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Review article

Pharmacophore-based SAR Analysis and Synthetic Route Review of Imidazole Core Analogues

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Abstract

The five-membered nitrogen-containing heterocyclic moiety imidazole forms part of molecules that have been used to treat various diseases including life-threatening cancer. Moreover, the imidazole moiety is naturally present in various plants, marine, and microorganism-based metabolites and possesses various medicinal benefits. In this review, the pharmacophore-based substitution effect on the imidazole skeleton is primely compiled. A plethora of synthetic approaches have been adopted to develop imidazole hybrids, a number of which have been used as a basic skeleton for synthesizing other fused hybrids. Second, various recent synthetic methods, both *in vitro* and *in vivo* activities, are reviewed. Pharmacophoric examination showed that imidazole acts as a ring aromatic, or hydrophobic center depending on the type of substitution. While substitution with benzene ring, it acts only as a hydrogen bond donor and substitution with a hydrophobic ring and an aliphatic long chain on the imidazole ring leads to anticonvulsant and anti-inflammatory activity. The substitution of various electron-sharing features increases the antiulcerogenic property as well as anticancer activity. The results of this review work suggest that fabrication with specific pharmacophoric features aids in the synthesis of selective antagonist for various diseases.

Keywords: imidazole; green synthesis; antimicrobial; anticancer; anti-inflammatory; SAR

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1. Introduction

Health problems are increasing in the modern era along with technological advancements, and the world is looking for new chemical entities that can serve as lead molecules to develop them as drugs (Gopalakrishnan et al., 2021). Medicinal chemistry plays a crucial role in various phases of drug discovery, and the current multidisciplinary approach makes chemists medicinal chemists. The synthesis of new molecules and development of compound libraries is always a trending field that progressively cherishes into an interdisciplinary field. Heterocyclic chemistry primarily nitrogen based heterocyclic compounds are renowned for its diversified clinical applications (Bhatnagar et al., 2011).

Imidazole is a five-membered nitrogen-based heterocyclic skeleton and one of the most studied moieties for its role in medicinal and combinatorial chemistry (Irfan et al., 2023). Naturally, imidazole moiety is present in amino acids (histidine), vitamins (Vitamins B7 and B12), neurotransmitters (histamine), alkaloids (pilocarpine, theophylline), and marine alkaloids (oroidin, hymenialdisine and dispacamide). A wide variety of chemical hybrids have been reported in the recent literature, and a few of them are clinically essential to treat various diseases (Gueiffier et al., 1998). Imidazole-based antifungal agents such as ketoconazole and clotrimazole are common in the market. Antihypertensive (clonidine), anxiolytics (alpidem), anti-sedative agents (flumazenil), antibiotics (metronidazole), anticancer agents (methotrexate), anti-ulcer agents (omeprazole), anthelminthic (albendazole) are a few examples that parades the importance of the imidazole and fused imidazole rings in drug discovery (Alghamdi et al., 2021; Shrivastava et al., 2013; Liu et al., 2014).

Imidazole (1,3-diazole) is amphoteric, contains two non-adjacent nitrogen atoms, and can exist in two tautomeric forms. The lone pairs on the nitrogen in the imidazole ring contain different dissociation constants (Vessally et al., 2017). This planar structure is convenient for electrophilic and nucleophilic reactions and makes the imidazole form 2-substituted and trisubstituted analogs (Lombardino & Lowe, 2004). However, the polar nature of the imidazole ring renders its oral absorption and bioavailability, fusing with other non-polar skeletons, resulting in the development of various pharmacophores that address current clinical needs. Different synthetic approaches have been reported for the imidazole hybrids and can be applicable in agrochemicals, solar cells, optics, dyes, and catalysis (Romero et al., 2014; Skoĉibusic et al., 2018). This work compiled all data of synthesis and the related pharmacophoric-based activity relationships for the development of safe and potent imidazole ring-containing molecules.

2. Biological Applications of Imidazole Derivatives

The 5 membered imidazole moiety significantly plays a role in the binding of targets for the treatment of various diseases.

2.1 Antimicrobial activity

N-substituted imidazole oximes were reported to have potent antimicrobial activity against gram-negative bacteria (MDR). These imidazole oximes illustrated Figure 1 were synthesized by transforming imidazole-2- carbaldehyde (1) with hydroxyl amine (Bamoro et al., 2021). The 2-(benzylthio)-4,5-diphenyl-1H-imidazoles (3) were prepared from 4,5-diphenyl-1H-imidazol-2-thiol and benzyl bromide derivative by refluxing in ethyl alcohol for 3 h, as illustrated in Figure 2 The basic workup procedure yielded a series of imidazole

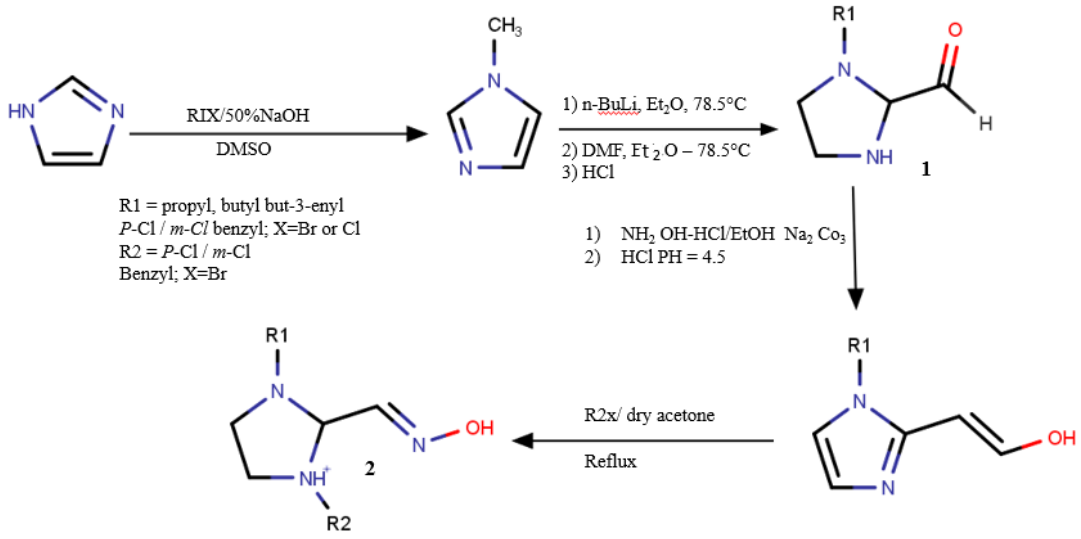


Figure 1. Antimicrobial N-substituted imidazole oximes

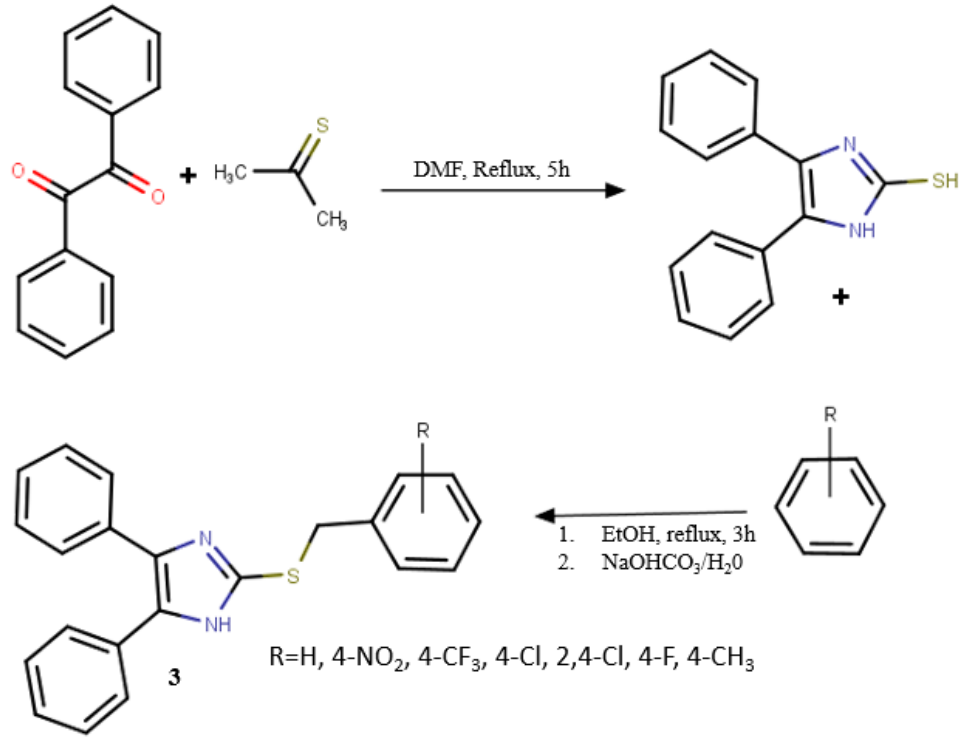


Figure 2. Antimicrobial 2-(benzylthio)-4,5-diphenyl-1H-imidazoles

derivatives, and they were evaluated against various gram-positive and gram-negative bacteria using the liquid dilution method, taking ciprofloxacin as a reference standard (Khabnadideh et al., 2003).

