“Exploring the Versatile Applications of Imidazole Derivatives: A Comprehensive Review on Synthesis, Properties and Biological Activities”

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Abstract:
Imidazole derivatives have gained significant attention in the fields of chemistry and biology due to their diverse range of applications. This comprehensive review delves into the synthesis, properties, and biological activities of imidazole derivatives, highlighting their versatility and potential. Various synthetic routes for the preparation of imidazole derivatives are discussed, along with an exploration of their physical and chemical properties. The review also delves into the wide array of biological activities exhibited by imidazole derivatives, including antimicrobial, anticancer, anti-inflammatory, and antioxidant properties. The potential for imidazole derivatives to serve as valuable therapeutic agents in drug development is also explored. Overall, this review provides a thorough examination of the multifaceted nature of imidazole derivatives and their promising applications in various scientific disciplines.

Keywords: Imidazole, Biological Activity, Physical Property, Chemical Property, Synthesis.

Introduction –
Throughout the previous century, nitrogen-based heterocycles, notably the imidazole ring, discovered in the 1840s, captivated numerous researchers due to their potent anti-cancer, anti-microbial, and anti-inflammatory properties. The structural characteristics of the imidazole ring augment its capacity to establish numerous interactions between drugs and ligands, facilitated by hydrogen bonds, van der Waals forces, and hydrophobic interactions. The imidazole core is found in various naturally occurring compounds and FDA-approved drugs, making it significant in medicinal applications. Fused imidazole derivatives, such as Methotrexate, Metronidazole, and Omeprazole, serve as anti-cancer, anti-microbial, and anti-inflammatory agents. However, despite their therapeutic potential, these drugs often entail severe side effects, leading to treatment challenges.

Imidazole, also known as 1,3-diazo, consists of a planar five-member ring system containing three carbon and two nitrogen atoms positioned at 1 and 3 positions. Within the imidazole family, it is the simplest member with the molecular formula C3H4N2. One of its nitrogen atoms carries a hydrogen atom, resembling a pyrrole-type nitrogen. Due to this configuration, imidazole is soluble in water and other polar solvents. It exhibits two equivalent tautomeric forms, distinguished by the location of the hydrogen atom, which can reside on either nitrogen atom. Imidazole exhibits high polarity, evident from its calculated dipole moment of 3.61D, and complete solubility in water. Its classification as aromatic stems from the presence of a sextet of π-electrons, derived from a pair of electrons from the protonated nitrogen atom and one from each of the remaining four ring atoms. Imidazole demonstrates amphoteric properties, capable of acting as both an acid and a base. With a pKa of 14.5, it is less acidic than carboxylic acids, phenols, and imides, yet slightly more acidic than alcohols. The acidic proton is found on N-1 of imidazole. When acting as a base, the conjugate acid’s pKa (referred to as pKBBH+ to distinguish it) is around 7, indicating imidazole is about sixty times more basic than pyridine. The basic site is located at N-3.

Structure –

Imidazole is a component of numerous crucial biological molecules. One of the most prevalent is the amino acid histidine, which contains an imidazole side chain. Histidine is found in various proteins and enzymes, contributing significantly to the structure and binding functions of hemoglobin. Additionally, histidine can undergo decarboxylation to form histamine, another commonly occurring biological compound. Imidazole also finds application in purifying proteins labeled with His tags through immobilized
metal affinity chromatography (IMAC). Imidazole has become essential in many medications. Synthetic imidazoles are found in numerous fungicides and drugs used to combat fungal, protozoal, and high blood pressure conditions. It’s also a component of theophylline, found in tea and coffee, which stimulates the central nervous system. Besides its pharmaceutical uses, imidazole is also widely employed in industries. For instance, it’s extensively used as a corrosion inhibitor for certain metals like copper. Preventing copper corrosion is crucial, especially in water-based systems, where corrosion reduces copper’s conductivity. Imidazole derivatives are found in many important industrial and technological compounds. For example, thermostable polybenzimidazole (PBI) contains imidazole fused with a benzene ring and linked to benzene, serving as a fire retardant. Imidazole is also present in various compounds used in photography and electronics. However, this review primarily focuses on highlighting the pharmaceutical significance of the imidazole moiety.

