RESEARCH PAPER

Pharmacophore Modeling of Benzothiazole Derivatives in Computer-Aided Drug Design: A Review

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ABSTRACT

Benzothiazole is an important heterocyclic scaffold widely investigated in medicinal chemistry because of its diverse pharmacological activities. Benzothiazole derivatives exhibit significant therapeutic potential as anticancer, antimicrobial, antiviral, anti-inflammatory, antitubercular, and antioxidant agents. Owing to their structural versatility and favorable physicochemical properties, these compounds have emerged as promising candidates in modern drug discovery.

Pharmacophore modeling is an important component of computer-aided drug design (CADD) for identifying the steric and electronic features responsible for biological activity and ligand–target interactions. This review summarizes recent advances in the chemistry, pharmacological importance, and pharmacophore modeling of benzothiazole derivatives. Ligand-based and structure-based pharmacophore approaches and their applications in virtual screening, lead optimization, and scaffold hopping are discussed.

The review also highlights the integration of pharmacophore modeling with molecular docking, molecular dynamics simulations, QSAR analysis, ADMET prediction, and artificial intelligence-based approaches. Current challenges and future perspectives associated with benzothiazole-based computational drug discovery are also discussed. Overall, pharmacophore-guided strategies provide a promising platform for developing safer and more effective therapeutic agents.

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1. INTRODUCTION

Benzothiazole is an important bicyclic heterocyclic scaffold extensively investigated in medicinal chemistry because of its broad spectrum of biological activities and favorable physicochemical properties. Structurally, benzothiazole consists of a benzene ring fused with a thiazole ring containing nitrogen and sulfur heteroatoms, which contribute to improved electronic distribution and interactions with biological targets. Due to its planar aromatic structure, synthetic accessibility, and ease of modification, benzothiazole is considered a privileged scaffold in drug discovery.

Benzothiazole derivatives exhibit diverse pharmacological activities including anticancer, antimicrobial, antiviral, anti-inflammatory, antitubercular, anticonvulsant, and antioxidant effects. Structural modifications, especially at the C-2 position, strongly influence biological activity and selectivity. Several derivatives have shown promising interactions with kinases, BCL-2 proteins, p53–MDM2 complexes, and microbial enzymes (Aayishamma et al., 2024; Ismail et al., 2023; Khan et al., 2023).

Conventional drug discovery is associated with high cost and long development timelines. Computer-aided drug design (CADD) has therefore emerged as an efficient strategy for rational drug discovery. Among CADD techniques, pharmacophore modeling is widely used for identifying steric and electronic features required for ligand–target interactions (Yang, 2010; Kaserer et al., 2015).

A pharmacophore represents the three-dimensional arrangement of molecular features necessary for biological activity. Important pharmacophoric features include hydrogen bond donors, hydrogen bond acceptors, aromatic rings, hydrophobic centers, and ionizable groups (Langer & Hoffmann, 2006; Talele et al., 2010). Pharmacophore-guided approaches are extensively applied in virtual screening, lead identification, scaffold hopping, and lead optimization.

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Integration of pharmacophore modeling with molecular docking, molecular dynamics (MD) simulations, QSAR studies, and ADMET prediction has improved computational drug discovery efficiency (Lionta et al., 2014; Trott & Olson, 2010; Daina et al., 2017). In addition, artificial intelligence (AI) and machine learning (ML) approaches have further enhanced prediction of biological activity and analysis of chemical datasets (Schneider et al., 2020; Vamathevan et al., 2019).

This review summarizes the chemistry, pharmacological importance, pharmacophore modeling, and computational applications of benzothiazole derivatives in modern drug discovery.

