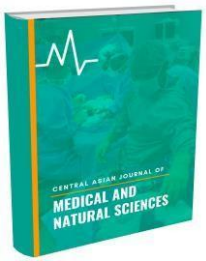

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Article

Synthesis and Characterization of Thiazolidin-4-one Derivatives and Evaluation of Their Biological Activity and Molecular Docking Studies

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Abstract: This study aims to synthesize and characterize a series of thiazolidin-4-one derivatives (B_1–B_8) and to evaluate their biological activity as well as predict their interaction behavior using molecular docking techniques, these compounds were synthesized via the reaction of hydrazones with thioglycolic acid in the presence of zinc chloride as a catalyst,the results demonstrated good yields and variability in physical properties depending on the nature of the substituents, the chemical structures of the synthesized compounds were confirmed using various spectroscopic techniques, including FT-IR, ^{1}H-NMR, and ^{13}C-NMR. The biological evaluation revealed that the compounds exhibited good inhibitory activity against both Gram-positive and Gram-negative bacteria. In particular, compounds B3, B8, and B4 showed the highest activity against *Escherichia coli*, while compounds B1, B4, and B8 demonstrated superior activity against *Staphylococcus aureus*, furthermore, the molecular docking results supported the experimental findings, indicating that the compounds possess good binding affinity toward the target protein, with binding energy values ranging from −5.04 to −5.97 kcal/mol, Among them, compound B8 exhibited the highest stability within the active site.

Keywords: Thiazolidin-4-one, Molecular Docking, Biological Activity

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1. Introduction

Molecular docking is considered one of the most important computational techniques used in drug discovery and development [1], as it has significantly contributed to a deeper understanding of molecular interactions at the atomic level. The importance of this technique lies in its ability to predict how small molecules (ligands) bind to large biological macromolecules such as proteins or nucleic acids, in addition to estimating the strength of this interaction, which helps explain many fundamental biological processes [2,3] ,this methodology primarily relies on the availability of accurate three-dimensional models of target proteins, which are obtained using advanced experimental techniques such as X-ray crystallography [4] and nuclear magnetic resonance (NMR) spectroscopy [5], these structural data are then utilized as a basis for computational simulations that enable the study of molecular behavior and the prediction of binding modes with high accuracy.

The interactions analyzed in molecular docking studies include a variety of non-covalent forces, such as hydrogen bonding, ionic interactions, hydrophobic interactions, and van der Waals forces [6], the docking process typically involves several key steps, starting with the preparation of the protein structure, followed by ligand preparation,

calculation of binding energy, and finally comprehensive analysis and interpretation of the results [7].

Heterocyclic compounds are defined as cyclic structures that contain at least one atom other than carbon within the ring [8], such as nitrogen, oxygen, or sulfur [9], these compounds are of great importance in medicinal chemistry due to their diverse biological properties, as they are present in many active pharmaceutical agents, including antibiotics [10], anti-inflammatory drugs [11], and anticancer agents [12], this diversity in structure and activity makes heterocyclic compounds essential components in drug design and development.

The thiazolidin-4-one scaffold is considered a distinctive structure and is one of the important derivatives of thiazolidine. It contains a carbonyl group (C=O) at the fourth position in addition to the presence of sulfur and nitrogen atoms [13], as shown in Figure 1, owing to its unique structural features, the thiazolidin-4-one ring has been widely utilized in medical and pharmaceutical fields as antimicrobial [14], antibacterial [15], anti-inflammatory [16], antifungal [17], and anticancer agents [18], moreover, it has been applied in the treatment of diabetes [19], as well as in the development of membrane-active agents [20], as illustrated in Figure 2.

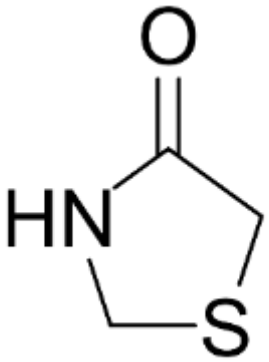


Figure 1. Structure of Thiazolidin-4-one

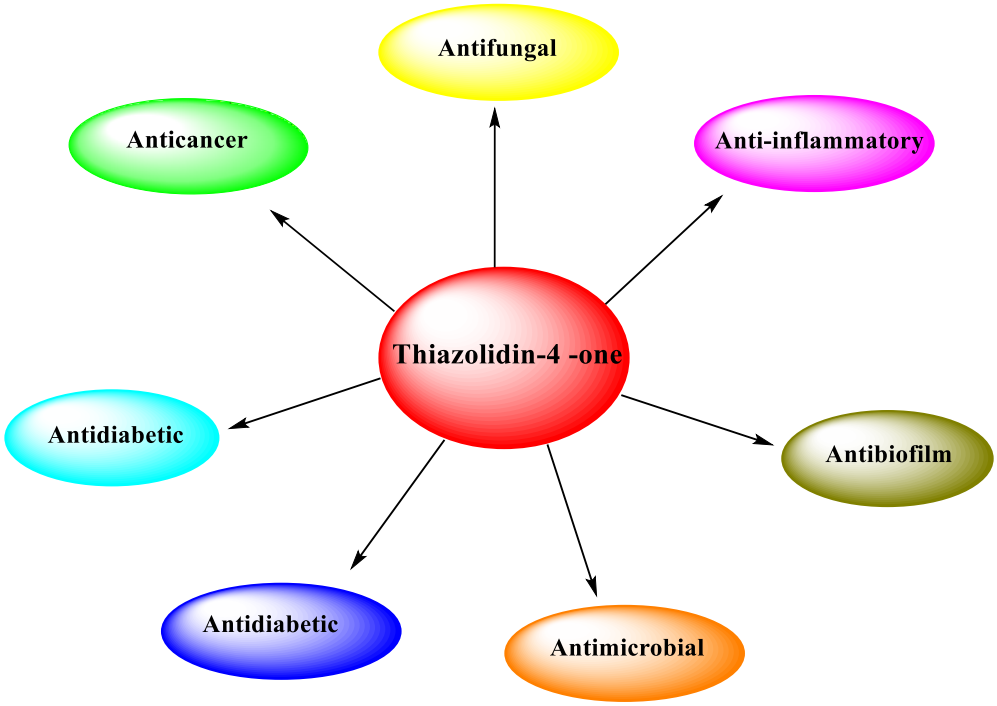


Figure 2. Biological Activity of Thiazolidin-4-one

2. Materials and Methods

Experimental Section

2.1. Materials

All chemicals used in this study were obtained from Alfa Aesar and BDH.

