How to Cite:
Shehab, A. K., & Rasheed, M. K. (2022). Synthesis, characterization and antibacterial activity of thiazolidine-4-one and imidazolidine-4-one derived from Mesalazine drug by microwave method. *International Journal of Health Sciences*, *6*(S1), 12446–12456.
https://doi.org/10.53730/ijhs.v6nS1.8088

Synthesis, characterization and antibacterial activity of thiazolidine-4-one and imidazolidine-4-one derived from Mesalazine drug by microwave method

Abdullah Khalid Shehab
Department of Chemistry, College of Education, University of Samarra, Samarra, Iraq
Email: us4010520007@uosamarra.edu.iq

Malath Khalaf Rasheed
Department of Chemistry, College of Education, University of Samarra, Samarra, Iraq
Email: us4010520007@uosamarra.edu.iq

***Abstract*---**The Schiff bases (A1- A5) were produced from the reaction of the 5-aminosalicylic acid with a variety of aldehydes by microwave method. Schiff bases were reacted with thioglycolic acid to obtain thiazolidine-4-one compounds (A6 – A10). Imidazolidine-4-one compounds (A11 - A15) were prepared from the prepared Schiff bases with the amino acid (alanine). Spectroscopic methods were used to diagnose the produced compounds (IR, ^{1}H-NMR). The biological activity against two types of bacteria *Proteus mirabilis* –GVe and *Enterococcus faecalis* +GVe have tested and compared with the Mesalazine drug. The results proved that some of the prepared compounds are effective against these bacteria at different concentrations of 5 mg/ml, 10 mg/ml, and 15 mg/ml.

***Keywords*---**Mesalazine, thiazolidine-4-one, imidazolidine-4-one, antibacterial.

Introduction

Azomethine group (CH=N-), named was Schiff base, who first prepared it In (1864) a simple intensification reaction of aldehydes or ketones with primary amines [1].Schiff base derived from condensation of aldehydes with amines are known as aldiamines, while compounds derived from ketone intensification with primary amines known as ketamine [2,3]. It's have important biological effects as they are

anti-bacterial, fungi and viruses, especially viral hepatitis in rats, and they are anti-cancer and herbicide [4]. Thiazolidinedones are one of the heterocyclic compounds that contain sulfur and nitrogen, and when they contain a carbonyl group in the 4-site called thiazolidine-4-on, these systems appear more stable than thiophene, as they are stable towards acid at moderate temperatures [5]. Thiazolidine-4-ones also have extensive biological activities, anti-bacterial, anti-cancer and anti-inflammatory HIV-inhibitors [6]. Thiazolidines are a key breakthrough in diabetes treatment because they increase insulin sensitivity [7]. So it is also called "insulin sensors" when PPAR γ is activated by binding to thiazolidin, its receptor where it is left in DNA to activate a number of specific genes that eventually boost the target tissue of allergies [8].

The imidazolidine-4-one is a five-atom imidazole derivative of a five-aromatic molecule consisting of two cyclic nitrogens, one of which is in position 1, one of the nitrogens behaves like a pyrrole type nitrogen and the other two exhibit a close similarity to nitrogen [9]. Imidazolidine-4-one is a class of medicinal drugs that act on adrenaline receptors and/or imidazolidine-4-one [10]. For example, α 2 agonists are useful for treating high blood pressure, glaucoma, opium and alcohol withdrawal, muscle spasm and behavior disorders. They are also used as anxiety, calming and antibacterial agents, while potential therapeutic applications of anti- α 2 include depression, Reinodis disease and type II diabetes [11-13]. Compounds that possess aggressive activity in α 1-adrenoceptors may protect against abnormal heartbeat and stress incontinence. On the other hand, antibiotics α1 are effective agents in managing arterial hypertension. The blockade of α 1-adrenocepator has also been shown to reduce the development of benign hyperprostate [14.15].

Practical part
"**Experimental Materials and Physical Measurements**"

All chemicals applied in our study can be obtained from Fluka. Sigma Aldrich]; Melting points were determined by the electrical thermal capillary system. The replication of the reaction was monitored by the color of the thin layer (TLC) using Merck silica plates and a mobile phase combination of toluene and ethanol (3:2). IR, - spectra it was received use ATR technicality Shimadzu,8400S, fourier transform IR, - copy (SHIMADZU) in the range (400 – 4000)cm^{-1}. The "^{1}H-NMR spectra were obtained on a Bruker, model ultra-shield" 400MHz in the laboratories of the College of Education for Pure Sciences at the University of Basra. Using tetra methyl silane "(TMS) as internal reference and DMSO-d^6 as solvent".

