Routes of synthesis and biological significances of Imidazole derivatives: Review

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ABSTRACT

Imidazole is a five membered, heterocyclic ring containing two hetero (nitrogen) atoms and two double bonds. Many imidazoles molecules are synthesized either through fusion or substituting various functional groups in the lead moiety. Several methods of synthesis were reported till date. Imidazole has already been reported to possess many biological activities like anticancer, analgesic, anti-inflammatory, antiviral, antihelminthic, anticonvulsant, aniallergic, antiulcer etc. the article here focus on various synthetic procedures and biological properties chemistry and major reactions of various imidazole derivatives in a comprehensive manner.

Keywords: imidazole, anticancer, analgesic, antiinflammatory, antiviral, antihelminthic, anticonvulsant, aniallergic, antiulcer

INTRODUCTION

Imidazole is a five-member heterocyclic ring with three Carbon and two Nitrogen atom and the position of N is in 1st and 3rd positions of the molecule. Being a major constituent of various natural products, including purine, histamine, histidine and nucleic acid, Imidazole derivatives have occupied a unique place in the field of medicinal chemistry, thus incorporation of the imidazole nucleus to prepare or synthesis novel imidazole derivatives has always carried the attention of many medicinal chemist and hence proved to be a vital synthetic strategy in drug discovery. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents[1].Numerous methods for the synthesis of imidazole and also their various structure reactions offer enormous scope in the field of medicinal chemistry

Imidazole is a colourless organic compound having melting point 89-91 °C and boiling point is 256° C. It has high boiling point as compared all other five membered heterocyclic compounds, the boiling point of 1-methylimidazole is comparatively low because the hydrogen bonding exists in imidazole ring and may consists upto 20 molecules[2].
Imidazole exists in two equivalent tautomeric forms, because the proton can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound, calculated dipole of 3.61D, making it more soluble in water. The compound is classified as aromatic due to the presence of a sextet of $\pi$-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring[3]. Some resonance structures of imidazole are shown below:

**CHEMISTRY**

**Amphotericity:** Imidazole is amphoteric in nature, i.e., acts as an acid and as a base. Acidic pKa is 14.5. The acidic proton is located on N-1. Basic pKa of the conjugate acid is approximately 7. The basic site is N-3. Protonation gives the imidazolium cation, symmetrical in nature[4].

**Electrophillic substitution:** Imidazole is more susceptible to electrophillic attack than pyrazole, thiazole, furan and thiophene. The attack of electrophile takes place at the 4th and 5th position in imidazole ring. The attack at C-2 involves a canonical form which is highly unfavored at positive N at position 3[4].

**CHEMICAL PROPERTIES**

1) **Reaction with acids:** Imidazole is a mono acidic base. It forms crystalline salts with acids and also possesses weakly acidic property[5].
2) **Quaternization:** Quaternization of the nitrogen atom of the imidazole is normally achieved by the reaction of alkyl halides or dialkyl sulfates in an organic solvent under strongly basic conditions. Alkylation of imidazoles is achieved by heating 1-carboethoxyimidazoles\(^{(5,6)}\).

![Quaternization Reaction](image)

3) **Halogenation:** Halogenation of imidazole is a bit complicated reaction and depends on the substrate, reagents and reaction conditions. Direct chlorination gives undefined products. Bromination yields 2,4,5-tribromo derivative. Iodination takes place in alkaline conditions to give 2,4,5-triiodoimidazole\(^{(5)}\).

![Halogenation Reaction](image)

4) **Reaction with Oxidizing and Reducing Agents:** Imidazole shows stability for autoxidation. Oxygen in the presence of sensitizer reacts to give an imidazole derivative. Imidazolium Dichromate, a mild oxidizing agent which is employed for the oxidation of allylic and benzylic alcohols\(^{(5)}\).

5) **Cycloaddition Reactions:** Imidazoles gives addition across the carbon-carbon double bond. This kind of reaction performed under photochemical conditions. The reaction of imidazole with acrylonitrile is representative from the reaction given below\(^{(5)}\).

![Cycloaddition Reaction](image)
GENERAL SYNTHESIS OF IMIDAZOLE

Imidazoles were prepared in 1858 from glyoxal and ammonia, glyoxal breaks down into formic acid & formaldehyde, and then the latter reacts as follows\(^7\)

\[
\begin{align*}
(\text{i}) & \quad \text{CHO} + \text{CHO} + \text{H}_2\text{O} & \rightarrow & \text{HCHO} \\
(\text{ii}) & \quad \text{CHO} + \text{CHO} + 2\text{NH}_3 + \text{HCHO} & \rightarrow & \text{imidazole} + 3\text{H}_2\text{O}
\end{align*}
\]

1) RADISZEWSKI SYNTHESIS

The synthesis denotes condensing a dicarbonyl compound such as glyoxal, a- keto aldehyde or a- diketones with an aldehyde in the presence of ammonia, with benzaldehyde and two molecules of ammonia react to yield 2,4,5-triphenylimidazole. Formamide often proves a convenient substitute for ammonia\(^8,9,10\). In recent studies it was found that urea is also a better substitute for ammonia as a source of nitrogen.

