Recent Advances in the Synthesis and Biological Activities of Benzothiazole Compounds: A Comprehensive Review

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Abstract: Benzothiazole derivatives have emerged as an important class of heterocyclic compounds in medicinal and pharmaceutical chemistry due to their wide range of biological properties and structural versatility. In recent years, significant progress has been made in developing efficient synthetic strategies that enhance yield, selectivity, and functional diversity of benzothiazole-based compounds. This comprehensive review highlights the latest advancements in synthetic methodologies for benzothiazole compounds. The review further discusses the biological activities exhibited by these compounds.

Keywords: Benzothiazole derivatives; Synthesis strategies; Heterocyclic compounds; Biological activities; Antimicrobial activity.

Introduction: -

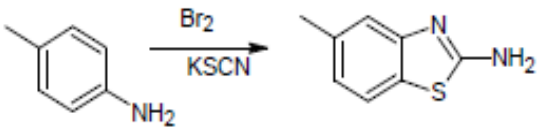
Medicinal chemistry has transformed into a highly interdisciplinary domain that amalgamates principles of organic chemistry, biochemistry, pharmacology, and molecular biology to formulate and enhance therapeutic molecules with superior safety and efficacy. The study of heterocyclic compounds is fundamental to contemporary medical chemistry, since their structural diversity, chemical reactivity, and biological significance render them essential in drug discovery and development. A heterocyclic compound is defined as any organic molecule that possesses a cyclic structure or an aromatic ring in conjunction with heteroatoms, like nitrogen, oxygen, or sulfur. Heteroatoms significantly affect electrical distribution, three-dimensional shape, and intermolecular interactions, rendering heterocycles highly versatile in their binding to biological targets. The possible heterocyclic systems are almost infinite, with about half of the million molecules cataloged in the Chemical Abstracts database including at least one heterocyclic ring. Their ring sizes vary from basic five-membered structures to intricate fused systems such as quinolines, illustrating the enormous range of chemical possibilities. Heterocyclic compounds are ubiquitous in nature and

essential to all life forms. Crucial biomolecules—such as hemoglobin and bile pigments, folic acid and biotin, along with amino acids like proline, histidine, and tryptophan—possess heterocyclic structures that govern essential metabolic functions. Hormones like serotonin and histamine, along with nucleic acid bases (pyrimidines and purines) that constitute the backbone of DNA and RNA, also originate from heterocyclic systems. A variety of phytoconstituents, including chlorophyll, carbohydrates, and vitamins such as B_1, B_2, B_3, B_6, B_{12}, E, and C, contain heterocycles that incorporate oxygen, nitrogen, or sulfur. These naturally occurring systems highlight the essential biological importance and evolutionary favor for heterocyclic frameworks.

Benzothiazoles have become significant scaffolds in medicinal chemistry among the extensive variety of heterocycles. The benzothiazole ring structure, comprising a fused benzene and thiazole moiety, has distinctive chemical diversity and considerable biological promise owing to the inclusion of nitrogen and sulfur heteroatoms. Compounds with the benzothiazole nucleus are well documented for their broad pharmacological spectrum, encompassing antibacterial, anti-inflammatory, anticancer, antitubercular, antidiabetic, antiviral, antileishmanial, antioxidant, and CNS-active effects. Structural alterations to the benzothiazole ring provide the precise adjustment of electronic properties, lipophilicity, and receptor-binding attributes, rendering it an optimal framework for producing derivatives with improved therapeutic effectiveness. Benzothiazole derivatives demonstrate significant potential in addressing medication resistance and enhancing specificity towards molecular targets, which is crucial given the rise of microbial threats and chronic inflammatory conditions. The synthesis of new bioactive benzothiazole derivatives remains a focal point of extensive research, especially for antibacterial and anti-inflammatory purposes. Therefore, the present review focuses on the recent advancements in the synthesis strategies and biological activity of benzothiazole derivatives.

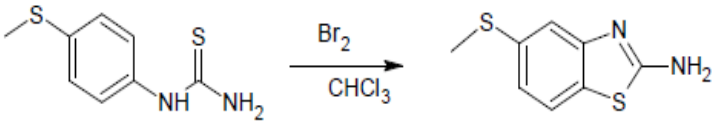
Review on the Synthesis of Benzothiazole Derivatives: -

Hugerschoff (1901) reported that substituted anilines could undergo cyclization with liquid bromine in chloroform, resulting in the formation of 2-aminobenzothiazoles.

