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Proton Pump Inhibitors: A Brief Overview of Discovery, Chemistry and Process Development.

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ABSTRACT

Proton pump inhibitors (PPIs) are the most potent gastric acid–suppressing agents in clinical use. Omeprazole was the first effective proton pump inhibitor approved by US FDA. From then a series of proton pump inhibitors have been developed and introduced into the market.These compounds primarily contain a substituted benzimidazole moiety and a substituted pyridine connected by a sulfoxide linkage. Recently these compounds also have been reported to possess anti-cancer activity.

Keywords: Proton pump inhibitors; Benzimidazole; asymmetric oxidation;chloromethylpyridine

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INTRODUCTION

Proton pump inhibitors (PPIs) are drugs which irreversibly inhibit proton pump (H^+/K^+ ATPase) function and are the most potent gastric acid–suppressing agents in clinical use. PPI's are a class of very effective and generally safe medicines used to treat heart burn, Gastro Oesophageal Reflux Disease (GERD) and gastric ulcers. In 2014, sales of the top ten proton pump inhibitors made up $9.2 billion in U.S. prescription sales, according to IMS Health. One of them NEXIUM was the top selling of all the drugs earning nearly $ 6 billion according to a research firm IMS which compiled a rolling 12-month history (Oct 2013 to Sept 2014) of the top 100 drugs by total prescriptions and total sales in the United States.

Gastric acid is a key factor in normal functioning of upper gastrointestine, like protein digestion, calcium and iron absorption, protection against bacterial as well as other infections. However, inappropriate levels of gastric acid underlie several widespread pathological conditions, including peptic ulcers and GASTROESOPHAGEAL REFLUX DISEASE (GERD), for which HEARTBURN is the most common symptom.

GERD sometimes causes injury of the *oesophagus*. These injuries may include one or more of the following:

- **Reflux oesophagitis** – necrosis of oesophageal epithelium causing ulcers near the junction of the stomach and oesophagus
- **Oesophageal strictures** – the persistent narrowing of the oesophagus caused by reflux-induced inflammation
- **Barrett's oesophagus** – intestinal metaplasia (changes of the epithelial cells from squamous to intestinal columnar epithelium) of the distal oesophagus
- **Oesophageal adenocarcinoma** – a rare form of cancer

Thirty years ago GERDwasconsidered as life-threatening 'if untreated'. Treatment options then, however,were limited. For example, for peptic ulcers, the main treatment was administration of antacids to neutralize excess gastric acid, but this provided only a temporary relief. The alternative was an operation (gastrectomy, in which part of the stomach is removed, and/or vagotomy, in which nerves to the stomach are sectioned). The surgery could, however, have serious side effects. Pharmacological control of the complex mechanism of gastric acid secretion has therefore long been desirable.

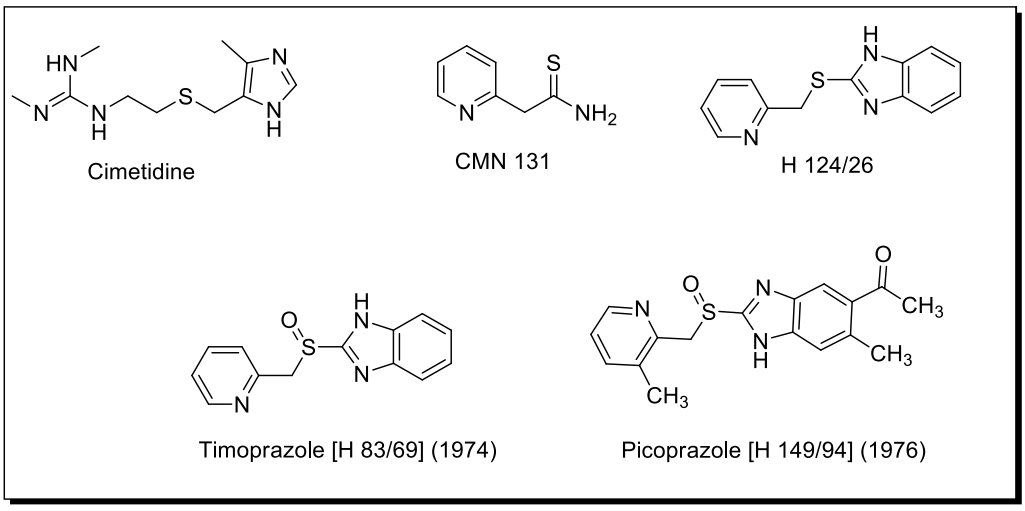

Figure:1

For peptic ulcers and GERD diseases, there was a breakthrough in the late 1970s with the introduction of the antisecretory drug CIMETIDINE, which was an antagonist of the Histamine 2 (H_2) receptor,which has a key role in gastric acid secretion.But these products also got obsolete as H_2 -receptor antagonists have a relatively shortduration of action.Pharmaceuticalcompany Astra in 1970 developedspecificinhibitors of the proton pump in the acid-secretingparietal cells of the stomach, which were blocking the secretion of the acid

in final step.These compounds were very potentinhibitors of gastric acid secretion, and demonstrated a surprisingly long duration of action.

Then after two years anantisecretory compound (CMN 131) (Fig-1)was developed by the pharmaceutical company SERVIER, however this compound showed acute toxicity, thus further research on this compound was cancelled. Later it was found that the thioamide group in the chemical structure of CMN 131 was responsible for the toxicity, and then newer approaches aimed at scissoring this group and incorporate heterocyclic ring systems into or in between. In 1973, the first hit Benzimidazole H 124/26(Fig-1) came out as an outcome of that research[1].

After the discovery of BenzimidazoleH124/26 it was identifiedthatthesame compound was already patentedbya Hungarian company, which claimed it asa drug for the tuberculosis treatment. But the company did not claim the metabolite of H 124/26, which was found to be an even more potent antisecretory compound. The metabolite named as H 83/69 was found to be the sulphoxide of H 124/26 and was named as Timoprazole(Fig-2). It became the new lead compound. Surprisingly a site of inhibitory action in the pathway leading to acid secretion was not known.Long-term toxicological studies of timoprazole revealed that it causes enlargement of the thyroid gland.A literature search of the chemistry of thiourea compounds showed a few substituted mercaptobenzimidazoles having no effect on iodine uptake, thus applying these substituents on timoprazole resulted in elimination of the effects on the thyroidwithout reducing the antisecretory effect of drug. Researchshowed that thyroid and antisecretory effect are the results ofaspecific range of lipophilicity of these compounds.The most potent of them without thyroid effects was H 149/94, which was named as Picoprazole[2]. Picoprazole was used in a concept study in human volunteers, and showed a potent antisecretory action for a very long duration however longterm studies showed Necrotizing vasculitis in a few treated dogs.

