"TECHNOLOGY-DRIVEN STRATEGIES FOR EXPLORING THE PHARMACEUTICAL APPLICATIONS OF BENZIMIDAZOLES"

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Abstract:

The bicyclic heteroaromatic compound benzimidazole is an extremely versatile scaffold in medicinal chemistry because of its amphoteric nature and electron-rich structure. The combination of an imidazole moiety and a benzene ring result in notable functionalisation flexibility, solubility tunability, and chemical stability. Environmental sustainability and benzimidazole derivative production efficiency have been improved by a variety of synthetic routes, including green chemistry techniques like solvent-free conditions and solid-phase catalysis. Resonance stabilisation and tautomerization also contribute to its acidic nature and chemical reactivity. With antimicrobial, antiviral, antifungal, anti-inflammatory, anticancer, antineoplastic, analgesic, and antiulcer properties, benzoimidazole derivatives have a wide range of pharmacological activities. The reason for these bioactivities is their interaction with biological targets like receptors, enzymes, and microtubules. Drugs such as carbendazim, nocodazole, pantoprazole, maribavir, and pimobendan demonstrate the clinical significance of this scaffold in a number of therapeutic domains. This review highlights benzimidazole derivatives varied biological functions, structural traits, and synthetic processes, highlighting their ongoing importance in drug development and discovery.

Key words: Benzimidazole, heterocyclic compounds, synthesis, biological activity, antimicrobial, anticancer, anti-inflammatory, antifungal, antiviral, analgesic, antiulcer, drug design, tautomerization, green chemistry

Introduction:

Benzimidazole is a bicyclic heteroaromatic compound with an amphoteric property, consisting of bicyclic structure consisting of a benzene ring and an imidazole ring fused together [1]. Its structure is useful for optimising drug candidates because it exhibits a notable electron-rich heterocyclic pharmacophore. Research has shown that adding a substituent at the 1-position lowers the melting point of a variety of benzimidazole derivatives [2]. Two nitrogen atoms give benzimidazole derivatives their polar properties. Their solubility in organic media and polar solvents is typically improved by this polarity. The benzimidazole ring can have non-polar substituents added at different locations to increase solubility in non-polar solvents. Benzimidazole, on the other hand, becomes more acidic when polar groups are added, which makes it dissolve in aqueous alkali solutions. [3] This characteristic is essential. Metal-catalyzed cyclisation reactions are effective methods for creating nitrogen-containing heterocycles like imidazole; the resulting ion's stability through resonance is what gives benzimidazole its acidic nature. Benzimidazole becomes more acidic and dissolves more readily in water when it is in a weak basic solution, such as K2CO3. Enhancing the benzimidazole cycle with functional groups at the location of a molecule's functional groups has a significant impact on its physical characteristics, such as its melting point and solubility in polar and organic 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 [4,5].

The chemical formula for benzimidazole is $C_7H_6N_2$, and its molecular weight is 118.14 g/mol. Benzoglyoxaline, 1,3-benzodiazole, o-benzimidazole, 3-azaindole, and 1H-benzimidazole are some of its other names. The low water solubility of benzimidazole can have a major effect on its absorption [6]. Benzimidazole has both basic and acidic characteristics. Its NH group is both weakly basic and strongly acidic. The basic character of the pyrrole nitrogen at position 1 (N-H group) is as follows: pKa = 10.24 and can undergo replacement reactions with various other reactive groups [7,8].

