Synthesis, characterization and Antibacterial Evaluation of Novel 1,3-Oxazepine Derivatives Using A Cycloaddition Approach

Farah M. Muhammad [1], Bushra A. Khairallah [1], K. A. Albadrany [1*]

Abstract

This study demonstrated the synthesis and characterization of novel heterocyclic compounds, particularly oxazepine derivatives, using a cycloaddition procedure. The synthesis involved the reaction of chloroacetohydrazide with various aromatic aldehydes under acidic conditions in ethanol solvent to produce hydrazone compounds. These hydrazones subsequently underwent pericyclic synthesis with phthalic anhydride to yield oxazepine derivatives. The physicochemical properties of the synthesized compounds (F1 to F13) were characterized using FT-IR and H-NMR spectroscopy. The antibacterial activity of the synthesized oxazepine derivatives (F8, F9, F10, F11, F12, and F13) was evaluated against both Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacterial strains using the cup plate agar diffusion technique. Notably, compounds F8, F9, and F10 exhibited potent antibacterial activity against both Gram-positive and Gram-negative bacteria, suggesting their potential as effective antibacterial agents. Molecular docking studies were also conducted to investigate the binding interactions of selected compounds with bacterial protein receptors, specifically Escherichia coli K-12 (PDB ID: 4QGS) and Staphylococcus aureus (PDB ID: 7PQ1). The results demonstrate the potential of these novel oxazepine derivatives as antibacterial agents, highlighting their promising biological activities and molecular interactions with bacterial proteins.

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

Significance | This study demonstrated a novel approach to the synthesis of oxazepine derivatives, key heterocyclic compounds with potential pharmacological applications.

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Editor Mohamed Khadeer Ahamed Basheer, And accepted by the Editorial Board Mar 05, 2024 (received for review Jan 02, 2024)

Introduction

Heterocyclic compounds have a ring structure containing a different atom, such as oxygen, sulfur, or nitrogen. These compounds are widely spread in nature and have multiple important uses in many fields, including industrial and medical applications. They are involved in the synthesis of sugars and their derivatives, as well as enzymes, proteins, and nucleic acids (Al-Mulla, A. 2017).

These substances typically have a heptagonal ring that is heterogeneous and unsaturated; they are referred to as oxazepine (Gomha et al. 2017), but they can also be saturated and classified as such. Oxazepine compounds have two heterogeneous atoms: an oxygen atom, a nitrogen atom, and five carbon atoms. Additionally, there are three isomers of oxazepine compounds, 1.2, 1.3, and 1.4-oxazepine (Gomha et al. 2016), which are numbered based on the positions of the oxygen and nitrogen atoms in the heptagonal ring (Scheme 1).

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Please cite this article.
Farah M. Muhammad, Bushra A. Khairallah et al. (2024). Synthesis, characterization and Antibacterial Evaluation of Novel 1,3-Oxazepine Derivatives Using A Cycloaddition Approach, Journal of Angiotherapy, 8(3), 1-9, 9506

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Hydrazones are considered precursors of oxazepine and other heterocyclic rings. 1,3-Oxazepine refers to any seven-membered ring containing oxygen in position one, nitrogen in position three, and five carbon atoms (Xiao et al. 2019). These compounds have been identified as potential antibacterial agents due to their ability to inhibit the growth of various bacterial strains (Kshash, A. H. 2020). The chemistry of oxazepane derivatives has been of interest due to their useful applications in medicine (Khalil, M. I. 2021).

Several methods for synthesizing oxazepam include cyclization reactions and ring-closing metathesis reactions. One commonly used approach is the condensation of a primary amine with an aldehyde, leading to the formation of an intermediate imine that can be reduced to yield the oxazepane ring (Shaabani et al. 2019). Studies have investigated the molecular properties of this pharmaceutically important nucleus, which belongs to some natural products and biologically active compounds with antithrombotic, antiepileptic, anticonvulsant, anti-inflammatory, antifungal, progesterone agonist, antipsychotic, antagonist, analgesic, antihistaminic, anxiolytic, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitory, and antiaggregating activities (Hajishaabanha et al. 2014).

Various oxazepine derivatives have been found to possess a wide range of biological actions, including antibacterial, hypnotic, muscle relaxant, antiepileptic, and antimicrobial properties (Hamad et al. 2022).

