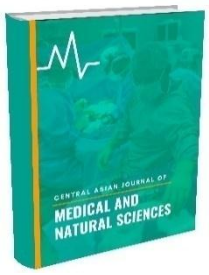
CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES



Volume: 04 Issue: 06 | Nov-Dec 2023 ISSN: 2660-4159

http://cajmns.centralasianstudies.org

Synthesis and Study of the Biological Activity of Some Oxazepine Containing the Pyrrolidine Ring

1. **Ayad Sulaiman Hamad**
2. **Qader Abdulla Shnak**
3. **Marwan Hasan Ali**

Received 2nd Oct 2023,
Accepted 19th Oct 2023,
Online 30th Nov 2023

[1, 2] Department of Chemistry, College of Education for Pure Sciences, Tikrit University/ Iraq

[3] Nineveh Education Directorate / Iraq

Abstract: In this study, amine compounds (HA1, HA2) were prepared. Schiff bases (HA3-HA6) were prepared by reacting amine compounds with benzaldehyde substitutes. Oxazepane derivatives (HA7-HA10) were prepared by reacting Schiff bases with phthalic anhydride. Characterization by using melting point, TLC, FT-IR, 1H-NMR, and 13C-NMR. The biological activity of some of the prepared compounds was evaluated.

Key words: Pyrrolidine, Thiosemicarbazide, Oxazepine, heterocyclic rings.

1. Introduction

Heterocyclic compounds are compounds that contain nitrogen, oxygen, sulfur, and carbon atoms [1,2]. Heterocyclic compounds are important; Because of its widespread in nature, and it is included in the composition of many organic compounds that are essential in the basic formation of life, as there are various forms, including sugars and their derivatives [3], and also that some enzymes and vitamins that play an important role in the metabolic processes of all cells contain in their structure non-rings Homogeneous as a vitamin (ascorbic acid) that contains the furan ring [4].

2. Experimental part:

2.1. Preparation of 2-Amino-5-(-4-(pyrrolidine-1-yl)phenyl)thiazole-4-carboxylic acid (HA)

(0.025 mol, 4.375 g) of 4-(1-pyrrolidinyl) benzaldehyde) and (0.025 mol, 1g) of sodium hydroxide were mixed with ethanol in (15) ml of absolute ethanol, with (0.025 mol,3.2g) alpha-dichloro acetic acid and (0.025 mol, 1.9 g) of thiourea, and the mixture was escalated for (4) hours, cooled to the laboratory temperature, then the precipitate was filtered and recrystallized from ethanol to give a pink precipitate [5],with a melting point of (207-210) C° and the percentage of the product (64%).

2.2. Preparation of 5-(2-amino-5-(4-(pyrrolidin-1-yl)phenyl)thiazol-4-yl)-1,3,4-thiadiazol-2-amine (HA_2)

In an appropriate glass beaker that could withstand heat and didn't need a solvent, equal moles of (HA) and thiosemicarbazide were combined. The mixture was heated at the melting point with stirring and thorough mixing for 5 to 10 minutes or until it changed. The nature of the molten reactants in terms of

color and texture, the amount of product (91%), the melting point of the product (225-227 °C), and the collection and recrystallization of the product with ethanol [6].

2.3. Preparation of Schiff base derivatives (HA_3-HA_6)

(HA) and thiosemicarbazide was mixed in a suitable glass beaker that could endure heat and didn't need a solvent. For five to ten minutes, or until it changed, the mixture was heated to the melting point while well mixed and stirred. The characteristics of the molten reactants, including their color and texture, their quantity (91%), their melting point (225-227 °C), and their collection and recrystallization with ethanol [6].

Table (1): The physical properties of Schiff bases derivatives (HA_3-HA_6)

Comp. No.	R	M.P (C)^0	Yield %	Powder Color
HA_3	2- OH	211-213	68	Gray
HA_4	2- Cl	226-228	72	Light Yellow
HA_5	4- NO_2	231-233	70	Light brown
HA_6	4- OCH_3	221-223	69	Yellow

2.4. Preparation of oxazepine derivatives (HA_7-HA_{10})

Equal moles of (HA_3-HA_6) (0.001) moles were dissolved with (0.001) moles of phthalic anhydride in 20 ml of methanol, and the mixture was elevated for 6 hours, added to crushed ice, and recrystallized with acetone [7].

Table (2): The physical properties of oxazepine derivatives (HA_7-HA_{10})

Comp. No.	R	M.P (C)^0	Yield %	Powder Color
HA_7	2- OH	242-244	77	Gray
HA_8	2- Cl	248-250	81	Light Yellow
HA_9	4- NO_2	247-249	84	Light brown
HA_{10}	4- OCH_3	239-241	73	Yellow

2.5. Measurement of biological activity

The biological activity was measured by the agar-well diffusion method [8,9], where the method included spreading the bacterial inoculum on the entire culture medium using a glass diffuser and then drilling wells in the agar medium using a hole punch [10]. A sterilizer with a diameter of 6 mm was to load the solutions with a volume of 100 microliters of each concentration in one dish in which one bacterial sample was grown separately. This step was repeated for all the solutions prepared with their concentrations and each bacterial sample used under study [11]. The compounds' biological activity (antibacterial activity test) was studied on two types of bacteria [12]. After selecting the above isolates, they were activated using Nutrient Broth liquid medium by re-cultivating them in the above medium and then incubating them in a laboratory incubator at 37 °C for 24 hours to be ready to make the bacterial Vaccine at a concentration of 1.5 x 108 bacterial cells per ml of the physiological solution by comparing Vaccine with a McFarland standard score of 0.5 [13].

