RESEARCH ARTICLE

Synthesis, Molecular Docking, and Biological Evaluation of novel thiazole based thiazolidine-4-one derivatives

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ABSTRACT
A series of 2-(substituted aryl)-3-(thiazol-2-yl)thiazolidin-4-one derivatives (2a–2j) were synthesized using conventional organic chemistry methods and characterized through melting point determination, Thin Layer Chromatography (TLC), Fourier Transform Infrared (FT-IR) spectroscopy, Nuclear Magnetic Resonance (NMR) spectroscopy, and Mass Spectrometry. The compounds were purified by recrystallization and column chromatography. In-silico docking studies, performed using Autodock/PyRx software, predicted the potential interactions of the compounds with PDB ID-1KZN. The antimicrobial activity was evaluated using the Zone of Inhibition method, with compound 2b showing the strongest effect against *S. aureus* and compound 2j demonstrating the largest inhibition zone against *E. coli*. Molecular docking studies indicated that the presence of methoxyphenyl and indole moieties contributed to stronger binding affinity to the target proteins. All compounds met Lipinski's Rule of Five, indicating favorable drug-like properties and a high potential for oral bioavailability. These findings suggest that the synthesized compounds are promising candidates for further antimicrobial and therapeutic development, warranting in vitro and in vivo studies for validation.
Keywords: thiazole, thiazolidine derivatives, molecular docking
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INTRODUCTION

The ongoing battle against infectious diseases, particularly those caused by drug-resistant pathogens, underscores the critical need for the discovery and development of new antibacterial agents[1]. Despite the introduction of numerous antibiotics over the past several decades, the rise of antimicrobial resistance (AMR) continues to threaten global health, rendering many existing drugs ineffective[2]. In addition to resistance, the side effects associated with current pharmaceuticals further complicate the treatment of bacterial infections, making it essential for the scientific community to focus on novel drug candidates with improved therapeutic profiles[1]. The discovery of novel chemical entities, particularly those with broad-spectrum biological activity, has become one of the most significant areas of research[3].

One such class of promising compounds are thiazolidine derivatives, specifically thiazolidine-4-ones, which have emerged as a significant focus in medicinal chemistry[4]. Thiazolidine-4-one, a five-membered heterocyclic compound containing sulfur, nitrogen, and two carbonyl groups, has been extensively studied for its diverse pharmacological potential[5]. Over the years, it has garnered special interest not only for its broad spectrum of biological activities but also for its structural versatility, which allows for modification to enhance its efficacy and target specificity[6]. These derivatives have demonstrated a wide range of therapeutic effects, including antibacterial[7], anticancer[8], anti-HIV[9], anti-inflammatory[10], and antioxidant[11] activities. The diversity of their biological activities makes thiazolidine-4-ones an attractive scaffold for the design of new drug candidates.

Among the many applications of thiazolidine-4-ones, their antibacterial properties stand out. Recent studies have identified 4-thiazolidinones as novel inhibitors of Mur B[12], an essential enzyme involved in the biosynthesis of peptidoglycan, a key component of the bacterial cell wall[13]. Inhibition of this enzyme disrupts bacterial cell wall synthesis, leading to cell death, making 4-thiazolidinones potential candidates for the development of new antibacterial drugs[14]. . Beyond antibacterial action, thiazolidine-4-ones have been found to exhibit other valuable pharmacological effects, including antitumor[15], antimicrobial[16], analgesic[17], anti-histaminic[18], and anti-tuberculosis[19] activities. Given these diverse biological effects, thiazolidine-4-ones offer considerable promise as multi-targeted therapeutic agents, capable of addressing various diseases simultaneously.

However, the discovery of promising new drug candidates is only the first step in the drug development process. In the face of rising drug discovery costs and lengthy development timelines, modern drug discovery strategies increasingly emphasize the evaluation of a compound's pharmacokinetic properties early in the research process. The ADME

