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Green design and synthesis of some novel thiazolidinone appended benzothiazole–triazole hybrids as antimicrobial agents†

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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 heterocyclic fragments into a unified framework.[1] 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.[2–4] Some of the biological properties of benzothiazole-containing heterocyclic scaffolds include antitumor activity,[5] immunosuppressive activity,[6] and antimicrobial activity.[7] They have also been explored as scintillating fluorescent compounds,[8] luminescent Ir(III) complexes containing benzothiazole-based ligands with application in organic light-emitting diodes,[9] and Pd(II) pincer complexes as anticancer agents.[10] Among the class of benzothiazole derivatives, benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazole scaffolds stand out as the most potent member known to exhibit a broad range of biological activities, as shown in Fig. 1, such as anti-inflammatory activity,[11] promising antimicrobial agents,[12] commercially available fungicides,[13,14] and act as specific kinase inhibitors & receptors,[15] and show anticancer activities.[16] Moreover, recently it was reported to be a nicotinamide mimicking chemotype that can inhibit different PARP family enzymes.[17] In contrast, thiazolidinone has been proven to be an excellent core moiety for the development of various synthetic drugs because of its structural and synthetic diversity and broad spectrum of biological activities.[18,19] Various 4-thiazolidinone derivatives have been proposed as anticancer biotargets, such as phosphatase of a regenerating liver (PRL-3),[20] tumor necrosis factor TNFα,[21] non-nucleoside inhibitors of HIV-RT,[22] COX-2 inhibitors,[23] SARS-COV-2 protease inhibitors[24] and ALR2 inhibitors.[25] However, the potent nature of thiazolidinone has been noted for its versatile behavior when combined with other bioactive scaffolds, showcasing a wide range of biological properties.[26–28] More specifically, the condensation of the 4-thiazolidinone ring with a benzothiazole nucleus led to compounds that showed promising biological activities.[29]

Due to their intriguing biological properties and potential as pharmaceutical agents, thiazolidinone-based benzothiazole derivatives have garnered significant interest from the synthetic community. Consequently, various researchers have meticulously documented the progress of this scaffold through chemical modifications.[30–32] Recently, Geronikaki *et al.* reported the potential pharmacological exploitation of thiazole/benzothiazole-based thiazolidinone derivatives as promising drug candidates.[24] Khan *et al.* conducted a stepwise synthesis of

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† Electronic supplementary information (ESI) available: Characterization data of all the synthesized compounds. See DOI: https://doi.org/10.1039/d4ra00990h

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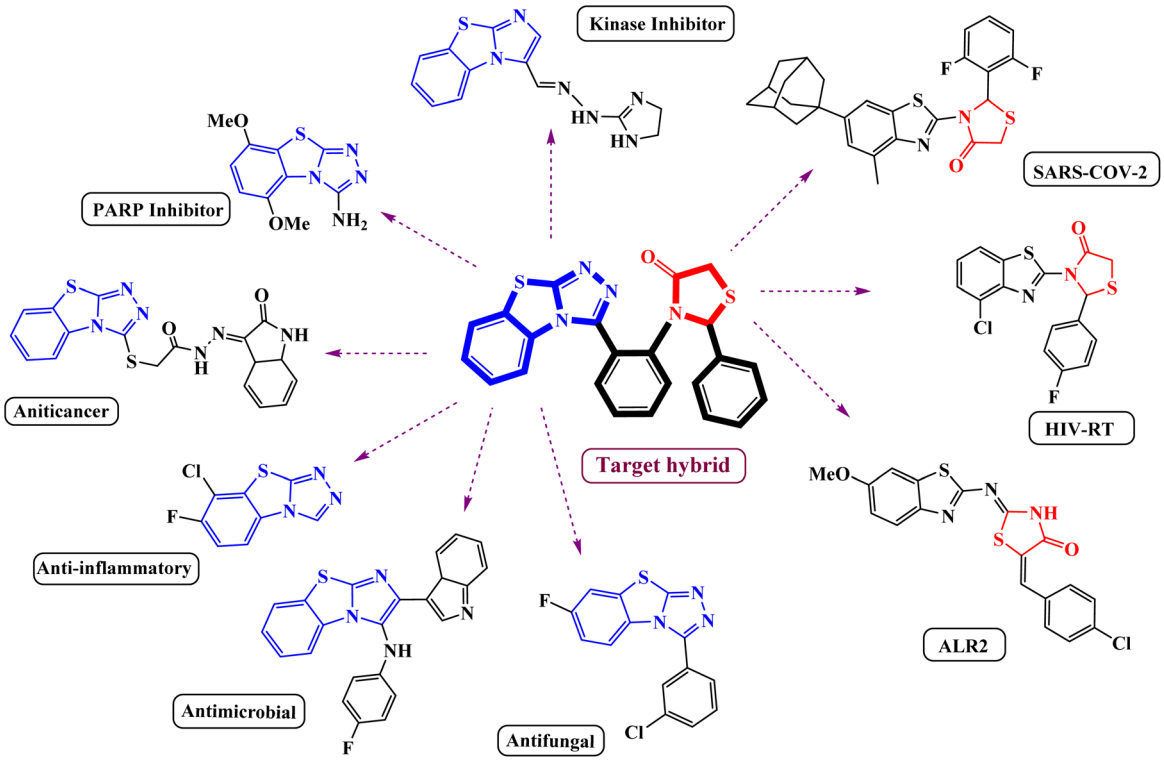

Fig. 1 Synthetic drugs bearing pharmacophore sub-units.

thiazolidinone-based benzothiazole derivatives and demonstrated their inhibitory activity.[33] The previously studied approaches to access these pharmacophores involve a common strategy employing conventional methods with synthetic precursors and catalysts. Despite the simplicity of this type of sequential synthesis, it remains challenging for chemists to

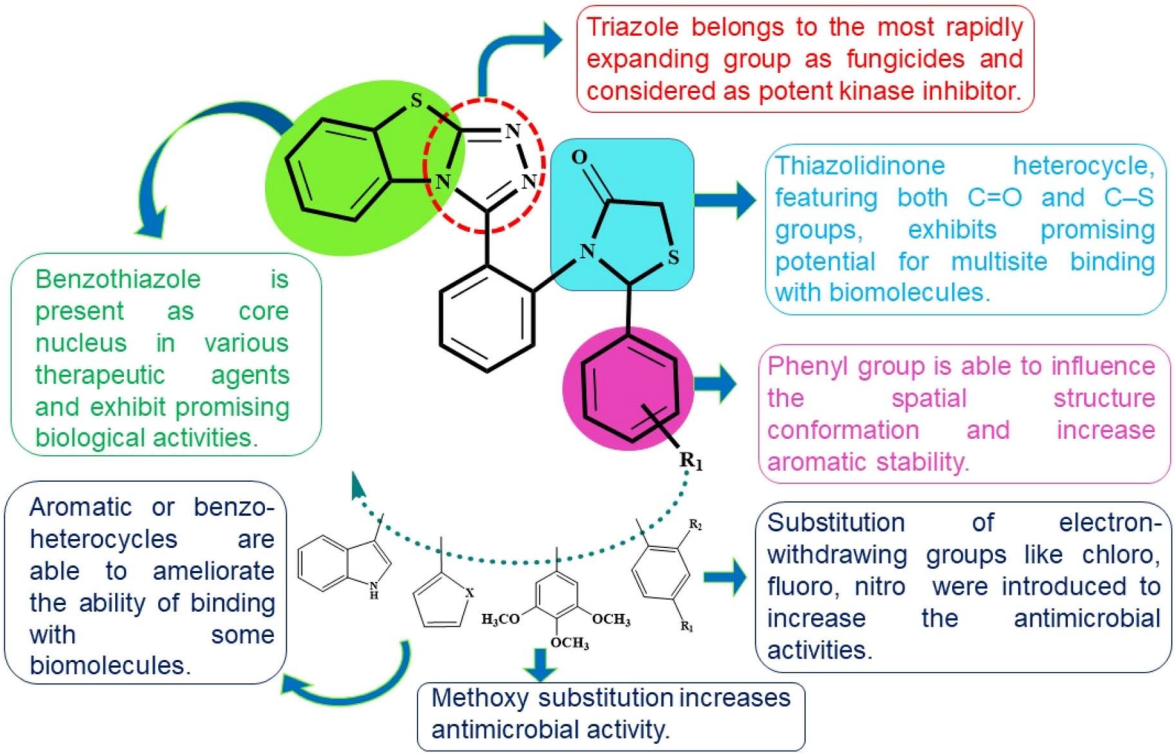

Fig. 2 Design SAR of the target compound.

