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DESIGN AND SYNTHESIS OF IMIDAZOPYRIDINE DERIVATIVES AS ANTIULCER DRUG

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Abstract: Imidazopyridine derivatives are a proton pump inhibitor that reduces gastric acid secretion and has been successfully used to heal and relieve symptoms of gastric or duodenal ulcers and gastro-esophageal reflux. It has been synthesized by an oxidation of sulfide produced from a substitution reaction between 2-mercaptobenzimidazole and pyridine derivatives. The transformation of sulfide into sulfinyl has been generally carried out with peroxyacid such as mCPBA. The method for optical resolution includes fractional recrystallisation. The fractional recrystallisation method includes a method in which a salt is formed between a racemate and an optically active compound [eg. (+)-Mandellic acid, (-)-Mandellic acid] and salt is separated by fractional recrystallisation etc. and if desired subjected to neutralization process to give a free optical isomer. The chiral column method includes a method in which a racemate or a salt is applied to a column for optical isomer separation. In High performance liquid chromatography for example optical isomer are separated by adding the racemate to a chiral column (such as Daicel series) and eluting in water a buffer (for example, a phosphate), an organic solvent (for example, hexane, ethanol, methanol, isopropanol, acetonitrile, triethylamine or mixture thereof) or mixture of the foregoing.

Index Terms **-Imidazopyridine, Recrystallisation, Chromatography, Racemate, Proton-pump inhibitor**

1.1 Introduction

Proton pump inhibitor (or "PPI"s) is a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available today. The group followed and has largely superseded another group of pharmaceuticals with similar effects, but different mode-of-action called as H_2-receptor antagonists. These drugs are among the most widely-selling drugs in the world and are generally considered safe and effective. The majority of these drugs are benzimidazole derivatives; however, promising new research indicates that Benzimidazopyridine derivatives may be a more effective means of treatment (1).

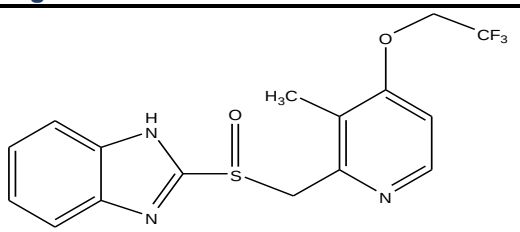
1.2 Classification of PPIs: -

1.2.1: - Irreversible gastric PPIs: -

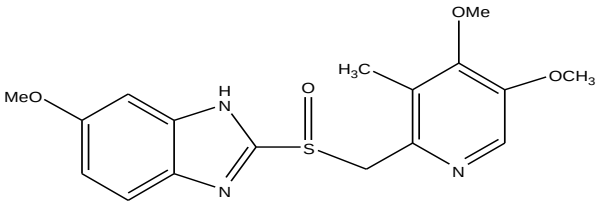
- Three main structural features of this class are the substituted pyridine ring; the substituted benzimidazole ring, and the methylsulfinyl linking group.
- Irreversible PPIs lacking one or more of these features are rare. They are further classified according to their chemical structure as follows.

1.2.1.1: -Pyridinylmethylsulfinyl benzimidazoles: -

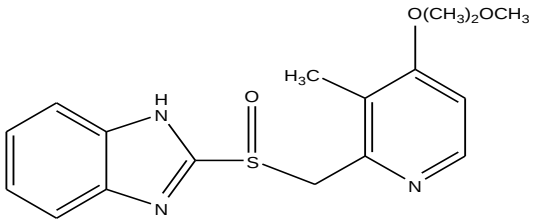
- The same chemical features are retained by clinically used PPIs, differing only in the substituents present in the benzimidazole and pyridine ring.
  Examples-omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazol.