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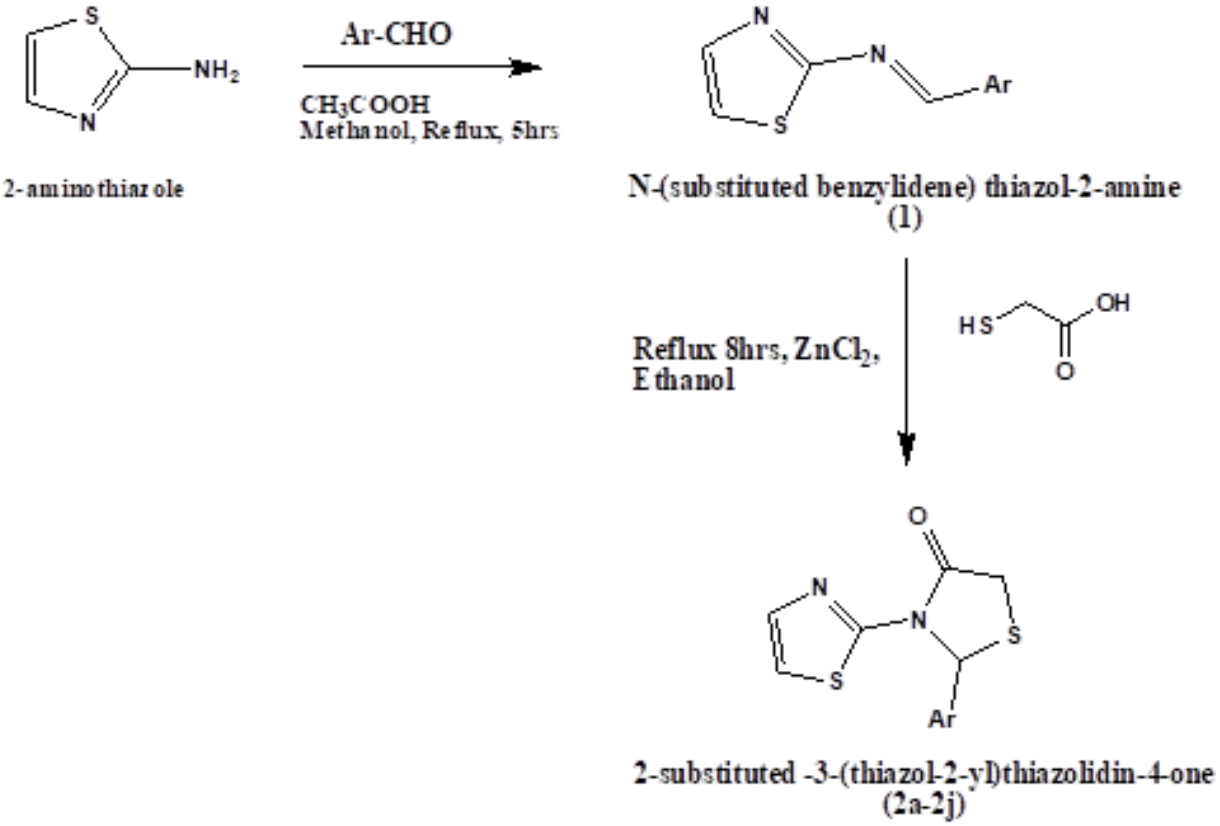


Scheme 1: Synthesis of 2-substituted -3-(thiazol-2-yl)thiazolidin-4-one derivative.

(Absorption, Distribution, Metabolism, and Excretion) profile of a compound plays a crucial role in its clinical success, affecting its bioavailability, safety, and therapeutic effectiveness[20]. A compound with poor ADME properties may face limitations in oral bioavailability or could exhibit unexpected toxicity, ultimately resulting in its removal from the market and causing significant financial losses[21]. Therefore, it is imperative to assess these properties in tandem with biological evaluations to ensure that the new chemical entities not only have therapeutic potential but also possess the necessary pharmacokinetic characteristics for clinical use.

With this understanding, the present study focuses on the synthesis, biological evaluation, and molecular docking studies of novel 2-substituted-3-(thiazol-2-yl)thiazolidin-4-one derivatives. The goal of this research is to develop new thiazolidine-based compounds with potent antimicrobial activities. These derivatives are synthesized using standard synthetic routes and characterized using various analytical techniques. The biological activity of these compounds will be screened against a range of pathogenic microorganisms to assess their therapeutic potential[22]. Additionally, in-silico molecular docking studies were employed to predict the interactions of these derivatives with key biological targets, particularly bacterial enzymes and cancer-related proteins. Molecular docking simulations provided insights into the binding modes and affinities of the synthesized compounds, aiding in the identification of those with the most promising mechanisms of action. Furthermore, the ADME properties of the most active compounds will be predicted through computational models, allowing for an early assessment of their pharmacokinetic profiles. This in-silico approach will help prioritize compounds with optimal drug-like properties, enhancing the efficiency of the drug discovery process[23]. By combining experimental biological testing with computational methods, this study aims to identify lead candidates with both strong biological activity and favorable pharmacokinetic properties, paving the way for further development into clinical candidates[24].

