Imidazole Scaffold: A Review of Synthetic Strategies and Therapeutic Action

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Imidazole heterocycles possess a very special place in biological chemistry making their derivatives receive considerable attention among researchers. Several natural products including nucleic acids, histamine, and histidine consist of the imidazole nucleus. It is an ionizable compound that renders good pharmacokinetic properties to the compounds contained in it. The nucleus presents some interesting pharmacological properties like antibacterial, antitubercular, anticancer, larvicidal, and antifungal. The present paper attempts to review the significant pharmacological actions of imidazole derivatives over the past few years. The paper summarizes the preparation methods like condensation method, microwave-assisted method, ultrasonic method and heating process employed for synthesis of imidazoles. The paper summarizes the current improvements of imidazole-based mixtures in the entire range of restorative science. The significant analysis of the published research infers that optimization of the microwave method for synthesis of the imidazole nucleus could be an effective method in the preparation of the motif.

Keywords: Imidazole, heterocycle, histamine, anticancer, antibacterial, larvicidal.

The design of novel and newer potent molecules has been the thirst of researchers worldwide. An important approach towards this incorporates the modification of the existing molecules with established biological actions utilizing the various approaches for drug designing. Heterocyclic compounds either of synthetic or natural origins have found applicability in several physiological neurotransmitters as well as in the modulators of certain neurotransmission processes.

Heterocyclic compounds containing two N atoms at 1-3 positions are gifted with a broad spectrum of microbial actions. A plethora of sulphur and nitrogen-possessing compounds are found in the biological and non-biological systems. Amongst the heterocyclic compounds containing sulphur and nitrogen, the six and five-membered heterocycles have gathered the maximum interest, owing to their biological and industrial applications.

Since the time of its disclosure during the 1840s, the examination and advancements of imidazole based mixtures have been a significant quickly creating, and progressively dynamic region inferable from their wide expected applications as restorative medications, agrochemicals, synthetic materials, unnatural acceptors, supramolecular ligands, biomimetic impetuses, and so on.
Imidazole ring is a 5-membered heterocycle structure having two nitrogen iotas and amphoteric nature with exceptionally polar characteristics. It occurs in two identical tautomeric structures, in which the hydrogen (H) particle can be situated on both of the two nitrogen (N) molecules. It is a sweet-smelling compound. Besides, the electron-rich nitrogen heterocycle couldn’t promptly acknowledge or give proton, yet in addition, effectively structure different powerless cooperations. These exceptional primary qualities of the imidazole ring are helpful for its subsidiaries to promptly tie with an assortment of chemicals and receptors in natural frameworks employing hydrogen bonding, coordination linkages, particle dipole interaction, cation-pi, pi-pi stacking, hydrophobic impacts, van der Waals powers, etc, in this way displaying wide bioactivities.

Compounds containing the imidazole ring are vital in living frameworks, like nutrient B12 and a few pilocarpine alkaloids. Imidazole framework happens in the fundamental amino corrosive histidine; histidines inside catalysts are personally associated with catalysis requiring protein transfer. The existence of imidazole moiety in concerned compounds may be good for further developing water dissolvability somewhat because of its two nitrogen iotas effectively prompting the arrangement of hydrogen bonds. In addition, imidazole ring with different restricting destinations is fit for planning with a selection of inorganic metal particles or interfacing with natural atoms through noncovalent securities to form supramolecular drugs, which might have microbial activities of imidazoles themselves, however also the benefits of various supramolecular drugs, potentially applying twofold activity mechanisms that are useful to defeat drug resistance.

The imidazole ring is present in several natural and synthetic biologically active compounds, such as biotin, histidine, histamine, and pilocarpine alkaloids. This has led to several compounds based on the imidazole motif being optimized for commercial success as medicinal agents. Some of the most prominent marketed products containing imidazole are presented in Table 1.

