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AN OVERVIEW OF IMIDAZOLE AND ITS ANALOGUE

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Abstract-

Imidazole ring is an important five-membered aromatic heterocycle widely present in natural products and synthetic molecules. The unique structural feature of imidazole ring with desirable electronrich characteristic is beneficial for imidazole derivatives to readily bind with a variety of enzymes and receptors in biological systems through diverse weak interactions, thereby exhibiting broad bioactivities. The related research and developments of imidazole-based medicinal chemistry have become a rapidly developing and increasingly active topic. Particularly, numerous imidazole-based compounds as clinical drugs have been extensively used in the clinic to treat various types of diseases with high therapeutic potency, which have shown the enormous development value. This work systematically gives a comprehensive review in current developments of imidazole-based compounds in the whole range of medicinal chemistry as anticancer, antifungal, antibacterial, antitubercular, anti-inflammatory, antineuropathic, antihypertensive, antihistaminic, antiparasitic, antiobesity, antiviral, and other medicinal agents, together with their potential applications in diagnostics and pathology. It is hoped that this review will be helpful for new thoughts in the quest for rational designs of more active and less toxic imidazole-based medicinal drugs, as well as more effective diagnostic agents and pathologic probes. Imidazole and its derivatives encompass a vast range of medical activities, Imidazole is a five-member heterocyclic aromatic compound with two nitrogen atoms. Both Nitrogen atoms are sp2 hybridized. The natural products like histamine, histidine, and nucleic acid are the important constituent of imidazole ring2 . Imidazole susceptible to nucleophilic and electrophilic attack. Imidazole generally colorless or pale yellow solid and it has amine like order.

Key- Words- Imidazole, Derivatives, Biological Activities, Synthesis.

Introduction-

Widely used in natural products and pharmaceutical molecules, the imidazole ring is one of the most prominent five-membered nitrogen-containing heterocyclic scaffolds. In addition, imidazole heterocyclic compounds, which occupy an important position in medicinal chemistry, play a central role in the treatment of various diseases, and the development of new derivatives for pharmaceutical purposes is actively carried out worldwide. The imidazole scaffold has a special structural feature with electron-rich features, which is advantageous for the imidazole group to associate with various receptors and enzymes in biological systems through various weak interactions to exert various biological activities [1].

Many of the highly potent imidazole-containing compounds are now widely used as clinical agents to treat various types of diseases, including: and enzyme inhibition. Imidazole and its derivatives cover a wide range of medicinal properties. Imidazoles are five-membered heteroaromatic compounds containing two nitrogen atoms. Both nitrogen atoms are sp2 hybridized 1. Natural products such as histamine, histidine, and nucleic acids are important parts of the imidazole ring 2. Imidazoles are susceptible to nucleophilic and electrophilic attacks. Imidazoles are generally colorless or pale yellow solids with an amine-like ordering [2, 3].

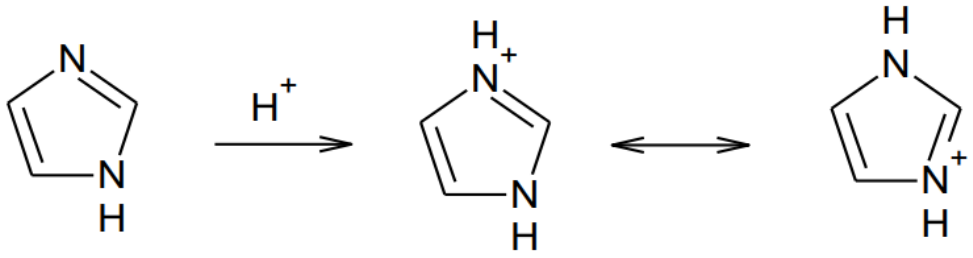
Soluble in water and other polar solvents. Imidazole has a melting point of 88.9°C and a boiling point of 267.8°C. The molecular formula of imidazole is C3H4N2. The highly beneficial properties of imidazole-containing drugs have prompted medicinal chemists to create a large number of new therapeutic molecules. Imidazole drugs have a wide range of applications in the pharmaceutical field. Imidazole derivatives are pharmacologically and physiologically active and are used in the treatment of various diseases. Imidazoles are important ingredients and are found in a wide variety of natural products and clinically active drug molecules. Synthetic imidazoles are found in many antifungal, antifungal, antiprotozoal, and antihypertensive agents. Its importance makes it a favorable target for synthesis and clinical practice [4,5,6].

