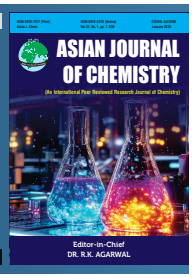
Asian Journal of Chemistry; Vol. 37, No. 3 (2025), 680-688

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2025.33151



Design, Synthesis, Molecular Docking and Antimicrobial Activity of New Thiazole-Fused Pyrimidine Derivatives

K.M. AZAMAT[1], BHUPENDRA CHAUHAN[2], MD ARIF NASEER[3], NAVEEN KUMAR[1] and ZULPHIKAR ALI[2,*]

[1]Department of Basic & Applied Sciences, Shobhit University, Gangoh-247341, India
[2]Department of Pharmaceutical Sciences, Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University, Gangoh-247341, India
[3]School of Pharmacy and Paramedical Sciences, K.K. University, Biharsharif-803115, India

*Corresponding author: E-mail: zulfequar83@gmail.com

Received: 8 December 2024; *Accepted*: 14 February 2025; *Published online*: 28 February 2025; AJC-21925

A new class of compounds formed by the linkage of –N=C– (Schiff base) with pyrimidine fused thiazole moieties was designed and synthesized. All the synthesized novel 15 compounds were characterized by spectral analysis and screened for their antimicrobial activity. To gain a prior evidence for obtaining a good antimicrobial property a molecular docking study was carried out on the 3D structure of enzyme using Maestro 16.0 program (Schrödinger Inc., USA). Molecular docking studies demonstrated a better docking score and interacted well with the target protein. Antimicrobial results revealed that compounds **4d**, **4i** and **4k** showed the overall good result against tested microbes. Physico-chemical parameters of the designed compounds were predicted *in silico* using the QikProp module of Schrödinger. Compound **4i** exhibited the best ADME features and highest binding affinity. The *in silico* molecular docking study revealed their FabH inhibitory action. According to the *in silico* findings, all the 15 newly framed derivatives would be regarded as leads for the discovery of novel antimicrobial agent. Compound **4d** emerged as a significant bioactive molecule among all the docked analogues.

Keywords: Thiazole, Pyrimidine, Schiff base, Biological studies, Molecular docking.

INTRODUCTION

Recent advancements in medicinal chemistry have revolutionized the processes that efficiently and cost-effectively developed new drug molecules [1,2]. Among nitrogen containing heterocyclic compounds, aromatic derivatives account for approximately 85% of biologically active compounds [3]. Thiazole is a five-membered heterocyclic compound characterized by the presence of sulfur and nitrogen atoms located at the 1 and 3 positions within its aromatic ring structure. Its significance lies in its role as a bioisostere of the imidazole ring, which is prevalent in numerous antifungal agents [4]. The imidazole ring system is a notable component of various antifungal drugs, such as miconazole and ketoconazole [5]. The class of medications known as azoles represents a category utilized in antifungal treatment. It was hypothesized that a similar effect to that of an imidazole ring could be achieved through the application of the thiazole ring [6]. Some thiazole containing compounds possess dual effects as a broad spectrum anticancer and antimicrobial agents may be considered as useful template for future development of the new lead [7].

In heterocyclic chemistry, thiazole and pyrimidine are regarded as privileged structures due to their significance in various biological processes, including their potential as antimicrobial agents [8-10]. In a thiazole moiety combined with a pyrimidine, the pyridine component exhibits π-deficiency due to the presence of electronegative nitrogen atoms, which act as electron withdrawing groups on thiazole, resulting in a decrease in its electronic density. This characteristic is crucial for facilitating chemical interactions that contribute to various biological activities. Modifications to the pyrimidine framework, such as the attachment of benzyloxybenzaldehyde, have enhanced its efficacy against bacteria, with some derivatives demonstrating significant effectiveness across a broad spectrum of bacterial strains [11,12].

In the antimicrobial drug discovery process, a range of computational tools, including molecular docking, molecular dynamics, density functional theory, ADMET, pharmacophores

and quantitative structure-activity relationship (QSAR), has been utilized to identify common targets shared among different microbes [13]. Moreover, *in silico* approaches leveraging artificial intelligence are increasingly being reported as a means to enhance the efficiency of the drug discovery process. These computational methods are characterized as more rational, cost-effective and time-efficient [14]. Molecular docking is used to analyze the binding affinity between the target protein and the ligand. The ADMET study assesses the drug-likeness and toxicity of ligand molecules. Lipinski's rule of five is applied to evaluate the drug-likeness. The pharmacophore identifies the molecular characteristics of the ligand molecules. QSAR studies investigate the correlation between the physio-chemical properties of the ligand molecules and their biological activity [15]. *In silico* methods are now available to complement *in vitro* and *in vivo* toxicity tests, which may reduce the necessity for animal testing and safety assessments. In future, computational methods are expected to evolve to encompass models for unique and novel toxicity endpoints and chemicals, offering insights into toxicological pathways [16].

The management of infectious diseases continues to be a global challenge due to the rising issue of multi-drug resistance. Consequently, the development of new therapeutic agents could potentially address the challenges posed by drug resistance and the adverse effects associated with existing treatments [17]. To tackle these challenges, it is essential to create new drugs that possess improved toxicity profiles. Despite years of comprehensive research on the structural modification of established antibacterial scaffolds, the discovery of new leads remains challenging. Consequently, the emphasis in antibacterial research has shifted towards identifying new chemical classes aimed at combating invading bacteria [18]. The rise of multi-drug resistant pathogens is leading to increasingly difficult-to-treat infections in humans worldwide, highlighting the urgent necessity for the development of new therapeutic agents [19]. Antimicrobial agents either inhibit or eliminate microorganisms [20].

In this context, we have chosen to investigate new thiazole-pyrimidine derivatives as potential antimicrobial agents, building on findings from earlier research. This study involves the design, synthesis and evaluation of the antimicrobial properties of thiazole based heterocyclic compounds. Additionally, molecular docking studies were performed to analyze the binding patterns at the 1HNJ protein site.

EXPERIMENTAL

The reagents and solvents were obtained from Merona Scientific, Roorkee, India, or from Bhatt Educational Scientific & Technological Services Pvt. Ltd. in Dehradun, India and were utilized without any purification. The solvents and reagents utilized were of laboratory reagent grade and were purified prior to application. The advancement of the reactions was tracked using TLC plates (silica gel G), employing toluene: ethyl acetate:formic acid (5:4:1, v/v/v) and benzene:acetone (9:1, v/v) as the solvent systems. The locations of the spots were identified through exposure to iodine vapours and several developed plates were also analyzed using UV lamps (254 nm). The melting points were measured using the open tube capillary method and no corrections were applied. Infrared spectra were obtained using a Shimadzu infrared spectrometer (FTIR-8400S) with KBr pellets at Shobhit University, Gangoh. The ^{1}H NMR spectra were obtained using a Brucker Avace 300 spectrometer, with TMS serving as the internal standard. High-resolution mass spectrometry (HRMS) data is presented in terms of *m/z* (relative intensity).

General procedure for synthesis of compounds (1a-e): Using compound **1a** as reference, a solution of 2-amino-2-{(mercaptomethyl)amino}acetic acid hydrate and $NaHCO_3$ (1.1 equiv.) in 200 mL of water was prepared, to which benzaldehyde (1.1 equiv.) in 200 mL of 95% ethanol was added all at once. The reaction mixture was agitated for a duration of 6 h. The resulting product was then filtered, rinsed with ethanol and dried, yielding a white solid.

