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Benzothiazole-Based Hybrids as Next Generation Antibacterials: Structure-Activity Relationships, Multi-Target Mechanisms and Anti-Virulence Effects

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Abstract

Benzothiazole has emerged as a promising scaffold for new antibacterial agents against multidrug-resistant pathogens. Its tunable electronics, ease of derivatization and compatibility with hybrid designs allow efficient exploration of structure–activity relationships. Recent benzothiazole derivatives, including thiazole, isatin and pyrimidine hybrids, show low-µg/mL activity against diverse Gram-positive and Gram-negative bacteria and, in some cases, outperform standard antibiotics in vitro. Enzyme and docking studies indicate multi-target mechanisms involving MurB, DNA gyrase, peptide deformylase, folate enzymes and quorum-sensing regulators, alongside antibiofilm and ant virulence effects. Together, these advances position benzothiazole chemistry as a compact, drug-like platform for the rational design of next-generation antibacterials.

Keywords: Benzothiazole, Antibacterial, MDR Bacteria, SAR

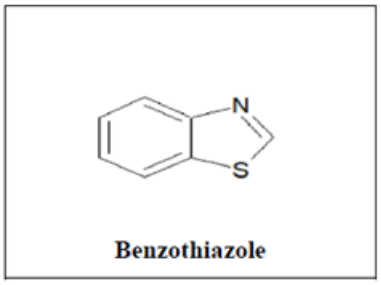
Introduction

The rapid emergence and global spread of multidrug-resistant (MDR) bacteria is now recognized as one of the most serious threats to public health, compromising the efficacy of almost all major antibiotic classes introduced since the mid-20th century [1,2,3]. MDR pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant Pseudomonas aeruginosa, and Acinetobacter baumannii are associated with high mortality, prolonged hospital stays, and increased healthcare costs [4,2]. The World Health Organization and other agencies have repeatedly highlighted the urgent need for new antibacterial agents with novel scaffolds and mechanisms of action to outpace resistance development [5,6,7].

At the same time, the current antibacterial pipeline remains limited and is dominated by derivatives of existing classes, with only a few agents truly representing new pharmacophores or innovative targets [8,9]. This

"innovation gap" is partly due to scientific challenges (difficulty in identifying selective bacterial targets, poor penetration into Gram-negative bacteria) and partly due to economic disincentives for antibiotic development [10,11]. Against this backdrop, heterocyclic scaffolds with rich medicinal chemistry, such as benzothiazoles, have received growing attention as privileged structures capable of interacting with a variety of biological targets [12,13,14].

Benzothiazole is a fused bicyclic heteroaromatic system comprising a benzene ring condensed with a thiazole ring, which contains both sulfur and nitrogen atoms in the five-membered ring [14,15]. The presence of these heteroatoms and the extended π-system facilitate hydrogen bonding, π–π stacking, and coordination with metal ions, making benzothiazole a versatile pharmacophore in medicinal chemistry [16,17,18]. Numerous benzothiazole-containing molecules exhibit diverse biological activities, including anticancer, anti-inflammatory, antitubercular, antidiabetic, and antimicrobial properties [16,17]. In recent years, a substantial body of work has focused on benzothiazole derivatives as antibacterial agents, including against MDR clinical isolates, with detailed studies on synthesis, structure–activity relationship (SAR), mechanisms of action, and molecular docking [12,18,19].



Benzothiazole

This review aims to provide an updated and comprehensive overview of benzothiazole-based antibacterials with emphasis on: (i) the context of MDR and unmet needs, (ii) the medicinal significance of the benzothiazole scaffold, (iii) synthetic strategies used to access antibacterial benzothiazole derivatives, (iv) in vitro activity against MDR pathogens, (v) mechanisms of action and molecular targets, (vi) SAR trends, and (vii) future perspectives and challenges. The main focus is on literature from approximately the last 5–10 years, with particular weight on detailed mechanistic and SAR studies [12].

Multidrug Resistance and Need for New Antibacterials

➢ Global burden of MDR bacteria

Multidrug resistance is generally defined as non-susceptibility to at least one agent in three or more antimicrobial categories [20]. MDR organisms are now prevalent in both hospital and community settings, with especially alarming rates reported for Gram-negative pathogens such as carbapenem-resistant Enterobacterales, Pseudomonas aeruginosa, and Acinetobacter baumannii [21,22,23]. These organisms frequently harbor extended-spectrum β-lactamases (ESBLs), carbapenemases (KPC, NDM, OXA-type), efflux pumps, and porin alterations, leading to resistance to β-lactams, fluoroquinolones, aminoglycosides, and sometimes colistin [24,25,26].

Recent clinical data show that infections by MDR Gram-negatives are associated with mortality rates exceeding 30–40% in severe cases, especially in intensive care units [27]. Similar concerns exist for MDR Gram-positive pathogens, including MRSA, VRE, and penicillin-resistant Streptococcus pneumoniae, which complicate treatment of skin/soft tissue infections, pneumonia, and bloodstream infections [28].

➢ Mechanisms underlying MDR

Bacteria employ multiple, often overlapping mechanisms to achieve multidrug resistance: Enzymatic inactivation [29], target modification [30,31], reduced permeability[32], efflux

pumps [33] biofilm formation [32]. The convergence of these mechanisms severely limits the effectiveness of existing antibiotics and promotes cross-resistance within and across classes [32].

- **Limitations of current antibiotic pipeline**

The clinical pipeline includes a few recently approved or late-stage agents (e.g., cefiderocol, ceftazidime–avibactam, imipenem–cilastatin–relebactam, meropenem–vaborbactam) that restore activity against certain MDR Gram-negative pathogens by combining β-lactams with β-lactamase inhibitors or by exploiting siderophore-mediated uptake [34,35,36]. However, most are modifications of existing scaffolds (β-lactams, tetracyclines, oxazolidinones) and target the same cellular processes, raising concerns about rapid development of resistance [6,34].

