RESEARCH PAPER

Synthesis, antimicrobial activity and *in silico* studies of novel sulfonamide-benzothiazole conjugate compounds

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Abstract
The emergence of multidrug-resistant pathogens and polymicrobial infections underscores the urgent need for novel broad-spectrum antimicrobial agents. In this study, a series of sulfonamide–benzothiazole conjugates (4a–4j) were synthesized via a straightforward, scalable route employing thioamide formation, nucleophilic substitution, and Schiff base condensation. Structural characterization was confirmed by ^1H NMR, EI-MS, FTIR, and elemental analysis. Antimicrobial activity was evaluated against Gram-positive (*Staphylococcus aureus, Bacillus subtilis*), Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*), and fungal strains (*Aspergillus niger, Candida albicans*) using the Kirby–Bauer disk diffusion assay. Several derivatives, notably 4c, 4d, 4i, and 4j, exhibited significant inhibition zones comparable to standard drugs, demonstrating broad-spectrum efficacy. *In silico* ADME profiling using SwissADME revealed favorable lipophilicity (LogP 4.75–7.48) and acceptable TPSA values (120.40–212.04 Å²), suggesting good membrane permeability and oral bioavailability. Although most compounds violated two Lipinski's rules (molecular weight and molar refractivity), compound 4a satisfied four criteria, indicating promising drug-likeness. These findings highlight sulfonamide–benzothiazole hybrids as potential scaffolds for developing multifunctional antimicrobial agents with enhanced pharmacokinetic properties.

Keywords
Sulfonamide, benzothiazole, anti-microbial, *in silico*, disk diffusion assay
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Introduction

The global health landscape is increasingly jeopardized by the emergence of refractory microbial diseases. A considerable issue in clinical practice is the therapy of polymicrobial illnesses, which involve both bacteria and fungi, as well as the initial empirical treatment of sepsis while the underlying culprit remains unidentified.[1] In crucial conditions, employing a singular, broad-spectrum drug with both antibacterial and antifungal characteristics may provide significant therapeutic benefits. Conventional antibiotic discovery methodologies, which frequently depend on natural products or single-target small compounds, have failed to keep up with this escalating threat. The necessity for new antimicrobial medicines exhibiting broad-spectrum efficacy, innovative modes of action, and distinct mechanisms of action has become critical.[2] The construction of hybrid compounds that integrate two or more physiologically active scaffolds into a single chemical entity presents a tempting strategy. These hybrids possess the potential to demonstrate increased biological activity, superior target

selectivity, and enhanced pharmacokinetic characteristics, while engaging several biological targets.[3]

Sulfonamides are among the first synthetic antibacterial drugs, functioning by blocking dihydropteroate synthase in bacterial folate production. They function as carbonic anhydrase inhibitors, facilitating anti-inflammatory and diuretic actions. Structural changes of benzenesulfonamides have produced compounds exhibiting broad-spectrum antibacterial and antifungal efficacy.[4-7]

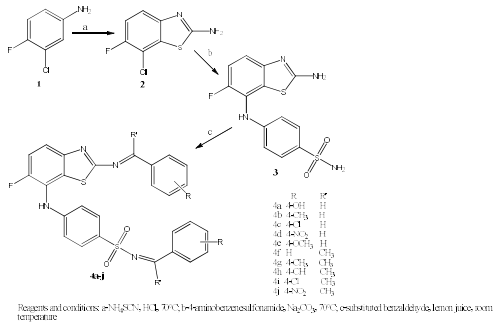
Benzothiazoles are heterocyclic compounds exhibiting a range of biological actions, such as anti-inflammatory, antibacterial, anticancer, and antiviral properties.[8-12] Their function is ascribed to the electron-dense heteroaromatic system, which engages with biological targets including enzymes and receptors. Numerous benzothiazole-derived pharmaceuticals and experimental compounds have been documented for anti-inflammatory and antibacterial purposes.

Conjugating benzenesulfonamide with benzothiazole amalgamates two bioactive entities, potentially augmenting efficacy and specificity. Research has shown that benzothiazole–sulfonamide compounds had considerable anti-inflammatory properties in vivo, diminishing edema and inflammatory indicators.[13] These hybrids demonstrate antibacterial activity against both Gram-positive and Gram-negative bacteria, in addition to fungus, indicating extensive therapeutic potential.[14]

Results and Discussion

Synthesis and characterization

The benzothiazole–sulfonamide conjugates (4a–4j) were designed with the aim of integrating two well-established bioactive heterocycles into a single molecular framework. The synthetic strategy was formulated to enable efficient access to structural diversity while maintaining simplicity and scalability using previously reported methods (Scheme 1).