Several recent studies have focused on developing novel oxazepane derivatives with enhanced antibacterial activity, as well as other therapeutic properties such as anti-inflammatory (Kherallah, B. A. 2014), anticancer (Abbas, A. K. et al. 2020), antitumor (Noser, A. A. et al. 2023), antifungal (Nazeri, M. T. et al. 2023), hypnotic muscle relaxant (Ramesh, G. et al. 2022), antiepileptic (Jumaa, F. H. et al. 2022), enzyme inhibitor (Allamy, A. K. N., & Mejbel, S. A. 2022), psychoactive drugs (Al-Mustafa, A. et al. 2023), and antidepressant (Momen, N. C. et al. 2022).

Overall, synthesizing oxazepanes as antibacterial agents holds promise for developing new treatments for bacterial infections. Following this route, we prepared some new oxazepine derivatives by condensing hydrazone with phthalic anhydride in the presence of ethanol.

Materials and Methods

All chemicals and solvents used were purchased from Fluka and Aldrich without additional purification. Melting points were recorded using a Stuart melting point apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded using KBr discs on a Shimadzu FTIR-8100 spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were measured using a 500 MHz spectrometer with DMSO-d6 as the solvent. Thin-layer chromatography (TLC) was used to monitor reactions and confirm the purity of the compounds, utilizing type 60 F254 Merck alumina sheets with silica gel.

Preparation of 2-chloroacetohydrazide (F1) (Wensink, M. et al. 2022):

To a solution of 0.1 mole of ethyl chloroacetate in 5 ml absolute ethanol, 0.2 mole of hydrazine dissolved in 5 ml absolute ethanol was added dropwise while maintaining the temperature below 5°C. The mixture was stirred for three hours. After the addition of hydrazine was complete, the mixture was filtered. The precipitate was collected, dried, and recrystallized from ethanol.

Preparation of hydrazone (F2-6) (Bondock, S. et al. 2006):

A mixture of 0.01 mole of F1 and 0.01 mole of aromatic benzaldehyde in 20 ml of absolute ethanol was centrifuged for one hour and then allowed to cool. The product was isolated by filtration and recrystallized from ethanol. The physicochemical characteristics of the produced compounds are listed in Table 1.

Preparation of 1,3-oxazepine (F7-11) (Rollas, S. et al. 2007):

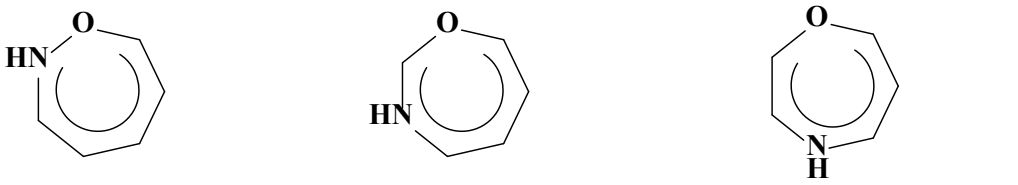
A mixture of 0.001 mole of phthalic anhydride and 0.001 mole of hydrazone derivatives in 25 ml of absolute ethanol was refluxed for four hours. The resulting product was filtered and recrystallized from ethanol. The physical characteristics of the created compounds are displayed in Table 2.

Biological Activity

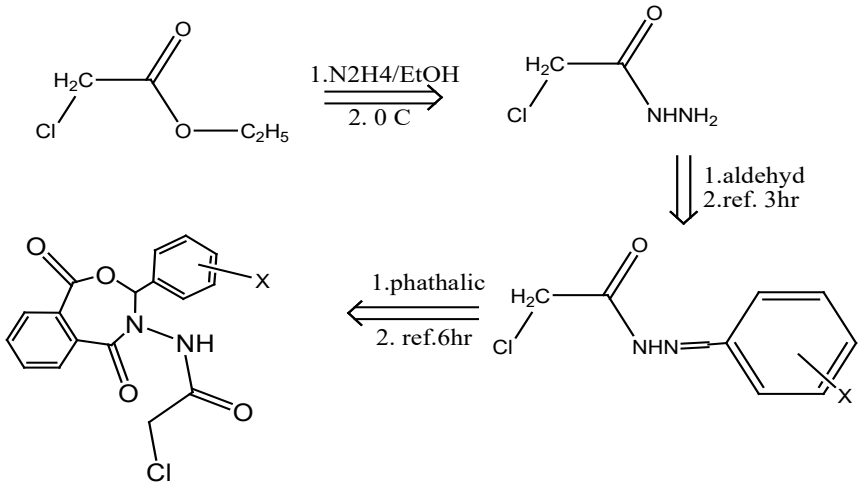
The biological activity was evaluated using the propagation technique. The Kirby-Bauer method was utilized to quantify biological activity by adding 0.1 ml of bacterial solution to Muller-Hinton agar dishes and allowing them to absorb the suspension for five minutes (Allamy, A. K. N., & Mejbel, S. A. 2022; Sadeek, G. T. et al. 2023). After making holes in each dish with a 5 mm diameter cork borer, the dishes were incubated for 24 hours at 37°C. Using amoxicillin and ciprofloxacin as control samples, 0.1 ml of each solution was added to the holes (Saleh, M. J., & Al-Badrany, K. A. 2023; Saleh, J. N., & Khalid, A. 2023). The inhibitory zone diameters surrounding each hole were measured in millimeters using the Prescott technique.

Molecular Docking Study of Some Prepared Compounds

Molecular docking investigations were performed using the Ministry of the Environment (MOE) program (version 2015.10) for several prepared compounds (F8-F13) against common bacterial strains, Escherichia coli and Staphylococcus aureus (Bae, J. Y. et al. 2022). The goal was to minimize the energy of the compounds to achieve the most stable conformation. The protein structures of Escherichia coli and Staphylococcus aureus were obtained from the Protein Data Bank. High-performance computing resources were used due to the demanding nature of these programs, which require sophisticated, multi-core processors for fast and efficient calculations, especially when working with large molecules and complex atomic configurations.



Scheme 1. Additionally, there are three isomers of oxazepine compounds, 1.2, 1.3, and 1.4-oxazepine (Gomha et-al 2016), which are numbered based on where the oxygen and nitrogen atoms are located in the heptagonal ring (Scheme 1)



Scheme 2. 1,3-Oxazepine derivatives are produced when the synthesized chemical (F8–13) reacts with phthalic anhydride.

Table 1. Physical properties and elemental analysis of prepared compounds (F2-7)

Comp. No.	X	Color	M.P (C^0)	Yield (%)	Molecular Formula
F2	**2,4-Cl**	**Wight**	**202-203**	**56**	**C9H7Cl3N2O**
F3	**4-F**	**Yellow**	**178-180**	**76**	**C9H8ClFN2O**
F4	**4-OCH3**	**Brown**	**160-162**	**85**	**C10H11ClN2O2**
F5	**4-Cl**	**Slight yellow**	**170-172**	**45**	**C9H8Cl2N2O**
F6	**4-CH3**	**Wight**	**105-107**	**63**	**C10H8ClN2O**
F7	**H**	**Yellow**	**123-125**	**79**	**C9H9ClN2O**

Table 2. Physical properties and elemental analysis of prepared compounds (F8-13)

Comp. No.	**X**	**Color**	**M.P(C^0)**	**Yield (%)**	**Molecular Formula**
F8	2,4-Cl	yellow	2017-2019	34	C17H11Cl3N2O4
F9	4-F	yellow	200-202	43	C17H12ClFN2O4
F10	4-OCH3	red	184-186	25	C18H15ClN2O4
F11	4-Cl	yellow	207-210	42	C17H12Cl2N2O4
F12	4-CH3	Wight	120-123	33	C18H15ClN2O4
F13	H	yellow	188-190	23	C17H13ClN2O4

Table 3. IR –spectral data of Compounds (F2-7)

IR (KBr) cm^{-1}					X	Comp. No.
Other	**(CH)Ar.**	**N-C=O**	**N-H**	**C=N**		
865 for C-Cl	3083	1664	3139	1618	**2,4-Cl**	F2
829 for C-f	3076	1674	3404	1631	**4-F**	F3
2800-2900 for CH3	3100	1672	3204	1598	**4-OCH3**	F4
817 for C-Cl	3097	1677	3182	1622	**4-Cl**	F5
2800-2900 for CH3	3010	1661	3242	1606	**4-CH3**	F6
--	3043	1664	3444	1618	**H**	F7

Table 4. IR –spectral data of Compounds (F8-13)

IR (KBr) cm^{-1}					X	Comp. No.
Other	**C=C**	**N-C=O**	**O-C=O**	**NH**		
865 for C-Cl	**1524**	**1643**	**1729**	**3233**	**2,4-Cl**	**F8**
829 for C-f	**1506**	**1674**	**1741**	**3404**	**4-F**	**F9**
2800-2900 for CH3	**1500**	**1667**	**1732**	**3198**	**4-OCH3**	**F10**
817 for C-Cl	**1509**	**1685**	**1746**	**3245**	**4-Cl**	**F11**
2800-2900 for CH3	**1503**	**1676**	**1733**	**3197**	**4-CH3**	**F12**
--	**1569**	**1664**	**1734**	**3444**	**H**	**F13**

Table 5. ^{1}HNMR of Compounds (F8-11)

^{1}HNMR chemical shift in ppm	X	Comp. No.
3.98 ppm for(2H,CH2) , 8.05 ppm for(H,NH) & (7.0-8.9 ppm) due to the phenyl group	**2,4-Cl**	**F8**
4.65 ppm for(2H,CH2) , 8.3 ppm for(H,NH) & (7.0-8.54 ppm) due to the phenyl group	**4-F**	**F9**
1.34 ppm for (3H,CH3), 4.34 ppm for(2H,CH2) , 8.07 ppm for(H,NH) & (7.1-8.8 ppm) due to the phenyl group	**4-OCH3**	**F10**
3.89 ppm for(2H,CH2) , 8.05 ppm for(H,NH) & (7.3-8.6ppm) due to the phenyl group	**4-Cl**	**F11**
1.25 ppm for (3H,CH3), 4.78 ppm for(2H,CH2) , 8.25 ppm for(H,NH) & (7.31-8.75 ppm) due to the phenyl group	**4-CH3**	**F12**
4.6 ppm for(2H,CH2) , 8.4 ppm for(H,NH) & (7.1-8.7 ppm) due to the phenyl group	**H**	**F13**

Table 6. molculer docking for compound f8-13 with *Escherichia coli* K-12 (ID; 4QGS)

					Escherichia coli K-12 (ID; 4QGS)		Comp.No.
S	rmsd	E (kcal/mol)	Distance	Interaction	Receptor	Ligand	
-6.87258	1.8088	-1.7	3.46	H-donor	HIS 281	N2	F8
		-1.9	3.17	H-Pi	Asn 190	O4	
		-0.7	3.31	Pi-H	Leu 139	6-ring	
-7.491719	5.3357	-0.9	3.32	H-donor	ASP 194	C1	F9
		-0.8	3.42	H-acceptor	GLY 95	O1	
-6.65746	1.3030	-6.5	2.75	H-donor	ASP 194	N2	F10
		-1.8	2.85	H-acceptor	ALA 282	O4	
		-4.2	2.89	H-acceptor	SER 96	O1	
-7.32933	1.1645	-1.5	3.07	H-acceptor	ASP 99	CL1	F11
					SER 96	O3	
-6.7494	4.8729	-0.6	4.67	pi-H	HIS 271	6-ring	F12
-6.6431	5.7267	-2.7	2.86	H-acceptor	HIS 271	O4	F13
		-0.7	3.71	Pi-H	VAL 151	6-ring	

Table 7. molculer docking for compound f8-13 with *Staphylococcus. Aurous* (ID; 7PQ1

Staphylococcus. Aurous (ID; 7PQ1)							Comp.No.
S	rmsd	E (kcal/mol)	Distance	Interaction	Receptor	Ligand	
-6.7436	4.412	-1.7	3.46	H-donor	HIS 348	N2	F8
-7.8308	4.413	-0.4 -0.5	3.18 4.24	H-donor H-acceptor	HIS 348 LEU 75	CL1 6-ring	F9
-8.9245	2.899	-0.7	3.70	H-acceptor	ARG 283	CL1	F10
-6.7258	4.4146	-0.7	3.72	H-acceptor	Leu 230	O3	F11
-7.16458	4.5701	-4.3 -0.9 -0.6 -0.8	2.80 3.29 3.58 3.74	H-acceptor H-acceptor pi-H pi-H	ASN 227 Cys 350 ALA 76 Cys 350	O3 O1 6-ring 6-ring	F12
-6.76346	3.47984	-2.9	2.81	H-acceptor	VAL 351	O4	F13

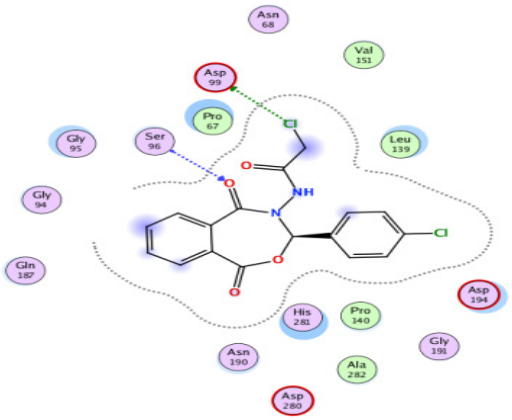


Figure 5. 2D interactions of compound F11 with 4QGS.

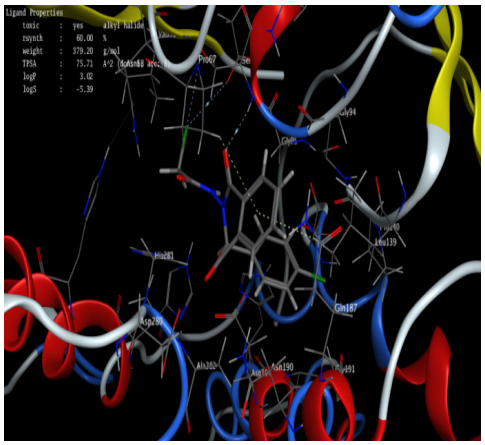


Figure 6. 3D interactions of compound F11 with 4QGS.

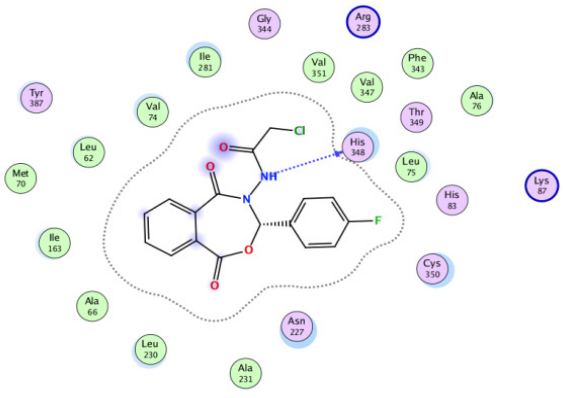


Figure 7. 2D interactions of compound F9 with 7PQ1.

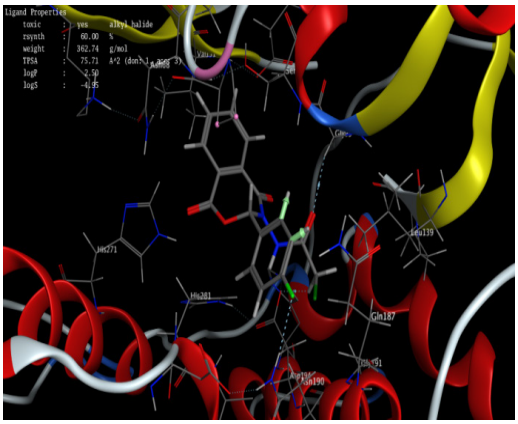
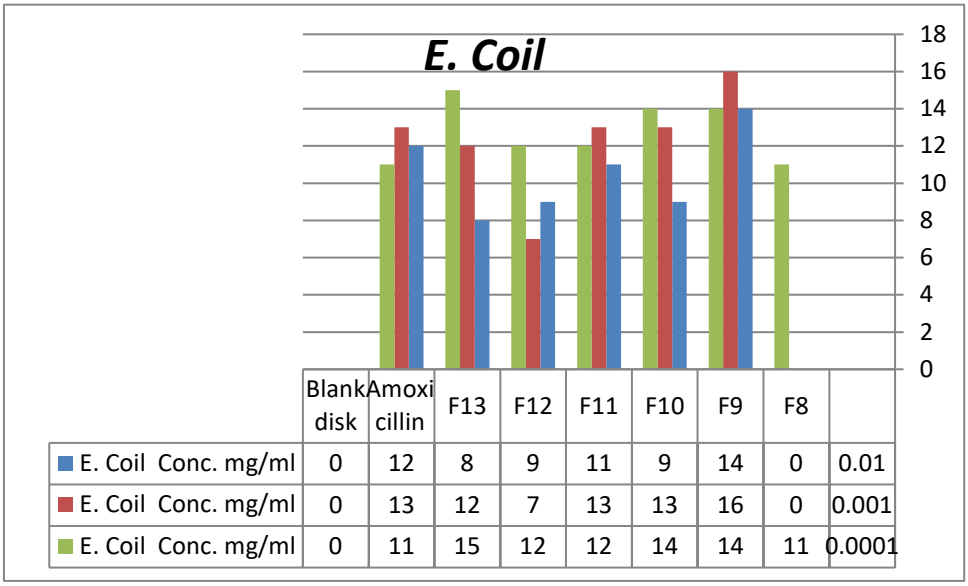
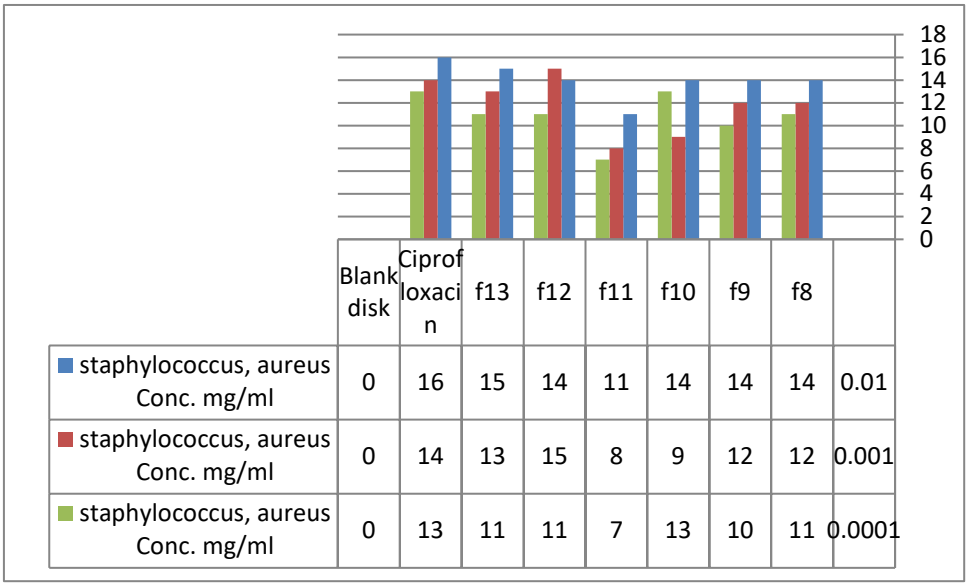


Figure 8. 3D interactions of compound F9 with 7PQ1.



	Blank disk	Amoxicillin	F13	F12	F11	F10	F9	F8	
E. Coil Conc. mg/ml	0	12	8	9	11	9	14	0	0.01
E. Coil Conc. mg/ml	0	13	12	7	13	13	16	0	0.001
E. Coil Conc. mg/ml	0	11	15	12	12	14	14	11	0.0001

Figure 9. Differential effect and different concentrations of compounds (F8-13) studied against bacteria (*E.Coli*).



	Blank disk	Ciprofloxacin	f13	f12	f11	f10	f9	f8	
staphylococcus, aureus Conc. mg/ml	0	16	15	14	11	14	14	14	0.01
staphylococcus, aureus Conc. mg/ml	0	14	13	15	8	9	12	12	0.001
staphylococcus, aureus Conc. mg/ml	0	13	11	11	7	13	10	11	0.0001

Figure 10. Differential effect and different concentrations of compounds (F8-13) studied against bacteria (*staphylococcus, aureus*)

Results and Discussion

Characterization of Acid Hydrazide (F1):

As mentioned in the experimental section, 2-chloroacetohydrazide was synthesized using hydrazine hydrate and ethyl 2-chloroacetate. The infrared spectra of this compound displayed stretching bands at 3417, 3218, and 2960 cm^{-1}, corresponding to the symmetrical and asymmetrical bands of the NH2 and NH groups, as well as the CH group. The carbonyl group for acid hydrazide was assigned to the band at 1666 cm^{-1} (Figure 7).

Characterization of Hydrazones (F2-6):

By reacting 2-chloroacetohydrazide with aromatic benzaldehyde in the presence of ethanol, several hydrazone compounds (F2-6) were created. The synthesized compounds' structures were verified using IR spectroscopy, ^1H-NMR, and ^13C-NMR, along with their melting points. Tables 3 to 5 and Figure 8 display the typical absorption bands (KBr cm^{-1}).

