Int. J. Sci. R. Tech., 2026 3(4)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Benzimidazole Scaffold: Advances In Structural Modifications And Diverse Pharmacological Activities

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ABSTRACT

Benzimidazole is an important nitrogen-containing heterocyclic scaffold widely recognized as a privileged pharmacophore in medicinal chemistry. Structurally, it comprises a benzene ring fused with an imidazole moiety, a feature that contributes to its remarkable chemical stability and biological versatility. Benzimidazole derivatives have demonstrated a broad spectrum of pharmacological activities, including antimicrobial, antiviral, anticancer, antidiabetic, antihypertensive, antitubercular, antimalarial, antioxidant, antihistaminic, and anti-inflammatory effects. The structural adaptability of the benzimidazole nucleus allows diverse substitutions, enabling fine-tuning of physicochemical and biological properties. Recent research highlights that substituted benzimidazole-based pharmacophores interact effectively with various biological targets such as enzymes, receptors, and nucleic acids, often exhibiting potent activity with comparatively low toxicity. These characteristics make them attractive candidates for the development of novel therapeutic agents. This review summarizes recent advances in the design, synthesis, structure-activity relationship (SAR), and therapeutic applications of benzimidazole derivatives, emphasizing their emerging biological profiles and significance in modern drug discovery.

Keywords: Benzimidazole; Pharmacophore; Heterocyclic scaffold; Biological activities; Structure–activity relationship; Drug discovery.

INTRODUCTION

Benzimidazole constitutes a prominent class of nitrogen-containing heteroaromatic compounds exhibiting extensive biological and pharmacological significance. Structurally, it is characterized by a fused bicyclic system comprising a benzene ring condensed with an imidazole moiety bearing two nitrogen atoms [2]. The presence of these heteroatoms imparts unique electronic distribution, hydrogen-bonding capacity, and amphoteric behavior, which collectively contribute to its broad spectrum of biological interactions. Heterocyclic compounds are ubiquitous in nature and play indispensable roles in cellular metabolism and biochemical processes [3]. Benzimidazole derivatives demonstrate diverse pharmacokinetic and pharmacodynamic properties, making them valuable scaffolds in medicinal chemistry [1]. A wide range of biological activities has been reported, including anti-inflammatory, antimicrobial, antiviral, anticancer, anticonvulsant, antidiabetic, and antioxidant effects [2]. Additionally, benzimidazole-based compounds exhibit inhibitory activity against the Zika virus, function as α-glucosidase inhibitors, antitubercular and antiglycation agents, NOX-2 antagonists, antileukemic agents, and possess antihypertensive properties. These multifaceted activities highlight the versatility of the benzimidazole core as a privileged pharmacophore. Several clinically approved drugs incorporate the benzimidazole nucleus, such as Candesartan (antihypertensive), Albendazole (antimicrobial), Bendamustine, Nocodazole, Abemaciclib (antitumor), Enviradene (antiviral), Omeprazole (antiulcer), and Benoxaprofen analogues (anti-inflammatory) [4,5]. The successful integration of this scaffold into marketed therapeutics underscores its structural and pharmacological relevance. Furthermore, transition metal complexes of benzimidazole derivatives have been extensively investigated as biologically active molecular models. In several instances, metal coordination enhances biological efficacy compared to the corresponding free ligands [6]. Due to its structural resemblance to

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

nucleotide bases, the benzimidazole framework can act as a bioisostere, facilitating interactions with biologically derived polymers and enabling the development of compounds with improved therapeutic profiles and reduced toxicity. The chemical stability and synthetic flexibility of the benzimidazole nucleus allow for extensive structural modification and lead optimization. Consequently, it serves as a robust template for the generation of novel derivatives with enhanced biological potential, contributing significantly to modern drug discovery [7].

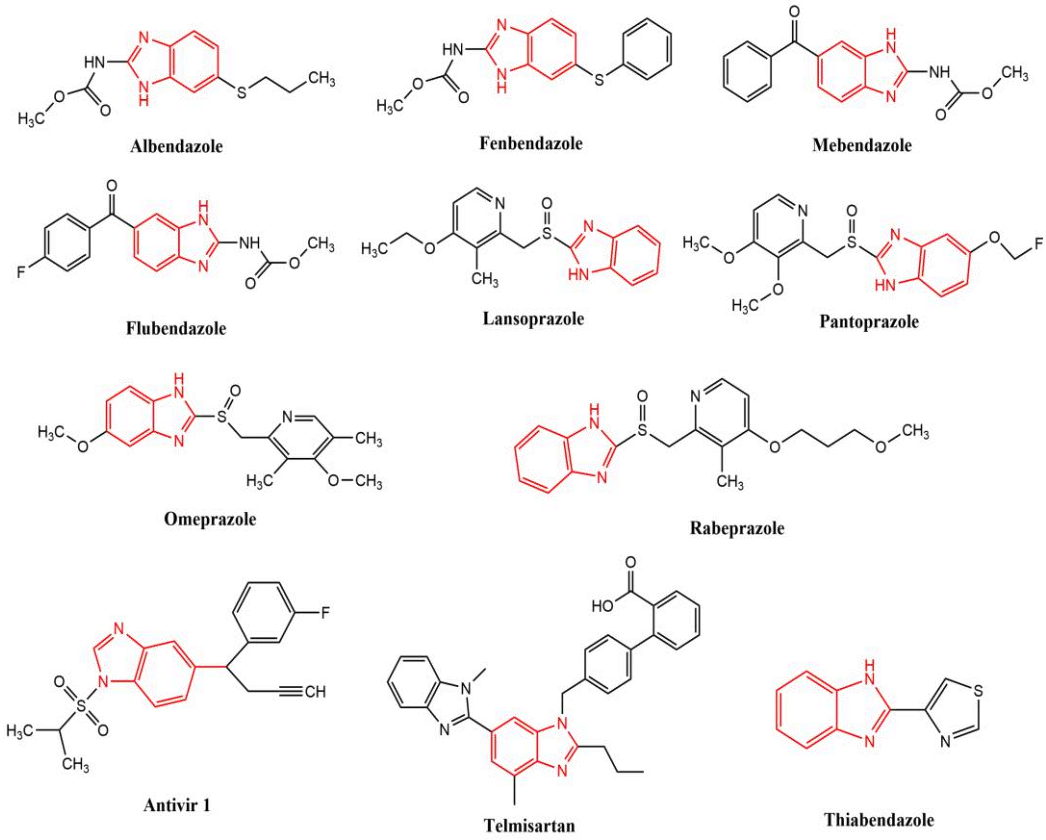


Figure 1. Chemical structures of benzimidazole scaffolds

BIOLOGICAL ACTIVITY OF BENZIMIDAZOLE-BASED COMPOUNDS

Antimicrobial agents are classified according to their target microorganisms, such as antibacterial and antifungal drugs. Based on their mechanism of action, they are further categorized as microbicidal agents, which eliminate microorganisms, and microbiostatic agents, which inhibit microbial growth. Benzimidazole derivatives exhibit notable antimicrobial activity, primarily attributed to their structural similarity to purine bases [3]. This resemblance enables them to interfere with essential microbial processes, including nucleic acid and protein synthesis. In rational drug design, the development of novel antimicrobial agents often involves incorporating structural features of biologically active heterocycles. The fusion of pyrimidine and imidazole rings forms the purine nucleus [8], a key structural component of microbial genetic material. Owing to its critical biological role, purine and its bioisosteric analogues, such as benzimidazole, are considered promising scaffolds for the design of new antimicrobial agents with broad-spectrum activity [7].

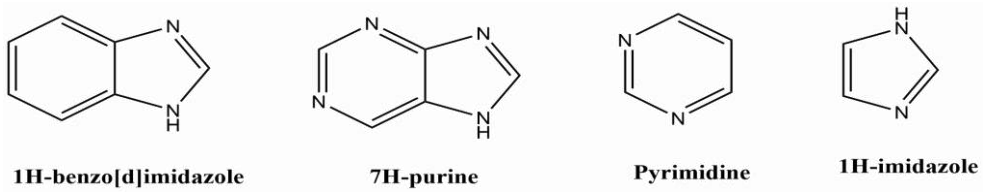
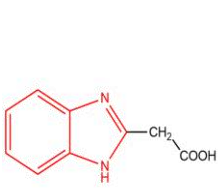
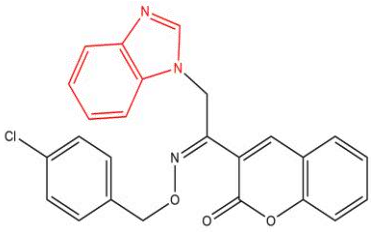


Figure 2. Structural comparison of the benzimidazole and purine heterocyclic

The antibacterial potential of synthesized benzimidazole derivatives has shown promising results. Substituted benzimidazoles prepared from benzene-1,2-diamine and dicarboxylic acids, followed by acylation with benzoyl chloride (NaH), were structurally confirmed by spectral analysis. Among them, compound SB1 exhibited significant activity against *Pseudomonas aeruginosa*, comparable to ciprofloxacin [7]. Similarly, coumarin–benzimidazole hybrids synthesized by Singh L. R. *et al*. demonstrated potent antibacterial effects. Compound 12 showed strong activity against *P. aeruginosa* (MIC = 3.12 µg/mL), outperforming ampicillin (25 µg/mL), tetracycline, and kanamycin (450 µg/mL). It also exhibited excellent efficacy against *Staphylococcus aureus* (MIC = 1.56 µg/mL) and *Escherichia coli* (MIC = 3.12 µg/mL) [9]. Structure–activity relationship studies indicated that antibacterial potency is strongly influenced by halogen substitution, with para-chloro derivatives displaying maximum activity, while meta- and ortho-substituted analogues showed reduced effects.

