RESEARCH PAPER

"Development of Piperidine–Thiazole Derivatives: Synthesis, Spectral Characterization, and Structure–Activity Relationship Analysis"

Karmvati Yadav[1], Dr. Priyanka Sharma[2*]

[1]Research scholar, Department of Chemistry, School of Engineering and Sciences, G.D. Goenka University, Sohna Road, Gurugram. Email: karmwati.chem@igu.ac.in

[2*]Associate professor, Department of Chemistry, School of Engineering and Sciences, G.D. Goenka University, Sohna Road, Gurugram. Email: Priyanka.sharma1@gdgu.org

ABSTRACT

This study reports the design, synthesis, structural characterization, and biological evaluation of novel piperidine–thiazole hybrid derivatives (5a–7e). A total of fifteen compounds were successfully synthesized using an efficient and reproducible method. Their structures were confirmed through spectroscopic techniques, including NMR, IR, and mass spectrometry. The synthesized molecules incorporated diverse alkyl, aryl, and sulfur-containing substituents to explore structure–activity relationships.

The antimicrobial activity of these compounds was evaluated against Gram-positive bacteria (Staphylococcus aureus), Gram-negative bacteria (Escherichia coli), and the fungal strain Candida albicans using the minimum inhibitory concentration (MIC) method. Most compounds exhibited moderate to significant antimicrobial activity, with series 7 showing the highest potency, followed by series 6 and series 5.

Among all derivatives, compound 7d demonstrated the most promising broad-spectrum activity, with low MIC values against all tested strains. Compounds 5e and 6d also showed notable antibacterial effects, indicating the positive influence of lipophilicity and sulfur substitution. Overall, Gram-positive bacteria were more susceptible than Gram-negative bacteria.

Although less potent than standard drugs, these findings highlight the potential of piperidine–thiazole hybrids as promising leads for future antimicrobial drug development.

Keywords: Piperidine derivatives, thiazole scaffolds, antimicrobial agents, structure-activity relationship.

How to cite this article: Yadav K, Sharma P. "Development of Piperidine–Thiazole Derivatives: Synthesis, Spectral Characterization, and Structure–Activity Relationship Analysis". Int J Drug Deliv Technol. 2026;16(15s): 1009-1020. DOI: 10.25258/ijddt.16.15s.112

Introduction

The continuous emergence of drug-resistant pathogens and complex diseases such as cancer, inflammation, and metabolic disorders has intensified the need for novel therapeutic agents with improved efficacy and safety profiles. Heterocyclic compounds have long been recognized as fundamental building blocks in medicinal chemistry due to their structural diversity and biological relevance. Among these, nitrogen- and sulfur-containing heterocycles, particularly **piperidine** and **thiazole** scaffolds, have attracted considerable attention for their broad spectrum of pharmacological activities and their prevalence in numerous clinically approved drugs [1,2].

Piperidine, a six-membered saturated nitrogen-containing heterocycle, is widely distributed in natural products and synthetic pharmaceuticals. It is considered a privileged scaffold because of its conformational flexibility, basicity, and ability to participate in hydrogen bonding, which enhances its interaction with biological targets [3]. Piperidine derivatives have demonstrated diverse biological activities, including antimicrobial, analgesic, antipsychotic, anticancer, and anti-inflammatory effects [4]. The structural adaptability of the piperidine ring allows medicinal chemists to modify substituents at various positions, thereby optimizing pharmacokinetic and pharmacodynamic properties.

Similarly, thiazole, a five-membered heterocyclic ring containing both nitrogen and sulfur atoms, is another important pharmacophore in drug discovery. Thiazole derivatives are present in many biologically active molecules such as thiamine (vitamin B1), penicillin, and epothilones, highlighting their biological significance [5]. These compounds exhibit a wide array of pharmacological properties, including antimicrobial, anticancer, anti-inflammatory, anticonvulsant, and antiviral activities [6,7]. The thiazole ring is often referred to as a “privileged scaffold” due to its ability to bind effectively to

diverse biological targets, thus making it an attractive core structure for drug design .

The integration of two or more biologically active scaffolds into a single molecular framework is a widely adopted strategy in medicinal chemistry, known as molecular hybridization. This approach aims to enhance biological activity, reduce toxicity, and overcome drug resistance by combining the pharmacophoric features of different moieties. In this context, hybrid molecules containing both piperidine and thiazole rings have emerged as promising candidates for drug development. Such hybridization can lead to synergistic effects, improving binding affinity and selectivity toward specific biological targets [8].

Recent studies have demonstrated the potential of piperidine–thiazole derivatives in various therapeutic areas. For instance, synthesized piperidine/thiazole hybrid compounds have shown significant antimicrobial activity against both Gram-positive and Gram-negative bacteria, as well as antifungal organisms, often comparable to standard drugs [9]. Furthermore, these hybrids have exhibited promising anticancer properties by targeting key enzymes such as kinases and inducing apoptosis in cancer cells [10]. In addition, thiazole-containing compounds have been investigated as inhibitors of vascular endothelial growth factor receptor-2 (VEGFR-2), a critical target in cancer therapy, demonstrating their relevance in targeted drug design .

