Abstract: The present invention relates to one pot process for preparing 2-[(pyridinyl)methyl]sulfinyl-substituted benzimidazoles of Formula (F) or a pharmaceutically acceptable salt, hydrate, or solvate thereof. More particularly, the present invention relates to the process for preparation of omeprazole by in-situ oxidation of compound of general formula (H).
ONE POT PROCESS FOR PREPARING OMEPRAZOLE AND RELATED COMPOUNDS

Field of the Invention
The present invention relates to one pot process for preparing 2-[(pyridinyl)methylsulfinyl]-substituted benzimidazoles of Formula (F) or a pharmaceutically acceptable salt, hydrate, or solvate thereof. More particularly, the present invention relates to the process for preparation of omeprazole by in-situ oxidization of compound of general formula (H')

Background and Prior art
The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

There are a large number of patents and patent applications disclosing different substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles. This class of compounds has properties making the compounds useful as inhibitors of gastric acid secretion and generally known as proton pump inhibitors.

For example the compound (5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl) methyl]sulfinyl}-1H-benzimidazole), with the generic name omeprazole, described in i.e. EP 5129. It is marketed under the brand name Prilosec® for treatment of duodenal ulcer, gastric ulcer and GERD; maintenance of healing of erosive esophagitis, and long term treatment of pathological hyperscretory conditions.

Rabeprazole is another compound of the same class and chemically known by 2-[[4-(3-methoxypropoxy)-2-methyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazoles. It was reported in U.S. Pat. No. 5045552 and marketed in the United States under the brand name Aciphex® for healing of erosive or ulcerative GERD, maintenance of healing of GERD and treatment of symptomatic GERD.

Pantoprazole is the active ingredient of a pharmaceutical product that is marketed in the United States by Wyeth-Ayerst Inc. under the brand name Protonix®. Pantoprazole is

Lansoprazole another compound represented by 2-[[3-methyl-4(2,2,2,- triflouroethoxy)-2-pyridiyl]methyl]sulfinyl]-lH-benzimidazole and reported in U.S Patent No. 4628098. It is marketed under the brand name Prevacid® for short-term treatment of duodenal ulcer, H. Pylori eradication to prevent recurrence of duodenal ulcer and maintenance of healed duodenal ulcers.

These compounds as well as structurally related sulfoxides, have a stereogenic centre at the sulphur atom and thus exist as two optical isomers, i.e. enantiomers. If there is another stereogenic center in the molecule, these compounds can exist as pairs of enantiomers. Corresponding sulphides of such compounds, which already contain a stereogenic center, are not pro-chiral compounds, but chiral compounds. However, the sulphur atom in these compounds does not have asymmetry and therefore they are referred to as pro-chiral sulphides in respect of this invention.

The preparation of 2-[(pyridinyl)methyl]sulfinyl-substituted benzimidazoles of Formula (I) by oxidation of compound of Formula (II) is generally known and is discussed in U.S. patent Nos. 5045552, 4508905 and 4628098.

\[
\begin{align*}
\text{(II)} & \quad \text{Oxidation} \quad \text{(I)} \\
R_4 & \quad R_3 & \quad N \quad S \quad H & \quad R_1 & \quad R_4 & \quad R_3 & \quad N \quad S \quad H & \quad R_1
\end{align*}
\]

However, it has been reported that the sulfone compound of formula (III) is also generated because of over oxidation of thioether compound of formula (II).

\[
\begin{align*}
\text{(II)} & \quad \text{Oxidation} & \quad \text{(III)} \\
R_4 & \quad R_3 & \quad N \quad S \quad H & \quad R_1 & \quad R_3 & \quad N \quad S \quad H & \quad R_1
\end{align*}
\]

Various methods employing various different oxidants to perform this oxidation are known. For example, Canadian Patent No. 1,263,119 describes the use of hydrogen peroxide over a vanadium catalyst (such as vanadium pentoxide, sodium vanadate and
vanadium acteylacetonate). Canadian Patent No. 1,127,158 similarly describes the use of peracids, peresters, ozone, etc. European Patent Application, Publication No. 533,264 describes the use of magnesium monoperoxyphthalate as the oxidizing agent. PCT Publication No. WO91/18895 describes the use of m-chloroperoxy benzoic acid as the oxidizing agent. GB Pat. No. 2,069,492 generally describes this acid and other peroxy acids in the oxidation of substituted (phenylthiomethyl)pyridines.

According to example 32 of 505552, thioether is oxidized by using 0.96 equivalent (on a purity basis) of m-chloroperoxybenzoic acid, to produce sulfoxide at a yield of 80%, which is not an industrially satisfactory yield. Depending on the reaction conditions, disadvantageous, the reaction does not ceased at the stage of sulfoxide production but further proceeds to a side reaction where a part of the produced sulfoxide is furthermore oxidized to sulfone as shown below. When sulfone is formed, there is a problem not only that the yield of the objective sulfoxide is reduced, but also that is difficult to separate and purify them, since there is a close resemblance in physicochemical property between the two. Additionally, the oxidation is conducted in dichloromethane (methylene chloride), but, from a viewpoint of environmental strategies and regulatory aspects, use of halogenated hydrocarbon solvents is preferably avoided. Moreover, m-chloroperoxybenzoic acid is expensive, it is extremely disadvantageous from a viewpoint of the production cost.