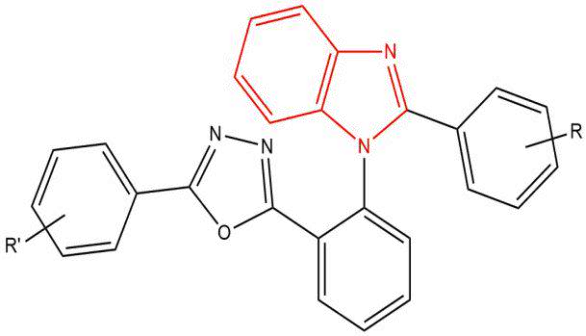


SB1



12

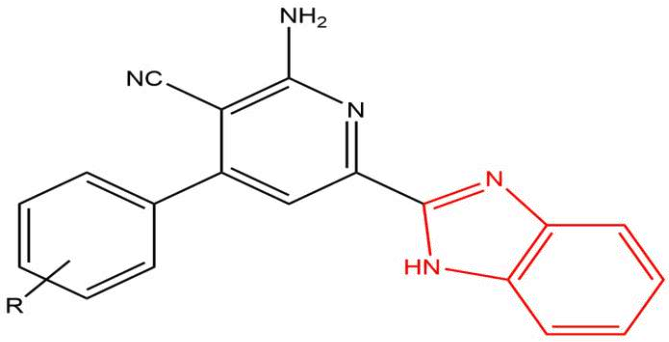
Kapoor A. *et al*. synthesized a series of 2-substituted benzimidazole derivatives and evaluated their antimicrobial activity. Among them, compound 5d exhibited the highest potency against *Escherichia coli* with a MIC of 1.30 µmol/mL. Compounds 5e–5h also demonstrated significant activity (MIC = 1.58–1.88 µmol/mL) against *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Aspergillus niger*. The observed activity was superior or comparable to standard drugs such as ciprofloxacin (MIC = 2.33 µmol/mL) and fluconazole (MIC = 1.99 µmol/mL). Structure–activity relationship analysis indicated that the introduction of electron-donating substituents on the benzylidene phenyl ring enhances antimicrobial efficacy [10].



5d; R= 4-OCH3, R'= NO2
5e; R= 4-OCH3, R'= 4-OCH3
5f; R= 4-F, R' = 4-NO2
5g; R= 4-F, R'= 4-OCH3
5h; R= 4-F, R'= 3,4-CH3NH2

Compound 5

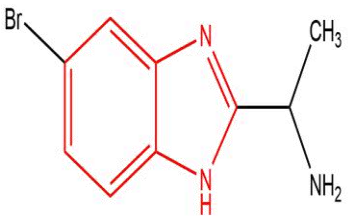
Yadav *et al*. reported the synthesis of novel 2-substituted benzimidazole derivatives incorporating a pyridine moiety (4a–4f). The structures were confirmed by elemental analysis, IR, ^{1}H-NMR, and mass spectroscopy. The synthesized compounds were evaluated *in vitro* for antibacterial and antifungal activity using the disc diffusion method. At a concentration of 500 µg/mL, the compounds exhibited measurable zones of inhibition against *Escherichia coli*, *Pseudomonas pseudomonas*, *Bacillus subtilis*, and *Klebsiella pneumoniae*, as well as antifungal activity against *Candida albicans* and *Aspergillus niger*. Fluconazole and cefuroxime HCl were used as standard antifungal and antibacterial drugs, respectively [11].



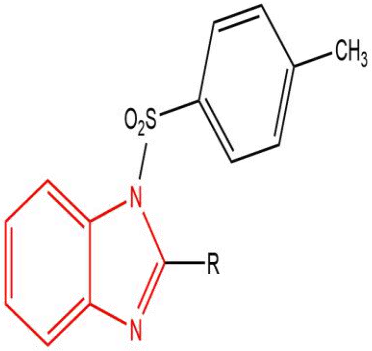
4a; R= H
4b; R= 4-OCH3
4c; R= 3,4-OCH3
4d; R= 3,4,5,-OCH3
4e; R= 4-Cl
4f; R= 4-N(CH3)2

Compound 4

Alasmary F.A. *et al*. synthesized a library of 53 benzimidazole derivatives substituted at the 1-, 2-, and 5-positions and evaluated them against 26 bacterial and 10 fungal strains. Compounds 17 and 18 (2-ethanamine derivatives) exhibited potent antibacterial activity, with MIC values comparable to ciprofloxacin against two MRSA strains. Several 5-halogenated derivatives, particularly 5-bromo analogues, showed strong antifungal activity, with MICs comparable to or better than amphotericin B. Compound 18 was identified as one of the most active antibacterial candidates [12]. Gupta S.K. *et al*. synthesized 2-alkyl and 2-aryl benzimidazoles using acetic, o-chlorobenzoic, benzoic, and cinnamic acids, followed by N-substitution with benzoyl and tosyl chlorides. Compounds 2a and 2d demonstrated significant antibacterial activity against *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans*, showing efficacy comparable to standard drugs [13]. Tuncbilek M. *et al*. prepared novel 2-substituted benzimidazole derivatives, where compound 32 exhibited superior antibacterial activity compared to ciprofloxacin [7,14]. Shingalapur R.V. *et al*. synthesized 5-bromostyryl-2-benzimidazoles via condensation of cinnamic acids with 5-bromo-1,2-phenylenediamine in ethylene glycol. Compound 40 showed potent antimicrobial activity against various bacterial and fungal strains, comparable to ciprofloxacin and fluconazole [7,15].

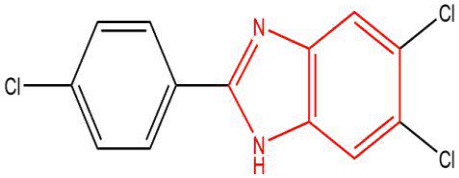


Compound 18

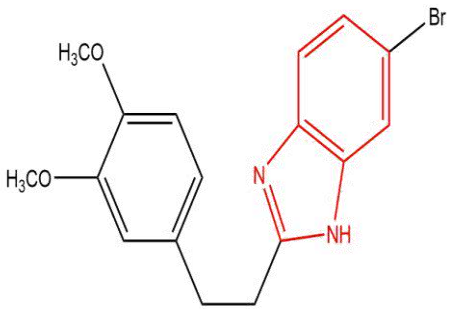


2a; R= methyl
2d; R= 2-phenyl-1-ethenyl

Compound 2

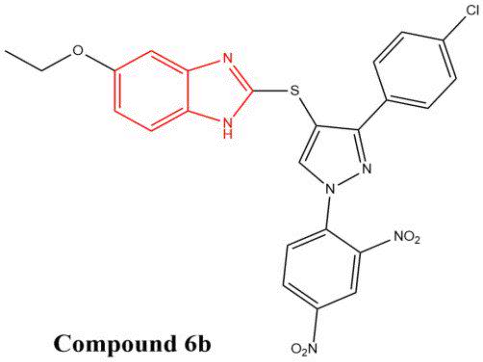


Compound 32

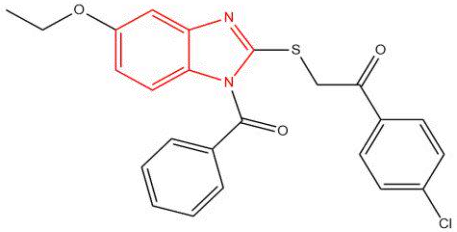


Compound 40

Turkey R. H. *et al*. synthesized novel 5-ethoxy-2-mercaptobenzimidazole derivatives and confirmed their structures by elemental microanalysis, IR, and ^1H-NMR spectroscopy. The antibacterial activity was evaluated by the agar diffusion method at concentrations of 50 and 100 µg/mL against *Staphylococcus aureus*, *Streptococcus agalactiae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Compounds 6b and 7b exhibited the highest potency, producing zones of inhibition ranging from 21–37 mm, comparable to standard antibiotics cefotaxime and imipenem [16].

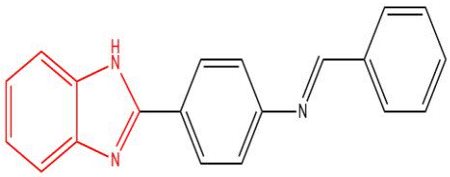


Compound 6b

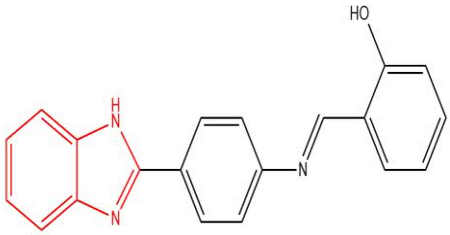


Compound 7b

Alam S.A.M.F. *et al*. synthesized Schiff base derivatives of 2-phenylbenzimidazole via cyclocondensation of benzene-1,2-diamine with *p*-aminobenzoic acid in the presence of polyphosphoric acid and xylene, followed by condensation with various aldehydes. The synthesized Schiff bases were evaluated for antibacterial activity using the tube dilution method. Compounds SAM-2 and SAM-10 exhibited superior antibacterial potency compared to the standard drug vancomycin, indicating enhanced efficacy of the azomethine-linked benzimidazole derivatives [17].