Physical properties:

- Imidazoles are a colourless liquid with a high boiling point of 256°C, higher than all other five-membered heterocyclic compounds, due to intermolecular hydrogen bonding, which causes a linear association of molecules.
- They are aromatic compounds with a resonance value of 14.2 kcal/mol, nearly half that of pyrazole.
- Electrophilic substitution is common in imidazole, while nucleophilic substitution occurs when there’s an electron-withdrawing group present in its nucleus.
- Imidazoles have a melting point of 90°C and are weak bases and tautomeric substances, as positions 4 and 5 are equivalent.

Its spectroscopic parameters include:

- $\lambda_{max}$ of 207 nm
- IR peaks at 1550, 1492, and 1451 cm$^{-1}$
- $\tau$ values of 2.30 and 2.86
- Mass spectroscopy is extensively studied for heterocyclic compounds with a single heteroatom, but not as thoroughly for those with two or more heteroatoms.

Chemistry of imidazole

Imidazole, a heterocyclic aromatic organic compound, possesses several chemical properties:

- Basicity: Imidazole behaves as a weak base due to the lone pair of electrons on the nitrogen atom in the five-membered ring, allowing it to accept a proton.
- Nucleophilicity: The nitrogen atom in imidazole can act as a nucleophile in various reactions, such as nucleophilic substitution and addition reactions.
- Coordination: Imidazole can coordinate with metal ions due to its nitrogen atom, forming metal complexes.
- Electrophilicity: Imidazole can also act as an electrophile in certain reactions, particularly in electrophilic aromatic substitution reactions.
- Tautomerism: Imidazole exhibits tautomeric equilibrium between its 1H-imidazole and 3H-imidazole forms, where the position of the hydrogen atom on the nitrogen atom changes.
- Oxidation: Imidazole can undergo oxidation reactions under certain conditions, resulting in the formation of imidazole derivatives.

General methods for synthesis of imidazole:

1. Radiszewski Synthesis

Radiszewski reported the condensation of a dicarbonyl compound, benzil and α-keto aldehyde, benzaldehyde or α-diketones in the presence of ammonia, yield 2, 4, 5-triphenyl-imidazole. Here is the general reaction for Radiszewski Synthesis:
2. Dehydrogenation of Imidazoline

A milder reagent barium magenate to convert imidazolines to imidazoles in the presence of Sulphur. Imidazolines obtained from 1, 2 ethanediamine and alkyl nitriles on reaction with BaMnO4 yield 2-substituted imidazoles.³

3. 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.³

4. From α- Halo Ketone

This method is based on an interaction between an alpha halo ketones and imidine. This method has been applied successfully for the synthesis of 2, 4- or 2, 5- biphenyl imidazole. Similarly, acyloin reacts with amidine or alpha halo ketones to yield imidazole.⁵,⁶

5. Markwald Synthesis

The preparation of 2- mercaptoimidazoles from α-amino ketones or aldehyde and potassium thiocyanate are used for the synthesis of 2-thiol substituted imidazole. The sulfur can readily be removed by a variety of oxidative method to give the desired imidazole.⁵,⁸

6. From Hydroxyamino ketone, aldehyde and ammonia

Hydroxyamino ketone reacts with aldehyde and ammonia to form substituted imidazole.⁵,¹¹
7. From Aminonitrile and orthoformate

Mixture of aminonitrile and orthoformate in presence of primary amine condensed under suitable reaction condition to give substituted imidazole as shown below.\textsuperscript{5,14}

8. From formaldehyde and tartaric acid dinitrate

Imidazole can best be prepared itself by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and then heating the dicarboxylic acid in quinoline in presence of cooper\textsuperscript{5,18}

9. Cyclization of N-haloamidines with sodium ethoxide

The cyclization of N-haloamidines with sodium ethoxide forms benzimidazoles through a nitrene intermediate.

**Biological properties of imidazole:**

Imidazole’s are well-known heterocyclic compounds which 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:

1. Antifungal activity
2. Anticancer activity
3. Antibacterial activity
4. Anti-tubercular activity
5. Anti-HIV activity
6. Anti-inflammatory and analgesic activity
7. Antiviral activity
8. Anthelmintic activity
9. Antidepressant activity.\textsuperscript{6}

1. **Antifungal activity:**

Imidazole compounds are well-known for their potent antifungal activity. They work by interfering with the synthesis of ergosterol, an essential component of fungal cell membranes. By disrupting the integrity of the fungal cell membrane, imidazole derivatives effectively inhibit fungal growth and replication. Some common imidazole antifungal agents include clotrimazole, miconazole, ketoconazole, and econazole. These drugs are used to treat a variety of fungal infections, such as athlete's foot, ringworm, candidiasis (yeast infections), and fungal nail infections. Imidazole antifungal agents are available in various formulations, including
creams, ointments, powders, and oral medications. They are generally well-tolerated and have a good safety profile when used as directed. Overall, imidazole compounds are valuable tools in the treatment of fungal infections due to their strong antifungal properties and broad spectrum of activity against various fungal species.