The alkylated imidazoles produced by the condensation of unsubstituted imidazoles with alkyl bromides with phase transfer catalysts as shown in Figure 3 were screened against *Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* using the disc diffusion method and were found to effectively inhibit bacterial growth compared to the standards (de Araújo et al., 2019).

The 4-phenyl-2-ureaimidazoles molecules (5&6) were synthesized by taking 1,1'-carbonyldiimidazole as a starting material (Figure 4). They were then screened for inhibition activity. All the derivatives showed significant antitrypanosomal activity and could be studied further to apply them to Chagas disease (Ganguly et al., 2011).

The 1-(3'-chloroacetonyl)-2-methyl-4-nitroimidazole was refluxed with aromatic amines in the presence of triethylamine in DMF for 5 h to produce 1-(2-methyl-4-nitro-imidazol-1-yl)-3-arylamino-propan-2-one, and their antibacterial activity against *Escherichia coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* were reported. In addition, its anti-HIV activity was assessed using the HIV-1 RT RNA dependent DNA polymerase activity assay (Ganguly et al., 2011; Mariappan et al., 2012). The pharmacophoric features of four FDA approved antimicrobial drugs shown in Figure 5 illustrated the four different features responsible for the antibacterial activity of metronidazole. The imidazole core ring possibly changes its nature depending on the environment of the binding place such as a nature of an aromatic ring or a hydrogen bond acceptor (amine group).

The three bulky aromatic groups present on the imidazole ring system in the clotrimazole drug active against various skin diseases caused by fungi due to the hydrophobic binding with the proteins of the fungi. Moreover, the elongation of nitrogen position of imidazole with different aromatic ring systems indicated broad-spectrum activity especially against various skin diseases. The substitution of different chains in 3 carbon and one nitrogen atom of imidazole core produced antiviral drugs such as capravirin (Bolla et al., 2019).

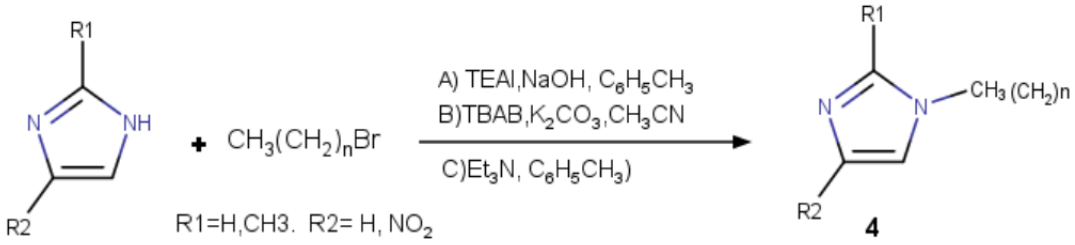


Figure 3. Antimicrobial active alkylated imidazole molecule

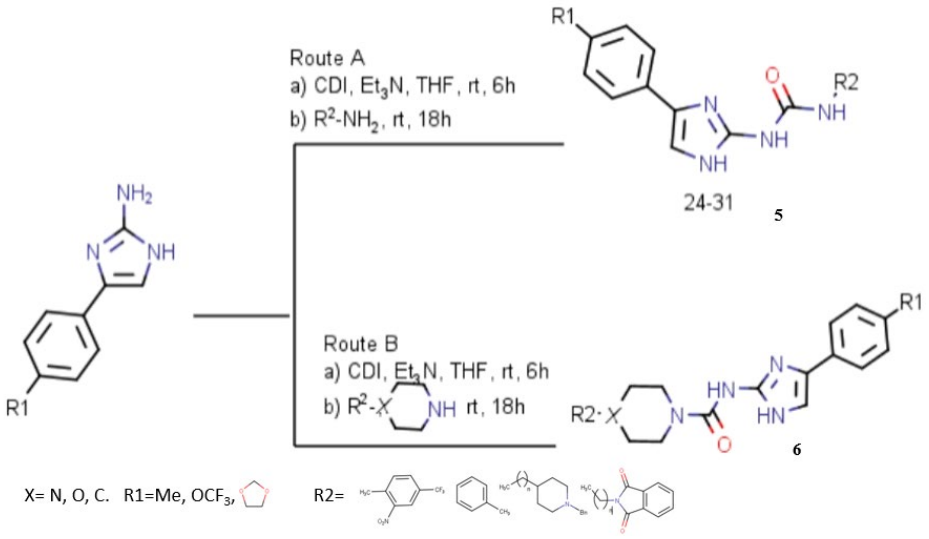


Figure 4. Anti-trypanosomal active urea imidazoles

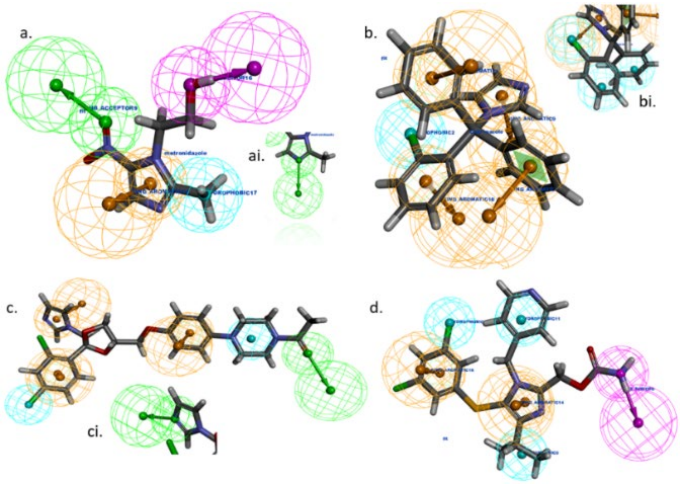


Figure 5. Pharmacophoric features of FDA-approved antimicrobial agents.
a. Metronidazole. b. Clotrimazole. c. Ketoconazole. d. Capravirin.
(ai and ci are acceptor features of imidazole. bi. is the hydrophobic benzene ring feature.)

2.2 Anti-epileptic activity

Marzouk et al. (2020) designed 25 multi-substituted imidazoline compounds and evaluated the anticonvulsant activity by in silico. The results of in silco study confirmed that the molecules 7-9 (Figure 6) exhibited statistically significant results. These 3 compounds were synthesised and *in vivo* activity was performed. Among the three, molecule 8 possessed a higher electroshock-induced convulsion activity of 103.33±1.79 sec compared to other molecules.

Some of the imidazole derivatives (10) were synthesized by the catalytic efficiency of the ionic liquid, diethyl ammonium hydrogen sulphate (DEAHS). Condensation of three reactants (Dione, aldehyde and amine) forms various imidazole derivatives in the solvent-free environment (Figure 7). The prepared hybrids were found to exhibit *in vivo* anticonvulsant activity in two models, namely, PTZ and MES-induced seizures in rodents (Bastaki et al., 2018).

The SAR of two FDA-approved imidazole rings containing anticonvulsant activity was examined and the structures of the substituted groups are illustrated in Figure 8. It shows that the hydrophobic center and aromatic ring structures are necessary for anticonvulsant activity. The nifamidaone drug is substituted with a naphthalene ring which acts as a hydrophobic center as well as ring aromatic depending on the binding cavity nature of the target disease protein (Figure 8a). The azepine ring fused onto imidazole ring acts as a ring aromatic and an aliphatic chain moiety increasing the potency of the drug (Figure 8b).

