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IMIDAZOLE DERIVATIVES AND ITS PHARMACOLOGICAL ACTIVITIES

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ABSTRACT

Imidazole have a distinctive position in heterocyclic chemistry. Imidazole ring have planer nature contains five member ring with 3C and 2N atom in structure. It is a nitrogen based ring which exhibit pharmaceutical as well as biological importance. As imidazole contains two Nitrogen atom both having SP^2 Hybridization. The imidazole ring Contains natural bases like Purine, Histidine, and Amino acid. As imidazole is a polarizable ionic aromatic compound it enhance pharmacological properties of lead molecules. It is useful for efficient solubility and bioavailability of some main molecules. The imidazole possess activities like Antibacterial, Antifungal, Antitubercular, and Analgesic. Imidazole nucleus is main strategy for drug discovery. The derivatives containing imidazole have broadened Scope used as remedy for various clinical medicine. Various methods are developed for Synthesis of imidazole and its derivatives having extensive scope in medicinal chemistry. This paper Focuses on chemistry and various pharmacological Actions of imidazole and is derivatives.

KEYWORDS: Analgesic; Anticancer; Antifungal; Antitubercular; Antimicrobial; Imidazole.

INTRODUCTION

Imidazole is a five member ring, it is solubilize in Water. It has wide spectrum of application in pharmaceutical field. Both nitrogen are SP[2] hybridized. Imidazole contains components of human organisms such as amino acid histidine, Cyanocobalamin, and the bases of DNA structures like purines, histamines and biotin.[1]

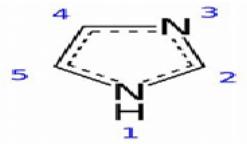


fig-1

The derivatives of imidazole are pharmacologically and biologically active found its application for curing of various infections and disease therapies. Imidazole has amphoteric in nature it acts as acid as well as base.[2]

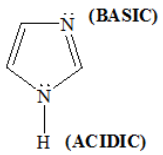


fig-2

Imidazole is planar, heteroatom compound containing 3C and 2N atom in one and two positions. Imidazole are Capable of nucleophilic attack and electrophilic attack. Imidazole having Melting point 88.9^0C and it has boiling point 267.8^0C. It has molecular formula $C_3H_4N_2$. Imidazole found firstly then it named as glyoxalin it was prepared by reaction of glyoxal and ammonia.(fig-4). The derivative of 1, 3-diazole shows different biological activities like anticancer, antibacterial, antifungal, analgesic, antimicrobial. As it was present equivalently undergoes tautomerism because hydrogen atom can be present either of two nitrogen atom. (fig-3).[4]

fig-3

Tautomerism of compounds

Synthesis of imidazole and its derivatives

Imidazole was first reported in 1858 by Heinrich debus from glyoxal with formaldehyde.

The Medicinal Chemistry serving development, discovery, Interpretation, and identification of various biologically active compounds.

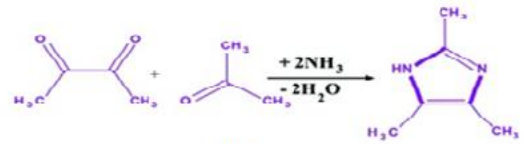


fig-4

There are various methods are available for synthesizing imidazole derivatives some of these are mention below.

Scheme-I

Debus- Radziszewski Synthesis.

In this synthesis imidazole is formed using dicarbonyl, aldehyde and ammonia. The dicarbonyl compound generally used is glyoxal, and 1.2-diketone. Benzil in addition with benzaldehyde in presence of ammonia it gives 2, 4, 5 – triphenylimidazole[4][Figure-5]

Scheme-II

Wallach synthesis

When N, N- dimethyloxamide is react with phosphorous pentachloride gives compound containing Chlorine using hydrogen iodide as reducing agent it gives substituted derivative of imidazole that is N-methyl imidazole.[3][Figure-6]

Scheme-III

Mark Wald synthesis

2-mercaptoimidazole synthesized by using aminoketone and Potassium thiocyanate.[4][Figure-7]

