

Comprehensive Review of Tri- and Tetra-Substituted Imidazoles and Their Therapeutic Applications

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Abstract. The term “tri- and tetra-substituted imidazole’s” refers to a noteworthy class of heterocyclic compounds that occupy a central position in modern chemistry due to their remarkable structural flexibility and diverse pharmacological profiles. In recent years, the imidazole core and its derivatives have attracted significant attention because of their occurrence in numerous pharmaceutical agents and their therapeutic potential against a wide range of diseases. Moreover, this fundamental scaffold is found in several natural products, including the essential amino acid L-histidine and its derivatives, which exhibit notable pharmacological activities.

In this review, we present a detailed account of the historical advancement in the production of imidazole’s with three and four substituents via the Radziszewski reaction a well-known condensation process involving an aldehyde, an α -dicarbonyl compound, and two equivalents of ammonia. Additionally, we discuss the various synthetic methodologies and biological applications described in the literature, with special emphasis on their bacteriological assessments.

Keywords: Tri- and Tetra-substituted imidazole’s, Heterocyclic reaction, Therapeutic applications

1 Introduction

For more than two decades, green chemistry has served as a guiding paradigm enabling chemists and chemical engineers to make significant contributions to global sustainability [1]. This discipline focuses on the design of chemical processes and reactions that minimize or eliminate the use and formation of hazardous substances. It promotes the development of safer feedstocks and environmentally benign methodologies that mitigate risks to both human health and the ecosystem [2].

Beyond the boundaries of research laboratories, the principles of green chemistry have had a major influence on industry, education, environmental policy, and public awareness [3]. The ultimate goal of green chemistry is to confront environmental challenges by re-evaluating, redesigning, and re-inventing the scientific approaches used to produce, transform, and apply chemical substances thus improving efficiency and productivity while reducing waste and pollution [4]. To achieve these objectives, the concepts of atom economy and energy efficiency are central, together with the use of renewable and non-toxic raw materials. Within this framework, catalysis plays a crucial role by lowering energy requirements and minimizing waste generation. Another key aspect involves the design of degradable and non-toxic products, thereby reducing both environmental and occupational hazards associated with industrial processes [5,6].

Among the various eco-friendly strategies, solvent-free reactions have gained prominence as sustainable alternatives to conventional solvent-based organic synthesis. These methods offer several advantages, including shorter reaction times often completed within minutes higher yields, and greater product purity, often eliminating the need for labor-intensive purification steps such as chromatography. Additionally, they require simpler experimental setups, making them both practical and environmentally sustainable [7,8].

In recent years, research on heterocyclic compounds, particularly those containing nitrogen atoms, has intensified due to their broad range of biological and pharmacological applications. Indeed, nitrogen-containing heterocycles are found in more than 90% of newly developed pharmaceuticals, underscoring their crucial role at the intersection of chemistry and biology [9,10]. These compounds exhibit diverse biological activities, including antifungal, anti-inflammatory, antibacterial, anti-allergic, and other therapeutic effects.

Among these, imidazoles constitute a particularly significant class of nitrogen-containing heterocycles, forming the core structure of numerous natural products and pharmacologically active compounds [11]. Due to their remarkable structural adaptability and broad spectrum of biological activities, imidazoles hold a key position in both heterocyclic and medicinal

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chemistry [12]. Their distinctive electronic characteristics and reactivity make them valuable scaffolds for the design and development of new therapeutic agents. Imidazole derivatives exhibit a wide range of pharmacological effects, including antibacterial, anticancer, antifungal, analgesic, antitubercular, and anti-HIV activities [13].

Furthermore, multicomponent reactions (MCRs) have emerged as efficient and sustainable methodologies for constructing complex heterocyclic frameworks. These reactions combine several substrates in a single synthetic operation, leading to products that incorporate nearly all the atoms of the reactants, thus minimizing by-product formation. Their one-pot nature, eco-friendly character, and synthetic efficiency have made MCRs a highly attractive approach in organic synthesis and drug discovery [14].

