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(54) Title: PROCESS FOR THE PREPARATION OF BREXPIRAZOLE

(57) Abstract: The present disclosure provides processes for the preparation of brexiprazole or pharmaceutically acceptable salts thereof. The present disclosure also provides intermediates useful in the preparation of brexiprazole.
PROCESS FOR THE PREPARATION OF BREXPIPAZOLE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the earlier filing date of Indian provisional patent application no. 4179/CHE/2015 filed on August 11, 2015, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present disclosure relates generally to processes for the preparation of brexipiprazole and pharmaceutically acceptable salts thereof. The present disclosure also relates to novel intermediates that may be formed during the preparation of brexipiprazole.

BACKGROUND OF THE INVENTION

Brexipiprazole is a serotonin-dopamine activity modulator (SDAM) having a dopamine D2 receptor partial agonist action, 5-HT₁A receptor agonistic action, and also 5-HT₂A receptor antagonism. Brexipiprazole is marketed under the proprietary name REXULTI® by Otsuka Pharmaceutical Co. Ltd. It was co-developed by Otsuka Pharmaceutical Co. Ltd. and Lundbeck. REXULTI® is indicated as adjuvant treatment for schizophrenia and severe depression.

Brexipiprazole is chemically named 7-[4-(4-benzo[b]thien-4-yl-1-piperazinyl)butoxy]-2(1H)-quinolone and is represented by the following chemical structure (I):

\[ \text{I} \]

Brexipiprazole and salts thereof are disclosed in U.S. Patent No. 7,888,362.
The present disclosure provides a process for the preparation of brexpiprazole and pharmaceutically acceptable salts thereof. This process employs the use of novel intermediates.

**SUMMARY OF THE INVENTION**

The present invention provides a process for the preparation of brexpiprazole.

In one embodiment, brexpiprazole may be prepared by the following steps:

a) reacting a compound of formula X with a compound of formula IX, in the presence of a first base and a first solvent to obtain a compound of formula VIII;

b) hydrolyzing the compound of formula VIII obtain a compound of formula VII in the presence of a second solvent;

c) converting the compound of formula VII to a compound of formula VI in the presence of a second base and a third solvent;

d) reacting the compound of formula VI with a compound of formula V in the presence of a third base to obtain a compound of formula IV;

e) deprotecting the compound of formula IV to obtain a compound of formula III; and
f) condensing the compound of formula III with a compound of formula II, wherein “Y” is a halogen, to obtain brexipiprazole of formula I

Within the context of this embodiment, the “R” is a hydroxyl protecting group. Examples of suitable hydroxyl protecting groups include, but are not limited to, benzoyl, benzyl, acetyl, tert-butyldimethoxysilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), methoxymethyl ether (MOM), tetrahydropyranyl (THP), allyl ether, and tert-butyl ether. In some particularly useful embodiments, an acetyl group is used as hydroxyl protecting group.

Within the context of this embodiment, the “X and Y” moiety on the compounds of formulas IX and II are independently halogen, which may be, for example, -F, -Cl, -Br, or -I.

Within the context of this embodiment, “PG” is an amine protecting group. Examples of suitable amine protecting groups include di-tert-butyl dicarbonate (BOC)$_2$O, carbobenzyloxy (Cbz), 9-fluorenylmethyloxycarbonyl (FMOC), and optionally substituted benzyl groups.

Within the context of this embodiment, “LG” is a leaving group. Examples of suitable leaving groups include C$_1$-C$_{10}$ alkylsulfonylate, perfluoro-C$_1$-C$_{10}$ alkylsulfonate, arylsulfonate, phosphate, phosphonate, and aralkylsulfonate groups. In some embodiments, a methane sulfonate group is used as a leaving group.

Within the context of this embodiment, the first solvent may be, for example, acetonitrile, tetrahydrofuran, ethyl acetate, dimethyl sulfoxide, dimethylformamide, 1,4-dioxane, N-methylpyrrolidone, isopropyl ether, or mixtures thereof.

Within the context of this embodiment, the second solvent may be an alcoholic solvent, water, or mixtures thereof. Examples of suitable alcoholic solvents include methanol, ethanol, isopropanol, 1-butanol, isobutyl alcohol, 1-pentanol, and mixtures thereof.
Within the context of this embodiment, the third solvent may be, for example, toluene, dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, xylene, isopropyl ether, and mixtures thereof.

Within the context of this embodiment, the first base may be an organic base or an inorganic base. Examples of suitable inorganic bases include potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof. Examples of suitable organic bases include trimethylamine, N,N-diisopropylethylamine, diisopropylamine, pyridine, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof.

Within the context of this embodiment, the second base may be, for example, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof.

Within the context of this embodiment, the third base may be, for example, trimethylamine, N,N-diisopropylethylamine, diisopropylamine, pyridine, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof.

Optionally, the compound of formula VI may be reacted with a compound of formula V in the presence of a catalyst. The catalyst may be, for example, copper halide, potassium iodide, sodium iodide, nickel, sodium bromide, potassium bromide, palladium-based catalyst, rhodium-based catalyst, ruthenium-based catalyst, platinum-based catalyst, a transition metal-based catalyst, or mixtures thereof.

