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by FK Husnun Amalia

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Benzimidazole and Its Derivatives: Exploring Their Crucial Role in Medicine and Agriculture: A Short Review

Sarah Basil Fawzi[1], Khalid Younis Zainulabdeen[1], Emad Abdul-Hussain Yousif[1]
Husnun Amalia Enus Yunus[2], Nany Hairunisa Muhaini Umar[3]

[1]Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq
[2]Departement of Ophthalmology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[3]Department of Occupational Medicine, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

Corresponding Author: emad_yousif@nahrainuniv.edu.iq

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Keywords: Benzimidazole, Derivatives, Medicine, Agriculture.

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Abstract:

Benzimidazole and its structural analogues have garnered significant attention across diverse disciplines, including the fields of medicine and agriculture, owing to their remarkable versatility and immense potential. This review article aims to elucidate the multifaceted importance of benzimidazole-based compounds and their derivatives within these spheres. The paper starts by establishing the pivotal role of benzimidazoles in human health and pharmaceutical applications. A comprehensive examination of their therapeutic utility in treating and managing various diseases is undertaken, underscoring the compounds' potent biological activities and clinical relevance. Furthermore, the review focused on the applications of benzimidazole-based compounds as powerful fungicides and pesticides within the agricultural sector. The discussion covers the mechanistic underpinnings of their efficacy, formulation challenges, and regulatory considerations surrounding their deployment in the agrochemical industry. This paper aims to demonstrate the extensive applications of these heterocyclic moieties and their derivatives in medicine and farming. The in-depth analysis presented herein is intended to facilitate a deeper understanding of the versatility and importance of benzimidazole compounds, thus enriching future research and development endeavors within these critical domains.

Keywords: Benzimidazole, Derivatives, Medicine, Agriculture.

استكشاف الدور المهم للبنزيميدازول ومشتقاته: في الطب والزراعة: مراجعة قصيرة

سارة باسل فوزي[1]، خالد يونس زين العابدين[1]، عماد عبد الحسين يوسف[1]، حسنون أماليا اونس يونس[2]، ناني خير النسا مهيني عمر[3]

[1]قسم الكيمياء، كلية العلوم، جامعة النهرين، بغداد، العراق
[2]قسم طب العيون، كلية الطب، جامعة تريساكتي، جاكرتا، إندونيسيا
[3]قسم طب العمل، كلية الطب، جامعة تريساكتي، جاكرتا، إندونيسيا

sarah.mchs24@ced.nahrainuniv.iq, khalid.waleed21@nahrainuniv.edu.iq, emad_yousif@nahrainuniv.edu.iq, husnun_a@trisakti.ac.id, nanyhairunisa@trisakti.ac.id

الخلاصة:

البنزيميدازول ومشتقاتها هي مركبات متعددة الاستخدامات تظهر تطورا كبيرا في العديد من المجالات، بما في ذلك الطب والزراعة. يقدم هذا البحث للقارئ أهمية البنزيميدازولات في مجالات مختلفة. بينما يتم سرد التطبيقات الصحية والصيدلانية لفحص وعلاج الأمراض للتأكيد على أهمية البنزيميدازولات، حيث يتم مناقشة تطبيقاتها في الزراعة كمبيدات فعالة للفطريات والحشرات أيضًا. من خلال تقديم آلية العمل التركيب وتنظيم المركبات المعتمدة على البنزيميدازول. ويهدف التحليل المتعمق المقدم هنا إلى تسهيل فهم أعمق لتنوع وأهمية مركبات البنزيميدازول، وبالتالي إثراء مساعي البحث والتطوير المستقبلية في هذه المجالات الحاسمة.

الكلمات المفتاحية: البنزيميدازول، المشتقات، الطب، الزراعة.

1. Introduction:

1.1 Definition and Structure of Benzimidazole: Benzimidazole is a class of heterocyclic aromatic compounds characterized by the fundamental structural feature of a six-membered benzene ring fused to a five-membered imidazole ring [1]. This unique structure gives benzimidazole compounds various pharmacological properties, making them valuable in biological and clinical applications [1]. Benzimidazoles have shown efficacy as anticancer, antimicrobial, antiparasitic, analgesic, antiviral, and antihistamine agents [1]. They are widely used in the treatment of cardiovascular diseases, neurological disorders, endocrinological conditions, and ophthalmic problems [1-5].

