CHAPTER-V

Copper Triflate mediated synthesis of Benzimidazole and Benzoxazole derivatives
5.1 INTRODUCTION TO 2-SUBSTITUTED BENZIMIDAZOLES

The benzimidazoles contain a phenyl ring fused to an imidazole ring, as indicated in the structure for benzimidazole (Fig. 5.1).

This important group of substances has found practical applications in a number of fields. Recently the interest in benzimidazole chemistry has been revived by the discovery that the 5, 6- dimethylbenzimidazole moiety is part of the chemical structure of vitamin B12.

The presence of acid is a fundamental factor in the pathogenesis of gastric and duodenal ulcers, reflux-oesophagitis and nonsteroidal anti-inflammatory drug-induced lesions\(^1\). Many issues responsible for the imbalance between aggressive factors (like acid, pepsin, \textit{H.pylori} infection) and local mucosa defense (secretion of bicarbonates, mucus and prostaglandin) results in acid-peptic and duodenal ulcer, gastroesophageal reflux disease, Zolinger-ellision syndrome and gastritis\(^2\). These are all treated by blocking acid secretion through proton pump inhibitors such as benzimidazole derivatives. The discovery of benzimidazole derivatives as proton pump inhibitors may be traced back to the 1960 when Fort \textit{et al},
Sachs and Hirschowitz\textsuperscript{3} described K\textsuperscript{+} stimulated phosphatase activity in the gastric mucosa. It was shown later that a K\textsuperscript{+} dependent ATPase acidifies a vesicular compartment in the dog gastric mucosa, subsequently attributed to an electroneutral H\textsuperscript{+}/K\textsuperscript{+} exchange. This biochemical work coincided with synthetic work focusing on gastric acid inhibition by substituted benzimidazoles. These derivatives potently inhibit gastric proton pump by converting into active metabolite, that is, thiophilic cyclic sulphenamides. This transformation takes place in the luminal compartment of secreting parietal cell.

Almost all benzimidazole derivatives with their two ring systems bear different functional substituents and this leads to essential modification of the physico-chemical, metabolic and pharmacokinetic properties of these drugs. Tissue selectivity of this type of antiulcer drugs is based on both their pH dependent accumulation, as weak bases in the acidic compartment of secreting parietal cell, and the subsequent acid-induced rearrangement of the parent compound to the pharmacologically active principle\textsuperscript{3}. The enzyme H\textsuperscript{+}/K\textsuperscript{+}ATPase is responsible for gastric acid production and is located in the secretary membranes of the parietal cell\textsuperscript{4}. Gastric acid secretion is regulated by interaction of basolateral parietal cell receptors with their physiological stimulants gastrin, acetylcholine, and histamine\textsuperscript{5}. The irreversible inhibition of the H\textsuperscript{+}/K\textsuperscript{+}ATPase, a means of controlling gastric PH has attracted considerable attention in recent years with the discovery of the
benzimidazole sulfoxide class of antisecretory agents. Synthesis and utility of novel substituted benzimidazole derivatives is evaluated by their ability to inhibit gastric H$^+$/K$^+$ATPase and by blocking the gastric acid secretion. The macroaerophilic bacterium *Helicobacter pylorus* has been recognized as the major cause of gastritis, a significant determinant in peptic and duodenal ulcer disease and gastric cancer. Benzimidazole class of many substituted compounds such as 2-[[[(2-pyridyl) methyl] thio]-1-H benzimidazole has shown selective activities against gastric pathogen *Helicobacter pylori*, the probable mechanism being as inhibitor of *H.pylori*. Various therapeutics strategies have been utilized for the acid induced ulcer, such as acid neutralizing agents, acid inhibitory agents, antigastrin agents, ulcer insulators and promoters of ulcer healing agents.

Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2, 5 (or 2, 6) dimethylbenzimidazole (2 or 3) by the reduction of 2-nitro-4-methylacetanilide (4) (Scheme-5.1).

**Scheme-5.1:**

![Scheme-5.1](image-url)
Several years later Ladenburg obtained the same compound by refluxing 3, 4-diamino toluene 5 with acetic acid (Scheme-5.2).

**Scheme-5.2:**

Since compounds of this type were formed by the loss of water, they were called “anhydro bases” in the very early literature. It was subsequently shown that “anhydrobases” of this type were formed only by compounds in which the nitrogen-containing groups were ortho to each other; that the ring formed was an imidazole ring was indicated by certain reactions of benzimidazoles, such as the fact that imidazole dicarboxylic acid may be obtained, although in small yield, by the oxidation of benzimidazole (Scheme-5.3).

**Scheme-5.3:**
Benzimidazole is a bicyclic heterocycle system consisting of two nitrogen atoms and fused phenyl ring shows wide range of biological activities. Benzimidazole can be synthesized using O-Phenylenediamine and carboxylic acid. Benzimidazole posses wide spectrum of biological activities like including antibacterial, antifungal, antiviral, anti-inflammatory, anticonvulsant, antidepressant, antihypertensive, analgesic, and hypoglycemic properties. A series of benzimidazole derivatives have proven anti-ulcer activity as potential inhibitors of H⁺/K⁺-ATPase. Therapeutic significance of these clinically useful drugs in treatment of peptic ulcer and associated gastrointestinal diseases encouraged the development of some more potent and significant compounds. The pathophysiology of disease, different disorders associated with gastric acid secretion, physiology of gastric acid secretion, structural and molecular chemistry of the benzimidazole derivatives, possible mode of action are discussed.
5.2 MEDICINAL PROPERTIES OF SUBSTITUTED BENZIMIDAZOLES.