2.2. Instruments

The melting points were determined using an Automatic Melting Point apparatus (SMP40). Infrared (IR) spectra were recorded as KBr pellets using a Shimadzu FT-IR-600 Fourier Transform Infrared Spectrophotometer over the range of 400–6000 cm^{-1}, The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 using a JEOL spectrometer operating at 400 MHz and 125 MHz, respectively. Thin-layer chromatography (TLC) was carried out on silica gel plates to monitor the progress of reactions, and the spots were visualized using bromine.

2.3. Synthesis of Thiazolidin-4-one Derivatives(B_1-B_8)

Dissolve (0.005 mol) of the hydrazones in (10 mL) of 1,4-dioxane, then, (0.005 mol, 0.4 mL) of thioglycolic acid was added along with (0.002 g) of anhydrous zinc chloride dissolved in (5 mL) of 1,4-dioxane. The reaction mixture was subsequently heated under reflux for 10 hours in a water bath at (60°C), The progress of the reaction was monitored using thin-layer chromatography (TLC) [21], after completion of the reaction, the mixture was allowed to cool, and the resulting solid product was filtered off, washed with cold water, and recrystallized from dioxane, as illustrated in Figure 3 and Table 1 presents the physical properties of the prepared compounds.

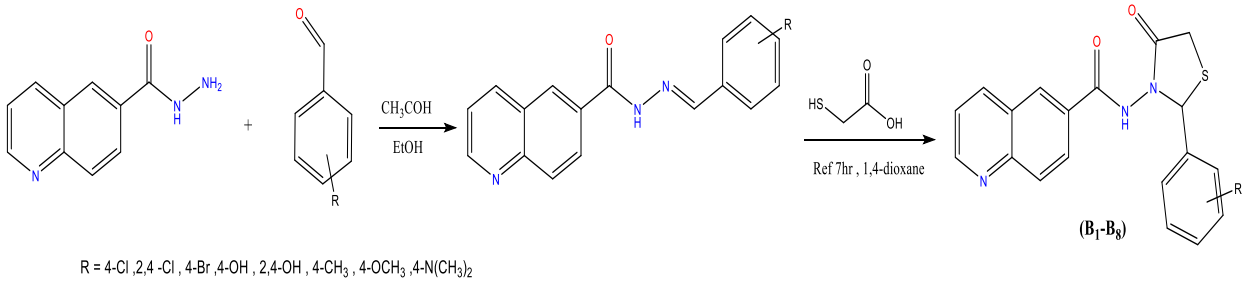


Figure 3. Synthesis of Thiazolidin-4-one Derivatives (B_1–B_8)

Table 1. Physical Properties of Thiazolidin-4-one Derivatives (B_1–B_8)

COM.NO	R	Molecular Formula	Color	M.P. (^{0}C)	Yield (%)
B_1	4-Cl	$C_{19}H_{14}ClN_3O_2S$	White	230-232	80
B_2	2,4-Cl	$C_{19}H_{13}Cl_2N_3O_2S$	Yellow	275-277	78
B_3	4-Br	$C_{19}H_{14}BrN_3O_2S$	Light Crimson	220	77
B_4	4-OH	$C_{19}H_{15}N_3O_3S$	Red	264-266	70
B_5	2.4-OH	$C_{19}H_{15}N_3O_4S$	Brown	255-257	75
B_6	4-CH_3	$C_{20}H_{17}N_3O_2S$	Light yellow	279	64
B_7	4-OCH_3	$C_{20}H_{17}N_3O_3S$	White	295	78
B_8	4-$N(CH_3)_2$	$C_{21}H_{20}N_4O_2S$	Orang	219-220	80

2.4. Evaluation of Antibacterial Activity

Suitable culture media were prepared and sterilized using an autoclave. The media were then poured into sterile Petri dishes and allowed to solidify. Bacterial and fungal inocula were prepared separately for each isolate, with the cell density adjusted to

approximately 1.5 × 10^8 cells/mL using sterile physiological saline as a diluent, and standardized according to the 0.5 McFarland standard,mueller–Hinton agar plates were inoculated by evenly spreading the bacterial suspension over the surface of the medium using sterile cotton swabs. After inoculation, uniform wells were made in the agar to load the test solutions, the plates were incubated at 37 °C for 24 hours [22],following incubation, the biological activity of the tested compounds was evaluated by observing and measuring the zones of inhibition formed around the wells, which serve as an indicator of antimicrobial activity [23].

2.5. Molecular Docking Study of the Prepared Compounds

Molecular docking studies were performed on a number of the synthesized compounds to investigate their binding behavior with the bacterium Escherichia coli (PDB ID: 1JXA), using the MOE software ,The study focused on identifying the lowest possible energy values for these compounds in order to determine the most stable molecular conformations,the crystal structure of the target protein was obtained from the Protein Data Bank (PDB) ,due to the computational complexity associated with molecular docking processes, high-performance computing techniques were employed, as these applications require advanced multi-core processing capabilities to ensure speed and efficiency, particularly when dealing with large molecules and complex atomic structures [24, 25].

3. Results and Discussion

3.1 Characterization of Thiazolidin-4-one Derivatives (B_1–B_8)

He FT-IR spectra of the prepared compounds exhibited a sharp peak in the range of (2249-2326) cm^{-1} attributed to the amine group (NH). Additionally, a band appeared within the range of (3043-3089) cm^{-1} corresponding to the aromatic (C-H) stretching vibration. Meanwhile, the spectra showed two stretching bands at (2839-2925) cm^{-1} and (2879-2952) cm^{-1}, assigned to the symmetric and asymmetric stretching of the aliphatic (C-H) bond. Furthermore, a peak emerged in the range of (1697-1720) cm^{-1} representing the amidic (C=O) stretching, while a band at (1639-1679) cm^{-1} was observed for the (C=N) stretching. The spectra also displayed a band at (1269-1276) cm^{-1} due to the (C-N) stretching, along with a band in the range of (748-780) cm^{-1} corresponding to the (C-S) bond stretching [26], as shown in Figures (4-7). Table 2 illustrates the infrared absorption results for the synthesized compounds.

