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Synthesis of Thiazolidinone-Thiadiazole Hybrids: Molecular Docking and Antimicrobial Evaluation

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***Abstract*—A green synthesis of bis-thiazolidinone-thiadiazole hybrids (6a-h) exhibiting mild to potent antibacterial activity is reported. The hybrid compounds were synthesized in one-pot three-component Microwave-assisted reaction under solvent-free condition from the corresponding bis- thiadiazole amines (3) reaction with various aldehydes, and thioglycolic acid. The products were obtained in acceptable yields and characterized based on spectroscopic techniques (Fourier transform infrared, proton nuclear magnetic resonance, carbon-13 nuclear magnetic resonance, and carbon-attached proton test nuclear magnetic resonance). Antibacterial screening was performed on the synthesized compounds (6a-h) against both Grampositive strains (*Staphylococcus* and *Streptococcus*) and Gramnegative strains (*Escherichia coli* and *Klebsiella pneumoniae*), with their efficacy compared to the reference antibiotics ciprofloxacin and vancomycin. Overall, the synthesized compounds demonstrated highly antibacterial properties. Among the series, compounds (6b, 6d, and 6e) exhibited broad-spectrum and potent levels of antibacterial activity against species; furthermore, they showed notable activity against *K. pneumoniae* as the most antibacterial-resistant pathogen. The result of Molecular docking studies indicated that OH, OCH_3 substituents, such as in compounds (6b), enhanced binding ability interaction and producing conventional hydrogen bond with the minimum energy affinity (ΔG).**

***Index Terms*—Antimicrobial activity, Green organic chemistry, Molecular docking studies, Multidrug-resistant, Thiazolidinones.**

I. Introduction

Multidrug resistance (MDR), defined as bacterial developed resistance to multiple classes of antibiotics, it is a critical global threatening concern in the management of infectious diseases, *Staphylococcus aureus* and *Klebsiella pneumoniae,* among the causative death factors (Murray, et al., 2022; World Health Organization, 2024). The MDR challenge has drawn considerable attention to the researchers to the discovery of new antimicrobial agents or modifications on the existing drugs. Thiazolidinone compounds are one of the promising drug candidates and have attracted considerable attention in the literature, demonstrating multiple bioactivities (Chaban, et al., 2021; Hussein, Ali, and Al-Saady, 2023).

Thiazolidinone is essential in the pharmaceutical industry, and biochemists and medicinal chemists studied these molecules intensively (Kumar, et al., 2015). These compounds serve as an important scaffold for pharmacophores with a variety of bioactivities (Abeed and Abdel-Mohsen). This family of heterocyclic chemicals can be used to treat a variety of diseases (Drzał and Trotsko, 2025; Fesatidou, Petrou and Geronikaki, 2024; Kasmi-Mir, et al., 2006; Sharma, et al., 2023), particularly show interesting anti-acquired immunodeficiency syndrome properties (Barreca, et al., 2001; Tratrat, et al., 2025), antimalarial (Solomon, et al., 2007), insecticidal (Cunico, et al., 2007), antidiarrheal, cyclooxygenase inhibitory, antidiabetic, antiplatelet activating factor (Baviskar, Khadabadi and Deore, 2013), anti-histaminic (Diurno, et al., 1992), antibacterial (Desai and Desai, 2006), antiarrhythmic (Jackson, et al., 2007), antioxidant activities (Fesatidou, et al., 2018), anticancer, anti-tubercular (Drzał and Trotsko, 2025), anti-inflammatory, anti-fungal, and cardiovascular effects (El Azab and Abdel-Hafez, 2015). Moreover, it is used to diabetic nephropathy disease treatment (Al-khyaat, 2020).

Recently, potent activity of thiazolidinone against Gram-negative bacteria, including *K. pneumoniae*, in both *in vitro* assays and molecular docking studies was also reported (Hussein, Ali, and Al-Saady, 2023), suggested that thiazolidinones may also inhibit penicillin-binding proteins and other bacterial enzymes.

Thiadiazole is another biologically significant compound that exhibits multi-functional biological applications antibacterial (Hamad, Taher and Aziz, 2022), antituberculosis (Patel, et al., 2017).

Several drugs have received approval by the Food and Drug Administration containing thiazolidinones or thiadiazoles, such as anti-biotic (actithiazic acid), anti-cancer

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(Les-3377), antiviral (LJ-001) (Abo-Bakr, et al., 2021), methazolamide as a diuretic drugs, cefazolin, sulfamethazine as an antimicrobial sulfonamide, acetazolamide as diuretic carbonic anhydrase, and the anti-parasitic drug, megazol (Tahghighi and Babalouei, 2017), as shown in Fig. 1.

Combinations of two pharmacologically active heterocyclic compounds like sulfur- and nitrogen- containing heterocycles may lead to the new drug discovery (Abo-Bakr and Hashem, 2019; Singh, et al., 2026). Notably, Thiazolidinone-thiadizole hybrids have been showing promising biological activity due to the combination of two pharmacologically active heterocyclic cores (Aggarwal, Jain, and Chopra, 2022; Gummidi, et al., 2021; Nasab, et al., 2023).