2) DEHYDROGENATION OF IMIDAZOLINE

Knapp and coworkers have reported a milder reagent barium managanate for the conversion of imidazolines to imidazoles in presence of sulphur. Imidazolines obtained from alkyl nitriles and 1, 2 ethanediamine on reaction with BaMnO\(_4\) yield 2-substituted imidazoles\(^11\).

3) FROM a- HALO KETONE

This reaction involves an interaction between an imidine and alpha halo ketones. This method was applied successfully for the synthesis of 2, 4- or 2, 5- biphenyl imidazole phenacyl bromide and benzimididine according to this method afford 2,4-diphenyl imidazole. Similarly, amidine reacts with acyloin or alpha halo ketones to yield imidazoles\(^11\).
4) WALLACH SYNTHESIS
The synthesis denotes that when \( N, N' \)-dimethyloxamide is reacted with phosphorus pentachloride, a chlorine containing compound is obtained which on reduction with hydroiodic acid give \( N \)- methyl imidazole. Under the same condition \( N, N' \)-diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl – 2- methyl imidazole. The chlorine compound has been shown to be 5- chloral imidazole.\(^{[11-15]}\).

![WALLACH SYNTHESIS Diagram]

5) FROM AMINONITRILE AND ALDEHYDE
Mixture of an aldehyde and aminonitrile both condensed under suitable reaction condition to give substituted imidazole.\(^{[11]}\)

![FROM AMINONITRILE AND ALDEHYDE Diagram]

6) MARKWALD SYNTHESIS
The preparation of 2- mercaptoimidazoles from a- amino ketones or aldehyde and potassium thiocyanate or alkyl isothiocyanates is a common method for the synthesis of imidazoles. The sulfur is easily removed by a variety of oxidative methods to give the desired imidazoles.\(^{[11]}\).

![MARKWALD SYNTHESIS Diagram]
Some other methods by which imidazole and its derivatives can be synthesized

7) Benzimidazole a derivatives of imidazole is more important than imidazole as the former occur in Vit B12 and has been prepared by a number of methods, 1, 2-diaminobenzene condenses with a carboxylic acid on heating in an acidic medium to give benzimidazole

\[
\text{N-HBr} \xrightarrow{\text{NaNO}_2} \text{N-Br} \xrightarrow{\text{NaO}^+\text{C}_2\text{H}_5^-} \text{N-Br} \xrightarrow{\text{N}} \text{N-Br} \xrightarrow{\text{N}} \text{N-Br} \xrightarrow{\text{N}} \text{N-Br} \xrightarrow{\text{N}} \text{N-Br} \]

The cyclization of N-haloamidines with sodium ethoxide forms benzimidazoles (imidazole derivative) through a nitrene intermediate.\[16\].

8) Imidazole can be prepared itself by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and then heating the dicarboxylic acid in quinoline in presence of copper\[16\]
9) CYCLIZATION OF \( \alpha \)-ACYLAMINOKETONES
\( \alpha \)-acylaminoketones, also behave as 1, 4-diketo compounds. This compound undergo ready cyclization, in the presence of anhydride and ammonium acetate\[^{17}\].

10) In this scheme, the synthesis of imidazole is carried out by refluxing 9, 10-phenanthraquinone with aryl aldehyde, primary amines and ammonium acetate in the presence of glacial acetic acid in round bottom flask for 3 hrs. Completion of reaction is checked out by TLC. \[^{18}\].
In this scheme the intermediate 2-chloro-N substituted phenyl acetamide is to prepared by reacting substituted aromatic amines with chloro acetyl chloride. The final products is synthesized by treating intermediate with ethylenediamine in presence of Toluene and Sulphur\(^{(19)}\).

Aryl imidazole derivatives are prepared by the condensation of compounds containing primary aromatic amine (Sulphanilamide, Sulphacetamide sodium, Sulphamethoxazole, Para-amino benzoic acid and 2-amino pyridine) with aryl aldehydes to give respective Schiff’s bases, which were further treated with ammonium acetate and isatin in the presence of glacial acetic acid\(^{(20)}\).

**BIOLOGICAL ACTIVITY**

Imidazoles are considered as an important pharmacophore in medicinal chemistry encompassing wide spectrum of biological activities. On the basis of various literature surveys Imidazole derivatives shows various pharmacological activities:

- Anti fungal and Anti-bacterial activity
- Antihelmintic activity
- Anti inflammatory activity and analgesic activity
- Anti tubercular activity
- Anti depressant activity
- Anti cancer activity
- Anti viral activity
- Anticonvulsant activity
- Anti allergic activity
Banerjee et al., World J Pharm Sci 2015; 3(8): 1668-1681

- Anti ulcer and Gastrointestinal disorder.

