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REVIEW ARTICLE

A review on benzimidazoles: Synthesis, properties, and therapeutic applications in medicinal chemistry

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ABSTRACT

Heterocyclic compounds, characterized by rings containing non-carbon atoms like nitrogen, oxygen, or sulfur, are fundamental in diverse fields. This review provides an overview of heterocyclic chemistry, with a focused examination of benzimidazoles. It covers their structure, chemical properties, synthetic methods (including classical and modern techniques emphasizing efficiency and sustainability), and broad therapeutic applications across various disease areas, highlighting their significance in drug development and materials science. From (2018-2024)

Keywords: benzimidazole; heterocyclic compounds; biological activity; antiviral agents; microwave-assisted synthesis; green chemistry

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1. Introduction

Heterocyclic compounds are organic molecules characterized by the presence of one or more atoms other than carbon within their ring structures. These non-carbon atoms, referred to as heteroatoms, are most commonly oxygen, nitrogen, and sulfur. While The structures of heterocyclic compounds are predominantly cyclic (ring-shaped) or acyclic (non-ring-shaped)[1-3], examples of cyclic heterocycle include furan, pyridine, thiophene, and pyrrole as seen in **Figure 1**. Heterocyclic compounds, often referred to as heterocycles, constitute a vital class of organic compounds exhibiting unique physical and chemical properties distinct from their carbocyclic counterparts. These molecules are characterized by the presence of a cyclic ring structure containing at least one heteroatom (an atom other than carbon)[4]. The classification of heterocycles based on ring size is a fundamental and widely used approach because ring size has a significant impact on the properties and reactivity of heterocycles.

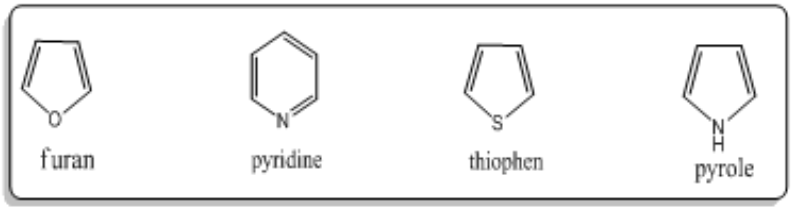


Figure 1. Heterocyclic compounds.

Heterocyclic compounds feature cyclic structures where atoms other than carbon are part of the ring. These rings are most commonly five- or six-membered, Simple heterocyclic derivatives include pyridine, pyrrole, furan, and thiophene[5,6], Pyridine and pyrrole are

classified as nitrogen heterocyclic compounds because their ring structures incorporate both nitrogen and carbon atoms. Pyridine is a ring molecule containing five carbon atoms and one nitrogen atom. Five-membered rings are also common in organic chemistry, with four carbon atoms and one heteroatom (nitrogen, oxygen, or sulfur) such as pyrrole (contains four carbon atoms and one nitrogen atom), Furan (contains four carbon atoms and one oxygen atom), and thiophene contains four carbon atoms and one sulfur atom[7-10]. Pyridine and pyrrole, originally discovered in the 1850s from the heated remains of bones and now synthetically produced, are fascinating molecules found in many biological compounds (From bone char to versatile building blocks) While pyridine and pyrrole themselves have some uses, their true value lies in their ability to be transformed into a wide range of other important products, especially dyes and medications[11,12].

Heterocyclic ring sizes can vary significantly; they encompass three- and four-membered rings (like aziridine and azetidine) **Figure 2**, five- and six-membered rings (such as pyrrole and pyridine), and larger rings with seven or more members (like thiepines) **Figure 3**.

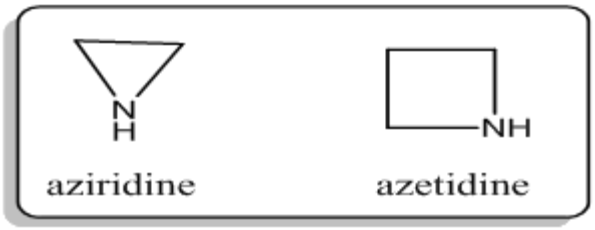


Figure 2. Three and four membered ring.

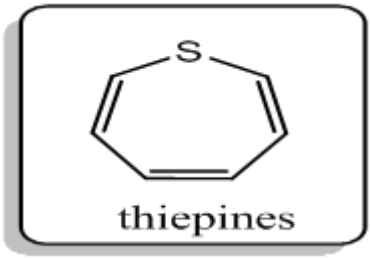


Figure 3. Seven membered ring.

Heterocyclic compounds, display a wide range of chemical properties and the number of heteroatoms and their types significantly influence their characteristics. For example, imidazole, thiazole, and morpholine, as shown in **Figure 4** featuring various combinations of heteroatoms. The stability of a heterocyclic ring is intricately linked to its aromaticity and size. Aromatic character and reduced ring strain contribute to greater stability. Consequently, five- and six-membered rings generally exhibit higher stability compared to other ring sizes[13].

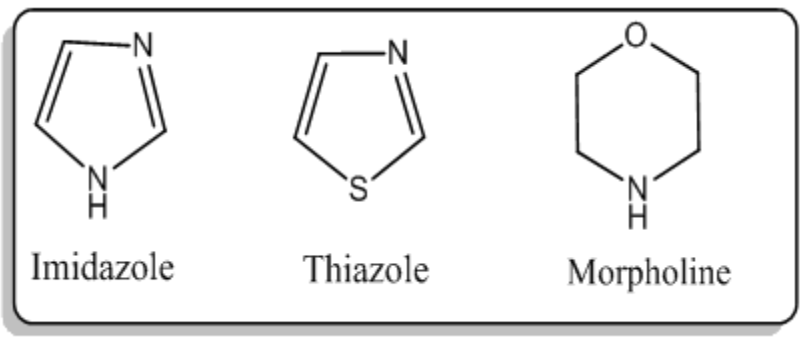


Figure 4. Examples of hetero atoms compounds.

Aromatic compounds, characterized by their cyclic and planar structures with conjugated π systems, generally adhere to Hückel's Rule. This rule stipulates that an organic compound exhibiting aromaticity must possess a specific number of π electrons: $4n + 2$, where 'n' is any non-negative integer. Aromatic compounds commonly possess 6 π electrons, with this configuration being most prevalent when $n = 1$.

However, exceptions exist, such as furan, thiophene, and pyrrole. Contrary to the initial statement, these heterocyclic compounds possess only 4 π electrons (derived from 2 π bonds). In these cases, aromaticity arises from the participation of a one pair of electrons residing in the sp^2 hybridized orbital of the heteroatom (oxygen, sulfur, or nitrogen). This one pair contributes the additional two electrons necessary to fulfill the $4n + 2$ π electron requirement for aromaticity[14-16].

Heterocyclic compounds are not merely laboratory creations; they are found everywhere in nature, playing vital roles within living organisms, including humans. These compounds are integral to the fundamental building blocks of life, particularly evident in human DNA (deoxyribonucleic acid). The nucleic acid bases that form the very foundation of DNA (deoxyribonucleic acid) are themselves composed of heterocyclic compounds. Specifically, these bases originate from two core structures: purine (Gives rise to adenine and guanine) and pyrimidine (Yields thymine and cytosine) **Figure 5**. These four bases are essential for the accurate replication of genetic material, inspired by the natural occurrence and significance of these heterocyclic compounds, a vaccine named puromycin has been developed[17,18], **Figure 6**.

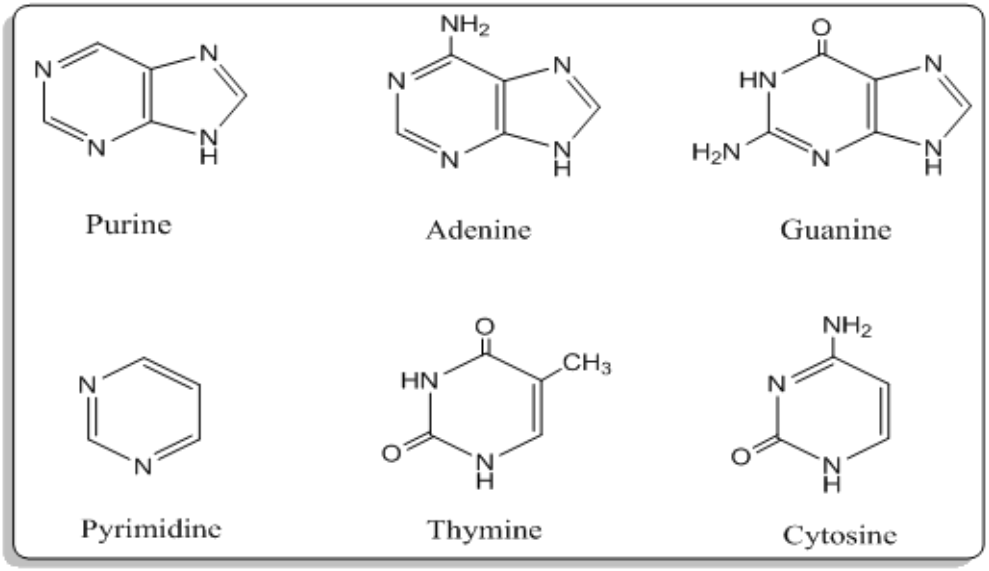


Figure 5. Nucleic acid bases.

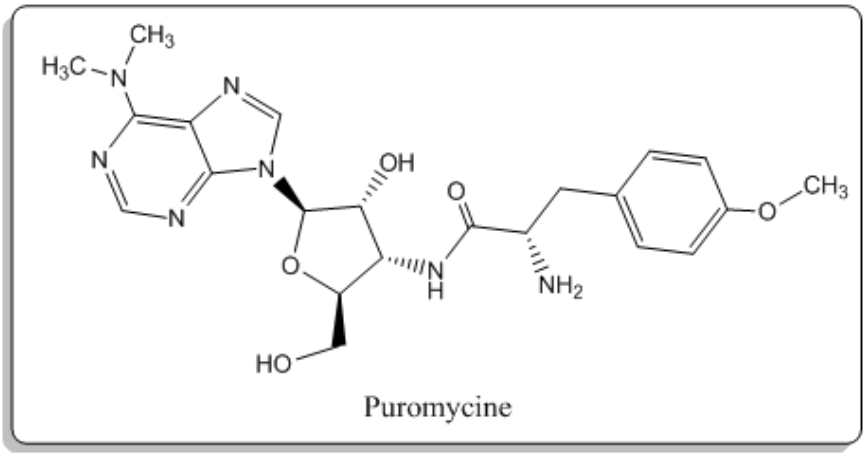


Figure 6. Heterocyclic compound as vaccine.

Numerous heterocyclic compounds are found in nature and are distributed throughout the animal and plant kingdoms. For example, derivatives of the porphyrin ring systems, such as chlorophyll and heme **Figure 7**, are essential components for vital biological processes. Chlorophyll plays a crucial role in photosynthesis in plants, while heme is integral to oxygen transport in both plants and animals. Furthermore, necessary dietary ingredients such as ascorbic acid (vitamin C), pyridoxal (vitamin B_6), thiamin (vitamin B_1), riboflavin (vitamin B_2), and nicotinamide (vitamin B_3) are heterocyclic compounds[19] **Figure 8**.

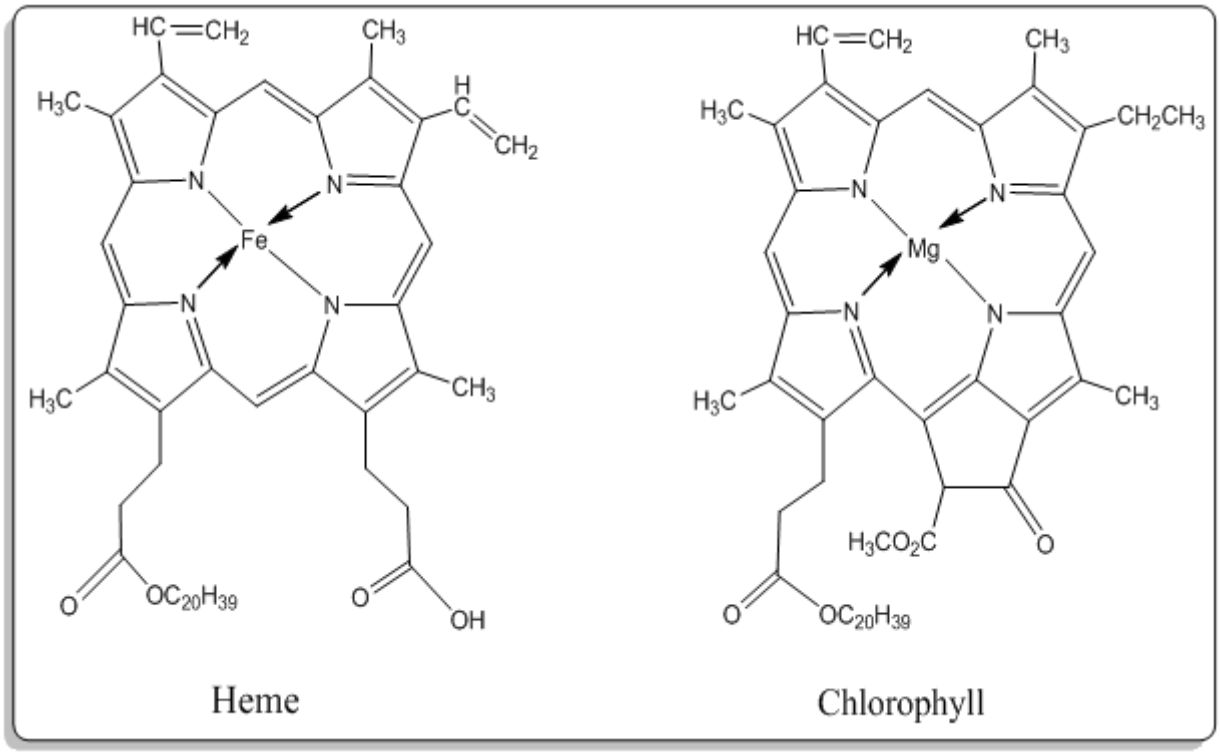


Figure 7. Natural heterocyclic compounds.

