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Der Chemica Sinica, 2010, 1 (3): 36-47

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

# Imidazole and its biological activities: A review

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## ABSTRACT

*Imidazole is a planer five-member heterocyclic ring with 3C and 2N atom and in ring N is present in 1st and 3rd positions. 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. Imidazole derivatives have occupied a unique place in the field of medicinal chemistry. The incorporation of the imidazole nucleus is an important synthetic strategy in drug discovery. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Numerous methods for the synthesis of imidazole and also their various structure reactions offer enormous scope in the field of medicinal chemistry. This articles aims to review the work reported, their chemistry and biological activities of imidazole during past years.*

**Key words-** Imidazole, antibacterial, antifungal, heterocyclic, biological active

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## INTRODUCTION

Medicinal chemistry is the discipline concerned with determing the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity [1, 2]. Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level [3]. Various biologically active synthetic

compounds have five-membered 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. In the field of five membered heterocyclic structures imidazole nucleus shows various properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole include anticancer, b-lactamase inhibitors, 20-HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial [5-18]. This group presents in azoles antifungal which inhibit the accumulation of methylated sterols distroy the composition of the lipid bilayer of membranes. Some imidazole drugs, at high concentrations, could exert direct inhibitory action on membranes, without interference with sterols and sterol esters [19, 20]. Infectious microbial disease causes worldwide problem, because microbes have resisted prophylaxis or therapy longer than any other form of life. In recent decades, problems of multidrug-resistant microorganisms have reached an alarming level in many countries around the world. Resistance of anti-microbial agents such as β-lactam antibiotics, macrolides, quinolones and vancomycin etc. and different species of bacteria causes increased important global problem [21]. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases.

**Structure and pharmacological activities**

Imidazoles are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents. Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. It is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely 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. Imidazole is amphoteric, *i.e.* it can function as both an acid and as a base.

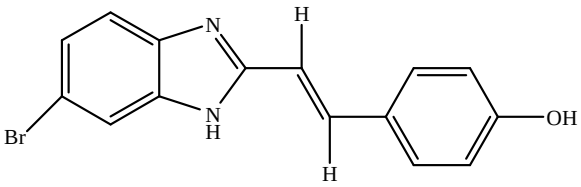
On the basis of various literature surveys Imidazole derivatives shows various pharmacological activities

- Anti fungal and Anti-bacterial activity
- Anti inflammatory activity and analgesic activity
- Anti tubercular activity
- Anti depressant activity
- Anti cancer activity
- Anti viral activity
- Antileishmanial activity

1. **Antifungal and anti bacterial activity**

*Ramya v et al* synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazole derivatives and tested for the antibacterial activity against *Staphylococcus aureus, Escherichia coli,*

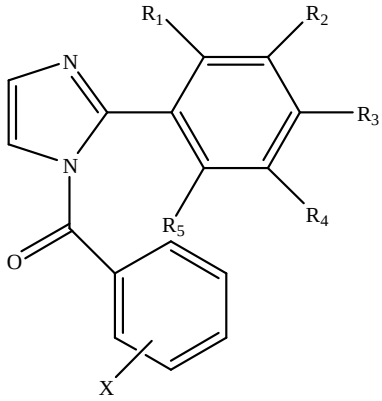
*Enterococcus faecalis*, and *Klebsiella pneumoniae* and anti fungal activity against *Candida albicans* and *Aspergillus fumigates*. This was comparable with ciprofloxacin. [21]




4-((*E*)-2-(6-bromo-1*H*-benzo[*d*]imidazol-2-yl)vinyl)phenol

**Fig 1**

*Deepika Sharma et al* have synthesized 2-(substituted phenyl)-1H-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-menthanone analogues and screened for antimicrobial activity against gram positive, Gram negative, and fungal species. Norfloxacin used as standard [22] and following compound is most potent.




