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(54) Title: SYNTHESIS OF INHIBITORS OF EZH2

(57) Abstract: Provided herein are synthetic methods for the preparation of EZH2 inhibitors.



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SYNTHESIS OF INHIBITORS OF EZH2

RELATED APPLICATIONS

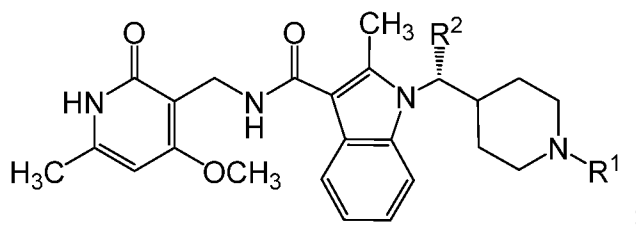
[0001] This application claims the benefit of priority to U.S. Provisional Application No. 62/410,113, filed October 19, 2016, the contents of which are incorporated herein by reference.

BACKGROUND

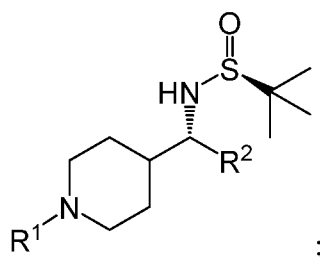
[0002] Inhibitors of Enhancer of Zeste Homolog (EZH2) are promising drugs for the treatment of various cancers. See e.g., WO 2013/120104 and WO 2014/124418. Of particular importance due to their heightened activity for EZH2 are those inhibitors which, among other structural features, contain a chiral center between a substituted piperidinyll and indolyl moiety. See e.g., (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide described in U.S. Patent No. 9,085,583. Economical and efficient means for preparing these stereoselective inhibitors are needed.

SUMMARY

[0003] Disclosed herein are economical and efficient methods for the preparation of EZH2 inhibitors and related intermediates. In one aspect, an EZH2 inhibitor of the formula:



is stereoselectively prepared from a diastereomerically enriched sulfonamide compound having the formula:

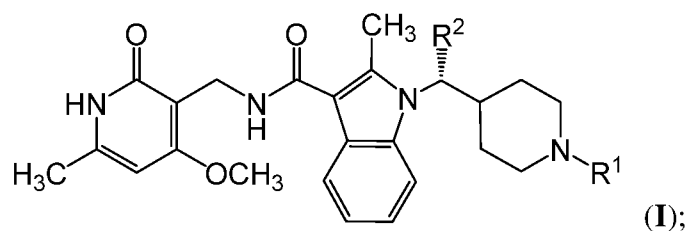


wherein the variables R^1 and R^2 are as described herein. This diastereomerically enriched sulfonamide can be prepared in approximately a 3:1 ratio of the desired S-absolute configuration (e.g., about 75% dr) over five steps from readily available starting materials.

See **Scheme 2**. In addition, the sulfinyl group can be cleaved near quantitatively to afford the resulting amine. The resulting amine can then be optionally resolved as a chiral salt to improve the enantiomeric excess of the preferred enantiomer (e.g., >99% ee). This process can be performed on large scale (>25 kg) using commercially available reagents.

DETAILED DESCRIPTION

[0004] Provided herein is a method for preparing an EZH2 inhibitor having the Formula **I**:



wherein R¹ is halo(C₁-C₆)alkyl and R² is (C₁-C₆)alkyl.

Definitions

[0005] The term “optically active” means that the compound associated with this term rotates the vibrational plane of plane polarized light, i.e., the compound is not achiral. Typically, the compound is an enantiomer which is enantiomerically enriched over the possible enantiomer.

[0006] The term “diastereomerically enriched” means that the depicted diastereomer is present in excess over all other possible diastereomers. The diastereomeric excess of the depicted diastereomer can be e.g., at least 55%, at least 60%, at least 70%, at least 80%, at least at least 90%, at least 95%, at least 97%, at least 99% or at least 99.9% by weight over all other possible diastereomers.

[0007] The term “enantiomerically enriched” means that the depicted enantiomer is present in excess over the other possible enantiomer. The enantiomeric excess of the depicted enantiomer can be e.g., at least 55%, at least 60%, at least 70%, at least 80%, at least at least 90%, at least 95%, at least 97%, at least 99% or at least 99.9% by weight over the other possible enantiomer.

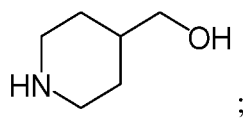
[0008] Diastereomeric excess (de) is defined as $|D_1 - D_2|$ [(and the percent diastereomeric excess as $100(D_1 - D_2)$], where D_1 is the mole fraction of the depicted diastereomer and D_2 is the mole fraction of all other possible diastereomers.

[0009] Enantiomeric excess (ee) is defined as $|F_{(+)} - F_{(-)}|$ (and the percent enantiomer excess by $100|F_{(+)} - F_{(-)}|$), where the mole fractions of two enantiomers are $F_{(+)}$ and $F_{(-)}$ (where $F_{(+)} + F_{(-)} = 1$).

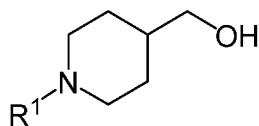
[0010] Unless indicated otherwise, when a particular enantiomer of a compound is named or depicted by structure, that enantiomer is present in an enantiomeric excess of at least 55%, at least 60%, at least 70%, at least 80%, at least at least 90%, at least 95%, at least 97%, at least 99% or at least 99.9% over the other possible enantiomer. Similarly, unless indicated otherwise, when a particular diastereomer of a compound is named or depicted by structure, that diastereomer is present in a diastereomeric excess of at least 55%, at least 60%, at least 70%, at least 80%, at least at least 90%, at least 95%, at least 97%, at least 99% or at least 99.9% over all other possible diastereomers.

Preparation of the Optically Active Acid/Indole

[0011] In a first step of the preparation of the optically active acid indole a secondary amine compound of the formula:



is reacted with R^1-L , where L is a leaving group, to form an alcohol compound of the formula:

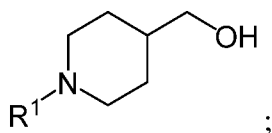


R^1 in the alcohol compound is as defined above for Formula I. The leaving group for this reaction is a molecular fragment that upon reaction with the secondary amine, departs with a pair of electrons in heterolytic bond cleavage. Leaving groups are known to those skilled in the art and include, but are not limited to halides (Cl, Br, or I) and sulfonate esters (e.g., mesylate, triflate, tosylate, methyl sulfate, and the like). In one aspect, the leaving group L in the formula R^1-L is a triflate, e.g., R^1-L is $R^1-O(SO_2)CF_3$. In one aspect, at least one equivalent of R^1-L is used.

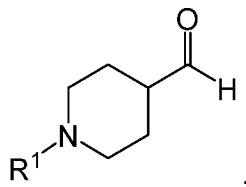
[0012] The reaction can optionally be carried out in the presence of base. For example, a carbonate base (e.g., K_2CO_3 , $KHCO_3$, Na_2CO_3 , $NaHCO_3$, $Na_3H(CO_3)_2$, Li_2CO_3 , $LiHCO_3$, $MgCO_3$, $Mg(HCO_3)_2$, $CaCO_3$, $Ca(HCO_3)_2$, and the like) may be used. Other examples include non-nucleophilic bases and/or sterically hindered bases such as N,N-diisopropylethylamine, 1,8-Diazabicycloundec-7-ene, 2,6-Di-*tert*-butylpyridine, 2,6-lutidine, dimethylaminopyridine,

and pyridine. In one aspect, the leaving group is triflate such that R^1-L is of the formula: $R^1-O(SO_2)CF_3$ and the base is K_2CO_3 . In one aspect, at least one equivalent of base relative to the secondary amine compound is used. Appropriate solvents for this reaction would be apparent to one of skill in the art. In one aspect, the solvent is an alcoholic solvent such as t-amyl alcohol, benzyl alcohol, butanol, t-butyl alcohol, ethanol, isobutanol, isopropyl alcohol, methanol, 1-propanol, and the like. In one aspect the solvent used in the reaction between the secondary amine compound and R^1-L is isopropanol.

[0013] In a second step, the alcohol compound of the formula:



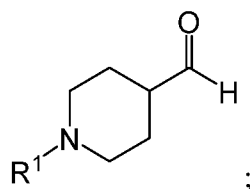
is oxidized with an oxidizing agent to the corresponding aldehyde compound of the formula:



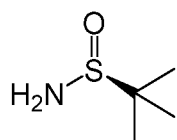
wherein R_1 is as defined defined above for Formula I.

