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Synthesis, Characterization, and Biological Activity Evaluation of Thiazolidine-4-One Derivatives Derived From Schiff Bases

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Annotation: In this study, a series of novel derivatives of thiazolidin-4-one ring (H11–H15) were synthesized via the reaction of Schiff bases with thioglycolic acid in tetrahydrofuran (THF) medium. The structures of the synthesized compounds were confirmed using various spectroscopic techniques, including FT-IR, ^{1}H-NMR, ^{13}C-NMR, and UV-Vis. The obtained spectra revealed significant changes indicating the success of the reaction and the formation of the heterocyclic ring. The antibacterial activities of the synthesized compounds were evaluated against two clinically significant bacterial strains: Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative). The results showed that compound H14 exhibited the highest activity against E. coli, whereas compound H15 showed strong activity against S. aureus, in some cases surpassing the efficacy of the reference antibiotic amoxicillin. This selective activity highlights the potential of these compounds as promising future antibiotics in combating resistance to conventional antimicrobial agents.

Keywords: Schiff bases, thiazolidin-4-one, biological activity.

1. Introduction

Microbial infections remain among the leading causes of mortality worldwide. The shortage of effective antibiotics to treat infectious diseases, combined with the continuous emergence of

microbial resistance to previously used antimicrobial drugs, poses a major global challenge. Therefore, discovering new and effective antimicrobial agents may represent the most viable approach to overcoming this problem and ensuring effective treatment for infectious diseases [1].

In this context, considerable attention has been directed by researchers in synthetic and medicinal chemistry toward the synthesis of nitrogen-containing heterocyclic rings. Heterocyclic compounds play a significant role in pharmaceutical industries due to their wide-ranging applications. These compounds are of high value in various pharmaceutical applications [2].Among these, 3,1-thiazolidin-4-ones constitute a five-membered ring system containing two heteroatoms—sulfur and nitrogen—along with a carbonyl group located at positions 1, 3, and 4, respectively. This heterocyclic core, through its diverse derivatives, exhibits a wide array of biological and pharmacological properties [3]. Researchers continue to explore the potential of this scaffold for the synthesis and development of novel compounds [4].New derivatives can be synthesized by modifying the substituent groups attached to the methylene and nitrogen atoms. It is worth noting that the carbonyl group in thiazolidine-2,4-dione exhibits very low reactivity [5]. This compound is extensively used in the development of new antidiabetic agents and has significantly contributed to advancements in this field [6].Several researchers have conducted extensive studies on the synthesis, characterization, and biological evaluation of compounds incorporating dual thiazolidinone units. Efficient one-pot synthetic methods have been developed for the preparation of bis-thiazolidinones, which further expand the utility of thiazolidinone-based compounds in various scientific domains [7].Additionally, computational studies such as molecular docking and frontier molecular orbital analysis (HOMO and LUMO) have been employed in the design of new thiazolidin-4-one derivatives due to their remarkable biological importance. These designed compounds were subsequently synthesized and evaluated for their antimicrobial potential.

2. Experimental Section

2.1. Materials

All chemical reagents used in this study were purchased from Fluka, Aldrich, and BDH companies, and were of high analytical grade purity.

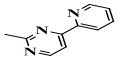
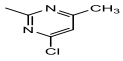
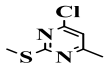
2.2. Instruments

Melting points were determined using an Electrothermal Melting Point Apparatus model 9300. FT-IR spectra were recorded on a Shimadzu FT-IR 8400S spectrophotometer using KBr pellets in the range of 400–4000 cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker spectrometer operating at 400 MHz. UV-Visible spectra were recorded on a Shimadzu UV-1800 spectrophotometer using quartz cells in the range of 200–800 nm at Tikrit University**.** Thin-layer chromatography (TLC) was performed on Fluka silica gel plates with a thickness of 0.2 mm, activated with fluorescent silica gel. Spots were visualized under UV light. The microbial media used in this study were sterilized using a Raypa steam autoclave (Spain) at the Advanced Microbiology Research Laboratory, Tikrit University. Incubation of the petri dishes used in antimicrobial testing was carried out in a Heraeus incubator model D-63450 (Germany).

