Review Article

Therapeutic Potential of Benzimidazole Derivatives:AComprehensive Review of Biological Activities

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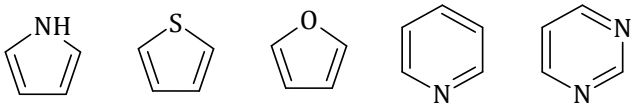
ABSTRACT

Background: Benzimidazole is a privileged heterocyclic scaffold widely recognized for its structural similarity to purines and its extensive role in medicinal chemistry. Over the decades, benzimidazole derivatives have demonstrated diverse pharmacological activities, making them valuable candidates in drug discovery and development. **Objective:** This review aims to provide a comprehensive overview of the chemistry, synthesis, mechanism of action, and broad spectrum of biological activities of benzimidazole derivatives, with particular emphasis on their therapeutic potential and recent advancements in green synthetic approaches. **Methods:** A comprehensive review of published literature was conducted focusing on synthetic methodologies, structure–activity relationships (SAR), and pharmacological evaluations of benzimidazole derivatives. Both classical and modern catalytic approaches, including environmentally sustainable synthesis methods, were analyzed alongside reported biological assays. **Results:** Benzimidazole derivatives exhibit a wide range of biological activities, including antimicrobial, anticancer, antioxidant, antihypertensive, antidiabetic, and analgesic effects. Their mechanism of action primarily involves interaction with β-tubulin, inhibition of microtubule formation, and disruption of cellular metabolism. Advances in synthesis, particularly green chemistry techniques and catalyst-driven methods, have improved yield, selectivity, and environmental compatibility. Structure–activity relationship studies highlight that substitution at specific positions of the benzimidazole nucleus significantly enhances pharmacological efficacy. **Conclusion:** Benzimidazole remains a highly versatile and promising scaffold in medicinal chemistry due to its broad-spectrum biological activities and modifiable structure. Continued research focusing on targeted drug design, sustainable synthesis, and optimization of pharmacokinetic properties is essential to fully exploit its therapeutic potential in treating complex diseases.

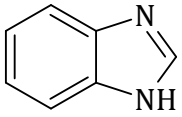
Key words: Benzimidazole, Hoebrecker, beta tubulin, biological activities.

Although N, O, and S are the most common heteroatoms. But sometimes, these rings can also have extra different atoms. Carbocyclic compounds are ring molecules made only of carbon atoms. Heterocyclic compounds are very important organic chemicals. They contain atoms like N, O or S in the rings and are widely used in medicines. Hemoglobin, DNA, RNA, vitamins, and chlorophyll are just a few of the biological substances that contain the heterocyclic ring as a basic structural element [1].



Pyrrole Thiophene Furan Pyridine Pyrimidine

When Woolley postulated in 1944 that benzimidazole have a purine-like structure and invoke some organic application, the natural use of benzimidazole core was discovered. Benzimidazole was first used many years ago in 1990. Increased strength, bioavailability, and notable natural action were the outcomes of numerous combinations of benzimidazole analogues [2].



The German scientist Hoebrecker created benzimidazole for first time in 1872. Although it was first employed as a chemical intermediary, its biological relevance became apparent in the 1940s and 1950s after its function in vitamins was identified [3]. Numerous synthetic 'N' based heterocyclic compound gained prominence due to their extensive use in

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industrial, agricultural, and medicinal applications. Benzimidazole is one of the most frequently used as a building block in therapeutic medications. Previous research has demonstrated the potential of these high-performance materials to enhance human well-being. These materials may find use in the development of medications to treat chronic illnesses, in agriculture as bio-pesticides, and in the chemical industry to create polymers and other organic compounds (Table 1) [4].

The goal of benzimidazole review papers is to summarize recent developments in the synthesis, chemical characteristics, and multi-pharmacological uses of benzimidazole derivatives, with an emphasis on their function as adaptable heterocyclic scaffolds in medicinal chemistry. Highlighting anticancer and antibacterial capabilities, investigating structure-activity correlations (SAR) for optimal drug design, and determining future research directions are some of the main goals. Give a thorough update on the various pharmacological activities and recent advancements of benzimidazole derivatives. Examine novel and enhanced sustainable synthetic methods, such as the effective synthesis of benzimidazole derivatives using catalysts.