[0014] Exemplary oxidizing reagents for this reaction include e.g., Pyridinium chlorochromate, pyridinium dichromate; chromium(VI) oxide with pyridine in dichloromethane; chromium trioxide in dilute sulfuric acid and acetone; DMSO and oxalyl chloride; dimethyl sulfoxide (DMSO) activated with a carbodiimide, such as dicyclohexylcarbodiimide; dimethyl sulfide (Me_2S) is treated with *N*-chlorosuccinimide (NCS), TEA; Dess-Martin periodinane, 2-iodoxybenzoic acid, tetrapropylammonium perruthenate optionally in the presence of *N*-Methylmorpholine *N*-oxide and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (aka TEMPO)-derived reagents. In one aspect, the oxidizing agent is TEMPO and (diacetoxyiodo)benzene $PhI(OAc)_2$. TEMPO is typically present in catalytic amounts. Suitable solvents for this reaction would be apparent to one of skill in the art and include halogenated solvents such as methylene chloride, carbon tetrachloride, chloroform, dichloroethane, and the like. Although, in one aspect, the solvent used is methylene chloride. In one aspect, at least on equivalent of $PhI(OAc)_2$ relative to the alcohol compound is used.

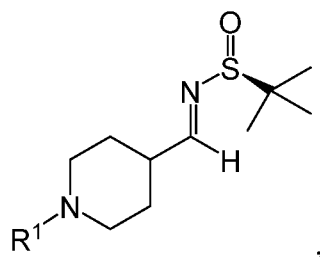
[0015] In a third step, the aldehyde compound of the formula:



is reacted with an optically active sulfoxide compound of the formula:

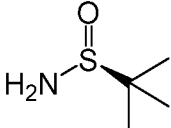


to form an optically active sulfinylimine compound of the formula:



wherein R_1 is as defined above for Formula I.

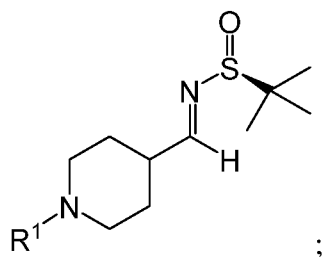
[0016] This chiral sulfoxide in the sulfinylimine compound acts as a chiral auxiliary to induce the desired stereochemistry at the imine carbon during the subsequent Grignard addition to form the diastereomerically enriched sulfonamide. Typically, the chiral sulfoxide is present in at least one equivalent relative to the aldehyde compound. The optically active

sulfoxide compound  has an enantiomeric excess of >90% such as e.g., >95, >96%, >97%, >98%, >99%, >99.5%, or >99.9%. The reaction between the aldehyde and the optically active sulfoxide compound to form the sulfinylimine compound can be carried out in the presence of a base e.g., a carbonate base (e.g., K_2CO_3 , $KHCO_3$, Na_2CO_3 , $NaHCO_3$, $Na_3H(CO_3)_2$, Li_2CO_3 , $LiHCO_3$, $MgCO_3$, $Mg(HCO_3)_2$, $CaCO_3$, $Ca(HCO_3)_2$, and the like). Typically, the amount of carbonate base present is from 1 to 2 equivalents relative to the aldehyde compound. Alkoxide and amine bases can also be used e.g., titanium isopropoxide, potassium tert-butoxide, sodium methoxide, sodium ethoxide, triethylamine, N,N-diisopropylethylamine, dimethylaminopyridine, and pyridine. In one aspect, the base is K_2CO_3 . The reaction between the aldehyde and the optically active sulfoxide compound to form the sulfinylimine compound can also be carried out in the presence of a Lewis acid (e.g.,

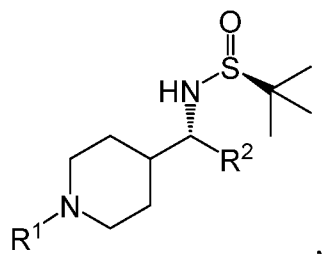
ZnCl₂, BF₃, SnCl₄, AlCl₃, MeAlCl₂, and the like) or protic acids (e.g., sulfurous, phosphoric, carbonic, hydrosulfuric, oxalic, and the like).

[0017] Suitable solvents for this reaction would be apparent to one of skill in the art and include ethereal solvents such as diethyl ether, di-tert-butyl ether, diisopropyl ether, 1,4-dioxane, dimethoxy ethane, dimethoxy methane, diglyme, ethyl tert-butyl ether, methyl tert-butyl ether, tetrahydrofuran, tetrahydropyran, and the like. In one aspect, the solvent used is tetrahydrofuran. Because bonds to the chiral sulfur atom are not broken, the sulfinylimine compound has an enantiomeric excess of >90% such as e.g., >95, >96%, >97%, >98%, >99%, >99.5%, or >99.9%.

[0018] In a fourth step, the sulfinylimine compound of the formula:

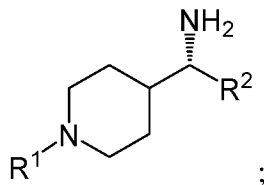


is reacted with a Grignard reagent having the formula R²MgX, where X is bromide, iodide, or chloride; and R² is as described in the first embodiment to form a diastereomerically enriched sulfonamide compound having the formula:



wherein R¹ and R² are as described above for Formula I. Typically at least 1.5 equivalents of Grignard reagent is used. Suitable solvents for this reaction would be apparent to one of skill in the art and include Grignard compatible solvents such as ethereal solvents (e.g., diethyl ether, di-tert-butyl ether, diisopropyl ether, 1,4-dioxane, dimethoxy ethane, dimethoxy methane, diglyme, ethyl tert-butyl ether, methyl tert-butyl ether, tetrahydrofuran, tetrahydropyran, and the like). In one aspect, the solvent used is tetrahydrofuran. The stereoselectivity of this reaction generally produces about a 3:1 ratio favoring the desired sulfonamide compound with S-absolute configuration.

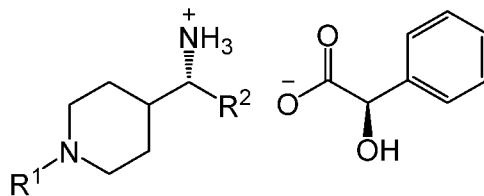
[0019] In a fifth step, the sulfinyl group of the diastereomerically enriched sulfonamide compound is hydrolyzed e.g., by reacting it with acid to form an optically active amine compound of the formula:



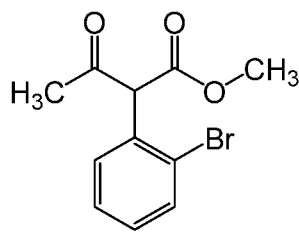
wherein R¹ and R² are as described above for Formula I. Hydrolysis of the sulfonamide for example by acidic removal of the sulfinyl group is known to those skilled in the art and can be achieved e.g., using inorganic acids (such as HCl) with an alcoholic solvent such as isopropanol.

[0020] To remove the undesired enantiomer, the optically active amine can be reacted with an optically active organic acid to prepare a pair of diastereomeric salts comprising the optically active amine compound and the optically active acid, and the enantiomer of the optically active amine and the optically active acid. The optically active organic acids are typically of high optical purity (e.g., with enantiomeric excesses of greater than 98% such as e.g., >99%, >99.5%, and >99.9%). The reaction with the amine forms a pair of diastereomers (one having the desired stereochemistry), which can then be separated by conventional techniques. For example, in one instance the diastereomers can be separated via crystallization from a suitable solvent. The diastereomeric excess after separation (e.g., crystallization) is typically greater than 97% such as e.g., >98% or >99%. Neutralization of the separated salt of the optically active amine with base regenerates the optically active amine in higher optical purity than before the chiral resolution, typically with an enantiomeric excesses of greater than 99% ee).

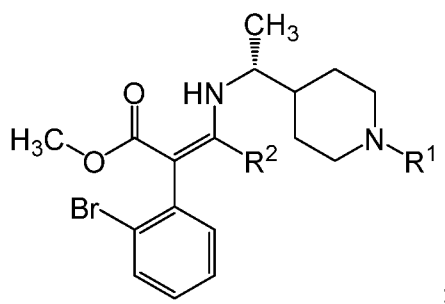
[0021] Optically active acids that are capable of forming a chiral salt complex with the intended compound are known to one of skill in the art. For example, in the above chiral resolution, the optically active organic acid can be selected from aspartic acid, mandelic acid, camphanic acid, camphoric acid, camphorsulfonic acid, tartaric acid, glutamic acid, maleic acid, menthyloxyacetic acid, and methoxyphenylacetic acid. In one aspect, the optically active acid is a mandelic acid such that the resulting diastereomeric salt comprising the optically active amine compound and the optically active organic acid has the following formula:



[0022] In a sixth step, the optically active amine or a salt form of the optically active amine including the diastereomeric salt form used in the chiral resolution is then reacted with a di-keto ester compound having the formula:

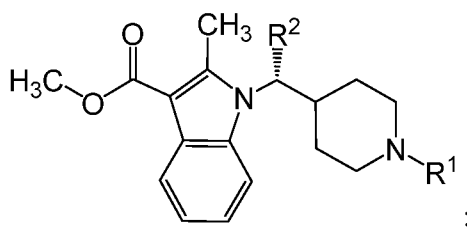


to form an optically active enamine compound of the formula:



or a salt thereof, wherein R^1 is defined above for Formula I. Appropriate solvents for this reaction would be apparent to one of skill in the art and include, in some aspects, those with boiling points above 65 °C, e.g., isopropyl acetate, acetonitrile, dimethylformamide, benzene, cyclohexane, 1,2-dichloroethane, glyme, ethyl acetate, hexamethylphosphorous triamide, hexamethylphosphoramide, dimethyl sulfoxide, and toluene. To facilitate formation of the enamine, the reaction may be performed at temperatures ranging from room temperature to 120 °C. In one aspect the reaction is performed in isopropyl acetate at reflux.

