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REVIEW ARTICLE

Indispensability of Imidazole Moiety in new drug development-A Review

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ABSTRACT
The significance of imidazole heterocyclic nucleus in new drug development is worth mentioning. The wide range of its application has drawn an immense attention to the researchers to synthesize various imidazole derivatives, which may possess various pharmacological efficacies. In view of these observations we tried to track down the immense potentiality of imidazole ring system when accompanied with different scaffolds are reported herein. This study may help the researchers to hold the importance of various substituent's in attenuating the pharmacological activity and incorporate these understanding in designing novel derivatives.
KEY WORDS: *Imidazole, Anti-inflammatory, anti-tubercular, Debus Synthesis*

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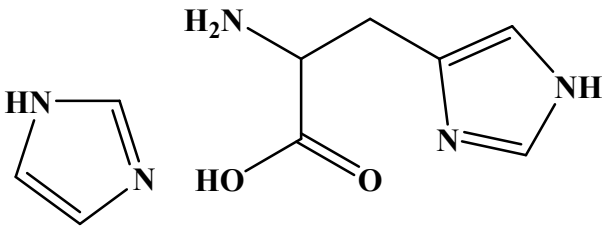
INTRODUCTION

Imidazole is a compound with the formula $C_3H_4N_2$. It was first named as gluoxaline (first synthesis is with glyoxal and ammonia). Amphoteric nature is liable to electrophilic and nucleophilic attack [1]. This aromatic heterocyclic may also be a "one,three-diazole" and is classed as achemical compound. Imidazole (1) relate to the parent compound, whereas imidazole's are a category of heterocyclic with similar ring structure, however variable substituents. This ring system is present in necessary biological building blocks, like histidine (2), and therefore the connected hormone histamine (3). Imidazole can perform as a base and as a weak acid. Many medicines contain an imidazole ring, like antifungal medication and Nitro imidazole (4) [2-6].



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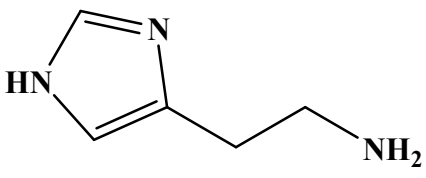

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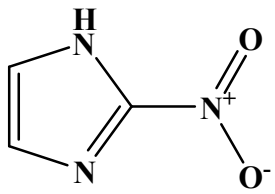


(4)

Imidazole's are common scaffolds in extremely vital biomolecules as well as the essential amino acid histidine, histamine, pilocarpine alkaloids [7,8] and alternative alkaloids, that are shown to exhibit touching biological activities such as antimicrobial, anti-inflammatory drug [9,10], Histamine H_3 antagonist [9,11], antioxidant [12], farnesyl transferase and geranyltrasferase-inhibitor [13], antitumor [14], antiparasitic [15], antiprotozoal [16,17] and antidiabetic, action [18]. 2-substituted imidazolines are synthetically vital because of their use as a synthetic intermediates [19], catalysts [20], chiral auxiliaries [21], chiral catalysts [22] and ligands for asymmetric catalysis [23] innumerous synthetic reactions. To date, there are many synthetic methods for 2-imidazolines beginning in themain from aldehydes and ethylenediamine with NBS [24]. Some ways includes synthesis from nitriles [25], c arboxylic acids [26], esters [27], ortho-esters [28], hydroxy-amides [29] and mono or disubstituted chlorodicyanovinyl benzene [30]. It's also known as a very important synthon for the preparation of biologically active compounds [31].

Properties

Imidazole may be a monoacidic base having the power to make crystalline salts with acids. The melting point of number of characteristic imidazolium salts [32]. Imidazole is a 5-membered planar ring that is soluble in water and different polar solvents. It exists in two equal tautomeric forms, 1*H*-imidazole and 3*H*-imidazole; because the hydrogen atoms are often located on either of the two nitrogen atoms. Imidazole is an extremely polar compound, as evidenced by a calculated dipole of 3.61D, and is ab solutely soluble in water. The compound is classed as aromatic due to the presence of a sextet of π-electrons, consisting of a combine of electrons from the protonated N- atom and one from each of the remaining four atoms of the ring [33].

