

METHODS OF PREPARING MELANOCORTIN 4 RECEPTOR AGONISTS

CLAIM OF PRIORITY

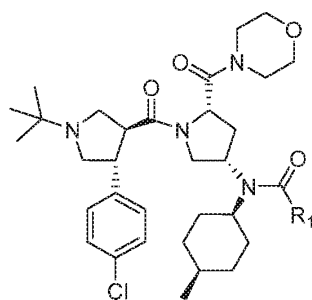
The present application claims priority to KR Application No. 10-2024-0008342, filed on 18-Jan-2024; KR Application No. 10-2024-0010985, filed on 24-Jan-2024; KR Application No. 10-2024-0009488, filed on 22-Jan-2024; KR Application No. 10-2024-0008338, filed on 18-Jan-2024; and KR Application No. 10-2024-0004302, filed on 10-Jan-2024. The entire contents of each of the foregoing applications are incorporated by reference in their entirety.

BACKGROUND

Melanocortin receptor (MCR) is a type of G-protein coupled receptor (GPCR). The primary role of G-proteins is to regulate cellular responses to many physiological stimuli through signal transduction by activating secondary messengers. There are five types of melanocortin receptors that have been discovered so far. It has been shown that among these melanocortin receptors, MC4R is deeply involved in pathways that regulate body weight and metabolism. For example, knockout studies in mice lacking the MC4R develop obesity due to overeating. In recent years, small molecule modulators of the MC4R have been developed; however, there is a need for improved methods of preparing these small molecules.

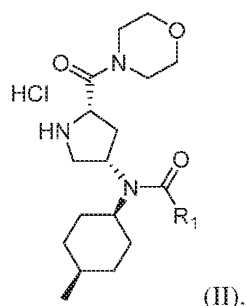
SUMMARY

The present disclosure features a method for preparing an MC4R agonist and related compositions thereof. In one aspect, provided herein is a compound of the following Formula (I):

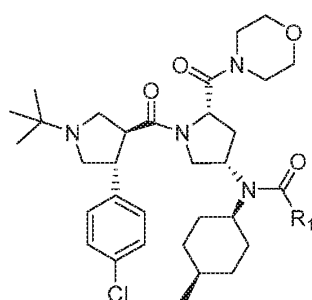


, wherein R₁ is C₂-C₅ alkyl. In particular, the present disclosure

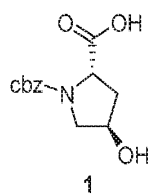
features methods for improving the method of synthesis, wherein a compound of Formula (I) using a compound of Formula (II) having a morpholine structure as an intermediate:



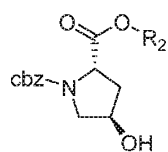
In some embodiments, the present disclosure features a method of preparing a compound of Formula (XI):



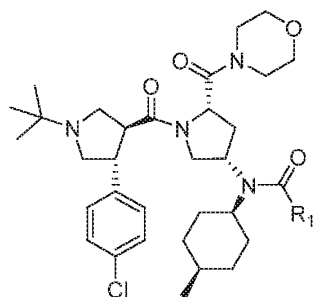
wherein R_1 is C_2 - C_5 alkyl, comprising Step A of reacting Compound **1**



with an alcohol having 1 to 6 carbon atoms and an acid catalyst to form a compound of Formula (IV):

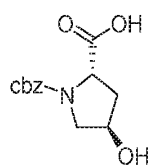


In a second aspect, the present disclosure features a method of preparing a compound of Formula (XI):



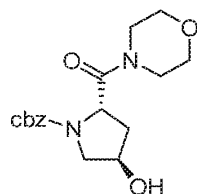
(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein R₁ is C₂-C₅ alkyl, comprising Step H of reacting Compound 1



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with morpholine to form Compound 9:

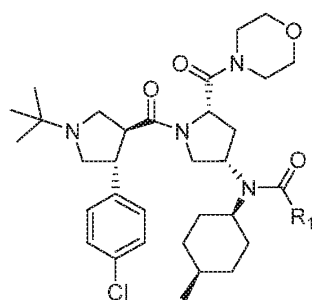


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9. In some embodiments, Step H is facilitated by a coupling agent. Exemplary coupling agents include ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC); N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim), 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminoxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU). In some embodiments, Step H with a coupling agent is further facilitated by a reaction accelerating additive.

Exemplary reaction accelerating additives include 1-hydroxybenzotriazole (HOBt) and its derivatives such as hydroxy-3,4-dihydro-4-oxo-1,2,3-benzo-triazine (HOObt), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), resin-supported derivatives thereof, and hydrates thereof; N-hydroxysuccinimide (NHS); and 4-dimethylpyridine (DMAP).

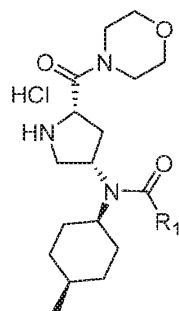
In a third aspect, the present disclosure features a method for preparing a compound of Formula (XI):



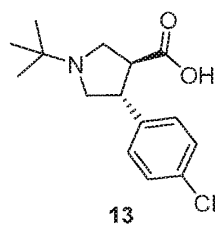
(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

comprising a step M of reacting a compound of Formula (II):

Formula (II):



(II), or a conjugate base, or a solvate thereof, with Compound **13**:



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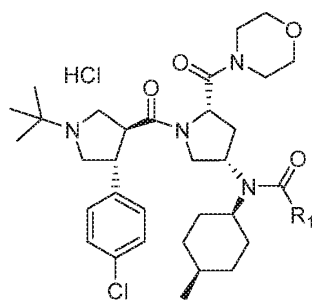
, or a salt, or a solvate thereof, wherein R₁ is C₂-C₅ alkyl. In some embodiments,

Step M further comprises crystallization of the synthesized compound of Formula (XI). In some embodiments, Step M is facilitated by a coupling agent. Exemplary coupling agents include ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC); N,N'-carbonyldiimidazole

(CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim), 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylammonium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylammonium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminooxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU). In some embodiments, Step M with a coupling agent is further facilitated by a reaction accelerating additive. Exemplary reaction accelerating additives include 1-hydroxybenzotriazole (HOBt) and its derivatives such as hydroxy-3,4-dihydro-4-oxo-1,2,3-benzo-triazine (HOObt), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), resin-supported derivatives thereof, and hydrates thereof; N-hydroxysuccinimide (NHS); and 4-dimethylpyridine (DMAP).

In some embodiments, the method including Step M further comprises a Step N of purifying the compound of Formula (XI), pharmaceutically acceptable salt thereof, or solvate thereof. In certain embodiments, Step N comprises dissolving the compound of Formula (XI) in an organic solvent or solvent mixture, stirring, cooling, and stirring again to obtain a purified precipitate.

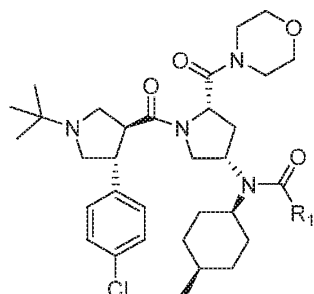
In other embodiments, the method including Step M further comprises a Step O of reacting the compound of Formula (XI) generated from Step M with HCl without an additional purification process to prepare a compound of Formula (XII):



(XII), pharmaceutically acceptable salt thereof, or solvate thereof,

wherein R₁ is a C₂-C₅ alkyl group. In some embodiments, Step O is performed in an organic solvent.

In a fourth aspect, the present disclosure features a method for preparing a compound of Formula (XI):



(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein R_1 is C_2 - C_5 alkyl, comprising Step P of preparing crystalline Form III particles of a compound of Formula (XI) and wherein

the crystalline Form III has the following diffraction angles (2θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among $6.62\pm0.2^\circ$, $7.44\pm0.2^\circ$, $9.18\pm0.2^\circ$, $9.89\pm0.2^\circ$, $10.83\pm0.2^\circ$, $11.42\pm0.2^\circ$, $12.92\pm0.2^\circ$, $14.61\pm0.2^\circ$, $15.36\pm0.2^\circ$, $15.79\pm0.2^\circ$, $15.95\pm0.2^\circ$, $17.37\pm0.2^\circ$, $18.20\pm0.2^\circ$, $18.99\pm0.2^\circ$, $19.34\pm0.2^\circ$, $19.69\pm0.2^\circ$, $20.40\pm0.2^\circ$, $21.66\pm0.2^\circ$, $21.98\pm0.2^\circ$, $22.45\pm0.2^\circ$, $22.85\pm0.2^\circ$, $24.66\pm0.2^\circ$, $25.52\pm0.2^\circ$, $26.55\pm0.2^\circ$, $28.08\pm0.2^\circ$, $29.31\pm0.2^\circ$ and $29.54\pm0.2^\circ$. In some embodiments, Step P is comprised of:

- (a) preparing a mixed solution by dissolving the compound of Formula (XI) in a crystallization solvent comprising water or a mixture of water and an organic solvent;
- (b) crystallizing by adding HCl dropwise to the solution; and
- (c) maturing the solution.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a drawing comparing the stereoselectivity effect of performing reductive amination of Compound **3** to Compound **4** according to Example 1 and performing reductive amination of Compound **10** to Compound **11** according to Example 2.

FIG. 2 is a graph of the XRD result of Example 5-1.

FIG. 3 is a graph of the DSC result of Example 5-1.

FIG. 4 is a graph of the TGA result of Example 5-1.

FIGS. 5A-5D show SEM images of crystalline Form III particles prepared in Examples 5-2 to 5-4 and Comparative Examples 2-1 and 2-2.

FIG. 6 is a unified scheme illustrating the steps of Scheme 1 and Scheme 2.

DETAILED DESCRIPTION

Provided herein are methods for making an MC4R agonist, for example, a compound of Formula (I). This method entails steps involving deprotection, oxidation, amide coupling, deprotection, and purification, for example, as show in FIG. 6. In some embodiments, the methods comprise making a compound of Formula (I) at a large scale, for example, greater than 500 mg, 1 kg, 1.25 kg, 1.5 kg, 2 kg, 2.5 kg, 3 kg, 4 kg, 5 kg, 7.5 kg, 10 kg, 12.5 kg, 15 kg, or higher. The details of the various steps of the synthetic routes are described in more detail herein.

Selected Chemical Definitions

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

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C₁-C₆ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₃-C₆, C₃-C₅, C₃-C₄, C₄-C₆, C₄-C₅, and C₅-C₆ alkyl.

The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

As used herein, “alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 24 carbon atoms (“C₁-C₂₄ alkyl”). In some embodiments, an alkyl group has 1 to 12 carbon atoms (“C₁-C₁₂ alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“C₁-C₈ alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁-C₆ alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C₂-C₆ alkyl”). In some embodiments, an alkyl group has 2 to 5 carbon atoms (“C₂-C₅ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). Examples of C₁-C₆ alkyl groups include methyl (C₁), ethyl (C₂), n-propyl (C₃), isopropyl (C₃), n-butyl (C₄), tert-butyl (C₄), sec-butyl (C₄), iso-butyl (C₄), n-pentyl (C₅), 3-pentanyl (C₅), amyl (C₅), neopentyl (C₅), 3-methyl-2-butanyl (C₅), tertiary amyl (C₅), and n-hexyl (C₆). Additional examples of alkyl groups include n-heptyl (C₇), n-octyl (C₈) and the like. Each instance of an alkyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted C₁-C₁₀ alkyl (e.g., -CH₃). In certain embodiments, the alkyl group is substituted C₁-C₆ alkyl.

As used herein, the terms “cyano” or “-CN” refer to a substituent having a carbon atom joined to a nitrogen atom by a triple bond, e.g., C≡N.

As used herein, the term “alcohol” refers to a molecule having from 1 to 24 carbon atoms that is functionalized with at least one hydroxyl group, i.e., -OH. In some embodiments, an alcohol has two or more hydroxyl groups. Exemplary alcohols include methanol, ethanol, propanol, isopropanol, butanol, *tert*-butanol, isobutanol, cyclobutanol, 1-pentanol, 3-pentanol, 1-hexanol, 1-octanol, 2,2-dimethylbutan-1-ol, 2-ethylbutan-1-ol, ethylene glycol, 2-methoxyethan-1-ol, 2,3-butanediol, glycerol, and 1,10-decanediol. Each instance of an alcohol may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted alcohol”) or substituted (a “substituted alcohol”) with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alcohol has 1-6 carbon atoms and is unsubstituted (e.g., ethanol). In certain embodiments, the alcohol has 1-6 carbon atoms and is substituted (e.g., 2-methoxyethan-1-ol).

As used herein, the term “acid chloride” refers to a molecule having from 1 to 24 carbon atoms that is functionalized with at least one chlorocarbonyl group, i.e., -C(=O)-Cl. In some embodiments, an acid chloride has two or more chlorocarbonyl groups. Exemplary acid chlorides

include acetyl chloride, propionyl chloride, butyryl chloride, isobutyryl chloride, pentanoyl chloride, cyclopentanecarbonyl chloride, acryloyl chloride, oleoyl chloride, benzoyl chloride, and oxalyl dichloride. Each instance of an acid chloride may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted acid chloride”) or substituted (a “substituted acid chloride”) with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the acid chloride has 3-6 carbon atoms and is unsubstituted (e.g., isobutyryl chloride). In certain embodiments, the acid chloride has 3-6 carbon atoms and is substituted (e.g., 3-methoxypropanoyl chloride). In certain embodiments, the acid chloride is of the formula $R_1-C(=O)-Cl$, wherein R_1 is C_2-C_5 alkyl.

As used herein, the term “oxidizing agent” or “oxidant” is an agent that oxidizes another substance, i.e. increases the oxidation state of another substance. In some embodiments, an oxidizing agent is a chemical compound. In other embodiments, an oxidizing agent may be composed of two or more chemical compounds. Exemplary oxidizing agents include oxygen (O_2), hydrogen peroxide, bromine (Br_2), nitric acid, sodium hypochlorite, ammonium perchlorate, potassium permanganate, pyridinium chlorochromate, sodium dichromate, nitrous oxide, lead dioxide, ceric ammonium nitrate, aminoxyl radicals such as (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) and 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (4-hydroxy-TEMPO), mixtures of DMSO and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride, or phosphorous pentoxide, a complex of pyridine-sulfuric anhydride, transition metal complexes, and combinations thereof. In some embodiments, an oxidizing agent is a mixture of TEMPO, NaOCl solution, and other salts.

As used herein, the term “reducing agent” or “reductant” is an agent that reduces another substance, i.e. decreases the oxidation state of another substance. In some embodiments, a reducing agent is a chemical compound. In other embodiments, a reducing agent may be composed of two or more chemical compounds. Exemplary reducing agents include hydrogen (H_2), metals such as sodium, lithium, potassium, zinc, and magnesium, hydrazine, formic acid, carbon monoxide, carbon, borohydride complexes such as $NaBH(OAc)_3$, $NaBH_4$, $NaBH(CN)_3$, and $NaBH_3CN$, aluminum hydride complexes such as lithium aluminum hydride and diisobutylaluminum hydride, NaH_2PO_2 , transition metals, transition metal complexes, and combinations thereof. In some embodiments, a reducing agent is $NaBH(OAc)_3$.

As used herein, the term “coupling agent” or “coupling reagent” is an agent that assists the formation of an amide bond between an amine and a carboxylic acid. In some embodiments, a coupling agent is a chemical compound. In some embodiments, a coupling agent may be composed of two or more chemical substances. Exemplary coupling agents include N,N'-disubstituted carbodiimides such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; phosphonium reagents such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromotripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim), and 3-(diethoxyphosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); and aminium/uronium reagents such as 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminoxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU). In some embodiments, a coupling agent is EDC·HCl.

As used herein, the term “hydrogenation catalyst” is a substance that facilitates the reaction between hydrogen gas (H₂) and another reactant. In some embodiments, the reaction transforms a double bond into a single bond, wherein the two atoms forming the bond have their newly formed valencies completed with one hydrogen atom each. In some embodiments, the reaction cleaves a single bond, wherein the two atoms forming the bond have their newly formed valencies completed with one hydrogen atom each. In some embodiments, the reaction may comprise combinations of two or more of the above transformations upon the reactant. In some embodiments, the hydrogenation catalyst is a chemical compound. In other embodiments, the hydrogenation catalyst may be composed of two or more chemical substances (e.g., a transition metal supported on a solid). Exemplary hydrogenation catalysts include palladium, palladium supported on activated carbon, palladium(II) hydroxide, palladium(II) acetate, palladium(II) chloride, platinum, rhodium, ruthenium, nickel, Lindlar's catalyst, chloridotris(triphenylphosphine)rhodium(I), cyclooctadiene rhodium chloride dimer, and

Crabtree's catalyst. In some embodiments, a hydrogenation catalyst is palladium supported on activated carbon, with palladium comprising 0.5% to 20% (w/w) of the catalyst.

As used herein, the term "acid catalyst" is a chemical substance that facilitates a reaction and is capable of either donating a proton or forming an adduct with a heteroatom (e.g. N, O, P, S) of a reactant. In some embodiments, the acid catalyst is a chemical compound. In other embodiments, the acid catalyst is a mixture of two or more substances. Exemplary acid catalysts include hydrogen chloride, sulfuric acid, combination of sulfuric acid and potassium fluoride, hydrogen fluoride, alumina, phosphoric acid, p-toluene sulfonic acid, scandium(III) triflate, mixtures thereof, and solutions thereof. In some embodiments, the acid catalyst is sulfuric acid.

As used herein, the term "solvent" is a fluid that a compound or mixture of compounds is dissolved in to form a solution. The dissolved compounds are known as "solutes." In some embodiments, a solvent is comprised of one chemical compound. In other embodiments, the solvent is composed of multiple chemical compounds. Exemplary solvents include water, formic acid, methanol, ethanol, acetic acid, dimethyl sulfide, dimethylformamide, acetonitrile, acetone, dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, 1,4-dioxane, chloroform, diethyl ether, methyl tert-butyl ether, toluene, benzene, hexanes, heptane, perfluorooctane, supercritical carbon dioxide, liquid ammonia, concentrated sulfuric acid, and mixtures thereof. In some embodiments, a solvent may comprise a mixture of miscible fluids, some of which aid dissolution of the solute, and others of which hinder dissolution of the solute; the latter fluid may be referred to as an "anti-solvent." Addition of anti-solvent to a solution may aid precipitation or crystallization of a solute.

As used herein, the term "washing solvent" describes a fluid used to rinse a precipitate in order to remove impurities.

As used herein, the term "organic solvent" is a solvent containing at least one carbon atom.

As used herein, the term "aprotic solvent" is a solvent that does not contain a hydrogen atom directly bonded to a heteroatom (e.g., O, N, S).

As used herein, the term "polar solvent" is a solvent with the ability to dissolve salts and/or compounds with high dipole moments.

As used herein, "oxo" refers to a carbonyl, i.e., -C(O)-.

The symbol "" as used herein in relation to a compound of Formula (I) refers to an attachment point to another moiety or functional group within the compound.

Alkyl, alcohol, and acid chloride, as defined herein, are optionally substituted. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, such as any of the substituents described herein that result in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

The compounds provided herein may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to: *cis*- and *trans*-forms; *E*- and *Z*-forms; *endo*- and *exo*-forms; *R*-, *S*-, and *meso*-forms; *D*- and *L*-forms; *d*- and *l*-forms; (+) and (-) forms; *keto*-, *enol*-, and *enolate*-forms; *syn*- and *anti*-forms; *synclinal*- and *anticlinal*-forms; α - and β -forms; *axial* and *equatorial* forms; *boat*-, *chair*-, *twist*-, *envelope*-, and *half chair*-forms; and combinations thereof, hereinafter collectively referred to as “isomers” (or “isomeric forms”).

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. In an embodiment, the stereochemistry depicted in a compound is relative rather than absolute. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*,

Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). This disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

As used herein, a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (i.e., in enantiomeric excess). In other words, an “S” form of the compound is substantially free from the “R” form of the compound and is, thus, in enantiomeric excess of the “R” form. The term “enantiomerically pure” or “pure enantiomer” denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 99% by weight, more than 99.5% by weight, or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

In the compositions provided herein, an enantiomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising an enantiomerically pure R-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R-compound. In certain embodiments, the enantiomerically pure R-compound in such compositions can, for example, comprise, at least about 95% by weight R-compound and at most about 5% by weight S-compound, by total weight of the compound. For example, a pharmaceutical composition comprising an enantiomerically pure S-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure S-compound. In certain embodiments, the enantiomerically pure S-compound in such compositions can, for example, comprise, at least about 95% by weight S-compound and at most about 5% by weight R-compound, by total weight of the compound.

In some embodiments, a diastereomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising a diastereomerically pure exo compound can comprise, for example, about 90% excipient and

about 10% diastereomerically pure exo compound. In certain embodiments, the diastereomerically pure exo compound in such compositions can, for example, comprise, at least about 95% by weight exo compound and at most about 5% by weight endo compound, by total weight of the compound. For example, a pharmaceutical composition comprising a diastereomerically pure endo compound can comprise, for example, about 90% excipient and about 10% diastereomerically pure endo compound. In certain embodiments, the diastereomerically pure endo compound in such compositions can, for example, comprise, at least about 95% by weight endo compound and at most about 5% by weight exo compound, by total weight of the compound.

In some embodiments, an isomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising an isomerically pure exo compound can comprise, for example, about 90% excipient and about 10% isomerically pure exo compound. In certain embodiments, the isomerically pure exo compound in such compositions can, for example, comprise, at least about 95% by weight exo compound and at most about 5% by weight endo compound, by total weight of the compound. For example, a pharmaceutical composition comprising an isomerically pure endo compound can comprise, for example, about 90% excipient and about 10% isomerically pure endo compound. In certain embodiments, the isomerically pure endo compound in such compositions can, for example, comprise, at least about 95% by weight endo compound and at most about 5% by weight exo compound, by total weight of the compound.

In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

Compound described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; N may be in any isotopic form, including ^{14}N and ^{15}N ; F may be in any isotopic form, including ^{18}F , ^{19}F , and the like.

The term "pharmaceutically acceptable salt" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by

contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge et al, *Journal of Pharmaceutical Science* 66: 1-19 (1977)). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. These salts may be prepared by methods known to those skilled in the art. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention.

In addition to salt forms, the present disclosure provides compounds in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

The term "solvate" refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds of Formula (I) may be prepared, e.g., in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include

both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

The term "hydrate" refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x \text{ H}_2\text{O}$, wherein R is the compound and wherein x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5 \text{ H}_2\text{O}$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2 \text{ H}_2\text{O}$) and hexahydrates ($R \cdot 6 \text{ H}_2\text{O}$)).

The term "tautomer" refers to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane that are likewise formed by treatment with acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

Carboxylic Acid Protection Step – Example 1, Step A

In one aspect, the present disclosure includes a method of protecting a carboxylic acid, for example, converting a carboxylic acid to an ester, *e.g.*, by converting Compound 1 to Compound 2. In an embodiment, the reaction comprises reacting Compound 1 with an alcohol, *e.g.*, an alcohol comprising between 1 and 6 carbon atoms, in the presence of an acid. In one example, the reaction comprises contacting Compound 1 with methanol in the presence of an acid, such as H_2SO_4 .

In some embodiments, Compound 1 is provided in a reaction vessel, and the alcohol, *e.g.*, an alcohol comprising between 1 and 6 carbon atoms (*e.g.*, MeOH), is added to the reaction vessel. In another embodiment, an alcohol, *e.g.*, an alcohol comprising between 1 and 6 carbon atoms

(e.g., MeOH), is provided in a reaction vessel, and Compound **1** is added to the reaction vessel. In some embodiments, the acid (e.g., H₂SO₄) is added to Compound **1** dissolved in the alcohol comprising between 1 and 6 carbon atoms (e.g., MeOH). In another embodiment, the acid is added to the alcohol prior to addition of Compound **1**. In some embodiments, the alcohol comprising between 1 and 6 carbon atoms (e.g., MeOH) is provided in excess relative to Compound **1**. In other embodiments, the alcohol comprising between 1 and 6 carbon atoms (e.g., MeOH) is provided in approximately a molar ratio of 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 25:1, 50:1, 100:1, 250:1, 500:1 or greater relative to Compound **1**. In some embodiments, the acid (e.g., H₂SO₄) is provided in approximately a molar ratio of 0.01:1, 0.05:1, 0.1:1, 0.2:1, 0.3:1, 0.4:1, 0.5:1, 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1, 1.25:1, 1.5:1, 2:1, or greater relative to Compound **1**. In some embodiments, the acid is provided in a molar ratio between 25% to 50% of the amount of Compound **1**.

The reaction may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, above 25 °C, or at the reflux temperature of the reaction. In some embodiments, the reaction progress is sampled by any known method, such chromatography or spectrometry. In some embodiments, once the reaction is completed, the reaction mixture is extracted between two phases. In some embodiments, there are multiple extraction separations that are run consecutively, for instance first separating organic (or oil) layer from water layer, and then mixing that organic layer with 5% (w/w) NaHCO₃ (aq.) and separating the organic layer again. In some embodiments, the reaction mixture is concentrated under reduced pressure. In some embodiments, the reaction mixture is further purified, by chromatography, distillation, precipitation, or crystallography. In some embodiments, the yield of this reaction is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Oxidation Step – Example 1, Step B and Example 2, Step I

In another aspect, the present disclosure includes a method of oxidizing an alcohol to a ketone, e.g., by converting Compound **2** to Compound **3**, and/or by converting Compound **9** to Compound **10**. In an embodiment, the reaction comprises reacting the alcohol (e.g., Compound **2** or Compound **9**) with an oxidizing agent. In one example, the reaction comprises contacting Compound **2** with TEMPO and NaOCl, in the presence of a base, such as NaHCO₃, and a salt,

such as NaBr. In another example, the reaction comprises contacting Compound 9 with TEMPO and NaOCl, in the presence of a base, such as NaHCO₃, and a salt, such as NaBr.

In some embodiments, a solution of the alcohol (e.g., Compound 2 or Compound 9) in an organic solvent (e.g., DCM) is provided in the reaction vessel, and base (e.g., NaHCO₃), salt additive (e.g., NaBr), oxidizing agent component (e.g., TEMPO), and water are added sequentially to the reaction vessel. In another embodiment, a solution of the alcohol (e.g., Compound 2 or Compound 9) in an organic solvent (e.g., DCM) is provided in the reaction vessel, and an aqueous solution of base (e.g., NaHCO₃), salt additive (e.g., NaBr), oxidizing agent component (e.g., TEMPO) is added to the reaction vessel. In another embodiment, an aqueous solution of base (e.g., NaHCO₃), salt additive (e.g., NaBr), oxidizing agent component (e.g., TEMPO) is provided in the reaction vessel, and a solution of the alcohol (e.g., Compound 2 or Compound 9) in an organic solvent (e.g., DCM) is added to the reaction vessel. In another embodiment, an aqueous solution of base (e.g., NaHCO₃), salt additive (e.g., NaBr), oxidizing agent component (e.g., TEMPO) is provided in the reaction vessel, and the alcohol (e.g., Compound 2 or Compound 9) and an organic solvent (e.g., DCM) are added separately to the reaction vessel. In the above embodiments, a solution of oxidizing agent (e.g., aqueous NaOCl), is subsequently added to the reaction mixture. In some embodiments, a base (e.g., NaHCO₃) is dissolved in the oxidizing agent solution (e.g., aqueous NaOCl) prior to addition to the reaction mixture. In some embodiments, the solution of oxidizing agent may be added to the reaction mixture in multiple portions. In some embodiments, the solution of oxidizing agent may be added to the reaction mixture via dropwise addition.

In some embodiments, the base (e.g., NaHCO₃) is provided in less than one molar equivalent relative to the alcohol (e.g., Compound 2 or Compound 9). In other embodiments, the base (e.g., NaHCO₃) is provided in approximately a molar ratio of 0.05:1, 0.1:1, 0.2:1, 0.3:1, 0.4:1, 0.5:1, 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1, 1.25:1, 1.5:1, 2:1, or greater relative to the alcohol (e.g., Compound 2 or Compound 9). In some embodiments, the base (e.g., NaHCO₃) is provided in a molar ratio of between 25% and 50% relative to the alcohol (e.g., Compound 2 or Compound 9). In some embodiments, the salt additive (e.g., NaBr) is provided in less than one molar equivalent relative to the alcohol (e.g., Compound 2 or Compound 9). In other embodiments, the salt additive (e.g., NaBr) is provided in approximately a molar ratio of 0.01:1, 0.05:1, 0.1:1, 0.125:1, 0.15:1, 0.2:1, 0.3:1, 0.4:1, 0.5:1, or greater relative to the alcohol (e.g.,

Compound 2 or Compound 9). In some embodiments, the salt additive (e.g., NaBr) is provided in a molar ratio of between 2% and 15% relative to the alcohol (e.g., Compound 2 or Compound 9). In some embodiments, the oxidizing agent component (e.g., TEMPO) is provided in less than 0.1 molar equivalent relative to the alcohol (e.g., Compound 2 or Compound 9). In other embodiments, the oxidizing agent component (e.g., TEMPO) is provided in approximately a molar ratio of 0.1%, 0.25%, 0.5%, 0.75%, 1%, 1.5%, 2%, 2.5%, 3%, or greater relative to the alcohol (e.g., Compound 2 or Compound 9). In some embodiments, the oxidizing agent component (e.g., TEMPO) is provided in molar ratio between 0.1% and 10% relative to the alcohol (e.g., Compound 2 or Compound 9). In some embodiments, an oxidizing agent (e.g., NaOCl) is provided in excess relative to the alcohol (e.g., Compound 2 or Compound 9). In other embodiments, an oxidizing agent (e.g., NaOCl) is provided in approximately a molar ratio of 1:1, 1.025:1, 1.05:1, 1.075:1, 1.1:1, 1.2:1, 1.3:1, 1.5:1, or greater relative to the alcohol (e.g., Compound 2 or Compound 9). In some embodiments, an oxidizing agent (e.g., NaOCl) is provided in molar ratio between 100% to 120% relative to the alcohol (e.g., Compound 2 or Compound 9).

In some embodiments, once the reaction is completed, a mild reducing agent (e.g. $\text{Na}_2\text{S}_2\text{O}_3$) is added to quench the reaction. In some embodiments, the reaction mixture containing the mild reducing agent is heated to facilitate quenching. In some embodiments, the mild reducing agent (e.g., $\text{Na}_2\text{S}_2\text{O}_3$) is added in less than 1 molar equivalent relative to the starting amount of alcohol (e.g., Compound 2 or Compound 9). In other embodiments, the mild reducing agent (e.g., $\text{Na}_2\text{S}_2\text{O}_3$) is added in approximately a molar ratio of 0.01:1, 0.05:1, 0.1:1, 0.125:1, 0.15:1, 0.2:1, 0.3:1, 0.4:1, 0.5:1, or greater relative to the starting amount of alcohol (e.g., Compound 2 or Compound 9). In some embodiments, the mild reducing agent (e.g., $\text{Na}_2\text{S}_2\text{O}_3$) is added molar ratio between 5% to 25% relative to the starting amount of alcohol (e.g., Compound 2 or Compound 9).

The reaction may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, above 25 °C, or at the reflux temperature of the reaction mixture. In some embodiments, the reaction is conducted between -20 and 10 °C or between -5 and 5 °C. In some embodiments, the reaction progress is sampled by any known method, such chromatography or spectrometry. In some embodiments, the reaction mixture is extracted between two phases. In some embodiments, there are multiple extraction separations that are run

consecutively, for instance first separating organic (or oil) layer from water layer, and then mixing that organic layer with 5% (w/w) NaHCO_3 (aq.) and separating the organic layer again. In some embodiments, the reaction mixture is concentrated under reduced pressure. In some embodiments, the reaction mixture is further purified, by chromatography, distillation, precipitation, or crystallography. In some embodiments, the yield of this reaction is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Reductive Amination Step – Example 1, Step C and Example 2, Step J

In another aspect, the present disclosure includes a method of converting a ketone into a secondary amine, e.g., by converting Compound **3** into Compound **4**, and/or by converting Compound **10** into Compound **11**. In an embodiment, the reaction comprises reacting a ketone (e.g., Compound **3** or Compound **10**) with a primary amine and a reductant. In another embodiment, the reaction comprises reacting a ketone (e.g., Compound **3** or Compound **10**) with a primary ammonium salt, a base, and a reducing agent (reductant). In one example, the reaction comprises contacting Compound **3** with ammonium salt Compound **12** in the presence of a base, such as NaOAc , and a reductant, such as $\text{NaBH}(\text{OAc})_3$.

In some embodiments, a solution of primary amine is pre-generated by reacting ammonium Compound **12** and a base (e.g., NaOAc) in a solvent (e.g., MeCN). In some embodiments, a solution of reductant and/or a solution of ketone (e.g., Compound **3** or Compound **10**) are separately prepared. In some embodiments, the primary amine solution is provided in the reaction vessel, and subsequent reductant (e.g., $\text{NaBH}(\text{OAc})_3$) addition is followed by ketone (e.g., Compound **3** or Compound **10**) addition to the reaction vessel. In other embodiments, the primary amine solution is provided in the reaction vessel, and subsequent ketone (e.g., Compound **3** or Compound **10**) addition is followed by reductant (e.g., $\text{NaBH}(\text{OAc})_3$) addition to the reaction vessel. In some embodiments, the ketone (e.g., Compound **3** or Compound **10**) is contacted with ammonium Compound **12** in the presence of base (e.g., NaOAc), followed by addition of reductant (e.g., $\text{NaBH}(\text{OAc})_3$). In some embodiments, the solution of reducing agent or the solution of ketone may be added to the reaction mixture via dropwise addition.

In some embodiments, the ammonium salt (e.g., Compound **12**) is provided in about 90% to 110% molar ratio relative to the ketone (e.g., Compound **3** or Compound **10**). In other

embodiments, Compound **12** is provided in approximate molar ratio of 0.8:1, 0.85:1, 0.9:1, 0.95:1, 0.98:1, 1:1, 1.02:1, 1.05:1, 1.1:1, 1.15:1, or 1.2:1 relative to the ketone (e.g., Compound **3** or Compound **10**). In some embodiments, the base (e.g. NaOAc) is provided in about 95 to 105% molar ratio relative to the ammonium salt (e.g., Compound **12**). In other embodiments, is provided in approximate molar ratio of 0.8:1, 0.85:1, 0.9:1, 0.95:1, 0.98:1, 1:1, 1.02:1, 1.05:1, 1.1:1, 1.15:1, or 1.2:1 relative to the ammonium salt (e.g., Compound **12**). In some embodiments, the reductant (e.g. $\text{NaBH}(\text{OAc})_3$) is provided in excess relative to the ketone (e.g., Compound **3** or Compound **10**). In other embodiments, the reductant (e.g. $\text{NaBH}(\text{OAc})_3$) is provided in approximate molar ratio of 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.75:1, 2:1, or greater relative to the ketone (e.g., Compound **3** or Compound **10**). In some embodiments, the reductant (e.g. $\text{NaBH}(\text{OAc})_3$) is provided in molar ratio between 110% and 140% relative to the ketone (e.g., Compound **3** or Compound **10**).

In some embodiments, once the reaction is completed, an aqueous solution (e.g., 1N NaOH) is added to quench the reaction. In some embodiments, the quenching solution contains an excess of base (e.g. NaOH) relative to starting amount of reductant (e.g., $\text{NaBH}(\text{OAc})_3$). In other embodiments, the quenching base (e.g., NaOH) is added in approximately a molar ratio of 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.75:1, 2:1, or greater relative to the starting amount of reductant (e.g., $\text{NaBH}(\text{OAc})_3$). In some embodiments, the product is further purified by dissolution in a solvent and treatment with an acid. In some embodiments, the acid (e.g., oxalic acid) is provided in excess relative to the starting amount of ketone. In other embodiments, the acid (e.g., oxalic acid) is provided in approximate molar ratio of 1:1, 1.2:1, 1.4:1, 1.6:1, 1.8:1, 2:1, 2.25:1, 2.5:1, 3:1, 5:1, 10:1 or greater relative to the starting amount of ketone.

