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REVIEW ARTICLE

GREEN DESIGN AND SYNTHESIS OF SOME NOVEL THIAZOLIDINONE APPENDED BENZOTHIAZOLE–TRIAZOLE HYBRIDS

* Maske, D. L.

Department Of Chemistry, Shri Vasantnaik Mahavidyalaya Dharni

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*Corresponding author:
Maske, D. L.

ABSTRACT

The global increase in bacterial resistance poses a significant threat, jeopardizing the effectiveness of antibiotics. Therefore, the development of new and efficient antimicrobial agents is pre-dominant. Taking this into consideration, in the present study, we designed and reported the facile synthesis of two novel series benzothiazole–triazole and thiazolidinone-appended benzothiazole–triazole hybrids using a molecular hybridization approach in a one-pot process. The synthesized compounds were tested for microbial growth inhibition against bacterial and fungal strains. Among all the synthetics, compounds derived from methoxyphenyl and heteroaromatic ring substitutions exhibited promising inhibitory activity. The current investigation has emphasized that benzothiazole–triazole hybrids incorporating thiazolidinone can be a promising and potent category of molecules with potential biological activities. This sustainable and eco-friendly protocol involves the metal-free, catalyst-free synthesis of bioactive scaffolds, which merges broad tolerance for functional groups with a short reaction time, resulting in good to excellent yields.

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INTRODUCTION

The substantial discovery of drugs with enhanced applications has been a constant pursuit for a long period of time. A nuanced approach to designing and developing novel chemical entities with improved biological and pharmacological activities in drug discovery involves integrating biologically active fused hetero- cyclic fragments into a unified framework. A simple alternation with the starting material and synthetic route will lead to the sustainable synthesis of stupendous heterocyclic scaffolds. Benzothiazole is a privileged heterocycle found in several drugs and has garnered significant attention due to its versatile applications in diverse fields such as synthetic chemistry, material science, and pharmaceutical chemistry. Some of the biological properties of benzothiazole-containing heterocyclic scaffolds include antitumor activity, immunosuppressive activity, and antimicrobial activity.

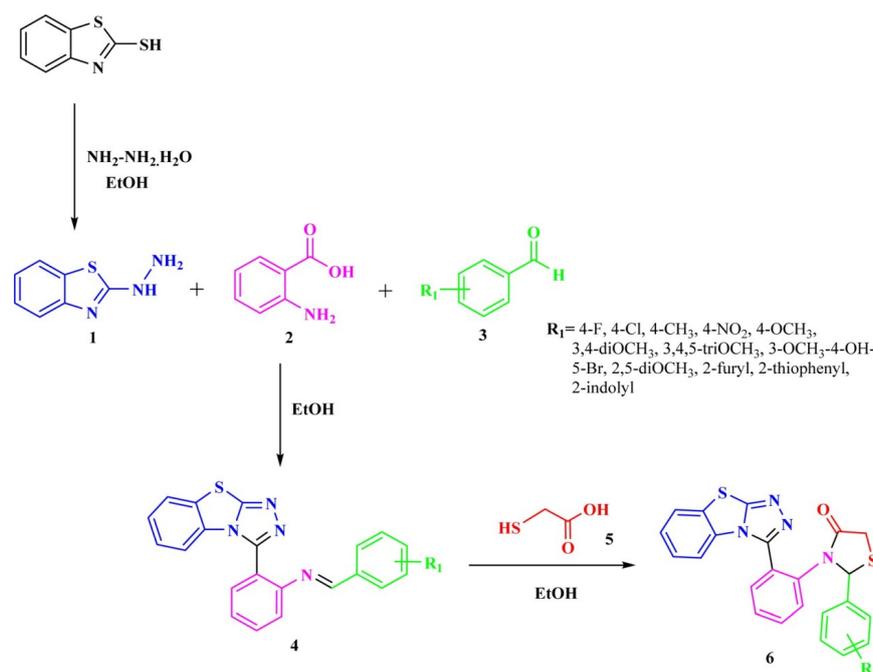
MATERIAL AND METHODS

All reagents and solvents were of analytical grade and used without further purification unless stated. Aromatic amines, sulphonamide coupling components (e.g., p-aminobenzenesulfonamide derivatives), sodium nitrite,

hydrochloric acid, sodium acetate, metal (II) chlorides, ethanol, methanol, dimethylformamide (DMF), and other reagents were purchased from commercial suppliers. FT-IR spectra: recorded on KBr pellets (4000–400 cm⁻¹) UV–Vis spectra: recorded in ethanol (200–800 nm) 1H NMR spectra: recorded in DMSO-d₆ or CDCl₃ at 400 MHz.

