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Mahesh Kumar N
PG Scholar, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru, Karnataka, India

Priya A
PG Scholar, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru, Karnataka, India

Dr. Shachindra L Nargund
Professor & Principal, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru, Karnataka, India

Dr. V Murugan
Professor & Academic Director, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru, Karnataka, India

Bharath Kumar Chagaleti
Assistant Professor, Department of Pharmaceutical Chemistry, SRM College of Pharmacy, Kattankulathu, Karnataka, India

Corresponding Author:
Mahesh Kumar N
PG Scholar, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru, Karnataka, India

Benzimidazole-based therapeutics: A comprehensive review of approved drugs and their pharmacological actions

Mahesh Kumar N, Priya A, Shachindra L Nargund, V Murugan and Bharath Kumar Chagaleti

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Abstract
Benzimidazole is a privileged heteroaromatic scaffold that has contributed to the development of several clinically approved drugs across therapeutic areas. Its bicyclic structure, consisting of a benzene ring fused with an imidazole, enables strong interactions with biomolecular targets via hydrogen bonding, π-π stacking, and hydrophobic interactions. Benzimidazole derivatives have been extensively explored as anthelmintic agents, antifungal drugs, antivirals, anticancer agents, and proton pump inhibitors. This review provides a comprehensive overview of benzimidazole-based drugs, focusing on their pharmacological actions, clinical applications, mechanisms of action, and structural modifications that have contributed to their therapeutic potential. Special emphasis is placed on FDA-approved benzimidazole drugs such as albendazole, mebendazole, thiabendazole, omeprazole, lansoprazole, rabeprazole, and benomyl, among others. The review also discusses challenges, safety concerns, drug resistance, and the future potential of benzimidazole scaffolds in precision medicine.

Keywords: PPIs, anthelmintic, antifungal, antiviral, anticancer

1. Introduction
The benzimidazole nucleus is one of the most versatile scaffolds in medicinal chemistry. It is a bicyclic heteroaromatic ring system formed by the fusion of benzene and imidazole. The two nitrogen atoms in the imidazole moiety act as hydrogen bond donors and acceptors, facilitating interactions with enzymes, receptors, and nucleic acids [1].
Historically, benzimidazole derivatives were first identified in the late 19th century, but their pharmacological importance became evident in the 20th century when thiabendazole and mebendazole were developed as anthelmintics [2]. Since then, benzimidazoles have diversified into several therapeutic domains, including antiulcer therapy with the discovery of omeprazole, the first Proton Pump Inhibitor (PPI), and oncology with drugs targeting microtubules and kinases [3]. The privileged status of benzimidazole in drug discovery arises from the structural similarity to purines and nucleotides, ability to form multiple hydrogen bonds with biological macromolecules and synthetic feasibility for substitution at C-2, C-5, and N-1 positions to modulate pharmacological activity.
This review compiles all clinically relevant benzimidazole-based drugs, their mechanisms of action, clinical indications, and future perspectives.

2. Chemistry and Structural Features of Benzimidazoles
Benzimidazole represents a privileged bicyclic heteroaromatic scaffold consisting of a benzene ring fused with an imidazole moiety. This unique structural motif imparts both aromatic stability and the ability to participate in hydrogen bonding and π-π stacking interactions, making benzimidazoles attractive for drug discovery across multiple therapeutic domains [4].

