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Benzimidazole and its Derivatives: A Comprehensive Review on Synthetic Approaches and Pharmacological Significance

Gauri R. Bhoite, Sangita M. Choudhary

Department of Pharmaceutical Chemistry, Indala Institute of Pharmacy, Kalyan, MH, India

ABSTRACT: Benzimidazole derivatives constitute an important class of heterocyclic compounds with broad significance in medicinal and synthetic organic chemistry. Structurally composed of a fused benzene and imidazole ring, benzimidazole offers a privileged scaffold that can be readily functionalized to generate a wide array of bioactive molecules. These derivatives exhibit diverse pharmacological properties including antimicrobial, antiviral, anticancer, anti-inflammatory, antiparasitic, and antihypertensive activities. The biological efficacy of benzimidazole-based compounds is largely attributed to their ability to interact with various biological targets such as enzymes, receptors, and nucleic acids. In addition to their pharmaceutical applications, benzimidazole derivatives have found utility in material science as corrosion inhibitors, dyes, and building blocks in supramolecular and coordination chemistry. Recent advances in synthetic methodologies, including green chemistry approaches and metal-catalyzed reactions, have facilitated the development of novel benzimidazole analogs with enhanced potency and selectivity. This growing interest in benzimidazole derivatives underscores their continuing relevance in drug discovery and applied chemical research.

KEYWORDS: Benzimidazole derivatives; Heterocyclic compounds; Antibacterial activity; Green synthesis; Antimicrobial.

I. INTRODUCTION

Heterocyclic compounds are fundamental classes of organic molecules that play a significant role in the synthesis of various chemical substances, particularly pharmaceuticals. These compounds are characterized by the presence of one or more heteroatoms—such as nitrogen, oxygen, or sulfur—within their ring structures, which imparts a wide range of chemical and biological properties. Due to this structural diversity, heterocyclic compounds are considered highly versatile and are extensively utilized in medicinal chemistry, agriculture, polymer science, and industrial processes. Their importance is especially evident in drug discovery, where many therapeutic agents are built upon heterocyclic frameworks owing to their biological activity and functional adaptability. Among the vast family of heterocyclic compounds, benzimidazole stands out as a particularly important scaffold in pharmaceutical chemistry.

Benzimidazole is a fused heterocycle, consisting of a benzene ring fused to an imidazole ring, which imparts unique chemical and biological properties. Due to its versatile structure, benzimidazole and its derivatives exhibit a broad range of pharmacological activities, including antimicrobial, antiviral, and anticancer, anti-inflammatory, and antiparasitic effects. These properties have made benzimidazole derivatives a focus of extensive research and development in drug discovery. Moreover, their ability to interact with various biological targets, such as enzymes and receptors, highlights their potential as therapeutic agents for numerous diseases.

Imidazole and Benzimidazole Imidazoles represent an important class of heterocyclic compounds owing to their significant medicinal properties, which have made them valuable scaffolds in drug design and development. Imidazole is a planar, heteropentacyclic polar nature, with a calculated dipole moment of 3.61, it exhibits good solubility in water and other polar solvents. Notably, imidazole is an amphoteric molecule, capable of acting both as an acid and a base. It exists in two tautomeric forms, namely 1H-imidazole and 3H-imidazole, which interconvert through the migration of a hydrogen atom between the two nitrogen atoms in the ring. Furthermore, imidazoles are aromatic compounds, owing to the presence of a delocalized sextet π -electron system.

This system comprises a lone pair of electrons on the protonated nitrogen atom as well as the π -electrons from the remaining four atoms of the ring, contributing to the compound's overall stability and chemical behavior. Benzimidazole derivatives were initially identified in the late 19th and early 20th centuries, representing a key advancement in the field of chemistry. Since their discovery, these compounds have played an essential role in pharmacology, exhibiting a diverse range of biological activities that have significantly influenced medicine and healthcare. The importance of benzimidazole derivatives in therapeutic science is well established. Extensive research has been conducted to explore and develop their wide-ranging and beneficial properties.

Many of these derivatives demonstrate strong anticancer effects, with certain compounds capable of inhibiting the proliferation of cancer cells, providing potential therapeutic options in oncology. Additionally, benzimidazole derivatives have been utilized in the treatment of cardiovascular disorders as antihypertensive agents, assisting in blood pressure regulation. Their role as antidiabetic agents, through modulation of glucose metabolism and enhancement of insulin secretion, also shows considerable promise in managing diabetes. Recent patent studies have concentrated on modifying the benzimidazole nucleus to create new and more effective pharmaceutical agents.

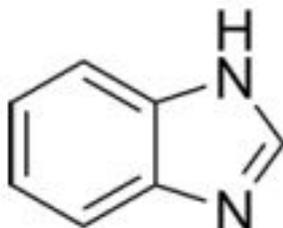
II. ORIGIN OF BENZIMIDAZOLE

Benzimidazole was first synthesized in the late 19th century, with its initial preparation reported by Hoebrecker in 1872. The compound is formed by the fusion of a benzene ring with an imidazole ring, creating a bicyclic heterocyclic system. This unique structure combines the chemical properties of both aromatic rings, making benzimidazole a significant scaffold in organic and medicinal chemistry. Over time, benzimidazole and its derivatives gained attention due to their stability and diverse biological activities. The synthesis and study of benzimidazole compounds expanded considerably during the 20th century, leading to the development of various pharmacologically active derivatives widely used in drug discovery and pharmaceutical applications.