The synthesis , molecular docking and evaluation antimicrobial activity of novel thiazolidin-4-one derivatives represent a crucial step in the ongoing effort to develop new, effective, and safe therapeutic agents in the present work. By focusing on both the biological potential and pharmacokinetic optimization of these compounds, this research seeks to address some of the most pressing challenges in modern drug discovery. The outcome of this study has the potential to contribute to the development of novel, multifunctional drugs with significant promise for the treatment of infectious diseases, cancer, and other health conditions.

MATERIALS AND METHODS

Synthesis of Thiazole-based Schiff bases (1)

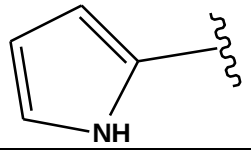
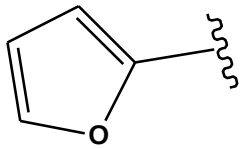
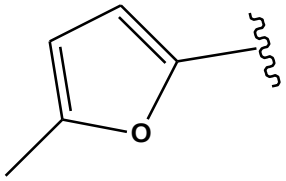
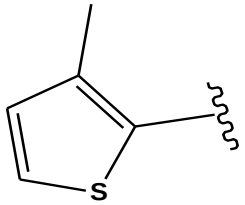
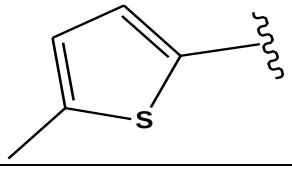
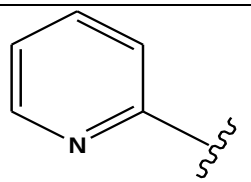
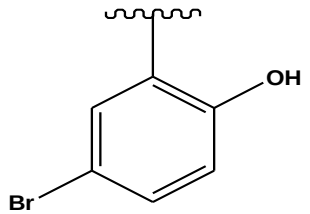
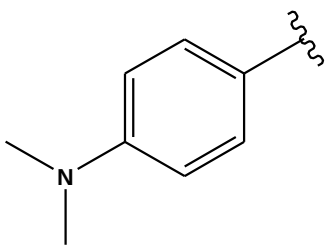
Equimolar quantities of 2-aminothiazole (0.01M) and substituted aromatic aldehyde (0.01M), to which was added 2-3 drops of glacial acetic acid in methanol (20mL), were refluxed on a water bath for about 5 hours to obtain N-(substituted benzylidene) thiazol-2-amine (1) and kept overnight for the precipitation to form. The solid was

separated and recrystallized with ethanol. TLC monitored the completion of the reaction.

Synthesis of Thiazole-based Thiazolidinedione derivatives (2a-2j)

A mixture of compound (1) (0.01M) in ethanol (50ml) and mercaptoacetic acid (0.01M) with a pinch of $ZnCl_2$ was refluxed on a water bath for 8 hours to obtain 2-substituted-3-(thiazol-2-yl)thiazolidine-4-one. The solid was recrystallized from methanol. The completion of the reaction was monitored by the TLC.

Table 1: Physicochemical data of compound 2a-2j

Comp no	Ar	Mole. Formula	MW	% Yield	M.P.^{0}C	R_f.
2a		$C_{10}H_9N_3OS_2$	251	72	164	0.64
2b		$C_{10}H_8N_2O_2S_2$	252	62	172	0.65
2c		$C_{11}H_{10}N_2O_2S_2$	266	65	174	0.73
2d		$C_{11}H_{10}N_2OS_3$	282	60	166	0.68
2e		$C_{11}H_{10}N_2OS_3$	282	64	164	0.65
2f		$C_{11}H_9N_3OS_2$	263	74	150	0.75
2g		$C_{12}H_9BrN_2O_2S_2$	356	78	163	0.78
2h		$C_{14}H_{15}N_3OS_2$	305	78	172	0.69

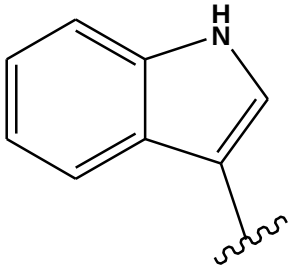
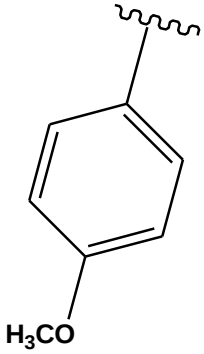
2i		$C_{14}H_{11}N_3OS_2$	301	69	178	0.74
2j		$C_{13}H_{12}N_2O_2S_2$	292	82	184	0.73

