

Medicinal importance of benzimidazole and its metal complexes : A review

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Abstract : Benzimidazole is a vital component in medicine due to its distinctive bicyclic aromatic structure, which is a characteristic of heterocyclic compounds. The predominant naturally occurring benzimidazole molecule, N-ribosyl-dimethyl benzimidazole, acts as a ligand for cobalt in vitamin B12. Scientists have been studying heterocyclic compounds like Indole, Benzimidazole, Benzothiazole, and Benzoxazole, along with their associated complexes due to their therapeutic characteristics. Transition metal-based complexes such as Silver (I), Ruthenium (II), Zinc (II), Copper (II), Cobalt (II), Nickel (II), and Gold(I) ions have attracted significant interest as promising anti-tumour therapeutic agents. These substances have been shown to be effective against a wide range of ailments, such as ulcers, cancer, hypertension, fungal infections, inflammation, TB, parasites, obesity, malaria, glycation, viruses, neuropathy, pain, oxidation, and allergies. The purpose of this review is to aid researchers in creating and combining novel and exceptionally potent variations of benzimidazole and their corresponding metal compounds. These compounds show significant potential for use in several medicinal fields.

(Keywords: Benzimidazole, Heterocyclic, Metal Complexes, Antibacterial, Antifungal)

Introduction

Benzimidazoles are a group of chemical compounds that has the characteristics of being heterocyclic, aromatic, and bioactive. Benzimidazole is a bicyclic compound consisting of a benzene ring fused with an imidazole ring¹. The chemical exhibits the same structural

arrangement as naturally occurring nucleotides. They exhibit a wide range of biological characteristics² and are utilized as therapeutic treatments. Benzimidazoles are synthesized via the condensation reaction between o-phenylenediamine and formic acids. Scientists have synthesized and recorded various forms of benzimidazole derivatives for application in the field of medicine, as benzimidazoles and their metal complexes are associated with clinical medicine and the advancement of novel pharmaceuticals³. Benzimidazole derivatives are structural variations of naturally occurring nucleotides, which allows them to easily interact with biopolymers in living systems⁴. Therefore, benzimidazoles, together with their derivatives and metal complexes, are extremely fascinating because of their substantial potential for therapeutic applications. The benzimidazole backbone is a useful structural motif for conveying chemical functionality in molecules that are relevant to physiological processes. Several of its compounds demonstrate potent biological effects, such as anticancer⁵, anti-HIV⁶, anti-Parkinson⁷, and antibacterial⁸ characteristics. In recent times, there has been extensive investigation into chelating ligands that contain benzimidazole groups. These ligands function as coordinators in transition metal compounds, mostly because of their coordination chemistry in azoles. The objective of this study is to duplicate biological systems⁹. The metal complexes display antibacterial activity and indicate superior effectiveness in comparison to the unbound ligand. Metal chelation significantly

influences the antimicrobial/bioactive action of organic ligands¹⁰⁻¹¹. The objective of this study is to examine the antibacterial properties of benzimidazole-based Schiff bases and their metal complexes containing Cu (II) and Zn (II) ions.

2.0 Benzimidazole Synthesis Utilizing Metal Oxide Nano catalyst:

Metal oxide-based nanoparticles (MONPs) can act as catalysts. Nanoparticle metals possess distinctive physicochemical characteristics because of their confined high-density surface area and size¹². This article displays the structures of benzimidazole derivatives, which are important in medicine and physiology. The process utilizes conventional and distinctive techniques to produce pharmacologically active benzimidazole derivatives, utilizing metal oxide nanoparticles as catalysts and adopting diverse approaches for nucleus building. In 2015, Nikoofar et al. created ZnO nanorods and used them as a catalyst to generate 2,4,5-triaryl-1H-imidazoles from various aldehydes and benzils in the presence of ammonium acetate in H₂O. This reaction was carried out by reflux at a constant temperature. The chemistry of benzimidazole is characterized by its properties and reactions^{13,14}.

Benzimidazole is a chemical molecule that consists of a fused aromatic imidazole ring system, with a benzene ring connected to the 4 and 5 positions of an imidazole ring. It can also be called azindole, 1-H-benzimidazole, O-benzimidazolebenzoxoglyoxaline, and 1, 3-diazaindene. It displays characteristics of both acidity and alkalinity. The NH group present in benzimidazole has high acidity and moderate basicity. Benzimidazole exhibits the capacity to undergo salt production. Benzimidazole molecules that do not have substituted NH groups exhibit fast prototropic tautomerism, leading to an equilibrium mixture of compounds with asymmetric substitutions.