Moreover, agents that effectively penetrate and accumulate in Gram-negative bacteria while avoiding efflux remain scarce, and few compounds exploit truly new bacterial targets such as novel enzymes in nucleotide, fatty acid, or cell wall biosynthesis [7,37,38]. Thus, there is a critical and ongoing need for new chemotypes with distinct physicochemical properties and mechanisms of action [6,34].

- **Rationale for exploring benzothiazoles**

Benzothiazoles offer several advantages as core scaffolds for antibacterial drug discovery:

Benzothiazoles offer tunable lipophilicity and electronic properties via substitution on the benzene ring or heterocycle, and they can form hydrogen bonds and coordinate metal ions at enzyme active sites [18,38,39]. They show activity against diverse bacterial enzymes, including dihydroorotase, MurB, peptide deformylase, dihydrofolate reductase, enoyl-ACP reductase, dehydrosqualene synthase, and DNA gyrase [12]. Their synthetic accessibility through multiple reliable routes allows rapid SAR optimization, making them attractive scaffolds for new antibacterials targeting both conventional and underexploited pathways, including in MDR strains [18].

Benzothiazole Scaffold and Its Medicinal Significance

- **Structural features**

Benzothiazole is a fused benzene–thiazole ring system in which the thiazole carries nitrogen and sulfur that confer aromaticity and enable π–π stacking, hydrogen bonding, and dipole interactions important for enzyme binding [19,40,41]. Substitution is commonly made at the 2-position and on the 5-, 6-, or 7-positions of the benzene ring, where aryl, heteroaryl, alkyl, or linker groups are introduced to tune biological activity, selectivity, and pharmacokinetics [40,42].

- **Broader medicinal roles of benzothiazoles**

Beyond antibacterial activity, benzothiazole derivatives have shown notable anticancer (e.g., 2-(4-aminophenyl) benzothiazoles), antitubercular (often as benzothiazole–pyrimidine or –thiazole hybrids), anti-inflammatory/analgesic/CNS effects, and enzyme inhibition (e.g., carbonic anhydrase, aldose reductase, dihydrofolate reductase) [40,43,44]. Several benzothiazole-based compounds have progressed to clinical use or advanced development, particularly in oncology and neurology, supporting the scaffold's drug-like and safety potential when properly optimized [39,40].

- **Medicinal significance specifically in antibacterial drug discovery**

In the context of antibacterial research, benzothiazole moieties frequently serve as:

Benzothiazoles act as enzyme-binding pharmacophores that target catalytic or allosteric sites in key bacterial pathways, including peptidoglycan (MurB, Ddl), folate (DHFR, DHPS), and nucleotide (dihydroorotase) biosynthesis [12,45]. They can also function as quorum-

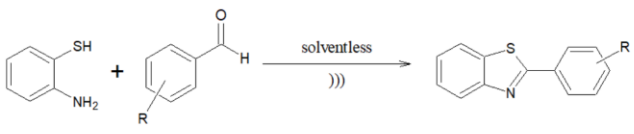
sensing and virulence modulators, inhibiting systems such as Gac/Rsm or LuxR-type regulators and biofilm formation, providing non-bactericidal ways to disarm pathogens [12,46]. In addition, benzothiazoles serve as metal-binding ligands (e.g., Ag, Cu, Zn complexes) and can be hybridized with other privileged pharmacophores (isatin, pyrimidine, triazole, quinoline, thiazole, phthalimide) to create multi-target or synergistic antibacterial agents [19,43,47].

Synthetic Strategies for Antibacterial Benzothiazole Derivatives

A variety of synthetic methodologies have been employed to access benzothiazole-based antibacterials, ranging from classical condensation cyclization to modern multi-component and metal-catalyzed processes. Below, major strategies are summarized with emphasis on those frequently used in antibacterial studies.

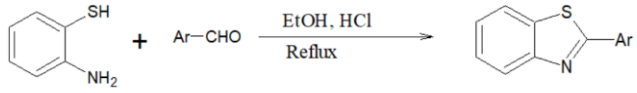
- **Classical cyclization of o-halo anilines or o-aminothiophenols**

Classical synthesis of benzothiazoles commonly uses intramolecular cyclization of substituted o-amino thiophenols or o-haloanilines with sulfur or thiocyanate sources [48]. Reaction of o-amino thiophenol with carboxylic acids, aldehydes, or nitriles under oxidative conditions, or cyclization of o-halo anilines (e.g., o-iodoaniline) with KSCN or thiourea in acid, affords 2-substituted benzothiazoles [48]. By varying the carbonyl or nitrile precursors, a wide range of aryl, heteroaryl, or alkyl 2-substituents can be introduced, making these routes well suited for SAR library generation [48].



- **One-pot condensation approaches**

One-pot syntheses using 2-aminothiophenol are highly popular for antibacterial benzothiazoles because of operational simplicity and good yields: Condensation of 2-aminothiophenol with aldehydes, followed by oxidative cyclization, produces 2-arylbenzothiazoles in ethanol or other solvents with acid catalysis (e.g., HCl, acetic acid) [49,50]. Multi-component reactions involving 2-aminothiophenol, aldehydes, and active methylene compounds or isatin derivatives can directly yield benzothiazole-based Schiff bases, thiazolidinones, or hybrid heterocycles [12,51]. Such methods have been used to prepare amino-benzothiazole Schiff bases, benzothiazole–isatin hybrids, and benzothiazole–pyrimidine derivates that show potent antibacterial activity [12,52].



Acid-catalyzed one-pot synthesis of 2-arylbenzothiazoles from 2-aminothiophenol and aromatic aldehydes in ethanol.

- **Synthesis of benzothiazole–thiazole and other hybrid systems**

Hybridization of benzothiazole with other heterocycles (thiazole, triazole, pyrimidine, quinoline, phthalimide) is widely used to enhance biological activity [12,38]. Benzothiazole–thiazole hybrids are typically obtained by thionation/cyclization of acetonitrile intermediates followed by condensation with phenacyl bromides, whereas benzothiazole–pyrimidine or –triazole hybrids arise from benzothiazolyl aldehydes or Schiff bases cyclized with guanidine or azide/alkyne partners [12,19]. Benzothiazole–phthalimide hybrids are formed by nucleophilic substitution or condensation of benzothiazolyl amines with phthalic anhydrides, and, overall, these strategies introduce extra H-bond donors/acceptors, aromatic groups, and flexible linkers

that tune lipophilicity, target binding, and cellular uptake [38,53].

