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A Review on "Imidazole and Various Biological Activities"

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HUMAN

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ABSTRACT

Imidazole is a five-member heterocyclic ring having three carbon atoms and two nitrogen atoms in the first and third places. Purine, histamine, histidine, and nucleic acid all include the imidazole ring, which is found in a variety of natural compounds. Because it is a polar and ionizable aromatic chemical, it enhances the pharmacokinetic properties of lead molecules and may thus be utilized to increase the solubility and bioavailability of poorly soluble lead compounds. In the realm of medicinal chemistry, imidazole derivatives have a special role. In drug development, incorporating the imidazole nucleus is a significant synthesis approach. The excellent therapeutic qualities of imidazole-related medicines have prompted medicinal chemists to develop a slew of new chemotherapy medications. In clinical medicine, imidazole medications have expanded their reach in treating a variety of ailments. In the realm of medicinal chemistry, there are several ways for synthesizing imidazoles as well as their diverse structural reactions. This page will go through the work that has been done in the past, as well as the chemistry and biological activity of imidazole

INTRODUCTION:

Medicinal chemistry is a branch of chemistry concerned with determining the impact of chemical structure on biological activity. It evolved from an empirical approach including organic synthesis of novel compounds based mostly on structural change and then determining their biological activity [1,2]. Medicinal chemistry is concerned with the discovery, development, interpretation, and identification of biologically active substances' mechanisms of action at the molecular level [3]. A five-membered nitrogen-containing heterocyclic ring can be found in the structures of a variety of physiologically active synthetic substances [4]. Privy structures have been described as structural frameworks, and N-containing polycyclic structures, In particular have been linked to a wide spectrum of biological activities. The imidazole nucleus has a variety of features in the realm of five-membered heterocyclic structures. The excellent therapeutic qualities of imidazole-related medicines have prompted medicinal chemists to develop a slew of new chemotherapy medications. In clinical medicine, imidazole medications have expanded their reach in treating a variety of ailments. Anticancer, b-lactamase inhibitors, 20-HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic, and antimalarial properties of imidazole are among its medicinal properties [5,8]. This family of antifungal azoles inhibits the buildup of methylated sterols, which disrupts the makeup of the membrane's lipid bilayer. At high doses, some imidazole medications may have a direct inhibitory effect on membranes, without interfering with sterolsand sterol esters [19,20]. Because microorganisms have defied prophylactic therapy longer thanany other form of life, infectious microbial sickness is a worldwide concern. Multidrug-resistant bacteria have become a serious concern in many nations throughout the world in recent decades. Antimicrobial resistance to -lactam antibiotics, macrolides, quinolones, and vancomycin, among other antimicrobial drugs, has become a major global concern [21]. Imidazole and its derivatives are said to be physiologically and pharmacologically active, andthey're used to treat a variety of illnesses.

Structure and Pharmacological Activities

Imidazoles are well-known heterocyclic compounds that are found in a wide range of pharmacological medicines and have key properties. Imidazole is a planar ring with five members that is soluble in water and other polar solvents. Because the hydrogen atom may

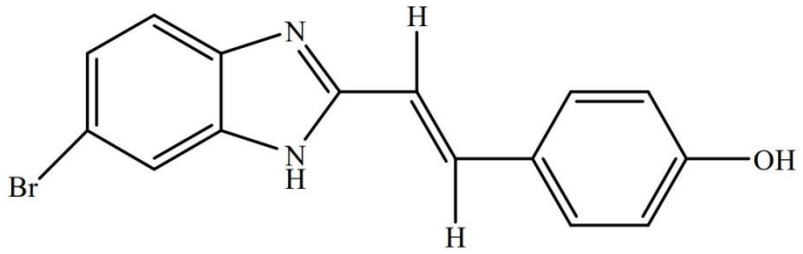
befound on either of the two nitrogen atoms, it exists in two equivalent tautomeric forms. It is a highly polar molecule with a predicted dipole of 3.61D and is completely water-soluble. The presence of a sextet of -electrons, consisting of a pair of electrons from the protonated nitrogenatom and one from each of the other four atoms in the ring, classifies the chemical as aromatic.Imidazole is amphoteric, which means it may act as an acid and a base.