4-Aminothiazolidine-5-carboxylic acid (1a): Yield: 82%; white solid; m.p.: 114-112 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 3.48 (1H, m, -NH-), 4.29 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.35 (1H, m, -S-CH-N), 4.65 (1H, d, *J* = 6.8 Hz, -N-CH-N-), 5.11 (2H, S, -NH_2), 8.80 (1H, s, -OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 53.3, 61.4, 174.8. ESI MS (*m/z*): 336 (M+). Anal. calcd. (found) % for $C_4H_8N_2O_2S$ (*m.w.* 148.18): C, 65.08 (66.11); H, 6.12 (6.14); N, 11.84 (11.89); O, 10.15 (10.19); S, 6.77 (6.79). The other compounds **1b-1e** were obtained following the same method.

General procedures for the synthesis of 2-substituted-5-phenyl-3,3a-dihydro-2*H*-thiazolo[4,5-*d*][1,3]oxazin-7-(7a*H*)-one (2a-e): Taking compound **2a** as an example, benzoyl chloride (0.02 mol) was added dropwise to a solution of 4-amino-thiazolidine-5-carboxylic acid (**1a**, 0.1 mol) in pyridine (30 mL) while constantly stirring at 2-8 ºC; over the course of 1 h. After stirring the reaction mixture for 30 min at room temperature, then treated it with aqueous Na_2CO_3 to eliminate any unreacted acid. After obtaining a stable product, it was filtered and rinsed with cold water to eliminate the inorganic components. Subsequently, it was washed with *n*-hexane and recrystallized using ethanol.

5-Phenyl-3,3a-dihydro-2*H*-thiazolo[4,5-*d*][1,3]oxazin-7-(7a*H*)-one (2a): Yield: 62%; white solid; m.p.: 196-198 ºC, ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 3.48 (1H, m, -NH-), 4.36 (1H, d, *J* = 10.1 Hz, S-CH-CO), 4.46 (2H, m, -S-CH_2-N-), 5.17 (1H, m, -N-CH-N-), 7.43 (2H, m, Ph-H), 7.61 (1H, m, Ph-H), 8.30 (2H, Ph-H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 53.3, 71.0, 71.1, 126.5, 128.1, 128.6, 129.7, 156.6, 171.3. ESI MS (*m/z*): 336 (M+). Anal. calcd. (found) % for $C_{11}H_{10}N_2O_2S$ (*m.w.* 220.25): C, 66.08 (66.10); H, 5.12 (5.14); N, 11.86 (11.88); O, 10.16 (10.18); S, 6.79 (6.77). The other compounds **2b-h** were also synthesized using the same method.

General procedure for synthesis of 6-amino-2-substituted 5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7(2*H*)-one (3a-e): Compound **3a** underwent a transformation as follows: 5-phenyl-3,3a-dihydro-2*H*-thiazolo[4,5-*d*][1,3]-oxazin-7(7a*H*)-one was converted to 6-amino-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-d]pyrimidin-7(2*H*)-one upon reflux with hydrazine monohydrate in ethanol for 6-7 h. Upon pouring the concentrated solution into ice-cold water, we were able to

procure a solid product. The solid was thoroughly washed with water, filtered, dried and recrystallized using ethanol.

6-Amino-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]-pyrimidin-7-(2*H*)-one (3a): Yield: 72%; white solid; m.p.: 234-236 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 3.48 (1H, m, -NH-), 3.82 (2H, s, -NH_2), 4.07 (1H, d, *J* = 10.1 Hz, S-CH-CO), 4.53 (2H, d, *J* = 13.2 Hz, -S-CH_2-N-), 4.79 (1H, d, *J* = 10.1 Hz, -N-CH-N-), 7.40-7.55 (3H, m, Ph-H), 8.23-8.37 (2H, m, Ph-H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 53.3, 71.0, 71.1, 126.5, 128.1, 128.6, 131.7, 155.2, 167.5. ESI MS (*m/z*): 336 (M+). Anal. calcd. (found) % for $C_{11}H_{12}N_4O_2S$ (*m.w.* 248.30): C, 66.09 (66.10); H, 6.12 (5.14); N, 14.86 (11.88); O, 12.16 (10.18); S, 6.80 (6.77). The other compounds **3b-e** were obtained using the same method.

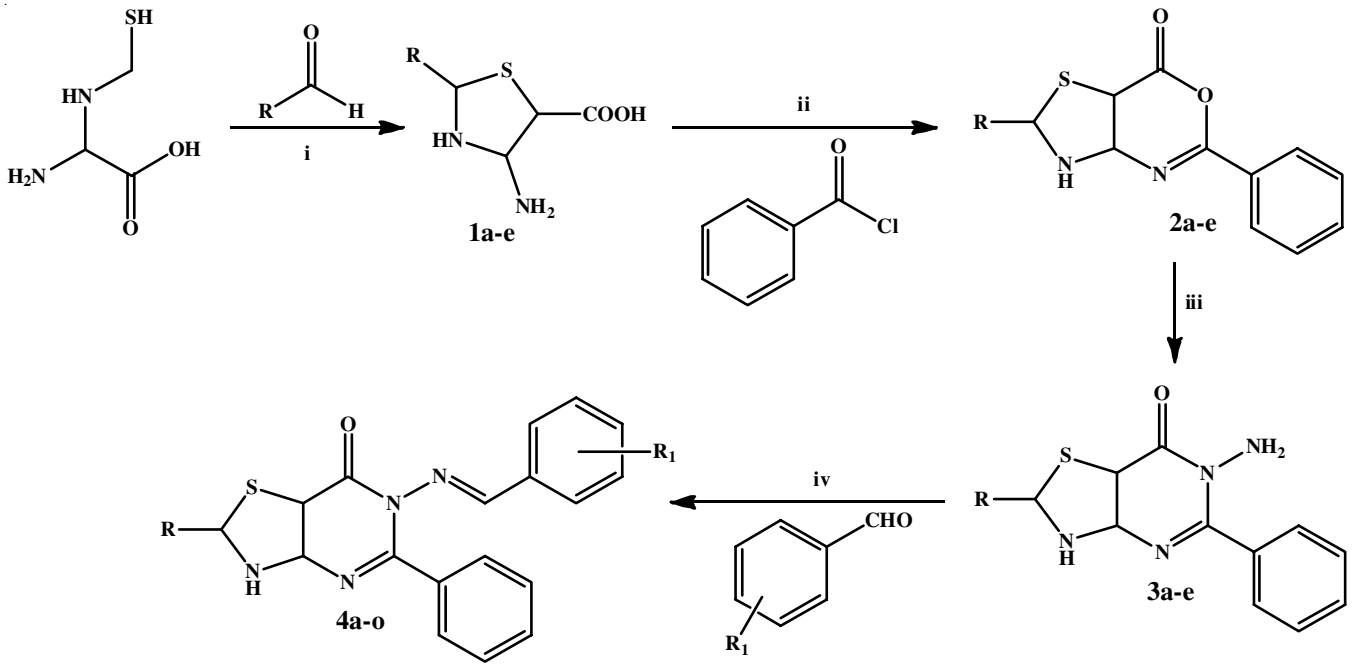
2-Substituted-6-((substituted benzylidene)amino)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4a-o): A mixture of 6-amino-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7(2*H*)-one and its substituted analogs (**3a-e**) along with the appropriate aromatic aldehydes was dissolved in 50 mL of ethanol with a few drops of glacial acetic acid. The solution was then heated under reflux for 7-8 h. The solution was cooled and the resulting precipitated solid was collected, filtered, washed with water, dried under vacuum and recrystallized from ethanol (**Scheme-I**).

6-(Benzylideneamino)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4a): Yield 70.9%; white solid; m.p.: 286-288 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.48 (1H, m, -NH-), 4.29 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.47 (2H, d, *J* = 13.2 Hz, S-CH_2-N), 4.67 (1H, m, N-CH-N=), 7.36-7.57 (6H, m, Ph-H), 8.16-8.31 (2H, m, Ph-H) 8.58 (1H, s, N=CH-Ph), 9.14 (1H, S, -C=N-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 53.3, 71.0, 71.1, 126.5, 127.3, 128.0, 128.2, 128.5, 128.7 131.7, 134.9, 155.2, 159.4, 167.5. ESI MS (*m/z*): 336 (M+). Anal. calcd. (found) % for $C_{18}H_{16}N_4OS$ (*m.w.* 336.40): C, 64.26 (64.28); H, 4.79 (4.81); N, 16.65 (16.63); O, 4.76 (4.78); S, 9.53 (9.56).