Optionally, the compound of formula III may be in the form of a pharmaceutically acceptable salt of the compound of formula III and may result in the formation of a pharmaceutically acceptable salt of brexipiprazole when reacted with a compound of formula II.

Another aspect of the present invention provides a compound of formula VIII

\[
\text{VIII}
\]

\[\text{VIII}, \text{ wherein } R \text{ is a hydroxyl protecting group, as defined above.}\]

Another aspect of the present invention provides a process for the preparation of anhydrous brexipiprazole, comprising the following steps:

a) dissolving brexipiprazole in an alcohol solvent at an elevated temperature;
b) cooling the solution to 20-30 °C, and

c) isolating anhydrous brexiprazole.

Within the context of this embodiment, the alcohol solvent may be, for example, anhydrous ethanol, isopropanol, methanol, isobutanol, n-butanol, or mixtures thereof.

**DETAILED DESCRIPTION OF THE INVENTION**

One aspect of the present invention provides a process for the preparation of brexiprazole by the following steps:

a) reacting a compound of formula X with a compound of formula IX, in a solvent in the presence of a base to obtain a compound of formula VIII;

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\[ \text{RO}_1\text{H} \quad \text{IX} \quad \text{O}_1\text{H} \quad \text{X} \quad \text{RO}_2\text{H} \]
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b) hydrolyzing the compound of formula VIII obtain a compound of formula VII;

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\[ \text{RO}_1\text{H} \quad \text{VIII} \quad \text{O}_1\text{H} \quad \text{VII} \text{hydrolysis} \quad \text{RO}_2\text{H} \]
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c) converting the compound of formula VII to a compound of formula VI in the presence of a base;

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\[ \text{RO}_1\text{H} \quad \text{VII} \quad \text{O}_1\text{H} \quad \text{VI} \quad \text{LG}_1\text{H} \quad \text{LG}_2\text{H} \]
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d) reacting the compound of formula VI with a compound of formula V in the presence of a base, optionally in the presence of a catalyst, to obtain a compound of formula IV;

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\[ \text{OPG}_1\text{H} \quad \text{V} \quad \text{OPG}_2\text{H} \quad \text{VI} \quad \text{LG}_1\text{H} \quad \text{LG}_2\text{H} \text{IV} \]
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e) deprotecting the compound of formula IV to obtain a compound of formula III or salt thereof; and

f) condensing the compound of formula III or a salt thereof with a compound of formula II to obtain brexpiprazole (compound of formula I) or a salt thereof.

According to this embodiment, a compound of formula X may be reacted with a compound of formula IX in the presence of a base in a solvent to obtain a compound of formula VIII. Within the context of this embodiment, the “R” moiety on the compound of formula IX is a hydroxyl protecting group and the “X” moiety on the compound of formula IX and the compound of formula II is a halogen. The “X” moiety on the compound of formula IX and the “Y” moiety on the compound of formula II may be the same or may be different from one another. The halogen may be, for example, –F, –Cl, –Br, or –I. In some particularly useful embodiments, both “X” moieties are bromine, such that the compound of formula IX is 4-bromobutyrylacetate and the compound of formula II is 4-bromobenzothiophene.

Within the context of this embodiment, the solvent may be, for example, acetonitrile, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, dimethylformamide, 1,4-dioxane, N-methylpyrrolidone, isopropyl ether, or mixtures thereof. In some particularly useful embodiments, dimethylformamide is used as solvent. In some embodiments, the reaction may be carried out at about 70 °C to about 90 °C for about 3 to 5 hours. As used herein, “about” means plus or minus 10% of the referenced value.

Within the context of this embodiment, the base may be an inorganic base or an organic base. Examples of suitable inorganic bases include potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, and potassium hydroxide. Examples of
suitable organic bases include, but are not limited to, trimethylamine, N, N-diisopropylethyl amine, diisopropylamine, and pyridine. In some particularly useful embodiments, potassium carbonate is utilized as a base.

According to this embodiment, a compound of formula VIII may then be hydrolyzed in a solvent to remove the hydroxyl protecting group in the presence of a base or acid to obtain a compound of formula VII.

Within the context of this embodiment, the solvent useful for this step may be, for example, an alcohol, water, or mixtures thereof. Examples of suitable alcohol solvents include, but are not limited to, methanol, ethanol, isopropanol, 1-butanol, isobutyl alcohol, 1-pentanol, or mixtures thereof. In some embodiments, a mixture of methanol and water are used as the solvent. In some embodiments, the reaction is carried out at room temperature for about 1 to 3 hours.

Within the context of this embodiment, the base utilized in this step may be an inorganic base. Examples of suitable inorganic bases include potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide. In some particularly useful embodiments, potassium carbonate is used as a base.

According to this embodiment, the compound of formula VII may then be converted to a compound of formula VI by treating the compound of formula VII with a leaving group source and a base in the presence of a solvent.

Within the context of this embodiment, the solvent useful for this step may be, for example, toluene, dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, xylene, isopropyl ether, or mixtures thereof. In some particularly useful embodiments, tetrahydrofuran is used as a solvent. In some embodiments, the reaction is carried out at 20 °C to 30 °C for about one to two hours.