3. Results and Discussion

3.1. FT-IR of Prepared compounds

Table (3): FT-IR of Prepared compounds

Comp. No	R	ν Ar-H	ν C=N		ν C=C-Ar	νC-N	Others
HA_3	2-OH	3029	1641		1593,1527	1386	ν OH 3423
HA_4	2-Cl	3047	1623		1533,1502	1384	ν C-Cl 808
HA_5	4-NO_2	3041	1631		1602,1521	1388	νNO_2 asy 1456 sy 1311
HA_6	4-OCH_3	3053	1623		1531,1512	1385	νCH_3 sy 2860 asy 2947
Comp. No	R	ν Ar-H	νC=O ester	νC=O amide	νC=C-Ar	νC-N	Others
HA_7	2-OH	3031	1730	1677	1600,1523	1386	ν OH 3477
HA_8	2-Cl	3024	1728	1682	1598,1567	1388	ν C-Cl 802
HA_9	4-NO_2	3053	1724	1693	1601,1564	1367	νNO_2 asy 1493 sy 1330
HA_{10}	4-OCH_3	3039	1735	1687	1600,1523	1388	νCH_3 sy 2856 asy 2941

3.2. ^{1}H-NMR of Prepared compounds

The (^{1}H-NMR) of (HA_3) also showed a signal at the chemical shift= (2.00 ppm) and a signal at the chemical shift= (3.27) ppm due to the (CH_2) protons of the pyrrolidine ring, with multiple signals appearing at the chemical shift= (7.57-6.53). ppm refers to the protons of the aromatic ring (Ar-CH), with the appearance of a signal at chemical shift= (8.21) ppm belonging to a proton (H-C=N), and the appearance of a signal at chemical shift= (9.66) ppm belonging to a proton (OH) [14, 15], as shown in the figure (5) for the compound (HA_3).

The (^{1}H-NMR) of (HA_5) also showed a signal at the chemical shift= (2.00) ppm and a signal at the chemical shift= (3.30) ppm due to the protons (CH_2) of the pyrrolidine ring, with multiple signals appearing at the chemical shift= (7.70-6.58) ppm refers to the protons of the aromatic ring (Ar-CH), with the appearance of a signal at chemical shift= (8.23) ppm belonging to a proton (H-C=N) [16, 17], as shown in Figure (6) of the compound (HA_5)

The (^{1}H-NMR) of (HA_8) also showed a signal at (2.00) ppm and a signal at (3.30) ppm due to the (CH_2) protons of the pyrrolidine ring, with multiple signals appearing at (8.25-6.58) ppm refers to the protons of the aromatic ring (Ar-CH) [18], as shown in Figure (7) of the compound (HA_8).

The (^{1}H-NMR) of (HA_9) also showed a signal at the chemical shift= (1.99) ppm and a signal at the chemical shift= (3.31) ppm due to the (CH_2) protons of the pyrrolidine ring, with multiple signals appearing at the chemical shift= (8.21-6.56). ppm refers to the protons of the aromatic ring (Ar-CH) [19, 20], as shown in Figure (8) of the compound (HA_9).

3.3. ^{13}C-NMR of Prepared compounds

When studying the (^{13}C-NMR) of (HA_3), it was noted that a signal appeared at the chemical shift= (33.64) ppm and a signal at the chemical shift= (47.73) ppm belonging to carbon (CH2) of the pyrrolidine ring, and multiple signals at the chemical shift= (175.52-111.76) ppm belonging to carbon (C=C)) of the aromatic rings [21, 22], as shown in Figure (9) for compound (HA_3)

When studying the (^{13}C-NMR) spectrum of the prepared (HA_5) compound, it was noted that a signal appeared at the chemical shift= (33.38) ppm and a signal at the chemical shift= (47.84) ppm due to carbon (CH_2) of the pyrrolidine ring, and multiple signals at the chemical shift= (190.17-111.75) ppm

belonging to carbon (C=C)) for the aromatic rings [23, 24], as shown in Figure (10) for the compound (HA_5).

When studying the (^{13}C-NMR) of (HA_7), it was noted that a signal appeared at the chemical shift= (34.77) ppm and a signal at the chemical shift= (47.72) ppm belonging to carbon (CH_2) of the pyrrolidine ring, and multiple signals at the chemical shift= (154.17-111.97) ppm belonging to Carbon (C=C)) for aromatic rings, and a signal at 168.56)) ppm refers to carbon (C=O) [25], as shown in Figure (11) for compound (HA_7).

3.4. Biological activity

After conducting tests related to the effectiveness of the solutions against different bacterial species, we obtained the results shown in Tables (3), where the solutions were tested on two types, namely S. aureus and E. coli. The tests showed that the selected solutions had high efficacy [26], as shown in Table (3) and Figure (12), where the solutions gave a clear variation in the effectiveness of the compounds against both types of the selected bacterial genera, meaning that the solutions were effective against the antimicrobial activity towards these Types [27], and as shown in Table (3). It is worth noting that the secondary dilutions inhibition drops showed a similar effectiveness to the concentrated solutions, meaning that the low concentrations have a low concentration antibacterial activity (LCAA) [28], meaning that low concentrations can be used to inhibit bacteria, in other words, with a lower economic cost (LEC) Low [29].

Table (3): The biological activity of some compounds against S. aureus and E. coli bacteria

Concentrations and diameter of inhibition in (mm)						Sample code
E. coli			*Staphylococcus aureus*			
0.0001	**0.001**	**0.1**	**0.0001**	**0.001**	**0.1**	
7	9	13	9	13	14	HA7
niz	6	14	niz	7	11	HA8
niz	4	16	8	12	15	HA9
0	11	11	8	8	9	HA10

