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# A review: Imidazole synthesis and its biological activities

**Purnima Manocha, * Dr. SR Wakode, Avneet Kaur, Keshav Anand, Hitesh Kumar**

Department of pharmaceutical chemistry, Delhi Institute of Pharmaceutical Science And Research, New Delhi, India

**Abstract**
Imidazole is a planar five-member heterocyclic ring with 3C and 5N atom with N atom present at the 1st and 3rd positions of the ring. The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Being a polar and ionisable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble lead molecules. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole is an entity which explores different types of pharmacological and biological activities like metronidazole and nitrosoimidazole as bactericidal, 1-vinylimidazole as fungicidal, megazol as trypanocidal, imidazole-2-one as a ntileishmanial and other antimicrobial activities. This article aims to review the process of synthesis of imidazole and its derivatives by different methods and pharmacological activities.

**Keywords:** Imidazole synthesis, metronidazole, nitrosoimidazole

## Introduction

Medicinal chemistry is the discipline concerned with determining the influence of chemical structure on biological activity [1, 2]. It is concerned with the discovery, development, interpretation, identification and mechanism of action of biologically active compounds at the molecular level [3]. Various biologically active synthetic compounds have five-member nitrogen-containing heterocyclic ring in their structures [4]. Structural frameworks have been described as privileged structures and in particular, N-containing polycyclic structures have been reported to be associated with a wide range of biological activity.

Imidazole moiety has attracted special attention in chemistry and biochemistry. These heterocycles show various pharmaceutical properties such as anti-bacterial [5, 6], anti-fungal [7], anti-inflammatory [8], analgesic activities [9] anti-tubercular [6, 10], anti-depressant [11], antiviral [5] and anti-cancer [12]. Furthermore, some of them have found applications as fluorescent whitening agents. A number of methods have been reported for the preparation of these heterocycles including the condensation of dicarbonyl compounds with aldehydes such as glyoxal, α- keto aldehyde or α-diketones, aminonitrile with aldehyde. Generally in the pharmaceutical field, new drugs are continuously discovered by molecular modification of lead compound of established activity. Molecular modification can possibly result in augmenting the activity. This modification involves combination of separate group having similar activity in one compound by eliminating, substituting or adding new moiety to parent lead compound.

In the survey of literature, it is seen that drug design by molecular modification is a productive source of new drug; therefore the need to synthesize new molecules as potential medicinal agents is more relevant today. Among medicinal agents, there is growing interest in the development of newer, effective antifungal and antimicrobial agents. Among the variety of compounds studied, imidazole derivatives form an important class.

## Imidazole

The name "imidazole"(Fig. 1) was coined in 1887 by the German chemist Arthur Rudolf Hantzsch (1857–1935). It is a five membered aromatic heterocyclic compound, having mol formula of $C_3N_2H_4$. It is classified as diazole having non-adjacent nitrogen atom. Imidazole can serve as a weak cid and weak base. When fused to a pyrimidine ring, it forms purine, which is the most widely occurring nitrogen-containing heterocycle in nature. Many drugs contain an imidazole ring, such as nitroimidazole an antifungal drug.

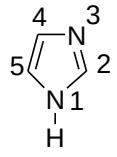

**Fig 1**

Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms (Fig. 2), because the positive charge can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound, as evidenced by its electric dipole moment of 3.67 D [9]. It is highly soluble in water. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring.

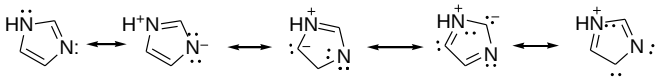

**Fig 2**

Imidazole is amphoteric. That is, it can function as both an acid and as a base. As an acid, the p$K_a$ 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 located

on N-1. As a base, the p$K_a$ of the conjugate acid is approximately 7, making imidazole approximately sixty times more basic than pyridine.

Imidazole (Fig. 3) can be considered as having properties similar to both pyrrole and pyridine. The electrophilic reagent would attack the unshared electron pair on N-3, but not the pyrrole nitrogen since it is the part of the aromatic sextet. While the imidazole ring is rather susceptible to electrophilic attack on an annular carbon, it is much likely to become involved in nucleophilic substitution reaction unless there is a strongly electron withdrawing substituent's elsewhere in the ring. In the absence of such activation the position most prone to nucleophilic attack is -2. The fused benzene ring in Benzimidazole provides sufficient electron withdrawal to allow a variety of nucleophilic substitution reaction at C-2.

