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RECENT ADVANCES IN THE BIOLOGICAL ACTIVITIES OF BENZOTHIAZOLE DERIVATIVES: A REVIEW OF ANTI-MICROBIAL AND ANTI-DIABETIC ACTIVITIES

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Abstract: The present paper provides a comprehensive overview of the therapeutic potential of benzothiazole-based compounds, with particular emphasis on their antimicrobial and antidiabetic activities. Various studies have demonstrated that structural modifications in the benzothiazole nucleus significantly influence their biological performance. The presence of different substituents and functional groups plays a key role in enhancing activity against a variety of microbial pathogens as well as in regulating glucose metabolism.

Keywords: Benzothiazole derivatives; Biological activity; Antimicrobial activity; Antidiabetic activity.

Introduction: -

Heterocyclic compounds represent one of the largest and most structurally diverse groups of organic molecules. These compounds may exist in both cyclic and acyclic forms. When a ring system contains only carbon atoms, it is described as carbocyclic; however, when one or more atoms other than carbon are incorporated into the ring, the system is classified as heterocyclic. Although various heteroatoms can be present, nitrogen, oxygen, and sulfur are the most commonly encountered in heterocyclic structures. Over time, the number of known heterocyclic compounds has expanded enormously, reflecting their vast chemical diversity and functional significance. Among heterocyclic compounds, nitrogen- and sulfur-containing systems such as triazoles, thiazoles, oxadiazoles, pyrimidines, and isoxazoles are particularly noteworthy because of their significant biological activities. The increasing recognition of their pharmacological relevance has stimulated extensive research into the synthesis of new therapeutic agents incorporating these moieties. Piperazine, for example, is often referred to as a "privileged" structure due to its strong affinity for multiple biological receptors. The prevalence of heterocyclic ring systems in biologically active molecules highlights their indispensable role in medicinal chemistry.

Within this extensive family of heterocycles, benzothiazole occupies a prominent position. Benzothiazole is a fused bicyclic heterocyclic compound formed by the fusion of a benzene ring with a thiazole ring. The thiazole component contains both sulfur and nitrogen atoms within a five-membered aromatic ring, contributing to the compound's chemical reactivity and biological potential. Benzothiazole itself is described as a white, slightly viscous liquid with a boiling point of approximately 227–228°C. It has a molecular weight of 135.19 g/mol and a density of 1.24 g/mL (Verma et al., 2022; Gill et al., 2015; Agarwal et al., 2017; Afaque et al., 2026; Kaur et al., 2024). The unique fused-ring structure of benzothiazole provides a versatile platform for structural modification, enabling the development of derivatives with diverse pharmacological properties. In view of this, the aim of the present review is to systematically compile and analyze the recent advancements in the biological activities of benzothiazole derivatives, with particular emphasis on their antimicrobial and antidiabetic potential.

A Review of Antimicrobial Activity of Benzothiazole Derivatives: -

Early investigations into benzothiazole derivatives highlighted their promising antimicrobial potential. Gopkumar et al. (2001) synthesized a series of benzothiazolyl derivatives and evaluated their antimicrobial properties. Biological screening revealed that derivatives bearing chlorine and *p*-methoxy phenyl substituents exhibited particularly strong activity. Compounds containing methyl and