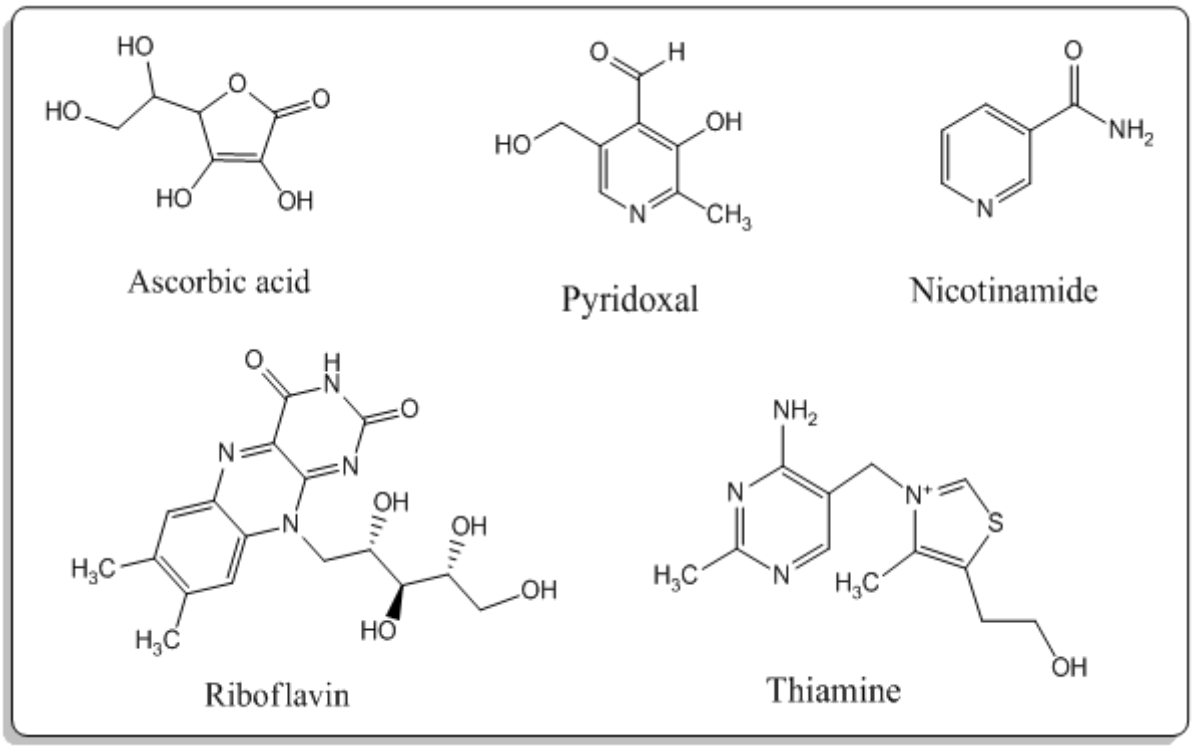


Figure 8. Heterocyclic compounds as vitamins.

Heterocyclic compounds hold significant importance in the field of medicine, and this is particularly evident in the treatment of leukemia. Scientific interest in these compounds is steadily growing due to their therapeutic potential. For instance, studies have demonstrated that substituted aromatic five-membered-ring heterocycles, such as obatoclax, can effectively treat leukemia in children[20]. Furthermore, the potential of heterocyclic compounds extends beyond leukemia treatment. The purpose of this review is to evaluate the antibacterial activity of a heterocyclic hydrazone against Gram-positive and Gram-negative bacteria. [21] as well as explore their role antimalarial drugs such as chloroquine[22], and inhibitors targeting breast cancer such as benzo furans[23]. **Figure 9**.

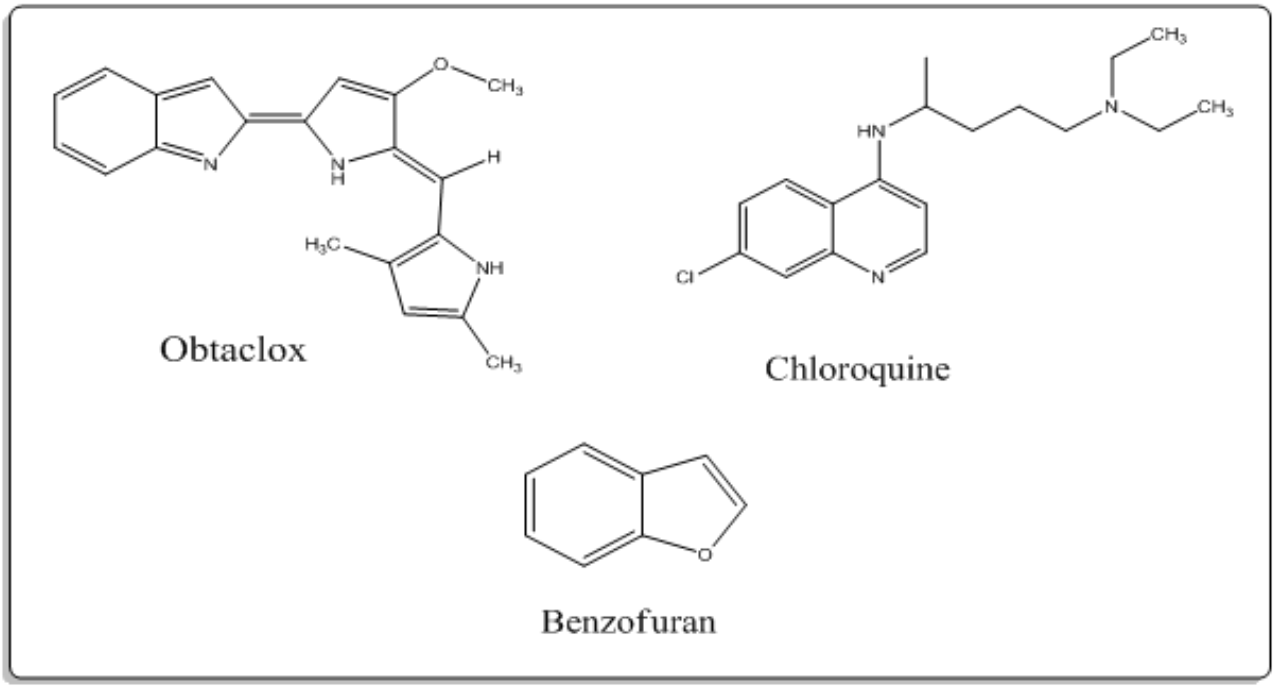


Figure 9. Medicine contain heterocyclic compounds.

2. History of heterocyclic compound:

The history of heterocyclic compounds began in the year 1800.

- Isolation heterocyclic compounds from alloxan by Brugnatelli in 1818
- Preparing furfural from starch and sulphuric acid by Dobereiner in 1832
- Synthesize pyrrole from bone oil by via dry distillation method by Runge in1834.
- A synthetic process for indigo dye was developed, impacting both the chemical and agricultural industries in 1906,
- Synthesize many types of chlorophyll derivatives from crude oil by Treibs in 1936
- Elucidate the significance of heterocyclic compounds, specifically purine and pyrimidine bases, in the context of the genetic code by Chargaff in 1951[24] **Figure 10**.

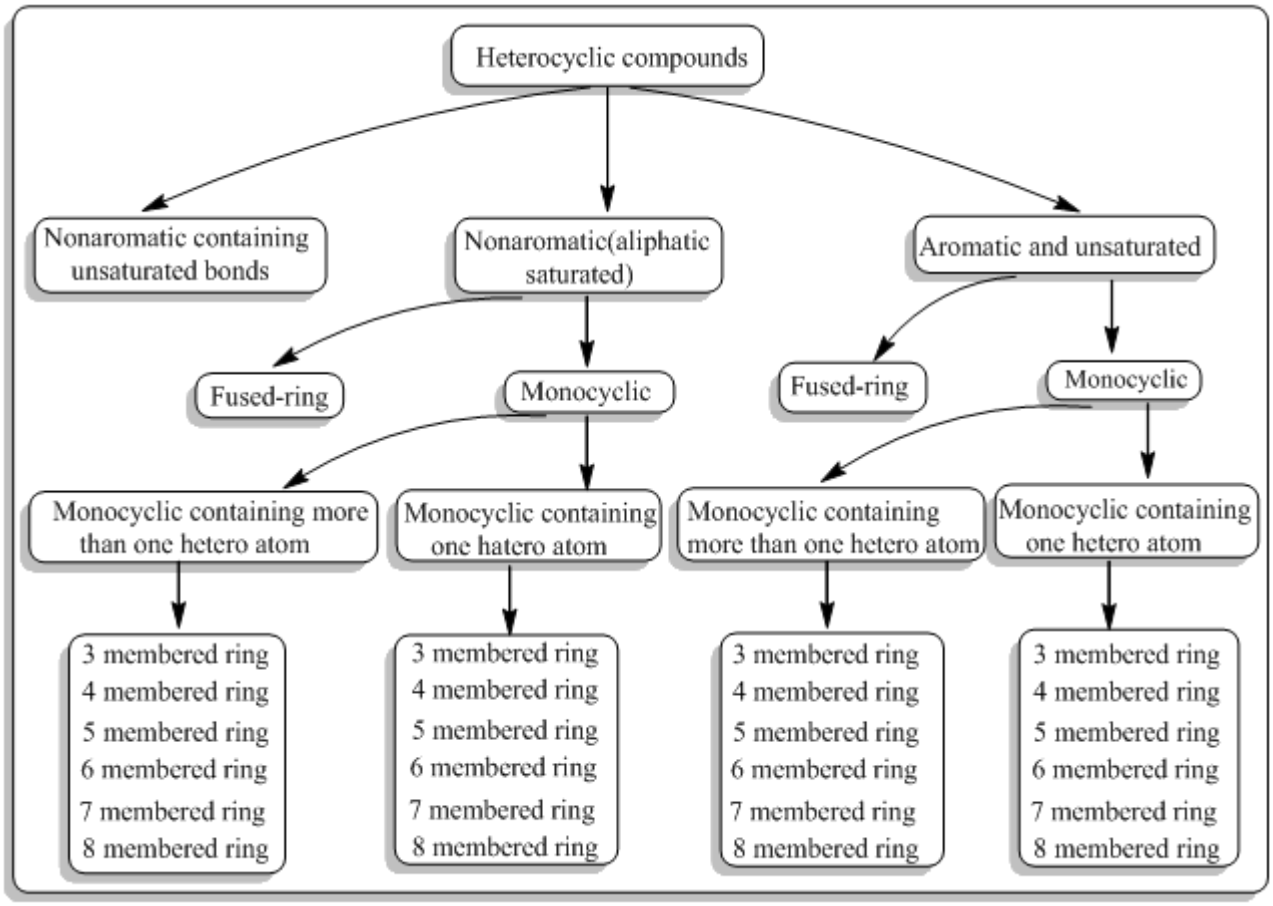


Figure 10. Types of heterocyclic.

2.1. Applications of Heterocyclic Compounds

Heterocyclic compounds stand as essential building blocks in modern medicine, with over 90% of novel medications incorporating them. These unique molecules directly interact with the chemical processes within and biology systems[25], exhibiting remarkable properties such as bio-luminescence, photochromism, and solvatochromism. This versatility has led to widespread applications across various fields, including: life sciences (dyes, fluorescent sensors, sanitizers, brightening agents, pharmaceuticals, antioxidants), materials science (corrosion inhibitors, molecular devices, plastics, analytical reagents, conjugated polymers, information storage), and technology (Organic conductors, optical data carriers, organic light-emitting diodes(OLEDs), photovoltaic cells, semiconductors, molecular wires, light-harvesting systems, liquid crystals, and chemically controllable switches, ionic liquids can act both as green solvents and catalysts)[26,27].

Heterocyclic compounds are indispensable in the synthesis of numerous organic derivatives. These compounds are essential components of many natural products, including alkaloids like morphine, vinblastine, and reserpine, as well as antibiotics such as cephalosporin[28] as shown in **Figure 11**. Furthermore, numerous biological molecules essential for cellular function, such as vitamins and antibiotics, possess heterocyclic structures[29]. Among heterocyclic compounds, those containing nitrogen atoms stand out as the most significant class. In recent years, researchers have developed and established various systematic approaches for the synthesis of nitrogen-containing heterocycles[30].