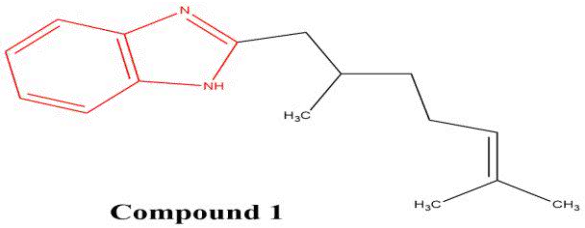


Compound SAM-2



Compound SAM-10

U. Kankeaw *et al.* reported a facile synthesis of benzimidazole derivatives via condensation of citronellal with *o*-phenylenediamine in ethanol. The structures of the obtained products were confirmed by FTIR and 1H-NMR spectral analysis. The antibacterial activity was evaluated using the agar diffusion method, with gentamicin as the reference drug. The synthesized derivatives exhibited measurable zones of inhibition, indicating promising antibacterial potential [18].

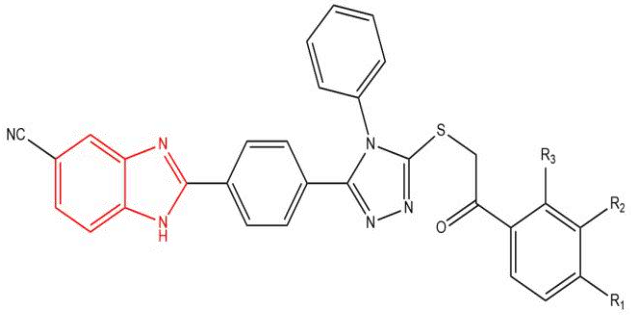


Compound 1

1. Antifungal Activities

Benzimidazole derivatives are widely recognized as effective antifungal agents due to their potency and favorable safety profiles. Clinically used examples include Carbendazim, Benomyl, and Thiabendazole [19]. Their antifungal mechanism is primarily associated with inhibition of ergosterol biosynthesis. Ergosterol is an essential sterol regulating fungal membrane permeability and fluidity [20]. A key molecular target is lanosterol 14α-demethylase (CYP51), a cytochrome P450 enzyme. Azole antifungals act as non-competitive inhibitors by coordinating to the heme iron of CYP51, thereby blocking ergosterol formation and exerting fungistatic effects [21]. Emir Güzel *et al*. synthesized benzimidazole–1,2,4-triazole derivatives (6a–l),

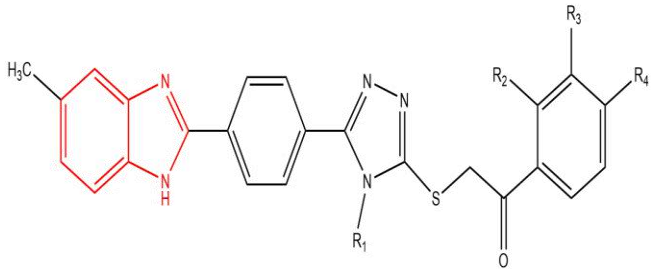
structurally confirmed by ^{1}H-NMR, ^{13}C-NMR, and HR-MS analysis. The compounds were evaluated *in vitro* against *Candida albicans*, *C. parapsilosis*, *C. glabrata*, and *C. krusei*. Compounds 6b, 6i, and 6j demonstrated superior antifungal activity with MIC values of 0.97 µg/mL, particularly against *C. glabrata*, outperforming standard drugs Voriconazole and Fluconazole [22].



Compound ID	R1	R2	R3
6b	OCH3	H	H
6i	Cl	H	H
6j	Cl	H	Cl

Compound 6a-l

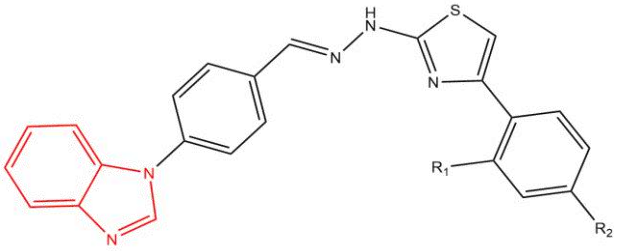
The antifungal efficacy of azoles depends on the affinity of the N-1 substituent toward cytochrome P450 and the strength of coordination with the heme iron of lanosterol 14α-demethylase (CYP51). Inhibition of ergosterol biosynthesis disrupts fungal membrane integrity, leading to growth inhibition or cell death [23]. Both benzimidazole and triazole rings are recognized as key pharmacophores contributing to potent antifungal activity [24]. Can N. Ö. *et al.* synthesized a series of benzimidazole–triazole derivatives (5a–s) as ergosterol biosynthesis inhibitors. The compounds were evaluated against *Candida glabrata* (ATCC 90030), *C. parapsilosis* (ATCC 22019), *C. krusei* (ATCC 6258), and *C. albicans* (ATCC 24433). Compounds 5i and 5s demonstrated significant antifungal activity with MIC_{50} values of 0.78–1.56 µg/mL. Cytotoxicity assessment against NIH/3T3 cells showed IC_{50} values markedly higher than the MIC_{50} values, indicating favorable selectivity. LC–MS/MS analysis confirmed that both compounds significantly reduced intracellular ergosterol levels, validating CYP51 inhibition as the probable mechanism of action [25].



5i; R1=CH3, R2=H, R3=OH, R4=OH
5s; R1=C2H5, R2=H, R3=OH, R4=OH

Compound 5a

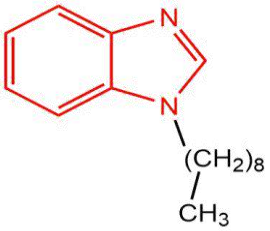
A series of 12 benzimidazole–thiazole derivatives (3a–l) was synthesized and structurally characterized by 1H-NMR, 13C-NMR, IR, and ESI-MS spectroscopy. The compounds were evaluated for anticandidal activity against *Candida krusei*, *C. glabrata*, *C. albicans*, and *C. parapsilosis*. In silico ADME analysis predicted favorable pharmacokinetic profiles for all derivatives. Among them, compounds 3c and 3d exhibited the highest antifungal potency against all tested *Candida* species. Cytotoxicity studies indicated low toxicity, with IC_{50} values > 500 µg/mL. LC–MS/MS analysis confirmed that compounds 3c and 3d significantly reduced ergosterol levels in *C. albicans*, supporting inhibition of ergosterol biosynthesis as the probable mechanism of action [26].



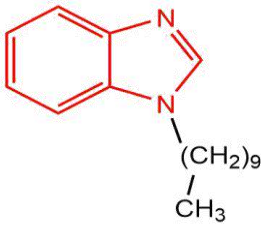
3C; R1=H, R2=NO2
3D; R1=H, R2=CN

Compound 3

Khabnadideh S. *et al*. synthesized novel alkylated benzimidazole and benzotriazole derivatives via N-alkylation with bromoalkanes and by coupling amino thiazole amide derivatives with 2-piperazino-1-ethanol using tetraethylammonium bromide or triethylamine as catalysts. The structures were confirmed by standard spectroscopic techniques. Antifungal activity was evaluated using the CLSI-recommended broth microdilution method. The results indicated that alkylbenzimidazole derivatives exhibited higher antifungal potency than the corresponding alkylbenzotriazoles. Compounds 1a and 2a from the benzimidazole series showed broad-spectrum activity against all tested fungal strains [27].

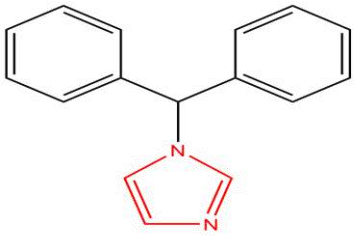


Compound 1a

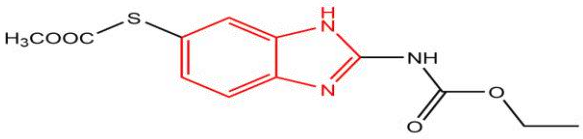


Compound 2a

Sadeghian S. *et al*. synthesized imidazole, benzimidazole, and benzotriazole derivatives (C1–C8) and evaluated their antimicrobial activity using the CLSI broth microdilution method against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Salmonella typhi*, and *Candida albicans*. Among them, imidazole derivative C5 exhibited the highest potency, showing superior activity against *S. aureus* (MIC = 2–16 µg/mL) compared to ampicillin, and strong anticandidal activity against *C. albicans* (MIC = 1 µg/mL), comparable to Amphotericin B. MTT cytotoxicity assays indicated low toxicity (< 35%) for all tested compounds [28]. Yang L. *et al*. synthesized benzimidazole derivatives bearing thioether and carbamate functionalities and assessed their antifungal activity using the mycelial growth inhibition method against *Cytospora mandshurica*, *Thanatephorus cucumeris*, *Botrytis cinerea*, *Verticillium dahliae*, *Phytophthora infestans*, and *Gibberella zeae*. Compound E11 showed significant antifungal efficacy at 50 µg/mL, with inhibition rates of 70% against *V. dahliae* and 75% against *P. infestans*, outperforming Albendazole [29].