2. Anticancer activity
Imidazole compounds have also shown promising anti-cancer activity in research studies. Imidazoles can act as potential anticancer agents by targeting specific pathways involved in cancer cell growth, proliferation, and survival. One mechanism through which imidazole compounds exhibit anti-cancer activity is by inhibiting angiogenesis, which is the formation of new blood vessels that supply nutrients to tumors. By disrupting angiogenesis, imidazole derivatives can inhibit tumor growth and metastasis. Additionally, imidazoles have been found to induce apoptosis (programmed cell death) in cancer cells, leading to their destruction. They can also interfere with cell cycle progression, DNA repair mechanisms, and signaling pathways that are dysregulated in cancer cells. Some imidazole derivatives have been studied for their potential as chemotherapeutic agents in various types of cancer, including breast cancer, lung cancer, prostate cancer, and leukemia. These compounds have shown promising results in preclinical studies and may offer new treatment options for cancer patients in the future.
Overall, imidazole compounds hold great potential as anti-cancer agents due to their diverse mechanisms of action and ability to target specific pathways involved in cancer progression. Further research is needed to fully understand the therapeutic potential of imidazoles in cancer treatment.

3. Antibacterial activity
Imidazole compounds have also been studied for their antibacterial activity. Imidazoles exhibit antimicrobial properties by interfering with essential processes in bacterial cells, leading to their inhibition or destruction. One of the mechanisms through which imidazoles exert antibacterial activity is by disrupting the cell membrane integrity of bacteria. Imidazole derivatives can interact with and disrupt the structure and function of bacterial cell membranes, leading to leakage of cellular contents and ultimately bacterial cell death. Imidazoles can also inhibit enzymes involved in essential metabolic pathways in bacteria, such as nucleic acid synthesis, protein synthesis, and cell wall formation. By targeting these key enzymes, imidazole compounds can disrupt bacterial growth and replication. Some imidazole derivatives have shown antibacterial activity against a wide range of bacterial species, including both Gram-positive and Gram-negative bacteria. They have been investigated as potential antibacterial agents for the treatment of various infections, such as skin infections, respiratory tract infections, and urinary tract infections.
Overall, imidazole compounds have demonstrated promising antibacterial activity in research studies and may offer new treatment options for bacterial infections in the future. Further research is needed to optimize the efficacy and safety of imidazoles as antibacterial agents and to explore their potential use in clinical settings. Anti-tubercular activity:
4. Anti-HIV activity:

Imidazole compounds have also been investigated for their potential anti-HIV activity. HIV (Human Immunodeficiency Virus) is the virus that causes AIDS (acquired immunodeficiency syndrome), a chronic and potentially life-threatening condition. Research studies have explored the antiviral properties of imidazole derivatives against HIV. Imidazoles have been shown to inhibit various stages of the HIV replication cycle, including viral entry, reverse transcription, integration, and viral maturation. One mechanism through which imidazoles exert their anti-HIV activity is by targeting viral enzymes essential for viral replication, such as reverse transcriptase and protease. Imidazole compounds can interfere with the function of these enzymes, thereby inhibiting viral replication and reducing the production of new infectious viral particles. Imidazole have also been found to modulate host immune responses and inhibit HIV-induced inflammation and immune activation. By targeting host factors involved in the immune response to HIV infection, imidazole derivatives may help reduce the progression of HIV disease and improve immune function in infected individuals.

Overall, imidazole compounds show promise as potential anti-HIV agents, and further research is ongoing to explore their efficacy, safety, and potential use in the treatment of HIV/AIDS. Developing new antiretroviral therapies and drug combinations involving imidazoles may help enhance the current treatment options for HIV infection and improve outcomes for individuals living with HIV/AIDS.