Imidazole is amphoteric i.e. it will perform as each an acid and as a base. As an acid, the p*K*a of imidazole is 14.5. As a base, the p*K*a of the conjugate acid is nearly 7, makingimidazole around sixty times more basic than alkali. Being a polar and ionisable aromatic compound, it improves pharmacokinetic attributes of lead molecules and thus usedas a remedy to optimise solubility and bioavailability parameters of proposed poorly soluble leadmolecules. It's a colourless organic compound having melting point 89-91 °C and boiling pointis 256 ° C. It has high boiling point as related all different five membered heterocyclic compounds[34].

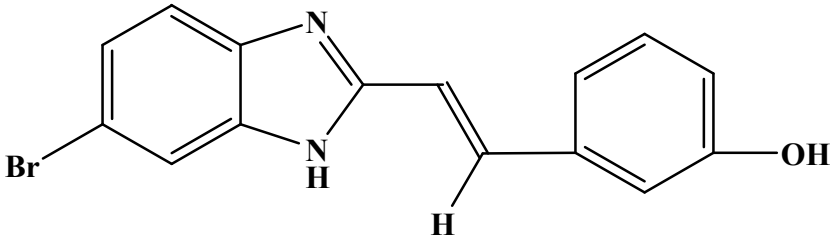
Pharmacological activities

On the premise of numerous literature surveys Imidazole derivatives shows various pharmacological activities,

- Anti-fungousand Anti-bacterial activity
- Anti-inflammatory activity and analgesic activity
- Anti-tubercular activity
- Anti-depressant activity
- Anti-cancer activity
- Anti-viral activity
- Antileishmanial activity
- Anticonvulsant activity
- Antitumor activity

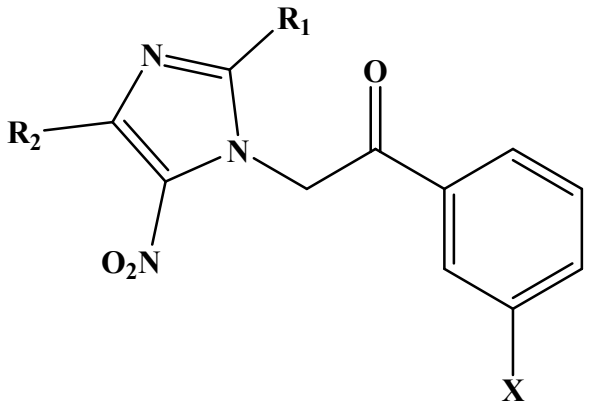
1. Antifungal and Anti-bacterial activity

A series of novel 5-(nitro/bromo)-styryl-2-benzimidazole derivatives and safe for the antibacterial activity against Staphylococciaureus, Escherichia coli, Enterococcus faecalis, and Klebsiellapneumoniae and antifungal activity against fungus albicans and Aspergillus fumigates synthesized by *Ramya v et al*(2009). This was comparable with ciprofloxacin[35].

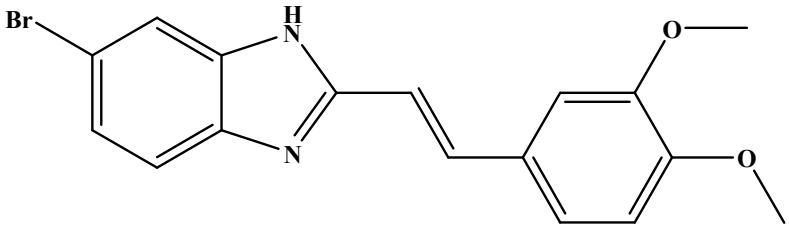


3-((*E*)-2-(6-bromo-1*H*-benzo[*d*]imidazol-2-yl)vinyl)phenol

Nitroimidazole derivatives are synthesized and tested for their antifungal activity by *Dorota Olender et al* (2009), using the quality nutrient methodology against *sclerophoma pityophila*. This compound shows stronger fungistatic activity [36].