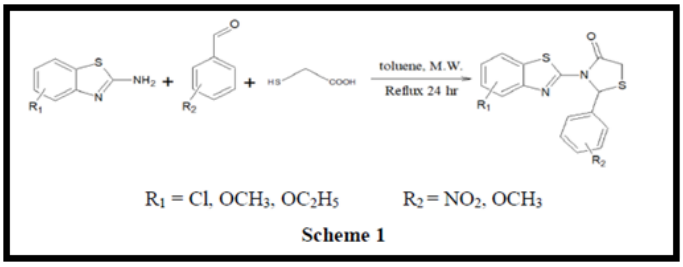
- **Metal-catalyzed and green synthetic methods**

Recent developments emphasize greener, more efficient methods:

Metal-catalyzed (e.g., Cu, Fe) oxidative cyclization of anilines with sulfur sources or 2-aminothiophenols with aldehydes enables benzothiazole formation under milder conditions [54,55]. Heterogeneous catalysts such as TiO_2, as well as solvent-free, microwave-assisted, and ionic-liquid-mediated methods, have further improved yields, shortened reaction times, and reduced environmental impact in one-pot syntheses of benzothiazole derivatives [55,56].

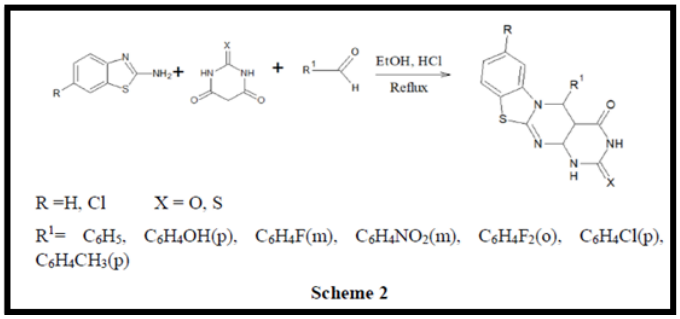
- **Representative synthetic schemes in antibacterial studies**

The review by Kashyap et al. summarizes numerous schemes (over 10) representing different benzothiazole-based antibacterials. For example:[12]



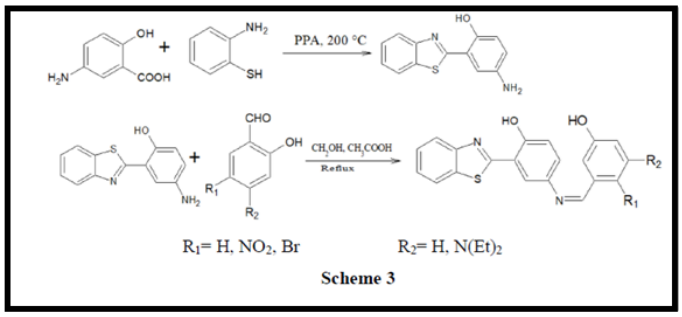
Scheme 1

Pyrimidine–benzothiazole derivatives were synthesized by Venkatesh et al. via condensation of benzothiazolyl aldehydes with barbituric acid derivatives, yielding compounds 4j and 4k with significant antibacterial activity [57].



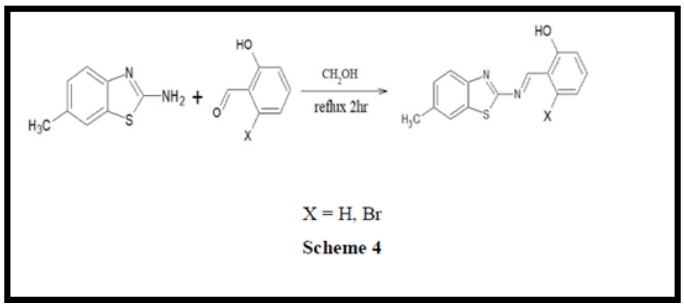
Scheme 2

Benzothiazole–isatin hybrids were prepared by Mishra et al. using Schiff base formation followed by cyclization; certain derivatives showed MIC values superior to ciprofloxacin against Gram-negative bacteria [58].



Scheme 3

Amino-benzothiazole Schiff base analogues synthesized by Suyambulingam et al. via condensation with salicylaldehyde or other aldehydes exhibited potent activity and were investigated as casdihydrofolate reductase inhibitors [59].



Scheme 4

These schemes collectively demonstrate that benzothiazoles can be flexibly constructed and derivatized, enabling systematic exploration of SAR in antibacterial applications.

Antibacterial Activity against MDR Pathogens: In Vitro Studies

- **General antibacterial profiles**

Multiple benzothiazole derivatives have been evaluated against a broad panel of Gram-positive and Gram-negative strains, including clinical MDR isolates. Frequently tested organisms include Staphylococcus aureus, MRSA, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae,

Listeria monocytogenes, and Streptococcus pneumoniae [12].

Typical in vitro endpoints are minimum inhibitory concentrations (MICs) determined by broth microdilution and zones of inhibition (ZOI) measured by agar diffusion assays. Many benzothiazole derivatives display MIC values in the low μg/mL range, often comparable to or better than standard drugs such as ciprofloxacin, ampicillin, gentamicin, or streptomycin against certain strains [60].

- **Selected studies illustrating activity against MDR Gram-negative bacteria**

Mishra et al. evaluated benzothiazole–isatin hybrids and reported that compound 41c exhibited MIC values of 3.1 μg/mL against E. coli and 6.2 μg/mL against P. aeruginosa, outperforming ciprofloxacin (MIC 12.5 μg/mL) in the same assays [12].

Amino-benzothiazole Schiff base analogues synthesized by Suyambulingam et al. showed MICs of 15.62 μg/mL against E. coli and P. aeruginosa, comparable to ciprofloxacin [12].