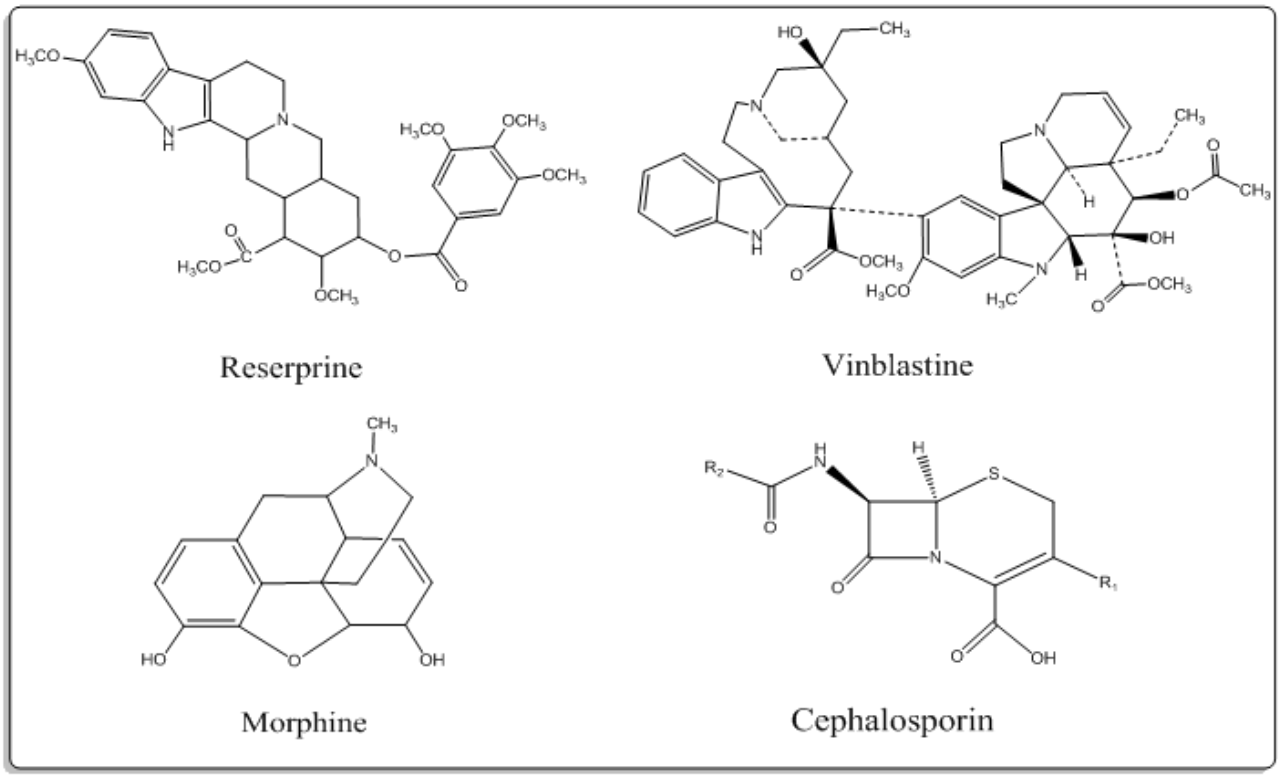


Figure 11. Heterocyclic compounds as alkaloids and antibiotics.

Heterocyclic compounds are predominantly found in various pharmaceutical applications. For instance, cancer treatment, they are key components of drugs used to combat leukemia and in tumor irradiation therapies, Furthermore, they are essential antibiotic development, playing a vital role in the production of broad-spectrum antibiotics like ofloxacin, In chemotherapy, certain heterocyclic compounds act as antioxidants. Beyond pharmaceuticals, these compounds exhibit significant biological activity; for example, methylxanthines contribute to overall health within the human body. Interestingly, heterocyclic compounds are naturally present in many foods[31]. **Figure 12**.

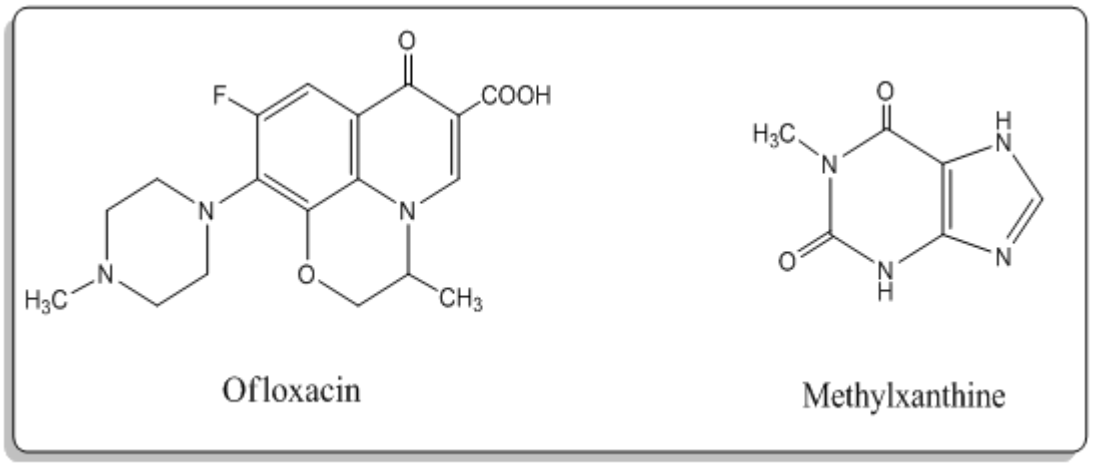


Figure 12. Heterocyclic compounds in pharmaceutical application.

Heterocyclic compounds hold substantial promise as biodegradable agrochemicals, stemming from their varied biological activities and the ease with which they can be synthesized from common laboratory starting materials. Beyond their agricultural potential, heterocyclic compounds exhibit a broad spectrum of pharmacological properties. These include anticancer, anti-inflammatory, antifungal, antimicrobial, and anti-malarial (Pharmaceutical Significance)[32], as well as anticonvulsant, antiviral, & antimycobacterial and anti-HlV (human immunodeficiency virus) activities. Furthermore, these compounds demonstrate various biological activities, such as antiproliferative effects against liver and breast carcinomas[33]. They also possess anti-diabetic, antibacterial, anti-hypertensive, and anti-Alzheimer's properties. Notably, heterocyclic compounds are not limited to pharmaceutical applications; they are prevalent in natural products and pharmaceuticals. They are also widely utilized in the food industry as flavoring agents for various products, encompassing vegetables, meat, and chocolate (Natural Occurrence and Applications)[34-36].

Several review articles have previously explored aspects of heterocyclic chemistry, Hafiz Muhammad Attaullah et al.[37] presents a significant contribution to the field of anti-TB drug discovery. The identification of the compounds as potent Mycobacterium tuberculosis (Mtb) inhibitors with a plausible mechanism of action and favorable in silico safety profiles highlights their potential as leads for the development of new anti-tuberculosis therapies. Further research is necessary to fully evaluate their translational potential, while Samet Poyras et al.[38] describes a significant and timely review that offers a broad and insightful perspective on the biological activities of imidazole-containing hybrid molecules. By encompassing a wide range of activities and incorporating mechanistic studies, the review aims to contribute meaningfully to the development of new drugs to tackle critical health challenges[38].

In contrast to these prior works, our article uniquely compiles a holistic perspective by integrating both classical and cutting-edge sustainable synthetic methodologies alongside an in-depth exploration of the latest therapeutic applications and emerging roles in materials science. This review offers a consolidated and updated resource for researchers seeking a broad yet detailed understanding of benzimidazoles.

3. Benzimidazole

Benzimidazole is a bicyclic heteroaromatic compound with an amphoteric property. Its bicyclic structure comprises a benzene ring and an imidazole ring fused together[39]. The structure features a significant electron-rich heterocyclic pharmacophore, making it valuable for the optimization of drug candidates. Studies on the melting point for various benzimidazole derivatives have revealed that introducing a substituent at the 1-position results in a lower melting point[40].

Benzimidazole derivatives, with two nitrogen atoms, exhibit polar characteristics. This polarity generally enhances their solubility in polar solvents and organic media. To improve solubility in non-polar solvents, non-polar substituents can be introduced at various positions on the benzimidazole ring.

Conversely, the addition of polar groups to benzimidazole increases its acidity, allowing it to dissolve in aqueous alkali solutions. This property is crucial Metal-catalyzed cyclization reactions are powerful tools for constructing nitrogen-containing heterocycles such as imidazole. The acidic character of benzimidazole can be attributed to the stabilization of its resulting ion through resonance. In a weak basic solution like K_2CO_3, benzimidazole becomes more acidic and dissolves better in water. Adding functional groups to the benzimidazole cycle at various positions Considerably influences its physical properties, including melting point and solubility in both organic and polar solvents. Benzimidazole exhibits substantial electronic transitions, suggesting that resonance-stabilized ion formation contributes to its acidic nature, similar to imidazole. To dissolve benzimidazole, a less basic solution might be more effective[41,42].

Benzimidazole, a heteroaromatic compound with the chemical formula$C_7H_6N_2$ and molecular weight of 118.14 g/mol. It is also known as 1H-benzimidazole, 1,3-benzodiazole, ortho-benzimidazole, 3-azaindole, and

benzoglyoxaline. Its low water solubility can significantly impact its absorption[43]. Benzimidazole exhibits both acidic and basic properties; specifically, the NH group displays weak basicity. However, the pyrrole nitrogen at position 1 (N-H group) has a basic character (pKa = 10.24)[44] (pKa is the negative base-10 logarithm of the acid dissociation constant (Ka)) and can undergo replacement reactions with various other reactive groups[45]. In contrast, pyridine possesses a nitrogen atom at position 3. This nitrogen atom, due to its ion pair of electrons, acts as a proton acceptor, enabling it to form coordination bonds with transition metal ions[46] Furthermore, the carbon atom at position 2, exhibiting sp^2 hybridization, plays a crucial role in the tautomerization process that occurs between the nitrogen atoms at positions 1 and 3[47]. **Figure 13**.

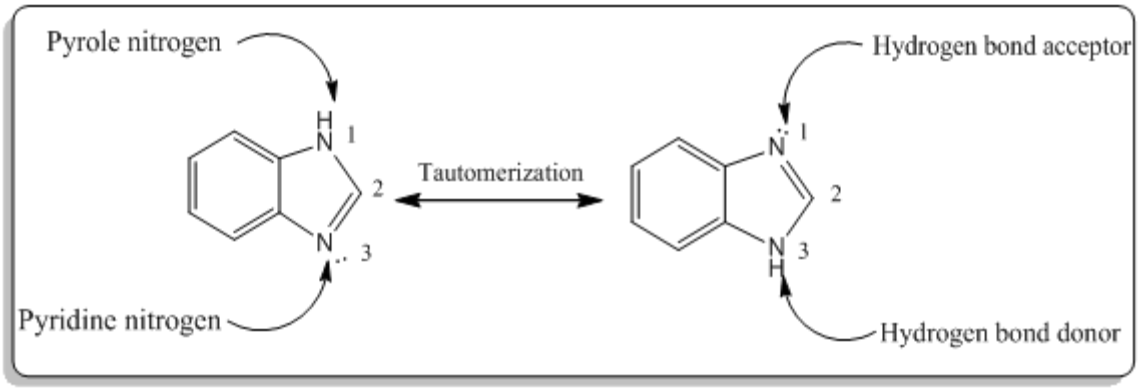


Figure 13. Benzimidazole tautomerization.

Benzimidazole's ability to form salts indicates its amphoteric nature, possessing both acidic and basic properties. Introducing non-polar substituents like alkyl groups (e.g., methyl, ethyl, not H_2 or N_2 which are gases, or Cl_2 which is highly reactive) at various positions on the benzimidazole ring can improve its solubility in non-polar solvents by increasing its lipophilicity. The benzimidazole ring exhibits exceptional stability, remaining unaffected by treatment with alkalis, hot hydrochloric acid, or concentrated sulfuric acid. While the benzene ring of benzimidazole is generally resistant to oxidation, under specific, vigorous conditions, oxidation can occur, potentially disrupting the ring structure. The benzimidazole ring maintains its structural integrity under most conditions; however, certain extreme circumstances can lead to a decrease in its structural stability. Benzimidazole has a high boiling point, typically exceeding $300°C$ during distillation[48,49].

4. Chemistry

Benzimidazole and its derivatives showcase a broad spectrum of biological activities, driving efforts to create comprehensive libraries of these compounds. Diverse synthetic methods have been developed to produce these compounds in the quantities, purity, and quality demanded by customers. The first benzimidazole, identified as either 2,5-dimethyl benzimidazole or 2,6-dimethyl benzimidazole, was synthesized in 1872 by Hoebrecker through the reduction of 2-nitro-4-methylacetanilide. This achievement was a result early investigations into the chemical structure of benzimidazole[50]. (**Scheme 1**)

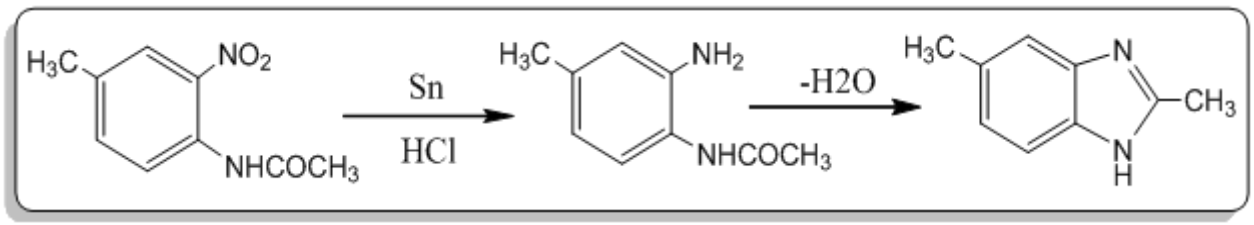
Ladenburg successfully synthesized a compound with the desired properties by refluxing 3,4-diamino toluene with acetic acid. This "refluxing" technique involved continuous boiling and condensation of the reaction mixture. Early scientific literature referred to these newly created compounds as "Anhydrous bases" because their formation involved the loss of water during the process the term "benzimidazole" was adopted, and these compound undergo several nomenclature changes. Derivatives of ortho-phenylenediamine, such as methyl-ortho-phenylenediamine, were utilized to produce benzimidazole. For instance, ethenyl-o-phenylenediamine was used to synthesize 2-methylbenzimidazole[51].