In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclised compound which resulted in compounds with increased stability, bioavailability and significant biological activity\textsuperscript{10-13}. It was also showed that substitution on pyridine by electron donating group increases activity. In 1991, benzimidazole derivatives were synthesized by derivatization at N-H of benzimidazole by electron donating group and substitution with long chain of propyl acetamido thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good antiulcer activity\textsuperscript{14-17}. Subsequently, in 1992 Katsura \textit{et.al}\textsuperscript{19} prepared compounds with substitution of dimethyl imidazopyridine at sixth position of benzimidazole showing strong antisecretory activity. Pantoprazole\textsuperscript{10} synthesis by Bernhard \textit{et.al}\textsuperscript{20} explained role of methoxy group of pyridine for maximum biological activity. Introduction of rigid ring with benzimidazole and their conversion to biological active sulfenamide in acidic media has been verified by Shin-ichi \textit{et.al}\textsuperscript{21} in 1994. Kohl \textit{et.al}\textsuperscript{22} substituted pyridine by triazole-3-yl 1-3 dithiane and reported promising results when biologically evaluated against \textit{H.Pylori}. One more approach was applied to reduce the basicity of ring nitrogen of pyridine and to reduce irreversibility of compound with enzyme by using pyridine as ring
substituent by Shimamura et al.\textsuperscript{23} in 1995. Synthesis of leminiprazole was carried out by replacing pyridine with phenyl isobutyl methyl amine reported by Tsukahara et al.\textsuperscript{26} in 1996 showing potent proton pump inhibitory activity. Further in 1997 Yum et al.\textsuperscript{27} replaced pyridine by 2, 2-dimethyl pyrranopyridine ring. Yoo et al.\textsuperscript{28} synthesized 2-dimethyl amino thiazo cyclobenzene benzimidazole showed good proton pump inhibitory activity. Woo T, et al.\textsuperscript{26} in 1998 replaced pyridine with pyrrolo benzimidazolyl moiety, which showed proton pump inhibitory activity. Synthesis of esomeprazole \textsuperscript{11} by asymmetric oxidation of prochiral sulfide of omeprazole \textsuperscript{7} showed potent antiulcer activity reported by Hanna et al.\textsuperscript{29} in 2000.

\textbf{Fig: 5.2} \hspace{1cm} \textbf{Established antiulcer agents in clinical practice}

![Established antiulcer agents in clinical practice](image-url)
In 2002 pyridine substituted by phenyl sulfanyl ethanol, carbamates and benzimidazole substituted by methyl acetate showed high stability, absorption and good antiulcer activity.\textsuperscript{1, 31} Grast et.al\textsuperscript{32} in 2003 substituted benzimidazole at first position by pyridyl sulfanyl and resulted in potentially active compounds. Recently substitution was carried out by n-propyl and N-(cyclohex-3-enylmethyl) piperidin-4-yl)-5-carboxamide and resulted in significant antiulcer activity, explained by shrinivasulu et.al\textsuperscript{33} in 2005.

Keiji Kubo \textit{et.al} \textsuperscript{10} reported the synthesis of 2-[(3-methyl, 4- trifluoro ethoxy)-2-pyridyl] methyl, sulfanyl benzimidazole \textsuperscript{8} which showed antisecretory, antiulcer, cytoprotective activity. After examining the pharmacological and toxicological properties Lansoprazole \textsuperscript{8} was selected as a promising antiulcer agent.

\begin{center}
\textbf{Fig: 5.3}
\end{center}

Brumagniez \textit{et.al}\textsuperscript{11} reported the synthesis of 2-(thiopropyne)-5-(imidazole-1-yl) benzimidazole \textsuperscript{12} which exhibited moderate antiulcer activity against ulcer induced by anti inflammatory agents in rats orally.
The synthesis of 2-[[1-ethyl, 4-N-methyl-N-(1-propen) 1, 2, 3, 4 tetrahydroquinoline-8yl]methylsulfinyl] 5-fluro, 6-methoxy benzimidazole 13 by Minoru Uchida et.al\textsuperscript{12} showed high activity. It appears from these results that the presence of basic amino group may be an important contributing factor in activity of the molecule.

Kovalev et.al\textsuperscript{13} reported the synthesis of 9-(diethyl amino ethylene) 2-phenyl imidazo [1, 2-\(\alpha\)] benzimidazole 14 which showed greater chemical stability and good \textit{in-vivo} antisecretory, gastroprotective and proton pump inhibitory activity than parent N-H compound. Which was found to be more potent than omeprazole.
Sih et al.\textsuperscript{6} reported the synthesis of 1-(diethyl ether 2-yl) 2- pyridyl, methyl, sulfinyl benzimidazole 15 which showed good antiulcer activity.

Endo et al.\textsuperscript{14} reported the synthesis of 2- [(3-piperido methyl phenoxy) propyl] acetamido thio] benzimidazole 16 which however did not show much activity.
Alessandro et.al\textsuperscript{15} reported that the sulphur in thiazole ring 17 may be implicated in gastroprotective action.

![Fig: 5.9](image1)

Katano et.al\textsuperscript{16} reported the synthesis of 2-[(2, 2, 6, 6-tetramethyl piperidine) ethyl thio] 5-methoxy benzimidazole 18 which showed moderate activity.

![Fig: 5.10](image2)

Braendstroem et.al\textsuperscript{17} reported the synthesis of 2- [(3, 4 dimethoxy, 2-pyridyl) methyl, sulfinyl] 5-acetyl, 6-methyl benzimidazole 19 which inhibited gastric acid secretion in dogs.

![Fig: 5.11](image3)
Studied by Sohda et al.\textsuperscript{18} 2-[(3-methyl, 4-difluromethoxy, 2-pyridyl) methyl, sulfinyl] benzimidazole \textbf{20} inhibited ethanol induced ulcers in rats orally.

![Fig: 5.12]

Katsura et al.\textsuperscript{19} reported that, 2-amino 6-[[2-(3, 6-dimethyl imidazo) (1, 2-\(\alpha\)) pyridine 2-yl] ethyl] benzimidazole \textbf{21} exhibited strong antisecretory activity.

