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# Synthesis of degradants and impurities of rabeprazole

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***Abstract*---**Rabeprazole is an antiulcer drug comes under the Pharmacological class (antisecretory compounds) which is Proton-pump inhibitor, and It's used for heartburn, acid reflux and GORD (gastro-oesophageal reflux disease). Rabeprazole is also used to prevent and treat stomach ulcers. We have observed some of the metabolite and impurities during the process of synthesis of Rabeprazole. The main aim of the present work is to synthesis and characterisation of impurities and metabolites.

***Keywords*---**metabolite, impurities, rabeprazole, anti-ulcerative drug.

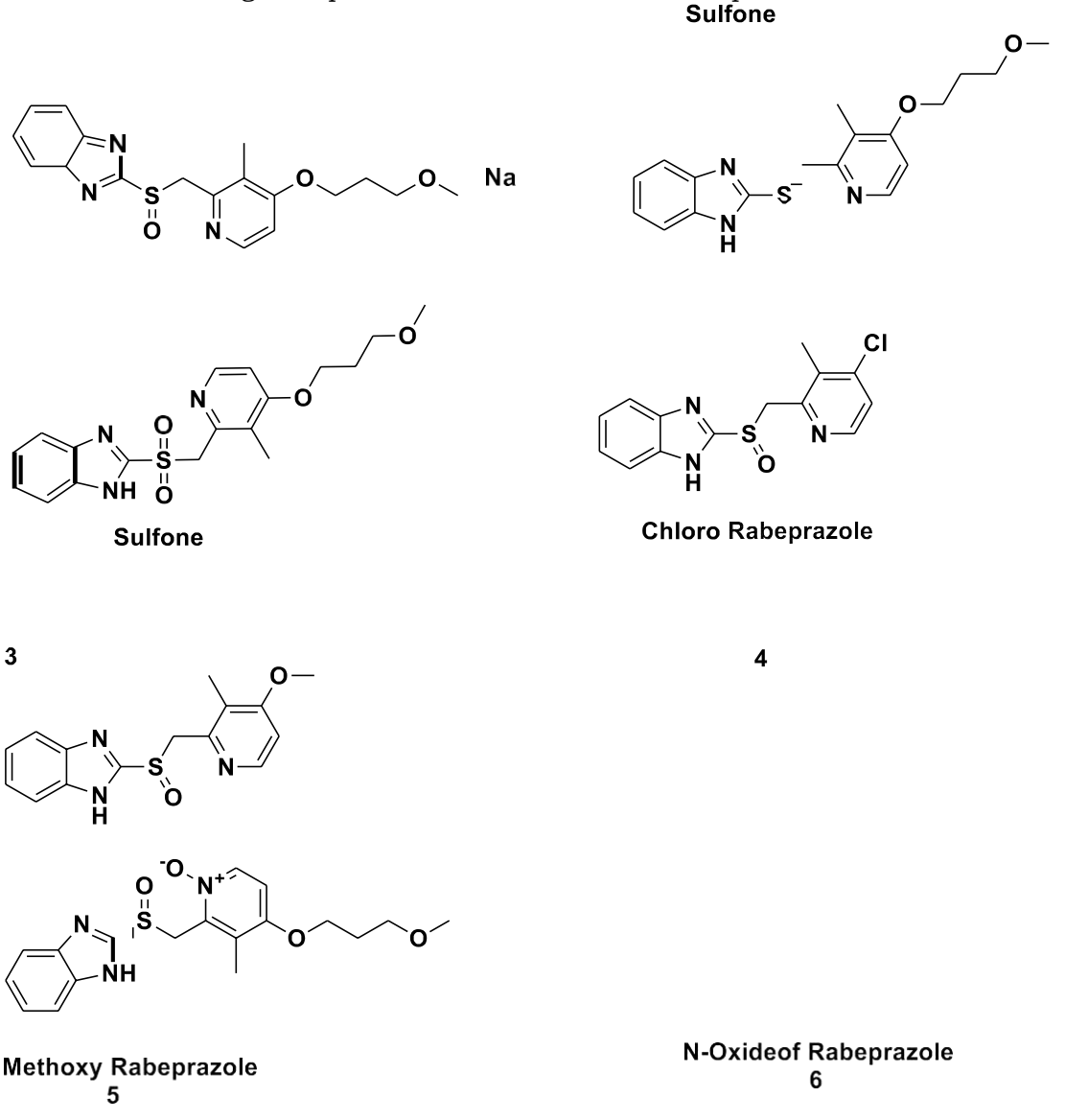
## Introduction

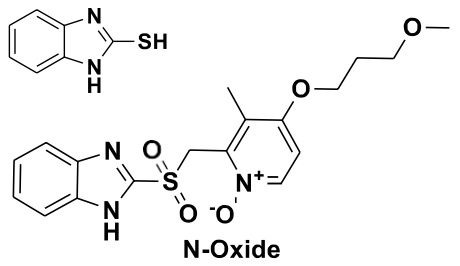
Rabeprazole belongs to class of antisecretory compounds which do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but supress gastric acid secretion by inhibiting the gastric H+/K+ATPase ( ATP- Adenosine Triphosphatase) at the secretory surface of the gastric parietal cell. Rabeprazole blocks the final step of the gastric acid secretion. The presence of the impurities and metabolites which will have a significant impact on the quality and safety of the final drug. As per the ICH and EP and USP Monograph all the impurities and related substances must be in the limits of < 0.10%, by identifying and minimizing these impurities to can get high purity desired compound or product, as these impurities are not available in the market and which are highly useful to companies producing Rabeprazole. This is the main objective in the synthesis of these impurities.

**Results and Discussions**

Synthesis and information regarding these impurities and some of the precursors which are important for the synthesis of these impurities which are notavailable are also synthesised which are highly useful for the bulk manufacturers of Proton-pump inhibitor drug Rabeprazole and useful for the analytical development of the drug and regulatory agencies.