This review focuses on the synthetic methodologies developed for the preparation of tri- and tetra-substituted imidazole's from a variety of precursors, such as benzil, Phenanthrene-9,10-dione, isatin, and acenaphthenequinone, outlining their evolution from the earliest reports to the most recent advancements. It also highlights the different synthetic strategies documented in the literature and evaluates their relative efficiencies. Historically, imidazole was first synthesized through the reaction of ammonia with glyoxal, producing imidazole as the main product. Although the mechanism of this transformation remained uncertain for many years, one proposed pathway suggested that a molecule of glyoxal decomposes into formic acid and formaldehyde, the latter subsequently reacting to form the imidazole ring [15] (Fig. 1).

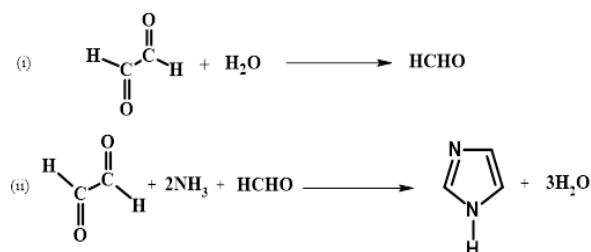


Fig. 1.

2 Principal Synthetic Methods

Debus et al [16]. Were the first to prepare tri-substituted imidazole's in 1858 by reacting ammonia with glyoxal and formaldehyde, resulting in the formation of imidazole, as shown in (Fig. 2) below.

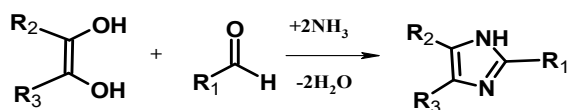


Fig. 2.

Radiszewski et al [17]. Almost a century later, reported the formation of triphenyl imidazole obtained through the Benzil condensation derivatives such as dicarbonyl or glyoxal compounds with benzaldehyde or α -keto

aldehydes in the presence of two molecules ammonia, as illustrated in (Fig. 3).

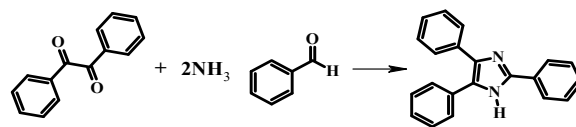


Fig. 3.

Bourissou et al [18]. Subsequently synthesized 1-substituted-aryl-diphenylimidazoles by reacting primary amines, benzonitrile, and benzil on silica gel under solvent-free conditions, using microwave irradiation, as shown in (Fig. 4).

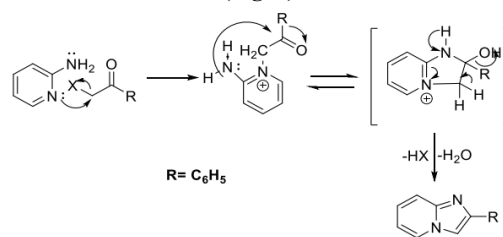


Fig. 4.

► The mechanism involved in the formation of tri-substituted imidazole's

Banothu et al [19]. Described the mechanism of the Radziszewski reaction leading to the synthesis of tri-substituted imidazole's, as illustrated in (Fig. 5).

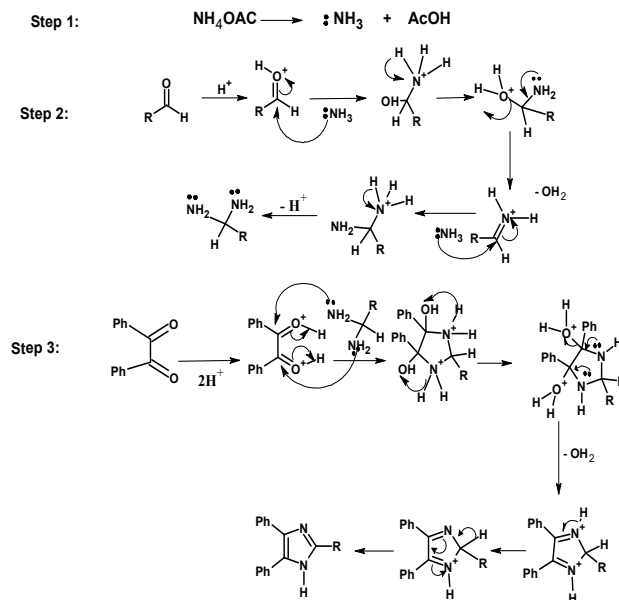


Fig. 5.

Safari et al [20]. Successfully synthesized tri-substituted imidazole's in excellent yields under solvent-free conditions through the condensation of benzil, NH_4OAc , and various aldehydes, using $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ as an efficient catalyst under microwave irradiation, as shown in (Fig. 6).