2. LITERATURE SEARCH METHODOLOGY

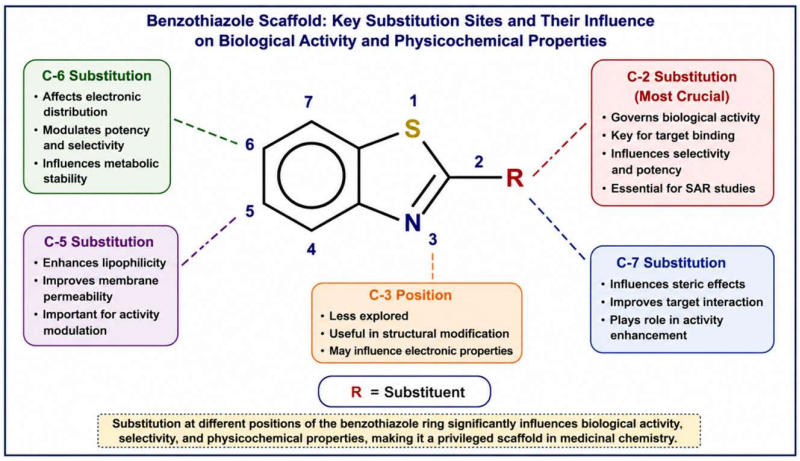
A literature survey was conducted using PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect databases for articles published between 2000 and 2025. Keywords included "benzothiazole derivatives," "pharmacophore modeling," "computer-aided drug design," "virtual screening," "molecular docking," "QSAR," "ADMET prediction," and "artificial intelligence in drug discovery."

Studies involving ligand-based and structure-based pharmacophore modeling, docking, QSAR, ADMET prediction, and AI-assisted drug discovery were included. Only peer-reviewed English-language articles with sufficient experimental or computational validation were considered.

3. CHEMISTRY AND STRUCTURE OF BENZOTHIAZOLE DERIVATIVES

Benzothiazole is a bicyclic heteroaromatic compound formed by fusion of benzene and thiazole rings containing nitrogen and sulfur heteroatoms. The scaffold facilitates hydrophobic interactions, π–π stacking, and hydrogen bonding with biological targets (Mohamed-Ezzat et al., 2023).

Substitution on the benzothiazole nucleus significantly affects biological activity and physicochemical properties. Among various positions, C-2 substitution is particularly important because incorporation of aryl, heteroaryl, alkyl, or amino groups enhances receptor binding and biological activity. Several 2-substituted benzothiazoles exhibit potent anticancer, antimicrobial, antitubercular, and antiviral activities (Khan et al., 2023; Ismail et al., 2023). Major substitution sites are illustrated in Figure 1.



Substitutions at C-5 and C-6 influence lipophilicity and metabolic stability. Electron-withdrawing groups such as halogens often enhance activity, whereas methoxy and amino groups improve interaction dynamics (Mohamed-Ezzat et al., 2023; Aljuhani et al., 2024).

Benzothiazole derivatives are commonly synthesized through condensation of 2-aminothiophenol with aldehydes or ketones followed by oxidative cyclization. Recent advances including microwave-assisted synthesis, multicomponent reactions, and green chemistry approaches have improved reaction efficiency and environmental sustainability (Bora et al., 2024; Bhagwat et al., 2025).

Hybrid molecules such as benzothiazole–triazole and benzothiazole–thiazole derivatives have shown enhanced biological activity by combining multiple pharmacophoric features within a single framework.

4. PHARMACOLOGICAL IMPORTANCE OF BENZOTHIAZOLE DERIVATIVES

Benzothiazole derivatives possess broad pharmacological activities because of their ability to interact with enzymes, receptors, nucleic acids, and signaling proteins (Mohamed-Ezzat et al., 2023).

4.1 Anticancer Activity

Anticancer activity is one of the most studied properties of benzothiazole derivatives. These compounds act through inhibition of tubulin polymerization, induction of apoptosis, and modulation of signaling pathways (Ismail et al., 2023; Khan et al., 2023). Structural modification at the C-2 position improves potency and selectivity.

