IASR J. Med. Pharm. Sci.
ISSN: 2582-9343
Website: https://ijmps.com/
Open Access Journal
Country: India

IASR Journal of
Medical and
Pharmaceutical Science

REVIEW ARTICLE OPEN ACCESS

Synthesis and Pharmacological Activity of Benzimidazole as Antifungal Agents

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Received: 05 March 2026
Revised: 28 March 2026
Accepted: 12 April 2026
Published: 28 April 2026

ABSTRACT

Heterocyclic compounds are cyclic compounds with one or more atoms of other elements in addition to carbon. Heteroatoms are non-carbon atoms like these rings. The most prevalent heteroatoms are oxygen, sulfur, and nitrogen. A benzene ring (B) is fused to the 4 and 5 positions of an imidazole ring (C) to form benzimidazole (A), a fused aromatic imidazole ring system. Another name for benzimidazoles is 1,3-benzodiazoles. A family of bioactive substances with significant use in the pharmaceutical industry is benzimidazole and its derivatives. Benzimidazole Derivatives' Antifungal Action Mechanism through a variety of ways, benzimidazole derivatives demonstrate their antifungal actions, frequently impacting vital fungal cellular functions. Different medicinal uses for substituted benzimidazole derivatives include anti-histaminic, anti-ulcer, anti-psychotic, and antifungal properties. Numerous medications are already available on the market as a result of the optimization of benzimidazole-based structures. Benzimidazole fungicides are a broad-spectrum, extremely effective fungicide that significantly reduces a range of crop diseases.

Key Words: *Heterocyclic Chemistry, Benzimidazole, Synthesis, Pharmacological Activity, Disease Prevention and Control*

Introduction

Heterocyclic Chemistry

Heterocyclic compounds are cyclic compounds with one or more atoms of other elements in addition to carbon. Heteroatoms are non-carbon atoms like these rings. The most prevalent heteroatoms are oxygen, sulfur, and nitrogen. In recent years, a lot of research has been done on heterocyclic compounds with less frequent atoms including phosphorus, tin, boron, silicon, bromine, etc. Heterocyclic rings are present in a number of significant substances, such as the majority of vitamin B complex members, alkaloids, antibiotics, chlorophyll, other plant pigments, amino acids, dyes, medications, enzymes, genetic material, DNA, etc. Below is a list of some of the fundamental rings of heterocyclic compounds [1].

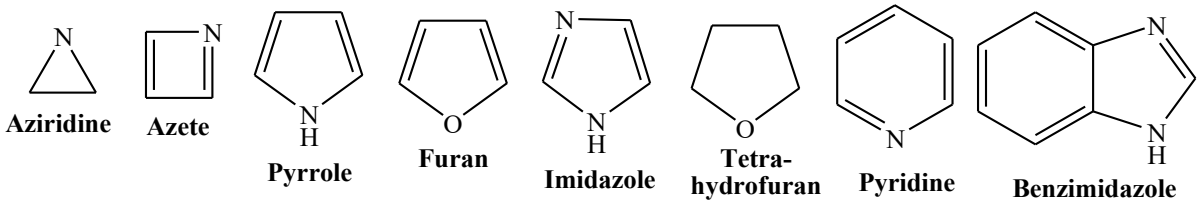


Figure: 1. Heterocyclic Compounds

Benzimidazole

A benzene ring (B) is fused to the 4 and 5 positions of an imidazole ring (C) to form benzimidazole (A), a fused aromatic imidazole ring system. Another name for benzimidazoles is 1, 3-benzodiazoles [2].