for compound 1 $R_1$=Cl, $R_2$=H,$R_3$=H,$R_4$=H,$R_5$=H,X=4-$NO_2$

2 $R_1$=COOH,$R_2$=H,$R_3$=H,$R_4$=H,$R_5$=H,X=4-$NO_2$

3 $R_1$=H,$R_2$=H,$R_3$=Cl,$R_4$=H,$R_5$=H,X=2-Br

4 $R_1$=H,$R_2$=H,$R_3$=$NO_2$,$R_4$=H,$R_5$=H,X=2-Br

**Fig -2**

*Daniele Zampieri et al* synthesized bis-imidazole derivatives and screened for antifungal and anti mycobacterial activity. All compounds showed moderate to good activity against *Candidaalbicans* and *Candida glabrata*. Miconazole used as reference drug. [23]

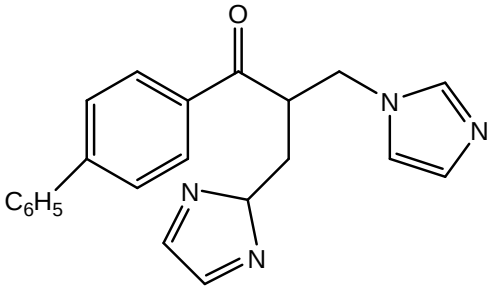
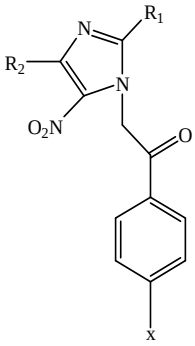



**Fig- 3**

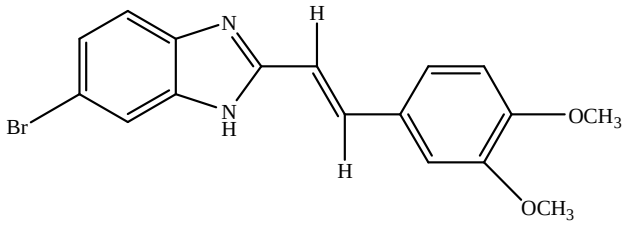
*Dorota Olender et al* synthesized nitroimidazole derivatives and tested for their antifungal activity using the standard nutrient method against *sclerophoma pityophila*. This compound shows more potent fungistatic activity. [24]



A $R_1$=H, $R_2$=Morpholine, X=H

B $R_1$=$CH_3$,$R_2$=Piperidine methyl, X=Cl

Fig-4

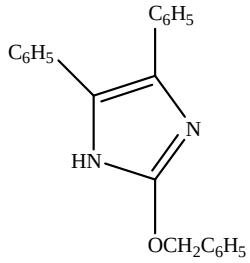


2-(3,4-dimethoxystyryl)-6-bromo-1*H*-benzo[*d*]imidazole

**Fig-5**

**2**. **Anti -inflammatory and analgesic activity**

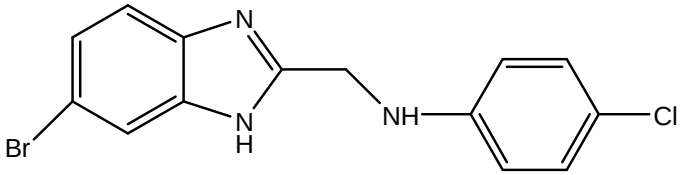
*Puratchikody A.et al* studies on 2-substituted-4, 5-diphenyl-1H-imidazoles and checked the anti-inflammatory activity based on Carrageenan-induced paw edema method. This compound shows maximum activity and indomethacin used as reference drug. [25]



2-(benzyloxy)-4,5-diphenyl-1*H*-imidazole

**Fig-6**

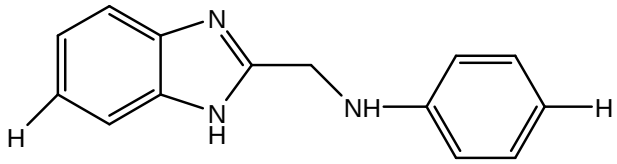
*Kavitha C.S.et al* has synthesized a series of 2-methylaminibenzimidazole derivatives and newly synthesized compounds were screened for analgesic and anti-inflammatory activities. This compound shows analgesic activity and compared with standard nimesulide drug. [26]



*N*-((6-bromo-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-chlorobenzenamine

**Fig-7**

This compound shows potent anti inflammatory activity and also compared with nimesulide.