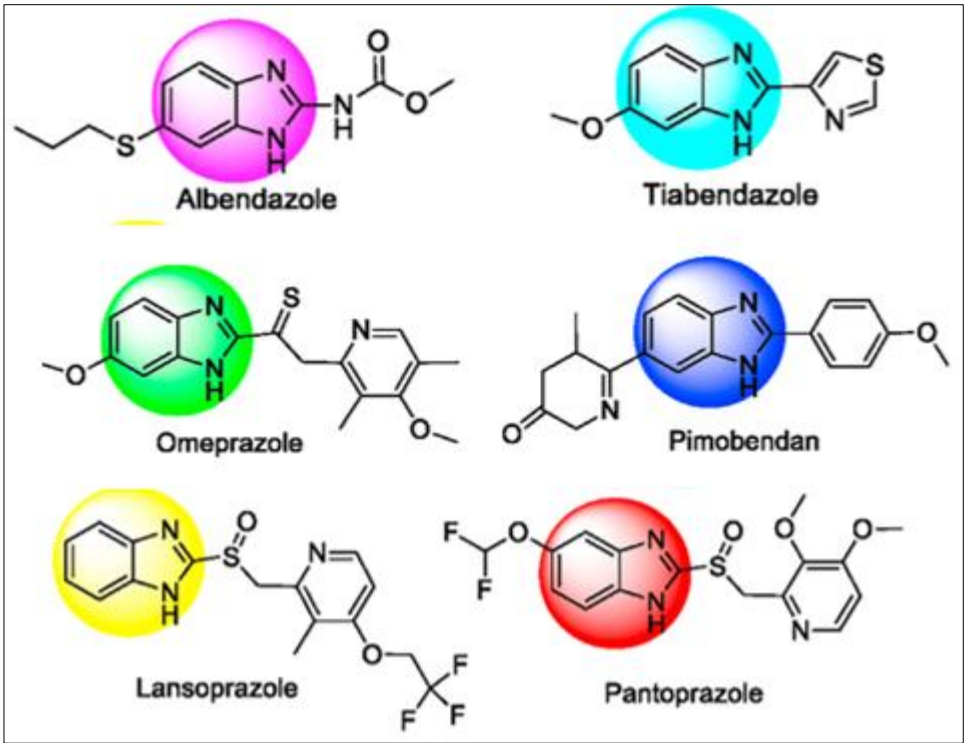

Fig 1: Approved Benzimidazole drugs (Antihelmintic & Antiulcer agents)

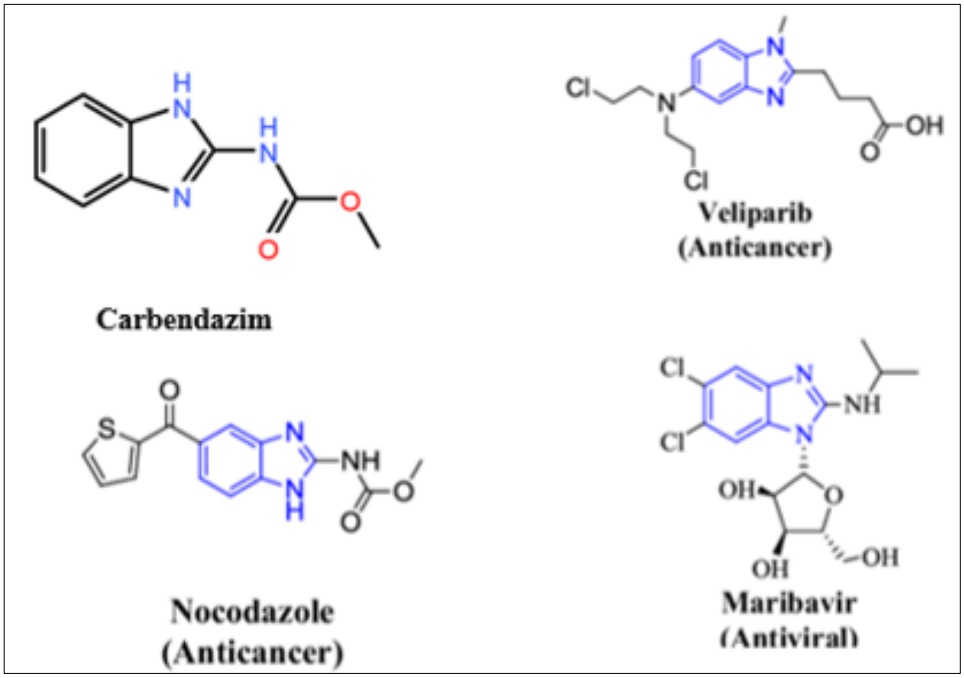

Fig 2: Approved Benzimidazole drugs (Anticancer & Antiviral agents)

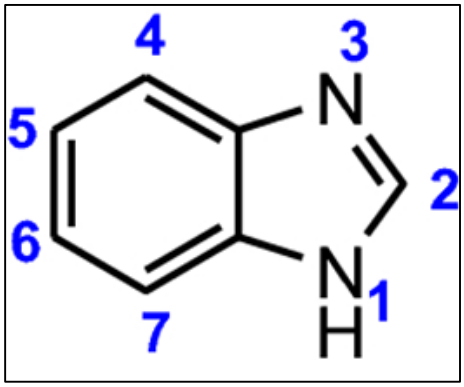

Fig 3: Structure of Benzimidazole

2.1 Several key structural features modulate pharmacological activity:

- **C-2 substitutions:** Introduction of alkyl, aryl, or heteroaryl groups at the C-2 position significantly influences binding affinity toward enzymatic and receptor targets. For instance, aryl substitutions have been shown to enhance antiparasitic potency, while heteroaryl groups improve kinase inhibition potential.
- **C-5 and C-6 substitutions:** Electron-donating or withdrawing groups at these positions modulate solubility, bioavailability, and pharmacokinetic stability. Nitro- and halogen-substituted derivatives at C-5/C-6 often display enhanced antimicrobial and anticancer activity.
- **N-1 substitution:** Substituents on the N-1 atom modify lipophilicity, permeability, and metabolic resistance. N-alkyl benzimidazoles, for example, show improved oral bioavailability compared to their unsubstituted analogues.