There are various techniques that have been used to assemble and modify the imidazole ring with various functional groups. The basic site of the imidazole nucleus is N-3. Imidazoles are five-membered planar rings that are soluble in water and other polar solvents. Since the hydrogen atom can be located on either of the two nitrogen atoms, two equivalent tautomers exist. Imidazole is a highly polar compound and is completely soluble in water, as evidenced by the calculated dipole. Imidazole is amphoteric. That is, it functions as both an acid and a base. The compound is classified as aromatic due to the presence of a sextet of π electrons, consisting of a pair of electrons from the protonated nitrogen atom and a pair of electrons from each of the four remaining atoms in the ring [7, 8].

Chemical Properties-

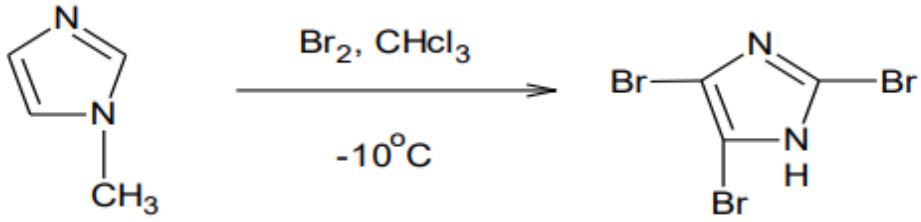
Reaction with acids [9-11]-

Imidazole is a monoacid base. It reacts with acid to form a crystalline form and also has weakly acidic properties.



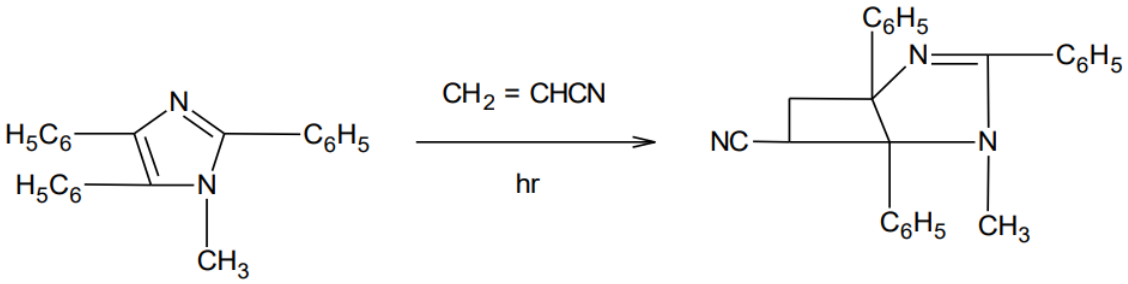
Halogenation [12,13]-

Halogenation of imidazole is depending on the substrate, 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



Cycloaddition Reactions [14-17]-

Imidazoles undergo additions through carbon-carbon double bonds. This type of reaction takes place under photochemical conditions. The reaction of imidazole and acrylonitrile is representative of the reactions shown below.



Method of synthesis-

RE-Diszewski Synthesis [18-20]-

Synthesis refers to the condensation of dicarbonyl **compounds** such as glyoxal, **ketoaldehydes,** or diketones with **aldehydes** in the presence of ammonia, **where benzaldehyde reacts** with two **ammonia** molecules to **form 2,4,5-triphenyl- Forms 1H-imidazole.**