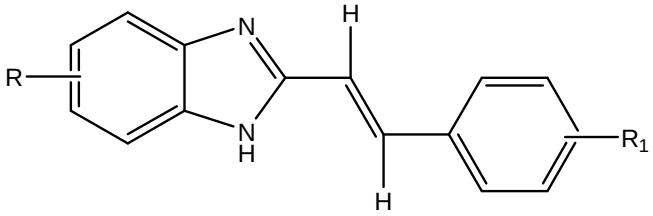


*N*-((1*H*-benzo[*d*]imidazol-2-yl)methyl)benzenamine

**Fig-8**

**3. Antitubercular activity**

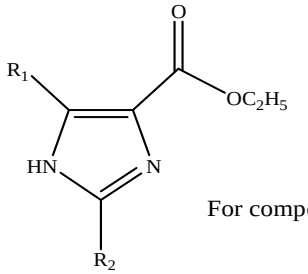
*Ramya V et al* synthesized series of novel 5-(nitro/bromo)-styryl-2-benzimidazoles (1–12) derivatives and screened for in vitro anti-tubercular activity against *Mycobacterium tuberculosis*, and these compounds showed good antitubercular activities. Streptomycin was used as reference drug [21].



For This compound A R=Br, $R_1$=H
B R=Br, $R_1$=3,4-$OCH_3$
C R=Br, $R_1$=4-$CH_3$
D R=Br, $R_1$=2,4-Cl

**Fig-9**

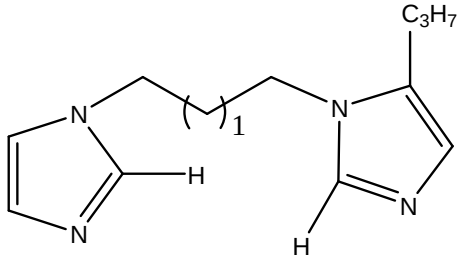
*Preeti Gupta et al* describe anti-mycobacterium tuberculosis activities of ring substituted -1H-imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives against durg-sensetive and durg-resistent *M. tuberculosis* strains. 2f and 2h compounds were most potent compound. [27]



For compound 2f=$R_1$=$R_2$=c-$C_5H_9$
2h=$R_1$=$R_2$=$C_6H_{11}$

**Fig-10**

*Jyoti Pandey et al* synthesized a series of imidazole derivatives and compounds were screened against *M .tuberculosis* where this compound showed good antitubercular activity [28]

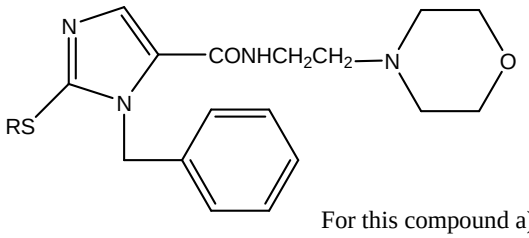


1-(3-(1*H*-imidazol-1-yl)propyl)-5-propyl-1*H*-imidazole

**Fig-11**

**4. Antidepressant activity**

*Farzin Hadizadeh et al* synthesized moclobemide analogues 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. [29]




For this compound a)R=$CH_3$,

b)R=$C_2H_5$

c)R=$CH_2C_6H_5$

**Fig-12**

**5. Anticancer activity**

*Yusuf Ozkay et al* synthesized many novel imidazole-(Benz) azole and imidazole epiperazine derivatives in order to investigate the anticancer activity. Anticancer activity screening results revealed that these were the most active compounds in the series. Cisplatin was used as reference drug. [30]

