The present invention is related to the process for the preparation aripiprazole and intermediates thereof. The process comprises reacting 7-hydroxy-3,4-dihydro-2(1H)-quinolinone with 1-bromo-4-chlorobutane in aqueous solvent in the presence of a phase transfer catalyst and a base.
A PROCESS FOR THE PREPARATION OF ARIPIPRAZOLE AND INTERMEDIATES THEREOF

Field of the invention

The invention is related to the process for the preparation aripiprazole and intermediates thereof.

Background of the invention

Aripiprazole or 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyi]butoxy]-3,4-dihydro-2(lH)-quinolinone is represented by formula (I):

![Formula I](image)

Aripiprazole is an antipsychotic agent useful in the treatment of schizophrenia.

EP 0367141 B1 describes a method for preparing aripiprazole by reacting 7-hydroxy-3,4-dihydro-2(IH)quinolinone with 1,4-dibromobutane to produce 7-(4-bromobutoxy)-3,4-dihydro-2(IH)quinolinone intermediate, which is then converted to aripiprazole by reaction with l-(2,3-dichlorophenyl)piperazine. A similar process of preparing aripiprazole starting from 7-hydroxy-3,4-dihydro-2(IH)quinolinone and 1,4-dibromobutane is described in Oshiro, Y. et al, J. Med. Chem., 1998, 41, 658-667. The above mentioned methods suffer from formation of dimeric byproduct (VII)

![Formula VII](image)

as well as other impurities which cause low yield and difficult purification of the intermediate product.
The problem of the formation of dimeric impurity has been tried to solve in processes described in US 2006/0258869 and US 2006/0079689. Both of them describe the preparation of the 7-(4-bromobutoxy)-3,4-dihydro-2(H)quinolinone intermediate by a reaction of 7-hydroxy-3,4-dihydro-2(H)quinolinone and 1,4-dihalobutane in an organic solvent. These methods, however, require the evaporation of the organic solvent from the reaction mixture, and also excess purification steps in some cases.

A method of reacting hydroxy-3,4-dihydro-2(H)quinolinone compounds with Br(CH₂)nCl is described in Banno, K. et al., Chem. Pharm. Bull., 36(11), 4377-4388, 1988. The reaction is carried out in non-aqueous solvent using solid KOH as a base. The method is difficult to conduct in large scale and suffers from low yield.

Other methods related to the preparation of aripiprazole are described e.g. in WO 2004/063162, WO 2004/099152, WO 2005/077904 and CN 1513838.

Thus, it is desirable to provide an improved method for producing aripiprazole in high yield and purity the method also being economically feasible and suitable for use in a large scale.

**Summary of the invention**

The present invention provides a process for the preparation of aripiprazole (I) which comprises reacting 7-hydroxy-3,4-dihydro-2(H)quinolinone of formula (II)

![Formula II](image)

with 1-bromo-4-chlorobutane of formula (III)

![Formula III](image)

in an aqueous solvent, in the presence of a phase transfer catalyst and a base, to produce a mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(H)quinolinone of formula (IV) and 7-(4-bromobutoxy)-3,4-dihydro-2(H)quinolinone of formula (V);
and reacting the obtained mixture of (IV) and (V) with l-(2,3-dichlorophenyl)-piperazine of formula (VI) or a salt thereof.

In another aspect, the present invention provides a method for the preparation of a mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(1H)quinolinone of formula (IV) and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)quinolinone of formula (V), which mixture is a useful intermediate in the preparation of aripiprazole. The method comprises reacting 7-hydroxy-3,4-dihydro-2(1H)-quinolinone of formula (II) with 1-bromo-4-chlorobutane of formula (ID) in an aqueous solvent, in the presence of a phase transfer catalyst and a base.

In still another aspect the present invention provides a method for the preparation of aripiprazole from a mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(1H)quinolinone of formula (IV) and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)-quinolinone of formula (V) by reacting the mixture with l-(2,3-dichlorophenyl)-piperazine (VI) or a salt thereof.

