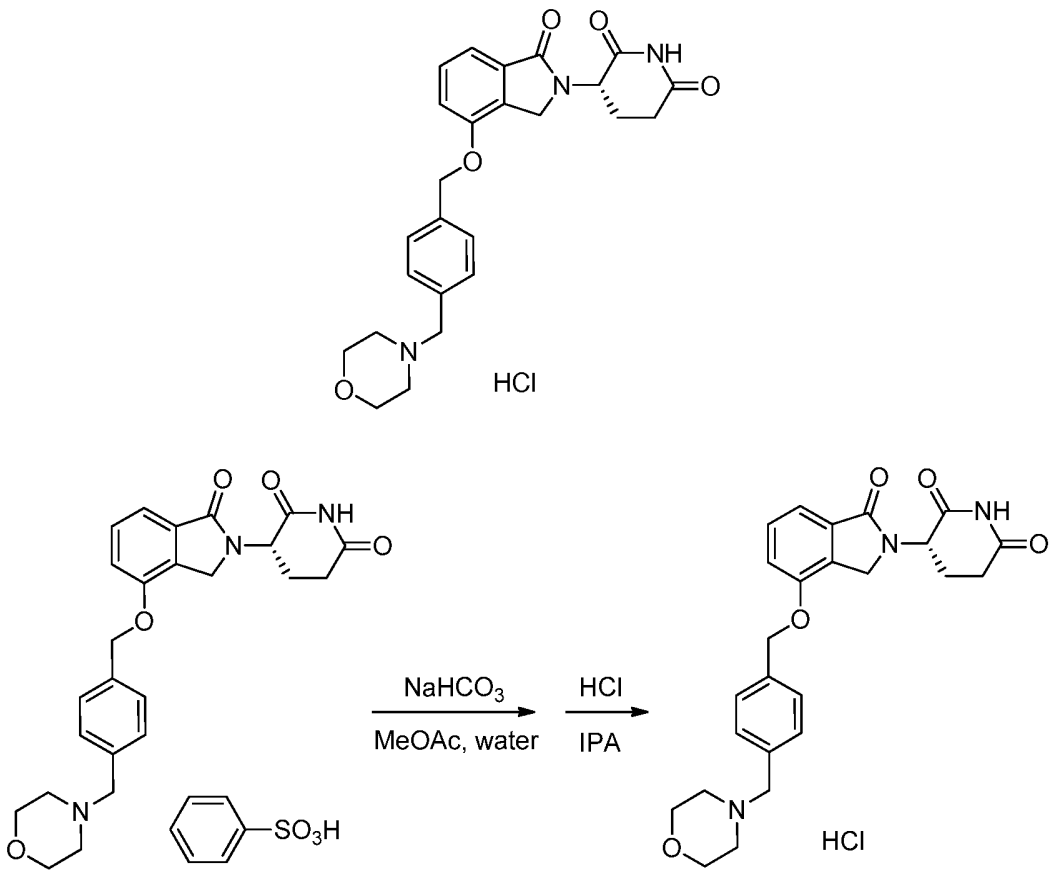




[00213] Benzenesulfonic acid (68.7 g, 0.39X) was added to acetonitrile (1400 mL, 8X) in a 5 liter jacketed flask equipped with overhead agitation, thermocouple, addition funnel, and a Dean Stark trap with condenser, with nitrogen flowing from the addition funnel, over the reaction, and out the condenser. The mixture was atmospherically continuously distilled with acetonitrile, if necessary, until KF ≤ 0.1%. (*S*)-*tert*-Butyl 5-amino-4-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate (175 g, 1X) was then added. The mixture was distilled at 90 °C at a rate of 1 to 3X volume of acetonitrile per hour for 4 hours. Seeds (1.75 g, 0.01X, as a slurry in 17.5 mL of acetonitrile) were added. The mixture was continuously distilled at a rate of 1 to 3X volume of acetonitrile per hour for 4 to 5 additional hours (8 to 9 hours total). The mixture was cooled to 15 to 25 °C over about 1 to 4 hours, and agitated at 15 to 25 °C for at least 1 hour. The solid was filtered, washed with acetonitrile (350 mL, 2X), and dried under reduced pressure at 35 to 50 °C with nitrogen bleed, to give (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione besylate as a white solid (169.1 g, 83% yield); MS *m/z*: 450.3 (M+1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.98 (s, 1H), 9.74 (br s, 1H), 7.61 – 7.56 (m, 4H), 7.53 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.53 – 7.26 (m, 5H), 5.31 (s, 2H), 5.12 (dd, J = 13.2, 5.1 Hz, 1H), 4.44 (d, J = 17.4 Hz, 1H), 4.37 (br d, J = 4.8 Hz, 2H), 4.27 (d, J = 17.4 Hz, 1H), 3.96 (br d, J = 12.6 Hz, 2H), 3.61 (br dd, J = 11.4, 11.4 Hz, 2H), 3.26 (br d, J = 12.3 Hz, 2H), 3.17 – 3.10 (m, 2H), 2.92 (ddd, J = 17.7, 13.8, 5.4 Hz, 1H), 2.59 (br d, J = 16.5 Hz, 1H), 2.43 (dddd, J = 17.4, 13.2, 13.2, 4.2 Hz, 1H), 2.01 – 1.97 (m, 1H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.9, 171.0, 168.0, 153.3, 148.2, 138.3, 133.4, 131.5, 130.0, 129.9, 128.8, 128.5, 127.9, 127.7, 125.5, 115.4, 115.0, 69.0, 63.2, 59.0, 51.6, 50.9, 45.1, 31.2, 22.4 ppm.

Example 6

Synthesis of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride

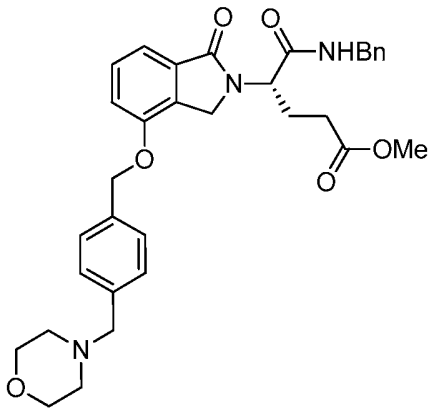


[00214] (*S*)-3-(4-((4-(Morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione besylate (75 g, 1X) and sodium bicarbonate (11.4 g, 0.15X) were added to methyl acetate (1350 mL, 18X) and water (300 mL, 4X) in a 3 liter jacketed bottom drop vessel with overhead agitation and nitrogen blanket. The mixture was agitated at 15 to 25 °C until the solid dissolved. The mixture was settled and split. Water (75 mL, 1X) was added to the organic phase, agitated for 5 minutes at 15 to 25 °C, settled, and split. 6M HCl (24.7 mL, 0.33X) was added to isopropanol (IPA, 300 mL, 4X) in a separate vessel with good agitation. Seeds (1.5 g, 0.02X) were added to the HCl/IPA solution and the temperature was adjusted to 35 to 45 °C. The methyl acetate solution was then added to the HCl/IPA solution over 4 to 5 hours. After addition, the mixture was agitated at 40 °C for 0.5 hour, cooled to 22 °C over 0.5 hour, and held at 22 °C overnight (~16 hours). The solid was filtered, washed twice with methyl acetate (225

mL, 3X, each time), and dried under reduced pressure with nitrogen bleed at 40 °C, to give (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride as a white solid (48.1 g, 80% yield, 99.55% purity (HPLC), 98.3% ee); analysis for $C_{25}H_{28}ClN_3O_5$ calculated: C 61.79, H 5.81, N 8.65, Cl 7.30; found C 61.70, H 5.71, N 8.58, Cl 7.46; MS *m/z*: 450.2 (M+1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.56 (s, 1H), 10.97 (s, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 2H), 5.29 (s, 2H), 5.12 (dd, J = 13.2, 5.1 Hz, 1H), 4.44 (d, J = 17.4 Hz, 1H), 4.33 (d, J = 5.4 Hz, 2H), 4.28 (d, J = 17.4 Hz, 1H), 3.93 – 3.79 (m, 4H), 3.19 (d, J = 11.7 Hz, 2H), 3.17 – 3.00 (m, 2H), 2.91 (ddd, J = 18.9, 13.8, 5.4 Hz, 1H), 2.58 (d, J = 18.3 Hz, 1H), 2.43 (dddd, J = 17.4, 13.2, 13.2, 4.2 Hz, 1H), 2.02 – 1.95 (m, 1H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.8, 171.0, 168.0, 153.4, 138.0, 133.4, 131.7, 130.0, 129.8, 128.9, 127.8, 115.4, 115.0, 69.0, 63.0, 58.6, 51.6, 50.6, 45.1, 31.2, 22.4 ppm; the differential scanning calorimetric (DSC) thermogram is depicted in FIG. 1; the X-ray powder diffractogram (XRD) is depicted in FIG. 2; the thermogravimetric (TGA) thermogram is depicted in FIG. 3.

Example 7

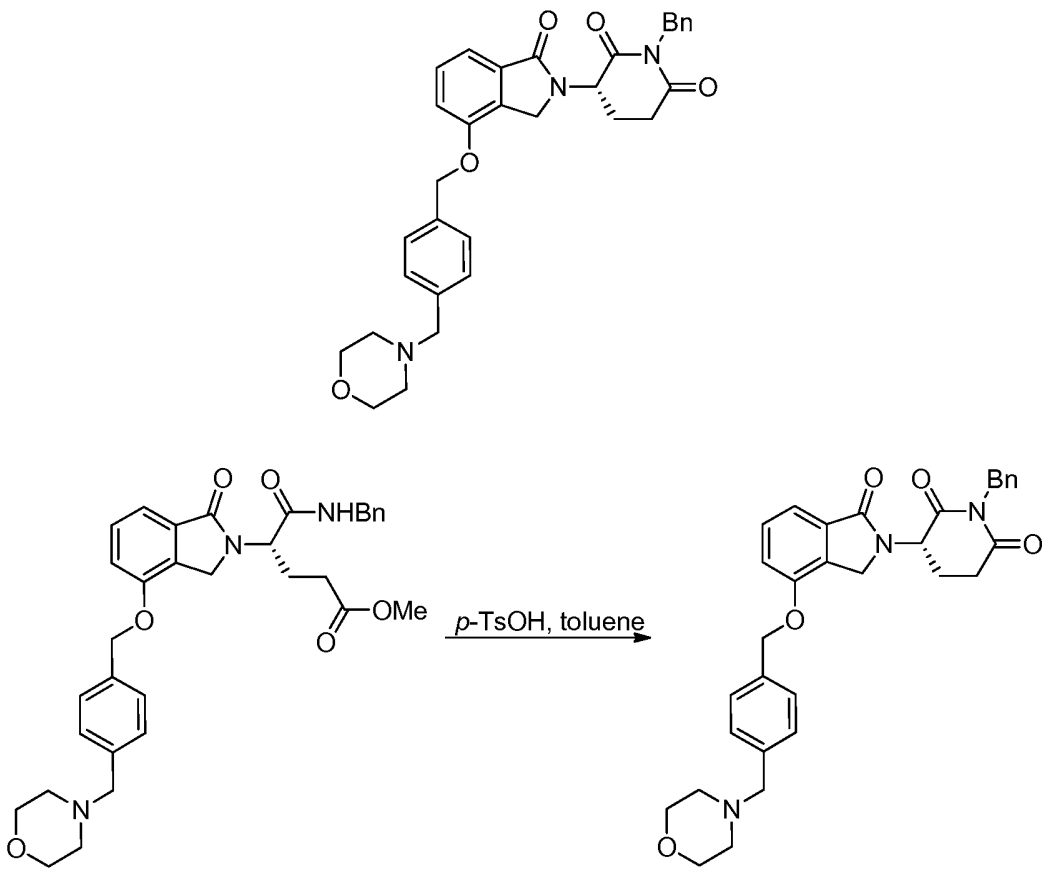
Synthesis of (*S*)-methyl 5-(benzylamino)-4-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate



[00215] (*S*)-Methyl 5-(benzylamino)-4-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate is prepared under the same conditions as examples 2 and 4 by replacing (*S*)-*tert*-butyl 4,5-diamino-5-oxopentanoate hydrochloride with (*S*)-methyl 4-amino-5-(benzylamino)-5-oxopentanoate.

Example 8

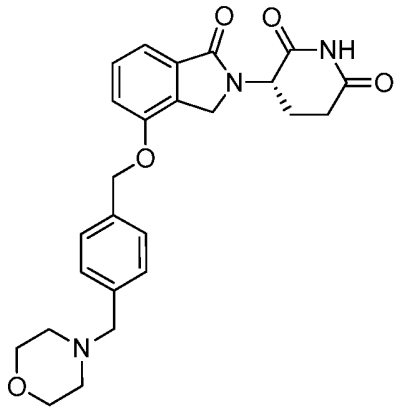
Synthesis of (*S*)-1-benzyl-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione



[00216] A mixture of (*S*)-methyl 5-(benzylamino)-4-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate (2.5 mmol) and *p*-TsOH monohydrate (1.25 mmol) in toluene, under argon, is refluxed for 8 hours. The solvent is evaporated. The crude is taken up in ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 20 mL). The organic layer is dried and purified by silica gel chromatography to afford (*S*)-1-benzyl-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione.

Example 9

Synthesis of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione



[00217] (*S*)-3-(4-((4-(Morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione is prepared from (*S*)-1-benzyl-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione by hydrogenation in acetic acid in the presence of Pd/C for 2 days.

Example 10

Screening of conditions for enhancement of enantiopurity of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione

[00218] Initially the ee_{eu} was evaluated using *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione freebase and its corresponding anhydrous freebase racemic compound in acetonitrile at 22 °C, and was found to be was unfavorably high (94.7%). A hydrated form of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione freebase was subsequently obtained, and the ee_{eu} of the *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrate with its corresponding hydrate racemic compound at 22 °C remained unfavorably high (89.2%). A THF solvate of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione was also obtained, and the ee_{eu} of the solvate with its corresponding anhydrate racemic compound at 22°C was improved (68.5%). However, a THF solvate of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione is not a suitable drug substance due to the toxicity of

THF, and so an alternative approach was sought.

[00219] The ee_{eu} of the HCl salt of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione and the HCl salt of the corresponding racemic compound was studied and found to be dependent on the ratio of water:co-solvent (isopropanol was used as co-solvent) at 22 °C, which suggested the presence of a hydrate of either or both of the *(S)*-enantiomer or the racemic compound (FIG. 4). Physical characterization confirmed that the HCl salt of the racemic compound was a hydrate, which was determined to be a thermodynamically stable crystal form. The HCl salt of the single enantiomer remained as the thermodynamically stable anhydrous form. The ee_{eu} at low water fractions (~5%) was favorably low (~70%) but the absolute solubility was quite low. The quantities of solvent and equipment capacity needed to provide chiral upgrade would be impractical and uneconomical. For instance, to upgrade from 90% ee to 98% ee, it was calculated to require 200 L solvent per kg starting material.

[00220] A methanol solvate of the HCl salt of racemic 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione was subsequently produced and showed a slightly modified XRPD pattern from the corresponding hydrate. In the presence of methanol, at ambient temperature (22 °C), a favorable ee_{eu} between the HCl salts of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione and the corresponding racemic compound was achieved (72.4%). From this ee_{eu}, it was calculated that achieving an upgrade from 90% ee to 98% ee would require 46 L solvent per kg starting material which, while an improvement, is still undesirable.

[00221] Solvated crystalline forms often have lower melting points than their anhydrous counterparts, and by extension have a relatively greater solubility as temperature is increased, relative to the corresponding anhydrate. This phenomenon was used to obtain improved ee_{eu}. The eutectic solubility of the HCl salt was determined as a function of temperature for neat methanol, 90/10 isopropanol/water and 95/5 isopropanol/water (FIG. 5). In all three systems, it was confirmed that ee_{eu} decreased as temperature increased, as expected from the general solvate/anhydrate thermodynamic relationship.

[00222] The methanol system showed the strongest sensitivity to temperature and

generally a low ee_{eu}. The lowest ee_{eu} obtained across all crystal forms of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, solvents and temperatures occurred with the HCl salt in methanol at 55 °C, with ee_{eu} = 8%. Based on this result, it was calculated that to upgrade from 90% ee to 98% ee at 55 °C in methanol would require 2.1 L solvent per kg starting material, which is a vast improvement over other conditions.

Example 11

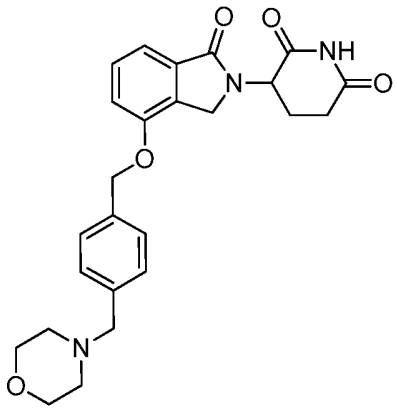
Trial run for enhancement of enantiopurity of (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride

[00223] A crude *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride mixture (4 g) with 75% ee was triturated in 28 mL methanol at 55 °C for approx. 1.5 hours and then filtered at 55 °C. The wet product was then washed with methanol and dried in a vacuum oven. The resulting enantiopurity of the dried product was determined to be 97.5% ee (2.5 g, 70% recovery yield of the *(S)*-enantiomer).

CLAIMS

What is claimed is:

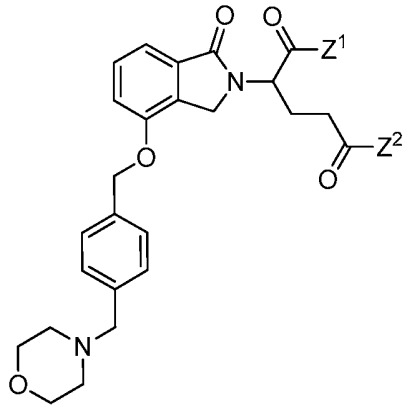
1. A process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (I):



(I)

or a pharmaceutically acceptable form thereof, comprising

(step1.1) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II):



(II)

or a salt thereof, wherein

(i) Z^1 is NHY, and Z^2 is OR; or

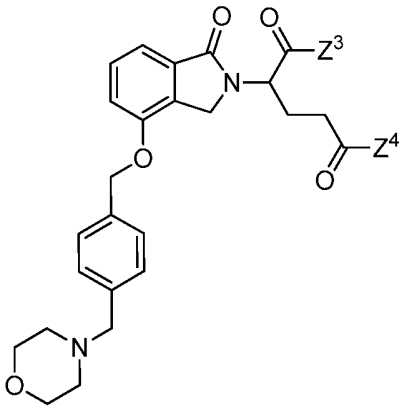
(ii) Z^1 is OR, and Z^2 is NHY; wherein

R is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted

or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or a suitable protecting group of a carboxy group; and

Y is hydrogen, or a suitable amino protecting group;

to an enantiomerically enriched or enantiomerically pure compound of Formula (III), or a salt thereof:



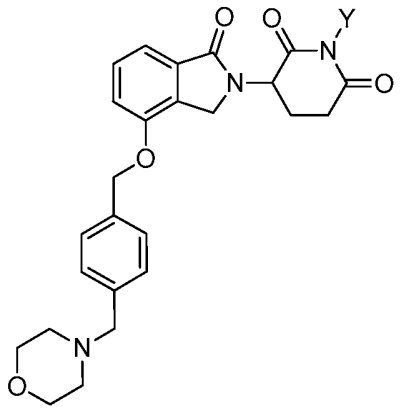
(III), wherein

(i) Z^3 is NHY, and Z^4 is OH; or

(ii) Z^3 is OH, and Z^4 is NHY;

under conditions suitable for ester to acid transformation;

(step 1.2) cyclizing the enantiomerically enriched or enantiomerically pure compound of Formula (III) to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a):



(I-a)

under conditions suitable for cyclization;

(step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I) under conditions suitable for deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation.

2. The process of claim 1, wherein step 1.1 and step 1.2 occur in one-pot.

3. The process of any one of claims 1–2, wherein step 1.1 occurs in the presence of an acid.

4. The process of any one of claims 1–3, wherein step 1.1 occurs in the presence of R^bCOOH wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl.

5. The process of any one of claims 1–4, wherein step 1.1 occurs in the presence of formic acid, acetic acid, trifluoroacetic acid, or benzoic acid.

6. The process of any one of claims 1–5, wherein step 1.1 occurs in the presence of R^bSO_3H wherein R^b is hydrogen, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{1-10} haloalkyl, or substituted or unsubstituted C_{5-14} aryl.

7. The process of any one of claims 1–6, wherein step 1.1 occurs in the presence of sulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, methanesulfonic acid, or trifluoromethanesulfonic acid.

8. The process of any one of claims 1–7, wherein step 1.1 occurs in the presence of benzenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, or methanesulfonic acid.

9. The process of any one of claims 1–8, wherein step 1.1 occurs in the presence of benzenesulfonic acid.

10. The process of any one of claims 1–9, wherein step 1.2 occurs in the presence of a dehydrating agent.

11. The process of any one of claims 1–10, wherein step 1.2 occurs in the presence of 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide (EDCI) or 2-(1H-benzotriazole-1-yl)-1,1,3,3-

tetramethyluronium tetrafluoroborate (TBTU).

12. The process of any one of claims 1–11, wherein step 1.2 occurs by azeotropic distillation.

13. The process of any one of claims 1–12, wherein step 1.1 and step 1.2, separately or in one-pot, occur in a solvent of, or a combination of solvents containing, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone.

14. The process of any one of claims 1–13, wherein step 1.1 and step 1.2, separately or in one-pot, occur in a solvent of acetonitrile.

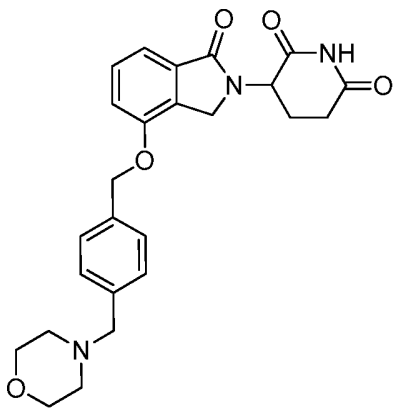
15. The process of any one of claims 1–14, wherein the reaction temperature for step 1.1 and step 1.2, separately or in one-pot, is from about -100 °C to about 200 °C.

16. The process of any one of claims 1–15, wherein the reaction temperature for step 1.1 and step 1.2, separately or in one-pot, is about 90 °C.

17. The process of any one of claims 1–16, wherein the reaction time for step 1.1 and step 1.2, separately or in one-pot, is from about 1 minute to about 14 days.

18. The process of any one of claims 1–17, wherein the reaction time for step 1.1 and step 1.2, separately or in one-pot, is from about 8 hours to about 9 hours.

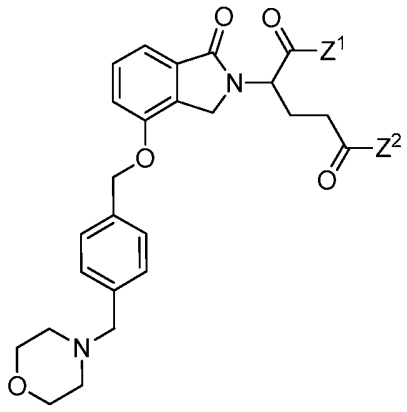
19. A process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (I):



(I)

or a pharmaceutically acceptable form thereof, comprising

(step1.i) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II):



(II)

or a salt thereof, wherein

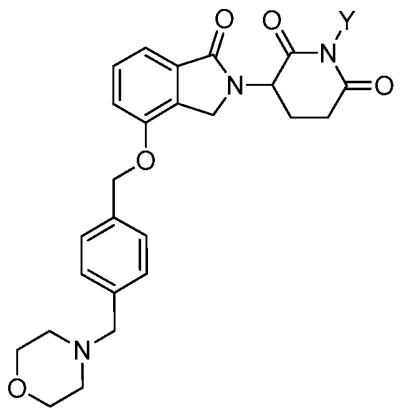
(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY; wherein

R is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or a suitable protecting group of a carboxy group; and

Y is hydrogen, or a suitable amino protecting group;

to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a):



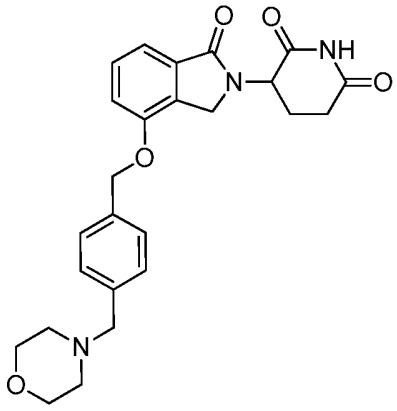
(I-a)

under conditions suitable for cyclization;

(step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I) under conditions suitable for deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation.

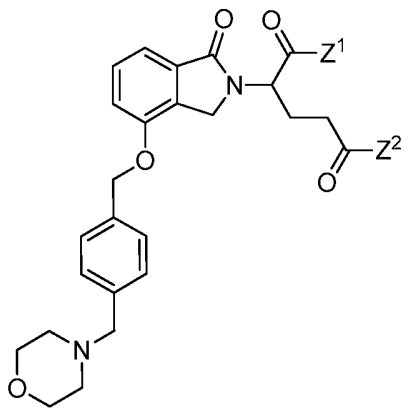
20. A process for preparing an enantiomerically enriched or enantiomerically pure compound of Formula (I):



(I)

or a pharmaceutically acceptable form thereof, comprising

(step1.a) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II):



(II)

or a salt thereof, wherein

(i) Z^1 is NHY, and Z^2 is OR; or

(ii) Z^1 is OR, and Z^2 is NHY; wherein

R is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or a suitable protecting group of a carboxy group; and

Y is hydrogen, or a suitable amino protecting group;

to an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a salt thereof, under conditions suitable for cyclization and deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation.

21. The process of any one of claims 1–20, wherein R is C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{1-6} haloalkyl; C_{2-10} heteroalkyl; C_{3-6} heterocycloalkyl; C_{1-6} alkyl or C_{2-10} heteroalkyl substituted with 1 to 3 aryl; or $-SiR^a_3$ wherein each R^a is independently C_{1-6} alkyl or C_{5-14} aryl.

22. The process of any one of claims 1–21, wherein R is methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, *tert*-butyl, methoxymethyl (MOM), methylthiomethyl (MTM), tetrahydropyranyl (THP), methoxyethoxymethyl (MEM), 2-(trimethylsilyl)ethoxymethylamine (SEM), benzyloxymethyl (BOM), 2-(trimethylsilyl)ethyl (TMSE), 2,2,2-trichloroethyl, benzyl, triphenylmethyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS),

t-butyldimethylsilyl (TBDMS), or *t*-butyldiphenylsilyl (TBDPS).

23. The process of any one of claims 1–22, wherein R is methyl, *tert*-butyl, or benzyl.

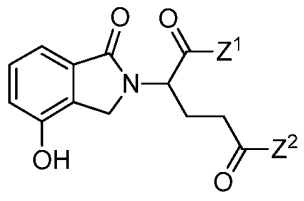
24. The process of any one of claims 1–23, wherein R is *tert*-butyl.

25. The process of any one of claims 1–24, wherein Y is a suitable amino protecting group.

26. The process of any one of claims 1–25, wherein Y is benzyl, 4-methoxybenzyl, *t*-butyldimethylsilyl, *t*-butoxycarbonyl, or benzyloxycarbonyl.

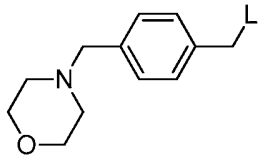
27. The process of any one of claims 1–24, wherein Y is hydrogen.

28. The process of any one of claims 1–27, wherein the enantiomerically enriched or enantiomerically pure compound of formula (II) is prepared by a process comprising:
(step 2) contacting an enantiomerically enriched or enantiomerically pure compound of Formula (IV):



(IV)

with a compound with Formula (V):



(V)

or a salt thereof, wherein L is halogen, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, $-OSO_2C_6H_4$-*p*-Me, or a suitable leaving group,
under conditions suitable for displacement.

29. The process of any one of claims 1–28, wherein L is halogen, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, or $-OSO_2C_6H_4$-*p*-Me.

30. The process of any one of claims 1–29, wherein L is halogen.

31. The process of any one of claims 1–30, wherein L is chloro.

32. The process of any one of claims 1–31, wherein step 2 occurs in the presence of a base.

33. The process of any one of claims 1–32, wherein step 2 occurs in the presence of potassium carbonate.

34. The process of any one of claims 1–33, wherein step 2 occurs in a solvent of, or a combination of solvents containing, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone.

35. The process of any one of claims 1–34, wherein step 2 occurs in a solvent of dimethylformamide.

36. The process of any one of claims 1–35, wherein the reaction temperature for step 2 is from about -100 °C to about 200 °C.

37. The process of any one of claims 1–36, wherein the reaction temperature for step 2 is from about 40 °C to about 50 °C.

38. The process of any one of claims 1–37, wherein the reaction time for step 2 is from about 1 minute to about 14 days.

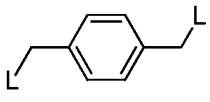
39. The process of any one of claims 1–38, wherein the reaction time for step 2 is from about 12 hours to about 24 hours.

40. The process of any one of claims 1–39, wherein the molar ratio of the compound of formula (IV) to the compound of formula (V) is from about 10:1 to about 1:10.

41. The process of any one of claims 1–40, wherein the molar ratio of the compound of formula (IV) to the compound of formula (V) is from about 1.1:1 to about 1:1.1.

42. The process of any one of claims 1–41, wherein the compound of formula (V), or a salt thereof, is prepared by a process comprising:

(step 3.1) contacting a compound of Formula (VI):



(VI)

wherein each L is independently halogen, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, $-OSO_2C_6H_4$-*p*-Me, or a suitable leaving group;
with morpholine, or a salt thereof, under conditions suitable for displacement; and
(step 3.2) optionally purifying the compound of Formula (V), or a salt thereof, by selective extraction.

43. The process of any one of claims 1–42, wherein each L is independently halogen, $-OSO_2CH_3$, $-OSO_2CF_3$, $-OSO_2CCl_3$, $-OSO_2CH_2CF_3$, $-OSO_2CH_2CCl_3$, or $-OSO_2C_6H_4$-*p*-Me.

44. The process of any one of claims 1–43, wherein both L are chloro.

45. The process of any one of claims 1–44, wherein step 3.1 occurs in the presence of a base.

46. The process of any one of claims 1–45, wherein step 3.1 occurs in the presence of a base and morpholine itself serves as the base.

47. The process of any one of claims 1–46, wherein step 3.1 occurs in a solvent of, or a combination of solvents containing, diethyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, methanol, ethanol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, glyme, diglyme, dimethylacetamide, or N-methyl-2-pyrrolidone.

48. The process of any one of claims 1–47, wherein step 3.1 occurs in a solvent of isopropyl acetate.

49. The process of any one of claims 1–48, wherein the reaction temperature for step 3.1 is from about -100 °C to about 200 °C.

50. The process of any one of claims 1–49, wherein the reaction temperature for step 3.1 is about room temperature.

51. The process of any one of claims 1–50, wherein the reaction time for step 3.1 is from

about 1 minute to about 14 days.

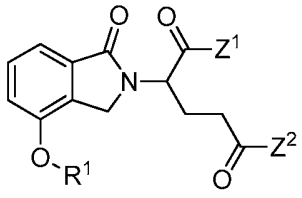
52. The process of any one of claims 1–51, wherein the reaction time for step 3.1 is from about 20 hours to no more than 24 hours.

53. The process of any one of claims 1–52, wherein the molar ratio of the compound of formula (VI) to morpholine is from about 10:1 to about 1:10.

54. The process of any one of claims 1–53, wherein the molar ratio of the compound of formula (VI) to morpholine is about 1:1.5.

55. The process of any one of claims 1–54, wherein step 3.2 occurs in a solvent of methanol.

56. The process of any one of claims 1–55, wherein the enantiomerically enriched or enantiomerically pure compound of formula (IV) is prepared by a process comprising:
(step 4) deprotecting an enantiomerically enriched or enantiomerically pure compound of Formula (VII):



(VII), wherein

R^1 is a suitable phenol protecting group,

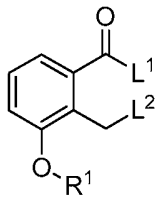
under conditions suitable for deprotection.

57. The process of any one of claims 1–56, wherein R^1 is methyl, isopropyl, cyclopropylmethyl, *tert*-butyl, cyclohexyl, allyl, propargyl, cyanomethyl, 2-bromoethyl, methoxymethyl (MOM), methylthiomethyl (MTM), methoxyethoxymethyl (MEM), 2-(trimethylsilyl)ethoxymethylamine (SEM), tetrahydropyranyl (THP), benzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), *t*-butyldimethylsilyl (TBDMS), or *t*-butyldiphenylsilyl (TBDPS), formate, acetate, benzoate, methyl carbonate, *t*-butyl carbonate (BOC), benzyl carbonate, dimethylphosphinyl, methanesulfonate, or toluenesulfonate.

58. The process of any one of claims 1–57, wherein R^1 is *t*-butyldimethylsilyl (TBDMS) and step 4 occurs in methanol in the presence of tetrabutylammonium fluoride (TBAF).

