



Design And Biological Evaluation Of New 1,3-Oxazepine,4,7-Dione Based Heterocycles As Potential Antibacterial And Anticancer Agents Dhamer Ismael Madab

Open Education college – Dujail Branch – Ministry of Education

Correspondence. www.dhammer.84@gmail.com

Abstract:

Heterocyclic scaffolds play a crucial role in drug discovery, as their versatile structures interact strongly with biological targets. This study aims to synthesize Schiff base derivative S precursor by condensing

1-[(1-methyl-1H-pyrazol-4-yl)methyl]-1H-imidazol-2-amine with 2-hydroxy-4-methylbenzaldehyde under reflux in ethanol with glacial acetic acid as a catalyst. This schiff base derivative was cyclized with malic, phthalic, succinic, or glutaric anhydride in dry benzene under reflux for 14-15 hours to of four 1,3-oxazepine-4,7-dione derivatives (OI-OIV). The products were purified by recrystallization in dry 1,4-dioxane and confirmed using FTIR, ¹H NMR, and ¹³C NMR spectroscopy. The antibacterial activity was evaluated using the cup-plate diffusion method against *Staphylococcus spp.*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* at concentrations of 0.1, 0.001, and 0.00001 mg mL⁻¹, these derivatives OI-OIII, inhibited *Staphylococcus* at 29 mm and 28 mm zones of inhibition, respectively, at 0.1 mg mL⁻¹, approaching the zone of inhibition of azithromycin (28 mm), while Gram-negative strains showed weaker responses. Cytotoxic activity against the MCF-7 breast cancer cell line revealed dose-dependent reductions in cell viability, with derivative OIII have an IC₅₀ as 48.88 and derivative OIV had an IC₅₀ as 45.99. *In silico*, molecular docking study against dihydrofolate reductase (PDB ID: 4P66) by using MOE software showed that derivative OI (ligand A) in pose 1 achieved a binding affinity of (-7.48 kcal/mol) and formed four hydrogen bond interactions SER49, ASP27, and MET20, which that supported by favorable placement and refinement energies, while ADMET predictions by using swissADMET indicated high gastrointestinal absorption, good solubility, and moderate bioavailability.

Keywords: Antibacterial, Anticancer, Oxazepine-4,7-dione, Schiff base.



Introduction

Heterocyclic compounds is a play a big role as essential modern medicinal sciences because their versatile ring systems with some interaction bonds with biological targets [Ebenezer et L.,2022], and these compounds, such s 1,3-oxazepine-4,5-dione derivatives have been widely study as antimicrobial, anticancer, and enzyme-inhibitory properties, in addition to anticorrosion (Muhee & Kabhim, 2024). These structures using to improve binding with enzymes active sites (Kumar & Goel,2022). In recent studies, researchers have designed 1,3-oxazepine-4,7-dione derivatives that target to binds with dihydrofolate reductase (DHFR) protein, a recognized antibacterial enzyme, to suppress the development of bacteria (Ali et al., 2023), These results suggest that 1,3-oxazepine-4,5-dione compounds replacement patterns change binding pocket hydrogen bonding systems and hydrophobic interactions, which affect biological function (Jawad et al., 2023).

DHFR is a key folate cycle enzyme that found in *Escherichia coli* [Singh et al., 2021], and using a cofactor needed to synthesize heterocyclic, and amino acids. The inhibiting with this enzyme stops nucleotide production and DNA replication, stopping bacterial development, and this mechanism is used in various antibacterial drugs ([Moreira et al., 2024). The some heterocyclic used as inhibitors with selectivity and pharmacokinetics are needed to overcome resistance and toxicity, and recent developments in silico, such as molecular docking and molecular dynamic screening that accurately anticipate ligand-enzyme associations, allowing rational drug design during synthesis (Kar, 2025).

1,3-Oxazepine compounds is a unsaturated heterocycles group that have seven atoms, with one position, a nitrogen atom takes the place of a carbon atom, and in another position, an oxygen atom takes the place of a carbon atom (Malki et al., 2021). The study looks at how similar drugs are and how they move through the body using ADMET modeling to guess how they will be absorbed and if they are safe (Shiney et al., 2024). In this study, we synthesized a new 1,3-oxazepane bearing schiff base that was synthesized by aldehyde and primary amine aromatic, then reacted with imine with anhydride compounds. These derivatives characterized by spectroscopy, such as FTIR, ^1H -NMR, and ^{13}C -NMR,

and study molecular docking via synthesized derivatives with target protein as DHFR (PDB ID: 4P66). The compounds antibacterial activities tested against different bacteria, and cytotoxic effects were evaluated against the MCF-7 cell line. Finally, ADMET profiling was performed to assess solubility, permeability, and compliance with drug-likeness rules.

Experimental Part

Materials

All materials used without further purification, such as 1-[(1-methyl-1H-pyrazol-4-yl)methyl]-1H-imidazol-2-amine (95% purity, BLD Pharm), 2-hydroxy-4-methylbenzaldehyde (98% purity, Merck), malic anhydride (99% purity, Sigma-Aldrich), phthalic anhydride (99% purity, Merck), succinic anhydride (98% purity, BDH Chemicals), glutaric anhydride (98% purity, Sigma-Aldrich), glacial acetic acid (99.7% purity, Merck), absolute ethanol (99.8% purity, Scharlau), anhydrous benzene (99.5% purity, Merck), and anhydrous 1,4-dioxane (99.5% purity, Scharlau).

Synthesis of Schiff base derivative (s)

A (1.77 g, 0.01 mol) of 1-[(1-methyl-1H-pyrazol-4-yl)methyl]-1H-imidazol-2-amine and (1.36 g, 0.01 mol) of 2-hydroxy-4-methylbenzaldehyde were mixed and dissolved in 20 mL of absolute ethanol, and added 3 drops of glacial acetic acid as a catalyst. The mixture was reflux for 3 hours, and after cooling in room temperature, a solid precipitate formed after filtered. The precipitate was collected and washed with ethanol, according to the reported procedure [Hamid & Salih, 2022]. The synthesized derivative had a molecular weight of 295.346 g/mol, and molecular formula of $C_{16}H_{17}N_5O$, with melting point (192-196 °C), yield 71% and yellow color.

Table 1. Summary of the Synthesis of Schiff base derivative (S)
 $C_{16}H_{17}N_5O$.

Step	Operation	Details/Conditions
1	Reagents weighed	1.36 g (0.01 mol) aldehyde
2	Solvent added	20 mL absolute ethanol
3	Catalyst introduced	2–3 drops glacial acetic acid
4	Reagents weighed	1.77 g (0.01 mol) imidazol-amine
5	Reflux reaction	3 hours under constant heating
6	Cooling	Room-temperature cooling to induce precipitation
7	Product isolation	Vacuum filtration followed by washing with cold ethanol
8	Drying	Ambient drying to remove residual solvent
9	Purification	Recrystallization from ethanol

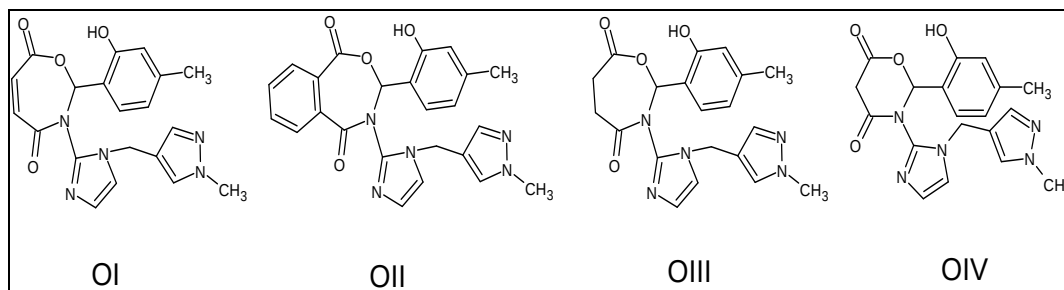
Synthesis of 1,3-Oxazepine-4,7-dione derivatives (OI-OIV)

A weighed amount of Schiff base S (0.01 mol) was combined with an equimolar quantity (0.01 mol) of each selected anhydride derivative: malic anhydride (0.98 g), phthalic anhydride (1.48 g), succinic anhydride (1.00 g), or glutaric anhydride (1.14 g). The mixture was dissolved in 20 mL of dry benzene and transferred to a round-bottom flask fitted with a condenser. The reaction mixture was refluxed under continuous heating for 15 hours. After cooling to room temperature, the solid product was isolated by filtration. The collected crystals were washed with small portions of cold benzene and recrystallized from dry 1,4-dioxane to afford the pure derivatives OI-OIV as colored crystalline solids [Abbas & Jber, 2020]. The physico properties of derivative OI, molecular weight 393.403, yield 68%, and molecular formula $C_{20}H_{19}N_5O_4$ and light yellow. Derivative OII, molecular weight 443.463, yield 72%, and molecular formula $C_{24}H_{21}N_5O_4$ and brown. Derivative OIII, molecular weight 395.419, yield 67%, and molecular formula $C_{20}H_{21}N_5O_4$ and light brown.