Benzimidazole Properties

Melting Point	169-171 °C (lit.)
Boiling Point	360 °C
Density	1.1151 (rough estimate)
Refractive Index	1.5500 (estimate)
Flash Point	360°C
Storage Temperature	Store below +30°C.
Solubility	xylene: soluble 1g in 2g (boiling)(lit.)
Form	Crystalline Powder or Crystals
Pka	5.532(at 25°C)
Color	Beige to brown
Water Solubility	sparingly soluble
Stability	Stable. Combustible. Incompatible with strong oxidising agents.

Structure of Benzimidazole

**Sar Of Benzimidazole Derivatives For Antibacterial Activity**

Structure–activity relationship (SAR) studies of benzimidazole derivatives highlight how small changes to the molecular structure can have a big impact on their antibacterial effectiveness. One of the most significant findings is that introducing halogen atoms like chlorine or bromine at the 5-position of the benzimidazole ring tends to boost antibacterial activity—especially against Gram positive bacteria such as *Staphylococcus aureus* and MRSA. These halogens act as electron-withdrawing groups, which help increase the molecule's lipophilicity and improve its interaction with bacterial targets. Similarly, adding functional groups like **chloromethyl** or aminoalkyl chains at the 2 position often enhances binding with bacterial enzymes and improves the compound's ability to cross cell membranes. When both the 5- and 2-positions are optimally substituted, many of these compounds have shown antibacterial activity comparable to, or even better than, well-known antibiotics like ciprofloxacin. Substituents on any attached phenyl rings also make a big difference.

In particular, meta-substituted phenyl rings— especially those with polar or electron-withdrawing groups like fluorine, sulfonamides, or nitro groups—tend to show stronger antibacterial activity than para-substituted versions. On the other hand, placing electron-donating groups like methyl or **methoxy** at the para position usually leads to a drop in activity. Interestingly, substitutions like **para-fluoro** or meta-NHSO₂CH₃ have been especially promising.

Moreover, researchers have found that combining the benzimidazole ring with other biologically active fragments— like **hydrazones, thiazoles, or pyridones**—can expand the spectrum of activity and increase potency, particularly against drug-resistant strains. In summary, the SAR analysis shows that choosing the right substituents—especially electron-withdrawing and moderately lipophilic ones—at key positions like the 2- and 5-positions, and carefully designing attached aryl groups, can significantly enhance antibacterial performance. Finding the right balance between electronic effects and lipophilicity is crucial for improving both target binding and cell penetration.

Structure-Activity Relationship (SAR) in Anticancer Activity

The anticancer potential of benzimidazole derivatives largely depends on how their molecular structure interacts with key biological targets such as tubulin, topoisomerases, and kinases. Structure–activity relationship (SAR) analyses have provided valuable insights into optimizing these compounds for enhanced efficacy. One effective approach involves introducing halogen atoms—such as chlorine, bromine, or fluorine—at specific positions (typically 4, 5, or 6) on the benzimidazole ring.

These modifications tend to improve cytotoxic activity by increasing membrane permeability and promoting more efficient binding to intracellular targets. Additionally, incorporating electron-withdrawing groups like nitro (-NO₂) and cyano (-CN) can strengthen interactions with enzymes commonly linked to cancer progression, thereby enhancing therapeutic activity. Alkylation at the N1 and N3 positions has been found to improve both the bioavailability and metabolic stability of these compounds. Functional groups such as hydroxyl (-OH) and sulfonamide (-SO₂NH₂) further contribute to activity by forming strong hydrogen bonds with target proteins. Conversely, substitutions at the R5 position—especially bulky or electron-donating groups like methyl or methoxy—often lead to reduced anticancer activity, likely due to steric hindrance or less favorable electronic interactions.

Mechanism of Anticancer Action of Benzimidazoles

Benzimidazole derivatives exhibit potent anticancer activity through multiple mechanisms that interfere with the growth, division, and survival of cancer cells. These mechanisms include inhibition of tubulin polymerization, DNA intercalation, topoisomerase inhibition, modulation of apoptotic pathways, kinase inhibition, induction of cell cycle arrest, and suppression of angiogenesis and metastasis. Their ability to target several critical pathways simultaneously makes benzimidazole compounds attractive candidates in the development of novel anticancer therapies.

Inhibition of Tubulin Polymerization

One of the most well-characterized anticancer mechanisms of benzimidazoles is their ability to disrupt microtubule dynamics by inhibiting tubulin polymerization. Microtubules, essential components of the cytoskeleton, play a pivotal role in mitosis. Benzimidazole derivatives such as albendazole and mebendazole exert their effects by binding to β -tubulin, thereby preventing microtubule formation and stability. This disruption leads to mitotic arrest and ultimately induces apoptosis, as it hinders proper chromosomal segregation during cell division. For instance, mebendazole has been shown to induce G2/M phase arrest and apoptosis in melanoma and lung cancer cells through tubulin inhibition. Similarly, in leukemia and colon cancer models, it has demonstrated significant anticancer activity by blocking microtubule assembly.

