International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

# Review on Various Protocol to Access Imidazole and It's Versatile Biological Activities

**Karan C. Waghmare[1], Babasaheb B. Maind[2], Adesh V. Kharate[3], Gajanan Y. Shinde[4], Dr. Bapurao B. Shingate[*]**

[1,2]Department of Chemistry, Shrimant Bhaiyyasaheb Rajemane Mahavidyalaya Mhaswad, (Satara), Maharashtra, India
[3]Department of Chemistry, Rajasthan Aryan Arts, Shri Mithulalji Kacholiya Commerce & Shri Satyanarayanji Ramkrishnaji Rathi Science College, Washim, Maharashtra, India
[4]Department of Chemistry, Raja Shripatrao Mahavidyalaya, Aundh (Satara), Maharashtra, India
[*]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Chhatrapati Sambhajinagar, Maharashtra, India

**Abstract**
Imidazole occupies a significant role in heterocyclic chemistry, with its derivatives drawing increasing interest recently due to their diverse chemistry and pharmacological properties. It is a nitrogen containing heterocyclic ring crucial in both biological processes and pharmaceutical applications. Consequently, imidazole compounds have captivated researchers for over a century, serving as a compelling source of investigation. These derivatives exhibit a wide array of biological activities, including antibacterial, anticancer, anti-tubercular, anti-diabetic activity, anti-fungal, anti-inflammatory activity and anti-HIV effects. This review aims to chronicle the historical evolution of imidazole's biological activities and the work reported on the synthesis of imidazole derivatives. A multitude of imidazole derivatives are available and the incorporation of the imidazole nucleus remains a pivotal strategy in synthetic drug discovery.

**Keywords:** Imidazole, Heterocyclic chemistry, Biological activities, Antibacterial, Anticancer, Anti-tubercular, Anti-fungal, Anti-diabetic activity, Anthelmintics activity, Anti-inflammatory activity and Anti-HIV effects.

## Introduction:

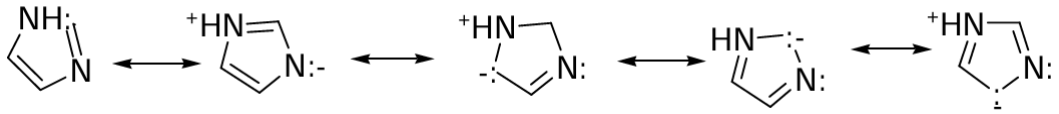
Heterocyclic chemistry is one of the most complex and fascinating branches of the field, characterized by a high degree of structural diversity and significant economic value as therapeutic agents [1,2]. A key goal in modern medicine is to discover new biologically active compounds that are both highly effective and exhibit low toxicity to humans. Currently, research in synthetic organic chemistry focuses on developing methods for the directed synthesis of complex organic molecules to create physiologically active substances with selective effects.

The imidazole ring is a five-membered structure composed of three carbon atoms and two nitrogen atoms, with the nitrogen atoms positioned at the 1$^{st}$ and 3$^{rd}$ locations. This ring features both a hydrogen bonding domain and an electron-donating nitrogen system [3-5]. Fischer first described the imidazole ring in 1882, and Freud and Kuhn later clarified its ring system in 1890[6-8].

Imidazole containing drugs are widely used in clinical medicine due to their broad range of applications. The imidazole component is present in several pharmacologically significant drugs, including Metronidazole, Pretomanid, Ketoconazole, Clotrimazole, Tipifarnib, Megazol, Miconazole, Nafimidon, Losartan, Azathioprine, Dicarbazine, Cimetidine, Naphthyzin, Xylometazoline, Mercazolil, and Thiamazole etc [9].

