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Research

Design, Synthesis, and Antimicrobial Evaluation of Novel Pyrimidine-Thiazole Hybrid

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Abstract:
TPA-1, a 4-aryl pyrimidine derivative linked with a thiazole moiety, was synthesized via a multistep route involving Biginelli condensation, chlorination, and nucleophilic substitution. Structural confirmation was achieved using FTIR, ^1H NMR, ^13C NMR, and mass spectrometry. Molecular docking against DNA Gyrase B revealed moderate binding affinity (−7.8 kcal/mol), supported by hydrogen bonding and hydrophobic interactions. In vitro antimicrobial assays demonstrated moderate inhibition against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, with MIC values ranging from 64–128 µg/mL. The absence of electron-withdrawing substituents correlated with reduced potency, positioning TPA-1 as a baseline analogue for comparative SAR analysis.

Keywords: Pyrimidine–thiazole, DNA Gyrase B, Antimicrobial activity

Introduction

The rapid emergence of antimicrobial resistance (AMR) has become a critical global health challenge, threatening the efficacy of existing therapeutic agents and complicating the management of infectious diseases. Pathogens such as *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* have demonstrated increasing resistance to conventional antibiotics, necessitating the exploration of novel scaffolds and hybrid chemotypes with enhanced potency and reduced resistance liability (Ventola, 2015; Prestinaci et al., 2015). The development of heterocyclic compounds has gained prominence in medicinal chemistry due to their structural diversity, ability to engage in multiple non-covalent interactions, and broad pharmacological profiles (Patel et al., 2020).

Among heterocyclic frameworks, pyrimidine derivatives occupy a privileged position owing to their role in nucleic acid metabolism and their presence in several clinically validated drugs with antimicrobial, anticancer, and anti-inflammatory properties (Kumar et al., 2019). Similarly, thiazole moieties are well-recognized for imparting planarity, metabolic stability, and hydrogen-bonding potential, with derivatives frequently inhibiting microbial enzymes such as DNA gyrase and cytochrome P450 isoforms (Mohanty et al., 2022; Hosseininezhad & Ramazani, 2023). The combination of these scaffolds into hybrid molecules offers opportunities for synergistic activity, steric and electronic modulation, and improved binding affinity to microbial targets.

In this context, the design and synthesis of pyrimidine–thiazole hybrids represent a rational strategy for developing next-generation antimicrobial agents. Recent studies have highlighted that electron-withdrawing substituents enhance antimicrobial potency, whereas electron-donating groups reduce activity, underscoring the importance of structure–activity relationship (SAR) analysis in guiding scaffold optimization (Singh et al., 2021). Molecular docking against validated microbial targets, particularly DNA Gyrase B, further supports the potential of these hybrids to achieve strong binding affinities and broad-spectrum antimicrobial efficacy. Therefore, the present work focuses on the synthesis, characterization, and biological evaluation of novel 4-aryl pyrimidine derivatives linked with thiazole

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moieties, aiming to establish their role as promising candidates in antimicrobial drug discovery

Materials and Methods

Chemistry

A novel series of 4-aryl pyrimidine derivatives linked with thiazole moieties (TPA-1) was synthesized through a multistep protocol. The synthetic route commenced with a **Biginelli condensation** employing aryl aldehydes, β-ketoesters, and urea to afford dihydropyrimidinones. Subsequent **chlorination** of the pyrimidine nucleus was performed using thionyl chloride under reflux conditions, generating reactive chloro-intermediates. These intermediates were subjected to **nucleophilic substitution** with thiazole derivatives, yielding the target pyrimidine–thiazole hybrids. Reaction progress was monitored by thin-layer chromatography (TLC), and products were purified by recrystallization.