6-((3-Nitrobenzylidene) amino)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4b): Yield 89%; white solid; m.p.: 183-185 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.52 (1H, m, -NH-), 4.27 (1H, d, *J* = 10.4 Hz, S-CH-CO), 4.46 (2H, d, *J* = 12.8 Hz, S-CH_2-N), 4.72 (1H, m, N-CH-N=), 7.40-7.64 (4H, m, Ph-H), 8.22-8.37 (3H, m, Ph-H), 8.62-8.75 (2H, m, Ph-H), 9.15 (1H, S, -C=N-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 53.3 (1C, s), 71.0, 71.1, 121.8, 122.8), 126.5, 127.3, 128.1, 128.6, 129.4, 131.7, 134.8, 146.8, 155.2, 159.4, 167.5. ESI MS (*m/z*): 381 (M+). Anal. calcd. (found) % for $C_{18}H_{15}N_5O_3S$ (*m.w.* 381.42): C, 56.68 (56.70); H, 3.96 (3.98); N, 18.36 (18.34); O, 12.58 (12.61); S, 8.41 (8.44).

6-((2-Methoxybenzylidene)amino)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7(2*H*)-one (4c): Yield: 88%; white solid; m.p.: 348-350 ºC. H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 3.82 (3H, S, OCH_3), 4.30 (1H, d, *J* = 10.4 Hz, S-CH-CO), 4.52 (2H, d, *J* = 12.8 Hz, S-CH_2-N), 4.70 (1H, m, N-CH-N=), 7.42-7.66 (4H, m, Ph-H), 8.24-8.39 (3H, m, Ph-H), 8.64-8.77 (2H, m, Ph-H), 9.17 (1H, S, -C=N-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 53.3, 55.9, 71.0, 71.1, 111.9, 124.9, 126.5, 128.1, 128.3, 128.5, 128.7, 131.7, 155.2, 156.8, 159.4, 167.5. ESI MS (*m/z*): 366 (M+). Anal. calcd. (found) % for $C_{19}H_{18}N_4O_2S$ (*m.w.* 366.43): C, 62.28 (62.30); H, 4.95 (4.97); N, 15.29 (15.28); O, 8.73 (8.74); S, 8.75 (8.77).

6-((3-Nitrobenzylidene)amino)-2,5-diphenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4d): Yield: 92%; colourless solid; m.p.: 320-322 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 4.22 (1H, d, *J* = 10.2



Reactions and conditions:
(i) $NaHCO_3$, $EtOH/H_2O$, (ii) Anhydrous pyridine, 30 mL, constant stirring at 2-8 °C, Aqueous sodium bicarbonate, 1 h
(iii) $NH_2NH_2H_2O$, 6 h ethanol (iv) Different aldehydes, ethanol, few drops of glacial acetic acid, reflux for 8 h

Scheme-I: Synthesis of compounds **4a-o**

Hz, S-CH-CO), 4.71 (1H, d, *J* = 10.2 Hz, N-CH-N=), 5.10 (1H, s, S-CH-N), 7.21 (2H, m, Ph-H), 7.28-7.64 (7H, m, Ph-H), 8.22-8.37 (3H, m, Ph-H), 8.62-8.75 (2H, m, Ph-H), 8.82 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 71.0, 71.1, 116.5, 125.7, 126.5, 126.7, 127.3, 128.0, 128.2, 128.5, 128.7, 131.7, 134.9, 153.3, 155.2, 159.4, 167.5. ESI MS (*m/z*): 457 (M+). Anal. calcd. for: $C_{24}H_{19}N_5O_3S$ (*m.w.* 457.49): C, 63.01 (63.03); H, 4.19 (4.22); N, 15.31 (15.29); O, 10.49 (10.51); S, 7.01 (7.03).

6-(Benzylideneamino)-2-(2-hydroxyphenyl)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4e): Yield: 92%; buff solid; m.p.: 225-227 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 4.22 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.71 (1H, d, *J* = 10.2 Hz, N-CH-N=), 4.97 (1H, s, -OH), 6.68 (1H, s, S-CH-N), 6.96 (1H, m, Ph-H), 7.25 (1H, m, Ph-H), 7.34-7.57 (7H, m, Ph-H) 8.16 (2H, m, Ph-H), 8.31 (2H, m, Ph-H), 8.58 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 71.0, 71.1, 116.5, 125.7, 126.5, 126.7, 127.3, 128.0, 128.2, 128.5, 128.7, 131.7, 134.9, 153.3, 155.2, 159.4, 167.5. ESI MS (*m/z*): 428 (M+). Anal. calcd. (found) % for $C_{24}H_{20}N_4O_2S$ (*m.w.* 428.50): C, 67.27 (67.29); H, 4.70 (4.73); N, 13.07 (13.01); O, 7.47 (7.46); S, 7.48 (7.45).

2-(2-Hydroxyphenyl)-6-((2-isocyanobenzylidene)-amino)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]-pyrimidin-7-(2*H*)-one (4f): Yield: 79%; white solid; m.p.: 132-133 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 4.22 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.72 (1H, d, *J* = 10.2 Hz, N-CH-N=), 4.97 (1H, s, -OH), 6.68 (1H, s, S-CH-N), 6.96 (1H, m, Ph-H), 7.25 (2H, m, Ph-H), 7.34-7.71 (6H, m, Ph-H), 7.89 (1H, m, Ph-H), 8.02 (1H, m, Ph-H), 8.31 (2H, m, Ph-H), 8.87 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 66.7, 71.0, 71.1, 110.7, 116.0, 126.5, 127.0, 128.0, 128.2, 128.3, 128.5, 128.7, 130.3, 130.7, 135.9, 137.7, 143.9, 159.4, 167.5. ESI MS (*m/z*): 453 (M+). Anal. calcd. (found) % for $C_{25}H_{19}N_5O_2S$ (*m.w.* 453.53): C, 66.21 (66.23); H, 4.22 (4.24); N, 15.44 (15.42); O, 7.06 (7.08); S, 7.07 (7.09).

2-(2-Hydroxyphenyl)-6-((3-nitrobenzylidene)amino)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4g): Yield: 75%; white solid; m.p.: 260-262 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 4.22 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.71 (1H, d, *J* = 10.2 Hz, N-CH-N=), 5.97 (1H, s, -OH), 6.68 (1H, s, S-CH-N), 6.96 (2H, m, Ph-H), 7.25 (1H, m, Ph-H), 7.34-7.64 (5H, m, Ph-H), 7.82 (1H, m, Ph-H), 8.22-8.37 (3H, m, Ph-H), 8.62-8.76 (2H, m, Ph-H), 8.92 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 71.0, 71.1, 116.5, 121.8, 122.8, 125.7, 126.5, 126.7, 127.3, 128.1, 128.5, 128.7, 129.4, 131.7, 134.8, 146.8, 153.3, 155.2, 159.4, 167.5. ESI MS (*m/z*): 473 (M+). Anal. calcd. (found) % for $C_{24}H_{19}N_5O_4S$ (*m.w.* 473.49): C, 60.88 (60.90); H, 4.04 (4.06); N, 14.79 (14.81); O, 13.52 (13.54); S, 6.77 (6.78).