59. The process of any one of claims 1–58, wherein the enantiomerically enriched or enantiomerically pure compound of formula (VII) is prepared by a process comprising:

(step 5) contacting a compound of Formula (VIII):

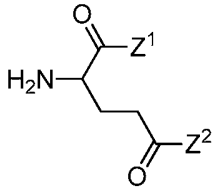


(VIII), wherein

L^1 and L^2 are, independently, halogen, OR^2, $OCOR^2$, OSO_2R^2, OPO_3R^2, or a suitable leaving group;

wherein R^2 is saturated, partially saturated, or unsaturated $C_{1\text{-}10}$ alkyl, optionally substituted with one or more halogen; or 5 to 10 membered aryl or heteroaryl, optionally substituted with one or more halogen;

with an enantiomerically enriched or enantiomerically pure compound of Formula (IX):



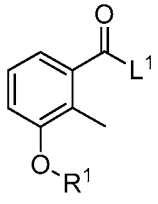
(IX), or a salt thereof,

under conditions suitable for cyclization.

60. The process of any one of claims 1–59, wherein R^2 is methyl, and X is bromo, and step 5 occurs in acetonitrile in the presence of diisopropylethylamine.

61. The process of any one of claims 1–60, wherein the compound of formula (VIII) is prepared by a process comprising:

(step 6) halogenating a compound of Formula (X) at its benzylic position:



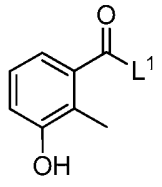
(X),

under conditions suitable for halogenation.

62. The process of any one of claims 1–61, wherein step 6 occurs in isopropyl acetate in the presence of 1-bromopyrrolidine-2,5-dione (NBS) and 2,2'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (AIBN).

63. The process of any one of claims 1–62, wherein the compound of formula (X) is prepared by a process comprising:

(step 7) reacting a compound of Formula (XI):



(XI),

with a protecting group under conditions suitable for protection.

64. The process of any one of claims 1–63, wherein step 7 occurs in N,N-dimethylformamide in the presence of *tert*-butyldimethylsilyl chloride and imidazole.

65. The process of any one of claims 1–64, wherein the compound of formula (XI) is prepared by a process comprising:

(step 8) reacting 3-hydroxy-2-methylbenzoic acid with an alcohol under conditions suitable for esterification.

66. The process of any one of claims 1–65, wherein step 8 occurs by reacting 3-hydroxy-2-methylbenzoic acid with methanol in the presence of sulfuric acid.

67. The process of any one of claims 1–66, wherein an enantiomerically enriched or enantiomerically pure compound of Formula (I), or a pharmaceutically acceptable form thereof, is prepared by a process comprising:

(step 1.1) transforming an enantiomerically enriched or enantiomerically pure compound of Formula (II), or a salt thereof, to an enantiomerically enriched or enantiomerically pure compound of Formula (III), or a salt thereof, under conditions suitable for ester to acid transformation;

(step 1.2) cyclizing the enantiomerically enriched or enantiomerically pure compound of Formula (III) to an enantiomerically enriched or enantiomerically pure compound of Formula (I-a) under conditions suitable for cyclization;

(step 1.3) where Y is not hydrogen, deprotecting the enantiomerically enriched or enantiomerically pure compound of Formula (I-a) to an enantiomerically enriched or enantiomerically pure compound of Formula (I) under conditions suitable for deprotection; and

(step 1.4) optionally transforming the enantiomerically enriched or enantiomerically pure compound of Formula (I) to a pharmaceutically acceptable salt thereof under conditions suitable for salt formation;

wherein step 1.1 and step 1.2 occur in one-pot; and

wherein the enantiomerically enriched or enantiomerically pure compound of Formula (II) is prepared by a process comprising:

(step 2) contacting an enantiomerically enriched or enantiomerically pure compound of Formula (IV) with a compound with Formula (V), or a salt thereof, under conditions suitable for displacement;

wherein the compound of Formula (V) is prepared by a process comprising:

(step 3.1) contacting a compound of Formula (VI) with morpholine; or a salt thereof, under conditions suitable for displacement, and

(step 3.2) optionally purifying the compound of Formula (V) by selective extraction;

wherein the enantiomerically enriched or enantiomerically pure compound of Formula (IV) is prepared by a process comprising:

(step 4) deprotecting an enantiomerically enriched or enantiomerically pure compound of Formula (VII) under conditions suitable for deprotection;

wherein the enantiomerically enriched or enantiomerically pure compound of Formula (VII) is prepared by a process comprising:

(step 5) contacting a compound of Formula (VIII) with an enantiomerically enriched or enantiomerically pure compound of Formula (IX), or a salt thereof, under conditions suitable for cyclization;

wherein the compound of Formula (VIII) is prepared by a process comprising:

(step 6) halogenating a compound of Formula (X) at its benzylic position under conditions suitable for halogenation;

wherein the compound of Formula (X) is prepared by a process comprising:

(step 7) reacting a compound of Formula (XI) with a protecting group under conditions suitable for protection;

wherein the compound of Formula (XI) is prepared by a process comprising:

(step 8) reacting 3-hydroxy-2-methylbenzoic acid with an alcohol under conditions suitable for esterification.

68. A process to increase the enantiopurity of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a salt and/or solvate thereof, comprising recrystallization or trituration of a first sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a salt and/or solvate thereof, in a solvent or a mixture of solvents, resulting in a second sample of *(S)*-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a salt and/or solvate thereof, wherein the second sample has a higher ee than the first sample.

69. The process of claim 68, wherein the solvent is methanol.

70. The process of any one of claims 68–69, wherein both the first and the second samples are in the HCl salt form.

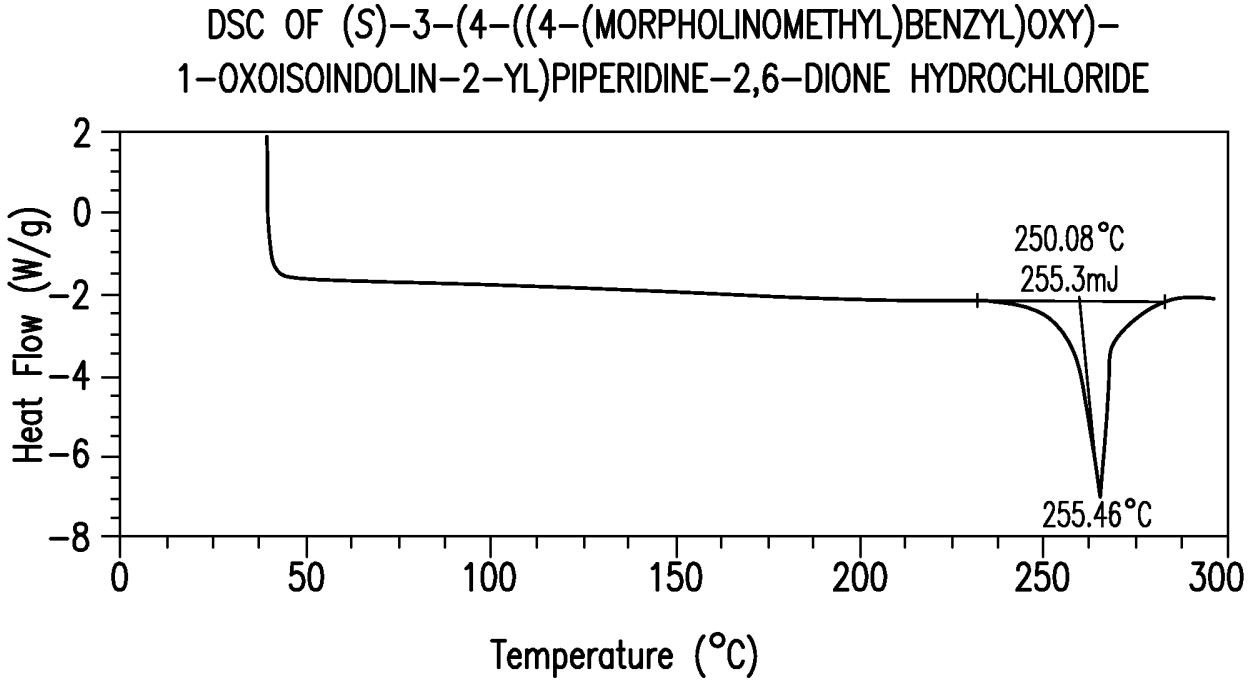

DSC OF (S)-3-(4-((4-(MORPHOLINOMETHYL)BENZYL)OXY)-1-OXOISOINDOLIN-2-YL)PIPERIDINE-2,6-DIONE HYDROCHLORIDE
Heat Flow (W/g)
2
0
-2
-4
-6
-8
0
50
100
150
200
250
300
Temperature (°C)
250.08°C
255.3mJ
255.46°C

FIG. 1

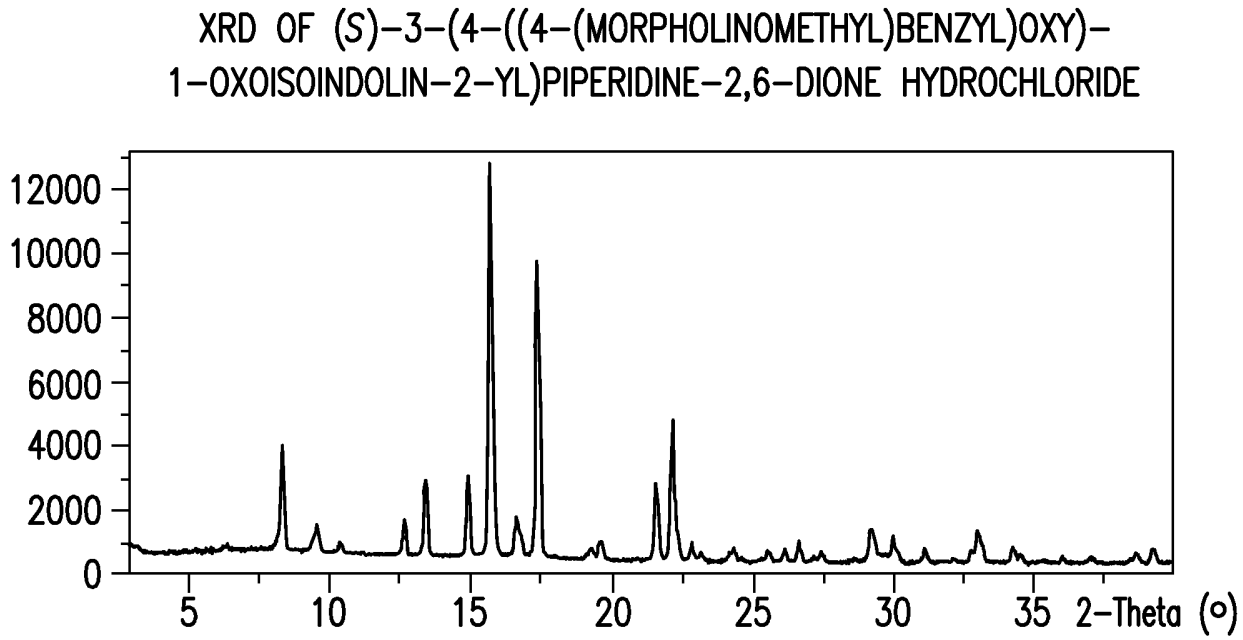

XRD OF (S)-3-(4-((4-(MORPHOLINOMETHYL)BENZYL)OXY)-1-OXOISOINDOLIN-2-YL)PIPERIDINE-2,6-DIONE HYDROCHLORIDE
12000
10000
8000
6000
4000
2000
0
5
10
15
20
25
30
35
2-Theta (°)

FIG. 2

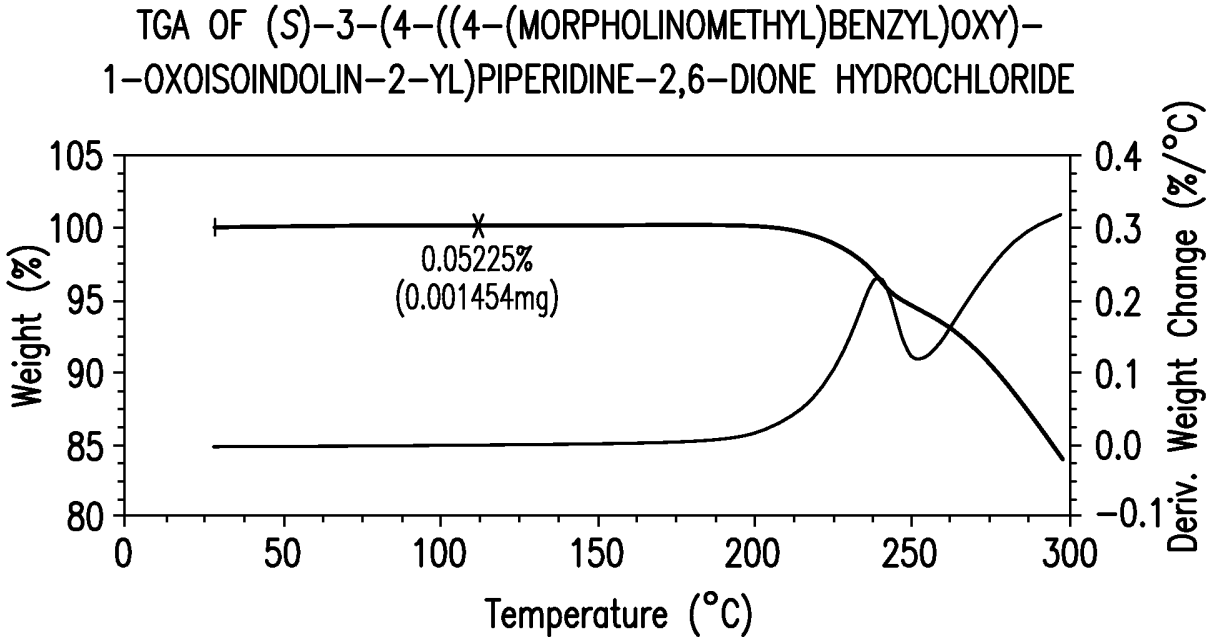

TGA OF (S)-3-(4-((4-(MORPHOLINOMETHYL)BENZYL)OXY)-1-OXOISOINDOLIN-2-YL)PIPERIDINE-2,6-DIONE HYDROCHLORIDE
Weight (%)
105
100
95
90
85
80
0.05225%
(0.001454mg)
0
50
100
150
200
250
300
Temperature (°C)
Deriv. Weight Change (%/°C)
0.4
0.3
0.2
0.1
0.0
-0.1

FIG. 3

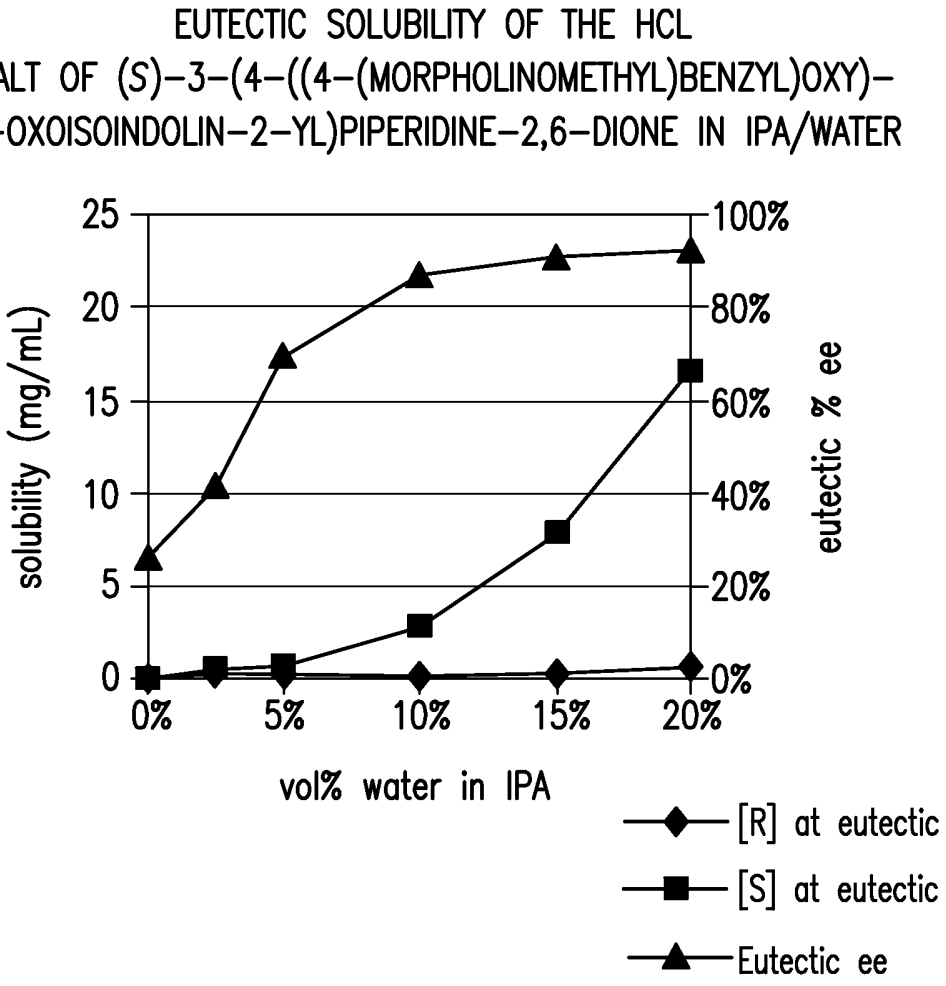

EUTECTIC SOLUBILITY OF THE HCL SALT OF (S)-3-(4-((4-(MORPHOLINOMETHYL)BENZYL)OXY)-1-OXOISOINDOLIN-2-YL)PIPERIDINE-2,6-DIONE IN IPA/WATER
solubility (mg/mL)
25
20
15
10
5
0
100%
80%
60%
40%
20%
0%
eutectic % ee
0%
5%
10%
15%
20%
vol% water in IPA
[R] at eutectic
[S] at eutectic
Eutectic ee

FIG. 4

EUTECTIC SOLUBILITY OF THE HCL SALT OF (S)-3-(4-((4-(MORPHOLINOMETHYL)BENZYL)OXY)-1-OXOISOINDOLIN-2-YL)PIPERIDINE-2,6-DIONE AS A FUNCTION OF TEMPERATURE IN VARIOUS SOLVENT SYSTEMS

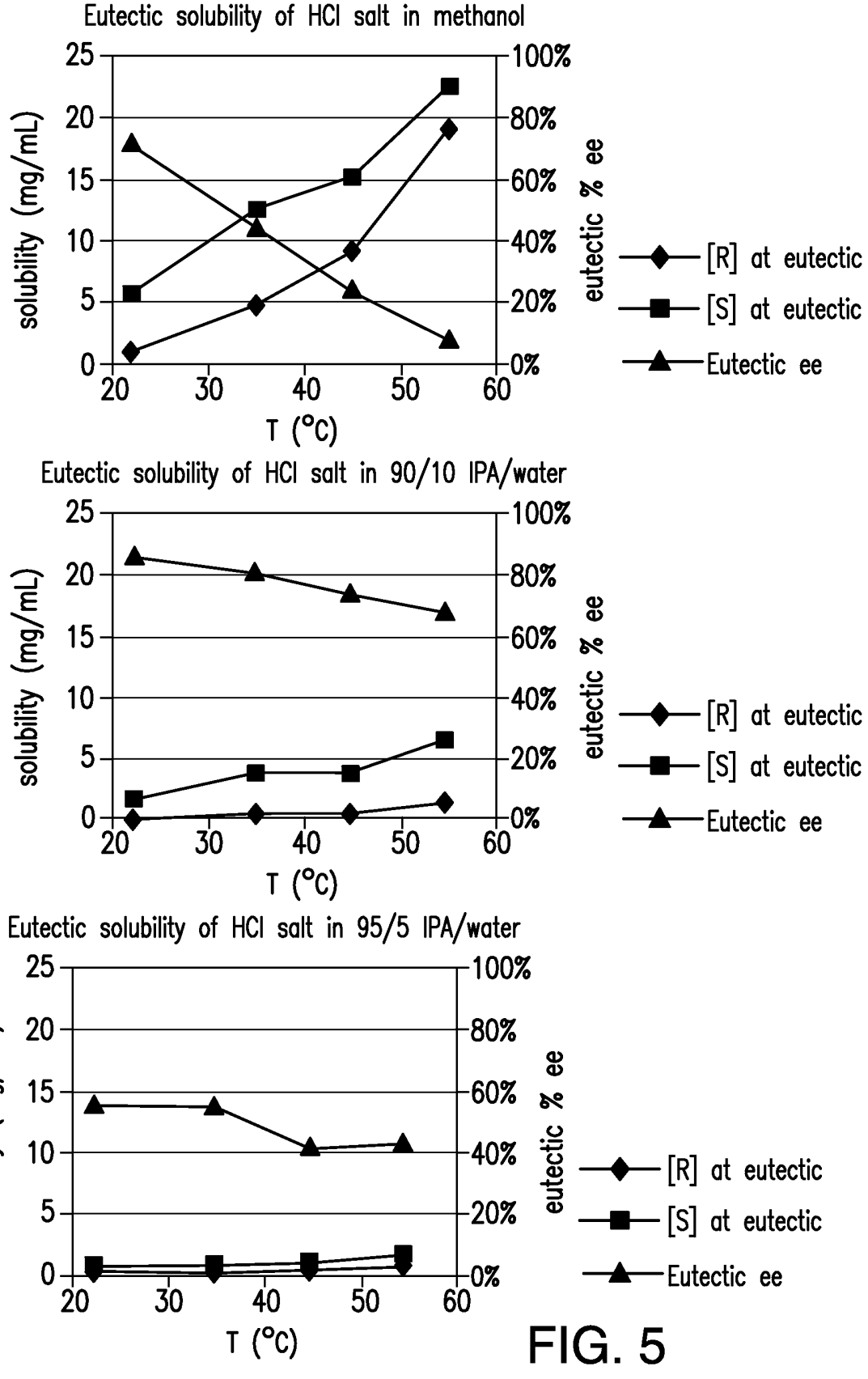


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/054099

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/100380 A1 (CELGENE CORP [US]; MAN HON-WAH [US]; MULLER GEORGE W [US]; RUCHELMAN A) 18 August 2011 (2011-08-18) cited in the application	19-23,27
Y	paragraph [0200] - paragraph [0204] paragraph [0355] - paragraph [0362] paragraph [0386] - paragraph [0388] examples 5.2, 5.52, 5.61	1-67
Y	WO 2007/005972 A1 (CELGENE CORP [US]; MULLER GEORGE W [US]; SAINDANE MANOHAR T [US]; GE C) 11 January 2007 (2007-01-11) Schemes A, D and D'; paragraphs [0037], [0064]; examples 3,7, 10,11	1-67

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2013	30/01/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kirsch, Cécile

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/054099

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-67

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-67

   Process for preparing an enantiomerically enriched or enantiomerically pure 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl) piperidine- 2,6-dione comprising cyclization of the 5-amino-5-oxopentanoate containing part

   ---

2. claims: 68-70

   Process to increase the enantiopurity of (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)- I -oxoisoindolin-2-yl)piperidine-2,6-dione comprising recrystallization

   ---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/054099

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011100380 A1	18-08-2011	AR 081058 A1	06-06-2012
		AU 2011215877 A1	16-08-2012
		CA 2787823 A1	18-08-2011
		CN 102822165 A	12-12-2012
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		CR 20120414 A	31-10-2012
		EP 2536706 A1	26-12-2012
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		US 2013324518 A1	05-12-2013
		WO 2011100380 A1	18-08-2011
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		EP 1907373 A1	09-04-2008
		EP 2380887 A1	26-10-2011
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		HR P20130966 T1	22-11-2013
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		PE 01032007 A1	06-02-2007
		PE 01512010 A1	05-03-2010
		PT 1907373 E	18-02-2013
		PT 2380887 E	18-09-2013
		RS 52704 B	30-08-2013
		SI 1907373 T1	29-03-2013
		SI 2380887 T1	31-12-2013
		US 2007004920 A1	04-01-2007
		US 2011224440 A1	15-09-2011
		WO 2007005972 A1	11-01-2007
		ZA 200800828 A	26-08-2009

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104718202 A
(43)申请公布日 2015.06.17

(21)申请号 201380052461.7
(22)申请日 2013.08.08
(30)优先权数据
61/681,477 2012.08.09 US
(85)PCT国际申请进入国家阶段日
2015.04.08
(86)PCT国际申请的申请数据
PCT/US2013/054099 2013.08.08
(87)PCT国际申请的公布数据
WO2014/025978 EN 2014.02.13
(71)申请人 细胞基因公司
地址 美国新泽西州
(72)发明人 约翰·F·特拉弗斯 成敏·张
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(74)专利代理机构 北京安信方达知识产权代理有限公司 11262
代理人 郑霞
(51)Int.Cl.
C07D 401/04(2006.01)

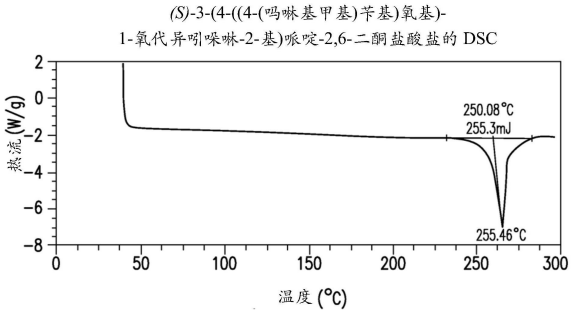
权利要求书10页 说明书43页 附图4页

(54)发明名称

用于制备(S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮及其可药用形式的方法

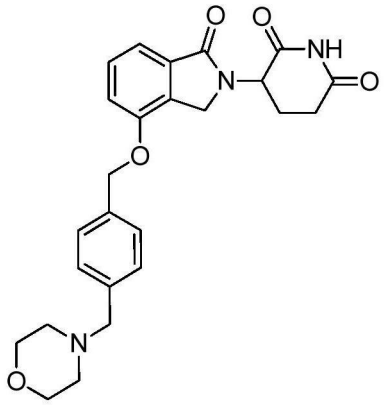
(57)摘要

提供了用于制备对映异构体富集的或对映异构体纯的3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮或其可药用形式的方法。



CN 104718202 A

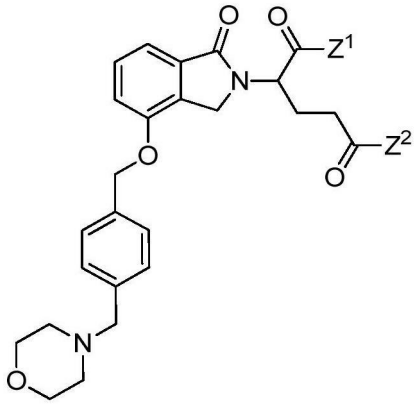
1.一种制备对映异构体富集的或对映异构体纯的式(I)的化合物或其可药用形式的方法：



(I),

包括：

(步骤1.1)在适于酯向酸转化的条件下,将对映异构体富集的或对映异构体纯的式(II)的化合物或其盐：



(II)

其中

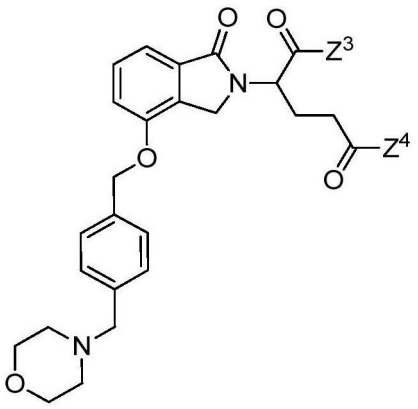
(i)Z^1为NHY,和Z^2为OR;或

(ii)Z^1为OR,和Z^2为NHY;其中

R为取代的或未取代的烷基、取代的或未取代的环烷基、取代的或未取代的杂烷基、取代的或未取代的杂环烷基、取代的或未取代的芳基、取代的或未取代的杂芳基、取代的或未取代的芳烷基、或合适的羧基保护基;和

Y为氢,或合适的氨基保护基;

转化成对映异构体富集的或对映异构体纯的式(III)的化合物或其盐：



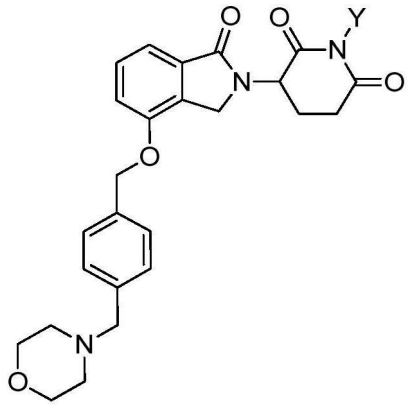
其中

(III),

(i)Z^3为 NHY,和 Z^4为 OH ;或

(ii)Z^3为 OH,和 Z^4为 NHY ;

(步骤 1.2) 在适于环化的条件下,使对映异构体富集的或对映异构体纯的式 (III) 的化合物环化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物 :



(I-a);

(步骤1.3) 当Y不为氢时,在适于脱保护的条件下,使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物 ;和

(步骤 1.4) 任选地在适于成盐的条件下,将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐。

2.权利要求 1 所述的方法,其中,步骤 1.1 和步骤 1.2 在一锅中发生。

3.权利要求 1-2 中任一项所述的方法,其中,步骤 1.1 在酸的存在下发生。

4.权利要求 1-3 中任一项所述的方法,其中,步骤 1.1 在 R^bCOOH 的存在下发生,其中 R^b 为氢、取代的或未取代的 C_{1-10}烷基、取代的或未取代的 C_{1-10}卤代烷基、或取代的或未取代的 C_{5-14}芳基。

5.权利要求 1-4 中任一项所述的方法,其中,步骤 1.1 在甲酸、乙酸、三氟乙酸或苯甲酸的存在下进行。

6.权利要求 1-5 中任一项所述的方法,其中,步骤 1.1 在 R^bSO_3H 的存在下发生,其中 R^b 为氢、取代的或未取代的 C_{1-10}烷基、取代的或未取代的 C_{1-10}卤代烷基、或取代的或未取代的 C_{5-14}芳基。

7.权利要求 1-6 中任一项所述的方法,其中,步骤 1.1 在磺酸、苯磺酸、对甲苯磺酸、樟脑磺酸、甲磺酸或三氟甲磺酸的存在下发生。

8.权利要求 1-7 中任一项所述的方法,其中,步骤 1.1 在苯磺酸、对甲苯磺酸、樟脑磺酸

或甲磺酸的存在下发生。

9. 权利要求 1-8 中任一项所述的方法，其中，步骤 1.1 在苯磺酸的存在下发生。

10. 权利要求 1-9 中任一项所述的方法，其中，步骤 1.2 在脱水剂的存在下发生。

11. 权利要求 1-10 中任一项所述的方法，其中，步骤 1.2 在 1- 乙基 -3-(3- 二甲基氨基丙基）碳二亚胺 (EDCI) 或 2-(1H- 苯并三唑 -1- 基)-1,1,3,3- 四甲基脲鎓四氟硼酸酯 (TBTU) 的存在下发生。

12. 权利要求 1-11 中任一项所述的方法，其中，步骤 1.2 通过共沸蒸馏发生。

13. 权利要求 1-12 中任一项所述的方法，其中，步骤 1.1 和步骤 1.2 分别或在一锅中在如下溶剂或溶剂组合中发生，所述溶剂包含 ：乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。

14. 权利要求 1-13 中任一项所述的方法，其中，步骤 1.1 和步骤 1.2 分别或在一锅中在乙腈溶剂中发生。

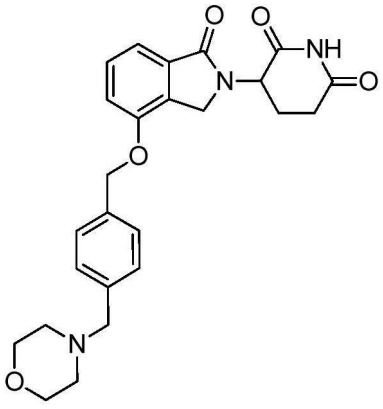
15. 权利要求 1-14 中任一项所述的方法，其中，步骤 1.1 和步骤 1.2 分别或在一锅中反应的反应温度为约 -100℃至约 200℃。

16. 权利要求 1-15 中任一项所述的方法，其中，步骤 1.1 和步骤 1.2 分别或在一锅中反应的反应温度为约 90℃。

17. 权利要求 1-16 中任一项所述的方法，其中，步骤 1.1 和步骤 1.2 分别或在一锅中反应的反应时间为约 1 分钟至约 14 天。

18. 权利要求 1-17 中任一项所述的方法，其中，步骤 1.1 和步骤 1.2 分别或在一锅中反应的反应时间为约 8 小时至约 9 小时。

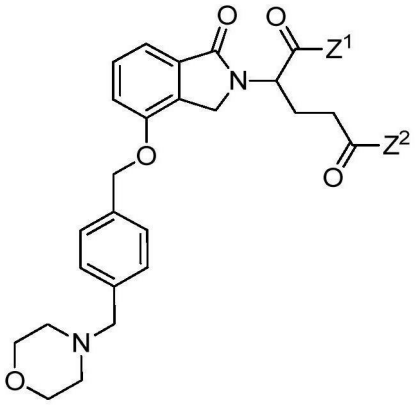
19. 一种制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法 ：



(I)

包括 ：

(步骤 1.i) 在适于环化的条件下，将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐 ：



(II)

其中

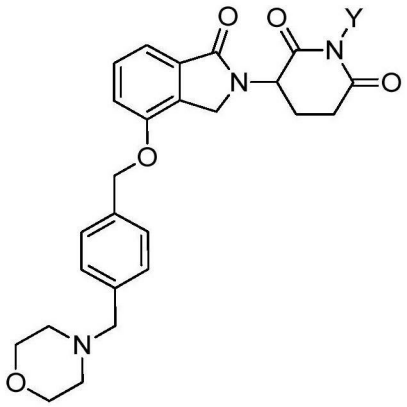
(i)Z^1为 NHY,和 Z^2为 OR ;或

(ii)Z^1为 OR,和 Z^2为 NHY ;其中

R 为取代的或未取代的烷基、取代的或未取代的环烷基、取代的或未取代的杂烷基、取代的或未取代的杂环烷基、取代的或未取代的芳基、取代的或未取代的杂芳基、取代的或未取代的芳烷基、或合适的羧基保护基 ;和