Derivative OIV, molecular weight 381.392, yield 74%, and molecular formula $C_{19}H_{19}N_5O_4$ and brown yellowish.

Table 2. Summary of the Synthesis of 1,3-Oxazepine-4,7-Dione Derivatives (OI–OIV).

Step	Operation	Details and Conditions
1	Reactant preparation	0.01 mol Schiff base S
2	Solvent addition	20 mL dry benzene
3	Anhydride selection	0.01 mol: malic, phthalic, succinic, or glutaric
4	Reaction	Reflux for 14 hours under constant heating
5	Cooling	Mixture allowed to cool to room temperature
6	Product isolation	Filtration to collect the solid product
7	Washing	Rinsed with small portions of cold benzene
8	Purification	Recrystallized from dry 1,4-dioxane
9	Product description	Colored crystalline derivatives OI-OIV obtained



Scheme 1. Routes of synthesis of 1,3-Oxazepine-4,7-dione derivatives (OI–OIV).
Antimicrobial Evaluation of Chalcone Derivatives OI–OIII

The antibacterial activity of derivatives OI–OIII was investigated using cup-plate agar diffusion. *Staphylococcus aureus* and *Escherichia coli* from clinical infections were examined with compounds at 0.1, 0.001, and 0.00001 mg/mL. Muller-Hinton agar discs were coated with bacterial suspensions and filled with DMSO-based test solutions in 12 mm wells (ceftriaxone in sterile water). After 1 hour of pre-diffusion, plates were incubated at 37 °C for 48 hours. Each derivative's antibacterial activity

was compared to the reference using the millimeter inhibition zones (Chen et al., 2023, Hu et al., 2023).

Applying the Intron Biotech MTT readily available kit, several synthesized compounds were tested for cytotoxicity

Following manufacturer instructions, synthesized compounds were evaluated for cytotoxicity against MCF-7 breast cancer cells using the MTT assay. MCF-7 cells were seeded at 4.5×10^5 per well in sterile 96-well plates with 200 μ L of growth medium. To improve cell adherence, plates were sealed with parafilm, spun gently, and incubated at 37 °C in 5% CO₂ for 24 hours. After incubation, cells were treated with produced derivatives at dosages of 0, 20, 40, 80, 160, and 320 μ g/mL using a 2-fold serial dilution. Each concentration, including the untreated control, was triple-tested for statistical validity, and controlled 24-hour plate incubation. Following drug exposure, 10 μ L MTT solution was added to each well and incubated for 4 hours to convert MTT into insoluble formazan crystals by metabolically active cells. After incubation, remove supernatant and dissolve formazan with 100 μ L DMSO per well to preserve crystals. The plates melted after 5 minutes of moderate shaking. German Bio-Rad ELISA microplate reader detected 575 nm absorbance (Eneama & Salman, 2024).

Molecular Docking

The Protein Data Bank provided 4P66's validated biological macromolecule crystal structure, and water at the active site enzyme stabilizes the ligand-receptor hydrogen bond, hence it was maintained. Restoring bonds from X-ray diffraction and adding all hydrogen atoms repaired the structure. Folate manufacturing needs dihydrofolate reductase to convert dihydrofolate to tetrahydrofolate in *Escherichia coli*. This mechanism facilitates purine and thymidylate synthesis for DNA replication. By blocking this enzyme, bacteria cease developing (Selvaraj et., 2022). The MOE (2019) computed all docking and scoring, and obtained the 1.84 Å crystal structure of 4P66 from the Protein Data Bank, a reliable source for macromolecular data, with resolution of 1.5 to 2.5 Å improves binding prediction accuracy in docking investigations (Obaid & Saliem, 2024).

Results and Discussion

The FTIR spectrum of Schiff base derivative S, shown appeared a new band of imine groups at 1631, while broad band of OH at 3343 and disappeared primary amine group, while the ^1H NMR spectroscopy (ppm) showed a (s, 1H, C=NH) at 8.51, (1, 1H, OH) at 10.58, 8.51 as (s, 1H, HC=N), and (m, 7H, Ar) at 7.23-7.78, and (s, 3H, methyl) at 2.87, as shown in Figure 1 and 2.

The FTIR spectrum of derivatives OI, OII, OIII, OIV showed a new bands carbonyl lactone groups showed at 1728, 1722, 1720, and 1743, in addition to carbonyl lactam 1651, 1655, 1647, and 1643, respectively, while the hydroxyl groups appeared at 3375, 3344, 3379, and 3379. The derivative OI, the 9.69 showed as (s, 1H, OH), 7.08-8.05 for (m, 11H, Ar.), 5.41 as (s, 2H, methylene), 3.83 as (s, 3H, methyl), while the derivative OII, the 9.29 showed as (S, 1H, OH), 7.08-8.05 for (m, 11H, Ar.) [18], 5.42 as (s, 1H, methylene in oxazepine ring), 4.68 as (s, 3H, methyl). The derivative OIII, the 9.37 showed as (S, 1H, OH), 7.14-7.98 for (m, 7H, Ar.), 5.41 as (s, 2H, methylene), 3.70 as (s, 3H, methyl), 2.59-2.87 as (terta, 2H, methylene in oxazepine ring), and The derivative OIV, the 9.46 showed as (S, 1H, OH), 7.14-7.81 for (m, 7H, Ar.), 5.64 as (s, 2H, methylene), 3.72 as (s, 3H, methyl), 3.95 as (s, 2H, methylene in oxazepine ring) (Ali et al., 2023). The ^{13}C -NMR spectroscopy (ppm) of derivative OI, 161 and 165 for carbonyl carbon, 115-155 for aromatic carbons, 84 for methylene in oxazepine ring, 43 for carbon of methylene group, and 20 and 38 for carbons of methyl groups, derivative OII showed 164 and 167 for carbonyl carbon, 115-155 for aromatic carbons, 85 for methylene in oxazepine ring, 43 for carbon of methylene group, and 20 and 38 for carbons of methyl groups (Khalat, 2025), derivative OIII showed 172 and 173 for carbonyl carbon, 115-158 for aromatic carbons, 88 for methylene in oxazepine ring, 48 for carbon of methylene group, and 27 and 40 for carbons of methyl groups, 35 and 47 for carbons of methylene groups at oxazepine ring. Finally, derivative OIV showed 171 and 166 for carbonyl carbon, 117-153 for aromatic carbons, 90 for methylene in the oxazepine ring, 45 for the carbon of the methylene group, and 23 and 36 for carbons of methyl groups, 43 for carbons of

methylene groups at the oxazepine ring (Hassan & Hame, 2019), as shown in Figures 3-14.

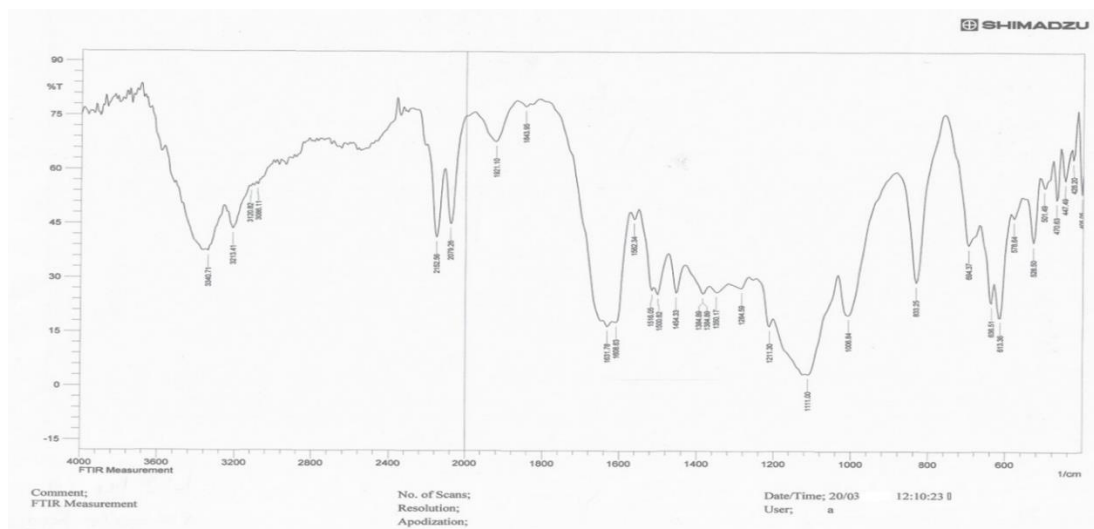


Figure 1. FTIR spectrum of derivative S.

