# PROCESSES FOR PREPARING (*R*)-2-METHYLPYRROLIDINE AND (*S*)-2-METHYLPYRROLIDINE AND TARTRATE SALTS THEREOF

## CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/927,356, filed May 3, 2007, the entirety of which is incorporated herein by reference.

## BACKGROUND OF THE INVENTION

(*R*)- and (*S*)-2-methylpyrrolidine are starting materials useful in the synthesis of various pharmaceutical products. For example, (*R*)-2-methylpyrrolidine can be used to prepare many $H_3$ receptor ligands. For this reason, there has been great interest in developing cost effective routes to prepare (*R*)- and (*S*)-2-methylpyrrolidine. But the procedures previously developed either employ costly starting materials or require many tedious synthetic steps.

Pu et al. (*Org. Process Res. & Dev.*, **2005**, *9*, 45-50) discloses the preparation of (*R*)-2-methylpyrrolidine L-tartrate by fractional crystallization of racemic 2-methylpyrrolidine in the presence of L-tartaric acid. Racemic 2-methylpyrrolidine costs approximately $20/gram.

Van de Kuil et al. (*Recl. Trav. Chim. Pays-Bas*, **1994**, *113*, 267-277) discloses a four (4) step synthesis of (*R*)-2-methylpyrrolidine L-tartrate and (*S*)-2-methylpyrrolidine D-tartrate from 2-methylpyrroline (approximately $5/gram). However, the process is disadvantageous for several reasons. First, the process requires the preparation of three intermediates, two of which must be isolated. Additionally, the process requires isolation of the intermediate HCl salt by *in vacuo* removal of glacial acetic acid and excess 37% aqueous hydrochloric acid, which is time consuming, expensive, and corrosive. Moreover, the synthesis requires isolation of an intermediate by two sequential flash distillations from potassium hydroxide.

Ku et al. (*Tetrahedron*, **2006**, *62*, 4584-4589) discloses a four (4) step synthesis of (*R*)-2-methylpyrrolidine hydrochloride from *N*-Boc-L-prolinol. The process is disadvantageous for several reasons. First, the process requires the preparation and isolation of three different synthetic intermediates. Second, the process employs the environmentally deleterious solvent dichloromethane, as well as corrosive gaseous hydrochloric acid and phosphoric acid. Third, the process employs expensive lithium iodide (approximately $13/gram). In addition, the resulting hydrochloride salt is very hygroscopic.

Zhao et al. (*J. Org. Chem.*, **2006**, *71*, 4336-4338) discloses a four (4) step synthesis of (*R*)-2-methylpyrrolidine benzenesulfonate from *N*-Boc-L-proline. The process is disadvantageous for several reasons. First, the process requires the preparation and isolation of three (3) separate synthetic intermediates. Second, the process employs corrosive reagents such as phosphoric acid, boron trifluoride etherate, sodium hydroxide, sodium borohydride, and Super-Hydride®.

A need exists for a process to prepare (*R*)- and (*S*)-2-methylpyrrolidine that is short, safe, inexpensive, commercially scalable, and which can be performed without the need to isolate multiple synthetic intermediates.

## SUMMARY OF THE INVENTION

We have surprisingly found that (*R*)-2-methylpyrrolidine L-tartrate and (*S*)-2-methylpyrrolidine D-tartrate can be prepared in two steps from inexpensive 2-methylpyrroline using non-corrosive reagents without the necessity of isolating any synthetic intermediates. In one embodiment, the present invention provides processes for preparing (*R*)-2-methylpyrrolidine L-tartrate, comprising the steps of:

(a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(b) optionally removing the hydrogenation catalyst from the mixture;

(c) dissolving L-tartaric acid in the mixture to form a solution;

(d) crystallizing (*R*)-2-methylpyrrolidine L-tartrate from the solution; and

(e) isolating the crystalline (*R*)-2-methylpyrrolidine L-tartrate.

Preferably, the hydrogenation catalyst is a platinum catalyst. Preferably, the platinum catalyst is platinum (IV) oxide. More preferably, the platinum catalyst is 5% Pt-C.

Preferably, the alcohol solvent is a mixture of ethanol and methanol. More preferably, the alcohol solvent is a mixture of ethanol and methanol at a ratio of about 2:1 to about 3:1 (v/v).

Preferably, step (a) is performed at ambient temperature.

Preferably, the platinum catalyst is removed in step (b) by filtration.

Preferably, the isolated (*R*)-2-methylpyrrolidine L-tartrate has an optical purity of at least 50% ee.

Optionally, the process further comprises the steps of:

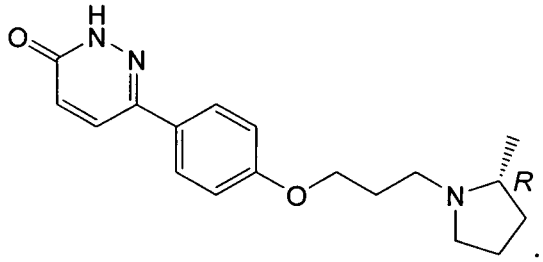
(f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate;

(g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate; and

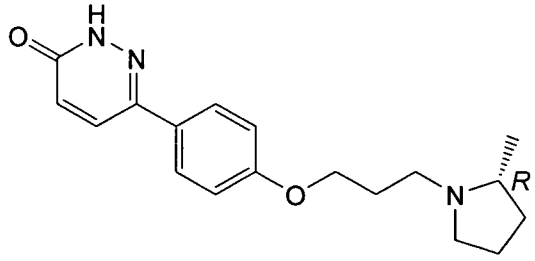
(h) optionally repeating steps (f) and (g).

Optionally, the process further comprises the step of reacting the isolated recrystallized (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine.

Preferably, the process further comprises the step of converting the prepared (*R*)-2-methylpyrrolidine L-tartrate into a pharmaceutical composition, preferably an $H_3$ receptor ligand, preferably 2-(6-{2-[(2*R*)-2-methyl-1-pyrrolidin-1-yl]ethyl}-2-naphthalen-2-yl)-2H-pyridazin-3-one:



In one embodiment, the present invention provides a process for preparing 6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one:



comprising the steps of:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate; and

(2) reacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base; and

(3) reacting the (R)-2-methylpyrrolidine with 6-[4-(3-halo-propoxy)-phenyl]-2H-pyridazin-3-one for a time and under conditions sufficient to form (R)-6-{4-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one.

Preferably, the 6-[4-(3-halo-propoxy)-phenyl]-2H-pyridazin-3-one is prepared by the steps of:

(a) contacting 1-(4-hydroxy-phenyl)-ethanone with 1,3-dihalopropane, for a time and under conditions sufficient to form 1-[4-(3-halo-propoxy)-phenyl]-ethanone; and

(b) contacting the 1-[4-(3-halo-propoxy)-phenyl]-ethanone with glyoxalic acid for a time and under conditions sufficient to produce 6-[4-(3-halo-propoxy)-phenyl]-2H-pyridazin-3-one.

The present invention also provides processes for preparing (*S*)-2-methylpyrrolidine D-tartrate, comprising the steps of:

(a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(b) optionally removing the hydrogenation catalyst from the mixture;

(c) dissolving D-tartaric acid in the mixture to form a solution;

(d) crystallizing (*S*)-2-methylpyrrolidine D-tartrate from the solution; and

(e) isolating the crystalline (*S*)-2-methylpyrrolidine D-tartrate.

Preferably, the hydrogenation catalyst is a platinum catalyst. Preferably, the platinum catalyst is platinum (IV) oxide. More preferably, the platinum catalyst is 5% Pt-C.

Preferably, the alcohol solvent is a mixture of ethanol and methanol. More preferably, the alcohol solvent is a mixture of ethanol and methanol at a ratio of about 2:1 to about 3:1 (v/v).

Preferably, step (a) is performed at ambient temperature.

Preferably, the platinum catalyst is removed in step (b) by filtration.

Preferably, the isolated (*S*)-2-methylpyrrolidine D-tartrate has an optical purity of at least 50% ee.

Optionally, the process further comprises the steps of:

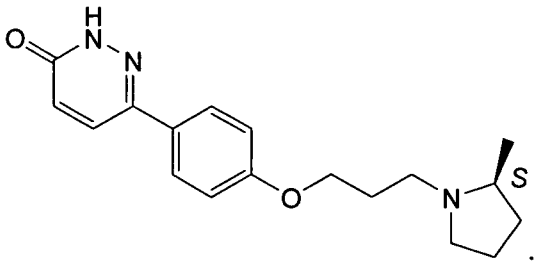
(f) recrystallizing the isolated (*S*)-2-methylpyrrolidine D-tartrate;

(g) isolating the recrystallized (*S*)-2-methylpyrrolidine D-tartrate; and

(h) optionally repeating steps (f) and (g).

Optionally, the process further comprises the step of reacting the isolated recrystallized (*S*)-2-methylpyrrolidine D-tartrate with a base to provide (*S*)-2-methylpyrrolidine.

Optionally, the process further comprises the step of converting the prepared (*S*)-2-methylpyrrolidine D-tartrate into an $H_3$ receptor ligand, preferably 2-(6-{2-[(2S)-2-methyl-1-pyrrolidin-1-yl]ethyl}-2-naphthalen-2-yl)-2H-pyridazin-3-one:



## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

"About" refers to a range of values ± 10% of a specified value; for example, the phrase "about 50" includes ± 10% of 50, or from 45 to 55.

"Alcohol solvent" refers to a $C_1$-$C_6$alkyl alcohol or a mixture of $C_1$-$C_6$alkyl alcohols.

"Commercial scale" refers to a single batch of at least about 500 grams.

"Crystallizing" refers to causing crystals to form.

"$H_3$ receptor ligand" refers to a compound that interacts with the histamine $H_3$ receptor as an antagonist, agonist, or partial agonist.

"Heterogeneous catalyst" refers to a hydrogenation catalyst that is not soluble in an alcohol solvent.

"Homogeneous catalyst" refers to a hydrogenation catalyst that is soluble in an alcohol solvent.

"Hydrogenation catalyst" refers to a composition suitable for catalyzing the reaction of 2-methylpyrroline with hydrogen to form 2-methylpyrrolidine.

"Isolating" refers to separating a component (e.g., a reagent or product) from a mixture.

"Optical purity" refers to the proportion of one enantiomer in a mixture of enantiomers, and is expressed as enantiomeric excess (% ee), which is defined as $(|R - S|/(R + S))*100\%$, wherein $R$ and $S$ are the respective fractions of enantiomers such that $R + S = 1$.

"Pharmaceutical product" refers to a compound or composition that can be used to treat a disease, condition, or disorder in a human.

"Platinum catalyst" refers to a hydrogenation catalyst that contains platinum.

"Purifying" refers to increasing the purity of a compound.

"Purity" refers to the percentage by weight of one component in a mixture.

"Solution" refers to a solvent containing a substance(s) that is at least partially dissolved; and which may contain an undissolved (e.g., solid) substance(s).

All publications referenced herein are incorporated by reference in their entireties for all purposes.

**Description**

The present invention provides processes for preparing (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate, comprising the steps of:

(a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(b) optionally removing the hydrogenation catalyst from the mixture;

(c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(d) crystallizing (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate from the solution; and

(e) isolating the crystalline (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate.

Step (a)

In step (a), 2-methylpyrroline is hydrogenated in a mixture comprising an alkyl alcohol solvent and a hydrogenation catalyst. The 2-methylpyrroline used in the hydrogenation reaction may be purchased from commercial sources (e.g., Sigma-Aldrich Corp.; St. Louis, MO). An important benefit of the present process is that 2-methylpyrroline is less expensive than other starting materials used for the production of (*R*)- and (*S*)-2-methylpyrrolidine.

The hydrogenation catalyst used in the reaction may be purchased from commercial sources (e.g., Sigma-Aldrich Corp.; St. Louis, MO). The hydrogenation catalyst can be a homogeneous catalyst or a heterogeneous catalyst. Examples of hydrogenation catalysts include, but are not limited to, platinum catalysts. Examples of platinum catalysts include, but are not limited to, platinum on carbon (Pt/C), platinum (IV) oxide, and mixtures thereof. Examples of homogeneous catalysts include, but are not limited to, chlorotris(triphenylphosphine)rhodium (Wilkinson's catalysts) and catalysts disclosed in U.S. Patent Nos. 4,581,417, 4,631,315, and 5,670,437. Preferably, the hydrogenation catalyst is platinum (IV) oxide. More preferably, the hydrogenation catalyst is 5% Pt-C.

The alcohol solvent used in the reaction is a $C_1$-$C_6$alkyl alcohol or a mixture of $C_1$-$C_6$alkyl alcohols. Examples of $C_1$-$C_6$alkyl alcohols include, but are not limited to, methanol, ethanol, isopropanol, and *n*-butanol. Preferably, the alcohol solvent comprises ethanol. Preferably, the alcohol solvent comprises methanol. More preferably, the alcohol solvent is a mixture of ethanol and methanol. More preferably, the alcohol solvent is a mixture of ethanol and methanol at a ratio of about 0.5:1 to about 10:1 (v/v). More preferably, the alcohol solvent is a mixture of ethanol and methanol at a ratio of about 1:1 to about 5:1 (v/v). More preferably, the alcohol solvent is a mixture of ethanol and methanol at a ratio of about 2:1 to about 3:1 (v/v). More preferably, the alcohol solvent is a mixture of ethanol and methanol at a ratio of about 2.4:1 (v/v).

The alcohol solvent may be present in any suitable amount in the step (a) reaction mixture. Preferably, the alcohol solvent comprises at least about 50% (w/w) of the reaction mixture. More preferably, the alcohol solvent comprises at least about 70% (w/w) of the reaction mixture. More preferably, the alcohol solvent comprises at least about 90% (w/w) of the reaction mixture. More preferably, the alcohol solvent comprises at least about 95% (w/w) of the reaction mixture. Notably, $C_1$-$C_6$alkyl alcohols are more readily removed from the reaction mixture as compared to acetic acid. In addition, $C_1$-$C_6$alkyl alcohols are non-corrosive.

The hydrogen ($H_2$) used in the hydrogenation reaction may be added to the reaction mixture as a gas, such as by performing the reaction in a hydrogen atmosphere, or generated in situ, such as by treatment of $H_2PtCl_6$ or $RhCl_3$ with $NaBH_4$ (*see* Brown and Sivasankaran, *J. Am. Chem. Soc.* **1962**, *84*, 2828). In certain embodiments, the hydrogenation reaction is performed by adding gaseous hydrogen to the reaction mixture. In preferred embodiments, the hydrogenation is performed above atmospheric pressure. In certain embodiments, the reaction is performed by generating hydrogen in situ.

The hydrogenation reaction may be performed at any suitable temperature. Preferably, the reaction is performed at ambient temperature.

An advantage of the present process is that the hydrogenation reaction is performed in a non-corrosive alkyl alcohol solvent. Another advantage of the present process is that the product of the hydrogenation reaction (i.e., 2-methylpyrrolidine) is obtained directly without the need to prepare or isolate intermediates, such as intermediate salts.

Step (b)

Step (b) is an optional step. In step (b), the hydrogenation catalyst is removed from the hydrogenation reaction mixture. Preferably, the hydrogenation catalyst is removed from the hydrogenation reaction mixture after step (a). Preferably, step (b) is performed prior to step (d), particularly when the hydrogenation catalyst is a heterogeneous catalyst. Suitable methods for removing the hydrogenation catalyst include, but are not limited to, filtering, decanting, and centrifuging. In certain embodiments, the hydrogenation catalyst is removed by filtration. While hydrogenation catalysts are generally precious metal-based, an advantage of the present process is that the hydrogenation catalyst may be removed from the mixture, recycled and reused in subsequent hydrogenation reactions (*see, e.g.,* US 5,554,353 (Schneider et al.); EP 1 739 104 A1 (Kobayashi et al.); Setty-Fichman, et al., *J. Mol. Cat. A: Chem.*, **1999**, *144(1)*, 159-163.

Step (c)

In step (c), L-tartaric acid or D-tartaric acid is dissolved in the hydrogenation reaction mixture to form a solution. If the desired product is (*R*)-2-methylpyrrolidine, then L-tartaric acid is used. If the desired product is (*S*)-2-methylpyrrolidine, then D-tartaric acid is used. The L-tartaric acid or D-tartaric acid used in the present process may be purchased from commercial sources (e.g., Sigma-Aldrich Corp.; St. Louis, MO).

Preferably, the solution formed in step (e) is homogeneous. If the solution is not homogeneous (e.g., contains undissolved particles), the solution is preferably heated to promote dissolution.

An advantage of the present process is that it does not require the 2-methylpyrrolidine prepared in the hydrogenation reaction to be isolated from the reaction mixture before the addition of tartaric acid. This makes the process simpler, faster, less expensive, and less wasteful as compared to prior art processes.

Step (d)

In step (d), (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate is crystallized from the solution prepared in step (c). If L-tartaric acid is added in step (c), then (*R*)-2-methylpyrrolidine L-tartrate is crystallized from the solution in step (d). If D-tartaric acid is added in step (c), then (*S*)-2-methylpyrrolidine D-tartrate is crystallized from the solution in step (d). Any suitable method may be used to crystallize (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate from the solution. In

certain embodiments, the solution is heated to promote dissolution, and then cooled to induce crystallization.

Step (e)

In step (e), the crystalline (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate is isolated. If L-tartaric acid is added in step (c), then (*R*)-2-methylpyrrolidine L-tartrate is crystallized from the solution in step (d) and isolated in step (e). If D-tartaric acid is added in step (c), then (*S*)-2-methylpyrrolidine D-tartrate is crystallized from the solution in step (d) and isolated in step (e). Suitable methods for isolating the crystalline (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate include, but are not limited to, filtering, decanting, and centrifuging. An advantage of the present process is that the product can be isolated by simple filtration. Preferably, the (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate is isolated by filtration. It is understood that the isolated (*R*)-2-methylpyrrolidine L-tartrate is likely to contain some (*S*)-2-methylpyrrolidine L-tartrate, and the isolated (*S*)-2-methylpyrrolidine D-tartrate is likely to contain some (*R*)-2-methylpyrrolidine D-tartrate, which will reduce the optical purity of the isolated product. Preferably, the isolated (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate has an optical purity of at least 40% ee. More preferably, the isolated (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate has an optical purity of at least 50% ee. More preferably, the isolated (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate has an optical purity of at least 55% ee.

Optional additional steps

The present process for preparing (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate is advantageous in that it utilizes inexpensive and non-corrosive reagents and solvents, can be conveniently and inexpensively conducted at temperatures between 0 °C and 25 °C, requires the preparation of only one intermediate compound, does not require the isolation of synthetic intermediates, permits catalyst recycling, and provides a product that can be isolated by simple filtration and then used in subsequent processes.

The isolated product is a tartrate acid addition salt of (*R*)- or (*S*)-2-methylpyrrolidine free base. If desired, the salt may be converted to (*R*)- or (*S*)-2-methylpyrrolidine free base. The resulting free base may be isolated using techniques

known in the art. Preferably, the free base may be generated *in situ* and used in the next synthetic step without isolation. The methods described herein are applicable to both the isolated 2-methylpyrrolidine free base and the 2-methylpyrrolidine free base generated *in situ* in a reaction mixture.

Thus, in certain embodiments the process further comprises the step of: reacting the isolated (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate with a base to provide (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine. Suitable bases for use in this reaction include, but are not limited to, ammonium hydroxide, alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide), alkylamines (e.g., triethylamine, diisopropylethylamine), and mixtures thereof. Suitable solvents for use in this reaction include, but are not limited to, diethyl ether and dichloromethane. In addition, the 2-methylpyrrolidine free base can be generated from the corresponding tartrate salt using ion-exchange resin using procedures known to those in the art.

Preferably, the prepared (*R*)-2-methylpyrrolidine L-tartrate, (*S*)-2-methylpyrrolidine D-tartrate, (*R*)-2-methylpyrrolidine, or (*S*)-2-methylpyrrolidine has an optical purity of at least 50% ee. This means that the major enantiomer constitutes 75% of the mixture, and the minor enantiomer 25% (50% ee = ((0.75-0.25)/(0.75+0.25)*100%). This level of purity is often sufficient for the product to be used as a reagent in a subsequent synthetic process. For example, when (*R*)-2-methylpyrrolidine L-tartrate having an optical purity of 50% ee is used to prepare a compound having an additional stereogenic center(s), the reaction will produce a mixture of diastereomers, and the minor diastereomer(s) formed from the (*S*)-2-methylpyrrolidine may be removed during ordinary purification of the major diastereomer(s) formed from the (*R*)-2-methylpyrrolidine.

If a higher level of optical purity is desired, the obtained (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate may be recrystallized. Therefore, in certain embodiments the process may further comprise the steps of:

(f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate;

(g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate; and

(h) optionally repeating steps (f) and (g).

Step (f)

In step (f), the (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate isolated in step (e) is recrystallized. Suitable methods for recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate include, but are not limited to, dissolving the isolated tartrate salt in a suitable solvent and then cooling the solution to promote crystallization. Suitable recrystallization solvents include, but are not limited to, alcohol solvents. Preferably, the recrystallization solvent is an alcohol solvent comprising at least about 70% (v/v) of ethanol and methanol. More preferably, the recrystallization solvent is an alcohol solvent comprising at least about 70% (v/v) of ethanol and methanol at a ratio of about 1:1 to about 5:1 (v/v). More preferably, the recrystallization solvent is an alcohol solvent comprising at least about 70% (v/v) of ethanol and methanol at a ratio of about 2:1 to about 3:1 (v/v). More preferably, the recrystallization solvent is an alcohol solvent comprising at least about 90% (v/v) of ethanol and methanol. More preferably, the recrystallization solvent is an alcohol solvent comprising at least about 90% (v/v) of ethanol and methanol at a ratio of about 1:1 to about 5:1 (v/v). More preferably, the recrystallization solvent is an alcohol solvent comprising at least about 90% (v/v) of ethanol and methanol at a ratio of about 2:1 to about 3:1 (v/v).

Step (g)

In step (g), the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate is isolated. Suitable methods for isolating the recrystallized tartrate salt include, but are not limited to, filtering, decanting, and centrifuging. Preferably, the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate is isolated by filtration.

Subjecting the tartrate salt isolated in step (e) to a single recrystallization sequence according to steps (f) and (g) preferably provides isolated (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate having an optical purity of at least 80% ee. More preferably, the (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate isolated in step (g) has an optical purity of at least 85% ee. An optical purity of 85% ee means that the major enantiomer constitutes more than 92% of the mixture, and the minor enantiomer less than 8% (84% ee = ((0.925-0.075)/(0.925+0.075)*100%), which is often of sufficient purity for use in subsequent synthetic processes.

Step (h)

If higher optical purity is desired, the recrystallization sequence (i.e., steps (f) and (g)) may be repeated one or more times to increase the optical purity of the (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate. After two recrystallizations, the (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate preferably has an optical purity of at least 90% ee. More preferably, the isolated recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate has an optical purity of at least 93% ee. After three (3) recrystallizations, the (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate preferably has an optical purity of at least 95% ee. More preferably, the isolated recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate has an optical purity of at least 97% ee. After four (4) recrystallizations, the (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate preferably has an optical purity of at least 98% ee.

Free base

Optionally, the process may further comprise the step of reacting the isolated recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate with a base to provide (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine. Suitable bases for use in this reaction include, but are not limited to, ammonium hydroxide, alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide), alkylamines (e.g., triethylamine, diisopropylethylamine), and mixtures thereof. Suitable solvents for use in this reaction include, but are not limited to, diethyl ether and dichloromethane. In addition, the 2-methylpyrrolidine free base can be generated from the corresponding tartrate salt using ion-exchange resin using procedures known to those in the art.

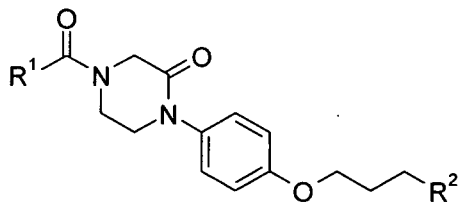
The resulting free base may be isolated using techniques known in the art. Preferably, the free base may be generated *in situ* and used in the next synthetic step without isolation. The methods described herein are applicable to both the isolated 2-methylpyrrolidine free base and the 2-methylpyrrolidine free base generated *in situ* in a reaction mixture.

Additional compounds

In addition to providing convenient methods of preparing (R)- and (S)-2-methylpyrrolidine and their respective tartaric acid salts, the present invention also provides methods for incorporating 2-methylpyrrolidine into other compounds, in particular, pharmaceutically useful compounds. The (*R*)-2-methylpyrrolidine L-tartrate or

(*S*)-2-methylpyrrolidine D-tartrate obtained after steps (e), (g) or (h) may be used. In certain embodiments, an initial step in the conversion may be to transform the (*R*)-2-methylpyrrolidine L-tartrate or (*S*)-2-methylpyrrolidine D-tartrate salt form into the corresponding free base form (i.e., (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine, respectively) by reaction with a base or an ion exchange resin. This (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine, whether isolated or prepared *in situ*, may then be used to prepare a number of pharmaceutical compounds, for example, histamine-3 receptor ligands, known in the art.

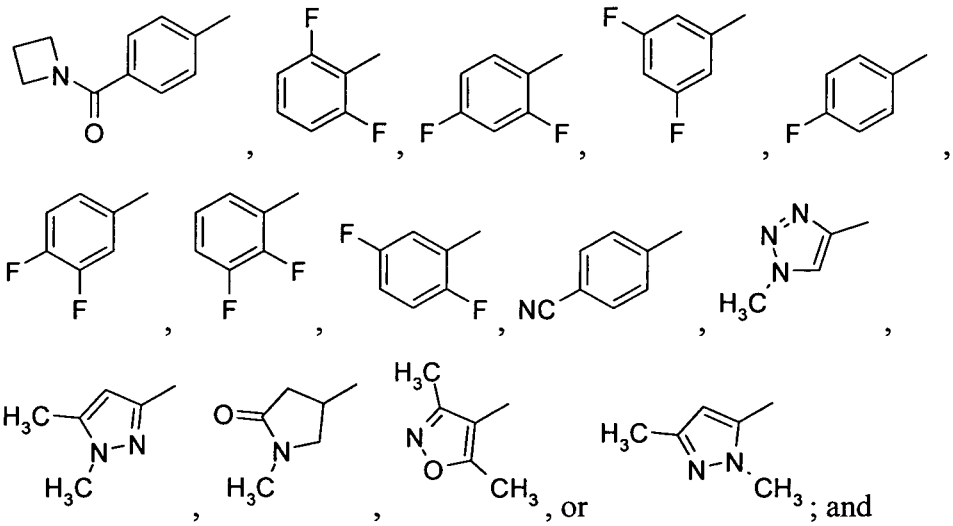
For example, the (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine prepared by the foregoing processes may be converted into an $H_3$ receptor antagonist and/or inverse agonist of formula (I):



(I)

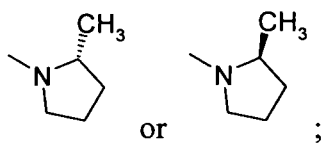
wherein

$R^1$ is



; and

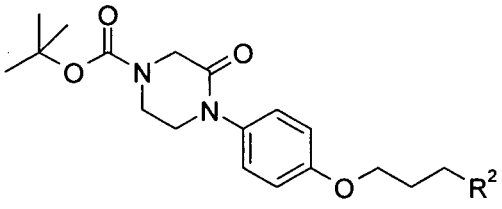
$R^2$ is



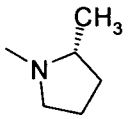
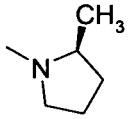
;

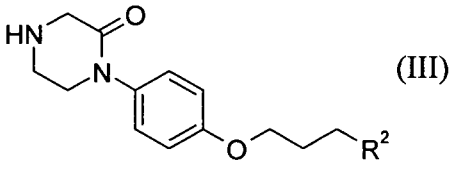
or a pharmaceutically acceptable salt thereof.

Suitable methods for preparing a compound of formula (I) from 2-methylpyrrolidine are described in WO 2007/009741, and may be adapted for use with the (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine prepared in accordance with foregoing processes. For example, a solution of 1,1 dimethylethyl 4-{4-[(3-chloropropyl)oxy]phenyl}-3-oxo-1-piperazinecarboxylate dissolved in 2 butanone may be provided. Potassium carbonate, potassium iodide and (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine free base may be added, and the mixture heated at 80°C for 24 hours. The reaction may then be cooled to room temperature and partitioned between EtOAc and water. The organic phase may be dried and concentrated, the residue purified by flash chromatography and the appropriate fractions combined and concentrated to give a BOC-protected amine of formula (II):

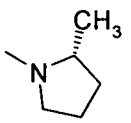
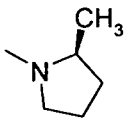


(II)

wherein $R^2$ is  or  (*i.e.*, the compound 1,1-dimethylethyl 4-(4-{[3-(2*R*-methyl-1-pyrrolidinyl)propyl]oxy}phenyl)-3-oxo-1-piperazinecarboxylate or 1,1-dimethylethyl 4-(4-{[3-(2*S*-methyl-1-pyrrolidinyl)propyl]oxy}phenyl)-3-oxo-1-piperazinecarboxylate). The BOC protecting group in the compound of formula (II) can then be removed (e.g., by reaction with trifluoroacetic acid) to form an amine of formula (III):



(III)

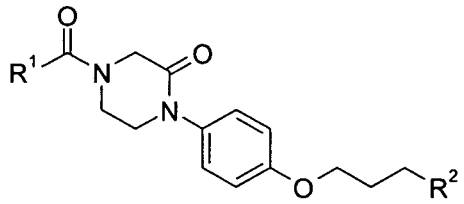
wherein $R^2$ is  or . The amine of formula (III) can then be reacted with a carboxylic acid chosen from 4-cyanobenzoic acid, 4-(1-azetidinylcarbonyl)benzoic acid, 2,4-difluorobenzoic acid, 3,5-difluorobenzoic acid, 4-fluorobenzoic acid, 1-methyl-1*H*-1,2,3-triazole-4-carboxylic acid, 1,5-dimethyl-1*H*-pyrazole-3-carboxylic acid, 1-methyl-5-oxo-3-pyrrolidinecarboxylic acid, 3,5-dimethyl-4-isoxazolecarboxylic acid, 1,3-

dimethyl-1*H*-pyrazole-5-carboxylic acid, 2,3-difluorobenzoic acid, 2,5-difluorobenzoic acid, 2,6-difluorobenzoic acid, and 3,4-difluorobenzoic acid to form a compound of formula (I).