4.2 Antimicrobial Activity and Antitubercular Activity

Several benzothiazoles exhibit antimicrobial activity against Gram-positive, Gram-negative, and fungal pathogens through inhibition of microbial enzymes and DNA synthesis (Bhagwat et al., 2025). Antitubercular activity has also been reported against Mycobacterium tuberculosis, particularly for derivatives containing electron-withdrawing groups.

4.3 Anti-inflammatory and Antiviral Activity

Benzothiazole derivatives inhibit cyclooxygenase enzymes and inflammatory mediators, producing anti-inflammatory effects comparable to NSAIDs. In addition, antiviral activity has been reported through inhibition of viral replication and viral enzymes (Mohamed-Ezzat et al., 2023).

Major pharmacological activities and important structural features of benzothiazole derivatives are summarized in Table I.

Table I. Major Pharmacological Activities of Benzothiazole Derivatives.

Pharmacological Activity	Major Target/Mechanism	Important Structural Features	Representative References
Anticancer	BCL-2 inhibition, p53–MDM2 modulation, kinase inhibition	C-2 substituted aromatic and heterocyclic moieties	(Aayishamma et al., 2024; Ismail et al., 2023; Khan et al., 2023)
Antimicrobial	Inhibition of microbial enzymes and DNA synthesis	Halogenated and heterocyclic substitutions	(Bhagwat et al., 2025; Mohamed-Ezzat et al., 2023)
Antitubercular	Inhibition of *Mycobacterium tuberculosis* metabolic pathways	Electron-withdrawing groups at C-2 position	(Aayishamma et al., 2024; Khan et al., 2024)
Anti-inflammatory	COX inhibition and suppression of inflammatory mediators	Hydrophobic and electron-donating groups	(Mohamed-Ezzat et al., 2023)
Antiviral	Viral enzyme inhibition and blockade of viral replication	Aromatic and lipophilic substitutions	(Mohamed-Ezzat et al., 2023)
Antioxidant	Free radical scavenging activity	Electron-rich substituents	(Aayishamma et al., 2024)

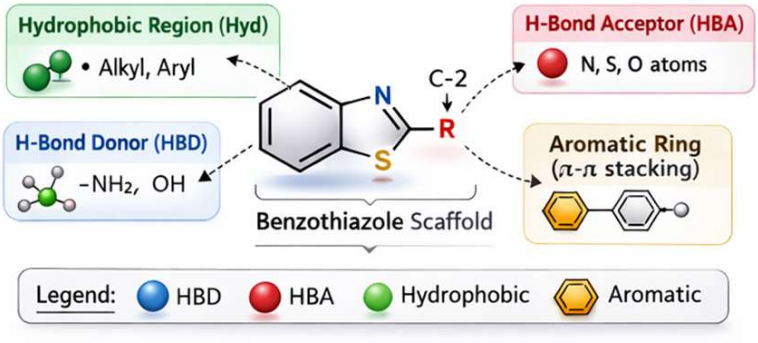
4.4 Structure–Activity Relationship Perspective

Structure–activity relationship (SAR) studies indicate that aromatic substitutions, hydrophobic groups, and hydrogen bonding functionalities strongly influence biological activity and pharmacokinetic behavior (Talele et al., 2010). Pharmacophore-guided optimization therefore plays an important role in improving potency and selectivity.

Despite promising pharmacological activities, challenges such as poor solubility, metabolic instability, and toxicity remain important limitations.

5. PHARMACOPHORE MODELING IN DRUG DESIGN

Pharmacophore modeling is an important CADD technique used to identify steric and electronic features necessary for biological activity. It is widely applied in virtual screening, lead optimization, and scaffold hopping (Yang, 2010). The general workflow is illustrated in Figure 2.



Pharmacophoric features commonly include hydrogen bond donors, hydrogen bond acceptors, aromatic rings, hydrophobic centers, and ionizable groups (Langer & Hoffmann, 2006).

5.1 Types of Pharmacophore Modeling

Pharmacophore modeling is classified into ligand-based and structure-based approaches (Table II).