Y 为氢,或合适的氨基保护基 ;

转化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物 :

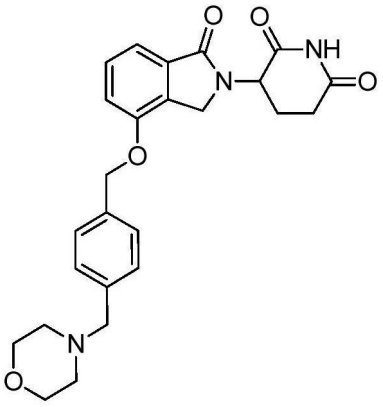


(I-a);

(步骤1.3) 当Y不为氢时,在适于脱保护的条件下,使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物 ;和

(步骤 1.4) 任选地在适于成盐的条件下,将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐。

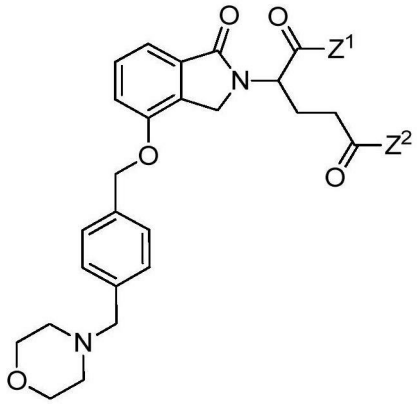
20.一种制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法 :



(I)

包括：

(步骤 1.a) 在适于环化和脱保护的条件下，将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐：



(II)

其中

(i)Z^1为 NHY，和 Z^2为 OR；或

(ii)Z^1为 OR，和 Z^2为 NHY；其中

R 为取代的或未取代的烷基、取代的或未取代的环烷基、取代的或未取代的杂烷基、取代的或未取代的杂环烷基、取代的或未取代的芳基、取代的或未取代的杂芳基、取代的或未取代的芳烷基、或合适的羧基保护基；和

Y 为氢，或合适的氨基保护基；

转化成对映异构体富集的或对映异构体纯的式 (I) 的化合物或其盐；和

(步骤 1.4) 任选地在适于成盐的条件下，将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐。

21. 权利要求 1-20 中任一项所述的方法，其中，R 为 C_{1-6}烷基；C_{3-6}环烷基；C_{1-6}卤代烷基；C_{2-10}杂烷基；C_{3-6}杂环烷基；被 1 至 3 个芳基取代的 C_{1-6}烷基或 C_{2-10}杂烷基；或 $-SiR^a_3$，其中每个 R^a独立地为 C_{1-6}烷基或 C_{5-14}芳基。

22. 权利要求 1-21 中任一项所述的方法，其中，R 为甲基、乙基、丙基、异丙基、环丙基、丁基、异丁基、叔丁基、甲氧基甲基 (MOM)、甲基硫甲基 (MTM)、四氢吡喃基 (THP)、甲氧基乙氧基甲基 (MEM)、2-(三甲基甲硅烷基) 乙氧基甲基胺 (SEM)、苄氧基甲基 (BOM)、2-(三甲基甲硅烷基) 乙基 (TMSE)、2,2,2- 三氯乙基、苄基、三苯甲基、对 - 甲氧基苄基、2,6- 二甲氧基苯甲基、三甲基甲硅烷基 (TMS)、三乙基甲硅烷基 (TES)、三异丙基甲硅烷基 (TIPS)、

二甲基异丙基甲硅烷基 (IPDMS)、二乙基异丙基甲硅烷基 (DEIPS)、叔丁基二甲基甲硅烷基 (TBDMS) 或叔丁基二苯基甲硅烷基 (TBDPS)。

23. 权利要求 1-22 中任一项所述的方法，其中，R 为甲基、叔丁基或苯甲基。

24. 权利要求 1-23 中任一项所述的方法，其中，R 为叔丁基。

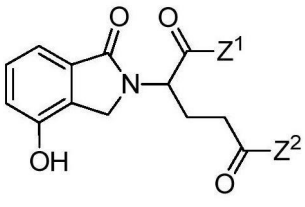
25. 权利要求 1-24 中任一项所述的方法，其中，Y 为合适的氨基保护基。

26. 权利要求 1-25 中任一项所述的方法，其中，Y 为苯甲基、4- 甲氧基苄基、叔丁基二甲基甲硅烷基、叔丁氧基羰基或苄氧基羰基。

27. 权利要求 1-24 中任一项所述的方法，其中，Y 为氢。

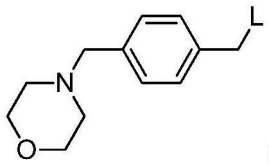
28. 权利要求 1-27 中任一项所述的方法，其中，所述对映异构体富集的或对映异构体纯的式 (II) 的化合物是通过包括如下步骤的方法制备的 ：

(步骤2) 在适于置换的条件下，使对映异构体富集的或对映异构体纯的式 (IV) 的化合物 ：



(IV)

接触式 (V) 的化合物或其盐 ：



(V)

其中 L 为卤素、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$、$-OSO_2C_6H_4$-p-Me 或合适的离去基团。

29. 权利要求 1-28 中任一项所述的方法，其中 L 为卤素、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$、或 $-OSO_2C_6H_4$-p-Me。

30. 权利要求 1-29 中任一项所述的方法，其中，L 为卤素。

31. 权利要求 1-30 中任一项所述的方法，其中，L 为氯。

32. 权利要求 1-31 中任一项所述的方法，其中，步骤 2 在碱的存在下发生。

33. 权利要求 1-32 中任一项所述的方法，其中，步骤 2 在碳酸钾的存在下发生。

34. 权利要求 1-33 中任一项所述的方法，其中，步骤 2 在如下溶剂或溶剂组合中发生，所述溶剂包含 ：乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。

35. 权利要求 1-34 中任一项所述的方法，其中，步骤 2 在二甲基甲酰胺溶剂中发生。

36. 权利要求 1-35 中任一项所述的方法，其中，步骤 2 的反应温度为约 -100℃至约 200℃。

37. 权利要求 1-36 中任一项所述的方法，其中，步骤 2 的反应温度为约 40℃至约 50℃。

38. 权利要求 1-37 中任一项所述的方法，其中，步骤 2 的反应时间为约 1 分钟至约 14

天。

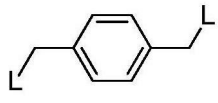
39. 权利要求 1-38 中任一项所述的方法，其中，步骤 2 的反应时间为约 12 小时至 24 小时。

40. 权利要求 1-39 中任一项所述的方法，其中，式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 10:1 至约 1:10。

41. 权利要求 1-40 中任一项所述的方法，其中，式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 1.1:1 至约 1:1.1。

42. 权利要求 1-41 中任一项所述的方法，其中，所述式 (V) 的化合物或其盐是通过包括如下步骤的方法制备的：

(步骤 3.1) 在适于置换的条件下，使式 (VI) 的化合物：


(VI)

其中每个 L 独立地为卤素、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$、$-OSO_2C_6H_4$-p-Me 或合适的离去基团；

接触吗啉或其盐；和

(步骤 3.2) 任选地通过选择性萃取来纯化式 (V) 的化合物或其盐。

43. 权利要求 1-42 中任一项的方法，其中，每个 L 独立地为卤素、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$或 $-OSO_2C_6H_4$-p-Me。

44. 权利要求 1-43 中任一项所述的方法，其中，两个 L 都为氯。

45. 权利要求 1-44 中任一项所述的方法，其中，步骤 3.1 在碱的存在下发生。

46. 权利要求 1-45 中任一项所述的方法，其中，步骤 3.1 在碱的存在下发生，并且吗啉本身起到碱的作用。

47. 权利要求 1-46 中任一项所述的方法，其中，步骤 3.1 在如下溶剂或溶剂组合中发生，所述溶剂包含：乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。

48. 权利要求 1-47 中任一项所述的方法，其中，步骤 3.1 在乙酸异丙酯溶剂中发生。

49. 权利要求 1-48 中任一项所述的方法，其中，步骤 3.1 的反应温度为约 -100℃至约 200℃。

50. 权利要求 1-49 中任一项所述的方法，其中，步骤 3.1 的反应温度为约室温。

51. 权利要求 1-50 中任一项所述的方法，其中，步骤 3.1 的反应时间为约 1 分钟至约 14 天。

52. 权利要求 1-51 中任一项所述的方法，其中，步骤 3.1 的反应时间为约 20 小时至不超过 24 小时。

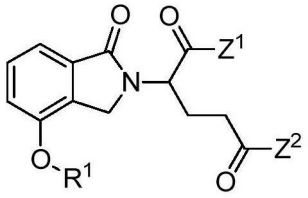
53. 权利要求 1-52 中任一项所述的方法，其中，式 (VI) 的化合物与吗啉的摩尔比为约 10:1 至约 1:10。

54. 权利要求 1-53 中任一项所述的方法，其中，式 (VI) 的化合物与吗啉的摩尔比为约 1:1.5。

55. 权利要求 1-54 中任一项所述的方法，其中，步骤 3.2 在甲醇溶剂中发生。

56. 权利要求 1-55 中任一项所述的方法，其中，所述对映异构体富集的或对映异构体纯的式 (IV) 的化合物是通过包括如下步骤的方法制备的：

(步骤 4) 在适于脱保护的条件下，使对映异构体富集的或对映异构体纯的式 (VII) 的化合物脱保护：



(VII)，其中

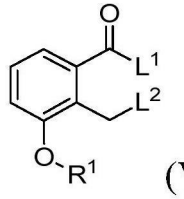
R^1为合适的苯酚保护基。

57. 权利要求 1-56 中任一项所述的方法，其中，R^1为甲基、异丙基、环丙基甲基、叔丁基、环己基、烯丙基、炔丙基、氰基甲基、2- 溴甲基、甲氧基甲基 (MOM)、甲基硫甲基 (MTM)、甲氧基乙氧基甲基 (MEM)、2-(三甲基甲硅烷基) 乙氧基甲基胺 (SEM)、四氢吡喃基 (THP)、苄基、对 - 甲氧基苄基、2,6- 二甲氧基苯甲基、2,6- 二氯苯甲基、三甲基甲硅烷基 (TMS)、三乙基甲硅烷基 (TES)、三异丙基甲硅烷基 (TIPS)、二甲基异丙基甲硅烷基 (IPDMS)、二乙基异丙基甲硅烷基 (DEIPS)、叔丁基二甲基甲硅烷基 (TBDMS) 或叔丁基二苯基甲硅烷基 (TBDPS)、甲酸酯基、乙酸酯基、苯甲酸酯基、碳酸甲基酯基、碳酸叔丁酯基 (BOC)、碳酸苄酯基、二甲基膦基、甲磺酸酯基或甲苯磺酸酯基。

58. 权利要求 1-57 中任一项所述的方法，其中，R^1为叔丁基二甲基甲硅烷基 (TBDMS)，并且步骤 4 在四丁基氟化铵 (TBAF) 的存在下在甲醇中发生。

59. 权利要求 1-58 中任一项所述的方法，其中，所述对映异构体富集的或对映异构体纯的式 (VII) 的化合物是通过包括如下步骤的方法制备的：

(步骤 5) 在适于环化的条件下，使式 (VIII) 的化合物：

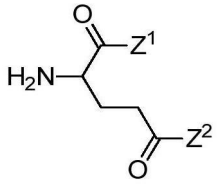


(VIII)，其中

L^1和 L^2独立地为卤素、OR^2、$OCOR^2$、OSO_2R^2、OPO_3R^2或合适的离去基团；

其中 R^2为饱和的、部分饱和的或不饱和的 C_{1-10}烷基，任选地被一个或多个卤素取代；或 5 至 10 元芳基或杂芳基，任选地被一个或多个卤素取代；

接触对映异构体富集的或对映异构体纯的式 (IX) 的化合物或其盐：



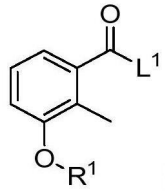
(IX)。

60. 权利要求 1-59 中任一项所述的方法，其中，R^2为甲基，X 为溴，并且步骤 5 在二异丙基乙胺的存在下在乙腈中发生。

61. 权利要求 1-60 中任一项所述的方法，其中，式 (VIII) 的化合物是通过包括如下步

骤的方法制备的：

（步骤 6）在适于卤化的条件下，使式 (X) 的化合物在其苄基化位点处发生卤化：

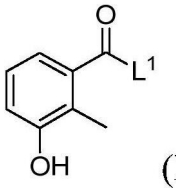


(X)。

62. 权利要求 1-61 中任一项所述的方法，其中，步骤 6 在 1- 溴吡咯烷 -2,5- 二酮 (NBS) 和 2,2'-（偶氮 -1,2- 二基）双 (2- 甲基丙腈)(AIBN) 的存在下在乙酸异丙酯中发生。

63. 权利要求 1-62 中任一项所述的方法，其中，式 (X) 的化合物是通过包括如下步骤的方法制备的：

（步骤 7）使式 (XI) 的化合物：



(XI)，

与保护基在适于保护的条件下反应。

64. 权利要求 1-63 中任一项所述的方法，其中，步骤 7 在叔丁基二甲基甲硅烷基氯化物和咪唑的存在下在 N,N- 二甲基甲酰胺中发生。

65. 权利要求 1-64 中任一项所述的方法，其中，式 (XI) 的化合物是通过包括如下步骤的方法制备的：

（步骤 8）在适于酯化的条件下使 3- 羟基 -2- 甲基苯甲酸与醇反应。

66. 权利要求 1-65 中任一项所述的方法，其中，步骤 8 是通过在硫酸的存在下使 3- 羟基 - 甲基苯甲酸与甲醇反应而发生的。

67. 权利要求 1-66 中任一项所述的方法，其中，对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式是通过包括如下步骤的方法制备的：

（步骤 1.1）在适于酯向酸转化的条件下，将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐转化成对映异构体富集的或对映异构体纯的式 (III) 的化合物或其盐；

（步骤 1.2）在适于环化的条件下，使对映异构体富集的或对映异构体纯的式 (III) 的化合物环化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物；

（步骤 1.3）当 Y 不为氢时，在适于脱保护的条件下，使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物；和

（步骤 1.4）任选地在适于成盐的条件下，将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐；

其中步骤 1.1 和步骤 1.2 在一锅中发生；和

其中所述对映异构体富集的或对映异构体纯的式 (II) 的化合物是通过包括如下步骤的方法制备的：

（步骤 2）在适于置换的条件下，使对映异构体富集的或对映异构体纯的式 (IV) 的化合

物接触式 (V) 的化合物或其盐 ;

其中所述式 (V) 的化合物是通过包括如下步骤的方法制备的 :

(步骤 3.1) 在适于置换的条件下,使式 (VI) 的化合物接触吗啉或其盐 ;和

(步骤 3.2) 任选地通过选择性萃取纯化式 (V) 的化合物 ;所述对映异构体富集的或对映异构体纯的式 (IV) 的化合物是通过包括如下步骤的方法制备的 :

(步骤 4) 在适于脱保护的条件下,使对映异构体富集的或对映异构体纯的式 (VII) 的化合物脱保护 ;

其中所述对映异构体富集的或对映异构体纯的式 (VII) 的化合物是通过包括如下步骤的方法制备的 :

(步骤 5) 在适于环化的条件下,使式 (VIII) 的化合物接触对映异构体富集的或对映异构体纯的式 (IX) 的化合物或其盐 ;

其中所述式 (VIII) 的化合物是通过包括如下步骤的方法制备的 :

(步骤 6) 在适于卤化的条件下,使式 (X) 的化合物在其苄基化位点处发生卤化 ;

其中所述式 (X) 的化合物是通过包括如下步骤的方法制备的 :

(步骤 7) 在适于保护的条件下,使式 (XI) 的化合物与保护基反应 ;

其中所述式 (XI) 的化合物是通过包括如下步骤的方法制备的 :

(步骤 8) 在适于酯化的条件下,使 3- 羟基 -2- 甲基苯甲酸与醇反应。

68. 一种增加 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮或其盐和 / 或溶剂化物的对映异构纯度的方法,包括在溶剂或溶剂混合物中将 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮或其盐和 / 或溶剂化物的第一样品重结晶或研磨,得到 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮或其盐和 / 或溶剂化物的第二样品,其中所述第二样品具有比叔所述第一样品更高的 ee。

69. 权利要求 68 所述的方法,其中,所述溶剂为甲醇。

70. 权利要求 68-69 中任一项所述的方法,其中,第一样品和第二样品都为 HCl 盐形式。

用于制备(S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮及其可药用形式的方法

[0001] 1.优先权的要求

[0002] 本文要求2012年8月9日提交的发明名称为“用于制备(S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮及其可药用形式的方法(Processes for the Preparation of(S)-3-(4-((4-(Morpholinomethyl)Benzyl)Oxy)-1-Oxoisoindolin-2-Yl)Piperidine-2,6-Dione and Pharmaceutically Acceptable Forms Thereof)”的美国临时申请No.61/681,477的优先权。将上述参考申请的全部教导并入本文作为参考。

2.发明领域

[0003] 本文提供用于制备对映异构体富集的或对映异构体纯的3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮或其可药用形式的方法,其用于治疗、预防和控制各种病症。

3.背景技术

[0004] 许多类型的癌症与新血管形成(一种称为血管生成的过程)有关。已经阐明了在肿瘤诱导的血管生成中涉及的几种机制。这些机制中最直接的机制是肿瘤细胞分泌具有血管生成性质的细胞因子,包括肿瘤坏死因子α(TNF-α)。

[0005] 多种其他疾病和病症也与不期望的血管生成有关,或以其为特征。例如,增强或不受调节的血管生成已经涉及许多疾病或医学病症,包括,但不限于眼部新血管疾病、脉络膜新血管疾病、视网膜新血管疾病、虹膜红变(角的新血管形成)、病毒性疾病、遗传性疾病、炎症性疾病、变应性疾病和自身免疫性疾病。这样的疾病和病症的实例包括,但不限于:糖尿病性视网膜病;早产儿视网膜病;角膜移植排斥;新生血管性青光眼;晶状体后纤维增生症;关节炎;和增殖性玻璃体视网膜病变。

[0006] 已经报道了某些4’-芳基甲氧基异吲哚啉化合物(包括3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮)能够控制血管生成或抑制某些细胞因子(包括TNF-α)的产生,并且用于治疗和预防各种疾病和病症。参见美国专利公开号No.2011/0196150,将其全文并入本文作为参考。

[0007] 用于合成外消旋的3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮的方法之前描述在美国专利公开号No.2011/0196150中。仍然需要用于制备对映异构体富集的或对映异构体纯的3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮或其可药用形式的有效且可规模化方法。

[0008] 在用于提供对映异构体富集的或对映异构体纯的化合物的一般方法中,利用天然或市售可获得的对映体纯的起始原料是最直接的方法,并且通常优选地用于工业规模加工。该方法所遇到的挑战之一是合成过程期间完全或部分外消旋化,其导致物质的对映异

构体过量 (ee) 减少。为了将外消旋化的概率降至最低,只要可能,通常避免苛刻的反应条件。

[0009] 除了需要用于制备对映异构体富集的或对映异构体纯的化合物的合成方法之外,仍然需要提高化合物的对映异构纯度的方法,因为方法偏差可以导致 ee 较低,即使该方法能够提供具有高 ee 的化合物。进一步,开发可以提高产品 ee 的方法可以提供给对映异构体富集的或对映异构体纯的化合物可替代的合成路线,得到商品成本较低和更流线的 (streamlined) 制造过程。

[0010] 已经报道了基于外消旋混合物和对映体纯的种类之间热力学关系通过结晶提高 ee 的一般方法 (Wang 等人 ,Org.Proc.Res.Dev.,2005,9,670 ;Wang 等人 ,Org.Proc.Res.Dev.,2008,12,282 ;Jacques,J. ;Collet,A. ;Wilen,S.H.Enatniomers,Racemates and Resolution ;John Wiley&Sons:New York,1981)。用于直接提高 ee 的结晶方法的开发通常包括三个步骤 :(1) 确定外消旋物 (聚集物 (conglomerate)、外消旋化合物或假外消旋物 (pseudoracemate)) 在感兴趣的温度的热力学稳定相,(2) 获得关键溶解度数据 ;和 (3) 设计结晶方法。

[0011] 大部分外消旋混合物优选地形成外消旋化合物 (参见 Jacques 的著作)。外消旋化合物和纯对映异构体在溶剂存在下的饱和溶解度被称为共晶点 (eutectic point)。溶解度的比例,即“共晶对映体过量”(ee_{eu}) 是评价给定体系的手性提升能力 (upgrade capability) 的一个有用参数。ee_{eu}是由 R- 和 S- 对映异构体的相对溶解度计算的 :ee_{eu} = ([主要的 -[少量的])/([主要的]+[少量的]),其中 [主要的] 为处于共晶状态的主要对映异构体的溶解度,[少量的] 为处于共晶状态的少量对映异构体的溶解度。条件是使用外消旋化合物和单一对映异构体在稀溶液中的最稳定的结晶形式,ee_{eu}应当与溶剂选择无关,除非所述形式的一种或两种为溶剂化物和 / 或研究的溶剂是手性的。在所有情形中,ee_{eu}都可以取决于温度。

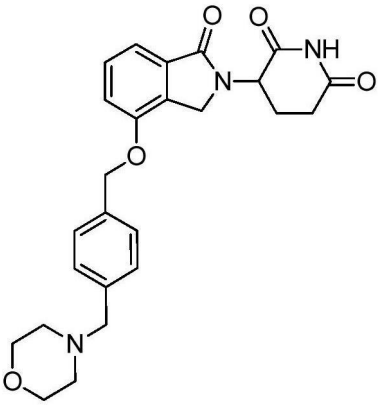
[0012] 在外消旋化合物的情形中,为了提高化合物在固体中的 ee 期望低 ee_{eu}。当外消旋化合物具有比单一对映异构体相对高溶解度时,这可以发生。在低 ee_{eu}的情形中,可以通过在指定溶剂中研磨或重结晶粗混合物、接着过滤进行方便的纯化,其将得到对映异构体富集的或对映异构体纯的固体,两种对映异构体的混合物都溶于滤液中。

[0013] 鉴别低 ee_{eu}条件通常需要大量结晶形式的溶解性、溶剂和条件的广泛筛选,在许多情形下仍然不可获得。

[0014] 4. 发明简述

[0015] 本文提供了制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法 :

[0016]

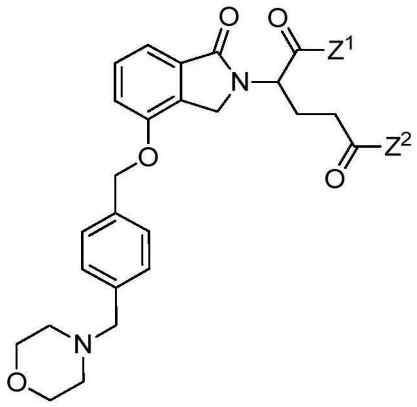


(I)

[0017] 式 (I) 的化合物具有化学名称 3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉 -2- 基)哌啶 -2,6- 二酮。在一种实施方式中,化合物为 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉 -2- 基)哌啶 -2,6- 二酮或其可药用盐。在一种实施方式中,化合物为 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉 -2- 基)哌啶 -2,6- 二酮盐酸盐,其也称为 (3S)-3-(4--{[4-(吗啉 -4- 基甲基)苯甲基]氧基}-1-氧代 -1,3- 二氢 -2H- 异吲哚 -2- 基)哌啶 -2,6- 二酮盐酸盐 (1:1),或 2,6- 哌啶二酮,3-[1,3- 二氢 -4-[[4-(4- 吗啉基甲基)苯基]甲氧基]-1- 氧代 -2H- 异吲哚 -2- 基]-、(3S)-、盐酸盐 (1:1)。

[0018] 在一种实施方式中,本文提供了用于制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法,包括 :

[0019] (步骤 1.1) 在适于酯向酸转化的条件下,将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐 :



(II)

[0020] 其中

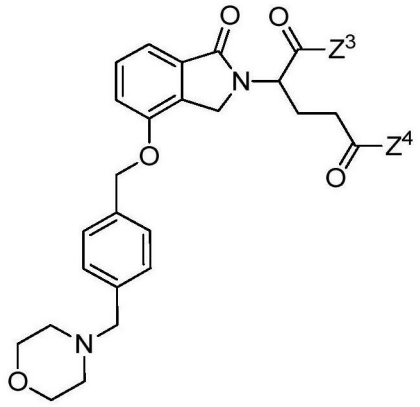
[0021] (i)Z^1为 NHY,和 Z^2为 OR ;或

[0022] (ii)Z^1为 OR,和 Z^2为 NHY ;

[0023] 其中 R 和 Y 为本文别处定义的 ;

[0024] 转化成对映异构体富集的或对映异构体纯的式 (III) 的化合物或其盐 :

[0025]



(III),

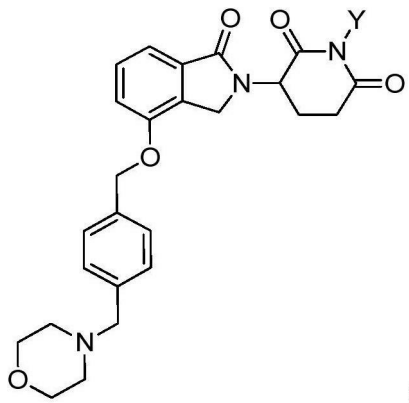
[0026] 其中

[0027] (i)Z^3为 NHY,和 Z^4为 OH ;或

[0028] (ii)Z^3为 OH,和 Z^4为 NHY ;

[0029] (步骤 1.2) 在适于环化的条件下,使对映异构体富集的或对映异构体纯的式 (III) 的化合物环化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物 :

[0030]



(I-a),

[0031] (步骤 1.3) 当 Y 不为氢时,在适于脱保护的条件下,使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物 ;和

[0032] (步骤 1.4) 任选地在适于成盐的条件下,将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐。

[0033] 本文还提供了用于提高式 (I) 的化合物或其盐和 / 或溶剂化物的对映异构纯度的方法。在一种实施方式中,不受任何特定理论的束缚,这种方法是基于 (S)- 和外消旋的 3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮或其盐和 / 或溶剂化物之间的热力学关系。

5. 附图说明

[0034] 图 1 描绘了 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮盐酸盐的差示扫描量热法 (DSC) 的热分析图。

[0035] 图 2 描绘了 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮盐酸盐的 X- 射线粉末衍射图 (XRD)。

[0036] 图 3 描绘了 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉 -2- 基)哌啶 -2,6- 二酮盐酸盐的热重量分析 (TGA) 的热分析图。

[0037] 图 4 描绘了 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉 -2- 基)哌啶 -2,6- 二酮的 HCl 盐在 IPA/ 水中的共晶溶解度。

[0038] 图 5 描绘了 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉 -2- 基)哌啶 -2,6- 二酮的 HCl 盐在多种溶剂体系中呈温度的函数的共晶溶解度。

[0039] 6. 详细说明

[0040] 6.1 定义

[0041] 如本文使用的且除非另有说明,术语本文提供的“方法(工艺)”是指用于制备本文提供的化合物的本文公开的方法。本发明也涵盖对本文公开的方法(例如,起始原料、试剂、保护基、溶剂、温度、反应时间、纯化)的修饰。

[0042] 如本文使用的且除非另有说明,术语“加入”、“反应”、“处理”等是指使一种反应物、试剂、溶剂、催化剂、反应基团等与另一种反应物、试剂、溶剂、催化剂、反应基团等接触。反应物、试剂、溶剂、催化剂、反应基团等可以单独、同时或分开加入,并且可以以任何顺序加入。它们可以在热的存在或不存在下并且可以任选地地在惰性气氛下加入。“反应”可以指原位形成或其中反应基团在同一分子中的分子内反应。

[0043] 如本文使用的且除非另有说明,术语“转化”是指使现有 (at hand) 化合物接受适于进行期望的现有化合物的形成的反应条件。

[0044] 如本文使用的且除非另有说明,“一锅”法是指制备期望的产物的方法,其中同时或连续地加入所有反应物,并且其中在期望产物的形成基本上完成之前不进行所形成任何中间体的分离、隔离和 / 或纯化。“一锅”法优选地在单个容器中进行,但是可以在多于一个容器中进行。

[0045] 如本文使用的且除非另有说明,“基本上完成 (substantially complete)”或推进至“实质上完成 (substantial completion)”的反应是指包含超过约 50%(产率%)、在一种实施方式中超过约 60%(产率%)、在一种实施方式中超过约 70%(产率%)、在一种实施方式中超过约 80%(产率%)、在一种实施方式中超过约 90%(产率%)、在另一种实施方式中超过约 95%(产率%)以及在另一种实施方式中,超过约 97%(产率%)的期望产物的反应。

[0046] 如本文使用的且除非另有说明,“可药用形式”包括化合物的任何可药用盐、溶剂化物、立体异构体、多晶型物或前药。

[0047] 如本文使用的且除非另有说明,术语“盐”包括,但不限于本文公开的化合物中可以存在的酸性或碱性基团的盐。天然碱性的化合物能够与各种无机酸和有机酸形成广泛种类的盐。可以用于制备这种碱性化合物的酸是形成包含阴离子的盐的那些酸,所述盐包括,但不限于乙酸盐、苯磺酸盐、苯甲酸盐、碳酸氢盐、酒石酸氢盐、溴化物、乙二胺四乙酸钙、樟脑磺酸盐、碳酸盐、氯化物、溴化物、碘化物、柠檬酸盐、二盐酸盐、乙二胺四乙酸盐、乙二磺酸盐、依托酸盐 (estolate)、乙磺酸盐、富马酸盐、葡庚酸盐、葡糖酸盐、谷氨酸盐、乙醇酰对氨基苯基砷酸盐 (glycollylarsanilate)、己基间苯二酚酸盐 (hexylresorcinate)、哈胺 (hydrabamine)、羟基萘甲酸盐、羟乙基磺酸盐、乳酸盐、乳糖醛酸盐、苹果酸盐、马来酸盐、扁桃酸盐、甲磺酸盐、甲基硫酸盐、肉豆蔻醇盐 (panthothenate)、磷酸盐 / 二磷酸盐、

聚半乳糖醛酸盐、水杨酸盐、硬脂酸盐、琥珀酸盐、硫酸盐、丹宁酸盐、酒石酸盐、茶氯酸盐(teoclate)、三乙基碘酸盐和双羟萘酸盐。除了上述酸之外，包括氨基的化合物也可以与各种氨基酸形成盐。天然酸性的化合物能够与各种阳离子形成碱盐。这种盐的非限制性实例包括碱金属盐或碱土金属盐，并且在某些实施方式中，包括钙盐、镁盐、钠盐、锂盐、锌盐、钾盐、和铁盐。天然酸性的化合物也能够与包括氨基的化合物形成碱盐。

[0048] 如本文使用的且除非另有说明，术语“溶剂化物”是指进一步包括化学计量的或非化学计量的量的非共价分子间作用力结合的溶剂的化合物。当溶剂为水时，溶剂化物为水合物。

[0049] 如本文使用的且除非另有说明，术语“前药”是指可以在生物学条件（体外或体内）下水解、氧化、或以其他方式反应性提供化合物的该化合物的衍生物。前药的实例包括，但不限于包含可生物水解的部分的化合物，所述可生物水解的部分为如可生物水解的酰胺、可生物水解的酯、可生物水解的氨基甲酸酯、可生物水解的碳酸酯、可生物水解的酰脲和可生物水解的磷酸酯类似物。前药的其他实例包括包含 -NO、$-NO_2$、-ONO 或 $-ONO_2$部分的化合物。前药通常可以使用熟知的方法制备，如在 Burger's Medicinal Chemistry and Drug Discovery,172-178,949-982(Manfred E.Wolff 编著，第 5 版，1995) 和 Design of Prodrugs(H.Bundgaard 编著，Elselvier,New York1985) 中描述的方法。

[0050] 如本文使用的且除非另有说明，术语“可生物水解的氨基甲酸酯”、“可生物水解的碳酸酯”、“可生物水解的酰脲”和“可生物水解的磷酸酯”分别是指具有下述性质的化合物的氨基甲酸酯、碳酸酯、酰脲和磷酸酯：1) 不会干扰化合物的生物活性，但是在体内可赋予化合物有利的性质如摄取、作用持续时间或作用开始；或 2) 无生物学活性，但是在体内转化成生物学活性化合物。可生物水解的氨基甲酸酯的实例包括，但不限于氨基甲酸酯，其包括低级烷基胺、取代的乙二胺、氨基酸、羟基烷基、杂环和杂芳香族胺和聚醚胺部分。

[0051] 如本文使用的且除非另有说明，术语“立体异构体”涵盖所有对映异构体 / 立体异构体纯的和对映异构体 / 立体异构体富集的本文提供的化合物。

[0052] 如果例如没有用粗体或虚线指示结构或其部分的立体化学，则该结构或其部分应解释为涵盖化合物的所有对映异构体纯的、对映异构体富集的、非对映异构体纯的、非对映异构体富集的和外消旋的混合物。