The 1,1-dimethylethyl-4-{4-[(3-chloropropyl)oxy]phenyl}-3-oxo-1-piperazinecarboxylate used in the preparation of the BOC-protected amine of formula (II) can be prepared by reacting 1-bromo-3-chloropropane with 1,1-dimethylethyl-4-(4-hydroxyphenyl)-3-oxo-1-piperazinecarboxylate, which can be prepared by catalytic hydrogenolysis of 1,1-dimethylethyl-3-oxo-4-{4-[(phenylmethyl)oxy]phenyl}-1-piperazinecarboxylate, which can be prepared by reacting methanesulfonyl chloride with 1,1-dimethylethyl-(2-hydroxyethyl)[2-oxo-2-({4-[(phenylmethyl)oxy]phenyl}amino)ethyl]carbamate, which can be prepared by BOC protection of $N^2$-(2-hydroxyethyl)-$N^1$-{4-[(phenylmethyl)oxy]phenyl}glycinamide, which can be prepared by reacting 4-[(phenylmethyl)oxy]aniline with chloroacetyl chloride and then 2-aminoethanol.

As an alternative to BOC, other nitrogen protecting groups known in the art may be used. Examples of suitable nitrogen protecting groups are described in Green, T.W.; Wutz, P.G.M. Protective Groups in Organic Synthesis, 2d ed.; John Wiley and Sons: New York, 1991.

Thus one embodiment of the invention relates to a process for preparing a compound of formula (I):



(I)

wherein $R^1$ and $R^2$ are defined as set forth above comprising the steps of:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate; and

(2a) converting the isolated (R)-2-methylpyrrolidine L-tartrate into a compound of formula I.

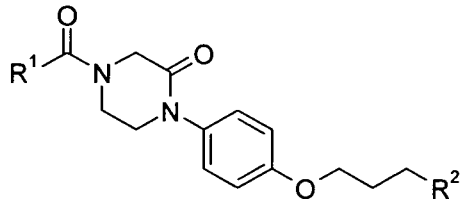
This process may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate; and

(1h) optionally repeating steps (f) and (g).

In another embodiment, the invention relates to a process for preparing a compound of formula (I):



(I)

wherein $R^1$ and $R^2$ are defined as set forth above comprising the steps of:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

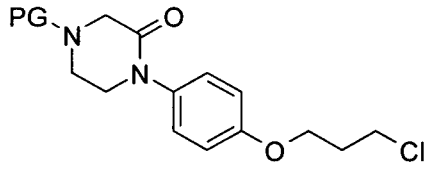
(1c) dissolving L-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate;

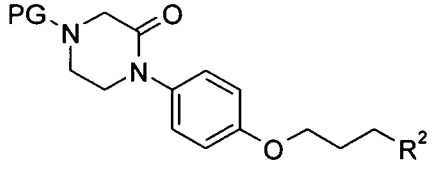
(1f) reacting the (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine;

(2) reacting the (R)-2-methylpyrrolidine with a protected amine of formula (Ia)



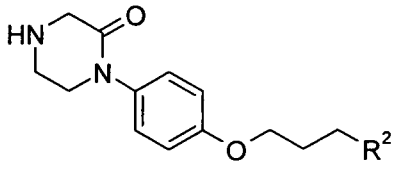
(Ia)

wherein PG is a protecting group, to form a protected amine of formula (II)



(II);

(3) removing the protecting group from the protected amine of formula (III) to form an amine of formula (III)




(III); and

(4) reacting the amine of formula (III) with a carboxylic acid chosen from 4-cyanobenzoic acid, 4-(1-azetidinylcarbonyl)benzoic acid, 2,4-difluorobenzoic acid, 3,5-difluorobenzoic acid, 4-fluorobenzoic acid, 1-methyl-1*H*-1,2,3-triazole-4-carboxylic acid, 1,5-dimethyl-1*H*-pyrazole-3-carboxylic acid, 1-methyl-5-oxo-3-pyrrolidinecarboxylic acid, 3,5-dimethyl-4-isoxazolecarboxylic acid, 1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid, 2,3-difluorobenzoic acid, 2,5-difluorobenzoic acid, 2,6-difluorobenzoic acid, and 3,4-difluorobenzoic acid to form a compound of formula (I).

This process may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate; and

(1h) optionally repeating steps (f) and (g).

Preferably, the protecting group is BOC.

Another compound which demonstrates histamine-3 receptor ligand activity is 2-(6-{2-[(2*R*)-2-methyl-1-pyrrolidin-1-yl]-ethyl}-2-naphthalen-2-yl)-2H-pyridazin-3-one. One process for the preparation of this compound is described in US 2005/0256127.

6-Bromo-naphthalen-2-ol can be treated with any suitable trifluoromethanesulfonic reagent in the presence of an organic base to provide a trifluoro-methanesulfonic acid 6-bromo-naphthalen-2-yl ester. Examples of suitable trifluoromethanesulfonic reagents are, for example, trifluoromethanesulfonyl acid anhydride, trifluoromethanesulfonyl chloride, N-phenyltrifluoromethanesulfonimide, trifluoromethanesulfonyl-1- -H-imidazole, trifluoromethanesulfonyl acid anilide, trifluoromethanesulfony acid-2-nitrophenyl ester, trifluoromethanesulfony- l acid-4-nitrophenyl ester. Examples of organic base are, for example, triethylamine, diisopropylamine, diisopropylethylamine, 2,6-lutidine, pyridine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The reaction can be accomplished in any suitable organic solvent. Examples of suitable solvents are $CH_2Cl_2$, dimethyl ether (DME), and toluene. The reaction also can be carried out in a biphasic condition where an inorganic base is used. For example, suitable

inorganic bases are $K_3PO_4$, $NaHCO_3$, $Na_2CO_3$, NaOH, and the like. The preferred solvent is toluene. Typically, the reaction is accomplished in biphasic conditions, for example use of toluene and 30% potassium phosphate, at low temperatures. The preferred temperature range for the reaction is from about -5 °C to about 0 °C.

The trifluoro-methanesulfonic acid 6-bromo-naphthalen-2-yl ester is converted to 2-bromo-6-vinyl-naphthalene via reaction with a vinyltrifluoroborate reagent. Suitable vinyltrifluoroborate reagents are, for example, potassium vinyltriflurorborate, 2-vinyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, dibutyl vinylboronate. The reagent is used in an amount of from about 1.0 molar equivalent to about 1.5 molar equivalents relative to the trifluoro-methanesulfonic acid 6-bromo-naphthalen-2-yl ester. Typically, the reaction is carried out in a polar organic solvent, for example an alcohol, and a basic solution, for example a metal carbonate solution. A preferred solvent is ethanol. Examples of other solvents that can be used for the reaction are n-propanol, iso-propanol, methanol, and other suitable alcohols. The metal carbonate preferably is cesium carbonate. Alternatively, other salts, for example $Na_2CO_3$, and $K_3PO_4$ also can be used. The amount of metal carbonate for the reaction is from about 2 molar equivalents to about 4 molar equivalents relative to the trifluoro-methanesulfonic acid 6-bromo-naphthalen-2-yl ester. The reaction is accomplished in the presence of a palladium catalyst and an organic amino base, for example, such as triethylamine, diisopropylamine, and the like. Examples of palladium catalysts for the reaction include, but are not limited to, tetrakis(triphenylphosphine)palladium, $PdCl_2(dppf)_2$, $PdCl_2(Ph_3P)_2$, and $PdCl_2(CH_3CN)_2$. The preferred palladium catalyst is tetrakis(triphenylphosphine)palladium.

2-Bromo-6-vinyl-naphthalene may treated with an (*R*)-2-methylpyrrolidine anion generated with n-butyllithium to provide 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-(*R*)-2-methyl-pyrrolidine. The method described in US2005/0256127 may be improved by preparing (R)- and/or (S)-2-methylpyrrolidine in accordance with foregoing processes. 2-bromo-6-vinyl-naphthalene may then be reacted with an (*R*)-2-methylpyrrolidine anion generated with n-butyllithium, or any other suitable base, to provide 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-2*R*-methyl-pyrrolidine. 2-Bromo-6-vinyl-naphthalene may treated with an (*R*)-2-methylpyrrolidine anion generated with n-butyllithium to provide 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-(*R*)-2-methyl-pyrrolidine. Preferably, about 1.2 to about 2.5 molar equivalents of (*R*)-2-methylpyrrolidine are used for the reaction. The reaction

typically is accomplished in an organic solvent, for example, THF, methyl-t-butyl ether (MTBE), $Et_2O$, and DME. The preferred solvent is tetrahydrofuran (THF). The n-butyllithium is added to a THF solution of (*R*)-2-methylpyrrolidine in a controlled fashion, typically in a dropwise manner. To this solution is added a THF solution of 2-bromo-6-vinyl-naphthalene. Alternatively, it is also suitable to add the THF solution of 2-bromo-6-vinyl-naphthalene to the solution of (*R*)-2-methylpyrrolidine and n-butyllithium. The reaction is accomplished at below room temperature, typically in a temperature range from about 0 °C to about -20 °C. From about 0.3 to about 0.7 molar equivalents of n-butyllithium are used relative to the 2-bromo-6-vinylnaphthalene compound. The resulting compound is 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-(*R*)-2-methyl-pyrrolidine.

The 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-(*R*)-2-methyl-pyrrolidine may then be reacted with 2H-pyridazin-3-one to provide the desired 2-{6-[2-((*R*)2-methyl-pyrrolidin-1-yl)-ethyl]-naphthalen-2-yl}-2H-pyridazin-3-one compound, which can be further processed to prepare a suitable salt. The reaction is accomplished using 2H-pyridazin-3-one, 8-hydroxyquinoline, a copper catalyst in the presence of base. From about 1.0 to about 1.5 molar equivalents of (2H)-pyridazin-3-one are used relative to the 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-(*R*)-2-methyl-pyrrolidine. The copper catalyst can be any suitable copper catalyst, for example copper (I) catalysts. Examples of suitable catalysts for the reaction include but are not limited to copper (0) powder, copper (I) chloride, copper (I) bromide, copper (I) iodide, copper (I) oxide, copper (I) acetate, copper (II) chloride, copper (II) bromide, copper (II) iodide, copper (II) oxide, or copper (II) acetate. The preferred copper catalyst is copper (I) chloride. About 0.02 to about 1.0 molar equivalents of copper catalyst are used relative to the 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-(*R*)-2-methyl-pyrrolidine. Examples of suitable ligands for the reaction include, but are not limited to p-dimethylaminopyridine, pyridine, 3-picoline, 4-picoline, 8-hydroxyquinoline, 7-methyl-8-hydroxyquinoline, 7-n-propyl-8-hydroxyquinoline, 1,10-phenanthroline, and 2,2'-dipyridyl. The preferred ligand is 8-hydroxyquinoline, which is used in an amount of from about 0.02 to about 2.0 molar equivalents relative to the 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-(*R*)-2-methyl-pyrrolidine. Preferably, the base is a metal carbonate or a metal alkoxide, for example cesium carbonate, potassium carbonate, sodium carbonate, and sodium tert-butoxide. The preferred base is potassium carbonate, which is used in an amount of from about 1.0 to about 2.0 molar equivalents relative to the 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-(*R*)-2-methyl-pyrrolidine. The reaction is

accomplished at elevated temperatures in a polar organic solvent. Examples of suitable solvents include but are not limited to N,N'-dimethylformamide, N-methylpyrrolidinone, N,N'-dimethylacetamide, pyridine, 3-picoline, 4-picoline, and the like. The preferred solvent is dimethylformamide (DMF). Typically, the reaction is accomplished under a nitrogen atmosphere, and the reaction mixture is heated to temperatures of from about 100 °C. to about 160 ° C. The reaction typically can be accomplished in about 10 to about 48 hours. When the reaction is completed and cooled to 25 °C., a non-water miscible solvent, for example ethyl acetate, is added. The organic solution is washed with a brine aqueous solution, for example 25% NaCl solution or other suitable salt solution several times. The organic solution is dried, and concentrated to dryness to give the product.

Alternatively, a 2-(6-{2-[(2*R*)-2-methyl-1-pyrrolidin-1-yl]-ethyl}-2-naphthalen-2-yl)-2H-pyridazin-3-one active agent can be prepared according to procedures described in US 7,153,889, filed on Oct. 22, 2003, at least in, for example, the general procedures and Example 31, or any other suitable procedure for providing a stable active agent. Briefly, for example, a 6-bromo-2-naphthoate is reduced using $BH_3$-THF to provide the corresponding alcohol. 6-Bromo-naphthalen-2-yl-methanol is treated with 3(2H)-pyridazinone, copper powder, and base to provide 2-[6-(2-hydroxy-ethyl)-naphthalen-2-yl-]-2H-pyridazin-3-one, which is activated with a sulfonate, such as tosylate. (*R*) 2-methylpyrrolidine that has been prepared in accordance with the foregoing steps (a) to (e), with or without optional steps (f) to (h) and reacting the (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine is provided, and the sulfonate reacted with said (*R*)-2-methylpyrrolidine to afford 2-(6-{(2*R*)2-methyl-1-pyrrolidin-1-yl]-ethyl}-2-naphthalen-2-yl)-2H-pyridazin-3-one.

Thus one embodiment of the invention relates to a method of preparing a 2-{6-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-naphthalen-2-yl}-2H-pyridazin-3-one, comprising the steps of:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) converting trifluoro-methanesulfonic acid 6-bromo-naphthalen-2-yl ester to 2-bromo-6-vinyl-naphthalene;

(3b) reacting 2-bromo-6-vinyl-naphthalene with (*R*)-2-methylpyrrolidine or (S)-2-methylpyrrolidine in the presence of n-butyllithium to provide 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-2*R*-methyl-pyrrolidine or 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-2*S*-methyl-pyrrolidine; and

(3c) reacting 1-[2-(6-bromo-naphthalen-2-yl)-ethyl]-2-methyl-pyrrolidine with 2H-pyridazin-3-one to provide 2-{6-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-naphthalen-2-yl}-2H-pyridazin-3-one.

This method may optionally further include the steps of:

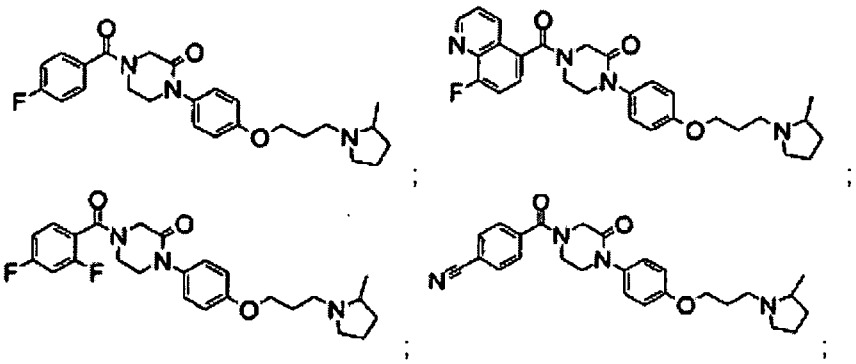
(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate;

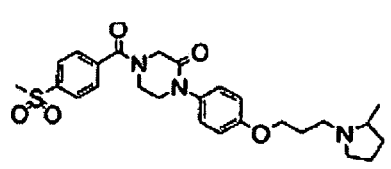
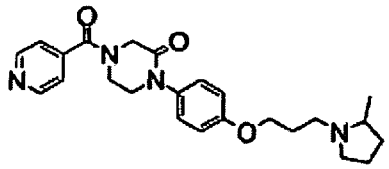
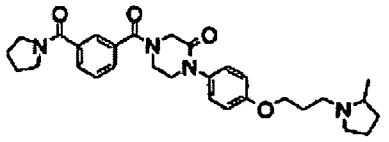
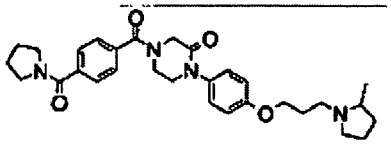
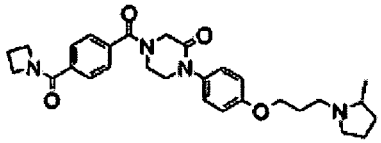
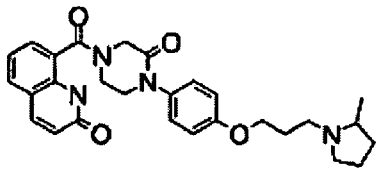
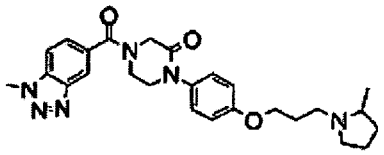
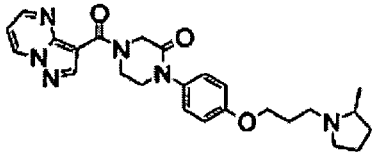
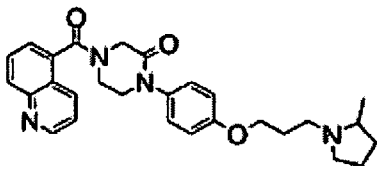
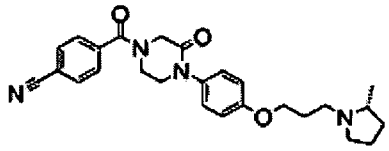
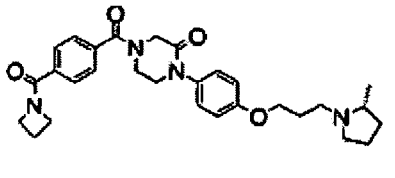
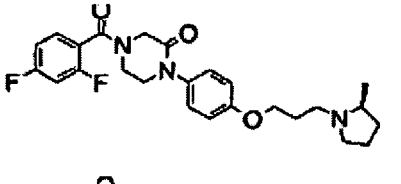
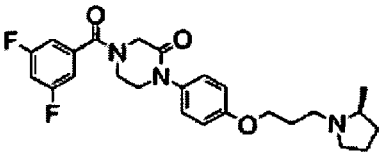
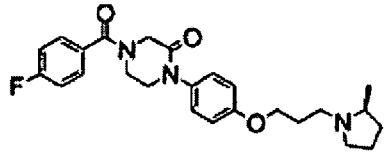
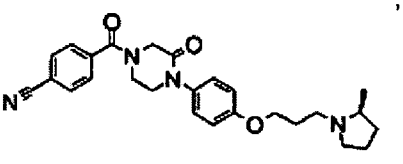
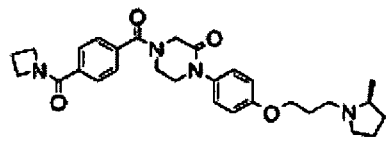
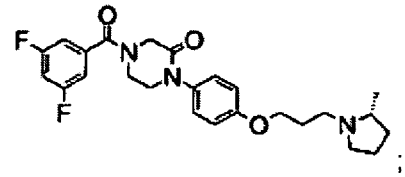
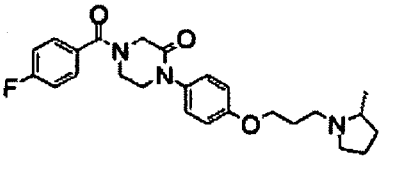
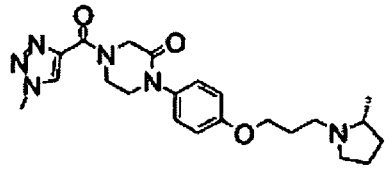
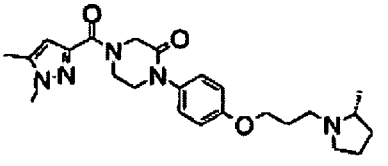
(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate; and

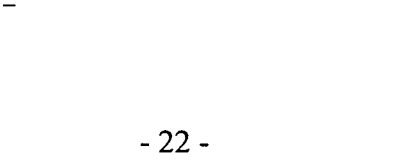
(1h) optionally repeating steps (f) and (g).

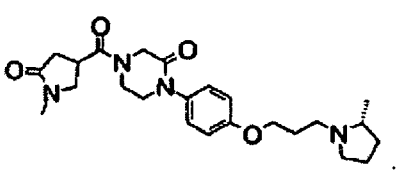
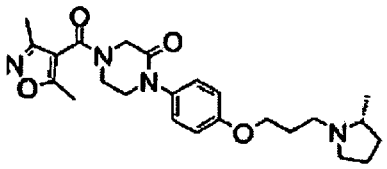
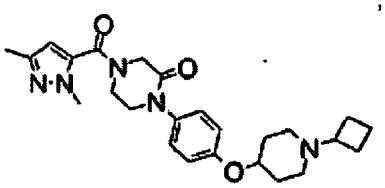
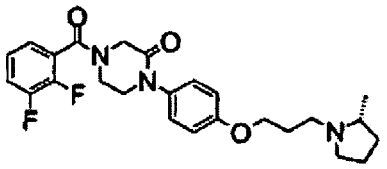
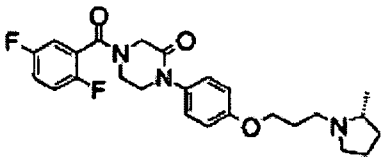
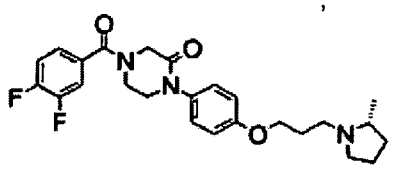
Additionally, the trifluoro-methanesulfonic acid 6-bromo-naphthalen-2-yl ester may be obtained by: providing 6-bromo-naphthalen-2-ol; and reacting 6-bromo-naphthalen-2-ol with a suitable trifluoromethanesulfonic reagent.

Exemplary compounds that can be produced using the methods of the present invention include:

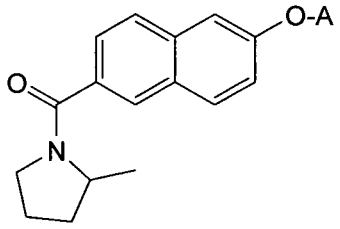



;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

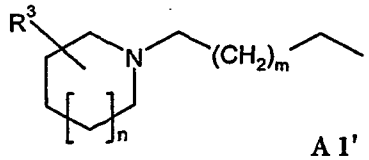
;

;

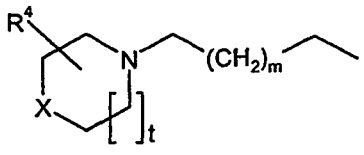

;

;

;

;


; and

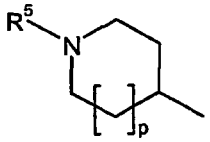
WO 2005/117865 also describes histamine-3-receptor ligands that include a 2-methyl-pyrrolidinyl moiety of the following general formula III:

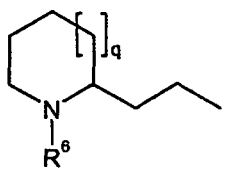

III

wherein A is selected from:

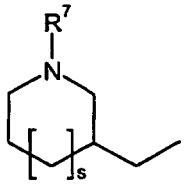

A 1'


A 2


A 3


A 4

or


A 5

,

wherein:

| | | |
|---|---|---|
| m | is 0, 1, or 2; |
| n | is 0, 1 or 2; |
| $R^3$ | is hydrogen or lower alkyl; |
| t | is 1 or 2; |
| $R^4$ | is hydrogen or lower alkyl |

X is O, S. or N-$R^8$, wherein $R^8$ is hydrogen or lower alkyl;

p is 0, 1 or 2;

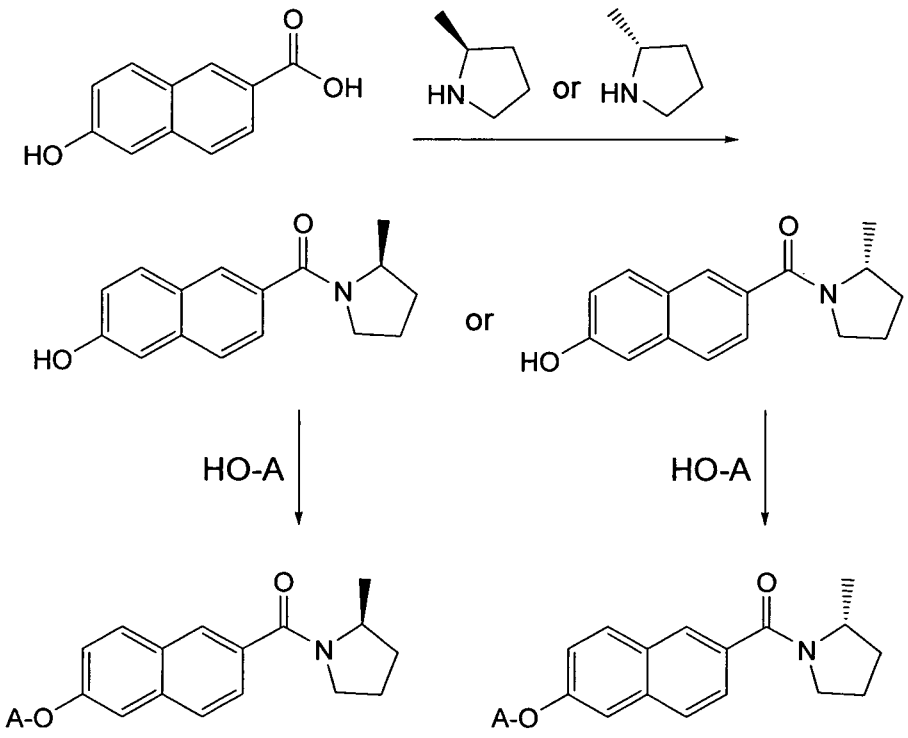
$R^6$ is lower alkyl;

s is 0, 1 or 2; and

$R^7$ is lower alkyl.

Compounds of formula III can be prepared according to the Scheme 1:

SCHEME 1




The coupling of carboxylic acids with amines is widely described in literature and the procedures are known to those in the art (For reaction conditions described in literature affecting such reactions see for example: Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999). 6-Hydroxy-2-naphthoic acid can conveniently be transformed to the respective amide through coupling with (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with the foregoing steps (a) to (e) (with or without optional steps (f) to (h)) and reacting the (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine. Any suitable coupling agent can be employed to effect the transformation. For example coupling reagents like 1,1'-carbonyldiimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

hydrochloride (EDCI), 1 - [bis(dimethylamino)methylene] - 1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxidhexafluorophosphate (HATU), l-hydroxy-1,2,3-benzotriazole (HOBT), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and the like can equally well be employed to affect such transformation.

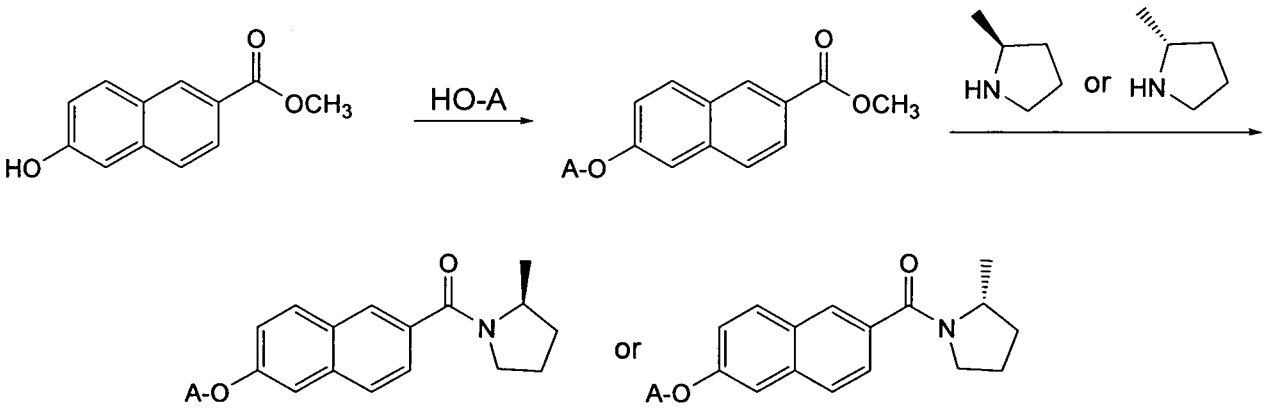
There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: DMF, dichloromethane (DCM), dioxane, THF, and the like. Typically, a base is used with the coupling agent. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include triethylamine and diisopropylethylamine, and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It is convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield the amide derivative.

