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(54) Title: PROCESS FOR THE PREPARATION OF RABEPRAZOLE

(57) Abstract: The present invention provides a compound of Formula III, process of its preparation and its use as a reference mark-
er or as a reference standard. The present invention further provides a process for the preparation of rabeprazole, a salt or a solvate
thereof. The invention also provides a chromatographic method for testing the purity of rabeprazole, a salt or a solvate thereof.



WO 2014/091450 A1

PROCESS FOR THE PREPARATION OF RABEPRAZOLE

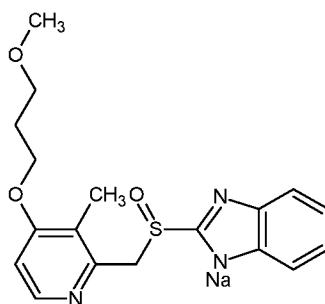
Field of the Invention

The present invention provides a compound of Formula III, process of its preparation and its use as a reference marker or as a reference standard. The present invention further provides a process for the preparation of rabeprazole, a salt or a solvate thereof. The invention also provides a chromatographic method for testing the purity of rabeprazole, a salt or a solvate thereof.

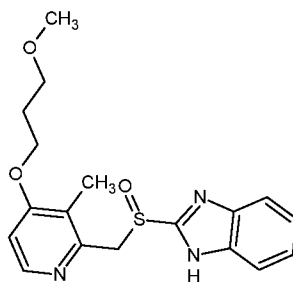
Background of the Invention

Rabeprazole sodium is marketed in the United States under the brand name Aciphex[®] and is indicated for the treatment in healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD).

Rabeprazole sodium of Formula I is chemically described as sodium salt of 2-({[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl}sulfinyl)-1*H*-benzimidazole of Formula II.



FORMULA I



FORMULA II

Processes for the preparation of rabeprazole and its sodium salt are described in U.S. Patent Nos. 5,045,552, 6,313,303, and 7,439,367; European Patent EP 1,000,943 B1; European

Patent Application EP 0,268,956 A; Indian Patent IN 192030 and PCT Publication Nos. WO 2007/023393, WO 2003/101452, WO 2006/024890 and WO 2009/116072.

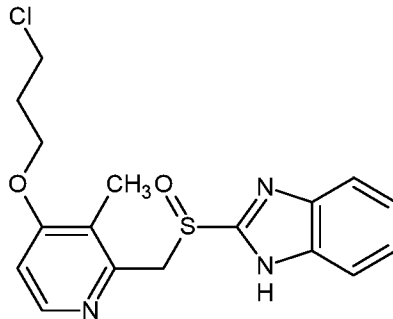
Summary of the Invention

The present inventors have found that the existing processes for the preparation of
5 rabeprazole result in the formation of impurities including genotoxic impurities. The present invention provides a process for the control of the impurities in the final active pharmaceutical ingredient and dosage form. The present invention provides a compound of Formula III, process of its preparation and its use as a reference marker or as a reference standard. The present invention further provides a process for the preparation of rabeprazole, a salt or a solvate
10 thereof. The invention also provides a chromatographic method for testing the purity of rabeprazole, a salt or a solvate thereof.

Detailed Description of the Invention

The term "about" as used herein, refers to any value which lies within the range defined by a number up to $\pm 10\%$ of the value.

15 A first aspect of the present invention provides a compound of Formula III.

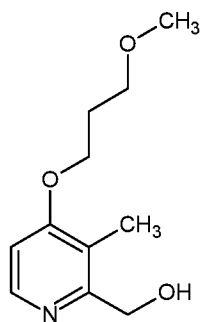


FORMULA III

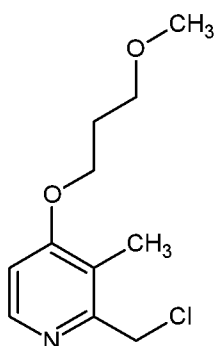
The compound of Formula III is found to be genotoxic in nature. This was confirmed by using various techniques like DEREK (Deductive Estimation of Risk from Existing Knowledge)
20 analysis and Ames biological assays.

A second aspect of the present invention provides a process for the preparation of rabeprazole, a salt or a solvate thereof, substantially free from a compound of Formula III, wherein the process comprises:

25 a) reacting a compound of Formula IV or a salt thereof with a chlorinating agent at a temperature not exceeding 0°C

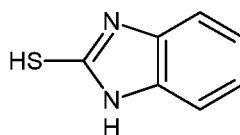
**FORMULA IV**

to prepare a compound of Formula V or a salt thereof;

**FORMULA V**

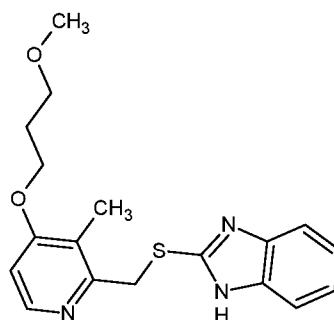
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b) reacting the compound of Formula V or a salt thereof with a compound of Formula VI

**FORMULA VI**

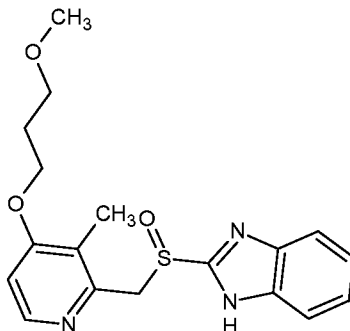
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to prepare a compound of Formula VII;



FORMULA VII

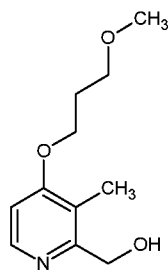
c) converting the compound of Formula VII to rabeprazole of Formula II; and

**FORMULA II**

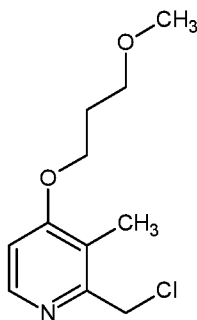
5 d) optionally converting the rabeprazole of Formula II to its salt or a solvate thereof.