The reaction may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, above 25 °C, or at the reflux temperature of the reaction mixture. In some embodiments, the reaction is carried out between -15 and 10 °C. In some embodiments, the reaction is carried out between 0 and 25 °C. In some embodiments, the reaction progress is sampled by any known method, such chromatography or spectrometry. In some embodiments, the reaction mixture is extracted between two phases. In some embodiments, there are multiple extraction separations that are run consecutively, for instance first separating organic (or oil) layer from water layer, and then mixing that organic layer with 5% (w/w) NaHCO_3 (aq.) and separating the organic layer again. In some embodiments, the reaction mixture or combined

organic extracts are concentrated under reduced pressure. In some embodiments, the reaction mixture is further purified, by chromatography, distillation, precipitation, or crystallography. In some embodiments, the yield of this reaction is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

N-alkylation Step – Example 1, Step D and Example 2, Step K

In another aspect, the present disclosure includes a method of N-alkylating a secondary amine, e.g. by converting deprotonated Compound **4** to Compound **5**, and/or by converting Compound **11** to Compound **7**. In embodiments starting with an ammonium (e.g. Compound **4**), pre-treatment with a base may be necessary to obtain a suitable starting secondary amine. In an embodiment, the reaction comprises reacting the secondary amine (e.g., Compound **11** or deprotonated Compound **4**) with an acid chloride $R_1-C(=O)-Cl$, wherein R_1 is C_2-C_5 alkyl, in the presence of base. In one example, ammonium Compound **4** is pre-treated with a base (e.g. aqueous NH_3 solution) and purified by solvent extraction to obtain a crude amine, which is then treated with an acid chloride (e.g., isobutyryl chloride) and base (e.g., TEA) in organic solvent (e.g., DCM). In another example, secondary amine Compound **11** is treated with an acid chloride (e.g., isobutyryl chloride) and base (e.g., DIPEA) in organic solvent (e.g., DCM).

In some embodiments, a solution of starting ammonium (e.g. Compound **4**) in an organic solvent (e.g., EtOAc) is provided in a reaction vessel, and a suitable base (e.g. aqueous NH_3 solution) is added to the reaction vessel to generate a secondary amine. In such embodiments, quenching progress may be tracked by recording pH measurements. The resulting mixture may be worked up by solvent extraction with an organic solvent (e.g. EtOAc) and concentration under reduced pressure to obtain a secondary amine suitable for N-alkylation. In some embodiments, base (e.g. aqueous NH_3 solution) is provided in excess relative to the ammonium (e.g., Compound **4**). In other embodiments, base (e.g. aqueous NH_3 solution) is provided in approximate molar ratio of 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 20:1, 50:1, 100:1, 500:1, 1000:1, or greater relative to the ammonium. In some embodiments, the base is provided neat or in a solution. In some embodiments, the base solution is approximately 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, or greater (w/w) concentration. In some embodiments, the base solution is between 10% to 40% (w/w) concentration.

In some embodiments, a solution of secondary amine (e.g., Compound **11** or deprotonated Compound **4**) in organic solvent (e.g., DCM) is provided in the reaction vessel, and base (e.g., TEA or DIPEA) and acid chloride (e.g. isobutyryl chloride) are added to the reaction vessel sequentially. In other embodiments, a solution of base (e.g. TEA or DIPEA) in organic solvent (e.g., DCM) is provided in the reaction vessel, and secondary amine (e.g., Compound **11** or deprotonated Compound **4**) and acid chloride (e.g. isobutyryl chloride) are added to the reaction vessel sequentially. In other embodiments, a mixture of base (e.g. TEA or DIPEA) and secondary amine (e.g., Compound **11** or deprotonated Compound **4**) is provided in the reaction vessel, and organic solvent (e.g., DCM) and acid chloride (e.g. isobutyryl chloride) are added to the reaction vessel sequentially.

In some embodiments, the acid chloride (e.g., isobutyryl chloride) is provided in excess relative to the secondary amine (e.g., Compound **11** or deprotonated Compound **4**). In some embodiments, the acid chloride (e.g., isobutyryl chloride) is provided in approximate molar ratio of 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.75:1, 2:1, 2.25:1, 2.5:1, 3:1, or greater relative to the secondary amine (e.g., Compound **11** or deprotonated Compound **4**). In some embodiments, the acid chloride (e.g., isobutyryl chloride) is provided in molar ratio between 150% and 300% relative to the secondary amine (e.g., Compound **11** or deprotonated Compound **4**). In some embodiments, the base (e.g., TEA or DIPEA) is provided in excess relative to the secondary amine (e.g., Compound **11** or deprotonated Compound **4**). In some embodiments, the base (e.g., TEA or DIPEA) is provided in approximate molar ratio of 1:1, 1.2:1, 1.4:1, 1.7:1, 2:1, 2.5:1, 3:1, 4:1, 5:1, or greater relative to the secondary amine (e.g., Compound **11** or deprotonated Compound **4**). In some embodiments, the base (e.g., TEA or DIPEA) is provided in molar ratio between 200% and 500% relative to the secondary amine (e.g., Compound **11** or deprotonated Compound **4**).

The reaction may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, above 25 °C, or at the reflux temperature of the reaction mixture. In some embodiments, the reaction is carried out between -15 and 10 °C. In some embodiments, the reaction is carried out between 0 and 5 °C. In some embodiments, the reaction progress is sampled by any known method, such chromatography or spectrometry. In some embodiments, the reaction mixture is extracted between two phases. In some embodiments, there are multiple extraction separations that are run consecutively, for instance first separating organic (or oil)

layer from water layer, and then mixing that organic layer with 5% (w/w) NaHCO_3 (aq.) and separating the organic layer again. In some embodiments, the reaction mixture or combined organic extracts are concentrated under reduced pressure. In some embodiments, the reaction mixture is further purified, by chromatography, distillation, precipitation, or crystallography. In some embodiments, the yield of this reaction is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Ester Deprotection Step – Example 1, Step E

In another aspect, the present disclosure includes a method of converting an ester into a carboxylic acid, e.g., by converting Compound **5** to Compound **6**. In an embodiment, the reaction comprises reacting Compound **5** with an inorganic base. In an embodiment, the reaction further comprises subsequent treatment with an acid. In one example, the reaction comprises contacting Compound **5** with an inorganic base (e.g., LiOH) in a mixture of water and organic solvents (e.g. MeOH and/or THF), followed by treatment with an acid (e.g., HCl aqueous solution).

In some embodiments, the ester (e.g., Compound **5**) is provided in a reaction vessel with the organic solvents (e.g., MeOH and THF), and a solution of inorganic base (e.g., LiOH) in water is added to the reaction vessel. In some embodiments, the ester (e.g., Compound **5**) is provided in a reaction vessel with the organic solvents (e.g., MeOH and THF) and water, and inorganic base (e.g., LiOH) is added to the reaction vessel. In some embodiments, a solution of inorganic base (e.g., LiOH) in water is provided in the reaction vessel, and a solution of the ester (e.g., Compound **5**) dissolved in organic solvents (e.g., MeOH and THF) is added to the reaction vessel. In some embodiments, a mixture of inorganic base (e.g., LiOH) in water and organic solvents (e.g., MeOH and THF) is provided in the reaction vessel, and ester (e.g., Compound **5**) is added to the reaction vessel.

In some embodiments, the inorganic base (e.g., LiOH) is provided in excess relative to the ester (e.g., Compound **5**). In some embodiments, the inorganic base (e.g., LiOH) is provided in approximate molar ratio of 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 20:1, or greater relative to the ester (e.g., Compound **5**). In some embodiments, the inorganic base (e.g., LiOH) is provided in molar ratio between 200% and 500% relative to the ester (e.g., Compound **5**).

After completion of the initial reaction with inorganic base (e.g. LiOH), in some embodiments the mixture is treated with an acid (e.g. HCl). In some embodiments, the acid is

provided as a solution. In some embodiments, the acid is provided as an aqueous solution (e.g., HCl aqueous solution). In some embodiments, the acid solution is approximately 0.1, 0.2, 0.3, 0.4, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, or greater molarity concentration. In some embodiments, the subsequent acid (e.g., HCl) is provided in excess relative to the ester (e.g., Compound **5**). In some embodiments, the acid (e.g., HCl) is provided in approximate molar ratio of 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 20:1, or greater relative to the ester (e.g., Compound **5**). In some embodiments, the subsequent acid (e.g., HCl) is provided in molar ratio between 200% to 500% relative to the ester (e.g., Compound **5**). In some embodiments, the addition of acid (e.g., HCl solution) is tracked by monitored pH level of the reaction mixture.

The reaction may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, above 25 °C, or at the reflux temperature of the reaction mixture. In some embodiments, the reaction progress is sampled by any known method, such chromatography or spectrometry. In some embodiments, the reaction mixture is extracted between two phases. In some embodiments, there are multiple extraction separations that are run consecutively, for instance first separating organic (or oil) layer from water layer, and then mixing that organic layer with 5% (w/w) NaHCO₃ (aq.) and separating the organic layer again. In some embodiments, the reaction mixture or combined organic extracts are concentrated under reduced pressure. In some embodiments, the reaction mixture is further purified, by chromatography, distillation, precipitation, or crystallography. In some embodiments, the yield of this reaction is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Amide Coupling Step – Example 1, Step F; Example 2, Step H; Example 3 Step M; and Example 4, Step M.

In another aspect, the present disclosure includes a method of converting a carboxylic acid into an amide, e.g., by converting Compound **6** to Compound **7**, Compound **1** into Compound **9**, and/or Compound **13** into Compound **14**. In an embodiment, the reaction comprises contacting a carboxylic acid (e.g., Compound **6**, Compound **1**, or Compound **13**) with a secondary amine (e.g., morpholine) or secondary ammonium (e.g., Compound **8**) in the presence of a coupling agent, a reaction accelerating additive, a solvent, and (optionally) a base. In one example, the reaction comprises Compound **6** reacting with morpholine in the presence of a coupling agent

(e.g., EDC•HCl), reaction accelerating additive (e.g., HOBt•H₂O), organic solvent (e.g., DMF), and base (e.g., DIPEA). In another example, the reaction comprises Compound **1** reacting with morpholine in the presence of a coupling agent (e.g., EDC•HCl), reaction accelerating additive (e.g., HOBt•H₂O), and organic solvent (e.g., DMF). In a third example, the reaction comprises Compound **13** reacting with Compound **8** in the presence of a coupling agent (e.g., EDC•HCl), reaction accelerating additive (e.g., HOBt•H₂O), and organic solvent (e.g., DCM or acetone).

In some embodiments, a solution of the carboxylic acid (e.g., Compound **6**, Compound **1**, or Compound **13**), reaction accelerating additive (e.g., HOBt•H₂O), coupling agent (e.g., EDC•HCl), and base (e.g., DIPEA) in an organic solvent (e.g., DMF, DCM, or acetone) is provided in the reaction vessel, and the secondary amine (e.g., morpholine) or secondary ammonium (e.g., Compound **8**) is added to the reaction flask. In some embodiments, a solution of the carboxylic acid (e.g., Compound **6**, Compound **1**, or Compound **13**), the secondary amine (e.g., morpholine) or secondary ammonium (e.g., Compound **8**), reaction accelerating additive (e.g., HOBt•H₂O), and base (e.g., DIPEA) in an organic solvent (e.g., DMF, DCM, or acetone) is provided in the reaction vessel, and coupling agent (e.g., EDC•HCl) is added to the reaction flask. In some embodiments, a solution of the carboxylic acid (e.g., Compound **6**, Compound **1**, or Compound **13**), reaction accelerating additive (e.g., HOBt•H₂O), and coupling agent (e.g., EDC•HCl) in an organic solvent (e.g., DMF, DCM, or acetone) is provided in the reaction vessel, and the secondary amine (e.g., morpholine) or secondary ammonium (e.g., Compound **8**) is added to the reaction flask. In some embodiments, a solution of the carboxylic acid (e.g., Compound **6**, Compound **1**, or Compound **13**), the secondary amine (e.g., morpholine) or secondary ammonium (e.g., Compound **8**), and reaction accelerating additive (e.g., HOBt•H₂O) in an organic solvent (e.g., DMF, DCM, or acetone) is provided in the reaction vessel, and coupling agent (e.g., EDC•HCl) is added to the reaction flask. In some embodiments, coupling agent (e.g., EDC•HCl) is provided in excess relative to the carboxylic acid (e.g., Compound **6**, Compound **1**, or Compound **13**). In other embodiments, coupling agent (e.g., EDC•HCl) is provided in approximate molar ratio of 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.75:1, 2:1, 2.5:1, 3:1, or greater relative to the carboxylic acid (e.g., Compound **6**, Compound **1**, or Compound **13**). In some embodiments, coupling agent (e.g., EDC•HCl) is provided in molar ratio between 100% and 300% relative to the carboxylic acid (e.g., Compound **6**, Compound **1**, or Compound **13**). In some embodiments, reaction accelerating additive (e.g., HOBt•H₂O) is provided in subcess or

excess relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13). In other embodiments, reaction accelerating additive (e.g., HOBt•H₂O) is provided in approximate molar ratio of 0.01:1, 0.05:1, 0.1:1, 0.2:1, 0.3:1, 0.4:1, 0.5:1, 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1, 1.25:1, 1.5:1, 1.75:1, 2:1, or greater relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13). In some embodiments, the reaction accelerating additive (e.g., HOBt•H₂O) is provided in molar ratio between 0.5% and 200% relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13). In some embodiments, secondary amine (e.g., morpholine) or secondary ammonium (e.g., Compound 8) is provided in near equivalent molar amount relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13). In other embodiments, secondary amine (e.g., morpholine) or secondary ammonium (e.g., Compound 8) is provided in approximate molar ratio of 0.8:1, 0.85:1, 0.9:1, 0.95:1, 0.98:1, 1:1, 1.02:1, 1.05:1, 1.1:1, 1.15:1, 1.2:1, or greater relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13). In some embodiments, secondary amine (e.g., morpholine) or secondary ammonium (e.g., Compound 8) is provided in molar ratio between 80% and 120% relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13). In some embodiments, base (e.g., DIPEA) is absent or provided in excess relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13). In other embodiments, base (e.g., DIPEA) is provided in approximate molar ratio of 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.75:1, 2:1, 2.5:1, 3:1, or greater relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13). In some embodiments, base (e.g., DIPEA) is absent or provided in molar ratio between 100% to 300% relative to the carboxylic acid (e.g., Compound 6, Compound 1, or Compound 13).

The reaction may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, above 25 °C, or at the reflux temperature of the reaction mixture. In some embodiments, the reaction progress is sampled by any known method, such as chromatography or spectrometry. In some embodiments, the reaction mixture is extracted between two phases. In some embodiments, there are multiple extraction separations that are run consecutively, for instance first separating organic (or oil) layer from water layer, and then mixing that organic layer with 1N HCl (aq.) and separating the organic layer again. In some embodiments, the reaction mixture or combined organic extracts are concentrated under reduced pressure. In some embodiments, the reaction mixture is further purified, by chromatography,

distillation, precipitation, or crystallography. In some embodiments, the yield of this reaction is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Benzyloxycarbonyl Deprotection Step – Example 1, Step G and Example 2, Step G

In another aspect, the present disclosure includes methods of converting a benzyloxycarbonyl-protected amine into an ammonium salt, e.g. by converting Compound 7 to Compound 8. In one embodiment, Compound 7 is deprotected under hydrogenation conditions and then protonated with an acid. In one example, Compound 7 is contacted with hydrogen gas in the presence of hydrogenation catalyst (e.g., 10% Pd/C) and solvent (e.g., MeOH); subsequent reaction with acid (e.g., 4M HCl in EtOAc) affords the ammonium salt Compound 8.

In some embodiments, a solution of Compound 7 is provided in the reaction vessel, and hydrogenation catalyst (e.g. 10% Pd/C) is added to the reaction vessel. In some embodiments, a solution of Compound 7 is provided in the reaction vessel, and a mixture of hydrogenation catalyst (e.g. 10% Pd/C) and solvent is added to the reaction vessel. In some embodiments, a mixture of hydrogenation catalyst (e.g. 10% Pd/C) and solvent is provided in the reaction vessel, and Compound 7 is added to the reaction vessel. In all embodiments, the reaction vessel is subsequently pressurized with hydrogen gas. In some embodiments, the deprotected Compound 7 is dissolved in solvent (e.g., MTBE) in a reaction vessel, and then acid (e.g. 4M HCl in EtOAc) is added to afford product ammonium salt Compound 8.

In some embodiments, the hydrogen gas is provided in excess relative to Compound 7. In other embodiments, the hydrogen gas pressure is provided at 0.05, 0.1, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 bar or higher pressure. In other embodiments, the hydrogen gas pressure is provided at 0.05 to 1 bar pressure. In some embodiments, the reaction vessel is sealed over the duration of the reaction. In other embodiments, the reaction vessel is repressurized with hydrogen during the reaction. In some embodiments, the hydrogenation catalyst (e.g. 10% Pd/C) is provided in subcess relative to Compound 7. In other embodiments, the hydrogenation catalyst (e.g. 10% Pd/C) is provided in approximate molar ratio of 1%, 2.5%, 5%, 7.5%, 10%, 12.5%, 15%, 20%, 25%, or greater relative to Compound 7. In some embodiments, the hydrogenation catalyst (e.g. 10% Pd/C) is provided in a molar ratio of between 5% to 25% of the amount of Compound 7. In some embodiments, the acid is provided in excess relative to initial amount of Compound 7. In

other embodiments, the acid is provided in approximate molar ratio of 1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, 2:1, 2.5:1, 3:1, or greater relative to initial amount of Compound 7. In some embodiments, the acid is provided in approximate molar ratio between 100% and 200% relative to initial amount of Compound 7.

The reaction may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, above 25 °C, or at the reflux temperature of the reaction mixture. In some embodiments, the reaction is carried out between -15 and 10 °C. In some embodiments, the reaction is carried out between 0 and 5 °C. In some embodiments, the reaction progress is sampled by any known method, such chromatography or spectrometry. In some embodiments, the reaction mixture is extracted between two phases. In some embodiments, there are multiple extraction separations that are run consecutively, for instance first separating organic (or oil) layer from water layer, and then mixing that organic layer with 5% (w/w) NaHCO₃ (aq.) and separating the organic layer again. In some embodiments, the reaction mixture or combined organic extracts are concentrated under reduced pressure. In some embodiments, the reaction mixture is further purified, by chromatography, distillation, precipitation, or crystallography. In some embodiments, the yield of this reaction is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Benzyloxycarbonyl Deprotection Step—Example 2, Step G, Version 4

In another aspect, the present disclosure includes methods of converting a benzyloxycarbonyl-protected amine into an ammonium salt, e.g. by converting Compound 7 to Compound 8. In one embodiment, Compound 7 is initially reacted with acid to deprotect the amine group. In one example, Compound 12 is contacted with acid (e.g., 35% HCl aqueous solution); subsequent neutralization with base (e.g., 10N NaOH aqueous solution) and reaction with HCl affords ammonium salt Compound 8.

In some embodiments, Compound 7 is provided in the reaction vessel, and acid (e.g., 35% HCl aqueous solution) is added to the reaction vessel. In other embodiments, acid (e.g., 35% HCl aqueous solution) is provided in the reaction vessel, and Compound 7 is added to the reaction vessel. In some embodiments, after reaction with acid, the reaction mixture is neutralized with base (e.g., 10N NaOH aqueous solution). In some embodiments, the deprotected Compound 7 is

dissolved in solvent (e.g., MTBE) in a reaction vessel, and then HCl (e.g. 4M solution of HCl in EtOAc) is added to afford product ammonium salt Compound 8.

In some embodiments, acid (e.g., 35% HCl) is provided in excess relative to Compound 7. In other embodiments, acid (e.g., 35% HCl) is provided in approximate molar ratio of 1:1, 1.5:1, 2:1, 5:1, 10:1, 15:1, 20:1, 25:1, 30:1, or higher relative to Compound 7. In some embodiments, acid (e.g., 35% HCl) is provided in molar ratio between 1500% to 3000% relative to Compound 7. In some embodiments, base (e.g., NaOH) is provided in excess relative to acid (e.g., 35% HCl) during neutralization. In other embodiments, base (e.g., NaOH) is provided in approximate molar ratio of 0.7:1:1, 0.8:1, 0.9:1, 1:1, 1.1:1, 1.2:1, 1.3:1, or higher relative to acid (e.g., 35% HCl) during neutralization. In some embodiments, base (e.g., NaOH) is provided in molar ratio between 60% to 140% relative to acid (e.g., 35% HCl) during neutralization. In some embodiments, after neutralization, HCl (e.g., 4M HCl in EtOAc) is provided in approximately equal molar amount relative to starting amount of Compound 7. In other embodiments, after neutralization, HCl (e.g., 4M HCl in EtOAc) is provided in approximate molar ratio of 0.8:1, 0.9:1, 0.95:1, 0.98:1, 1:1, 1.02:1, 1.05:1, 1.1:1, or 1.2:1 relative to starting amount of Compound 7. In some embodiments, after neutralization, HCl (e.g., 4M HCl in EtOAc) is provided in molar ratio between 90% to 110% relative to starting amount of Compound 7.

The reaction may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, above 25 °C, or at the reflux temperature of the reaction mixture. In some embodiments, the deprotection reaction with acid (e.g. 35% HCl) is carried out at one temperature range (e.g., 42 to 47 °C), the neutralization is carried out at another temperature range (e.g., 0 to 25 °C), and the final HCl addition is conducted at another temperature range (e.g. 20 to 25 °C). In some embodiments, the reaction progress is sampled by any known method, such pH measurement, chromatography or spectrometry. In some embodiments, the reaction mixture is extracted between two phases. In some embodiments, there are multiple extraction separations that are run consecutively, for instance first separating organic (or oil) layer from water layer, and then mixing that organic layer with 5% (w/w) NaHCO₃ (aq.) and separating the organic layer again. In some embodiments, the reaction mixture or combined organic extracts are concentrated under reduced pressure. In some embodiments, the reaction mixture is further purified, by chromatography, distillation, precipitation, or crystallography. In some

embodiments, the yield of this reaction is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Purification of free base of API –Example 3, Step N

In another aspect, the present disclosure includes a method of purifying the free base of the API, e.g. by purifying Compound **14** to Compound **15**. In one embodiment, Compound **14** is treated with solvent, anti-solvent, and temperature variation. In one example, Compound **14** is treated with solvent (e.g., acetone), anti-solvent, (heptane), and cooled (e.g. to 0 to 5 °C) to obtain precipitated Compound **15**.

In some embodiments, Compound **14** is dissolved in solvent (e.g., acetone) in a vessel, and then anti-solvent (e.g., heptane) is added to the vessel. In other embodiments, Compound **14** is dissolved in mixture of solvent (e.g., acetone) and anti-solvent (e.g., heptane) in a vessel, and then additional anti-solvent (e.g., heptane) is added to the vessel. In some embodiments, the mixture of Compound **14**, solvent (e.g., acetone), and anti-solvent (e.g., heptane) is subjected to cooling (e.g. to 0 to 5 °C). In some embodiments, the anti-solvent (e.g., heptane) is provided in excess of the solvent (e.g., acetone). In some embodiments, the anti-solvent (e.g., heptane) is provided in approximate weight ratio of 1:1, 2:1, 4:1, 6:1, 8:1, 10:1, 16:1, 25:1, or greater relative to solvent (e.g., acetone). In some embodiments, the anti-solvent (e.g., heptane) is provided in weight ratio of between 500% and 2500% relative to solvent (e.g., acetone).

The purification may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, or above 25 °C. In some embodiments, the dissolving Compound **14** is carried out at one temperature range (e.g., around room temperature), and precipitate formation is conducted at another temperature range (e.g. 0 to 5 °C). In some embodiments, the yield of this purification is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Making hydrochloride salt of API –Example 4, Step O

In another aspect, the present disclosure includes a method of making the hydrochloride salt of the API, e.g. by converting Compound **14** to Compound **16**. In one embodiment, Compound **14** is treated with HCl in organic solvent while controlling the solution temperature. In one example, Compound **14** is dissolved in organic solvent (e.g. a mixture of MTBE and heptane),

cooled (e.g. to -5 to 5 °C), and treated with 4M solution of HCl in EtOAc at another temperature range (e.g. 0 to 5 °C).

In some embodiments, Compound **14** is dissolved in a solvent or mixture of solvents (e.g., MTBE and heptane) in a vessel, and then HCl (e.g., 4M HCl in EtOAc) is added to the vessel. In other embodiments, a solution of Compound **14** in a solvent or mixture of solvents (e.g., MTBE and heptane) is added to a vessel containing HCl (e.g., 4M HCl in EtOAc). In some embodiments, Compound **14** is dissolved in a solvent (e.g., MTBE) in a vessel, and then HCl (e.g., 4M HCl in EtOAc) and a solvent (e.g. heptane) are sequentially added to the vessel. In some embodiments, the total weight of solvents (e.g., MTBE, heptane, and EtOAc) provided in the vessel exceeds the weight of Compound **14**. In other embodiments, the total weight of solvents (e.g., MTBE, heptane, and EtOAc) provided in the vessel is 1.5×, 2.5×, 5×, 7.5×, 10×, 12.5×, 15×, 17.5×, 20×, or more relative to the weight of Compound **14**. In some embodiments, the total weight of solvents (e.g., MTBE, heptane, and EtOAc) provided in the vessel is between 5× to 20× relative to the weight of Compound **14**. In some embodiments, HCl is provided in molar equivalence or excess relative to Compound **14**. In other embodiments, HCl is provided in approximate molar ratio of 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, 2:1, or greater relative to Compound **14**. In some embodiments, HCl is provided in molar ratio between 100% to 180% relative to Compound **14**.

The purification may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, or above 25 °C. In some embodiments, the dissolving Compound **14** is carried out at one temperature range (e.g., around room temperature), cooling is performed at another temperature range (e.g. -5 to 5 °C), HCl addition is conducted at another temperature range (e.g. 0 to 5 °C), and precipitate formation is conducted at another temperature range (e.g. 0 to 5 °C). In some embodiments, the yield of this purification is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

Purifying hydrochloride salt of API –Example 4, Step P

In another aspect, the present disclosure includes a method of purifying the hydrochloride salt of the API, e.g. by converting Compound **16** to Compound **17** and/or by converting Compound **15** to Compound **17**. In one embodiment, Compound **16** subjected to a mixture of

organic solvent and water while controlling solution temperature to obtain a purified particles. In another embodiment, Compound **15** is subjected to HCl, organic solvent, and water while controlling solution temperature to obtain a purified particles. In one example, Compound **16** is dissolved in a mixture of organic solvent (e.g., EtOAc) and water at one temperature (e.g., 60 °C), matured at another temperature (e.g., 3 °C), and filtered to obtain Compound **17**. In another example, Compound **15** is dissolved in a mixture of organic solvent (e.g., EtOAc) and water at one temperature (e.g., room temperature), contacted with HCl (e.g., concentrated aqueous solution) at another temperature (e.g., 20 °C), matured at another temperature (e.g., 10, 13, or 15 °C), and filtered at another temperature (e.g. 20 °C); repeated cycles of the last two steps (maturation and filtration) resulted in collection of precipitate Compound **17**.

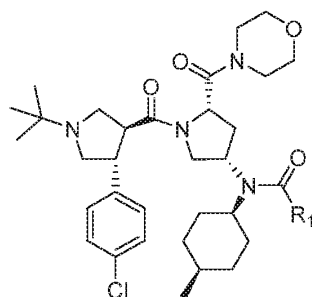
In some embodiments, a mixture of organic solvent (e.g. EtOAc) and water is used to dissolve Compound **16** or Compound **15** in a crystallizing vessel (crystallizer). In other embodiments, organic solvent (e.g. EtOAc) is used to dissolve Compound **16** or Compound **15** in a crystallizer, and water is then added to the crystallizer. In some embodiments, HCl is omitted, or HCl is added to the solution of Compound **16** prior to crystallization.

In some embodiments, the organic solvent (e.g. EtOAc) is in excess relative to water. In other embodiments, the organic solvent (e.g. EtOAc) is provided in approximate volumetric ratio of 1:1, 5:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 50:1, or greater relative to water. In some embodiments, the organic solvent (e.g. EtOAc) is provided in volumetric ratio between 500% and 4000% relative to water. In some embodiments, the organic solvent (e.g. EtOAc) is in near gravimetric equivalence or gravimetric excess relative to Compound **16** or Compound **15**. In other embodiments, the organic solvent (e.g. EtOAc) is provided in approximate gravimetric ratio of 0.5:1, 0.75:1, 1:1, 1.25:1, 1.5:1, 1.75:1, 2:1, 2.25:1, 2.5:1, 2.75:1, 3:1, 4:1, 5:1, or greater relative to Compound **16** or Compound **15**. In some embodiments, the organic solvent (e.g. EtOAc) is provided in gravimetric ratio between 80% and 400% relative to Compound **16** or Compound **15**. In some embodiments, HCl is provided as a solution of 1M, 2M, 4M, 6M, 12M, or higher concentration. In other embodiments, HCl is provided as a concentrated solution. In some embodiments, HCl is added in near equimolar amount relative to Compound **15**. In other embodiments, HCl is added in approximate molar ratio of 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, or higher relative to Compound **15**. In some embodiments, HCl is added in molar ratio of between 80% to 120% relative to Compound **15**.

The purification may be carried out at any temperature, for example, below 25 °C, at room temperature, about 25 °C, or above 25 °C. In some embodiments, the temperature may be adjusted in various phases of the purification process. In some embodiments, the yield of this purification is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% or greater.

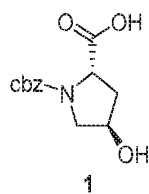
ENUMERATED EMBODIMENTS

1. A method for preparing a compound of Formula (XI):



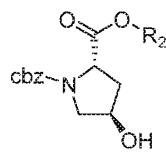
(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein R_1 is C_2 - C_5 alkyl, comprising Step A of reacting Compound **1**



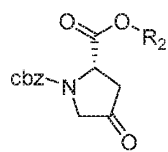
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with an alcohol having 1 to 6 carbon atoms and an acid catalyst to form a compound of Formula (IV):



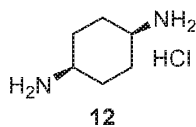
(IV), wherein R_2 is C_1 - C_6 alkyl.

2. The method of embodiment 1, wherein the method further comprises Step B of reacting a compound of Formula (IV) with an oxidizing agent in a solvent to form a compound of Formula (V):

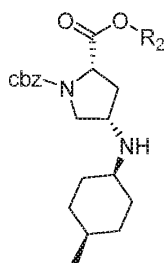


(V), wherein R_2 is C_1 - C_6 alkyl.

3. The method of any one of the preceding embodiments, wherein the method further comprises Step C of reacting a compound of Formula (V) with Compound **12**

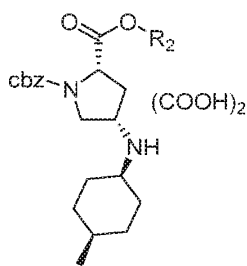


, base, and reducing agent in a solvent to form a compound of Formula (VII'):



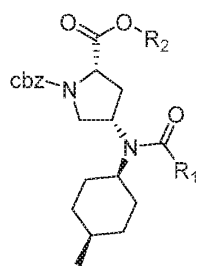
(VII'), wherein R_2 is C_1 - C_6 alkyl.

4. The method of any one of the preceding embodiments, wherein Step C further includes reacting a compound of Formula (VII') with an acid in an organic solvent.
5. The method of any one of the preceding embodiments, wherein Step C further includes reacting a compound of Formula (VII') with oxalic acid in an organic solvent to form a compound of Formula (VII):



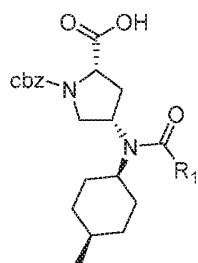
(VII), wherein R_2 is C_1 - C_6 alkyl.

6. The method of any one of the preceding embodiments, wherein the method further comprises Step D of subjecting a compound of Formula (VII) or a compound of Formula (VII') to a reaction with at least one base and a compound of formula R_1 -C(=O)-Cl (e.g. isobutyryl chloride) to form a compound of Formula (VIII):



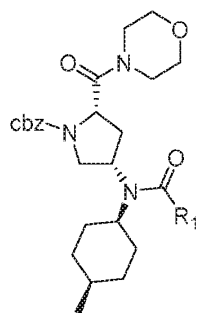
(VIII), wherein R₁ is C₂-C₅ alkyl, and R₂ is C₁-C₆ alkyl.

7. The method of any one of the preceding embodiments, wherein the method further comprises Step E of reacting a compound of Formula (VII) and inorganic base in a solvent to prepare a compound of Formula (IX):



(IX), or a salt or solvate thereof, wherein R₁ is C₂-C₅ alkyl.

8. The method of any one of the preceding embodiments, wherein the method further comprises Step F of reacting a compound of Formula (IX) with morpholine to form a compound of Formula (X):



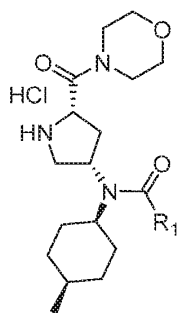
(X), or a salt or solvate thereof, wherein R₁ is C₂-C₅ alkyl.

9. The method of any one of the preceding embodiments, wherein Step F is facilitated by a coupling agent.

10. The method of any one of the preceding embodiments, wherein Step F is further facilitated by a reaction accelerating additive.

11. The method of any one of the preceding embodiments, wherein Step F includes the use of base.

12. The method of any one of the preceding embodiments, wherein the method further comprises Step G of reacting a compound of Formula (X) in a solvent with a hydrogenation catalyst and H₂ or with deprotecting acid solution, and treatment with HCl solution to form a compound of Formula (II):



13. The method of any one of the preceding embodiments, wherein R₂ is methyl, ethyl, propyl, isopropyl, or butyl.

14. The method of any one of the preceding embodiments, wherein R₂ is methyl.

15. The method of any one of the preceding embodiments, wherein the acid catalyst of Step A is at least one selected from the group of HCl, H₂SO₄, H₂SO₄ and KF, a combination of Al₂O₃ (KF + Al₂O₃), H₃PO₄, p-toluene sulfonic acid, and scandium(III) triflate.

16. The method of any one of the preceding embodiments, wherein the acid catalyst of Step A is H₂SO₄.

17. The method of any one of the preceding embodiments, wherein the acid catalyst of Step A is 0.1 to 1 molar equivalent with respect to Compound 1.

18. The method of any one of the preceding embodiments, wherein the acid catalyst of Step A is 0.2 to 0.5 molar equivalent with respect to Compound 1.

19. The method of any one of the preceding embodiments, wherein the acid catalyst of Step A is 0.2 to 0.4 molar equivalent with respect to Compound 1.

20. The method of any one of the preceding embodiments, wherein the reaction time of Step A above is 2 to 5 hours.

21. The method of any one of the preceding embodiments, wherein the solvent of Step B is water and at least one organic solvent selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide,

dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

22. The method of any one of the preceding embodiments, wherein the solvent of Step B is water and dichloromethane.

23. The method of any one of the preceding embodiments, wherein the solvent of Step C, Step D, Step E, and/or Step F is at least one independently selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile, dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

24. The method of any one of the preceding embodiments, wherein the oxidizing agent of Step B is a combination of a chromic acid compound; a co-oxidizing agent, (2,2,6,6-tetramethylpiperidinyl)oxyl free radical (TEMPO) and other salts; a complex of dimethyl sulfoxide and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride or phosphorus pentoxide or a complex of pyridine-sulfuric anhydride; or a combination of a transition metal catalyst and oxygen, or a transition metal catalyst and an organic oxidizing agent.

25. The method of any one of the preceding embodiments, wherein the oxidizing agent of Step B is (2,2,6,6-tetramethylpiperidinyl)oxyl free radical (TEMPO) and other salts.

26. The method of any one of the preceding embodiments, wherein the other salts referenced include at least one of sodium bromide and sodium hypochlorite.

27. The method of any one of the preceding embodiments, wherein Step B includes at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaHCO₃.

