Preamble

Organic synthesis has a long history that can be traced back to ancient times. However, it was not recognized as such, because it was practiced randomly and historically. In 1825 on one hand, the beginning of the nineteenth century was the dawn of chemistry where Professor Wöhler [1] was the first who succeeded in synthesizing an organic compound (Urea) in laboratory from ammonium cyanate. This synthesis was followed by other milestones such as synthesis of acetic acid, glucose, camphor, quinine etc. On the other hand, twentieth century was devoted to the development of various processes for the organic syntheses that can bring about increase in molecular complexity from the simple building blocks. These processes were referred to as “Named Organic Reactions.”

The main focus of the organic synthesis lies not only in its capacity to prepare enormous organic substances but more significantly in its capacity to create new entities which have beneficial impact on the health and welfare of human civilization. The important applications of these compounds in everyday life are pharmaceuticals that can cure or prevent diseases, for population control and agricultural growth, textiles and dyes, paints, polymers, cosmetics, detergents and high technological materials used in automobile, aerospace, electronics and computers. Consequently the science of organic synthesis is driven by the continuous discovery of novel and complex molecules that fascinate and challenge to the organic chemists to synthesize more efficient and economic ways. Therefore zeal towards higher level of achievements in organic synthesis both in terms of methodology and in terms of complexity of targets remains unabated. In this context, in the last century more expedient and economical processes reported in literature are:

- Microwave assisted synthesis of various organic compounds.
- Solid phase synthesis of peptides and different organic reactions (oxidation, reduction, nitration, sulphonation, etc.) using phase transfer catalyst.
- Total organic synthesis of natural products.
- Multicomponents reactions such as Diels-Alder reaction, Enamine reaction, Mannich reaction, Biginelli reaction, etc.
- Asymmetric synthesis of chiral drugs
- Catalysis, Transition metal complexes in organic synthesis.
As a result, in the 21st century these are the frontiers of enormous potential providing wonderful opportunities for the synthesis of various complex moieties like natural products, amino acids, hormones, nucleic acids, chiral drugs, etc. as well as challenge for a sustainable environment calls for the use of clean procedures (ecofriendly) which can avoid the use of harmful solvents. In addition to this, the impact of science of organic synthesis on biology and medicine in particular, merits special mention in this century. Eventually with its share of glorious moments, the science of organic synthesis determine and direct the path of discovery of new synthetic strategies and methods and new chemical entities for both academically oriented organic chemists and industry for their potential to lead to practical and profitable applications with sustainable technology.

In this context, five membered nitrogen containing heterocyclic ring system is one of simple strategy reported for preparing variety of various organic compounds of high medicinal and biological value. Its importance in organic synthesis is clearly evident in the reviews of Blick, Karbe, Nobles, Reichert, and others [2-9]. Besides this, the chemistry of quinoline and imidazoles have also been reviewed in a considerable number of publications and patents deals with the heterocyclic system based useful as chemotherapeutic agents as well as reactive intermediates for the synthesis of various organic compounds. Hence, we have planned to undertake the work on “Synthesis, characterization and material applications of imidazoles”. Therefore it would be reasonable at this juncture to describe imidazoles derivatives in brief.
1.1 INTRODUCTION OF QUINOLINE

Quinoline (1-azanaphthalene or benzo[b]pyridine) is a stable base and an important class of heterocyclic compound known for long time. Quinoline was first isolated in an impure state in 1834 by Runge from coal-tar distillate [10]. Gerhardt obtained quinoline, probably contaminated by lepidine by distillation of cinchonine and quinine with caustic alkali, and named it quinoleine. This name was subsequently changed to quinoline by Berzelius. Many valuable synthetic dyes and medicines have been produced from various quinoline derivatives. Since the preparation of quinoline must proceed from available materials, the different methods have been described below.

1.1.1 Synthesis of Quinolines

(1) Skraup’s synthesis

Skraup’s synthesis is one of the most common methods for the preparation of quinoline compounds. Quinoline is produced when aniline, concentrated sulfuric acid, glycerol and a mild oxidizing agent are heated together. It is acid catalyzed reaction [11,12].

(2) Combes synthesis

Condensation of a 1,3-diketone and aryl amine produces a high yield of a β-amino-enone, which can then be cyclized in the presence of concentrated acid to give quinoline [13,14].
(3) Conrad-Limpach-Knorr synthesis

Reaction of anilines with β-ketoester gives quinolones [15].

\[
\text{NH}_2 + O
\] \[
OEt
\] \[
\text{CH}_3
\] \[
\text{O}
\] \[
\text{O}
\] \[
\text{CH}_3
\] \[
\text{H}
\] \[
\text{H}
\] \[
\text{N}
\] \[
\text{O}
\] \[
\text{CH}_3
\] \[
\text{N}
\] \[
\text{O}
\] \[
\text{CH}_3
\] \[
\text{H}
\] \[
\text{H}
\] \[
\text{N}
\] \[
\text{O}
\] \[
\text{CH}_3
\] \[
\text{N}
\] \[
\text{O}
\] \[
\text{CH}_3
\] \[
\text{H}
\] \[
\text{H}
\]

At room temperature, product is kinetically and thermodynamically controlled at 140 °C.

(4) Pfitzinger synthesis

Isatin is hydrolysed to o-amino keto acid which condenses with ketones or acids that have a reactive methylene group.

(5) Friedlander synthesis

It comprises condensation of o-aminobenazaldehyde [16,17] and compound having active methylene group, adjacent to an aldehyde, ketone, or acid group.

Other method for the synthesis of quinoline and its various derivatives has been reported in literature [18-21].

