Synthesis, Characterization and Antibacterial Evaluation of Novel Thiazolidine Derivatives

Shaima H. Abdullah [1*], Mahmoud M. Salih [1], Khalid, A. Al-Badrany [1]

Abstract

Background: Heterocyclic compounds, which incorporate atoms such as nitrogen and sulfur alongside carbon, play a crucial role in nature and organic chemistry. Thiazolidine derivatives, characterized by sulfur and nitrogen atoms with a carbonyl group at the -4 position, are particularly noteworthy for their stability and diverse biological activities. We synthesized novel thiazolidine derivatives and determined their antibacterial properties. the synthesis of novel thiazolidine compounds was perforemd using thioglycolic acid with hydrazides, generated from the combination of hydrazides with benzaldehyde. Methods: The esters, hydrazides, hydrazones, and thiazolidines, were synthesized and characterized using infrared spectroscopy, nuclear magnetic resonance, and melting point analysis. Assessment of anti-bacterial activity was carried out against Gram-positive and Gram-negative bacterial strain of Staphylococcus aureus, Acinetobacter baumannii, Aeromonas sobria, and Escherichia coli. . Results: We synthesized ethyl 2-acetate (benzo[d]thiazol-2-yloxy), followed by the formation of 2-(benzo[d]thiazol-2-yloxy)acetohydrazide (hydrazide) through the reaction of this acetate with hydrazine. 16 compounds were synthesized with rigorous validation at each stage through spectral analysis. Thiazolidine derivatives exhibited promising inhibitory effects against bacterial growth, indicating their potential as antibacterial agents.Compound SH8 exhibited moderate to strong inhibitory effects against all tested species, notably Aeromonas sobria and Staphylococcus aureus, at a concentration of 0.1 mg/ml. Conclusion: In conclusion, the synthesized compounds exhibited both structural integrity and potent antibacterial activity, suggesting avenues for further exploration in pharmaceutical research.

Keywords: Heterocyclic compounds, Thiazolidine derivatives, Antibacterial properties, Synthesis methods, Biological activity assessment

Significance | Thiazolidine derivatives, synthesized from heterocyclic compounds, exhibit diverse biological activities, including antibacterial effects against various bacterial strains, suggesting potential pharmaceutical applications.

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Introduction

Heterocyclic compounds are those that, in addition to carbon atoms, also include atoms of nitrogen, oxygen, phosphorus, sulfur, etc., in their composition (Sarvary & Maleki, 2015; Shaabani et al., 2011). Heterocyclic compounds are essential because, due to their extensive dispersion in nature, they are commonly found in sugars and their derivatives and are involved in synthesizing numerous organic chemicals essential to life's fundamental structure (Maleki & Sarvary, 2015). One of these compounds is thiazolidine derivatives, which are heterocyclic compounds that contain sulfur and nitrogen, and when they contain a carbonyl group at the -4 position, they are called thiazolidine-4-one. These systems appear more stable than thiophene, which is stable towards acid at moderate temperatures (Abhinit et al., 2009). It is often prepared by reacting Schiff bases or hydrazones with thioglycolic acid using

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dioxane as a solvent (Amin et al., 2023).

Thiazolidinedione compounds are biologically active. It is essential because it contains a sulfur atom and a nitrogen atom. A series of anti-diabetic agents for type 2 diabetes have been developed (Singh et al., 2024) and have mainly been studied at the blood sugar level and the extent to which the cell genetically reduces its activities in resisting obesity. This means that cells sometimes become resistant to insulin, as the latest breakthrough in anti-diabetic treatment by increasing insulin secretion. Therefore, it is also called "insulin sensitizer" (Bansal et al., 2020), and it has shown effectiveness as an antioxidant (Nasir et al., 2023), against malaria (Tuszewska et al., 2023), against infections (Ahmed et al., 2023), against fungi (Srivastava et al., 2023), and against viral immunodeficiency (Sriharsha et al., 2023), against bacteria (Sena et al., 2022), viruses (Ibrahim et al., 2023), tuberculosis (Chintakunta & Subbareddy, 2022), pain receptors and hypersensitivity (Benvenutti et al., 2023), and it also has good effectiveness as an anti-cancer (Paneth et al., 2023). Peptide and protein (Bi et al., 2017), chemotactic protein synthesis (Katayama & Morisue, 2017), enhancers of innate immunity (Oh et al., 2018), and anti-hyperglycemic agents (Hamdi et al., 2023). Moreover, heterocyclic compounds play a crucial role in organic chemistry. Reactions of hydrazones with thioglycolic acid always give rise to thiazolidine-derived heterocyclic compounds. This work aims to prepare new heterocyclic compounds and evaluate their antibacterial activity.

