Synthesis and Characterization of Imidazole Derivatives and Catalysis Using Chemical Pharmaceutical Compounds

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Abstract--- This review is an updated and expanded version of imidazole represent an important class of heterocycles, which contains two hetero (nitrogen) atoms and two double bonds. There are so many compounds which contain Imidazole ring and exhibit different types of pharmacological and biological activities such as antimicrobial, antitumor, antiepileptic, and antihistaminic, anti oxidative, anti-inflammatory, anti diarrhoeal, analgesic, which has caused an excessive use of drugs.

Keywords--- Imidazole, Catalysis, Chemical Pharmaceutical Compounds.

I. Introduction

Cyclic organic compounds which have N, O or S as the replacement of one or more than one ring carbon atoms are known as heterocyclic compounds. The rings can be either non-aromatic rings or simple aromatic rings. Examples include- Imidazole ($C_3H_4N_2$), pyridine (C_5H_5N), dioxane ($C_4H_8O_2$) and pyrimidine ($C_4H_4N_2$). (Fig 1) (Ashish and Pandeya, 2011). (p3).

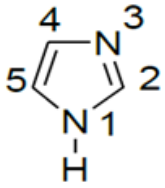

Fig. 1: Numeric Structure of Imidazole Ring

Imidazole exists in two equivalent tautomeric forms with 5-membered ring planner. Either of the two nitrogen has positive charge in it. Imidazole, as a compound is highly soluble in water, has electric dipole moment of 3.67D and has high polarity. Due to the presence of a sextet of π-electrons, the compound is categorized as aromatic that contains electron pairs from each of the remaining four atoms of the ring and from the protonated nitrogen atom (Manocha et al., 2016).

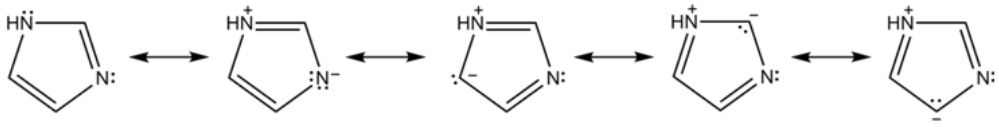

Fig. 2: Numbering System of Imidazole Ring (Structure of imidazole)

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II. Imidazole Derivatives

Global progress and demand of imidazole derivatives have been emerged as the treatment of various complicated diseases. Imidazole ring is a highly polar heterocyclic and an amphoteric, and contains two nitrogen atoms in a five membered aromatic framework (Zhang et al., 2014). But, among the commonly used scaffolds, heterocyclic compounds are the ones where pharmacophores remain to attach the selective and potent drugs (Tamuli et al., 2017).

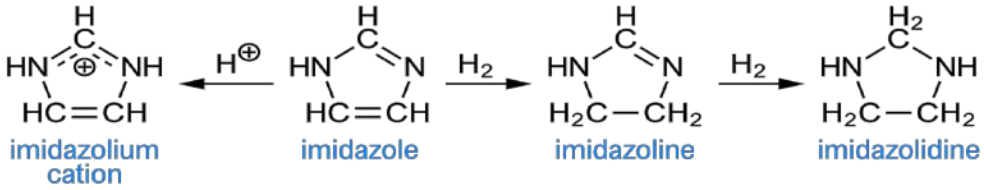
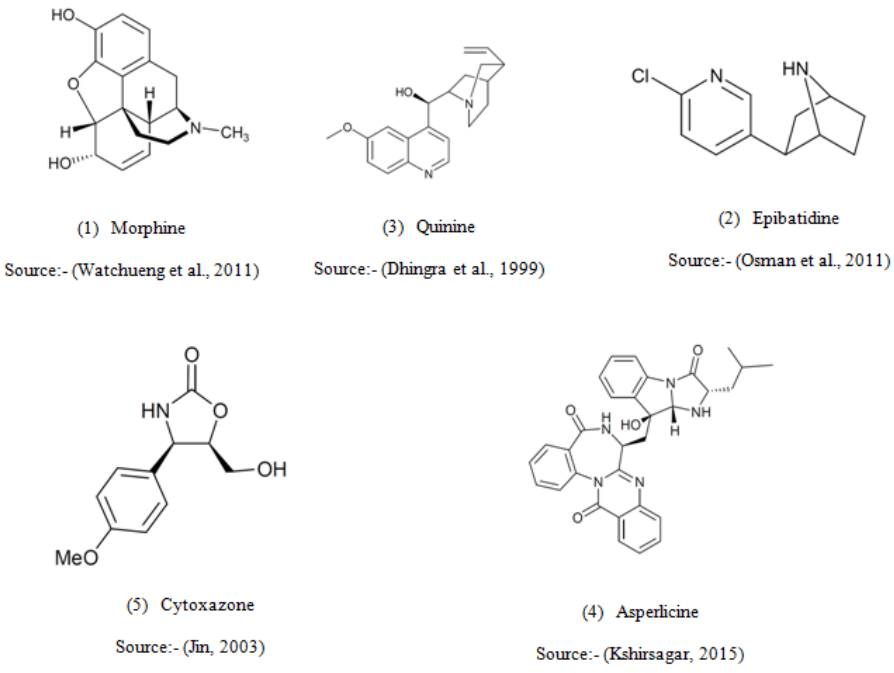