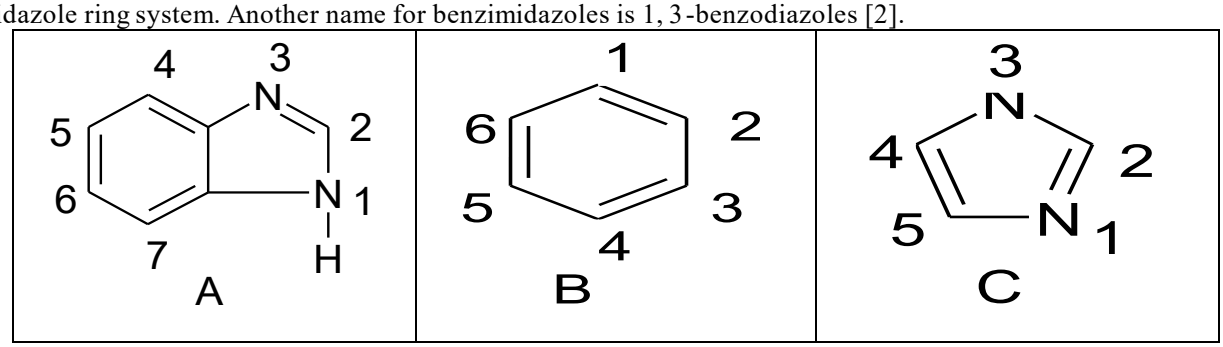


Figure: 1. Chemical Structure of Benzimidazole, Benzene and Imidazole.

One of the fundamental organic elements used in the synthesis of various organic molecules, including medications, is heterocyclic compounds. Because they include heteroatoms and have a wide range of characteristics, heterocyclic compounds are extremely difficult classes in chemistry.

Heterocyclic compounds are crucial not only in human life, where they play a significant role, but also in a variety of industrial uses, medicine, agriculture, and the synthesis of other organic chemicals and polymers.

Numerous heterocyclic compounds, such as hypnotics, anticonvulsants, anti-tumors, antihistamines, antiseptics, and antifungals, are also employed as medications [3,4,5,6,7,8,9].

Benzimidazole has been employed as a pharmacophore in a number of drug development procedures to increase the value of pharmacological activity [10]. It is the most fundamental and widely utilized of the top five hetero-aromatic five-membered nitrogen-containing pharmacophores [11]. Benzimidazole is a very stable chemical that is unaffected by high temperatures or concentrated acid. For the oxidative cleavage, the ring is sufficiently stable [12].

A family of bioactive substances with significant use in the pharmaceutical industry is benzimidazole and its derivatives [13]. Imidazole, sometimes referred to as imidazoline, is a heterocyclic compound containing two nitrogen atoms divided by a single carbon atom that is categorized as an azapyrrole [14].

Because of their therapeutic qualities, imidazoles are highly significant heterocyclic chemicals that can be utilized to make a variety of medications. With the general formula $C_3H_4N_2$, imidazole is a planar hetero pentacyclic molecule that dissolves readily in polar liquids like water due to its predicted dipole of 3.61. It is an amphoteric substance that has both basic and acidic properties. Because a hydrogen atom can change from one nitrogen atom to another, imidazole can exist in two equivalent tautomeric forms: 1H-imidazole and 3H-imidazole [15,16].

Due to the presence of the sextet π-electron system, which consists of two electrons from the protonated nitrogen atom and the remaining electrons from the other four atoms in the ring, imidazoles are also regarded as aromatic compounds [17].

Because of their distinctive chemical and biological characteristics, benzimidazole derivatives represent a significant family of medications. Pharmacologists and medicinal chemists have been fascinated by them. These derivatives serve as the foundation for a wide range of pharmaceutical substances that can be used to treat a wide range of illnesses, from bacterial and fungal infections to chronic and complicated conditions like cancer and high blood pressure.

Because of their broad biochemical activity and structural adaptability, these compounds can effectively interact with a variety of biological systems, enabling them to function as multitarget medications [18].

Physical Properties

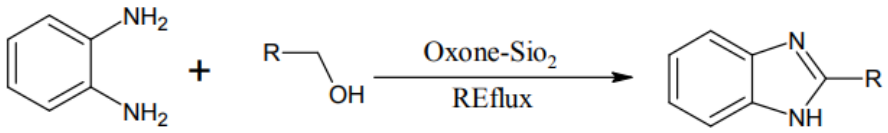
Amphotericity: Benzimidazole is amphotric in nature i.e. acts as acid and as a base.