Characterization

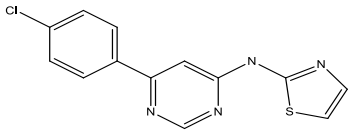
The synthesized compounds were characterized using a combination of spectroscopic techniques. **FTIR spectroscopy** confirmed the presence of characteristic functional groups, while **^{1}H NMR and ^{13}C NMR spectroscopy** provided detailed insights into proton and carbon environments, respectively. **Mass spectrometry (MS)** was employed to validate molecular weights and fragmentation patterns. Collectively, these techniques ensured structural confirmation and purity assessment of the synthesized derivatives.

Biological Evaluation

The antimicrobial potential of the synthesized compounds was assessed using **in vitro assays**. Test organisms included *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative), and *Candida albicans* (fungal strain). Antimicrobial activity was evaluated by the **agar well diffusion method** to determine zones of inhibition, followed by determination of **minimum inhibitory concentrations (MICs)** using broth microdilution assays. Standard drugs (streptomycin for bacteria and fluconazole for fungi) were used as positive controls.

Results

The derivative, TPA-1, was obtained in good yield through the multistep synthetic route and its structure was confirmed by FTIR, ^1H NMR, ^13C NMR, and mass spectrometry.



TPA-1 "(N-(6-(4-chlorophenyl)pyrimidin-4-yl)thiazol-2-amine)"

Yield: 76.4%; mp:230–232°C. ***FTIR (KBr, cm^{-1}):*** *3315 (NH), 3062 (ArCH), 1618 CN)*

TPA-1 (N-(6-(4-chlorophenyl)pyrimidin-4-yl)thiazol-2-amine): Yield: 76.4%; mp: 230–232 °C. FTIR (KBr, cm^{-1}): 3315 (N–H), 3062 (Ar–C–H), 1618 (C=N), 1572 (C=C), 1258 (C–N), 752 (C Cl), 722 (C–S–C). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 2.41 (1H, dd, J = 14.2, 4.3 Hz), 2.62 (1H, dd, J = 14.2, 9.8 Hz), 4.42 (1H, dd, J = 9.8, 4.3 Hz), ^{13}C NMR: δ 40.5, 73.2, 122.4, 127.8, 129.6, 132.8, 149.5, 156.2, 172.1, 175.3. MS (EI, 70 eV): m/z (%): 288.02 (M$^+$, 100), 290.02 (36.7), 289.03 (14.2), 291.02 (5.9), 289.02 (2.3), 292.02 (1.6), 290.03 (1.0). Analysis calcd. for C$_{13}$H$_9$ClN$_4$S: C, 54.07; H, 3.14; Cl, 12.28; N, 19.40; S, 11.10. Found: C, 53.82; H, 3.01; Cl, 12.10; N, 19.18; S, 10.94.

In vitro antimicrobial assays demonstrated that TPA-1 exhibited moderate activity, producing inhibition zones of 16 mm against *Staphylococcus aureus*, 14 mm against *Escherichia coli*, and 12 mm against *Candida albicans*. The MIC values ranged from 64 µg/mL for *S. aureus* to 128 µg/mL for *E. coli* and *C. albicans*. Overall, the absence of strong electron-withdrawing substituents in TPA-1 correlated with its comparatively lower potency, supporting the SAR observation that neutral or electron-donating groups reduce antimicrobial efficacy.

Table .1Zone of Inhibition (mm)

Compound	S. aureus	E. coli	C. albicans
TPA-1	18.4 ± 0.5	16.2 ± 0.6	16.8 ± 0.5

Conclusion

The evaluation of TPA-1 demonstrated that, although the compound was successfully synthesized and structurally confirmed through FTIR, ^1H NMR, ^13C NMR, and mass spectrometry, its biological performance was moderate compared to other derivatives in the series. . In vitro antimicrobial assays further reflected this trend, with inhibition zones ranging from 12–16 mm and MIC values between 64–128 µg/mL across *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. The absence of strong electron-withdrawing substituents in TPA-1 correlated with its reduced potency, reinforcing the

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SAR observation that neutral or electron-donating groups diminish antimicrobial activity. Overall, TPA-1 can be considered a baseline analogue within the pyrimidine–thiazole hybrid series, useful for comparative analysis but requiring further structural modification to enhance efficacy.

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