Synthesis of prepared compounds
1- Synthesis of bases Schiff derivatives (A_1-A_5).
In a round flask, (0.5gm, 0.003mol) of 5-aminosalicylic acid was dissolved in 25 ml absolute methanol and stirring for 5 minutes at room temperature. With continuous stirring for several minutes, the solution was added (0.003mol) of various aldehydes. The reaction mixture was refluxed in the microwave for 5-8 minutes (425watt) after adding a few drops of glacial acetic acid. TLC confirmed the completion of reaction (ethanol: Toluene 2:3 v/v). After confirming the end of

the reaction, the reaction mix cooled at room temperature and the reaction mix was poured on cold water, and crystals were obtained.

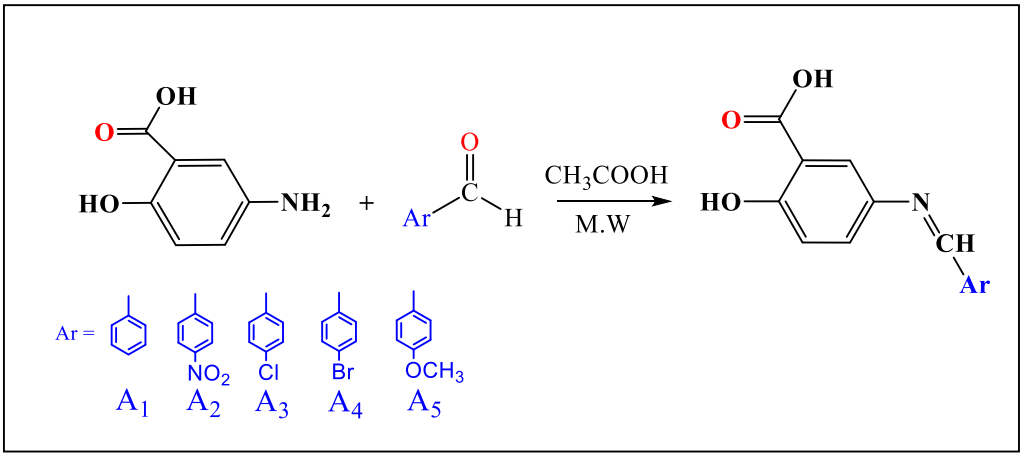

Figure 1: equation for the synthesis of Schiff bases (A_1-A_5)

Table 1
Some physical properties of the synthesized compounds (A_1-A_5)

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P ^{0}C	Yield %	R_f
A_1	$C_{14}H_{10}N_2O_5$	286.24	Dark yellow	247-248	78	0.48
A_2	$C_{14}H_{10}NO_3$	241.7	Dark yellow	221-222	93	0.36
A_3	$C_{14}H_{10}NO_3Cl$	275.69	Yellow	225-226	96	0.40
A_4	$C_{14}H_{10}NO_3Br$	320.14	Yellow	220-221	95	0.54
A_5	$C_{15}H_{13}NO_4$	271.27	Yellow	210-212	83	0.61

2- Synthesis of thiazolidine-4-one compounds (A_6-A_{10}).
(0.0001mol) of the prepared Schiff bases (A1-A5) were dissolved in 25 ml of ethanol with continuous move, (0.0002 mol, 0.07 ml) of addition thioglycolic acid Then add anhydrous zinc chloride, the mixture was refluxed in the microwave for 5-8 minutes (425watt). The completion of the interaction was confirmed by TLC (ethanol: Toluene 2:3 v/v). The reaction mix was cooled and the product was deposited. It is filtered and washed with water and dried to give the pure product.