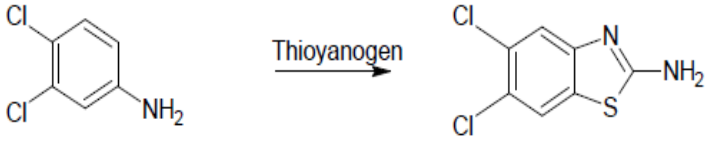


Johanson and Hamilton (1949) synthesized 2-amino-6-substituted-mercaptobenzothiazole

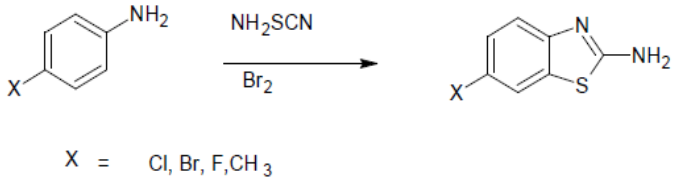
using bromine as a catalytic agent.



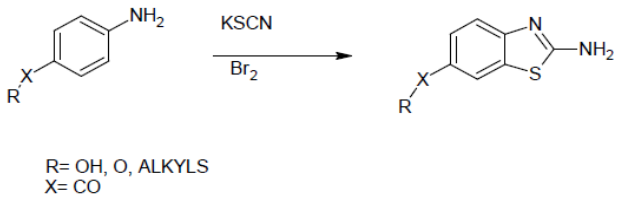
Alaimo (1971) successfully prepared 2-amino-5,6-dichloro- and 2-amino-6,7-dichlorobenzothiazole.



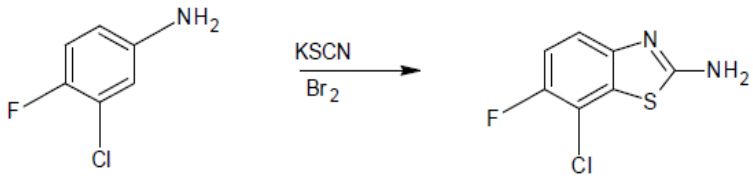
Lin and Kasina (1981) reported the synthesis of 6-substituted 2-aminobenzothiazoles using *p-substituted anilines* as starting materials.



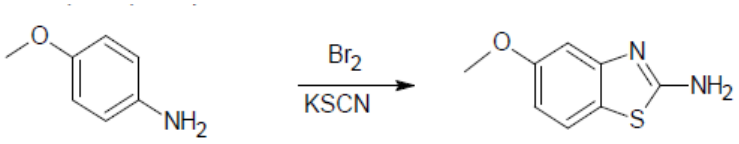
Naim et al. (1991) obtained a series of benzothiazoles through the oxidative cyclization of thioureas with bromine.



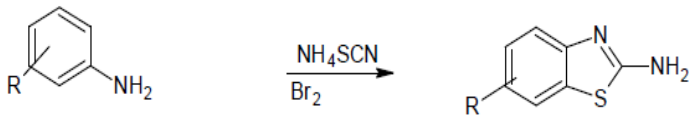
Dogruer et al. (1998) synthesized 2-amino-6-fluoro-7-chlorobenzothiazole.



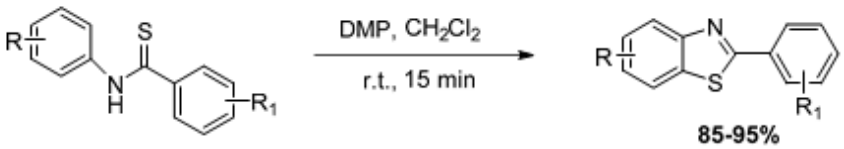
Several recent studies have also demonstrated the utility of bromine as a catalyst. Stuckwisch (2002) synthesized 2-amino-6-substituted benzothiazoles using Br_2 and potassium thiocyanate.



Patel and Agravat (2006) synthesized a diverse array of 2-(5 or 6)-substituted aminobenzothiazoles.

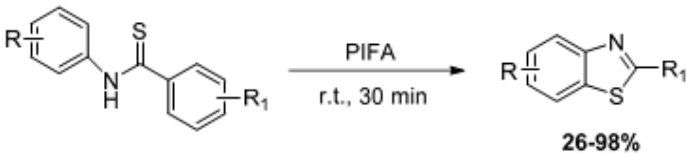


Bose et al. (2006) reported the formation of benzothiazoles in the presence of DMP and dichloromethane at room temperature. This solid-phase method allows combinatorial synthesis of heterocycles and operates via a thiyl-radical mechanism, yielding oxybis-benzothiazole in high efficiency. The mild conditions, short reaction time, operational simplicity, and environmental compatibility make this strategy particularly attractive.