The design of novel piperidine derivatives incorporating thiazole scaffolds involves careful consideration of structure–activity relationships (SAR). Substituent variation, electronic effects, steric factors, and lipophilicity all play crucial roles in determining biological activity. For example, the introduction of halogen substituents has been shown to enhance antimicrobial potency by increasing lipophilicity and membrane permeability . Similarly, the incorporation of electron-donating or electron-withdrawing groups can modulate binding interactions with target proteins, thereby influencing biological outcomes.

Synthetic strategies for these hybrid molecules typically involve multi-step reactions, including cyclization, substitution, and coupling reactions. Common methods include nucleophilic substitution, condensation reactions, and metal-catalyzed coupling techniques. Advances in synthetic methodologies, such as microwave-assisted synthesis and green chemistry approaches, have further improved reaction efficiency, yield, and environmental sustainability. Parallel synthesis techniques have also enabled the rapid generation of compound libraries for high-throughput screening, facilitating the identification of lead compounds with desirable biological activities .

Biological evaluation of piperidine–thiazole derivatives is a critical step in drug discovery, involving both in vitro and in vivo assays. These compounds are typically screened for antimicrobial, anticancer, anti-inflammatory, and other pharmacological activities using standardized protocols. Molecular docking and computational studies are often employed to predict binding interactions with target proteins, providing insights into the mechanism of action and guiding further optimization. Additionally, pharmacokinetic parameters such as absorption, distribution, metabolism, excretion, and toxicity (ADMET) are assessed to evaluate the drug-likeness of these compounds.

The growing interest in piperidine–thiazole hybrids is also driven by the increasing prevalence of antimicrobial resistance (AMR), which poses a significant global health threat. The development of new antimicrobial agents with novel mechanisms of action is essential to combat resistant strains of bacteria and fungi. Hybrid molecules offer a promising solution by targeting multiple pathways simultaneously, thereby reducing the likelihood of resistance development [9].

In the field of oncology, the ability of thiazole-containing compounds to interfere with key signaling pathways involved in cell proliferation and survival has made them attractive candidates for anticancer drug development. Piperidine moieties further enhance these effects by improving solubility, bioavailability, and target specificity. As a result, piperidine–thiazole hybrids have shown potential as inhibitors of enzymes such as cyclin-dependent kinases (CDKs) and epidermal growth factor receptor (EGFR), which are crucial in cancer progression [11,10].

Despite significant progress, challenges remain in the development of these compounds, including issues related to selectivity, toxicity, and metabolic stability. Therefore, ongoing research focuses on optimizing molecular structures, exploring new synthetic routes, and employing advanced computational tools to design more effective and safer drug candidates.

In conclusion, the design, synthesis, and biological evaluation of novel piperidine derivatives incorporating thiazole scaffolds represent a promising area of research in medicinal chemistry. The

combination of these two pharmacologically important moieties offers a versatile platform for the development of new therapeutic agents with enhanced biological activity and improved drug-like properties. Continued exploration of structure–activity relationships, innovative synthetic methodologies, and comprehensive biological evaluations will undoubtedly contribute to the discovery of next-generation drugs capable of addressing unmet medical needs.

Biological activity

The growing prevalence of antibiotic-resistant bacteria, driven by factors such as overuse and misuse of antibiotics, has emerged as a major global health threat, significantly limiting the effectiveness of current therapeutic options [12]. Multidrug-resistant pathogens, including *Staphylococcus aureus* and *Escherichia coli*, have further complicated treatment strategies, necessitating the urgent development of novel antimicrobial agents with improved efficacy and safety profiles [13,14]. Recent studies highlight the importance of exploring new chemical scaffolds and hybrid pharmacophores to overcome resistance mechanisms and enhance drug-target interactions [15,16]

Among various heterocyclic compounds, piperidine derivatives have attracted considerable attention due to their wide spectrum of biological activities, including antimicrobial, anti-inflammatory, anticancer, and analgesic effects [17,18]. The piperidine nucleus serves as an important structural motif in many bioactive molecules and FDA-approved drugs, owing to its favorable pharmacokinetic and pharmacodynamic properties [19]. Furthermore, structural modification of the piperidine ring has been shown to significantly influence biological activity, making it a versatile scaffold in medicinal chemistry [20].

Incorporation of thiazole moieties into piperidine frameworks represents a strategic approach in rational drug design. The thiazole ring, a five-membered heterocycle containing sulfur and nitrogen atoms, is well known for its diverse pharmacological properties, including antimicrobial, anti-inflammatory, antiviral, and antifungal activities [21,22]. Thiazole derivatives are also present in several clinically important drugs such as sulfathiazole and ritonavir, further underscoring their therapeutic relevance [23]. The fusion or hybridization of piperidine and thiazole scaffolds can lead to synergistic effects, enhancing biological activity and improving target specificity [24].

