International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.12, No.03, pp 57-70, 2019

Novel Synthesis of Omeprazole and Pharmaceutical Impurities of Proton pump inhibitors : A Review

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Abstract : The objective of this review was to study the novel methods to the omeprazole synthesis and pharmaceutical impurities of proton pump inhibitors that provide an insight to researchers about the development of proton pump inhibitors. However, this paper emphasized on the study of various pharmaceutical impurities of anti-ulcer drug. The drug used for the study was omeprazole which is chemically known as (5-methoxy-2-[[(4-metboxy-3,5-dimethylpyridinyl) methyl] sulfinyl]-l-benzimidazole) that inhibits gastric ATPase enzyme by oxidizingits sulfhydryl groups.The process involved during synthesis. The novel process come into existence due to incomplete oxidation of pyrmetazole and overoxidation to sulfone that leads to the formation of sulfone N-oxide. The procedure involved 5-methoxy thiobenzimidazole to the formation of an ester followed by coupling of the ester with the Grignard reagent of 2-chloromethyl-4-methoxy-3,5-dimethyl-pyridine. The novel synthesis process for pharmaceutical impurities achieve the expected yield and process observed to be short, simple. The synthesized impurity of proton pump inhibitors can be used as standard impurity, that can be utilized for further studied in various aspects. This review article will describe about the various novel impurities of omeprazole that available as marketed formulation.

Keywords : Proton pump inhibitors, Omeprazole, Grignard reagent, oxidation, Impurity, Synthesis.

Introduction

PPIs are heterocyclic benzimidazole derivatives organic molecules that contains both benzimidazole and pyridine moiety that linked by methylsulfinyl group. They are acid-labile weak bases which acts as membrane permeable that prevent degradation and activation of luminal gastric acid. The effective and safe use of proton pump inhibitors used to treat gastroesophageal reflux disease treated with proton pump inhibitors.[1]

The estimation of GERD in the East Asia mainly in adult population is reported as 2.5-7.8% while in Western World it ranges from 10-20%. In the United States GERD outpatient adult population diagnosis and affected with 20% weekly and 7% daily.[2]

DOI: http://dx.doi.org/10.20902/IJPTR.2019.120307

Pharmaceutical impurities are the substances that co-exist with the Active pharmaceutical ingredients and formed during synthesis and ageing. Impurities identification, isolation and quantification carries important role in drug development and regulatory assessment**.** [3]Impurity profiling gives information about impurities present in an API drugs, which acts as tool for quality control.It deals with the toxicity, safety, limits of quantification, limits of detection, organic and inorganic impurities. [4]Synthesized impurity used as an impurity standard that can be used for the development of analytical methods and quantitative determination of impurities.It is importance to submit impurities as standard for regulatory analysis to various drug authorities.[5]The improved process of PPI's included the list of essential medicines. By understanding the chemistry and process the compound helps in development of new molecules which also insight the activity and knowledge about the impurity profile and stability of the compound.[6]

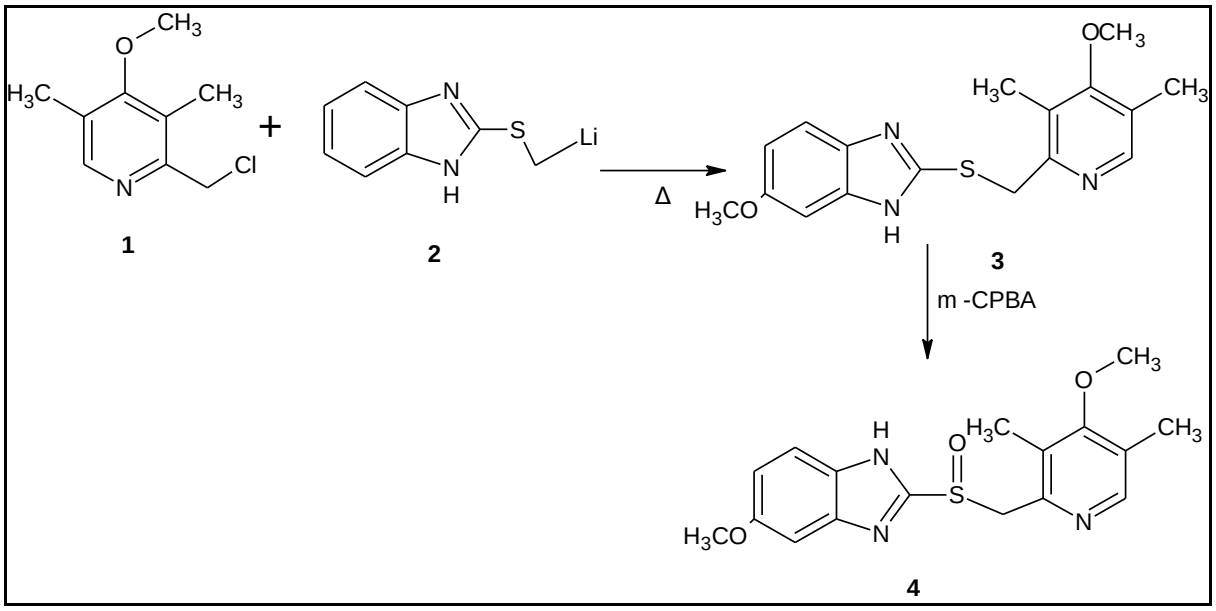
1. Synthesis of Proton Pump Inhibitors And Structure of Their Impurities

1.1 Omeprazole

The chemical name of omeprazole is 6-methoxyl-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methyl sulfinyl)-1 H-benzo[d]imidazole. [7]It contains pyramidal structure which tricoordinated sulfinylsulfur that exist either (*S*)- or (*R*)-enantiomers in the acidic medium acts by inhibiting canaliculi of parietal cell that converted to chiral product .The cysteine group reacted with H+/K+ ATPase by inhibiting parietal cells that produce gastric acid .[8]

1.1.2 Synthesis and Structure of Omeprazole

2-(Lithium methyl sulphinyl)-5-methoxy-1H benzimidazole**2**20g was reacted with 2-chloro-3,5-dimethyl-4- methoxy pyridine **1**21 g to form sulphide intermediate **3**and then converted to Omeprazole **4** when treated with m-CPBA which used as anoxidizingagents. The acetamide-sulfide compounds modification are oxidised to form the amide sulfinyl compound and gives the sulfinyl carboxylate or salts upon alkaline hydrolysis.[9]On further decarboxylation leads to the target molecules. The residual, unreacted salt, inorganic by-products and other minor by-products can be easily purified by a simple washing from omeprazole or lansoprazole. The amide compounds containing crystalline solids as opposed to the sulphide and sulfoxides of the reported procedures[10](**Scheme-1**).