***NIZ (No Inhibition Zone)**

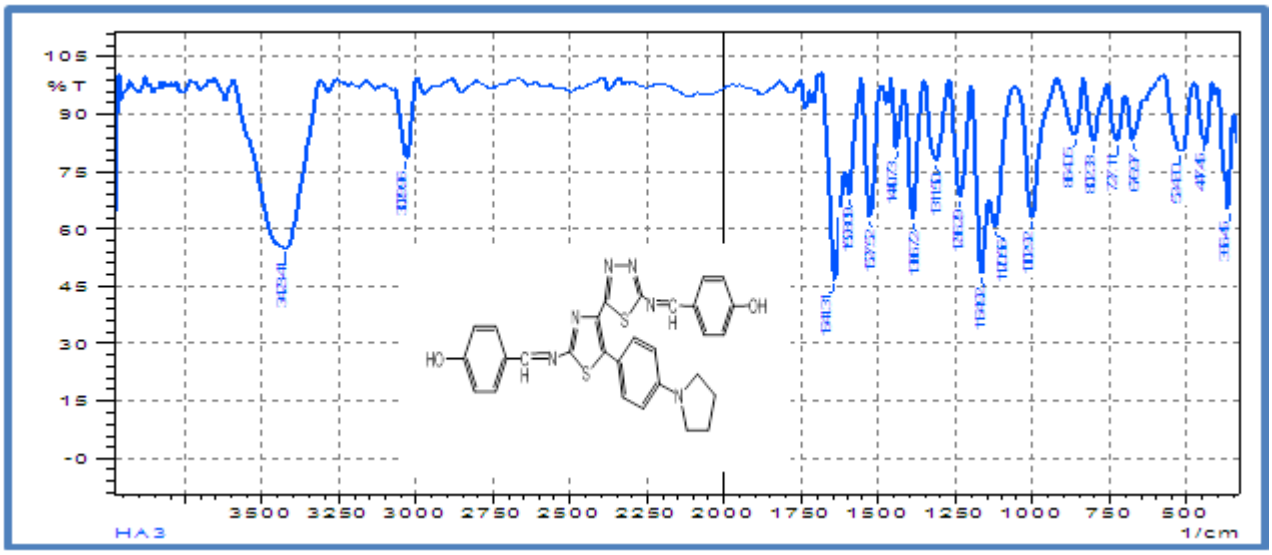


Figure (1): FT-IR spectrum of (HA_3).

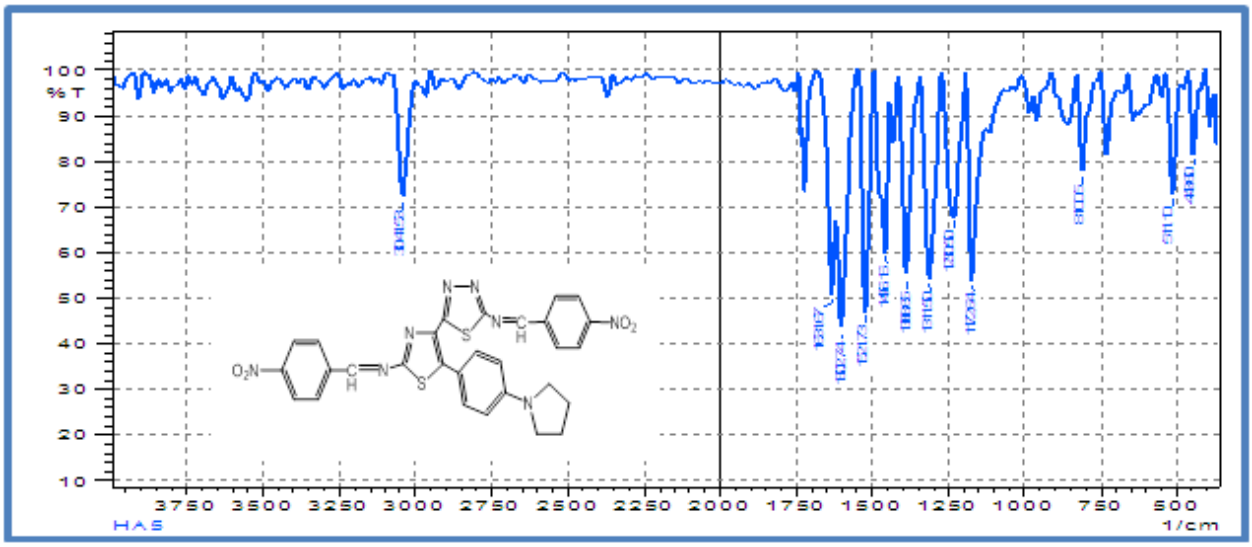


Figure (2) : FT-IR spectrum of (HA_5).

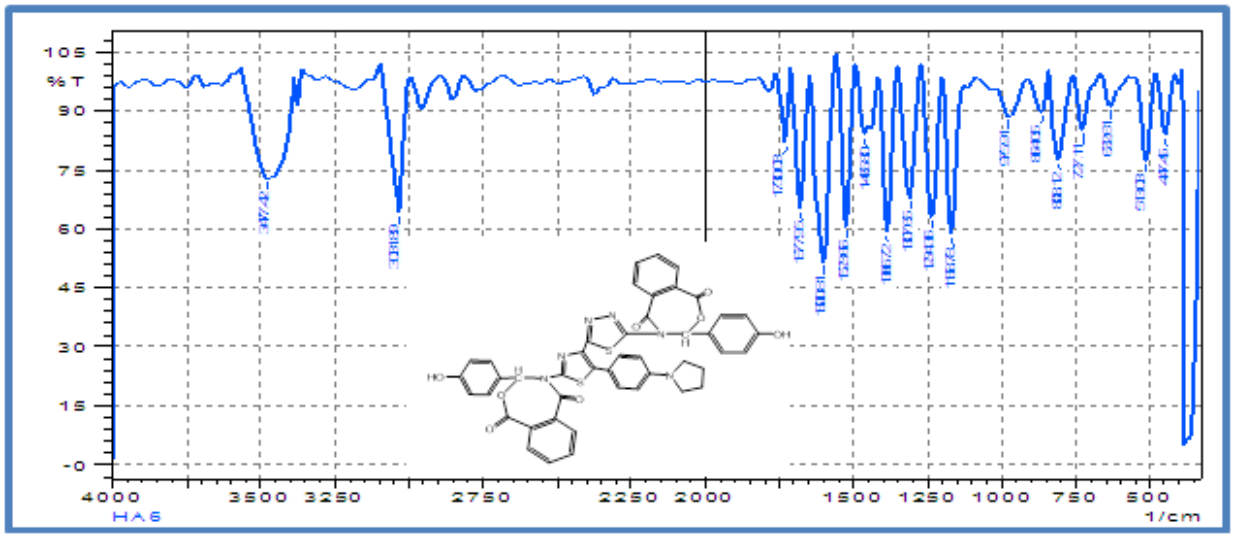


Figure (3) : FT-IR spectrum of (HA_6).