US 5374730 relates to omeprazole and lansoprazole, in particular, two novel synthetic methods for their preparation. According to the process, amide analogues of the thioether compounds are oxidized to the corresponding sulfanyl compounds by using hydrogen peroxide as oxidizing agent.

US 6313303 B1 discloses the process for preparing Rabeprazole, Lansoprazole and other related compounds by oxidation thioether precursor compound with N-halosuccinamide, 1,3-dihalo-5,5-dimethylhydantoin or dichloroisocyanurate in the presence of a base.

EP 0484265 A1 discloses the process for the preparation of omeprazole (see example 32 and 33) by oxidation of 2-(((3,5-dimethyl-4-methoxy-2-pyridinyl)methyl)sulfinyl)-5-methoxy-1H-benzimidazole in suitable organic solvent with 50% H₂O₂ in presence of catalyst like (P(WaO₄)₄-XH₂O; ammonium Molybdate, having the formula (NH₄)₂MoO₄; sodium tungstate, having the formula Na₂WO₄; phosphomolybdic acid, having the formula H₃(P(Mo₃O₁₀)₄).XH₂O; and silicotungstic acid, having the formula H₄(Si(W₅O₁₇)₄).XH₂O at lower temperatures. Use of base in
the oxidation process is essential. The process is suffering from tedious and costlier work up for the isolation of the product. The use of organic solvent like methylene dichloride and ethyl acetate and then washing with the same solvent at -15°C is very tedious workup procedure.

EP 0484265 discloses in example-28 and 29, oxidation of omeprazole sulphide of general formula (II) in a mixture of ethyl acetate and 2-ethylhexanoic acid with 68\% m-CPBA to obtain omeprazole. Similarly in example-31, oxidation of omeprazole sulphide of general formula (II) is disclosed in a mixture of ethyl acetate and acetic acid.

The reference work reported in Shanxi Yike Daxue Xuebao, Vol. 34 (4), Pg. 330-332, (2002) discloses the condensation of 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in water/methanol solvent mixture in presence of sodium hydroxide. The omeprazole sulphide of general formula (II) is isolated and oxidized with m-CPBA in MDC to obtain omeprazole.

The Journal of Labelled compounds and Radiopharmaceuticals, Vol. 23(1), Pg. 21-33, (1986) discloses the condensation of 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in water/ethanol solvent mixture in presence of sodium hydroxide. The 14C, 35S and 13C labelled forms of omeprazole were prepared by oxidation of omeprazole sulphide with m-CPBA in MDC.

Russian Patent 2215739 discloses the process for the condensation of 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) to obtain omeprazole sulphide of general formula (II). The reaction is performed in ethanol in presence of sodium hydroxide at 45°C to 50°C at pH 8-10.

WO 2004035565 A1 discloses the process for the condensation of 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) to obtain omeprazole sulphide of general formula (II). The reaction is performed in water at 45°C at pH 12.5 for 2 hours in presence of sodium hydroxide.

There is no report available in the prior for the one pot process for the preparation of omeprazole using 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) and 2-mercapto-5-methoxy benzimidazole of formula
(HI) as the starting material. Hence, there is a need to provide a one-pot process for manufacturing of omeprazole of formula (I), which provides direct isolation of omeprazole by filtration with shorter reaction time and high yield and purity.

There are some patents related to the purity as well as residual alcohols in omeprazole. U.S. Patent No. 6,191,148 B1 claims 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-IH-benzimidazole (omeprazole) of greater than 99.94% purity as determined by high-performance liquid chromatography and having less than 500 parts per million (p.p.m) of residual ethanol relative to omeprazole.

U.S. Patent No. 6,147,103 and U.S. Patent No. 6,166,213 claims 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-IH-benzimidazole (omeprazole) containing less than three parts per million (p.p.m) of residual aromatic hydrocarbon solvent and less than 20 p.p.m of residual methanol relative to omeprazole.

Thus, there is a need to provide a process for the preparation of omeprazole with higher residual methanol greater than 20 ppm and well within the standards of ICH guidelines. Also, the purity of omeprazole is very essential and hence, the process of the present invention provides omeprazole with all the known and unknown individual impurities well within the pharmacopial limits.

The polymorphism is an important criteria for omeprazole. U.S. Patent No. 6,150,380 discloses two polymorphic forms of Omeprazole. Form A and Form B. Form A and Form B are characterized by XRD, Raman Spectra, single crystal, IR etc. analytical evidences. According, to the disclosure in US ’380, the single crystal data and the molecular structure prepared according to EP 5129 and as disclosed in Acta Cryst. (1989), C45, 1921-1923 by Ohishi et al. is omeprazole Form-B.

Eur. Patent No. 1,390,360 claims yet another crystalline Form of omeprazole i.e. omeprazole Form C characterized by X-ray powder diffraction pattern exhibiting the d-spacings, single crystal analysis and IR. Also claimed is the process for the preparation of omeprazole Form C by dissolving crude omeprazole in a solvent or a mixture of solvents in which omeprazole is freely soluble, and precipitating Omeprazole Form C with a solvent in which omeprazole is poorly soluble.