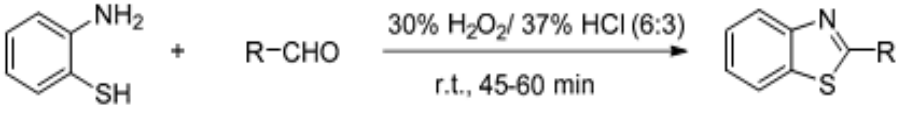
85-95%

Downer et al. (2008) demonstrated that, under mild conditions, aryl radical cations serve as intermediates during the intramolecular cyclization of thiobenzamides to form benzothiazoles.



26-98%

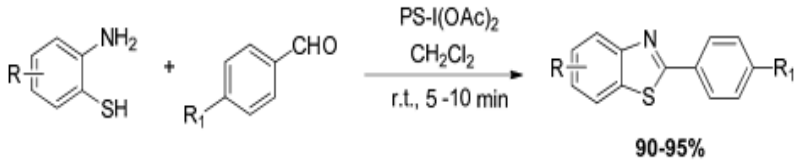
Guo et al. (2009) synthesized a variety of benzothiazole derivatives using H_2O_2 and HCl as catalysts in ethanol at room temperature (1 h). The optimal substrate ratio was 1:1:6:3 for 2-aminothiophenol, aromatic aldehyde, hydrogen peroxide, and hydrochloric acid, respectively. Its advantages include short reaction time, high yields, and easy product isolation.



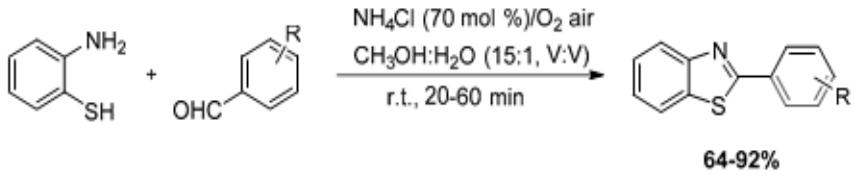
85-94%

Kumar et al. (2009) reported that condensation of 2-aminobenzenethiol to form benzothiazole derivatives is facilitated by polystyrene-supported iodine acetate catalysts. The catalyst is easily prepared and allows combinatorial synthesis of heterocycles without loss of diversity during the synthetic sequence. After use, the catalyst can be regenerated via conversion to polymer-supported iodobenzene and subsequently back to poly(4-diacetoxyiodo)styrene

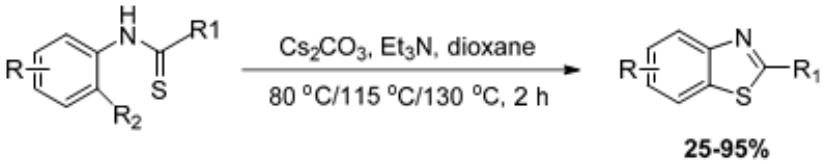
(PDAIS) without loss of catalytic efficiency.



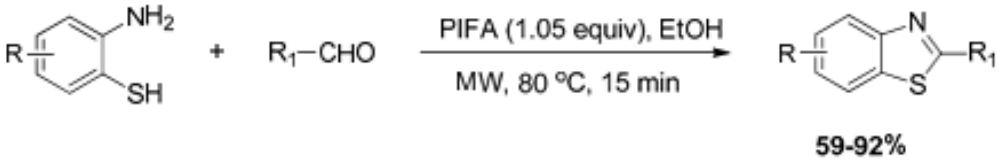
Maleki et al. (2010) discovered that NH_4Cl efficiently catalyzes the reaction between 2-aminothiophenol and benzaldehyde, producing benzothiazoles in high yields in a methanol–water mixture at room temperature within 1 hour. This environmentally friendly method offers short reaction times, good yields, and a recyclable catalyst, making it consistent with green chemistry principles.



Feng et al. (2010) prepared a new series of 2-substituted benzothiazoles under the reaction conditions shown in the accompanying figure. A broad range of functional groups was tolerated, and excellent yields were obtained. This method is advantageous due to the absence of transition metals, mild reaction conditions, extensive functional group compatibility, and short reaction times.

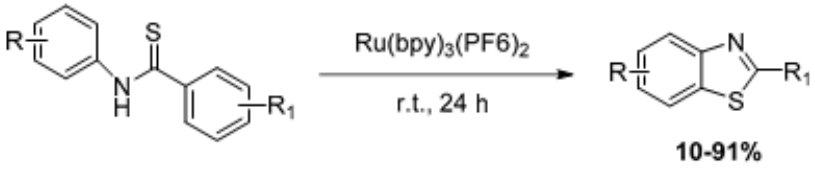


Praveen et al. (2012) demonstrated that microwave-assisted conditions can significantly enhance the synthesis of benzothiazoles. Compared to conventional thermal heating, microwave irradiation accelerates reaction rates, improves product yields, and broadens substrate compatibility, making it an efficient alternative for benzothiazole construction.