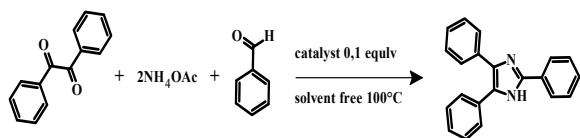
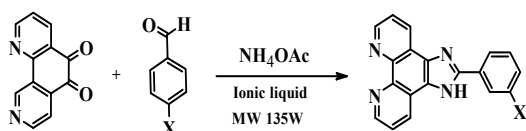


Fig. 6.

3 Development of tri- and tetra-substituted imidazole derivatives using microwave-assisted methods.

Qasim et al [21]. Prepared Phenylimidazo phenanthroline via a three-component reaction of various aldehydes, NH_4OAc , and 1,10-phenanthroline-dione, using $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ as a non-hazardous and cost-effective catalyst, achieving excellent isolated yields at room temperature, as shown in (Fig. 7).



X = H; 4-Cl; 4-F; 2- NO_2 ; 3- NO_2 ; 4- NO_2 ; 2-OH; 4-OH; 4-OMe; 2,4,6-OMe; 4-CN; 4-N(Me)₂

Fig. 7.

Nalage et al [22]. Synthesized tri-aryl-imidazole's in excellent yields under microwave irradiation using polyethylene glycol as a medium, through the condensation of NH_4OAc , benzil, and isovanillin, as illustrated in (Fig. 8).

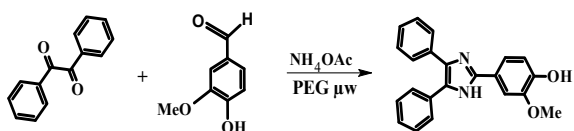


Fig. 8.

Wahyuningrum et al [23]. synthesized 4,5-disubstituted imidazole's under MAOS conditions by reacting diketones with NH_4OAc and various aldehydes or ketones in glacial acetic acid, using microwave-assisted methods, as shown in (Fig. 9).

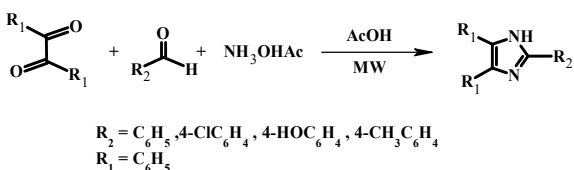


Fig. 9.

Sparks et al [24]. Prepared tri-substituted imidazole's by reacting keto-oximes with aldehydes and NH_4OAc in AcOH under microwave irradiation, achieving N-hydroxy imidazole's in excellent yields through

cyclization at approximately 200 °C within 20 minutes, as depicted in (Fig. 10).

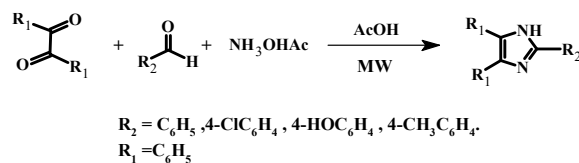


Fig. 10.

4 Other strategies for creating imidazole's that are tri- or tetra-substituted include:

This review focuses on highlighting different strategies for the production of imidazole's with three and four substituents. As a result, Many research teams have been working hard to create imidazole derivatives and investigate their diverse pharmacological properties.

Shaterian and Runge et al [25]. Using the Brønsted acidic ionic liquid N-methyl-two-pyrrolidonium hydrogen sulfate as an efficient catalyst, three- and four-substituted imidazole's were synthesized under solvent-free conditions with excellent yields (Fig. 11).

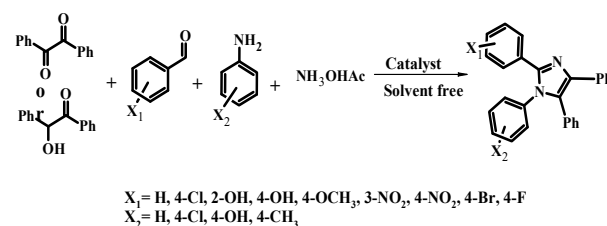


Fig. 11.