Within the context of this embodiment, the leaving group source may be a lower alkyl sulfonate, a perfluoro-lower alkyl sulfonate, an aryl sulfonate, a phosphate, a phosphonate, or an aralkyl sulfonate. In some particularly useful embodiments, the leaving group source is a methane sulfonate where the compound of formula VII is reacted with methane sulfonyle chloride to
produce a compound of formula VI. Within the context of this embodiment, the term “lower” as used herein, refers to a C₁₋C₁₀ alkyl chain.

Within the context of present disclosure, the base useful in the step may be an organic base. Examples of suitable organic bases include trimethylamine, N, N-diisopropylethyl amine, diisopropylamine, and pyridine. In some particularly useful embodiments, trimethylamine is used as a base.

Next, the compound of formula VI may be reacted with a compound of formula V in a solvent in the presence of a base to obtain a compound of formula IV. Within the context of the present embodiment, the “PG” moiety of the compound of formula V is an amine protecting group.


Amine protecting groups include, for example, -Rᵖ, =R⁰, -C(O)R⁰, -C(O)OR⁰, -S(O)₂R⁰, and 2-nitrophenylsulfenyl, wherein

Rᵖ is a -C(Rᵖᵢ)₃, wherein each Rᵖᵢ is hydrogen or optionally substituted aryl, provided that at least one Rᵖᵢ is not hydrogen;

R⁰ is =C(H)-R⁰; and

R⁰ is hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ haloalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein each alkyl, aryl, and heteroaryl group is optionally substituted.
“Optionally substituted” as used herein means the reference group is substituted by one or more groups (e.g., 1 to 5, or 1 to 3, or 1 to 2 groups, or 1 group) that are each independently halo, alkyl, alkoxy, nitro, cyano, tri(C₁₃:alkyl)silyl (e.g., trimethylsilyl).

Particular examples of amine protecting groups include, carbonyls (e.g., methyl carbamate, 9-fluorenylmethoxycarbonyl (Fmoc), trichloroethoxycarbonyl (Troc), tert-butylxycarbonyl (BOC), 2-trimethylsilylthoxycarbonyl (Teoc), allyloxycarbonyl (Alloc), p-methoxybenzyl carbonyl (Moz), and carboxybenzyl (Cbz)), sulfonyls (e.g., p-toluenesulfonyl (Ts), trimethylsilylthanesulfonyl (Ses), tert-butylsulfonyl (Bus), 4-methoxyphenylsulfonyl, 4-nitrobenzenesulfonyl (nosulfonyl), trityl (trt), benzyl (Bn), 3,4-dimethoxybenzyl, p-methoxybenzyl (PMB), p-methoxyphenyl (PMP), acetyl (Ac), formyl, trifluoroacetyl (Tfa), benzoyl (Bz), or 2-nitrophenylsulfonyl (Nps).

The term “alkenyl” as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons, unless otherwise specified, and containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-deceny1, and 3, 7-dimethylocta-2, 6-dienyl.

The term “alkoxy” as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term “alkyl” as used herein, means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms, unless otherwise specified. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term “aryl,” as used herein, means a monocyclic (i.e., phenyl), bicyclic, or tricyclic ring fused or bridged system containing at least one phenyl ring. Non-phenyl rings that are part of a bicyclic or tricyclic ring system may be fully or partially saturated, may contain one or more
heteroatoms, each selected from N, S, and O, and may be optionally substituted with one or two oxo and/or thia groups. Examples of aryl groups include phenyl, napthyl, anthracenyl, and fluorenyl.

The term “arylalkyl” as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, fluorenylethylmethyl and 2-naphth-2-ylethyl.

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

The term “haloalkyl” as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, perfluorononyl, and 2-chloro-3-fluoropentyl.

The term “heteroaryl,” as used herein, means a monocyclic, bicyclic, or tricyclic ring system containing at least one heteroaromatic ring. Any additional rings that are part of a bicyclic or tricyclic ring system may be fully or partially saturated or may be aromatic rings, and each may optionally contain one or more heteroatoms, each selected from N, S, and O. Representative examples of monocyclic and bicyclic heteroaryl include, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, triazinyl, benzimidazolyl, benzofuranyl, benzothienyl, benzoxadiazolyl, benzoxathiazolyl, benzothiazolyl, cinnolinyl, dihydroquinolinyl, furopyridinyl, indazolyl, indolyl, isoquinolinyl, naphthyridinyl, quinolinyl, purinyl, and tetrahydroquinolin-yl.

The term “heteroarylalkyl” as used herein, means a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heteroarylalkyl include, but are not limited to, furylmethyl, imidazolylmethyl, pyridinylethyl, pyridinymethyl, pyrimidinylmethyl, and thienylmethyl.
The term “oxo” as used herein means a =O group. The term “thia” as used herein means a =S group.

Examples of particularly useful amine protecting group include t-butoxycarbonyl (Boc), benzylxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (FMOC), and benzyl groups. In some embodiments, Boc is used as an amine protecting group.

Examples of particularly useful hydroxyl protecting groups include, but are not limited to, benzoyl, benzy1, acetyl, tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), methoxymethyl ether (MOM), tetrahydropryanyl (THP), allyl ether, and tert-butyl ether. In some embodiments, acetyl group is used as hydroxyl protecting group.