Scheme-IV

Dehydrogenation of Imidazolines

Knapp and coworkers are introduced milder agent barium manganite for converting Imidazolines in the imidazole's in presence Sulphur. Imidazolines synthesized using alkyl nitriles in addition with 1, 2 ethanediamine in presence of $BaMnO_4$ yield-substituted Imidazoles.[3][Figure-8]

Imidazole derivative synthesis Reaction

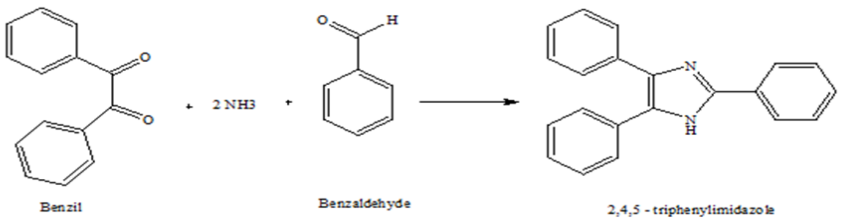


fig-5

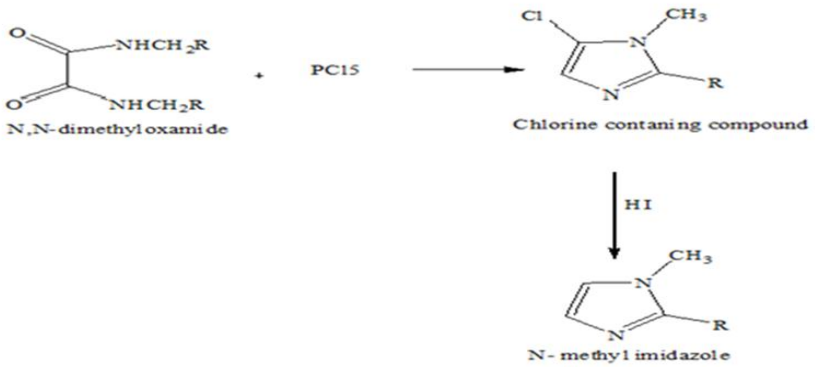


fig-6

fig-7

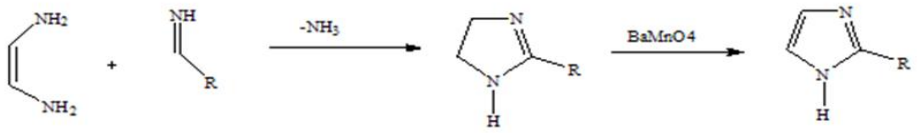
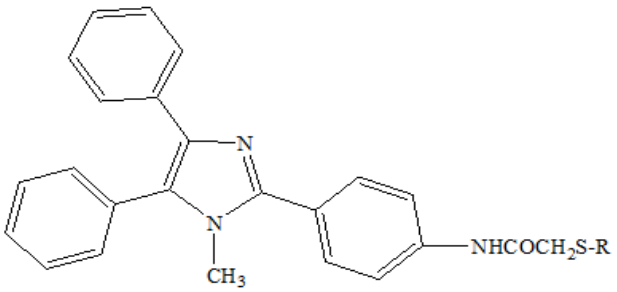


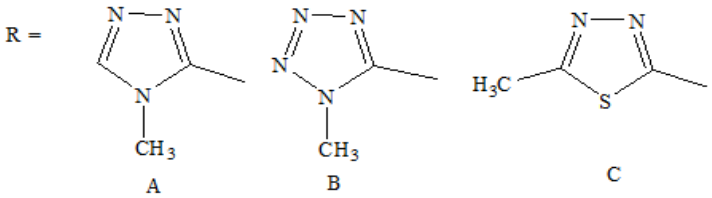
fig-8

Pharmacological Activities

Anticancer Activity

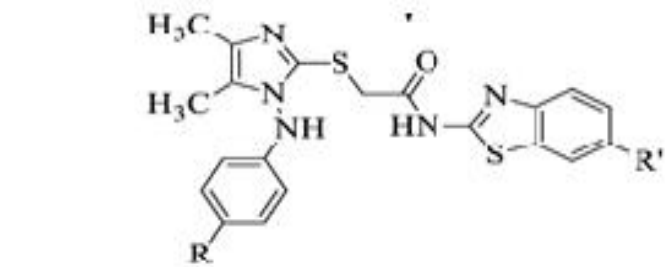
Yusuf et al synthesized many novel imidazole-(Benz) azole and imidazole derivatives of epiperazine for investigation of anticancer activity. After screening it was revealed that these are the most active compounds. Epiperazine derivatives acts on dopaminergic antagonists. Cisplatin is used as Reference drug.[3]