It's interesting to note how the naming conventions for derivatives of the imidazole ring system, like benzimidazole, have evolved over time. For example, benzimidazole was historically referred to as ortho-

phenylene formamide. Similarly, 2(3H)-benzimidazole and benzimidazole-2(3H)-thione were previously termed ortho-phenyl urea and o-phenylene thiourea, respectively. While ortho-phenyl urea was a more common term, ortho-phenylene thiourea is no longer in use. This nomenclature shift arises from the rapid tautomerization of the hydrogen atom attached to the N-1 position within these compounds[52]. When discussing tautomeric compounds, it is common practice to use two sets of numbers to indicate the location of substituent groups. The second set of numbers is enclosed in parentheses to distinguish it from the first set. For example, the compound 5(or 6)-methyl benzimidazole is often referred to by its chemical name[53].

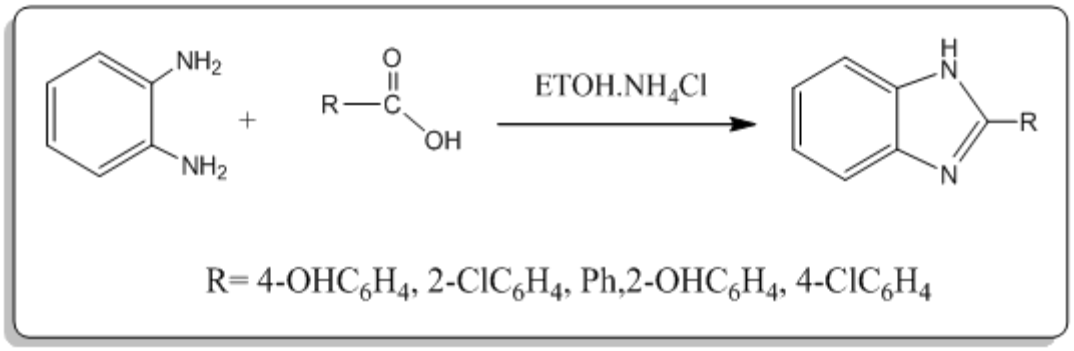
5. General procedure for the synthesis of benzimidazole

1. The benzimidazole ring system was first synthesized in 1872 by Hoebrecker (also known as Wright), he achieved this by subjecting equal moles of 2-nitro-4-methyl acetanilide to a two-step process: reduction followed by dehydration. Shown in (**Scheme 1**)[54,55].

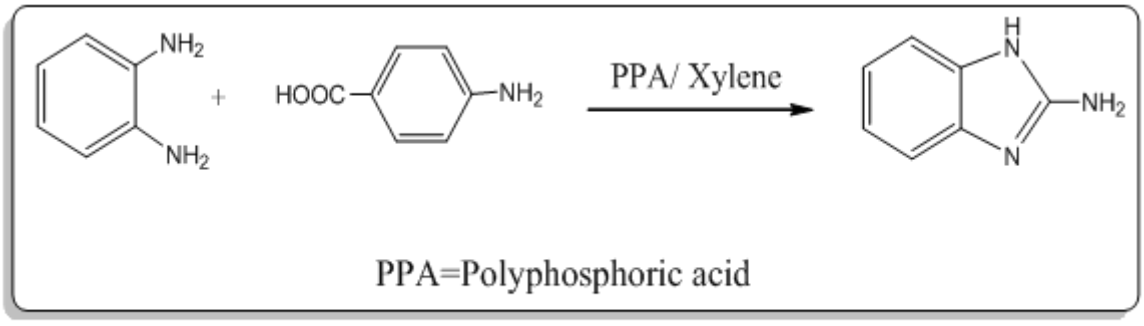


Scheme 1:-Synthesies benzimidazole from 2-nitro,5-dimethyl acetanilide

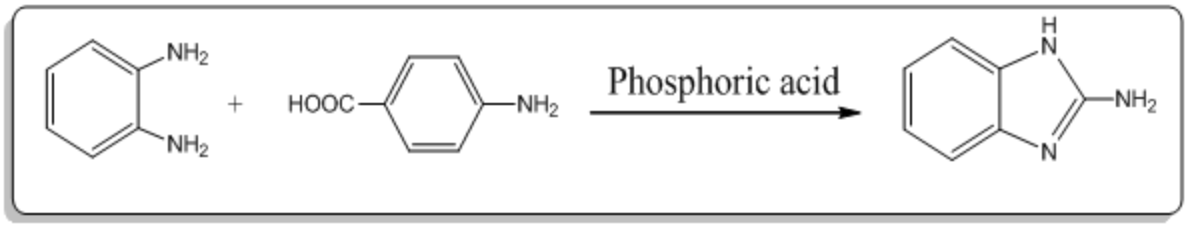
2. Dilute mineral acid promotes the condensation of carboxylic acids with 1,2-diaminobenzene derivative and ammonium chloride (NH_4Cl) as a catalyst in ethanol (equal moles) (**Scheme 2**)[56], using polyphosphoric acid (**Scheme 3**)[57] and ortho-phosphoric acid[58] (**Scheme 4**), produce benzimidazole compounds. The method is known as the Phillips-Ladenburg reaction, first described in 1875.



Scheme 2:-Binzimidazole preparation by Ammonium Chloride catalyst



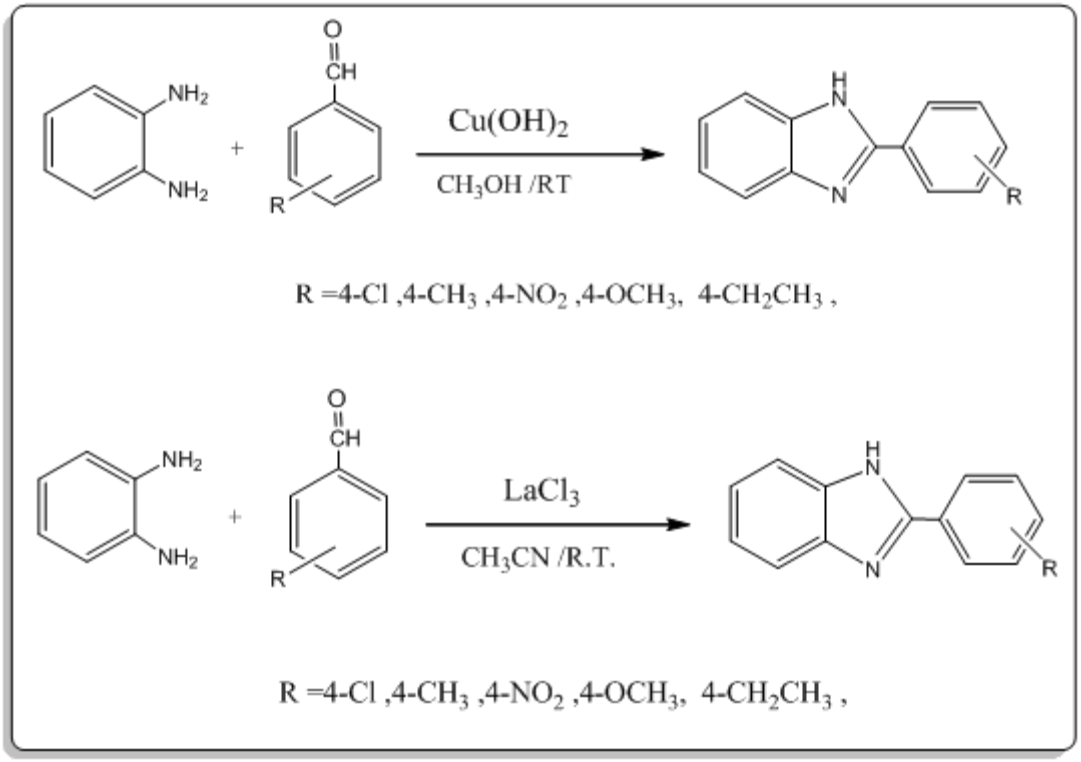
Scheme 3:-Binzimidazole preparation by Polyphosphoric acid



Scheme 4:-Binzimidazole preparation by phosphoric acid

During this process, dehydration occurred, leading to the term 'anhydrous base.' Benzimidazole, also known as benzoglyoxaline, is derived from ortho-phenylenediamine[59].

3. Another traditional technique for producing benzimidazole is the Weidenhagen reaction (**Scheme 5**), this describes a reaction involving 1,2-diaminobenzene with aldehydes or ketones (equal moles) in a water or alcohol solvent. The reaction requires an oxidizing agent, specifically a bivalent copper salt such as copper acetate[60].

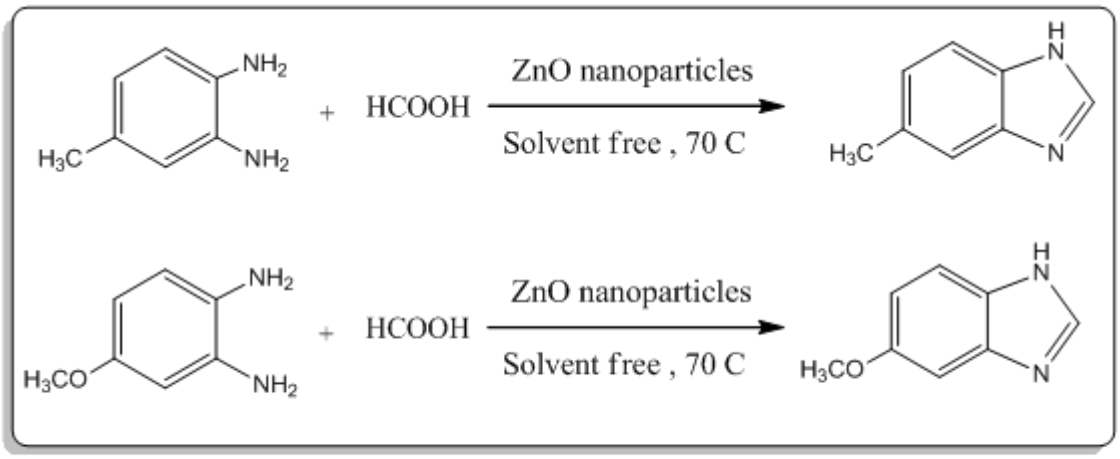


Scheme 5:-Weidenhagn reaction

4. Benzimidazole can be synthesized using various catalytic approaches, including:(Photo redox catalysis) employing photosensitizers like rose Bengal, (Lanthanide catalysis) utilizing lanthanide metals such as Ytterbium (Yb), often in the form of Ytterbium tris (perfluoro octane sulfonate) ($Yb(OTf)_3$), (base catalysis) utilizing organic or inorganic bases and (metal catalysis) utilizing transition metals or other metallic species[61].

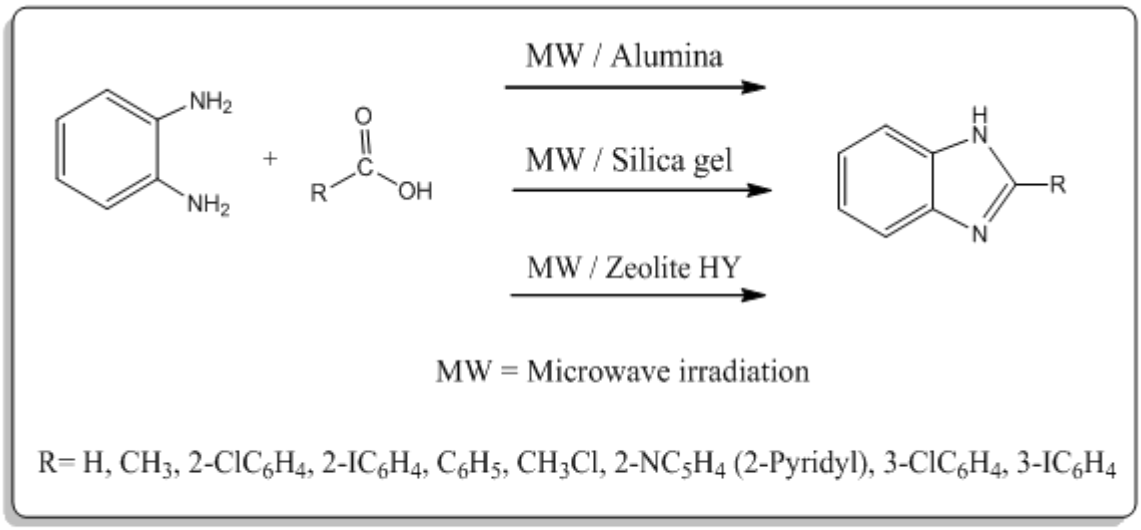
5. A highly efficient and eco-friendly method for synthesizing benzimidazole scaffolds utilizes ZnO nanoparticles (NAP-ZnO) (Near-Ambient Pressure –ZnO) as a catalyst. This approach involves heating substituted ortho-aryl diamines with formic acid at 70°C for a relatively short duration (6-240 minutes), eliminates the use of organic solvents, reducing environmental impact and costs, and produces benzimidazole derivatives with yields ranging from 90-98%. Solvent-Free NAP-ZnO (Near-Ambient Pressure –ZnO) is easily prepared, non-toxic, and cost-effective, acts as a reusable heterogeneous catalyst, minimizing waste. The

reaction conditions are: Short reaction times and simple product purification enhance efficiency, solvent-free conditions, and catalyst recyclability minimize environmental impact and scalability allows for large-scale production. This method provides a promising and sustainable approach for the synthesis of benzimidazole derivatives, offering a valuable contribution to green chemistry practices[62-64]. (**Scheme 6**)