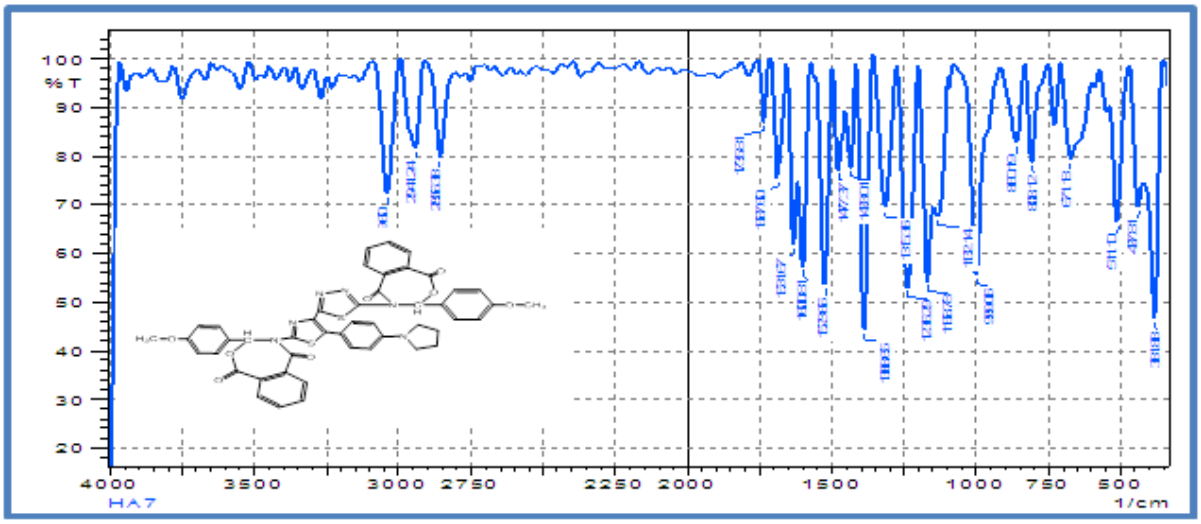


Figure (4): FT-IR spectrum of (HA7).

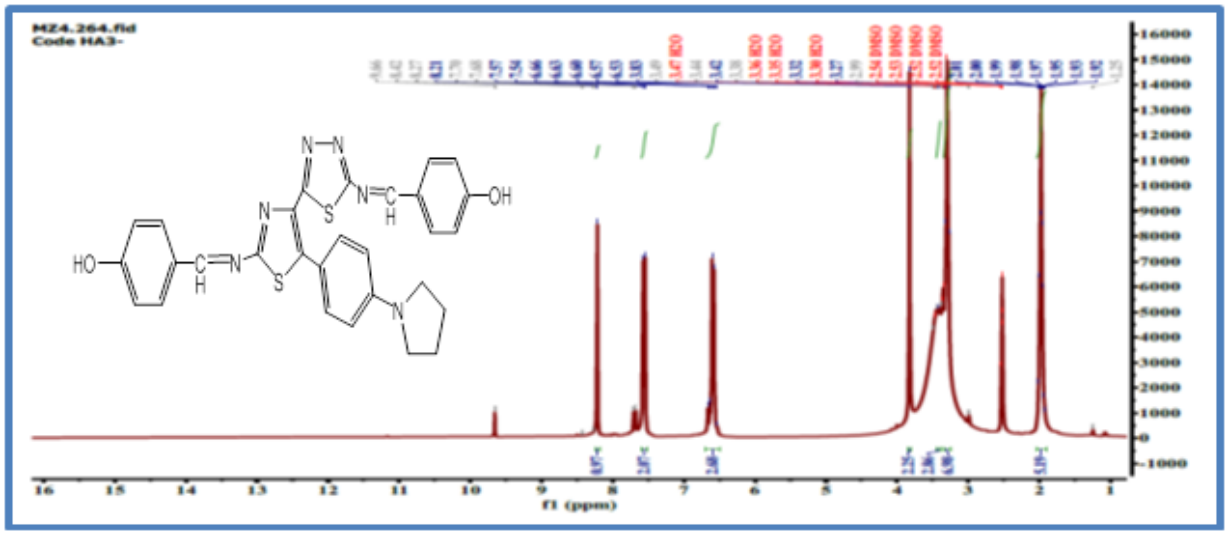


Figure (5): (^{1}H-NMR) spectrum of (HA_3).