**Structure and Properties**

Imidazole is an organic compound with the chemical formula $C_3H_4N_2$. Imidazole is a monoacidic base capable of forming crystalline salts with acids and exhibits a characteristic melting point in its imidazolium salts [10]. The molecule consists of a planar, five-membered ring that is soluble in water and other polar solvents. Imidazole exists in two tautomeric forms- 1H-imidazole and 3H-imidazole depending on the position of the hydrogen atom relative to the nitrogen atoms. It is a highly polar compound, with a dipole moment of 3.61 D, and is fully soluble in water. Classified as an aromatic compound, imidazole contains a sextet of π-electrons: a pair from the protonated nitrogen atom and one from each of the four other ring atoms. Some of imidazole's resonance structures are depicted below [11].

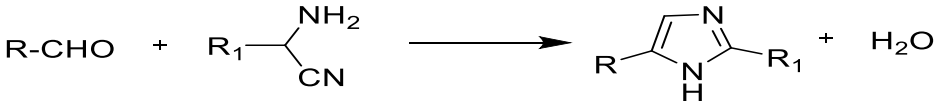


**A) General Methods of Preparation**

Imidazole can be synthesized through a diverse array of methodologies, many of which offer the flexibility to generate various substituted imidazole and their derivatives by altering the functional groups on the precursor molecules. Prominent synthetic strategies encompass Debus synthesis, Radiszewski synthesis, dehydrogenation of imidazolines, transformations involving α-halo ketones, Wallach synthesis, synthesis from aminonitriles and aldehydes, as well as the Marckwald synthesis [11]. The intricate details of these synthetic protocols are elaborated upon below.

**I. From Aminonitrile and Aldehyde** [11]

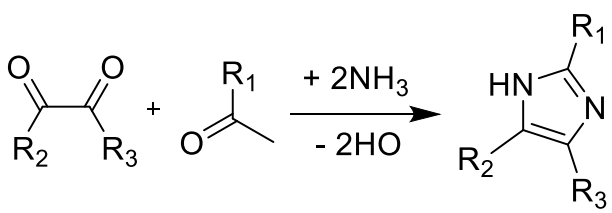
When an aldehyde (01) and an aminonitrile (02) are combined and subjected to suitable reaction conditions, they condense to form a substituted imidazole (03), as depicted below.



(01) (02) (03)

**II. Debus synthesis** [12]

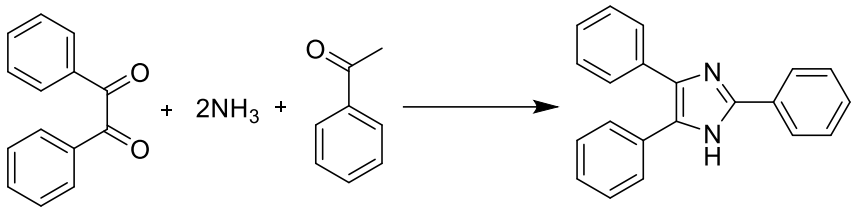
Debus synthesized imidazole via the reaction of glyoxal (04) and formaldehyde (05) in an ammonia environment. Despite the relatively modest yields, this method continues to be employed for the generation of C-substituted imidazole (06).



(04) (05) (06)

### III. Radiszewski synthesis [13-15]

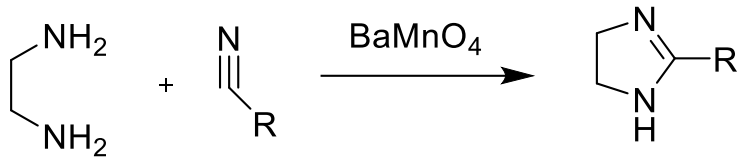
Radiszewski documented the condensation of a dicarbonyl compound, benzil (07), with an α-keto aldehyde, benzaldehyde (08), or α-diketones in the presence of ammonia, resulting in the synthesis of 2,4,5-triphenyl imidazole (09).