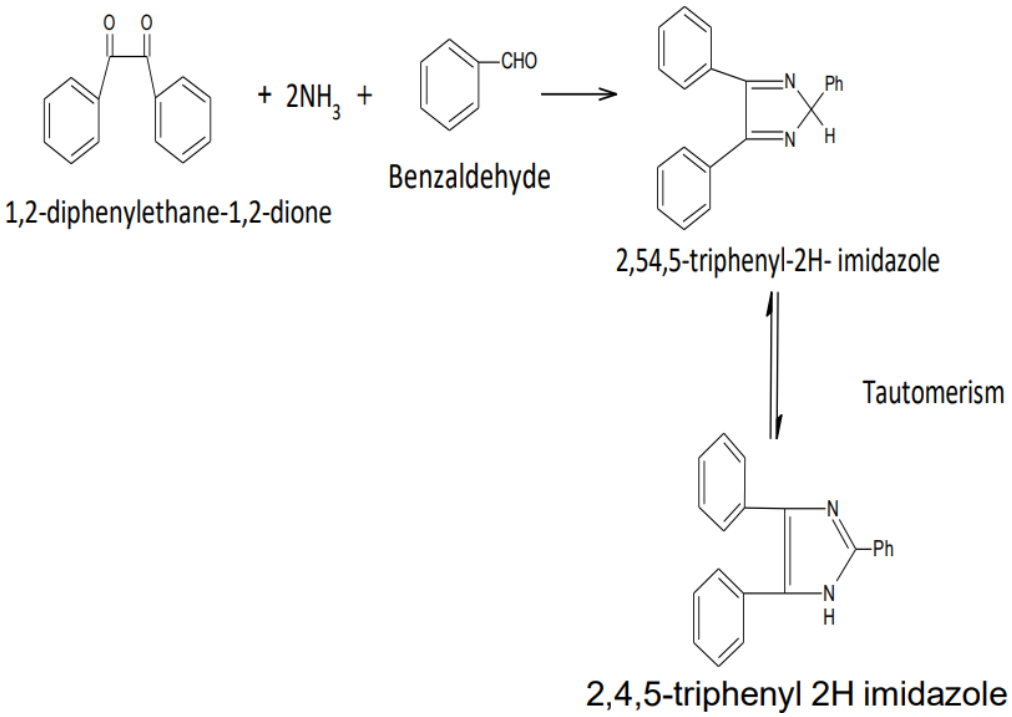


Figure Number- Synthesis of 2,4,5- triphenyl-1H-imidazole

Wallach Synthesis [21-23]-

When N, N-dimethyl oxamide is treated with phosphorus pentachloride, a chlorine-containing compound is obtained which on reduction with hydroiodic acid gives N-methyl imidazole.

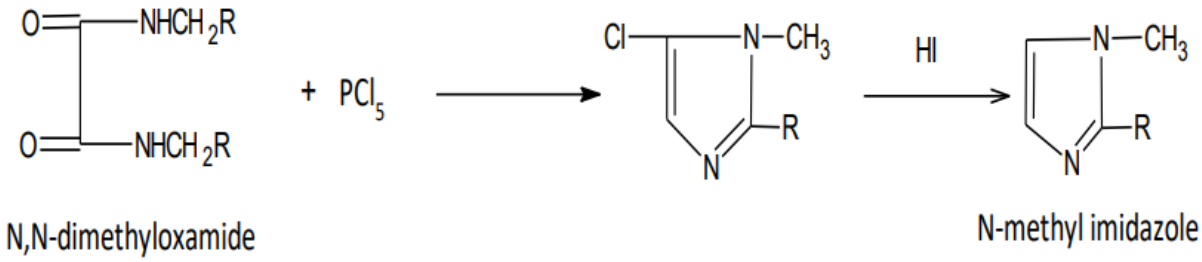


Figure Number- Synthesis of N-methyl imidazole

Markwald Synthesis [24] –

Preparation of 2-mercaptoimidazoles from aminoketones or aldehydes and potassium thiocyanates or alkyl isothiocyanates is a common method for imidazole synthesis. Sulfur is easily removed by oxidation.