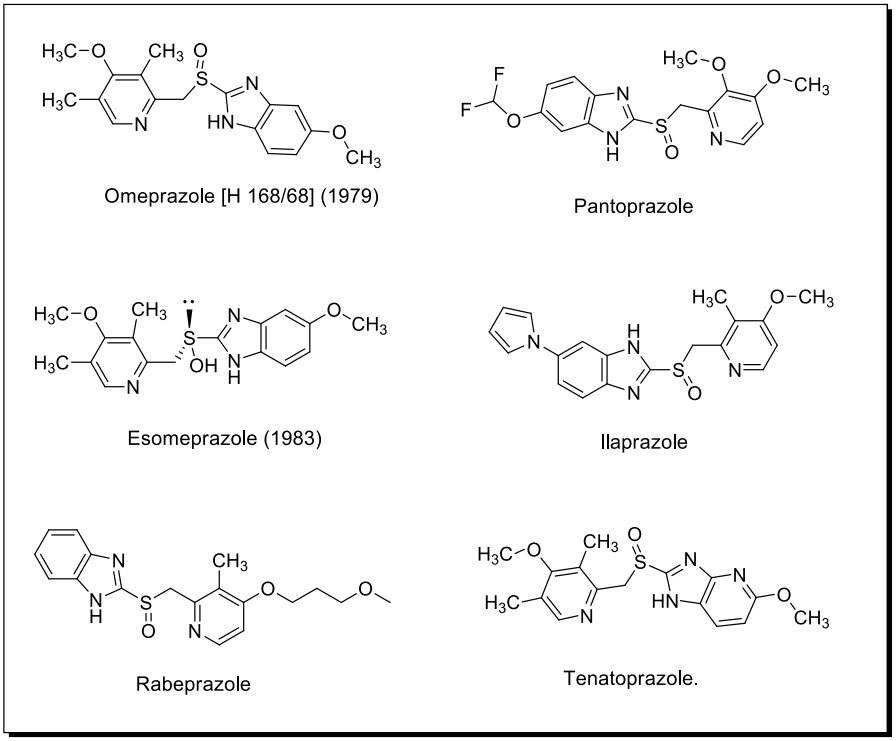

Figure:2

Aktiebolaget Hässle a Swedish company invented the Omeprazole in 1978[2], the first proton-pump inhibitor used inclinical practice. Astra which is now AstraZeneca, launched in 1988 as LOSECinEurope, and in 1990 as PRILOSECin the United States. Omeprazole introduced a new approach for the effectiveinhibition of acid secretion and the treatment ofacid-related diseases. By 1996, Losec became the world's biggest ever selling pharmaceutical product, and by 2004 over 800 million patients had been treated with the drug worldwide[3].

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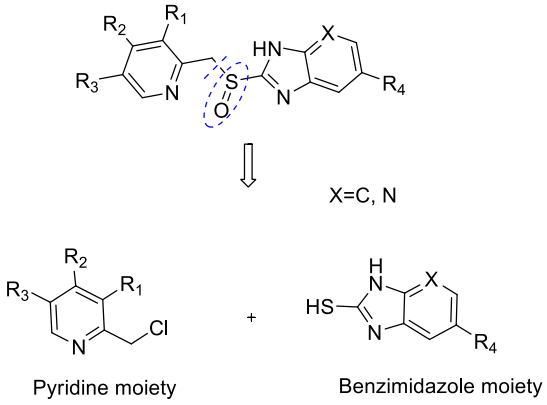
General Synthetic strategy

In principle the general synthetic strategy adapted for these sulphoxide molecules is the coupling of the substituted chloromethyl pyridine with an appropriately substituted 2-mercaptobenzimidazole which inturn is oxidised to get the final required product.



R_1=CH_3, R_2=OCH_3, R_3=CH_3, R_4=OCH_3 Omeprazole

R_1=R_2= OCH_3 , R_4=OCH_3 pantoprazole

R_1=CH_3,R_2=OCH_3, R_3=H R_4=OCH_3 Ilaprazole

R_1=CH_3, R_2=$O(CH_2)_3CH_3$, R_4=H Rabeprazole

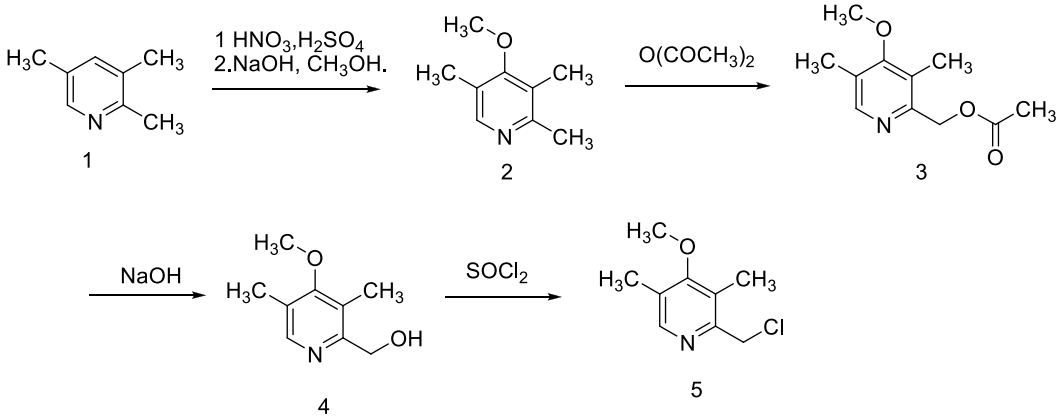
R_1=CH_3, R_2=$O(CH_2$ CF_3, R_3=R_4=H Lansoprazole

Figure-3

Synthesis of substituted chloromethylpyridine

((5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole):

The original process patented by AktiebolagetHassle company synthesized the chlromethyl precursor from 2,3,5-trimethyl pyridine, which is nitrated in the 4th position to form the 4-nitropyridine derivative. The 4-nitro pyridine precursor is treated with sodium methoxide and acetic anhydride to generate methoxide ion which replaces the nitro group. The methyl group at the second position is converted to the acetoxymethyl group using acetic anhydride. This acetoxy methyl group in turn is hydrolysed and chlorinated using thionyl chloride to generate the 2-chloromethyl pyridine precursor(Scheme-1).