Benzimidazole compounds with Anthelmintic activity

Several benzimidazole-based compounds have been successfully developed and marketed as anthelmintic agents, including albendazole, cicloheximide, fenbendazole, flubendazole, mebendazole, oxfendazole, oxibendazole, triclabendazole, and thiabendazole. In an effort to discover new candidates with potent anthelmintic properties, a series of 5-nitrobenzimidazole derivatives were synthesized and evaluated for their efficacy against adult Indian earthworms (*Pheretima posthuma*). Preliminary biological assays demonstrated that all tested compounds showed significant anthelmintic activity.

In another study, a library of 2-substituted benzimidazoles was synthesized and assessed for their activity against adult earthworms (*Eisenia fetida*). Among the synthesized compounds, several (notably compounds 23–25) displayed potent anthelmintic effects that were comparable to the standard drug albendazole.⁽⁶⁾ Further, benzimidazole derivatives were also prepared via the condensation of o-phenylenediamine with various acids. These newly synthesized molecules were tested against parasitic worms and exhibited notable anthelmintic activity, with several outperforming the reference compound, piperazine citrate.

Benzimidazole derivatives with antiviral activity.

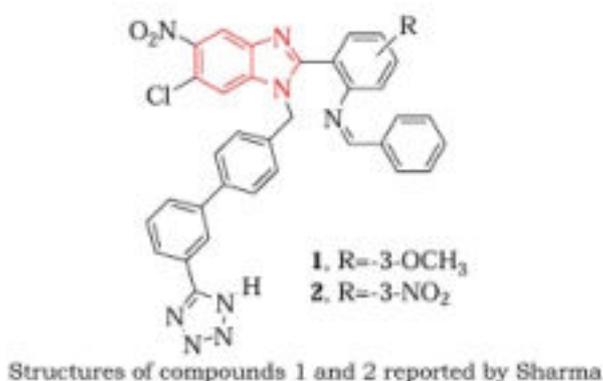
Several benzimidazole-based compounds have demonstrated promising antiviral properties, with some advancing to clinical use. Notably, envirodin and maribavir are benzimidazole derivatives that have been utilized as antiviral agents. In a study by Pan et al., a series of benzimidazole derivatives were synthesized and assessed for anti-HIV activity. Among these, compounds 29 and 30 exhibited potent inhibitory effects, with IC_{50} values of 3.45 nM and 58.03 nM, respectively. Similarly, Masoudi et al. developed a set of benzimidazole analogs and evaluated their efficacy against both HIV-1 and HIV-2. Compound 31 showed significant antiviral activity, with an EC_{50} of 1.15 μ g/mL.

Ferro et al. synthesized two series of benzimidazol-2-one derivatives and tested their activity against HIV-1. Among these, compounds 32 and 33 demonstrated higher potency (IC_{50} = 1.3 μ M and 0.79 μ M, respectively) than the standard antiretroviral drug nevirapine (IC_{50} = 1.55 μ M). In a different approach, Tsay et al. created a range of benzimidazole-coumarin hybrids, which were evaluated for antiviral activity against the hepatitis C virus (HCV). Compounds 34 and 35 showed potent effects, with EC_{50} values of 3.0 nM and 5.5 nM, respectively. Additionally, research by Shaker et al. revealed that compounds 36–38 had notable inhibitory effects against the rotavirus Wa strain, suggesting their potential as broad-spectrum antiviral agents. Furthermore, compound 39, synthesized by Dai et al., was identified as a highly potent inhibitor of Lassa virus (LASV) envelope glycoprotein (GP) pseudotypes, with an EC_{50} of 1.1 nM, highlighting its potential in combating arenavirus infections.

Benzimidazole derivatives as Antihypertensive Agents

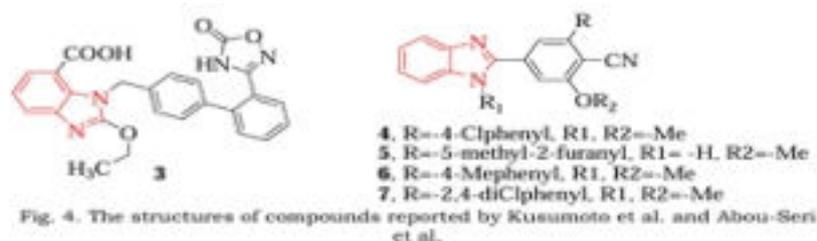
Candesartan cilexetil and telmisartan are two widely prescribed antihypertensive drugs that incorporate a benzimidazole moiety in their structure. These agents function as angiotensin II receptor antagonists, commonly known as sartans, and are effective in the management of hypertension by blocking the vasoconstrictive and

aldosterone-secreting effects of angiotensin II (Keri et al., 2015). In recent years, researchers have focused on designing new benzimidazole-based antihypertensive agents, some of which have demonstrated comparable or even superior efficacy relative to existing therapies. For instance, Sharma et al. (2010) synthesized a series of substituted benzimidazole derivatives and evaluated their antihypertensive potential using Wistar rat models. Among the synthesized compounds, compounds 1 and 2 emerged as the most potent angiotensin II receptor antagonists, showing greater efficacy than the reference drug losartan.



