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RATIONAL APPROACHES FOR SYNTHESIS OF SOME NOVEL IMIDAZOLE HETEROCYCLES WITH THEIR BROAD SPECTRUM OF PHARMACOLOGICAL ACTIVITIES: A BRIEF REVIEW

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ABSTRACT: Imidazole has a special role in heterocyclic chemistry, and its derivatives have piqued interest in recent years due to its diverse chemistry and pharmacology properties. Imidazole is a nitrogen-containing heterocyclic ring that is essential in biology and pharmaceuticals. As a result, imidazole compounds have piqued the attention of researchers for more than a decade. Thus imidazole compounds have been an interesting source for researchers for more than a century. Antibacterial, anticancer, anti-tubercular, anti-fungal, analgesic, and anti-HIV activities are among the biological activities of imidazole derivatives. This paper aims to look back on the biological activities of imidazole over the years. A large number of imidazole derivatives are available. The incorporation of the imidazole nucleus is an important synthetic Strategy in drug discovery. The high therapeutic properties of imidazole-related drugs have prompted medicinal chemists to develop a slew of new chemotherapeutic agents. In clinical medicine, imidazole medications have a broader application in treating a variety of conditions. Imidazole can be synthesized using a variety of methods.

INTRODUCTION: Imidazole **Fig. 1.** is an organic compound with the formula $C_3N_2H_4$. It is a white or colourless solid that is soluble in water, producing a mildly alkaline solution. In chemistry is given in **Table 1.** It is an aromatic heterocycle, classified as a diazole, and has non-adjacent nitrogen atoms [1].

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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 on the 'pyrrole' nitrogen since it is part of the therapeutic or 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 are 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 Benzimidazole provides sufficient

electron withdrawal to allow a variety of nucleophilic substitution reactions at C-2. The overall reactivity of imidazole and Benzimidazole is referred from sets of resonance structures in which the dipolar contributors have finite importance. These predict electrophilic attack in imidazole at N-3 or any ring carbon atom, nucleophilic attack at C-2 or C-1, and the molecule's amphoteric nature. In Benzimidazole, the nucleophilic attack is predicted at C-2. The reactivity of the Benzimidazole ion at the C-2 position with nucleophiles is enhanced compared with the neutral molecule [2].

Structure:

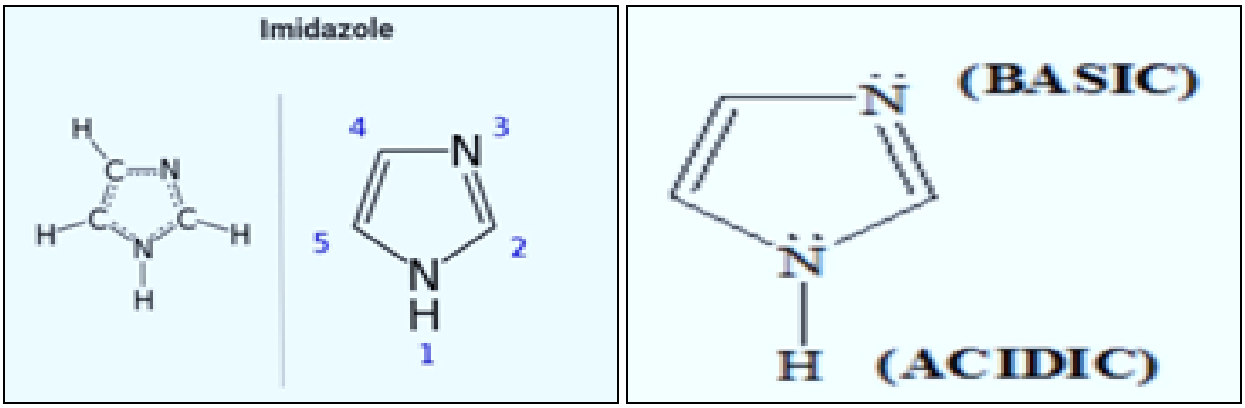

FIG. 1: STRUCTURE OF IMIDAZOLE

TABLE 1: PROPERTIES OF IMIDAZOLE

S. no.	Chemical formula	$C_3H_4N_2$
1	Molar mass	68.077g/mol
2	Appearance	White or pale yellow
3	Density	1.23g/cube cm
4	Melting point	89 to 91°C
5	Boiling point	256°c
6	Solubility in water	633 g/L
7	Acidity	6.95
8	Crystal structure	Monoclinic
9	Coordination geometry	Planar 5 membered ring
10	Dipole moment	3.61 D
11	Pair of electrons	6π electron