[0053] 除非另有说明，否则如本文可互换使用的术语“对映异构体富集的”和“对映异构体纯的”是指其中一种对映异构体的重量百分数大于外消旋组合物的对照混合物中一种对映异构体的含量（例如，大于 1:1 重量）的组合物。例如，(S)- 对映异构体的对映异构体富集的制剂指具有相对于 (R)- 对映异构体大于 50％重量（如至少 75％重量，并且甚至如至少 80％重量）的 (S)- 对映异构体的化合物制剂。在某些实施方式中，富集可以远大于约 80％重量，规定“基本上光学富集的”、“基本上对映异构体富集的”、“基本上对映异构体纯的”或“基本上非外消旋的”制剂指相对于其他对映异构体具有至少 85％重量（如，至少 90％重量，并且如至少 95％重量）的一种对映异构体的组合物的制剂。在某些实施方式中，每单位质量的对映异构体富集的组合物具有比该组合物的外消旋混合物对于治疗应用更高的效价。

[0054] 如本文使用的且除非另有说明，“多晶型物”是指以超过一种结晶形式 / 结构存在的结晶化合物。当由于晶体堆积 (crystal packing) 中差异存在多晶型时，其被称为堆积

型多晶型(packing polymorphism)。多晶型也可以由于构象多晶型中同一分子的不同构象异构体(conformers)引起。在假多晶型中,不同的晶体类型是水合或溶剂化的结果。

[0055] 如本文使用的且除非另有说明,术语“卤代”、“卤素”等是指 -F、-Cl、-Br 或 -I。

[0056] 如本文使用的且除非另有说明,术语“烷基”是指具有如本文指定的碳原子数的饱和的直链或支链烃。在某些实施方式中,烷基基团具有 1 至 15、1 至 10、1 至 6、或 1 至 3 个碳原子。代表性的饱和的直链烷基包括 - 甲基、- 乙基、- 正丙基、- 正丁基、- 正戊基和 - 正己基 ;而饱和的支链烷基包括 - 异丙基、- 仲丁基、- 异丁基、- 叔丁基、- 异戊基、2- 甲基丁基、3- 甲基丁基、2- 甲基戊基、3- 甲基戊基、4- 甲基戊基、2- 甲基己基、3- 甲基己基、4- 甲基己基、5- 甲基己基、2,3- 二甲基丁基等。术语“烷基”也涵盖环烷基。

[0057] 如本文使用的且除非另有说明,术语“杂烷基”是指其中一个或多个(在某些实施方式中,1 至 3 个)碳原子被杂原子(例如,但不限于 N、S、O 和 Si)替代,并且氮和硫原子可以任选地被氧化且氮原子可以任选地被季铵化的烷基。实例包括 $-CH_2-CH_2-O-CH_3$、$-CH_2-CH_2-NH-CH_3$、$-CH_2-CH_2-N(CH_3)_2$、$-CH_2-S-CH_2-CH_3$、$-CH_2-CH_2-S(O)-CH_3$、$-CH_2-CH_2-S(O)_2-CH_3$、$-Si(CH_3)_3$和 $-CH_2-CH=N-OCH_3$。至多两个杂原子可以是连续的,如例如 $-CH_2-NH-OCH_3$ 和 $-CH_2-O-Si(CH_3)_3$。当前缀如 C_{2-6} 用于指杂烷基基团时,碳的数量(在该实例中,2-6 个)意味着也包括杂原子。例如,C_{2-6} 杂烷基基团意味着包括例如 $-CH_2OH$(一个碳原子和一个替代碳原子的杂原子)和 $-CH_2SH$。在某些实施方式中,杂烷基基团具有 2 至 15、2 至 10、2 至 6、或 2 至 3 个碳和杂原子。

[0058] 如本文使用的且除非另有说明,术语“环烷基”是指烷基类型,其为环状的且包含 3 至 15、3 至 9、3 至 6、或 3 至 5 个碳原子,而在碳原子之间没有交替或共振的双键。其可以包含 1 至 4 个环。未取代的环烷基的实例包括,但不限于环丙基、环丁基、环戊基、环己基和金刚烷基。环烷基可以用一个或多个取代基取代。在某些实施方式中,环烷基可以是稠合芳基或杂芳基基团的环烷基。

[0059] 如本文使用的且除非另有说明,术语“杂环烷基”是指其中一个或多个(在某些实施方式中,1 至 3)个碳原子被杂原子如但不限于 N、S 和 O 替代的环烷基。在某些实施方式中,杂环烷基基团包含 3 至 15、3 至 9、3 至 6、或 3 至 5 个碳和杂原子。在某些实施方式中,杂环烷基可以是稠合芳基或杂芳基基团的杂环烷基。当前缀如 C_{3-6} 用于指杂环烷基时,碳的数量(在该实例中,3-6 个)意味着也包括杂原子。例如,$C3_{-6}$ 杂环烷基基团意味着包括例如四氢吡喃基(五个碳原子和一个取代碳原子的杂原子)。

[0060] 如本文使用的且除非另有说明,术语“芳基”是指包含 5 至 14 个环原子的碳环芳香环芳基基团的环原子全部是碳原子。芳基环结构包括具有一个或多个环结构(如单环、二环或三环化合物)以及苯并稠合的碳环部分(如 5,6,7,8- 四氢萘基)等的化合物 . 特别地 , 芳基基团可以是单环、二环或三环环。代表性的芳基基团包括苯基、蒽基、芴基、茚基、奠基、菲基和萘基。

[0061] 如本文使用的且除非另有说明,术语“杂芳基”是指单环或多环芳香环体系,在某些实施方式中,该体系具有约 5 至约 15 个成员,其中环体系的一个或多个(在某些实施方式中,1 至 3 个)原子为杂原子,即不同于碳的元素,包括但不限于 N、O 或 S。杂芳基基团可以任选地稠合苯环。杂芳基基团包括,但不限于呋喃基、咪唑基、吲哚啉基、吡咯烷基、嘧啶基、四唑基、噻吩基、吡啶基、吡咯基、N- 甲基吡咯基、喹啉基和异喹啉基。

[0062] 如本文使用的且除非另有说明，术语“芳烷基”指其中烷基的一个氢原子被芳基基团替代的烷基。

[0063] 当没有指定任何给定取代基（例如“卤代烷基”）的数量时，可以存在一个或多个取代基。例如，“卤代烷基”可以包括一个或多个相同或不同的卤素。

[0064] 如本文使用的且除非另有说明，术语“醇”是指用 -OH 基团取代的任何化合物。

[0065] 如本文使用的且除非另有说明，术语“氨基”或“氨基基团”是指下式的一价基团：$-NH_2$、-NH（烷基）、-NH（芳基）、$-N(烷基)_2$、$-N(芳基)_2$或 -N（烷基）（芳基）。

[0066] 除非另有说明，否则本文提供的化合物，包括用于制备本文提供的化合物的包含反应性官能团（如，不限于羧基、羟基和氨基部分）的中间体，还包括保护的其衍生物。“保护的衍生物”为其中反应性位点用一个或多个保护基（也称为封端基团）封阻的那些化合物。合适的保护基是本领域普通技术人员熟知的。保护基的选择和用途及设置或除去保护基的反应条件描述在 T.W.Green,Protective Groups in Organic Synthesis（第三版，Wiley,New York,1999）中，将其全文并入本文作为参考。

[0067] 氨基保护基是本领域公知的，包括在 T.W.Green,Protective Groups in Organic Synthesis 中详细描述的那些。氨基保护基包括，但不限于 $-OH$、$-OR^{aa}$、$-N(R^{cc})_2$、$-C(=O)R^{aa}$、$-C(=O)N(R^{cc})_2$、$-CO_2R^{aa}$、$-SO_2R^{aa}$、$-C(=NR^{cc})R^{aa}$、$-C(=NR^{cc})OR^{aa}$、$-C(=NR^{cc})N(R^{cc})_2$、$-SO_2N(R^{cc})_2$、$-SO_2R^{cc}$、$-SO_2OR^{cc}$、$-SOR^{aa}$、$-C(=S)N(R^{cc})_2$、$-C(=O)SR^{cc}$、$-C(=S)SR^{cc}$、C_{1-10}烷基（例如，芳烷基）、C_{2-10}烯基、C_{2-10}炔基、C_{3-10}碳环基、3-14 元杂环基、C_{6-14}芳基和 5-14 元杂芳基基团，其中每个烷基、烯基、炔基、碳环基、杂环基、芳烷基、芳基和杂芳基独立地被 0、1、2、3、4 或 5 个 R^{dd}基团取代；其中

[0068] R^{aa}每次出现时独立地选自 C_{1-10}烷基、C_{1-10}全卤烷基、C_{2-10}烯基、C_{2-10}炔基、C_{3-10}碳环基、3-14 元杂环基、C_{6-14}芳基和 5-14 元杂芳基，其中每个烷基、烯基、炔基、碳环基、杂环基、芳基和杂芳基独立地被 0、1、2、3、4 和 5 个 R^{dd}基团取代；

[0069] R^{bb}每次出现时独立地选自氢、$-OH$、$-OR^{aa}$、$-N(R^{cc})_2$、$-CN$、$-C(=O)R^{aa}$、$-C(=O)N(R^{cc})_2$、$-CO_2R^{aa}$、$-SO_2R^{aa}$、$-C(=NR^{cc})OR^{aa}$、$-C(=NR^{cc})N(R^{cc})_2$、$-SO_2N(R^{cc})_2$、$-SO_2R^{cc}$、$-SO_2OR^{cc}$、$-SOR^{aa}$、$-C(=S)N(R^{cc})_2$、$-C(=O)SR^{cc}$、$-C(=S)SR^{cc}$、$-P(=O)_2R^{aa}$、$-P(=O)(R^{aa})_2$、$-P(=O)_2N(R^{cc})_2$、$-P(=O)(NR^{cc})_2$、C_{1-10}烷基、C_{1-10}全卤烷基、C_{2-10}烯基、C_{2-10}炔基、C_{3-10}碳环基、3-14 元杂环基、C_{6-14}芳基和 5-14 元杂芳基，或者连接 N 原子的两个 R^{cc}基团结合形成 3-14 元杂环基或 5-14 元杂芳基环，其中每个烷基、烯基、炔基、碳环基、杂环基、芳基和杂芳基独立地被 0、1、2、3、4 或 5 个 R^{dd}基团取代。

[0070] R^{cc}每次出现时独立地选自氢、C_{1-10}烷基、C_{1-10}全卤烷基、C_{2-10}烯基、C_{2-10}炔基、C_{3-10}碳环基、3-14 元杂环基、C_{6-14}芳基和 5-14 元杂芳基，或者连接 N 原子的两个 R^{cc}基团结合形成 3-14 元杂环基或 5-14 元杂芳基环，其中每个烷基、烯基、炔基、碳环基、杂环基、芳基和杂芳基独立地被 0、1、2、3、4 或 5 个 R^{dd}基团取代。

[0071] R^{dd}每次出现时独立地选自卤素、$-CN$、$-NO_2$、$-N_3$、$-SO_2H$、$-SO_3H$、$-OH$、$-OR^{ee}$、$-ON(R^{ff})_2$、$-N(R^{ff})_2$、$-N(R^{ff})_3^+X^-$、$-N(OR^{ee})R^{ff}$、$-SH$、$-SR^{ee}$、$-SSR^{ee}$、$-C(=O)R^{ee}$、$-CO_2H$、$-CO_2R^{ee}$、$-OC(=O)R^{ee}$、$-OCO_2R^{ee}$、$-C(=O)N(R^{ff})_2$、$-OC(=O)N(R^{ff})_2$、$-NR^{ff}C(=O)R^{ee}$、$-NR^{ff}CO_2R^{ee}$、$-NR^{ff}C(=O)N(R^{ff})_2$、$-C(=NR^{ff})OR^{ee}$、$-OC(=NR^{ff})R^{ee}$、$-OC(=NR^{ff})OR^{ee}$、$-C(=NR^{ff})N(R^{ff})_2$、$-OC(=NR^{ff})N(R^{ff})_2$、$-NR^{ff}C(=NR^{ff})N(R^{ff})_2$、$-NR^{ff}SO_2R^{ee}$、-

$SO_2N(R^{ff})_2$、-SO_2R^{ee}、-SO_2OR^{ee}、-OSO_2R^{ee}、-S(=O)R^{ee}、-$Si(R^{ee})_3$、-$OSi(R^{ee})_3$、-C(=S)$N(R^{ff})_2$、-C(=O)SR^{ee}、-C(=S)SR^{ee}、-SC(=S)SR^{ee}、-P(=O)$_2R^{ee}$、-P(=O)$(R^{ee})_2$、-OP(=O)$(R^{ee})_2$、-OP(=O)$(OR^{ee})_2$、C_{1-6}烷基、C_{1-6}全卤烷基、C_{2-6}烯基、C_{2-6}炔基、C_{3-10}碳环基、3-10元杂环基、C_{6-10}芳基、5-10元杂芳基，其中每个烷基、烯基、炔基、碳环基、杂环基、芳基和杂芳基独立地被0、1、2、3、4或5个R^{gg}基团取代，或者两个成对的R^{dd}取代基可以结合形成=O或=S。

[0072] R^{ee}每次出现时独立地选自C_{1-6}烷基、C_{1-6}全卤烷基、C_{2-6}烯基、C_{2-6}炔基、C_{3-10}碳环基、C_{6-10}芳基、3-10元杂环基和3-10元杂芳基，其中每个烷基、烯基、炔基、碳环基、杂环基、芳基和杂芳基独立地被0、1、2、3、4和5个R^{gg}基团取代；

[0073] R^{ff}每次出现时独立地选自氢、C_{1-6}烷基、C_{1-6}全卤烷基、C_{2-6}烯基、C_{2-6}炔基、C_{3-10}碳环基、3-10元杂环基、C_{6-10}芳基和5-10元杂芳基，或者连接N原子的两个R^{ff}基团结合形成3-14元杂环基或5-14元杂芳基环，其中每个烷基、烯基、炔基、碳环基、杂环基、芳基和杂芳基独立地被0、1、2、3、4或5个R^{gg}基团取代；和

[0074] R^{gg}每次出现时独立地为卤素、-CN、-NO_2、-N_3、-SO_2H、-SO_3H、-OH、-OC_{1-6}烷基、-ON(C_{1-6}烷基)$_2$、-N(C_{1-6}烷基)$_2$、-N(C_{1-6}烷基)$_3$X、-NH(C_{1-6}烷基)$_2$X、-NH_2(C_{1-6}烷基)X、-NH_3X、-N(OC_{1-6}烷基)(C_{1-6}烷基)、-N(OH)(C_{1-6}烷基)、-NH(OH)、-SH、-SC_{1-6}烷基、-SS(C_{1-6}烷基)、-C(=O)(C_{1-6}烷基)、-CO_2H、-CO_2(C_{1-6}烷基)、-OC(=O)(C_{1-6}烷基)、-OCO_2(C_{1-6}烷基)、-C(=O)NH_2、-C(=O)N(C_{1-6}烷基)$_2$、-OC(=O)NH(C_{1-6}烷基)、-NHC(=O)(C_{1-6}烷基)、-N(C_{1-6}烷基)C(=O)(C_{1-6}烷基)、-$NHCO_2$(C_{1-6}烷基)、-NHC(=O)N(C_{1-6}烷基)$_2$、-NHC(=O)NH(C_{1-6}烷基)、-NHC(=O)NH_2、-C(=NH)O(C_{1-6}烷基)、-OC(=NH)(C_{1-6}烷基)、-OC(=NH)OC_{1-6}烷基、-C(=NH)N(C_{1-6}烷基)$_2$、-C(=NH)NH(C_{1-6}烷基)、-C(=NH)NH_2、-OC(=NH)N(C_{1-6}烷基)$_2$、-OC(NH)NH(C_{1-6}烷基)、-OC(NH)NH_2、-NHC(NH)N(C_{1-6}烷基)$_2$、-NHC(=NH)NH_2、-$NHSO_2$(C_{1-6}烷基)、-SO_2N(C_{1-6}烷基)$_2$、-SO_2NH(C_{1-6}烷基)、-SO_2NH_2、-SO_2C_{1-6}烷基、-SO_2OC_{1-6}烷基、-OSO_2C_{1-6}烷基、-SOC_{1-6}烷基、-Si(C_{1-6}烷基)$_3$、-$OSi(C_{1-6}烷基)_3$-C(=S)N(C_{1-6}烷基)$_2$、C(=S)NH(C_{1-6}烷基)、C(=S)NH_2、-C(=O)S(C_{1-6}烷基)、-C(=S)SC_{1-6}烷基、-SC(=S)SC_{1-6}烷基、-P(=O)$_2$(C_{1-6}烷基)、-P(=O)(C_{1-6}烷基)$_2$、-OP(=O)(C_{1-6}烷基)$_2$、-OP(=O)(OC_{1-6}烷基)$_2$、C_{1-6}烷基、C_{1-6}全卤烷基、C_{2-6}烯基、C_{2-6}炔基、C_{3-10}碳环基、C_{6-10}芳基、3-10元杂环基、5-10元杂芳基；或两个成对的R^{gg}取代基可以结合形成=O或=S；

[0075] 其中X^-为抗衡离子。

[0076] 如本文使用的“抗衡离子”是与带正电荷的季胺缔合的带负电荷的基团，以便保持电子中性。示例性的抗衡离子包括卤化物离子（例如，F^-、Cl^-、Br^-、I^-）、NO_3^-、ClO_4^-、OH^-、$H_2PO_4^-$、HSO_4^-、磺酸盐离子（例如，甲磺酸盐、三氟甲磺酸盐、对-甲苯磺酸盐、苯磺酸盐、10-樟脑磺酸盐、萘-2-磺酸盐、萘-1-磺酸-5-磺酸盐、乙烷-1-磺酸-2-磺酸盐等）和羧酸盐离子（例如，乙酸盐、醋酸盐(ethanoate)、丙酸盐、苯甲酸盐、甘油酸盐、乳酸盐、酒石酸盐、羟乙酸盐等）。

[0077] 例如，氨基保护基如酰胺基（例如，-C(=O)R^{aa}）包括，但不限于，甲酰胺、乙酰胺、氯乙酰胺、三氯乙酰胺、三氟乙酰胺、苯基乙酰胺、3-苯基丙酰胺、吡啶酰胺、3-吡啶基甲酰胺、N-苯甲酰基苯基丙氨酰基衍生物、苯甲酰胺、对苯基苯甲酰胺、邻硝基(nito)苯基乙酰

胺、邻硝基苯氧基乙酰胺、乙酰乙酰胺、(N'- 二硫代苄氧基羰基氨基）乙酰胺、3-（对羟基苯基）丙酰胺、3-（邻硝基苯基）丙酰胺、2- 甲基 -2-（邻硝基苯氧基）丙酰胺、2- 甲基 -2-（邻苯基偶氮苯氧基）丙酰胺、4- 氯丁酰胺、3- 甲基 -3- 硝基丁酰胺、邻硝基肉桂酰胺、N- 乙酰基甲硫氨酸衍生物、邻硝基苯甲酰胺和邻 -（苯甲酰氧基甲基）苯甲酰胺。

[0078] 氨基保护基如氨基甲酸酯基团（例如，-C(=O)OR^{aa}）包括，但不限于，氨基甲酸甲酯、氨基甲酸乙酯、9- 芴基甲基氨基甲酸酯 (Fmoc)、9-(2- 磺基）芴基甲基氨基甲酸酯、9-(2,7- 二溴）芴基甲基氨基甲酸酯、2,7- 二叔丁基 -[9-(10,10- 二氧代 -10,10,10,10- 四氢硫代呫吨基)] 甲基氨基甲酸酯 (DBD-Tmoc)、4- 甲氧基苯甲酰甲基氨基甲酸酯 (Phenoc)、2,2,2- 三氯乙基氨基甲酸酯 (Troc)、2- 三甲基甲硅烷基乙基氨基甲酸酯 (Teoc)、2- 苯基乙基氨基甲酸酯 (hZ)、1-(1- 金刚烷基）-1- 甲基乙基氨基甲酸酯 (Adpoc)、1,1- 二甲基 -2- 卤代乙基氨基甲酸酯、1,1- 二甲基 -2,2- 二溴乙基氨基甲酸酯 (DB-t-BOC)、1,1- 二甲基 -2,2,2- 三氯乙基氨基甲酸酯 (TCBOC)、1- 甲基 -1-(4- 联苯基）乙基氨基甲酸酯 (Bpoc)、1-(3,5- 二 - 叔丁基苯基）-1- 甲基乙基氨基甲酸酯 (t-Bumeoc)、2-(2'- 和 4'- 吡啶基）乙基氨基甲酸酯 (Pyoc)、2-(N,N- 二环己基甲酰胺基）乙基氨基甲酸酯、氨基甲酸叔丁酯 (BOC)、1- 金刚烷基氨基甲酸酯 (Adoc)、氨基甲酸乙烯酯 (Voc)、氨基甲酸烯丙酯 (Alloc)、1- 异丙基烯丙基氨基甲酸酯 (Ipaoc)、肉桂基氨基甲酸酯 (Coc)、4- 硝基肉桂基氨基甲酸酯 (Noc)、8- 喹啉基氨基甲酸酯、N- 羟基哌啶基氨基甲酸酯、烷基二硫代氨基甲酸酯、氨基甲酸苄酯 (Cbz)、对甲氧基苄基氨基甲酸酯 (Moz)、对硝基 (nito) 苄基氨基甲酸酯、对溴苄基氨基甲酸酯、对氯苄基氨基甲酸酯、2,4- 二氯苄基氨基甲酸酯、4- 甲基亚磺酰基苄基氨基甲酸酯 (Msz)、9- 蒽基甲基氨基甲酸酯、二苯基甲基氨基甲酸酯、2- 甲硫基乙基氨基甲酸酯、2- 甲基磺酰基乙基氨基甲酸酯、2-（对甲苯磺酰基）乙基氨基甲酸酯、[2-(1,3- 二噻烷基)] 甲基氨基甲酸酯 (Dmoc)、4- 甲硫基苯基氨基甲酸酯 (Mtpc)、2,4- 二甲硫基苯基氨基甲酸酯 (Bmpc)、2- 磷鎓基乙基氨基甲酸酯 (Peoc)、2- 三苯基磷鎓基异丙基氨基甲酸酯 (Ppoc)、1,1- 二甲基 -2- 氰基乙基氨基甲酸酯、间氯 - 对酰氧基苄基氨基甲酸酯、对（二羟基硼基）苄基氨基甲酸酯、5- 苯并异噁唑基甲基氨基甲酸酯、2-（三氟甲基）-6- 色酮基 (chromonyl) 甲基氨基甲酸酯 (Tcroc)、间硝基苯基氨基甲酸酯、3,5- 二甲氧基苄基氨基甲酸酯、邻硝基苄基氨基甲酸酯、3,4- 二甲氧基 -6- 硝基苄基氨基甲酸酯、苯基（邻硝基苯基）甲基氨基甲酸酯、叔戊基氨基甲酸酯、S- 苄基硫代氨基甲酸酯、对氰基苄基氨基甲酸酯、环丁基氨基甲酸酯、环己基氨基甲酸酯、环戊基氨基甲酸酯、环丙基甲基氨基甲酸酯、对癸氧基苄基氨基甲酸酯、2,2- 二甲氧基羰基乙烯基氨基甲酸酯、邻 -(N,N- 二甲基甲酰胺基）苄基氨基甲酸酯、1,1- 二甲基 -3-(N,N- 二甲基甲酰胺基）丙基氨基甲酸酯、1,1- 二甲基丙炔基氨基甲酸酯、二 (2- 吡啶基）甲基氨基甲酸酯、2- 呋喃基甲基氨基甲酸酯、2- 碘乙基氨基甲酸酯、异冰片基氨基甲酸酯、异丁基氨基甲酸酯、异烟酰基氨基甲酸酯、对（对甲氧基苯基偶氮基）苄基氨基甲酸酯、1- 甲基环丁基氨基甲酸酯、1- 甲基环己基氨基甲酸酯、1- 甲基 -1- 环丙基甲基氨基甲酸酯、1- 甲基 -1-(3,5- 二甲氧基苯基）乙基氨基甲酸酯、1- 甲基 -1-（对苯偶氮苯基）乙基氨基甲酸酯、1- 甲基 -1- 苯基乙基氨基甲酸酯、1- 甲基 -1-(4- 吡啶基）乙基氨基甲酸酯、氨基甲酸苯酯、对（苯基偶氮基）苄基氨基甲酸酯、2,4,6- 三 - 叔丁基苯基氨基甲酸酯、4-（三甲基铵）苄基氨基甲酸酯和 2,4,6- 三甲基苄基氨基甲酸酯。

[0079] 氨基保护基团如磺酰胺基团（例如 $-S(=O)_2R^{aa}$）包括，但不限于，对甲苯磺酰胺（Ts）、苯磺酰胺、2,3,6,-三甲基-4-甲氧基苯磺酰胺（Mtr）、2,4,6-三甲氧基苯磺酰胺（Mtb）、2,6-二甲基-4-甲氧基苯磺酰胺（Pme）、2,3,5,6-四甲基-4-甲氧基苯磺酰胺（Mte）、4-甲氧基苯磺酰胺（Mbs）、2,4,6-三甲基苯磺酰胺（Mts）、2,6-二甲氧基-4-甲基苯磺酰胺（iMds）、2,2,5,7,8-五甲基苯并二氢吡喃-6-磺酰胺（Pmc）、甲烷磺酰胺（Ms）、β-三甲基甲硅烷基乙烷磺酰胺（SES）、9-蒽磺酰胺、4-(4',8'-二甲氧基萘基甲基）苯磺酰胺（DNMBS）、苄基磺酰胺、三氟甲基磺酰胺和苯甲酰甲基磺酰胺。

[0080] 其他氨基保护基包括，但不限于，吩噻嗪基-(10)-羰基衍生物、N'-对甲苯磺酰基氨基羰基衍生物、N'-苯基氨基硫代羰基衍生物、N-苯甲酰基苯基丙氨酰基衍生物、N-乙酰基甲硫氨酸衍生物、4,5-二苯基-3-噁唑啉-2-酮、N-邻苯二甲酰亚胺、N-二硫杂琥珀酰亚胺（Dts）、N-2,3-二苯基马来酰亚胺、N-2,5-二甲基吡咯、N-1,1,4,4-四甲基二甲硅烷基氮杂环戊烷加合物（STABASE）、5-取代的1,3-二甲基-1,3,5-三氮杂环己烷-2-酮、5-取代的1,3-二苄基-1,3,5-三氮杂环己烷-2-酮、1-取代的3,5-二硝基-4-吡啶酮、N-甲基胺、N-烯丙基胺、N-[2-(三甲基甲硅烷基）乙氧基]甲基胺（SEM）、N-3-乙酰氧基丙基胺、N-(1-异丙基-4-硝基-2-氧代-3-吡咯啉-3-基）胺、季铵盐、N-苄基胺、N-二（4-甲氧基苯基）甲基胺、N-5-二苯并环庚基胺、N-三苯基甲基胺（Tr）、N-[(4-甲氧基苯基）二苯基甲基]胺（MMTr）、N-9-苯基芴基胺（PhF）、N-2,7-二氯-9-芴基亚甲基胺、N-二茂铁基甲基氨基（Fcm）、N-2-吡啶甲基氨基N'-氧化物、N-1,1-二甲基硫代亚甲基胺、N-亚苄基胺、N-对甲氧基亚苄基胺、N-二苯基亚甲基胺、N-[(2-吡啶基）2,4,6-三甲苯基]亚甲基胺、N-(N',N'-二甲基氨基亚甲基）胺、N,N'-亚异丙基二胺、N-对硝基亚苄基胺、N-亚水杨基胺、N-5-氯亚水杨基胺、N-(5-氯-2-羟基苯基）苯基亚甲基胺、N-亚环己基胺、N-(5,5-二甲基-3-氧代-1-环己烯基）胺、N-硼烷衍生物、N-二苯基硼酸衍生物、N-[苯基（五羰基铬-或钨）羰基]胺、N-铜螯合物、N-锌螯合物、N-硝基胺、N-亚硝基胺、胺N-氧化物、二苯基膦酰胺（Dpp）、二甲基硫代膦酰胺（Mpt）、二苯基硫代膦酰胺（Ppt）、二烷基氨基磷酸酯、二苄基氨基磷酸酯、二苯基氨基磷酸酯、苯亚磺酰胺、邻硝基苯亚磺酰胺（Nps）、2,4-二硝基苯亚磺酰胺、五氯苯亚磺酰胺、2-硝基-4-甲氧基苯亚磺酰胺、三苯基甲基亚磺酰胺、和3-硝基吡啶亚磺酰胺（Npys）。

[0081] 如本文使用的且除非另有说明，基团或试剂的简称或符号具有下述定义：HPLC＝高效液相色谱法；TFA＝三氟乙酸；TFE＝2,2,2-三氟乙醇，THF＝四氢呋喃；CH_3CN＝乙腈；HOAc＝乙酸；DCM＝二氯甲烷。

[0082] 如本文使用的且除非另有说明，术语“取代的”或“取代”当用于描述化学结构或部分时，指其中一个或多个其氢原子被取代基替代的结构部分的衍生物，所述取代基如，但不限于：烷基、烯基、炔基和环烷基；烷氧基烷基；芳酰基；卤素；卤代烷基（例如，三氟甲基）；杂环烷基；卤代烷氧基（例如，三氟甲氧基）；羟基；烷氧基；环烷氧基；杂环氧基；氧代；烷酰基；芳基；杂芳基（例如，吲哚基、咪唑基、呋喃基、噻吩基、噻唑基、吡咯烷基、吡啶基和嘧啶基）；芳基烷基；烷基芳基；杂芳基；杂芳基烷基；烷基杂芳基；杂环基；杂环烷基-烷基；芳氧基、烷酰基氧基；氨基；烷基氨基；芳氨基；芳基烷基氨基；环烷基氨基；杂环氨基；单和二取代的氨基；烷酰基氨基；芳酰基氨基；芳烷酰基氨基；氨基烷基；氨甲酰基（例如，$CONH_2$）；取代的氨甲酰基（例如，CONH-烷基、CONH-芳基、CONH-芳基烷基或其中氮上

存在两个取代基的情形）；羰基；烷氧基羰基；羧基；氰基；酯；醚；胍基；硝基；磺酰基；烷基磺酰基；芳基磺酰基；芳基烷基磺酰基；亚磺酰氨基（例如，SO_2NH_2）；取代的亚磺酰氨基；硫醇；烷硫基；芳硫基；芳基烷硫基；环烷硫基；杂环烷硫基；烷基硫羰基（alkylthiono）；芳基硫羰基；和芳基烷基硫羰基。在某些实施方式中，取代基本身可以被一个或多个化学部分如但不限于本文描述的那些部分取代。

[0083] 如本文使用的且除非另有说明，术语“约”用于说明所给的值是近似的。例如，术语“约”当与反应温度一起使用时，表示所指示温度涵盖在 30％、25％、20％、15％、10％或 5％之内的温度偏差。类似地，术语“约”当与反应时间一起使用时，表示所指示的时期涵盖在 30％、25％、20％、15％、10％或 5％之内的时期偏差。

[0084] 如本文使用的且除非另有说明，“合适的离去基团”是指可以可以离开其连接的碳原子的任何原子或原子团。特别地，合适的离去基团为可以通过接近亲核试剂转移的基团。本领域普通技术人员可以确定什么原子或原子团可以充当合适的离去基团。另外，常规实验可以鉴定任何特定原子或原子团是否可以充当合适的离去基团。优选的合适的离去基团包括其为伯离去基团（例如，伯卤素）的那些，尽管也可以使用仲离去基团。合适的离去基团的实例包括卤素和磺化酯。在卤素中，溴、氯、碘和氟是优选的，溴和氯是特别优选的卤素型离去基团。对于磺化酯，甲磺酸酯、三氟甲磺酸酯、三氯甲磺酸酯、2,2,2- 三氟乙磺酸酯、2,2,2- 三氯乙磺酸酯和对甲苯磺酸酯是特别优选的，但是也可以使用本领域普通技术人员已知其他磺化酯和类似构成的离去基团。

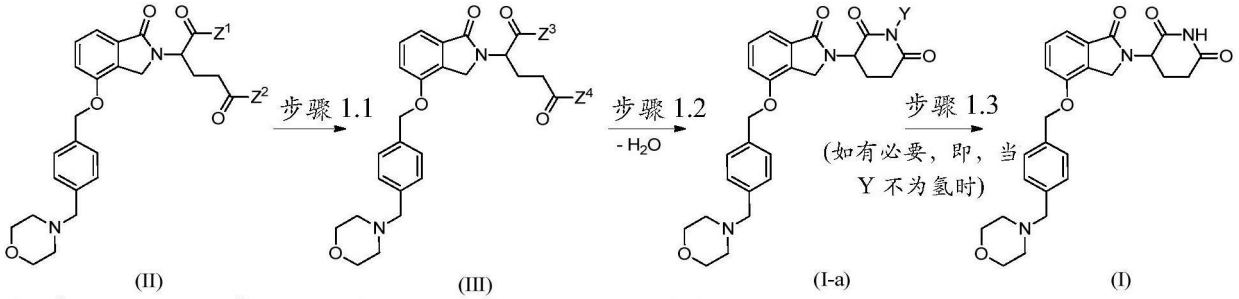
[0085] 应当注意到，如果描述的结构和结构提供的名称之间存在矛盾，则以描述的结构为准。另外，如果结构或结构一部分的立体化学没有以例如粗体或虚线表示，则将该结构或结构部分解释为涵盖其所有立体异构体。

[0086] 6.2 方法

[0087] 6.2.1 化合物 (I) 的制备

[0088] 如下方案 1 中描绘的，本文提供了用于制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法，包括：（步骤 1.1）将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐转化成对映异构体富集的或对映异构体纯的式 (III) 的化合物或其盐；（步骤 1.2）使对映异构体富集的或对映异构体纯的式 (III) 的化合物环化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物；（步骤 1.3）当 Y 不为氢时，使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物；和（步骤 1.4）任选地，将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成可药用盐。在一种实施方式中，在高保持手性中心的构型下发生式 (I) 化合物中戊二酰亚胺环的形成。在一种实施方式中，该方法是有效且可规模化的。