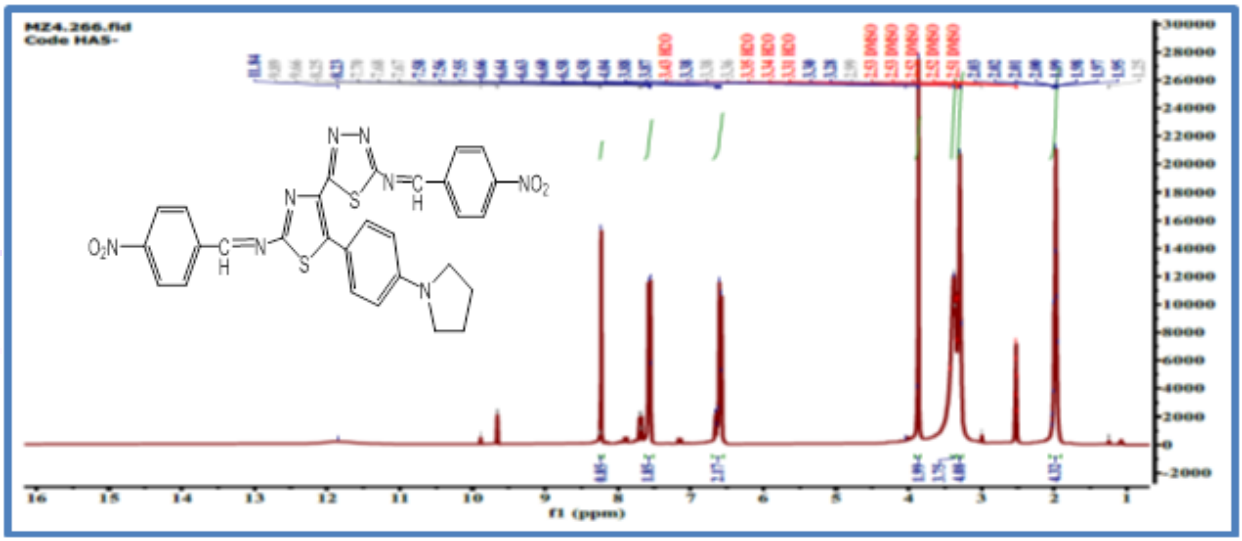


Figure (6): (^{1}H-NMR) spectrum of (HA5).

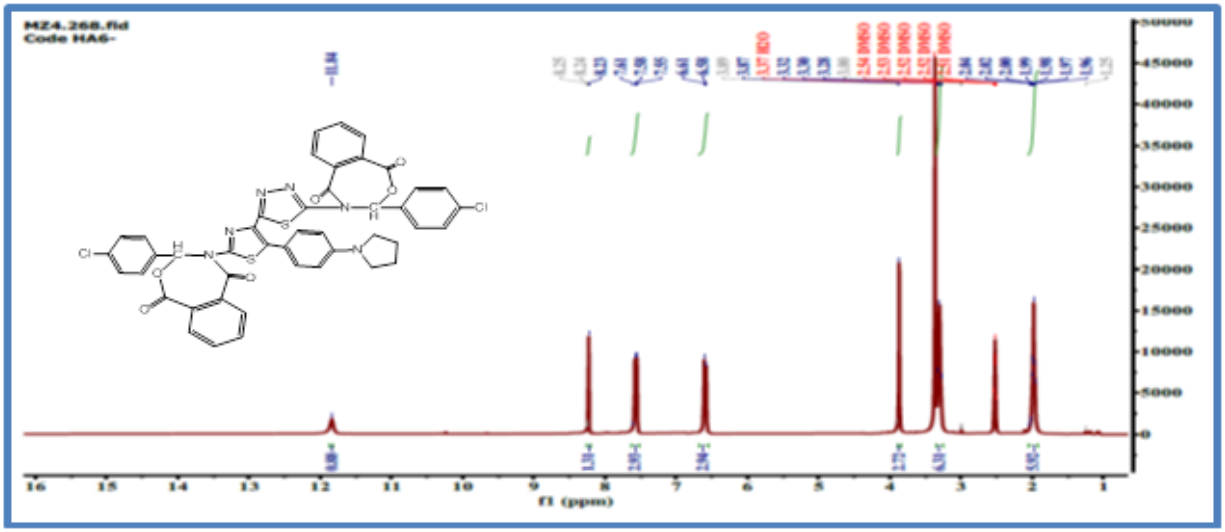


Figure (7): (^{1}H-NMR) spectrum of (HA_6).

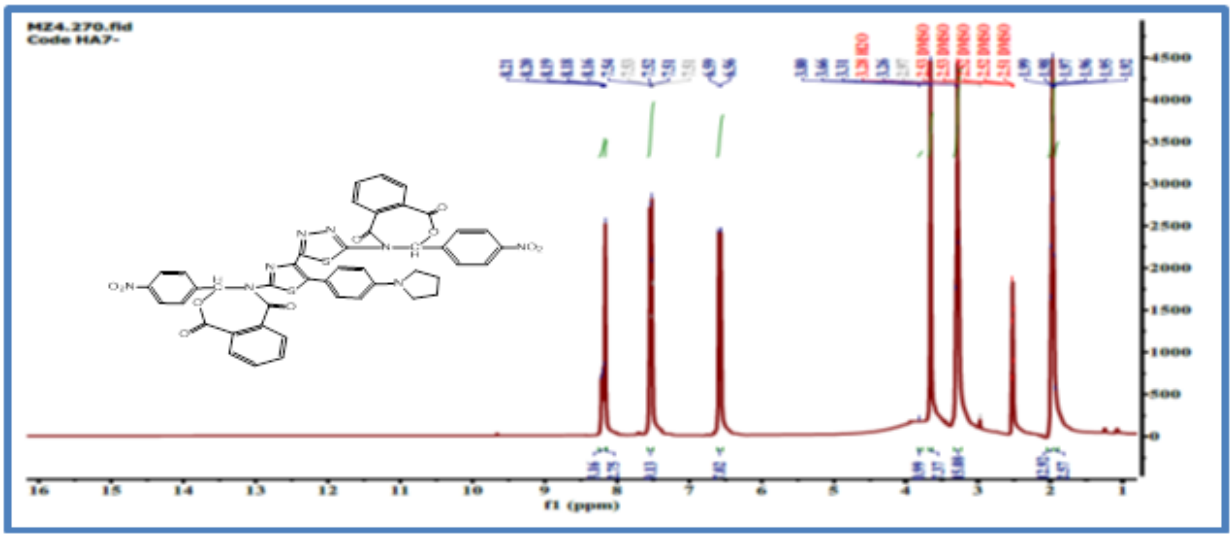


Figure (8): (^{1}H-NMR) spectrum of (HA_8).