Despite the significant pharmacological promise of Thiazolidinone-thiadizole hybrids, the classical routes to synthesize these compounds have disadvantages (multi-step processes, environmental impact, waste generation, poor Atom economy, and low efficiency), all of which limit synthesis applicability in clinical trials and the pharmaceutical industry. Consequently, considerable, but few research efforts have been reported toward developing green, efficient, and straightforward synthetic approaches for these hybrid compounds (AL-Abayechi, Al-Nayili, and Balakit, 2024; Dwivedi, Bhardwaj, and Choudhary, 2024; Kumar, et al., 2025).

To address these challenges, we report an optimized only two step (one-pot *in situ* and three-component) green synthetic route of bis-Thiazolidinone-thiadizole hybrids (**6a-h**). This approach improves step economy and sustainability, and the synthesized compounds were checked for antibacterial properties and investigated by molecular docking studies in order to identify their potential binding sites.

II. Materials and Methods

A. Chemicals, Instruments

The highest purity chemical compounds were purchased and used without purification. Thin-layer chromatography (TLC) tested using SiO_2 coated plate (200 mesh). Eluting solvent (n-hexane and methyl acetate) were used in different ratio percentages (ranges from 3:1 to 5:1). TLC spots were visualized using a ultraviolet lamp, as well as iodine or $KmnO_4$ staining reagents, supplied by the Research Center at Koya University. Melting points were recorded using Electro thermal apparatus (BUCHI Germany.B-540). Infrared spectra were recorded on a THERMO scientific Spectrometer (Nicolet I S 10 at Raparin University and Shimadzu 1 S at the research center at Koya University).

Nuclear magnetic resonance (NMR) characterization was carried out on a 400 MHz Bruker spectrometer using dimethyl sulfoxide (DMSO) as a solvent. Proton NMR (^{1}H-NMR), carbon-13 NMR (^{13}C-NMR), and attached proton test (APT) at Basra university/Iraq, and at Firat University/Turkey.

Molecular docking study used MOE 2015.10 software, designing the synthesized ligands generated using PubChem and ChemDraw software programs. Data Bank of Protein was used for downloading of a protein model.

B. Chemistry

Synthesis of (3)

A mixture of thiosemicarbazide **(1)** (1.0 mmol) with carbon disulfide (4 mmol) in Dimethyl Formamide (DMF) (5 mL) was heated under reflux at 70–80°C for 7 h. The completion of the reaction was monitored by TLC (Petrow, et al., 1958; Samir, Ali, and Saeed, 2017). The mixture was cooled to ambient temperature, then 1 mL of triethylamine was added, stirred for more10 min. Dibromoethane **(2)** (1 mmole) was then added dropwise to the mixture, refluxed at 70–80°C for 6 h until completion, which was monitored by TLC using n-hexane and methyl acetate (3:1) as eluting solvent. The reaction was quenched with 10 mL of ice-cold water, filtered, and washed with cold water several times. The crude product was recrystallized from n-hexane: ethyl acetate (1:1) to give the product **(3)** as a faint brown precipitate (yield 75% and M.P = 178–180°C), FT-IR (cm^{-1}) 3307.92, 3267.41, 3095.75, 2941.44, 2868.15, 1629.85, 1614.42. ^{1}H-NMR (DMSO) ppm: δ 2.89 (s, 4H, $2CH_2$), 7.33 (s, 4H, $2NH_2$). ^{13}C-NMR, (DMSO) ppm: δ 34.4 (CH_2), 149.4 (C-$S_{thiadiazole}$),170.6 (C-$N_{thiadiazole}$).

Synthesis of (6a-h)

(10 mmol) of the compound (**3**), and (20 mmol) of aldehydes **(5),** was dissolved excess amount of thioglycolic acid **(4)** with a few drops of acetic acid. The mixture was irradiated for 6–8 min in microwave oven reactor (300 watt); until a dark-red solution is formed, which was later confirmed by TLC using eluting solvent n-hexane/methyl acetate (3:1). The reaction mixture was permitted to reach

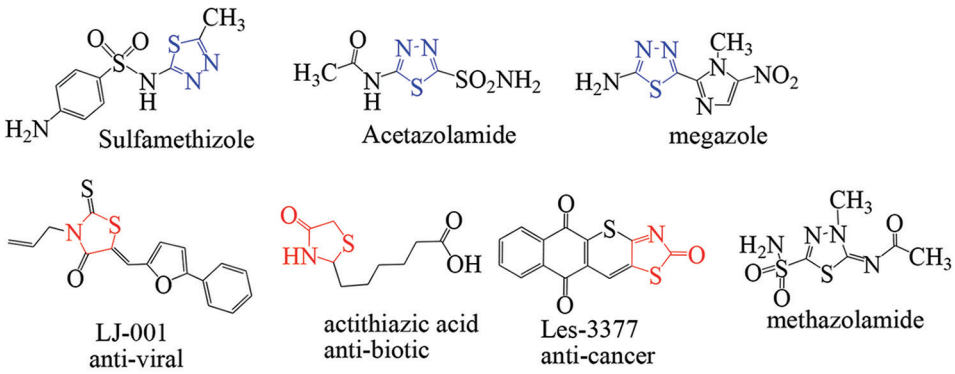

Fig. 1. Thiadiazole and thiazolidinone-containing drugs.

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room temperature, and then 10 mL of %10 $NaHCO_3$ was added to remove the excess of thioglycolic acid. The mixture was cooled to 5°C by adding crushes of ice to precipitate the product; finally, the crude product was collected as a semi-solid product, which was later recrystallized with in diethyl ether to give pure product **(6a-h).** The physical properties of compounds (6a-h) are presented in Table I.