![Fig: 5.13]

Bernhard et al.\textsuperscript{20} reported that the introduction of 3-methoxy group produced inhibitors possessing a combination of high potency, similar to omeprazole and lansoprazole and increased stability. As a result of these studies, Pantoprazole \textbf{10} was selected as drug for further clinical studies.

![Fig: 5.14]
Shin-ichi et al.\textsuperscript{21} reported the synthesis of 2-[(4-methoxy, 6, 7, 8, 9-tetra hydro-5H-cyclohepta (b)pyridine-9-yl) sulfinyl] 1-H-benzimidazole sodium salt \textbf{22} which showed promising antiulcer activity and stability on isolated H\textsuperscript{+}/K\textsuperscript{+} ATPase of rabbit gastric mucosa.

![Image](image1.png)

**Fig: 5.15**

Bernhard et al.\textsuperscript{22} showed that 2-[(difluoro methoxy-2-pyridyl) methyl sulfinyl] 5-difuromethoxy benzimidazole \textbf{23} was highly active against H\textsuperscript{+}/K\textsuperscript{+}-ATPase.

![Image](image2.png)

**Fig: 5.16**

T Shimamura et al.\textsuperscript{23} reported the synthesis of 2-[(4-dimethylamino, 5-carboxylate 2-pyrimidinyl) methyl sulfinyl] benzimidazole \textbf{24} in which the pyridine nucleus of omeprazole is replaced by ethyl-4-dimethyl amino-5-pyrimidine carboxylate, which showed good antiulcer, gastroprotective and antisecretory activity.
Kim et al.\textsuperscript{24} reported the synthesis of 2-[(3-methyl, 4-methoxy, 2-pyridyl) methyl, sulfinyl 5-(1-pyrrolyl) benzimidazole 25 which showed moderate activity against H\textsuperscript{+}/K\textsuperscript{+} ATPase with low toxicity.

Kohl et al.\textsuperscript{22} reported the synthesis of 2-[3-methyl, 4-(N-methyl, 1, 2, 4 triazole 3-yl, 1, 3-dithiane) 2-pyridyl] methyl thio benzimidazole 26 which showed high activity against \textit{Helicobacter Pylori}.
Braendstroem et al.\textsuperscript{25} reported the synthesis of Methyl 2-((3, 4-dimethoxypyridin-2-yl)methylsulfinyl)-6-methyl-1H-benzimidazole-5-carboxylate \textsuperscript{27} which showed high activity in dog & rat.

![Fig: 5.20](image)

Tsukahara et al.\textsuperscript{26} reported that the synthesis of 2-(1-H benzimidazole 2-sulfinyl methyl) phenyl isobutyl methyl amine \textsuperscript{27} which showed good antiulcer activity.

![Fig: 5.21](image)

Woo T. et al.\textsuperscript{26} reported that the 2-[3(2, 3-dihydro-1- H pyrrolo [1, 2-\(\alpha\)] benzimidazolyl) sulfinyl] 5-methyl benzimidazole (YJA 20379-4) \textsuperscript{28} showed effect on H\textsuperscript{+}/K\textsuperscript{+} ATPase, \textit{H.Pylori}, mucosal defense and antiulcer activity.
Yum et al.\textsuperscript{27} reported the synthesis of 2-[[2, 2 dimethyl 2-H pyrrano (3, 2, c) 2-pyridyl] methyl, sulfinyl] 4-methoxy benzimidazole \textbf{29} which showed high activity against H\textsuperscript{+} K\textsuperscript{+} ATPase.
5.3 LITERATURE OF SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES

Benzimidazole is a bicyclic heterocycle system consisting of two nitrogen atoms and fused phenyl ring shows wide range of biological activities. Benzimidazole can be synthesized using O-phenylenediamine and carboxylic acid. Benzimidazole possesses wide spectrum of biological activities like including antibacterial, antifungal, antiviral, anti-inflammatory, anticonvulsant, antidepressant, antihypertensive, analgesic, and hypoglycemic properties. Benzimidazoles are readily formed by heating O-Phenylenediamine with carboxylic acid.

**Fig: 5.24** Following drugs containing Benzimidazole moiety possessing anthelmentic activity.

![Chemical Structures of Benzimidazole Derivatives]

- **Thiobendazole (30)**
- **Cambendazole (31)**
- **Parbendazole (32)**
- **Mebendazole (33)**
- **Albendazole (34)**
- **Flubendazole (35)**
Zemin Wu et al. reported\textsuperscript{35} the solid-phase synthesis of benzimidazole \textit{N}-oxides on SynPhase\textsuperscript{TM} Lanterns (Scheme 5.4).

\textbf{Scheme 5.4:}

A solid-phase synthesis of benzimidazole \textit{N}-oxides was developed while attempting to synthesize 1, 5-benzo diazepine-2, 4-diones. The key step of the synthesis involves the reduction of an aryl nitro to a hydroxyamino intermediate which subsequently condenses with an internal carbonyl group to give a benzimidazole \textit{N}-oxide. A library of nine benzimidazole \textit{N}-oxides was prepared on SynPhase\textsuperscript{TM} Lanterns using this reduction–cyclization methodology.

Wolin Huang et al. reported\textsuperscript{36} that a new "traceless" solid-phase synthesis strategy: synthesis of a benzimidazole library (Scheme 5.5).
A new strategy to achieve "traceless" solid-phase synthesis has been developed. Using this strategy, a "traceless" benzimidazole library with diversity on the benzene, moiety was synthesized efficiently in high yield with high purity. During the final step of this new synthetic sequence, cleavage and cyclic nucleus elaboration take place by a series of substitution and elimination reactions on the solid phase followed by release to the solution phase.