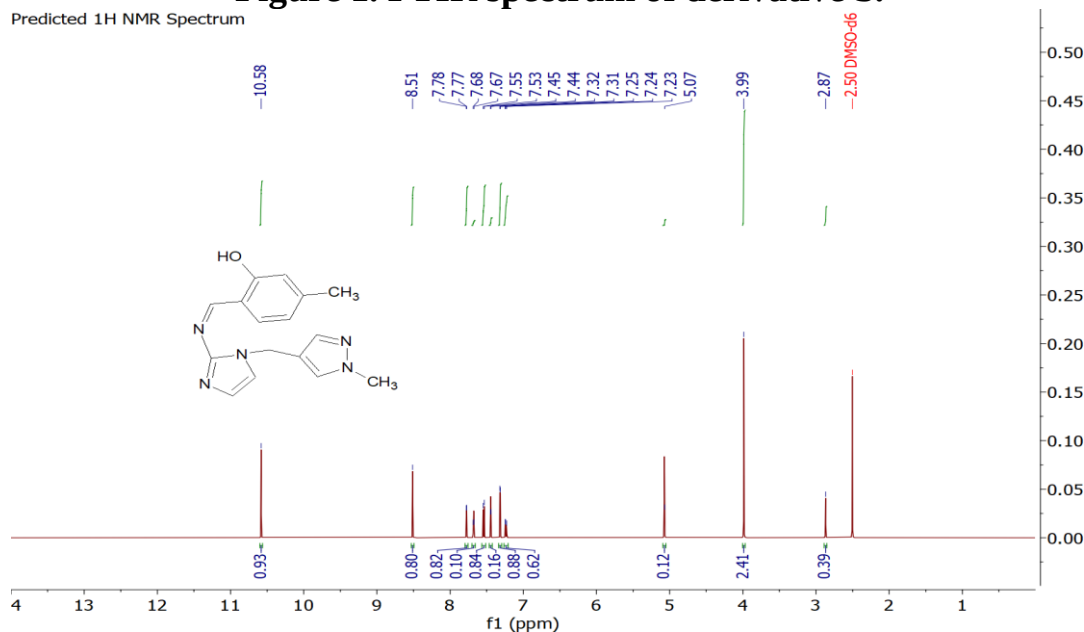


Figure 2. ¹H-NMR spectrum of derivative S.

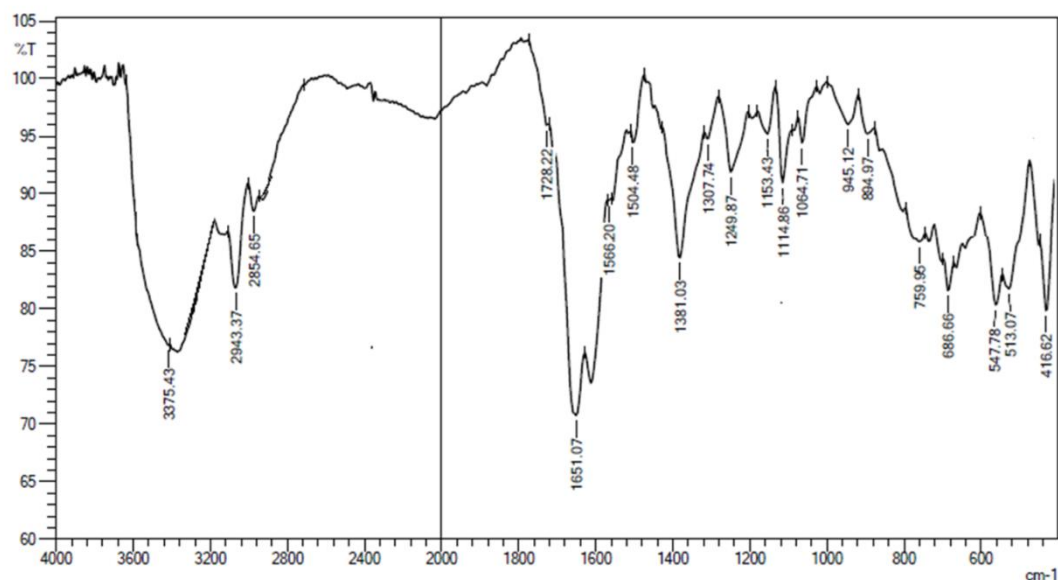


Figure 3. FTIR spectrum of derivative OI.

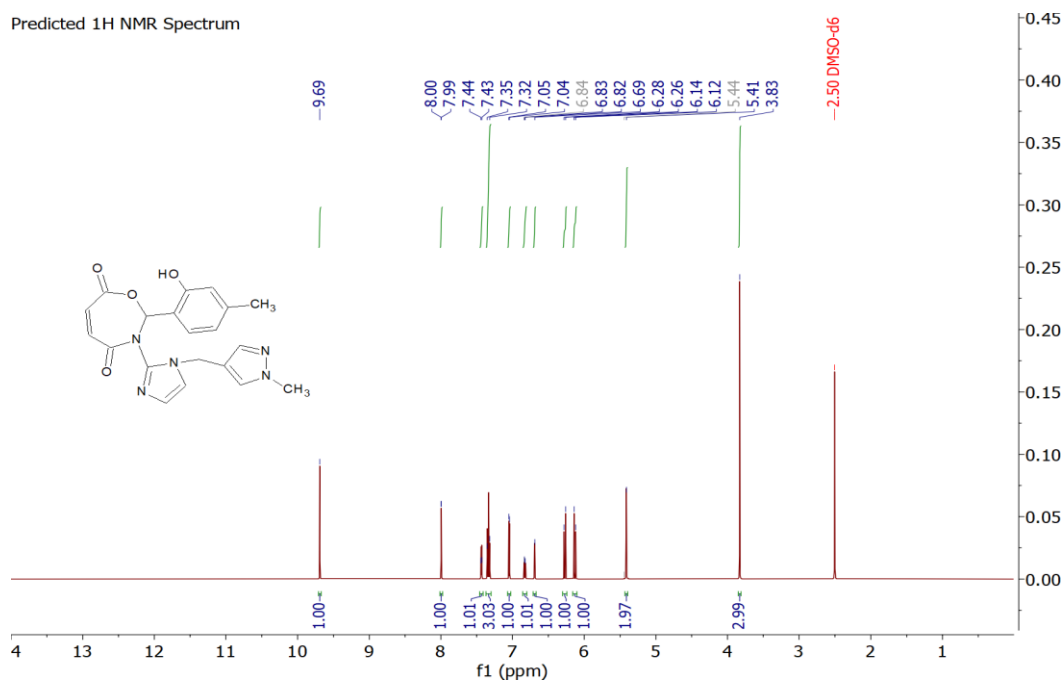
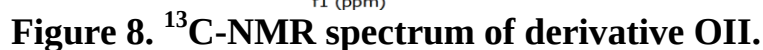


Figure 4. ¹H-NMR spectrum of derivative OI.



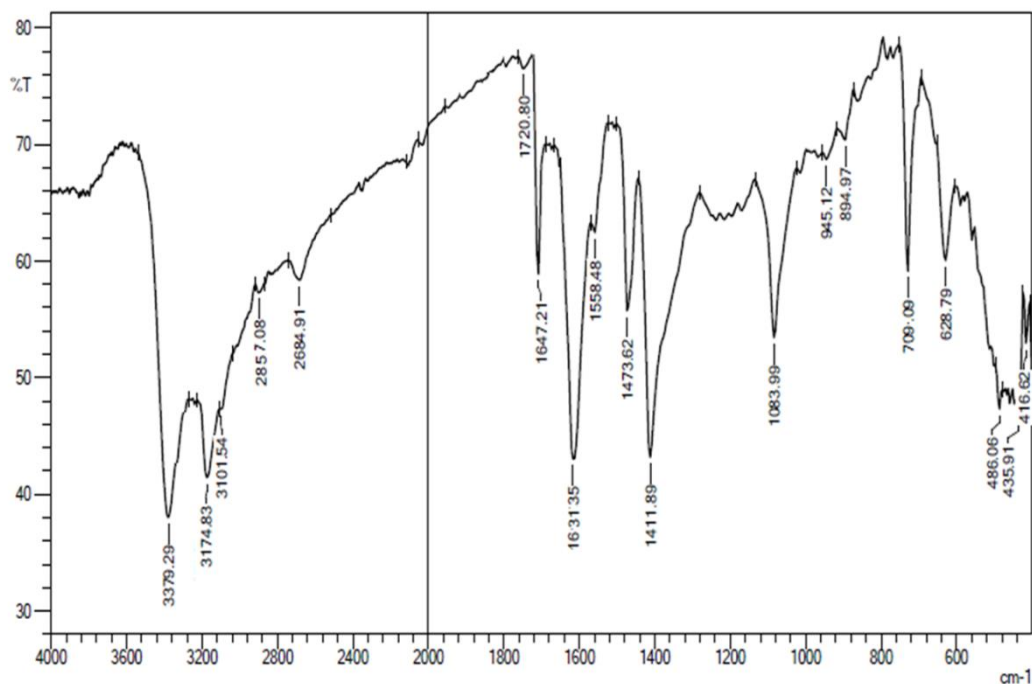


Figure 9. FTIR spectrum of derivative OIII.

