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A Literature Review on Antimicrobial Activities of Imidazole

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Abstract: Imidazole is an heterocyclic compound that is used as raw material by the pharmaceutical industries for manufacturing anti-fungal drugs such as ketoconazole and clotrimazole or the bactericide imazilil and prochloraz. Similarly, the pesticide industries use the imidazole as intermediary in the synthesis of some pesticides and insecticides. This literature review aims to investigate archival literatures of past authors regarding new compounds that can be used as antimicrobial agent. The research adopts an extensive review of literature such as conference papers, journal articles, internet sources, books to find out the effect of synthetic compounds on antimicrobial organism. The study concludes that imidazole is an active drug for microbial resistance. The study further recommends that more derivatives of imidazole should be synthesized in the laboratory. This is important in other to inhibit the growth of new strains of organisms.
Keywords: Antimicrobial: Imidazole: Antifugal: Pesticides: Insecticides: Heterocyclic Compound
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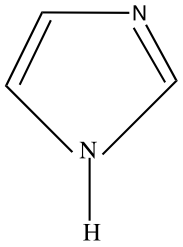
1.0 Introduction of the Study

Imidazole 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, it is an aromatic heterocycle, classified as a diazole, and has non-adjacent nitrogen atoms. Kashyap et al. (2011) argued that many natural products, especially alkaloids, contain the imidazole ring. These imidazoles share the 1,3-C_3N_2 ring but feature varied substituents (Kashyap et al., 2011; Valverde & Torroba, 2005; Shabalin, 2020). This ring system is present in important biological building blocks, such as histidine and the related hormone histamine. Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam (Brown, 1998; Adewole, 2021). When fused to a pyrimidine ring, it forms a purine, which is the most widely occurring nitrogen-containing heterocycle in nature (Amir, 2007; Singh & Kapoor, 2008). The chemical structure, including the resonance structures, can be written as below:



Imidazole

Figure 1.1 Structure of Imidazole

The name "imidazole" was coined in 1887 by the German chemist Arthur Rudolf Hantzsch (1857–1935). Bhatnagar et al. (2011) posited that Imidazole is a planar 5-membered ring. 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. It is highly soluble in water (Javed, 2007; Nawwar et al., 2013; Shalini et al., 2011). The compound is classified as aromatic due to the presence of a planar ring containing 6 π-electrons (a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring).This interesting group of heterocyclic compounds has wide range biological activities such as, analgesic, anti-inflammatory, anticancer, antiviral, anthelmintic, anticonvulsant, antiulcer, antimicrobial, anti-allergic activity etc (Zala et al., 2012; Hadizadeh et al., 2008; Harish, 2007; Adewole, 2021). Various methods employed for the synthesis of imidazole's and their chemical structure reactions offer enormous scope in the field of medicinal chemistry (Baroniya et al., 2010; Kumar et

al., 2017). However, the main objective of this article is to conduct a detailed literature review of the synthesis of imidazole and its derivatives coupled with the review of the biological activities against microbes such as bacteria and fungi.

2.0 Review of Extant Literature

2.1 Imidazole

Imidazole is a five-membered aromatic molecule containing two annular nitrogen atoms. One nitrogen behaves like a pyrrole-type nitrogen and the other one shows a close resemblance to a pyridine-type nitrogen (Pandeya, 2004; Liu, 2001; Reddy et al., 2004).The molecular formula of imidazole is $C_3H_4N_2$ and its molar mass is 68.08 g mol^{-1}. Kapoor (2008) reported that it is a five-membered aromatic heterocycle where two nitrogen atoms substituting two CH- groups. The two nitrogen atoms are non-adjacent positions (Singh, 2008). Imidazole is a planar molecule; so there is an unshared electron pair under a nitrogen in a sp2 orbital. This electron pair is responsible by various of chemical properties of imidazole, such as the basicity of molecule. Free imidazole is not frequently found in nature. However, the imizadole derivatives are extended in nature, for examples: the amino acid histidine or the compounds histamine, bezimidazole and some alkaloids have the imidazole ring in their structures (Jain & Sharma, 2005; Lednicer & Mitscher, 1984).