Scheme-1

1.1.3 Omeprazole Impurities

The analytical method HPLC had been used for the separation of optically active drug from the enantiomeric impurity and organic impurities. In the monograph of European Pharmacopoeia(EP) for ESO the structure of the impurities has been reported in (**Fig. 1**). According to recent paper PPIs direct enantioseparation on the immobilised Chiralpak IA CSP in multimodal conditions [11,12] **Fig:1.**

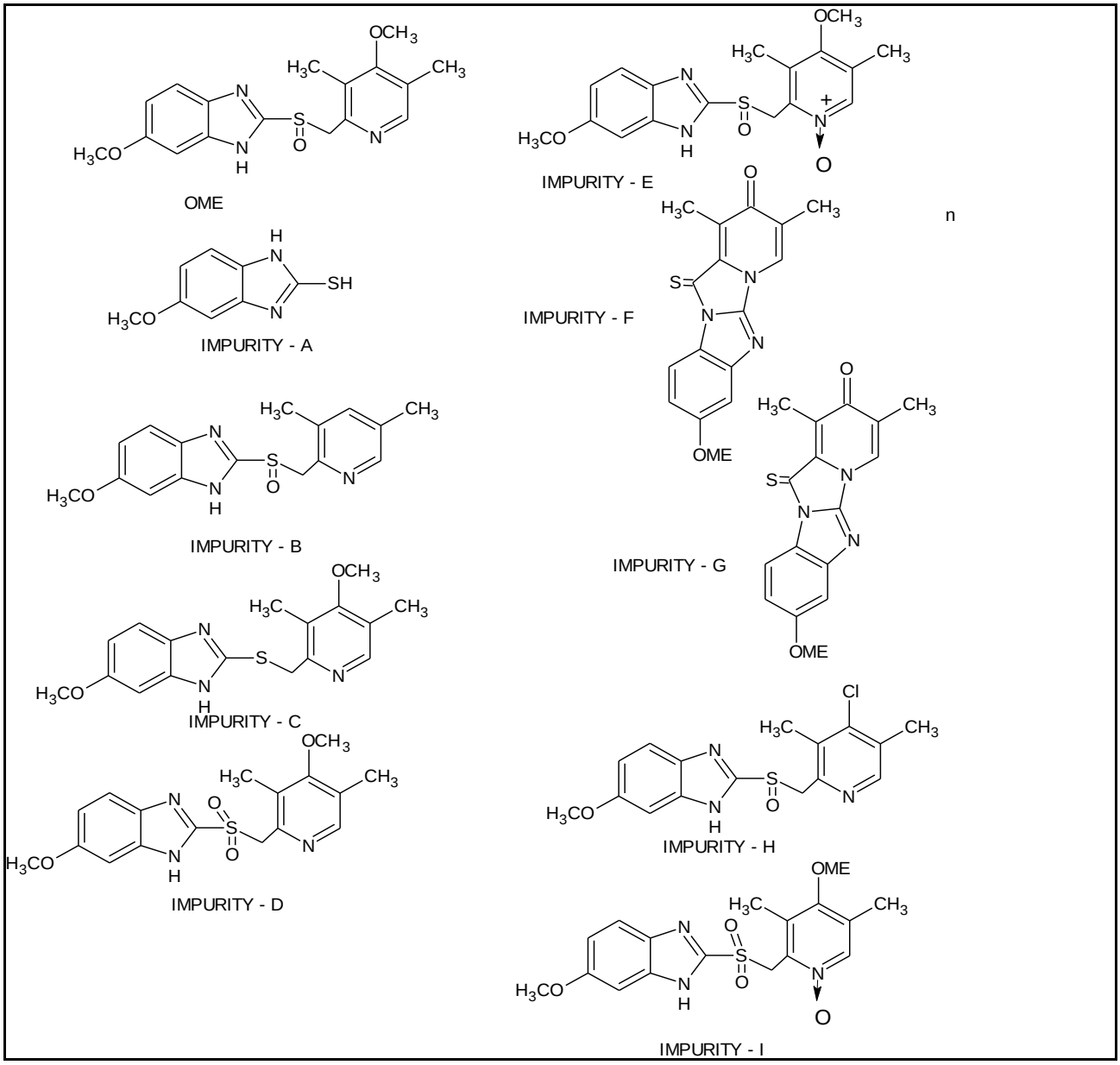
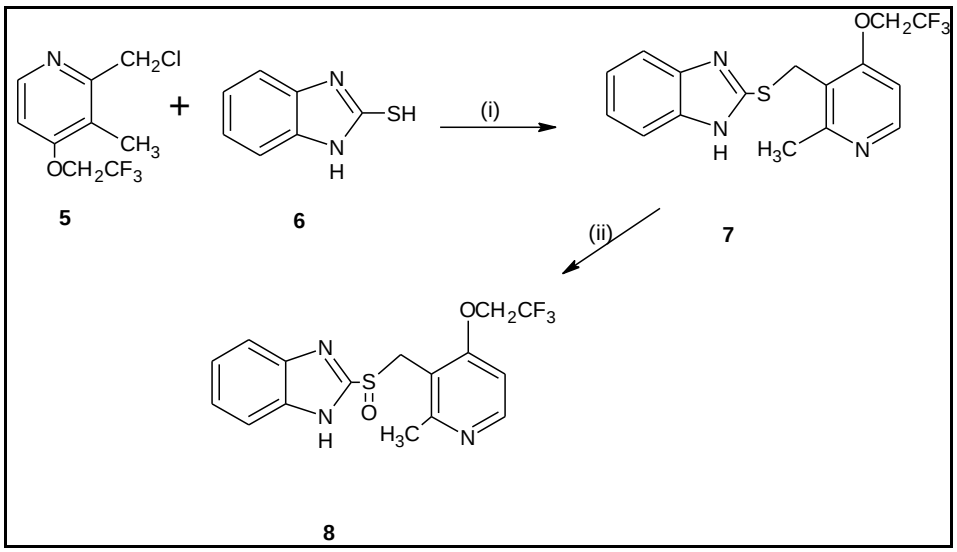