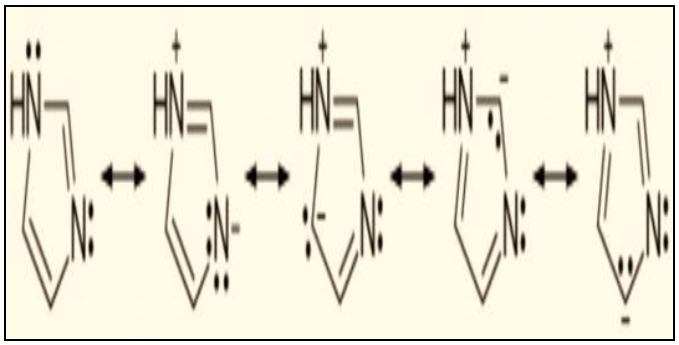

FIG. 2: RESONANCE STRUCTURE OF IMIDAZOLE.

Amphoteric Nature: Imidazole is amphoteric. That is, it can function as both an acid and as a base. As an acid, the pKa 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 imidazoline anion, which is symmetrical. As a base, the pKa of the conjugate acid (cited as pKBH+ 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 [3]. resonance of the imidazole is shown in **Fig. 3.**

General Methods of Preparation: Imidazole can be synthesized by numerous methods. Many of these syntheses can also be applied to different substituted imidazole's and imidazole derivatives simply by varying the functional groups on the reactants. Several approaches are available for the synthesis of imidazole's as.

Debus synthesis, Radziszewski synthesis, dehydrogenation of imidazolines, from alpha halo ketones, Wallach synthesis, from aminonitrile and aldehyde and Marckwald synthesis. Details of the synthetic procedures are given below [2, 4, 5].

Debus: Debus Synthesized imidazole by using glyoxal and formaldehyde in ammonia. This synthesis **Fig. 3**B, while producing relatively low yields, is still used for creating C-substituted imidazole's.

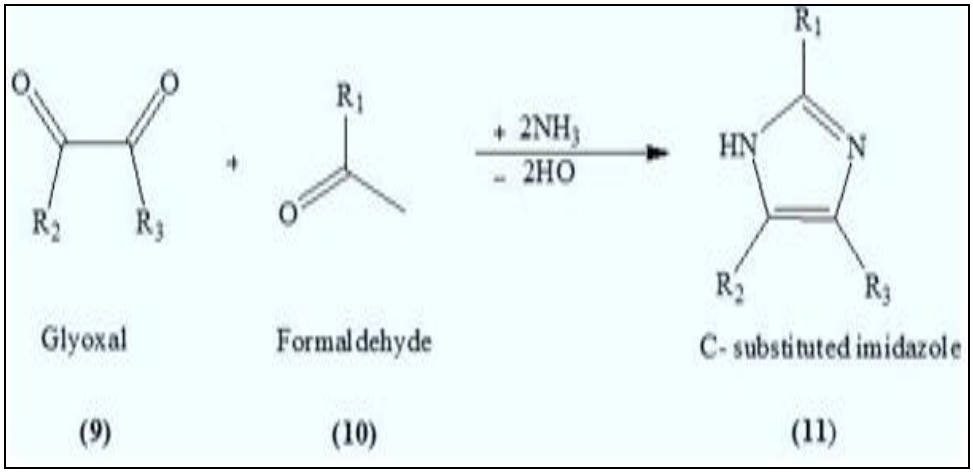

FIG. 3: DEBUS SYNTHESIS

Radziszewski Synthesis: Radziszewski reported the condensation of a tricarbonyl compound, benzyl and a- ketoaldehyde, benzaldehyde or a-diketones in the presence of ammonia, yield 2, 4, 5 triphenylimidazole. The proposed scheme is shown in **Fig. 4.**