Mohamed Afzal et al [26]. Prepared the synthesis of tri-phenyl-2-substituted imidazole's Through the condensation of different aldehydes, aniline, benzoin, and NH_4OAc employing p-toluene sulfonic acid as an efficient catalyst in ethanol under reflux. This approach is simple, rapid, and affords excellent yields, as shown in (Fig. 12).

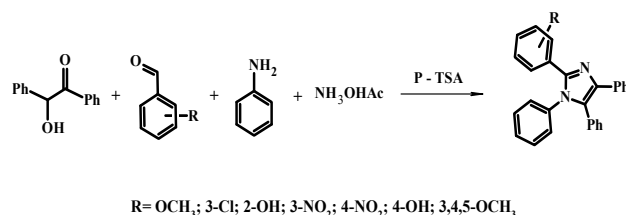


Fig. 12.

Majid M. Heravi et al [27]. Synthesized tri-phenyl imidazoles in excellent yields through the condensation of ammonium acetate and benzil with aldehydes, using a catalytic amount of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ in ethanol under reflux, as illustrated in (Fig. 13).

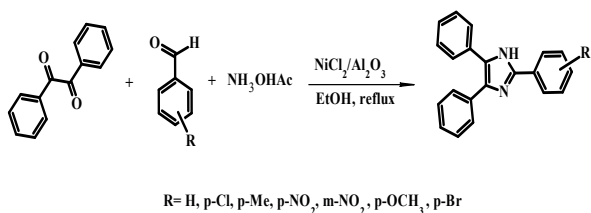


Fig. 13.

Saikat Das Sharma et al [28]. Described the synthesis of three- and four-substituted imidazoles in excellent yields at room temperature, achieved by reacting benzil and NH₄OAc, with benzaldehydes using InCl₃·3H₂O as a catalyst, as shown in (Fig. 14).

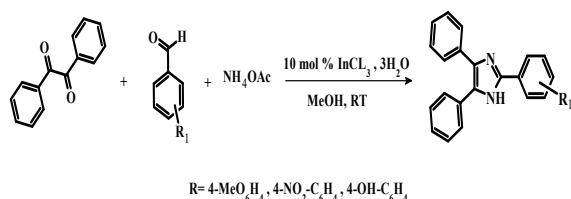


Fig. 14.

Bahareh et al [29]. Prepared tetra-substituted imidazole's via a one-step reaction of benzil, aromatic aldehydes, amines, and NH₄OAc, in the presence (BF₃·SiO₂) silica-supported boron trifluoride as a reusable and economical catalyst. The procedure is straightforward, rapid, efficient, and provides excellent yields, as shown in (Fig. 15).

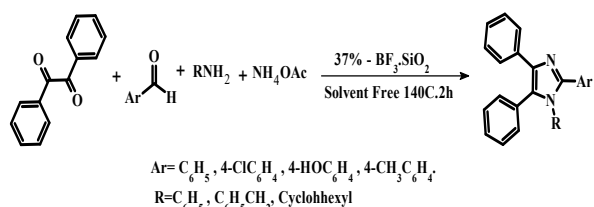


Fig. 15.

Ratnadeep S. Joshi et al [30]. Synthesized 2-aryl-diphenylimidazoles by refluxing benzoin or benzil with ammonium acetate and various aldehydes in ethanol for 40–90 minutes under mild conditions. This simple and efficient method, using potassium dihydrogen phosphate (KH₂PO₄) as a catalyst, afforded excellent yields, as illustrated in (Fig. 16).

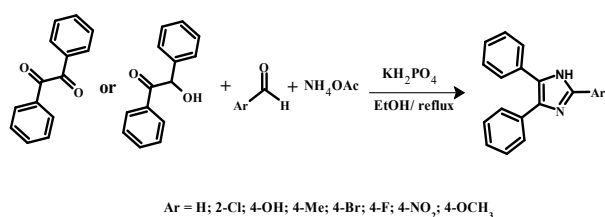


Fig. 16.

Sadia Naureen et al [31]. Synthesized indole-based tetra-arylimidazoles by refluxing anilines, 2-Phenyl-1H-indole-3-carbaldehyde, NH₄OAc and benzil in the

presence of acetic acid. The resulting compounds exhibited antioxidant and anti-urease activities, as illustrated in (Fig. 17).