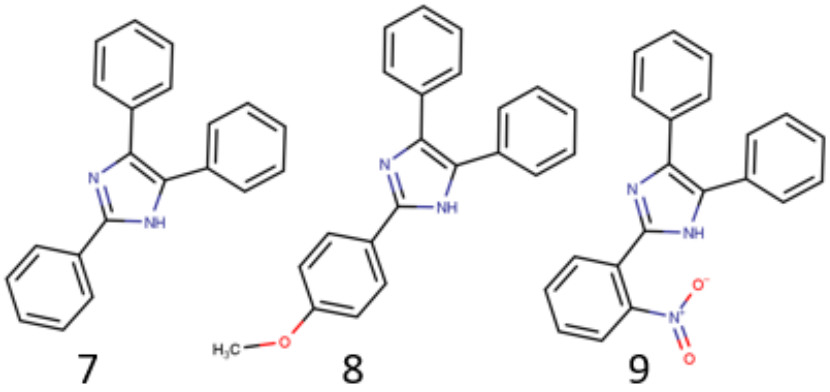


Figure 6. Anti-epileptic 2-substituted-4,5-diphenyl imidazole derivatives

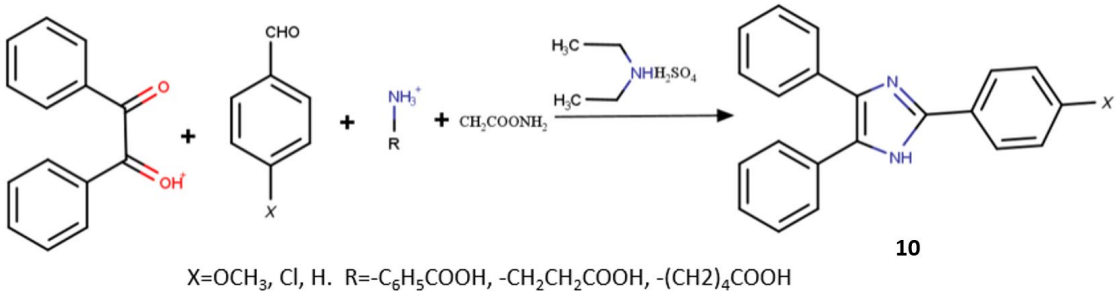


Figure 7. Anti-convulsant imidazole hybrids

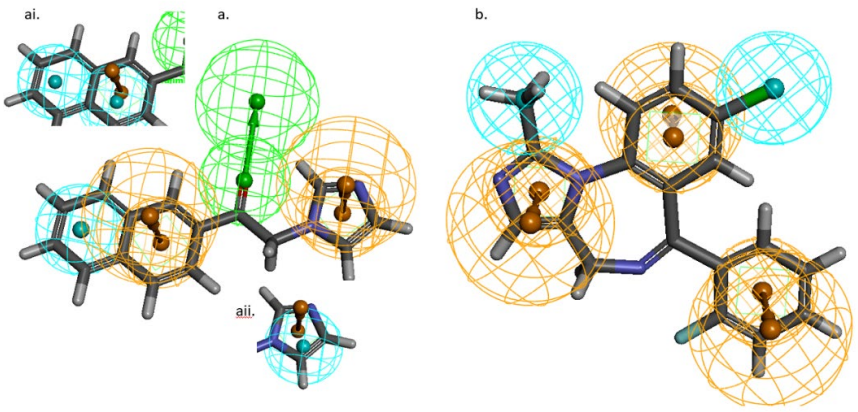


Figure 8. Pharmacophoric features of FDA approved anticonvulsant agents
a. Nifamidone b. Midazolam
ai. Hydrophobic feature of naphthalin ring system of Nifamidone.
aii. Hydrophobic feature of imidazole

2.3 Anti-inflammatory activity

Mono-substituted 2,4,5-triphenyl imidazole derivatives were synthesized by condensing the 2,4,5-triphenyl imidazole with acid chloride using pyridine (11), as illustrated in Figure 9. These derivatives were screened for anti-inflammatory activity using the carrageenan-induced rat paw edema model, and the treatment was found effective in reducing the edema volume in rodents under given conditions (Nascimento et al., 2018).

Tetrasubstituted imidazoles were synthesized by condensing methyl 3-phenyl-2H-azirine-2-acetate, aromatic aldehydes, and amines in the presence of propane-2-ol at room temperature. These derivatives were evaluated for *in vitro* and *in vivo* anti-inflammatory activities. The results showed that the molecules exhibited significant anti-inflammatory activity, working through the inhibition of p65 NF-kB translocation to the nucleus. Furthermore, these molecules (12, 19) depicted in Figure 10 were found to suppress pro-inflammatory mediators (Sharma et al., 2021).

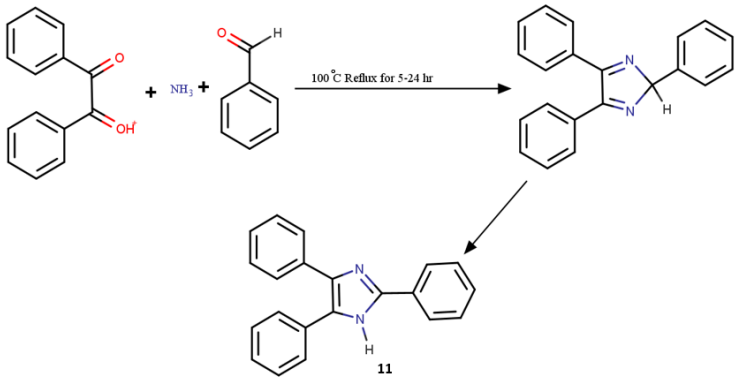


Figure 9. Anti-inflammatory imidazole derivatives

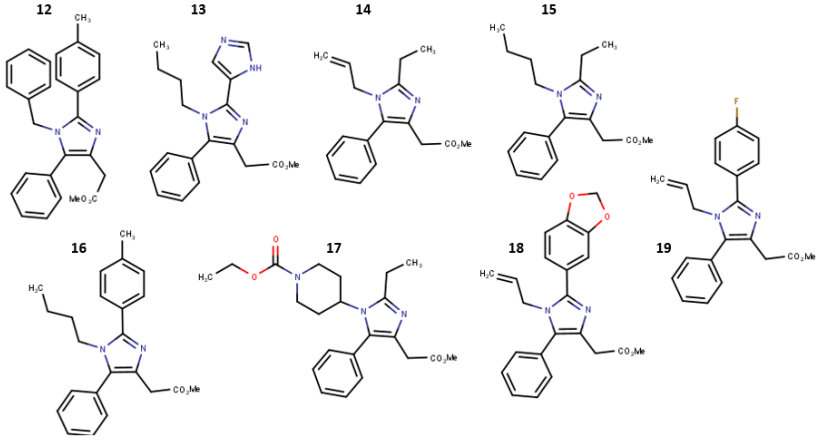


Figure 10. Anti-inflammatory tetrasubstituted imidazole derivatives

Molecule 19 showed the inhibition of proinflammatory cytokines. Specifically, it showed TNF-α inhibition of 57.0±3.2% and IL-6 inhibition of 63.0±2.5% in mice. The inhibition of p65 NF-κB by the tetra substituted molecule 19 was found to be 69.9±6.1% compared to the standard dexamethasone. Dexmedetomidine is one of the FDA approved anti-inflammatory agents and Figure 11 illustrates the pharmacophoric features of the molecule. It possesses three hydrophobic sites and the imidazole structure acts in dual mode such as a ring aromatic as well as a hydrogen bond donor to produce better antagonism of the COX-2 site. The presence of the CH_2 group extension in the 4^{th} carbon position of imidazole made possible the racemization of the medetomidine, which then displayed additional behaviour and further toxic effects.

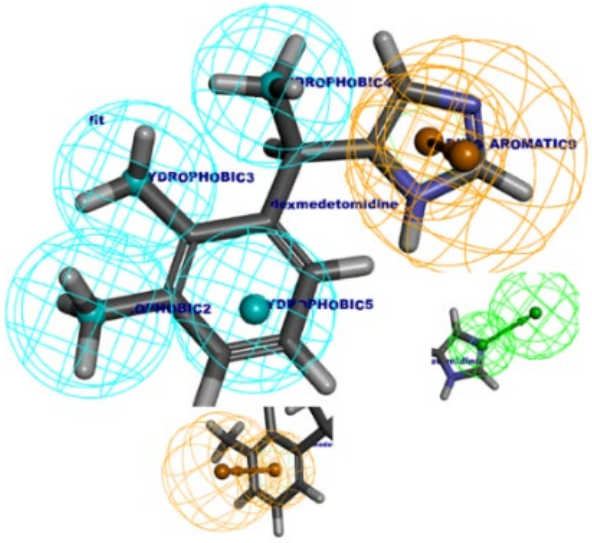


Figure 11. Pharmacophoric features of the FDA-approved anti-inflammatory imidazole ring containing agent dexmedetomidine

2.4 Anticancer activity

1-substituted-2-aryl imidazoles were synthesized by C-N coupling of the imidazole moiety prepared by the condensation of 3,4,5-trimethoxy benzaldehyde, glyoxal, and a mild base, as illustrated in Figure 12. These substituted imidazoles were evaluated for *in vitro* antiproliferation assay using cancer cell lines. These compounds also exhibited antiproliferative potential against breast cancer in the animal model (Ciaffaglione et al., 2020). SAR studies of the various R substitutions (series 1) and aromatic ring system (series 2 and 3) revealed that varying the aliphatic chain did not affect activity but the aromatic system played a vital role in cancer cell apoptosis.