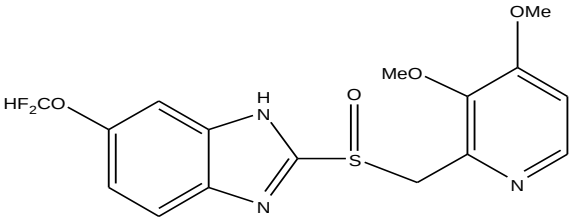
Lansoprazole



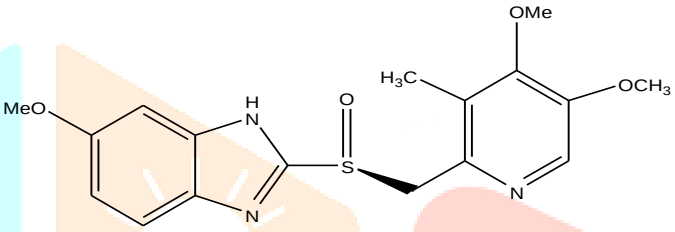
Omeprazole



Rabeprazole



Pantoprazole



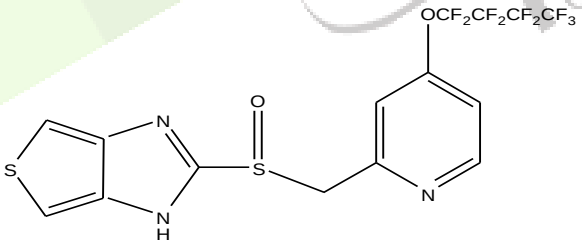
Esomeprazole

Figure 1: Pyridinyl methyl sulfinyl benzimidazoles

1.2.1.2:- Pyridylmethylsulfinyl thienoimidazoles:-

- In this class, the benzene ring of imidazole is replaced by thiophene, keeping other structural features same.

Examples- Saviprazole



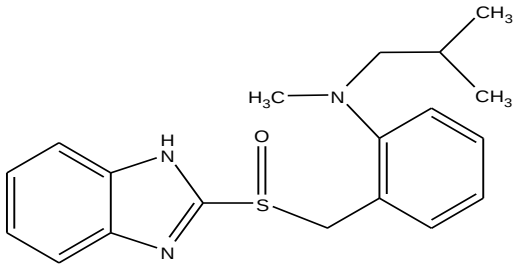
Saviprazole

Figure 2: Pyridyl methyl sulfinyl thienoimidazoles

1.2.1.3:- Aminobenzylsulfinyl benzimidazoles:-

- Here, pyridine ring is replaced by substituted amino benzyl ring.

Examples- leminoprazole



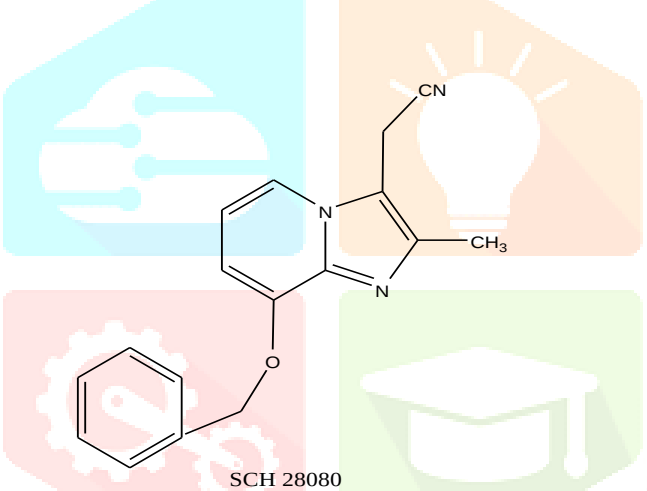
Leminiprazole

Figure 3: Amino benzyl sulfinyl benzimidazoles

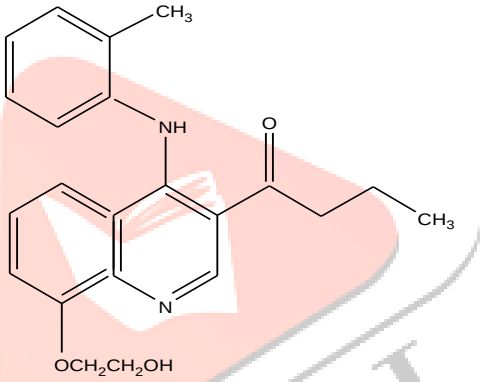
1.2.2. Reversible gastric PPIs:-

- To overcome the drawbacks associated with the use of irreversible PPIs, research has been directed toward discovery of reversible inhibitors.