6-((4-Chlorobenzylidene)amino)-2-(2-hydroxyphenyl)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4h): Yield: 76%; yellowish brown powder; m.p.: 216-218 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 4.22 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.71 (1H, d, *J* = 10.2 Hz, N-CH-N=), 5.35 (1H, s, -OH), 6.68 (1H, s, S-CH-N), 6.96 (2H, m, Ph-H), 7.18-7.66 (9H, m, Ph-H), 8.31 (2H, m, Ph-H), 8.96 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 71.0, 71.1, 116.5, 125.7, 126.5, 126.7, 128.1, 128.3, 128.5, 128.7, 128.9, 131.7, 134.1, 134.9, 153.3, 155.2, 159.4, 167.5. ESI MS (*m/z*): 462 (M+). Anal. calcd. (found) % for $C_{24}H_{19}ClN_4O_2S$ (*m.w.* 462.96): C, 62.27 (62.28); H, 4.14 (4.16); Cl, 7.66 (7.68); N, 12.10 (12.08); O, 6.91 (6.93); S, 6.93 (6.96).

2-(2-Hydroxyphenyl)-6-((2-methoxybenzylidene)-amino)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]-pyrimidin-7-(2*H*)-one (4i): Yield: 80%; yellow powder; m.p.: 194-196 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 3.76 (1H, d, *J* = 10.2 Hz, N-CH-N=), 3.87 (3H, s, O-CH_3), 4.86 (1H, d, *J* = 10.2 Hz, S-CH-CO), 5.04 (1H, s, -OH), 6.25 (1H, s, -S-CH-N), 6.68 (1H, m, Ph-H), 6.88-7.05 (2H, m, Ph-H), 7.18-7.46 (9H, m, Ph-H), 7.68 (1H, m, Ph-H), 8.46 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 55.9, 71.0, 71.1, 111.9, 116.5, 124.9, 125.7, 126.5, 126.7, 128.1, 128.3, 128.5, 128.7, 131.7, 153.3, 155.2, 156.8, 159.4, 167.5. ESI MS (*m/z*): 458 (M+). Anal. calcd. (found) % for $C_{25}H_{22}N_4O_3S$ (*m.w.* 458.52) C, 65.48 (65.50); H, 4.84 (4.84); N, 12.22 (12.20); O, 10.47 (10.49); S, 6.99 (7.01).

2-(((2-(3-Nitrophenyl)-7-oxo-5-phenyl-3,3a,7,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-6(2*H*)-yl)imino)methyl)-benzonitrile (4j): Yield: 75%; yellow powder; m.p.: 310-315 ºC. ^{1}H NMR: (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 4.22 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.72 (1H, d, *J* = 10.2 Hz, N-CH-N=), 5.36 (1H, s, -S-CH-N), 7.38-7.71 (6H, m, Ph-H), 7.78-7.96 (2H, m, Ph-H), 7.96-8.08 (2H, m, Ph-H), 8.14-8.37 (3H, m, Ph-H), 8.87 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 71.0, 71.1, 110.7, 116.0, 121.7, 121.8, 126.5, 127.0, 128.1, 128.3, 128.5, 128.7, 129.4, 130.3, 130.7, 131.7, 137.7, 146.8, 155.2, 159.4, 167.5. ESI MS (*m/z*): 482 (M+). Anal. calcd. (found) % for $C_{25}H_{18}N_6O_3S$ (*m.w.* 482.52): C, 62.23 (62.24); H, 3.76 (3.78); N, 17.42 (17.45); O, 9.95 (9.98); S, 6.65 (6.63).

6-((3-Nitrobenzylidene)amino)-2-(3-nitrophenyl)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4k): Yield 78%; pale yellow solid; m.p.: 114-116 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 4.22 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.71 (1H, d, *J* = 10.2 Hz, N-CH-N=), 5.36 (1H, s, -S-CH-N), 7.38-7.64 (5H, m, Ph-H), 7.75-7.91 (2H, m, Ph-H), 8.01 (1H, m, Ph-H), 8.14-8.37 (4H, m, Ph-H), 8.62-8.76 (2H, m, Ph-H), 8.94 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 71.0, 71.1, 121.7, 121.8, 122.8, 126.5, 127.0, 127.3, 128.1, 128.6, 129.3, 129.5, 131.7, 134.8, 137.7, 146.8, 146.9, 155.2, 159.4, 167.5. ESI MS (*m/z*): 502 (M+). Anal. calcd. (found) % for $C_{24}H_{18}N_6O_5S$ (*m.w.* 502.49): C, 57.36 (57.34); H, 3.61 (3.62); N, 16.72 (16.70); O, 15.92 (15.90); S, 6.38 (6.40).

6-((4-Chlorobenzylidene)amino)-2-(3-nitrophenyl)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4l): Yield: 70%; white solid, m.p.: 182-184 ºC. ^{1}H NMR: (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 4.22 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.71 (1H, d, *J* = 10.2 Hz, N-CH-N=), 5.36 (1H, s, -S-CH-N), 7.26-7.66 (8H, m, Ph-H), 7.85 (1H, m, Ph-H), 8.01 (1H, m, Ph-H), 8.14-8.37 (3H, m, Ph-H), 8.60 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz): δ ppm: 71.0, 71.1, 121.7, 121.8, 122.8, 126.5, 127.0, 127.3,

128.1, 128.6, 129.3, 129.5, 131.7, 134.8, 137.7, 146.8, 146.9, 155.2, 159.4, 167.5. ESI MS (*m/z*): 491 (M+). Anal. calcd. (found) % for $C_{24}H_{18}ClN_5O_3S$ (491.96): C, 58.59 (58.62); H, 3.69 (3.67); Cl, 7.21 (7.23); N, 14.24 (14.26); O, 9.76 (9.78); S, 6.52 (6.50).

2-(2-Methoxyphenyl)-6-((3-nitrobenzylidene)amino)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4m): Yield: 85%; white solid; m.p.: 150-152 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 3.80 (3H, s, -O-CH_3), 4.56 (1H, d, *J* = 10.1 Hz, S-CH-CO), 5.02 (1H, d, *J* = 10.1 Hz, N-CH-N=), 5.17 (1H, s, -S-CH-N), 6.88-7.11 (2H, m, Ph-H), 7.23 (1H, m, Ph-H), 7.33-7.64 (5H, m, Ph-H), 8.22-8.37 (3H, m, Ph-H), 8.62-8.75 (2H, m, Ph-H), 8.80 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 55.9, 71.0, 71.1, 111.9, 121.8, 122.8, 125.7, 126.5, 126.7, 127.3, 128.1, 128.5, 128.7, 129.4, 131.7, 134.8, 146.8, 155.2, 157.0, 159.4, 167.5. ESI MS (*m/z*): 487 (M+). Anal. calcd. (found) % for $C_{25}H_{21}N_5O_4S$ (*m.w.* 487.52): C, 61.59 (61.62); H, 4.34 (4.37); N, 14.36 (14.34); O, 13.13 (13.14); S, 6.58 (6.60).

6-((4-Chlorobenzylidene)amino)-2-(2-methoxyphenyl)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-7-(2*H*)-one (4n): Yield: 84%; white solid; m.p.: 132-134 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 3.80 (3H, s, -O-CH_3), 4.22 (1H, d, *J* = 10.2 Hz, S-CH-CO), 4.71 (1H, d, *J* = 10.2 Hz, N-CH-N=), 4.94 (1H, s, -S-CH-N), 6.88-7.11 (2H, m, Ph-H), 7.16-7.66 (9H, m, Ph-H), 8.31 (2H, m, Ph-H), 8.60 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 55.9, 71.0, 71.1, 111.9, 125.7, 126.5, 126.7, 128.1, 128.3, 128.5, 128.7, 128.9, 131.7, 134.1, 134.9, 155.2, 157.0, 159.4, 167.5. ESI MS (*m/z*): 476 (M+). Anal. calcd. (found) % for $C_{25}H_{21}ClN_4O_2S$ (*m.w.* 476.99): C, 62.95 (62.97); H, 4.44 (4.42); Cl, 7.43 (7.45); N, 11.75 (11.72); O, 6.71 (6.73); S, 6.72 (6.74).