2 .Materials and Methods

2.1 .Material

All the chemicals used in this experiment were purchased from BDH Companies and Fluka.

2.2 .Tools Utilized

Melting points were measured with an uncorrected measuring instrument (Automatic melting point: SMP40). Iodine was used to improve the spots in sheet polygram silica gel as the stationary phase in thin layer chromatography (TLC). Using the KBr disk, infrared spectra on a scale of 400-4000 cm^{-1} were produced using the Fourier-Transform Infrared Spectrophotometer FT-IR-600. A Bruker 500 MHz MS5973 Agilent Technology was used to study the nuclear magnetic resonance (1H, 13C-NMR) spectra of substances produced at Sannati Sharif University in Iran. DMSO-d6 was used as a solvent.

2.3 .Preparation of Ester

Equal moles of ester and phenol were mixed, then four times the moles of potassium carbonate were added. The mixture was left stirring for 7 hours, then recrystallized from ethanol with a yield of 91% and a melting point of 130°C (Apostol et al., 2023).

2.4 .Preparation of Hydrazide (SH2)

Dissolve 0.087 ml of the ester in 20 ml of ethanol, add 3 ml of hydrazine in drops, and leave it stirring for 4 hours. The product recrystallized from the ethanol and gave a yield of 71% and a melting point of 215°C (Sadeek et al., 2023).

2.5 .Preparation of Hydrazone (SH3-9)

Equal molar ratios of hydrazide were mixed with the aromatic benzaldehyde derivatives in 15 ml of ethanol. The mixture was left stirring for 3 hours and recrystallized from ethanol, as shown in Table 1 (Wen et al., 2023).

2.6 .Preparation of Thiazolidine (SH10-16)

An equimolar combination of sulfuric acid and a chemical (SH3-9) was added to 25 ml of 1,4-dioxane. The liquid was agitated for six hours at 80°C with a small addition of zinc chloride. It was then kept at room temperature for an entire day. The pulverized water was then covered with it. After being extracted from the ether (EtOH), the product was cleaned, dried, and recrystallized. Table 1 lists the physical characteristics of the substances that were produced (Mekhlef et al., 2023).

2.7 .An Assessment of Biological Activity

This study used two pathogenic bacteria types: Gram-positive (Acinetobacter et al. aureus) and Gram-negative (Escherichia et al.). These bacteria were taken from the Department of Life Sciences lab at the College of Education for Pure Sciences and cultured on a Mueller Hinton Agar medium (Saleh & Al-Badrany, 2023). Chemical solutions of (SH8, SH11, SH12, and SH16) were produced at concentrations of 0.01, 0.001, and 0.0001 mg/ml using the solvent dimethyl sulfoxide (DMSO). In the process, the minimum inhibitory concentration (MIC) was calculated. Mueller-Hinton agar was employed as the nutritional medium for the diffusion technique to perform the sensitivity test for the bacteria isolates utilized in the study (Saleh & Khalid, 2023; Al-Joboury et al., 2022). After being prepared, the medium was autoclaved, divided across plates, and given time to solidify. Subsequently, four tiny holes were punched into each plate. After that, it was incubated for an entire day at 37°C. The data were read the following day to demonstrate that the employed derivatives' biological activity depends on the diameter of inhibition seen in the dishes around the holes. As the diameter increases, so does the substance's biological activity, comparable to the antibiotics' diameter of inhibition (Mohamed et al., 2022; Al-Hadidi et al., 2022).

Sixteen substances were synthesized for this study. The reaction of 2-hydroxybenzothiazole with ethyl chloroacetate in acetone formed ester derivatives (SH1). Ethanol and hydrazine were then used to generate hydrazide derivatives (SH2). The next stage involved producing hydrazone derivatives (SH3–SH9) by reacting hydrazide derivatives with benzaldehyde derivatives. Thioglycolic acid interacted with hydrazone derivatives to produce seven thiazolidine derivatives (SH10–SH16), as illustrated in Scheme 1. These compounds were identified by 1313C-NMR, 11H-NMR, and FT-IR spectra.

3. Results and Discussion

The ester derivative SH1 was successfully characterized using IR and NMR spectroscopy. IR spectra showed characteristic absorption bands, and proton and carbon NMR spectra provided detailed signals, confirming the structure and successful synthesis of SH1.

3.1. Diagnosis of Ester (SH1)

Infrared spectra of the ester derivatives (SH1) revealed absorption bands related to bond stretching (C-H) in the 2900–2990 cm^{-1} range and (Ar–H) in the 3058–3076 cm^{-1} range. Additionally, absorption bands were observed between 1664 and 1674 cm^{-1} and 1600 and 1620 cm^{-1}, corresponding to bond stretching (C=O) and the benzothiazole ring's (C=N) bond, respectively. Bands of absorption also appeared in the 1413–1558 cm^{-1} range, consistent with aromatic bond dilation (C=C) (Al-Hadidi et al., 2022).