Ming-Gui Shen et. al reported\textsuperscript{37} the Ytterbium perfluorooctanesulfonates catalyzed synthesis of benzimidazole derivatives in fluorous solvents (Scheme-5.6).
Catalytic condensation of o-Phenylenediamine and aldehydes was accomplished using rare earth (III) perfluorooctane sulfonates \((\text{RE(OPf})_3)\), \(\text{RE} = \text{Sc, Y, La - Lu}\) as catalysts in fluorous solvents. Ytterbium perfluoro octanesulfonates \((\text{Yb(OPf})_3)\) catalyzes the high-efficient synthesis of benzimidazole derivatives in fluorous solvents.

Tharmalingam Punniyamurthy et.al reported\(^{38}\) the ligand-free copper-catalyzed synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles (Scheme-5.7).

**Scheme-5.7:**

An experimentally simple, general, efficient, and ligand-free synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles via intramolecular cyclization of o-bromoaryl derivatives is catalyzed by copper(II) oxide nanoparticles in
DMSO under air. The heterogeneous catalyst can be recovered and recycled without loss of activity.

T. Itoh et al. reported\textsuperscript{39} that the various 2-bromoanilides were reacted with 2-ethylhexyl 3-mercaptopropionate in high yields using a palladium catalyst. Subsequent generation of thiols and condensation under basic or acidic conditions allows a convenient synthesis of substituted benzothiazoles (Scheme-5.8).

**Scheme-5.8:**

![Scheme 5.8](image)

K. Bahrami et al. reported\textsuperscript{40} that a convenient method for the synthesis of 2-substituted benzimidazoles and benzothiazoles offers short reaction times, large-scale synthesis, easy and quick isolation of the products, excellent chemoselectivity, and excellent yields as main advantages (Scheme-5.9).

**Scheme-5.9:**

![Scheme 5.9](image)
D. S. Bose et.al reported\textsuperscript{41} that various benzothiazoles were synthesized by the intramolecular cyclization of thioformanilides using 2, 6-dichloro-3,5-dicyano-1, 4-benzoquinone (DDQ) in dichloromethane at ambient temperature in high yields (Scheme-5.10).

**Scheme-5.10:**

\[
\begin{array}{c}
\text{R}^1 \text{N} \text{Ar} \text{S} \\
49 \xrightarrow{1.1 \text{EQ. DDQ}} \text{DMC, RT, 20 MINS} \\
\text{R}^2 \text{N} \text{A}
\end{array}
\]

L. L. Joyce et.al reported\textsuperscript{42} that \textit{N}-Arylthioureas are converted to 2-aminobenzothiazoles via intramolecular C-S bond formation/C-H functionalization in the presence of an unusual cocatalytic Pd (PPh\textsubscript{3})\textsubscript{4}/MnO\textsubscript{2} system under an oxygen atmosphere at 80°C. This method eliminates the need for an \textit{ortho}-halo substituted precursor, instead achieving direct functionalization of the \textit{ortho}-aryl C-H bond (Scheme-5.11).

**Scheme-5.11:**

\[
\begin{array}{c}
\text{R}^1 \text{N} \text{Ar} \text{S} \\
51 \xrightarrow{\text{Pd}(\text{PPh}_3)_4} \text{O}_2 \\
\text{R}^2 \text{N} \text{A}
\end{array}
\]
Seijas J. A. et.al reported\textsuperscript{43} that lawesson’s reagent is an efficient promoter in the solvent-free microwave-assisted synthesis of 2-substituted benzoazoles and benzothiazoles from carboxylic acids and 2-aminophenol or 2-aminothiophenol, respectively. Various aromatic, heteroaromatic and aliphatic carboxylic acids react under the conditions developed with good yields (Scheme-5.12).

**Scheme-5.12:**

![Scheme-5.12](image-url)
5.4 PRESENT WORK

Benzimidazoles (Table: 5.2; 1a-1p) have been efficiently synthesized in high yields by treatment of 1, 2-phenylenediamine 2 with aldehydes 3 using efficient Copper Triflate [Cu(OTf)₂] as catalyst at room temperature. As the same procedure, it can also be prepared the Benzoxazoles (Table: 5.3; 6a-6g) efficiently in high yields by treatment of 2-Amino Phenol 4 with aldehydes 5 using efficient Copper Triflate [Cu(OTf)₂] as catalyst at room temperature.

PRESENT SCHEMES:

Scheme: 5.13 Synthesis of 2-Substituted Benzimidazoles.

Scheme: 5.14 Synthesis of 2-Substituted Benzoxazoles

5.5 RESULTS & DISCUSSION

In continuation of the development of useful synthetic methodologies, we have observed that benzimidazoles (Entries 1-16 in
Table: 5.2, i.e. 1a-1p) can be synthesized efficiently by treatment of 1, 2-phenylenediamine with aldehydes using Cu(OTf)₂ as an efficient catalyst at room temperature. As the same procedure, we can also prepare the benzoxazoles (Entries 17-23 in Table: 5.3, i.e. 6a-6g) have been efficiently synthesized in high yields by treatment of 2-Amino Phenol 4 with aldehydes 5 using efficient Cu(OTf)₂ as catalyst at room temperature.

Cu(OTf)₂, this substance is a powerful lewis acid, used as catalyst in several organic reactions. It has been used mainly as a catalyst but its scope has not been fully explored. Here it has been applied for oxidative dehydrogenation of the cyclic intermediates formed from the condensation of 1, 2-phenylenediamine and substituted aldehydes.

The condensation reaction between 2-phenylenediamine and substituted aldehydes is known for practical synthesis of N-substituted amides. The major drawback of these reactions is the use of toxic isocyanate. Apart from handling these toxic substances several aldehydes (aromatic, hetero aromatic and aliphatic) underwent the above conversion to form a series of benzimidazoles. Aromatic aldehydes containing both electron-donating and electron-withdrawing groups worked well. Similarly, different solvents were tested for the synthesis of benzimidazoles and benoxazoles. The reaction in DCM, THF gave the corresponding benzimidazoles in low yield and also required prolonged reaction times (entries 1 and 2), whereas the reaction in MeOH, DME,
ACN has resulted in slightly improved yields of the product (entries 3-5). However, the reaction in DMF gave 80% of the corresponding benzimidazoles in 3 hours. It can be seen from the Table 5.2.

