

RESEARCH ARTICLE

Synthesis, Characterization, Molecular Docking and Study biological Activity of some New Heterocyclic Derivatives from a Sulfa Drug

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ABSTRACT

A series of novel heterocyclic derivatives were synthesized starting from sulfadiazine via Schiff base intermediates, followed by cyclization to afford five-membered heterocyclic rings including imidazolidine, thiazolidine, and tetrazole derivatives. The synthesized compounds were obtained in good to excellent yields ranging from 74.5% to 97.5%. The structures of the synthesized compounds were confirmed using FT-IR, ¹H NMR, and ¹³C NMR spectroscopy. The disappearance of the azomethine (C=N) stretching band in FT-IR spectra and the absence of the corresponding proton signal in ¹H NMR confirmed the successful cyclization of Schiff bases into the desired heterocyclic systems. Molecular docking studies against dihydropteroate synthase (DHPS) from *Escherichia coli* (PDB ID: 3SRW) revealed that compound H1 exhibited the lowest binding energy (−8.40 kcal/mol), indicating strong binding affinity within the active site. Interaction analysis showed hydrogen bonding along with van der Waals and hydrophobic (alkyl and π -alkyl) interactions. Compound Z3 also showed favorable binding energy (−7.68 kcal/mol) with key interactions involving amino acid residues such as SER, GLN, TRP, and LEU. Biological evaluation demonstrated that the synthesized compounds exhibited varying antibacterial activity against both Gram-negative (*Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus*) bacteria. The inhibition zones ranged from 10 to 28 mm, with compound H4 showing the highest activity (28 mm) compared to *Pseudomonas aeruginosa*, while compounds Z3, Z4, H3, and H4 exhibited significant activity against *Staphylococcus aureus* at higher concentration (500 mg/mL). In contrast, compounds Z1 and Z showed no detectable activity. Overall, the results indicate that structural modification of sulfadiazine through heterocyclic ring formation significantly enhances antibacterial activity and binding affinity, suggesting their potential as promising antimicrobial agents.

Keywords: Sulfadiazine, Schiff base, Imidazolidine, Thiazolidine, Tetrazole.

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1. Introduction

Sulfonamide drugs represent one of the earliest and most significant classes of antibacterial agents^[1,2], with sulfadiazine being widely used due to its ability to inhibit dihydropteroate synthase (DHPS)^[3,4], a key enzyme involved in bacterial folic acid synthesis^[5]. Despite their clinical importance, the therapeutic efficacy of sulfonamides has been limited by the emergence of bacterial resistance and reduced permeability^[6], particularly in Gram-negative bacteria. Consequently, structural modification of sulfonamide scaffolds has become a crucial strategy in medicinal chemistry to enhance biological activity^[7] and overcome resistance mechanisms^[8].

Moieties into existing pharmacophores^[9]. Heterocyclic compounds constitute a major portion of bioactive molecules and are widely employed in the development of antimicrobial agents^[10,11] due to their structural diversity and ability to interact with biological targets.

Among these, five-membered heterocycles^[12] such as imidazolidine^[13], thiazolidine^[14], and tetrazole^[15] have attracted considerable attention because of their pharmacological relevance and structural versatility.^[16]

Tetrazole derivatives are recognized as important bioisosteres of carboxylic acids and exhibit enhanced metabolic stability, improved hydrogen bonding capacity, and strong interactions with biological targets. These properties contribute significantly to their antimicrobial and pharmacological activities, making them valuable scaffolds in modern drug discovery.^[16]

Similarly, thiazolidine derivatives have been extensively investigated due to their potent biological activities, especially their antibacterial properties. The incorporation of sulfur-containing heterocycles enhances lipophilicity and facilitates better penetration through bacterial cell membranes, thereby improving antimicrobial efficacy^[17].

Schiff bases (azomethine compounds, C=N) serve as key intermediates in the synthesis of heterocyclic systems^[18, 19] due to their high reactivity and ease of cyclization. They play a vital role in introducing structural diversity and enabling the formation of various biologically active heterocycles, which can significantly influence pharmacological activity^[20]. Based on these considerations, the present study focuses on the design and synthesis of new sulfadiazine-derived heterocyclic compounds via Schiff base intermediates, followed by cyclization to form imidazolidine, thiazolidine, and tetrazole derivatives. The aim of this work is to investigate the effect of structural modification on the biological activity and binding affinity of the synthesized compounds, particularly against bacterial targets^[21].

This strategy is expected to improve lipophilicity, enhance membrane permeability, and strengthen ligand–protein interactions.^[22,23]

2. Materials and Methods

2.1. Instruments and apparatus:

Reaction and reagents are used like obtained from commercial companies without further purification. Solvents were purified beforehand. The purity of derivatives and path of reaction were monitored using thin layer chromatography on silica gel-G (Merck grade) with ethanol and benzene mixture as mobile phase. The Melting points were measured in open capillaries, with the help of (Stuart) melting point (SMP30, England) melting point apparatus are expressed in °C and are uncorrected. Infrared spectra(FT-IR) were recorded on Shimadzu prestige-21 Spectrophotometer by using potassium bromide (KBR pellets) and the values are expressed in cm⁻¹, H-NMR and C-NMR Spectra of the derivatives were recorded on Bruker (Avance III, Bruker 400MHz NMR spectrophotometer using TMS as an interior standard and the values are expressed in ppm in university o in Iran.

Molecular docking was performed using Auto Dock Vina to evaluate binding affinities of the synthesized compounds with target proteins obtained from the PDB.

Antibacterial activity was assessed by agar well diffusion method against selected bacterial strains, and inhibition zones were measured after incubation at 37°C.

Antioxidant activity was determined using the DPPH assay by measuring absorbance at 517nm and calculating radical scavenging percentage.

2.2. General procedure for synthesis of Schiff bases (Z, H) ^[14]:

Dissolve a mixture of sulfadiazine (1 gm, 0.004 mmol) and the equivalent aldehyde (0.004 mmol) 1-methyl-1H-indole-3-carbaldehyde and (0.004mmole,0.744g)6-methyl-2-naphthaldehyde respectively, in 40ml of glacial acetic acid was employed. The mixture was then refluxed for 20 hrs at 85 °C while the reaction was taking place. The course of the reaction was monitored with TLC using a mixture of ethanol and benzene with

an eluent ratio of (3:2). Following the cooling of the reaction mixture to room temperature, the precipitated product was filtered, dried, and then recrystallized from solvent ethanol to obtain the Schiff base that corresponded to the precipitated product.

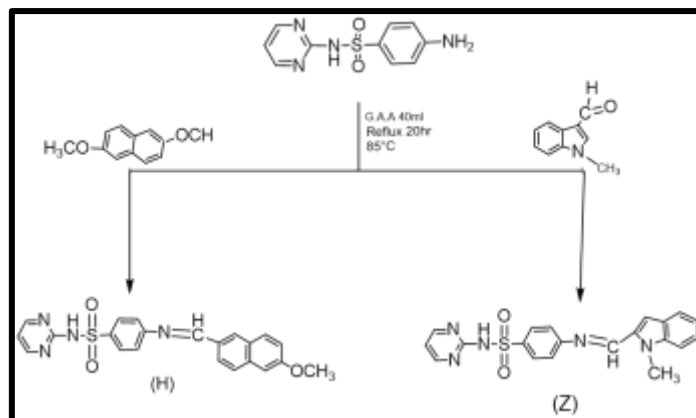


Figure 1. Preparation of Schiff bases (Z and H) from sulfadiazine.

2.3. General procedure for cyclization to five-membered heterocycles:

The corresponding five-membered heterocyclic derivatives were obtained by cyclization under the following general conditions using the prepared Schiff bases as essential intermediates:

2.3.1. General procedure for synthesis of imidazolidinone derivatives (Z1 and H1)^[10]:

The Schiff base (0.1gm,0.0002mole) from Schiff base Z and (0.1g,0.0002mol) from Schiff base H was dissolved in Benzene 20ml and Tyrosine (0.04g,0.0002mole) respectively. The mixture was reflux to 80°C for 20hr. TLC (3:2) of ethanol and benzene was used to track the reaction's progress. After cooling, the precipitate was filtered, recrystallized from ethanol, and dried.

2.3.2. General procedure for synthesis of thiazolidine derivatives (Z3 and H3)^[24]:

The Schiff base (0.1g,0.0255mole) from Schiff base Z and (0.1g,0.00232mole) from Schiff base H is dissolved in acetone 20ml and Thioglycolic acid (0.024g,0.0256mmol) and (0.0184g,0.0256mmol) respectively. The mixture was reflux to 56°C for 22hr. TLC (3:2) of ethanol and benzene was used to track the reaction's progress. The mixture was cooled, washing, drying, and recrystallizing the resultant solid.

2.3.3. General procedure for synthesis of tetrazole derivatives (Z4 and H4) ^[14]:

The Schiff base (0.1g,0.0002mmol) from Schiff base Z and (0.1g,0.0002mol) from Schiff base H was dissolved in DMF 10ml and NaN₃ (0.151g, 0.0232mol) respectively. The mixture was reflux to 153°C for 22hr. TLC (3:2) of ethanol and benzene was used to track the reaction's progress. The mixture was finished, cooled, the corresponding imidazolidinone derivative was obtained by filtering, washing, drying, and recrystallizing the resultant solid.

2.4. Characterization and purification:

All synthetic chemicals were purified by recrystallization. The purity of the compounds was confirmed using TLC. A melting point device was used to determine the uncorrected melting points. ¹H-NMR, ¹³C-NMR and FTIR for structural characterization.

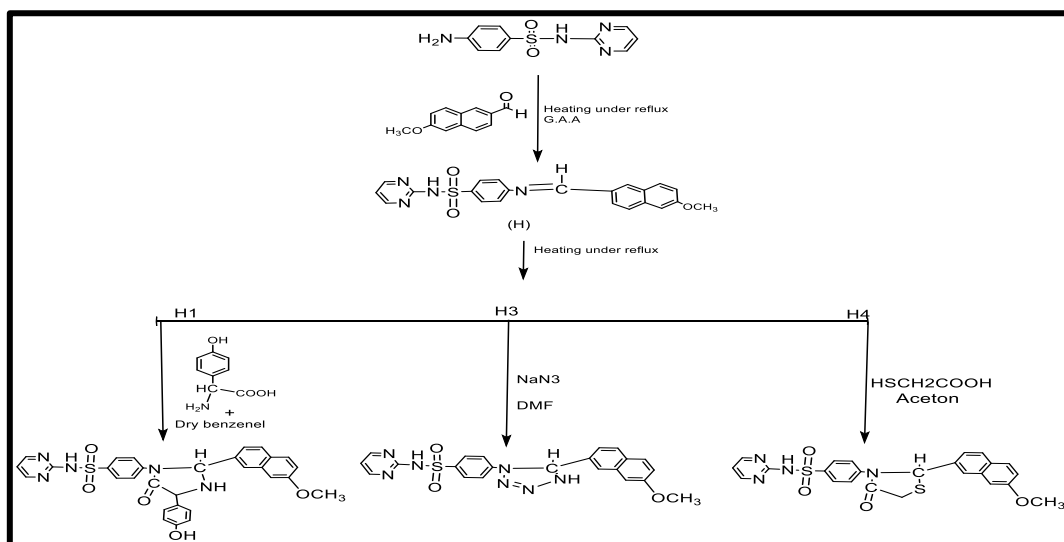


Figure 2. Preparation of (H1, H3, H4) from Schiff base (H).