4.0 Synthesis of benzimidazole complexes

4.1 Complexes with Zinc

The zinc-benzimidazole complexes were synthesized using the methodology outlined in a prior publication¹³. Benzimidazole and its derivatives (0.25 mmol) and zinc chloride dihydrates (0.25 mmol) were diluted in 96% v/v ethanol until the solutions became homogenous. The mixture was combined with a reflux condenser and a magnetic stirrer for a duration of 12 hours. The whole volume of the reaction mixture amounted to 30 mL. The reaction was conducted at continuous ambient temperature (25 °C) and carefully regulated pH (6-7) until a precipitate of the coordination compounds developed. The precipitate was subsequently washed with a solution consisting of 40% ethanol (EtOH) and a mixture of ethanol and water in equal volumes. Finally, the reaction products were dried at room temperature in the presence of air. The coordination compounds were identified using elemental C/H/N analysis, determination of the Zn (II) content, FTIR spectra, TG-MS method, and dissolution of the crystalline structures of the single crystals.

4.2 Cobalt and Nickel-based benzimidazole complexes synthesis

The objective is to create cobalt- and nickel-based benzimidazole complexes by synthesis. The Co (III) and Ni (II) complexes, which are based on heterocyclic imines, were produced by combining a hot methanolic solution of metal chloride (CoCl₂ · 6H₂O and NiCl₂ · 6H₂O) with a methanolic solution of the heterocyclic imine base ligand (HBMB). The mixtures obtained were subjected to reflux in a water bath for a duration of 3 to 4 hours, resulting in the formation of a brown precipitate for the cobalt complex and a red precipitate for the nickel complex.

5.0 The medicinal importance of benzimidazole and its complexes

The presence of a substituent in the first position of benzimidazole lowers its melting point. Additionally, the molecule's solubility in non-polar solvents is increased as a result of the

incorporation of H₂, N₂, and Cl₂ substituents at various locations. Typically, it dissolves readily in a polar solution containing imide.

Incorporating a polar group into the molecule enhances its solubility in liquids with polarity. Benzimidazole exhibits solubility in dilute acids due to its inherent weak basic character. It evaporates at temperatures over 300°C.⁷ Certain transition metal ions, including copper (II), nickel (II), and platinum (II), exhibit notable biological activity¹⁵. For instance, Cu (II) complexes imitate cis-platinum and play a crucial role in the catalytic activity of some enzyme activities¹⁶. Cobalt has had a significant impact on DNA synthesis, albeit indirectly. Cobalt-dependent proteins rely on it as a crucial biological component¹⁶. Co (III) ion-containing complexes have become highly favored in the fields of coordination chemistry and biomedicine due to their therapeutic capabilities¹⁷. The presence of the nickel metal ion is crucial in the study of urease as a nickel enzyme. This has been extensively examined in the field of bioinorganic chemistry since 1975¹⁸. The binding affinity between nickel complexes and DNA constructions mostly relies on the structural characteristics of the ligand involved, particularly its intercalative nature¹⁹. Recently, there have been reports of square planar Pt (II) complexes that exhibit high antitumor activity and low renal toxicity²⁰⁻²¹. These complexes induce cancer cell death through a distinct mechanism compared to other metal complexes and have shown effectiveness against cisplatin-resistant cancer cell lines²¹⁻²². The current research focused on the synthesis of platinum complexes using tridentate benzimidazole nitrogen and oxygen donor/ halogen ligands as leaving groups.

