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EXPLORING THIAZOLE-DERIVED HETEROCYCLES: ASSESSING ANTIBACTERIAL, ANTIFUNGAL PROPERTIES, AND ADME PROFILING

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Abstract
This research focused on the synthesis and comprehensive biological evaluation of a series of thiazole-based bioactive heterocycles. The compounds were synthesized and characterized, followed by an evaluation of their antibacterial and antifungal activities.. Additionally, ADME (Adsorption, Distribution, Metabolism, Excretion) profiling was conducted to assess the pharmacokinetic properties of the compounds. The antibacterial and antifungal activities of the strains were assessed against a bacterial strains including *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes* and fungal *C. albicans*, *A. niger* and *A. clavatus* strains. Furthermore, the compounds were subjected to thorough ADME profiling to predict their adsorption, distribution, metabolism, and excretion behaviors.
Keywords: Thiazole, Antibacterial, Antifungal, ADME, SAR study.

Introduction

Antimicrobial resistance occurs when bacteria and fungi acquire the capacity to overcome the medications created to destroy them. Drug resistance makes treating illnesses more difficult or impossible and antibiotics and other antimicrobial medications are useless. The healthcare, veterinary, and agricultural sectors, as well as individuals at any stage of life, could be impacted by antimicrobial resistance. This makes it one of the world's most important public health issues. Antimicrobial resistance is becoming increasingly dangerous, and this problem may worsen in developing nations due to the egregious overuse of antibiotics[i] . Antimicrobial usage, regardless of how reasonable or justified, is recognized as contributing to the emergence of resistance, but broad, indiscriminate use only exacerbates the problem [ii] . The accessibility of antimicrobial drugs across the market, without the need for a prescription, and through uncontrolled supply chains encourage their abuse in developing countries [i,iii]. Each year, approximately 2.2 million people die due to waterborne infections worldwide [iv, v]. Consequently, it is imperative to discover new antibacterial agents. *E. coli* causes various health issues in humans such as diarrhea. Lu Li reported the mechanism of antibiotic resistance to ampicillin and the similar inactivity of chloramphenicol against *E.coli* [vi,vii]. The development and analysis of several structural scaffold modifications with known antibacterial properties over the past few decades have created numerous novel scaffolds.

Bacteria that cause different diseases, for example, E. coli, are among the most common bacterial illnesses and include cholecystitis, bacteremia, cholangitis, urinary tract infection (UTI), traveler's diarrhea, and other therapeutic diseases such as neonatal meningitis and pneumonia.

The diverse properties and applications of heterocyclic compounds make them an important class of chemicals in both natural and synthetic chemistry [viii-xii]. Healthcare has benefited greatly from the use of heterocyclic compounds [xiii-xx]. Because of their distinctive regulatory features within a medication, such as solubility, lipophilicity, and polarity, heterocyclic compounds are thus widely used in the field of pharmaceuticals, such as antibacterial[xxi], antifungal [xi], antioxidant, anti-inflammatory[xxii] and anticancer agents[xxiii] . They are actively being explored for the creation of desirable therapeutic ingredients[xiv,xxiv].

The thiazole ring is a five-membered heterocyclic compound containing nitrogen and sulfur. Thiazole compounds have attracted researchers' interest for several years due to their broad range of biological and pharmacological properties, including antimicrobial[xxv, xxvi], anti-inflammatory[xxvii,xxviii], anticonvulsant[xxix], anticancer [xxx], and antimalarial effects[xxviii]. Medicinal chemistry and chemical biology researchers have evaluated molecules with thiazole skeletons since they exhibit substantial biological activity. A few examples of thiazole derivatives are shown in Figure 1. In addition, the hydrazinylthiazolyl core is a significant organic structure that has sparked intense interest among researchers working in both medical and industrial fields. Hydrazinylthiazolyl analogs have a unique pharmacological profile that includes antitubercular, antimalarial, anti-inflammatory, anticancer, antiproliferative, antioxidant, and antibacterial effects [xxvi,xxxi].