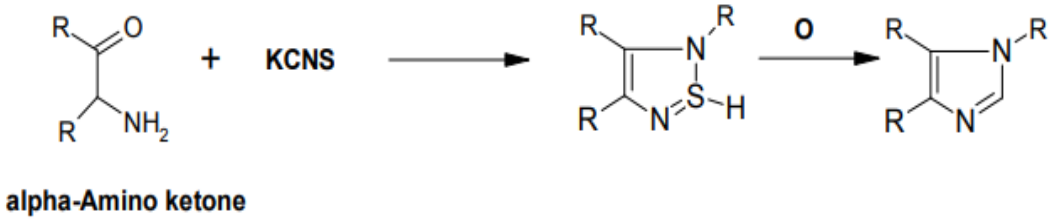


Figure Number- Synthesis of imidazoles by Markwald Synthesis

Electrophillic substitution [25-17]-

Imidazole makes it more reactive to electrophilic attack. It is more susceptible to electrophilic attack than pyrazole and thiazole, and more sensitive than furan and thiophene. The resonance structures of the intermediate ions below show that the attack occurs at her 4th and her 5th positions on the imidazole ring. We can see that the attack on C-2 contains a normal form that is very unfavorable with positive N in the 3rd place. Halogenation of imidazoles is highly complex and highly dependent on substrates, reagents, and reaction conditions.

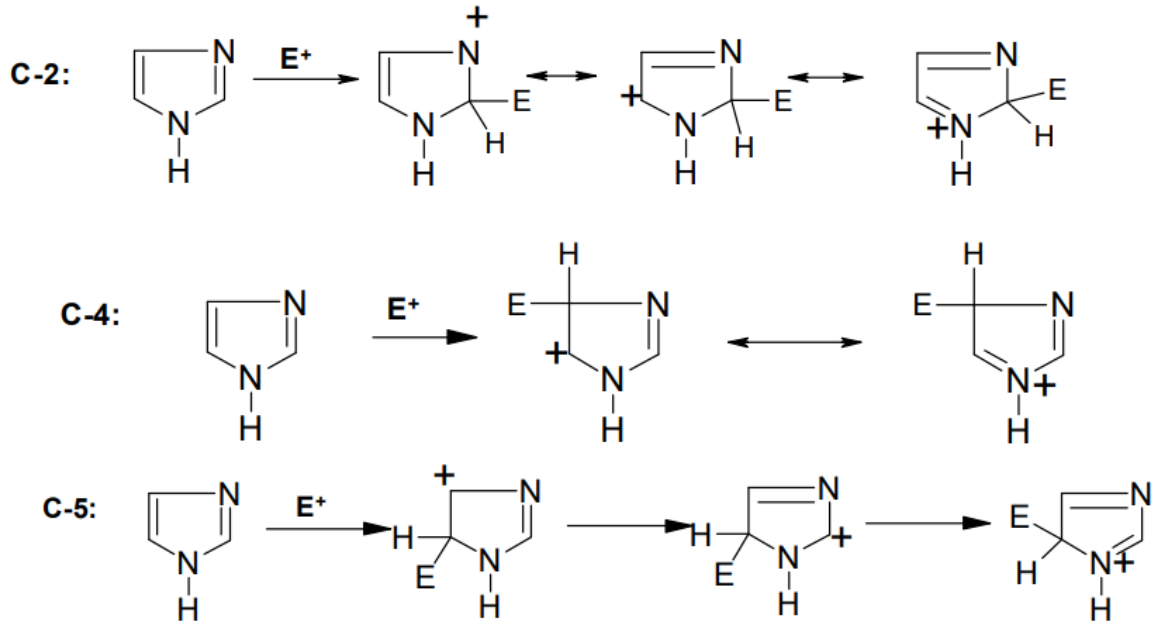


Figure Number- The flow of Electrophillic substitution

Pharmacological activities –

Imidazoles have a wide range of biological activities. Drugs containing imidazole rings act on different receptors. For example, dopamine receptors, histamine receptors, and adrenergic receptors. Based on various literature searches, imidazole derivatives show different pharma cological effects.

Anti-fungal and anti-bacterial activity-

We synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazole derivatives and tested their antibacterial and antifungal activities. This was comparable to ciprofloxacin. The search for new antifungal agents in recent years has mainly focused on the chemical field of imidazoles and triazoles. The class of drugs collectively referred to as azoles, which includes a series of 1-substituted imidazole and triazole compounds, arguably represents a modern approach to topical and systemic treatment of fungal diseases. As an antifungal agent, imidazole exhibits remarkable pharmacological and biochemical activity [28, 29].