Several 8-hydroxyquinoline-substituted benzothiazole derivatives displayed enhanced activity against Gram-negative bacteria compared with naphthalenol-based analogues, supporting the role of chelating heterocycles in improving efficacy [61,62]. These findings suggest that appropriately substituted benzothiazoles can penetrate or circumvent Gram-negative outer membranes and efflux systems, at least in vitro [12].

- **Activity against Gram-positive and MDR Gram-positive strains**

Venkatesh et al.'s pyrimidine–benzothiazole derivatives (35d, 35e, 35g) showed potent activity against S. aureus, with ZOI values of 17–19 mm compared to 14 mm for ciprofloxacin, indicating superior efficacy in disc diffusion assays [12].

Benzothiazole–thiazole hybrids studied by Bhagwat et al. exhibited broad-spectrum activity; compound 4b with a meta-nitro substituent showed the lowest MICs across bacterial, fungal, and mycobacterial strains [19].

Other studies reported MICs in the range 3.9–15.63 μg/mL against MRSA and other resistant Gram-positive pathogens for selected benzothiazole derivatives, reflecting strong potency[19,63].

- **Metal complexes and enhanced activity**

Benzothiazole ligands can form complexes with metal ions (Ag, Cu, Zn), often leading to enhanced antibacterial activity: Silver(I) complexes of benzothiazole derivatives demonstrated larger zones of inhibition against Gram-positive and Gram-negative bacteria than the parent ligands or AgNO3 alone, suggesting synergistic effects of ligand-metal coordination on membrane interaction and enzyme inhibition[12]. Copper and zinc complexes of benzothiazole Schiff bases have also shown improved activity and, in some cases, lower MIC values than free ligands [12].

- **Anti-quorum sensing and anti-biofilm properties**

In addition to direct bactericidal or bacteriostatic effects, some benzothiazole derivatives act as anti-quorum sensing agents: Novel benzothiazole derivatives were reported to inhibit quorum-sensing regulated virulence factors and biofilm formation in plant pathogenic bacteria, with in vitro and in planta activity demonstrating their potential as non-bactericidal antimicrobials [64].

Similar approaches targeting quorum-sensing systems in human pathogens (e.g., Pseudomonas Gac/Rsm two-component system) are under exploration using functionalized benzothiazoles [65]. These data underscore

the versatility of benzothiazole derivatives in targeting both growth and virulence of MDR pathogens.

Mechanism of Action and Molecular Targets

Recent benzothiazole studies systematically combine MIC testing, enzyme assays, and docking to clarify mechanisms [12].

- **MurB inhibition**

MurB, essential for peptidoglycan synthesis and absent in humans, is a prime target. Several benzothiazoles show strong docking to E. coli MurB via H-bonds and π–π interactions; compound 11a (trifluoromethoxy) gives a docking score ≈ −10.74 kcal/mol and high antibacterial activity, and SAR indicates chloro/nitro groups enhance MurB binding and potency [12].

- **DNA gyrase/ topoisomerase**

Benzothiazole–thiazole hybrids display high interaction energies against DNA gyrase from S. aureus and M. tuberculosis; meta-nitro derivative 4b shows excellent MICs. Other substituted benzothiazoles (4-chloro, 4-methoxy, 6-nitro) dock well into gyrase and tyrosine kinase, typically forming π–π stacking and H-bonds in the active site [12,19].

- **Peptide deformylase**

Benzothiazole–isatin hybrids from Mishra et al. act as peptide deformylase inhibitors; compound 41c is more active than ciprofloxacin against Gram-negative bacteria, with docking supporting good PDF active-site fit [12,58].

- **Folate pathway enzymes**

Amino-benzothiazole Schiff bases show MICs comparable to ciprofloxacin and have been docked as cas-dihydrofolate reductase inhibitors, forming stable H-bond networks in the active site [12,59].

- **Other enzyme targets**

Kashyap et al. report benzothiazoles inhibiting dihydroorotase, enoyl-ACP reductase, dehydrosqualene synthase, dihydropteroate synthase, and tyrosine kinase, with halogen/nitro substitution on the core often improving binding, highlighting their multi-target potential [12].

- **Anti-quorum sensing**

Some benzothiazoles act as anti-QS agents, blocking LuxR-type receptors and biofilm formation in plant pathogens, and others inhibit the Gac/Rsm system in Pseudomonas, reducing virulence factor expression; such non-bactericidal actions may lessen resistance pressure [64].

Structure–Activity Relationship (SAR) of Benzothiazole Antibacterials

Extensive SAR analyses across different benzothiazole series reveal consistent trends regarding substitution patterns, electronic effects, and hybridization with other heterocycles.

- **SAR trends**

Across multiple studies, key SAR conclusions include:

Electron-withdrawing substituents (nitro, halogen) at specific positions on the phenyl or benzothiazole ring generally enhance antibacterial potency and docking scores [19]. Heteroaryl substituents at C-2 (e.g., quinoline, triazole, pyrimidine, thiazole, isatin) often yield stronger activity than simple aryl or alkyl groups [12,19,38].

Hybrid molecules combining benzothiazole with other bioactive heterocycles frequently outperform their individual fragments, supporting the "molecular hybridization" strategy [12,19].

Subtle changes in substituent position (meta vs. para) and nature (electron-withdrawing vs. donating) can shift not only potency but also selectivity toward bacterial vs. fungal targets [19]. These SAR insights guide rational design of next-generation benzothiazole antibacterials with improved potency and spectrum.

Future Perspectives

Despite substantial progress, several challenges and opportunities remain for benzothiazole-based antibacterials.

- **In vivo evaluation and pharmacokinetics**

Most benzothiazole derivatives have been evaluated primarily in vitro, with limited data on in vivo efficacy, pharmacokinetics, and toxicity. Future work should prioritize [66]:

Assessment in appropriate animal infection models (e.g., MRSA, CRE, Pseudomonas pneumonia or sepsis models). Detailed pharmacokinetic studies to optimize bioavailability, half-life, tissue distribution, and clearance. Toxicity profiling (acute, sub-chronic) to identify safe candidates for further development. Translation from *invitro* potency to *invivo* efficacy will be crucial for advancing benzothiazoles toward clinical trials.

