SYNTHESIS AND CHARACTERIZATION OF SOME HYDRAZONE AND THIAZOLIDINE DERIVATIVES AND EVALUATION OF THEIR ANTIBACTERIAL ACTIVITY

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Abstract: *In this study, hydrazone and thiazolidine derivatives were synthesized. The hydrazone derivatives (F2–F6) were prepared from 3-bromomethylbenzohydrazide, followed by their reaction with thioglycolic acid to form thiazolidine derivatives (F7–F11). The structures of the synthesized compounds were confirmed through physical changes, such as variations in melting point and color, in addition to spectroscopic analyses, including FT-IR, ^{1}H-NMR, and ^{13}C-NMR. The antibacterial activity of the synthesized compounds was evaluated against two types of bacteria: Escherichia coli and Staphylococcus aureus. The compounds showed varying activity levels ranging from good to excellent.*
Keywords: *Heterocyclic, Hydrazone, Thiazolidine, Biological activity*

1. Introduction

Heterocyclic compounds are cyclic structures containing at least one heteroatom, such as nitrogen, oxygen, or sulfur [1, 2]. Other heterocycles may also contain additional atoms like phosphorus, iron, magnesium, and selenium [3, 4]. These rings represent a vital branch of traditional organic chemistry and are the focus of growing research interest due to their medical [5], antimicrobial [6], and industrial applications [7]. Heterocyclic rings play key roles in many natural biomolecules, including DNA, RNA, chlorophyll, hemoglobin, and vitamins [8-10]. Hydrazones and their derivatives have gained significant attention in recent years due to their biological activities. They have been widely used in pharmaceuticals and medicine and have shown antifungal [11], antimicrobial [12], anti-tubercular [13], anti-leukemic [14], anti-Alzheimer's [15], anti-cancer [16], anti-inflammatory [17], antiviral [18], and antibacterial properties [19, 20]. Saturated five-membered heterocyclic organic compounds with an amino group at position three and a thioether group at position one are known as thiazolidines. They are oxazolidine analogues of sulfur. Usually, a thiol and an aldehyde or ketone undergo a condensation reaction to create thiazolidines. Many thiazolidines are unstable in aqueous solutions because of hydrolysis, and this process is reversible, reverting to their original thiol and aldehyde components [21]. Many studies have highlighted the wide range of potential applications for thiazolidines, especially in the medical field, including antimicrobial [22], antibacterial [23], antifungal [24, 25], anticancer [26], anticonvulsant [27], antidiabetic [28], anti-inflammatory [29], and antioxidant uses [30].

2. Experimental part

Materials. All of the compounds used in the studies were bought from Sigma-Aldrich, BHD, and Fluka.

Devices and methods. An automatic melting point device (SMP40) was used to measure melting points. Using KBr pellets, infrared (IR) spectra were acquired in the 400–6000 cm^{-1} range using a Shimadzu FT-IR-600 Fourier-transform infrared spectrophotometer. A JEOL spectrometer was used to record nuclear magnetic resonance (^{1}H-NMR) and ^{1}C-NMR spectra in DMSO-d_6 at 500 MHz and 125 MHz, respectively. Thin-layer chromatography (TLC) using silica gel plates was used to track the reaction's progress, and bromine was used to view it.

Synthesis Procedures

a. Synthesis of 3-Bromo Methyl Benzohydrazide (F1). A mixture of methyl 3-bromo benzoate (0.004 mol, 0.916 g) and 80% aqueous hydrazine (0.09 mol) was refluxed in a round-bottom flask for 8 hours. Afterward, the mixture was concentrated, filtered, and dried to obtain a yellow liquid product with a yield of 80% [31]. The molecular formula of the compound is $C_8H_9BrN_2O$, and the molecular weight is 227.08 g/mol.

b. Synthesis of Hydrazone Derivatives (F2–F6). Substituted benzaldehydes (0.001 mol) were dissolved in 20 mL of absolute ethanol. To this solution, 3-bromo methyl benzohydrazide (F1) (0.001 mol, 2.44 g) was incorporated, and five hours were spent refluxing the mixture. The completion of the reaction was observed by TLC [32]. Upon completion, the reaction mixture was cooled slowly and filtered, and the precipitate was collected and dried to a constant weight. Ethanol was used to recrystallize the crude product.