Table II. Types of Pharmacophore Modeling Approaches.

Pharmacophore Modeling Type	Description	Advantages	Limitations	Representative References
Ligand-Based Pharmacophore Modeling	Uses structurally active ligands to identify common pharmacophoric features	Useful when target structure is unavailable	Depends on dataset quality and alignment	(Schuster, 2010; Kaserer et al., 2015)
Structure-Based Pharmacophore Modeling	Derived from ligand–protein interaction patterns	Provides detailed interaction information	Requires high-quality protein structure	(Wolber et al., 2006; Drwal & Griffith, 2013)
Hybrid Pharmacophore Modeling	Combines ligand-based and structure-based approaches	Improved predictive accuracy	Computationally intensive	(Yang, 2010; Talele et al., 2010)

Ligand-based pharmacophore modeling is applied when target structures are unavailable. Structurally diverse active compounds are aligned to identify common features responsible for biological activity (Schuster, 2010).

Structure-based pharmacophore modeling uses protein structures obtained from X-ray crystallography or cryo-electron microscopy to derive interaction patterns within active sites (Wolber et al., 2006).

5.2 Pharmacophoric Features of Benzothiazole Derivatives

The benzothiazole scaffold contains aromatic rings and heteroatoms that facilitate hydrogen bonding, hydrophobic interactions, and π–π stacking. Hydrophobic substituents at the C-2 position improve receptor binding, whereas polar groups enhance solubility and interaction potential (Aayishamma et al., 2024).

5.3 Workflow and Validation

Pharmacophore modeling generally involves dataset preparation, conformational analysis, pharmacophore generation, validation, and virtual screening. Validation methods include ROC curves, enrichment factor analysis, and decoy set validation (Kaserer et al., 2015).

5.4 Software and Computational Tools

Common pharmacophore tools include LigandScout, PHASE, Discovery Studio, MOE, and AutoDock-based workflows (Wolber & Langer, 2005; Dixon et al., 2006). Integration with docking, MD simulations, QSAR, and ADMET prediction improves predictive reliability.

5.5 Applications in Benzothiazole Drug Discovery

Pharmacophore-guided approaches have facilitated identification of benzothiazole derivatives targeting cancer, microbial infections, and inflammatory disorders. However, predictive accuracy depends on dataset quality, conformational flexibility, and proper validation. Integration with experimental studies remains essential.

Recent AI and ML advances have significantly enhanced pharmacophore modeling through automated feature extraction and prediction of biological activity (Schneider et al., 2020).

6. APPLICATIONS OF PHARMACOPHORE MODELING IN BENZOTHIAZOLE DRUG DESIGN

Pharmacophore modeling is widely used in virtual screening, lead identification, scaffold hopping, docking, QSAR, and ADMET prediction.

6.1 Virtual Screening and Lead Identification

Validated pharmacophore hypotheses are used to screen chemical databases such as ZINC, PubChem, and ChEMBL for compounds with similar pharmacophoric arrangements (Sterling & Irwin, 2015). Pharmacophore-guided lead optimization improves potency, selectivity, and pharmacokinetic properties. Major applications of pharmacophore modeling in drug discovery are summarized in Table III.

Table III. Applications of Pharmacophore Modeling in Drug Discovery.

Application	Purpose	Importance in Drug Discovery	Representative References
Virtual Screening	Identification of active compounds from databases	Reduces time and cost of screening	(Sterling & Irwin, 2015; Kim et al., 2021)
Lead Identification	Discovery of bioactive lead compounds	Facilitates early-stage drug discovery	(Khan et al., 2024)

Lead Optimization	Structural refinement of lead molecules	Improves potency and selectivity	(Kaserer et al., 2015)
Scaffold Hopping	Discovery of structurally diverse compounds	Overcomes resistance and improves novelty	(Schneider, 2010)
ADMET Prediction	Evaluation of pharmacokinetic properties	Reduces late-stage drug failure	(Daina et al., 2017; Yang et al., 2019)
AI-Assisted Drug Design	Prediction of biological activity using ML/AI	Improves predictive accuracy	(Schneider et al., 2020; Vamathevan et al., 2019)

6.2 Scaffold Hopping

Scaffold hopping identifies structurally diverse compounds that retain essential pharmacophoric features. Benzothiazole-based scaffold hopping has generated hybrid molecules containing triazole, chromone, and thiazole moieties (Aljuhani et al., 2024).

