

A Review on 'Imidazole': There Chemistry, Methods of Preparation and Pharmacological Potentials

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Date of Submission: 05-02-2025

Date of Acceptance: 15-02-2025

ABSTRACT: In contemporary synthetic organic chemistry, a key role is played by the creation of a systematic, directed synthesis of complex organic compounds with the goal of obtaining the physiologically active material with selective action. Derivatives of imidazoles are an essential part of a wide variety of bioactive substances, both synthetic and natural. In recent years, they have drawn the attention of numerous scientists in the fields of pharmaceutical chemistry and pharmacology. This is a result of their remarkable chemical characteristics and biological activity. Modifying and creating novel imidazole derivatives is a significant task for scientists.

KEYWORDS:imidazole, synthesis, formamide,.

I. INTRODUCTION

Imidazole (ImH) is an organic compound with the formula $(CH)_3(NH)N$. It is a white or colourless solid that is soluble in water, producing a mildly alkaline solution. It can be classified as a heterocycle, specifically as a diazole. Many natural products, especially alkaloids, contain the imidazole ring. These imidazoles share the 1,3-C₃N₂ ring but feature varied substituents. This ring system is present in important biological building blocks, such as histidine and the related hormone histamine. Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam.

When fused to a pyrimidine ring, it forms a purine, which is the most widely occurring nitrogen-containing heterocycle in nature.^[10]

The name "imidazole" was coined in 1887 by the German chemist Arthur Rudolf Hantzsch (1857–1935).

Imidazole is a planar 5-membered ring, that exists in two equivalent tautomeric forms because hydrogen can be bound to one or another nitrogen atom. Imidazole is a highly polar compound, as evidenced by its electric dipole moment of 3.67 D,^[12] and is highly soluble in water. The compound is classified as aromatic due to the presence of a planar ring containing 6 π -electrons (a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring).

Imidazole is amphoteric, which is to say that it can function both as an acid and as a base. As an acid, the pK_a of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is the one bound to nitrogen. Deprotonation gives the imidazolid anion, which is symmetrical. As a base, the pK_a of the conjugate acid (cited as pK_{BH}⁺ to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is the nitrogen with the lone pair (and not bound to hydrogen). Protonation gives the imidazolium cation, which is symmetrical.

Imidazole was first reported in 1858 by the German chemist Heinrich Debus, although various imidazole derivatives had been discovered as early as the 1840s. It was shown that glyoxal, formaldehyde, and ammonia condense to form imidazole (glyoxaline, as it was originally named).^[13] This synthesis, while producing

relatively low yields, is still used for generating C-substituted imidazoles.

General method for synthesis of imidazole

Debus-Radziszewski imidazole synthesis

A dicarbonyl, benzaldehyde, and ammonia are used in an organic process to create the Debus-Radziszewski imidazole. It involves combining a

benzaldehyde with a dicarbonyl molecule, such as glyoxal, -ketoaldehydes, or -diketones, while the reaction is occurring in the presence of ammonia. For instance, 2, 4, 5- triphenyl imidazole are produced when benzoyl reacts with benzaldehyde and two molecules of ammonia. Kumar et al. [30]



Wallach synthesis of imidazole

Wallach said that a Cl holding molecule is produced when N, N-diethyl oxamide reacts with

PCl_5 and further reduction by HCl results in (N-methyl imidazole).

Markwald synthesis

An efficient way to create imidazoles is by converting amino ketones, aldehydes, and potassium thiocyanate or alkyl isothiocyanates into

2-mercaptoimidazoles. Oxidation is a simple method for removing sulphur.

From aminonitrile

Aldehyde and aminonitrile are both condensed given the proper reaction conditions to produce substituted imidazole.

Dehydrogenation of imidazoline

2-substituted imidazoles are produced by converting imidazolines to imidazoles using the milder reagent barium manganate and in the presence

of sulphur. Alkyl nitriles and 1, 2 ethane diamine were used to create imidazolines, which were then converted to BaMnO₄.