1.1.2 Synthesis of 2-Chloro-3-Formyl Quinoline:

In the broad field of quinoline, 2-chloro-3-formyl quinoline possesses a prominent position in the intermediate category as it can be utilized for the synthesis
of many heterocyclic compounds. There has been much more interest towards the use of Vilsmeier-Haack reagent in organic synthesis of several nitrogen and oxygen heterocycles. It has proved to be a mild and efficient method for the formylation of reactive aromatic and hetero aromatic and carbonyl compounds. The utility of this reagent also explores the powerful route for the synthesis of substituted 2-chloro-3-formyl quinoline. Meth-Cohn Otto and co-workers have shown that treatment of acetonilide with the Vilsmeier-Haack reagent with POCl₃ as solvent allows the preparation of 2-chloro-3-formyl quinoline(i) [22-27].

\[
\text{DMF} + \text{POCl}_3 \rightarrow \text{Vilsmeier Haack reagent}
\]

Kidwai Mazahir and Jindal Shelly have described [28] the method for the preparation of substituted 2-chloro-3-formyl quinoline(ii) starting from acetoacetanilide.
Pawar P. A., Bajare P. B. and co-workers [29] have also reported synthesis of 2-chloro-3-formyl-4-methyl quinoline(iii) from acetophenone oxime under the Vilsmeier cyclization conditions.

\[
\text{DMF} + \text{POCl}_3 \rightarrow \begin{array}{c}
\text{N} \\
\text{CHO} \\
\text{Cl} \\
\text{CH}_3 \\
\end{array}
\]

(iii)

Synthesis of 4-chloro-3-quinolinecarboxaldehyde(iv) [30] can also be prepared from o-aminoacetophenone using Vilsmeier reagent.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CHO} \\
\text{Cl} \\
\text{NH}_2 \\
\text{CH}_3 \\
\end{array}
\]

\[
\text{DMF} + \text{POCl}_3 \rightarrow \begin{array}{c}
\text{Cl} \\
\text{CHO} \\
\text{N} \\
\end{array}
\]

(iv)

1.1.3 Reactions of 2-chloro-3-formyl quinoline:

The substituted 2-chloro-3-formyl quinolines are the unique intermediates as they can be utilized for various functional group interconversions. It undergoes various electrophilic and nucleophilic substitution reactions. Some examples are shown below.
The presence of electron rich nitrogen at 1-position and electron withdrawing formyl group at 3-position activates the chlorine towards various displacement reactions. Some examples of the displacement reaction at 2-position are cited below. Formyl group of the 2-chloro-3-formyl quinoline also undergoes various addition and condensation reactions to give different compounds. Formyl group at 3-position is highly reactive towards hydrazine hydrate, phenyl hydrazine and hydroxylamine.

It also reacts with the compounds containing active methylene group. Some important reactions at formyl group of 2-chloro-3-formyl quinoline are illustrated here.
It also undergoes oxidation, reduction and Grignard reactions.

For the replacement of chlorine by sulphur, sodium sulphide in DMF was found to be an efficient reagent which also provides scope for further reaction. The corresponding ortho-nucleophilic substitution achieved by refluxing quinolines in aqueous acetic acid affords the 2(H) quinolone and further reaction of quinolones with electrophile favours N-alkylation. Reaction with sodium azide in PTSA and EtOH affording tetrazoloquinolines.
3-Phenyl-2H-pyrano [2,3-b] quinolin-2-ones and 3-acetamido-2H-pyrano [2,3-b] quinolin-2-ones have been prepared by Perkin type condensation of 3-formyl-2-quinolin-2-ones with sodium salt of phenylacetic acid and acetylglucine, respectively.

\[
\begin{align*}
&\text{Phenylacetate} \\
&\text{Ac}_2\text{O} \\
&\text{Acetyl glycine} \\
&\text{Et}_3\text{N}
\end{align*}
\]

Among quinolines, 2-chloro-3-formyl quinolines are versatile intermediate for various heterocyclic ring systems. When 2-chloro-3-formyl quinoline is condensed with ethyl mercaptoacetate in ethanol, it generates a five membered thiophene ring(v).

\[
\begin{align*}
&\text{CHO} \\
&\text{Cl} \\
&\text{NaOEt, EtOH} \\
&\text{EtOH, H}_2\text{SO}_4
\end{align*}
\]

Kalluraya B. and other have prepared fused tetracyclic derivatives 3-aryl/alkyl-9-substituted-1,2,4-triazolo[3,4-b] [1,3,4] quinoline [3,2-f] thiadiazepines(vi) by reaction of 6-substituted-2-chloro-3-formyl quinolines and 3-substituted-4-amino-5-mercaptop-1,2,4-triazole [31].

\[
\begin{align*}
&\text{CHO} \\
&\text{H}_2\text{N} \\
&\text{EtOH, H}_2\text{SO}_4
\end{align*}
\]

Where, \( R = \text{H, CH}_3, \text{OCH}_3 \), \( R' = \text{methyl, n-propyl, phenyl, p-chloro phenyl} \)
Nandha Kumar R. and co-workers [32] have prepared 2,3-heteroannelated quinoline derivatives like quino[3,2-f]benzoxazepines (vii) by reaction of substituted 2-chloro-3-formyl quinoline and 2-aminophenol in methanol.

\[
\begin{align*}
\text{CHO} & \quad \text{Cl} & \quad \text{CHO}_2\text{N} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{2} & \quad \text{1} & \quad \text{2} \\
\end{align*}
\]

\[
\begin{align*}
\text{anhy. MeOH} & \quad \text{anhy. MeOH} \\
\text{R}^1 & \quad \text{R}^1 & \quad \text{R}^1 \\
\text{H} & \quad \text{CH}_3 & \quad \text{OCH}_3 \\
\text{2} & \quad \text{1} & \quad \text{2} \\
\end{align*}
\]

Where, \( R^1 = \text{H, CH}_3, \text{OCH}_3 \)
\( R^2 = \text{H, CH}_3 \)
\( R^3 = \text{H, OCH}_3 \)

When 2-chloro-3-formyl quinoline is condensed with guanidine nitrate in alcoholic sodium hydroxide to give 3-amino pyrimido [4, 5-b] quinoline (viii).