Imidazole compounds have a variety of pharmacological effects, according to numerous literature reviews;

- 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 antibacterial activity

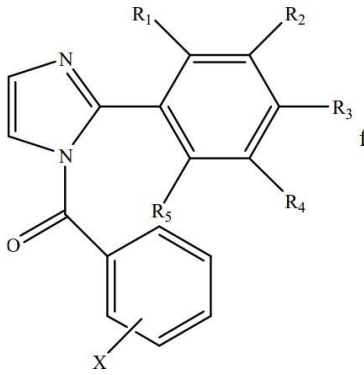
- *Ramya v et al* produced a variety of new 5-(nitro/Bromo)-styryl-2-benzimidazole derivatives and examined them for antibacterial, antifungal, and antibacterial activities against *Staphylococcus aureus, Escherichia coli, Enterococcus faecalis, and Klebsiella pneumoniae*. This was similar to ciprofloxacin [21].



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

Fig. 1

➢ *Deepika Sharma* and colleagues have created 2-(substituted phenyl)-1H-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]. Antimicrobial activity against gramme positive, Gram-negative, and fungal species was tested using -menthanone analogs. The antibiotic norfloxacin is used as a standard [22] and the following compound is the 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* bis-imidazole derivatives were produced and tested for antifungal and antimycobacterial activities. Against *Candidaalbicans* and *Candida glabrata,* all drugs exhibited moderate to good efficacy. Miconazole was utilized asa control medication [23].

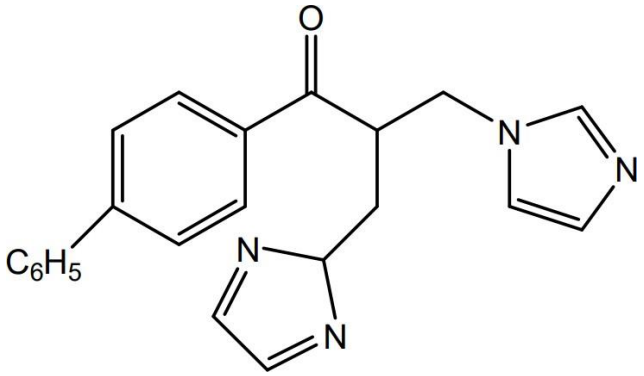


Fig. 3

➢ *Dorota Olender et al* nitroimidazole derivatives were produced and evaluated for antifungal activity against Sclerophoma pityophila using the usual nutrition technique. This chemical has a stronger antifungal effect [24].

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

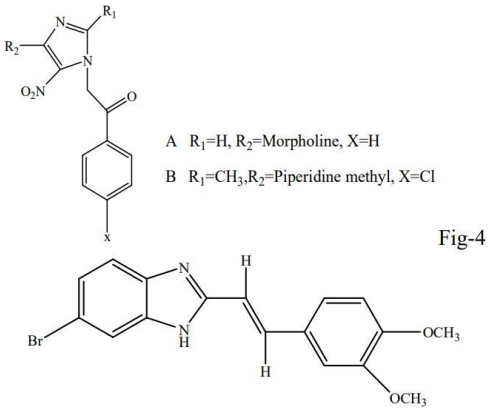
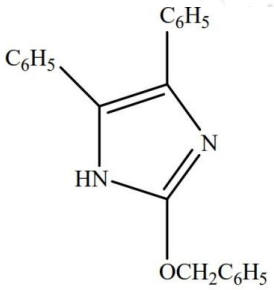


Fig. 5

2. Anti-inflammatory and analgesic activity

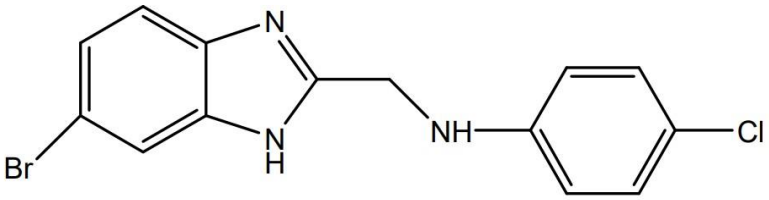
➢ *Puratchikody et al* the antiinflammatory effect of 2-substituted-4, 5-diphenyl-1H-imidazoles were tested using the Carrageenan-induced paw edoema technique. Thischemical has the most action, and indomethacin is employed as a control [25].