Compounds with either an aliphatic or a phenyl sulfonyl group (20) attached to the nitrogen of the imidazole ring (such as 3A to 3J) had weak activity, with IC_{50} values above 100 mM. On the other hand, most of the compounds with an aromatic ring attached to the same nitrogen, such as 3K to 3Z, exhibited strong activity, with IC_{50} values in the range of 80 to 1000 nM. The most active compound was 3X, which demonstrated IC_{50} values of 90 nM, 100 nM, 200 nM, and 80 nM against four different cancer cell lines. A close examination of the structure of 3X revealed that it possessed the same 3-hydroxy-4-methoxy groups as 3Y but had an amino group instead of a hydroxy group.

Microwave irradiation was employed to synthesize aryl ethanol imidazole derivatives using a mixture of bromo ethyl benzene and imidazole in TBAB, as illustrated in Figure 13. The basic workup procedure yielded pure compounds of (21-23), and they were screened via the heme oxygenase-1 (HO-1) inhibition assay. The majority of the compounds were found to inhibit MCF-7 breast cancer cells more efficiently than the standard drug tamoxifen (Lakshmanan et al., 2010).

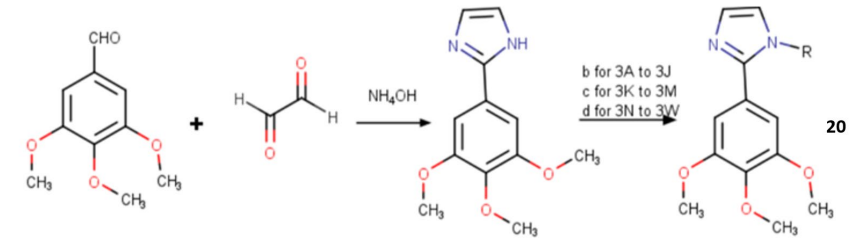
Azathioprine (Figure 14a) and dacarbazine (Figure 14b) are the FDA-approved effective chemotherapy agents. Specifically, azathioprine contains the fused imidazole and separate imidazole ring system. Four pharmacophoric features were identified in the molecule and the nitrogen atom of imidazole ring (Calderón-Arancibia et al., 2015).

The imidazole ring fused with benzene acts only as a donor, while the single imidazole ring acts as ring aromatic, and a hydrogen bond acceptor. The substitution hydrazine chain (Figure 14b) in the imidazole ring increases the hydrophobicity of the molecule dacarbazine. Also, this imidazole changes its nature, acting as donor, acceptor and ring aromatic to better orient itself inside the hydrophobic cavity of the cancer proteins (Shukla et al., 2014).

Chronic myeloid leukemia drug, nilotinib, is illustrated with the pharmacophoric feature in Figure 15. In this moiety, one of the imidazole nitrogens was substituted with an aromatic ring and extended with an amine link. Figure 15a illustrates the three features of nilotinib such as hydrophobic center, hydrogen bond acceptor and aromatic ring. Also, the effects of this system change based on the substitution in the imidazole ring system and its extension.

2.5 Anti-ulcer activity

Para-substituted phenacyl bromides were reacted at low temperatures with the imidazole moiety in DMF to produce 1-substituted imidazole derivatives (22), as illustrated in Figure 16. The synthesized derivatives were screened *in vivo* for anti-ulcer activity using a combination of indomethacin, a pylorus ligation-induced ulcer model, and an alcohol-induced ulcer model by comparing with ranitidine. From the results, it was evident that these compounds significantly reduced gastric secretions and protected against ulcers (Fang et al., 2019).



Series 1

3A: R=CH_3
3B: R=C_2H_5
3C: R=C_3H_7
3D: R=$CH(CH_3)_2$
3E: R=C_4H_9
3F: R=$CH_2CH(CH_3)_2$
3G: R=C_5H_{13}

Series 2

3H: Ar=$PhSO_2$
3I: Ar=4-CH_3PhSO_2
3J: Ar=CH_2-Phenyl
3K: Ar=4-OCH_3-3-NO_2-Phenyl
3L: Ar=5-yl-benzo[b]thiophene
3M: Ar=3-(benzyloxy)-4-OCH_3-Phenyl
3N: Ar=5-yl-1H-indole
3O: Ar=6-yl-1H-indole
3P: Ar=4-CH_3-Phenyl

Series 3

3Q: Ar=3-CH_3-Phenyl
3R: Ar=3-OCH_3-Phenyl
3S:Ar=3,5-$(OCH_3)_2$-Phenyl
3T: Ar=3-NO_2-Phenyl
3U: Ar=4-F-Phenyl
3V: Ar=4-Br-Phenyl
3W:Ar=4-OCH_3-Phenyl
3X: Ar=4-OCH_3-3-NH_2-Phenyl
3Y: Ar=4-OCH_3-3-OH-Phenyl

Figure 12. Antiproliferative activity of 1-substituted-2-aryl imidazole

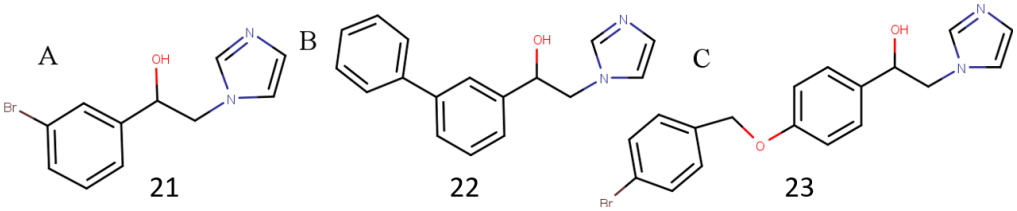


Figure 13. Cytotoxic aryl ethanol imidazole derivatives

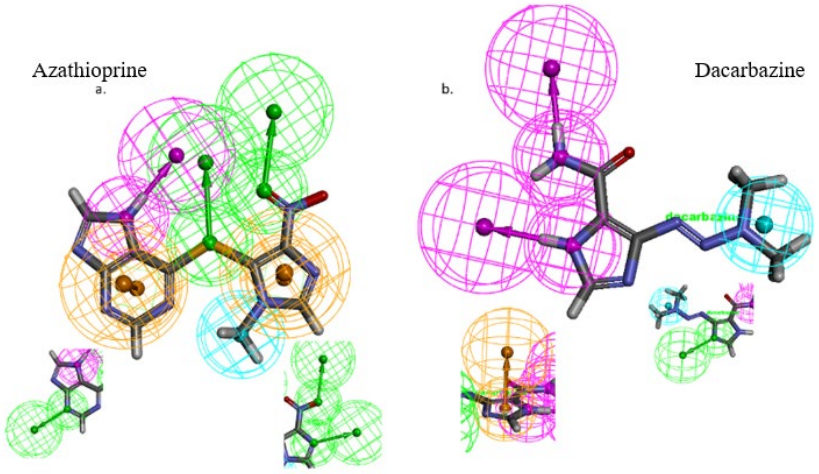


Figure 14. Pharmacophoric features of FDA anticancer agents. a. Azathioprine b. Dacarbazine