Fig. 3: Imidazole Derivatives

Source:- (Hantzsch and Weber, 1887)

III. Natural Products of Imidazole

The central theme of chemistry and biological research is natural products. The complex structures captivate the chemical thinking of scientists, both by offering countless opportunities to flex synthetic organic muscles and by engaging chemical intuition in thinking about how these molecules might have originated in the cell. Biological functions of secondary metabolites are focused by the natural products research. So, for giving to living organisms and conducting various functions, nature depends on various compounds (Simpson et al., 2012). In the field of drug discovery, heterocyclic compounds such as; pyrazoles and imidazoles have gained popularity for their five membered ring and structure . Fig (4 form (1-9)) (K Gupta et al., 2014). Furthermore, the understanding of natural things is being expanded, the subtleties of chemical diversities also should be put in front of the public to see. Combination of the high content of imidazole in animal and human tissues have long been a serious challenge to pharmacologists, clinicians, physiologists and biologists (Babizhayev, 2006).



(1) Morphine

Source:- (Watchueng et al., 2011)

(3) Quinine

Source:- (Dhingra et al., 1999)

(2) Epibatidine

Source:- (Osman et al., 2011)

(5) Cytoxazone

Source:- (Jin, 2003)

(4) Asperlicine

Source:- (Kshirsagar, 2015)

Fig. 4: Part Important Natural Products Bearing N-Heterocyclic Moeity

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IV. Chemical Composition of Imidazole

Compounds that have one carbon atom or one element aside from carbon, such as; S, N or O in a ring structure are known as heterocyclic compounds (Santos and Moreno, 2013).

The name originates from ancient Greece 'heteros' means "different." Heterocycles are called hetero atoms because here, usually, non-carbons replace carbon atoms. Heterocycles are usually considered to be the opposite of homocycles with only one ring, also known as heteroatom. When sulfur, nitrogen or oxygen, or an atom is incorporated into the ring structure replacing the carbon atom then it enhances the h of the heterocyclic compound (Fig. 1.1).

There is a stable ring structure in heterocyclic compounds of aromatic or non-aromatic nature which can easily hydrolyze and de-hydrolyze. The ring that has one atom are generally more stable but heterocycles that have three atom in rings, have more strain which lead them to be more active (Liu et al., 2014). Heterocycles become reactive intermediates when they possess two atoms.

There can be a broad classification for heterocyclic rings; three and four membered rings readily opened and formed because they are strained. Imidazole (Fig. 5) has the same kind of attributes like pyridine and pyrrole. The unshared electron pair on N-3 would be attacked by the electrophilic reagent. The imidazole ring can be involved in the reaction of nucleophilic substitution despite the ring being susceptible to electrophilic attack. If there is no activation, then the number 2 position is susceptible to nucleophilic attack Benz imidazole has benzene ring fused in it which gives enough withdrawal of electron for allowing different reaction of nucleophilic substitution at C-2.

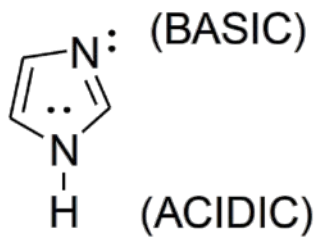

Fig. 5: Benz Imidazole

Benzimidazole and imidazole react from sets of resonance structs where the dipolar contributors have massive importance. It suggests that there will be nucleophilic attack at C-2 or C-1, electrophilic attack in imidazole at N-3 or any ring carbon atom, and also the molecule's amphoteric nature. A large value of dipole moment of 4.8 D in dioxane was shown which has a pKa of 7.2 more than pyridine and pyrazole. They have an M.P. 90 C, it is a tautomeric substance with a weak base, equivalent positions are number 4 and 5 (Shalini et al., 2010).

