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Benzothiazole Derivatives in Modern Drug Discovery: A Review

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Abstract: *Benzothiazole derivatives have gained considerable attention in recent years for their diverse pharmacological activities and potential applications in modern drug discovery. As a privileged heterocyclic scaffold, benzothiazole offers structural flexibility, allowing extensive chemical modifications to enhance therapeutic efficacy. This review highlights recent advances in the synthesis of benzothiazole-based compounds, including conventional methods, catalyst-assisted protocols, and green chemistry approaches. It further explores the structure–activity relationships (SAR), particularly the influence of substitutions at key positions on biological activity. Benzothiazole derivatives have shown promising results in a wide range of therapeutic areas, notably anticancer, antimicrobial, antidiabetic, antiviral, anti-inflammatory, and neuroprotective applications. Several compounds have demonstrated superior efficacy compared to existing drugs, underlining their potential as lead molecules in drug development. This article aims to provide a consolidated view of current progress in benzothiazole research and to guide future efforts in designing novel bioactive agents based on this important chemical framework.*

Key words: Benzothiazole, heterocyclic compounds, drug discovery, structure–activity relationship

Introduction: Heterocyclic compounds form the backbone of numerous bioactive molecules and continue to play a pivotal role in drug discovery and medicinal chemistry. Their unique ring systems, often containing nitrogen, sulfur or oxygen atoms, provide structural diversity and functional versatility, making them attractive scaffolds for pharmaceutical development. Due to this structural flexibility, benzothiazole derivatives have been widely investigated for therapeutic applications, including anticancer, antimicrobial, antiviral, neuroprotective Anti-inflammatory Activity, Analgesic, Antidiabetic, Cardioprotective[8] Antiparasitic, Antioxidant, Anticonvulsant and Antifungal[1-3] properties.The aromatic and planar nature of benzothiazole (fig 1.1) contributes to its stability and ability to interact with various biological targets such as enzymes, receptors, and nucleic acids.

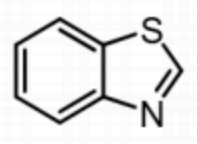

Fig 1.1

First reported by Hantzsch and Waber[4] in 1887 and structurally confirmed in 1889, benzothiazole has evolved from a simple heterocycle to a privileged structure in drug design. Advances in synthetic methodologies—ranging from classical condensation reactions to modern microwave-assisted and green chemistry protocols—have enabled the generation of structurally diverse derivatives with improved potency and selectivity. In light of growing interest and ongoing research, this review aims to provide a comprehensive overview of benzothiazole derivatives, focusing on recent synthetic approaches, structure–activity relationships (SAR) and their multifaceted therapeutic applications in modern drug discovery.

2. Chemistry of Benzothiazole

2.1 Basic structure and physicochemical properties: Benzothiazole is a bicyclic aromatic heterocycle composed of a benzene ring fused with a thiazole ring. The thiazole moiety contains one sulfur and one nitrogen atom, contributing to its electron-rich and electron-donating character. The molecular formula of benzothiazole is C_7H_5NS, with a molecular weight of 135.18 g/mol. It is a rigid, planar and aromatic system, which plays a significant role in π–π stacking and hydrophobic interactions with biological targets such as enzymes and nucleic acids[5]. The electron-withdrawing nature of nitrogen and sulfur induces unique

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dipole moments and chemical reactivity, enabling selective substitution, particularly at the C-2 and C-6 positions. Benzothiazole exhibits moderate lipophilicity, allowing membrane permeability and target binding—making it a valuable scaffold in medicinal chemistry[6-7].

2.2 Methods of synthesis:

2.2.1 Classical synthesis: The most common classical route to benzothiazole involves the condensation of 2-aminothiophenol with various carboxylic acids (Fig 1.2), aldehydes or acyl chlorides, followed by intramolecular cyclization under acidic or oxidative conditions[5].

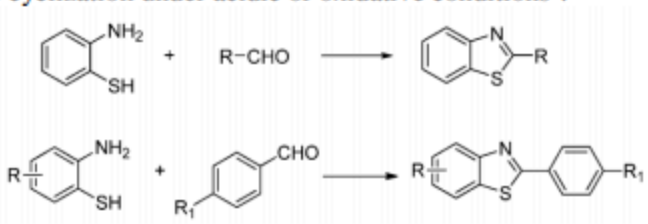

Fig 1.2

2.2.2 Modern methods (microwave-assisted, catalyst-based, green synthesis):

2.2.2.1 Microwave-Assisted Synthesis: Microwave-assisted synthesis has been successfully applied to the preparation of various benzothiazole derivatives, significantly improving traditional methods (fig 1.3). Synthesis of benzothiazole using phenyl iodoniumbis(triuoroacetate) (PIFA) as an oxidation reagent for the condensation reaction of 2-aminobenzenethiol and benzaldehyde compounds[8].