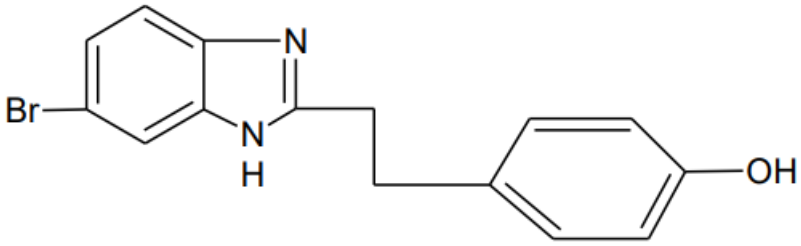


Figure Number- Structure of Ciprofloxacin

Anti-inflammatory and analgesic activities-

We synthesized a series of 2-methyl amino benzimidazole derivatives and screened the synthesized compounds for analgesic and anti-inflammatory activity. This connection (Connection: Exhibiting analgesic and anti-inflammatory activity, nimesulide is used as a standard drug. The search for new and better agents in anti-inflammatory therapy is a never-ending process. The search for anti-inflammatory agents to relieve the swelling, redness, pain and fever associated with rheumatism dates back to ancient times [30, 31].

Synthetic studies include work on various heterocyclic ring systems isolated or fused into other systems. Amino acids have been reported to have anti-inflammatory properties, and with this in mind, various heterocyclic derivatives bearing both carboxyl and amino groups have been prepared. Structure-activity relationship studies have shown that conversion of the carboxyl group to a heterocycle usually enhances edema suppression. Conversion to benzimidazole and 1,2,3,4- tetrahydro quinoline rings resulted in compounds with better activity than those formed by conversion of the carboxyl group to the imidazole ring [32, 33].