28. The method of any one of the preceding embodiments, wherein Step B includes NaHCO₃.

29. The method of any one of the preceding embodiments, wherein Step B is performed with reaction temperature between -10 and 10 °C, and the reaction time is 0.5 h or longer.

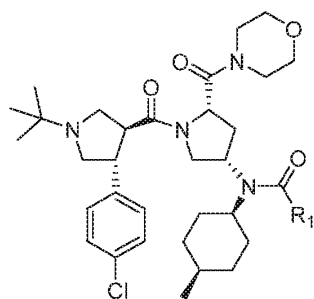
30. The method of any one of the preceding embodiments, wherein the reducing agent of Step C is at least one inorganic base selected from the group consisting of NaBH(OAc)₃, NaBH₄, NaBH(CN)₃, NaBH₃CN, and NaH₂PO₂.

31. The method of any one of the preceding embodiments, wherein the reducing agent of Step C is NaBH(OAc)₃.

32. The method of any one of the preceding embodiments, wherein the reaction temperature of Step C is 1 to 30 °C, and the reaction time is 1 to 30 hours.
33. The method of any one of the preceding embodiments, wherein the reaction temperature of Step C is 15 to 25 °C.
34. The method of any one of the preceding embodiments, wherein the base of Step D is at least one selected form the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaHCO₃.
35. The method of any one of the preceding embodiments, wherein the base of Step D includes ammonia aqueous solution for pre-treating the compound of Formula (VII').
36. The method of any one of the preceding embodiments, wherein the base of Step D includes TEA during reaction with acid chloride.
37. The method of any one of the preceding embodiments, wherein the amount of acid chloride in Step D is 1 molar equivalent or more with respect to the compound of Chemical Formula (VII).
38. The method of any one of the preceding embodiments, wherein the amount of acid chloride in Step D is 1.5 to 3.0 molar equivalent with respect to the compound of Chemical Formula (VII).
39. The method of any one of the preceding embodiments, wherein the reaction temperature of Step D is 1 to 30 °C, and the reaction time is 1 to 30 hours.
40. The method of any one of the preceding embodiments, wherein the reaction temperature of Step D is below 20 °C, and the reaction time is 5 to 15 hours.
41. The method of any one of the preceding embodiments, wherein Step E includes at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaHCO₃.
42. The method of any one of the preceding embodiments, wherein Step E includes LiOH as inorganic base.
43. The method of any one of the preceding embodiments, wherein Step E includes an acidic workup.
44. The method of any one of the preceding embodiments, wherein the reaction temperature of Step E is 1 to 30 °C, and the reaction time is 1 to 30 hours.
45. The method of any one of the preceding embodiments, wherein the reaction temperature of Step E is 1 to 20 °C, and the reaction time is 1 to 10 hours.

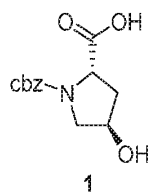
46. The method of any one of the preceding embodiments, wherein the coupling agent of Step F is selected from the group consisting of N,N'-disubstituted carbodiimides such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; phosphonium reagents such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidiny)-phosphonium hexafluorophosphate (PyOxim), and 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); and aminium/uronium reagents such as 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminoxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU).
47. The method of any one of the preceding embodiments, wherein the coupling agent of Step F is ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl).
48. The method of any one of the preceding embodiments, wherein the coupling agent of Step F is used in an amount of 1 to 2 equivalents with respect to the compound of Chemical Formula (IX).
49. The method of any one of the preceding embodiments, wherein the additive of Step F is selected from the group consisting of 1-hydroxybenzotriazole (HOBt) and its derivatives such as hydroxy-3,4-dihydro-4-oxo-1,2,3-benzo-triazine (HOOBt), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), resin-supported derivatives, and hydrates thereof; N-hydroxysuccinimide (NHS); and 4-dimethylpyridine (DMAP).
50. The method of any one of the preceding embodiments, wherein the additive of Step F is 1-hydroxybenzotriazole (HOBt) or its hydrate (HOBt·H₂O).
51. The method of any one of the preceding embodiments, wherein the additive of Step F is used in an amount of 0.01 to 2 equivalents with respect to the compound of Chemical Formula (IX).
52. The method of any one of the preceding embodiments, wherein the base of Step F is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

53. The method of any one of the preceding embodiments, wherein the base of Step F is DIPEA.
54. The method of any one of the preceding embodiments, wherein the reaction temperature of Step F is 1 to 30 °C, and the reaction time is 1 to 30 hours.
55. The method of any one of the preceding embodiments, wherein the reaction temperature of Step F is 1 to 20 °C, and the reaction time is 1 to 8 hours.
56. The method of any one of the preceding embodiments, wherein the hydrogenation catalyst of Step G is at least one selected from the group consisting of Pd/C, Pd(OH)₂, Pd(OAc)₂, PdCl₂ and Pd.
57. The method of any one of the preceding embodiments, wherein the hydrogenation catalyst of Step G is Pd/C.
58. The method of any one of the preceding embodiments, wherein the reaction temperature of Step G is 1 to 50 °C, and the reaction time is 1 to 30 hours.
59. The method of any one of the preceding embodiments, wherein the deprotecting acid solution of Step G is HCl aqueous solution of >10% (w/w) concentration.
60. The method of any one of the preceding embodiments, wherein the deprotecting acid solution of Step G is HCl aqueous solution of >30% (w/w) concentration.
61. A method for preparing a compound of Formula (XI):

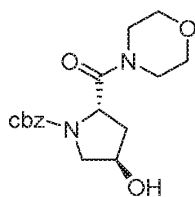


(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

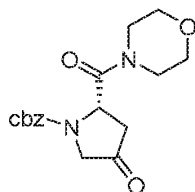
wherein R₁ is C₂-C₅ alkyl, comprising Step H of reacting Compound **1**



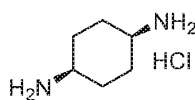
with morpholine to form Compound **9**:

**9**

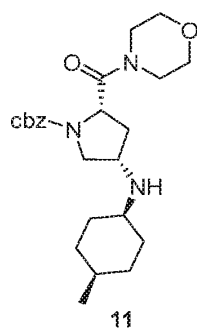
62. The method of any one of the preceding embodiments, wherein Step H is facilitated by a coupling agent.
63. The method of any one of the preceding embodiments, wherein Step H is further facilitated by a reaction accelerating additive.
64. The method of any one of the preceding embodiments, wherein Step H includes the use of base.
65. The method of any one of the preceding embodiments, wherein the method further comprises Step I of reacting Compound **9** with an oxidizing agent in a solvent to form Compound **10**:

**10**

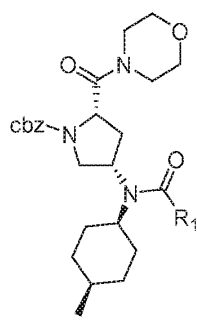
66. The method of any one of the preceding embodiments, wherein the method further comprises Step J of reacting Compound **10** with Compound **12**:

**12**

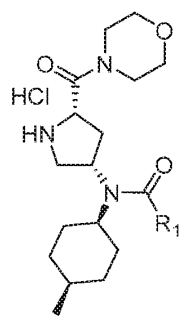
, base, and reducing agent in a solvent to form Compound **11**:



67. The method of any one of the preceding embodiments, wherein the method further comprises Step K of reacting Compound **11** with at least one base and an acid chloride compound of formula $R_1-C(=O)-Cl$ (e.g. isobutyryl chloride) to form a compound of Formula (X):



68. The method of any one of the preceding embodiments, wherein the method further comprises Step G of reacting a compound of Formula (X) in a solvent with a hydrogenation catalyst and H_2 or with deprotecting acid solution, and treatment with HCl solution to form a compound of Formula (II):



69. The method of any one of the preceding embodiments, wherein the coupling agent of Step H is selected from the group consisting of N,N'-disubstituted carbodiimide such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide

(DCC), diisopropylcarbodiimide (DIC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; phosphonium reagents such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidiny)-phosphonium hexafluorophosphate (PyOxim), and 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); and aminium/uronium reagents such as 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminoxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU).

70. The method of any one of the preceding embodiments, wherein the coupling agent of Step H is ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl).

71. The method of any one of the preceding embodiments, wherein the coupling agent of Step H is used in an amount of 1 to 2 equivalents with respect to Compound 1.

72. The method of any one of the preceding embodiments, wherein the additive of Step H is selected from the group consisting of 1-hydroxybenzotriazole (HOBt) and its derivatives such as hydroxy-3,4-dihydro-4-oxo-1,2,3-benzo-triazine (HOObt), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), resin-supported derivatives, and hydrates thereof; N-hydroxysuccinimide (NHS); and 4-dimethylpyridine (DMAP).

73. The method of any one of the preceding embodiments, wherein the additive of Step H is 1-hydroxybenzotriazole (HOBt) or its hydrate (HOBt·H₂O).

74. The method of any one of the preceding embodiments, wherein the additive of Step H is used in an amount of 0.01 to 2 equivalents with respect to the compound of Chemical Formula (IX).

75. The method of any one of the preceding embodiments, wherein the base of Step H is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

76. The method of any one of the preceding embodiments, wherein Step H does not contain any base among the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and

Na₂CO₃.

77. The method of any one of the preceding embodiments, wherein the reaction temperature of Step H is 1 to 30 °C, and the reaction time is 1 to 30 hours.

78. The method of any one of the preceding embodiments, wherein the reaction temperature of Step H is 1 to 20 °C, and the reaction time is 1 to 8 hours.

79. The method of any one of the preceding embodiments, wherein the solvent of Step I is water and at least one organic solvent selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

80. The method of any one of the preceding embodiments, wherein the solvent of Step I is water and dichloromethane.

81. The method of any one of the preceding embodiments, wherein the solvent of Step H, Step J, and/or Step K is at least one independently selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

82. The method of any one of the preceding embodiments, wherein the oxidizing agent of Step I is a combination of a chromic acid compound; a co-oxidizing agent, (2,2,6,6-tetramethylpiperidinyloxy) free radical (TEMPO) and other salts; a complex of dimethyl sulfoxide and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride or phosphorus pentoxide or a complex of pyridine-sulfuric anhydride; or a combination of a transition metal catalyst and oxygen, or a transition metal catalyst and an organic oxidizing agent.

83. The method of any one of the preceding embodiments, wherein the oxidizing agent of Step I is (2,2,6,6-tetramethylpiperidinyloxy) free radical (TEMPO) and other salts.

84. The method of any one of the preceding embodiments, wherein the other salts referenced include at least one of sodium bromide and sodium hypochlorite.

85. The method of any one of the preceding embodiments, wherein Step I includes at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaHCO₃.

86. The method of any one of the preceding embodiments, wherein Step I includes NaHCO₃.

87. The method of any one of the preceding embodiments, wherein Step I is performed with reaction temperature between -10 and 10 °C, and the reaction time is 0.5 h or longer.
88. The method of any one of the preceding embodiments, wherein the reducing agent of Step J is at least one inorganic base selected from the group consisting of $\text{NaBH}(\text{OAc})_3$, NaBH_4 , $\text{NaBH}(\text{CN})_3$, NaBH_3CN , and NaH_2PO_2 .
89. The method of any one of the preceding embodiments, wherein the reducing agent of Step J is $\text{NaBH}(\text{OAc})_3$.
90. The method of any one of the preceding embodiments, wherein the amount of reducing agent in Step J is more than 1 equivalent relative to Compound **10**.
91. The method of any one of the preceding embodiments, wherein the amount of reducing agent in Step J is 1.01 to 1.2 equivalents relative to Compound **10**.
92. The method of any one of the preceding embodiments, wherein the base in Step J is selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO_4 , LiOH, NaH, KH, NaOCH_3 , $\text{NaOCH}_2\text{CH}_3$, $\text{NaOC}(\text{CH}_3)_3$, $\text{KOC}(\text{CH}_3)_3$, K_2CO_3 , Na_2CO_3 , and NaOAc.
93. The method of any one of the preceding embodiments, wherein the base in Step J is NaOAc.
94. The method of any one of the preceding embodiments, wherein the reaction temperature of Step J is 1 to 30 °C, and the reaction time is 1 to 30 hours.
95. The method of any one of the preceding embodiments, wherein the reaction temperature of Step J is -5 to 30 °C.
96. The method of any one of the preceding embodiments, wherein the base of Step J is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO_4 , LiOH, NaH, KH, NaOCH_3 , $\text{NaOCH}_2\text{CH}_3$, $\text{NaOC}(\text{CH}_3)_3$, $\text{KOC}(\text{CH}_3)_3$, K_2CO_3 , Na_2CO_3 , and NaHCO_3 .
97. The method of any one of the preceding embodiments, wherein the base of Step J is DIPEA.
98. The method of any one of the preceding embodiments, wherein the base of Step J is TEA.
99. The method of any one of the preceding embodiments, wherein the amount of acid chloride in Step J is 1 molar equivalent or more with respect to the compound of Chemical Formula (VII).
100. The method of any one of the preceding embodiments, wherein the amount of acid chloride in Step J is 1.0 to 3.0 molar equivalent with respect to the compound of Chemical Formula (VII).

101. The method of any one of the preceding embodiments, wherein the reaction temperature of Step J is 1 to 30 °C, and the reaction time is 1 to 30 hours.

102. The method of any one of the preceding embodiments, wherein the reaction temperature of Step J is below 20 °C, and the reaction time is 5 to 15 hours.

103. The method of any one of the preceding embodiments, wherein the hydrogenation catalyst of Step G is at least one selected from the group consisting of Pd/C, Pd(OH)₂, Pd(OAc)₂, PdCl₂ and Pd.

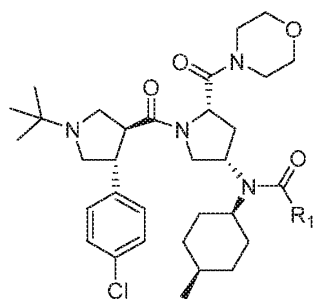
104. The method of any one of the preceding embodiments, wherein the hydrogenation catalyst of Step G is Pd/C.

105. The method of any one of the preceding embodiments, wherein the reaction temperature of Step G is 1 to 50 °C, and the reaction time is 1 to 30 hours.

106. The method of any one of the preceding embodiments, wherein the deprotecting acid solution of Step G is HCl aqueous solution of >10% (w/w) concentration.

107. The method of any one of the preceding embodiments, wherein the deprotecting acid solution of Step G is HCl aqueous solution of >30% (w/w) concentration.

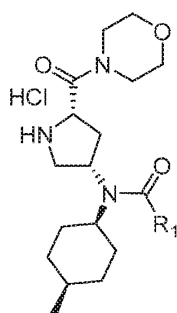
108. A method for preparing a compound of Formula (XI) according to any one of the preceding embodiments:



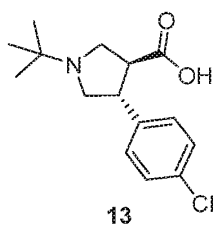
(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

comprising Step M of reacting a compound of Formula (II):

Formula (II):



(II), or a conjugate base, or a solvate thereof, with Compound **13**:



, or a salt, or a solvate thereof,

wherein R₁ is C₂-C₅ alkyl.

109. The method of any one of the preceding embodiments, wherein Step M is facilitated by a coupling agent.

110. The method of any one of the preceding embodiments, wherein Step M is further facilitated by a reaction accelerating additive.

111. The method of any one of the preceding embodiments, wherein Step M includes the use of base.

112. The method of any one of the preceding embodiments, wherein the coupling agent of Step M is selected from the group consisting of N,N'-disubstituted carbodiimide such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; phosphonium reagents such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim), and 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); and aminium/uronium reagents such as 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-

yl)-N,N,N',N'-tetramethylammonium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminooxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU).

113. The method of any one of the preceding embodiments, wherein the coupling agent of Step M is ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl).

114. The method of any one of the preceding embodiments, wherein the coupling agent of Step M is used in an amount of 1 to 2 equivalents with respect to Compound 1.

115. The method of any one of the preceding embodiments, wherein the additive of Step M is selected from the group consisting of 1-hydroxybenzotriazole (HOBt) and its derivatives such as hydroxy-3,4-dihydro-4-oxo-1,2,3-benzo-triazine (HOObt), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), resin-supported derivatives, and hydrates thereof; N-hydroxysuccinimide (NHS); and 4-dimethylpyridine (DMAP).

116. The method of any one of the preceding embodiments, wherein the additive of Step M is 1-hydroxybenzotriazole (HOBt) or its hydrate (HOBt·H₂O).

117. The method of any one of the preceding embodiments, wherein the additive of Step M is used in an amount of 0.01 to 2 equivalents with respect to the compound of Chemical Formula (II).

118. The method of any one of the preceding embodiments, wherein the base of Step M is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

119. The method of any one of the preceding embodiments, wherein Step M does not contain any base among the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

120. The method of any one of the preceding embodiments, wherein the reaction temperature of Step M is -10 to 30 °C, and the reaction time is 0.5 to 30 hours.

121. The method of any one of the preceding embodiments, wherein the reaction temperature of Step M is 1 to 25 °C, and the reaction time is 0.5 to 6 hours.

122. The method of any one of the preceding embodiments, wherein the reaction solvent of Step M is selected from the group consisting of ethyl ether, tetrahydrofuran, dioxane, dichloromethane, chloroform, methyl acetate, ethyl acetate, isopropyl acetate, acetone, methyl ethyl ketone, acetonitrile, propionitrile, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, and a

mixed solvent thereof.

123. The method of any one of the preceding embodiments, wherein the reaction solvent of Step M is acetone.

124. The method of any one of the preceding embodiments, wherein Step M further comprises crystallization of the synthesized compound of Formula (XI).

125. The method of any one of the preceding embodiments, wherein the crystallization step of Step M is comprised of the following steps:

a) concentrating the synthesized compound of Formula (XI), dissolving the concentrated residue using a solvent, and then washing it using a washing solvent;

b) separating an aqueous layer from the product of Step a) above, concentrating the separated aqueous layer, adding H₂O, and then cooling it; and

c) adding a base aqueous solution dropwise and stirring to obtain a crystallized compound of Formula (XI).

126. The method of any one of the preceding embodiments, wherein the cooling temperature in Step b) is -10 to 30 °C.

127. The method of any one of the preceding embodiments, wherein the cooling temperature in Step b) is 0 to 5 °C.

128. The method of any one of the preceding embodiments, wherein the base aqueous solution of Step c) is an aqueous solution containing at least one base selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

129. The method of any one of the preceding embodiments, wherein the base aqueous solution of Step c) is an aqueous solution containing NaOH.

130. The method of any one of the preceding embodiments, wherein the stirring time of Step c) is 0.5 to 24 h.

131. The method of any one of the preceding embodiments, wherein the stirring time of Step c) is 1 to 6 h.

132. The method of any one of the preceding embodiments, wherein Step M further comprises a step of filtering, washing, or drying the product.

133. The method of any one of the preceding embodiments, wherein the method further comprises Step N of purifying a compound of Formula (XI), a pharmaceutically acceptable salt thereof, or a solvate thereof.

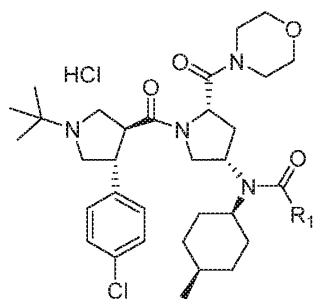
134. The method of any one of the preceding embodiments, wherein Step N comprises dissolving the compound of Formula (XI) in an organic solvent or organic solvent mixture, stirring the mixture, cooling it, and stirring the mixture again to obtain purified precipitate.

135. The method of any one of the preceding embodiments, wherein the organic solvent of Step N is selected from the group consisting of acetone, acetonitrile, dichloromethane, dimethylformamide, dimethylacetamide, dimethylpropyleneurea, dimethylsulfoxide, ethyl acetate, hexamethylphosphoramide, tetrahydrofuran, methyl-tert-butyl ether, pentane, hexane, heptane, ether, toluene, methyl acetate, isopropyl acetate, alcohols with 1 to 6 carbon atoms, diethyl ether, dichloromethane, chloroform, and a mixture thereof.

136. The method of any one of the preceding embodiments, wherein the organic solvent of Step N is selected from the group consisting of acetone, pentane, hexane, heptane, or a mixture thereof.

137. The method of any one of the preceding embodiments, wherein the first stirring time of Step 2) of Step N is 10 hours or more, the cooling temperature after stirring is 0 to 10 °C, and the second stirring time is 0.5 to 2 hours.

138. The method of any one of the preceding embodiments, wherein the method further comprises Step O of reacting a compound of Formula (XI) generated from Step M with HCl without an additional purification process to prepare a compound of Formula (XII):



(XII), a pharmaceutically acceptable salt thereof, or a solvate thereof.

wherein R₁ is a C₂-C₅ alkyl group.

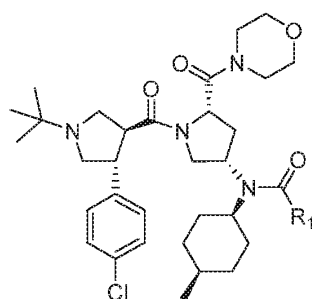
139. The method of any one of the preceding embodiments, wherein Step O is carried out through the preparation of the compound of Formula (XII) by reacting the crude compound of Chemical Formula (XI) generated in Step M with HCl in an organic solvent without an additional purification

process.

140. The method of any one of the preceding embodiments, wherein the organic solvent is selected from the group consisting of acetone, acetonitrile, dichloromethane, dimethylformamide, dimethylpropyleneurea, dimethylsulfoxide, ethyl acetate, hexamethylphosphoamide, tetrahydrofuran, methyl-tert-butylether, pentane, hexane, heptane, ether, diethylether, and a mixed solvent thereof.

141. The method of any one of the preceding embodiments, wherein the reaction temperature of Step O is -20°C to 100°C , and the reaction time is 10 minutes or more.

142. A method for preparing a compound of Formula (XI) according to any one of the preceding embodiments:



(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein R_1 is $\text{C}_2\text{-C}_5$ alkyl, comprising Step P of preparing crystalline Form III particles of a compound of Formula (XI) and wherein

the crystalline Form III has the following diffraction angles (2θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among $6.62\pm 0.2^{\circ}$, $7.44\pm 0.2^{\circ}$, $9.18\pm 0.2^{\circ}$, $9.89\pm 0.2^{\circ}$, $10.83\pm 0.2^{\circ}$, $11.42\pm 0.2^{\circ}$, $12.92\pm 0.2^{\circ}$, $14.61\pm 0.2^{\circ}$, $15.36\pm 0.2^{\circ}$, $15.79\pm 0.2^{\circ}$, $15.95\pm 0.2^{\circ}$, $17.37\pm 0.2^{\circ}$, $18.20\pm 0.2^{\circ}$, $18.99\pm 0.2^{\circ}$, $19.34\pm 0.2^{\circ}$, $19.69\pm 0.2^{\circ}$, $20.40\pm 0.2^{\circ}$, $21.66\pm 0.2^{\circ}$, $21.98\pm 0.2^{\circ}$, $22.45\pm 0.2^{\circ}$, $22.85\pm 0.2^{\circ}$, $24.66\pm 0.2^{\circ}$, $25.52\pm 0.2^{\circ}$, $26.55\pm 0.2^{\circ}$, $28.08\pm 0.2^{\circ}$, $29.31\pm 0.2^{\circ}$ and $29.54\pm 0.2^{\circ}$;

143. The method of any one of the preceding embodiments, wherein Step P is comprised of:

- (a) preparing a mixed solution by dissolving the compound of Formula (XI) in a crystallization solvent comprising water or a mixture of water and an organic solvent;
- (b) crystallizing by adding HCl dropwise to the solution; and
- (c) maturing the solution.

144. The method of any one of the preceding embodiments, wherein the organic solvent of the

crystallization solvent of Step P is a polar aprotic organic solvent.

145. The method of any one of the preceding embodiments, wherein the polar aprotic organic solvent comprises ethyl acetate, methyl isobutylketone, dimethylsulfoxide, tetrahydrofuran, acetone, dimethylformamide, acetonitrile, and the mixtures thereof.

146. The method of any one of the preceding embodiments, wherein the dropwise addition of HCl is administered through a 4 M HCl solution, a 6 N HCl solution, or a concentrated HCl (conc. HCl) solution in water or ethyl acetate.

147. The method of any one of the preceding embodiments, wherein for Step P, the dropwise addition of HCl is administered in an amount of 1 equivalent or less to the compound of Formula (XI).

148. The method of any one of the preceding embodiments, wherein for Step P, the crystallization solvent is a mixed solvent in which water and an organic solvent are mixed in a volume ratio of 1:20 to 1:40.

149. The method of any one of the preceding embodiments, wherein for Step P, the crystallization solvent is a mixed solvent in which water and an organic solvent are mixed in a volume ratio of 1:27 to 1:32.

150. The method of any one of the preceding embodiments, wherein for Step P, HCl addition is performed at 15 °C to 25 °C,

151. The method of any one of the preceding embodiments, wherein for Step P, maturing the solution is performed at 10 °C to 20 °C.

152. The method of any one of the preceding embodiments, wherein for Step P, maturing the solution comprises:

(c-1) maturing at 10 °C to 15 °C until filtrate area decreases to 80% to 85% of the initial area; and

(c-2) maturing by raising the temperature to 20 °C until the filtrate area no longer decreases.

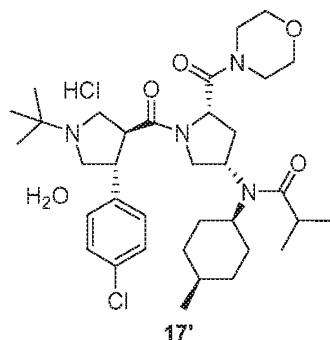
153. The method of any one of the preceding embodiments, wherein Step P further comprises:

(d) filtering the solution.

154. The method of any one of the preceding embodiments, wherein the crystalline Form III particles formed by Step P are crystalline form particles of a solvate of the hydrochloride salt of the compound of Formula (XI).

155. The method of any one of the preceding embodiments, wherein the solvate is a hydrate.

156. The method of any one of the preceding embodiments, wherein the compound of Formula (XI) is Compound **17'**:



157. The method of any one of the preceding embodiments, wherein the crystalline Form III particles have a flow function value of at least 8 under a pressure of 9 kPa.

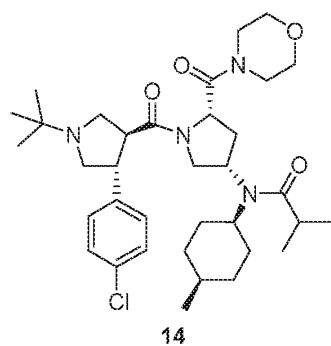
158. A crystalline Form III particle of a compound of Formula (XI), a pharmaceutically acceptable salt thereof, or a solvate thereof, prepared by the preparation method according to any one of the preceding embodiments, wherein

the crystalline Form III has the following diffraction angles (2θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among $6.62 \pm 0.2^\circ$, $7.44 \pm 0.2^\circ$, $9.18 \pm 0.2^\circ$, $9.89 \pm 0.2^\circ$, $10.83 \pm 0.2^\circ$, $11.42 \pm 0.2^\circ$, $12.92 \pm 0.2^\circ$, $14.61 \pm 0.2^\circ$, $15.36 \pm 0.2^\circ$, $15.79 \pm 0.2^\circ$, $15.95 \pm 0.2^\circ$, $17.37 \pm 0.2^\circ$, $18.20 \pm 0.2^\circ$, $18.99 \pm 0.2^\circ$, $19.34 \pm 0.2^\circ$, $19.69 \pm 0.2^\circ$, $20.40 \pm 0.2^\circ$, $21.66 \pm 0.2^\circ$, $21.98 \pm 0.2^\circ$, $22.45 \pm 0.2^\circ$, $22.85 \pm 0.2^\circ$, $24.66 \pm 0.2^\circ$, $25.52 \pm 0.2^\circ$, $26.55 \pm 0.2^\circ$, $28.08 \pm 0.2^\circ$, $29.31 \pm 0.2^\circ$ and $29.54 \pm 0.2^\circ$; and

the crystalline Form III particle has a flow function value of at least 8 under a pressure of 9 kPa.

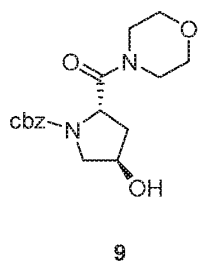
159. A pharmaceutical composition for preventing or treating obesity, diabetes, inflammation or erectile dysfunction, comprising the crystalline Form III particle according to any one of the preceding embodiments and a pharmaceutically acceptable carrier.

160. The method of any one of the preceding embodiments, wherein the compound of Formula (XI) is Compound **14**:

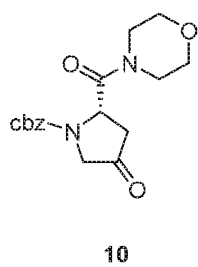


, or a pharmaceutically acceptable salt, or a solvate thereof.

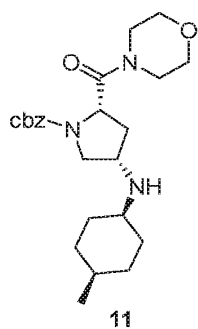
161. The Compound **9**:



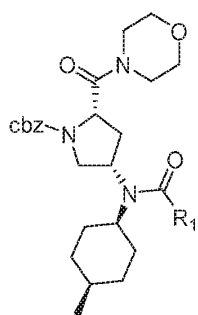
162. The Compound **10**:



163. The Compound **11**:

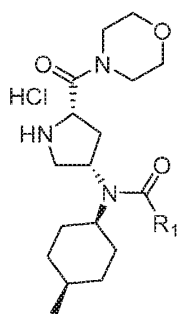


164. A compound of Formula (X) according to any one of the preceding embodiments:



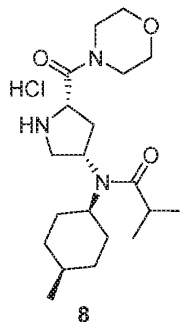
(X), wherein R₁ is C₂-C₅ alkyl.

165. A compound of Formula (II) according to any one of the preceding embodiments:

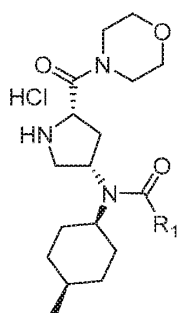


(II), wherein R₁ is C₂-C₅ alkyl.

166. A compound of Formula (II) according to any one of the preceding embodiments, wherein R₁ is isopropyl, e.g., Compound 8:

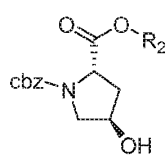


167. A method for preparing Formula (II):

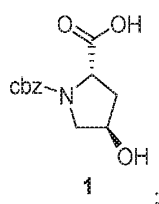


(II), including the steps of:

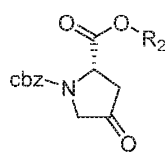
- 1) Preparing a compound of Formula (IV):



(IV), through an alkylation reaction by adding an alcohol having 1 to 6 carbon atoms and an acid catalyst to Compound **1**:

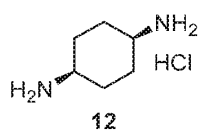


- 2) Preparing a compound of Formula (V):



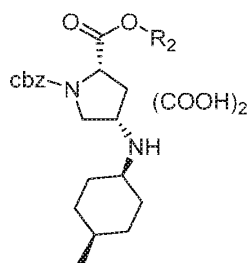
(V), by oxidizing the compound of Formula (IV) obtained in Step 1) above with an oxidizing agent in a solvent;

- 3) Introducing a Compound **12**:



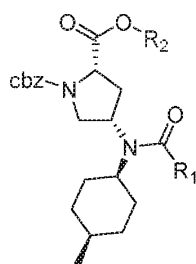
adding a compound of Formula (V) dissolved in the organic solvent dropwise, stirring, and performing a reductive amination reaction, concentrating and obtaining a synthesized crude compound, adding an organic solvent to the residue of the crude compound to prepare a crude compound/organic solvent solution, and adding this

solution dropwise to a solution in which oxalic acid is dissolved in an organic solvent to obtain a compound of Formula (VII):



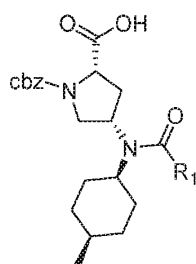
(VII), which is an oxalate of the crude compound;

- 4) Adding an organic solvent to the compound of Formula (VII) prepared in Step 3) above, adjusting the pH with a base, adding water to separate the layers, extracting the aqueous layer with the organic solvent, adding a base after dissolving the resulting residue obtained after washing, concentrating, and azeotroping along with the oil layer in an organic solvent, and adding $R_1-C(=O)-Cl$ dropwise to perform an N-acylation reaction to prepare a compound of Formula (VIII):



(VIII);

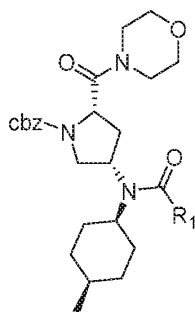
- 5) Adding an alcohol having 1 to 6 carbon atoms and an organic solvent to the compound of Formula (VIII) and then performing dealkylation by adding a solution containing an inorganic base dropwise to prepare a crude compound of Formula (IX):



(IX);

- 6) Adding an organic solvent to the crude compound of Formula (IX) prepared in Step 5) above and dissolving it, sequentially adding a reaction accelerating additive, a

base, and a coupling agent, and then adding morpholine dropwise to prepare a compound of Formula (X):



- 7) Dissolving the compound of Formula (X) prepared in Step 6) above in an alcohol having 1 to 6 carbon atoms, deprotecting it by adding Pd/C and H₂, and adding HCl dissolved in ethyl acetate dropwise to synthesize the compound of Formula (II);

wherein in the above Formulas, R₁ is C₂-C₅ alkyl and R₂ is C₁-C₆ alkyl.

168. The preparation method of any one of the preceding embodiments, wherein the alcohol having 1 to 6 carbon atoms in Step 1), 5) or 7) above is methanol, ethanol, propanol, isopropanol or butanol.

169. The preparation method of any one of the preceding embodiments, wherein the acid catalyst of Step 1) above is at least one selected from the group consisting of HCl, H₂SO₄, H₂SO₄ and KF, and a combination of Al₂O₃ (KF+Al₂O₃).

170. The preparation method of any one of the preceding embodiments, wherein the content of the acid catalyst of Step 1) above is 0.1 to 1 equivalent with respect to the Compound 1.

171. The preparation method of any one of the preceding embodiments, wherein the reaction time of Step 1) above is 2 to 5 hours.

172. The preparation method of any one of the preceding embodiments, wherein the solvent of Step 2) above is water and at least one organic solvent selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile, dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

173. The preparation method of any one of the preceding embodiments, wherein the organic solvent of Step 3), 4), 5) or 6) above is at least one selected from the group consisting of alcohol,

toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

174. The preparation method of any one of the preceding embodiments, wherein the oxidizing agent of Step 2) above is a combination of a chromic acid compound; a co-oxidizing agent, (2,2,6,6-tetramethylpiperidinyloxy) free radical (TEMPO) and other salts; a complex of dimethyl sulfoxide and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride or phosphorus pentoxide or a complex of pyridine-sulfuric anhydride; or a combination of a transition metal catalyst and oxygen, or a transition metal catalyst and an organic oxidizing agent.

175. The preparation method of any one of the preceding embodiments, wherein the base of Step 2) above is at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

176. The preparation method of any one of the preceding embodiments, wherein the reaction temperature of Step 2) above is -10 °C to 10 °C, and the reaction time is 0.5 hour or longer.

177. The preparation method of any one of the preceding embodiments, wherein the reducing agent of Step 3) above is at least one inorganic base selected from the group consisting of NaBH(OAc)₃, NaBH₄, and NaBH(CN)₃.

178. The preparation method of any one of the preceding embodiments, wherein the reaction temperature of Step 3) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

179. The preparation method of any one of the preceding embodiments, wherein the base of Step 4) above is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

180. The preparation method of any one of the preceding embodiments, wherein the content of R₁-C(=O)-Cl in Step 4) above is 1 equivalent or more with respect to the compound of Chemical Formula (VII).