(07) (08) (09)

### IV. Dehydrogenation of Imidazoline [16]

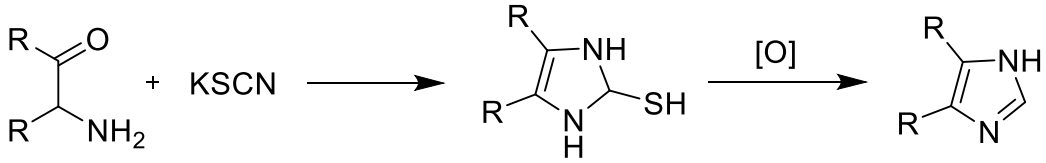
A milder reagent, barium manganate, is employed to oxidize imidazolines into imidazoles in the presence of sulfur. Imidazolines, derived from the reaction of 1,2- ethanediamine (10) and alkyl nitriles (11), are converted by $BaMnO_4$ to produce 2-substituted imidazoles (12).




(10) (11) (12)

### V. Markwald synthesis [16]

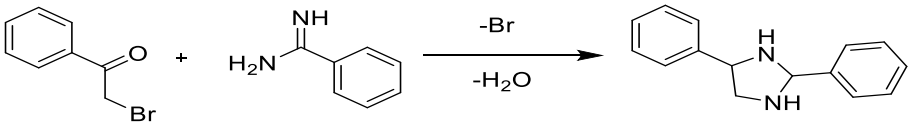
The synthesis of 2-mercaptoimidazoles involves the reaction of α-amino ketones (13) or aldehydes with potassium thiocyanate, leading to the formation of 2-thiol substituted imidazoles (14). The sulfur group can then be easily removed through various oxidative methods to yield the target imidazoles (15).



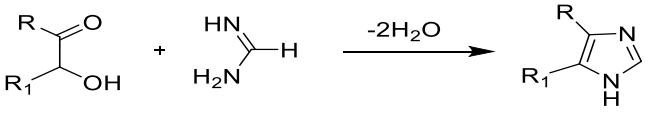

(13) (14) (15)

### VI. From α-Halo Ketone [16]

This method relies on the interaction between an α-halo ketone (16) and an imidine (17). It has been successfully applied in the synthesis of 2,4- or 2,5-biphenyl imidazole (18). Likewise, acyloin (19) can react with amidine (20) or α-halo ketones to produce imidazole (21).



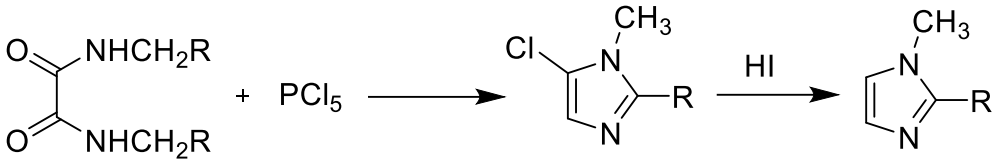

(16) (17) (18)




(19) (20) (21)