**Scheme-5.13:**

![Scheme-5.13](image)

**Scheme-5.14:**

![Scheme-5.14](image)

**Table-5.1:** Effect of solvent on the synthesis of benzimidazoles / benzoxazoles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>5-6</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>5-6</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>CH₃OH</td>
<td>6</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>4</td>
<td>50</td>
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<tr>
<td>6</td>
<td>DMF</td>
<td><strong>3.5-4</strong></td>
<td><strong>80</strong></td>
</tr>
</tbody>
</table>

*Reaction conditions: 1,2-Phenylenediamine, Substituted aldehydes, Cu(OTf)₂ (1 Eq), solvent (6 ml).*
The method is suitable for the preparation of benzimidazoles and benzoxazoles from an acid sensitive aldehyde such as furfuraldehyde and the sterically hindered aldehydes. The reaction conditions are mild and the experimental procedure is simple. The products were formed (Table-5.2 & Table-5.3) in high yields (74–90%). The structures of the products were determined from their spectral (\(^1\)H NMR, IR and MS) data. Cu(OTf)\(_2\) an acid catalyst here, has been applied for oxidative dehydrogenation of the cyclic intermediates formed from the condensation of 1, 2-phenylenediamine and aldehydes and 2-amino phenol and aldehydes.

Table-5.2: LIST OF BENZIMIDAZOLES SYNTHESISED

<table>
<thead>
<tr>
<th>S.No</th>
<th>Diamine</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time Hrs</th>
<th>MP</th>
<th>Yield</th>
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| 1    | \[
\begin{array}{c}
\text{NH}_2 \\
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\] | \[
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\text{CHO} \\
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\] | 3.0   | 165-168 | 70    |
| 2    | \[
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\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\end{array}
\] | \[
\begin{array}{c}
\text{1.b} \\
\text{1.b} \\
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\] | 3.5   | 168-170 | 72    |
| 3    | \[
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\] | \[
\begin{array}{c}
\text{1.b} \\
\text{1.b} \\
\text{1.b} \\
\text{1.b} \\
\end{array}
\] | 3.5   | 150-153 | 84    |
<p>| | | | | | |</p>
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<td>Structure 1</td>
<td>Structure 2</td>
<td>pKa</td>
<td>M.p.</td>
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<tr>
<td>10</td>
<td><img src="image" alt="Structure 10" /></td>
<td><img src="image" alt="Structure 2.j" /></td>
<td>3.5</td>
<td>212-213</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Structure 11" /></td>
<td><img src="image" alt="Structure 1.j" /></td>
<td>3.5</td>
<td>172-175</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Structure 12" /></td>
<td><img src="image" alt="Structure 2.l" /></td>
<td>3.5</td>
<td>168-172</td>
<td>78</td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Structure 13" /></td>
<td><img src="image" alt="Structure 1.m" /></td>
<td>3.5</td>
<td>164-168</td>
<td>76</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Structure 14" /></td>
<td><img src="image" alt="Structure 1.n" /></td>
<td>3.5</td>
<td>170-174</td>
<td>72</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Structure 15" /></td>
<td><img src="image" alt="Structure 1.o" /></td>
<td>3.5</td>
<td>174-172</td>
<td>80</td>
</tr>
</tbody>
</table>
We have also observed that benzoxazoles (6a-6g) can be synthesized efficiently by treatment of 2-amino phenols with substituted aldehydes using Cu(OTf)$_2$ as an efficient catalyst at room temperature (Table: 5.3).

**Table: 5.3: List of Benzoxazoles synthesized**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Diamine</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time Hrs</th>
<th>MP</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td><img src="#" alt="Dia 1" /></td>
<td><img src="#" alt="Alde 1" /></td>
<td><img src="#" alt="Prod 1" /></td>
<td>3.5</td>
<td>159-160-</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
<td>--------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>158-160</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>248-250</td>
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<tr>
<td>20</td>
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<td><img src="image" alt="Chemical Structure" /></td>
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<td>248-250</td>
<td>74.5</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>194-196</td>
<td>70.7</td>
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<tr>
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<td>3.5</td>
<td>148-150</td>
<td>82</td>
<td></td>
</tr>
</tbody>
</table>
5.6 EXPERIMENTAL SECTION

5.6.1 TYPICAL EXPERIMENTAL PROCEDURE (Scheme-5.13):

SYNTHESIS OF BENZIMIDAZOLES:

Both the starting materials (1, 2-Phenylenediamines and aldehyde) were taken in a single neck R.B and DiMethyl Formamide (DMF) (5ml) was added to that. To this 0.1 eq of Cu(OTf)$_2$ was added. The reaction mixture was stirred at room temperature under nitrogen and the reaction is monitored by TLC. After completion of the reaction, the crude reaction mixture poured into the ice tray. The mixture was extracted with ethyl acetate leaving the water layer free of compound. Organic layers were separated and dried them over magnesium sulfate and concentrated on rotavapor. Compounds were purified by recrystalization by using acetone to obtain the pure derivatives of benzimidazoles 1(a-p).
5.6.2 TYPICAL EXPERIMENTAL PROCEDURE (Scheme-5.14):

SYNTHESIS OF BENZOXAZOLES:

Both the starting materials (2-amino phenol and aldehyde) were taken in a single neck R.B and DiMethyl Formamide (DMF) (5ml) was added to that. To this 0.1 eq of Cu(OTf)$_2$ was added. The reaction mixture was stirred at room temperature under nitrogen and the reaction is monitored by TLC. After completion of the reaction, the crude reaction mixture poured into the ice tray. The mixture was extracted with ethyl acetate leaving the water layer free of compound. Organic layers were separated and dried them over magnesium sulfate and concentrated on rotavapor. Compounds were purified by recrystallization by using acetone to obtain the pure derivatives of benzimidazoles 6(a-g).