Physical properties of synthesized compounds are represented in Table 1.

Table 1. Some physical properties of synthesized compounds

Comp No.	R	Exact Formula	M.Wt g/mol	Color	M.P (^{0}C)	Yield (%)
F_2	4-Br	$C_{15}H_{12}Br_2N_2O$	396	Yellow	218-220	83
F_3	4-No_2	$C_{15}H_{12}BrN_3O_3$	362	Orang	122-124	85
F_4	4-Cl	$C_{15}H_{12}BrClN_2O$	351	Light yellow	192-194	79
F_5	4-$(CH_3)_2$	$C_{17}H_{18}BrN_3O$	360	Yellow	228-230	85
F_6	4-CH_3	$C_{16}H_{15}BrN_2O$	331	Light yellow	158-160	80

c. Synthesis of 4-Thiazolidine Derivatives (F7–F11). A solution of the synthesized hydrazones (F2–F6) (0.0005 mol) in tetrahydrofuran (THF) was mixed with thioglycolic acid (0.005 mol, 0.4 mL) and anhydrous zinc chloride ($ZnCl_2$, 0.002 g). The mixture was refluxed for 10 hours in a water bath at 60°C. Completion of the reaction was confirmed using thin-layer chromatography (TLC). The mixture was then neutralized with sodium bicarbonate ($NaHCO_3$), cooled, and the precipitate that resulted was filtered [33], recrystallized from dioxane after being cleaned with cold water. Measurable physical features of the synthesized 4-thiazolidinone derivatives are shown in Table 2.

Table 2. Some Physical Properties of 4-Thiazolidinone Derivatives (F7–F11)

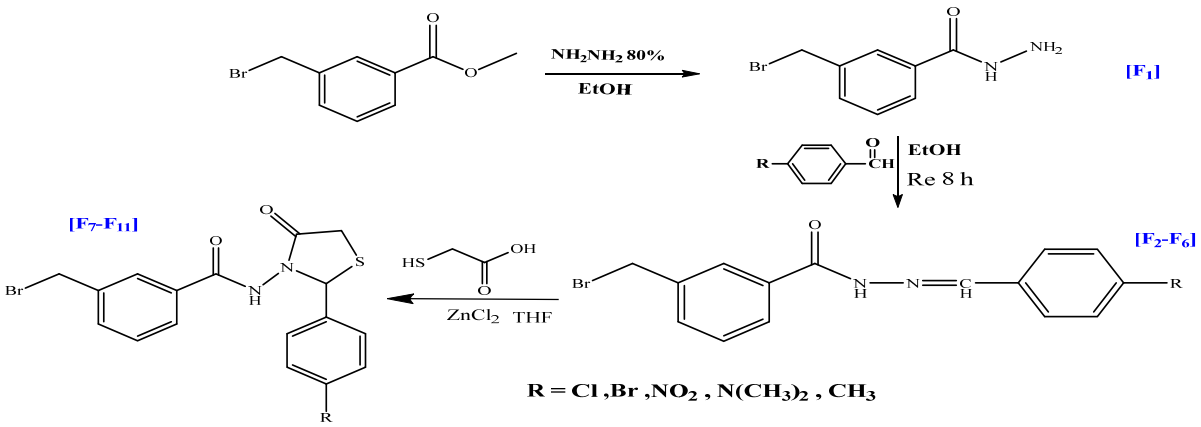
Comp No.	R	Molecular Formula	M.Wt g/mol	Color	M.P (^{0}C)	Yield (%)
F_7	Br	$C_{17}H_{14}Br_2N_2O_2S$	467	Light yellow	234-236	83
F_8	Cl	$C_{19}H_{20}BrN_3O_2S$	433	White	142-144	85
F_9	CH_3	$C_{17}H_{14}BrN_3O_4S$	434	Yellow	264-266	79
F_{10}	NO_2	$C_{17}H_{14}BrClN_2O_2S$	423	Orang	153-155	85
F_{11}	$N(CH_3)_2$	$C_{18}H_{17}BrN_2O_2S$	404	Light yellow	196-198	80

