PROCESSES FOR THE PREPARATION OF 8-CHLORO-1-METHYL-2,3,4,5-TETRAHYDRO-1H-3-BENZAZEPINE AND INTERMEDIATES RELATED THERETO

FIELD OF THE INVENTION

The present invention provides processes, methods and intermediates for the preparation of 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, salts, hydrates and crystal forms thereof which are useful as serotonin (5-HT) receptor agonists for the treatment of, for example, central nervous system disorders such as obesity.

BACKGROUND OF THE INVENTION

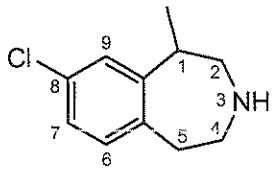
Serotonin (5-HT) neurotransmission plays an important role in numerous physiological processes both in health and in psychiatric disorders. For example, 5-HT has been implicated in the regulation of feeding behavior. 5-HT is believed to work by inducing a feeling of fullness or satiety so eating stops earlier and fewer calories are consumed. It has been shown that a stimulatory action of 5-HT on the $5HT_{2C}$ receptor plays an important role in the control of eating and in the anti-obesity effect of d-fenfluramine. As the $5\text{-}HT_{2C}$ receptor is expressed in high density in the brain (notably in the limbic structures, extrapyramidal pathways, thalamus and hypothalamus i.e. PVN and DMH, and predominantly in the choroid plexus) and is expressed in low density or is absent in peripheral tissues, a selective $5\text{-}HT_{2C}$ receptor agonist can be a more effective and safe anti-obesity agent. Also, $5\text{-}HT_{2C}$ knockout mice are overweight with cognitive impairment and susceptibility to seizure. Thus, the $5HT_{2C}$ receptor is recognized as a well-accepted receptor target for the treatment of obesity, psychiatric, and other disorders.

In view of the growing demand for compounds for the treatment of disorders related to the $5\text{-}HT_{2C}$ receptor, new and more efficient routes to 3-benzazepines are needed. The processes and compounds described herein help meet these and other needs.

SUMMARY ~~OF THE INVENTION~~

The processes and intermediates of the present ~~invention~~disclosure are useful in the preparation of therapeutic agents for the treatment or prophylaxis of 5-HT mediated disorders such as obesity and other central nervous system diseases.

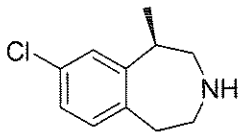
The present ~~invention~~disclosure provides, *inter alia*, processes and intermediates for preparing 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine having Formula (**I**), salts and crystal form thereof:



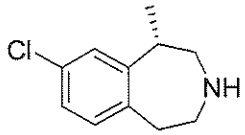
(I)

In some embodiments, the compound of Formula (**I**) is the R enantiomer.

In one aspect, there is provided a method of resolving a mixture of compounds of Formula (**Ia**) and (**Ib**):



(Ia)



(Ib)

comprising:

contacting said mixture of compounds with L-(−)-tartaric acid in the presence of a solvent comprising acetone to form L-(+)-tartaric acid salts of said compounds; and

precipitating the L-(+)-tartaric acid salt of said compound of Formula (**Ia**), wherein the L(+)-tartaric acid salt of said compound of Formula (**Ia**) has an enantiomeric excess of about 90% or greater.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

The processes and intermediates of the present invention are useful in the preparation of the therapeutic agents of Formula (**I**), salts and crystal form thereof. Compounds of Formula (**I**) are useful for the treatment or prophylaxis of 5-HT associated disorders such as obesity and other central nervous system diseases.

In some embodiments, [2-(4-chloro-phenyl)-ethyl]-(2-chloro-propyl)-ammonium chloride is the starting material for the preparation of 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, HCl salts and a crystal form thereof.

Certain processes for the preparation of Compounds of Formula (**I**) and salts thereof are disclosed in PCT Patent Publication, WO2005/019179. One particular process has been disclosed for the preparation of a certain crystal form of the Compound of Formula (**Ia**) in PCT Patent Publication, WO2006/069363.

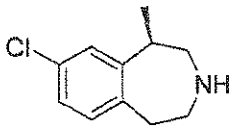
Several improvements have now been discovered for the processes useful in the preparation of Compounds of Formula (**I**), salts and crystal form thereof. These improvements are described herein.