Molecular Formula	$C_7H_6N_2$
Molecular Weight	118.14 g/mol
Melting Point	170 0C -172 0C
Activity (PKa)	12.8(for benzimidazole) & 5.6 (for the conjugate acid)

Chemical Properties

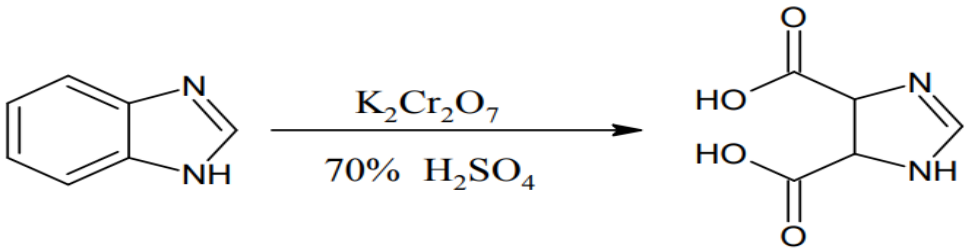
Benzimidazole undergoes following types of organic reactions:

1. **Addition Reaction:** When ethanol and silicon oxidation are present, O-phenylenediamine is added to create 2-methyl-1H-benzimidazole.



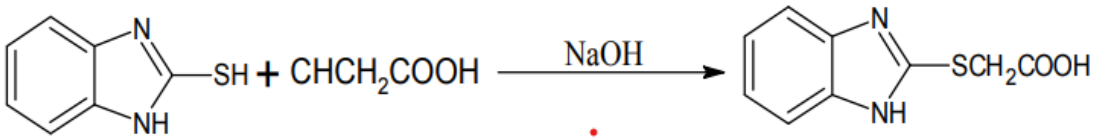
O-Phenylenediamine 2-Methyl-1H-Benzimidazole

2. **Oxidation Reaction:** Benzimidazole oxidation to produce a4, 5-dihydro-1H-imidazole-4, and 5-dicarboxylic acid in the presence of potassium dichromate and 70% H2SO4.



Benzimidazole 4, 5-Dihydro-1H-Imidazole -4, 5-DicarboxylicAcid

3. **Substitution Reaction:** 1H-benzimidazole-2-thiol substitution to produce [(1H-benzimidazole-2-yl) sulfanyl] acetic acid when carboxylic acid and NaOH are present [19].

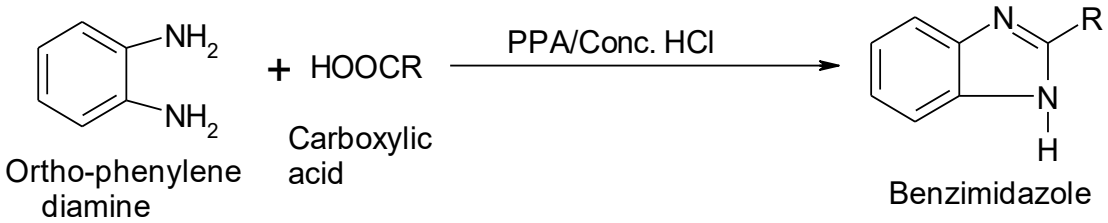


1H-Benzimidazole-2-Thiol [(1H-Benzimidazole-2-Yl) Sulfanyl] Acetic Acid

Synthesis Of Benzimidazoles

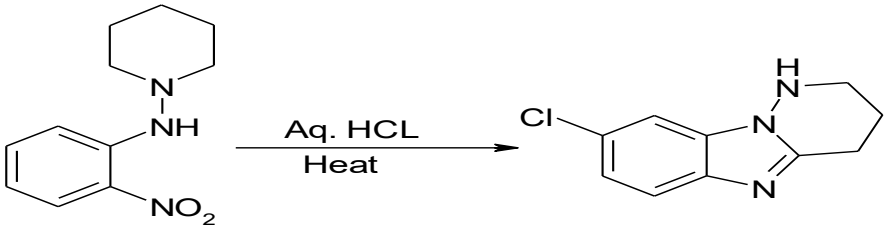
From reactions of o-Arylene Diamines with Carbonyl-Containing Compounds.