Therefore, in the present work, we report the synthesis of 2-hydrazinyl-thiazole. The antibacterial and antifungal activities of the synthesized compounds were tested.

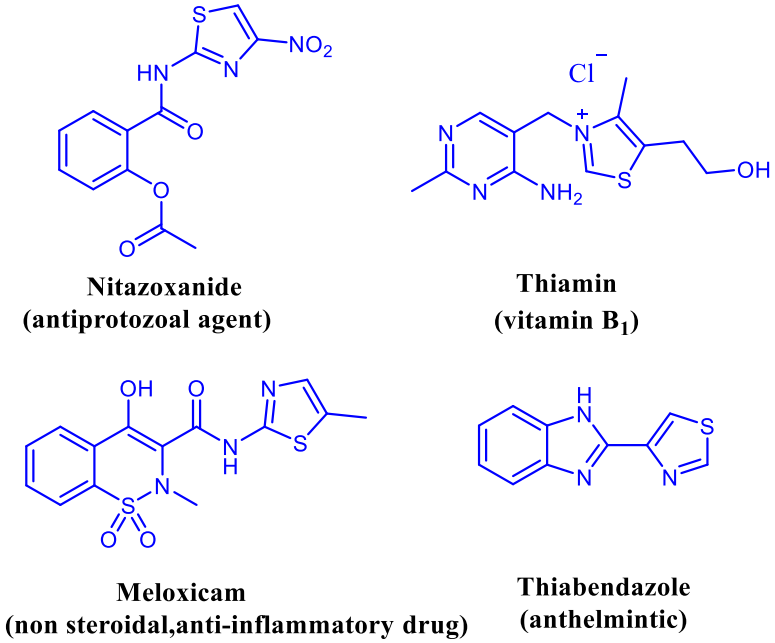


Figure 1 Several reported drugs containing thiazoles

2. Materials and Methods

2.1. General remarks

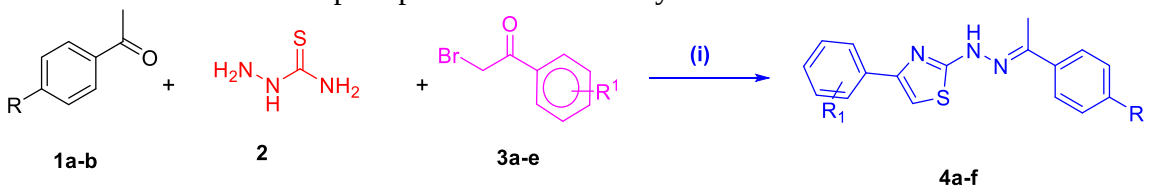
All of the high-purity compounds were purchased from commercial sources (Sigma Aldrich and Avra Synthesis). The compounds were used without purification. Melting points were determined in open capillaries and uncorrected. Potassium bromide pellets were used to obtain FT-IR spectra, and a Bruker was used to obtain ^{1}H NMR (500 MHz) and ^{13}C NMR

(126 MHz) spectra while using DMSO-d6 as the solvent. The reactions were visualized using thin-layer chromatography with silica gel 60 F254 and aluminum sheets (Merck).

2.2. Procedure

2.2.1 General procedure for the synthesis of 2-hydrazinyl-thiazol derivatives

The substituted acetophenones 1a-b (0.01 mol) were added to a conical flask containing 10 mL of ethanol. Then, acetic acid was added and stirred at 70–80°C. Thiosemicarbazide 2 (0.01 mol) was subsequently added, after which the mixture was stirred for an additional 30 minutes. After that, unsubstituted/substituted phenacyl bromides 3a-e (0.01 mol) were gradually added. The solid product formed. After that, the reaction mixture was stirred for an additional 5 minutes. The product was poured into ice-cold water, and the product was filtered and dried to form pure products 4a-f. The synthetic route is shown below.