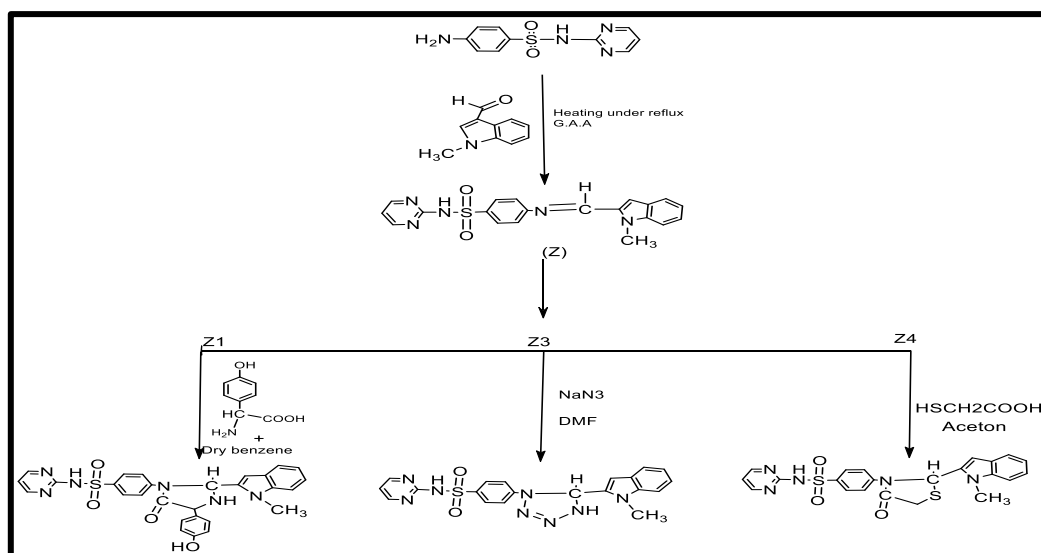


Figure 3. Preparation of (Z1, Z3, Z4) from Schiff base (Z).

Table 1. Physical properties of the synthesized compounds.

Co. code	structure	Name of compound	M.F	M. wt. g/mol	M.P °C	R _f	Color	Yield %
Z		4-(((1-methyl-1H-indol-2-yl)methylene)amino)-N-(pyrimidin-2-yl)benzenesulfonamide	C ₁₉ H ₁₆ N ₆ O ₂ S	392.44	203-205	0.71	Red	75.76
Z1		4-(4-(4-hydroxyphenyl)-2-(1-methyl-1H-indol-2-yl)-5-oxoimidazolidin-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide	C ₂₆ H ₂₀ N ₇ O ₄ S	442.56	194-196	0.63	Orange	78.9
Z3		4-(5-(1-methyl-1H-indol-2-yl)-4,5-dihydro-1H-tetrazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide	C ₂₂ H ₂₈ N ₅ O ₃ S	434.48	210-212	0.62	Red	92.50

Z4		4-(2-(1-methyl-1H-indol-2-yl)-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl)benzenesulfonamide	C ₂₀ H ₁₈ N ₈ O ₂ S ₂	419.46	Oil	0.66	Green	97.58
H		4-(((6-methoxynaphthalen-2-yl)methylene)amino)-N-(pyrimidin-2-yl)benzenesulfonamide	C ₂₁ H ₁₇ N ₅ O ₃ S	419.46	200-202	0.78	Yellow	89.74
H1		4-(5-(7-methoxynaphthalen-2-yl)-4,5-dihydro-1H-tetrazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide	C ₂₄ H ₂₁ N ₆ O ₅ S	509.54	193-196	0.69	Yellow	81.1
H3		4-(5-(7-methoxynaphthalen-2-yl)-4,5-dihydro-1H-tetrazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide	C ₂₄ H ₂₀ N ₄ O ₃ S	476.57	Oil	0.80	Yellow	92.58
H4		4-(2-(7-methoxynaphthalen-2-yl)-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl)benzenesulfonamide	C ₂₂ H ₂₈ N ₇ O ₃ S ₂	470.57	Oil	0.62	Yellow	74.5

3. Results and Discussion

The formation of Schiff base intermediates was carried out through a condensation reaction between the primary amino group of sulfadiazine and the carbonyl group of the corresponding aromatic aldehydes under acidic conditions. The reaction mechanism proceeds via an initial nucleophilic addition, where the lone pair of electrons on the nitrogen atom of the amino group attacks the electrophilic carbonyl carbon of the aldehyde, leading to the formation of a carbinolamine intermediate.

Subsequently, the intermediate undergoes proton transfer followed by the elimination of a water molecule, resulting in the formation of the azomethine (C=N) linkage characteristic of Schiff bases. The acidic medium facilitates both the activation of the carbonyl group and the dehydration step, thereby enhancing the overall reaction efficiency.

The formation of the Schiff base is evidenced by the appearance of the characteristic C=N functional group, which serves as a key reactive center for subsequent cyclization reactions leading to the formation of heterocyclic derivatives. This step represents a crucial intermediate stage in the synthetic pathway, enabling further structural modification of the sulfadiazine scaffold.

The formation of imidazolidine derivatives was achieved through the cyclization of the corresponding Schiff base with tyrosine. The mechanism involves an initial nucleophilic attack by the amino group of tyrosine on the electrophilic carbon of the azomethine (C=N) linkage, leading to the formation of an intermediate. Subsequently, intramolecular cyclization occurs through the interaction of the carboxyl group of tyrosine, resulting in the formation of a five-membered imidazolidine ring. This process is accompanied by the elimination of a water molecule. The successful cyclization is confirmed by the disappearance of the characteristic azomethine (C=N) group and the formation of a new heterocyclic system.

The formation of thiazolidine derivatives was achieved through the cyclization of the corresponding Schiff base with thioglycolic acid. The mechanism involves an initial nucleophilic attack by the sulfur atom of

thioglycolic acid on the electrophilic carbon of the azomethine (C=N) group, leading to the formation of an intermediate. Subsequently, intramolecular cyclization occurs through the interaction of the carboxyl group with the nitrogen atom, resulting in the formation of a five-membered thiazolidine ring. This process is accompanied by the elimination of a water molecule. The successful cyclization is confirmed by the disappearance of the azomethine (C=N) group and the formation of a new heterocyclic system.

Molecular docking studies were performed to evaluate the binding affinity of the synthesized compounds toward dihydropteroate synthase (DHPS), a key enzyme involved in bacterial folate biosynthesis. Among the tested derivatives, compound H1 exhibited the lowest binding energy (−8.40 kcal/mol), indicating the strongest binding affinity within the active site. However, biological activity cannot be solely interpreted based on binding energy values. Detailed interaction analysis revealed that H1 forms hydrogen bonds in addition to hydrophobic interactions such as alkyl and π -alkyl interactions, which contribute significantly to the stability of the ligand–protein complex.

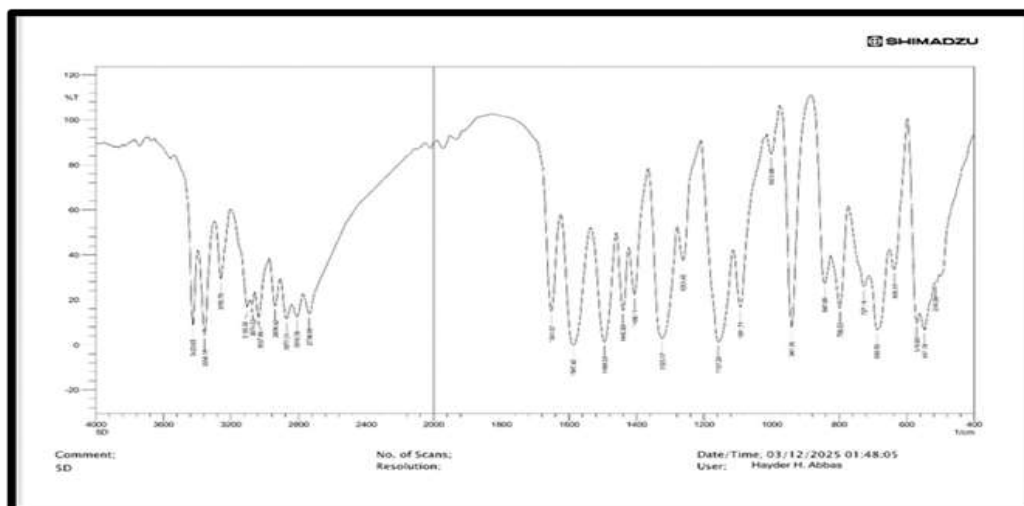
Compound Z3 also demonstrated favorable binding energy (−7.68 kcal/mol), and its interaction with key amino acid residues such as SER, GLN, TRP, and LEU highlights its effective accommodation within the active site pocket. These interactions suggest that the presence of heterocyclic moieties enhances the binding capability through multiple non-covalent interactions.

The antibacterial activity results further support the docking findings. The synthesized compounds exhibited variable activity against both Gram-negative (*Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus*) strains. Notably, compound H4 showed the highest antibacterial activity with an inhibition zone of 28 mm against *Pseudomonas aeruginosa*, while compounds Z3, Z4, H3, and H4 demonstrated significant activity against *Staphylococcus aureus* at higher concentration. In contrast, compounds Z1 and Z showed no observable activity, indicating that specific structural features are required for effective antibacterial performance.

A comparative analysis with the parent drug sulfadiazine indicates that several of the synthesized derivatives exhibited enhanced antibacterial activity, suggesting that structural modification through heterocyclic ring formation improves biological efficacy. This enhancement can be attributed to increased lipophilicity and improved membrane permeability, which facilitate better interaction with bacterial targets.

Overall, the results demonstrate a clear structure–activity relationship, where the incorporation of heterocyclic rings such as imidazolidine, thiazolidine, and tetrazole plays a crucial role in enhancing both binding affinity and antibacterial activity. These findings highlight the potential of the synthesized compounds as promising candidates for further development as antimicrobial agents.