Scheme 1.

The synthesis started with the formation of thioamide derivative (benzothiazole) from 3-chloro-4-fluoroaniline (1). The $–NH_2$ group of the aniline reacts with thiocyanate under acidic conditions, forming a thioamide ($-CSNH_2$) functionality. Protonation of thiocyanate generates isothiocyanic acid, which couples with the amine to yield the thioamide (2). In the second step, nucleophilic substitution occurs linking the benzoxazole moiety with the sulfonamide group leading to the formation of molecule containing both sulfonamide and benzoxazole moieties (3). The base (Na_2CO_3) deprotonates the sulfonamide, enhancing nucleophilicity for condensation. In the last step, condensation between the $–NH_2$ group of the sulfonamide/benzoxazole and the carbonyl group of aldehyde/ketone forms Schiff bases (–C=N–). Acid catalysis (citric acid in lemon juice) facilitates imine formation by activating the carbonyl group.

The final compounds were obtained in yield of 70 % to 74% as crystalline solids. Structural confirmation of the synthesized compounds was achieved using a combination of ^1H NMR spectroscopy and mass spectrometry (EI-MS), and elemental analysis.

Antimicrobial evaluation

Subsequent to the successful synthesis and structural validation of compounds 4a–4j, their antibacterial efficacy was assessed against a varied array of harmful microbes. The screening included both bacterial and fungal strains, comprising clinically relevant Gram-positive (*S. aureus, B. subtilis*) and Gram-negative (*E. coli, P. aeruginosa*) bacteria, together with fungal

species (*A. niger, C. albicans*). The objective was to evaluate both broad-spectrum efficacy and compound-specific selectivity.[15] The Kirby–Bauer disc diffusion assay is utilized to ascertain zones of inhibition as an in vitro approach for antimicrobial evaluation. Each test chemical was assessed at a constant concentration of 1 mg mL^{-1} in the disc assay. Azithromycin and ketoconazole were used as standard controls for antibacterial and antifungal activities, respectively. Although many investigations have indicated minimal antibacterial effects of azole antifungals such as ketoconazole, their incorporation in this study functions as a widely recognized standard to authenticate the antifungal test.[16] Consequently, their efficacy against bacterial strains was deemed 'Not Applicable' (NA) for the direct comparison objectives of this study. All experiments were conducted in triplicate to guarantee reproducibility, and the findings are encapsulated in Table 1.

Table 1. Zone of inhibition data of 4a-4j

	Gram negative		Gram positive		Fungus	
	E. coli	*S. aureus*	*B. subtilis*	*P. aeuroginosa*	*A. niger*	*C. albicans*
4a	7.67 ± 0.577	7.67 ± 0.577	8.67 ± 0.577	8.67 ± 0.577	7.67 ± 0.577	7.67 ± 0.577
4b	10.33 ± 0.577	11.33 ± 0.577	12.00 ± 0.000	12.33 ± 0.577	9.67 ± 0.577	10.33 ± 0.577
4c	13.33 ± 1.528	14.00 ± 1.000	14.00 ± 1.732	14.00 ± 1.732	14.00 ± 1.000	14.33 ± 0.577
4d	16.33	15.33	15.67	16.33	15 ±	15.67 ± 1.155
4e	8.67 ± 0.577	7.67 ± 0.577	8.67 ± 0.577	8.67 ± 0.577	7.67 ± 0.577	7.67 ± 0.577
4f	11.67 ± 0.577	12.00 ± 0.000	10.67 ± 0.577	11.67 ± 0.577	10.67 ± 0.577	10.00 ± 0.000
4g	8.67 ± 0.577	9.00 ± 0.000	7.67 ± 0.577	8.00 ± 0.000	7.00 ± 0.000	7.00 ± 0.000
4h	NZ	NZ	7.67 ± 0.577	7.67 ± 0.577	NZ	NZ
4i	12.67 ± 0.577	13.67 ± 0.577	11.67 ± 0.577	12.00 ± 0.000	11.67 ± 0.577	11.67 ± 0.577
4j	12.67 ± 0.577	13.67 ± 0.577	13.00 ± 0.000	12.67 ± 0.577	12.67 ± 0.577	12.67 ± 0.577
Azithromycin	17.67 ± 0.577	18.00 ± 0.000	18.00 ± 0.000	17.67 ± 0.577	NA	NA
Ketoconazole	NA	NA	NA	NA	17.67 ± 0.577	17.67 ± 0.577