2.1.1 Physical Properties

(i) Imidazole is a white or colorless solid (ii) It can show a prismatic crystal appearance. (iii) Imidazole is highly soluble in water, ethanol, ethyl ether and chloroform. (iv) It is insoluble in non-polar solvents. (v) In water, it produces an alkaline solution. (vi) Its melting point is 88-91 ºC and its boiling point is 256 ºC. (vii) Imidazole has a molecular weight of 68.077g/mol with chemical formular C3H4N2. (viii) Imidazole has a density of 1.23 g/cm3 (Jain & Sharma, 2005). Imidazole exists as a resonance hybrid, the positions-4 and-5 are equivalent in the unsubstituted imidazole (Finar, 2006; Grimmett, 1997; Shabalin et al., 2020).

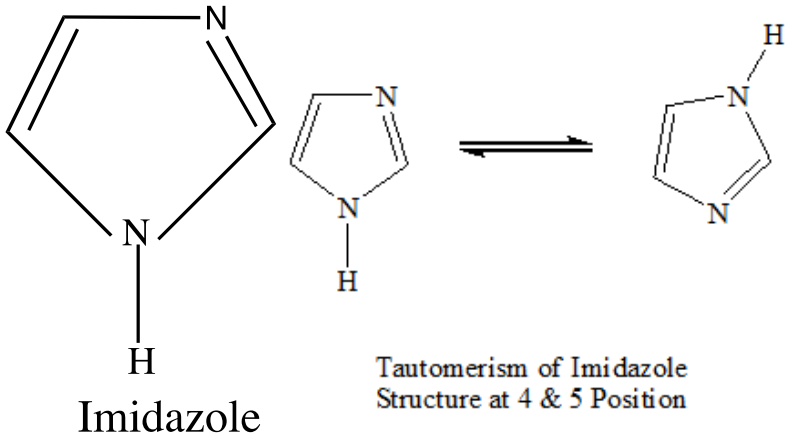


Figure 2.1: Structure of Imidazole

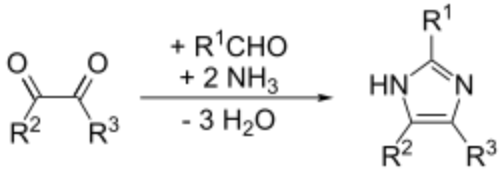
2.1.2 Chemical Properties

Wiley (2006) argued that Imidazole is a 5-member rings that show two tautomeric structures due the positive charge can be located in both of the nitrogen atoms. The author stressed further that the hydrogen binds to the

nitrogen atom can be removed easily because the lesser electron density of this nitrogen atom (Bosserman et al., 2004). On the other hand, the other nitrogen atom has an unshared electron pair in a sp2 orbital that can accept protons. Consequently, imidazole shows an amphoteric behavior: it can act as a weak base or a weak acid (Bhatnagar, 2011; Sharma et al., 2013; Prasanthy et al., 2011). Imidazole is used as raw material by the pharmaceutical industries for manufacturing anti-fungal drugs such as ketoconazole and clotrimazole or the bactericide imazilil and prochloraz. Adewole (2021) found that the pesticide industries use the imidazole as intermediary in the synthesis of some pesticides and insecticides. It can also be used as corrosion inhibitor of metals such as copper. Moreover, imidazole has found application as epoxy curing agent, to improve the electrical properties in electronic devices. Owing to the fact an imidazole ring is present in the aminoacid histidine, imidazole solutions is extensively apply in molecular biology techniques to purify recombinant proteins through metal affinity chromatography (IMAC) (Kumar, 2011). The proteins can be expressed with a histidine tails to promote the retention in a chromatography column that contains nickel ions and then, imidazole solution are used to displace the histidine tagged protein.Imidazole is harmful by oral ingestion. It is also corrosive and can cause severe skin burns and eye damage (Abdel-Hafez, 2008; Mittal, 2009; Dave & Sureja, 2013).