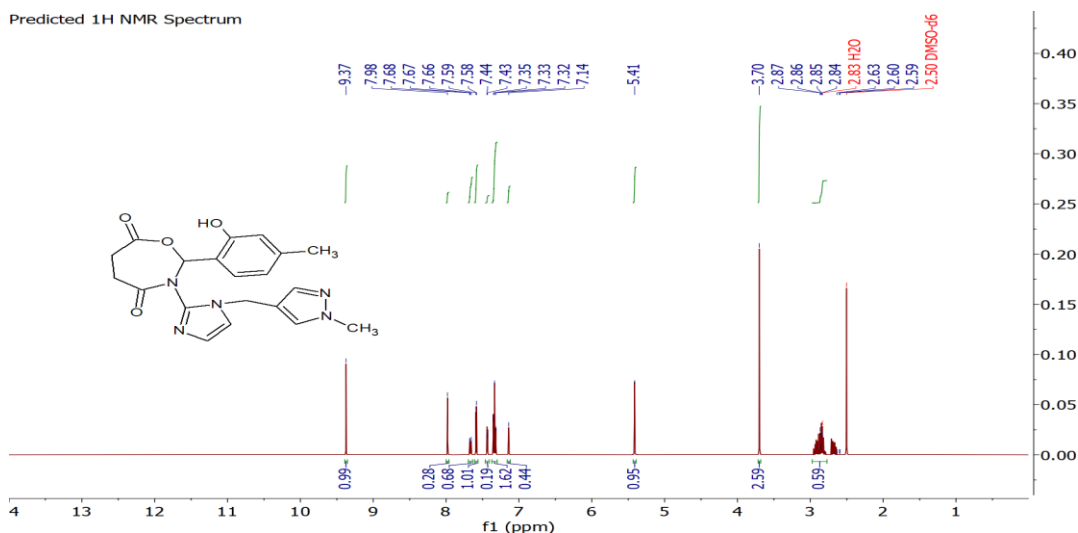
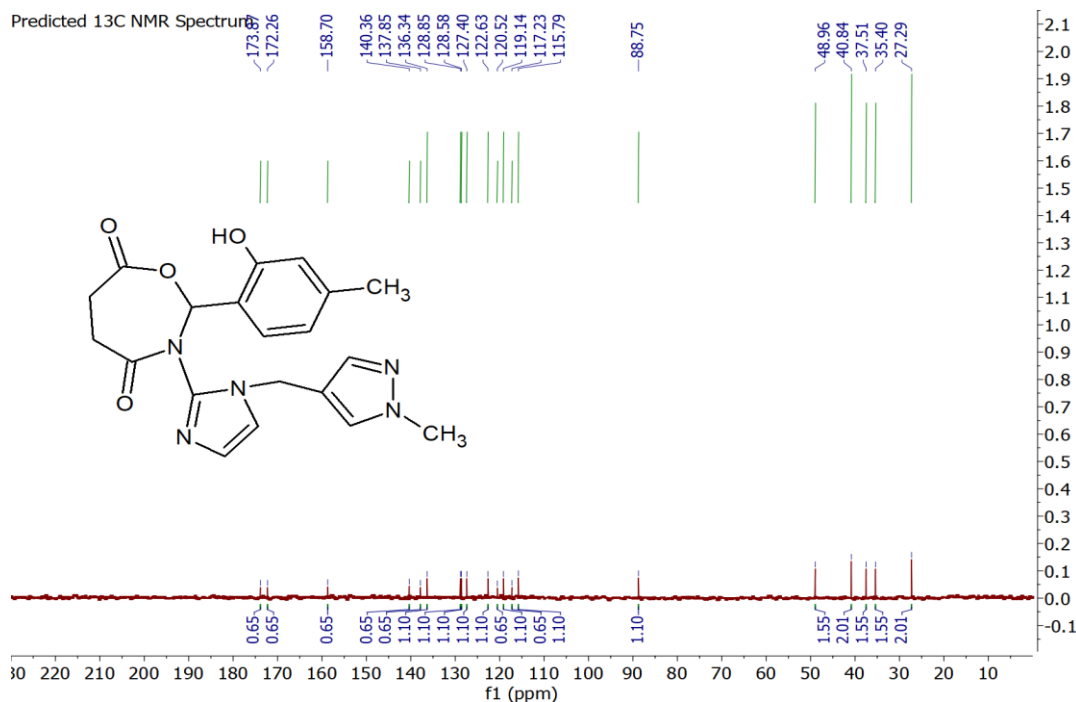
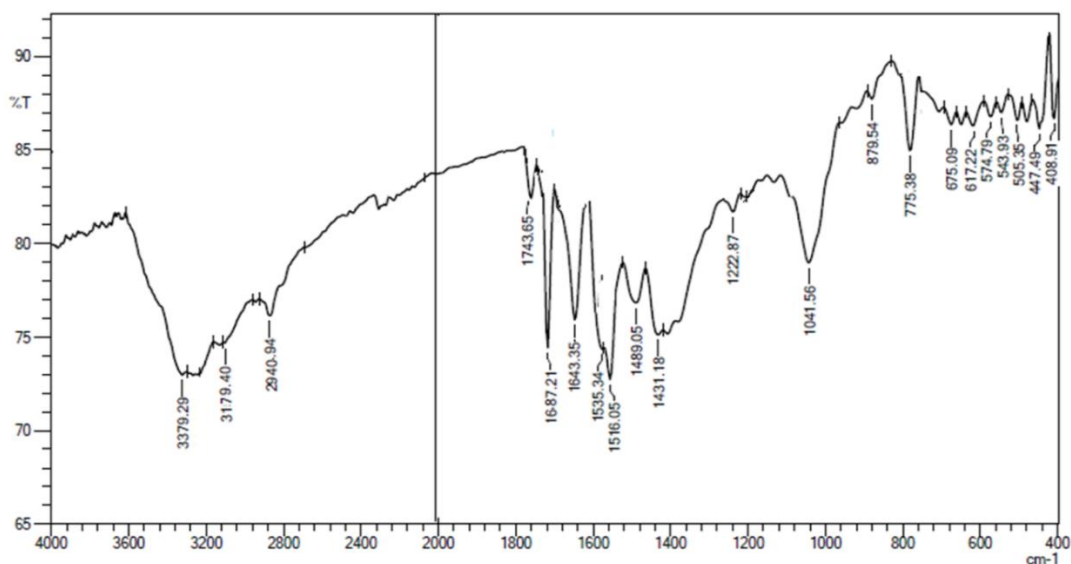


Figure 10. ¹H-NMR spectrum of derivative OIII.



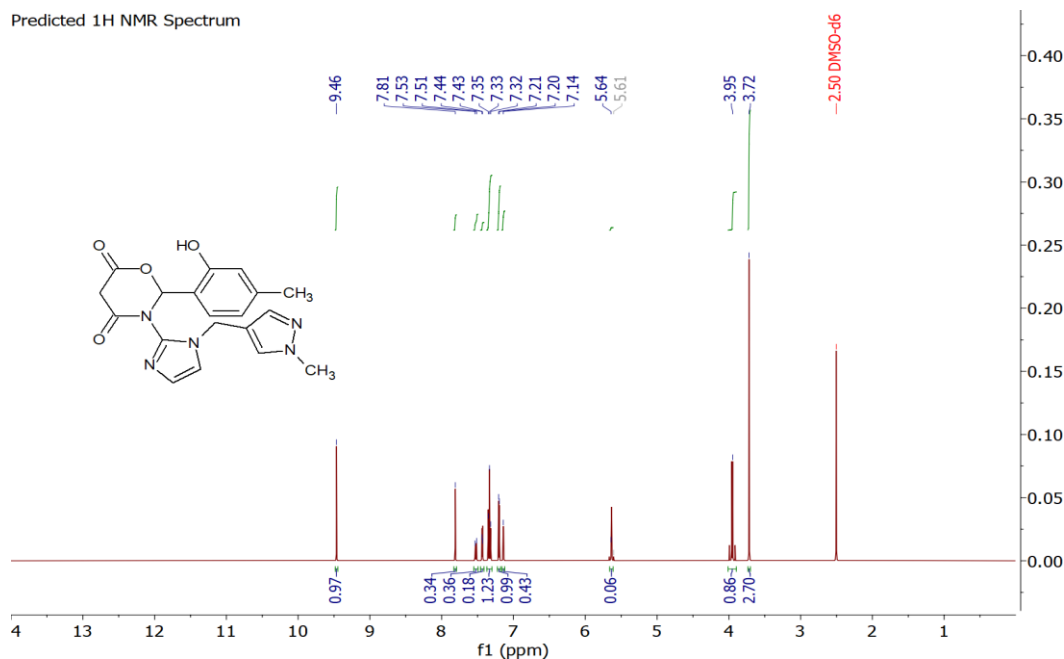


Figure 13. ^1H -NMR spectrum of derivative OIV.