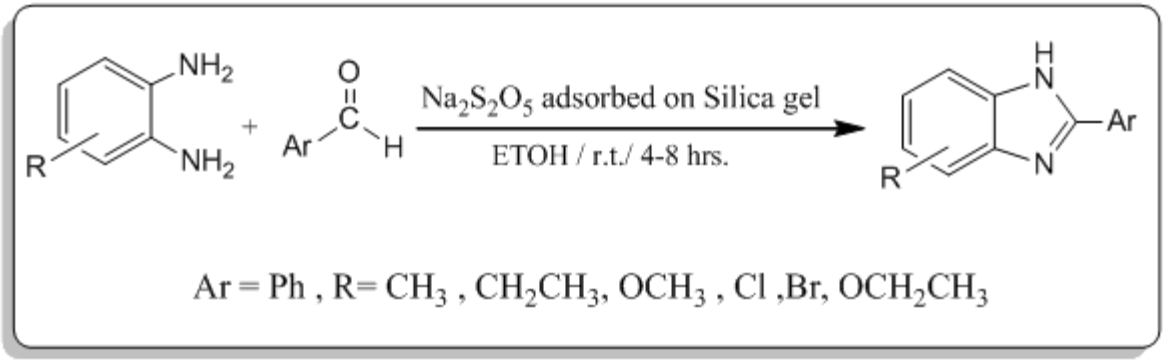
Scheme 6 :- Ppreparation of Binzimidazole by nanoparticles

6. One such approach involves condensing ortho-phenylenediamine with monocarboxylic acids (equal moles) under microwave irradiation. This technique offers several advantages: Microwave irradiation accelerates the reaction, reducing reaction times and energy consumption, eliminating the use of organic solvents minimizes environmental impact and waste disposal, and various solid catalysts, including alumina, silica gel, and zeolite HY, can be employed, offering flexibility and potential for optimization. This microwave-assisted, solvent-free synthesis of benzimidazole represents a promising green approach, contributing to the development of more sustainable chemical processes[65]. (**Scheme 7**)



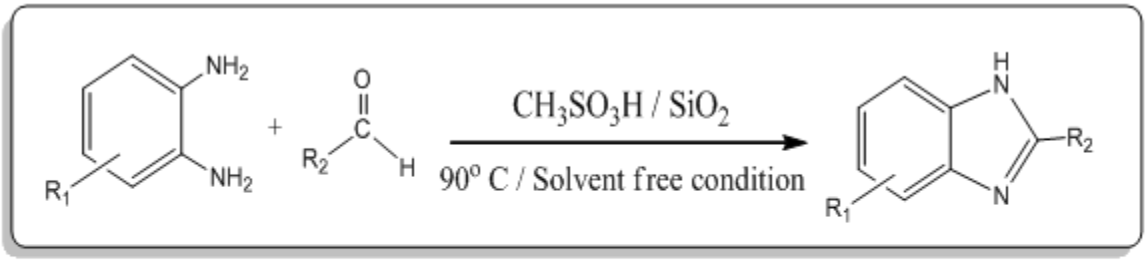
Scheme 7:- Synthesis of Binzimidazole using Microwave irradiation

7. Successful synthesis of benzimidazole utilizing adsorbed on silica gel as an eco-friendly reagent. The immobilized sodium metabisulphite on silica gel facilitates a faster and more efficient reaction compared to traditional methods. By employing this green chemistry approach, the need for expensive and potentially harmful chemicals is significantly reduced. This method provides access to benzimidazole, a crucial building block in pharmaceutical compounds, in high quantities[66]. (**Scheme 8**)



Scheme 8 :- Synthesis of benzimidazole with Sodium metabisulfite adsorbed on silica gel in ethanol

8. The synthesis of benzimidazole derivatives via the reaction of ortho-phenylenediamine with various aldehydes (equal moles) under solvent-free conditions at 90°*C*, catalyzed by solid-phase organic methane sulfonic acid-silica, offers a facile and expeditious approach[67]. (**Scheme 9**)



Scheme 9 :- Synthesis of substituted benzimidazoles catalysed by Methanesulphonic acid-silica under solvent free condition at 90°C

6. Approaches to classical synthesis

Traditional methods for benzimidazole derivative synthesis, frequently relying on multi-step procedures involving functional group modifications and using numerous reagents. Common pathways include reactions between ortho-diamines and aromatic carboxylic acids (or their derivatives). These classical pathways can be associated with extended reaction times and difficulties in achieving high yields and product purity [68]. (**Table 1**)

Table 1. Different approaches to the synthesis of benzimidazole.

NO.	Methods	Reaction component	Different Catalyst	Benefits	Limitations
1.	Hantzsch reaction	Aromatic aldehyde + ortho Phenylenediamine	Acidic catalysts (e.g.. Hcl, acetic acid)	Widely used, simple procedure	Limited scope of substituents requires reflux
2.	Bischler-Napieralski reaction	Ortho Phenylenediamine + +Ketone	Acidic catalyst, heat	Produces 2-amino benzimidazole	Limited to ketones, Low - yield
3.	Debus-Radziszewski reaction	Ortho Phenylenediamine + +Formic Acid	Sulfuric acid, heat	Useful for 2-alkyl benzimidazoles	Requires high temperatures, formic acid handling
4.	Duff reaction	Ortho Phenylenediamine + Aldehyde	Sulfuric acid, heat	Efficient for various substituents	Harsh reaction conditions

5.	Cyclodehydration of diamides	Diamide+ Phosphorous Oxychloride	Using base or heating	A wide range of substrates	Produce byproduct Such as$POCl_3$
6.	Condensation with diaminomaleonitrile	Diaminomaleonitrile + Aldehyde	Base, heat	Provides functionalized benzimidazole	Limited to specific starting materials
7.	Microwave-assisted synthesis	Aromatic Diamine + Aldehyde	Irradiation of Microwave	Faster reactions, higher yields	Specialized equipment, limited scale
8.	Green chemistry approaches	Aromatic aldehyde + Diamine	Catalysis in solvent-free, water-based systems	Waste minimization 1 greener environment	Reaction optimization, substrate limitations
9.	Solid-phase synthesis	Resin-bound amine + Aldehyde	Solid-phase conditions	High-throughput, efficient for combinatorial	Requires specialized equipment, specific resins

Table 1. (*Continued*)

Table 2. Omparable analysis: Classical vs. modern synthesis methodologies: For benzimidazole derivatives.

Synthetic method	**Benefits**	**Limitations**
Traditional methods	Established protocols, Widely available starting materials	Multistep Procedures Limited, Regioselectivity, Longer reaction times
Modern methods	"Microwave-assisted synthesis offers rapid reaction rates and high yields. promotes energy efficiency and aligns with green chemistry principles through approaches that reduce environmental impact. Specifically, it enables solvent-free or water-based reactions and facilitates catalytic processes.	Limited reaction scope Specialized equipment Reaction optimization
Solid phase synthesis	Improved efficiency through parallel synthesis, enhanced purification, and accelerated reaction rates	Restricted compound scope, necessitates solid-phase equipment, complex library synthesis

7. Biological activity for benzimidazole derivatives

Benzimidazole, a significant nitrogen-containing heterocyclic compound, finds widespread use in organic synthesis and exhibits a diverse range of therapeutic properties [73]. The benzimidazole nucleus, a key heterocyclic ring system, provides the fundamental framework for a broad spectrum of pharmacologically active compounds. Its derivatives have demonstrated significant therapeutic potential across various disease areas, leading to the development and commercialization of numerous drugs such as anti-helminthic, antiulcer, cardiotonic, antihypertensive, antibacterial, antifungal, anti-allergic, anti-neoplastic, local analgesic, anti-leishmanial, vasodilator, spasmolytic, antimicrobial, antitumor, antiviral, anti-inflammatory, anticancer, antioxidant and antitubercular properties[74-86]. **Figure 14**.

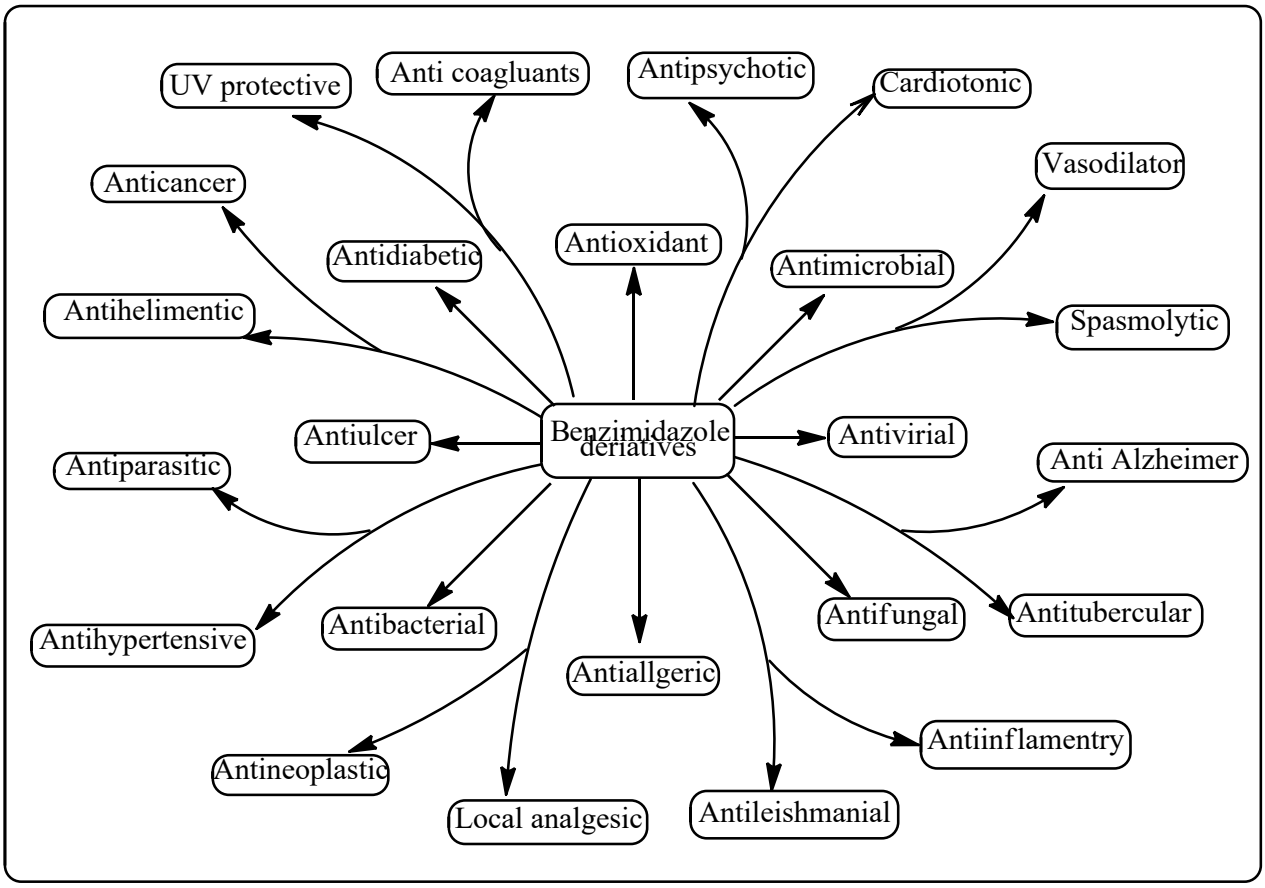


Figure 14. Biological activity for benzimidazole derivatives.

Benzimidazole derivatives demonstrate a wide spectrum of antiviral activity, effectively targeting viruses, such as HIV (human immunodeficiency virus), herpes simplex virus 1 (HSV-1), RNA (ribonucleic acid) viruses, influenza, and human cytomegalovirus (HCMV). Remarkably, the substitution of the hydrogen atom at the C-2 position of the benzimidazole ring with a sugar residue results in a significant shift in its biological activity, transforming it into a potent inhibitor of glycogen phosphorylase. This discovery holds substantial promise for the development of medications for diabetes mellitus [87-90]. Moreover, even with the progress in modern drug discovery, molecules capable of interacting with DNA and RNA remain fundamental components of chemotherapy in medicinal chemistry[91-95].

The considerable interest of medicinal chemists in benzimidazole derivatives stems from their promising therapeutic applications. Consequently, this has spurred the synthesis of a multitude novel benzimidazole-based compounds, with a particular focus on those incorporating pyrimidine fragments. These pyrimidine-linked benzimidazole hybrids have exhibited encouraging antibacterial and antifungal properties. Additionally, they have shown potential in inhibiting crucial proteins of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), specifically the main protease and spike glycoprotein[96-100].

Benzimidazole has attracted considerable interest in its role as a UV-protective (ultraviolet) agent due to several key advantages: First, they efficiently filter both UVA (ultraviolet A) and UVB (ultraviolet B) radiation. Second, their straightforward molecular structure facilitates easy and scalable industrial production. Finally, their high water solubility enhances their compatibility with various cosmetic formulations. For instance, Bisdisulizole known as Neo Heliopan AV (INN(International Nonproprietary Name) : Sodium salt of 2,2'-bis(1,4-phenylene)-1H-benzimidazole-5,5'-disulfonic acid)absorbs mainly in the UVA range,Ensulizole (INCI (International Nomenclature of Cosmetic Ingredients): 2-phenyl-1H-benzimidazole-5-sulfonic acid, PBSA) is a UVB filter[101]. **Figure 15**.