A third aspect of the present invention provides a process for the preparation of rabeprazole, a salt or a solvate thereof, substantially free from a compound of Formula III, wherein the process comprises:

10 a) reacting a compound of Formula IV or a salt thereof with a chlorinating agent at a temperature not exceeding 0°C

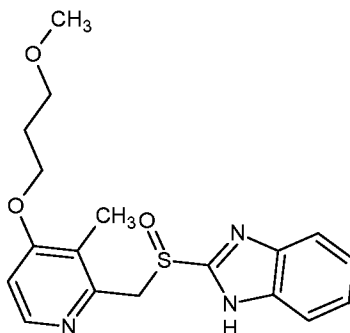
**FORMULA IV**

to prepare a compound of Formula V or a salt thereof;



FORMULA V

- b) converting the compound of Formula V to rabeprazole of Formula II; and

**FORMULA II**

- 5 c) optionally converting the rabeprazole of Formula II to its salt or a solvate thereof.

The compound of Formula IV or a salt thereof may be prepared by any method known in the literature, for example U.S. Patent No. 5,045,552. The chlorinating agent may be selected from the group consisting of thionyl chloride, phosphorous trichloride, phosphorous oxychloride, phosphorous pentachloride and sulfuryl chloride. A preferred chlorinating agent is thionyl chloride. The temperature for the chlorination of the compound of Formula IV or a salt thereof is less than about 0°C. The temperature for chlorination is, for example, from about -5°C to about -30°C, for example, from about -10°C to about -20°C.

The chlorination of the compound of Formula IV or a salt thereof is carried out optionally in the presence of a base. The base may be selected from the group consisting of inorganic bases and organic bases. The inorganic bases may be selected from the group consisting of hydroxides, carbonates and bicarbonates. Hydroxides may be, for example, sodium hydroxide, potassium hydroxide or barium hydroxide. Carbonates may be, for example, sodium carbonate, potassium carbonate or barium carbonate. Bicarbonates may be, for example, sodium bicarbonate, magnesium bicarbonate or potassium bicarbonate. The organic bases may be, for example, triethyl amine, ethyl amine, ammonia or diisopropyl ethyl amine. A preferred base is sodium carbonate.

The compound of Formula IV or a salt thereof may be reacted with the chlorinating agent in the presence of a solvent. The solvent may be selected from the group consisting of water, alcohols, halogenated hydrocarbons, esters, nitriles, and a mixture thereof. Alcohols may be, for example, methanol, ethanol or methylated ethanol. Halogenated hydrocarbons may be,

for example, dichloromethane. Esters may be, for example, ethyl acetate, or diisopropyl ethyl acetate. Nitriles may be, for example, acetonitrile. Preferred solvents include dichloromethane, methylated ethanol, or mixtures thereof.

The salt of the compound of Formula V may be, for example hydrochloride salt. The compound of Formula IV or its salt may be chlorinated to prepare the compound of Formula V or its salt for about 3 hours to 8 hours, for example for about 4 hours to about 6 hours. The compound of Formula V or its salt may optionally be isolated from the reaction mixture. The term "isolation" includes filtration, distillation, decantation, vacuum drying, evaporation or a combination thereof.

The compound of Formula V or a salt is reacted with the compound of Formula VI in a solvent and optionally in the presence of base.

The base may be selected from the group consisting of inorganic bases and organic bases. The inorganic bases may be selected from the group consisting of hydroxides, carbonates and bicarbonates. Hydroxides may be, for example, sodium hydroxide, potassium hydroxide or barium hydroxide. Carbonates may be, for example, sodium carbonate, potassium carbonate or barium carbonate. Bicarbonates may be, for example, sodium bicarbonate, magnesium bicarbonate or potassium bicarbonate. The organic bases may be, for example, triethyl amine, ethyl amine, ammonia or diisopropyl ethyl amine. A preferred base is sodium hydroxide.

The solvent for the reaction of the compound of Formula V or a salt and the compound of Formula VI may be selected from the group consisting of water, alcohols, halogenated hydrocarbons, esters, nitriles, and mixtures thereof. Alcohols may be, for example, methanol, ethanol, or methylated ethanol. Halogenated hydrocarbons may be, for example, dichloromethane. Ester solvents may be, for example, ethyl acetate or diisopropyl ethyl acetate. Nitriles may be, for example, acetonitrile. Preferred solvents include water, methylated ethanol or mixtures thereof.

The reaction of the compound of Formula V or a salt and the compound of Formula VI may be carried out at about 15°C to about 55°C, for example, at about 25°C to about 45°C. The reaction of the compound of Formula V or a salt and the compound of Formula VI may be carried in about 1 hour to about 4 hours, for example, in about 2 hours to about 3 hours.

The compound of the Formula VII obtained by the reaction of the compound of Formula V and the compound of Formula VI may optionally be isolated from the reaction mixture. The

term "isolation" includes filtration, distillation, decantation, vacuum drying, evaporation or a combination thereof.

The compound of the Formula VII may be converted to rabeprazole of the compound of Formula II in the presence of an oxidizing agent, a base and a solvent. The oxidizing agent may be selected from the group consisting of sodium hypochlorite, hydrogen peroxide, m-chloroperoxybenzoic acid, and cumene hydroperoxide. Preferred oxidizing agent is sodium hypochlorite. Sodium hypochlorite may be used in any strength, for example from about 2% to about 15%, for example from about 6% to about 9%. The compound of Formula VII may be converted to the compound of Formula II in the presence of sodium thiosulphate.