The synthesis of benzimidazoles typically involves the fusion of benzene with an imidazole moiety [1]. The numbering system for benzimidazole according to IUPAC standards is depicted in **Figure 1** [6]. Benzimidazoles with a hydrogen atom attached to nitrogen in the 1-position are easy to tautomerize. This basic "6 + 5" heterocyclic structure is shared by other important molecules found in nature like adenine and guanine, which are essential building blocks for biopolymers [2].

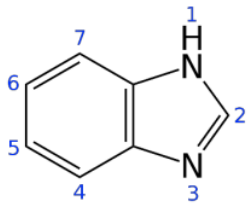

Fig. 1 benzimidazoles structure [6]

The exceptional properties of benzimidazole compounds, such as improved stability, bioavailability, and notable biological activity, have led to their growing attention [7]. Omeprazole, bendamustine, albendazole, and mebendazole are among the benzimidazole drugs of note. Researchers have conducted extensive research on these compounds in recent years, focusing on their synthesis methods, mechanisms of action, structural aspects, and pharmacological applications [8].

The importance of benzimidazole as a pharmacophore in medicinal chemistry and drug discovery has been well established. The benzimidazole moiety is a substructure present in numerous significant compounds that are renowned for their diverse biological activities [7-9]. There are different ways to make different benzimidazole derivatives by adding functional groups to one or more positions on the benzimidazole ring [10]. The administration of an additional quantity of benzimidazole and its derivatives has exhibited a diverse array of biological and pharmacological effects, including antitumor, antiviral, and antiparasitic activities [11]. They play a crucial role in the development of effective pharmaceuticals and insecticides [12]. These derivatives have demonstrated considerable potential in addressing drug-resistant diseases and enhancing crop productivity, rendering them a subject of substantial interest and investigation in both the medical and agricultural domains [13]. This study aims to present an overview of the diverse synthetic methods employed in the synthesis of benzimidazole derivatives. Furthermore, it will emphasize the significance of these methods for tackling drug resistance and enhancing crop productivity. Additionally, the potential applications of benzimidazole and its inorganic derivatives in biomedicine and agriculture will be discussed.

1.2 Benzimidazole and derivatives: Benzimidazole and its derivatives, shown in **Figure 2** are classified differently based on their applications [1-5], [7-9]. For example, in pharmacology, the benzimidazole ring system serves as the core for drugs such as albendazole and anesthetics like etomidate [9]. The registration of benzimidazole itself as a new drug laid down specifications for an incredible class of chemical entities [14]. Humankind was fortunate to develop the first drug with an extended spectrum of antibacterial activity, Nizatidine, in 1975

[15]. And from then to now, some benzimidazole and its derivative drugs have developed, and many of them are on the market [13-15]. Also, the benzimidazole ring is present in many fungicides and insecticides, most of which are used in horticulture or viticulture [16]. This class of molecules exhibits antifungal and/or anti-insect properties [16]. On the other hand, heterocyclic molecules have a long history of biological activity, including their use as pesticides in the agricultural industry [17]. These materials are essential in the quest for the development of new products that are biologically active, environmentally acceptable, sustainable, and provide an economic return [18]. These are some of the most important organic building blocks for technological materials, like liquid crystals [18-20]. The Grubbs catalyst is often used for olefin metathesis, and ligands are used in the Heck reaction [21]. These heterocyclic molecules and their derivatives have continued to attract great medicinal chemistry interest since the discovery of the first benzimidazole derivative used as a drug [22]. This chapter provides a crucial and elaborate account to expound on the importance of benzimidazole and its inorganic derivatives in the field of medicinal chemistry and also in the agricultural industry concerning the structural activity relationships, pharmacological studies, and various molecular modeling studies so far reported.