Evaluation of Antibacterial Activity. After being autoclave sterilized, the culture medium was transferred into Petri plates. Using sterile physiological saline as a diluent, a bacterial inoculum was made for every bacterial strain independently, with a concentration of 1.5 x 10^8 bacterial cells per milliliter. On the McFarland standard scale, the suspension's turbidity was corrected to equal 0.5. The bacterial inoculum was evenly distributed across the Mueller Hinton agar surface using a sterilized cotton swab. The test solutions were then introduced by boring wells into the agar. For twenty-four hours, the plates were incubated at 37°C in a lab incubator. Following incubation, the

antibacterial activity was evaluated by looking for inhibitory zones surrounding the test compound-containing wells [34].

3. Results and Discussion

General scheme of the synthesized compounds is below:



3.1 Characterization of 3-Bromo Methyl Benzohydrazide [F1]. The infrared profile of the compound F1 displayed signature absorption bands at 3292 and 3329 cm^{-1} corresponding to the stretching vibrations of the –NH_2 group and at 3181 cm^{-1} caused by the –NH stretching. The aromatic C–H stretching appeared at 3045 cm^{-1}, while the carbonyl (C=O) stretch was observed at 1654 cm^{-1}. Additionally, bands were seen at 1583 and 1481 cm^{-1}, corresponding to C=C aromatic stretching, and at 2941 and 2995 cm^{-1}, corresponding to aliphatic C–H stretches [35] (see Fig. 1).

The ^{1}H-NMR spectrum of compound F1 demonstrated a monoplet at δ 8.79 ppm caused by the proton of the –NH group, multiplets in the range δ 7.22–7.68 ppm for aromatic protons, a monoplet at δ 4.33 ppm corresponding to the CH_2 family, a monoplet at δ 4.20 ppm for the –NH_2 family, and a monoplet at δ 2.52 ppm for the residual DMSO-d_6 solvent (see Fig. 2).

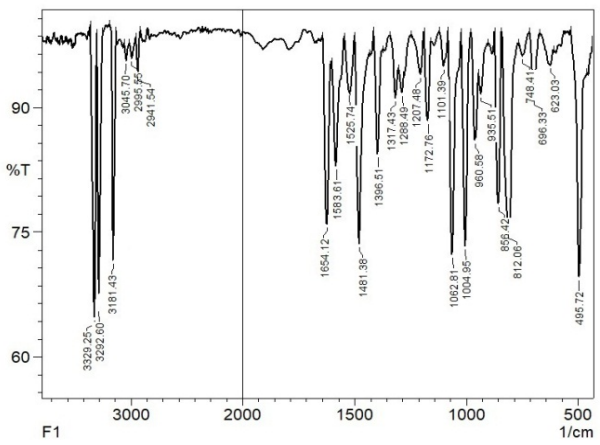


Fig. 1. Infrared (IR) spectrum of compound (F1)

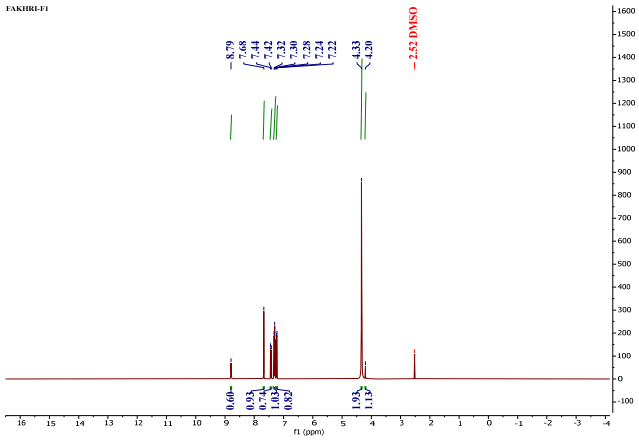


Fig. 2. ^{1}H-NMR spectrum of compound F1

The ^{13}C-NMR spectrum revealed a monoplet at δ 169.56 ppm corresponding to the carbon of the carbonyl group (C=O), multiple signals between δ 123.66 and 149.71 ppm for the aromaticity carbons, a singlet at δ 29.05 ppm for the CH_2 carbon, and solvent signals in the range of δ 39.49–40.47 ppm for DMSO-d_6 (see Fig. 3).