At position three, pyridine has a nitrogen atom. This nitrogen atom can create coordination bonds with transition metal ions because of its ion pair of electrons, which act as a proton acceptor. Additionally, the tautomerization process between the nitrogen atoms at positions 1 and 3 depends critically on the carbon atom at position 2, which exhibits Sp2 hybridization. Figure 1. [9,10]

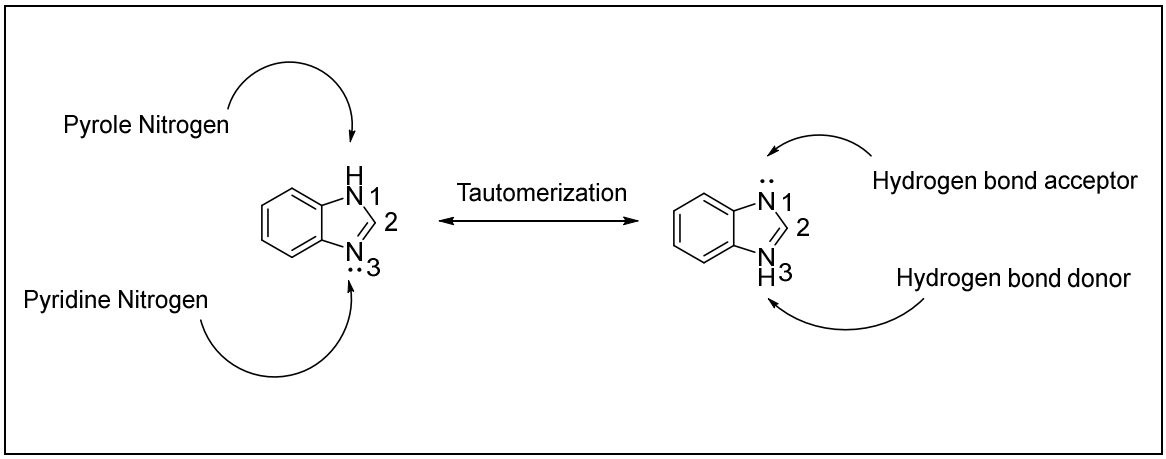
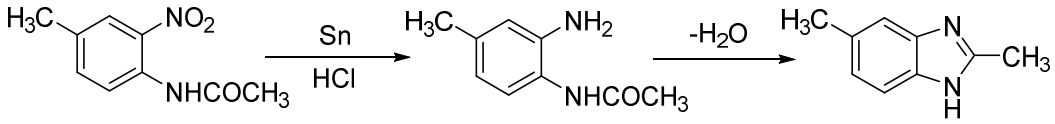


Fig (1): Benzimidazole Tautomerization

Benzimidazole can form salts. Non-polar substituents (H_2, N_2, Cl_2) can be added to the benzimidazole ring at different locations to increase solubility in non-polar solvents. Outstanding stability is exhibited by the benzimidazole ring. Alkali treatment, hot hydrochloric acid treatment, and concentrated sulphuric acid treatment have no effect on it. In general, the benzene ring of benzimidazole resists oxidation. But oxidation can happen in certain situations, which could break the ring structure. Generally speaking, the benzimidazole ring keeps its structural integrity. However, its structural stability may decline under specific conditions. Benzimidazole has a high boiling point; during distillation, it usually reaches over 300°C [11-12].

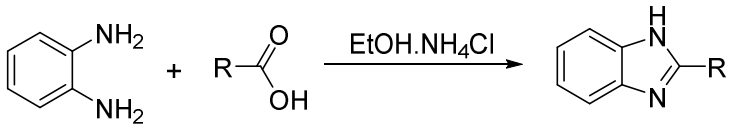
General procedure for the synthesis of benzimidazole:

Hoebrecker, also known as Wright, created the benzimidazole ring system for the first time in 1872 by two-step reduction and dehydration of 2-nitro-4-methyl acetanilide [13-14].



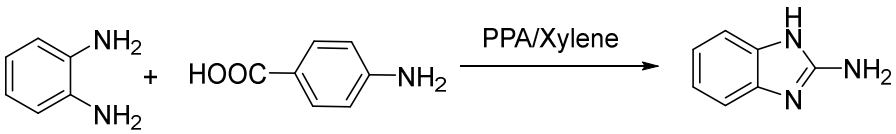
Scheme 1: Synthesis benzimidazole from 2-nitro,5-dimethyl acetanilide

In ethanol (Scheme 2) [15], diluted mineral acid facilitates the condensation of carboxylic acids with 1,2-diaminobenzene derivative and ammonium chloride (NH4Cl) as a catalyst. Polyphosphoric acid (Scheme 3) [16] and o-phosphoric acid [17] (Scheme 4) are then used to create benzimidazole compounds. First reported in 1875, the process is called the Phillips-Ladenburg reaction.