- **Overcoming Gram-negative barriers and resistance**

Although several benzothiazoles show promising activity against Gram-negatives, achieving robust and consistent efficacy remains challenging due to the outer membrane barrier and efflux pumps. Strategies include [67,68]:

Structural optimization guided by Gram-negative permeation rules (e.g., appropriate polar surface area, charge, rigidity). Conjugation with siderophore or other uptake motifs to exploit active transport pathways, analogous to cefiderocol. Combination therapies with efflux pump inhibitors or β-lactamase inhibitors to enhance intracellular concentrations [68,69].

- **Target validation and multi-target design**

While docking and in vitro enzyme assays suggest multiple targets for benzothiazole derivatives, further validation is needed: Genetic knock-out/overexpression studies and biochemical assays to confirm target engagement [70,71]. Use of resistance selection and whole-genome sequencing to identify mutations conferring reduced susceptibility, thereby validating primary targets [70,72]. Design of multi-target benzothiazole hybrids that simultaneously inhibit two or more essential enzymes (e.g., MurB and DNA gyrase), potentially reducing resistance development [73].

- **Anti-virulence and anti-biofilm approaches**

Benzothiazole derivatives that modulate quorum sensing or virulence rather than directly killing bacteria may reduce selection pressure for resistance [74,75]. Future efforts could focus on: Optimizing anti-quorum sensing benzothiazoles for human pathogens such as P. aeruginosa, S. aureus, and Enterobacterales [76,77]. Targeting biofilm formation and persistence with benzothiazole-based agents that disrupt extracellular polymeric substances or biofilm regulatory pathways [76,77].

- **Integration of computational design and AI**

Recent advances in computational chemistry, docking, and AI can greatly speed benzothiazole optimization. Machine-learning models trained on existing SAR can predict activity and ADMET for new analogues, while high-throughput virtual screening against multiple bacterial targets helps identify improved scaffolds. Multi-objective optimization can then balance potency, selectivity, and drug-like properties to guide synthesis more efficiently [73].

Conclusion

Benzothiazole is a versatile scaffold for discovering new antibacterials against MDR pathogens. Recent studies show that suitably substituted and hybrid benzothiazole derivatives can display potent in vitro activity against diverse Gram-positive and Gram-negative bacteria, including MDR strains, and can hit multiple targets such as MurB, DNA gyrase, peptide deformylase, folate

enzymes, and quorum-sensing regulators. Structure–activity work highlights the value of electron-withdrawing groups, heteroaryl substitution at C-2, and optimized linkers for maximizing potency and spectrum, but progress toward clinical use still demands in vivo efficacy, better Gram-negative penetration/PK, and rigorous target validation. With modern synthetic, computational, and anti-virulence approaches, benzothiazole chemistry remains a rich platform for future antibacterial drug discovery [12,19,38,73].

References

1. Salam MA, Al-Amin MY, Salam MT, Pawar JS, Akhter N, Rabaan AA, et al. Antimicrobial Resistance: a Growing Serious Threat for Global Public Health. Healthcare [Internet]. 2023 Jul 5;11(13). Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10340576/
2. Baruah, J., Shantikumar Singh, L., Salvia, T. and Sarma, J. (2024) Antimicrobial Resistance a Continued Global Threat to Public HealthA Perspective and Mitigation Strategies. Journal of Laboratory Physicians, 16, 429-440. - References - Scientific Research Publishing [Internet]. Available from: https://www.scirp.org/reference/ references papers?referenceid=4187850
3. Marino A, Maniaci A, Lentini M, Ronsivalle S, Nunnari G, Cocuzza S, et al. The Global Burden of Multidrug-Resistant Bacteria. Epidemiologia [Internet]. 2025 May 5;6(2):21. Available from: https:// www.mdpi.com/ 2673-3986/6/2/21#B15-epidemiologia-06-00021
4. Nelson RE, Hyun D, Jezek A, Samore MH. Mortality, Length of Stay, and Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Elderly Hospitalized Patients in the United States. Clinical Infectious Diseases. 2021 Oct 7;74(6).
5. World Health Organization. Antimicrobial resistance [Internet]. World Health Organization. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
6. Heimann D, Kohnhäuser D, Kohnhäuser AJ, Brönstrup M. Antibacterials with Novel Chemical Scaffolds in Clinical Development. Drugs. 2025 Jan 23;
7. Gupta P, Yadav P, Lata M, Chaudhary S, Vrushti Telang, Kishore R, et al. Potential next generation targets for antibacterial agent's discovery and development. European Journal of Medicinal Chemistry. 2025 Sep 1;118188–8.
8. Beyer P, Paulin S. The Antibacterial Research and Development Pipeline Needs Urgent Solutions. ACS Infectious Diseases. 2020 Jun 12;6(6):1289–91.
9. Gigante V, Sati H, Beyer P. Recent advances and challenges in antibacterial drug development. ADMET and DMPK. 2022 Mar 4;10(2):147–51.
10. Silver LL. Appropriate Targets for Antibacterial Drugs. Cold Spring Harbor Perspectives in Medicine. 2016 Sep 6;6(12):a030239.
11. Chan LW, Hern KE, Chayanon Ngambenjawong, Lee K, Kwon EJ, Hung DT, et al. Selective Permeabilization of Gram-Negative Bacterial Membranes Using Multivalent Peptide Constructs for Antibiotic Sensitization. ACS Infectious Diseases [Internet]. 2021 Mar 9;7(4):721–32.
12. Kashyap P, Verma S, Gupta P, Narang R, Lal S, Manish Devgun. Recent insights into antibacterial potential of benzothiazole derivatives. Medicinal Chemistry Research. 2023 May 29;32(8):1543–73.
13. I A, Purawarga Matada GS, Pal R, Ghara A, Aishwarya NVSS, B K, et al. Benzothiazole a

privileged scaffold for Cutting-Edges anticancer agents: Exploring drug design, structure-activity relationship, and docking studies. European Journal of Medicinal Chemistry [Internet]. 2024 Sep 5; 279:116831.