3.2 Characterization of Hydrazone Derivatives [F2–F6]. The IR spectra of the synthesized hydrazone derivatives [F2–F6] showed characteristic bands in the range of 1593–1608 cm^{-1} corresponding to the C=N stretching vibrations. Carbonyl (C=O) stretching bands were observed

between 1647 and 1656 cm^{-1}. Aromatic C–H stretching appeared within 3037–3066 cm^{-1}, while aliphatic C–H stretches were found between 2814–2941 cm^{-1} and 2922–2993 cm^{-1}. NH stretching bands appeared in the range of 3307–3423 cm^{-1}. Additionally, aromatic C=C stretching bands were noted between 1519–1577 cm^{-1} and 1449–1491 cm^{-1} [36] (see Fig.s 4 and 5).

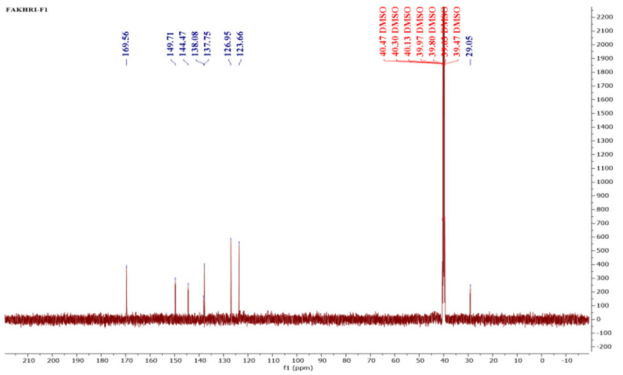


Fig. 3. ^{13}C-NMR spectrum of compound F1

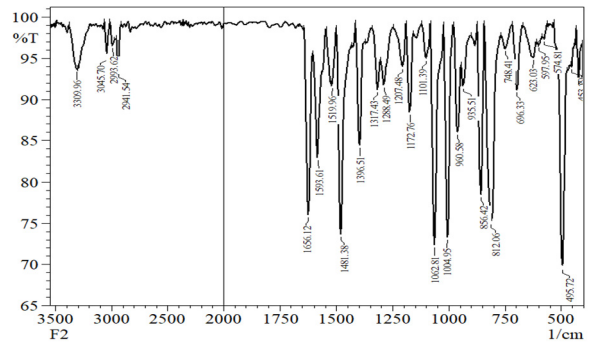


Fig. 4. Infrared (IR) spectrum of compound (F2)

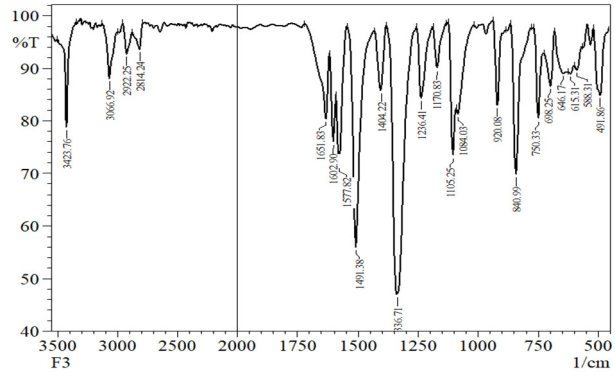


Fig. 5. Infrared (IR) spectrum of compound (F3)