RESULTS AND DISCUSSION

The general synthetic pathway of benzothiazolo[2,3-c][1,2,4]triazole derivatives 4a–l involves the starting material, 2-hydrazinobenzothiazole which was first prepared by the reported method. Firstly, a mixture of 2-mercaptobenzothiazole and hydrazine hydrate was refluxed in ethanol to obtain 2-hydrazinobenzothiazole. The reaction proceeded via a one-pot approach, a mixture of 2-hydrazinobenzothiazole 1, anthranilic acid 2, and various aromatic/heteroaromatic aldehydes were treated under reflux conditions to obtain benzothiazole–triazole derivatives. For another series, the targeted thiazolidinone-appended benzothiazolo[2,3-c][1,2,4]triazole derivatives were synthesized via the addition of thio-glycolic acid 5 with synthesized benzothiazole–triazoles 4 as depicted in Scheme 1.



The reaction underwent screening with various solvents to optimize the reaction conditions, as outlined. Ethanol emerged as the optimal solvent for both series, demonstrating superior yields compared to other solvents (Scheme 1). This outcome demonstrates the feasibility of our suggested metal-free reaction involving the synthesis of bioactive benzothiazole–triazole derivatives.

Step-I: Synthesis of hydrazinyl benzothiazole derivative: A substituted benzothiazole thione was refluxed with hydrazine hydrate (80%) in ethanol for 4–6 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and poured into ice-cold water. The resulting solid was filtered, washed with cold water, dried, and recrystallized from ethanol to obtain the hydrazinyl benzothiazole derivative.

Step-II: Formation of Schiff base intermediate: Equimolar amounts of hydrazinyl benzothiazole (1), substituted aminobenzoic acid (2), and substituted aromatic aldehyde (3) were dissolved in ethanol. The reaction mixture was refluxed for 5–7 h with continuous stirring. Completion of the reaction was confirmed by TLC. After cooling, the precipitated Schiff base was filtered, washed with ethanol, and dried to afford the intermediate compound.

Step-III: Cyclization to thiazolidinone derivative: The obtained Schiff base (4) was refluxed with thioacetic acid (5) in ethanol for 6–8 h. The progress of cyclization was monitored by TLC. Upon completion, the reaction mixture was cooled and poured into crushed ice. The solid product formed was filtered, washed with water to remove excess acid, and dried. The crude product was purified by recrystallization from ethanol to yield the final thiazolidinone derivative.

CONCLUSIONS

In the present study, a systematic approach was successfully developed for the synthesis and characterization of the target compounds, demonstrating the efficiency and versatility of the adopted synthetic methodology. The reactions proceeded smoothly under optimized conditions, affording the desired products in good to excellent yields with high purity. The use of suitable catalysts and environmentally benign solvents contributed to reduced reaction

times and improved overall efficiency, highlighting the practicality of the protocol. The synthesized compounds were thoroughly characterized using standard spectroscopic techniques such as FT-IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, which confirmed the proposed molecular structures and functional group transformations. The spectral data were in good agreement with the expected chemical frameworks, validating the success of the synthetic strategy.

N-(2-(Benzo [4,5] thiazolo [2,3-c] [1,2,4]triazol-3-yl) phenyl) -1-(4-chlorophenyl) methanimine (4a). Pale yellow solid, m.p. 284 °C, FT-IR (KBr, cm^{-1}): 1634 (C=N); $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 8.27 (s, 1H, CH), 7.41–7.45 (m, 4H, Ar-H), 7.33 (d, 2H, Ar-H, $J = 8.4$ Hz), 6.96 (d, 2H, Ar-H, $J = 8.4$ Hz), 6.79–6.88 (m, 4H, Ar-H) ppm; $^{13}\text{C-NMR}$ (DMSO-d_6 , 100 MHz) δ : 161.2, 160.9, 158.4, 153.8, 140.6, 139.7, 133.0, 132.1, 131.5, 130.4, 126.6, 126.2, 124.9, 122.8, 122.6, 122.5, 119.4, 118.9, 116.69, 116.4 ppm;