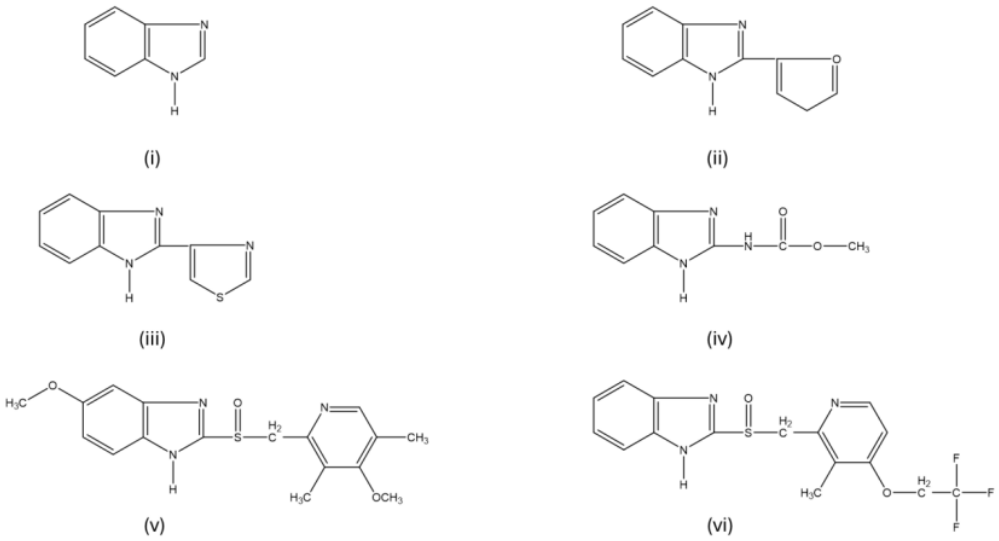

Fig.2 Benzimidazole derivatives such as
(i) Benzimidazole, (ii) Fuberidazole, (iii) Carbendazim, (iv) Thiabendazole, (v) Omeprazole, and (vi) Lansoprazole

1.3 Importance of Benzimidazole in Medicine and Agriculture: Benzimidazole plays a crucial role in both medicine and agriculture due to its diverse pharmacological properties and applications. Benzimidazole and its derivatives are crucial therapeutic agents in the field of

medicine [23]. They play a vital role as medications that treat ulcers, eliminate parasitic worms, combat microbial and viral infections, fight against cancer, reduce inflammation, and provide pain relief [23-25]. These chemicals are used to treat a variety of ailments, such as hypertension, malaria, cancer, microbial infections, and inflammatory disorders, demonstrating a diverse spectrum of biological actions [26]. In addition, benzimidazole derivatives have been utilized in agriculture, specifically as anthelmintic drugs to combat parasitic illnesses in animals [27]. The ongoing investigation of benzimidazoles and their analogs for their chemical and pharmacological properties highlights their importance in both the medical and agricultural sectors [28]. The antiparasitic activity of benzimidazoles is widely utilized as an anthelmintic drug for the treatment of parasitic infections in both humans and animals [29]. The antiparasitic drugs albendazole and mebendazole are standard treatment options for several parasitic diseases [30]. Since they possess antifungal properties, benzimidazole derivatives are extremely useful in the treatment of fungal infections [3].

Additional research has shown that several benzimidazole compounds possess anti-cancer properties, suggesting their potential as effective choices for cancer treatment [31]. Furthermore, benzimidazoles have demonstrated antiviral activity against specific viruses, which enhances their potential for use in the development of antiviral drugs [32].

Agriculture is the process of cultivating plants and rearing animals for food, fiber, medicinal plants, and other products used to sustain human life [33]. Furthermore, benzimidazole compounds, with their fungicidal properties, are widely used as agricultural fungicides to control fungal infections in crops [34]. They aid in safeguarding crops against several fungal diseases, hence enhancing agricultural productivity and quality [34].

Benzimidazoles exhibit potent nematocidal activity, targeting nematodes and pernicious parasites that inflict harm on plant roots and diminish agricultural yield [35]. Some work studies suggested that benzimidazoles aid in the regulation of nematode populations, hence promoting the overall health of crops [36].