6-((2-Methoxybenzylidene)amino)-2-(2-methoxyphenyl)-5-phenyl-3,3a,6,7a-tetrahydrothiazolo[4,5-*d*]-pyrimidin-7-(2*H*)-one (4o): Yield: 85%; white solid, m.p.: 160-162 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.50 (1H, m, -NH-), 3.64-3.93 (6H, s, O-CH_3), 4.56 (1H, d, *J* = 10.1 Hz, S-CH-CO), 4.99 (1H, d, N-CH-N=), 6.35 (1H, s, -S-CH-N), 6.86-7.11 (3H, m, Ph-H), 7.16-7.69 (10H, m, Ph-H), 8.41 (1H, s, -N=CH-). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 55.9, 55.9, 71.0, 71.1, 111.9, 112.0, 124.9, 125.7, 126.5, 126.7, 128.1, 128.3, 128.5, 128.7, 131.7, 155.2, 156.8, 157.0, 159.4, 167.5. ESI-MS (*m/z*): 473 (M+). Anal. calcd. (found) % for $C_{26}H_{24}N_4O_3S$ (*m.w.* 472.55): C, 66.96 (66.11); H, 6.12 (6.14); N, 12.86 (11.87); O, 9.16 (10.19); S, 6.78 (6.76).

Antimicrobial activity: Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) and fungi (*Candida albicans* and *Fusarium oxysporum*) were utilized in this study for the evaluation of antimicrobial activity. The antimicrobial activity of newly synthesized organic compounds was examined against the tested microorganisms and the results were quantified as the diameter of the inhibition zones using the agar plate diffusion method [21]. Test bacteria and fungi (100 µL) were cultivated in 10 mL of mid-log phase Mueller-Hinton broth (MHB) or tryptone soya broth (TSB) nutrient media until a concentration of approximately 10^8 cells/mL for bacteria or 10^5 cells/mL for fungi was achieved. Test compound dissolved in DMSO (0.5 mg/mL) was added to each well, which had 10 mm diameter holes cut in the agar gel. The plates were sealed with paraffin film and incubated for 24 h at 37 ºC; for the bacterial strain and for 72 h at 27 ºC; for the fungal strain. Each test was repeated three times. After incubation, the growth of the microorganisms was assessed for a zone of inhibition, indicating its antimicrobial potential [22]. Tetracycline served as the standard antibacterial agent, while nystatin was utilized as the standard antifungal agent. The diameters of the resulting inhibition zones were measured in millimeters and analyzed as a criterion for antimicrobial activity. Solvent DMSO was used as a negative control in each experiment. The minimum inhibitory concentration (MIC) of the active compounds was assessed using the paper disk diffusion method [23].

Molecular docking: To obtain evidence for achieving good antibacterial properties, a molecular docking study was conducted on the 3D structure of the enzyme using the Maestro 16.0 program (Schrödinger Inc., USA). The chemical structure was sketched using ACD/ChemSketch (molecular modeling software). The energy of the depicted 2D structure was optimized utilizing Chem3D Pro software. The crystal structure of the target enzyme was obtained from the RCSB Protein Data Bank and subsequently processed with the Protein Preparation Wizard module of the software. The ligand molecule was then created using the molecular builder and underwent energy minimization. The active site was defined through the application of a grid box [24]. The Protein Preparation Wizard (version 2019-1, Schrödinger) served as the primary instrument for the preparation and minimization of the protein. Hydrogen atoms were incorporated into the protein structure and charge assignments were made accordingly. The protein underwent preprocessing and refinement, with modifications implemented through the analysis of water molecules in the workspace and other components. The essential water molecules were preserved, while all other molecules, excluding heteroatoms, were removed. A grid was established by taking into account the co-crystal ligand, which was incorporated into the active site of the chosen target protein (PDB ID: 1HNJ). Following the docking process with the co-crystal ligand in XP mode, the root mean square deviation (RMSD) was assessed to confirm the integrity of the protein, yielding an RMSD value of 0.20 Å.

***In silico* ADME study:** In order to evaluate the pharmacological effects, the most suitable ligands identified through molecular docking studies were examined for their ADME properties using the QuikPro tool [25]. The evaluation included various characteristics such as lipophilicity (log P), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) and permeability across the blood-brain barrier (BBB), human oral absorption and gut blood barrier (QPPCaco). Lipinski's rule of five was utilized to determine the drug-likeness of the substances [23].

RESULTS AND DISCUSSION

The synthetic pathway for the synthesis of a novel class of substituted benzylidene-5-phenyl-hydrothiazolo-pyrimidinone from 4-amino-2-substituted thiazolidine-5-carboxylic acid is illustrated in **Scheme-I**. In the first step, compounds

1a-e were derived from 2-amino-2-{(mercaptomethyl)amino}-acetic acid was synthesized using a previously established method, replacing 2-amino-3-(hydroxyamino)propanoic acid with serine [26]. Following acylation and cyclization reaction of compounds **1a-e** with benzoyl chloride in pyridine led to the formation of compounds **2a-e**. Subsequently, hydrazides **3a-e** of intermediates II were synthesized through the interaction with hydrazine hydrate in ethanol. Ultimately, the desired compounds **4a-o** were obtained by condensing intermediates III with various benzaldehydes in glacial acetic acid. The spectral characterization of the synthesized compounds was conducted using ^{1}H & ^{13}C NMR and mass spectrometry, with compound **4a** serving as a representative example for the structure confirmation. The ^{1}H NMR spectrum revealed a doublet peak at δ 4.29 ppm attributed to the C–H of pyridine, while another doublet peak corresponding to the CH_2 of thiazole was noted at δ 4.47 ppm. Additionally, a multiplet peak at δ 4.67 ppm was identified as another C–H of pyridine. The spectrum also displayed signals for six protons from the two benzene rings, which were observed in the range of δ 7.36 to 7.57 ppm, along with two protons detected between δ 8.16 and 8.31 ppm. A distinct peak attributed to the C-H bond of the Schiff base was observed at δ 8.58 ppm. Furthermore, the ^{13}C NMR spectra provide precise insights into the structure of compound, revealing the presence of 18 different types of carbon in various chemical environments. Furthermore, the high-resolution mass spectrometry analysis of compound **4a** exhibited an $[M + H]^+$ signal at *m/z* 336.10, which corresponds to its molecular weight.

Antimicrobial activity: The outcomes for the synthesized compounds **4a-o** are displayed in Table-1, indicating the mean diameter of the inhibition zone (mm) against both Gram-positive and Gram-negative bacteria as well as fungi. The evaluation of the tested compounds revealed that compounds **4d**, **4i** and **4k** exhibited superior antibacterial activity compared to tetracycline against Gram-negative strains assessed. Compounds **4l** and **4m** demonstrated superior efficacy exclusively against *E. coli* strains, whereas compounds **4b** and **4f** exhibited significant activity against *P. aeruginosa*. In contrast, compounds **4b**, **4n** and **4c** displayed similar effectiveness against *B. subtilis*, while compounds **4g** and **4c** showed comparable activity towards *S. aureus*. Furthermore, compounds **4i** and **4k** presented more promising antibacterial properties than tetracycline against the two evaluated Gram-negative bacteria. Compounds **4g**, **4d** and **4m** outperformed tetracycline in their activity against *E. coli*, while compounds **4e**, **4m** and **4a** demonstrated significant effectiveness against *P. aeruginosa*. Moreover, compounds **4c**, **4a** and **4j** exhibited comparable activity against the tested strain of *E. coli.* Compounds **4k** and **4i** demonstrated antifungal activity that surpassed that of the reference drug amphotericin B against the microorganisms *C. albicans* and *F. oxysporum*. Conversely, compounds **4d**, **4a** and **4j** exhibited superior efficacy against *F. oxysporum*, while compound **4f** displayed activity comparable to that of amphotericin B against both fungal strains, *C. albicans* and *F. oxysporum*.