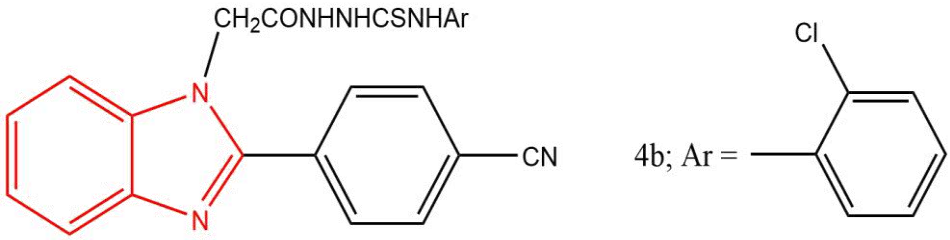


Compound C5



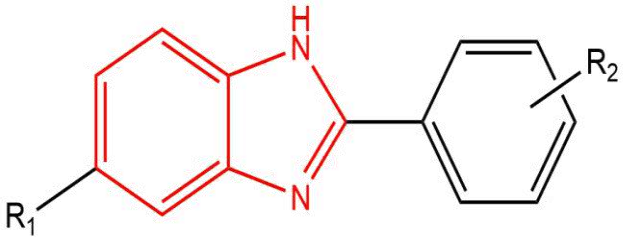
Compound E11

Kerimov *et al*. synthesized novel benzimidazole derivatives and evaluated there *in vitro* effects on NADPH-dependent lipid peroxidation (LP), ethoxyresorufin O-deethylase (EROD) activity, and antifungal potential. At a concentration of 10^{-3} M, compounds 4c (52%), 4e (58%), and 4h (43%) significantly inhibited lipid peroxidation in male rat liver microsomes. In the EROD assay, compounds 4c (100%), 4h (100%), 5c (98%), and 5h (100%) exhibited stronger inhibitory activity than the reference inhibitor caffeine (85%). Antifungal screening revealed that only compounds 4b and 4h demonstrated notable activity against *Candida albicans*, whereas other derivatives showed moderate effects [30].



Compound 4

Zamani L. *et al*. synthesized ten 2-substituted benzimidazole derivatives (J1–J10) via condensation of *o*-phenylenediamine with substituted aldehydes using nano-$SnCl_4/SiO_2$ as a mild heterogeneous catalyst. The structures were confirmed by spectroscopic analysis. Among the series, compound J2 exhibited the most potent antifungal activity against *Cryptococcus neoformans*, *Candida krusei*, *C. dubliniensis*, *Microsporum canis*, and *C. albicans*, with MIC values ranging from 8–64 µg/mL. Cytotoxicity evaluation against MCF-7 and A549 cell lines (MTT assay) revealed that J2 showed promising antitumor activity, J5 and J6 displayed moderate effects, while J7 was essentially non-toxic [31].

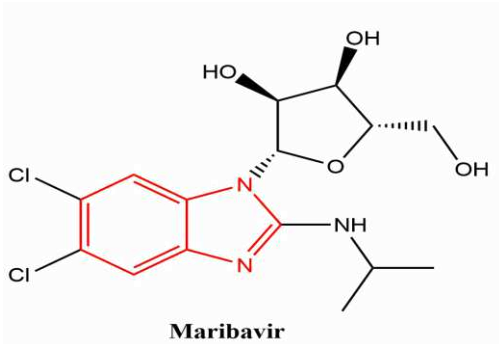


J2; R1=H, R2=4-F
J5; R1=H, R2=2,3-di (OH)
J6; R1=CH3, R2=4-NO2
J7; R1=NO2; R2=4-NO2

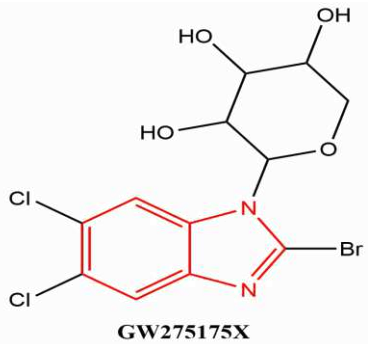
Compound J1-J10

2. Antiviral Activities

Heterocyclic scaffolds play a crucial role in antiviral drug development, particularly purine-based analogues containing the imidazole ring. Clinically important agents such as Ganciclovir, Valganciclovir, Valacyclovir, Entecavir, and Adefovir dipivoxil derive their antiviral efficacy largely from imidazole- or purine-based structural motifs. In contrast, anti-cytomegalovirus activity in Maribavir (1263W94) and GW275175X is attributed to the benzimidazole nucleus [32]. Despite their clinical utility, prolonged antiviral therapy often leads to resistance and systemic toxicity, necessitating the development of novel agents with improved safety and reduced resistance profiles. Benzimidazole nucleosides represent promising candidates due to their structural versatility and distinct mechanisms of action [33]. Numerous benzimidazole derivatives have demonstrated antiviral activity against diverse viral pathogens, including human cytomegalovirus (HCMV), human immunodeficiency virus (HIV), and hepatitis B and C viruses, highlighting the therapeutic potential of this heterocyclic scaffold in antiviral drug discovery [34].

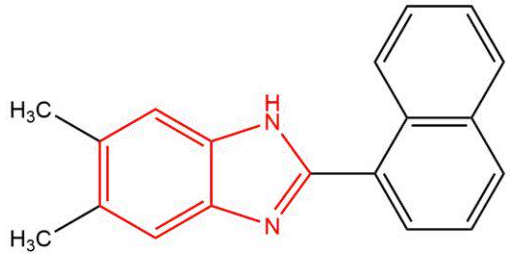


Maribavir



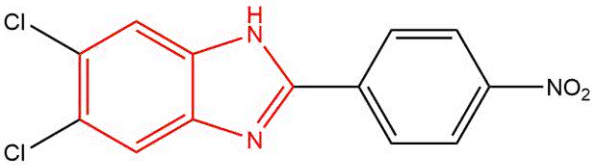
GW275175X

Vitale *et al*. synthesized a series of 2-arylbenzimidazole derivatives and evaluated their antiproliferative and antiviral activities using cell-based assays. The compounds were screened against a broad panel of viruses, including members of the *Flaviviridae* (flaviviruses and pestiviruses), *Retroviridae*, *Picornaviridae*, *Paramyxoviridae*, *Rhabdoviridae*, *Reoviridae*, as well as DNA viruses from the *Herpesviridae* and *Poxviridae* families. Compounds 15, 28, and 29 exhibited moderate antiviral activity against the yellow fever virus, with effective concentrations in the range of 6–27 µM. However, none of the synthesized benzimidazole derivatives demonstrated significant antiviral effects at non-cytotoxic concentrations in resting cell monolayers [35].



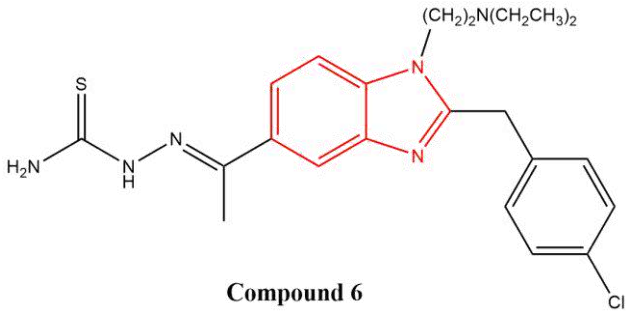
Compound 15

Tonelli M. *et al*. synthesized 76 derivatives of 2-phenylbenzimidazole and evaluated their cytotoxic and antiviral profiles against 10 RNA and DNA viruses. The most susceptible viruses were BVDV, CVB-2, HSV-1, Sb-1, and YFV, whereas HIV-1 and VSV were inactive, and RSV, VV, and Reo-1 were minimally affected. Compound 24 (5,6-dichloro-2-(4-nitrophenyl) benzimidazole) exhibited potent and selective activity against vaccinia virus (VV) with an EC_{50} of 0.1 µM, demonstrating 18- and 110-fold higher potency than reference drugs mycophenolic acid (EC_{50} = 1.8 µM) and 6-azauridine (EC_{50} = 11 µM), respectively. Additionally, compounds 50, 51, and 53 showed strong and selective activity against BVDV with EC_{50} values of 0.8–1.5 µM, comparable to the standard NM 108 (EC_{50} = 1.7 µM) [36].



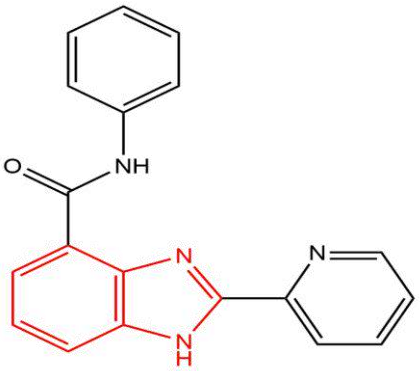
Compound 24

Francesconi *et al*. synthesized two series of benzimidazole derivatives bearing 5-(thio) semicarbazone and 5-hydrazone functionalities via modification of 5-acetylbenzimidazole. The compounds were evaluated for antiviral activity against multiple viruses and for cytotoxicity in mammalian cell lines. Derivatives 6, 8, 16, and 17, containing 5-(thio) semicarbazone or 5-hydrazone groups along with a 2-benzyl substituent on the benzimidazole core, exhibited significant inhibitory activity against influenza A virus and human coronavirus. For respiratory syncytial virus (RSV), activity was primarily observed in 5-thiosemicarbazone (25) and 5-hydrazone (22) derivatives possessing a 2-[(benzotriazol-1/2-yl) methyl] benzimidazole framework. These compounds demonstrated potent antiviral efficacy with activity comparable to the reference drug Ribavirin [37].

