AN IMPROVED PROCESS FOR THE PREPARATION OF PANTOPRAZOLE AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

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Abstract: The present invention relates to an improved process for the preparation of Pantoprazole sodium sesquihydrate comprising the reaction of 5-difluoromethoxy-2-mercapto benzimidazole with 2-chloromethyl-3,4-dimethoxy pyridine hydrochloride in an aqueous alkali, which upon oxidation with sodium hypochlorite having pH of about 8.5-9.0 and assay of about 3.0-3.5 in chloro solvent followed by reaction with sodium hydroxide in acetone. The invention also relates to the process for the preparation of pantoprazole sodium sesquihydrate form-I.
An Improved process for the preparation of Pantoprazole and its pharmaceutically acceptable salts

Related Applications:

This application claims the benefit of Indian patent application number 1480/CHE/2005 and Indian patent application number 1121/CHE/2006 filed on June 30, 2006, all of which are incorporated herein by reference.

Field of the Invention:

The present invention relates to an improved process for the preparation of substituted benzimidazole compounds having pharmaceutical activity and their pharmacologically acceptable salts thereof, especially pantoprazole and its sodium salt. Pantoprazole is chemically known as 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. Pantoprazole and its pharmaceutically acceptable salts represented by the compound of general formula-1.

![Formula-1]

Wherein M is Na⁺, Ca²⁺, K⁺

Gastric proton pump inhibitors include substituted 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles, such as lansoprazole, omeprazole, pantoprazole and rebeprazole. These compounds can produce profound and sustained inhibition of gastric acid secretion, with responses of proton pump inhibitors being more rapid compared with those seen with other anti-secretary drugs. Proton pump inhibitors work by inhibiting the production of gastric acid, by shutting down a system in the stomach known as proton pump, the full name of which is the hydrogen-potassium adenosine triphosphate enzyme system. Proton pump inhibitors are the drugs of choice in dyspepsia and peptic ulcers, and also Zollinger-
Ellyson syndrome. In particular proton pump inhibitors are used in the treatment of peptic ulcers.

Pantoprazole is an active ingredient of a pharmaceutical product that is marketed in the United States by Wyeth-Ayerst Inc., under the brand name Protonix®. Protonix® is approved by U.S. Food and Drug Administration for short-term treatment of erosive esophagitis associated with gastro esophageal reflux disease (GERD), maintenance of healing erosive esophagitis and pathological hypersecretory conditions including Zollinger-Ellison syndrome. According to the package insert for Protonix®, the product contains a monosodium salt of pantaprazole in sesiquihydrate state of hydration.

**Background of the Invention**

Benzimidazole type compounds particularly pantoprazole and process for its preparation was first disclosed in US patent 4758579. The process disclosed in the patent enumerated as example-6 gives the preparation of 2-[(4,5-dimethoxy-2-pyridyl)-methylsulfanyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole (i.e., a analogue of pantoprazole) comprises of dissolving 2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole in 15 ml of dioxane and 2.5 ml of 1N sodium hydroxide solution, followed by a dropwise addition of a solution of 3 ml of 8% sodium hypochlorite and 3.5 ml of 1N sodium hydroxide over a period of 2 hours by maintaining the reaction temperature at 0 to -5°C. After that, 5 ml of 5% sodium thiosulfate solution was added and the reaction mixture was concentrated to dryness. The residue obtained was combined with water, phosphate buffer was added to adjust the pH approximately to 7. The title compound precipitated out, was filtered, dried and recrystallized from ethyl acetate/diisopropyl ether. This patent does not speak about the pH of sodium hypochlorite solution, which plays major role in oxidation reaction. There is no disclosure of purity of the product. Moreover, use of dioxane as a solvent itself has disadvantages of its cost and hazards associated with it.
US Patent publication 2005/075370 discloses a process for the preparation of pantoprazole. The disclosed process for the preparation of pantoprazole comprises of reacting 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole in ethyl acetate solvent with aqueous sodium hydroxide at -10°C followed by the addition of 9.7% sodium hypochlorite drop wise over 15 minutes. The two phase mixture is stirred at room temperature for 3 hours. The phases are then separated and 27% aqueous sodium metabisulfite (7 ml) is added to the aqueous phase to quench unreacted oxidant. The organic phase is washed with water, and the aqueous phase is washed twice with ethyl acetate. The organic phases are combined, dried over sodium sulfate, and evaporated under 20 mm Hg vacuum. The resulting oil is triturated with methyl t-butyl ether and filtered to obtain pantoprazole and the reported yield is 71%. The main drawback of this patent is the presence of unreacted sulfide compound of formula (IV) (0.08%) as an impurity in pantoprazole.

International publication WO02062786 discloses the selective oxidation process for the preparation of Benzimidazole-type compounds using tertiary butyl hydroperoxide in presence of catalyst selected from the group consisting of vanadyl bis-acetylacetonate, sodium meta-vanadate and vanadium pentoxide. Vanadium compounds are costly and produce large amount of effluent.