5.6.3 Spectral Data of 2-substituted benzimidazoles prepared in Table: 5.2:

1. a: 2-Phenyl-1H-Benzimidazole:

Pale Yellow; EI MS: 195 (M$^+$); $^1$H NMR (400 MHz, DMSO); δ7.23(4H, m), 7.53 (3H, m), 7.82(1H, J=7.2Hz, d), 8.23(1H, m), 13.22 (1H, s), FTIR (KBr, Cm$^{-1}$): 3434.97, 2924.47, 1410.38 (Fig.No. 5.1, 5.2, 5.3).

1. b: 2- (2-Nitro Phenyl)-1H- Benzimidazole:
Off White; EI MS: 240.2(M⁺); ¹H NMR (400 MHz, DMSO); δ7.28(2H, m), 7.6(2H, m), 7.8(1H, J=2Hz, t), 7.9 (1H, J=6Hz, t), 8.04(2H, d, J=8Hz), 13.07(1H, s); FTIR (KBr, cm⁻¹): 3433.39, 2924.61, 1527.99(NO₂) (Fig.No. 5.4, 5.5, 5.6).

1.c: 2- (2-Nitro Phenyl)-1H- Benzimidazole:

Off White; EI MS: 240.2 (M⁺); ¹H NMR (400 MHz, DMSO); δ9.22(H, br, s), 8.60(1H, J=8Hz, d), 8.40(1H, dd), 7.8-8.0 (2H, m), 7.68-7.82(2H, m), 7.36(2H, m); FTIR (KBr, cm⁻¹): 3434.33, 2925, 533.26(NO₂).

1.d: 2-(2-Chloro Phenyl)-1H-Benzimidazole:
Off White; EI MS: 229 (M\(^+\)); \(^1\)H NMR (400 MHz, DMSO); \(\delta\) 12.8 (H, br, s), 7.96 (1H, dd), 7.6 (2H, dd), 7.5-7.58 (3H, m), 7.22-7.33 (2H, m), FTIR (KBr, cm\(^{-1}\)); 3436.31, 2921.73, 1589.98 (Fig.No. 5.7, 5.8, 5.9).

1.e: \(2-(1H\)-Benzimidazol-2-yl\)-phenol:

Off White; EI MS: 211 (M\(^+\)); \(^1\)H NMR (400 MHz, DMSO); \(\delta\) 13.23 (1H, br, s), 8.1 (1H, \(J=0.8\), d), 7.5-7.75 (2H, m), 7.31-7.41 (2H, m), 7.5 (1H, \(J=4Hz\), t), 7.1 (2H, \(J=8Hz\), d), FTIR (KBr, Cm\(^{-1}\)); 3432.25, 2925.75, 3342 (Fig.No. 5.10, 5.11).

1.f: \(2-(4\)-Chloro-phenyl\)-1H-benzoimidazole:

Off White; EI MS: 195 (M\(^+\)); \(^1\)H NMR (400 MHz, DMSO); \(\delta\) 12.34 (1H, Br), 7.93 (2H, \(J=8Hz\), d), 7.83 (4H, dd), 7.53 (2H, \(J=8Hz\), d), MASS; M+H: 229, FTIR (KBr, cm-1); 3189.99, 2851.70, 1428.90, 746.51 (Fig.No. 5.12, 5.13, 5.14).
1.g: 3-(1H-Benzoimidazol-2-yl)-phenol:

Benzene-1,2-diamine + M-Hydroxy Benzaldehyde → 3-(1H-Benzoimidazol-2-yl)-phenol

Off White; EI MS: 211 (M⁺); ¹H NMR (400 MHz, DMSO); δ 9.72(1H, s), 9.24(1H, s), 7.93(2H, J=8Hz, d), 7.72(2H, d,d), 6.93 (1H, d,d), 6.82(2H, d); MASS; M+H: 211;

1.h: 2-(4-Methoxy-phenyl)-1H-benzoimidazole:

Benzene-1,2-diamine + 4-Methoxy Benzaldehyde → 2-(4-Methoxy-phenyl)-1H-benzoimidazole

Off White; EI MS: 225 (M⁺); % of yield: 75; ¹H NMR (400 MHz, DMSO); δ 12.35(1H, br s), 8.15(1H, J=8Hz, d), 7.73(2H, J=7Hz, d), 7.42 (2H, 8Hz, d), 7.25(2H, dd), 3.64 (3H, s); FTIR (KBr, cm⁻¹); 3430.06, 1609.04, 1244.26.

1.i: 2-Cyclooctyl-1H-benzoimidazole:

Benzene-1,2-diamine + Cyclooctane Carbaldehyde → 2-Cyclooctyl-1H-benzoimidazole
Off White; EI MS: 225 (M+); ¹H NMR (400 MHz, DMSO); δ 11.32 (1H, br, s), 9.24(1H, s), 7.93(2H, J=8Hz, d), 7.72(2H, d,d), 6.93(1H, dd), 6.82(2H, dd); FTIR (KBr, cm⁻¹); 3434.77, 2920.24 (Fig.No. 5.15, 5.16, 5.17).

1.j: 2-Thiophen-2-yl-1H-benzimidazoloe:

Off White; EI MS: 201(M⁺); ¹H NMR (400 MHz, DMSO); δ; 12.25(1H, br s), 7.9 (1H, d), 7.79(1H, m), 7.53(2H, m), 7.26 (3H, m) (Fig.No.5.18, 5.19).

1.k: 2-(3, 4, 5 – Trimethoxy-phenyl)-1H-benzimidazole:

Off White; EI MS: 285(M⁺); ¹H NMR (400 MHz, DMSO); δ 3.8(9H, s), 6.62 (2H, s), 6.87(1H, J=2Hz, t), 6.74(1H, J=3Hz, t), 6.65 (2H, J=8Hz, d); δ; 13.07(1H, s) (Fig.No. 5.20, 5.21).