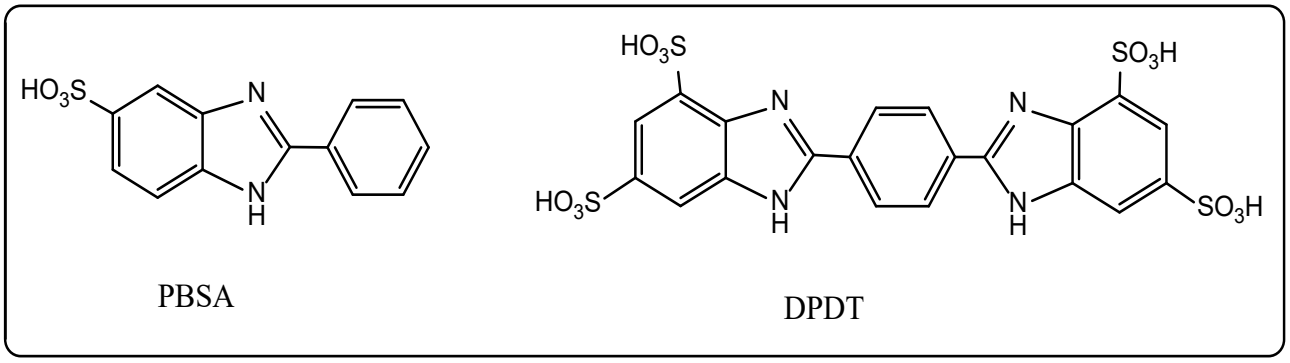


Figure 15. Benzimidazole derivatives as a UV-Protective agent.

Chloro-substituted benzimidazole can inhibit cholinergic enzymes, specifically Acetylcholinesterase (AChE) and Butyrylcholinesterase (BuChE). Previously reported chloro-substituted benzimidazole derivatives show potential as anti-Alzheimer's agents[102-104]. **Figure 16**.

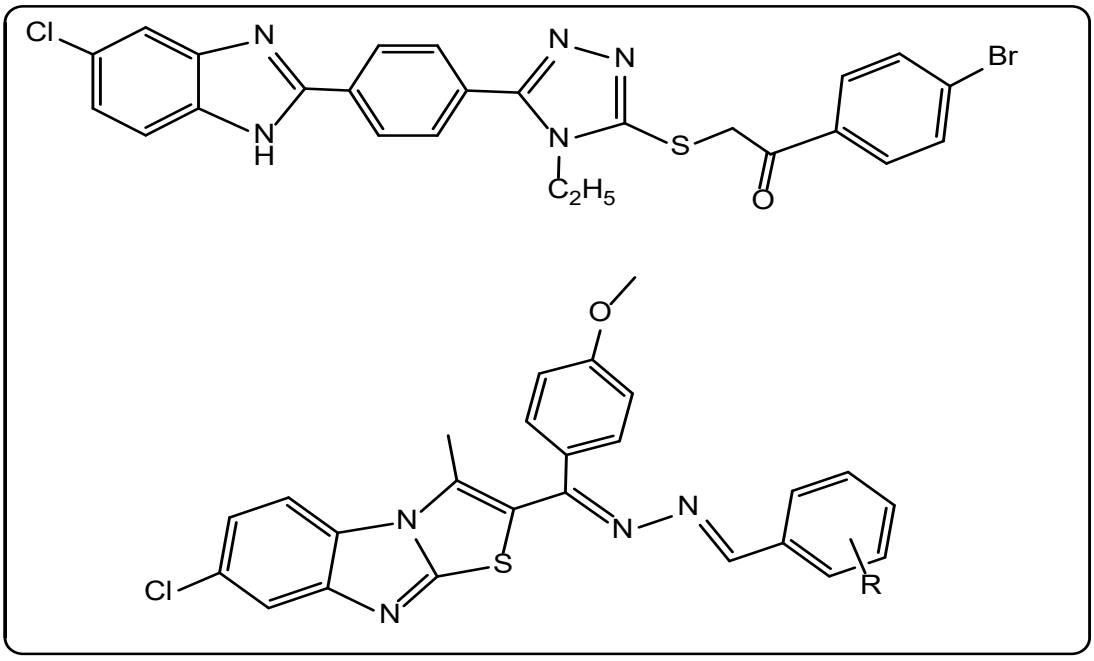


Figure 16. Benzimidazole derivatives as anti-Alzheimer's agents.

8. Drugs having benzimidazole nucleus

1. As oral antiviral: Antivirals are a class of medications used to treat viral infections. They target various viruses, including HIV (human immunodeficiency virus), influenza, hepatitis, herpes, and cytomegalovirus. Maribavir and Enviradine a benzimidazole-containing antiviral, is a key examples of this class of medication. **Figure 17**.

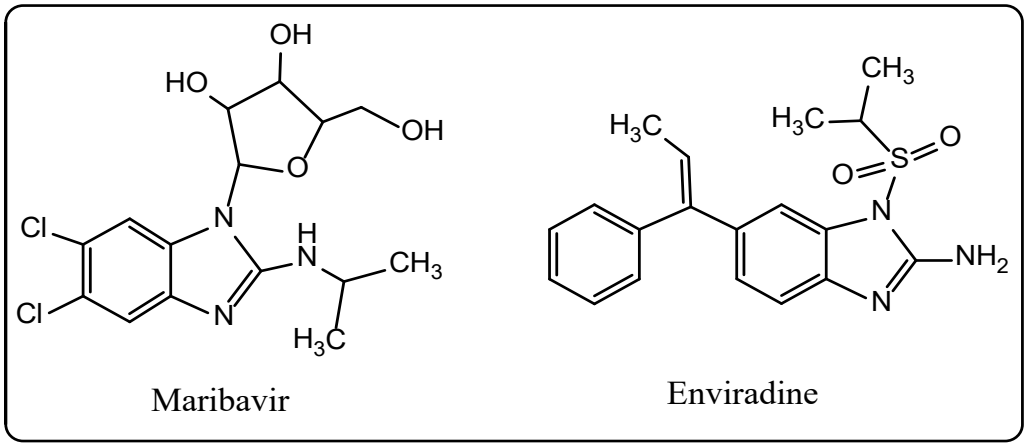


Figure 17. Benzimidazole dervatives as oral antiviral.

2. As anti-hypertensive: Antihypertensive medications are drugs used to treat high blood pressure and lower it to a normal range. For example, Candesartan, candesartan cilexetil, and Telmisartan are such a medication. **Figure 18**.

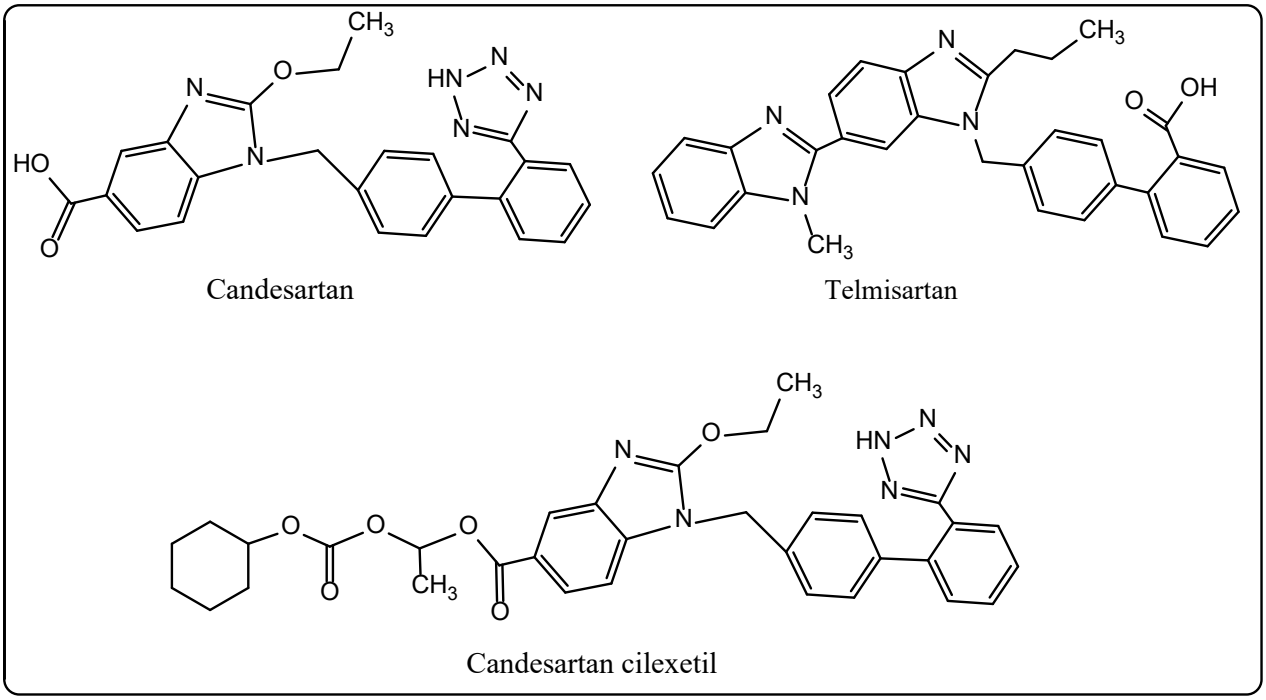


Figure 18. Benzimidazole dervative sas anti-Hypertensive.

3. As fungicides: Benzimidazoles, particularly their derivatives, exhibit fungicidal or fungistatic properties against a wide spectrum of fungal species. Their mode of action often involves interfering with crucial cellular processes, this broad-spectrum activity, coupled with their effectiveness against both systemic and superficial fungal infections, makes Benzimidazoles valuable tools in the development of novel antifungal drugs. Carbendazim serves as a prominent example of a benzimidazole-based antifungal agent. **Figure 19**.

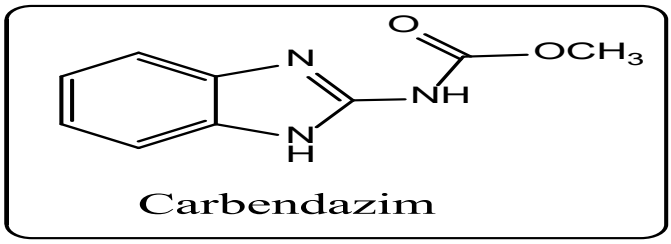


Figure 19. Benzimidazole dervative as fungicidal.

4. **As anti-helminthic:** Benzimidazoles are a class of medications used to treat parasitic worm infections. This group includes drugs such as Albendazole, mebendazole, thiabendazole, Flubendazole, Albendazole sulfoxide, Oxibendazole, Fenbendazole, mebendazole oxide, and Oxfendazole. These medications effectively target various helminths, including nematodes (roundworms, hookworms, whipworms) and cestodes (tapeworms), in both animals and humans. **Figure 20**.

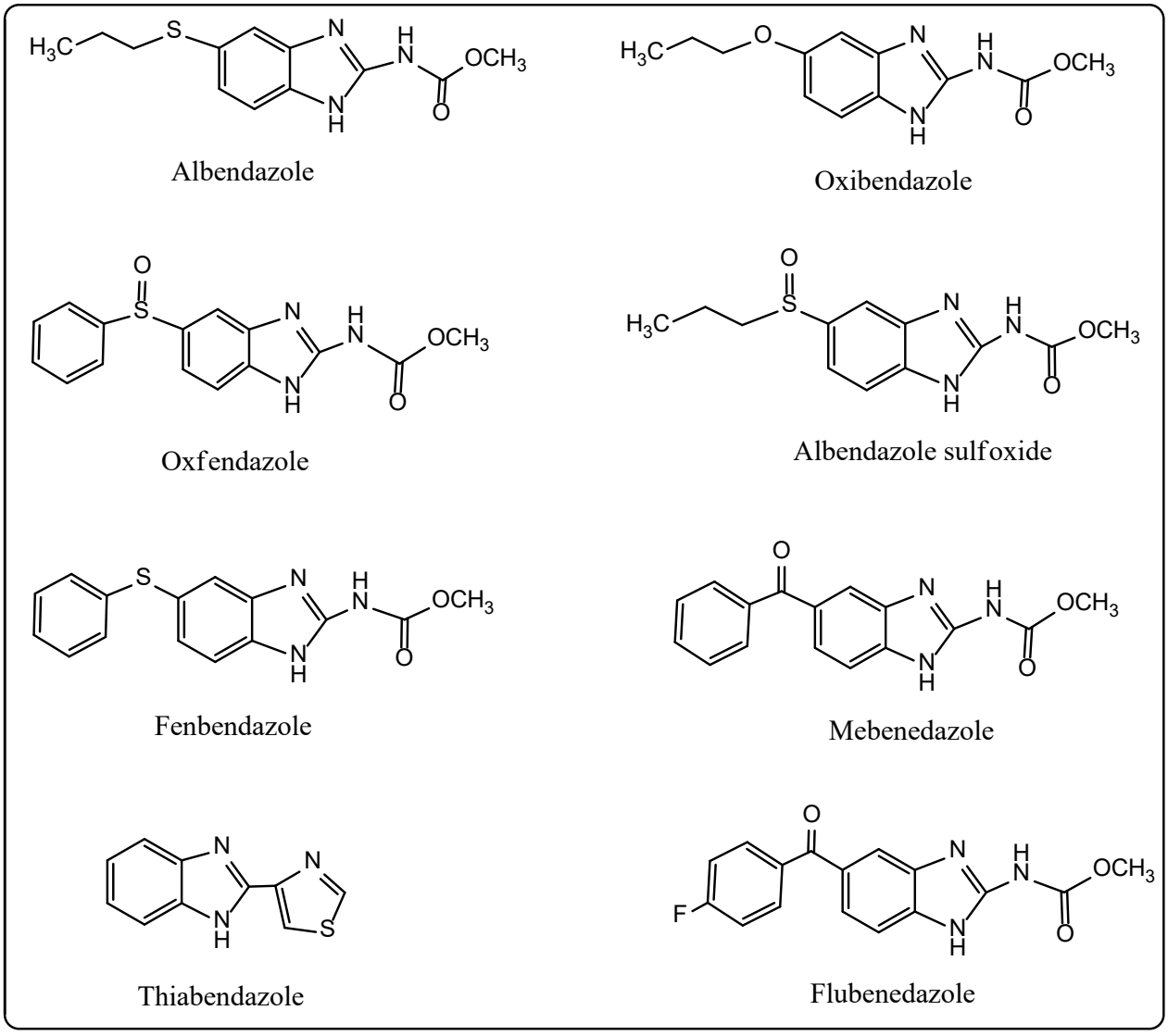


Figure 20. Benzimidazole dervatives as anti-Helminthic.