The formation of thiazolidine derivatives was achieved through the cyclization of the corresponding Schiff base with thioglycolic acid. The mechanism involves an initial nucleophilic attack by the sulfur atom of thioglycolic acid on the electrophilic carbon of the azomethine (C=N) group, leading to the formation of an intermediate. Subsequently, intramolecular cyclization occurs through the interaction of the carboxyl group with the nitrogen atom, resulting in the formation of a five-membered thiazolidine ring. This process is accompanied by the elimination of a water molecule. The successful cyclization is confirmed by the disappearance of the azomethine (C=N) group and the formation of a new heterocyclic system.



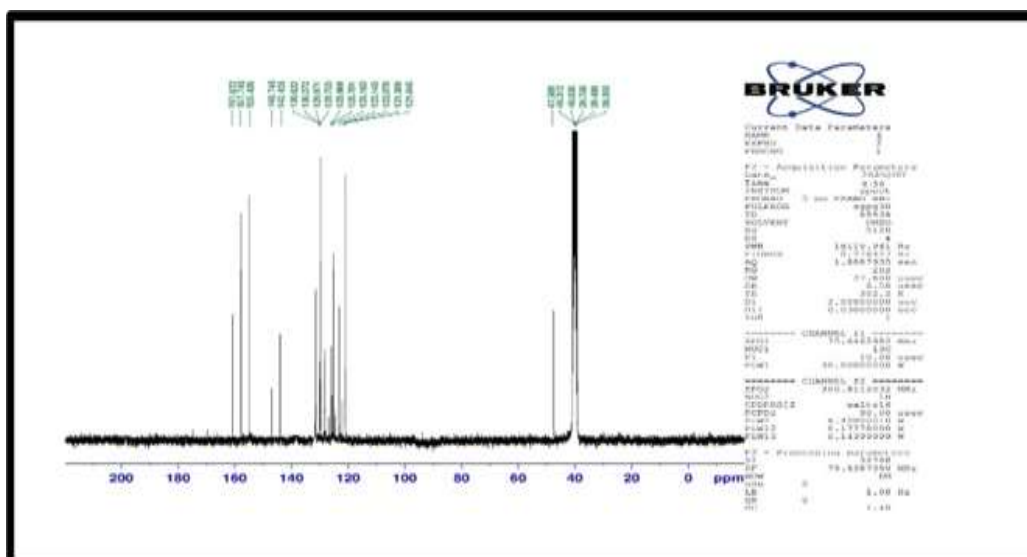


Figure 7. ^{13}C -NMR spectrum of Schiff base (Z).

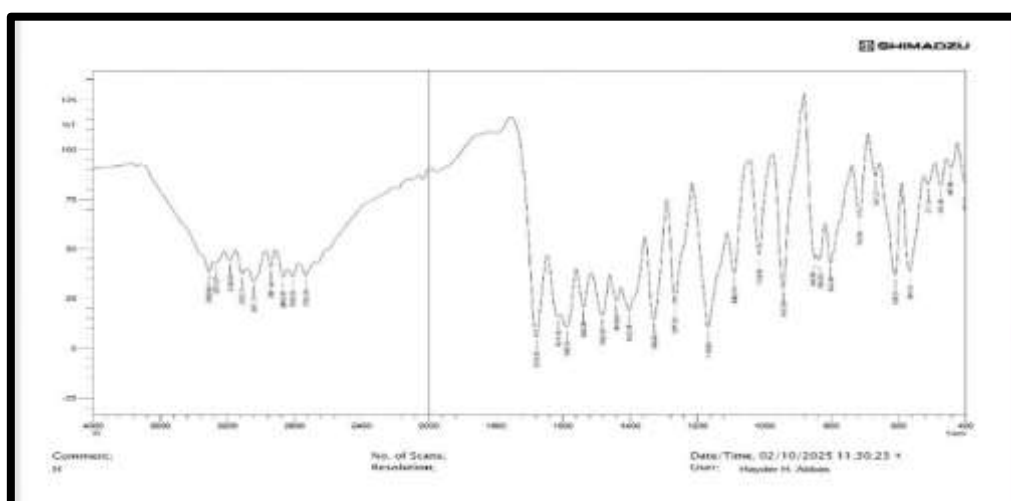


Figure 8. FT-IR Spectrum of Schiff base (H).

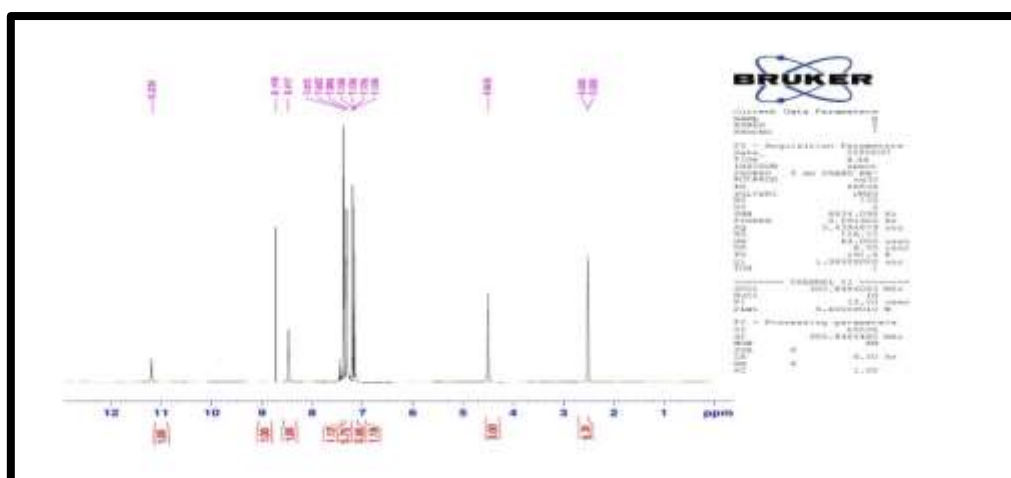


Figure 9. ^1H -NMR spectrum of (H).

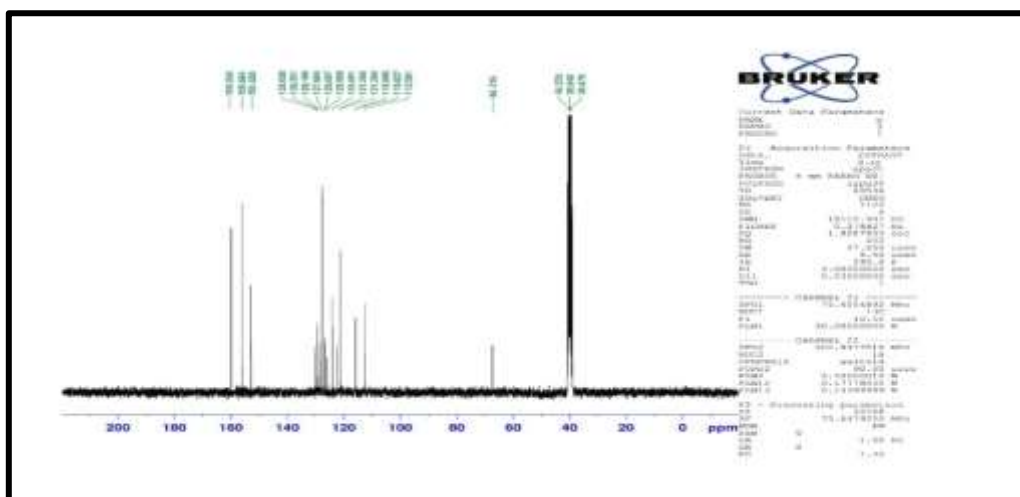


Figure 10. ^{13}C -NMR spectrum of (H).

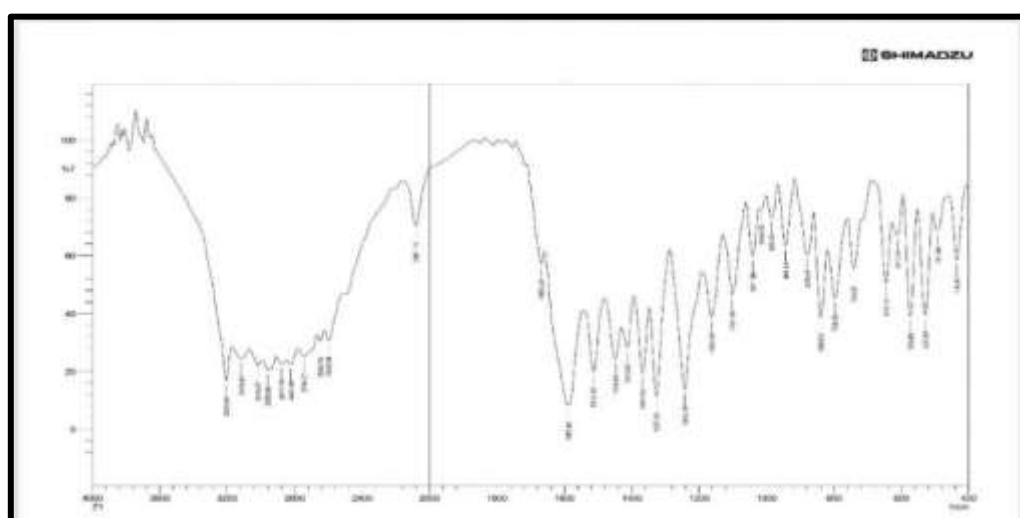


Figure 11. FT-IR Spectrum of (Z1).

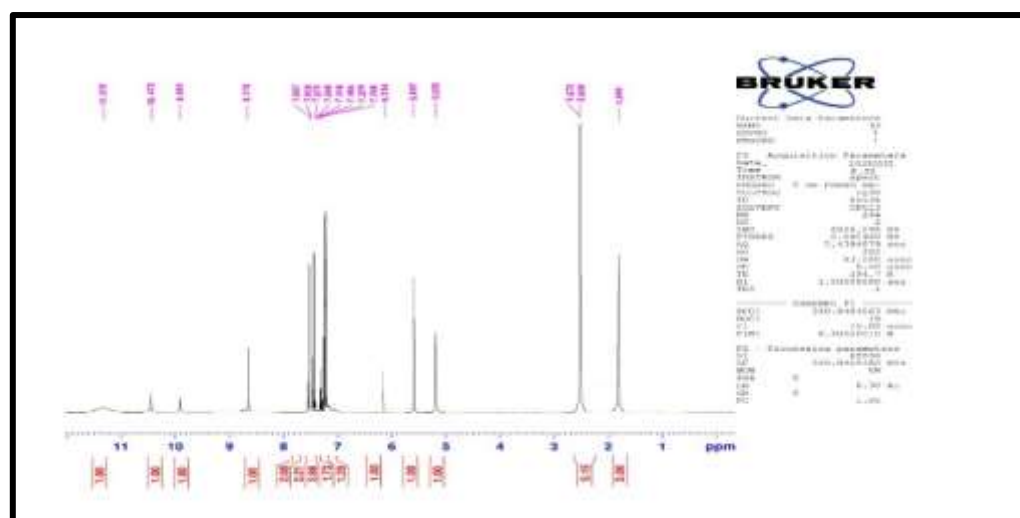


Figure 12. ^1H -NMR spectrum of (Z1).