Table 2. Infrared Absorption (cm^{-1}) Results for Thiazolidinone Derivatives (B_1–B_8).

Comp. No.	R	IR (KBr) cm^{-1}							
		ν(C-N)	ν(C-H) Arom.	ν(C-H) Aliph.	ν(C=O) Aimd.	ν (C=N)	ν(C=C) Arom.	ν(C-N) ν(C-S)	Others
B_1	4-Cl	3249	3089	2923 2885	1720	1650	1568 1508	1274 777	ν (C-Cl) 609
B_2	2,4-Cl	3273	3075	2968 2890	1714	1643	1520 1487	1245 742	ν (C-Cl) 654
B_3	4-Br	3274	3078	2941 2877	1716	1654	1527 1494	1232 748	ν (C-Br) 688
B_4	4-OH	3282	3043	2952 2879	1706	1639	1506 1446	1276 831	ν (O-H) 3456

B_5	2,4-OH	3286	3056	2945 2859	1710	1640	1533 1478	1243 723	ν (O-H) 3489
B_6	4-CH_3	3326	3087	2925 2839	1697	1679	1550 1506	1269 783	
B_7	4-OCH_3	3290	3067	2965 2861	1716	1660	1523 1467	1224 724	ν (C-O) 1267
B_8	4-$N(CH_3)_2$	3278	3060	3091	1712	1670	1495 1434	1267 745	

Compound B_1 : ^{1}H-NMR (, 400 MHz): δ(ppm) =10.93 (s, 1H, NH), 7.98-7.05 (10H, m, Ar–H), 5.15(s,1H,CH),3.73(s,2H,CH_2) ;^{13}C-NMR (101 MHz): δ(ppm) = 168.85 (C=O), 164.33(C=O)$_{Aimd}$,152.15,147.63,137.32,136.12,134.15,132.54,130.43,130.78,129.60,129.19,128.56,127.76, 122.60 (Ar-C-C), 64.45 (CH), 35.78 (CH_2) [27].

Compound B_2: ^{1}H-NMR (, 400 MHz): δ(ppm) =12.45 (s, 1H, NH), 7.99-6.89 (10H, m, Ar–H), 5.87(s,1H,CH), 4.19 (s,2H,CH_2) ; ^{13}C-NMR (101 MHz): δ(ppm) = 168.12 (C=O), 163.33 (C=O)$_{Aimd}$,151.45,149.33,138.22,137.72,133.55,133.84,131.33,133.38,129.10,129.15,127.36,127.34,-123.50 151.30-115.73 (Ar-C-C), 65.12 (CH), 34.37 (CH_2).

Compound B_3: ^{1}H-NMR (, 400 MHz): δ(ppm) =12.36 (s, 1H, NH), 8.98-7.17 (10H, m, Ar–H), 5.90(s,1H,CH), 3.88 (s,2H,CH_2) ; ^{13}C-NMR (101 MHz): δ(ppm) = 170.28 (C=O), 165.11 (C=O)$_{Aimd}$,150.48,149.18,145.05,142.25,131.27,130.56,130.42,129.61,128.15,124.35,123.5,122.23 (Ar-C-C), 65.53 (CH), 32.04 (CH_2).

Compound B_4 : ^{1}H-NMR (, 400 MHz): δ(ppm) =12.42 (s, 1H, NH), 11.47(s,1H,OH), 9.34 - 7.77 (10H, m, Ar–H), 6.05(s,1H,CH), 3.44 (s,2H,CH_2) ; ^{13}C-NMR (101 MHz): δ(ppm) = 169.28(C=O),166.11(C=O)$_{Aimd}$158.22,150.33,146.22,136.13,133.61,130.10,130.50,128.77,125.58 ,122.66,117.80(Ar-C=C), 65.53 (CH), 32.04 (CH_2).

Compound B_5: ^{1}H-NMR (, 400 MHz): δ(ppm) =12.42 (s, 1H, NH), 10.11-10.98 (s,2 H,OH), 8.95 -6.89 (9H, m, Ar–H), 5.69 (s,1H,CH), 3.93 (s,2H,CH_2) ; ^{13}C-NMR (101 MHz): δ(ppm) = 168.62(C=O),165.00(C=O)$_{Aimd}$,157.50,155.23,148.76,145.71,141.86,137.74,131.59,130.72,130.46,128.16,123.78,123.56,115.81,107.56,103.77 (Ar-C=C), 59.45 (CH), 35.39 (CH_2).

Compound B_6: ^{1}H-NMR (, 400 MHz): δ(ppm) =11.78 (s, 1H, NH), 8.90 -7.10 (9H, m, Ar–H), 5.12 (s,1H,CH), 3.52 (s,2H,CH_2), 2.25 (s,3H,CH_3) ; ^{13}C-NMR (101 MHz): δ(ppm) = 167.88 (C=O),164.18(C=O)$_{Aimd}$,153.35,149.07,138.98,137.60,136.22,135.82,130.33,129.38,129.10,127.15,125.36,127.34,-123.19 (Ar-C=C), 63.57 (CH), 37.22 (CH_2), 22.50 (CH_2) [28].

Compound B_7: ^{1}H-NMR (, 400 MHz): δ(ppm) =12.09 (s, 1H, NH), 8.87 - 6.88 (10H, m, Ar–H), 5.92 (s,1H,CH), 3.96 (s,2H,CH_2),3.81 (s,3H,CH_3) ; ^{13}C-NMR (101 MHz): δ(ppm) = 168.13 (C=O),164.14(C=O)$_{Aimd}$,149.27,144.22,142.71,138.65,136.10,131.21,130.53,130.41,128.12,124.47,123.50,127.34,115.48 (Ar-C=C), 65.20 (CH), 56.15 (CH_3), 35.25 (CH_2).