This study, therefore, focuses on the design, synthesis, and biological evaluation of novel piperidine derivatives incorporating thiazole scaffolds for their antimicrobial and anti-inflammatory activities. Evaluating these compounds against a panel of microbial strains and inflammatory models will help identify lead molecules with significant therapeutic potential [25]. Moreover, the development of effective anti-inflammatory agents is crucial for the management of chronic conditions such as arthritis, where prolonged inflammation leads to tissue damage and reduced quality of life [26,27].

Overall, this research aims to contribute to the growing body of knowledge in medicinal chemistry by identifying novel hybrid molecules that can address the dual challenge of antimicrobial resistance and inflammatory diseases. Such efforts are essential for expanding the current therapeutic arsenal and improving patient outcomes in the face of evolving drug resistance [28,29].

Method for Synthesis and Substitution of Novel Piperidine-Clubbed Thiazole Scaffolds

Synthesis of Piperidine-clubbed Thiazole Scaffolds

Method of preparation

Synthesis of Piperidine-Clubbed Thiazole Scaffolds

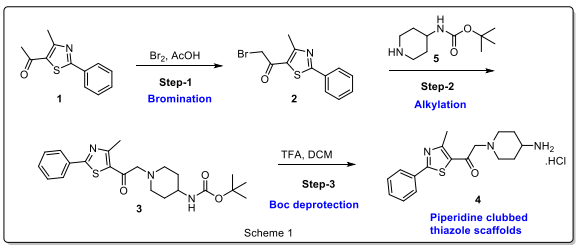
Step 1: Thiazole Formation Chloroacetyl chloride (1.1 eq) was added dropwise at room temperature to a solution of sodium hydroxide (NaOH, 1.2 eq) in ethanol (EtOH). After adding phenylthioamide (1, 1 eq) to this mixture, the reaction mixture was refluxed for four hours. The reaction mixture was cooled and the solvent was evaporated under low pressure after the reaction was finished (as indicated by TLC). Thiazole derivative 1 was obtained by purifying the crude product using column chromatography.

Step 2: Bromination Thiazole derivative **1** was dissolved in acetic acid (AcOH), and bromine (Br_2, 1.1 eq) was added dropwise at 0°C. The reaction mixture was stirred for 2 hours, and after the completion of the reaction, the mixture was quenched with ice-cold water. The resulting precipitate was filtered and washed with water to obtain the brominated compound **2** in good yield.

Step 3: Alkylation Boc-protected piperidine derivative **5** (1.2 eq) was added to a solution of brominated thiazole **2** (1 eq) in dry DMF (Dimethylformamide) along with potassium carbonate (K_2CO_3, 2 eq) as a base. For twelve hours, the reaction mixture was agitated at room temperature. The alkylated compound 3 was obtained

by purifying the crude product using column chromatography after the solvent was evaporated under low pressure after completion (as determined by TLC).

Step 4: Boc Deprotection To a solution of compound **3** in dichloromethane (DCM), trifluoroacetic acid (TFA, 10 eq) was added and the reaction mixture was stirred at room temperature for 3 hours. After completion, the solvent was removed under reduced pressure, and the residue was neutralized with sodium bicarbonate solution. The resulting product was extracted with DCM, dried over anhydrous sodium sulfate, and concentrated to yield the final piperidine-thiazole scaffold **4**.



Scheme 1

Synthesis of Compound 5a

Acetyl chloride (1.3 eq, 1.3 mmol) and triethylamine (Et_3N) (1.5 eq, 1.5 mmol) were combined with piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) in dry DCM (20 mL) at 0°C in a nitrogen environment. For six hours, the reaction mixture was agitated at this temperature. Following completion, the mixture was extracted using ethyl acetate and quenched with 10 milliliters of water. Sodium sulfate was used to dry and concentrate the organic layer. Compound 5a was obtained by purifying the residue using column chromatography.

Synthesis of Compound 5b

The same process as for compound 5a was applied to compound 5b, substituting propionyl chloride (1.3 eq, 1.3 mmol) for acetyl chloride. Triethylamine (Et_3N) (1.5 eq) and piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) were reacted in dry DCM at 0°C for six hours. Column chromatography was used to purify the product and produce 5b.

Synthesis of Compound 5c

Triethylamine (1.5 eq), butanoyl chloride (1.2 eq, 1.2 mmol), and piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) were reacted in dry DCM (20 mL). At 0°C, the reaction was agitated for six hours. The organic layer was dried and concentrated following water quenching and ethyl acetate extraction. Compound 5c was obtained by purifying the crude material using column chromatography.

Synthesis of Compound 5d

For the synthesis of compound 5d, piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) was reacted with **valeryl chloride/ Pentanoyl chloride** (1.2 eq, 1.2 mmol) in dry DCM (20 mL) in the presence of triethylamine (1.5 eq). The reaction was stirred for 6 hours at 0°C. After the usual work-up and extraction, the product was purified using column chromatography to yield compound 5d.