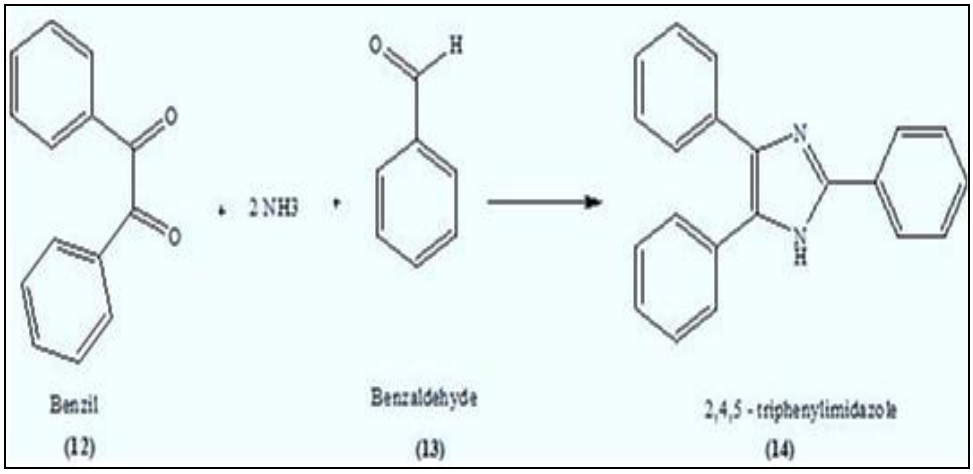

FIG. 4: RADZISZEWSKI SYNTHESIS

Dehydrogenation of Imidazole: Knapp and coworkers have reported a milder reagent barium manganate to convert imidazolines to imidazole's in the presence of Sulphur. Imidazolines obtained from alkyl nitriles and 1, 2 ethane diamines on reaction with BaMnO4NH yield 2-substituted imidazole's reaction of hydrogenation of imidazole is shown in **Fig. 5.**

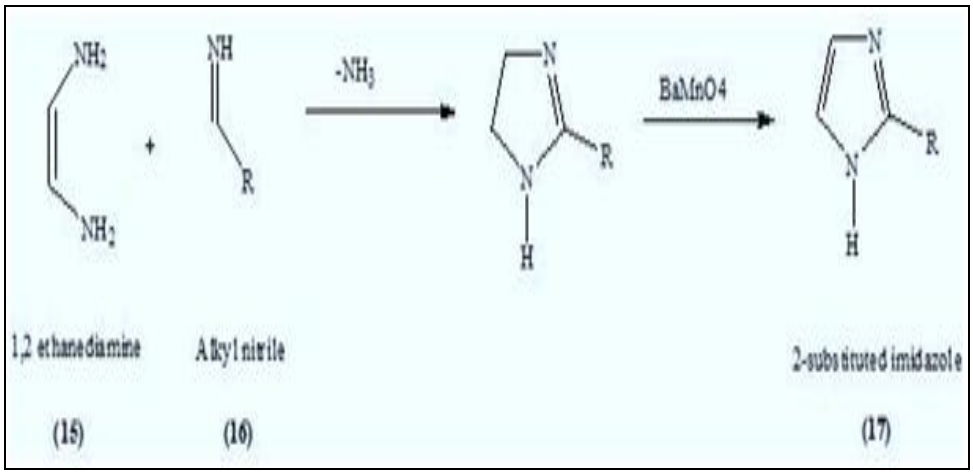

FIG. 5: DEHYDROGENATION OF IMIDAZOLE

Wallach Synthesis: Wallach reported **Fig. 6.** that when N, N- dimethyl oxamide [18] is treated with phosphorus pentachloride, a chlorine-containing compound [19] is obtained, which on reduction with hydroiodic acid give N- methyl imidazole [20]. Under the same condition N, N-diethyl oxamide is converted to a chlorine compound, which on reduction gives 1- ethyl –2methyl imidazole [20].