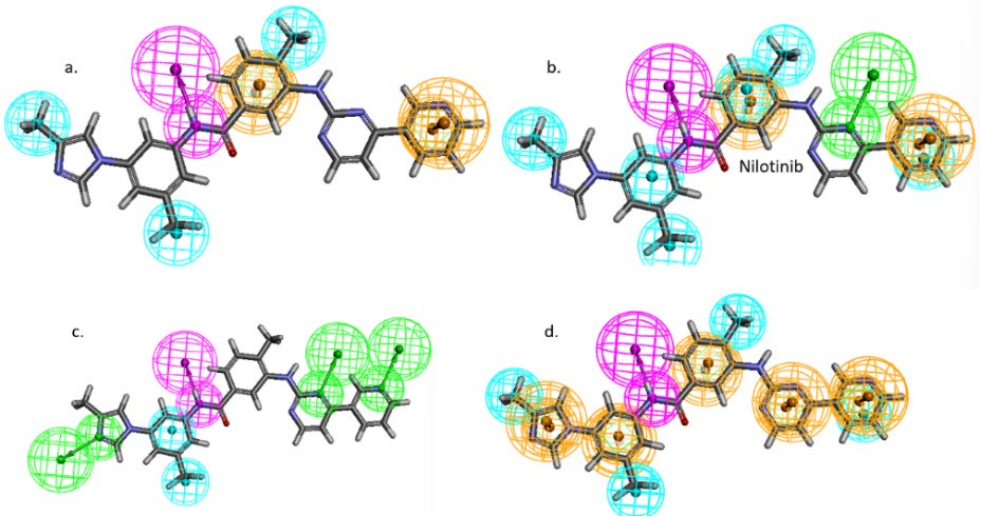


Figure 15. Pharmacophoric features of FDA anticancer agent nilotinib

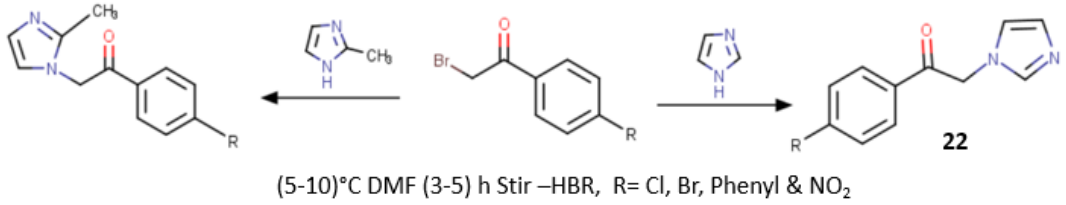


Figure 16. Anti-ulcer 1-substituted imidazole derivatives

One of the popular proton pump inhibitors, omeprazole, is a benzene-fused imidazole derivative (Figure 17) and analysis of the functional group feature of omeprazole showed that its main active structures were hydrophobic fragments. However, the imidazole ring acts as a hydrogen bond donor. The extended substitution carried out on the imidazole-free carbon between the two nitrogens with a pyridine ring link promotes better inhibition of the proton pump in the stomach, reducing acid secretion (Ali et al., 2022).

Similarly, another molecule cimetidine (histamine 2 receptor antagonist) possesses two hydrogen bond acceptors, two hydrogen bond donors and one hydrophobic fragment in the structure. The imidazole ring acts as a dual face (HBA or HBD) based on the chemical space of the binding site (Figure 18). In comparison to omeprazole, cimetidine lacks a hydrophobic group which makes cimetidine H_2 receptor-specific and less effective in acid reduction (Gaba et al., 2014).

3. Synthetic approaches for novel imidazole derivatives

Recent reports suggest that the cyclization of amide nitriles can form di-substituted imidazole derivatives. This Ni-catalyzed synthesis is a novel approach to the synthesis of disubstituted imidazole (Figure 19) (Fang et al., 2019; Gupta & Pathak, 2011).

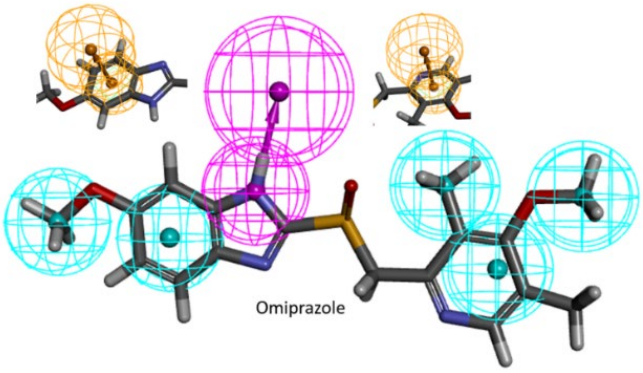


Figure 17. Pharmacophoric features of FDA-approved PPI- omeprazole

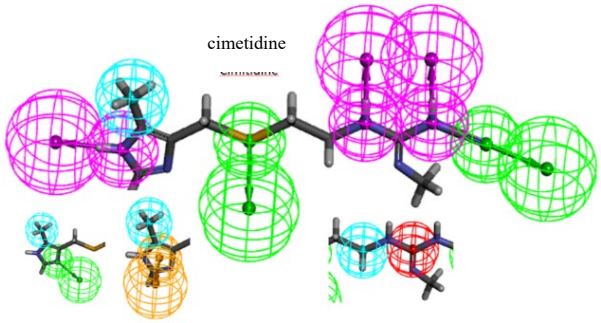


Figure 18. Pharmacophoric features of FDA-approved drug cimetidine

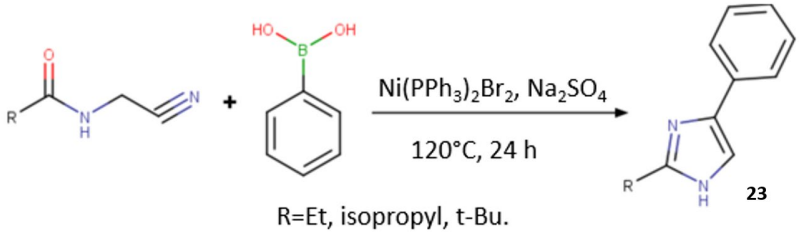


Figure 19. Ni catalyzed synthesis of di-substituted imidazole derivatives

Novel 2-(substituted phenyl)-1H-imidazoles (24) were prepared by the coupling reactions. The condensation reaction conditions were maintained by aryldiazonium salts (made through the diazotization process) under CH_3COONa and C_7H_5ClO as mentioned below it was illustrated in Figure 20 (Bhat et al., 2015).

The n-substituted imidazole derivatives (25) were prepared by refluxing imidazole esters (ethyl 1H-imidazol-1-yl acetate) with the amines and workup with chloroform as shown in Figure 21 (Maleki & Alirezvani, 2016).

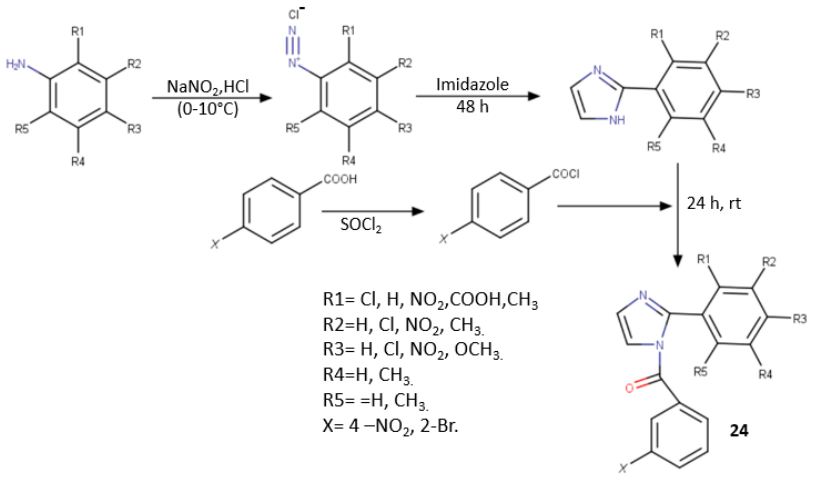


Figure 20. Novel 2-(substituted phenyl)-1H-imidazole derivative

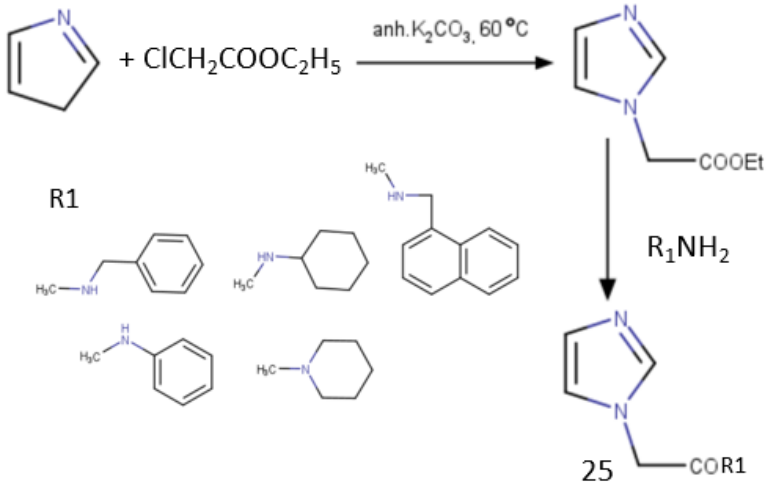


Figure 21. Synthesis of N-substituted imidazole derivatives

Trisubstituted imidazole derivatives (26) were prepared by simple condensation reaction with benzil using a heterogenous solid acid green catalyst (Zeolite H-ZSM22). The desired amines were refluxed for 30 min along with various aromatic aldehydes, ammonium ester and ethyl alcohol. After workup with the same solvent, the pure product was yielded (Figure 22) (Singh & Bajpai, 2019).

2,4,5-trisubstituted imidazole derivatives (27) were prepared by a simple and efficient condensation reaction in ethyl alcohol using a green catalyst, urea-hydrogen peroxide (UHP). This green catalyst condenses the benzyl and benzoyl moieties with the desired aromatic aldehydes and ammonium esters. This reaction proved that the selected catalyst is an efficient choice for the green synthesis of 2,4,5-trisubstituted imidazole derivatives as illustrated in Figure 23 (Wong et al., 2013).