NA-not applicable; NZ-no zone; results are the mean of triplicate analysis

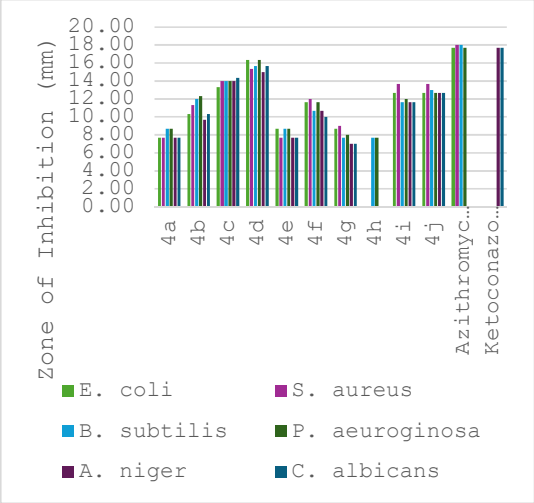


Figure 1. Zone of inhibition of benzothiazole-sulfonamide conjugates (4a-4j) and standard drugs against bacteria and fungi

***In silico* studies**

The ADME (Absorption, Distribution, Metabolism, and Elimination) properties and drug-likeness of compounds 4a-4j were assessed utilizing the SwissADME web application. ADME offers essential insights into the pharmacokinetic characteristics and biological features of the compounds. An effective compound must be properly disseminated, digested gradually, and excreted safely. If ADME deterioration is suboptimal, these findings are likely to be erroneous.[17] Lipinski's Rule of Five is commonly employed to evaluate drug-like characteristics and ascertain the drug-likeness of a prospective molecule. As per these criteria, a compound must possess: fewer than 5 hydrogen bond donors, fewer than 10 hydrogen bond acceptors, a lipophilicity coefficient (LogP) below 5, a molar refractive index ranging from 40 to 130, and a molecular weight under 500 daltons. Compounds satisfying a minimum of two of these criteria exhibit elevated drug-likeness, whereas those fulfilling less than two criteria exhibit diminished drug-likeness.[18] The physicochemical and lipophilic characteristics of the produced molecule are presented in Table 2. Among the produced compounds, compound 4a was determined to satisfy four of Lipinski's rules. All remaining compounds contravened two criteria: molecular weight (500 daltons) and molar refractive index (40–130). Compounds exhibiting positive LogP values are lipophilic, whereas those with negative values are not. LogP values indicate hydrophilicity.[19] The chemicals examined in the study had LogP values ranging from 4.75 to 7.48, signifying their lipophilic nature. Lipophilic compounds readily traverse cell membranes and dissolve in lipids, enhancing bioavailability. Alongside Lipinski's guidelines, a drug's topological polar surface area (TPSA) serves as a significant pharmacokinetic factor. Compounds exhibiting TPSA values under 140 Å² often demonstrate favourable oral bioavailability.[20] The TPSA values of the compounds produced in this investigation ranged from 120.40 to 212.04 Å², indicating their potential as viable therapeutic candidates.

Table 2. *In silico* predicted physicochemical features of 4a-4j

	Consensus Log $P_{o/w}$	MW (g mol-1)	NRbond	HAbond	HDbond	MR	TPSA (Å²)	BS
4a	5.4	546.59	7	8	3	148.13	160.86	0.55
4b	6.71	542.65	7	6	1	154.02	120.4	0.17
4c	7.11	583.48	7	6	1	154.1	120.4	0.17

4d	4.75	604.59	9	10	1	161.73	212.04	0.17
4e	5.99	574.65	9	8	1	157.07	138.86	0.17
4f	6.52	542.65	7	6	1	153.7	120.4	0.17
4g	7.15	570.70	7	6	1	163.63	120.4	0.17
4h	5.74	574.65	7	8	3	157.74	160.86	0.17
4i	7.48	611.54	7	6	1	163.72	120.4	0.17
4j	5.06	632.64	9	10	1	171.34	212.04	0.17