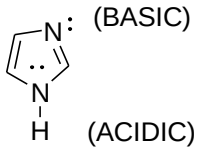


**Fig 3**

The overall reactivity of imidazole's and Benzimidazole is referred from sets of resonance structure in which the dipolar contributors have finite importance. These predict electrophilic attack in imidazole at N-3 or any ring carbon atom, nucleophilic attack at C-2 or C-1 and also the amphoteric nature of the molecule. Imidazole's shows a large value of dipole moment of 4.8 D in dioxane, and has a pKa of 7.2 more than pyrazole and pyridine. Imidazoles have a M.P. 90 C, it is a weak base and tautomeric substance, position 4 and 5 are equivalent.

**Synthesis of Imidazole**

**Radziszewski synthesis**

It involves condensation of dicarbonyl compound such as glyoxal with an aldehyde in the presence of ammonia, to yield 2, 4, 5-triphenylimidazole [13-14].

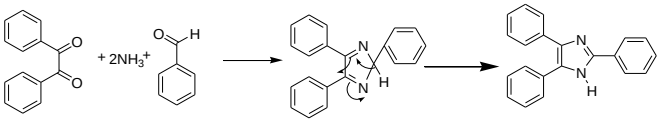

**Fig 4**

**Dehydrogenation of imidazoline**

Alkyl nitriles and 1, 2 ethanediamine on reaction with $BaMnO_4$ yield 2-substituted imidazoles [15].

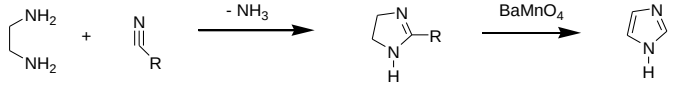

**Fig 5**

**From α-halo ketone**

This reaction involves an interaction between an imidine and α-halo ketone. This method has been applied successfully for the synthesis of 2, 4- or 2, 5- biphenyl imidazole phenacyl bromide and benzimidine according to this method afford 2, 4-diphenyl imidazole [15].

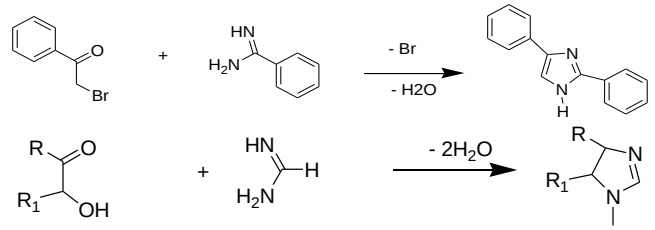

**Fig 6**

**Wallach synthesis**

When N, N-dimethyloxamide is treated with phosphorus pentachloride, a chlorine containing compound is obtained which on reduction with hydroiodic acid give N- methyl imidazole [15-19].

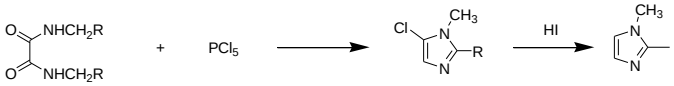

**Fig 7**

**Markwald synthesis**

The preparation of 2- mercaptoimidazoles from a- amino ketones or aldehyde and potassium thiocyanate or alkyl isothiocyanates is a common method for the synthesis of imidazoles. The sulfur can readily be removed by a variety of oxidative method to give the desired imidazoles. The starting compounds, a- amino aldehyde or ketone, are not readily available, and this is probably the chief limitation of the Markwald synthesis [15].

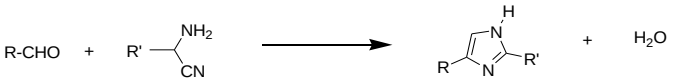

**Fig 8**

**By action of Ammonia**

Imidazole can best be prepared itself by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and then heating the dicarboxylic acid in quinoline in presence of copper [20].

