A Review on Synthetic and Pharmacological Profile of Some Imidazole Derivatives

Keywords: Imidazole; Heterocyclic; Aromatic; Anticonvulsant; Anti-ulcer; Anti-allergic; Anti-viral

ABSTRACT

Imidazoles have occupied a unique position in heterocyclic chemistry and derivatives of imidazole have attracted considerable interest in recent years for their different pharmacological properties. Imidazole is a nitrogen-containing heterocyclic ring which possesses biological and pharmaceutical importance. Thus, imidazole compounds have been an interesting source for researchers for more than a century. The imidazole ring is a constituent of many important natural products, including purine, histamine, histidine, and nucleic acid. Being a polar and ionizable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus is used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble lead molecules. There are several methods used for the synthesis of imidazole-containing compounds and also their various structure reactions offer scope in the field of medicinal chemistry. The imidazole derivatives possess an extensive spectrum of biological activities such as antibacterial, anticancer, antitubercular, antifungal, analgesic, and anti-HIV activities. This paper aims to review the synthetic and pharmacological profile of imidazole during the past years.
1. INTRODUCTION

Heterocyclic compounds represent an important function in medicinal chemistry and serve as a key template for the deovlement of various chemotherapeutic agents. Most of the researcher has maintained their interest in nitrogen-containing heterocyclic compounds through decades of historical deovlement of medicinal synthesis. Heterocyclic form a major class of medicinal and organic chemistry and are used industrially and biologically. There is a wide range of therapeutic activity of synthetic heterocycles such as anticancer, antimicrobial, antidepressant, antimalarial, anticonvulsant, anthelmintic, and insecticidal agents. The explorations for the new biologically active heterocyclic compounds continue to be an area of major research in medicinal synthetic chemistry.¹

Nitrogen-containing heterocycles are contributing to the deovlement of society from a pharmacological and industrial point of view as well as to improve quality of life.² Basic ideas for the development of biologically active synthesized compounds evoke from the consideration that active molecules binding to a protein or enzyme with a response in the form of certain pharmacological activity.³ Rational drug discovery of small biologically active compounds form the basis of the practical compilation of chemical science with the life science discoveries of the target molecule and disease mechanism.⁴ Moreover, synthetic compounds have been and will be an important source of new pharmaceuticals. The advances in molecular biology and functional genomics focus on tackling disorders through an understanding of drug targets.⁵

Drug discovery is the time consuming and inventive process of finding new molecules based on the biological target knowledge which involves small molecules that complementary structure, shape, charge to the biomolecular target with which they bind.⁶

1.1 Imidazole

1.1.1 Introduction

Imidazole is an entity that is synthesized in many of its derivative forms from the past few years and is a major source of interest for the researcher to explore its various biological activity potentials.

Imidazole (1, 3-diaza-2,4-cyclopentadiene) is a five-member planner ring system with 3C and 2N in 1 and 3 positions having molecular formula C₃H₄N₂. IUPAC name for the imidazole is
1, 3-diazole, one of the annular N bears an H atom and can be regarded as pyrrole type N. Imidazole is basic aromatic in nature, less basic than ammonia and more basic than pyridine. It exhibits tautomerism because the hydrogen atom that can be located on either of the two nitrogen atoms.\textsuperscript{7}

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N}
\end{array}
\quad \rightleftharpoons \quad
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N}
\end{array}
\]

Imidazole was first synthesized by Heinrich Debus in 1958, but various imidazole derivatives had been reported as early as the 1840s. The synthesized imidazole shown below used formaldehyde and glyoxal in ammonia.\textsuperscript{8}

\[
\begin{array}{c}
\text{O} \\
\text{C} \quad \text{C}
\end{array}
\quad + \quad
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{H}
\end{array}
\quad \xrightarrow{+2 \text{NH}_3 \quad -2 \text{H}_2\text{O}}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\quad \begin{array}{c}
\text{HN} \\
\text{C} \quad \text{C}
\end{array}
\quad \begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3
\end{array}
\quad \begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3
\end{array}
\]

1.1.2 Chemistry

**Amphoteric:** Imidazole is amphoteric, i.e. acts as an acid and as a base. Acidic pKa is 14.5. N-1 is located as an acidic proton. The basic pKa of the conjugate is nearly 7. N-3 is the basic site. Protonation of the imidazole gives the imidazolium cation which is symmetrical.

