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Review Article

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FIVE MEMBER NITROGENATED HETROCYCLIC COMPOUNDS [A REVIEW]

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ABSTRACT

This review article aims to represent the chemistry and applications of five membered nitrogenous heterocyclic compound containing one or more than one nitrogen atom in ring. All of the five membered nitrogenous heterocyclic compounds have different types of applications in pharmaceuticals and other fields like agriculture. This review paper generally highlight the chemistry and application of several five membered nitrogenous heterocyclic compounds and their derivatives which were synthesized recently as well as in past years. Heterocyclic organic compounds applied as pharmaceuticals, agrochemicals and veterinary fields, applied as optical brightening agents, like antioxidants, like corrosion inhibitors and like additives with a variety of else functions. Also, numerous dyestuffs and pigments were heterocyclic structures. They show biological activities, including antibacterial, antifungal, and anticancer. characterization, and aiming to further biochemical studies. The nitrogenated containing heterocyclic compounds to increase the physical working capacity in conditions of hyperthermia, hypothermia,and acute normobaric hypoxia and hypercapnia has been investigated. The main aim of this paper is to represent the information regarding the five membered hetrocyclic compounds that constitude the largest family or organic compounds.These are extremely important with wide array of synthetic pharmacological activity and industrial applications.

KEYWORDS: Heterocyclic, Nitrogenous, Pharmaceuticals, Agrochemicals, Veterinary, Antibacterial, Antifungal, Anticancer, Hyoercapnia.

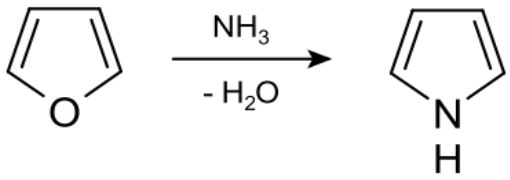
1. PYRROLE
INTRODUCTION

All of the five membered nitrogenous heterocyclic compounds have different types of applications in pharmaceuticals and other fields like agriculture. This review paper generally highlight the chemistry and application of several five membered nitrogenous heterocyclic compounds and their derivatives which were synthesized recently as well as in past years. Heterocyclic organic compounds applied as pharmaceuticals, agrochemicals and veterinary fields, applied as optical brightening agents, like antioxidants, like corrosion inhibitors and like additives with a variety of else functions. Also, numerous dyestuffs and pigments were heterocyclic structures. They show biological activities, including antibacterial, antifungal, and anticancer. characterization, and aiming to further biochemical studies. The nitrogenated containing heterocyclic compounds to increase the physical working capacity in conditions of hyperthermia, hypothermia, and acute normobaric hypoxia and hypercapnia has been investigated. The main aim of this paper is to represent the information regarding the five membered hetrocyclic compounds that constitude the largest family or organic compounds. These are extremely important with wide array of synthetic pharmacological activity and industrial applications. Pyrrole is a five membered heterocyclic compound, corresponding to the C_4H_4NH general formula.[1] It is a colorless volatile liquid, unstable in the presence of air, where it easily darkens. Thus a preliminary distillation before use is necessary.[2] Pyrrole is included in the group of aromatic compounds, and its hydrogenated is difficult. The Diels Alder reactions or usual olefin reactions are not characteristic for this ring. Due to the fact, that it can easy polymerize, most of the electrophilic reaction, used in benzene chemistry, are not applicable to pyrroles. On the other hand, the substituted pyrrole derivatives have been included in various transformations.[3] Pyrrole itself is not naturally occurring, but many of its derivatives are found in a variety of cofactors and natural products. Pyrroles are components of more complex macrocycles, including vitamin B_{12}, bile pigments like bilirubin and biliverdin, and the porphyrins of heme, chlorophyll, chlorins, bacteriochlorins, and porphyrinogens.[4-5] Pyrrole is a constituent of tobacco smoke and not as an ingredient.[6]

Synthesis

Industrial preparation

Pyrrole is prepared industrially by treatment of furan with ammonia in the presence of solid acid catalysts, like SiO_2 and Al2O3.[7]

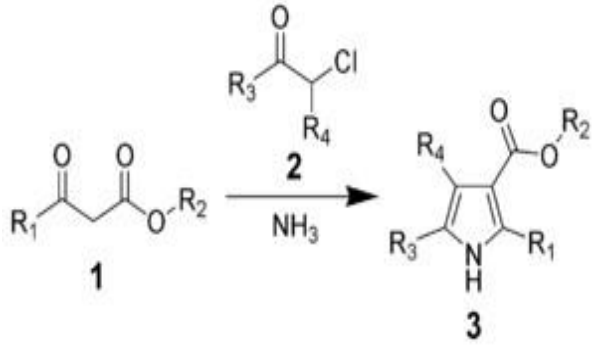


Pyrrole can also be formed by catalytic dehydrogenation of pyrrolidine.