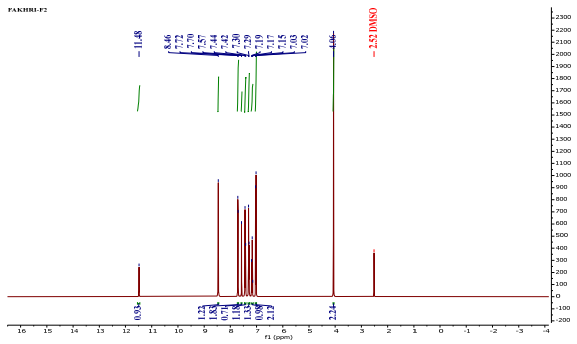


Fig. 6. ^{1}H-NMR spectrum of compound F_2

Table 3. FT-IR Absorption Bands (cm^{-1}) of Hydrazone Derivatives (F2–F6)

Comp. No.	R	IR (KBr) cm^{-1}						
		ν(N-H)	ν (C-H) Arom.	ν (C-H) Aliph.	νC=O	νC=N	ν C=C) Arom.	Others
F2	Br	3309	3045	2941 2993	1656	1593	1519 1481	νC-Br 696
F3	Cl	3423	3066	2814 2922	1651	1602	1577 1491	νC-Cl 750
F4	CH_3	3319	3037	2877 2987	1651	1604	1562 1449	---
F5	NO_2	3307	3044	2865 2984	1653	1608	1542 1479	ν (NO_2). *asy*.(1326) *sym*.(1273)
F6	$N(CH_3)_2$	3326	3065	2835 2949	1647	1603	1545 1459	---

The proton NMR spectrum F2 revealed a singlet at δ 11.48 ppm assigned to the proton of the –NH group and another singlet at δ 8.46 ppm corresponding to the –CH proton. Multiple monoplets in the range of δ 7.45–7.93 ppm were attributed to aromatic protons. A monoplet at δ 4.65 ppm was

observed for the methylene (–CH_2) group, while the DMSO-d_6 solvent proton showed up as a monoplet at δ 2.52 ppm (see Fig.s 6 and 7).

The ^{13}C-NMR spectrum exhibited a signal at δ 163.2 ppm in line with the carbonyl carbon (C=O) and a signal at δ 146.8 ppm for the imine carbon (C=N). Multiple signals in the range δ 125.4–138.1 ppm were assigned to aromatic carbons. The methylene (CH_2) carbon appeared as a singlet at δ 33.3 ppm, and DMSO-d_6 solvent carbons gave signals between δ 40.02 and 41.1 ppm (see Fig.s 8 and 9).