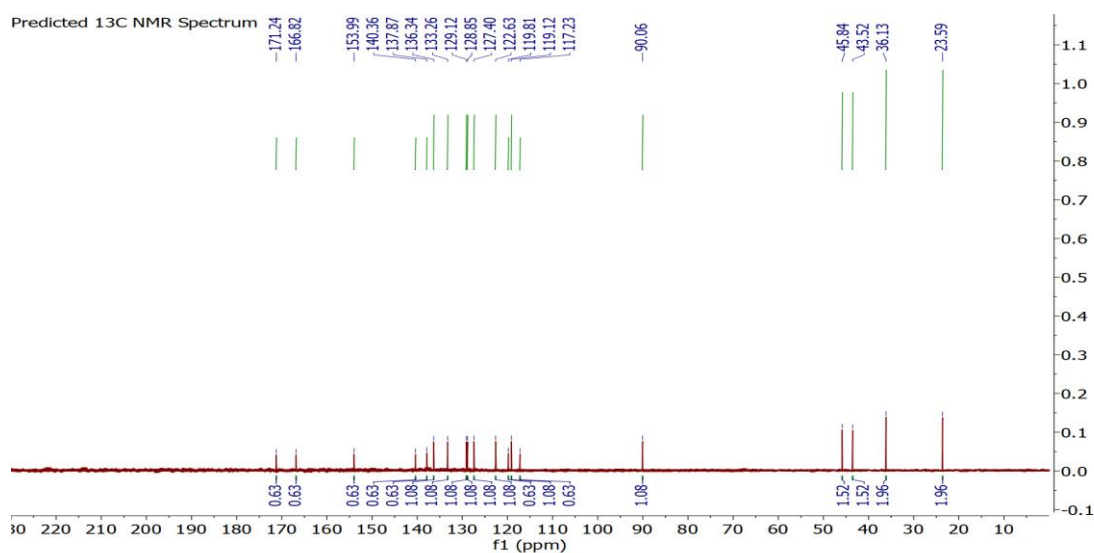


Figure 14. ^{13}C -NMR spectrum of derivative OIV.

Applications:

1. Anti-Bacteria

Antibacterial activity of 1,3-oxazepine-4,5-dione derivatives varies across studied bacterial strains and is closely related to concentration, at 0.1 mg/mL, derivatives O II and O I showed significant effectiveness against *Staphylococcus*, resulting in inhibition zones at 29 mm and 28 mm, that equivalent to azithromycin. This effectiveness decreased significantly with concentration, demonstrating a dose-dependent response, and shows that final products core interacts well with bacteria's peptidoglycan-rich cell walls, especially at greater exposure levels, supporting prior heterocyclic system results.

Streptococcus pneumoniae was inhibited by final product derivatives B6 and B1 at high concentrations, and these derivatives have increased action because their substituents can penetrate the organism's polysaccharide capsule. Fewer bacteria were sensitive, known permeability barriers and efflux systems, such as inhibited *Pseudomonas aeruginosa*'s reactivity. The low sensitivity of *E. coli* indicated limited chemical penetration, and results highlight structural features and particle size distribution because nanoscale uniformity may increase surface reactivity and antibacterial effectiveness.

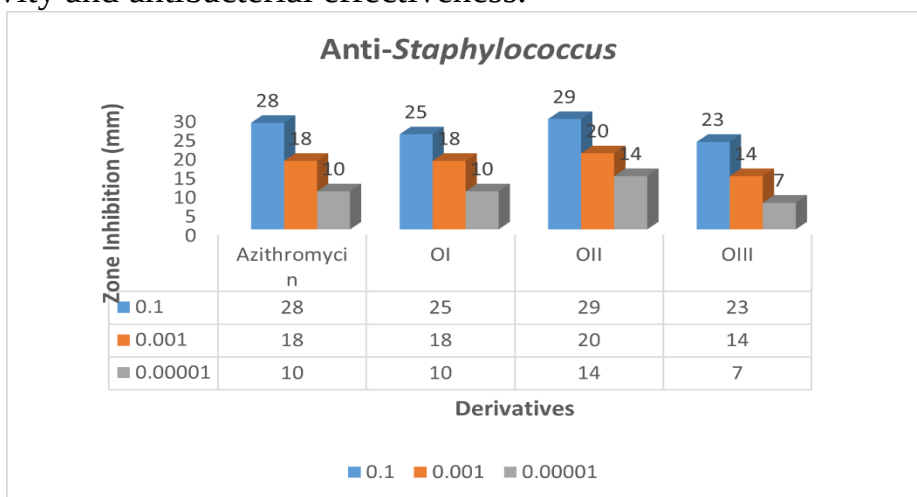


Figure 15: Zone of inhibition of 1,3-oxazepine derivatives (OI-OIII) against *Staphylococcus* spp. at three concentrations compared with azithromycin.

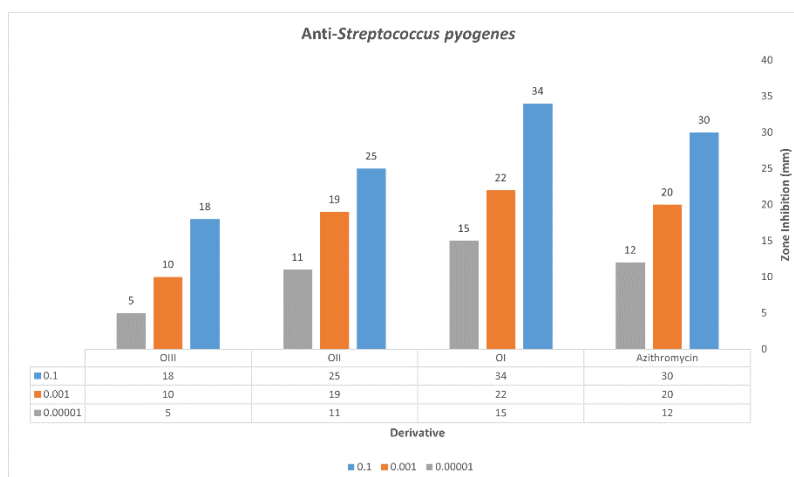


Figure 16: Zone of inhibition of 1,3-oxazepine derivatives (OI-O III) against *Streptococcus pneumoniae* at three concentrations compared with azithromycin.

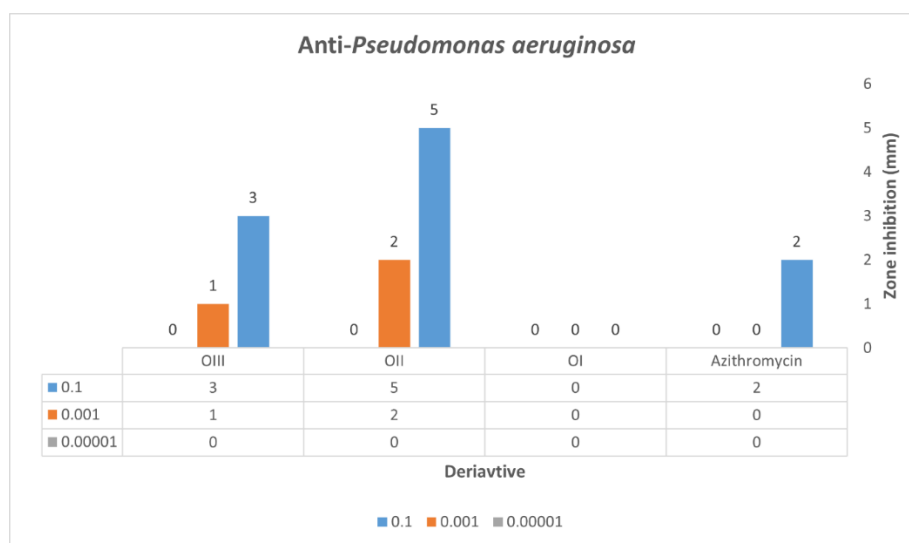


Figure 17: Zone of inhibition of 1,3-oxazepine derivatives (OI-OIII) against *Pseudomonas aeruginosa* at three concentrations compared with azithromycin.

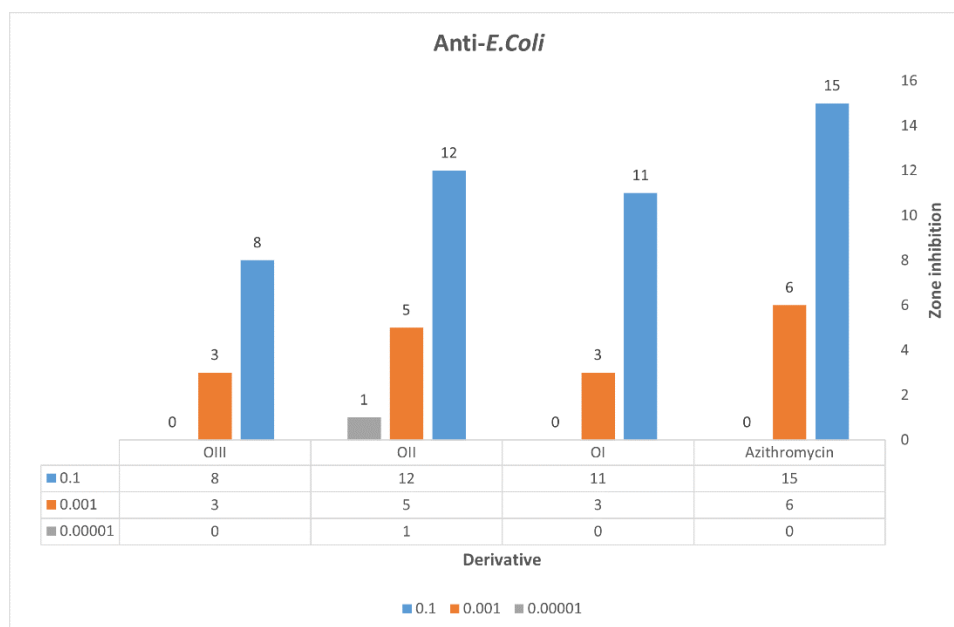


Figure 18: Zone of inhibition of 1,3-oxazepine derivatives (OI-OIII) against *E. coli* at three concentrations compared with azithromycin.

Anti-breast cancer MCF-7 cell line

The 1,3-oxazepine derivative MIII displays a concentration-dependent cytotoxic response against MCF-7 breast cancer cell line, as shown in Figure 19 illustrates a bar chart where cell viability decreases as the concentration increases from 20 ppm to 320 ppm. At the lowest concentration of 20 ppm, the viability remains about 63%, and viability reduces to 55% at 40 ppm, 37.9% at 80, and 27% at 160. A dose-response curve in Figures 19 and 20 confirms this trend, and viability reduces substantially between 20 and 80 ppm and more at 160 ppm, and IC₅₀ as 48.88.

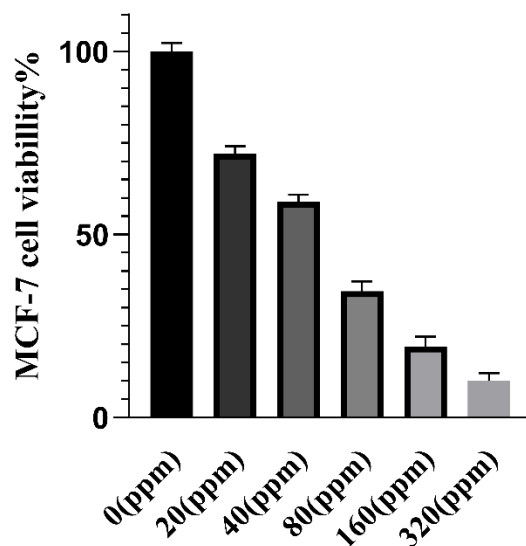


Figure 19. Viability (%) of 1,3-oxazepine derivative OIII.

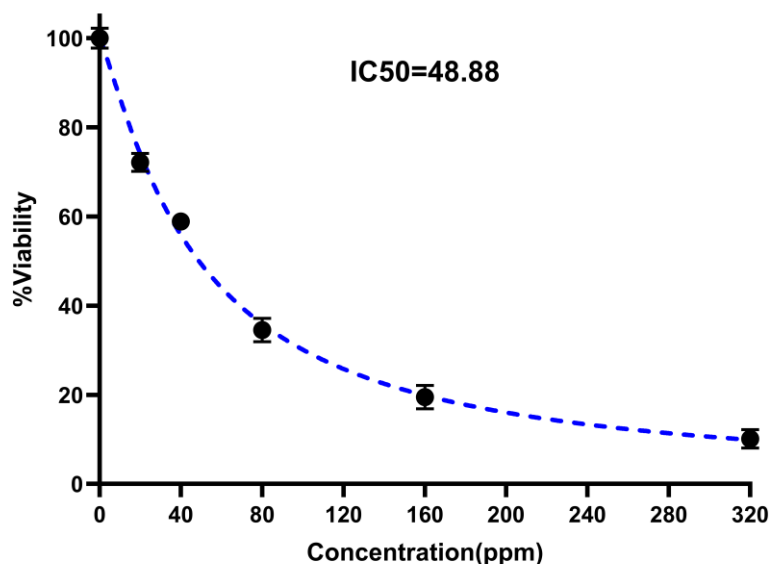


Figure 20. IC₅₀ of 1,3-oxazepine derivative OIII.

The 1,3-oxazepine derivative OIV affects MCF-7 cells on a dose-dependent basis. In Figure 21, the bar chart of cell viability at 20-320 ppm suggests a dose-dependent decline, and at 20 ppm, viability is 67%, to 19% at 320 ppm, and the dose-response curve is depicted in Figure 22

with IC₅₀ of 45.99 at 320 ppm. Similar trends have been seen in oxazepine-based scaffolds, demonstrating that aromatic ring replacement increases lipophilicity and cancer cell uptake.

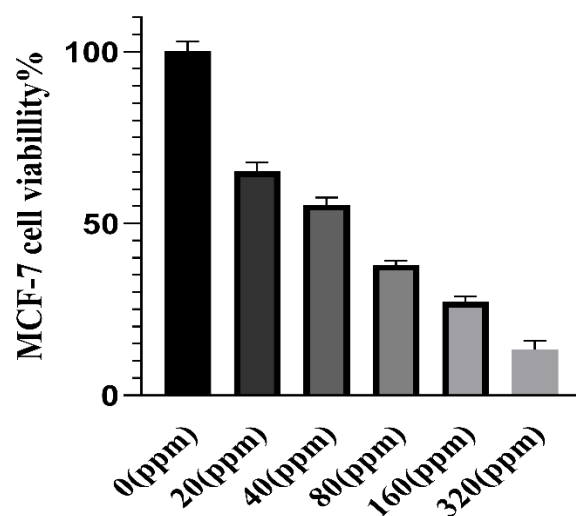


Figure 21. Viability (%) of 1,3-oxazepine derivative OIV.

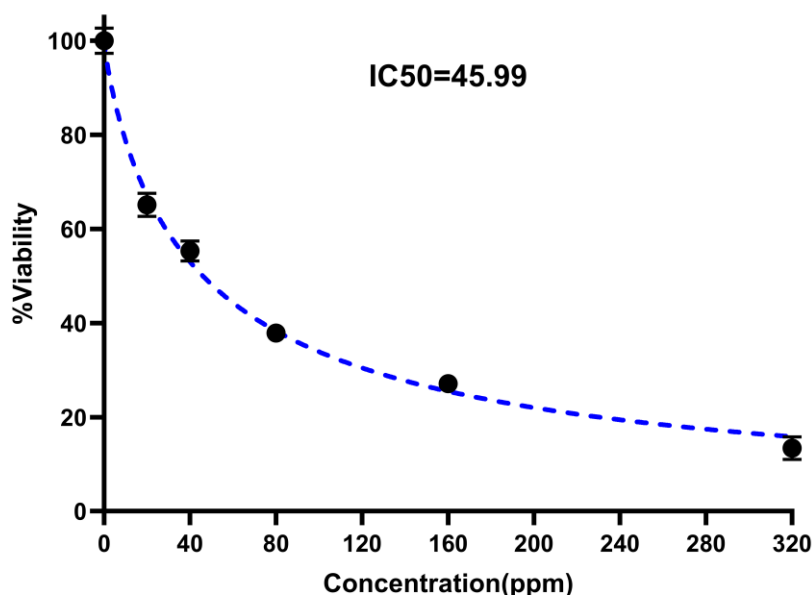


Figure 22. IC₅₀ of 1,3-oxazepine derivative OIV.

Molecular Docking

The 2D and 3D of interaction diagrams elucidate various bonds, such as the hydrogen bonds and hydrophobic contacts between derivative A and the enzyme active site residues of 4P66 protein; in which, synthesized derivative OI, as one final product has displayed advantageous binding affinity values and has interacted with multiple amino acid residues, as shown in Tables 3 and 4, that suggest bond distances and interaction energies have been measured and detailed visualization of the interaction network provides insight into the structural basis of ligand recognition, as shown in Figure 23.

Table 3: Molecular docking result of synthesized derivative.

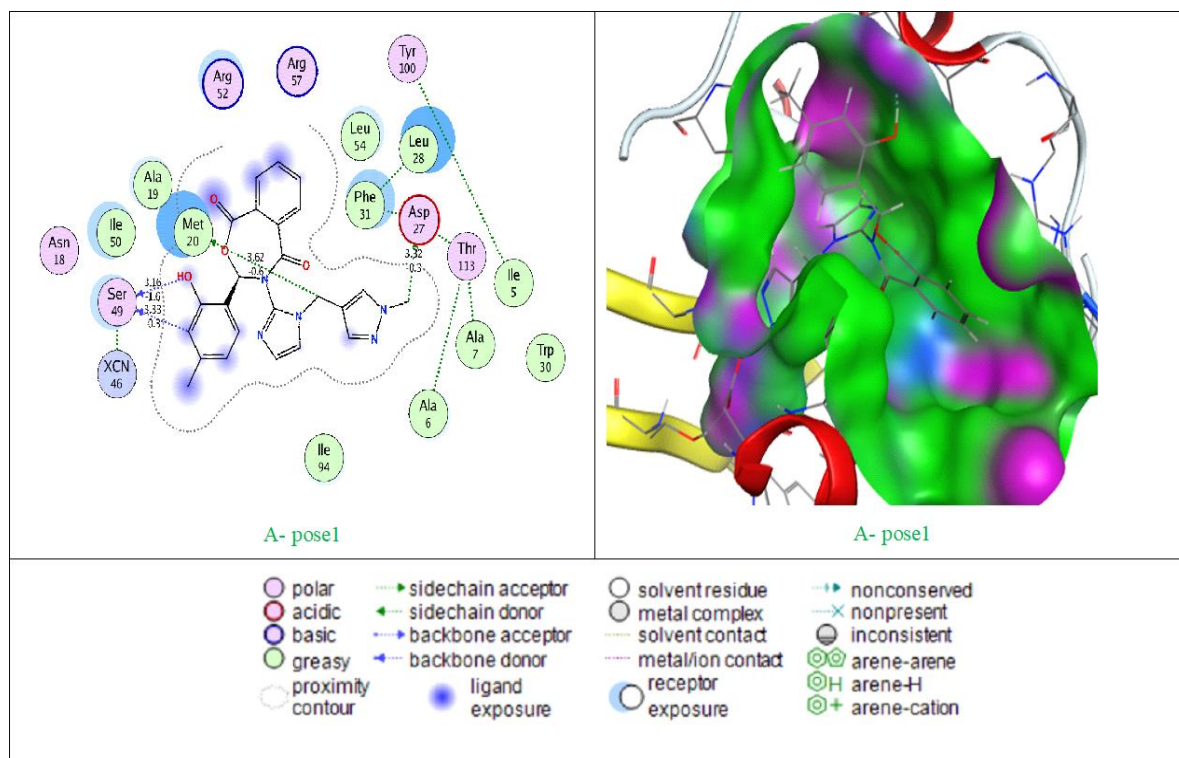
Compounds	mseq	Binding Affinity Kcal/mol	Rmsd (Å)	E_conf	E_place	E_score1	E_refine	E_score2
A- pose1	1	-7.48253	2.051515	-26.5241	-8.81412	-9.38185	-23.2567	-7.48253
A- pose2	1	-6.70339	2.057643	-32.5145	-10.1803	-8.91934	-28.267	-6.70339
A- pose 3	1	-6.55873	1.0587	-36.1953	-14.4466	-10.1299	-29.1733	-6.55873
A- pose4	1	-6.55625	3.384501	-33.8047	-14.6759	-9.62075	-35.2287	-6.55625
A- pose5	1	-6.42953	2.090348	-29.7161	-13.9095	-8.97011	-30.0719	-6.42953