Scheme-1

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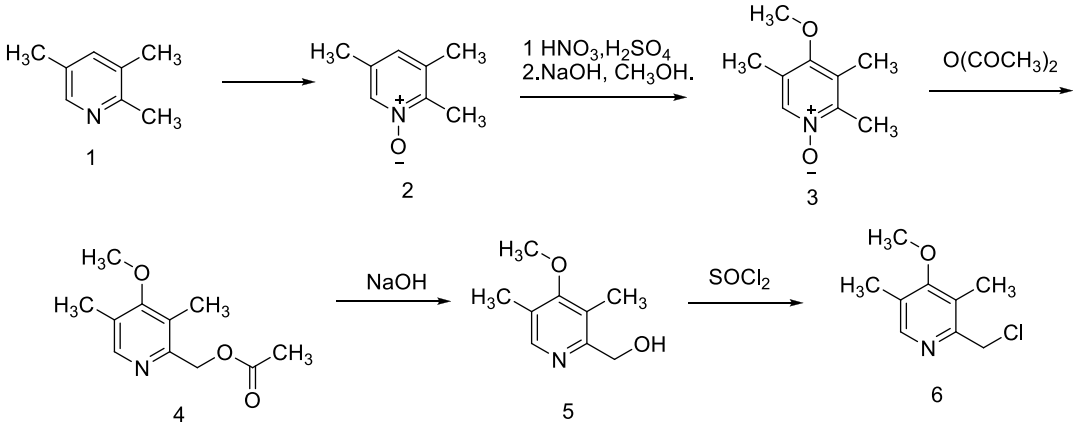
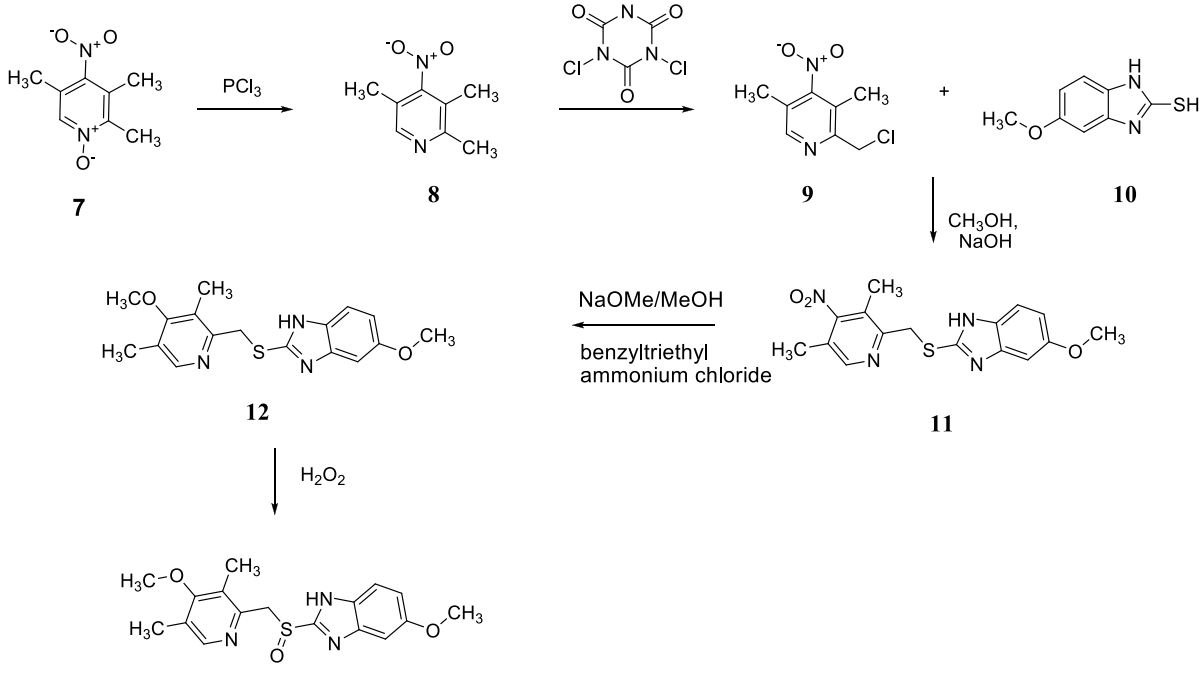
An improved process(Scheme-2) for the synthesis of the pyridine moiety was reported by the same companyAktiebolagetHassle[4]. The synthesis starts with the N-oxidation of the substituted pyridines. The main advantage as reported is that the compounds are more stable and the subsequent conversion to hydroxymethyl pyridine is easy and gives good yield. The N-oxide intermediate is more stable than the corresponding simple pyridine intermediate which makes it more suitable for large scale synthesis.



Scheme-2

In 2001 patent filed by Konakanchi Durga Prasad *et al* by NatcoPharma**[5]** claimed an improved process for the preparation of Omeprazole and the synthetic improvement mainly consisted of the avoidance of basic conditions in the initial stages which degraded the starting materials and hampered the reactions thereafter. The synthesis mainly involved the reaction of substituted-4-amino pyridine- N-oxide with phosphorous trichloride to generate the 4-amino pyridine which upon treatment with trichloroisocyanuric acid gave the chloromethyl pyridine intermediate **16.** Compound **16** and **6** were treated with sodium hydroxide in methanol yielded sulphide intermediate **17** which is novel than previously reported schemes, compound **17** reacted with hydrogen peroxide in the presence of ammonium molybdate to give omeprazole**(Scheme-3)**.



Scheme-3

Strategies of coupling the substituted chloromethylpyridine and Benzimidazoles and their process improvements:

The final step in the synthesis of the Benzimidazole based PPI's involves the oxidation of sulphide to sulfoxide. Various oxidising agents have been reported for this transformation[6] which includesperoxides such as hydrogen peroxide, meta chloroperbenzoic acid and per acetic acid[7]. Hypohalite salts such as sodium hypochlorite(EP-0268-956), iodosobenzene, 3-methyliodosobenzene[8].

The most preffered oxidising agent however is mCPBA. Oxidation usingaqueous hydrogen peroxide in presence of Vanadium catalyst has also been reported in EP 0 302 720. Further it says that this condition results in higher yields of desired sulfoxide and less of N-oxide by products and the isolation of the product from the reaction mixture directly also has been reported sometimes.

P.Brougham et al[9]have reported that magnesium monoperoxyphthalate(MMPP)is a useful oxidising agent which can be used as a substitute to m-CPBA. The main advantages reported include the lower costs and reduced hazard when compared to m-CPBA.

Improved processes

The main challenge lies in the purification of the sulphide intermediate which is an oil and the penultimate step while the final sulfoxide product is a low melting solid. These two features make the isolation and purification of the pure API very difficult. Keeping this in view Slemon *et al*in 1994[10]have invented the novel procedure for the synthesis of pure Omeprazole involving novel synthetic intermediates. The modification involves the corresponding acetamide-sulfide compounds which are oxidised to form the amide sulfinyl compound which upon alkaline hydrolysis gives the sulfinyl carboxylate or salts which on further decarboxylation leads to the target molecule The end product omeprazole or lansoprazole produced by this process is easily purified from the residual, unreacted salt, inorganic by-products and other minor by-products by a simple washing as these amide compounds are crystalline solids as opposed to the corresponding sulphide and sulfoxides of the earlier reported procedures.Purificationwhich was a major problem was overcome by the following synthetic modifications. Moreover the discolouration of the final product which is common in the other processes was significantly avoided(Scheme-4).

