Article published on 2026-2-14

1 Review

In Silico Approaches in Benzimidazole Derivatives Research: Recent Insights

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Chinese Journal of Applied Physiology, 2026: e20260003

Abstract Benzimidazole remains a privileged heteroaromatic scaffold with broad therapeutic potential, spanning antimicrobial, anticancer, antitubercular, and antiviral domains. In recent years (2020–2025), computational methodologies have significantly accelerated benzimidazole-based drug discovery by elucidating structural determinants of activity and streamlining lead optimization. Molecular docking and dynamics simulations consistently reveal the scaffold's ability to engage in π–π stacking, hydrogen bonding, and hydrophobic interactions within protein active sites. Substituent modifications at C2, C5, and C6 critically modulate affinity and selectivity across diverse targets, including InhA, DprE1, kinases, and viral proteases. Complementary strategies such as QSAR, pharmacophore modeling, and in silico ADMET predictions strengthen early hit prioritization and reduce experimental attrition. Emerging approaches integrating artificial intelligence, machine learning, and free energy perturbation further enhance predictive accuracy and enable multi-target drug design. This short communication highlights recent computational insights, best practices, and future trends in benzimidazole research, emphasizing the value of combining docking, MD, QSAR, ADMET, and AI/ML workflows. Together, these advances provide a robust, cost-effective pipeline for the rational design of next-generation benzimidazole derivatives with improved efficacy and translational potential.

Keywords Benzimidazole derivatives, Molecular docking, Molecular dynamics, QSAR modeling, ADMET prediction, Artificial intelligence (AI), Multitarget drug design, Rational drug design

1. Introduction

Benzimidazole is a versatile heteroaromatic scaffold with broad pharmacological potential, including antimicrobial, anticancer, antitubercular, and antiviral activities [1–7,9–12]. Its aromatic core and hydrogen bonding capacity enable interactions with diverse biological targets, making it a key motif in drug design [7,10,12]. Computational approaches—molecular docking, molecular dynamics, QSAR modeling, and in silico ADMET prediction—have accelerated the identification and optimization of benzimidazole derivatives while reducing experimental costs [3,6,14,15,17,19,22,24]. Recent integrated workflows (2020–2025) combining docking, MD, QSAR, and ADMET have demonstrated the scaffold's promise against infectious, cancer, and resistant microbial targets [1–7,9–12]. This review highlights these computational strategies, key findings, and emerging trends to guide the rational design of next-generation benzimidazole therapeutics.

DOI: 10.62958/j.cjap.2026.003
www.cjap.ac.cn

Published by CJAP Editorial Office and Asian BioMed Innovation Press

Table 1: Recent applications of docking, QSAR, MD, and ADMET to benzimidazole derivatives

Year	Target(s /Disease area	Computational methods used	Key findings/Insights
2025	α-glucosidase	3D-QSAR, docking, MD simulations, ADMET, DFT	Designed benzimidazole-oxadiazole hybrids; key interactions identified; predicted favorable ADMET and stability in MD runs
2025	Multi-target anti-tubercular (InhA, DprE1)	Atom-based 3D-QSAR, pharmacophore modelling, molecular docking, MD, ADMET, DFT	High predictive QSAR model ($R^2 \approx 0.95$, $Q^2 \approx 0.86$); identified a lead (MK3) stable in 100 ns MD bound to both InhA & DprE1; good ADMET profile
2024	Antibacterial / antimicrobial	QSAR, docking, MD, ADME	Benzimidazole derivatives examined for bacterial target(s); docking and MD validated binding modes; ADME profiling to weed out poor candidates
2023	Coxsackie B3 virus	3D-QSAR, docking, ADMET	Built a 3D-QSAR model correlating benzimidazole structure with antiviral activity; docking rationalised binding to viral protein; ADMET to assess druglikeness
2023	Benzimidazole–thiadiazole hybrids (antibacterial)	Quantum chemical (DFT), docking, MD, ADMET	Hybrid compounds designed; DFT used to analyse electronic properties; docking & MD show stable binding; ADMET filters applied
2025	RSV fusion protein (antiviral)	QSAR, docking, ADMET	Screening of benzimidazole derivatives vs RSV fusion protein; docking predicted binding and ADMET to select safer hits
2025	Inflammation / cytotoxicity (COX-2 etc.)	3D-QSAR, docking	Derivatives targeting COX-2 and related enzymes; QSAR and docking used to suggest substituent effects for potency/ toxicity balance

2. Docking Studies of Benzimidazole Derivatives

Benzimidazole derivatives are widely explored by molecular docking due to their planar aromatic core and hydrogen-bonding capacity, enabling π–π, hydrophobic, and hydrogen-bond interactions [1,3,6,14,15]. Key targets include antimicrobial/ antitubercular enzymes (DNA gyrase, DHFR, InhA, DprE1), anticancer proteins (kinases, topoisomerases, tubulin), and viral enzymes (proteases, polymerases) [2,4,5,9,11,27,28]. Across studies (2020–2025), the benzimidazole core generally occupies hydrophobic/ aromatic pockets, while substituents at positions 2, 5, and 6 engage hydrogen bonds or sub-pockets to modulate affinity and selectivity [1,6,14,15].