[0089]



(II) (III) (I-a) (I)

(i) Z^1 为 NHY，和 Z^2 为 OR；或 (i) Z^3 为 NHY，和 Z^4 为 OH；或

(ii) Z^1 为 OR，和 Z^2 为 NHY； (ii) Z^3 为 OH，和 Z^4 为 NHY；

[0090] 方案 1

[0091] R 可以为合适的羧基保护基，包括甲基、叔丁基、苯甲基等。其他合适的保护基是本领域普通技术人员熟知的。Y 可以是任何合适的氨基保护基。保护基的选择和使用及设置和除去保护基的反应条件描述在 T.W.Green,Protective Groups in Organic Synthesis(第三版,Wiley,New York,1999) 中，将其全文并入本文作为参考。

[0092] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法，包括：

[0093] (步骤 1.1) 在适用于酯向酸转化的条件下，将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐，其中：

[0094] (i)Z^1为 NHY，和 Z^2为 OR；或

[0095] (ii)Z^1为 OR，和 Z^2为 NHY；其中

[0096] R 为取代的或未取代的烷基、取代的或未取代的环烷基、取代的或未取代的杂烷基、取代的或未取代的杂环烷基、取代的或未取代的芳基、取代的或未取代的杂芳基、取代的或未取代的芳烷基、或合适的羧基保护基；和

[0097] Y 为氢或合适的氨基保护基；转化成对映异构体富集的或对映异构体纯的式 (III) 的化合物或其盐，其中

[0098] (i)Z^3为 NHY，和 Z^4为 OH；或

[0099] (ii)Z^3为 OH，和 Z^4为 NHY；

[0100] (步骤 1.2) 在适于环化的条件下，使对映异构体富集的或对映异构体纯的式 (III) 的化合物环化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物：

[0101] (步骤 1.3) 当 Y 不为氢时，在适于脱保护的条件下，使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物；和

[0102] (步骤 1.4) 任选地在适于成盐的条件下，将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐。

[0103] 在一种实施方式中，式 (I) 的化合物为 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮，其也被称为 (3S)-3-(4-{[4-(吗啉-4-基甲基)苯甲基]氧基}-1-氧代-1,3-二氢-2H-异吲哚-2-基)哌啶-2,6-二酮、或 2,6-哌啶二酮、3-[1,3-二氢-4-[[4-(4-吗啉基甲基)苯基]甲氧基]-1-氧代-2H-异吲哚-2-基]-、(3S)-。

[0104] 在一种实施方式中，R 为 C_{1-6}烷基；C_{3-6}环烷基；C_{1-6}卤代烷基；C_{2-10}杂烷基；C_{3-6}杂

环烷基；被 1 至 3 个芳基取代的 C_{1-6}烷基或 C_{2-10}杂烷基；或 $-SiR^a_3$其中，每个 R^a独立地为 C_{1-6}烷基或 C_{5-14}芳基。

[0105] 在一种实施方式中，R 为甲基、乙基、丙基、异丙基、环丙基、丁基、异丁基、叔丁基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、四氢吡喃基 (THP)、甲氧基乙氧基甲基 (MEM)、2-(三甲基甲硅烷基) 乙氧基甲基胺 (SEM)、苄氧基甲基 (BOM)、2-(三甲基甲硅烷基) 乙基 (TMSE)、2,2,2- 三氯乙基、苄基、三苯基甲基、对 - 甲氧基苄基、2,6- 二甲氧基苄基、三甲基甲硅烷基 (TMS)、三乙基甲硅烷基 (TES)、三异丙基甲硅烷基 (TIPS)、二甲基异丙基甲硅烷基 (IPDMS)、二乙基异丙基甲硅烷基 (DEIPS)、叔丁基二甲基甲硅烷基 (TBDMS)、或叔丁基二苯基甲硅烷基 (TBDPS)。在一种实施方式中，R 为甲基、叔丁基或苄基。在一种实施方式中，R 为甲基。在另一种实施方式中，R 为叔丁基。在又一种实施方式中，R 为苄基。

[0106] 在一种实施方式中，Y 为氢。

[0107] 在一种实施方式中，Y 为合适的氨基保护基。在一种实施方式中，Y 为烯丙基、叔丁基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、苄氧基甲基 (BOM)、2,2,2- 三氯乙氧基甲基、叔丁基二甲基甲硅烷氧基甲基、新戊酰氧基甲基、氰基甲基、吡咯烷子基甲基、甲氧基、苄氧基、甲硫基、三苯基甲硫基、叔丁基二甲基甲硅烷基 (TBDMS)、三异丙基甲硅烷基 (TIPS)、4- 甲氧基苯基、4-(甲氧基甲氧基) 苯基、2- 甲氧基 -1- 萘基、苄基、4- 甲氧基苄基、2,4- 二甲氧基苄基、3,4- 二甲氧基苄基、2- 乙酰氧基 -4- 甲氧基苄基、2- 硝基苄基、双 (4- 甲氧基苯基) 甲基 (DAM)、双 (4 ＝甲氧基苯基) 苯基甲基、双 (4- 甲基亚磺酰基苯基) 甲基、三苯甲基 (Tr)、9- 苯基芴基 (Pf)、双 (三甲基甲硅烷基) 甲基、叔丁氧基羰基 (BOC)、苄氧基羰基 (Cbz)、甲氧基羰基、乙氧基羰基、对 - 甲苯磺酰基 (Ts)、丁烯基、(E)-2-(甲氧基羰基) 乙烯基、二乙氧基甲基、1- 甲氧基 -2,2- 二甲基丙基、或 2-(4- 甲基苯基磺酰基) 乙基。在一种实施方式中，Y 为苄基、4- 甲氧基苄基、叔丁基二甲基甲硅烷基、叔丁氧基羰基或苄氧基羰基。在一种实施方式中，Y 为苄基。

[0108] 用于将酯转化成酸 (步骤 1.1) 的方法是本领域普通技术人员熟知的。一般参见 T.W.Green,Protective Groups in Organic Synthesis(第三版,Wiley,New York,1999)。

[0109] 在一种实施方式中，步骤 1.1 在酸的存在下发生。在某些实施方式中，酸是原位产生的。在一种实施方式中，步骤 1.1 在有机酸的存在下发生。在一种实施方式中，步骤 1.1 在 R^bCOOH 的存在下发生，其中 R^b为氢、取代的或未取代的 C_{1-10}烷基、取代的或未取代的 C_{1-10}卤代烷基、或取代的或未取代的 C_{5-14}芳基。在一种实施方式中，步骤 1.1 在甲酸、乙酸、三氟乙酸或苯甲酸的存在下发生。

[0110] 在一种实施方式中，步骤 1.1 在 R^bSO_3H 的存在下发生，其中 R^b为氢、取代的或未取代的 C_{1-10}烷基、取代的或未取代的 C_{1-10}卤代烷基、或取代的或未取代的 C_{5-14}芳基。在一种实施方式中，步骤 1.1 在磺酸、苯磺酸、对甲苯磺酸、樟脑磺酸、甲磺酸或三氟甲磺酸的存在下发生。在一种实施方式中，步骤 1.1 在苯磺酸、对甲苯磺酸、樟脑磺酸或甲磺酸的存在下发生。在一种实施方式中，步骤 1.1 在苯磺酸的存在下发生。在另一种实施方式中，步骤 1.1 在对甲苯磺酸的存在下出现。在又一种实施方式中，步骤 1.1 在樟脑磺酸的存在下发生。在又一种实施方式中，步骤 1.1 在甲磺酸的存在下发生。

[0111] 在一种实施方式中，步骤 1.1 在无机酸的存在下发生。在一种实施方式中，步骤 1.1 在盐酸、硫酸、硝酸或磷酸的存在下发生。在一种实施方式中，步骤 1.1 在盐酸的酸的存

在下发生。

[0112] 在一种实施方式中，步骤 1.1 在碱的存在下发生。在某些实施方式中，碱是原位产生的。在一种实施方式中，步骤 1.1 在碱金属碱的存在下发生。在一种实施方式中，步骤 1.1 在碱金属氢氧化物、碳酸盐、碳酸氢盐、磷酸盐、磷酸氢盐或磷酸二氢盐的存在下发生。在一种实施方式中，步骤 1.1 在 LiOH、NaOH、KOH、Na_2CO_3、K_2CO_3、Cs_2CO_3、$NaHCO_3$、$KHCO_3$、Na_3PO_4、K_3PO_4、Na_2HPO_4、K_2HPO_4、NaH_2PO_4或 KH_2PO_4的存在下发生。

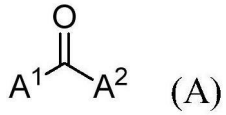
[0113] 在一种实施方式中，步骤 1.1 在 M-R^c或 M-OR^c的存在下发生，其中 M 为碱金属；和 R^c为取代的或未取代的 C_{1-10}烷基。在一种实施方式中，步骤 1.1 在甲醇钠、乙醇钠、叔丁醇钠、甲醇钾、乙醇钾或叔丁醇钾的存在下发生。在一种实施方式中，步骤 1.1 在叔丁醇钠或叔丁醇钾的存在下发生。

[0114] 在一种实施方式中，步骤 1.1 在含氮碱的存在下发生。在一种实施方式中，步骤 1.1 在 NH_4OH、三乙胺、二异丙基乙胺、吡啶、4- 二甲基氨基吡啶、咪唑或 1,8- 二氮杂二环 [5.4.0] 十一碳 -7- 烯 (DBU) 的存在下发生。

[0115] 在一种实施方式中，步骤 1.1 通过氢化发生。

[0116] 式 (III) 的化合物的环化 (步骤 1.2) 可以在根据本领域普通技术人员知晓的任何脱水剂或脱水剂的任何组合下发生。在某些实施方式中，脱水剂是 (或脱水剂的组合是) 原位产生的。在某些实施方式中，脱水剂是 (或脱水剂的组合是) 亚硫酰、氯磺酰氯、4- 二甲基氨基吡啶、光气、双光气、三光气、草酰氯、碳二亚胺、酸酐或混合酸酐、苯酚、或式 (A) 的化合物：

[0117]



(A)

[0118] 其中 A^1和 A^2各自独立地为未取代的或取代的杂芳基基团。在某些实施方式中，脱水剂为 (脱水剂的组合包含) 苯并三唑 -1- 基 - 氧基 - 三 -(二甲基氨基)- 磷鎓六氟磷酸酯 (BOP)、N,N’- 羰基二咪唑 (CDI)、3-(二乙氧基磷酰氧基)-1,2,3- 苯并三嗪 -4(3H)- 酮 (DEPBT)、1- 乙基 -3-(3- 二甲基氨基丙基) 碳二亚胺 (EDCI)、2-(7- 氮杂 -1H 苯并三唑 -1- 基)-1,1,3,3- 四甲基脲鎓六氟磷酸酯 (HATU)、2-(1H- 苯并三唑 -1- 基)-1,1,3,3- 四甲基脲鎓六氟磷酸酯 (HBTU)、1- 羟基苯并三唑 (HOBt)、苯并三唑 -1- 基 - 氧代 - 三吡咯烷子基 - 磷鎓六氟磷酸酯 (PyBOP)、2-(1H- 苯并三唑 -1- 基)-1,1,3,3- 四甲基脲 - 四氟硼酸酯 (TBTU)、O-(3,4- 二氢 -4- 氧代 -1,2,3- 苯并三嗪 -3- 基)-N,N,N,N- 四甲基脲鎓四氟硼酸酯 (TDBTU)、3-(二乙氧基磷酰氧基)-1,2,3- 苯并三嗪 -4(3H)- 酮 (DEPBT)、二环己基碳二亚胺 (DCC)、N,N’- 二异丙基碳二亚胺 (DIC) 或 1- 羟基 -7- 氮杂苯并三唑 (HOAt)。在某些实施方式中，脱水剂为 1- 乙基 -3-(3- 二甲基氨基丙基) 碳二亚胺 (EDCI) 或 2-(1H- 苯并三唑 -1- 基)-1,1,3,3- 四甲基脲鎓四氟硼酸酯 (TBTU)。在另一种实施方式中，脱水剂为分子筛。

[0119] 当从反应混合物中除去水时，可以发生式 (III) 的化合物的环化 (步骤 1.2)。在步骤 1.2 的一种实施方式中，通过共沸蒸馏除去水。从反应混合物中除去水的其他技术是本领域普通技术人员公知的。

[0120] 式 (III) 的化合物的环化 (步骤 1.2) 也可以在不存在脱水剂或没有除去水下发生。

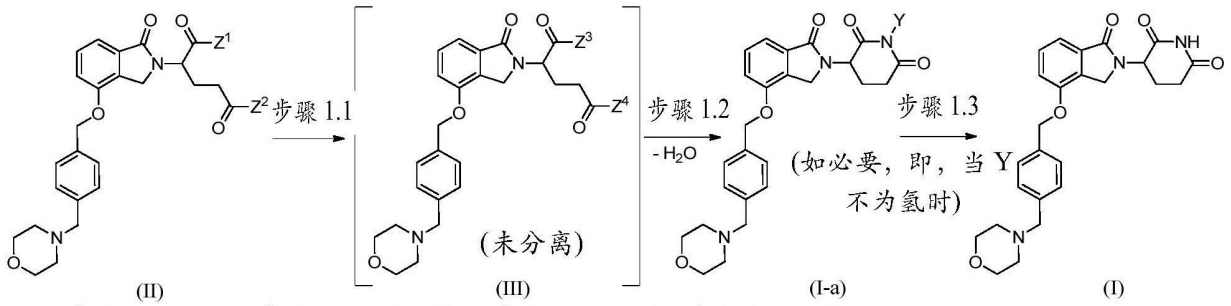
[0121] 在一种实施方式中,其中 Y 为氢,式 (I-a) 的化合物为式 (I) 的化合物,并且步骤 1.3 不是必需的。

[0122] 在一种实施方式中,其中 Y 不为氢,式 (I-a) 的化合物不为式 (I) 的化合物,并且步骤 1.3 是必需的。设置和除去合适的氨基保护基的反应条件是本领域普通技术人员公知的,包括在 T.W.Green,Protective Groups in Organic Synthesis(第三版 ,Wiley,New York,1999) 中描述的那些。在一种实施方式中,Y 为苄基,并且步骤 1.3 通过氢化发生。

[0123] 任选地,式 (I) 的化合物或其盐可以通过与酸反应被转化成不同的可药用盐 (步骤 1.4)。在一种实施方式中,步骤 1.4 包括将式 (I) 的化合物的游离碱转化成其可药用盐。在另一种实施方式中,步骤 1.4 包括将式 (I) 的化合物的盐转化成游离碱,并且将该游离碱转化成其可药用盐。在仍然另一种实施方式,步骤 1.4 包括将式 (I) 的化合物的盐直接转化成其不同的可药用盐。在一种实施方式中,所述可药用盐为盐酸盐。

[0124] 在一种实施方式中,如下方案 1a 中所述,步骤 1.1 和步骤 1.2 在一锅中发生,而不用分离式 (III) 的化合物。

[0125]



(i) Z^1 为 NHY, 和 Z^2 为 OR; 或 (i) Z^3 为 NHY, 和 Z^4 为 OH; 或

(ii) Z^1 为 OR, 和 Z^2 为 NHY (ii) Z^3 为 OH, 和 Z^4 为 NHY

[0126] 方案 1a

[0127] 在一种实施方式中,本文提供了一种用于制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法,包括 :

[0128] (步骤 1.1) 在适用于酯向酸转化的条件下,将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐,其中 :

[0129] (i)Z^1为 NHY,和 Z^2为 OR ;或

[0130] (ii)Z^1为 OR,和 Z^2为 NHY ;其中

[0131] R 为取代的或未取代的烷基、取代的或未取代的环烷基、取代的或未取代的杂烷基、取代的或未取代的杂环烷基、取代的或未取代的芳基、取代的或未取代的杂芳基、取代的或未取代的芳烷基、或合适的羧基保护基 ;和

[0132] Y 为氢,或合适的氨基保护基 ;

[0133] 转化成对映异构体富集的或对映异构体纯的式 (III) 的化合物或其盐,其中 :

[0134] (i)Z^3为 NHY,和 Z^4为 OH ;或

[0135] (ii)Z^3为 OH,和 Z^4为 NHY ;

[0136] (步骤 1.2) 在适于环化的条件下,使对映异构体富集的或对映异构体纯的式

(III) 的化合物环化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物 :

[0137] (步骤 1.3) 当 Y 不为氢时,在适于脱保护的条件下,使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物 ;和

[0138] (步骤 1.4) 任选地在适于成盐的条件下,将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐 ;

[0139] 其中步骤 1.1 和步骤 1.2 在一锅中发生。

[0140] 在一种实施方式中,式的化合物 (I) 为 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮。

[0141] 在一种实施方式中,其中步骤 1.1 和步骤 1.2 在一锅中发生 ;和 R 为 C_{1-6}烷基 ;C_{3-6}环烷基 ;C_{1-6}卤代烷基 ;C_{2-10}杂烷基 ;C_{3-6}杂环烷基 ;被 1 至 3 个芳基取代的 C_{1-6}烷基或 C_{2-10}杂烷基 ;或 $-SiR^a_3$,其中每个 R^a独立地为 C_{1-6}烷基或 C_{5-14}芳基。

[0142] 在一种实施方式中,其中步骤 1.1 和步骤 1.2 在一锅中发生 ;和 R 为甲基、乙基、丙基、异丙基、环丙基、丁基、异丁基、叔丁基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、四氢吡喃基 (THP)、甲氧基乙氧基甲基 (MEM)、2-(三甲基甲硅烷基) 乙氧基甲基胺 (SEM)、苄氧基甲基 (BOM)、2-(三甲基甲硅烷基) 乙基 (TMSE)、2,2,2- 三氯乙基、苄基、三苯基甲基、对 - 甲氧基苄基、2,6- 二甲氧基苄基、三甲基甲硅烷基 (TMS)、三乙基甲硅烷基 (TES)、三异丙基甲硅烷基 (TIPS)、二甲基异丙基甲硅烷基 (IPDMS)、二乙基异丙基甲硅烷基 (DEIPS)、叔丁基二甲基甲硅烷基 (TBDMS)、或叔丁基二苯基甲硅烷基 (TBDPS)。在一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;并且 R 为甲基、叔丁基或苄基。在一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;和 R 为甲基。在另一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;和 R 为叔丁基。在又一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;和 R 为苄基。

[0143] 在一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;和 Y 为氢。

[0144] 在一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;和 Y 为合适的氨基保护基。在一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;和 Y 为烯丙基、叔丁基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、苄氧基甲基 (BOM)、2,2,2- 三氯乙氧基甲基、叔丁基二甲基甲硅烷氧基甲基、新戊酰氧基甲基、氰基甲基、吡咯烷子基甲基、甲氧基、苄氧基、甲硫基、三苯基甲硫基、叔丁基二甲基甲硅烷基 (TBDMS)、三异丙基甲硅烷基 (TIPS)、4- 甲氧基苯基、4-(甲基氧基甲氧基) 苯基、2- 甲氧基 -1- 萘基、苄基、4- 甲氧基苄基、2,4- 二甲氧基苄基、3,4- 二甲氧基苄基、2- 乙酰氧基 -4- 甲氧基苄基、2- 硝基苄基、双 (4- 甲氧基苯基) 甲基 (DAM)、双 (4- 甲氧基苯基) 苯基甲基、双 (4- 甲基亚磺酰基苯基) 甲基、三苯甲基 (Tr)、9- 苯基芴基 (Pf)、双 (三甲硅烷基) 甲基、叔丁氧基羰基 (BOC)、苄氧基羰基 (Cbz)、甲氧基羰基、乙氧基羰基、对 - 甲苯磺酰基 (Ts)、丁烯基、(E)-2-(甲氧基羰基) 乙烯基、二乙氧基甲基、1- 甲氧基 -2,2- 二甲基丙基或 2-(4- 甲基苯基磺酰基) 乙基。在一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;和 Y 为苄基、4- 甲氧基苄基、叔丁基二家基甲硅烷基、叔丁氧基羰基或苄氧基羰基。在一种实施方式中,步骤 1.1 和步骤 1.2 在一锅中发生 ;和 Y 为苄基。

[0145] 在一种实施方式中,其中步骤 1.1 和步骤 1.2 在一锅中通过氢化发生。在一种实

施方式中，R 为苄基，步骤 1.1 和步骤 1.2 在一锅中通过氢化发生。

[0146] 在一种实施方式中，步骤 1.1 和步骤 1.2 在一锅中通过氢化 / 环化发生，其中酸或碱促进环化。

[0147] 在一种实施方式中，步骤 1.1 和步骤 1.2 在碱的存在下在一锅中发生。在一种实施方式中，步骤 1.1 和步骤 1.2 在碱金属氢氧化物、碳酸盐、碳酸氢盐、磷酸盐、磷酸氢盐或磷酸二氢盐的存在下在一锅中发生。在一种实施方式中，其中步骤 1.1 和步骤 1.2 在 LiOH、NaOH、KOH、Na_2CO_3、K_2CO_3、Cs_2CO_3、$NaHCO_3$、$KHCO_3$、Na_3PO_4、K_3PO_4、Na_2HPO_4、K_2HPO_4、NaH_2PO_4、或 KH_2PO_4 的存在下在一锅中发生。在一种实施方式中，R 为甲基，并且步骤 1.1 和步骤 1.2 在 NaOH 或 KOH 的存在下在一锅中发生。

[0148] 在一种实施方式中，步骤 1.1 和步骤 1.2 在 M-R^c 或 M-OR^c 的存在下在一锅中发生，其中 M 为碱金属；和 R^c 为取代的或未取代的 C_{1-10} 烷基。在一种实施方式中，步骤 1.1 和步骤 1.2 在甲醇钠、乙醇钠、叔丁醇钠、甲醇钾、乙醇钾或叔丁醇钾的存在下在一锅中发生。在一种实施方式中，R 为甲基，并且步骤 1.1 和步骤 1.2 在叔丁醇钠或叔丁醇钾的存在下在一锅中发生。

[0149] 在一种实施方式中，步骤 1.1 和步骤 1.2 在酸的存在下在一锅中发生。在某些实施方式中，酸是原位产生的。在一种实施方式中，步骤 1.1 和步骤 1.2 在有机酸的存在下在一锅中发生。在一种实施方式中，步骤 1.1 和步骤 1.2 在 R^bCOOH 的存在下在一锅中发生，其中 R^b 为氢、取代的或未取代的 C_{1-10} 烷基、取代的或未取代的 C_{1-10} 卤代烷基、或取代的或未取代的 C_{5-14} 芳基。在一种实施方式中，步骤 1.1 和步骤 1.2 在甲酸、乙酸、三氟乙酸或苯甲酸的存在下在一锅中发生。在一种实施方式中，R 为叔丁基，并且步骤 1.1 和步骤 1.2 在三氟乙酸的存在下在一锅中发生。

[0150] 在一种实施方式中，步骤 1.1 和步骤 1.2 在布朗斯台德酸 (Bronsted acid) 或路易斯酸的存在下在一锅中发生。在某些实施方式中，酸是原位产生的。

[0151] 在一种实施方式中，步骤 1.1 和步骤 1.2 在一锅中在 R^bSO_3H 的存在下发生，其中 R^b 为氢、取代的或未取代的 C_{1-10} 烷基、取代的或未取代的 C_{1-10} 卤代烷基、或取代的或未取代的 C_{5-14} 芳基。在一种实施方式中，步骤 1.1 和步骤 1.2 在磺酸、苯磺酸、对甲苯磺酸、樟脑磺酸、甲磺酸或三氟甲磺酸的存在下在一锅中发生。在一种实施方式中，步骤 1.1 和步骤 1.2 在苯磺酸、对甲苯磺酸、樟脑磺酸或甲磺酸的存在下在一锅中发生。在一种实施方式中，步骤 1.1 和步骤 1.2 在苯磺酸的存在下在一锅中发生。在另一种实施方式中，步骤 1.1 和步骤 1.2 在对甲苯磺酸的存在下在一锅中发生。在又一种实施方式中，步骤 1.1 和步骤 1.2 在樟脑磺酸的存在下在一锅中发生。在又一种实施方式中，步骤 1.1 和步骤 1.2 在甲磺酸的存在下在一锅中发生。在一种实施方式中，R 为叔丁基，并且步骤 1.1 和步骤 1.2 在一锅中在苯磺酸的存在下发生。

[0152] 在一种实施方式中，步骤 1.1 和步骤 1.2 在无机酸的存在下在一锅中发生。在一种实施方式中，步骤 1.1 和步骤 1.2 在盐酸、硫酸、硝酸或磷酸的存在下在一锅中发生。在一种实施方式中，步骤 1.1 和步骤 1.2 在盐酸的存在下在一锅中发生。在一种实施方式中，R 为叔丁基，并且步骤 1.1 和步骤 1.2 在盐酸的存在下在一锅中发生。

[0153] 步骤 1.1 和步骤 1.2 分别或在一锅中可以在任何溶剂任何溶剂组合中发生。在某些实施方式中，溶剂为或溶剂组合包含：乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙

酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。在某些实施方式中，溶剂为乙腈。

[0154] 步骤 1.1 和步骤 1.2 分别或在一锅中可以在任何反应温度下发生。在某些实施方式中，反应温度为约 -100℃至约 200℃。在某些实施方式中，反应温度为约 -50℃至约 150℃。在某些实施方式中，反应温度为约 0℃至约 100℃。在某些实施方式中，反应温度为约 85℃至约 95℃。在某些实施方式中，反应温度为约 90℃。

[0155] 步骤 1.1 和步骤 1.2 分别或在一锅中可以在任何反应时间下发生。在某些实施方式中，反应时间为约 1 分钟至约 14 天。在某些实施方式中，反应时间为约 5 分钟至约 48 小时。在某些实施方式中，反应时间为约 1 小时至约 24 小时。在某些实施方式中，反应时间为约 3 小时至约 12 小时。在某些实施方式中，反应时间为约 8 小时至约 9 小时。

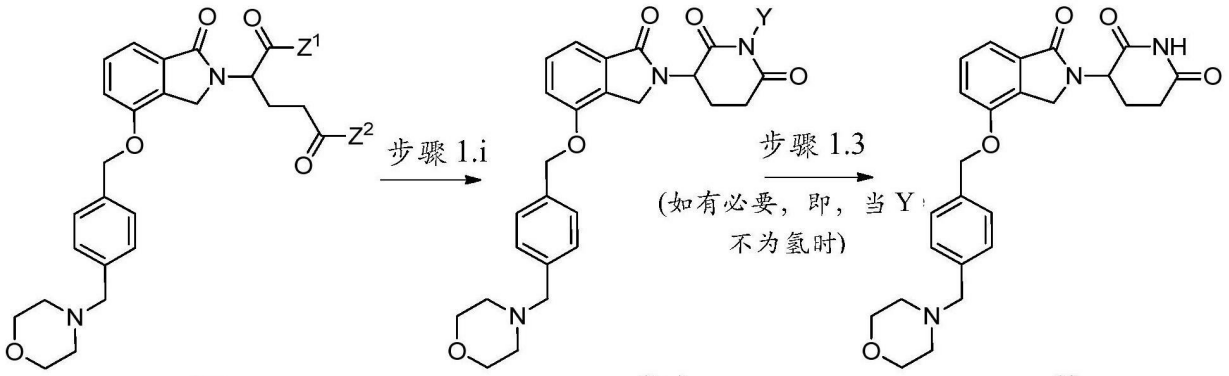
[0156] 在一种示例性的实施方式中，Y 为氢，R 为叔丁基，并且步骤 1.1 和步骤 1.2 在苯磺酸的存在下在一锅中发生，其中溶剂为乙腈，反应温度为约 90℃，并且反应时间为约 8 小时至约 9 小时。

[0157] 在一种示例性的实施方式中，Y 为氢，R 为叔丁基，并且步骤 1.1 和步骤 1.2 在苯磺酸的存在下在一锅中发生，其中溶剂为乙腈，反应温度为约 90℃，反应时间为约 8 小时到约 9 小时，并且通过共沸蒸馏除去水。

[0158] 步骤 1.3 和 1.4 为如上和本文所述的。

[0159] 在另一种实施方式中，如下述方案 1b 所描绘的，而不限于任何中间体或任何理论，式 (I-a) 的化合物可以在一个步骤中由式 (II) 的化合物制备。

[0160]



(i) Z^1 为 NHY，和 Z^2 为 OR；或

(ii) Z^1 为 OR，和 Z^2 为 NHY

[0161] 方案 1b

[0162] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法，包括：

[0163] (步骤 1.i) 在适于环化的条件下，将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐，其中：

[0164] (i) Z^1 为 NHY，和 Z^2 为 OR；或

[0165] (ii) Z^1 为 OR，和 Z^2 为 NHY；其中

[0166] R 为取代的或未取代的烷基、取代的或未取代的环烷基、取代的或未取代的杂烷

基、取代的或未取代的杂环烷基、取代的或未取代的芳基、取代的或未取代的杂芳基、取代的或未取代的芳烷基、或合适的羧基保护基；和

[0167] Y 为氢，或合适的氨基保护基；

[0168] 转化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物或其盐；

[0169] (步骤 1.3) 当 Y 不为氢时，在适于脱保护的条件下，使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物；和

[0170] (步骤 1.4) 任选地在适于成盐的条件下，将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐。

[0171] 在一种实施方式中，式 (I) 的化合物为 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮。

[0172] 在一种实施方式中，R 为 C_{1-6}烷基；C_{3-6}环烷基；C_{1-6}卤代烷基；C_{2-10}杂烷基；C_{3-6}杂环烷基；被 1 至 3 个芳基取代的 C_{1-6}烷基或 C_{2-10}杂烷基；或 $-SiR^a_3$，其中每个 R^a独立地为 C_{1-6}烷基或 C_{5-14}芳基。

[0173] 在一种实施方式中，R 为甲基、乙基、丙基、异丙基、环丙基、丁基、异丁基、叔丁基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、四氢吡喃基 (THP)、甲氧基乙氧基甲基 (MEM)、2-(三甲基甲硅烷基) 乙氧基甲基胺 (SEM)、苄氧基甲基 (BOM)、2-(三甲基甲硅烷基) 乙基 (TMSE)、2,2,2- 三氯乙基、苄基、三苯甲基、对 - 甲氧基苄基、2,6- 二甲氧基苄基、三甲基甲硅烷基 (TMS)、三乙基甲硅烷基 (TES)、三异丙基甲硅烷基 (TIPS)、二甲基异丙基甲硅烷基 (IPDMS)、二乙基异丙基甲硅烷基 (DEIPS)、叔丁基二甲基甲硅烷基 (TBDMS) 或叔丁基二苯基甲硅烷基 (TBDPS)。在一种实施方式中，R 为甲基、叔丁基或苄基。在一种实施方式中，R 为甲基。在另一种实施方式中，R 为叔丁基。在又一种实施方式中，R 为苄基。

[0174] 在一种实施方式中，Y 为氢。

[0175] 在一种实施方式中，Y 为合适的氨基保护基。在一种实施方式中，Y 为烯丙基、叔丁基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、苄氧基甲基 (BOM)、2,2,2- 三氯乙氧基甲基、叔丁基二甲基甲硅烷氧基甲基、新戊酰氧基甲基、氰基甲基、吡咯烷子基甲基、甲氧基、苄氧基、甲硫基、三苯基甲硫基、叔丁基二甲基甲硅烷基 (TBDMS)、三异丙基甲硅烷基 (TIPS)、4- 甲氧基苯基、4-(甲氧基甲氧基) 苯基、2- 甲氧基 -1- 萘基、苄基、4- 甲氧基苄基、2,4- 二甲氧基苄基、3,4- 二甲氧基苄基、2- 乙酰氧基 -4- 甲氧基苄基、2- 硝基苄基、双 (4- 甲氧基苯基) 甲基 (DAM)、双 (4- 甲氧基苯基) 苯基甲基、双 (4- 甲基亚磺酰基苯基) 甲基、三苯基甲基 (Tr)、9- 苯基芴基 (Pf)、双 (三甲基甲硅烷基) 甲基、叔丁氧基羰基 (BOC)、苄氧基羰基 (Cbz)、甲氧基羰基、乙氧基羰基、对 - 甲苯磺酰基 (Ts)、丁烯基、(E)-2-(甲氧基羰基) 乙烯基、二乙氧基甲基、1- 甲氧基 -2,2- 二甲基丙基、或 2-(4- 甲基苯基磺酰基) 乙基。在一种实施方式中，Y 为苄基、4- 甲氧基苄基、叔丁基二甲基甲硅烷基、叔丁氧基羰基或苄氧基羰基。在一种实施方式中，Y 为苄基。

[0176] 在一种实施方式中，步骤 1.i 通过氢化发生。在一种实施方式中，R 为苄基，并且步骤 1.i 通过氢化发生。

[0177] 在一种实施方式中，步骤 1.i 在碱的存在下发生。在一种实施方式中，步骤 1.i 在碱金属氢氧化物、碳酸盐、碳酸氢盐、磷酸盐、磷酸氢盐或磷酸二氢盐的存在下发生。在一

种实施方式中，步骤 1.i 在的 LiOH、NaOH、KOH、Na_2CO_3、K_2CO_3、Cs_2CO_3、$NaHCO_3$、$KHCO_3$、Na_3PO_4、K_3PO_4、Na_2HPO_4、K_2HPO_4、NaH_2PO_4或 KH_2PO_4存在下发生。在一种实施方式中，R 为甲基，并且步骤 1.i 在 NaOH 或 KOH 的存在下发生。