Fig 1. Impurities and metabolites of Rabeprazole

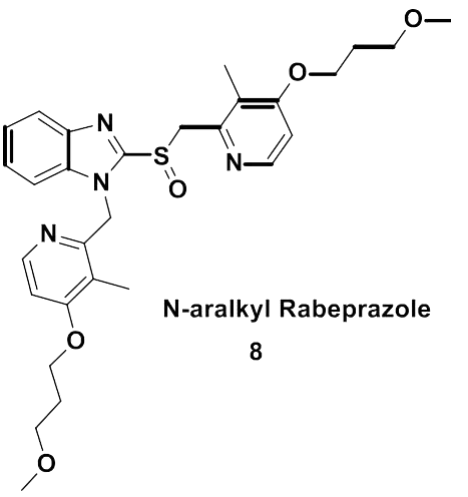




N-Oxide

Rabeprazole sulfone-N-oxide

7

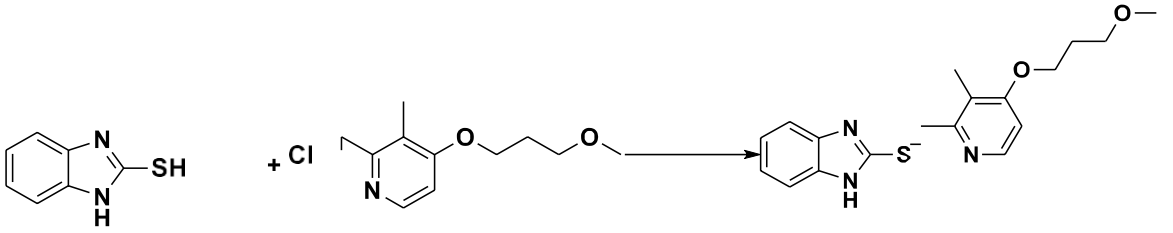


N-aralkyl Rabeprazole

8

**Synthesis Schemes**

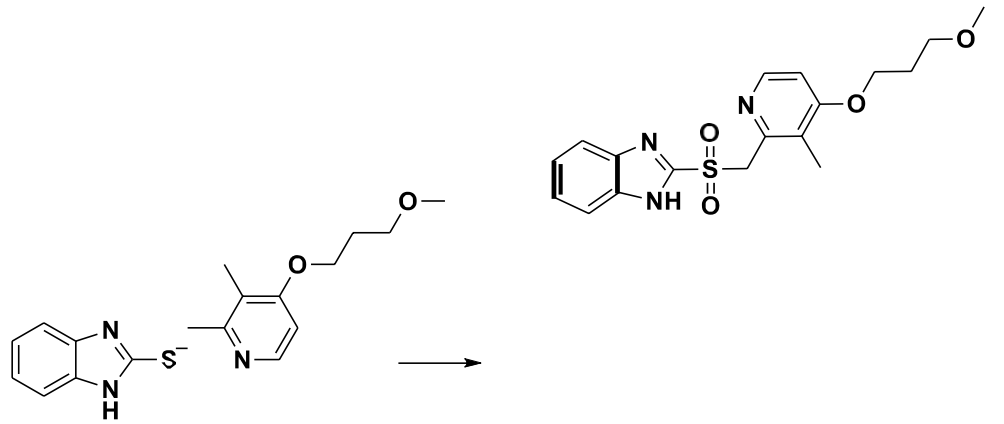