**Table 1: Imidazole as Antifungal and Antibacterial Agent**

<table>
<thead>
<tr>
<th>Name of Author</th>
<th>Structure/Compound</th>
<th>Active against strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramya v et al\cite{21}</td>
<td><img src="image1" alt="Structure" /></td>
<td>Antibacterial activity against <em>Staphylococcus aureus</em>, <em>Escherichia coli</em>, <em>Enterococcus faecalis</em>, and <em>Klebsiella pneumonia</em> <em>Enterococcus faecalis</em>, and anti fungal activity against <em>Candida albicans</em> and <em>Aspergillus fumigates</em>.</td>
</tr>
<tr>
<td>Mohd Amir et al\cite{22}</td>
<td><img src="image2" alt="Structure" /></td>
<td><em>S. aureus</em>, <em>E. coli</em>, <em>B. subtilis</em>, <em>C. Albicans</em></td>
</tr>
<tr>
<td>Dennis Dixon et al\cite{23}</td>
<td><img src="image3" alt="Structure" /></td>
<td><em>C. albicans</em>, <em>C. tropicalis</em>, <em>C. parapsilosis</em>.</td>
</tr>
<tr>
<td>Raymond G. Lovey et al\cite{24}</td>
<td><img src="image4" alt="Structure" /></td>
<td><em>C. albicans</em>, <em>C. tropicalis</em>, <em>E. floccosum</em> etc.</td>
</tr>
</tbody>
</table>

**Table 2: Imidazole as Antihelmintic agent**

<table>
<thead>
<tr>
<th>Name of author</th>
<th>Structure</th>
<th>Activity against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richard J. Bochis et al\cite{25}</td>
<td><img src="image5" alt="Structure" /></td>
<td><em>pheritima posthuma</em>(earthworm)</td>
</tr>
</tbody>
</table>
Table 3: Imidazole as Antiviral agent

<table>
<thead>
<tr>
<th>Name of author</th>
<th>Structure</th>
<th>Activity against virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozenna Golankiewicz et al(^{27})</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>VIRUS: Influenza A virus, respiratory syncytial virus.</td>
</tr>
<tr>
<td>Prem C. Srivastava et al(^{28})</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>VIRUS: Herpes virus, rhinovirus, parainfluenza virus, vaccinia virus.</td>
</tr>
</tbody>
</table>

Table 4: Imidazole as Anticancer agent

<table>
<thead>
<tr>
<th>Name of author</th>
<th>Structure</th>
<th>Activity against specific cellines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wen-Tai Li et al(^{29})</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>P 388 leukemic cells</td>
</tr>
</tbody>
</table>
### Table 5: Imidazole as Antitubercular agent

<table>
<thead>
<tr>
<th>Name of author</th>
<th>Structure</th>
<th>Activity against strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramya V et al([31])</td>
<td><img src="image1" alt="Structure" /></td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
</tbody>
</table>
| | For This compound A R=Br, R1=H  
B R=Br, R1=3,4-OCH3  
C R=Br, R1=4-CH3  
D R=Br, R1=2,4-Cl | |
| Preeti Gupta et al\([32]\) | ![Structure](image2) | *M. tuberculosis* strains. |
| | For compound 2f=R3=R2=C6H5  
2h=R3=R2=C6H11 | |

### Table 6: Imidazole as Anti inflammatory activity and analgesic agent

<table>
<thead>
<tr>
<th>Name of author</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tina M. Ross et al([33])</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
</tbody>
</table>
Table 7: Imidazole as Anticonvulsant agent

<table>
<thead>
<tr>
<th>Name of Author</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keith A. M. Walker et al[^35]</td>
<td><img src="image1.png" alt="Structure" /></td>
</tr>
<tr>
<td>Rahul Mishra et al[^36]</td>
<td><img src="image2.png" alt="Structure" /></td>
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</tbody>
</table>

Table 8: Imidazole as Antiallergic agent

<table>
<thead>
<tr>
<th>Name of Author</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ian R. Ager et al[^37]</td>
<td><img src="image3.png" alt="Structure" /></td>
</tr>
</tbody>
</table>
Conclusion

This article aims to review the works reported, their chemistry and biological activities of imidazole during past years. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Having structural similarity with histidine imidazole compound can bind with protein molecules with ease compared to the some other heterocyclic moieties. Thus imidazole offers to some extent better biological and pharmacological characteristics in comparison to other heterocycles.

References

13. Wallach., Ber., 1876, 184,33-35.