Maquenne synthesis

Shahzad Farooq et al. (2021) design and synthesized N-Mannich base derivatives containing 2-phenyl-2-imidazoline. The biological activities of the synthesized substances (**1a**) including their antioxidant, α-amylase

inhibiting, anti-microbial, cytotoxic, and anti-inflammatory properties were evaluated. All bacterial and fungal strains were successfully inhibited by compounds with good to moderate activity. [45]

K. Nandni et al. (2020) in the current investigation, created few imidazole analogues by synthetic means. Spectral data was used to confirm the structures of freshly synthesized compounds, while fluconazole and streptomycin were used as

reference drugs to determine their anti-microbial activity. The strongest analogues in the series were discovered to be compounds (**2a**) and (**2b**). [22]



Heba E Hashem et al. (2020) The development and production of the several novel thiourea derivatives with different moieties. In the experiments to ascertain their antibacterial activity, Gram (+ve) and Gram (–ve) bacteria were utilized,

and the fungus *Aspergillus flavus* have a MIC value that varied from 0.95 0.22 to 3.25 1.00 g/mL. Additionally, experiments on cell toxicity showed that compounds **(3a)** and **(3b)** were the most powerful. [19]

Dumitrelea Diaconu et al. (2020). The antibacterial and anti-cancer properties of two new classes of hybrid quinoline-imidazole/benzimidazole

compounds were developed, synthesized, and tested. The compound **(4a)** exhibits outstanding quasi-nonselective action. [13]

Mohammed kareemsamad et al. (2019) developed and improved a powerful new azo-oxazolone that served as a model for the manufacture of two series of azo-benzimidides and azo-imidazolones. The biological efficiency was

determined by evaluating antimicrobial action against gram (+ve) and gram (–ve) bacteria. Compounds **(5a)** were the more potent. Determined by using the burning rats which contaminated by *Staphylococcus aureus*. [31]

Pratik G. Shobhashana et al. (2018) synthesized 2,4,5-trisubstituted imidazole from benzyl, 2-phenoxyquinoline-3-carbaldehyde and ammonium acetate with ceric ammonium nitrate used as

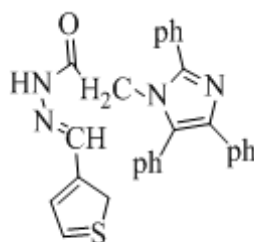
catalyst with excellent yield. Among them compound **(6a)** was discovered to have great antibacterial action against Gram (+ve) and Gram (-ve) bacteria, including *E. coli*. [35]

Anna Bielenica et al. (2015) synthesized 3-(trifluoromethyl) aniline with aliphatic and aromatic isothiocyanates produced a total of 31 thiourea derivatives. Compounds **(7a)** most potent for in vitro anti-microbial activity. The strongest suppression against Gram-positive (+ve) cocci was

shown with derivatives. The MIC values that were actually measured fell between 0.25 to 16 g/ml. Thioureas' inhibitory effects on topoisomerase IV, which was isolated from *S. aureus*, were investigated. [7]

Delia HernándezRomero et al. (2014) synthesized imidazole derivatives, which have demonstrated biological activity in the form of antibacterial, anti-inflammatory, analgesic,

antifungal, anticancer, and antidepressant properties, within the biological processes of various therapeutic diseases. The compounds **(8a)** show important anti-microbial activity. [11]



8a

Shailesh P.Zala et al. (2012) synthesized 2,4,5-triphenyl-1H-imidazole-1-yl derivatives and tested for anti-microbial action using standard drug of

ciprofloxacin and clotrimazole. Compound (**9a**) more potent drug. [44]

H.R. Parabh et al.(2011) Preparation of 6-bromo-2-chloro-3-formylquinoline was used to create oxazole and its imidazole derivatives. The structures of each chemical were clarified using elemental analysis along with IR, ^1H NMR, and ^{13}C