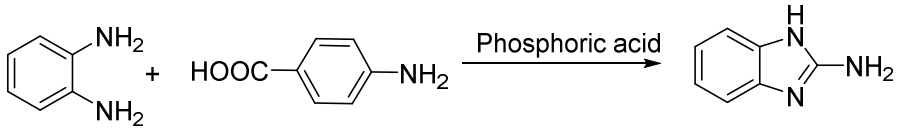
R= 4-OHC_6H_4, 2-ClC_6H_4, Ph, 2-OHC_6H_4, 4-ClC_6H_4

Scheme 2: Benzimidazole preparation by Ammonium Chloride catalyst



PPA= Polyphosphoric acid

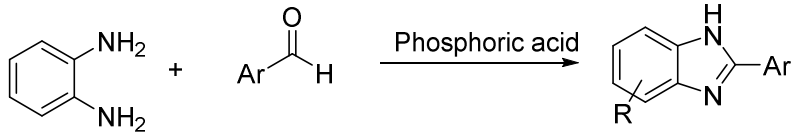
Scheme 3: Benzimidazole preparation by Polyphosphoric acid



Scheme 4: Benzimidazole preparation by phosphoric acid

Dehydration happened during this process, hence the term "anhydrous base." o-phenylenediamine (OPDA) is the source of benzoglyoxaline, another name for benzimidazole. [15-18]

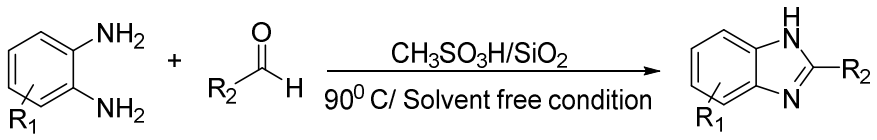
Benzimidazole was successfully synthesised using sodium metabisulphite (SBM) adsorbed on silica gel as an environmentally friendly reagent. Compared to conventional techniques, the immobilised SBM on silica gel promotes a quicker and more effective reaction. The use of costly and possibly hazardous chemicals is greatly decreased by using this green chemistry strategy. This process makes large amounts of benzimidazole, an essential component of pharmaceutical compounds, accessible [20].



Ar = Ph, R=CH_3, CH_2CH_3, OCH_3, Cl, Br, OCH_2CH_3

Scheme 5: Synthesis of Benzimidazole with sodium metabisulfite adsorbed on silica gel in ethanol

Solid-phase organic methane sulfonic acid-silica catalyses the reaction of ortho-phenylenediamine with different aldehydes at 90°C without the use of solvents, providing a simple and quick method for producing benzimidazole derivatives. [21]



Scheme 6: Synthesis of substituted benzimidazoles catalysed by Methanesulphonic acid-silica under solvent free condition at 90^0 C

Biological activity for Benzimidazole derivatives:

The important nitrogen-containing heterocyclic compound benzoimidazole is used extensively in organic synthesis and has a variety of medicinal uses [22]. Numerous pharmacologically active compounds are based on the fundamental framework provided by the benzimidazole nucleus, a crucial heterocyclic ring system. Numerous medications, including anti-helminthic, anti-ulcer, cardiotonic, antihypertensive, antibacterial, antifungal, anti-allergic, anti-neoplastic, local analgesic, anti-leishmanial, vasodilator, spasmolytic, antimicrobial, antitumor, antiviral, anti-inflammatory, anticancer, antioxidant, and antitubercular, have been developed and commercialised as a result of its derivatives' substantial therapeutic potential across a variety of disease areas [23-35].