imidazole-(Benz) azole and imidazole epiperazine derivatives

fig-9



2-((1-((4-substitutedphenyl)amino)-4,5-dimethyl-1*H*-imidazol-2-yl)thio)-*N*-(6-substitutedbenzo[*d*]thiazol-2-yl)acetamide

fig-10

2-((1-((4-substituted phenyl) amino) 4,5-dimethyl-1H-imidazole-2-yl)-N(6-substitued benzo)d) thiazol-2-yl)acetamide was developed by Yurttas et al by reaction of 3-cholorobutan-2-one and 4-substituted phenyl hydrazine (fig-10). Cisplatin used as standard drug.[5]

Alkahatani et al Synthesized benzo[d]imidazole derivatives as probable anticancer agents.5,6- Dichloro-1-cyclopentyl-1H-benzo[d] imidazole it shows activity of cancer cells in potent anti-proliferative form.[6]

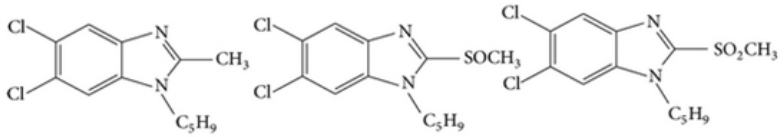
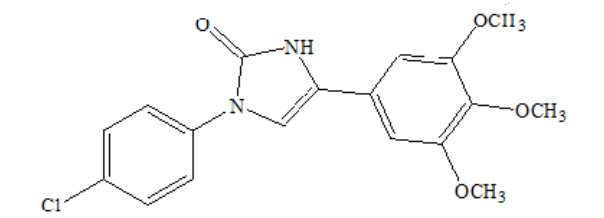


fig-11

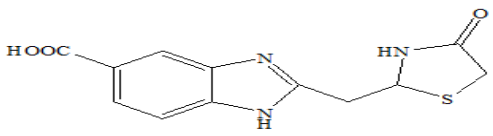
Cenzo et al Synthesized compound of 1-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1H-imidazol-2(3H)-one derivatives and analogues of thione aslo evaluated for the activity. (fig 12). It shows a antitumor activity.[7]



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

fig-12

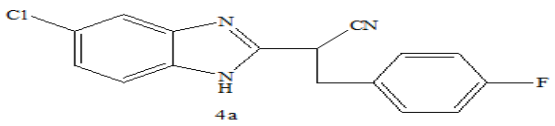
Hanan et al. synthesized derivatives of imidazole they are undergoing activity of antitumour. In this compounds revealed that tested compounds shows antitumour activity against Various types of cancers like malignant hepatoma, breast,and human colon. 3a fig(13) and 4a fig (14) both figure showed highest potency against malignant hepatoma.[8]



3a

2-((4-oxothiazolidin-2-yl)methyl)-1*H*-benzo[*d*]imidazole-5-carboxylic acid

fig-13



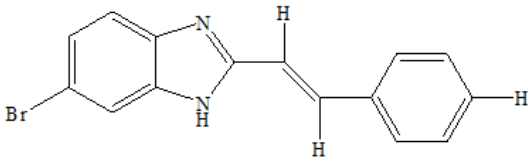
4a

2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-fluorophenyl)propanenitrile

fig-14

Antitubercular Activity

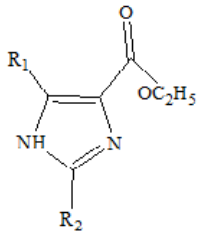
Ramya et al Synthesized series of novel (6-(nitro/bromo)-styryl-2-benzimidazole derivatives undergoing anti-tubercular activity against Mycobacterium tuberculosis it shows better antitubercular activities (fig-15). Streptomycin used as reference drug.