2.3. Synthesis of Thiazolidin-4-one Derivatives (H_{11}–H_{15}) [8–10]

Equimolar amounts (0.004 mol) of the prepared Schiff bases (H_1–H_5), dissolved in 20 mL of tetrahydrofuran (THF), were mixed with thioglycolic acid (0.004 mol, 0.27 mL). To this mixture, 0.2 g of anhydrous zinc chloride was added. The reaction mixture was refluxed for 11–12 hours, and the progress of the reaction was monitored by TLC.Upon completion of the reaction, the mixture was allowed to cool to room temperature, and then neutralized using 10% sodium bicarbonate solution. The precipitate was filtered, washed thoroughly with cold water, and recrystallized from THF to yield the pure thiazolidin-4-one derivatives (H_{11}–H_{15}). The physical properties and analytical data are summarized in Table 1.

Table 1: Physical Properties, Yields, Reaction Times, and Rf Values of Thiazolidin-4-one Derivatives (H_{11}–H_{15})

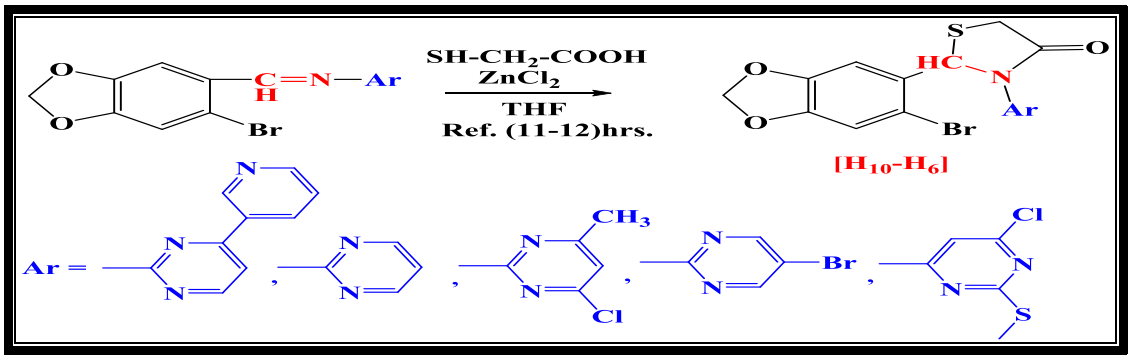
Comp. No.	Ar	Molecular Formula/ M.Wt g/mol	Color	M.P (^{0}C)	R.T hour	R_f	Yield (%)
H_{11}		$C_{19}H_{13}BrN_4SO_3$ 457.24	Light Yellow	163-165	11	0.81	63
H_{12}		$C_{14}H_{10}BrN_3SO_3$ 380.16	Off White	178-180	11	0.78	65
H_{13}		$C_{15}H_{11}BrClN_3SO_3$ 428.62	Orange	234-236	11	0.73	70
H_{14}		$C_{14}H_9Br_2N_3SO_3$ 459.05	Light Brown	186-188	12	0.82	59
H_{15}		$C_{15}H_{11}BrClN_3O_3S_2$ 460.68	Yellow	213-215	11	0.76	62

2.4. Biological Activity Evaluation

In this study, two medically significant bacterial strains were selected due to their antibiotic resistance: Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative). These bacterial strains were obtained from the Department of Biology, College of Education for Pure Sciences.Mueller Hinton Agar (MHA) was used as the culture medium to evaluate the biological activity of the synthesized compounds, particularly in determining the minimum inhibitory concentration (MIC) [11–13]. Stock solutions of compounds H14 and H15 were prepared using dimethyl sulfoxide (DMSO) at concentrations of 0.1, 0.01, and 0.001 mg/mL.The antimicrobial activity was assessed the next day by measuring the diameter of the inhibition zones formed around the wells in the agar plates, and comparing them with those formed by the reference antibiotic (amoxicillin) [14–16]. An increase in the inhibition zone diameter is considered indicative of stronger antimicrobial activity.