Laboratory routes

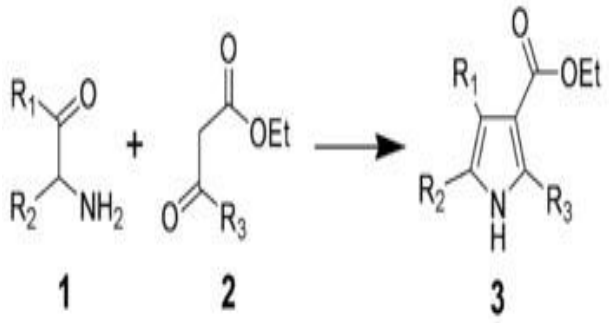
Hantzsch Pyrrole Synthesis:

The Hantzsch pyrrole synthesis is the reaction of β-ketoesters **(1)** with ammonia (or primary amines) and α-haloketones **(2)** to give substituted pyrroles **(3)**.[8-9]



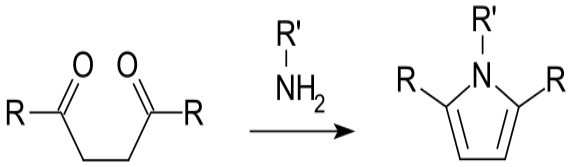
- **Knorr pyrrole synthesis**

The Knorr pyrrole synthesis involves the reaction of an α-amino ketone or an αamino-β-ketoester with an activated methylene compound.[10-11] The method involves the reaction of an αaminoketone **(1)** and a compound containing a methylene group α to (bonded to the next carbon to) a carbonyl group **(2)**.[12]



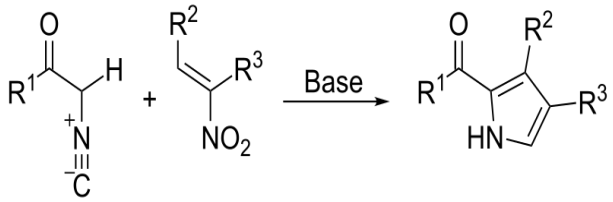
- **Paal–Knorr pyrrole synthesis**

In the Paal–Knorr pyrrole synthesis, a 1,4dicarbonyl compound reacts with ammonia or a primary amine to form a substituted pyrrole.[13-14]



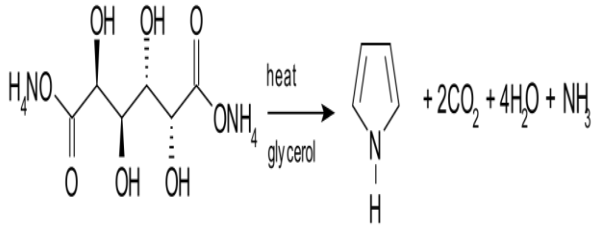
- **Barton–Zard synthesis**

The Barton–Zard synthesis proceeds in a manner similar to the Van Leusen synthesis. An isocyanoacetate reacts with a nitroalkene in a 1,4-addition, followed by 5-*endo-dig* cyclization, elimination of the nitro group, and tautomerization.[15]



- **Other methods**

One synthetic route to pyrrole involves the decarboxylation of ammonium mucate, the ammonium salt of mucic acid. The salt is typically heated in a distillation setup with glycerol as a solvent.[16]



Characterization

Pyrrole is a colorless volatile liquid that darkens readily upon exposure to air, and is usually purified by distillation immediately before use.[17] Pyrrole has a nutty odor. Pyrrole is a 5-membered aromatic heterocycle, like furan and thiophene. Unlike furan and thiophene, it has a dipole in which the positive end lies on the side of the heteroatom, with a dipole moment of 1.58 D. In $CDCl_3$, it has chemical shifts at 6.68 (H2, H5) and 6.22 (H3, H4). Pyrrole is weakly basic, with a conjugate acid pK_a of −3.8. The most thermodynamically stable pyrrolium cation ($C_4H_6N^+$) is formed by protonation at the 2 position. Substitution of pyrrole with alkyl substituents provides a more basic molecule—for example, tetramethylpyrrole has a conjugate acid pK_a of +3.7. Pyrrole is also weakly acidic at the N–H position, with a pK_a of 17.5.