B. In vitro Antibacterial Evaluation

The synthesized thiazolidinones () were screened for *in vitro* antibacterial activity (*Staphylococcus, streptococcus*), and (*Escherichia coli, K. pneumoniae*). Ciprofloxacin and Vancomycin were utilized as standard to be compared with the synthesized compounds. Several known concentrations, such as 100, 200, 350, 500 ppm, were applied in order to be compared to the standard drugs.

C. Disc Diffusion Susceptibility Method

According to the method reported by (Bakht, et al., 2011), the agar medium culture plates were prepared within 18–24 h. Whitman No. 2 filter paper discs (6 mm in diameter) were positioned on the agar medium using sterile forceps, and then the synthesized compounds () in conc.;.; 100, 200, 350, and 500 ppm/50 µL were applied to the discs. Antibiotics, same diameter, as positive control placed on the same discs. All plates were sterilized in the incubator at 37°C for 18–24 h. The next day, the inhibition zones around the disc on each plate were recorded in millimeters. Ciprofloxacin and vancomycin were applied as positive controls.

D. Molecular Docking Studies

Molecular docking software (Moe-Dockk 2015.10), (MOE, 2015), and (Auto dock.1.5.6) were used to evaluate the binding affinities of the synthesized compounds and identify their active sides with the target proteins. The structure of the compounds was constructed using ChemDraw tool (Cambridge, 1986), and the threedimensional crystallographic structure of Ciprofloxacin-target protein (protein Data Bank [PDB] ID: 1VQQ) was downloaded from PDB and employed as a template for the target. Furthermore, docking experiments were performed after subjecting the ligand structures to energy minimization using the default MMFF94x force field in the Molecular Operating Environment program software MOE. The active binding pocket of the ciprofloxacintarget protein 1VQQ was identified using the MOE-Alpha site finder module. Ligands structures were subsequently docked into the active side region within the MOE Dock. The MOE was further applied to calculate the optimum binding score between each ligand and the protein active binding sites.

III. Results and Discussion

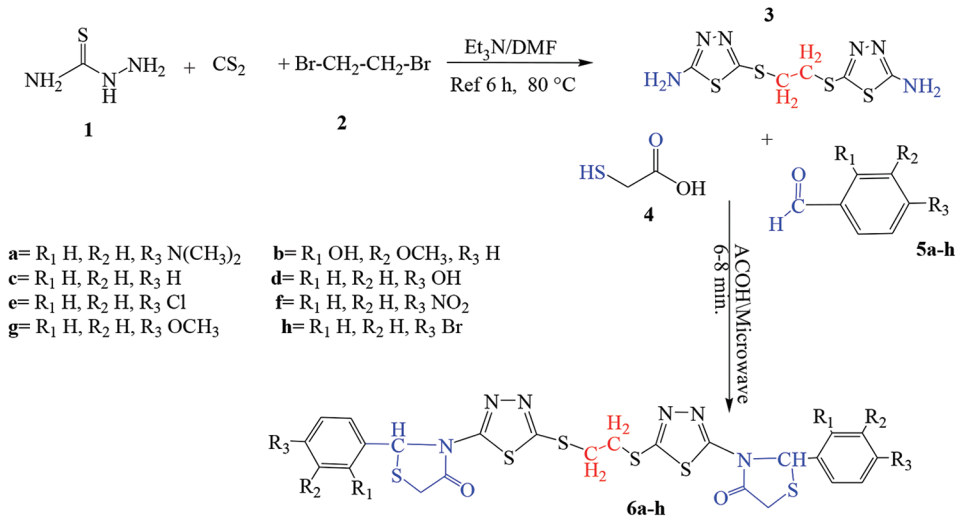
A. Chemistry

The bis-thiadiazole amines (**3**) were first synthesized through a cyclization reaction of the thiosemicarbazide **(1)** with carbon disulfide **(2)**, followed by *in situ*, S_N2 reaction of the formed thiadiazole with dibromoethane (**2**) to give bis-thiadiazole amine (**3**) which illustrated in Scheme 1.

The structure of (**3**) was elucidated using Fourier transform infrared (FT-IR), ^{1}H-NMR, and ^{13}C-NMR techniques. The FT-IR spectra showed the characteristic bands, which showed the symmetrical and asymmetrical bands of the amine group at (3307.9 asym. and 3267.4 sym.) cm^{-1}, and aliphatic protons (CH_2-CH_2) in the region (2968–2868) cm^{-1} (Hamad, Taher, and Aziz, 2022).

The ^{1}H-NMR spectra further confirmed the success of the reaction, which displayed a distinct singlet peak at 2.89 ppm attributable to the aliphatic CH_2 linkage between thiadiazole ring and the singlet peak at 7.38 ppm for the (NH_2).