The base used for the conversion of the compound of Formula VII may be selected from the group consisting of inorganic bases, and organic bases. The inorganic bases may be selected from the group consisting of hydroxides, carbonates and bicarbonates. Hydroxides may be, for example, sodium hydroxide, potassium hydroxide or barium hydroxide. Carbonates may be, for example, sodium carbonate, potassium carbonate or barium carbonate. Bicarbonates may be, for example, sodium bicarbonate, magnesium bicarbonate or potassium bicarbonate. The organic bases may be, for example, triethyl amine, ethyl amine, ammonia or diisopropyl ethyl amine. A preferred base is sodium hydroxide.

The solvent used for the conversion of the compound of Formula VII to rabeprazole of the compound of Formula II may be selected from the group consisting of water, glacial acetic acid, alcohols, halogenated hydrocarbons, ketones, esters, nitriles, and a mixture thereof. Alcohols may be, for example, methanol, ethanol or methylated ethanol. Halogenated hydrocarbons may be, for example, dichloromethane. Ester solvents may be, for example, ethyl acetate, or diisopropyl ethyl acetate. Nitriles may be, for example, acetonitrile. Ethers may be, for example, diisopropyl ether. Ketones may be, for example, acetone. Preferred solvents include water, glacial acetic acid, acetonitrile, ethyl acetate and diisopropyl ether.

The conversion of the compound of Formula VII to rabeprazole of the compound of Formula II may be carried out in the presence of a seed of rabeprazole. The seed of rabeprazole may be prepared by the process disclosed in U.S. Patent No. 5,045,552.

The conversion of the compound of Formula VII to rabeprazole of the compound of Formula II may be carried out at about -20°C to about 60°C, for example, at about -10°C to about 50°C. The conversion of the compound of Formula VII to rabeprazole of the compound

of Formula II may be carried in about 4 hours to about 8 hours, for example, in about 6 hours to 7 hours.

Rabeprazole of the compound of Formula II may optionally be isolated. The term “isolation” includes filtration, distillation, decantation, vacuum drying, evaporation or a
5 combination thereof.

Rabeprazole of the compound of Formula II may optionally be purified using a solvent selected from the group consisting of water, glacial acetic acid, alcohols, halogenated hydrocarbons, ketones, esters, nitriles, and mixtures thereof. Alcohols may be, for example, methanol, ethanol or methylated ethanol. Halogenated hydrocarbons may be, for example,
10 dichloromethane. Esters may be, for example, ethyl acetate, or diisopropyl ethyl acetate. Nitriles may be, for example, acetonitrile. Ethers may be, for example, diisopropyl ether. Ketones may be, for example, acetone. Preferred solvents include acetone and diisopropyl ether.

Rabeprazole of the compound of Formula II may optionally be converted to its salt or a solvate thereof. The salt of the rabeprazole may be, for example, sodium salt. The solvate of the
15 compound of Formula II may be, for example, acetone solvate or alcohol solvate. Alcohol solvate may include ethanol solvate or methanol solvate. Rabeprazole of the compound of Formula II may be converted to the sodium salt of the Formula I using a base and a solvent. The base may be selected from sodium hydroxide and sodium carbonate.

The solvent used for the preparation of rabeprazole sodium of Formula I may be selected
20 from the group consisting of water, alcohols, halogenated hydrocarbons, ketones, esters, nitriles, and a mixtures thereof. Alcohols may be, for example, methanol, ethanol or methylated ethanol. Halogenated hydrocarbons may be, for example, dichloromethane. Esters may be, for example, ethyl acetate or diisopropyl ethyl acetate. Nitriles may be, for example, acetonitrile. Ethers may be, for example, diisopropyl ether. Ketones may be, for example, acetone. A preferred solvent is
25 ethanol.

Rabeprazole sodium of the compound of Formula I may be isolated and characterized. The term “isolation” includes filtration, distillation, decantation, vacuum drying, evaporation or a combination thereof. Rabeprazole sodium of the compound of Formula I may be amorphous in nature.

A fourth aspect of the present invention provides use of a compound of Formula III as a reference marker or a reference standard to analyze the purity of rabeprazole, a salt or solvate thereof.

5 An embodiment of the present invention provides use of the compound of Formula III as a reference marker or a reference standard to analyze the purity of rabeprazole, a salt or solvates thereof wherein the sample comprises any of the following:

- a) rabeprazole active pharmaceutical ingredient or its sodium salt;
- b) a pharmaceutical composition comprising active pharmaceutical ingredient or its sodium salt;
- 10 c) a solvate or salt of rabeprazole; and
- d) a pharmaceutical composition comprising solvates or a salt of rabeprazole.

A fifth aspect of the present invention provides a chromatographic method for testing the purity of rabeprazole, a salt or solvates thereof, wherein the method comprises:

- 15 a) dissolving rabeprazole, a salt or solvates thereof in a solvent to produce a sample solution;
- b) dissolving a sample of a compound of Formula III in a solvent to make a reference marker solution;
- c) subjecting the sample solution and the reference marker solution to a chromatographic method; and
- 20 d) determining the compound of Formula III in the sample solution, using the reference marker solution.

The chromatographic method may be, for example, HPLC (high-performance liquid chromatography), LC-MS (liquid chromatography–mass spectrometry), or TLC (thin layer chromatography).

25 The determination of the presence of the compound of Formula III in the sample solution is effected by comparing the retention [(retention time in HPLC (high-performance liquid chromatography) or LC-MS (liquid chromatography–mass spectrometry), or retention factor in TLC (thin layer chromatography)] of the different components of the sample solution separated by the chromatographic method with the retention of the compound of Formula III under the
30 same chromatographic conditions (i.e. same stationary phase, mobile phase, temperature,

pressure). A preferred chromatographic method is a liquid chromatographic method, such as a LC-MS method.