Compound B_8: ^{1}H-NMR (, 400 MHz): δ(ppm) =12.36 (s, 1H, NH), 9.33 - 8.00 (10H, m, Ar–H), 6.05 (s,2 H,CH_2), 3.35 (s,1H,CH_2),2.48 (s,6H,CH_3) ; ^{13}C-NMR (101 MHz): δ(ppm) =168.80(C=O),162.14(C=O)$_{Aimd}$,152.69,149.44,147.27,138.86,135.32,135.28,130.44,129.44.129.05,128.33,127.55,127.98,115,70 (Ar-C-C), 64.20 (CH), 41.17 (CH_3), 35.62 (CH_2).

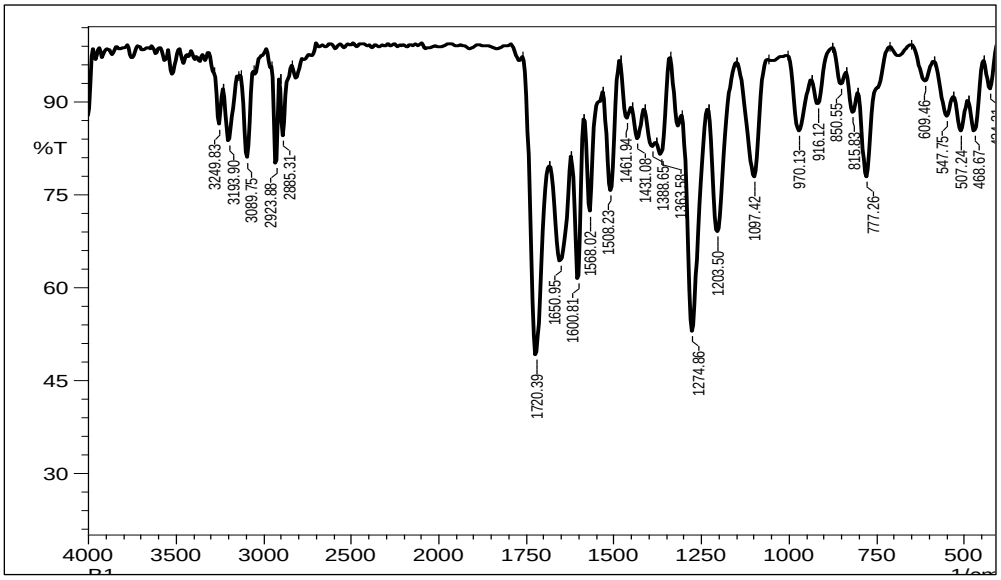


Figure 4. FT-IR Spectrum of Compound B_1

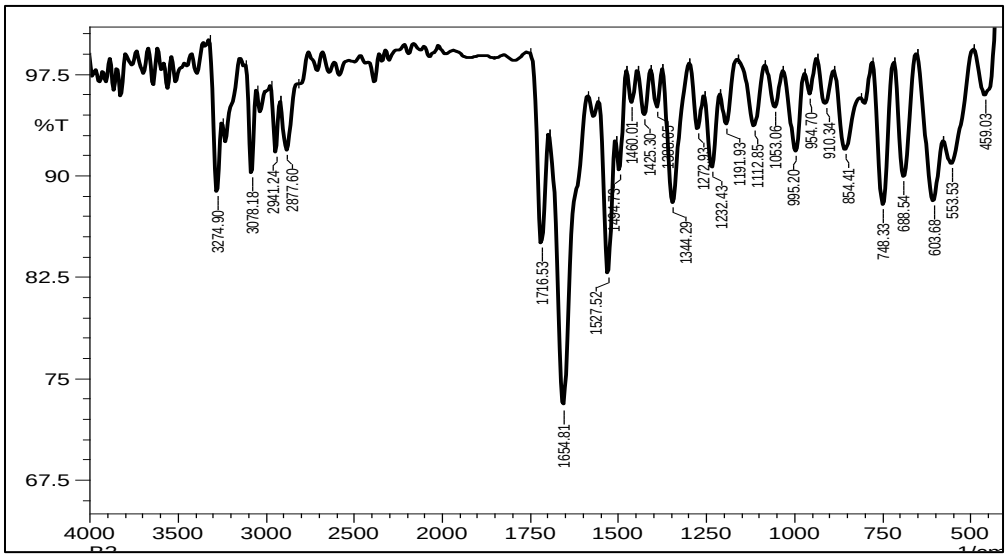


Figure 5. FT-IR Spectrum of Compound B_3

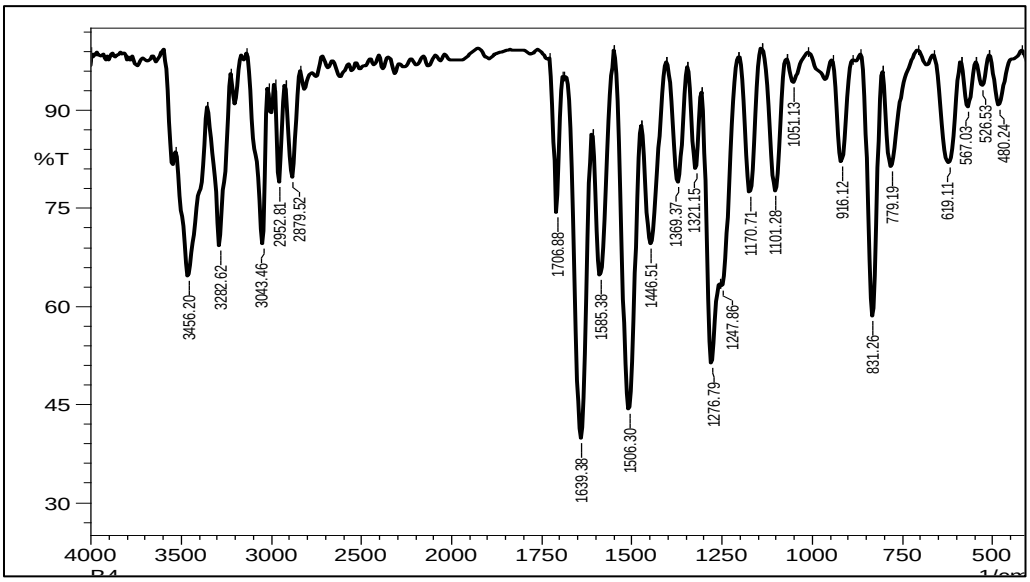


Figure 6. FT-IR Spectrum of Compound B_4

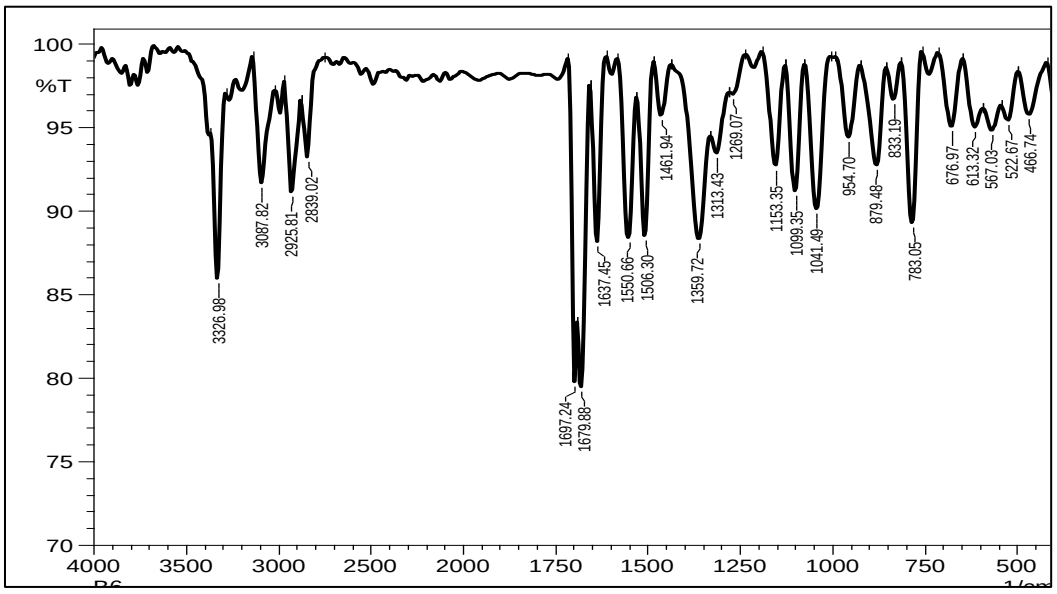


Figure 7. FT-IR Spectrum of Compound B_6

3.2 Biological Activity Results of the Prepared Compounds

The biological activity of the prepared compounds [B_1–B_8] was evaluated against two types of bacteria: Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative). The assay was carried out on Petri dishes using