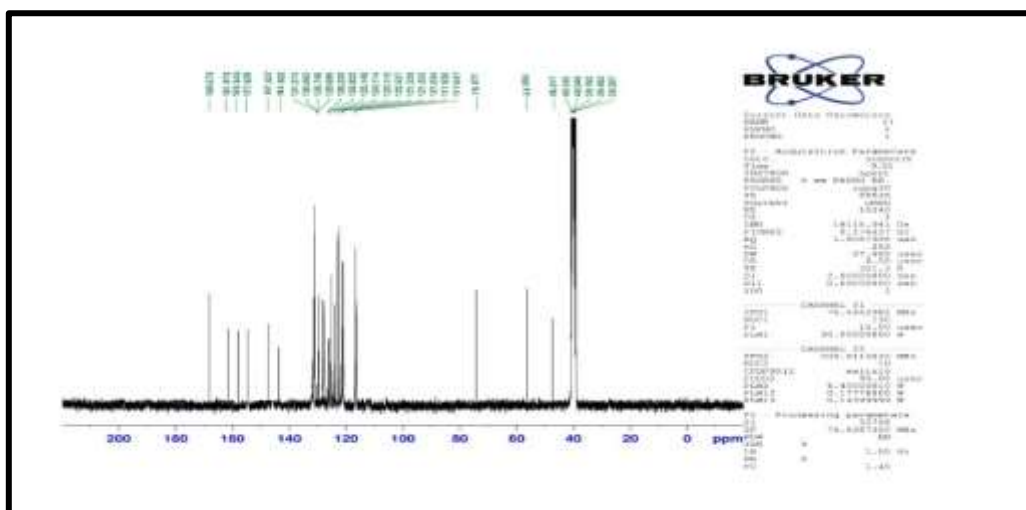


Figure 13. ^{13}C -NMR spectrum of (Z1).

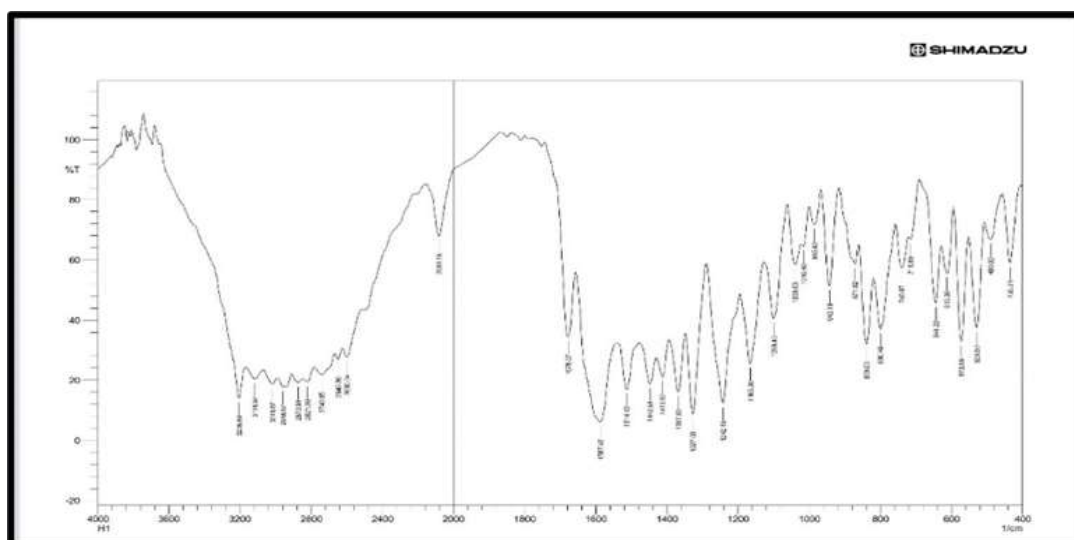


Figure 14. FT-IR Spectrum of (H1).

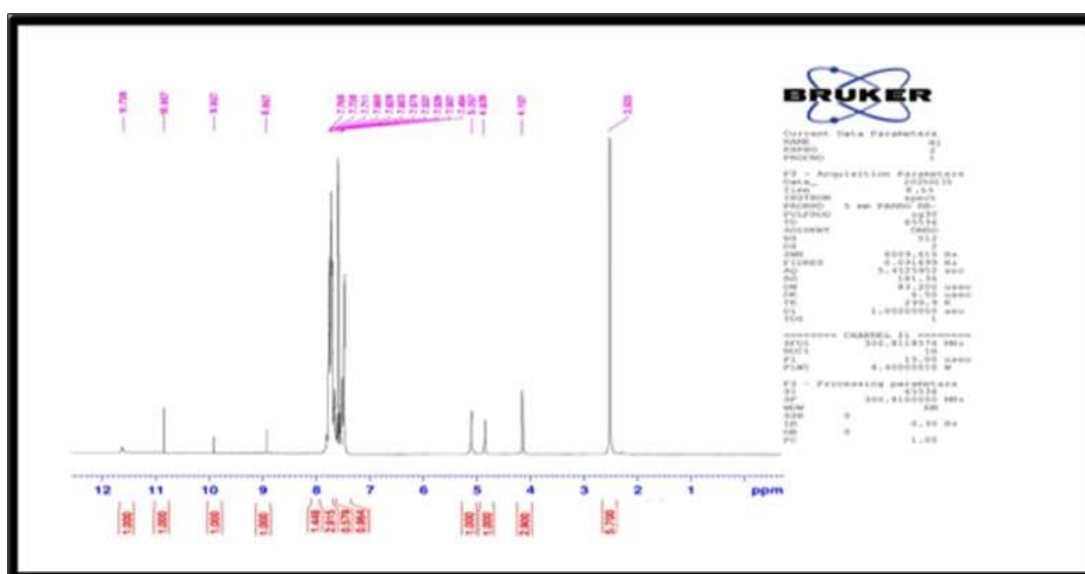


Figure 15. ^1H -NMR spectrum of (H1).

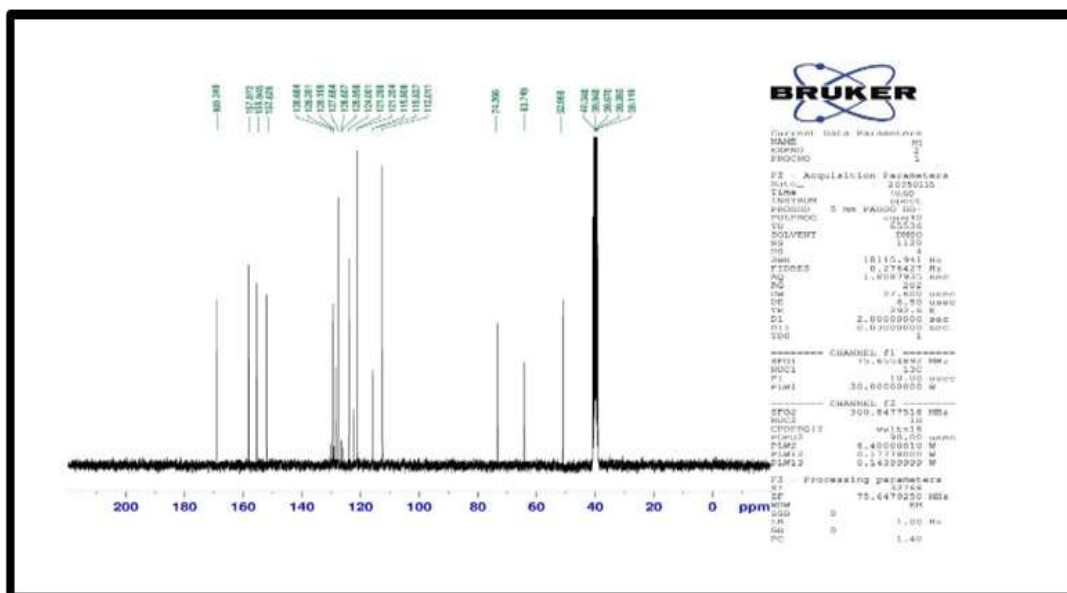


Figure 16. ^{13}C -NMR spectrum of (H1).

The formation of tetrazole derivatives was achieved through the cyclization of the corresponding nitrile intermediate with sodium azide via a [3+2] cycloaddition reaction. The mechanism involves the nucleophilic attack of the azide ion (N_3^-) on the electrophilic carbon of the nitrile group ($-\text{C}\equiv\text{N}$), leading to the formation of a linear intermediate. This is followed by intramolecular cyclization and protonation steps to yield the five-membered tetrazole ring. The reaction proceeds efficiently under thermal conditions and results in the formation of a stable heterocyclic system. The successful formation of the tetrazole ring is supported by the disappearance of the nitrile ($\text{C}\equiv\text{N}$) group and the appearance of new characteristic signals corresponding to the tetrazole moiety.

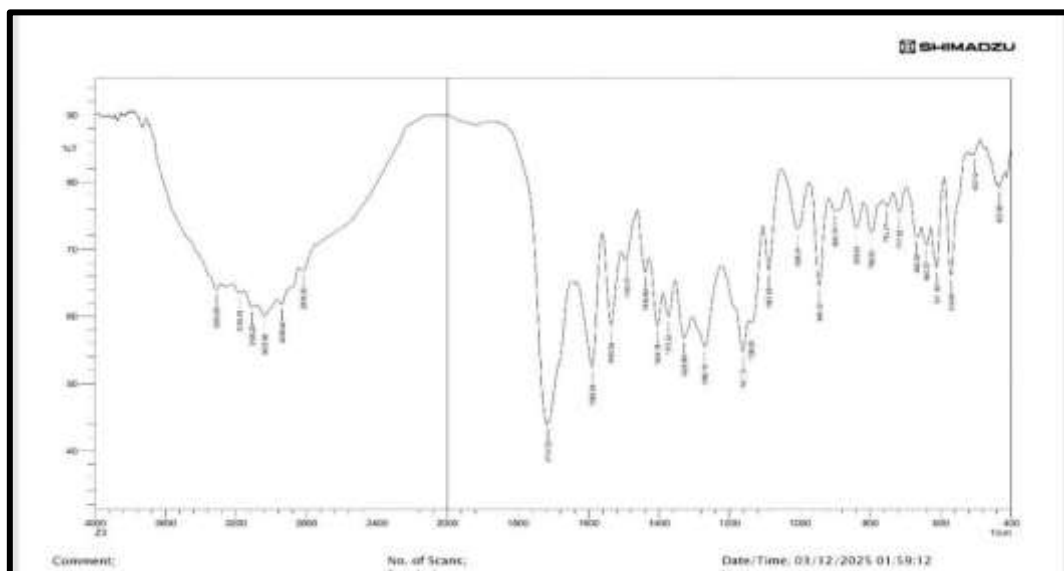


Figure 17. FT-IR Spectrum (Z3).