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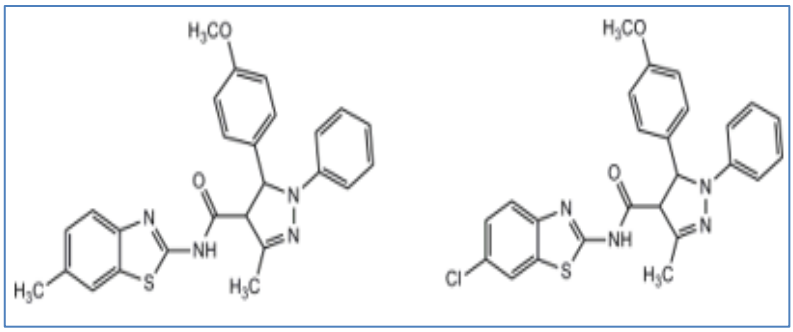
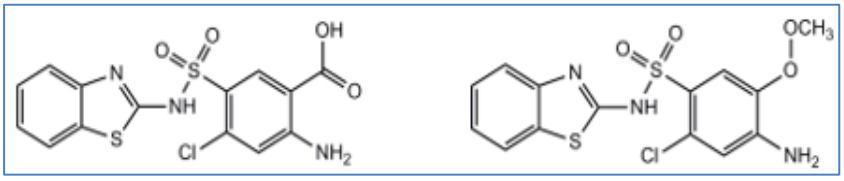
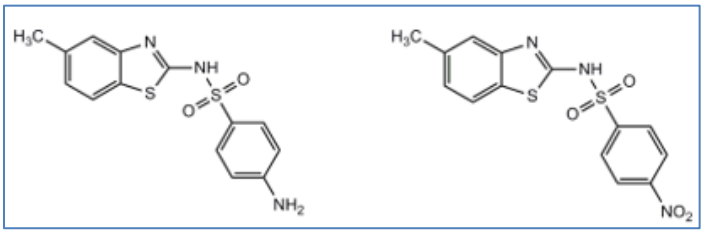
p-methoxy phenyl groups also demonstrated notable antimicrobial performance. These findings indicated that specific substituents on the aromatic ring significantly influence biological activity, laying the groundwork for future structure–activity relationship (SAR) studies.



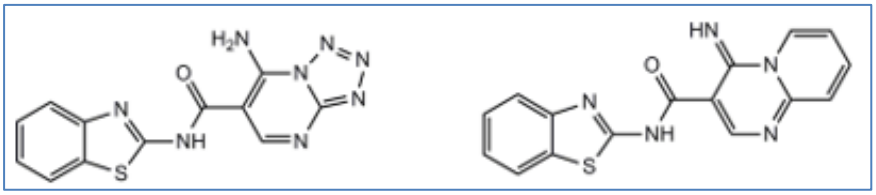
Building upon this foundation, Bhusari et al. (2008) synthesized benzothiazole derivatives intended for use as antibacterial and antitubercular agents. The study demonstrated that compounds featuring chloro and carboxyl substitutions showed effective antibacterial activity against *Bacillus subtilis* and *Escherichia coli*. In addition, chloro- and methoxy-substituted derivatives exhibited antifungal activity. Regarding antitubercular potential, derivatives containing chloro or bromo substituents proved more effective than those with nitro groups. These results underscored the role of halogen substitution in enhancing antimicrobial and antitubercular efficacy.



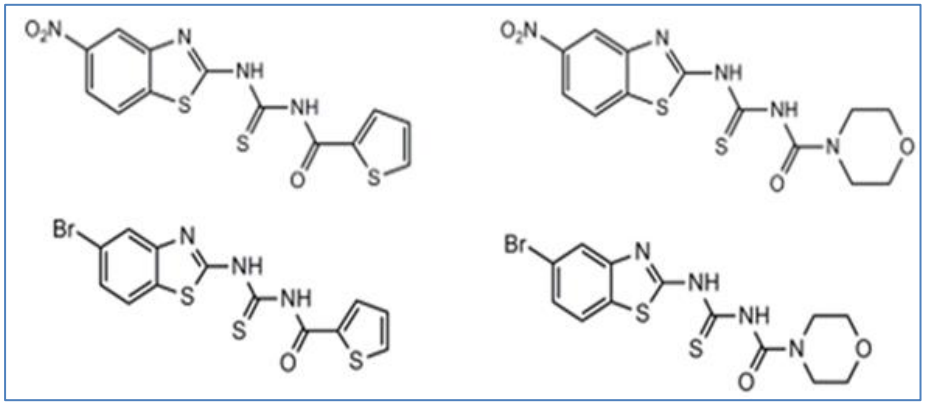
Similarly, Argyropoulou et al. (2009) synthesized benzothiazole derivatives and assessed their antimicrobial activity, particularly against Gram-positive bacteria. The compounds displayed significant potency, with MIC ranging from 0.3 to 100 µg/mL. Among the tested organisms, *Bacillus subtilis* was found to be the most sensitive. Nitro-substituted derivatives emerged as the most active compounds within the series, further emphasizing the importance of electron-withdrawing groups in improving antimicrobial performance.