3. Results and Discussion:

Thiazolidine-4-one derivatives [H_{11}–H_{15}] were prepared by reacting equal moles of prepared Schiff bases [H_1–H_5] with thioglycolic acid, using tetrahydrofuran (THF) as a solvent and anhydrous zinc chloride as a catalyst.



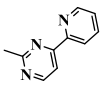
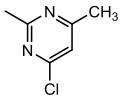
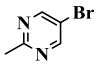
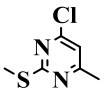
Scheme 1: Shows the series of prepared compounds [H_{11}–H_{15}]

3.2. Characterization of Thiazolidin-4-one Derivatives [H11–H15]

The ultraviolet–visible (UV–Vis) spectra of the synthesized compounds [H11–H15] were investigated using absolute ethanol as the solvent at concentrations ranging from 10^{-5} to 10^{-4} M. The compounds exhibited absorption peaks at shorter wavelengths (λ_max) in the range of 222–245 nm, which are attributed to π→π* electronic transitions. Additionally, absorption peaks at longer wavelengths (λ_max) between 327–384 nm were observed, corresponding to n→π* transitions, as presented in Table 2.

The Fourier-transform infrared (FT-IR) spectra of the synthesized compounds [H11–H15] revealed significant shifts in absorption bands compared to the original Schiff base ligands, indicating successful reactions and the formation of a heterocyclic ring. Notably, the characteristic absorption band of the azomethine group (C=N), which appeared in the Schiff base compounds at 1610–1620 cm^{-1}, disappeared. In its place, a new medium-intensity absorption band appeared in the range of 1672–1677 cm^{-1}, attributed to the carbonyl group (C=O) present in the thiazolidine ring. Furthermore, a medium-intensity band was observed at 1601–1603 cm^{-1}, corresponding to the (C=N) group within the pyrimidine ring. An additional absorption band in the range of 3034–3083 cm^{-1} was noted, which is assigned to the stretching vibration of aromatic C–H bonds. Symmetric and asymmetric absorption bands of the aliphatic methylene (CH_2) group were also recorded at 2839–2852 cm^{-1} and 2918–2955 cm^{-1}, respectively. Moreover, absorption bands appeared at 1457–1491 cm^{-1} and 1541–1571 cm^{-1}, corresponding to C=C stretching vibrations within aromatic rings. A medium-intensity band was also detected in the range of 827–862 cm^{-1}, which is attributed to the C–S bond vibrations associated with the formation of the thiazolidine ring. Additional bands in the range of 1205–1230 cm^{-1} were attributed to the stretching of the C–N bond. Medium to strong bands were also observed at 1233–1276 cm^{-1} and 1301–1375 cm^{-1}, corresponding to the symmetric and asymmetric vibrations of the ether group (C–O–C), as shown in Table 2 and Figures 1 and 2 [17,18].

Table 2: IR absorption (cm-1) and UV absorption spectra of thiazolidine derivatives [H15-H11].

Comp. No.	λ max$_1$ λ max$_2$ EtOH Nm	Ar	IR (KBr) cm^{-1}					
			ν (C-H) ν Arom. νAliph. Sym. /asy.	ν (C=O) (C=N)	ν (C=C) Arom.	ν C-O-C sym. asy.	ν(C-N) ν (C-S)	Others
H_{11}	241 382		3054 2839 2955	1673 1600	1475 1564	1251 1375	1219 862	---
H_{12}	223 372		3076 2850 2920	1677 1602	1457 1571	1234 1335	1205 845	---
H_{13}	244 383		3066 2848 2918	1676 1603	1491 1541	1276 1329	1220 827	(761) υ (C-Cl)
H_{14}	245 384		3083 2852 2922	1672 1601	1477 1570	1265 1301	1230 846	(675)υ (C-Br)
H_{15}	222 327		3034 2850 2922	1673 1601	1472 1546	1233 1320	1212 857	(742) υ (C-Cl)