International publication WO 2006/040778 discloses process for the preparation of pantoprazole sodium sesquihydrate incorporated herein by reference. The disclosed process describes the oxidation of sulfide analog with sodium hypochlorite in methylene chloride at 0-5°C. This application uses diisopropyl ether as an anti solvent to give pantoprazole sodium which is not recommendable for commercial scale up. The present invention avoids the usage of diisopropyl ether as a solvent and avoids the reaction at low temperatures.

International publication WO 2006/064249 discloses a one pot process for the preparation of pantoprazole sodium. The disclosed process for the preparation of pantoprazole sodium comprises of reacting 2-chloromethyl-3,4-dimethoxy pyridine hydrochloride with 2-
mercapto-5-difluoromethoxy benzimidazole in an organic solvent in presence of a phase transfer catalyst and further treating it with an aqueous sodium hypohalite solution comprising sodium hydroxide.

International publication WO 2006/100243 discloses a process for the preparation of pantoprazole. The disclosed process comprises of introducing methoxy group in the 4th position of pyridine ring by replacing chlorine atom by reacting it with alkaline methoxide in a mixture of methanol and an aprotic polar solvent.

International publication WO 2007/026188 discloses a process for the preparation of antiulceratives like pantoprazole, lansoprazole, omeprazole and rabeprazole. The disclosed process for the preparation of benzimidazole compounds comprises of subjecting 2-(2-pyridylmethylthio)benzimidazole compounds to oxidation with sodium hypochlorite solution in presence of an alkali.

US Patent application US 2004/0186139 discloses the process for the preparation of pantoprazole sodium sesquihydrate form-I by reacting pantoprazole with stoichiometric quantity of aq. sodium hydroxide in C1-C4 alcohol or THF or ethyl acetate or acetonitrile, optionally filtering the solution, adding the anti solvent such as aliphatic or alicyclic hydrocarbon, dichloro methane, chloroform, ethers of C1-C4 straight or branched chains for isolation.

Benzimidazole derivatives which act as proton pump inhibitors are very susceptible to degradation under acidic or neutral conditions, hence specific reaction conditions are needed for their preparation. The main problem with the oxidation reaction to convert the sulfide intermediates of formula-4 into the sulfoxide compounds of formula-1 is over-oxidation, i.e. oxidation from sulfoxide compounds of formula-1 to sulfone compounds of formula-6.
Wherein M is hydrogen or Na⁺

The formation of sulfone compounds of formula-6 due to over-oxidation is almost impossible to avoid but can be minimized by performing the oxidation reaction at a low temperature and by restricting the amount of oxidizing agent. Typically the amount of oxidizing agent is less than 1 molar equivalent of the starting material, i.e. sulfide intermediates of formula-4, which inevitably results in a less than 100% conversion of starting material. Usually the amount of oxidizing agent is a compromise between maximum conversion of starting material, maximum formation of sulfoxides of formula-1 and minimum formation of unwanted sulfones of formula-6. Furthermore removal of the sulfones of formula-6 has often proved to be difficult, time-consuming and costly on an industrial scale, particularly when high performance chromatography is needed.

The present invention provides an improved process for the preparation of pantoprazole and its pharmaceutically acceptable salts, preferably sodium salt compound of formula-1, which avoids all the prior art problems.

**Brief description of the Invention:**

Accordingly the first aspect of the present invention is to provide an improved process for the preparation of pantoprazole and its pharmaceutically acceptable salts, preferably sodium salt. Pantoprazole sodium is chemically known as 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benimidazole sodium compound of formula-1a. Pantoprazole and its pharmaceutically acceptable salts thereof represented by the compound of general formula-1,
Wherein M is Mg\textsuperscript{2+}, Ca\textsuperscript{2+}, Na\textsuperscript{+}, K\textsuperscript{+}

An improved process for the preparation of pantoprazole and its pharmaceutically acceptable salts i.e., compounds of formula-1, comprises of the following steps;

a) Reacting the 5-difluromethoxy-2-mercapto benzimidazole compound of formula-2 with 2-chloromethyl-3,4-dimethoxy pyridine hydrochloride compound of formula-3 in presence of an alkali or alkaline metal hydroxide in a suitable polar solvent followed by extracting the reaction mixture with water immiscible solvent like chloro solvent gives the condensed compound of formula-4,

b) Reacting the condensed compound of formula-4, in-situ (without distillation and isolation of compound of formula-4) with an suitable oxidizing agent in a suitable chloro solvent and

c) Decomposing the reaction mixture by adding inorganic salts,

d) Extracting the reaction mixture with suitable chloro solvent and removing the aqueous layer having unreacted sulfide of formula-4 and sulfone by-product which is formed at very minimum level in the reaction,

e) Concentrating the organic layer gives pantoprazole, which on in-situ reaction with suitable alkali metal hydroxide salts in a suitable ketone solvent gives corresponding alkali metal salt of pantoprazole compound of formula-1.