\[
\begin{align*}
\text{CHO} & \quad \text{Cl} & \quad \text{NH}_2 \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{2} & \quad \text{1} & \quad \text{2} \\
\end{align*}
\]

\[
\begin{align*}
\text{Guanidine nitrate} & \quad \text{Guanidine nitrate} \\
\text{alc. NaOH} & \quad \text{alc. NaOH} \\
\text{R}^1 & \quad \text{R}^1 & \quad \text{R}^1 \\
\text{H} & \quad \text{CH}_3 & \quad \text{OCH}_3 \\
\text{2} & \quad \text{1} & \quad \text{2} \\
\end{align*}
\]

Where, \( R^1 = R^2 = R^3 = \text{H} ; R^1 = \text{R}^2 = \text{CH}_3, R^3 = \text{H} ; R^1 = \text{OCH}_3, R^2 = R^3 = \text{H}; \\
R^1 = \text{CH}_3, R^2 = \text{H}, R^3 = \text{H} ; R^1 = \text{OCH}_3, R^1 = \text{R}^2 = \text{H} \)

Some tricyclic condensed quinoline system can be obtained from 2-chloro-3-formyl quinoline; for example, the preparation of thieno quinoline derivative (ix) is described as under.
Kombarov P.V. and his co-workers have reported synthesis of 3,4-dihydro-2H-[1,3] thiazino [6,5-b] quinolines (x) based on 7,8-dimethyl 2-chloro-3-formyl quinoline via the consecutive step conversion in to its Schiff’s base with a primary amine, reduction to the corresponding amino methyl derivative, conversion to thiourea with isothiocyanates and heterocyclization by intramolecular substitution of the chlorine atom [33].

Rajendran S. P. and his co-workers [34] have reported the synthesis of some fused quinoline derivatives, thieno[2,3-b]quinoline (xi) from 3-(2-chloro-3-quinoly)acrylic esters which in turn were prepared from 2-chloro-3-formyl quinolines.
2-Chloro-3-formyl quinoline on treatment with benzil in the presence of ammonium acetate and acetic acid gives 2-amino-3-[(4’5’-diphenyl)-imidazol-2’-yl] quinoline(xii) while with ethyl aminocrotonate gives 2-amino-3-[4’-(2’,6’-dimethyl-3’,5’-dicarbethoxy-1’,4’-dihydropyridyl)] quinolines(xiii).

Parekh and co-workers [35] have reported the synthesis of some 5-oxoimidazolines derivatives by the reaction of 2-chloro-3-formyl-8-methyl quinoline with hydrazine hydrate and then fusion with 4-aryl-2-phenyl-5-oxazolinones(xiv).

where \( R = \) unsubstituted phenyl, 2-furyl, 2-thienyl
Dubey P.K. et al [36] have prepared some novel 3-(2-chloro-3-quinolyl)-5-phenyl[1,3]thiazolo [2,3-c] [1,2,4]triazoles(xv).

\[
\begin{align*}
\text{R}^1 & = \text{H, Me} \\
\text{R}^2 & = \text{H, Me, Br, Cl}
\end{align*}
\]

Mogilaiah K. and co-workers [37] have synthesized a pyrazolo[3,4-b]quinoline derivatives by reaction of 2-hydrazino-3-(4-methoxyphenyl)-1,8-naphthyridine and substituted 2-chloro-3-formyl quinolines(xvi).

Where, \( R = \text{H, 6-CH}_3, 7-\text{CH}_3, 8-\text{CH}_3, 8-\text{OCH}_3, 6-\text{Cl, 6-Br} \)

Korodi Ferene and co-workers [38] have reported [1,2,4] triazolo[5’1’:2,3] thiazino [6,5-b]quinoline derivatives(xvii) synthesized by reaction of 2-chloro-3-formyl quinoline with 1,2,4-triazols.

\[
\begin{align*}
\text{R} & = \text{OH, OEt, OAc, Cl, OCH}_2\text{CH}_2\text{OH, S CH}_2\text{CH}_2\text{OH, NH-[CH}_3]\text{,} \\
\text{R}^1 & = -6, -7, -8- \text{ Me, -6,7,8-OMe, -7, -8-Cl} \\
\text{R}^2 & = \text{H, Me, Et}
\end{align*}
\]
1.1.4 Therapeutic interest of quinoline

A number of derivatives of quinoline serve as valuable therapeutic agents. Some hundred years ago cinchona bark was introduced for the treatment of malaria, and until very recently quinine has remained the standard remedy for this disease. Several other synthetic antimalarial drugs are based on quinoline nucleus e.g. chloroquine. Considerable interest has been created in the chemistry of quinoline due to their versatile therapeutic activities like bactericidal, antihistaminic, antimalarial, antidepressant, analgesic, anti-ulcer, antiviral, herbicidal, antitumor, anti-allergic, anticonvulsant, anti-inflammatory etc. Some of the therapeutically active compounds derived from 2-chloro-3-formyl quinoline derivatives are reviewed here [39-44]. Suresh T. and co-workers [45] have reported the synthesis of various 4-phenyl-3-thiopyrimido[4, 5-b]quinoline derivatives which shows antibacterial and antifungal activities(xviii).

Gupta Rajiv et al [46] have reported anti-inflammatory, antibacterial and antifungal activities of quinoline derivatives, 2-chloro-6/8-subtistuted-3-(3-alkyl/aryl-5,6-dihydro-5-triazolo-[3,4-b][1,3,4]thiadiazol-6-yl)-quinolines(xix).

\[
\begin{align*}
\text{R}^1 &= \text{R}^2 = \text{R}^3 = \text{H} \\
\text{R}^1 &= \text{CH}_3, \text{R}^2 = \text{R}^3 = \text{H} \\
\text{R}^3 &= \text{CH}_3, \text{R}^1 = \text{R}^2 = \text{H}
\end{align*}
\]

(xviii)

\[
\begin{align*}
\text{R}^1 &= \text{OCH}_3, \text{R}^2 = \text{R}^3 = \text{H} \\
\text{R}^3 &= \text{OCH}_3, \text{R}^1 = \text{R}^2 = \text{H}
\end{align*}
\]

(xix)

where \( \text{R}^2 = \text{OMe, Me, H} \)

\( \text{R}^2 = \text{H} \)
Pyranoquinoline alkaloids have gained considerable importance in recent years due to their pharmacological activities like anticonvulsant, coronary constricting, optically brightening and antifungal activities.