The ^{1}H-NMR spectrum of compound [H14], recorded in DMSO-d_6 as the solvent, displayed a singlet at a chemical shift of δH = 8.22 ppm, which was attributed to the proton of the (CH=N) group within the pyrimidine ring. Additionally, two singlets were observed at δH = 7.69 and 7.33 ppm, corresponding to aromatic (C–H) protons.A further singlet at δH = 6.87 ppm was assigned to the proton on the (CH) group of the newly formed five-membered ring, while another singlet at δH = 6.54 ppm was attributed to the protons of a methylene (CH_2) group. An additional singlet appeared at δH = 4.56 ppm, which was interpreted as the methylene (CH_2) protons located within the five-membered ring. These signals collectively support the proposed chemical structure of the compound, as illustrated in Figure 3.

In the ^{13}C-NMR spectrum of compound [H14], a signal was recorded at δ = 168.92 ppm, corresponding to the carbon atom of the carbonyl group (C=O). Multiple signals were observed within the range δ = 154.01–120.92 ppm, which are attributed to carbon atoms in the aromatic rings (C–H–Ar).Moreover, a signal at δ = 100.14 ppm was assigned to the carbon atom of the (CH_2) group, while a signal at δ = 53.10 ppm was attributed to the carbon atom of the (C–H) group within the newly formed thiazolidine ring. Another signal at δ = 24.47 ppm corresponds to the methylene (CH_2) carbon within the same ring.In addition, several signals appeared in the range δ = 40.46–39.47 ppm, which were attributed to carbon atoms from the solvent (DMSO) used during the analysis.

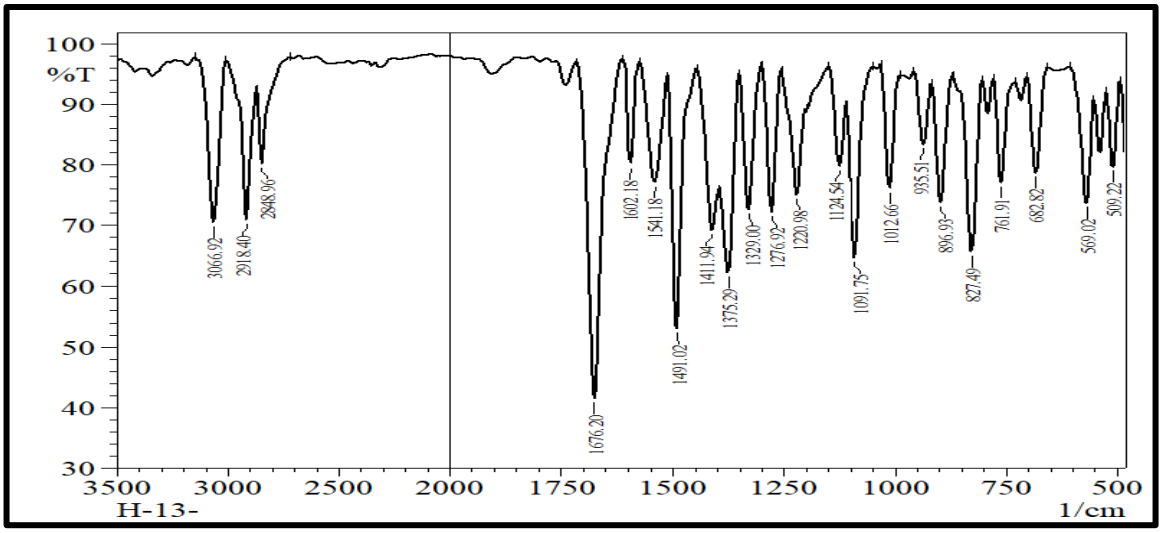


Figure 1: FT-IR spectrum of compound (H13)