Researchers also discovered the intricate activity of fuberidazole (ii) shown in **Figure 2**, and its wide-ranging uses in both medical and industrial agricultural fields [37]. Fuberidazole demonstrates great potential as an antifungal drug in medicine, namely in fighting a range of fungal diseases [37]. Endophytic fungi contain this substance, which has a role in protecting plants, promoting their growth, and competing with other microorganisms [37]. Its extensive distribution makes it suitable for use in medical applications [38]. Industrial agriculture uses fuberidazole and other fungal species as biofertilizers and biocontrol agents [39]. They can promote plant development and inhibit the growth of soil-borne diseases [39]. Ectomycorrhizae are essential in forestry as they enhance the growth of commercially significant crops and

decrease the need for fertilizers, thereby contributing to environmental sustainability [40]. All of these uses show how flexible and useful fuberidazole and related fungi can be in promoting environmentally friendly practices and improving plant health in a number of areas [40].

Therefore, benzimidazole compounds are essential in medicine and agriculture due to their diverse medicinal and preventive advantages.

1.4 Benzimidazole Compounds and Proton Pump Inhibitors (PPI) in the Medical and Agricultural Applications: Proton pump inhibitors (PPIs) are a class of drugs with a common structural foundation of a pyridine and benzimidazole ring as shown in **Figure 3**, differing only in the substituents attached to these rings [41]. Analgesics widely prescribe PPIs like Pantoprazole for conditions like gastritis and gastric irritation [42]. Studies have shown that PPI use is associated with increased risks of certain cancers, like gastric, pancreatic, colorectal, and liver cancer, while potentially decreasing the risk of breast cancer [43]. PPIs may interact with the cancer microbiome and affect the efficacy of antineoplastic agents, although only a few interactions are clinically significant [44]. Deprescribing PPIs when they are not clinically justified is advised to avoid unnecessary drug interactions and adverse effects [45].

The pharmacological relevance of benzimidazole compounds, especially proton pump inhibitors, is well-known [46]. Gastric acid-related illnesses like GERD and peptic ulcer disease are treated.

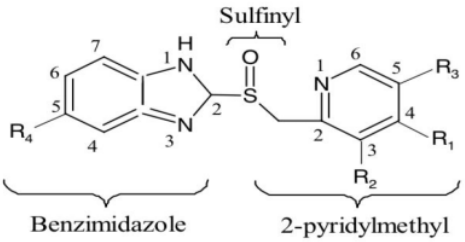

Figure 3. Structure of proton pump inhibitors (PPIs) that contain benzimidazole, sulfinyl, and 2-pyridylmethyl groups [41]

with PPIs [47]. PPIs such as omeprazole, lansoprazole, and pantoprazole are widely used benzimidazole derivatives [43]. These substances permanently block the action of the proton pump (H+/K+ ATPase) in the stomach lining cells, which stops gastric acid from entering the inside of the stomach [44]. Proton pump inhibitors (PPIs) alleviate symptoms of acid reflux and promote the healing of ulcers by reducing the production of stomach acid [48]. These proton pump inhibitors (PPIs) contain a benzimidazole molecule that forms covalent bonds with the proton pump enzyme. This stops the production of acid [45]. The correlation between benzimidazole compounds and PPIs underscores their clinical significance in treating acid-related gastrointestinal disorders [42].

The extensive spectrum of pharmacological activity exhibited by benzimidazole and its derivatives has also resulted in its use in the agriculture industry [43]. These chemicals have been used in the creation of proton pump inhibitors (PPIs) [44-45], which have shown associations with many types of cancer [46]. In addition, benzimidazole derivatives have demonstrated antibacterial capabilities, making them highly valuable for managing microbial infections in agricultural environments [47]. Research has been conducted on the manufacturing of benzimidazole PPIs using advanced methods such as catalytic reactions and catalysts utilizing graphene oxide [48]. These methods offer efficient and eco-friendly processes for industrial applications [48]. Benzimidazole compounds possess a diverse range of characteristics, which renders them highly favorable for use in agricultural applications [49]. They can be utilized to create innovative protein-protein interactions (P-PIs) to enhance crop protection and disease control [50].