**Electrophilic substitution:** Imidazole is more favored to electrophilic attack than the pyrazole, thiazole, furan, and thiophene. The attack of electrophile takes place at the 4\textsuperscript{th} and 5\textsuperscript{th} position of the imidazole ring.
The resonance structure of the imidazole ring is shown below

1.1.3 Structure-Activity Relationship of Imidazole Ring (9-14)

SAR of imidazole had shown that ring-substituted only at position N-1 is most essential for the activity. Lipophilic substituents usually one or more with a five or six-membered ring system were attached for activity. The more potent antiviral, antidepressants, antimicrobial, anticancer imidazoles were reported with two or three aromatic substituents on the imidazole ring or annealing with imidazole ring which were with Halogen, Hydroxy, Methoxy substituents at positions 2, 4, 6.

The addition of other alkyl substituents on the imidazole ring generally decreases the activity but imidazole’s with N-substitutions on N-1 or N-3 position with methyl group results in nearly inactive agents. Substitutions with aliphatic amines result in decreasing the activity of the imidazole ring. Annealing of the imidazole ring with other heterocycles or aromatics results in pharmacologically active derivatives such as Benzodiazepine.

E.g. Imidazobenzodiazepine midazolam was popularly prescribed as potent anxiolytic agents.
GENERAL METHODS FOR SYNTHESIS OF IMIDAZOLE

1.1.4.1 Radiszewski synthesis:

Radiszewski reported the synthesis of 2, 4, 5-triphenyl-imidazole by the condensation of dicarbonyl compound and aldehydes in the presence of ammonia.¹⁵

\[
\text{O} \quad \text{O} \quad + \quad 2 \text{NH}_3 \quad + \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{H} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{H}
\]

1.1.4.2 from α-haloketones:

This synthesis involves an interaction between an imidine and alpha ketones. This method is applicable for the synthesis of 2, 4 or 2, 5 biphenyl imidazole.¹⁶

\[
\text{H}_2\text{N} \quad \text{NH} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{N}
\]

1.1.4.3 from Imidazoline:

Knapp had reported the conversion of imidazolines to imidazole in presence of sulfur with mild reagent barium manganate yields 2-substituted imidazoles.¹⁷
1.1.4.4 Wallach synthesis:

The reaction of N, N dimethylformamide with phosphorus pentachloride which is a chlorine-containing compound on reduction with hydroiodic acid gives N-methyl imidazole by using the same conditions N, N- dimethylformamide is converted to chlorine compound which on reduction gives 2-methyl-1-ethyl imidazole.18

1.1.4.5 Markwald synthesis:

Markwald reported the synthesis of 2-mercaptoimidazoles from α-amino ketones or aldehydes and alkyl isothiocyanates which is a common method for the synthesis of imidazoles.19
1.1.5 PHARMACOLOGICAL ACTIVITIES OF IMIDAZOLE:

1.1.5.1 Imidazole as anti-cancer agents:

Okay, et al. reported 18 novel imidazole piperazine derivatives. The structures of the synthesized agents were characterized by $^{1}$HNMR, IR, and EI-MS spectral data. Among the synthesized compounds most of the compounds showed significant activity against carcinogenic cell lines.

Congiu et al. had reported the synthesis of a series of 1, 4-diarylimidazole-2(3H)-one derivatives and evaluated them for in vitro anticancer activity. Compounds with a 3, 4, 5-trimethoxypheny ring attached to either N-1 or C-4 position of the imidazole ring showed anticancer activity against leukemic cell lines.

1.1.5.2 Imidazoles as anti-microbial agents:

Kallappa Hosamani et al. had reported the synthesis of a novel series of 5-(nitro/bromo) styryl-2-benzimidazoles by condensation of 5-(nitro/bromo)-o-phenylenediamine with trans-cinnamic acids. Synthesized compounds were evaluated for anti-tubercular activity against Escherichia coli, Enterococcus faecalis, and Klebsiella pneumoniae antibacterial strains and Candida Albicans, Aspergillusfumigatus antifungal strains were performed. Compounds showed significant activity against the group of all microorganisms.
1.1.5.3 Imidazoles as anti-tubercular agents:

Qidong You et al. had reported the synthesis of 4-(2, 6-dichlorobenzyloxy) phenyl thiazole imidazole derivatives. Derivatives were evaluated for in vitro anti-tubercular activities against *Mycobacterium tuberculosis* H37Rv by the Microplate Alamar Blue Assay (MABA). Compounds show good anti-tubercular activities with MIC values between 1μM and 61.2μM.22

1.1.5.4 Imidazoles as antidepressant agents:

Kumarishalini had reported substituted imidazole with a moclobemide phenyl ring and evaluated them for antidepressant activity using a forced swimming test. Synthesized compounds show a more potent activity than moclobemide.23

R = CH₃, C₂H₅, CH₂C₆H₅
1.1.5.5 Imidazoles as anticonvulsant agents:

Bhragual et al. had reported imidazole derivatives with substitution of chloro and nitro group at 2\textsuperscript{nd} position in the ring showed anticonvulsant activity without neurotoxicity.\textsuperscript{24}

\[
\begin{align*}
\text{R} & : \text{H, 2-Cl, 2-NO}_2, \text{4-NO}_2 \\
\end{align*}
\]