Azilsartan medoxomil, along with its active metabolite azilsartan (compound 3, Figure 4), has been recognized as a potent and long-acting angiotensin II type 1 (AT1) receptor blocker. In a study conducted by Kusumoto et al. (2011), the pharmacological profile of azilsartan medoxomil was evaluated in both spontaneously hypertensive rats (SHRs) and renal hypertensive dogs.

The findings revealed that oral administration of azilsartan medoxomil at doses ranging from 0.1 to 1 mg/kg produced a significantly greater and more sustained reduction in blood pressure compared to the standard antihypertensive agent olmesartan medoxomil. Further contributions to benzimidazole-based antihypertensive research were made by Abou-Seri et al. (2011), who designed and synthesized a novel series of 2 alkoxy-4-aryl 6-(1H-benzimidazol-2-yl)-3 pyridinecarbonitrile derivatives. These compounds exhibited notable vasodilatory properties, with compounds 4–7 (Figure 4) demonstrating the most pronounced activity. The IC₅₀ values for these compounds were 0.145, 0.202, 0.210, and 0.214 mM, respectively—considerably lower than that of the reference vasodilator prazosin hydrochloride (IC₅₀ = 0.487 mM), indicating superior potency.



Benzimidazole derivatives as anti-diabetic

The benzimidazole scaffold has also emerged as a valuable bioactive pharmacophore in the development of novel antidiabetic agents. Given the widespread prevalence of hyperglycaemia globally, there is an ongoing need for effective compounds to help maintain blood glucose levels within the recommended clinical range. Over the years, numerous drug candidates and lead molecules based on benzimidazole structures have been explored for their antidiabetic potential.

Among recent developments, two notable compounds—3,6 dimethyl-5-oxo-pyrido[3,4-f][1,2,4]triazepino[2,3 a]benzimidazole (271) and 10-amino-2-methyl-4 oxopyrimido[1,2-a]benzimidazole (272)—have been synthesized

and evaluated for their enzyme inhibitory activity. In one synthetic route, a benzimidazole containing intermediate, compound 270 (6-methyl-7H,9H-4b,5,9,10 tetra-azabenz[a]azulen-8-one), underwent cyclization with DMF–DMA, resulting in the fused tetra-heterocyclic compound 271, with a 58% yield. Alternatively, treatment of the same precursor with excess methyl sulphate in aqueous conditions led to an intramolecular rearrangement, producing the fused tricyclic compound 272 in 67% yield.

Biological evaluations revealed that compound 271 exhibited strong inhibitory activity against both α amylase and α -glucosidase enzymes, key targets in diabetes management. In contrast, compound 272 showed relatively weaker inhibition of these enzymes, indicating a structure–activity relationship (SAR) worth further exploration.

Benzimidazoles as Antimalarial Agents

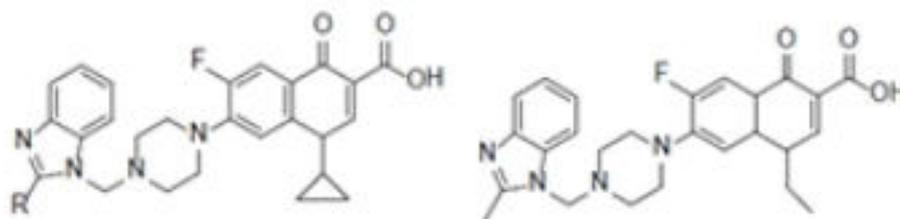
A wide range of benzimidazole derivatives have been proposed, synthesized, and investigated for their potential as antimalarial agents, targeting various Plasmodium species responsible for malaria, including *P. falciparum*, *P. ovale*, *P. malariae*, *P. vivax*, and *P. knowlesi*. One notable synthetic approach involves the condensation of 6-O and N-substituted diamino pyridine derivatives (compound 217) with cyanogen bromide, leading to the formation of 2-aminobenzimidazole analogues (compound 218). These intermediates were then reacted with phenacyl bromide to yield 6-substituted 2-amino-3 benzoylbenzimidazole derivatives (compound 219), which upon reduction gave the corresponding alcohol derivatives (compound 220).

In addition, various 2-amino-pyridinyl-benzimidazole derivatives were synthesized and found to exhibit potent antimalarial activity. These compounds were particularly effective in rapidly killing malaria parasites and were non cross-resistant, meaning they retained activity against strains resistant to existing antimalarial drugs. Moreover, they demonstrated low rates of resistance development and excellent oral bioavailability, making them promising candidates for further development. More recently, a novel antimalarial agent—fused pyrido[1,2-a]benzimidazole (compound 223)—was synthesized using microwave-assisted nucleophilic substitution. This compound was derived from the tetracyclic intermediate compound 222, which itself was synthesized from 3, 4-disubstituted aniline (compound 221), highlighting a concise and efficient synthetic strategy for generating structurally complex antimalarial scaffolds.