181. The preparation method of any one of the preceding embodiments, wherein the reaction temperature of Step 4) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

182. The preparation method of any one of the preceding embodiments, wherein the inorganic base in Step 5) above is at least one selected from the group consisting of KOH, NaOH, CaSO₄, LiOH,

NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

183. The preparation method of any one of the preceding embodiments, wherein the reaction temperature of Step 5) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

184. The preparation method of any one of the preceding embodiments, wherein the coupling agent of Step 6) above is an N,N'-disubstituted carbodiimide such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, or alkoxyacetylene.

185. The preparation method of any one of the preceding embodiments, wherein the coupling agent is used in an amount of 1 to 2 equivalents with respect to the compound of Chemical Formula (IX).

186. The method of any one of the preceding embodiments, further comprising hydroxybenzotriazole as an additive for increasing reactivity together with a coupling agent.

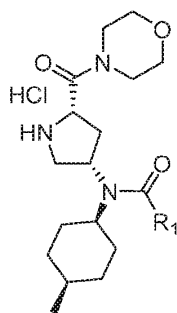
187. The preparation method of any one of the preceding embodiments, wherein the base of Step 6) above is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

188. The preparation method of any one of the preceding embodiments, wherein the reaction temperature of Step 6) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

189. The preparation method of any one of the preceding embodiments, wherein the Pd catalyst of Step 7) above is at least one selected from the group consisting of Pd/C, Pd(OH)₂, Pd(OAc)₂, PdCl₂ and Pd.

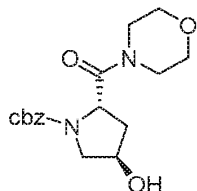
190. The preparation method of any one of the preceding embodiments, wherein the reaction temperature of Step 7) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

191. A method for preparing Formula (II) according to any one of the preceding embodiments:

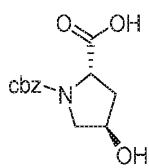


(II), comprising steps of:

- 1) preparing Compound **9**:

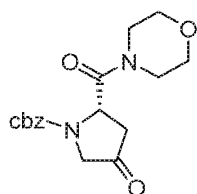
**9**

, by adding an organic solvent, a reaction accelerating additive, a base, and a coupling agent to Compound **1**:

**1**

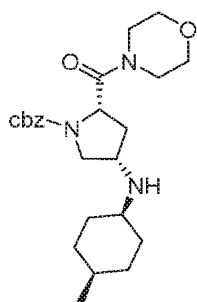
, and then adding morpholine dropwise;

- 2) preparing Compound **10**:

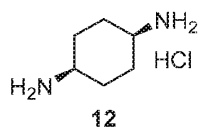
**10**

, by oxidizing the Compound **9** prepared in the Step 1) using an oxidizing agent under the presence of a solvent;

- 3) preparing Compound **11**:

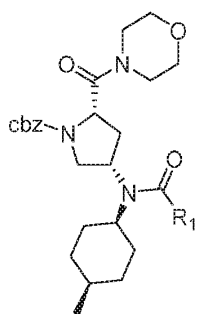
**11**

, by adding Compound **12**:



, and NaOAc to an organic solvent, adding a reducing agent, adding Compound **10** dissolved in the organic solvent dropwise, stirring, and performing a reductive amination reaction;

- 4) preparing a compound of Formula (X):



(X), by adding an organic solvent to Compound **11** prepared in the Step 3), adding $R_1-C(=O)-Cl$ and a base, and performing an N-acylation reaction; and

- 5) synthesizing a compound of Formula (II) by dissolving the compound of Formula (X) prepared in the Step 4) in an alcohol having 1 to 6 carbon atoms, adding Pd/C and H_2 for deprotection, and adding HCl dissolved in ethyl acetate dropwise;

wherein in the above Formulas, R_1 is C_2-C_5 alkyl.

192. The method of any one of the preceding embodiments, wherein the coupling agent of Step 1) is an N,N'-disubstituted carbodiimide such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC); an azolide such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, or alkoxyacetylene.

193. The method of any one of the preceding embodiments, wherein the coupling agent is used in an amount of 1 equivalent or more for the Compound **1**.

194. The method of any one of the preceding embodiments, further comprising hydroxybenzotriazole as an additive for increasing reactivity together with a coupling agent.

195. The method of any one of the preceding embodiments, wherein the reaction temperature of Step 1) is 1 to 30 °C and the reaction time is 1 to 30 hours.

196. The method of any one of the preceding embodiments, wherein the organic solvent of Step 1) is at least one selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile, dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether, and diethyl ether.

197. The method of any one of the preceding embodiments, wherein the oxidizing agent of Step 2) is a chromic acid compound; a combination of a co-oxidizing agent, (2,2,6,6-tetramethylpiperidinyl)oxyl free radical (TEMPO) and other salts; a complex of dimethyl sulfoxide and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride or phosphorus pentoxide or a complex of pyridine-sulfuric anhydride; or a combination of a transition metal catalyst and oxygen, or a transition metal catalyst and an organic oxidizing agent.

198. The method of any one of the preceding embodiments, wherein the base of Step 2) is at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

199. The method of any one of the preceding embodiments, wherein the reaction temperature of Step 2) is -10 to 5 °C and the reaction time is 0.5 hour or longer.

200. The method of any one of the preceding embodiments, wherein the reducing agent of Step 3) is at least one inorganic base selected from the group consisting of NaBH(OAc)₃, NaBH₄, and NaBH(CN)₃.

201. The method of any one of the preceding embodiments, wherein the reaction temperature of Step 3) is 1 to 30 °C and the reaction time is 1 to 30 hours.

202. The method of any one of the preceding embodiments, wherein the organic base of the Step 4) is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, and ammonia.

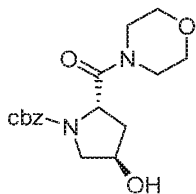
203. The method of any one of the preceding embodiments, wherein the content of R₁-C(=O)-Cl in Step 4) is 1 equivalent or more compared to Compound **11**.

204. The method of any one of the preceding embodiments, wherein the reaction temperature of the 4) is 1 to 30 °C and the reaction time is 1 to 30 hours.

205. The method of any one of the preceding embodiments, wherein the Pd catalyst of the 5) is at least one selected from the group consisting of Pd/C, Pd(OH)₂, Pd(OAc)₂, PdCl₂ and Pd.

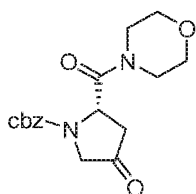
206. The method of any one of the preceding embodiments, wherein the reaction temperature of the 5) is 1 to 30 °C and the reaction time is 1 to 30 hours.

207. The Compound **9** according to any one of the preceding embodiments :



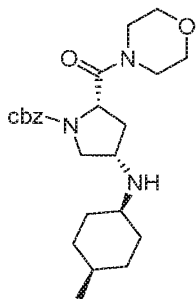
9

208. The Compound **10** according to any one of the preceding embodiments:



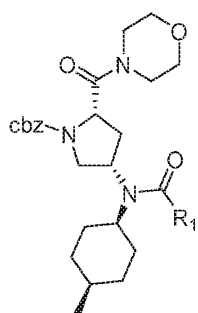
10

209. The Compound **11** according to any one of the preceding embodiments:



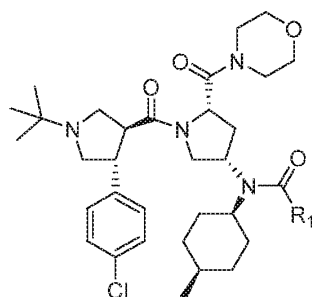
11

210. A compound represented by Formula (X) according to any one of the preceding embodiments:



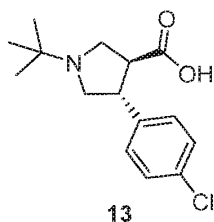
(X), wherein R₁ is C₂-C₅ alkyl.

211.A method for preparing Chemical Formula (XI) according to any one of the preceding embodiments:

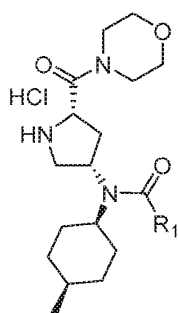


(XI), comprising the steps of:

- 1) reacting Compound **13**:



13, and a compound of Formula (II):



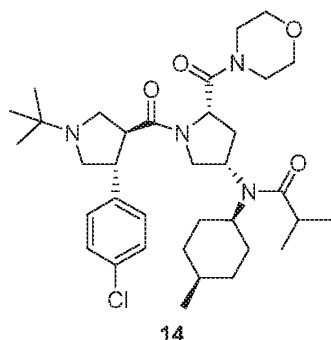
(II), to synthesize a compound of Formula (XI), and then

crystallizing the synthesized compound of Formula (XI); and

- 2) purifying the compound of Formula (XI) obtained in Step 1) above;

wherein in the Formulas above, R₁ is C₂-C₅ alkyl.

212. The preparation method of any one of the preceding embodiments, wherein the compound of Chemical Formula (XI) above is N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidin-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide **14**:



213. The preparation method of any one of the preceding embodiments, wherein the synthesis of Formula (XI) of Step 1) above is carried out by performing acylation reaction between Compound **13** and the compound of Formula (II) in a reaction solvent using a coupling agent.

214. The preparation method of any one of the preceding embodiments, wherein the coupling agent used for the acylation reaction is an N,N'-disubstituted carbodiimides, such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl) and N,N'-dicyclohexylcarbodiimide (DCC); an azolide such as N,N'-carbonyldiimidazole (CDI); and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, or alkoxyacetylene.

215. The preparation method of any one of the preceding embodiments, wherein the coupling agent used for the acylation reaction is used in an amount of 1.0 to 2.0 equivalents relative to Compound **13**.

216. The preparation method of any one of the preceding embodiments, further comprising hydroxybenzotriazole as an additive for increasing reactivity together with a coupling agent.

217. The preparation method of any one of the preceding embodiments, wherein the reaction temperature during the synthesis of the compound of Chemical Formula (XI) in Step 1) above is -10 °C to 30 °C, and the reaction time is 0.5 to 6 hours.

218. The preparation method of any one of the preceding embodiments, wherein the reaction solvent is selected from the group consisting of ethyl ether, tetrahydrofuran, dioxane,

dichloromethane, chloroform, methyl acetate, ethyl acetate, isopropyl acetate, acetone, methyl ethyl ketone, acetonitrile, propionitrile, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, and a mixed solvent thereof.

219. The preparation method of any one of the preceding embodiments, wherein the crystallization step in Step 1) above comprises the following steps of:

- a) concentrating the compound of the synthesized Formula (XI), dissolving the concentrated residue using a solvent, and then washing it using a washing solvent;
- b) separating an aqueous layer from the product of Step a) above, concentrating the separated aqueous layer, adding H₂O, and then cooling it; and
- c) adding a base aqueous solution dropwise and stirring to obtain a crystallized compound of Formula (XI).

220. The preparation method of any one of the preceding embodiments, wherein the cooling temperature in Step b) above is -10 to 30 °C.

221. The preparation method of any one of the preceding embodiments, wherein the base aqueous solution in Step c) above is an aqueous solution containing at least one base selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

222. The preparation method of any one of the preceding embodiments, wherein the stirring time in Step c) above is 0.5 to 24 hours.

223. The preparation method of any one of the preceding embodiments, comprising a step of filtering, washing or drying the product after carrying out Step 1) above.

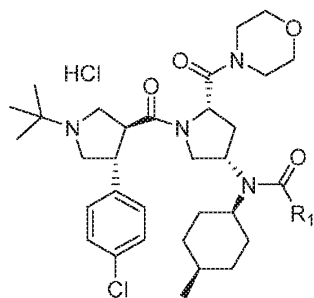
224. The preparation method of any one of the preceding embodiments, wherein Step 2) above is carried out by dissolving the crystallized compound of Formula (XI) produced in Step 1) in an organic solvent, stirring it for the first time, then cooling it, and stirring it for the second time.

225. The preparation method of any one of the preceding embodiments, wherein the organic solvent is selected from the group consisting of acetone, acetonitrile, dichloromethane, dimethylformamide, dimethylpropyleneurea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, tetrahydrofuran, methyl-tert-butyl ether, pentane, hexane, heptane, ether, toluene, methyl acetate, isopropyl acetate, alcohols with 1 to 6 carbon atoms, diethyl ether, and a mixture thereof.

226. The preparation method of any one of the preceding embodiments, wherein the first stirring

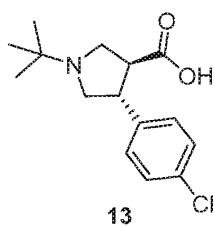
time of Step 2) above is 10 hours or more, the cooling temperature after stirring is 0 to 10 °C, and the second stirring time is 0.5 to 2 hours.

227. A preparation method of Formula (XII) according to any one of the preceding embodiments:

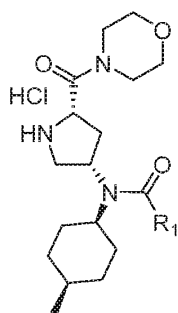


(XII), comprising the steps of:

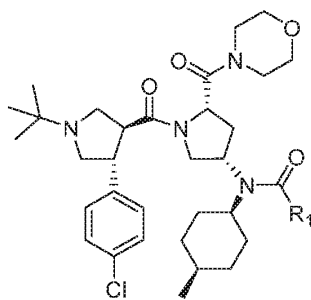
- 1) reacting Compound **13**:



, with a compound of Formula (II):



(II), to synthesize a compound of Formula (XI):



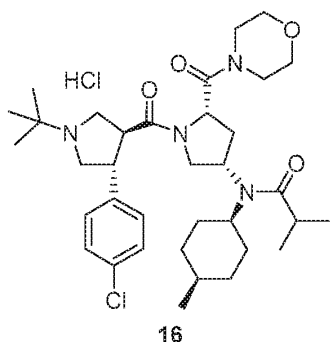
(XI); and

- 2) reacting the compound of Formula (XI) generated in Step 1) with HCl without an

additional purification process to prepare a compound of Formula (XII).

wherein in the above Formulas, R_1 is a C_2 - C_5 alkyl group.

228. A preparation method of any one of the preceding embodiments, wherein the compound of Formula (XII) above is N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidin-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide hydrochloride **16**:



229. A preparation method of any one of the preceding embodiments, wherein Step 1) is carried out by synthesizing the compound of Formula (XI) through an acylation reaction of Compound **13** and the compound of Chemical Formula (II) in a reaction solvent using a coupling agent.

230. A preparation method of any one of the preceding embodiments, wherein the coupling agent used for the acylation reaction may include N,N'-disubstituted carbodiimides such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl) and N,N'-dicyclohexylcarbodiimide (DCC); azolides such as N,N'-carbonyldiimidazole (CDI); and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, oxalyl chloride, or alkoxyacetylenes.

231. A preparation method of any one of the preceding embodiments, wherein the coupling agent used for the acylation reaction is employed in an amount of 1.0 to 2.0 equivalents relative to Compound **13**.

232. A preparation method of any one of the preceding embodiments, further comprising hydroxybenzotriazole as an additive for increasing reactivity with a coupling agent.

233. A preparation method of any one of the preceding embodiments, wherein the reaction temperature of Step 1) is -20 °C to 100 °C, and the reaction time is 0.5 to 24 hours.

234. A preparation method of any one of the preceding embodiments, wherein the reaction solvent is selected from the group consisting of n-hexane, benzene, toluene, ethyl ether, tetrahydrofuran

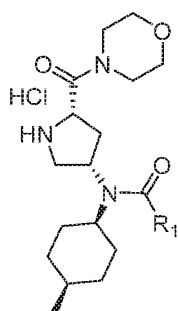
dioxine, methanol, ethanol, dichloromethane, chloroform, ethyl acetate, methylacetate, acetone, methylethylketone, acetonitrile, propionitrile, dimethylformamide, dimethylacetamide, dimethylsulfoxide, and a mixed solvent thereof.

235. A preparation method of any one of the preceding embodiments, wherein Step 2) is carried out through the preparation of the compound of Formula (XII) by reacting the crude compound of Chemical Formula (XI) generated in Step 1) with HCl in an organic solvent without an additional purification process.

236. A preparation method of any one of the preceding embodiments, wherein the organic solvent is selected from the group consisting of acetone, acetonitrile, dichloromethane, dimethylformamide, dimethylpropyleneurea, dimethylsulfoxide, ethyl acetate, hexamethylphosphoamide, tetrahydrofuran, methyl-tert-butylether, pentane, hexane, heptane, ether, diethylether, and a mixed solvent thereof.

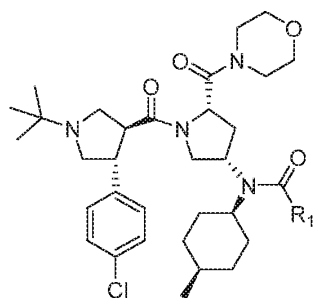
237. A preparation method of any one of the preceding embodiments, wherein the reaction temperature is -20 °C to 100 °C, and the reaction time is 10 minutes or more, in Step 2).

238. A compound represented by the structure of Formula (II):



(II), wherein R₁ is C₂-C₅ alkyl.

239. A method of any one of the preceding embodiments for preparing crystalline Form III particles of a compound of Formula (XI):



(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein R_1 is C_2 - C_5 alkyl, and wherein

the crystalline Form III has the following diffraction angles (2θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among $6.62\pm0.2^\circ$, $7.44\pm0.2^\circ$, $9.18\pm0.2^\circ$, $9.89\pm0.2^\circ$, $10.83\pm0.2^\circ$, $11.42\pm0.2^\circ$, $12.92\pm0.2^\circ$, $14.61\pm0.2^\circ$, $15.36\pm0.2^\circ$, $15.79\pm0.2^\circ$, $15.95\pm0.2^\circ$, $17.37\pm0.2^\circ$, $18.20\pm0.2^\circ$, $18.99\pm0.2^\circ$, $19.34\pm0.2^\circ$, $19.69\pm0.2^\circ$, $20.40\pm0.2^\circ$, $21.66\pm0.2^\circ$, $21.98\pm0.2^\circ$, $22.45\pm0.2^\circ$, $22.85\pm0.2^\circ$, $24.66\pm0.2^\circ$, $25.52\pm0.2^\circ$, $26.55\pm0.2^\circ$, $28.08\pm0.2^\circ$, $29.31\pm0.2^\circ$ and $29.54\pm0.2^\circ$; and

the preparation method comprises:

(a) preparing a mixed solution by dissolving the compound of Formula (XI) in a crystallization solvent comprising water or a mixture of water and an organic solvent;

(b) crystallizing by adding HCl dropwise to the solution; and

(c) maturing the solution.

240. The method of any one of the preceding embodiments, wherein the organic solvent of the crystallization solvent is a polar aprotic organic solvent.

241. The method of any one of the preceding embodiments, wherein the polar aprotic organic solvent comprises ethyl acetate, methyl isobutylketone, dimethylsulfoxide, tetrahydrofuran, acetone, dimethylformamide, acetonitrile, and the mixtures thereof.

242. The method of any one of the preceding embodiments, wherein the dropwise addition of HCl is administered through a 4 M HCl solution or a 6 N HCl solution in concentrated HCl (conc. HCl) solution and ethyl acetate.

243. The method of any one of the preceding embodiments, wherein the dropwise addition of HCl is administered in an amount of 1 equivalent or less to the compound of Formula (XI).

244. The method of any one of the preceding embodiments, wherein the crystallization solvent is a mixed solvent in which water and an organic solvent are mixed in a volume ratio of 1:20 to 1:40.

245. The method of any one of the preceding embodiments, wherein the crystallization solvent is a mixed solvent in which water and an organic solvent are mixed in a volume ratio of 1:27 to 1:32.

246. The method of any one of the preceding embodiments, wherein Step (b) is performed at 15°C to 25°C , and Step (c) is performed at 10°C to 20°C .

247. The method of any one of the preceding embodiments, wherein the (c) comprises:

(c-1) maturing at 10 °C to 15 °C until filtrate area decreases to 80% to 85% of the initial area;
and

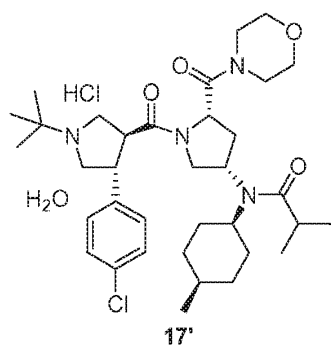
(c-2) maturing by raising the temperature to 20 °C until the filtrate area no longer decreases.

248. The method of embodiment 239 further comprising: (d) filtering the solution.

249. The method of any one of the preceding embodiments, wherein the crystalline Form III particles are crystalline form particles of a solvate of the hydrochloride salt of the compound of Formula (XI).

250. The method of any one of the preceding embodiments, wherein the solvate is a hydrate.

251. The method of any one of the preceding embodiments, wherein the compound of Formula (XI) is Compound **17'**:



252. The method of any one of the preceding embodiments, wherein the crystalline Form III particles have a flow function value of at least 8 under a pressure of 9 kPa.

253. A crystalline Form III particle of a compound of Formula (XI), a pharmaceutically acceptable salt thereof, or a solvate thereof, prepared by the preparation method of any one of the preceding embodiments, wherein

the crystalline Form III has the following diffraction angles (2θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among $6.62\pm0.2^\circ$, $7.44\pm0.2^\circ$, $9.18\pm0.2^\circ$, $9.89\pm0.2^\circ$, $10.83\pm0.2^\circ$, $11.42\pm0.2^\circ$, $12.92\pm0.2^\circ$, $14.61\pm0.2^\circ$, $15.36\pm0.2^\circ$, $15.79\pm0.2^\circ$, $15.95\pm0.2^\circ$, $17.37\pm0.2^\circ$, $18.20\pm0.2^\circ$, $18.99\pm0.2^\circ$, $19.34\pm0.2^\circ$, $19.69\pm0.2^\circ$, $20.40\pm0.2^\circ$, $21.66\pm0.2^\circ$, $21.98\pm0.2^\circ$, $22.45\pm0.2^\circ$, $22.85\pm0.2^\circ$, $24.66\pm0.2^\circ$, $25.52\pm0.2^\circ$, $26.55\pm0.2^\circ$, $28.08\pm0.2^\circ$, $29.31\pm0.2^\circ$ and $29.54\pm0.2^\circ$; and

the crystalline Form III particle has a flow function value of at least 8 under a pressure of 9 kPa.

254.A pharmaceutical composition for preventing or treating obesity, diabetes, inflammation or erectile dysfunction, comprising the crystalline Form III particle of any one of the preceding embodiments and a pharmaceutically acceptable carrier.

EXAMPLES

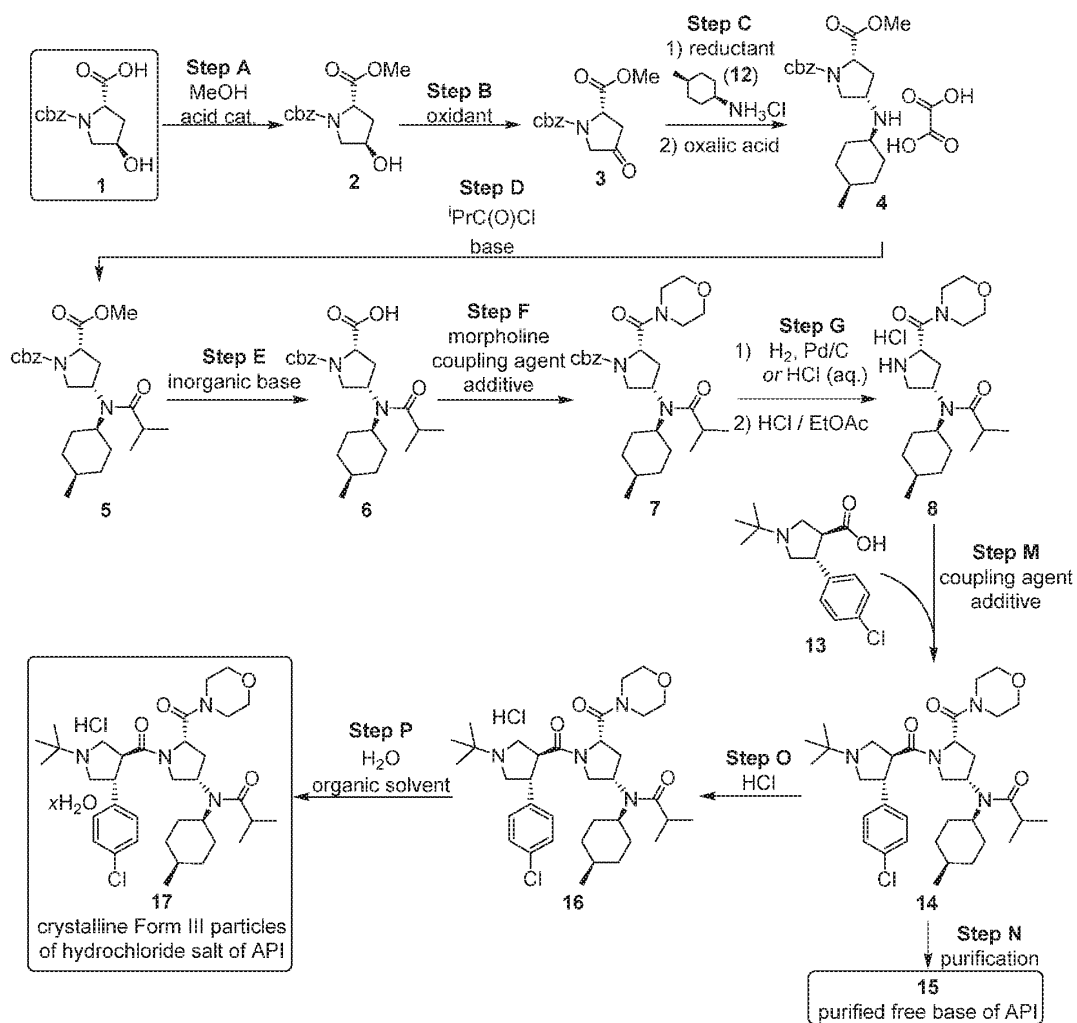
Abbreviations used in the following examples and elsewhere herein are:

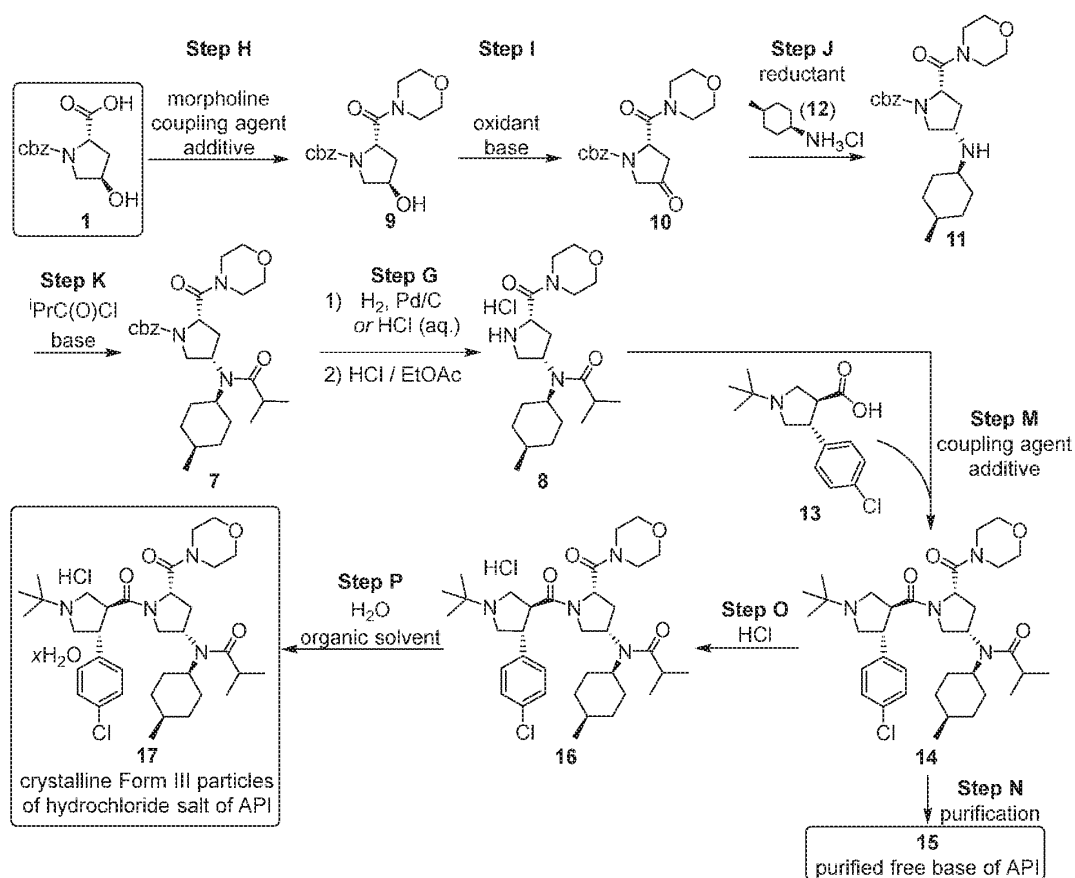
AcOH	acetic acid
API	active pharmaceutical ingredient
aq.	aqueous solution
Boc	tert-butyloxycarbonyl
Bn	benzyl
Bu	butyl
br	broad
cbz	benzyloxycarbonyl
CD ₂ Cl ₂	dichloromethane- <i>d</i> ₂
CD ₃ OD	methanol- <i>d</i> ₄
CDCl ₃	chloroform- <i>d</i>
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
dt	doublet of triplets
DC ₅₀	half maximal degradation concentration
DCM	dichloromethane
DIPEA	diisopropylethylamine or N,N-diisopropylethylamine
D _{max}	maximum level of degradation
DMAc	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EC ₅₀	half maximal effective concentration
EDC•HCl	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

EtOH	ethanol
Et ₂ O	diethyl ether
Et ₃ N	triethylamine
EtOAc	ethyl acetate
h or hr	hour(s)
H ₂	hydrogen (diatomic compound)
H ₂ O	water
H ₂ SO ₄	sulfuric acid
HCl	hydrogen chloride
HOBt•H ₂ O	1-hydroxybenzotriazole hydrate
HPLC	high-performance liquid chromatography
Hz	hertz
g	gram
IC ₅₀	half maximal inhibitory concentration
IPA or ⁱ PrOH	isopropyl alcohol
iPrC(O)Cl	isobutyryl chloride
kg	kilogram
L	liter
LiOH	lithium hydroxide
m	multiplet
M	molar
MTBE	methyl tert-butyl ether
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute(s)
mL	milliliter
mmol	millimole
mol	mole

N	normality
Na ₂ S ₂ O ₃	sodium thiosulfate
NaHCO ₃	sodium bicarbonate
NaBH(OAc) ₃	sodium triacetoxymethylborohydride
NaBr	sodium bromide
NaCl	sodium chloride
NaOAc	sodium acetate
NaOCl	sodium hypochlorite
NaOH	sodium hydroxide
Na ₂ SO ₄	sodium sulfate
n-BuLi	n-butyllithium
NH ₃	ammonia
NMR	nuclear magnetic resonance
PAR	peak area ratio
Pd/C	palladium supported on activated carbon
q	quartet
RH	relative humidity
rt	room temperature
s	singlet
t	triplet
TEA (NEt ₃)	triethylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl free radical
TFA	trifluoroacetic acid
THF	tetrahydrofuran
v/v	volume percentage
w/w	weight percentage

General Synthetic Schemes

Scheme 1. Synthesis of Compound **14**, or salts or solvates thereof, via intermediate Compound **3**.



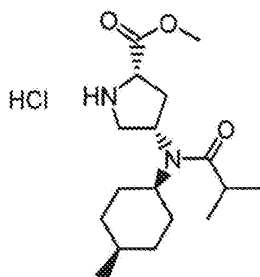
Scheme 2. Synthesis of Compound **14**, or salts or solvates thereof, via intermediate Compound **10**.

General Procedure for Powder X-Ray Diffraction (XRD) Analysis

Powder XRD diffraction patterns were obtained using a PANalytical X'Pert Pro MPD system equipped with a monochromatized radiation source and Ni filter as a solid-state detector according to the following method.

About 20 to 30 mg of sample was placed on a glass sample holder so as to have a flat surface, and the generator of the instrument was set to 45 kV (acceleration voltage) and 40 mA (filament emission), and measurements were made in reflection mode (not-spin). The Bragg angle (2θ) in the range of 4 to 40° was measured under the conditions of a step size of 0.026° and a time per step of 51 seconds.

Preparation Example 1: Preparation of methyl (2S,4S)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate hydrochloride



The title compound was obtained using the method described in International Publication No. WO 2008/007930. Specifically, the title compound was obtained through the following steps A, B, C, D, and E.

Step A: Preparation of 1-(*tert*-butyl) 2-methyl (2S,4S)-4-azidopyrrolidine-1,2-dicarboxylate

1-(*tert*-butyl) 2-methyl (2S,4S)-4-((methylsulfonyl)oxy)pyrrolidine-1,2-dicarboxylate (48.5 g, 150 mmol) was dissolved in *N,N*-dimethylformamide (250 ml) under a nitrogen atmosphere, and sodium azide (19.5 g, 300 ml) was added. After stirring at 80 °C for 16 hours and concentrating the reaction solvent under reduced pressure, water was added and extraction was performed twice using ethyl acetate. The organic layer was washed with aqueous sodium chloride solution and water, then dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain a crude (39.59 g, 98%), which was used in the next step without purification. MS: [M+H] = 271. ¹H NMR (400 MHz, CD₃OD) δ 4.43-4.37 (m, 1H), 4.35-4.27 (br, 1H), 3.77 (s, 1.8H), 3.76 (s, 1.2H), 3.73-3.66 (m, 1H), 3.44-3.38 (m, 1H), 2.63-2.49 (m, 1H), 2.19-2.11 (m, 1H), 1.50 (s, 4.5H), 1.44 (s, 4.5H).

Step B: Preparation of 1-(*tert*-butyl) 2-methyl (2S,4S)-4-aminopyrrolidine-1,2-dicarboxylate

After 1-(*tert*-butyl) 2-methyl (2S,4S)-4-azidopyrrolidine-1,2-dicarboxylate (24.59 g, 91.0 mmol) obtained in step A above was dissolved in tetrahydrofuran (180 ml), 1M trimethylphosphine tetrahydrofuran solution (109.2 ml, 109.2 mmol) was slowly added at 0 °C. Stirring was performed at the same temperature for 1 hour, then at room temperature for 3 hours. After concentrating the reaction solvent under reduced pressure, dichloromethane (100 ml) and water (150 ml) were added and stirred for about 30 minutes. After separating the layers and

extracting once more using dichloromethane, the organic layer was dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure to obtain a crude (20.62 g, 93%), which was used in the next step without purification. MS [M+H] = 245. ¹H NMR (400 MHz, CD₃OD) δ 4.27 (m, 1H), 3.77 (s, 1.8H), 3.76 (s, 1.2H), 3.75-3.67 (m, 1H), 3.50-3.42 (m, 1H), 3.22-3.17 (m, 1H), 2.58-2.47 (m, 1H), 1.82-1.71 (m, 1H), 1.48 (s, 4.5H), 1.42 (s, 4.5H).

Step C: Preparation of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-(((1*S*,4*R*)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (20.62 g, 84.4 mmol) obtained in step B above was dissolved in dichloroethane (150 ml) and 4-methylcyclohexanone (9.5 ml, 101.3 mmol) was added. Sodium triacetoxyborohydride (26.8 g, 126.6 mmol) was added at 0 °C, and stirred at room temperature for 16 hours. The reaction solvent was concentrated under reduced pressure, water was added, and extraction was performed twice using ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, then dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (22.9 g, 80%). MS: [M+H] = 341. ¹H NMR (400 MHz, CD₃OD) δ 4.26 (m, 1H), 3.76 (s, 1.8H), 3.75 (s, 1.2H), 3.78-3.71 (m, 1H), 3.49-3.40 (m, 1H), 3.22-3.16 (m, 1H), 2.69-2.60 (br, 1H), 2.58-2.46 (m, 1H), 1.87-1.77 (m, 1H), 1.73-1.63 (m, 1H), 1.62-1.35 (m, 8H), 1.48 (s, 4.5H), 1.42 (s, 4.5H), 0.96 (d, 3H).