Quinoline ring fused with heterocyclic system is also found in natural as well as in the synthetic compounds of biological interest. Dictemine and Skimmianine are the example of such naturally occurring compounds, which are associated with smooth muscle contracting properties. B.Kalluraya and co-workers have reported antifungal and antibacterial activities of thiadiazepines derivatives of 2-chloro-3-formyl quinoline.

It is a well known fact that the presence of azomethine linkage in the compound is found to exhibit biological activity, particularly antifungal activity. Rajendran S. P. and Karvembu R. have prepared Schiff bases of type(xx), which displayed an antifungal activity.

Parikh et al [47] have reported antifungal and antibacterial activities of some Schiff bases(xxia) and their 2-azetidinones derivatives(xxib) of 2-chloro-3-formyl quinoline.
Fathy N. M. and Aly A. S. have prepared azomethine derivatives of 2-chloro-3-formyl quinoline of the type (xxii), which shows bactericidal and fungicidal activity.

A number of pyrazole derivatives are reported to possess diverse biological activities like, analgesics, anti-inflammatory, antipyretic, sedative and hypoglycemic. Bell, Malcom R. and co-workers have patented pyrazolo quinoline derivatives as potent antiviral agents. Antimicrobial activity of some novel pyrazolo[3,4-b]quinoline derivatives have been reported by El-Sayed O. A. and Aboul-Enein H.Y. A large number of hydrazones are reported as antibacterial, antiviral and antitubercular agents. Amir Mohd. and co-workers have reported synthesis and anti-inflammatory activities of some new hydrazones of aryl alkanoic acid (xxiii).

Antimicrobial activity of quinoline derivatives (xxiv, xxv) of type are reported by Khunt et al.
Selvi G. and Rajendran S. P. have reported [48] 2-[3-(2-choloro quinolinyl)]-3-aryl-4-thiazolidinones (xxvi) as potential antibacterial agents.

Acrkman J. H. and co-workers have reported [49] pyrazolo[3,4-b]quinolines (xxvii) as antiviral agents.

\[
R^1 = R^2 = R^3 = R^4 = R^5 = H; R^7 = H
\]
\[
R^1 = R^2 = R^3 = R^4 = H; R^5 = R^7 = -CH=CH=CH=CH-;
\]
\[
R^1 = R^2 = R^3 = R^4 = H; R^5 = -OCH_3
\]
\[
R^1 = R^2 = R^3 = R^4 = H; R^5 = -CH=CH=CH=CH-;
\]
1.2 APPLICATIONS OF IMIDAZOLE DERIVATIVES

The emergence of powerful and elegant imidazoles has stimulated major advances in chemotherapeutic agents of remarkable significance in medicine, biology and pharmacy. As the work incorporated in the present thesis deals with synthesis of imidazoles and their antimicrobial activity as well as reactive intermediates, it would be worthwhile to discuss in brief about the history and developments of these Mannich Bases as chemotherapeutic agents and reactive intermediates.

Chemotherapeutic Agents

Until 1960 considerable work had been reported on synthesis and pharmacological activity of imidazoles derivatives for analgesic, antispasmodic, anaesthetic and antimicrobial activity [50-57]. In this context W.I.Nobles has patented imidazoles having antibacterial, anticonvulsant, analgesic and anti-inflammatory activity [58]. Besides these Mannich Bases, there are many reports envisaged the application of imidazole based on Mannich reaction to the compounds containing an acidic hydrogen on a nitrogen atom to yield N-Mannich Bases of imidazole which have been evaluated for their pharmacological action [59-71]. The chemical structure of some of five membered nitrogen containing heterocycles having significant biological activity are furnished in Table-1.1 and Table-1.2, respectively.
Table-1.1 Chemical structures of Five memberd nitrogen containing heterocycles and their biological activity

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Amine</th>
<th>C-Mannich Base</th>
<th>Biological activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>NH(CH₃)₂</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>Analgesic</td>
<td>45</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>R = HNMe₂, HNEt₂, HNC₆H₁₀</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>Antimalarial agent</td>
<td>46</td>
</tr>
<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>HN(C₂H₅)₂</td>
<td><img src="image6" alt="Structure 6" /></td>
<td>Antimalarial agent</td>
<td>47</td>
</tr>
<tr>
<td><img src="image7" alt="Structure 7" /></td>
<td></td>
<td><img src="image8" alt="Structure 8" /></td>
<td>Amebacibal agent</td>
<td>48</td>
</tr>
<tr>
<td><img src="image9" alt="Structure 9" /></td>
<td></td>
<td><img src="image10" alt="Structure 10" /></td>
<td>Anti amebic agent</td>
<td>49</td>
</tr>
<tr>
<td><img src="image11" alt="Structure 11" /></td>
<td>NHR₂⁺, R₂⁺ = Me₂, = Et₂</td>
<td><img src="image12" alt="Structure 12" /></td>
<td>Hypotensive and Antiaggregant agent</td>
<td>50</td>
</tr>
<tr>
<td><img src="image13" alt="Structure 13" /></td>
<td></td>
<td><img src="image14" alt="Structure 14" /></td>
<td>Antimicrobial agent</td>
<td>51</td>
</tr>
</tbody>
</table>
Table-1.2  Chemical structures of Five memberd nitrogen containing heterocycles and their biological activity