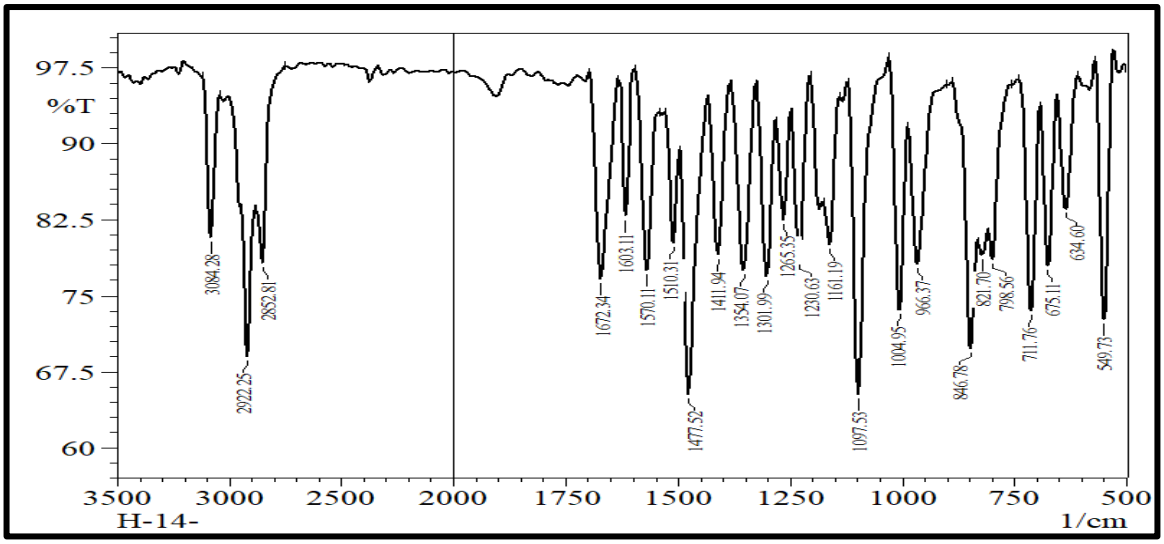


Figure 2: FT-IR spectrum of compound (H14)

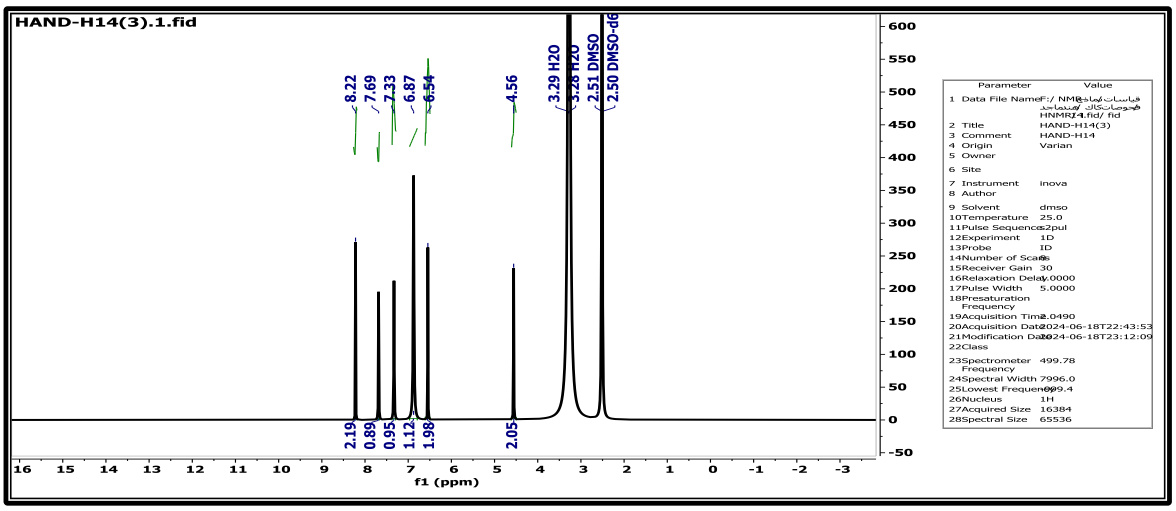


Figure 3: 1H-NMR spectrum of compound (H14)

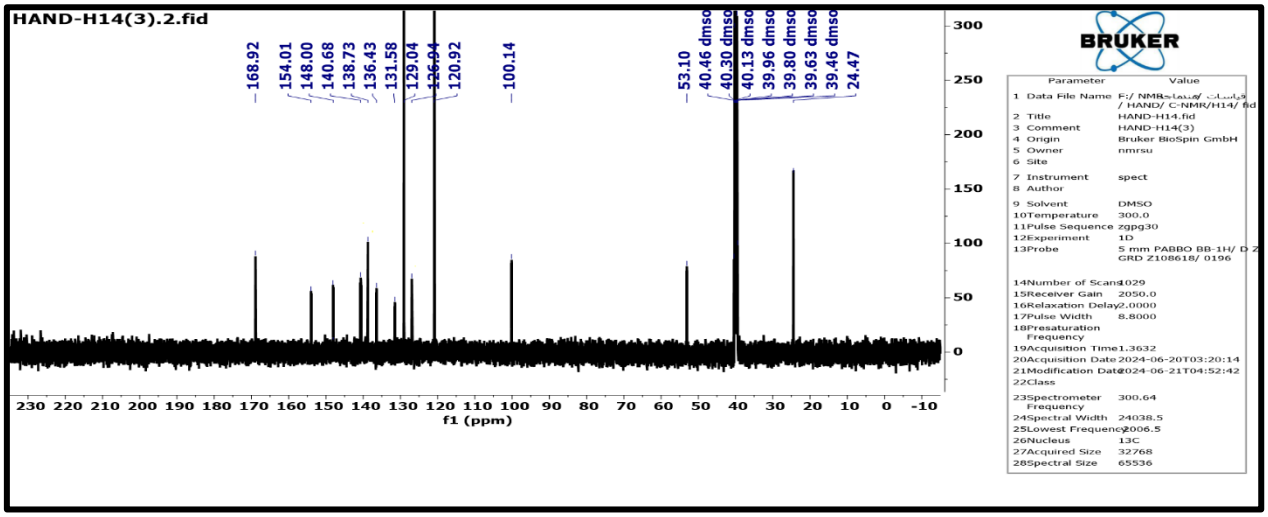


Figure 4: 13C-NMR spectrum of compound (H14)

2.3. Biological Activity Results

Heterocyclic compounds are known for their distinctive biological properties, making them promising candidates as effective antimicrobial agents against both Gram-positive and Gram-negative bacteria. In this context, the biological activity of compounds H14 and H15 was evaluated against two bacterial strains representing the two major classes of bacteria: Escherichia coli (a Gram-negative bacterium) and Staphylococcus aureus (a Gram-positive bacterium).The antimicrobial activity was assessed using the inhibition zone diameter method (measured in centimeters), a widely accepted indicator of antimicrobial efficacy. The results demonstrated that compound H14 exhibited significant activity against E. coli at all tested concentrations, in some cases surpassing the activity of the standard antibiotic amoxicillin [19–21], particularly at a concentration of 0.1 mg/mL. This suggests its potential effectiveness against Gram-negative bacteria.Conversely, compound H15 showed marked activity against S. aureus, recording the largest inhibition zones across all concentrations tested, outperforming the standard antibiotic used in the study. This variation in antimicrobial activity is attributed to differences in the structural composition of bacterial cell walls, which influence the compounds' mechanisms of action.These findings indicate that compounds H14 and H15 possess selective antimicrobial properties, reinforcing their potential as future antimicrobial agents, especially in light of the ongoing rise in resistance to conventional antibiotics [22–24], as presented in Table 3.