Table 2: Zone of inhibition of compound 2a-2i for antimicrobial activity

Sr. No.	Compound	*Zone of Inhibition in mm*	
		S. aureus	***E. coli***
1.	**2a**	10.66	7.45
2.	**2b**	17.32	13.76
3.	**2c**	15.41	13.22
4.	**2d**	8.37	7.31
5.	**2e**	8.80	10.08
6.	**2f**	6.50	7.29
7.	**2g**	6.78	9.29
8.	**2h**	8.19	7.88
9.	**2i**	8.50	7.58
10.	**2j**	9.62	**16.71**
Control	DMSO	-	-
Standard	Ciprofloxacin	**14.45**	**13.74**

Compound 2a: 2-(1H-pyrrol-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one

White coloured solid powder (72% yield); mp.162-164^{0}C; ^{1}HNMR (300MHz, DMSO-d6) δ-value: 2.29(s, 3H, CH_3), 4.64 (d, J=5.4Hz, 2H, CH_2), 7.29-7.59(m, 11H, ArH), 7.99 (dd, J=8.5, 1.05Hz, 2H, ArH), 8.54 (t, J= 5.3Hz, 1H, NH), 8.73(s, 1H, CH), ppm: ^{13}CNMR(75 MHz, DMSO-d6) δ 14.0, 20.6, 35.1, 115.1, 120.3, 121.5, 125.8, 126.6, 126.8, 128.2, 129.3, 129.8, 129.9, 130.9, 130.9, 135.2, 135.9, 137.7, 140.5, 141.9, 146.5, 149.4, 161.9 ppm ; IR(KBr): 3406, 3180, 2924, 1639, 1531,1493cm^{-1}. HRMS: m/z 250.14 $[M]^+$

Compound 2b: 2-(furan-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one

White solid powder (62% yield); mp. 170-172°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 3.47 (s, 2H, CH2), 6.77 (d, J = 8.3 Hz, 1H, ArH), 7.25 (d, J = 8.5 Hz, 1H, ArH), 7.46 (t, J = 5.1 Hz, 1H, ArH), 7.59 (m, 2H, ArH), 8.23 (dd, J = 7.5, 1.0 Hz, 2H, ArH), 8.61 (s, 1H, CH), 8.90 (t, J = 5.4 Hz, 1H, NH).13C NMR (75 MHz, DMSO-d6) δ (ppm): 21.2, 35.3, 111.2, 113.3, 120.4, 121.6, 126.2, 128.5, 129.2, 130.8, 137.9, 141.6, 146.1, 149.2, 161.5. IR (KBr): 3402, 3185, 2922, 1651, 1519, 1482 cm^{-1}.

Compound 2c: 2-(5-methylfuran-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one

White solid powder (65% yield); mp. 172-174°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 2.11 (s, 3H, CH3), 3.47 (s, 2H, CH2), 6.87 (d, J = 8.2 Hz, 1H, ArH), 7.18 (d, J = 8.5 Hz, 1H, ArH), 7.47 (t, J = 5.0 Hz, 1H, ArH), 7.63 (m, 2H, ArH), 8.21 (dd, J = 7.4, 1.0 Hz, 2H, ArH), 8.48 (s, 1H, CH), 8.82 (t, J = 5.5 Hz, 1H, NH).13C NMR (75 MHz, DMSO-d6) δ (ppm): 21.8, 33.2, 111.5, 113.4, 118.3, 120.2, 124.1, 125.7, 128.9, 130.2, 137.4, 141.2, 146.9, 149.6, 161.7.IR (KBr): 3400, 3180, 2925, 1635, 1512, 1491 cm^{-1}.

Compound 2d: 2-(3-methyl thiophene-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one

Yellow solid powder (60% yield); mp. 164-166°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 2.34 (s, 3H, CH3), 3.56 (s, 2H, CH2), 6.96 (d, J = 8.0 Hz, 1H, ArH), 7.12 (d, J = 7.8 Hz, 1H, ArH), 7.39 (t, J = 5.2 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 8.35 (dd, J = 7.2, 1.3 Hz, 2H, ArH), 8.60 (s, 1H, CH), 8.78 (t, J = 5.6 Hz, 1H, NH).^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 19.5, 34.0, 108.9, 112.6, 119.8, 120.5, 123.1, 125.4, 129.0, 131.4, 137.5, 140.2, 146.3, 150.5, 161.4.IR (KBr): 3404, 3172, 2920, 1631, 1513, 1488 cm^{-1}.

Compound 2e: 2-(5-methyl thiophene-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one

Light yellow solid powder (64% yield); mp. 172-174°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 2.12 (s, 3H, CH3), 3.48 (s, 2H, CH2), 6.96 (d, J = 8.3 Hz, 1H, ArH), 7.13 (d, J = 8.6 Hz, 1H, ArH), 7.37 (t, J = 5.3 Hz, 1H, ArH), 7.50 (m, 2H, ArH), 8.30 (dd, J = 7.4, 1.2 Hz, 2H, ArH), 8.55 (s, 1H, CH), 8.72 (t, J = 5.4 Hz, 1H, NH).^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 21.1, 34.3, 109.3, 113.0, 119.4, 120.7, 124.3, 125.6, 128.2, 129.9, 138.3, 141.0, 146.8, 150.9, 161.3.IR (KBr): 3405, 3180, 2921, 1633, 1518, 1489 cm^{-1}.