One exemplary procedure for the preparation of (6-hydroxy-naphthalen-2-yl)-(2-methyl-pyrrolidin-1-yl)-methanone is as follows. A mixture of 6-hydroxy-2-naphthoic acid, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, 2.3 mL N-ethyldiisopropylamine, and (R) or (S)-2-methyl-pyrrolidine that has been prepared in accordance with the foregoing procedures, is prepared in 10 mL DMF is stirred for 16 hours at room temperature. The mixture is then concentrated to dryness and 50 mL ethyl acetate, 30 mL water and 20 mL $NaHCO_3$ aq. (10%) is added. The aqueous phase may then be extracted with 50 mL ethyl acetate and the combined organic layers purified with column chromatography on silica. The product fractions may be concentrated to dryness and triturated twice with 20 mL diethyl ether/heptane 1/1, and the residue dried under vacuum at 50 °C. Practice of this method with (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine prepared in accordance with the methods described herein will produce (6-hydroxy-naphthalen-2-yl)-(2*R*-methyl-pyrrolidin-1-yl)-methanone or (6-hydroxy-naphthalen-2-yl)-(2*S*-methyl-pyrrolidin-1-yl)-methanone, which may then be used to produce histamine-3-receptor ligands.

In order to make the histamine-3-receptor ligands, the foregoing (*R*) or (*S*) intermediates are reacted with an alcohol of the formula HO-A (wherein A is defined as above) to form an ether. The syntheses of ethers are widely described in literature and the procedures are known to those in the art. (For reaction conditions described in literature affecting such reactions see for example: Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999). The transformation can be affected by employing reaction conditions which are commonly utilized in the so called *"Mitsunobu reaction"* which is known to those in the art and widely described (Hughes, David L. The Mitsunobu reaction. Organic Reactions (New York) (1992), 42, 335-656.) Conditions employing a trialkylphosphine such as tributylphosphine, triphenylphosphine and the like and a diazo-compound like diethyl-azodicarboxylate (DEAD), diisopropylazodicarboxylate (DIAD) (optionally polymer bound), tetramethyl azodicarboxamide and the like in a solvent commonly used in such transformations like tetrahydrofuran (THF), toluene, dichloromethane and the like. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. Ambient temperature to reflux is generally appropriate. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield the desired compounds.

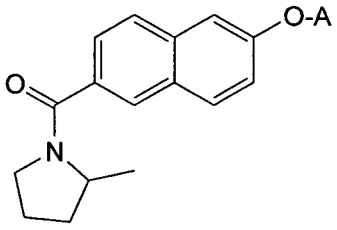
As an alternative, the following synthetic approach may be used:

SCHEME 2



As shown in Scheme 2, starting alcohol HO-A, wherein A is as described above, is reacted with the methyl ester under Mitsunobu reaction conditions followed by cleavage of the ester. The intermediately formed acid is then coupled with (R)- or (S)-2-methylpyrrolidine, which has been prepared in accordance with the foregoing steps (a) to (e) (with or without optional steps (f) to (h)) and reacting the (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine or the (*S*)-2-methylpyrrolidine D-tartrate with a base to provide (*S*)-2-methylpyrrolidine, to arrive at the desired compound. Suitable coupling agents and conditions are described above.

Thus, one embodiment of the invention relates to processes for preparing a compound of formula III:




III

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

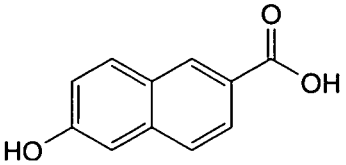
(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting a carboxylic acid of the following formula




with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the corresponding amide phenol; and

(3b) contacting the amide phenol with an alcohol of formula HO-A, wherein A is as described above, for a time and under conditions sufficient to provide the corresponding amide ether.

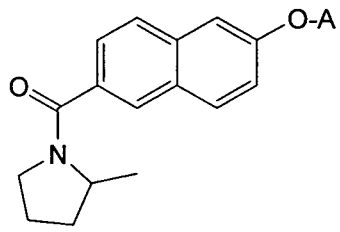
This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Another embodiment relating to processes for the preparation of compounds of formula III:




III

wherein the variables are as set forth above, comprises:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

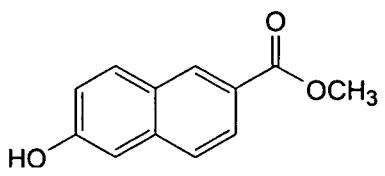
(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting an ester phenol of the following formula



with an alcohol of formula HO-A, wherein A is as previously described, for a time and under conditions sufficient to form the corresponding ester ether; and

(3b) contacting the ester ether with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the corresponding amide ether.

This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Particularly preferred compounds that can be prepared using the methods of the present invention include:

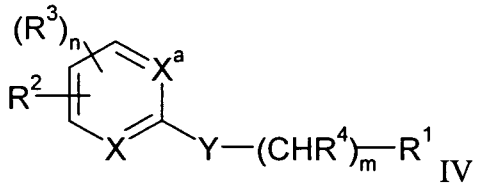
(2-methyl-pyrrolidin-1-yl)-{6-[2-(l-methyl-pyrrolidin-2-yl)-ethoxy]-naphthalen-2-yl}-methanone;

[6-(1-isopropyl-pyrrolidin-3-y1oxy)-naphthalen-2-yl]-(2 -methyl-pyrrolidin-1-yl)-methanone;

[6-(1-isopropyl-piperidin-4-yloxy-)naphthalen-2-yl]- (2-methyl-pyrrolidin-1-yl)-methanone; and

[6-(1-isobutyl-piperidin-4-y1oxy)-naphthalen-2-y-l]-(2-methyl-pyrrolidin-1-y1)-methanone.

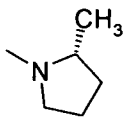
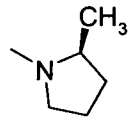
Another group of compounds that may be prepared from the (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine produced in accordance with the methods described herein is disclosed in US 2008/0027041A1. Specifically, disclosed in that application are compounds of the general formula IV



IV

and the pharmaceutical salts thereof;

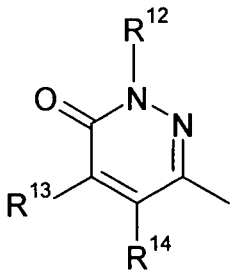
wherein:

$R^1$ is  or ,

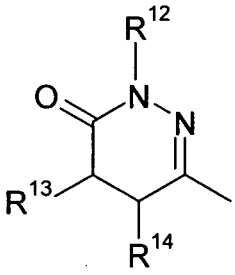
X and $X^a$ are each independently CH or N;

Y is $S(O)_q$, O, or $NR^{15}$;

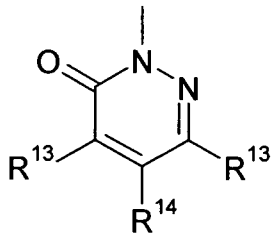
$R^2$ is



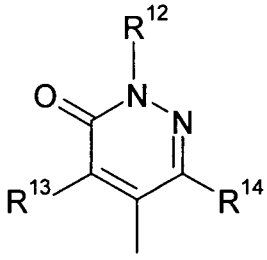
(i)



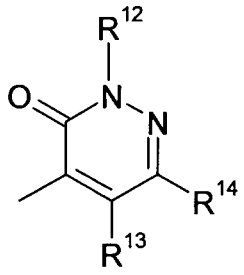
(ii)



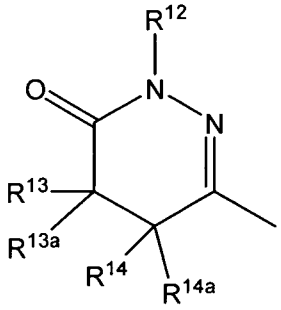
(iii)



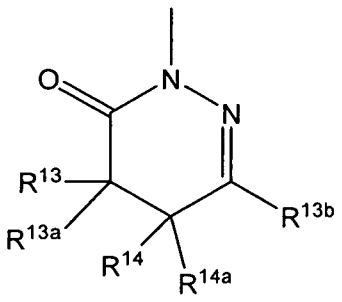
(iv)



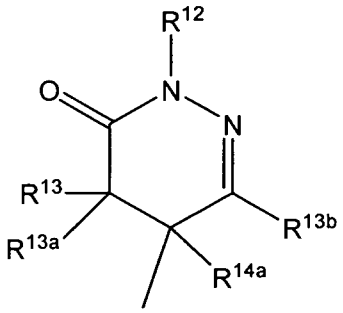
(v)



(vi)

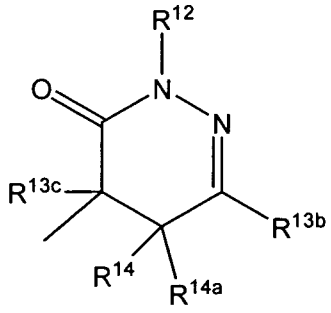


(vii)



(viii)

or



(ix)

wherein:

when X and $X^a$ are both CH, then $R^2$ is meta or para to the Y-$(CHR^4)_m$-$R^1$group; and

when either X or $X^a$ are N, then $R^2$ is para to the Y-$(CHR^4)_m$-$R^1$group;

each $R^3$ is:

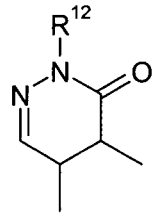
independently H, F, Cl, Br, I, $OR^{21}$, $NR^{23}R^{24}$, $NO_2$, CN, $CF_3$, $C_1$-$C_6$alkyl, $C(=O)R^{21}$, $CO_2R^{21}$, or $C(=O)NR^{23}R^{24}$; or

when $R^3$ is ortho to $R^2$, and $R^2$ is (i), (ii), (iv), (vi), or (ix), then $R^3$ and $R^{14}$ taken together may form -$(CH_2)_s$-, -$CH_2Z$- , -$ZCH_2$-, -$ZCH_2CH_2$- or $CH_2CH_2Z$-; wherein Z is O, $S(O)_y$, or $NR^{27}$; or

when $R^3$ is ortho to $R^2$, and $R^2$ is (iv), (v), or (viii), then $R^3$ and $R^{13}$ taken together may form -$(CH_2)_s$-, -$CH_2Z$- , -$ZCH_2$-, -$ZCH_2CH_2$- or $CH_2CH_2Z$-; or

when $R^3$ is ortho to $R^2$, and $R^2$ is (viii), then $R^3$ and $R^{13b}$ taken together may form -$(CH_2)_s$-, -$CH_2Z$- , -$ZCH_2$-, -$ZCH_2CH_2$- or $CH_2CH_2Z$-; or

when $R^3$ is ortho to $X^a$ and $R^2$ is ortho to $R^3$ and meta to $X^a$, then $R^2$ and $R^3$ taken together may form:



;

each $R^4$ is independently H, $C_1$-$C_6$alkyl, or $OR^{21}$, wherein the alkyl group is optionally substituted with 1 to 3 $R^{20}$ groups;

$R^{12}$ is H, $C_1$-$C_6$alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heterocycloalkyl, $C(=O)R^{27}$, or $CO_2R^{27}$, wherein the alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, or heterocycloalkyl group is optionally substituted with 1 to 3 $R^{20}$ groups;

$R^{13}$ and $R^{14}$ are each independently H, $C_1$-$C_6$alkyl, aryl, arylalkyl $C_1$-$C_6$alkoxyl, $S(=O)_y$-$C_1$-$C_6$alkyl, cycloalkyl, heterocycloalkyl, or heteroaryl;

$R^{13a}$, $R^{13b}$, $R^{13c}$, and $R^{14a}$ are each independently H, $C_1$-$C_6$alkyl; or $R^{13}$ and $R^{14}$, taken together with the carbon atoms through which they are connected form a fused phenyl, thienyl, pyrrolyl, oxazolyl, pyridinyl, or $C_3$-$C_6$cycloalkyl ring; or $R^{13b}$ and $R^{14}$, or $R^{13}$ and $^{14a}$, or $R^{13b}$ and $^{14a}$, or $R^{13c}$ and $R^{14a}$, taken together with the carbon atoms through which they are connected form a fused $C_3$-$C_6$cycloalkyl ring; or $R^{13}$ and $R^{13a}$, or $R^{14}$ and $R^{14a}$, taken together with the carbon atom to which they are attached form a $C_3$-$C_8$cycloalkyl ring; provided that no more than one pair of $R^{13}$ and $R^{14}$, $R^{13b}$ and $R^{14}$, $R^{13}$ and $R^{14a}$, $R^{13b}$ and $R^{14a}$, $R^{13c}$ and $R^{14a}$, $R^{13}$ and $R^{13a}$, and $R^{14}$ and $R^{14a}$ are taken together with the carbon atoms through which they are connected or to which they are attached to form a ring; and

wherein the fused phenyl, thienyl, pyrrolyl, oxazolyl, pyridinyl, or cycloalkyl ring is optionally substituted with 1 to 3 $R^{20}$ groups;

$R^{15}$ is H, $C_1$-$C_6$ alkyl, $C(=O)R^{25}$, $CO_2R^{25}$;

$R^{20}$ at each occurrence is independently, H, F, Cl, Br, I, $OR^{21}$, $OR^{22}$, $NR^{23}R^{24}$, NHOH, $NO_2$, CN, $CF_3$, $C_1$-$C_6$ alkyl optionally substituted with $OR^{26}$, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_7$cycloalkyl$C_0$-$C_4$alkyl, 3- to 7-membered heterocycloalkyl$C_0$-$C_4$alkyl, phenyl, 5- or 6-membered heteroaryl$C_0$-$C_4$alkyl, arylalkyl, (=O), $C(=O)R^{21}$, $CO_2R^{21}$, $OC(=O)R^{21}$, $C(=O)NR^{23}R^{24}$, $NR^{27}C(=O)R^{21}$, $NR^{27}C(=O)OR^{21}$, $OC(=O)NR^{23}R^{24}$, $NR^{27}C(=S)R^{21}$, or $S(O)_qR^{21}$;

each $R^{21}$ is independently H, $C_1$-$C_6$alkyl, aryl, or arylalkyl;

each $R^{22}$ is independently the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;

each $R^{23}$ and $R^{24}$ is independently selected from H, $C_1$-$C_6$alkyl, and aryl, or $R^{23}$ and $R^{24}$, together with the nitrogen atom to which they are attached, form a 3 to 7 membered heterocyclic ring optionally substituted with =O;

$R^{25}$ is $C_1$-$C_6$alkyl, aryl, or alkylaryl;

$R^{26}$ is H, $C_1$-$C_6$alkyl, aryl, or alkylaryl;

$R^{27}$ is H or $C_1$-$C_6$alkyl;

m is 1, 2, 3, 4, or 5 when $R^1$ is attached via a nitrogen atom, and m is 0, 1, 2, 3, 4, or 5 when $R^1$ is attached via a carbon atom;

n is 1, 2, or 3;

q is 0, 1, or 2;

s is 1, 2, or 3; and

y is 0, 1, or 2.

Specific examples of such compounds that can be prepared using the 2-methylpyrrolidine preparation methods of the present invention include:

2-methyl-6-{4-[(R)-2-methyl-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{3,5-difluoro-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-methyl-2H-pyridazin-3-one;

6-{3-chloro-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-methyl-2H-pyridazin-3-one;

2,6-dimethyl-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-methyl-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
2-methyl-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-pyridin-2-yl-2H-pyridazin-3-one;
2-(6-methyl-pyridin-2-yl)-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
2-(3-methyl-pyridin-2-yl)-5-{4-[3-((R)-2-methylpyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
6-methyl-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-pyridin-2-yl-2H-pyridazin-3-one;
6-methyl-2-(3-methyl-pyridin-2-yl)-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
6-methyl-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-thiophen-3-yl-2H-pyridazin-3-one;
5-{4-[3-((S)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-pyridin-2-yl-2H-pyridazin-3-one;
6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-5-pyridin-2-yl-4,5-dihydro-2H-pyridazin-3-one;
6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-5-pyridin-2-yl-2H-pyridazin-3-one;
2-(2-fluoro-ethyl)-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
6-{3-fluoro-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
4-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one;
4-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
2-methyl-4-{3-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2,5,6,7-tetrahydro-cyclopenta[d]pyridazin-1-one;
2-isopropyl-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;
2-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-5-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzonitrile;
2-(2-hydroxyethyl)-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{4-[(S)-2-methyl-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{3-methoxy-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-pyrimidin-2-yl-2H-pyridazin-3-one;

6-{6-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-pyridin-3-yl}-2H-pyridazin-3-one;

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-(2,2,2-trifluoro-ethyl)-4,5-dihydro-2H-pyridazin-3-one;

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-(2,2,2-trifluoro-ethyl)-2H-pyridazin-3-one;

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.2.0]oct-4-en-2-one;

4-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2,4a,5,6,7,7a-hexahydro-cyclopenta[d]pyridazin-1-one;

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one;

4,4-dimethyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one;

6-{3-fluoro-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one;

5,5-dimethyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one;

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-pyridin-2-yl-4,5-dihydro-2H-pyridazin-3-one;

6-{3,5-difluoro-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{3,5-dibromo-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{3,5-difluoro-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one;

5-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one racemate;

5-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one diastereomer;

5-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one diastereomer;

6-{(R)-2-methyl-4-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyriazin-3-one;

2-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-6-phenyl-2H-pyridazin-3-one;

6-methyl-2-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

2-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-phthalazin-1-one;

2-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-6-pyridin-3-yl-2H-pyridazin-3-one;

3-methyl-4-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-6H-isoxazolo[3,4-d]pyridazin-7-one;

8-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-5,6-dihydro-2H-benzo[h]cinnolin-3-one;

5-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

5-ethyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

8-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-4,4a,5,6-tetrahydro-2H-benzo[h]cinnolin-3-one;

6-{2-methoxy-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{2-fluoro-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-pyridin-2-yl-2H-pyridazin-3-one;;

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4-pyridin-2-yl-4,5-dihydro-2H-pyridazin-3-one;

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4-pyridin-2-yl-2H-pyridazin-3-one;

8-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-5,6-dihydro-3H-benzo[f]cinnolin-2-one;

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

2-methoxymethyl-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

5-{4-[(S)-2-methyl-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

5-{4-[(R)-2-methyl-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

5-{3,5-dibromo-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

2-methoxymethyl-5-{2-methyl-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

5-{2-methyl-4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

4-methoxy-2-methoxymethyl-5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

5-methoxy-2-methoxymethyl-4-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

5-methoxy-4-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{4-[3-((S)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.1.0]hept-4-en-2-one;

5-{4-[(S)-2-methyl-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.1.0]hept-4-en-2-one;

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.1.0]hept-4-en-2-one single isomer;

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.1.0]hept-4-en-2-one single isomer;

6-{4-[2-hydroxy-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{4-[(S)-2-hydroxy-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

6-{4-[(R)-2-hydroxy-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

and

6-cyclopropyl-2-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

or a stereoisomeric form, mixture of stereoisomeric forms, or a pharmaceutically acceptable salt thereof.

Preferred among these are compounds selected from the group consisting of:

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-pyridin-2-yl-2H-pyridazin-3-one;

6-{4-[(S)-2-methyl-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

4,4-dimethyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one;

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.1.0]hept-4-en-2-one;

5-{4-[(S)-2-methyl-3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.1.0]hept-4-en-2-one;

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.1.0]hept-4-en-2-one;

5-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-3,4-diaza-bicyclo[4.1.0]hept-4-en-2-one;

5-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one one diastereomer;

5-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one one diastereomer;

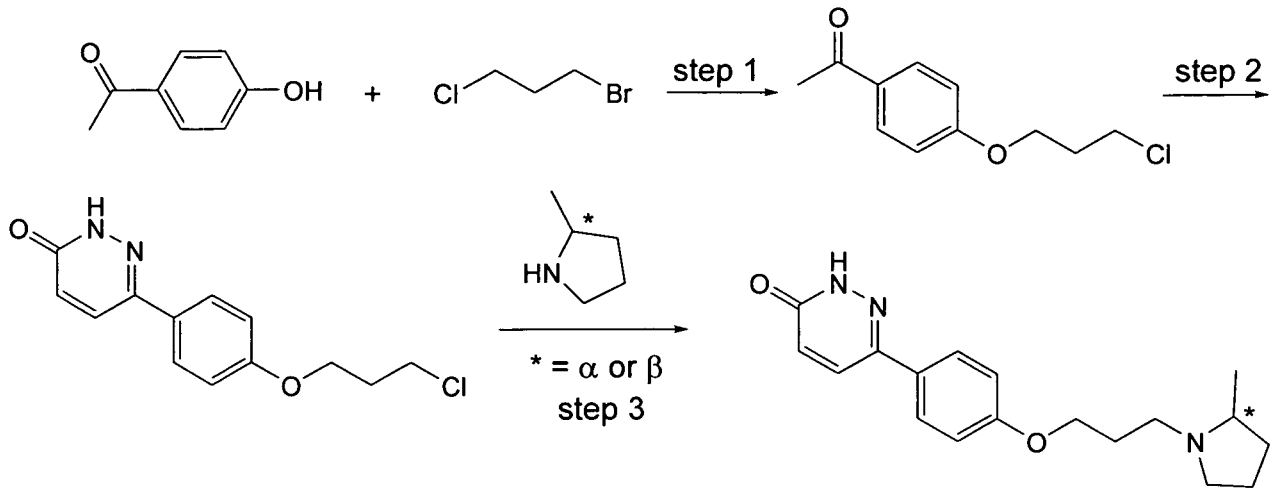
5-methyl-6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-4,5-dihydro-2H-pyridazin-3-one; and

6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one;

or a stereoisomeric form, mixture of stereoisomeric forms, or a pharmaceutically acceptable salt thereof.

Particularly preferred of the foregoing is the compound is 6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one, or a stereoisomeric form, mixture of stereoisomeric forms, or a pharmaceutically acceptable salt thereof. This compound may be prepared from (*R*)-2-methylpyrrolidine prepared in accordance with the methods described above. Scheme 3 sets forth an exemplary process for the preparation of 6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one.

SCHEME 3

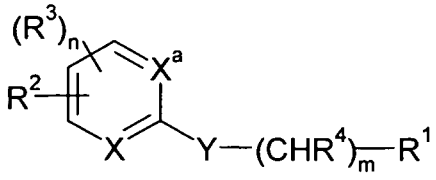



In accordance with Scheme 3, in step 1, a mixture of 1-(4-hydroxyphenyl)ethanone and 3-bromo-1-chloropropane in $CH_3COCH_3$ is heated to 65 °C overnight. The mixture is filtered, washed with acetone, and concentrated to dryness. The crude product is dissolved in $CH_2Cl_2$, and washed with saturated $NaHCO_3$, NaCl solution and dried over $Na_2SO_4$. Concentration to dryness under vacuum affords product.

A mixture of the product from step 1 and glyoxalic acid monohydrate is stirred in 15 mL of acetic acid at 100 °C for 2 h. The solvent is evaporated, water is added to the residue and cooled to 0 °C while conc. aqueous $NH_4OH$ is added to pH 8. To this mixture, hydrazine hydrate is added and heated to 100 °C for 1 h. The resulting solid may be filtered and washed with water. The crude material may be dissolved in $CH_2Cl_2$/MeOH and purified by column chromatography with $CH_2Cl_2$ to 10 % MeOH in $CH_2Cl_2$.

A mixture of the product from step 2, $K_2CO_3$, 100 mg of NaI, and R-2-methylpyrrolidine hydrochloride in acetonitrile is heated to 80 °C for 2 days. The reaction mixture is then filtered, washed with $CH_2Cl_2$, and concentrated. The residue is dissolved in $CH_2Cl_2$, and washed with saturated $NaHCO_3$, saturated NaCl, dried with $Na_2SO_4$ and concentrated. The residue may be purified by ISCO gradient chromatography with 100% $CH_2Cl_2$ to 5%MeOH: 95% $CH_2Cl_2$ in 2-aminopropane and then to 10%MeOH: 90% $CH_2Cl_2$ in 2-aminopropane to give the product. The free base of the product may be converted to the HCl salt by dissolving in MeOH and adding 0.5 N HCl in EtOH, followed by evaporation of the solvent and crystallization from MeOH: $Et_2O$.

Thus, one embodiment of the invention relates to processes for preparing a compound of formula IV:



IV, in particular (R)- or (S)-6-{4-[3-(2-Methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one,

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting 1-(4-hydroxy-phenyl)-ethanone with 1,3-dihalopropane, for a time and under conditions sufficient to form 1-[4-(3-halo-propoxy)-phenyl]-ethanone;

(3b) contacting the 1-[4-(3-halo-propoxy)-phenyl]-ethanone with glyoxalic acid for a time and under conditions sufficient to produce 6-[4-(3-halo-propoxy)-phenyl]-2H-pyridazin-3-one; and

(3c) contacting the 6-[4-(3-hal-propoxy)-phenyl]-2H-pyridazin-3-one with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the corresponding (R)- or (S)-6-{4-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one.

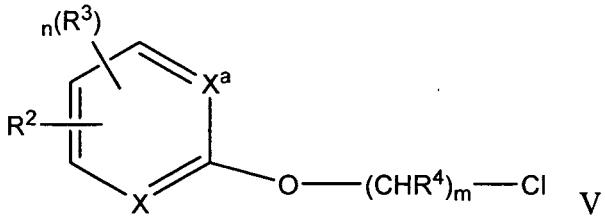
This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

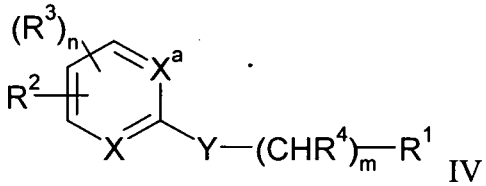
More generally, the foregoing methodology may be adapted to preparing the compounds described in US 2008/0027041A1 by providing a compound of the formula V:



V

with (*R*) or (*S*) 2-methylpyrrolidine hydrochloride, prepared according to the foregoing methodology, $K_2CO_3$ and NaI in $CH_3CN$ and recovering the product.

A further embodiment of the invention relates to processes for preparing a compound of formula IV:



IV

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) converting the (R)-2-methylpyrrolidine or the (S)-2-methylpyrrolidine to the compound of formula IV.

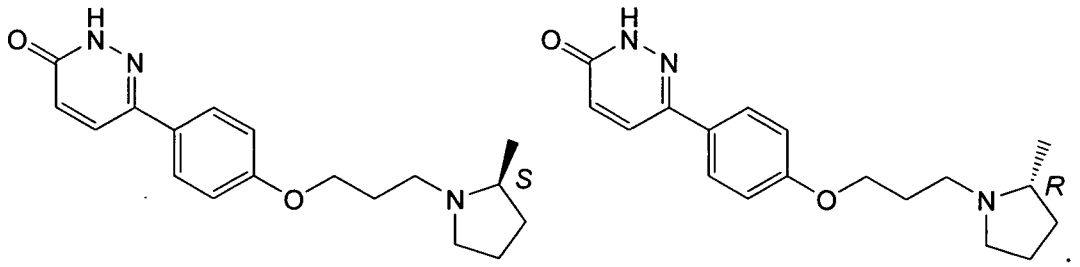
This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

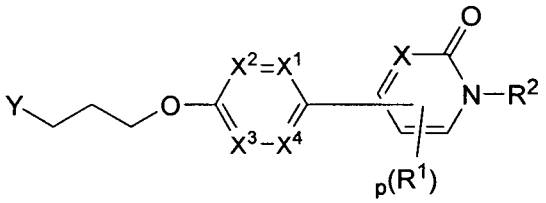
(1h) optionally repeating steps (f) and (g).

Exemplary compounds that can be produced according to these methods include (R)- or (S)-6-{4-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one:



Preferably, the compound is 6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one

A further group of histamine-3-receptor ligands that may be prepared using (*R*) or (*S*) 2-methylpyrrolidine prepared in accordance with the methods described herein is described in WO 2006/059778. These compounds include compounds of the general formula VI:



VI

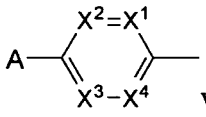
and the pharmaceutical salts thereof;

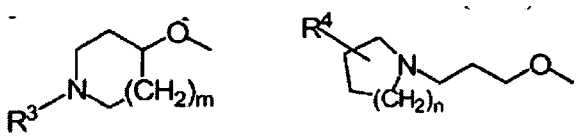
wherein Y is (R) or (S) 2-methylpyrrolidine;

$R^1$ each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a lower alkoxy-lower alkyl group, or a halo-lower alkoxy-lower alkyl group;

p indicates an integer from 0 to 4;

$R^2$ represents a hydroxyl group, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a lower alkoxy-lower alkyl group, or a halo-lower alkoxy-lower alkyl group, or

$R^2$ represents a group of the formula,  wherein A represents a compound of formula (III-1) or of formula (III-2)



(III-1) (III-2)

wherein R3 represents a hydrogen atom, or a cycloalkyl group optionally substituted with a lower alkyl group, a halo-lower alkyl group, a cycloalkyl group, a halogen atom or a hydroxyl group and R4 represents a hydrogen atom, a hydroxyl group, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a lower alkoxy-lower alkyl group, or a halo-lower alkoxy-lower alkyl group;

m indicates 0 or 1; n indicates 0, 1 or 2; and

$X^1$ to $X^4$ each independently represent a carbon atom optionally substituted with a lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group or a halogen atom.

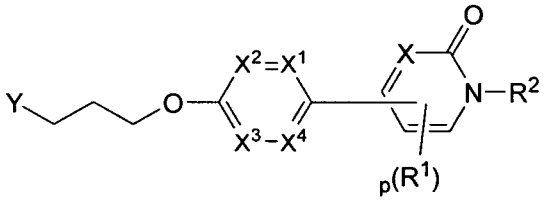
Specifically disclosed compounds within this group that can be prepared according to the methods described herein include:

1-methyl-4-{4-[3-((2S)-2-methyl-1-pyrrolidinyl)propoxy]phenyl}-2(1H)-pyridone; and

1-methyl-4-{4-[3-((2R)-2-methyl-1-pyrrolidinyl)propoxy]phenyl}-2(1H)-pyridone.