V. Production Aspect of Imidazole

The future thinking of scientists has become in the field of the chemistry of imidazole, especially the interest in biochemistry heterocycles show various pharmaceutical properties such as in the pharmaceutical field (Manocha et al., 2016). Heterocycles act as renowned reactive intermediates. Five and six membered rings enable the improvement of aromatic character and the rings can be easily generated and can be immensely stable. There are larger rings which are not as stable as the others and are not easily generated, that's why, they are not studied properly. So, a thorough study of function and structure of the receptor system is required to assess the therapeutic aspects of these compounds in complicated diseases such as; depression, stroke, hypertension, gastric ulcer and diabetes (Kumar, 2010). Heterocycles are very common in therapeutic activities specially, imidazole core. It has gained an interest among researchers in pharmacology, biology, electronics, optics and material sciences (Gupta et al., 2012).

VI. Synthesis of Imidazole

Although there had been discoveries of various derivatives of imidazole in 1840, it was first reported in 1858. The synthesis process of imidazole follows the reaction between formaldehyde in ammonia and glyoxal. This process gives low yield of imidazole but it is still used to form imidazole with C-substitution (Wolkenberg et al., 2004).

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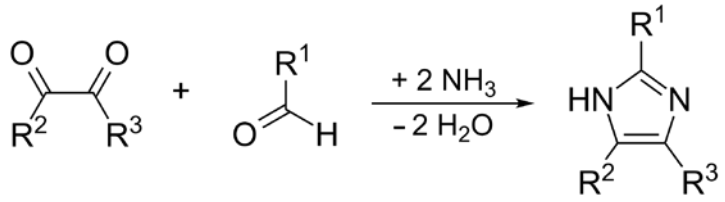

Figure 6 : First Synthesis of Imidazole

It comprises of a condensed di-carbonyl compound such as; in the presence of ammonia; a- keto aldehyde, glyoxal or a- diketones with an aldehyde,, benzyl for example, ammonia (2 molecule) react with benzaldehyde to yield 2,4,5-triphenylimidazole. As a convenient substitute of ammonia, formamide is used (Bhatnagar et al., 2011).

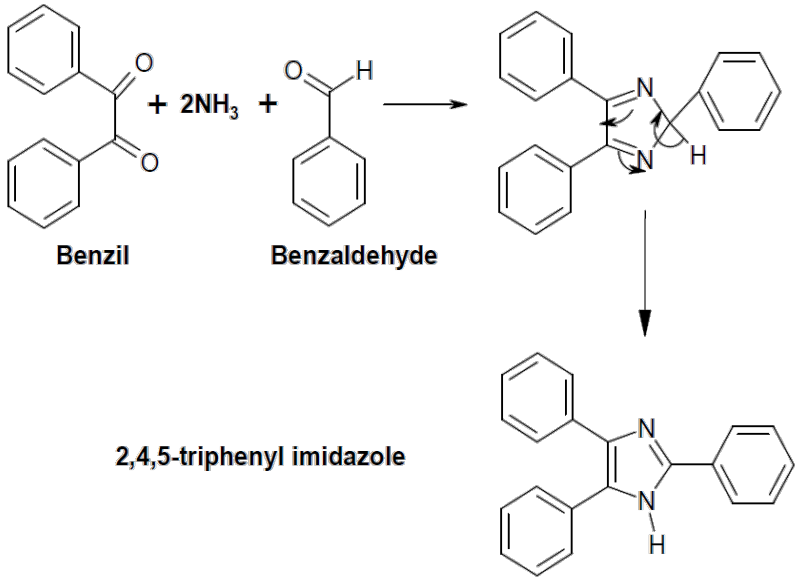

Figure 7: Condensing A Dicarbonyl Compound

VII. Dehydrogenation of Imidazoline

In the presence of sulfur, it was reported that, for converting to imidazole from imidazoline, a milder reagent, barium managanate was used. Imidazolines are derived from 1, 2 ethane diamine and alkyl nitriels after reacting with BaMnO4 yield 2-substituted imidazole (Bhatnagar et al., 2011).

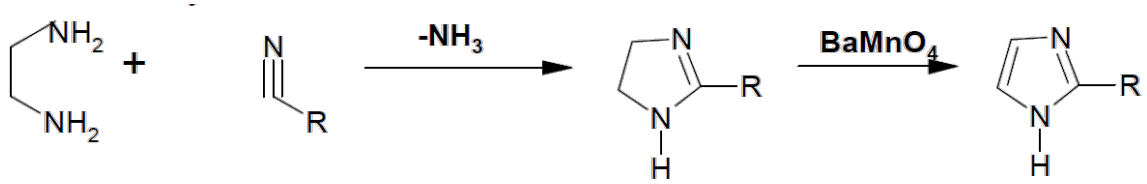

Figure 8: Dehydrogenation of Imidazole

α- Halo Ketone

This reaction includes alpha halo ketones and imidine. For the synthesis of benzamidine and 2, 4- or 2, 5-biphenyl imidazole phenacyl bromide, this method has been successfully applied, based on the process that can be afforded by2,4-diphenyl imidazole. To produce imidazole, acyloin or alpha halo ketones react with amidine (Bhatnagar et al., 2011).