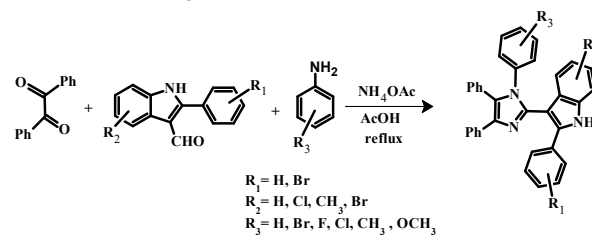


Fig. 17.

Swati D. Burungale et al [32]. Prepared 1-substituted-tri-phenylimidazoles by reacting acid chlorides with triphenyl imidazole in the presence of pyridine as a catalyst and benzene as the solvent, refluxing for 5 hours. The products were then dried, recrystallized from ethanol, and obtained in good yields, as shown in (Fig. 18).

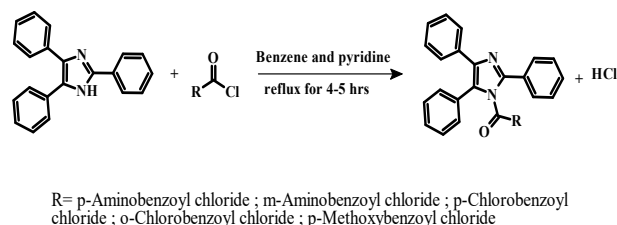


Fig. 18.

Maleki et al [33]. Prepared 2-substituted-diphenylimidazoles by refluxing benzil or benzoin with aldehydes and NH₄OAc in ethanol, employing urea hydrogen peroxide (UHP) as a catalyst, which afforded high yields, as shown in (Fig. 19).

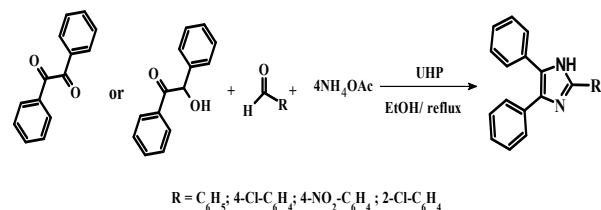


Fig. 19.

Gharib et al [34]. Performed a multicomponent synthesis of three- or four-substituted 1H-imidazole derivatives by condensing benzil or benzoin, benzaldehydes, and NH₄OAc in the presence of silica-supported heteropoly acid as a catalyst under reflux, obtaining excellent yields, as shown in (Fig. 20).

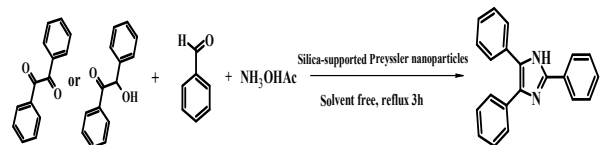


Fig. 20.

A.M. Vijesh et al [35]. Synthesized trisubstituted imidazole's by refluxing 2-diketones and NH_4OAc with aryl-pyrazole-carbaldehyde in glacial AcOH , achieving good yields, as illustrated in (Fig. 21).

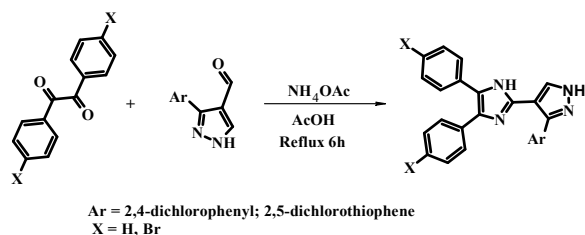


Fig. 21.

Harshad et al [36]. Synthesized novel derivatives of tri-substituted imidazole (C) via the well-established Radziszewski reaction by refluxing various 1H-pyrazole-substituted-4-carbaldehyde (B) with benzil (A) and NH_4OAc in glacial $\text{CH}_3\text{-CO-OH}$ achieving good to excellent yields, as shown in (Fig. 22).

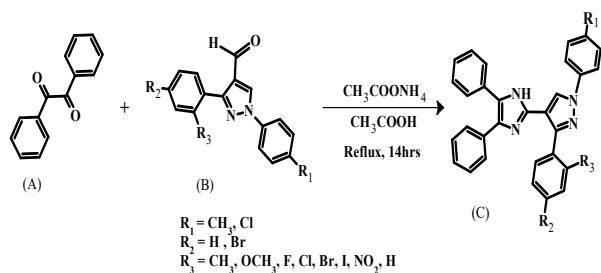


Fig. 22.

