

Sustainable Advances In The Synthesis And Antimicrobial Effectiveness Of Benzothiazole And Its Derivatives: A Mini-Review

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ABSTRACT

Benzothiazole derivatives were Nitrogen (N) and Sulfur (S) containing pharmacologically important heterocyclic scaffolds. In recent years they have becoming more prominent as they found to be useful to treat various diseases. In that regard, they have demonstrated different pharmacological activities including anticancer, antibacterial, antibiotic, antiviral, antifungal, anti-inflammatory and anti-diabetic. Hence, synthesis of benzothiazole derivatives becomes a hotspot to researchers, and there are different conventional and non-conventional methods have been accomplished to their synthesis. Present study gives overview of their different reaction methods associated with synthesis and its antimicrobial activities.

Keywords: Benzothiazole derivatives, antimicrobial activities, green approach, Medicinal chemistry.

INTRODUCTION

The heterocyclic organic compounds are having ring structure with at least one heteroatom other than carbon. The most commonly Nitrogen (N), Oxygen (O) and Sulphur (S) they were performs as the functions of heteroatoms [1]. These compounds were effectively highlighted its impact as they are building blocks of various biologically active drug molecules. The benzothiazole is a Nitrogen (N) and Sulphur (S) embedded heterocyclic scaffolds [2]. The presence of these heteroatoms makes them important for pharmaceutical effectiveness such as anticancer agents, antibacterial agents, antibiotic agents, antiviral agents, antifungal agents, anti-inflammatory agents and anti-diabetic agents Fig.1 [3-9].

In these considerations, a few years ago conventional methods were utilized to synthesize different benzothiazole derivatives. These conventional methods have several disadvantages like they are time consuming, requires high operation cost and responsible for environmental concerns [10]. Hence in recent years researchers have been developed

various sustainable approaches to synthesize benzothiazole derivatives. This sustainable approach includes solvent free synthesis, one pot multicomponent synthesis, use of green solvent systems and use of different catalyst systems etc. [11-12].

The humans, animals and plants were suddenly affected with different types of diseases. Different type's microorganisms were responsible for these conditions. These microorganisms may be fungi, bacteria, and viruses. Researchers were introduced various medicines to control, cure the diseases and infections among living things [13]. Antimicrobial agents are compounds that eliminates the microorganisms or inhibits the growth of organisms. The benzothiazole derivatives were exhibits different antimicrobial activities towards various microorganisms [14].

In the present review, we have considered various sustainable methods to synthesize benzothiazole derivatives with their antimicrobial importance.

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

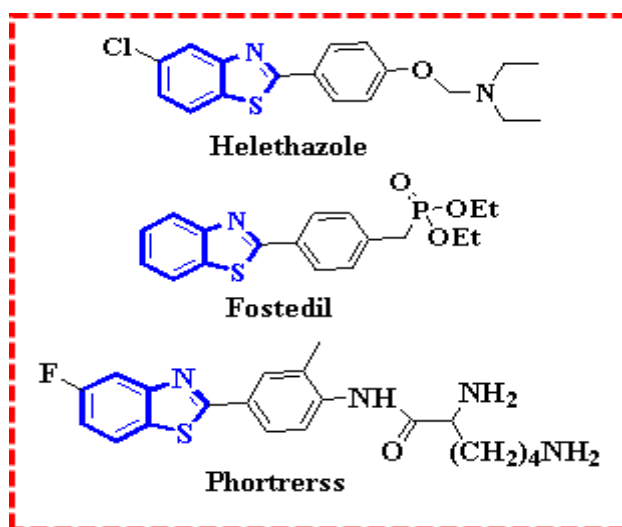
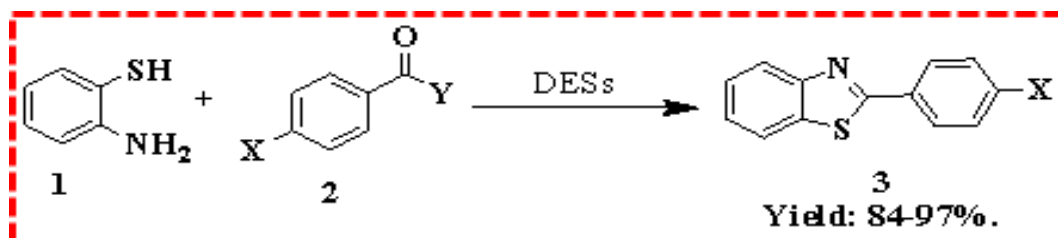


Fig.1 Examples of benzothiazoles based bioactive molecules.

Sustainable approaches for the synthesis of benzothiazole derivatives.