Table 4: Smiles structure with Rmsd of ligand.

Compounds	Binding Affinity Kcal/mol	Rmsd (Å)	Smile
A- pose1	-7.48253	2.051515	<chem>O=C1N(c2n(Cc3cn(C)nc3)ccn2)C(c2c(O)cc(C)cc2)OC(=O)c2c1cccc2</chem>
A- pose2	-6.70339	2.057643	<chem>O=C1N(c2n(Cc3cn(C)nc3)ccn2)C(c2c(O)cc(C)cc2)OC(=O)c2c1cccc2</chem>
A- pose 3	-6.55873	1.0587	<chem>O=C1N(c2n(Cc3cn(C)nc3)ccn2)C(c2c(O)cc(C)cc2)OC(=O)c2c1cccc2</chem>
A- pose4	-6.55625	3.384501	<chem>O=C1N(c2n(Cc3cn(C)nc3)ccn2)C(c2c(O)cc(C)cc2)OC(=O)c2c1cccc2</chem>
A- pose5	-6.42953	2.090348	<chem>O=C1N(c2n(Cc3cn(C)nc3)ccn2)C(c2c(O)cc(C)cc2)OC(=O)c2c1cccc2</chem>

Table 5: Details of the best poses of ligand (A) with protein 4P66.

Compounds	Binding Affinity Kcal/mol	Rmsd (Å)	Atom of a compound	Atom of Receptor	Involved receptor residues	Type of interaction bond	Distance (Å)	E (kcal/mol)
A- pose1	-7.48253	2.05 1515	C 19	O	SER 49	(A) H-donor	3.33	-0.3
			C 21	OD1	ASP 27	(A) H-donor	3.32	-0.3
			C 33	SD	MET 20	(A) H-donor	3.62	-0.6
			C 53	O	SER 49	(A) H-donor	3.16	-1.6



weaker by 0.8–1.05. Despite excellent placement energies (-10 to -14), they show little refinement and irregular geometries (RMSD values: 1.06 to 3.38 Å), with Pose 1 being the most effective binding mode.

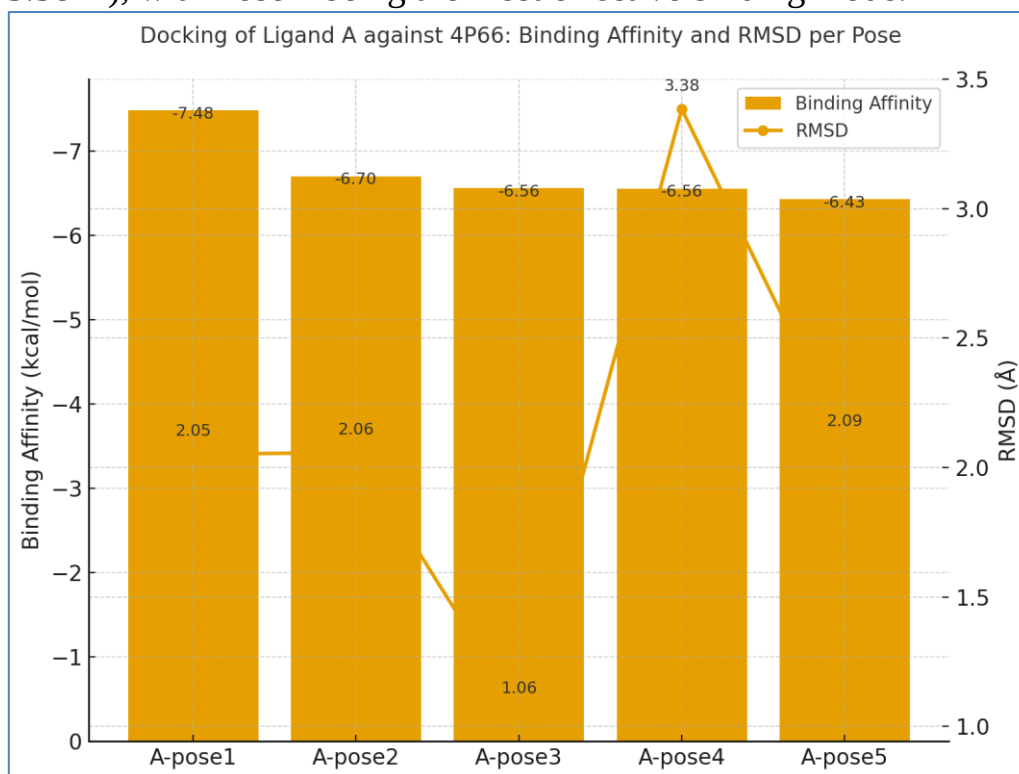
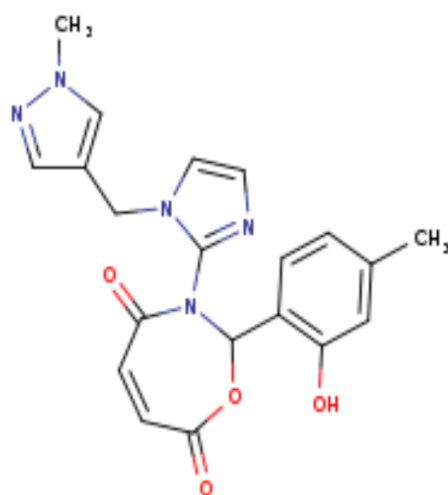
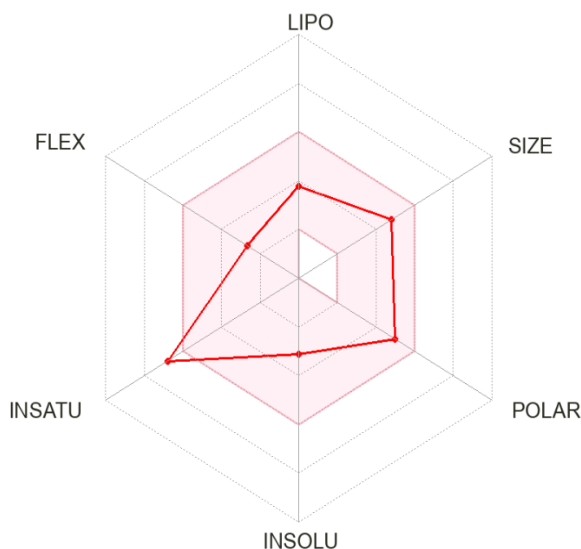


Figure 24. Docking performance of derivative A against DHFR (PDB ID: 4P66).

At the bottom bars of Figure 24 is A-pose1, which binds the best. Compared to A-pose 1, poses 2-5 showed 0.8-1.0 kcal/mol lower affinities. The line graph exhibits sturdy stance. These are A-pose3 with the lowest RMSD and most consistent geometry, and A-pose4 with the highest and least stable. A-pose1 gives best balance between high affinity and geometric stability. This high-performance is achieved by four hydrogen bond interactions with the enzyme pocket residues Ser49, Asp27, and Met20. These interactions keep the ligand in the binding site.