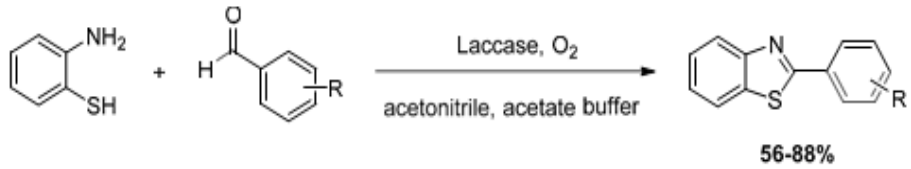


Cheng et al. (2012) established an aerobic visible-light photoredox method for the synthesis of 2-substituted benzothiazoles. Their investigations into the scope of this novel photocatalytic transformation revealed excellent functional-group tolerance, high selectivity,

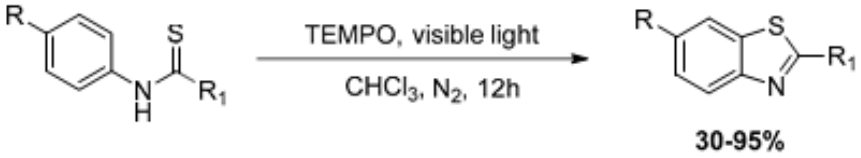
and notable reaction efficiency. The process is particularly appealing due to its mild conditions and minimal environmental impact.



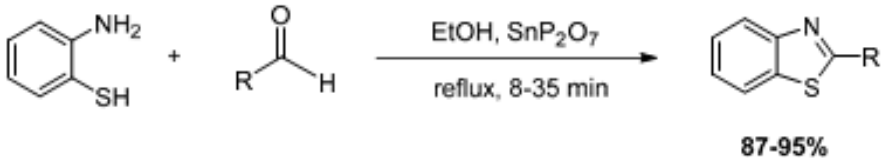
A room-temperature strategy for synthesising 2-arylbenzothiazole derivatives was developed by Maphupha et al. (2018), offering a straightforward and operationally simple approach.



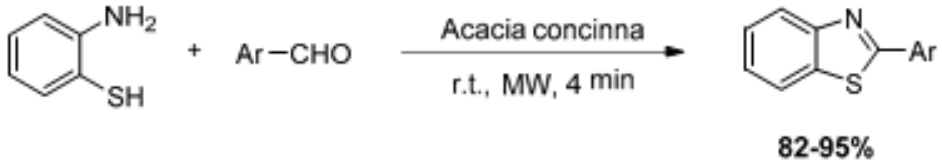
Xu et al. (2018) introduced an innovative photochemical cyclization method for the synthesis of benzothiazoles. Remarkably, this transformation proceeds without the use of photoredox catalysts, transition-metal catalysts, or bases, making it an environmentally benign alternative.



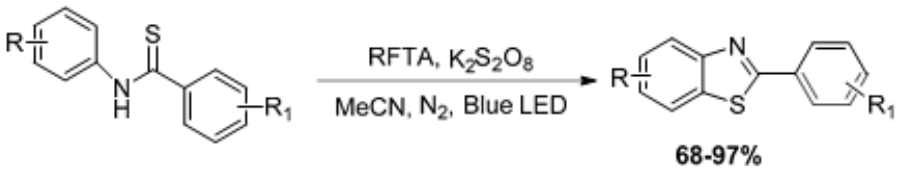
Merroun et al. (2019) developed an efficient and green synthetic method for benzothiazole formation via the condensation of 2-aminothiophenol with various aromatic aldehydes using SnP_2O_7 as a heterogeneous catalyst. The catalyst exhibited excellent reusability, maintaining its activity for at least five cycles. The reactions proceeded rapidly (8–35 min) with high yields ranging from 87–95%.



Bhat et al. (2019) explored a rapid microwave-assisted synthesis of 2-aryl-benzothia(oxa)zoles through condensation reactions. Microwave irradiation resulted in significantly shorter reaction times and improved yields compared to traditional heating methods. The solvent-free nature of the procedure further enhances its environmental compatibility.

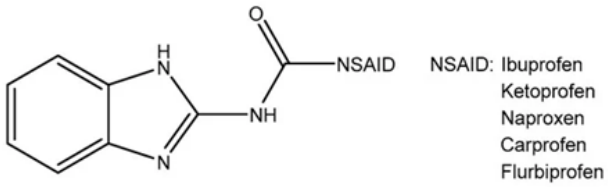


Bouchet et al. (2019) reported that riboflavin can function as an efficient photosensitizer in the synthesis of benzothiazoles. As an inexpensive, naturally occurring reagent, riboflavin proved to be a superior photocatalyst compared to many transition-metal systems. This method not only afforded the desired products efficiently but also tolerated a wide range of functional groups, providing an environmentally friendly strategy potentially valuable to the pharmaceutical industry.



