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Chemical and Pharmacological Properties of Imidazoles

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ABSTRACT

Imidazole is major source of interest for many of medicinal chemist. It has various pharmacological potentials. This present review focused on different derivatives, chemistry of imidazole and its pharmacological actions as anti-helmintics, anticancer, antifungal and anti-inflammatory agent. Imidazoles being hetero-atomic planar five-member ring system have diverse chemistry with varying physical and chemical properties which may be exploited via forming various derivatives having varying pharmacological actions. Results of various combinations of different moieties with imidazole and their substitutions are reviewed in present article. Various methods for synthesizing imidazoles are discussed with their chemistry. Studying this chemistry, different substituted and fused compounds of imidazole are analyzed here for varying pharmacological activities.

INTRODUCTION

Imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar five-member ring system with three carbon and two nitrogen atoms in 1 and 3 positions The simplest member of the imidazole family is imidazole itself, a compound with molecular formula $C_3H_4N_2$. It 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. Imidazole 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. As an acid, the pKa of imidazole is 14.0, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols.

Imidazole is incorporated into many important biological molecules. The most pervasive is the amino acid “histidine”, which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin. Synthetic imidazoles are present in many fungicides, antifungal, antihypertensive, antiprotozoal and medications. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, which stimulates the central nervous system.

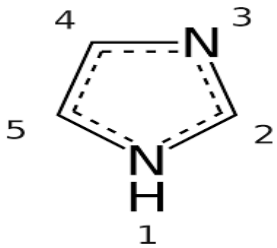
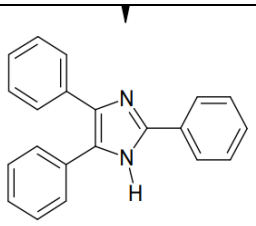
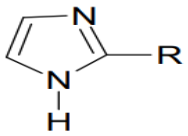
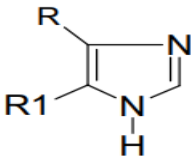
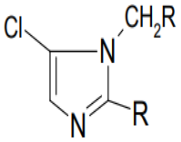
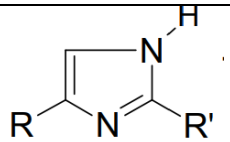
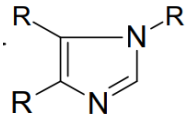


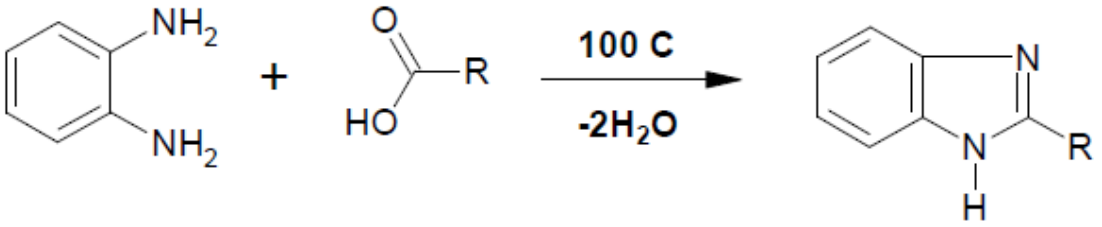
Fig 1: Structure of Imidazole

Table No.1: Chemical reactions for synthesis of Imidazole derivatives

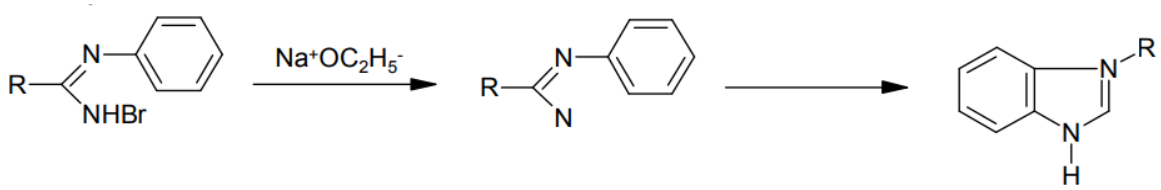
Sr. No	Reaction name	Product
1	Radiszewski Synthesis[1-3]	
2	Dehydrogenation of Imidazoline [4]	
3	From alpha- Halo Ketone [4]	
4	Wallach Synthesis [4 - 8]	
5	From Amino-nitrile and aldehyde	
6	Markwald Synthesis [4]	