14. Okonkwo1 VI, Chinedu Emmanuel Nnadi1, Ebuka Leonard Onyeyilim2, 3. Der Pharma Chemica [Internet]. 2023 Aug 31 [cited 2026 Mar 13];15(5). Available from: https://www. derpharmachemica. com/pharma-chemica/advances-in-benzothiazole-scaffold-a-review-of-synthesis-and-medicinal-significance-100799.html
15. Yadav PS, Devprakash D, Senthilkumar GP. ChemInform Abstract: Benzothiazole: Different Methods of Synthesis and Diverse Biological Activities. ChemInform. 2011 Sep 8;42(40):no.
16. Keri RS, Patil MR, Patil SA, Budagumpi S. A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry. European Journal of Medicinal Chemistry. 2015 Jan;89:207–51.
17. SCOPE OF BENZOTHIAZOLE SCAFFOLD: A REVIEW. International Journal of Biology, Pharmacy and Allied Sciences. 2024 Jun 1;13(6).
18. Mohamed-Ezzat RA, Elgemeie GH. Synthetic strategies towards benzothiazole-based compounds of therapeutic potency: experimental, investigational and approved drugs. RSC Advances. 2025;15 (49):41724–832.
19. Bhagwat SK, Chobe SS, Alavala RR, Vora A, More RA, Bobade VD, et al. Benzothiazole–thiazole hybrids as broad-spectrum antimicrobial agents: synthesis, SAR analysis, and molecular docking against bacterial and fungal targets. RSC Advances [Internet]. 2025 [cited 2026 Feb 27];15(38):31752–62.
20. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases [Internet]. 2012 Mar;18(3):268–81. Available from: https:// www. ncbi.nlm.nih.gov/pubmed/21793988
21. CDC. Background [Internet]. Infection Control. 2024. Available from: https://www.cdc.gov/ infection-control/ hcp/ mdro-management/ background. html
22. Golli AL, Cristea OM, Zlatian O, Glodeanu AD, Balasoiu AT, Ionescu M, et al. Prevalence of Multidrug-Resistant Pathogens Causing Bloodstream Infections in an Intensive Care Unit. Infection and Drug Resistance. 2022 Oct;Volume 15:5981–92.
23. Research Article. Burden of Multidrug-Resistant Gram-Negative Bacterial Infections in a Tertiary Care Hospital. Journal of Pure and Applied Microbiology [Internet]. 2024 Jul 31; Available from: https:// microbiologyjournal.org/burden-of-multidrug-resistant-gram-negative-bacterial-infections-in-a-tertiary-care-hospital/
24. Rihane R, Hecini-Hannachi A, Bentchouala C, Benlabed K, Diene SM. Molecular Characterization of Carbapenem and Colistin Resistance in Klebsiella pneumoniae Isolates Obtained from Clinical Samples at a University Hospital Center in Algeria. Microorganisms. 2024 Sep 25;12(10):1942.
25. Jesus MBD, Ehlers MM, Kock RFDS and MM. Review - Understanding β-lactamase Producing Klebsiella pneumoniae [Internet]. www. intechopen.

com. IntechOpen; 2015. Available from: https://www.intechopen.com/chapters/49539

26. Alkofide H, Alhammad AM, Alruwaili A, Aldemerdash A, Almangour TA, Alsuwayegh A, et al. Multidrug-Resistant and Extensively Drug-Resistant Enterobacteriaceae: Prevalence, Treatments, and Outcomes – A Retrospective Cohort Study. Infection and Drug Resistance. 2020 Dec;Volume 13:4653–62.
27. Olga Tsachouridou, Dimitrios Pilalas, Sideris Nanoudis, Antoniou A, Isidora Bakaimi, Theofilos Chrysanthidis, et al. Mortality Due to Multidrug-Resistant Gram-Negative Bacteremia in an Endemic Region: No Better Than a Toss of a Coin. Microorganisms. 2023 Jun 30;11(7):1711–1.
28. Rivera AM, Boucher HW. Current Concepts in Antimicrobial Therapy Against Select Gram-Positive Organisms: Methicillin-ResistantStaphylococcus aureus, Penicillin-Resistant Pneumococci, and Vancomycin-Resistant Enterococci. Mayo Clinic Proceedings [Internet]. 2011 Dec 1;86(12):1230–43
29. Egorov AM, Ulyashova MM, M Yu Rubtsova. Bacterial Enzymes and Antibiotic Resistance. Acta Naturae [Internet]. 2018 Oct;10(4):33. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6351036/
30. Spencer AC, Panda SS. DNA Gyrase as a Target for Quinolones. Biomedicines. 2023 Jan 27;11(2):371.
31. LAMBERT P. Bacterial Resistance to antibiotics: Modified Target Sites. Advanced Drug Delivery Reviews. 2005 Jul 29;57(10):1471–85.
32. Munita JM, Arias CA. Mechanisms of antibiotic resistance. Virulence Mechanisms of Bacterial Pathogens, Fifth Edition. 2016 Oct 1;4(2):481–511.
33. Augusto Dulanto Chiang, Dekker JP. Efflux pump-mediated resistance to new beta lactam antibiotics in multidrug-resistant gram-negative bacteria. Communications Medicine. 2024 Aug 29;4(1).
34. Terreni M, Taccani M, Pregnolato M. New Antibiotics for Multidrug-Resistant Bacterial Strains: Latest Research Developments and Future Perspectives. Molecules [Internet]. 2021 May 2;26 (9):2671.
35. Matlock A, Garcia JA, Moussavi K, Long B, Liang SYT. Advances in novel antibiotics to treat multidrug-resistant gram-negative bacterial infections. Internal and Emergency Medicine. 2021 May 6;
36. Hayden DA, White BP, Bennett KK. Review of Ceftazidime-Avibactam, Meropenem-Vaborbactam, and Imipenem/Cilastatin-Relebactam to Target Klebsiella pneumoniae Carbapenemase-Producing Enterobacterales. Journal of Pharmacy Technology. 2020 Jun 17;36(5):202–10.
37. Zhao S, Adamiak JW, Bonifay V, Mehla J, Zgurskaya HI, Tan DS. Defining new chemical space for drug penetration into Gram-negative bacteria. Nature Chemical Biology. 2020 Nov 16;16(12): 1293–302.
38. Haider K, Shrivastava N, Pathak A, Prasad Dewangan R, Yahya S, Shahar Yar M. Recent advances and SAR study of 2-substituted benzothiazole scaffold based potent chemotherapeutic agents. Results in Chemistry. 2022 Jan;4:100258.
39. Nishad RK, Singh KA, Rahman MA. Synthesis and Pharmacological Activities of Benzothiazole Derivatives. Indian Journal of Pharmaceutical Education and Research [Internet]. 2024 Aug 10;58 (3s):s704–19.
40. Sharma PC, Sinhmar A, Sharma A, Rajak H, Pathak DP. Medicinal significance of benzothiazole