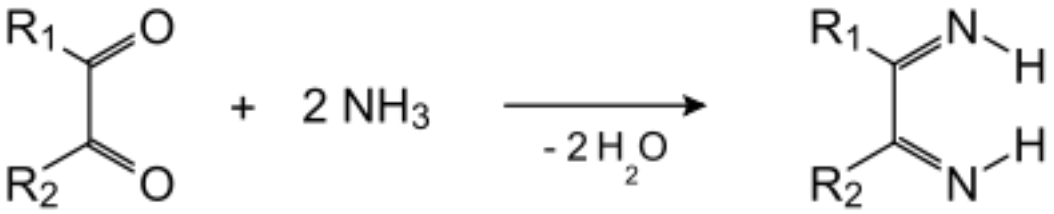
2.2 Synthesis of Imidazole and the Derivatives

Imidazole was first reported in 1858 by the German chemist Heinrich Debus, although various imidazole derivatives had been discovered as early as the 1840s. It was shown that glyoxal, formaldehyde, and ammonia condense to form imidazole (glyoxaline, as it was originally named). This synthesis, while producing relatively low yields, is still used for generating *C*-substituted imidazoles (Baroniya, 2010; Katritzky, 1992; De Clercq et al., 1991).



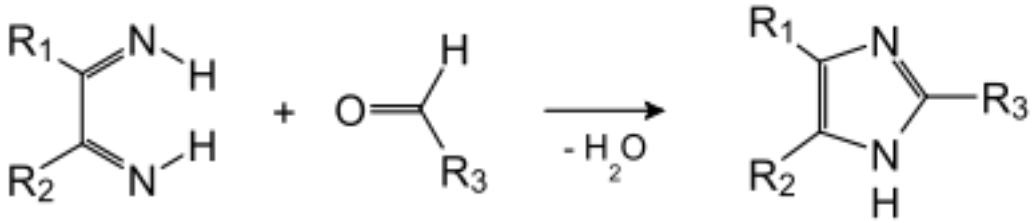
Scheme 2.1

In one microwave modification, the reactants are benzil, benzaldehyde and ammonia in glacial acetic acid, forming 2,4,5-triphenylimidazole ("lophine").Imidazole can be synthesized by numerous methods besides the Debus method. Many of these syntheses can also be applied to substituted imidazoles by varying the functional groups on the reactants. These methods are commonly categorized by the number of reacting component (Anwer, 2010; Nagalakshmi, 2008; Nekrasov, 2001). Debus-Radziszewski Imidazole synthesis is an organic reaction used for the synthesis of imidazoles from a dicarbonyl, an aldehyde, and ammonia. De Carvalho et al. (2010) reported that the dicarbonyl component is commonly glyoxal, but can also include various 1,2-diketones and ketoaldehydes. The method is used commercially to produce several imidazoles. The process is an example of a multicomponent reaction.The reaction can be viewed as occurring in two stages. In the first stage, the dicarbonyl and ammonia condense to give a diimine (shown with unusual orientation of N-H groups) (Dudhe, 2010; Dandale et al., 2012).