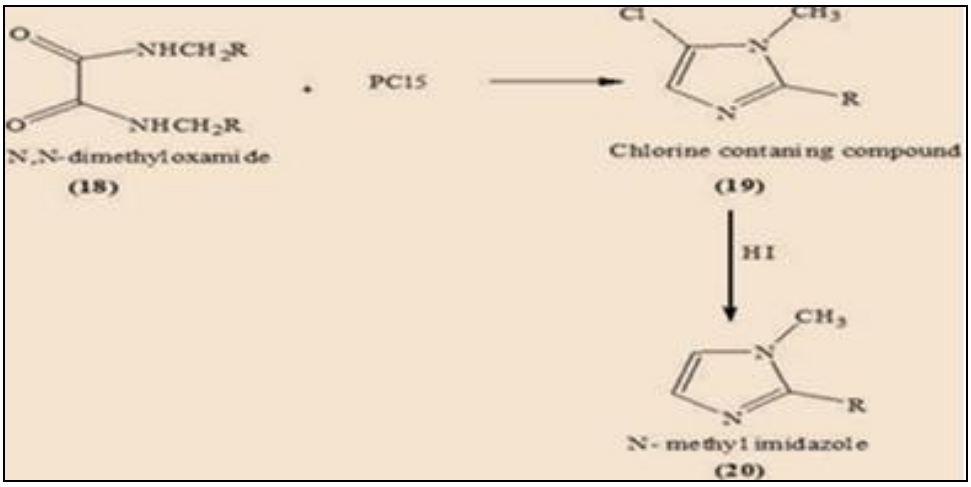

FIG. 6: WALLACH SYNTHESIS OF IMIDAZOLE

Synthesis: One-bond formed there has been limited recent research on the synthesis of imidazole's via methods that only include one of the heterocycle's core bonds. Fang *et al.* reported a novel protocol for the cyclization of amido-nitriles 1 to form disubstituted imidazole's 2 (Scheme1a) [19]. The reaction conditions were mild enough to include a variety of functional groups, including aryl halides and aromatic and saturated heterocycles (Scheme 1b). This reaction is reported to proceed *via* nickel-catalyzed addition to nitrile 1, which is followed by proto-demetallation, tautomerization, and dehydrative cyclization afforded the desired 2, 4disubstituted NH-imidazole's 2 in poor to excellent yield depending on the coupling partners.

By The Formation of One Bond: The (1, 5) or (3, 4) bond can be formed by the reaction **Fig. 7.** of an imitated (22) and an amino aldehyde or a-amino acetal (21), resulting in the cyclization of an imidine (23) to imidazole (24). The example below applies to imidazole when R=R1=Hydrogen [6, 21].

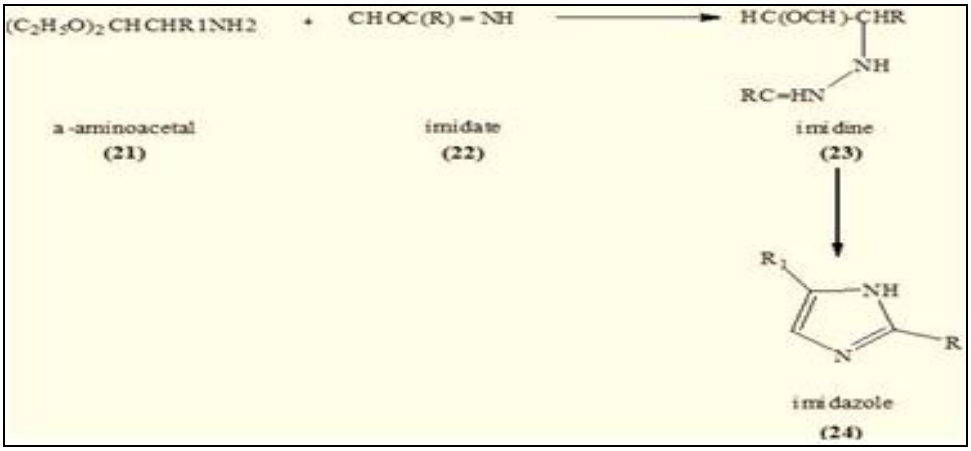

FIG. 7: IMIDAZOLE FORMATION BY ONE BOND

Pharmacological Action: Imidazole's are well-known heterocyclic compounds that are common and have an important feature of a variety of medicinal agents. On the basis of various literature surveys, imidazole derivatives show various pharmacological activities [7, 9]. Antibacterial activity Anticancer activity, Anti-tubercular activity Anti-HIV activity