**Novel synthetic strategies for imidazole derivatives**

It was seen from the literature that most of the imidazole and derivatives has been prepared through conventional synthesis method like Debus synthesis, Radiszewski synthesis, dehydrogenation, Wallach synthesis, etc., and takes several hours to the completion of the reaction. The classical methods also suffer from the disadvantages of poor yield, side reactions, slow rate, and inappropriate conditions. Researchers are constantly working to develop clean, high-yielding reactions with reusable catalysts using environmentally friendly reaction systems with an emphasis on their therapeutic advantages.

This review paper mentions the most relevant reaction strategies for the synthesis of imidazoles. The earlier reviews have not covered the research work done on imidazoles in the last 5 years, which have been included in our paper.

The present work highlights the important findings on the pharmacological actions of imidazole and its derivatives, especially during the last decade.

Substituted imidazoles were prepared by the multicomponent condensation method or microwave-assisted or heating method. The synthesis of five optically active compounds based on the imidazole scaffold via a four-step reaction (Scheme 1) was reported by a team of researchers. The microwave-assisted method for synthesis could not yield the desired products while the condensation reaction of α-bromo ketones and formamidine acetate in presence of liquid ammonia was found to be a successful approach for the synthesis.

Table 2 summarizes a few of the catalyst-based synthesis of imidazoles and derivatives.

A novel one-pot three-component scheme for the production of imidazole using ultrasonic irradiation has been reported. They used nickel catalyst in ethanol to obtain 2-phenyl-1H-phenanthro[9,10-d]imidazoles and reported a short reaction time.

Three imidazole derivatives from oxazolone and dinitrophenyl hydrazine using pyridine as a catalyst were synthesized. The prepared compounds were confirmed by FTIR and NMR spectra.

The synthesis of N-Arylimidazole derivatives using aluminium oxy-hydroxide-supported palladium nanoparticles has been reported. The finest results were reported by
employing water-isopropyl solvent mixture. Ultrasonic conditions facilitated high yields of N-aryl imidazole derivatives. The catalyst employed was purified economically from the reaction medium and was reused without losing its efficacy, thereby presenting an environment-friendly and economical method. ICP-MS result of 1% validated the fact that the method is eco-friendly in approach.

A novel synthesis of 2,4,5-trisubstituted imidazoles under microwave irradiation as a novel neutral liquid-catalyzed solvent-free method was used.

To achieve superior selectivity and output, a wide range of catalysts have been explored. Researchers have employed titanium-based silica for one-pot synthesis of imidazole compounds. In another attempt, copper oxide over silica was employed for the synthesis of solvent-aided imidazole derivative and offered the advantage of simple and cost-effective preparation.

Similarly, SbCl$_3$-silica catalyst was used to prepare microwave-assisted trisubstituted imidazole. This method proved advantageous over previously explored ones due to appreciable results, short reaction time, diminished expenses, and eco-friendliness. The catalyst was renewable with no significant reduction in activity.

Microwave irradiation was also used for solvent-free preparation of imidazole derivatives. The excellent yield with good reaction time was observed by the researchers. Easy and quick high yield synthesis of trisubstituted imidazole was done by microwave-assisted one-pot cyclo condensation. Sodium hydrogen sulphate supported by silica was employed as a renewable and thermally stable catalyst.

Through this review, we could figure out that optimizing a microwave-assisted method for the synthesis of imidazoles could be beneficial in a significant reduction of reaction time as well as improving the yield of the product formed.

**Therapeutic Efficacy of Imidazole Motif**

The enormous utility of imidazole-based moieties in curative chemistry has led to a lot of work being directed toward the feasible prolific applications of imidazole derivatives in diverse areas. The current area is expected to summarize the current improvements of imidazole-based mixtures in the entire range of restorative science including anticancer, anti-neuropathic, fungal, antibacterial, antitubercular, antiparasitic, anti-histaminic, anti-hypertensive, anti-inflammatory, viral defending, so on.

**Antimicrobial action**

In a recent study, 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole derivatives were synthesized (Figure 1) and examined for fungal and mycobacterial activity against Candida albicans strain and Mycobacterium tuberculosis H(37)Rv strain, respectively.