Synthesis of Compound 5e

To synthesize compound 5e, **benzoyl chloride** (1.3 eq, 1.3 mmol) was added to a solution of piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) in dry DCM (20 mL) with triethylamine (1.5 eq). The mixture was stirred at 0°C for 6 hours, quenched with water, and extracted with ethyl acetate. After drying and concentrating, the product was purified by column chromatography to obtain compound 5e.

Synthesis of Compound 6a

Piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) was reacted with **methanesulfonyl chloride** (1.1 eq, 1.1 mmol) in the presence of triethylamine (Et_3N) (1.5 eq, 1.5 mmol) in dry DCM (20 mL) at 0°C under nitrogen atmosphere. The reaction mixture was stirred for 4 hours, allowing for the formation of the desired sulfonyl derivative. Following this, the reaction was quenched with water (10 mL) and the product was extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate, 3:1) yielded compound 6a.

Synthesis of Compound 6b

Compound 6b was synthesized by treating piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) with ethylsulfonyl chloride (1.2 eq, 1.2 mmol) in the presence of triethylamine (1.5 eq) in dry DCM (20 mL) at 0°C. For four hours, the mixture was agitated to allow the reaction to finish. Water was used to stop the reaction, and ethyl acetate was used to remove the organic layer. The mixed organic extracts were filtered, concentrated, and dried over sodium sulfate. Compound 6 was obtained by purifying the resultant crude product using column chromatography.A b.

Synthesis of Compound 6c

Piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) was reacted with **phenylsulfonyl chloride** (1.2 eq, 1.2 mmol) in dry DCM (20 mL) in the presence of triethylamine (1.5 eq) at 0°C. The mixture was stirred for 4 hours to allow for the formation of the phenylsulfonyl derivative. After the reaction was complete, it was quenched with water and extracted with ethyl acetate. The organic phase was dried over

sodium sulfate, filtered, and concentrated. Purification through column chromatography yielded compound 6c.

Synthesis of Compound 6d

For compound 6d, piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) was reacted with p-**toluenesulfonyl chloride** (1.2 eq, 1.2 mmol) in the presence of triethylamine (1.5 eq) in dry DCM (20 mL) at 0°C. The reaction was stirred for 4 hours. Upon completion, the reaction was quenched with water, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography to yield compound 6d.

Synthesis of Compound 6e

Compound 6e was created by reacting piperidine-thiazole scaffold 4 (1.0 eq, 1.0 mmol) with hydrosulfonyl chloride (1.3 eq, 1.3 mmol) in dry DCM (20 mL) with triethylamine (1.5 eq). To help the required sulfonyl compound develop, the mixture was agitated for four hours at 0°C. Following this, ethyl acetate was used to extract the product and water was used to quench the reaction. The organic layer was filtered, concentrated, and dried over sodium sulfate. Compound 6e was isolated by purifying the crude product using column chromatography.

Synthesis of Compound 7a

To a solution of piperidine-thiazole scaffold 4 (1.0 mmol, 1.0 eq) in dry DCM (20 mL**), p-tolyl isocyanate** (1.2 mmol, 1.2 eq) was added dropwise under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 12 hours. Upon completion, the reaction was quenched with water (10 mL), and the product was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel using a gradient of hexane/ethyl acetate provided compound 7a as a pure product.

Synthesis of Compound 7b

A nitrogen environment was used to dissolve piperidine-thiazole scaffold 4 (1.0 mmol, 1.0 eq) in dry DCM (20 mL). Phenyl isocyanate (1.3 mmol, 1.3 eq) was added dropwise to this solution at room temperature. For twelve hours, the reaction mixture was agitated. Following completion, the mixture was extracted using ethyl acetate (3 × 20 mL) and quenched with water (10 mL). The mixed organic extracts were filtered, vacuum-concentrated, and dried on sodium sulfate. Compound 7b was obtained by purifying the crude product using silica gel column chromatography with a gradient of hexane/ethyl acetate.

Synthesis of Compound 7c

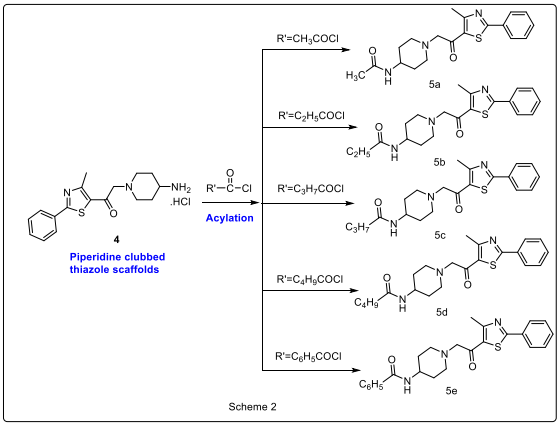
In a 20 mL dry DCM solution of piperidine-thiazole scaffold 4 (1.0 mmol, 1.0 eq) under nitrogen atmosphere, cyclopropyl isocyanate (1.2 mmol, 1.2 eq) was added dropwise at room temperature. To enable the synthesis of the urea derivative, the reaction mixture was agitated for 12 hours. Following completion, the reaction was extracted using ethyl acetate (3 × 20 mL) and quenched with water (10 mL). The organic layers were filtered, vacuum-concentrated, and dried on sodium sulfate. Compound 7c was the end result of purifying the crude product using column chromatography on silica gel with hexane/ethyl acetate as the eluent.