Furthermore,^{13}C-NMR spectra of compound (**3**) revealed signals at 170.6 and 149.4 ppm for C_2 and C_4 of the thiadiazole ring, respectively. The appearance signal at 34.45 ppm for aliphatic carbon (CH_2) is clear evidence of the



Scheme 1. Green synthesis of thiazolidinone-thiadiazole hybrids **(6a-h).**

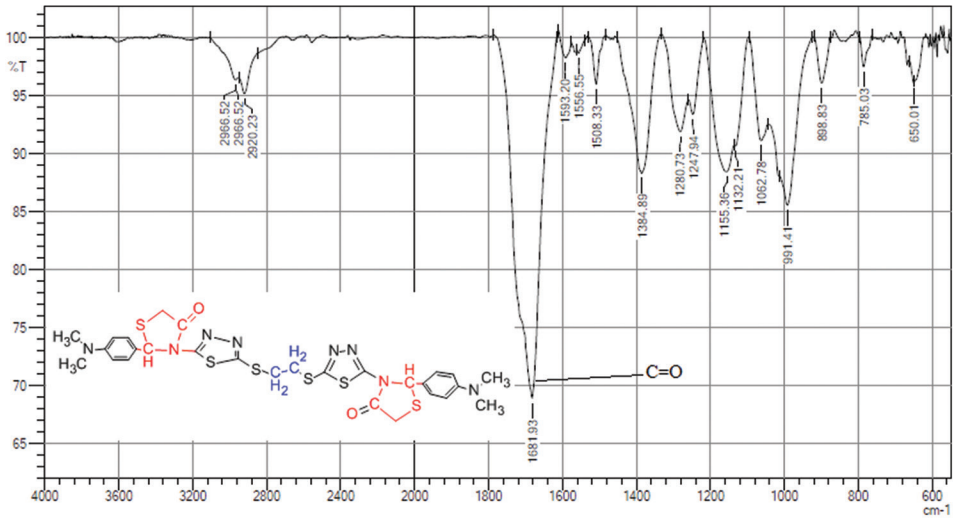


Fig. 2. Fourier transform infrared spectra of the thiazolidinone compound **(6a).**

TABLE *I*
PHYSICAL PROPERTIES OF COMPOUNDS (**6A-H**)

Comp. 6	R	Chemical Formula	M.Wt	Yield %	Color
A	N, N-Dimethyl benzaldehyde	$C_{28}H_{30}N_8O_2S_6$	703	75	Dark-brown
B	2-Hydroxy-3-methoxy benzaldehyde	$C_{26}H_{24}N_6O_6S_6$	708.1	85	Dark-red
C	Benzaldehyde	$C_{24}H_{20}N_6O_2S_6$	616.8	82	Dark-brown
D	4-Hydroxy benzaldehyde	$C_{24}H_{20}N_6O_4S_6$	648.8	80	Pale brown
E	4-Chloro benzaldehyde	$C_{24}H_{18}Cl_2N_6O_2S_6$	685.7	65	Dark-brown
F	4-Nitro benzaldehyde	$C_{24}H_{18}N_8O_6S_6$	706.8	69	Dark-brown
G	4-Methoxy benzaldehyde	$C_{26}H_{24}N_6O_4S_6$	676.9	78	Dark-brown
H	4-Bromo benzaldehyde	$C_{24}H_{18}Br_2N_6O_2S_6$	774.6	60	Dark-brown

formation compound (**3**). The ^{1}H NMR and ^{13}C-NMR spectra are presented in Appendix Figs. 1 and 2, respectively.

The current proposed green synthesis route includes two-step reactions. Firstly, a one-pot, in situ reaction of thiosemicarbazide with carbon disulfide CS_2 and dibromoethane in dimethylformamide (DMF) to yield the intermediate bis-thiadiazole amine **(3)**. Secondly, one-pot three-component reaction of compound **(3)** with appropriate aldehydes and thioglycolic acid under solvent-free condition using microwave irradiation to synthesize the bis thiazolidinone-thiadiazole Hybrids **(6a-h),** Scheme 1.

Utilization microwave irradiation energy was the among only helpful tool of green chemistry led to the desired product, unlike the conventional reflux method. Another general advantage of the microwave technique is the potential of the method to give the highest yields and less reaction time compared with the ordinary reflux method (Baviskar, Khadabadi and Deore, 2013) (reaction time 12 h and yield of 40–70%), while microwave-assisted reactions (reaction time 6–8 min. and yield of 65–85%). The product was in a form a semi solid, which was later recrystallized with diethyl ether to give the product **(6a-h)**.

The FT-IR spectrums of (**6a-h**) displayed important characteristic bands, the appearance of new sharp peak at (1681-1700) cm^{-1} belong to the C=O$_{str.}$ thiazolidinone. The disappeared (NH_2) group band of the bis thiadiazole amine **(3)** is another clue that confirms the success of the reaction. A representative IR spectrum of compound 6a is shown in Fig. 2, while the complete IR spectral characterization data for compounds (6a–h) are presented in Table II.

TABLE II
ASSIGNMENT OF IR (CM^{-1}) COMPOUNDS (6A-H)

Comp.	υ(C-H) aliph.	C=O	υ(C=C)	υ(C-N)	Others
6a	2883, 2926	1682	1557	1384	----------
6b	2880, 2920	1684	1562	1371	υ(O-H) = 3468
6c	2872, 2924	1693	1571	1392	----------
6d	2885, 2929	1681	1568	1380	υ(O-H) = 3398
6e	2882, 2920	1692	1562	1375	----------
6f	2888, 2929	1695	1542	1377	υ(NO_2) = 1349-1531
6g	2880, 2928	1700	1569	1382	----------
6h	2878, 2928	1681	1553	1372	----------

The ^{1}H-NMR spectra of (**6a-e)** showed clear evidence of the success of the reaction, and thiazolidinone ring formation. Where the CH_2 group of the thiazolidinone ring was observed in the range of 3.92–4.02 ppm, and the CH_2 methylene groups linkage of the thioether remained constant in the region of 3.42–3.73 ppm. A broad singlet corresponding to the CH of the thiazolidinone ring was also appeared downfield at 5.28–5.63 ppm. The aromatic protons were appeared in the range of 6.79–7.46 ppm. Notably, a highly downfield singlet at 14.26 ppm, assigned to the OH group, and another singlet peak integrated for three protons at 3.73 ppm for the methoxy group in compound (6b) provided additional confirmation of the successful synthesis. As shown in Fig. 3.