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Amine</th>
<th>N-Mannich Base</th>
<th>biological activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td><img src="image2.png" alt="Amine 1" /></td>
<td><img src="image3.png" alt="N-Mannich Base 1" /></td>
<td>Tranquilizing effect</td>
<td>52</td>
</tr>
<tr>
<td><img src="image4.png" alt="Substrate 2" /></td>
<td><img src="image5.png" alt="Amine 2" /></td>
<td><img src="image6.png" alt="N-Mannich Base 2" /></td>
<td>Anticonvulsive agent</td>
<td>53</td>
</tr>
<tr>
<td><img src="image7.png" alt="Substrate 3" /></td>
<td><img src="image8.png" alt="Amine 3" /></td>
<td><img src="image9.png" alt="N-Mannich Base 3" /></td>
<td>Antiviral agents</td>
<td>54</td>
</tr>
<tr>
<td><img src="image10.png" alt="Substrate 4" /></td>
<td><img src="image11.png" alt="Amine 4" /></td>
<td><img src="image12.png" alt="N-Mannich Base 4" /></td>
<td>Antimicrobial agents</td>
<td>55</td>
</tr>
<tr>
<td><img src="image13.png" alt="Substrate 5" /></td>
<td><img src="image14.png" alt="Amine 5" /></td>
<td><img src="image15.png" alt="N-Mannich Base 5" /></td>
<td>Antifungal agent</td>
<td>56</td>
</tr>
<tr>
<td><img src="image16.png" alt="Substrate 6" /></td>
<td><img src="image17.png" alt="Amine 6" /></td>
<td><img src="image18.png" alt="N-Mannich Base 6" /></td>
<td>Antifungal agent</td>
<td>56</td>
</tr>
<tr>
<td><img src="image19.png" alt="Substrate 7" /></td>
<td><img src="image20.png" alt="Amine 7" /></td>
<td><img src="image21.png" alt="N-Mannich Base 7" /></td>
<td>Antileishman ial agent</td>
<td>56</td>
</tr>
<tr>
<td><img src="image22.png" alt="Substrate 8" /></td>
<td><img src="image23.png" alt="Amine 8" /></td>
<td><img src="image24.png" alt="N-Mannich Base 8" /></td>
<td>Antibacterial agent</td>
<td>57</td>
</tr>
</tbody>
</table>
Bryant [72] in 1965 reported the synthesis of nitrogen containing pyrrole derived from various nitrogen containing five membered ring systems such as pyrrole, pyrazole, benzimidazole and benzotriazole. He also studied the pharmacological activity of a series of nitrogen compounds for example antimalarial, anaesthetics, analgesic activity. Pyrrole condensed with formaldehyde and secondary amines according to the following equation.

Before the detection of chloroquine resistant falciperum malaria in the early 1960’s, chloroquine (I) and the Amodiaquine (II) were the best therapeutic and suppressive drugs available for combating malarial infections. Both drugs had rapid therapeutic action and few side effects and they were cheap to produce. Then pyronaridine (III), a drug developed in China [73] during 1970, structurally similar to Amodiaquine and is a potent blood Schizontocide. This has been shown to be highly effective against *P.falciperum* and *plasmodium vivax* malaria. This has been stimulated the interest in Mannich Base drugs for the treatment of Malaria.

Parmar Surendra *et. al* [74] have reported that hydrazine derivatives reported to be potent inhibitors of the enzyme MAO and inhibitors of this enzymes have exhibited pronounced anticonvulsant activity. Further Benzimidazole derivatives have also been shown to possess CNS depressant activity. On the basis of these observations they have carried out the synthesis of substituted benzimidazole hydrazides by using Mannich Bases as reactive intermediate treated with hydrazine
hydrate as shown in **Scheme-1.1**. They have prepared the aminomethylated compounds of 2-alkyl benzimidazole by o-phenylenediamine, formalin and ethyl p-amino benzoate. The corresponding hydrazides were prepared by the reaction of esters with hydrazine hydrate. All of the benzimidazole hydrazides exhibited lower anticonvulsant activity against pentylene tetrazol-induced inhibitory activity.

**Scheme-1.1**

A series of nitrogen containing Quinazolinone derivatives (**Scheme-1.2**) have been synthesized from Quinazoline-4-one and various primary aromatic amines in the presence of formaldehyde.

**Scheme-1.2**
Varma R.S. and coworkers [75] have reported the synthesis of series of 5-methoxy 1,3-disubstituted benzimidazoline-2-thione as potential biological active agents. They have carried out the reaction of 5-methoxybenzimidazoline-2-thione with formaldehyde and secondary as well as secondary and primary aromatic amino compounds (Scheme-1.3). They have investigated the antiviral activity against Sunnhemp rosette virus (SRV) and observed that majority of these compounds inhibited the growth of SRV invitro and invivo.

**Scheme-1.3**

![Scheme-1.3](image)

Barbara et. al [76] have reported the comparative study of exvivo antimalarial activity of twelve new quinoline di-Mannich Base compounds containing 7-chloroquine or 7-trifluoromethyl quinoline moiety along with amodiquine, chloroquine and pyronaridine antimalarials. Of these twelve Mannich Bases tested against six culture of p.falciparum and of these eight Mannich Bases showed exvivo and invitro antimalarial activity in serum greater then amodiquine, chloroquine and pyronaridine and following four Mannich Bases DM-1, DM-2, DM-3 and DM-4 (Scheme-1.4) induced a very high level of activity.
Burckhalter and coworkers [77] have described the application of N-substituted heterocyclic intermediates in drug synthesis. On the basis of these discoveries, Afaf H. El-masry and co-workers [78] have made efforts to incorporate a benzimidazole into a triazole moiety by Mannich reaction of oxadiazole with different secondary amines namely diethyl amine, morpholine or N-methyl piperazine and paraformaldehyde to give Mannich Base compounds MO-1, MO-2 and MO-3 (Scheme-1.5). These compounds were tested against Gram +Ve bacteria, Gram –Ve bacteria, yeast and fungi for antibacterial and antifungal activity.
Perusal of literature has revealed that aminomethylated derivatives of compounds belonging to aromatic and heterocyclic systems exhibit a broad spectrum of pharmacological activity [79-82]. In this context a series of imidazo [1,2-a] benzimidazole derivatives were prepared by V.A.Anismanov et al. and studied the pharmacological activity viz. hypotensive effect, antiaggregant effect, membrane stability effect, spasmolytic effect, neuroprotective effect and toxicity of these products. For this purpose aminomethylation of imidazo-[1,2-a]-benzimidazoles (I) with formaldehyde and various dialkyl amines under the mild condition of HCl yielded water soluble dihydrochlorides (Scheme-1.6).
Recently, Joshi H.S. and coworkers [83] have described an efficient method for the heterocyclic synthesis by the reaction of 3-phenoxy benzaldehyde with secondary amines such as piperidine, morpholine, indole and N-methyl piperazine and amides like acetamide, urea and thiourea (Scheme-1.7). They have also been tested these Mannich Bases for their antituburcular and antimicrobial activity.