Step D: Preparation of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-(N-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-1,2-dicarboxylate

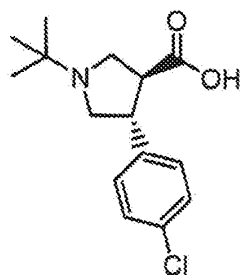
1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-(((1*S*,4*R*)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate (37.29 g, 109.5 mmol) obtained in step C above was dissolved in dichloromethane (500 ml), triethyl amine (61.1 ml, 438.1 mmol) was added, and then isobutyryl chloride (11.7 ml, 219 mmol) was slowly added at 0 °C. After stirring at room temperature for 16 hours, the reaction solvent was concentrated under reduced pressure, then sodium bicarbonate aqueous solution was added and extracted twice using ethyl acetate. The organic layer was washed with aqueous sodium chloride solution and water, then dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (38.79 g, 86%). MS: [M+H] = 411. ¹H NMR (400 MHz, CD₃OD) δ 4.27 (m, 1H), 3.76 (s, 1.8H), 3.75 (s, 1.2H), 3.78-3.72 (m, 1H), 3.50-3.41 (m,

1H), 3.33-3.14 (m, 1H), 2.69-2.60 (m, 2H), 2.57-2.43 (m, 1H), 1.87-1.79 (m, 1H), 1.70-1.61 (m, 1H), 1.60-1.32 (m, 8H), 1.47 (s, 4.5H), 1.41 (s, 4.5H), 1.10 (dd, 6H), 0.99 (d, 3H).

Step E: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate hydrochloride

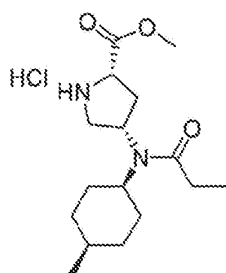
After 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-1,2-dicarboxylate (34.0 g, 82.8 mmol) obtained in step D above was dissolved in dichloromethane (200 ml), 4N HCl 1,4-dioxane solution (82.8 ml, 331.3 mmol) was added at 0 °C. After stirring at room temperature for 6 hours, the reaction solvent was concentrated under reduced pressure to obtain a crude (28.7 g, 99%), which was used in the next step without purification. MS: [M+H] = 311.

Preparation Example 2: Preparation of (3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid



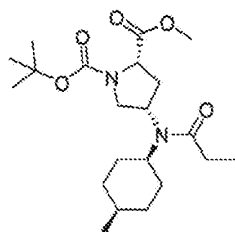
The title compound was obtained using the method described in International Publication No. WO 2004/092126. MS: [M+H] = 282. ¹H NMR (400 MHz, CD₃OD) δ 7.43-7.33 (m, 4H), 3.90-3.69 (m, 3H), 3.59 (dd, J = 11.2, 10.0 Hz, 1H), 3.29 (dd, J = 11.2, 11.2 Hz, 1H), 3.18-3.09 (m, 1H), 1.44 (s, 9H).

Preparation Example 3: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate hydrochloride



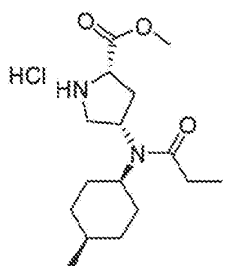
The title compound was obtained through the following steps A and B.

Step A: Preparation of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-1,2-dicarboxylate



The title compound (0.98 g, 84%) was obtained using the same method as in Step D of Preparation Example 1, using 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate (1.0 g, 2.9 mmol) obtained in Step C of Preparation Example 1 and propionyl chloride (0.33 g, 3.5 mmol). MS: $[M+Na] = 419.5$ ($M+23$). 1H NMR (400 MHz, CD_3OD) δ 4.33 (m, 1H), 4.00-3.80 (m, 2H), 3.75 (m, 3H), 3.58 (m, 1H), 3.47 (m, 1H), 2.85-2.68 (m, 1H), 2.38 (q, 2H), 2.31 (m, 1H), 1.93 (m, 1H), 1.80 (m, 2H), 1.72-1.55 (m, 4H), 1.45 (m, 2H), 1.45-1.41 (m, 9H), 1.07 (m, 6H).

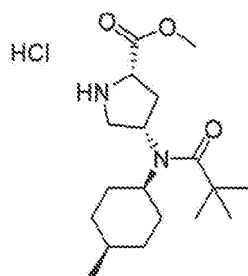
Step B: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate hydrochloride



The title compound (0.76 g, 93%) was obtained using the same method as in Step E of Preparation Example 1, using 1-(*tert*-butyl) 2-methyl(2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-

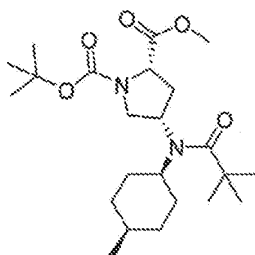
methylcyclohexyl)propionamido)pyrrolidine-1,2-dicarboxylate (0.98 g, 2.4 mmol) obtained in step A above. MS: $[M+H] = 297.4$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.95 (br s, 1H), 8.63 (br s, 1H), 4.38 (m, 1H), 4.21 (m, 1H), 3.77 (s, 3H), 3.53 (m, 1H), 3.40 (m, 2H), 2.53 (m, 1H), 2.37 (q, 2H), 2.24 (m, 1H), 1.88 (m, 1H), 1.68-1.55 (m, 4H), 1.52 (m, 2H), 1.40 (m, 2H), 0.97 (m, 6H).

Preparation Example 4: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate hydrochloride



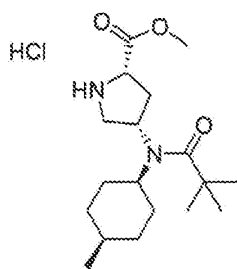
The title compound was obtained through the following steps A and B.

Step A: Preparation of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-1,2-dicarboxylate



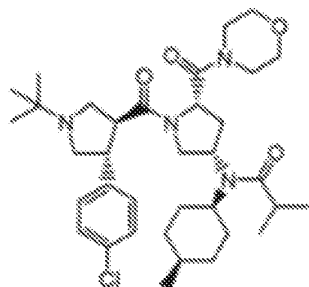
The title compound was obtained using the method described in International Publication No. WO 2008/007930. MS: $[M+Na] = 447.5$ ($M+23$). ^1H NMR (400 MHz, CD_3OD) δ 4.34 (m, 1H), 3.90-3.75 (m, 2H), 3.73 (m, 3H), 3.45 (m, 2H), 2.75-2.60 (m, 1H), 2.30 (m, 1H), 1.95 (m, 1H), 1.85 (m, 2H), 1.66 (m, 4H), 1.50 (m, 2H), 1.45-1.41 (m, 9H), 1.25-1.20 (m, 9H), 1.05 (d, 3H).

Step B: Preparation of methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate hydrochloride



The title compound (0.68 g, 99%) was obtained using the same method as in Step E of Preparation Example 1, using 1-(*tert*-butyl) 2-methyl(2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-1,2-dicarboxylate (0.80 g, 1.88 mmol) obtained in Step A above. MS: [M+H] = 325.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.24 (brs, 1H), 8.60 (brs, 1H), 4.41 (m, 1H), 4.22 (m, 1H), 3.77 (m, 3H), 3.40-3.28 (m, 3H), 2.55 (m, 1H), 2.20 (m, 1H), 1.87 (m, 1H), 1.70-1.50 (m, 6H), 1.40 (m, 2H), 1.21-1.10 (m, 9H), 1.00 (m, 3H)

Preparation Example 5: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*'-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide



The title compound was obtained through the following steps A, B, and C.

Step A: Preparation of methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate

Methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate hydrochloride (28.7 g, 82.73 mmol) obtained in Preparation Example 1, (3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid (24.5 g, 86.87 mmol) obtained in Preparation Example 2, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (22.2 g, 115.83 mmol), and 1-hydroxybenzotriazole hydrate (15.7 g, 115.83 mmol) were dissolved in *N,N*'-

dimethylformamide (400 mL) and *N,N'*-diisopropylethylamine (72.0 ml, 413.66 mmol) was slowly added. After stirring at room temperature for 16 hours and concentrating the reaction solvent under reduced pressure, 0.5N aqueous sodium hydroxide solution was added and extraction was performed twice using ethyl acetate. The organic layer was washed twice with aqueous sodium chloride solution and water, then dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (41.19 g, 87%). MS: [M+H] = 575.

Step B: Preparation of (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylic acid

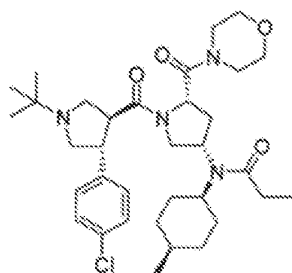
After methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylate (39.4 g, 68.62 mmol) obtained in step A above was dissolved in methanol (450 ml), 6N aqueous sodium hydroxide solution (57.2 ml, 343.09 mmol) was added. After stirring at room temperature for 16 hours and adjusting the pH to about 5 using a 6N aqueous HCl solution, the reaction solution was concentrated under reduced pressure. After dissolving the concentrate in dichloromethane, the insoluble solid was filtered through a paper filter. The filtrate was concentrated under reduced pressure to obtain a crude (38.4 g, 99%), which was used in the next step without purification. MS: [M+H] = 561.

Step C: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide

(2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylic acid (38.4 g, 68.60 mmol) obtained in step B above, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (18.4 g, 96.04 mmol), and 1-hydroxybenzotriazole hydrate (13.0 g, 96.04 mmol) were dissolved in *N,N'*-dimethylformamide (200 ml) and then sequentially morpholine (5.9 ml, 68.80 mmol) and *N,N'*-diisopropylethylamine (59.7 ml, 343.02 mmol) were slowly added. After stirring at room temperature for 16 hours, the reaction solution was concentrated under reduced pressure, 0.5N sodium hydroxide aqueous solution was added, and extraction was performed twice using ethyl acetate. The organic layer was washed twice with aqueous sodium chloride solution and water, then dried and filtered over anhydrous magnesium sulfate. The filtrate was concentrated under

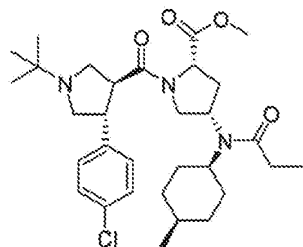
reduced pressure and purified by column chromatography to obtain the title compound (37.05 g, 86%). MS: $[M+H] = 630$.

Preparation Example 6: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide



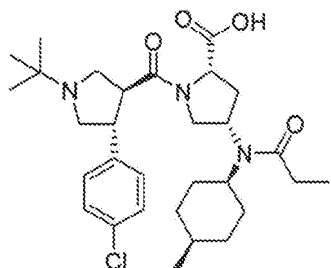
The title compound was obtained through the following steps A, B, and C.

Step A: Preparation of methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate



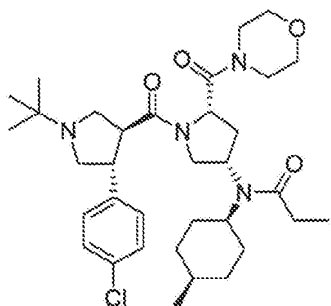
The title compound (0.45 g, 35%) was obtained using the same method as in Step A of Preparation Example 5, using methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate hydrochloride (0.76 g, 2.28 mmol) obtained in Preparation Example 3 and (3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid (0.64 g, 2.28 mmol) obtained in Preparation Example 2. MS: $[M+H] = 560.4$. ^1H NMR (400 MHz, CD_3OD) δ 7.39-7.30 (m, 4H), 4.45 (m, 1H), 4.04 (m, 1H), 3.71 (s, 3H), 3.65-3.35 (m, 6H), 3.13 (m, 2H), 2.99 (m, 1H), 2.71 (m, 1H), 2.34 (q, 2H), 2.20 (m, 1H), 1.92 (m, 1H), 1.75-1.55 (m, 6H), 1.42 (m, 2H), 1.22 (m, 9H), 1.03 (m, 6H).

Step B: Preparation of (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylic acid



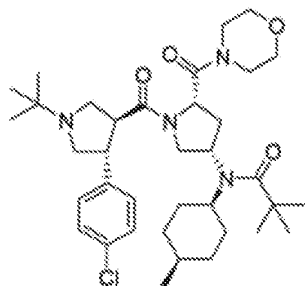
The title compound (0.44 g, 99%) was obtained using the same method as in Step B of Preparation Example 5 using methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylate (0.45 g, 0.80 mmol) obtained in step A above. MS: [M+H] = 546.4.

Step C: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamide



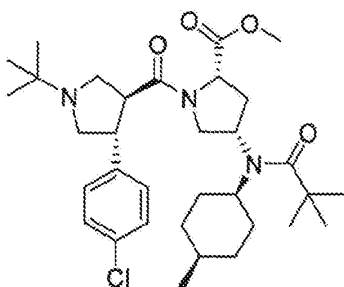
The title compound (0.28g, 53%) was obtained using the same method as in Step C of Preparation Example 5 using (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)propionamido)pyrrolidine-2-carboxylic acid (0.44 g, 0.80 mmol) obtained in Step B above. MS: [M+H] = 615.5. ¹H NMR (400 MHz, CD₃OD) δ 7.36 (m, 4H), 4.79 (m, 1H), 4.18 (m, 1H), 3.80-3.40 (m, 15H), 3.20 (m, 1H), 3.03 (m, 1H), 2.70 (m, 1H), 2.33 (q, 2H), 2.15 (m, 1H), 1.93 (m, 1H), 1.71-1.56 (m, 6H), 1.40-1.20 (m, 11H), 1.00 (m, 6H).

Preparation Example 7: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide



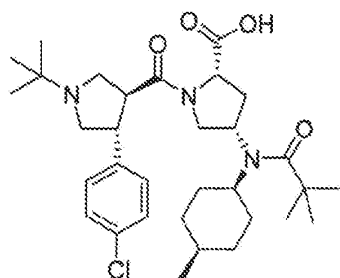
The title compound was obtained through the following steps A, B, and C.

Step A: Preparation of methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate



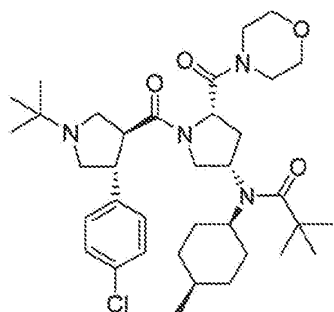
The title compound (0.70 g, 66%) was obtained using the same method as in Step A of Preparation Example 5, using methyl (2*S*,4*S*)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate hydrochloride (0.65 g, 1.8 mmol) obtained in Preparation Example 4 and (3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid (0.50 g, 1.8 mmol) obtained in Preparation Example 2. MS: [M+H]⁺ = 588.5. ¹H NMR (400 MHz, CD₃OD) δ 7.40-7.30 (m, 4H), 4.49 (m, 1H), 4.00-3.50 (m, 4H), 3.71 (s, 3H), 3.40 (m, 3H), 3.20-3.05 (m, 2H), 3.00 (m, 1H), 2.70 (m, 1H), 2.27 (m, 1H), 1.90 (m, 1H), 1.73-1.60 (m, 6H), 1.60-1.35 (m, 2H), 1.25-1.17 (m, 18H), 1.01 (m, 3H).

Step B: Preparation of (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylic acid



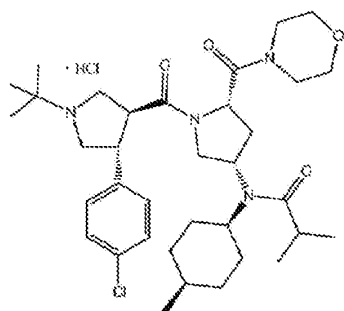
The title compound (0.10 g, 99%) was obtained using the same method as in Step B of Preparation Example 5 using methyl (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylate (0.10 g, 0.18 mmol) obtained in step A above. MS: [M+H] = 574.4.

Step C: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamide



The title compound (0.020 g, 17%) was obtained using the same method as in Step C of Preparation Example 5 using (2*S*,4*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-4-(*N*-((1*S*,4*R*)-4-methylcyclohexyl)pivalamido)pyrrolidine-2-carboxylic acid (0.10 g, 0.18 mmol) obtained in step B above. MS: [M+H] = 643.5. ¹H NMR (400 MHz, CD₃OD) δ 7.40-7.30 (m, 4H), 4.79 (m, 1H), 4.17 (m, 1H), 3.80-3.40 (m, 15H), 3.10 (m, 1H), 2.96 (m, 1H), 2.71 (m, 1H), 2.15 (m, 1H), 1.90 (m, 1H), 1.80-1.35 (m, 8H), 1.21-1.15 (m, 18H), 1.02 (m, 3H).

Preparation Example 8: Preparation of *N*-((3*S*,5*S*)-1-((3*S*,4*R*)-1-(*tert*-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-*N*-((1*S*,4*R*)-4-methylcyclohexyl)isobutyramide hydrochloride

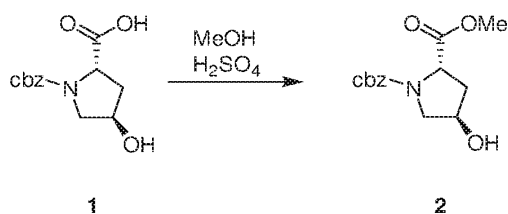


MBTE (19 mL) was used to dissolve, at 25 °C, 1 g of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramido as prepared in Preparation Example 5. After the dissolution was completed, 1 mL of heptane was added and cooled to -5 to 0 °C. After reaching the set temperature, 1 equivalent of 4M HCl/EtOAc was added dropwise, stirred for about 90 minutes, and filtered to obtain N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide hydrochloride. (Yield: about 90%)

Example 1: Making the hydrochloride salt of intermediate N-((1S,4R)-4-methylcyclohexyl)-N-((3S,5S)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)isobutyramido (8)

Step A: Synthesis of 1-benzyl 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (2)

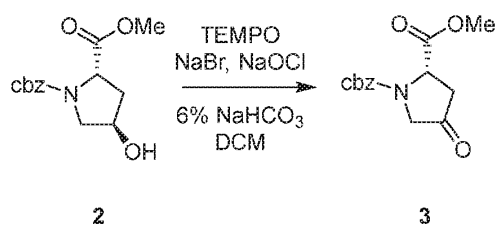
Step A



After adding MeOH (80.92 L) to (2S,4R)-1-((benzyloxy)carbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (**1**, 16.18 kg, 61.01 mol), concentrated H₂SO₄ (1.11 L, 20.74 mol) was added and stirred for 4 hours while refluxing. When the reaction was completed, the internal temperature was cooled to 35 - 40 °C and concentrated under reduced pressure. After that, EtOAc (121 L) and water (80 L) were added to the residue and stirred, and the layers were separated. After extracting the water layer with EtOAc (48 L), the combined oil layers were washed with 5% (w/w) NaHCO₃ (aq., 80 L) and concentrated under reduced pressure to obtain 1-benzyl 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (**2**) (expected amount 15.34 kg, expected yield 90%), which was used in the next reaction without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.23 (m, 5H), 5.20-5.06 (m, 1.5H), 5.00-4.94 (m, 0.5H), 4.52-4.39 (m, 2H), 3.72 (s, 1.4H), 3.61 (s, 1.6H), 3.52 (s, 2H), 2.71 (br s, 1H), 2.34-2.21 (m, 1H), 2.09-1.99 (m, 1H).

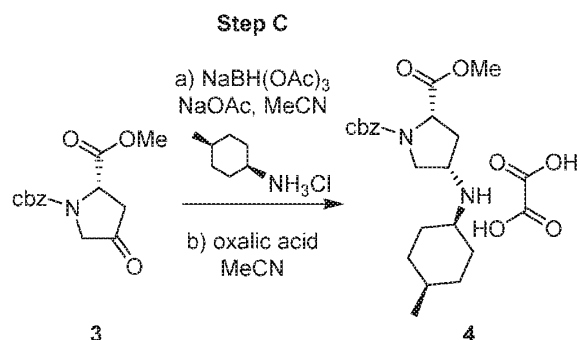
Step B: Synthesis of 1-benzyl 2-methyl (S)-4-oxopyrrolidine-1,2-dicarboxylate (3)

Step B



DCM (46.01 L) was added to Compound **2** (15.34 kg, 54.91 mol), and then it was cooled. After that, 6% (w/w) NaHCO₃ (117 L) was added. NaBr (6.8 kg, 65.89 mol) and TEMPO (0.43 kg, 2.75 mol) were added below 5 °C, and sodium hypochlorite solution (36.26 L, 58.75 mol) was added dropwise while maintaining the temperature below 5 °C. After stirring for 1 hour at 5 °C or lower, sodium thiosulfate (5 kg) was added. After 6N HCl (2.3 L), water (15 L), and DCM (30 L) were added, the temperature was raised to room temperature, and the layers were separated. The oil layer was washed with 10% (w/w) NaCl (76.4 L), concentrated under reduced pressure, and azeotropically treated with acetonitrile to obtain 1-benzyl 2-methyl (S)-4-oxopyrrolidine-1,2-dicarboxylate (**3**) (15.6 kg, expected yield 102.5%), which was used in the next reaction without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.26 (m, 5H), 5.26-5.06 (m, 2H), 4.90-4.77 (m, 1H), 3.92 (s, 2H), 3.74 (s, 1.7H), 3.61 (s, 1.3H), 3.00-2.84 (m, 1H), 2.57 (dd, *J* = 19.0, 2.6 Hz, 1H).

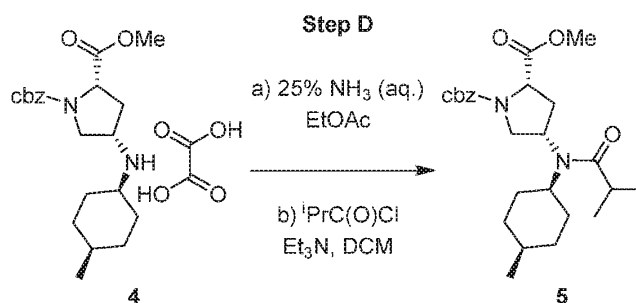
Step C: Synthesis of oxalic acid salt of 1-benzyl 2-methyl (2S,4S)-4-(((1s,4R)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate (**4**)



After adding (1s,4s)-4-methylcyclohexan-1-amine hydrochloride (6.98 kg, 46.65 mol) and NaOAc (3.83 kg, 46.65 mol) to acetonitrile (47.04 L) in the reactor, the mixture was cooled to 0 to 5 °C and stirred for 1 h, and then NaBH(OAc)₃ (11.69 kg, 55.14 mol) was added. A solution of the Compound **3** (11.76 kg, 42.41 mol) in acetonitrile (14.74 L) was added dropwise to the above solution at 20 to 25 °C and stirred for 18 hours. 1N NaOH (69 L) was added below 15 °C and stirred for 30 minutes. After that, EtOAc (176 L) was added, and the layers were separated. The organic layer was washed sequentially with a solution of NaCl (11.76 kg) dissolved in 5% (w/w) NaHCO₃ (58.8 L) and then 20% (w/w) NaCl (58.8 L) and concentrated under reduced pressure to obtain crude intermediate 1-benzyl 2-methyl (2S,4S)-4-(((1s,4R)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate (12.92 kg, crude yield 81%).

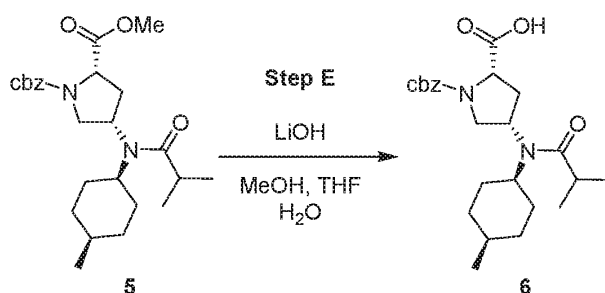
Acetonitrile (129.2 L) was added to the intermediate (12.92 kg, 34.50 mol) prepared above at room temperature and stirred. Acetonitrile (94.32 L) and oxalic acid (6.34 kg, 70.38 mol) were added to another reactor and stirred, and then the prepared intermediate / acetonitrile solution was added dropwise at room temperature. After 3 h, the reaction mixture was filtered, washed four times using acetonitrile (38 L), and dried with nitrogen to obtain the oxalic acid salt of 1-benzyl 2-methyl (2S,4S)-4-(((1s,4R)-4-methylcyclohexyl)amino)pyrrolidine-1,2-dicarboxylate (**4**) (8.82 kg, yield 55%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.83 (s, 2H), 7.49-7.20 (m, 5H), 5.19-4.90 (m, 2H), 4.29 (dt, *J* = 28.0, 8.4 Hz, 1H), 4.05-3.94 (m, 1H), 3.94-3.80 (m, 1H), 3.67 (s, 1.4H), 3.56 (s, 1.6H), 3.47-3.32 (m, 1H), 3.12-2.98 (m, 1H), 2.78-2.63 (m, 1H), 2.12-1.94 (m, 1H), 1.78-1.56 (m, 5.5H), 1.56-1.26 (m, 4.5H), 0.90 (d, *J* = 5.6 Hz, 3H).

Step D: Synthesis of 1-benzyl 2-methyl (2S,4S)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)pyrrolidine-1,2-dicarboxylate (5)



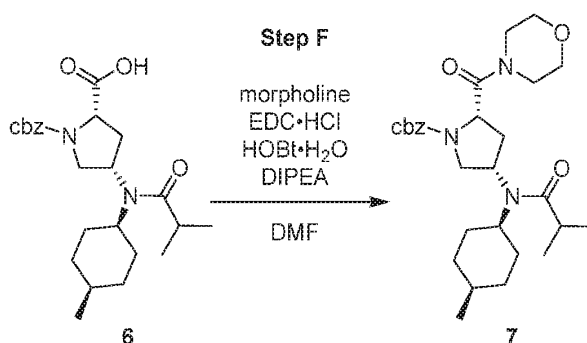
Compound 4 (8.5 kg, 18.30 mol) and EtOAc (127.5 L) were added to the reactor at room temperature, and the pH was adjusted to 10 - 11 using a 25% (w/w) NH_3 (16 kg) aqueous solution. Water (85 L) was added and stirred, and the layers were separated. After that, the aqueous layer was extracted with EtOAc (59.5 L). The combined organic extracts were washed with 5% (w/w) NaCl (85 L), concentrated under reduced pressure, and azeotroped using DCM (30 L). After dissolving the residue in DCM (68 L), TEA (7.65 L, 54.90 mol) was added, and then it was cooled. While maintaining the temperature below 20 °C, isobutyryl chloride (3.83 L, 36.60 mol) was added dropwise and stirred for 10 h. After cooling the reaction solution, 1N HCl (29.75 L) was added dropwise while maintaining the temperature below 20 °C. After that, DCM (59.5 L) was added and stirred, and the layers were separated. The organic layer was washed sequentially with 5% NaHCO_3 (59.5 L), 1N HCl (59.5 L), and 5% (w/w) NaCl (59.5 L), and then concentrated under reduced pressure to obtain 1-benzyl 2-methyl (2S,4S)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)pyrrolidine-1,2-dicarboxylate (**5**) (theoretical amount 8.14 kg, theoretical yield 100%), which was used in the next reaction without further purification.

Step E: Synthesis of (2S,4S)-1-((benzyloxy)carbonyl)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylic acid (6)



MeOH (40.68 L) and THF (20.34 L) were added to Compound **5** (8.14 kg, 18.30 mol) and cooled. Then LiOH (2.3 kg, 54.90 mol) / water (20.34 L) solution was added dropwise while maintaining the temperature below 20 °C. After stirring at room temperature for 2 h, 3N HCl (16 L) was added dropwise while maintaining the mixture temperature below 20 °C. The mixture was concentrated under reduced pressure, EtOAc (105.76 L) and 10% (w/w) citric acid (aq., 24.41 L) were added to the residue and stirred, and the layers were separated. The organic layer was washed with water (56.95 L) and then concentrated under reduced pressure to obtain (2S,4S)-1-((benzyloxy)carbonyl)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)pyrrolidine-2-carboxylic acid (**6**) (theoretical weight 7.88 kg, theoretical yield 100%), which was used in the next reaction without further purification.

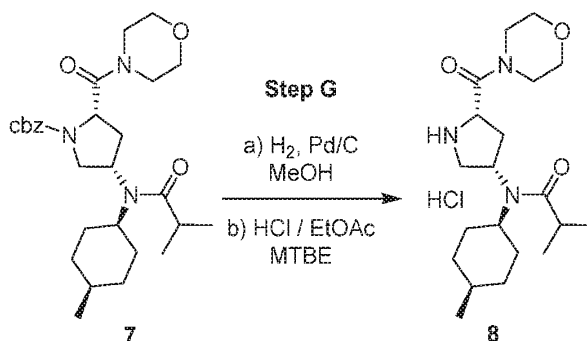
Step F: Synthesis of benzyl (2S,4S)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (7)



Compound **6** (7.88 kg, 18.30 mol) was dissolved in DMF (31.51 L), and then HOBT·H₂O (4.2 kg, 27.45 mol), DIPEA (4.78 L, 27.45 mol), and EDC·HCl (5.26 kg, 27.45 mol) were sequentially added. Then morpholine (2.37 L, 27.45 mol) was added dropwise while maintaining the temperature below 20 °C. After stirring at room temperature for 4 h, water (94.54 L) was

added to the mixture dropwise while maintaining the temperature below 25 °C. EtOAc (94.54 L) was added and stirred, and the layers were separated. The aqueous layer was further extracted with EtOAc (31.51 L), and the combined organic extracts were sequentially washed with 1N HCl (78.78 L) and 5% (w/w) NaCl (78.78 L) and then concentrated under reduced pressure. The residue was completely dissolved in THF (39.39 L), and then water (118.18 L) was added dropwise followed by stirring at room temperature for 16 h. The mixture was then filtered, washed with a solution of THF (3.94 L) in water (11.82 L), and then dried under a stream of nitrogen to obtain benzyl (2S,4S)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (**7**) (6.36 kg, yield 70%). ¹H NMR (400MHz, CDCl₃) δ 7.50-7.21 (m, 5H), 5.28-4.97 (m, 2H), 4.78-4.50 (m, 1H), 4.50-3.94 (m, 1H), 3.94-3.23 (m, 1H), 3.16-2.66 (m, 2H), 2.66-2.26 (m, 1H), 2.24-1.90 (m, 2H), 1.83-1.70 (m, 1H), 1.70-1.38 (m, 6H), 1.10 (s, 6H), 1.00 (s, 3H).

*Step G (version 1): Synthesis of hydrochloride salt of N-((1S,4R)-4-methylcyclohexyl)-N-((3S,5S)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)isobutyramide (**8**)*

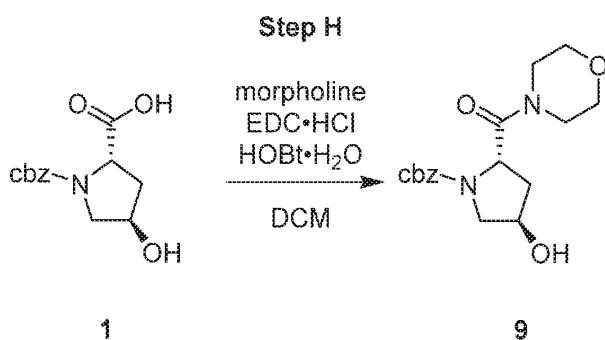


Compound **7** (6.0 kg, 12.01 mol) was dissolved in MeOH (60 L) in the reactor, and then 10% Pd/C (1.8 kg) was added. The reactor was pressurized with H₂ gas to 0.1 bar and stirred at room temperature until reaction completion. Then the mixture was filtered through celite, washed with MeOH (12 L), and concentrated under reduced pressure. The residue was suspended in MTBE (18 L) and re-concentrated under reduced pressure. The residue was dissolved in MTBE (60 L), and then 4M HCl in EtOAc (4.5 L, 18.01 mol) was added dropwise at room temperature over 1 h. After stirring for 16 h, the mixture was filtered, washed with MTBE (12 L), and dried with a stream of nitrogen to obtain the hydrochloride salt of N-((1S,4R)-4-methylcyclohexyl)-N-((3S,5S)-5-

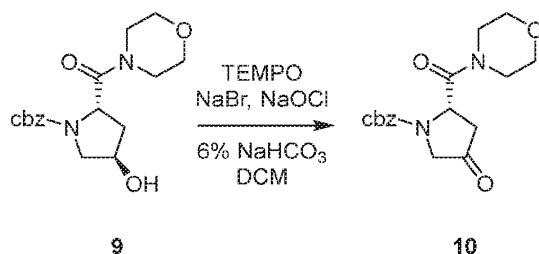
(morpholine-4-carbonyl)pyrrolidin-3-yl)isobutyramide (**8**) (4.08 kg, yield 84%). ¹H NMR (400MHz, CDCl₃) δ 11.18 (s, 1H), 8.03 (s, 1H), 5.21-5.07 (m, 1H), 4.43-4.32 (m, 1H), 3.85-3.34 (m, 11H), 2.75-2.58 (m, 2H), 2.12-2.00 (m, 1H), 1.98-1.88 (m, 1H), 1.83-1.69 (m, 2H), 1.66-1.50 (m, 4H), 1.44-1.34 (m, 2H), 1.06 (dd, J = 6.8, 0.8 Hz, 6H), 1.00 (d, J = 7.2 Hz, 3H).

Example 2: Alternative route for making the hydrochloride salt of intermediate N-((1*S*,4*R*)-4-methylcyclohexyl)-N-((3*S*,5*S*)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)isobutyramido (8**)**

*Step H: Synthesis of benzyl (2*S*,4*R*)-4-hydroxy-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (**9**)*

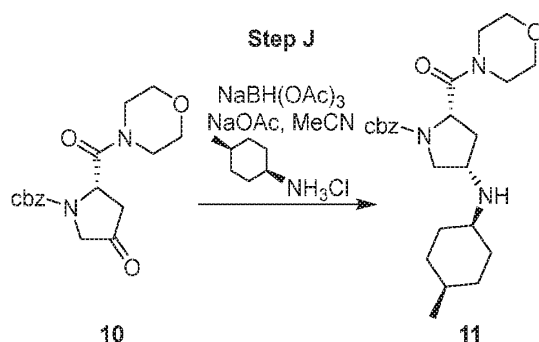


(2*S*,4*R*)-1-((Benzyloxy)carbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (**1**, 45.0 kg, 169.6 mol), HOBT·H₂O (2.6 kg, 17.0 mol), EDC·HCl (39.0 kg, 203.6 mol), and DCM (450 L) were added to the reactor and cooled to below 10 °C. Morpholine (16.3 kg, 186.6 mol) was added dropwise, and then the temperature was raised to room temperature. After 2 h, the mixture was washed with 5% (w/w) NaHCO₃ aqueous solution (225.0 kg). The separated NaHCO₃ aqueous solution layer was extracted with DCM (135 L). The combined organic extracts was washed with a solution of concentrated HCl (4.7 kg) diluted with H₂O (220.3 kg), and the separated aqueous layer was re-extracted with DCM (135 L) and then combined with the DCM layer. The combined DCM extracts were concentrated under reduced pressure to obtain benzyl (2*S*,4*R*)-4-hydroxy-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (**9**) (expected amount 48.2 kg, expected yield 85%), which was used in the following reaction without further purification. ¹H NMR (500MHz, CDCl₃) δ 7.41-7.30 (m, 5H), 5.27-4.99 (m, 2H), 4.93-4.75 (dt, 1H), 4.67-4.54 (br d, 1H), 3.91-3.65 (m, 5H), 3.62 (d, J = 11.3 Hz, 1H), 3.57 (d, J = 13.4 Hz, 1H), 3.53-3.42 (m, 2H), 3.42-3.25 (m, 1H), 2.30-2.05 (m, 2H).