Table 3: Docking parameters Binding affinity for compounds 2a- 2i

Compound	Ligand	Binding Affinity(kcal/mol)
2a	2-(1H-pyrrol-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.5
2b	2-(furan-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.3
2c	2-(5-methylfuran-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.4
2d	2-(3-methyl thiophene-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.3
2e	2-(5-methyl thiophene-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.5
2f	2-(pyridin-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.4
2g	2-(5-bromo-2-hydroxyphenyl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.3
2h	2-(4-(dimethylamino)phenyl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.5
2i	2-(1*H*-indol-3-yl)-3-(thiazol-2-yl)thiazolidin-4-one	-5.7
2j	2-(4-methoxyphenyl)-3-(thiazol-2-yl)thiazolidin-4-one.	-6.8
Std.	Chloramphenicol	-7.4

Compound 2f: 2-(pyridin-2-yl)-3-(thiazol-2-yl)thiazolidin-4-one

White solid powder (74% yield); mp. 174-176°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 7.43 (d, J = 7.8 Hz, 1H, ArH), 7.65 (d, J = 7.8 Hz, 1H, ArH), 7.89 (t, J = 5.3 Hz, 1H, ArH), 8.19 (dd, J = 7.1, 1.2 Hz, 2H, ArH), 8.63 (s, 1H, CH), 8.72 (t, J = 5.3 Hz, 1H, NH).^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 34.0, 109.3, 116.4, 120.1, 121.2, 125.5, 127.0, 129.7, 137.0, 138.5, 141.4, 146.9, 149.7, 161.8.IR (KBr): 3400, 3185, 2920, 1645, 1511, 1483 cm^{-1}.

Compound 2g: 2-(5-bromo-2-hydroxyphenyl)-3-(thiazol-2-yl)thiazolidin-4-one

Light yellow solid powder (78% yield); mp. 164-166°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 6.91 (d, J = 8.4 Hz, 1H, ArH), 7.14 (d, J = 8.3 Hz, 1H, ArH), 7.46 (t, J = 5.2 Hz, 1H, ArH), 7.57 (m, 2H, ArH), 8.11 (dd, J = 7.3, 1.1 Hz, 2H, ArH), 8.45 (s, 1H, CH), 8.68 (t, J = 5.4 Hz, 1H, NH).^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 21.2, 35.0, 111.0, 118.7, 120.2, 121.3, 125.8, 128.1, 129.2, 130.5, 137.2, 141.5, 146.4, 148.8, 161.0. IR (KBr): 3405, 3182, 2923, 1632, 1517, 1485 cm^{-1}.HRMS: m/z 354 $[M-1]^+$

Compound 2h: 2-(4-(dimethylamino)phenyl)-3-(thiazol-2-yl)thiazolidin-4-one

Yellow solid powder (78% yield); mp. 172-174°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 2.83 (s, 6H, N-CH3), 6.96 (d, J = 8.0 Hz, 1H, ArH), 7.11 (d, J = 7.8 Hz, 1H, ArH), 7.34 (t, J = 5.4 Hz, 1H, ArH), 7.45 (m, 2H, ArH), 8.22 (dd, J = 7.3, 1.0 Hz, 2H, ArH), 8.60 (s, 1H, CH), 8.75 (t, J = 5.5 Hz, 1H, NH).^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 21.7, 35.2, 109.5, 114.3, 120.1, 122.8, 126.5, 128.2, 129.5, 130.7, 138.1, 142.3, 146.9, 149.2, 161.9.IR (KBr): 3403, 3181, 2922, 1635, 1510, 1483 cm^{-1}.

Compound 2i: 2-(1*H*-indol-3-yl)-3-(thiazol-2-yl)thiazolidin-4-one

Light yellow solid powder (69% yield); mp. 176-178°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 6.52 (d, J = 7.5 Hz, 1H, ArH), 6.78 (d, J = 7.3 Hz, 1H, ArH), 7.25 (t, J = 5.1 Hz, 1H, ArH), 7.49 (m, 3H, ArH), 8.08 (dd, J = 7.3, 1.1 Hz, 2H, ArH), 8.45 (s, 1H, CH), 8.75 (t, J = 5.5 Hz, 1H, NH).^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 35.1, 109.1, 111.3, 119.7, 120.2, 122.0, 125.2, 126.3, 128.9, 130.6, 137.6, 141.3, 146.2, 149.0, 161.2.IR (KBr): 3404, 3184, 2921, 1634, 1512, 1486 cm^{-1}.