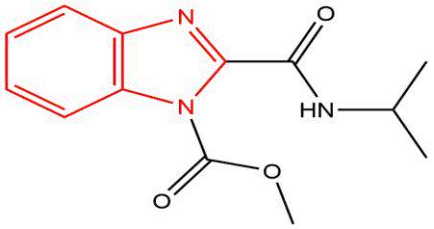


Compound 6

Gudmundsson *et al*. synthesized amine-substituted N-(1H-benzimidazol-2-ylmethyl)-5,6,7,8-tetrahydro-8-quinolinamines and evaluated their anti-HIV-1 activity. Structural modification of amine substituents significantly influenced antiviral potency, leading to the identification of highly active derivatives exhibiting sub-nanomolar inhibitory activity against HIV-1 [38]. Additionally, 2-pyridyl-1H-benzimidazole-4-carboxamide derivatives 59 and 60 demonstrated selective inhibition of Coxsackie virus B3 in VERO cells. Compound 61, a 2-substituted benzimidazole N-carbamate derivative, showed moderate antiviral activity against Coxsackie virus B2 [39, 40].

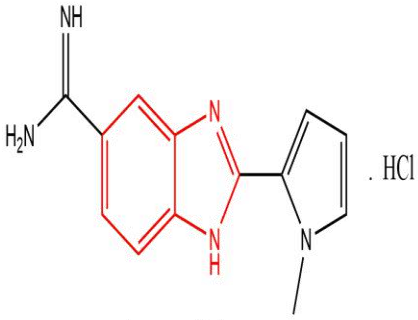


Compound 59

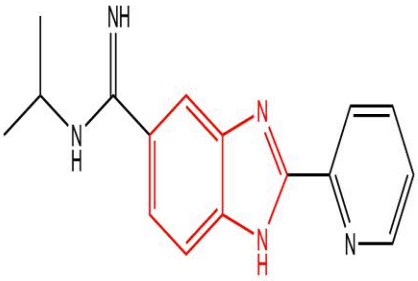


Compound 61

Starčević *et al.* synthesized C-5 amidino-substituted benzimidazole derivatives bearing heterocyclic moieties at C-2 (pyridine, N-methyl-pyrrole, imidazole) and evaluated their antitumor and antiviral activities against coxsackieviruses, echoviruses, and adenovirus. Among them, 2-(1-methyl-1H-pyrrol-2-yl)-1H-benzimidazole-5-carboxamidine hydrochloride (16) and N-isopropyl-2-pyridin-2-yl-1H-benzimidazole-5-carboxamidine (17) showed significant anti-adenoviral activity, indicating their potential to inhibit adenoviral replication with promising IC_{50} values in the micromolar range [41].



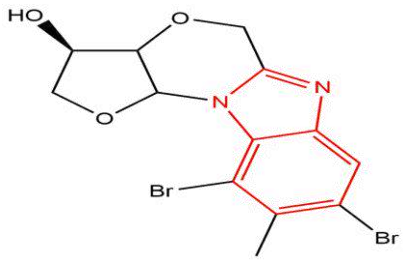
Compound 16



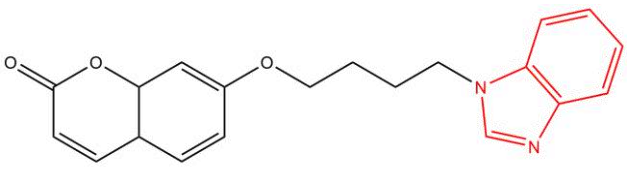
Compound 17

Huo *et al*. synthesized a series of benzimidazole derivatives and assessed their antiviral potential against the respiratory syncytial virus (RSV). Among the synthesized compounds, a27 exhibited the most potent activity with an EC_{50} = 9.49 µM, significantly suppressing viral replication and pro-inflammatory cytokine production across multiple RSV strains. In vivo evaluation in a murine model demonstrated reduced body-weight loss and attenuation of lung tissue damage. Structure–activity relationship (SAR) studies indicated that substitution at the C-3 position of the benzimidazole core markedly influenced antiviral potency and cytotoxicity [42].

Liu *et al.* investigated the antiviral mechanism of 7-(4-benzimidazolebutoxy) coumarin (BBC) against Spring viraemia of carp virus (SVCV). Mechanistic studies demonstrated that BBC modulates protein kinase C (PKC) activity, leading to activation of the Nrf2-mediated antiviral pathway. BBC treatment significantly reduced viral replication, enhanced interferon (IFN) response, and upregulated heme oxygenase-1 (HO-1) expression, thereby strengthening host antiviral defense. These findings indicate that BBC exerts antiviral activity through PKC/Nrf2 pathway modulation and immune response enhancement [43].

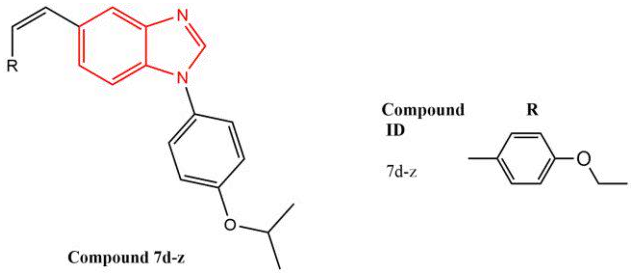


Compound a27

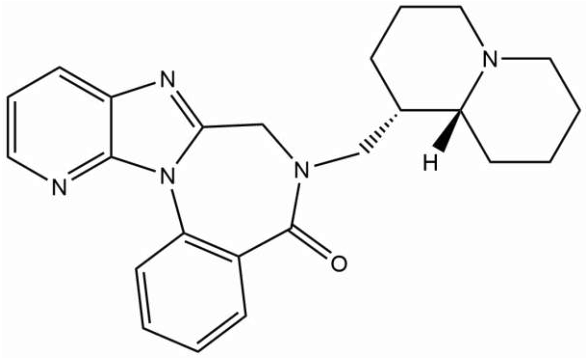


Compound BBC

Chen J. *et al*. designed two series of benzimidazole-based inhibitors targeting Lassa virus (LASV) entry. Lentiviral pseudotypes expressing LASV glycoprotein complex (GPC) were employed to screen viral entry inhibitors, and binding affinities were validated by surface plasmon resonance (SPR). Compounds 7d–z, 7h–z, 13c, 13d, and 13f exhibited potent antiviral activity with IC_{50} values of 7.58–15.46 nM and selectivity index (SI) > 1251. SPR studies showed strong target binding with $K_D < 8.25 \times 10^{-7}$ M. Notably, compound 7h-Z demonstrated the highest potency (IC_{50} = 7.58 nM; SI = 2496), identifying it as a promising lead candidate for further antiviral development [44].

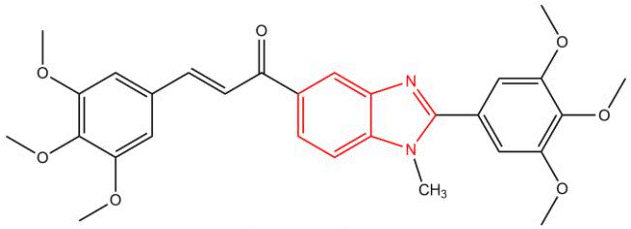


Tonelli M. *et al*. evaluated a library of 86 benzimidazole derivatives for antiviral activity against 10 RNA and DNA viruses. Among them, 52 compounds exhibited measurable antiviral effects, with the most pronounced activity observed against Coxsackievirus B5 (CVB-5), Respiratory syncytial virus (RSV), Bovine viral diarrhea virus (BVDV), and Suid herpesvirus 1 (Sb-1). Most active compounds were based on the 2-benzylbenzimidazole scaffold, while other effective derivatives included 1-phenylbenzimidazole (2), 2-trifluoromethylbenzimidazole (69), dihydropyrido[3,2′:4,5]imidazo[1,2-a][1,4]benzodiazepine-5-one (3), dibenzo[c,e] benzimidazo[1,2-a]azepine (22), and 2-(tetrahydropyran-2-yl)benzimidazoles (81, 82, 86). These scaffolds demonstrated significant antiviral potential, highlighting benzimidazole-based frameworks as promising lead structures for further optimization against CVB-5, RSV, BVDV, and Sb-1 infections [45].



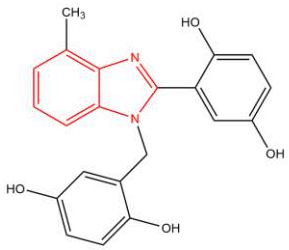
3. Antidiabetic Activities

Benzimidazole has emerged as an important scaffold in the development of antidiabetic agents, particularly for managing hyperglycemia, a globally prevalent metabolic disorder. Several benzimidazole-based derivatives have demonstrated significant glucose-lowering potential through enzyme inhibition mechanisms. Rai P. V. *et al*. synthesized a novel series of benzimidazole–chalcone hybrids via a one-pot nitro reductive cyclization method. The compounds were structurally confirmed by ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectroscopy. Biological evaluation revealed that compound 7l exhibited potent inhibitory activity with IC_{50} = 22.45 ± 0.36 µg/mL (α-glucosidase) and 20.47 ± 0.60 µg/mL (α-amylase). Molecular docking studies further demonstrate strong binding interactions of 7l within the active sites of both enzymes, supporting its potential as a promising antidiabetic lead molecule [2].