Minimum inhibitory concentrations (MIC): Based on the antimicrobial screening results for all the synthesized compounds presented in Table-2, the minimum inhibitory concentrations (MIC) of the most effective thiazolo-pyrimidines **4k**, **4m**, **4a**, **4l**, **4n**, **4i** were established. Compound **4k**, which contains 3-nitrobenzylidene and 3-nitro-phenyl demonstrated remarkable antibacterial efficacy against *B. subtilis* and *S. aureus*, with minimum inhibitory concentrations (MIC) of 5.19 μM and 20.76 μM, respectively. In comparison, the standard positive control, tetracycline, exhibited MIC values of 34.36 μM and 68.72 μM for the same bacteria. Additionally, compound **4i**, featuring 2-methoxybenzylidene and 2-hydroxyphenyl, displayed the highest antibacterial activity among all derivatives against *S. aureus*, achieving an MIC of 15.21 μM, significantly lower than the MIC of 68.72 μM for tetracycline.

Furthermore, compounds **4i** and **4m** demonstrated superior antibacterial efficacy against *E. coli*, with minimum inhibitory concentrations (MIC) of 20.44 and 20.79 μM, respectively, in

TABLE-1
ANTIMICROBIAL ACTIVITY SCREENING OF THE SYNTHESIZED COMPOUNDS (*in vitro*) WITH MEAN DIAMETER OF INHIBITION ZONE (mm)

Compound	Gram-positive		Gram-negative		Fungi	
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*F. oxysporum*
4a	26 ± 0.71	16 ± 0.72	25 ± 0.12	13 ± 0.32	22 ± 0.52	19 ± 0.34
4b	31 ± 0.12	28 ± 0.98	23 ± 0.81	22 ± 0.42	17± 0.43	20 ± 0.51
4c	27 ± 0.66	24 ± 0.5	24 ± 0.41	17 ± 0.12	13 ± 0.3	20 ± 0.87
4d	15 ± 0.13	13 ± 0.87	16 ± 0.42	18 ± 0.56	13 ± 0.52	15 ± 0.73
4e	14 ± 0.4	23 ± 0.62	27 ± 0.22	14 ± 0.52	24 ± 0.77	19 ± 0.44
4f	26 ± 0.12	22 ± 0.72	24 ± 0.18	21 ± 0.32	20 ± 0.2	21 ± 0.97
4g	22 ± 0.11	22 ± 0.33	22 ± 0.41	15 ± 0.42	19 ± 0.78	20 ± 0.44
4h	32 ± 0.71	29 ± 0.53	21 ± 0.21	11 ± 0.12	22 ± 0.45	22 ± 0.23
4i	16 ± 0.21	22 ± 0.53	19 ± 0.25	15 ± 0.45	19 ± 0.54	12 ± 0.53
4j	17 ± 0.24	13 ± 0.52	24 ± 0.21	12 ± 0.22	21 ± 0.16	18 ± 0.14
4k	22 ± 0.23	16 ± 0.24	25 ± 0.23	19 ± 0.56	17 ± 0.23	14 ± 0.66
4l	18 ± 0. 43	15 ± 0.56	20 ± 0.56	19 ± 0.35	14 ± 0.57	16 ± 0.86
4m	21 ± 0.85	19 ± 0.57	19 ± 0.41	18 ± 0.44	16 ± 0.56	18 ± 0.57
4n	25 ± 0.87	23 ± 0.42	21 ± 0.44	19 ± 0.02	13 ± 0.2	15 ± 0.49
4o	15 ± 0.5	22 ± 0.42	23 ± 0.11	12 ± 0.12	19 ± 0.56	23 ± 0.33
Tetracycline	24 ± 0.96	24 ± 0.87	22 ± 0.21	19 ± 0.51	–	–
Amphotericin B	–	–	–	–	21 ± 0.08	20 ± 0.14

TABLE-2
MINIMUM INHIBITORY CONCENTRATIONS (MIC) OF THE MOST ACTIVE COMPOUNDS

Compound	Gram-positive		Gram-negative		Fungi	
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*F. oxysporum*
4k	5.19	20.76	21.76	70.69	24.03	47.36
4m	33.48	132.14	20.44	117.96	59.83	132.14
4a	21.8	61.92	68.48	136.96	34.19	68.48
4j	17.59	121.94	61.92	136.96	34.19	77.24
4n	17.44	136.11	136.11	181.41	68.55	120.89
4i	10.24	15.21	20.97	80.22	20.97	40.95
Tetracycline	34.36	68.72	17.18	68.72	–	–
Amphotericin B	–	–	–	–	17.18	34.36

comparison to tetracycline, which had an MIC of 17.18 µM. In contrast, compound **4k** exhibited enhanced antibacterial activity against *P. aeruginosa*, with an MIC of 70.69 µM, surpassing that of tetracycline, which recorded an MIC of 68.72 µM. Furthermore, compound **4i** showed antifungal properties with MIC values of 20.97 and 40.95 µM against *C. albicans* and *F. oxysporum* strains, respectively. Compound **4k** also demonstrated notable antifungal activity, ranking second among the tested compounds, with MIC values of 24.03 and 47.36 µM, compared to the standard positive control Amphotericin B, which had MIC values of 17.18 and 34.36 µM.

Molecular docking studies: In order to determine the proposed binding mode of the significant active compound against the *E. coli* FabH-CoA complex, docking studies were conducted. Docking scores of the compounds against the target *E. coli* FabH-CoA complex is presented in Table-3. The active compound **4d** (Figs. 1 and 2) demonstrated a single aromatic bond interaction with the amino acid residue GLY-306 *via* the thiazole moiety, achieving a docking score of –7.23 kcal/mol. Similarly, compound **4i** (Figs. 3 and 4) displayed one aromatic bond interaction with the phenol residue ILE-203 through the thiazole moiety, resulting in a docking score of –6.83 kcal/mol. Likewise, compound **4k** (Figs. 5 and 6) showed a single aromatic bond interaction with the amino acid residue GLY-306 through the thiazole moiety, yielding a docking score of –7.13 kcal/mol.

***In silico* prediction of physico-chemical and ADME parameters:** The pharmacokinetics and physico-chemical characteristics, as presented in Table-4, offer a quantitative analysis of the interactions between the human body and an administered compound. In accordance with Lipinski's rule of five (RO5), the majority of these compounds meet the criteria for drugs that are active when taken orally. Consequently, these compounds cafsn be regarded as promising candidates for antimicrobial drug development. Compounds **4d** and **4i** showed

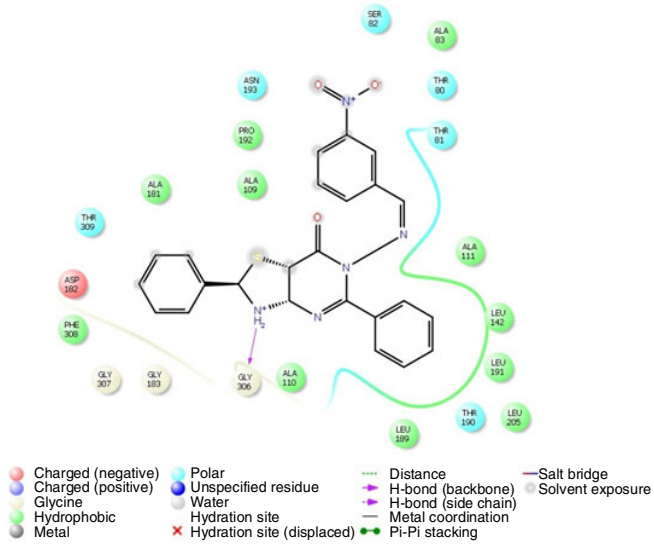


Fig. 1. 2D Ligand receptor interaction between compound **4d** and *E. coli* FabH-CoA complex