the diffusion method. Three concentrations (25%, 50%, and 100%) were prepared for each compound using Mueller–Hinton agar as the culture medium,the inhibition zone diameters were measured in centimeters and compared with a control sample [29-32], the prepared compounds exhibited good inhibitory activity against both types of bacteria, as shown in Table 3 and Figure 8.

Table 3. Antibacterial Activity Results of the Prepared Compounds

Com	***Staphylococcus aureus***			***Escherichia coli***		
.No	**100%**	**50%**	**25%**	**%100**	**50%**	**25%**
B_1	16.8	12.7	10.6	15.8	15.5	14.6
B_2	13.1	12.6	11.7	15.4	11.3	11
B_3	17.1	13.5	9.9	19.10	17.5	14.9
B_4	21.1	15.9	12.4	16.3	12.7	.910
B_5	16.7	15.5	13.9	11.3	10.7	10.9
B_6	16	13.9	10.3	15.5	11.5	13.8
B_7	10.0	12.5	19.3	10.4	15.5	13.3
B_8	16.3	15.3	13.8	17.2	15.7	12.2

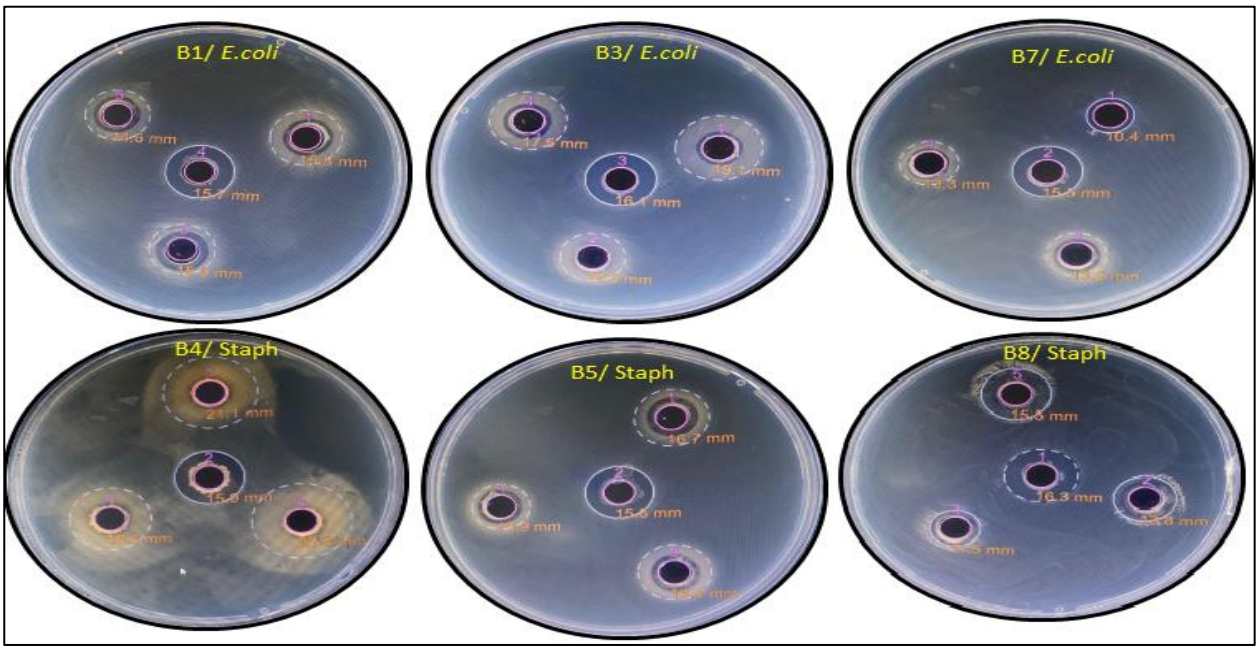


Figure 8. Antibacterial Activity Results of the Prepared Compounds Against Staphylococcus aureus