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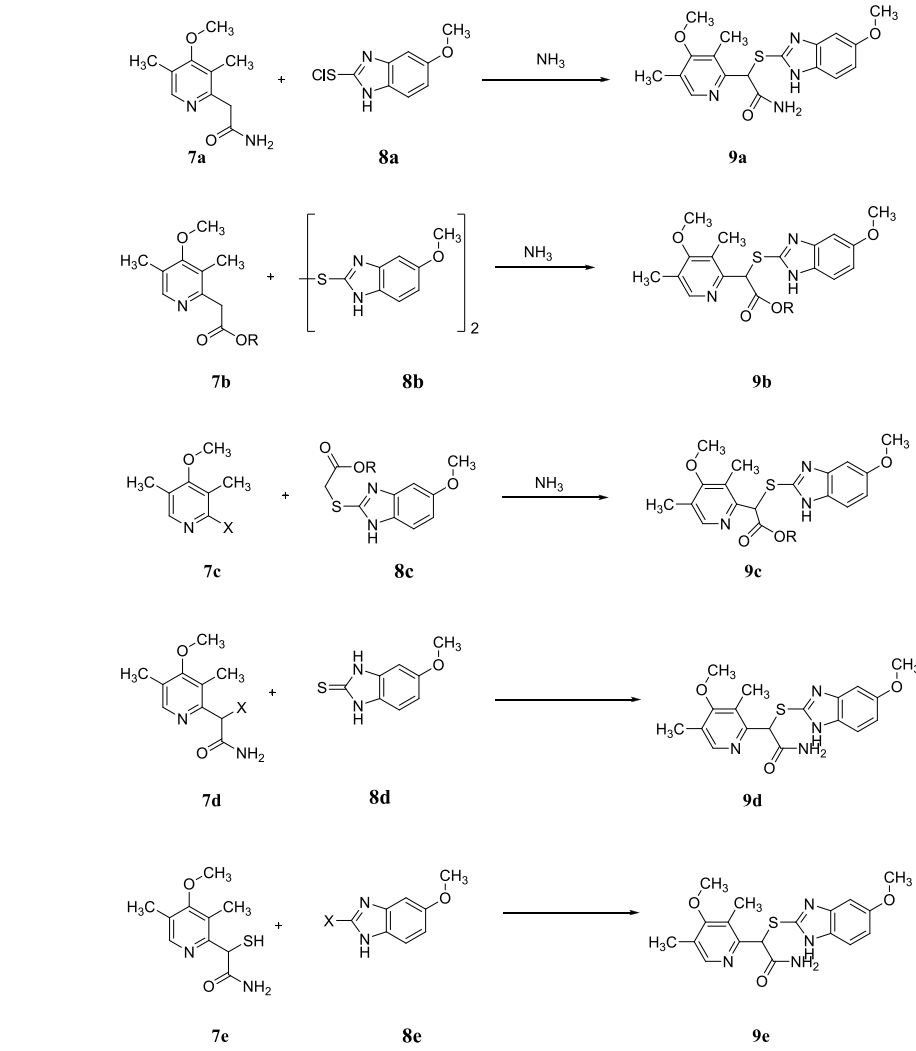
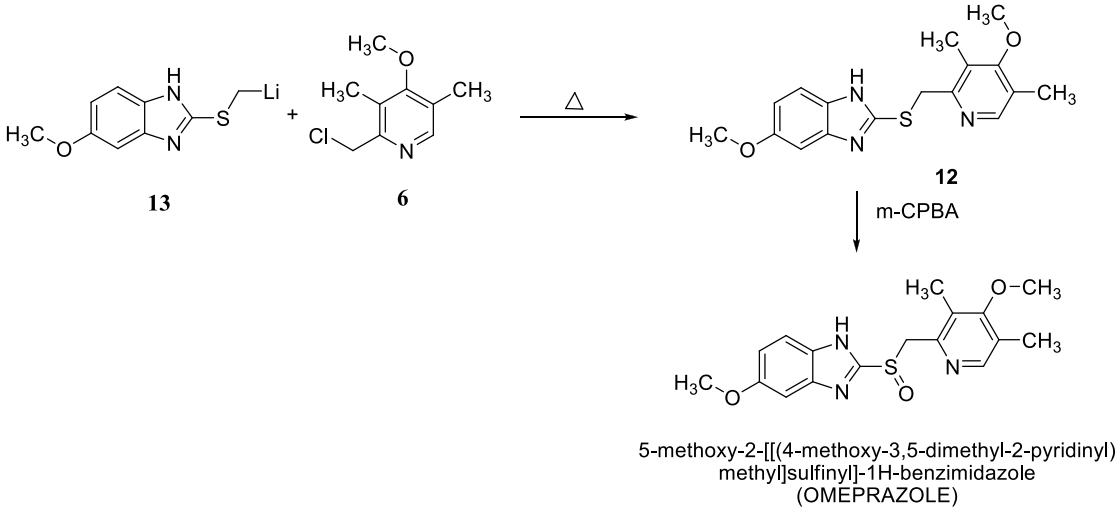


Scheme-4



Scheme-5

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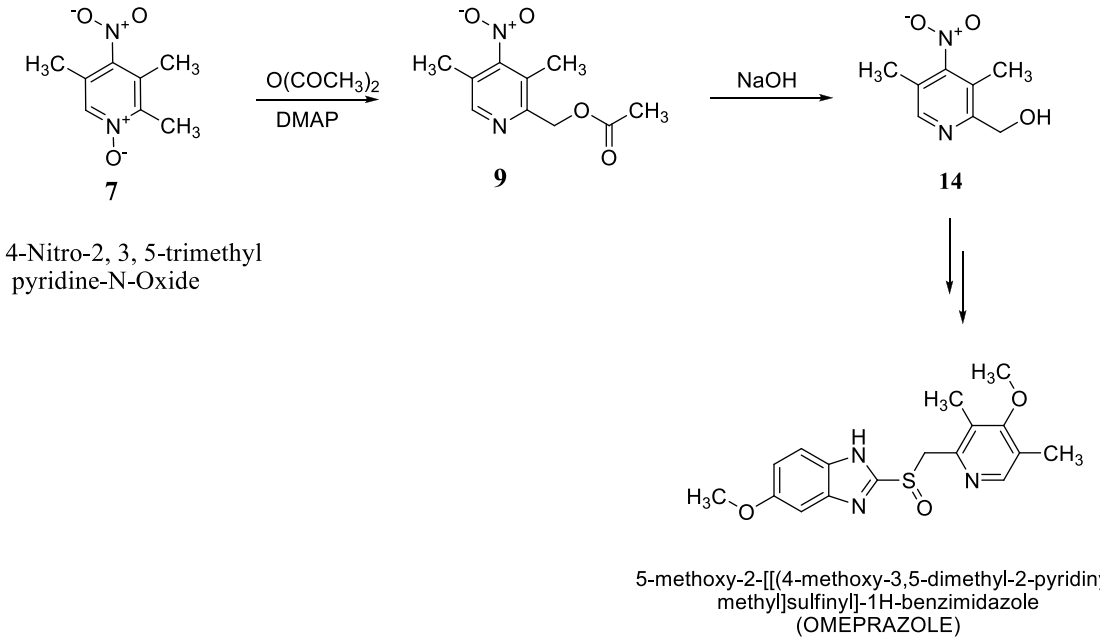

Scheme-6

2-(Lithium methyl sulphinyl)-5-methoxy-1H benzimidazole 20 is reacted with 2-chloro-3,5-dimethyl-4-methoxy pyridine 21 to give the sulphide intermediate which was converted to Omeprazole by treatment with m-CPBA(Shcheme-5).

4-nitro-2,3,5-trimethylpyridine-N-oxide is treated with acetic anhydride in presence of DMAP to get2-acetyloxymethyl-3,5-dimethyl-4-nitropyridine22, which on hydrolysis with sodium hydroxide gave 2-hydroxymethyl-3, 5 dimethyl-4-nitropyridine 23 (Scheme-6).

Synthesis of Lansoprazole:

Takeda and AB Hässle (Astra) both coincidentally, started their research on peptic ulcer drugs with same starting compound (2-pyridylthioacetamide coded by Takeda as AG-35).Takeda found that the compound and its analogues had strong anti-secretory and anti-ulcer activities[11].After screening more than 800 compounds eventually it was found that introduction of fluorine, such as a trifluoroethoxy group, into the backbone improved the physicochemical and pharmacological properties of the compound, Takeda got a patent for 2-(((3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl)methyl)sulfinyl)-1H-benzo[d]imidazole (Lansoprazole) as anti-ulcer drug in 1984[12],which showedsuperioractivity to those of AB hassle's molecule Omeprazole. The synthetic scheme involved the reaction of compound 15 with 2,2,2-trifloroethanol in presence of potassium carbonate to give compound 16(Scheme-7). The rest is same as the earlier procedures.