The second aspect of the present invention provides an improved process for the preparation of sulfide compound of general formula-7.

\[
\begin{align*}
R & \rightarrow S \rightarrow R_1 \\
\text{Formula-7}
\end{align*}
\]

wherein R is selected from
wherein $R_2$ is selected from methoxy, ethoxy, monohalomethoxy, dihalomethoxy and trihalomethoxy or hydrogen.

and $R_1$ is selected from the following

![Formula-9a](image)

![Formula-9b](image)

![Formula-9c](image)

![Formula-3](image)

An improved process for the preparation of sulfide compound of formula-7 comprises of reacting the compound of general formula-8 with any one compound of formula selected from 9a, 9b, 9c and 3 in presence of a base in a suitable polar solvent, followed by extracting the reaction mixture with water immiscible solvent like chloro solvent gives the corresponding compound of formula-7.

The third aspect of the present invention provides a process for the preparation of pantoprazole sodium sesquihydrate form-I comprising the steps of;

a) Forming a heterogeneous mixture by contacting any prior art anhydrous or monohydrate crystalline form of pantoprazole sodium with methylene chloride,

b) Aging the heterogeneous mixture,

c) Recovering pantoprazole sodium sesquihydrate form-I from heterogeneous mixture.
The term “proton pump inhibitors of the benzimidazole-type”, “benzimidazole-type compounds” or “compound of formula-1” is meant to include both the neutral form of said compounds and the alkaline salt forms of the said compounds. Alkaline salt forms are for instance the Mg$^{2+}$, Ca$^{2+}$, Na$^+$, K$^+$ or Li$^+$ salts, preferably the Mg$^{2+}$ or Na$^+$ salts. Where applicable, the benzimidazole-type compounds of formula-1 include the racemic form, or a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Any suitable oxidizing agent could be used for the oxidation of sulfide compound of formula-4 and sulfide compounds of general formula-7. Preferable oxidizing agent for the oxidation of sulfides of formula-4 and sulfide compounds of general formula-7 is sodium hypochlorite. Said oxidizing agent is preferably used in an amount of 1.0 molar equivalents of starting material w.r.t sulfide of formula-4 and formula-7. The optimum amount of oxidizing agent depends on the type of the oxidizing agent used, the specific sulfide of formula-4 and further reaction conditions such as solvent and temperature, can easily be determined by the skilled person.

Particular benzimidazole-type compounds of formula-1 that can be prepared by the improved process of the present invention are pantoprazole, rabeprazole, omeprazole, lansoprazole and esomeprazole; in particular Pantoprazole.

The structural formulae of some of these proton pump inhibitors of the benzimidazole-type are represented below

![Pantoprazole](image)
Advantages of the present invention:

- Provides an improved process for the preparation of pantaprazole sodium without isolating sulfide compound of formula-4.
- Use of water as a solvent medium for the preparation of sulfide compounds of general formula-7 and sulfide compound of formula-4.
- Commercially viable and most economical process for industrial scale up.
- Provides a process which controls and reduces the formation of sulfone compound of formula-6 by over oxidation of compound of formula-1.
- Removing any sulfones of formula-6 formed as well as unreacted sulfides of formula-4 by simple extraction in reaction step c) whereby the organic layer contains only the desired benzimidazole-type compound of formula-1 which can be easily isolated using acetone and methylene chloride as solvents.
- Usage of higher amounts of oxidizing agent giving a higher yield of the desired compound of formula-1 and fewer unreacted sulfides of formula-4, since any
undesired sulfones of formula-6 formed, are easily removed by the first extraction step thereby making further purification of the isolated sulfoxides of formula-1 much more easy.

- Oxidation reaction at 25-35°C instead of at 0-5°C, which avoids cooling step.

**Detailed description of the Invention:**

The present invention relates to an improved process for the preparation of pantoprazole and its pharmaceutically acceptable salts, preferably sodium salt. Pantoprazole sodium is chemically known as 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfanyl]-1H-benimidazole sodium compound of formula-1a. Pantoprazole and its pharmacologically acceptable salts are represented by the general formula-1,

![Formula-1](image)

Wherein M is $\text{Na}^+$, $\text{Ca}^{2+}$, $\text{K}^+$

Accordingly the first aspect of the present invention is to provide an improved process for the preparation of pantoprazole and its pharmaceutically acceptable salt compounds of formula-1 which comprises the following steps;

a) Reacting the 5-difluoromethoxy-2-mercapto benzimidazole compound of formula-2

![Formula-2](image)

with 2-chloromethyl-3,4-dimethoxy pyridine hydrochloride compound of formula-3
in presence of an alkali or alkaline metal hydroxide such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, preferably sodium hydroxide in a suitable polar solvent like dimethyl formamide, dimethyl acetamide, dimethylsulfoxide, water and mixtures thereof, preferably water, followed by extracting the reaction mixture with a suitable chlоро solvents like methylene chloride, chlороform, carbon tetrachloride preferably methylene chloride gives the condensed compound of formula-4,

![Formula-3](image)