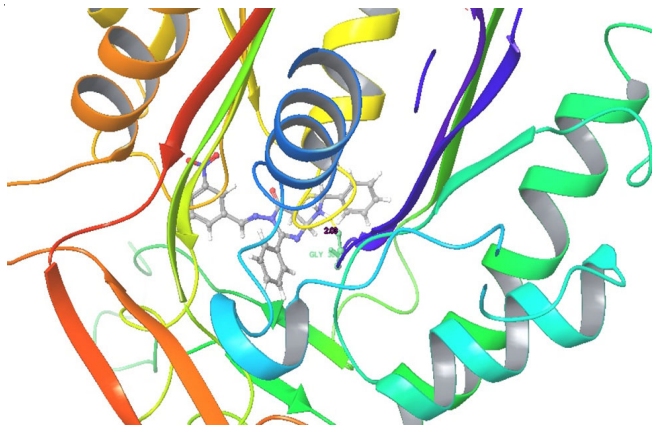


Fig. 2. 3D Ligand receptor interaction between compound **4d** and *E. coli* FabH-CoA complex

TABLE-3
DOCKING SCORES OF THE COMPOUNDS AGAINST THE TARGET *E. coli* FabH-CoA COMPLEX (PDB ID: 1HNJ)

Compound	Docking score (Kcal/mol)	Compound	Docking score (Kcal/mol)	Compound	Docking score (Kcal/mol)
4a	-6.29	**4f**	-6.43	**4k**	-7.13
4b	-6.47	**4g**	-6.32	**4l**	-6.50
4c	-6.38	**4h**	-6.11	**4m**	-6.49
4d	-7.23	**4i**	-6.83	**4n**	-6.43
4e	-6.30	**4j**	-6.18	**4o**	-6.16

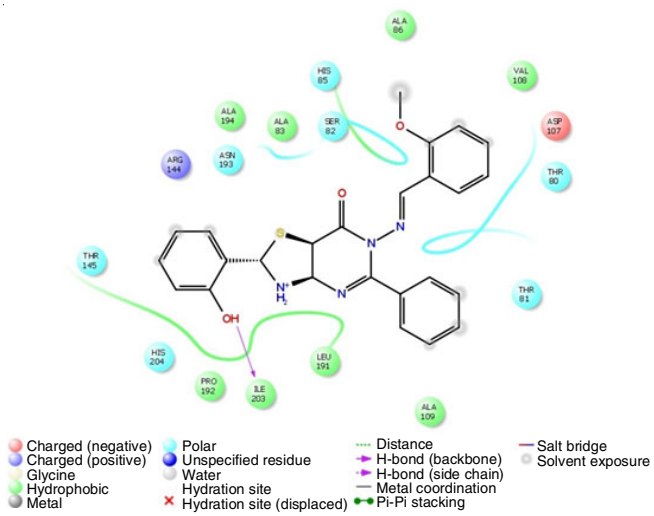


Fig. 3. 2D Ligand receptor interaction between compound **4i** and *E. coli* FabH-CoA complex

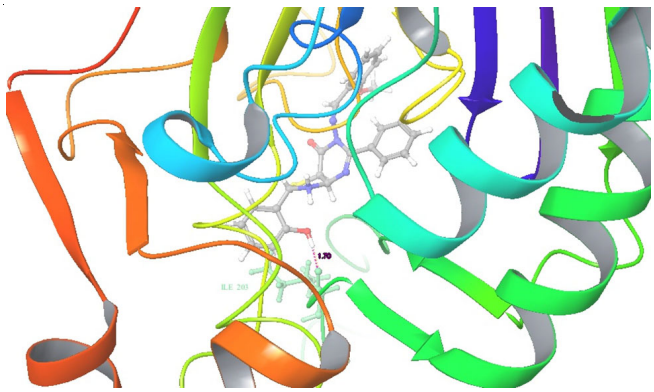


Fig. 4. 3D Ligand receptor interaction between compound **4i** and *E. coli* FabH-CoA complex

anticipated log P values of 3.82 and 4.13, respectively, indicating a degree of permeability across the blood-brain barrier (BBB). Additionally, both compounds exhibited significant oral absorption.

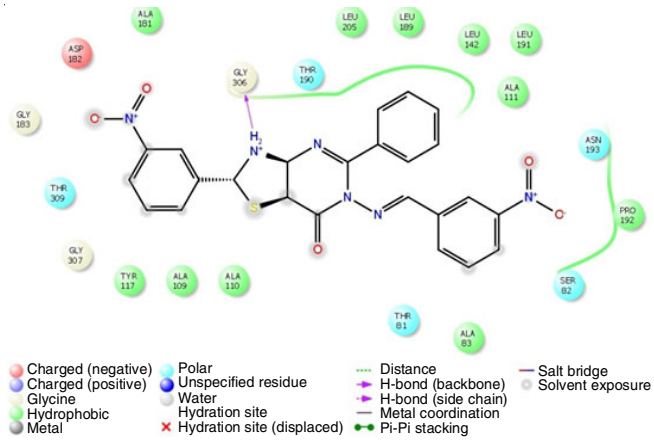


Fig. 5. 2D Ligand receptor interaction between compound **4k** and *E. coli* FabH-CoA complex

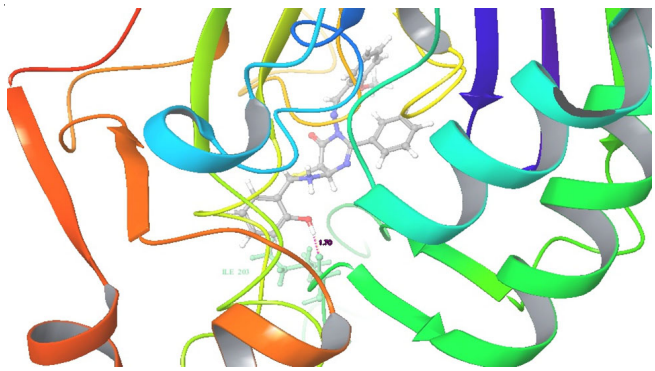


Fig. 6. 3D Ligand receptor interaction between compound **4k** and *E. coli* FabH-CoA complex

Lipinski's rule of five serves as a framework for assessing the ADME properties and drug-likeness of compounds with potential oral bioavailability in the medicinal chemistry. The physico-chemical attributes of a lead compound significantly influence its ADME characteristics. Therefore, a thorough analysis of these physico-chemical parameters was conducted, which included the evaluation of ADME specifications such

TABLE-4
ADME SPECIFICATION OF NOVEL DESIGNED COMPOUND

Compd.	Rotatable bonds	m.w.	HBD	HBA	Log P	BBB permeability	Lipinski rule	% Human oral absorption	QPPCaco
4a	4	336.41	1	5.50	3.29	0.20	0	95.37	567.16
4b	5	381.41	1	6.50	2.52	-0.97	0	73.05	56.25
4c	5	366.44	1	6.25	3.09	-0.04	0	91.06	372.29
4d	5	457.51	1	6.50	3.82	-0.34	0	89.13	168.24
4e	5	428.51	2	6.25	3.97	-0.10	0	95.50	340.85
4f	6	453.52	2	7.75	3.65	-0.79	0	85.20	115.02
4g	6	473.50	2	7.25	3.51	-1.46	0	74.31	31.44
4h	5	462.95	2	6.25	4.04	-0.23	0	91.27	186.52
4i	6	458.53	2	7.00	4.13	-0.48	0	92.91	216.31
4j	6	482.52	1	8.00	2.99	-1.18	0	71.28	31.50
4k	6	502.50	1	7.50	3.59	-2.07	2	40.32	10.47
4l	5	491.95	1	6.50	4.70	-0.90	0	87.15	67.26
4m	6	487.53	1	7.25	3.97	-0.46	0	89.48	156.74
4n	5	476.98	1	6.25	4.93	0.48	0	100	1010.12
4o	6	472.56	1	7.00	5.14	0.07	1	95.25	723.63

HBA = Hydrogen bond acceptor, HBD = Hydrogen bond donor, Log P = partition coefficient.

as rotatable bonds, molecular weight, hydrogen bond donors (HBDs), hydrogen bond acceptors (HBAs), log P and blood-brain barrier (BBB) permeability.