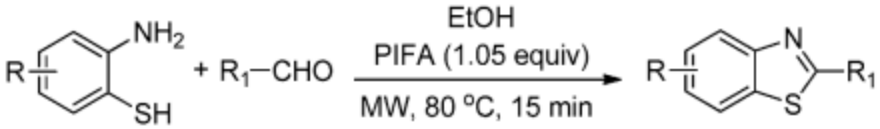

Fig 1.3

2.2.2.2 Catalyst-based Synthesis: copper-catalyzed reactions have shown improved yields and reduced reaction times, making the process more efficient. The polystyrene polymer catalysts grafted with iodine acetate could promote the efficient condensation of 2-aminobenzenethiol and benzaldehyde compounds in dichloromethane to synthesize benzothiazole compounds[9].

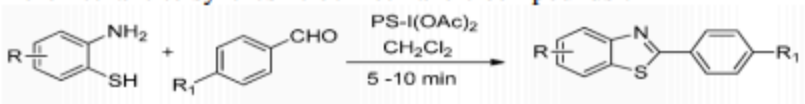

Fig 1.4

2.2.2.3 Green Chemistry Approaches: It includes utilization of renewable solvents and reducing waste generation are critical aspects of modern synthetic strategies. Its examples include solvent-free reactions and reactions conducted in water or using biodegradable solvents (fig 1.5). an efficient, easy and green method for the benzothiazoles synthesis by a condensation reaction of 2-aminothiophenol with various aromatic aldehydes using SnP_2O_7 as a new heterogeneous catalyst[10].

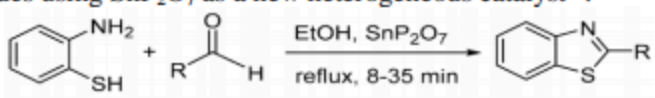

Fig 1.5

3. Structure Activity Relationship (SAR): The biological activity of benzothiazole derivatives is highly influenced by the nature and position of substituents on the aromatic and thiazole rings. SAR studies have demonstrated that variations at the C-2, C-5, C-6 and C-7 positions significantly affect the pharmacological profile of these compounds. In addition, planarity, lipophilicity and electronic effects determine the molecular interactions with biological targets.

3.1 Influence of Substitutions at C-2, C-5, C-6 and C-7 Positions: The C-2 position is the most commonly modified site. Substituting it with aryl, alkyl, heteroaryl or amide groups enhances a wide range of activities. For instance, 2-phenylbenzothiazoles have shown potent anticancer activity[2,6] due to their ability to intercalate DNA and inhibit enzymes like topoisomerase I. the Halogen (Cl, Br), methyl or

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nitro groups at the C-5 or C-6 positions improve antimicrobial, anti-inflammatory and anticancer activities. These groups increase lipophilicity and membrane permeability while enhancing binding to target sites[7]. Substituents at C-7, such as –OH or –OCH_3, improve antioxidant and neuroprotective potential through hydrogen bonding and radical scavenging. These groups also assist in metal chelation, supporting antioxidant mechanisms[1].

3.2 Planarity and Electronic Effects: The planarity of benzothiazole enables effective π–π stacking interactions with nucleic acids and aromatic amino acid residues in proteins, making its flat, conjugated structure essential for DNA intercalation and for fitting into enzyme binding pockets. Substituents significantly influence its biological behavior—electron-withdrawing groups such as –NO_2, –Cl and –CF_3 at the C-2 or C-5 positions enhance cytotoxicity and enzyme inhibition by increasing the electrophilicity of the molecule[3]. In contrast, electron-donating groups like –OH, –OCH_3 and –NH_2 improve antioxidant and anti-inflammatory activities by stabilizing reactive intermediates or scavenging free radicals.