[0023] Cyclization to an optically active indole compound of the formula:



or a salt thereof, wherein R¹ and R² are as defined above for Formula I, occurs under palladium-mediated cyclization conditions. See e.g., *Org. Lett.*, 2014, 16 (16), pp 4114–4117. For example, cyclization can occur in the presence of palladium(II) catalysts (e.g., bis(acetonitrile)palladium(II) chloride, palladium(II) acetate, palladium(II) bromide, palladium(II) chloride, palladium(II) trifluoroacetate, tetrakis(acetonitrile)palladium(II) tetrafluoroborate, [1,2-bis(diphenylphosphino)ethane] dichloropalladium(II), bis(triethylphosphine)palladium(II) chloride, bis(triphenylphosphine) palladium(II) acetate, bis(triphenylphosphine)palladium(II) chloride, bis[tri(o-tolyl)phosphine]palladium(II) chloride, dichlorobis(tricyclohexylphosphine)palladium(II), trans-benzyl (chloro) bis(triphenylphosphine)palladium(II), and the like or commercially available palladium(0) catalysts (e.g., tris(dibenzylideneacetone)dipalladium(0), bis(tricyclohexylphosphine) palladium(0), bis(tri-t-butylphosphine)palladium(0), bis[1,2-bis(diphenylphosphino)ethane] palladium(0), tetrakis(triphenylphosphine)palladium(0), and the like. In one aspect, the palladium catalyst used in the cyclization is tris(dibenzylidene acetone) dipalladium(0).

[0024] Ligands for use in facilitating palladium-mediated cyclizations may also be used. See e.g., *Org. Lett.*, 2014, 16 (16), pp 4114–4117. Typically, ligands are used in catalytic amounts and may be selected from a monodentate or bidentate ligands. Examples of monodentate ligands include, but are not limited to, general ligands (e.g., triphenylphosphine, tri-(2-furyl)phosphine, tri-o-tolylphosphine, trimesitylphosphine, tricyclohexylphosphine, tri-tert-butylphosphine tetrafluoroborate, triisopropylphosphine, tri-n-butylphosphine, di-tert-butylmethylphosphine, and tri-tert-butylphosphine), Buchwald-type ligands (e.g., 2-(dicyclohexylphosphino)-2'-isopropylbiphenyl, 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl, 2-(di-tert-butylphosphino)biphenyl, 2-(dicyclohexylphosphino) biphenyl, 2-dicyclohexylphosphino-2'-(N,Ndimethylamino)biphenyl, 2-diphenylphosphino-2'-(N,Ndimethylamino)biphenyl, 2-(dicyclohexylphosphino)-2'-methylbiphenyl, 2-(di-tert-butylphosphino)-2'-methylbiphenyl, 2-di-tert-butylphosphino-2'-(N,Ndimethylamino) biphenyl, 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl, and 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl), and NHC ligands (e.g., 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, 1,3-bis(adamant-1-yl)imidazolium chloride, 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate, 1,3-bis(2,6-diisopropylphenyl) imidazolidinium tetrafluoroborate, 1,3-bis(2,4,6-trimethylphenyl) imidazolidinium chloride, and 1,3-bis(2,6-diisopropylphenyl) imidazolidinium chloride. Examples of bidentate ligands include, but are

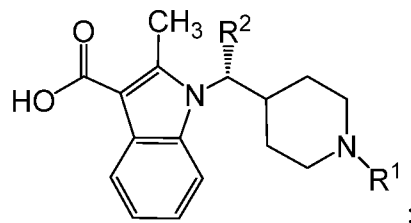
not limited to, general ligands (e.g., bis(diphenylphosphino)methane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(dicyclohexylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,3-bis(dicyclohexylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 1,5-bis(diphenylphosphino)pentane, bis(2-diphenylphosphinophenyl)ether, 1,1'-bis(diphenylphosphino)ferrocene, 1,1'-bis(diisopropylphosphino)ferrocene, 1,1'-bis(di-tert-butylphosphino)ferrocene, 1,2-bis(diphenylphosphino)benzene, and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene), BINAP ligands (e.g., (S)-(-)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl, (R)-(+)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl, (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, rac-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl, rac-2,2'-bis(di(3,5-dimethylphenyl)phosphino)-1,1'-binaphthyl, and (\pm)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), and Josiphos ligands (e.g., (R)-(-)-1-[(S)-2-di-t-butylphosphino ferrocenyl]ethyl-di-(4-trifluoromethylphenyl) phosphine, (R)-(-)-1-[(S)-2-diphenylphosphino ferrocenyl]ethyl-bis(3,5-dimethylphenyl)phosphine, (R)-(-)-1-[(S)-2-dicyclohexylphosphino ferrocenyl]ethyl-dicyclohexylphosphine, (R)-(-)-1-[(S)-2-diphenylphosphino ferrocenyl] ethyl-di-tert-butylphosphine, and (R)-(-)-1-[(S)-2-diphenylphosphino ferrocenyl]ethyl-dicyclohexylphosphine). In one aspect, the ligand tri-tert-butylphosphine tetrafluoroborate is used in the cyclization to form the enamine.

[0025] Suitable solvents that can be used for palladium-mediated cyclizations are known and include e.g., ethereal (diethyl ether, di-tert-butyl ether, diisopropyl ether, 1,4-dioxane, dimethoxy ethane, dimethoxy methane, diglyme, ethyl tert-butyl ether, methyl tert-butyl ether, tetrahydrofuran, tetrahydropyran, and the like), alcoholic (e.g., t-amyl alcohol, benzyl alcohol, butanol, t-butyl alcohol, ethanol, isobutanol, isopropyl alcohol, methanol, 1-propanol, and the like), cyclic ureas (e.g., 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone), and those with moderate to high boiling points (e.g., isopropyl acetate, acetonitrile, dimethylformamide, dimethyl sulfoxide, toluene, and the like). In one aspect, the solvent is 1,4-dioxane, t-butanol, acetonitrile, dimethoxyethane, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, or ethanol.

[0026] Suitable bases that can be used for palladium-mediated cyclizations are known and include e.g., carbonate bases (e.g., K_2CO_3 , $KHCO_3$, Na_2CO_3 , $NaHCO_3$, $Na_3H(CO_3)_2$, Li_2CO_3 , $LiHCO_3$, $MgCO_3$, $Mg(HCO_3)_2$, $CaCO_3$, $Ca(HCO_3)_2$, and the like) alkyl amine bases (such as trimethylamine, N,N-diisopropylethylamine, n-BUNMe₂, and the like), and

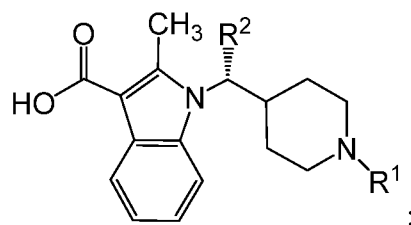
methoxide bases (such as NaOMe, NaOEt, and the like). In one aspect, the base is Cs₂CO₃, K₂CO₃, n-BUNMe₂, or NaOMe.

[0027] In a seventh step, the ester of the optically active indole compound is hydrolyzed to the free acid e.g., with hydroxide base to afford an active acid/indole compound of the formula:

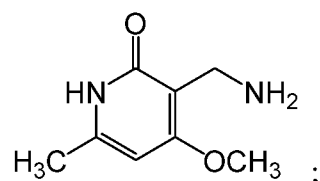


as described above in the first embodiment. The hydrolysis can be performed according to conditions known to one of skill in the art e.g., under aqueous basic conditions e.g., in the presence of hydroxide base (e.g., potassium hydroxide, lithium hydroxide, sodium hydroxide, magnesium hydroxide, calcium hydroxide, ammonium hydroxide, and the like) in water optionally with an alcoholic solvent (e.g., t-amyl alcohol, benzyl alcohol, butanol, t-butyl alcohol, ethanol, isobutanol, isopropyl alcohol, methanol, 1-propanol, and the like). In one aspect, the hydrolysis is performed using potassium hydroxide in water and ethanol.