[0178] 在一种实施方式中，步骤 1.i 在 M-R^c或 M-OR^c的存在下发生，其中 M 为碱金属；和 R^c为取代的或未取代的 C_{1-10}烷基。在一种实施方式中，步骤 1.i 在甲醇钠、乙醇钠、叔丁醇钠、甲醇钾、乙醇钾或叔丁醇钾的存在下发生。在一种实施方式中，R 为甲基，并且步骤 1.i 在叔丁醇钠或叔丁醇钾的存在下发生。

[0179] 在一种实施方式中，步骤 1.i 是在酸的存在下发生。在某些实施方式中，酸是原位产生的。在一种实施方式中，步骤 1.i 在有机酸的存在下发生。在一种实施方式中，步骤 1.i 在 R^bCOOH 的存在下发生，其中 R^b为氢、取代的或未取代的 C_{1-10}烷基、取代的或未取代的 C_{1-10}卤代烷基、或取代的或未取代的 C_{5-14}芳基。在一种实施方式中，步骤 1.i 在甲酸、乙酸、三氟乙酸或苯甲酸的存在下发生的。在一种实施方式中，R 为叔丁基，并且步骤 1.i 在三氟乙酸的存在下发生。

[0180] 在一种实施方式中，步骤 1.i 是在布忍司特酸或路易斯酸的存在下发生。在某些实施方式中，酸是原位产生的。

[0181] 在一种实施方式中，步骤 1.i 在 R^bSO_3H 的存在下发生，其中 R^b为氢、取代的或未取代的 C_{1-10}烷基、取代的或未取代的 C_{1-10}卤代烷基、或取代的或未取代的 C_{5-14}芳基。在一种实施方式中，步骤 1.i 在磺酸、苯磺酸、对甲苯磺酸、樟脑磺酸、甲磺酸或三氟甲磺酸的存在下发生。在一种实施方式中，步骤 1.i 在苯磺酸、对甲苯磺酸、樟脑磺酸或甲磺酸的存在下发生。在一种实施方式中，步骤 1.i 在苯磺酸的存在下出现。在另一种实施方式中，步骤 1.i 在对甲苯磺酸的存在下发生。在又一种实施方式中，步骤 1.i 在樟脑磺酸的存在下发生。在又一种实施方式中，步骤 1.i 在甲磺酸的存在下发生。在一种实施方式中，R 为叔丁基，并且步骤 1.i 在苯磺酸的存在下发生。

[0182] 在一种实施方式中，步骤 1.i 在无机酸的存在下发生。在一种实施方式中，步骤 1.i 在盐酸、硫酸、硝酸或磷酸的存在下发生。在一种实施方式中，步骤 1.i 在盐酸的酸的存在下发生。在一种实施方式中，R 为叔丁基，并且步骤 1.i 在盐酸的存在下发生。

[0183] 步骤 1.i 可以在任何溶剂或溶剂的任何组合下发生。在某些实施方式中，溶剂为或溶剂组合包含乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。在某些实施方式中，溶剂为乙腈。

[0184] 步骤 1.i 可以在任何反应温度下发生。在某些实施方式中，反应温度为约 -100℃至约 200℃。在某些实施方式中，反应温度为约 -50℃至约 150℃。在某些实施方式中，反应温度为约 0℃至约 100℃。在某些实施方式中，反应温度为约 85℃至约 95℃。在某些实施方式中，反应温度为约 90℃。

[0185] 步骤 1.i 可以在任何反应时间下发生。在某些实施方式中，反应时间为约 1 分钟至约 14 天。在某些实施方式中，反应时间为约 5 分钟至约 48 小时。在某些实施方式中，反应时间为约 1 小时至约 24 小时。在某些实施方式中，反应时间为约 3 小时至约 12 小时。在某些实施方式中，反应时间为约 8 小时至约 9 小时。

[0186] 在一种示例性的实施方式中，Y 为氢，R 为叔丁基，并且步骤 1.i 在苯磺酸的存在下

发生，其中溶剂为乙腈，反应温度为约 90℃，和反应时间为约 8 小时至约 9 小时。

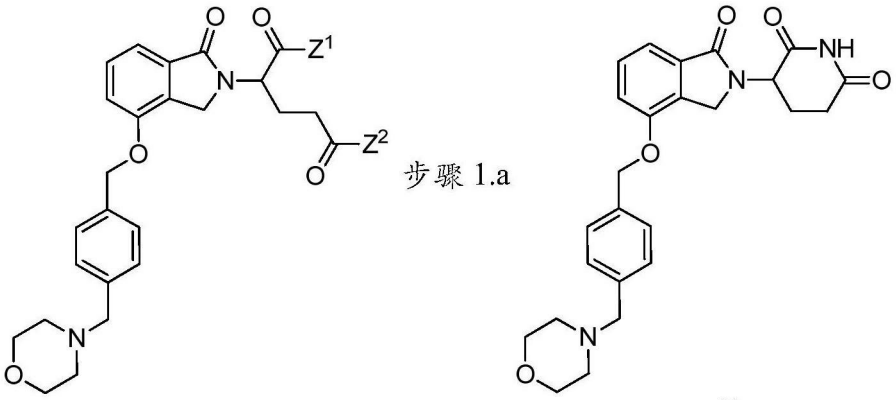
[0187] 在一种示例性的实施方式中，Y 为氢，R 为叔丁基，并且步骤 1.i 在苯磺酸的存在下发生，其中溶剂为乙腈，反应温度为约 90℃，反应时间为约 8 小时至约 9 小时，和通过共沸蒸馏除去水。

[0188] 在一种示例性的实施方式中，Y 为苄基，R 为甲基，并且步骤 1.i 在对甲苯磺酸的存在下发生。在一种示例性的实施方式中，Y 为苄基，R 为甲基，并且步骤 1.i 在对甲苯磺酸的存在下发生，其中溶剂为乙酸，反应温度为约 100℃，反应时间为约 8 小时。

[0189] 步骤 1.3 和 1.4 为如上和本文所述的。

[0190] 在另一种实施方式中，Y 的脱保护可以与戊二酰亚胺环的形成同时发生。如下述方案 1c 所描绘的，而不限于任何中间体或任何理论，式 (I) 的化合物可以在一个步骤中由式 (II) 的化合物制备。

[0191]



(II) (I)

(i) Z^1 为 NHY，和 Z^2 为 OR；或

(ii) Z^1 为 OR，和 Z^2 为 NHY

[0192] 方案 1c

[0193] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的式 (I) 的化合物或其可药用形式的方法，包括：

[0194] (步骤 1.a) 在适于环化和脱保护的条件下，将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐，其中：

[0195] (i)Z^1为 NHY，和 Z^2为 OR；或

[0196] (ii)Z^1为 OR，和 Z^2为 NHY；其中

[0197] R 为取代的或未取代的烷基、取代的或未取代的环烷基、取代的或未取代的杂烷基、取代的或未取代的杂环烷基、取代的或未取代的芳基、取代的或未取代的杂芳基、取代的或未取代的芳烷基、或合适的羧基保护基；和

[0198] Y 为氢，或合适的氨基保护基；

[0199] 转化成对映异构体富集的或对映异构体纯的式 (I) 的化合物或其盐；

[0200] (步骤 1.4) 任选地在适于成盐的条件下，将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐。

[0201] 在一种实施方式中，式 (I) 的化合物为 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮。

[0202] 在一种实施方式中，R 为 C_{1-6}烷基；C_{3-6}环烷基；C_{1-6}卤代烷基；C_{2-10}杂烷基；C_{3-6}杂环烷基；被 1 至 3 个芳基取代的 C_{1-6}烷基或 C_{2-10}杂烷基；或 $-SiR^a_3$，其中每个 R^a独立地为 C_{1-6}烷基或 C_{5-14}芳基。

[0203] 在一种实施方式中，R 为甲基、乙基、丙基、异丙基、环丙基、丁基、异丁基、叔丁基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、四氢吡喃基 (THP)、甲氧基乙氧基甲基 (MEM)、2-(三甲基甲硅烷基) 乙氧基甲基胺 (SEM)、苄氧基甲基 (BOM)、2-(三甲基甲硅烷基) 乙基 (TMSE)、2,2,2- 三氯乙基、苄基、三苯甲基、对 - 甲氧基苄基、2,6- 二甲氧基苄基、三甲基甲硅烷基 (TMS)、三乙基甲硅烷基 (TES)、三异丙基甲硅烷基 (TIPS)、二甲基异丙基甲硅烷基 (IPDMS)、二乙基异丙基甲硅烷基 (DEIPS)、叔丁基二甲基甲硅烷基 (TBDMS) 或叔丁基二苯基甲硅烷基 (TBDPS)。在一种实施方式中，R 为甲基、叔丁基或苄基。在一种实施方式中，R 为甲基。在另一种实施方式中，R 为叔丁基。在又一种实施方式中，R 为苄基。

[0204] 在一种实施方式中，Y 为氢。

[0205] 在一种实施方式中，Y 为合适的氨基保护基。在一种实施方式中，Y 为烯丙基、叔丁基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、苄氧基甲基 (BOM)、2,2,2- 三氯乙氧基甲基、叔丁基二甲基甲硅烷氧基甲基、新戊酰氧基甲基、氰基甲基、吡咯烷子基甲基、甲氧基、苄氧基、甲硫基、三苯基甲硫基、叔丁基二甲基甲硅烷基 (TBDMS)、三异丙基甲硅烷基 (TIPS)、4- 甲氧基苯基、4-(甲氧基甲氧基) 苯基、2- 甲氧基 -1- 萘基、苄基、4- 甲氧基苄基、2,4- 二甲氧基苄基、3,4- 二甲氧基苄基、2- 乙酰氧基 -4- 甲氧基苄基、2- 硝基苄基、双 (4- 甲氧基苯基) 甲基 (DAM)、双 (4 ＝甲氧基苯基) 苯基甲基、双 (4- 甲基亚磺酰基苯基) 甲基、三苯甲基 (Tr)、9- 苯基芴基 (Pf)、双 (三甲基甲硅烷基) 甲基、叔丁氧基羰基 (BOC)、苄氧基羰基 (Cbz)、甲氧基羰基、乙氧基羰基、对 - 甲苯磺酰基 (Ts)、丁烯基、(E)-2-(甲氧基羰基) 乙烯基、二乙氧基甲基、1- 甲氧基 -2,2- 二甲基丙基或 2-(4- 甲基苯基磺酰基) 乙基。在一种实施方式中，Y 为苄基、4- 甲氧基苄基、叔丁基二甲基甲硅烷基、叔丁氧基羰基或苄氧基羰基。在一种实施方式中，Y 为苄基。

[0206] 在一种实施方式中，步骤 1.a 通过氢化发生。在一种实施方式中，RR 为苄基，并且步骤 1.a 通过氢化发生。

[0207] 在一种实施方式中，步骤 1.a 在碱的存在下发生。在一种实施方式中，步骤 1.a 在碱金属氢氧化物、碳酸盐、碳酸氢盐、磷酸盐、磷酸氢盐或磷酸二氢盐的存在下发生。在一种实施方式中，步骤 1.a 在 LiOH、NaOH、KOH、Na_2CO_3、K_2CO_3、Cs_2CO_3、$NaHCO_3$、$KHCO_3$、Na_3PO_4、K_3PO_4、Na_2HPO_4、K_2HPO_4、NaH_2PO_4或 KH_2PO_4的存在下发生。在一种实施方式中，R 为甲基，并且步骤 1.a 在 NaOH 或 KOH 的存在下发生。

[0208] 在一种实施方式中，步骤 1.a 在 $M-R^c$或 $M-OR^c$的存在下发生，其中 M 为碱金属；和 R^c为取代的或未取代的 C_{1-10}烷基。在一种实施方式中，步骤 1.a 在甲醇钠、乙醇钠、叔丁醇钠、甲醇钾、乙醇钾或叔丁醇钾的存在下发生。在一种实施方式中，R 为甲基，并且步骤 1.a 在叔丁醇钠或叔丁醇钾的存在下发生。

[0209] 在一种实施方式中，步骤 1.a 在酸的存在下发生。在某些实施方式中，酸是原位产生的。在一种实施方式中，步骤 1.a 在有机酸的存在下发生。在一种实施方式中，步骤 1.a 在 R^bCOOH 的存在下发生，其中 R^b为氢、取代的或未取代的 C_{1-10}烷基、取代的或未取代的 C_{1-10}卤代烷基、或取代的或未取代的 C_{5-14}芳基。在一种实施方式中，步骤 1.a 在甲酸、乙酸、三氟

乙酸或苯甲酸的存在下发生的。在一种实施方式中，R 为叔丁基，并且步骤 1.a 在三氟乙酸的存在下发生。

[0210] 在一种实施方式中，步骤 1.a 在 R^bSO_3H 的存在下发生，其中 R^b 为氢、取代的或未取代的 C_{1-10} 烷基、取代的或未取代的 C_{1-10} 卤代烷基、或取代的或未取代的 C_{5-14} 芳基。在一种实施方式中，步骤 1.a 在磺酸、苯磺酸、对甲苯磺酸、樟脑磺酸、甲磺酸或三氟甲磺酸的存在下发生。在一种实施方式中，步骤 1.a 在苯磺酸、对甲苯磺酸、樟脑磺酸或甲磺酸的存在下发生。在一种实施方式中，步骤 1.a 在苯磺酸的存在下出现。在另一种实施方式中，步骤 1.a 在对甲苯磺酸的存在下发生。在又一种实施方式中，步骤 1.a 在樟脑磺酸的存在下发生。在又一种实施方式中，步骤 1.a 在甲磺酸的存在下发生。在一种实施方式中，R 为叔丁基，并且步骤 1.a 在苯磺酸的存在下发生。

[0211] 在一种实施方式中，步骤 1.a 在无机酸的存在下发生。在一种实施方式中，步骤 1.a 在盐酸、硫酸、硝酸或磷酸的存在下发生。在一种实施方式中，步骤 1.a 在盐酸的存在下发生。在一种实施方式中，R 为叔丁基，并且步骤 1.a 在盐酸的存在下发生。

[0212] 步骤 1.a 可以在任何溶剂或溶剂的任何组合下发生。在某些实施方式中，溶剂为或溶剂组合包含乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。在某些实施方式中，溶剂为乙腈。

[0213] 步骤 1.a 可以在任何反应温度下发生。在某些实施方式中，反应温度为约 -100℃至约 200℃。在某些实施方式中，反应温度为约 -50℃至约 150℃。在某些实施方式中，反应温度为约 0℃至约 100℃。在某些实施方式中，反应温度为约 85℃至约 95℃。在某些实施方式中，反应温度为约 90℃。

[0214] 步骤 1.a 可以在任何反应时间下发生。在某些实施方式中，反应时间为约 1 分钟至约 14 天。在某些实施方式中，反应时间为约 5 分钟至约 48 小时。在某些实施方式中，反应时间为约 1 小时至约 24 小时。在某些实施方式中，反应时间为约 3 小时至约 12 小时。在某些实施方式中，反应时间为约 8 小时至约 9 小时。

[0215] 步骤 1.4 为如上和本文所述的。

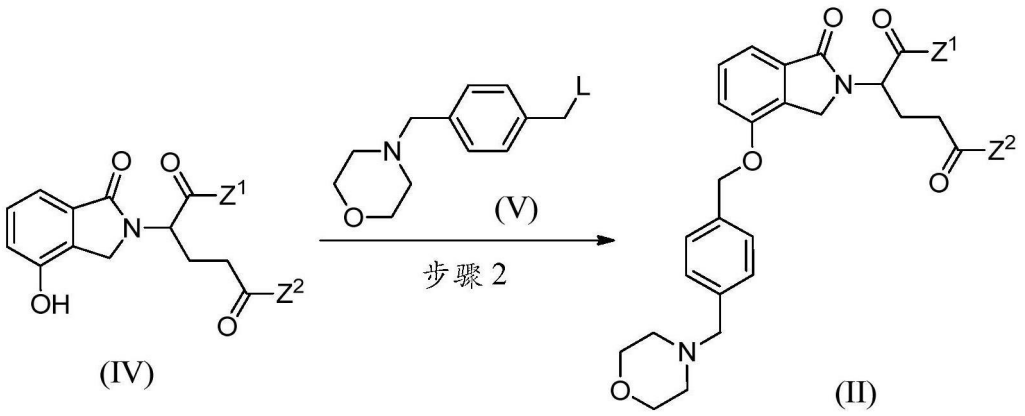
[0216] 6.2.2 化合物 (II) 的制备

[0217] 在一种实施方式中，如下方案 2 所描绘的，本文提供了一种用于制备对映异构体富集的或对映异构体纯的式 (II) 的化合物或或其盐的方法，包括 :(步骤 2) 在适于置换的条件下，使对映异构体富集的或对映异构体纯的式 (IV) 的化合物接触式 (V) 的化合物或其盐，其中 :

[0218] Z^1 和 Z^2 为如上和本文定义的 ;和

[0219] L 为卤素、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$、$-OSO_2C_6H_4$-p-Me(对甲苯磺酸酯)、或合适的离去基团 ;

[0220]



(i) Z^1 为 NHY，和 Z^2 为 OR；或
(ii) Z^1 为 OR，和 Z^2 为 NHY

(i) Z^1 为 NHY，和 Z^2 为 OR；或
(ii) Z^1 为 OR，和 Z^2 为 NHY

[0221] 方案 2

[0222] L 可以是本领域普通技术人员已知的任何合适的离去基团。在一种实施方式中，L 为卤素、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$或 $-OSO_2C_6H_4$-p-Me（对甲苯磺酸酯）。在一种实施方式中，L 为卤素。在一种实施方式中，L 为氟。在另一种实施方式中，L 为氯。在仍然另一种实施方式中，L 为溴。在又一种实施方式中，L 为碘。

[0223] Z^1、Z^2、R 和 Y 为如上和本文定义的。R 基团的选择对于步骤 2 很重要。相比于非空间位阻的 R 基团（如甲基），空间位阻的 R 基团（如叔丁基）通常使得式 (IV) 的化合物向式 (II) 的化合物具有更高的转化率。

[0224] 在式 (IV) 的化合物中用苯酚置换离去基团 L（步骤 2）可以在碱的存在下发生。在某些实施方式中，碱是原位产生的。在一种实施方式中，步骤 2 在碱金属碱的存在下发生。在一种实施方式中，步骤 2 在碱金属氢氧化物、碳酸盐、碳酸氢盐、磷酸盐、磷酸氢盐或磷酸二氢盐的存在下发生。在一种实施方式中，步骤 2 在 LiOH、NaOH、KOH、Na_2CO_3、K_2CO_3、Cs_2CO_3、$NaHCO_3$、$KHCO_3$、Na_3PO_4、K_3PO_4、Na_2HPO_4、K_2HPO_4、NaH_2PO_4或 KH_2PO_4的存在下发生。在一种实施方式中，步骤 2 在 K_2CO_3存在下发生。

[0225] 在一种实施方式中，步骤 2 在 M-R^c或 M-OR^c的存在下发生，其中 M 为碱金属；和 R^c 为取代的或未取代的 C_{1-10}烷基。在一种实施方式中，步骤 2 在甲醇钠、乙醇钠、叔丁醇钠、甲醇钾、乙醇钾或叔丁醇钾的存在下发生。

[0226] 在一种实施方式中，步骤 2 在含氮碱的存在下发生。在一种实施方式中，步骤 2 在三乙胺、二异丙基乙胺、吡啶、4- 二甲基氨基吡啶或 1,8- 二氮杂二环 [5.4.0] 十一碳 -7- 烯 (DBU) 的存在下发生。

[0227] 步骤 2 可以在任何溶剂或溶剂的任何组合中发生。在某些实施方式中，溶剂为或溶剂组合包含乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。在一种实施方式中，溶剂为乙腈。在另一种实施方式中，溶剂为二甲基甲酰胺。

[0228] 步骤 2 可以在任何反应温度下发生。在某些实施方式中，反应温度为约 -100℃至约 200℃。在某些实施方式中，反应温度为约 -50℃至约 150℃。在某些实施方式中，反应温度为约 0℃至约 100℃。在某些实施方式中，反应温度为约 40℃至约 50℃。

[0229] 步骤 2 可以在任何反应时间下发生。在某些实施方式中，反应时间为约 1 分钟至

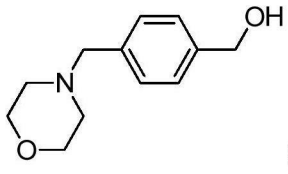
约 14 天。在某些实施方式中，反应时间为约 5 分钟至约 48 小时。在某些实施方式中，反应时间为约 1 小时至约 24 小时。在某些实施方式中，反应时间为约 12 小时至约 24 小时。

[0230] 步骤 2 可以在任何摩尔比的式 (IV) 的化合物与式 (V) 的化合物下发生。在某些实施方式中，式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 10:1 至约 1:10。在某些实施方式中，式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 5:1 至约 1:5。在某些实施方式中，式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 3:1 至约 1:3。在某些实施方式中，式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 1.5:1 至约 1:1.5。在某些实施方式中，式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 1.1:1 至约 1:1.1。在某些实施方式中，式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 1:1。

[0231] 在一种实施方式中，Y 为氢，R 为叔丁基和 L 为氯。在一种实施方式中，Y 为氢，R 为叔丁基和 L 为氯，其中步骤 2 在 K_2CO_3 的存在下发生。在一种示例性的实施方式中，Y 为氢，R 为叔丁基和 L 为氯，其中步骤 2 在 K_2CO_3 的存在下发生，溶剂为二甲基甲酰胺，反应温度为约 40℃至约 50℃，反应时间为约 12 小时至约 24 小时，并且式 (IV) 的化合物与式 (V) 的化合物的摩尔比为约 1:1。

[0232] 式 (II) 的化合物中醚键的形成可以通过本领域普通技术人员已知的其他化学转化实现。例如，在偶氮二羧酸二异丙酯 (DIAD) 和 PPh_3 的存在下，外消旋形式的式 (IV) 的化合物和式 (B) 的醇之间的光延反应 (Mitsunobu 反应) 已经报道在美国专利公开 No.2011/0196150 中。

[0233]



(B)

[0234] 对于 Mitsunobu 反应的偶联产物的纯化，通常需要硅胶色谱法。如方案 2 中描绘的碱置换法与报道的 Mitsunobu 反应相比具有下述优点 :(1) 有效且可规模化 ;(2) 高转化率 ;和 (3) 纯化简单而不需要硅胶色谱法。

[0235] 6.2.3 化合物 (V) 的制备

[0236] 在一种实施方式中，如下方案 3 所描绘的，本文提供了一种用于制备式 (V) 的化合物或或其盐的方法，包括 :

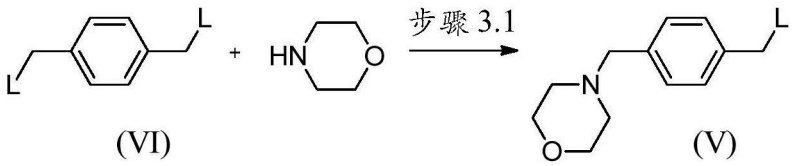
[0237] (步骤 3.1) 在适于置换的条件下，使式 (VI) 的化合物，其中

[0238] 每个 L 独立地为卤素、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$、$-OSO_2C_6H_4$-p-Me(对甲苯磺酸酯) 或合适的离去基团 ;

[0239] 接触吗啉或其盐 ;和

[0240] (步骤 3.2) 任选地通过选择性萃取纯化式 (V) 的化合物。

[0241]



(VI) (V)

[0242] 方案 3

[0243] 每个 L 可以独立地为本领域普通技术人员已知的任何合适的离去基团。在一种实施方式中，每个 L 独立地为卤素、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$或 $-OSO_2C_6H_4$-p-Me（对甲苯磺酸酯）。在一种实施方式中，每个 L 独立地为卤素。在一种实施方式中，两个 L 都为氯。在另一种实施方式中，一个 L 为氯且另一个 L 为 $-OSO_2Me$。

[0244] 用吗啉置换离去基团 L（步骤 3.1）可以在碱的存在下发生。在某些实施方式中，碱是原位产生的。在一种实施方式中，步骤 3.1 在碱金属碱的存在下发生。在一种实施方式中，步骤 3.1 在碱金属氢氧化物、碳酸盐、碳酸氢盐、磷酸盐、磷酸氢盐或磷酸二氢盐的存在下发生。在一种实施方式中，步骤 3.1 在 LiOH、NaOH、KOH、Na_2CO_3、K_2CO_3、Cs_2CO_3、$NaHCO_3$、$KHCO_3$、Na_3PO_4、K_3PO_4、Na_2HPO_4、K_2HPO_4、NaH_2PO_4或 KH_2PO_4的存在下发生。

[0245] 在一种实施方式中，步骤 3.1 在 M-R^c或 M-OR^c的存在下发生，其中 M 为碱金属；和 R^c为取代的或未取代的 C_{1-10}烷基。在一种实施方式中，步骤 3.1 在甲醇钠、乙醇钠、叔丁醇钠、甲醇钾、乙醇钾或叔丁醇钾的存在下发生。

[0246] 在一种实施方式中，步骤 3.1 在含氮碱的存在下发生。在一种实施方式中，步骤 3.1 在三乙胺、二异丙基乙胺、吡啶、4- 二甲基氨基吡啶或 1,8- 二氮杂二环 [5.4.0] 十一碳 -7- 烯 (DBU) 的存在下发生。在一种实施方式中，步骤 3.1 在二异丙基乙胺的存在下发生。在另一种实施方式中，吗啉本身起到碱的作用。

[0247] 步骤 3.1 可以在任何溶剂或溶剂的任何组合中发生。在某些实施方式中，溶剂为或溶剂组合包含乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。在一种实施方式中，溶剂为乙腈。在另一种实施方式中，溶剂为四氢呋喃。在又一种实施方式中，溶剂为乙酸异丙酯。

[0248] 反应温度、反应时间和式 (VI) 的化合物与吗啉的摩尔比对于获得式 (V) 的化合物最佳转化很重要。在某些情况下，提高反应温度、延长反应时间和 / 或大量过量的吗啉可以导致形成大量副产物 1,4- 双（吗啉基甲基）苯或其盐。

[0249] 步骤 3.1 可以在任何反应温度下发生。在某些实施方式中，反应温度为约 -100℃至约 200℃。在某些实施方式中，反应温度为约 -50℃至约 150℃。在某些实施方式中，反应温度为约 0℃至约 100℃。在某些实施方式中，反应温度为约室温。

[0250] 步骤 3.1 可以在任何反应时间下发生。在某些实施方式中，反应时间为约 1 分钟至约 14 天。在某些实施方式中，反应时间为约 5 分钟至约 48 小时。在某些实施方式中，反应时间为约 1 小时至约 24 小时。在某些实施方式中，反应时间为约 20 小时至不超过 24 小时。

[0251] 步骤 3.1 可以在任何摩尔比的式 (VI) 的化合物与吗啉下发生。在某些实施方式中，式 (VI) 的化合物与吗啉的摩尔比为约 10:1 至约 1:10。在某些实施方式中，式 (VI) 的化合物与吗啉的摩尔比为约 5:1 至约 1:5。在某些实施方式中，式 (VI) 的化合物与吗啉的摩尔比为约 3:1 至约 1:3。在某些实施方式中，式 (VI) 的化合物与吗啉的摩尔比为约 1.5:1 到约 1:1.5。在一种实施方式中，式 (VI) 的化合物与吗啉的摩尔比为约 1:1.5。在另一种实施方式中，式 (VI) 的化合物与吗啉的摩尔比为约 1:1。

[0252] 步骤 3.1 通常得到式 (V) 的化合物或其盐和副产物 1,4- 双（吗啉基甲基）苯或其盐。该混合物可以任选地通过在合适的溶剂或合适的溶剂组合中选择性萃取分离（步

骤 3.2)。在某些实施方式中，溶剂为或溶剂组合包含：乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。在一种实施方式中，溶剂为甲醇。

[0253] 在一种示例性的实施方式中，两个 L 为氯，其中步骤 3.1 在乙酸异丙酯溶剂中发生，反应温度为约室温，反应时间为约 20 小时至不超过 24 小时，式 (VI) 的化合物与吗啉的摩尔比为约 1:1.5；和式 (V) 的化合物任选地通过在甲醇中选择性萃取来纯化。

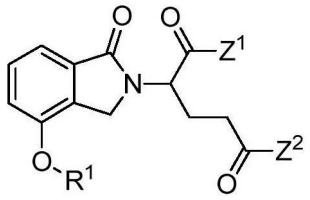
[0254] 在另一种示例性的实施方式中，一个 L 为氯且另一个 L 为 $-OSO_2CH_3$，其中步骤 3.1 在二异丙基乙胺的存在下发生，溶剂为乙腈。

[0255] 6.2.4 化合物 (IV) 的制备

[0256] 式 (IV) 的化合物可以使用本领域普通技术人员已知的方法制备。例如，其中 R 为甲基的式 (IV) 的化合物及其外消旋形式的该化合物的制备已经报道在美国专利公开 No.2011/0196150 中。

[0257] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的式 (IV) 的化合物的方法，包括

[0258] (步骤 4) 在适于脱保护的条件下，使对映异构体富集的或对映异构体纯的式 (VII) 的化合物脱保护：

[0259]  其中

(VII)，

[0260] (i)Z^1 为 NHY，和 Z^2 为 OR；或

[0261] (ii)Z^1 为 OR，和 Z^2 为 NHY；和

[0262] R^1 为合适的苯酚保护基。

[0263] 合适的苯酚保护基是本领域普通技术人员公知的。保护基的选择和使用及设置和除去保护基的反应条件描述在 T.W.Green,Protective Groups in Organic Synthesis(第三版，Wiley,New York,1999) 中。在一种实施方式中，R^1 为甲基、异丙基、环丙基甲基、叔丁基、环己基、烯丙基、炔丙基、氰基甲基、2- 溴甲基、甲氧基甲基 (MOM)、甲硫基甲基 (MTM)、甲氧基乙氧基甲基 (MEM)、2-(三甲基甲硅烷基) 乙氧基甲基胺 (SEM)、四氢吡喃基 (THP)、苄基、对 - 甲氧基苄基、2,6- 二甲氧基苄基、2,6- 二氯苄基、三甲基甲硅烷基 (TMS)、三乙基甲硅烷基 (TES)、三异丙基甲硅烷基 (TIPS)、二甲基异丙基甲硅烷基 (IPDMS)、二乙基异丙基甲硅烷基 (DEIPS)、叔丁基二甲基甲硅烷基 (TBDMS)、或叔丁基二苯基甲硅烷基 (TBDPS)、甲酸酯基、乙酸酯基、苯甲酸酯基、碳酸甲基酯基、碳酸叔丁酯基 (BOC)、碳酸苄酯基、二甲基膦基、甲磺酸酯基或甲苯磺酸酯基。

[0264] 在一种示例性的实施方式中，Y 为氢，R 为叔丁基且 R1 为叔丁基二甲基甲硅烷基 (TBDMS)，其中反应在四丁基氟化铵 (TBAF) 的存在下在甲醇中发生。

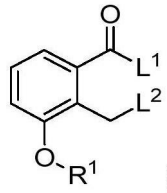
[0265] 6.2.5 化合物 (VII) 的制备

[0266] 式 (VII) 的化合物可以使用本领域普通技术人员已知的方法制备。例如，其中 R 为甲基、R^1 为叔丁基二甲基甲硅烷基 (TBDMS) 且该化合物处于其外消旋形式的式 (VII) 的

化合物的制备，已经报道在美国专利公开 No.2011/0196150 中。

[0267] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的式 (VII) 的化合物的方法，包括

[0268] (步骤 5) 在适于环化的条件下，使式 (VIII) 的化合物：

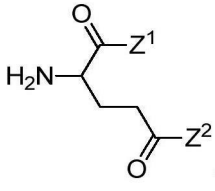
[0269]  其中

(VIII)，

[0270] R^1为合适的苯酚保护基；L^1和 L^2独立地为卤素、OR^2、$OCOR^2$、OSO_2R^2、OPO_3R^2或合适的离去基团；

[0271] 其中 R^2为饱和的、部分饱和的或不饱和的 C_{1-10}烷基，任选地被一个或多个卤素取代；或 5 至 10 元芳基或杂芳基，任选地被一个或多个卤素取代；

[0272] 接触对映异构体富集的或映异构体纯的式 (IX) 的化合物或其盐：

[0273]  其中

(IX)，

[0274] (i)Z^1为 NHY，和 Z^2为 OR；或

[0275] (ii)Z^1为 OR，和 Z^2为 NHY。

[0276] L^1和 L^2可以独立地为本领域普通技术人员已知的任何合适的离去基团。在一种实施方式中，L^1和 L^2独立地为卤素、甲氧基、$-OSO_2CH_3$、$-OSO_2CF_3$、$-OSO_2CCl_3$、$-OSO_2CH_2CF_3$、$-OSO_2CH_2CCl_3$、或 $-OSO_2C_6H_4$-p-Me(对甲苯磺酸酯)。在一种实施方式中，L^1为甲氧基，和 L^2为溴。

[0277] 在一种示例性的实施方式中，Y 为氢，R 为叔丁基，R1 为叔丁基二甲基甲硅烷基 (TBDMS)，L^1为甲氧基，和 L^2为溴，其中该反应在 KH_2PO_4的存在下在乙腈中发生。

[0278] 在另一种示例性的实施方式中，Y 为氢，R 为甲基，R^1为叔丁基二甲基甲硅烷基 (TBDMS)，L^1为甲氧基，和 L^2为溴，其中该反应在二异丙基乙胺的存在下在乙腈中发生。