The proton's NMR spectra revealed a single signal at 5.09 ppm for the protons (CH_2), and three signals at various chemical shifts. Multiple signals were observed at 4.57–4.59 ppm for the protons of (CH_3), a quadruple signal at 4.91–4.93 ppm, and signals at 7.18–7.71 ppm associated with the protons of the aromatic ring (Figure 2).

The 1313C-NMR spectrum showed a signal at 44.01 and 55.77 ppm for the esterified carbon (CH_2, CH_3), a signal at 169.70 ppm for the carbonyl group (C=O), and a signal at 167.51 ppm for the isomethene group (C=N). A multiple signal for the aromatic ring was observed at 121.60–144.70 ppm (Figure 3).

3.2. Diagnosis of Hydrazide (SH2)

Infrared spectra of the hydrazide derivatives (SH2) showed absorption bands in the 2900–2990 cm^{-1} and 3186–3257 cm^{-1} regions, indicating stretch and (N-H) bonding. Absorption bands extending back to the 3058–3076 cm^{-1} range were seen in the (C-H) bond, suggesting stretching of the (C=N) bond of the benzothiazole ring. Absorption bands appeared in the 1600–1620 cm^{-1} region for the (C=O) bond, and in the 3300–3400 cm^{-1} region for the (Ar–H) bond. Bands in the 1413–1558 cm^{-1} range indicated aromatic (C=C) bond stretching (Bedair et al., 2023), as shown in Figure 4.

In the 11H-NMR spectrum, the proton of the NH_2 group was identified by a single signal at 4.37 ppm, the proton of the (N-H) group by a signal at 9.47 ppm, and the protons of the benzene ring by multiple signals at 7.18–7.68 ppm (Figure 5).

The 1313C-NMR spectrum showed a signal at 165.84 ppm for the amide carbonyl group (C=O), a multiple signal at 111.85–137.75 ppm for the isomethene carbon (C=N), and a signal at 169.56 ppm for the carbonate of the aromatic ring (Figure 6).

3.3. Diagnosis of Hydrazone (SH3-9)

Infrared spectra of the hydrazone derivatives (SH3–SH9) revealed absorption bands in the ranges 3186–3257 cm^{-1}, 2900–2990 cm^{-1}, and 3058–3076 cm^{-1} for (N-H) and (C-H) bonding. Absorption bands in the 1664–1674 cm^{-1} range suggested (C=O) bond stretching, while bands in the 1600–1620 cm^{-1} range indicated (C=N) stretching. Absorption bands at 1223–1267 cm^{-1} were associated with (C-N) extension, and bands at 1413–1558 cm^{-1} with aromatic (C=C) bond stretching (Bedair et al., 2023).

The 11H-NMR spectrum showed a signal at 10.52 ppm for the amine group (N-H), a signal at 8.41 ppm for the isomethene group (N=CH), and multiple signals at 7.20–7.81 ppm for the protons of the aromatic ring (Figure 9).

The 1313C-NMR spectrum showed a signal at 137.90 ppm for the isomethene hydrazone carbon, a signal at 169.71 ppm for the benzothiazole isomethene, a signal at 167.88 ppm for the amide carbonyl group, and a multiple signal at 112.06–143.52 ppm for the aromatic ring's carbons (Figure 10).

3.4. Diagnosis of Thiazolidine (SH10-16)

Infrared spectra of the thiazolidine derivatives (SH10-SH16) showed absorption bands in the ranges 3182–3241 cm^{-1} for (N-H) bonding, 3057–3101 cm^{-1} for (Ar-H) bonding, and 2834–2977 cm^{-1} for (C-H) bond stretching. Absorption bands formed in the 1684–1701 cm^{-1} range for (C=N) and (C=O) amide bonds' stretching. Bands were also observed in the 1623–1644 cm^{-1} and 1660–1678 cm^{-1} ranges, associated with the stretching of the aromatic (C=C) bond (Lone et al., 2023).

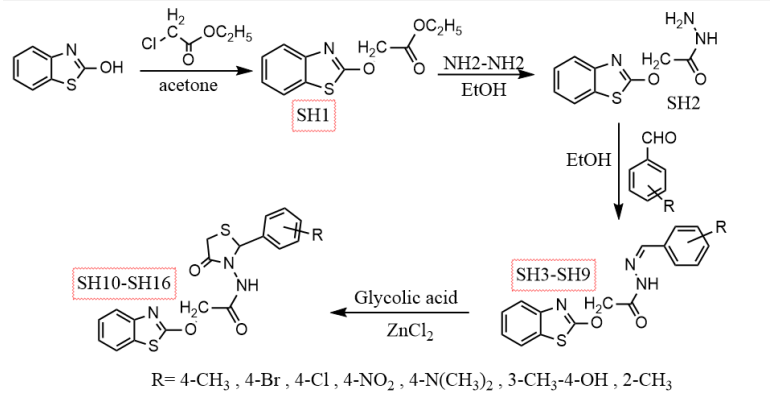
Absorption bands started to form between 1531–1592 cm^{-1} and 1436–1493 cm^{-1}, as seen in Tables 3 and Figures 11 and 12.