1a-b 2 3a-e 4a-f

R =ethyl, methoxy

Reaction conditions

i = EtOH, AcOH (cat.), stir at 70-80° C

2.3. Spectral data of the synthesized compounds

(*E*)-4-(4-bromophenyl)-2-(2-(1-(4-ethyl-phenyl)ethylidene)hydrazineyl)thiazole (4a)

^{1}H NMR (500 MHz, DMSO) δ 11.11 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.16 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 2.68 – 2.62 (m, 2H), 2.30 (s, 3H), 1.25 (t, J = 7.6 Hz, 3H);^{13}C NMR (126 MHz, DMSO) δ 169.67, 158.62, 144.36, 135.40, 128.25, 127.92, 127.68, 126.72, 123.1, 125.57, 113.83, 101.72, 27.82, 15.42, 13.91.

(*E*)-2-(2-(1-(4-Ethyl-phenyl)ethylidene)hydrazineyl)-4-(4-methoxy-phenyl)thiazole (4b)

^{1}H NMR (500 MHz, DMSO) δ 11.14 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.13 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 2.65 – 2.58 (m, 2H), 2.31 (s, 3H), 1.20 (t, J = 7.6 Hz, 3H);^{13}C NMR (126 MHz, DMSO) δ 169.56, 158.62, 144.36, 135.40, 128.25, 127.92, 127.68, 124.18, 126.72, 125.57, 113.83, 101.72, 54.99, 27.78, 15.36, 13.85

(*E*)-2-(2-(1-(4-Methoxyphenyl)ethylidene)hydrazineyl)-4-(4-nitrophenyl)thiazole(4c)

^{1}H NMR:(500 MHz, DMSO) δ 11.27(s, 1H), 8.29(d, J = 9.0 Hz, 2H), 8.13(d, J = 9.0 Hz, 2H),7.74 (d, J = 8.9 Hz, 2H), 7.72 (s, 1H), 6.99 (d, J =8.9 Hz, 2H), 3.80 (s, 3H), 2.31 (s, 3H).^{13}C NMR: (126 MHz, DMSO) 170.85,160.41, 149.12,147.46, 146.61, 141.37, 130.76, 127.64, 126.77, 124.60, 114.30, 109.28, 55.70, 14.52.

(*E*)-2-(2-(1-(4-Methoxyphenyl)ethylidene)hydrazineyl)-4(4-cyanophenyl)thiazole (4d)

^{1}H NMR (500 MHz, DMSO) δ 11.10 (s, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.32 (s, 1H), 7.28 –7.24 (d, J=8.0 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 3.76 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 169.98, 162.46, 159.79, 149.22, 146.59, 131.31, 130.31, 127.46, 127.12, 122.82, 115.32, 113.62, 103.45, 55.16, 14.18.

(*E*)-2-(2-(1-(4-Methoxyphenyl)ethylidene)hydrazineyl)4-(4-hydroxyphenyl)thiazole (4e)

^{1}H NMR (500 MHz, DMSO) δ 11.14 (s, 1H), 7.91 (d, J= 8.2 Hz, 2H), 7.74 (d, J= 8.8 Hz, 2H), 7.62 (d, J= 8.2 Hz, 2H), 7.26 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 169.96, 159.77, 149.20, 146.57, 131.29, 130.28, 127.01, 122.28,115.38, 115.21, 113.67, 103.47, 55.06, 13.85.

(*E*)-2-(2-(1-(4-Methoxyphenyl)ethylidene)hydrazineyl)-4-phenyl-thiazole (4f)

^{1}H NMR (500 MHz, DMSO) δ 10.98 (s, 1H), 7.86-7.78 (m, 5H), 7.34 (s, 1H), 7.25-7.21 (d, J = 7.1 Hz 2H), 6.97 (d, J = 7.1 Hz, 1H), 3.79 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (126 MHz,

DMSO) δ 168.92, 160.48, 159.74, 149.16, 146.59, 131.26, 130.31, 127.44, 127.38, 115.34, 113.69, 103.49, 55.06, 13.91.