NMR spectra. Their anti-bacterial activity was evaluated in vitro. It was discovered that some synthetic compounds (**10a**) have biological action against bacterial species that are both gram (-ve) and gram (+ve) as well as fungi. [17]

N. C. Desai et al. (2011) synthesized N-(4-((2-chloroquinoline-3-yl) methyl)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazole-1-yl)(aryl)amides. All the compounds are tested in vitro anti-microbial

activity with bioassay that is serial broth dilution method. Among them compounds (**11a**) show more potent against different microbial strains. [34]

S. P. Nanda et al. (2010) synthesized imidazole and benzothiazolyl derivatives starting at easy precursors. The particular compounds (**12a**) were

evaluated as potential for anti-microbial activities. [41]

Deepika Sharma et al. (2008) synthesized substituted phenyl)-[2-(substituted phenyl)-imidazole-1-yl] and 2-substituted phenyl)-1H-imidazole methanone analogues and they were

examined for their ability to fight of fungus, bacteria, and gram (+ve), gram (–ve), and the fungal species. The compounds (**13a**) and (**13b**) was found to be most potent antimicrobial activity. [10]

Andrzej Olczak et al. (2023) design structures of three novels 1H-benzo[d]imidazole derivatives. A similar system of hydrogen bonds, Solid-state NMR was used to assess the sample quality that

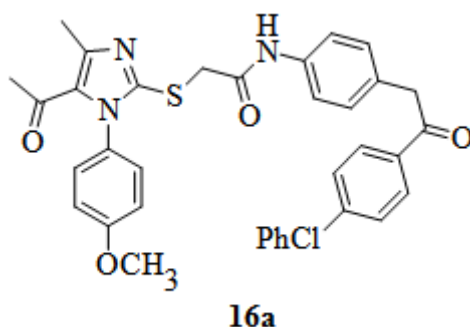
was obtained. By examining their selectivity, Gram-positive with Gram-negative bacteria are both resistant to in vitro antibacterial and antifungal activity. Compounds (**14a**) were more potent. [5]

Salunke PrashantRamrao et al. (2021) novel 4,5-diphenyl-1H-imidazole connected to piperazine hybrids were developed. By using spectroscopic methods, the targeted compounds were located, and

their abilities to inhibit BACE-1, displace Propidium iodide, inhibit in vitro cholinesterase, and break down A were evaluated. The compound **(15a)** and **(15b)** was found to be most active. [42]

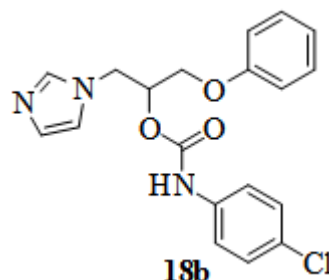
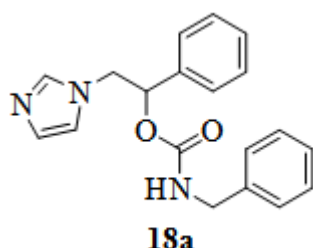
Drashti G.Daraji et al. (2021) derivatives of N-(4-((benzyl)oxy)phenyl)acetamide, which were produced as 2-((5-acetyl-1-(phenyl)-4-methyl-1H-imidazol-2-yl) thio).Imidazole derivative shown

more anti-bacterial efficacy against the all bacterial strains tested, including VRE, ESBL, and MRSA strains. The molecule **(16a)** was determined to be the most effective. [12]



Adel A. Marzouka et al. (2020) designed, synthesized, and tested for the anticonvulsant activity of tetra-substituted imidazole derivatives and imidazolidindiones via maximum electroshock testing using valproate sodium and convulsions produced by pentylenetetrazole and phenytoin sodium as reference drugs, respectively. Compounds **(17a)** and **(17b)** showed higher activity. [1]

Alessandra Ammazalorso et al. (2020) created and manufactured imidazole and triazole derivative using carbamate. It was tested for in vitro kinetic study against human aromatase against letrozole. Additionally, molecular-level explanations of the binding mechanisms that will be employed to bind to the human aromatase will be provided through docking simulations. The result of human breast cancer cell line showed that compound **(18a)** and **(18b)** are more active. [2]