Table No. 1: History of Benzimidazole

Year	Work reported
1872s	First synthesis benzimidazole derivatives reported (2,5 dimethyl benzimidazole) by Hoebrecker
1940s	Woolly identified benzimidazole as purine analogous with anti-bacterial activity
1950s-60s	Development of anthelmintic (Thiabendazole, 1961)
1970s-80s	Development of proton pump inhibitors (omeprazole)

Chemistry of benzimidazole:

The structure for benzimidazole shows that the benzimidazole has a phenyl ring fused to an imidazole ring (Figure 1).

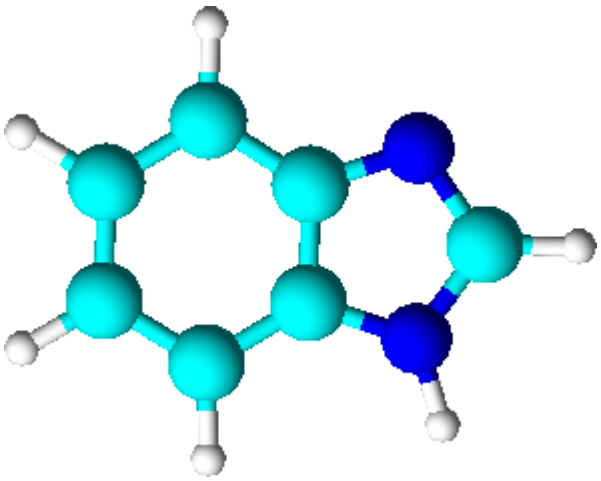


Figure 1: Benzimidazole

Benzimidazole ($C_7H_6N_2$) is a heterocyclic aromatic compound consisting of an imidazole ring fused to a benzene ring. When two ring configurations share a wall, the imidazole contributes 5 membered ring containing two N atoms, while the benzene contributes a ring with six carbon atoms [5].

Because benzimidazole and its derivatives exhibit a diversity of bioactivities, there have occasionally been attempts to construct collection of these compounds. Numerous ways of making compounds have been created and refined to make goods that meet customer requirements for quantity, purity, and quality. The compound was formed through the reduction and subsequent dehydration of 2-nitro-4-methylacetanilide by Hoebrecker in 1872. Which was either 2, 5-dimethylbenzimidazole or 2, 6-dimethylbenzimidazole. This finding resulted into benzimidazole. Afterwards, 3, 4-diamino toluene was refluxed with acetic acid. Ladenburg managed to produce a substance with similar characteristics.

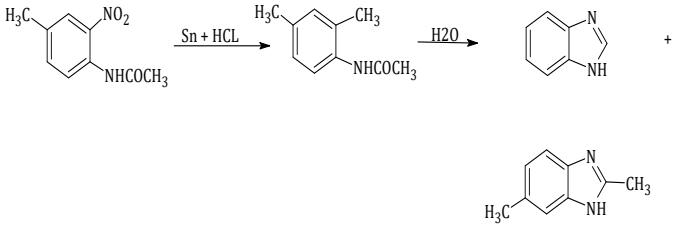
His strategy was referred to as "refluxing." In the advanced research studies, these substances were termed "Anhydro bases" since water was lost in the process of making them [6]. These compounds have also been referred to as compounds made from those groups that comprise the rings 1,3-diazole structure. For instance, benzimidazole is also known as o-phenylene formamidine.$C_7H_6N_2O$ and $C_7H_6N_2S$ were previously known as monophenyl urea &benzimidazole-2-thione but monophenyl urea to greater extent often used name. The hydrogen at N_1 atom undergoes isomerization to create by rapid tautomerization. While explaining tautomeric compounds, it is customary to present two groups of numbers that specify where the replacement is located; another collection of groups is distinguished from the first set by being contained in brackets (Table 2) [7].