Antibacterial Activity: Increasing the emergence of bacterial resistance to existing antibacterial has become a major concern among medicinal

Chemists worldwide. So, it has sparked a keen interest in developing new potent drugs with low toxicity and high Bioavailability. Extensive use of antibacterial and their resistance has led to severe health problems in the hospitals and communities. To treat bacterial infections, many heterocyclic Compounds are under study. These include furans, Hydrazides, pyrimidine, thiazepines, pyrazolines, Chalcones, imidazole's, *etc.* The imidazole scaffold is an interesting building block in various biomolecules Such as histidine, histamine, and natural products, *i.e.*, pilocarpine alkaloid (Podocarpus jaborandi). Imidazole Analogues has generated keen interest over the years due to Their wide range of biological properties, including Antimicrobial, anti-inflammatory, analgesic, anti-ulcerative, Histamine H3 antagonist, antioxidant, farnesyltransferase and geranylgeranyl transferase-I inhibitor, antitumor, anti-protozoal, and anti-diabetic activities. Some imidazole derivatives such as, e.g., Cimetidine, Etomidate, Ketoconazole, Metronidazole, Ornidazole, Azomycin, Oxiconazole, and Clonidine have found application in drug Therapy.

Mechanism of Action: Imidazole's acts *via* different mechanisms. According to One study, nitroimidazoles enter into the cell by passive Diffusion, where it undergoes reduction to yield nitro radical anion. This anion oxidizes the DNA, which results in the Breakage of the DNA strand and causes cell death. Another study found that flavohaemoglobins Present in bacteria, which metabolize nitric oxide (NO) to Nitrates and prevent NO-mediated damage, growth inhibition, and death. The imidazoles act by coordinating the Flavohaemoglobins and inhibit its NO dioxygenase (NOD) Function, thus inhibiting the metabolism of NO and finally Leading to bacterial cell death. Another group of researchers Stated that the inhibition of enol acyl carrier protein reductase (FabI), an enzyme involved in the synthesis of Bacterial fatty acids, is a novel target for antibacterial activity [10].

Anticancer Activity: The success of imidazole as anti-cancer agents started with dacarbazine, which triggered interest in the development of imidazole agents. Several classes of various structured heterocyclic molecules, including imidazoles, have been designed and developed to cure cancer *via* various targets for different types of cancer treatment. Imidazole can overcome the various drawbacks of currently available clinical drugs and develop anticancer agents. Therefore, attempts have been made to highlight some important classes of imidazole based on mechanisms of action via various targets like DNA, VEGF, mitotic spindle microtubules, histone deacetylases, receptor tyrosine kinases, topoisomerases, CYP26A1 enzyme, rapid accelerated fibrosarcoma (RAF) kinases, *etc. Imidazoles as antiangiogenic agents Angiogenesis* is essential to the growth of cells and tissues.

Tumors cannot grow through a defined volume if they are not vascularized. The vascular endothelial growth factor (VEGF) is an important angiogenic factor secreted by tumor cells. Most human cancer cells express elevated levels of VEGF and VEGF receptors on their surface. An antiangiogenic drug (*e.g.*, bevacizumab) impairs the VEGF pathway and tumor vasculature by targeting VEGF 76 or their receptors. Several small molecules have been evaluated as antiangiogenic agents in the last two decades, but only a few molecules have worked. For example, vincristine, taxol, and topside are currently being used for the treatment of acute lymphocytic leukemia, ovarian and lung cancers, respectively. Several imidazole has been explored as anticancer agents with anti-angiogenesis as the mode of action. Hansen *et al.* l reported levamisole derivatives in vitro inhibition of angiogen [11, 12].

General Mechanism of Action of Imidazole: Generally, imidazoles come under the category of antimetabolite, which have a specific mechanism of action in cancer. Antimetabolite is a type of chemical that inhibits the use of a metabolite. They have toxic effects on cells, such as halting cell growth and cell division. That's why these Compounds are used as chemotherapy for cancer. Antimetabolites can be used in cancer treatment, as they interfere with DNA production and, therefore, cell division and the growth of Tumors. These are the chemicals that become the building blocks of DNA. They prevent these substances from becoming incorporated into DNA during the S phase of the cell cycle, stopping Normal development and division. They also affect RNA synthesis because thymidine is used in DNA but not in RNA where uracil is used instead of

cytosine; inhibition of thymidine synthesis *via* thymidylate synthase selectively inhibits DNA synthesis over RNA synthesis [13].

