(51) International Patent Classification:

C07D 401/02 (2006.01)

(21) International Application Number:

PCT/IN2011/000840

(22) International Filing Date:

7 December 2011 (07.12.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

302/CHE/2011 1 February 2011 (01.02.2011) IN

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Declarations under Rule 4.17:

— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(ii))

— of inventorship (Rule 4.17(iv))

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: PROCESS FOR CONTROLLING THE CONTENT OF SINGLE ENANTIOMER OF OMEPRAZOLE

(57) Abstract: The present invention relates to process for controlling the content of single enantiomer of omeprazole with respect to other enantiomers.
PROCESS FOR CONTROLLING THE CONTENT OF SINGLE ENANTIOMER
OF OMEPRAZOLE

Filed of the Invention

The present invention relates to process for controlling the content of single
enantiomer of omeprazole with respect to other enantiomers.

Background of the Invention

Omeprazole, chemically 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-
pyridinyl]methyl]sulfinyl]-1H-benzimidazole and its therapeutic uses were disclosed in
European Patent No. 5129. Omeprazole is a well-known gastric acid secretion inhibitor,
and is useful as an anti ulcer agent. Omeprazole has a stereogenic center at sulfur and
therefore exist as two optical isomers such as R-omeprazole and S-omeprazole
(esomeprazole).

The alkaline salts of (S)-enantiomer of omeprazole (esomeprazole), the
pharmaceutical preparations of these salts and the method of treatment of gastric acid-
related diseases using them were disclosed in U.S. patent nos. 4,738,974; 5,877,192 and
5,714,504. The U.S. patents 4,738,974; 5,877,192 and 5,714,504 were incorporated
herein by reference.

These compounds and structurally related compounds have a stereogenic center
at sulfur and therefore exist as two optical isomers. The resolution processes of
racemates of these compounds were, for example, disclosed in DE 4035455 and WO
94/27988. According to these processes chiral ether such as fenchylloxymethyl or chiral
acyloxy methyl group such as mandeloyl- is introduced into the 1-position of
benzimidazole ring of racemic sulfoxide compound to obtain a diastereomeric mixture,
diastereomers are then separated and desired isomer is liberated from a separated
diastereomer. The process requires either the preparation of fenchylloxymethyl chloride
and then reaction with the racemic compound; or introduction of chloromethyl group on
1-position of benzimidazole ring, followed by reaction with the chiral auxiliary. We
found that these intermediates are difficult to prepare and involve in many steps.
PCT publication no. WO 96/02535 disclosed a process for the preparation of the single enantiomers of omeprazole and structurally related compounds as well as salts thereof.

PCT publication no. WO 97/02261 disclosed a process for the optical purification of certain enantiomerically enriched benzimidazole derivatives by using a crystallization method.

PCT publication nos. WO 2008/004245, WO 2006/094904, WO 2007/013743; CN 1087739 and CN 1223262 disclosed processes for preparation of an optically pure or optically enriched enantiomer of a sulfoxide compound using R- or S-1,1'-bi-2-naphthol (R- or S-BINOL).

The resolution of sulfoxide compounds including racemic omeprazole was described in PCT publication no. WO 2004/002982. The method requires expensive reagents like titanium compounds, two chiral reagents namely diethyl-D-tartarate and L-mandelic acid.

Enantioselective synthesis was described for example in Euro. J. Biochem. 166 (1987) 453 and US Patent No. 5,948,789. Disadvantages of these methods are that strict control of conditions is to be maintained and strict control of quantities of oxidizing agents is required for avoiding oxidation of desired sulfoxide to sulfone impurity. Moreover, these methods require expensive reagents like titanium isoproxide and diethyl-D-tartarate.


PCT publication no. WO 2007/074099 disclosed process for the preparation of optically pure benzimidazole derivatives by inclusion complex with (S)-1,1,2-triphenyl-1,2-ethanediol.