Pharmacological activity of pyrrole and its derivatives

Pyrrole and its derivatives play an important role in pharmaceutical and natural chemistry. Commonly they

are widely used as an intermediate in the synthesis of pharmachemicals, perfumes and other organic compounds. For example, chlorophyll, heme are derivatives which are made by four pyrrole ring formation of porphyrin ring system (Fig. 1). In addition they are used as catalysts for polymerization process, corrosion inhibitors, preservatives, solvents for resins and terpenes, standard in a chromatographic analysis and they are also used in organic synthesis in the pharmaceutical industry. It is an important constituent in the structure of a number of pharmaceutical products and new active agents with variety of pharmacological effects like: atorvastatine - antihyperlipidemic, aloracetam for treatment of Alczheimer' disease, elopiprazole - antipsychotic, lorpiprazole - anxiolytic, tolmetin- anti-inflammatory activity.[18]

2. Pyrazole

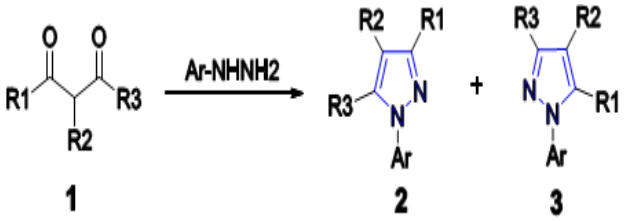
Introduction

Pyrazoles are five-membered heterocycles that constitute a class of compounds particularly useful in organic synthesis. They are one of the most studied groups of compounds among the azole family. Indeed, a huge variety of synthesis methods and synthetic analogues have been reported over the years. The presence of the pyrazole nucleus in different structures leads to diversified applications in different areas such as technology, medicine and agriculture. In particular, they are described as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, antiinflammatory, anti-tuberculosis, antioxidant as well as antiviral agents.[19-20]

Nowadays, pyrazole systems, as biomolecules, have attracted more attention due to their interesting pharmacological properties. This heterocycle can be traced in a number of well-established drugs belonging to different categories with diverse therapeutic activities.[21-28]

Synthesis

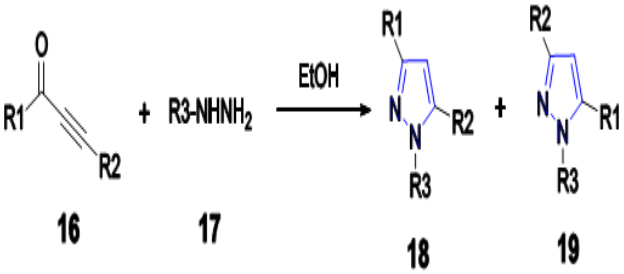
1. From 1,3-Diketones: The cyclocondensation of the 1,3-dicarbonyl compounds with the hydrazine derivatives is a simple and rapid approach to obtain polysubstituted pyrazoles. The first synthesis of the substituted pyrazoles was carried out in 1883 by Knorr et al.[29] who reacted β-diketone 1 with hydrazine derivatives to give two regioisomers 2 and 3[.Scheme 1.]



Scheme 1. Synthesis of polysubstituted pyrazoles form 1,3-dicarbonyl compound.

2. From Acetylenic Ketones

The cyclocondensation reaction of hydrazine derivatives **17** on acetylenic ketones **16** to form pyrazoles has been known for more than 100 years.[30] However, the reaction again results in a mixture of two regioisomers **18** and **19** (Scheme 2).



Scheme 2. Synthesis of pyrazoles from acetylenic ketones.