A R1=H, R2=Morpholin, X=H

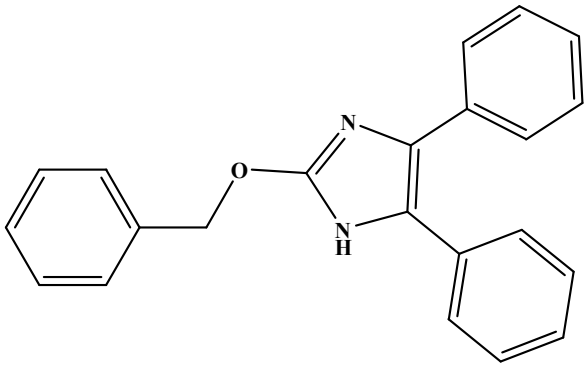


2-(3,4-dimethoxystyryl)-6-bromo-1*H*-benzo[d]imidazole

B R1=CH3, R2= Piperidine methyl, X= Cl

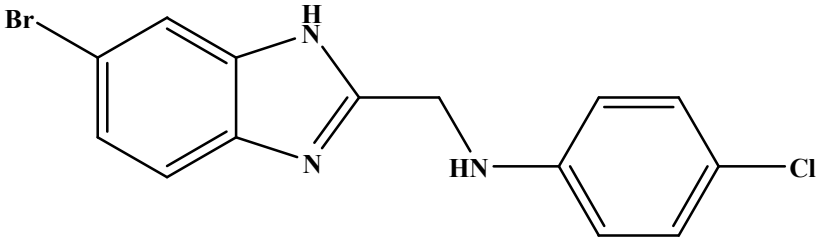
2. Anti -inflammatory and analgesic activity

A study on 2-substituted-4, 5-diphenyl-1-imidazole, checked the anti-inflammatory activity *Puratchikody A. et al* (2007), supported on Carrageenan-induced paw edema methodology. Indomethacin used as reference drug and this compound shows best activity [37].



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

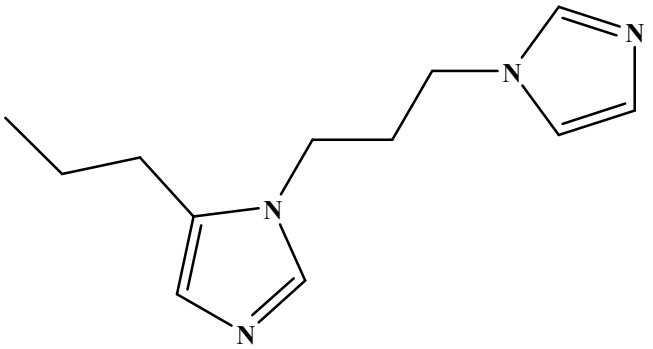
A series of 2 methylaminibenzimidazole derivatives synthesized by *Kavitha C.S.et al* (2010) were screened for analgesic and Anti-inflammatory activities. Nimesulide is employed as reference drug and this compound shows best analgesic activity[38].



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

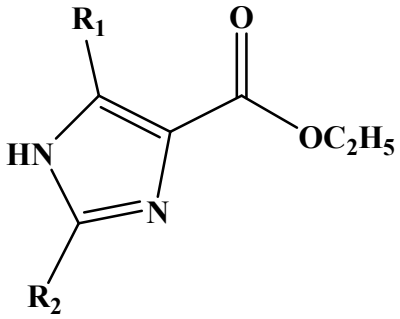
3. Antitubercular activity

A series of imidazole derivatives and compounds were synthesized and screened against M .tuberculosis where this compound showed good antitubercular activity [39].