Resolution of omeprazole with chiral 1,1'-binaphtyl-2-2'-diyl hydrogen (BNPPA) was disclosed in co-pending application no. PCT/IN2009/000567.
PCT publication no. WO 2008/092939 disclosed a process for the preparation of substantially optically pure omeprazole with the formation of a complex by using chiral amine or chiral quaternary ammonium salt. Magnesium salt of esomeprazole trihydrate was disclosed in PCT publication no. WO 98/54171.

The omeprazole can be separated or resolved into enantiomers by using BINOL reagent has described in co-pending application no. PCT/IN2009/000634.

It has know been found that the composition of the enantiomers of omeprazole in the resolution process can be controlled by using variable quantities of BINOL.

Thus, an object of the present invention is to provide a process for controlling the content of single enantiomer of omeprazole with respect to other enantiomers.

**Detailed Description of the Invention**

The term “room temperature” refers to temperature at about 25 to 35°C.

According to an aspect of the present invention, there is provided a process for controlling the content of single enantiomer of omeprazole with respect to other enantiomers, which comprises:

a) reacting omeprazole with a single enantiomer of 1,1'-bi-2-naphthol (BINOL) in pre-determined quantity;

b) subjecting the separation of diastereomers formed; and

c) converting diastereomers into the enantiomer of omeprazole.

As a specific embodiment of the invention, BINOL is used in the quantity of 1.0 to 1.2 moles per mole of omeprazole to obtain the product having esomeprazole to R-omeprazole ratio of 99.2:0.8 to 99.9:0.1.

As a specific embodiment of the invention, BINOL is used in the quantity of 1.3 to 1.5 moles per mole of omeprazole to obtain the product having esomeprazole to R-omeprazole ratio of 99.8:0.2 to 100:0.

The chemical formulae of (S)-BINOL and (R)-BINOL are represented as:
The reaction in step (a) may preferably be carried out in a solvent selected from methylene chloride, ethylene chloride, chloroform, toluene, xylene, benzene, styrene, cyclohexane, hexane, n-heptane or mixture thereof. More preferably the solvents are methylene chloride and toluene.

The diastereomers formed in step (a) are then separated. It is well known that diastereomers differ in their properties such as solubility and they can be separated based on the differences in their properties. The separation of the diastereomers can be performed by using the methods known to the person skilled in the art. These methods include chromatographic techniques and fractional crystallization, preferable method being fractional crystallization.

Crystallization of preferentially one diastereomer from the solution of diastereomers can be performed by conventional methods such as cooling, partial removal of solvents, seeding or a combination thereof. Fractional crystallization may also occur from the solution under condition of diastereomeric formation. Isolation can be repeated until the desired chiral purity is obtained. But, usually one or two isolations may be sufficient. The separated solid may be collected by the method known such as centrifugation or filtration.

The separated diastereomers is converted into enantiomer of omeprazole in step (c) by the methods such as by addition of cyclic amine salt and a solvent or mixture of solvents.

Preferably the cyclic amine used in the process may be five or six member cyclic amine salts. More preferably the five and six member cyclic amine salts is selected from piperidine, pyrrolidine and piperazine, and still more preferably the six member cyclic amine salt is piperidine.
Preferably the solvent used in the process may be selected from water, methylene chloride, ethylene chloride, chloroform, toluene, xylene, benzene, styrene, cyclohexane, hexane, n-heptane, methanol, ethanol, isopropyl alcohol, n-butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone. More preferably the solvents are water, toluene, methylene chloride, acetone and methanol.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitations on the scope or spirit of the invention.

**Examples**

**Example 1:**

**Preparation of omeprazole**

Vanadyl acetylacetonate (4.8 gm) was added to water (210 ml) and then cooled to 0 to 10°C. To the reaction mixture was added hydrogen peroxide (50 %, 120 ml) at 0 to 10°C and stirred for 20 minutes. 5-Methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]thio]-1H-benzimidazole (480 gm) and acetone (1950 ml) were added to the reaction mixture. The reaction mixture was maintained for 3 hours 30 minutes at 10 to 15°C and then added sodium hydroxide (46 %, 16 ml) and water (1600 ml). The reaction mass was then cooled to 0 to 5°C and pH of the reaction mass was adjusted to 7.5 to 8.5 with acetic acid (11 gm) at 0 to 10°C. The reaction mass was stirred for 2 hours and filtered to obtain a wet solid. To the wet solid was added water (700 ml) and then added liquor ammonia (38 gm) and methanol (700 ml) at room temperature. The reaction mass was then cooled to 0 to 10°C, stirred for 45 minutes and filtered. The solid obtained was dried to give 405 gm of omeprazole.