Fig. 1 : List and structure of omeprazole impurities

1.2. Lansoprazole

Lansoprazole is chemically known as (RS)-2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridine-2-yl]methylsulfinyl) -1-H-benzo[d] imidazole. Lansoprazole also acting as is a proton pump inhibitor (PPIs) and inhibits by acting on the hydrogen/potassium adenosine tri-phosphatase (H+/K+ATPase) in parietal cells.[13] Stomach acid will be reduced by blocking the enzyme system.The reaction involved with the starting material **(**2-mercapto benzimidazole)**6** and **(**Lanso–chloro [2-(Chloromethyl)-3- methyl-4- (2,2,2- trifluoroethoxy) pyridine hydrochloride)**5** in presence of sodium hydroxide is condensed to get Lanso-sulphide **7**and on oxidation with hydrogen peroxide gives Lansoprazole**8**(**Scheme-II**).[14]



i) NaOH ; ii) H_2O_2;

Scheme-II

1.2.1Lansoprazole Impurities

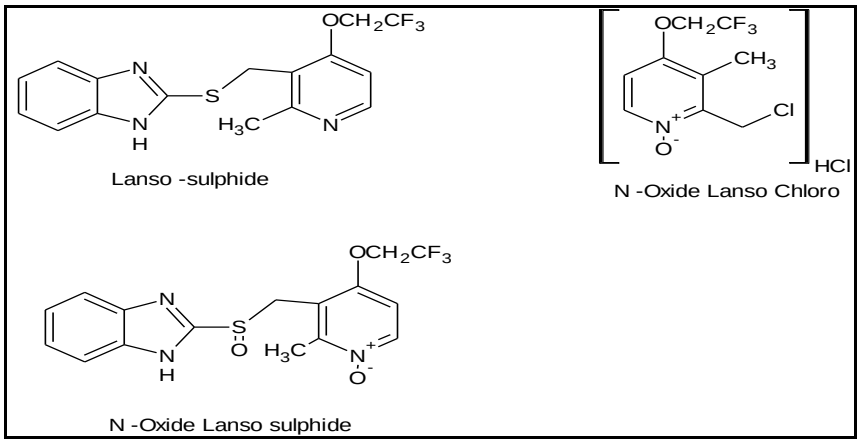
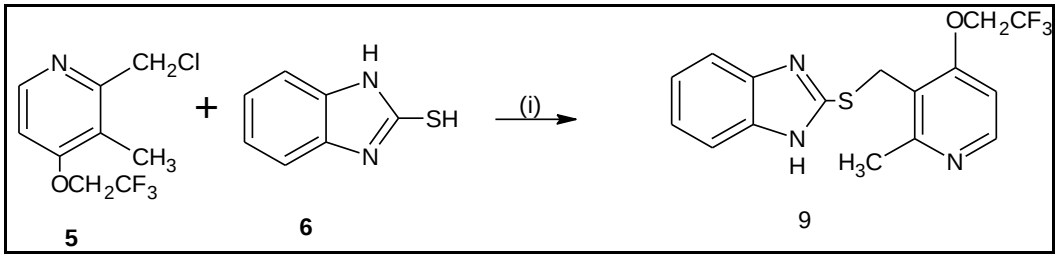


Fig. 2 :Structure of Lansoprazole impurities

1.2.1.1Lanso Sulphide

Lanso sulphide impurity prepared from 2-mercaptobenzimidazole **6** by the condensation with lanso-chloro**5** at room temperature in presence of sodium hydroxide and water at ambient temperature . [15]The solid was filtered and dried to give lanso sulphide **9**(**Scheme -III).**

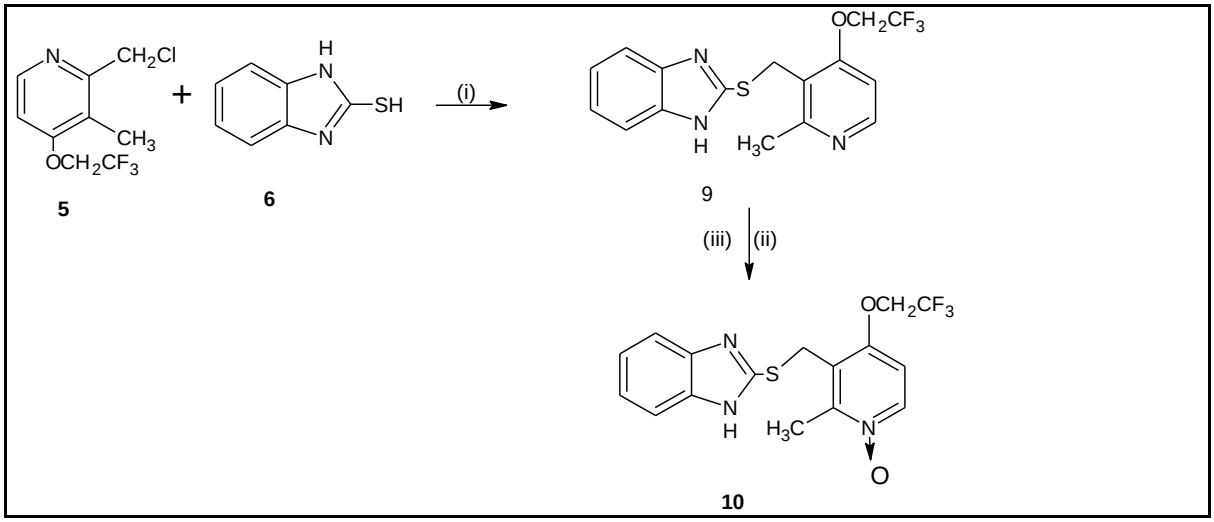


i) NaOH /H_2O;

Scheme –III

1.2.1.2 N-Oxide Lansoprazole

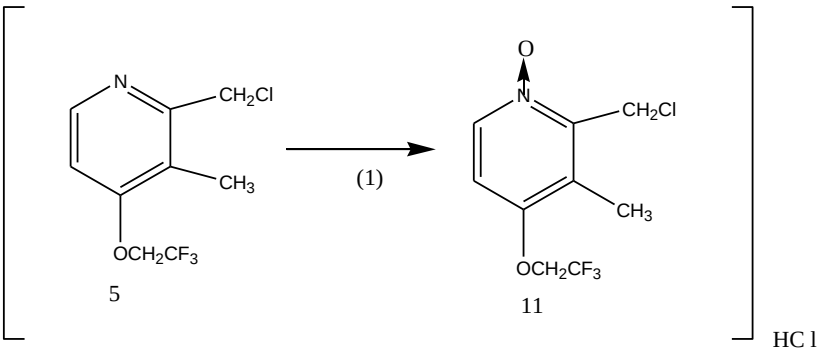
Lanso-sulphide **9**was dissolved in IPA and methanol mixture and reaction mass was heated to 45-50ºC filtered hot and then cooled to 18 to 15ºC. Catalyst solution was added under stirring and maintained for 2 hour. The completion of reaction was checked on TLC. Layer separation occur through Chloroform and aqueous layer .[16]Aqueous layer charged into reactor and cooled to 10 -15 ºC and re-precipitation when methanol added dropwise. White coloured solid compound was obtained and dried when filtered and washed to obtain N-oxide Lansoprazole**10**(**Scheme -IV).**