Compound 2j: 2-(4-methoxyphenyl)-3-(thiazol-2-yl)thiazolidin-4-one.

Light yellow solid powder (82% yield); mp. 184-186°C;^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 6.52 (d, J = 7.5 Hz, 1H, ArH), 6.78 (d, J = 7.3 Hz, 1H, ArH), 7.25 (t, J = 5.1 Hz, 1H, ArH), 7.49 (m, 3H, ArH), 8.08 (dd, J = 7.3, 1.1 Hz, 2H, ArH), 8.45 (s, 1H, CH), 8.75 (t, J = 5.5 Hz, 1H, NH).^{13}C NMR (75 MHz, DMSO-d6) δ (ppm): 35.1, 109.1, 111.3, 119.7, 120.2, 122.0, 125.2, 126.3, 128.9, 130.6, 137.6, 141.3, 146.2, 149.0, 161.2.IR (KBr): 3404, 3184, 2921, 1634, 1512, 1486 cm^{-1}.HRMS: m/z 291 $[M]^+$

ANTIMICROBIAL EVALUATION

To determine the antimicrobial activity of the synthesized compounds, bacterial suspensions of *Staphylococcus aureus* and *Escherichia coli* were prepared to a concentration of 10^8 CFU/mL (0.5 McFarland standard) and spread evenly on nutrient agar plates. Wells were created on the agar surface, and various concentrations (100 µg/mL) of the synthesized compounds, along with a positive control (ciprofloxacin), were introduced into the wells. The plates were incubated at 37°C for 18-24 hours, after which the zone of inhibition (the clear area around each well where bacteria were unable to grow) was measured in millimeters. The results were compared to the positive and negative controls, and the antimicrobial activity is reported in Table 2.

MOLECULAR DOCKING STUDIES

Molecular docking simulations were performed to investigate the binding interactions between the synthesized compounds and target proteins. The target proteins were selected based on their relevance to antimicrobial activity against C. albicans, as well as their involvement in breast and ovarian cancer. The protein structures 1KZN was downloaded from the Protein Data Bank (RCSB.org), with resolution values below 2.30 Å, which are considered acceptable for docking studies. The docking studies were carried out using the AutoDock Vina software, and the binding modes and interaction energies were analyzed to predict the potential of these compounds as therapeutic agents.

DRUG LIKENESS AND ADME PREDICTION

The drug-likeness of the synthesized compounds was evaluated using established pharmacokinetic rules, including Lipinski's Rule of Five, the Ghose filter, Veber's

