RESEARCH PAPER

Translating in Benz-imidazole Research as Antibacterial and anti-proliferating scaffolds: A Systematic review (1976-To present)

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Abstract:

The global challenge of antimicrobial resistance arises as various pathogens, including bacteria and fungi, evolve to bypass existing drug treatments. In response, recent research has highlighted the significant potential of nitrogen-based heterocyclic, particularly Benz imidazole derivatives. Benzimidazoles are recognized for their broad clinical utility and effectiveness against resistant strains like MRSA. Similarly, Benz imidazole has emerged as a high-priority pharmacophore in medicinal chemistry due to its versatile pharmacological profile, which spans from antibacterial and antifungal actions to sedative and analgesic effects. This review evaluates the advancement of pharmacophore models, and also focus on FDA patents approved as antibacterial scaffolds available market. These insights provide a strategic framework for synthesizing next-generation Benz imidazole hybrids with optimized substituents and linkers to produce more effective antimicrobial agents.

Keywords: Benz imidazole, Antibacterial, Hybrid derivatives, resistance, Heterocyclic ring.

How to cite this article: Pallavi Bhaugonda Patil*1 Mrs. Sarita2 Ritu Singh3 Mr. Jainendra Kumar gautam4 Kajal Rani5 Dr. Rubal rathi6 Mrs. Kreetika Teotia7 Dr. Mohd. Shuaib8 Sachin kumar yadav9. Translating in Benz-imidazole Research as Antibacterial and anti-proliferating scaffolds: A Systematic review (1976-To present). Int J Drug Deliv Technol. 2026;16(89s):981-990. DOI: 10.25258/ijddt.16.89s.103.

INTRODUCTION:

While global healthcare initiatives have made significant strides in advancing human wellness, the emergence of novel infectious threats remains a persistent challenge. The scarcity of potent antimicrobial agents increasingly jeopardizes sophisticated medical interventions, such as organ transplants and the management of chronic conditions like cancer and diabetes. At the heart of this crisis is the accelerated pace at which pathogens develop immunity to current therapeutic regimens.[1,2] A wide variety of microbial groups are contributing to this rising tide of resistance, rendering many standard treatments ineffective. Among the most concerning pathogens is *Staphylococcus aureus*, a versatile Gram-positive bacterium capable of inhabiting diverse environments within human and animal hosts. The clinical management of *S. aureus* has become particularly difficult as it continues to evolve defenses against existing medicine, with a notable and growing resistance to beta-lactam antibiotics. The global rise of antibiotic-resistant bacterial strains has rendered many conventional therapies ineffective, creating a significant public health crisis. [1,2] This decline in drug efficacy is largely attributed to the inappropriate or excessive use of existing antibiotics.[3,6]According to the Global Research on Antimicrobial Resistance (GRAM) report, this phenomenon has become a primary cause of mortality, particularly within low- and middle-income regions.[7,8] The emergence of these "drug-resistant" pathogens necessitates the urgent design of innovative and unique antibacterial agents.[9] In recent years, benzimidazole derivatives have gained prominence for their broad pharmacological versatility, ranging from antibacterial to anti-helminthic activities.[10,11] Beyond their role in treating infections, these molecules exhibit a wide array of biological functions, including anti-cancer, anti-tubercular, anti-inflammatory, and anti-diabetic properties.[12-18] The therapeutic breadth of the benzimidazole scaffold makes it a "privileged

structure" in medicinal chemistry. A particularly effective strategy in drug discovery is the hybridization of different Pharmacophores into a single molecular entity.[19-27] This review summarizes the last two decades of research into Benz imidazole hybrids as high-potency antibacterial candidates. By analyzing Structure-Activity Relationships (SAR), this work provides a framework for the rational design of more effective clinical agents.