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

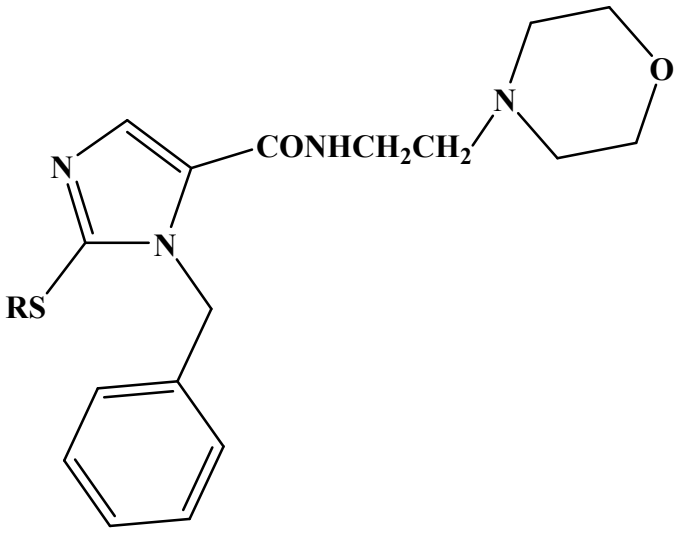
Anti-mycobacterium tuberculosis activities of ring substituted -1*H*Imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives against durg-sensetive and durg-resistent M. tuberculosis strains described by *Preeti Gupta et al* (2010). 2f and 2h compounds were most potent com-



For compound 2f=R1=R2=c-C5H9; 2h=R1=R2=C6H11

4.Antidepressant activity

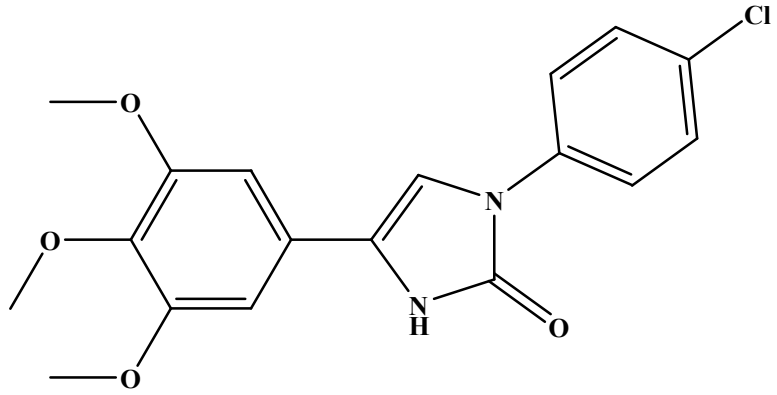
Moclobemide analogues synthesized by replacing moclobemide phenylring with substituted imidazole by *FarzinHadizadeh et al* (2010) and studied for the antidepressant activity using forcedSwimming test. Analogues 7a-c was found to be more potent than moclobemide[41].



a) R= CH3
b) R=C2H5
c) R=CH2C6H5

5. Anticancer activity

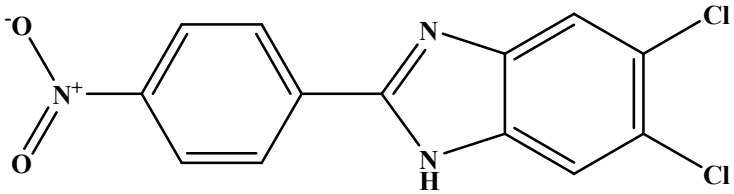
A series of 1, 4-diarylimidazole-2(3H)-one derivativesand their2-thione analogues are synthesized by *Cenzo-congiu et al* (2008) and evaluated antitumor activity. This Compound show potent antitumoractivity [42].