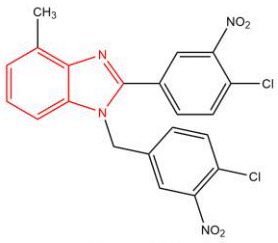


Tocco G. *et al*. synthesized a series of 1,2-disubstituted benzimidazoles via condensation of *o*-phenylenediamine with substituted aromatic aldehydes. The compounds were evaluated for α-glucosidase and α-amylase inhibitory activity. Notably, compound 8s showed the highest α-glucosidase inhibition with IC_{50} = 0.39 ± 0.04 µM, followed by 8k (IC_{50} = 7.4 ± 1.6 µM) and 8r (IC_{50} = 13.8 ± 2.7 µM). However, all tested derivatives exhibited weak α-amylase inhibitory activity,

indicating selective α-glucosidase inhibition and potential utility in postprandial hyperglycemia management [46].

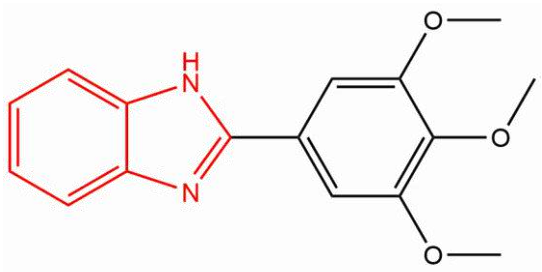


Compound 8r



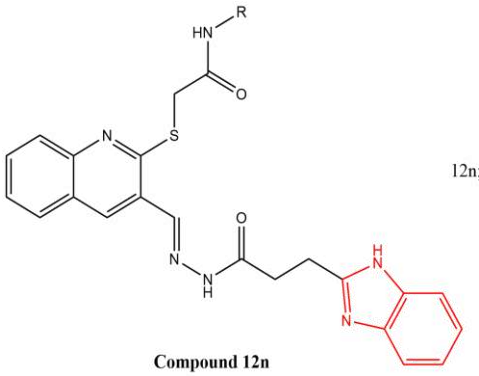
Compound 8k

Gidado I. *et al*. synthesized two 2-substituted benzimidazoles using a boric acid–catalyzed protocol, affording high yields with sharp melting points. Structural elucidation was performed by FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy. Biological evaluation revealed significant antioxidant and α-glucosidase inhibitory activity, with compound BL24 exhibiting the strongest radical scavenging capacity and enzyme inhibition, highlighting its potential as an antidiabetic lead [47]. Similarly, Ullah H. *et al*. synthesized a series of oxadiazole–benzimidazole hybrids (1–16) and characterized them by ^{1}H-NMR, ^{13}C-NMR, and HREI-MS. Among the series, analogue 8 showed the most potent α-glucosidase inhibition, while analogue 2 demonstrated significant α-amylase inhibitory activity. Molecular docking studies confirmed strong binding interactions within the active sites of both enzymes, suggesting that these hybrid scaffolds possess promising dual inhibitory potential for antidiabetic therapy [48].



Compound BL24

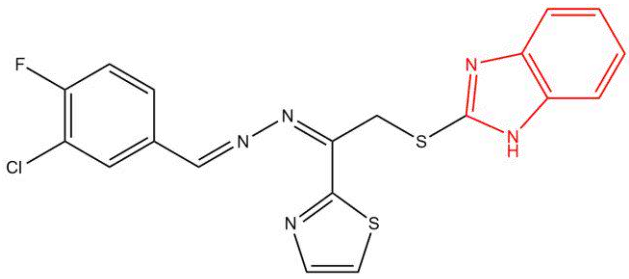
Nikfar P. *et al*. designed and synthesized a series of quinolone-2-thio-acetamide-propane hydrazide benzimidazole derivatives (12a–o) targeting key carbohydrate-hydrolyzing enzymes involved in type-2 diabetes, namely α-glucosidase and α-amylase. Among the series, compound 12n (a 4-fluorophenylacetamide analogue) exhibited the most potent dual inhibitory activity against both enzymes and showed superior efficacy compared to the standard drug Acarbose. These findings highlight compound 12n as a promising lead candidate for further antidiabetic drug development [49].



12n; R = 4-Fluorophenyl

Compound 12n

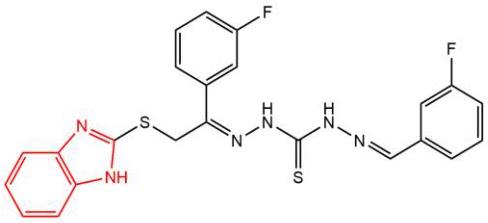
Khan S. *et al*. synthesized a series of benzimidazole-derived thiazole-based bis-Schiff bases (1–14) and confirmed their structures by ^{1}H-NMR, ^{13}C-NMR, and HREI-MS analyses. The compounds were evaluated for α-glucosidase and α-amylase inhibitory activity in comparison with the standard drug Acarbose (IC_{50} = 8.30 ± 0.20 µM and 9.30 ± 0.10 µM, respectively). Among them, compound 8 exhibited superior potency with IC_{50} = 4.20 ± 0.20 µM (α-glucosidase) and 3.50 ± 0.20 µM (α-amylase), significantly outperforming acarbose. Molecular docking studies revealed favorable protein–ligand interactions within enzyme active sites, while ADME analysis indicated improved pharmacokinetic properties of the active analogues, supporting their potential as promising antidiabetic lead candidates [50].



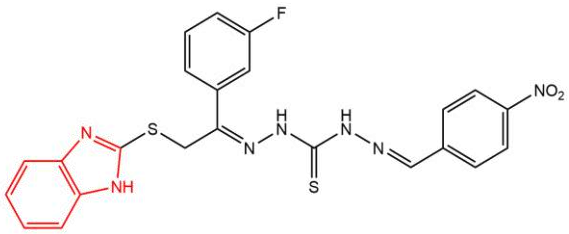
Compound 8

A series of benzimidazole-based thiosemicarbazone derivatives (7–21) was synthesized and structurally characterized by ^{1}H-NMR, ^{13}C-NMR, and HREI-MS spectroscopy. The compounds were evaluated for α-glucosidase and α-amylase inhibitory activity as potential antidiabetic agents. All derivatives exhibited good to excellent enzyme inhibition. Notably, compound 19 showed remarkable potency with IC_{50} =

1.30 ± 0.20 µM (α-glucosidase) and 1.20 ± 0.20 µM (α-amylase), while compound 20 demonstrated IC_{50} = 1.60 ± 0.20 µM and 1.10 ± 0.01 µM, respectively. These values were significantly superior to the standard drug Acarbose (IC_{50} = 11.29 ± 0.07 µM and 11.12 ± 0.15 µM), indicating strong dual inhibitory potential. The results suggest that benzimidazole–thiosemicarbazone hybrids represent promising lead scaffolds for the development of novel antidiabetic therapeutics [51].

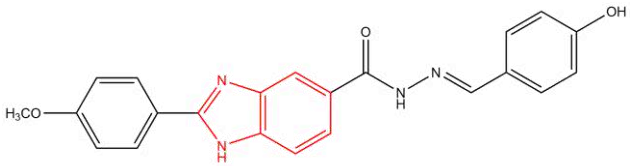


Compound 19



Compound 20

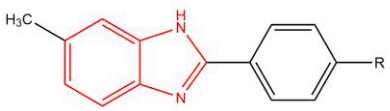
Azizian H. *et al*. synthesized a novel series of benzimidazole–Schiff base hybrids (8a–p) and evaluated their α-glucosidase inhibitory activity. Structural characterization was carried out using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and CHNS elemental analysis. The majority of the synthesized compounds exhibited superior α-glucosidase inhibition compared to the standard drug Acarbose. Among them, compounds 8p (thiophene substituent), 8h (phenyl), and 8a (2-fluorophenyl) demonstrated the highest inhibitory potency. In contrast, compound 8g, bearing a 3,4,5-trimethoxyphenyl moiety, was inactive against α-glucosidase. These findings highlight the significant influence of the Schiff base substituent on enzyme inhibition and support further optimization of benzimidazole-based antidiabetic agents [52].



Compound 8a

4. Antioxidant Activities

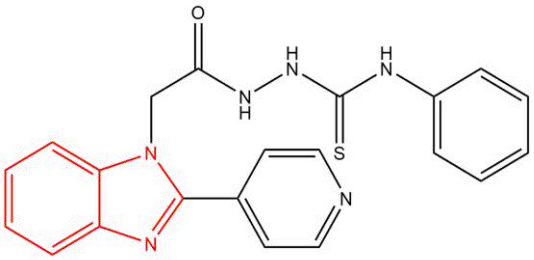
Oxidative stress plays a crucial role in the pathogenesis of degenerative disorders such as diabetes, atherosclerosis, ischemic heart disease, cancer, and ageing [53]. Consequently, extensive research has focused on identifying potent antioxidant agents [54], and benzimidazole derivatives have emerged as promising candidates due to their broad pharmacological potential. Karmaker N. *et al*. synthesized a series of 2-substituted-5-methylbenzimidazole derivatives (3a–e) by condensing 4-methyl-1,2-phenylenediamine with various *p*-substituted benzaldehydes (2a–e). Structural characterization was performed using standard spectroscopic techniques. Antioxidant activity was evaluated via the DPPH free radical scavenging assay, where the compounds exhibited significant activity with IC_{50} values ranging from 1.054 to 19.05 µg/mL, outperforming the reference antioxidant Butylated hydroxytoluene (IC_{50} = 26.96 µg/mL). These results highlight the strong antioxidant potential of substituted benzimidazole derivatives [53].



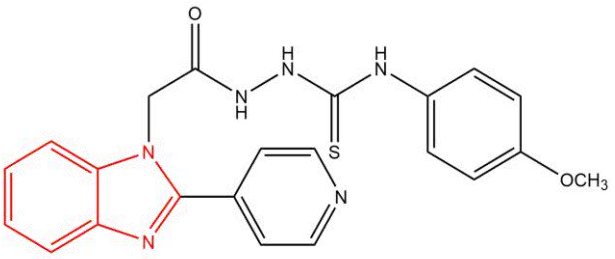
Compound 3a-e

Compound ID	R
3a	Cl
3b	Br
3c	F
3d	OCH3
3e	NO2

Ayhan-Kılcıgil G. *et al*. synthesized a series of novel benzimidazole derivatives (10–24) and evaluated their antioxidant potential using multiple *in vitro* assays, including microsomal NADPH-dependent lipid peroxidation inhibition, DPPH radical scavenging, and superoxide anion scavenging assays. Among the tested compounds, 12 and 13 exhibited outstanding antioxidant activity. In the DPPH assay, they showed IC_{50} values of 1.3×10^{-5} M and 1.2×10^{-5} M, respectively, which were significantly more potent than the reference antioxidant Butylated hydroxytoluene ($IC_{50} = 2.3 \times 10^{-4}$ M). These findings indicate that selected benzimidazole derivatives possess strong free radical scavenging capacity and potential therapeutic relevance against oxidative stress–related disorders [54].

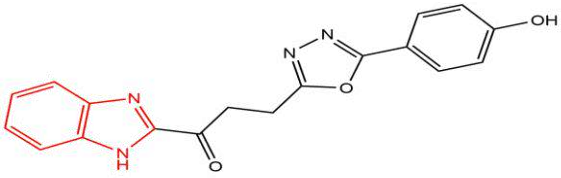


Compound 12

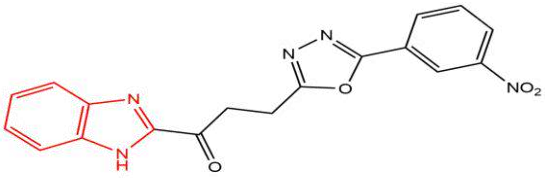


Compound 13

Bhandari S. V. *et al*. synthesized novel benzimidazole–1,3,4-oxadiazole hybrids and evaluated their *in vitro* antioxidant potential using the DPPH radical scavenging assay. Structural characterization was carried out by ^{1}H-NMR and FT-IR spectroscopy. Molecular docking studies revealed that compounds 1A, 2A, and 3A exhibited favorable Glide scores of −7.575, −6.932, and −6.911 kcal/mol, respectively, compared to reference antioxidants Propyl gallate (−4.757 kcal/mol) and Ascorbic acid (−4.50 kcal/mol). Biological evaluation showed that compound 2A displayed the highest antioxidant activity with IC_{50} = 53.00 ± 1.31 µg/mL, though it was less potent than ascorbic acid (IC_{50} = 11.51 ± 0.31 µg/mL). These findings suggest that benzimidazole–oxadiazole hybrids possess promising antioxidant properties and warrant further structural optimization [55].

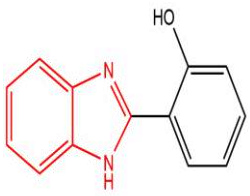


Compound 1A

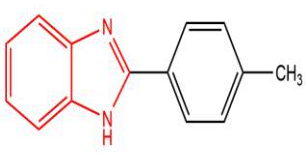


Compound 2A

Odame F. *et al*. reported a base-catalyzed synthesis of benzimidazoles via condensation of aldehydes with *o*-phenylenediamine. The synthesized derivatives were characterized by IR, elemental microanalysis, ^{1}H/^{13}C-NMR, and GC–MS techniques. Additionally, single-crystal X-ray analysis was performed for 2-(2-chlorophenyl)-1H-benzimidazole (4) and 2-(1H-benzimidazol-2-yl)-4-nitrophenol (8) to confirm their molecular structures. Antioxidant activity assessed by the DPPH radical scavenging assay showed that 2-(1H-benzimidazol-2-yl) phenol (2), 2-*p*-tolyl-1H-benzimidazole (3), and 2-(4-methoxyphenyl)-1H-benzimidazole (7) exhibited IC_{50} values of 1974, 773, and 800 µM, respectively, indicating moderate free radical scavenging potential [56].



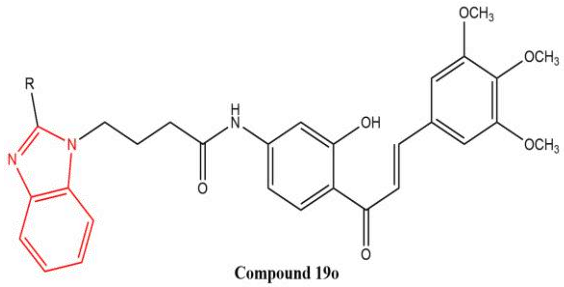
Compound 2



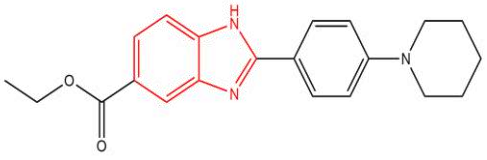
Compound 3

5. Anticancer Activities

Wang Q. *et al*. synthesized a series of benzimidazole-containing flavone and chalcone derivatives and evaluated their antiproliferative activity against various tumor cell lines. The benzimidazole–chalcone hybrids displayed stronger growth inhibition compared to benzimidazole–flavone analogues. Among them, compound 19 emerged as a promising lead, demonstrating significant antitumor efficacy in both *in vitro* and *in vivo* models [57]. In another study, ethyl-2-(4-(piperidine-1-yl) phenyl)-1H-benzo[d]imidazole-5-carboxylate (BZD9L1) showed high selectivity against colorectal cancer (CRC), with IC_{50} values of 16.82 µM (HCT-116) and 20.11 µM (HT-29) cell lines. Colony formation assays revealed a 96.50% reduction (HCT-116) and 1.33% reduction (HT-29) at 25 µM, compared to the standard drug Fluorouracil (103.5% and 163.7%, respectively). Mechanistic studies indicated that BZD9L1 induces apoptosis through inhibition of SIRT1 and SIRT2 (sirtuins), leading to DNA damage and suppression of tumor cell proliferation [58,59].

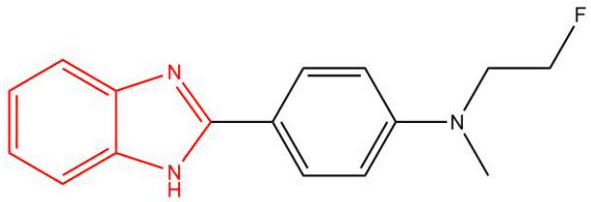


Compound 19o



BZD9L1

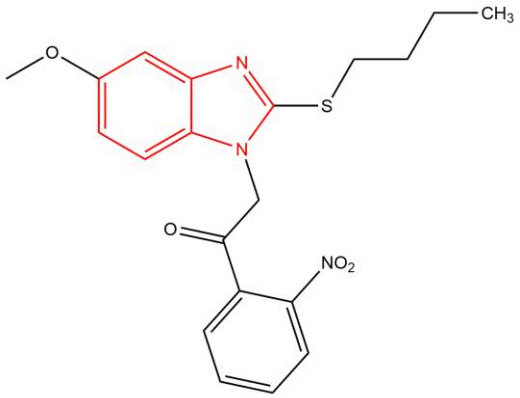
Nguyen *et al*. synthesized fourteen transition metal complexes along with five free benzimidazole ligands. Structural characterization was performed using FT-IR, ^{1}H-NMR, powder XRD, and ESI-MS, while UV–Visible spectroscopy and ICP-OES confirmed metal incorporation in the complexes. Biological evaluation demonstrated that most metal complexes exhibited enhanced anticancer activity compared to their corresponding free ligands. Notably, complexes C1, C3, and C14 showed potent antiproliferative effects with IC_{50} values of 5.8–10.4 µM, outperforming the reference drug Cisplatin (IC_{50} = 16.5 ± 1.0 µM for A549 and 19.4 ± 1.7 µM for MDA-MB-231) [60]. Similarly, Morais G. R. *et al*. synthesized fluorinated and hydroxylated alkyl-substituted benzimidazole derivatives and evaluated their antitumor activity. Among them, compound (2) bearing an unsubstituted benzimidazole core with a 2-fluoroethyl chain at the aniline nitrogen displayed the highest activity, showing moderate cytotoxicity against the U87 glioblastoma cell line with IC_{50} = 45.2 ± 13.0 µM, compared to Doxorubicin (IC_{50} = 16.6 ± 2.5 µM) [61].