5. Anti-inflammatory and analgesic activity:

Imidazole compounds have also been studied for their potential anti-inflammatory and analgesic activities. Inflammation is a complex biological response of the immune system to harmful stimuli, such as pathogens, injuries, or irritants. Chronic inflammation can contribute to the development of various diseases, including arthritis, cardiovascular diseases, and neurodegenerative disorders. Research has shown that imidazole derivatives exhibit anti-inflammatory effects by modulating inflammatory pathways and reducing the production of pro-inflammatory mediators, such as cytokines and prostaglandins. Imidazole can inhibit enzymes involved in the inflammatory process, such as cyclooxygenase (COX) and lipoxygenase (LOX), which are responsible for the production of inflammatory prostaglandins and leukotrienes. Imidazole compounds have also been found to possess analgesic properties by interfering with pain signaling pathways in the central nervous system and peripheral tissues. Imidazole can act on neurotransmitter systems involved in pain perception, such as opioid receptors, serotonin receptors, and ion channels, to modulate pain sensitivity and transmission. Furthermore, imidazole derivatives have been investigated for their antioxidant activity, which can help reduce oxidative stress and inflammation in various disease conditions. By scavenging reactive oxygen species and inhibiting oxidative damage, imidazole may protect cells and tissues from inflammatory injury and contribute to overall health and well-being.

Overall, imidazole compounds show promise as potential anti-inflammatory and analgesic agents, and further research is needed to explore their efficacy, safety, and potential clinical applications in the management of inflammatory disorders and pain-related conditions. Developing novel imidazole-based drugs with optimized pharmacological properties may help address unmet medical needs and improve the quality of life for individuals suffering from inflammatory diseases and chronic pain.

6. Antiviral activity:

Imidazole compounds have also been investigated for their potential antiviral activity. Viral infections are a significant global health concern, and the development of effective antiviral agents is crucial for managing and controlling viral diseases. Imidazole derivatives have shown promising antiviral properties against a variety of viruses, including herpes simplex virus (HSV), hepatitis B virus (HBV), influenza virus, and others. Imidazoles can exert their antiviral effects through various mechanisms, including:

- Inhibition of viral replication: Imidazole compounds may interfere with the replication of viral genetic material or inhibit viral enzymes essential for viral replication, such as viral polymerases or proteases.
- Modulation of host immune response: Imidazoles can modulate the host immune response to enhance antiviral defenses or reduce excessive inflammation caused by viral infections.
- Disruption of viral entry: Imidazole derivatives may block viral entry into host cells by targeting viral attachment proteins or fusion processes.
- Inhibition of viral protein synthesis: Imidazoles can interfere with the synthesis of viral proteins necessary for viral replication and assembly.

Research studies have demonstrated the antiviral activity of imidazole derivatives against a range of viruses, both in vitro and in animal models. Some imidazole-based compounds have shown potent antiviral effects with low cytotoxicity, making them promising candidates for further development as antiviral drugs.
Overall, imidazole compounds hold potential as antiviral agents due to their diverse mechanisms of action and broad-spectrum activity against different types of viruses. Further research is needed to optimize the antiviral properties of imidazole derivatives, assess their safety profiles, and evaluate their efficacy in clinical settings for the treatment of viral infections. The development of novel imidazole-based antiviral drugs may offer new therapeutic options for combating viral diseases and improving public health outcomes.

7. Anthelmintic activity:

Imidazole compounds have been investigated for their potential anthelmintic activity, meaning their ability to treat parasitic worm infections. Research suggests that imidazoles can interfere with the nervous system or metabolism of parasitic worms, leading to their paralysis or death. Drugs like albendazole and mebendazole, which contain imidazole moieties, are commonly used as anthelmintics to treat various worm infections in humans and animals. However, the effectiveness of imidazole-based anthelmintics can vary depending on the specific parasite species and the drug's formulation.

8. Antidepressant activity:

While imidazole compounds are not typically used as antidepressants themselves, they can serve as building blocks or pharmacophores in the development of antidepressant drugs. For example, some tricyclic antidepressants (TCAs) contain imidazole rings in their chemical structure, such as imipramine and trimipramine. These TCAs work by blocking the reuptake of neurotransmitters like serotonin and norepinephrine, leading to increased levels of these neurotransmitters in the brain, which can alleviate symptoms of depression.

Additionally, imidazole-containing compounds may be used in the development of novel antidepressants as researchers explore new chemical scaffolds and mechanisms of action for treating depression. However, it's essential to note that the clinical use of imidazole-based antidepressants is not as common as other classes of antidepressant medications.

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Reference:


