American Journal of Bioscience and Clinical Integrity
https://biojournals.us/index.php/AJBCI
ISSN: 2997-7347

Use of the Fusion Method to Preparation and Bioactivity Evaluation of Novel Benzo-Oxazepine Derivatives

Shahba Naji Hadid, Iman Aywb Yass
Department of Chemistry / College of Education for Women / Tikrit University
shahbaa.haded23@st.tu.edu.iq, emanaywb@tu.edu.iq

Received: 2025, 15, Apr
Accepted: 2025, 21, May
Published: 2025, 23, Jun

Annotation: In this study, Schiff base and phthalic anhydride were reacted using the melting technique without the use of solvents to produce a series of oxazepine-4,7-dione (SH20–SH25). The success of the chemical procedure was confirmed by spectroscopic methods (UV-Vis, IR, 1H-NMR, 13C-NMR) that confirmed the structure of the produced compounds and revealed the distinctive patterns of carbonyl groups, aromatic bonds, and oxazepine. Additionally, the biological effectiveness of SH22 and SH24 against two pathogenic bacterial species—Escherichia coli (Gram-negative) and Escherichia coli (Gram-positive)—was tested as part of the study, using three different concentrations, and comparing them to the standard antibiotics ciprofloxacin and amikacin. SH22 showed moderate activity against E. coli at its highest concentration (2.1 cm), while it showed weak activity against Staphylococcus aureus. In contrast, SH24 showed significant activity against both strains at high concentrations, outperforming standard antibiotics. These results show the potential of new oxazepine compounds as antibacterial agents, especially SH24. Further studies should be conducted to evaluate the possible mechanisms of action and potential future uses of these compounds.

Keywords: heterocyclic, oxazepine, Biological activity.

1. Introduction

They are compounds that contain a heterocyclic, primarily unsaturated, seven-membered ring called oxazepine [1] or a whole, called oxazepine, which contains five carbon atoms and two atoms: An oxygen atom and a nitrogen atom (86). The larger size of an oxazepine heptadecane is obvious compared to an aromatic benzene hexadecane ring. Due to its larger size, heptadecane resembles a boat with a more stable atom distribution and reduces ring tension, which is not aromatic [2]. Due to the increase in ring size, the rate of formation of these compounds has increased and they are easier to prepare due to the difference in structure, type and location of atoms. We discover that there are a large number of diverse compounds being created and released in the field [3]. Many studies have shown that oxazepine compounds can be used to treat various diseases and psychiatric issues, which has prompted many researchers to try to devise new ways to produce them [4]. Oxazepine is essential in the synthesis of many organic compounds that contain nitrogen and oxygen in their structure, and these compounds have multiple medicinal properties and are used in the pharmaceutical industry. Among their chemical compounds are heteropolymers with cancer inhibition and potency [5]. The following compound has been shown to be effective as an antioxidant [6].

2. Experimental:

2.1. Material: Fluka, Aldrich, and BDH supplied all of the compounds utilized in this investigation, and none required additional purification.

2.2. Preparation of oxazepine derivatives (SH_{20}-SH_{25})

In an appropriate heat-resistant glass bowl, combine 0.004 mol of a schiff base derivative with 0.004 mol of 0.59 g of phthalic anhydride without the use of a solvent. The mixture is heated gradually until it melts, stirring and thoroughly mixing for 6–44 minutes. At that point, the interactive material's color and texture change. Following that, 1,4-dioxane was used to collect and recrystallize the product[7]. The results are shown in Table 1

Table (1): Physical properties of oxazepine-7,4-dione derivatives (SH_{20}-SH_{25})

Comp. No.	R	Molecular Formula/ M.Wt g/mol	Color	M.P (^{0}C)	R.T mint	R_f	Yield (%)
SH_{20}	4-NO_2	$C_{32}H_{20}N_6O_5$ 568.55	Dark brown	150-152	26	0.82	63
SH_{21}	4-F	$C_{32}H_{20}FN_5O_3$ 541.54	Dark Brown	164-167	16	0.83	59
SH_{22}	4-OH	$C_{32}H_{21}N_5O_4$ 539.55	Brown	130-132	7	0.71	62
SH_{23}	4-OCH_3	$C_{33}H_{23}N_5O_4$ 553.58	Light yellow	153-156	16	0.75	64
SH_{24}	4-$N(CH_3)_2$	$C_{34}H_{26}N_6O_3$ 566.62	Red	202-204	6	0.72	61
SH_{25}	3,4-di Cl	$C_{32}H_{19}Cl_2N_5O_3$ 592.44	Dark Red	174-177	44	0.81	66

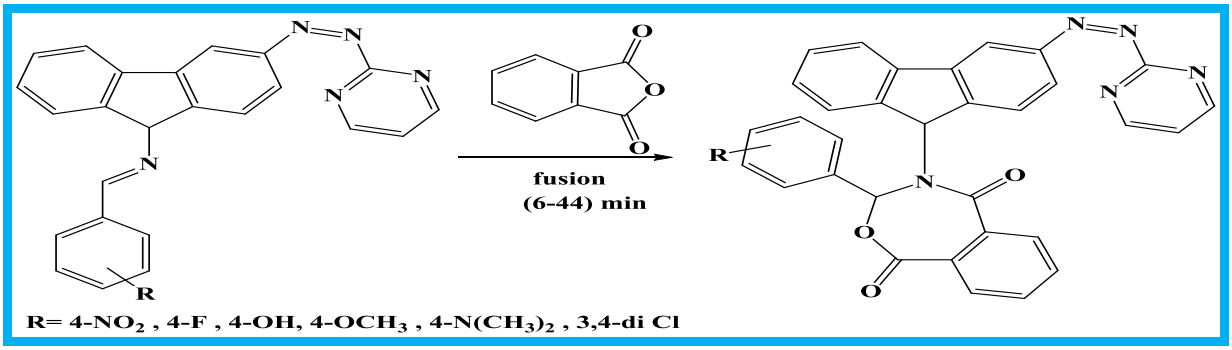
2.3. Biological activity study:

Two bacteria isolated from the Laboratory of the Department of Biology, the first Tikrit University, positively for a generous dye called staphylococcus, and the second negative called Aishiria Qaluna using DMSO as a solvent, vehicles [SH_{22}, SH_{24}] was diluted to three concentrations (0.1, 0.01, and 0.001) mg/ml in order to examine their effectiveness[8-10]. Then they were placed in the culture dish and were wiped with dry bacterial solution in three different

directions to ensure a uniform distribution. Then the solution is poured into the three holes that were performed in the culture dish using a cork digger with a diameter of 6 mm. Next, he used a millimeter ruler to read the results a day after keeping the culture board in a custom container at 37 ° C. As controls, ammecine and ciprofloxacin were used [11,12].

3. Results and discussion

According to the following formula, 1,3-Benzoxepin-4,7-dione derivatives [SH_{20}-SH_{25}] are made by reacting equal parts of Schiff base derivatives [SH_2-SH_7] with phthalic anhydride without the need of a solvent:



Scheme (1): Route of prepared compounds (SH_{20}-SH_{25})

3.1. Characterization of tetrazole derivatives (SH_{20}-SH_{25})

Using anhydrous ethanol as the solvent, when the concentration range of the prepared compounds was [10^{-5}-10^{-4}] molar, the UV-Vis spectrum of the prepared compounds [SH25-SH20] was studied, and it was found that the short wavelength (λmax) appeared at (256- 285 nm, which was due to the ($^{*}\pi\leftarrow\pi$) type electronic transition, and the long wavelength (λmax) was in the range of (311-357) nm, which was due to the ($^{*}\pi\leftarrow n$) type electronic transition.

Upon studying the IR spectra of the prepared compounds [SH_{25}-SH_{20}], it was found that in the prepared Schiff base compounds [SH_7-SH_2], the stretching band (1629-1632) cm^{-1} of the azomethine group due to the exocyclic group (C=N) disappeared and an absorption band appeared in the range (3030-3084) cm^{-1}, due to the stretching of the aromatic bond (C-H). In addition, absorption bands appeared in the range of (2912-2972) cm^{-1} and (2845-2891) cm^{-1}, resulting from the stretching of the aliphatic bond (CH). Two strong bands appeared at frequencies (1713-1719) cm-1 and (1665-1671) cm^{-1}, due to the stretching of the carbonyl bond (C=O) of lactone and lactam, respectively. A medium-intensity stretching band appeared in the range of (1600-1603) cm^{-1}, attributed to the stretching of the pyrimidine ring. In addition, two bands attributed to aromatic bond (C=C) stretching appeared in (1552-1572) cm^{-1} and (1473-1483) cm^{-1}, a medium band attributed to N=N groups appeared in (1428-1442) cm^{-1}, the FTIR spectrum showed additional bands attributed to C-O stretching in (1334-1359) cm^{-1}, and a band attributed to C-N stretching appeared in (1223-1251) cm^{-1}[13,14].in Table (2) and Figures (2, 3).

Table 2: Infrared and UV spectrum of the prepared compounds (SH_{20}-SH_{25})

Comp. No.	λ max$_1$ λ max$_2$ EtOH	R	IR (KBr) cm^{-1}						
			νC-H Arom.	νC-H Aliph.	νC=O Lactone Lactam	νC=N	νC=C Arom.	νN=N νC-N	Others
SH_{20}	256 311	4-NO_2	3055	2929 2845	1714 1669	1603	1562 1483	1440 1246	ν(NO_2) *asy*. (1506) *sym*. (1359)
SH_{21}	268 322	4-F	3084	2972 2891	1717 1665	1601	1572 1475	1434 1223	ν (C-F) 822

SH_{22}	281 343	4-OH	3046	2912 2854	1719 1671	160 0	1564 1482	1441 1232	ν (OH) 3426
SH_{23}	261 346	4- OCH_3	3054	2965 2851	1713 1665	160 1	1552 1473	1435 1241	ν (C-O-C) *asy*. (1357) *sym*. (1284)
SH_{24}	282 342	4- $N(CH_3)_2$	3030	2953 2887	1715 1669	160 2	1564 1479	1442 1251	ν (C-H) *asy*. (2953) *sym*. (2887)
SH_{25}	285 357	3,4-di Cl	3038	2913 2845	1718 1669	160 3	1571 1483	1428 1235	ν (C-Cl) 701

In the ^{1}H-NMR spectra of compound [SH_{20}] using the solvent (DMSO-d^{6}) a signal at a chemical shift of (8.66) ppm was attributed to the protonation of the CH group on the oxazepine ring, several signals attributed to the protonation of the aromatic ring appeared in the chemical shift range from (6.60 - 8.39) ppm, and a signal attributed to the solvent (DMSO-d^{6}) proton at a chemical shift of (2.50) ppm, as in Figure 3.

In the $_{13}$C NMR spectrum of [SH_{20}], the carbonyl group (C=O) in lactam and lactone, respectively, was responsible for two signals in chemical shifts (162.82, 161.26) ppm; the ring aromatic carbon atoms were responsible for several signals in chemical shifts (177.96-117.99) ppm; the carbon atom of the group (CH) in the oxazepine ring was responsible for a signal in chemical shifts (83.07) ppm, and the carbon atom in the solvent (DMSO-d_6) at the range (39.31-40.57) ppm.As in Figure (4).

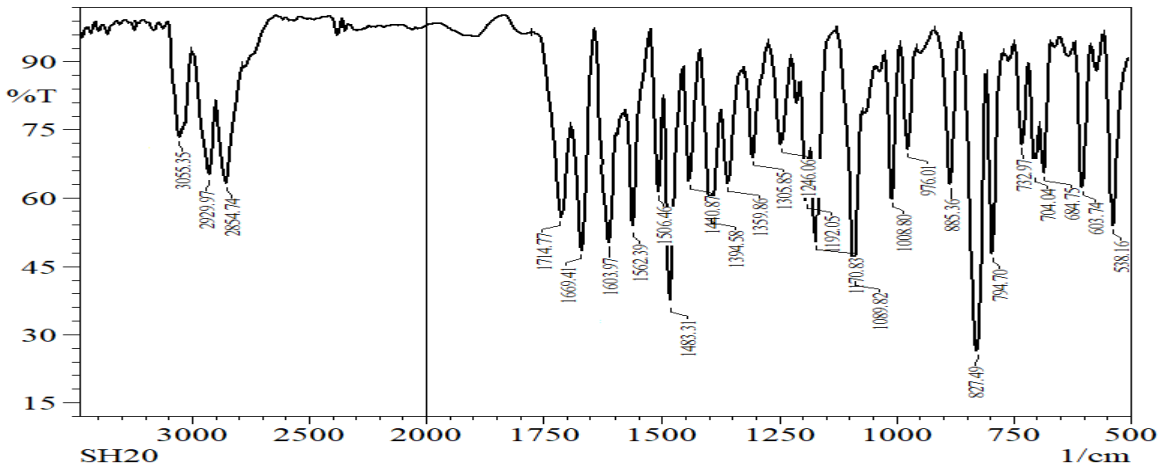


Figure (1): FT-IR spectrum of the compound [SH_{22}].

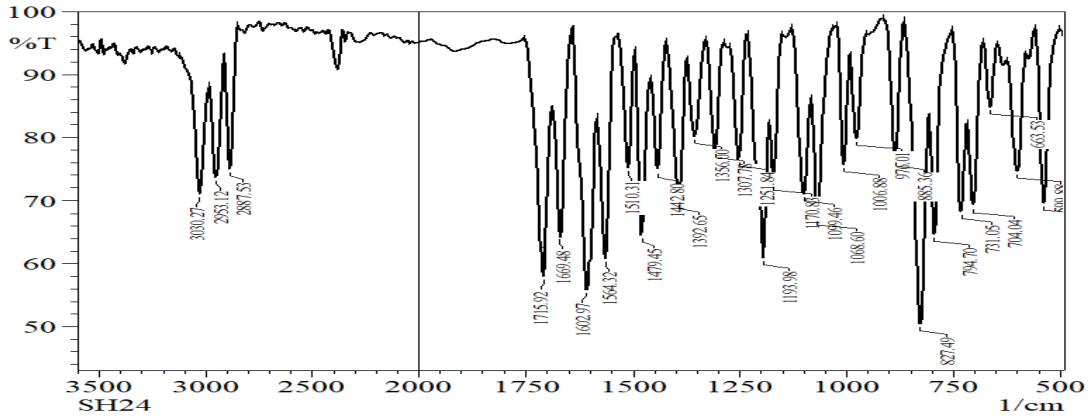


Figure (2): FT-IR spectrum of the compound [SH_{24}].

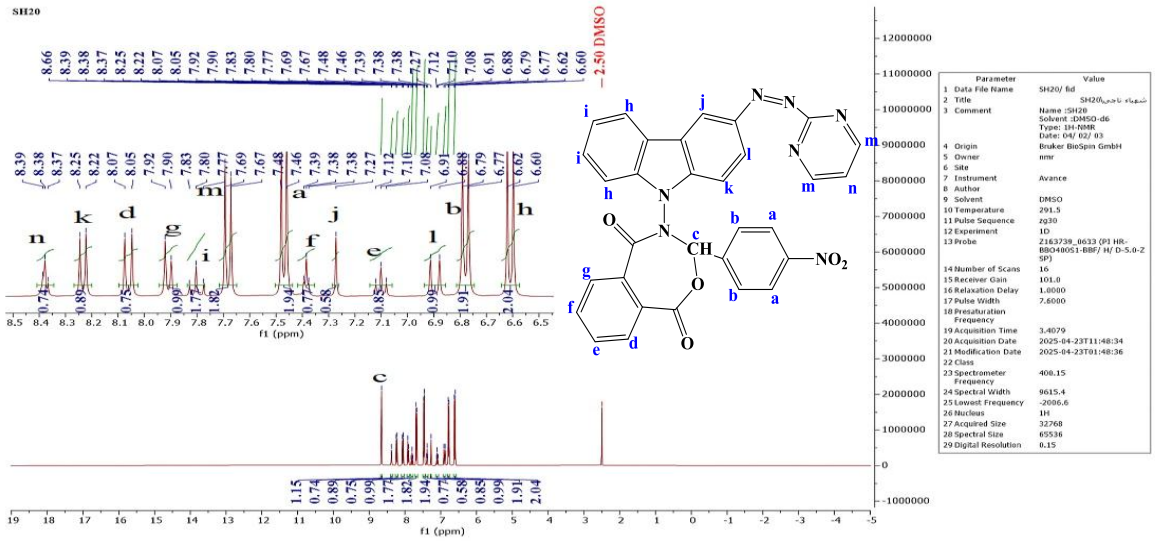


Figure (3): 1H-NMR spectrum of the compound (SH_{20}).

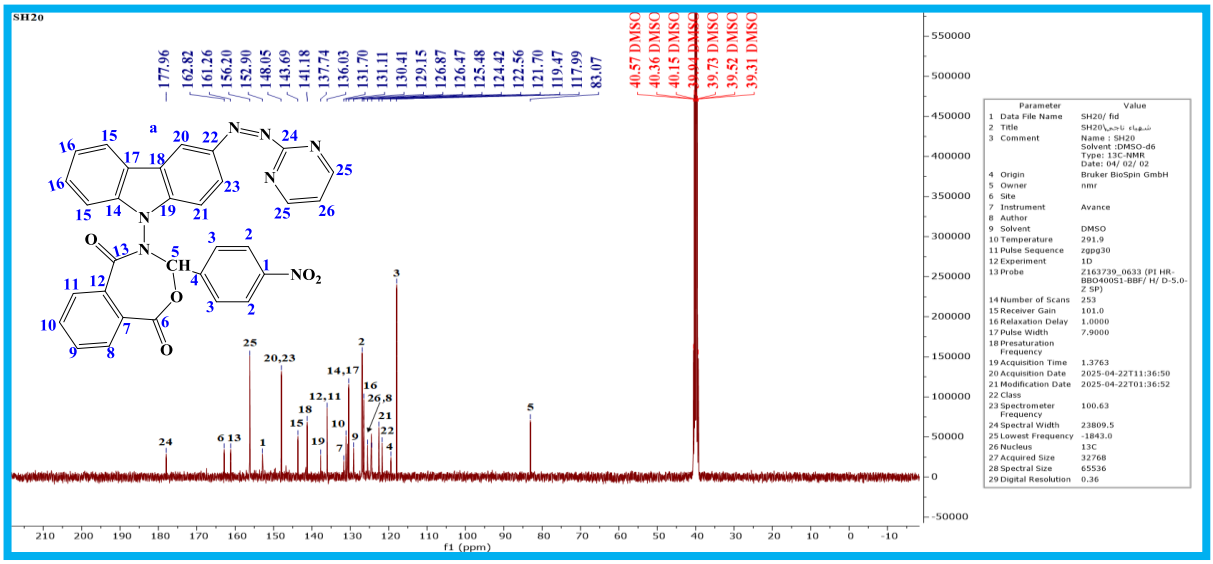


Figure (4): ^{13}C-NMR spectrum of the compound (SH_{20}).

3.2. Biological Effectiveness Results

Table (3) shows the biological activity of the two compounds [SH_{22}, SH_{24}], at three different concentrations (0.1, 0.01 and 0.001 mg/ml) in comparison to the standard antibiotics ciprofloxacin and amikacin, against two different types of bacteria representing the two main Gram-negative species: Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive). Compound [SH_{22}] showed a moderate degree of efficacy against E. coli, with a diameter of 2.1 cm at the highest concentration and a decrease in efficacy with decreasing concentration. Its efficacy against Staphylococcus aureus was modest, with an inhibitory diameter of 0.9 cm at the highest concentration[15,16]. However, its activity increased slightly at the lowest concentration, reaching 1.2 cm, suggesting that the bacterial response to this substance may be curvilinear. [SH_{24}] showed a weak ability to control E. coli at the highest concentration (0.6 cm), but this ability increased significantly at the intermediate concentration of 2.5 cm, exceeding the ability of standard antibiotics, reflecting a concentration-dependent biological activity. [SH_{24}] also showed potent activity against Staphylococcus aureus, with an inhibition diameter of 1.7 cm at the median concentration, which was greater than that of both ciprofloxacin and amikacin[17,18]. Regarding the standard treatments, ciprofloxacin showed a moderate degree of efficacy against E. coli (1.5 cm) and a weak degree of efficacy against S.

aureus (0.8 cm), while amikacin had a relatively low degree of efficacy against both strains. These results suggest that [SH_{22},SH_{24}], especially the latter, have antibacterial properties that could make them suitable for the development of effective therapeutic alternatives, especially against resistant strains[19]. as in Table (3) and Figure (5,6).

Table (3): Biological effectiveness of prepared compounds and control treatments (inhibition in cm).

Compounds NO.	Conc. Mg per ml	*Escherichia coli* *Gram negative*	*Staphylococcus aureus* *Gram positive*
SH_{22}	0.1	2.1	0.9
	0.01	2.0	0.8
	0.001	0.9	1.2
SH_{24}	0.1	0.6	1.5
	0.01	2.5	1.7
	0.001	0.6	0.9
Ciprofloxacin	10mg	1.5	0.8
Amikasin	10mg	0.5	0.8

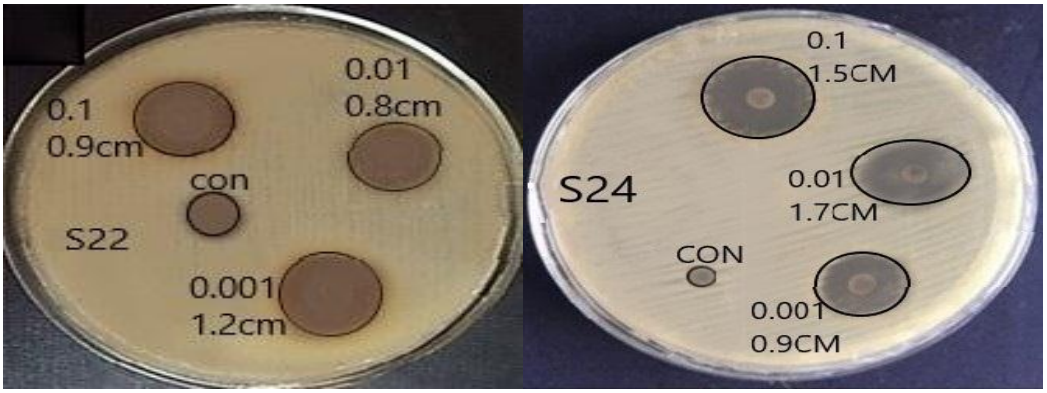


Figure (5): Inhibitory effectiveness of compounds (SH_{22}, SH_{24}) against S. aureus bacteria

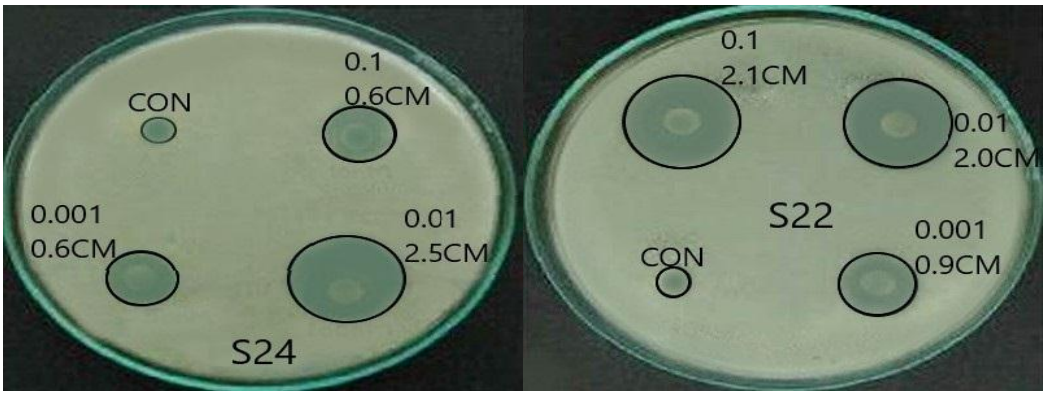


Figure (6): Inhibitory effectiveness of compounds (SH_{22}, SH_{24}) against E. Coli bacteria

4. Conclusions

A series of oxazepine-7,4-dione derivatives (SH_{20}-SH_{25}) were successfully prepared using a direct reaction between Schiff base derivatives and phthalic anhydride without the need for a solvent, reflecting the simplicity and efficiency of the preparation methodology. Various spectroscopic analyses (UV, FT-IR, ^{1}H-NMR, ^{13}C-NMR) confirmed the chemical structures of the prepared compounds through the appearance of characteristic signals of the active groups such as carbonyl, oxazepine and aromatic groups. Biological evaluations showed that SH_{22} and SH_{24} possess antibacterial activity to varying degrees, with SH_{24} exhibiting clear efficacy against both E. coli (Gram-negative bacteria) and Staphylococcus aureus (Gram-positive bacteria),

outperforming at some concentrations standard antibiotics such as ciprofloxacin and amikacin. The results indicate that the nature of the substituted groups on the basic ring directly affects bioactivity, providing a promising basis for the development of more effective derivatives. Based on the above, some of these compounds, particularly SH_{24}, can be considered as candidates as antibacterial agents, especially in light of the challenges associated with resistance to conventional antibiotics.

References

1. Z. A. Sallal and H. T. Ghanem, "Synthesis and Identification of New Oxazepine Derivatives bearing Azo group in their structures," *Iraqi Journal of Science*, pp. 1–8, 2018.
2. M. H. Serrano-Wu, D. R. S. Laurent, Y. Chen, S. Huang, K. R. Lam, J. A. Matson *et al.*, "Sordarin oxazepine derivatives as potent antifungal agents," *Bioorg. Med. Chem. Lett.*, vol. 12, no. 19, pp. 2757–2760, 2002.
3. D. Sunil, C. Ranjitha, M. Rama, and P. KSR, "Oxazepine derivative as an antitumor agent and snail1 inhibitor against human colorectal adenocarcinoma," *Int. J. Innov. Res. Sci. Eng. Technol.*, vol. 3, no. 8, pp. 15357–15363, 2014.
4. A. T. Mohammad, G. Y. Yeap, and H. Osman, "Synthesis, characterization and theoretical study of a new liquid crystal compound with an oxazepine core," *J. Mol. Struct.*, vol. 1087, pp. 88–96, 2015.
5. R. A. Ali, L. S. Ahamed, and S. I. C. AL-Khazraji, "Synthesis, Characterization, and Study of Anticancer Activities of New Schiff Bases and 1,3-Oxazepine Containing Drug," *Russ. J. Bioorg. Chem.*, vol. 50, no. 1, pp. 28–33, 2024.
6. K. F. Hamak and H. H. Eissa, "Synthesis, characterization, biological evaluation and anti corrosion activity of some heterocyclic compounds oxazepine derivatives from Schiff bases," *Org. Chem.: Curr. Res.*, vol. 2, no. 3, p. 1, 2013.
7. A. S. T. Abdul Wahed, "Preparation and Evaluation of Bacterial Activity and Study of the Crystalline Properties of Some 1,3-Oxazepine-4,7-Dione Derivatives," *Cent. Asian J. Theor. Appl. Sci.*, vol. 5, no. 2, pp. 15–26, 2024.
8. R. S. Najm and A. W. A. S. Talluh, "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.
9. 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.
10. 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.
11. 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.
12. J. N. Saleh and A. Khalid, "Synthesis, characterization and biological activity evaluation of some new pyrimidine derivatives by solid base catalyst AL2O3-OBa," *Cent. Asian J. Med. Nat. Sci.*, vol. 4, no. 4, pp. 231–239, 2023.
13. F. M. Muhammad, B. A. Khairallah, and K. A. Albadrany, "Synthesis, characterization and antibacterial evaluation of novel 1,3-oxazepine derivatives using a cycloaddition approach," *J. Angiother.*, vol. 8, no. 3, pp. 1–5, 2024.

14. A. W. A. S. Talluh, R. S. Najm, M. J. Saleh, and J. N. Saleh, “Synthesis, Characterization, and Evaluation of the Biological Activity of Novel Oxazepine Compounds Derived From Indole-5-Carboxylic Acid,” *Am. J. Biosci. Clin. Integr.*, vol. 1, no. 8, pp. 10–19, 2024.
15. A. W. A. S. Talluh, M. J. Saleh, J. N. Saleh, and H. M. S. Al-Jubori, “Synthesis and Characterization of Some New Imine Graphene Derivatives and Evaluation of Their Biological Activity,” *Cent. Asian J. Med. Nat. Sci.*, vol. 5, no. 4, pp. 272–290, 2024.
16. A. W. A. S. S. Talluh, J. N. Saleh, M. J. Saleh, and H. M. Saleh Al-Jubori, “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.
17. M. J. Saleh, J. N. Saleh, K. Al-Badrany, M. Yaseen, M. H. Ali, and A. W. A. S. Talluh, “Preparation and Characterization of Some Oxazolidine-5-one Derivatives and Evaluation of their Biological Activity,” *South Asian Res. J. Nat. Prod.*, vol. 8, no. 1, pp. 74–84, 2025.
18. F. M. Muhammad, B. A. Khairallah, and J. N. Saleh, “Preparation and Characterization of New Rings of Oxazine Derivatives and Studying Their Biological and Laser Effectiveness and Molecular Docking,” *Cent. Asian J. Theor. Appl. Sci.*, vol. 5, no. 4, pp. 190–201, 2024.
19. M. J. Saleh and K. A. Al-Badrany, “Preparation, characterization of new 2-oxo pyran derivatives by AL2O3-OK solid base catalyst and biological activity evaluation,” *Cent. Asian J. Med. Nat. Sci.*, vol. 4, no. 4, pp. 222–230, 2023.