LinglingFan et al. (2020) synthesized and characterized 3,6-disubstituted imidazo [1,2-b]pyrazine. Using the mycelium growth rate method, the potency of these compounds against the nine phytopathogenic fungi was tested. These

compounds, notably **(19a)** and **(19b)**, have more antifungal in vitro action against Corn Curvalaria Leaf Spot than the widely used fungicide hymexazol. [25]

Lingling Fana et al. (2019) Spectroscopic experiments have been utilized to describe a class of newly created imidazo[1,2-b]pyridine that are 3,6-disubstituted. Using the mycelium growth rate

method, the antifungal efficacy of these compounds against the nine phytopathogenic fungi was assessed. Compounds **(20a)** and **(20b)** were more potent. [25]

Vasilichia Antoci et al. (2019) designed, and synthesized bis-(benzimidazole/imidazole)-pyridine derivative tested for the antibacterial activity. Compound **(21a)** performed extremely well anti-tubercular activity against the both

replicating and non-replicating Mtb. strains. Some of the synthesized compounds also have bacterial mechanism. [49]

Rajesh KumarSingh et al. (2019) created by the reaction Aryl-4-fluoro-5-(2-Chloropyridinyl) aryl-2 substituted derivatives of 2-(2-chloropyridin-4-yl) -1H-imidazoleethyl-4-fluorobenzoate reacts with 2-chloro-4-methylpyridine to produce 1-(4-

fluorophenyl)ethanone, which is then cyclized with an aryl (or hetero aryl)aldehyde while being present in the ammonium acetate and acetic acid. Compounds **(22a)** and **(22b)** most potent for antimicrobial activity. [38]

Sundaram M. et al. (2019) created and produced bisimidazoles and bisimidazo [1,2a] pyridines from Schiff base dimmers. Both compounds were tested for anti-cancer activity. The compounds **(23a)**

show the most potent inhibitory effects against the breast tumor cell line (19, GI50 = 0.43 M; 24) and were much more potent than the control medication Adriamycin (GI50 = 0.51 M. [20]

Anupam et al. (2018) equimolar quantities of benzil and substituted benzaldehydes are used to create imidazole; the resultant mixture is then refluxed with acetyl chloride. For gram +ve (Staphylococcus aureus and Bacillus subtilis), gram -ve (E. coli and P. aureginosa), and fungal strain

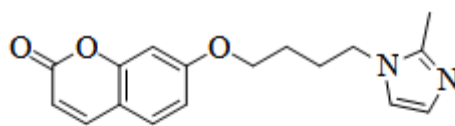
(Candida albicans) bacteria, all the produced compounds were evaluated using the agar diffusion techniques. The compound **(24a)** was more potent for antibacterial activity. [8]

C. B. Pradeep Kumar et al. (2017) Based on 1,2,3-triazoles, a brand-new family of imidazole compounds has been developed. Utilizing spectral analysis including ^1H NMR, ^{13}C NMR, mass spectrometry, and the elemental analysis, the

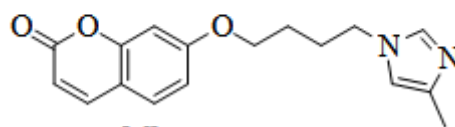
produced product is evaluated. In vitro, the compounds **(25a)** have strong anti-tubercular action. [9]

Yang Hu et al. (2017) A few coumarin compounds were created, produced, and physiologically assessed in an effort to utilize the synthesis of fatty acids as a lens through which to comprehend why bacteria are resistant to them. The structural study of coumarin indicated that its derivatives could be

helpful for controlling and inhibiting the growth of microorganisms. Their antibacterial against *Staphylococcus aureus* and *E. coli* and demonstrated the strong antibacterial activity of compounds **(26a)** and **(26b)**. [53]