WO 2007008588 A2 discloses the process for the preparation of omeprazole Form-B free from Form-A after being kept under stability for 3 to 6 months at 2°C to 8°C at 60% RH.
Thus, there is still a need to provide a process for preparing omeprazole form-B substantially free from other crystalline forms and having purity of at least 99.75% by HPLC and meeting the pharmacopial requirements for individual impurities.

**Objects of the Invention**

It is an object of the present invention to overcome or substantially ameliorate one or more of the disadvantages of the prior art or at least to provide a useful alternative.

It is another object of the invention to provide a one-pot process for preparing omeprazole of formula (I).

It is another object of the present invention to provide a one-pot process for manufacturing of omeprazole by using 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) and 2-mercapto-5-methoxy benzimidazole of formula (III) as the starting material.

**Summary of Invention:**

According to the first aspect of the present invention, there is provided one pot process for preparing omeprazole of formula (I)

\[
\begin{align*}
&\text{Me} \quad \text{OMe} \\
&\text{N} \quad \text{Me} \\
&\text{S} \quad \text{OMe} \\
&\text{H} \\
&\text{Me} \quad \text{OMe} \\
&\text{N} \quad \text{H} \\
&\text{Me} \quad \text{OMe} \\
&\text{Cl} \quad \text{HCl}
\end{align*}
\]

which comprises of:

(a) reacting 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in organic solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl-thio)-1H-benzo[d]imidazole of formula (II);

\[
\begin{align*}
&\text{Me} \quad \text{OMe} \\
&\text{N} \quad \text{Me} \\
&\text{S} \quad \text{OMe} \\
&\text{H} \\
&\text{Me} \quad \text{OMe} \\
&\text{N} \quad \text{H} \\
&\text{Me} \quad \text{OMe} \\
&\text{Cl} \quad \text{HCl} \\
&\text{OMe} \\
&\text{N} \quad \text{H} \\
&\text{Me} \quad \text{OMe} \\
&\text{S} \\
&\text{OMe}
\end{align*}
\]

(b) in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d] imidazole of formula (II) with an oxidizing agent in presence of catalyst in organic solvent to obtain omeprazole of formula (I).
According to the another aspect of the present invention, there is provided one-pot process for preparing omeprazole of formula (I)

![Chemical structure of formula (I)](image)

which comprises of:

(a) reacting 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in C₁₋₄ alkyl acetate solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d]imidazole of formula (II);

![Reaction of (IV) and (III) to form (II)](image)

(b) in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d]imidazole of formula (II) with an oxidizing agent in presence of catalyst in C₁₋₄ alkyl acetate solvent to obtain omeprazole of formula (I);

According to the second aspect of the present invention, there is provided one-pot process for preparing 2-[(pyridinyl)methyl]sulfinyl-benzimidazoles of Formula (I') or its pharmaceutically acceptable salt, hydrate, or solvate thereof

![Chemical structure of formula (I')] (image)

wherein R₁ is selected from the group consisting of hydrogen or substituted or unsubstituted Q-C₄-alkoxy; R₂ and R₄ are independently selected from the group consisting of hydrogen, Ci-C₄-alkyl or Ci-C₄-alkoxy; R₃ is selected from the group consisting of substituted or unsubstituted Ci-C₄-alkoxy;

which comprises of:

(a) reacting 2-chloromethyl-substituted pyridine hydrochloride of formula (FV") with 2-mercapto-5-substituted benzimidazole of formula (IH') in Ci-C₄ alkyl acetate
solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylthio)-1H-benzo[d] imidazole of formula (H');

(b) in-situ oxidizing thioether compound of formula (H') with suitable oxidizing agent formed by the reaction product of hydrogen peroxide and a catalyst in C1-C4 alkyl acetate solvent; and

wherein Rj, R2, R3 and R4 is same as described above,

(c) isolating 2-[(pyridinyl)methyl]sulfinyl-benzimidazoles of Formula (I) or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

According to another aspect of the present invention, there is provided one pot process for preparation of a crystalline omeprazole form-B, characterized by having at least one of the following properties:

(a) a powder x-ray diffraction (PXRD) pattern substantially in accordance with Figure I; and/or

(b) a powder x-ray diffraction (PXRD) having characteristic peaks at about 9.6, 8.9, 8.0, 7.8, 7.0, 5.9, 5.6, 5.2, 5.0, and 4.4 d-values ±0.04 (Å)

(c) a melting point in the range of about 156°C to about 159°C; and/or

(d) differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure II and having endothermic peak at about 158.3°C; and/or

(e) an Infrared (IR) absorption spectrum in potassium bromide comprising peaks at about 545, 821, 1011, 1017, 1202, 1407, 1587, 3006, 3061 ± 5 cm⁻¹

(f) an Infrared (IR) spectrum substantially in accordance with Figure III.

Brief Description of Drawings

The above and other objects and features of the present invention will become apparent from the following description of the invention taken in conjunction with the following accompanying drawings, which respectively show:

FIG. 1: X-ray diffraction pattern of omeprazole Form-B as obtained in example 1.

FIG. 2: Differential Scanning Calorimetry analysis of omeprazole Form-B as obtained in example 1.
**FIG. 3:** Infrared spectra analysis of omeprazole Form-B as obtained in example 1.