***Scheme-1*** Synthesis of Rabeprazole Sulfide **(2)**



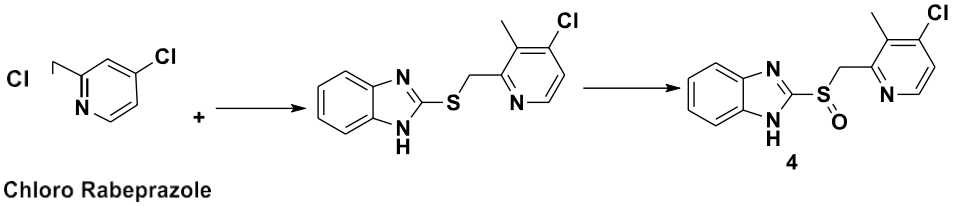
Rabeprazole Sulfide

2

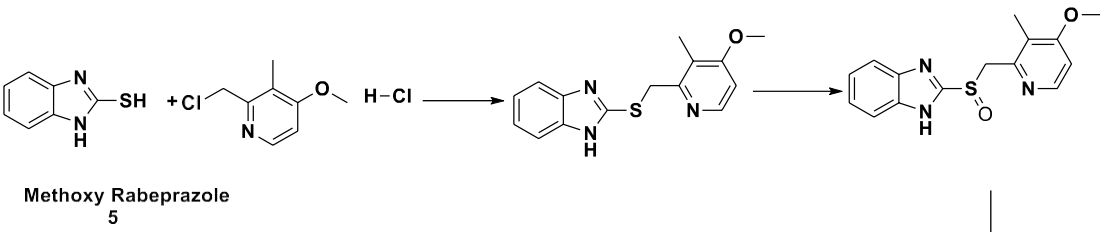
***Scheme-2*** Synthesis of Rabeprazole Sulfone **(3)** from Rabeprazole Sulfide **(2)**



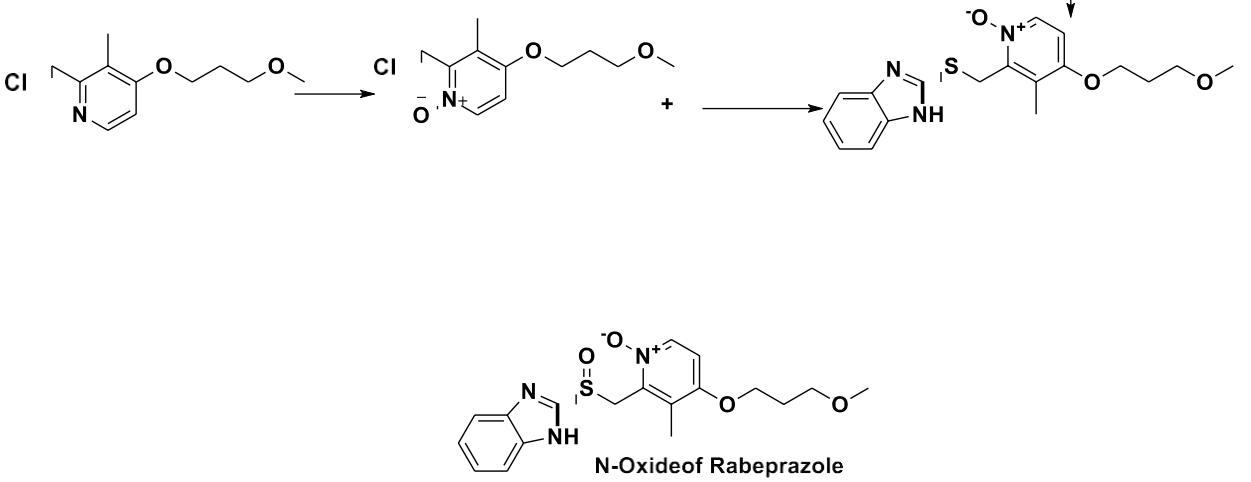
***Scheme-3*** Synthesis of Chloro Rabeprazole **(4)**