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The carbon-APT spectra of the compounds (**6b**), contains three newly appeared characteristic peaks, such as CH_2, CH, and C=O of thiazolidinone at (34.21, 54.65, and 169.86) ppm, respectively, which confirms the formation thiazolidinone. The remaining aromatic carbons and the two signals of carbon in thiadiazole ring appeared at 111–147 ppm.

A typical signal at 55.8 ppm of the methoxy substituted in the compound (**6b**) is mentioned here as a distinctive peak that further confirms the success of the reaction, as shown in Fig. 4.

Additional ^{1}H-NMR and ^{13}C-NMR spectral characterization data are provided in Tables III and IV respectively.

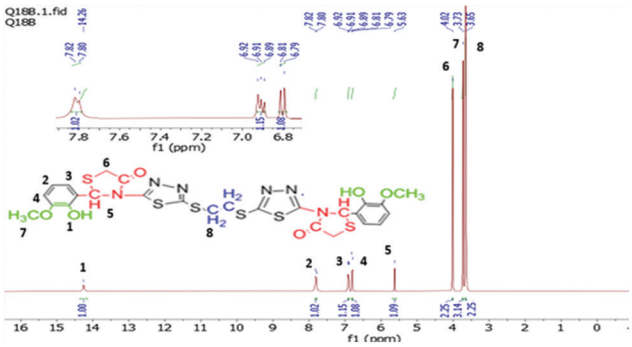

Fig. 3. Proton nuclear magnetic resonance spectra of thiazolidinone compound (**6b**).

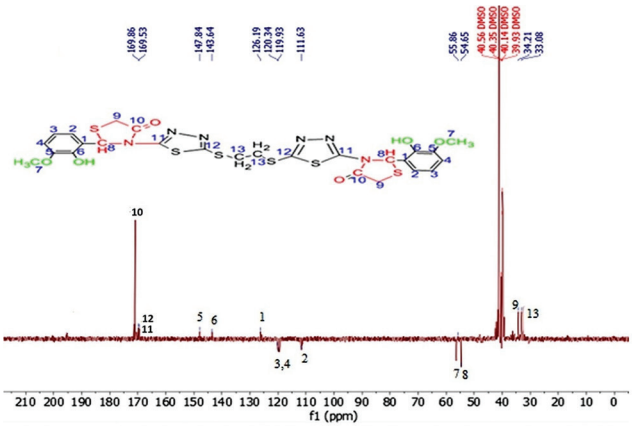

Fig.4. ^{13}Carbon attached proton test nuclear magnetic resonance spectra of the thiazolidinone compound (**6b**).

C. Antimicrobial Activity

All of the target compounds (**6a-h**) were evaluated against gram-positive bacteria (*Staphylococcus* and *streptococcus*), and Gram-negative (*E. coli* and *K. pneumoniae*) using discdiffusion method with results presented in Fig. 5 and Table V. The finding showed a concentration-dependent antibacterial intensity, with the highest inhibition zone was achieved at the concentration of 500 ppm.

The results showed that the maximum zones of inhibition (21–25 mm) mm against gram-positive bacteria *Staphylococcus* and *streptococcus*, which is significantly higher than the standard antibiotics Ciprofloxacin and Vancomycin. Specifically, compounds **(6b),** which possesses the hydroxyl (-OH) and methoxy- OCH_3) substituent groups, displayed the highest inhibition zones (24 and 25 mm) against these two strains. Furthermore, compounds **(6b, 6d**and **6e)** also showed notable activity against highly resistant bacterial pathogen *K. pneumonia*, indicating promising potential antimicrobial agent.

Overall, compound **(6b)** displayed broad-spectrum antibacterial activity against four different bacterial strains**,** highlighting it as the most significant finding of this study, with promising potential as an antimicrobial drug candidate.

Fig. 5. *In vitro* antimicrobial activity of compounds (**6a-h**).

TABLE III
ASSIGNMENT OF CHARACTERISTIC ^{1}H-NMR DATA IN PPM FOR SYNTHESIZED COMPOUNDS (6A-E)

Comp.	CH_2-CH_2	CH_2 thiazolidinone	*J* value Hz	C-H thiazolidinone	(C-H) Ar. ($H_{1,1}$)	*J* value Hz	(C-H) Ar. ($H_{2,2}$)	*J* value Hz	Others
6a	3.5, s	3.92, s		5.61, s	7.34, d	8.1	6.82, d	8	----------
6b	3.65, s	4.02, s		5.63, s	H_2=6.79, d	8	H_3=7.8, m	----	H_3=6.89, m (O-H)=14.26, s
6c	3.73, s	4.02, d	6.9	5.28, s	7.41, m	---	7.39, m	----	(C-H) Ar. (H_4)=7.39, m
6d	3.42, s	4.04, br.s		5.57, s	7.46, d	8	6.96, d	8	(O-H)=12.50, s