3.3 Molecular Docking Results of the Prepared Compounds

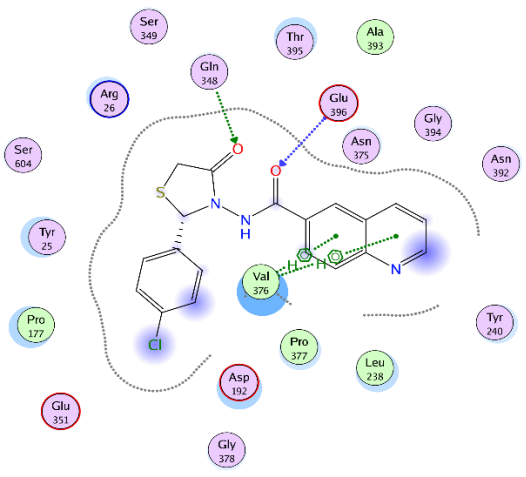
The molecular docking results of compounds [B_1–B_8] against the protein of Escherichia coli demonstrated good binding affinity, with binding energy values ranging from −5.04 kcal/mol to −5.97 kcal/mol. Compound B8 showed the highest activity, followed by B4 and B3, indicating greater stability of these complexes within the active site,this stability is attributed to the formation of a network of non-covalent interactions, particularly hydrogen bonds with polar amino acids such as GLU 396, ASP 192, and GLN 348 [33-35], in addition to π–H and π–cation interactions with residues such as ARG 173 and VAL 376, which enhanced stabilization within the active site,furthermore, the presence of active atoms (N, O, S) and aromatic rings contributed to strengthening these interactions, while the presence of halogens in some compounds improved hydrophobic interactions. The RMSD values (1.81–2.38 Å) fall within acceptable limits, confirming the reliability of the docking results.Overall, these findings indicate that the compounds possess good binding affinity toward the target protein, supporting the antibacterial activity results of the compounds as inhibitors against Escherichia coli, as shown in Table 4 and Figure 9.

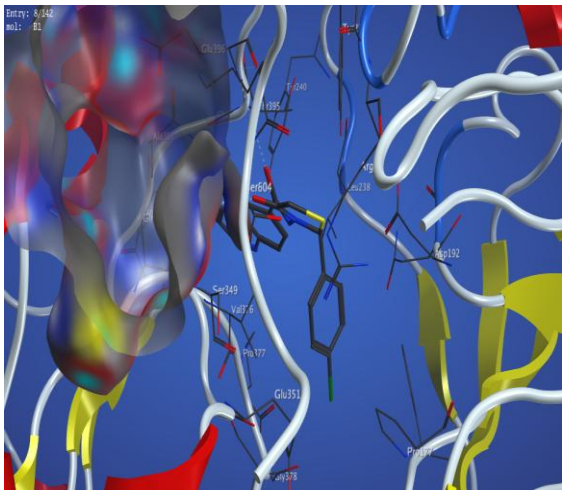
Table 4. The Results Obtained from Docking of Thiazolidin-4-one Derivatives with 1JXA

Com.	S score (kcal/mo)	RMSD	Atom of compound	Atom of receptor	Involved receptor residues	Type of interaction bond	Distance	E(kcal/mol)
B_1	-5.7433	1.817839	O 12	N	GLU 396	H-acceptor	3.45	-1.0
			O 25	NE2	GLU 348	H-acceptor	3.09	-2.7
			6-ring	CA	VAL 376	pi-H	3.93	-1.3
			6-ring	CA	VAL 376	pi-H	4.52	-0.8

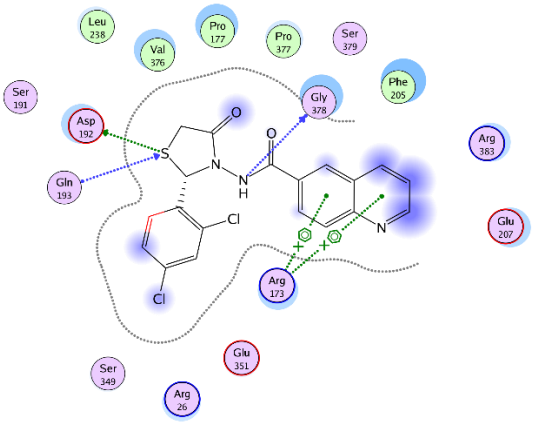
			N 13	O	GLY 378	H-donor	3.13	-2.8
			S 22	OD1	ASP 192	H-donor	3.63	-0.8
B_2	-5.0431	1.96333	S 22	N	GLN 193	H-acceptor	4.00	-2.1
			6-ring	NH1	ARG 173	pi-cation	3.74	-0.7
			6-ring	NH2	ARG 173	pi-cation	4.89	-0.6
			BR 26	O	GLY 378	H-donor	3.36	-0.7
B_3	-5.8412	2.140054	O 25	NE2	GLN 348	H-acceptor	3.32	-1.3
			6-ring	CA	VAL 376	pi-H	4.01	-0.9
			6-ring	CA	VAL 376	pi-H	4.43	-0.9
			S 22	O	GLU 396	H-donor	3.44	-0.1
			O 26	OD1	ASP 192	H-donor	2.97	-3.3
B_4	-5.9046	1.991843	S 22	NE2	GLN 348	H-acceptor	3.46	-2.0
			S 22	N	GLU 396	H-acceptor	4.28	-1.6
			S 22	NZ	LYS 603	H-acceptor	4.32	-1.8
			O 26	O	GLY 175	H-donor	3.27	-1.2
B5	-5.7580	2.240936	O 27	OE1	GLU 351	H-donor	3.26	-1.4
			S 22	NH1	ARG 173	H-acceptor	3.26	-0.9
			N 13	O	GLY 378	H-donor	2.96	-6.3
			S 22	OD1	ASP 192	H-donor	4.27	-0.5
B6	-5.1422	2.053243	S 22	O	HOH 706	H-acceptor	3.71	-1.1
			6-ring	NH1	ARG 173	pi-cation	4.47	-1.0
			6-ring	NH2	ARG 173	pi-cation	4.53	-1.4
			N 13	O	PRO 377	H-donor	3.03	-3.5
			S 22	OE1	GLU 351	H-donor	3.50	-1.8
B7	-5.6897	1.976599	S 22	CA	SER 379	H-acceptor	4.07	-0.7
			6-ring	CB	PRO 377	pi-H	4.70	-0.6
			6-ring	CB	PRO 377	pi-H	4.45	-0.7
			N 13	O	GLY 378	H-donor	3.02	-3.4
B8	-5.9731	2.381066	S 22	OE1	GLU 207	H-donor	3.94	-2.1
			C 15	6-ring	PHE 205	H-pi	4.76	-0.7