1.l: 2-(3,4-DiMethoxy-phenyl)-1H-benzimidazole:
Off White; EI MS: 255(M⁺); ¹H NMR (400 MHz, DMSO); δ 4.63(1H, s, br), 6.95 (2H, dd), 6.84(2H, m), 6.7(3H, m), 3.89 (6H, s).

1.m: 2-(2, 3, 4-Trimethoxy-phenyl)-1H-benzimidazole:

\[
\text{Benzene-1,2-diamine} + \begin{array}{c}
\text{CHO} \\
\text{OMe} \\
\text{OMe} \\
\text{OMe}
\end{array} \rightarrow \begin{array}{c}
\text{MeO} \\
\text{OMe}
\end{array}
\]

Off White; EI MS: 259(M⁺); ¹H NMR (400 MHz, DMSO); δ 4.63(1H, br s), 7.0 (1H, dd), 6.89(1H, m), 6.70 (3H, m), 6.63 (1H, dd), 3.93 (3H, s), 3.89 (3H, s), 3.82 (3H, s).

1.n: 2-(2,5-Dimethoxy-phenyl)-1H-benzimidazole:

\[
\text{Benzene-1,2-diamine} + \begin{array}{c}
\text{CHO} \\
\text{OMe} \\
\text{OMe} \\
\end{array} \rightarrow \begin{array}{c}
\text{MeO} \\
\text{OMe}
\end{array}
\]

Off White; EI MS: 256(M⁺); ¹H NMR (400 MHz, DMSO); δ 4.45(1H, br s), 6.92 (1H, s), 6.83(3H, m), 6.42 (3H, m), 3.62 (3H, s), 3.41 (3H, s).

1.o: 2-(2,4-Dimethoxy-phenyl)-1H-benzimidazole:
Off White; EI MS: 255(M+); ¹H NMR (400 MHz, DMSO): δ; 4.34 (1H, b s), 7.23 (1H, s), 6.80(4H, m), 6.5(2H, m), 6.5 (2H, m), 3.84(6H, s).

1.p: 5-Bromo-2-Phenyl-1H-Benzimidazole:

<table>
<thead>
<tr>
<th>4-Bromo-benzene-1,2-diamine</th>
<th>+</th>
<th>Benzaldehyde</th>
<th>→</th>
<th>5-Bromo-2-Phenyl-1H-Benzimidazole</th>
</tr>
</thead>
</table>

Off White; EI MS: 273(M+); ¹H NMR (400 MHz, DMSO); δ12.2 (H, br, s), 8.17(2H, d), 7.8(1H, J=7.2Hz, d), 7.56-7.58 (2H, m), 7.38(2H, m), 7.35(1H, d); FTIR (KBr, cm⁻¹): 3436.58, 2924.53, 694.32.

5.6.4 Spectral Data of 2-Substituted Benoxazoles Prepared in Table: 5.3

6.a: 2-(2-Nitro-phenyl)-benzoxazole:

<table>
<thead>
<tr>
<th>2-Amino Phenol</th>
<th>+</th>
<th>O-Nitro Benzaldehyde</th>
<th>→</th>
<th>2-(2-Nitro-phenyl)-benzoxazole</th>
</tr>
</thead>
</table>

Off White; EI MS: 242.5(M+); ¹H NMR (400 MHz, DMSO); δ8.1(1H, d), 7.8(3H, m), 7.63(1H, J=8Hz, d), 6.98(2H, m), 6.42(1H, J=6Hz, d); FTIR (KBr, cm⁻¹): 3436.69, 1602.78, 1528.71.

6.b: 2-(3-Nitro-phenyl)-benzoxazole:
Off White; EI MS: 241.2(M⁺); ¹H NMR (400 MHz, DMSO): δ8.4(1H, d), 7.9-8.0(2H, m), 7.6-7.73(2H, m), 7.5(2H, q), 7.4(1H, m); FTIR (KBr, cm⁻¹): 3390.38, 1600.67, 1528.75.

**6.c: 3-Benzooxazole-2-yl-phenol:**

Off White; EI MS: 213(M⁺); ¹H NMR (400 MHz, DMSO): δ7.93(1H, d), 7.34-7.67(4H, m), 6.99(2H, J=6Hz, d), 6.5-6.6(2H, m), 7.4(1H, m); FTIR (KBr, Cm⁻¹): 3412.24, 1586.34, 2924.61.

**6.d: 2-Thiophen-2-yl-benzooxazole:**

Off White; EI MS: 202(M⁺); % of yield: 74.5; ¹H NMR (400 MHz, DMSO): δ7.78(1H, J=8Hz, d), 7.53-7.60(2H, m), 7.4(1H, q), 6.8(2H, J=6Hz, d), 6.5(1H, s); FTIR (KBr, Cm⁻¹): 3410.98, 1587.26.
6.e: 2-(4-Methoxy-phenyl)-benzoxazole:

![Chemical structure of 2-(4-Methoxy-phenyl)-benzoxazole]

Off White; EI MS: 226.2(\text{M}^+); ^1\text{H} NMR (400 MHz, DMSO); δ7.98(1H, s), 7.7-7.8(3H, m), 6.99(2H, J=8Hz, d), 6.53(2H, d,d), 3.6(3H, s); FTIR (KBr, cm\textsuperscript{-1}): 3412.01, 1585.37, 1171.87.

6.f: 2-Phenyl-benzoxazole:

![Chemical structure of 2-Phenyl-benzoxazole]

Off White; EI MS: 196.2(\text{M}^+); ^1\text{H} NMR (400 MHz, DMSO); δ7.83(1H, d), 7.62-7.7(3H, m), 6.98(2H, J=6Hz, d), 6.56(2H, d)\text{d); FTIR (KBr, cm}\textsuperscript{-1}): 3409.27, 1587.29.