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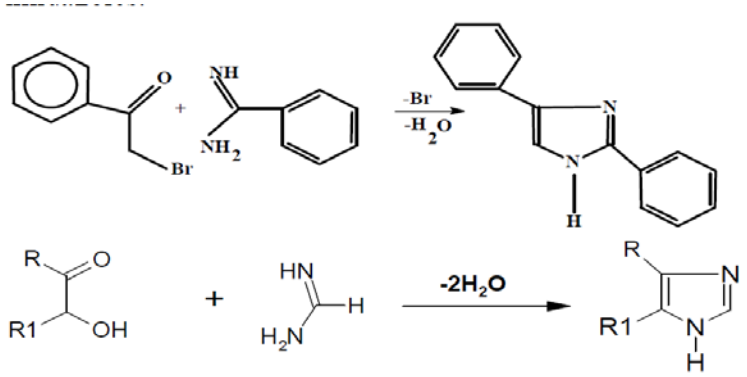
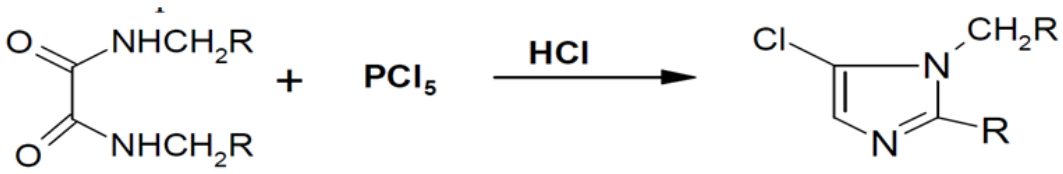


Figure 9: Produce Imidazole, Acyloin or Alpha Halo Ketones React with Amidine

VIII. Wallach Synthesis

A compound containing chlorine is derived when N, N′ -dimethyl oxamide is treated with phosphorus pentachloride which decreases with hydroiodic acid and provides N- methyl imidazole. N, N′ -diethyl oxamide is converted to a chlorine compound under the same condition, which on decrease yields 1- ethyl –2- methyl imidazole. 5- chloral imidazole is the chlorine compound (Bhatnagar et al., 2011)



N, N- Dimethyl Oxamide

From Aldehyde and Aminonitrile

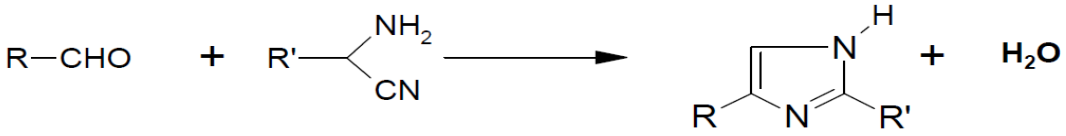


Fig. 10: Wallach Synthesis

Mark Wald Synthesis

The common process of synthesizing 2- mercapto imidazole from a- aldehyde or amino ketones and alkyl is othiocyanates or potassium thiocyanate. In order to obtain the desirable imidazole, various oxidative methods can be used to remove the sulfur. A- amino aldehyde or ketone are not always prevalent which makes the Markwald synthesis more limited (Manocha et al., 2016).