In the context of the present invention, "comparing the retention" is to be understood as determining whether two retention values are substantially the same, for example, the first value being the retention of one of the different components of the sample solution separated by the chromatographic technique and the second value being the retention of the compound of Formula III under the same chromatographic conditions. In the present invention, "substantially the same" means that the retention values differ in less than 10%, preferably less than 5%, even more preferably less than 1%, still more preferably less than 0.5%, the most preferably less than 0.1%.

A sixth aspect of the present invention provides a method for the purification of rabeprazole, salt or solvate thereof suitable for pharmaceutical use, comprising the steps of:

- a) preparing rabeprazole, salt or solvate thereof;
- b) assessing the purity of rabeprazole, salt or solvate thereof by using a compound of Formula III as a reference marker; and
- c) subjecting rabeprazole, salt or solvate thereof to purification, wherein step c) may also be carried out before step b).

A seventh aspect of the present invention provides rabeprazole, a salt or solvate thereof substantially free from the compound of Formula III.

The term "substantially free" includes less than 10%, preferably less than 5%, even more preferably less than 1%, still more preferably less than 0.5%, the most preferably less than 0.1% of the compound of Formula III. The term "substantial free" may include rabeprazole completely free from a compound of Formula III.

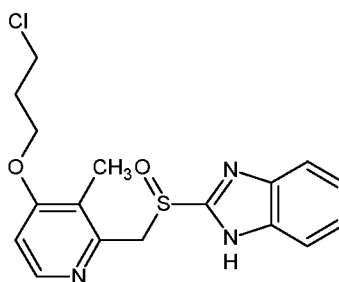
The term "reference marker", as used herein, refers to a compound that may be used in qualitative analysis to identify components of a mixture based on their position, e.g. in a HPLC chromatogram, LC-MS chromatogram or on a Thin Layer Chromatography (TLC) plate, and/or in quantitative analysis to determine the concentration of said compound in a mixture by reference to the concentration of a solution comprising a known amount of said compound.

The purification steps mentioned in step (c) refer to conventional purification techniques, such as chromatography, distillation and crystallization.

The term "reference standard", as used in the context of the present invention, has an equivalent meaning to "reference marker".

An eighth aspect of the present invention provides a process for the preparation of a compound of Formula III

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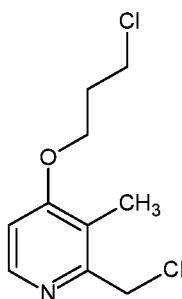


FORMULA III

wherein the process comprises:

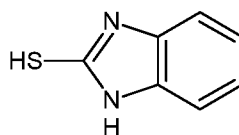
- a) reacting a compound of Formula VIII or a salt

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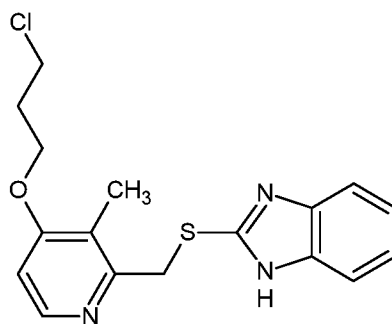
FORMULA VIII

with a compound of Formula VI



FORMULA VI

to prepare a compound of Formula IX; and



FORMULA IX

b) converting the compound of Formula IX to the compound of Formula III.

The compound of Formula VIII may be prepared as described herein in step a) of

5 Example 6.

The reaction of the compound of Formula VIII with the compound of Formula VI is carried out in a solvent optionally in the presence of a base.

The base may be selected from the group consisting of inorganic bases and organic bases. The inorganic bases may be selected from the group consisting of hydroxides, carbonates and bicarbonates. Hydroxides may be, for example, sodium hydroxide, potassium hydroxide or barium hydroxide. Carbonates may be, for example, sodium carbonate, potassium carbonate or barium carbonate. Bicarbonates may be, for example, sodium bicarbonate, magnesium bicarbonate or potassium bicarbonate. The organic bases may be, for example, triethyl amine, ethyl amine, ammonia or diisopropyl ethyl amine. A preferred base is sodium hydroxide.

15 The solvent may be selected from the group consisting of water, alcohols, halogenated hydrocarbons, esters, nitriles, and mixtures thereof. Alcohols may be, for example, methanol, ethanol or methylated ethanol. Halogenated hydrocarbons may be, for example, dichloromethane. Esters may be, for example, ethyl acetate, diisopropyl ethyl acetate. Nitriles may be, for example, acetonitrile. Preferred solvents include water, methylated methanol or
20 mixtures thereof.

The reaction of the compound of Formula VIII with the compound of Formula VI may be carried out at about 10°C to about 50°C, for example, at about 20°C to about 40°C. The reaction of the compound of Formula VIII with the compound of Formula VI may be carried in about 1 hours to about 6 hours, for example in about 2 hours to about 4 hours.

The compound of Formula IX obtained by the reaction of the compound of Formula VIII and the compound of Formula VI may optionally be isolated from the reaction mixture. The term "isolation" includes filtration, distillation, decantation, vacuum drying, evaporation or a combination thereof.

5 The compound of Formula IX is converted to the compound of Formula III in the presence of an oxidizing agent, a base and a solvent. The oxidizing agent may be selected from the group consisting of sodium hypochlorite, hydrogen peroxide, m-chloroperoxybenzoic acid, and cumene hydroperoxide. A preferred oxidizing agent is sodium hypochlorite. Sodium hypochlorite may be used in any strength, for example, from about 2% to about 15 %, for
10 example, from about 6% to about 9 %. The compound of Formula IX is converted to the compound of Formula III in the presence of sodium thiosulphate.

 The base may be selected from the group consisting of inorganic bases and organic bases. The inorganic bases may be selected from the group consisting of hydroxides, carbonates and bicarbonates. Hydroxides may be, for example, sodium hydroxide, potassium hydroxide or
15 barium hydroxide. Carbonates may be, for example, sodium carbonate, potassium carbonate or barium carbonate. Bicarbonates may be, for example, sodium bicarbonate, magnesium bicarbonate or potassium bicarbonate. The organic bases may be, for example, triethyl amine, ethyl amine, ammonia or diisopropyl ethyl amine. Preferred base is sodium hydroxide.