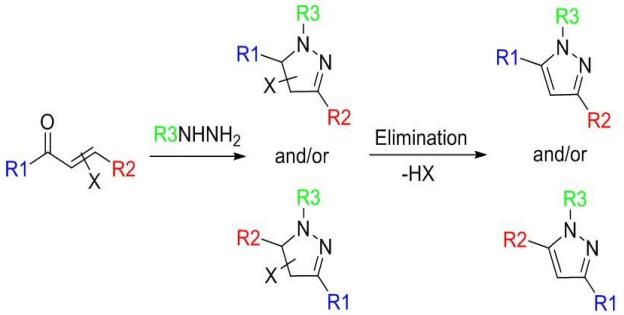
3. From Vinyl Ketones

The cyclocondensation reaction between an α,β-ethylenic ketone and a hydrazine derivative results in the synthesis of pyrazolines which, after oxidation, provide the pyrazole ring (Scheme 3).

Scheme 3. Synthesis of pyrazoles by cyclo condensation reaction of α,β-ethylenic ketone.

4. From Vinyl Ketones Having a Leaving Group

The α,β-ethylenic ketones having a leaving group may react with hydrazine derivatives to form pyrazolines which, after removal of the leaving group, provide the desired pyrazoles (Scheme 4).



Scheme 4. Synthesis of pyrazoles via cyclocondensation of α,β-ethylenic ketones having a leaving group.

Pharmacological activity of Pyrazole

The pyrazole ring is found within a variety of pesticides as fungicides, insecticides and herbicides, including chlorfenapyr, fenpyroximate, fipronil, tebufenpyrad,

tolfenpyrad, and tralopyril.[31] Pyrazole moieties are listed among the highly used ring systems for small molecule drugs by the US FDA.[32] The pyrazole possess the pharmacological activities in such as anti-microbial, anti-fungal, anti-tubercular, anti-inflammatory, anti-convulsant, anti cancer, anti viral, angiotension converting enzymes(ACE) inhibitory.[33] The main applications of pyrazole is anti-inflammmatory drugs clinically, such as anti-pyrine or phenazone(analgesic and antipyretic), metamizole or dipyrone,aminopyrine or aminophenazone(anti-inflammatory, antipyretic, analgesic), phenylbutazone (anti-inflammatory, antipyretic mainlyusedin osteoarthritis,r heumatoid, arthritis, spondylitis, reiters diseases), sulfinpyrazone (chronic gout), and oxyphenbutazone (antipyretic, analgesic, anti-inflammmatory, mild uricosuric.[34]

3. Imidazole

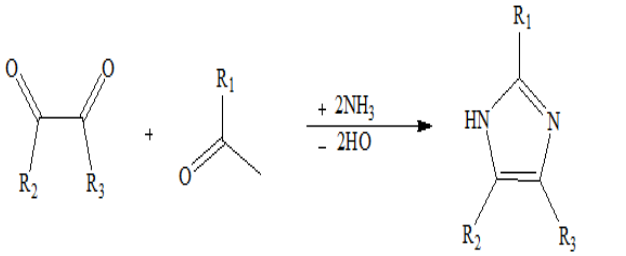
Introduction

Imidazole is an organic compound in which general formula is $C_3N_2H_4$ .In the field of five membered heterocyclic structures imidazole nucleus shows various properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole include anticancer, b-lactamase inhibitors, 20HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial.[35-48] This group presents in azoles antifungal which inhibit the accumulation of methylated sterols distroy the composition of the lipid bilayer of membranes. Some imidazole drugs, at high concentrations, could exert direct inhibitory action on membranes, without interference with sterols and sterol esters.[49-50] Infectious microbial disease causes worldwide problem, because microbes have resisted prophylaxis or therapy longer than any other form of life. In recent decades, problems of multidrug-resistant microorganisms have reached an alarming level in many countries around the world. Resistance of anti-microbial agents such as β-lactam antibiotics, macrolides, quinolones and vancomycin etc. and different species of bacteria causes increased important global problem.[51] Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases.

Synthesis

1. Debus Synthesis

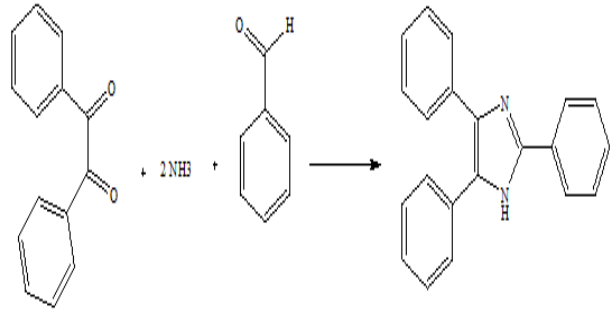
Debus Synthesised imidazole by using glyoxal and formaldehyde in ammonia. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazole.[52]