Improved process: In 2010, Srinivas Gangula*et al* from Dr. Reddy's Laboratories[13] Ltd reported the efficient, eco-friendly, and robust process for the synthesis of lansoprazole. The final two steps i.e., coupling and oxidation of sulfide to sulfoxide were the mother of impurities generated in final API. Thus as a part of extensive research done in their lab, they suggested a change of solvent in the coupling step of 26 and 27, and selected water as a solvent which not only provided 28as a solid in 97.5% yield and 99.5% purity but also served as an eco-friendly media.

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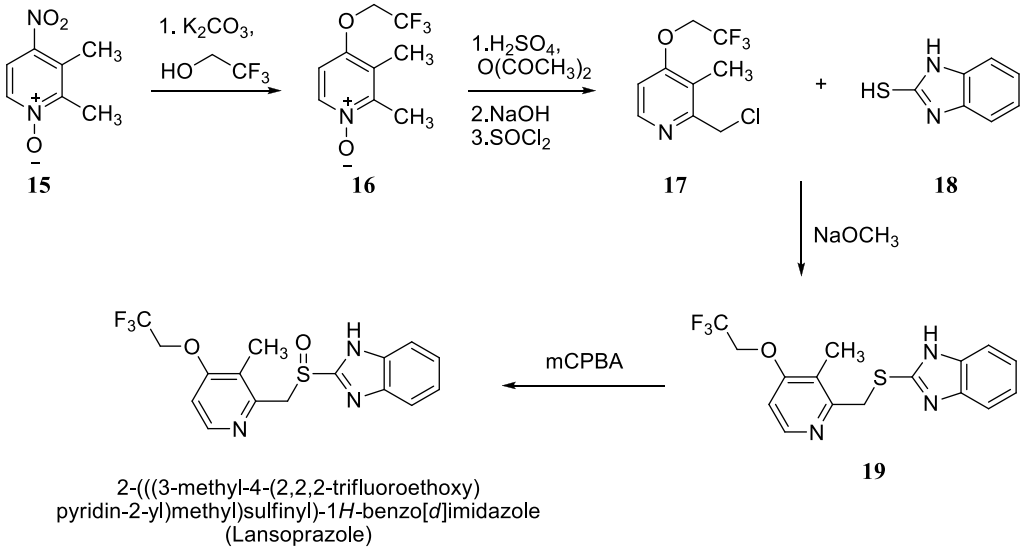
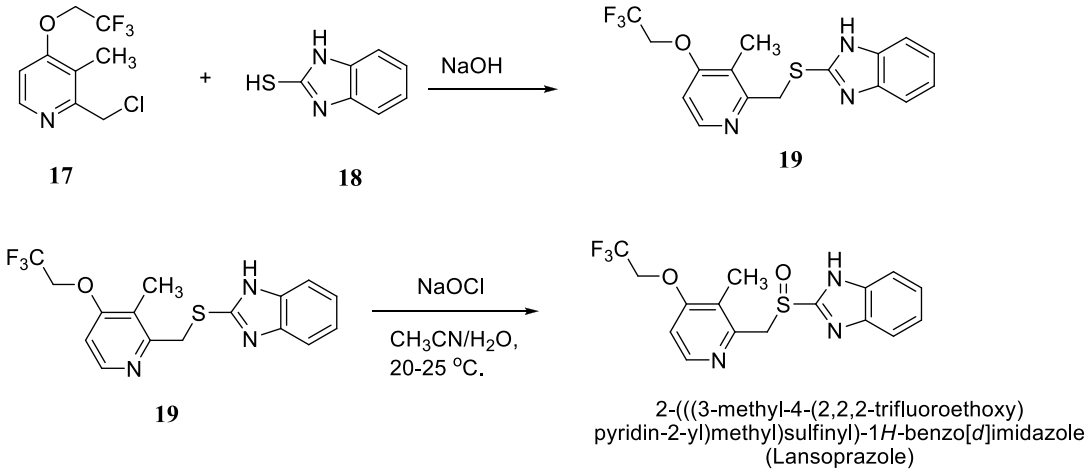


Scheme-7



Scheme-8

Further controlled oxidation of 28to Lansoprazoleby use of sodium hypochlorite (NaOCl) was found to be effective followed by a facile workup procedure which purges any possible impurities(Scheme-8). Advantages of this process are avoiding the usage of hydrogen peroxide or *m*-CPBA which can pose environmental problems, avoidance of cryogenic conditions (-30 to -20 °C) and control of the formation of sulfone and *N*-oxide impurities. The byproduct obtained in both the stages is only sodium chloride and hence it is a greener process.

Synthesis of Pantoprazole:

In 1985 Byk Gulden Lomberg*et al* discovered anotherPPIPantoprazole[14]. Itwas inferred that the cyclic sulfenamide which is generated in acidic conditions was the active principle of the PPIs. Finally, it was understood that seemingly small alterations in the backbone of substituents of timoprazole led in the false direction. However, necessary intramolecular rearrangement of the benzimidazole into sulfenamide posed severe geometricconstraints. Optimal compounds would be those that were stable at neutral pH but were quickly activated at low P^H. During the course of the discovery of pantoprazole, more than 650 PPIs had been synthesized and evaluated; finally Pantoprazole was identified after nearly seven years of research and was registered for clinical use after a further seven years of development. The synthesis of pantoprazole was reported as follows(Scheme-9) .