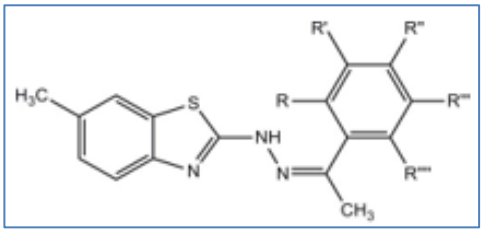
Bondock et al. (2009) prepared benzothiazole-containing derivatives and evaluated their antibacterial and antifungal properties in vitro. The incorporation of a benzothiazole moiety into pyrimidine derivatives through acid–amine coupling was found to enhance biological activity. Additionally, several pyrazole-conjugated benzothiazole compounds exhibited remarkable antimicrobial effects when compared to standard reference drugs. This study demonstrated that hybridization of benzothiazole with other pharmacophores can lead to synergistic improvements in activity.



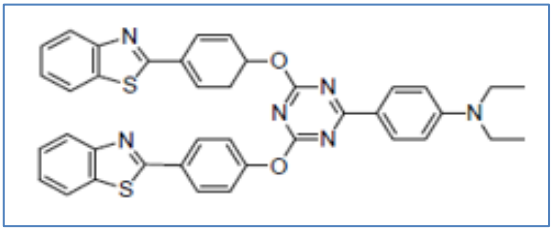
In another study, Saeed et al. (2010) synthesized benzothiazole derivatives and evaluated both their antibacterial and anticancer activities. The compounds demonstrated varying degrees of activity against different microorganisms, with some derivatives showing greater efficacy against fungi than bacteria. Notably, a nitro-substituted benzothiazole derivative at the fifth position exhibited MIC values of 10 µg/mL against both bacterial and fungal strains. The presence of electron-withdrawing substituents appeared to enhance biological activity, consistent with earlier SAR findings comparing substituted and unsubstituted analogues. Furthermore, MTT-based cytotoxicity assays revealed significant anticancer activity against MCF-7 and HeLa cell lines, indicating dual antimicrobial and anticancer potential.



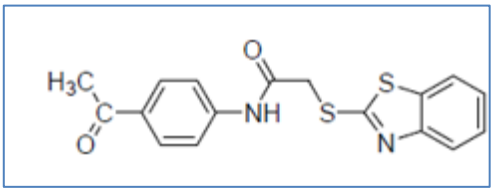
Alang et al. (2010) examined the antifungal properties of halogen- and methoxy-substituted benzothiazole derivatives. Their results showed that compounds containing halogen substituents at the ortho position were more effective antifungal agents than those with methoxy groups at the para position. This finding again emphasized the influence of substitution pattern and electronic effects on biological performance.



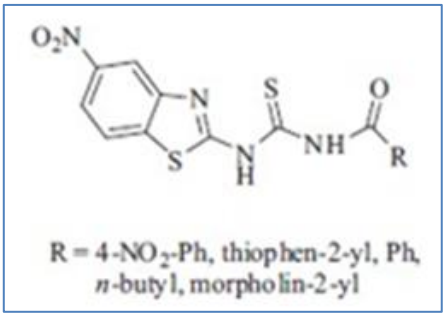
Padalkar et al. (2011) investigated the structural, photophysical, and antimicrobial properties of newly synthesized dipodal benzimidazole, benzothiazole, and benzoxazole derivatives. The majority of these novel compounds displayed good antimicrobial activity, demonstrating that structural diversification within heterocyclic frameworks can yield biologically active molecules.



Maru et al. (2014) developed new benzothiazole derivatives and reported strong antimicrobial activity, supported by low MIC values against various bacterial and fungal strains. These findings further established benzothiazole derivatives as promising antimicrobial agents.