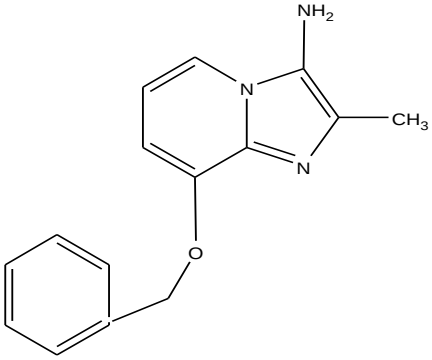
Examples-SCH28080, SK& F 97574, SCH 32651, and SK& F 96067.



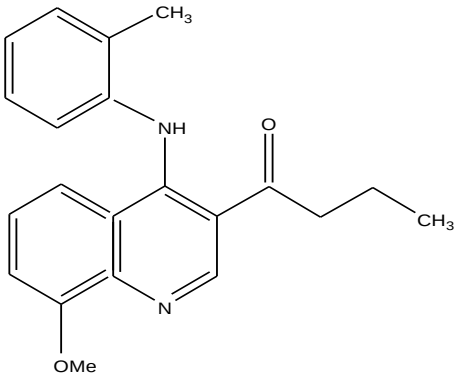
SCH 28080



SK&F 97574



SCH 32651



SK&F 96067

Figure 4: Reversible gastric PPIs

1.3 Mechanism of action:

1.3.1. Irreversible proton pump inhibitors: -

Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system of the gastric parietal cell. The proton pump is the terminal stage in gastric acid secretion being directly responsible for secreting H^+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion. ("Irreversibility" refers to the effect on a single copy of the enzyme; the effect on the overall human digestive system is reversible, as the enzymes are naturally destroyed and replaced with new copies (2).

Targeting the terminal-step in acid production, as well as the irreversible nature of the inhibition, results in a class of drugs that are significantly more effective than H_2 antagonists and reduce gastric acid secretion up to 99%.The lack of the acid in the stomach will aid in the healing of duodenal ulcers and reduces the pain from indigestion and heartburn which can be exacerbated by stomach acid. However lack of stomach acid is also called hypochlorhydria, the lack of sufficient hydrochloric acid (HCl). Hydrochloric acid is required for the digestion of proteins and for the absorption of nutrients, particularly of vitamin B12 and calcium.

The proton pump inhibitors are given in an inactive form. The inactive form is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) that have acidic environments. In an acid environment, the inactive drug is protonated and rearranges into its active form. As described above, the active form has covalently and irreversibly bind to the gastric proton pump, deactivating it (3).

1.3.2. Reversible proton pump inhibitors: -

Omeprazole and SCH 28080 differ in inhibition kinetics for their proton pump inhibitory activity. In contrast to omeprazole, SCH 28080 is a competitive inhibitor of high affinity luminal K^+ site of the gastric proton pump. In contrast to Na^+/K^+-ATPase, it is highly selective to H^+/K^+-ATPase activity. SCH 28080 is a protonable weak base (pKa = 5.6), hence like omeprazole it accumulates in the acidic compartments of the parietal cells in its protonated form SCH 28080 is chemically stable and after protonation, is itself active and does not need an acid-induced transformation, as required by omeprazole and its congeners (4,5).

1.4 Structure–activity relationships: -

1.4.1. Irreversible proton pump inhibitors: -

The pyridinyl methyl sulfinyl benzimidazole (PMSB) can be considered to possess three structural elements:

(a) The pyridine ring

(b) The benzimidazole ring system

(c) The linking chain

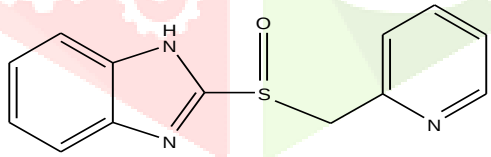


Figure 5. General structure of irreversible PPIs.

- Replacement of $SOCH_2$ of the linking chain, by a variety of other groups like $–SCH_2$, $–SO_2CH_2$, $–SCH_2CH_2$, and various carbon and oxygen containing chains, leads to loss of activity in vitro.
- Extending the length of chain by $–SOCH_2CH_2$ gives rise to inactive acid stable compound.
- In the pyridine ring system, degree of nucleophilicity (rather than basicity) of nitrogen atom reflects the ease of spiro intermediate formation. For example, substitution in 6-position of the ring results in loss of activity as disfavoring steric interaction. When significant steric effects are absent, a pKa value of greater or equal than 4 is probably optimal for activity.
- Weak bases like timoprazole and $4\text{-}CO_2CH_3$ derivatives show greatly reduced activity, as 4-methyl compound is several times less active than 4-alkoxy analogs. In case of omeprazole (pKa = 4), the 40-methyl substitution has little effect on pKa, as it is bent out of plane by the two flanking methyl groups.
- The substitution in benzimidazole ring does not change the activity to a great extent. Introduction of electron withdrawing substituents like $5\text{-}NO_2$, 5-MeSO, $5\text{-}CF_3$ and leads to decreased enzyme inhibition.