One of the research team performed the production of a run of novel imidazole-based compounds with broad chemotherapeutic activity.

<table>
<thead>
<tr>
<th>Name</th>
<th>Therapeutic category</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem</td>
<td>CNS depressant</td>
<td>GABA$_A$ inhibitor</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Antineoplastic</td>
<td>DNA alkylator</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Antineoplastic/</td>
<td>Cytochrome P450 3A4 inhibitor</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Antineoplastic/</td>
<td>Cytochrome P450 3A4 inhibitor</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Antineoplastic/</td>
<td>DNA Alkylation</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Antifungal</td>
<td>Impairs ergosterol synthesis</td>
</tr>
<tr>
<td>Oxiconazole</td>
<td>Antifungal</td>
<td>Impairs ergosterol synthesis</td>
</tr>
<tr>
<td>Butaconazole</td>
<td>Antifungal</td>
<td>Inhibition of steroid synthesis</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Antifungal</td>
<td>Impairs ergosterol synthesis</td>
</tr>
<tr>
<td>Metronizazole</td>
<td>Antibacterial</td>
<td>Inhibits protein synthesis leading to loss of helical DNA structure</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Antibacterial</td>
<td>Reduction of the NO$_2$ (nitro) by susceptible bacteria</td>
</tr>
<tr>
<td>Ornidazole</td>
<td>Antibacterial</td>
<td>Reduction of the NO$_2$ (nitro) group by susceptible bacteria</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Antihypertensive</td>
<td>Alpha adrenoceptor antagonist</td>
</tr>
</tbody>
</table>

Table 1. Marketed products with imidazole scaffold
properties. The compounds showed comparable degree of activity to metronidazole but lower activity than efavirenz. They screened the compounds for anti-HIV and antibacterial actions and suggested that the series of compounds synthesized could prove to be efficient starting moieties for broad-spectrum action. The synthesis of an innovative and new series of imidazole subordinates was achieved by refluxing 9, 10-phenanthraquinone with aryl aldehyde, essential amines, and ammonium acetic acid using a catalytic amount of glacial acetic acid. The combined mixtures were evaluated for antimicrobial exercises against Candida albicans. They reported 200µg/ml dose of every synthesized derivative had better activity than the dose of 100µg/ml.

Antimicrobial action of newly synthesized mono, di, and tri-substituted imidazole derivatives against bacteria and fungi was reported by researchers. Streptomycin and Amphotericin B were employed as standards during the screening action.

Another investigator performed the synthesis of imidazole by cyclo condensation of hippuric acid and m-methyl benzaldehyde.

<table>
<thead>
<tr>
<th>Catalyst type</th>
<th>Category</th>
<th>Operating conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl3-SiO2</td>
<td>Silica-based</td>
<td>Heat at 90 ºC</td>
<td>92%</td>
</tr>
<tr>
<td>Activated fullers earth</td>
<td>Clay-based</td>
<td>Heat at 100°C</td>
<td>95%</td>
</tr>
<tr>
<td>Zeolite</td>
<td>Mineral based</td>
<td>Heat at 110°C</td>
<td>90%</td>
</tr>
<tr>
<td>Silica gel</td>
<td>Heteropolyacids</td>
<td>Microwave at 130 ºC</td>
<td>78.9%</td>
</tr>
<tr>
<td>HPA</td>
<td></td>
<td>Microwave</td>
<td>95%</td>
</tr>
<tr>
<td>PPA-SiO2</td>
<td>PPA</td>
<td>Microwave</td>
<td>96%</td>
</tr>
<tr>
<td>ZrO2-Al2O3</td>
<td>Alumina</td>
<td>Heat at 120°C</td>
<td>99.2%</td>
</tr>
<tr>
<td>Fe3O4</td>
<td>Magnetic nanoparticles</td>
<td>Ultrasonic at room temperature</td>
<td>97%</td>
</tr>
<tr>
<td>CuO/Fe3O4</td>
<td></td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td>HMS-SA</td>
<td></td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td>BNPs-SiO2</td>
<td>Silica based nanocatalyst</td>
<td>Heat at 140 ºC</td>
<td>97%</td>
</tr>
<tr>
<td>SiSaln</td>
<td></td>
<td>Heat at 80°C</td>
<td>80%</td>
</tr>
<tr>
<td>AgNP-CS</td>
<td>Biohybrid nanocatalyst</td>
<td>Heat at 100°C</td>
<td>90%</td>
</tr>
<tr>
<td>Au-RGO</td>
<td></td>
<td>Heat at 5 ºC</td>
<td>90%</td>
</tr>
</tbody>
</table>