Table No.2: Physiological Properties of Benzimidazole

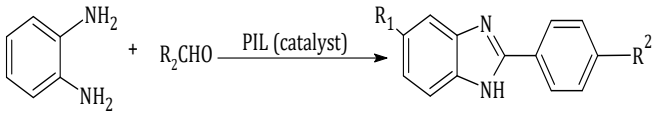
Properties	Values
Molecular formula	$C_7H_6N_2$
Composition	C(71.17%),H(5.12%) and N(23.71%)
Molar mass	118.14g/mole
Melting point	170°C-172°C
Molar refractivity	36.61± cm^3
Molar volume	95.0 ± 3.0 cm^3
Refraction Index	1.696 ± 0.02
Parachor	264.8 ± 4.0 cm^3
Surface tension	60.1 ± 3.0 dyne/cm
Density	1.242 ± 0.06 g/cm^3
Polarizability	14.51 + 0.5 x 10 -24 cm^3
Transform From	Crystalline to crystal
RDBE	6
pKa	5.532
Colour	Beige to brown
Water Solubility	Sparingly soluble
Nominal mass	118 Da
Monoisotopic mass	118.053098 Da
Average mass	118.1359 Da
M+	118.05255 Da

The development of enhanced processes that selectively produce either 2-substitued benzimidazole or 1, 2-disubstituted benzimidazole the only product has dominated recent advancement in terms of operational simplicity, atom economy, and environmentally favorable viability [8]. Numerous catalysts for the synthesis of 2-substituted benzimidazole have been reported. Hoebrecker created the first benzimidazole in history in 1872 [9]. (I)

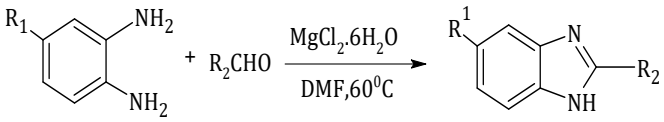
Synthesis of Benzimidazole by Hoebrecker



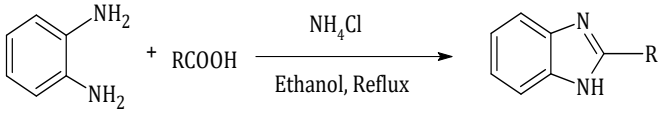
The literature has a variety of techniques for the synthesis of benzimidazole. Majumdar and colleagues reported a green synthesis of 2-substituted benzimidazole by grinding an imidazolium trifluoroacetate protic ionic liquid catalyst with o-phenylenediamine and appropriate aldehydes [10].



Ghosh and colleagues developed a series of substituted benzimidazole. Using a small quantity of magnesium chloride hexa-hydrate, 1, 2-diaminobenzene is combined with benzene based and heterocyclic aldehydes [11].

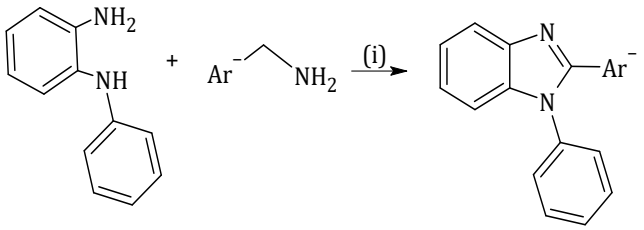


Rithe and colleagues effectively used ammonium chloride to synthesis a variety of substituted benzimidazole derivatives in moderate to good yield. Phenylenediamine and other aromatic acids are condensed in ethanol under reflux conditions [12].



From o-Arylene Diamines

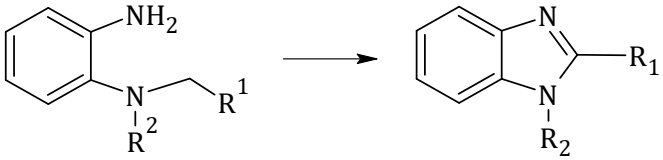
Using an catalyst such as topaquinone and a biocompatible CuBr2 electron transfer reconciler, primary aliphatic amines undergo oxidative C-H transformation to produce 1, 2-disubstituted benzimidazole 25a-h. Equimolar levels of each precursor were employed in this one -pot method, which also used ambient air [13].



(I) $CuBr_2$ air, MeOH, 45° C

Ar=C_6H_5, 4-ClC_6H_4, 4-$NH_2C_6H_4$, 4-BrC_6H_4, 4-MeC_6H_4, 4-$CF_3C_6H_4$

1, 2- Diamines 26a-e was oxidized and then cyclized using ligand-free copper bromide to produce benzimidazole derivatives 27a-e [14].