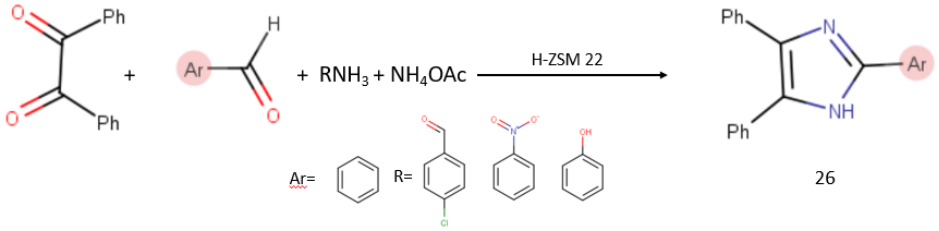


Figure 22. Synthesis of tetra-substituted imidazole derivatives

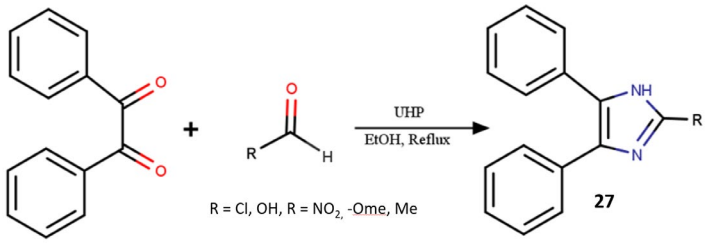


Figure 23. Synthesis of 2,4,5-trisubstituted imidazole derivatives using UHP

Fused imidazole derivatives (28) have been reported under solvent-free reaction methods using the NOSE approach. In this one-pot MCR, the isatin derivatives were condensed with the methods using zirconia nanoparticles as shown in Figure 24 (Singh & Bajpai, 2019).

Carbon substituted imidazole derivatives (29) were synthesized by the condensation of tricarbonyls (α-acetoxy-α-chloro-β-keto esters) with aminomethane in ethyl alcohol at regular conditions followed by condensation with aromatic aldehydes, ammonium esters under acetic conditions. Workup was done using ethyl acetate and basic wash (Figure 25) (Ziarani et al., 2015).

2H-azirin was refluxed with $ZnCl_2$ catalyst, benzimidate, and methyl cyanide for 12 h to produce multi-substituted imidazoles (30) with better yields compared to other conventional methods (Figure 26) (Narasimhan et al., 2011).

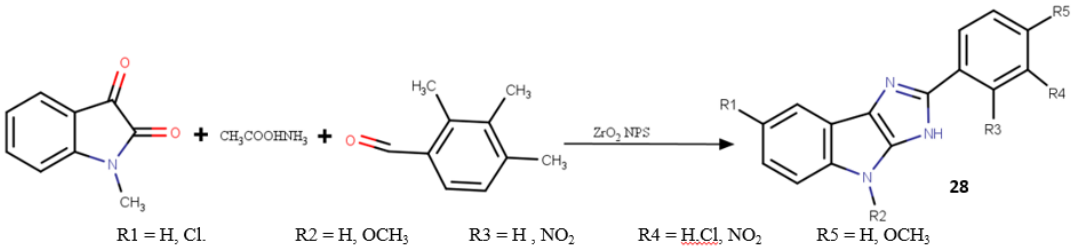


Figure 24. Synthesis of substituted imidazoles by one-pot multicomponent reaction of Isatin derivatives

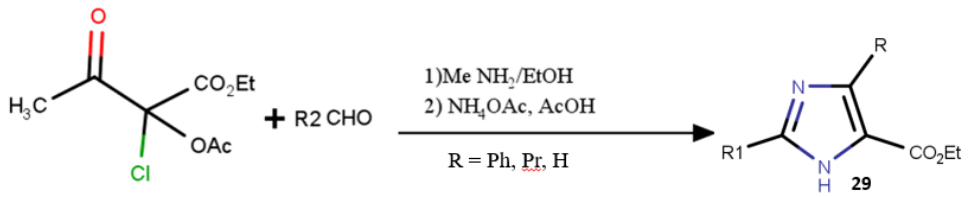


Figure 25. Synthesis of substituted imidazoles by the condensation of tricarbonyls

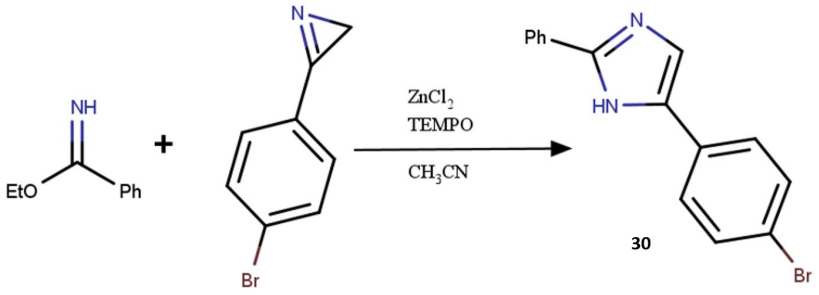


Figure 26. Synthesis of substituted imidazoles by cycloaddition reaction

1,2,4,5-tetrasubstituted imidazoles were reported by the condensation reaction of 1,2-diketones with aromatic amines, ammonium esters, and aromatic aldehydes using a one-pot synthesis. This MCR was catalyzed by silica-functionalized sulfonic acid to give a more facile and convenient synthesis of the imidazole hybrids (31), as illustrated in Figure 27 (Safari et al., 2013).

2-(o-chlorophenyl)-1-imidazole was produced by condensing diazotized *o*-chloroaniline (with $NaNO_2$ under acetic conditions at cold temperature) with the sodium acetate at cool temperatures. This product was purified and reacted with nicotinoyl chloride to produce [2-(o-chlorophenyl)-imidazol-1-yl]-pyridin-3-yl-methanone (32) as depicted in Figure 28 (Messa et al., 2023)

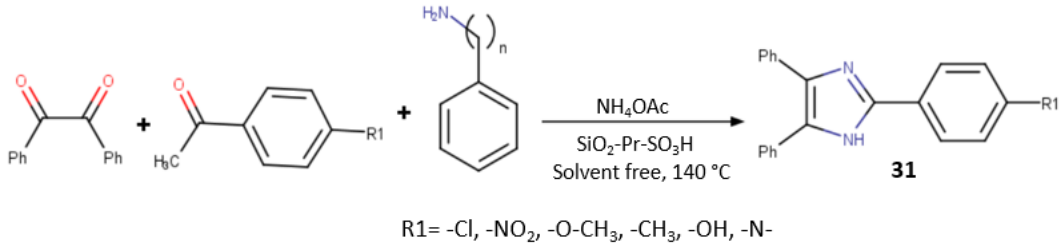


Figure 27. One pot multicomponent reaction for the synthesis of tetra-substituted imidazoles

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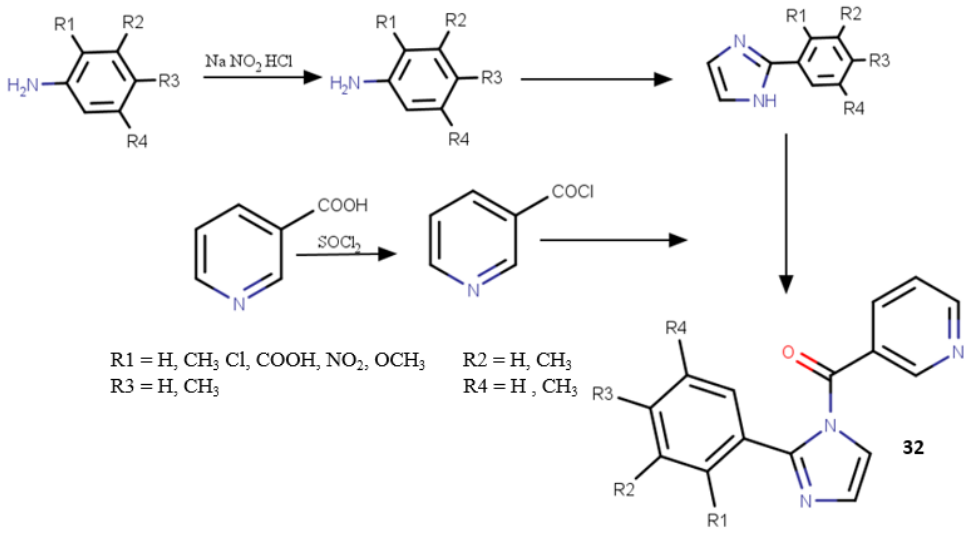

Figure 28. Synthesis of [2-(o-chlorophenyl)-imidazol-1-yl]-pyridin-3-yl-methanones

4-methoxyphenyl glyoxal was refluxed with aromatic aldehydes and ammonium acetate under acetic conditions. This yielded a series of 2-4-disubstituted -1-imidazole (33) derivatives (Figure 29) (Hamdi et al., 2024).