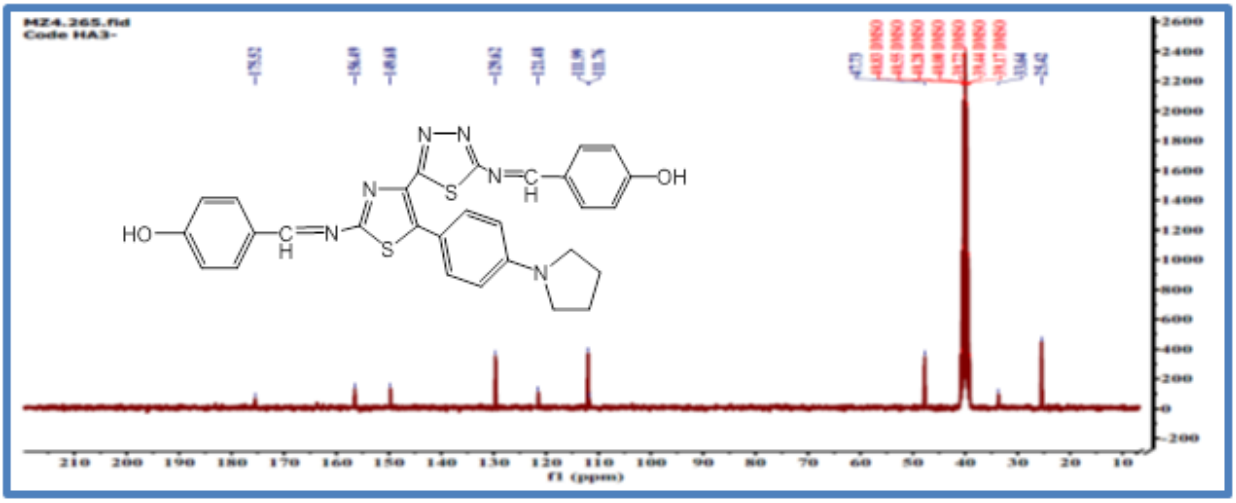


Figure (9): (^{13}C-NMR) spectrum of (HA_3)

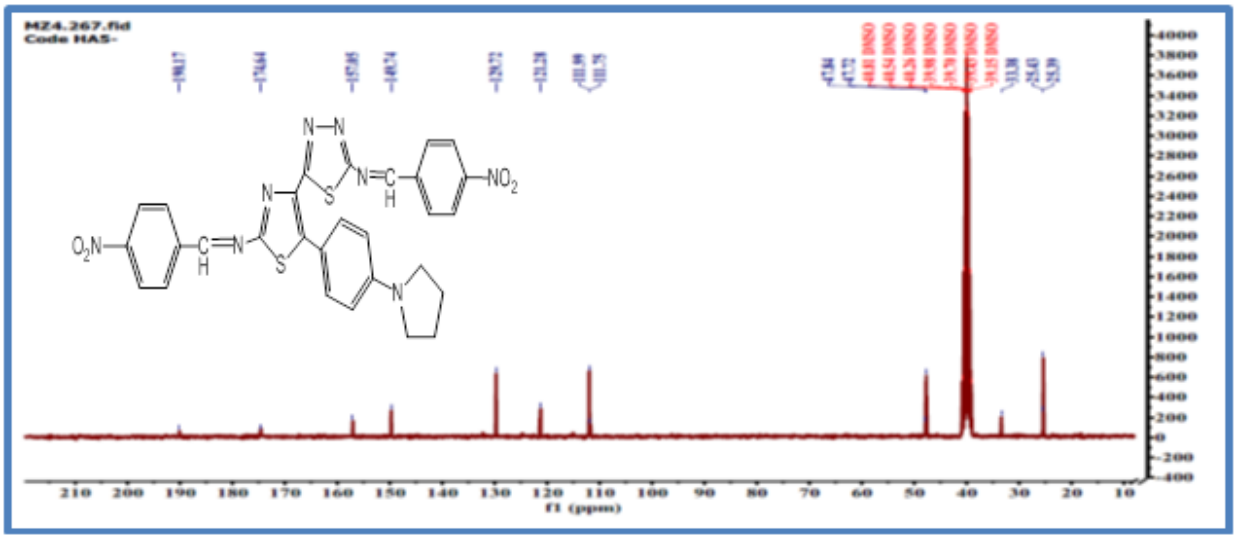


Figure (10): (^{13}C-NMR) spectrum of (HA_5)

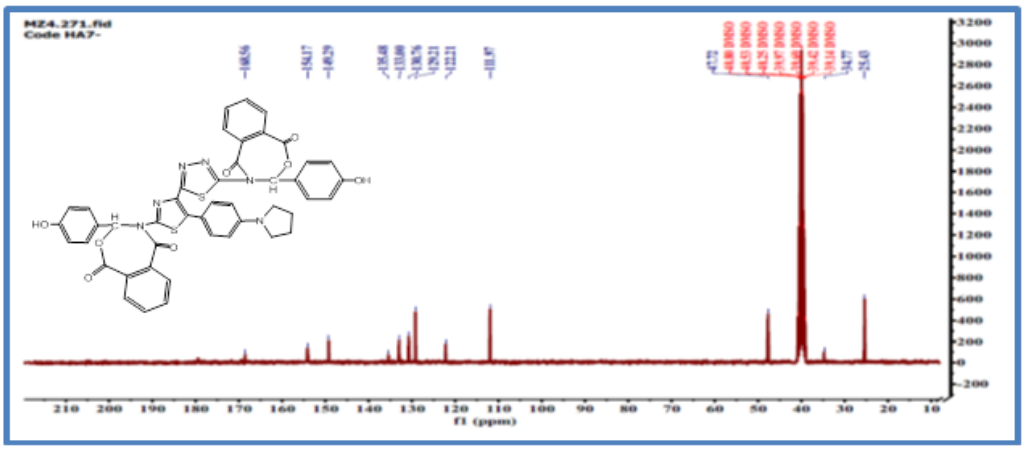


Figure (11): (^{13}C-NMR) spectrum of (HA_7)