Compound 2

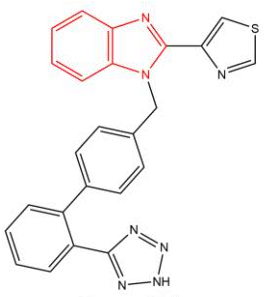
6. Antihypertensive Activities

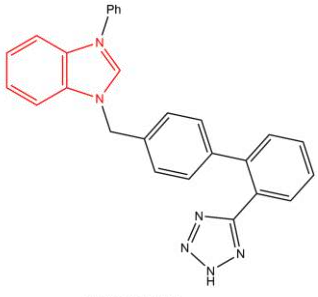
Telmisartan and Candesartan cilexetil are well-known antihypertensive agents containing a benzimidazole moiety, acting as angiotensin II (AT_1) receptor antagonists. Owing to the pharmacological significance of this scaffold, several benzimidazole-based derivatives have been developed with comparable or improved antihypertensive efficacy [62]. Alanazi A. H. *et al*. designed and synthesized a series of benzimidazole derivatives as potential angiotensin-converting enzyme (ACE) inhibitors and performed molecular docking studies. Among them, compound 17 [2-(2-(butylthio)-5-methoxy-1H-indol-1-yl)-1-(2-nitrophenyl) ethan-1-one] demonstrated strong binding affinity toward ACE. In *in vitro* ACE inhibition assays, it exhibited an IC_{50} = 0.86 µM, nearly comparable to the reference drug Lisinopril (IC_{50} = 0.81 µM). In silico toxicity profiling further supported its potential as a promising antihypertensive lead compound [63].



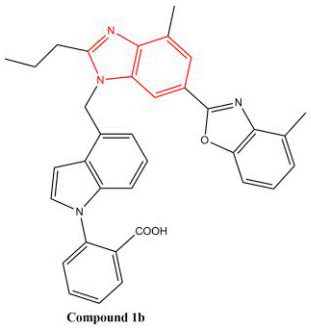
Compound 17

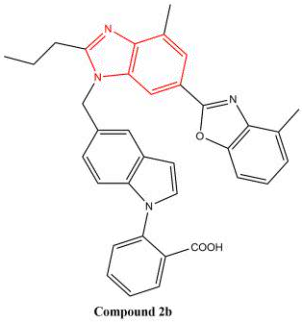
Silky S. *et al*. synthesized a series of benzimidazole and benzindazole derivatives as potential angiotensin II receptor (AT_1) antagonists for antihypertensive therapy. The antihypertensive efficacy of the synthesized compounds was evaluated *in vivo* using an acute renal hypertension model. Among the tested molecules, TG-1 and TG-3 demonstrated significant blood pressure–lowering effects comparable to the standard drug Telmisartan, a well-known angiotensin II receptor antagonist. These findings suggest that benzimidazole-based derivatives represent promising lead candidates for the development of novel antihypertensive agents [64].


Compound TG-1


Compound TG-3

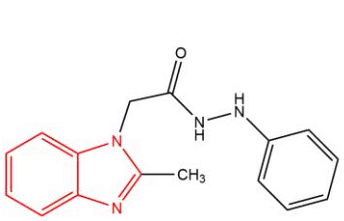
Wu Z. *et al*. designed and synthesized novel 6-substituted benzimidazole–indole derivatives incorporating 1,4- or 1,5-disubstituted indole and benzoic acid moieties as potential angiotensin II type 1 (AT_1) receptor antagonists. Biological evaluation demonstrated that these compounds effectively bound to the AT_1 receptor and significantly reduced blood pressure. Notably, compounds 1b and 2b exhibited strong antagonistic activity against the angiotensin II type 1 receptor and showed antihypertensive efficacy comparable to or greater than the reference drug Losartan. These findings highlight their promise as potential next-generation anti-hypertensive agents [65].

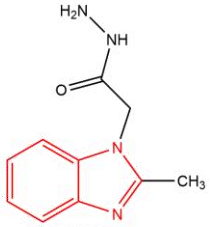

Compound 1b


Compound 2b

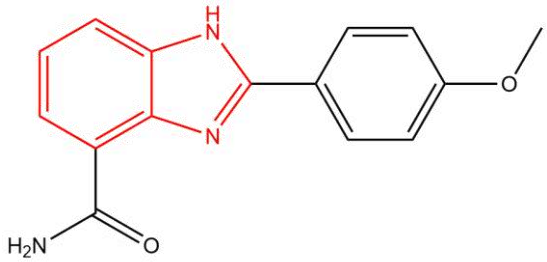
7. Anti-inflammatory Activities

Benzimidazole derivatives have been widely reported to exhibit significant analgesic and anti-inflammatory activities, primarily through inhibition of cyclooxygenase-2 (COX-2), a key enzyme involved in prostaglandin-mediated inflammatory pathways. Suppression of COX-2 correlates with reduced pain and inflammation in various experimental models, highlighting the therapeutic relevance of this scaffold in chronic inflammatory disorders [66]. Moharana A. K. *et al*. synthesized two novel benzimidazole derivatives, MBPHYD and MBNHYD, and evaluated their anti-inflammatory potential. In *in vitro* cytotoxicity studies using Vero cells, both compounds were found to be non-toxic at 100 µM for 24 h. Additionally, *in silico* ADMET profiling indicated favorable drug-like characteristics, including high predicted oral bioavailability. Notably, MBPHYD demonstrated predicted blood–brain barrier (BBB) permeability, suggesting its potential utility in treating central nervous system (CNS) inflammation. These findings support further development of benzimidazole-based anti-inflammatory agents [67].

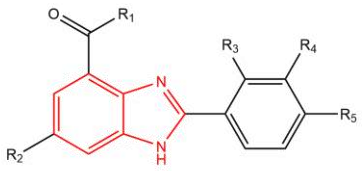

MBPHYD

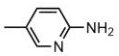
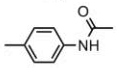
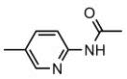

MBNHYD

Picconi *et al*. synthesized a series of benzimidazole derivatives and evaluated their anti-inflammatory potential by testing inhibition of key pro-inflammatory mediators, including IL-6, TNF-α, COX, LOX, and secretory phospholipase A2. The compounds exhibited broad-spectrum inhibitory activity, with compound 58 showing the strongest inhibition across COX, LOX, TNF-α, and IL-6, highlighting its promise as a potent anti-inflammatory agent [68].


Compound 58

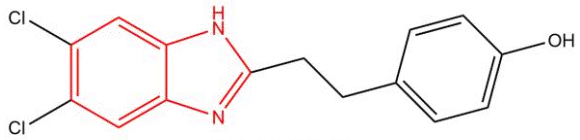
Bukhari S. N. A. *et al.* synthesized benzimidazole derivatives and evaluated their anti-inflammatory activity by measuring inhibition of pro-inflammatory cytokines and enzymes. Compound 3 showed the strongest inhibition of IL-6, COX, LOX, and TNF-α, highlighting its potential as a therapeutic anti-inflammatory agent. Other derivatives such as 3, 4, 6, and 7 exhibited notable enzyme and cytokine inhibition, while 4, 8, 17, 19, and 20 inhibited TNF-α, IL-6, and several other enzymes, but not all targets significantly [68,69].



Compound ID	R1	R2	R3	R4	R5
3	H	NH2	H	H	OCH3
4	CH3	NH2	H	H	-
6	CH3	NH2	H	H	-
7	CH3	NH2	H	H	CN
8	H	NH2	H	H	
17	H	NH2	H	H	
19	CH3	NH2	H	H	-
20	H	NH2	H	H	

8. Antitubercular Activities

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, primarily affects the lungs but can involve other organs. The benzimidazole scaffold has attracted attention for designing novel antitubercular agents due to its potent activity [70]. Yalcin-Ozkat *et al*. studied 23 benzimidazole derivatives via molecular docking and dynamics, identifying compounds 20, 21, and 30 as promising candidates. These derivatives target the DprE1 enzyme, a key antitubercular target. In-silico ADME modeling and MD simulations highlighted compound 21 as the most potent, based on its superior binding affinity [71].



Compound 21

CONCLUSION

Benzimidazole and its derivatives constitute a versatile nitrogen-containing heterocyclic scaffold with remarkable pharmacological potential. Insights from this review indicate that specific functional groups at key positions of the benzimidazole core, notably 1-, 2-, and 5-positions, directly govern biological activity. Substituents such as halogens, hydroxyl, amino, Schiff bases, thiazole, triazole, and oxadiazole moieties have been identified as critical determinants for antimicrobial, antifungal, antiviral, antidiabetic, antioxidant, anticancer, anti-inflammatory, antihypertensive, and antitubercular effects. The structure-activity relationship (SAR) analysis demonstrates that electronic effects, steric factors, and hydrogen-bonding capacity of these functional groups significantly influence target binding, enzyme inhibition, and selectivity. These findings provide a rational blueprint for drug design, allowing future development of benzimidazole-based therapeutics to incorporate these bioactive functional motifs strategically. By leveraging these functional features, green synthetic methodologies, in-silico ADMET profiling, and in-vivo validation, it is possible to design highly potent, selective, and safe derivatives. The accumulated SAR knowledge establishes the benzimidazole scaffold as a robust lead structure for next-generation drug development with broad-spectrum therapeutic applications.

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HOW TO CITE: Mansa Shrivastava, Anju Daharia*, Benzimidazole Scaffold: Advances In Structural Modifications And Diverse Pharmacological Activities, Int. J. Sci. R. Tech., 2026, 3 (4), 920-940. https://doi.org/10.5281/zenodo.19753557