B_1





B2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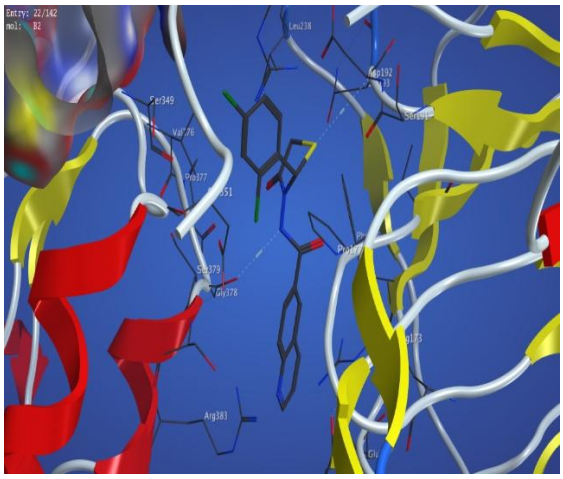
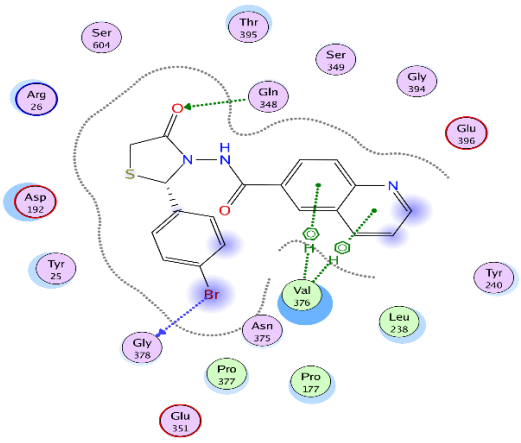


B3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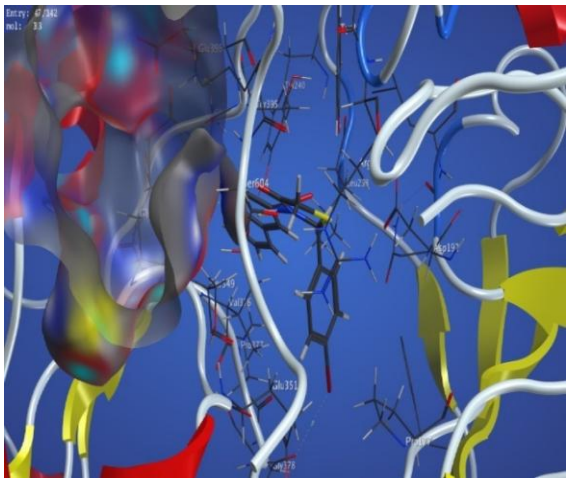

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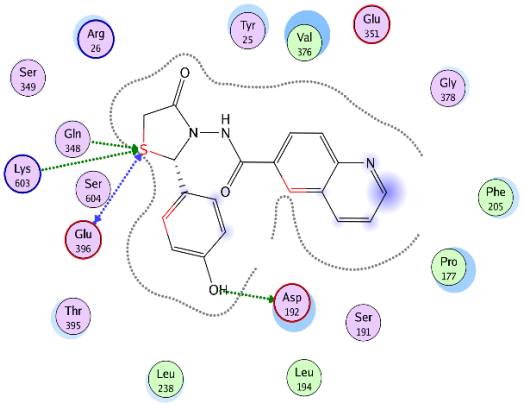
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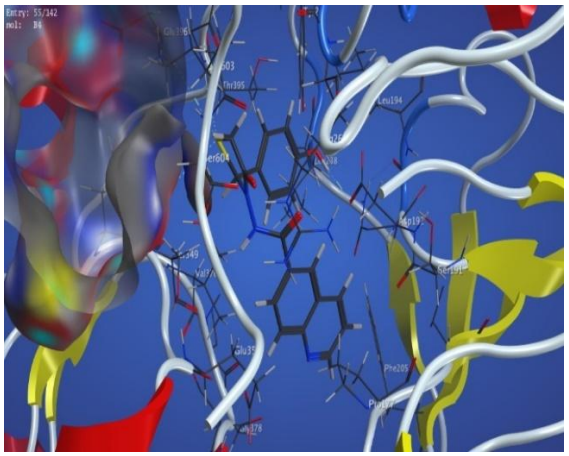

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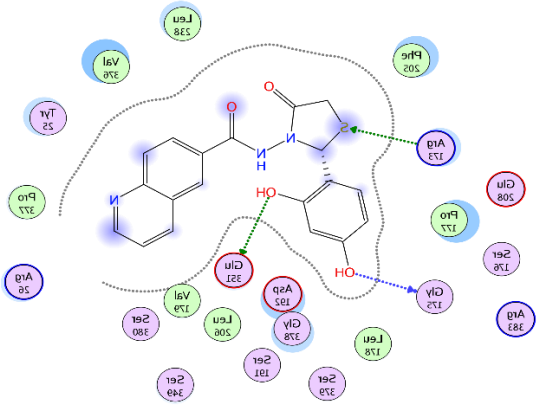