**Detailed Description of the Invention:**

The present invention provides an one pot process for preparing omeprazole of formula (I)

![Chemical Structure](image1)

which comprises of:

(a) reacting 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in organic solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5- dimethylpyridin-2-yl)methylthio)-1H-benzo[d]imidazole of formula (II);

![Chemical Structure](image2)

(b) in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d]imidazole of formula (II) with an oxidizing agent in presence of catalyst in organic solvent to obtain omeprazole of formula (I).

Further the present invention provides an one pot process for preparing omeprazole of formula (I)

![Chemical Structure](image3)

which comprises of:

(a) reacting 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in Ci-C₄ alkyl acetate solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylthio)-1H-benzo[d]imidazole of formula (II);
in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-lH-benzo[d]imidazole of formula (H) with an oxidizing agent in presence of catalyst in C_1-C_4 alkyl acetate solvent to obtain omeprazole of formula (I).

Preferably, the one pot process for preparing omeprazole of formula (I) which comprises of:

(a) reacting 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in C_1-C_4 alkyl acetate solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-lH-benzo[d]imidazole of formula (II);

(b) in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-lH-benzo[d]imidazole of formula (II) with an oxidizing agent in presence of catalyst in C_1-C_4 alkyl acetate solvent in absence of base at about -10^0C to 5^0C;

(c) isolating omeprazole of formula (I);

(d) optionally, purifying said omeprazole by treating with base in a suitable organic solvent;

(e) treating with weak acid; and

(f) isolating omeprazole of formula (I).

According to an embodiment of the present invention, C_1-C_4 alkyl acetate solvent can be selected from ethyl acetate, isopropyl acetate, tert-butyl acetate, n-butyl acetate and the like, preferably ethyl acetate. The condensation can be carried out in presence
of base selected from alkali metal or alkaline earth metal hydroxide, alkoxide, carbonates, bicarbonates, hydrides or ammonia and the like.

According to an embodiment of the present invention, the base can be selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydride or ammonia, preferably sodium hydroxide.

According to an embodiment of the present invention, oxidizing agent can be selected from m-chloroperbenzoic acid, hydrogen peroxide, N-chlorosuccinimide, N-bromosuccinimide, vanadium acetylacetonate and the like. The preferred oxidizing agent is 49% solution of hydrogen peroxide.

Suitable catalyst can be selected from \( \text{P(W}_3\text{O}_4)\text{X}_2\cdot \text{H}_2\text{O}; \) ammonium Molybdate, having the formula \((-\text{NH}_2)_2\text{MoO}_4\); sodium Molybdate, having the formula \(\text{Na}_2\text{MoO}_4\); sodium tungstate, having the formula \(\text{Na}_2\text{WO}_4\); phosphomolybdic acid, having the formula \(\text{H}_3\text{(P(W}_3\text{O}_4)\text{X}_2\cdot \text{H}_2\text{O}; }\) and silicotungstic acid, having the formula \(\text{H}_4\text{(Si(W}_3\text{O}_4)\text{X}_2\cdot \text{H}_2\text{O; preferably sodium Molybdate, having the formula Na}_2\text{MoO}_4\).

According to the present invention, hydrogen peroxide in presence of suitable catalyst itself generates the oxidizing agent. The reaction is preferably carried out in absence of base in an organic solvent for the oxidation of thioether linkage in order to obtain highly pure 2-[(pyridinyl)methyl]sulfanyl-benzimidazoles of formula (II).

According to another embodiment of the present invention, in-situ oxidation of thioether compound of formula (II) is carried out Cl-C\(_4\) alkyl acetate solvent inactive to compound of formula (II), or Formula (I). Preferably oxidation is carried out in ethyl acetate, isopropyl acetate, tert-butyl acetate, n-butyl acetate and the like, preferably ethyl acetate.

Suitable catalyst can be selected from \( \text{P(W}_3\text{O}_4)\text{X}_2\cdot \text{H}_2\text{O; }\) ammonium Molybdate, having the formula \((-\text{NH}_2)_2\text{MoO}_4\); sodium Molybdate, having the formula \(\text{Na}_2\text{MoO}_4\); sodium tungstate, having the formula \(\text{Na}_2\text{WO}_4\); phosphomolybdic acid, having the formula \(\text{H}_3\text{(P(W}_3\text{O}_4)\text{X}_2\cdot \text{H}_2\text{O; }\) and silicotungstic acid, having the formula \(\text{H}_4\text{(Si(W}_3\text{O}_4)\text{X}_2\cdot \text{H}_2\text{O; preferably sodium Molybdate, having the formula Na}_2\text{MoO}_4\).

The substantially pure compound of formula (I) is further isolated by well known techniques used in the art such as filtration, concentration followed by drying.

The said solution of compound of formula (II) is oxidized with 50% hydrogen peroxide in presence of sodium molybdate catalyst. The reaction is preferably carried
out at temperature of -10 to 50°C. More preferably, the reaction is carried out at about 0° to 5°C. The complete reaction time is about 10 minutes to about 3 hours to obtain omeprazole crude.