### VII. Wallach synthesis [17-20]

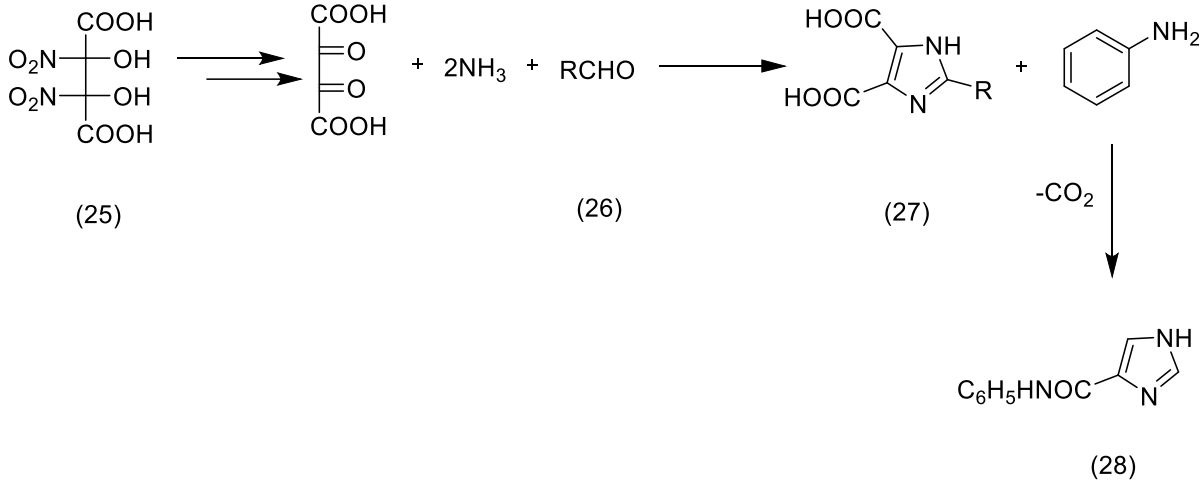
Wallach observed that when N, N-dimethyloxamide (22) is treated with phosphorus pentachloride, it forms a chlorinated intermediate (23), which upon reduction with hydroiodic acid, produces N- methyl imidazole (24). In an analogous reaction, N, N-diethyloxamide is converted into a chlorinated compound, which after reduction yields 1-ethyl-2-methyl imidazole.



(22) (23) (24)

### VIII. From formaldehyde and tartaric acid dinitrate [21]

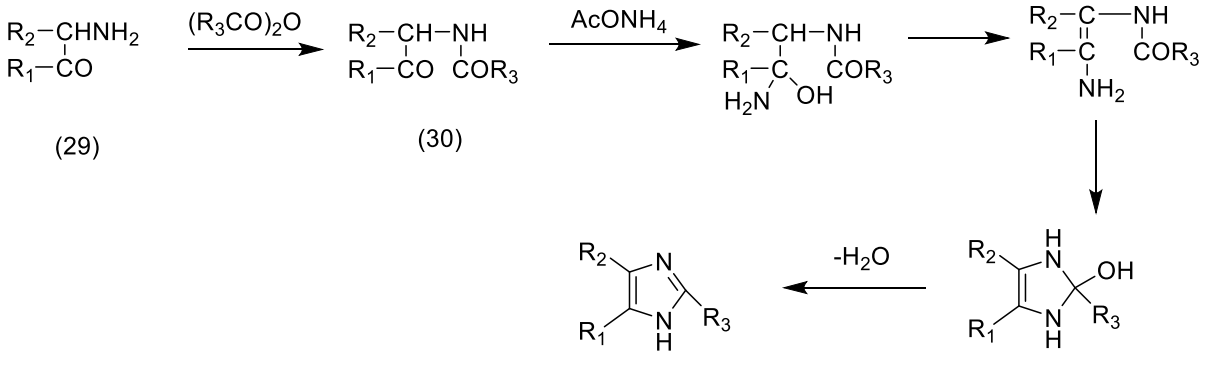
Imidazole can be effectively synthesized by reaction ammonia with a mixture of tartaric acid dinitrate (25) and formaldehyde (26). This is followed by heating the resulting dicarboxylic acid with quinoline in the presence of copper to produce 2-alkyl substituted 4,5-dicarboxylic acid imidazole (27). Subsequently, this intermediate is reacted with aniline to yield a 4-substituted benzamide (28).



(25) (26) (27) (28)

### IX. Cyclization of α-Acylaminoketones [21]

α-Acylaminoketones (29) can also act as 1,4-diketo compounds (30). These compounds undergo facile cyclization (31) in the presence of an anhydride, followed by treatment with ammonium acetate.



(29) (30) (31)

**B) Biological Activities**

Imidazole are well-established heterocyclic compounds, known for their widespread occurrence and significant medicinal properties. Various literature reviews reveal that imidazole imidazole derivatives exhibit a broad spectrum of pharmacological activities.

1. Antitubercular activity
2. Anti-fungal activity
3. Anti- bacterial activity
4. Anti-diabetic activity
5. Anti-cancer activity
6. Anti-inflammatory activity
7. Anti-HIV activity.