![Formula-4](image)

b) Reacting the condensed compound of formula-4, in-situ (i.e. without distillation of solvent and without isolating the compound of formula-4) with sodium hypochlorite having pH ranges from 7.5 to 12.0, preferably 8.0 to 11.0, more preferably 8.5 to 9.0 and assay ranging from 2.0 to 4.0, preferably 3.0 to 4.0 more preferably 3.0-3.5, in a suitable chlоро solvents like methylene chloride, chlороform, carbon tetrachloride and chlorobenzene, preferably methylene chloride, at a temperature of about (-5)-35°C, preferably at 25-35°C,

c) Decomposing the reaction mixture by adding inorganic salts like ammonium sulphate, ammonium chloride preferably ammonium sulphate to deactivate an oxidizing reagent which is left unreacted after the reaction i.e., to control over-oxidation of compound of formula-1,
d) Extracting the reaction mixture with a suitable chloro solvents like methylene chloride and removing the aqueous layer having unreacted sulfide of formula-4 and sulfone by-product which is formed at very minimum level in the reaction,

e) Concentrating the organic layer gives pantoprazole compound of formula-5

\[
\begin{align*}
\text{Formula-5} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{S}
\end{array} \\
\begin{array}{c}
\text{OCH}_3 \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{F} \\
\text{F}
\end{array}
\end{align*}
\]

which is then reacting in-situ with a suitable alkali metal hydroxide like aqueous sodium hydroxide in a suitable ketone solvents like acetone, propanone, butanone or acetonitrile preferably acetone followed by purification in ketone solvents like acetone or methylene chloride or mixtures thereof, preferably in acetone followed by wet compound slurry in methylene chloride gives sodium salt of pantoprazole sesquihydrate compound of formula-1a with purity of more than 99.9%.

\[
\begin{align*}
\text{Formula-1a} \\
\begin{array}{c}
\text{F} \\
\text{M} \\
\text{N}
\end{array} \\
\begin{array}{c}
\text{OCH}_3 \\
\text{H}_3\text{CO}
\end{array} \\
\begin{array}{c}
\text{F} \\
\text{O}
\end{array}
\end{align*}
\]

\[.15 \text{ H}_2\text{O}\]

Wherein M is Na$^+$

The second aspect of the present invention is to provide an improved process for the preparation of sulfide compound of general formula-7,

\[
\begin{align*}
R\text{-S} \text{-R}_1 \\
\text{Formula-7}
\end{align*}
\]

wherein R is selected from
wherein $R_2$ is selected from methoxy, ethoxy, monohalomethoxy, dihalomethoxy and trihalomethoxy or hydrogen.

and $R_1$ is selected from the following

5

![Formula-9a](image)

![Formula-9b](image)

![Formula-9c](image)

![Formula-3](image)

an improved process for the preparation of sulfide compound of general formula-7 comprises of reacting the compound of general formula-8 with any one compound of formula selected from 9a, 9b, 9c and 3 in presence of a alkali or alkali metal hydroxide such as sodium hydroxide, sodium carbonate, potassium hydroxide, potassium carbonate, preferably sodium hydroxide in a suitable polar solvent like dimethyl formamide, dimethylsulfoxide, dimethyl acetamide, water and mixtures thereof, preferably water, followed by extracting the reaction mixture with water immiscible solvent such as chloro solvents like methylene chloride, chloroform, or ester solvents like ethyl acetate gives the corresponding compound of general formula-7.

15

The preferred embodiments according to the second aspect of the present invention are, pantoprazole sulfide compound of formula-4, omeprazole sulfide compound of formula-10, lansoprazole sulfide compound of formula-11 and rabeprazole sulfide compound of formula-12.
The third aspect of the present invention provides a process for the preparation of pantoprazole sodium sesquihydrate form-I comprising the steps of:

a) Forming a heterogeneous mixture by contacting any prior art anhydrous or monohydrate crystalline form of pantoprazole sodium with methylene chloride,

b) Aging the heterogeneous mixture for 30-90 minutes at 25-35°C,

c) Recovering pantoprazole sodium sesquihydrate form-I from heterogeneous mixture.
Anhydrous and monohydrate crystalline forms of pantoprazole sodium can be prepared as per the known processes.

The pantoprazole sodium can be micronized to get required particle size for better formulation of the drug substance. Pantoprazole sodium sesquihydrate was milled by a 50 mm micronizer for about 20-30 minutes. The feed nitrogen rate was 6.0 bar and the grinding nitrogen was 1.0 bar pressure at a feed rate of 2-3 kgs per hour to get desired particle size. Micronization of pantoprazole sodium sesquihydrate is carried out by applying one side 1.0 bar nitrogen pressure and another side 6 bar pressure at a feed rate of 2-3 kgs per hour.

The amount of sulfone compound of formula-6 and compound of formula-1 was measured by HPLC Analysis, which is carried out using Inertsil C18, 250 X 4.6, 5 µm, or equivalent, at the wavelength of 290 nm with the flow rate of 1.0 ml/min, at ambient temperature, load is 20 µl, runtime is 40 minutes, RT of the main peak is at about 9 minutes, the diluent is a mixture of 0.01 M borax solution (3.81 grams of borax in 1000 ml of water) and acetonitrile in the ratio of 1:1 and using dilute phosphoric acid as a buffer.