Benzimidazole-Based Ligands as Potential Antipsychotic Agents

Deana Andrić et al. designed and synthesized a series of eight novel benzimidazole-2-thione derivatives with halogen atoms strategically introduced into the pharmacophore to enhance dopaminergic and serotonergic receptor binding. These compounds—classified as 5-[2-(4 arylpiperazin-1-yl)ethyl]-1,3-dihydro-2H benzimidazole 2-thiones—were rationally developed using arylpiperazine moieties known to exhibit high receptor affinity based on established structure–activity relationships (SARs). The *in vitro* receptor-binding affinities were assessed through competitive radioassays targeting dopamine D₁, D₂, and serotonin 5-HT_{1A} receptors, using synaptosomal membranes prepared from fresh bovine caudate nuclei and hippocampi.

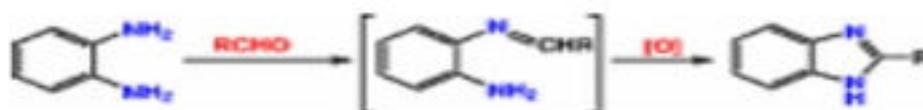
The results demonstrated that all synthesized compounds were highly competitive inhibitors at the D₂ dopamine and 5-HT_{1A} serotonin receptors, with the most potent derivatives exhibiting 34-fold and 170-fold higher affinity, respectively, than their non-halogenated counterparts in D₂ receptor assays. Importantly, these compounds showed minimal affinity for the D₁ dopamine receptor, suggesting a selective receptor profile that aligns with the pharmacological profile of atypical antipsychotics, which often act through D₂ antagonism and 5-HT_{1A} modulation. This dual activity profile supports the potential of these halogenated benzimidazole derivatives as promising antipsychotic candidates, particularly for treating conditions like schizophrenia and bipolar disorder, where dopaminergic and serotonergic imbalances are implicated.



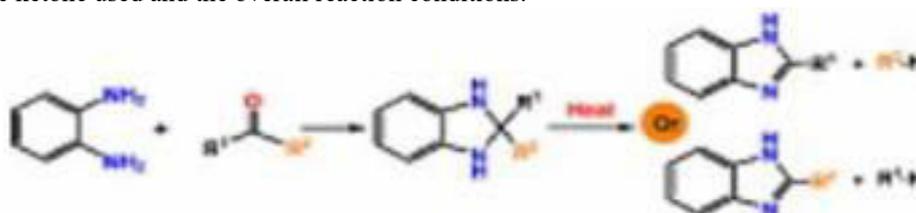
III. METHODS OF SYNTHESIS BENZIMIDAZOLE DERIVATIVES

1. Condensation of 2-Aminoaniline (o Phenylenediamine)

A commonly employed method for the synthesis of benzimidazole derivatives involves the condensation reaction between various aldehydes and 2-aminoaniline (also known as o-phenylenediamine). This transformation typically proceeds via an oxidative cyclization, in which the intermediate undergoes an intramolecular ring closure to form the benzimidazole core. The oxidation step can be facilitated by molecular oxygen (air) or a variety of oxidising agents, depending on the reaction conditions and desired product profile.

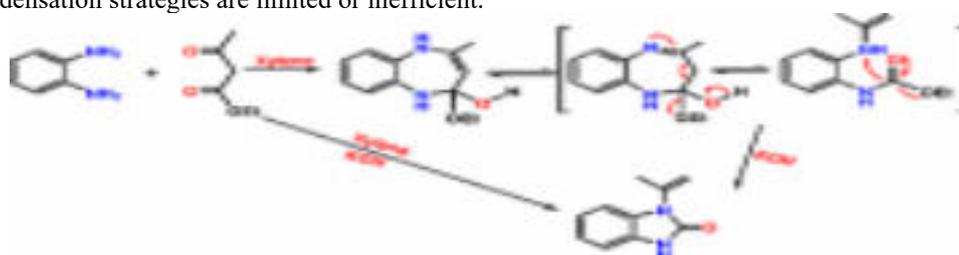


An alternative approach for the synthesis of benzimidazole derivatives involves the condensation of ketones with o-phenylenediamine. While this method can successfully yield benzimidazole scaffolds, it is less commonly employed than the aldehyde-based route due to certain limitations—such as lower reactivity of ketones, harsh reaction conditions, and reduced product yields. These drawbacks will be discussed in detail in subsequent sections. In general, this method involves condensation between a ketone and a diamine, followed by cyclisation to form the benzimidazole ring system. The reaction typically requires elevated temperatures, which may vary depending on the specific ketone used and the overall reaction conditions.



2. via Rearrangement

Condensation reactions remain one of the most widely used strategies for synthesizing benzimidazole derivatives. However, beyond these classical methods, several highly effective synthetic approaches have been developed that rely on the rearrangement of heterocyclic compounds. These rearrangement-based pathways often provide access to structurally diverse and functionally enriched benzimidazole derivatives, sometimes under milder or more selective reaction conditions. Such methods expand the chemical space of benzimidazoles and are particularly valuable when traditional condensation strategies are limited or inefficient.



2. Green Synthesis of Benzimidazole

Green chemistry is defined as the design, development, and implementation of chemical products and processes that minimize or eliminate the use and generation of hazardous substances, thereby reducing their impact on human health and the environment. Since its conceptualisation in the early 1990s, green chemistry has emerged as a vital discipline, addressing the growing concerns over environmental pollution and chemical safety. Its principles aim to make chemical synthesis not only more sustainable but also more efficient and safer across all stages—from initial design to final production.