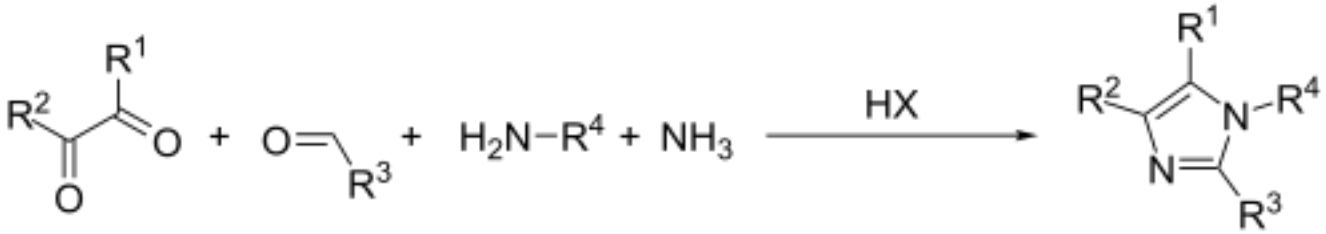
Scheme 2.2

In the second stage, this diimine condenses with the aldehyde



Scheme 2.3: This reaction is named after Heinrich Debus and Bronisław Leonard Radziszewski

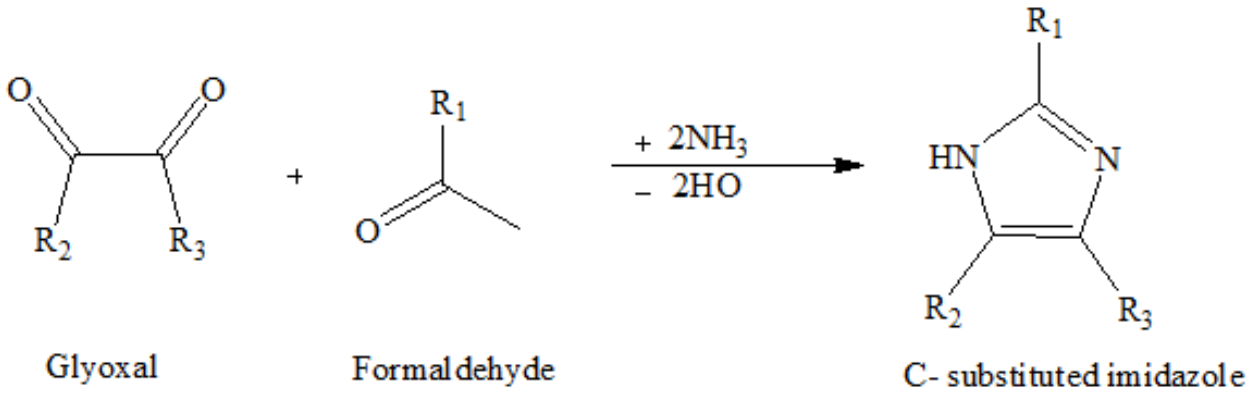
A modification of this general method, where one equivalent of ammonia is replaced by an amine, affords *N*-substituted imidazoles in good yields (Sinica, 2010; Adewole, 2021).