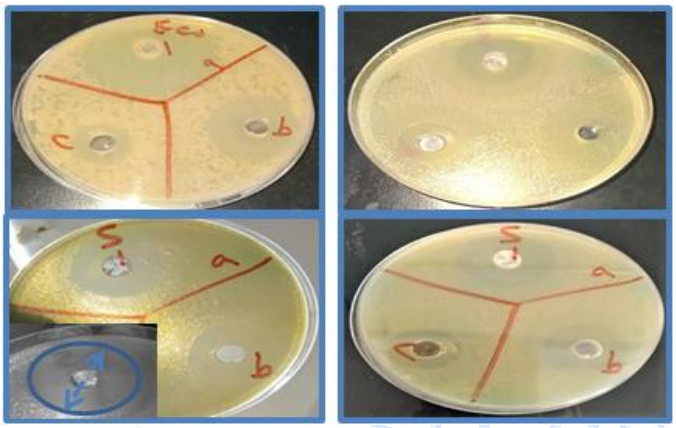
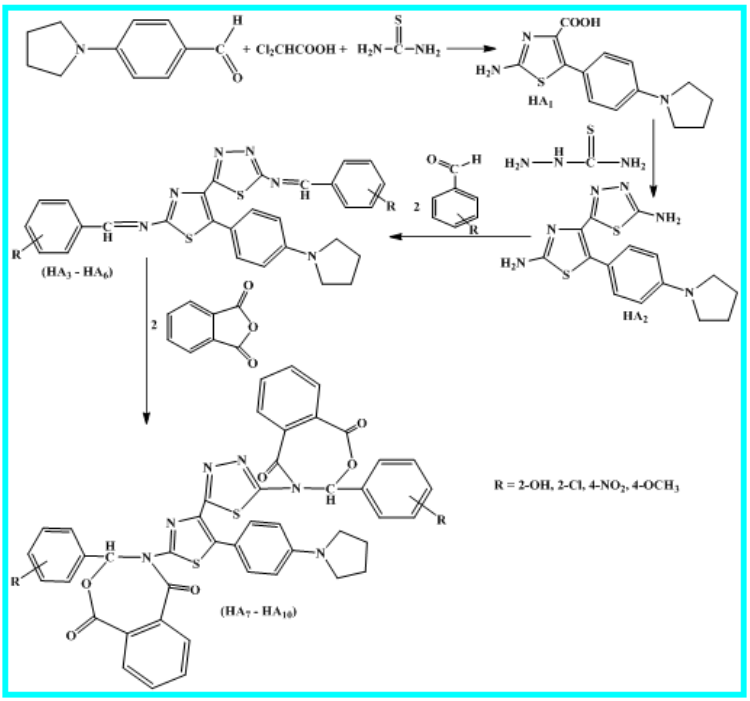


Figure (12): Result of culturing the bacteria and its effect on the additive, B shows the diameter of the inhibition



Scheme 1. Route of prepared compounds (HA1-HA10)

4. Conclusions: The accuracy and validity of the prepared compounds were confirmed through spectral and physical measurements, where the infrared spectrum proved the presence of active aggregates accurately, and this confirmation increased the nuclear magnetic resonance spectrum of the proton and carbon, which accurately agreed on the validity of the structures of the prepared compounds. These compounds are stable at laboratory temperature and do not degrade or change color. The prepared compounds showed high and good inhibitory activity against Gram-positive and Gram-negative bacteria, and the results were compared with control samples, which are antibiotics.

References

1. Koy, M., Bellotti, P., Das, M., & Glorius, F. (2021). N-Heterocyclic carbenes as tunable ligands for catalytic metal surfaces. *Nature Catalysis*, *4*(5), 352-363.
2. Flaherty, P. T. (2007). Heterocyclic Chemistry at a Glance By John A. Joule and Keith Mills. Blackwell Publishing, Oxford, UK 2007. vii+ 150 pp. 21× 19.5 cm. ISBN 9781405139182.£ 17.99.
3. Makosza, M. (1991). Vicarious nucleophilic substitution of hydrogen in the chemistry of heterocyclic compounds. *Synthesis*, *1991*(02), 103-111.
4. Jackman, L. M., & Sternhell, S. (2013). *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry: International Series in Organic Chemistry* (Vol. 10). Elsevier.
5. Dalaf, A. H., Jumaa, F. H., & Yass, I. A. (2022, November). Synthesis, characterization, biological evaluation, molecular docking, assess laser efficacy, thermal performance and optical stability study for new derivatives of bis-1, 3-oxazepene and 1, 3-diazepine. *In AIP Conference Proceedings* (Vol. 2394, No. 1, p. 040037). AIP Publishing LLC.
6. Dalaf, A. H., & Jumaa, F. H. (2020). Synthesis, Identification and Assess the Biological and Laser Efficacy of New Compounds of Azetidine Derived from Benzidine. *Muthanna Journal of Pure Science (MJPS)*, 7(2):12-25.
7. Yass, I. A., Aftan, M. M., Dalaf, A. H., & Jumaa, F. H. (Nov. 2020). Synthesis and Identification of New Derivatives of Bis-1,3-Oxazepene and 1,3-Diazepine and Assess the Biological and Laser Efficacy for Them. *The Second International & The Fourth Scientific Conference of College of Science – Tikrit University*. (P4): 77-87. Alasadi, Y. K., Jumaa, F. H., & Dalaf, A. H. (2022, November). Synthesis, identification, antibacterial activity and laser effect of new derivatives of bis-1, 3-oxazepene-4, 7-dione and 1, 3-diazepine-4, 7-dione. In *AIP Conference Proceedings* (Vol. 2394, No. 1, p. 040019). *AIP Publishing LLC*.
8. Toma, M. A., Ibrahim, D. A., Dalaf, A. H., Abdullah, S. Q., Aftan, M. M., & Abdullah, E. Q. (2022, November). Study the adsorption of cyclopentanone on to natural polymers. In *AIP Conference Proceedings* (Vol. 2394, No. 1, p. 040007). *AIP Publishing LLC*.
9. Hamad, A. M., Atiyea, Q. M., Hameed, D. N. A., & Dalaf, A. H. (2023). Green synthesis of copper nanoparticles using strawberry leaves and study of properties, anti-cancer action, and activity against bacteria isolated from Covid-19 patients. *Karbala International Journal of Modern Science*, *9*(1), 12.
10. Jassim, A. S., Dalaf, A. H., and Abdullah. T. F. (2022). Studying the Biological Activity and Properties of Copper Nanoparticles Prepared by Pulsed Laser Ablation in Liquid. *The Third International and The Fifth Scientific Conference for College of Science –Tikrit University*, 1(25), 213-221.