Methods of imidazole synthesis

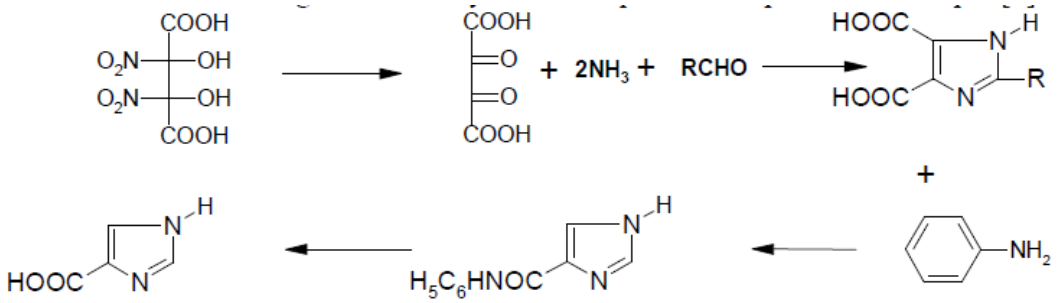
1. Benzimidazole is more important than imidazole as the former occur in Vit B_{12} and has been prepared by a number of methods. 1, 2-diaminobenzene condenses with a carboxylic acid on heating in an acidic medium to give benzimidazole.



2. The cyclization of N-haloamidines with sodium ethnoxide forms benzimidazoles through a nitrene intermediate.

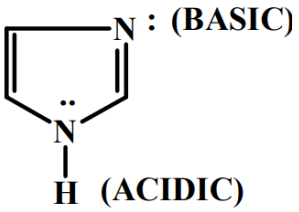


3. Imidazole can best be prepared itself by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and then heating the dicarboxylic acid in quinoline in presence of cooper [9].



Reactivity:

Imidazole 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 that on 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 less likely to become involved in nucleophilic substitution reaction unless there is a strongly electron withdrawing substituents elsewhere in the ring. In the absence of such activation the position most prone to nucleophilic attack is C-2. The fused benzene ring in benzimidazoles provides sufficient electron withdrawal to allow a variety of nucleophilic substitution reaction at C-2.



In benzimidazole the nucleophilic attack is predicted at C-2. The reactivity of benzimidazole ion at the C-2 position with nucleophiles is enhanced compared with the neutral molecule [10].

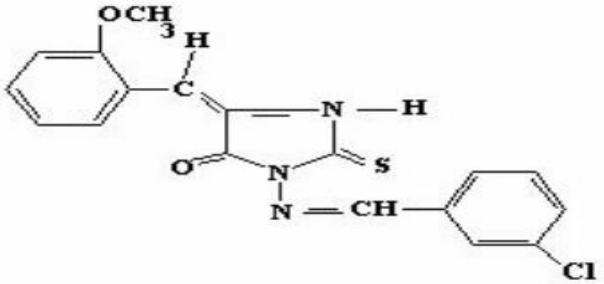
PHYSICAL PROPERTIES:

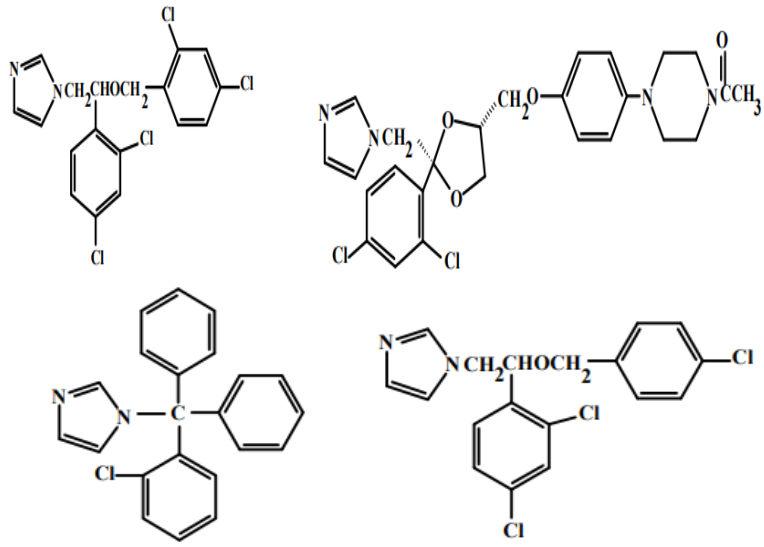
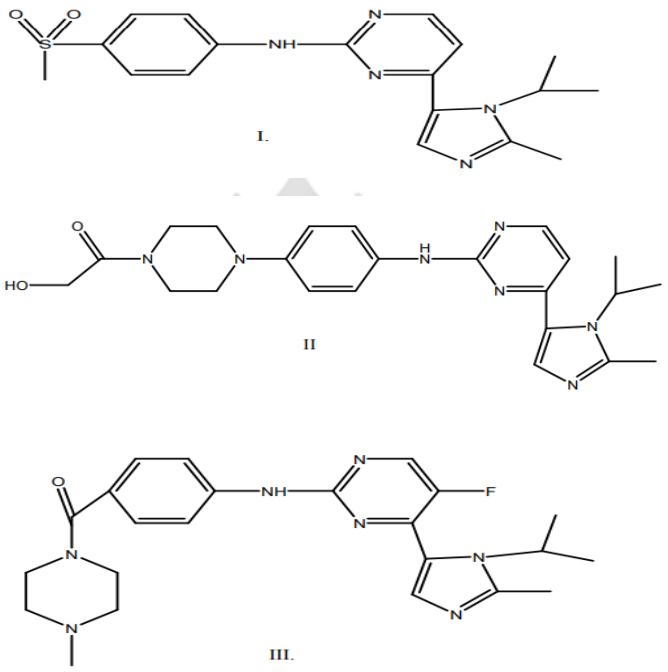
It is colourless liquid having a high B.P. of 256^{o}C than all other 5- membered heterocyclic compounds due to the intermolecular H-bonding, where there is linear association of molecule [11].

Imidazoles are an aromatic compound possessing a resonance value of 14.2 K cal/ mol, which is almost half the value for pyrazole. The electrophillic substitution occurs frequently in imidazole and nucleophillic substitution happens in the presence of electron withdrawing group in its nucleus. Imidazoles have melting point 90^{0}C, it is a weak base and tautomeric substance, since position 4 and 5 are equivalent.

It's spectroscopic parameters are λmax of 207 nm, I.R.=1550, 1492, 1451(cm^{-1}), τ = 2.30, 2.86, mass spectroscopy is studied for heterocyclic compounds containing one hetero-atom, in detail, not in case containing two or more heteroatom [11].

Table No.2: Imidazole derivatives with pharmacological activity

Sr. No	Activity	Structure
1	Anti-inflammatory [12-14]	

2	Anti-fungal [15]	
3	Anti-Cancer [16-18]	

CONCLUSION

Imidazole is an entity which has interesting physical and chemical properties. In the present article focus lies on analysis of these properties which in turn may be exploited for different pharmacological activities, cytotoxicity with specific activity against leukemia cell lines. Combination of indole-imidazole compounds formed demonstrated substantial in vitro anti proliferative activities against cancer cell lines, effective substitutions are also made in the entity which resembles structures of various natural compounds whose anti cancerous activity

has already been examined. Substitutions are discussed in pharmacological actions as anti neoplastic agent.

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