Antimicrobial/Antitubercular Targets

Docking against InhA and DprE1 shows hydrogen bonding to catalytic residues and hydrophobic anchoring, with AutoDock/Vina scores typically −7 to −10 kcal·mol^{-1} [1,6,15]. Crystal structures (e.g., DprE1 PDB 4P8C, InhA PDB 2NSD) guide substituent design, and short MD simulations confirm H-bond persistence [1,6].

Anticancer Targets

For kinases, topoisomerases, and tubulin, benzimidazole rings engage in π-stacking or occupy binding clefts, while polar substituents interact with active-site residues. Docking scores often correlate with experimental potency and are validated via MD [4,5,9,17].

Antiviral and Anti-inflammatory Targets

Docking into viral proteases and polymerases shows

Table 2: Computational docking studies on benzimidazole derivatives: targets, interactions, and scores

Target	Representative PDB used	Common substituents on benzimidazole (examples)	Typical docking score (reported /range)
InhA (enoyl-ACP reductase, anti-TB)	2NSD (InhA)	2-aryl, 5-nitro/5-chloro, flexible side chains (alkyl/ether linkers)	−7.0 to −9.0 kcal·mol^{-1} (poses validated by MD).
DprE1 (anti-TB)	4P8C (DprE1)	2-substituted benzimidazoles, polar linkers, aromatic extensions	many hits < −8.0 kcal·mol^{-1}; best series reported ≤ −9 kcal·mol^{-1}.
DNA gyrase B (antibacterial)	4DUH / 4KFG (GyrB)	2-phenyl, halogenated 5/6-substituents, heteroaryl linkers	typical docking: −6.5 to −9.0 kcal·mol^{-1} (varies by scaffold).
DHFR (antibacterial/ antiproliferative)	common DHFR crystal structures (varies by species)	pyrimidine-clubbed benzimidazoles, hydrophilic side chains	−7 to −10 kcal·mol^{-1} reported for top analogues.
Kinases / topoisomerase (anticancer)	various kinase hinge & topo II structures	2-aryl/2-heteroaryl benzimidazoles; H-bond donors at pendant chains	docking scores correlate with activity; typical ranges −8 to −11 kcal·mol^{-1} in high-potency series.
Viral proteases / polymerases (antiviral)	target specific (varies by virus)	small aryl/alkyl substitutions, polar H-bonding groups	−6 to −9 kcal·mol^{-1}; ADMET used to triage hits.

the scaffold mimicking substrate interactions, forming hydrogen bonds, and occupying S1/S2 subpockets. ADMET filters are commonly applied to prioritize hits for synthesis [2,11,27,28].

Trends and Best Practices

Substituent position critically affects binding: 2-position groups influence hydrophobic fit, 5/6-position groups tune hydrogen bonding and solubility. High docking scores alone are insufficient; short MD simulations (10–100 ns) confirming H-bond occupancy and RMSD stability strengthen predictions. Variability across scoring functions highlights the need for cross-validation with experimental data [1–7,9–12,14,15,17,19,22,24].

3. Other Computational Approaches

Beyond docking, additional computational methods provide deeper insight and reliability in benzimidazole research [1–7,9–12,14,15,17,19,22,24].

Molecular Dynamics (MD)

MD simulations assess the stability of protein–ligand complexes over time. Parameters such as RMSD, RMSF, hydrogen-bond occupancy, and MM-PBSA/GBSA energies confirm that docking poses are stable and highlight pocket flexibility [3,6,14,15]. For example, antitubercular benzimidazoles in InhA and DprE1 showed persistent H-bonds in 50–100 ns MD runs [1,6,15].