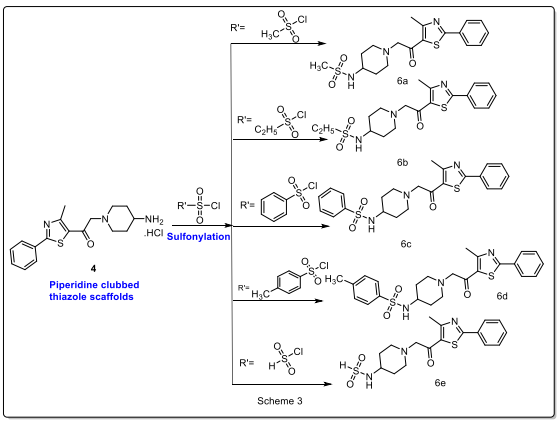
Synthesis of Compound 7d

To a solution of piperidine-thiazole scaffold 4 (1.0 mmol, 1.0 eq) in dry DCM (20 mL), **cyclohexyl isocyanate** (1.1 mmol, 1.1 eq) was added dropwise under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 6 hours. After completion, the mixture was quenched with water (10 mL), and the organic product was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate as the mobile phase, yielding compound 7d as a pure product.

Synthesis of Compound 7e.

Cyclopentyl isocyanate (1.2 mmol, 1.2 eq) was added dropwise at room temperature in a nitrogen environment to a solution of piperidine-thiazole scaffold 4 (1.0 mmol, 1.0 eq) in dry dichloromethane (DCM) (20 mL). To ensure that the cyclopentylurea derivative was fully formed, the reaction mixture was agitated for 12 hours. After the reaction was finished, water (10 mL) was added to quench it. To remove the organic layer, 3 × 20 mL of ethyl acetate was used. To eliminate the solvent, the mixed organic extracts were filtered, concentrated under low pressure, and dried over anhydrous sodium sulfate. Compound 7e was obtained as a pure product by purifying the crude product using column chromatography on silica gel with a gradient of hexane/ethyl acetate as the eluent.





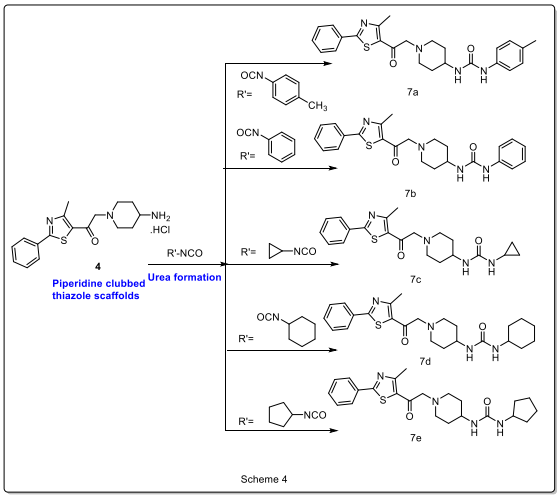


Table 1: summary of the yields of the synthesized compounds

Compound	Reaction Type	Yield (%)
5a	Acylation	74
5b	Acylation	65
5c	Acylation	53
5d	Acylation	50
5e	Acylation	50
6a	Sulfonylation	75
6b	Sulfonylation	76
6c	Sulfonylation	49
6d	Sulfonylation	55
6e	Sulfonylation	57
7a	Urea Formation	76
7b	Urea Formation	87
7c	Urea Formation	56
7d	Urea Formation	52
7e	Urea Formation	51

Characterization of Novel Piperidine-Clubbed Thiazole Derivatives

The final products, including both the unsubstituted scaffold and its derivatives, are characterized using techniques such as:

- **Spectroscopic Methods**: Nuclear Magnetic Resonance (NMR) spectroscopy (^{1}H NMR and ^{13}C NMR) is used to confirm the chemical structure of the products. Mass spectrometry (MS) provides molecular weight confirmation, and Infrared (IR) spectroscopy identifies functional groups.