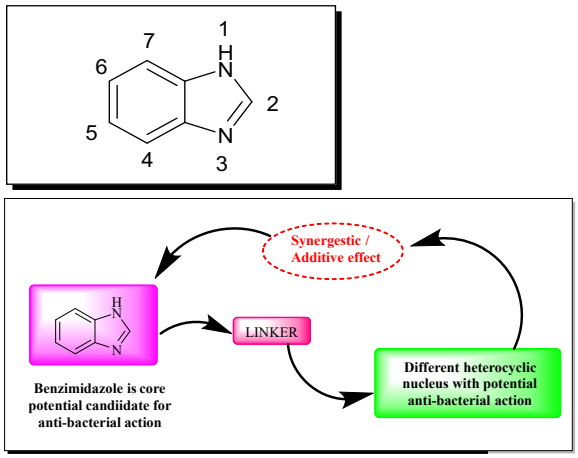
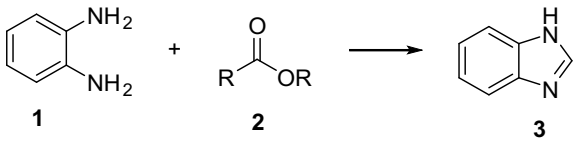


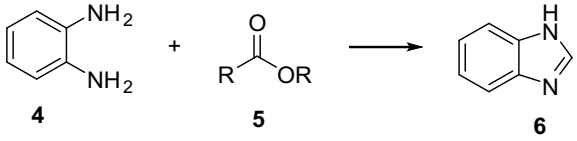
Figure:1 Mixing of variety of different nucleus having anti-bacterial action with benzimidazole.[2]

1. CHEMISTRY OF BENZIMIDAZOLE

The scaffold of Benz imidazole ring developed through coupling of benzene and imidazole ring together joint with 4 and 5 the position of imidazole ring. Benzimidazole is a heterocyclic scaffold which is formed when the benzene and imidazole rings are fused at 4th and 5th position. During 1872 a chemist named Hobrecker promptly synthesized first time Benz imidazole through the reduction of 2 –nitro-4-methylacetanlde shown in the reaction scheme following: followed by the Ladenburg in 1875, he reported further scaffold 3,4-diamine toluene in acetic acid **(Scheme 2).** During this process, dehydration occurred and the term 'anhydrobase' was derived. Benz imidazole was commonly was commonly called benzimidazoles and benzoglyoxaline, derivatives of o-phenylenediamine (OPDA).[28,29]



Scheme:1 Synthesis of benzimidazole from OPDA and carboxylic acid.



Scheme:2 Synthesis of benzimidazole from 2,5-dimethylbenzimidazole.

As illustrated in **(Figure1),** benzimidazole exhibits annular tautomerism, a process where the hydrogen atom shifts between the nitrogen atoms. This proton migration results in the formation of isomers that exist in dynamic equilibrium. Historically, as shown in **Figure 3**, benzimidazole (1) and 2-methylbenzimidazole (2) were identified as methenyl-o-phenylenediamine and ethenyl-o-phenylenediamine, respectively. These names reflect their chemical origins as derivatives synthesized from *o-phenylenediamine* and specific carbon-containing groups. Furthermore, in early chemical literature, benzimidazole compounds were classified based on their identity as derivatives containing the core imidazole scaffold fused to a benzene ring.



Figure:1 Tautamerism in benzimidazole core.

As o-phenylene formamidine, benzimidazole was previously known. The compounds 2(3H)-benzimidazolone (4a) and 2 (3H)-benzimidazolethione (4b) were historically been referred as o- phenylurea and o-phenylenethiourea respectively. In order to investigate the potential uses of benzimidazole in pharmaceuticals, Goodman and Nancy Hart published the first research paper on benzimidazole in 1943. Woolley represented its antibacterial activities in 1944. Brink et al. in 1949 recognized 5,6-dimethylbenzimi dazole as a vitamin B12 degradation product. It was found that the other derivatives showed the same properties like vitamin B12 studied by Emerson et al.[10,11] From ,this time, various synthetic approaches were developed to synthesis of the benzimidazole derivatives, like Norman G.B. and Karl Folker synthesized the degradation product 5,6- dimethyl benzimidazole.[7,12] Because of –NH group present in the molecule benzimidazole is amphoteric in nature.

Due to its ability to form salt, it exhibits both acidic as well as basic behavior. Wang et al. explained that benzimidazole can form the hydrogen bonding with the biological enzymes as well as receptors and can function as a ligand for metal ions.[29] After studying these properties of benzimidazole, it came to light as an important heterocyclic scaffold showing bioactivities and has multiple roles as antiviral, anticancer, anti-inflammatory.