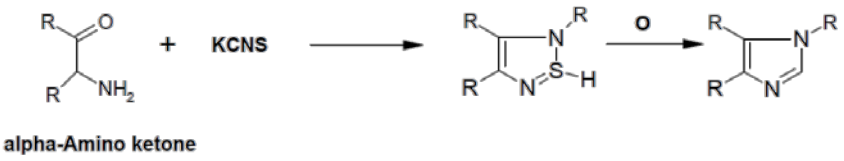


Fig. 11: Marwald Synthesis

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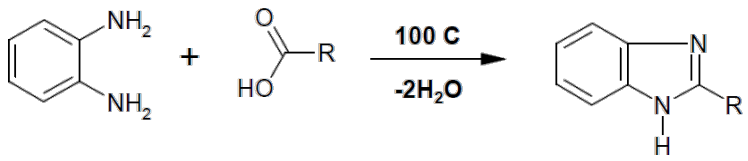
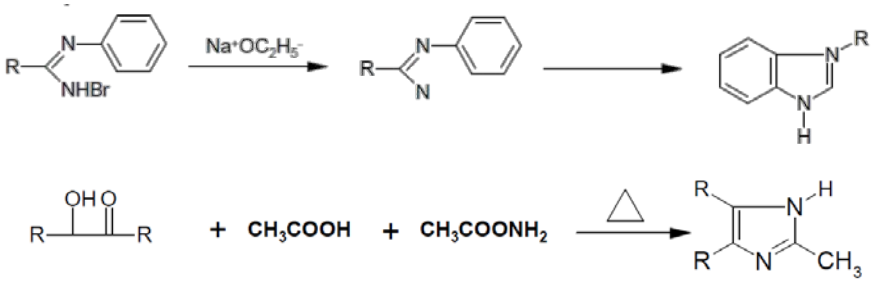
Some other methods by which imidazole can be synthesized are Vitamin B12 has benzimidazole in it which is more important than imidazole to be prepared by various processes, upon heating in acidic medium, 1, 2-diaminobenzene condenses with a carboxylic acid for providing benzimidazole.



Benzimidazole is produced through a nitrene intermediate from cycling N-halo amidines with sodium ethnoxide.



By Action of Ammonia

The mixture of ammonia and tartaric acid dinitrate and formaldehyde can prepare imidazole upon heating the dicarboxylic acid in quinoline in presence of copper (Chawla et al., 2012).

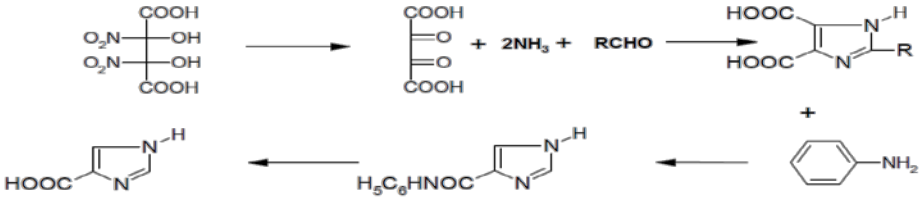
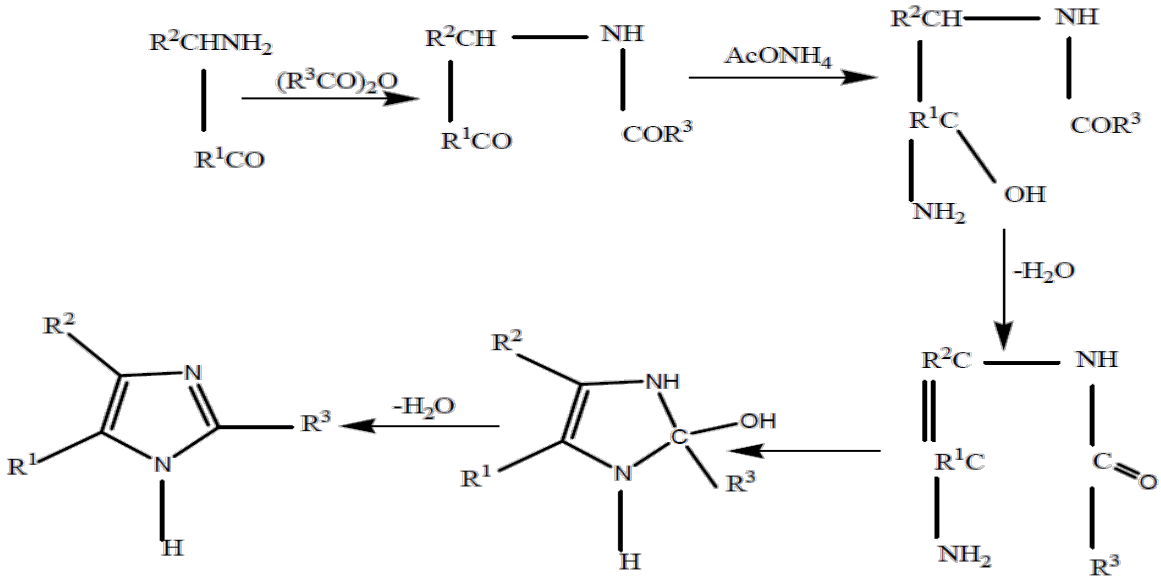


Fig. 12: Methods By Which Imidazole Can Be Synthesized

Cyclization of α-Acylaminoketones

1, 4-diketo compounds behave as α-acyl aminoketones (Manocha et al., 2016).