It has been found that the method of the invention produces the mixture of intermediates (IV) and (V) in high yield while the amount of dimeric impurity (VII) and other impurities remains low. The isolation and purification of the intermediate product is also simple. No evaporation steps are needed and the product can be crystallized easily from the reaction mixture. Furthermore, it was found that aripiprazole can be conveniently prepared from the mixture of intermediates (IV) and (V). The purity of aripiprazole thus obtained is high and the process is very easy to scale up.

Additional objects and advantages of the invention will be set forth in part in the
description, which follows, and in part will be obvious from the description, or may be learned by practice of the invention. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed.

Detailed description of the invention

In accordance with the present invention 7-hydroxy-3,4-dihydro-2(1H)-quinolinone is reacted with 1-bromo-4-chlorobutane in a two-phase liquid-liquid reaction system comprising water, a base, 7-hydroxy-3,4-dihydro-2(1H)quinolinone, a phase transfer catalyst and 1-bromo-4-chlorobutane, which is suitably used in excess.

1-Bromo-4-chlorobutane is suitably used in an amount of about 2 to 10 molar equivalents, typically in an amount of about 3-6 equivalents, to 7-hydroxy-3,4-dihydro-2(1H)quinolinone.

The base is suitably an inorganic basic substance such as alkali metal carbonate or alkali metal hydroxide, e.g. potassium carbonate or sodium carbonate, sodium hydroxide or potassium hydroxide. Potassium carbonate is particularly preferred. The base, preferably potassium carbonate, is used suitably in an amount of about 1 to 1.5 equivalents, typically in an amount of about 1.0 to 1.05 equivalent, to 7-hydroxy-3,4-dihydro-2(1H)quinolinone (II).

Various types of phase transfer catalysts are known in the art. Suitable phase transfer catalysts include, but are not limited to, quaternary ammonium salts, quaternary phosphonium salts, crown ethers, cryptands and polyethylene glycols. In particular, suitable phase transfer catalysts include tetrabutylammonium bromide, tetrabutylammonium hydrogen sulfate, benzyltriethylammonium chloride, tricaprylylmethylammonium chloride, methyltrioctylammonium chloride, methyltributylammonium chloride, tetrabutylphosphonium bromide, tetraphenylphosphonium bromide, hexadecyltrimethylammonium bromide and sodium lauryl sulfate.

Quaternary ammonium salts are preferred phase transfer catalysts. Tetrabutylammonium bromide is particularly preferred. The phase transfer catalyst such as tetrabutylammonium bromide may be present in an amount from about 2 to
about 20 % per weight, typically about 10 % per weight, of 7-hydroxy-3,4-dihydro-
2(1H)-quinolinone used.

The reaction between 7-hydroxy-3,4-dihydro-2(1H)-quinolinone and 1-bromo-
4-chlorobutane is preferably carried out under heating. Suitably, the reaction
temperature is higher than about 50 0C, preferably higher than about 70 0C, for
example about 90 0C. The reaction is typically completed within few hours, e.g.
between 2 and 4 hours, more typically in about 3 hours. The amount of unreacted
starting materials is less than 0.02 % per weight.

The aqueous solvent comprises suitably at least 50 %, preferably at least 75 %,
more preferably at least 90 %, per weight of water. Most preferably the aqueous
solvent is free of other solvents than water.

The intermediate product is preferably isolated and purified before its use in
the next reaction step. Thus, after completion of the reaction between 7-hydroxy-3,4-
dihydro-2(1H)-quinolinone and 1-bromo-4-chlorobutane, the reaction phases are
separated and the organic phase is suitably washed with water. The intermediate
product consisting of a mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(1H)-quinolinone
(IV) and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)-quinolinone (V) is isolated from the
organic phase by methods known in the art such as crystallization. Thus, after
cooling the organic phase a suitable crystallization solvent, preferably an aliphatic
hydrocarbon, is added. In one embodiment of the invention hexane is used as a
crystallization solvent. The mixture is stirred at room temperature after which the
mixture may optionally be cooled e.g. to 0 - 5 0C, for example to about 0 0C. The
crystalline intermediate product is filtered, washed with a suitable solvent such as
hexane, and dried preferably under reduced pressure. Yield is typically high, e.g.
about 95 % and HPLC-purity about 98 %, per weight. The ratio of 7-(4-
chlorobutoxy)-3,4-dihydro-2(1H)-quinolinone (IV) and 7-(4-bromobutoxy)-3,4-
dihydro-2(1H)-quinolinone (V) in the intermediate product is typically about 75:25 to
95:5. The amount of dimeric impurity is typically from about 1 % to about 5 % per
weight. This is very low compared to prior methods where the amount of dimeric
impurity is typically above 10 % per weight.