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

6. Antiviral activity

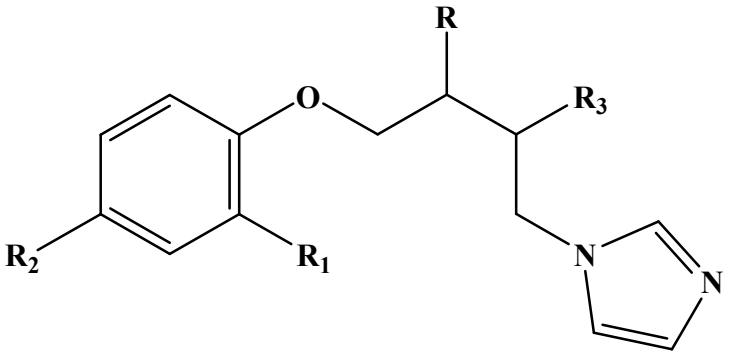
Seventy six 2-phenylbenzimidazole derivatives are synthesized by *Michele Tonelli et al* (2010) and evaluated for cytotoxicity and anti-viral activity against a panel of RNA and DNA viruses. Compound ([56- dichloro-2-(4-nitrophenyl) benzimidazole]) exhibited a high activity resulting more potent thanreference drugs smycophe-nolic acid and 6-azauridine [43].



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

7. Antilishmanial activity

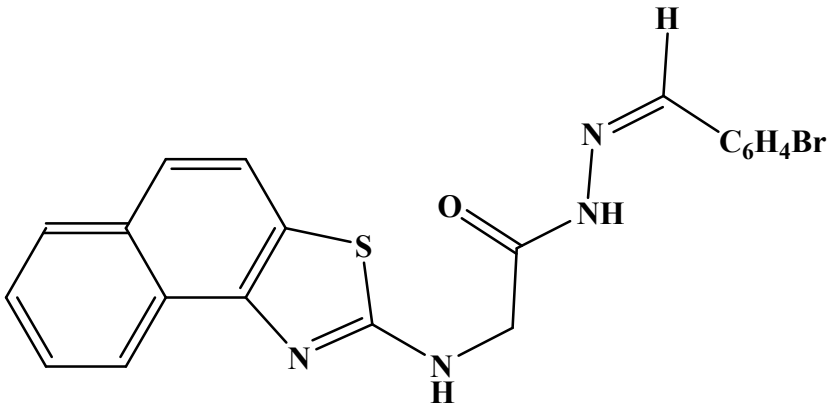
A series of substituted aryloxy alkyl and aryloxy aryl alkylimidazole are synthesized by *Kalpanabhandari et al* (2010) and evaluated in vitro as antileishmanial against *Leshmaniadonovani*. Among allcompounds exhibited 94–100% inhibition [44].



R,	R1,	R2,	R3
A =Ph,	H,	CF3,	H
B =CH3,	H,	CF3,	H
C =CH3,	H,	NO2,	H
D =CF3,	F,	NO2,	H
E =CH3,	NO2,	H,	H
F =CH3,	CH3,	NO2,	H

8) Anticonvulsant activity:

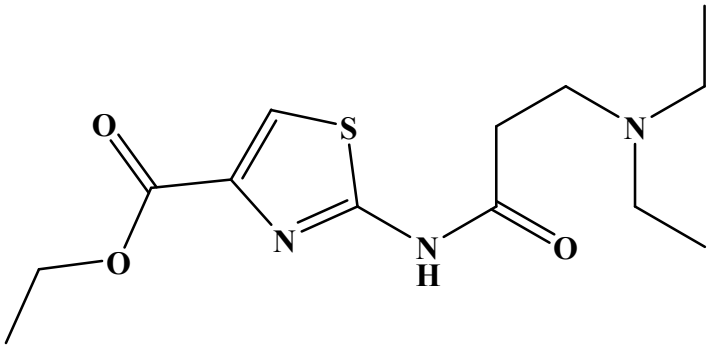
A series of N4-(naphtha [1,2-d]thiazol-2- yl)semicarbazides33 weresynthesized and designedby Azam*et al.* (2009), evaluated for theiranticonvulsant and neurotoxicity studies [45].



(*Z*)-*N*'-(7-bromohepta-2,4,6-triynylidene)-2-(naphtho[1,2-*d*]thiazol-2-ylamino)acetohydrazide

9) Antitumor activity:

The synthesis of several new ethyl 2-substituted aminothiazole-4-carboxylate analogs havebeen described and the prepared compounds were tested for their in vitro antitumor activity against 60 human tumor cell lines by the National Cancer Institute (NCI) and showed potential anticancer activity. Ethyl 2-[3- (diethylamino)-propanamido]-thiazole-4-carboxylate exhibited remarkable activity against RPMI-8226 leukemia cell line with GI value of 0.08 μM and a broad spectrum activity against all the tumor cell lines used with GI (MG-MID) value of 38.3 μM[46].