 The solvent used for the conversion of the compound of Formula IX to the compound of
20 Formula III may be selected from the group consisting of water, acetic acid, alcohols, halogenated hydrocarbons, ketones, esters, nitriles, and mixtures thereof. The acetic acid solution may be aqueous or glacial acetic acid. Alcohols may be, for example, methanol, ethanol or methylated ethanol. Halogenated hydrocarbons may be, for example, dichloromethane. Esters may be, for example, ethyl acetate, diisopropyl ethyl acetate. Nitriles may be, for example,
25 acetonitrile. Ethers may be, for example, diisopropyl ether. Ketones may be, for example, acetone. Preferred solvents include water, acetic acid, acetonitrile, ethyl acetate or a mixture thereof.

 The base may be selected from the group consisting of inorganic bases, and organic bases. The inorganic bases may be selected from the group consisting of hydroxides, carbonates and bicarbonates. Hydroxides may be, for example, sodium hydroxide, potassium hydroxide or
30 barium hydroxide. Carbonates may be, for example, sodium carbonate, potassium carbonate or barium carbonate. Bicarbonates may be, for example, sodium bicarbonate, magnesium

bicarbonate or potassium bicarbonate. The organic bases may be, for example, triethyl amine, ethyl amine, ammonia or diisopropyl ethyl amine. A preferred base is sodium hydroxide.

The conversion of the compound of Formula IX to the compound of Formula III may be carried out at about -20°C to about 60°C, for example, at about -10°C to about 50°C. The conversion of the compound of Formula VIII to the compound of Formula III may be carried in about 4 hours to about 8 hours, for example in about 6 hours to about 7 hours.

The compound of Formula III may optionally be isolated. The term "isolation" includes filtration, distillation, decantation, vacuum drying, evaporation or a combination thereof.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of 2-(chloromethyl)-4-(3-methoxypropoxy)-3-methyl pyridine (Formula V)

Dichloromethane (300 mL) was added to [4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methanol (Formula IV) hydrochloride (100 g) and the reaction mixture was cooled to -10°C to -5°C. Thionyl chloride (57.7 g) was added to the reaction mixture at -10°C to -5°C for 30 minutes to 60 minutes. The reaction mixture was stirred at -10°C to -5°C for 30 minutes to 60 minutes. The pH was adjusted to 7.0 to 7.5 with the aqueous sodium carbonate solution (prepared by dissolving 120 g of sodium carbonate in 500 mL of de-ionized water at 20°C to 25°C) at -10°C to -5°C. The temperature of the reaction mixture was raised to 0°C to 5°C. The mixture was allowed to settle for 10 minutes to 20 minutes and the layers obtained were separated. The organic layer was concentrated at 15°C to 30°C at 50 mm to 100 mm Hg of pressure. The residue obtained was dissolved in denatured spirit (100 mL). The mixture was concentrated at 15°C to 30°C at 20 mm to 30 mm Hg of pressure. The residue obtained was used in the next step.

Example 2: Preparation of 2-([4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl)sulfanyl)-1H-benzimidazole (Formula VII)

Sodium hydroxide (24.3 g) was added to de-ionized water (500 mL) and the mixture was stirred. The mixture was cooled to 25°C to 30°C. Denatured spirit (100 mL) and 2-

mercaptobenzimidazole (Formula VI) (63.7 g) were added to the reaction mixture and it was stirred at 25°C to dissolve the solid material. The product obtained in Example 1 was dissolved in 100 mL of methylated ethanol and added to the reaction mixture at 25°C to 30°C for 20 minutes to 30 minutes. The reaction mixture was stirred at 25°C to 30°C for 30 minutes to 60 minutes. De-ionized water (500 mL) was added at 25°C to 30°C for 30 minutes to 45 minutes. The mixture was stirred at 25°C to 30°C for 60 minutes to 70 minutes. The solid obtained was filtered and washed with de-ionized water (2 X 500 mL). The wet solid obtained was dried at 50°C to 55°C till the moisture content was not more than 0.5% w/w in an oven to obtain the title compound.

Yield: 1.32 w/w

Example 3: Preparation of rabeprazole (Formula II)

2-({[4-(3-Methoxypropoxy)-3-methylpyridin-2-yl]methyl}sulfanyl)-1H-benzimidazole (Formula VII) obtained in Example 2 (125 g) was added to acetonitrile (625 mL) and the reaction mixture was cooled to 10°C to 15°C. Sodium hydroxide solution (prepared by dissolving 29.2 g of sodium hydroxide in 475 mL of de-ionized water) was added to the reaction mixture at 8°C to 15°C for 5 minutes to 10 minutes. The reaction mixture was stirred at 8°C to 15°C and cooled to -7°C to -8°C. Sodium hypochlorite (1.05 mole equivalent) was added to the reaction mixture at -8°C to -2°C for 30 minutes to 50 minutes. Sodium thiosulphate solution (prepared by dissolving 12.5 g sodium thiosulphate in 125 mL de-ionized water) was added to the reaction mixture at -8°C to +5°C. The pH of the mixture was adjusted to 8.7 to 9.1 with aqueous acetic acid solution (80 mL; prepared by dissolving 40 mL glacial acetic acid with 40 mL de-ionized water) at 0°C to 5°C. Ethyl acetate (625 mL) was added to the mixture and the temperature was increased to 10°C to 20°C. The mixture was allowed to settle for 10 minutes to 30 minutes and the layers obtained were separated. The organic layer was concentrated at 15°C to 30°C and 20 mm to 30 mm of Hg pressure.