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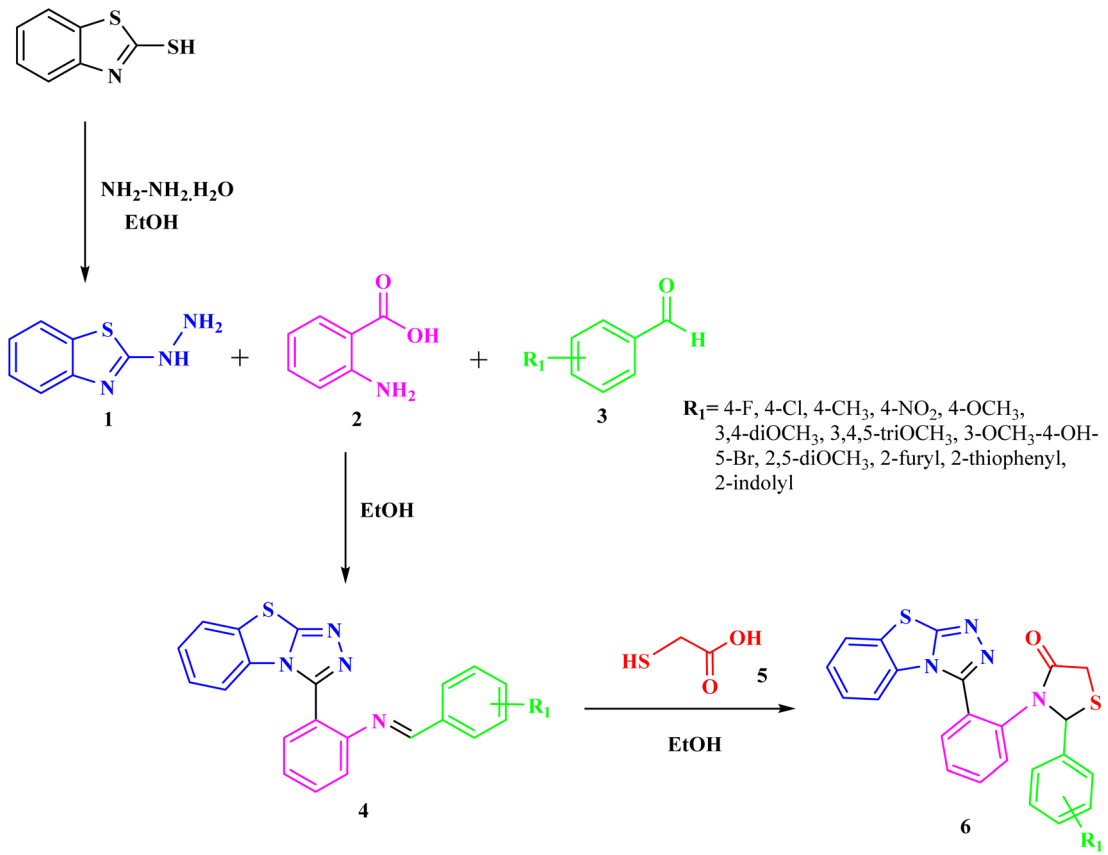
construct molecular hybrids from such a convergent route. As part of our green synthetic strategy toward the synthesis of these potent hybrids, we envisioned that our metal-free approach to designing such a hybrid framework could provide a platform to synthesize a series of compounds with catalyst-free direct functionalizations on readily available starting precursors. Furthermore, such a modular strategy would be amenable to the preparation of analogs of this important scaffold.

Therefore, in light of the above three pharmacophores (benzothiazole, triazole, and thiazolidinones) have been amalgamated within a single novel hybrid using a molecular hybridization approach. With the recent advances in molecular hybridization (MH) strategies, new hybrid structures that exhibit higher biological activity, improved efficiency, and a safer toxicity profile when compared to the parent compounds could be developed by combining the active moieties of various compounds.[34,35]

The correlation between chemical structure and biological activity is employed to aim that the synergistic effect of these pharmacophores could lead to derive drugs that are both more potent and more specific. In this context, structure–activity relationships (SAR) have been employed to gain a comprehensive understanding of the mechanisms of multi-target mode of action of drugs[36] (Fig. 2). Herein, as a part of our endeavour to create a novel bioactive heterocyclic hybrids[37–40] we report the synthesis of benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazole derivatives and thiazolidinone-appended benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazole derivatives by employing cost-effective starting materials in a one-pot process and further evaluated them for their antimicrobial activities.

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.[41] 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 **3a–l** were treated under reflux conditions to obtain benzothiazole–thiazole derivatives. For another series, the targeted thiazolidinone-appended benzothiazolo[2,3-*c*][1,2,4]triazole derivatives **6a–h** were synthesized *via* the addition of thioglycolic 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 in Table 1. Ethanol emerged as the optimal solvent for both series, demonstrating superior yields compared to other solvents (Scheme 1 and Table 1). This outcome demonstrates the feasibility of our suggested metal-free reaction involving the synthesis of bioactive benzothiazole–triazole derivatives.



Scheme 1 Synthesis of benzothiazole–triazole **4** and thiazolidinone-appended benzothiazole–triazole hybrids **6**.

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Table 1 Optimization of the reaction conditions of Scheme 1 for the synthesis of compounds **4a** and **6a**

Entry	Solvent	Reaction temp (°C)	Time (hrs)	Yield[a] (%)
1	Dioxane	60	5	Traces
2	ACN	70	5	46
3	THF	70	5	42
4	DMF	70	5	52
5	MeOH	80	4	65
6	**EtOH**	**80**	**2**	**87**

[a] Isolated yields.

The mechanistic pathway for the formation of target hybrids **4** and **6** is depicted in Scheme 2. First of all, 2-mercaptobenzothiazole A was reacted with hydrazine hydrate in ethanol to give compound 2-hydrazinobenzothiazole **1**. The hydrazine derivative compound was then refluxed with anthranilic acid **2** to obtain intermediate compound **E** through intramolecular cyclization (**C**) and dehydrative aromatization (**D**). In the next step, compound **E** was treated with aromatic/heteroaromatic aldehydes **3** in ethanol and underwent proton transfer and dehydration to obtain benzothiazolo[2,3-*c*][1,2,4]triazole derivatives (**4a–l**) in excellent yields. For the synthesis of our next series, as a result of the condensation reaction of compound **4** and thioglycolic acid **5**, the target thiazolidinone appended benzothiazole–triazole hybrids (**6a–h**) were obtained.

The substrate scope and complete reaction conditions involved in the synthesis of benzothiazole–triazole derivatives (**4a–l**) and thiazolidinone appended benzothiazole–triazole derivatives (**6a–h**) are illustrated in Schemes 3 and 4 respectively. The structures of all the synthetics **4a–l** and **6a–h** were in agreement with their spectral and analytical analyses which are summarized in ESI.† From the IR spectrum of compound **4a**, the appearance of peaks at 1634 cm^{-1} indicated the presence of C=N attached to the phenyl ring. The peaks of CH proton in ^{1}H-NMR spectra which are common to all of the compounds, were observed as singlets in the range of 8.27–8.93 ppm. The signals belonging to aromatic protons of benzothiazole ring and phenyl rings were found between 6.58–7.99 ppm. In ^{13}C-NMR spectra, signals belonging to CH proton in all synthesized compounds were detected in the range of 159.0–160.9 ppm. All masses were in accordance with the estimated $M^{+}H$ values.

In IR spectra, characteristic peaks were observed for C=O stretching and C–S stretching of the thiazolidinone derivatives in the range of 1690–1710 cm^{-1} and 685–692 cm^{-1} respectively. ^{1}H-NMR spectra of compound **6a** indicated the presence of two diastereotopic protons at the C-5 position appearing as doublets at 3.59, and 3.90 ppm and one single proton at C-2 position appearing as singlet at 5.93 ppm. In ^{13}C NMR spectra, chemical shifts of the thiazolidinone hybrids resonate in the region of 33.1–35.1 ppm (methylene carbon, thiazolidinone ring), 168.5–169.9 ppm (carbonyl carbon (>C=O) thiazolidinone ring), 112.0–158.2 ppm (aromatic carbons).