Upon completion of the reaction, the product is isolated by filtration and washed with suitable organic solvent or mixture thereof with water. Suitable organic solvent can be selected from alcoholic solvent like methanol, ethanol, isopropanol, propanol, ethyl acetate, butyl acetate, isopropyl acetate etc, preferably mixture of methanol and water followed by ethyl acetate to obtain optimum result in terms of better purity and better yield.

Optionally, the isolated omeprazole is purified by treating with base selected from alkali metal or alkaline earth metal hydroxides like sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, lithium hydroxide and the like, alkali metal or alkaline earth metal carbonates or bicarbonates like sodium carbonate, potassium carbonate, calcium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate and the like, preferably sodium hydroxide.

The reaction of omeprazole with base can be carried out in suitable organic solvent selected from alcohols like methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol; hydrocarbons like toluene, xylene, ethylbenzene; ethers like diethyl ether, diisopropyl ether, tetrahydrofuran; esters like ethyl acetate, methyl acetate, isopropyl acetate, butyl acetate; dimethylformamide, dimethyl sulfoxide or mixture thereof with water, preferably methanol or mixture thereof with water.

The pure omeprazole is isolated by treating the reaction mixture with weak acid like acetic acid.

Thus obtain omeprazole is crystalline Form-B which is characterized by a powder x-ray diffraction (PXRD) having characteristic peaks at about 9.7, 8.0, 7.9, 7.1, 5.9, 5.6, 5.3, 5.1, and 4.5 d-values ±0.04 (A).

Further, crystalline omeprazole Form-B is characterized by differential scanning calorimetry analysis having endothermic peak at about 158.3°C.

A crystalline omeprazole Form-B is also characterized by IR having characteristic peaks at about 545, 821, 1011, 1017, 1202, 1407, 1587, 3006, 3061 ± 5 cm⁻¹.
A crystalline omeprazole form-B prepared by the process of the present invention is having particle size distribution D10 less than about 10 µm, D50 less than about 20 µm and D90 less than about 50 µm.

The purity by high-performance liquid chromatography and residual solvent by gas chromatography can be performed by using the known methods as disclosed in U.S. Patents No. 6,191,148, 6,166,213 and 6,147,103 are incorporated herein as reference.

The HPLC purity of omeprazole form-B obtained in the following examples were determined by following HPLC (high performance liquid chromatography) conditions listed below:

- **Column**: Zorbax SB C8 (150x4.6 mm, 5 μ)
- **Flow rate**: 1.0 mL/min
- **Wavelength**: 280 nm
- **Oven temp**: 25°C
- **Buffer**: 1.4 g Na₂HPO₄ → 1000 mL with water, pH 7.8 with OPA (orthophosphoric acid)
- **Mobile Phase**: Buffer : Acetonitrile:::76:24
- **Diluent**: Mobile Phase

According to the another preferred embodiment, there is provided a one-pot process for preparing 2-[(pyridinyl)methyl]sulfinyl-benzimidazoles of Formula (I) or its pharmaceutically acceptable salt, hydrate, or solvate thereof

\[
\text{(I')}
\]

wherein R₁ is selected from the group consisting of hydrogen or substituted or unsubstituted C₁-C₄ alkoxy; R₂ and R₄ are independently selected from the group consisting of hydrogen, C₁-C₄ alkyl or C₁-C₄ alkoxy; R₃ is selected from the group consisting of substituted or unsubstituted Q-C₄ alkoxy; which comprises of:

(a) reacting 2-chloromethyl-3,4,5-substituted pyridine hydrochloride of formula (IV) with 2-mercapto-5-substituted benzimidazole of formula (IIP) in C₁-C₄ alkyl acetate solvent in presence of base to obtain thioether compound of formula (H')
(b) in-situ oxidizing thioether compound of formula (H');

wherein R₁, R₂, R₃ and R₄ is same as described above, with suitable oxidizing agent
formed by the reaction product of hydrogen peroxide and a catalyst in absence of
base in C₁-C₄ alkyl acetate solvent at about -10°C to 50°C; and

(c) isolating 2-[(pyridinyl)methyl]sulfinyl-substituted benzimidazoles of Formula (I')
or its pharmaceutically acceptable salt, hydrate, or solvate thereof

In the case where R₁ represents substituted alkoxy substantially as hereinbefore
described, suitable substituents is selected from the group consisting of hydrogen or
substituted or unsubstituted Q-C₄ alkoxy, especially methoxy.

In the case where R₃ represents substituted alkoxy substantially as hereinbefore
described, suitable substituents one or more alkoxy substituents, such as C₁-C₃ alkoxy,
especially methoxy.

In the preferred embodiment, R₁ is selected from hydrogen atom, methoxy
group or difluoromethoxy group; represents methyl group or methoxy group; R₂
represents methyl group or methoxy group; R₃ represents methoxy group, or 2,2,2-
trifluoroethoxy group; and R₄ represents hydrogen atom or methyl group.

A preferred compound prepared according to a process of the present invention
is lansoprazole, wherein in formula (I) R₄ represents methyl, R₃ represents
trifluoroethoxy, R₂ represents hydrogen and R₁ represents hydrogen.

A further preferred compound prepared according to a process of the present
invention is omeprazole, wherein in formula (I) R₄ represents methyl, R₃ represents
methoxy, R₂ represents methyl and R₁ represents methoxy.