Novel 1,2-disubstituted derivatives (2-(4-aminophenyl)-3-(1-methyl-1H-imidazol-2-yl) acrylonitrile) (34) were reported by the Knoevenagel condensation of 1-methyl-1H-imidazole-2-carbaldehyde with 2-(4-nitrophenyl) acetonitrile. Piperidine was used to facilitate the reaction. The resultant compound was reduced with Fe and ammonium chloride mixture catalyst and condensed with various substituted aldehydes to get the Schiff bases (Figure 30) (Barnett & Brundage, 2010). This multistep reaction was carried out to generate the imidazole hybrids for the assessment of anti-tubercular properties (*in silico*).

2-amino-1- morpholinoethanone hydrochloride was mixed carefully with pyrrolidine in DMF-DMA. After refluxing for 4 h, the mixture temperature was brought to room temperature and processed to get an oily material. Then, it was refluxed with 4-bromoaniline under acidic conditions to get 1,4-disubstituted imidazoles (35), i.e., (1-(4-Bromophenyl)-1H-imidazol-4-yl) (morpholino) methanone, as illustrated in Figure 31 (Mohamed et al., 2015).

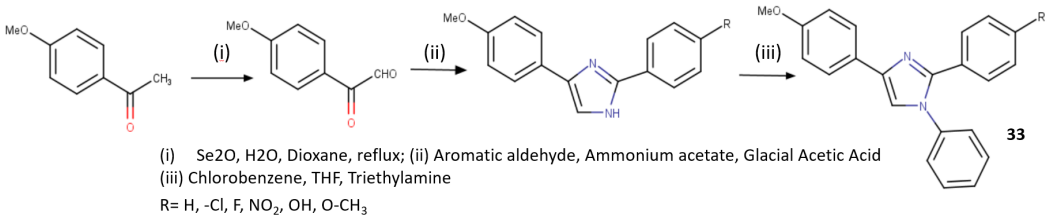

Figure 29. Synthesis of 2-4-di-substituted -1-imidazole derivatives

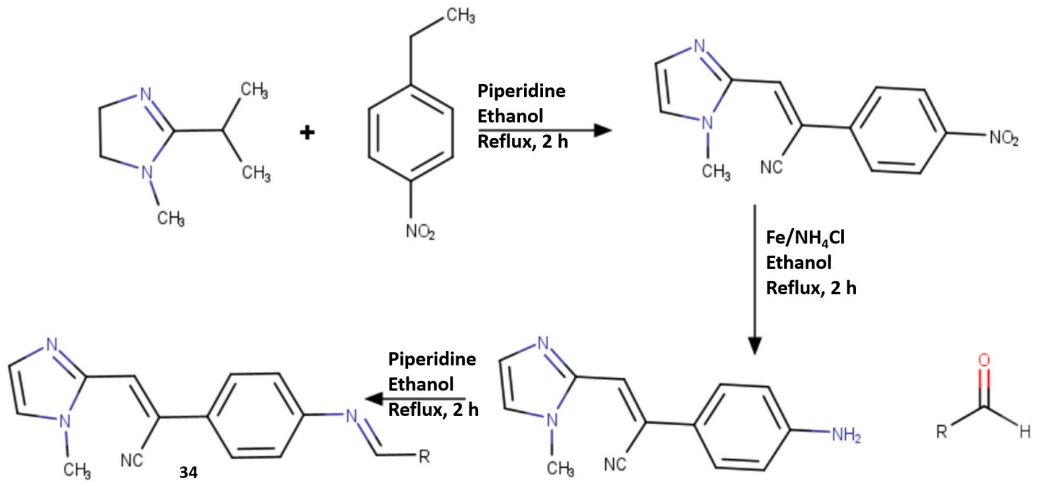

Figure 30. Synthesis of 1,2-disubstituted derivatives using multistep reaction

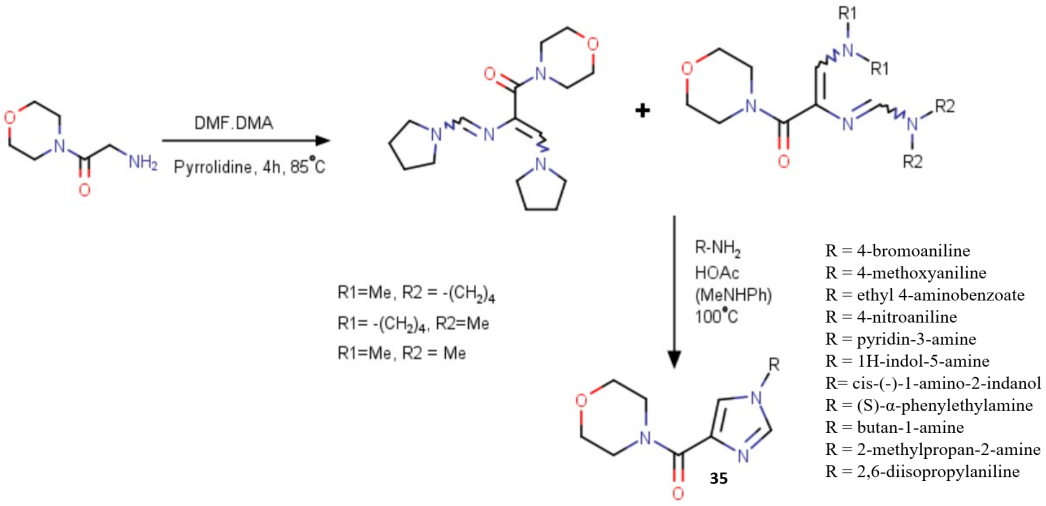

Figure 31. A novel regioselective synthesis of 1,4-disubstituted derivatives

Microwave-assisted irradiation was used for the facile synthesis of substituted imidazole using isatin and Schiff base. One kilowatt power was set for 20 min with regular cooling at one-minute intervals. This method is a solvent-free method that supports the green synthesis of imidazole derivatives (36), as shown in Figure 32 (Al-Masoudi et al., 2009).

Diethyl ammonium hydrogen sulphate was used as a catalyst to facilitate the green synthesis of multi-substituted imidazole derivatives (37), as shown in Figure 33, by condensing benzyl and aromatic aldehydes. These components were subjected to reflux for 35 min at 100°C (Patel et al., 2022).

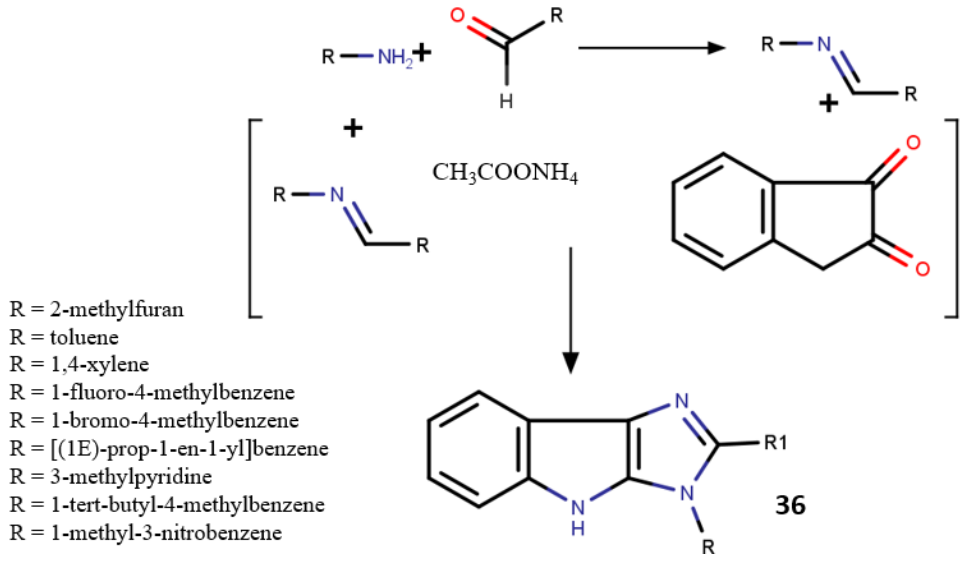

Figure 32. Microwave-assisted synthesis of disubstituted imidazole derivatives

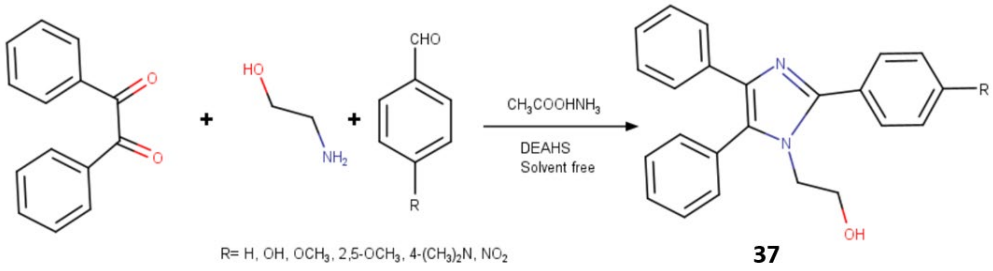

Figure 33. Green synthesis of multi-substituted imidazole derivatives by condensation reactions

2-substituted 4,5-diphenyl-1H-imidazole derivatives (38), as illustrated in Figure 34, were synthesized using similar starting materials under microwave irradiation conditions to facilitate the condensation of benzil and aldehyde in ammonium acetate. This green approach has increased the reaction rate and yield of the product with an easy workup process (Uçucu et al., 2001).