scaffold: an insight view. Journal of Enzyme Inhibition and Medicinal Chemistry. 2012 Oct 3;28(2):240–66.

41. Usman M, Alam A, Zainab, Khan M, Elhenawy AA, Ayaz M, et al. Synthesis, characterization, enzyme inhibition and molecular docking studies of benzothiazole derivatives bearing alkyl phenyl ether fragments. Journal of Molecular Structure. 2025 Jan; 1319:139504.
42. Yadav KP, Rahman MA, Nishad S, Maurya SK, Anas M, Mujahid M. Synthesis and biological activities of benzothiazole derivatives: A review. Intelligent Pharmacy [Internet]. 2023 Oct 1;1(3): 122–32.
43. Hemeda LR, Mahmoud, Abdelgawad MA, Khaleel EF, Abdel-Aziz MM, Binjubair FA, et al. Discovery of pyrimidine-tethered benzothiazole derivatives as novel anti-tubercular agents towards multi- and extensively drug resistant Mycobacterium tuberculosis. Journal of Enzyme Inhibition and Medicinal Chemistry. 2023 Aug 30;38(1).
44. Siddiqui N, Rana A, Khan SA, Ahsan W, Alam MS, Ahmed S. Analgesic and Antidepressant Activities of Benzothiazole-Benzamides. Biomedical and Pharmacology Journal [Internet]. 2015 Jan 22 [cited 2026 Mar 27];1(2):297–300.
45. Morsy MA, Ali EM, Kandeel M, Venugopala KN, Nair AB, Greish K, et al. Screening and Molecular Docking of Novel Benzothiazole Derivatives as Potential Antimicrobial Agents. Antibiotics. 2020 Apr 29;9(5):221.
46. Dzoyem JP, Tsemeugne J, Pone Kamdem B, Foyou Meupiap R, Kuate BA, Mkounga P, et al. Antibacterial, antibiofilm and anti-quorum sensing activities of 1,2,3,5-tetrazine derivatives linked to a benzothiazole moiety. Dinamarca MA, editor. PLOS One [Internet]. 2025 Jun 3 [cited 2026 Mar 27];20(6):e0318135.
47. Sharma PC, Sharma D, Sharma A, Saini N, Goyal R, Ola M, et al. Hydrazone comprising compounds as promising anti-infective agents: chemistry and structure-property relationship. Materials Today Chemistry. 2020 Dec;18:100349.
48. Padilla-Martínez II, Cruz A, García-Báez EV, Mendieta-Wejebe JE, Rosales-Hernández MC. Condensation Reactions of 2-Aminothiophenoles to Afford 2-Substituted Benzothiazoles of Biological Interest: A Review (2020–2024). International Journal of Molecular Sciences [Internet]. 2025 Jun 19 [cited 2026 Mar 28];26(12):5901–1.
49. Shaikh KA, Chaudhar UN. Lanthanum (III) nitrate hexahydrate catalyzed one-pot synthesis of 2-arylbenzothiazoles under mild reaction conditions. Organic Communications. 2017 Nov 28;10(4):288–97.
50. Ji Ram V, Sethi A, Nath M, Pratap R. Five-Membered Heterocycles. The Chemistry of Heterocycles. 2019;149–478.
51. Shainyan BA, Zhilitskaya LV, Yarosh NO. Synthetic Approaches to Biologically Active C-2-Substituted Benzothiazoles. Molecules. 2022 Apr 18;27(8):2598–8.
52. Abdullah HI, Al-Joboury WMR, Aljoboury IFO, Hameed IK, Al-Badrany KA, Abdulqader MA. Synthesis and Characterization of Schiff base Compounds Produced from 6-Bromo-4-Fluoro-2 Aminobenzothazol Assessment against Antibacterial Activity. AUIQ Complementary Biological System [Internet]. 2025 May 12 [cited 2026 Mar 28];2(1):118–30. Available from: https://acbs.alayen.edu.iq/ journal/vol2/iss1/10/