Table 3: Efficacy of compounds H14 and H15 against the two types of bacteria measured in (cm)

Comp. No.	*Escherichia coil*			*Staphylococcus aureus*		
Conc. mg/ml	0.1	0.01	0.001	0.1	0.01	0.001
H_{14}	3.5	2.9	2.9	1.2	1.0	0.8
H_{15}	1.0	0.5	0.5	4.0	2.0	2.0
Amoxicillin	2.0	2.0	10	2.4	1.6	1.0

4. Conclusions

This study successfully synthesized a new series of thiazolidine-4-one derivatives using a one-pot reaction method, with the structures of the compounds confirmed through various spectroscopic techniques including FT-IR, ^{1}H-NMR, ^{13}C-NMR, and UV–Vis. The synthesized compounds exhibited consistent physicochemical properties indicative of the targeted ring formation and successful functional group modifications.Biologically, the investigation demonstrated that some of these derivatives, particularly compounds H14 and H15, possess notable antimicrobial activity against both Gram-positive and Gram-negative bacteria, occasionally surpassing the efficacy of conventional antibiotics such as amoxicillin. This selective antimicrobial activity highlights the significant potential of these compounds as novel sources for the development of antimicrobial agents—a critical need in the context of escalating bacterial resistance to existing drugs.Thiazolidine-4-one derivatives thus represent a promising platform for future research aimed at developing effective and safe antimicrobial therapies. However, further studies are required to evaluate their safety profiles and therapeutic efficacy in medical applications.

References

1. D. L. Hawksworth, “The magnitude of fungal diversity: the 1·5 million species estimate revisited,” *Mycol. Res.*, vol. 105, no. 12, pp. 1422–1432, 2001.
2. N. Foroughifar and S. Ebrahimi, “One-pot synthesis of 1,3-thiazolidin-4-one using $Bi(SCH_2COOH)_3$ as catalyst,” *Chin. Chem. Lett.*, vol. 24, no. 5, pp. 389–391, 2013.
3. S. Huber-Villaume *et al.*, “2-(Thienothiazolylimino)-1,3-thiazolidin-4-ones inhibit cell division cycle 25 A phosphatase,” *Bioorg. Med. Chem.*, vol. 24, no. 13, pp. 2920–2928, 2016.
4. G. Revelant *et al.*, “Synthesis and biological evaluation of novel 2-heteroarylimino-1,3-thiazolidin-4-ones as potential anti-tumor agents,” *Eur. J. Med. Chem.*, vol. 94, pp. 102–112, 2015.
5. A. Umar *et al.*, “Design, synthesis, in vitro antiproliferative effect and in situ molecular docking studies of a series of new benzoquinoline derivatives,” *J. King Saud Univ. Sci.*, vol. 34, no. 4, Art. no. 102003, 2022.
6. J. T. Hwang *et al.*, “Apoptotic effect of EGCG in HT-29 colon cancer cells via AMPK signal pathway,” *Cancer Lett.*, vol. 247, no. 1, pp. 115–121, 2007.
7. S. A. Hassan and D. M. Aziz, “Synthesis, in vitro Antimicrobial assay and Molecular Docking Studies of some new Symmetrical Bis-Schiff Bases and their 2-Azetidinones,” *Zanco J. Pure Appl. Sci.*, vol. 33, no. 2, pp. 34–50, 2021.
8. R. H. Saleh *et al.*, “Synthesis of some new thiazolidinone compounds derived from schiff bases compounds and evaluation of their laser and biological efficacy,” *Ann. Trop. Public Health*, vol. 23, no. 7, pp. 1012–1031, 2020.