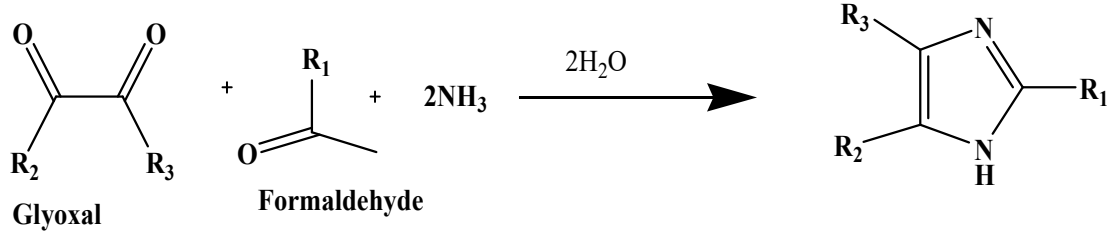
Ethyl 2-[3- (diethylamino)-propanamido]-thiazole-4-carboxylate

General Methods of Preparation

Imidazole can be synthesized by numerous methods. Many ofthese syntheses can also be applied to different substituted imidazoles and imidazole derivatives simply by varying the functional groups on the reactants. Several approaches are available for synthesis of imidazoles as, Debus synthesis, Radiszewski synthesis, Wallach synthesis, dehydrogenation of imidazolines, and Marckwald synthesis [47]. Details of the synthetic procedures are given below.

Debus Synthesis [48]

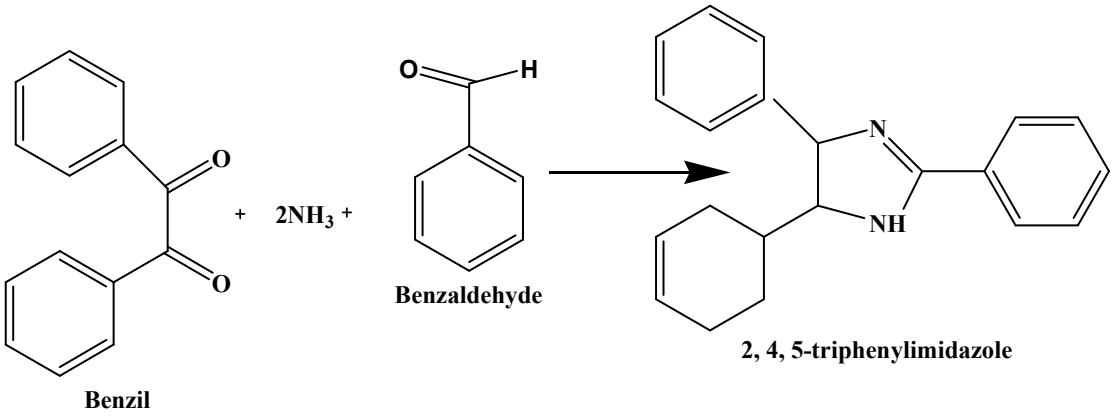
Debus Synthesised imidazole by using glyoxal and formaldehyde in ammonia. This synthesis, while producing relatively low yields, is still used for creating C-substituted Imidazoles.