MW- molecular weight; R bond- rotational bonds; HA- hydrogen acceptor; HD- hydrogen donor; MR- molar refractivity; TPSA- topological polar surface area

Experimental

General Information

All chemicals and reagents were acquired from commercial providers (CDH, Loba Chemie, and Avra) and utilized without additional purification. Analytical grade organic solvents (ethanol, methanol, chloroform, ethyl acetate, hexane) were utilized. Reactions were seen via thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} aluminium plates, utilizing UV light (254/365 nm) for visualization. The melting points were ascertained utilizing a computerized melting point instrument and are uncorrected. ^{1}H NMR spectra were obtained using a Bruker Avance III 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6, with chemical shifts (δ) expressed in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal reference. Mass spectra were obtained via electron ionization (EI-MS) on an Agilent mass spectrometer.[21]

Synthesis and characterization of compounds

Synthesis of 7-chloro-6-fluorobenzo[d]thiazol-2-amine (2). To a stirred solution of ammonium thiocyanate (0.025 mol) in ethanol (10 mL) was added 3-chloro-4-fluoroaniline (0.025 mol) and 2-3 drops of concentrated HCl. The reaction flask was attached to reflux condenser and the reaction was heated at 70-80°C for 7-8 h. The reaction was monitored by TLC for completion. The resulting mixture was cooled in an ice-bath (15°C), diluted with water (10mL) and neutralized with 5% aqueous NaOH solution. The resultant solid precipitated was recrystallized from hot ethanol and dried.[22] Yield: 81%.

Synthesis of 4-((2-amino-6-fluorobenzo[d]thiazol-7-yl)amino)benzenesulfonamide (3). In a flat-bottom stoppered flask, sodium carbonate (0.005 mol) and 4-aminobenzenesulfonamide (0.001 mol) were added in methanol (10 ml). To this mixture, 7-chloro-6-fluorobenzo[d]thiazol-2-amine (2) (0.001 mol) was slowly added. The flask was then attached with a reflux condenser, and the contents were refluxed at 70–80°C for 12 hours to obtain the solid

product. The product was recrystallized using ethanol.[23] Yield: 74%.

General procedure for the synthesis of benzothiazole–sulfonamide hybrids (4a–4j). Appropriate benzaldehyde/acetophenone (0.02 mol) was dissolved in a small amount of absolute ethanol (5 mL) in a beaker. This solution was gradually poured into a beaker containing a solution of 4-((2-amino-6-fluorobenzo[d]thiazol-7-yl)amino)benzenesulfonamide (3) (0.01 mol) in ethanol, with constant stirring. While stirring the mixture at room temperature, freshly squeezed lemon juice (2 mL) was added to the reaction. Stirring was continued at room temperature and the reaction progress was monitored by TLC. The product obtained was filtered, washed with water, and recrystallized using DMSO.[24]

(Z)-4-((6-fluoro-2-((E)-(4-hydroxybenzylidene)amino)benzo[d]thiazol-7-yl)amino)-N-(4-hydroxybenzylidene)benzenesulfonamide (4a). Yield: 72%; mp: 157-159 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.91 (s, 1H), 8.83 (s, 1H), 8.56 (d, 1H), 7.21–7.82 (m, 14H), 7.37 (s, 2H). MS (EI, 70 eV): m/z: 546.05 (M+). Analysis calcd. For $C_{27}H_{19}FN_4O_4S_2$: C, 59.33; H, 3.50; F, 3.48; N, 10.25; O, 11.71; S, 11.73. Found: C, 58.97; H, 3.31; N, 10.10.

(Z)-4-((6-fluoro-2-((E)-(4-methylbenzylidene)amino)benzo[d]thiazol-7-yl)amino)-N-(4-methylbenzylidene)benzenesulfonamide (4b). Yield: 74%; mp: 102-104 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 8.90 (s, 1H), 8.81 (s, 1H), 8.56 (d, 1H), 7.21–7.82 (m, 14H), 2.31 (s, 6H). MS (EI, 70 eV): m/z: 542.10 (M+). Analysis calcd. For $C_{29}H_{23}FN_4O_2S_2$: C, 64.19; H, 4.27; F, 3.50; N, 10.32; O, 5.90; S, 11.82. Found: C, 63.89; H, 4.15; N, 10.22.