6.3 Molecular Docking and MD Simulation

Molecular docking predicts ligand orientation and binding affinity within protein active sites (Trott & Olson, 2010). Docking-guided pharmacophore optimization has been widely applied in anticancer drug discovery.

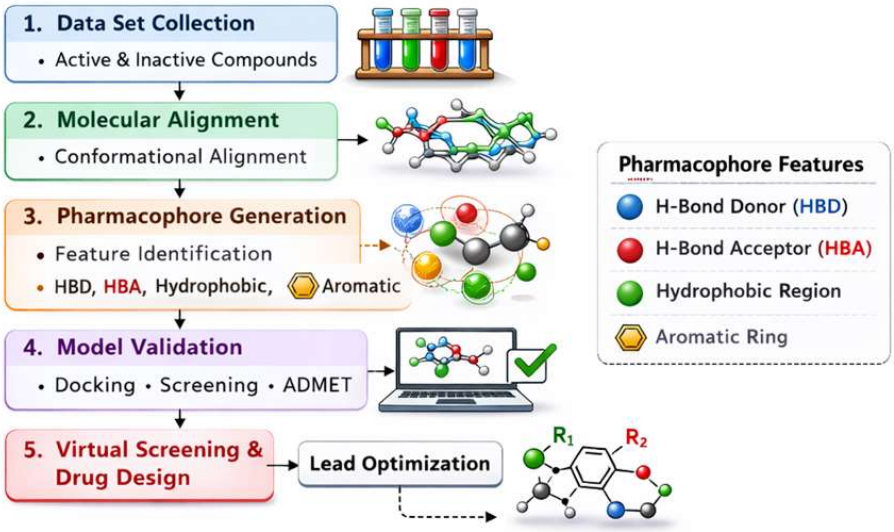
MD simulations provide information regarding conformational stability and ligand–protein interactions under physiological conditions (Hollingsworth & Dror, 2018).

6.4 QSAR and ADMET Prediction

QSAR studies establish relationships between molecular descriptors and biological activity, whereas ADMET prediction evaluates pharmacokinetic and toxicity properties before experimental testing (Cherkasov et al., 2014; Daina et al., 2017).

6.5 Artificial Intelligence in Drug Design

AI and ML approaches have transformed computational drug discovery by improving biological activity prediction, feature extraction, and de novo molecular design (Schneider et al., 2020). Integration of AI-assisted pharmacophore modeling is illustrated in Figure 3.



Despite significant progress, challenges including protein flexibility, solvent effects, and false-positive screening remain limitations.

7. COMPUTATIONAL TOOLS USED IN PHARMACOPHORE-BASED DRUG DESIGN

Computational tools are extensively used in pharmacophore modeling, docking, MD simulations, QSAR analysis, and ADMET prediction (Macalino et al., 2015).Common computational tools and their applications in benzothiazole-based drug discovery are summarized in Table IV.

Table IV. Common Computational Tools Used in Benzothiazole Drug Discovery.