Antimicrobial evaluation

The newly desired synthesized molecular hybrids (**6a–h**) were screened for their antimicrobial activity against some selected bacterial and fungal strains and examined for the inhibition of the growth of the organism by employing the agar well diffusion method.[42] Both Gram-positive (*Staphylococcus aureus* [MTCC 96], *Bacillus subtilis* [MTCC 441]) and Gram-negative (*Klebsiella planticola* [MTCC 530], *Pseudomonas aeruginosa* [MTCC 2453]) pathogenic bacterial strains were used in the present work with ciprofloxacin as the standard drug. Antifungal activity was conducted against *Candida albicans* [MTCC 3017], *Candida albicans* [MTCC 1637], and *Aspergillus niger* [MTCC 872] using miconazole as the standard drug. The minimum inhibitory concentration (MIC) of the synthesized compounds were tabulated in Tables 2 and 3.

In general, most of the tested compounds (**6a–h**) exhibited a certain degree of inhibitory activity. The SAR studies suggested that compounds **6b**, **6d**, **6e**, **6f**, **6g**, and **6h** exhibited significant inhibitory effects on bacterial and fungal growth (Tables 2 and 3). Among thiazolidinone derivatives, compound **6h** bearing indolyl ring was the most active antibacterial agent compared to standard drugs. The hybrid, **6b** with a 3,4-diOCH_3 phenyl substitution showed a very good activity against different bacterial strains. Compound **6d** shows better activity than compound **6a**, replacement of 4-fluorophenyl with the 4-nitrophenyl group resulted in a significant increase in the activity. The compound **6c** with 3-OCH_3 and 4-OH phenyl substitution with bromo at the 5th position exhibited good to moderate antimicrobial activity against the test pathogens except for *S. aureus* [MTCC 96]. In addition, compound **6e** with 3,4,5-triOCH_3 phenyl substitution showed excellent activity than **6c** and **6d**. The compounds **6f** and **6g** bearing furan and thiophene ring exhibited good to excellent antimicrobial activity against the tested pathogens.

Additionally, our novel synthesized compounds were also screened for antifungal activity (Table 3). The results showed that compound **6h** showed potent activity and compound **6e** displayed excellent antifungal activity as compared to standard. The superiority of the former could be attributed to the higher basicity given by indole moiety as the pyrrole ring fused with benzene has yielded more fruitful results than phenyl-substituted groups. Interestingly, the replacement of the indole ring with a thiophene ring to afford compound **6g** produced stronger antifungal activity but less than compound **6h**. In general, the rest of the tested compounds showed significant results. Like in antimicrobial activity, compound **6e** also showed excellent to good activity against antifungal strains. Moreover, the methoxy-substituted derivative **6b** favored the activity. This demonstrates the substantial impact of the indolyl ring in augmenting the activity of the targeted compounds in both series. The presence of methoxy groups either on *o*/*m*/*p*-positions of the phenyl ring is evident for optimum activity.

We believe that the significant antimicrobial activities of the synthesized compounds could be due to the fusion of the

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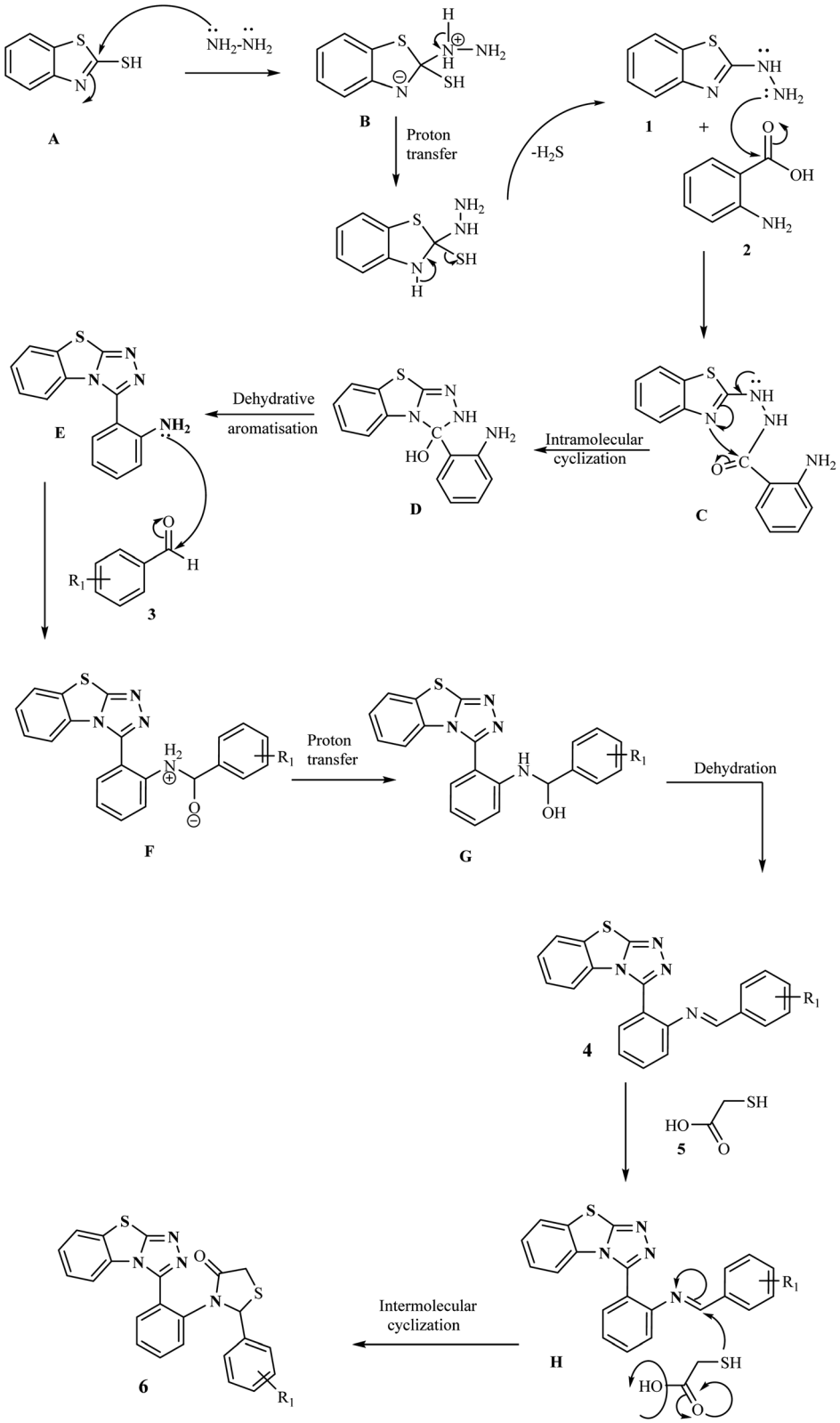

Scheme 2 Plausible mechanistic pathway for the synthesis of target hybrids.

thiazolidinone ring with the benzothiazole–triazole pharmacophore. To date, several papers have shown that 4-thiazolidinone derivatives could potentially be more effective against antibiotic-resistant bacterial strains. Skora *et al.* reported that synthesized thiazolidinone derivatives showed high antibacterial activity, as they caused a decrease in biofilm biomass at the concentrations.[43]