1.4.2. Reversible proton pump inhibitors:-

Totally 81 derivatives of imidazo [1, 2-a] pyridines 32a and 32b, related to SCH 28080, were synthesized and studied, based on which following observations were made:
(1) A small alkyl group at C-2 (methyl or ethyl) favoured activity.
(2) Cyano methyl or amino group at C-3 was a requirement for maintaining bothanti-secretory and cytoprotective activity;
(3) Activity at 8-position was maximized with benzyloxy, 3-thienylmethoxy or phenylmethylamino substitution.
(4) Replacement of C-7 by N leads to retention of activity. Surprisingly little work has been reported on these reversible inhibitors of H^+/K^+-ATPase. Although, highly efficacious drugs could emerge from research on APAs.

These drugs are utilized in the treatment of many conditions such as: Dyspepsia, Peptic ulcer disease (PUD), Gastroesophageal reflux disease (GORD/GERD), extra esophageal reflux disease, Barrett's esophagus, Prevention of stress gastritis , Zollinger-Ellison syndrome.
The most commonly observed adverse effects are constipation, diarrhea, dizziness, headache, skin itch, and skin rash. Less often, the following adverse effects have been reported: abdominal pain with cramps, appetite changes, and nausea.

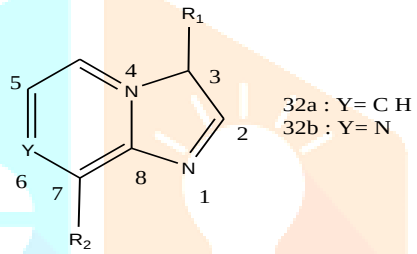


Figure 6. General structure of reversible PPIs

1.5 Mechanism of gastric acid secretion: Stomach is a primary site of digestion. Presence of food stimulates release of acids and enzymes in stomach. The chemo- and mechanosensitive receptors present in stomach are triggered by presence of food to produce specific responses (6).The acid secreting parietal cell is the principle cell in gastric glands. The physiological regulation of acid secretion by the parietal cells is thus an important factor behind the rationale of use of various agents to reduce gastric acidity. Three major pathways activating parietal acid secretion include:
(1) Neuronal stimulation via the vagus nerve.
(2) Paracrine stimulation by local release of histamine from entero chromaffin -like (ECL) Cells.
(3)Endocrine stimulation via gastrin released from antral G cells.
In neuronal pathway, acetylcholine (Ach) released by vagal nerve directly stimulates gastric acid secretion through muscarinic M3 receptors located on the basolateral membrane of parietal cells. The CNS is considered to be the chief contributor for initiating gastric acid secretion in response to the anticipation of food. Ach indirectly stimulates release of histamine from enterochromaffin-like (ECL) cells in the fundus and gastrin from the G cells in the gastric antrum. ECL cells, the sole source of gastric histamine involved in acid secretion, are present in close proximity to parietal cells. Histamine released from ECL cells activates parietal cells in paracrine fashion by binding to H_2 receptors. Gastrin is primarily present in antral G cells. Release of gastrin is under regulation of central neural activation, local distension, and chemical composition of gastric content. Gastrin stimulates parietal cells by binding with gastrin receptors. Gastrin also exerts its action in an indirect manner by causing the release of histamine from ECL cells (7). Binding to respective G-protein coupled receptors by Ach, gastrin, and histamine results in activation of second-messenger systems .Vagal stimulation and the action of gastrin (from duodenal and antral G cells) stimulate release of histamine from paracrine-ECL cells or mast cells. Increased levels of both intracellular Ca^{2+} by gastrin/Ach and cyclic AMP by histamine finally cause acid secretion (8). The final step in acid secretion is mediated by H^+/K^+-ATPase also called as gastric proton pump (9) Activation of either the cAMP or Ca^{2+} dependent pathway or both causes stimulation of H^+/K^+ -ATPase on parietal cells (10).