Traditional organic synthesis methods are known contributors to environmental degradation due to the release of toxic gases, volatile organic compounds (VOCs), and the generation of hazardous waste. Therefore, there is a pressing need to adopt environmentally benign alternatives for the preparation of organic compounds. Today, various green technologies have been successfully applied to organic synthesis.

These include:

- Microwave-assisted synthesis
- Photochemical reactions
- Aqueous-phase reactions (water as a solvent)
- Ultrasound-assisted methods
- Catalysis (including enzyme or metal catalysts)

These approaches not only reduce environmental impact but also improve reaction efficiency, enhance product quality, reduce energy consumption, and minimize waste. Benzimidazole derivatives, which are important heterocyclic compounds with a broad range of biological activities, have also benefited from green synthetic strategies. For example, microwave-assisted synthesis has been employed to prepare benzimidazole compounds by condensing aldehydes with o-phenylenediamine in the presence of a mild acid catalyst, such as acetic acid.

This method offers multiple advantages:

- Shorter reaction times
- Use of non-toxic or benign solvents
- High product yields
- Reduced energy consumption

Such green synthetic methods represent a significant shift away from conventional industrial processes and support the global movement toward sustainable chemical manufacturing.

IV. PHARMACOLOGICAL ACTIVITIES OF BENZIMIDAZOLE DERIVATIVES

Antiepileptic Activity of Benzimidazole Derivatives R. V. Shingalapur et al. reported the synthesis and evaluation of a series of (1H-benzimidazol-2-ylsulfanyl) thiazolidin-4-one derivatives for their antiepileptic potential, employing the maximal electroshock seizure (MES) model. This model is widely used for screening compounds effective against generalized tonic-clonic seizures. The study highlighted that certain structural features were critical for anticonvulsant activity.

These included:

- The hydrophobic character of the benzimidazole ring,
- The presence of electron-donating groups, and
- A hydrogen-bonding domain.

These characteristics aligned with known pharmacophores of standard antiepileptic drugs such as phenytoin and carbamazepine. Among the synthesized compounds, derivatives of 2-(1H benzimidazol-2-ylsulfanyl)-N-(4-oxo 2-phenyl-1,3 thiazolidin-3-yl)acetamide demonstrated significant activity in suppressing tonic-extensor seizures

in the MES model. Structure–activity relationship (SAR) analysis further revealed that the introduction of hydroxyl (–OH) groups at the 2- and 4-positions of the phenyl ring played a pivotal role in maintaining and enhancing anticonvulsant activity. These findings suggest that appropriately substituted benzimidazole–thiazolidinone hybrids may serve as promising leads in the development of new antiepileptic agents.

Antidiabetic Activity of Benzimidazole Derivatives

R. V. Shingalapur et al. synthesized a series of 2-(5-phenyl-[1,3,4]-oxadiazole-2-ylmethylsulfanyl)-1H benzimidazole derivatives and evaluated their antidiabetic potential using in vivo models. The study focused on the compounds' ability to reduce blood glucose levels in comparison to the standard drug glibenclamide. Among the four synthesized compounds, all demonstrated a significant reduction in blood glucose levels by the 9th day of treatment, outperforming glibenclamide in some cases. The most potent compound was identified as 3-[5-(1H-benzimidazol-2-ylsulfanylmethyl)-[1,3,4]-oxadiazole-2-yl]-naphthalene-2-ol, which showed superior glucose lowering activity in diabetic animals. In addition to this lead compound, several other derivatives also exhibited significant antihyperglycemic effects during the Oral Glucose Tolerance Test (OGTT).

These include:

- 2-(5-phenyl-[1,3,4]-oxadiazole-2-ylmethylsulfanyl)-1H-benzimidazole
- 2-(5-chlorophenyl-[1,3,4]-oxadiazole-2-ylmethylsulfanyl)-1H-benzimidazole
- 5-[5-(1H-benzimidazol-2-ylsulfanylmethyl)-[1,3,4]-oxadiazole-2-yl]-benzene-1,2,3-triol
- 2-[5-(4-nitrophenyl)-[1,3,4]-oxadiazole-2-ylmethylsulfanyl]-1H-benzimidazole
- These compounds were statistically significant compared to the diabetic control group and in some cases even the normal control group, indicating their strong potential as novel oral antidiabetic agents.

Antibacterial Activity of Benzimidazole Derivatives

Varadaraj et al. synthesized a series of 2-substituted phenoxyethyl benzimidazoles and 1-alkyl-2-substituted phenoxyethyl benzimidazoles, which were evaluated for their antibacterial properties. The compounds were tested against several bacterial strains, including *Escherichia coli* and *Pseudomonas aeruginosa* (both Gram negative bacteria), as well as Coagulase positive *Staphylococcus aureus* (COPS), a Gram-positive bacterium. Antibacterial activity was assessed using the punch well and disc diffusion methods on Muller Hinton agar medium, with Gentamycin (100 µg/mL) serving as the standard reference antibiotic. The synthesized compounds were screened at three different concentrations: 1 µg/mL, 10 µg/mL, and 100 µg/mL, using 50% dimethylformamide (DMF) as the solvent. Results demonstrated that all tested compounds exhibited promising antibacterial activity against *E. coli* and *P. aeruginosa* at all concentrations. However, fewer compounds showed activity against COPS. Although the compounds displayed activity comparable to Gentamycin against *E. coli*, their overall potency was significantly lower than that of the standard drug. These findings suggest that the synthesized benzimidazole derivatives possess moderate antibacterial properties, particularly against Gram-negative bacteria, and warrant further structural optimization to enhance their efficacy.