\[ \text{Secondary Amine} + \text{3-Phenoxy benzaldehyde} \rightarrow \text{Mannich Base} \]

N- containing heterocycles of benztriazole [84] were synthesized by reacting benztriazole with formaldehyde and various secondary amines (Scheme-1.8). These synthesized heterocycles were evaluated for analgesic and anti-epileptic activity. Among these synthesized compounds MT-1, MT-2, MT-3, MT-4 and MT-5 showed significant analgesic activity.
Moreover, Senthilraja M. and Anand S. Thangadhurai [85] have synthesized isatin based heterocycles (Scheme-1.9) by the reaction of schiff bases of isatin with pyrimethamine. All these new derivatives have screen for antibacterial and antifungal activity and have exhibited higher potency compared to standard drugs against all bacterial as well as fungal organisms.
Varma R.S. [86] has recently delivered memorial lecture on aminomethylation reaction of nitrogen and sulfur containing five membered heterocyclic compounds (shown below) such as isatin, benzimidazoles, benzotriazole, benzimidazoline-2-thione, benzothiazoline-2-thione, 1,3,4-oxadiazolin-5-thione and 1,2,4-triazolin-5-thiones with formaldehyde and amines. Secondary as well as primary amines bearing different substituents have been employed successfully in aminomethylation reaction. The resulting aminomethylated product have been tested for antibacterial, antifungal, antiviral, anticancer, antileishmanial and antifilarial activity. A number of such nitrogen containing ring systems have exhibited promising antifungal and antileishmanial activities.

1.3 MISCELLANEOUS

The nitrogen containing ring systems had since been extended and is increasingly used in preparative chemistry providing pool of information for synthetic chemistry. Originally mannich reaction has been used to synthesize β-amino carbonyl compounds from the three components; a ketone, an amine and aldehyde. Later, Auwers and Wagner et.al [87,88] have reported the synthesis of amino methyl phenols by the reaction of phenols, formaldehyde and secondary amines
(Scheme-1.10). The phenols prepared were found to exhibit a partially cryptophenolic character (insoluble in cold aqueous NaOH but dissolved on heating.)

**Scheme-1.10**

![Scheme-1.10](image)

2-Substituted imidazoles, 2-substituted benzimidazoles and 3,5-substituted pyrazoles can be prepared in good yields through the lithiation of N-(dialkyl amino methyl) derivatives of imidazole, benzimidazole and pyrazole [89]. The lithiation occurs smoothly at the 2-, 2- and 3- or 5- positions respectively upon treatment with n-butyl lithium in THF followed by the reaction with electrophiles like primary alkyl halides, aldehyde, ketones, tertiary alcohols, isocynates and subsequent facile acid-catalyzed hydrolysis of protecting groups on nitrogen atom (Scheme-1.11). Thus the method for the functionalized heterocycles offers advantages over number of other methods in which the protecting groups can be introduced and especially removed very easily. A lithiation procedure is simple and a wide range of electrophiles can be used where yields are generally high. The method appears to be quite general and should be applicable to a variety of other analogous heterocyclic systems.
Bradshaw and co-workers [90] have reported the 8-hydroxyquinoline ligand synthesized by Mannich reaction of secondary macrocyclic (azacrown ether) diamines with 8-hydroxy quinoline and its 2- and 7- substituted derivatives and formaldehyde in benzene. The resulting manich bases (AC-1 and AC-2) had a high affinity and selectivity for mercury (Hg\(^{+}\)) and had proven to be a chemo-sensor for mercury (Hg\(^{+}\)).
Mannich Base of Crown ethers of 8-hydroxy quinoline

\[
\begin{align*}
\text{7-substituted derivative} \\
\text{Where, } X = \text{Cl, NO}_2, \text{H}
\end{align*}
\]

\[
\text{2-substituted derivative} \\
\text{Where, } X = \text{Cl, H}
\]

With the increasing occurrence of nitrogen in drugs and natural products, highly asymmetric variants of multicomponent reaction has been recently investigated by Barry M. Trost and Terrell L. R. [91]. They have demonstrated the application of dinuclear zinc catalyst in catalytic asymmetric type reaction. The reaction of glyoxalate imines with different hydroxyl acetophenone derivatives by using standard dinuclear catalyst gave a high yield of amino alcohol of good diastereo selectivity (syn adduct) and excellent enantioselectivity (Scheme-1.12).