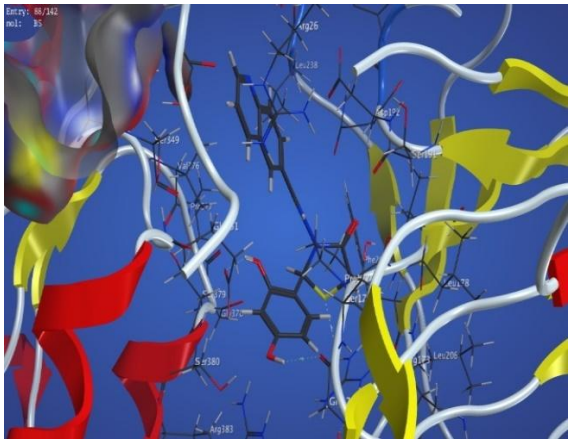

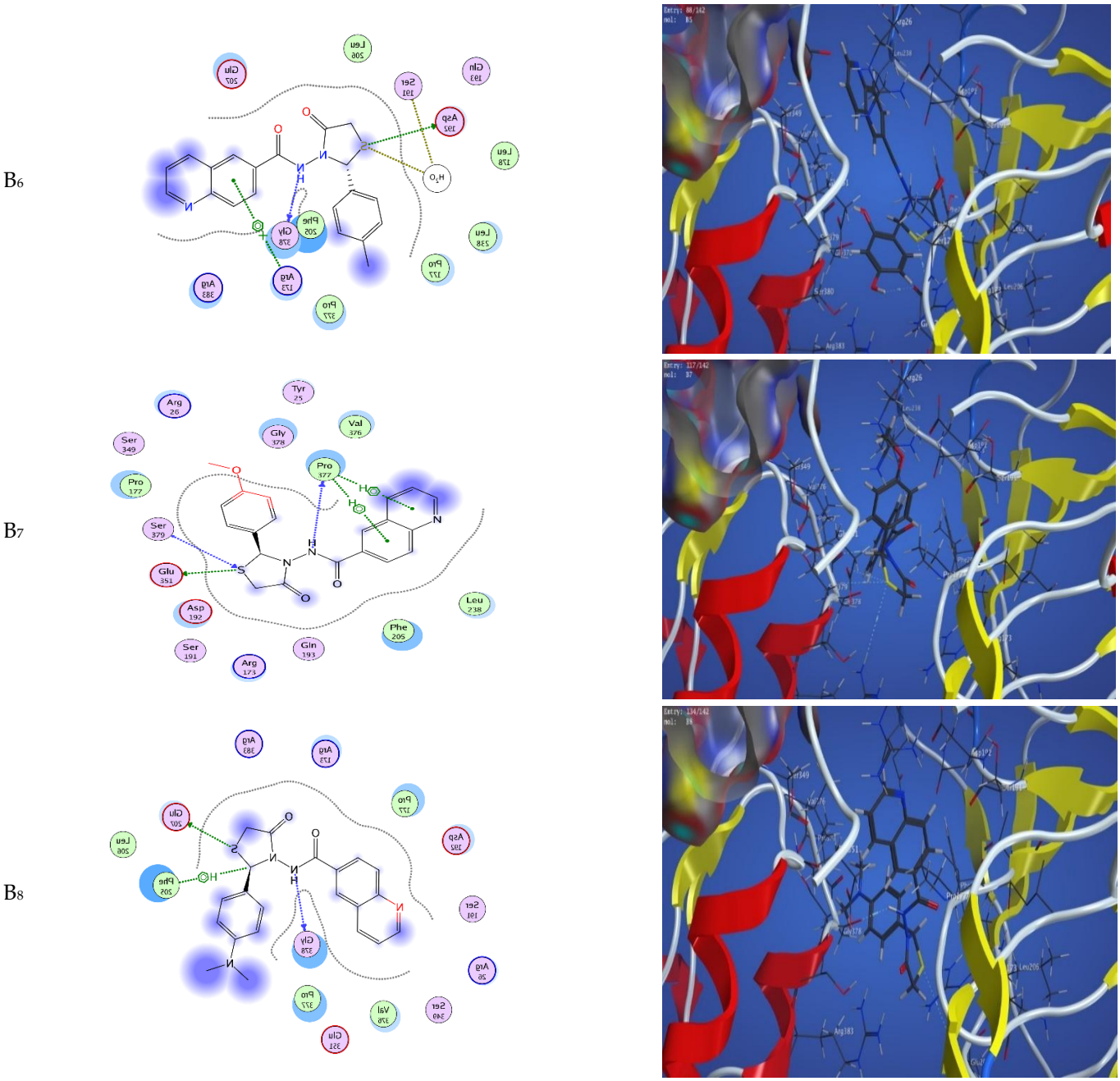

Figure 9. 2D and 3D Interactions Between the Ligand and the Protein.

4. Conclusion

This study indicates the successful synthesis of a series of thiazolidin-4-one derivatives (B1–B8) using an efficient method with good yields. Their chemical structures were confirmed by various spectroscopic techniques, including FT-IR, ^{1}H-NMR, and ^{13}C-NMR, which verified the presence of the expected functional groups within the synthesized compounds,the biological evaluation results demonstrated that these compounds exhibit notable inhibitory activity against both Gram-positive and Gram-negative bacteria, particularly against *Escherichia coli*. Some compounds, such as B3, B4, and B8, showed superior activity compared to the rest of the series.

Molecular docking studies further supported these findings, revealing a good binding affinity of the compounds toward the target protein, with favorable binding energy values. Compound B8 exhibited the highest stability, followed by B4 and B3. This enhanced activity can be attributed to the formation of multiple non-covalent interactions,

especially hydrogen bonds and π-interactions, in addition to the contribution of active atoms (N, O, S) and aromatic rings in stabilizing the compounds within the active site.Accordingly, these compounds can be considered promising candidates for the development of antibacterial agents; however, further studies are required to comprehensively evaluate their biological efficacy.

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