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

Fig. 6

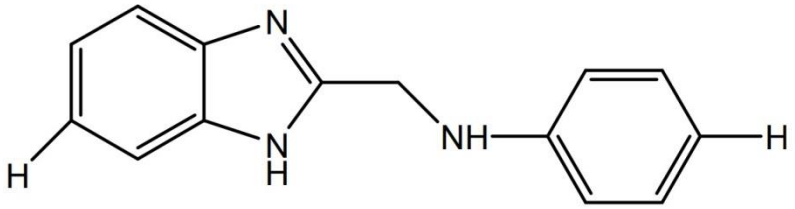
➢ *Kavitha C.S.et al* have created a variety of 2-methylaminibenzimidazole derivatives,which were then tested for analgesic and anti-inflammatory properties. When compared to the normal nimesulide medication, this molecule has analgesic efficacy [26].



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

Fig. 7

When compared to nimesulide, this chemical has a strong anti-inflammatory effect.

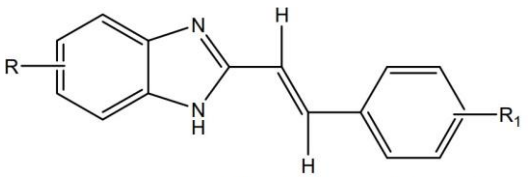


N-((1*H*-benzo[*d*]imidazol-2-yl)methyl)benzenamine

Fig. 8

3. Anti-tubercular activity

➢ *Ramya V et al* in vitro anti-tubercular activity against *Mycobacterium TB* was tested using a series of new 5-(nitro/bromo)-styryl-2-benzimidazoles (1–12) derivatives, and these compounds demonstrated good antitubercular activity. The reference medication was streptomycin [21].

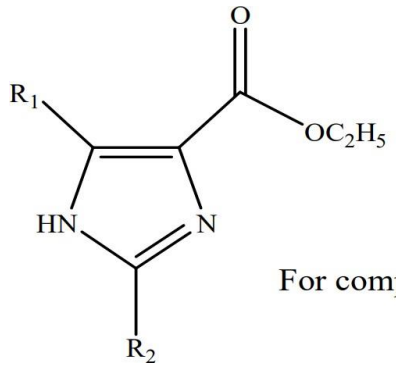


For This compound A R=Br, R_1=H
B R=Br, R_1=3,4-OCH_3
C R=Br, R_1=4-CH_3
D R=Br, R_1=2,4-Cl

Fig. 9

➢ *Preeti Gupta et al* discuss the anti-tuberculosis properties of ring-substituted -1H-imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid

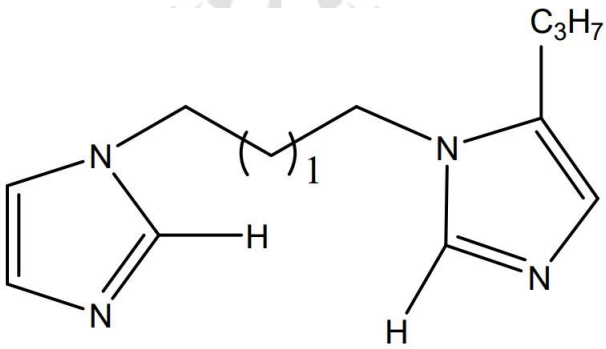
derivatives against drug-sensitive and drug-resistant *M. tuberculosis* strains The most powerful molecules were 2f and 2h [27].



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* series of imidazole derivatives were synthesized, and the compounds were tested against *M.tuberculosis*, with this drug showing strong antitubercular action [28].