1.1.5.6 Imidazoles as anti-inflammatory agents:

Mukeshdoble and A. Puratchikody had reported 2-substituted-4, 5-diphenyl-1\textit{H}-imidazole derivatives and evaluated them for anti-inflammatory activity using the carrageenan-induced rat paw edema method. Derivatives having phenyl substitution with –F, -Cl, -NH\textsubscript{2}, -OH, OCH\textsubscript{3}, -N(CH\textsubscript{3})\textsubscript{2} at Para position showed maximum activity than the other substitutions.\textsuperscript{25}

\[
\begin{align*}
\text{H} & : \text{N} \\
\text{R} & : \text{Ph} \\
\end{align*}
\]

Also, imidazoles having potent antiviral\textsuperscript{26}, cardiotonic\textsuperscript{27}, antioxidant\textsuperscript{28}, anti-diabetic, antifungal\textsuperscript{30}, antinociceptive activity\textsuperscript{31}. Given the above activities in present work we have synthesized 1, 2, 4, 5-tetra substituted imidazole derivatives and evaluated them for antibacterial and antifungal activity.

2. REVIEW OF LITERATURE

In the past few years 1, 2, 4, 5-tetra substituted imidazole compounds are being actively studied by the researchers. Various molecules having antimicrobial, antimalarial, anticancer,
antidepressant activity are being designed and synthesized to study the effects of various substituents present on the target molecules. In the present work we have focused on the 1, 2, 4, 5-tetra substituted imidazole derivatives which have been identified as the new class of antimicrobial agents.

The extensive literature survey had been carried out about the synthesis and biological activity of 1, 2, 4, 5-tetra substituted imidazole derivatives by using books, peer-review journals, and internet sources.

1. **Javad Safari et al.** (2014) had synthesized 1, 2, 4, 5-tetra substituted imidazole derivatives by the one-pot cyclo condensation of aldehydes, benzil, ammonium acetate, and primary amines under microwave irradiation using silica-supported SbCl$_3$ as a catalyst. This method makes operational simplicity, applicability, and practicability to the previous methods of the synthesis.$^{32}$

2. **Zong-Ze Zhang et al.** (2015) had synthesized 1, 2, 4, 5-tetrasubstituted imidazole derivatives using a one-pot reaction of 1, 2-diketones, ammonium acetate, aromatic aldehydes, and substituted aromatic amines. Synthesis had carried out using β-cyclodextrin-propyl sulphonic acid as a catalyst under solvent-free medium and synthesized compounds were evaluated for local anesthetic activity. The local anesthetic activities of synthesized compounds were assessed in comparison to lidocaine as standard by using the rabbit corneal and mouse tail anesthesia model. Amongst the synthesized compounds 4-((1-benzyl-4, 5-diphenyl-1H-imidazole-2-yl)-N, N-dimethylaniline was reported most potent with minimum toxicity.$^{33}$
3. Ghodsi Mohammadi Ziarani et al. (2015) reported a one-pot four-component reaction between 1, 2-diketones, aromatic aldehydes, ammonium acetate, and substituted amines for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using sulfonic acid functionalized silica (SiO$_2$-Pr-SO$_3$H) as an efficient catalyst.

4. Manal Mohammed et al. (2014) had prepared series of 1-methyl-5-(1-substituted-4, 5-diphenyl-1H-imidazole-2-yl)-1, 2, 5, 6-tetrahydropyridine) derivatives by the refluxing mixture of benzil, arylamines, pyridine-3-carboxaldehyde, and ammonium acetate. Molecular docking study for the anti-inflammatory activity with the protein p38 MAP kinase showed a maximum binding affinity with the experimental values. Compounds were screened for anthelmintic and in vitro anti-inflammatory activity on comparison with standard Albendazole and standard diclofenac sodium respectively. All compounds showed significant activity with high practical yield.
5. **Abolghasem Davoodina et al.** (2015) had synthesized 1,2,4,5-tetrasubstituted imidazole derivatives by one-pot four-component condensation of benzi, aromatic aldehydes, ammonium acetate, and primary amines using nano-Fe$_3$O$_4$ encapsulated-silica particles bearing sulfonic groups as a separable catalyst. Parameters like reaction temperature, catalyst loading, and solvent effect on synthesis reaction were also studied.$^{36}$

6. **Iftikhar Ahsan et al.** (2014) had synthesized imidazole derivatives from 2-(4-chlorophenyl)-4, 5-diphenyl-1H-imidazole-1-yl)-acetic acid hydrazide which being synthesized from benzi, 4-chlorobenzaldehydes, ammonium acetate. All derivatives were evaluated for anti-inflammatory and antimicrobial activity. Compounds bearing 4-fluoro, methyl, and fluorophenyl group showed maximum anti-inflammatory activity in comparison to standard indomethacin.