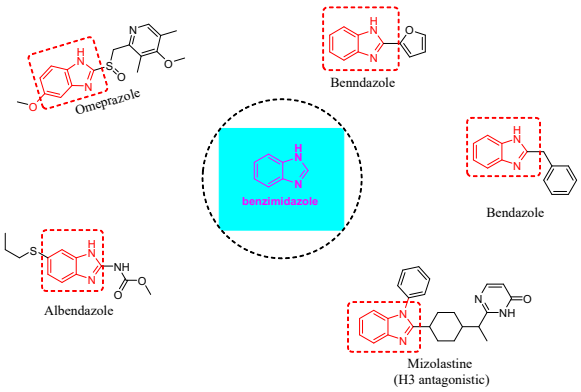


Figure 2. Drug molecules that have a benzimidazole pharmacophore.

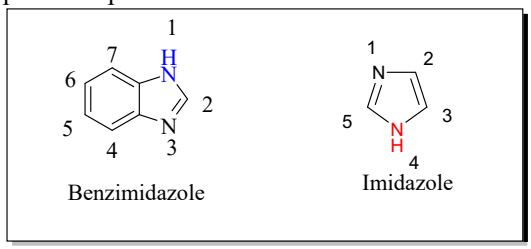


Figure. 3 numbering system in both nucleus.

3. CURRENT RATIONALITY AND APPLICATION OF BENZ IMIDAZOLE

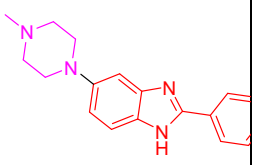
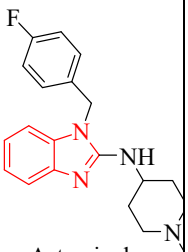
Recent advancements in Benz imidazole chemistry underscore its increasing importance in medical applications, especially owing to its structural adaptability and extensive pharmacological activities. Benz imidazole, a fused heterocyclic compound consisting of benzene and imidazole rings, has become a notable framework for drug development, especially in oncology and infectious disease areas. Its derivatives demonstrate a broad spectrum of biological activities, such as antibacterial, antiviral, anticancer, anti-inflammatory, and anti-tubercular effects [30,31]. The simplicity of synthesizing Benz imidazole derivatives has captured researchers' attention, spurring innovative methods that amplify their therapeutic capabilities. Recent investigations have delved into diverse synthetic strategies, encompassing green processes, to advance the creation of new compounds with heightened effectiveness and diminished toxicity. Investigations into the structure-activity relationship (SAR) are vital for comprehending how alterations at particular sites on the Benz imidazole ring affect biological activity, thus directing the logical development of novel drug candidates.[30,32]

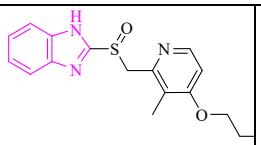
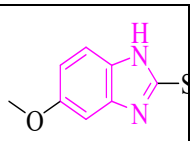
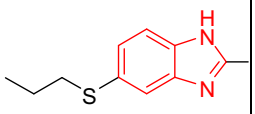
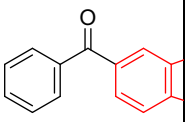
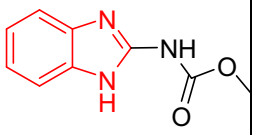
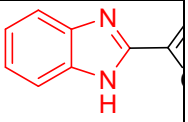
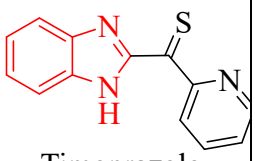
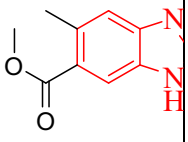
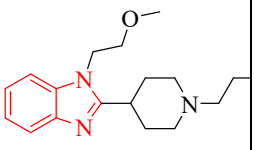
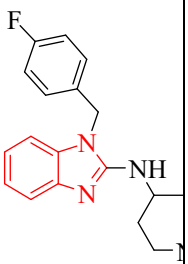
3.1 ADDRESSING FDA APPROVED MARKETED BENZMIDAZOLE AS PROMISING MOIETIES

At present, thousands of new heterocyclic compounds, either isolated from natural sources or synthesized in the laboratory, are reported every year. Several of these have attracted much research interest due to their biological and therapeutic potentials besides industrial usefulness.[34] Among these can be highlighted benzimidazoles as important intermediates in the design and development of biologically and pharmaceutically significant molecules. Substituted benzimidazole derivatives possess a wide range of biological properties which include antitumor, antimicrobial, anthelmintic, antibacterial, analgesic and inflammation reduction effects.[35-38] The versatile and diverse biological activities associated with the benzimidazole nucleus arise primarily from the variety of substituents and fragments attached to the benzimidazole ring system.[39-41] These structural modifications enable the benzimidazole structural hybrids to demonstrate a broad spectrum of medicinal and pharmacological activities, including antiviral[42] , anti-inflammatory[43-45], Several Benz imidazole core-based drugs currently in clinical use against various diseases are listed in Table 1.