In the ongoing search for new antibiotics, researchers have extensively explored heterocyclic compounds, including benzothiazole derivatives, against diverse microbial strains. Numerous structural modifications of the benzothiazole nucleus have been undertaken to enhance antimicrobial potency. Hybrid molecules combining multiple pharmacophores have also been synthesized to achieve synergistic effects. Thiourea-derived benzothiazoles, for example, have demonstrated considerable antimicrobial activity. Gill et al. (2015) reported that many such derivatives exhibited stronger antifungal effects compared to antibacterial activity. Additionally, compounds substituted with a nitro group at the fifth position of the benzothiazole ring displayed both antifungal and antibacterial activities, highlighting the importance of specific substitution patterns.



More recently, Mahajan et al. (2024) synthesized and structurally characterized a new series of benzothiazole derivatives using various spectroscopic techniques. Molecular docking studies were conducted to predict binding affinities toward key microbial enzymes, providing insight into possible mechanisms of action. Biological screening revealed that compounds A_1, A_2, A_4, A_6, and A_9 exhibited significant antifungal activity against *A. niger* and *C. albicans*, using Amphotericin-B as the reference standard. Additionally, compounds A_1, A_2, and A_9 showed promising antibacterial activity against *E. coli* and *S. aureus*, compared to ciprofloxacin. These results indicated that specific structural modifications within the benzothiazole framework enhance antimicrobial potency. The authors recommended further optimization and in vivo studies to confirm therapeutic applicability.

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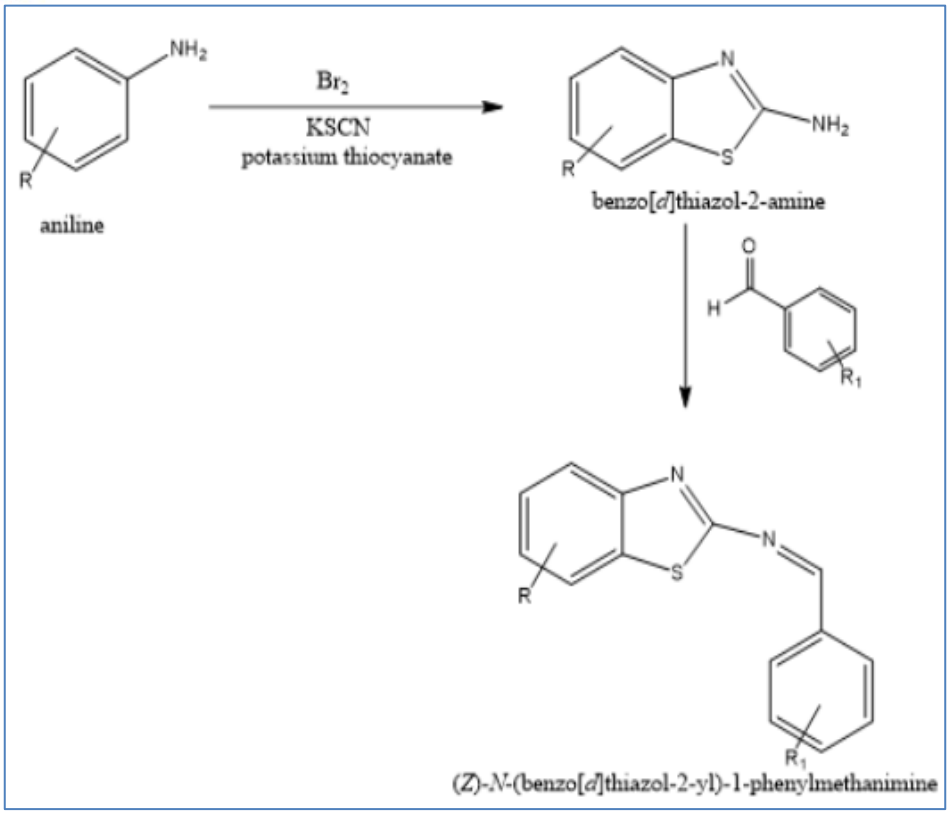
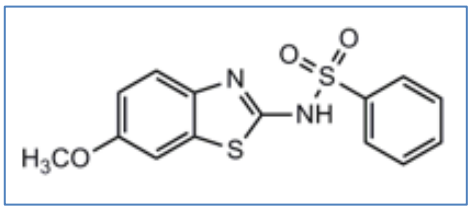
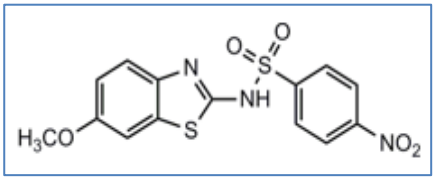