Admet

The synthesized derivative OI may be an orally active drug with physicochemical and pharmacokinetic limitations, and possesses 393.4 g/mol, six hydrogen-bond acceptors, one donor, four rotatable bonds, and 102.48 Å² topological polar surface area. They pass Lipinski, Ghose, Veber, Egan, and Muegge filters, and display oral absorption. Bioavailability (0.55) is moderate. ESOL, Ali, and SILICOS-IT models dissolve the chemicals, with no blood brain barrier permeation from high gastric absorption, and is a substrate for P-gp but does not inhibit major cytochrome P450 isoenzymes, minimizing metabolic drug-drug interactions. A drug-likeness test results in one PAINS alert and one molecular weight violation above 350 g/mol. Figure 25 and Table 5 show the synthetic accessibility limit of 4.10.



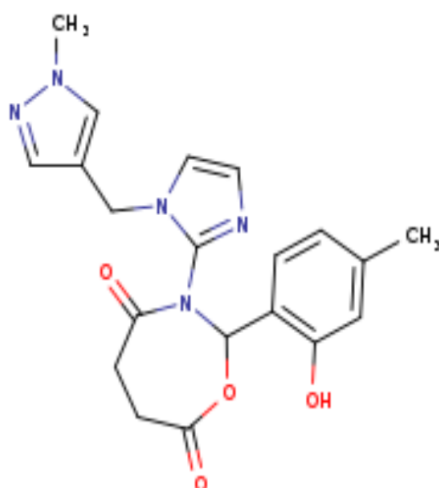
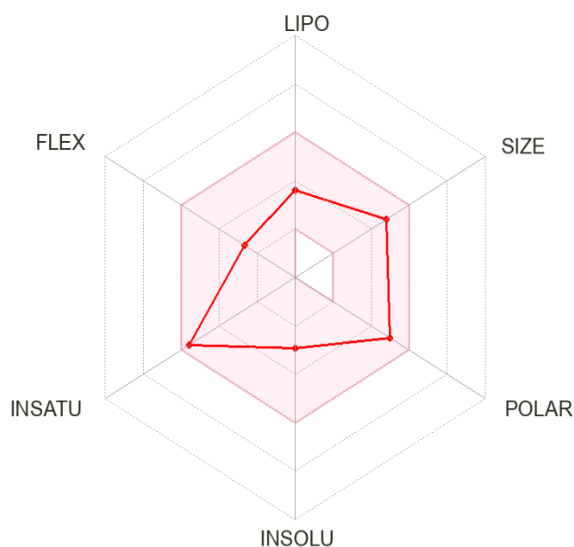
SMILES O=C1C=CC(=O)N(C(O1)c1ccc(cc1O)C)c1nccn1Cc1cnn(c1)C

Figure 25. ADME of derivative OI.

Table 5. Property of 1,3-oxazpine derivative OI.

Property	Value / Class
Molecular weight	393.4 g/mol
TPSA	102.48 Å ²
H-bond acceptors/donors	6 / 1
Rotatable bonds	4
GI absorption	High
BBB permeation	No
Bioavailability score	0.55
Log P (consensus)	1.20
PAINS / Lipinski	1 alert / 0 violations

A 1,3-oxazpine derivative OII presents significant oral drug-like properties with minor structural changes, and weighs 395.41 g/mol, has six hydrogen bond acceptors, one donor, and four rotatable bonds; a TPSA of 102.48 Å² that ensures high intestinal permeability. It presents a moderate bioavailability score of 0.55 (Fig. 26), is soluble in all solubility models with log S values of -2.93 (ESOL), -2.51 (Ali), and -4.00 (SILICOS-IT). It is a P-gp substrate but is not a potent CYP450 isoform inhibitor that reduces metabolic drug-drug interactions and indicates high gastrointestinal absorption. The drug-likeness assessment meets Lipinski, Ghose, Veber, Egan, and Muegge criteria, although has one PAINS alert (mannich_A) and one lead-likeness violation due to molecular weight above 350 g/mol, synthetic accessibility score is 3.84, somewhat higher than derivative OII.



SMILES O=C1CCC(=O)N(C(O1)c1ccc(cc1O)C)c1nccn1Cc1cnn(c1)C

Figure 26. ADME of 1,3-oxazpine derivative OII.

Table 6. Property of derivative OII.

Property	Value / Class
Molecular weight	395.41 g/mol
TPSA	102.48 Å ²
H-bond acceptors / donors	6 / 1
Rotatable bonds	4
GI absorption	High
BBB permeation	No
Bioavailability score	0.55
Log P (consensus)	1.24
PAINS / Lipinski	1 alert / 0 violations

Conclusion

In this work was developed new 1,3-oxazepine derivatives based on Schiff base derivatives which have a big role in medicine because its heterocyclic compounds. The Schiff base intermediate was cyclized with various anhydrides to yield four spectroscopically substantiated 1,3-oxazepine-4,7-dione derivatives OI-OIV. The synthesized derivatives OI and derivative OII inhibit different types of bacteria at high dosages. Furthermore, the synthesis of the derivative OIV reduces MCF-7 cell line viability dose-dependently with a 10% reduction at 320 ppm. For docking studies, derivative OI also binds with 4 hydrogen bonds to dihydrofolate reductase with a binding energy of -7.48 kcal/mol. ADMET projections reveal high solubility, gastrointestinal absorption, moderate bioavailability, and no CYP450 inhibition. Research on structural modifications to increase activity, in vivo safety, and bacterial DHFR selectivity, and kinetic blockade studies with resistant bacteria are required to verify docking predictions and increase clinical usefulness.

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تحضير وتقييم بيولوجي لمركبات حلقية غير متجانسة جديدة مشتقة من 3،1-أوكسازيبين، 4،7-ديون كعوامل محتملة مضادة للبكتيريا ومضادة للسرطان م.د. ضامر إسماعيل مدب

الكلية التربوية المفتوحة- فرع الدجيل/وزارة التربية

مستخلص البحث:

تلعب المركبات الحلقية غير المتجانسة دوراً حاسماً في اكتشاف الأدوية، نظراً لتفاعل بنيتها المتعددة الاستخدامات بقوة مع الأهداف البيولوجية. تهدف هذه الدراسة إلى تحضير مركب مشتق قاعدة شيف (Schiff base) عن طريق تكثيف مركب 1-[(1-methyl-1H-pyrazol-4-yl)-H-imidazol-2-amin مع مركب 2-hydroxy-4-methylbenzaldehyde تحت مكثف عاكس (reflux) في الإيثانول مع استخدام حامض الخليك الثلجي كعامل مساعد. تم إجراء تفاعل حلقي لمشتق قاعدة شيف هذا مع أنهيدريد المالنك، أو الفثاليك، أو السوكسينيك، أو الكلوتاريك (malic, phthalic, succinic, or glutaric anhydride) في البنزين الجاف تحت مكثف عاكس لمدة 14-15 ساعة للحصول على أربعة من مشتقات 1،3-أوكسازيبين-4،7-ديون (OI-OIV) نقيت النواتج عن طريق إعادة البلورة في 1،4-ديوكسان الجاف، وتأكدت بنيتها باستخدام مطيافية الأشعة تحت الحمراء (FT-IR)، والرنين المغناطيسي النووي للبروتون للبروتون ($^1\text{H-NMR}$)، والكربون ($^{13}\text{C-NMR}$) تُبع تقييم النشاط المضاد للبكتيريا باستخدام طريقة انتشار القرص في الطبق (cup-plate diffusion method) ضد سلالات البكتيريا العنقودية (Staphylococcus spp) والعقدية الرئوية (Streptococcus pneumoniae) والإشريكية القولونية (Escherichia coli) والزائفة الزنجارية (Pseudomonas aeruginosa) عند تراكيز 0.1 mg/ml، و 0.001mg/ml و 0.0001 mg/ml. تُبُطت المشتقات (OI-OIII) بكتيريا المكورات العنقودية (Staphylococcus) عند منطقتي تثبيط بلغت 29 ملم و 28 ملم على التوالي، مقتربة من منطقة التثبيط الخاصة بمضاد الأزيثروميسين (28 ملم)، في حين أظهرت السلالات سالبة الغرام استجابات أضعف. وكشف نشاط السمية الخلوية ضد خط خلايا سرطان الثدي MCF-7 عن انخفاضات تعتمد على الجرعة في حيوية الخلايا، حيث سجل المشتق OIII تركيزاً مثبطاً نصفياً IC_{50} بلغ 48.88، بينما سجل المشتق OIV تركيزاً مثبطاً نصفياً IC_{50} بلغ 45.99. أظهرت دراسة الإرساء الجزيئي الحاسوبية (In silico molecular docking study) ضد إنزيم ديهيدروفولات ريدوكتاز (dihydrofolate reductase) (PDB ID: 4P66) باستخدام برنامج MOE أن المشتق OI (الربيطة A) حقق في الهينة 1 (pose 1) طاقة ارتباط بلغت -7.48 كيلو كالوري/مول، وشكل أربعة تفاعلات روابط هيدروجينية مع SER49 و ASP27 و MET20، وهو ما دعمته طاقات التوضع والتنقية المواتية. في حين أشارت تنبؤات ADMET باستخدام أداة swissADMET إلى امتصاص هضمي عالٍ، وذوبانية جيدة، وتوافر حيوي معتدل

الكلمات المفتاحية: مضاد للبكتيريا، مضاد للسرطان، أوكسازيبين-4،7-ديون، قاعدة شيف