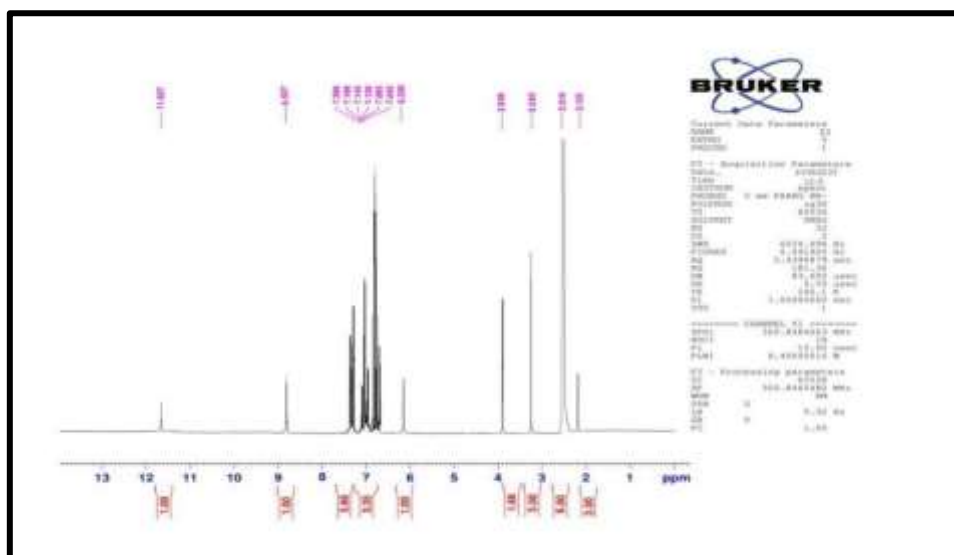


Figure 18. ¹H-NMR spectrum of (Z3).

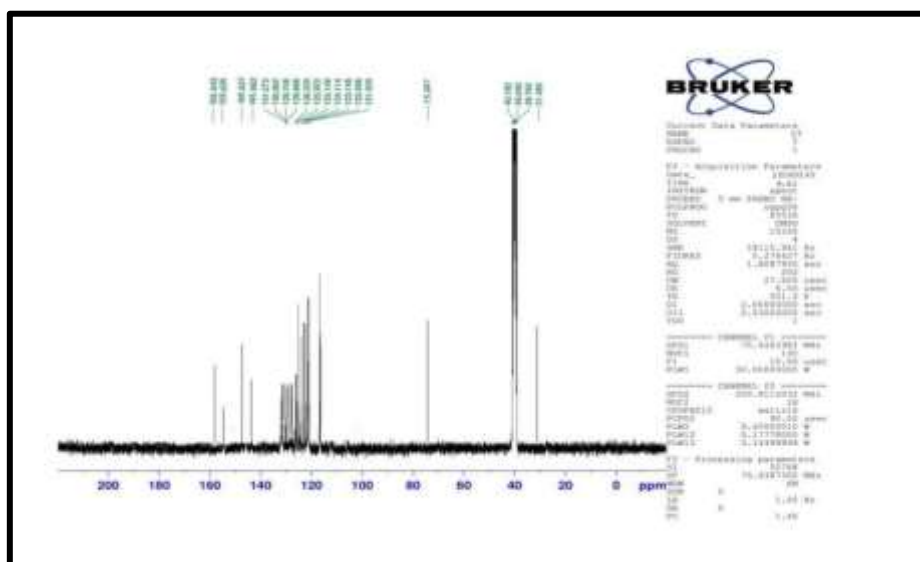


Figure 19. ¹³C-NMR spectrum of (Z3).

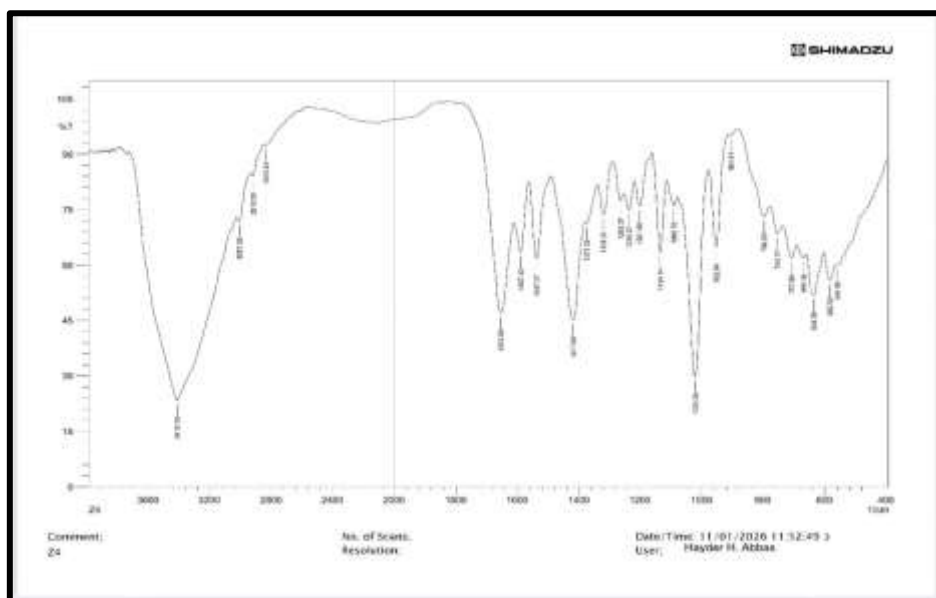


Figure 20. FT-IR Spectrum of (Z4).

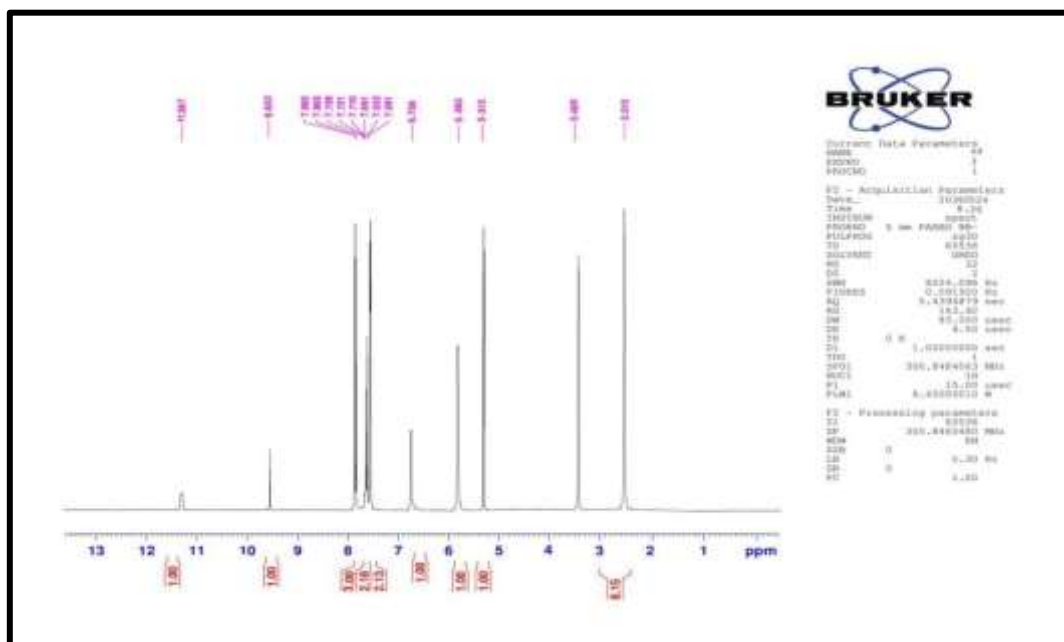


Figure 21. ¹H-NMR spectrum of (Z4).

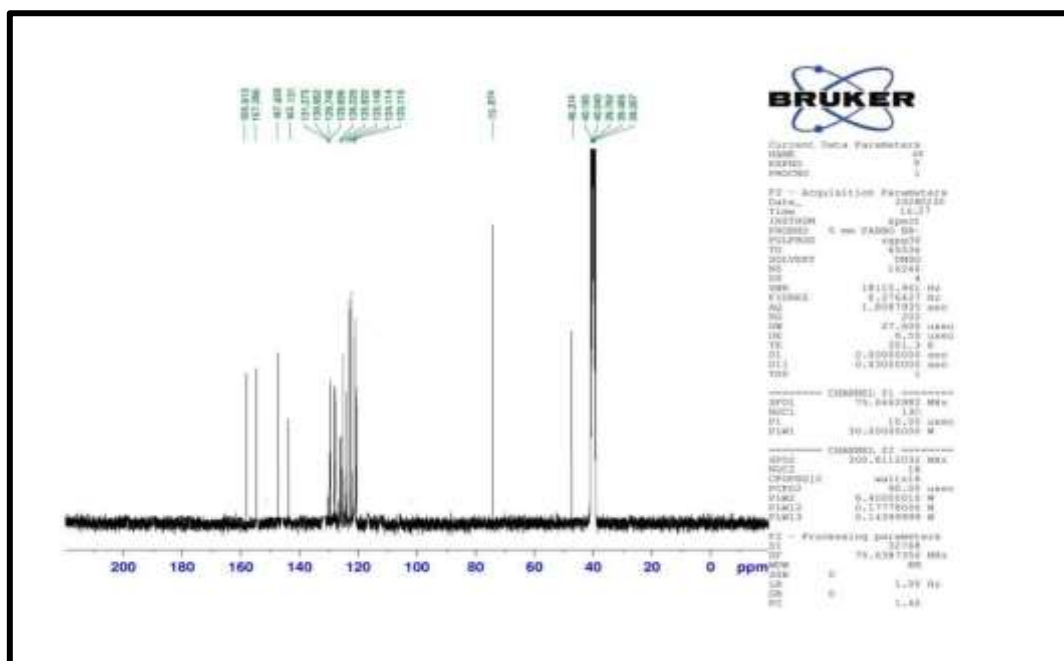


Figure 22. ¹³C-NMR spectrum of (Z4).