Gao et al. (2020) summarized recent advances in green synthetic approaches for benzothiazole derivatives. Their review highlighted emerging trends, future prospects, and the growing emphasis on environmentally responsible benzothiazole synthesis.

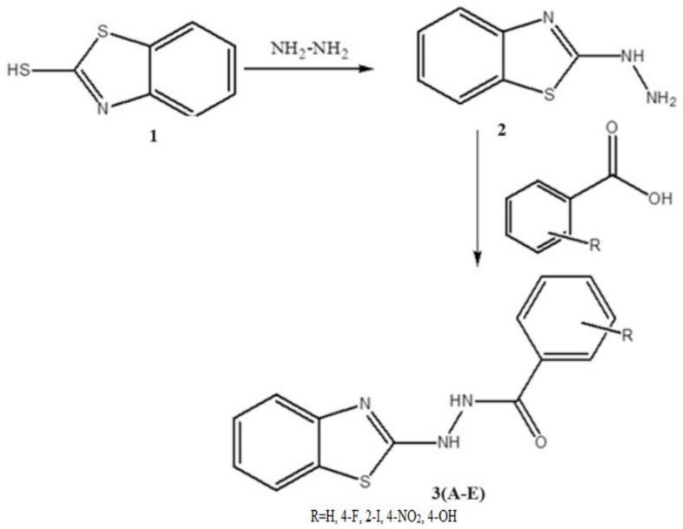
Ivanov et al. (2024) reported the synthesis of a new series of compounds obtained by coupling 2-aminobenzothiazole with various profen derivatives. Their in-vitro biological evaluation revealed notable anti-inflammatory and antioxidant activities, comparable to established standard drugs. Collectively, the findings indicate that these newly synthesized hybrids possess promising biological properties and exhibit strong affinities toward HSA. Among them, the hybrid formed between 2-aminobenzothiazole and ketoprofen (compound 3b) demonstrated exceptional potential.



Mohamed-Ezzat and Elgemeie (2025) reviewed the synthetic strategies employed for developing novel, therapeutically targeted benzothiazole derivatives. Their discussion highlights the emergence of various benzothiazole-based structures as potent bioactive agents, underscoring their relevance in advancing therapeutic research. The review compiles contemporary synthetic approaches for anti-neurodegenerative, anti-inflammatory, antitumor, antimicrobial, and antiviral benzothiazoles, alongside summaries of the biological evaluations

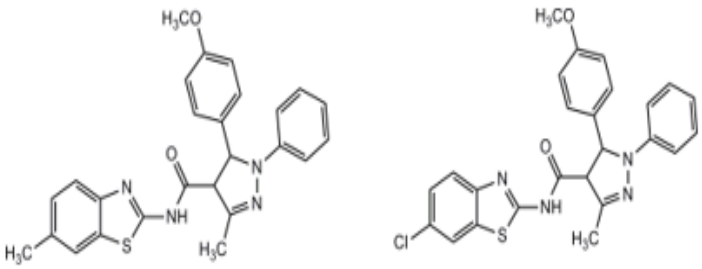
of these newly developed compounds. Structural modifications and hybridization with complementary pharmacophores have further enhanced the pharmacological efficacy and selectivity of benzothiazole derivatives. Numerous approved and investigational benzothiazole-based drugs, as well as newly synthesized molecules, have demonstrated promising preclinical and, in some cases, clinical outcomes. However, to successfully translate these heterocyclic molecules into effective therapeutic agents, continued research is necessary to deepen understanding of their structure–activity relationships (SAR), molecular mechanisms, and *in vivo* performance. Integration of computational methodologies, advanced drug-delivery systems, and environmentally friendly (green) synthetic techniques is expected to further accelerate the development of safer and more efficacious benzothiazole-based pharmaceuticals.

Bora *et al.* (2025) synthesized a series of benzothiazole-containing benzohydrazide derivatives to investigate how structural modifications influence the pharmacological profile, therapeutic efficacy, and toxicity reduction associated with benzothiazole-based drug candidates.