According to the present invention, aripiprazole can be prepared starting from
the isolated mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(H)quinolinone (IV) and 7-(4-bromobutoxy)-3,4-dihydro-2(H)quinolinone (V) by reacting said mixture with 1-(2,3-dichlorophenyl)piperazine or a salt thereof such as 1-(2,3-dichlorophenyl)piperazine hydrochloride.

The intermediate mixture useful for preparing aripiprazole can comprise intermediate compounds (IV) and (V) in any ratio, e.g. from about 99:1 to about 1:99, per weight. Typically, the ratio of compound (IV) to compound (V) in the mixture is from about 50:50 to about 99:1, more typically from about 70:30 to about 98:2, still more typically from about 75:25 to about 95:5, per weight.

Preferably, the mixture of intermediate compounds (IV) and (V) used in the preparation of aripiprazole is previously isolated. Its purity should be at least 90%, preferably at least 95%. In a preferred embodiment of the invention the mixture of intermediate compounds (IV) and (V) is isolated by crystallization, and if needed, recrystallized to obtain the purity required.

The reaction between the intermediate mixture of compounds (TV) and (V) and 1-(2,3-dichlorophenyl)piperazine or a salt thereof is carried out preferably in a suitable solvent such as acetonitrile, ethanol, methanol, isopropanol, 1-butanol, 1-pentanol or water. Acetonitrile is particularly preferred. The reaction temperature is suitably between 60 and 120 °C. The reaction is advantageously carried out in the presence of a basic compound. Suitable inorganic basic compounds include calcium carbonate, sodium carbonate, sodium hydroxide or sodium hydrogen carbonate. Suitable organic basic compounds include triethylamine, tripropylamine, pyridine or quinoline. In one preferred embodiment of the invention, the reaction is carried out in the presence of an alkali metal iodide such as potassium iodide or sodium iodide as the reaction accelerator. Sodium iodide is particularly preferred. The reaction time ranges typically from about 15 to about 40 hours.

Aripiprazole prepared by the process described above can be isolated by known methods. For example, the reaction mixture can be cooled to room temperature. In case that organic solvent was used as a reaction medium, water may be added during crystallization stage. The crystalline product can be collected by filtration, washed with suitable solvent and dried under reduced pressure.
According to the present invention, aripiprazole can be prepared in high yield and high purity without any complicated purification steps.

The invention is further illustrated by the following non-limiting examples.

**Examples**

**EXAMPLE 1.** Preparation of the mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(H)quinolinone and 7-(4-bromobutoxy)-3,4-dihydro-2(H)quinolinone

7-Hydroxy-3,4-dihydro-2(H)quinolinone (20 g), 1-bromo-4-chlorobutane (85 ml), K$_2$CO$_3$ (17 g), tetrabutylammonium bromide (2.0 g) and water (200 ml) were charged. The mixture was heated to 90 °C and stirred for 3 hours at about 90 °C. The water phase was separated off. The organic phase was washed with 100 ml of water at about 90 °C. Hexane (400 ml) was added at about 20 °C. The mixture was stirred for about 20 hours at room temperature and then cooled to about 0 °C. The crystalline mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(H)quinolinone and 7-(4-bromobutoxy)-3,4-dihydro-2(H)quinolinone was filtered and washed with hexane (3*20 ml). The product was dried under reduced pressure at 40-50 °C. The yield was 30.5 g (95.6 %). The product was a 85:15 mixture of Cl- and Br-compounds. The HPLC-purity was 98.2 %, the amount of dimeric impurity was 1.1 %, per weight.