2.4. Antimicrobial activity

The antimicrobial activity was determined as described in our previous report [xxxii]. To determine the proper concentrations for screening standard bacterial strains, the minimum inhibitory concentrations (MICs) of synthesized compounds were assessed using broth microdilution methods with DMSO as diluent. In the primary and secondary testing, successive dilutions were made. Before the test organism was inoculated, a loopful of a control tube with no antibiotic was evenly distributed over a portion of the plate of media suitable for growth. The cells were then incubated overnight. The tubes were then kept in an incubator overnight. The MIC for the control organism was evaluated to confirm that the drug concentrations were precise. The minimum inhibitory concentration (MIC) was determined to be the lowest concentration of an antimicrobial or test compound that permitted no discernible growth. The control tube was used as a transplant, and all the other tubes that showed no visible growth were incubated at 37°C overnight. A second batch of identical dilutions infected with a microbe of known sensitivity was added to the test. Before incubation, the amount of fungus developed in the test tube containing the initial inoculum was measured. The synthesized chemicals were diluted to a standard solution concentration of 2000 μg/mL. In the primary screening, the synthesized compounds were tested at concentrations of 500, 250, and 200 μ/mL. In the second set of dilutions, the active synthetic compounds identified during this initial screening were evaluated against every type of bacterium. The substances that demonstrated activity in the initial screening were similarly diluted to obtain concentrations of 100, 62.5, 50, 25, 40, 32, and 12.5 μ/mL

3. Results and Discussion

3.1. Chemistry

Thiazoles (4a-f) were synthesized. Here, we synthesized a thiazole using a green reaction medium, requiring less reaction time and yielding well. All the synthesized compounds were confirmed by ^{1}H NMR and ^{13}C NMR. These compounds exhibited prominent signals in the range of 11.27-10.98 ppm and were assigned to the N-H group, while the normal signal for the methyl group appeared as a singlet in the range of 2.32-2.30 ppm in the 1H NMR spectra. The presence of C=O and C=N groups in the region of 170-162.92 and 168.92-158.62 ppm, respectively, as well as methyl carbon in the range of 14.52-13.85 ppm, was confirmed by ^{13}C NMR spectroscopy.

3.2. Antimicrobial activity

The antimicrobial effects of the synthesized 3-(1-(2-(thiazol-2-yl)hydrazineylidene)ethyl)-2H-chromen-2-one derivatives were studied by using the broth dilution method. All synthesized compounds were screened for in vitro antibacterial activity against *E.coli*, *P.aeruginosa*, *S. aureus*, and *S. pyogenus*. The MIC was determined by the highest dilution that showed at least 99% inhibition. The results of the antibacterial screening of synthesized compounds are reported as MIC values in Table 1 and Figure 2.

Compounds 6a (R = 4-F), 6c (R = 4-H), and 6 g (R = 2-F, 4-F) showed equipotent activity (MIC = 50 μ/mL) compared to standard chloramphenicol (MIC = 50 μ/mL)and ampicillin (MIC = 40 μ/mL) against E. coli. Furthermore, compound 6j (R= 3-OH) exhibited good activity against *P. aeruginosa*. All the synthesized compounds exhibited moderate to good activity against *E.coli* and *P. aeruginosa*. All the synthesized compounds exhibited weak antifungal activity, as shown in Table 2

Table 1 Minimum inhibitory concentrations of synthesized 2-hydrazinyl-thiazol derivatives (4a to 4f) against several bacterial strains

Sample code	***E.coli***	***P. aeruginosa***	***Staphylococcus aureus***	***S. pyogenus.***
4a	100	125	125	250
4b	100	125	200	200
4c	50	62.5	100	100
4d	62.5	50	125	100
4e	50	125	100	100
4f	100	125	125	200
Ampicillin	40	NA	32	25
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