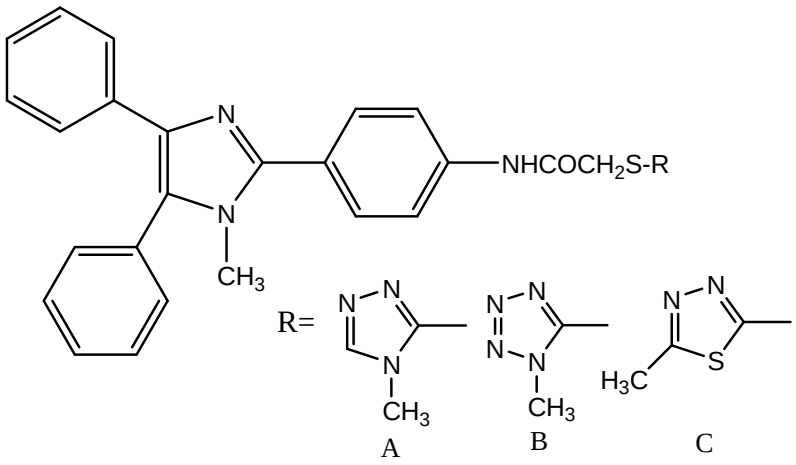
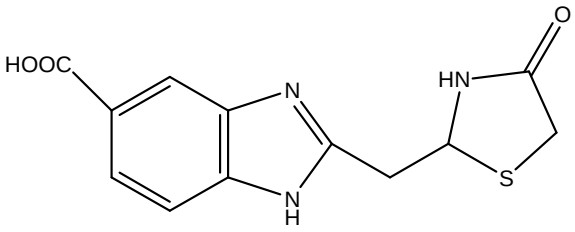


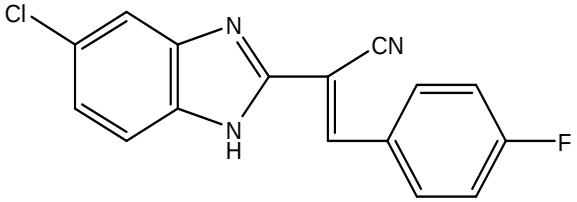

**Fig-13**

*Hanan M. Refaat* synthesized various series of 2-substituted benzimidazole. Several of the synthesized products were subjected for anticancer screening which revealed that all the tested compounds exhibited antitumor activity against human hepatocellular carcinoma, breast, adenocarcinoma, and human colon carcinoma. 3a and 4a showed the highest potency against human hepatocellular carcinoma. [31]




3a

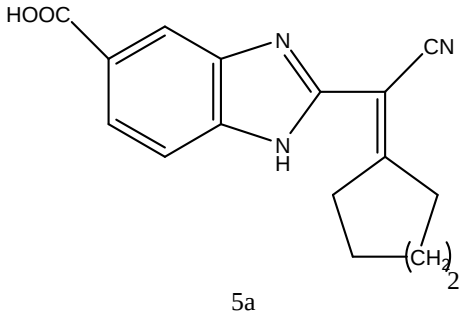
**Fig-14**




4a

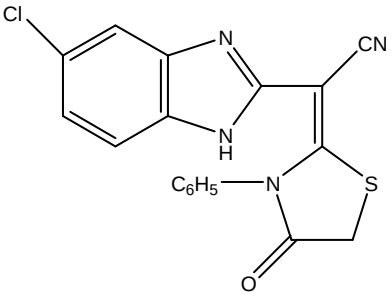
**Fig-15**

Compounds 5a 6a and 7a were most active against human breast adenocarcinoma.