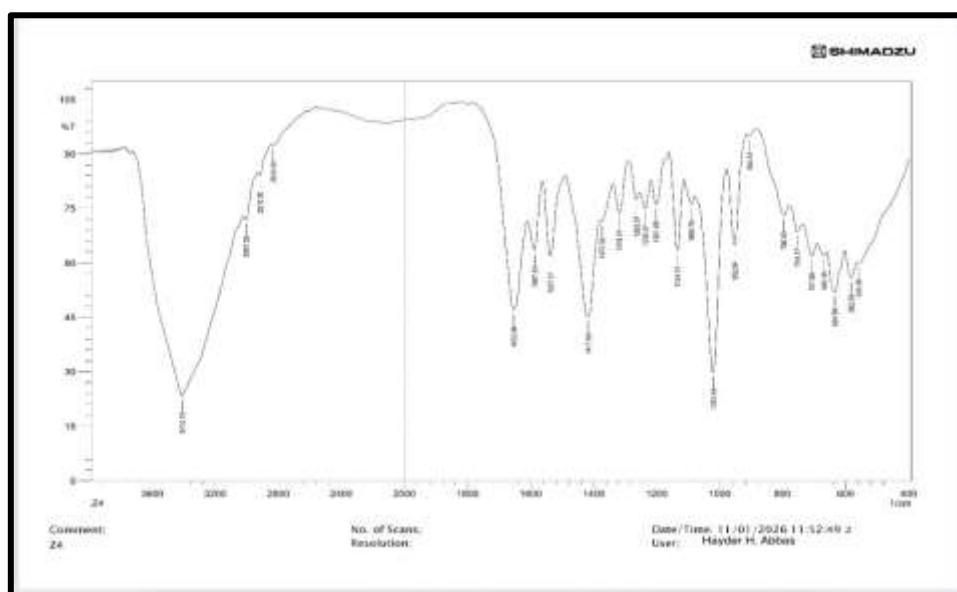


Figure 23. FT-IR Spectrum of (Z4)

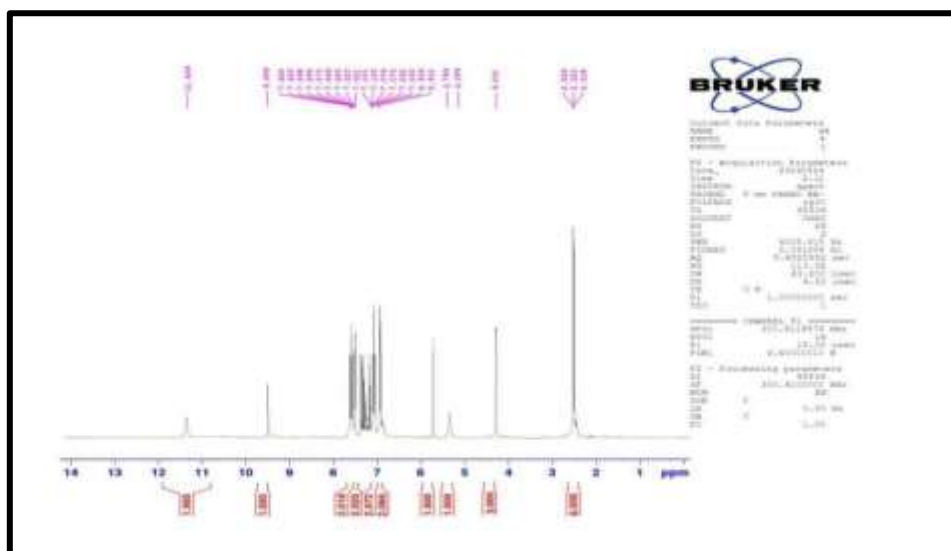


Figure 24. ¹H-NMR spectrum of (H4).

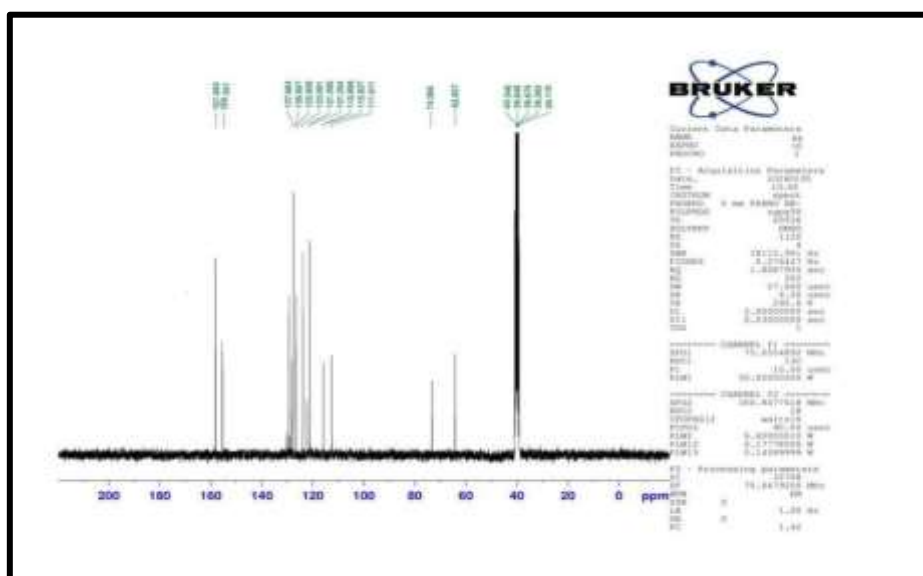


Figure 25. ¹³C-NMR spectrum of (H4).

3.1. Biological Activity

The results of antibacterial activity revealed that the biological performance of the synthesized compounds strongly depends on the concentration and the nature of the incorporated heterocyclic ring. Compound H4 showed the highest activity against *Pseudomonas aeruginosa* with inhibition zone of 28 mm at 0.50 mg/mL, compound Z4 showed the strongest activity against *Staphylococcus aureus* with inhibition zone of 20 mm. Most of the derivatives showed increased antibacterial effect with the increase in concentration. The results revealed that the introduction of heterocyclic rings especially tetrazole and thiazolidinone moieties increased the antibacterial activities of the parent sulfadiazine molecule.

Table 2

Code of compounds	<i>pseudomonas aeruginosa</i>		<i>Staphylococcus aureus</i>	
	0.025mg/ml	0.50mg/ml	0.025mg/ml	0.50mg/ml
Z	20mm	22mm	Zero	Zero
Z1	Zero	Zero	Zero	Zero

Z3	12mm	16mm	11mm	17mm
Z4	Zero	10mm	17mm	20mm
H	Zero	11mm	Zero	11mm
H1	10mm	13mm	Zero	12mm
H3	15mm	19mm	16mm	20mm
H4	22mm	28mm	12mm	14mm

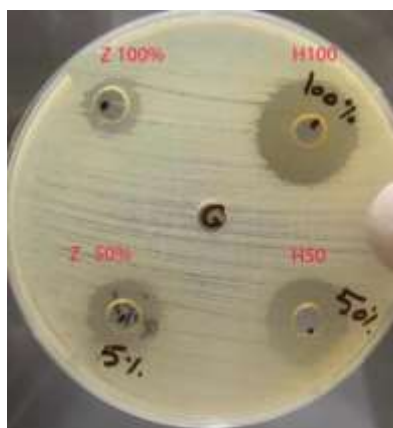


Figure 26. Anti bacterial activity of compounds H and Z against *Staphylococcus aureus* at full strength 100% and half strength 50% concentration.



Figure 27. Anti bacterial activity of compounds H and Z against *Pseudomonas aeruginosa* at full strength 100% and half strength 50% concentration.

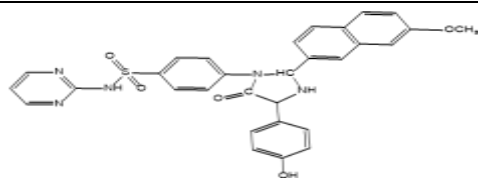
3.2. Molecular Docking Study

The molecular docking study showed that compounds H1 and Z3 have good binding affinities to the DHPS active site with binding energies of -8.40 and -7.68 kcal/mol, respectively, thinking about the activity of the compounds. Both compounds exhibited several stabilizing interactions, namely hydrogen bonds, van der Waals contacts and hydrophobic interactions. Z3 had hydrogen bonds with key residues such as SER and GLN, while H1 had the highest binding affinity. The results show that the synthesized derivatives can interact efficiently with the target enzyme and are in truce with the antibacterial activity observed.

Table 3

Compound Code	Stricture	Lowest Binding Energy	Run
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H1



-8.40

17

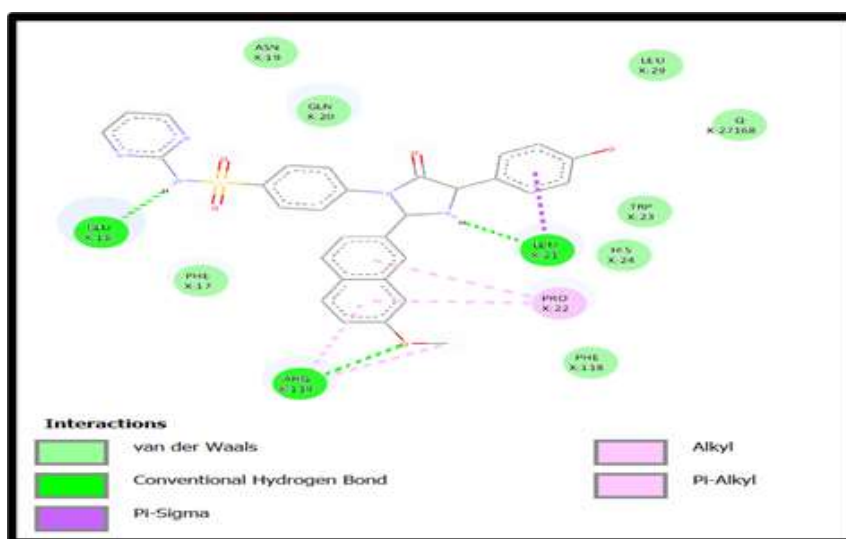


Figure 28. 2D interaction diagram illustrating the binding mode of compound H1 inside the active site of dihydropteroate synthase (DHPS) From *Escherichia coli* (PDB ID :3 SRW). The figure highlights conventional hydrogen bonds, van der Waals interactions, and hydrophobic (alkyl and π -alkyl) contacts responsible for stabilizing the ligand-protein complex.

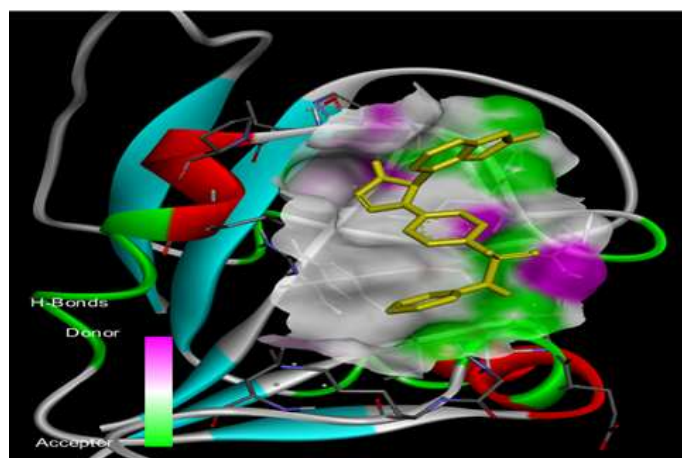


Figure 29. 3D binding pose of compound H1 inside the active site of dihydropteroate synthase (DHPS) From *Escherichia coli* (PDB ID :3 SRW), complementing the 2D interaction map and highlighting the conformational fit and key stabilizing interactions.