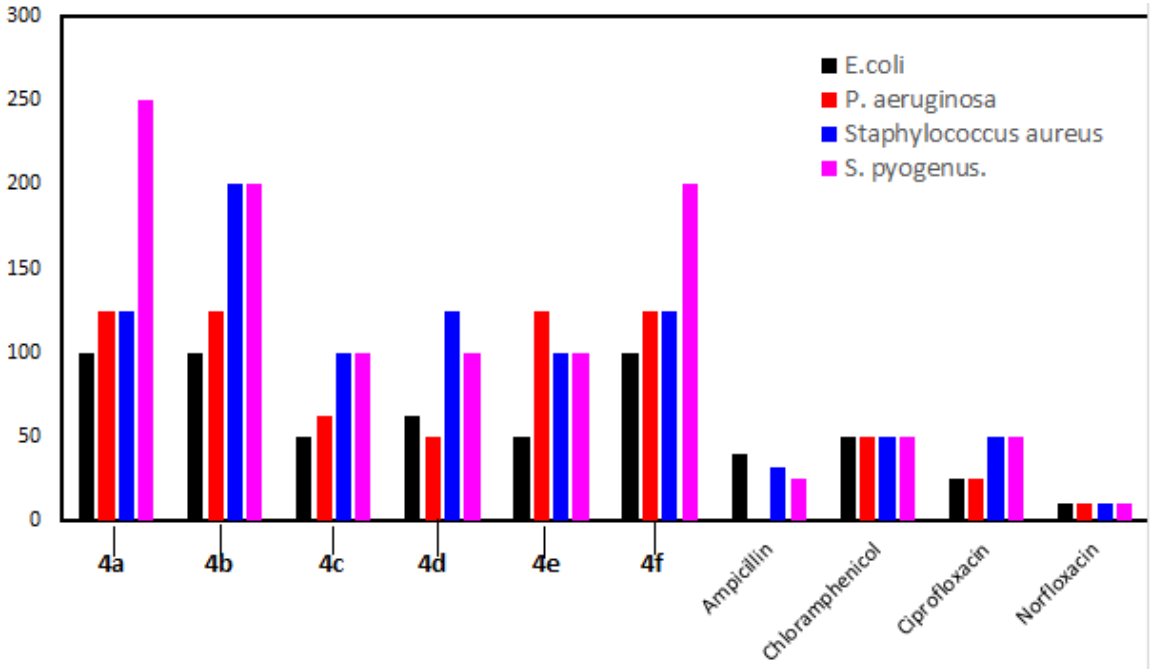


Figure 2 MICs of synthesized compounds against bacterial strains

Table 2 Minimum inhibitory concentrations of synthesized 2-hydrazinyl-thiazol derivatives (4a to 4f) against several fungal strains

Entry	***C. albicans***	***A. niger***	***A. clavatus***
	MTCC 227	MTCC 282	MTCC 1323
4a	250	1000	1000
4b	500	1000	1000
4c	500	1000	1000
4d	250	500	500
4e	500	1000	1000
4f	500	1000	1000
Nystatin	100	100	100