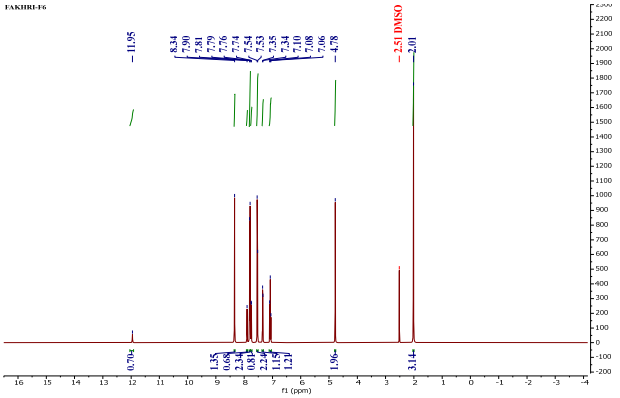


Fig. 7. ^{1}H-NMR spectrum of compound F3

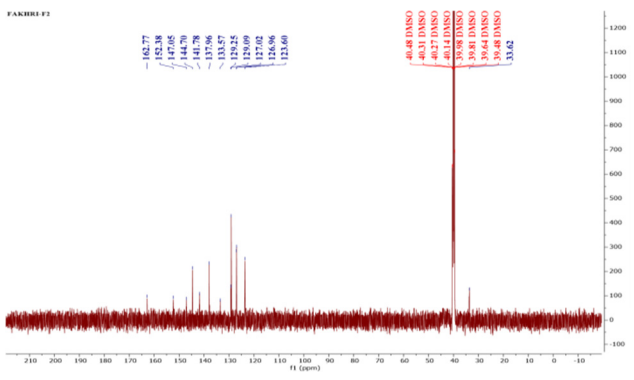


Fig. 8. ^{13}C-NMR spectrum of compound F2

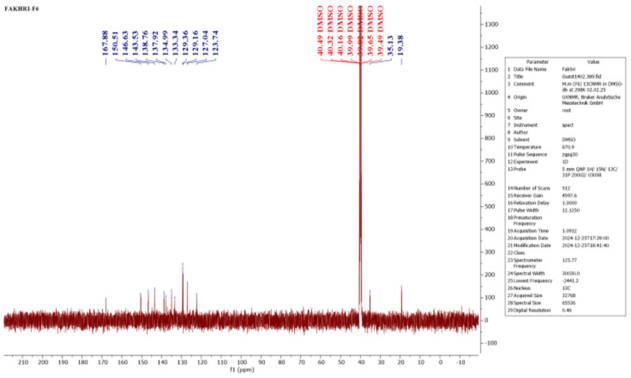


Fig. 9. ^{13}C-NMR spectrum of compound F3

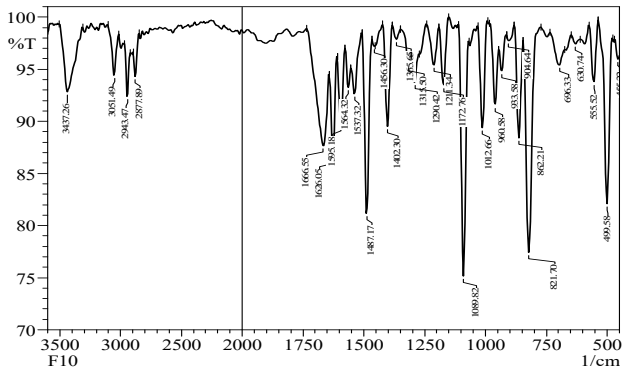


Fig. 10. Infrared (IR) spectrum of compound (F_7)

3.4 Characterization of 4-Thiazolidinone Derivatives [F7–F11]. The infrared profile of the synthesized thiazolidinone compound [F7–F11] substitutes exhibited the disappearance of the C=N stretching band present in the hydrazones [F2–F6]. Two new strong absorption bands appeared in the ranges 1678–1659 cm^{-1} and 1632–1626 cm^{-1}, corresponding to the carbonyl (C=O) stretching within the thiazolidine ring and outside the ring, respectively. A medium-intensity band was observed in the range 3437–3392 cm^{-1} attributed to N–H stretching. Bands in the range 875–847 cm^{-1} were assigned to C–S vibrations. Aromatic C–H stretching bands appeared in the range 3060–3043 cm^{-1}, and symmetric and asymmetric aliphatic C–H stretching bands were observed at 2835–2877 cm^{-1} and 2920–2960 cm^{-1}, respectively. Additionally, aromatic C=C stretching bands were observed in the ranges 1595–1558 cm^{-1} and 1487–1473 cm^{-1} [37] (see Fig.s 10 and 11).

Table 4. FT-IR absorption bands (cm^{-1}) of 4-thiazolidinone derivatives (F7–F11)

Comp. No.	R	IR (KBr) cm^{-1}						
		νN-H	νC-H Arom.	νC-H Aliph.	νC=O	νC=C Arom.	νC-S	Others
F7	Br	3402	3048	2844 2960	1663 1628	1575 1477	851	νC-Br 626

F8	Cl	3392	3060	2848 2920	1672 1632	1570 1475	847	νC-Cl 735
F9	CH_3	3415	3046	2835 2949	1659 1627	1558 1474	875	---
F10	NO_2	3437	3051	2877 2943	1666 1626	1595 1487	862	ν (NO_2). *asy*.(1537) *sym*.(1315)
F11	$N(CH_3)_2$	3423	3043	2852 2935	1678 1627	1581 1473	856	-----

The ^{1}H-NMR spectra exhibited a singlet at δ 10.37 ppm attributed to the proton of the –NH group. Multiplet signals in the range of δ 7.25–7.81 ppm were assigned to aromatic protons. A singlet at δ 5.93 ppm was observed for the proton of the –CH group within the thiazolidine ring. Additionally, a singlet at δ 4.55 ppm corresponded to a methylene (–CH_2) group, and another singlet at δ 3.37 ppm was also attributed to –CH_2 protons in the thiazolidine ring. The solvent peak of DMSO-d_6 appeared as a singlet at δ 2.52 ppm (see Fig. 12).