*Step I: Synthesis of benzyl (S)-2-(morpholine-4-carbonyl)-4-oxopyrrolidine-1-carboxylate (10)***Step I**

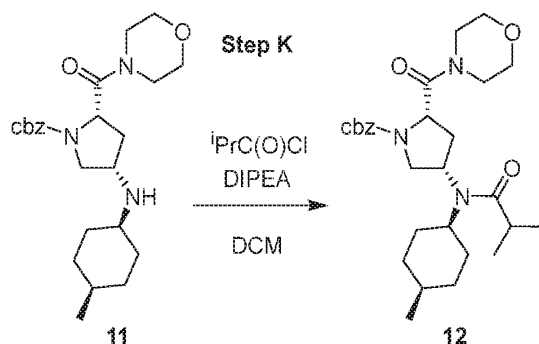
DCM (169 L) was added to the Compound **9** (48.2 kg, 144.2 mol) in the reactor, and then NaHCO_3 (3.6 kg, 43.3 mol), NaBr (1.5 kg, 14.4 mol), TEMPO (0.2 kg, 1.4 mol), and H_2O (48 L) were added while maintaining a mixture temperature below 5 °C. NaHCO_3 (1.6 kg, 19.0 mol) was dissolved in NaOCl (aq., 85.9 kg, 115.4 mol) and added dropwise while maintaining the temperature below 5 °C. Then more NaHCO_3 (0.5 kg, 6.0 mol) and NaOCl (aq., 27.3 kg, 36.7 mol) were added to complete the reaction. $\text{Na}_2\text{S}_2\text{O}_3$ (2.3 kg, 14.4 mol) was dissolved in H_2O (9.1 L), added to the reaction mixture, heated, and then left to stand. After separating the layers and concentrating the DCM layer, benzyl (S)-2-(morpholine-4-carbonyl)-4-oxopyrrolidine-1-carboxylate (**10**) (expected amount 43.1 kg, expected yield 90%) was obtained and used in the following reaction without further purification. ^1H NMR (500MHz, CDCl_3) δ 7.24-7.14 (m, 5H), 5.22-4.94 (m, 3H), 4.11-3.86 (m, 2H), 3.86-3.69 (m, 2H), 3.69-3.58 (m, 2H), 3.57-3.47 (m, 1H), 3.47-3.34 (m, 2H), 3.34-3.14 (m, 1H), 2.76 (ddd, $J = 39.6, 17.9, 9.5$ Hz, 1H), 2.43 (dd, $J = 27.5, 18.0$ Hz, 1H).

Step J: Synthesis of benzyl (2S,4S)-4-(((1S,4R)-4-methylcyclohexyl)amino)-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (11)



DCM (129 L), (1*S*,4*S*)-4-methylcyclohexan-1-amine hydrochloride (21.4 kg, 142.8 mol), and NaOAc (11.7 kg, 142.8 mol) were added to the reactor and cooled to below 5 °C. Then NaBH(OAc)₃ (35.8 kg, 168.7 mol) was added. A solution of Compound **10** (43.1 kg, 129.8 mol) in DCM (129 L) was added dropwise to the above solution below 10 °C and then stirred at 20 to 25 °C for 2 h. 1*N* NaOH (387.6 kg) was added below 15 °C and stirred for 30 min, and then the layers were separated. The organic layer was washed sequentially with 7% (w/w) NaHCO₃ (258.8 kg) and 10% (w/w) NaCl (129.4 kg), and then concentrated under reduced pressure to obtain benzyl (2*S*,4*S*)-4-(((1*S*,4*R*)-4-methylcyclohexyl)amino)-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (**11**) (expected amount 52.4 kg, expected yield 94%), which was used in the following reaction without further purification. ¹H NMR (500MHz, CDCl₃) δ 7.40-7.30 (m, 5H), 5.25-4.98 (m, 2H), 4.61 (ddd, *J*=49.1, 8.8, 5.9Hz, 1H), 4.00-3.82 (m, 1H), 3.82-3.70 (m, 2H), 3.70-3.60 (m, 3H), 3.60-3.16 (m, 6H), 2.72-2.56 (m, 1H), 2.49-2.33 (m, 1H), 1.85-1.68 (m, 1H), 1.68-1.56 (m, 1H), 1.56-1.38 (m, 5H), 1.38-1.27 (m, 2H), 0.96-0.85 (d, *J*=6.7Hz, 3H).

Step K: Synthesis of benzyl (2S,4S)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (12)



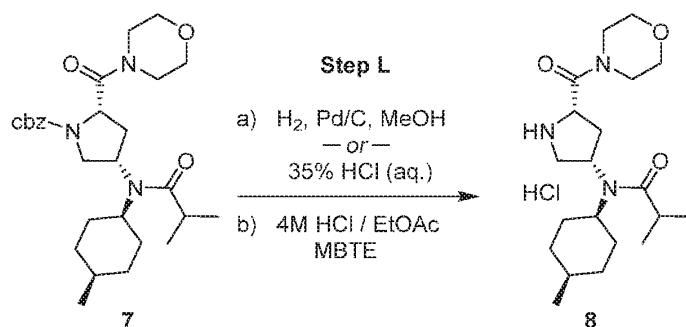
Version 1: Compound **11** (52.4 kg, 122.0 mol) and DCM (419 L) were added to the reactor and then cooled to below 20 °C. Isobutyryl chloride (29.0 kg, 244.0 mol) and DIPEA (37.0 kg, 366.0 mol) were sequentially added below 20 °C, and then stirred at 20 to 25 °C for 2 h. The reaction solution was cooled and maintained at below 20 °C while H₂O (262 L) and 1N HCl (52.5 kg) were sequentially added to wash the solution. The separated organic layer was treated sequentially with H₂O (105 L) and 1N NaOH (52.4 kg) and then washed with 10% (w/w) NaCl (aq., 104.8 kg). After the DCM layer was concentrated under reduced pressure, MTBE (367 L) was added, and the temperature was raised. After ~3 h of reflux, the mixture was cooled and filtered. The collected precipitate was washed with MTBE (147 L) and dried under a stream of nitrogen gas to obtain benzyl (2S,4S)-4-(N-((1S,4R)-4-methylcyclohexyl)isobutyramido)-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (**12**) (46.9 kg, yield 77%).

Version 2: Compound **11** (39.5 kg, 81.3 mol) and DCM (370.3 kg) were added to the reactor at room temperature, and then cooled to below 20 °C. Isobutyryl chloride (19.4 kg, 181.6 mol) and DIPEA (24.7 kg, 192.0 mol) were sequentially added below 20 °C, and then stirred at 20 to 25 °C for 3 h. The reaction solution was cooled and maintained below 20 °C, and H₂O (174.7 L) and 1N HCl (34.9 kg) were sequentially added to wash the solution. The separated organic layer was treated sequentially with H₂O (69.9 L) and 1N NaOH (39.5 kg), and then washed with 10% (w/w) NaCl (69.9 kg). After the DCM layer was concentrated under reduced pressure, isopropyl acetate (100.3 kg) was added. After stirring at 80 to 90 °C for 0.5 to 1 h, the mixture was cooled, and then MTBE (85.3 kg) was added dropwise at 60 °C for about 1 h. The mixture was then refluxed for 1 h, cooled to room temperature, stirred for 16 h, and filtered. The collected precipitate was washed with MTBE (107.0 kg) and dried under a stream of nitrogen gas. The residue (29.4 kg) was dissolved in isopropyl acetate (102.2 kg) at 80 to 90 °C, cooled,

and treated dropwise with MTBE (87.2 kg) at 65 °C. The mixture was then refluxed for 0.5 hours, cooled to room temperature, stirred for 12 hours, and filtered. The collected precipitate was washed with MTBE (43.48 kg) and dried under a stream of nitrogen gas to obtain benzyl (2S,4S)-4-(N-((1s,4R)-4-methylcyclohexyl)isobutyramido)-2-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate (**12**) (25.06 kg, yield 62%).

¹H NMR (400MHz, CDCl₃) δ 7.50-7.21 (m, 5H), 5.28-4.97 (m, 2H), 4.78-4.50 (m, 1H), 4.50-3.94 (m, 1H), 3.94-3.23 (m, 1H), 3.16-2.66 (m, 2H), 2.66-2.26 (m, 1H), 2.24-1.90 (m, 2H), 1.83-1.70 (m, 1H), 1.70-1.38 (m, 6H), 1.10 (s, 6H), 1.00 (s, 3H).

Step G (versions 2 to 4): Synthesis of hydrochloride salt of N-((1s,4R)-4-methylcyclohexyl)-N-((3S,5S)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)isobutyramide (8)



Version 2: Compound **7** (30.0 kg, 60.04 mol) was dissolved in MeOH (300 L) in the reactor, and then 10% Pd/C (9.0 kg) was added. The reactor was pressurized with H₂ gas to 0.5 bar and stirred at room temperature. After the reaction was completed, the mixture was filtered through Celite and washed with MeOH (60 L). 4M HCl in EtOAc (22.5 L, 90.1 mol) was added below 20 °C, and the mixture was concentrated under reduced pressure. After concentration under reduced pressure, the residue was azeotroped with DCM (45 L), and then DCM (45 L) was added to the residue to dissolve it. A reactor was loaded with MBTE and a seed portion of Compound **7** (30.0 g). At room temperature, the DCM solution was added dropwise the reactor containing seed in MBTE and aged for 2 h. After filtration, washing with MTBE (45 L), and drying under a stream of nitrogen gas, the hydrochloride salt of N-((1s,4R)-4-methylcyclohexyl)-N-((3S,5S)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)isobutyramide (**8**) was obtained (16.8 kg, yield 70%).

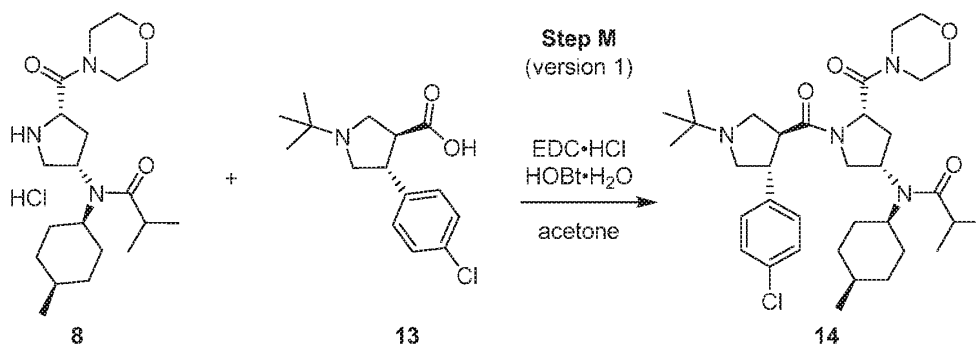
Version 3: Compound **7** (86.0 kg, 172.1 mol) was dissolved in MeOH (340.6 kg) in the reactor and dissolved, and then 10% Pd/C (4.3 kg) was added. The reactor was pressurized with H₂ gas at 0.5 to 1.3 bar and stirred at room temperature. After the reaction was completed, the mixture was filtered through Celite and washed with MeOH (100 L). After concentrating the filtrate under reduced pressure, the residue was azeotroped with EtOAc (465.4 kg) and MTBE (422.2 kg) and then dissolved in MTBE (592 kg). 4M HCl in EtOAc (43 L, 172.1 mol) was added, and the mixture was aged for 2 h, filtered, and washed with MTBE (63.6 kg). Drying under a stream of nitrogen gas afforded the hydrochloride salt of N-((1s,4R)-4-methylcyclohexyl)-N-((3S,5S)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)isobutyramide (**8**) (67.2 kg, yield 97%).

Version 4: Compound **7** (17.8 kg, 35.6 mol) was dissolved in 35% HCl (aq., 94.7 kg) in the reactor and stirred at an external temperature of 42 to 47 °C for 2 h. After the reaction was completed, it was washed using heptane (73.1 kg). After cooling the water layer to below 0 °C, 10N NaOH (75 L) was added dropwise while maintaining the temperature below 25 °C to adjust the pH to approximately 11. The mixture was extracted with EtOAc (2 × 64.2 kg). The combined EtOAc layers were concentrated under reduced pressure at an external temperature of 40 °C. Then MTBE (21.5 kg) was added and azeotroped. MTBE (131.7 kg) was added to completely dissolve the residue, and then 4M HCl in EtOAc (8.9 L) was added at an internal temperature of 20 to 25 °C and stirred for ~30 min. The precipitate was collected by filtration, washed with MTBE (13.2 kg), and dried under a stream of nitrogen gas to afford the hydrochloride salt of N-((1s,4R)-4-methylcyclohexyl)-N-((3S,5S)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)isobutyramide (**8**, 12.56 kg, yield 88%).

¹H NMR (400MHz, CDCl₃) δ 11.18 (s, 1H), 8.03 (s, 1H), 5.21-5.07 (m, 1H), 4.43-4.32 (m, 1H), 3.85-3.34 (m, 11H), 2.75-2.58 (m, 2H), 2.12-2.00 (m, 1H), 1.98-1.88 (m, 1H), 1.83-1.69 (m, 2H), 1.66-1.50 (m, 4H), 1.44-1.34 (m, 2H), 1.06 (dd, J = 6.8, 0.8 Hz, 6H), 1.00 (d, J = 7.2 Hz, 3H).

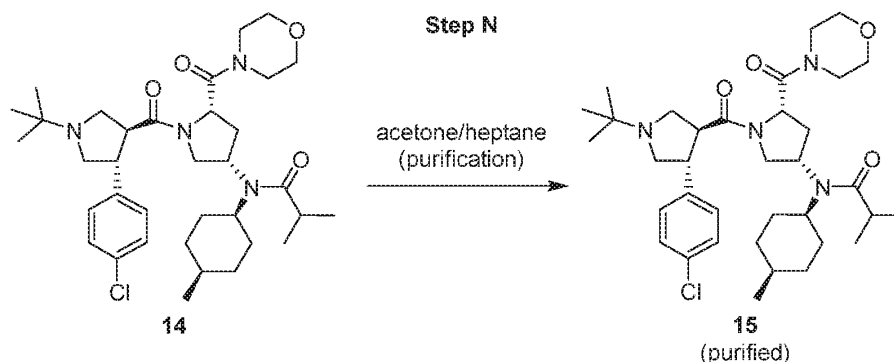
Example 3: Making N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (15**)**

Step M (version 1): Synthesis of crude N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (14-1)



Compound **8** (23.43 kg, 79.61 mol), (3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid (**13**, as afforded by Preparation Example 2, 32.00 kg, 79.61 mol), HOBT·H₂O (0.61 kg, 3.98 mol), and acetone (125.38 kg) were added to the reactor, and then the internal temperature was cooled to 10 to 15 °C. EDC·HCl (16.78 kg, 87.57 mol) was added, and the reactor temperature was raised to 20 to 25 °C. After 1 h of stirring, H₂O (32.07 kg) was added, and then the mixture was concentrated under reduced pressure. The residue was dissolved completely in H₂O (96.00 kg) and washed with isopropyl acetate (167.04 kg). The separated aqueous layer was concentrated under reduced pressure and reconstituted by the addition of H₂O (480.00 kg). After cooling to an internal temperature of 0 to 5 °C, 1N NaOH aqueous solution (96.00 kg) was added via slow dropwise addition. After stirring for 3 hours, the precipitate was collected by filtration, washed with H₂O (799.65 kg), and dried under a stream of nitrogen gas to obtain crude N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**14**) (43.70 kg, yield 87%). ¹H NMR (400 MHz, CD₂Cl₂) δ 7.33-7.16 (m, 4H), 4.64 (t, *J* = 8.8 Hz, 1H), 4.04 (t, *J* = 9.4 Hz, 1H), 3.74-3.30 (m, 11H), 3.16 (t, *J* = 8.4 Hz, 1H), 3.11-2.98 (m, 3H), 2.83 (t, *J* = 8.2 Hz, 1H), 2.75 (t, *J* = 7.8 Hz, 1H), 2.71-2.58 (m, 2H), 2.02-1.86 (m, 2H), 1.69-1.49 (m, 5H), 1.45-1.33 (m, 2H), 1.29-1.17 (m, 1H), 1.07 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 6H), 0.95 (d, *J* = 7.2 Hz, 3H).

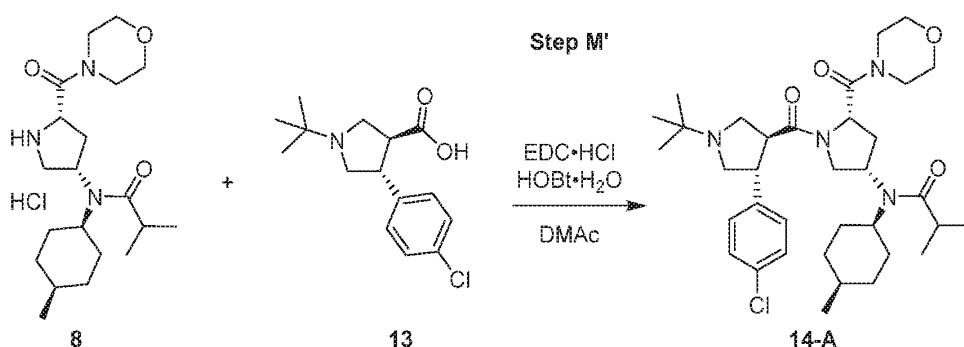
Step N: Preparation of purified N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (15)



Crude Compound **14** (43.00 kg, 63.33 mol) was dissolved in acetone (35.39 kg) and heptane (44.12 kg). More heptane (176.47 kg) was added, and after stirring for 12 h or more, the mixture was cooled to an internal temperature of 0 to 5 °C and stirred for an additional 1 h. The resulting precipitate was collected via filtration, washed with heptane (58.82 kg), and dried under a stream of nitrogen gas to obtain purified N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (**15**) (40.68 kg, yield 95%).

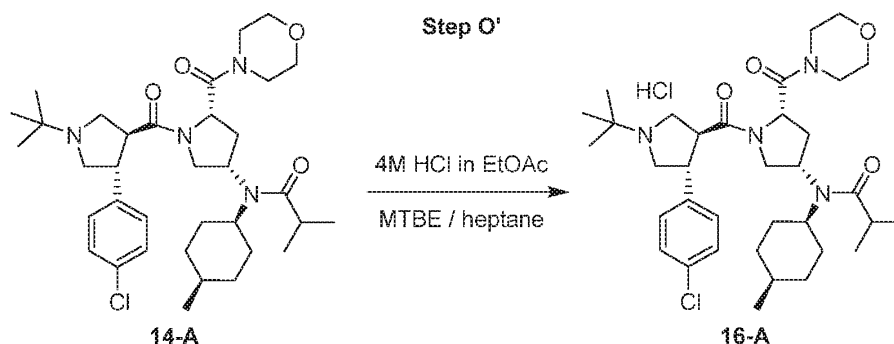
Comparative Example 1: Making N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (14-A)

Step M': Synthesis of crude N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (14-A)



Compound **13** (5.61 kg, 19.90 mol), Compound **8** (8.00 kg, 19.90 mol), HOBt·H₂O (4.57 kg, 29.84 mol), and DMAc (37.60 kg) were added to the reactor, and then the internal temperature was cooled to 0 to 5 °C. After cooling, EDC·HCl (5.72 kg, 29.84 mol) was added, and then it was stirred for 14 h. After the completion of the reaction, H₂O (40.00 kg) was added while the internal temperature was kept below 20 °C, and EtOAc (60.11 kg) was added for washing. The upper organic layer was allowed to stand while the lower aqueous layer was separated, and then a 25% NH₃ aqueous solution (7.93 kg) was slowly added dropwise, followed by the addition of EtOAc (36.08 kg) to carry out the extraction. The combined organic layers were washed sequentially with a 5% (w/w) NaHCO₃ aqueous solution (56.1 kg) and then H₂O (80.00 kg). The separated organic layer was concentrated under reduced pressure and azeotropically distilled using MTBE (12.45 kg) to obtain crude N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**14-A**) (11.28 kg, yield 90%), which was used in the next reaction without any purification process. ¹H NMR (400 MHz, CD₂Cl₂) δ 7.33-7.16 (m, 4H), 4.64 (t, *J* = 8.8 Hz, 1H), 4.04 (t, *J* = 9.4 Hz, 1H), 3.74-3.30 (m, 11H), 3.16 (t, *J* = 8.4 Hz, 1H), 3.11-2.98 (m, 3H), 2.83 (t, *J* = 8.2 Hz, 1H), 2.75 (t, *J* = 7.8 Hz, 1H), 2.71-2.58 (m, 2H), 2.02-1.86 (m, 2H), 1.69-1.49 (m, 5H), 1.45-1.33 (m, 2H), 1.29-1.17 (m, 1H), 1.07 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 6H), 0.95 (d, *J* = 7.2 Hz, 3H).

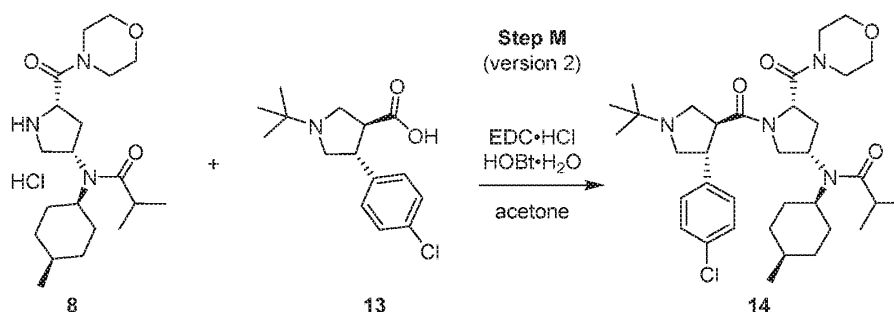
*Step O': Synthesis of the hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**16-A**)*



The procedure for Step O' is identical to that for Step O in Example 4 below.

Example 4: Making the hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (17)

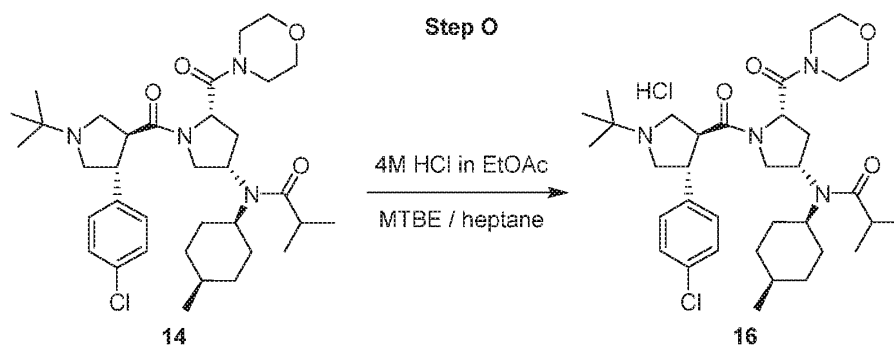
Step M (version 2): Synthesis of crude N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (14-2)



(3S,4R)-1-(Tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carboxylic acid (**13**, 23.43 kg, 79.61 mol), Compound **8** (32.00 kg, 79.61 mol), HOBT·H₂O (0.61 kg, 3.98 mol), and acetone (125.38 kg) were added to the reactor and cooled to 10 to 15 °C. Then EDC·HCl (16.78 kg, 87.57 mol) was added, and the reaction temperature was raised to 20 to 25 °C. After 1 h of stirring, the mixture was treated with H₂O (32.07 kg) and then concentrated under reduced pressure. The residue was dissolved completely in H₂O (96.00 kg) and washed with isopropyl acetate (167.04 kg). The separated aqueous layer was concentrated under reduced pressure, followed by the addition of H₂O (480.00 kg) and cooling to 0 to 5 °C. After slow dropwise addition of 1N NaOH aqueous solution (96.00 kg) and stirring for 3 h, the precipitate was collected by filtration, washed

with H₂O (799.65 kg), and dried with nitrogen to obtain N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**14**) (43.70 kg, yield 87%). ¹H NMR (400 MHz, CD₂Cl₂) δ 7.33-7.16 (m, 4H), 4.64 (t, *J* = 8.8 Hz, 1H), 4.04 (t, *J* = 9.4 Hz, 1H), 3.74-3.30 (m, 11H), 3.16 (t, *J* = 8.4 Hz, 1H), 3.11-2.98 (m, 3H), 2.83 (t, *J* = 8.2 Hz, 1H), 2.75 (t, *J* = 7.8 Hz, 1H), 2.71-2.58 (m, 2H), 2.02-1.86 (m, 2H), 1.69-1.49 (m, 5H), 1.45-1.33 (m, 2H), 1.29-1.17 (m, 1H), 1.07 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 6H), 0.95 (d, *J* = 7.2 Hz, 3H).

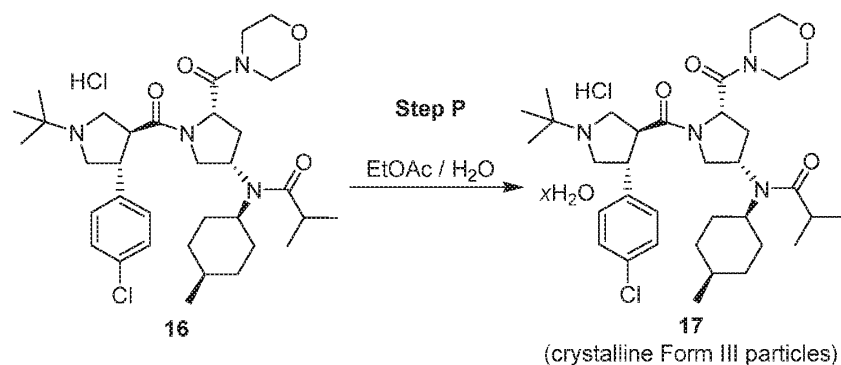
*Step O: Synthesis of the hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**16**)*



MTBE (158.45 kg) and heptane (7.71 kg) were added to the Compound **14** (11.28 kg, 16.94 mol), then the mixture was cooled to an internal temperature of -5 to 5 °C, followed by the addition of 4M HCl in EtOAc (4.12 kg). The temperature was then adjusted to 0 to 5 °C, and the mixture was stirred for at least 30 min. The resulting precipitate was collected by filtration, washed with heptane (15.42 kg), and dried under a stream of nitrogen gas to obtain the hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**16**) (9.38 kg, yield 72%). ¹H NMR (400 MHz, CD₂Cl₂) δ 12.91 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.57 (t, *J* = 8.8 Hz, 1H), 4.14 (t, *J* = 9.6 Hz, 1H), 3.93-3.16 (m, 16H), 2.98 (t, *J* = 8.2 Hz, 1H), 2.68-2.53 (m, 2H), 1.98-1.84 (m, 2H), 1.73-1.64 (m, 1H), 1.62-1.46 (m, 4H), 1.41 (s, 9H), 1.37-1.20 (m, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H).

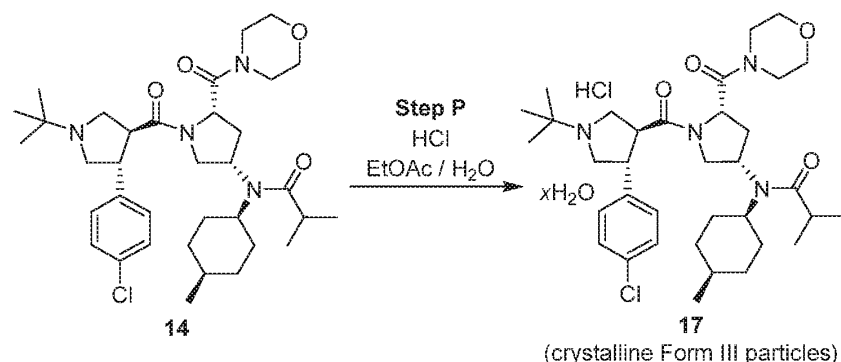
Example 5: Making crystalline Form III particles of hydrate of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (17)

Step P (version 1): Making the crystalline Form III particles of hydrate of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (17)



Example 5-1: Compound **16** (1 g) was completely dissolved at 60 °C using 1 mL of EtOAc and 0.15 mL of distilled water. Then the mixture was cooled to 3 °C and stirred for 25 h at that temperature. The precipitate was collected by filtration under nitrogen pressure to obtain crystalline Form III particles of hydrate of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (**17**) (Yield: ~80%). Powder XRD pattern exhibited characteristic peaks (2θ) at 6.62°, 7.44°, 9.18°, 9.89°, 10.83°, 11.42°, 12.92°, 14.61°, 15.36°, 15.79°, 15.95°, 17.37°, 18.20°, 18.99°, 19.34°, 19.69°, 20.40°, 21.66°, 21.98°, 22.45°, 22.85°, 24.66°, 25.52°, 26.55°, 28.08°, 29.31° and 29.54° and is shown in FIG 2.

Step P (version 2): Making the crystalline Form III particles of hydrate of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (17)



Example 5-2: Compound **14** (16 g) was added to a 100 mL crystallizer, and 46.464 mL of EtOAc and 1.477 mL of distilled water were added to dissolve it. After the dissolution was completed, the internal temperature was set to 20 °C and 2.113 mL (~1 molar equivalent) of concentrated HCl was added. After the addition was completed, the mixture was matured at 15 °C until particles were formed. The filtrate area was analyzed, and when the filtrate area decreased to approximately 80 to 85% of the initial area, the internal temperature was raised to 20 °C. The mixture was subjected to alternating cycles of maturing and filtering until the filtrate area no longer decreased after temperature elevation. The particles collected by filtration are crystalline Form III-1 particles of hydrate of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**17-1**). The powder XRD pattern of **17-1** exhibited characteristic peaks (2θ) at 6.54°, 7.33°, 9.10°, 9.81°, 10.75°, 11.30°, 12.84°, 14.46°, 15.28°, 15.64°, 15.79°, 17.29°, 18.08°, 18.91°, 19.22°, 19.58°, 20.29°, 21.59°, 21.90°, 22.33°, 22.77°, 24.54°, 25.45°, 26.47°, 28.05°, 29.19°, and 29.46°, identifying it as the same crystal form (crystalline Form III) as in **17**.

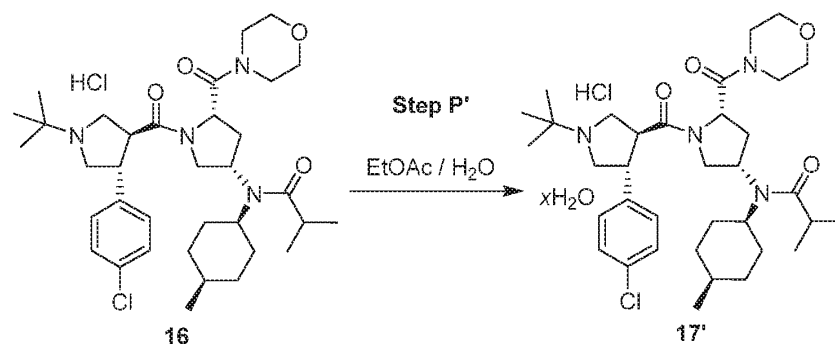
Example 5-3: Compound **14** (16 g) was added to a 100 mL crystallizer, and 46.464 mL of EtOAc and 1.477 mL of distilled water were added to dissolve it. After the dissolution was completed, the internal temperature was set to 20 °C and 2.113 mL (~1 molar equivalent) of concentrated HCl was added. After the addition was completed, the mixture was matured at 10 °C until particles were formed. The filtrate area was analyzed and when the filtrate area decreased to approximately 80 to 85% of the initial area, the internal temperature was raised to 20 °C. The mixture was subjected to alternating cycles of maturing and filtering until the filtrate area no longer decreased after temperature elevation. The particles collected by filtration are

crystalline Form III-2 particles of hydrate of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (**17-2**). The powder XRD pattern of **17-2** exhibited characteristic peaks (2 θ) at 6.46°, 7.36°, 9.10°, 9.73°, 10.63°, 11.30°, 12.80°, 14.42°, 15.20°, 15.68°, 15.79°, 17.25°, 18.08°, 18.87°, 19.18°, 19.54°, 20.25°, 21.51°, 21.86°, 22.33°, 22.73°, 24.54°, 25.37°, 26.43°, 28.01°, 29.19°, and 29.42°, identifying it as the same crystal form (crystalline Form III) as in **17**.

Example 5-4: Compound **14** (16 g) was added to a 100 mL crystallizer, and 46.421 mL of EtOAc and 1.708 mL of distilled water were added to dissolve it. After the dissolution was completed, the internal temperature was set to 20 °C and 2.111 mL (~1 molar equivalent) of concentrated HCl was added. After the addition was completed, the mixture was matured at 13 °C until particles were formed. The filtrate area was analyzed, and when the filtrate area decreased to approximately 80 to 85% of the initial area, the internal temperature was raised to 20 °C. The mixture was subjected to alternating cycles of maturing and filtering until the filtrate area no longer decreased after temperature elevation. The particles collected by filtration are crystalline Form III-3 particles of hydrate of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (**17-3**). The powder XRD pattern of **17-3** exhibited characteristic peaks (2 θ) at 6.42°, 7.29°, 9.06°, 9.73°, 10.71°, 11.26°, 12.80°, 14.42°, 15.20°, 15.60°, 15.76°, 17.25°, 18.04°, 18.83°, 19.18°, 19.50°, 20.25°, 21.51°, 21.82°, 22.29°, 22.69°, 24.50°, 25.37°, 26.43°, 28.01°, 29.19° and 29.42°, identifying it as the same crystal form (crystalline Form III) as in **17**.

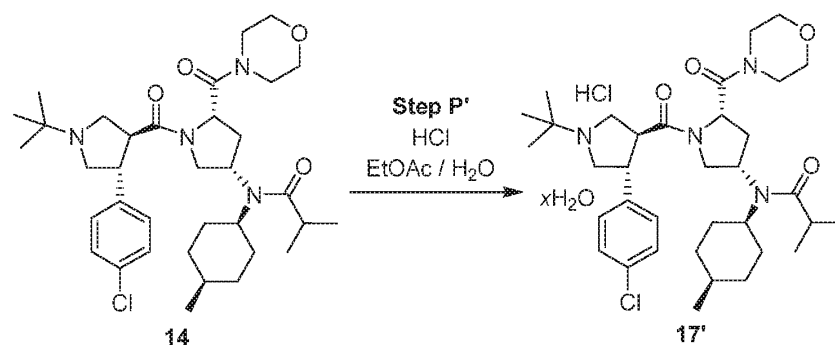
Comparative Example 2: Making particles of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (17'**)**

*Step P' (version 1): Making particles of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1s,4R)-4-methylcyclohexyl)isobutyramide (**17'**)*



Comparative Example 2-1: 1 g of Compound **16** was dissolved using 1 mL of EtOAc at room temperature. After the dissolution was completed, stirring continued for 43 h, but crystals similar to those in Example 5 were not obtained.

*Step P' (version 2): Making particles of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**17'**)*



Comparative Example 2-2: 16 g of Compound **14** was added to a 100 mL crystallizer, and 46.464 mL of EtOAc and 0.703 mL of distilled water were added to completely dissolve it. The internal temperature was set to 20 °C and 2.113 mL (~1 molar equivalent) of conc. HCl was added. After the addition was completed, the mixture was matured at 10 °C until particles were formed. The filtrate area was analyzed, and when the filtrate area decreased, the internal temperature was raised to 20 °C. The mixture was subjected to alternating cycles of maturing and filtering until the filtrate area no longer decreased after temperature elevation. The particles collected by filtration are crystalline Form III-A particles of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**17'-A**). The powder

XRD pattern of the prepared crystalline Form III-A particles exhibited characteristic peaks (2 θ) identifying it as the same crystal form (crystalline Form III) as obtained from Example 5-1.

Comparative Example 2-3: 16 g of Compound **14** was added to a 100 mL crystallizer, and 46.464 mL of EtOAc and 0.440 mL of distilled water were added to completely dissolve it. The internal temperature was set to 20 °C and 2.113 mL (~1 molar equivalent) of conc. HCl was added. After the addition was completed, the mixture was matured at 12.5 °C until particles were formed. The filtrate area was analyzed, and when the filtrate area decreased to approximately 40 to 45% of the initial area, the internal temperature was raised to 20 °C. The mixture was subjected to alternating cycles of maturing and filtering until the filtrate area no longer decreased after temperature elevation. The particles collected by filtration are crystalline Form III-B particles of hydrochloride salt of N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidine-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide (**17'-B**). The powder XRD pattern of the prepared crystalline Form III-B particles exhibited characteristic peaks (2 θ) identifying it as the same crystal form (crystalline Form III) as obtained from Example 5-1.