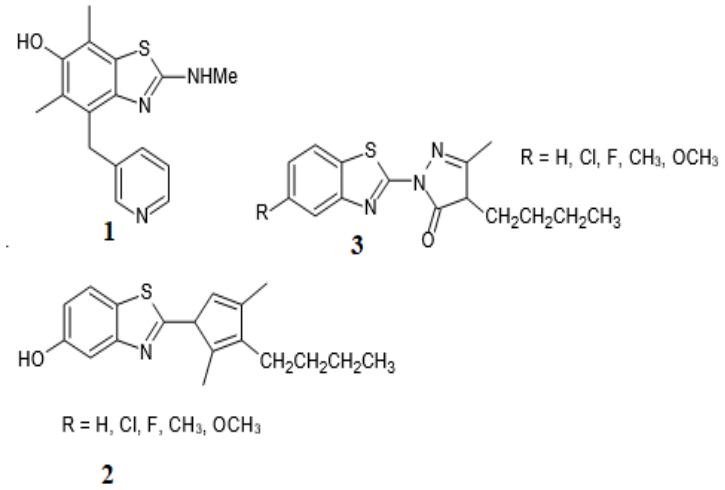


Review on the Biological Activity of Benzothiazole Derivatives: -

In 2001, Gopkumar *et al.* reported the synthesis of several benzothiazolyl derivatives, which were subsequently evaluated for their antimicrobial properties. Their findings indicated that derivatives bearing chlorine and *p*-methoxyphenyl substituents exhibited excellent antimicrobial activity, while those containing methyl and *p*-methoxyphenyl groups also demonstrated comparatively high activity.

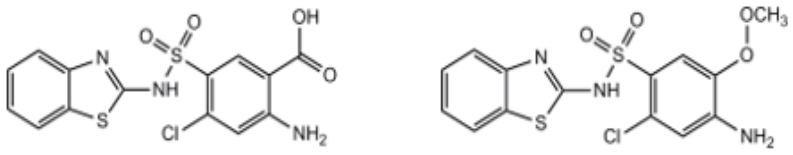


Oketani *et al.* (2001) investigated the in-vitro pharmacological profiles, including anti-inflammatory activity, of newly synthesized benzothiazole derivatives. Their study revealed that certain benzothiazole–pyridazinone derivatives displayed low to moderate anti-inflammatory effects, whereas the pyrazole-substituted benzothiazole compounds exhibited marked anti-inflammatory potency.

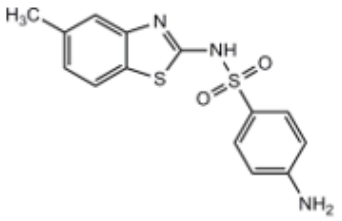
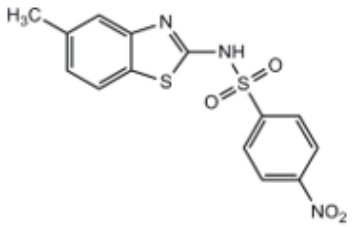


1 3 2

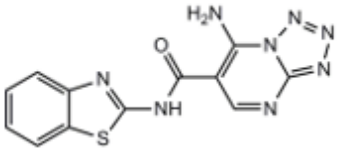
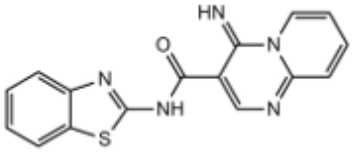
Bhusari *et al.* (2008) synthesised benzothiazole derivatives intended for antibacterial and antitubercular applications. Compounds containing chloro and carboxyl substituents showed notable antibacterial activity against *B. subtilis* and *E. coli*. Antifungal activity was also observed for derivatives incorporating chloro and methoxy groups. Regarding antitubercular action, derivatives possessing chloro or bromo substituents were more effective than those containing nitro groups.



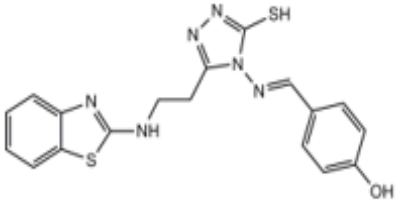
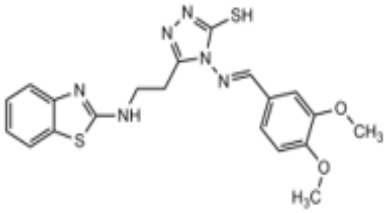
Argyropoulou *et al.* (2009) synthesised a series of benzothiazole derivatives and reported significant antimicrobial activity, with MIC values ranging from 0.3 to 100 μg/mL. Among the tested organisms, *B. subtilis* exhibited the highest sensitivity. Notably, derivatives containing nitro substituents were identified as the most active compounds within the series.