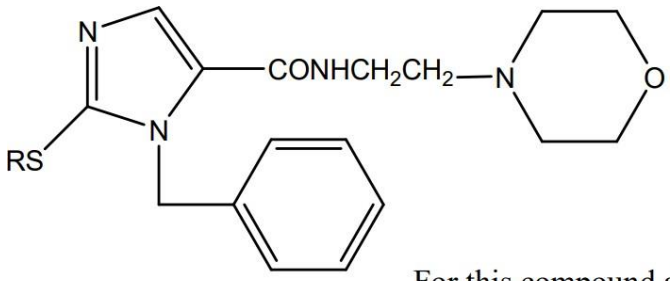


1-(3-(1*H*-imidazol-1-yl)propyl)-5-propyl-1*H*-imidazole

Fig. 11

4. Antidepressant activity

➢ *Farzin Hadizadeh et al* the antidepressant effect of moclobemide analogues was investigated using a forced swimming test after the phenyl ring of the moclobemide was replaced with a substituted imidazole. The analogues 7a-c were discovered to be more effective 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* examined the anticancer activity, and various new imidazole- (Benz) azole and imidazole piperazine compounds were synthesized. These were the most active compounds in the series, according to anticancer activity screening findings. Cisplatin was utilized as a control [30].

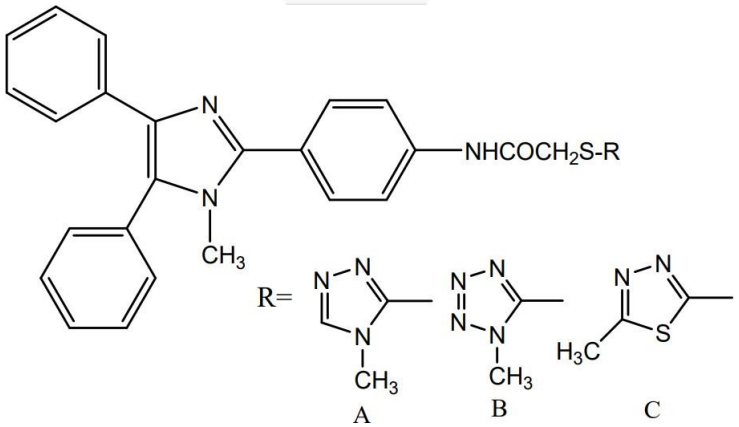
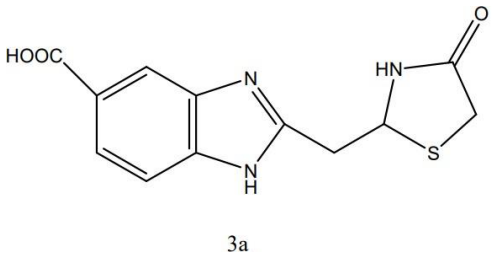


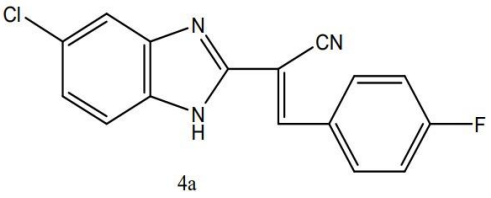
Fig. 13

➢ *Hanan M. Refaat et al* different series of 2-substituted benzimidazole produced Anti-cancer screening of many of the synthesized products found that all of the tested compounds had antitumor activity against human hepatocellular carcinoma, breast, adenocarcinoma, and human colon carcinoma. The most potent against human hepatocellular cancer was 3a and 4a [31].