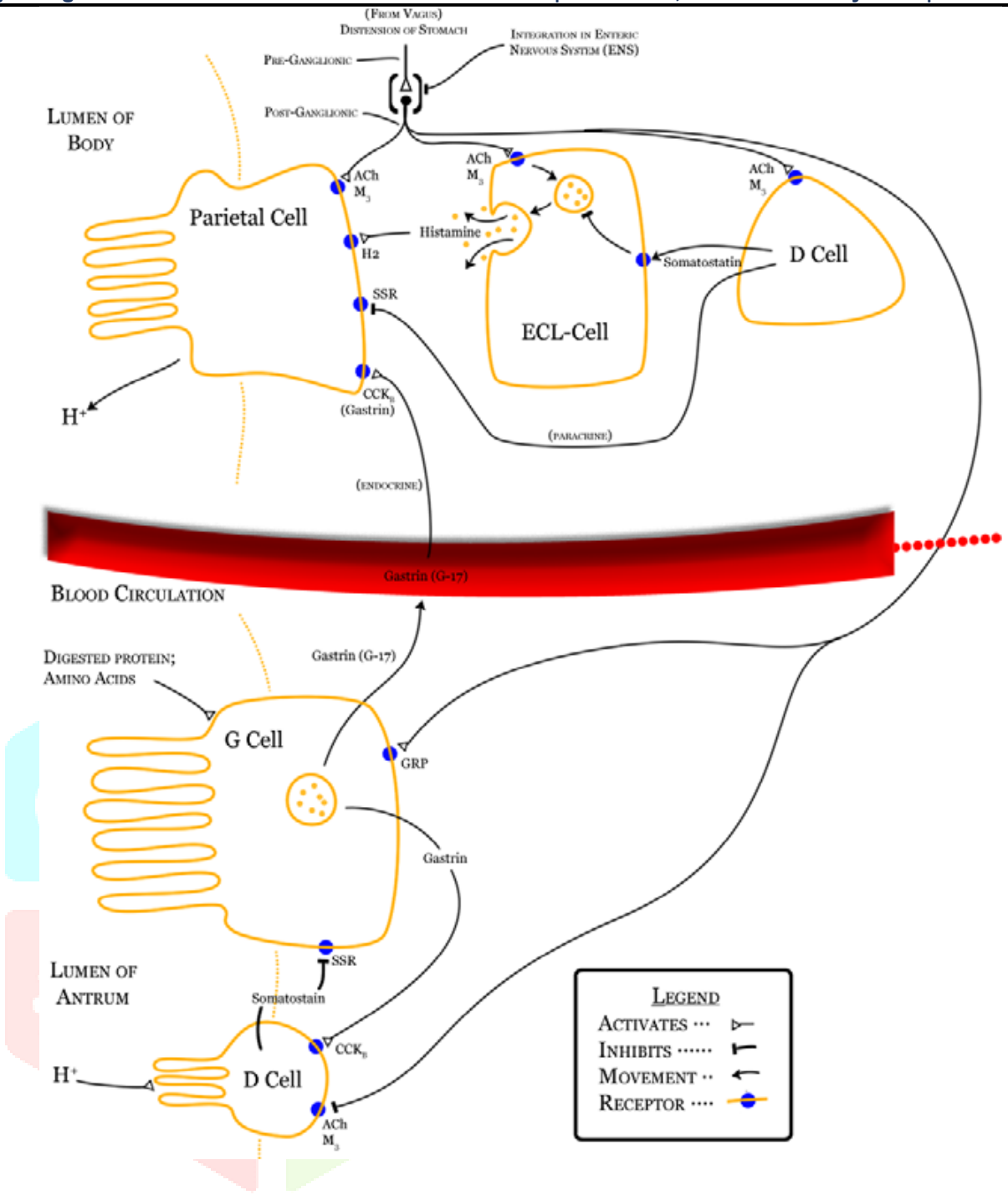
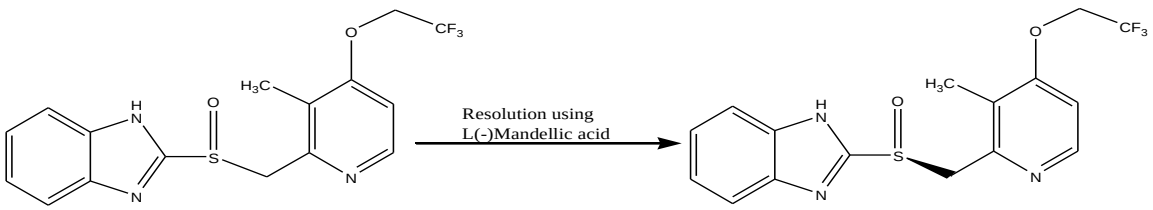