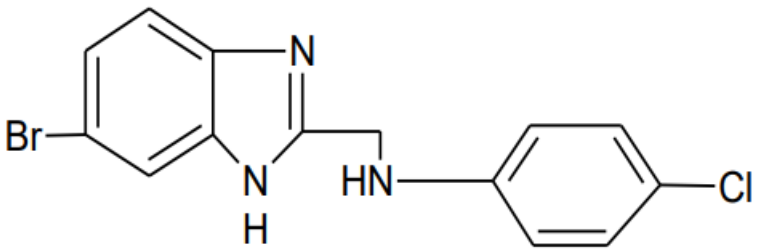


Figure Number- Structures of 1, 2, 3, 4-tetrahydro quinoline ring

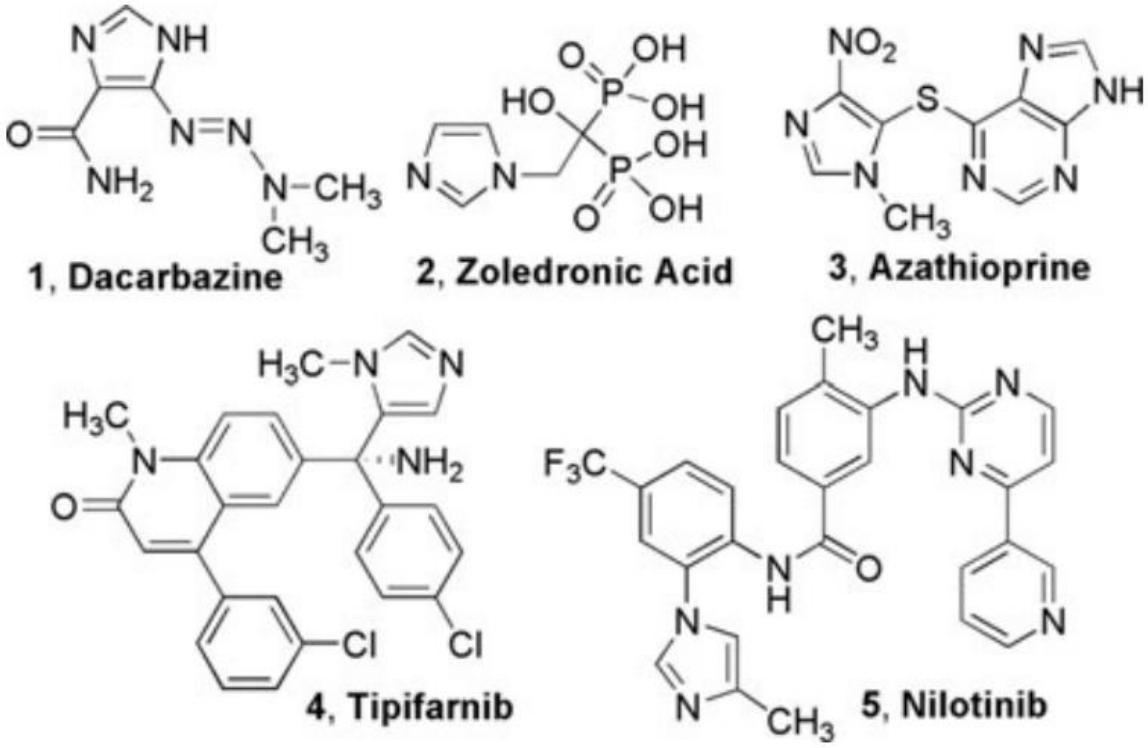
Anti-cancer activity-

In recent years, only imidazole residues have been studied as important structures for anticancer and anticancer agents. The key here is different permutations at different positions within the unit. The cyclin-dependent kinase (CDK) family is two groups of serine-threonine protein kinases involved in eukaryotic cell cycle regulation and transcriptional regulation. Due to their important role in cell cycle regulation and their expression/activity patterns observed in most human cancers, considerable effort has been devoted to developing small molecule CDK cell cycle inhibitors as potential therapeutics [34].

The incorporation of basic groups into the CDK imidazole pyrimidinamide inhibitor series provided the best opportunity to achieve CDK inhibitor properties. The imidazole sulfone AZD5438 (I) was further investigated as an orally bioavailable anticancer agent. Replacement of sulfones by piperazines has led to a new series of potent CDK inhibitors (II) with improved physical properties that are also suitable for oral administration [35].

Many secondary amides, such as the 5-fluoropyrimidine-ortho-fluoroamide substitution, show the highest enzymatic potency against both CDK1 and CDK2. This very potent CDK1/2 inhibition results in very potent inhibition of cell proliferation in cancer cell lines. Chiral non-racemic pyrrolidines (both S and R forms) also showed good potency against CDK1 and CDK2, again demonstrating potent antiproliferative activity [36].

In contrast to piperazinamide, the corresponding homopiperazine (III) showed significantly improved properties, with both enzymatic and cellular potency greatly increased. The increased basicity of homopiperazine (pKa 8.1 measured in comp. III) also greatly enhanced solubility and showed potent anti-proliferative effects in vitro against many cancer cell lines [37].