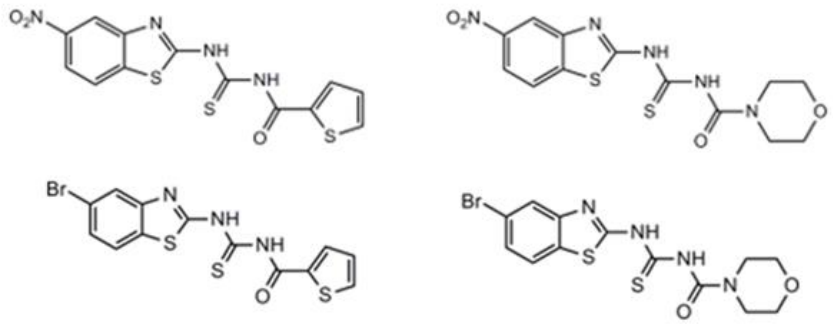
In another contribution, Bondock *et al.* (2009) synthesized benzothiazole-containing derivatives and evaluated their antibacterial and antifungal activity. Incorporation of the benzothiazole moiety into pyrimidine derivatives via acid–amine coupling enhanced biological activity. Several pyrazole-conjugated benzothiazoles also demonstrated remarkable antimicrobial effects when compared to standard reference drugs.

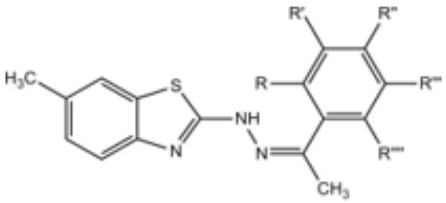
Soni *et al.* (2010) synthesised Schiff bases of triazole-conjugated benzothiazoles and screened them against various bacterial strains. Derivatives containing 4-hydroxy, 4-dimethylamino, and 3,4-dimethoxy substituents showed the highest antibacterial activity. In contrast, substitution with nitro or chloro groups at the para position decreased activity, indicating that strong electron-withdrawing groups reduce antibacterial efficacy.

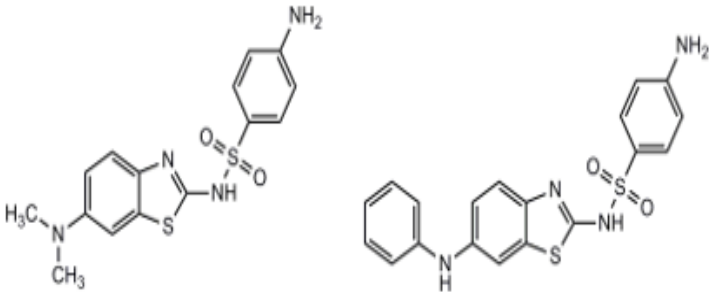
Saeed *et al.* (2010) synthesised a range of benzothiazole derivatives and evaluated them for antibacterial and anticancer properties. The biological response varied depending on the nature of substituents, with some derivatives demonstrating stronger antifungal than antibacterial activity. Benzothiazoles bearing a nitro group at the C-5 position displayed MIC values of 10 μg/mL against both bacterial and fungal strains. SAR analysis confirmed that electron-withdrawing substituents enhanced antimicrobial potency. Cytotoxicity assays (MTT-based) further showed notable anticancer effects, particularly against MCF-7 and HeLa cell lines.



Studies by Alang *et al.* (2010) indicated that derivatives containing halogen substituents at the ortho-position exhibited superior antifungal activity compared to those with para-methoxy substituents.

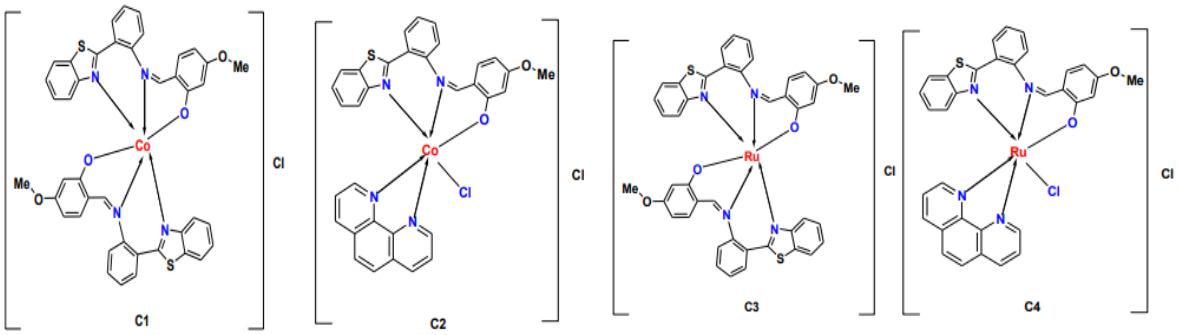


Lagishetty et al. (2013) developed sulfonamido-benzothiazole derivatives and screened them against a range of bacterial and fungal organisms. Most of the compounds demonstrated promising bioactivity.