An additional fascinating feature is the structural resemblance of benzimidazoles to purine bases (adenine and guanine). This similarity facilitates recognition by enzymes and receptors associated with nucleic acids, accounting for their efficacy in antiviral therapy, DNA-interactive anticancer agents, and kinase inhibitors [4].

3. Pharmacological Classes of Benzimidazole-Based Drugs

Benzimidazole scaffolds have yielded a wide range of clinically successful agents, spanning anthelmintic, antifungal, antiulcer, antiviral, and anticancer categories. Their versatility arises from the scaffold's ability to interact with diverse biological targets.

3.1 Anthelmintic Drugs

The introduction of benzimidazole derivatives transformed the treatment of helminthic infections, offering orally active, broad-spectrum antiparasitic drugs.

- **Mechanism of action:** These agents act primarily by binding to β-tubulin in parasitic cells, preventing microtubule polymerization. Since microtubules are essential for glucose uptake, their disruption causes glycogen depletion, impaired ATP synthesis, and eventual parasite death [5]. This selective mechanism spares mammalian cells due to structural differences in tubulin isoforms.

3.2 Approved Anthelmintics

- **Albendazole:** Broad-spectrum drug effective against intestinal helminths (e.g., Ascaris, hookworm, Trichuris) and tissue parasites (e.g., hydatid disease, neurocysticercosis). Albendazole also demonstrates experimental anticancer activity by destabilizing microtubules in tumor cells.
- **Mebendazole:** Widely prescribed for soil-transmitted helminths, including Trichuris trichiura and hookworm. Mebendazole is well tolerated and has been explored for repurposing in oncology.
- **Thiabendazole:** One of the earliest agents used in strongyloidiasis; however, gastrointestinal side effects limited its long-term application.
- **Fenbendazole and Oxfendazole:** Predominantly veterinary anthelmintics, used against gastrointestinal nematodes in livestock. Fenbendazole has attracted research interest for its potential anticancer effects in humans.

Thus, benzimidazole anthelmintics remain essential in both human and veterinary medicine, while their mechanism of disrupting tubulin continues to inspire cancer drug discovery.

3.3 Antifungal Benzimidazoles

Apart from their antiparasitic activity, benzimidazoles also exhibit antifungal effects by interfering with fungal microtubule assembly.

- Mechanism of action: Benzimidazole antifungals inhibit fungal β-tubulin polymerization, leading to mitotic arrest and growth inhibition.
- **Representative agents**
  - **Carbendazim:** A systemic fungicide widely used in agriculture for crop protection.
  - **Benomyl:** Another fungicide that undergoes in vivo conversion to carbendazim.

Although these compounds are not employed in clinical medicine, their structural features provided valuable insights for medicinal chemistry, guiding the design of antifungal scaffolds and broadening the understanding of benzimidazole-tubulin interactions.

3.4 Proton Pump Inhibitors (PPIs)

The discovery of benzimidazole-derived proton pump inhibitors (PPIs) revolutionized the treatment of acid-related disorders such as peptic ulcer disease and gastroesophageal reflux disease (GERD).

- **Mechanism of action:** PPIs are administered as prod rugs. Once absorbed, they are activated within the acidic canaliculi of gastric parietal cells. The activated sulphonamide form irreversibly binds to cysteine residues of the gastric H^+/K^+ ATPase enzyme, suppressing gastric acid secretion for prolonged periods [6].
- **Approved PPIs**
  - **Omeprazole:** The first marketed PPI; remains widely prescribed.
  - **Esomeprazole:** The S-enantiomer of omeprazole, designed for improved pharmacokinetics.
  - **Lansoprazole:** Effective with rapid onset; available in orally disintegrating formulations.
  - **Pantoprazole:** Exhibits favourable drug-drug interaction profile; commonly used in hospitalized patients.
  - **Rabeprazole:** Distinguished by rapid activation and potency.

These PPIs are among the most successful benzimidazole drugs in terms of clinical and commercial impact, demonstrating the scaffold's adaptability beyond anti-infective therapy.

3.5 Antiviral and Anticancer Applications

The purine-like structure of benzimidazoles lends itself to antiviral and anticancer drug design.

- **Antiviral agents**: Ribavirin, a triazole-carboxamide nucleoside analog with structural resemblance to benzimidazole, has long been used in hepatitis C

treatment. Several benzimidazole derivatives are being explored as inhibitors of viral proteases and polymerases against influenza, HIV, and coronaviruses [7].