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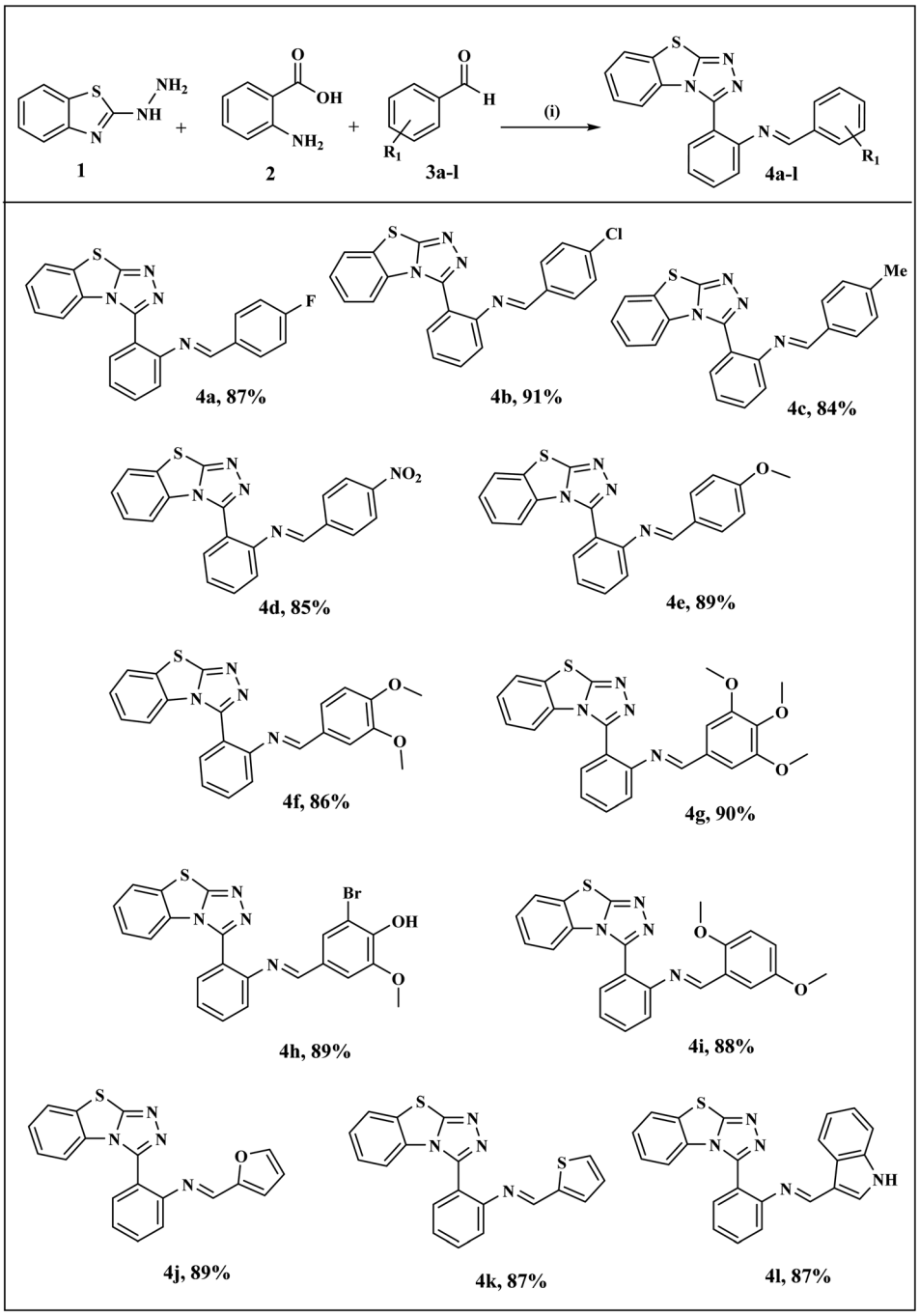

Scheme 3 Synthesis of benzothiazolo[2,3-c][1,2,4]triazole derivatives (**4a–l**) Reagents and conditions: (i) EtOH, reflux, 2 h.

As reported by Haroun *et al.*, some new benzothiazole-based thiazolidinones showed potent antimicrobial activity, causing inhibition of bacterial and fungal growth.[44] Tratrat *et al.* highlighted that some synthesized thiazolidinones showed excellent antifungal and antibacterial activities against different pathogenic strains.[45] Considering the literature data cited above and our results, it can be concluded that some synthesized thiazolidinone-appended benzothiazole–triazole derivatives can be valuable compounds in the treatment of antibiotic-resistant bacterial strains.

Experimental

Materials and techniques for analysis

All the solvents and reagents (analytical grade) were purchased from commercial suppliers and were used in synthesis without additional purification in the experimental procedures. The melting points of all synthesized compounds were analyzed using a digital melting point apparatus. The purity of the compounds was assessed using thin-layer silica gel-G-coated glass plates with a benzene: ethyl acetate (8 : 2)

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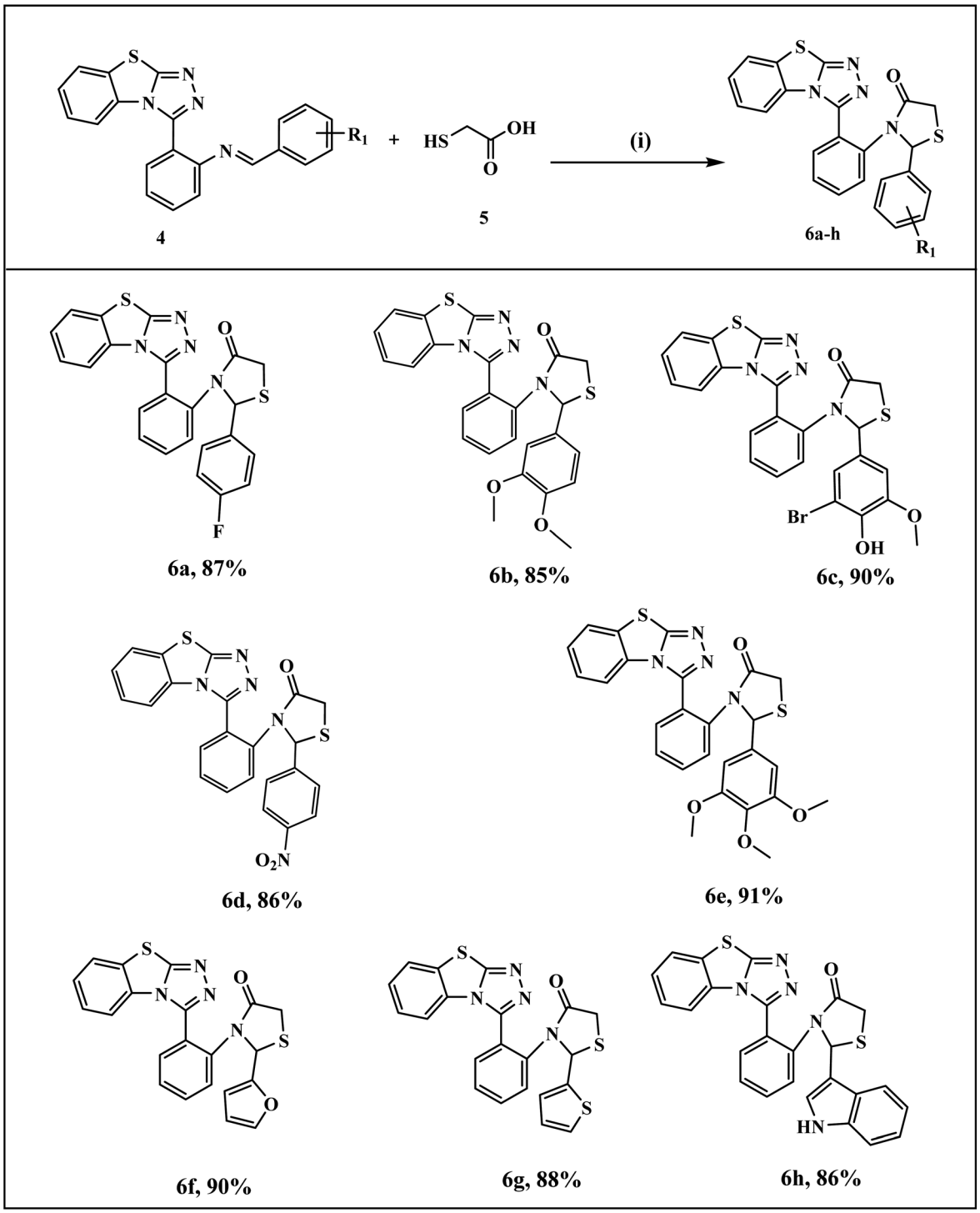

Scheme 4 Synthesis of benzo[4,5]thiazolo[2,3-c][1,2,4]triazol-2-phenylthiazolidin-4-one derivatives (**6a–h**) Reagents and conditions: (i) EtOH, reflux, 2 h.

eluent. Infrared (IR) spectra were recorded using a Shimadzu FT IR-8400S spectrophotometer with KBr pellets. Mass spectrometry measurements were obtained on Waters Xevo G2-S QT LC/MS spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol Resonance at 400 and 100 MHz, respectively in dimethyl sulfoxide (DMSO-d_6) and $CDCl_3$ as a solvent. Chemical shifts and absorption frequency have been expressed in terms of δ (ppm) and ν (cm^{-1}), respectively. The abbreviations have been used in the spectral data as singlet (s), doublet (d), doublet of doublet (dd), and multiplet (m). ElementarVarioEL III Elemental analyzer is found helpful in elemental analyses.