Figure 7. Mechanism of gastric acid secretion.

Detailed Manufacturing Process

Step-3: Synthesis of R-(+) -2 -[[2-(3-methyl-4-(2,2,2-trifluoroethoxy) pyridyl) methyl] sulfinyl]-1H-benzimidazole



2 -[[2-(3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl) methyl] sulfinyl]-1H-benzimidazole

Dexlansoprazole

Table 1: List of raw materials required for the synthesis of Dexlansoprazole

S. No.	Chemicals	Quantity (gm)	M.W.	Mole	Mole-Ratio	Remarks
1.	Step-2nd	5.00	393	0.012	1.0	--
2.	(+)-diethyl-L-tartarate	2.62	206	0.012	1.0	--
3.	Titanium isopropoxide	1.76	284	0.006	0.5185	--
4.	Tiethylamine	3.63	101	0.036	3.0	--
5.	L(-)Mandellic acid	1.83	152	0.012	1.008	--
6.	Isopropyl alcohal	50.0ml	--	--	--	--
7.	M.D.C.	15.0ml	--	--	--	--
8.	Sodiumbicarbonate solution	17.5ml	--	--	--	--

Standard operating procedure:

1. Step-2nd (5gm.) was dissolved in 50 ml of isopropyl alcohol in a RBF.
2. (+)-Diethyl-L-Tartarate (2.62gm), Titanium isopropoxide (1.76gm) and triethylamine (3.63gm) was mixed at 35-40c.
3. Add L (+)-Mandellic acid (1.83gm) at 35 to 40c and stirred for 30min.
4. Solid mass obtained was filtered and washed with acetone to give mandellic acid Titanium complex salt of Dexlansoprazole.
5. Solid mass was dissolved in M.D.C. (15ml) and add sodium bicarbonate solution (5%, 15ml) and stirred for 30min.
6. Separate the organic layer and distill off the solvent to obtained Dexlansoprazole as residue.

❖ **Results:**

(i) Appearance: Brown coloured residue**.**

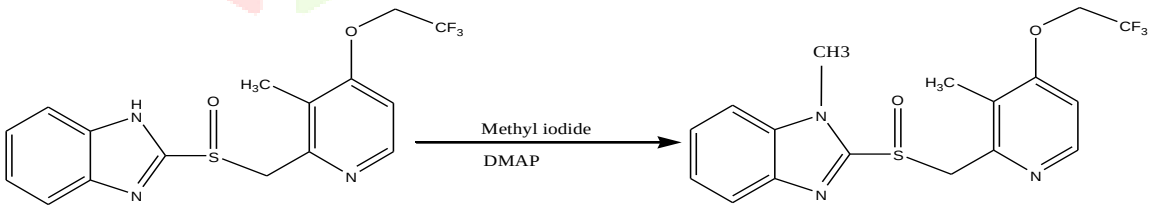
(ii) Chiral HPLC: R Enantiomer>99%

(iii)Yield:38%

(iv)%M/C: NMT 0.5%

Detailed Manufacturing Process

Step-1. Synthesis of N-Methyl lansoprazole



2 -[[2-(3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl) methyl] sulfinyl]-1H-benzimidazole

N-Methyllansoprazole

Table 2: List of raw materials required for the synthesis of N-Methyl lansoprazole

S. No.	Chemicals	Quantity (gm)	M.W.	Mole	Mole-Ratio	Remarks
1.	Lansoprazole	2.0	384	0.0052	1.00	--
2.	Potassium carbonate	3.9	178	0.0219	1.05	
3.	Methyliodide	0.918	142	0.0064	1.197	--
4.	DMAP	--	--	--	--	--
5.	MDC	5.00ML	--	--	--	--