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Synthesis of Imidazole Derivatives by Microwave Reactions

With reaction between di-carbonyl compound (A) and p-substituted benzaldehyde (B), 2- phenyl imidazo [4,5-f] [1,10] Phenanthroline derivatives (C) was synthesized. Neutral ionic liquid, 1-methyl-3-heptylimidazolium tetrafluoroborate [(HeMIM) BF4] is produced from reaction catalyzed by acid, under various conditions such as; microwave assisted and solvent free conditions.

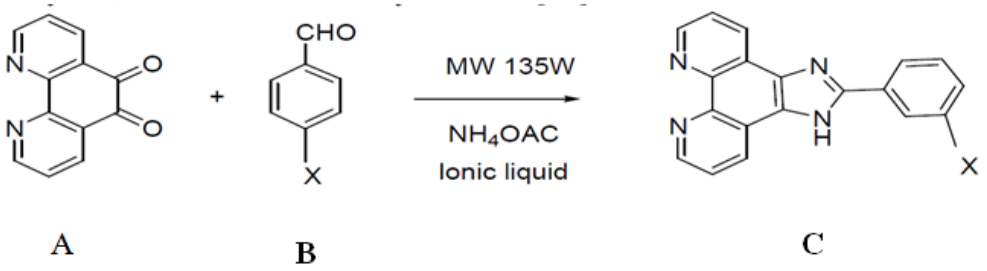

Fig. 13: 1-Methyl-3-Heptylimidazolium Tetrafluoroborate

IX. Physical Properties

It is a colorless liquid that has a high B.P. of 256C because of the intermolecular H-bond. A linear association of molecule is observed here (Bhatnagar et al., 2011)

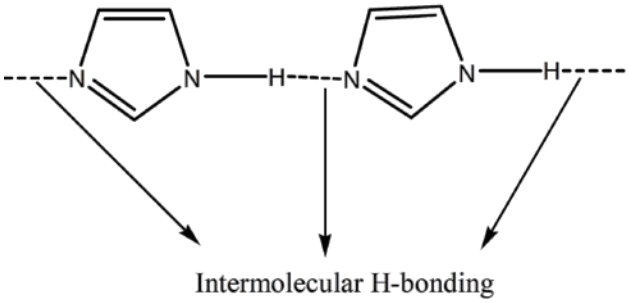

Fig. 14: Intermolecular H-Bonding

The high dipole moment value of dioxane (4.8D) is observed in imidazole. It also has pKa more than pyridine and pyrazole along with amphoteric properties. It is considered as an aromatic compound that contains 14.2K cal/mol of resonance value. It is legit half the value than pyrazole. Imidazole often goes through nucleophilic and electrophilic substitution.

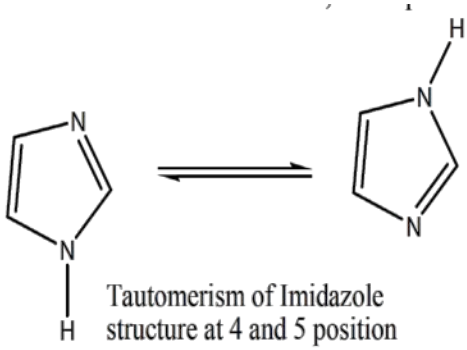

Figure 15: Tautomerism of Imidazole Structure at 4 and 5 Position

If the nucleus has withdrawing electrons, then their presence enables to have these substitutions. The other properties of imidazole include- weak basicity, tautomerizm, having equivalent number 4 and 5 position, and M. pt. 90C (Bhatnagar et al., 2011).

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Chemical Properties of Imidazole

Imidazole is considered as a strong base in comparison to its other compounds such as; pyrrole, pyridine or pyrazole. In acidic medium, pyrazole and imidazole remain more stable than the other compounds.

Both the pyrazole and imidazole contain two atoms of nitrogen. When they are protonated, the positive charge is delocalized over them. But imidazole is stronger than pyrazole as a base. Because, pyrazolium ion has a positive charge in it which is less delocalized in comparison to imidazolium ion (Mabkhot et al., 2013). Reaction with acids: Being a mono acidic base, imidazole has weak acid properties and generates acids with crystalline salts (Bellina et al., 2007)

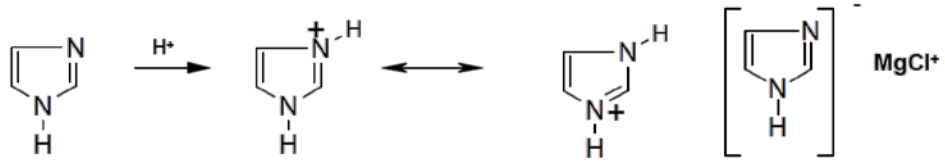

Figure 16: Imidazole has Weak Acid Properties and Generates Acids with Crystalline Salts

Imidazole also generates silver salt with ammonium silver nitrate and it has sparing water solubility.