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Table 2 Antibacterial activity (in μg mL^{-1}) of the synthesized compounds (6a–h)

	Gram-positive bacteria (MIC)		Gram-negative bacteria (MIC)	
Compound	*S. aureus* MTCC 96	*B. subtilis* MTCC 441	*K. planticola* MTCC 530	*P. aeruginosa* MTCC 2453
6a	>125	>125	>125	>125
6b	7.8	3.9	7.8	7.8
6c	>125	7.8	15.9	7.8
6d	7.8	3.9	7.8	>125
6e	1.9	3.9	3.9	3.9
6f	3.9	7.8	7.8	3.9
6g	7.8	7.8	3.9	7.8
6h	1.9	1.9	3.9	1.9
Ciprofloxacin	0.9	0.9	0.9	0.9

Table 3 Antifungal activity (in μg mL^{-1}) of the synthesized compounds (6a–h)

Compound	*C. albicans* MTCC 3017 (MIC)	*C. albicans* MTCC 1637 (MIC)	*A. niger* MTCC 872 (MIC)
6a	>125	>125	>125
6b	7.8	>125	15.9
6c	15.9	>125	>125
6d	7.8	15.9	7.8
6e	3.9	7.8	7.8
6f	7.8	3.9	15.9
6g	3.9	7.8	7.8
6h	3.9	7.8	3.9
Miconazole	1.9	1.9	1.9

Antimicrobial activity

Gram-positive (*Staphylococcus aureus* [MTCC 96], *Bacillus subtilis* [MTCC 441]) and Gram-negative (*Klebsiella planticola* [MTCC 530], *Pseudomonas aeruginosa* [MTCC 2453]) pathogenic bacterial strains and *Candida albicans* [MTCC 3017], *Candida albicans* [MTCC 1637] and *Aspergillus niger* [MTCC 872] fungal strains were used in this experiment. The antimicrobial properties of various synthesized compounds were assessed using the agar well diffusion method. Mueller Hinton agar plates were evenly inoculated with pathogenic strains, each at a concentration equivalent to 0.5 McFarland standards (1.5 × 108 cfu mL^{-1}). In a sterile laminar airflow chamber, 6 mm diameter wells were created on the agar plates. These wells were then filled with test samples dissolved in 2% DMSO, with concentrations ranging from 125 to 0.97 μg mL^{-1}. Ciprofloxacin and miconazole were used as positive controls, while DMSO served as the vehicle control. The plates were incubated at 37 °C for 24 hours for bacteria and 28 °C for 48 hours for fungi. After incubation, the minimum inhibitory concentration (MIC) was determined as the lowest concentration in the series where no inhibition of visual growth was observed in the wells. The entire experiment was conducted in duplicate, and the mean values were reported.

General procedure for the synthesis of benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl-phenyl-1-phenylmethanimine (4a–l)

The reaction was carried out by using an equimolar mixture of 2-hydrazinobenzothiazole **1** (1 mmol), anthranilic acid **2** (1 mmol), and aromatic/heteroaromatic aldehydes **3a–l** (1 mmol), the mixture was refluxed in ethanol (10 mL) as solvent at 80 °C for 2 h which afforded pale yellow colored solid. After the completion of the reaction as indicated by TLC, the reaction mixture was cooled at room temperature, and obtained precipitate was filtered under vacuum, washed with chilled water a few times, dried, and used in the next step without further purification.

General procedure for the synthesis of benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl-phenyl-2-phenylthiazolidin-4-one (6a–h)

To pure synthesized compounds, benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl-phenyl-1-phenylmethanimine **4** (1 mmol) with thioglycolic acid **5** (1 mmol) in ethanol (10 mL) were heated at refluxing for 2 h at 80 °C which afforded solid mass. After the completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, and the resulting precipitate was filtered under vacuum. It was then washed several times with chilled water, and dried, and the desired compounds were obtained with good to excellent yields after further recrystallization. The products were determined *via* the use of melting point, FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra.

***N*-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-1-(4-fluorophenyl)methanimine (4a).** Pale yellow solid, m.p. 284 °C, FT-IR (KBr, cm^{-1}): 1634 (C=N); ^{1}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}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; MS (*m*/*z*): 373.084 $[M+H]^+$; anal. calcd for $C_{21}H_{13}FN_4S$: C 67.73; H 3.52; N 15.04; S 8.61%; found C 67.85; H 3.49; N 14.99; S 8.55%.

***N*-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-1-(4-chlorophenyl)methanimine (4b).** Pale yellow solid, m.p. 282 °C, FT-IR (KBr, cm^{-1}): 1646 (C=N); ^{1}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}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;

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MS(*m*/*z*): 389.055 [M+H]$^+$; anal. calcd for $C_{21}H_{13}ClN_4S$: C 64.86; H 3.37; Cl 9.12; N 14.41; S 8.24%; found C 64.98; H 3.34; N 14.36; S 8.18%.

***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}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, CH$_3$) ppm; ^{13}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 [M+H]$^+$; anal. calcd for $C_{22}H_{16}N_4S$: C 71.72; H 4.38; N 15.21; S 8.70%; found C 71.84; H 4.35; N 15.16; S 8.64%.

***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}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}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; MS(*m*/*z*): 400.079 [M+H]$^+$; anal. calcd for $C_{21}H_{13}N_5O_2S$: C 63.15; H 3.28; N 17.53; O 8.01; S 8.03%; found C 63.27; H 3.25; N 17.48; O 7.93; S 7.97%.

***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); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 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, OCH$_3$) ppm; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 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; MS(*m*/*z*): 385.104 [M+H]$^+$; anal. calcd for $C_{22}H_{16}N_4OS$: C 68.73; H 4.20; N 14.57; O 4.16; S 8.34%; found C 68.85; H 4.17; N 14.52; O 4.08; S 8.28%.

***N*-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-1-(3,4-dimethoxyphenyl)methanimine (4f).** White solid, m.p. 281 °C, FT-IR (KBr, cm^{-1}): 1641 (C=N); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.34 (s, 1H, CH), 7.42–7.59 (m, 4H, Ar–H), 7.31 (s, 1H, Ar–H), 6.95–7.07 (m, 2H, Ar–H), 6.79 (d, 2H, Ar–H, J = 7.6 Hz), 6.64 (d, 2H, Ar–H, J = 7.4 Hz), 3.75 (s, 3H, OCH$_3$), 3.73 (s, 3H, OCH$_3$) ppm; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 161.9, 161.8, 153.1, 152.9, 146.5, 146.4, 140.5, 140.3, 136.2, 133.8, 133.6, 130.0, 129.8, 124.5, 124.3, 122.7, 122.5, 118.4, 118.1, 53.1, 53.0 ppm; MS(*m*/*z*): 415.115 [M+H]$^+$; anal. calcd for $C_{23}H_{18}N_4O_2S$: C 66.65; H 4.38; N 13.52; O 7.72; S 7.73%; found C 66.77; H 4.35; N 13.47; O 7.64; S 7.67%.

***N*-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-1-(3,4,5-trimethoxyphenyl)methanimine (4g).** White solid, m.p. 220 °C, FT-IR (KBr, cm^{-1}): 1645 (C=N); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.93 (s, 1H, CH), 7.68–7.73 (m, 5H, Ar–H), 7.50–7.54 (m, 3H, Ar–H), 7.38 (s, 1H, Ar–H), 7.36 (s, 1H, Ar–H), 3.61 (s, 3H, di-OCH$_3$), 3.45 (s, 3H, OCH$_3$) ppm; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 161.3, 160.9, 153.4, 153.1, 148.2, 147.0, 141.9, 141.7, 133.9, 133.2, 132.9, 132.7, 127.1, 126.9, 126.8, 123.2, 123.0, 117.6, 117.5, 117.2, 56.4, 53.1, 53.0 ppm; MS(*m*/*z*): 445.126 [M+H]$^+$; anal. calcd for $C_{24}H_{20}N_4O_3S$: C 64.85; H 4.54; N 12.60; O 10.80; S 7.21%; found C 64.73; H 4.51; N 12.55; O 10.72; S 7.15%.

4-(((2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)imino)methyl)-2-bromo-6-methoxyphenol (4h). Pale yellow solid, m.p. 278 °C, FT-IR (KBr, cm^{-1}): 1639 (C=N); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 9.49 (s, 1H, OH), 8.64 (s, 1H, CH), 7.46–7.64 (m, 8H, Ar–H), 7.30 (s, 1H, Ar–H), 7.07 (s, 1H, Ar–H), 3.85 (s, 3H, OCH$_3$) ppm; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 162.2, 159.7, 152.6, 147.9, 147.7, 145.8, 143.8, 143.6, 140.1, 139.8, 137.9, 135.5, 134.3, 130.0, 129.9, 129.8, 128.5, 126.1, 125.3, 120.9, 120.8, 56.4 ppm; MS(*m*/*z*): 479.010 [M+H]$^+$; anal. calcd for $C_{22}H_{15}BrN_4O_2S$: C 55.12; H 3.15; N 11.69; O 6.68; S 6.69%; found C 55.24; H 3.12; N 11.64; O 6.60; S 6.63%.