S. Amala et al [37]. employed the Radziszewski reaction to synthesize triphenyl-imidazole-1-(chloromethylpyridine) derivatives. The trisubstituted 1H-imidazole was reacted with 2-chloro-6-methylpyridine in ethanol using anhydrous potassium carbonate, stirred at low temperature for 6 hours, yielding good results, as shown in (Fig. 23).

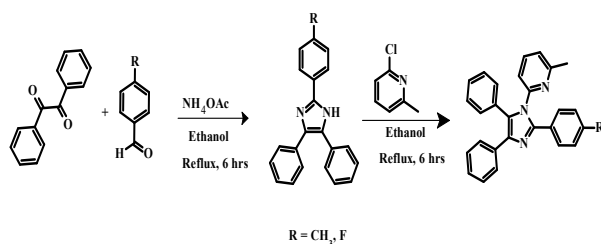


Fig. 23.

Nipate et al [38]. Prepared dihydroimidazo-indoles involved isatin, aldehydes, and NH_4OAc in a H_2O - EtOH mixture under reflux, using β -cyclodextrin (β -CD) as an efficient catalyst. achieving high yields in a short reaction time. This approach is economical, non-toxic, eco-friendly, and employs readily accessible starting materials, as shown in (Fig. 24).

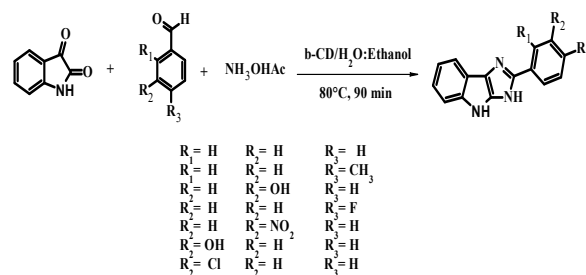


Fig. 24.

Raza Sandroos et al [39]. Reported a novel and efficient synthesis of aryl-H-acenaphtho-imidazole's, achieving excellent yields under reflux. The reaction involved substituted aldehydes, NH_4OAc , acenaphthylene-1,2-dione, and acidic hydrogen sulfate in EtOH , as illustrated in (Fig. 25).

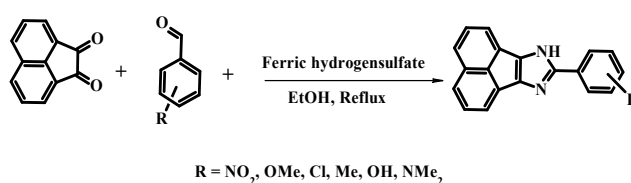


Fig. 25.

Steck and Day et al [40]. Prepared 4-(phenanthroimidazol-2-yl) benzaldehyde by reacting phenanthrenequinone with terephthalaldehyde and NH_4OAc in AcOH acid, obtaining excellent yields, as illustrated in (Fig. 26).

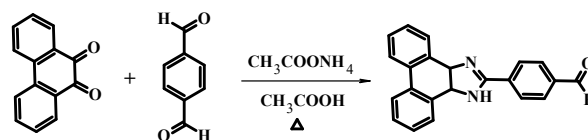


Fig. 26.

Jayaraman et al [41]. prepared 2-(bromostyryl)-1-(naphthalen-1-yl)-phenanthroimidazoles by refluxing phenanthrenequinone, trans-4-Bromocinnamaldehyde, naphthylamine, and NH_4OAc in acetic acid or EtOH for about 15 hours, as illustrated in (Fig. 27).

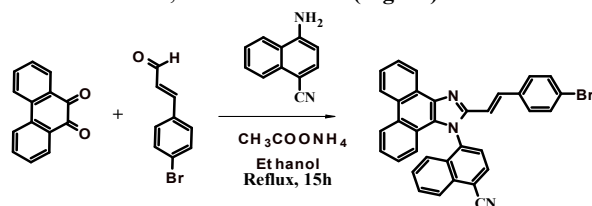


Fig. 27.

Singh et al [42]. Synthesized a novel compound, 2-(7-phenyl-acenaphthoimidazoles-8-yl)phenol, in 64% yields via the condensation of aniline,

acenaphthoquinone, and salicylaldehyde with NH_4OAc in glacial acetic acid, as shown in (Fig. 28).