i) NaOH; ii) IPA and methanol mixture; iii) H_2O_2

1.2.1.3 Synthesis Of N-Oxide Lanso - Chloro

2- chloromethyl-3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridine hydrochloride **5** was dissolved in acetic acid at ambient temperature. Reaction mass was heated at temperature of 80-85ºC and then addition per acetic acid dropwise and maintained for 2-3 hour. [17]The completion of reaction was checked on TLC. Distilled under vacuum to get yellowish coloured semisolid compound of (N-oxide 2-chloromethyl-3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridine hydrochloride) N-oxide Lanso-chloro**11**. (**Scheme-V**)

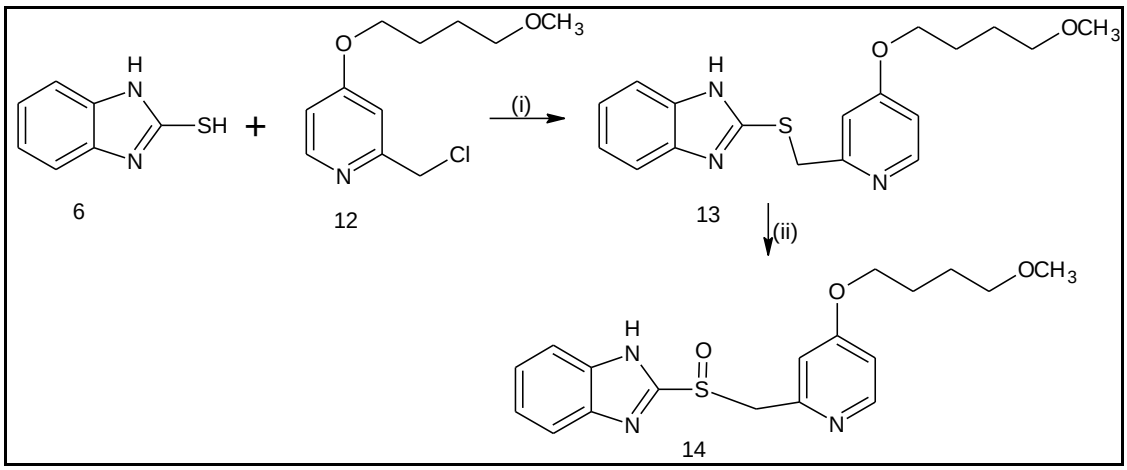


Scheme-V

i) CH_3COOH

1.3 Rabeprazole

The preparation of Rabeprazole from Rabeprazole sulphide **13** through oxidation process by oxidizing agent with m-chloroperoxybenzoic acid in a mixture of dichloromethane and diethyl ether. Through mixture of dichloromethane and diethyl ether oily product was obtained and then further crystallized [18]. Azeotropic distillation was carried out with ethanol to remove water followed by addition of ether to obtain base of rabeprazole**14(Scheme-VI).**



i) CH_3; ii)m- CPBA/CH_3CN;

Scheme-VI

1.3.1 Rabeprazole Impurities

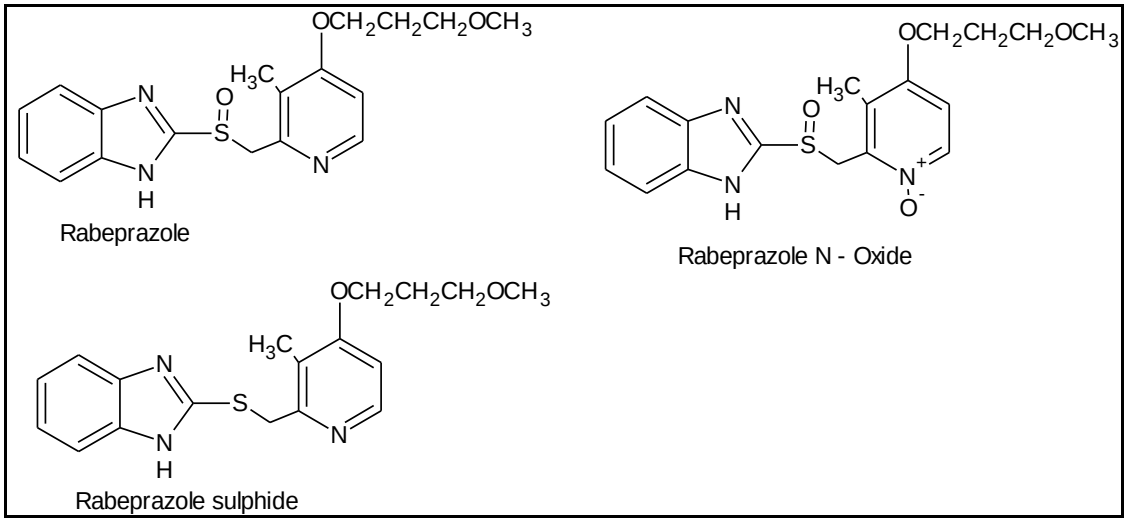


Fig. 3: Structure of Rabeprazole impurities

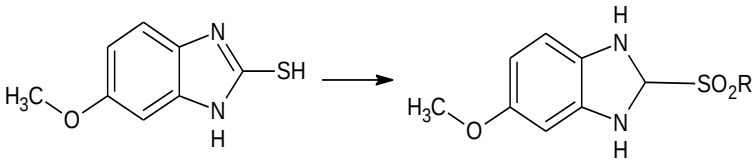
2.Strategies For The Novel Synthesis Of Omeprazole

2.1 Omeprazole novel synthesis

Omeprazole previously synthesis by the mechanism of nucleophilic substitutiom reaction between5-methoxythiobenzimidazole **15** and 2-chloromethyl-4-methoxy-3,5-dimethyl-pyridine **16** give pyrmetazole with the help of oxidizing agents m-chloroperoxybenzoic acid and peroxide that undergoes oxidation to give omeprazole.[19]

In new approaches according to literature survey 5-methoxythiobenzimidazole reacting with 30% aqueous H_2O_2 the formation of ester of 5-methoxythiobenzimidazole in the presence of peroxide and (m-CPBA) containing methanol, ethanol, benzyl alcohol, menthol, diacetonide glucose at -10^0C give the corresponding esters on which benzyl alcohol give high percentage yield .[20]