The residue obtained was dissolved in acetone (625 mL) at 25°C to 30°C and the reaction mixture was cooled to 0°C to 5°C. Rabeprazole seed (0.25 g) was added to the reaction mixture and the reaction mixture was stirred at 0°C to 5°C. Diisopropyl ether (625 mL) was added to the mixture at 0°C to 5°C for 30 minutes to 45 minutes. The reaction mixture was stirred at 0°C to 5°C for 60 minutes to 70 minutes. The solid obtained was filtered and washed with pre-cooled (0°C to 5°C) acetone-diisopropyl ether (2 X 125 mL; prepared by dissolving 125 mL acetone in

125 mL diisopropyl ether). The solid obtained was dried at 40°C to 45°C at 10 mm to 20 mm of Hg pressure till the loss on drying was not more than 1.0% w/w to obtain the title compound.

Yield: 0.72 w/w

5 Example 4: Purification of rabeprazole

Rabeprazole (80 g) prepared in Example 3 was added to acetone (1280 mL). The mixture was heated to 30°C to 35°C. Activated carbon (8.0 g) was added to the reaction mixture and it was stirred at 30°C to 35°C for 25 minutes to 35 minutes. The reaction mixture obtained was filtered through celite. The celite was washed with acetone (2 X 180 mL). The mixture obtained
10 was concentrated to 360 mL to 400 mL at 15°C to 30°C and 20 mm to 30 mm of Hg pressure. Diisopropyl ether (400 mL) was added to the reaction mixture at 15°C to 30°C for 30 minutes to 45 minutes. The reaction mixture was cooled to 10°C to 15°C and stirred for 50 minutes to 70 minutes. The solid obtained was filtered and washed with pre-cooled (10°C to 15°C) acetone-
15 diisopropyl ether (2 X 80 mL; prepared by dissolving 80 mL acetone in 80 mL diisopropyl ether). The solid obtained was dried at 40°C to 45°C at 10 mm to 20 mm of Hg till the loss on drying was not more than 0.5% w/w to obtain the title compound.

Yield: 0.825 w/w

Example 5: Preparation of rabeprazole sodium

20 Ethanol (325 mL) was added to sodium hydroxide (7.24 g) and the mixture was heated to 40°C to 45°C. The mixture was stirred at 40°C to 45°C and cooled to 20°C to 25°C. Rabeprazole (65 g) obtained in Example 4 was added to the reaction mixture and it was stirred at 20°C to 25°C. Activated carbon (3.25 g) was added to the reaction mixture and the mixture was stirred at 20°C to 25°C for 30 minutes. The mixture was filtered through celite and washed with
25 ethanol (2 X 130 mL). The filtrates were combined and filtered. The filter paper was washed with ethanol (65 mL) and spray dried under following conditions.

Inlet temperature: 110°C to 120°C

Oxygen Level: Not more than 3.0%

The solid obtained was dried at 60°C to 65°C at 10 mm to 20 mm Hg till the ethanol content is not more than 5000 ppm and water content was not more than 4.5% w/w to obtain the title compound.

Yield: 0.95 w/w

5 **Content of Form III:** 1.5 ppm

HPLC purity: 99.7%

Example 6: Preparation of 2-([4-(3-chloropropoxy)-3-methylpyridin-2-yl]methyl} sulfinyl)-1H-benzimidazole (Formula III)

10 **Step a): Preparation of 2-(chloromethyl)-4-(3-chloropropoxy)-3-methylpyridine (Formula VIII)**

3-[2-(Hydroxymethyl)-3-methylpyridin-4-yl]oxy}propan-1-ol (44 g) was added to dichloromethane (220 mL) at 28°C. The reaction mixture was cooled to 0°C to 5°C. Thionyl chloride (41 mL) dissolved in dichloromethane (88 mL) was added to the reaction mixture at 15 0°C to 5°C for 30 minutes. The reaction mixture was stirred at 20°C to 30°C for 12 hours. The mixture obtained was concentrated at 15°C to 30°C for 30 minutes and used as such in the next step.

Step b): Preparation of 2-([4-(3-chloropropoxy)-3-methylpyridin-2-yl]methyl}sulfanyl)-1H-benzimidazole (Formula IX)

20 Sodium hydroxide (19.14 g) was added to the reaction mixture of water (220 mL) and methylated ethanol (44 mL). 2-Mercapto benzimidazole (Formula VI) (29.67 g) was added to the reaction mixture at 28°C. 2-(Chloromethyl)-4-(3-chloropropoxy)-3-methylpyridine (Formula VIII) obtained in Step a) was dissolved in methylated ethanol (88 mL) and added to the reaction mixture at 20°C to 25°C for 30 minutes and the reaction mixture was stirred for 1 25 hour. The solid obtained was filtered and washed with 50 mL of mixture of methylated ethanol and water (1:1) and then washed with water (200 mL). The solid obtained was dried at 35°C for 12 hours to obtain the title compound.

Yield: 61.2 g

Step c): Preparation of 2-([4-(3-chloropropoxy)-3-methylpyridin-2-yl]methyl)sulfinyl)-1H-benzimidazole (Formula III)

2-([4-(3-Chloropropoxy)-3-methylpyridin-2-yl]methyl)sulfanyl)-1H-benzimidazole (Formula IX) (35 g) obtained in step b) was added to acetonitrile (175 mL) at 28°C. Sodium hydroxide (8.09 g) dissolved in water (131 mL) was added to the reaction mixture at 10°C to 15°C. The reaction mixture was cooled to -2°C to -8°C and sodium hypochlorite (60.86 g) was added in 30 minutes. The reaction mixture was stirred at -2°C to -8°C for 5 hours. A 10% sodium thiosulphate solution (35 mL) was added to the reaction mixture. The pH of the mixture was adjusted to 8 to 9 with acetic acid, and then ethyl acetate (175 mL) was added to the reaction mixture. The solid obtained was filtered and washed with ethyl acetate (2x 20 mL). The solid obtained was dried at 35°C to 40°C for 2 hours to 3 hours to obtain the title compound.