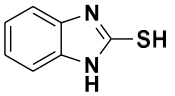



***Scheme-4*** Synthesis of Methoxy Rabeprazole **(5)**

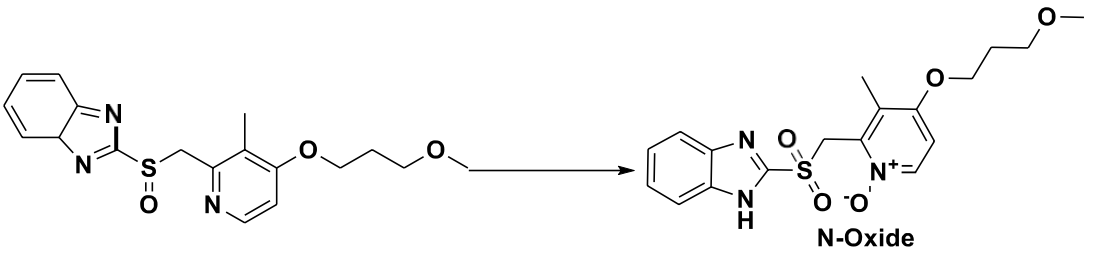



***Scheme-5*** Synthesis of N-Oxide of Rabeprazole **(6)**





***Scheme-6*** Synthesis of Rabeprazole sulfone-N-oxide **(7)**



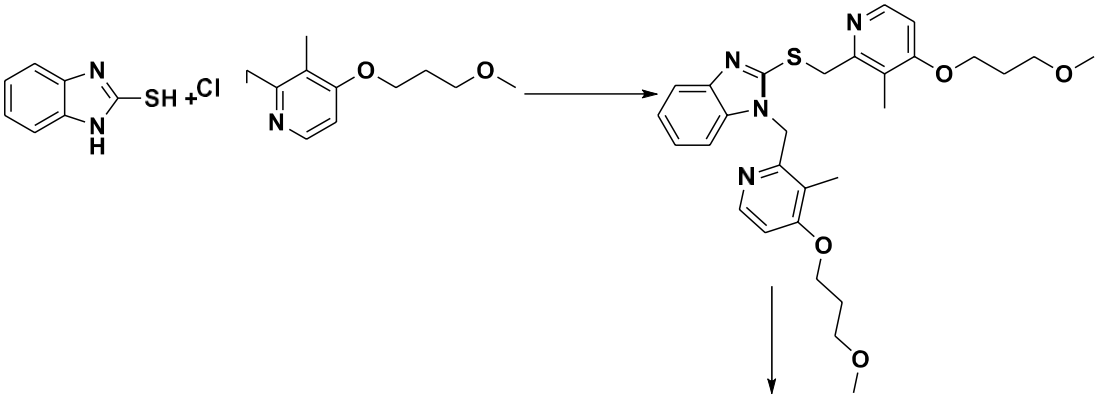

**Rabeprazole free base**

**Rabeprazole sulfone-N-oxide**

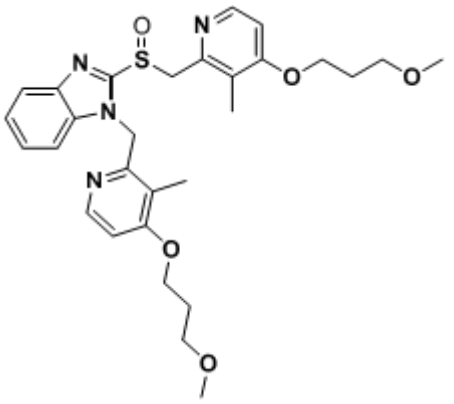
**1** **7**

***Scheme-7 ROS-1*** Synthesis of N-aralkyl Rabeprazole **(8)**

**N-aralkyl Rabeprazole ROS-1**



**N-aralkyl Rabeprazole**



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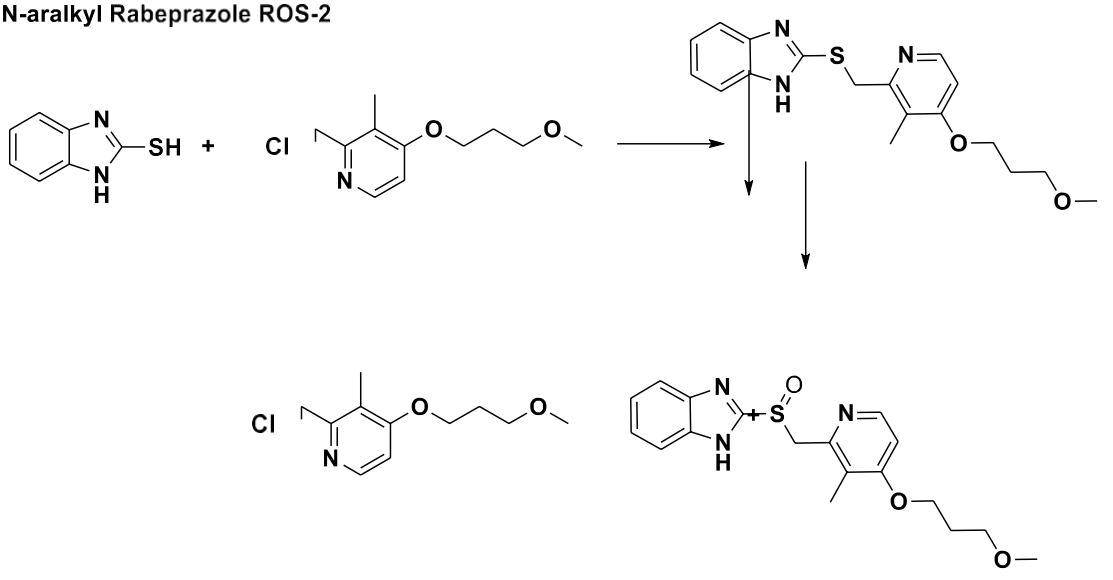
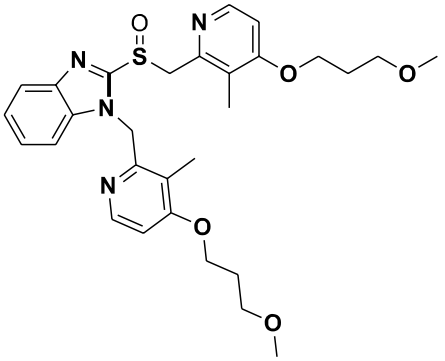
***Scheme-8 ROS-2*** Synthesis of N-aralkyl Rabeprazole **(8)**





N-aralkyl Rabeprazole

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**Experimental**

All compound synthesised were well analysed and charactered, 1H NMR were recorded at 400 MHz. The mass analysis was performed on Waters LC-MS mass spectrometer. Melting points were determined on capillary melting-point apparatus without correction. The solvents and reagents were used without any further purification.

**Rabeprazole Sulfide 2**

*2-(((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methyl)thio)-1H- benzo[d]imidazole*

To a stirred solution of 1H-benzo[d]imidazole-2-thiol (3.85g), NaOH (1.875g) in acetone 25mL, and water 25mL, a solution of 2-(chloromethyl)-4-(3-methoxypropoxy)-3-methylpyridine (5.0 g,) in water (25.0 mL) was added dropwise over a period of 45 min at 15–25°C. after the addition completed, the precipitated solid was filtered, washed with 50:50 mixture of acetone and water (10.0 mL),dried in vaccum oven at 45° C to provide compound Rabeprazole Sulfide 6.0 g, 85% yield.
Mp: 116–118° C; m/z+1H ES-MS : 344;

**Rabeprazole Sulfone 3**

*2-(((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methyl)sulfonyl)-1H-benzo[d]imidazole*