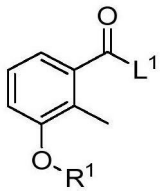
[0279] 6.2.6 化合物 (VIII) 的制备

[0280] 式 (VIII) 的化合物可以使用本领域普通技术人员已知的方法制备。例如，其中 R^1为叔丁基二甲基甲硅烷基、L^1为甲氧基和 L^2为溴的式 (VIII) 的化合物的制备已经报道在美国专利公开 No.2011/0196150 中。

[0281] 在一种实施方式中，本文提供了一种用于制备式 (VIII) 的化合物的方法，包括

[0282] (步骤 6) 在适于卤化的条件下，使式 (X) 的化合物在其苄基化位点处发生卤化：

[0283]



(X)。

[0284] 在一种实施方式中，卤化反应是自由基溴化。自由基溴化可以在自由基引发剂的存在下由紫外线、日光或加热引发。自由基溴化的溴化试剂和条件是本领域普通技术人员公知的。在一种示例性的实施方式中，溴化试剂为 1- 溴吡咯烷 -2,5- 二酮 (NBS)，自由基引发剂为 2,2’ -(偶氮 -1,2- 二基) 双 (2- 甲基丙腈)(AIBN)，溶剂为乙酸异丙酯。

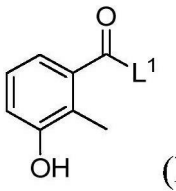
[0285] 6.2.7 化合物 (X) 的制备

[0286] 式 (X) 的化合物可以使用本领域普通技术人员已知的方法制备。例如，其中 R^1为叔丁基二甲基甲硅烷基和 L^1为甲氧基的式 (X) 的化合物的制备已经报道在美国专利公开 No.2011/0196150 中。

[0287] 在一种实施方式中，本文提供了一种用于制备式 (X) 的化合物的方法，包括

[0288] (步骤 7) 使式 (XI) 的化合物 ：

[0289]



(XI);

[0290] 与保护基在适于保护的条件下反应。

[0291] 在一种示例性的实施方式中，L^1为甲氧基，其中保护在 N,N- 二甲基甲酰胺溶剂中且在叔丁基二甲基甲硅烷基氯化物和咪唑的存在下发生。

[0292] 6.2.8 化合物 (XI) 的制备

[0293] 式 (XI) 的化合物可以使用本领域普通技术人员已知的方法制备。例如，其中 L1 为甲氧基的式 (XI) 的化合物的制备已经报道在美国专利公开 No.2011/0196150 中。

[0294] 在一种实施方式中，本文提供了一种用于制备式 (XI) 的化合物的方法，包括

[0295] (步骤 8) 在适于酯化的条件下使 3- 羟基 -2- 甲基苯甲酸与醇反应。

[0296] 由酸制备酯的方法是本领域普通技术人员公知的。在某些实施方式中，通过在酸性条件下使酸与醇反应发生酯化。在一种示例性的实施方式中，醇为甲醇，该反应在硫酸的存在下发生。

[0297] 6.2.9 另外的实施方式

[0298] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮的方法，，其中 Y 为氢，R 为叔丁基，步骤 1.1 和步骤 1.2 在苯磺酸的存在下在一锅中发生 ；其中 L 为氯，步骤 2 在 K_2CO_3的存在下发生。

[0299] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮的方法，其中 Y 为氢，R 为叔丁基，步骤 1.1 和步骤 1.2 在苯磺酸的存在下在一锅中发生 ；其中 L 为氯，步骤 2 在 K_2CO_3的存在下发生 ；其中步骤 3.1 在乙酸异丙酯溶剂中发生，反应温度为约室温，反应时间为约 20 小时至不超过 24 小时，式 (VI) 的化合物与吗啉的摩尔比为约 1:1.5 ；和式 (V) 的化合物任选地通过在甲醇中选择性萃取来纯化。

[0300] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮

的方法，其中 Y 为氢，R 为叔丁基，步骤 1.1 和步骤 1.2 在苯磺酸的存在下在一锅中发生；其中 L 为氯，步骤 2 在 K_2CO_3 的存在下发生；其中 R^1 为叔丁基二甲基甲硅烷基 (TBDMS)，步骤 4 在四丁基氟化铵 (TBAF) 的存在下在甲醇中发生。

[0301] 在一种实施方式中，本文提供了一种用于制备对映异构体富集的或对映异构体纯的 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮或其可药用形式的方法，包括：

[0302] (步骤 1.1) 在适于酯向酸转化的条件下，将对映异构体富集的或对映异构体纯的式 (II) 的化合物或其盐转化成对映异构体富集的或对映异构体纯的式 (III) 的化合物或其盐；

[0303] (步骤 1.2) 在适于环化的条件下，使对映异构体富集的或对映异构体纯的式 (III) 的化合物环化成对映异构体富集的或对映异构体纯的式 (I-a) 的化合物：

[0304] (步骤 1.3) 当 Y 不为氢时，在适于脱保护的条件下，使对映异构体富集的或对映异构体纯的式 (I-a) 的化合物脱保护为对映异构体富集的或对映异构体纯的式 (I) 的化合物；和

[0305] (步骤 1.4) 任选地在适于成盐的条件下，将对映异构体富集的或对映异构体纯的式 (I) 的化合物转化成其可药用盐；

[0306] 其中步骤 1.1 和步骤 1.2 在一锅中发生；和

[0307] 其中所述对映异构体富集的或对映异构体纯的式 (II) 的化合物是通过包括如下步骤的方法制备的：

[0308] (步骤 2) 在适于置换的条件下，使对映异构体富集的或对映异构体纯的式 (IV) 的化合物接触式 (V) 的化合物或其盐；

[0309] 其中所述式 (V) 的化合物是通过包括如下步骤的方法制备的：

[0310] (步骤 3.1) 在适于置换的条件下，使式 (VI) 的化合物接触吗啉或其盐；和

[0311] (步骤 3.2) 任选地通过选择性萃取纯化式 (V) 的化合物；其中对映异构体富集的或对映异构体纯的式 (IV) 的化合物是通过包括如下步骤方法制备的：

[0312] (步骤 4) 在适于脱保护的条件下，使对映异构体富集的或对映异构体纯的式 (VII) 的化合物脱保护：

[0313] 其中所述对映异构体富集的或对映异构体纯的式 (VII) 的化合物是通过包括如下步骤的方法制备的：

[0314] (步骤 5) 在适于环化的条件下，使式 (VIII) 的化合物接触对映异构体富集的或对映异构体纯的式 (IX) 的化合物；

[0315] 其中所述式 (VIII) 的化合物是通过包括如下步骤的方法制备的：

[0316] (步骤 6) 在适于卤化的条件下，使式 (X) 的化合物在其苄基化位点卤化；其中所述式 (X) 的化合物是通过包括如下步骤的方法制备的：

[0317] (步骤 7) 使式 (XI) 的化合物与保护基在适于保护的条件下反应；

[0318] 其中所述式 (XI) 的化合物是通过包括如下步骤的方法制备的：

[0319] (步骤 8) 在适于酯化的条件下，使 3- 羟基 -2- 甲基苯甲酸与醇反应；

[0320] 其中 R、R^1、R^2、Y、L、L^1 和 L^2 为如上和本文定义的。

[0321] 本发明涵盖所有上述实施方式的组合。

[0322] 应当理解，本发明的方法也适于经由用式 (IX) 的化合物的相应 R- 对映异构体或消旋物替代其来制备 3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮的对映异构体或外消旋物。另外，3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮的外消旋物可以通过根据本领域已知的和本文提供的方法的合成路线通过对映异构体富集的或纯的化合物的消旋作用来合成。

[0323] 6.3 对映异构纯度的提高

[0324] 在一种实施方式中，本文提供增加式 (I) 的化合物或其盐和 / 或溶剂化物的对映异构纯度的方法。通常，可以通过在产生最佳 ee_{eu} 的条件下重结晶或研磨增加对映异构纯度。

[0325] 在一种实施方式中，本文提供了一种用于增加或提高 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮或其盐和 / 或溶剂化物的方法，包括在溶剂或溶剂混合物中重结晶或研磨 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮或其盐和 / 或溶剂化物的第一样品，得到 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮或其盐和 / 或溶剂化物的第二样品，其中所述第二样品具有比第一样品更高的 ee。

[0326] 在一种实施方式中，通过重结晶增加对映异构体纯度。在另一种实施方式中，通过研磨增加对映异构体纯度。

[0327] 在一种实施方式中，与重结晶或研磨之前的对映异构体纯度相比，在重结晶或研磨之后，对映异构体纯度可以增加 1%、5%、10%、15%、20%、25%、30% 或以上。

[0328] (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮的第一样品 (即，其对映异构纯度增加的样品) 可以为无水形式、游离碱形式、水合物形式、溶剂化物形式、盐形式、或其任意组合。在一种实施方式中，第一样品为无水游离碱形式。在另一种实施方式中，第一样品为游离碱水合物形式。在另一种实施方式中，第一样品为游离碱 THF 溶剂化物形式。在又一种实施方式中，第一样品为 HCl 盐形式。在又一种优选的实施方式中，第一样品为无水 HCl 盐形式。

[0329] 第一样品的 ee 可以为 0% 至约 95%。在一种实施方式中，第一样品的 ee 为约 25% 至约 90%。在一种实施方式中，第一样品的 ee 为约 50% 至约 80%。在一种实施方式中，第一样品的 ee 为约 75%。

[0330] 重结晶或研磨可以在任何溶剂或溶剂的任何组合中发生。在某些实施方式中，溶剂为或溶剂组合包含水、乙醚、1,4- 二噁烷、四氢呋喃、乙酸乙酯、乙酸异丙酯、乙腈、甲醇、乙醇、异丙醇、二甲基甲酰胺、二甲亚砜、甘醇二甲醚、二甘醇二甲醚、二甲基乙酰胺、或 N- 甲基 -2- 吡咯烷酮。在一种实施方式中，溶剂为乙腈。在另一种实施方式中，溶剂为四氢呋喃。

[0331] 在一种实施方式中，溶剂为醇。在一种实施方式中，溶剂为甲醇。

[0332] 在一种实施方式中，溶剂为醇和水的混合物。在一种实施方式中，溶剂为异丙醇和水的混合物。在一种实施方式中，溶剂为异丙醇和水的 90:10 混合物。在另一种实施方式中，溶剂为异丙醇和水的 95:5 混合物。

[0333] 重结晶或研磨可以在任何温度下发生。在某些实施方式中，温度为约 0℃至约 100℃。在某些实施方式中，温度为约 10℃至约 80℃。在一种实施方式中，温度为约 22℃。

在另一种实施方式中，温度为约 55℃。

[0334] (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮的第二样品(即，在增加对映异构纯度之后的化合物)可以与(S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮的第一样品是相同或不同的形式。在一种实施方式中，第二样品与第一样品是不同形式。在另一种实施方式中，第二样品与第一样品是相同形式。在一种实施方式中，第一样品和第二样品都是 HCl 盐形式。

[0335] 第二样品的 ee 高于第一样品的 ee。在一种实施方式中，第二样品的 ee 不少于约 50％、不小于约 60％、不少于约 70％、不少于约 80％、不少于约 85％、不少于约 90％、不少于约约 91％、不少于约 92％、不少于约 93％％、不少于约 94％、不少于约 95％、不少于约 96％、不少于约 97％、不少于约 98％、不少于约 99％、不少于约 99.5％、不少于约 99.9％、不少于约 99.95％、不小于约 99.99％或约 100％。

[0336] 在一种实施方式中，(S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮的第一样品为具有 ee 75％的 HCl 盐形式，在 55℃ C 下在甲醇中发生研磨，得到 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮的第二样品，其为具有 ee 97.5％的 HCl 盐形式。

[0337] 本发明涵盖所有上述实施方式的组合。

[0338] 7. 实施例

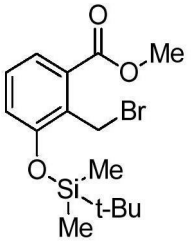
[0339] 如本文使用的，与是否特别地定义特定的缩写无关，在这些方法、方案和实施例中使用的符号和惯例与当代科学文献(例如美国化学学会杂志(Journal of the American Chemical Society)或生物化学杂志(Journal of Biological Chemistry))中使用的那些一致。特别地，但不限于，在实施例和整个说明书中可以使用下述缩略语：g(克)；mg(毫克)；mL(毫升)；μL(微升)；M(摩尔)；mM(毫摩尔)；μM(微摩尔)；eq.(当量)；mmol(毫摩尔)；Hz(赫兹)；MHz(兆赫兹)；hr 或 hrs(小时)；min(分钟)；和 MS(质谱学)。除非另有说明，否则本文提供的化合物中的水含量是通过 Karl Fisher(KF)方法测定的。

[0340] 对于下述实施例，除非另有说明，否则可以使用本领域技术人员已知的标准处理和纯化方法。除非另有说明，否则所有的温度都以℃ C(摄氏度)表示。除非另有说明，否则所有的反应都在室温下进行。本文举例说明的合成方法意欲通过使用特定实施例来例证可适用的化学过程，而不是表示本发明的范围。

[0341] 实施例 1

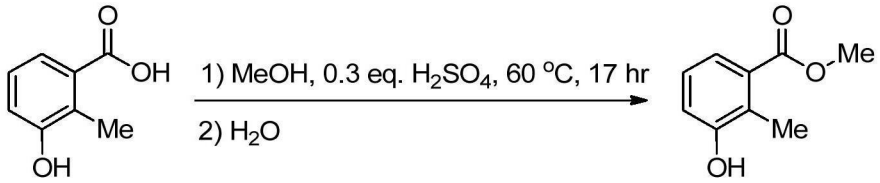
[0342] 2-(溴甲基)-3-((叔丁基二甲基甲硅烷基)氧基)苯甲酸甲酯的合成

[0343]



[0344] 步骤 1：

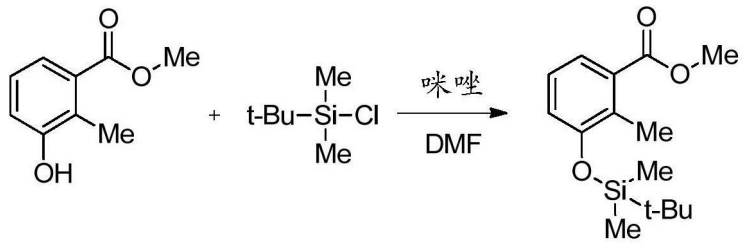
[0345]



[0346] 在氮气下，将 3- 羟基 -2- 甲基苯甲酸 (250g，1.32mol) 加入到带夹套的底卸式 (bottom drop) 三颈烧瓶中的甲醇 (2500mL，10X) 中。向上述溶液中加入硫酸 (48.3g，0.49mol)。将该混合物加热至 60℃，并搅拌 8 至 17 小时。一旦转化率 >98％，则将该混合物常压蒸馏至 3X 体积。将残余物冷却至 20℃，并且经至少 30 分钟，慢慢地加入到水 (500mL，2X) 中。加入晶种 (2g，0.01X)，并且在 20℃下搅拌该混合物至少 1 小时。在 20℃下，经至少 3 小时加入水 (1500mL，6X)，并且在 20℃下，再搅拌该混合物至少一个小时。将固体过滤，用 9:1 的水：甲醇 (500mL，每次 2X) 洗涤三次，至少 pH ≥ 3。在 35 至 45℃下，在真空下干燥固体直到 KF ≤ 0.1％，得到 3- 羟基 -2- 甲基苯甲酸甲酯 (235.3g，产率 86％)；^{1}H NMR(DMSO-d_6，300MHz) δ 9.68(s，1H)，7.18(dd，J = 7.5，1.2Hz，1H)，7.08(t，J = 7.5Hz，1H)，7.00(dd，J = 8.1，1.2Hz，1H)，3.80(s，3H)，2.29(s，3H)ppm。

[0347] 步骤 2 ：

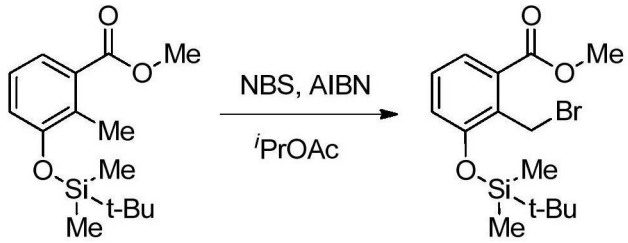
[0348]



[0349] 将 3- 羟基 -2- 甲基苯甲酸甲酯 (110g，662mmo) 加入到在 3 升带夹套的底卸式反应器中的 DMF(660mL，6X) 中。将混合物冷却至 5℃，并且将咪唑 (113g，1655mmol，1.03X) 加入到溶液中。加入叔丁基二甲基氯硅烷 (110g，728mmol，1X)，并且在 5℃下搅拌该混合物 1 小时。将该混合物温热至 20℃，并搅拌至少 2 小时直到剩余不超过 0.2％的起始苯酚。加入乙酸异丙酯 (770mL，7X)，然后慢慢地加入水 (1100mL，10X)，保持温度低于 30℃。搅拌该混合物，沉降和分离。将有机层用水 (770mL，每次 7X) 再洗涤三次，在 40 至 55℃下真空蒸馏至 6X 体积且直到 KF 不超过 0.05％。将 3-((叔丁基二甲基甲硅烷基) 氧基)-2- 甲基苯甲酸甲酯产物储存为乙酸异丙酯溶液，将其用于下一步而无需进一步纯化 (预期 168g，产率 90％)；^{1}H NMR(DMSO-d_6，300MHz) δ 7.15(dd，J = 7.8，1.2Hz，1H)，6.97(t，J = 7.8Hz，1H)，6.82(dd，J = 8.1，1.2Hz，1H)，3.60(s，3H)，2.29(s，3H)，0.97(s，9H)，0.18(s，6H)ppm。

[0350] 步骤 3 ：

[0351]

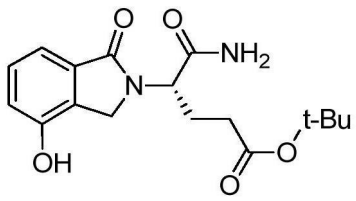


[0352] 将3-((叔丁基二甲基甲硅烷基)氧基)-2-甲基苯甲酸甲酯(157g,560mmol,来自步骤2,具有的残余物单体酚的量≤0.2%)的乙酸异丙酯溶液加入到3升带夹套的底卸式反应器中。加入另外的乙酸异丙酯,并在40至55℃下真空蒸馏该混合物(如有必要),得到总体积约9X(1410mL,KF≤0.05%)。将1-溴吡咯烷-2,5-二酮(NBS,103.6g,580mmol,0.66X)和2,2'-(偶氮-1,2-二基)双(2-甲基丙腈)(AIBN,1.9g,11mmol,0.012X)加入到该溶液中。经至少2小时,将反应混合物加热至70℃,并在70℃下搅拌2小时。颜色从橙色变成黄色。如果转化少于95%,则加入另外0.05摩尔当量的NBS,并在70℃下搅拌该混合物1小时。当必要时,重复该过程,直到转化达到95%。将该混合物冷却至20℃,并保持在20℃下至少1小时。过滤固体(琥珀酰亚胺),并用乙酸异丙酯(75mL,0.5X)洗涤。先用亚硫酸钠(157g,1X)的水(1413mL,9X)溶液,接着用水(315mL,2X)洗涤滤液。将有机层在30至40℃下真空蒸馏至～2X体积。加入另外的乙酸异丙酯(315mL,2X),并蒸馏返回至2X体积(如有必要),直到KF不超过0.1%。然后,在30至40℃下蒸馏有机层,得到呈油状物的2-(溴甲基)-3-((叔丁基二甲基甲硅烷基)氧基)苯甲酸甲酯(预期180g,产率90%);^{1}H NMR(DMSO-d_6,300MHz)δ7.47(dd,J=7.8,1.2Hz,1H),7.37(t,J=8.1Hz,1H),7.15(dd,J=8.1,1.2Hz,1H),4.96(s,2H),3.86(s,3H),1.03(s,9H),0.30(s,6H)ppm。

[0353] 实施例2

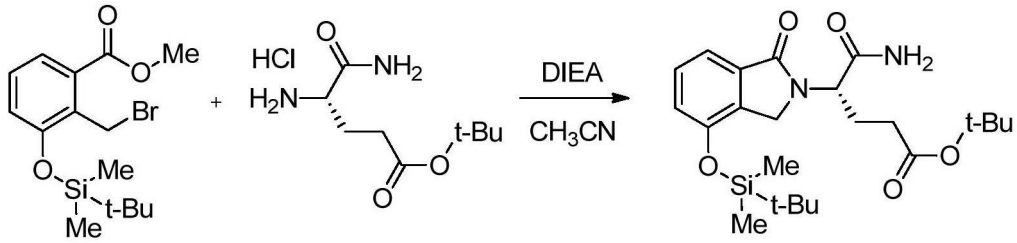
[0354] (S)-5-氨基-4-(4-羟基-1-氧代异吲哚啉-2-基)-5-氧代戊酸叔丁酯的合成

[0355]



[0356] 步骤1:

[0357]

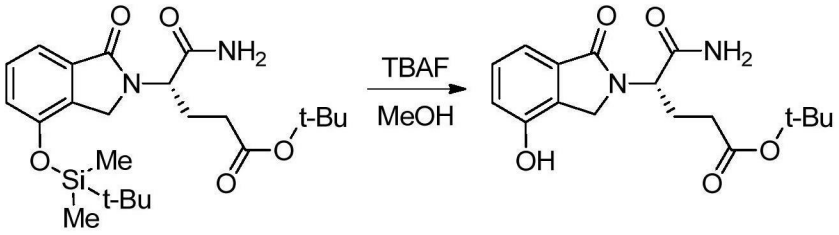


[0358] 在氮气下,将2-(溴甲基)-3-((叔丁基二甲基甲硅烷基)氧基)苯甲酸甲酯(250g,696mmol)和(S)-4,5-二氨基-5-氧代戊酸叔丁酯盐酸盐(183g,765mmol)加入到在具有顶置式搅拌器的5升带夹套的底卸式容器中的乙腈(2150mL,8.6X)中。加入二异

丙基乙胺 (DIEA,303mL,1.74mmol,1.2X),并在 45 至 50℃下加热该混合物 24 至 45 小时。一旦转化≥ 97%,在低于 50℃下真空蒸馏该混合物至 4X 体积。在一个单独的容器中制备 KH_2PO_4(190g,1.32mmol,0.75X) 在水 (2500mL,10X) 中的水性洗涤溶液。将反应混合物冷却至 20 至 25℃,加入甲基叔丁基醚 (MTBE,1500mL,6X)。用一半磷酸盐溶液洗涤该混合物两次,并用水 (500mL,2X) 洗涤两次。将该混合物常压蒸馏至 4X 体积 (1000mL)。加入另外的 MTBE,并将该混合物蒸馏返回至 4X 体积 (如有必要),直到 KF ≤ 0.2%。然后,加入甲醇 (1500mL,6X),并在 25 至 35℃下真空蒸馏该混合物至 4X 体积。加入另外的甲醇,并将该混合物蒸馏返回至 4X 体积 (如有必要),直到以摩尔计 MTBE 相对于甲醇不超过 5%。将粗制的 (S)-5- 氨基 -4-(4-((叔丁基二甲基甲硅烷基) 氧基)-1- 氧代异吲哚啉 -2- 基)-5- 氧代戊酸叔丁酯用于下一步中,而无需进一步纯化。

[0359] 步骤 2:

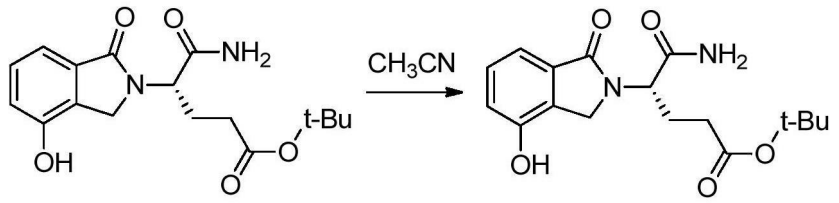
[0360]



[0361] 将甲醇 (1500mL,6X) 加入到来自步骤 1 的粗制的 (S)-5- 氨基 -4-(4-((叔丁基二甲基甲硅烷基) 氧基)-1- 氧代异吲哚啉 -2- 基)-5- 氧代戊酸叔丁酯中。加入四丁基氟化铵三水合物 (35g,0.14X)。在 15 至 25℃下,搅拌该混合物 12 至 24 小时。如有必要,延长搅拌时间,直到转化达到 99.5%。在低于 45℃下,真空蒸馏该混合物至 3.5 至 4X 体积 (875 至 1000mL)。将挡板插入到反应器中,温度调节至 15 至 25℃,并且加入晶种 (1.25g,0.005X)。经 7 小时加入水 (1750mL,7X)。搅拌该混合物 12 至 24 小时。过滤固体,用水 (500mL,2X) 洗涤,并在 40℃下,在减压与氮气吹扫下干燥直到 KF ≤ 0.5%。将粗的 (S)-5- 氨基 -4-(4- 羟基 -1- 氧代异吲哚啉 -2- 基)-5- 氧代戊酸叔丁酯用于下一步中,而无需进一步纯化。

[0362] 步骤 3 :

[0363]



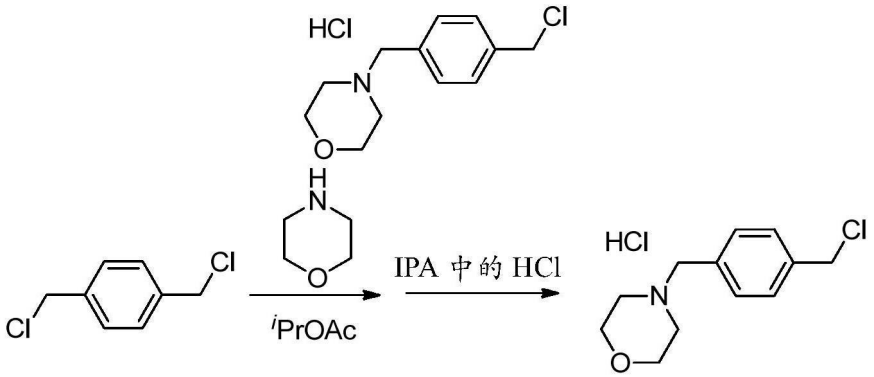
[0364] 将来自步骤 2 的粗的 (S)-5- 氨基 -4-(4- 羟基 -1- 氧代异吲哚啉 -2- 基)-5- 氧代戊酸叔丁酯加入到在 2 升烧瓶中的乙腈 (750mL,3X) 中,所述烧瓶具有顶置式搅拌器、热电偶和氮气氛。将该混合物加热至 60 至 70℃,并在该范围中搅拌 4 至 5 小时。经 4 至 5 小时将该混合物冷却至 15 至 25℃,并在该范围中搅拌 12 至 24 小时。过滤固体,用乙腈 (250mL,1X) 洗涤,并在 35 至 45℃下,在减压与氮气吹扫下干燥直到干燥损失 (LOD) ≤ 1%,得到 (S)-5- 氨基 -4-(4- 羟基 -1- 氧代异吲哚啉 -2- 基)-5- 氧代戊酸叔丁酯 (182g,产率 78%) ; MS m/z:335.1(M+1) ;^{1}H NMR(DMSO-d_6,300MHz) δ 10.03(s,1H),7.56(br s,1H),7.31(dd,J = 7.8,7.8Hz,1H),7.18(br s,1H),7.15(dd,J = 7.5,0.6Hz,1H),6.98(dd,J =

7.8,0.6Hz,1H),4.71(dd,J = 10.2,4.2Hz,1H),4.49(d,J = 17.7Hz,1H),4.32(d,J = 17.4Hz,1H),2.21 - 1.93(m,4H),1.34(s,9H)ppm。

[0365] 实施例 3

[0366] 4-(4-(氯甲基)苄基)吗啉盐酸盐的合成

[0367]



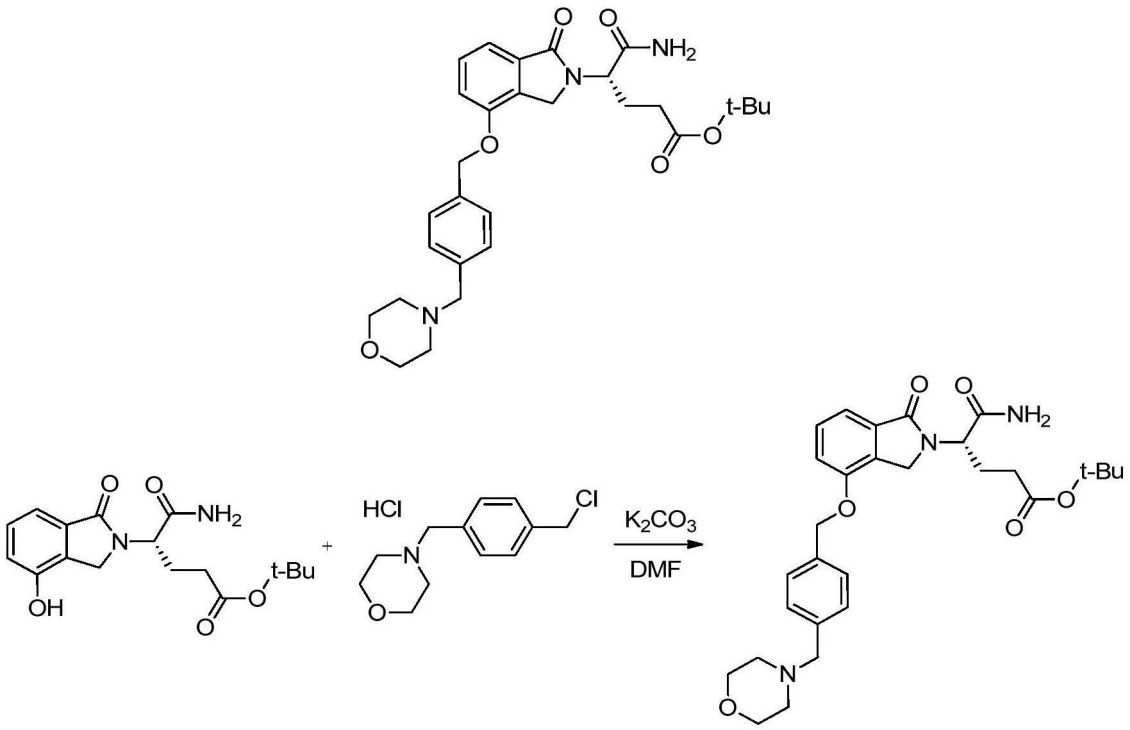
[0368] 将 1,4- 双(氯甲基)苯(50g,286mmol)加入到在反应容器中的乙酸异丙酯(500mL,10X)中。一旦固体溶解,一次性加入吗啉(37.5mL,428mmol)。在室温下,搅拌混合物 20 至不超过 24 小时。过滤固体(吗啉 -HCl 和双 - 吗啉副产物),并用乙酸异丙酯(50mL)洗涤。用水(125mL)洗涤滤液两次,并用 5% 盐水(100mL)洗涤一次。将有机相共沸干燥或用 $MgSO_4$ 干燥。向干燥的有机相中加入在 2- 丙醇中的 HCl(IPA,50mL,5-6N)。慢慢地加入第一个 20mL 以建立良好的晶种床。过滤得到的白色固体,用乙酸异丙酯(100mL)洗涤,在过滤器上干燥至恒重,得到粗产物(39.4g,包括 80.3% 强度的产物和 19.7% 双 - 吗啉副产物,产率 56.4%)。

[0369] 将粗产物(2.0g,80.3% 强度,48.8mmol)加入到甲醇(20mL,10X)中,并在室温下搅拌该混合物 3 小时。过滤固体(双吗啉副产物)而不用冲洗。向滤液中加入乙酸异丙酯(20mL),并且通过在大气压下蒸馏除去甲醇。当顶部温度从甲醇的沸点温度(64-65℃)快速降低时,认为甲醇的除去充分完全。将该混合物冷却至室温,并搅拌过夜。通过快速真空过滤得到的固体,用乙酸异丙酯(1-2mL)洗涤,在漏斗上经真空干燥至恒重,得到呈白色晶体产物的 4-(4-(氯甲基)苄基)吗啉盐酸盐(1.3g,产率 81%);MS m/z:226.1,228.0(M+1);^{1}H NMR(DMSO-d_6,300MHz) δ 11.56(br s,1H),7.65(d,J = 8.1Hz,2H),7.51(d,J = 8.1Hz,2H),4.79(s,2H),4.32(d,J = 5.4Hz,2H),3.94 - 3.78(m,4H),3.20 - 3.00(m,4H)ppm;^{13}C NMR(DMSO-d_6,75MHz) δ 138.9,131.8,129.3,129.1,63.0,58.4,50.6,45.5ppm。

[0370] 实施例 4

[0371] (S)-5- 氨基 -4-(4-((4-(吗啉基甲基)苄基)氧基)-1- 氧代异吲哚啉 -2- 基)-5- 氧代戊酸叔丁酯的合成

[0372]