(*E*)-6-bromo-2-styryl-1*H*-benzo[*d*]imidazole

fig-15

Preeti et al showing antimycobacterial activities for derivatives 1H-imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid in opposite to Drug-Sensitive and Drug-resistant strains of mycobacterium tuberculosis. 2f and 2h compounds are refer as most potent compound (fig-16).[10]

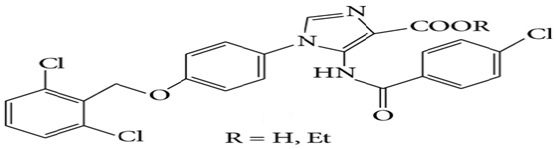


For Compound: 2f=R_1=R_2= C_5H_9
2h=R_1=R_2= C_6H_{11}

1H imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives

fig-16

Lu et al synthesizing series of substituted 4-(2,6-dichlorobenzyloxy)phenyl thiazole,Oxazole and imidazole derivatives. This derivatives screening antitubercular activities against Mycobacterium tuberculosis fig(17)[12]

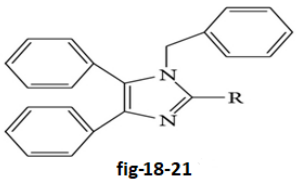


R = H, Et

fig-17

Analgesic activity

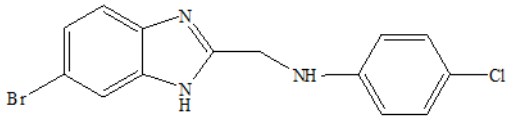
Ucucu et al synthesized compound 1-benzyl-2-substituted-4,5-diphenyl-1H-imidazole derivatives. For analgesic acivivity Swiss albino rat were used having both sexes weight of that is approximately 23–36 g. The derivatives which Screened for acitvity Shows moderate response.Only 18 and 19 Showing a good activity and compound 20 and 21 ranges is not far from morphine compound. As morphine used as reference drug.(fig-18)[11]



R=18-Ph-o-Br
19-Ph-M-OCH3,p-OH
20-Ph-o-OH
21-Ph-o-No2

fig-18-21

Kavitha et al synthesized series of N-((6-bromo-1H-benzo[d]imidazol-2-yl)-4-chloroanilline and newly synthesized compounds were screened for analgesic activity (fig 22).This compound shows analgesic activity in comparison with reference drug nimesulide.[13]

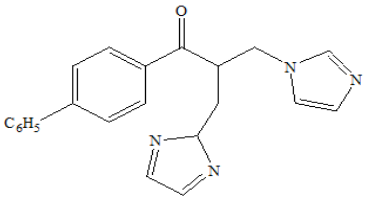


N-((6-bromo-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-chloroaniline

fig-22

Antifungal Activity

Daniele et al synthesized 2-((1H-imidazol-1-yl) methyl)-1-(biphenyl-4-yl)-3-(2H-imidazol-2-yl) propan-1-one were screening for antifungal activity. The compound shows mediate activity against *Candida Albicans* and *Candida glabarata.* Miconazole used as reference drug. (Fig-23).[25]

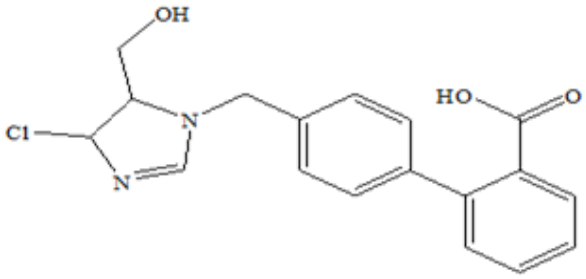


2-((1*H*-imidazol-1-yl)methyl)-1-(biphenyl-4-yl)-3-(2*H*-imidazol-2-yl)propan-1-one

fig-23

Antimicrobial Activity

Hreenivas et. al. Compounds were screening for their antibacterial activity. In Nutrient agar media concentration of 100µg/ml performing cup-plate method against S. *aureus* and *B. subtilis* and it includes antifungal activity against *C. albicans and A.niger by* cup plate method at 100µg/ml in agar media. DMSO used as standard solvent for antimicrobial activity. Streptomycin used as reference drug. Results are mentioned in cm.[16]