[0028] In an eighth step, the optically active acid/indole compound of the formula:



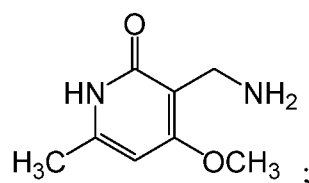
wherein R₁ and R₂ are as defined in the first step, is reacted with the free amine of a compound of the formula:



to generate the amide bond linkage in the optically active indole pyridine-one. The free amine compound can be prepared following the procedure set forth in WO 2013/120104 and as described. The reaction can be performed under standard amide bond formation conditions that include e.g., the use of one or more carboxylic acid couple reagents. Carboxylic acid coupling reagents are known in the art and include e.g., carbodiimides, phosphonium reagents, aminium/uranium-imonium reagents, N-ethoxycarbonyl-2-ethoxy-1,2-

dihydroquinoline, 2-propanephosphonic acid anhydride, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium salt, bis-trichloromethylcarbonate, or 1,1'-carbonyldiimidazole. In one aspect, the coupling reagent used in the preparation of the optically active indole pyridine-one is 1,1'-carbonyldiimidazole. Suitable solvents for this reaction would be apparent to one of skill in the art and include ethereal solvents such as diethyl ether, di-tert-butyl ether, diisopropyl ether, 1,4-dioxane, dimethoxy ethane, dimethoxy methane, diglyme, ethyl tert-butyl ether, methyl tert-butyl ether, tetrahydrofuran, tetrahydropyran, and the like. In one aspect, the solvent used is tetrahydrofuran.

[0029] The preparation of the free amine compound described in the first embodiment, and having the formula:



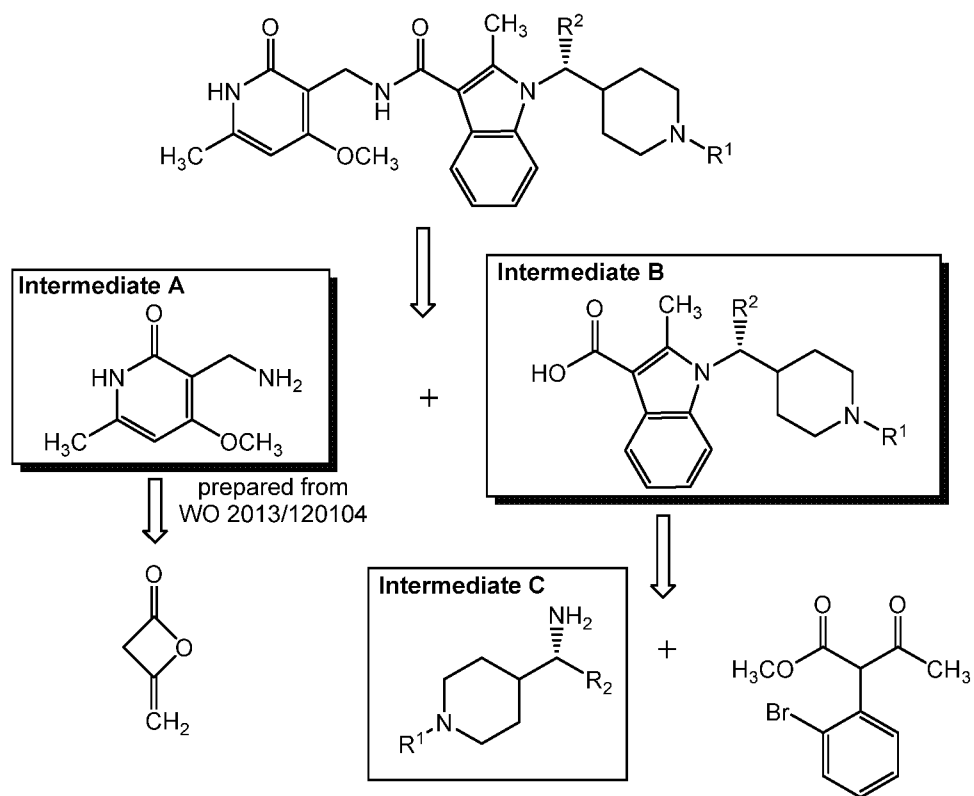
can be prepared following the procedure set forth in WO 2013/120104 and as described in the Exemplification section below.

[0030] Specific examples of synthetic methods described herein are provided in the Exemplification section below. Neutral forms as well as salts of the compounds described in the synthesis are included in the invention.

EXEMPLIFICATION

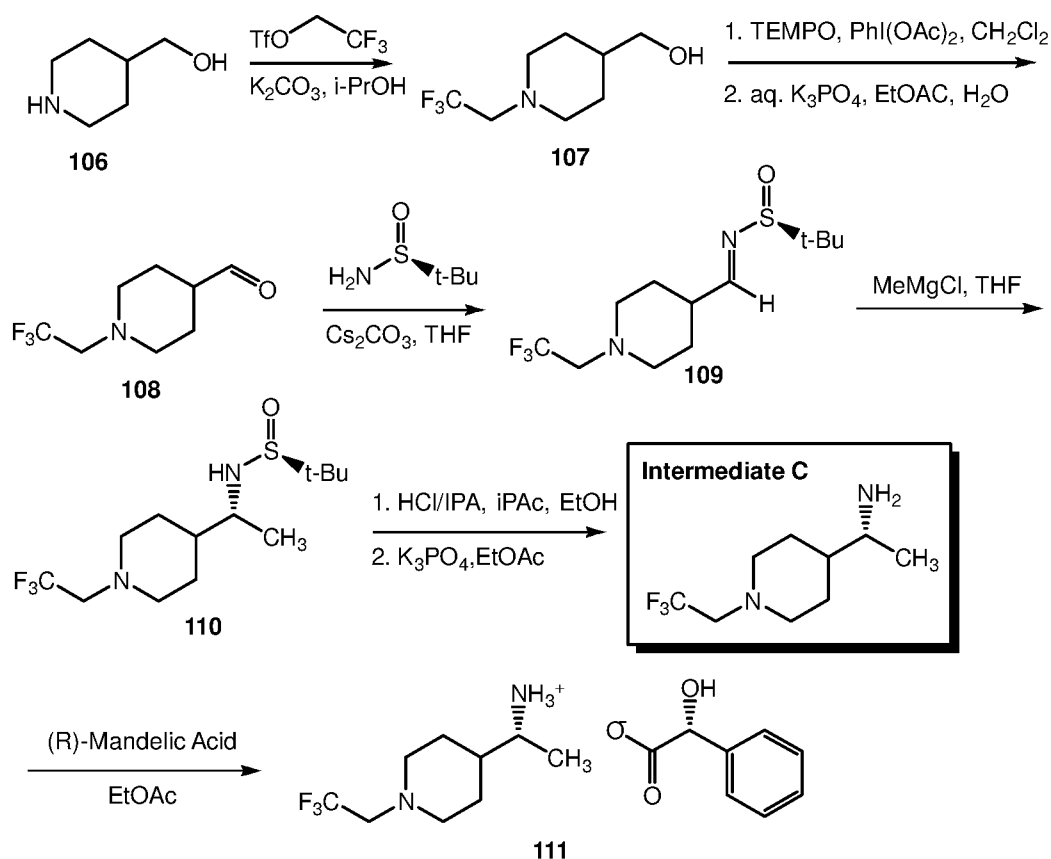
[0031] **Scheme 1** below is a retrosynthetic analysis for forming EZH2 inhibitors comprising a chiral methylene bridging a substituted piperidinyl and indolyl moiety.

Scheme 1



[0032] Scheme 2 illustrates an exemplary synthesis for **Intermediate C** as a mandelate salt, where R^1 is $-\text{CH}_2\text{CF}_3$, and R^2 is $-\text{CH}_3$.

Scheme 2



[0033] Preparation of (1-(2,2,2-trifluoroethyl)piperidin-4-yl)methanol 107:

[0034] A 1000 L reactor was charged piperidin-4-ylmethanol **106** (46.7 Kg, 405 mol) and THF (292.8 Kg). The reactor was charged with K_2CO_3 (72.8 Kg) before adding 2,2,2-trifluoroethyl trifluoromethanesulfonate (94.0 Kg, 405 mol in 41.8 kg of THF) dropwise maintaining the temperature below 55 °C. The mixture was warmed to 60-65°C and stirred for 4 hrs before being allowed to cool down to ambient temperature. Methyl *tert*-butyl ether (MTBE) (104.3kg) was then added and the mixture was stirred for 20 mins. The resulting solid was collected by filtration, rinsed by MTBE (104.3 kg). The filtrate was concentrated under vacuum, and then the cake was mixed with MTBE (104.3kg), celite (23.5 kg) and PE (97.3 kg) and was stirred for 30 mins. Filtered and the cake was rinsed by MTBE/PE (1:1, 103.8 kg). The combined filtrate was concentrated to afford compound **107** as an oil (75.3 kg, 93.5 yield, 99.3% HPLC purity).

[0035] Preparation of 1-(2,2,2-trifluoroethyl)piperidine-4-carbaldehyde 108:

[0036] A 500 L reactor was charged with (1-(2,2,2-trifluoroethyl)piperidin-4-yl)methanol **107** (75.3Kg, 381 mol), DCM (299 kg) and TEMPO (11.9 Kg, 76 mol). Iodo-benzene-bis-acetate (147.6Kg, 458 mol) was added portionwise, maintaining the temperature at 25-30°C.

The reaction was stirred at ambient temperature for 2 hrs then cooled to 5-10°C. MTBE (666 kg) was added and 10 wt % aqueous Na₂S₂O₃ (300 kg) was slowly added, maintaining the temperature between 10 and 15°C. The mixture was stirred for 20 mins, treated with 40% aqueous NaOH aqueous (90.0kg) at such a rate to maintain the temperature at 10-15°C, and pH was adjusted to 13~14. The layers were separated and the organic layer was washed with 2N HCl (300 kg) at 10-15°C and then with brine (375 kg), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude aldehyde **108** as an oil (68.5 kg, 92% yield, 64.6 % GC purity).