^{1}H-NMR: Proton nuclear magnetic resonance

TABLE IV
ASSIGNMENT OF CHARACTERISTIC ^{13}C-NMR DATA FOR SYNTHESIZED COMPOUNDS (6A-E)

Comp.	CH_2 thiazolidinone	C-H thiazolidinone	C_1.Aro.	CH_4.Ar.	CH_2.Ar.	C_3.Ar.	C=O thiazolidinone	Others
6a	33.9	54.8	124.7	122	111.2	146.4	170.2	C (CH_3)=32.72
6b	34.2	54.6	126.2	111	120	119	169.8	C (OCH_3)=55.6
6c	33.9	54.9	127.4	126	112.6	131.2	171.7	----------
6d	33.7	54.7	125.6	124.2	116.4	145.5	169.5	--------

^{13}C-NMR: Carbon-13 nuclear magnetic resonance

TABLE V
THE ANTIMICROBIAL ACTIVITY OF (6A-H)

Comp. No.	Zone of Inhibition (mm) Conc.ppm															
	Staphylococcus				*Streptococcus*				*Escherichia coli*				*Klebsiella pneumonia*			
	100	200	350	500	100	200	350	500	100	200	350	500	100	200	350	500
6a	0	07	10	17	0	07	11	16	0	04	09	15	0	0	05	12
6b	0	08	10	25	0	12	18	24	0	0	05	18	0	0	08	15
6c	0	08	10	18	0	09	12	17	0	0	06	15	0	0	08	13
6d	0	08	12	20	0	09	14	19	0	05	09	16	0	05	10	14
6e	0	07	13	21	0	8	12	20	0	06	10	15	0	0	07	15
6f	0	07	09	15	0	06	10	14	0	0	06	12	0	0	06	10
6g	0	09	11	19	0	10	14	18	0	05	09	15	0	04	08	14
6h	0	08	10	18	0	09	14	19	0	0	08	14	0	0	07	13
Ciprofloxacin	6				5				25				18			
Vancomycin	20				18				7				5			

TABLE VI
THE SYNTHESIZED COMPOUNDS DOCKED INTO THE CIPROFLOXACIN - BINDING PROTEIN

Comp.	ΔG (kcal/mol)	Interaction
6a	−8.4	Van der Waals: ALA152, ALA154, ALA147, ALA248, GLY237, SER238, TYR187, ILE140, GLU308, PHE240, PHE247, GLN241, GLN229. Conventional hydrogen bond: ARG188, ARG225, GLY153, ILE140. Carbon hydrogen bond: GLY146. Sulfur-X: ASN83. Unfavorable donor-donor: ARG242. Pi-alkyl: ARG242. Pi-Cation: ARG188.
6b	−10.1	Van der Waals: ALA147, ALA152, ALA154, ASN80, GLY81, GLY142, GLY145, GLY146, GLY153, GLY79, GLY237, ARG225, TYR77, ILE140, LEU98, LEU78, VAL199, PHE274, GLN229, PRO141. Conventional hydrogen bond: SER82, SER143, SER238 ASN83, ARG188. Unfavorable donor-donor: ARG310. Pi-Pi Stacked: TYR149. Pi-alkyl: ILE84, MET150.
6c	−9.1	Van der Waals: ALA152, ASN80, ASN83, GLY81, GLY142, GLY145, GLY146, GLY153, GLY79, GLY237, SER115, SER143, ARG225, ARG188, ARG310, TYR149, ILE84, ILE140, ILE192, MET150, LEU98, LEU78, LEU197, VAL198, PHE274, HIS196. Conventional hydrogen bond: VAL199, PRO141, PRO141, SER82. Pi-Sigma: TYR77. Pi-alkyl: PRO141.
6d	−9.8	Van der Waals: GLY273, ARG225, TYR187, ILE140, MET150, LEU231, GLU308, GLN229, PHE274, PHE247, LYS250. Conventional hydrogen bond: GLY237, GLY249, ALA248, ARG242, ARG188, SER82, SER238, PHE240, ASN83. Sulfur-X: PHE240. Pi-Sulfur: HIS271. Pi-Pi Shaped: HIS271. Pi-alkyl: PRO141.
6e	−7.5	Polar bond: GLY374, TYR223, TYR369, TYR373. Acetic bond: GLU189, GLU379, ASP221, ASP226, ASP367. Basic bond: LYS219, LYS230, LYS215. Greasy: PHE227, PHE231, LEU224, VAL217, PRO370.
6f	−8.2	Polar bond: GLY374, TYR223, TYR369, TYR373, THR216, SER376, SER191. Acetic bond: GLU189, GLU378, GLU379, ASP221, ASP367. Basic bond: LYS219, LYS215. Greasy: PHE227, LEU190, LEU224, VAL217, PRO370.
6g	−8	Polar bond: GLY374, TYR223, TYR369, TYR373, THR216, SER376, SER191. Acetic bond: GLU189, GLU378, GLU379, ASP221, ASP226. Basic bond: LYS188, LYS215, LYS218, LYS219, LYS230. Greasy: PHE227, LEU190, VAL217, PRO370.
6h	−8.6	Polar bond: GLY374, TYR223, TYR369, TYR373, THR216, SER376, SER191. Acetic bond: GLU189, GLU378, GLU379, ASP221, ASP226. Basic bond: LYS188, LYS215, LYS218, LYS219, LYS230. Greasy: PHE227, LEU190, LEU224, VAL217, PRO370, ILE171. Arene-Cation: LYS215.
Ciprofloxacin	−6.9	Van der Waals: GLY249, SER238, TYR187, PHE247, HIS271, GLN241, LYS228. Conventional hydrogen bond: PHE240, ARG242, ALA248, LYS250. Pi-cation: ARG242. Pi-alkyl: PHE247