❖ Standard operating procedure:

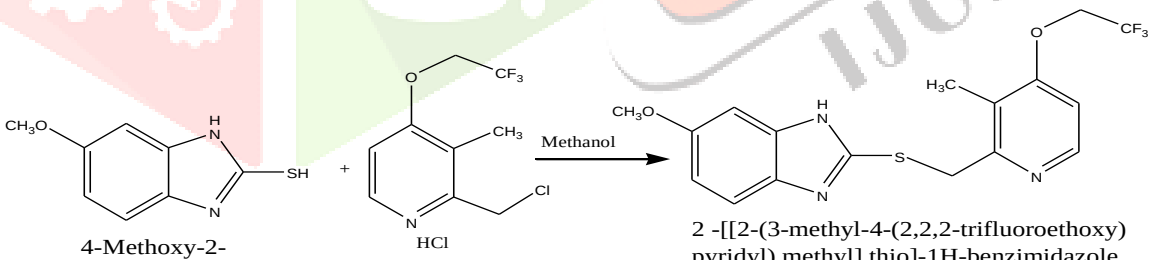
1. Lansoprazole(2gm) , Potassium carbonate(5.59gm) and a catalytic amount of N,N-(dimethyl amino)pyridine was added in methylene chloride at 25 to 30c
2. Methyl iodide (0.918gm) was added slowly over a period of 20min.
3. The reaction mixture was stirred for 10hr.
4. The reaction mass was filtered through the hyflow bed and washed with DCM(5ml)
5. The filtrate was washed with water (3x 50ml) and dried over anhydrous sodium sulphate.
6. The organic layer was concentrated under reduced pressure, isolated from ethyl acetate and dried at 45 to 60c.

❖ Results:

(i) Appearance: White solid
(ii) Yield:83%
(iii) %M/C: NMT 0.5%

Detailed Manufacturing Process

Step-1. . Synthesis of 2 - [[2-(3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridyl) methyl] thio]-1H-5-methoxybenzimidazole



4-Methoxy-2-Mercaptobenzimidaole

2- chloromethyl 3- methyl-4-(2,2,2-trifluoroethoxy)pyridine

2 -[[2-(3-methyl-4-(2,2,2-trifluoroethoxy) pyridyl) methyl] thio]-1H-benzimidazole

Table 3: List of raw materials required for the synthesis of N-Methyl lansoprazole

S. No.	Chemicals	Quantity (Kg)	M.W.	Mole	Mole Ratio	Remarks
1.	Pyridine derivative	5.00	239.5	0.0208	1.00	--
2.	2-mercapto-5-methoxy benzimidazole	3.90	178	0.0219	1.05	--
3.	Methanol	50ml	--	--	--	--
4.	Acetone	5ml	--	--	--	--
5.	Sodium bicarbonate	--	--	--	--	--

Standard operating procedure:

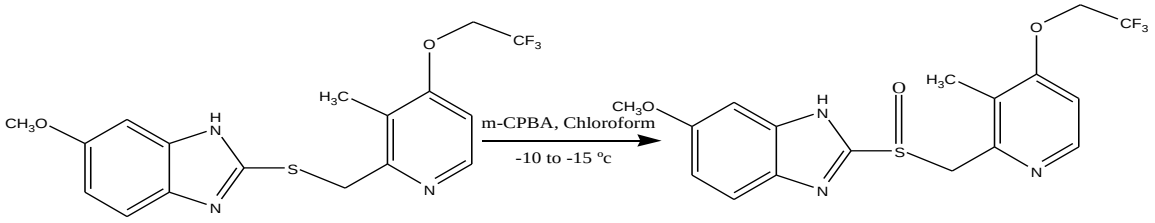
1. Charge 4-Methoxy-2-mercaptobenzimidazole (3.90gm.), pyridine derivative (5.00gm) and methanol (50ml) in R.B.F.
2. Charge 2-Chloromethyl-3-methyl-4-(2, 2, 2-trifluoro methoxy) pyridine (20gm).
3. Stirred at room temperature.
4. Then it refluxed for 1.5-2 hour.
5. HPLC analysis of sample
6. Cool at R.T.
7. Distilled out methanol at the temperature 40c with vacuum.
8 The residue was triturated with acetone (20ml).
9. Filter it at the temperature 5-10c with the help of Buchner funnel.
10. Weight of crude product was 28gm.
11 Then it was dissolved in D.M Water and pH was adjusted 7-8with the help of sodium bicarbonate solution.
12. Filter it with the help of Buchner funnel.
13. Dried in vacuum oven at the temperature 65-70c