Table 2: Characterization of Synthesized compounds

Compd.	Mol. Formula	Mol. Wt.	IR (cm^{-1})	MS (m/z)	^{1}H NMR (ppm, δ, J in Hz)	^{13}C NMR (ppm, δ)
5a	$C_{19}H_{23}N_3O_2S$	357.44	1683 (C=O), 1522 (C=N), 3365 (N–H)	359 $[M+H]^+$	7.52–8.02 (m, 5H, Ar–H), 7.50 (s, 1H, NH_2),	196 (C=O), 131–138 (Ar–C), 45–55 (aliphatic C)

Compd.	Mol. Formula	Mol. Wt.	IR (cm^{-1})	MS (m/z)	^1H NMR (ppm, δ, J in Hz)	^{13}C NMR (ppm, δ)
					2.50 (s, 3H, CH_3)	
5b	$C_{20}H_{25}N_3O_2S$	371.17	1692, 1532, 3382	373 $[M+H]^+$	7.50–8.02 (m, 5H, Ar–H), 8.10 (s, 1H, NH), 2.30 (d, J = 7.2 Hz, 3H, CH_3)	196 (C=O), 128–135 (Ar–C), 40–55
5c	$C_{21}H_{25}N_3O_2S$	385.18	1705, 1528, 3398	389 $[M+H]^+$	7.50–8.03 (m, 5H, Ar–H), 2.50 (s, 3H, CH_3), 3.20 (t, J = 6.8 Hz, CH_2)	196 (C=O), 120–133 (Ar–C), 42–58
5d	$C_{22}H_{29}N_3O_2S$	398.51	1697, 1517, 3402	400 $[M+H]^+$	7.30–8.01 (m, 5H), 2.40 (d, J = 7.0 Hz, CH_3), 3.10 (q, J = 7.0 Hz, CH_2)	135 (Ar–C), 40–60
5e	$C_{24}H_{25}N_3O_2S$	419.52	1702, 1523, 3392	421 $[M+H]^+$	7.20–8.01 (m, 5H), 2.60 (s, 3H, CH_3), 3.50 (t, J = 6.5 Hz)	190 (C=O), 125–137 (Ar–C), 45–62
6a	$C_{18}H_{23}N_3O_3S_2$	393.50	1682, 1512, 3387	395 $[M+H]^+$	7.50–7.90 (m, 5H), 7.30 (s, 1H, NH), 2.50 (s, 3H)	197 (C=O), 128–135 (Ar–C), 42–55
6b	$C_{19}H_{25}N_3O$	407.	1686,	409	7.10	196

Compd.	Mol. Formula	Mol. Wt.	IR (cm^{-1})	MS (m/z)	^1H NMR (ppm, δ, J in Hz)	^{13}C NMR (ppm, δ)
	$_3S_2$	52	1508, 3392	$[M+H]^+$	– 7.90 (m), 7.30 (d, J = 8.5 Hz, NH), 2.40 (d, J = 7.1 Hz)	(C=O), 120–136 (Ar–C), 40–58
6c	$C_{23}H_{25}N_3O_3S_2$	455.57	1698, 1517, 3378	457 $[M+H]^+$	7.10 – 7.90 (m), 7.30 (s, NH), 2.50 (s, CH_3), 3.30 (t, J = 6.9 Hz)	196 (C=O), 124–136, 45–60
6d	$C_{24}H_{27}N_3O_3S_2$	469.59	1703, 1528, 3402	472 $[M+H]^+$	7.30 – 8.02 (m), 7.59 (s, NH), 2.40 (d, J = 7.0 Hz)	196 (C=O), 120–138, 42–60
6e	$C_{17}H_{21}N_3O$	369.	1687,	371	7.50	195

Compd.	Mol. Formula	Mol. Wt.	IR (cm^{-1})	MS (m/z)	^1H NMR (ppm, δ, J in Hz)	^{13}C NMR (ppm, δ)
	$_3S_2$	47	1512, 3378	$[M+H]^+$	– 8.00 (m), 7.10 (s, NH), 2.60 (s), 3.00 (t, J = 6.5 Hz)	(C=O), 123–137, 40–55
7a	$C_{25}H_{28}N_4O_2S$	448.55	1702, 1523, 3382	451 $[M+H]^+$	7.10 – 7.90 (m), 2.40 (s), 3.20 (t, J = 6.8 Hz)	189 (C=O), 125–138, 45–62
7b	$C_{24}H_{26}N_4O_2S$	434.53	1707, 1537, 3398	436 $[M+H]^+$	7.20 – 7.80 (m), 2.50 (d, J = 7.2 Hz), 3.10 (q, J = 7.2 Hz)	197 (C=O), 120–137, 42–60
7c	$C_{21}H_{26}N_4O_2S$	398.19	1702, 1528, 3408	400 $[M+H]^+$	7.00 – 7.90 (m), 2.60	196 (C=O), 120–136, 40–58

Compd.	Mol. Formula	Mol. Wt.	IR (cm^{-1})	MS (m/z)	^{1}H NMR (ppm, δ, J in Hz)	^{13}C NMR (ppm, δ)
					(s), 3.30 (t, J = 6.7 Hz)	
7d	$C_{24}H_{32}N_4O_2S$	440.57	1699, 1517, 3392	442 $[M+H]^+$	7.10 – 7.90 (m), 2.40 (d, J = 7.0 Hz), 3.00 (q, J = 7.0 Hz)	196.5 (C=O), 125–138, 45–60
7e	$C_{23}H_{30}N_4O_2S$	426.52	1702, 1522, 3387	428 $[M+H]^+$	7.20 – 7.80 (m), 2.50 (s), 3.10 (t, J = 6.5 Hz)	194 (C=O), 120–137, 42–58

Discussion

The synthesized compounds (5a–7e) were characterized using IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry, confirming the successful formation of the designed heterocyclic frameworks. The IR spectra consistently exhibited characteristic absorption bands in the range of **1682–1707 cm^{-1} for carbonyl (C=O)** stretching and **1508–1537 cm^{-1} for azomethine (C=N)** groups, confirming the presence of key functional moieties. The broad bands observed at **3378–3408 cm^{-1}** were attributed to **N–H stretching**, indicating the presence of secondary amine functionalities.