Computational Tool	Major Application	Important Features	Representative References
LigandScout	Pharmacophore modeling	Automatic pharmacophore generation	(Wolber & Langer, 2005)
PHASE	Pharmacophore modeling and virtual screening	Ligand- and structure-based modeling	(Dixon et al., 2006)
AutoDock Vina	Molecular docking	Fast and accurate docking	(Trott & Olson, 2010)

Glide	Molecular docking	Extra precision docking	(Friesner et al., 2006)
GROMACS	Molecular dynamics simulation	High-performance MD simulations	(Abraham et al., 2015)
SwissADME	ADMET prediction	Drug-likeness and pharmacokinetics	(Daina et al., 2017)
pkCSM	Toxicity and pharmacokinetic prediction	Graph-based prediction models	(Pires et al., 2015)
PaDEL-Descriptor	QSAR descriptor calculation	Molecular descriptor generation	(Yap, 2011)

LigandScout and PHASE are widely used for pharmacophore modeling, whereas AutoDock Vina and Glide are commonly employed for molecular docking (Trott & Olson, 2010). GROMACS and AMBER are widely used MD simulation platforms (Abraham et al., 2015).

QSAR tools such as PaDEL-Descriptor support descriptor generation, while SwissADME and pkCSM predict pharmacokinetic and toxicity properties (Daina et al., 2017).

Chemical databases including ZINC, PubChem, and ChEMBL support pharmacophore-guided virtual screening. AI- and ML-assisted platforms have further improved prediction of ligand–target interactions and biological activity.

However, computational predictions still depend heavily on dataset quality, conformational sampling, and availability of reliable structural information.

8. FUTURE PERSPECTIVES

Future research is expected to increasingly integrate pharmacophore modeling with AI, ML, and deep learning approaches to improve drug discovery efficiency. AI-assisted methods can analyze large chemical datasets, predict biological activity, and support de novo molecular design (Zhavoronkov et al., 2019).

Hybrid benzothiazole-based molecules containing triazole, chromone, and quinoline scaffolds are expected to provide improved potency and selectivity. Advances in genomics, proteomics, and structural biology may further support precision medicine approaches targeting specific molecular pathways.

Challenges including poor solubility, toxicity, and metabolic instability remain barriers to clinical translation. Therefore, future research should emphasize optimization of physicochemical properties, integration of MD simulations, and experimental validation.

Environmentally friendly synthetic approaches such as microwave-assisted and solvent-free synthesis are also expected to gain increasing importance.

The major advantages and limitations of pharmacophore modeling are summarized in Table V.

Table V. Advantages and Limitations of Pharmacophore Modeling.

Advantages	Limitations
Reduces cost and time in drug discovery	Dependent on quality of input dataset
Facilitates virtual screening of large libraries	May generate false-positive hits
Enables scaffold hopping and lead optimization	Limited consideration of protein flexibility
Supports identification of key interaction features	Requires experimental validation
Integrates with docking, QSAR, and ADMET tools	Computationally intensive for large datasets

CONCLUSION

Benzothiazole derivatives represent valuable heterocyclic scaffolds with broad pharmacological potential including anticancer, antimicrobial, antiviral, anti-inflammatory, and antitubercular activities. Structural modifications and hybridization strategies have improved potency and selectivity of these compounds.

Pharmacophore modeling has become an essential computational strategy for understanding ligand–target interactions and accelerating rational drug discovery. Integration with docking, MD simulations, QSAR, ADMET prediction, and AI-assisted approaches has significantly improved predictive reliability and efficiency.

Despite progress, challenges such as toxicity, poor bioavailability, and insufficient experimental validation continue to limit clinical translation. Future multidisciplinary approaches combining computational prediction, medicinal chemistry, and biological validation are expected to facilitate development of safer and more effective benzothiazole-based therapeutics.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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FIGURE CAPTIONS/LEGENDS

Figure 1. Structural features and major substitution sites of the benzothiazole scaffold influencing biological activity, selectivity, and physicochemical properties.

Figure 2. General workflow of pharmacophore-guided computer-aided drug design (CADD) for benzothiazole derivatives including virtual screening, docking, QSAR, ADMET prediction, and lead optimization.

Figure 3. Integration of artificial intelligence and machine learning approaches in pharmacophore-guided benzothiazole drug discovery for virtual screening, QSAR analysis, ADMET prediction, and lead optimization.