Prepare a solution of mCPBA (5.0 g, 20.2 mmol) in chloroform (17.0 mL) was added to a solution of 2 (10.0 g, 20.2 mmol) in chloroform (17.0 mL) and MeOH(9.0 mL) dropwise for about 30mins at room temperature condition. Stir for 30 mins after additions, TLC indicates completions of starting material. Reaction mass was added to the 5% NaOH solution), and the pH was adjusted to 7–7.5 with acetic acid, organic layer was separated, and extracted with 3% NaOH aqueous solution, washed with chloroform, Acetone (25.0 mL) was added to the aqueous phase and cooled to 5–10 C. pH was adjusted to 8–8.5 with AcOH; the isolated solid was

filtered, washed with 1:1 mixture of water and acetone (20.0 mL), and dried, to get compound Rabeprazole Sulfone 2.5 g, 76% yield.
Mp: 138–142 C; m/z+1H ES-MS 376.0

**Rabeprazole Chloro Impurity 4**

*2-{[(4-chloro-3-methylpyridin-2-yl)-methyl]-sulfinyl}-1H-benzimidazole*

To a round bottom flask, 1H-benzo[d]imidazole-2-thiol (3.9 g, 12.95mmol), NaOH (4.6 g, 115.0 mmol), and water (30 mL), was added a solution of 4- chloro-2-(chloromethyl)-3-methylpyridine (4.6g, 12.25mmol) in water (10 mL) at Room Temparature for 30 min. Stirring was continued for additional 1h at the same temperature, a solid was separated which was filtered,dried under vacuum to get 2-(((4-chloro-3-methylpyridin-2-yl)methyl)thio)-1H- benzo[d]imidazole 6g, 95%.

To a solution of 2-(((4-chloro-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (3.2g, 11.04mmol), 35ml of dichloromethane was added m-CPBA (2.29gm, 13.25mmol) in 20ml of dichloromethane temperature 10°C to 15°C for 20 mins. After stirring for 20 mins, 10ml of 50% NaOH solution was added to the reaction mass. The reaction mass pH was adjusted to 8.0 – 8.5with acetic acid, extracted with dichloromethane (3X10 mL). The solvent was evaporated. The obtained crude was treated with ether at 10°C to get a solid precipitated . Filtered,dried to get Rabeprazole Chloro Impurity : 2g, 50%.

**Methoxy Rabeprazole 5**

*2-(((4-methoxy-3-methylpyridin-2-yl)methyl)sulfinyl)-1H-benzo[d]imidazole*

To a solution of 2-chloromethyl-4(methoxy)-3-methylpyridine (3gm 10 g, 14.42mmol) in 10ml of water was added a solution of 3.5gm 23.3mmol of 1H-benzo[d]imidazole-2-thiol, in 3% NaOH Solution 30ml is added dropwise at room temperature for 30min. Solid precipitated was filtered and washed with cold water to get *2-(((4-methoxy-3-methylpyridin-2-yl)methyl)thio)-1H- benzo[d]imidazole* 3.2g, 82%.

*2-(((4-methoxy-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole* 3g, 10.51mmol) in 30 ml of dichloromethane was added a solution of m-CPBA (2.58gm, 14.93mmol) in 25ml of dichloromethane at 10°C for 30mins. 10ml of 50% NaOH solution was added to the reaction mass. pH was adjusted to 8.0 with acetic acid, extracted with dichloromethane, organic layer was evaporated, crude was treated with ether at 5°C to get solid precipitate.to get **Methoxy Rabeprazole 5** 1.3g, 50%.

**N-Oxideof Rabeprazole**

*2-(((1H-benzo[d]imidazol-2-yl)sulfinyl)methyl)-4-(3-methoxypropoxy)-3-methylpyridine 1-oxide*

To a solution of 2-(chloromethyl)-4-(3-methoxypropoxy)-3-methylpyridine (3.0gm, 13.06mmol) in 27ml of chloroform, was added m-CPBA (2.48gm, 14.37mmol) was

added in portion wise at 5°C for about 1hr and maintained for 1 h. Then, the reaction mixture was washed with saturated sodium bicarbonate solution, water, dried, and concentrated in vacuo. The obtained residue was triturated with ethyl acetate; the separated solid was filtered and dried at 40°C overnight to get 2.57gm,80% This compound stability and were immediately used for the next step.

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