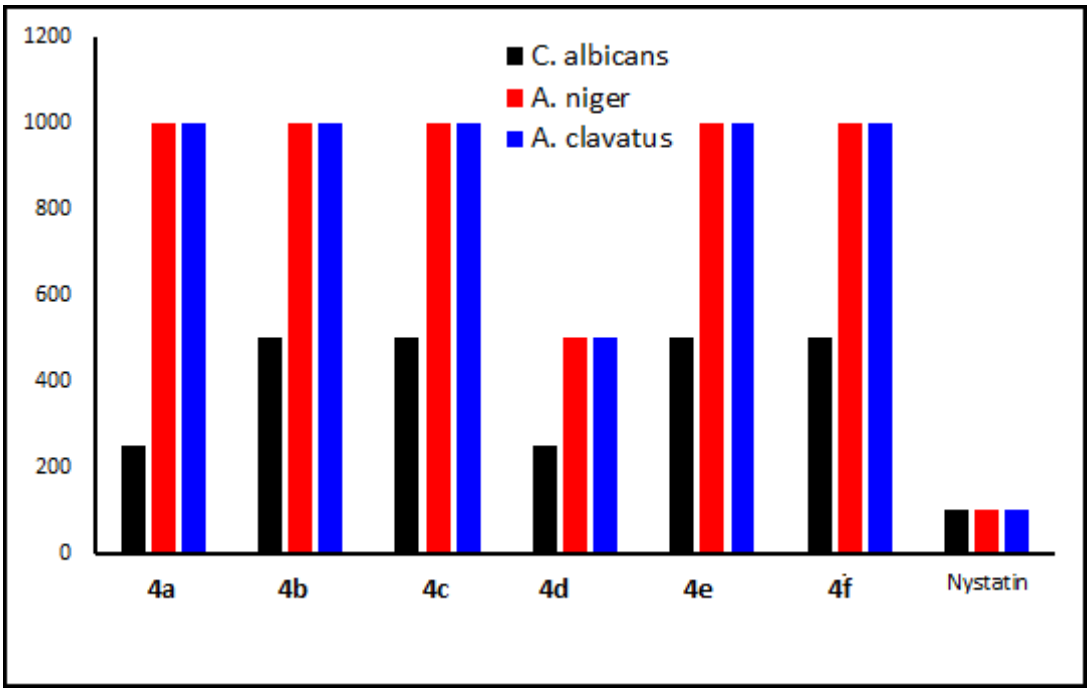


Figure 3 MICs of synthesized compounds against fungal strains

3.3. Structure-activity relationship study

The synthesized 2-hydrazinyl thiazole derivatives (3a to 3) were screened for antibacterial activity against two gram-negative strains of the bacteria *Escherichia coli* (MTCC 443) and *Pseudomonas aeruginosa* (MTCC 1688); two gram-positive bacteria, *Staphylococcus aureus* (MTCC 96) and *Streptococcus pyogenes* (MTCC 442); and in vitro antifungal activities against *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323). The general structures of the synthesized compounds are shown in Figure 4.

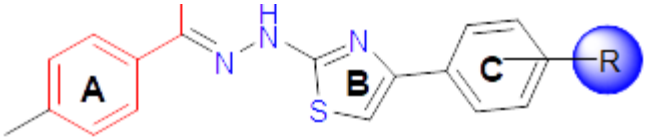


Figure 4 General structures of 2-hydrazineyl thiazole derivatives

The study of the structure-activity relationships (SARs) of thiazoles involves examining how changes in the chemical structure of these compounds affect their biological activity. This has been done by synthesizing a series of compounds with varying chemical modifications and testing them for antimicrobial activity. Overall, a SAR study of thiazoles provides valuable insights into the molecular features that are important for the biological activity of these compounds, which could ultimately facilitate the design of more potent and selective drugs. In the SAR study, electron-donating groups (hyperconjugation and resonance effects), such as methoxy, phenyl, bromo, and hydroxy groups, exhibited less antimicrobial activity than did the electron-withdrawing nitro and cyano groups. In the present research, SAR studies were used to investigate the relationship between the chemical structure of the synthesized thiazoles and their biological activity. In the case of antimicrobial activity, electron-withdrawing groups (EWGs) are known to increase the effectiveness of certain compounds[xxvi] [26]. EWGs are groups of atoms that tend to accept electrons from other atoms in a molecule. This can affect the chemical properties of a molecule, including its ability to interact with and inhibit microbial growth. We found that moderate EWGs (with a -R effect), such as nitro (3c and 3d) and cyano groups, exhibited good antibacterial activity. In contrast, the electron-donating groups (EDGs) bromo (3a) and methoxy (3b) groups containing thiazole derivatives showed weak antibacterial activity. The unsubstituted phenyl ring containing the thiazole derivative (3f) has shown weaker antibacterial activity than the thiazoles containing EDGs.