***N*-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-1-(2,5-dimethoxyphenyl)methanimine (4i).** Pale yellow solid, m.p. 283 °C, FT-IR (KBr, cm^{-1}): 1640 (C=N); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.86 (s, 1H, CH), 7.51 (d, 2H, Ar–H, J = 8 Hz), 7.39 (d, 2H, Ar–H, J = 8 Hz), 7.12–7.28 (m, 2H, Ar–H), 6.88 (d, 2H, Ar–H, J = 8 Hz), 6.75–6.81 (m, 3H, Ar–H), 3.75 (s, 3H, OCH$_3$), 3.61 (s, 3H, OCH$_3$), ppm; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 161.9, 160.4, 156.5, 155.0, 148.9, 140.0, 135.4, 134.1, 133.8, 129.6, 126.8, 124.9, 124.1, 119.6, 118.5, 118.2, 116.1, 112.7, 111.6, 111.5, 56.0, 55.2 ppm; MS(*m*/*z*): 415.115 [M+H]$^+$; anal. calcd for $C_{23}H_{18}N_4O_2S$: C 66.65; H 4.38; N 13.52; O 7.72; S 7.73% found C 66.77; H 4.35; N 13.47; O 7.64; S 7.67%.

(*E*)-*N*-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-1-(furan-2-yl)methanimine (4j). Pale yellow solid, m.p. 276 °C, FT-IR (KBr, cm^{-1}): 1643 (C=N); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.55 (s, 1H, CH), 7.34–7.49 (m, 7H, Ar–H), 7.06–7.14 (m, 2H, Ar–H), 6.74 (dd, 2H, Ar–H, J = 6.8, 7.2 Hz) ppm; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 161.1, 154.7, 148.9, 138.4, 133.4, 130.8, 129.8, 126.9, 126.4, 124.9, 124.7, 123.2, 123.1, 121.7, 121.6, 119.7, 119.6, 117.9, 112.7 ppm; MS(*m*/*z*): 345.073 [M+H]$^+$; anal. calcd for $C_{19}H_{12}N_4OS$: C 66.26; H 3.51; N 16.27; O 4.65; S 9.31% found C 66.38; H 3.48; N 16.22; O 4.57; S 9.25%.

(*E*)-*N*-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-1-(thiophen-2-yl)methanimine (4k). Pale yellow solid, m.p. 295 °C, FT-IR (KBr, cm^{-1}): 1641 (C=N); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 8.63 (s, 1H, CH), 7.42–7.48 (m, 4H, Ar–H), 7.26–7.32 (m, 2H, Ar–H), 7.12 (d, 2H, Ar–H, J = 7.4 Hz), 7.03–7.08 (m, 3H, Ar–H) ppm; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 162.4, 154.9, 154.8, 152.1, 148.9, 142.7, 131.5, 129.4, 128.1, 126.9, 125.9, 124.9, 124.7, 124.6, 122.5, 122.3, 122.1, 119.6 ppm; MS(*m*/*z*): 361.050 [M+H]$^+$; anal. calcd for $C_{19}H_{12}N_4S_2$: C 63.31; H 3.36; N 15.54; S 17.79% found C 63.43; H 3.33; N 15.49; S 17.73%.

(*E*)-*N*-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-1-(1*H*-indol-3-yl)methanimine (4l). Yellow solid, m.p. 289 °C, FT-IR (KBr, cm^{-1}): 1638 (C=N), 3424 (*N*–H); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 10.55 (s, 1H, NH), 8.79 (s, 1H, CH), 7.33–7.42 (m, 5H, Ar–H), 7.11–7.18 (m, 3H, Ar–H), 6.96 (s, 1H, Ar–H), 6.71 (dd, 4H, Ar–H, J = 7.2, 6.4 Hz) ppm; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 162.4, 160.4, 154.9, 148.9, 143.1, 134.4, 134.1, 130.8, 129.7, 128.4, 128.2, 126.9, 124.9, 124.6, 123.8, 123.6, 122.3, 122.2, 121.1, 119.6, 113.5, 112.7, 112.6 ppm; MS(*m*/*z*): 394.105 [M+H]$^+$; anal. calcd for $C_{23}H_{15}N_5S$: C 70.21; H 3.84; N 17.80; S 8.15% found C 70.33; H 3.81; N 17.75; S 8.09%.

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3-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-2-(4-fluorophenyl)thiazolidin-4-one (6a). Pale yellow solid, m.p. 280 °C, FT-IR (KBr, cm^{-1}): 1690 (C=O), 685 (C–S); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.60–7.62 (m, 2H, Ar–H), 7.54–7.58 (m, 2H, Ar–H), 7.42–7.46 (m, 2H, Ar–H), 7.21–7.32 (m, 2H, Ar–H), 6.64–7.05 (m, 4H, Ar–H), 5.93 (s, 1H, CH), 3.90 (d, 1H, CH_2, J = 8.8 Hz), 3.59 (d, 1H, CH_2, J = 8.8 Hz) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 35.5, 77.7, 112.3, 112.7, 119.2, 119.5, 121.9, 123.6, 123.9, 124.8, 126.2, 126.5, 126.8, 129.2, 131.2, 131.6, 133.0, 133.3, 139.8, 140.1, 148.9, 155.4, 169.6 ppm; MS(m/z): 447.067 $[M+H]^+$; anal. calcd for $C_{23}H_{15}FN_4OS_2$: C 61.87; H 3.39; F 4.25; N 12.55; O 3.58; S 14.36% found C 61.99; H 3.36; N 12.50; O 3.50; S 14.30%

3-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-2-(3,4-dimethoxyphenyl)thiazolidin-4-one (6b). White solid, m.p. 278 °C, FT-IR (KBr, cm^{-1}): 1710 (C=O), 692 (C–S); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.60–7.62 (m, 1H, Ar–H), 7.43–7.45 (m, 3H, Ar–H), 7.18–7.27 (m, 3H, Ar–H), 7.06 (s, 1H, Ar–H), 6.86–6.99 (m, 3H, Ar–H), 6.042 (s, 1H, CH), 4.162 (d, 1H, CH_2, J = 9.6 Hz), 3.70 (d, 1H, CH_2, J = 9.6 Hz), 3.40 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 35.3, 53.1, 53.8, 68.3, 112.7, 116.4, 116.7, 119.6, 119.7, 123.2, 123.5, 124.9, 126.4, 126.9, 129.9, 130.8, 133.4, 133.7, 139.4, 139.8, 142.2, 148.9, 154.7, 168.9 ppm; MS(m/z): 489.098 $[M+H]^+$; anal. calcd for $C_{25}H_{20}N_4O_3S_2$: C 61.46; H 4.13; N 11.47; O 9.82; S 13.12% found C 61.58; H 4.10; N 11.42; O 9.74; S 13.06%

3-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-2-(3-bromo-4-hydroxy-5-methoxyphenyl)thiazolidin-4-one (6c). Pale yellow solid, m.p. 272 °C, FT-IR (KBr, cm^{-1}): 1704 (C=O), 689 (C–S); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.53 (s, 1H, OH), 7.72 (s, 1H, Ar–H), 7.52–7.54 (m, 1H, Ar–H), 7.25–7.32 (m, 6H, Ar–H), 6.98–7.11 (m, 1H, Ar–H), 6.77 (s, 1H, Ar–H),6.30 (s, 1H, CH), 4.26 (d, 1H, CH_2, J = 5.2 Hz), 3.70 (d, 1H, CH_2, J = 5.2 Hz), 3.40 (s, 3H, OCH_3) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 35.1, 56.0, 72.5, 112.1, 112.7, 119.6, 124.7, 124.9, 125.9, 126.9, 128.1, 129.8, 131.5, 133.7, 133.9, 134.1, 135.5, 139.7, 140.0, 142.7, 148.9, 154.7, 154.9, 169.4 ppm; MS(m/z): 552.993 $[M+H]^+$; anal. calcd for $C_{24}H_{17}BrN_4O_3S_2$: C 52.09; H 3.10; N 10.12; O 8.67; S 11.59% found C 52.21; H 3.07; N 10.07; O 8.59; S 11.53%.