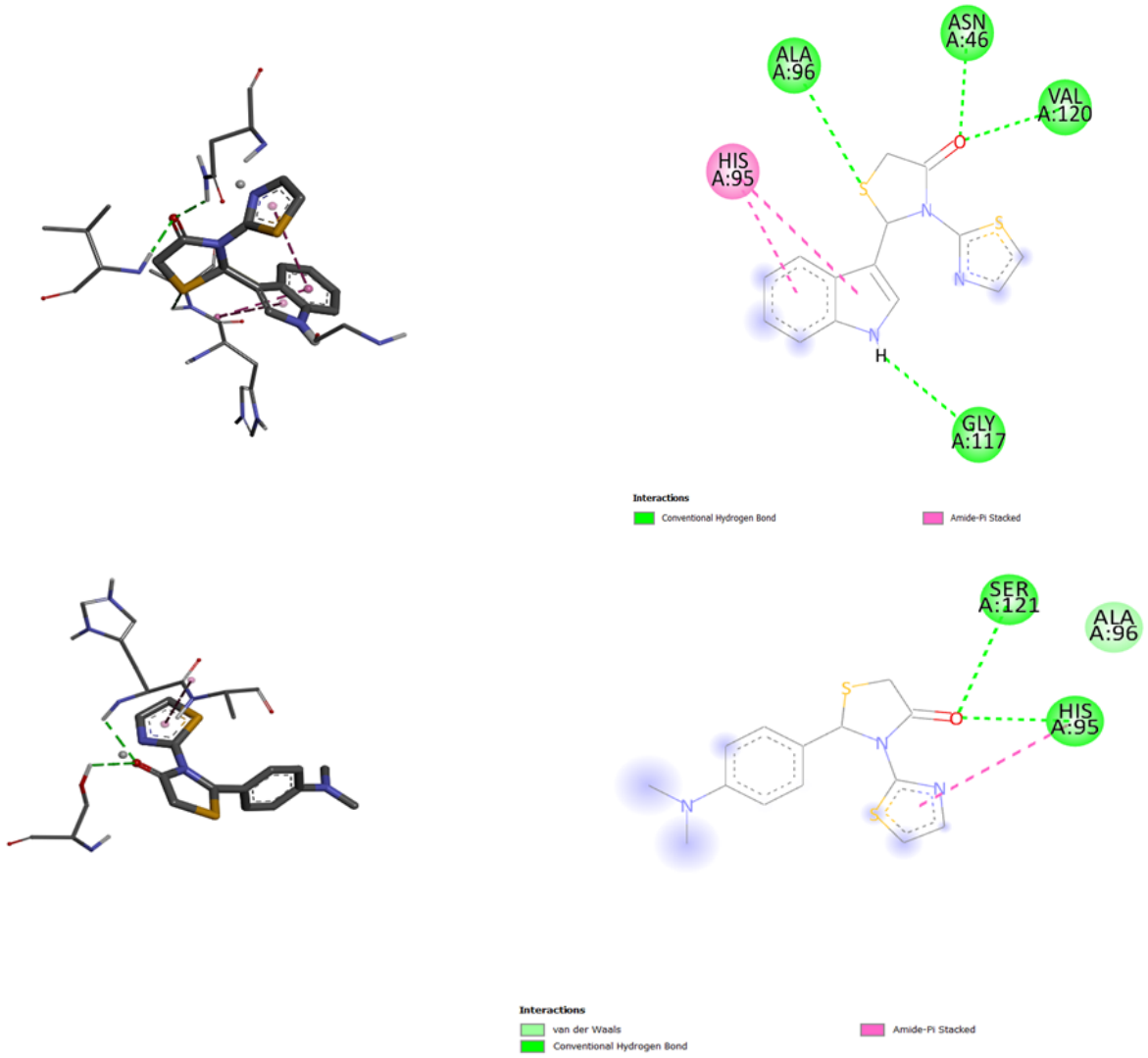


Fig. 1. 3D and 2D docking pose showing interactions of the least active compound 2a and the most active compound 2i, in the binding sites of 1KZN protein.

rule, and Muegge's rule. These rules consider various physicochemical properties such as molecular weight, lipophilicity (LogP), hydrogen-bond acceptors (HBA), polar surface area (PSA), and rotatable bonds. These parameters help to predict the oral bioavailability and absorption potential of the compounds. In addition, the ADME (Absorption, Distribution, Metabolism, and Excretion) properties were predicted to assess the pharmacokinetic profiles of the compounds.

RESULTS AND DISCUSSION

Synthesis of 2-substituted -3-(thiazol-2-yl)thiazolidin-4-one derivative

All the compounds (2a-2j) were synthesized in good yields, ranging from 60% to 82%. The spectral data, including 1H NMR, 13C NMR, IR, and HRMS, strongly supports the proposed structures. The NMR spectra clearly reveal the characteristic signals corresponding to the thiazolidin-4-one core, along with the unique signals for the various heterocyclic and aromatic substituents, confirming the successful synthesis and accurate structural assignment of each compound (Table 1).

Antimicrobial Activity

The antimicrobial activity of the tested compounds against *S. aureus* and *E. coli* showed varying results. Compound 2b exhibited the strongest antibacterial effect against S. aureus (17.32 mm), closely followed by 2c (15.41 mm), both of which showed comparable effectiveness to the standard antibiotic Ciprofloxacin. Against E. coli, compound 2j demonstrated the largest inhibition zone (16.71 mm), outperforming all other compounds, including Ciprofloxacin. Compounds 2b and 2c also displayed significant activity against E. coli, with inhibition zones of 13.76 mm and 13.22 mm, respectively. Other compounds like 2e, 2g, and 2h showed moderate activity, while several, including 2f, 2a, and 2d, displayed minimal or weak antibacterial effects. These findings suggest that compounds 2b, 2c, and 2j hold the most potential for further investigation as broad-spectrum antimicrobial agents, but further research is needed to explore their mechanisms of action and efficacy in vivo. (Table 2)

Table 4: Drug-likeness and ADME properties predications.