The most typical method for producing benzimidazoles is to react 1, 2-diaminobenzenes with carbonyl-containing substances (carboxylic acids, aldehyde, etc.) under severe dehydration reaction conditions using strong acids like hydrochloric acid and polyphosphoric acid.

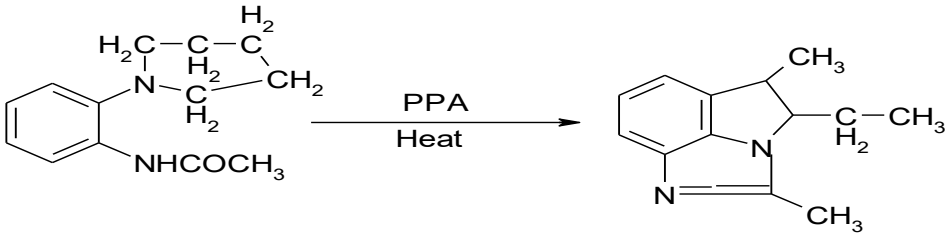


From o-Nitroarylamines and o-Dinitroarenes.

An acid-catalyzed cyclization reaction produces benzimidazole from o-nitroarylamines and o-diniotroarenes. This reaction occurs in aqueous hydrochloric acid under reflux conditions, cyclizing N-(o-nitroanilino)-substituted amines to N-aminobenzimidazoles.



From o-(N-Acylamino and -aroylamino) arylamines and –Nitrobenzenes:
Additionally, polyphosphoric acid is employed as a dehydrating agent in this cyclization reaction. Acetyl and piperidine derivatives provide the highest amounts of benzimidazoles [20].



Mechanism of Antifungal Action
Benzimidazole Derivatives' Antifungal Action Mechanism through a variety of ways, benzimidazole derivatives demonstrate their antifungal actions, frequently impacting vital fungal cellular functions. The target fungal species, hybridization with other pharmacophores, and the type of substituents all influence the exact process. Designing more effective and specific antifungal drugs requires a thorough understanding of these mechanisms.

Ergosterol Biosynthesis: Inhibition of ergosterol production, a crucial part of fungal cell membranes, is one of the main antifungal actions of benzimidazole derivatives. The fluidity, integrity, and functionality of membranes depend on ergosterol. It has been demonstrated that benzimidazole compounds, especially those with electron-withdrawing substituents or heterocyclic fusions, inhibit lanosterol 14α-demethylase (CYP51), the enzyme that converts lanosterol to ergosterol [21,22]. When CYP51 is inhibited, ergosterol is depleted and hazardous sterol intermediates build up, which causes membrane instability, stunted cell development, and fungal cell death.

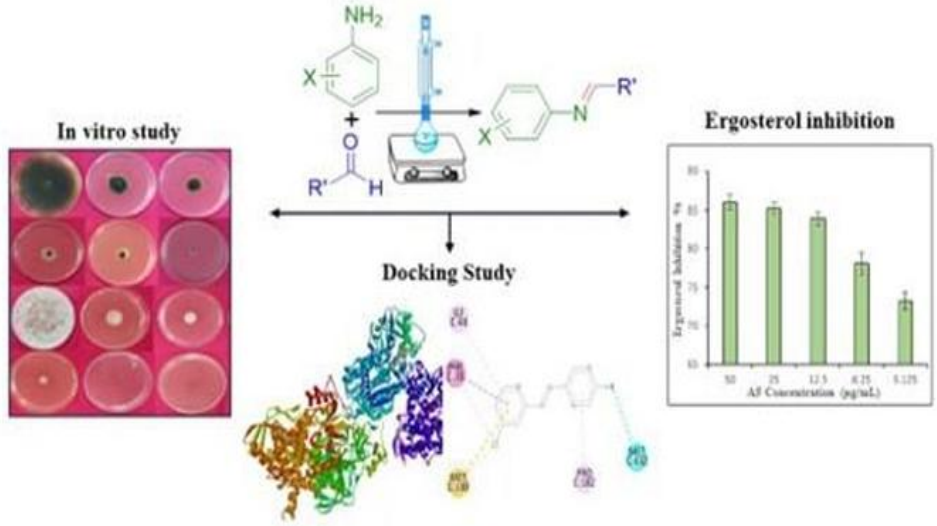


Figure: 3. Inhibition of Ergosterol Biosynthesis [21,22].