Scheme 2.4

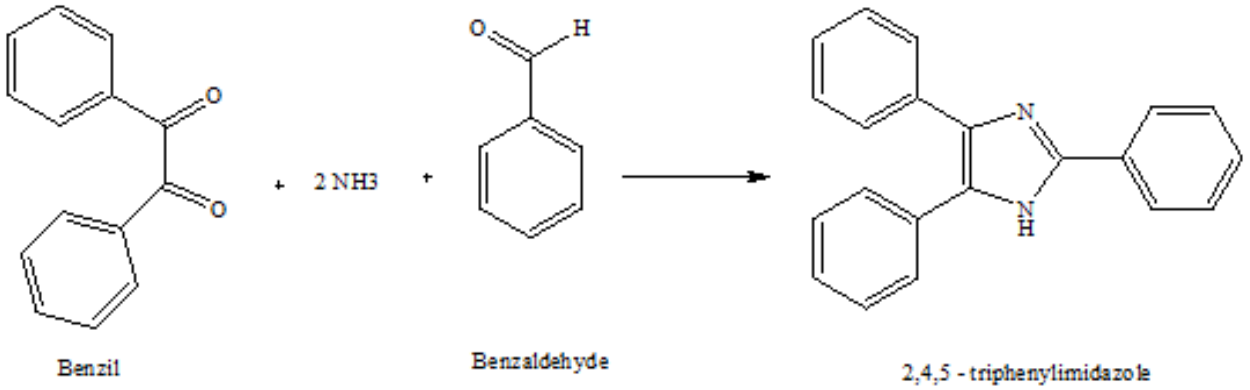
2.3 General Methods of Preparation

Finar (2006) suggested that Imidazole can be synthesized by numerous methods. Many of the synthesis can also be applied to different substituted imidazoles and imidazole derivatives simply by varying the functional groups on the reactants. Several approaches are available for synthesis of imidazoles as, Debus synthesis, Radiszewski 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. (a) Debus Synthesis:- Debus Synthesised imidazole by using glyoxal and formaldehydein ammonia. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles (Nagalakshmi, 2008; Nekrasov, 2001).



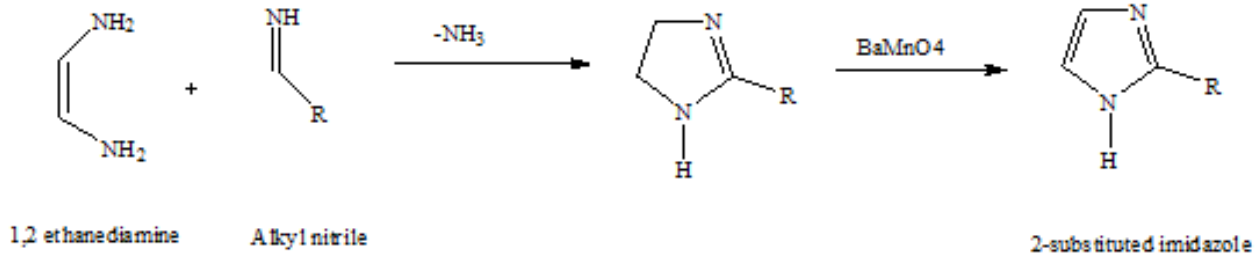
Scheme 2.5

(b) Radiszewski Synthesis: Radiszewski reported the condensation of a dicarbonyl compound, benzil and a-ketoaldehyde, benzaldehydeor a-diketones in the presence of ammonia, yield 2, 4, 5-triphenylimidazole.



Scheme 2.6

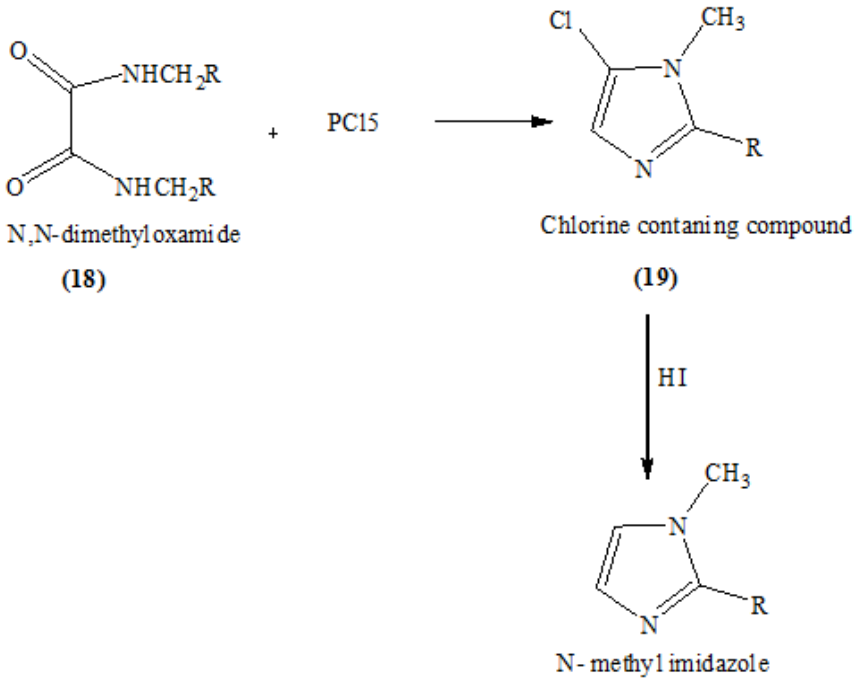
(c) Dehydrogenation of Imidazoline:- Knapp and coworkers have reported a milder reagent barium managanate for the conversion of imidazolines to imidazoles in presence of sulphur. Imidazolines obtained from alkyl nitriles and 1, 2 ethanediamine on reaction with $BaMnO_4NH$ yield 2-substituted imidazoles (Kawashita, 2009).