(i)[Ir(cod)Cl_2(5 mole %), CF_3CH_2OH, REFLUX; R_1=H, Me, C_2H_5, Ph; R_2=Me, C_2H_5, C_3H_7

Mechanism of Action of Benzimidazole

1. **The energy path, or metabolic failure**
   The medication attaches itself to the parasite's beta-tubulin.
   Starvation: This prevents the parasite's main food source, glucose from being absorbed. Cellular depletion and death result a decrease in ATP production (energy) in the absence of glucose.
2. **The division path, or structural failure**
   Disruption: The medication stops the microtubules that serve as the cell's "Scaffolding" from forming.
   Stoppage: This results in direct physical harm to the cell structure and hinders cellular division (mitosis) (Figure 2) [15].

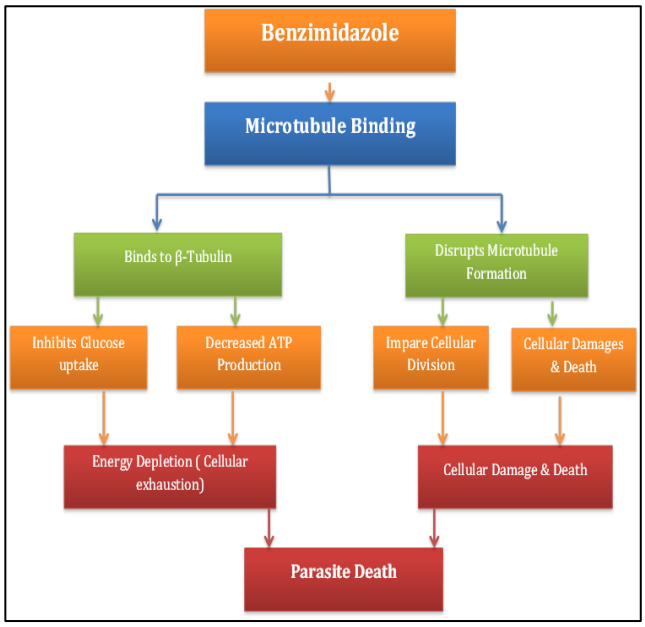


Figure 2: Mechanism of Action of Benzimidazole

Benzimidazole Significance and Their Derivatives (Figure 3)**:**

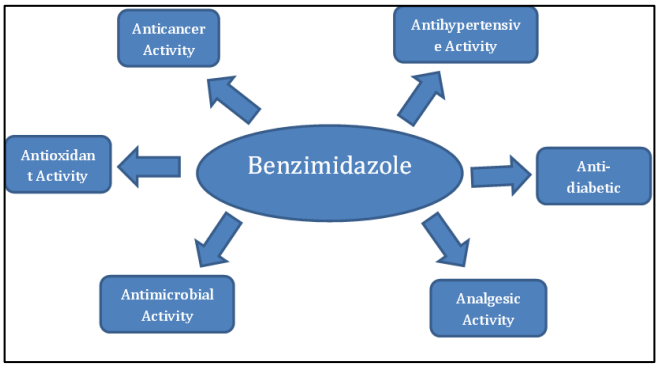
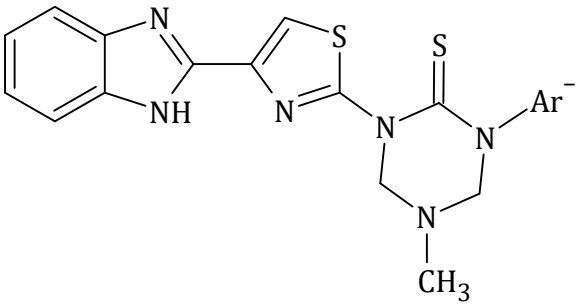


Figure 3: Biological Activities

Antimicrobial Activity:

Kumaraswamy Gullapelli et.al, (2017) synthesized novel benzimidazole-fused heterocyclic chemical analogues, including triazine and oxadiazinanes, utilizing conventionally methyl group where one hydrogen atom has been replaced by an amino group with different aryl unsymmetrical thiourea using a panel of gram-negative bacterial strains that were carefully selected and demonstrated.