(Z)-N-(4-chlorobenzylidene)-4-((2-((E)-(4-chlorobenzylidene)amino)-6-fluorobenzo[d]thiazol-7-yl)amino)benzenesulfonamide (4c). Yield: 70%; mp: 189-191 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 8.90 (s, 1H), 8.83 (s, 1H), 8.56 (d, 1H), 7.21–7.85 (m, 14H). MS (EI, 70 eV): m/z: 582.05 (M+, 100). Analysis calcd. For $C_{27}H_{17}Cl_2FN_4O_2S_2$: C, 55.58; H, 2.94; Cl, 12.15; F, 3.26; N, 9.60; O, 5.48; S, 10.99. Found: C, 55.21; H, 2.67; N, 9.45.

(Z)-4-((6-fluoro-2-((E)-(4-nitrobenzylidene)amino)benzo[d]thiazol-7-yl)amino)-N-(4-nitrobenzylidene)benzenesulfonamide (4d). Yield: 70%; mp: 190-192 °C. ^{1}H NMR (400 MHz, DMSO-d6): 8.91 (s, 1H), 8.84 (s, 1H), 8.56 (d, 1H), 7.21–8.31 (m, 14H), 2.31 (s, 6H). MS (EI, 70 eV): m/z: 604.01 (M+). Analysis calcd. For $C_{27}H_{17}FN_6O_6S_2$: C, 53.64; H, 2.83; F, 3.14; N, 13.90; O, 15.88; S, 10.61. Found: C, 53.25; H, 2.57; N, 13.61.

(Z)-4-((6-fluoro-2-((E)-(3-methoxybenzylidene)amino)benzo[d]thiazol-7-yl)amino)-N-(4-methoxybenzylidene)benzenesulfonamide (4e). Yield: 74%; mp: 104-106 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 8.85 (s, 1H), 8.83 (s, 1H), 8.56 (d, 1H), 7.21–7.82 (m, 14H), 3.79 (d, 6H). MS (EI, 70 eV): m/z: 574.10 (M+). Analysis calcd. For $C_{29}H_{23}FN_4O_4S_2$: C, 60.61; H, 4.03; F, 3.31; N, 9.75; O, 11.14; S, 11.16. Found: C, 60.43; H, 3.88; N, 9.58.

(Z)-4-((6-fluoro-2-((E)-(1-phenylethylidene)amino)benzo[d]thiazol-7-yl)amino)-N-(1-phenylethylidene)benzenesulfonamide (4f). Yield: 71%; mp: 197-199 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 8.73 (d, 1H), 7.22–7.84 (m, 16H), 2.50 (s, 6H). MS (EI, 70 eV): m/z: 542.10 (M+). Analysis calcd. For $C_{29}H_{23}FN_4O_2S_2$: C, 64.19; H, 4.27; F, 3.50; N, 10.32; O, 5.90; S, 11.82. Found: C, 63.96; H, 4.02; N, 10.13.

(Z)-4-((6-fluoro-2-((E)-(1-(p-tolyl)ethylidene)amino)benzo[d]thiazol-7-yl)amino)-N-(1-(p-tolyl)ethylidene)benzenesulfonamide (4g). Yield: 74%; mp: 120-122 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 8.73 (d, 1H), 7.22–7.84 (m, 14H), 2.50 (s, 6H), 2.31 (t, 6H). MS (EI, 70 eV): m/z: 570.15 (M+). Analysis calcd. For $C_{31}H_{27}FN_4O_2S_2$: C, 65.24; H, 4.77; F, 3.33; N, 9.82; O, 5.61; S, 11.24. Found: C, 64.96; H, 4.51; N, 9.59.

(Z)-4-((6-fluoro-2-((E)-(1-(4-hydroxyphenyl)ethylidene)amino)benzo[d]thiazol-7-yl)amino)-N-(1-(4-hydroxyphenyl)ethylidene)benzenesulfonamide (4h). Yield: 70%; mp: 187-189 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 8.73 (d, 1H), 7.22–7.84 (m, 14H), 7.42 (s, 2H), 2.50 (s, 6H). MS (EI, 70 eV): m/z: 574.10 (M+). Analysis calcd. For $C_{29}H_{23}FN_4O_4S_2$: C, 60.61; H, 4.03; F, 3.31; N, 9.75; O, 11.14; S, 11.16. Found: C, 60.39; H, 3.87; N, 9.54.