26a



26b

Narasashetty Jagadishbabu et al. (2017) The 2,4,5-triphenyl imidazole derivative is created by a three-component process involving ammonium

acetate and aldehyde benzil. Compounds **(27a)** were identified using IR and ^1H NMR. [35]

Khaled R.A Abdellatif et al. (2017) created, manufactured, and evaluated for COX-2 inhibition of 5,4-H-imidazolone, 1,2-diaryl-4-substituted benzylidene derivatives. All of the substances were

more COX-2 isozyme specific and had strong in vivo anti-inflammatory action. The compounds **(28a)** were more potent. [23]

Rutuja Sonawane et al. (2015) synthesis 1,5-disubstituted-4-chloro-1H-imidazoles and was tested for anticonvulsant activity. Imines and p-toluenesulfonyl methyl cyanide were used to create

5-disubstituted-4-chloro-1H-imidazole. Imines were produced utilizing commercially available amines and aldehydes. Compound **(29a)** and **(29b)** were more powerful in anticonvulsant action. [40]

Harun M. Patel et al. (2013) synthesize and characterize [1,3,4]thiadiazole derivatives of 6-(4-nitrophenyl)-2-(1-methyl-1H-imidazol-2-yl)imidazo[2,1-b]. The effectiveness of the compounds

against *Mycobacterium tuberculosis* was evaluated with a MIC of 3.14 lg/ml, [1,3,4]thiadiazole(**30a**) showed the highest studied. [18]

Arzu Karakurt et al. (2012) a total of 23 brand-new nafimidone oxime ester compounds were created with the hope of developing anticonvulsant activity the rotorod test was used to detect neurological impairments. It was discovered that 18

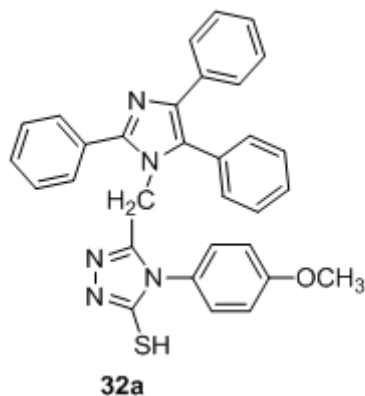
substances prevented MES seizures. Aryl oxime ester compounds were discovered to be less active than alkyl and arylalkyl oxime ester derivatives. At all dosage levels, compound **(31a)** was the most active. [8]

M. Amir et al. (2011) synthesis of acetic acid hydrazide (2,4,5-triphenylimidazole-1-yl) has been

used to create a digit ofazole derivatives. Compounds **(32a)** evaluated for their anti-

inflammatory, antibacterial, and antifungal activities, each and every synthetic azole

derivatives have moderate to excellent efficacy. [26]



Balasubramanian Lakshmanan et al. (2011) synthesized 1-substituted imidazoles and their spectrum data was used to characterize them. At different doses (5, 10 and 20 mg/ml), was tested against *Eudriluseugeniae*, an African earthworm. It

was found that every prototype was both vermifugal and vermifuge killing. The phenacyl imidazole compounds (**33a**) were show important anthelmintic activity. [10]

V.S.V. Satyanarayana et al. (2010) As a crucial step in the creation of the Schiff bases, the production of 2-(2,4,5-Triphenyl-1H-imidazol-1-yl)acetohydrazide was performed (**34a**). Each

molecule was then as shown by IR, ^1H NMR, and ^{13}C NMR, and HRMS spectrum analyses. Antioxidant and anti-cancer tests have been conducted on Schiff base molecules. [48]

II. CONCLUSION

Based on the above-presented literature survey we have underlined the importance of imidazole and its synthetic derivatives. In an

attempt to help the medicinal chemists or pharmacists by researches, we have presented new, easy-to-use and environmentally safe synthetic strategies. This review presents further synthetic

approaches in applying the most usable strategy for obtaining a huge scope of modified imidazoles bearing different pharmacophores, allowing structures with better effects and low toxicity

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