Yield: 20.2 g

¹H NMR (400 MHz, CDCl₃), δ (in ppm): 2.13 (s, 3H, C24-H₃), 2.24 (m, 2H, C21-H₂), 3.70 (t, 2H, J = 6.2 Hz, C22-H₂), 4.12 (m, 2H, C20-H₂), 4.78 (dd, 2H, J = 13.7 Hz C12-H₂), 6.72 (d, 1H, J = 5.6 Hz, C16-H), 7.30 (m, 2H, C7-H, C8-H), 7.48-7.77 (m, 2H, C6-H, C9-H), 8.31 (d, 1H, J = 5.6 Hz, C15-H).

Mass (API 2000), Ion Spray in +ve ion mode: 364.3 [M + H]⁺; MS/MS: 246.0, 199.0.

IR (FT-IR, Perkin Elmer, Spectrum One), in KBr, (in cm⁻¹): 1582 & 1462 (benzimidazole and pyridine ring stretchings), 1224 and 1043 (alkyl aryl C-O stretchings), 1083 (-S=O stretching), 746 (aromatic C-H bending).

Example 7: HPLC method of analysis for the compound of Formula III

The chromatographic separation was carried out in a Kromasil C18, 5 µm, 4.6 mm x 150 mm column at 50°C. The mobile phase was prepared by filtering and degassing an acetonitrile / buffer solution (70:30) v/v mixture. The buffer solution was obtained by dissolving 0.77 g of ammonium acetate in 2000 mL water. The pH of the solution was adjusted to 7.0 ± 0.05 with 1% ammonia solution (prepared by dissolving 1 ml of 25 % ammonia solution in 99 mL water) and filtered through 0.45 µm.

The chromatograph was equipped with a mass spectrometer detector and the flow rate was 1.5 mL per minute. 10 µL of the test samples were injected. The samples were prepared by

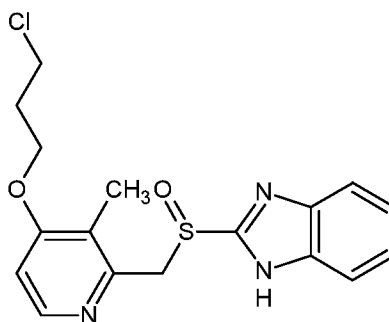
dissolving 50 mg of sample in 100 mL of diluent and diluting 25 mL of solution to 100 mL with diluent. The diluent was prepared by dissolving water and methanol at the ratio of 50:50. The chromatogram was run for at least 15 minutes. The approximate retention time for the compound of Formula III was found to be 10.8 minutes.

5 **LOD (limit of detection):** 0.24 ppm

LOQ (limit of quantitation): 0.31ppm

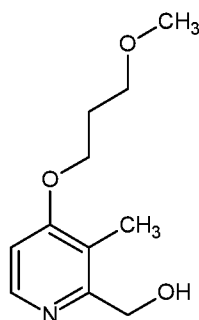
We claim:

- 1 1. A process for the preparation of rabeprazole, a salt and a solvate thereof,
 2 substantially free from the compound of Formula III,

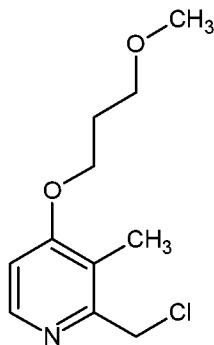
**FORMULA III**

5 wherein the process comprises:

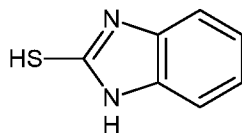
- 6 a) reacting a compound of Formula IV or a salt with a chlorinating agent at a
 7 temperature not exceeding 0°C

**FORMULA IV**

10 to prepare a compound of Formula V or salt thereof;

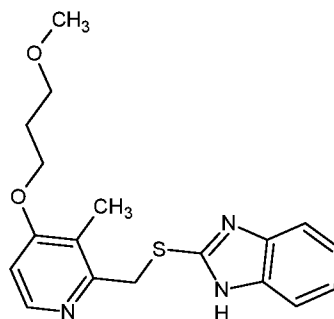
**FORMULA V**

- b) reacting the compound of Formula V or salt with a compound of Formula VI



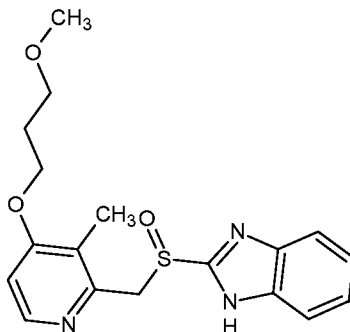
FORMULA VI

- to prepare a compound of Formula VII;



FORMULA VII

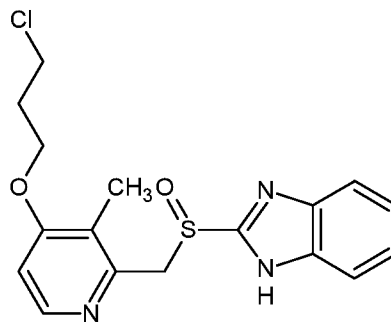
- c) converting the compound of Formula VII to rabeprazole of Formula II; and



FORMULA II

- d) optionally converting the compound of Formula II to its salt or solvate.