Antifungal Activity of Benzimidazole Derivatives

Kilcigil et al. synthesized a series of benzimidazole derivatives that were evaluated for antifungal activity against *Candida albicans* and *Aspergillus niger*. The antifungal screening was conducted using the punch well and disc diffusion methods on Sabouraud Dextrose Agar Broth, with Fluconazole (100 µg/mL) as the standard reference drug. The synthesized compounds were tested at three different concentrations: 1 µg/mL, 10 µg/mL, and 100 µg/mL, using 50% dimethylformamide (DMF) as the solvent.

The results revealed that all compounds showed promising antifungal activity against *Candida albicans*, with 1-alkyl-2-substituted phenoxyethyl benzimidazoles and their derivatives demonstrating activity comparable to Fluconazole. Against *Aspergillus niger*, fewer compounds exhibited activity; however, substituted phenoxyethyl benzimidazoles showed higher antifungal activity than the standard Fluconazole. Interestingly, some compounds displayed a non-linear relationship between concentration and the zone of inhibition, suggesting variable efficacy depending on dosage.

Antitubercular Activity of Benzimidazole Derivatives

Jaseela et al. synthesized a series of 1-(1H-benzimidazol-2-yl)-3-(substituted phenyl)-2-propen-1-one derivatives, which were further reacted with hydrazine hydrate and phenyl hydrazine to obtain pyrazoline, phenyl pyrazoline, and benzimidazole derivatives. These compounds were tested for antitubercular activity against the *Mycobacterium tuberculosis* H37RV strain using Lowenstein-Jensen medium, with Isoniazid and Rifampicin as standard reference drugs. The media preparation followed the guidelines set by the International Union against Tuberculosis. Remarkably, all synthesized compounds demonstrated significant antitubercular activity, even at a low concentration of 1 µg/mL, showing comparable or superior efficacy to the standard drugs Rifampicin and Isoniazid. 11

Antihypertensive Activity of Benzimidazole Derivatives

Sharma et al. synthesized a series of 6-chloro-5-nitro benzimidazole derivatives and evaluated their potential as antihypertensive agents. All the synthesized compounds demonstrated notable antihypertensive activity when compared with standard drugs. Most of these newly developed 6-chloro-5-nitro-benzimidazole derivatives showed promising effects in lowering blood pressure. To better understand the structure–activity relationships (SAR) of these benzimidazole-based molecules, fifteen analogs were synthesized. These derivatives featured various electron-donating and electron-withdrawing groups, particularly at the 5-position nitro group and different aryl groups at the 2-position, aiming to optimize their antihypertensive properties.

Anthelmintic Activity of Benzimidazoles

The benzimidazole class of anthelmintics began with the discovery of thiabendazole in 1961, followed by the development of several broad-spectrum benzimidazole derivatives. These compounds have been extensively studied for their biochemical effects. Their anthelmintic efficacy primarily stems from their ability to disrupt the cytoskeleton by selectively binding to β -tubulin. In the model organism *Caenorhabditis elegans*, benzimidazoles cause impaired locomotion, reduced reproduction, and harmful effects on oocytes—effects that align with the disruption of microtubule-dependent processes. The sensitivity of *C. elegans* to benzimidazoles is controlled by a single gene, *ben-1*, which encodes β -tubulin. This genetic insight has been crucial for understanding benzimidazole resistance in parasitic nematodes. For example, resistance in *Haemonchus contortus* is linked to specific β -tubulin alleles found in drug-resistant isolates, highlighting the molecular basis of resistance mechanisms in these parasites.

Antioxidant Activity

Sandhya Rani et al. synthesized nine new [1-benzyl-2 phenyl-substituted]-1H-5, 6-substituted benzimidazoles by reacting substituted o-phenylenediamines with substituted benzaldehydes. The structures of these compounds were confirmed using IR, ^1H NMR, and Mass Spectroscopy. The antioxidant activity was evaluated using ferrous ion induced lipid peroxidation in rat brain homogenate. Compounds containing electron-donating groups such as dimethylamino, methoxy, and hydroxyl at positions 1 and 2 of the benzimidazole ring showed significantly enhanced antioxidant activity compared to unsubstituted benzimidazoles.

Analgesic and Anti-inflammatory Activity

B. G. Mohamed et al. synthesized a series of 1-acyl-2 alkylthio-1,2,4-triazolobenzimidazoles and evaluated their biological activities. These compounds exhibited significant analgesic and anti-inflammatory properties. Additionally, Black et al. and Kalgutkar et al. highlighted the critical role of the p-chlorobenzoyl substituent in the activity of indomethacin and related compounds. The tested benzimidazole derivatives, considered as 3-aza indolotriazole analogs, demonstrated promising anti-inflammatory and analgesic effects.