Scheme-VII

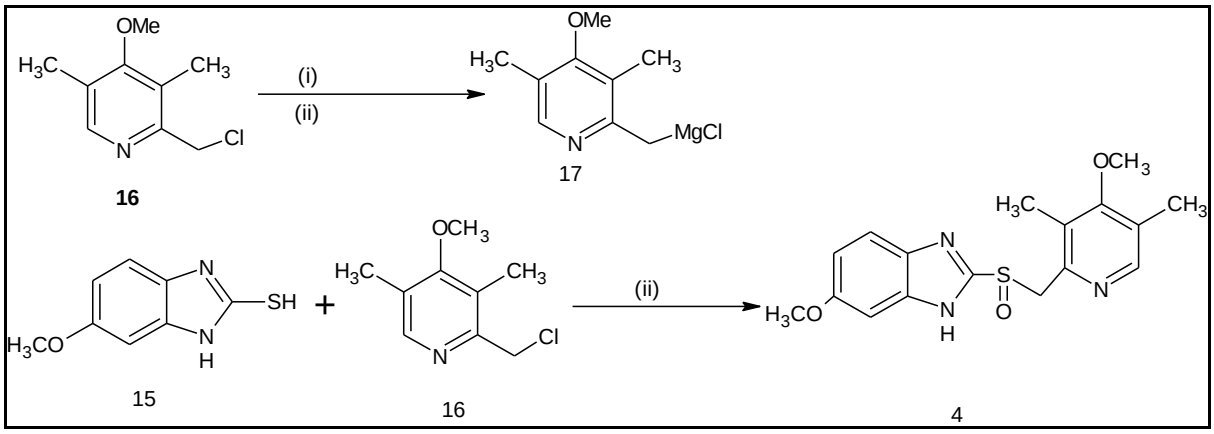


15

R=CH_3,C_2H_5,Benzyl alchol,menthol ,Diacetonide glucose

Due to getting problem with the Grignard reagents because there is problem in the formation of organic halide because formation of allylic and benzylic radicals, which leads to migration from metal surface that yield wurtz coupled products. So this problem can be treated with the magnesium–anthracene complex **17** with reagents THF at 40 ^{0}C**.**[21]

Scheme-VIII



i) Mg- Anthracene ii) THF , 0-5^{0}C

Mg anthracene complex is oranged -coloured crystalline compound which is prepared by activating magnesium which ethyl bromide in a catalytic amount followed with the addition of anthracence in THF at 40 ^{0}C under inert condition.[22]Mg anthracene complex react with 2-chloromethyl-4-methoxy-3,5-dimethyl-pyridine **16** to give pyridylgrignard reagent .Now ester fragments of 5-methoxythiobenzimidazole **15** was then added to Grignard reagents ie magnesium anthracene complex to give omeprazole**4.** [23]

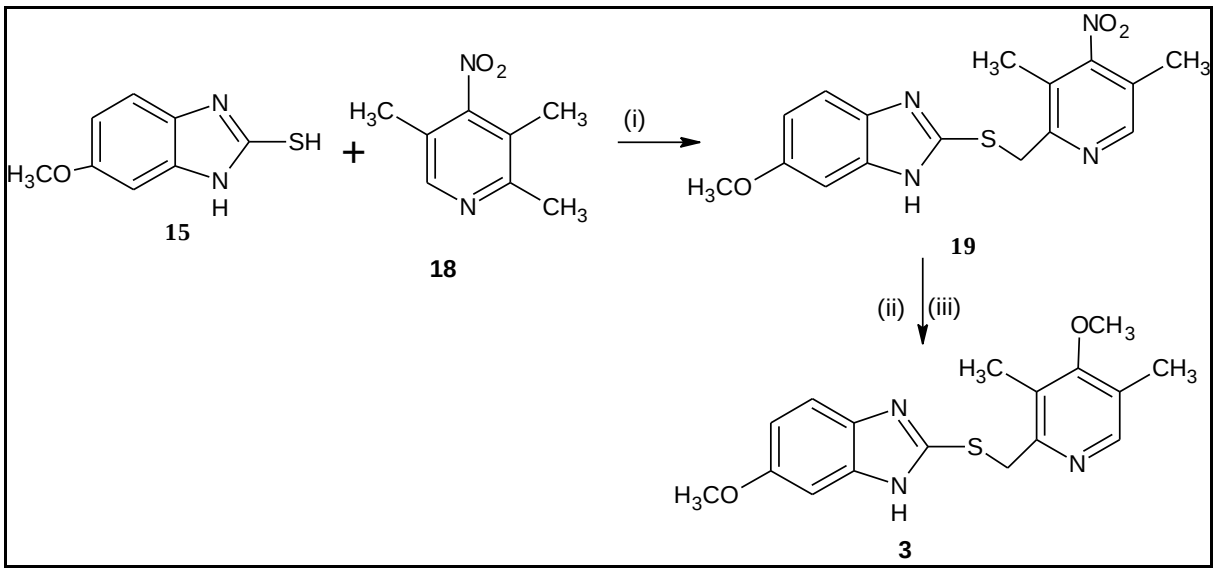
2.2 $H_3PW_{12}O_{40}$: An Efficient And Green Catalyst For The Facile And Selective Oxidation Of Sulfides To Sulfoxides, Applied To The Last Step Of The Synthesis Of Omeprazole

The novel synthesis of omeprazole occur between the catalyst which is economical,facile and selective oxidant for the oxidation using $H_3PW_{12}O_{40}$ .Heteropolyacids as catalyst and oxidant reported as a selective oxidation of sulphide to sulfoxide moiety in the last step of the synthesis of omeprazole using H_2O_2 and different HPAs as co-oxidant and catalysts . [24]

The synthesis of (5-methoxy-2-[(4-nitro-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole) occurs between 5-methoxy-2-mercaptobenzimidazole **15 r**eacted with 2-chloromethyl-3,5-dimethyl-4-nitropyridine **18** in the presence of sodium hydroxide that give **19**. Compound **19** reacted with potassium carbonate in the presence of sodium methoxide lead to formation of compound **3.**In the presence of methanol, hydrogen peroxide and heteropoly acids **3** undergoes oxidation which give **4**.[25]