5. **As anti-histamine:** Drugs such as Emedastine, Mizolastine, Clemizole, and Astemizole function as successful H_1receptor antagonists. This means that they effectively block the action of histamine, a natural substance primarily responsible for allergy symptoms. **Figure 21**.

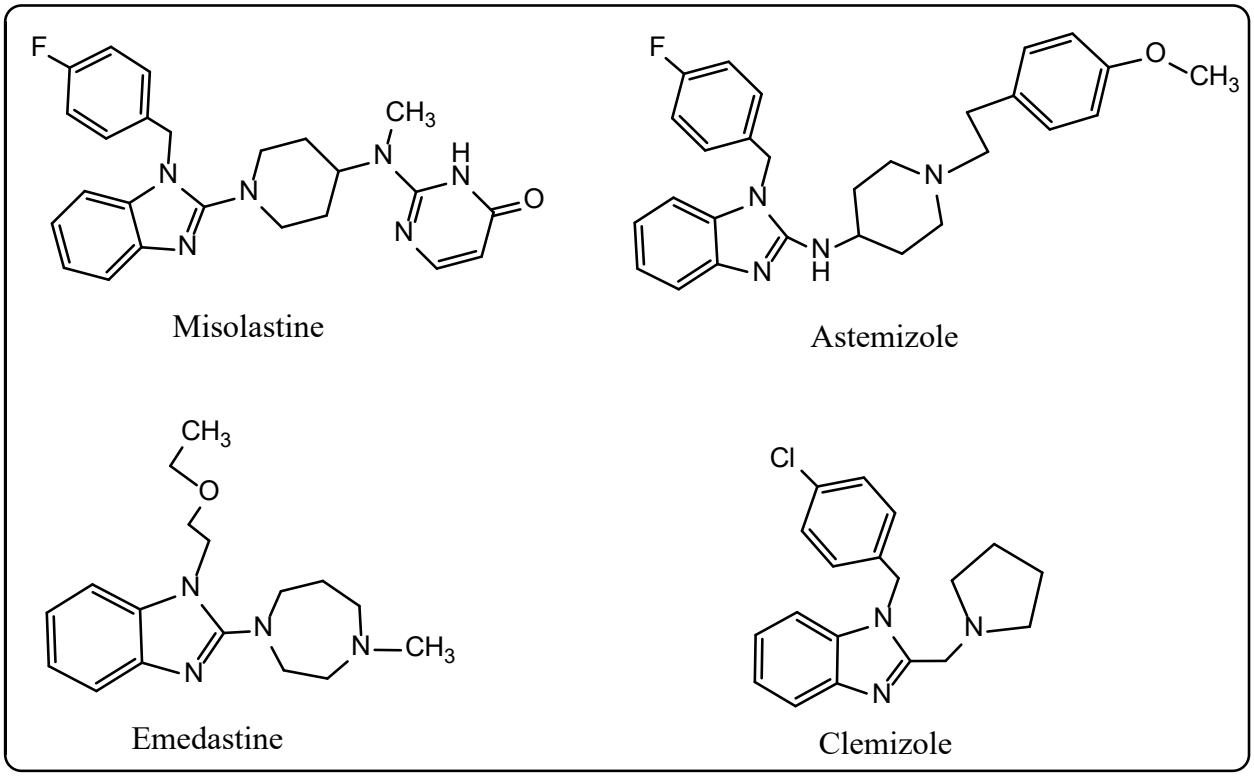


Figure 21. Benzimidazole dervatives as anti-histamine.

6. **As analgesic:** Bezitramide is a potent anesthetic analgesic. This medication undergoes significant metabolism within the gastrointestinal tract, primarily into its main metabolite, despropionyl-Bezitramide. **Figure 22**.

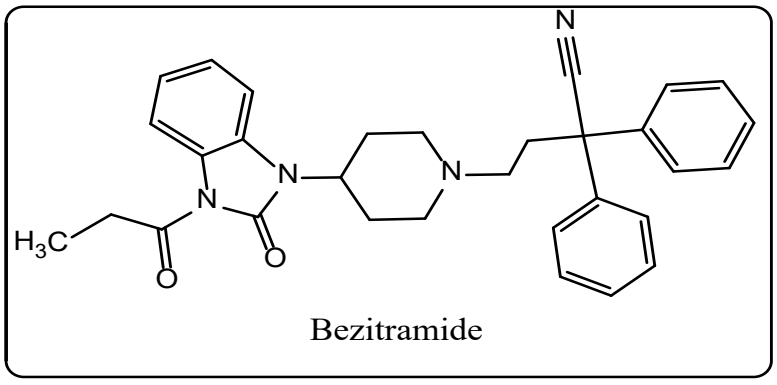


Figure 22. Benzimidazole dervative as analgesic.

7. **As anti-diarrheal:** Rifaximin is a valuable semi-synthetic antibiotic. Its clinical applications extend beyond traditional uses. It has demonstrated effectiveness in treating traveler's diarrhea and has also shown promise in managing hepatic encephalopathy. This versatility underscores the importance of Rifaximin in clinical practice. **Figure 23**.

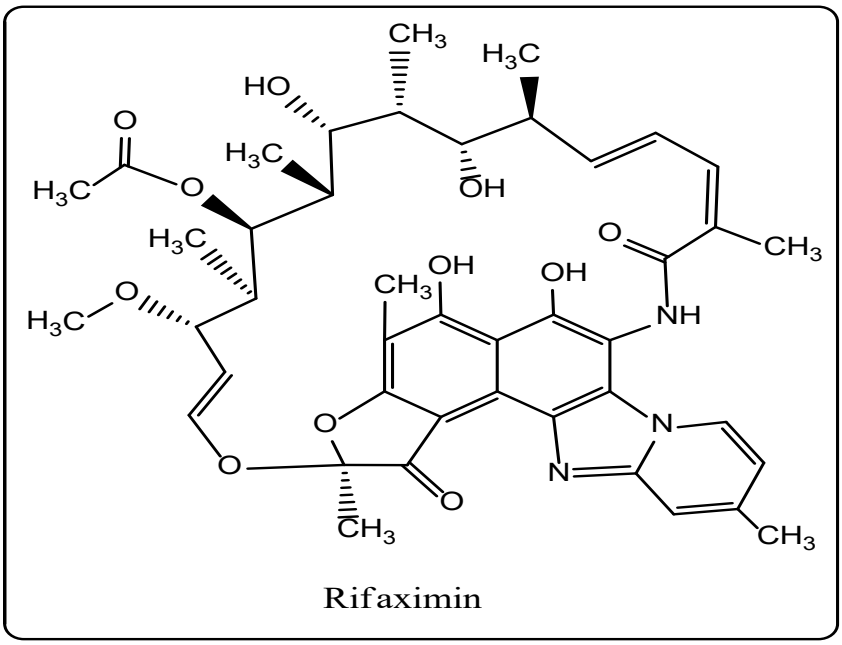


Figure 23. Benzimidazole dervative as anti-Diarrheal.

8. **As anti-neoplastic:** Nocodazole, an important anti-tumor agent, exerts its therapeutic effect by directly interfering with microtubule polymerization in human cells, which is evidenced by a significant reduction in microtubule formation. **Figure 24**.

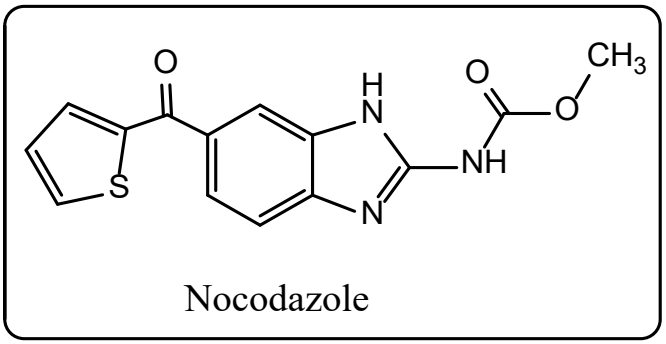


Figure 24. Benzimidazole dervative as anti-Neo plastic.

9. **As anti-ulcer drug:** Proton Pump Inhibitors (PPIs) are a class of medications widely used as antiulcer drugs for short-term treatment of conditions like duodenal ulcers, erosive gastroesophageal reflux disease (GERD), and ulcerative conditions. Examples of PPIs include Rabeprazole, Omeprazole, Lansoprazole, and Pantoprazole. **Figure 25**.

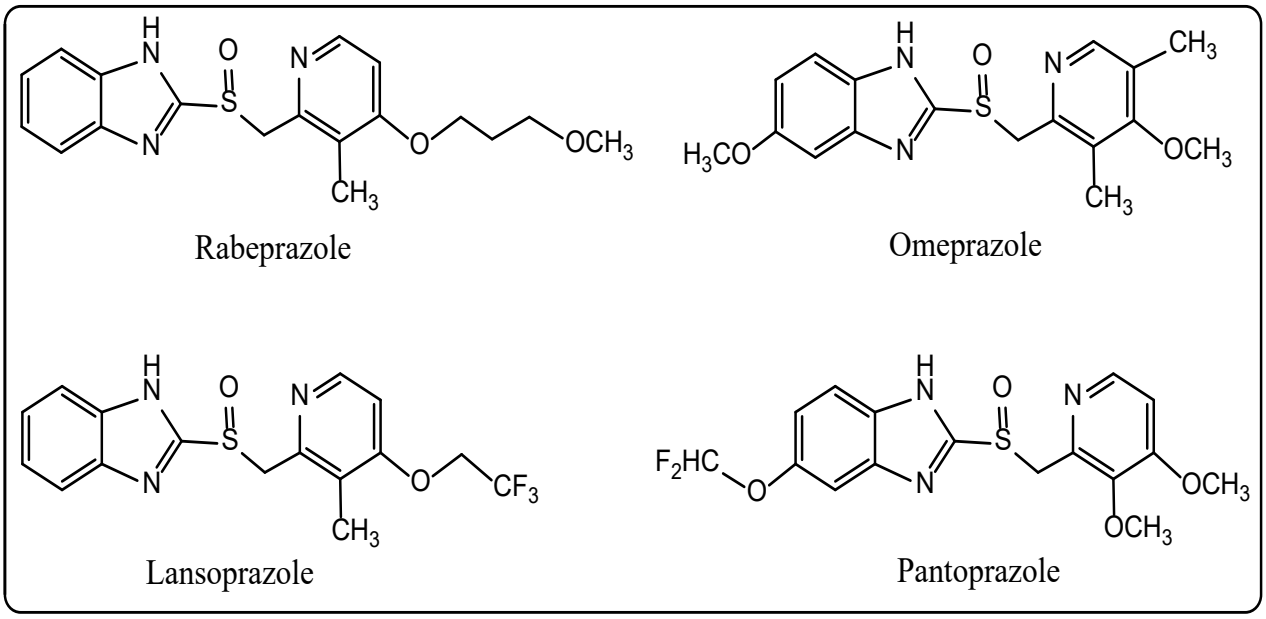


Figure 25. Benzimidazole dervatives as anti-Ulcer drug.

10. **As calcium sensitizer:** Pimobendan, a calcium sensitizer, improves heart function by increasing the force of muscle contractions. **Figure 26**.

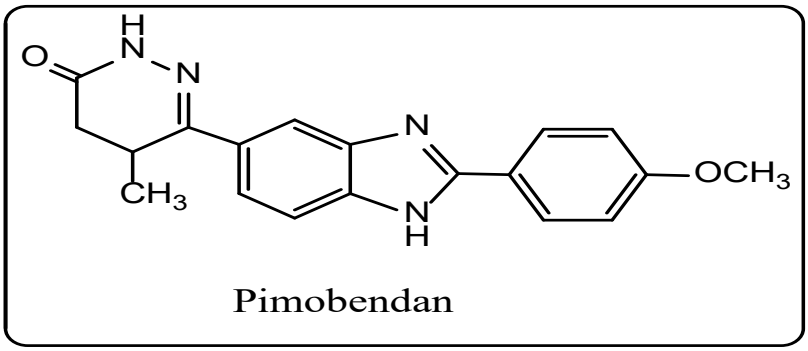


Figure 26. Benzimidazole dervative as calcium sensitizer.