A further preferred compound prepared according to a process of the present
invention is pantoprazole, wherein in formula (I) R₄ represents methoxy, R₃ represents
methoxy, R₂ represents hydrogen and R₁ represents difluoromethoxy.
A further preferred compound prepared according to a process of the present invention is rabeprazole, wherein in formula (I) R₄ represents methyl, R₃ represents -OCH₂CH₂CH₂OMe, R₂ represents hydrogen and R₁ represents hydrogen.

According to the important embodiment of the present invention, there is provided one pot process for the preparation of crystalline omeprazole Form-B of formula (I) comprises of:

(a) reacting 2-chloromethyl-3,4,5-substituted pyridine hydrochloride of formula (IV) with 2-mercapto-5-substituted benzimidazole of formula (III) in presence of sodium hydroxide in ethyl acetate to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d]imidazole of formula (II);

(b) in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d] imidazole of formula (II) with 50% hydrogen peroxide in presence of sodium molybdate catalyst in ethyl acetate at 0°C to 5°C to obtain omeprazole;

(c) purifying crude omeprazole using aqueous sodium hydroxide followed by treatment with acetic acid; and

(d) drying omeprazole wet-cake at 40°C to 45°C to isolate omeprazole of formula (I).

According to the embodiment, the one pot process for the preparation of crystalline omeprazole Form-B of formula (I) having total reaction time of less than 35 hours is in the batch sizes of greater than 30 Kg crystalline omeprazole Form-B.

According to the embodiment, the one pot one pot process for the preparation of crystalline omeprazole Form-B of formula (I) having total reaction time of less than 35 hours is in the batch sizes of greater than 50 Kg crystalline omeprazole Form-B.

According to the present invention, one pot process for the preparation crystalline omeprazole Form B of formula (I) can be illustrated by below mentioned scheme-1, which should not be considered as limiting the scope of the invention.
While the present invention is described with respect to particular examples and preferred embodiments, it is understood that the present invention is not limited to these examples and embodiments. The present invention, therefore, includes variations from the particular examples embodiments described herein, as will be applicant to one of skill in the art.

**Example 1:**

**Preparation of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-IH-benzimidazole (Omeprazole) (I)**

2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride (IV) (100.0 g) and 2-mercapto-5-methoxy benzimidazole (III) (81.0 g) were taken in RBF. Ethyl Acetate (400 mL) was added to RBF at 25°C to 35°C. Sodium hydroxide (50.0 g) solution in water (200 mL) was added to the reaction mass within 30 mins. The reaction mass was stirred for 1 hr and heated to 50°C to 55°C for 1 hr. After completion of the reaction on TLC, reaction mass was cooled to 25°C to 30°C. Water (200 mL) was added and stirred to separate the organic and aqueous layers. Aqueous layer was extracted with ethyl acetate (150 mL) and separated. The combined ethyl acetate layer was charcoalised (5.0 g) and stirred for 30 mins. The reaction mass was filtered through
hyflow bed and washed with ethyl acetate (50 mL). The pH of the organic layer was
adjusted to about 6.0 to 6.5 with acetic acid (0.5 mL) and cooled to 5°C to 10°C.

Sodium molybdate (1.33 g) solution in water (13.2 mL) was added to the
reaction mass and stirred for 15 mins. 50% hydrogen peroxide (37.0 g) was added into
the reaction mass within 1.5 hrs at 5°C to 12°C. The reaction mass was stirred for 5 hrs.
After completion of the reaction on TLC, the reaction mass is treated with sodium
thiosulphate (11.0 g) solution in water (11.0 mL). Sodium hydroxide (6.0 g) solution in
water (6 mL) was added into the reaction mass to adjust the pH of about 7.0 to 7.5. The
reaction mass was further cooled to 0°C to 5°C and stirred for 60 mins. The product was
filtered and washed with mixture of methanol (50 mL) and water (50 mL) followed by
washing with chilled ethyl acetate (75 mL).

Crude omeprazole (120.0 g) wet-cake as obtained above and methanol (160
mL) were taken in another RBF at 25°C to 35°C. Sodium hydroxide (15.8 g) solution in
water (176 mL) was added into the reaction mass. Charcaol (2.6 g) was added and
stirred for 30 mins. The reaction mass was filtered on hyflow bed and washed with
mixture of methanol (10 mL) and water (10 mL). The filtrate was treated with sodium
hydrosulphite (2.0 g). The reaction mass was slowly treated with acetic acid (22.5 mL)
to adjust the pH of about 7.5 to 7.9. The product was filtered and washed with water
(244 mL) and dried at 40°C to 45°C to obtain 100.0 g crystalline omeprazole Form B.

Yield 68% based on input 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine
hydrochloride (IV).