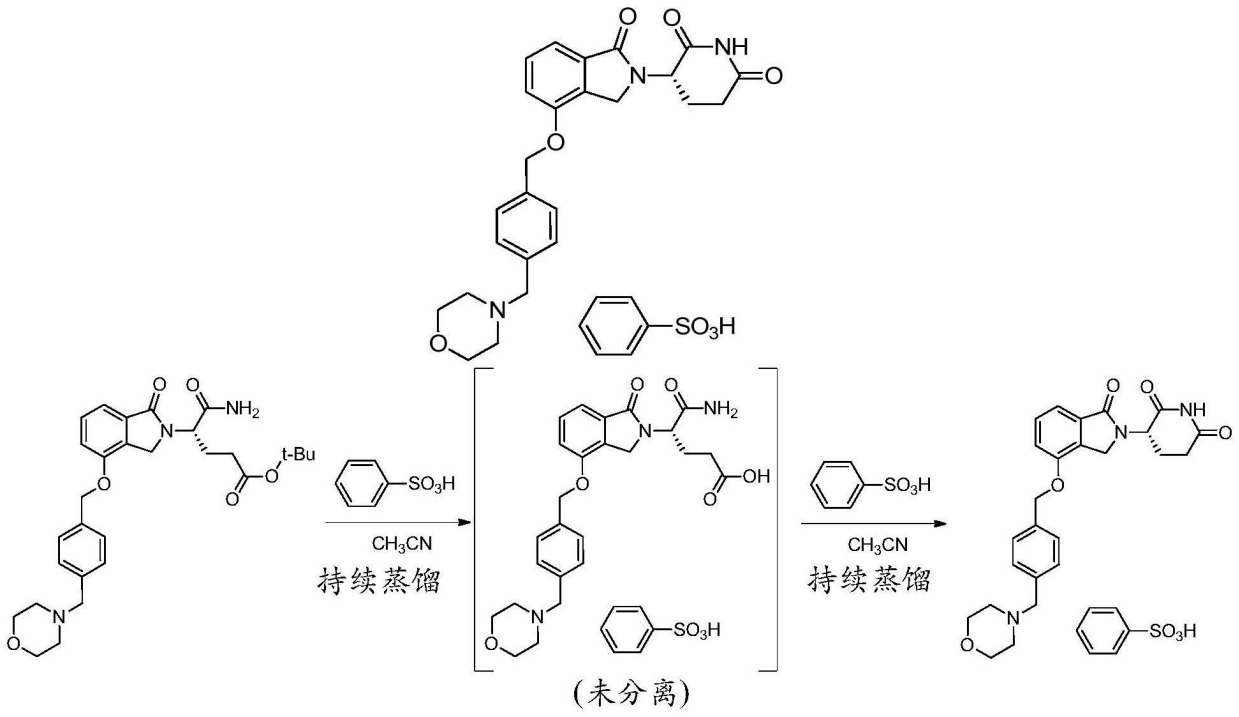


[0373] 将(S)-5-氨基-4-(4-羟基-1-氧代异吲哚啉-2-基)-5-氧代戊酸叔丁酯(160g)、4-(4-(氯甲基)苄基)吗啉盐酸盐(138g,0.87X)和碳酸钾(165g,1.04X)加入到在5升夹套容器中的DMF(960mL,6X)中。将混合物加热至40至50℃,并搅拌12至24小时。将该混合物冷却至25至35℃,然后加入乙酸乙酯(1600mL,10X)和水(1600mL,10X)。在25至35℃下搅拌该混合物,沉降并分离。加入另外的乙酸乙酯(800mL,5X)和水(800mL,5X)。在25至35℃下搅拌该混合物,沉降并分离。将合并的有机相用水(400mL,2.5X)洗涤四次。在低于50℃下真空蒸馏有机相至6X体积。连续地加入另外的乙酸乙酯(2880mL,18X),并继续蒸馏以保持约6X体积。将温度调节至40至45℃,然后加入晶种(0.8g,0.005X)。将该混合物保持约30分钟以建立晶种床,然后经约1.5小时加入庚烷(960mL,6X)。经约1至1.5小时将该混合物冷却至15至25℃,在15至25℃下搅拌至少1小时,并保持16小时。过滤固体,用庚烷:乙酸乙酯(总共5X,2.5X庚烷,2.5X乙酸乙酯)洗涤,并且在35至45℃下,在减压和氮气吃扫下干燥直到LOD≤1%,得到呈白色固体的(S)-5-氨基-4-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)-5-氧代戊酸叔丁酯(215.3g,产率86%);MS m/z:524.3(M+1);^{1}H NMR(DMSO-d_6,300MHz)δ7.57(br s,1H),7.48-7.43(m,3H),7.34(d,J = 8.1Hz,2H),7.29(d,J = 7.5Hz,2H),7.19(br s,1H),5.21(s,2H),4.71(dd,J = 10.2,4.2Hz,1H),4.54(d,J = 17.4Hz,1H),4.40(d,J = 17.7Hz,1H),3.56(dd,J = 4.5,4.5Hz,4H),3.45(s,2H),2.34(dd,J=4.5,4.5Hz,4H),2.15-1.99(m,4H),1.32(s,9H)ppm;^{13}C NMR(DMSO-d_6,75MHz)δ171.8,171.3,167.8,153.4,137.7,135.3,133.3,130.2,129.5,129.0,127.6,115.1,114.6,79.7,69.4,66.2,62.1,53.5,53.1,44.8,31.8,27.6,24.8ppm。

[0374] 实施例5

[0375] (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮苯磺酸酯的合成

[0376]

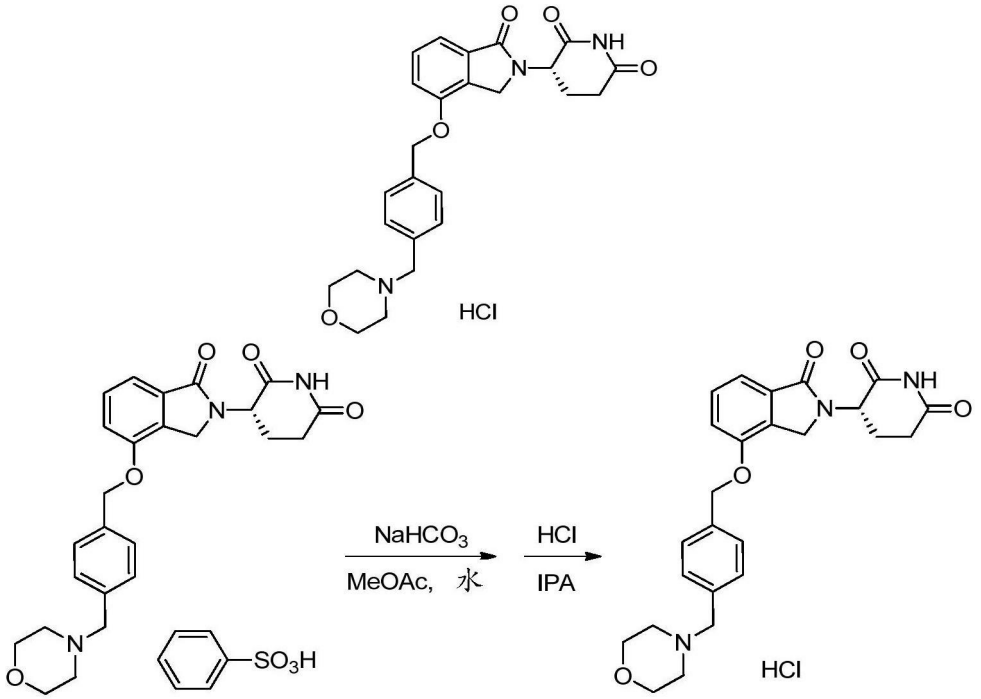


[0377] 将苯磺酸 (68.7g,0.39X) 加入到在 5 升夹套烧瓶中的乙腈 (1400mL,8X) 中,所述夹套烧瓶装有顶置式搅拌器、热电偶、加料漏斗和具有冷凝器的 Dean Stark 收集器,氮气流来自的加料漏斗,其位于反应上方和冷凝器外。如有必要,用乙腈持续地常压蒸馏该混合物,直到 KF ≤ 0.1%。然后,加入 (S)-5- 氨基 -4-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基)-5- 氧代戊酸酯 (175g,1X)。在 90℃下,以每小时 1 至 3X 体积的乙腈蒸馏该混合物 4 小时。加入晶种 (1.75g,0.01X,呈在 17.5mL 的乙腈中的浆液)。以每小时 1 至 3X 体积的乙腈的速率持续地蒸馏该混合物另外 4 至 5 小时 (总共 8 至 9 小时)。经约 1 至 4 小时,将该混合物冷却至 15 至 25℃,并在 15 至 25℃下搅拌至少 1 小时。过滤固体,用乙腈 (350mL,2X) 洗涤,并在 35 至 50℃下,在减压与氮气吃扫下干燥,得到呈白色固体的 (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮苯磺酸酯 (169.1g, 产率 83%);MS m/z:450.3(M+1) ; ^{1}H NMR(DMSO-d_6,300MHz) δ 10.98(s,1H),9.74(br s,1H),7.61 - 7.56(m,4H),7.53(d,J = 7.8Hz,2H),7.48(d,J = 7.8Hz,1H),7.53 - 7.26(m,5H),5.31(s,2H),5.12(dd,J = 13.2,5.1Hz,1H),4.44(d,J = 17.4Hz,1H),4.37(br d,J = 4.8Hz,2H),4.27(d,J = 17.4Hz,1H),3.96(br d,J = 12.6Hz,2H),3.61(br dd,J = 11.4,11.4Hz,2H),3.26(br d,J = 12.3Hz,2H),3.17 - 3.10(m,2H),2.92(ddd,J = 17.7,13.8,5.4Hz,1H),2.59(br d,J = 16.5Hz,1H),2.43(dddd,J = 17.4,13.2,13.2,4.2Hz,1H),2.01 - 1.97(m,1H)ppm ; ^{13}C NMR(DMSO-d_6,75MHz) δ 172.9,171.0,168.0,153.3,148.2,138.3,133.4,131.5,130.0,129.9,128.8,128.5,127.9,127.7,125.5,115.4,115.0,69.0,63.2,59.0,51.6,50.9,45.1,31.2,22.4ppm。

[0378] 实施例 6

[0379] (S)-3-(4-((4-(吗啉基甲基) 苄基) 氧基)-1- 氧代异吲哚啉 -2- 基) 哌啶 -2,6- 二酮盐酸盐的合成

[0380]

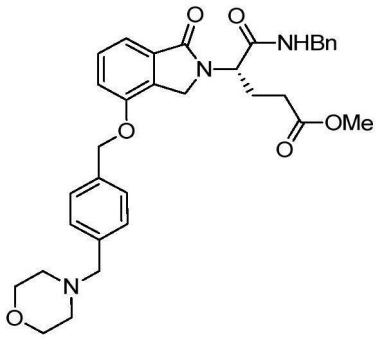


[0381] 将 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮苯磺酸酯 (75g,1X) 和碳酸氢钠 (11.4g,0.15X) 加入到在 3 升带夹套的底卸式容器中的乙酸甲酯 (1350mL,18X) 和水 (300mL,4X) 中,所述带夹套的底卸式容器具有顶置式搅拌器和氮气层。在 15 至 25℃下搅拌该混合物直到固体溶解。将该混合物沉降和分离。向有机相中加入水 (75mL,1X),在 15 至 25℃下搅拌 5 分钟,沉降并分离。将 6M HCl(24.7mL,0.33X) 加入到在单独容器中的异丙醇 (IPA,300mL,4X) 中,良好地搅拌。向 HCl/IPA 溶液中加入晶种 (1.5g,0.02X),并将温度调节至 35 至 45℃。然后,经 4 至 5 小时向 HCl/IPA 溶液中加入乙酸甲酯溶液。在加入之后,在 40℃下搅拌该混合物 0.5 小时,经 0.5 小时冷却至 22℃,并保持在 22℃过夜 (～ 16 小时)。过滤固体,用乙酸甲酯 (225mL,3X,每次) 洗涤两次,并且在 40℃下,在减压和氮气吹扫下干燥,得到呈白色固体的 (S)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮盐酸盐 (48.1g,产率 80％,纯度 99.55％ (HPLC),98.3％ ee);$C_{25}H_{28}ClN_3O_5$ 的分析,理论值:C 61.79,H 5.81,N 8.65,Cl 7.30;实测值:C 61.70,H 5.71,N 8.58,Cl 7.46;MS m/z:450.2(M+1);^{1}H NMR(DMSO-d_6,300MHz) δ 11.56(s,1H),10.97(s,1H),7.67(d,J = 8.1Hz,2H),7.57(d,J = 8.1Hz,2H),7.49(dd,J = 7.8,7.8Hz,1H),7.33(d,J = 7.8Hz,2H),5.29(s,2H),5.12(dd,J = 13.2,5.1Hz,1H),4.44(d,J = 17.4Hz,1H),4.33(d,J = 5.4Hz,2H),4.28(d,J = 17.4Hz,1H),3.93-3.79(m,4H),3.19(d,J = 11.7Hz,2H),3.17-3.00(m,2H),2.91(ddd,J = 18.9,13.8,5.4Hz,1H),2.58(d,J = 18.3Hz,1H),2.43(dddd,J = 17.4,13.2,13.2,4.2Hz,1H),2.02-1.95(m,1H)ppm;^{13}C NMR(DMSO-d_6,75MHz) δ 172.8,171.0,168.0,153.4,138.0,133.4,131.7,130.0,129.8,128.9,127.8,115.4,115.0,69.0,63.0,58.6,51.6,50.6,45.1,31.2,22.4ppm;差示扫描量热法 (DSC) 的热分析图描绘在图 1 中;X-射线粉末衍射图 (XRD) 描绘在图 2 中;热重量分析 (TGA) 的热分析图描绘在图 3 中。

[0382] 实施例 7

[0383] (S)-5-(苄基氨基)-4-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)-5-氧代戊酸甲酯的合成

[0384]

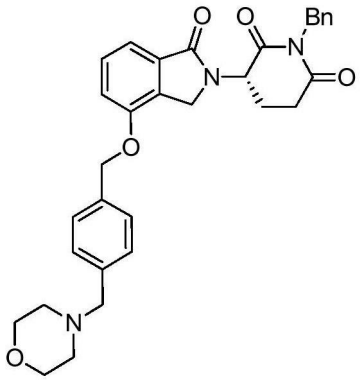


[0385] 在与实施例2和4相同条件下,通过用(S)-4-氨基-5-(苄基氨基)-5-氧代戊酸甲酯代替(S)-4,5-二氨基-5-氧代戊酸叔丁酯盐酸盐制备(S)-5-(苄基氨基)-4-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)-5-氧代戊酸甲酯。

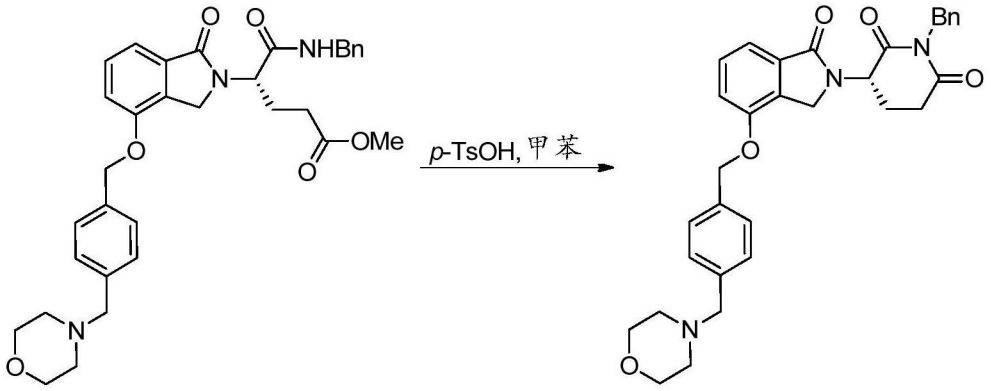
[0386] 实施例8

[0387] (S)-1-苄基-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮的合成

[0388]



[0389]



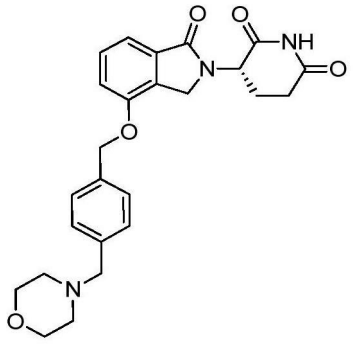
[0390] 在氩气下,将(S)-5-(苄基氨基)-4-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)-5-氧代戊酸甲酯(2.5mmol)和对-TsOH一水合物(1.25mmol)在甲苯中的混合物回流8小时。蒸发溶剂。将粗物质收集在醚(50mL)中,用饱和的$NaHCO_3$水溶液(2×20mL)洗涤。干燥有机层,并通过硅胶色谱法纯化,得到(S)-1-苄基-3-(4-((4-(吗啉

基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮。

[0391] 实施例 9

[0392] (S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮的合成

[0393]



[0394] 通过在 Pd/C 的存在下在乙酸中氢化 2 天，由 (S)-1- 苄基 -3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮制备 (S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮。

[0395] 实施例 10

[0396] 用于提高 (S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮的对映异构纯度的条件的筛选

[0397] 最初，在 22℃下，使用 (S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮游离碱及其相应无水游离碱外消旋化合物在乙腈中评价 ee_{eu}，发现其不利地高 (94.7％）。接着，获得 (S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮游离碱的水合物形式，并且在 22℃下，(S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮水合物与其相应水合物外消旋化合物的 ee_{eu} 保持不利地高 (89.2％）。也获得 (S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮的 THF 溶剂化物，并且提高了该溶剂化物与其相应脱水外消旋化合物在 22℃下的 ee_{eu}(68.5％）。然而，由于 THF 的毒性，(S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮的 THF 溶剂化物不是合适的药物物质，因此寻求一种可替代的方法。

[0398] 在 22℃下，研究 (S)-3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮的 HCl 盐和相应外消旋化合物的 HCl 盐的 ee_{eu}，发现其取决于水 :共溶剂（异丙醇用作共溶剂），其表明存在 (S)- 对映异构体或外消旋化合物两者的水合物（图 4)。物理表征证实该外消旋化合物的 HCl 盐为水合物，其测定为热力学稳定的晶体形式。单一对映异构体的 HCl 盐仍然是热力学稳定的无水形式。低水级分（～ 5％）的 ee_{eu} 有利地低（～ 70％），但是绝对溶解度相当低。提供手性提升需要的溶剂量和设备容量将是不切实际的和不经济的。例如，为了从 90％ ee 提升至 98％ ee，计算需要 200 L 溶剂 / kg 起始原料。

[0399] 接着，得到外消旋的 3-(4-((4-(吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮的 HCl 盐的甲醇溶剂化物，并且显示 XRPD 图案由相应水合物稍有改变。在甲醇的存在下，在环境温度 (22℃）下，获得 (S)-3-(4-((4-(吗啉基甲基）苄

基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮的 HCl 盐和相应外消旋化合物之间的有利的 ee_{eu}(72.4％）。由该 ee_{eu}，据计算获得从 90％ ee 提升至 98％ ee 应当需要 46L 溶剂 /kg 起始原料，而该改善仍是不想要的。

[0400] 溶剂化的结晶形式通常具有比它们的无水相应物更低的熔点，并且扩展而言其相对于相应脱水物随温度升高具有相对更大的溶解度。该现象用于获得提高的 ee_{eu}。对于纯甲醇、90/10 的异丙醇 / 水和 95/5 的异丙醇 / 水，HCl 盐的共晶溶解度测定为温度的函数（图 5)。在所有三个体系中，证实 ee_{eu}随温度升高而降低，如对于一般溶剂化物 / 脱水物的热力学关系所预期的。

[0401] 甲醇体系显示对温度最强的敏感性，并且通常具有低 ee_{eu}。所有 (S)-3-(4-((4-（吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮的晶体形式获得的最低 ee_{eu}、溶剂和温度都是在 55℃下在甲醇中用 HCl 盐，以 ee_{eu}＝ 8％进行的。基于该结果，据计算在 55℃下在甲醇中由 90％ ee 提升至 98％ ee 需要 2.1L 溶剂 /kg 起始原料，这是超越其他条件的巨大改善。

[0402] 实施例 11

[0403] 用于提高 (S)-3-(4-((4-（吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮盐酸盐的对映异构纯度的试验

[0404] 在 55℃下，将具有 75％ ee 的粗制 (S)-3-(4-((4-（吗啉基甲基）苄基）氧基）-1- 氧代异吲哚啉 -2- 基）哌啶 -2,6- 二酮盐酸盐混合物 (4g) 在 28mL 甲醇中研磨约 1.5 小时，然后在 55℃下过滤。然后，将湿产物用甲醇洗涤，并在真空烘箱中干燥。得到的干燥产物的对映异构纯度测定为 97.5％ ee(2.5g，(S)- 对映异构体的回收率 70％）。

(*S*)-3-(4-((4-(吗啉基甲基)苄基)氧基)-
1-氧代异吲哚啉-2-基)哌啶-2,6-二酮盐酸盐的 DSC

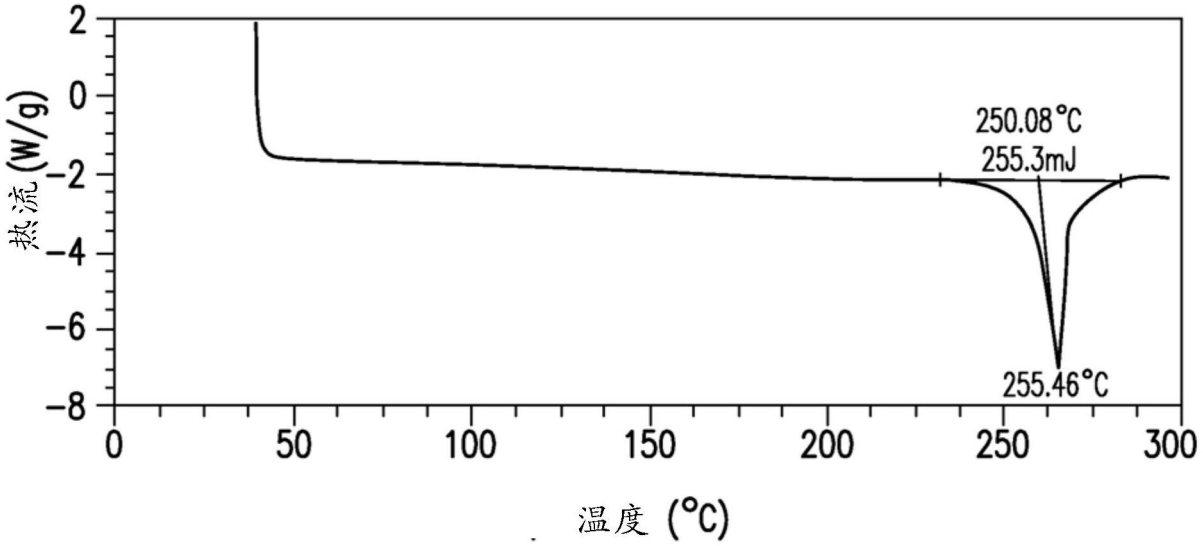


图 1

(*S*)-3-(4-((4-(吗啉基甲基)苄基)氧基)-
1-氧代异吲哚啉-2-基)哌啶-2,6-二酮盐酸盐的 XRD

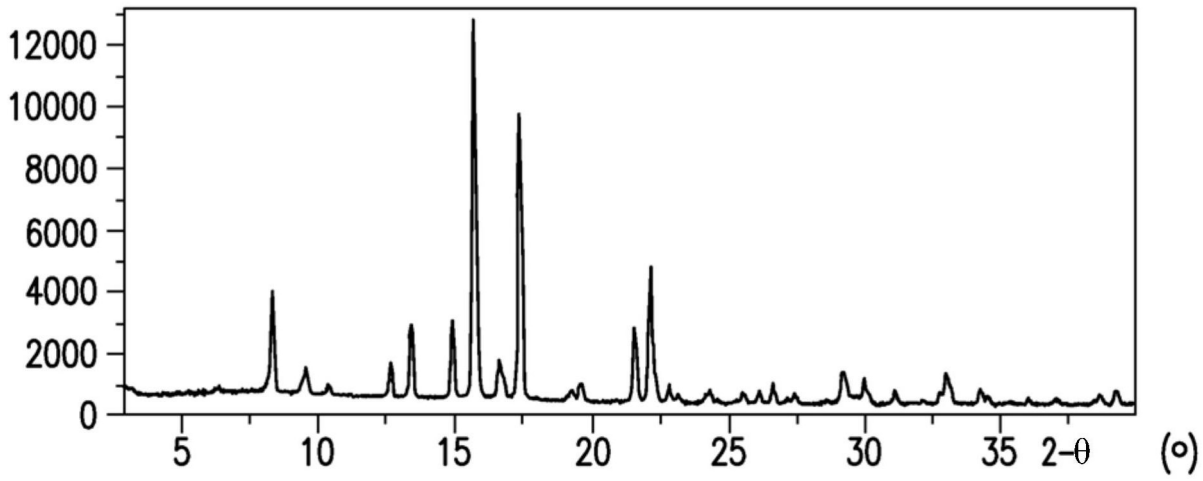


图 2

(*S*)-3-(4-((4-(吗啉基甲基)苄基)氧基)-
1-氧代异吲哚啉-2-基)哌啶-2,6-二酮盐酸盐的 TGA

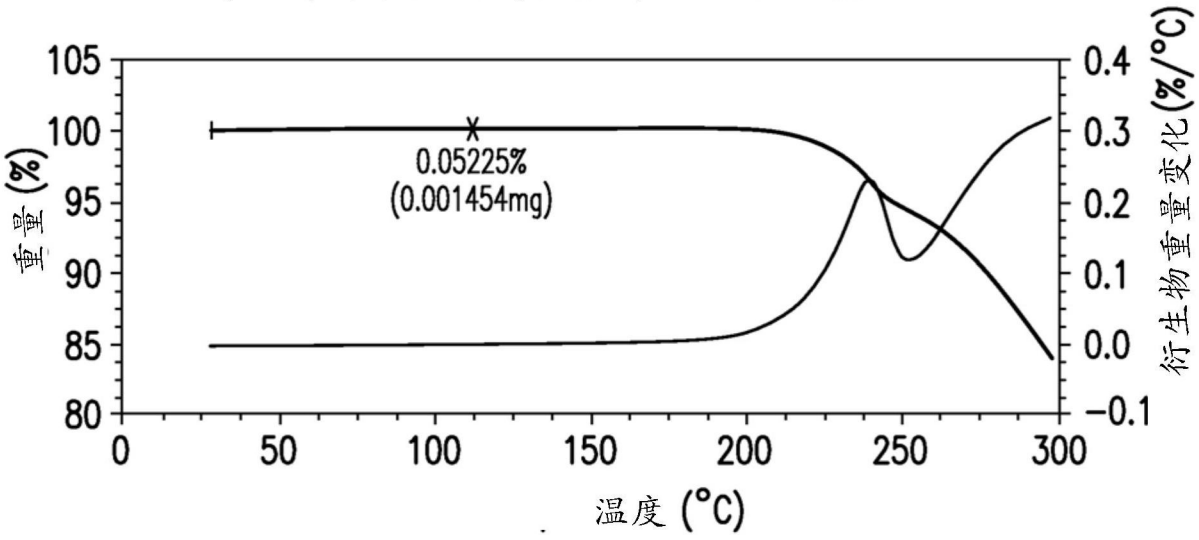


图 3

(*S*)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮的 HCL 盐在 IPA/水中的共晶溶解度

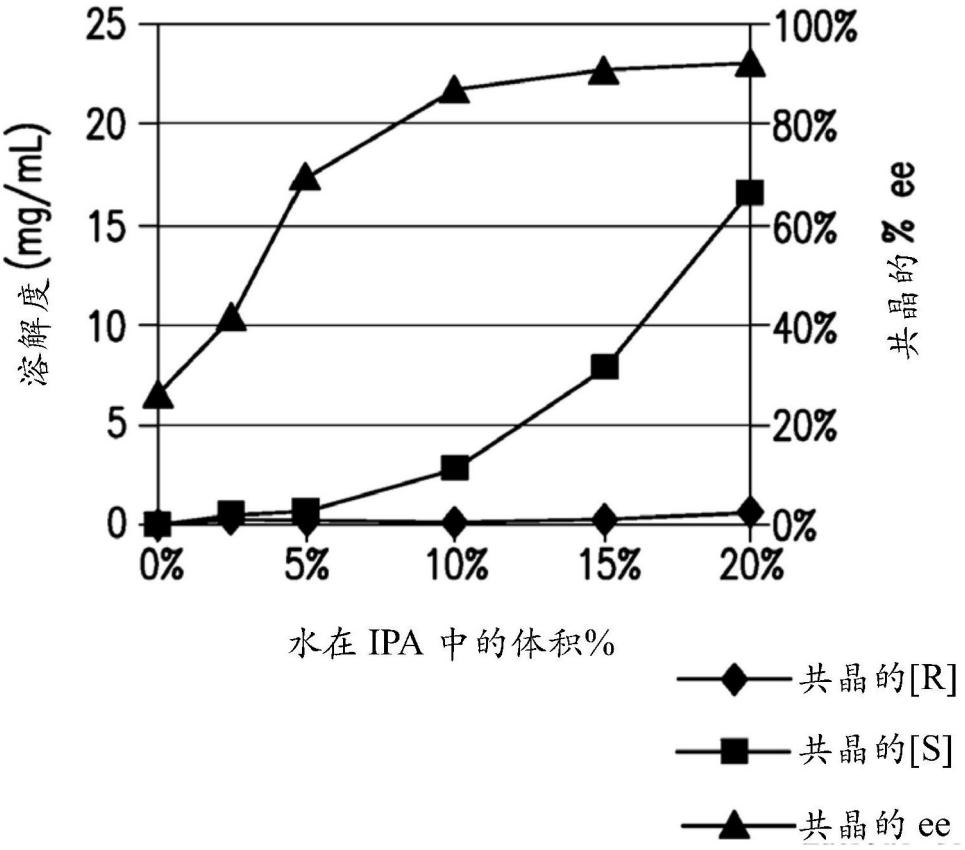


图 4

(*S*)-3-(4-((4-(吗啉基甲基)苄基)氧基)-1-氧代异吲哚啉-2-基)哌啶-2,6-二酮的 HCL 盐在多种溶剂体系中呈温度的函数的共晶溶解度

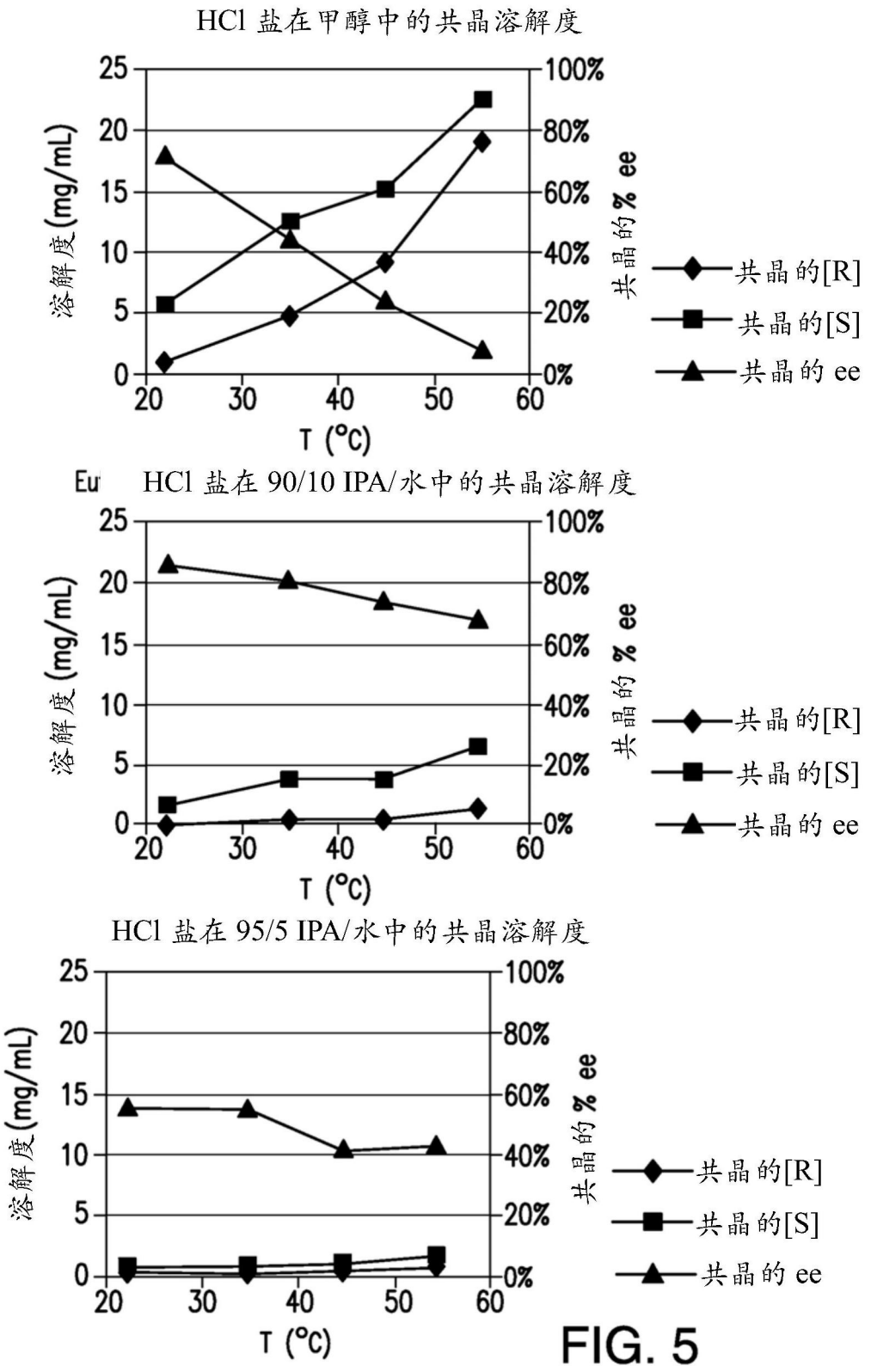


FIG. 5

Abstract

Provided are processes for the preparation of enantiomerically enriched or enantiomerically pure 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable form thereof.