Such compounds may be prepared by providing an intermediate compound of Formula (VI) wherein Y is Cl, and reacting the compound with (*R*) or (*S*) 2-methylpyrrolidine, prepared according to the foregoing methodology, $K_2CO_3$ and NaI in $CH_3CN$ and recovering the product, much as described above for the compounds of US 2008/0027041A1.

Thus, another embodiment of the invention relates to processes for preparing a compound of formula VI:



VI

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting a compound of formula VI wherein Y is Cl with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the corresponding amide.

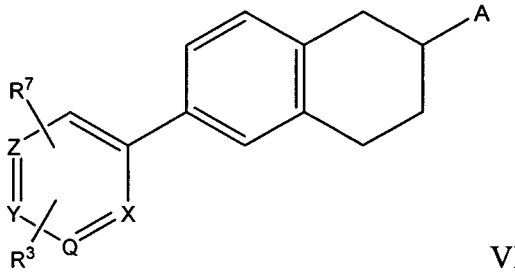
This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Yet another application describing histamine-3-receptor ligands containing a 2-methylpyrrolidine moiety is WO 2007/105053. This application describes preparation of compounds of the following formula VII:




VII

wherein

A is (R) or (S) 2-methyl pyrrolidine;

Z, Y, Q, X are independently nitrogen or carbon;

$R^3$ is hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy, halo, 5 to 6-membered aryl, 5 to 6-membered heteroaryl, hydroxyl, methylene hydroxyl, $-(C{=}O)NR^4R^5$, and $S(O)_p(C_1\text{-}C_4)$alkyl, wherein p is 1 or 2;

wherein $R^4$ and $R^5$ are independently selected from the group consisting of:

hydrogen; ($C_1$-$C_8$) alkyl optionally substituted with 1 to 4 halogens; ($C_1$-$C_8$) alkyl group optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 ($C_1$-$C_4$)alkyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)dialkylamino, ($C_6$-$C_{10}$)aryl optionally substituted with a halogen and optionally substituted with ($C_6$-$C_{10}$)aryloxy optionally substituted with 1 to 2 halogens, and 5 to 10-membered heteroaryl optionally substituted with a ($C_6$-$C_{10}$)aryl group and optionally substituted with 1 to 3 ($C_1$-$C_4$)alkyl groups; ($C_3$-$C_7$)cycloalkyl; ($C_6$-$C_{14}$)aryl; -($C_2$-$C_3$)alkyl-O-($C_1$-$C_3$)alkyl optionally substituted with ($C_1$-$C_3$)alkyl; -($C_1$-$C_3$)alkyl-C(=O)O-($C_1$-$C_3$)alkyl; 3-8-membered heterocycloalkyl optionally substituted with one or more ($C_1$-$C_4$)alkylcarbonyl groups; ($C_6$-$C_{14}$)arylsulfonyl optionally substituted with one or more ($C_1$-$C_2$)alkyl; 5-10-membered heteroaryl; and ($C_6$-$C_{14}$)aryl-($C_0$-$C_4$)alkylene-O-($C_0$-$C_4$)alkyl, wherein each ($C_0$-$C_4$)alkyl and each ($C_0$-$C_4$)alkylene is optionally substituted with 1 to 4($C_1$-$C_4$)alkyl; or optionally $R^4$ and $R^5$, together with the nitrogen to which they attached, form a 4 to 6-membered heterocyclic ring, wherein one of the carbons of said heterocyclic ring that is separated by at least two atoms from said nitrogen in said heterocyclic ring is optionally replaced by O or $NR^6$, herein $R^6$ is hydrogen, ($C_1$-$C_3$)alkyl, or -C(=O) ($C_1$-$C_3$)alkyl; and wherein said heterocyclic ring is optionally substituted with halo, ($C_1$-$C_3$)alkyl, or hydroxyl;

$R^7$ is hydrogen;

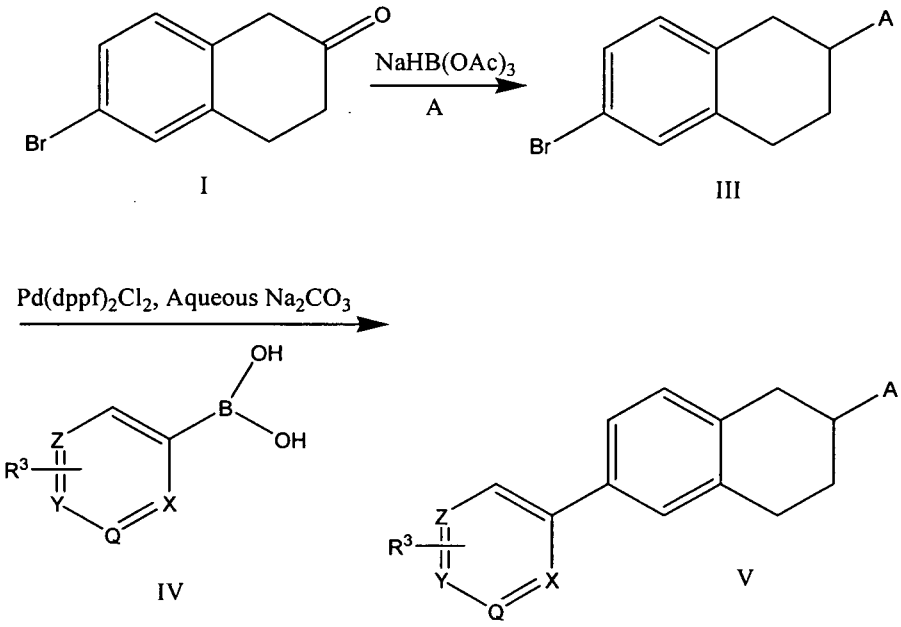
or optionally $R^3$ and $R^7$ together with two adjacent atoms in the ring comprising Z , Y, Q and X to which they are attached, form a 5- or 6-membered heterocyclic ring; wherein one of the carbons of said heterocyclic ring that is separated by at least two atoms from said nitrogen in said heterocyclic ring is optionally replaced by O or $NR^8$; wherein $R^8$ is hydrogen or ($C_1$-$C_3$)alkyl.

Scheme 4 illustrates a method for the preparation of compounds having the basic structure of formula VII, where A, $R^3$, Y, Q, Z and X are defined as above. Referring to Scheme 4 below, a compound (III) can be prepared by treatment of a bromo-tetralone compound of formula (I) with (R) or (S) 2-methyl pyrrolidine prepared in accordance with the methods described above and a suitable reducing agent such as $NaHB(OAc)_3$ in a solvent such as $CH_2Cl_2$ or DCE, at temperatures ranging from -5 °C to room temperature, preferably at about room temperature, to produce the desired compound of formula (III). Other suitable reducing agents for this reaction include $NaCNBH_3$ or $NaBH_4$, in solvents such as MeOH or EtOH. Other suitable conditions for this transformation include treatment of the corresponding tetralone of formula (I) with (R)- or (S)-2-methylpyrrolidine, prepared in accordance with the procedures of the present invention, in

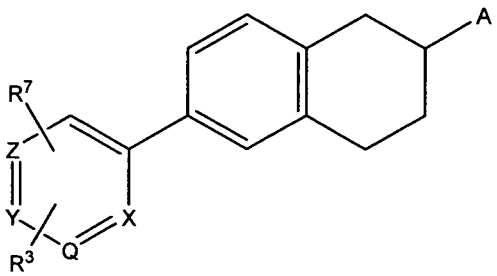
$CH_2Cl_2$ or DCE in the presence of 4 Å molecular sieves and a base such as TEA at room temperature, followed by treatment with $NaBH_4$ or NaHB(OAc).

Compound III can then be treated with an appropriately substituted boronic acid of formula (IV), in the presence of a suitable palladium catalyst such as 1,1-bis(diphenylphosphino)ferrocene palladium (II) chloride and a suitable aqueous solution of an alkali base such as sodium carbonate and in solvents such as dimethoxy ethane, at temperatures ranging from room temperature to about 100 °C, preferably at about 90 °C, to produce the desired compound of formula (V). Other suitable conditions for this transformation include treatment of the compound of formula (III) and the appropriately substituted boronic acid of formula. (IV) with tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in ethanol/water mixture at temperatures ranging from 30 °C to 110 °C, preferably at about the reflux temperature, to produce the corresponding compound of formula (V).

SCHEME 4




Thus, one embodiment of the invention relates to processes for preparing a compound of formula VII:




VII

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

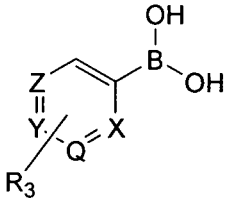
(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting 6-halo-3,4-dihydro-1H-naphthalen-2-one with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the corresponding amine; and

(3b) contacting the amide with a boronic acid of formula




wherein the variables are as described above, for a time and under conditions sufficient to provide the compound for formula VII.

This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

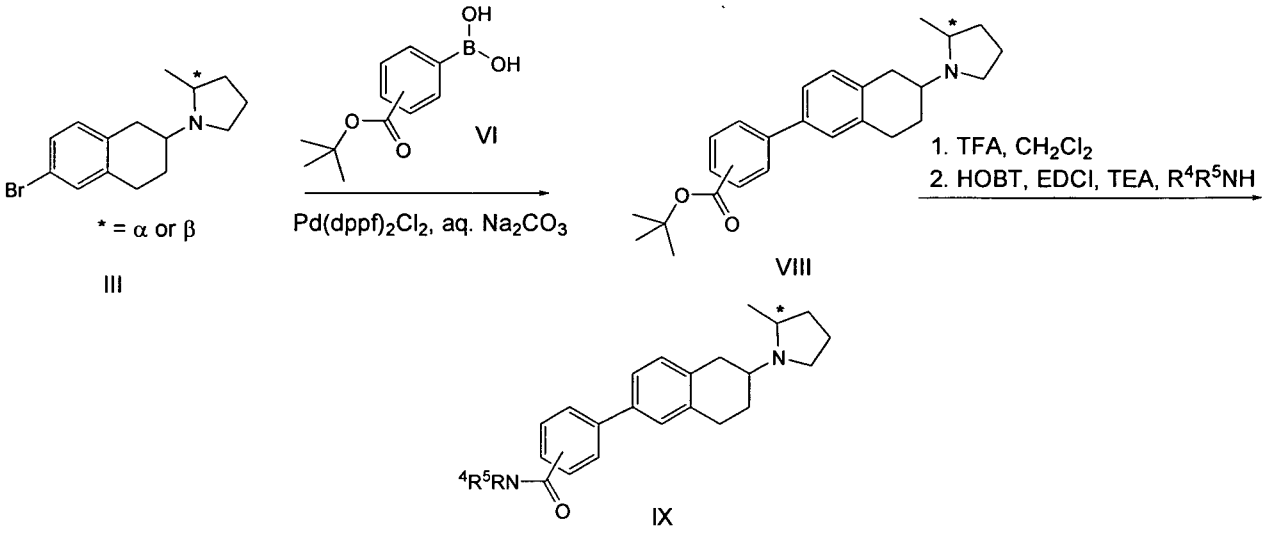
(1h) optionally repeating steps (f) and (g).

Scheme 5 illustrates an alternative method for the preparation of compounds having

the basic structure of formula VII, where $R^3$ is $CONR^4R^5$ and Y, Z, Q and X are defined as above. Referring to Scheme 5, coupling of the bromide (III) and a suitable boronic acid

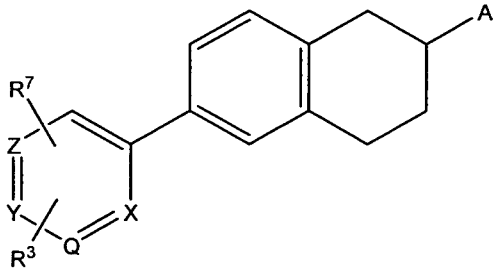
reagent of formula (VI) can be carried out as described above in scheme 4 to produce the desired compound of formula (VIII). Treatment of the corresponding t-butyl ester derivative of formula (VIII) with trifluoroacetic acid in methylene chloride at room temperature produces the corresponding carboxylic acid (not depicted). Treatment of the carboxylic acid with an amine of formula $NHR^4R^5$, in the presence of a suitable coupling reagent such as HOBT and EDCI, and a tertiary amine such as triethyl amine, can produce the desired compounds of formula (IX).

SCHEME 5




Alternatively, compounds of formula (IX) can also be prepared by treatment of the carboxylic acid and suitable amine with 2-chloro-1,3-dimethyl imidazolinium chloride and a suitable base such as diisopropylethyl amine, in solvents such as methylene chloride.

In another embodiment are processes for preparing a compound of formula VII:




VII

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

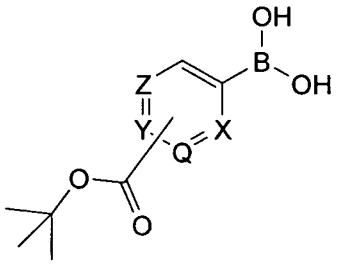
(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

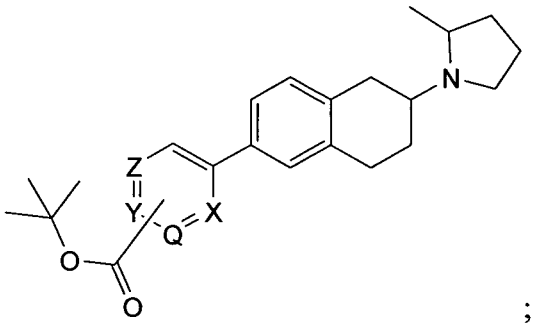
(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting 1-(6-halo-1,2,3,4-tetrahydro-naphthalen-2-yl)-(R)-2-methyl-pyrrolidine or 1-(6-halo-1,2,3,4-tetrahydro-naphthalen-2-yl)-(S)-2-methyl-pyrrolidine with a boronic acid of formula

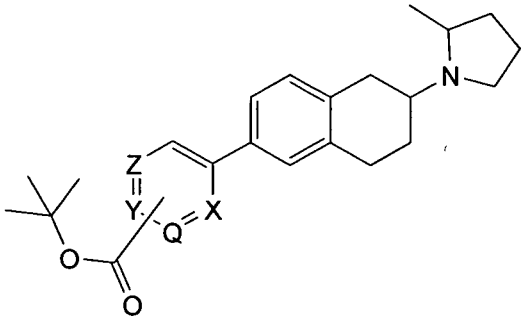


wherein the variables are as described above, for a time and under conditions sufficient to provide a compound of the following formula:



; and

contacting the compound of formula



with an amine for a time and under conditions sufficient to form the compound of formula VII.

This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

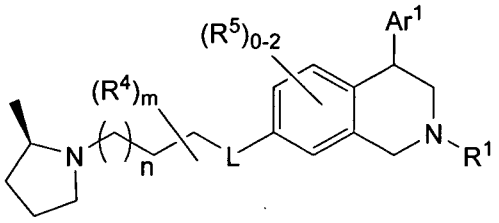
Specific examples of compounds that may be prepared in accordance with these methods include: (S,R)-3-[6-(2-Methyl-pyrrolidin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-pyridine;

(R,R)-3-[6-(2-Methyl-pyrrolidin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-pyridine;

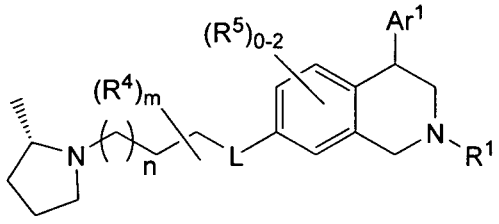
(R, R)-3[6-(2-Methyl-pyrrolidin-l-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-benzamide; and

(S,R)3-[6-(2-Methyl-pyrrolidin-l-yl)-5,6,7,8-tetra hydro-naphthalen-2-yl]-benzamide.

Compounds described in WO 2006/066197 can also be more easily prepared using the (R)- and (S) 2-methylpyrrolidine synthesis of the present invention. WO 2006/066197 describes the following compounds of formulas VIII and IX:




VIII




IX

And the pharmaceutical salts thereof;

wherein

L is -O- and n is 1 or 2; or L is -C≡C- or -$CH_2CH_2$- and n is 0 or 1;

$R^1$ is –H or is $C_{1-6}$alkyl$C_{3-7}$cycloaklyl, -$COOC_{1-6}$alkyl, or -COObenzyl, each optionally mono-, di-, or tri-substituted with Ra;

where Ra is selected from -OH, -$OC_{1-6}$alkyl, phenyl optionally substituted with -$OC_{1-4}$alkyl or halo, -CN, -$NO_2$, -$N(R^b)R^c$, -$C(O)N(R^b)R^c$ , -$N(R^b)C(O)$ $R^b$, -$N(R^b)SO_2C_{1-6}$alkyl, -$C(O)C_{1-6}$alkyl, -$S(O)_{0-2}$-$C_{1-6}$alkyl, -$SO_2N(R^b)^{Rc}$, -$SCF_3$, halo, -$CF_3$, -$OCF_3$, -COOH, and

-$COOC_{1-6}$alkyl; wherein $R^b$ and $R^c$ are each independently -H or -$C_{1-6}$alkyl;

$R^4$ is -OH, -$OC_{1-6}$alkyl,-$CF_3$, -$C_{1-6}$alkyl, or halo; two $R^4$ substituents may be taken together to form methylene or ethylene;

M is 0, 1, or 2;

$R^5$ is selected from the group consisting of $-C_{1-6}$alkyl, -OH, $-OC_{1-6}$alkyl, $-SC_{1-6}$alkyl, and halo;

$Ar^1$ is an aryl or heteroaryl ring selected from the group consisting of:

a) phenyl, optionally mono-, di-, or tri-substituted with $R^j$ and optionally di-substituted on adjacent carbons with $-OC_{1-4}$alkyleneO-optionally mono or di-substituted with fluoro,

$-(CH_2)_{2-3}NH-$, $-(CH_2)_{1-2}NH(CH_2)-$, $-(CH_2)_{2-3}N(C_{1-4}alkyl)-$, or $-(CH_2)_{1-2}N(C_{1-4}alkyl)(CH_2)-$;

where $R^j$ is selected from the group consisting of

1) -OH, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl optionally mono-, di-, or tri-substituted with halo, $-C_{2-6}$alkenyl, $-OC_{3-6}$alkenyl, $-C_{2-6}$alkynyl optionally substituted with trimethylsilyl, $-OC_{3-6}$alkynyl, $-C_{3-6}$cycloalkyl, $-OC_{3-6}$cycloalkyl, -CN, $-NO_2$, $-N(R^k)R^l$ , $-N(R^k)C(O)R^l$, $-N(R^k)SO_2C_{1-6}$alkyl, $-C(O)C_{1-6}$alkyl, $-S(O)_{0-2}-C_{1-6}$alkyl, $-C(O)N(R^m)R^n$, $SO_2N(R^m)R^n$, $-SCF_3$, halo, $-CF_3$, -COOH,

$-COOC_{1-6}$alkyl, and $-COOC_{3-7}$cycloalkyl;

where $R^k$ and $R^l$ are each independently -H or $-C_{1-6}$alkyl;

where $R^m$ and $R^n$ are each independently -H or $-C_{1-6}$alkyl, or $R^m$ and $R^n$ taken together with their nitrogen of attachment form a 4-8 membered heterocyclic ring having 1 or 2 heteroatom members selected from >O, $>S(O)_{0-2}$, >NH, and $>NC_{1-6}$alkyl, having 0 or 1 double bond, having 0 or 1 carbonyl members;

2) $-G-Ar^2$, where G is a bond, -O-, or -S-, and $Ar^2$ is phenyl or is a monocyclic aromatic hydrocarbon group having five or six ring atoms, having one carbon atom replaced by >O, >S, >NH, or >N(C1.4alkyl), having up to one additional carbon atom optionally replaced by -N=, each optionally mono-, di-, or tri-substituted with $R^p$; where $R^p$ is a substituent independently selected from the group consisting of: -OH, $-C_{1-6}$clkyl, $-OC_{1-6}$alkyl, phenyl, -CN, $-NO_2$,

$-N(R^q)R^r-$, $-C(O)N(R^q)R^r$, $-N(R^q)C(O)R^r$,- $N(R^q)SO_2C_{1-6}$alkyl, $-C(O)C_{1-6}$alkyl, $-S(O)_{0-2}-C_{1-6}$alkyl, $-SO_2N(R^q)R^r$,- $SCF_3$, halo, $-CF_3$, $-OCF_3$, $-OCHF_2$, -COOH, and $-COOC_{1-6}$alkyl;

wherein $R^q$ and $R^r$ are each independently selected from -H, $-C_{1-6}$alkyl, and $-C_{2-6}$alkenyl; and

3) a 4-8 membered saturated or partially saturated heterocyclic ring, having 1 or 2 heteroatom members selected from >O, $>S(O)_{0-2}$, >NH, and $>NC_{1-6}$alkyl, having 0 or 1 carbonyl members, said ring optionally mono-, di-, or tri-substituted with $R^p$;

b) phenyl or pyridyl fused at two adjacent carbon ring members to a three membered hydrocarbon moiety to form a fused five membered aromatic ring, which

moiety has one carbon atom replaced by >O, >S, >NH, or >N($C_{1-4}$alkyl), and which moiety has up to one additional carbon atom optionally replaced by -N=, the fused rings optionally mono-, di-, or tri-substituted with $R^t$; where $R^t$ is a substituent independently selected from the group consisting of: -OH, -$C_{1-6}$alkyl, -O$C_{1-6}$alkyl, phenyl, -CN, -$NO_2$, -N($R^u$)$R^v$, -C(O)N($R^u$)$R^v$, -N($R^u$)C(O)$R^v$, -N($R^u$)$SO_2C_{1-6}$alkyl, - C(O)$C_{1-6}$alkyl. -$S(O)_{0-2}$-$C_{1-6}$alkyl,- $SO_2$N($R^u$)$R^v$, -$SCF_3$, halo, -$CF_3$, -$OCF_3$, -$OCHF_2$, -COOH, and –$COOC_{1-6}$alkyl;

where $R^u$ and $R^v$ are each independently -H or -$C_{1-6}$alkyl;

c) phenyl fused at two adjacent ring members to a four membered hydrocarbon moiety to form a fused six membered aromatic ring, which moiety has one or two carbon atoms replaced by -N=, the fused rings optionally mono-, di-, or tri-substituted with $R^t$;

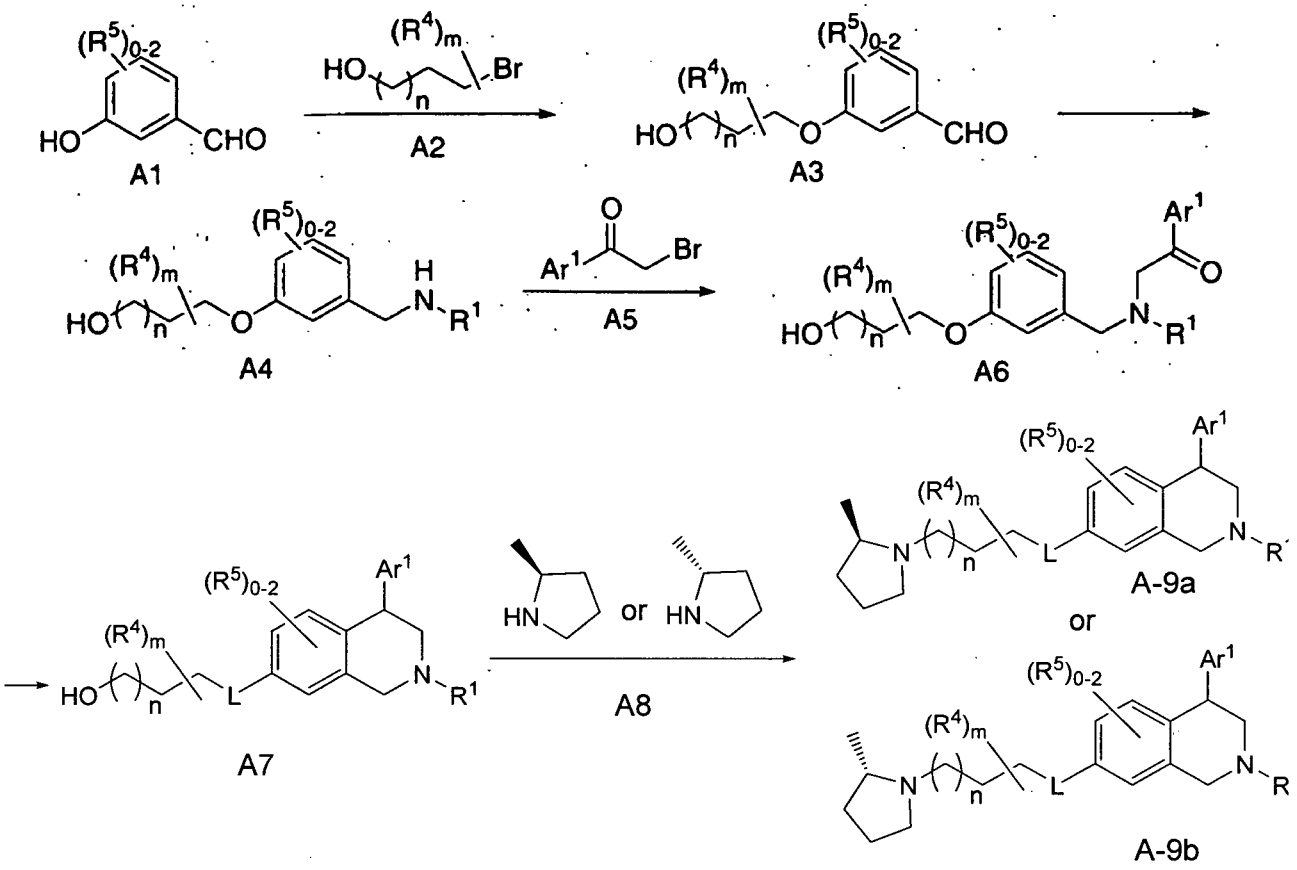
d) naphthyl, optionally mono-, di-, or tri-substituted with $R^t$;

e) a monocyclic aromatic hydrocarbon group having five ring atoms, having a carbon atom which is the point of attachment, having one carbon atom replaced by >O, >S, >NH, or >N($C_{1-4}$alkyl), having up to one additional carbon atom optionally replaced by -N=, optionally mono- or di-substituted with $R^j$ and optionally benzofused or pyridofused at two adjacent carbon atoms, where the benzofused or pyridofused moiety is optionally mono-, di-, or tri-substituted with $R^t$; and

f) a monocyclic aromatic hydrocarbon group having six ring atoms, having a carbon atom which is the point of attachment, having one or two carbon atoms replaced by -N=, optionally mono- or di-substituted with $R^j$ and optionally benzofused or pyridofused at two adjacent carbon atoms, where the benzofused or pyridofused moiety is optionally mono- or di-substituted with $R^j$; and enantiomers, diastereomers, hydrates, solvates and pharmaceutically acceptable salts, esters and amides thereof.

These compounds can be prepared, for example, according to Scheme 6.

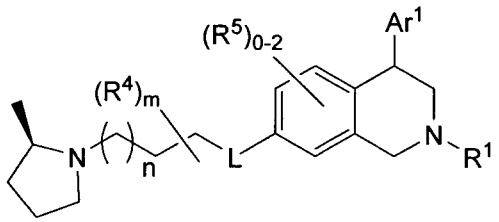
SCHEME 6



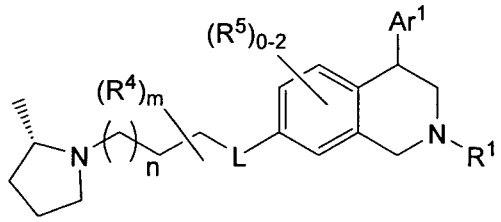

Referring to Scheme 6, reagents of formulae Al, A2, and A5 are commercially available or are prepared according to known methods. 3-5 Hydroxybenzaldehyde derivatives A1 are reacted with alcohols A2 according to a Williamson ether synthesis protocol to form ethers A3, using a suitable base such as $K_2CO_3$, $Na_2CO_3$, or NaH, in a solvent such as acetonitrile, with or without catalytic KI or NaI. Alternatively, ethers of formula A3 may be prepared under Mitsunobu conditions where A2 contains a protected hydroxyl in place of the bromide substituent. Reductive amination of the aldehyde functionality of compounds A3 will provide compounds of formula A4. The aldehyde can be treated with a suitable $R^1$-containing amine, with or without the addition of an activating agent such as a protic or Lewis acid, and with an appropriate reducing agent such as $NaBH_4$, $NaCNBH_3$, or $NaHB(OAc)_3$. Preferred conditions include $NaBH_4$ in methanol. Alkylation of amines A4 with alpha-haloketones A5 to form ketones A6 is accomplished in the presence of a tertiary amine base such as TEA or DIPEA, in a suitable solvent such as THF or DCM. Cyclization to generate tetrahydroisoquinolines A7 involves effecting cyclization to a tetrahydroisoquinolinium salt by exposure to a suitable protic or Lewis acid, such as methanesulfonic acid (MSA), trifluoroacetic acid (TFA), $AlCl_3$, $TiCl_4$, or $BF_3$*$OEt_2$ with or without a solvent such as DCM. Preferred conditions

are neat MSA or MSA in DCM. The intermediate salt may be reduced using standard reducing agents such as $NaCNBH_3$ in an acidic methanol medium. Alternatively, ketones A6 may first be reduced by known methods, including NaBH4, to their corresponding alcohols. Treatment of the intermediate alcohols with MSA in DCM provides cyclic species A7. Finally, the pendant primary alcohol group in compounds A7 may be converted to the corresponding amines A9 by activation to form an appropriate leaving group (such as a mesylate or bromide), followed by displacement of the leaving group with (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with the present invention. The displacement may be performed using a suitable base such as $Na_2CO_3$, in a polar solvent such as n-BuOH, with or without catalytic KI or NaI. Alternatively, amines A9 may be prepared through oxidation of the alcohol and reductive amination of the resulting aldehyde.