When examining the 11H-NMR spectrum, two signals were detected at 3.64 ppm and 5.57 ppm, respectively, representing the protons (CH_2) of the thiazolidine ring. The protons (NH) were represented by a signal at 10.80 ppm, -OCH_2 was represented by a signal at 4.02 ppm, and the protons of the aromatic compound were reflected by several signals at 7.20–7.65 ppm. Rings (Ar-CH) were shown as a compound (SH12,13) in Figures 13 and 15.

The thiazolidine ring's carbon (CH_2) group was identified as the signal source at 34.09 ppm in the compound's 1313C-NMR spectrum. The ring's (CH-N) group was identified as the source of a signal at 68.12 ppm, and the carbonyl group of the same ring was identified as the source at 165.85 ppm. Many signals associated with the aromatic ring were found at positions 121.58–162.77 ppm, as shown in Figures 14 and 16.

3.3 Evaluation of Biological Activity

Gram-positive bacteria: The gram-negative and *Streptococcus faecalis* bacterial strains (SH8, SH11, SH12, SH16) were used in the tests of the generated compounds. The Agar Diffusion Method on a Cup Plate was employed, utilizing *Proteus* bacteria (Doddagaddavalli et al., 2023). After eight hours of incubation at 37°C, 0.8% sterile saline was added to the microbial cultures (Al-Joboury et al., 2022). The concentration of the drug solution in DMSO was maintained at 100 µg/mL, with amoxicillin used as a



Scheme 1. SH1–SH16 compound pathway prepared

Table 1. The produced chemicals' physical attributes (SH1–SH16)

Color	Yield%	m.p. °C	Molecular formula	R	Comp. No.
White	97	265-267	C17H18N3SO3	Green	SH3
pearly white	97	190-192	$C_{16}H_{12}N_3SO_2Br$	4-Br	SH4
White	86	261-263	$C_{16}H_{12}N_3SO_2Cl$	4-Cl	SH5
Yellow	71	297-298	$C_{16}H_{12}N_4SO_4$	4-NO2	SH6
Yellow	76	244	$C_{18}H_{18}N_4SO_4$	4-N$(CH_3)_2$	SH_7
Gray	78	289	$C_{17}H_{15}N_3SO_4$	2-OCH_3 4-OH	SH_8
Orange	67	182-184	$C_{17}H_{15}N_3SO_2$	2-CH_3	SH_9
White	64	216-218	$C_{19}H_{17}N_3S_2O_4$	4-OCH3	SH10
White	51	241-243	$C_{18}H_{14}N_3S_2O_3Br$	4-Br	SH11
White	57	252-254	$C_{18}H_{14}N_3S_2O_3Cl$	4-Cl	SH12
White	41	224-226	$C_{18}H_{14}N_3S_2O_5N$	4-NO2	SH13
Green	45	210-212	$C_{20}H_{20}N_4S_2O_3$	4-N$(CH_3)_2$	SH14
Yellow	63	276-278	$C_{19}H_{17}N_3S_2O_5$	2-OCH_3 4-OH	SH15
White	43	264-266	$C_{19}H_{17}N_3S_2O_4$	2-CH_3	SH16

Table 2. FT-IR measurements (cm-1, SH3–SH16) for produced chemicals

Others	ν C–H Arom.	ν C=N	ν C=O	ν C–H Aliph.	ν C–H Arom.	νN-H	R	Comp. No.
ν(C-O) 1272	1521 1473	1666 1622	1695	2964	3095	3188	4-OCH_3	SH3
ν(C–Br) 623	1596 1472	1651 1621	1682	2940	2066	3265	4-Br	SH4
(C–Cl) 744	1591 1475	1658 1627	1687	2950	2056	3313	4-Cl	SH5
ν(C–NO_2) 1272,1363	1582 1473	1652 1623	1688	2979	3095	3216	4-NO_2	SH6
---	1586 1461	1656 1621	1678	2923	3104	3225	4-N$(CH_3)_2$	SH_7
ν (C–OH) 3493	1574 1443	1640 1610	1676	2946	3089	3196	2-OCH_3 4-OH	SH_8
---	1586 1479	1636 1619	1669	2928	2056	3189	2-CH_3	SH_9
ν(C-O) 1282	1589 1469	1635	1691 1664	2842	3072	3182	4-OCH_3	SH10
ν(C–Br) 648	1592 1471	1640	1692 1662	2834	3069	3184	4-Br	SH11
ν(C–Cl) 817	1563 1436	1628	1701 1678	2958	3064	3241	4-Cl	SH12
ν(C–NO_2) 1327,1386	1536 1466	1634	1692 1664	2973	3103	3183	4-NO_2	SH13
---	1531 1473	1641	1691 1662	2977	3101	3184	4-N$(CH_3)_2$	SH14
ν (C–OH) 3448	1589 1493	1632	1684 1661	2943	3057	3186	2-OCH_3 4-OH	SH15
---	1587 1486	1623	1687 1660	2927	3064	3184	2-CH_3	SH16