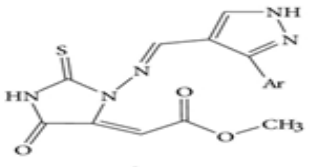


4'-((4-chloro-5-(hydroxymethyl)-4,5-dihydro-1*H*-imidazol-1-yl)methyl)biphenyl-2-carboxylic acid

fig-24

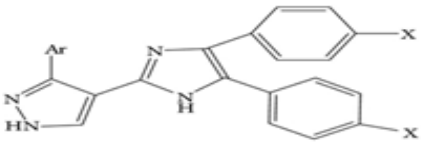
Antibacterial Activity

Vijesh et al Synthesized compounds undergoing antibacterial activity 1a-d and 2a-j.(fig-25) *E.coli, S.aureus, B. subtilis, P. aeruginosa* were used for investigation of activity. Antibacterial screening revealing some of tested compounds showing good inhibition against various microbial strains. Streptomycin used as standard drug.[21]



1a–d

1a	2,4-Dichlorophenyl
1b	2,5-Dichlorothiophene
1c	4-SCH_3-C_6H_4
1d	4-CH_3-C_6H_4



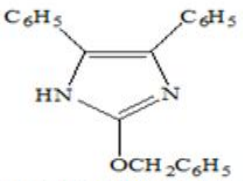
2a–j

	Ar	X
2a	4-SCH_3-C_6H_4	H
2b	2,4-Dichlorophenyl	H
2c	Biphenyl	H
2d	4-CH_3-C_6H_4	H
2e	2,5-Dichlorothiophene	H
2f	4-SCH_3-C_6H_4	Br
2g	2,4-Dichlorophenyl	Br
2h	Biphenyl	Br
2i	4-CH_3-C_6H_4	Br
2j	2,5-Dichlorothiophene	Br

fig-25

Anti-inflammatory Activity

Puratchikody et al Synthesized derivative 2-substituted-4, 5-diphenyl-1H-imidazole. Carrageenan –induced Paw edema used for screening anti-inflammatory activity (fig-26). It shows maximum activity. Indomethacin used as reference drug.[19]



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

fig-26

- Imidazole Drug combination with interactions.

Combination	Interactions
Alcohol/ imidazole	Metronidazole has an Antabuse effect. Alcohol is prohibited during therapy of metronidazole. Imidazole derivative Ketoconazole shows interaction with alcohol.
Antacid/imidazole	Absorption of imidazoles reduces by antacid.
Cisapride /imidazole	Cisapride should not taken orally or parenterally fluconazole, itraconazole, ketoconazole, or miconazole. Due to risk of ventricular arrhythmias.
Cytotoxic/ imidazoles	Metabolism of cyclosporine inhibited by Ketoconazole and Metabolism of fluorouracil inhibited by Metronidazole
Rifampicin / imidazoles	Due to administration of Rifampicin by mouth or intravenous route reduction of plasma concentration of Ketoconazole happen it leads to failure of antifungal treatment.

CONCLUSION

Drugs containing nucleus of imidazole shows wide spectrum of applications in heterocyclic as well as pharmaceutical field. The imidazole having excessive attention because of their various pharmacological assets. Imidazole and its derivatives shows pharmacological activities like anticancer, antibacterial, analgesic, antifungal, anti-inflammatory and antitubercular. Imidazole having structural similarities with histidine compound thus it binds to Protein molecules with alleviate comparison with different heterocyclic moieties. Imidazole derivatives having low toxic nature it provided as a therapeutic agent to serve a mankind. It shows that improvement in activity achieved by substitution on imidazole nucleus. Imidazole shows better pharmacodynamics properties, and it also shown wide range of pharmaceutical applications.

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