Characterization of 1,3-Oxazepine (F8-13):

1,3-Oxazepine derivatives were produced when the synthesized compounds (F8-13) reacted with phthalic anhydride. The structure of the synthesized compounds was validated by their melting points and ^1H-NMR and IR spectroscopy. Tables 4 and 5, as well as Figures 9 and 10, display the distinctive absorption bands (KBr cm^{-1}).

Evaluation of Biological Activity:

Numerous synthesized compounds (F8, F9, F10, F11, F12, and F13) were tested against various bacterial strains using the cup plate agar diffusion technique. These strains included Gram-positive bacteria, Staphylococcus aureus, and Gram-negative bacteria, Escherichia coli (Talluh, A. W. A. S. 2024; Lgaz, H., & Lee, H. S. 2022). After an eight-hour incubation period at 37°C, 0.8% sterile saline was added to the microbial cultures to dilute them. The concentration of the medication solution in DMSO was kept constant at 100 µg/mL. Amoxicillin and ciprofloxacin were used as standards, while DMSO was the negative control.

Anti-Bacterial Screening for Selected Compounds:

Some of the selected compounds showed acceptable efficacy against the bacteria. Compound 9 was highly effective against E. coli, comparable to the strength of the drugs used for comparison. Compounds 11 and 13 showed activity against E. coli close to the drugs. Compounds showed less activity against Staphylococcus aureus compared to the drug used for comparison. The rest of the prepared compounds exhibited varying activities from weak to medium, close to the activity of amoxicillin and ciprofloxacin. Gram-positive bacteria are dense and lack an external lipid membrane, whereas Gram-negative bacteria have an external lipid membrane and a small peptidoglycan layer. The compounds have the ability to affect both the peptidoglycan of the wall and the outer lipid membrane of the bacteria. The biological activity was measured using the diameter of the inhibition zones surrounding the disks (Jawad, M., & Adnan, S. 2023; Jebur, H. K. et al. 2020) (Figures 5 and 6).

Molecular docking

MOE, 2015.10, was used for all molecular modeling investigations—energy conservation measures. The goal of the experiment was to determine the biological activities of the chemical (f8-13) (ligand) docking with several protein receptors, e.g., Escherichia coli K-12 (ID; 4QGS) crystal structure (Esharkawy, E. R.et-al 2022). Acquired from the Protein Data Bank, staphylococcus aureus (ID: 7PQ1)(LaMattina, J. W.et-al 2015),(Snee, M., Levy et-al 2022). Preparing the protein for docking experiments involved atoms of hydrogen added to the protein while water molecules were disregarded. The protein's active site was searched using MOE Site Finder, which was then used to dock the newly targeted structures and remove the co-crystallized ligand. Table 6 displayed the docking's computed energies, affinities, and hydrogen bond distance. As seen in Fig. (1-4), the results verified the potent intra-hydrogen bonding interaction between protein and 1,3-oxazepine derivative hydrogen bond. In the current work, we explored the binding interactions of all substances with the amino acids inside the E. coli active site using molecular docking. For this reason, the protein data bank files (PDB: 4QGS and PDB: 7PQ1) were used. The MOE (Molecular et al.) software 2015.10 was used for all docking processes. Re-docking the ligand near the protein's active site using root mean standard deviation (RMSD) allowed for verifying the docking procedure. The ligands interact with the active site, such as a hydrogen-bonding amino acid. Tables (6,7) and Figs. 1–4 list the energy scores (S) and amino acid interactions for each docked molecule that fits the protein's active site.

Conclusion

This study successfully synthesized and characterized novel oxazepine derivatives through a cycloaddition procedure, involving the reaction of chloroacetohydrazide with various aromatic aldehydes to produce hydrazone compounds, which were subsequently transformed into oxazepine derivatives via reaction with phthalic anhydride. The compounds (F1 to F13) were thoroughly characterized using FT-IR and ^1H-NMR spectroscopy. Evaluation of their antibacterial activity revealed that several synthesized compounds, particularly F8, F9, and F10, exhibited potent antibacterial activity against both Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacterial strains. Molecular docking studies further supported the potential of these compounds as effective antibacterial agents by demonstrating their stable binding interactions with bacterial protein receptors. Overall, these findings highlight the promising biological activities and potential therapeutic applications of the synthesized oxazepine derivatives.

Author contributions

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

Acknowledgment

Authors were grateful to their department, Chemistry Department, College of Education for Pure Sciences, Tikrit University.

Competing financial interests

The authors have no conflict of interest.

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