Experimental Example 1. Comparison of yield of the process of Example 1 with that of Example 2

Compared to Example 1, the preparation method according to Example 2 improves the process of synthesizing **8** by omitting the methyl-protection and deprotection processes and introducing morpholine early. As a result, the process was simplified by reducing 2 steps, and the yield also increased.

Table 1. Comparison of yields of Example 1 with those of Example 2

Example 1	Yield (%)	Example 2	Yield (%)
Compound 2	90.0	Compound 9	85.0
Compound 3	102.5	Compound 10	90.0
Compound 4	44.8	Compound 11	94.0
Compound 5	100.0	Compound 12	76.9
Compound 6	100.0	Compound 8	97.1
Compound 7	70.0	-	-

Compound 8	83.7	-	-
Total Yield (%)	24.2	Total Yield (%)	53.7

Experimental Example 2. Comparison of the reductive amination reaction of the process of Example 1 (Step C) with that of Example 2 (Step J)

In the reductive amination reaction of Example 1 (Step C), about 13% of undesired stereoisomer was generated during the reductive amination reaction from Compound **3** to Compound **4**, and in order to selectively purify this, there was a problem of poor filterability in the process of creating an oxalate salt and filtering it, and there was also a problem of low yield of 55%. When reductive amination is performed with (1s,4s)-4-methylcyclohexan-1-amine hydrochloride, two stereoisomers can be generated, and the ratio is determined depending on the direction in which borohydride is added in the imine reaction intermediate state. If bulkier groups are present on one side of the cyclic ketone (e.g. morpholine compared to methyl ester), the probability borohydride will come from the opposite side should increase. Whereas in Step C the product isomer ratio was 13 to 87, in Step J the ratio was <1 to 99. The results of several batch reproducibility experiments also showed that the minor product isomer of Step J was 0.5 to 0.9%, confirming that the reaction proceeded in a highly stereoselective manner (see FIG. 1).

Experimental Example 3. Comparison of the Conventional Preparation Method According to Comparative Example 1 and the Preparation Method According to Example 3, and Purity Analysis of the Compounds Prepared by Each Method

The methods according to Comparative Example 1 and Example 3 were compared. The compounds prepared were analyzed for purity using HPLC (Column: CAPCELL PAK, TYPE UG120 5 μ m, 4.5 I.D $\times$ 250 mm; Manufacturer: Shiseido), and the results are shown in Table 3.

HPLC Purity Analysis Method

- 1) Column Type: CAPCELL PAK C18, TYPE UG120 5 μ m, 4.6 I.D $\times$ 250 mm
- 2) Injection Volume: 5 μ L
- 3) Mobile Phase A: Acetonitrile + 0.1% TFA (v/v)
- 4) Mobile Phase B: H₂O + 0.1% TFA (v/v)
- 5) Flow Rate: 1.0 mL / min
- 6) Concentration Gradient

- Stop time: 30 min

- Post time: 5 min

Table 2. HPLC solvent program for Experimental Example 3.

Analysis Time (Minutes)	Mobile Phase A (%)	Mobile Phase B (%)
5.00	30	70
10.00	40	60
18.00	50	50
22.00	100	0
25.00	100	0
30.00	30	70

7) Column Temperature: 25 °C (Left, Right)

8) Detector UV wavelength: 220 nm

Table 3. Reaction yields and HPLC purities of Comparative Example 1 vs Example 3.

Comparative Example 1	HPLC Purity (PAR %)	Yield (%)	Example 3	HPLC Purity (PAR %)	Yield (%)
Step M' (Compound 14-A)	89.6 (Reaction) 97.1 (Crude)	-	Step M (Compound 14)	95.6 (Reaction) / 98.4 (Solid)	87.2
Step O' (Compound 16-A)	97.0	71.5	Step N (Compound 15)	99.5	94.6
Overall Yield (%)	-	71.5	Overall Yield (%)	-	82.5

As confirmed in Table 3, the method of Example 3 affords Compound **15** in higher purity and yield compared to Compound **16-A** afforded by Comparative Example 1. In addition, the preparation method of Example 3 has the following advantages over the existing preparation method of Comparative Example 1.

Advantages in Step M vs Step M'

Reduction of HOBt•H₂O usage: 1.5 eq → 0.05 eq

Reduction of reaction time: 14 h → 1 h

Number of work-up extractions: 4 times → 2 times

Introduction of crystallization process: Isolated compounds of **15** may be introduced.

Advantages in Step N vs Step O'

Improvement of yield: 71.5% → 88–94.6%

Securing of process reproducibility

Experimental Example 4. Purity Analysis of Compound 14-2 and Compound 16 According to Example 4.

The purities of Compound **14** and Compound **16**, as prepared in Example 4, were measured as 97.2% and 99.8%, respectively, using HPLC (as detailed in Experimental Example 3).

Experimental Example 5. Differential Scanning Calorimetry (DSC) Analysis of Crystalline Form III Particles (17)

DSC was measured using a Mettler Toledo DSC 1 system. The sample (2 to 5 mg) was placed in a 40 μ L Alcrucible (a flat-bottomed aluminum pan) with a one pin-hole lid. The sample was heated from 25 °C to 350 °C at a rate of 10 °C/min, and DSC data was recorded. During measurement, nitrogen gas was supplied to the inside of the equipment at a rate of 70 mL/min to prevent the inflow of oxygen and other gases. Data collection and evaluation were performed using the software STARe.

The results of DSC measurement of the obtained crystalline Form III are shown in FIG. 3. The first endothermic peak of crystalline Form III was observed at approximately 42.3 °C (onset), and the second endothermic peak was observed at approximately 124.7 °C (onset). An endothermic peak due to decomposition appeared after approximately 220 °C. Temperature values have a margin of error of ± 5 °C.

Experimental Example 6. Thermogravimetric Analysis (TGA) of Crystalline Form III Particles (17)

TGA was measured using a Mettler Toledo TGA/DSC 1 module. The sample (~4 to 8 mg) was placed into a 100 μ L Alcrucible (flat-bottomed aluminum crucible). Afterwards, the sample was heated from 30 °C to 350 °C at a rate of 10 °C/min, and TGA data was measured. During measurement, nitrogen gas was supplied to the inside of the equipment at a rate of 80 mL/min to prevent the inflow of oxygen and other gases. Data collection and evaluation were performed

using the software STARe.

The results of TGA measurement of the obtained crystalline Form III are shown in FIG. 4. A weight loss of approximately 2.4% was observed in crystalline Form III at temperature below 100 °C. Afterwards, a weight loss of approximately 4.8% occurred at 110 to 150 °C. Weight loss due to decomposition occurred after approximately 220 °C. Temperature values have a margin of error of ± 5 °C.

Experimental Example 7. Stability Evaluation of Crystalline Form III Particles (17)

Samples weighing approximately 10 to 30 mg were stored in an open state under accelerated conditions (40 °C, 75% RH) or in a sealed state in an oven at 80 °C for 4 weeks under harsh conditions. To compare the samples with samples stored at room temperature, HPLC analysis was performed using the method in Table 2 below.

Table 2

Column temperature	30 °C	
Mobile phase A	Acetonitrile/Trifluoroacetic acid = 100/0.1 (% , v/v)	
Mobile phase B	Acetonitrile/Trifluoroacetic acid = 100/0.1 (% , v/v)	
Gradient system		
Time (minutes)	Mobile phase A (%)	Mobile phase B (%)
0	40	60
10	50	50
13	50	50
18	40	60
Flow rate	1 mL/min	
Detected wavelength	UV 214 nm	
Injection amount	5 µL	

The results of evaluating the stability of the obtained crystalline Form III are shown in Table 3 below.

Table 3

Time	Example 1-1	
	accelerated conditions	sealed conditions
Initial	99.68	
Week 2	99.27	99.11
Week 4	99.26	98.76

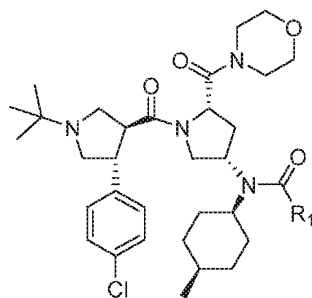
As can be confirmed in Table 3 above, the crystalline Form III according to the present invention showed chemical stability for 4 weeks under accelerated conditions (40 °C, 75% RH) and sealed conditions (80 °C), confirming that it exhibits excellent stability to heat and humidity.

The inventors of the present invention conducted subsequent studies and found that when HCl is added in excess of 1 molar equivalent, the pH of the solution decreases and particle formation does not occur easily.

In addition, the inventors of the present invention found that when crystallization is performed using a mixed solvent of water and an organic solvent, the particle formation rate, particle size, and degree of fine particle formation vary depending on the ratio of water content in the solution. Specifically, it was found that when the ratio of water in the solvent is lower than the appropriate ratio of water, crystalline Form III particles can be formed quickly, but the size of the particles decreases as the particle formation proceeds quickly, and a large number of fine particles are formed, and when the ratio of water in the solvent is higher than the appropriate ratio of water, the formation of crystalline Form III particles itself occurs very slowly or does not occur at all. It was found that when the ratio of water in the solvent is appropriate, the particle size is improved as the crystalline Form III particles are produced at an appropriate rate, and the formation of fine particles is also minimized. The appropriate ratio of water in the mixed solvent is a volume ratio of water and organic solvent of 1:20 to 1:40, specifically, a volume ratio of 1:27 to 1:32.

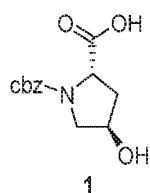
CLAIMS

1. A method for preparing a compound of Formula (XI):



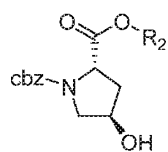
(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein R_1 is C_2 - C_5 alkyl, comprising Step A of reacting Compound **1**



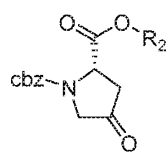
with an alcohol having 1 to 6 carbon atoms and an acid catalyst to form a compound

of Formula (IV):



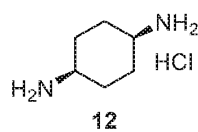
(IV), wherein R_2 is C_1 - C_6 alkyl.

2. The method of claim 1, wherein the method further comprises Step B of reacting a compound of Formula (IV) with an oxidizing agent in a solvent to form a compound of Formula (V):

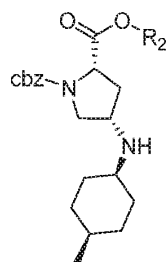


(V), wherein R_2 is C_1 - C_6 alkyl.

3. The method of claim 1, wherein the method further comprises Step C of reacting a compound of Formula (V) with Compound **12**

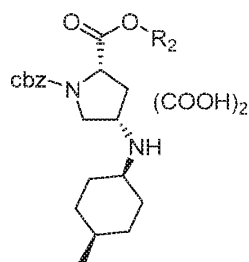


, base, and reducing agent in a solvent to form a compound of Formula (VII'):

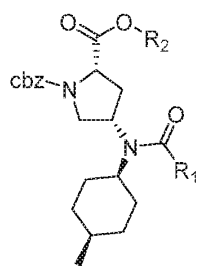


4. The method of claim 3, wherein Step C further includes reacting a compound of Formula (VII') with an acid in an organic solvent.

5. The method of claim 3, wherein Step C further includes reacting a compound of Formula (VII') with oxalic acid in an organic solvent to form a compound of Formula (VII):

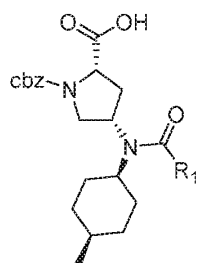


6. The method of claim 1, wherein the method further comprises Step D of subjecting a compound of Formula (VII) or a compound of Formula (VII') to a reaction with at least one base and a compound of formula R₁-C(=O)-Cl (e.g. isobutyryl chloride) to form a compound of Formula (VIII):



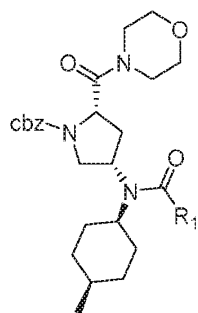
(VIII), wherein R₁ is C₂-C₅ alkyl, and R₂ is C₁-C₆ alkyl.

7. The method of claim 1, wherein the method further comprises Step E of reacting a compound of Formula (VII) and inorganic base in a solvent to prepare a compound of Formula (IX):



(IX), or a salt or solvate thereof, wherein R₁ is C₂-C₅ alkyl.

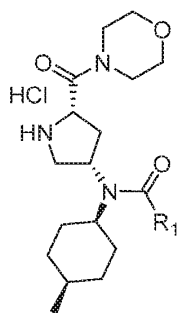
8. The method of claim 1, wherein the method further comprises Step F of reacting a compound of Formula (IX) with morpholine to form a compound of Formula (X):



(X), or a salt or solvate thereof, wherein R₁ is C₂-C₅ alkyl.

9. The method of claim 8, wherein Step F is facilitated by a coupling agent.
10. The method of claim 9, wherein Step F is further facilitated by a reaction accelerating additive.
11. The method of any one of claims 8-10, wherein Step F includes the use of base.

12. The method of claim 1, wherein the method further comprises Step G of reacting a compound of Formula (X) in a solvent with a hydrogenation catalyst and H₂ or with deprotecting acid solution, and treatment with HCl solution to form a compound of Formula (II):



13. The method of claim 1, wherein R₂ is methyl, ethyl, propyl, isopropyl, or butyl.

14. The method of claim 1, wherein R₂ is methyl.

15. The method of claim 1, wherein the acid catalyst of Step A is at least one selected from the group of HCl, H₂SO₄, H₂SO₄ and KF, a combination of Al₂O₃ (KF + Al₂O₃), H₃PO₄, p-toluene sulfonic acid, and scandium(III) triflate.

16. The method of claim 1, wherein the acid catalyst of Step A is H₂SO₄.

17. The method of claim 1, wherein the acid catalyst of Step A is 0.1 to 1 molar equivalent with respect to Compound 1.

18. The method of claim 1, wherein the acid catalyst of Step A is 0.2 to 0.5 molar equivalent with respect to Compound 1.

19. The method of claim 1, wherein the acid catalyst of Step A is 0.2 to 0.4 molar equivalent with respect to Compound 1.

20. The method of claim 1, wherein the reaction time of Step A above is 2 to 5 hours.

21. The method of claim 2, wherein the solvent of Step B is water and at least one organic solvent selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.
22. The method of claim 2, wherein the solvent of Step B is water and dichloromethane.
23. The method of claim 3, wherein the solvent of Step C, Step D, Step E, and/or Step F is at least one independently selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.
24. The method of claim 2, wherein the oxidizing agent of Step B is a combination of a chromic acid compound; a co-oxidizing agent, (2,2,6,6-tetramethylpiperidinyloxy) free radical (TEMPO) and other salts; a complex of dimethyl sulfoxide and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride or phosphorus pentoxide or a complex of pyridine-sulfuric anhydride; or a combination of a transition metal catalyst and oxygen, or a transition metal catalyst and an organic oxidizing agent.
25. The method of claim 2, wherein the oxidizing agent of Step B is (2,2,6,6-tetramethylpiperidinyloxy) free radical (TEMPO) and other salts.
26. The method of claim 25, wherein the other salts referenced include at least one of sodium bromide and sodium hypochlorite.
27. The method of claim 2, wherein Step B includes at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaHCO₃.

28. The method of claim 2, wherein Step B includes NaHCO_3 .
29. The method of claim 2, wherein Step B is performed with reaction temperature between -10 and $10\text{ }^\circ\text{C}$, and the reaction time is 0.5 h or longer.
30. The method of claim 5, wherein the reducing agent of Step C is at least one inorganic base selected from the group consisting of $\text{NaBH}(\text{OAc})_3$, NaBH_4 , $\text{NaBH}(\text{CN})_3$, NaBH_3CN , and NaH_2PO_2 .
31. The method of claim 5, wherein the reducing agent of Step C is $\text{NaBH}(\text{OAc})_3$.
32. The method of claim 5, wherein the reaction temperature of Step C is 1 to $30\text{ }^\circ\text{C}$, and the reaction time is 1 to 30 hours.
33. The method of claim 5, wherein the reaction temperature of Step C is 15 to $25\text{ }^\circ\text{C}$.
34. The method of claim 6, wherein the base of Step D is at least one selected form the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO_4 , LiOH, NaH, KH, NaOCH_3 , $\text{NaOCH}_2\text{CH}_3$, $\text{NaOC}(\text{CH}_3)_3$, $\text{KOC}(\text{CH}_3)_3$, K_2CO_3 , Na_2CO_3 , and NaHCO_3 .
35. The method of claim 6, wherein the base of Step D includes ammonia aqueous solution for pre-treating the compound of Formula (VII').
36. The method of claim 6, wherein the base of Step D includes TEA during reaction with acid chloride.
37. The method of claim 6, wherein the amount of acid chloride in Step D is 1 molar equivalent or more with respect to the compound of Chemical Formula (VII).
38. The method of claim 6, wherein the amount of acid chloride in Step D is 1.5 to 3.0 molar equivalent with respect to the compound of Chemical Formula (VII).

39. The method of claim 6, wherein the reaction temperature of Step D is 1 to 30 °C, and the reaction time is 1 to 30 hours.
40. The method of claim 6, wherein the reaction temperature of Step D is below 20 °C, and the reaction time is 5 to 15 hours.
41. The method of claim 7, wherein Step E includes at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaHCO₃.
42. The method of claim 7, wherein Step E includes LiOH as inorganic base.
43. The method of claim 7, wherein Step E includes an acidic workup.
44. The method of claim 7, wherein the reaction temperature of Step E is 1 to 30 °C, and the reaction time is 1 to 30 hours.
45. The method of claim 7, wherein the reaction temperature of Step E is 1 to 20 °C, and the reaction time is 1 to 10 hours.
46. The method of claim 8, wherein the coupling agent of Step F is selected from the group consisting of N,N'-disubstituted carbodiimides such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; phosphonium reagents such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim), and 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); and aminium/uronium reagents such as 2-(1H-benzotriazol-1-yl)-N,N,N',N'-

tetramethylammonium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylammonium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminoxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU).

47. The method of any one of the preceding embodiments, wherein the coupling agent of Step F is ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl).

48. The method of claim 8, wherein the coupling agent of Step F is used in an amount of 1 to 2 equivalents with respect to the compound of Chemical Formula (IX).

49. The method of claim 8, wherein the additive of Step F is selected from the group consisting of 1-hydroxybenzotriazole (HOBt) and its derivatives such as hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOObt), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), resin-supported derivatives, and hydrates thereof; N-hydroxysuccinimide (NHS); and 4-dimethylpyridine (DMAP).

50. The method of claim 8, wherein the additive of Step F is 1-hydroxybenzotriazole (HOBt) or its hydrate (HOBt·H₂O).

51. The method of claim 8, wherein the additive of Step F is used in an amount of 0.01 to 2 equivalents with respect to the compound of Chemical Formula (IX).

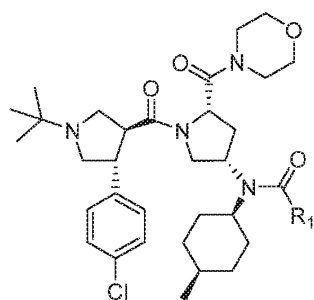
52. The method of claim 8, wherein the base of Step F is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

53. The method of claim 8, wherein the base of Step F is DIPEA.

54. The method of claim 8, wherein the reaction temperature of Step F is 1 to 30 °C, and the reaction time is 1 to 30 hours.

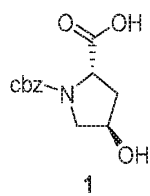
55. The method of claim 8, wherein the reaction temperature of Step F is 1 to 20 °C, and the reaction time is 1 to 8 hours.

56. The method of claim 12, wherein the hydrogenation catalyst of Step G is at least one selected from the group consisting of Pd/C, Pd(OH)₂, Pd(OAc)₂, PdCl₂ and Pd.
57. The method of claim 12, wherein the hydrogenation catalyst of Step G is Pd/C.
58. The method of claim 12, wherein the reaction temperature of Step G is 1 to 50 °C, and the reaction time is 1 to 30 hours.
59. The method of claim 12, wherein the deprotecting acid solution of Step G is HCl aqueous solution of >10% (w/w) concentration.
60. The method of claim 12, wherein the deprotecting acid solution of Step G is HCl aqueous solution of >30% (w/w) concentration.
61. A method for preparing a compound of Formula (XI):

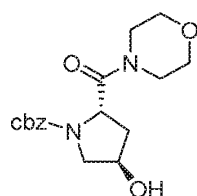


(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

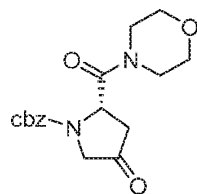
wherein R₁ is C₂-C₅ alkyl, comprising Step H of reacting Compound **1**



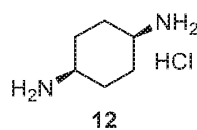
with morpholine to form Compound **9**:

**9**

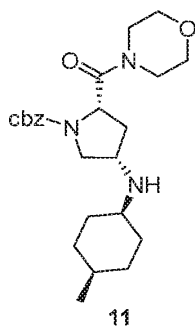
62. The method of claim 61, wherein Step H is facilitated by a coupling agent.
63. The method of claim 62, wherein Step H is further facilitated by a reaction accelerating additive.
64. The method of claim 61, wherein Step H includes the use of base.
65. The method of claim 61, wherein the method further comprises Step I of reacting Compound **9** with an oxidizing agent in a solvent to form Compound **10**:

**10**

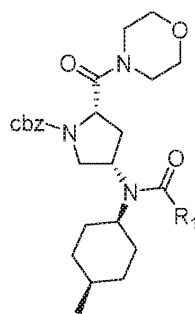
66. The method of claim 61, wherein the method further comprises Step J of reacting Compound **10** with Compound **12**:

**12**

, base, and reducing agent in a solvent to form Compound **11**:

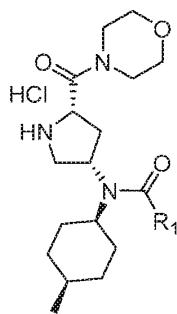


67. The method of claim 61, wherein the method further comprises Step K of reacting Compound **11** with at least one base and an acid chloride compound of formula $R_1-C(=O)-Cl$ (e.g. isobutyryl chloride) to form a compound of Formula (X):



(X), wherein R_1 is C₂-C₅ alkyl.

68. The method of claim 61, wherein the method further comprises Step G of reacting a compound of Formula (X) in a solvent with a hydrogenation catalyst and H_2 or with deprotecting acid solution, and treatment with HCl solution to form a compound of Formula (II):



(II), wherein R_1 is C₂-C₅ alkyl.

69. The method of claim 61, wherein the coupling agent of Step H is selected from the group

consisting of N,N'-disubstituted carbodiimide such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; phosphonium reagents such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim), and 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); and aminium/uronium reagents such as 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminoxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU).

70. The method of any one of the preceding embodiments, wherein the coupling agent of Step H is ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl).

71. The method of claim 61, wherein the coupling agent of Step H is used in an amount of 1 to 2 equivalents with respect to Compound 1.

72. The method of claim 61, wherein the additive of Step H is selected from the group consisting of 1-hydroxybenzotriazole (HOBt) and its derivatives such as hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOObt), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), resin-supported derivatives, and hydrates thereof; N-hydroxysuccinimide (NHS); and 4-dimethylpyridine (DMAP).

73. The method of claim 61, wherein the additive of Step H is 1-hydroxybenzotriazole (HOBt) or its hydrate (HOBt·H₂O).

74. The method of claim 61, wherein the additive of Step H is used in an amount of 0.01 to 2 equivalents with respect to the compound of Chemical Formula (IX).

75. The method of claim 61, wherein the base of Step H is at least one selected from the group

consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

76. The method of claim 61, wherein Step H does not contain any base among the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

77. The method of claim 61, wherein the reaction temperature of Step H is 1 to 30 °C, and the reaction time is 1 to 30 hours.

78. The method of claim 61, wherein the reaction temperature of Step H is 1 to 20 °C, and the reaction time is 1 to 8 hours.

79. The method of claim 61, wherein the solvent of Step I is water and at least one organic solvent selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

80. The method of claim 61, wherein the solvent of Step I is water and dichloromethane.

81. The method of claim 61, wherein the solvent of Step H, Step J, and/or Step K is at least one independently selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

82. The method of claim 61, wherein the oxidizing agent of Step I is a combination of a chromic acid compound; a co-oxidizing agent, (2,2,6,6-tetramethylpiperidinyl)oxyl free radical (TEMPO) and other salts; a complex of dimethyl sulfoxide and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride or phosphorus pentoxide or a complex of pyridine-sulfuric anhydride; or a

combination of a transition metal catalyst and oxygen, or a transition metal catalyst and an organic oxidizing agent.

83. The method of claim 61, wherein the oxidizing agent of Step I is (2,2,6,6-tetramethylpiperidinyl)oxyl free radical (TEMPO) and other salts.

84. The method of embodiment 83, wherein the other salts referenced include at least one of sodium bromide and sodium hypochlorite.

85. The method of claim 61, wherein Step I includes at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaHCO₃.

86. The method of claim 61, wherein Step I includes NaHCO₃.

87. The method of claim 61, wherein Step I is performed with reaction temperature between -10 and 10 °C, and the reaction time is 0.5 h or longer.

88. The method of claim 61, wherein the reducing agent of Step J is at least one inorganic base selected from the group consisting of NaBH(OAc)₃, NaBH₄, NaBH(CN)₃, NaBH₃CN, and NaH₂PO₂.

89. The method of claim 61, wherein the reducing agent of Step J is NaBH(OAc)₃.

90. The method of claim 61, wherein the amount of reducing agent in Step J is more than 1 equivalent relative to Compound **10**.

91. The method of claim 61, wherein the amount of reducing agent in Step J is 1.01 to 1.2 equivalents relative to Compound **10**.

92. The method of claim 61, wherein the base in Step J is selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaOAc.
93. The method of claim 61, wherein the base in Step J is NaOAc.
94. The method of claim 61, wherein the reaction temperature of Step J is 1 to 30 °C, and the reaction time is 1 to 30 hours.
95. The method of claim 61, wherein the reaction temperature of Step J is -5 to 30 °C.
96. The method of claim 61, wherein the base of Step J is at least one selected form the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, Na₂CO₃, and NaHCO₃.
97. The method of claim 61, wherein the base of Step J is DIPEA.
98. The method of claim 61, wherein the base of Step J is TEA.
99. The method of claim 61, wherein the amount of acid chloride in Step J is 1 molar equivalent or more with respect to the compound of Chemical Formula (VII).
100. The method of claim 61, wherein the amount of acid chloride in Step J is 1.0 to 3.0 molar equivalent with respect to the compound of Chemical Formula (VII).
101. The method of claim 61, wherein the reaction temperature of Step J is 1 to 30 °C, and the reaction time is 1 to 30 hours.
102. The method of claim 61, wherein the reaction temperature of Step J is below 20 °C, and the reaction time is 5 to 15 hours.

103. The method of claim 61, wherein the hydrogenation catalyst of Step G is at least one selected from the group consisting of Pd/C, Pd(OH)₂, Pd(OAc)₂, PdCl₂ and Pd.

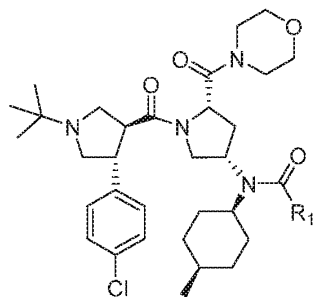
104. The method of claim 61, wherein the hydrogenation catalyst of Step G is Pd/C.

105. The method of claim 61, wherein the reaction temperature of Step G is 1 to 50 °C, and the reaction time is 1 to 30 hours.

106. The method of claim 61, wherein the deprotecting acid solution of Step G is HCl aqueous solution of >10% (w/w) concentration.

107. The method of claim 61, wherein the deprotecting acid solution of Step G is HCl aqueous solution of >30% (w/w) concentration.

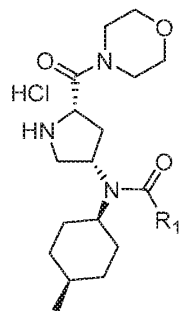
108. A method for preparing a compound of Formula (XI):



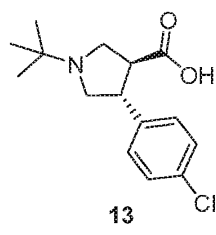
(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

comprising Step M of reacting a compound of Formula (II):

Formula (II):



(II), or a conjugate base, or a solvate thereof, with Compound **13**:



, or a salt, or a solvate thereof,

wherein R₁ is C₂-C₅ alkyl.

109. The method of claim 108, wherein Step M is facilitated by a coupling agent.

110. The method of claim 109, wherein Step M is further facilitated by a reaction accelerating additive.

111. The method of claim 109, wherein Step M includes the use of base.

112. The method of claim 109, wherein the coupling agent of Step M is selected from the group consisting of N,N'-disubstituted carbodiimide such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ); phosphorus oxychloride; alkoxyacetylene; phosphonium reagents such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PyBrOP), ethyl cyano(hydroxyimino)acetato-O²-tri-(1-pyrrolidiny)-phosphonium hexafluorophosphate (PyOxim), and 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d] triazin-4(3H)-one (DEPBT); and aminium/uronium reagents such as 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium (TBTU) tetrafluoroborate/hexafluorophosphate, 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HATU), and 1-[1-(cyano-2-ethoxy-2-oxoethylidene-aminoxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU).

113. The method of claim 109, wherein the coupling agent of Step M is ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl).

114. The method of claim 109, wherein the coupling agent of Step M is used in an amount of 1 to 2 equivalents with respect to Compound 1.

115. The method of claim 109, wherein the additive of Step M is selected from the group consisting of 1-hydroxybenzotriazole (HOBt) and its derivatives such as hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOObt), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), resin-supported derivatives, and hydrates thereof; N-hydroxysuccinimide (NHS); and 4-dimethylpyridine (DMAP).

116. The method of claim 109, wherein the additive of Step M is 1-hydroxybenzotriazole (HOBt) or its hydrate (HOBt•H₂O).

117. The method of claim 109, wherein the additive of Step M is used in an amount of 0.01 to 2 equivalents with respect to the compound of Chemical Formula (II).

118. The method of claim 109, wherein the base of Step M is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

119. The method of claim 109, wherein Step M does not contain any base among the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

120. The method of claim 109, wherein the reaction temperature of Step M is -10 to 30 °C, and the reaction time is 0.5 to 30 hours.

121. The method of claim 109, wherein the reaction temperature of Step M is 1 to 25 °C, and the reaction time is 0.5 to 6 hours.

122. The method of claim 109, wherein the reaction solvent of Step M is selected from the group consisting of ethyl ether, tetrahydrofuran, dioxane, dichloromethane, chloroform, methyl acetate,

ethyl acetate, isopropyl acetate, acetone, methyl ethyl ketone, acetonitrile, propionitrile, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, and a mixed solvent thereof.

123. The method of claim 109, wherein the reaction solvent of Step M is acetone.

124. The of claim 109, wherein Step M further comprises crystallization of the synthesized compound of Formula (XI).

125. The of claim 109, wherein the crystallization step of Step M is comprised of the following steps:

- a) concentrating the synthesized compound of Formula (XI), dissolving the concentrated residue using a solvent, and then washing it using a washing solvent;
- b) separating an aqueous layer from the product of Step a) above, concentrating the separated aqueous layer, adding H₂O, and then cooling it; and
- c) adding a base aqueous solution dropwise and stirring to obtain a crystallized compound of Formula (XI).

126. The method of claim 125, wherein the cooling temperature in Step b) is -10 to 30 °C.

127. The method of claim 125, wherein the cooling temperature in Step b) is 0 to 5 °C.

128. The method of claim 125, wherein the base aqueous solution of Step c) is an aqueous solution containing at least one base selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

129. The method of claim 125, wherein the base aqueous solution of Step c) is an aqueous solution containing NaOH.

130. The method of claim 125, wherein the stirring time of Step c) is 0.5 to 24 h.

131. The method of claim 125, wherein the stirring time of Step c) is 1 to 6 h.

132. The method of claim 108, wherein Step M further comprises a step of filtering, washing, or drying the product.

133. The method of claim 108, wherein the method further comprises Step N of purifying a compound of Formula (XI), a pharmaceutically acceptable salt thereof, or a solvate thereof.

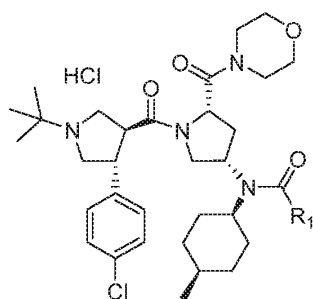
134. The method of claim 133, wherein Step N comprises dissolving the compound of Formula (XI) in an organic solvent or organic solvent mixture, stirring the mixture, cooling it, and stirring the mixture again to obtain purified precipitate.

135. The method of claim 134, wherein the organic solvent of Step N is selected from the group consisting of acetone, acetonitrile, dichloromethane, dimethylformamide, dimethylacetamide, dimethylpropyleneurea, dimethylsulfoxide, ethyl acetate, hexamethylphosphoramide, tetrahydrofuran, methyl-tert-butyl ether, pentane, hexane, heptane, ether, toluene, methyl acetate, isopropyl acetate, alcohols with 1 to 6 carbon atoms, diethyl ether, dichloromethane, chloroform, and a mixture thereof.

136. The method of claim 133, wherein the organic solvent of Step N is selected from the group consisting of acetone, pentane, hexane, heptane, or a mixture thereof.

137. The method of claim 133, wherein the first stirring time of Step 2) of Step N is 10 hours or more, the cooling temperature after stirring is 0 to 10 °C, and the second stirring time is 0.5 to 2 hours.

138. The method of claim 108, wherein the method further comprises Step O of reacting a compound of Formula (XI) generated from Step M with HCl without an additional purification process to prepare a compound of Formula (XII):



(XII), a pharmaceutically acceptable salt thereof, or a solvate thereof.

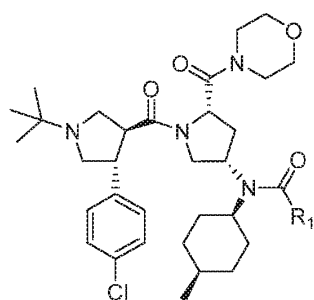
wherein R₁ is a C₂-C₅ alkyl group.

139. The method of claim 138, wherein Step O is carried out through the preparation of the compound of Formula (XII) by reacting the crude compound of Chemical Formula (XI) generated in Step M with HCl in an organic solvent without an additional purification process.

140. The method according to embodiment 139, wherein the organic solvent is selected from the group consisting of acetone, acetonitrile, dichloromethane, dimethylformamide, dimethylpropyleneurea, dimethylsulfoxide, ethyl acetate, hexamethylphosphoamide, tetrahydrofuran, methyl-tert-butylether, pentane, hexane, heptane, ether, diethylether, and a mixed solvent thereof.

141. The method of claim 138, wherein the reaction temperature of Step O is -20 °C to 100 °C, and the reaction time is 10 minutes or more.