Antiviral and Anticancer Activity

Gabriella et al. synthesized a series of benzimidazole 5 carboxamide derivatives that act as specific inhibitors of the NS5B polymerase enzyme of the hepatitis C virus (HCV). Interestingly, several benzimidazole derivatives have been reported to exhibit both antiviral and anticancer activities. Researchers such as Göker, Valdez, and Aguirre have synthesized benzimidazole derivatives featuring the 1H benzimidazole core. These compounds, notable for their basic properties due to nitrogen content, form the active components of several therapeutic drugs. Benzimidazole derivatives have been attributed with a wide range of biological activities, including anticancer, antibacterial, antifungal, antimicrobial, antiprotozoal, and antihelminthic effects.

V. CONCLUSION

Benzimidazole derivatives represent a highly significant class of compounds in medicinal chemistry due to their versatile and broad spectrum of biological activities. These compounds have demonstrated remarkable potential in treating various health conditions, including anti-ulcer, anthelmintic, antimicrobial, anticancer, antiviral, antidiabetic, antihypertensive, antimalarial, antiepileptic, and anti-inflammatory disorders. Their diverse pharmacological properties stem from the benzimidazole core's ability to interact with multiple biological targets, such as protein-DNA interactions, enzyme inhibition, and receptor modulation. Over the years, numerous synthetic approaches have been developed to create benzimidazole derivatives.

Traditional methods primarily involve condensation reactions with aldehydes and ketones or rearrangements of heterocyclic precursors. However, these conventional techniques often require harsh conditions and generate hazardous waste, raising environmental concerns. To address this, recent advancements emphasize green chemistry principles by employing eco-friendly methods such as microwave-assisted synthesis, ultrasound irradiation, and catalytic reactions using green solvents and biocatalysts. These green technologies not only reduce toxic by-products and energy consumption but also enhance reaction efficiency and product yield.

The biological evaluations of benzimidazole derivatives reveal their significant effectiveness in various fields. For instance, benzimidazole compounds have shown potent antiviral activities against hepatitis C virus, HIV, and other viruses, alongside noteworthy anticancer effects through mechanisms like polymerase inhibition and disruption of microtubules. Additionally, their antimicrobial and antifungal properties have been demonstrated against resistant bacterial and fungal strains, with some derivatives matching or surpassing standard drugs. Other derivatives have been identified as strong antihypertensive agents, targeting angiotensin II receptors, and as antidiabetic candidates by modulating enzymes involved in glucose metabolism. Furthermore, benzimidazole-based molecules have exhibited promising results as antimalarial agents, analgesics, and anti-inflammatory compounds.

The wide-ranging therapeutic potential of benzimidazoles also includes their use as dopaminergic receptor modulators and antihelminthics by targeting specific tubulin proteins in parasites. Moving forward, continued research on benzimidazole scaffolds will focus on optimizing their pharmacological profiles, minimizing side effects, and improving bioavailability. The integration of computational modeling, structure-activity relationship studies, and novel synthetic strategies will aid in designing next-generation benzimidazole derivatives with enhanced specificity and potency. In parallel, green chemistry will remain central to sustainable drug development, ensuring environmentally responsible production. In summary, benzimidazole derivatives stand at the forefront of medicinal chemistry innovation. Their versatile biological activities, combined with evolving synthetic methodologies, position them as promising candidates for future therapeutic agents across multiple disease areas. The ongoing exploration and refinement of benzimidazole chemistry hold great promise for advancing drug discovery and delivering safer, more effective treatments to patients worldwide.

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6. ²Department Of Pharmaceutical Chemistry, Dr.Babasaheb Ambedkar Technical University, Aditya institute of Pharmacy, Chalisgaon, Jalgaon-424101, India
7. ³Department Of Pharmaceutics, Savitribai Phule Pune University, MET's Institute Of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik-422003, India.
8. Hassan Y Aboul-Enein¹ * and Ahemd A El Rashedy² ¹ Pharmaceutical and Medicinal Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Dokki, Cairo 12311, Egypt ² Natural and Microbial Department, National Research Centre, Dokki, Giza 12622, Egypt.
9. ¹Pharmaceutical Chemistry Unit, Faculty of Pharmacy, AIMST University, Semeling 08100, Kedah, Malaysia ²Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai 600077, Tamil Nadu, India

Nguyen Thi Chung ^a, Vo Cong Dung ^b and Dau Xuan Duc

10. ^aDepartment of Chemistry, Institute of Education, Vinh University, 182 Le Duan Street, Nghe An 430000, Vietnam. E mail: Xuanduc80@gmail.com

11. ^bCentre for Education Accreditation, Vinh University, 182 Le Duan Street, Nghe An 430000, Vietnam

12. ¹Department of Organic Chemistry, Biochemistry and Catalysis, Faculty of Chemistry, University of Bucharest, 030018 Bucharest, Romania; maria.marinescu@chimie.unibuc.ro

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29. ²⁵Assistant Professor, Department of Chemistry, Annamalai University, Annamalainagar - 608 002, (Department of Chemistry, MR. Government Arts College, Mannargudi - 614001), Tamil Nadu, India.



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