Membrane Disruption: Because of their lipophilic 2-position substituents, which make it easier for them to enter the lipid bilayer, benzimidazole derivatives can directly interact with fungal cell membranes. This interaction may enhance permeability, compromise membrane integrity, and cause cytoplasmic contents to seep out. Hybrid compounds that combine benzimidazole with other amphiphilic pharmacophores frequently exhibit increased membrane-disrupting activity, resulting in quick fungicidal effects [23]. Benzimidazole derivatives have the ability to block not only CYP51 but also other vital fungal enzymes including β-(1,3)-glucan synthase, which is crucial in the manufacture of cell walls.

These substances weaken the structural integrity and rigidity of cell walls by interfering with the formation of glucan polymers, making fungi more susceptible to osmotic stress and antifungal medications [24].

Because the benzimidazole nucleus is planar and electron-rich, it can interact with these enzymes' active sites through coordination, π–π stacking, and hydrogen bonding. Interaction with the Synthesis of DNA and RNA Benzimidazole derivatives' planar, heterocyclic core is similar to purine bases, which may enable intercalation or interaction with nucleic acids. Fungal replication and transcription activities may be further hampered by this interaction, which may prevent the synthesis of DNA or RNA. Numerous investigations indicate that benzimidazole hybrids may disrupt nucleic acid metabolism, which may contribute to their overall antifungal activity, even if this mechanism is not as well understood as ergosterol inhibition [25,26].

Pharmacological Activities

Different medicinal uses for substituted benzimidazole derivatives include anti-histaminic, anti-ulcer, anti-psychotic, and antifungal properties. Numerous medications are already available on the market as a result of the optimization of benzimidazole-based structures [27].

Antifungal

The robust antifungal activity of the developed derivatives has demonstrated the adaptability of the benzimidazole molecular framework. With notable levels of bioactivity, new analogues with tertiary amine, substituted benzimidazole, and triazole moieties have been created and tested against Candida albicans spores. Strong antifungal activity was demonstrated by the products. However, the development of more recent derivatives with enhanced antifungal action was prompted by the intrinsic toxicity of this class of drugs and the antibacterial resistance [28].

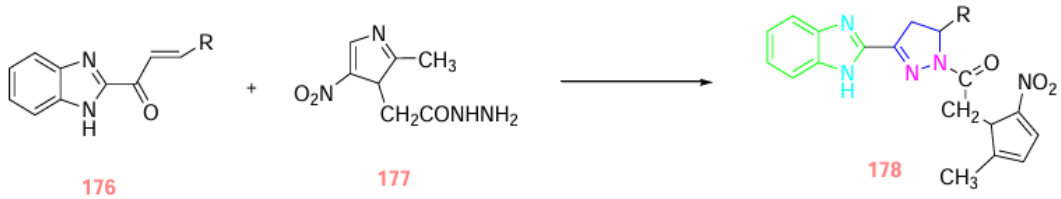
Anticancer

Cancer is the second most common cause of mortality globally. As a result, scientists have increasingly focused on creating substances that are highly effective as anticancer medications. High selectivity is necessary for effective anticancer medications to be toxic to cancer cells while having no effect on healthy cells. Anticancer medications that had previously been developed demonstrated strong toxic activity against cancer cells, but they also significantly affected normal cells. Chemotherapy for cancer patients is frequently stopped due to these side effects and the toxicity of anticancer medications.

Among all of this, heterocyclic compounds have frequently been found to be highly selective and side-effect-free anticancer medications. These benefits of anticancer medications have created a pressing need for humanity as well as a significant problem for researchers. It has been demonstrated that the benzimidazole derivatives are quite successful in this regard [29].