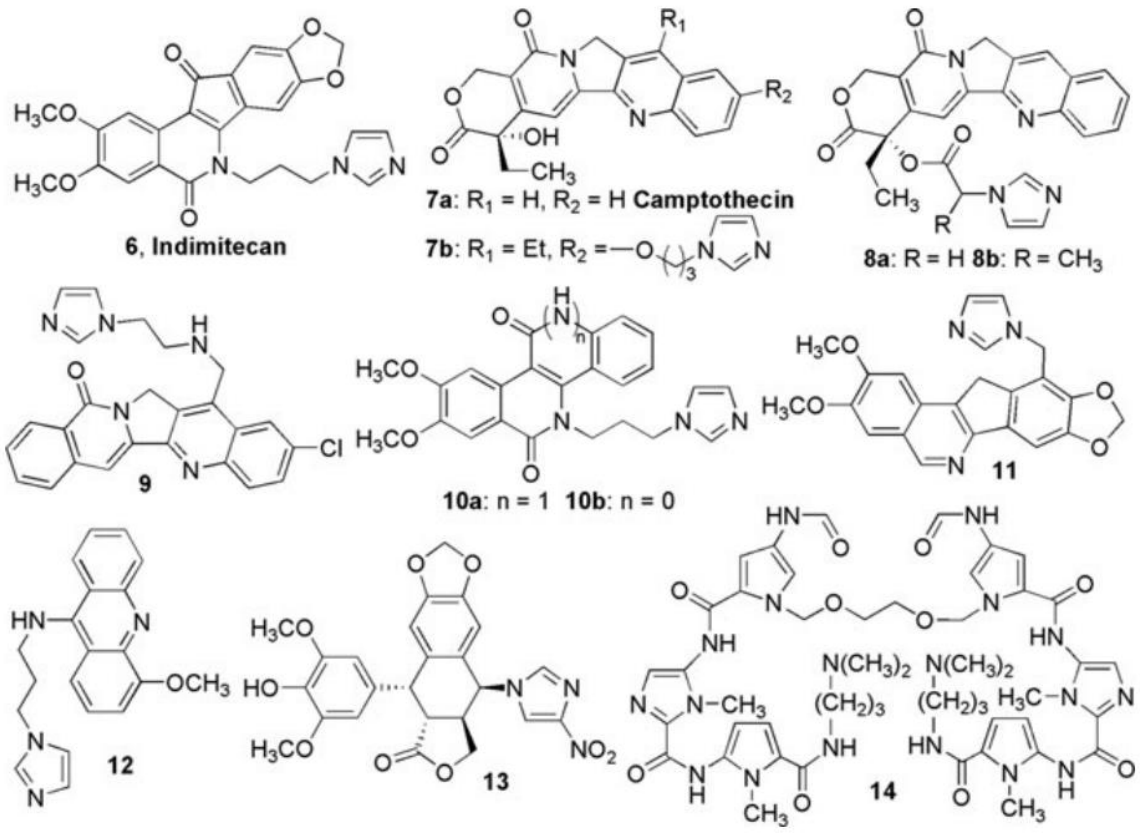
Imidazoles as Topoisomerase Inhibitors-

Topoisomerases (TOPs) have been identified as valuable and particularly interesting targets for chemotherapeutic agents because of their critical roles in cell progression, apoptosis, transcription, and other cell regulation. TOP targeting agents not only stabilize cleavable complexes formed between enzymes and DNA, but can also regulate DNA replication and transcription in malignant cells [38].

Many TOP inhibitors such as topotecan and irinotecan have been developed and used clinically. However, it cannot be used continuously because of its low solubility, short duration of action, and high toxicity associated with drug resistance. Much effort has been expended to search for safer and more effective TOP inhibitors. An imidazole

ring with two typical nitrogen atoms has the ability to form hydrogen bonds, which is advantageous for improving the water solubility of target compounds. For this reason, the imidazole ring is considered a valuable structural fragment and has been widely introduced into other bioactive scaffolds [39].

Structure of imidazole as a TOP inhibitor. Imidazole-containing intimitecans are clinical cancer candidates with improved aqueous solubility for the treatment of refractory solid tumors. Indomitecan, which does not have a labile lactone moiety, has improved stability compared to traditional top I inhibitors. Furthermore, it can induce sustained DNA breaks and Top I breaks at unique genomic locations, bind to different target sites, and cause cell cycle arrest in both S and G(2)-M phases, is a powerful potency to overcome [40].



Conclusion-

The imidazole moiety is the most studied and many of its analogs are effective against various pathological conditions briefly described in this article. Imidazole is an entity with interesting physical and chemical properties. This article focuses on the analysis of these characteristics. The N-1 or C-4 position of the imidazole moiety revealed an intriguing cytotoxic profile with specific activity against leukemia cell lines, and the indole-imidazole compound combinations formed were able to target cancer cells in vitro. Showed significant antiproliferative activity against the strain. Potent substitutions also created moieties with structural similarities to various natural compounds already being studied for their anti-cancer properties. The above studies on various imidazole derivatives, an important class of heterocyclic compounds, showed promising results in most pharmacological activities, antibacterial, anticancer, antituberculous, antifungal, analgesic, and anti HIV activities. We also show

some interesting results, including So far, modifications to the imidazole core have shown promising biological activity.

Conflicts of interest-

There are no conflicts of interest or disclosures regarding the manuscript.

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