Within the context of this embodiment, the solvent useful for this step may be, for example, dimethylformamide, dimethylsulfoxide, dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, dimethylformamide, toluene, dichloromethane, acetonitrile, dimethyl sulfoxide, and mixtures thereof. In some particularly useful embodiments, acetonitrile is used as a solvent.

Within the context of this embodiment, the base useful at this step may be an inorganic base. Examples of suitable inorganic bases include potassium carbonate, sodium carbonate, sodium hydroxide, and potassium hydroxide. In some embodiments, potassium carbonate is used as a base.

Within the context of this embodiment, the reaction may be carried out in the presence of a catalyst. Examples of suitable catalysts include potassium iodide, sodium iodide and phase transfer catalyst include, but are not limited to sodium bromide, tetrabutyl ammonium bromide (TBAB), tetrabutyl ammonium bisulfate, tetrabutyl ammonium hydroxide, benzyl triethyl ammonium chloride, tetrabutyl phosphonium bromide. In some embodiments, potassium iodide is used as a catalyst. In some embodiments, this reaction is carried out at 70 to 90 °C for about 3 to 5 hours.

According to the present embodiment, next, the compound of formula IV may be deprotected to get the compound of formula III or a salt thereof. Within the context of this embodiment, the
mechanism by which deprotection is carried out depends on the amine protecting group. One of skill in the art will be familiar with the various reagents and conditions necessary to effectively remove different amine protecting groups. For example, deprotection may be carried out by treatment with an acid or by catalytic hydrogenation.

For example, when the amine protecting group is a Boc group (t-butoxycarbonyl), the Boc group may be removed by treatment with an aqueous acid in a solvent at 50-65 °C for about 2 to 3 hours. The solvent may be, for example, methanol, ethanol, isopropanol, 1-butanol, isobutyl alcohol, 1-pentanol, acetonitrile, or mixtures thereof. In some particularly useful embodiments, isopropanol is used as solvent. Examples of suitable aqueous acids include, but are not limited to, hydrochloric acid, hydrobromic acid, and acetic acid. In some particularly useful embodiments, aqueous hydrochloric acid is used for deprotection.

Optionally, a salt of the compound of formula III may be additionally formed at this step. The salt may be formed directly during the deprotection of the compound of formula IV, or it may be formed as a separate step, where a non-salt compound of formula III is first formed and is then converted to a salt of the compound of formula III.

Methods for converting compounds into their acid salt forms are well known in the art, and may be carried out, for example, by reacting a free base moiety on the compound with a suitable reagent. The reagent may also be added as a reagent during a chemical reaction to form the compound.

For example, in some embodiments, a free base moiety on the compound of formula III can be reacted with a suitable acid to obtain a pharmaceutically acceptable salt of the compound of formula III. In other embodiments, the suitable acid may be added directly during the deprotection step wherein the compound of formula IV is converted to the salt form of a compound of formula III.

Examples of suitable acids include, for example, inorganic acids or organic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid. Suitable organic acids include, for example, acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, and malonic acid. A pharmaceutically acceptable salt may alternatively be prepared by other methods well known in the art, for
example, ion exchange. Additional examples of suitable salts include, for example, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycophosphatate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, (R,S)-malate, (S)-malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, phthalate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts. In certain embodiments, the acid is hydrochloric acid.

According to this embodiment, brexipiprazole or a salt thereof may then be formed by condensing the compound of formula III or a salt thereof with a compound of formula II. This may be carried out in a solvent in the presence of a base.

Within the context of this embodiment, the solvent useful for this step may be an aprotic solvent.

Examples of useful aprotic solvents include, but are not limited to, tetrahydrofuran, 2-methyltetrahydrofuran, dimethylformamide, dimethylsulfoxide, 1,4-dioxane, toluene, xylene, or mixtures thereof. In some embodiments, a mixture of 1, 4-dioxane and toluene is used as a solvent.

Examples of suitable bases useful for this step include sodium tert-butoxide, potassium tert-butoxide, lithium bis(trimethylsilyl)amide (LiHMDS), sodium methoxide, potassium carbonate, sodium carbonate, and potassium phosphate. In some particularly useful embodiments, sodium tert-butoxide is used as a base.

Optionally, this step may be further carried out in the presence of a metal catalyst. Examples of suitable metal catalysts include copper halide, palladium, platinum, nickel, rhodium, ruthenium, Pd(dba)3, PdCl2(o-tolyl)3P2, Pd(dppf)Cl2, Pd(OAc)2, Ni(COD)2, Pd(PPh3)4, Pd(PPh3)2Cl2, Pd(xantphos)Cl2, Pd[P(t-Bu)3P]2Cl2, and RuPhos-Pd with ligands such as, for example, BINAP, SEGHOS, PPh₃, xantphos, dtph, dpdpde, and dpdx. In some embodiments, BINAP is used as a ligand with a palladium catalyst. In some particularly useful embodiments, palladium (II) acetate is used as palladium catalyst.
In another embodiment, brexipirazole or a salt thereof may be further processed to prepare anhydrous brexipirazole by the following steps:

a) dissolving brexipirazole in an alcohol at elevated temperature to form a solution;

b) cooling the solution; and

c) isolating anhydrous brexipirazole.