3a

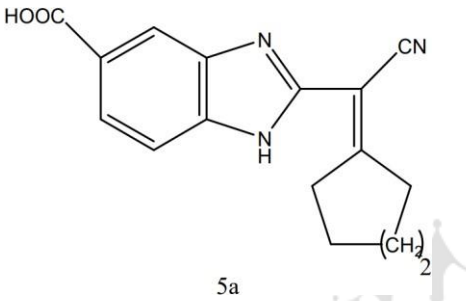
Fig. 14



4a

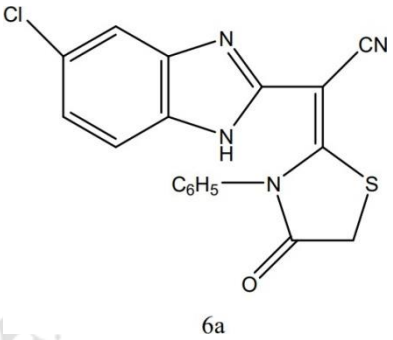
Fig. 15

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



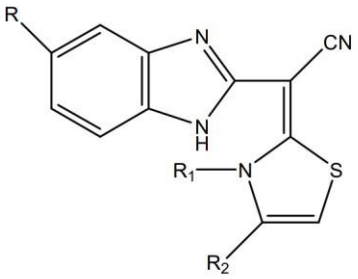
5a

Fig. 16



6a

Fig. 17

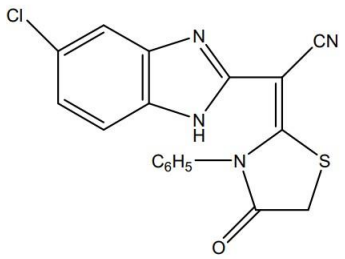


7a

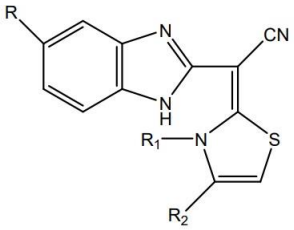
For this compound R=COOH
R_1=4-Br-C_6H_4
R_2=2-OCH_3-C_6H_4

Fig. 18

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



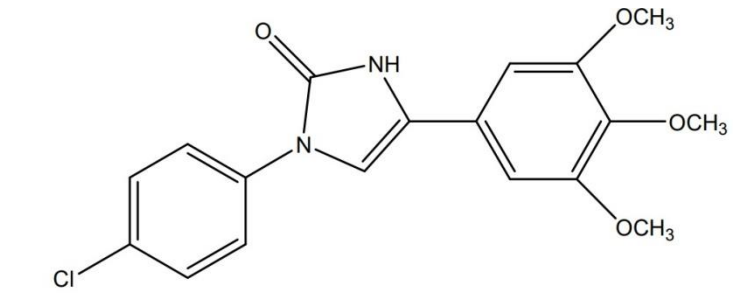
8a



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

Fig. 19 **Fig. 20**

➢ *Cenzo Congiu et al* and colleagues developed and tested a variety of 1, 4-diarylimidazole-2(3H)-one derivative and their 2-thione counterparts for anticancer activity. This compound has anti-cancer properties [32].

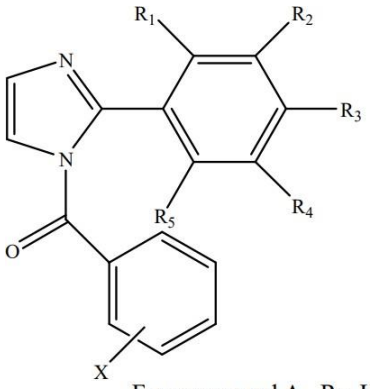


1-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1*H*-imidazol-2(3*H*)-one

Fig. 21

6. Antiviral activity

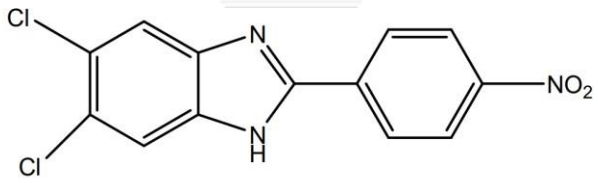
➢ Deepika Sharma and colleagues synthesized imidazole derivatives and tested(substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl] for antiviral activity. Compounds A and B were shown to be the most powerful antiviral agents when - methanones were tested against virus strains. The typical medication was ribavirin [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* and colleagues created 76 2-phenylbenzimidazole derivatives and tested them for cytotoxicity and antiviral efficacy against a variety of RNA and DNA viruses. The compound ([56- dichloro-2-(4-nitrophenyl) benzimidazole]) has a high activity, making it more powerful than smycophenolic acid and 6-azauridine as reference medicines [33].