Scheme 2.7

(d) Wallach Synthesis:- Wallach reported 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 condition N, N-diethyloxamide is converted to a chlorine compound, which

on reduction gives 1- ethyl –2- methyl imidazole (Schulze, 2000; Sperry & Wright, 2005; Polshettiwar & Varma, 2008).



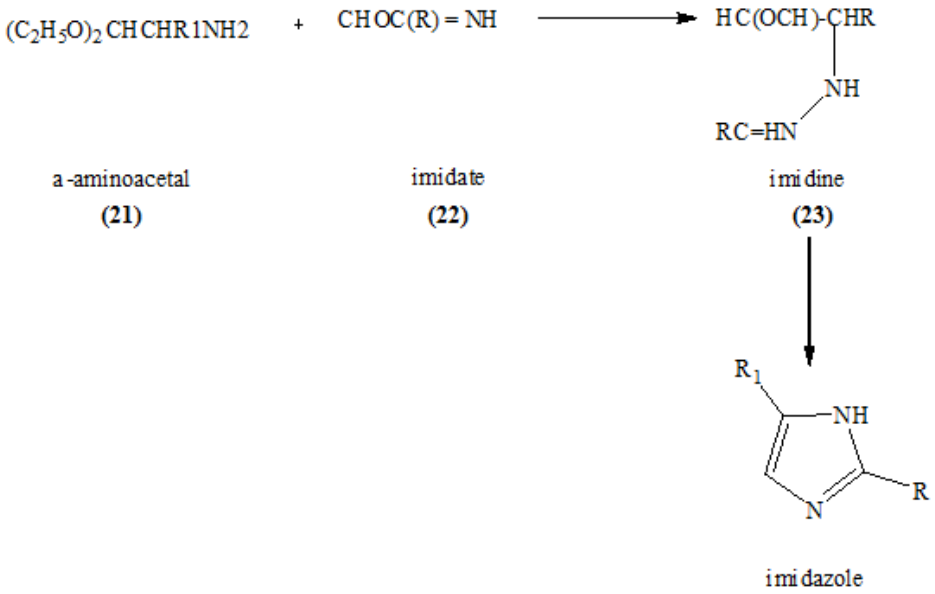
N,N-dimethyloxamide
(18)

Chlorine contaning compound
(19)

N-methyl imidazole

Scheme 2.8

(e) 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 example below applies to imidazole when R=R1=Hydrogen (Finar, 2006).



a-aminoacetal
(21)

imidate
(22)

imidine
(23)

imidazole

Scheme 2.9

3.0 Methodology of the Study

The study adopts an extensive review of literature such as conference papers, journal articles, internet sources, books to find out the effect of synthetic compounds on antimicrobial organism. This particular approach was

chosen in order to show the inhibition rate of the new compound on the antimicrobial organisms and make suggestions to future researchers who may decide to adopt an empirical method to investigate the results identified in this study.

4.0 Findings and Conclusion of the Study

From the literature review of existing studies relating to synthesis of bioactive compounds and how they are useful antimicrobial agent. This study which aimed to understand an organic compound called the imidazole. This research further found that Imidazole is a highly polar compound, and it is a heterocyclic compound that has wide range of biological activities such as, analgesic, anti-inflammatory, anticancer, antiviral, anthelmintic, anticonvulsant, antiulcer, antimicrobial, anti-allergic activity. Different methods were used for the synthesis of imidazole's and their chemical structure reactions offer enormous scope in the field of medicinal chemistry. This study suggests to future researchers who may decide to adopt an empirical method to investigate the results identified in this study.