Wagay et al., 2022 and co-workers [15], represented sustainable method to synthesize 2-substituted benzothiazoles (**3**) by using efficient low melting mixture. The reaction involved condensation of 2-aminobenzenethiol or o-phenylenediamine (**1**) and aliphatic aldehyde or aromatic aldehyde (**2**) in the occupancy of low melting mixture (**Scheme 1**). A

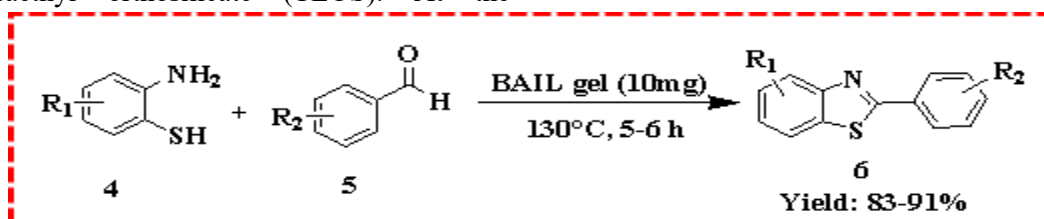
characteristic feature of this protocol is that there is no any use of external catalyst and organic solvents. The method initially optimized with various deep eutectic mixtures and shows best results with N, N-dimethyl urea (DMU) with L-(+)-tartaric acid (TA) and citric acid (CA) with DMU with 7:3 ratio and 4:6 ratio respectively. They were synthesized different benzothiazoles derivatives with the help of optimized conditions product yield were ranged from 84% to 97%.



Scheme 1. Synthesis of 2-substituted benzothiazoles catalysed by DESs.

Nguyen et al., 2019 [16], communicate the use of ionic liquid gel (BAIL gel) as reusable Bronsted acid heterogeneous catalyst to preparation of substituted benzimidazoles (**6**) (**Scheme 2**). In this development, ionic liquid gel was gained with treating 1-methyl-3-(4-sulfobutyl)-1*H*-imidazolium hydrogen sulphate with tetraethyl orthosilicate (TEOS). At the

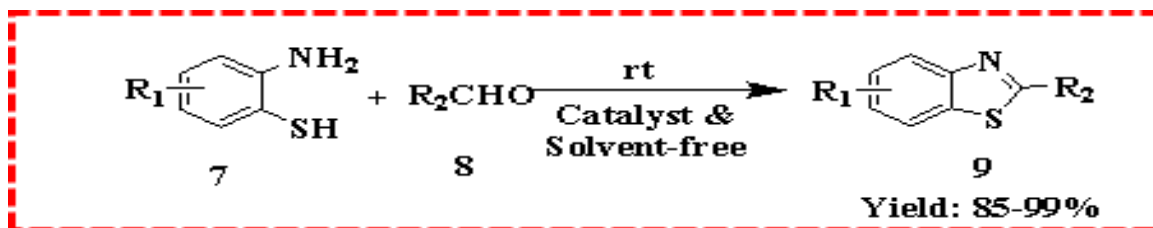
beginning, the catalysed screened with different catalyst, it shows that BAIL gel gives product yield with 98%. To check out scope of ionic liquid variety of substituted aromatic aldehydes were tested under optimized conditions. The results represent that 83% to 91% product yield were obtained.



Scheme 2. Synthesis of benzothiazoles using a BAIL GEL under solvent free conditions.

Vločko et al., 2024 [17], developed efficient green method without using any catalyst and solvents for the synthesis of nitrogen and sulphur containing heterocyclic compounds (benzothiazoles). The catalyst free approach facilitates efficient synthesis of various aryl- substituted benzothiazoles derivatives.

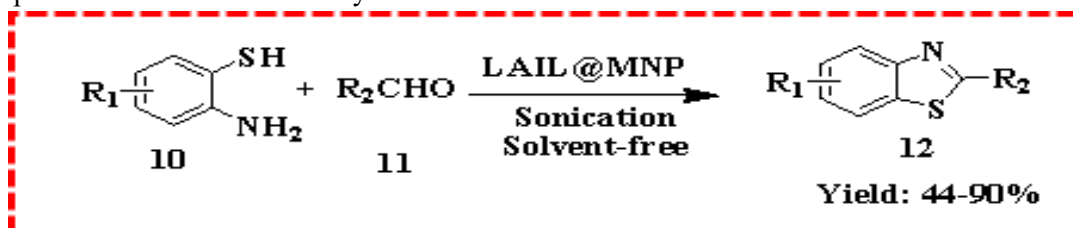
These compounds were synthesized with 2-aminophenols (**7**) and corresponding substituted aromatic aldehydes (**8**), to give excellent yield of up to 85% to 99% (**Scheme 3**). This method has characteristic properties like sustainable, simple workup procedure etc.