Scheme -IX

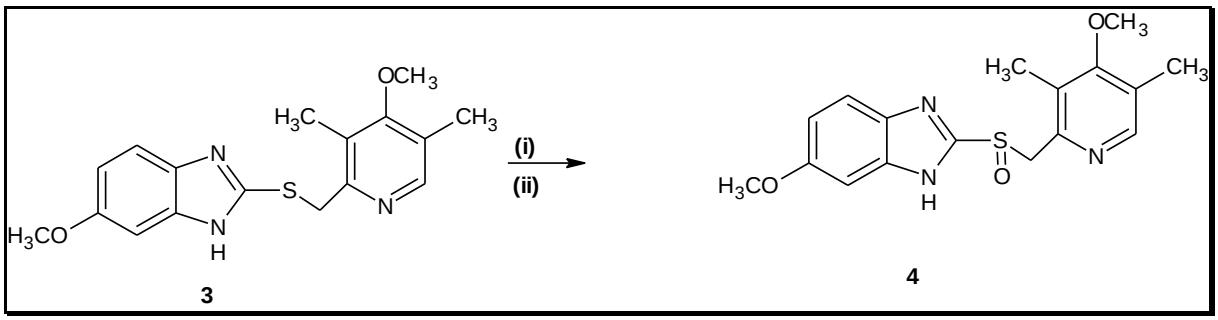
Synthesis of thioethers (5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole)



i) NaOH/MeOH ii) K_2CO_3,$MgCl_2$ iii) $NaOCH_3/CH_3OH$

Scheme -X

Synthesis of (5-methoxy-2-[(4-nitro-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole



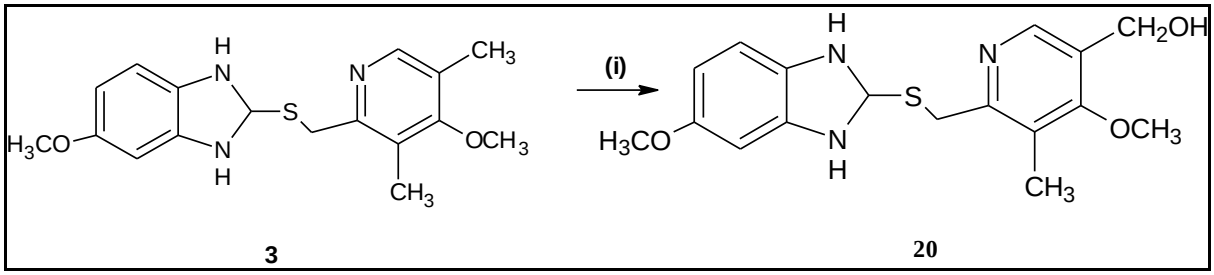
i) MeOH ii) H_2O_2, HPA

The reaction of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methylthio]-1H-benzimidazole **3**(1 equiv.) to give **20** in the presence of H_2O_2 and $H_3PW_{12}O_{40}$ in methanol at room temperature was examined. The comparison done between three types of heteropolyacids, including Preyssler, $H14[NaP_5W_30O_{110}]$, Keggin, $H3[PW_{12}O_{40}]$ and $H4[SiW_{12}O_{40}]$, and Wells-Dawson types $H_6[P_2W_{18}O_{62}]$ [26].

2.3 Strategies to Synthesis 5-Hydroxy Omeprazole Sulphide from Omeprazole Sulphide Through Enzyme Bacillus Megaterium Cyp102A1 Acting As Human Metabolite

Some metabolites prepared through chemical methods and other by using human cytochrome P450s enzymes. In human liver omeprazole contain metabolites ie CYP2C19 and CYP3A4 out of which CYP3A4 favours sulfoxidation of S-isomer of omeprazole while CYP3A4 favours hydroxylation of C-5. [27]It has been found that human urine contains 5-OH omeprazole Sulphide as minormetabolites. Mutant of CYP102A1 catalyse C-5' hydroxylation regioselective isomer of S- and R omeprazole. On the other hands Omeprazole Sulphide isthe major human metabolite of Omeprazole.[28]This is single step reaction which produce efficiently regioselective omeprazole Sulphide **3**hydroxylation to produce 5'-OH omeprazole Sulphide **20** and also give high conversion yields. This metabolites hydroxylated can also be used as a lead drug to avoid variation in individualsduring drug metabolism and drug interaction without further modification in hydroxylated group [29].

Scheme -XI



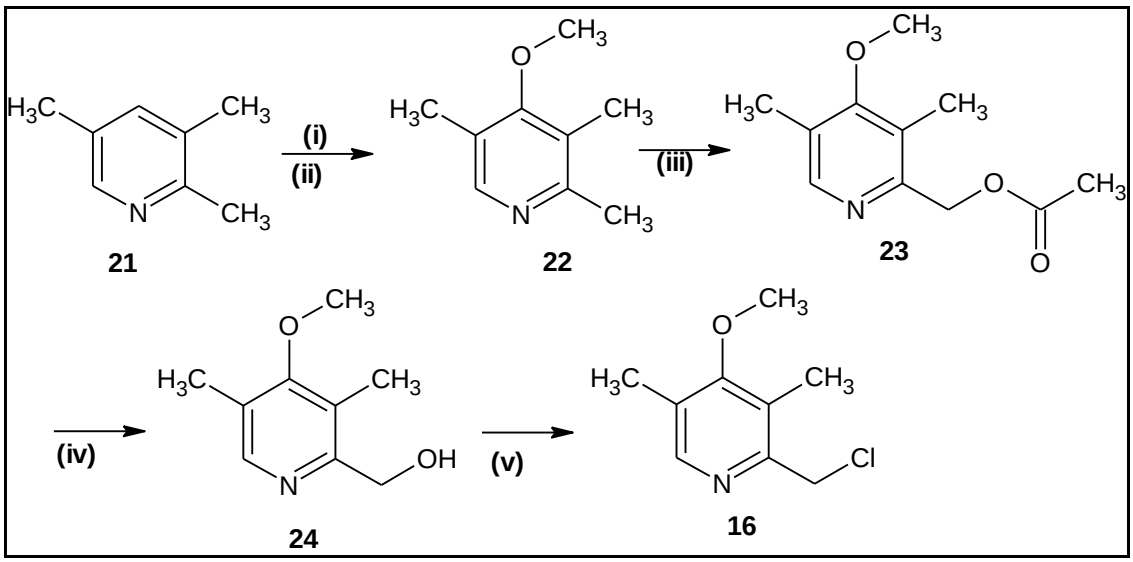
3 **20**

i) Benzyl Hydroxylation CYP102A1

2.4 ((5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole):