Particle size determination:

Pantoprazole sodium sesquihydrate samples PSD measurement by Malvern particle size analyzer “Master sizer S”

A Malvern master sizer S instrument was used to characterize the particle size distribution of pantoprazole sodium. A Mastersizer S model equipped with a small cell dispersion unit MS1 with small volume sample dispersion unit controller was used. The measurement was done using range lens 300 RF, beam length : 2.40 mm and presentation 3OHD. In this case, a solution of light liquid paraffin is used as a dilution medium. The measurement was started after 1 minute of recirculation after suspension addition into measurement cell at speed rate 2800 rpm. The sample about 200 mg in 20 ml of light liquid paraffin mixed for 2 minutes then sonicated for 30 seconds. According to the accepted rules of GMP, the sample of pantoprazole sodium is preferably measured after a successful blank measurement (% obscuration NMT 0.1%) is performed.

Apart from the regular packing conditions, pantoprazole sodium can be packed in presence of an oxybusters to avoid the formation of undesired sulfone compound in storage.
The present invention is schematically represented by the following scheme:

\[
\begin{align*}
\text{Formula-2} & \quad \text{Formula-3} \\
\text{NaOH/Water} & \quad \text{Methylenechloride} \\
\text{Methylenechloride} & \quad \text{sodiumhypochlorite} \\
\text{NaOH/Acetone} & \quad \text{Methylene chloride} \\
\text{Formula-1a} & \quad 1.5 \text{ H}_2\text{O}
\end{align*}
\]
The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as an illustration only and therefore should not be construed as limitation of the scope of the invention.

**Examples:**

5 Example 1: Preparation of Pantoprazole sodium compound of formula-1a:

Added a solution of 2-chloromethyl-3,4-dimethoxypyridine hydrochloride (50 grams in 250ml of water) to a solution of 49.8 grams of 5-difluoromethoxy 2-mercaptopbenzimidazole, 500 ml water and sodium hydroxide (22.5 grams of flakes in 27.5 ml of water), slowly at 25-35°C. Stirred the reaction mixture for 3 hours. Extracted the reaction mixture thrice with methylene chloride. Separated the organic and aqueous layer. Washed the organic layer with water. Cooled the organic layer to -5 to 0°C. Added 550 grams of 3.1% sodium hypochlorite solution having pH 8.75 and assay 3.2 to the above reaction mixture at -5 to 0°C. Stirred the reaction mixture for 3 hours at -5 to 0°C. Quenched the reaction mixture with 56 grams of ammonium sulphate at below 10°C. Stirred the reaction mixture for 30 minutes. Separated the organic and aqueous phases. Extracted the aqueous phase twice with methylene chloride. Washed the organic layer with water. Dried the organic phase over sodium sulphate. Distilled the solvent completely under reduced pressure at below 45°C. Added 37.5 ml of acetone to the above crude and distilled the solvent completely under reduced pressure at below 45°C. Dissolved the residue in 375 ml of acetone at 25-35°C. Heated the reaction mixture to reflux temperature. Stirred the reaction mixture for 30 minutes at reflux temperature. Cooled the reaction mixture to 18-23°C. Added aqueous sodium hydroxide solution (8.5 grams in 10 ml of water) at 18-23°C. Stirred the reaction mixture for 1 hour at 18-23°C. Cooled the reaction mixture to 0-5°C. Stirred the reaction mixture for 3 hours. Filtered the solid and washed with acetone followed by washed with methylene chloride. The obtained solid is purified in acetone to get pure compound.

The amount of sulfone compound of formula-6 and compound of formula-1 present in the obtained solid was measured using HPLC and the results are as follows.
<table>
<thead>
<tr>
<th>S.No</th>
<th>Experiment</th>
<th>HPLC (%)</th>
<th>Sulfone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PAN/A212/II/18</td>
<td>99.87</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>PAN/A144/II/03</td>
<td>99.91</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Yield: 65 grams

**Example 2: Preparation of Rabeprazole sulfide compound of formula-12:**

A solution of 300 grams of 2-chloromethyl-4(3-methoxy propyloxy)-3-methyl pyridine in 600 ml water is slowly added to a solution of 170 grams of 2-mercapto-1H-benzimidazole in 1200 ml of an aqueous solution of sodium hydroxide (113 grams) at 25-35°C. Stirred the reaction mixture for 4 hours. Quenched the reaction mixture with water and extracted reaction mixture with methylene chloride. Separated the organic and aqueous phases. Washed the organic phase with water. This organic layer containing sulfide compound of formula-12 can be used directly for oxidation step with out distillation and isolation of sulfide compound.