The anticipated characteristics of the synthesized compounds, as presented in Table-4, conform to Lipinski's rule of five. The Caco-2 cell permeability for all predicted compounds falls within the acceptable range, with the exception of compound **4k**, which demonstrated a lower permeability of 10.47 nm/sec. The majority of the compounds displayed oral human absorption values ranging from 77% to 96%. In summary, the predicted parameters of the synthesized compounds align with the physico-chemical properties typically observed in most clinically approved drugs, including tetracycline, which serves as a standard for *in vitro* antibacterial activity.

Conclusion

In current investigation, thiazole-fused pyrimidine derivatives (**4a-o**) were designed and synthesized to evaluate their antimicrobial efficacy. Compounds **4i** and **4k** exhibited superior activity within the series, accompanied by favourable pharmacokinetic profiles. Furthermore, the molecular docking studies corroborate the significant interactions with target molecules. This study suggests a promising pathway for the development of novel and effective antimicrobial agents.

ACKNOWLEDGEMENTS

The School of Pharmaceutical Education and Research at Jamia Hamdard, New Delhi facilitated this work by offering the essential resources for the docking studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. M. Fekadu, D. Zeleke, B. Abdi, A. Guttula, R. Eswaramoorthy and Y. Melaku, *BMC Chem.*, **16**, 1 (2022); https://doi.org/10.1186/s13065-022-00795-0
2. C.A. Taft, V.B. Da Silva and C.H.T.D.P. Da Silva, *J. Pharm. Sci.*, **97**, 1089 (2008); https://doi.org/10.1002/jps.21293
3. Ü. Elvan, N. Sahin, I. Özdemir, S. Günal, N. Gürbüz, I. Özdemir and D. Sémeril, *Arch. Pharm.*, **356**, 2300302 (2023); https://doi.org/10.1002/ardp.202300302
4. A.C. Karaburun, U.A. Çevik, D. Osmaniye, B.N. Saglik, S. Levent, Y. Özkay, B.K. Çavusoglu, A.S. Koparal, M. Behçet and Z.A. Kaplancikli, *Molecules*, **23**, 3129 (2018); https://doi.org/10.3390/molecules23123129
5. N. Shanmugapriya, V. Balachandran, B. Revathi, B. Narayana, V.V. Salian, K. Vanasundari and C. Sivakumar, *Heliyon*, **7**, e07634 (2021); https://doi.org/10.1016/j.heliyon.2021.e07634
6. D. Osmaniye, U. Kayis, Ü.D. Gül, Y. Özkay and Z.A. Kaplancikl, *Eur. J. Life Sci.*, **2**, 1 (2023); https://doi.org/10.55971/EJLS.1270394
7. A.M. El-Naggar, A. Zidan, E.B. Elkaeed, M.S. Taghour and W.A. Badawi, *J. Saudi Chem. Soc.*, **26**, 101488 (2022); https://doi.org/10.1016/j.jscs.2022.101488
8. M.A.A. Radwan, M.A. Alshubramy, M.A. Motaal, B.A. Hemdan and D.S. El-Kady, *Bioorg. Chem.*, **96**, 103516 (2020); https://doi.org/10.1016/j.bioorg.2019.103516
9. É. Frank and G. Szollosi, *Molecules*, **26**, 4617 (2021); https://doi.org/10.3390/molecules26154617
10. J. Jampilek, *Molecules*, **24**, 3839 (2019); https://doi.org/10.3390/molecules24213839
11. K. Elumalai, A. Shanmugam, M. Devaraji and S. Srinivasan, *Carbon. Resour. Convers.*, **7**, 100222 (2024); https://doi.org/10.1016/j.crcon.2024.100222
12. X.Q. Bai, C.S. Li, M.Y. Cui, Z.W. Song, X.Y. Zhou, C. Zhang, Y. Zhao, T.Y. Zhang and T.Y. Jiang, *Mol. Divers.*, **24**, 1165 (2020); https://doi.org/10.1007/s11030-019-10019-8
13. B. Akter, M.S. Uddin, M.R. Islam, K.U. Ahamed, M.N. Aktar, M.K. Hossain, A.M. Salamatullah and M. Bourhia, *Cell Biochem. Biophys.*, (2024); https://doi.org/10.1007/s12013-024-01540-1
14. J. Vora, S. Patel, M. Athar, S. Sinha, M.T. Chhabria, P.C. Jha and N. Shrivastava, *J. Biomol. Struct. Dyn.*, **38**, 1726 (2019); https://doi.org/10.1080/07391102.2019.1615002
15. M. Anguraj, and T. Sundarrajan, *Chem. Phys. Impac.*, **8**, 100512 (2024); https://doi.org/10.1016/j.chphi.2024.100512
16. A.B. Raies and V.B. Bajic, *Wiley Interdiscip. Rev. Comput. Mol. Sci.*, **6**, 147 (2016); https://doi.org/10.1002/wcms.1240
17. A.M. Naglah, A.A. Askar, A.S. Hassan, T.K. Khatab, M.A. Al-Omar and M.A. Bhat, *Molecules*, **25**, 1431 (2020); https://doi.org/10.3390/molecules25061431
18. Y.A. Ammar, A.A. Farag, A.M. Ali, A. Ragab, A.A. Askar, D.M. Elsisi, and A. Belal, *Bioorg. Chem*., **104**, 104164 (2020); https://doi.org/10.1016/j.bioorg.2020.104164
19. P. Prabhala, H.M. Savanur, S.M. Sutar, K.N. Naik, M.K. Mittal and R.G. Kalkhambkar, *Eur. J. Med. Chem. Rep.*, **5**, 100048 (2021); https://doi.org/10.1016/j.ejmcr.2022.100048
20. M. Makosha, S. Sithole and S. Mukanganyama, *Adv. Pharmacol. Pharm. Sci.*, **2021**, 6616133 (2021); https://doi.org/10.1155/2021/6616133
21. H.A. Mohamed, Y.A. Ammar, G.A.M. Elhagali, H.A. Eyada, D.S. Aboul-Magd and A. Ragab, *ACS Omega*, **7**, 4970 (2022); https://doi.org/10.1021/acsomega.1c05801
22. S. Ejaz, H. Nadeem, R.Z. Paracha, S. Sarwar and S. Ejaz, *BMC Chem.*, **13**, 115 (2019); https://doi.org/10.1186/s13065-019-0631-6
23. A.S. Hassan, A.A. Askar, E.S. Nossier, A.M. Naglah, G.O. Moustafa and M.A. Al-Omar, *Molecules*, **24**, 3130 (2019); https://doi.org/10.3390/molecules24173130
24. S.J. Laulloo, P. Caumul, N. Joondan, S. Jawaheer, S. Parboteeah, S.D. Dyall and M.G. Bhowon, *Biointerface Res. Appl. Chem.*, **12**, 7356 (2021); https://doi.org/10.33263/BRIAC126.73567375
25. Z. Ali, M.J. Akhtar, M.R. Haider, A.A. Khan, A.A. Siddiqui and M. Shahar Yar, *Bioorg. Chem.*, **71**, 181 (2017); https://doi.org/10.1016/j.bioorg.2017.02.004
26. K. Ono, M. Jung, T. Zhang, H. Tsutsuki, H. Sezaki, H. Ihara, F.-Y. Wei, K. Tomizawa, T. Akaike and T. Sawa, *Free Radic. Biol. Med.*, **106**, 69 (2017); https://doi.org/10.1016/j.freeradbiomed.2017.02.023