Antimalarial

The antimalarial activity of a new drug 1-[3-(1H-Benzoimidazol-2-yl)-4, 5-dihydro-pyrazol-1-yl]-2 (2-methyl-5-nitro-imidazol-1-yl)-ethanone was tested against dihydrofolate reductase. If the R group was replaced with a chlorophenyl group, the synthetic molecule was discovered to be more powerful [30].



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Scheme-51-Synthesis of 1-[3-(1H-Benzoimidazol-2-yl)-4,5-dihydro-pyrazol-1-yl]-2-(2-methyl-5-nitro-imidazol-1-yl)-ethanone.

R=2-chlorophenyl,4-fluorophenyl, 5styryl

Antiviral

Numerous investigations employing various virus strains, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), human cytomegalovirus (HCMV), and herpes simplex virus-1 (HSV-1), have demonstrated the antiviral capabilities of various benzimidazole derivatives [31].

Anti-Inflammatory Activity

The qualities of chemicals that lessen the consequences of inflammation in the body are referred to be "anti-inflammatory." In addition to relieving pain, many analgesics also have anti-inflammatory properties since they help to reduce inflammation, which in turn eliminates pain. When creating analgesic and anti-inflammatory medications that target approved medical targets for the treatment of pain and tissue inflammation, benzimidazoles are among the most

favoured pharmaceutical compounds. In a study by Sharma et al., a rat paw oedema model generated by carrageenan was used to examine a series of manufactured compounds. 5-methanesulfonamidobenzimidazole was one of the anti-inflammatory treatments that were examined; rofecoxib and indomethacin served as reference medications for comparison [32].

Anti-Plasmodial Activity.
BZ action in vitro. The HB3 strain of Pf was used to test all BZ derivatives at 10 μM. The IC50 values were calculated for those drugs that showed growth inhibition (% GI) greater than 50%. Additionally, their selectivity indexes (SI) were determined by assessing their cytotoxicity on epithelial Vero cell cultures [33].

Antiulcer Drug
These medications are used as a temporary treatment for duodenal ulcers, erosive or ulcerative gastroesophageal reflux disease (GERD), gastric ulcers (GU), peptic ulcer disease (PUD), Zollinger-Ellison syndrome, and Helicobacter pylori eradication to lower the risk of recurrent duodenal ulcers. Rabeprazole, Omeprazole, Lansoprazole, Pantoprazole, and other drugs have the benzimidazole nucleus. These drugs are members of the proton pump inhibitor class, which also includes omeprazole and rabeprazole [34].

Anti-Tubercular Activity
Tuberculosis (TB), a bacterial infection and disease caused by Mycobacterium tuberculosis (M. tuberculosis), is the second most common cause of death worldwide. Directly observed therapy short-course, or DOTS, is currently used to treat tuberculosis. It involves prescribing a combination of three to four medications for a period of six to twelve months. These include ethambutol, isoniazid, and other substances [35].

Antioxidant Activity
An antioxidant is a chemical that can lessen or stop the oxidation of free radicals, which can be fatal to an organism's cells. Free radicals will unavoidably occur since air-breathing organisms depend on the aerobic oxidation process, which is necessary for survival. These were recently freed. Radicals are exceedingly dangerous and can cause malfunction, malignant transformation, or cell death. Oxidative stress can damage DNA, lipids, and proteins. Chromosome rearrangements or genetic anomalies that cause malignant tumors, diabetes, dementia, and cardiovascular disease can be caused by DNA damage [36].

Antiproliferative Activity
Several sources suggest that modified aromatic aldehydes and two-aminobenzimidazole could be used to create novel Schiff bases. As an intermediate product, 2-benzylaminobenzimidazoles were created by reducing the compounds with NaBH4. These 2-benzyl aminobenzimidazoles were acylated with cinnamoyl chloride to create 2-(o-bromobenzyl amino)-1-cinnamoyl benzimidazole. This chemical has been linked to the emergence of autoimmune diseases. The compounds' antiproliferative properties were revealed by in vitro analysis [37].