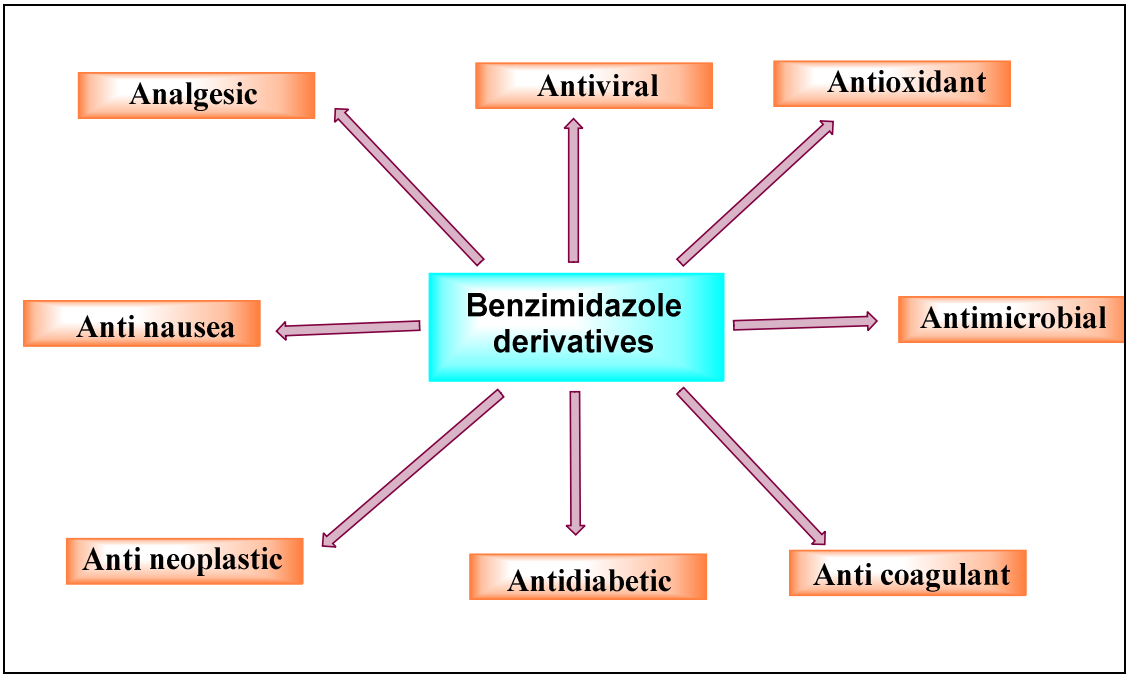
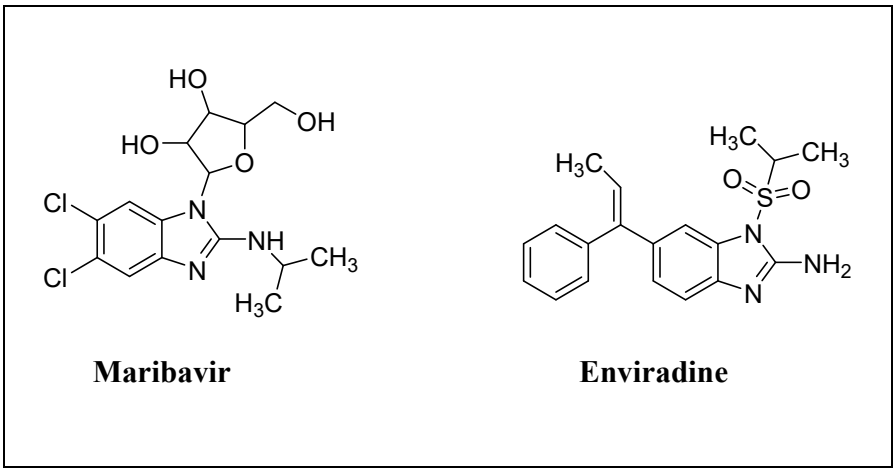