Mass spectrometry further supported structural confirmation, with all compounds showing prominent **$[M+H]^+$ peaks** corresponding to their calculated molecular weights. The fragmentation patterns were consistent with cleavage near heteroatoms, particularly sulfur and nitrogen, indicating structural stability of the heterocyclic core.

Spectral Analysis of Series 5 (5a–5e)

Compounds 5a–5e, containing mono-sulfur heterocyclic frameworks, exhibited consistent spectral trends with minor variations due to substituent effects.

IR Analysis

The carbonyl stretching frequencies for this series appeared between **1683–1705 cm^{-1}**, indicating conjugation with adjacent heterocyclic systems. Slight shifts in frequency were observed due to the electronic nature of substituents, with electron-donating groups causing marginal lowering of the C=O stretching frequency.

^{1}H NMR Analysis

The aromatic protons appeared as multiplets in the region **δ 7.20–8.03 ppm**, consistent with substituted phenyl rings. Methyl protons consistently appeared as singlets or doublets around **δ 2.30–2.60 ppm**, with coupling constants (J ≈ 7 Hz) indicating proximity to methine or methylene groups. In compounds such as 5c and 5d, additional **triplet and quartet patterns** confirmed the presence of ethyl-like substituents.

^{13}C NMR Analysis

The carbonyl carbons resonated around **δ 190–196 ppm**, confirming the presence of ketonic functionality. Aromatic carbons appeared in the range **δ 120–138 ppm**, while aliphatic carbons were observed between **δ 40–60 ppm**, consistent with substituted piperidine frameworks.

Interpretation

The spectral consistency across series 5 confirms the successful incorporation of alkyl and aryl substituents, with minor electronic variations influencing chemical shifts and coupling patterns.

Spectral Analysis of Series 6 (6a–6e)

Series 6 compounds are characterized by the presence of **two sulfur atoms**, which significantly influence their electronic environment.

IR Analysis

The C=O stretching bands appeared slightly lower (**1682–1703 cm^{-1}**) compared to series 5, suggesting increased conjugation and electron delocalization due to additional sulfur atoms. The C=N stretching also

showed slight shifts, indicating altered electron density.

^{1}H NMR Analysis

Aromatic protons appeared within **δ 7.10–8.00 ppm**, similar to series 5. However, the presence of **distinct N–H signals (δ 7.10–7.59 ppm)** indicates stronger hydrogen bonding or restricted rotation in these molecules. Methyl and methylene protons retained their typical positions but showed slight deshielding due to adjacent sulfur atoms.

^{13}C NMR Analysis

Carbonyl carbons were observed at **δ 195–197 ppm**, slightly downfield compared to some series 5 compounds, reflecting increased electron-withdrawing effects. Aromatic carbons remained within **δ 120–138 ppm**, while aliphatic carbons showed minor deshielding.

Interpretation

The introduction of an additional sulfur atom enhances conjugation and modifies the electronic distribution, resulting in observable spectral shifts. This indicates a stronger electron-withdrawing environment and potential impact on biological activity.

Spectral Analysis of Series 7 (7a–7e)

Series 7 compounds incorporate **additional nitrogen functionality**, leading to further complexity in spectral behavior.

IR Analysis

The IR spectra showed strong carbonyl absorption at **1699–1707 cm^{-1}** and C=N stretching at **1517–1537 cm^{-1}**, confirming the preservation of core functional groups. The N–H stretching bands remained prominent, indicating multiple nitrogen environments.

^{1}H NMR Analysis

Aromatic protons were consistently observed in the range **δ 7.00–7.90 ppm**. The absence of prominent NH_2 signals and the presence of substituted nitrogen systems led to simplified NMR patterns. Alkyl protons exhibited expected splitting patterns, with **doublets, triplets, and quartets (J ≈ 6.5–7.2 Hz)** confirming structured aliphatic chains.

^{13}C NMR Analysis

Carbonyl carbons appeared in the range **δ 189–197 ppm**, slightly broader compared to earlier series due to increased electronic interactions. Aromatic carbons remained consistent, while aliphatic carbons showed subtle variations.

Interpretation

The additional nitrogen atoms contribute to increased electron density and structural rigidity, influencing both IR and NMR characteristics. This may enhance hydrogen bonding and biological interactions.