**I. Antitubercular activity**

Tuberculosis continues to be one of the most prevalent, communicable and lethal diseases afflicting humanity worldwide. The emergence of drug resistance in Mycobacterium tuberculosis, which threatens to exacerbate the global tuberculosis crisis, has become a significant concern. Addressing this resistance necessitates the development of new drugs with innovative mechanisms of action. Imidazole-containing derivatives exhibit a range of biological properties, with several showing remarkable anti-tubercular efficacy. A prime example is 4-nitroimidazole dexaminid, which has been approved for treating patients infected with multidrug-resistant tuberculosis. Consequently, imidazole containing derivatives have garnered substantial interest in the search for new anti-tubercular agents. Numerous derivatives have been synthesized and drug-resistant Mycobacterium tuberculosis strains. This review seeks to highlight the recent progress in the development of imidazole-containing derivatives as anti-tubercular agents and to summarize their structure-activity relationships. A deeper understanding of these relationships may facilitate the rational design of more effective imidazole-based anti-tubercular agents [22].

**II. Anti-fungal activity**

In recent years, the pursuit of novel antifungal agents has largely concentrated on the domains of imidazole and triazole chemistry. The pharmacological cohort known as azoles, encompassing a variety of 1-substituted imidazole and triazole moieties, unequivocally represents the avant-garde approach to both topical and systemic antifungal therapy. Imidazoles, as antifungal agents, exhibit considerable pharmacokinetic and biochemical potency. However, lipophilic imidazole such as clotrimazole, econazole and miconazole demonstrate markedly poor systemic bioavailability post-oral administration, attributed to inadequate absorption and extensive first-pass hepatic metabolism, thus confining their utility to the topical treatment of superficial mycotic infections. The advent of ketoconazole, a more hydrophilic imidazole introduced in the late 1970s, heralded a pivotal breakthrough in antifungal therapeutics [23].

**III. Anti-bacterial activity**

According to the literature review, the subsequent most prevalently observed pharmacological effect of Imidazole derivatives is their antibacterial potency. The identification of this effect holds substantial importance, as the efficacy of nearly all principal antibiotic classes (including tetracyclines, cephalosporins, aminoglycosides and macrolides) may be compromised due to escalating microbial resistance. Currently, therapeutic failures associated with multidrug-resistant bacterial strains represent a formidable challenge to global public health.

For instance, the bactericidal properties of Imidazole compounds, particularly when complexed with silver (Ag), have been rigorously examined. In 2013, John McGinley et al.[24]. (National University of Ireland)

synthesized 1-(3-aminopropyl)imidazole and produced Schiff base ligands that readily coordinated with Ag(I) centres. The subsequent studies conducted against strains of S. aureus, MRSA, E.coli, and P. aeruginosa revealed that most Ag(I) complexes exhibited moderate antibacterial efficacy.

**IV. Anti-diabetic activity**

Numerous imidazoline-containing compounds have been shown to provoke insulin secretion from isolated pancreatic islets and crucially, enhance glucose tolerance in both rats and mice. The purported imidazoline receptor involved, situated on pancreatic β-cells, is designated as the a typical imidazoline or I3 site, distinguished by its unique pharmacological properties from the previously characterized I1 and I2 receptors found in other tissues[25].

**V. Anti-cancer activity**

In recent years, the imidazole moiety has garnered significant attention for its potential as an anticancer or antineoplastic agent. A key focus has been on optimizing various substitutions at different positions within the moiety. Cyclin-dependent kinases(CDKs), which are serine-threonine protein kinases, are instrumental in regulating the eukaryotic cell cycle and transcriptional control. Given their critical role in cell cycle management and their dysregulated expression in many human cancers, extensive research has been directed towards developing small molecule CDK inhibitors as promising therapeutic agents [26]. The integration of a basic group into the CDK imidazole pyrimidine amide inhibitor series has demonstrated considerable potential for achieving effective CDK inhibition. The imidazolesulfone AZD5438 (I) was explored further as an orally bioavailable anticancer agent. Replacing the sulfone group with piperazine led to the development of a new series of potent CDK inhibitors (II) with improved physicochemical properties, making them amenable to oral administration [27].