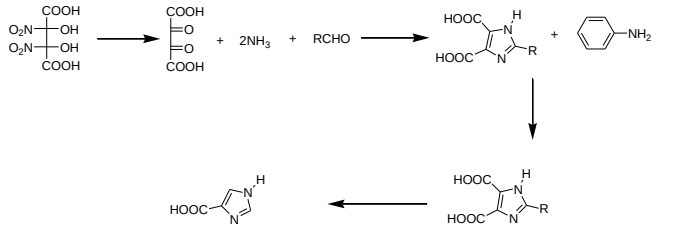

**Fig 9**

**Cyclization of α-acylaminoketones** [20]

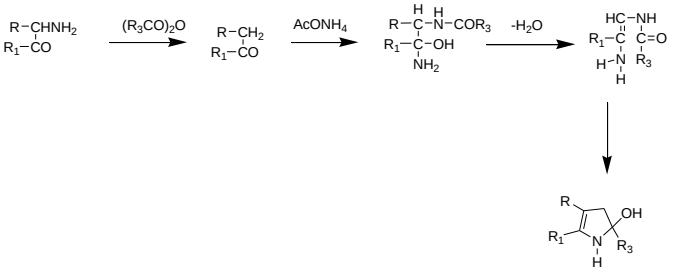

**Fig 10**

**Pharmacological Activity**

**Anti-fungal and anti-bacterial activity**

An antifungal drug is a pharmaceutical fungicide or fungi static used to treat and prevent mycoses such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others. Azole antifungal drugs (except for abafungin) inhibit the enzyme lanosterol 14 α-demethylase; the enzyme necessary to convert lanosterol to ergosterol. Depletion of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth. Examples are bifonazole, clotrimazole, econazole etc.

*Deepika Sharma et al*. synthesized 2-(substituted phenyl)-1H-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-menthanone analogues (Fig. 11) and screened for their antimicrobial activity against gram positive, gram negative, and fungal species. Norfloxacin was used as standard and following compound is most potent [5].

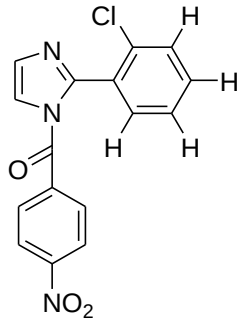

**Fig 11**

*Ramya V et al*. synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazole derivatives (Fig. 12) and tested for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, and *Klebsiella pneumoniae* and anti fungal activity against *Candida albicans* and *Aspergillus fumigates*. The synthesized compound showed moderate to good antibacterial activity as compared to the standard ciprofloxacin [6].

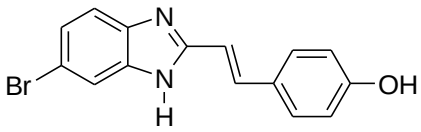

**Fig 12**

*Frank et al*. synthesized 5-substituted-2-(2-methyl-4-nitroimidazomethyl)-1, 3, 4- oxadiazoles (Fig. 13) containing the nitroimidazole moiety and evaluated for their antibacterial, antifungal activity. The prepared compound showed mild to moderate significant activity [7].

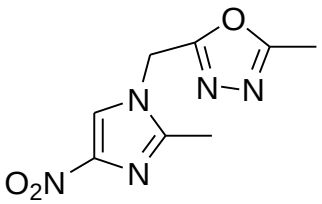

**Fig 13**

**Anti-inflammatory activity and analgesic activity**

An analgesic or painkiller is any member of the group of drugs used to achieve analgesia, relief from pain. Analgesic drugs act in various ways on the peripheral and central nervous systems.

*Raghavendra et al*. synthesized a series of 1-(2-((18Z)-4-substituted benzylidene-4, 5-dihydro-5- oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl (Fig. 14) imidazolo quinoline analogs. The title compounds were investigated for anti-inflammatory and its ulecerogenicity activities. The prepared compound found to have convincing activities against inflammation when compared with standard drug [8].

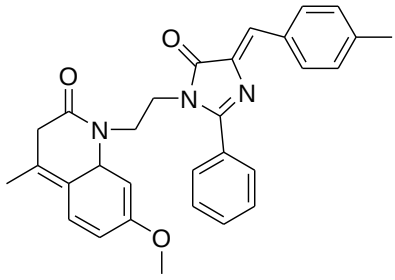

**Fig 14**

*Kavitha C.S. et al*. has synthesized a series of 2-methylaminibenzimidazole derivatives (Fig. 15) and newly synthesized compounds were screened for analgesic and anti-inflammatory activities. This compound shows analgesic activity and compared with standard nimesulide drug [9].

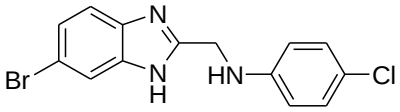

**Fig 15**

**Anti-tubercular activity**

Anti-tubercular drugs are those which help in the medical treatment of the infectious disease tuberculosis (TB).

*Preeti Gupta et al*. synthesized substituted -1H-imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives against durg-sensetive and durg-resistent *M. tuberculosis* strains. The title compound was found to be most potent compound when compared to standard [10].

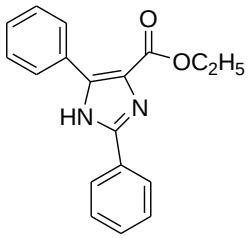

**Fig 16**

*Ramya V et al*. synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazoles derivatives (Fig. 17) and screened for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis*, and these compounds showed good antitubercular activities. Streptomycin was used as reference drug [5].