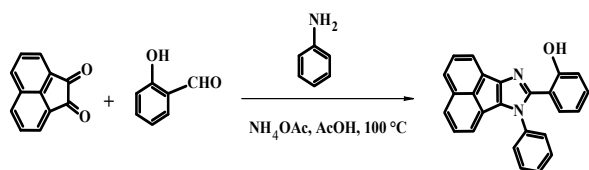
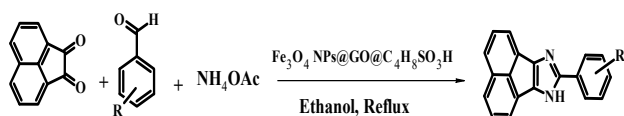


Fig. 28.

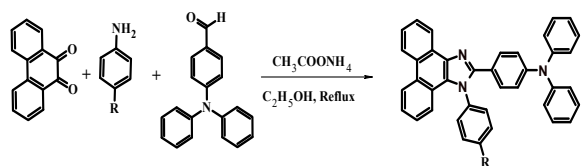
Hasanzadeh et al [43]. Prepared 8-aryl-acenaphthoimidazole's using Fe_3O_4 NPs@GO@ $\text{C}_4\text{H}_8\text{SO}_3\text{H}$ as a magnetic nano catalyst. The reaction of acenaphthene quinone with NH_4OAc in EtOH under reflux provided the products in high yields, as illustrated in (Fig. 29).



$\text{R} = 3\text{-NO}_2, 3\text{-OH}; 4\text{-Me}; 4\text{-Br}; 4\text{-F}; \text{H}; 2\text{-OH}; 2\text{-OH-3-OMe}; 2\text{-OMe}; 2,6\text{-Cl}_2$.

Fig. 29.

H. Peng et al [44]. Synthesized a novel compound (R-PPIM-TPA), with $\text{R} = \text{CH}_3, \text{Cl}$, or $\text{C}(\text{Me}_3)_3$, through the reaction of phenanthrenequinone, 4-(two-phenylamino) benzaldehyde, substituted anilines, and NH_4OAc in EtOH for 8 hours at 100°C , as illustrated in (Fig. 30).



$\text{R} = \text{CH}_3, \text{Cl}, \text{C}(\text{CH}_3)_3$

Fig. 30.

5 Pharmacological activities for Tri-substituted Imidazoles

5.1 Anticancer activity

Cancer is a disease marked by the uncontrolled growth of abnormal cells that can invade and damage healthy tissues, making it one of the leading causes of death globally. Imidazole and its derivatives have been extensively studied for their pharmacological properties, especially as potential anticancer agents. Numerous investigations have demonstrated the significant anticancer potential of imidazole-based compounds.

Shujian Hu et al [45]. Phenanthroline 1H-imidazole [4,5-f][1,10] has emerged as a promising compound in cancer therapy. Mr. Shujian Hu and his team synthesized a novel derivative, designated IPM714, which exhibited selective inhibitory activity against colorectal cancer (CRC) cells. The compound showed potent cytotoxic effects with IC_{50} values of $1.74\ \mu\text{M}$ and $2.00\ \mu\text{M}$ in HCT116 and SW480 cell lines, respectively. These findings suggest that IPM714 holds significant potential as a therapeutic agent for the treatment of colorectal cancer (Fig. 31).

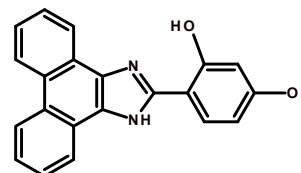
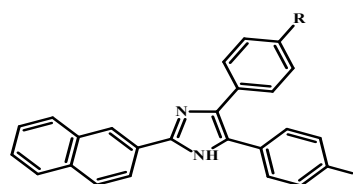


Fig. 31.

5.2 Antioxidant Activity

Bsomashekara et al [46]. Prepared a series of tri-substituted imidazole derivatives containing naphthalene rings via a multicomponent reaction in a single pot. The resulting compounds were evaluated in vitro for their antioxidant potential using the DPPH assay and for their α -amylase inhibitory activity via the DNS method. Among them, the synthesized derivatives displayed noteworthy antioxidant (Fig. 32).