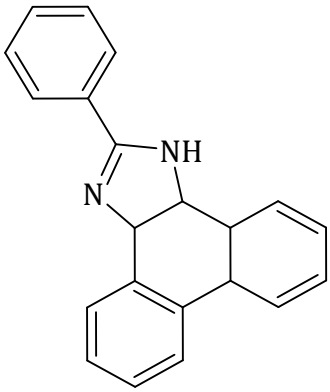
Triazinane and oxadiazinanes compounds' antibacterial activity was assessed using the zone of inhibition by well diffusion technique. Molecular docking studies were conducted using two proteins, DNA gyrase subunit B and topoisomerase II, with the synthesized chemicals. The antibacterial activity with a high binding energy and inhibition constant is confirmed by molecular docking investigations [16].



By blocking cell wall production, ergosterol biosynthesis, and important parasite metabolic processes, benzimidazole are highly potent, broad-spectrum antimicrobial drugs that show notable action against bacteria, fungi, and parasites. These heterocyclic substances include derivatives such as albendazole and mebendazole.

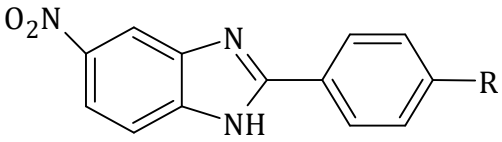
Jerad Suresh et al., (2016) reported a number of benzimidazole compounds were created and docked against the essential mtb enzyme target, cyclopropane mycolic acid synthase 2.

The compounds with high docking scores were selected for synthesis using the microwave irradiation approach, and the Micro plate Alamar Blue Assay method (MABA) was used to screen for anti-tubercular [17].

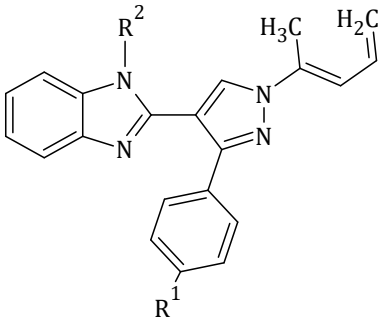


Anti-oxidant activity:

Sabrina Rahman Archie et al., (2017examined the antioxidant qualities of benzimidazole compounds and described their production [18].

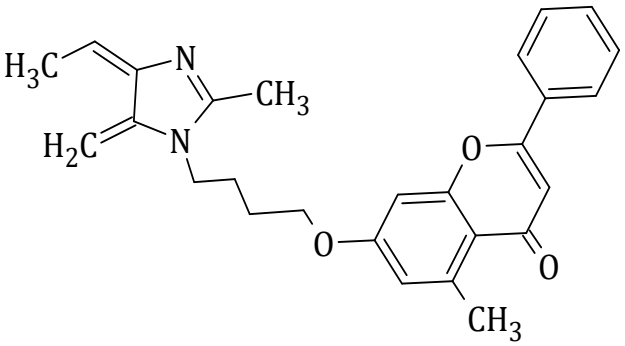


Mahesh Bellam et al., (2017synthesized benzimidazole, including N-substituted pyrazoles, and examined their antioxidant properties by evaluating their capacity to scavenge radicals against DPPH and H_2O_2 [19].

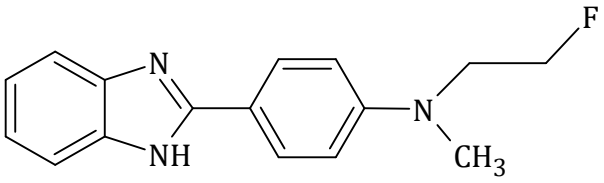


Anti-cancer Activity:

Zha Wanga et al., (2018) synthesis of compounds of chrysin benzimidazole and investigated their anticancer properties. With IC50 values of 25.72±3.95 mm, the synthesized molecule demonstrated the strongest anti-proliferative action against MFC cells [20].