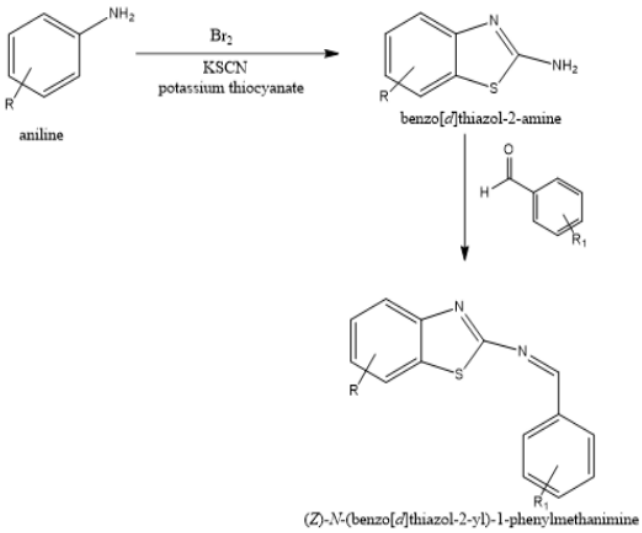
Ibrahim et al. (2022) reported the synthesis of BMM and its corresponding metal complexes, which were thoroughly characterized using spectroscopic, thermogravimetric, X-ray diffraction (XRD), and elemental analysis techniques. Multiple experimental observations confirmed the coordination number and overall geometry of the complexes. The Co(III) and Ru(III) complexes were suggested to adopt an octahedral configuration. Furthermore, the results indicated that complexes C_2 and C_4 exhibited significantly higher nuclease activity and moderate DNA-binding intercalation ability compared to complexes C_1 and C_3. Viscosity measurements, electronic absorption spectra, and fluorescence-quenching studies collectively verified DNA interaction and intercalative binding modes. The cytotoxic properties of complexes C_1–C_4 were also assessed in vitro against several human cancer cell lines,

followed by detailed evaluation of complexes C_2 and C_4. Their toxicity and safety profiles were further studied in vivo in mice. Antimicrobial screening using the well-diffusion method revealed that, relative to the free ligand, all complexes displayed only weak antimicrobial activity.



Kashyap *et al.* (2023) reviewed the synthesis, SAR, and mechanisms of action of benzothiazole derivatives reported between 2018 and 2022 for antibacterial applications. The review also summarized recent patents concerning the antimicrobial potential of benzothiazole-based molecules. Their findings provide valuable guidance for the development of novel antibacterial agents utilizing the benzothiazole scaffold. Similarly, Yadav *et al.* (2023) presented a comprehensive overview of the synthesis and biological activities of benzothiazole derivatives, offering an important resource for researchers in synthetic chemistry and drug discovery, and encouraging further exploration toward enhancing the pharmacological performance of benzothiazole-based compounds.

Mahajan *et al.* (2024) synthesized and structurally characterized a series of benzothiazole derivatives using various spectroscopic techniques. Molecular docking studies were conducted to predict binding affinities toward key microbial enzymes, offering insights into the probable mechanisms of action. Biological evaluation included antifungal and antibacterial assays against selected strains. Compounds A_1, A_2, A_4, A_6, and A_9 showed significant antifungal activity against *A. niger* and *C. albicans* (NCIM 3102), with Amphotericin-B as the standard. Additionally, compounds A_1, A_2, and A_9 demonstrated promising antibacterial activity against *E. coli* (ATCC 25922) and *S. aureus* (ATCC 29737), compared with ciprofloxacin. These findings indicate that specific structural variations in the benzothiazole core enhance antimicrobial potency, suggesting their promise as therapeutic leads. Further optimization and in vivo validation are recommended to fully explore their clinical potential.



Conclusion: Benzothiazole derivatives continue to attract considerable attention due to their broad spectrum of biological activities and their potential applications in modern drug discovery. This review highlights the substantial progress achieved in recent years through the development of innovative and sustainable synthetic methodologies. These strategies have not only improved efficiency, selectivity, and scalability but also expanded the structural diversity of benzothiazole compounds, enabling the exploration of new derivatives with enhanced therapeutic relevance. The reviewed studies demonstrate that benzothiazole scaffolds exhibit significant pharmacological properties. Despite the promising outcomes, challenges remain in terms of toxicity, selectivity, and clinical translation. Future research should focus on integrating computational drug design, high-throughput synthesis, and mechanistic biological studies to accelerate the development of clinically viable benzothiazole-based therapeutics. Overall, the advancements summarized in this review reaffirm benzothiazole derivatives as a valuable chemical framework with significant potential to contribute to the next generation of therapeutic agents.

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