3.3 SAR Trends Across Biological Activities: Benzothiazole derivatives exhibit a wide spectrum of biological activities, with their efficacy highly dependent on structural modifications. In anticancer applications, 2-arylbenzothiazoles bearing halogen or nitro groups at the C-5 position demonstrate enhanced cytotoxicity through mechanisms such as topoisomerase inhibition and tubulin disruption (Popli et al., 2021; Irfan et al., 2020). For antimicrobial activity, the presence of electron-withdrawing groups improves bacterial cell wall penetration and sulfonamide-linked benzothiazoles are especially effective (Yadav et al., 2023). In antidiabetic research, benzothiazole derivatives substituted with imidazole or thiazolidinone moieties at the C-2 position exhibit promising inhibitory activity against α-glucosidase and PPAR-γ, positioning them as potential agents for managing type 2 diabetes (Keri et al., 2015). Additionally, methoxy and carboxylic acid substitutions enhance COX-2 interaction, resulting in improved anti-inflammatory activity, while SAR data indicates that C-5 methyl and methoxy groups also contribute significantly to analgesic potential (Sharma et al., 2013).

4. Pharmacological Activities:

4.1 Anticancer Activity: Benzothiazole derivatives have gained considerable attention in cancer research due to their ability to interact with vital molecular targets involved in tumor progression, such as Topoisomerase I/II, microtubules and caspases, thereby affecting DNA replication, cell division and apoptosis. Among them, 2-arylbenzothiazole scaffolds, especially those substituted with electron-withdrawing groups (–NO_2, –Cl, –CF_3) at the C-5 or C-6 positions, exhibit significant cytotoxicity against cancer cell lines like MCF-7 (breast), HCT-116 (colon) and A549 (lung). These derivatives exert anticancer effects through multiple mechanisms including caspase-mediated apoptosis, disruption of microtubule polymerization, and Topoisomerase inhibition. Recent analogues have also been designed to target the NEDD8-activating enzyme (NAE) or to intercalate into DNA, enhancing their therapeutic relevance. The planarity, aromaticity and heteroatom content of the benzothiazole core promote π–π stacking and hydrogen bonding, increasing selectivity and affinity for biomolecular targets[11].

4.2 Antimicrobial Activity: Microorganisms are the causative agents of numerous diseases, including pneumonia, amoebiasis, typhoid, malaria, tuberculosis and influenza, contributing significantly to the global disease burden. The alarming rise in antibiotic resistance underscores the urgent need for new and effective antimicrobial agents. In recent years, benzothiazole derivatives have gained attention for their potential to inhibit microbial growth through various mechanisms. For example, Gupta et al. synthesized a series of pyrimido[2,1-b]benzothiazole derivatives via a conjugate addition of the imino nitrogen from 2-aminobenzothiazoles to the β-carbon of acetylenic acid, followed by cyclization. These compounds demonstrated notable antimicrobial activity, highlighting the potential of benzothiazole scaffolds as promising leads for antimicrobial drug development[12].

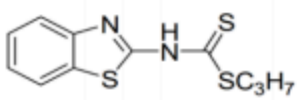

Fig 1.6

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4.3 Antiviral Activity: Benzothiazole derivatives have recently emerged as promising candidates for antiviral therapy, particularly targeting viral proteases essential for replication. Structural modifications of the benzothiazole scaffold have enabled effective binding to key viral enzymes such as the main protease (M_{pro}) of SARS-CoV-2 and proteases of H5N1 influenza and HSV-1. For instance, Hu et al. (2022)[13] designed benzothiazole-based inhibitors that exhibit strong binding affinity and selective inhibition of the SARS-CoV-2 $3CL_{pro}$ enzyme, validated through docking studies. In another recent study, benzothiazolyl–pyridine hybrid compounds were synthesized and screened for antiviral activity against SARS-CoV-2 and H_5N_1, showing significant protease inhibition and favorable interaction profiles (Kaur et al., 2023)[14]. These compounds also demonstrated synergistic potential when combined with known antivirals, supporting their utility in combating drug resistance. The presence of the benzothiazole ring enhances lipophilicity and π–π stacking, which are critical for interacting with viral protein pockets, making these derivatives potent candidates in modern antiviral drug discovery.

4.4 Anti-inflammatory and Antioxidant Properties: Benzothiazole derivatives exhibit notable anti-inflammatory and antioxidant activities, making them promising agents for managing chronic inflammatory conditions. Substituents like –OH, $–OCH_3$ and $–NH_2$ enhance free radical scavenging, while groups such as methoxy and carboxylic acid improve COX-2 inhibition, reducing prostaglandin-mediated inflammation. These structural features contribute to their efficacy in disorders like arthritis and neuroinflammation[15].