Fig 2: Biological activity for benzimidazole derivatives

Pharmacologically Active Compounds Containing a Benzimidazole Core

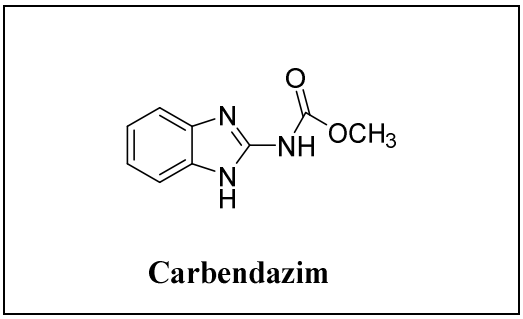
- **As an oral antiviral:** Antivirals are a class of drugs that are used to treat infections caused by viruses. HIV, influenza, hepatitis, herpes, and cytomegalovirus are among the viruses they target. One important example of this class of drugs is the antiviral drug maribavir, which contains enviradine a benzimidazole.



Maribavir **Enviradine**

Fig 3: Benzimidazole derivatives as oral antiviral

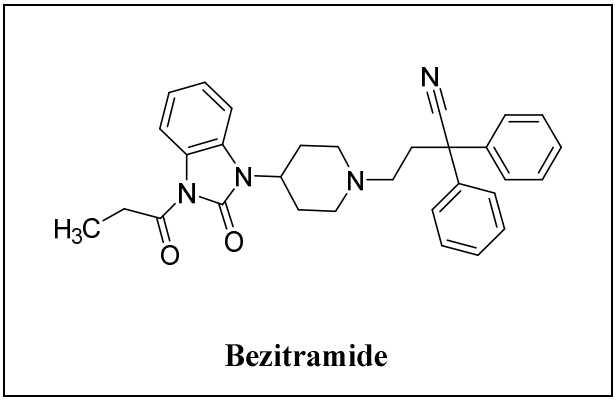
- **As fungicidal:** Benzimidazoles, especially their derivatives, have the ability to kill or inhibit a variety of fungal species. Because of their broad-spectrum activity and ability to effectively treat both systemic and superficial fungal infections, benzimidazoles are useful tools in the development of new antifungal medications. Their mode of action frequently involves interfering with essential cellular processes. One well-known example of an antifungal medication based on benzimidazoles is carbendazim.



Carbendazim

Fig 4: Benzimidazole derivatives as fungicidal

- **As analgesic:** Bezitramide is a strong analgesic and anaesthetic. This drug can undergo substantial gastrointestinal tract metabolism, mainly into despropionyl-bezitramide, its primary metabolite. Fig (5).



Bezitramide

Fig 5: Benzimidazole derivatives as Analgesic

- **As anti-neoplastic:** Nocodazole, a crucial anti-tumour agent, works therapeutically by directly disrupting human cell microtubule polymerisation, as demonstrated by a marked decrease in microtubule formation. Figure (6).

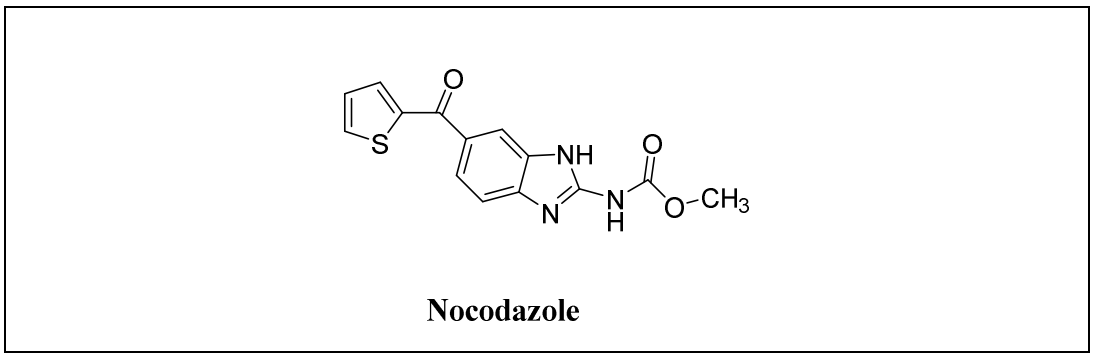


Fig 6: -Benzimidazole derivative as anti-Neo plastic

- **As an antiulcer drug:** Proton pump inhibitors (PPIs) are a class of drugs that are commonly used to treat ulcerative disorders, erosive gastro-oesophageal reflux disease (GERD), and duodenal ulcers in the short term. PPIs include, for example, pantoprazole, lansoprazole, omeprazole, and rabeprazole. Figure (7)