3.4. ADME study

The Swiss ADME web server[xxxiii] analyzes physiological parameters such as ADME (Adsorption, Distribution, Metabolism, Excretion) and medication similarity. The SMILE format for all synthesized thiazole compounds was uploaded to the web platform to predict physiological and pharmacokinetic parameters, and the detailed outcomes are summarized in Table 3. The ESOL (Log S) method was used to determine the aqueous solubility of the synthesized compounds, revealing that most of the thiazole derivatives are moderately soluble in water. Lipophilicity, assessed through Log Po/w, was found to be within acceptable limits for all synthesized thiazole compounds, except for 4a. Adhering to Lipinski's "rule of five" regarding hydrogen bond acceptors (HBAs) and donors (HBDs) demonstrated that all synthesized compounds met the criteria, with a minimum of 10 and a maximum of 5, respectively, in all the examined structures. The topological polar surface area (tPSA), a measure of the polar fragmentation effect, was confirmed to be less than 140 Å2 for all the thiazole derivatives. Gastrointestinal (GI) absorption was high for all the compounds, and none of the gastrointestinal tract components exhibited blood-brain barrier (BBB) permeability. Thiazole derivatives were identified as non-P-glycoprotein (P-gp) substrate inhibitors based on in silico data, except for 4a, 4b, 4c, and 4d. Moreover, all the thiazoles under investigation were CYP1A2, CYP2C19, CYP2C9, and CYP3A4 inhibitors, except for 4e and 4f, which also inhibit CYP2D6. According to the drug likeness data, all the evaluated thiazoles are considered drug-like compounds, and the majority of the compounds align with the Lipinski, Ghose, Veber, and Egan criteria.

Table 3 Physicochemical properties, lipophilicity, water solubility, pharmacokinetic characteristics, and drug likeness matching of the examined thiazole derivatives (4a–4f)

Entry	Physicochemical Properties			Lipophilicity	Water Solubility		Pharmacokinetics				Drug likeness matching
	Number of Hydrogen bond donors	Number of Hydrogen bond acceptors	Molecular Polar surface area (TPSA), $Å^2$	Log Po/w (Consensus)	Log S (ESOL)	Solubility	GI absorption	BBB permeability	P-gp substrate	Metabolic enzymes inhibition	
4a	1	2	65.52	5.31	-6.47	Poorly soluble	High	No	No	CYP1A2, CYP2C19, CYP2C9 CYP3A4	Lipinski, Veber, Egan
4b	1	3	74.75	3.20	-5.10	Moderately soluble	High	No	No	CYP1A2, CYP2C19, CYP2C9 CYP3A4	Lipinski, Ghose, Veber, Egan
4c	1	5	120.57	4.22	-5.55	Moderately soluble	High	No	No	CYP1A2, CYP2C19, CYP2C9 CYP3A4	Lipinski, Ghose, Veber, Egan, Muegge
4d	1	4	98.54	3.79	-5.00	Moderately soluble	High	No	No	CYP1A2, CYP2C19, CYP2C9, CYP3A4	Lipinski, Ghose, Veber, Egan, Muegge
4e	2	4	94.98	3.61	-4.91	Moderately soluble	High	No	No	CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4	Lipinski, Ghose, Veber, Egan, Muegge
4f	1	3	74.75	4.03	-5.06	Moderately soluble	High	No	No	CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4	Lipinski, Ghose, Veber, Egan, Muegge

4. Conclusion

In conclusion, the thiazole hybrids synthesized in this study exhibited significant antibacterial activity against a range of bacterial strains. These compounds could be developed as bioactive agents for treating infections caused by these microorganisms. The multicomponent reaction strategy used for synthesizing these compounds is convenient and efficient and can be used for synthesizing other bioactive heterocycles. Characterization of the synthesized compounds using various spectroscopic techniques confirmed their structure and purity. Overall, the results of this study provide insights into the potential of coumarin-appended thiazole hybrids as bioactive agents and pave the way for further research in this area.

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Compliance with ethical standards

The authors declare that they have no conflicts of interest.

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