**Example 2:**

**Preparation of esomeprazole-S-BINOL**

S-1,1'-bi-2-naphthol (364.5 gm) was added to a solution of omeprazole (405 gm) as obtained in example 1 in methylene chloride (1000 ml) at room temperature and stirred for 15 minutes. To the reaction mixture was added toluene (6000 ml) and
maintained for 4 hours at room temperature. The solid obtained was collected by filtration and dried to obtain 310 gm of esomeprazole-S-BINOL.

Example 3:

Preparation of esomeprazole piperidine salt

To esomeprazole-S-BINOL (310 gm) as obtained in example 2 was added toluene (1500 ml) under stirring and then added water (1200 ml) and piperidine (110 gm) at room temperature. The temperature of the reaction mass was raised to 35 to 40°C, stirred for 1 hour and then the layers were separated. The organic layer was cooled to 20 to 25°C and then added methylene chloride (1600 ml). The pH of the reaction mass was adjusted to 7.0 to 7.5 with hydrochloric acid (50%, 42 ml) and stirred for 1 hour. Then the layers were separated and the organic layer was added piperidine (50 gm). The solvent was distilled off under reduced pressure at below 40°C to obtain a residual solid. To the residual solid was added acetone (850 ml) and maintained for 2 hours at room temperature. The reaction mass was then cooled to 10 to 15°C and maintained for 1 hour. The solid obtained was collected by filtration and dried to obtain 155 gm of esomeprazole piperidine salt.

Example 4:

Preparation of esomeprazole magnesium dihydrate

Magnesium chloride (18 gm) was added to methanol (250 ml) and stirred for 15 minutes at room temperature. Esomeprazole piperidine salt (155 gm) as obtained in example 3 was added to the reaction mixture and then added acetone (850 ml). The reaction mass was maintained for 2 hours 30 minutes at room temperature and filtered. The solid obtained was dried to give 113 gm of esomeprazole magnesium dihydrate.
We claim:

1. A process for controlling the content of single enantiomer of omeprazole with respect to other enantiomers, which comprises:
   a. reacting omeprazole with a single enantiomer of 1,1’-bi-2-naphthol (BINOL) in pre-determined quantity;
   b. subjecting the separation of diastereomers formed; and
   c. converting diasteromers into the enantiomer of omeprazole.

2. The process as claimed in claim 1, wherein the BINOL is used in the quantity of 1.0 to 1.2 moles per mole of omeprazole to obtain the product having esomeprazole to R-omeprazole ratio of 99.2:0.8 to 99.9:0.1.

3. The process as claimed in claim 1, wherein the reaction in step (a) is carried out in a solvent selected from methylene chloride, ethylene chloride, chloroform, toluene, xylene, benzene, styrene, cyclohexane, hexane, n-heptane or mixture thereof.

4. The process as claimed in claim 3, wherein the solvents are methylene chloride and toluene.

5. The process as claimed in claim 1, wherein the separated diastereomers is converted into enantiomer of omeprazole in step (c) by addition of cyclic amine salt and a solvent or mixture of solvents.

6. The process as claimed in claim 5, wherein the cyclic amine used in the process is five or six member cyclic amine salts.

7. The process as claimed in claim 6, wherein the five and six member cyclic amine salts is selected from piperidine, pyrrolidine and piperazine.

8. The process as claimed in claim 7, wherein the six member cyclic amine salt is piperidine.

9. The process as claimed in claim 1, wherein the solvent used in the process is selected from water, methylene chloride, ethylene chloride, chloroform, toluene, xylene, benzene, styrene, cyclohexane, hexane, n-heptane, methanol, ethanol, isopropyl alcohol, n-butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone.

10. The process as claimed in claim 9, wherein the solvents are water, toluene, methylene chloride, acetone and methanol.