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6.0 References of the Study

Abdel-Hafez, S. H. (2008). Selenium Containing Heterocycles: Synthesis, Anti-Inflammatory, Analgesic and Anti- Microbial Activities of Some New 4-Cyanopyridazine- 3(2H) Selenone Derivatives. *Eur. J. Med. Chem.*, 43, 1971-1977.

Adewole, E. A. (2021). Synthesis of 1-methyl-4-nitro-5-N, N-diethylsulphonamide. An Unpublished Research Project Submitted in Partial Fufilment of the Requirement for the Award of Bachelor's Degree in Chemistry. Department of Chemistry, Federal University of Technology Akure.

Amir, M., Javed, S. A. and Kumar, H. (2007). Pyrimidine as Anti-inflamatory Agent: A Review. *Indian Journal of Pharmaceutical Sciences*, 7(2); 34-46.

Bhatnagar, A., Sharma, P. and Kumar, N. (2011). *Stereochemistry and Chemistry of Natural Products. Inter. J. Pharm Tech Res.*, 3(1); 268.

Baroniya, S., Anwer, Z., Sharma, P.K., Dudhe, R. and Kumar, N. (2010). Pyrimidine as Anti-inflamatory Agent: A Review. *Der Pharmacia Sinica.*, 1(3); 172-182.

Bosserman, D., Colussi, D. R., McMasters, J. P., Vacca, H. G. and Selnick, A. (2004). Pyrimidine as Anti-inflamatory Agent: A Review. *Bioorg. Med. Chem. Lett*, 14, 2141–2145.

Brown, E. G. (1998). Ring Nitrogen and Key Biomolecules. Kluwer Academic Press.

Dandale, S. G., Sonar, A. S. and Solanki, P. R. (2012). Antimicrobial Study of 4 (Substituted Phenyl)-1H-Imidazol-2(5H)-One/Thione/Imine. *Int. J. Chem. Environ. Pharm. Res.*, 3, 47-51.

De Carvalho, G. S., Machado, P. A., De Paula, D. T. S., Coimbra, E. S. and Da Silva, A. D. (2010). Synthesis, Cytotoxicity and Antileishmanial Activity Of N,N'-Disubstituted Ethylenediamine and Imidazolidine Derivatives. *Scient. World J.*, 10, 1723-1730.

De Clercq, E., Cools, M., Balzarini, J., Snoeck, R. and Andrei, G. (1991). Antiviral Activities of 5-Ethynyl-1-1-D-Ribofuranosylimidazole- 4-Carboxamide and Related Compounds. *Antimicrob. Agents Chemother.*, 35, 679-684.

Finar, I. L. (2006). *Stereochemistry and Chemistry of Natural Products*, *Organic Chemistry*, Pearson Education, South Asia, 2, 622, 629.

Grimmett, M. (1997). Imidazole and Benzimidazole Synthesis. Academic Press.

Hadizadeh, F., Hosseinzadeh, H., Motamed-Shariaty, V. S., Seifi, M. and Kazemi, S. (2008). Synthesis and Antidepressant Activity of N-Substituted Imidazole-5- Carboxamides in Forced Swimming Test Model. *Iran. J. Pharm. Res.*, 7, 29-33.

Jain M.K., and Sharma,S.C. (2005). Modern Organic Chemistry, Vishal publication, Kolkata,809.

John Wiley and Sons (2006).The Chemistry of Heterocyclic Compounds, Imidazole and Its Derivatives.

Kashyap, S. J., Sharma, P. K., Garg, V. K., Dudhe, R. and Kumar, N. (2011). Review on Synthesis and Various Biological Potential of Thiazolopyrimidine Derivatives. *J. Adv. Sci. Res.*, 2, 18-24.