Table 3. Display some produced compounds' (SH8, SH11, SH12, and SH16) biological activities

or bacterial species / COMP.NO	Aeromonas sobria			Escherichia coli			Acinetobacter baumannii			Staphylococcus aureus		
	0.1	0.001	0.001	0.1	0.01	0.001	0.1	0.01	0.001	0.1	0.001	0.001
SH8	20	10	5	17	12	7	24	17	--	25	18	10
SH11	18	01	7	10	10	--	12	11	11	15	15	15
SH12	13	01	01	14	11	10	10	10	5	13	10	5
SH16	10	--	--	13	10	--	--	--	--	20	15	6
Amoxicillin	23	15	11	23	16	16	26	18	13	19	19	16

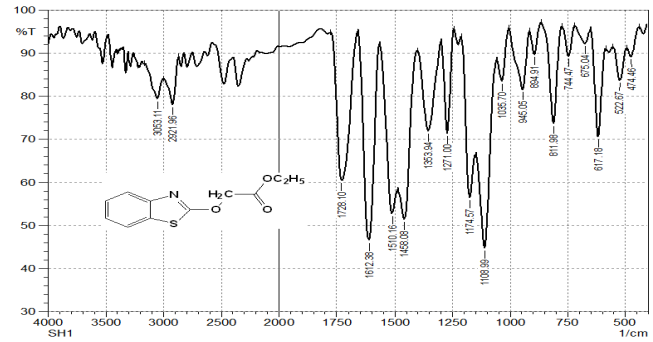


Figure 1. Infrared spectra of the chemical (SH1)

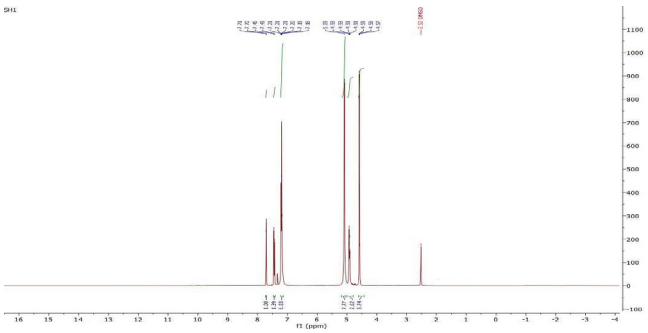


Figure 2. Compound 1H-NMR spectra (SH1)

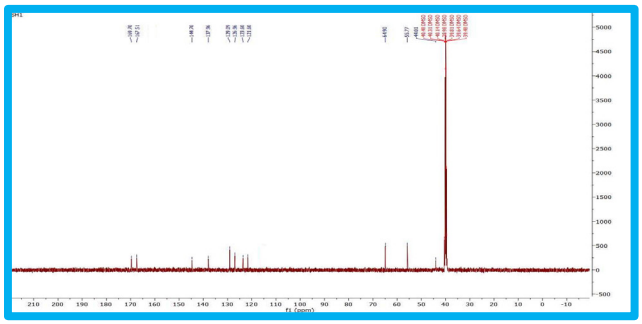


Figure 3. The compound's 13C-NMR spectra (SH1)

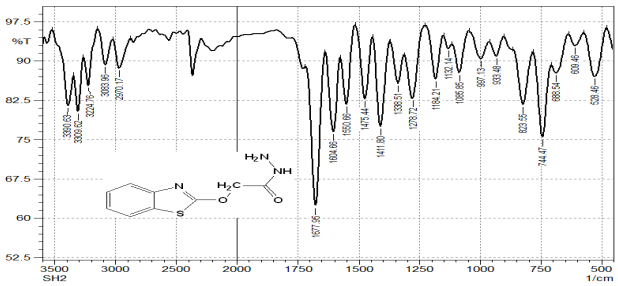


Figure 4. The compound's infrared spectrum (SH 2)