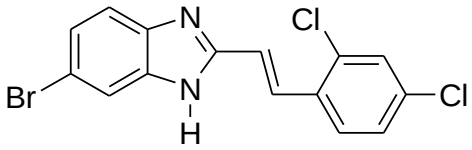

**Fig 17**

**Anti-depressant activity**

These drugs are used for the treatment of major depressive disorder and other conditions, including dysthymia, anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, neuropathic pain and, in some cases, dysmenorrhea, snoring, migraine, attention-deficit hyperactivity disorder (ADHD), addiction, dependence, and sleep disorders.

*Farzin Hadizadeh et al*. synthesized moclobemide analogues (Fig. 18) by replacing moclobemide phenyl ring with substituted imidazole and studied for the antidepressant activity using forced swimming test. Analogues 7a-c was found to be more potent than moclobemide [11].

**Fig 18**

**Anti-cancer activity**

These drugs, destroys or inhibit cancer cells *after* cancer has developed. It counteracts the effects of a carcinogen or inhibits the development of cancer.

*Yusuf Ozkay et al* synthesized many novel imidazole-(Benz)-azole and imidazole epiperazie derivatives (Fig. 19) and evaluated for the anticancer activity and found that these derivatives were the most active compounds when compared with the standard Cisplatin [12].

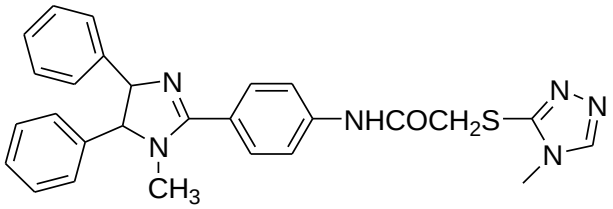

**Fig 19**

**Anti-viral activity**

Antiviral drugs are a class of medication used specifically for treating viral infections rather than bacterial ones [1]. Most antivirals are used for specific viral infections, while a broad-spectrum antiviral is effective against a wide range of viruses [2]. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

*Deepika Sharma et al*. synthesized imidazole derivatives and the antiviral screening of (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones (Fig. 20) against viral strains indicated that compounds A and B selected as the most potent antiviral agents. Ribavirin was used as standard drug [5].

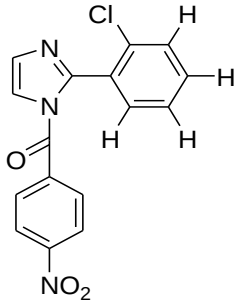

**Fig 20**

*Michele Tonelli et al*. synthesized seventy six 2-phenylbenzimidazole derivatives and evaluated for cytotoxicity and anti-viral activity against a panel of RNA and DNA viruses. Compound [5, 6-dichloro-2-(4-nitrophenyl) benzimidazole] (Fig. 21) exhibited a high activity resulting more potent than reference drugs smycophenolic acid and 6-azauridine [21].

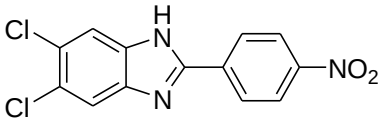

**Fig 21**

**Biological Significance of Imidazole**

The imidazole ring is a constitutent of several important natural product.It is incorporated into many important biological molecules including purine, histidine, histamine and nucleic acid. Histidine is present in many proteins and enzymes play a vital role in the structure and binding functions of hemoglobin. Histidine can be decarboxylated to histamine, which is also a common biological compound. It is a component of the toxin that causes urticaria, i.e. allergic.

**Conclusion**

Imidazole moiety have been most frequently studied, many of its analogs are active against various pathological conditions, such as antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc. Imidazoles are less sensitive in extra intestinal parasites particularly intravascular and intestinal dwelling parasites than gastrointestinal parasites. The members of class 2-alkyl benzimidazole are believed to be the most effective ones, had been found to remove various species of nematodes and trematodes from different hosts thus various compounds had been synthesized keeping 2-alkyl benzimidazole as basic moiety. Having structural similarity with histidine, imidazole compound can bind with protein molecules with ease compared to the some other heterocyclic moieties. Thus imidazole offers better pharmacodynamic characteristics. Furthermore, some imidazole drugs, at high concentrations, could exert direct inhibitory effects on membranes, without interference with sterols and sterol esters. Various recent new drugs developments in imidazole derivatives show better effect and less toxicity.

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