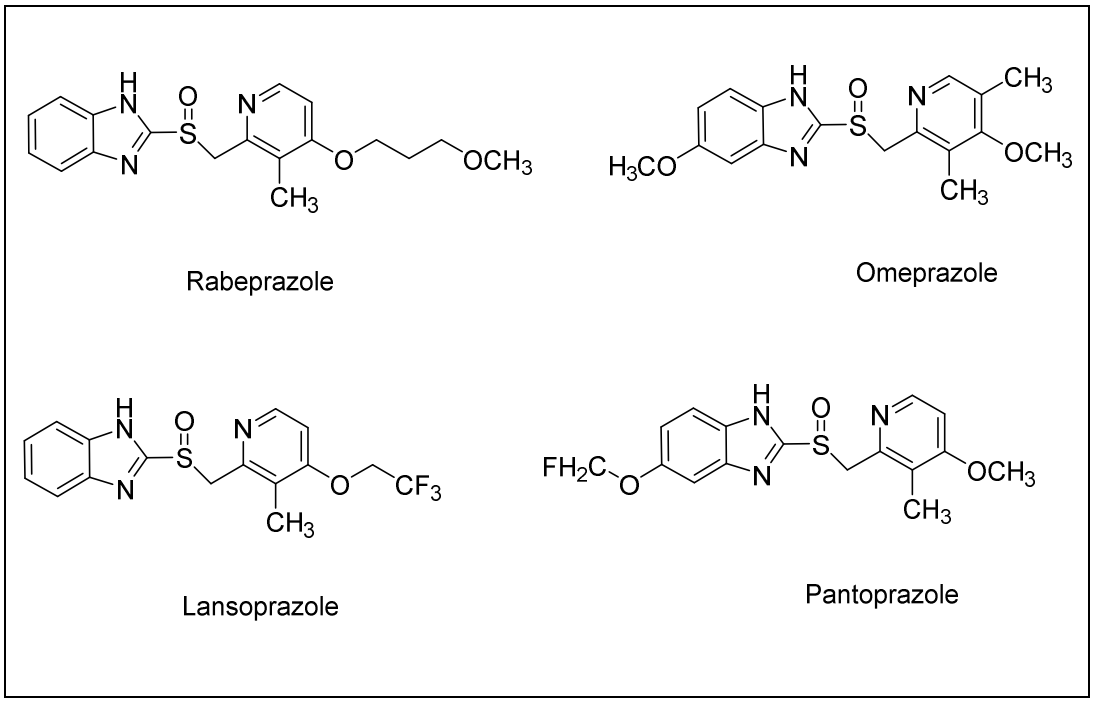


Fig 7: Benzimidazole derivatives as anti-Ulcer drug

- **As calcium sensitizer:** Pimobendan, a calcium sensitizer, improves heart function by increasing the force of muscle contractions. Fig (8).

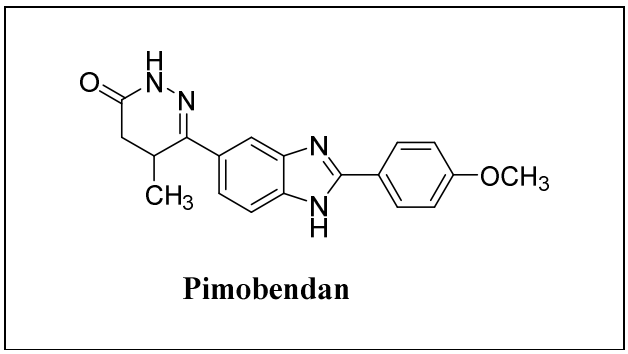


Fig 8: Benzimidazole derivative as Calcium sensitizer

- **As oral antidiabetic:** Type 2 diabetes is a disorder involving insulin resistance, secreted during the treatment phase like Rivoglitazone. Fig (9).