2. Synthesis of Proton Pump Inhibitors

2.1 Omeprazole: Omeprazole (v), depicted in **Figure 2**, is scientifically known as 6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl]. The compound -1H-benzimidazole exhibits a unique molecular structure [51]. Omeprazole, a widely used proton pump inhibitor, can be synthesized using various methods outlined in the research papers. One method involves the asymmetric oxidation of omeprazole thioether under specific conditions to generate esomeprazole, a more potent form of the drug [51]. Additionally, the synthesis of omeprazole involves the formation of coordination compounds with metal ions like copper, zinc, cadmium, and mercury, resulting in compounds with tetrahedral structures [52]. The structure and dynamics of omeprazole, particularly its chiral nature and molecular interactions, play a crucial role in its activity and stability, as revealed by NMR experiments [53]. Furthermore, novel synthesis processes have been developed to address impurities in omeprazole, enhancing its purity and efficacy for pharmaceutical use [54]. These diverse approaches contribute to the comprehensive understanding and efficient synthesis of omeprazole for proton pump inhibition.

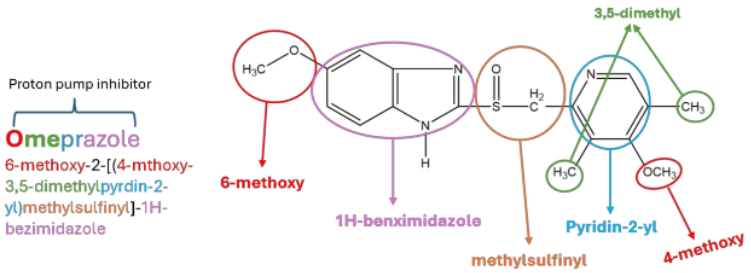

Fig. 4 Omeprazole functional groups structure

The substituted benzimidazole ring of omeprazole, shown in **Figure 4**, fights gastric acid [55]. Two strategically located nitrogens in this ring structure operate as a proton sponge, blocking H+/K+ ATPase and lowering stomach acid output [54]. The effectiveness of omeprazole relies on stomach acid activation, wherein the benzimidazole ring assumes a prominent role [56].

2.2 Synthesis and Structure of Omeprazole: A reaction was carried out with 2-chloro-3,5-dimethyl-4-methoxy pyridine (121 g) to form the sulphide intermediate 3 [57]. Then, 2-(Lithium methyl sulphinyl)-5-methoxy-1H benzimidazole (220 g) was treated with m-CPBA, an oxidizing agent, which resulted in the conversion to omeprazole 4 [58]. After undergoing alkaline hydrolysis, the acetamide-sulfide compound was altered and produced the sulfinyl carboxylate or salts, which were then oxidized to yield the amide

sulfinyl compound [59]. Following decarboxylation, the target compounds were formed [60]. The purification process simply involved washing out the remaining unreacted salt, inorganic byproducts, and other minor byproducts, allowing for the easy purification of either omeprazole or lansoprazole [61-63]. Unlike the sulfides and sulfoxides of previously published techniques, the amide compounds were crystalline solids [64-65] as shown in **Figure 5**.

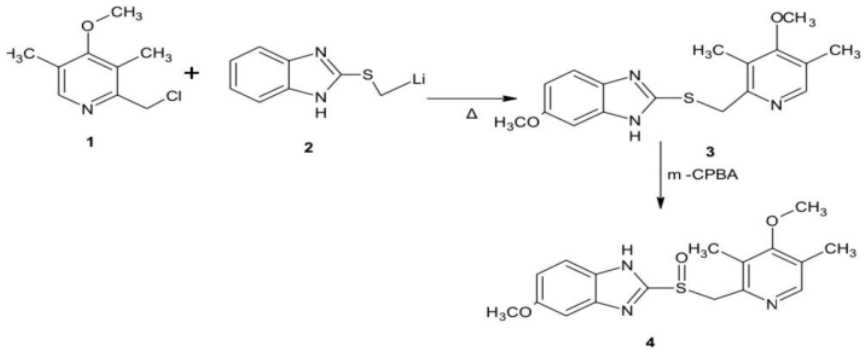

Fig. 5 The chemical reaction for preparing Omeprazole [64].

3. Conclusions:

In conclusion, benzimidazole and its derivatives are versatile molecules with great potential in medicine and agriculture. This study highlights the significance of benzimidazoles as powerful fungicides and insecticides in human health, pharmacology, disease treatment, and agriculture. This study has shown the importance of benzimidazole-based chemicals in medicinal and agricultural activities by investigating their modes of action, formulation obstacles, and regulatory issues. Further research into benzimidazole applications may lead to breakthroughs in these critical domains.

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