Quaternization: Quaterization of the nitrogen atom of the imidazole is normally achieved by the reaction of alkyl halides or dialkyl sulfates in an organic solvent under strongly basic conditions. Alkylation of imidazoles is achieved by heating 1-carboethoxyimidazoles (Bellina et al., 2007).

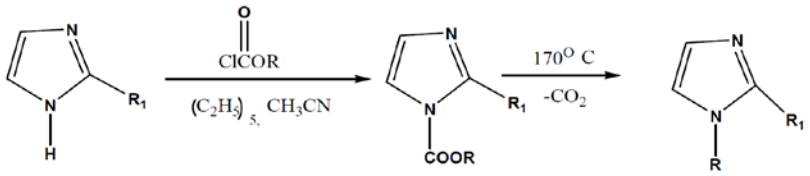

Figure 17: Alkylation of Imidazoles is Achieved by Heating 1-Carboethoxyimidazoles

Halogenation: Halogenation of imidazole is very complex. Its depends on the substrste, reagents and reaction conditions. Direct chlorination gives undefined products. Bromination yields 2,4,5-tribromo derivative. Iodination takes place in alkaline conditions to give 2,4,5-triiodoimidazole (Baroniya et al.)

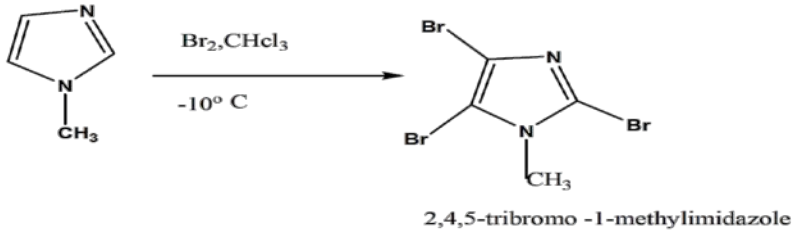

Fig. 18: 2,4,5-Triiodoimidazole

Reaction with Oxidizing and Reducing Agents: Imidazole shows stability for autoxidation. In the presence of sensitizer, oxygen and imidazole react with each other and form a derivative of imidazole, known as auto-oxidation. There is a mild oxidizing agent, imidazolium Dichromate, applied for oxidizing benzylic and allylic alcohols and (Chaudhury et al.) Cycloaddition Reactions: Imidazoles gives addition across the carbon-carbon double bond. This kind of reaction performed under photochemical conditions. The reaction of imidazole with acrylonitrile is representative from the reaction given below (Baroniya et al., 2010).

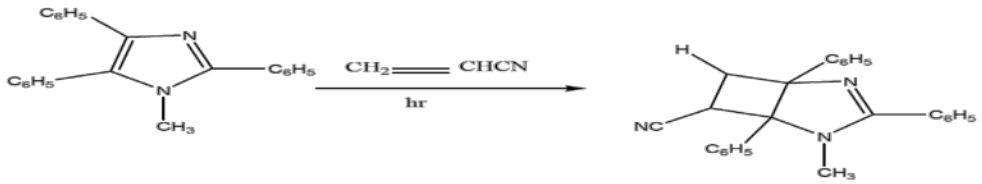

Fig. 19: Cycloaddition Reactions

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Imidazole Based Drugs

Diverse products contain imidazole in them (Fig. 10), sometimes known as benzimidazole when benzene is fused with imidazole. When imidazole has a-amino acid in it, then it is known as histidine (West and Stock, 2001). German physician Albrecht Kossel first isolated it in 1896. Histidine has its fair share of importance in animals, humans, adult humans and infants (Zhang et al., 2014).

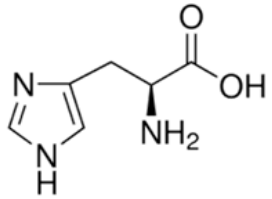


Figure 20: Histidine

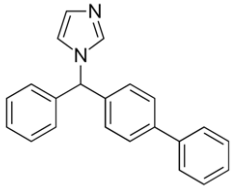


Figure 21: Bifonazole (Antifungal Drug)

Bifonazole is a substituted imidazole antifungal agent structurally related to other drugs in this group (Lackner and Clissold, 1989) With amnestic and anxiolytic properties, midazolam is a short-acting hypnotic-sedative drug. The pharmacological usage of this drug is as local anesthesia, in cardiac surgery, dentistry, preanesthetic medication and in endoscopic procedures. This drug is a good choice for less risk and elderly patients because of its cardiorespiratory stability and short duration. It is lipid-soluble at physiological pH and water soluble at pH less than 4 (Dere et al., 2010).