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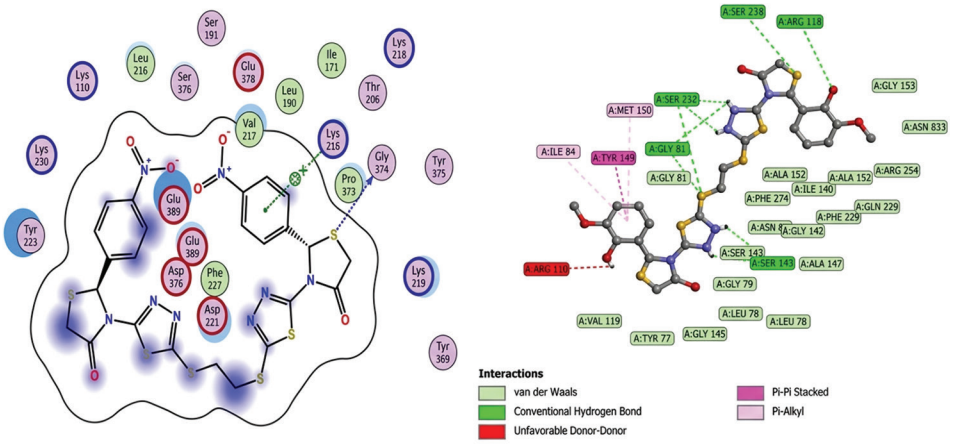

Fig. 6. The two-dimension interaction plot compound **6b** (right) and compound **6f** (left) docked into bacterial-binding protein's active site.

Docking Studies

MD study was carried out to investigate the binding affinities and interactions of the newly compounds with the target protein, supporting *in vitro* antibacterial activity of the synthesized compounds (Patel, et al., 2019). The stability of the ligand with receptors depends on the energy affinity to bind them (Hassan and Aziz, 2021). The docked compounds are shown in Table VI. The predicted binding energies (ΔG) that have lower binding energies than ciprofloxacin, the (ΔG) of the synthesized compounds were between −7.4 and −10.5 kcal/mol, as demonstrated in Table VI.

In the majority of cases, formed conventional hydrogen bonding were identified between ciprofloxacin and the compounds, such as Gly237, Pro141, and SER82. Furthermore, carbon-hydrogen bonding interaction, π- alkyl and π-π T-shaped were found in most compounds.

Moreover, due to presence a thiazolidinone group, the synthesized compounds **6a-h** have more interaction binding site for producing interaction, especially in the compound **6b**, which is illustrated in Fig 6, while the corresponding interactions for compounds **6c** and **6a** are presented in the Appendix Figs. 3 and 4, respectively.

Thiazolidinone has five conventional hydrogen bonds as the most binding affinity among the other synthesized compounds; first, OH site in the aromatic group is ARG188. Second, the methylene group in the thiazolidinone ring is SER238. Third and fourth, two bonds at thiadiazole ring as (SER82 and SER143), and the last one is sulfur element ASN83. The obtained results are consistent with the design of the compounds, as evidenced by the *in vitro* antibacterial findings. The docking analysis indicated that all structural moieties of the synthesized compounds participated in the bond interaction, the compound 6f has Arene-cation bond (LYS215) at the aromatic ring site Fig. 6.

IV. Conclusion

The current study describes the two-step green synthesis of novel bis-thiazolidinone-thiadiazole hybrids **(6a-h)** from their corresponding bis-thiadiazole amine **(3)** using microwave technique as a facile method in good yields.

The synthesized compounds **(6b, 6d, and 6e)** showed broad-spectrum levels of antibacterial activity against all bacterial strains. Of particular note, their effectiveness against *K. pneumonia* is especially significant, as it is a as one of the highly resistant bacterial pathogen.

Overall, the compound **(6b)** exhibits a broad-spectrum antibacterial activity**,** highlighting it as the most potent compound and a key finding of this study.

Finally, computational molecular docking analysis results revealed that the synthesized compounds expressed considerably good binding energies and strong interaction relative to standard reference drugs. The methoxy and hydroxysubstituent groups were in a well-orientation to facilitate binding interactions and form hydrogen bonds with the target protein.