Antibacterial Activity
The produced compounds were tested in vitro as antibacterial agents against Gram-positive (B. cereus/S. aureus) and Gram-negative (E. coli/K. pneumoniae) bacteria using the agar diffusion method. For all bacterial strains, the inhibitory zone in millimeters of the investigated drugs was compared to nitrofurantoin (300 μg/mL) as a reference, with DMSO serving as a negative control. **Table 1** summarizes the compounds' antimicrobial screening results. Depending on the type of substituent at the N-1 position of the benzimidazole nucleus, the antibacterial activity of all the produced derivatives ranged from moderate to good. Compounds 6e, 6f, 6h, and 6j had relatively bigger inhibitory zones, ranging from 13 to 16 mm, at a concentration of 10 μg/mL, especially against B. cereus, S. aureus, and E. coli. Among these, compound 6f showed broad-spectrum action, with inhibition zones of 11 mm against E. coli and 15 mm against S. aureus and B. cereus.
Similarly, 6h had exceptional activity (E. coli, 13 mm; K. pneumoniae, 12 mm) and 15 mm against S. aureus and B. cereus, whereas 6e shown strong inhibition (15 mm) against K. pneumoniae and 13 mm against B. cereus and E. coli. Compounds 6a–6d and 6i, on the other hand, showed comparatively weaker antibacterial activities, with inhibition zones smaller than 13 mm, suggesting a decreased effectiveness that may be caused by electronic variables [38,39,40].

Table: 1. Antibacterial Activity of Synthesized Benzimidazole Derivatives 6a-6j Presented as Diameter of Inhibition Zones (Mm) Against S. Aureus, B. Cereus, E. Coli and K. Pneumoniae At 10 μg/mL [38,39,40].

Antibacterial Activity				
Bacteria	**S. Aureus**	**B. Cereus**	**E. Coli**	**K. Pneumoniae**
Concentration	**10 μg/mL**			
Compound Code	**Diameter of Inhibition Zone (mm)**			

6a	0	12	0	11
6b	0	12	0	12
6c	0	12	0	11
6d	0	13	0	0
6e	0	13	13	15
6f	15	15	11	11
6g	0	15	11	12
6h	15	15	13	12
6i	0	11	0	10
6j	10	9	16	14
Nitrofurantoin (300 µg/mL)	16	13	14	14
DMSO	0	0	0	0

Disease Prevention and Control

Effective crop disease prevention and control is essential to modern agricultural production in order to guarantee food security and boost yield. Benzimidazole fungicides are a broad-spectrum, extremely effective fungicide that significantly reduces a range of crop diseases.

For instance, benomyl is ineffective against rusts, flagella, and zygomycetes, but it has a good inhibitory impact on infections caused by fungus from the subphyla Ascomycotina, Deuteromycotina, and certain Basidiomycotina [41]. A wide range of crop diseases, such as powdery mildew and scab in apples and pears, wheat scab, rice blast, cucurbit scab and anthracnose, egg plant gray mold, tomato leaf mold, scab of cucurbits, allium gray mold rot, celery gray-spot disease, asparagus stem blight, citrus scab and gray mold, soybean sclerotinia, peanut brown-spot disease, and dry rot are all treated with benomyl.

In addition to being useful for post-harvest preservation, thiabendazole is mainly used to prevent and treat a variety of plant diseases, such as citrus green mold, blue mold, and stem-end rot. Albendazole works well against diseases like rice blast and tobacco anthracnose that are brought on by different basidiomycetes and ascomycetes [42].

Fusarium head blight (scab), powdery mildew, and smut in cereal crops; rice blast, sheath blight, and kernel smut in rice; and other fungal diseases in fruits, vegetables, and other crops are only a few of the plant diseases that thiophanate can successfully prevent and treat [42,43]. Diseases like rice blast and sheath blight in rice, rust and powdery mildew in wheat, smut and Fusarium head blight (scab) in cereal crops, sclerotinia in rapeseed, downy mildew in tomatoes, anthracnose and leaf spot in various vegetables, scab in peanuts, and powdery mildew and anthracnose in fruit trees can all be controlled and prevented with thiophanate-methyl [42,43].