**V. Anti-inflammatory activity**

The quest for novel and more effective anti-inflammatory drugs is an ongoing endeavour. The pursuit of agents to alleviate swelling, redness, pain and fever related to rheumatism dates back to ancient times. Synthetic research encompasses a range of heterocyclic systems, either in isolation or fused with other structures. Amino acids have been reported to exhibit anti-inflammatory properties [28,29], prompting kumar et al. [30] to develop various heterocyclic derivatives featuring both carboxylic and amino groups. Structure-activity relationship studies revealed that transforming the carboxylic group into a heterocyclic ring typically enhanced edema inhibition. Specifically, the conversion to benzimidazole and 1,2,3,4-tetrahydroquinoline rings yielded compounds with superior activity compared to those derived from imidazole rings. While imidazole and benzimidazole derivatives are associated with a broad spectrum of biological activities, including anti-inflammatory effects, various N-substituted imidazoles [31] and substituted imidazolones [32] also exhibit notable anti- inflammatory properties.

**VI. Anti-HIV Activity**

HIV-1 (Human Immunodeficiency Virus Type-1) is a virulent retrovirus of the Lentivirus genus, recognized as the etiological agent of AIDS or AIDS Related Complex (ARC). HIV infection specifically afflicts monocytes bearing surface CD4 receptors, culminating in profound impairments in cell-mediated immunity. Over time, the infection precipitates a drastic depletion of CD4 lymphocytes (T-cells), which in turn leads to opportunistic infections (Ols) such as bacterial, fungal, viral, protozoal, and neoplastic pathologies, ultimately resulting in mortality. An optimal anti-HIV compound should not only suppress HIV replication but also exhibit efficacy against other opportunistic infections, including tuberculosis, hepatitis and other bacterial pathogens. Prior research conducted in our laboratory has identified various imidazole derivatives exhibiting broad-spectrum chemotherapeutic properties. In pursuit of this line of

inquiry and galvanized by the work of de Martino er al., we embarked on the current investigation to synthesize and evaluate novel imidazoles and nitroimidazoles capable of suppressing HIV replication while also inhibiting opportunistic microorganisms. Additionally, docking studies with HIV-1 RT (PDB ID 1FK9) were undertaken to elucidate the binding interactions of these compounds exhibiting inhibitory activity against HIV-1 [33].

**Conclusion:**

A significant array of imidazole derivatives is currently being developed for diverse therapeutic purposes. This article aims to review the literature on the synthesis of these imidazole derivatives. Imidazole and its derivatives are of paramount significance in medicinal chemistry, owing to their versatile synthetic applications. Their ability to facilitate the development of a broad spectrum of pharmaceuticals has garnered considerable interest from researchers. This review highlights the substantial promise of imidazole and its derivatives for the future synthesis of innovative drugs, which could offer profound societal advantages.