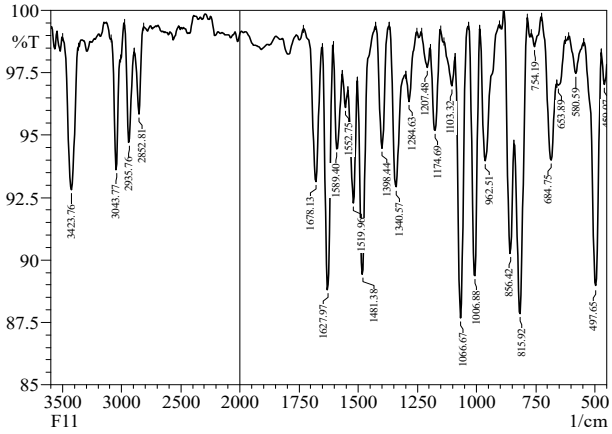


Fig. 11. Infrared (IR) spectrum of compound (F_{11})

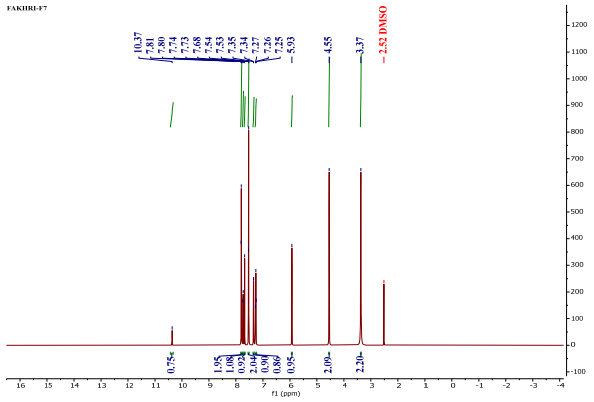


Fig. 12. ^{1}H-NMR spectrum of compound F7

The ^{13}C-NMR spectrum showed a signal at δ 169.92 ppm corresponding to the carbonyl carbon (C=O) within the thiazolidine ring and another signal at δ 163.19 ppm assigned to an external carbonyl group. Signals in the range δ 120.24–143.52 ppm were attributed to aromatic carbons. A singlet at δ 66.29 ppm was assigned to the CH carbon in the thiazolidine ring, while a singlet at δ 44.04 ppm corresponded to a methylene (CH_2) group in the same ring. Another singlet at δ 31.16 ppm was observed for an additional CH_2 group. The DMSO-d_6 solvent carbons appeared in the range of δ 39.45–40.46 ppm (see Fig. 13).

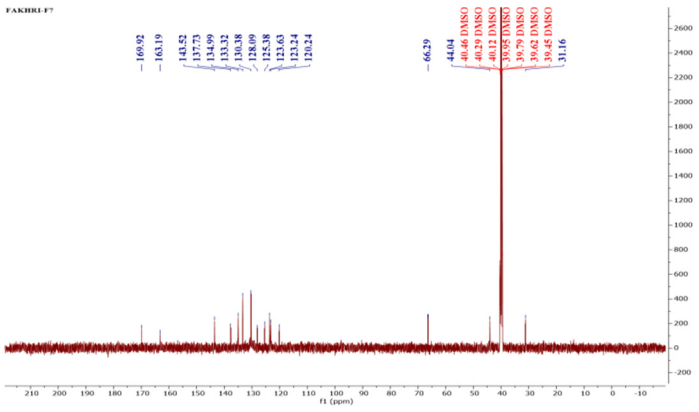


Fig. 13. ^{13}C-NMR spectrum of compound F7

3.5. Evaluation of Biological Activity. The biological activity of selected synthesized compounds (F1, F3, F4, F9, and F10) was evaluated against two bacterial strains: the Gram-positive *Staphylococcus aureus* and the Gram-negative *Escherichia coli* [38-42]. The antibacterial assay was performed using the agar well diffusion method. Petri dishes containing inoculated Mueller Hinton agar were incubated at 37°C for 24 hours. A volume of 0.8 mL of sterile saline was added to the bacterial cultures to prepare the inoculum [43-47]. The concentration of the test compounds dissolved in DMSO was maintained at 100 µg/mL. *Amoxicillin* was used as a positive control. Inhibition zones were measured in millimeters around the wells containing the test solutions [48-50], and the results are presented in Table 5 and illustrated in Fig. 14.