Thus, one embodiment of the invention relates to processes for preparing compounds of formulas VIII and IX:




VIII




IX

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

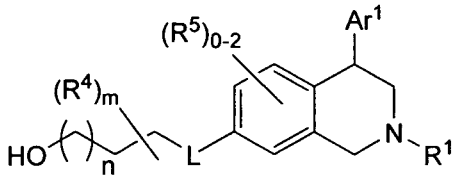
(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting a compound of formula



wherein the variables are as described above, with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the compound of formula VIII or IX.

This method may optionally further include the steps of:

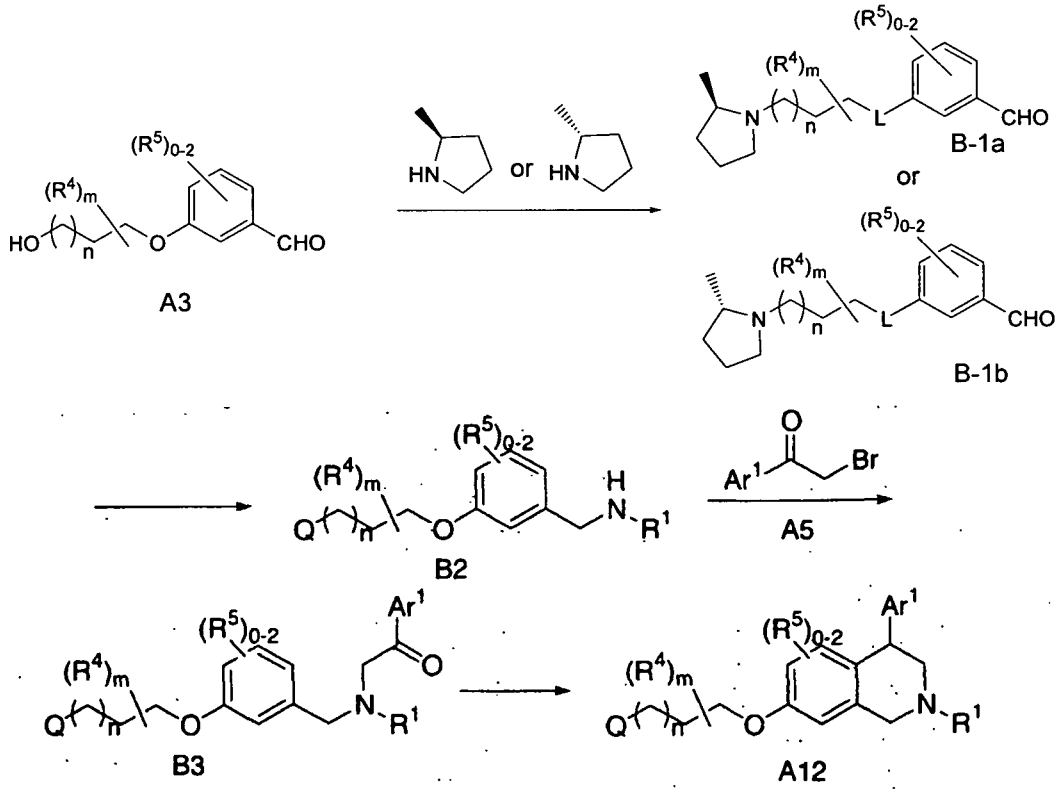
(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Alternatively, 2-methylpyrrolidine-containing compounds may be prepared according to Scheme 7:

SCHEME 7




Referring to Scheme 7, ethers of formula A3 may first be converted as described in Scheme A to the corresponding optionally protected amines B1 using (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with the present invention.

Benzaldehydes B1 may then be transformed into diamines B2, wherein Q is (R)- or (S)-2-methylpyrrolidinyl, using reductive amination protocols as in Scheme A. Alkylation to form ketones B3, and cyclization to produce compounds of formula A12 are accomplished as shown for Scheme 6.

Another embodiment of the invention relates to processes for preparing compounds of formulas VIII and IX comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

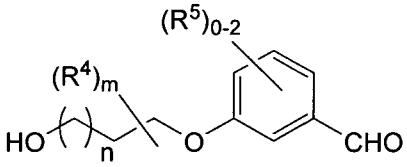
(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting a compound of formula




wherein the variables are as described above, with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the corresponding amine;

(3b) converting the amine to the compound of formula VIII or IX.

This method may optionally further include the steps of:

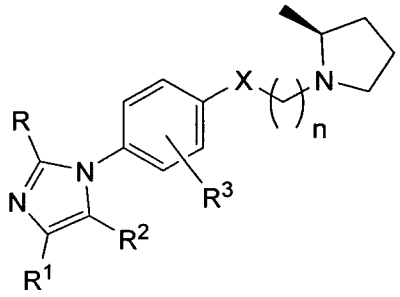
(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

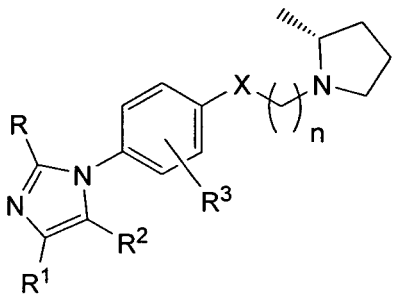
(1h) optionally repeating steps (f) and (g).

An exemplary compound that can be made using the methods of the present invention is 4-(4-methoxy-phenyl)-2-methyl-7-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-1,2,3,4-tetrahydro-isoqunoline.

The methods of the present invention are also useful in the preparation of compounds of the following formulas X and XI, as described in WO 06/078775:



X



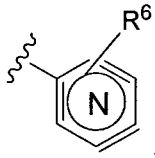
XI

and the pharmaceutically acceptable salts thereof, wherein:

n is 2, 3, 4, or 5

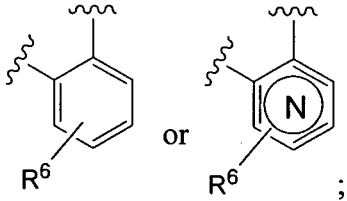
R is $R^3$-aryl, $R^3$-heteroaryl, $R^3$-cycloalkyl, $R^3$-heterocycloalkyl, alkyl, haloalkyl, -$OR^4$,

-$SR^4$ or -$S(O)_{1-2}R^5$;

$R^1$ is H and $R^2$ is $R^6$-phenyl or  ; or $R^1$ is $R^6$-phenyl or  and $R^2$ is H; or $R^1$ and $R^2$ are independently selected from the group consisting of $R^6$-phenyl and ; and X is

–O- or –S-;

or $R^1$ and $R^2$, together with the carbon atoms to which they are attached form

 ; and X is –O-, -S-, or –$NR^7$;

$R^3$ is 1-3 substituents independently selected from the group consisting of H, alkyl, halo, OH, alkoxy and –$NR^{11}R^{12}$,

$R^4$ is alkyl, arylalkyl or cycloalkyl;

$R^5$ is alkyl, -$NR^{11}R^{12}$, $R^3$-aryl or $R^3$-arylalkyl;

$R^6$ is 1-3 substituents independently selected from the group consisting of H, alkyl, $-CF_3$, halo,

$-NO_2$, -CN, $-C(O)OR^{13}$, $-C(O)NR^{11}R^{12}$, $-NR^{14}R^{15}$, $-OR^{13}$ and haloalkyl;

$R^7$ is H, alkyl, $-c(O)OR^{13}$, $-C(O)NR^{11}R^{12}$ or $-C(O)R^{13}$;

$R^{11}$ and $R^{12}$ are independently selected from the group consisting of H, alkyl, cycloalkyl, aryl and arylalkyl;

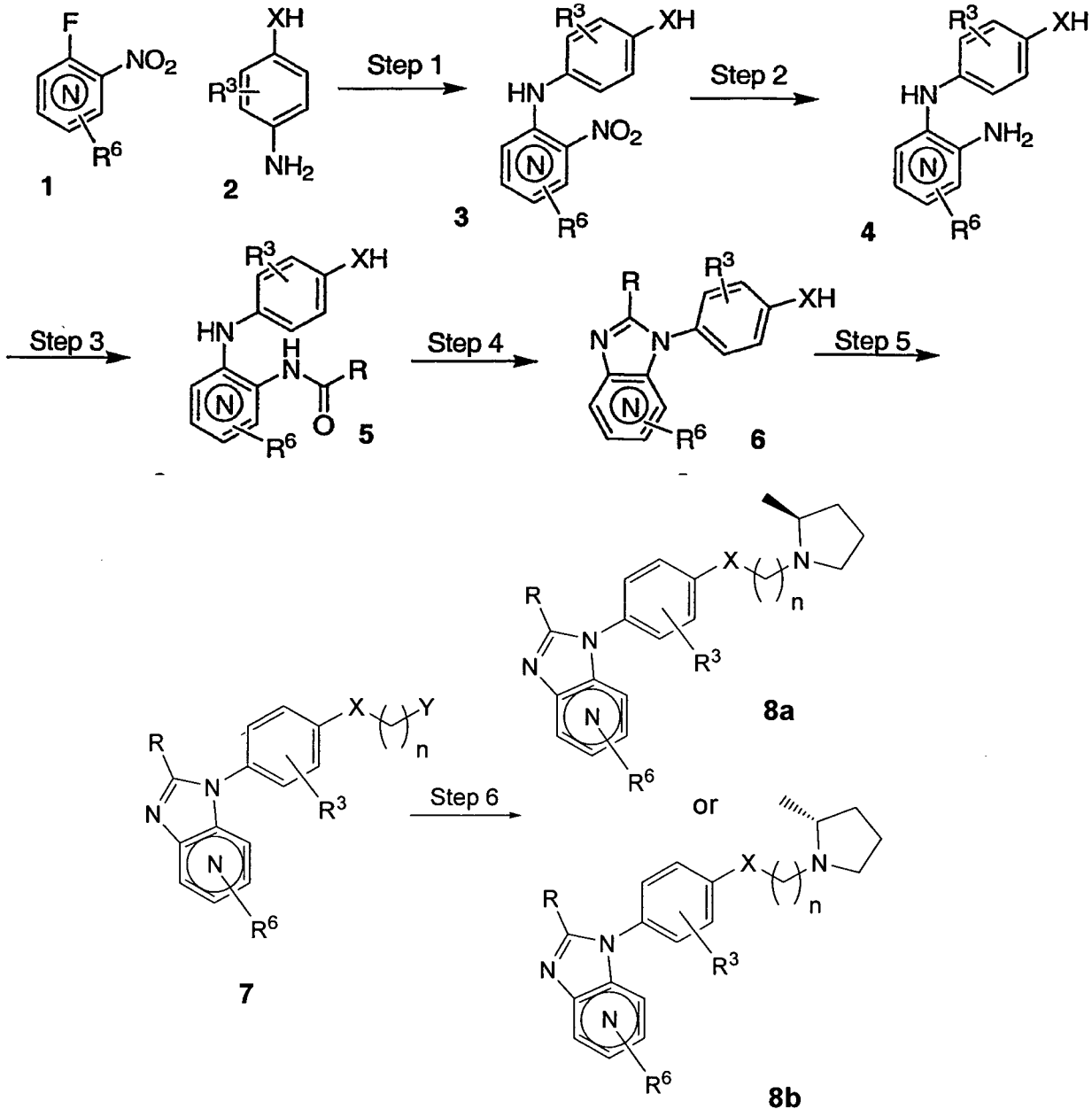
$R^{13}$ is H, alkyl, cycloalkyl or arylalkyl;

$R^{14}$ is H , alkyl, cycloalkyl or arylalkyl; and

$R^{15}$ is H, alkyl, cycloalkyl, $-C(O)OR^{13}$, $-C(O)NR^{11}R^{12}$ or $-CO)R^{13}$;

Compounds of formulas X and XI can be prepared according to the following Scheme 8.

SCHEME 8




Referring to Scheme 8, Compound **1** is reacted with an aniline derivative **2** in a suitable solvent such as THF or dioxane, preferably dioxane, at a temperature sufficient to effect the reaction, preferably 50 to 150 °C, to give compound 3. The nitro group of compound 3 is reduced to the amine **4** using hydrogen gas in the presence of a suitable catalyst such as Pd/C, $PtO_2$, Raney nickel, preferably Raney Nickel, in a suitable solvent such as methanol, ethanol, or isopropanol, preferably methanol or ethanol. Other reduction methods well known to those versed in the art are also suitable.

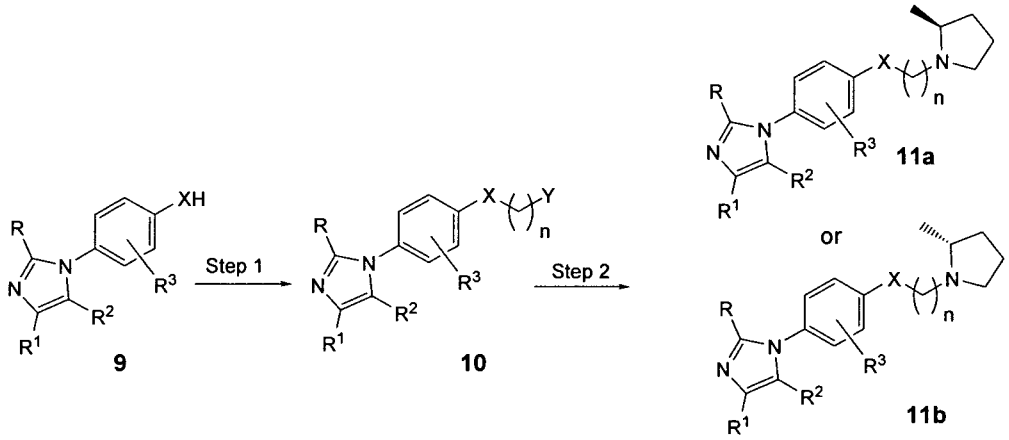
The primary amine of compound **4** is acylated by reaction with a carboxylic acid in the presence of coupling agents such as DEC and HOBT in a suitable solvent such as ether, THF, or $CH_2Cl_2$, preferably $CH_2Cl_2$ to give compound **5.** Alternatively, the amine

can be acylated by an acid chloride in the presence of a base. Compound **5** in acetic acid is heated for a sufficient time for cyclization to occur. In step 5, if a protecting group is present on the group X, it is removed at this point. Suitable protecting groups for X = O, N, or S and methods for their removal can be found in Green's *Protecting Groups in Organic Synthesis.* Compound **6** is reacted with an α, ω-dihaloalkane in a suitable solvent such as acetone, THF, ether or the like, preferably acetone, in the presence of a base such as $Na_2CO_3$ or $K_2CO_3$, preferably $K_2CO_3$, at a temperature from 0 to 65 °C to give compound **7** wherein Y is halo.

A solution of compound **7** in a suitable solvent such as $CH_3CN$, THF, ether, or the like, preferably $CH_3CN$, is treated with a tertiary amine base such as $Et_3N$, DIPEA or the like, preferably DIPEA, followed by (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with the present invention. The reaction is then heated at a temperature from 0 to 100°C to give compound **8.**

Alternatively, the following Scheme 9 can be followed.

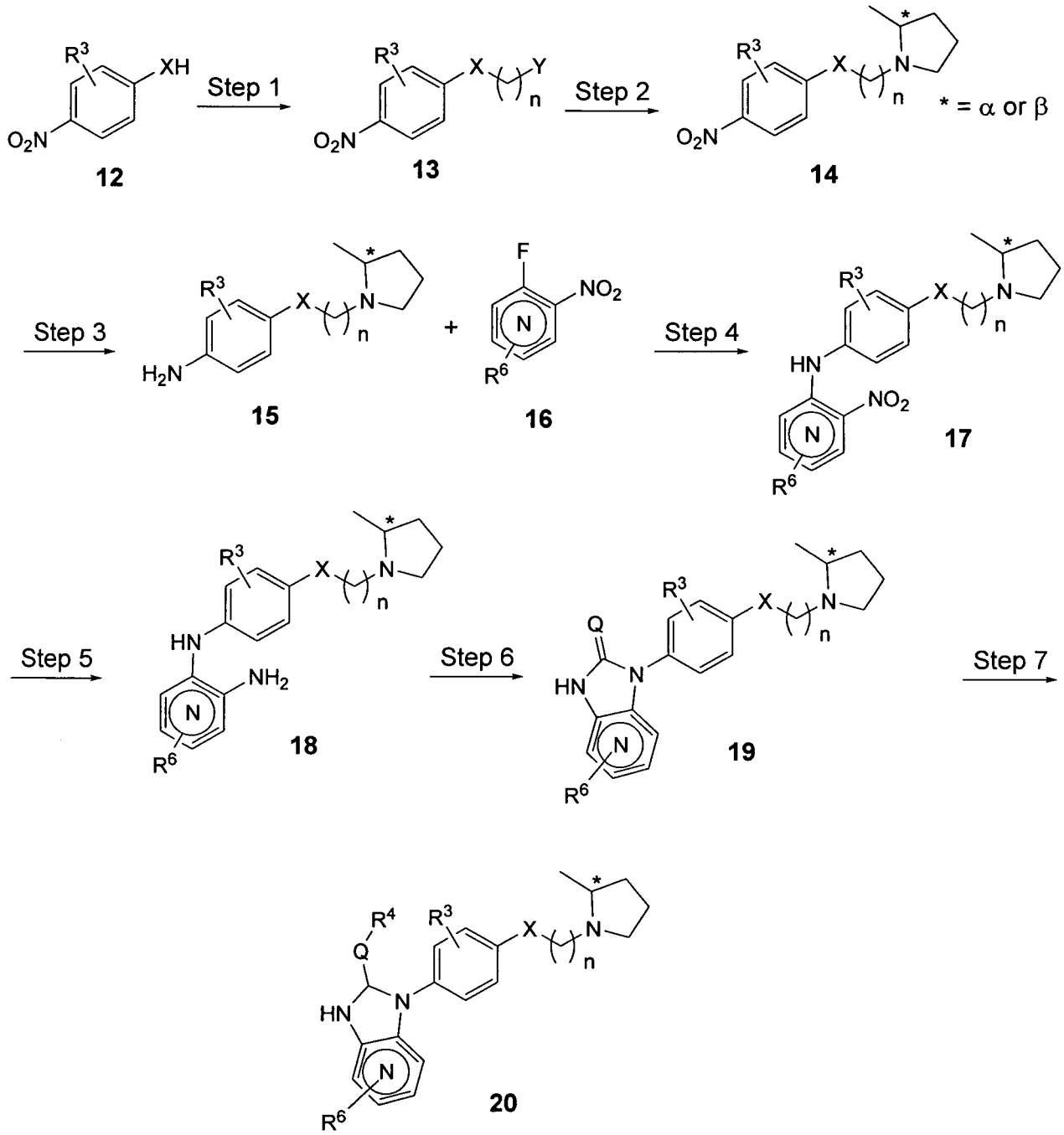
SCHEME 9




Referring to Scheme 9, Compound 9, known in the literature, is reacted with an α, ω-dihaloalkane in a suitable solvent such as acetone, THF, ether or the like, preferably acetone, in the presence of a base such as $Na_2CO_3$ or $K_2CO_3$, preferably $K_2CO_3$, at a temperature from 0 to 65°C to give compound **10.** A solution of compound **10** in a suitable solvent such as $CH_3CN$, THF, ether, or the like, preferably $CH_3CN$, is treated with a tertiary amine base such as $Et_3N$, DIPEA or the like, preferably DIPEA, followed by (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with the present invention. The reaction is then heated at a temperature from 0 to 100°C to give compound **11.**

As an alternative, the compounds can be made according to the following Scheme 10.

SCHEME 10



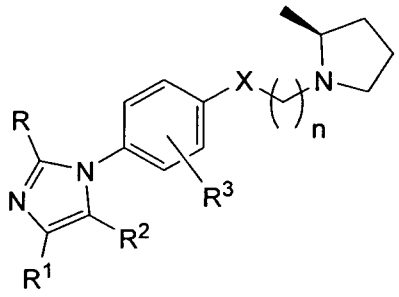

Referring to Scheme 10, compound **12** is reacted with an α, ω-dihaloalkane in a suitable solvent such as acetone, THF, ether or the like, preferably acetone, in the presence of a base such as $Na_2CO_3$ or $K_2CO_3$, preferably $K_2CO_3$, at a temperature from 0 to 65 °C to give compound 13, wherein Y is halo. A solution of compound **13** in a suitable solvent such as $CH_3CN$, THF, ether, or the like, preferably $CH_3CN$, is treated with a tertiary amine

base such as $Et_3N$, DIPEA or the like, preferably DIPEA, followed by (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with the present invention. The reaction is then heated at a temperature from 0 to 100°C to give compound **14.** The nitro group of compound **14** is reduced to the amine **15** using $H_2$ gas in the presence of a suitable catalyst such as Pd/C, $PtO_2$, or Raney nickel, preferably Raney Nickel, in a suitable solvent such as methanol, ethanol, or isopropanol, preferably methanol or ethanol. Other reduction methods well known to those versed in the art are also suitable.

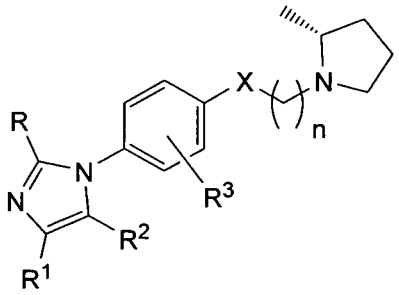
Still referring to Scheme 10, Compound **15** is reacted with **16** in a suitable solvent such as THF or dioxane, preferably dioxane, at a temperature sufficient to effect the reaction, preferably 50 to 150 °C, to give compound **17.** The nitro group of compound **17** is reduced to the amine and subsequently to compound **18.** The amine **18** in a suitable solvent such as THF, ether or the like is treated with either thiocarbonyldiimidazole (Q = S) or 1,1'-carbonyldiimidazole (Q = O) at a temperature of from 0 to 100 °C, preferably from 25 to 75 °C, to give compound **19**.

A solution of **19** in a suitable solvent such as DMSO, DMF or the like is treated with a base such as $K_2CO_3$ or the like and an alkylating agent $R^4L$, in which L is Cl, Br or I, or a mesylate or sulfonate, at a temperature of 0 to 100 °C, preferably from 25 to 75 °C, to give **20.**

Thus, one embodiment of the invention relates to processes for preparing compounds of formulas X and XI




X




XI

wherein the variables are as set forth above;

comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) converting the (R)- or (S)-2-methylpyrrolidine to the compound of formula VIII or IX.

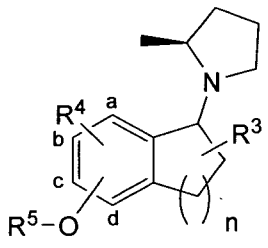
This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

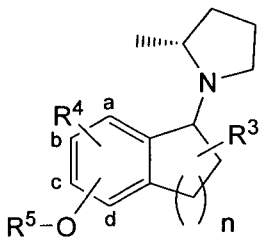
(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Also amenable to the methods of the present inventions are compounds of the following compounds of formulas XII and XIII, described in WO 2007/099423:




XII




XIII

or the pharmaceutically acceptable salts thereof, wherein

$R^3$ is $(C_{1-6})$-alkyl, aryl or heteroaryl, optionally substituted with up to 3 fluorine atoms;

$R^4$ is hydrogen, halogen, $(C_{1-6})$-alkyl or $(C_{3-7})$-cycloalkyl, $(C_{1-6})$-alkoxyl or $(C_{3-7})$-cycloalkoxyl (optionally substituted with up to 3 fluorine atoms), aryl, heteroaryl;

$R^5$ is $(CR^6R^9)_m$-$(CR^{10}R^{11})_p$-B, wherein $R^6$, $R^9$, $R^{10}$ and $R^{11}$ together with the carbon to which they are attached form a 3-10 member mono- or bi-cyclic ring system;

B is a 4-7 member heterocycloalkyl containing up to 3 heteroatoms selected from N, O, S (e.g., azetidine, pyrrolidine, piperdine, azeplne, morpholine, thiomorpholine, piperazine or l-4 diazepine) or $NR^{12}R^{13}$;

$R^8$, $R^9$, $R^{10}$, $R^{11}$, $R^{12}$ and $R^{13}$ are independently selected from hydrogen, $C_{1-6}$ alkyl, ($C_{1-6}$ alkyl)-aryl, ($C_{1-6}$ alkyl)-heteroaryl; or

$R^{12}$ and $R^{13}$ together with the nitrogen to which they are attached form a 3-10 member mono- or bi-cyclic ring system (e.g., azepine, piperidine, pyrrolidine or morpholine), and with the proviso that $NR^{12}R^{13}$ is not $NH_2$;

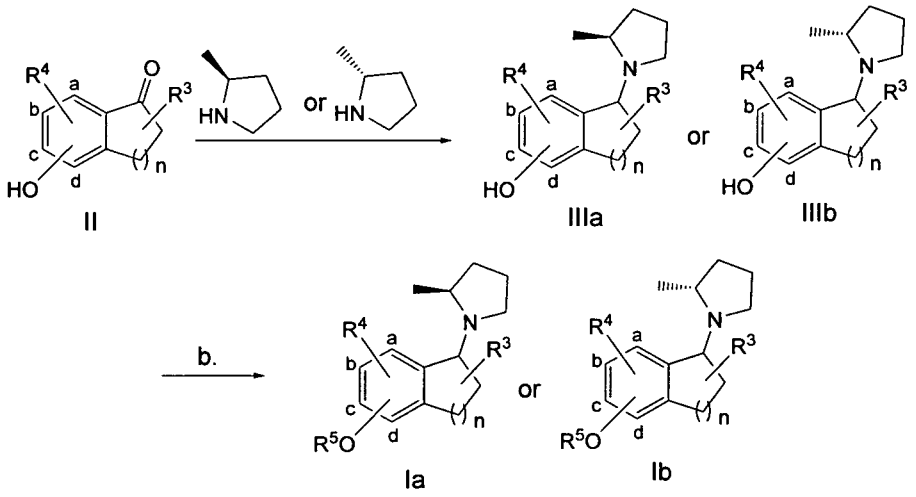
m is 0, 1, 2, 3, or 4;

n is 0, 1, 2 or 3; and

p is 0 to 3.

These compounds can be prepared by the general procedure shown in the following Scheme 11.

SCHEME 11

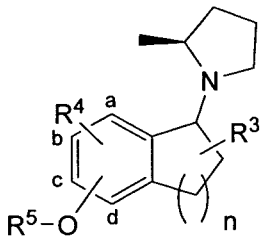



Referring to Scheme 11, a ketone of the general formula **II,** wherein the hydroxyl (-OH) group is unprotected, is reacted with (R)- or (S)-2-methylpyrrolidine that has been prepared in present invention, to generate an amino-phenol of general formula **III**. This transformation can be accomplished using one or more of the methods and procedures available to those skilled in the art. For example, a ketone of formula **II** and 2-methylpyrrolidine can be combined in an inert aprotic solvent, like chloroform or dichloromethane, in the presence of a Lewis acid reagent like titanium tetrachloride ($TiCl_4$) or titanium isopropoxide to produce an intermediate imine through the elimination of water. Alternatively, refluxing a solution of **II** and 2-methylpyrrolidine in a solvent like toluene in the presence of a catalytic amount of para-toluenesulfonic acid, with provision for removal of the water by using a Dean-Stark trap or activated molecular sieves, may also be employed to effectively produce the intermediate imine. This imine may then be converted in situ, or in a separate step following its isolation, to the amino-phenol

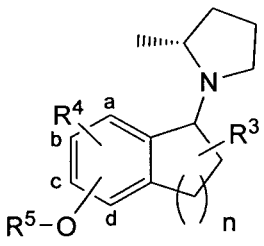
intermediate **III.** This can be accomplished by reduction of the C=N double bond using, for example, boron reagents like sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaBH_3CN$), sodium triacetoxyborohydride and the like, in reaction inert solvents like dichloromethane, methanol, THF or dioxane. Alternatively, the imine can be reduced using catalytic hydrogenation conditions, e.g., employing hydrogen gas ($H_2$) and a suitable metal catalyst like Raney nickel (RaNi), palladium on carbon (Pd/C) or similar catalysts in a reaction inert solvent like methanol or ethanol and at temperatures in the range of about 20 °C up to the boiling point of the solvent employed and at pressures in the range of about one to five atmospheres of hydrogen gas. Other related examples for the transformation may be found in the literature.

Still referring to Scheme 11, the phenolic OH group present in the intermediate of formula III .can be converted to an ether product of the general formula I by alkylation of III with a reagent of the general formula $R^5$-A, wherein $R^5$ is as defined previously and A is a leaving group including halogen (e.g., Cl, Br, I), mesylate (i.e., $-OSO_2CH_3$, or -OMs) or tosylate (i,e., $-OSO_2C_6H_5$ or –OTs), in the presence of a base and in a reaction inert solvent, as depicted in pathway b. Suitable bases will include sodium, potassium or cesium carbonate(s), sodium or potassium bicarbonate(s), sodium or potassium tert-butoxide(s), sodium or potassium hydride(s) and the like, with cesium carbonate being preferred. Suitable solvents will include DMF, DMSO, DMA, THF and the like, with DMSO preferred.

Thus, one embodiment of the invention relates to processes for preparing compounds of formula XII and XIII:




XII




XIII

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

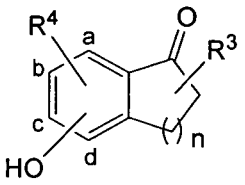
(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting a compound of formula




with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the corresponding amine phenol; and

(3b) contacting the amine phenol with an alcohol, for a time and under conditions sufficient to provide the compound of formula XII or XIII.