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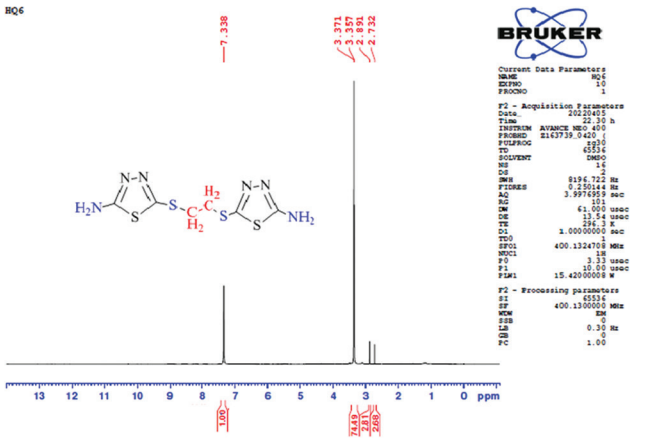
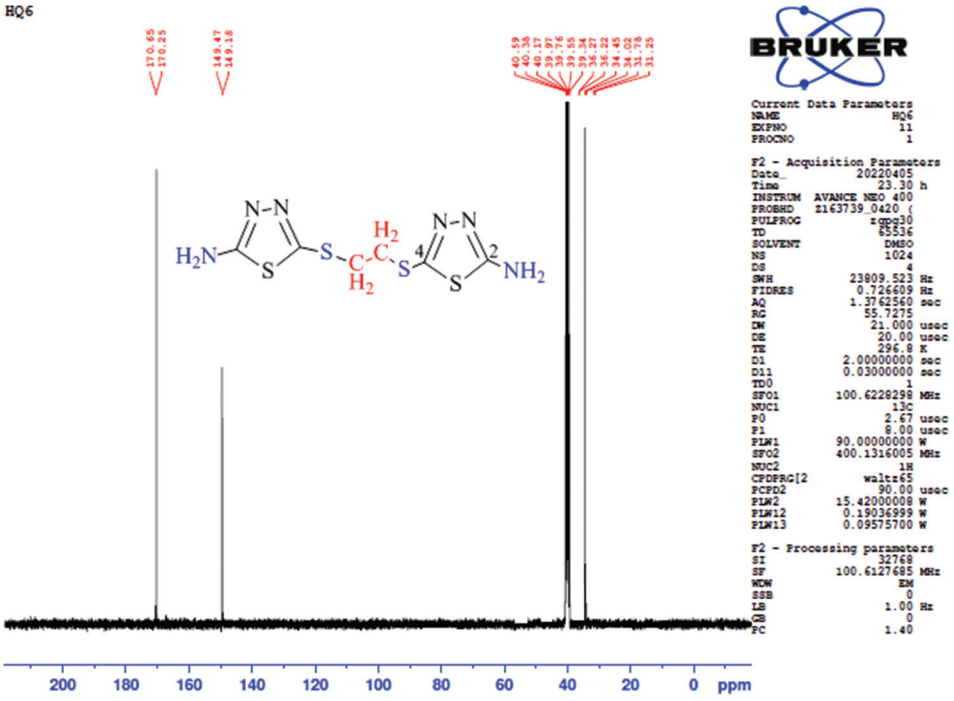
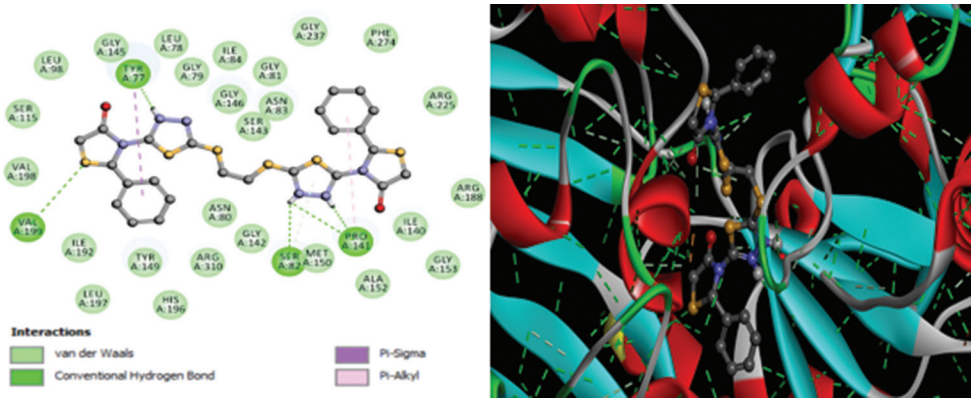
APPENDIX



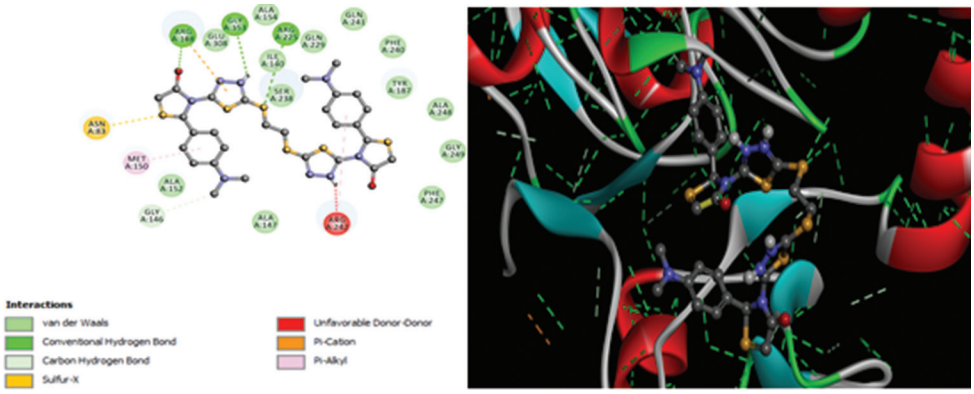
Appendix Fig. 1. Proton nuclear magnetic resonance spectrum of (3).



Appendix Fig. 2. Carbon-13 nuclear magnetic resonance spectrum of (3).



Appendix Fig. 3. Two-dimensional (right) and three-dimension (left) interaction plot compound (**6c**) docked into the bacterial binding proteins active site.



Appendix Fig. 4. Two-dimensional (right) and three-dimensional (left) interaction plot compound (**6a**) docked into the bacterial binding proteins active site.