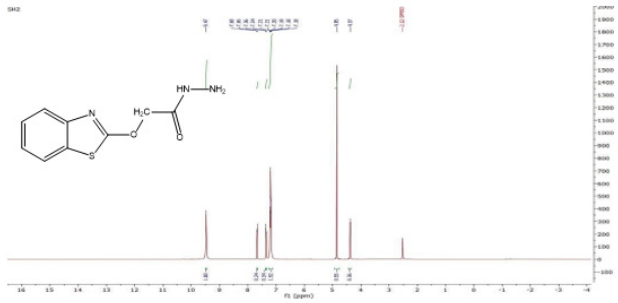


Figure 5. The material's 1H-NMR spectrum (SH 2)

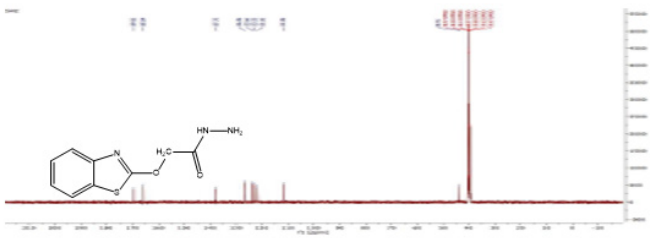


Figure 6. 13C-NMR (SH 2) chemical spectrum

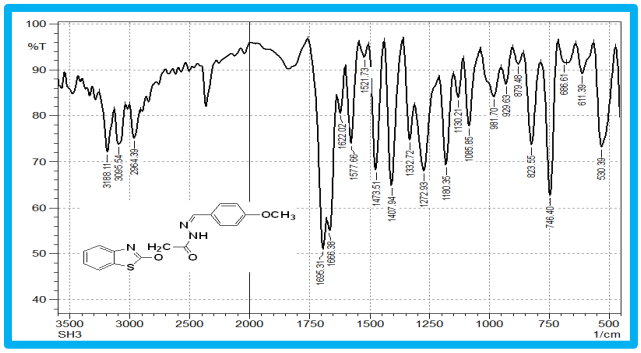


Figure 7. The infrared spectra of the molecule (SH 3)

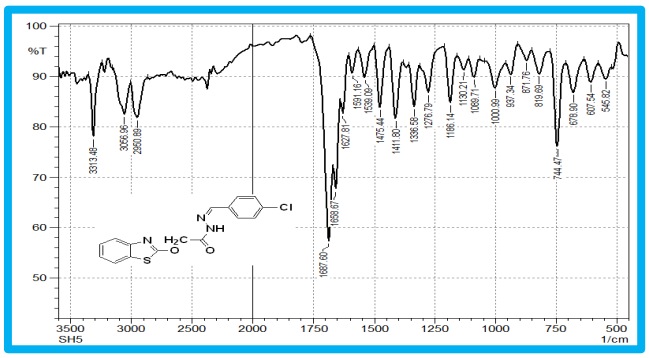


Figure 8. The infrared spectra of the molecule (SH5)

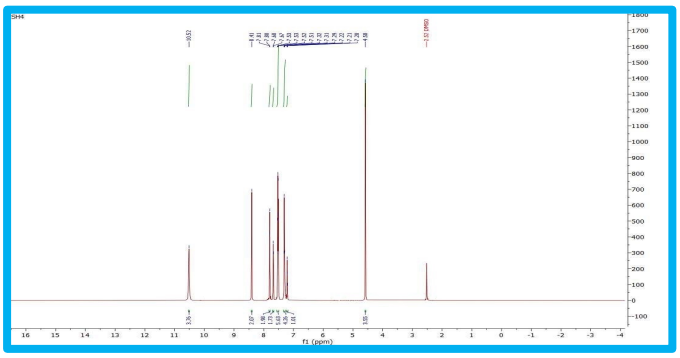


Figure 9. The 1H-NMR spectra of the substance (SH 4)

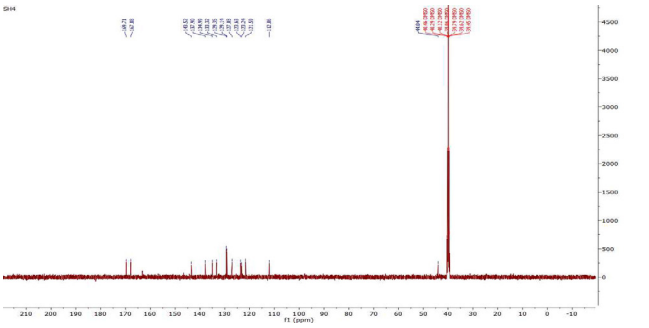


Figure 10. Chemical spectrum of 13C-NMR (SH 4)