Scheme 1.
The synthesized compounds were evaluated for antimicrobial action. The antibacterial behavior of the compounds was studied against species like Staphylococcus aureus, Bacillus subtilis, E. coli, and klebsiella promoe at a concentration of 50 microg/mL by agar cup plate method while the fungicidal action was studied at 10^3 ppm concentration in vitro.  

Novel imidazole derivatives were prepared by using a four-step reaction strategy involving the reaction of ethanone with selenium dioxide in dioxane followed by cyclization using aromatic aldehyde in the presence of acetic acid or ammonium acetate. The antibacterial effect of the synthesized compounds was also studied. In another report, the synthesis of 2-aminoimidazole derivatives from conventional dicarbonyl compounds in the presence of ammonium acetate and acetic acid. The screening of the imidazoles for antimicrobial activity highlighted the significance of the amine group at the 2-position of the imidazole in enhancing the antimicrobial potential.

One-pot synthesis of imidazole compounds based on a quinoline scaffold has been reported. The synthesis was carried out from benzil, ammonium acetate, and 2-phenoxyquinoline3-carbaldehyde employing ceric ammonium nitrate as a catalyst. The ready compounds were investigated for antimicrobial and antitubercular activities. Glucosamine-6-phosphate was considered a new target for antimicrobial action. They inferred that the compounds with the least binding energy act as a more active antimicrobial agent than standard drugs.

The scheme and synthesis of several 2-(substituted dithiocarbamoyl)-N-[4-((1H-imidazol-1-yl)methyl)phenyl]acetamide derivatives was reported by a team of researchers. They tested the compounds for antifungal effects on four fungal strains and also attempted to investigate the mode of action using molecular docking studies. The synthesis of tetra-substituted imidazole derivatives using one-pot condensation reaction was also performed. All compounds were analyzed for their melting point, Carbon Hydrogen Nitrogen (CHN) analysis, Fourier transform Infrared Spectroscopy (FT-IR), and UV-Visible spectra. The biological activity was verified against Staphylococcus aureus, Bacillus subtilis, and Escherichia, and significant action against bacterial strains was reported.

**Anticancer action**

In an investigation, a series of 1,2-heteroannulated anthraquinones and anthra [1,2-d] imidazole-6,11-dione homologues was synthesized, and reported the cell damage and human telomerase inhibition activities. A range of side-chain inclusion was done using synthetic routes including acylation, cyclization, condensation, and heterocyclization. Screening tests revealed varying levels of differential cytotoxicity.
A few derivatives of 2-(4-substituted piperazine-1-yl)-N-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl] acetamide was synthesized by researchers. The Infra Red (IR) spectra, Nuclear Magnetic Resonance (NMR) images, and Electron Ionization Mass Spectrum (EI-MS) data confirmed the structures of the compounds. These combined mixtures were evaluated for anticancer action against colon carcinoma cell lines. The prepared derivatives effectively exhibited cytotoxicity against the cell lines and were supported by DNA fragmentation.

The production of a series of novel imidazolium derivatives and studied the cytotoxicity against 5 human tumor cell lines using an MTS assay was carried out. They suggested the presence of 5,6-dimethyl-benzimidazole ring, naphthylacyl group as a substituent, and the existence of alkyl chain length between aromatic rings was significant for the antitumor action. The prepared compounds amazingly induced cell cycle seizure.