Comparative Structure–Spectral Relationship

A comparative evaluation of all three series reveals:

- **Series 5 → baseline electronic framework**
- **Series 6 → increased sulfur content → enhanced electron withdrawal**
- **Series 7 → increased nitrogen content → altered electronic density and hydrogen bonding**

Key observations include:

- Downfield shifts in **^{13}C NMR** for carbonyl carbons with increasing heteroatom substitution
- Consistent **aromatic proton region (δ 7.0–8.0 ppm)** across all compounds
- Systematic variation in **IR frequencies** reflecting substituent effects

Supporting Spectral Discussion

The spectral data presented in Table 2 strongly support the proposed structures of compounds (5a–7e). The presence of characteristic IR absorption bands for carbonyl, azomethine, and amine groups confirms the successful formation of the heterocyclic framework. The ^{1}H NMR spectra provide clear evidence of aromatic, aliphatic, and heterocyclic proton environments, with coupling constants supporting the proposed substitution patterns.

The ^{13}C NMR data further validate the structural assignments by clearly distinguishing between carbonyl, aromatic, and aliphatic carbons. The observed chemical shifts align well with expected values for such heterocyclic systems. Additionally, mass spectrometric analysis confirms the molecular weights and supports structural integrity through consistent molecular ion peaks.

Overall, the combined spectroscopic techniques provide complementary evidence, ensuring reliable structural elucidation. The observed trends across different series highlight the influence of substituents on electronic properties, which is crucial for understanding their potential biological activity.

Evaluation of Biological Activity

Compd.	*S. aureus*	*E. coli*	*C. albicans*
5a	25	50	40
5b	20	45	35
5c	18	40	32
5d	15	35	30
5e	12	30	28
6a	22	42	38

Compd.	*S. aureus*	*E. coli*	*C. albicans*
6b	18	38	34
6c	14	30	28
6d	12	28	25
6e	20	40	36
7a	16	32	30
7b	14	30	28
7c	12	28	26
7d	10	25	22
7e	13	27	24
Standard (Ciprofloxacin)	5	5	—
Standard (Fluconazole)	—	—	6

The synthesized compounds (5a–7e) exhibited moderate to significant antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, with activity trends strongly influenced by the nature of substituents present in each series. In series 5 (5a–5e), which primarily contains mono-sulfur heterocyclic frameworks with varying alkyl and aryl substituents, a clear improvement in activity was observed with increasing hydrophobic substitution. Compound 5e (MIC: 12 µg/mL against *S. aureus*) showed enhanced potency compared to 5a (25 µg/mL), suggesting that electron-donating alkyl groups and increased lipophilicity facilitate better membrane penetration and interaction with microbial targets. In series 6 (6a–6e), the introduction of additional sulfur functionalities contributed to improved biological activity, particularly in compounds 6c and 6d, which exhibited lower MIC values (14 and 12 µg/mL, respectively, against *S. aureus*). This enhancement may be attributed to the increased polarizability and binding affinity of sulfur-containing groups; however, compound 6e showed reduced activity, possibly due to steric hindrance or suboptimal substituent positioning. Notably, series 7 (7a–7e), characterized by increased nitrogen incorporation along with sulfur moieties, demonstrated the most potent antimicrobial profile. Compound 7d emerged as the most active derivative, with MIC values of 10 µg/mL against *S. aureus*, 25 µg/mL against *E. coli*, and 22 µg/mL against *C. albicans*, indicating that the combined presence of electron-rich nitrogen centers and optimal alkyl substitution enhances biological efficacy. Overall, Gram-positive *S. aureus* was more susceptible than Gram-negative *E. coli*, likely due to differences in cell wall structure, while antifungal activity against *C. albicans* followed a similar trend. Although the synthesized compounds were less potent than standard drugs such as ciprofloxacin and fluconazole, several derivatives—particularly 7d, 7c, and 6d—demonstrated promising broad-spectrum activity, highlighting the importance of substituent optimization and heteroatom incorporation in enhancing antimicrobial potential.

CONCLUSION

This study presents the design, synthesis, and evaluation of novel heterocyclic compounds (5a–7e) containing piperidine and sulfur-based scaffolds. The compounds were synthesized through an efficient and reproducible method, yielding structurally diverse molecules with high purity. Their structures were confirmed using IR, ^1H NMR, ^13C NMR, and mass spectrometry, which verified the presence of key functional groups such as carbonyl, imine, and amine, along with aromatic and aliphatic features. Variations in substituents influenced the electronic properties of the molecules.

Biological screening revealed promising antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. A clear structure–activity relationship was observed, with activity increasing from Series 5 to Series 7. Series 5 compounds showed moderate activity, while Series 6 demonstrated improved potency due to sulfur incorporation. The highest activity was observed in Series 7, where additional nitrogen atoms enhanced biological interactions.

Compound 7d emerged as the most potent derivative, exhibiting strong broad-spectrum antimicrobial activity with low MIC values. Although less active than standard drugs like ciprofloxacin and fluconazole, compounds such as 7c–7e displayed significant potential. Overall, the study highlights the importance of heteroatom incorporation and suggests that piperidine–thiazole hybrids are promising candidates for future antimicrobial drug development.

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