**Example-3: Preparation of pantoprazole sodium sesquihydrate compound of formula-1a:**

Added a solution of 2-chloromethyl-3,4-dimethoxypyridine hydrochloride (50 grams in 250ml of water) to a solution of 49.8 grams of 5-difluoromethoxy-2-mercaptobenzimidazole, 500 ml of water and aqueous sodium hydroxide (22.5 grams of flakes in 27.5ml of water), slowly at 25-35°C. Stirred the reaction mixture for 3 hours. Extracted the reaction mixture thrice with methylene chloride. Separated the organic and aqueous layer. Washed the organic layer with water. Added 550 grams of 3.1% sodium hypochlorite having pH 8.75 and assay 3.2 to the above reaction mixture at 25-30°C for 2 hours. Stirred the reaction mixture for 10 hours at 25-30°C. Quenched the reaction mixture with water at 25-30°C. Stirred the reaction mixture for 30 minutes at 25-30°C. Separated the organic and aqueous phases. Extracted the aqueous layer with methylene chloride. Washed the organic phase twice with aqueous sodium hydroxide solution. Separated the
phases. Cooled the aqueous layer to 10-15°C. Adjusted the pH of the reaction mixture to 9.3 with aqueous acetic acid. Added 250 ml of methylene chloride. Stirred the reaction mixture for 15 minutes. Separated the organic phase. Extracted the reaction mixture with methylene chloride. Washed the organic layer with water. Distilled the solvent completely from organic layer at below 45°C under reduced pressure. Added 37.5 ml of acetone to the crude and distilled the solvent completely under reduced pressure at below 45°C. Dissolved the residue in 375 ml of acetone at 25-35°C. Heated the reaction mixture to reflux temperature. Stirred the reaction mixture for 30 minutes at reflux temperature. Cooled the reaction mixture to 18-23°C. Added aqueous sodium hydroxide solution (8.5 grams in 10 ml of water) at 18-23°C. Stirred the reaction mixture for 1 hour at 18-23°C. Cooled the reaction mixture to 0-5°C and 35 ml of methylene chloride was added. Stirred the reaction mixture for 3 hours. Filtered the solid and washed with methylene chloride. The above obtained compound can optionally purified as follows.

Acetone (400 ml) was added to the above obtained wet compound and heated to reflux. The obtained solution was treated with carbon and cooled the filtrate to 0-5°C. Stirred for 2 hours. Filtered the precipitated solid and washed with 30 ml of chilled acetone followed by washing with 50 ml of methylene chloride. Methylene chloride (250 ml) was added to the obtained wet compound at 25-35°C. Stirred the reaction mixture for 90 minutes at 25-35°C. Filtered the precipitated solid and washed with 25 ml of methylene chloride. Dried the compound at 40-50°C for 10 hours.

Yield: 70 grams
W.C : 5.9 %
HPLC : 99.93 %; 0.02 % (Sulfone Impurity)
PSD : before micronization : D (v,0.1) is 0.4 μm ; D (v,0.5) is 8.73 μm; D (v,0.9) is 27.7 μm and D(4,3) is 12.02 μm.
PSD : after micronization :D (v,0.1) is 1.75 μm; D (v,0.5) is 4.92 μm; D (v,0.9) is 13.10 μm and D(4,3) is 6.35 μm.

Example-4: Preparation of pantoprazole sodium sesquihydrate compound of formula-1a:

Added a solution of 2-chloromethyl-3,4-dimethoxypyridine hydrochloride (50 grams in 250 ml of water) to a solution of 49.8 grams of 5-difluoromethoxy-2-mercaptopbenzimidazole, 500 ml of water and aqueous sodium hydroxide (22.5 grams of
flakes in 27.5ml of water), slowly at 25-35°C. Stirred the reaction mixture for 3 hours. Extracted the reaction mixture thrice with methylene chloride. Separated the organic and aqueous layer. Washed the organic layer with water. Added 550 grams of 3.1% sodium hypochlorite having pH 8.75 and assay 3.2 to the above reaction mixture at 25-30°C for 2 hours. Stirred the reaction mixture for 10 hours at 25-30°C. Quenched the reaction mixture with water at 25-30°C. Stirred the reaction mixture for 30 minutes at 25-30°C. Separated the organic and aqueous phases. Extracted the aqueous layer with methylene chloride. Washed the organic phase twice with aqueous sodium hydroxide solution. Separated the phases. Cooled the aqueous layer to 10-15°C. Adjusted the pH of the reaction mixture to 9.3 with aqueous acetic acid. Added 250 ml of methylene chloride. Stirred the reaction mixture for 15 minutes. Separated the organic phase. Extracted the reaction mixture with methylene chloride. Washed the organic layer with water. Distilled the solvent completely from organic layer at below 45°C under reduced pressure. Added 37.5 ml of acetone to the crude and distilled the solvent completely under reduced pressure at below 45°C. Dissolved the residue in 375 ml of acetone at 25-35°C. Heated the reaction mixture to reflux temperature. Stirred the reaction mixture for 30 minutes at reflux temperature. Cooled the reaction mixture to 18-23°C. Added aqueous sodium hydroxide solution (8.5 grams in 10 ml of water) at 18-23°C. Stirred the reaction mixture for 1 hour at 18-23°C. Cooled the reaction mixture to 0-5°C and 35 ml of methylene chloride was added. Stirred the reaction mixture for 3 hours. Filtered the solid and washed with methylene chloride. Acetone (400 ml) and methylene chloride (40 ml) was added to the obtained wet compound and heated to reflux. The obtained solution was treated with carbon and cooled the filtrate to 0-5°C. Stirred for 2 hours. Filtered the precipitated solid and washed with 30 ml of chilled acetone followed by washing with 50 ml of methylene chloride. Methylene chloride (250 ml) was added to the obtained wet compound at 25-35°C. Stirred the reaction mixture for 90 minutes at 25-35°C. Filtered the precipitated solid and washed with 25 ml of methylene chloride. Dried the compound at 40-50°C for 10 hours.