Table 4. Binding energy of the synthesized compound Z3:

Compound Code	Structure	Lowest Binding Energy	Run
Z3		-7.68	11

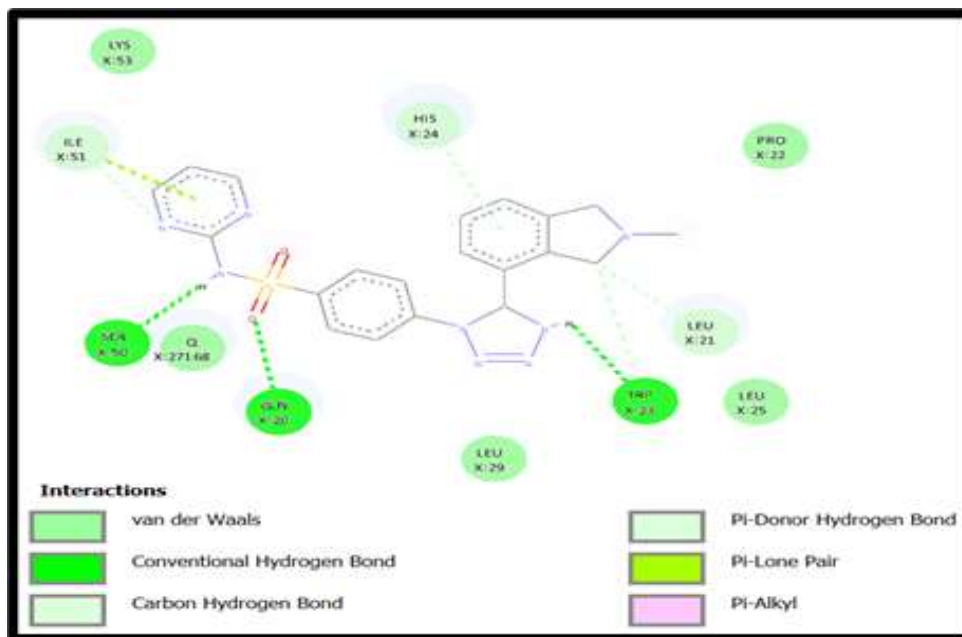


Figure 30. The 2D interaction map revealed that Z3 forms conventional hydrogen bonds with key residues such as SER and GLN, in addition to multiple hydrophobic (π - alkyl and alkyl) interactions with residues including TRP and LEU, alongside van der waals contacts that enhance stabilization.

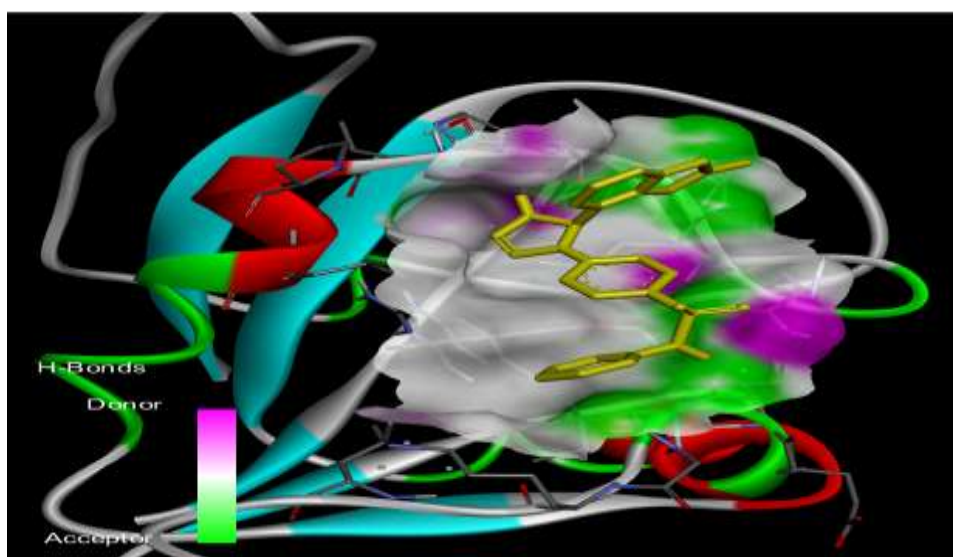


Figure 31. The 3D binding pose confirmed proper accommodation of Z3 inside the catalytic pocket, where the sulfonamide and heterocyclic moieties contribute to anchoring the ligand through hydrogen bonding and hydrophobic stabilization.

3.3. Antioxidant Activity:

The antioxidant activity of the synthesized compounds was evaluated using the DPPH free radical scavenging assay at different concentrations. The results demonstrated a clear concentration-dependent antioxidant effect, where the percentage of radical scavenging increased with increasing concentration, indicating the effectiveness of the tested compounds as electron donors.

Compound Z3 exhibited the highest antioxidant activity, reaching up to 80.33% inhibition at 1 mg/mL, which indicates a strong free radical scavenging ability. This significant activity can be attributed to the presence of heterocyclic moieties and electron-rich functional groups that enhance the electron donation capacity and stabilize the radical species.

Compounds H and Z1 showed moderate antioxidant activity, with scavenging percentages of approximately 62.46% and 62.31%, respectively, at the highest concentration. The observed activity suggests that these compounds possess reasonable antioxidant potential, although lower than that of Z3.

The decrease in scavenging activity with decreasing concentration further confirms the dose-dependent behavior of the synthesized compounds. The variation in antioxidant activity among the compounds can be explained based on structural differences, particularly the presence of conjugated systems and heteroatoms, which play a crucial role in enhancing radical stabilization.

Overall, the results indicate that the incorporation of heterocyclic structures significantly contributes to antioxidant activity, supporting the structure–activity relationship observed in the synthesized derivatives. These findings suggest that the compounds, especially Z3, may serve as potential candidates for further development as antioxidant agents.

Table 5. Antioxidant Activity of Compound (H) Determined by the DPPH Assay.

Sample Name	Concentration	Absorbency	Scavenging %
1	1mg/ml	0.3824	62.466
2	0.5mg/ml	0.5406	46.938
3	0.25mg/ml	0.5805	43.021
4	0.125mg/ml	0.7091	30.399
	Control	1.0188	

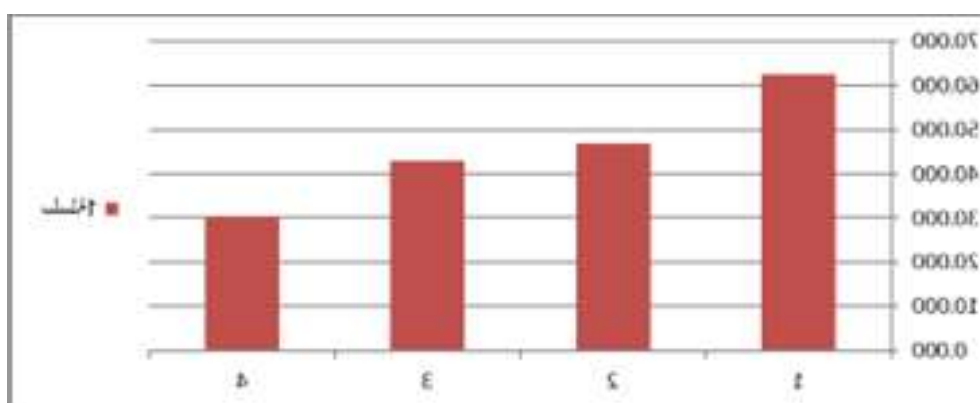


Figure 1. ANTIOXIDANT FOR (H)

Table 6. Antioxidant Activity of Compound Z1 Determined by the DPPH Assay.

Sample Name	Concentration	Absorbency	Scavenging %
1	1mg/ml	0.3839	62.318
2	0.5mg/ml	0.4533	55.506
3	0.25mg/ml	0.5413	46.869
4	0.125mg/ml	0.685	32.764
	Control	1.0188	

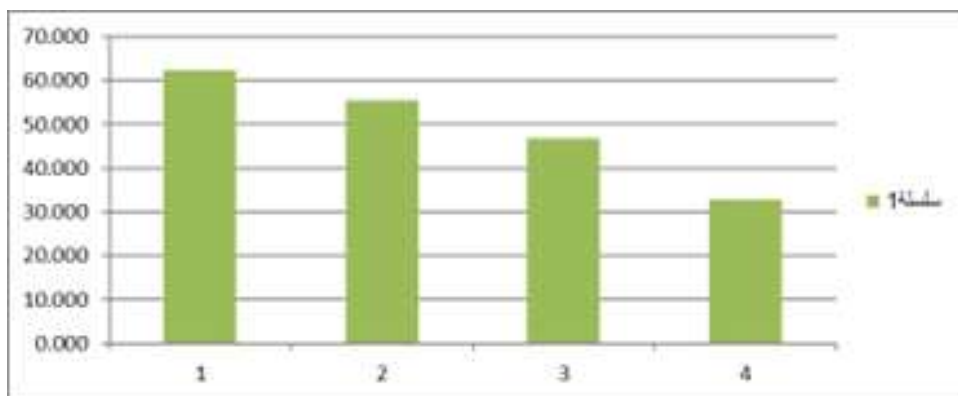


Diagram 2. ANTIOXIDANT FOR (Z1).

Table 7. Antioxidant Activity of Compound Z3 Determined by the DPPH Assay.

Sample Name	Concentration	Absorbency	Scavenging %
1	1mg/ml	0.2103	80.333
2	0.5mg/ml	0.2641	75.302
3	0.25mg/ml	0.4981	53.418
4	0.125mg/ml	0.6314	40.952
	Control	1.0188	

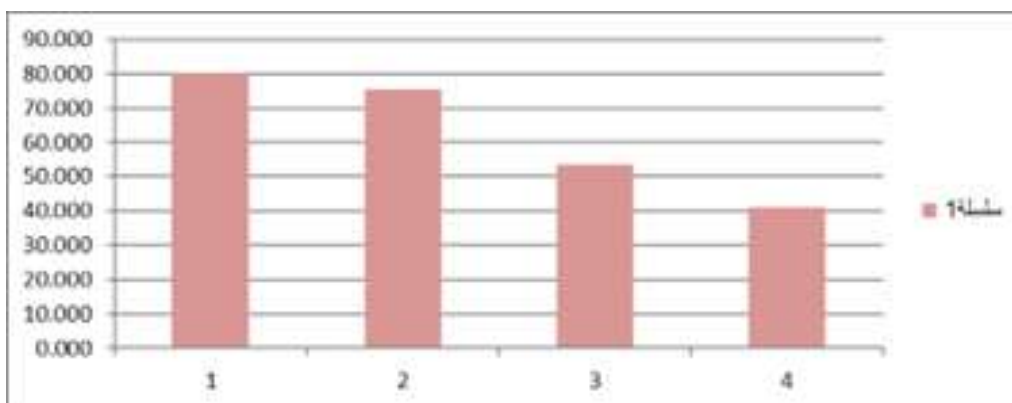


Diagram 3. ANTIOXIDANT FOR (Z3)

The overall results demonstrate a clear relationship between the chemical structure of the synthesized derivatives and their biological and antioxidant activities. While compound H1 exhibited the strongest binding affinity in molecular docking studies (-8.40 kcal/mol), compound H4 showed the highest antibacterial activity, suggesting that factors beyond binding energy, such as membrane permeability and lipophilicity, play a significant role in biological performance.