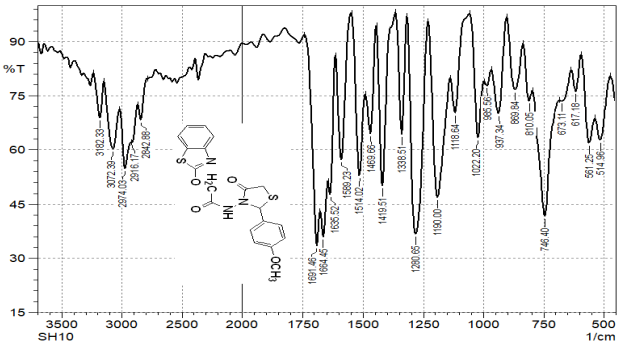


Figure 11. The infrared spectra of the molecule (SH 10)

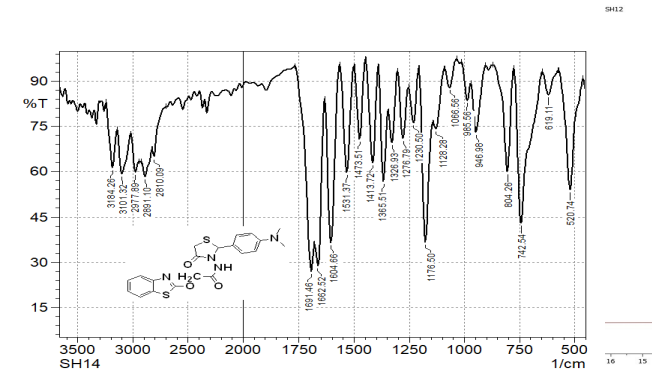


Figure 12. Infrared spectra of the chemical (SH 14)

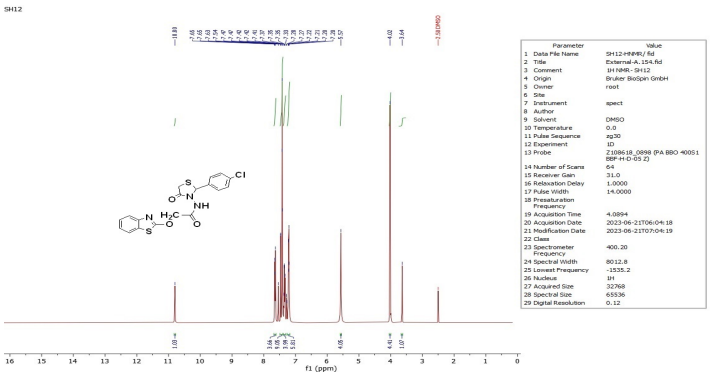


Figure 13. The 1H-NMR spectra of the substance (SH 12)

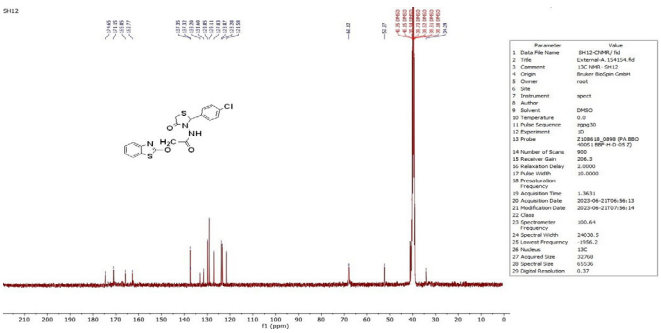


Figure 14. 13C-NMR spectral analysis (SH 12)

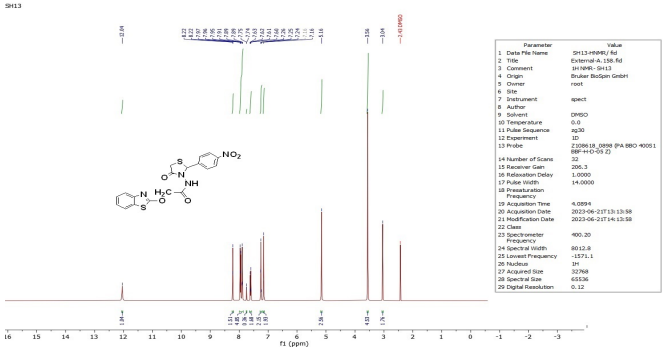


Figure 15. The 1H-NMR spectra of the substance (SH 13)