[0037] Preparation of (S,E)-2-methyl-N-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methylene)propane-2-sulfinamide 109:

[0038] A 1000L reactor was charged with 1-(2,2,2-trifluoroethyl)piperidine-4-carbaldehyde **108** (68.5kg, 351mol) and DCM (546.6 kg). (S)-2-methylpropane-2-sulfinamide (42.5 kg, 351 mol) was charged in portions follow by cesium carbonate (80 kg, 246 mol). The reaction was stirred at ambient temperature for 4 hrs. The slurry was filtered and the with DCM (273.3kg). Concentration in vacuo afforded compound **109** as an oil (108 kg, 100% yield, 91.2% HPLC purity).

[0039] Preparation of (S)-2-methyl-N-((R)-1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)propane-2-sulfinamide 110:

[0040] A 2000L reactor was charged THF (672.8 kg) under N₂ and with methylmagnesium chloride in THF (360 kg, 1038mol). The mixture was cooled to -5°C before adding (S,E)-2-methyl-N- ((1- (2,2,2- trifluoroethyl)piperidin-4-yl)methylene)propane-2- sulfinamide **109** (108.0 kg, 362 mol) as a solution in THF (91.6kg) and at such a rate as to maintain the temperature between -5 and 0°C. The mixture was stirred for 6 hrs and quenched with 20% NH₄Cl/deionized H₂O (1080 kg) before allowing the mixture to warm to ambient temperature. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to provide compound **110** as an oil (100.0 kg, 89.0% yield, 83.7 % HPLC purity).

[0041] Preparation of (R)-1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethan-1-amine (Intermediate C):

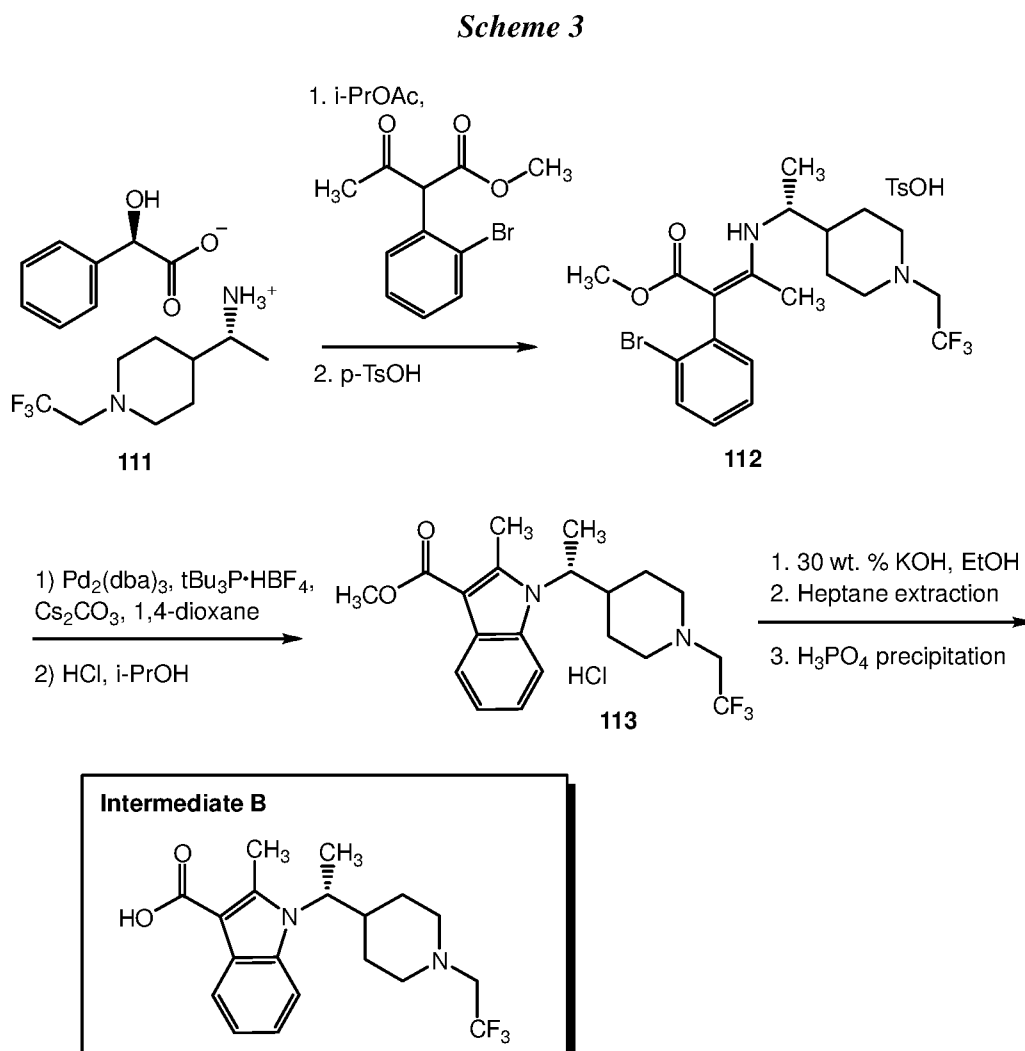
[0042] A 1000L reactor was charged 11% hydrochloric acid in EtOH (115.4 kg). A solution of (S)-2-methyl- N-((R)- 1-(1- (2,2,2- trifluoroethyl)piperidin-4-yl)ethyl)propane-2-sulfinamide **110** (42.7 Kg, 135.9 mol) in isopropylacetate (335.0 Kg) was then added over 3 hrs, maintaining the temperature between 20 and 25°C. After 1hr, the resulting solid was

collected by filtration and washed with isopropylacetate. The solids were transferred to a clean 1000 L reactor, and then K_3PO_4 (37% w/w, 271.0kg) and EtOAc (135.0 Kg) were added. The mixture was thoroughly stirred and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 135.0 Kg) and the combined organic phases were washed with brine (600kg) and concentrated *in vacuo* to provide **Intermediate C** as an oil (19.0 kg).

[0043] Preparation of (R)-1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethan-1-aminium (R)-2-hydroxy-2-phenylacetate 111:

[0044] The resulting oil from above (19.0 kg) was charged to a 1000 L reactor and diluted with ethyl acetate (171.0 kg). To the solution was added (R)-(-)-mandelic (16.5 kg), and the mixture was heated to 50-55 °C for 1 h. The slurry was cooled to ambient temperature and stirred for an additional 2 h. The slurry was filtered and washed with MTBE (33.0 kg), dried under vacuum at 45 °C to give the desired product (24.5 kg, ee 99.3%).

[0045] **Scheme 3** illustrates an exemplary synthesis for **Intermediate B**, where R^1 is $-CH_2CF_3$, and R^2 is $-CH_3$.



[0046] Preparation of Methyl (*R,Z*)-2-(2-bromophenyl)-3-((1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)amino)but-2-enoate 4-methylbenzenesulfonate 112:

[0047] A dry 100 L Büchi jacketed reactor was charged with (*R*)-1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethan-1-aminium (*R*)-2-hydroxy-2-phenylacetate **111** (6.0 kg, 16.56 mol), Methyl 2-(2-bromophenyl)-3-oxobutanoate (5.39 kg, 19.87 mol) and *i*PrOAc (42 L, 36.6 kg). To enable more efficient removal of water, MTBE (8 L, 5.9 kg) was charged to the reactor. The batch was agitated and heated to 85 °C. Atmospheric distillation was utilized to collect approximately 20 L of solvent, and the reaction was sampled for progress. Completion of the enamine formation was confirmed by HPLC analysis. The batch was cooled to <40 °C and treated with a saturated solution of sodium bicarbonate (30 L). The batch was agitated for 5 min, and the phases were allowed to separate for 5 min before removing the bottom aqueous layer.

[0048] To the reactor was added saturated brine solution (NaCl in H₂O, 30 L) to wash the organics. The batch was agitated for 5 min, and the phases were allowed to separate for 5 min before removing the bottom aqueous layer. MTBE (4 L, 3.0 kg) was added to the reactor, and the batch was concentrated to an oil. *i*PrOAc (30 L, 26.6 kg) was charged and the reaction was polish filtered (20 µm inline cartridge) directly into a 150 L cylindrical reactor. Additional *i*PrOAc (50 L, 26.1 kg) was charged followed by TsOH·H₂O (3.15 kg) to promote salt formation. The batch was agitated overnight at ambient temperature. The resulting slurry was filtered and washed with *i*PrOAc (30 L, 26.6 kg). The product was transferred to Teflon-lined trays and dried in a vacuum oven (270 mBar w/nitrogen bleed) at 45 °C until constant mass was achieved. Desired product **112** was obtained as a chalky, off-white solid (8.42 kg, 80% yield, 95.0 wt% purity).