Antibacterial and antifungal activities were performed using the plate agar diffusion method by using ofloxacin as standard drug for antibacterial activity and Voriconazole as a standard.
for antifungal activity. Compounds were evaluated against *E. coli*, *B. subtitles*, *S. aureus* in the nutrient agar medium for antibacterial activity, and *Candida albicans* in the Sabouraud’s medium for antifungal activity. Compounds having 4-chlorophenyl, 4-methylphenyl group’s shows the highest antibacterial activity and compounds with phenyl and 4-methoxyphenyl group showed the highest antifungal activity.\(^{37}\)

\[ \text{O} \text{O} \text{Ph} \text{Ph} \text{+} \text{O} \text{Cl} \text{Glacial acetic acid} \text{Ammonium acetate} \]

\[ \text{CICH}_2\text{COOC}_2\text{H} \text{Anhydrous Acetone} \text{K}_2\text{CO}_3 \]

7. **Haleh Sanaeishoar et al.** (2016) had prepared 1, 2, 4, 5-tetrasubstituted imidazole through one-pot condensation of amines, aldehydes, ammonium acetate, and 1,2-diketones using nano LaMnO\(_3\) perovskite type oxide as a catalyst under solvent-free conditions at 80\(^0\) C. This method of synthesis overcomes the problem of previous methods of synthesis like catalyst recovery, high catalyst loading, poor yield, difficult workup, and reuse of catalyst.\(^{38}\)
8. Kuppusamy Krishnamy et al. (2015) had devised a highly versatile, efficient, and simple method for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazole derivatives by the cyclo condensation of aminoethylpiperazine, an aromatic aldehyde, ammonium acetate, and benzil using sulfated yttria as a promising catalyst. This method of synthesis showed many advantages like high yield, simple operation, easy workup, low cost, catalyst recovery, and recyclability.39
9. **A. R. Moosavi-Zare et al.** (2015) had reported an efficient and recyclable catalyst system of sulfonic acid-functionalized pyridinium chloride for the one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using benzil, ammonium acetate, aldehydes, and amines. This method of synthesis had shown advantages like short reaction time, efficiency, recyclability and easy preparation with good compliance with eco-friendly green chemistry protocol.\(^{40}\)

\[
\begin{align*}
\text{Ph} & \quad + \quad R\text{--NH}_2 \quad + \quad \text{H} & \quad + \quad \text{NH}_4\text{OAc} \\
\text{Ph} \quad \text{CO} & \quad \text{CO} \quad \text{[Pyridine-SO}_3\text{H}]\text{Cl}, 10 \text{ mol}\% & \quad \text{Solvent free 90}^\circ\text{C} \\
\end{align*}
\]

10. **Harsha Tripathy et al.** (2010) had synthesized 1, 2, 4, 5-tetra substituted imidazoles by the microwave-assisted parallel synthetic method in solid-phase with advantages like high yield, short reaction time, and purity. The synthesized compounds were confirmed by Mass, NMR, TLC, and IR. The synthesized compounds were screened for anti-inflammatory activity using the rat paw edema method. Amongst the all synthesized compounds, anti-inflammatory was found to be active orally with reduced in paw volume.\(^{41}\)
11. **K. Krishnasamy et al.** (2014) had synthesized 1-[2-(4, 5-dimethyl-henyl-1H-imidazol-1-yl)-ethyl]-piperazine] derivatives by the cyclo condensation of aromatic aldehydes, ammonium acetate, diacetyl, and 2-(piperazine-1yl)-ethanamine in the presence of sulfated yttria. All the synthesized compounds were confirmed by MASS, NMR, IR and screened for antibacterial and antifungal activity. Amongst them, compounds having thiophene moiety with chlorine substitution showed excellent antibacterial activity against *E. coli*, *S. aureus*, *S. typhi*, and *P. aeruginosa* using ciprofloxacin as a standard. Excellent antifungal activities were shown by the compounds having chloro, fluoro, and 3-bromo, 4-fluoro substitution against *C. Albicans*, and *A. flavus* using amphotericin B as a standard.

![Chemical structure](image)

12. **Bibi Mirjalili et al.** (2015) had synthesized 1, 2, 4, 5-tetra substituted imidazole derivatives using Kaolin-SO₃H as an efficient catalyst by the reaction between benzyl, aromatic aldehydes, primary amines, and ammonium acetate. This method had shown key advantages over the other methods of synthesis including inexpensive, easy availability, high yields, and simple work-up.

![Chemical structure](image)
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