Glyoxal (9) Formaldehyde (10) C- substituted imidazole (11)

2. Radiszewski Synthesis

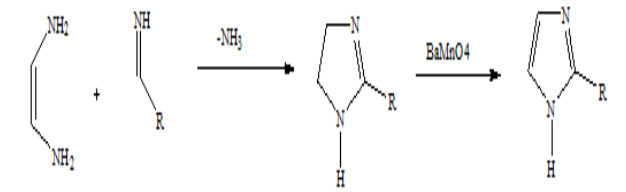
Rediszewski reported the condensation of a dicarbonyl compound, benzil and a ketoaldehyde,benzaldehyde or a diketones in the presence of ammonia, yield 2,4,5-triphenylimidazole.[53]



Benzil (12) Benzaldehyde (13) 2,4,5 - triphenylimidazole (14)

3. Dehyrdogenation of imidazoline

Knapp and coworkers have reported a milder reagent barium managanate for the conversion of imidazoline to imidazoles in presence of sulpur.Imidazolines obtained from alkyl nitriles and 1,2ethanediamine on reaction with BaMno4NH yield 2-substituted imidazoles.[54]

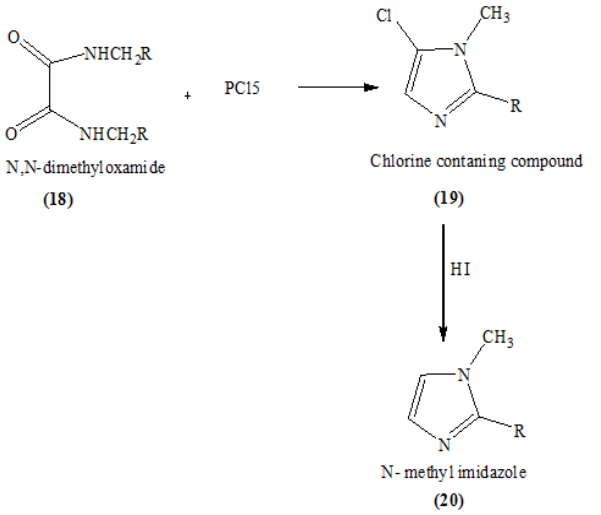


1,2 ethanediamine (15) Alkyl nitrile (16) 2-substituted imidazole (17)

4. Wallach Synthesis

Wallach repoted that when N,N-dimethyloxamide is treated with phosphorus pentachloride,a chlorine containing compound is obtained which on reduction with hydroiodic acid give N-methyl imidazole.under the same contition N,N diethyloxamide is converted to a

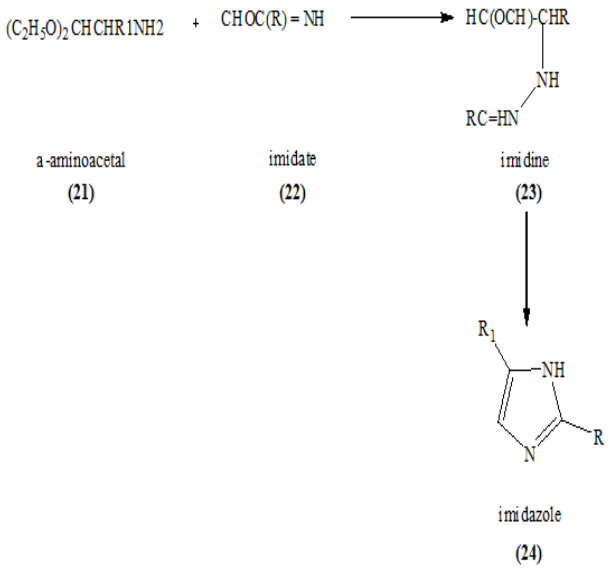
chlorine compound ,which on reduction gives 1-ethyl-2-methyl imidazole.[55]



N,N-dimethyloxamide (18) | Chlorine contaning compound (19) | N-methyl imidazole (20)