**EXAMPLE 2.** Preparation of the mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(H)quinolinone and 7-(4-bromobutoxy)-3,4-dihydro-2(H)quinolinone

7-Hydroxy-3,4-dihydro-2(H)quinolinone (20 g), 1-bromo-4-chlorobutane (42.4 ml), K$_2$CO$_3$ (17 g), tetrabutylammonium bromide (2.0 g) and water (200 ml) were charged. The mixture was heated to 90 °C and stirred for 2 hours at about 90 °C. The water phase was separated off. The organic phase was washed with 100 ml of water at about 90 °C. Hexane (300 ml) was added at 20-40 °C. The mixture was stirred for about 20 hours at room temperature. The crystalline mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(H)quinolinone and 7-(4-bromobutoxy)-3,4-dihydro-2(H)quinolinone was filtered and washed with hexane (3*50 ml). The product was dried under reduced pressure at 40-50 °C. The yield was 30.5 g (95 %) The product
was a 79.9:20.1 mixture of Cl- and Br-compounds. The HPLC-purity was 94.2 %, the amount of dimeric impurity was 3.1 %, per weight.

EXAMPLE 3. Preparation of 7-[4-[4-(2,3-dichlorophenyl)-l-piperazinyl]-butoxy]-3,4-dihydro-2(1H)-quinolinone (aripiprazole).

7-(4-Chlorobutoxy)-3,4-dihydro-2(1H)quinolinone and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)quinolinone (79.9:20.1 mixture, 2.0 g), sodium iodide (1.8 g) and acetonitrile (60 ml) were charged. The mixture was refluxed for 17 hours and then filtered. l-(2,3-Dichlorophenyl)piperazine hydrochloride (2.3 g) and triethylamine (3.7 ml) were added to the solution. The mixture was refluxed for 23 hours. Water (2.0 ml) was added and the solution was cooled to room temperature and stirred for 4 hours at room temperature. The crystalline 7-[4-[4-(2,3-dichlorophenyl)-l-piperazinyl]-butoxy]-3,4-dihydro-2(1H)-quinolinone (aripiprazole) was filtered and washed with acetonitrile. The product was dried under reduced pressure at 40-50 °C. The yield of aripiprazole was 2.89 g (83 %) and HPLC-purity was 99.4 %.

EXAMPLE 4. Preparation of 7-[4-[4-(2,3-dichlorophenyl)-l-piperazinyl]-butoxy]-3,4-dihydro-2(1H)-quolinone (aripiprazole).

7-(4-Chlorobutoxy)-3,4-dihydro-2(1H)quinolinone and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)quinolinone (79.9:20.1 mixture, 6.0 g), sodium iodide (4.9 g), diisopropylethylamine (4.6 ml) and l-(2,3-dichlorophenyl)piperazine (6.1 g) in 45 ml of 1-pentanol were charged. The mixture was kept at about 100 °C for 5 hours. The mixture was cooled and water (60 ml) and 50 % NaOH (6 ml) were added. The water phase was separated off. Water (10 m) was added to the organic phase and the solution was cooled to room temperature. The crystalline 7-[4-[4-(2,3-dichlorophenyl)-l-piperazinyl]-butoxy]-3,4-dihydro-2(1H)-quinolinone (aripiprazole) was filtered and washed with 1-pentanol and isopropanol. The product was dried under reduced pressure at 80-90 °C. The yield was 8.6 g (88 %) and the HPLC-purity was 99 %.

The raw product (3.0 g), ethanol (48 ml) and water (10 ml) were charged. The solution was refluxed until all dissolved. Water (10 ml) was added and the solution was cooled to room temperature. The crystalline compound was filtered and washed
with ethanol:water mixture. The product was dried under reduced pressure at 80-90 °C. The yield was 2.8 g (93 %) and the HPLC-purity was 99.7 %.
CLAIMS

1. A process for the preparation of aripiprazole (I)

\[
\text{\begin{align*}
\text{\text{(I)}}
\end{align*}}
\]

comprising

(a) reacting 7-hydroxy-3,4-dihydro-2(1H)-quinolinone (II)

\[
\text{\begin{align*}
\text{\text{(II)}}
\end{align*}}
\]

with 1-bromo-4-chlorobutane in aqueous solvent in the presence of a phase transfer catalyst and a base to produce a mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(1H)quinolinone (IV) and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)quinolinone (V);

\[
\text{\begin{align*}
\text{\text{(IV)}}
\end{align*}}
\]

and

\[
\text{\begin{align*}
\text{\text{(V)}}
\end{align*}}
\]

(b) reacting the obtained mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(1H)-quinolinone (IV) and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)quinolinone (V) with 1-(2,3-dichlorophenyl)piperazine or a salt thereof.