**References:**

1. Katritzky A. R., Karelson, Malhotra M. N., (1991), Heterocyclic Aromaticity in Heterocycles, 32, 127.
2. Eichner T., Hauptmann S., (2003), The Chemistry of Heterocycles, Second Edition, Wiley-VCH, Weinheim, Germany.
3. Yoon Y. K., Ali M. A., Wei A. C., Choon T. S., Osman H., Parange K., Shirazi A. N. (2010), Bioorganic & Medicinal Chemistry Letters 20, (23), 7064.
4. Rosa M. F., Batista, Susana P. G., Mannela M. M., Raposo (2013), The Journal of Organic Chemistry 78, 11389.
5. Rathod C. P., Rajukar R. M., Thoute S. S. (2013), Indo American Journal of Pharmaceutical Research, 3, (2), 2323.
6. Simonov A. M., Sitkina L. M., Pozharskii A. F., (1967), Chemical Industry London, 1454.
7. Clark H. T., Kimer W. R. (1941), Methy Red, Organic Synthesis, 374.
8. Hair S. R., Taylor G. A., Schultz LWJ (1990), Chemical Education, 67.
9. Sharipov I. M. Sintez i biologicheskaya aktivnost tiyetansoderzhashchikh proizvodnykh 4,5-dibromimidazola [in Russian]. Abstract of the dissertation. 2014
10. The Chemistry of Heterocyclic Compounds, Imidazole and Its Derivatives, Volume 6, By Klaus Hofmann, 13, John Wiley and Sons.
11. A. Bhatnagar, P. K. Sharma, N. Kumar. Inter. J. Pharm. Tech Res., 2011, 3(1), 268-282.
12. H. Debus, Annalen der Chemie und Pharmacie., 1858, 107, (2), 199-208.
13. E. Lunt, C. G. Newton, C. Smith, G. P. Stevens, M. F. Stevens, C. G. Straw, R. J. Walsh, P. J. Warren, C. Fizames, F. Lavelle, J. Med. Chem., Feb., 1987, 30(2), 357-66.
14. K. Hoffman, Interscience, 1953, 143-145.
15. H. Bredereck, R. Gompper, D. Hayer, Chem. Ber., 1959, 92, 338.
16. C. Robert, Elderfield, 1957, V-5, 744.
17. Wallach & Schuelze, Ber., 1881, 14, 420-423.
18. Wallach, Ber., 1876, 184, 33-35.
19. Wallach, Ber., 1881, 14, 735, Wallach 7 Stricker, Ber., 1880, 13, 51, Wallach & Schulze, Ber., 1880, 13, 1514.

20. Sarasin & Weymann, Helv. Chim, Acta, 1924, 7, 720.
21. I. L. Finar, stereochemistry and chemistry of natural products, Organic chemistry, vol 2, V 4th edition, 622, 629.
22. Shabalin D. A. And Camp J. E.: Recent advances in the synthesis of imidazoles. Organic and Biomolecular Chemistry 2020; 18(21): 3950-64.
23. Springer- Verlong Chemotherapy of Fungal Disease., Vol. 96, 257-267.
24. McGinley J., McCann M., Ni K., Talon T., et al. Imidazole Schiff base ligands: Synthesis, coordination complexes and biological activities. Polyhedron. 2013;55(2): 169-178.
25. Narasimhan B., Sharma D., Nov. 2011. Biological importance of imidazole nucleus in the new millennium, medicinal chemistry research.
26. Sharma P. S., Sharma R., Tyagi R., Curr. Canceer Drug Targets, 2008, 8, 53.
27. Finlay M. R. V., Acton D. G., Andrews D. M., Barker A. J., Loddick S. A., Morgentin R., Roberts A., Tucker J. A., Weir H. M., Bioorg. Med. Chem. Lett, 2008, 18, 4442.
28. Verma M., Saxena A. K., Shanker K., Pharmacol. Res. Commun. 1984, 16, 9.
29. Verma M., Gujrati V. R., Sharma M., Saxena A. K., Shanker K., Arch. Pharm. 1982, 315, 358.
30. Kumar A., Verma M., Saxena A. K., Shanker K., Indian J. Chem., 1988, 27b, 301.
31. Purohit M., Shrivastava S. K., Indian J Pharm. Sci, 1991, 53, 162.
32. Pandey K., Kali R., Bhalla T. N., Barthwal J. P., Pharmazie, 1987, 42, 269.
33. Ghorab M. M., Ismail Z. H., Abdel-Gawad S. M. And Aziem A. A.: Antimicrobial activity of amino acid, imidazole and sulphonamide derivatives of pyrazolo [3,4-d] pyrimidine. heteroatom chemistry: an international journal of main group elements 2004; 15(1): 57-62.