Table 5. The efficacy test, measured by the inhibition zone diameter, of the synthesized compounds against *Gram-positive* and *Gram-negative bacteria*

Materials		Inhibition zone (Biological activity) of materials against bacteria measured by millimeter (mm)					
		Escherichia coli			*Staphylococcus aureus*		
		100%	50%	25%	100%	50%	25%
1	F1	52	50	42	75	66	54
2	F3	37	20	16	50	40	33
3	F4	45	35	20	18	15	8
4	F9	55	12	5	6	3	0
5	F10	70	55	30	9	5	0

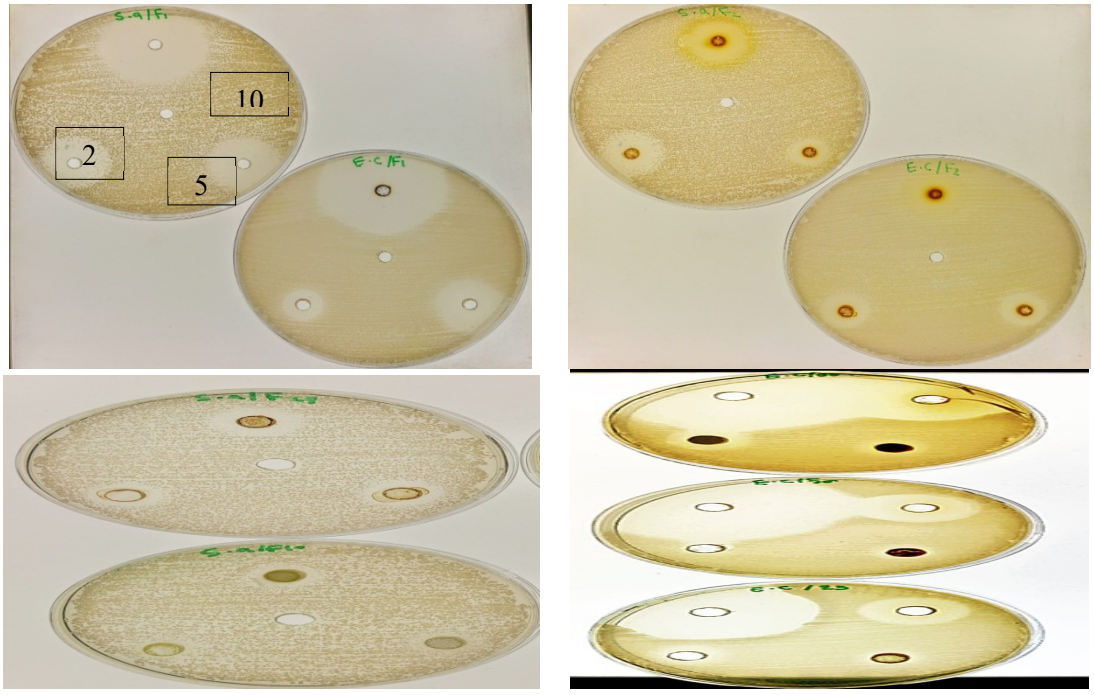


Fig. 14. Biological effect and sensitivity test of compounds against bacteria

4. Conclusion

The synthesized hydrazones and thiazolidine heterocycles exhibited notable antibacterial activity compared to the control substance, although some showed only weak inhibition. Spectroscopic measurements confirmed the successful synthesis of the compounds, as the IR, ^{1}H-NMR, and ^{13}C-NMR spectra indicated the presence of functional groups consistent with the proposed structures. Furthermore, some compounds demonstrated excellent inhibitory effects comparable to *amoxicillin*, suggesting their potential use as antibiotic agents.

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