3-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-2-(4-nitrophenyl)thiazolidin-4-one (6d). Yellow solid, m.p. 281 °C, FT-IR (KBr, cm^{-1}): 1708 (C=O), 691 (C–S); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.88–7.92 (m, 1H, Ar–H), 7.58–7.60 (m, 1H, Ar–H), 7.45–7.48 (m, 1H, Ar–H), 7.32–7.37 (m, 5H, Ar–H), 7.19–7.22 (m, 3H, Ar–H), 6.78–6.80 (m, 1H, Ar–H), 6.32 (s, 1H, CH),3.80 (d, 1H, CH_2, J = 8.0 Hz), 3.38 (d, 1H, CH_2, J = 8.0 Hz), ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 35.1, 72.6, 111.5, 111.6, 112.7, 116.0, 119.6, 124.1, 124.9, 126.8, 129.6, 136.2, 138.1, 140.0, 144.1, 144.5, 145.1, 146.3, 148.9, 155.0, 156.5, 169.5 ppm; MS(m/z): 474.062 $[M+H]^+$; anal. calcd for $C_{23}H_{15}N_5O_3S_2$: C 58.34; H 3.19; N 14.79; O 10.14; S 13.54% found C 58.46; H 3.16; N 14.74; O 10.06; S 13.48%.

3-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-2-(3,4,5-trimethoxyphenyl)thiazolidin-4-one (6e). White solid, m.p. 216 °C, FT-IR (KBr, cm^{-1}): 1700 (C=O), 687 (C–S); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.72 (s, 1H, Ar–H), 7.53–7.57 (m, 2H, Ar–H), 7.24–7.34 (m, 6H, Ar–H), 6.76 (s, 1H, Ar–H), 6.18 (s, 1H, CH), 4.08 (d, 1H, CH_2, J = 7.2 Hz), 3.90 (d, 1H, CH_2, J = 7.2 Hz), 3.42 (s, 3H, OCH_3), 3.35 (s, 6H, OCH_3), ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 35.1, 56.0, 56.8, 60.3, 72.2, 110.3, 110.7, 112.2, 112.6, 119.5, 122.3, 124.4, 124.8, 125.7, 126.5, 126.8, 128.9, 129.2, 130.2, 130.8, 141.3, 141.6, 148.9, 154.0, 155.3, 169.6 ppm; MS(m/z): 519.108 $[M+H]^+$; anal. calcd for $C_{26}H_{22}N_4O_4S_2$: C 60.22; H 4.28; N 10.80; O 12.34; S 12.36% found C 60.34; H 4.25; N 10.75; O 12.26; S 12.28%.

3-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-2-(furan-2-yl)thiazolidin-4-one (6f). Pale yellow solid, m.p. 271 °C, FT-IR (KBr, cm^{-1}): 1705 (C=O), 688 (C–S); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.72–7.73 (m, 1H, Ar–H), 7.52–7.54 (m, 1H, Ar–H), 7.42–7.45 (m, 1H, Ar–H), 7.24–7.31 (m, 4H, Ar–H), 6.98–7.19 (m, 2H, Ar–H), 6.71–6.75 (m, 1H, Ar–H), 6.31 (s, 1H, CH), 3.61 (d, 1H, CH_2, J = 8.8 Hz), 3.41 (d, 1H, CH_2, J = 8.8 Hz) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 35.2, 67.5, 112.6, 112.7, 113.5, 119.6, 122.0, 122.6, 124.6, 124.9, 126.9, 128.1, 129.7, 130.8, 133.2, 133.4, 134.4, 143.1, 148.9, 154.9, 169.4 ppm; MS(m/z): 419.056 $[M+H]^+$; anal. calcd for $C_{21}H_{14}N_4O_2S_2$: C 60.27; H 3.37; N 13.39; O 7.65; S 15.32% found C 60.39; H 3.34; N 13.34; O 7.57; S 15.24%.

3-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-2-(thiophen-2-yl)thiazolidin-4-one (6g). Pale yellow solid, m.p. 290 °C, FT-IR (KBr, cm^{-1}): 1700 (C=O), 689 (C–S); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.68–7.73 (m, 2H, Ar–H), 7.52–7.54 (m, H, Ar–H), 7.22–7.38 (m, 5H, Ar–H), 6.69–6.71 (m, 3H, Ar–H), 6.11 (s, 1H, CH), 3.61 (d, 1H, CH_2, J = 10 Hz), 3.39 (d, 1H, CH_2, J = 10 Hz) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 35.2, 64.4, 110.4, 110.6, 112.6, 115.4, 115.8, 119.5, 119.8, 121.0, 121.9, 123.7, 124.9, 126.9, 128.9, 129.8, 131.5, 143.8, 149.0, 155.3, 168.8 ppm; MS(m/z): 435.033 $[M+H]^+$; anal. calcd for $C_{21}H_{14}N_4OS_3$: C 58.04; H 3.25; N 12.89; O 3.68; S 22.13% found C 58.16; H 3.22; N 12.84; O 3.60; S 22.07%.

3-(2-(Benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazol-3-yl)phenyl)-2-(1*H*-indol-3-yl)thiazolidin-4-one (6h). White solid, m.p. 283 °C, FT-IR (KBr, cm^{-1}): 1695 (C=O), 686 (C–S), 3412 (N–H); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.78 (s, 1H, N–H), 7.72–7.78 (m, 3H, Ar–H), 7.52–7.60 (m, 3H, Ar–H), 7.25–7.32 (m, 2H, Ar–H), 7.14–7.17 (m, 3H, Ar–H), 6.88 (s, 1H, Ar–H), 6.74–6.76 (m, 1H, Ar–H), 6.31 (s, 1H, CH), 3.92 (d, 1H, CH_2, J = 7.2 Hz), 3.86 (d, 1H, CH_2, J = 7.2 Hz) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 33.4, 72.2, 112.0, 112.3, 112.8, 114.1, 116.3, 117.5, 119.3, 121.6, 121.9, 123.0, 124.3, 126.5, 127.7, 129.8, 130.0, 132.4, 132.7, 142.1, 142.4, 149.7, 158.2, 169.0 ppm; MS(m/z): 468.087 $[M+H]^+$; anal. calcd for $C_{25}H_{17}N_5OS_2$: C 64.22; H 3.66; N 14.98; O 3.42; S 13.71% found C 64.34; H 3.63; N 14.93; O 3.34; S 13.65%.

Conclusions

We have designed and synthesized two novel series of molecular hybrids (**4a–l** and **6a–h**) by amalgamating benzothiazole, triazole, and thiazolidinone pharmacophore sub-units and were screened for antimicrobial properties. Among the tested compounds, **6e** and **6h** showed promising antibacterial and antifungal activity against the tested pathogenic strains compared to standard. Compounds **6e**, **6g**, and **6h** also

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exhibited significant activity. The presence of pharmacologically active moieties, combined with a green protocol that operates efficiently in one pot manner under metal- and catalyst-free conditions, makes the synthesized compounds highly scalable. The evaluation results suggest that these compounds are promising candidates for further chemical modification and as biologically active agents.

Abbreviations

ACN	Acetonitrile
ALR2	Aldose reductase
COX	Cyclooxygenase
DMF	Dimethylformamide
EtOH	Ethanol
HIV-RT	Human immunodeficiency virus-reverse transcription
IR	Infrared
MeOH	Methanol
MH	Molecular hybridization
MIC	Minimum inhibitory concentration
MTCC	Microbial type culture collection
NMR	Nuclear magnetic resonance
PARP	Poly(ADP-ribose) polymerase
PRL	Phosphatase of a regenerating liver
SAR	Structure–activity relationships
SARS-COV-2	Severe acute respiratory syndrome Coronavirus 2
THF	Tetrahydrofuran
TNF	Tumor necrosis factor

Author contributions

Deepika Choudhary: conceptualization, methodology, resources, funding, validation, software, supervision; Bhaskar Dwivedi: investigation, methodology, formal analysis, data curation, writing – review & editing; Diksha Bhardwaj: investigation, methodology, formal analysis, visualization, writing – original draft.

Conflicts of interest

There are no conflicts to declare.