On the other hand, compound Z3 displayed superior antioxidant activity, which can be attributed to enhanced electron-donating ability and structural features that facilitate radical stabilization. The presence of heterocyclic rings and conjugated systems appears to contribute significantly to both binding interactions and biological activity.

These findings indicate that structural modification of sulfadiazine through the incorporation of heterocyclic moieties enhances ligand–protein interactions, improves membrane penetration, and increases

overall pharmacological activity. Moreover, the results are consistent with the observed improvement in activity compared to the parent drug sulfadiazine, confirming the effectiveness of this design strategy.

4. Conclusions

The present study successfully demonstrated the synthesis of novel heterocyclic derivatives derived from sulfadiazine via Schiff base formation followed by cyclization into five-membered rings, including imidazolidine, thiazolidine, and tetrazole derivatives. The structures of the synthesized compounds were confirmed using FT-IR, ¹H-NMR, and ¹³C-NMR analyses, indicating successful formation and ring closure.

The biological evaluation revealed that the synthesized compounds exhibited concentration-dependent antibacterial activity against both Gram-negative and Gram-positive bacteria. Among the tested compounds, H4 showed the highest antibacterial activity with an inhibition zone reaching 28 mm, indicating enhanced efficacy compared to the parent sulfadiazine. Furthermore, molecular docking studies supported the experimental findings, where compound H1 demonstrated the lowest binding energy (−8.40 kcal/mol) and strong interactions within the active site of dihydropteroate synthase (DHPS), confirming its high binding affinity and stability. In addition, antioxidant studies using the DPPH assay indicated that compound Z3 exhibited the highest radical scavenging activity (80.33%), reflecting its strong electron-donating capability. The observed enhancement in biological and antioxidant activities can be attributed to the introduction of azomethine (C=N) linkage and heterocyclic moieties, which improve lipophilicity, membrane permeability, and ligand–protein interactions.

Overall, these findings confirm that structural modification of sulfadiazine into heterocyclic derivatives significantly enhances its pharmacological potential. The synthesized compounds, particularly H1, H4, and Z3, represent promising candidates for further investigation as antimicrobial and antioxidant agents.

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Author's Contributions

Russull Zamil Abdulhassan performed research; contributed new reagents tools; analyzed data; coordinated research; and wrote the paper.

Prof.Dr.Nadia Sadiq Majeed coordinated and supervised the research, contributed analytical tools/instrumentation support, and reviewed and edited the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. T. G. Chow and D. A. Khan, "Sulfonamide Hypersensitivity.," *Clin. Rev. Allergy Immunol.*, vol. 62, no. 3, pp. 400–412, Jun. 2022, doi: 10.1007/s12016-021-08872-3.
2. P. A. Asyraf, I. F. Kusnadi, J. Stefanus, M. A. Khairinisa, and R. Abdulah, "Clinical Manifestations and Genetic Influences in Sulfonamide-Induced Hypersensitivity," *Drug Healthc. Patient Saf.*, vol. 14, no. July, pp. 113–124, 2022, doi: 10.2147/DHPS.S347522.
3. S. J. Ghosh *et al.*, "Drug Action of Sulfonamide Schiff Bases: Structure, Antimicrobial Activity and In-Silico Studies," *ES Chemistry and Sustainability*, pp. 1–12, 2024, doi: 10.30919/escs1320.
4. J. B. Ziwar, "Synthesis, Characterization, and Antimicrobial Evaluation of New Heterocyclic Compounds Bearing a Biologically Active Sulfadiazine Moiety," *Zanco J. Pure Appl. Sci.*, vol. 36, no. 1, pp. 70–81, 2024, doi: 10.21271/zjpas.36.1.7.

5. N. Xu, M. Li, Z. Lin, and X. Ai, "Comparative Pharmacokinetics of Sulfadiazine and Its Metabolite N4-Acetyl Sulfadiazine in Grass Carp (*Ctenopharyngodon idella*) at Different Temperatures after Oral Administration," *Pharmaceutics*, vol. 14, no. 4, 2022, doi: 10.3390/pharmaceutics14040712.
6. S. Mohammed, A. AL-Hadedi, and S. Abood, "The Role of Sulfa Drugs in our Life," *Rafidain Journal of Science*, vol. 31, no. 3, pp. 64–74, 2022, doi: 10.33899/rjs.2022.175395.
7. W. Liu, J. Chen, and W. Su, "Recent Advances in the Synthesis of Sulfonamides Intermediates," *Pharmaceutical Fronts*, vol. 6, no. 4, pp. e355–e381, 2024, doi: 10.1055/s-0044-1796646.
8. S. J. Kokre *et al.*, "Sulfonamides: a versatile scaffold for diverse biological activity," *Results Chem.*, vol. 18, no. July, p. 102858, 2025, doi: 10.1016/j.rechem.2025.102858.
9. T. Kosmalski *et al.*, "The Application of Green Solvents in the Synthesis of S-Heterocyclic Compounds—A Review," *Int. J. Mol. Sci.*, vol. 25, no. 17, 2024, doi: 10.3390/ijms25179474.
10. Ashwaq Abbas Ali and Nadia Sadiq Majeed, "Microwave-Assisted Synthesis of Five and Seven-Membered Heterocycles from Ibuprofen and Study Their Biological Activity," *Journal of Kufa for Chemical Sciences*, vol. 3, no. 3, pp. 223–239, 2024, doi: 10.36329/jkcm/2024/v3.i3.15885.
11. H. S. Lihumis, A. A. Alameri, and R. H. Zaooli, "Design, Synthesis of Sulfadiazine Derivatives bearing Some New Heterocyclic Compounds with study Antimicrobial and Antioxidant Activity," *Egypt. J. Chem.*, vol. 66, no. 2, pp. 81–91, 2023, doi: 10.21608/ejchem.2022.131305.5787.
12. A. Angeli, N. Paoletti, and C. T. Supuran, "Five-Membered Heterocyclic Sulfonamides as Carbonic Anhydrase Inhibitors," *Molecules*, vol. 28, no. 7, 2023, doi: 10.3390/molecules28073220.
13. Marwa Abdullah Saleh, Karima Fadhil Ali, and Basma M. Abd Razik, "Synthesizing, Studying Molecular Docking, Characterizing, and Preliminary Evaluating Anti-Bacterial Effects of Derivatives of Serotonin Contain Imidazolidine Ring," *Al Mustansiriyah Journal of Pharmaceutical Sciences*, vol. 22, no. 3, pp. 1–16, 2022, doi: 10.32947/ajps.v22i3.884.
14. Faten Jassim Mohammed and Nadia Sadiq Majeed, "Preparation. Identification and Antioxidant of some new Imidazolidine tetrazole, and thiazolidine derivatives from Schiff bases," *Journal of Kufa for Chemical Sciences*, vol. 3, no. 3, pp. 40–56, 2024, doi: 10.36329/jkcm/2024/v3.i3.15519.
15. S. L. Khalil and N. H. Saleem, "Synthesis and Characterization of Five-Membered Heterocyclic Compounds of Tetrazole Derivatives and Their Biological Activity," *Chemical Problems*, vol. 23, no. 3, pp. 365–374, 2025, doi: 10.32737/2221-8688-2025-3-365-374.
16. L. Maji *et al.*, "Exploring tetrazole chemistry: synthetic techniques, structure–activity relationship, and pharmacological insights in antimicrobial and anticancer therapy," *Front. Chem.*, vol. 13, no. December, pp. 1–42, 2025, doi: 10.3389/fchem.2025.1700143.
17. M. A. El-Zend, I. M. El-Deen, M. F. M. Reyad, S. Z. Alshawwa, A. A. Alrashidi, and E. M. Saied, "Design, synthesis, and multi-target anticancer evaluation of 1,3-thiazolidin-4-one analogues against breast cancer: mechanistic insights into estrogen metabolism, inflammation, angiogenesis, and oxidative stress," *RSC Adv.*, vol. 16, no. 3, pp. 2528–2554, 2026, doi: 10.1039/d5ra07680c.
18. M. Krátky *et al.*, "Sulfadiazine salicylaldehyde-based schiff bases: Synthesis, antimicrobial activity and cytotoxicity," *Molecules*, vol. 22, no. 9, pp. 1–15, 2017, doi: 10.3390/molecules22091573.
19. F. L. Yahya, F. A. Dawood, and R. K. R. Al-shemary, "Available online at www.derpharmachemica.com ISSN 0975-413X CODEN (USA): PCHHAX Synthesis and Applications of Schiff Bases from Some Sulfa Drugs and Their Metal Complexes: Review," vol. 14, no. 12, pp. 18–24, 2022.
20. J. Ceramella, D. Iacopetta, A. Catalano, F. Cirillo, R. Lappano, and M. S. Sinicropi, "A Review on the Antimicrobial Activity of Schiff Bases: Data Collection and Recent Studies," *Antibiotics*, vol. 11, no. 2, 2022, doi: 10.3390/antibiotics11020191.
21. A. A. Muhee and M. I. Kadhim, "Synthesis, antibacterial, and molecular docking of some new tetrazole, oxazepine, and thiazolidine derivatives contacting with an aromatic nucleus," *Chemical Review and Letters*, vol. 7, no. 3, pp. 647–654, 2024, doi: 10.22034/crl.2024.459423.1341.
22. D. P. Gavate *et al.*, "The Role of Heterocycles in Modern Pharmaceutical Chemistry: Synthesis, Biological Activity, and Drug Design," *International Journal of Pharmaceutical Research and Applications*, vol. 9, no. 4, p. 455, 2024, doi: 10.35629/4494-0904455463.
23. E. Abisola *et al.*, "Heterocyclic Compounds in Drug Development: A Medicinal Chemistry Perspective Review," *International Journal of Advances in Engineering and Management (IJAEM)*, vol. 7, no. 10, p. 69, 2025, doi: 10.35629/5252-07106978.
24. N. M. Abdulhussein and Z. H. Abood, "Synthesis and Study Biological Activity of Some New Substituted Thiazolidin-4-one Derivatives," *Iraqi Journal of Science*, vol. 65, no. 10, pp. 5370–5384, 2024, doi: 10.24996/ij.s.2024.65.10.3.