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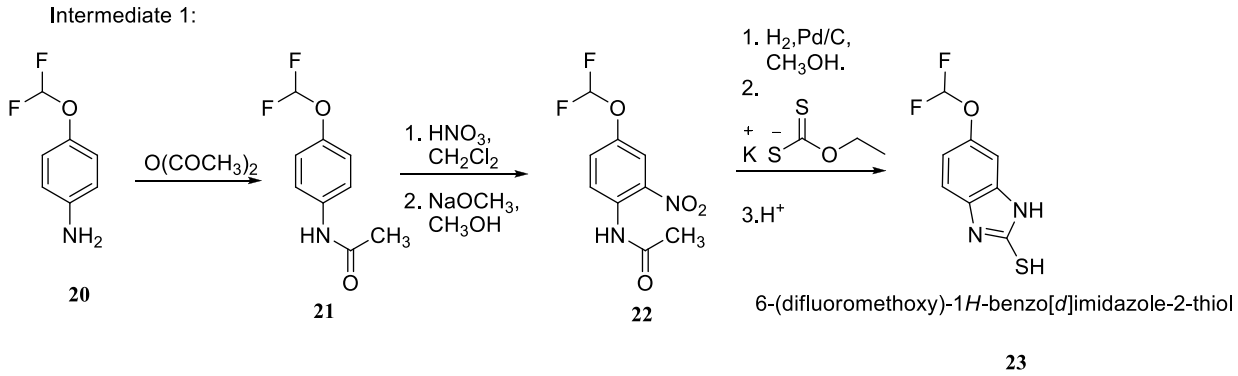
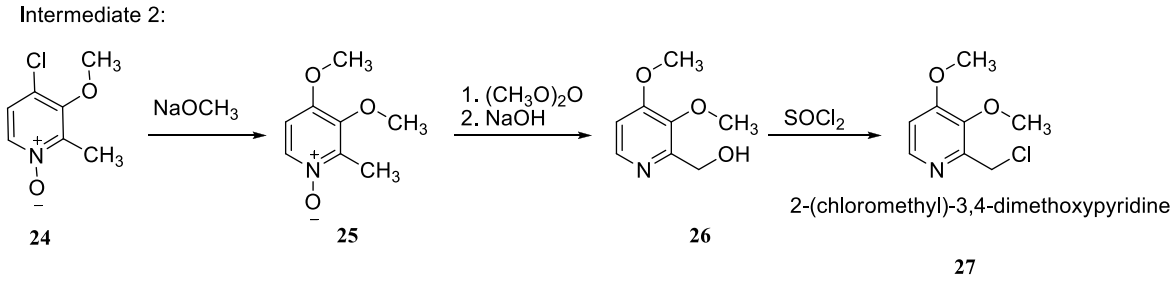
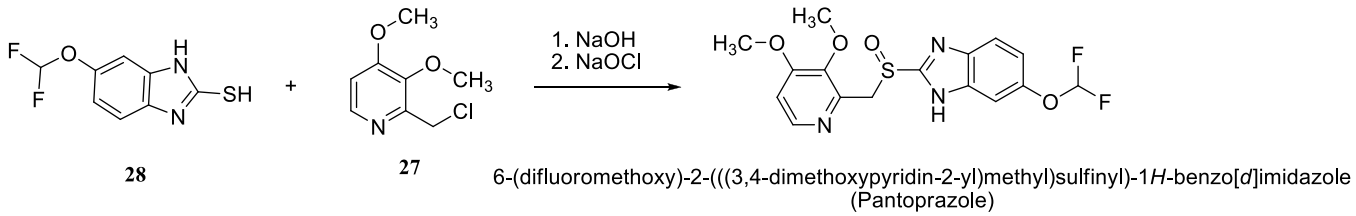
Improved process:

The most important and critical step in the process is the oxidation wherein there are chances of formation of two impurities viz., pantoprazole sulfone and pantoprazole *N*-oxide as mentioned in the recently published analytical drug profile[15].

N-oxide impurity was observed always in the range from 0.02 to 0.05 %, whereas sulfone was seen as a potential impurity the complete removal of which proved problematic. Thus in 2004 VijayavitthalMathad*etal*fromDr. Reddy's Laboratories Ltd reported one-pot process for the production of pantoprazole which was substantially free from sulfone impurity.Theyscreened different oxidizing agents such as peracids, peresters, and peroxides for the conversion of the sulfide to the sulfoxide (pantoprazole).The purity of compound was found to be depending on two factors- 1. % mol of peracetic acid used and 2) The temperature at which reaction proceeds. It was found that the oxidation carried out 0.7 % mol of peracid and







Scheme-9

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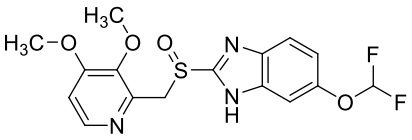
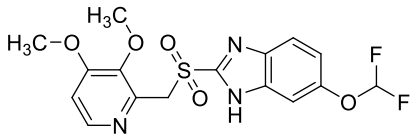
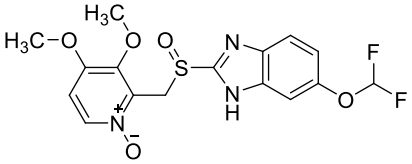


Pantoprazole



Sulfone impurity

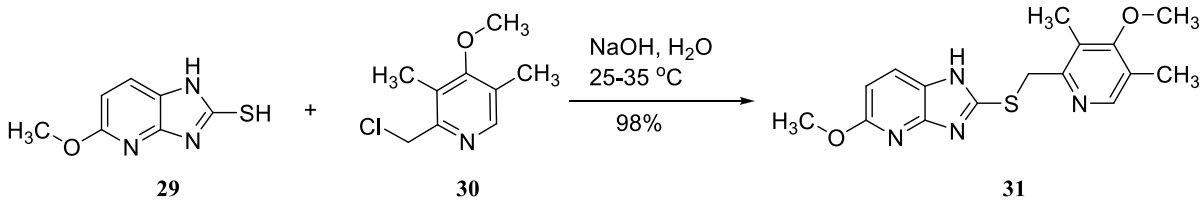


Pantoprazole-N-Oxide impurity

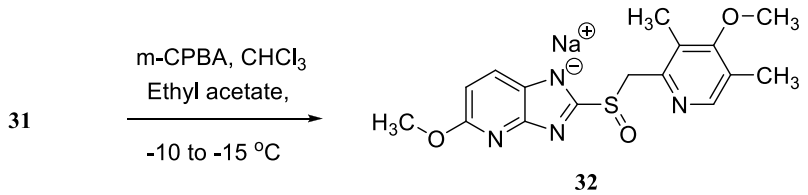
Figure-4

temperatures of -10 to -5 °C reduce the chances of formation of the sulfone impurity and produces high quality compound. Despite the precautions taken with respect to the mole ratio of the peracetic acid and temperature of the reaction, still there are chances that small amount of impurity might remain in the compound. Thus work up procedure developed by the Mathad and *et al* is more efficient in removing all the impurities from reaction mixture. The process included the stirring of the reaction mixture with sodium hydroxide which left the unreacted sulphide in organic layer and the product and sulphone in aqueous layer as a salt, these when treated with different pH conditions removed sulphone completely from product without any traces.Thus this process has proven as an efficient technique in removing the impurities from final product.

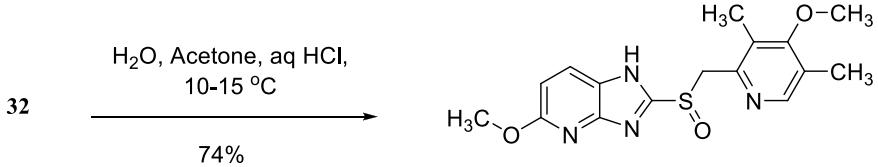
Synthesis of Tenatoprazole:



29 + 30 → 31



31 → 32

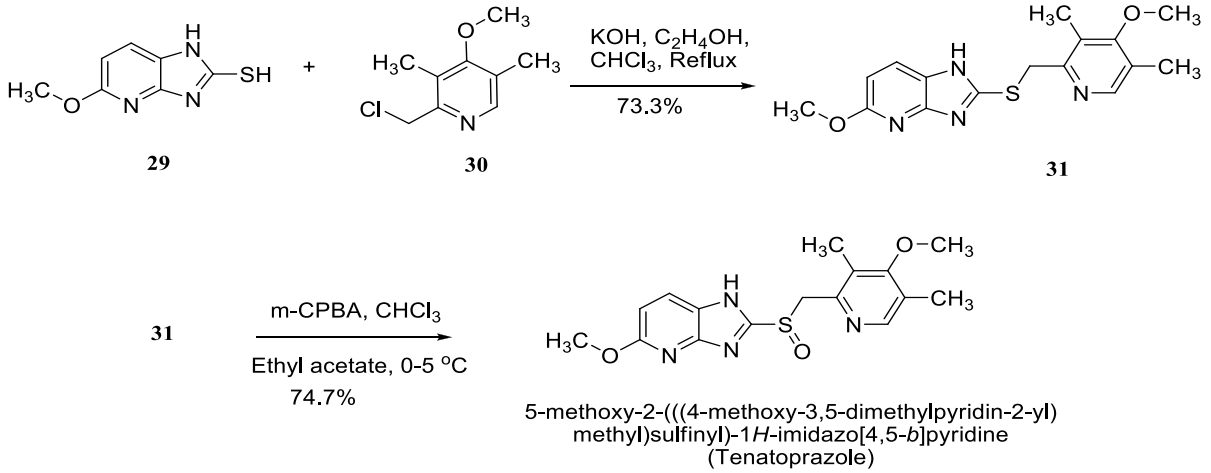


32 → 5-methoxy-2-(((4-methoxy-3,5-dimethylpyridin-2-yl) methyl)sulfinyl)-1*H*-imidazo[4,5-*b*]pyridine (Tenatoprazole)

Scheme-10

Tenatoprazole was invented by **Mitsubishi Tanabe Pharma** in 1987 and **Negma Laboratories** is a licensee of the drug. It is a PPI drug candidate which was undergoing clinical testing as a potential treatment for GERD and peptic ulcer from 2003 was still in Phase I clinical trials during 2007 to 2012. Tenatoprazole bears an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors, and has shown a half-life of about seven times longer than other PPIs.

The synthesis is as shown in scheme-11



Scheme-11

Improved method:

SomaiahSripathi *etal* from Srini Pharmaceuticals Ltd reported an improved process[16] for synthesis of tenatoprazole, which proved advantageous by 25 % increment in yield of sulphide synthesis step, also gave better purity than reported patented procedure. This new process requires no purification process and affords the target compound 1 with99.8% purity by HPLC.

Synthesis of Esomeprazole :

Esomeprazole was the second largest selling drug in 2008($5.9 billion in US dollars[17].Several synthetic methods are available in literature for the asymmetric oxidation of prochiral sulphides[18]. The most popular among them is the enantioselective sulfoxidation(Scheme-12) developed by Kagan et al[18,b] and Modena et al.[18,c]. Esomeprazole was successfully synthesized in 55% yield by Von Ungeusig by the modified Kagans method[19].The main drawback of this method however is the formation of sulfone as the impurity.

The reaction proceeds by the crucial formation of a complex involving the sulphide, titanium isopropoxide, water, diethyltartarate and diisopropylethylamine. Other metal catalysed processes are known for the synthesis of propton pump inhibitors[20].

Improved process:

In 2006, KoilkondaPurandhar *et al* from Dr. Reddy's Laboratories reported the optically pure method for the preparation of the optically pure (*S*)-isomer of omeprazole by use of the transition metal complex**[21]**.

Konstantin P. Bryliakov et al have reported a Titanium(IV) Salalen catalysts for the oxidation of pyridylmethylthiobenzimidazole precursors to esomeprazole and dexlansoprazole by H_2O_2 with high chemo and enantioselectivities**[22]**.

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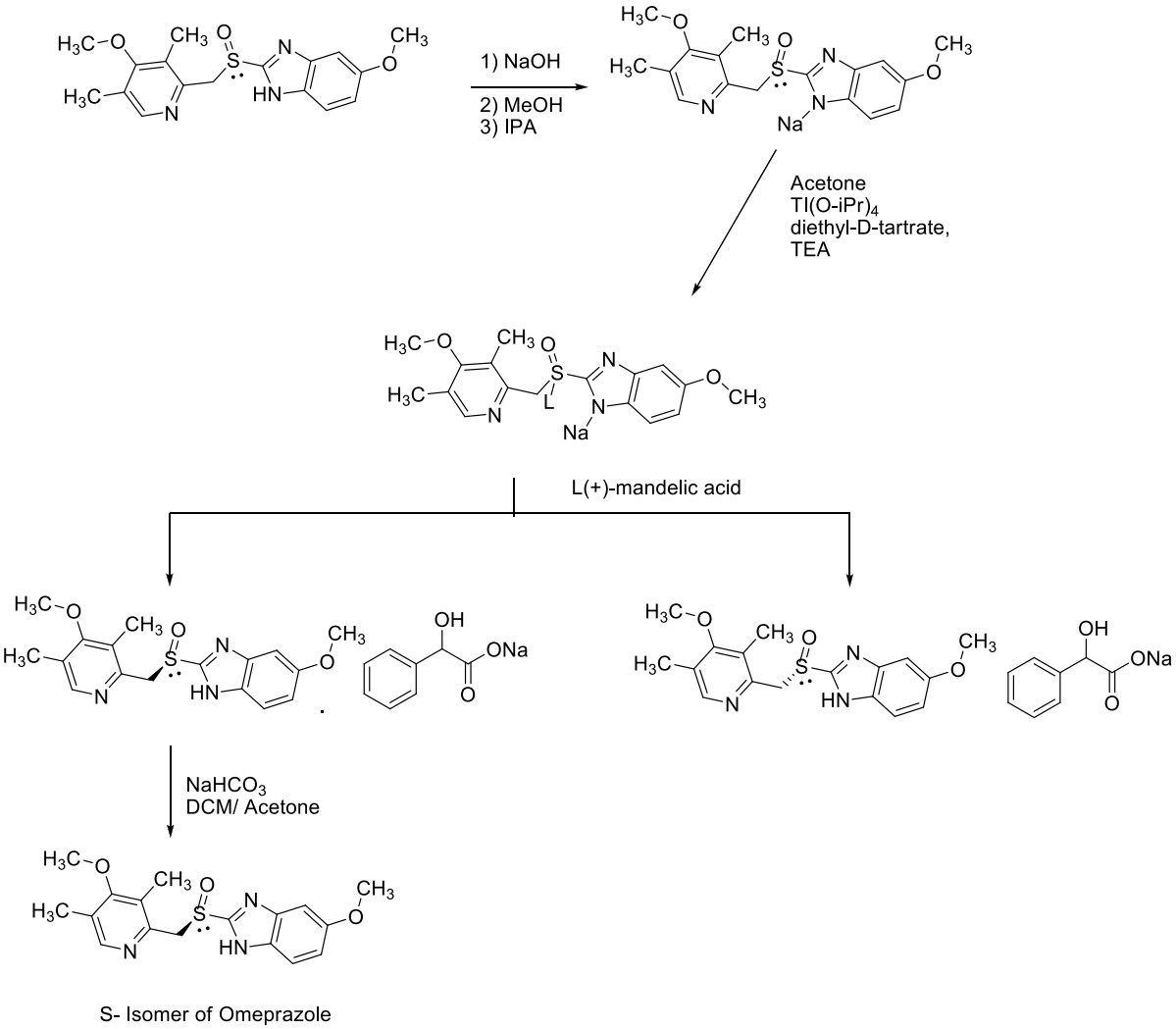
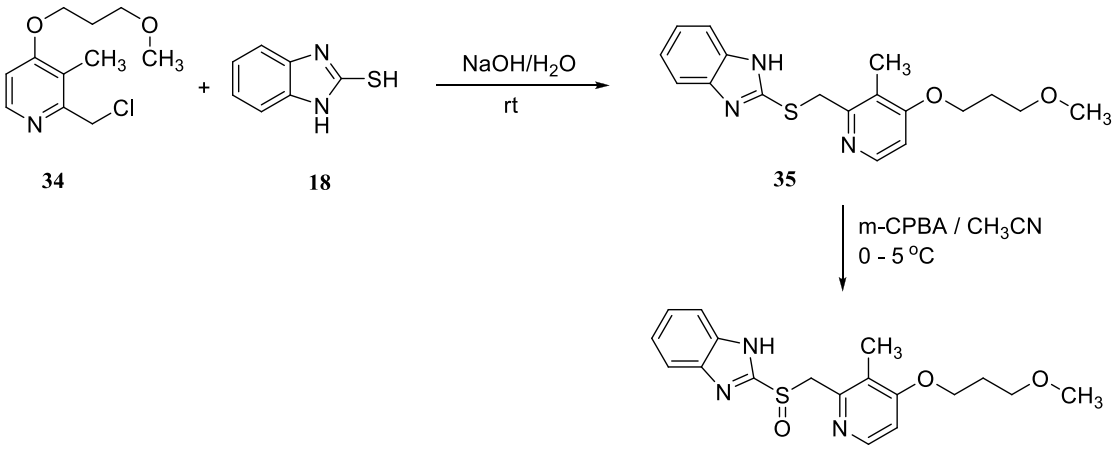
Synthesis of Rabeprazole:

In 1999, Souda *etal* at Eisai pharma introduced another proton pump inhibitor,which is marketed as Rabeprazole sodium salt[23]. Rabeprazole and many other substituted benzimidazole-type compounds having anti-ulcer activity were disclosed in the U.S. Pat. No. 5,045,552. This patent further discloses the oxidation process for preparation of Rabeprazole from Rabeprazolesulfide using 85% m-chloroperbenzoic acid in a mixture of dichloromethane and diethyl ether followed by work up9Scheme 13). The product which was obtained as an oilwas crystallized from a mixture of dichloromethane/ether. The oily crude was dissolved in aqueous solution of sodium hydroxide. The obtained solution was subjected to azeotropic distillation with ethanol to remove water followed by addition of etherto get crystalline Rabeprazole base.



Scheme 12

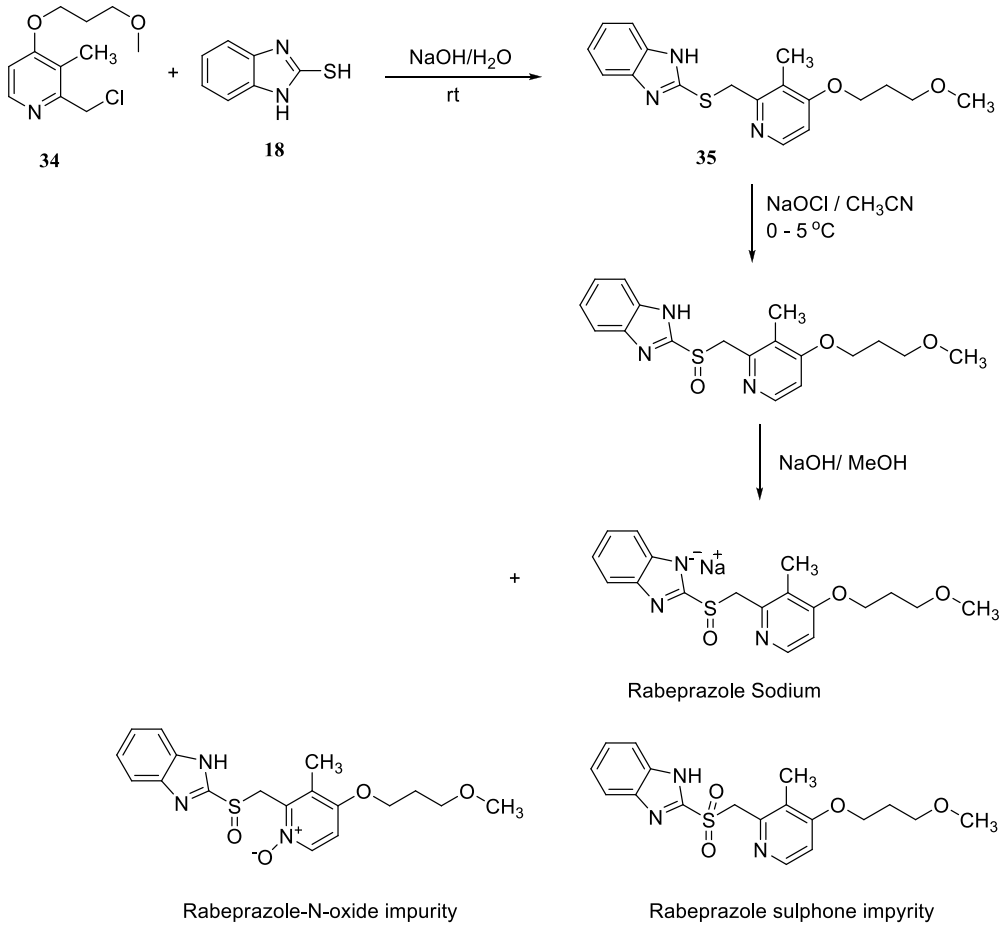


34 18 35

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

Scheme-13

Improved process : An improved process was disclosed in the patent WO2006/117802 PCT application wherein the oxidation of Rabeprazole sulphide was done using sodium hypohalite solution in water or in a mixture of water and water miscible solvent with alkali metal hydroxide and a catalyst. Finally a solvent – antisolvent combination gave Rabeprazole sodium.WO 2006/120701 PCT and WO 2003101452 PCT applications disclose the process for the preparation of amorphous Rabeprazole sodium which was obtained by lyophilisation of an aqueous solution of Rabeprazole sodium acetone complex and aqueous NaOHsoln of rabeprazole respectively.



34 18 35

Rabeprazole Sodium

Rabeprazole-N-oxide impurity

Rabeprazole sulphone impyrity

Scheme-14

In 2009, a process research group from Dr.Reddys laboratories[24] described the process to get pure rabeprazole free from impurities such as the sulfone and the rabeprazole N-oxide. Their process achieved the yield of 75% when compared to the yield of 40% in the reported process with the major improvement at the sulfoxidation stage. The workup process at the sulfoxidation stage was modified and optimised wherein the reaction mass was quenched with sodium thiosulfate after the reaction completion so that the sodium hypohalite which was left unreacted was completely quenched. A purification process with ethylacetate was introduced and the final pure API was isolated as its sodium salt.

A continuous Flow micromixing reactor Technology has also been reported by the Process engineering team of Dr.Reddys laboratories for the synthesis of benzimidazole drugs[25].

CONCLUSION

PPI's are the included in the world's list of essential medicines and have reported high sales through out the world. They also have been reported to be showing anti-cancer activity**[26]** by targeting the thioesterase domain of human fatty acid synthase. Understanding the chemistry behind the synthesis and process development of these compounds not only helps in developing new molecules of it's kind but also gives an insight into the activity of these compounds and also the knowledge about the stability and impurity profile of these compounds.

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