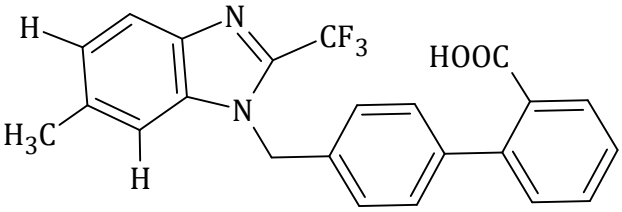


Goreti Ribeiro Morais et al., several benzimidazole derivatives with hydroxylated or fluorinated alkyl substituents were examined for their potential to treat cancer. They demonstrated the most promising antitumor effectiveness among the compounds under investigation. With an unreplaced benzimidazole and a 2-fluroethyl chain at the aniline N, a common anticancer drug, showed a good cytotoxic effect [21].

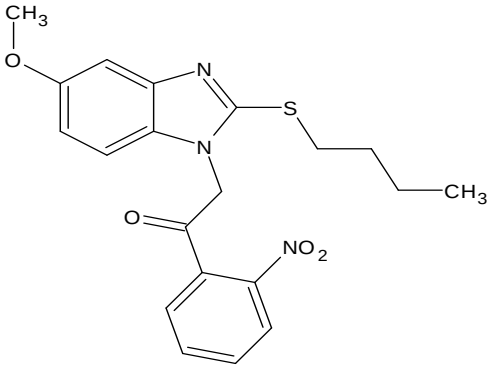


Anti-hypertensive Activity:

Rani S. Kankate et al., for the purpose to determine the parts that block angiotensin-II, a number of benzimidazole derivatives were produced. Antihypertensive activity tests were performed on each synthesized compound. Among all the compounds tested, this compound helps reduce high blood pressure. Dexamethasone can raise blood pressure, while losartan is used to control it [22].

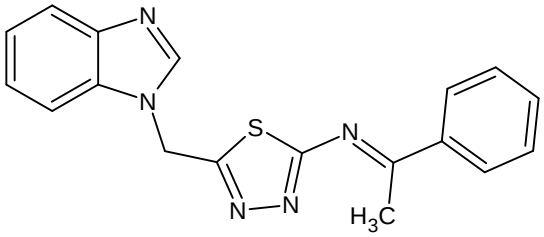


Abdulaziz Hammed G. et al., (2017) were synthesis of benzimidazole derivatives and conducted ACE inhibitor molecular docking research [23].



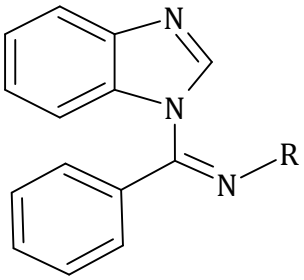
Anti-diabetes Activity:

Sandhya M. J. Nair created new analogs of 2-methyl benzimidazole with a thiadiazole group attached. The prepared compound was chosen for in-vitro antidiabetic activity, and it was discovered to exhibit 49.25% inhibition at 100µg conc. At a dosage of 100µg, reference acarbose demonstrated 68.61% inhibition [24].



Analgesic Activity:

Asma Eswayah et al., (2017) were reported N-substituted benzimidazole derivatives were synthesized and their analgesic properties were investigated [25].



CONCLUSION

A benzimidazole review article's conclusion usually identifies the compound as a "privileged scaffold" in medicinal chemistry because of its remarkable structural adaptability and strong biological profile. The benzimidazole ring is a fundamental component of several life-saving medications, including broad-spectrum anthelmintic, anti-ulcer medications (like omeprazole), and antihypertensive (like telmisartan). Reviewers come to the conclusion that scientists may fine-tune the molecule to target complicated diseases like cancer, bacterial infections that are resistant to several drugs, and even neurological disorders by carefully altering particular locations on the ring.

In order to ensure that benzimidazole stays at the forefront of drug discovery for the development of more potent, low-toxicity targeted medicines, attention is turning to "Green Chemistry"—the development of environmentally benign and high-yield synthetic processes. In addition to acting as amphoteric, adaptable lead scaffolds in drug development, benzimidazole derivatives are distinguished by their structural similarity to natural purines, which enables them to interact with DNA, RNA, and enzymes. These substances are crucial systemic fungicides in agriculture in addition to their medical applications.

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