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References

1 H. M. S. Kumar, L. Herrmann and S. B. Tsogoeva, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127514.
2 S. Agarwal, D. Gandhi and P. Kalal, *Lett. Org. Chem.*, 2017, **14**, 729.
3 T. Selvaraj, R. Rajalingam and V. Balasubramanian, *Appl. Surf. Sci.*, 2018, **434**, 781.
4 C. S. W. Law and K. Y. Yeong, *Expert Opin. Ther. Pat.*, 2022, **32**, 299.
5 G. Trapani, M. Franco, A. Latrofa, A. Reho and G. Liso, *Eur. J. Pharm. Sci.*, 2001, **14**, 209.
6 T. Mase, H. Arima, K. Tomioka, T. Yamada and K. Murase, *J. Med. Chem.*, 1986, **29**, 386.
7 X. Zhang, J. Jia and C. Ma, *Org. Biomol. Chem.*, 2012, **10**, 7944.
8 F. Yan, J. Sun, Y. Zang, Z. Sun, H. Zhang and X. Wang, *J. Iran. Chem. Soc.*, 2020, **17**, 3179.
9 J. Kuwabara, T. Namekawa, M.-A. Haga and T. Kanbara, *Dalton Trans.*, 2012, **41**, 44.
10 V. A. Kozlov, D. V. Aleksanyan, S. G. Churusova, A. A. Spiridonov, E. Y. Rybalkina, E. I. Gutsul, S. A. Aksenova, A. A. Korlyukov, A. S. Peregudov and Z. S. Klemenkova, *Int. J. Mol. Sci.*, 2023, **24**, 17331.
11 G. M. Srinivasa, E. Jayachandran, B. Shivakumar and D. S. Rao, *Orient. J. Chem.*, 2004, **20**, 103.
12 X. Q. Deng, M. X. Song, C. X. Wei, F. N. Li and Z. S. Quan, *Med. Chem.*, 2010, **6**, 313.
13 J. D. Froyd, C. J. Paget, L. R. Guse, B. A. Dreikorn and J. L. Pafford, *Phytopathology*, 1976, **66**, 1135.
14 S. Kukreja, A. Sidhu and V. K. Sharma, *Res. Chem. Intermed.*, 2016, **42**, 8329.
15 D. Geedkar, A. Kumar and P. Sharma, *J. Heterocycl. Chem.*, 2020, **57**, 4331.
16 A. H. Abdelazeem, A. M. Alqahtani, H. A. Omar and S. N. A. Bukhari, *J. Mol. Struct.*, 2020, **1219**, 128567.
17 S. Murthy, M. G. Nizi, M. M. Maksimainen, S. Massari, J. Alaviuhkola, B. E. Lippok, C. Vagaggini, S. T. Sowa, A. Galera-Prat, Y. Ashok, H. Venkannagari, R. Prunskaite-Hyyryläinen, E. Dreassi, B. Lüscher, P. Korn, O. Tabarrini and L. Lehtiö, *J. Med. Chem.*, 2023, **66**, 1301.
18 P. A. Chawla, S. K. Wahan, M. Negi, A. Faruk and V. Chawla, *J. Heterocycl. Chem.*, 2023, **60**, 1248.
19 D. Mech, A. Kurowska and N. Trotsko, *Int. J. Mol. Sci.*, 2021, **22**, 11533.
20 J. H. Ahn, S. J. Kim, W. S. Park, S. Y. Cho, J. D. Ha, S. S. Kim, S. K. Kang, D. G. Jeong, S. K. Jung, S. H. Lee, H. M. Kim, S. K. Park, K. H. Lee, C. W. Lee, S. E. Ryu and J. K. Choi, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2996.
21 P. H. Carter, P. A. Scherle, J. A. Muckelbauer, M. E. Voss, R. Q. Liu, L. A. Thompson, A. J. Tebben, K. A. Solomon, Y. C. Lo, Z. Li, P. Strzemienski, G. Yang, N. Falahatpisheh, M. Xu, Z. Wu, N. A. Farrow, K. Ramnarayan, J. Wang, D. Rideout, V. Yalamoori, P. Domaille, D. J. Underwood, J. M. Trzaskos, S. M. Friedman, R. C. Newton and C. P. Decicco, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 11879.
22 A. Petrou, P. Eleftheriou, A. Geronikaki, M. G. Akrivou and I. Vizirianakis, *Molecules*, 2019, **24**, 3821.
23 W. A. A. Fadalya, T. H. Zidana, N. M. Kahka, F. E. A. Mohameda, M. M. Abdelhakeema, R. G. Khalil and M. T. M. Nemr, *J. Enzyme Inhib. Med. Chem.*, 2023, **38**, 2281262.

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24 A. Petrou, P. Zagaliotis, N. F. Theodoroula, G. A. Mystridis, I. S. Vizirianakis, T. J. Walsh and A. Geronikaki, *Molecules*, 2022, **27**, 2180.
25 A. Kousaxidis, L. Kovacikova, I. Nicolaou, M. Stefek and A. Geronikaki, *Med. Chem. Res.*, 2021, **30**, 1837.
26 S. Cascioferro, B. Parrino, D. Carbone, D. Schillaci, E. Giovannetti, G. Cirrincione and P. Diana, *J. Med. Chem.*, 2020, **63**, 7923.
27 R. A. Rane, N. U. Sahu and C. P. Shah, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7131.
28 E. Pitta, E. Tsolaki, A. Geronikaki, J. Petrovic, J. Glamočlija, M. Soković, E. Crespan, G. Maga, S. S. Bhunia and A. K. Saxena, *MedChemComm*, 2015, **6**, 319.
29 S. Khan, S. Iqbal, M. Khan, W. Rehman, M. Shah, R. Hussain, L. Rasheed, Y. Khan, A. A. Dera, R. A. Pashameah, E. Alzahrani and A.-E. Farouk, *Pharmaceuticals*, 2022, **15**, 1164.
30 S. J. Gilani, K. Nagarajan, S. P. Dixit, M. Taleuzzaman and S. A. Khan, *Arab. J. Chem.*, 2016, **9**, S1523.
31 P. P. Prabhu, T. Panneerselvam, C. S. Shastry, A. Sivakumar and S. S. Pande, *J. Saudi Chem. Soc.*, 2015, **19**, 181.
32 A. Piozzi and J. Lee, *Int. J. Mol. Sci.*, 2024, **25**, 325.
33 S. Khan, S. Iqbal, M. Khan, W. Rehman, M. Shah, R. Hussain, L. Rasheed, Y. Khan, A. A. Dera and R. A. Pashameah, *Pharmaceuticals*, 2022, **15**, 1164.
34 D. Kaminskyy, A. Kryshchyshyn and R. Lesyk, *Eur. J. Med. Chem.*, 2017, **10**, 542.
35 P. Roszczenko, S. Holota, O. K. Szewczyk, R. Dudchak, K. Bielawski, A. Bielawska and R. Lesyk, *Int. J. Mol. Sci.*, 2022, **23**, 13135.
36 R. Perkins, H. Fang, W. Tong and W. J. Welsh, *Environ. Toxicol. Chem.*, 2003, **22**, 1666.
37 R. Singh, A. Singh and D. Bhardwaj, *ChemistrySelect*, 2019, **4**, 9600.
38 R. Singh, M. R. Saini, D. Bhardwaj and A. Singh, *New J. Chem.*, 2020, **44**, 7923.
39 D. Bhardwaj and R. Singh, *Tetrahedron Lett.*, 2021, **85**, 153491.
40 R. Singh, A. Singh, D. Bhardwaj and S. Sharma, *J. Sulfur Chem.*, 2024, **45**, 1.
41 S. Tariq, O. Alam and M. Amir, *Arch. Pharm. Chem. Life Sci.*, 2018, **351**, e1700304.
42 K. Vaarla, R. K. Kesharwani, K. Santosh, R. R. Vedula, S. Kotamraju and M. K. Toopurani, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 5797.
43 B. Skora, A. Lewinska, A. Kryshchyshyn-Dylevych, D. Kaminskyy, R. Lesyk and K. A. Szychowski, *Molecules*, 2022, **27**, 894.
44 M. Haroun, C. Tratrat, K. Kositzi, E. Tsolaki, A. Petrou, B. Aldhubiab, M. Attimarad, S. Harsha, A. Geronikaki, K. N. Venugopala, H. S. Elsewedy, M. Sokovic, J. Glamoclija and A. Ciric, *Curr. Top. Med. Chem.*, 2018, **18**, 75.
45 C. Tratrat, A. Petrou, A. Geronikaki, M. Ivanov, M. Kostic, M. Sokovic, I. S. Vizirianakis, N. F. Theodoroula and M. Haroun, *Molecules*, 2022, **27**, 1930.

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