5.1 Anti-Ulcer Agent:

An anti-ulcer agent is a substance that is used to treat sores that develop on the lining of the stomach, esophagus, or small intestine. The *Helicobacter pylori* bacteria is the causal agent of ulcers. An ulcer develops when the gastric acid

causes harm to the lining of the digestive tract. An anti-ulcer medication functions by blocking or suppressing the generation of stomach acid, safeguarding the gastrointestinal mucosa from acid-induced damage, or neutralizing acid. An example of this is Pantoprazole.²³

5.2 Anti-psychotic agents: Benzimidazole analogs used as medications for treating psychosis.

During psychosis, the individual experiences a state in which their thoughts become irrational, peculiar, and lacking coherence. The patient has impaired perception of both external reality and their own condition. The medications Droperidol, Pimozide, and Benperidol all contain the benzimidazole nucleus.²⁴

5.3 Benzimidazole Analogues as Anthelmintic Agents:

These medications have the ability to either kill the helminths or remove them from the body. Thiendazole, mebendazole, and albendazole are examples of medications that have benzimidazole as their central structure.²⁵

5.4 Benzimidazole Analogues as Anti-protozoal Agents:

Benzimidazole analogues have anti-protozoan properties. These medications are utilized for the treatment of *E. histolytica*, an infectious condition caused by amoebae. They induce cytotoxicity by causing DNA damage and disrupting the helical structure of the DNA strand. Metronidazole and Benzimidazole are examples of anti-protozoan medicines that include the benzimidazole nucleus.²⁶

5.5 Benzimidazole Analogues as Antifungal Agents:

Benzimidazole analogs are utilized as antifungal agents for the treatment of both superficial and deep fungal infections. Mycoses refer to fungal infections, which can be categorized into two types: superficial infections

affecting the skin, nails, and scalp, and systemic infections that affect deeper tissues and organs. Two examples of diseases that can result in fungal infections include blastomycosis and histoplasmosis. Additional diseases that can lead to fungal infections include candidiasis and coccidioidomycosis. Clotrimazole, miconazole, and ketoconazole are the most prevalent antifungal medicines that include imidazole.²⁷

5.6 Benzimidazole Analogues for Antibacterial and Antifungal Activity:

The majority of benzimidazole compounds demonstrate antibacterial action. An instance of this is the derivatives of pyrimidobenzimidazole, which belong to a novel category of DNA-gyrase inhibitors that demonstrate efficacy as antibacterial agents. Benzimidazole compounds, including benomyl, carbendazim, fuberidazole, and thia-bendazole, have been created as fungicides with high efficacy against numerous opportunistic fungi.²⁸

5.7 Benzimidazole Analogues as CNS Depressants:

Certain benzimidazole compounds exhibit diverse effects on the central nervous system, ranging in kind and potency. These effects include stimulating the mind, reducing psychotic symptoms, alleviating depression, inducing relaxation (anxiety reduction), preventing seizures, and promoting sleep. An example of this is pimozone.²⁹

5.8 Benzimidazole Analogues with properties of pain relief, reduction of inflammation, and fever reduction.

Recently, much attention has been focused on the investigation of the analgesic medication etonitazene, which is a benzimidazole derivative that specifically interacts with opiate receptors of the μ -subtype. Etonitazene is an extremely powerful pain-relieving medication, with a strength that is roughly 1000-1500 times greater than morphine. It possesses a powerful

efficacy comparable to morphine and exhibits a pronounced inclination to induce respiratory depression, rendering it unsuitable for human use.³⁰

5.9 Benzimidazole Analogues for Hypoglycemic Activity:

The compound diabenol, which is a condensed benzimidazole derivative with the chemical name 9-(2-diethyl aminoethyl)-2, 3-dihydroimi-dazo benzimidazole dihydrochloride, has been found to have hypoglycemic and antiaggregant effects.³¹

5.10 Benzimidazoles Analogues as Antiallergic Agents

Benzimidazoles are a class of chemical compounds. Analogues serving as antiallergic agents include astemizole and mizolastine, which are both efficient long-acting blockers of histamine receptors.³²⁻³³

5.11 Benzimidazole Analogues as Cardio-vascular Agents

2-benzylbenzimidazole (dibazole) can reduce the contraction of smooth muscles in blood vessels and internal organs. This chemical is commonly utilized as a medication to relieve muscle spasms and lower blood pressure. The majority of benzimidazole derivatives possess antihypertensive action due to their ability to inhibit calcium channels.³⁴⁻³⁵

Conclusion

The benzimidazole ring is a crucial pharmacophore in the field of drug research. Certain substituted benzimidazole derivative medicines exhibit higher levels of activity. Benzimidazole derivatives are a highly valuable structure that serves as a foundation for various therapeutic applications. These include the development of medications for treating tumors, fungal infections, parasites, pain relief, viral infections, allergies, cardiovascular diseases, neurological disorders, and endocrine disorders.

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