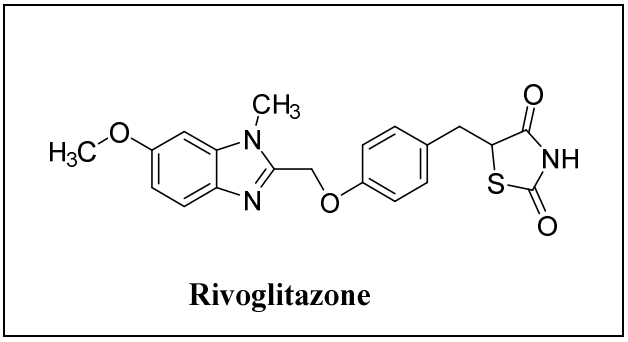


Fig 9: Benzimidazole derivative as oral anti Diabetic

- **As anti-psychotic:** Benzimidazole-containing medications are frequently used to treat mental illnesses such as chronic psychosis and schizophrenia. Benperidol, pimozide, and droperidol are important examples. Fig. 10.

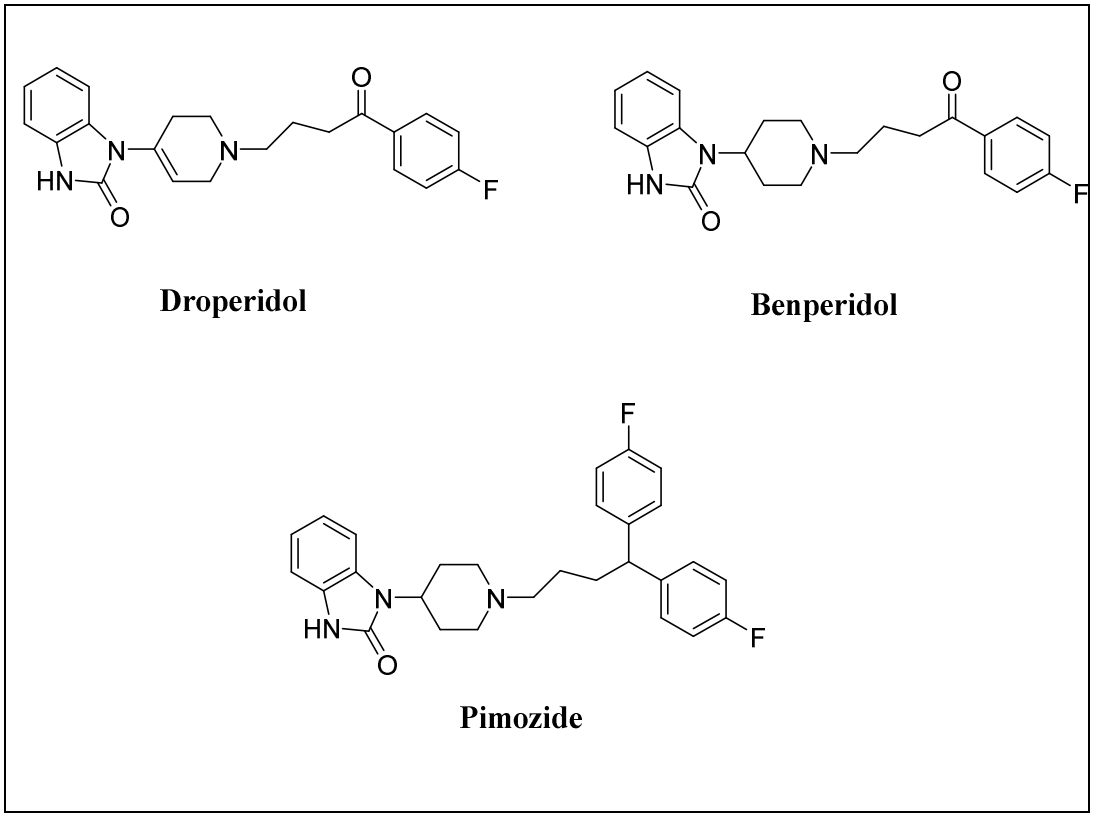


Fig 10: Benzimidazole derivatives as anti-Psychotic

- **As oral anticoagulants:** Dabigatran is a premium oral anticoagulant with a direct mechanism of action, specifically inhibiting thrombin. Fig (11).

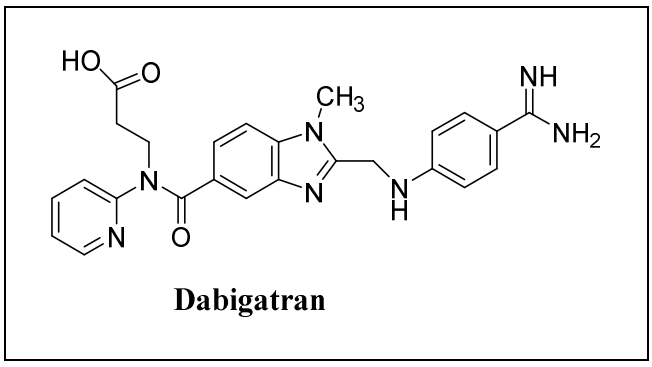
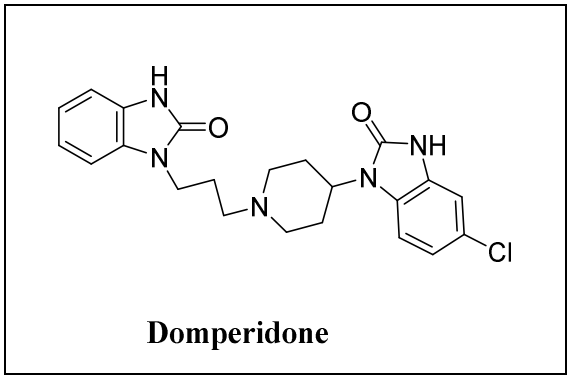


Fig 11: Benzimidazole derivative as oral anti Coagulants

- **As anti-nausea:** One example of a benzimidazole-containing drug is dopidemone, which is mainly used to treat nausea and vomiting. It helps to relax the muscles in the

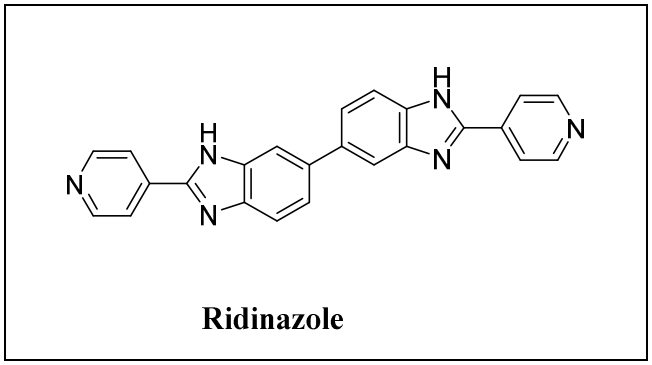
stomach and accelerate the passage of food through the intestines by blocking dopamine receptors in the digestive system. Figure (12).



Domperidone

Fig 12: Benzimidazole derivative as anti-Nausea

- **As Antibacterial:** Antibacterial 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. Fig (13).



Ridinazole

Fig 13: Benzimidazole derivative as anti-Bacterial

Conclusion: The diverse structure, chemical stability, and broad range of biological activities, including antimicrobial, anticancer, antiviral, and anti-inflammatory effects, make benzimidazole derivatives useful scaffolds in medicinal chemistry. They are crucial to drug development because of their capacity to interact with important biological targets. Benzimidazoles have a great deal of promise for upcoming pharmaceutical advancements

due to their effective synthetic techniques, including green chemistry approaches, and established clinical relevance.

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