11. **As oral antidiabetic:** Type 2 diabetes is a disorder involving insulin resistance. Rivoglitazone is an oral antidiabetic medication that is secreted/administered during the treatment phase. **Figure 27**.

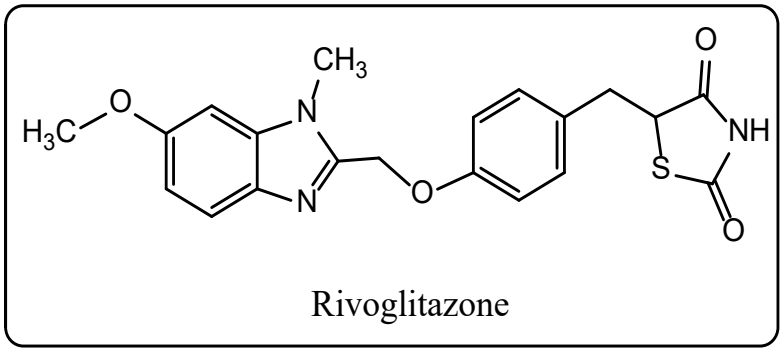


Figure 27. Benzimidazole dervative as oral anti-Diabetic.

12. **As anti-psychotic:** Medications containing benzimidazole are commonly used in the treatment of mental illnesses like schizophrenia and chronic psychosis. Key examples include Droperidol, Pimozide, and Benperidol. **Figure 28**.

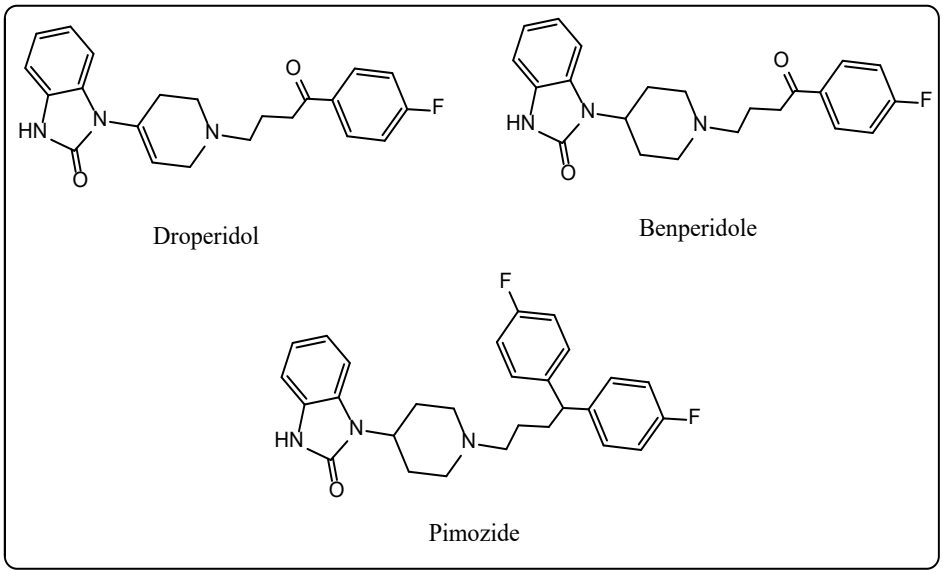


Figure 28. Benzimidazole dervatives as anti-Psychotic.

13. **As anti-bacterial:** Anti-bacterial drugs derived from benzimidazole have demonstrated effectiveness against a range of pathogens, including both Gram-positive and Gram-negative bacteria. Ridinazole serves as an example of such a benzimidazole-based antibacterial. **Figure 29**.

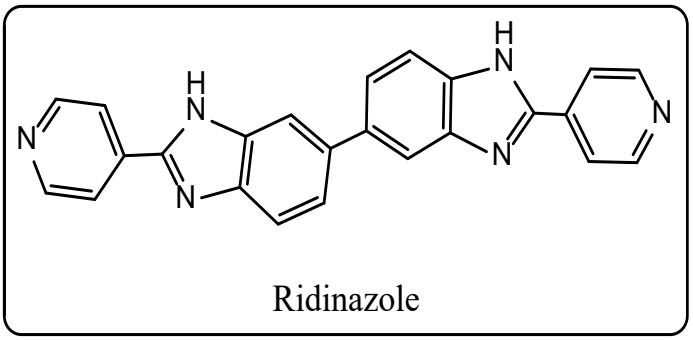


Figure 29. Benzimidazole dervative as anti-Bacterial.

14. **As oral anticoagulants:** Dabigatran stands out as a premium oral anticoagulant due to its direct mechanism of action, specifically inhibiting thrombin. **Figure 30**.

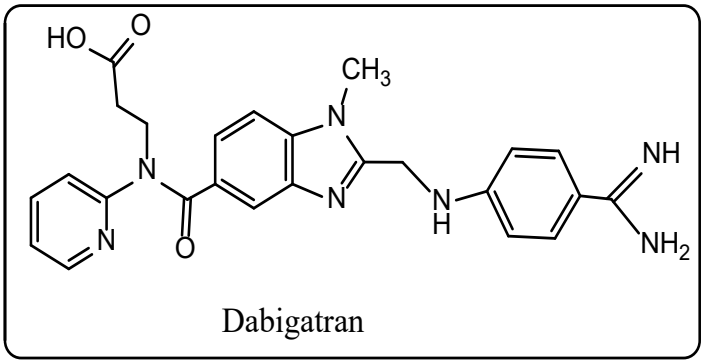


Figure 30. Benzimidazole dervative as oral anti-Coagulants.

15. **As anti-nausea:** Domperidone, a benzimidazole-containing medication, this medication is primarily used to treat nausea and vomiting by blocking dopamine receptors in the digestive system, which helps to relax the stomach muscles and speed up the movement of food through the intestines. **Figure 31**.

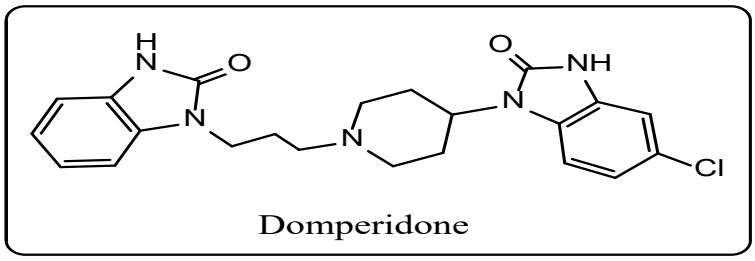


Figure 31. Benzimidazole dervative as anti-Nausea.

16. **As anti-cancer:** benzimidazole derivatives have demonstrated significant potential in cancer treatment. Several members of this class, including bendamustine, selumetinib, galeterone, liarozole, and pracinostat, have been successfully marketed as antitumor agents[105-112]. **Figure32**.

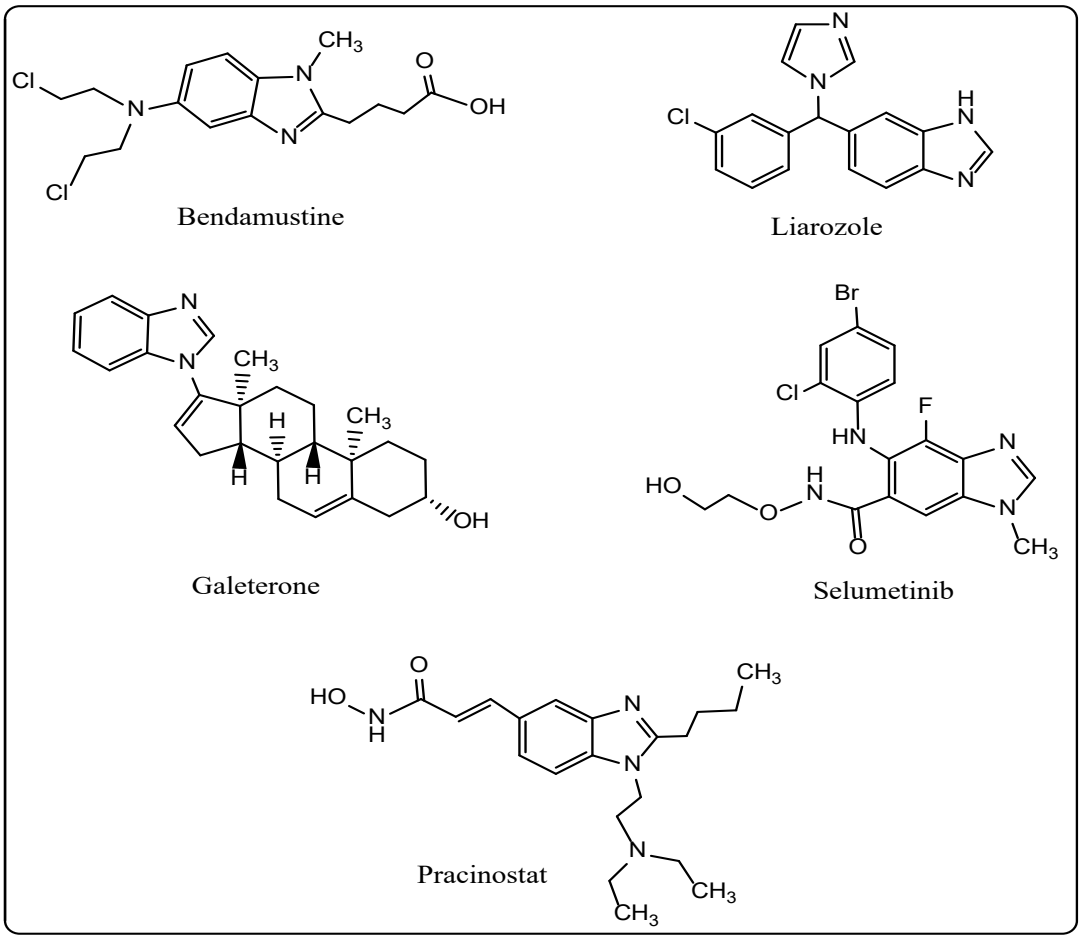


Figure 32. Benzimidazole dervatives as anti-Cancer.

Sabyasachi Banerjee et al.[113] provided review effectively introduces a comprehensive review focused on the medicinal chemistry of benzimidazole derivatives. It highlights the significance of the Benzimidazole scaffold, outlines the scope of the review, this review promises to be a valuable resource for medicinal chemists and researchers interested in the development of benzimidazole-based drugs, while Shankar Thapa et al.[114] presents a compelling case for the potential of substituted benzimidazole derivatives as promising candidates for the development of new drugs to combat tuberculosis. The combination of successful synthesis, significant

in vitro activity, supportive computational evidence, and initial safety assessment highlights the importance of this research in the ongoing fight against this global health threat.

9. Conclusion

Benzimidazole-based compounds, simple yet bioactive heterocyclic entities with their diverse chemical space, offer a rich platform for the discovery of novel bioactive molecules and made a substantial contribution to the advancement of medicinal chemistry. Their diverse applications stem from their ability to exhibit a wide range of biological activities. By modifying the benzimidazole ring with different substituents (location and type), researchers can optimize its properties, creating comprehensive library of compounds with conformed biological effects. These modifications significantly influence the compound's interactions with biological targets, enabling the development of treatments for various human, animal, and plant diseases. This versatility has stimulated the interest of researchers worldwide, driving ongoing investigations into their therapeutic potential; continued investigation into benzimidazole derivatives is expected to yield significant advancements in research inspiring medicinal chemists to leverage this promising heterocycle in the development of novel biological therapies.

The diverse biological activities of benzimidazole derivatives make them promising candidates for developing highly effective therapeutic agents. To enhance drug discovery efforts, researchers must understand the specific contributions of each functional group within these molecules thorough explanation of docking and in silico studies involving benzimidazoles goes beyond simply stating that these methods were used. It necessitates a detailed description of the methodology, including target and ligand preparation, the specific docking software and parameters, validation procedures, post-docking analysis of interactions and binding affinities, and potentially molecular dynamics simulations.

Understanding the key structural features of benzimidazoles and the impact of substituents on their properties is crucial, often explored through pharmacophore modeling. While not the primary focus, a brief mention of synthesis methods provides context for ligand availability. Most importantly, the studies should clearly link the diverse therapeutic applications being investigated to the specific biological targets and explain how the in silico findings contribute to understanding the mechanism of action and potency of the benzimidazole derivatives. Such detailed reporting enhances the scientific value and reproducibility of the research.

This knowledge is crucial for the rational design and development of novel drugs with improved biological activity. This review aims to assist aspiring researchers in the field of benzimidazole-based drug design by providing insights into this critical aspect and distinguishes itself by offering a comprehensive and integrated perspective, encompassing not only the fundamental aspects of heterocyclic chemistry with a specific focus on benzimidazoles (structure, properties, and synthesis) but also explicitly addressing modern trends in synthetic methodologies emphasizing efficiency and sustainability, alongside a detailed overview of their broad therapeutic applications and growing significance in materials science.

The future scope of a review focusing on heterocyclic compounds, particularly benzimidazoles, can be quite extensive, building upon the current understanding and trends in chemistry, biology, and materials science. In essence, the future of benzimidazole research lies in its continued evolution towards more sustainable, efficient, and targeted applications, driven by advancements in synthetic chemistry, computational science, and interdisciplinary collaborations.

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Conflict of Interest

The authors declare no conflict of interest.

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