- **Anticancer activity**: Benzimidazoles demonstrate multiple anticancer mechanisms:
  - **Tyrosine kinase inhibition:** Substituted benzimidazoles serve as ATP-competitive inhibitors for kinases such as EGFR and VEGFR.
  - **DNA intercalation and topoisomerase inhibition:** Certain derivatives bind DNA, impairing replication and transcription.
  - **Apoptosis induction:** Benzimidazole compounds can activate caspase-dependent pathways, enhancing tumor cell death.
  - **Microtubule destabilization:** Similar to their anthelmintic mechanism, benzimidazoles impair mitotic spindle function in tumor cells.

Notably, albendazole and mebendazole have been investigated in preclinical oncology studies, showing activity against colorectal, breast, and lung cancers through microtubule disruption and antiangiogenic effects.

4. Clinically approved Benzimidazole drugs and their pharmacological actions

Benzimidazole derivatives have successfully translated from chemical scaffolds into clinically approved drugs spanning anthelmintic, antifungal, gastroprotective, and anticancer applications. Their clinical utility stems from structural versatility, safety, and multitarget pharmacology. Below is a detailed review of approved benzimidazole-based drugs and their mechanisms.

Table 1: Approved benzimidazole drugs and their pharmacological actions

Drug	Pharmacological Action	Primary Use
Albendazole	Inhibits β-tubulin polymerization	Anthelmintic, anticancer(investigational)
Mebendazole	Disrupts microtubules	Anthelmintic, anticancer (repurposing)
Thiabendazole	Anthelmintic, antifungal	Strongyloidiasis, mycoses
Flubendazole	Anthelmintic, anticancer (repurposing)	Helminths, leukaemia
Omeprazole	Irreversible PPI	Peptic ulcers, GERD
Esomeprazole	S-isomer of omeprazole	GERD, erosive esophagitis
Pantoprazole	PPI with high oral stability	GERD, peptic ulcer
Rabeprazole	Rapid-acting PPI	Zollinger-Ellison syndrome
Lansoprazole	PPI with high bioavailability	Acid reflux, ulcer therapy
Maribavir	Antiviral	Cytomeg

5. Safety, Resistance and Limitations

Despite widespread clinical utility, benzimidazole drugs are constrained by resistance, side effects, and ecological issues

- **Helminth resistance**: A major limitation of albendazole and mebendazole is resistance, particularly due to point mutations in the β-tubulin gene (F200Y, F167Y, E198A), which reduce drug binding.
- **Adverse effects:** Albendazole has been linked with hepatotoxicity and bone marrow suppression, while mebendazole can cause leukopenia and teratogenicity. PPIs such as omeprazole and lansoprazole are associated with long-term risks, including hypomagnesemia, renal toxicity, and increased infection susceptibility [16].
- **Drug interactions:** PPIs undergo hepatic metabolism via CYP2C19 and CYP3A4, leading to significant drug-drug interactions, particularly with clopidogrel and anticoagulants.
- **Environmental concerns:** Fungicides like carbendazim persist in soil and aquatic systems, raising ecotoxicological risks [15].

6. Future Directions

The versatility of the benzimidazole scaffold ensures its continued relevance in drug discovery. Future perspectives include:

- **Scaffold optimization:** Rational modifications at C-2 and N-1 positions improve lipophilicity, solubility, and binding specificity.
- **Hybrid molecules:** Combining benzimidazole with pharmacophores such as quinazolines, triazoles, or oxadiazoles has shown enhanced anticancer and antimicrobial effects [17].
- **Drug repurposing:** Drugs like fenbendazole are being re-evaluated in oncology, while PPIs such as omeprazole demonstrate multidrug resistance reversal in cancer therapy [17].
- **Nanotechnology-based delivery:** Nano formulations of albendazole and mebendazole show enhanced bioavailability, reduced toxicity, and improved targeting in preclinical models [17].
- **Personalized medicine:** Genetic profiling of β-tubulin polymorphisms and CYP450 alleles could guide precision dosing of benzimidazole-based therapies in parasitic and gastric disorders.

7. Conclusion

Benzimidazole-based drugs span a wide range of therapeutic areas, from infectious diseases to cancer and gastroenterology. Their success stems from their structural flexibility, biological compatibility, and synthetic accessibility. Despite challenges such as resistance and safety concerns, benzimidazole scaffolds remain invaluable in medicinal chemistry. Continued scaffold hybridization, nanotechnology approaches, and drug repurposing will likely yield the next generation of benzimidazole-based therapeutics.

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