❖ **Results:**

(i) **Apperance:**White solid
(ii) **Yield:**85%
(iii) **%M/C:** NMT 0.5%

Detailed Manufacturing Process

Step2. Synthesis of 2 - [[2-(3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridyl) methyl] sulfinyl]-1H-5-methoxybenzimidazole



2 -[[2-(3-methyl-4-(2,2,2-trifluoroethoxy) pyridyl) methyl] thio]-1H-benzimidazole

2 -[[2-(3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl) methyl] thio]-1H-5-methoxybenzimidazole

Table 4: List of raw materials required for the synthesis of N-Methyl lansoprazole

S. No.	Chemicals	Quantity (gm.)	M.W.	Mole	Mole-Ratio	Remarks
1.	Step-1st	2.00	384.00	0.0052	1.000	--
2.	m-CPBA	0.748	172.57	0.0043	0.833	--
3.	Chloroform	20ml	--	--	--	--
4.	NaOH	1.21	40.00	0.0303	5.833	--
5.	Water	12ml	--	--	--	--

❖ Standard operating procedure:

1. Charged step-1st and chloroform in RBF and stirred the mixture at R.T.
2. Then temperature was maintained -10 to-15°C.
3. Meanwhile prepared a solution of m-CPBA in chloroform.
4. The solution was added at -10 to -15°C over a period of 30-45 min.
5. The reaction mixture was stirred for 60-90 min.
6. HPLC analysis of sample.
7. Meanwhile prepared a solution of NaOH (6.6gm) in water (70ml).
8. After completion of the reaction, the reaction mixture was poured into a NaOH solution and stirred for 2-3hr.
9. The separated solid was filtered and washed with chloroform, suck dried for 45-60 min.
10. Send sample for HPLC analysis (Purity).
11. Dried in hot air oven at 60°C

❖ **Results:**

(i) **Apperance:** White solid
(ii) **Yield:** 72%
(iii) **%M/C:** NMT 0.5%

RESULT and DISCUSSION

This work describes the total synthesis of imidazopyridine and its derivatives with their spectroscopical analysis. In the first step, synthesis of 2-[[2-(3-methyl-4-(2,2,2-trifluoroethoxy) pyridyl) methyl] thio]-1H-benzimidazole was done with the yield of 80%. In the second step, synthesis of 2-[[2-(3-methyl-4-(2,2,2-trifluoroethoxy) pyridyl) methyl] sulfinyl]-1H-benzimidazole was done with the yield of 80%. In the third step, R-(+)-2-[[2-(3-methyl-4-(2,2,2-trifluoroethoxy) pyridyl) methyl] sulfinyl]-1H-benzimidazole was done with yield of 38%. In the synthesis of N-Methyl Lansoprazole, the yield was 83%.

In the synthesis of 2-[[2-(3-methyl-4-(2,2,2-trifluoroethoxy) pyridyl) methyl] sulfinyl]-1H-5-methoxybenzimidazole, the yield was 85% (in first step) 72% 9in second step).

The sequence of reactions is shown in scheme and the reaction conditions described in the experimental section, such as solvents, temperature and workup conditions.

The synthetic route which furnishes the desired compound involves a condensation reaction. The transformation of sulfide into sulfinyl has been generally carried out with oxidation. After that optical resolution includes fractional recrystalisation. The chiral column method includes a method in which a racemate or a salt is applied to a column for optical isomer separation.

CONCLUSION: It was a considerable effort towards the synthesis of imidazopyridine derivatives especially dexlansoprazole, methylated & methoxy derivatives. In the class of pyridinyl methyl sulfinyl benzimidazole, all derivatives were formed successfully with great yield. In the above scheme, imidazopyridine derivatives were formed by the condensation reaction followed by oxidation. After that racemic resolution was done with the help of optically active compound.

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