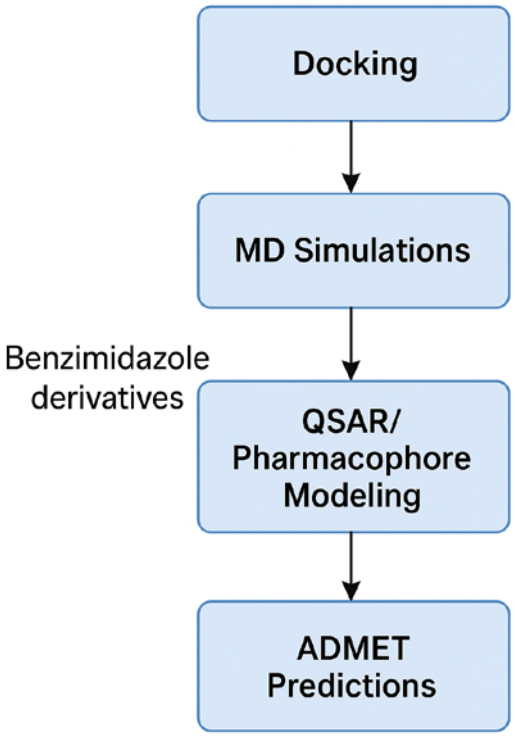
QSAR and Pharmacophore Modeling

QSAR identifies structure–activity trends, emphasizing substituents at 2- and 5/6-positions, while 3D contour maps guide favorable interactions [3,9,11,17,23]. Pharmacophore models define essential hydrogen-bond and aromatic features, as demonstrated for DNA gyrase and tubulin inhibitors [4,5,11].

ADMET Predictions

Early screening for drug-likeness, solubility, permeability, and toxicity (hepatotoxicity, hERG, mutagenicity) filters poor candidates before synthesis [2,6,7,11,27]. Hits with favorable docking but undesirable ADMET properties, such as CYP450 inhibition, are discarded [6,7,11].

Combining docking with MD, QSAR/pharmacophore, and ADMET enables multi-parameter optimization, validating binding stability, guiding structural design, and ensuring safety, forming a robust pipeline for benzimidazole-based drug discovery [1–7,9–12,14,15, 17,19,22,24,27].



4. Trends and Insights

Recent computational studies reveal consistent binding patterns and structural determinants in benzimidazole derivatives [1–7,9–12,14,15,17,19,22,24]. Docking and MD analyses show the benzimidazole core engaging in π–π stacking with aromatic residues (e.g., Phe, Tyr, Trp) and forming hydrogen bonds via the imidazole nitrogen, stabilizing interactions with catalytic or conserved residues [3,4,6,8,15]. Its hydrophobic core favors accommodation in lipophilic pockets of targets such as DNA gyrase, kinases, and viral proteases [2,5,7,27].

Substituent position strongly influences binding and selectivity. C2 and C5 modifications are most impactful: electron-withdrawing groups (halogens, nitro) enhance polarity or halogen bonding, while heteroaryl or bulky hydrophobic groups improve π-stacking, pocket complementarity, and deep binding, particularly for anticancer targets (tubulin, kinases) and antitubercular enzymes (InhA, DprE1) [1,3,4,7,9,15,17].

In silico approaches offer rapid, cost-effective screening and mechanistic insights that guide rational derivative design before synthesis [1–3,6,10,14]. However, limitations exist: docking scores alone may mislead due to neglected protein flexibility, solvation, and entropic effects. False positives are possible when scoring functions inadequately reflect true binding [3,6,9,15]. Therefore, experimental validation remains essential. Integrating docking with MD, QSAR, and ADMET enhances predictive reliability, but translating computational hits into viable drugs requires careful experimental follow-up [1–7,9–12,14,15,17,19,22,24,27].

5. Future Perspectives

The future of benzimidazole-based drug discovery is increasingly shaped by advanced computational methodologies [1–4,6,9,13,16,23,25–28]. AI and machine learning can enhance molecular docking by predicting ligand–protein interactions with greater accuracy [8,13,16,23,25,26], while deep learning QSAR models enable rapid identification of potent derivatives through complex pattern recognition [13,16,23,31]. Free energy perturbation (FEP) calculations further provide quantitative insights into binding affinities, complementing docking scores and guiding rational scaffold modifications [29].

Emerging research emphasizes polypharmacology, where single benzimidazole derivatives target multiple proteins or pathways. Multitarget docking approaches can uncover such interactions, supporting the design of broad-spectrum or resistance-resilient agents [9,22,27]. To strengthen these computational strategies, benchmark datasets of benzimidazole derivatives—including structural features, binding affinities, and biological activities—are essential. These datasets would improve AI/ML model training, standardize protocols, and accelerate lead optimization [18,23,25].

Overall, integrating AI/ML-driven docking, deep learning QSAR, FEP, and multitarget approaches, supported by curated benchmark data, promises a faster, more predictive, and cost-effective path for designing next-generation benzimidazole therapeutics [1–6,8,9,13,16,18,23,25–29].

6. Conclusion

Docking and other in silico approaches have become central to benzimidazole-based drug discovery, providing valuable insights into ligand–protein interactions, binding affinities, and structure–activity relationships. These computational tools offer a cost-effective and rapid strategy to prioritize promising derivatives before synthesis and experimental evaluation.

Looking forward, combining computational predictions with experimental validation is expected

to accelerate the hit-to-lead optimization process. Integrating AI/ML-driven docking, free energy calculations, and multitarget analyses with laboratory studies can enhance the design of potent, selective, and drug-like benzimidazole derivatives. This integrated approach is likely to streamline discovery pipelines and improve the efficiency of developing next-generation therapeutics.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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