(Z)-N-(1-(4-chlorophenyl)ethylidene)-4-((2-((E)-(1-(4-chlorophenyl)ethylidene)amino)-6-fluorobenzo[d]thiazol-7-yl)amino)benzenesulfonamide (4i). Yield: 73%; mp: 172-174 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 8.73 (d, 1H), 7.22–7.84 (m, 14H), 2.50 (s, 6H). MS (EI, 70 eV): m/z: 610.5 (M+). Analysis calcd. For $C_{29}H_{21}Cl_2FN_4O_2S_2$: C, 56.96; H, 3.46; Cl, 11.59; F, 3.11; N, 9.16; O, 5.23; S, 10.49. Found: C, 56.71; H, 3.29; N, 8.94.

(Z)-4-((6-fluoro-2-((E)-(1-(4-nitrophenyl)ethylidene)amino)benzo[d]thiazol-7-yl)amino)-N-(1-(4-nitrophenyl)ethylidene)benzenesulfonamide (4j). Yield: 71%; mp: 169-171 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 8.73 (d, 1H), 7.22–8.13 (m, 14H), 2.50 (s, 6H). MS (EI, 70 eV): m/z: 632.1 (M+). Analysis calcd. For $C_{29}H_{21}FN_6O_6S_2$: C, 55.06; H, 3.35; F, 3.00; N, 13.28; O, 15.17; S, 10.14. Found: C, 54.78; H, 3.14; N, 12.96.

Antimicrobial Studies

The antimicrobial activity of derivatives 4a–4f was evaluated against a panel of bacterial and fungal strains using standard in vitro methods.

Disk diffusion assay. The preliminary antimicrobial assessment was performed with the Kirby–Bauer disc diffusion technique.[25] The test organisms comprised Gram-positive bacteria (*S. aureus* MTCC 2408, *B. subtilis* MTCC 2048), Gram-negative bacteria (*E. coli* MTCC 2412, *P. aeruginosa* MTCC 2081), and fungal strains (*A. niger* MTCC 281, *C. albicans* MTCC 3147).

Recent overnight cultures were calibrated to the 0.5 McFarland standard (about 10^8 CFU mL^{-1}) and evenly inoculated onto Mueller–Hinton agar (for bacteria) or Sabouraud dextrose agar (for fungi). Sterile filter paper discs (6 mm) were saturated with 10 µL of each test chemical (1 mg mL^{-1} in DMSO), dried, and subsequently positioned onto the infected plates. DMSO functioned as a negative control, and azithromycin (10 µg $disc^{-1}$) and ketoconazole (10 µg $disc^{-1}$) acted as conventional positive controls for bacteria and fungi, respectively.

***In silico* ADME studies**

SwissADME web-based tool was used to evaluate the pharmacokinetic properties of the compounds 4a-4j. The 2D structures of the compounds were sketched using ChemDraw Ultra 12.0 and converted to SMILES notation. The SMILES string was uploaded on the server and the physicochemical and pharmacokinetic parameters were evaluated. Drug likeliness of the compounds was evaluated based on the Lipinski's Rule of Five.

Conclusions

The present work successfully demonstrates the synthesis, characterization, and biological evaluation of novel sulfonamide–benzothiazole conjugates. The hybridization strategy effectively combined two pharmacophores,

resulting in derivatives with notable antibacterial and antifungal activity. Compounds 4c, 4d, 4i, and 4j emerged as particularly potent, showing broad-spectrum inhibition against both bacterial and fungal strains. In silico ADME analysis further supported their potential as drug candidates, with favorable lipophilicity and TPSA values contributing to predicted bioavailability. While certain physicochemical parameters exceeded Lipinski's thresholds, the overall pharmacokinetic profile suggests that structural optimization could enhance drug-likeness without compromising activity. Collectively, these results establish sulfonamide–benzothiazole conjugates as promising leads for future antimicrobial drug development, addressing the pressing need for agents capable of combating resistant and polymicrobial infections.

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