5. By the formation of one bond

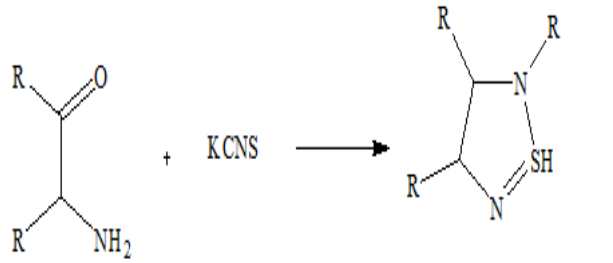
The (1,5)or (3,4) bond can be formed by the reaction of an imidate and an a-aminoaldehyde or a-aminoacetal resulting in the cyclization of an imidine to imidazole .The examples below applies to imidazole when R=R1=Hyrdogen.[56]



a-aminoacetal (21) | imidate (22) | imidine (23) | imidazole (24)

6. Markwald Synthesis

The preparation of 2-mercaptoimidazoles from a-aminoketones or aldehyde and potassium thiocyanate or alkylisothiocyanates is a common method for the synthesis of imidazoles. The sulphur can readily be removed by a variety of oxidative method to give the desired imidazoles. The starting compounds, a-amino aldehyde or ketone, are not readily available, and this is probably the chief limitation of the Markwald synthesis.[57]



a-aminoketone (25) | Potasium thiocynate (26) | 2- mercapto Imidazole (27)

Characterization

It is a white or colourless solid that is soluble in water, producing a mildly alkaline solution.

It exists in two equivalent tautomeric forms, because hydrogen can be bound to one or the other nitrogen atom. Imidazole is a highly polar compound, as evidenced by its electric dipole moment of 3.67 D.[58]. It is highly soluble in water.Imidazole is amphoteric. That is, it can function as both an acid and as a base. As an acid, the pK_a of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is the one bound to nitrogen. Deprotonation gives the imidazole anion, which is symmetrical. As a base, the pK_a of the conjugate acid (cited as pK_{BH}+ to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is the nitrogen with the lone pair (and not bound to hydrogen). Protonation gives the imidazolium cation, which is symmetrical.

Pharmacological activity Of Imidazole

Imidazole has become an important part of many pharmaceuticals. Synthetic Imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, which stimulates the central nervous system. It is present in the anticancer medication mercaptopurine, which used in leukemia by interfering with DNA activities.

Imidazole also used in industry as a corrosion inhibitor on certain transition metals, such as copper. Conductivity of the copper decreases due to corrosion. Many compounds of industrial and technological importance contain imidazole derivatives. The thermostable polybenzimidazole imidazole fused to a benzene ring and acts as a fire retardant. Imidazole can also be found in various compounds which are used for photography and electronics.

One of the applications of imidazole is in the purification of His tagged proteins in immobilized metal affinity

chromatography (IMAC). Imidazole is used to elute tagged proteins bound to Ni ions attached to the surface of beads in the chromatography column. An excess of imidazole is passed through the column, displaces the His-tagged from nickel coordination and free the His-tagged proteins.

Imidazole can be used to prepare buffers in the pH range of 6.2-7.8 at room temperature. It is recommended as a component of a buffer for assay of horseradish peroxides. It is also used as a chelator for the binding of different divalent cations.[59]

The oral administration of imidazole shows beneficial effects on psoriasis and seborrheic dermatitis. In psoriasis the improvement begins after a period of one and a half to three months. In seborrheic dermatitis the patients begin from less redness, itchiness, and scaling within a period of four to six weeks. The benefits of this treatment occur without the need for applications of ointments or other topical applications.

The imidazole nucleus is an important synthetic strategy in drug discovery. Many imidazoles have been prepared as pharmacological agents Azomycine, Clotrimazole, Miconazole, Ergothionine, Clonidine and Moxonidine. One of the most important applications of imidazole derivatives is their used as material for treatment of denture stomatities.[60,61]

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I would like to express my gratitude towards my parents & family members for their kind co-operation and encouragement, as both financially and mentally which help me in completion of this Review article.

CONCLUSION

This review study has shown that five membered heterocyclic compounds containing one more than one nitrogen atom into their ring are very important with respect to their biological and and industrial activities. This review article represent several laboratory methods to synthesize different types of five membered nitrogenous heterocyclic compounds like pyrrole, pyrazole, Imidazole and their derivatives. They have wide variety of applications in the field of pharmaceuticals, Agrochemicals and veterinary sciences as well as in industry. finally it's concluded that most of the Pharmaceuticals. Agrochemicals and industrial chemicals contain nitrogen as a heteroatom into their nucleus and most of the natural products contain nitrogenous five membered structure which are used in different types of drugs and other materials.

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