[0049] Preparation of Methyl (*R*)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1*H*-indole-3-carboxylate hydrochloride 113:

[0050] A dry 100 L Büchi jacketed reactor inerted with Argon was charged with Cs₂CO₃ (6.66 kg, 20.46 mol), Methyl (*R,Z*)-2-(2-bromophenyl)-3-((1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)amino)but-2-enoate 4-methylbenzenesulfonate **112** (5.20 kg, 8.18 mol), Pd₂(dba)₃ catalyst (225 g, 0.245 mol), and Tri-*tert*-butylphosphonium tetrafluoroborate ligand (142 g, 0.491 mol). To the reactants was added 1,4-dioxane (41.6 L, 42.8 kg), which had been sparged with argon for 30 min prior to the addition. The reaction was heated >95 °C and agitated for >6 h to completion (100% conversion by HPLC analysis). The batch was cooled to 60 °C and Silicycle metal scavenger (1029 g, 30 wt%) was charged

to the reactor to remove excess Pd metal catalyst. The slurry was agitated for 12-18 h and cooled to 20-25 °C. The slurry was filtered over Celite and washed with 50:50 IPA/Heptane (4.66 kg/5.35 kg). The filtrate was then passed through a fritted glass funnel (6 L) packed with Celite underneath a layer of Silicycle metal scavenger. The resulting filtrate was charged into the clean 100 L Büchi reactor, and the solvent was removed under reduced pressure. After ~25 L of solvent was distilled, IPA (4 L, 3.1 kg) and Heptane (4 L, 2.7 kg) were charged to the reactor, and the distillation continued until ~27 L of solvent was removed. The batch was cooled to 20-25 °C, IPA was charged (6.9 L, 5.39 kg), and the reaction was transferred through a cartridge filter (20 µm inline cartridge) into a 100 L RB flask equipped with temperature probe and batch concentrator. An addition funnel was used to charge 5 M HCl in IPA (1.8 L, 1.62 kg) dropwise.

[0051] Heptane (6.8 L, 4.66 kg) was added slowly to the reaction resulting in the precipitation of minor amounts of product. The reaction was seeded with target **113** crystals to promote seed bed formation. Additional heptane (6.8 L, 4.66 kg) was charged dropwise, and the reaction was agitated overnight. Heptane (13.6 L, 9.33 kg) was charged, and the reaction was concentrated under reduced pressure to remove 6 L of solvent. To the reaction was charged heptane (6 L, 4.1 kg) was charged dropwise, and the reaction was concentrated under reduced pressure to remove 14 L of solvent. Heptane (14 L, 9.6 kg) was charged dropwise. The slurry was sampled for loss to filtrate via HPLC analysis (result = 2.9 mg/mL) and was further concentrated to remove an additional 6 L of solvent. Heptane (6 L, 4.1 kg) was charged to the reactor, and the slurry was agitated overnight. The slurry was again sampled for loss to filtrate (result = 1.2 mg/mL), filtered, and washed with heptane (2 x 5.83 kg). The product was transferred to Teflon-lined trays and dried in a vacuum oven (270 mBar w/nitrogen bleed) at 50 °C until constant mass was achieved. Desired product **113** was obtained as an off-white solid (2.93 kg, 85% yield, 100 wt% purity).

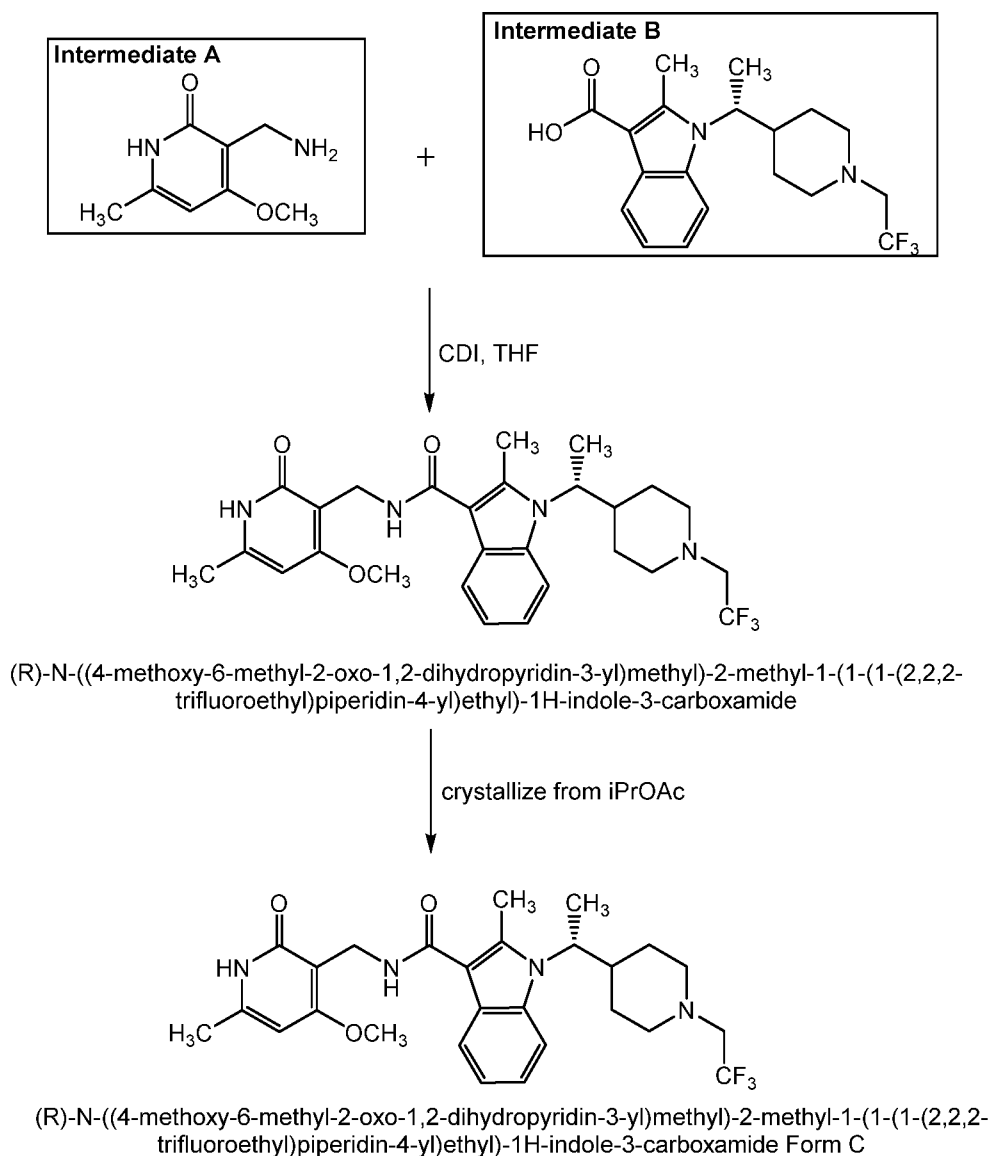
[0052] Preparation of (R)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxylic acid (Intermediate B):

[0053] A dry 100 L Büchi jacketed reactor was charged with Methyl (R)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxylate hydrochloride **113** (3.50 kg, 8.36 mol) followed by KOH (7.00 kg, 30 wt%) and EtOH (17.5 kg, 190 proof). The reaction was heated to 75 °C and agitated for approximately 18 h to completion (100% conversion by HPLC). The batch was cooled to <25 °C and diluted with HPP water (9 vol., 31.5 kg). To the reactor was added heptane (17.5 L, 12 kg). The batch was agitated for 5 min

and allowed to phase split for 5 min. The bottom aqueous layer was then transferred to a 100 L RB flask. Charcoal was charged to the reactor (350 g, 10 wt%). The slurry was heated to 50-60 °C and agitated for 2 h. The reaction was cooled to <25 °C and the slurry was pre-filtered over a tabletop funnel to remove a majority of the charcoal. The collected filtrate was then passed through a fritted glass funnel (6 L) packed with Celite (2-3" depth). The resulting filtrate was transferred into the clean 100 L Büchi reactor. To the reaction mixture was charged 2 M H₃PO₄ (approximately 18 L) with pH monitoring to achieve pH ~4.8 (calibrated pH probe). The slurry was then filtered and washed with HPP Water (2 x 17.5 kg). The product was transferred to Teflon-lined trays and dried in a vacuum oven (270 mBar w/nitrogen bleed) at 55 °C until constant mass was achieved. **Intermediate B** was obtained as an off-white solid (2.60 kg, 85% yield, 100 wt% purity).

[0054] **Scheme 4** illustrates an exemplary synthesis of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide (see e.g., U.S. Patent No. 9,085,583) using **Intermediate A** and **Intermediate B**, where R¹ is -CH₂CF₃, and R² is -CH₃, as well as a subsequent crystallization or trituration step to form a solid form of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide (see e.g., PCT/US2016/048616).