6.g: 2-(4-Chloro-phenyl)-benzoxazole:

![Chemical structure of 2-(4-Chloro-phenyl)-benzoxazole]
Off White; EI MS: 230(M+); $^1$H NMR (400 MHz, DMSO): $\delta$7.93(2H, d), 7.64(3H, m), 6.84(1H, m), 6.63(2H, d,d); FTIR (KBr, Cm$^{-1}$): 3410.82, 1587.21, 840.18.

5.7 CONCLUSION

In conclusion, Copper Triflate [Cu(OTf)$_2$] has been employed here for the first time as a mild and efficient catalyst for the convenient preparation of benzimidazoles and its derivatives in high yields from 1, 2-phenylenediamine and a wide variety of aldehydes.

Copper Triflate [Cu(OTf)$_2$] has been employed here for the first time as a mild and efficient catalyst for the convenient preparation of benzoxazoles and its derivatives in high yields from 2-amino phenol and a wide variety of aldehydes.
5.8 REFERENCES


2. Robert S, McDonald I.M, Burger’s Medicinal Chemistry & Drug Discovery, 6\textsuperscript{th} ed; John Wiley and Sons, New Jersey, 2003, 86-121.


Spectral Reports
Fig: 5.1  NMR Spectrum of 2-Phenyl-1H-Benzimidazole (1.a)

Fig: 5.2  MASS Spectrum of 2-Phenyl-1H-Benzimidazole (1.a)
Fig: 5.3  IR Spectrum of 2-Phenyl-1H-Benzimidazole (1.a)

Fig: 5.4  NMR Spectrum of 2- (2-Nitro Phenyl)-1H- Benzimidazole: (1.b)
Fig: 5.5  MASS Spectrum of 2- (2-Nitro Phenyl)-1H- Benzimidazole: (1.b)

![Mass Spectrum Image]

Fig: 5.6  IR Spectrum of 2- (2-Nitro Phenyl)-1H- Benzimidazole: (1.b)

![IR Spectrum Image]
Fig: 5.7  NMR Spectrum of 2-(2-Chloro Phenyl)-1H-Benzimidazole:

(1.d)

Fig: 5.8  MASS Spectrum of 2-(2-Chloro Phenyl)-1H-Benzimidazole:

(1.d)
Fig: 5.9  IR Spectrum of 2-(2-Chloro Phenyl)-1H-Benzimidazole: (1.d)

Fig: 5.10  NMR Spectrum of 2-(1H-Benzimidazol-2-yl)-phenol: (1.e)
Fig: 5.11  MASS Spectrum of 2-(1H-Benzimidazol-2-yl)-phenol: (1.e)

Fig: 5.12  NMR Spectrum of 2-(4-Chloro-phenyl)-1H-benzimidazole: (1.f)
Fig: 5.13  MASS Spectrum of 2-(4-Chloro-phenyl)-1H-benzimidazole:

(1.f)

Fig: 5.14  IR Spectrum of 2-(4-Chloro-phenyl)-1H-benzimidazole: (1.f)
Fig: 5.15 NMR Spectrum of 2-Cyclooctyl-1H-benzimidazole: (1.i)

Fig: 5.16 MASS Spectrum of 2-Cyclooctyl-1H-benzimidazole: (1.i)
Fig: 5.17  IR Spectrum of 2-Cyclooctyl-1H-benzimidazole: (1.i)

Fig: 5.18  NMR Spectrum of 2-Thiophen-2-yl-1H-benzimidazole: (1.j)
Fig: 5.19  MASS Spectrum of 2-Thiophen-2-yl-1H-benzimidazole: (1.j)

Fig: 5.20  NMR Spectrum of 2-(3,4,5-Trimethoxy-phenyl)-1H-benzimidazole: (1.k)
Fig. 5.21  MASS Spectrum of 2-(3,4,5-Trimethoxy-phenyl)-1H-benzimidazole: (1.k)

Fig. 5.22  NMR Spectrum of 2-(2-Nitro-phenyl)-benzoxazole: (6.a)
Fig. 5.23  MASS Spectrum of 2-(2-Nitro-phenyl)-benzoxazole: (6.a)

Fig. 5.24  IR Spectrum of 2-(2-Nitro-phenyl)-benzoxazole: (6.a)
Fig. 5.25  NMR Spectrum of 2-(3-Nitro-phenyl)-benzoxazole: (6.b)

Fig. 5.26  MASS Spectrum of 2-(3-Nitro-phenyl)-benzoxazole: (6.b)
Fig. 5.27  IR Spectrum of 2-(3-Nitro-phenyl)-benzoxazole: (6.b)

Fig. 5.28  NMR Spectrum of 2-Thiophen-2-yl-benzoxazole: (6.d)
Fig. 5.29  MASS Spectrum of 2-Thiophen-2-yl-benzooxazole: (6.d)

Fig. 5.30  IR Spectrum of 2-Thiophen-2-yl-benzooxazole: (6.d)
Fig. 5.31  NMR Spectrum of 2-(4-Methoxy-phenyl)-benzoxazole: (6.e)

Fig. 5.32  MASS Spectrum of 2-(4-Methoxy-phenyl)-benzoxazole: (6.e)
Fig. 5.33  IR Spectrum of 2-(4-Methoxy-phenyl)-benzooxazole: (6.e)

Fig. 5.34  NMR Spectrum of 2-Phenyl-benzooxazole: (6.f)
Fig. 5.35  MASS Spectrum of 2-Phenyl-benzooxazole: (6.f)

Fig. 5.36  IR Spectrum of 2-Phenyl-benzooxazole: (6.f)
Fig.5.37  NMR Spectrum of 2-(4-Chloro-phenyl)-benzoxazole: (6.g)

Fig.5.38  MASS Spectrum of 2-(4-Chloro-phenyl)-benzoxazole: (6.g)