4.5 Antitubercular Activity: Benzothiazole derivatives have shown promising activity against Mycobacterium tuberculosis, including drug-resistant strains. Modifications at the C-2 and C-6 positions with groups like nitro, hydrazone or oxadiazole enhance their efficacy. Some compounds demonstrate activity comparable to isoniazid and rifampicin, likely by disrupting cell wall synthesis or inhibiting key enzymes. Their lipophilic nature supports better penetration into mycobacterial cells, making them potential leads for new anti-TB drugs[16].

4.6 Neuroprotective and Antidepressant Effects: Benzothiazole derivatives have shown potential neuroprotective and antidepressant effects, primarily through acetylcholinesterase (AChE) inhibition, a key therapeutic target in Alzheimer's disease and other central nervous system (CNS) disorders. Structural modifications with electron-donating groups (e.g., –OH, $–OCH_3$) enhance binding affinity to AChE, improving memory and cognitive function. Some derivatives also modulate monoamine levels, contributing to antidepressant-like activity. Their ability to cross the blood-brain barrier and interact with neurological targets makes them promising candidates for treating neurodegenerative conditions[17].

5. Marketed Drugs and Clinical Candidates: Several benzothiazole-containing compounds have progressed to clinical development, with a few reaching the pharmaceutical market. One notable example is Zopolrestat (fig 1.7), an aldose reductase inhibitor developed for managing diabetic complications, which demonstrates the therapeutic value of the benzothiazole scaffold. Additionally, compounds such as Phortress, a 2-(4′-aminophenyl)benzothiazole derivative, have entered clinical trials for anticancer therapy due to their DNA-binding and metabolic activation mechanisms. The benzothiazole nucleus, with its high target selectivity, lipophilicity and bioavailability, continues to serve as a privileged structure in modern drug discovery. Ongoing clinical investigations highlight its potential across therapeutic areas including oncology, neurodegeneration and infectious diseases, making benzothiazoles pharmaceutically relevant scaffolds for future drug development[18].

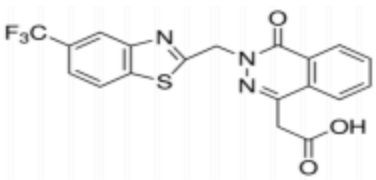

Fig 1.7 Structure of Zopolrestat

6. Challenges and Future Prospects: Despite the wide-ranging pharmacological potential of benzothiazole (BTA) derivatives, their clinical translation is often limited by challenges such as poor

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bioavailability, off-target toxicity and limited selectivity toward specific biological targets. These issues necessitate further structural optimization and exploration of structure–activity relationships (SAR). One promising direction involves the design of hybrid molecules, where the BTA scaffold is linked to other bioactive pharmacophores to improve target specificity and multifunctional activity. Additionally, advancements in artificial intelligence (AI) and machine learning (ML) are revolutionizing drug discovery, enabling predictive modeling of biological activity, toxicity profiling and virtual screening of large compound libraries. These technologies can accelerate the identification of potent, safe and selective BTA-based drug candidates, thus enhancing the success rate in preclinical and clinical development. The future of BTA research lies in integrating computational tools with rational drug design to overcome current limitations and harness their full therapeutic potential.

7. Conclusion: Benzothiazole derivatives have established themselves as valuable scaffolds in modern drug discovery due to their broad pharmacological spectrum, encompassing anticancer, antimicrobial, antiviral, antidiabetic, anti-inflammatory, antioxidant and neuroprotective activities. Their unique fused aromatic structure, incorporating sulfur and nitrogen atoms, facilitates strong interactions with biological targets through π–π stacking, hydrogen bonding and hydrophobic effects. Structure–activity relationship studies have shown that substitutions at positions C-2, C-5 and C-6 significantly influence biological activity, offering avenues for designing selective and potent drug candidates. Despite challenges related to bioavailability, toxicity and metabolic stability, advancements in synthetic strategies (including green and catalyst-based methods), hybrid molecule development and the integration of computational tools like QSAR, molecular docking and machine learning are accelerating the discovery of more effective benzothiazole-based therapeutics. As research progresses, benzothiazole is poised to remain a privileged core in rational drug design, supporting the development of safer, more targeted and multifunctional agents for treating complex diseases.

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