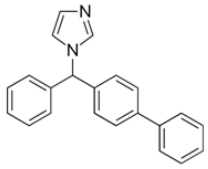
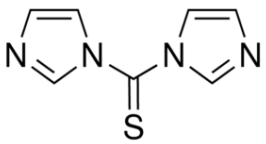


Fig. 22: Midazolam (Sedative)

To conduct various biological processes, thiocarbonyldiimidazole plays a massive importance. . The study of Hcymetabolism has gained much attention by the researchers. Vascular diseases become risky with increased levels of Hcy in serum or blood plasma, diseases are- thrombophilia, stroke, infarction, coronary artery disease, etc.(Ivanov et al., 2015).



Thiocarbonyldiimidazole

Fig. 23: A modem Alternative to Thiophosgene-Less Toxic

Applications of Imidazole

An enormous amount of research in the field of pharmacologically active imidazole has been reported (Medina et al., 2003). Reports on the physiological activities of substituted and condensed imidazole derivatives like

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antibacterial, fiingicidal, analgesic, anti-inflammatory and anti-tubercular etc. are well documented (Chang et al., 2009). Figure 14 exhibits several usages of imidazole.

Medicinal Chemistry: - If the side chains of nitrogen are varied in an imidazole structure, then structural changes can be observed. There are various synthesizes which have been reviewed and studied to attain the NHC ligands upon reactions along with the generation of carboxylic and borane intermediates (Shalini et al., 2010).

Fluorescent Dyes: - To study optoelectronic materials and conduct fundamental research, fluorescent dyes in solid state are much needed. So, researchers have shown massive interest in developing fluorophores with solid emission (Li et al., 2013).

Natural Products:- Anti-cancer drugs (around 50%) worldwide are mostle prepared from natural products or their mimics with the knowledge and usage of abundant natural products (Kaur et al., 2014).

Polymers: - the coordination sites of N or O donors containing multidentate organic ligands are extensively applied as building blocks. Tripodal and ditopic ones are the most used among them. (Chen et al., 2009). Organic compounds with oxygen, sulfur or nitrogen, multiple bonds and aromatic rings or multiple bonds are potent inhibitors for minimizing metal corrosions in corrosive media (Sherif, 2011).

Veterinary: - There are reviews of the mechanism of action of natural imidazole having antimicrobial potency. The researchers are studying to bring about novel biological compounds with potent activities against various diseases (K Gupta et al., 2014).

Liquid Crystals: - Liquid crystals have properties such as; non-flammability, high chemical stability, high thermal stability, low volatility, wide electrochemical window and high ionic conductivity. Ionic liquids based on imidazolium salts are specifically renowned for applying in electrochemical devices, wet double-layer capacitors, dye-sensitized solar cells, and ion transport systems (Dobbs et al., 2006).

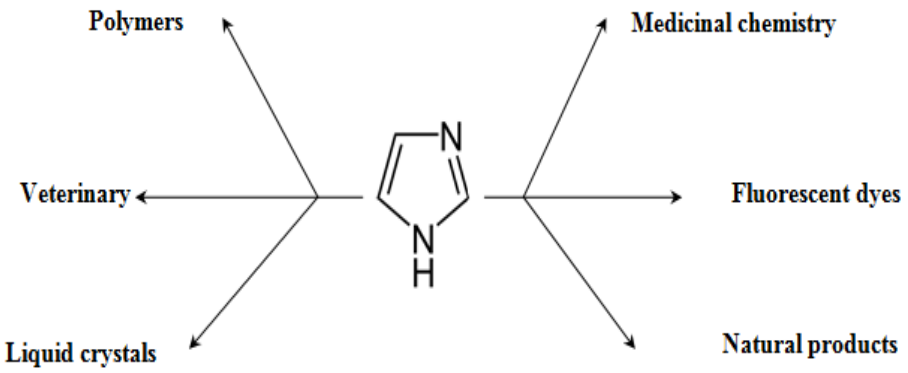

Fig. 24 : Applications of Imidazole

X. Conclusion and Future Prospects

According to the studies, imidazole and its derivatives are used as analgesic, antimicrobial, anti-tubercular, anti-inflammatory, anti-cancer drugs. The reason behind this is, imidazole is not sensitive in extra intestinal parasites than gastrointestinal parasites. There are new imidazole drugs that show less toxicity and better efficacy.

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