Scheme 3. Synthesis of benzothiazoles using 2-aminothiophenols under solvent free and catalyst free conditions.

Nguyen et al., 2021 [18], examined the use of imidazolium chlorozincate (II) ionic liquid supported into Fe₃O₄ nanoparticles (LAIL@MNP) as an efficient catalyst for the synthesis of pharmaceutically active heterocyclic compounds (**Scheme 4**). They developed systematic protocol via condensation of aminophenol and aromatic aldehydes in ultra-

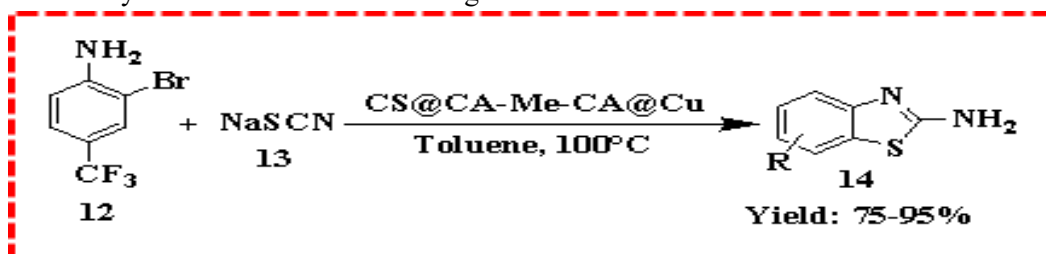
sonication, under solvent-free conditions. In this method, LAIL@MNP provide as an environment friendly, magnetic nanocatalyst that promotes efficient conversion. This work has an important property such as simple, efficient, and easy workup etc.



Scheme 4. The condensation of aminothiophenol with different aldehydes.

Fattahi et al., 2023 [19], reported the synthesis of CS@CA-Me-CA@Cu nanocatalyst by immobilizing Cu(II) nanoparticles and cross-linked chitosan by G1 dendrimer from melamine terminated by citric acid groups. This catalytic method was exhibiting a

condensation process of 2-bromoaniline, sodium thiocyanate and CS@CA-Me-CA@Cu catalyst resulting in the formation of 2-aminobenzothiazole derivatives (**Scheme 5**).



Scheme 5. Synthesis of 2-amino benzothiazoles derivatives in presences of CS@CA-Me-CA@Cu catalyst.

Benzothiazole Derivatives and its Antimicrobial Activities

Benzothiazole analogs were studied for antibacterial activity by Singh et al., 2013 [20], they used two strains of Gram +ve bacteria *Staphylococcus aureus* (ATCC 25323) and clinical isolates of *Enterococcus faecalis*, while five Gram -ve bacterial strains of *Escherichia coli* (ATCC 35218), *Salmonella typhi* (MTCC 3216), *Pseudomonas aeruginosa* (ATCC 27893) and clinical isolates of *Klebsiella pneumoniae* and *Shigella boydii* for study. The result of the study revealed that, benzothiazole compound containing 2,4-dichlorosubstituted benzene ring, shows moderate antibacterial activity, with MIC 50 to 100 mg/ml, comparably weak as showed by standard drug ciprofloxacin with MIC 6.25 mg/ml against all test strains of bacteria except *P. aeruginosa*

Benzothiazole derivative containing 3-chloro, 4-fluoro and 4-chloro substitutes on benzene ring, were reported most potent against *E. faecalis* with MIC 3.12 mg/ml, while against *S. aureus* and *Sal. typhi* MIC reported 6.25 mg/ml. the compound also showed a strong potency MIC 3.12 mg/ml against *P. aeruginosa*, while MIC value of (3b) 25 mg/ml and (3c) 12.5 mg/ml was reported against *E. coli*. An exceptional antibacterial activity of MIC value 3.12 mg/ml against all the six test organisms was reported with a derivative containing 2,4-difluorosubstituted benzene ring, except for *Shigella boydii*.

CONCLUSION

The benzothiazole based derivatives were exhibits antimicrobial efficacy. They were synthesized with simple and productive approaches with applications of different catalyst and reactions conditions. With this review paper deep eutectic mixtures, ionic liquid gel (BAIL gel), of imidazolium chlorozincate (II) ionic liquid supported into Fe₃O₄ (LAIL@MNP), immobilizing Cu(II) nanoparticles and cross-linked chitosan by G1 dendrimer from melamine terminated by citric acid groups CS@CA-Me-CA@Cu were function as catalyst for the synthesis of benzothiazole derivatives under environmentally sound conditions. Now a days greener approach for chemical synthesis is a best choice due to it focuses on reducing waste. Scientists were considered that synthesis of benzothiazoles derivatives using greener approach

over traditional methods is an essential. This review constitutes useful foundation for the researchers practicing in the field of organic synthesis and drug discovery development.

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