According to this embodiment, brexipirazole or a salt thereof may dissolved in an alcohol at elevated temperature to form a solution. Within the context of this embodiment, the elevated temperature may be the reflex temperature of the solvent.

Within the context of this embodiment, the brexipirazole starting material may be crystalline, semi-crystalline, or amorphous.

Within the context of this embodiment, the alcohol may be, for example, methanol, ethanol, isopropanol, 1-butanol, isobutyl alcohol, 1-pentanol, or mixtures thereof. In some particularly useful embodiments, ethanol is used as a solvent.

Next, the solution may be cooled. Within the context of this embodiment, cooling to a temperature of about 20 °C to about 30 °C may be used. Within the context of this embodiment, cooling of the solution may result in precipitation of a solid. The solution may then be filtered to isolate the solid, which may then be washed with an alcohol to get anhydrous brexipirazole.

In another embodiment, brexipirazole may be prepared by the steps depicted in Scheme-1.
Within the context of this embodiment, the “X” moiety is a leaving group or a halogen. The term “leaving group” is well known and understood in the art and one of skill in the art would know a variety of leaving groups that would be suitable for use in this embodiment as well as reaction conditions suitable for their use. Within the context of the present embodiment, the “PG” moiety of the compound of formula V is an amine protecting group. Within the context of the present embodiment, the “R” moiety is a hydroxyl protecting group.

In another embodiment, brexipiprazole may be prepared by the steps depicted in Scheme-2.
Within the context of this embodiment, the “LG” moiety is a leaving group or a halogen. The term “leaving group” is well known and understood in the art and one of skill in the art would know a variety of leaving groups that would be suitable for use in this embodiment as well as reaction conditions suitable for their use.

In yet other embodiment, brexpiprazole may be prepared by the steps depicted in Scheme-3.
Within the context of this embodiment, the “LG” moiety is a leaving group or a halogen. The term “leaving group” is well known and understood in the art and one of skill in the art would know a variety of leaving groups that would be suitable for use in this embodiment as well as reaction conditions suitable for their use.

In yet other embodiment, brexpiprazole may be prepared by the steps depicted in Scheme-4.

In yet other embodiment, brexpiprazole may be prepared by the steps depicted in Scheme-5.

Within the context of this embodiment, the “LG” moiety is a leaving group or a halogen. The term “leaving group” is well known and understood in the art and one of skill in the art would know a variety of leaving groups that would be suitable for use in this embodiment as well as reaction conditions suitable for their use.
Within the context of this embodiment, the “LG” moiety is a leaving group or a halogen. The term “leaving group” is well known and understood in the art and one of skill in the art would know a variety of leaving groups that would be suitable for use in this embodiment as well as reaction conditions suitable for their use.

Another aspect of the present invention provides a process for the preparation of an intermediate that may be used to prepare brexpiprazole. In one embodiment, the compound of formula XII may be prepared as depicted in the following synthetic Scheme-6.
Within the context of this embodiment, the “LG” moiety is a leaving group or a halogen. The term “leaving group” is well known and understood in the art and one of skill in the art would know a variety of leaving groups that would be suitable for use in this embodiment as well as reaction conditions suitable for their use.

Another aspect of the present invention provides a process for the preparation of an intermediate that may be used to prepare brexipiprazole. In one embodiment, a compound of formula VI may be prepared as depicted in the following synthetic Scheme-7.

![Scheme-7](image)

Within the context of this embodiment, the “LG” moiety is a leaving group or a halogen. The term “leaving group” is well known and understood in the art and one of skill in the art would know a variety of leaving groups that would be suitable for use in this embodiment as well as reaction conditions suitable for their use.

Another aspect of the present invention encompasses novel compounds, depicted below:

![Compounds](image)
Within the context of this embodiment, the “LG” moiety is a leaving group or a halogen. The term “leaving group” is well known and understood in the art and one of skill in the art would know a variety of leaving groups that would be suitable for use in this embodiment as well as reaction conditions suitable for their use.

Another aspect of the present invention provides brexiprazole and pharmaceutically acceptable salts thereof, which may be synthesized by the methods disclosed herein. Within the context of this invention, brexiprazole and pharmaceutically acceptable salts thereof may be formulated into an oral dosage form, for example, a tablet. Such an oral dosage form may include suitable excipients, such as lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc. Such oral dosage forms may include an effective amount of brexiprazole, including dosages of 0.25 mg, 0.6 mg, 1 mg, 2 mg, 3 mg, and 4 mg. Oral dosage forms including brexiprazole may be administered to patients suffering from major depressive disorder or schizophrenia.

In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of molecules, compositions, and formulations according to the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.
Examples

Example 1: Preparation of 7-(4-acetylbutoxy)-1H-quinolin-2-one (compound of formula VIII’)

7-hydroxy-1H-quinolin-2-one (60 g) was dissolved in dimethylformamide (600 mL). After dissolution, potassium carbonate (77 g) and 4-bromobutylacetate (compound of formula IX, 88 g) was added to the reaction mixture and the resulting solution was heated to 80-85 °C and maintained for four hours at same temperature. After the reaction was complete, the reaction mass was cooled to room temperature. Water (600 mL) was added to the reaction mass and extracted with ethyl acetate (3 x 300 mL). The solvent was distilled completely under vacuum. Isopropyl ether (100 mL) was added and the reaction mixture was maintained for one hour at room temperature. The solution was filtered and the product washed with water (100 mL) and dried at 50 °C to obtain 7-(4-acetylbutoxy)-1H-quinolin-2-one (70 g).