**HPLC purity: 99.87%**

**Individual Impurities are as under:**

**Impurity-A** at RRT 0.44 : 0.01%

**Impurity-B** at RRT 0.46 : Not detected

**Impurity-C** at RRT 0.80 : 0.02%

**Impurity-D** at RRT 0.90 : Not detected

**Impurity-E** at RRT 3.26 : Not detected

**Unk Impurity:** 0.03%

**Total Impurities : 0.13%**

Impurity-A: 5-methoxy-1H-benzimidazole-2-thiol

Impurity-B: 2-[(R,S)-[(3,5-dimethylpyridine-2-yl)methyl]sulphinyl]-5-methoxy-1H-
benzimidazole
Impurity-C: 5-methoxy-2-[[4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphanyl]-1H-benzimidazole [Omeprazole Sulfide]

Impurity-D: 5-methoxy-2-[[4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphonyl]-1H-benzimidazole [Omeprazole Sulfone]

Impurity-E: 4-methoxy-2-[[[(R,S)-(5-methoxy-1H-benzimidazole-2-yl)-sulphinyl)methyl]-3,5-dimethylpyridine-1-oxide [Omeprazole N-Oxide]

Advantages of Invention:

1) The present invention provides one pot process for the preparation of Omeprazole Form-B.

2) The present invention provides one pot for the preparation of Omeprazole Form-B having total reaction time of less than about 35 hours and purity of atleast 99.70% but not more than 99.90% by area percentage of HPLC.

3) The present invention provides an improved process for the purification of crude omeprazole to obtain polymorphic Form-B.

4) The present invention provides a simple, cost effective and large scale applicable process for the preparation of omeprazole Form-B in batch size of 30 Kg, preferably 50 Kg.

5) The present invention is very simple with shorter reaction time for large-scale production cycle.
Claims:

1. One pot process for preparing omeprazole of formula (I)

   ![Chemical Structure](image1)

   which comprises of:

   (a) reacting 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in organic solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl-thio)-1H-benzo[d]imidazole of formula (II);

   ![Chemical Reaction](image2)

   (b) in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d]imidazole of formula (II) with an oxidizing agent in presence of catalyst in organic solvent to obtain omeprazole of formula (I).

2. A process according to claim 1, wherein organic solvent is ethyl acetate.

3. One pot process for preparing omeprazole of formula (I)

   ![Chemical Structure](image3)

   which comprises of:

   (a) reacting 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in C_1-C_4 alkyl acetate solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylthio)-1H-benzo[d]imidazole of formula (II);
(b) in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d]imidazole of formula (II) with an oxidizing agent in presence of catalyst in Ci-C₄ alkyl acetate solvent to obtain omeprazole of formula (I).

4. One pot process for preparing omeprazole of formula (I) which comprises of:

(a) reacting 2-(chloromethyl)-3,5-dimethyl-4-methoxy pyridine hydrochloride of formula (IV) with 2-mercapto-5-methoxy benzimidazole of formula (III) in Ci-C₄ alkyl acetate solvent in presence of base to obtain 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d] imidazole of formula (II);

(b) in-situ oxidizing 5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1H-benzo[d]imidazole of formula (II) with an oxidizing agent in presence of catalyst in Ci-C₄ alkyl acetate solvent in absence of base at about -10°C to 50°C;

(c) isolating omeprazole of formula (I);

(d) optionally, purifying said omeprazole by treating with base in a suitable organic solvent;

(e) treating with weak acid; and

(f) isolating omeprazole of formula (I).

5. A process according to claims 2-3, wherein Ci-C₄ alkyl acetate solvent can be selected from ethyl acetate, isopropyl acetate, tert-butyl acetate, n-butyl acetate and the like, preferably ethyl acetate.
6. A process according to any one of claims 1-3, wherein base is selected from alkali metal or alkaline earth metal hydroxide, alkoxide, carbonates, bicarbonates, hydrides or ammonia and the like.

7. A process according to claim 6, wherein base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydride or ammonia.

8. A process to claims 1-3, wherein oxidizing agent is selected from m-chloroperoxybenzoic acid, hydrogen peroxide, N-chlorosuccinimide, N-bromosuccinimide, vanadium acetylacetonate and the like.

9. A process according to claims 1-3, wherein catalyst is selected from (P(W₃O₁₀)₄·X.H₂O; ammonium Molybdate, having the formula (NFL₄)₂MoO₄; sodium Molybdate, having the formula Na₂MoO₄; sodium tungstate, having the formula H₃(P(MO₄)₁₀)₄·XH₂O; and silicotungstic acid, having the formula H₄(Si(W₂O₁₀)₄·XH₂O), preferably sodium Molybdate, having the formula Na₂MoO₄.

10. A process according to claim 3 (d), wherein suitable organic solvent is selected from alcohols like methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol; hydrocarbons like toluene, xylene, ethylbenzene; ethers like diethyl ether, diisopropyl ether, tetrahydrofuran; esters like ethyl acetate, methyl acetate, isopropyl acetate, butyl acetate; dimethylformamide, dimethyl sulfoxide or mixture thereof with water.

11. A process according to claim 10, wherein suitable solvent is methanol or mixture thereof with water.

12. A process according to claim 3 (d), wherein base can be selected from alkali metal or alkaline earth metal hydroxides like sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, lithium hydroxide and the like, alkali metal or alkaline earth metal carbonates or bicarbonates like sodium carbonate, potassium carbonate, calcium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate and the like, preferably sodium hydroxide.