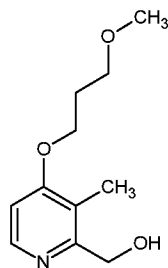
2. A process for the preparation of rabeprazole, a salt or a solvate thereof,
substantially free from a compound of Formula III,



FORMULA III

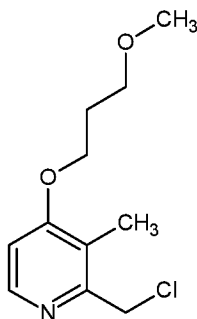
wherein the process comprises:

- a) reacting a compound of Formula IV or a salt thereof with a chlorinating agent at a temperature not exceeding 0°C



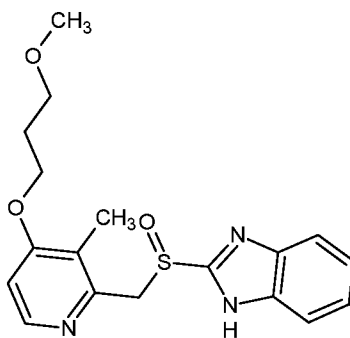
FORMULA IV

to prepare a compound of Formula V or a salt thereof;



FORMULA V

- b) converting the compound of Formula V to rabeprazole of Formula II; and



FORMULA II

c) optionally converting the rabeprazole of Formula II to its salt or a solvate thereof.

3. The process according to claims 1 or 2, wherein the chlorinating agent is selected from the group consisting of thionyl chloride, phosphorous trichloride, phosphorous oxychloride, phosphorous pentachloride, and sulfuryl chloride.

4. The process according to claim 3, wherein the chlorinating agent is thionyl chloride.

5. The process according to claims 1 or 2, wherein the chlorination of the compound of Formula IV or a salt is carried out in the presence of a base.

6. The process according to claim 5, wherein the base is sodium carbonate.

7. The process according to claims 1 or 2, wherein the compound of Formula IV or a salt is reacted with chlorinating agent in the presence of a solvent selected from the group consisting of water, alcohols, halogenated hydrocarbons, esters, nitriles, and a mixture thereof.

8. The process according to claim 1, wherein the compound of Formula V is reacted with the compound of Formula VI in the presence of a base and a solvent.

9. The process according to claim 8, wherein the base is sodium hydroxide.

10. The process according to claim 8, wherein the solvent is selected from the group consisting of water, alcohols, halogenated hydrocarbons, esters, nitriles, and a mixture thereof.

11. The process according to claim 1, wherein the compound of Formula VII is converted to rabeprazole of compound of Formula II in the presence of an oxidizing agent, a base and a solvent.

12. The process according to claim 11, wherein the oxidizing agent is sodium hypochlorite.

1 13. The process according to claim 11, wherein the solvent is selected from the group
2 consisting of water, glacial acetic acid, alcohols, halogenated hydrocarbons, ketones, esters,
3 nitriles, and a mixture thereof.

1 14. The process according to claim 11, wherein the base is organic base or inorganic
2 base.

1 15. The process according to claims 1 or 2, which further comprises the use of the
2 compound of Formula III as a reference marker or a reference standard to analyze the purity of
3 the rabeprazole, a salt or solvates thereof.

1 16. The process according to claim 15, wherein the sample of rabeprazole, a salt or
2 solvates thereof is selected from

- 3 a) rabeprazole active pharmaceutical ingredient or its sodium salt,
- 4 b) a pharmaceutical composition comprising active pharmaceutical ingredient or its
- 5 sodium salt,
- 6 c) a solvates or a salt of rabeprazole, or
- 7 d) a pharmaceutical composition comprising a solvates or a salt of rabeprazole.

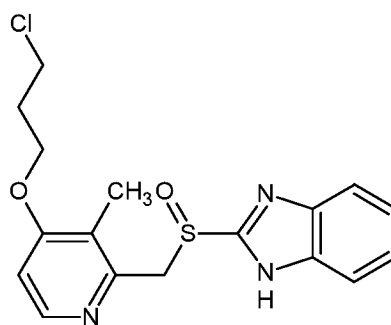
1 17. The process according to claims 1 or 2, which further comprises a
2 chromatographic method for testing the purity of rabeprazole, salt or solvate thereof, comprising
3 the steps of:

- 4 a) dissolving rabeprazole, a salt or solvates thereof in a solvent to produce a sample
- 5 solution;
- 6 b) dissolving a sample of a compound of Formula III in a solvent to make a
- 7 reference marker solution;
- 8 c) subjecting the sample solution and the reference marker solution to a
- 9 chromatographic method; and
- 10 d) determining the compound of Formula III in the sample solution using the
- 11 reference marker solution.

1 18. The process according to claims 1 or 2, which further comprises a method for the
2 purification of rabeprazole, a salt or solvate thereof suitable for pharmaceutical use, comprising
3 the steps of:

- 4 a) preparing rabeprazole, a salt or solvate thereof;
5 b) assessing the purity of rabeprazole, a salt or solvate thereof by using compound
6 of Formula III as a reference marker; and
7 c) subjecting the rabeprazole, a salt or solvate thereof to purification
8 wherein step c) may also be carried out before step b).

1 19. Rabeprazole, a salt or solvate thereof substantially free of the compound of
2 Formula III



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FORMULA III.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/060883

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	EP 0 369 208 A1 (CL PHARMA [AT]) 23 May 1990 (1990-05-23) example 4 ----- -/--	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

20 February 2014

Date of mailing of the international search report

04/03/2014

Name and mailing address of the ISA/

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Authorized officer

Kirsch, Cécile

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/060883

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	----- GANTA MADHUSUDHAN REDDY ET AL: "Identification and characterization of potential impurities of rabeprazole sodium", JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, vol. 43, no. 4, 1 March 2007 (2007-03-01), pages 1262-1269, XP055103321, ISSN: 0731-7085, DOI: 10.1016/j.jpba.2006.10.017 figures 1,3	19
X	----- R REDDY PINGILI ET AL: "Identification and synthesis of potential impurities of rabeprazole sodium", DIE PHARMAZIE, vol. 60, 1 November 2005 (2005-11-01), pages 814-818, XP055103323, figure 3 -----	19

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Information on patent family members

International application No

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