Originally, benzimidazoles were synthesized for their antiparasitic efficacy, but in the early twentieth century, several anthelmintic benzimidazoles, including mebendazole, oxibendazole, carbendazim, albendazole, and fenbendazole. In recent fenbendazole have since been repurposed for cancer research[46-49].

Table:1 Pharmacological characteristics of therapeutic medications based on Benz imidazole moieties.[50,51]

Therapeutic activity	Name and structure of drug	
Anti-viral	 Hoechst 3	 Astemizole

Anti-ulcer	 Rebeprazole	 Omeprazole
Anti-parasitic	 Albendazole	 Mebenda
Antifungal	 Carbendazim	 Fuberidazol
Proton pump inhibitors	 Timoprazole	 Picoprazo
Antihypertensive	 Bilastine	 Astemi

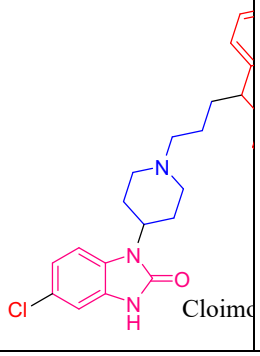
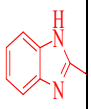
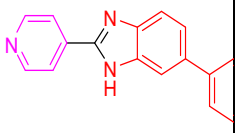
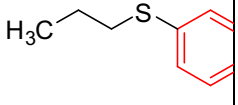
Anti-psychotic agents	 Cloimc	 2-((4-argiopiperazin-1-yl)m

Table 2 Clinically FDA approved Benz imidazole based anti-bacterial agents

Drugs Name	Designed core Structure	IUPAC NAME	Biological Target/Clinical Trial Phase
Ridinilazole [52] (SMT 19969)		2-pyridin-4-yl-6-(2-pyridin-4-yl-3H-benzimidazol-5-yl)-1H-benzimidazole	Under trial phase III
Albendazole [53]		Methyl[6-(propylsulfa	Approved

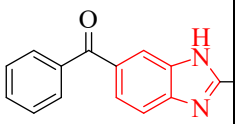
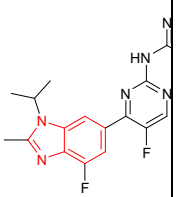
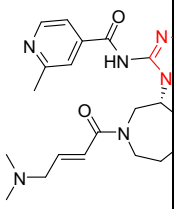
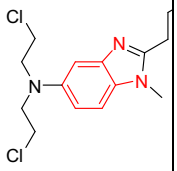
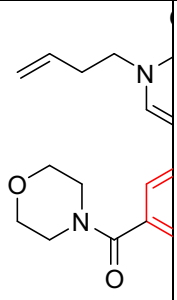
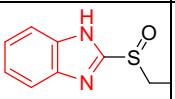
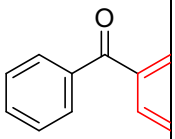
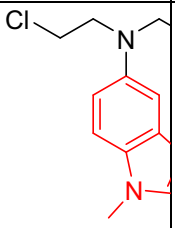
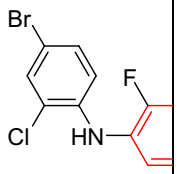
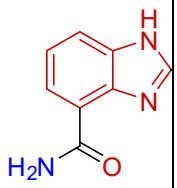
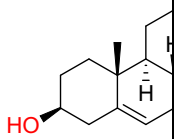
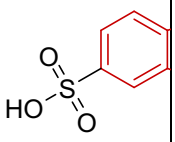
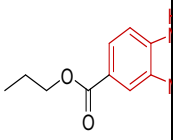
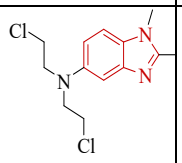
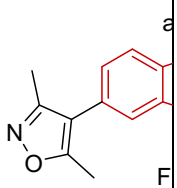
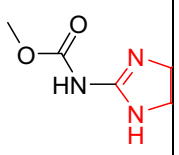
		nyl)-1H-benzimidazol-2-yl] carbamate	24January (2008).
Mebendazole[54,55]		methyl1H-benzimidazol-2-yl carbamate	Approved