142. A method for preparing a compound of Formula (XI):



(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein R₁ is C₂-C₅ alkyl, comprising Step P of preparing crystalline Form III particles of a compound of Formula (XI) and wherein

the crystalline Form III has the following diffraction angles (2θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among $6.62\pm 0.2^\circ$, $7.44\pm 0.2^\circ$, $9.18\pm 0.2^\circ$, $9.89\pm 0.2^\circ$, $10.83\pm 0.2^\circ$, $11.42\pm 0.2^\circ$, $12.92\pm 0.2^\circ$, $14.61\pm 0.2^\circ$, $15.36\pm 0.2^\circ$, $15.79\pm 0.2^\circ$, $15.95\pm 0.2^\circ$, $17.37\pm 0.2^\circ$, $18.20\pm 0.2^\circ$, $18.99\pm 0.2^\circ$, $19.34\pm 0.2^\circ$, $19.69\pm 0.2^\circ$, $20.40\pm 0.2^\circ$, $21.66\pm 0.2^\circ$, $21.98\pm 0.2^\circ$, $22.45\pm 0.2^\circ$, $22.85\pm 0.2^\circ$, $24.66\pm 0.2^\circ$, $25.52\pm 0.2^\circ$, $26.55\pm 0.2^\circ$, $28.08\pm 0.2^\circ$, $29.31\pm 0.2^\circ$ and $29.54\pm 0.2^\circ$;

143. The method of claim 142, wherein Step P is comprised of:

- (a) preparing a mixed solution by dissolving the compound of Formula (XI) in a crystallization solvent comprising water or a mixture of water and an organic solvent;
- (b) crystallizing by adding HCl dropwise to the solution; and
- (c) maturing the solution.

144. The method of claim 143, wherein the organic solvent of the crystallization solvent of Step P is a polar aprotic organic solvent.

145. The method of claim 144, wherein the polar aprotic organic solvent comprises ethyl acetate, methyl isobutylketone, dimethylsulfoxide, tetrahydrofuran, acetone, dimethylformamide, acetonitrile, and the mixtures thereof.

146. The method of claim 142, wherein the dropwise addition of HCl is administered through a 4 M HCl solution, a 6 N HCl solution, or a concentrated HCl (conc. HCl) solution in water or ethyl acetate.

147. The method of claim 142, wherein for Step P, the dropwise addition of HCl is administered in an amount of 1 equivalent or less to the compound of Formula (XI).

148. The method of claim 142, wherein for Step P, the crystallization solvent is a mixed solvent in which water and an organic solvent are mixed in a volume ratio of 1:20 to 1:40.

149. The method of claim 142, wherein for Step P, the crystallization solvent is a mixed solvent in

which water and an organic solvent are mixed in a volume ratio of 1:27 to 1:32.

150. The method of claim 142, wherein for Step P, HCl addition is performed at 15 °C to 25 °C.

151. The method of claim 142, wherein for Step P, maturing the solution is performed at 10 °C to 20 °C.

152. The method of claim 142, wherein for Step P, maturing the solution comprises:

(c-1) maturing at 10 °C to 15 °C until filtrate area decreases to 80% to 85% of the initial area;

and

(c-2) maturing by raising the temperature to 20 °C until the filtrate area no longer decreases.

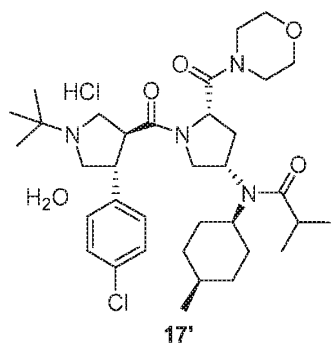
153. The method of any one of the preceding embodiments, wherein Step P further comprises:

(d) filtering the solution.

154. The method of claim 142, wherein the crystalline Form III particles formed by Step P are crystalline form particles of a solvate of the hydrochloride salt of the compound of Formula (XI).

155. The method of claim 154, wherein the solvate is a hydrate.

156. The method of claim 142, wherein the compound of Formula (XI) is Compound 17':



157. The method of claim 142, wherein the crystalline Form III particles have a flow function value of at least 8 under a pressure of 9 kPa.

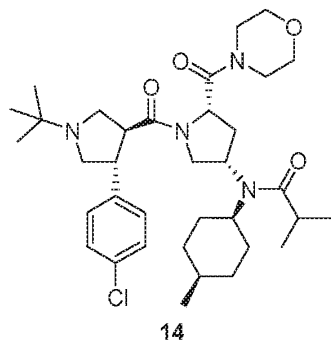
158. A crystalline Form III particle of a compound of Formula (XI), a pharmaceutically acceptable salt thereof, or a solvate thereof, prepared by the preparation method according to embodiments 142-157, wherein

the crystalline Form III has the following diffraction angles (2θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among $6.62\pm0.2^\circ$, $7.44\pm0.2^\circ$, $9.18\pm0.2^\circ$, $9.89\pm0.2^\circ$, $10.83\pm0.2^\circ$, $11.42\pm0.2^\circ$, $12.92\pm0.2^\circ$, $14.61\pm0.2^\circ$, $15.36\pm0.2^\circ$, $15.79\pm0.2^\circ$, $15.95\pm0.2^\circ$, $17.37\pm0.2^\circ$, $18.20\pm0.2^\circ$, $18.99\pm0.2^\circ$, $19.34\pm0.2^\circ$, $19.69\pm0.2^\circ$, $20.40\pm0.2^\circ$, $21.66\pm0.2^\circ$, $21.98\pm0.2^\circ$, $22.45\pm0.2^\circ$, $22.85\pm0.2^\circ$, $24.66\pm0.2^\circ$, $25.52\pm0.2^\circ$, $26.55\pm0.2^\circ$, $28.08\pm0.2^\circ$, $29.31\pm0.2^\circ$ and $29.54\pm0.2^\circ$; and

the crystalline Form III particle has a flow function value of at least 8 under a pressure of 9 kPa.

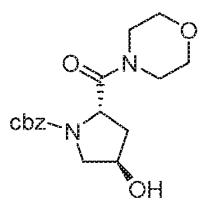
159. A pharmaceutical composition for preventing or treating obesity, diabetes, inflammation or erectile dysfunction, comprising the crystalline Form III particle according to claim 158 and a pharmaceutically acceptable carrier.

160. The method of claim 108, wherein the compound of Formula (XI) is Compound 14:

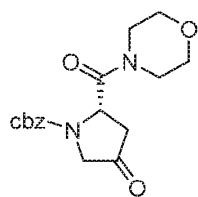


, or a pharmaceutically acceptable salt, or a solvate thereof.

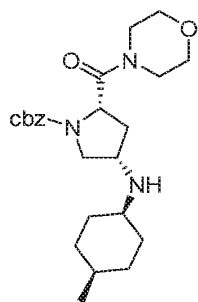
161. The Compound 9:

**9**

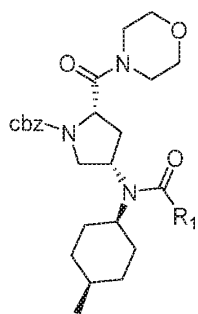
162. The Compound **10**:

**10**

163. The Compound **11**:

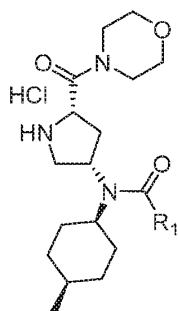
**11**

164. A compound of Formula (X):



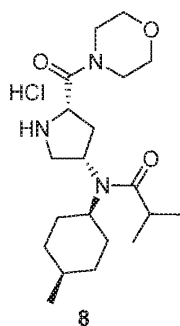
(X), wherein R₁ is C₂-C₅ alkyl.

165. A compound of Formula (II):

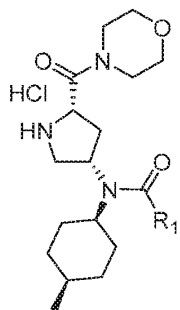


(II), wherein R₁ is C₂-C₅ alkyl.

166. A compound of Formula (II) according to claim 165, wherein R₁ is isopropyl, e.g., Compound 8:

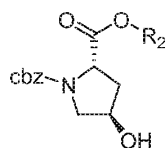


167. A method for preparing Formula (II):

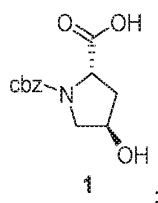


(II), including the steps of:

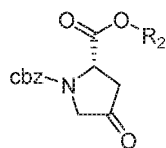
8) Preparing a compound of Formula (IV):



(IV), through an alkylation reaction by adding an alcohol having 1 to 6 carbon atoms and an acid catalyst to Compound 1:

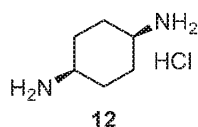


- 9) Preparing a compound of Formula (V):

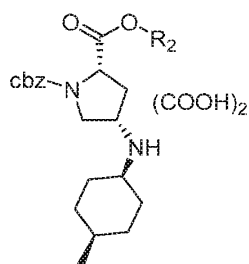


above with an oxidizing agent in a solvent;

- 10) Introducing a Compound **12**:

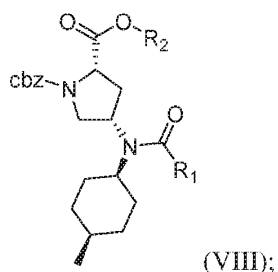


adding a compound of Formula (V) dissolved in the organic solvent dropwise, stirring, and performing a reductive amination reaction, concentrating and obtaining a synthesized crude compound, adding an organic solvent to the residue of the crude compound to prepare a crude compound/organic solvent solution, and adding this solution dropwise to a solution in which oxalic acid is dissolved in an organic solvent to obtain a compound of Formula (VII):

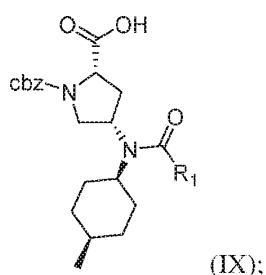


- 11) Adding an organic solvent to the compound of Formula (VII) prepared in Step 3) above, adjusting the pH with a base, adding water to separate the layers, extracting the aqueous layer with the organic solvent, adding a base after dissolving the resulting residue obtained after washing, concentrating, and azeotroping along with

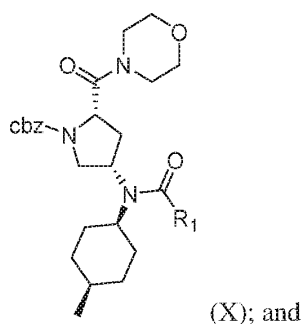
the oil layer in an organic solvent, and adding $R_1-C(=O)-Cl$ dropwise to perform an N-acylation reaction to prepare a compound of Formula (VIII):



- 12) Adding an alcohol having 1 to 6 carbon atoms and an organic solvent to the compound of Formula (VIII) and then performing dealkylation by adding a solution containing an inorganic base dropwise to prepare a crude compound of Formula (IX):



- 13) Adding an organic solvent to the crude compound of Formula (IX) prepared in Step 5) above and dissolving it, sequentially adding a reaction accelerating additive, a base, and a coupling agent, and then adding morpholine dropwise to prepare a compound of Formula (X):



- 14) Dissolving the compound of Formula (X) prepared in Step 6) above in an alcohol having 1 to 6 carbon atoms, deprotecting it by adding Pd/C and H_2 , and adding HCl dissolved in ethyl acetate dropwise to synthesize the compound of Formula (II):

wherein in the above Formulas, R_1 is C_2 - C_5 alkyl and R_2 is C_1 - C_6 alkyl.

168. The preparation method of claim 167, wherein the alcohol having 1 to 6 carbon atoms in Step 1), 5) or 7) above is methanol, ethanol, propanol, isopropanol or butanol.

169. The preparation method of claim 167, wherein the acid catalyst of Step 1) above is at least one selected from the group consisting of HCl, H_2SO_4 , H_2SO_4 and KF, and a combination of Al_2O_3 ($KF+Al_2O_3$).

170. The preparation method of claim 167, wherein the content of the acid catalyst of Step 1) above is 0.1 to 1 equivalent with respect to the Compound 1.

171. The preparation method of claim 167, wherein the reaction time of Step 1) above is 2 to 5 hours.

172. The preparation method of claim 167, wherein the solvent of Step 2) above is water and at least one organic solvent selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

173. The preparation method of claim 167, wherein the organic solvent of Step 3), 4), 5) or 6) above is at least one selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether and diethyl ether.

174. The preparation method of claim 167, wherein the oxidizing agent of Step 2) above is a combination of a chromic acid compound; a co-oxidizing agent, (2,2,6,6-tetramethylpiperidinyloxy) free radical (TEMPO) and other salts; a complex of dimethyl sulfoxide and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride or phosphorus pentoxide or a complex of pyridine-sulfuric anhydride; or a combination of a transition metal catalyst and oxygen,

or a transition metal catalyst and an organic oxidizing agent.

175. The preparation method of claim 167, wherein the base of Step 2) above is at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

176. The preparation method of claim 167, wherein the reaction temperature of Step 2) above is -10 °C to 10 °C, and the reaction time is 0.5 hour or longer.

177. The preparation method of claim 167, wherein the reducing agent of Step 3) above is at least one inorganic base selected from the group consisting of NaBH(OAc)₃, NaBH₄, and NaBH(CN)₃.

178. The preparation method of claim 167, wherein the reaction temperature of Step 3) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

179. The preparation method of claim 167, wherein the base of Step 4) above is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

180. The preparation method of claim 167, wherein the content of R₁-C(=O)-Cl in Step 4) above is 1 equivalent or more with respect to the compound of Chemical Formula (VII).

181. The preparation method of claim 167, wherein the reaction temperature of Step 4) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

182. The preparation method of claim 167, wherein the inorganic base in Step 5) above is at least one selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

183. The preparation method of claim 167, wherein the reaction temperature of Step 5) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

184. The preparation method of claim 167, wherein the coupling agent of Step 6) above is an N,N'-disubstituted carbodiimide such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl), N,N'-dicyclohexylcarbodiimide (DCC); azolides such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, or alkoxyacetylene.

185. The preparation method of claim 167, wherein the coupling agent is used in an amount of 1 to 2 equivalents with respect to the compound of Chemical Formula (IX).

186. The preparation method of claim 167, further comprising hydroxybenzotriazole as an additive for increasing reactivity together with a coupling agent.

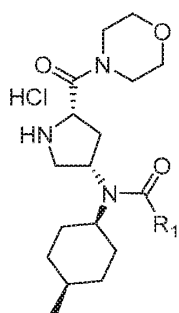
187. The preparation method of claim 167, wherein the base of Step 6) above is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

188. The preparation method of claim 167, wherein the reaction temperature of Step 6) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

189. The preparation method of claim 167, wherein the Pd catalyst of Step 7) above is at least one selected from the group consisting of Pd/C, Pd(OH)₂, Pd(OAc)₂, PdCl₂ and Pd.

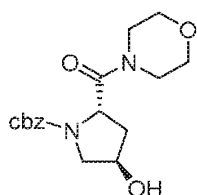
190. The preparation method of claim 167, wherein the reaction temperature of Step 7) above is 1 to 30 °C, and the reaction time is 1 to 30 hours.

191. A method for preparing Formula (II):



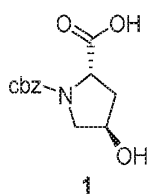
(II), comprising steps of:

- 6) preparing Compound **9**:



9

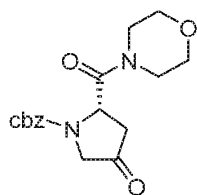
, by adding an organic solvent, a reaction accelerating additive, a base, and a coupling agent to Compound **1**:



1

, and then adding morpholine dropwise;

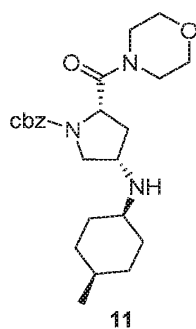
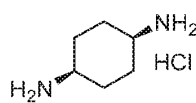
- 7) preparing Compound **10**:



10

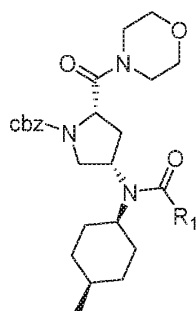
, by oxidizing the Compound **9** prepared in the Step 1) using an oxidizing agent under the presence of a solvent;

- 8) preparing Compound **11**:

**11**, by adding Compound **12**:**12**

, and NaOAc to an organic solvent, adding a reducing agent, adding Compound **10** dissolved in the organic solvent dropwise, stirring, and performing a reductive amination reaction;

- 9) preparing a compound of Formula (X):

(X), by adding an organic solvent to Compound **11** prepared in the

Step 3), adding $R_1-C(=O)-Cl$ and a base, and performing an N-acylation reaction; and

- 10) synthesizing a compound of Formula (II) by dissolving the compound of Formula (X) prepared in the Step 4) in an alcohol having 1 to 6 carbon atoms, adding Pd/C and H_2 for deprotection, and adding HCl dissolved in ethyl acetate dropwise;

wherein in the above Formulas, R_1 is C_2-C_5 alkyl.

192. The method of claim 191, wherein the coupling agent of Step 1) is an N,N'-disubstituted carbodiimide such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl),

N,N'-dicyclohexylcarbodiimide (DCC); an azolide such as N,N'-carbonyldiimidazole (CDI); N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, or alkoxyacetylene.

193. The method of claim 191, wherein the coupling agent is used in an amount of 1 equivalent or more for the Compound 1.

194. The method of claim 191, further comprising hydroxybenzotriazole as an additive for increasing reactivity together with a coupling agent.

195. The method of claim 191, wherein the reaction temperature of Step 1) is 1 to 30 °C and the reaction time is 1 to 30 hours.

196. The method of claim 191, wherein the organic solvent of Step 1) is at least one selected from the group consisting of alcohol, toluene, benzene, tetrahydrofuran, acetone, chloroform, dichloromethane, acetonitrile dimethylformamide, dimethylpropylene urea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, methyl-tert-butyl ether, pentane, hexane, heptane, ether, and diethyl ether.

197. The method of claim 191, wherein the oxidizing agent of Step 2) is a chromic acid compound; a combination of a co-oxidizing agent, (2,2,6,6-tetramethylpiperidinyloxy) free radical (TEMPO) and other salts; a complex of dimethyl sulfoxide and dicyclohexylcarbodiimide, oxalyl chloride, acetic anhydride or phosphorus pentoxide or a complex of pyridine-sulfuric anhydride; or a combination of a transition metal catalyst and oxygen, or a transition metal catalyst and an organic oxidizing agent.

198. The method of claim 191, wherein the base of Step 2) is at least one inorganic base selected from the group consisting of KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

199. The method of claim 191, wherein the reaction temperature of Step 2) is -10 to 5 °C and the reaction time is 0.5 hour or longer.

200. The method of claim 191, wherein the reducing agent of Step 3) is at least one inorganic base selected from the group consisting of $\text{NaBH}(\text{OAc})_3$, NaBH_4 , and $\text{NaBH}(\text{CN})_3$.

201. The method of claim 191, wherein the reaction temperature of Step 3) is 1 to 30 °C and the reaction time is 1 to 30 hours.

202. The method of claim 191, wherein the organic base of the Step 4) is at least one selected from the group consisting of TEA, DIPEA, DABCO, morpholine, and ammonia.

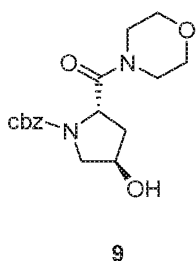
203. The method of claim 191, wherein the content of $\text{R}_1\text{-C}(=\text{O})\text{-Cl}$ in Step 4) is 1 equivalent or more compared to Compound **11**.

204. The method of claim 191, wherein the reaction temperature of the 4) is 1 to 30 °C and the reaction time is 1 to 30 hours.

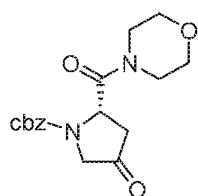
205. The method of claim 191, wherein the Pd catalyst of the 5) is at least one selected from the group consisting of Pd/C, $\text{Pd}(\text{OH})_2$, $\text{Pd}(\text{OAc})_2$, PdCl_2 and Pd.

206. The method of claim 191, wherein the reaction temperature of the 5) is 1 to 30 °C and the reaction time is 1 to 30 hours.

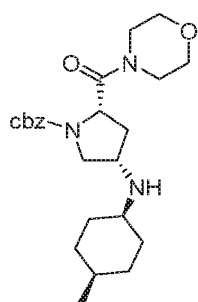
207. The Compound **9**:



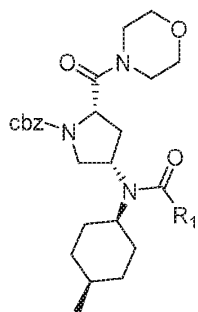
208. The Compound **10**:

**10**

209. The Compound **11**:

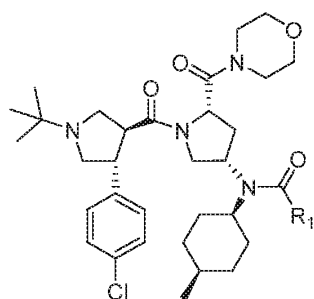
**11**

210. A compound represented by Formula (X):



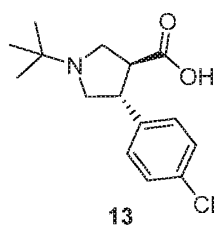
(X), wherein R₁ is C₂-C₅ alkyl.

211. A method for preparing Chemical Formula (XI):

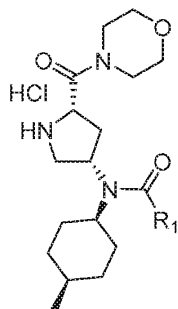


(XI), comprising the steps of:

- 2) reacting Compound **13**:



, and a compound of Formula (II):

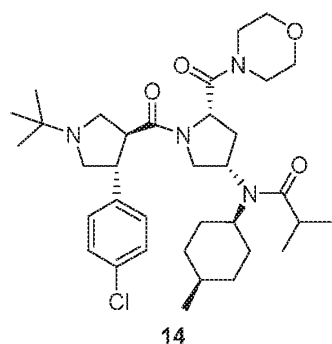


(II), to synthesize a compound of Formula (XI), and then crystallizing the synthesized compound of Formula (XI); and

- 2) purifying the compound of Formula (XI) obtained in Step 1) above;

wherein in the Formulas above, R₁ is C₂-C₅ alkyl.

212. The preparation method of claim 211, wherein the compound of Chemical Formula (XI) above is N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidin-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide **14**:



213. The preparation method of claim 211, wherein the synthesis of Formula (XI) of Step 1) above is carried out by performing acylation reaction between Compound **13** and the compound of Formula (II) in a reaction solvent using a coupling agent.

214. The preparation method of claim 213, wherein the coupling agent used for the acylation reaction is an N,N'-disubstituted carbodiimides, such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl) and N,N'-dicyclohexylcarbodiimide (DCC); an azolide such as N,N'-carbonyldiimidazole (CDI); and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, or alkoxyacetylene.

215. The preparation method of claim 213, wherein the coupling agent used for the acylation reaction is used in an amount of 1.0 to 2.0 equivalents relative to Compound **13**.

216. The preparation method of claim 213, further comprising hydroxybenzotriazole as an additive for increasing reactivity together with a coupling agent.

217. The preparation method of claim 211, wherein the reaction temperature during the synthesis of the compound of Chemical Formula (XI) in Step 1) above is -10 °C to 30 °C, and the reaction time is 0.5 to 6 hours.

218. The preparation method of claim 213, wherein the reaction solvent is selected from the group consisting of ethyl ether, tetrahydrofuran, dioxin, dichloromethane, chloroform, methyl acetate,

ethyl acetate, isopropyl acetate, acetone, methyl ethyl ketone, acetonitrile, propionitrile, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, and a mixed solvent thereof.

219. The preparation method of claim 211, wherein the crystallization step in Step 1) above comprises the following steps of:

- a) concentrating the compound of the synthesized Formula (XI), dissolving the concentrated residue using a solvent, and then washing it using a washing solvent;
- b) separating an aqueous layer from the product of Step a) above, concentrating the separated aqueous layer, adding H₂O, and then cooling it; and
- c) adding a base aqueous solution dropwise and stirring to obtain a crystallized compound of Formula (XI).

220. The preparation method of claim 219, wherein the cooling temperature in Step b) above is -10 to 30 °C.

221. The preparation method of claim 219, wherein the base aqueous solution in Step c) above is an aqueous solution containing at least one base selected from the group consisting of TEA, DIPEA, DABCO, morpholine, ammonia, KOH, NaOH, CaSO₄, LiOH, NaH, KH, NaOCH₃, NaOCH₂CH₃, NaOC(CH₃)₃, KOC(CH₃)₃, K₂CO₃, and Na₂CO₃.

222. The preparation method of claim 219, wherein the stirring time in Step c) above is 0.5 to 24 hours.

223. The preparation method of claim 211, comprising a step of filtering, washing or drying the product after carrying out Step 1) above.

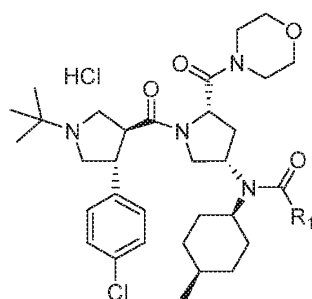
224. The preparation method of claim 211, wherein Step 2) above is carried out by dissolving the crystallized compound of Formula (XI) produced in Step 1) in an organic solvent, stirring it for the first time, then cooling it, and stirring it for the second time.

225. The preparation method of claim 224, wherein the organic solvent is selected from the group

consisting of acetone, acetonitrile, dichloromethane, dimethylformamide, dimethylpropyleneurea, dimethyl sulfoxide, ethyl acetate, hexamethylphosphoramide, tetrahydrofuran, methyl-tert-butyl ether, pentane, hexane, heptane, ether, toluene, methyl acetate, isopropyl acetate, alcohols with 1 to 6 carbon atoms, diethyl ether, and a mixture thereof.

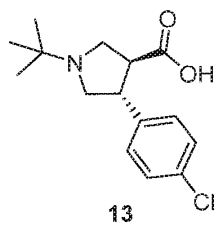
226. The preparation method of claim 224, wherein the first stirring time of Step 2) above is 10 hours or more, the cooling temperature after stirring is 0 to 10 °C, and the second stirring time is 0.5 to 2 hours.

227. A preparation method of Formula (XII):

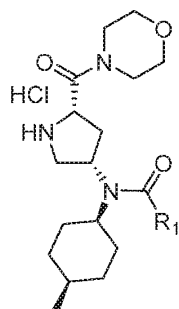


(XII), comprising the steps of:

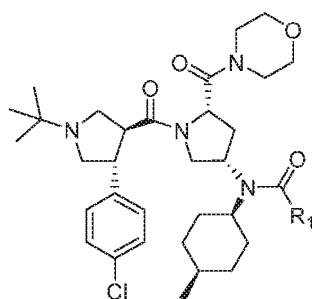
3) reacting Compound **13**:



, with a compound of Formula (II):



(II), to synthesize a compound of Formula (XI):

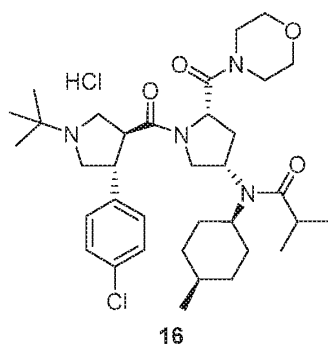


(XI); and

- 4) reacting the compound of Formula (XI) generated in Step 1) with HCl without an additional purification process to prepare a compound of Formula (XII).

wherein in the above Formulas, R_1 is a C_2 - C_5 alkyl group.

228. A preparation method of claim 227, wherein the compound of Formula (XII) above is N-((3S,5S)-1-((3S,4R)-1-(tert-butyl)-4-(4-chlorophenyl)pyrrolidin-3-carbonyl)-5-(morpholine-4-carbonyl)pyrrolidin-3-yl)-N-((1S,4R)-4-methylcyclohexyl)isobutyramide hydrochloride **16**:



229. A preparation method of claim 227, wherein Step 1) is carried out by synthesizing the compound of Formula (XI) through an acylation reaction of Compound **13** and the compound of Chemical Formula (II) in a reaction solvent using a coupling agent.

230. A preparation method of claim 229, wherein the coupling agent used for the acylation reaction may include N,N'-disubstituted carbodiimides such as ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl) and N,N'-dicyclohexylcarbodiimide (DCC); azolides such as N,N'-carbonyldiimidazole (CDI); and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, oxalyl chloride, or alkoxyacetylenes.

231. A preparation method according to embodiment 229, wherein the coupling agent used for the

acylation reaction is employed in an amount of 1.0 to 2.0 equivalents relative to Compound 13.

232. A preparation method of claim 229, further comprising hydroxybenzotriazole as an additive for increasing reactivity with a coupling agent.

233. A preparation method of claim 227, wherein the reaction temperature of Step 1) is -20 °C to 100 °C, and the reaction time is 0.5 to 24 hours.

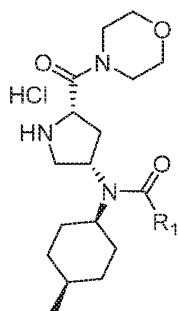
234. A preparation method of claim 229, wherein the reaction solvent is selected from the group consisting of n-hexane, benzene, toluene, ethyl ether, tetrahydrofuran dioxine, methanol, ethanol, dichloromethane, chloroform, ethyl acetate, methylacetate, acetone, methylethylketone, acetonitrile, propionitrile, dimethylformamide, dimethylacetamide, dimethylsulfoxide, and a mixed solvent thereof.

235. A preparation method of claim 227, wherein Step 2) is carried out through the preparation of the compound of Formula (XII) by reacting the crude compound of Chemical Formula (XI) generated in Step 1) with HCl in an organic solvent without an additional purification process.

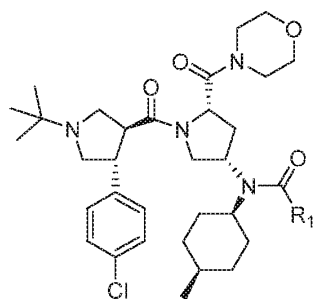
236. A preparation method of claim 235, wherein the organic solvent is selected from the group consisting of acetone, acetonitrile, dichloromethane, dimethylformamide, dimethylpropyleneurea, dimethylsulfoxide, ethyl acetate, hexamethylphosphoamide, tetrahydrofuran, methyl-tert-butylether, pentane, hexane, heptane, ether, diethylether, and a mixed solvent thereof.

237. A preparation method of claim 227, wherein the reaction temperature is -20 °C to 100 °C, and the reaction time is 10 minutes or more, in Step 2).

238. A compound represented by the structure of Formula (II):

(II), wherein R₁ is C₂-C₅ alkyl.

239. A method for preparing crystalline Form III particles of a compound of Formula (XI):



(XI), a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein R₁ is C₂-C₅ alkyl, and wherein

the crystalline Form III has the following diffraction angles (2 θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among 6.62 $\pm$ 0.2°, 7.44 $\pm$ 0.2°, 9.18 $\pm$ 0.2°, 9.89 $\pm$ 0.2°, 10.83 $\pm$ 0.2°, 11.42 $\pm$ 0.2°, 12.92 $\pm$ 0.2°, 14.61 $\pm$ 0.2°, 15.36 $\pm$ 0.2°, 15.79 $\pm$ 0.2°, 15.95 $\pm$ 0.2°, 17.37 $\pm$ 0.2°, 18.20 $\pm$ 0.2°, 18.99 $\pm$ 0.2°, 19.34 $\pm$ 0.2°, 19.69 $\pm$ 0.2°, 20.40 $\pm$ 0.2°, 21.66 $\pm$ 0.2°, 21.98 $\pm$ 0.2°, 22.45 $\pm$ 0.2°, 22.85 $\pm$ 0.2°, 24.66 $\pm$ 0.2°, 25.52 $\pm$ 0.2°, 26.55 $\pm$ 0.2°, 28.08 $\pm$ 0.2°, 29.31 $\pm$ 0.2° and 29.54 $\pm$ 0.2°; and

the preparation method comprises:

- (a) preparing a mixed solution by dissolving the compound of Formula (XI) in a crystallization solvent comprising water or a mixture of water and an organic solvent;
- (b) crystallizing by adding HCl dropwise to the solution; and
- (c) maturing the solution.

240. The method of claim 239, wherein the organic solvent of the crystallization solvent is a polar aprotic organic solvent.

241. The method of claim 240, wherein the polar aprotic organic solvent comprises ethyl acetate, methyl isobutylketone, dimethylsulfoxide, tetrahydrofuran, acetone, dimethylformamide, acetonitrile, and the mixtures thereof.

242. The method of claim 239, wherein the dropwise addition of HCl is administered through a 4 M HCl solution or a 6 N HCl solution in concentrated HCl (conc. HCl) solution and ethyl acetate.

243. The method of claim 239, wherein the dropwise addition of HCl is administered in an amount of 1 equivalent or less to the compound of Formula (XI).

244. The method of claim 239, wherein the crystallization solvent is a mixed solvent in which water and an organic solvent are mixed in a volume ratio of 1:20 to 1:40.

245. The method of claim 244, wherein the crystallization solvent is a mixed solvent in which water and an organic solvent are mixed in a volume ratio of 1:27 to 1:32.

246. The method of claim 239, wherein Step (b) is performed at 15 °C to 25 °C, and Step (c) is performed at 10 °C to 20 °C.

247. The method of claim 246, wherein the (c) comprises:

(c-1) maturing at 10 °C to 15 °C until filtrate area decreases to 80% to 85% of the initial area;
and

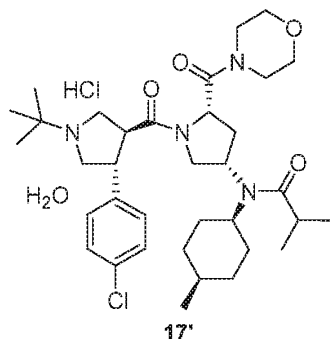
(c-2) maturing by raising the temperature to 20 °C until the filtrate area no longer decreases.

248. The method of claim 239 further comprising: (d) filtering the solution.

249. The method of claim 239, wherein the crystalline Form III particles are crystalline form particles of a solvate of the hydrochloride salt of the compound of Formula (XI).

250. The method of claim 249, wherein the solvate is a hydrate.

251. The method of claim 239, wherein the compound of Formula (XI) is Compound 17':



252. The method of claim 239, wherein the crystalline Form III particles have a flow function value of at least 8 under a pressure of 9 kPa.

253. A crystalline Form III particle of a compound of Formula (XI), a pharmaceutically acceptable salt thereof, or a solvate thereof, prepared by the preparation method according to claim 239, wherein

the crystalline Form III has the following diffraction angles (2θ values) in the X-ray powder diffraction pattern: three or more characteristic peaks selected from among $6.62\pm0.2^\circ$, $7.44\pm0.2^\circ$, $9.18\pm0.2^\circ$, $9.89\pm0.2^\circ$, $10.83\pm0.2^\circ$, $11.42\pm0.2^\circ$, $12.92\pm0.2^\circ$, $14.61\pm0.2^\circ$, $15.36\pm0.2^\circ$, $15.79\pm0.2^\circ$, $15.95\pm0.2^\circ$, $17.37\pm0.2^\circ$, $18.20\pm0.2^\circ$, $18.99\pm0.2^\circ$, $19.34\pm0.2^\circ$, $19.69\pm0.2^\circ$, $20.40\pm0.2^\circ$, $21.66\pm0.2^\circ$, $21.98\pm0.2^\circ$, $22.45\pm0.2^\circ$, $22.85\pm0.2^\circ$, $24.66\pm0.2^\circ$, $25.52\pm0.2^\circ$, $26.55\pm0.2^\circ$, $28.08\pm0.2^\circ$, $29.31\pm0.2^\circ$ and $29.54\pm0.2^\circ$; and

the crystalline Form III particle has a flow function value of at least 8 under a pressure of 9 kPa.

254. A method of making a compound of Formula (I), or a compound of any one of the preceding claims, wherein the method comprises making greater than about 500 mg, 1 kg, 1.25 kg, 1.5 kg, 2 kg, 2.5 kg, 3 kg, 4 kg, 5 kg, 7.5 kg, 10 kg, 12.5 kg, 15 kg, or more of a compound of Formula (I).

255. The method of claim 255, wherein the method comprises making greater than about 500 mg, 1 kg, 1.25 kg, 1.5 kg, 2 kg, 2.5 kg, 3 kg, 4 kg, 5 kg, 7.5 kg, 10 kg, 12.5 kg, 15 kg, or more of a

Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, or 17, or a pharmaceutically acceptable salt thereof.

256. A pharmaceutical composition for preventing or treating obesity, diabetes, inflammation or erectile dysfunction, comprising the crystalline Form III particle according to claim 253 and a pharmaceutically acceptable carrier.