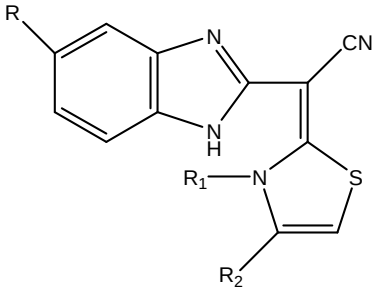

5a

**Fig-16**




6a

**Fig-17**

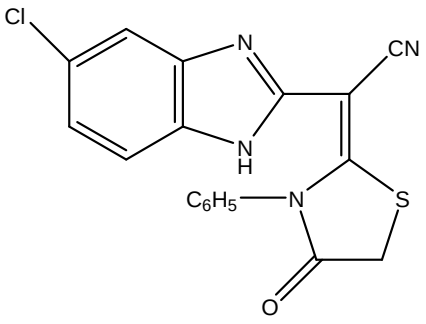



7a

For this compound R=COOH
$R_1$=4-Br-$C_6H_4$
$R_2$=2-$OCH_3$-$C_6H_4$

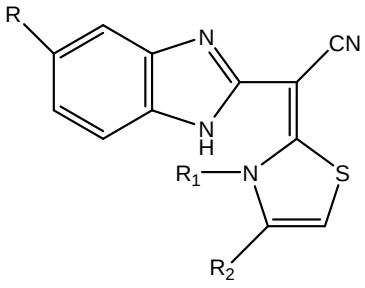
**Fig-18**

8a and 9a were moderately potent against human colon carcinoma.




8a

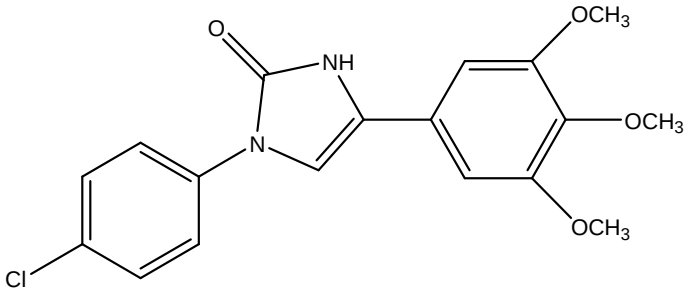
**Fig-19**




9a For this compound R=COOH
$R_1$=4-Br-$C_6H_4$
$R_2$=2-$OCH_3$-$C_6H_4$

**Fig-20**

*Cenzo congiu et al* synthesized a series of 1, 4-diarylimidazole-2(3H)-one derivatives and their 2-thione analogues and evaluated antitumor activity. This Compound show potent antitumor activity. [32]

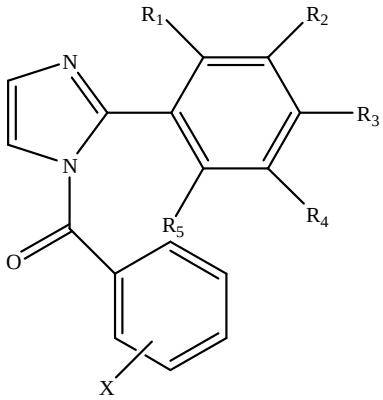



1-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1*H*-imidazol-2(3*H*)-one

**Fig-21**

**6. Antiviral activity**

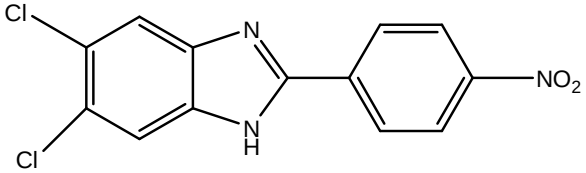
*Deepika Sharma et al* synthesized imidazole derivatives and the antiviral screening of (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones against viral strains indicated that compounds A and B selected as the most potent antiviral agents. Ribavirin was used as standard drug. [22]




For compound A, $R_1$=H,$R_2$=H,$R_3$=Cl,$R_4$=H,$R_5$=H,X=4-$NO_2$
B, $R_1$=H,$R_2$=H,$R_3$=$NO_2$,$R_4$=H,$R_5$=H,X=4-$NO_2$

**Fig-22**

*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 ([56-dichloro-2-(4-nitrophenyl) benzimidazole]) exhibited a high activity resulting more potent than reference drugs smycophenolic acid and 6-azauridine. [33]