Table 3 Clinically and FDA approved Benz imidazole drugs as anti-proliferative agents

Drug name	**IUPAC name**	**Structure**	**Biological target/ Clinical Trial Phase**
Abemaciclib[56]	*N*-[5-[(4-ethylpiperazin-1-yl)methyl]-2-pyridinyl]-5-fluoro-4-(7-fluoro-2-methyl-3-propan-2-ylbenzimidazol-5-yl)pyrimidin-2-amine		FDA approved / Human EGFR-2, early breast cancer
Nazartinib[57]	N-[7-chloro-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]azepan-3-yl]benzimidazol-2-yl]-2-methylpyridine-4-carboxamide		EGFR mutation/ FDA approved
Tinostamustine[58]	7-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]-N-hydroxyheptanamide		Dual inhibitor of DNA/ HDAC No FDA approval
GNE-371[59]	6-but-3-enyl-4-[1-methyl-6-(morpholine-4-carbonyl)ben		TAF1(2)-bromodomain

	zimidazol-4-yl]-1H-pyrrolo[2,3-c]pyridin-7-one		NO FDA approval
Rabeprazole[60] (Repurposed)	2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methylsulfinyl]-1H-benzimidazole		MLL 1-WDR 5 inhibitor Approved as GERD
Mebendazole	methyl *N*-(6-benzoyl-1*H*-benzimidazol-2-yl)carbamate		Malignant Glioma/ FDA approved
Bendamustine	4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)butanoic acid		B-cell lymphoma / Phase I

Selumetinib	5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-n-(2-hydroxyethoxy)-1-methyl-1h-benzimidazole-6-carboxamide		Mitogen-activated protein kinase (MAPK) pathway/ FDA approved
Veliparib	(R)-2-(2-methylpyrrolidin-2-yl)-1H-benzo[d]imidazole-4-carboxamide		PARP/ Phase I
Galeterone	(3S,8R,9S,10R,13S,14S)-17-(benzimidazol-1-yl)-10,13-dimethyl2,3,4,7,8,9,11,12,14,15-decahydro-1H		Metastatic pancreatic adenocarcinoma/ Phase III

	cyclopenta[a]phenanthren-3-ol		
Ensulizole	2-phenyl-1H-benzo[d]imidazole-5-sulfonic acid		HDAC3 inhibitor, enhances histone acetylation/ FDA Approved
BZD9L1	propyl 2-(4-(piperidin-1-yl)phenyl)-1H-benzo[d]imidazole-5-carboxylate		SIRT1 and SIRT2, Inhibits SIRT1, and SIRT2 deacetylase activity and with a dose-dependent reduction
			in cell survival and migration/ NO FDA approval
Tinostamustine	7-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-N-hydroxyheptanamide		Dual inhibitor of DNA/ HDAC
Inobrodib	(6S)-1-(3,4-difluorophenyl)-6-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-(4 methoxycyclohexyl)benzimidazol-2-yl]piperidin-2-one		CBP/ p300 inhibitor / Not Approved
Nocodazole	methyl N-[6-(thiophene-2-carbonyl)-1H-		UHRF1, gradual loss

	benzimidazol-2-yl] carbamate		of DNA

Conclusion and future clinical perspective:

Benzimidazole scaffolds are well-renowned and highly valuable therapeutic candidates in medicinal chemistry owing to their remarkable structural diversity, structurally close resemblance to purine bases, and favorable physicochemical properties. Additionally, this review discusses the broad therapeutic potential of Benz imidazole scaffolds, highlighting clinically and FDA-approved Benz imidazole drugs, patents, and their wide-spectrum anticancer chemotherapeutic applications. The Benz imidazole structural hybrids display significant therapeutic efficacy and cytotoxicity against multiple cancer cell lines through diverse molecular mechanisms that inhibit different key oncologic signaling pathways, thereby pre venting tumor growth and proliferation. Benz imidazole derivatives have been investigated as inhibitors of topoisomerase, PARP, protein kinase, dihydrofolate reductase, and microtubule, as well as DNA intercalates, alkylating agents, and androgen receptor antagonists.

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