Scheme 4



[0055] (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide

(Coupling of Intermediate A with Intermediate B):

[0056] A dry 100 L Büchi jacketed reactor was charged with CDI (1.21 kg, 7.46 mol, 1.10 equiv.) followed by THF (12.5 L, 11.11 kg). The reaction was heated to 60 ± 5 °C with agitation. A solution of (R)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxylic acid (Intermediate B, 2.50 kg, 6.79 mol) in THF (10 L, 8.89 kg) was added slowly (~1.5 h) to the reactor via an addition funnel maintaining the temperature at 60 ± 5 °C. The reaction was agitated at 60 ± 5 °C for ~3 h, after which a sample of the reaction was analyzed by HPLC (99% conversion to the acyl imidazole intermediate). To the reactor was added 3-(aminomethyl)-4-methoxy-6-methylpyridin-2(1H)-one (Intermediate A, 1.58 kg,

9.36 mol, 1.38 equiv), where THF (1.2 L, 1.11 kg) was used to aid in transfer. The reaction was agitated at $60 \pm 5^\circ\text{C}$ for 20 h to completion (>96% conversion by HPLC). The batch was then cooled to $<30^\circ\text{C}$ and filtered. The reactor and funnel were rinsed with THF (2.5 L, 2.22 kg). The THF filtrate was transferred to a 100 L separatory funnel. To the separatory funnel was charged HPP water (12.5 kg, 5 vol.), and the reaction was diluted with *i*PrOAc (62.6 L, 54.5 kg).

[0057] The contents were agitated for 5 min, and the aqueous layer was removed. The organic layer was washed three additional times with water (3×12.5 kg, 5 vol.). After the four water washes, the organic layer was polish filtered through a cartridge filter (1 μm inline cartridge) and transferred back into the cleaned 100 L Büchi reactor. The organic layer was concentrated until approximately 18 L remained, and then *i*PrOAc (6.3 L, 5.45 kg) was charged to the reactor. The reaction was again concentrated until approximately 18 L remained, and *i*PrOAc (25 L, 21.8 kg) was charged to the reactor. The contents were heated overnight (~17 h) at $65 \pm 5^\circ\text{C}$, after which the reaction was cooled to $25 \pm 5^\circ\text{C}$. The product was collected by filtration (table top filter, polypropylene cloth), and the product cake was washed with *i*PrOAc (2×4.36 kg). The product was transferred to Teflon-lined trays and dried in a vacuum oven (270 mBar w/nitrogen bleed) at 55°C until constant mass was achieved. Desired (*R*)-*N*-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1*H*-indole-3-carboxamide was obtained as an off-white solid (2.05 kg, 58% yield, 99 wt% purity).

[0058] Formation of (*R*)-*N*-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1*H*-indole-3-carboxamide, Form C (Trituration with *i*PrOAc):

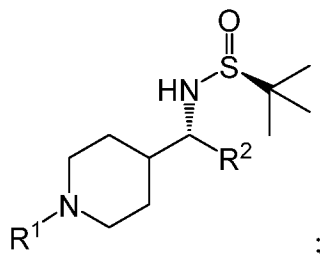
[0059] A dry 100 L RB flask was charged with (*R*)-*N*-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1*H*-indole-3-carboxamide (4.70 kg, 9.06 mol) followed by *i*PrOAc (47 L, 40.9 kg) that was charged through a cartridge filter (1.0 μm inline cartridge). The slurry was agitated at $65 \pm 5^\circ\text{C}$ for approximately 18 hours, after which the slurry was cooled to $25 \pm 5^\circ\text{C}$. The product was collected by filtration (tabletop funnel lined with Whatman filter paper underneath polypropylene filter cloth), and the product cake was washed with *i*PrOAc (2×8.2 kg). The product was transferred to Teflon-lined trays and dried in a vacuum oven (270 mBar w/nitrogen bleed) at 55°C until constant mass was achieved. (*R*)-*N*-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-

yl)ethyl)-1H-indole-3-carboxamide, Form C was obtained as a white solid (4.52 kg, 95% yield). See PCT/US2016/048616 for additional disclosure and characterization of Form C.

[0060] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Listing of Claims:

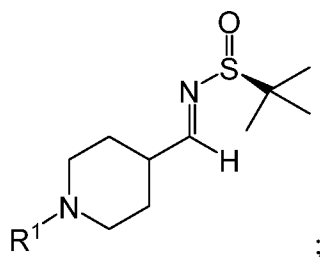
1. A method for preparing a diastereomerically enriched sulfinamide compound having the formula:



wherein R¹ is halo(C₁-C₆)alkyl and R² is (C₁-C₆)alkyl,

the method comprising

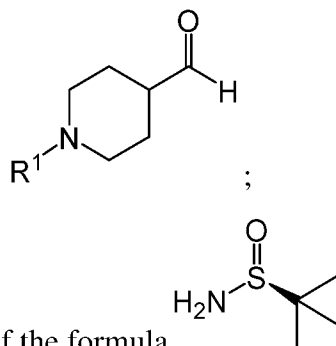
reacting an optically active sulfinylimine compound of the formula



with a nucleophile of the formula R²MgX, wherein X is bromide, iodide, or chloride to form the diastereomerically enriched sulfinamide compound.

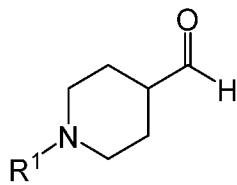
2. The method of Claim 1, wherein the sulfinamide compound is prepared by reacting the optically active sulfinylimine compound with R²MgBr to form the diastereomerically enriched sulfinamide compound.

3. The method of Claim 1 or 2, wherein the sulfinylimine compound is prepared by reacting an aldehyde compound of the formula:

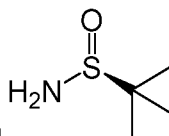


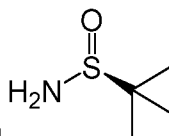
with an optically active compound of the formula to form the optically active sulfinylimine compound.

4. The method of any one of Claims 1 to 3, wherein the sufnylimine compound is prepared by reacting an aldehyde compound of the formula:

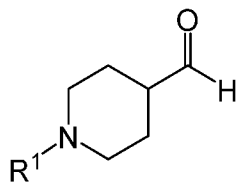


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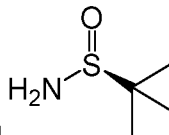


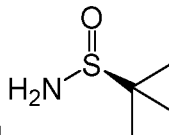
with an optically active compound of the formula  in the presence of an inorganic base to form the optically active sufnylimine compound.

5. The method of any one of Claims 1 to 4, wherein the optically active sufnylimine compound is prepared by reacting an aldehyde compound of the formula:

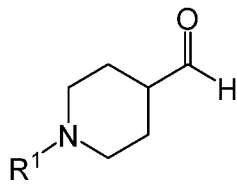


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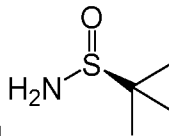


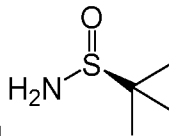
with an optically active compound of the formula  in the presence of water-soluble carbonate to form the optically active sufnylimine compound.

6. The method of any one of Claims 1 to 5, wherein the optically active sufnylimine compound is prepared by reacting an aldehyde compound of the formula:

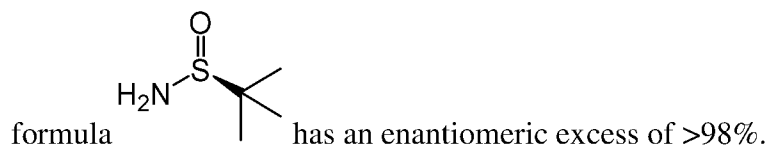


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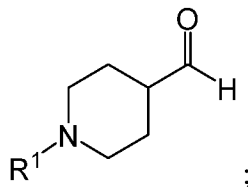


with an optically active compound of the formula  in the presence of Cs_2CO_3 to form the optically active sufnylimine compound.

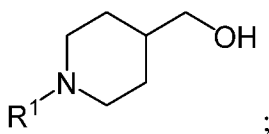
7. The method of any one of Claims 3 to 6, wherein the optically active compound of the



8. The method of any one of Claims 3 to 6, wherein the aldehyde compound of the formula:

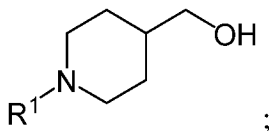


is prepared by reacting an alcohol of the formula:

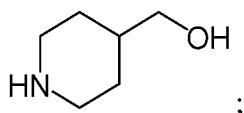


with an oxidizing agent to form the aldehyde compound.

9. The method of Claim 8, wherein the alcohol compound of the formula:



is prepared by reacting a secondary amine compound of the formula:

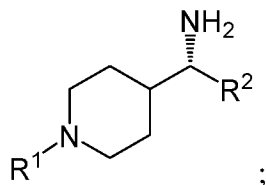


with R^1-L , where L is a leaving group to form the alcohol compound.

10. The method of Claim 8 or 9, wherein the alcohol compound is prepared by reacting the secondary amine compound with R^1-L , where L is a halogen, mesylate, tosylate, or trifluoroalkylsulfonate to form the alcohol compound.

11. The method of any one of Claims 8 to 10, wherein the alcohol compound is prepared by reacting the secondary amine compound with $R^1-O(SO_2)CF_3$ to form the alcohol compound.