The Ugi/Passerini-reaction was employed to synthesize highly substituted uracil-containing imidazole derivatives (39), as shown in Figure 35. 2-Oxo-2-phenylacetaldehyde was reacted with amines and isocyanides in a DCM and DMF mixture, followed by the reflux at 120°C with ammonium acetate and ethanol (Alikarami & Amozad, 2017).

2,4,5-trisubstituted imidazole derivatives were synthesized by a simple condensation reaction with aromatic aldehydes and ammonium acetate using lactic acid as a promoter. This environmentally friendly solvent under mild reaction conditions (160°C) can facilitate the synthesis of the imidazole derivatives (40) as illustrated in Figure 36 (Sonar et al., 2019).

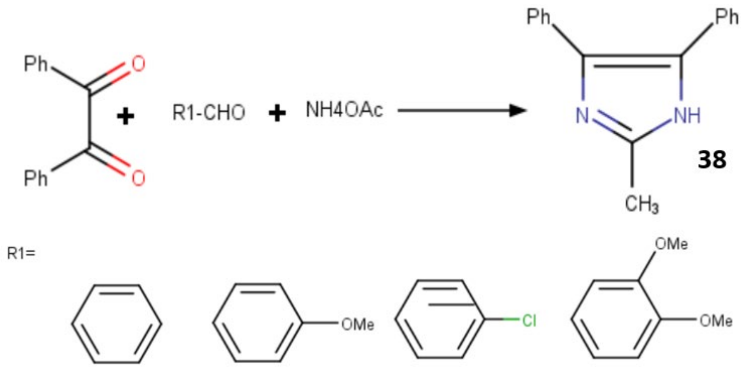

Figure 34. Green synthesis of 2-substituted 4,5-diphenyl-1H-imidazole derivatives by MW irradiation

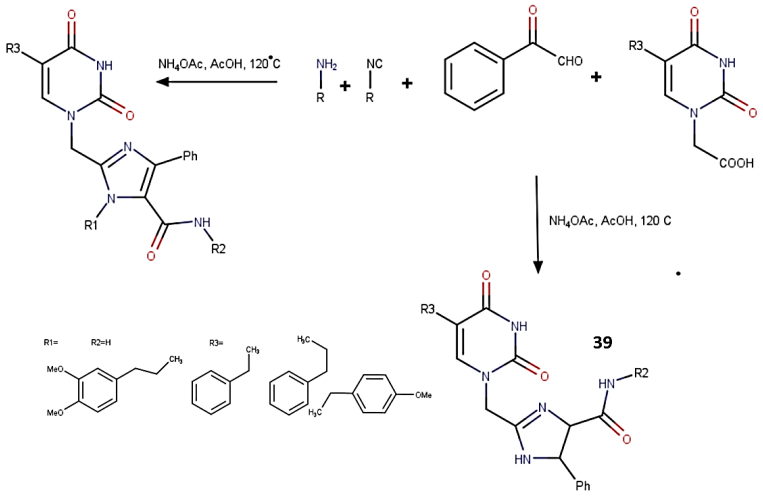

Figure 35. Ugi/Passerini-reaction for the synthesis of uracil containing imidazole derivatives

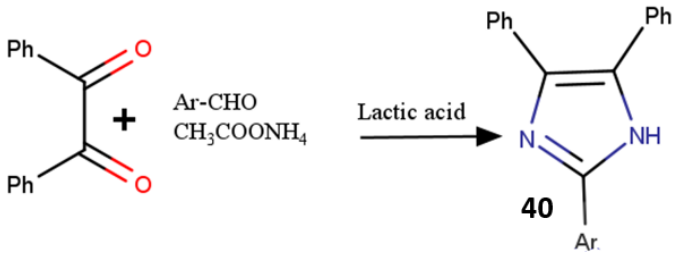

Figure 36. Synthesis of 2,4,5-trisubstituted imidazole derivatives using lactic acid

A nickel chloride and alumina mixture were used as the catalyst for the synthesis of 2,4,5-triaryl-imidazoles (41) (Figure 37), using benzyl and substituted aromatic aldehydes in ammonium acetate. This reaction mixture was refluxed in green solvent (ethyl alcohol) to get the desired imidazole derivative with high yield (Heravi et al., 2007).

2-aryl-4,5-diphenyl derivatives were synthesized by a condensation reaction using benzyl triphenyl phosphonium chloride (BTPPC) (42) as a catalyst under green conditions at 100°C without using any organic solvent as illustrated in Figure 38 (MaGee et al., 2013).

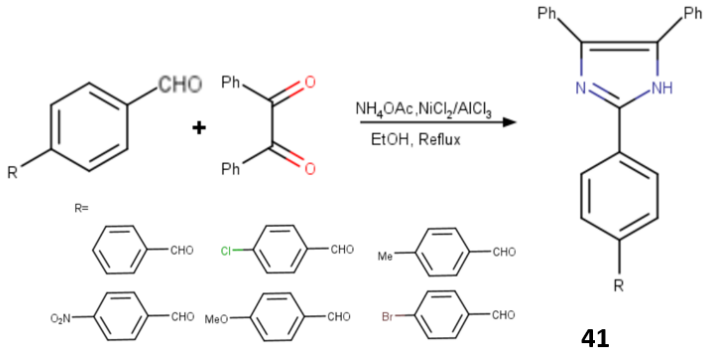

Figure 37. Synthesis of 2,4,5-triaryl-imidazole derivatives using $NiCl_2 \cdot 6H_2O/Al_2O_3$.

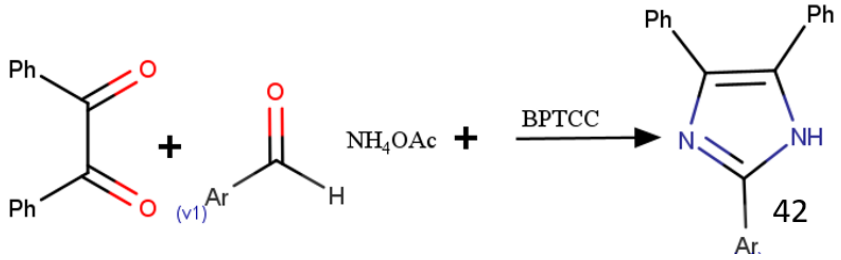

Figure 38. Green synthesis of 2-aryl-4,5-diphenyl derivatives using BTPPC

4. Conclusions

The above synthetic and biological aspects of imidazoles portray the contribution of imidazole molecules in the current medicinal and combinatorial chemistry. The proposed synthetic schemes and development of the compound libraries shed light on the drug discovery path. The literature indicates that various catalysts have been developed to increase the yield and rate of reaction. However, few researchers have developed economically feasible and environmentally compatible methods using green synthesis. The diversified biological applications of these derivatives explain the compatibility of these molecules with living systems to exert the reported pharmacological activities. The structure-activity relationship of the imidazoles dramatically affects the magnitude of the biological response. The scientific tailoring of the substitutions on the moiety has demonstrated the target specificity. The imidazole derivatives were proven to have significant applications in the treatment and as diagnostic agents. As mentioned, a number of imidazoles have been developed as drugs and are currently available in the market.

There is a need to study the molecular aspects of these libraries using advanced models to understand the primary mechanisms involved in the reported activity. Since some imidazole molecules were observed to possess toxic effects in the biological models, tailoring the functional groups and detailed SAR studies will be needed to enhance the drug ability of the developed ligands and to generate more lead molecules.

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6. Conflicts of Interest

No conflict of interest.

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