The improved process involved the synthesis of pyridine moiety in which 4-nitropyridine derivative from 2,3,5-trimethyl pyridine**21**which is a chloromethyl precursor is nitrated in the 4th position of nitropyridine derivatives. The precursor is treated with sodium methoxide and acetic anhydride to generate methoxide ion which replaces the nitro group.[30]In the second position methyl group is converted to the acetoxymethyl group **23** using acetic anhydride. The acetoxy methyl group then hydrolysed to give **24**and in the presence of thionyl chloride used for chlorination to generate the **16** 2-chloromethyl pyridine precursor.[31]

Scheme -XII



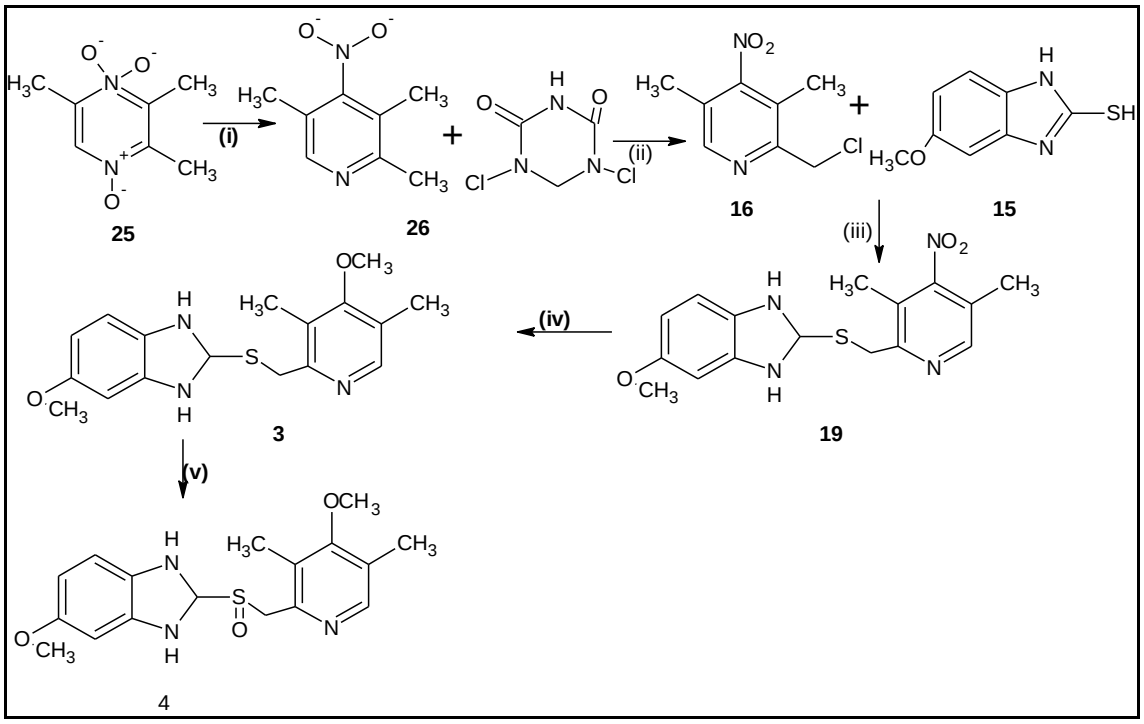
21 **22** **23**

24 **16**

i) HNO_3,H_2SO_4 ii)NaOH,CH_3OH iii) $O(COCH_3)_2$ iv) NaOH v) $SOCl_2$

The basic condition could be removed at initial stage of omeprazole synthesis which can degraded the starting material and hampered the reaction conditions. The synthesis of the pyridine moiety with the N-oxidation of the substituted pyridines gives N-oxide intermediate which is more stable than the simple pyridine intermediate.[32]The reaction involved with substituted-4-amino pyridine- N-oxide **25**with phosphorous trichloride to generate the 4-amino pyridine which upon treatment with trichloroisocyanuric acid gave the chloromethyl pyridine intermediate **16**.[33]Compound **16**and **15** were treated with sodium hydroxide in methanol yielded sulphide intermediate **19** which is novel than previously reported schemes. Compound **3** reacted with hydrogen peroxide in the presence of ammonium molybdate to give omeprazole **4** .[34]

Scheme -XIII



i) PCl_5 ii) NaOH iii) NaOMe/MeOH iii) H_2O_2

3. Novel process for synthesis of ESOMEPRAZOLE

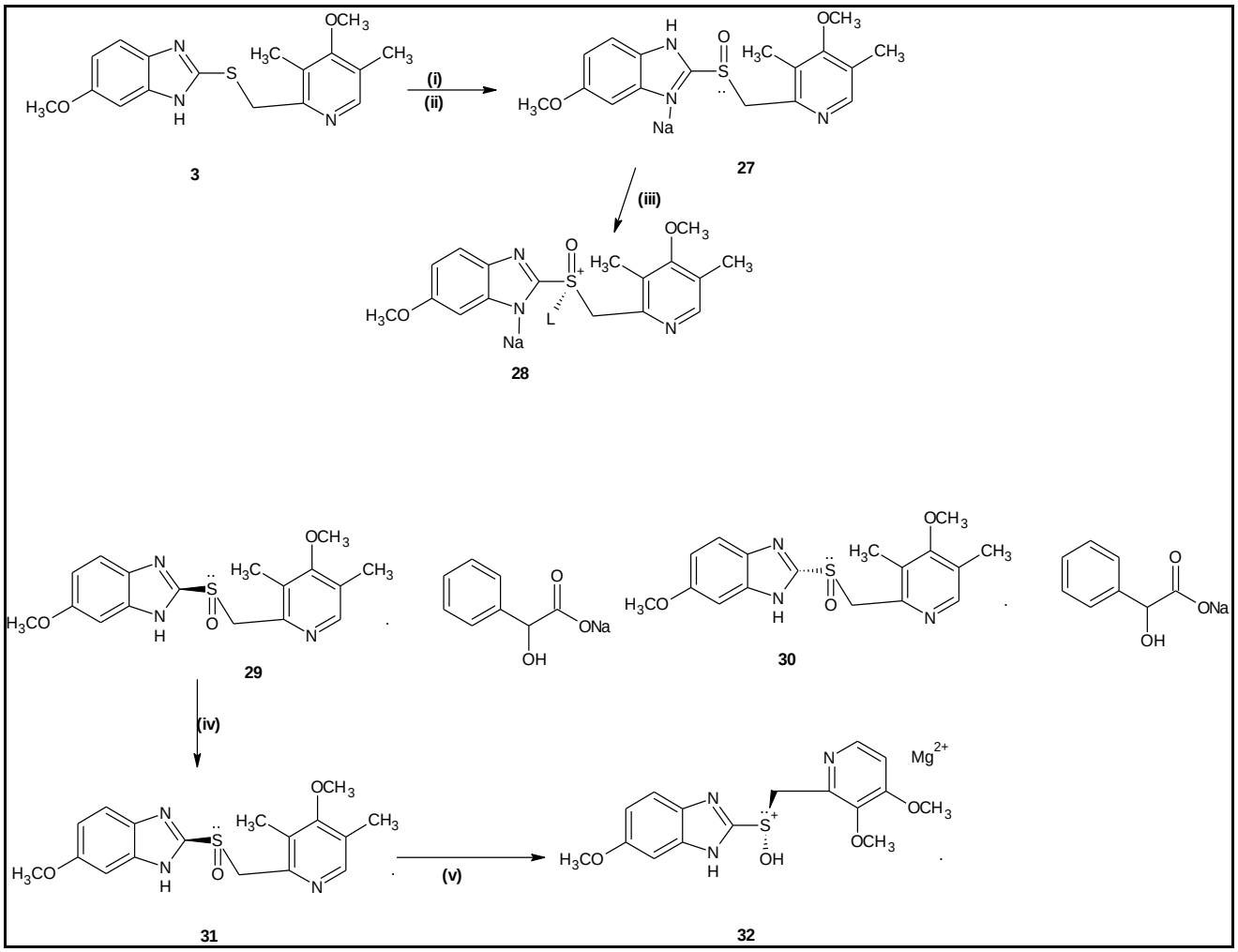
Esomeprazole is the S-isomer of omeprazole which is also acts as proton pump inhibitor that inhibits specifically on the gastric H+/K+-ATPase enzyme in the parietal cells of the stomach is responsible for acid secretion. [33]Chemically known as (T-4)-bis[5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2pyridinyl)methyl] sulfinyl]-1Hbenzimidazolato] magnesium **34**. According to Larsson et al he disclose the asymmetric oxidation using cumenehydroperoxide with TI(O-*i*Pr)4, diethyl-D-tartrate, of sulfides and water in the ratio of (1:2:1) in methylene chloride at -23 ^{O}C . [34]The highly efficient synthesis by oxidation of prochiral sulphide via asymmetric synthesis was described **.**