This method may optionally further include the steps of:

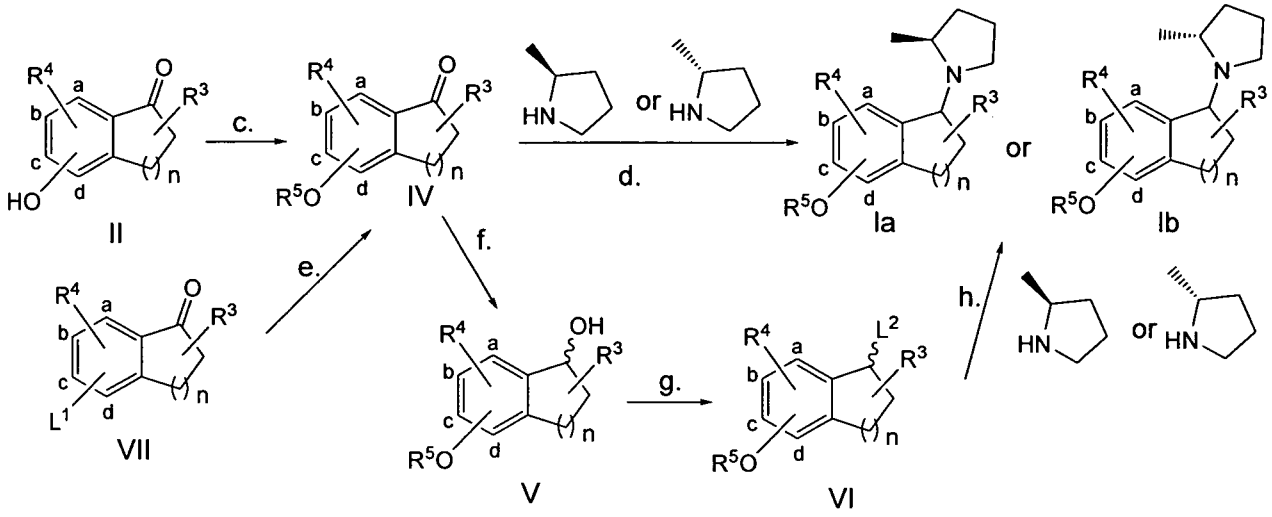
(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

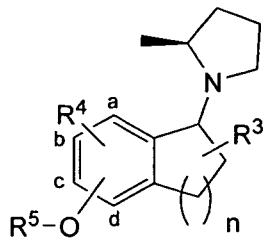
The compounds of the present general formulas XII and XIII may also be prepared via the routes shown in the following Scheme 12.

SCHEME 12

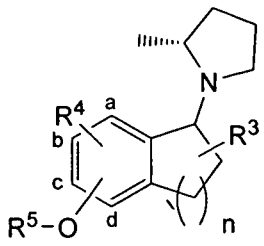



Referring to Scheme 12, a phenolic ketone of the general formula **II** may be converted to an ether (pathway c.) by methods generally known to one skilled in the art. For example, the phenol II can be reacted with a reagent of general formula $R^5$-A in the presence of a base, as described for pathway b in Scheme 1 to produce a ketone of general formula IV. Alternatively, a ketone of the general formula VII, wherein $L_1$ is a suitable leaving group (i.e., F, -OMs, etc.), may be reacted with a reagent of general formula $R^5$-OH in the presence of a suitable base and in an inert solvent to produce an intermediate of general formula **IV** (pathway e.). The ketone IV so obtained may then be converted, using reductive amination conditions as previously described in Scheme 11 to the desired products of general formula I (pathway d.). In some situations, it may also be advantageous to initially convert the intermediate ketone **IV** to the corresponding benzylic alcohol of general formula V (pathway f.) by using a reducing agent such as $NaBH_4$ in a solvent like methanol, then to activate the benzylic alcohol V (pathway g.) to produce an intermediate of formula **VI** in which $L^2$ is a leaving group (e.g., OMs, OTs, Cl), and finally to displace the leaving group w with (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with the foregoing steps (a) to (e) (with or without optional steps (f) to (h)) and reacting the (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine D-tartrate with a base to provide (*S*)-2-methylpyrrolidine (pathway h.).

Thus, another embodiment of the invention relates to processes for preparing compounds of formula XII and XIII:




XII




XIII

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

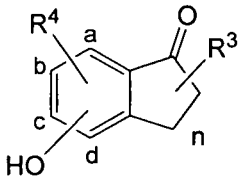
(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

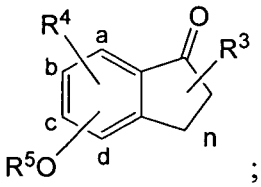
(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting a compound of formula

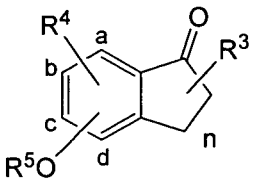



with a compound of formula $R^5$-LG, wherein LG is a leaving group, for a time and under conditions sufficient to form a compound of formula




; and

(3b) contacting the compound of formula



with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the compound of formula XII or XIII.

This method may optionally further include the steps of:

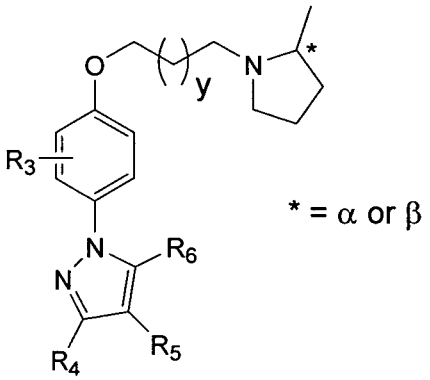
(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

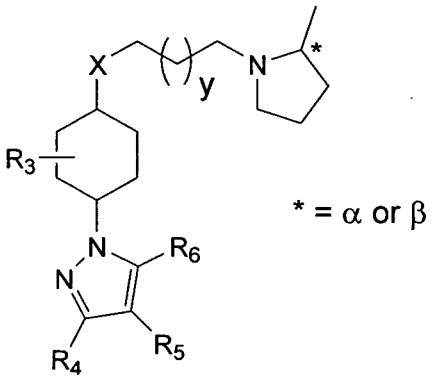
(1h) optionally repeating steps (f) and (g).

An exemplary compound that can be prepared using the methods of the present invention is 1-{3-[1-(2-methyl-pyrrolidin-1-yl)-indan-5-yloxy]-propyl}azepane.

The methods of the present invention are also suitable for preparing compounds such as those described in WO 2007/094962, for example, those of formulas XIV and XV.




XIV




XV

wherein

X is O or $NR_7$;

y is 0, 1, or 2;

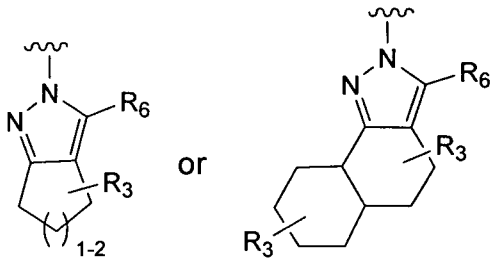
$R_3$ is 0-2 of groups selected from halogen, $(C_{1-8})$alkyl, $(C_{1-8})$alkoxyl, $(C_{3-7})$cycloalkyl, $(C_{3-7})$cycloalkyl-$(C_{1-6})$alkyl, heterocycloalkyl containing 1-3 hetero atoms selected from O, S, and $(C_{1-5})$alkyl-O-$(C_{1-5})$alkyl;

$R_4$ and $R_6$ are independently selected from $(C_{1-8})$alkyl, $(C_{1-8})$alkoxy, $(C_{3-7})$cycloalkyl, $(C_{3-7})$cycloalkyl-$(C_{1-6})$alkyl, heterocycloalkyl containing 1-3 heteroatoms selected from O, S, N, $(C_{1-5})$alkyl-O-$(C_{1-5})$alkyl, amide, $(C_{1-5})$alkyl-aryl, and $CF_3$;

$R_5$ is selected from the group consisting of hydrogen, $(C_{1-8})$alkyl, aryl, $(C_{1-5})$alkyl-O-$(C_{1-5})$alkyl, and $(C_{1-5})$alkyl-aryl,

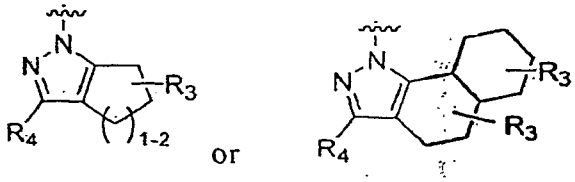
or

$R_5$ and $R_4$ and the atoms to which they are attached form a fused 5-6 member saturated carbocyclic ring or a fused 10 member bi-cyclic ring system, such as



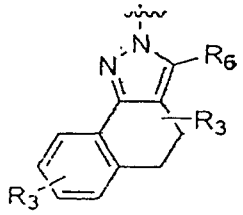
or

$R_5$ and $R_6$ and the atoms to which they are attached form a fused 5-6 member saturated carbocyclic ring or a fused 10 member bi-cyclic ring system, such as



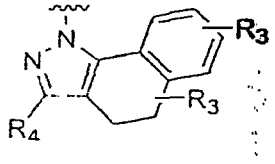
or

$R_5$ and $R_4$ and the atoms to which they are attached form a fused 5-6 member saturated carbocyclic ring to which a 6 member aromatic ring is fused, such as



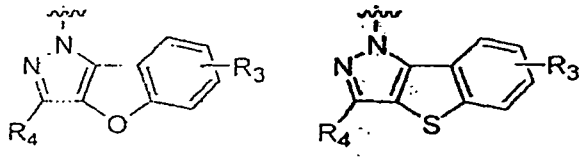
or

$R_5$ and $R_6$ and the atoms to which they are attached form a fused 5-6 member saturated carbocyclic ring to which a 6 member aromatic ring is fused, such as



or

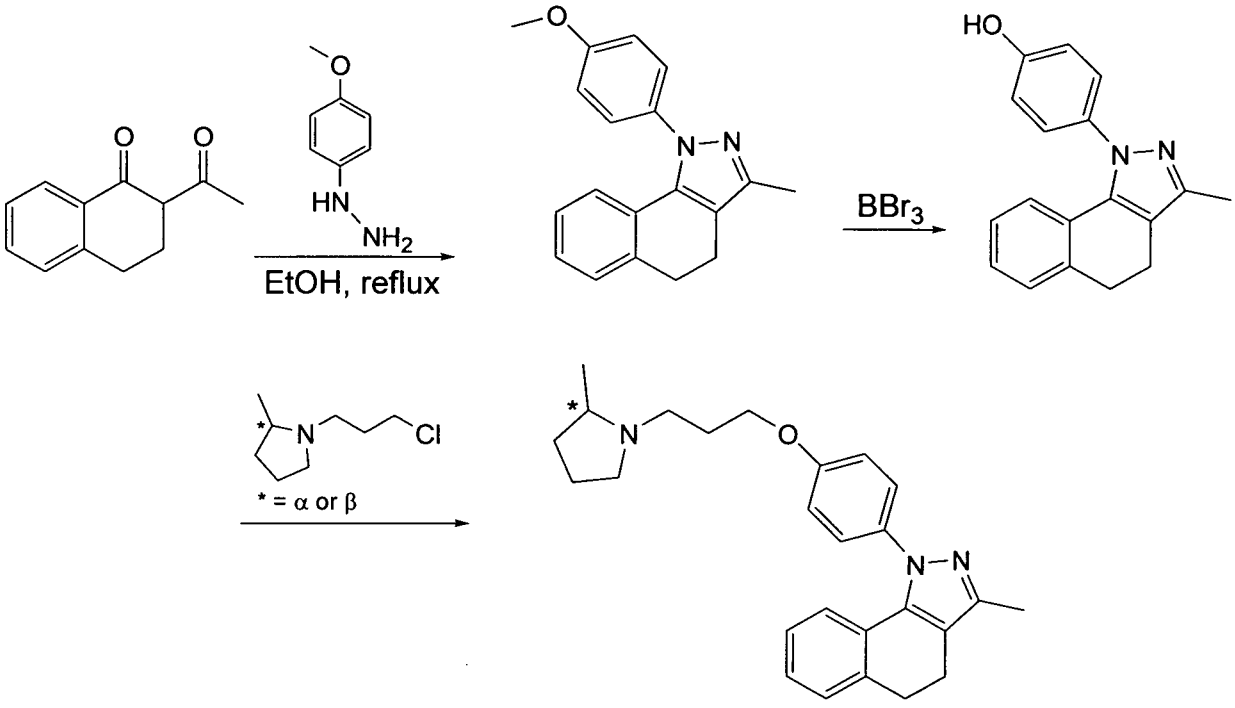
$R_5$ and $R_6$ and the atoms to which they are attached form a fused benzothiophene or fused benzofuran ring system, such as



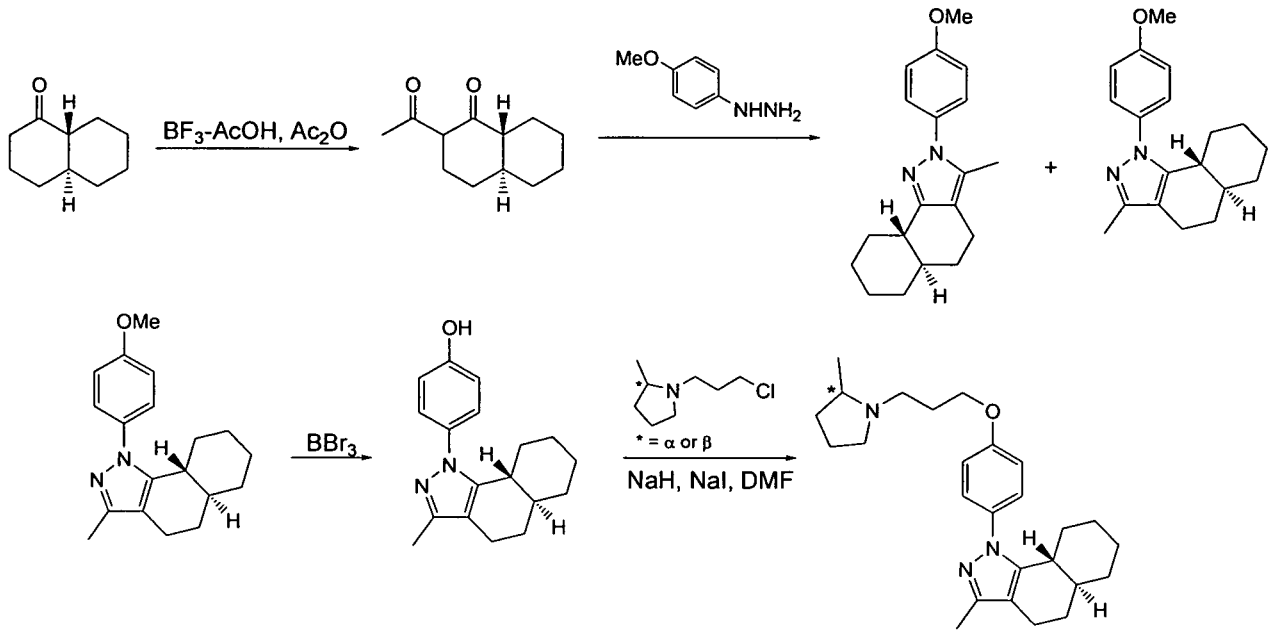
where X is $NR_7$, $R_7$ and $R_2$ taken together are $-(CH_2CH_2)-$ to form a two nitrogen containing ring where y is 0 (piperazine) or y is 1 (homopiperazine), and wherein $R_1$ is as defined previously, and the pharmaceutically acceptable salts thereof.

The above-described compounds having a 2-methylpyrrolidine group may be prepared in accordance with the following schemes. (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with present invention can be reacted, under conditions known in the art, with 1,3-dichloropropane to produce (R)- or (S)-1-(3-chloro-propyl)-2-methyl-pyrrolidine, which can be used as in the following schemes.

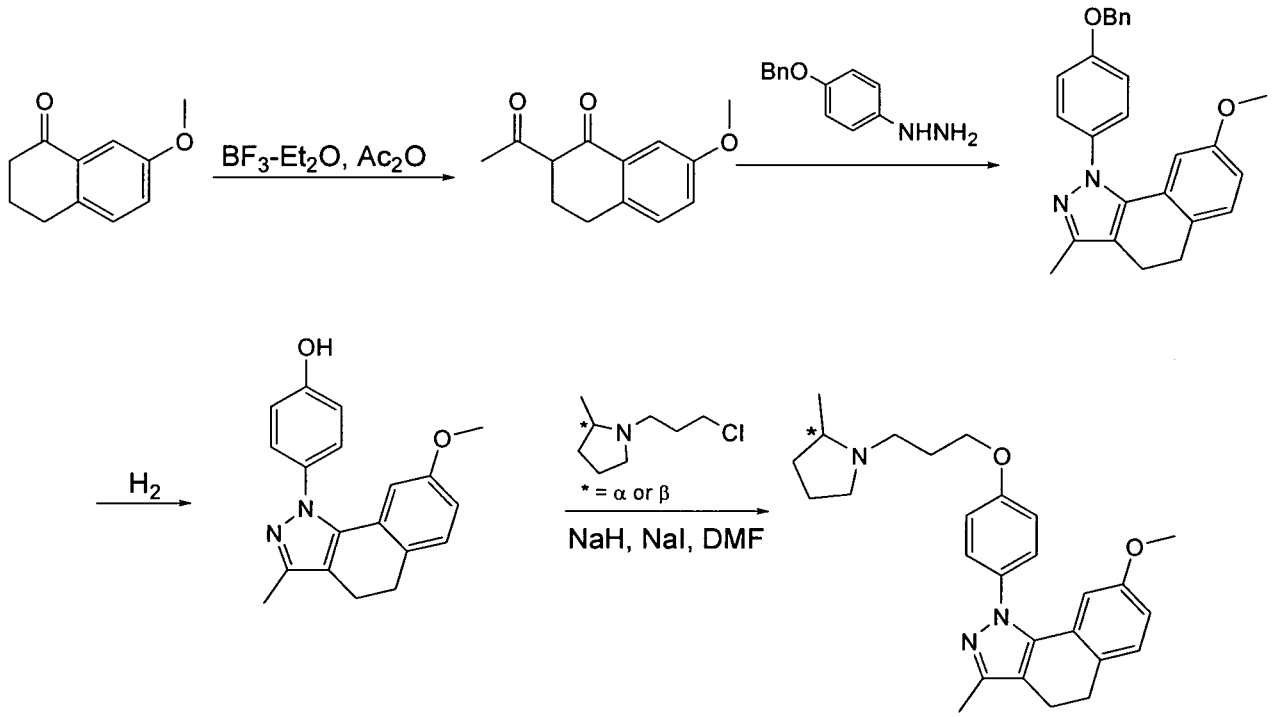
SCHEME 13



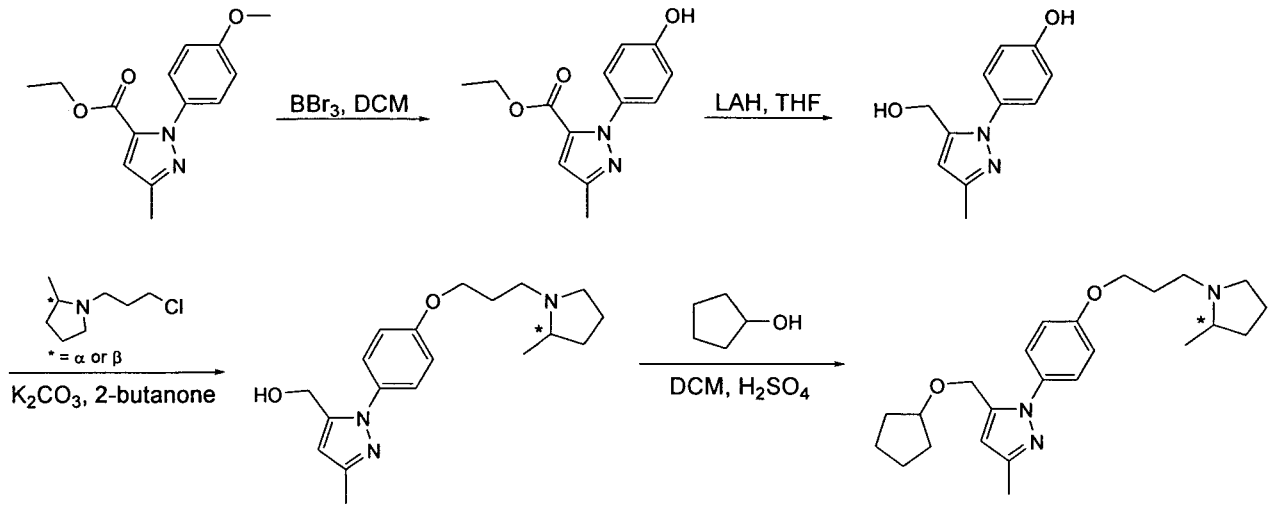

SCHEME 14



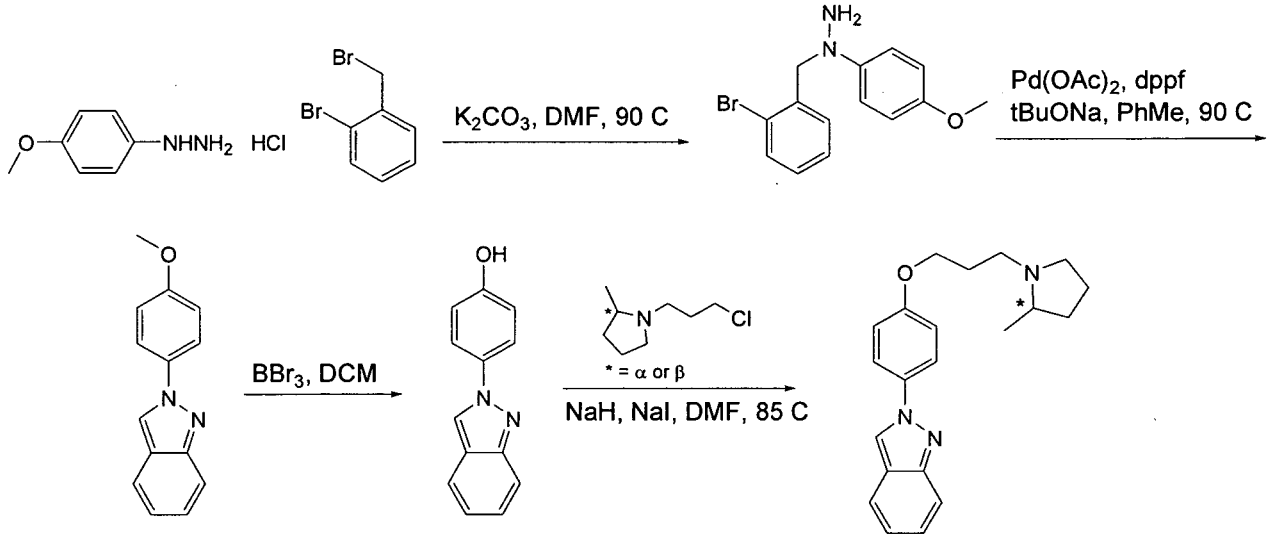

SCHEME 15



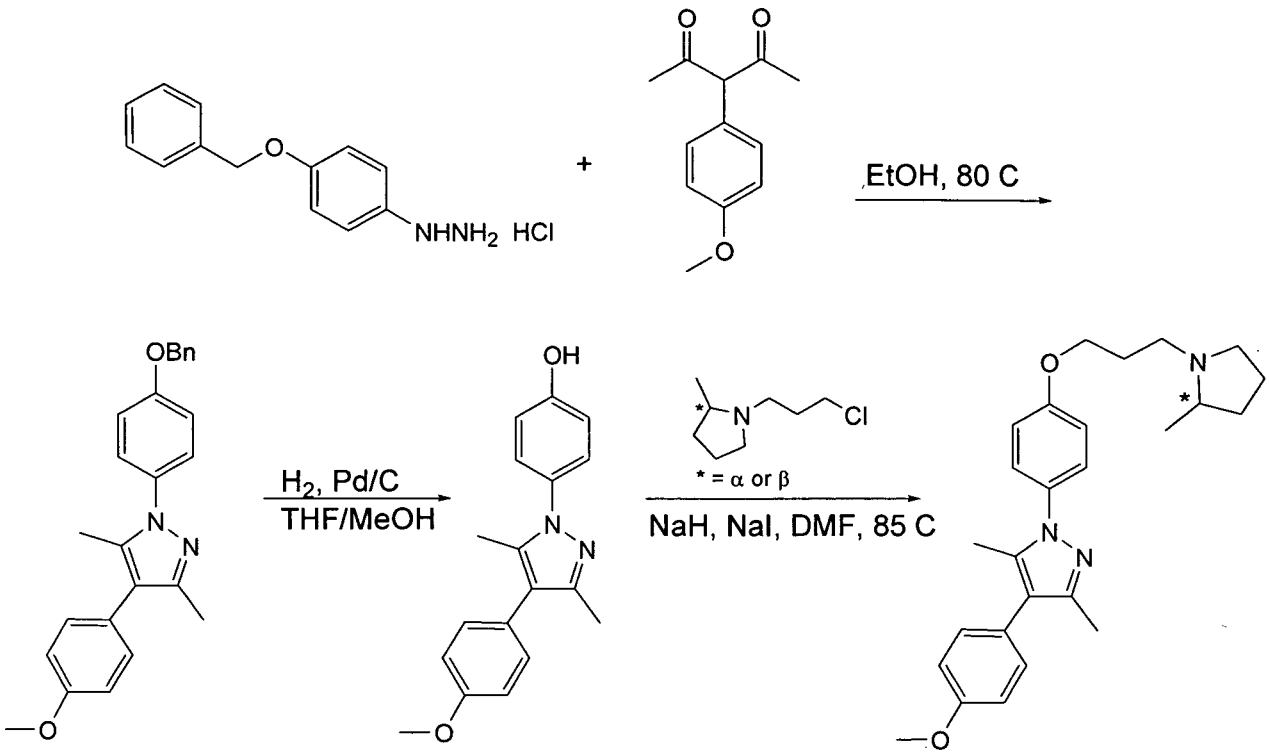

SCHEME 16



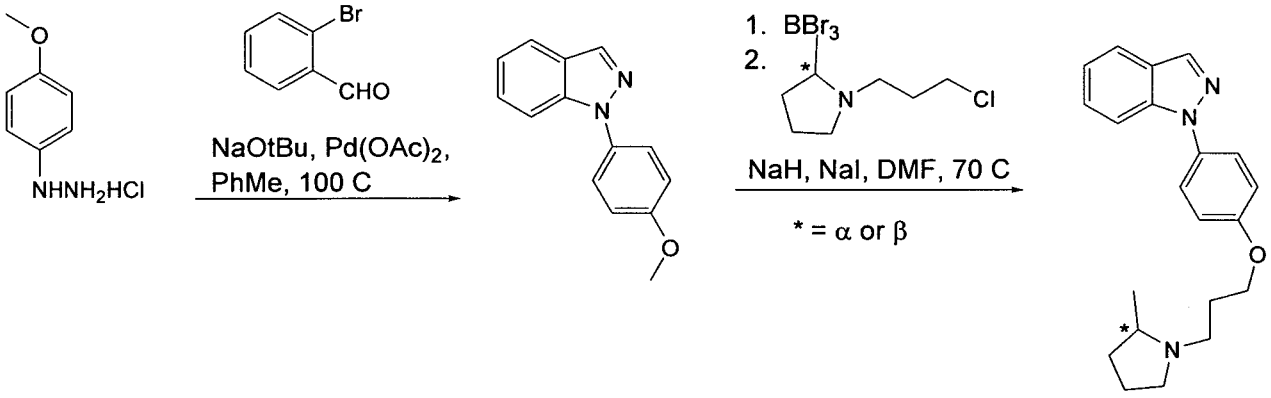

SCHEME 17



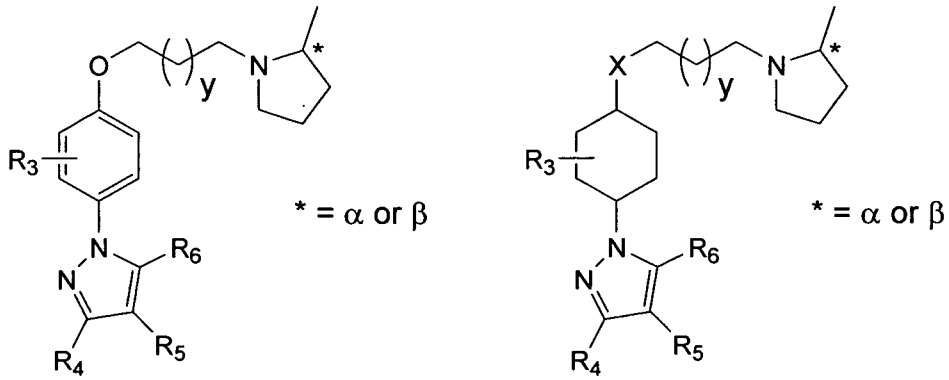

SCHEME 18




SCHEME 19




Thus, another embodiment of the invention relates to processes for preparing compounds of formula XIV and XV:



XIV XV

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) converting (R)- or (S)-2-methylpyrrolidine to 1-(3-halo-propyl)-(R)-2-methyl-pyrrolidine or 1-(3-halo-propyl)-(S)-2-methyl-pyrrolidine; and

(3b) converting 1-(3-halo-propyl)-(R)-2-methyl-pyrrolidine or 1-(3-halo-propyl)-(S)-2-methyl-pyrrolidine to the compound of formula XII or XIII.