Katritzky, A. R. (1992). Heterocyclic Chemistry: An Academic Subject of Immense Industrial Importance. *Chem. Heterocycl. Compd.*, 28, 241-259.

Lednicer, D. and Mitscher, L. A. (1984). In Organic Chemistry of Drug Synthesis, Wiley Interscience New York, 1, 226. Rees. Comprehensive Heterocyclic Chemistry, 5, 469-498.

Liu, R. S. (2001). Synthesis of Oxygen Heterocycles Via Alkynyltungsten Compounds. *Pure Appl. Chem.*, 73, 265-269.

Mittal, A. (2009). Synthetic Nitroimidazoles: Biological Activities and Mutagenicity Relationships. *Sci. Pharm.*, 77, 497-520.

Nagalakshmi, G. (2008). Synthesis, Antimicrobial and Antiinflammatory Activity of 2,5-Disubstituted-1,3,4-Oxadiazoles. *Indian J. Pharm. Sci.*, 70, 49-55.

Nekrasov, D. D. (2001). Biological Activity of 5- and 6-Membered Azaheterocycles and their Synthesis from 5-Aryl-2, 3-Dihydrofuran-2,3-Diones. Chem. *Heterocycl. Compd.,* 37, 263-275.

Nawwar, G. A. M., Grant, N. M., Swellem, R. H. and Elseginy, S. A. M. (2013). Design, Synthesis, Docking and Evolution of Fused Imidazoles as Antiinflammatory and Antibacterial Agents. *Der. Pharma. Chemica.,* 5, 241-255.

Pandeya, S. N. (2004). A Text Book of Medicinal Chemistry, SG Publisher, Grantham, 1(3), 2-3.

Polshettiwar, V. and Varma, R. S. (2008). Greener and Expeditious Synthesis of Bioactive Heterocycles Using Microwave Irradiation. *Pure Appl. Chem.,* 80, 777-790.

Prasanthy, G., Ramana, K. V., Reddy, V. K., Nirmala, K. and Ramesh, K. N. (2011). Synthesis and Biological Evaluation of 1- Substituted Imidazole Derivatives. *Int. J. Pharma.,* 1, 92-99.

Shalini, K., Kumar, N. and Sharma, P. K. (2011). Synthesis of N-((2-Substituted Phenyl)-4, 5-Diphenyl-1H-Imidazol-1yl) (Phenyl) Methyl) Substituted Amine Derivatives, Spectral Characterization and their Pharmacological Evaluation. *Biointerface Res.,* 1, 184-190.

Sharma, G. K., Sharma, N. K. and Pathak, D. (2013). Microwave Assisted Synthesis of some Substituted Imidazole Derivatives as Potential Antibacterial and Anti Cancer Agents. *Indian J. Chem.,* 52B, 266-272.

Sperry, J. B. and Wright, D. L. (2005). Furans, Thiophenes and Related Heterocycles in Drug Discovery. *Curr. Opin. Drug Discov. Devel.,* 8, 723-740.

Shabalin, S., Dmitrii, A. and Jason, E. (2020). Camp Recent Advances in the Synthesis of Imidazoles. Royal Society of Chemistry.

Singh, H. and Kapoor, V. K. (2008). Medicinal and Pharmaceutical Chemistry, Vallabh Prakashan, Delhi, 2, 1-2.

Reddy, P. V., Kiran, Y. B., Reddy, C. S. and Reddy, C. D. (2004). Synthesis and Antimicrobial Activity of Novel Phosphorus Heterocycles with Exocyclic P-C Link. *Chem. Pharm. Bull.,* 52, 307-310.

Valverde, M. G. and Torroba, T. (2005). Sulfur-Nitrogen Heterocycles. *Molecules,* 10, 318-320.

Zala, S. P., Badmanaban, R., Sen, D. J. and Patel, C. N. (2012). Synthesis and Biological Evaluation of 2,4,5-Triphenyl-1H-Imidazole-1-Yl Derivatives. *J. Applied Pharm. Sci.,* 2, 202-208.