3.1 Preparation of Esomeprazole Through Transistion Metalcomplex

The preparation of S isomer omeprazole with transtition metal complex chemically known as(T-4)-bis[5-methoxy-2-[(S)[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1Hbenzimidazolato] magnesium metal complexed**32**. The conversion of omeprazole salts **27**into esomeprazole **27** in the presence of sodium hydroxide in a mixture of Isopropyl alcohol.[35]Further reaction with titanium (IV) isopropoxide and diethyl-D-tartarate in acetone yields a transition metal complex**28**and after reacted with L(+)-mandelic acid converted intodiastereomeric salts **29** which gives free species of sulfoxide**30**.The free species is then converted to magnesium salts **32** that give optical purity of 99.97% by chiral HPLC with flow rate 0.5 mL/min with a UV detector at 280 nm **.**[36]

3.1.1 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Sodium

Scheme -XIV

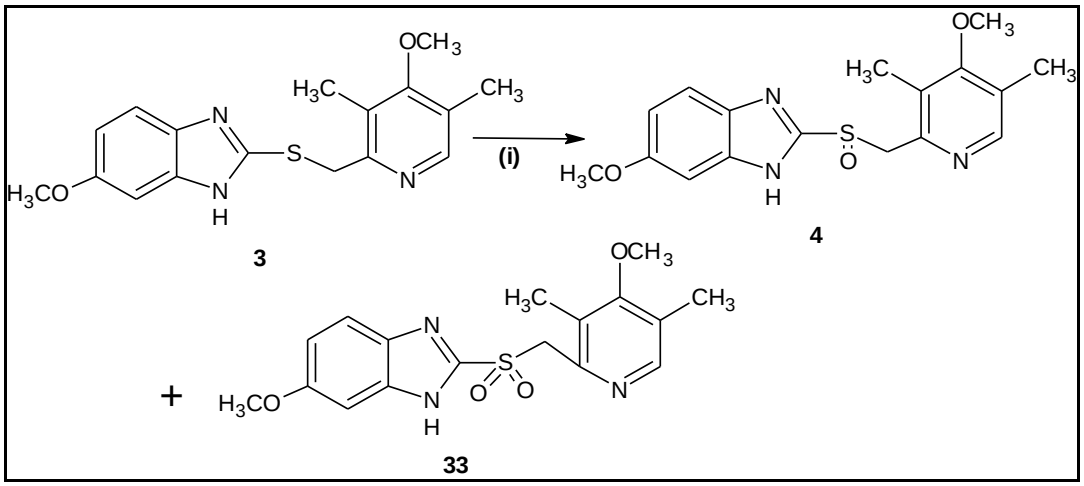


i) NaOH ii) MeOH/IPA iii) CH_3COCH_3, TEA, Titanium isopropoxide, Diethyl -D- tartate iv) $NaHCO_3$, DCM / Acetone v) Mg, Methanol, DCM, Acetone

3.2 An Efficient Procedure for the Synthesis of Esomeprazole Using a Titanium Complex with Two Chiral Ligands

The Esomeprazole preparation based on the separation of racemic mixture and synthesis of prochiral sulphide by method of asymmetric oxidation. The sulfoxide optically active with optical purity of 40% can be obtained through oxidation of sulphide **3** with Davis reagent, (3*S*,2*R*)-(−)-*N*-phenylsulfonyl-(3,3-dichlorocamphoryl)oxaziridine.[37]

Scheme-XV



i) [O]

The oxidation of sulphide **3**occurs in the presence of peroxide and catalytic complex of titanium(IV) isopropoxide Ti(OPr-*i*)4,maintaining temperature –20 to –40°C give omeprazole **8.**The crude product gives optical purity upto 94% and after converted into salt in which optical purity of sulfoxide**33**increased to 100%.[38]

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Contribution of Authors:

Sweety Saini being the first and corresponding author of the article who will be carrying out his research in this drug for his dissertation work. The literature survey and other related information's has been collected by me and they were arranged accordingly.

Chandana Majee is the Second author and Research supervisor who had helped SweetySaini in the selection of the drug and making her to understand about the importance of drug and its mechanism with respect to pharmacological work.

Guno Sindhu Chakraborthy serving as third author in the article has helped in arrangement of the literary work and selection of journal

Salahuddin serving as fourth author in the article who helped in the computation work.

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