\(^1\)H NMR (CDCl₃): 1.83-1.92 (m, 4H); 2.07 (s, 3H); 4.08-4.18 (m, 4H); 6.55 (d, J=9.3Hz, 1H); 6.79-6.86(m, 2H); 7.43 (d, 1H, J=8.7Hz); 7.73(d, 1H, J=9.3Hz), Mass: 276 (M+1)

Example 2: Preparation of 7-(4-hydroxybutoxy)-1H-quinolin-2-one (compound of formula VII)

7-(4-acetylbutoxy)-1H-quinolin-2-one (70 g), methanol (1000 mL), water (140 mL), and potassium carbonate (42 g) were mixed and stirred for two hours at room temperature. After the reaction was complete, water (500 mL) was charged to the reaction mass which was then maintained at the same temperature for one hour. The solution was filtered and the product was washed with water (100 mL) then dried at 50 °C to obtain 7-(4-hydroxybutoxy)-1H-quinolin-2-one (47 g).

Example 3: Preparation of 7-(4-mesyloxybutoxy)-1H-quinolin-2-one (compound of formula VI)

7-(4-hydroxybutoxy)-1H-quinolin-2-one (50 g), tetrahydrofuran (500 mL), and trimethylamine (35 g) were mixed and the solution was cooled to 20 °C. Methane sulfonyl chloride (32 g) was added to the reaction mixture at 20-25 °C over one hour and the reaction mass was maintained for two hours. After the reaction was complete, water (500 mL) was charged to the reaction mass and stirred for one hour at room temperature. The solution was filtered and the product
was washed with water (100 mL) and dried at 50 °C to obtain 7-(4-mesyloxybutoxy)-1H-quinolin-2-one (55 g).

$^1$H NMR (CDCl$_3$) : 1.99 (t, 4H, J=2.7Hz); 3.05 (s, 3H); 4.13 (t, 2H, J=5.4Hz); 4.35 (t, 2H, J=5.4Hz); 6.52(d, 1H, J=9.3Hz) 6.76-6.83(m, 2H); 7.45 (d, 1H, J=8.7Hz); 7.71(d, 1H, J=9.3Hz), Mass: 312 (M+1)

Example 4: Preparation of 7-(1-Boc piperazine) butoxy-1H-quinolin-2-one (compound of formula IV)

7-(4-mesyloxybutoxy)-1H-quinolin-2-one (30 g), acetonitrile (300 mL), potassium carbonate (40 g), potassium iodide (14.5 g), and 1-Boc piperazine (compound of formula V, 19.7 g) were mixed and heated to 80 °C. The reaction mixture was maintained for 3 hours at 75-80 °C. After the reaction was complete, water (600 mL) was added and the reaction mixture was maintained for one hour at room temperature. The solution was filtered and the obtained product was washed with water (100 mL) then dried at 50 °C to obtain 7-(1-Boc piperazine) butoxy-1H-quinolin-2-one (36 g).

$^1$H NMR (CDCl$_3$) : 1.46(s, 9H); 1.67-1.89 (m, 4H); 2.39-2.45 (m, 6 H); 3.45 (t, 4H, J=5.1Hz); 4.09 (t, 2H, J=6.0Hz); 6.54(d, 1H, J=9.3Hz) 6.76-6.82(dd, 1H, J=2.4 & 8.7Hz); 6.84(d, 1H, J=2.1Hz); 7.43 (d, 1H, J=8.7Hz); 7.72(d, 1H, J=9.6Hz), Mass: 402 (M+1)

Example 5: Preparation of 7-(1-piperazine) butoxy-1H-quinolin-2-one dihydrochloride (compound of formula III)

7-(1-Boc-piperazine) butoxy-1H-quinolin-2-one (30 g), isopropanol (150 mL), and CP hydrochloric acid (36 mL), were mixed and heated to 60-65 °C. The reaction mixture was maintained for two hours at same temperature. After the reaction was complete, the reaction mass was cooled to room temperature. The solution was filtered and the obtained product was washed with isopropanol (15 mL) then dried at 50 °C to obtain 7-(1-piperazine) butoxy-1H-quinolin-2-one dihydrochloride (27 g).