13. A process according to claim 3 (f), wherein weak acid is acetic acid.

14. A process according to any preceding claims, wherein isolated omeprazole is crystalline Form-B characterized by having atleast one of the following properties:
(a) a powder x-ray diffraction (PXRD) pattern substantially in accordance with Figure I; and/or
(b) a powder x-ray diffraction (PXRD) having characteristic peaks at about 9.6, 8.9, 8.0, 7.8, 7.0, 5.9, 5.6, 5.2, 5.0, and 4.4 d-values ±0.04 (A)
(c) a melting point in the range of about 156°C to about 159°C; and/or
(d) differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure II and having endothermic peak at about 158.3°C; and/or
(e) an Infrared (IR) absorption spectrum in potassium bromide comprising peaks at about 545, 821, 1011, 1017, 1202, 1407, 1587, 3006, 3061 ± 5 cm⁻¹
(f) an Infrared (IR) spectrum substantially in accordance with Figure III.
15. Crystalline omeprazole form-B according to claim 14, having purity of at least 99.70% but not more than 99.90% by area percentage of HPLC and having individual impurities as below:
impurity-A not more than about 0.05%, impurity-B not in detectable amount, impurity-C not more than 0.05%, impurity-D not in detectable amount, impurity-E not in detectable amount, impurity 8-methoxy-1,3-dimethyl-12-thioxopyrido-[r,2':3,4]imidazo[1,2'-a]- benzimidazol-2(12H)-one and impurity 9-methoxy-1,3-dimethyl-12-thioxopyrido [1',2':3,4]imidazo[1,2-a]benzimidazole-2[12H]-one not in detectable amount by area percentage of HPLC.
16. A process according to any preceding claim, wherein crystalline omeprazole form-B prepared by the process of the present invention is having particle size distribution D₁₀ less than about 10 µm, D₅₀ less than about 20 µm and D₉₀ less than about 50 µm.
17. A process according to any preceding claim, wherein crystalline omeprazole Form-B is prepared in the batch sizes of greater than 30 Kg.
18. A process according to claim 17, wherein crystalline omeprazole Form-B is prepared in the batch sizes of greater than 50 Kg.
19. A process for preparing 2-[(pyridinyl)methyl]sulfanyl-benzimidazoles of formula (I') or a pharmaceutically acceptable salt, hydrate, or solvate thereof,
wherein \( R_1 \) is selected from the group consisting of hydrogen or substituted or unsubstituted \( Q.Q\text{alkoxy} \); \( R_2 \) and \( R_4 \) are independently selected from the group consisting of hydrogen, \( C_1-C_4\text{alkyl} \) or \( Ci-C_4\text{alkoxy} \); \( R_3 \) is selected from the group consisting of substituted or unsubstituted \( Q-C_4\text{alkoxy} \); which comprises of:

(a) reacting 2-chloromethyl-3,4,5-substituted pyridine hydrochloride of formula (IV) with 2-mercapto-5-substituted benzimidazole of formula (III') in \( Ci-C_4\text{alkyl acetate} \) solvent in presence of base to obtain thioether compound of formula (III)

(b) in-situ oxidizing thioether compound of formula (III');

(c) isolating 2-[(pyridinyl)methyl]sulfinyl-substituted benzimidazoles of Formula (V) or its pharmaceutically acceptable salts, hydrates or solvate thereof.

20. A process according to claim 19, wherein \( R_1 \) represents substituted alkoxy substantially as hereinbefore described, suitable substituents is selected from the group consisting of hydrogen or substituted or unsubstituted \( Ci-C_4\text{alkoxy} \), especially methoxy.

21. A process according to claim 19, wherein \( R_3 \) represents substituted alkoxy substantially as hereinbefore described, suitable substituents one or more alkoxy substituents, such as \( C_1-C_3\text{alkoxy} \), especially methoxy.

22. A process according to claim 19, wherein \( R_1 \) is selected from hydrogen atom, methoxy group or difluoromethoxy group; represents methyl group or methoxy group; \( R_2 \) represents methyl group or methoxy group; \( R_3 \) represents methoxy group, or 2,2,2-trifluoroethoxy group; and \( R_4 \) represents hydrogen atom or methyl group.
23. A process according to claim 19, wherein compound prepared according to a process of the present invention is lansoprazole, wherein in formula (I) R₄ represents methyl, R₃ represents trifluoroethoxy, R₂ represents hydrogen and R₁ represents hydrogen.

24. A process according to claim 19, wherein compound prepared according to a process of the present invention is omeprazole, wherein in formula (I) R₄ represents methyl, R₃ represents methoxy, R₂ represents methyl and R₁ represents methoxy.

25. A process according to claim 19, wherein compound prepared according to a process of the present invention is pantoprazole, wherein in formula (I) R₄ represents methoxy, R₃ represents methoxy, R₂ represents hydrogen and R₁ represents difluoromethoxy.

26. A process according to claim 19, wherein compound prepared according to a process of the present invention is rabeprazole, wherein in formula (I) R₄ represents methyl, R₃ represents -OCH₂CH₂OMe, R₂ represents hydrogen and R₁ represents hydrogen.

27. A process of preparing crystalline omeprazole Form-B substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.
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 b the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

See patent family annex

Date of the actual completion of the international search
11 October 2010

Date of mailing of the international search report
15/10/2010

Name and mailing address of the ISA/
European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040,
Fax (+31-70) 340-3016

Authorized officer
Johnson, Claire
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