Comp.	MW (≤500 Da)	LogP (<5)	nHBD (≤5)	nHBA (≤10)	TPSA (<140 ˚A2)	Lipinski Violation	LogS (ESOL)	nRotB	GI absorption
2a	251.33	1.60	1	2	102.53	Yes; 0	-2.71	2	High
2b	252.31	1.87	0	3	99.88	Yes; 0	-2.89	2	High
2c	266.34	2.21	0	3	99.88	Yes; 0	-3.20	2	High
2d	282.40	2.19	0	2	114.98	Yes; 0	-3.66	2	High
2e	282.40	2.25	0	2	114.98	Yes; 0	-3.68	2	High
2f	263.34	1.72	0	3	99.63	Yes; 0	-2.88	2	High
2g	357.25	2.35	1	3	106.97	Yes; 0	-4.28	2	High
2h	305.42	2.28	0	2	89.98	Yes; 0	-3.74	3	High
2i	301.39	2.03	1	2	102.53	Yes; 0	-3.92	2	High
2j	292.38	2.63	0	3	95.97	Yes; 0	-3.58	3	High

Molecular Docking Studies

The binding affinity analysis of the compounds (2a–2j) against the target receptor reveals key structural insights influencing activity. The standard compound, chloramphenicol, exhibits the highest binding affinity (-7.4 kcal/mol), serving as a reference point for comparison. Among the tested compounds, 2j (2-(4-methoxyphenyl)-3-(thiazol-2-yl)thiazolidin-4-one) displayed the highest binding affinity (-6.8 kcal/mol), suggesting that the presence of a methoxy-substituted phenyl ring enhances interactions with the receptor (Figure 1). Similarly, 2i (2-(1H-indol-3-yl)-3-(thiazol-2-yl)thiazolidin-4-one) exhibits a relatively high binding affinity (-5.7 kcal/mol), indicating that the indole moiety contributes to favorable binding interactions, possibly through hydrogen bonding and π-stacking. Compounds 2a, 2e, and 2h showed moderate binding affinities (-5.5 kcal/mol), suggesting that heterocyclic substitutions such as pyrrole, thiophene, and dimethylamino phenyl groups contribute to receptor binding, albeit with slightly lower efficiency than the indole or methoxyphenyl moieties. Meanwhile, compounds 2b, 2c, 2d, 2f, and 2g demonstrated slightly lower binding affinities (-5.3 to -5.4 kcal/mol), implying that their respective heterocyclic substitutions do not contribute as significantly to receptor interactions. The SAR analysis indicates that the presence of electron-donating or π-rich aromatic systems (such as methoxyphenyl or indole) enhances binding affinity (Table 3). Future modifications should focus on increasing electron density in the ligand's core structure while maintaining optimal hydrogen bonding interactions. Additionally, further structural refinements, such as incorporating additional hydrogen bond donors or optimizing the hydrophobic balance, could enhance receptor binding and overall activity.

Drug Likeness and ADME Prediction

The physicochemical properties of the compounds (2a–2j) were analyzed to assess their drug-likeness based on Lipinski's Rule of Five and other pharmacokinetic parameters. The molecular weight (MW) of all compounds is below 500 Da, satisfying the first criterion of Lipinski's rule. Additionally, the calculated LogP values for all compounds are below the threshold value of 5, indicating favorable lipophilicity and suggesting good membrane permeability.The number of hydrogen bond donors (nHBD) and acceptors (nHBA) for all compounds adheres to Lipinski's parameters (≤5 and ≤10, respectively). The topological polar surface area (TPSA) values range from 89.98 to 114.98 Å², which is within the acceptable range for oral bioavailability (≤140 Å²), indicating potential for good intestinal absorption (Table 4).

All compounds exhibit zero violations of Lipinski's rule, suggesting good oral bioavailability and drug-like properties. Additionally, the solubility (LogS) values, obtained through the ESOL method, range from -2.71 to -4.28, which indicates moderate aqueous solubility. However, compounds with lower LogS values (such as 2g and 2i) may require further solubility enhancement strategies for formulation development.The number of rotatable bonds (nRotB) for all compounds is relatively low (2 or 3), which suggests a balance between molecular flexibility and rigidity, aiding in favorable binding interactions with biological targets. Finally, gastrointestinal (GI) absorption is predicted to be high for all compounds, reinforcing their potential for effective oral administration. In conclusion, all tested compounds meet Lipinski's criteria without violations, demonstrating favorable drug-like properties, good lipophilicity, and high GI absorption. Future studies should focus on further optimizing solubility and evaluating additional pharmacokinetic parameters such as metabolic stability and bioavailability.

CONCLUSION

The synthesized substituted Thiazole-based Thiazolidinedione derivatives exhibited significant antimicrobial activity against *S. aureus* and *E. coli.* The molecular docking studies revealed strong binding interactions with relevant target proteins, suggesting the compounds' potential as antimicrobial agents. The drug-likeness and ADME predictions further supported the suitability of these compounds for oral administration, making them promising candidates for future therapeutic development.

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