Fuberidazole is useful for preventing and controlling wheat illnesses like snow mold and black head mold because it has strong antibacterial qualities against important pathogens from Ascomycetes, Basidiomycetes, and Deuteromycetes [42,43]. While carbendazim salicylate can successfully manage a number of fungal diseases like wheat scab and cotton wilt, methyl (1-{[(5-cyanopentyl) amino] carbonyl}-1H-benzimidazol-2-yl) carbamate can prevent and treat diseases like rice bakanae disease and powdery mildew in apples and pears [42].

In Vitro Antifungal Activity

Target compounds 6a–6l were tested in vitro for their antifungal activity against Candida albicans, Candida glabrata, Candida krusei, and Candida parapsilopsis. **Table 2** lists the outcomes. All of the compounds in the series were found to be effective against C. glabrata when their antifungal properties were investigated. With MIC 50 values of 0.97–1.95 µg/mL, all synthesized compounds 6a–6l also demonstrated antifungal activity equivalent to reference medications.

With a minimum inhibitory concentration (MIC) of 0.97 µg/mL, compounds 6b, 6i, and 6j were particularly efficient. These substances were discovered to be four times more effective than fluconazole and two times more effective than the reference medication voriconazole. Compounds 6a, 6c, 6d, 6e, 6f, 6g, 6h, 6k, and 6l in the series were shown to be twice as effective as fluconazole but to exhibit the same activity as voriconazole. We started talking about structural activity relationships (SARs) because of the variations in the chemical structures and antibacterial activity profiles of drugs.

The benzimidazole ring's fifth position is designed as edaschloro, fluoro, and non-substituted in our earlier investigation. Based on the antifungal activity data, it was proposed that benzimidazole's C-5 position is crucial and that substituting this position with fluoro or chloro greatly boosts the antifungal activity. Therefore, the electron-withdrawing group, the cyano group, was used in this investigation in place of non-substituted benzimidazole. The methyl or ethyl substituents at

the triazole's N-4 position were found to have no discernible effect on biological activity in the prior investigation. Instead of the alkyl group in the fourth position of nofthetriazole, the phenyl ring was employed as the aromatic group in this investigation.

The phenyl ring of synthetic substances was derivatized using different substituents. Examining the chemical structures of the compounds (6b, 6i, and 6j) that exhibited more potent anticandidal activity reveals that they have methoxy and chloro substituents at the phenyl C-4 position. Therefore, it may be said that the position of phenyl C-4 is crucial for anticandidal action. The biological activity is greatly increased by methoxy and chloro substituents at this location [44].

Table 2: Antifungal Activity Data of Synthesized Compounds and Reference Drugs 6a-6l (µg/mL) [44].

Comp.	C. Albicans	C. Krusei	C. Glabrata	C. Parapsilosis
6a	31.25	125	1.95	62.5
6b	31.25	125	0.97	31.25
6c	31.25	125	1.95	31.25
6d	62.5	125	1.95	125
6e	62.5	125	1.95	62.5
6f	62.5	125	1.95	62.5
6g	125	250	1.95	31.25
6h	62.5	62.5	1.95	62.5
6i	62.5	125	0.97	31.25
6j	62.5	125	0.97	31.25
6k	31.25	125	1.95	31.25
6l	31.25	125	1.95	31.25
Voriconazole	3.90	3.90	1.95	3.90
Fluconazole	7.81	7.81	3.90	3.90

Conclusion

Different pharmacological characteristics of these novel compounds were revealed by antimicrobial evaluation; the benzimidazoles showed encouraging activity against S. aureus. Numerous medicinally utilized molecules include benzimidazole, a key nitrogen-containing heterocyclic moiety that is crucial in the treatment of numerous illnesses. The development of target-based benzimidazole derivatives has received a lot of attention thus far, and in recent years, there has been a noticeable increase in interest in creating novel therapeutically active molecules to treat various illnesses. However, there are a number of difficulties in this field, particularly when it comes to getting the many produced compounds that have demonstrated useful pharmacological qualities in various research into clinical trials and then ensuring their availability in the market and in clinical practice. This is the most comprehensive and educational description of the biological and medicinal potential of derivatives of benzimidazoles.

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