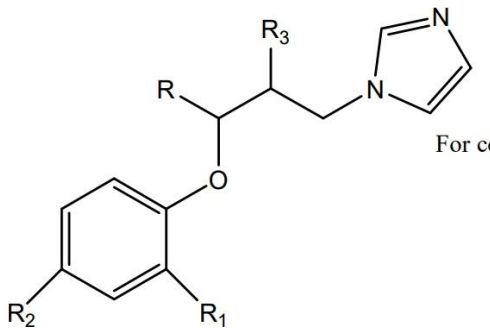


5,6-dichloro-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole

Fig. 23

7. Antilishmanial activity

➢ Kalpana Bhandari et al. developed a variety of substituted aryloxy alkyl and aryloxy aryl alkyl imidazoles and tested them for antileishmanial activity against Leshmania donovani in vitro. 94–100% inhibition was seen across all drugs [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

The biological significance of imidazole

Imidazole is found in a wide range of biological substances. The amino acid histidine, which possesses an imidazole side chain, is the most significant. Histidine is found in many proteinsand enzymes, and it is essential for hemoglobin's structure and binding capabilities. Decarboxylation of histidine produces histamine, a common biological molecule. It's a part ofthe toxin that causes urticaria, which is an allergic reaction. The following diagram depicts thelink between histidine and histamine.

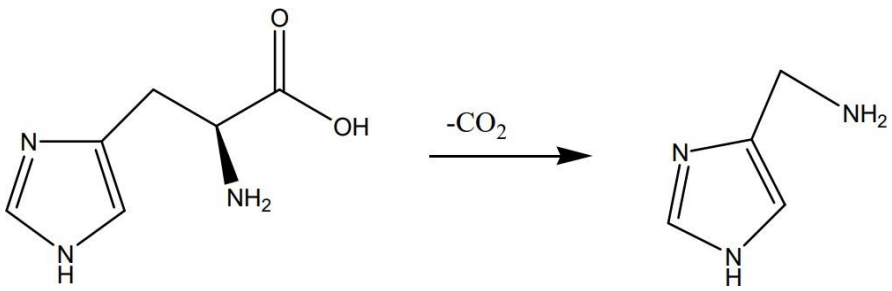


Fig. 25

Applications of imidazole

➢ Purification of His-tagged proteins in immobilized metal affinity chromatography is oneof the imidazole's uses (IMAC). To elute tagged proteins linked to Ni ions bonded to the surface of beads in the chromatography column, imidazole is utilized. An excess of imidazole passes through the column, dislodging the His-tagged proteins from nickel coordination and releasing them.

➢ Psoriasis and seborrheic dermatitis respond well to the oral intake of imidazole.

Improvement in psoriasis occurs after a period of one and a half to three months. Patientswith seborrheic dermatitis notice a reduction in redness, itching, and scale after four to six weeks. The advantages of this treatment are achieved without the use of ointments or other topical preparations.

➢ At room temperature, imidazole may be used to make buffers in the pH range of 6.2-

7.8. It's indicated as part of a buffer for horseradish peroxides testing. It may also be used as a chelator to bind certain divalent cations [35].

➢ Imidazole is also utilized as a corrosion inhibitor on transition metals like copper in industry. Copper's conductivity deteriorates as a result of corrosion. Imidazole derivatives are found in a wide range of industrial and technical chemicals. The fire retardant is a thermostable polybenzimidazole imidazole fused to a benzene ring. Imidazole can also be found in a variety of photographic and electrical chemicals.

➢ In drug development, the imidazole nucleus is an essential synthesis approach. Azomycine, Clotrimazole, Miconazole, Ergothioneine, Clonidine, and Moxonidine are only a few of the imidazoles that have been developed as pharmacological drugs. The use of derivatives as a material for treating denture stomatitis is one of their most important uses [36, 37].

➢ Imidazole has become a common ingredient in a variety of medications. Many fungicides, antifungal, antiprotozoal, and antihypertensive medicines contain synthetic imidazoles. Imidazole is a component of the theophylline molecule, which activates the central nervous system and is present in tea leaves and coffee beans. It's found in the anticancer drug mercaptopurine, which works by interfering with DNA activity to treat leukemia.

CONCLUSION

Based on the review imidazole derivatives have antibacterial, anti-inflammatory, analgesic, antitubercular, and anticancer properties. Slight changes to the substituents on the basic imidazole nucleus can further boost activity. When compared to other heterocyclic moieties, the histidine imidazole compound has a structural resemblance with histidine and may easily attach to protein molecules. As a result, imidazole has improved pharmacodynamic

properties.Furthermore, certain imidazole medications may have direct inhibitory effects on membranes at high doses, without interfering with sterols and sterol esters. Several recent novel therapeutic advancements in imidazole derivatives have demonstrated improved efficacy and reduced toxicity.

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