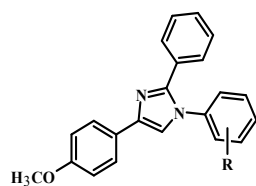


$\text{R} = \text{H}, \text{CH}_3, \text{OCH}_3, \text{Br}$

Fig. 32.

5.3 Antifungal Activities

Husain et al [47]. Developed a series of imidazole derivatives, specifically tri-substituted-1H-imidazoles, aiming to design dual-action molecules with both anti-inflammatory and antifungal properties. The produced substances' biological activity was assessed in vitro. Notably, one compound demonstrated strong anti-inflammatory effects accompanied by minimal gastrointestinal irritation. It also exhibited significant analgesic activity, providing notable protection in the saline torsion test, with indomethacin serving as the reference drug. Furthermore, antifungal screening revealed potent activity against the tested fungal strains, having a $12.5\ \mu\text{g/mL}$ the (MIC) minimum inhibitory concentration. Overall, this compound emerged as a promising lead candidate, combining effective anti-inflammatory and antifungal activities with a favorable safety profile (Fig. 33).

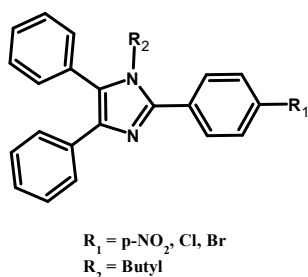


R = H, 2-Cl, 3-Cl, 4Cl, 4-F, 2-NO₂, 3-NO₂, 4-NO₂, 2-OH, 3-OH, 4-OH, 4-OCH₃

Fig. 33.

5.4 Antibacterial Activity

Abhishek K. Jain et al [48]. Prepared a series of 2-substituted-two-phenyl-N-alkyl imidazole derivatives and assessed their antibacterial activity. The compounds showed inhibitory effects against *Staphylococcus aureus* (3–9 mm inhibition zones), *Bacillus subtilis* (4 at 8 mm), and *Escherichia coli* (5 at 12 mm), demonstrating significant antibacterial potential across the tested strains. However, further structural modifications are recommended to enhance the antibacterial efficacy of the 2-substituted-two-phenyl-N-alkyl imidazole scaffold (Fig. 34).

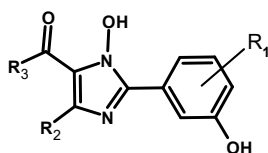


R₁ = p-NO₂, Cl, Br
 R₂ = Butyl

Fig. 34.

5.5 Antiviral activity

P. A. Nikitina et al [49]. Prepared a number of 2-(2-hydroxyphenyl) imidazole derivatives and assessed how well they worked against the vaccinia virus in Vero cell cultures. Among these, some 1-hydroxyimidazole compounds demonstrated discernible inhibitory effects and indicated interesting antiviral potential. (Fig. 35).



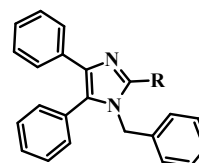
R₁ = H, Cl, Br
 R₂ = Me, Ph
 R = Me, OEt, NHPH

Fig. 35.

5.6 Analgesic Activity

Uçucu et al [50]. Prepared a series of 1-benzyl-2-substituted-two-phenyl-1H-imidazole derivatives and

evaluated their analgesic activity using two experimental models. Most of the compounds exhibited moderate analgesic effects in mice at a dose of 100 mg/kg (i.p.), while several derivatives showed potent activity comparable to morphine at 1 mg/kg (i.p.). Importantly, none of the tested compounds displayed any signs of toxicity at the administered doses, as illustrated in (Fig. 36).



R = H, CH₃, Ph, Ph-o-OH, Ph-m-OCH₃

Fig. 36.

5.7 Conclusion

Based on the findings of this review, tri- and tetra-substituted imidazole derivatives represent a prominent class of compounds in the ongoing quest for bioactive molecules, thereby expanding the repertoire of tools available to modern synthetic chemists. A comprehensive analysis of the literature highlights their notable biological potential and the accessibility of their synthetic pathways, which have garnered considerable attention from chemists, pharmacologists, and researchers alike. In recent years, these therapeutically active imidazole frameworks have been extensively utilized in the creation of diverse pharmacologically significant agents. Considering current research trends, it can be inferred that imidazole scaffolds hold substantial promise for future investigations, offering valuable opportunities for the creation and production of new derivatives with broad biological potential.

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