Conversion of commercially available compound, 2-(4'-chlorophenyl)ethanol to [2-(4-chloro-phenyl)-ethyl]-(2-chloro-propyl)-ammonium chloride (Stages 1 to 3):

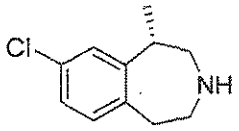
In some embodiments, [2-(4-chloro-phenyl)-ethyl]-(2-chloro-propyl)-ammonium chloride can be prepared in three stages from the commercially available compound, 2-(4'-chlorophenyl)ethanol, according to the process depicted in Synthetic Scheme 1.1.

What is claimed is:

1. A method of resolving a mixture of compounds of Formula (**Ia**) and (**Ib**):



(**Ia**)



(**Ib**)

comprising:

contacting said mixture of compounds with L-(+)-tartaric acid in the presence of a solvent comprising acetone to form L-(+)-tartaric acid salts of said compounds;

precipitating said L-(+)-tartaric acid salts of said compounds, wherein the resulting precipitate is enriched with the L-(+)-tartaric acid salt of said compound of Formula (**Ia**);

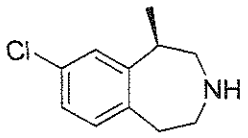
dissolving said precipitate in a solution comprising acetone and water at a temperature of about 45°C to about 60°C to form a solution containing the dissolved precipitate;

cooling said solution containing the dissolved precipitate to a temperature of about -5°C to about 10°C; and

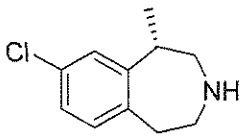
precipitating a second precipitate containing the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) with an enantiomeric excess of about 98% or greater.

What is claimed is:

1. A method of resolving a mixture of compounds of Formula (**Ia**) and (**Ib**):



(**Ia**)



(**Ib**)

comprising:

contacting said mixture of compounds with L-(+)-tartaric acid in the presence of a solvent comprising acetone to form L-(+)-tartaric acid salts of said compounds; and

precipitating the L-(+)-tartaric acid salt of said compound of Formula (**Ia**), wherein the L(+)-tartaric acid salt of said compound of Formula (**Ia**) has an enantiomeric excess of about 90% or greater.

2. The method according to claim 1, wherein the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has a chiral purity of greater than 98.0% enantiomeric excess.

3. The method according to claim 1, wherein the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has a chiral purity of greater than 99.0% enantiomeric excess.

4. The method according to claim 1, further comprising recrystallizing the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) from acetone and water.

5. The method according to claim 4, wherein the recrystallized L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has a chiral purity of greater than 98.0% enantiomeric excess.

6. The method according to claim 4, wherein the recrystallized L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has a chiral purity of greater than 99.0% enantiomeric excess.

7. The method according to claim 1, comprising:

dissolving a mixture of the L-(+)-tartaric acid salts of said compounds of Formula (**Ia**) and (**Ib**), wherein the mixture is enriched with the L-(+)-tartaric acid salt of said compound of Formula (**Ia**), in a solution comprising acetone and water at a temperature of about 45°C to about 60°C to form a solution;

cooling said solution to a temperature of about -5°C to about 10°C; and

precipitating the L-(+)-tartaric acid salt of said compound of Formula (**Ia**), wherein the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has an enantiomeric excess of about 90% or greater.

8. The method according to claim 7, wherein the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has a chiral purity of greater than 98.0% enantiomeric excess.

9. The method according to claim 7, wherein the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has a chiral purity of greater than 99.0% enantiomeric excess.

10. The method according to claim 7, further comprising recrystallizing the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) from acetone and water.

11. The method according to claim 10, wherein the recrystallized L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has a chiral purity of greater than 98.0% enantiomeric excess.

12. The method according to claim 10, wherein the recrystallized L-(+)-tartaric acid salt of said compound of Formula (**Ia**) has a chiral purity of greater than 99.0% enantiomeric excess.

13. The method according to claim 1, comprising:

contacting said mixture of compounds with L-(+)-tartaric acid in the presence of a solvent comprising acetone to form L-(+)-tartaric acid salts of said compounds;

precipitating said L-(+)-tartaric acid salts of said compounds, wherein the resulting precipitate is enriched with the L-(+)-tartaric acid salt of said compound of Formula (**Ia**);

dissolving said precipitate in a solution comprising acetone and water at a temperature of about 45°C to about 60°C to form a solution containing the dissolved precipitate;

cooling said solution containing the dissolved precipitate to a temperature of about -5°C to about 10°C; and

precipitating a second precipitate containing the L-(+)-tartaric acid salt of said compound of Formula (**Ia**) with an enantiomeric excess of about 98% or greater.