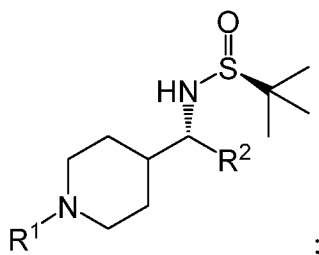
12. A method for preparing an optically active amine compound having the following formula:



or a salt thereof, wherein R¹ is halo(C₁-C₆)alkyl and R² is (C₁-C₆)alkyl,

the method comprising

hydrolyzing the sulfinyl group in a diastereomerically enriched sulfinamide compound having the formula:



with acid to form the optically active amine compound or the salt thereof.

13. The method of Claim 12, wherein the acid is an inorganic acid.

14. The method of Claim 12 or 13, wherein the acid is hydrochloric acid.

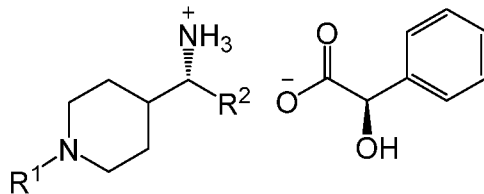
15. A method of any one of Claims 12 to 14, further comprising

a) reacting the optically active amine compound with an optically active organic acid to prepare a diastereomeric salt of the optically active amine compound and the optically active organic acid; and

b) separating the diastereomeric salt of the optically active amine compound and the optically active organic acid from the diastereomeric salt, if present, of the enantiomer of the optically active amine compound and the optically active organic acid.

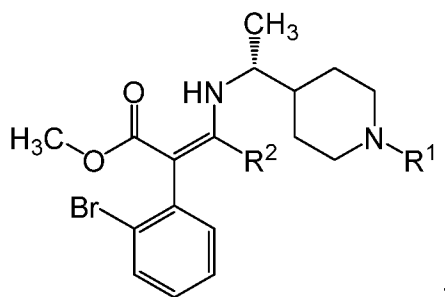
16. The method of Claim 15, wherein the optically active organic acid is selected from aspartic acid, mandelic acid, camphanic acid, camphoric acid, camphorsulfonic acid, tartaric acid, glutamic acid, maleic acid, menthylxyacetic acid, and methoxyphenylacetic acid.

17. The method of Claim 15 or 16, wherein diastereomeric salt of the optically active amine compound and the optically active organic acid has the following formula:



18. The method of any one of Claims 15 to 17, wherein the enantiomeric excess of the optically active organic acid is greater than 97%.

19. A method for preparing an optically active enamine compound of the formula:

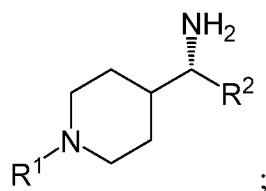


or a salt thereof, wherein R¹ is halo(C₁-C₆)alkyl and R² is (C₁-C₆)alkyl,

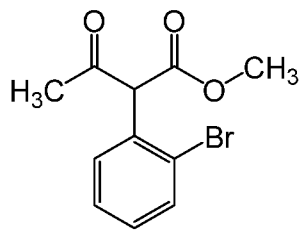
the method comprising

reacting an optically active amine compound or a salt thereof having the

formula:

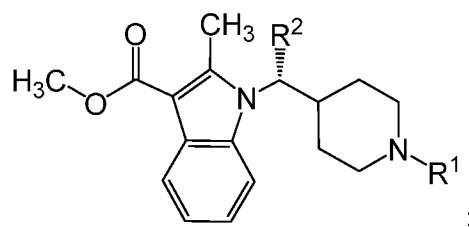


with a di-keto ester compound having the formula:



to form the optically active enamine compound or a salt thereof.

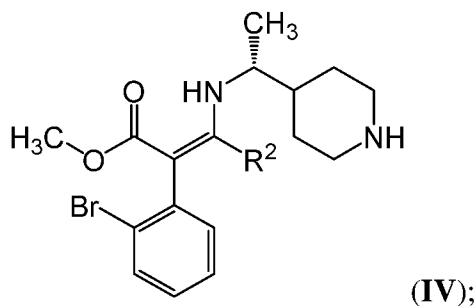
20. A method for preparing an optically active indole compound of the formula:



wherein R¹ is halo(C₁-C₆)alkyl and R² is (C₁-C₆)alkyl,

the method comprising

reacting an optically active enamine salt compound of the formula:



or a salt thereof with base and palladium catalyst to form the optically active indole compound.

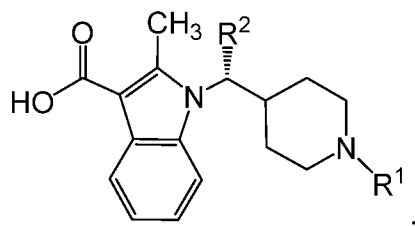
21. The method of Claim 20, wherein the palladium catalyst is selected from e.g., bis(acetonitrile)palladium(II) chloride, palladium(II) acetate, palladium(II) bromide, palladium(II) chloride, palladium(II) trifluoroacetate, tetrakis(acetonitrile)palladium(II) tetrafluoroborate, [1,2-bis(diphenylphosphino)ethane]dichloropalladium(II), bis(triethylphosphine)palladium(II) chloride, bis(triphenylphosphine)palladium(II) acetate, bis(triphenylphosphine)palladium(II) chloride, bis[tri(o-tolyl)phosphine]palladium(II) chloride, dichlorobis(tricyclohexylphosphine)palladium(II), trans-benzyl (chloro) bis(triphenylphosphine)palladium(II), tris(dibenzylideneacetone)dipalladium(0), bis(tricyclohexylphosphine)palladium(0), bis(tri-t-butylphosphine)palladium(0), bis[1,2-bis(diphenylphosphino)ethane]palladium(0), and tetrakis(triphenylphosphine)palladium(0).

22. The method of Claim 20 or 21, wherein the catalyst is tris(dibenzylideneacetone)dipalladium(0).

23. The method of any one of Claims 20 to 22 further comprising adding a ligand selected from triphenylphosphine, tri-(2-furyl)phosphine, tri-o-tolylphosphine, trimesitylphosphine,

tricyclohexylphosphine, tri-tert-butylphosphine tetrafluoroborate, triisopropylphosphine, tri-n-butylphosphine, di-tert-butylmethylphosphine, and tri-tert-butylphosphine.

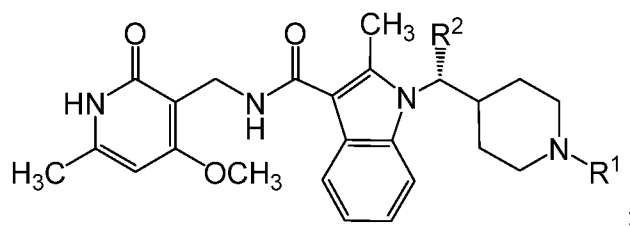
24. The method of any one of Claims 20 to 23, further comprising the step of hydrolyzing the optically active indole compound to form an optically active acid/indole compound having the formula:



or a salt thereof.

25. The method of Claim 24, wherein the optically active indole compound is hydrolyzed with a hydroxide base.

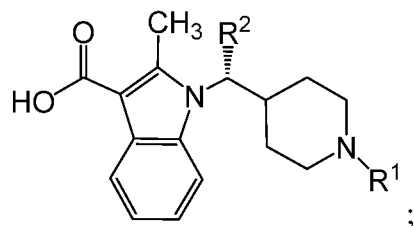
26. A method for preparing an optically active indole pyridine-one having the formula:



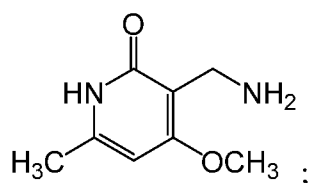
wherein R¹ is halo(C₁-C₆)alkyl and R² is (C₁-C₆)alkyl,

the method comprising

reacting an optically active acid/indole compound of the formula:



with a free amine compound of the formula:



and a carboxylic acid coupling reagent selected from a carbodiimide, a phosphonium reagent, an aminium/uranium-imonium reagent, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, 2-propanephosphonic acid anhydride, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium salt, bis-trichloromethylcarbonate, or 1,1'-carbonyldiimidazole to form the indole pyridine-one.

27. The method of Claim 26, wherein the coupling reagent is 1,1'-carbonyldiimidazole.
28. The method of any one of Claims 1 to 27, wherein R^2 is $-\text{CH}_3$.
29. The method of any one of Claims 1 to 28, wherein R^1 is $-\text{CH}_2\text{CF}_3$.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/057114

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D401/14 C07D211/26 C07D211/28
 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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/124418 A1 (CONSTELLATION PHARMACEUTICALS INC [US]) 14 August 2014 (2014-08-14) cited in the application page 17; examples 1,3; compounds 356,362,365,378	1-29
A	WO 2013/120104 A2 (CONSTELLATION PHARMACEUTICALS [US]) 15 August 2013 (2013-08-15) cited in the application Scheme of page 90, step 10; example 28	1-29

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search
 4 January 2018

Date of mailing of the international search report
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Authorized officer
 Rufet, Jacques

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2017/057114

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