This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Exemplary compounds that can be prepared according to the methods of the invention include:

3-Methyl-1-{4-[3-(2R-methylpyrrolidin-1-yl)propoxy]phenyl}-4,5-dihydro-1H-benzo[*g*]indazole;

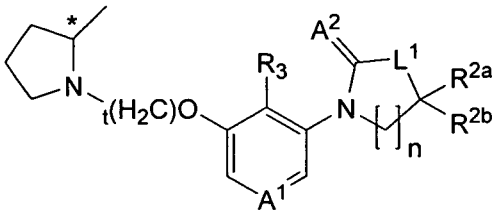
5-Methyl-2-{4-[3-(2R-methylpyrrolidin-1-yl)propoxy]phenyl}-2H-pyrazole-3-carboxylic acid cyclohexylamide;

1-{4-[3-(2-(R)-Methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-5-phenyl-3-trifluoromethyl-1H-pyrazole;

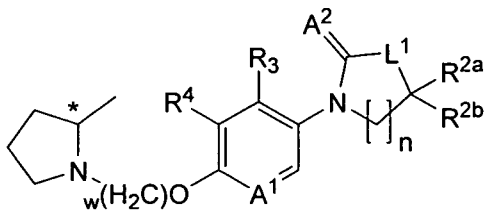
3-Methyl-1-{4-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl)}-1H-benzo[4,5]thieno[3,2-c]pyrazole; and

3-{4-[3-(2-Methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-1-trifluoromethyl-3H-8-oxa-2,3-diaza-cyclopenta[a]indene.

Further compounds that can benefit from the methods of preparing 2-methylpyrrolidine as set forth herein include those of formulas XVI and XVII described in WO 2007/048595:



XVI



XVII

and pharmaceutically acceptable salts thereof;

wherein $A^1$ is CH, C-halogen, or ;

$A^2$ is oxygen or sulfur;

$R^{2a}$ is hydrogen, aryl, $C_{1-6}$ alkoxy, amino, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, heteroaryl, $C_{3-8}$ cycloalkyl, 3-8-membered heterocycloalkyl, acyl, $C_{1-6}$-alkyl aryl, $C_{1-6}$-alkyl, heteroaryl, $C_{1-6}$-alkyl cycloalkyl, $C_{1-6}$-alkyl heterocycloalkyl, carboxy, alkoxycarbonyl, aminocarbonyl, $C_{1-6}$-alkyl carboxy, $C_{1-6}$-alkylacyl, $C_{1-6}$-alkylalkoxy, $C_{1-6}$-alkyl alkoxycarbonyl, $C_{1-6}$-alkyl aminocarbonyl, $C_{1-6}$-alkylacylamino, acylamino, $C_{1-6}$-alkyl ureido, $C_{1-6}$-alkyl carbamate, $C_{1-6}$-alkyl amino, $C_{3-8}$-cycloalkyl amino, hydroxy, $C_{1-6}$ alkyl hydroxy, halogen or cyano;

$R^{2b}$ is hydrogen, halogen, $C_{1-8}$-alkyl or $C_{3-8}$ cycloalkyl;

or $R^{2a}$ and $R^{2b}$ are linked together to form a $C_{3-8}$ cycloalkyl, a 3-8-membered heterocycloalkyl or an oxo group;

$R^3$ is hydrogen, halogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkoxy;

$R^4$ is hydrogen, halogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkoxy;

$L^1$ is $-(O)_v-(CR^{9a}R^{9b})_m-(CH_2)_z$;

$R^{9a}$ is hydrogen or unsubstituted $C_{1-8}$ alkyl;

$R^{9b}$ is a $C_{1-6}$-alkyl aryl or unsubstituted $C_{1-8}$ alkyl;

n is an integer equal to 0, 1 or 2;

t is an integer equal to 2, 3 or 4;

w is an integer equal to 2, 3 or 4;

v is an integer equal to 0 or 1;

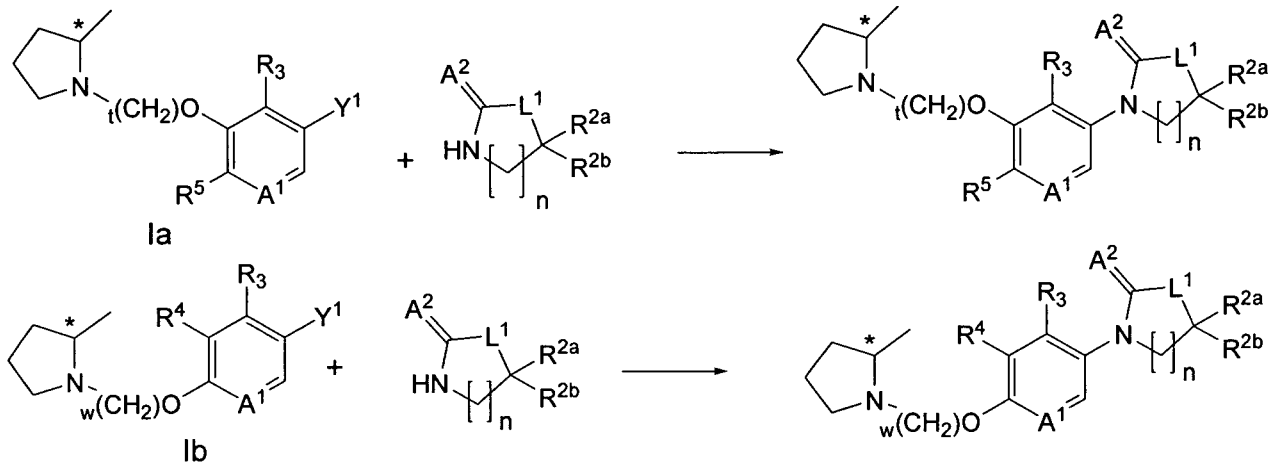
m is an integer equal to 0 or 1 ; and

z is an integer equal to 0, 1,2 or 3;

Similar compounds, such as those described in WO 2006/103045, the entirety of which is incorporated herein for all purposes, can also be prepared according to the methods of the invention.

Compounds described above may be prepared according to Scheme 20:

SCHEME 20

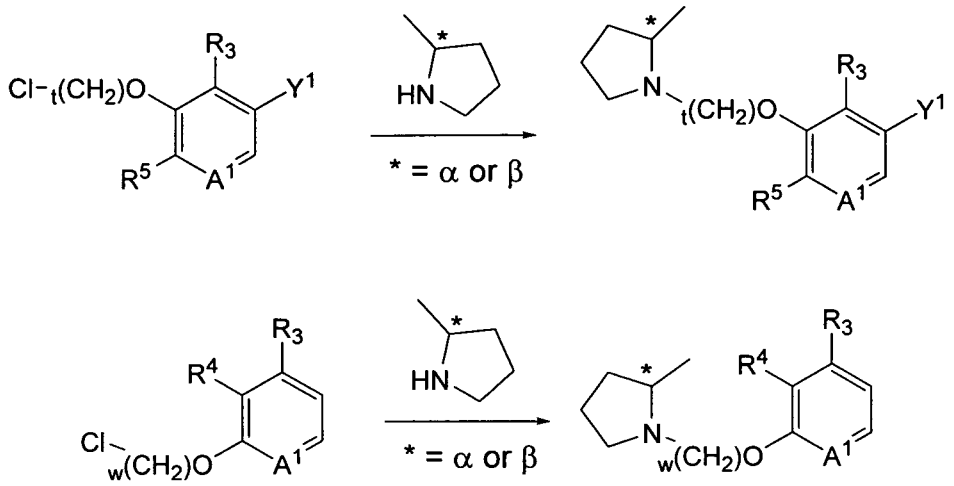



wherein $R^3$ is H, F, or Cl, and $Y^1$ is I or Br.

These reactions may be carried out using a catalyst such as copper iodide or palladium acetate, associated with a ligand such as 1,2-diamine (e.g. trans- 1,2-diaminocyclohexane), a phosphine (e.g. 1,1 '-bis(diphenylphosphino)ferrocene or 2-(dicyclohexylphosphino)-2'-(N,N-dimethylamino)-biphenyl) or an amino acid (e.g., glycine), in a solvent (such as dioxane, tetrahydrofuran, dimethylformamide or toluene), in the presence of a base (such as potassium phosphate or sodium tert-butylate), at a temperature ranging from 25 °C to 120 °C and under an inert atmosphere (argon or nitrogen). Alternatively, this reaction may be performed according to the methodology described by Klapars A. et al. in J. Am. Chem. Soc. 2002, 124, 7421.

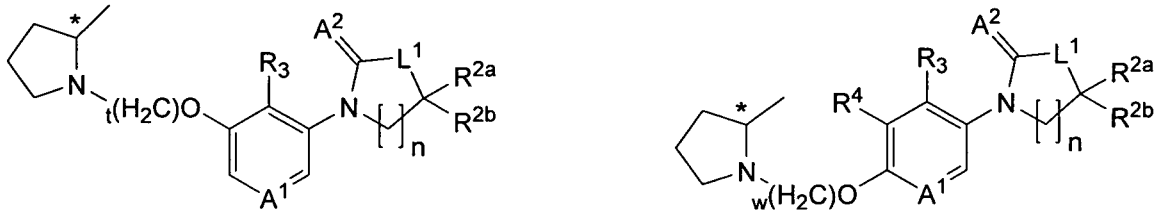
Compounds of formulas Ia and Ib set forth in Scheme 20 may be prepared using (R) or (S)-2-methylpyrrolidine prepared according to the methods of the instant invention, in accordance with Scheme 21.

SCHEME 21




These reactions may be carried out in the presence of a base such as triethylamine or potassium carbonate, in acetonitrile or acetone as solvent, or according to any conventional method known to the man skilled in the art.

Thus, one embodiment of the present invention relates to processes for the preparation of compounds of formulas XVI and XVII




XVI XVII

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

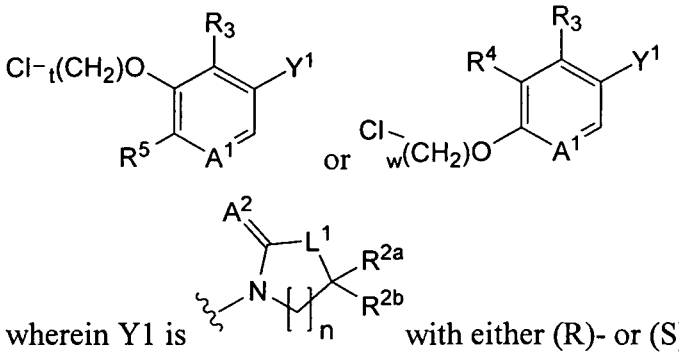
(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) contacting a compound of formula



wherein Y1 is  with either (R)- or (S)-2-methylpyrrolidine, for a time and under conditions sufficient to form the compound of formula XVI.

This method may optionally further include the steps of:

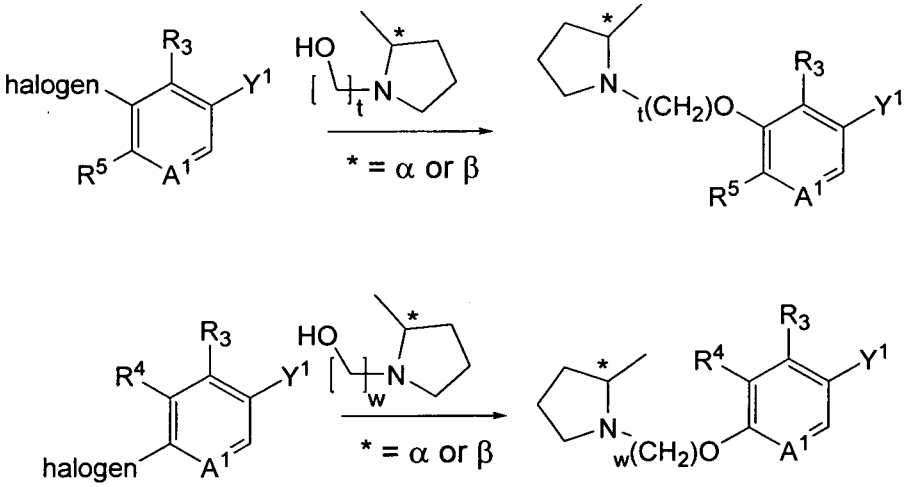
(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Alternatively, the following Scheme 22 may be implemented, wherein the 2-methylpyrrolidinealkoxy is prepared from (R)- or (S)-2-methylpyrrolidine that has been prepared in accordance with the foregoing steps (a) to (e) (with or without optional steps (f) to (h)) and reacting the (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine D-tartrate with a base to provide (*S*)-2-methylpyrrolidine, which is then reacted with a reagent such as halo-alkoxy.

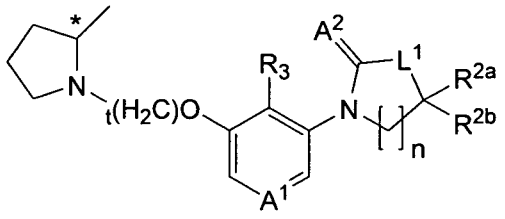
SCHEME 22



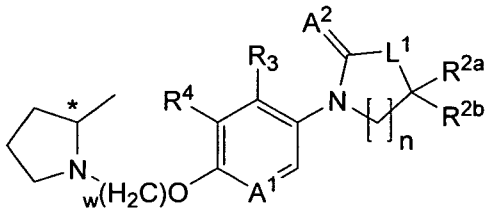
The reactions set forth in Scheme 22 may be performed in the presence of a base, such as potassium tert-butylate, cesium carbonate or sodium hydride, in a solvent, such as

dimethylformamide or tetrahydrofuran, in the presence of a palladium- or a copper based catalyst, according to method described by Penning et al. in J. Med. Chem. 2000, 43, 721.

Thus, another embodiment of the present invention comprises methods of preparing compounds of formulas XVI and XVII



XVI



XVII

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

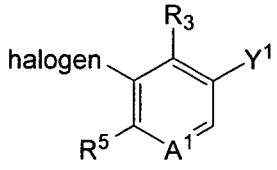
(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

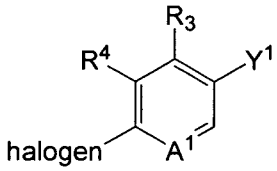
(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

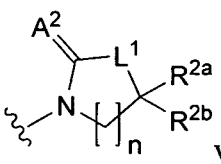
(3a) converting (R)- or (S)-2-methylpyrrolidine to the corresponding 2-methylpyrrolidinylalkyl-OH;

(3a) contacting a compound of formula



or





wherein Y1 is with either (R)- or (S)-2-methylpyrrolidinylalkyl-OH, for a time and under conditions sufficient to form the compound of formula XVI.

This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Exemplary compounds that can be prepared according to the methods of the invention include:

1-[3-(4-{4-[(2-methylpyrrolidin-1-yl)methyl]-1,3-oxazol-2-yl}phenoxy)propyl piperidine;

2-[(2-{4-[3-(2-methylpyrrolidin-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]-2-azaspiro[5.5]undecane;

4-[(2-methylpyrrolidin-1-yl)methyl]-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy] phenyl}-1,3-oxazole;

1-isopropyl-4-[3-(4-{4-[(2-methylpiperidin-1-yl)methyl]-1,3-oxazol-2-yl} phenoxy)propyl]piperazine;

4-methyl-1-[3-(4-{4-[(2-methylpyrrolidin-1-yl)methyl]-1,3-oxazol-2-yl}phenoxy)propyl]piperidine;

2-methyl-1-[3-(4-{4[(2-methylpyrrolidin-1-yl)methyl]-1,3-oxazol-2-yl}phenoxy)propylipiperidine;

4-[(2-methylpyrrolidin-1-yl)methyl]-2-(4-{3-[2-(pyrrolidin-1-yl)ethyl) pyrrolidin-1-yl]propoxy}phenyl)-1,3-oxazole;

1-cyclopentyl-4-[3-(4-{4-[(2-methylpyrrolidin-1-yl)methyl]-1,3 oxazol-2-yl}phenoxy)propylipiperazine;

N,N-dimethyl-1-[4-(4-{4-[(2-methylpyrrolidin-1-yl)methyl]-1,3-oxazol-2-yl}phenoxy)butyl]pyrrolidin-3-amine;

1-[2-(4-{4-[(2-methylpyrrolidin-1-yl)methyl]-1,3-oxazol-2-yl}phenoxy)ethyl]- 4-(2-pyrrolidin-1-ylethyl)piperazine;

2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]-[3-4-(2-oxo-2-pyrrolidin-1- ylethyl)-1,3-oxazole;

1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl]-1,3-oxazol-4-yl)methyl] pyrrolidin-2-one;

N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]-N-phenylamine;

2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]-[3-4-(2-pyrrolidin-1-ylethyl)-1,3-oxazole;

4-[(2-methyl-1H-imidazol-1-yl)methyl]-2-{4-[3-(2-methylpyrrolidin-yl)propoxy]phenyl}-1,3-oxazole;

1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]-1H-1,2,4-triazole;

1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl-1,3-oxazol-4-yl)methyl] piperidine;

1-[3-(4-[4-[(2-methylpyrrolidin-1-yl)methyl]-1,3-oxazo1-2-yl)phenoxy)propyl) azepane;

1-(3-{4-[4-methyl-5-(piperidin-1-yl)methyl)-1,3-oxazol-2-yl]phenoxy}propyl) piperidine;

(2R)-4-methyl-2-{[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]amino}pentan-1-ol;

N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl] cyclopentanamine;

1-[4-(4-{4-[(2-methylpyrrolidin-1-yl)methyl]-1,3-oxazol-2-yl}phenoxy)butyl]azepane;

1-[2-(4-{4-[(2-methylpyrrolidin-1-yl)methyl}-1,3-oxazol-2-yl}phenoxy) ethyl]azepane;

N-(1,3-dimethylbutyl)-N-[(2-{4-[3-(2-methylpyrroalin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]amine;

N-(cyclopropylmethyl)-N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]-N-propylamine;

1-[(2-{4-[2-(2-methylpyrrolidin-1-yl)ethoxy]phenyl}-1,3-oxazol-4-yl)methyl] piperidine;

2-methyl-1-[4-(4-{4-[(2-methylpyrrolidin-1-yl)methyl]-1,3-oxazol-2-yl} phenoxy) butyl]piperidine;

7,8-dimethyl-1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-thiazol-4-yl)methyl]-1-azaspiro[4.4]nonane;

N-(2-furylmethyl)-N-methyl-N-[(2-{4-[3-(2-methylpyrrodin-1-yl)propoxy] phenyl}-1,3-thiazol-4-yl)methyl]amine; N-(sec-butyl)-N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3- thiazol-4-yl)methyl]-N-propylamine;

1-[(2-[4-(3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-thiazol-4-yl)methyl]piperidine;

1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl acetyl]piperidine;

1-[2-(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)ethyl] piperidine;

2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-thiazole;

4-benzyl-1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]piperidine;

1-cyclopentyl-4-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3- oxazol-4-yl)methyllpiperazine;

4-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl) carbonyl]morpholine;

1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl) carbonyl]piperidine;

1-cyclopentyl-4-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)carbonyl]piperazine;

4-[(2-methylpyrrolidin-1-yl)methyl]-2-(4-{3-[(2S)-2-(pyrrolidin-1-ylmethyl) pyrrolidin1-yl]propoxy}phenyl)-1,3-oxazole;

1-[(2-{3-fluoro-4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol- 4-yl)methyl]piperidine;

1-[(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyll-1,3-oxazol- 5-yl)carbonyl]piperidine;

N-(cyclopropylmethyl)-4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy] -[3-N-propyl-1,3-oxazole-5-carboxamide;

N-cyclopentyl-4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}- 1,3-oxazole-5-carboxamide;

4-[(benzylamino)methyl]-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}- 1,3-oxazole-5-carboxylate;

4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-thiazole-5-carboxylate;

2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]-[3-4-(piperidin-1-ylmethyl)-1,3-oxazole-5-carboxylic acid;

N-(cyclopropylmethyl)-2-{4-[3-(2-methylpyrrolidin-l-yl)propoxy]-phenyl}-N-propyl-1,3-oxazole-4-carboxamide;

N-cyclopentyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazole-4-carboxamide;

N-(4-fluorobenzyl)-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazole-4-carboxamide;

N-benzyl-4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}- 1,3-oxazole-5-carboxamide;

1-cyclopentyl-4-[4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl)- 1,3-oxazol-5-yl)carbonyl]piperazine;

2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]-[3-4-(pyrrolidin-1-ylcarbonyl)-1,3-oxazo1e;

4-{(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol- 5-yl)carbonyl}morpholine;

4-{[4-methyl-2-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-1,3- oxazol-5-yl]carbonyl}morpholine;

4-{[4-methyl-2-(4-{3-[(2S)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-1,3- oxazol-5-yl]carbonyl}morpholine;

1-cyclopentyl-4-[(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl)-1,3-oxazol-5-yl)methyl]piperazine;

N-(cyclopropylmethyl)-N-[(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-5-yl)methyl]-N-propylamine;

N-benzyl-N-[(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxyiphenyll-1,3-oxazol5-yl)methyl]amine;

1-[(2-{3-methoxy-4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl-1,3-oxazol- 4-yl)methyl]piperidine;

N-(4-chlorobenzyl)-N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]amine;

N-{(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-5-yl)methyl]cyclopentanamine;

1-[(5-bromo-2-14-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol- 4-yl)methyl]piperidine;

1-{[2-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-1,3-oxazol-4-yl-methyl}piperidine;

1-{[2-(4-{3-[(2S)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-1 ,3-oxazol-4-yl)methyl]piperidine;

4-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]morpholine;

1-[2-(2-{4-[2-(2-methylpyrrolidin-1-yl)ethoxy]phenyl}-1,3-oxazol-4-yl)ethyl] piperidine;

1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl] piperidin-2-one;

(5S)-l-[(2-{4-[3-(2-methylpyrrolidlin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl) methyl]-5-(pyrrolidin-1-ylmethyl)pyrrolidin-2-one;

1-[(2-{3-chloro-4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]piperidine;

2-{3-bromo-4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyll-4-methyl-1,3-thiazole-5-carboxylate;

N-(4-fluorophenyl)-2-(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1, 3-oxazol-4-yl)acetamide; (4aR,8aS)-2-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]decahydroisoquinoline;

2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-4-{[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}-1,3-oxazole;

4-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1 ,3-oxazol-4-yl)acety]morpholine;

N-cyclopentyl-2-(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)acetamide;

N-(cyclopropylmethyl)-2-(2-(4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)-N-propylacetamide;

1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)-acetyl]azepane;

(5S)-1-[(2-{ 4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl)-1,3-oxazol-4-yl) methyl]-5-(morpholin-4-ylmethyl)pyrrolidin-2-one;

2-methyl-N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]-2H-tetraazol-5-amine;

N-(3-methoxyphenyl)-N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}- 1,3-oxazol-4-yl)methyl]amine;

N-(4-fluorophenyl)-N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol4-yl)methyl]amine;

N-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methylpyridin-3-amine;

4-[(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-5-yl)methyl]morpholine;

4-({(2S)-1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1 ,3-oxazol-4-yl)methyl]pyrrolidin-2-yl}methyl)morpholine;

1-[(2-{2-fluoro-4-{3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]piperidine;

4,4-difluoro-1-[(2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazol-4-yl)methyl]piperidine;

4-[(4-methyl-2-{6-[3-(2-methylpyrrolidin-1-yl)propoxy]pyridin-3-yl}-1,3- thiazol-5-yl)carbonyl}morpholine;

1-(2-{3 ,5-difluoro-4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyll-1,3-oxazol-4-yl)methyl]piperidine;

4,4-difluoro-1-{(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}- 1,3-thiazol-5-yl)earbonyl]piperidine;

4,4-difluoro-1-{{4-methyl-2-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy} phenyl)-1,3-thiazol-5-ylicarbonyl]piperidine;

4,4-difluoro-1-{[4-methyl-2-(4-{3-[(2S)-2-methylpyrrolidin-1-yl]propoxy] phenyl)-1,3-thiazol-5-yl}carbonyl)piperidine;

4-[(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-thiazol-5-yl)carbonyl]morpholine;

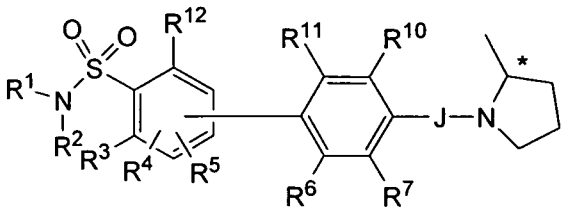
4-{[4-methyl-2-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-1,3- thiazol-5 yl]carbonyl}morpholine;

4-{[methyl-2-(4-{3-[(2S)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-1,3- thiazol-5-yl]carbonyl}morpholine;

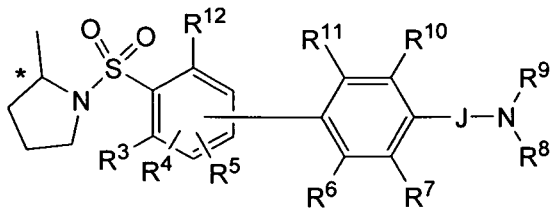
1-[(2-{2-methyl-4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-oxazo1-4-yl)methyl]piperidine; and

1-[(4-methyl-2-{4-[3-(2-methylpyrrolidin-1-yl)propoxy]phenyl}-1,3-thiazol-5-yl)methyl]pyrrolidin-2-one.