53. Barbarossa A, Ceramella J, Carocci A, Domenico Iacopetta, Rosato A, Limongelli F, et al. Benzothiazole-Phthalimide Hybrids as Anti-Breast Cancer and Antimicrobial Agents. Antibiotics. 2023 Nov 23;12(12):1651–1.
54. Sun Y, Jiang H, Wu W, Zeng W, Wu X. Copper-Catalyzed Synthesis of Substituted Benzothiazoles via Condensation of 2-Aminobenzenethiols with Nitriles. Organic Letters. 2013 Mar 15;15(7):1598–601.
55. Gao X, Liu J, Zuo X, Feng X, Gao Y. Recent Advances in Synthesis of Benzothiazole Compounds Related to Green Chemistry. Molecules. 2020 Apr 5;25(7):1675.
56. Sachin P. Kunde, Raghunath J. Katkar, Pramod B. Thakur, Nitin A. Sasane. Recent Advances of Modified TiO2 Nanostructure as Heterogeneous Catalyst in Organic Transformations. International Journal of Advanced Research in Science, Communication and Technology [Internet]. 2022 Mar 31 [cited 2026 Mar 29];77–85. Available from: https://ijarsct.co.in/Paper3064.pdf
57. Venkatesh T, Bodke YD, K N, Kumar S R. One-Pot Synthesis of Novel Substituted Phenyl-1,5-dihydro-2Hbenzo[4,5]thiazolo[3,2-a]pyrimido[4,5-d]pyrimidine Derivatives as Potent Antimicrobial Agents. Medicinal Chemistry [Internet]. 2018 [cited 2026 Mar 29];08(01).
58. Mishra V, Ghanavatkar CW, Mali SN, Chaudhari HK, Sekar N. Schiff base clubbed benzothiazole: synthesis, potent antimicrobial and MCF-7 anticancer activity, DNA cleavage and computational study. Journal of Biomolecular Structure & Dynamics. 2019 May 30;1–14.
59. Suyambulingam JK, Karvembu R, Bhuvanesh NSP, Enoch IVMV, Selvakumar PM, Premnath D, et al. Synthesis, structure, biological/chemosensor evaluation and molecular docking studies of aminobenzothiazole Schiff bases. Journal of Adhesion Science and Technology. 2020 Jun 4;34(23):2590–612.
60. Kadeřábková N, Ayesha, Mavridou, Despoina A. I. Antibiotic susceptibility testing using minimum inhibitory concentration (MIC) assays. npj Antimicrobials and Resistance [Internet]. 2024 Nov 7;2(1):1–9. Available from: https://www.nature.com/articles/s44259-024-00051-6
61. Nehra N, Ram Kumar Tittal, Ghule VD. 1,2,3-Triazoles of 8-Hydroxyquinoline and HBT: Synthesis and Studies (DNA Binding, Antimicrobial, Molecular Docking, ADME, and DFT). ACS Omega. 2021 Oct 6;6(41):27089–100.
62. Hany, Khalaf MM, Gouda M, Amer AA, Abdelhamid AA, Abdou A. Design, Synthesis of new Mixed azo-hydroxyquinoline complexes; in vitro anti-inflammatory, antifungal, antibacterial, theoretical, and molecular docking interactions Investigation. Journal of Molecular Structure. 2024 Mar 11;1307:138016–6.
63. Mahajan, D. Design, Synthesis and Biological Evaluation of Benzothiazole Derivatives for Antimicrobial Activity. Journal of Chemical Health Risks [Internet]. 2024;14(4):1920–30.
64. Chu PL, Feng YM, Long ZQ, Xiao WL, Ji J, Zhou X, et al. Novel Benzothiazole Derivatives as Potential Anti-Quorum Sensing Agents for Managing Plant Bacterial Diseases: Synthesis, Antibacterial Activity Assessment, and SAR Study. Journal of Agricultural and Food Chemistry. 2023 Apr 19;71 (17):6525–40.
65. Liu J, Wu W, Hu J, Zhao S, Chang Y, Chen Q, et al. Novel benzothiazole derivatives target the Gac/Rsm

two-component system as antibacterial synergists against Pseudomonas aeruginosa infections. Acta Pharmaceutica Sinica B. 2024 Aug 1;

66. Yadav RA, Meena D, Singh K, Tyagi R, Yadav Y, Sagar R. Recent advances in the synthesis of new benzothiazole based anti-tubercular compounds. RSC Advances. 2023 Jan 1;13(32):21890–925.
67. Temesgen AB, Shiferaw SA. Antimicrobial Multidrug Resistance and Mechanisms of Action: An Overview. BioMed Research International [Internet]. 2025 Jan 1;2025(1).
68. Machado E, Sousa JC. New Antibiotics for Treating Infections Caused by Multidrug-Resistant Bacteria. Antibiotics. 2025 Oct 5;14(10):997.
69. Yang X, Ye W, Qi Y, Ying Y, Xia Z. Overcoming Multidrug Resistance in Bacteria Through Antibiotics Delivery in Surface-Engineered Nano-Cargos: Recent Developments for Future Nano-Antibiotics. Frontiers in Bioengineering and Biotechnology. 2021 Jul 8;9.
70. Schnappinger D. Genetic Approaches to Facilitate Antibacterial Drug Development. Cold Spring Harbor Perspectives in Medicine. 2015 Feb 13;5 (7):a021139.
71. Jee Hyun Kim, O'Brien KM, Sharma R, Boshoff HI, Rehren G, Chakraborty S, et al. A genetic strategy to identify targets for the development of drugs that prevent bacterial persistence. 2013 Nov 19;110 (47):19095–100.
72. Mahé P, Tournoud M. Predicting bacterial resistance from whole-genome sequences using k-mers and stability selection. BMC Bioinformatics. 2018 Oct 17;19(1).
73. Sofi FA, Mayank, Masoodi MH, Tabassum N. Recent advancements in the development of next-generation dual-targeting antibacterial agents. RSC Medicinal Chemistry [Internet]. 2025 [cited 2026 Mar 29];16(5):1891–922.
74. Fihn CA, Lembke HK, Gaulin J, Bouchard P, Villarreal AR, Penningroth MR, et al. Evaluation of expanded 2-aminobenzothiazole library as inhibitors of a model histidine kinase and virulence suppressors in Pseudomonas aeruginosa. Bioorganic Chemistry [Internet]. 2024 Sep 21;153:107840.
75. Patel K, Panchal R, Sakariya B, Gevariya M, Raiyani R, Soni R, et al. Combatting antibiotic resistance by exploring the promise of Quorum Quenching in targeting bacterial virulence. The Microbe [Internet]. 2024 Dec 11;6:100224.
76. Mao S, Li Q, Yang Z, Li Y, Ye X, Wang H. Design, synthesis, and biological evaluation of benzoheterocyclic sulfoxide derivatives as quorum sensing inhibitors in Pseudomonas aeruginosa. Journal of Enzyme Inhibition and Medicinal Chemistry. 2023 Feb 7;38(1).
77. Mohammed EZ, El-Dydamony NM, Taha EA, Taha MN, Mehany ABM, Abdel Aziz HA, et al. Design, synthesis, and molecular dynamic simulations of some novel benzo[d]thiazoles with anti-virulence activity against Pseudomonas aeruginosa. European Journal of Medicinal Chemistry [Internet]. 2024 Dec [cited 2026 Mar 29];279:116880.