A Review of Antidiabetic Activity of Benzothiazole Derivatives: -

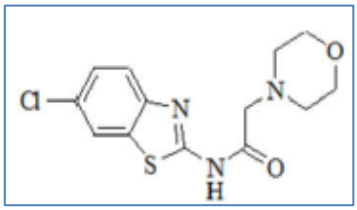
Hermenegilda et al. (2008) synthesized benzothiazole–benzene sulphonamide derivatives and evaluated their antidiabetic potential. The compounds significantly reduced plasma glucose levels in experimental models. Additionally, in vitro studies demonstrated inhibitory activity against 11β-hydroxysteroid dehydrogenase type 1 (11-HSD1), an enzyme implicated in glucose metabolism. Molecular docking analyses further supported the binding affinity of these derivatives to the target enzyme.



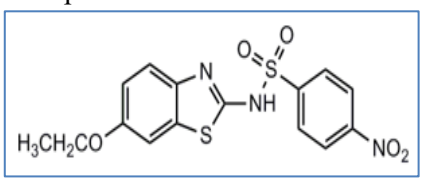
Gabriel et al. (2009) synthesized 2-aryl sulfonyl amino benzothiazoles and assessed their inhibitory activity. The compounds displayed micromolar IC_{50} values, and docking studies indicated the involvement of hydrogen bonding in stabilizing ligand–enzyme interactions. In vivo investigations demonstrated antihyperglycemic effects, with treated subjects exhibiting reduced plasma glucose levels.



Mariappan et al. (2012) synthesized N-(6-chlorobenzo[d]thiazol-2-yl)-2-morpholinoacetamide and reported its promising antidiabetic activity, further supporting the therapeutic relevance of benzothiazole derivatives.



Patil et al. (2013) developed benzothiazole-2-aminophenyl propane derivatives and evaluated them as glycosidase inhibitors. These compounds exhibited inhibitory activity against α-amylase, demonstrating antidiabetic potential. Enhanced activity was observed in derivatives containing a bromo-substituted benzoyl group and electron-donating substituents at the sixth position of the benzothiazole ring, highlighting the importance of substituent effects in enzyme inhibition.



Chandran et al. (2025) explored benzothiazole–coumarin hybrids as multi-targeted antidiabetic agents. Through an extensive literature review, they examined mechanisms of action, including α-glucosidase and DPP-IV inhibition, AMPK-mediated insulin secretion, and antioxidant effects. The analysis indicated that these hybrid derivatives enhance insulin secretion via AMPK activation, inhibit carbohydrate-digesting enzymes, and improve insulin sensitivity. Additionally, their antioxidant and anti-inflammatory properties provide protective effects on pancreatic β-cells. Although the findings highlight their therapeutic promise, the authors emphasized the need for further preclinical and clinical studies to establish long-term safety, efficacy, and pharmacokinetic stability.

Conclusion: Extensive research has demonstrated that the nature and position of substituents on the benzothiazole nucleus play a decisive role in determining biological activity. Halogenated, nitro, methoxy, and hybrid derivatives have shown enhanced antimicrobial efficacy against a wide range of pathogenic microorganisms, while structural modifications and pharmacophore hybridization have further improved their potency. Similarly, in the field of antidiabetic research, benzothiazole-based compounds have exhibited encouraging results through multiple mechanisms, including receptor activation, enzyme inhibition, and metabolic regulation. The integration of computational approaches such as molecular docking and ADMET analysis with experimental studies has accelerated the identification of potential drug candidates with improved efficacy and safety profiles. Despite these advancements, further research is required to optimize these compounds, understand their long-term safety, and validate their clinical applicability through in vivo and clinical studies. Future investigations focusing on rational drug design, hybrid molecule development, and targeted therapy may lead to the discovery of novel benzothiazole-based therapeutics. Overall, benzothiazole derivatives hold substantial promise as future candidates in the development of effective antimicrobial and antidiabetic drugs.

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