**Scheme-1.12**

Hydroxy Acetophenone + Glyoxalate imine $\xrightarrow{\text{dinuclear zinc catalyst}}$ amino alcohol adduct
One of the challenges for organic chemist is to synthesize optically active organic molecules from simple achiral starting materials using asymmetric catalysts. In this context the highly valuable optically active compounds of \( \alpha, \beta \)-diamino acids are synthesized by the development of the first enantioselective Lewis acid catalyzed condensation reaction [93] of imino glycin alkyl esters with imines (Scheme-1.13). The enantioselective Lewis acid catalyst are N-Tosyl-C-Phenyl imine. The mechanism of the highly enantioselective reaction is discussed. A various contributions of metal salts and the chiral copper (I) ligands are used as the catalysts, the most effective catalyst are chiral copper (I) complexes having phosphino-oxazoline (P,N) ligands as shown below.

\[ \text{Scheme-1.13} \]

\[
\begin{align*}
\text{Ph} = \text{Ph, p-MeOC}_6\text{H}_4, \text{o-BrC}_6\text{H}_4, \text{m-ClC}_6\text{H}_4 \\
\text{THF} = \text{Thiophenol} \\
\text{Et}_3\text{N} = \text{Triethylamine} \\
\text{-20°C} = \text{Methylcyclohexane} \\
\text{NHTs} = \text{N-Tosyl amine} \\
\text{P-N Ligand} = \text{Phosphino oxazoline ligand}
\end{align*}
\]
Sha Lou, B. M. Taoka and others [92] have proposed a chiral base mediated direct addition of β-keto esters to acyl imines. They also have reported the enantioselective addition of β-keto esters to acyl aryl imines catalyzed by cinchonine and cinchonidine and these products are being further used in the synthesis of enantiomeriched dihydro pyrimidones and α-amino alcohols (Scheme-1.14).

**Scheme-1.14**

Metal complex of nitrogen containing ring systems have been studied [94,95] extensively in recent years. Raman N. and others [96] in analogous way have prepared N–(1-morpholino benzyl) semicarbazide (MBS), formed by the condensation of morpholine, semicarbazide and benzaldehyde and its Cu(II), Ni(II), Co(II) and Zn(II) complexes. Their structure was elucidated on the basis of elemental analysis, magnetic susceptibility, electrical conductivity and spectral study. The complexes exhibited square-planar geometry. The monomeric and non-electrolyte nature of the complexes was evident by their magnetic susceptibility and low conductance data. The proposed structure of the complexes is shown in following structure.
In addition to the above mentioned applications, literature reports have revealed many other applications of imidazoles as:

- Cationic surfactant [97]
- Anti corrosive coating [98]
- Explosive [99]
- To synthesis two-photon absorption and blue upconversion fluorescence of novel nitrogen heterocyclic chromophores [100].
- Dyes in the development of drugs and pharmaceuticals [101].

1.4 OBJECTIVE

Looking to the above importance of various imidazole derivatives, the objective of the present work are synthesis, characterization and material applications (i.e. antibacterial and dyeing assessment) of imidazole derivatives.

1.5 PRESENT WORK

The brief review of organic synthesis of imidazoles and its applicability in various areas of science prompted the present author to focus on the targets regarding synthesis of eight different diamines m-phenylenediamine (MPD), p-phenylenediamine (PPD), benzidine (BD), ortho toluidine (OTD), 4,4’-diamino diphenyl sulphone (DDS), 4,4’-diamino diphenyl methane (DDM), 4,4’-diamino diphenyl sulphonamide (DASA) and 2,4’-diamino toluene (DT) to give a series of eight imidazoles. The details of synthesis and characterization of eight series of imidazole derivatives are furnished in Chapter-2 of the present thesis.
The applications of these eight series of imidazoles have been examined as antimicrobial agents by studying their antimicrobial activity against different bacteria and fungi microorganisms. This work is described in Chapter-3 of the thesis.

Further, four selected imidazoles have been used as dye precursors (diazonium component) in synthesis of disperse azo dyes to give four series of disperse azo dyes. The dyeability of these four series of disperse azo dyes have been studied on polyester and nylon fabrics. Finally, the dyeing behavior of these dyed patterns have been evaluated in terms of exhaustion and fixation study as well as by studying their fastness properties. Thus the work pertaining to synthesis, characterization of these disperse azo dyes and there applicability in textile dyeing is presented in Chapter-5 and Chapter-6 of the thesis.
REFERENCES