Compounds of formulas XVIII and XIX, as described in WO 2008/005338, can also be more readily prepared using the methods of the present invention:



XVIII



XIX

* = α or β

and the pharmaceutically acceptable salts thereof;

wherein

$R^1$ and $R^2$ are each selected independently from the group consisting of H, $C_{1-6}$ acyl, $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, aryl-$C_{1-4}$-alkylenyl, aryloxy-$C_{1-4}$-alkylenyl, heteroaryl-$C_{1-4}$-alkylenyl and heteroaryloxy-$C_{1-4}$-alkylenyl, and each $R^1$ and $R^2$ is optionally substituted with 1,2,3,4 or 5 substituents selected independently from the group consisting of $C_{1-6}$ acyl, $C_{1-6}$ acyloxy, $C_{2-8}$ alkenyl, $C_{1-6}$ alkoxy, $C_{1-8}$ alkyl, $C_{1-8}$ alkylcarboxanide, $C_{2-8}$ alkynyl, $C_{1-8}$ alkylsulfonamide, $C_{1-8}$alkylsulfinyl, $C_{1-8}$alkylsulfonyl, $C_{1-8}$ alkylthio, $C_{1-8}$alkylureyl, amino, aryl, $C_{1-8}$alkylamino, $C_{2-8}$dialkylamino, carbo-$C_{1-6}$-alkoxy, carboxamide, carboxy, cyano, $C_{3-7}$cycloalkyl, $C_{2-8}$ dialkylcarboxamide, $C_{2-8}$ dialkylsulfonamide, halogen, $C_{1-6}$ haloalkoxy, $C_{1-6}$ haloalkyl, $C_{1-6}$haloalkylsulfinyl, $C_{1-6}$haloalkylsulfonyl, $C_{1-6}$haloalkylthio, heterocyclyl, hydroxyl, thiol, nitro and sulfonamide; wherein each $C_{1-8}$ alkyl may be further substituted with hydroxyl;

substituted with hydroxy;

J is $-CH_2CH_2-$ or a 1 ,2-$C_{3-7}$-cycloalkylenyl group, each optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of $C_{1-3}$ alkyl, $C_{1-4}$alkoxy, carboxy, cyano, $C_{1-3}$ haloalkyl, halogen, hydroxyl and oxo;

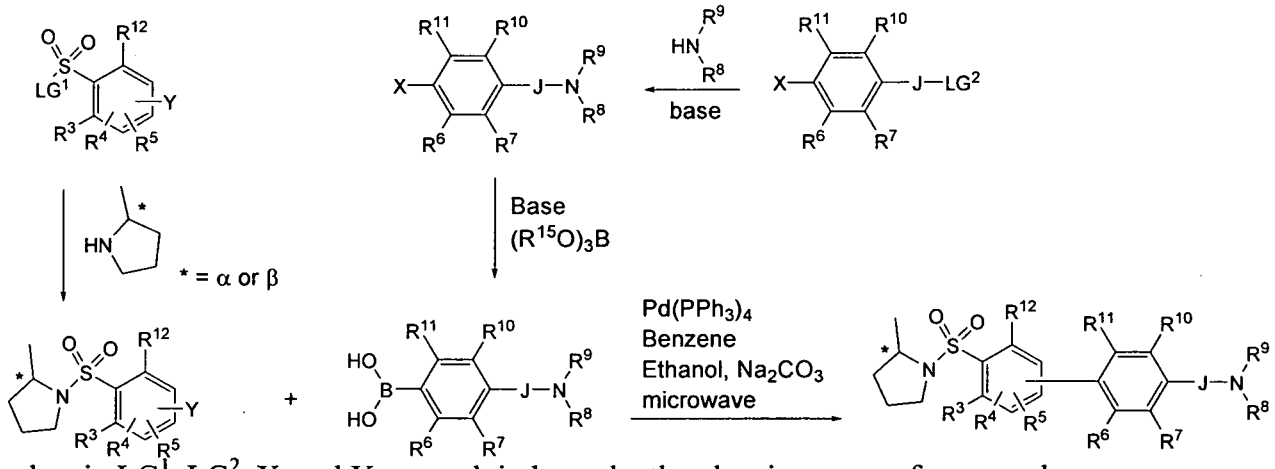
$R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^{10}$, $R^{11}$, and $R^{12}$ are each selected independently from the group consisting of H, $C_{1-6}$ acyl, $C_{1-6}$ acyloxy, $C_{2-8}$ alkenyl, $C_{1-6}$ alkoxy, $C_{1-8}$ alkyl, $C_{1-8}$ alkylcarboxamide, $C_{2-8}$ alkynyl, $C_{1-8}$ alkylsulfonamide, $C_{1-8}$ alkylsulfinyl, $C_{1-8}$alkylsulfonyl, $C_{1-8}$ alkylthio, $C_{1-8}$ alkylureyl, amino, $C_{1-8}$ alkylamino, $C_{2-8}$dialkylamino, carbo-$C_{1-6}$-alkoxy, carboxamide, carboxy, cyano, $C_{3-7}$ cycloalkyl, C2-8 dialkylcarboxamide,$C_{2-8}$ dialkylsulfonamide, halogen, $C_{1-6}$ haloalkoxy, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkylsulfinyl, $C_{1-6}$ haloalkylsulfonyl, $C_{1-6}$ haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;

and

$R^8$ and $R^9$ are each selected independently from the group consisting of H, $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, aryl-$C_{1-4}$-alkylenyl, aryloxy-$C_{1-4}$alkylenyl, heteroaryl-$C_{1-4}$-alkylenyl and heteroaryloxy-$C_{1-4}$-alkylenyl, and each $R^8$ and $R^9$ is optionally substituted with 1, 2, 3,4, or 5 substituents selected independently from the group consisting of $C_{1-6}$ acyl, $C_{1-6}$ acyloxy, $C_{2-8}$ alkenyl, $C_{1-6}$alkoxy, $C_{1-8}$ alkyl, $C_{1-8}$ alkylcarboxamide, $C_{2-8}$ alkynyl, $C_{1-8}$ alkylsulfonamide, $C_{1-8}$alkylsulfinyl, $C_{1-8}$ alkylsulfonyl, $C_{1-8}$ alkylthio, $C_{1-8}$ alkylureyl, amino, $C_{1-8}$ alkylamino, $C_{2-8}$ dialkylamino, carbo-$C_{1-6}$-alkoxy, carboxamide, carboxy, cyano, $C_{3-7}$ cycloalkyl, $C_{2-8}$dialkylcarboxamide, $C_{2-8}$ dialkylsulfonamide, halogen, $C_{1-6}$ haloalkoxy, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkylsulfinyl, $C_{1-6}$ haloalkylsulfonyl, $C_{1-6}$ haloalkylthio, hydroxyl, thiol, nitro and sulfonamide;

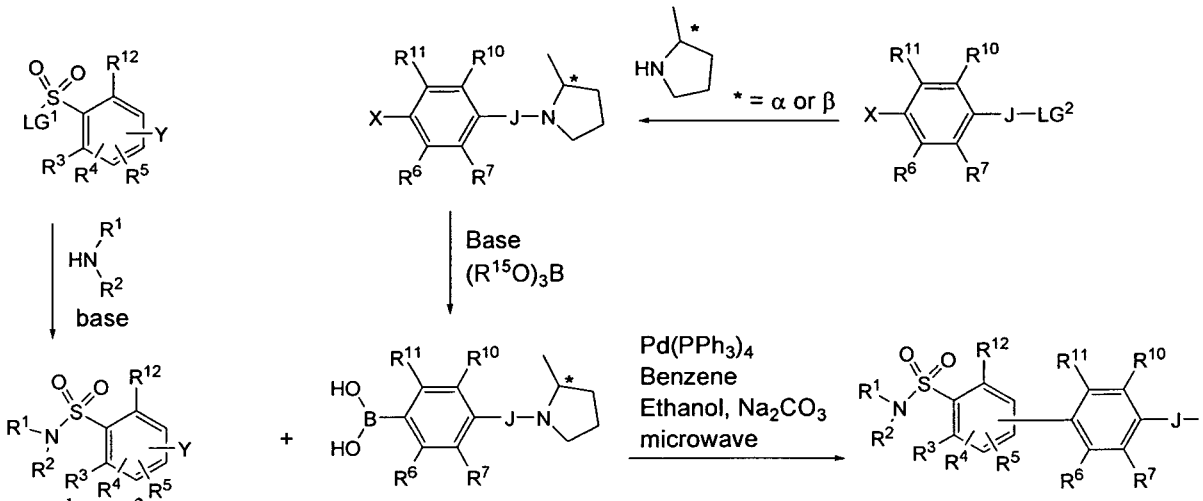
The methods of the present invention of preparing (R) and (S) 2-methylpyrrolidine can be used to more readily prepare the above mentioned compounds. (R)- or (S)-2-methylpyrrolidine can be prepared in accordance with the present invention and reacting the (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine or (*S*)-2-methylpyrrolidine D-tartrate with a base to provide (*S*)-2-methylpyrrolidine. The following schemes demonstrate the use of the so prepared 2-methylpyrrolidine.

SCHEME 23



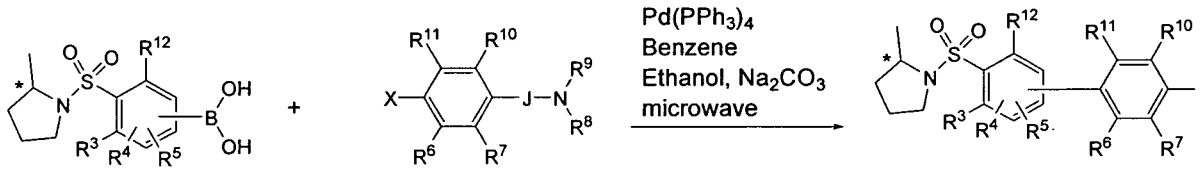

wherein $LG^1$, $LG^2$, X, and Y are each independently a leaving group, for example, halogen, triflate and the like and $R^{15}$ is $C_{1-8}$alkyl.

SCHEME 24



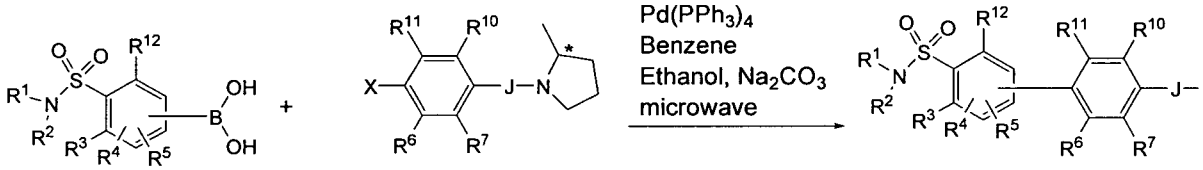

wherein $LG^1$, $LG^2$, X, and Y are each independently a leaving group, for example, halogen, triflate and the like and $R^{15}$ is $C_{1-8}$alkyl.

SCHEME 25



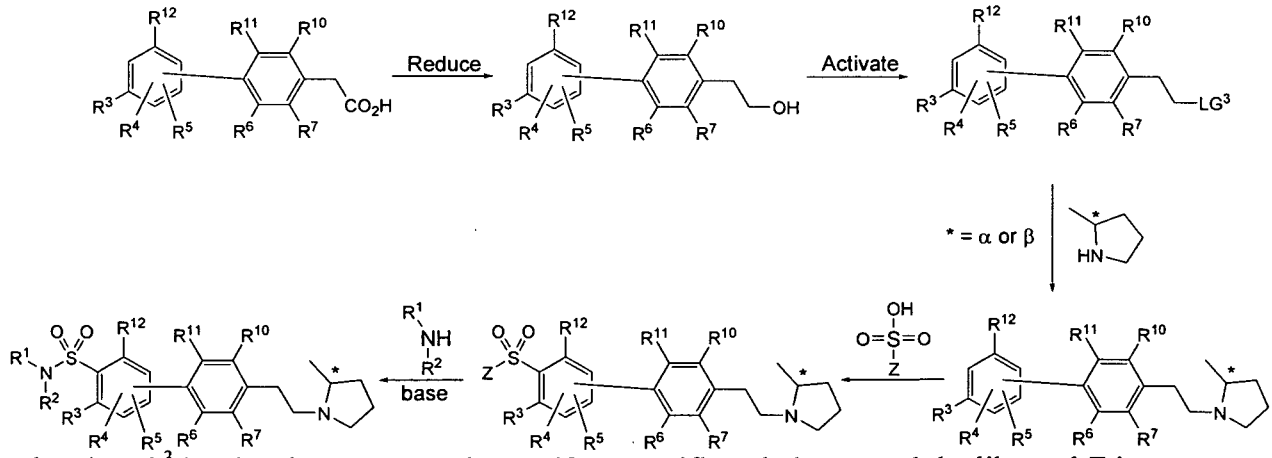

wherein X is a leaving group, for example halogen, triflate and the like.

SCHEME 26



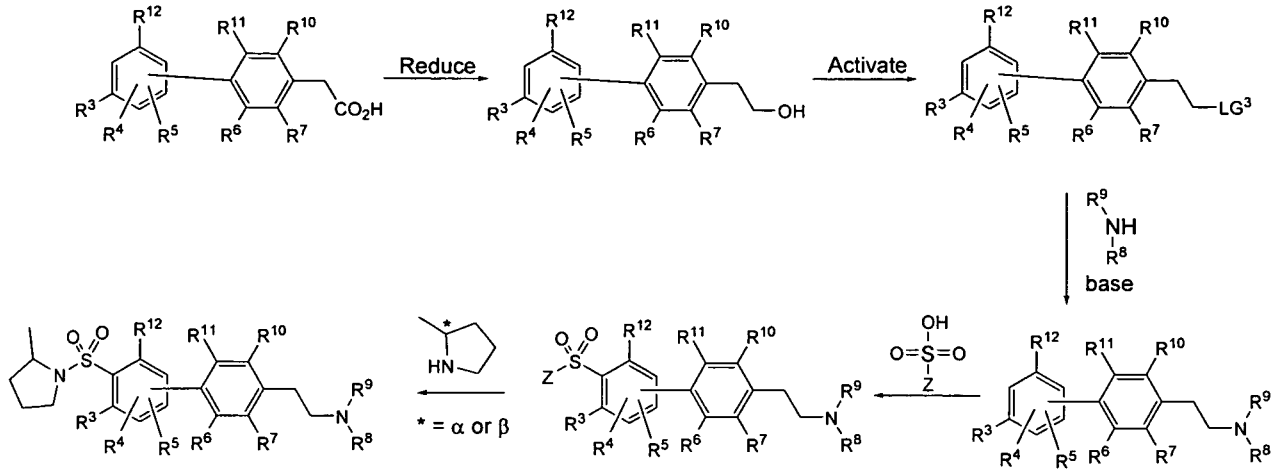

wherein X is a leaving group, for example halogen, triflate and the like.

SCHEME 27



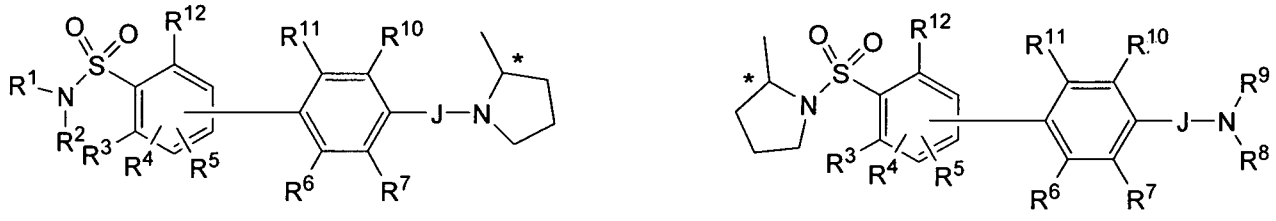

wherein $LG^3$ is a leaving group such as sulfonate, triflate, halogen and the like and Z is halogen.

SCHEME 28




wherein $LG^3$ is a leaving group such as sulfonate, triflate, halogen and the like and Z is halogen.

Thus, another embodiment of the present invention comprises methods of preparing compounds of formulas XVIII and XIX:




XVIII XIX

wherein the variables are as set forth above, comprising:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid or D-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(2a) contacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base or contacting the (S)-2-methylpyrrolidine D-tartrate with a base for form (S)-2-methylpyrrolidine;

(3a) converting (R)- or (S)-2-methylpyrrolidine the compound of formula XVIII or XIX.

This method may optionally further include the steps of:

(1f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate;

(1g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate or (S)-2-methylpyrrolidine D-tartrate; and

(1h) optionally repeating steps (f) and (g).

Exemplary compounds that can be prepared according to the methods of the invention include:

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid (tetrahydropyran-4-yl)-amide;

2-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-2,3-dihydro-1*H*-isoindole;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid (pyridin-2-ylmethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid 4-methyl-benzylamide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid (2-ethoxy-ethyl)-amide;

4-{4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonyl}-thiomorpholine 1,1-dioxide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid (2-isopropoxy-ethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]biphenyl-4-sulfonic acid (2-phenoxy-ethyl)-amide;

4'-[2-(2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid 4-methoxy-benzylamide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid cyclohexylamide;

2-methyl-1-{2-[4'-(pyrrolidine-l-sulfonyl)-biphenyl-4-yl]-ethyl}-pyrrolidine;

2-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid benzyl-ethyl-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid 4-trifluoromethyl-

benzylamide;

1-{2-[4'-(azetidine-l-sulfonyl)-biphenyl-4-yl]-ethyl}-2-methyl-pyrrolidine;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid cyclobutylamide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid tert-butylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid propylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid isopropylamide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid methylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (2-methoxy-ethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (4-fluoro-phenyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid 4-fluoro-benzylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid 4-chloro-benzylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (2-hydroxy-ethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid diethylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (1-propyl-butyl)-amide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid cyclohexylmethyl-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulionic acid benzylamide;

4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonic acid phenylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid cyclopropylmethyl-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid cyclopentylamide;

4-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-morpholine;

1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid amide;

4'-[2-(2-methyl-pyrrolidin-1-y1)-ethyl]-biphenyl-4-sulfonic acid cyclopropylamide;

4'-[2-(2-methyl-pyrrolidin-1-y1)-ethyl]-biphenyl-4-sulfonic acid ethylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyli-biphenyl-4-sulfonic acid (2-methoxy-1-methyl-ethyl)-amide;

1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-pyrrolidin-3-ol;

(1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidin-3-yl)-methanol;

1-{2-[4'-(aziridine-1-sulfonyl)-biphenyl-4-yl]-ethyl}-2-methyl-pyrrolidine;

2-(methoxymethyl)-1-(4'-(2-(2-methylpyrrolidin-1-3,1)ethyl)biphenyl-4-ylsulfonyl)pyrrolidine;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (2-methoxy-ethyl)-methyl-amide;

1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidin-3-ol;

propionic acid 1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidin-4-yl ester;

4'-(2-pyrrolidin-l-yl-ethyl)-biphenyl-4-sulfonic acid ethylamide;

(1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-pyrrolidin-2-yl)-methanol;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid benzyl-(2-hydroxy-ethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid 3,5-dichloro-benzylamide;

4'-{2-(2-methyl-pyrrolidin-1 -yl)-ethyl]-biphenyl-4-sulfonic acid acetyl-(2-hydroxy-ethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid 3,4-dichloro-benzylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (2-hydroxy-1-methyl-ethyl)-amide;

propionic acid 2-(1-(4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidin-4-yl)-ethyl ester;

1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine-4-carboxylic acid benzyl ester;

acetic acid 2-(acetyl-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-

sulfonyl}-amino)-ethyl ester;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid [2-(4-fluoro-phenyl)-ethyl]-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (tetrahydro-pyran-4-ylmethyl)-amide;

propionic acid 1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidin-4-yl methyl ester;

propionic acid 2-(methyl-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-amino)-ethyl ester;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (2-methoxyethyl)-(tetrahydro-pyran-4-ylmethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid benzhydrylamide;

2-methyl-7-{4-[2-(2-methyl-pyrrolidin-1-yl)-ethyl)-phenyl}-3,4-dihydro-*2H*-benzo[b][1,4,5]oxathiazepine 1,1-dioxide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;

propionic acid 1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-pyrrolidin-2-ylmethyl ester;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid isobutyl-(2-methoxy-ethyl)-amide;

7-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]phenyl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl]-sulfonic acid (2-hydroxy-ethyl)-methyl-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid bis-(2-hydroxy-ethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl] -biphenyl-4-sulfonic acid isopropyl-(2-methoxy-ethyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (2-hydroxyethyl)-isopropyl-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (3 -phenylpropyl)-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid benzyl-(2-methoxy-ethyl)-amide;

3-methoxymethyl-1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid phenethylamide;

(1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidin-4- yl)-methanol;

1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine-4-carboxylic acid ethyl ester;

4-(2-ethoxy-ethyl)-1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine;

1-(4-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperazin-1-yl)-propan-1-one;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl)-biphenyl-4-sulfonic acid (pyridin-4-ylmethyl)-amide;

3-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonylaminol-propionic acid methyl ester;

4-ethoxymethyl-1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine;

(1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyli-biphenyl-4-sulfonyl)-piperidin-3-yl)-methanol;

3-methoxy-1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (pyridin-3-ylmethyl)-amide;

2-(1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidin-4-yl)-ethanol;

2- {4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonylamino}-propionic acid methyl ester;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid (1-hydroxymethyl-cyclopentyl)-amide;

(1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidin-2- yl)-

methanol;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid 4-trifluoromethoxy-benzylamide;

4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonic acid bis-(2-methoxy-ethyl)-amide;

{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonylamino)-acetic acid methyl ester;

2-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonylarnino}-propionic acid isopropyl ester;

1-{4'-{2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-pyrrolidine-2-carboxylic acid;

6,7-dimethoxy-2-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-su1fonyl}-1,2,3,4-tetrahydro-isoquinoline;

4-methoxy-1-{"2-(2-methyl-pyrrolidin-l-yl)-ethyli-biphenyl-4-sulfonyl}-piperidine;

4-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl)-piperazin-2- one;

{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyli-biphenyl-4-sulfonylamino}-acetic acid isopropyl ester;

1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyll -pyrrolidine-2-carboxylic acid methylamide;

3,5-dimethyl-4-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl)-morpholine;

propionic acid 1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl-pyrrolidin-3-yl ester;

1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl)-biphenyl-4-sulfonyl}-piperidin-4-ol;.

propionic acid 2-methyl-2-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonylamino}-propyl ester;

2-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonylamino)-propionic acid tert-butyl ester;

1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine-4-carboxylic acid;

{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonylamino}-acetic acid tert-butyl ester;

4-hydroxy-1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-

pyrrolidine-2-carboxylic acid methyl ester;

4-(2-methoxy-ethyl)-1-{4'-[2-(2-methyl-pyrrolidin-l-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine; and

4-methoxymethyl-1-{4'-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-biphenyl-4-sulfonyl}-piperidine.

## EXAMPLES

### Methodology and Protocols

Determination of chiral purity of (R)-2-methylpyrrolidine by Gas Chromatography (GC)

| | |
|---|---|
| Column | Chiraldex B-DA, 30m × 0.25mm, 0.25μm df (mfr: Astec – Advanced Separation Technologies, Inc.) or equivalent |
| Injector temperature | 150°C |
| Split ratio | 40:1 |
| Carrier Gas | He, constant pressure at 8 psi |
| Injection volume | 2 μL |
| Detection | FID at 250°C |
| Flow | Hydrogen at 30 mL/min |
| | Air at 400 mL/min |
| Makeup gas | Helium at 30 mL/min |
| Oven program | 110°C isothermal for 25 minutes |
| Sample preparation | Add trifluoroacetic anhydride (200 μL) to sample (10 mg) in dichloromethane (1 mL). |
| | React at 60°C for 15 minutes. Remove solvent under gentle nitrogen stream and add dichloromethane (1 mL) to residue. |
| System suitability | resolution between enantiomers should be ≥ 1.2 |
| Retention times | (R)-2-methylpyrrolidine = 11 minutes |
| | (S)-2-methylpyrrolidine = 11.5 minutes |

**Example 1** Synthesis of (*R*)-2-methylpyrrolidine L-tartrate using 5% Pt-C

2-Methylpyrroline (2.50 g, 30.12 mmol) was hydrogenated at 55 psi at ambient temperature for 16 hours in a mixture of 5% Pt-C (250 mg, catalytic), absolute ethanol (62 mL) and methanol (26 mL). Gas chromatographic analysis showed a 93.7% conversion of starting material to product. The mixture was filtered through Celite® (4 g) and the filtrate placed in a 250 mL, single-neck round bottom flask with stir bar along with L-tartaric acid (3.80 g, 25.32 mmol). The mixture was heated to 25°C until a solution was obtained. Authentic (R)-2-methylpyrrolidine L-tartrate (10.0 mg) was added as seed crystals and the mixture stirred at ambient temperature for 16 hours. The mixture was cooled to 0°C using an ice bath and was stirred for an additional 2 hours. Solids were filtered and then air-dried for 1 hour to provide (R)-2-methylpyrrolidine L-tartrate (3.55 g, 15.09 mmol, 50.1%). Chiral gas chromatographic analysis showed 55% ee, 93% overall purity.

**Example 2** Synthesis of (*R*)-2-methylpyrrolidine L-tartrate using Pt(IV) oxide

2-Methylpyrroline (2.50 g, 30.12 mmol) was hydrogenated at 55 psi at ambient temperature for 5 hours in a mixture of platinum (IV) oxide (250 mg, catalytic), absolute ethanol (62 mL) and methanol (26 mL). Gas chromatographic analysis showed a 98.3% conversion of starting material to product. The mixture was filtered through Celite® (4 g) and the filtrate placed in a 250 mL, single-neck round bottom flask with stir bar along with L-tartaric acid (3.80 g, 25.32 mmol). The mixture was heated to 25°C until a solution was obtained. Authentic (R)-2-methylpyrrolidine L-tartrate (100.0 mg) was added as seed crystals and the mixture stirred at 25°C for 8 hours. The mixture was allowed to cool to ambient temperature and was stirred an additional 16 hours. The mixture was cooled to 0°C using an ice bath and was stirred for an additional 2 hours. Solids were filtered, washed with methanol (5 mL), and then air-dried for 1 hour to provide (R)-2-methylpyrrolidine L-tartrate (2.85 g, 12.12 mmol, 40.3%). Chiral gas chromatographic analysis showed 49.2% ee, 75% overall purity.

**Example 3** Recrystallization of (*R*)-2-methylpyrrolidine L-tartrate

General Recrystallization Procedure: A portion of the product obtained in Example 1 (2.71 g) was placed in a 100 mL, single-neck round bottom flask with stir bar along with absolute ethanol (38 mL) and methanol (16 mL). The mixture was heated to 60°C to form a solution and then allowed to cool to ambient temperature. Authentic (R)-2-methylpyrrolidine L-tartrate (2.50 mg) was added as seed crystals and the mixture was

stirred at ambient temperature for 16 hours, and then at 0°C (ice bath) for 2 more hours. Solids were filtered and dried at 60°C in a vacuum oven with a stream of nitrogen at 29 in. Hg for 1 hour to provide (R)-2-methylpyrrolidine L-tartrate (1.80 g, 66.4% recovery). Chiral gas chromatographic analysis showed 84.9% ee, 93% overall purity.

The obtained solids (1.79 g) were further resolved according to the General Recrystallization Procedure using 25 mL absolute ethanol and 11 mL methanol to provide (R)-2-methylpyrrolidine L-tartrate (1.70 g, 95.5% recovery). Chiral gas chromatographic analysis showed 93.4% ee, 97% overall purity.

The obtained solids (1.69 g) were further resolved according to the General Recrystallization Procedure using 24 mL of absolute ethanol and 10 mL of methanol to provide (R)-2-methylpyrrolidine L-tartrate (1.58 g, 93.5% recovery). Chiral gas chromatographic analysis showed 96.7% ee, 98% overall purity.

The obtained solids (1.57 g) were further resolved according to the General Recrystallization Procedure using 22.5 mL of absolute ethanol and 9.5 mL of methanol, except that no seeding was performed and the obtained crystals were dried for 4 hours, to provide (R)-2-methylpyrrolidine L-tartrate (1.49 g, 94.9% recovery, 6.334 mmol, 21.0% overall yield from 2-methylpyrroline). Chiral gas chromatographic analysis showed 98.4% ee, 99% overall purity.

As those skilled in the art will appreciate, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein, and the scope of the invention is intended to encompass all such variations.

**WHAT IS CLAIMED IS:**

1. A process for preparing (*R*)-2-methylpyrrolidine L-tartrate, comprising the steps of:
   (a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;
   (b) optionally removing the hydrogenation catalyst from the mixture;
   (c) dissolving L-tartaric acid in the mixture to form a solution;
   (d) crystallizing (*R*)-2-methylpyrrolidine L-tartrate from the solution; and
   (e) isolating the crystalline (*R*)-2-methylpyrrolidine L-tartrate.

2. The process of claim 1, wherein the hydrogenation catalyst is a platinum catalyst.

3. The process of claim 2, wherein the platinum catalyst is 5% Pt-C.

4. The process of claim 2, wherein the platinum catalyst is platinum (IV) oxide.

5. The process of any of claims 1-4, wherein the alcohol solvent is a mixture of ethanol and methanol.

6. The process of claim 5, wherein the alcohol solvent is a mixture of ethanol and methanol at a ratio of about 2:1 to about 3:1 (v/v).

7. The process of any of claims 1-6, wherein step (a) is performed at ambient temperature.

8. The process of any of claims 2-4, wherein the platinum catalyst is removed in step (b) by filtration.

9. The process of any of claims 1-8, wherein the isolated (*R*)-2-methylpyrrolidine L-tartrate has an optical purity of at least 50% ee.

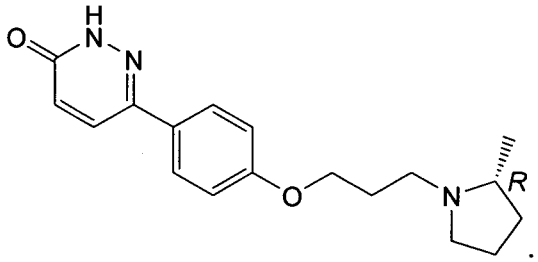
10. The process of any of claims 1-9, further comprising the steps of:
    (f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate;
    (g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate; and
    (h) optionally repeating steps (f) and (g).

11. The process of claim 10, further comprising the step of reacting the isolated recrystallized (*R*)-2-methylpyrrolidine L-tartrate with a base to provide (*R*)-2-methylpyrrolidine.

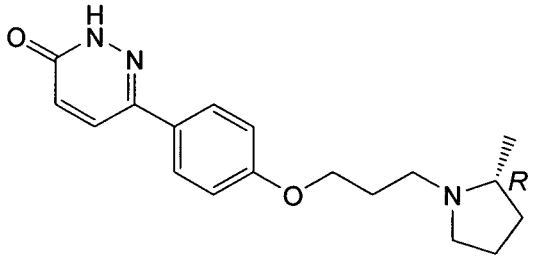
12. The process of any of claims 1-9, further comprising the step of converting the prepared (*R*)-2-methylpyrrolidine L-tartrate into an $H_3$ receptor ligand.

13. The process of claims 10 or 11, further comprising the step of converting the prepared (*R*)-2-methylpyrrolidine L-tartrate into an $H_3$ receptor ligand.

14. The process of claim 12 or 13, wherein the $H_3$ receptor ligand is 6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one:



15. A process for preparing 6-{4-[3-((R)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one:



comprising the steps of:

(1a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(1b) optionally removing the hydrogenation catalyst from the mixture;

(1c) dissolving L-tartaric acid in the mixture to form a solution;

(1d) crystallizing (R)-2-methylpyrrolidine L-tartrate from the solution;

(1e) isolating the crystalline (R)-2-methylpyrrolidine L-tartrate; and

(2) reacting the (R)-2-methylpyrrolidine L-tartrate with a base to form (R)-2-methylpyrrolidine free base; and

(3) reacting the (R)-2-methylpyrrolidine with 6-[4-(3-halo-propoxy)-phenyl]-2H-pyridazin-3-one for a time and under conditions sufficient to form (R)-6-{4-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2H-pyridazin-3-one.

16. The process of claim 15, wherein the 6-[4-(3-halo-propoxy)-phenyl]-2H-pyridazin-3-one is prepared by the steps of:

(a) contacting 1-(4-hydroxy-phenyl)-ethanone with 1,3-dihalopropane, for a time and under conditions sufficient to form 1-[4-(3-halo-propoxy)-phenyl]-ethanone; and

(b) contacting the 1-[4-(3-halo-propoxy)-phenyl]-ethanone with glyoxalic acid for a time and under conditions sufficient to produce 6-[4-(3-halo-propoxy)-phenyl]-2H-pyridazin-3-one.

17. The process of claim 15, further comprising the steps of:

(f) recrystallizing the isolated (*R*)-2-methylpyrrolidine L-tartrate;

(g) isolating the recrystallized (*R*)-2-methylpyrrolidine L-tartrate; and

(h) optionally repeating steps (f) and (g).

18. A process for preparing (*S*)-2-methylpyrrolidine D-tartrate, comprising the steps of:

(a) hydrogenating 2-methylpyrroline in a mixture comprising an alcohol solvent and a hydrogenation catalyst;

(b) optionally removing the hydrogenation catalyst from the mixture;

(c) dissolving D-tartaric acid in the mixture to form a solution;

(d) crystallizing (*S*)-2-methylpyrrolidine D-tartrate from the solution; and

(e) isolating the crystalline (*S*)-2-methylpyrrolidine D-tartrate.

19. The process of claim 18, wherein the hydrogenation catalyst is a platinum catalyst.

20. The process of claim 19, wherein the platinum catalyst is 5% Pt-C.

21. The process of claim 20, wherein the platinum catalyst is platinum (IV) oxide.

22. The process of any of claims 18-21, wherein the alcohol solvent is a mixture of ethanol and methanol.