Antitubercular Activity: Tuberculosis still remains one of the most common, communicable, and leading deadliest diseases known to mankind throughout the world. Drug resistance in Mycobacterium tuberculosis which threatens to worsen the global tuberculosis epidemic has caused great concern. To overcome the resistance, the development of new drugs with novel mechanisms of action is of great importance. Imidazole-containing derivatives endow with various biological properties, and some of them demonstrated excellent anti-tubercular activity.

As the most emblematic example, 4-nitroimidazole dexaminid has already received approval for the treatment of multidrug-resistant tuberculosis-infected patients. Thus, imidazole-containing derivatives have caused great interest in the discovery of new anti-tubercular agents. Numerous imidazole-containing derivatives were synthesized and screened for their *in-vitro* and *in-vivo* anti-mycobacterial activities against both drug-sensitive and drug-resistant Mycobacterium tuberculosis pathogens. This review aims to outline the recent advances of imidazole-containing derivatives as anti-tubercular agents and summarize the structure-activity relationship of these derivatives. The enriched structure-activity relationship may pave the way for the further rational development of imidazole-containing derivatives as anti-tubercular agents [14].

Anti-HIV Activity: HIV-1 (Human Immuno-deficiency Virus Type-1) is a pathogenic retrovirus of the Lentivirus family and causative agent of AIDS or AIDS Related Complex (ARC) (1–3). HIV infection targets the monocytes expressing surface CD4 receptors and produces Profound defects in cell-mediated immunity. Overtime infection leads to severe depletion of CD4 Lymphocytes (T-cells), resulting in opportunistic infections (OIs) such as Bacterial, fungal, viral, protozoal, and neoplastic diseases and ultimately death. An Ideal anti-HIV agent should suppress HIV replication and should also be able to combat Other opportunistic infections, like tuberculosis, hepatitis, and other bacterial infections. Earlier works in our laboratory have identified various imidazole derivatives exhibiting broad-spectrum chemotherapeutic properties. In continuation of our effort to develop imidazoles as broad-spectrum chemotherapeutic agents and encouraged by the work of de Martino *et al.,* we undertook the present study to synthesize and evaluate novel imidazoles and nitroimidazoles that could suppress HIV replication and also Inhibit opportunistic microorganisms. Docking studies with HIV-1 RT (PDB ID 1FK9) Were also performed in order to investigate the binding pattern of the compounds showing inhibitory activity on HIV-1 [15].

Biological Action of Imidazole Containing Compounds: There are so many Imidazole rings containing compounds that Manifest various types of physiological, biological, and pharmacological activities such as Anti-carcinogen, antibacterial, anti-fungal, anti-viral, anti-HIV agents, anti-ulcer agent, anti-leishmanial, Antimicrobial, anti-convulsant, anti-protozoal, anti-allergic, anti-Inflammatory, analgesic, anxiolytic, anti-diabetic activities and *etc.* Imidazole has a wide range of biological activities. The drugs which Contain imidazole act on a different type of receptors. For example, Dopamine receptor, histaminic receptor, adreno-receptor, *etc.* The pharmacogical activity of some important imidazole containing Compounds with their particular biological action [15].

Applications of Imidazole: 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 freezes 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 the assay of horseradish peroxides. It is also used as a chelator for the binding of different divalent cations. 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, Ergothioneine, Clonidine, and Moxonidine. One of the most important applications of Imidazole derivatives is there used as material for the treatment of denture stomatitis. Imidazole has become an important part of many pharmaceuticals. Synthetic Imidazoles are Present in many fungicides and anti-fungal, 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 is used in leukemia by interfering with DNA activities. Imidazole is 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 acted as a fire retardant [6, 12, 14].

CONCLUSION: Based on various literature survey imidazole derivatives shows Pharmacological activity against antimicrobial, anti-inflammatory, analgesic, anti-tubercular, anticancer, *etc.* Slight modifications can further achieve the Possible improvements in the activity in the Substituents on the basic imidazole nucleus.

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