9. S. H. Abdullah, M. M. Salih, and A. Al-Badrany, "Synthesis, Characterization and Antibacterial Evaluation of Novel Thiazolidine Derivatives," *J. Angiother.*, vol. 8, no. 3, pp. 1–9, 2024.
10. S. H. Abdullah, B. A. Khairallah, and K. A. Al-Badrany, "Preparation and characterization of some azetidine-2-one derivatives derived from benzothiazole-2-ol and evaluation of their biological activity," *Indian J. Heterocycl. Chem.*, vol. 35, no. 1, 2025.
11. B. A. Khairallah *et al.*, "Preparation, Characterization, Biological Activity Evaluation, and Liquid Crystallography Study of New Diazepine Derivatives," *World Med. J. Biomed. Sci.*, vol. 1, no. 7, pp. 65–76, 2024.
12. M. J. Saleh *et al.*, "Preparation And Evaluation Of The Biological Activity Of A 2-Amino Pyran Ring Using A Solid Base Catalyst," *Cent. Asian J. Med. Nat. Sci.*, vol. 5, no. 4, pp. 130–138, 2024.
13. A. W. A. S. Talluh, M. J. Saleh, and J. N. Saleh, "Preparation, Characterisation and Study of the Molecular Docking of Some Derivatives of the Tetrazole Ring and Evaluation of their Biological Activity," *World Med. J. Biomed. Sci.*, vol. 1, no. 7, pp. 15–23, 2024.
14. A. H. Dalaf, M. J. Saleh, and J. N. Saleh, "Green synthesis, characterization, and multifaceted evaluation of thiazolidinone derivatives: A study on biological and laser efficacy," *Eur. J. Mod. Med. Pract.*, vol. 4, no. 7, pp. 155–168, 2024.
15. M. J. Saleh, J. N. Saleh, and K. Al-Badrany, "Preparation, characterization, and evaluation of the biological activity of pyrazoline derivatives prepared using a solid base catalyst," *Eur. J. Mod. Med. Pract.*, vol. 4, no. 7, pp. 25–32, 2024.
16. A. W. A. S. Talluh *et al.*, "Preparation, characterization, and evaluation of the biological activity of new 2,3-dihydroquinazoline-4-one derivatives," *Eur. J. Mod. Med. Pract.*, vol. 4, no. 4, pp. 326–332, 2024.
17. A. W. A. S. Talluh, J. N. Saleh, and M. J. Saleh, "Preparation, Characterization and Evaluation of Biological Activity and Study of Molecular Docking of Some New Thiazolidine Derivatives," 2024.
18. A. W. A. S. Sattar Talluh *et al.*, "Preparation and Characterization of New Imidazole Derivatives Derived From Hydrazones and Study of their Biological and Laser Efficacy," *Cent. Asian J. Theor. Appl. Sci.*, vol. 5, no. 4, pp. 202–211, 2024.
19. A. H. Dalaf, "Synthesis and Characterization of Some Quartet and Quinary Hetero cyclic Rings Compounds by Traditional Method and Microwave Routes Method and Evaluation of Their Biological Activity," M.Sc. thesis, Tikrit Univ., Tikrit, Iraq, 2018.
20. A. H. Dalaf and F. H. Jumaa, "Synthesis, Characterization of some 1,3-Oxazepane-4,7-Dione by Traditional and Microwave routes method and evaluation of their biological activity," *Al-Utroha Pure Sci.*, no. 8, pp. 93–108, 2018.
21. A. H. Dalaf, F. H. Jumaa, and S. A. S. Jabbar, "Synthesis and Characterization of some 2,3-dihydroquinozoline and evaluation of their biological activity," *Tikrit J. Pure Sci.*, vol. 23, no. 8, pp. 66–67, 2018.
22. A. J. Salwa *et al.*, "Synthesis and Characterization of Azetidine and Oxazepine Compounds Using Ethyl-4-((4-Bromo Benzylidene) Amino) Benzoate as Precursor and Evaluation of Their Biological Activity," *J. Educ. Sci. Stud.*, vol. 16, no. 5, pp. 39–52, 2020.
23. I. Q. Abd *et al.*, "Synthesis and Identification of new compounds have Antioxidant activity Beta-carotene, from Natural Auxin Phenyl Acetic Acid," *Res. J. Pharm. Technol.*, vol. 13, no. 1, pp. 40–46, 2020.
24. B. D. Salih *et al.*, "Biological activity and laser efficacy of new Co(II), Ni(II), Cu(II), Mn(II) and Zn(II) complexes with phthalic anhydride," *Mater. Today Proc.*, vol. 43, pp. 869–874, 2021.