2. A process according to claim 1, wherein the amount 7-(4-bromobutoxy)-3,4-dihydro-2(1H)quinolinone in the mixture obtained is between 5 % and 25 %, by weight.

3. A process according to claim 1 or 2, wherein phase transfer catalyst is a quaternary ammonium salt.
4. A process according to any preceding claim, wherein the base is an alkali metal carbonate.

5. A process according to any preceding claim, wherein 1-bromo-4-chloro-butane is used in molar excess.

6. A process according to any preceding claim, wherein the aqueous solvent consists of water.

7. A process for the preparation of a mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(1H)quinolmone and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)-quinolinone comprising reacting 7-hydroxy-3,4-dihydro-2(1H)-quinolinone with 1-bromo-4-chlorobutane in aqueous solvent in the presence of a phase transfer catalyst and a base.

8. A process according to claim 7, wherein the phase transfer catalyst is a quaternary ammonium salt.

9. A process according to claim 7 or 8, wherein the base is an alkali metal carbonate.

10. A process according to any of claims 7-9, wherein 1-bromo-4-chlorobutane is used in molar excess.

11. A process according to any of claims 7-10, wherein the aqueous solvent consists of water.

12. A process according to any of claims 7-11, wherein the reaction is carried out under heating.

13. A process according to any of claims 7-12, wherein the process comprises a further step of isolating the end product by crystallization.

14. A process according to claim 12, wherein the end product is crystallized from hexane.

15. A process for the preparation of aripiprazole comprising reacting a mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(1H)quinolinone (IV) and 7-(4-
bromobutoxy)-3,4-dihydro-2(1H)quinolinone (V) with 1-(2,3-dichlorophenyl)-piperazine or a salt thereof.

16. A process according to claim 15, wherein the ratio of compound (IV) to compound (V) in the mixture is from about 50:50 to about 99:1, per weight.

17. A process according to claim 16, wherein the ratio of compound (IV) to compound (V) in the mixture is from about 70:30 to about 98:2, per weight.

18. A process according to claim 17, wherein the ratio of compound (IV) to compound (V) in the mixture is from about 75:25 to about 95:5, per weight.

19. A process according to any of claims 15-18, wherein said mixture of compounds (IV) and (V) is previously isolated by crystallization.

20. Aripiprazole or a pharmaceutically acceptable salt thereof made from a mixture of 7-(4-chlorobutoxy)-3,4-dihydro-2(1H)quinolinone and 7-(4-bromobutoxy)-3,4-dihydro-2(1H)quinolinone said mixture being prepared according to any of claims 7-14.
## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D215/22

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>BONACORSI S J JR ET AL: &quot;Synthesis of multi-labeled [14C]aripiprazole&quot; JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, JOHN WILEY, CHICHESTER, GB, vol. 49, 2006, pages 1-9, XP002428678 ISSN: 0362-4803 pages 6,7, figure 1; compounds 4, 5, IA</td>
<td>1-5, 7-10, 12, 13,15-19</td>
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Date of the actual completion of the international search: 31 August 2007

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### DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>X</td>
<td>OSHIRO YASUO ET AL: &quot;Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperaziny l)butoxy]-3,4-dihydro-2 (1H)-quinoline Derivatives&quot; JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, 1998, pages 658-667, XP002272484 ISSN: 0022-2623 cited in the application pages 659,661; figure 1; table 1; compound 28</td>
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<td>BANNO K ET AL: &quot;STUDIES ON 2(1H)-QUINOLINONE DERIVATIVES AS NEUROLEPTIC AGENTS. I. SYNTHESIS AND BIOLOGICAL ACTIVITIES OF (4-PHENYL-1-PIPERAZINYD-PROPXY-2(1H)-QUINOLINONE DERIVATIVES&quot; CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, Jp, vol. 36, no. 11, 1988, pages 4377-4388, XP001156231 ISSN: 0009-2363 cited in the application page 4377, paragraph SYNTHESIS; figure 1</td>
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