1. Wöhler F.,

2. Blick F.F.,
   “Organic Reactions” Vol-I
   John Wiley and Sons. New York, pp. 303-341

3. Karbe H.,
   Arch. Pharm., 38, 283 (1950)

4. Nobles L.,
   Pharm. Sci. 4th Ann.
   C.A.: 38, 1404 (1944)

5. Reichert B.,
   Pharm. Ind., 9, 375 (1952)
   C.A. 38, 1404 (1944)

6. Rosenmund K.W.,
   Pharm. Ztg-nachr., 88, 856 (1952)
   C.A. 47, 928 (1953)

7. Merz K.W.,
   Pharmazine, 11, 505 (1956)
   C.A. 55, 16665 (1956)

8. Reichert B.,
   “Die Mannich Reaction” springer-verlay, stuttgart, Germany (1959)

9. Hellman H; Ortiz, G.,
   “α-Aminoalkylierung“, Valag-chemie, weinhein, Ger, amu (1960)

10. Son Panosua and Kichar J.,

11. The Skraup Synthesis of Quinolines.,
    R. H. Mankyse,
    Org. React., 7, 59 (1953)

12. Clarke H. T. and Davis A. W.,
13. Long R. and Schofield K.,
14. Robert E. and Turner E.,
    J. Chem. Soc., 1832 (1927)
15. Lauer W. M. and Kaslow C. E.,
16. Moslier H. S., Yanko W.H. and Whitemore
17. The Friendlier Synthesis of Quinoline
    C.C.Cheng and S. Yan.,
18. Cook, Heibron and Steger
    J. Chem. Soc., 413 (1943)
19. Zhyungo S. amd Michel M.,
    Heterocyclic Chem., 17, 30 (1993)
20. Nathan L. and Harry D.,
    J. Am. Chem. Soc., 1536, 68 (1946)
21. Hauser R. and Bloom S.,
    J. Am. Chem. Soc., 1544, 68 (1946)
22. Marson C. M.,
23. Jutz C.,
    Advance in Organic Chemistry., 9, 225 (1976)
24. Meth Cohn and Tarnowski B.,
25. Meth Conh O.,
    Hetercocycles., 35, 539 (1993)
26. Taylor D. L.,
27. Otto Meth Cohn, Behma Narine and others
28. Jindal S. and Kohil S.,
29. Pawar R. and Bajare P.B., 
30. Vijaylakshmi S. and Rajendran S., 
31. Kalluraya B., 
32. Nandha Kumar R., 
33. Kombarov P. V., 
34. Rajendran S. P. and Karebu 
35. Parekh J. P. and Hinda H. N., 
   Ind. J. Chem., 21 B, (8), 729
36. Dubey P.K., 
   J. Pharm Sci., 84, 3 (1989)
37. Mogilaiah K. and Khimiya H. J., 
38. Korodi Ferene and co-workers 
39. Frexias B. J., Span E. S., 
   C. A. 114, 185302 Pm, (1991)
40. Ando R. and Ora 
   C. A. 114, 185301 n (1991)
41. Grachenva T. N. and Loffinna D. I., 
   Khim-Farm Zh, 25, 18 (1991)
42. Hagen H., Dupulius J. and Weurzuer B., 
   C. A. 114, 4037 t (1991)
43. Tripathi R. C., Saxena M. and Chaudhari I. M., 
44. Geiss K. H. and Traunt M., 
45. Suresh T. S. and Khalil M. A., 
   C. A. Vol. 120, 1994, 270336w
46. Rajiv G. and Maholi M.,
47. Parikh H. and Khumyo Y.,
48. Selvi G. and Rajendran S.P.,
49. James H. A. and Loffinna D. I.,
51. Burckhalter J.P. and Johnson S.H.,
J. Am. Chem. Soc., **73**, 4835 (1951)
52. Mannich C. and Lammering D.,
Ber., **55**, 3510 (1922)
53. Levy G.A. and Nisbet H.B.,
J. Chem. Soc., 1053 (1938)
54. Blanton C.D., Jr. and Nobles W.L.,
55. Rogers F.C. and Nobles W.L.,
56. Nobles W.L. and Burckhalter J.H.,
J. pharm. Sci., **47**, 77 (1958)
57. Caldwell H.C. and Nobles W.L.,
58. Varma R.S. and Nobles W.L.,
59. Hellmann H. and Loschman I.,
Chem., Ber., **87**, 1684 (1954)]
60. Moore M.B. and Rapela R.T.,
61. Atkinson R.O.,
63. Swaminathan S. and Narsimhan K.,
    Ber., 99, 889 (1966)
64. Leone Ruberg and Lyndon Small
    J. Am. Chem. Soc., 63, 736 (1941)
65. Bachman G.B. and Heisey L.V.,
    J. Am. Chem. Soc., 68, 2466 (1946)
66. Buckhalter J.H., Tendik F.H., Jones E.M., Holcomb W.F.,
    J. Am. Chem. Soc., 68, 1894 (1946)
    J. Am. Chem. Soc., 73, 4837 (1941)
68. Buckhalter J.H., Stephens V.C., Scarborough H.C., JR., Edgerton W.H.,
69. Anisimove V.A., Spasov A.A., Kovalev Y.G.,
70. Kalarani N., Angumeenal A.R., Kamalakannan P. and Venkappayya D.,
71. Foldeak S., Czombos J. and Matkovics B.,
    C.A., 64, 9670 (1966)
72. Bryant G., Heisey L.V.,
    J. Am. Chem. Soc., 68, 2486 (1946)
73. Looareesuwan,S., Kyle D.E., Viravan C., Vanijanota S.,
74. Parmar S.S., Misra R.S. and Gupta T.K.,
    J. Pharm. Sci., 61 (8), 1322 (1972)
75. Varma R. S. and Singh V. A.,
76. Barbara M. K., Barlin G. B., Edstein M. D., Rieckmann K. H.,
    Antimicrobial agents and chemotherapy, 41(6), 1369 (1997)
77. Burekhulter, J. H. Wells J.N., Mayer, W.J.,
    Tetrahedron Letters. 1353 (1964)
78. Afaf H. El-marry, fahmy H. H. and abdelwahed S.H.,
    Molecules, 5, 1429 (2000)
79. Tramontini M.,
Synthesis, **12**, 707 (1973)
80. Pascal G., Giron C. and Froissant J.,
French patent application No. 2593181 (1987)
81. Dianov V. M., Chikaeva I. G., Timirkhanova G.A.,
Khim-farm Zh, **28 (80)** 21 (1994)
82. Maskovski M. D., Drugs (in Russina),
Minisk, 359, 381, 483 (1987)
83. Joshi H. S., Vasoya S. L., Chovatia P.T., Purohit D.H.,
84. Rajasekaran A., Rajamanickam V. and Kumararan P.T.,
85. Senthilraja M. and Thangadhurai S.A.,
86. Varma R.S.,
87. Auwers and Dombrowski
J. Am. Chem. Soc., **61**, 2354 (1939)
88. Miller and Wagner
J. Am. Chem. Soc., **63**, 882 (1941)
89. Bachmann B., Heisey L.,
90. Bradshaw S., C. Krakowiak, Izatt
ARKIVOC. ISSN **25**, 1424-6375 (2001)
91. Trost B.M. and Terrell L.R.,
92. Sha Lou, Taoka B. M., Ting A. and Schaur S. E.,
93. Haidue, L.,
94. Cleare, M.J.,
95. Raman N., Esthar S. and Thanggraja C.,
96. Akimov., Kloesova., Pohomarov

97. Gordash., Grechko
Noftekhimiya, 23 (3), 399 (1983) (Russ.)

98. Kingma A.J., Lange, A., Rath H.P.,
BASF Aktiengesellschaft. Germany
Pct. Int. Appl. : WO 02 02.485

99. Pathak V.N., Singh R.P.,
Pharmazie, 35 (7), 434 (1980)

100. Yi-Feng Sun, Wei Huang, Chang-Guilu, Yi-Ping Cui
Dyes and Pigments, Vol. 81, Issue 1, 10-17 (2009)

101. Mark Wain Wright