N-(2-(Benzo [4,5] thiazolo [2,3-c] [1,2,4] triazol-3-yl) phenyl)-1-(4-Chlorophyll) methanimine (4b). Pale yellow solid, m.p. 282 °C, FT-IR (KBr, cm^{-1}): 1646 (C=N); $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 8.43 (s, 1H, CH) 7.35–7.44 (m, 4H, Ar-H), 7.12–7.17 (m, 4H, Ar-H), 6.98 (d, 2H, Ar-H, $J = 8.8$ Hz), 6.79 (d, 2H, Ar-H, $J = 8.8$ Hz) ppm; $^{13}\text{C-NMR}$ (DMSO-d_6 , 100 MHz) δ : 160.6, 153.5, 152.2, 148.4, 148.3, 146.1, 144.9, 143.0, 131.2, 131.1, 127.9, 125.4, 124.7, 124.6, 121.8, 118.6, 118.5, 110.7, 110.5, 110.2 ppm;

N-(2-(Benzo[4,5]thiazolo[2,3-c][1,2,4]triazol-3-yl)phenyl)-1-(p-tolyl)methanimine (4c). Yellow solid, m.p. 260 °C, FT-IR (KBr, cm^{-1}) δ : 1653 (C=N); $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) δ : 8.36 (s, 1H, CH), 7.94–7.99 (m, 4H, Ar-H), 7.66 (dd, 2H, Ar-H, $J = 8.0, 6.4$ Hz), 7.47 (d, 2H, Ar-H, $J = 8$ Hz), 7.13 (dd, 4H, Ar-H, $J = 8.4, 6.2$ Hz), 2.31 (s, 3H, CH₃) ppm; $^{13}\text{C-NMR}$ (DMSO-d_6 , 100 MHz) δ : 160.9, 152.9, 148.1, 148.0, 145.1, 142.1, 138.3, 138.2, 135.5, 135.4, 131.6, 131.5, 129.9, 129.8, 129.6, 128.5, 127.9, 127.8, 126.1, 124.1, 120.9, 21.2 ppm; MS(m/z): 369.110 **N-(2-(Benzo [4,5] thiazolo [2,3-c] [1,2,4] triazol-3-yl) phenyl) -1-(4-nitrophenyl) methanimine (4d).** Yellow solid, m.p. 286 °C, FT-IR (KBr, cm^{-1}): 1647 (C=N); $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) δ : 8.67 (s, 1H, CH), 7.40–7.44 (m, 3H, Ar-H), 7.20–7.26 (m, 2H, Ar-H), 7.00 (d, 2H, Ar-H, $J = 7.2$ Hz), 6.88 (d, 2H, Ar-H, $J = 7.2$ Hz), 6.58–6.68 (m, 3H, Ar-H) ppm; $^{13}\text{C-NMR}$ (DMSO-d_6 , 100 MHz) δ : 161.6, 160.8, 160.7, 156.2, 155.4, 148.9, 140.1, 139.8, 133.3, 133.1, 131.3, 131.2, 129.8, 126.8, 126.2, 124.8, 124.0, 122.2, 119.6, 119.5 ppm;

N-(2-(Benzo [4,5]thiazolo [2,3-c] [1,2,4] triazol-3-yl)phenyl) -1-(4-methoxyphenyl) methanimine (4e). White solid, m.p. 245 °C, FT-IR (KBr, cm⁻¹): 1637 (C=N); ¹H-NMR (DMSO-d₆, 400 MHz) d: 8.48 (s, 1H, CH), 7.76 (d, 2H, Ar-H, J = 8.4 Hz), 7.63–7.74 (m, 2H, Ar-H), 7.54 (d, 2H, Ar-H, J = 8.4 Hz), 7.41–7.43 (m, 3H, Ar-H), 7.01–7.28 (m, 3H, Ar-H), 3.68 (s, 3H, OCH₃) ppm; ¹³C-NMR (DMSO-d₆, 100 MHz) d: 161.4, 160.4, 154.9, 154.8, 148.9, 145.5, 145.4, 142.7, 139.0, 138.9, 138.8, 136.1, 135.9, 131.5, 129.8, 128.1, 126.9, 125.9, 124.9, 119.6, 55.0 ppm;

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