11. Hamad, A. M., Atiyea, Q. M., Jwair, W. A., Dalaf, A. H., Jasim, A. S., El-Saigher S. M., Saad, Z. H., Mohammed. L. J. (2022). In vitro Comparison of the Effect of Zinc Oxide Nanoparticles and Hibiscus sabdariffa Extract on Streptococcus mutans Isolated from Human Dental Caries. *The Third International and The Fifth Scientific Conference for College of Science –Tikrit University*, 2(02), 213-221.

12. Balouiri, M., Sadiki, M., & Ibnsouda, S. K. (2016). Methods for in vitro evaluating antimicrobial activity: A review. *Journal of pharmaceutical analysis*, *6*(2), 71-79.

13. Gonelimali, F. D., Lin, J., Miao, W., Xuan, J., Charles, F., Chen, M., & Hatab, S. R. (2018). Antimicrobial properties and mechanism of action of some plant extracts against food pathogens and spoilage microorganisms. *Frontiers in microbiology*, *9*, 1639.

14. Dalaf, A. H. (2018). Synthesis and Characterization of Some Quartet and Quinary Hetero cyclic Rings Compounds by Traditional Method and Microwave Routes Method and Evaluation of Their Biological Activity. *M.Sc. Thesis, Tikrit University*, Tikrit, Iraq: 1-94 pp.

15. Dalaf, A. H., & Jumaa, F. H. (2018). Synthesis, Characterization of some 1,3-Oxazepane -4,7-Dione by Traditional and Microwave routes method and evaluation of their biological activity. *Al-utroha for Pure Science*. (8): 93-108.

16. Dalaf, A. H., Jumaa, F. H., & Jabbar, S. A. S. (2018). Synthesis and Characterization of some 2, 3-dihydroquinozoline and evaluation of their biological activity. *Tikrit Journal of Pure Science*, 23(8): 66-67.

17. Salwa, A. J., Ali, L. H., Adil, H. D., Hossam, S. A. (2020). Synthesis and Characterization of Azetidine and Oxazepine Compounds Using Ethyl-4-((4-Bromo Benzylidene) Amino) Benzoate as Precursor and Evalution of Their Biological Activity. *Journal of Education and Scientific Studies*, ISSN: 24134732. 16(5): 39-52.

18. Abd, I. Q., Ibrahim, H. I., Jirjes, H. M., & Dalaf, A. H. (2020). Synthesis and Identification of new compounds have Antioxidant activity Beta-carotene, from Natural Auxin Phenyl Acetic Acid. *Research Journal of Pharmacy and Technology*, 13(1): 40-46.

19. Saleh, R. H., Rashid, W. M., Dalaf, A. H., Al-Badrany, K. A., & Mohammed, O. A. (2020). Synthesis of Some New Thiazolidinone Compounds Derived from Schiff Bases Compounds and Evaluation of Their Laser and Biological Efficacy. *Ann Trop & Public Health*, 23(7): 1012-1031.

20. Salih, B. D., Dalaf, A. H., Alheety, M. A., Rashed, W. M., & Abdullah, I. Q. (2021). Biological activity and laser efficacy of new Co (II), Ni (II), Cu (II), Mn (II) and Zn (II) complexes with phthalic anhydride. *Materials Today: Proceedings*, 43, 869-874.

21. Aftan, M. M., Jabbar, M. Q., Dalaf, A. H., & Salih, H. K. (2021). Application of biological activity of oxazepine and 2-azetidinone compounds and study of their liquid crystalline behavior. *Materials Today: Proceedings*, 43, 2040-2050.

22. Aftan, M. M., Talloh, A. A., Dalaf, A. H., & Salih, H. K. (2021). Impact para position on rho value and rate constant and study of liquid crystalline behavior of azo compounds. *Materials Today: Proceedings*, *45*, 5529-5534.

23. Aftan, M. M., Toma, M. A., Dalaf, A. H., Abdullah, E. Q., & Salih, H. K. (2021). Synthesis and Characterization of New Azo Dyes Based on Thiazole and Assess the Biological and Laser Efficacy for Them and Study their Dyeing Application. *Egyptian Journal of Chemistry*, 64(6), 2903-2911.

24. Khalaf, S. D., Ahmed, N. A. A. S., & Dalaf, A. H. (2021). Synthesis, characterization and biological evaluation (antifungal and antibacterial) of new derivatives of indole, benzotriazole and thioacetyl chloride. *Materials Today: Proceedings*. 47(17), 6201-6210.

25. Dalaf, A. H., Jumaa, F. H., & Salih, H. K. (2021). Preparation, Characterization, Biological Evaluation and Assess Laser Efficacy for New Derivatives of Imidazolidin-4-one. *International Research Journal of Multidisciplinary Technovation*, 3(4), 41-51.

26. Dalaf, A. H., Jumaa, F. H., & Salih, H. K. (2021). *MULTIDISCIPLINARY TECHNOVATION*. *Red*, *15*(A2), C44H36N10O8.

27. Dalaf, A. H., Jumaa, F. H., Aftana, M. M., Salih, H. K., & Abd, I. Q. (2022). Synthesis, Characterization, Biological Evaluation, and Assessment Laser Efficacy for New Derivatives of Tetrazole. *In Key Engineering Materials* (Vol. 911, pp. 33-39). Trans Tech Publications Ltd.

28. Alasadi, Y. Kh., Jumaa, F. H., Dalaf, A. H., Shawkat, S. M., & Mukhlif, M. Gh. (2022). Synthesis, Characterization, and Molecular Docking of New Tetrazole Derivatives as Promising Anticancer Agents. *Journal of Pharmaceutical Negative Results*. 13(3): 513-522.

29. Kovács, A., Vasas, A., & Hohmann, J. (2008). Natural phenanthrenes and their biological activity. *Phytochemistry*, *69*(5), 1084-1110.