Yield: 68 grams

W.C : 6.0 %
HPLC : 99.85 %; 0.01 % (Sulfone Impurity)
Example-5: Preparation of pantoprazole sodium sesquihydrate form-I:

A mixture of pantoprazole sodium anhydrous crystalline form (100 gr), methylene chloride (300 ml) and water (5 ml) was stirred for 90 minutes at 25-35°C. Filtered the solid and washed with 25 ml of methylene chloride. Dried the compound at 40-50°C for 10 hours.

Yield: 90 grams
W.C : 6.1 %

Example-6: Preparation of pantoprazole sodium sesquihydrate form-I:

A mixture of pantoprazole sodium monohydrate crystalline form (100 gr), methylene chloride (300 ml) and water (5 ml) was stirred for 90 minutes at 25-35°C. Filtered the solid and washed with 25 ml of methylene chloride. Dried the compound at 40-50°C for 10 hours.

Yield: 92 grams
W.C : 6.2 %
We claim:

1. An improved process for the preparation of pantoprazole sodium sesquihydrate compound of formula-1a

   \[
   \text{Na} \begin{array}{c}
   \text{H}_3\text{CO} \\
   \text{OCH}_3
   \end{array} \begin{array}{c}
   \text{F} \\
   \text{O}
   \end{array} \begin{array}{c}
   \text{N} \\
   \text{S} \\
   \text{N}
   \end{array} \begin{array}{c}
   \text{F} \\
   \text{O}
   \end{array} \begin{array}{c}
   \text{H}_2\text{O}
   \end{array} .1.5\text{H}_2\text{O}
   \]

   Formula-1a

   which comprises of the following steps

   a) Reacting the 5-difluoromethoxy 2-mercapto benzimidazole compound of formula-2

   \[
   \text{H} \\
   \text{SH}
   \]

   Formula-2

   with 2-chloromethyl-3,4-dimethoxy pyridine hydrochloride compound of formula-3

   \[
   \text{Cl} \begin{array}{c}
   \text{OCH}_3
   \end{array} \begin{array}{c}
   \text{H}_3\text{CO}
   \end{array} .\text{HCl}
   \]

   Formula-3

   in presence of an alkali or alkaline metal hydroxide such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, preferably sodium hydroxide in a suitable polar solvent like dimethyl formamide, dimethyl acetamide, dimethysulfoxide, water and mixtures thereof, preferably water, followed by extracting the reaction mixture with a suitable chloro solvents like methylene chloride, chloroform, carbon tetrachloride preferably methylene chloride gives the condensed compound of formula-4,
b) Reacting the condensed compound of formula-4, in-situ (i.e. without distillation of solvent and without isolating the compound of formula-4) with sodium hypochlorite having pH ranges from 7.5 to 12.0, preferably 8.0 to 11.0, more preferably 8.5 to 9.0 and assay ranging from 2.0 to 4.0, preferably 3.0 to 4.0 more preferably 3.0-3.5, in a suitable chloro solvents like methylene chloride, chloroform, carbon tetrachloride and chlorobenzene, preferably methylene chloride,

c) Decomposing the reaction mixture of step b) by adding inorganic salts like ammonium sulphate, ammonium chloride preferably ammonium sulphate to deactivate the oxidizing reagent which is left unreacted after the reaction i.e., to control over-oxidation of compound of formula-1,

d) Extracting the reaction mixture with a suitable chloro solvents like methylene chloride and removing the aqueous layer having unreacted sulfide of Formula-4 and sulfone by-product which is formed at very minimum level in the reaction,

e) Concentrating the organic layer gives pantoprazole compound of formula-5
which is then reacting in-situ with a suitable alkali metal hydroxide like aqueous sodium hydroxide in a suitable ketone solvents like acetone, propanone, butanone or acetonitrile preferably acetone followed by purification in ketone solvents like acetone and/or methylene chloride and/or mixtures thereof, preferably in acetone followed by wet compound slurry in methylene chloride gives sodium salt of pantoprazole sesquihydrate compound of formula-1a.

2. An improved process for the preparation of pantoprazole sodium sesquihydrate compound of formula-1a

\[
\text{Na} \begin{array}{c}
\text{H}_2\text{CO} \\
\text{OCH}_3
\end{array} \begin{array}{c}
\begin{array}{c}
\text{N} \\
\text{S}
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{F}
\end{array}
\end{array} \begin{array}{c}
\text{F} \\
\text{O}
\end{array} \begin{array}{c}
\text{H}_2\text{O}
\end{array} . 1.5 \text{ H}_2\text{O}
\]

Formula-1a

which comprises of the following steps:

f) Reacting the 5-difluoromethoxy 2-mercapto benzimidazole compound of formula-2

\[
\text{H} \begin{array}{c}
\text{N} \\
\text{SH}
\end{array} \begin{array}{c}
\begin{array}{c}
\text{N} \\
\text{F}
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{F}
\end{array}
\end{array} \begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\]