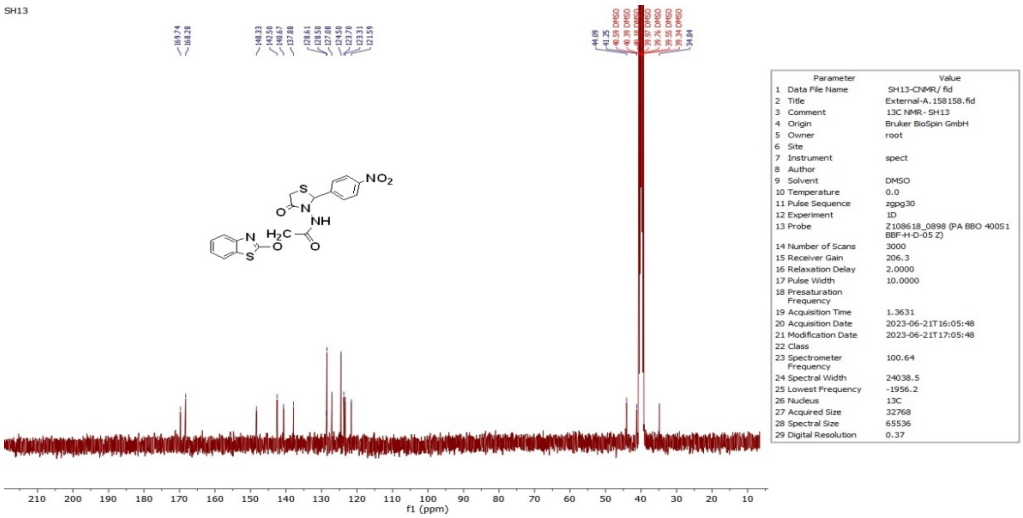


Figure 16. 13C-NMR spectral analysis (SH 13)

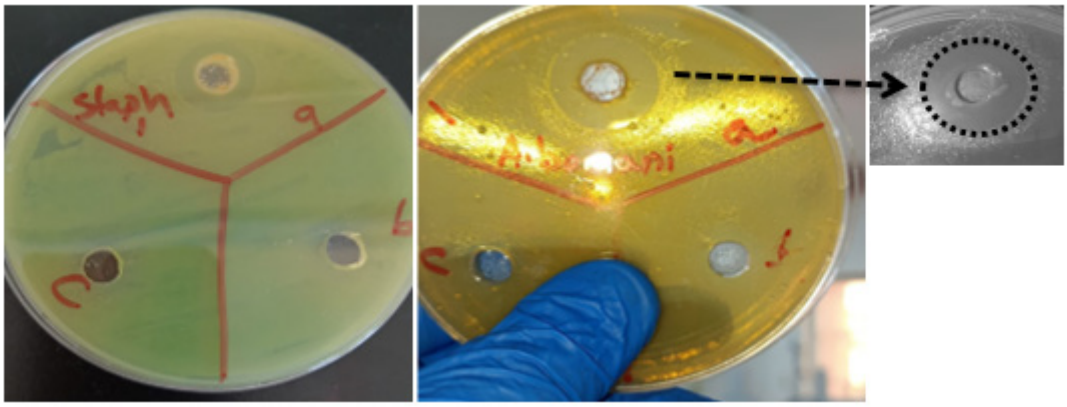


Figure 17.Inhibition zone formed due to activity of solutions.

negative control. Biological activity was determined by measuring the inhibition width of bacterial growth surrounding the in-use disk, as shown in Table 3 (Khalid et al., 2022; Al Rashidy et al., 2020).

The synthesized compounds displayed promising antibacterial properties across a range of bacterial strains. SH8 exhibited moderate to strong inhibitory effects against all tested species, notably *Aeromonas sobria* and *Staphylococcus aureus*, at a concentration of 0.1 mg/mL. SH11 demonstrated varying levels of antibacterial activity, with notable inhibition against *Aeromonas sobria* and *Acinetobacter baumannii* at 0.01 mg/mL. SH12 showed moderate activity against most species, particularly *Staphylococcus aureus* and *Acinetobacter baumannii* at 0.1 mg/mL. SH16 displayed moderate inhibition against *Escherichia coli* and *Staphylococcus aureus*, with slightly lower activity against other strains at concentrations ranging from 0.001 to 0.01 mg/mL. Overall, the synthesized compounds exhibited promising antibacterial properties, some of which were comparable or even superior to the reference antibiotic, amoxicillin.

4. Conclusion

The synthesized heterocyclic compounds, including thiazolidine derivatives, demonstrated significant antibacterial activity against both Gram-positive and Gram-negative bacteria. Spectral and physical analyses validated the structures and stability of these compounds, confirming their legitimacy. Infrared and nuclear magnetic resonance spectroscopy accurately identified the presence of active functional groups, consistent with the expected chemical structures. These compounds maintained stability and did not degrade under laboratory conditions. The results indicated that the synthesized compounds exhibited strong inhibitory effects on bacterial growth, with some compounds performing comparably or even better than the reference antibiotic, amoxicillin, highlighting their potential as effective antibacterial agents.

Author contributions

S.H.A., M.M.S., K.A.A. developed the concept and the design of the study, analyzed the data, and wrote the draft of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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