$^1$H NMR (CDCl$_3$) : 1.81-1.90 (m, 4H); 3.19-3.34 (m, 4 H); 3.44-3.49(br, 4H) 3.68 (br, 2H); 4.04 (t, 2H, J=5.4Hz); 6.29(d, 1H, J=9.3Hz) 6.78-6.82(dd, 1H, J=2.4 & 8.7Hz); 6.82(d, 1H, J=2.4Hz); 7.56 (d, 1H, J=8.4Hz); 7.80(d, 1H, J=9.3Hz), Mass: 302 (M+1 for Base)

Example 6: Preparation of anhydrous brexpiprazole (compound of formula I)
7-(1-piperazine)butoxy-1H-quinolin-2-one dihydrochloride (20 g) and 1,4-dioxane (200 mL) were combined in a round bottom flask. Sodium tert-butoxide (27 g) was charged to the reaction mass and stirred for 15-30 minutes. The reaction mass was purged with nitrogen gas and 4-bromobenzotriazole (compound of formula II, 10 g) was added to the reaction mass, followed by BINAP (150 mg), maintaining the nitrogen atmosphere. Palladium (II) acetate (100 mg) was added to the reaction mass, continuing to maintain a nitrogen atmosphere and the reaction mass was heated to 100-110 °C and maintained at that temperature for 24 hours. Water (100 mL) was added to the reaction mass, followed by ethyl acetate (100 mL). The aqueous layer of the reaction mixture was separated and the reaction mixture was once again extracted with ethyl acetate (100 mL). The organic layers were combined and washed with 10% sodium chloride solution (50 mL). The organic layer was then acidified with 10% hydrochloric acid solution to reach a pH of 2. The reaction mass was stirred at 10-15 °C for 30 minutes, filtered, and the obtained product was washed with ethyl acetate (10 mL) and water (10 mL). The solid was then dried under vacuum to get brexipiprazole hydrochloride (18 g).

Brexipiprazole hydrochloride (2.0 g) was taken in to mixture of water (40 mL) and dichloromethane (40 mL). Sodium hydroxide solution was added to the reaction mixture to reach a pH of 10-11. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layer was separated off and combined with the first organic layer. The combined organic layers were then washed with water, dried with sodium sulfate, and concentrated under vacuum to get amorphous brexipiprazole. Ethanol (20 mL) was added and the reaction mixture was heated to 60-70 °C and maintained at that temperature for 30 minutes to get clear solution. The reaction mixture was then cooled to 25-30 °C and stirred for one hour to obtain a solid. The solution was filtered and the solid was washed with ethanol to get anhydrous brexipiprazole.

Example 7: Preparation of anhydrous brexipiprazole (compound of formula I)

7-(1-piperazine) butoxy-1H-quinolin-2-one dihydrochloride (20 g) and 1, 4-dioxane (200 mL) were combined in a round bottom flask. Sodium tert-butoxide (27 g) was added to the reaction mass which was then stirred for 15-30 minutes. The reaction mass was purged with nitrogen gas and 4-bromobenzotriazole (compound of formula II, 10 g) was added to the reaction mass, followed by BINAP (150 mg), maintaining the nitrogen atmosphere. Palladium (II) acetate (100 mg) was added to the reaction mass, continuing to maintain the nitrogen atmosphere. The
reaction mass was heated to 100-110 °C and maintained at that temperature for 24 hours. Water (100 mL) was added to the reaction mass, followed by ethyl acetate (100 mL). The aqueous layer was separated and extracted with ethyl acetate (100 mL). The organic layers were combined and washed with 10% sodium chloride solution (50 mL). The organic layer was dried with sodium sulfate and the solution was distilled under reduced pressure to get a residue. Ethanol (100 mL) was added to the residue and the mixture was heated to 50-60 °C and maintained at that temperature for 30 minutes, after which the reaction mixture was cooled to 10-15 °C. The reaction mixture was stirred for one hour to obtain a solid. The solution was filtered to isolate the solid which was washed with ethanol to get anhydrous brexiprazole (12.6 g).

Example 8: Preparation of anhydrous brexiprazole (compound of formula I)

Palladium (20 mg) was taken in toluene (10 mL). BINAP (30 mg) was added to the solution under nitrogen atmosphere which was then heated to 40-45 °C. After 15 minutes, 7-(1-piperazine)butoxy-1H-quinolin-2-one (3.3 g) and 4-bromobenzo[b]thiophene (compound of formula II, 2.0 g) were taken in toluene (5 mL) and the solution was added to the above reaction mass. Sodium tert-butoxide (1.35 g) and toluene (5 mL) were then added. The reaction mass was heated to 95-100 °C and maintained at that temperature for 20 hours. The reaction mass was cooled to room temperature and water (10 mL) was added. The aqueous and organic layers were separated. The aqueous layer was back extracted with toluene (2 x 10 mL). The organic layers were combined and washed with 10% NaCl solution. The organic layer was acidified with 10% hydrochloride solution to bring the pH to 2.0 and the reaction mass was stirred for two hours. The reaction mass was then filtered and the obtained solid was dried under vacuum in an oven to get 3.0 g of brexiprazole hydrochloride salt.