Formula-2

with 2-chloromethyl-3,4-dimethoxy pyridine hydrochloride compound of formula-3

\[
\text{Cl} \begin{array}{c}
\text{N} \\
\text{H}_2\text{CO}
\end{array} \begin{array}{c}
\text{OCH}_3 \\
\text{HCl}
\end{array}
\]

Formula-3

in presence of an alkali or alkaline metal hydroxide such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, preferably sodium hydroxide in a suitable polar solvent like dimethyl formamide, dimethyl acetamide, dimethylsulfoxide, water and mixtures thereof, preferably water, followed by
extracting the reaction mixture with a suitable chloro solvents like methylene chloride, chloroform, carbon tetrachloride preferably methylene chloride gives the condensed compound of formula-4,

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{OCH}_3
\end{array}
\]

Formula-4

g) Reacting the condensed compound of formula-4, in-situ (i.e. without distillation of solvent and without isolating the compound of formula-4) with sodium hypochlorite having pH ranges from 7.5 to 12.0, preferably 8.0 to 11.0, more preferably 8.5 to 9.0 and assay ranging from 2.0 to 4.0, preferably 3.0 to 4.0 more preferably 3.0-3.5, in a suitable chloro solvents like methylene chloride, chloroform, carbon tetrachloride and chlorobenzene, preferably methylene chloride, at a temperature ranges from 10 to 35°C, preferably at 25-35°C,

h) Decomposing the reaction mixture of step b) by adding inorganic salts like ammonium sulphate, ammonium chloride preferably ammonium sulphate to deactivate the oxidizing reagent which is left unreacted after the reaction i.e., to control over-oxidation of compound of formula-1,

i) Extracting the reaction mixture with a suitable chloro solvents like methylene chloride and removing the aqueous layer having unreacted sulfide of Formula-4 and sulfone by-product which is formed at very minimum level in the reaction,

j) Concentrating the organic layer gives pantoprazole compound of formula-5
which is then reacting in-situ with a suitable alkali metal hydroxide like aqueous sodium hydroxide in a suitable ketone solvents like acetone, propanone, butanone or acetonitrile preferably acetone followed by purification in ketone solvents like acetone and/or methylene chloride and/or mixtures thereof, preferably in acetone followed by wet compound slurry in methylene chloride gives sodium salt of pantoprazole sesquihydrate compound of formula-1a.

3. An improved process for the preparation of sulfide compound of general formula-7

$$R^S_R_1$$

Formula-7

wherein R is selected from

$$\text{Formula-8}$$

wherein R₂ is selected from methoxy, ethoxy, monohalomethoxy, dihalomethoxy and trihalomethoxy or hydrogen.

and R₁ is selected from the following

Formula-9a

Formula-9b
which comprises of reacting the compound of general formula-8 with any one compound of formula selected from 9a, 9b, 9c and 3 in presence of a alkali or alkaline metal hydroxide such as sodium hydroxide, sodium carbonate, potassium hydroxide, potassium carbonate, preferably sodium hydroxide in a suitable polar solvent like dimethyl formamide, dimethylsulfoxide, dimethyl acetamide, water and mixtures thereof, preferably water, followed by extracting the reaction mixture with water immiscible solvent such as chloro solvents like methylene chloride, chloroform, or ester solvents like ethyl acetate gives the corresponding compound of general formula-7.

4. The sulfide compounds according to claim 2 are pantoprazole sulfide compound of formula-4, omeprazole sulfide compound of formula-10, lansoprazole sulfide compound of formula-11 and rabeprazole sulfide compound of formula-12.
5. An improved process according to claim 1a), wherein the solvent used for extraction is methylene chloride.

6. An improved process according to claim 1b), wherein the pH of the sodium hypochlorite solution is preferably 8.0 to 11.0, more preferably 8.5 to 9.0.

7. An improved process according to claim 1b), wherein the assay of the sodium hypochlorite solution is preferably 3.0 to 4.0, more preferably 3.0 to 3.5.

8. An improved process according to claim 1e), wherein the solvent used is acetone.

9. An improved process according to claim 1e), wherein the solvent used is acetonitrile.

10. An improved process according to claim 2 g), wherein the temperature of the oxidation reaction is 25-35°C.

11. Sulfone compound of formula-6 content is less than 0.2% in reaction itself.

12. Sulfide compound of Formula4 content is less than 0.2% in reaction itself.
13. Pantoprazole sodium sesquihydrate having mean particle size of approximately 20 µm or less.

14. Pantoprazole sodium sesquihydrate having mean particle size of approximately 10 µm or less.

15. Pantoprazole sodium sesquihydrate having particle size D (v,0.1) is 0.4 µm; D (v,0.5) is 8.73 µm; D (v,0.9) is 27.7 µm and D (4,3) is 12.02 µm.

16. A process for the preparation of pantoprazole sodium sesquihydrate form-I comprising the steps of:

   a) Forming a heterogeneous mixture by contacting any prior art anhydrous or monohydrate crystalline form of pantoprazole sodium with methylene chloride,

   b) Aging the heterogeneous mixture for 30-90 minutes at 25-35°C,

   c) Recovering pantoprazole sodium sesquihydrate form-I from heterogeneous mixture.