Radiszewski Synthesis [49-51]

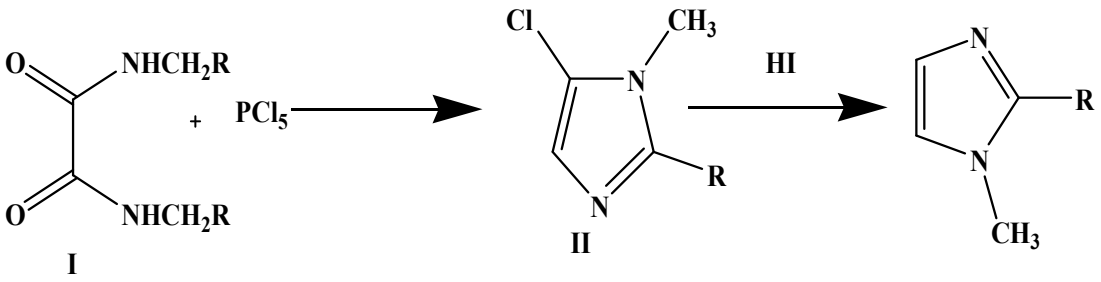
Radiszewski reported the condensation of a dicarbonyl compound, benzil and α- ketoaldehyde, benzalde-

hyde or α-diketones in the presence of ammonia, yield 2, 4, 5-triphenylimidazole.



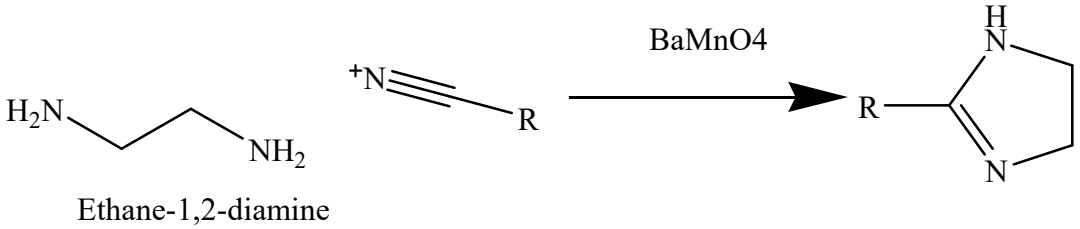
Wallach Synthesis [52-55]

Wallach reported that when N, N- dimethyloxamide (I) is treated with phosphorus Pentachloride, a chlorine containing compound (II) is obtained which on reduction with hydroiodic acid give N- methyl imidazole (III). Under the same condition N, N-diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl –2- methyl imidazole.



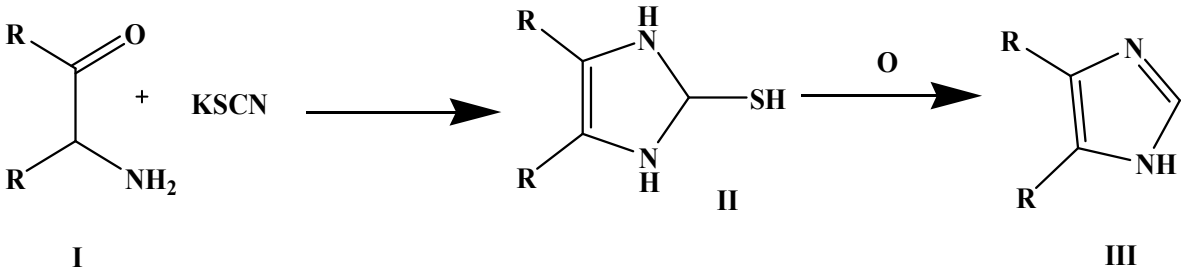
Dehydrogenation of Imidazoline[56]

A milder reagent barium managnateconvert imidazolines to imidazoles in the presence of sulphur. Imidazolines obtained from 1, 2 ethanediamine and alkyl nitriles on reaction with BaMnO4 yield 2-substituted imidazoles.



Markwald Synthesis [56]

The preparation of 2- mercaptoimidazoles from α-amino ketones (I) or aldehyde and potassium thiocyanate is used for the synthesis of 2-thiol substituted imidazoles (II). The sulfur can readily be removed by a variety of oxidative method to give the desired imidazoles (III).



CONCLUSION

Imidazole is a unique scaffold in the field of new drug research. The above studies distinctly mention the potentiality of imidazole moiety, when substituted with various groups in easing out diverse range of disease states. Thus we can conclude that this review will clearly provide the researchers a vast array of information about the pharmacological study, which in turn help in designing a handful number of novel imidazole derivatives and analogs with a strong impact in curing many diseases.

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