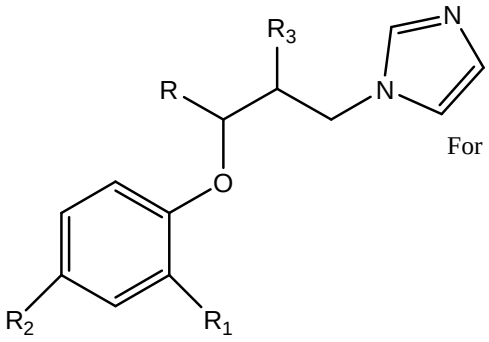



5,6-dichloro-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole

**Fig-23**

**7. Antilishmanial activity**

*Kalpana bhandari et al* synthesized a series of substituted aryloxy alkyl and aryloxy aryl alkyl imidazole and evaluated in vitro as antileishmanial against *Leshmania donovani*. Among all compounds exhibited 94–100% inhibition. [34]

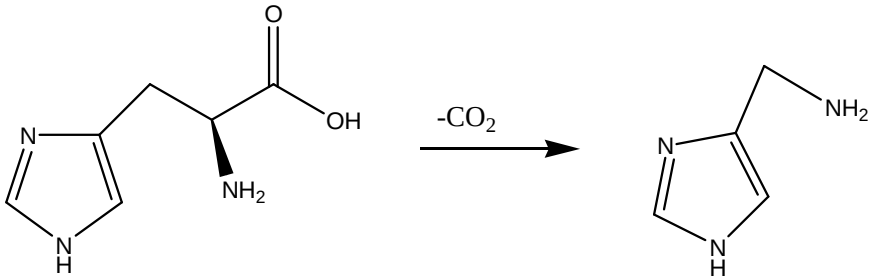



For compound R, $R_1$, $R_2$, $R_3$
A =Ph, H, $CF_3$, H
B =$CH_3$,H, $CF_3$, H
C =$CH_3$,H, $NO_2$, H
D =$CF_3$, F, $NO_2$, H
E =$CH_3$,$NO_2$,H, H
F =$CH_3$,$CH_3$,$NO_2$,H

**Fig-24**

**Biological significance of imidazole**

Imidazole is incorporated into many important biological molecules. The most important is the amino acid histidine, which has an imidazole side chain. 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. The relationship between histidine and histamine are shown below




**Applications of imidazole**

- One of the applications of imidazole is in the purification of His tagged proteins in immobilized metal affinity chromatography (IMAC). Imidazole is used to elute tagged proteins bound to Ni ions attached to the surface of beads in the chromatography column. An excess of imidazole is passed through the column, displaces the His-tagged from nickel co-ordination and free the His-tagged proteins.
- Imidazole can be used to prepare buffers in the pH range of 6.2-7.8 at room temperature. It is recommended as a component of a buffer for assay of horseradish peroxides. It is also used as a chelator for the binding of different divalent cations. [35]
- The oral administration of imidazole shows beneficial effects on psoriasis and seborrheic dermatitis. In psoriasis the improvement begins after a period of one and a half to three months. In seborrheic dermatitis the patients begin from less redness, itchiness, and scaling within a period of four to six weeks. The benefits of this treatment occur without the need for applications of ointments or other topical applications.

- The imidazole nucleus is an important synthetic strategy in drug discovery. Many imidazoles have been prepared as pharmacological agents Azomycine, Clotrimazole, Miconazole, Ergothionine, Clonidine and Moxonidine. One of the most important applications of imidazole derivatives is their used as material for treatment of denture stomatities. [36, 37]
- Imidazole has become an important part of many pharmaceuticals. Synthetic Imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, which stimulates the central nervous system. It is present in the anticancer medication mercaptopurine, which used in leukemia by interfering with DNA activities
- Imidazole also used in industry as a corrosion inhibitor on certain transition metals, such as copper. Conductivity of the copper decreases due to corrosion. Many compounds of industrial and technological importance contain imidazole derivatives. The thermostable polybenzimidazole imidazole fused to a benzene ring and acts as a fire retardant. Imidazole can also be found in various compounds which are used for photography and electronics.

## CONCLUSION

On the basis of various literature survey imidazole derivatives show various activity against antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. 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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