A report summarized the synthetic procedures of novel imidazole along with fused imidazole derivate. The key intermediate for the synthesis was 5-arylidene-2-hydrazino-3-phenyl imidazolin-4-one. Some of the prepared imidazoles were checked for cytotoxic action against carcinoma of the breast and colon cell lines and also for action against microbes using the cup plate diffusion method. A broad-spectrum activity was reported by the research team.

The synthesis of novel N-(6-substituted-benzothiazol-2-yl)-2-[(4,5-dimethyl-1-((p-tolyl/4-nitrophenyl)amino)-1H-imidazol-2-yl]thio] acetamide derivatives was reported by researchers. The synthesized compounds were winnowed for cytotoxic effect against C6 and HepG2 tumor cell lines. They reported an IC50 value of about 15.67 µg/mL via C6 tumor cell lines suggesting effective antiproliferative activity of the derivatives.

One-pot synthesis of imidazole derivatives using Mannich base method in the presence of copper catalyst was reported by an investigation team. Prepared compounds were analyzed by IR spectra, Proton NMR, Carbon NMR, and mass spectral data including elemental analysis. The synthesized imidazoles were evaluated for larvicidal actions using a standard bioassay protocol. The high larvicidal activity was confirmed based on their half-maximal lethal dose value.

Anticonvulsant action of a few novel tetra-substituted imidazoles against Pentylenetetrazole (PTZ-induced) convulsions and MES methods was performed by researchers. The maximum activity of 12.5 s of the Hind Limb Tonic Extensor Phase and convulsion time of 285.5 s supported the results. Also, imidazole-based mixtures have shown remarkable improvement in the entire range of restorative science.

**Conclusions**

Over the years, the quest for obtaining newer and better drug substances has been constantly increasing. The imidazole scaffold
shares a special mention in the pharmaceutical field as it can be found in endogenous neurotransmitters.

The critical analysis of the published research infers that optimization of the microwave method for synthesis of the imidazole nucleus and the derivatives thereof would help reduce the overall time required for the synthesis with a much lesser workup. It would also help in increasing the yield of the product obtained to up to 97%. This would help in overcoming the research gap in drug development related to imidazole scaffold.

The presented review reflects excellent pharmacological activities of the imidazoles and derivatives, including antibacterial, anticancer, antitubercular, anticonvulsant, and anti-larvicidal activities supported by maximal lethal dose values, HLTE phase and convulsions time, etc. Researchers have succeeded in fabricating compounds with promising biological output by modifying the imidazole nucleus. The current review will help the scientific community to add new pharmacological profiles for safer and more effective therapeutic compounds.

Conflict of Interest
The authors declare that they have no conflict of interest.

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REFERENCES
15. PubChem [Internet]. Bethesda (MD): National


XIA M, LU YD. A NOVEL NEUTRAL IONIC LIQUID-CATALYZED SOLVENT-FREE SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLES UNDER MICROWAVE IRRADIATION. J OF MOLECULAR CATALYSIS A 2007; 265: 205-08. DOI: 10.1016/j.molcata.2006.10.004


SAFARI J, NASEH S, ZARNEGAR Z, AKBARI Z. APPLICATIONS OF MICROWAVE TECHNOLOGY TO RAPID SYNTHESIS OF SUBSTITUTED IMIDAZOLES ON SILICA-SUPPORTED SbCl₅, AS AN EFFICIENT HETEROGENEOUS CATALYST. J TAIBAH UNI SCI 2014; 8 (4): 323-330. DOI: 10.1016/j.jtusci.2014.01.007

SAFARI J, KHALILI SD, BANITABA SH. THREE-COMPONENT, ONE-POT SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLES CATALYZED BY TiCl₄-SiO₂ UNDER CONVENTIONAL HEATING CONDITIONS OR MICROWAVE IRRADIATION. SYN COMMUNICATIONS 2011; 41 (16): 2359-2373. DOI: 10.1080/00397911.2010.502994


MAHALAKSHMI CM, KARTHICK M, SHANMUGAM...