Brexiprazole hydrochloride (2.0 g) was taken in to mixture of water (40 mL) and dichloromethane (40 mL). Sodium hydroxide solution was added to the reaction mixture to bring the pH to 10-11. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, washed with water, and dried with sodium sulfate. The organic layer was then concentrated under vacuum to get amorphous brexiprazole. Ethanol (20 mL) was added and the mixture was heated to 60-70 °C and maintained at that temperature for 30 minutes to get a clear solution. The reaction mixture was then cooled to 25-30 °C and stirred for one hour to obtain a solid. The solution was filtered to isolate the solid which was then washed with ethanol to get anhydrous brexiprazole.
We claim:

1. A process for the preparation of brexiprazole, comprising the steps of:

   a) reacting a compound of formula X with a compound of formula IX in the presence of a first base and a first solvent to obtain a compound of formula VIII, wherein X is a halogen and R is a hydroxyl protecting group;

   ![Diagram of reaction a)

   b) hydrolyzing the compound of formula VIII obtain a compound of formula VII in the presence of a second solvent;

   ![Diagram of reaction b)

   c) converting the compound of formula VII to a compound of formula VI in the presence of a second base and a third solvent, wherein “LG” is a leaving group;

   ![Diagram of reaction c)

   d) reacting the compound of formula VI with a compound of formula V in the presence of a third base to obtain a compound of formula IV, wherein “PG” is an amine protecting group;

   ![Diagram of reaction d)
e) deprotecting the compound of formula IV obtain a compound of formula III; and

\[ \text{IV} \xrightarrow{\text{deprotection}} \text{III} \]

f) condensing the compound of formula III with a compound of formula II to obtain brexpiprazole of formula I, wherein Y is a halogen

\[ \text{III} \xrightarrow{\text{condensation}} \text{I} \]

2. The process of claim 1, wherein the step of reacting the compound of formula VI with the compound of formula V is further performed in the presence of a catalyst.

3. The process of claim 1, wherein the compound of formula III is in the form of a pharmaceutically acceptable salt of the compound of formula III.

4. The process of claim 1, wherein brexpiprazole of formula I is in the form of a pharmaceutically acceptable salt of brexpiprazole.

5. The process according to claim 1, wherein the first solvent is selected from the group consisting of acetonitrile, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, dimethylformamide, 1,4-dioxane, N-methylpyrroldione, isopropyl ether, and mixtures thereof.

6. The process according to claim 1, wherein the second solvent is selected from the group consisting of methanol, ethanol, isopropanol, 1-butanol, isobutyl alcohol, 1-pentanol, water, and mixtures thereof.
7. The process according to claim 1, wherein the third solvent is selected from the group consisting of toluene, dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, xylene, isopropyl ether, and mixtures thereof.

8. The process according to claim 1, wherein the first base is selected from the group consisting of potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, trimethylamine, N,N-diisopropylethylamine, diisopropylamine, pyridine, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof.

9. The process according to claim 1, wherein the second base is selected from the group consisting of potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof.

10. The process according to claim 1, wherein the third base is selected from the group consisting of trimethylamine, N,N-diisopropylethylamine, diisopropylamine, pyridine, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof.

11. The process according to claim 2, wherein the catalyst is selected from the group consisting of potassium iodide, sodium iodide, sodium bromide, potassium bromide, tetrabutyl ammonium bromide, tetrabutyl ammonium bisulfate, tetrabutyl ammonium hydroxide, benzyl triethyl ammonium chloride, tetrabutyl phosphonium bromide and mixtures thereof.

12. The process according to claim 1, wherein the amine protecting group is selected from the group consisting of t-butyloxy carbonyl (BOC), benzyl oxycarbonyl (Cbz), 9-fluorenylethoxy carbonyl (FOMO), and optionally substituted benzyl.
13. The process according to claim 1, wherein the hydroxyl protecting group is selected from the group consisting of benzoyl, benzyl, acetyl, tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), methoxymethyl ether (MOM), tetrahydropropyranyl (THP), allyl ether, and tert-butyl ether.

14. The process according to claim 1, wherein the leaving group is selected from the group consisting of C₁-C₁₀ alkylsulfonate, perfluoro-C₁-C₁₀ alkylsulfonate, arylsulfonate, phosphate, phosphonate, and aralkylsulfonate.

15. The process according to claim 13, wherein the C₁-C₁₀ alkylsulfonyl group is methane sulfonate.

16. A compound of formula VIII

\[
\text{VIII}
\]

, wherein R is a hydroxyl protecting group.

17. A compound as claimed in claim 16, represented as

\[
\text{VIII'}
\]

18. A process for the preparation of anhydrous brexiprazole, comprising the steps of:

a) dissolving brexiprazole in alcohol solvent at elevated temperature;

b) cooling the solution to 20-30 °C, and

c) isolating anhydrous brexiprazole.
19. According to claim 18, wherein the alcohol solvent is selected from the group consisting of ethanol, isopropanol, methanol, isobutanol, n-butanol, and mixtures thereof.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D215/20 C07D215/22 C07D409/12

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

**B. FIELDS SEARCHED**

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 2015/054976 A1 (SUZHOU VIGONVITA LIFE SCIENCES CO LTD [CN]; TOPHARMAN SHANGHAI CO LTD) 23 April 2015 (2015-04-23) scheme 1 and 2 claims 1,5</td>
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☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

- **“A”** document defining the general state of the art which is not considered to be of particular relevance
- **“E”** earlier application or patent but published on or after the international filing date
- **“L”** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **“O”** document referring to an oral disclosure, use, exhibition or other means
- **“P”** document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

4 November 2016

Date of mailing of the international search report

21/11/2016

Name and mailing address of the ISA/

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Authorized officer

Fanni, Stefano

Form PCT/ISA/210 (second sheet) (April 2005)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

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

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

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

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

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

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

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

Remark on Protest

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

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

[ ] No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:
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