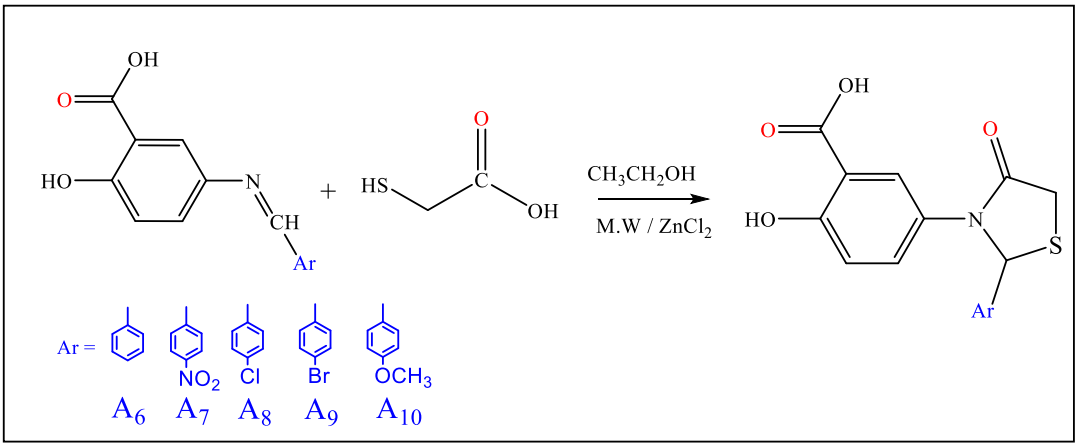

Figure 2: equation for the synthesis of thiazolidine-4-one compounds (A_6-A_{10}).

Table 2
physical characteristics of our synthesized compounds (A_6-A_{10})

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P ^{0}C	Yield %	R_f
A_6	$C_{15}H_{10}N_2O_6$	314.05	Dark yellow	285-286	78	0.86
A_7	$C_{15}H_{10}NO_5$	285.26	Yellow	297-298	93	0.84
A_8	$C_{15}H_{10}NO_4Cl$	303.70	Dark yellow	291-293	96	0.83
A_9	$C_{15}H_{10}NO_4Br$	348.15	Yellow	298-299	95	0.84
A_{10}	$C_{16}H_{13}NO_5$	299.28	Yellow	262-263	83	0.79

3- Synthesis of imidazolidine-4-one compounds (A_{11}-A_{15}).
(0.0001mol) of the produced Schiff bases (A1-A5) were dissolved in 25 ml of 100% ethanol with stirring, followed by the addition of (0.0001 mol) of the amino acid (alanine), and then anhydrous zinc chloride. For 5-8 minutes, the mixture was heated in the microwave (425watt). TLC (ethanol: Toluene 2:3 v/v) confirmed that the reaction was complete. The reaction mix was cooled and the product was deposited. It is filtered and washed with water and dried to give the pure product.

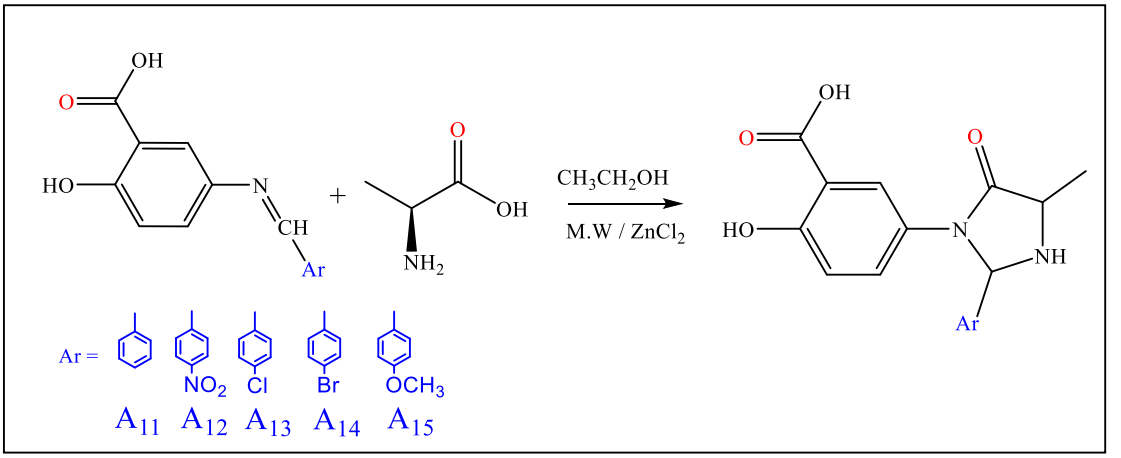

Figure 3: equation for the synthesis of compounds (A_{11}-A_{15}).

Table (3)
physical properties of the synthesis of imidazolidine-4-one (A_{11}-A_{15})

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P.^{0}C	Yield %	R_f
A_{11}	$C_{18}H_{15}N_3O_7S$	417.39	Brown	234-235	67	0.85
A_{12}	$C_{18}H_{16}N_2O_6S$	388.39	Orange	240-241	56	0.81
A_{13}	$C_{18}H_{15}ClN_2O_5S$	406.84	Dark brown	258-259	57	0.78
A_{14}	$C_{18}H_{15}BrN_2O_5S$	451.29	Light green	262-263	74	0.73
A_{15}	$C_{19}H_{18}N_2O_6S$	402.42		290-291	79	0.69

Results and discussion

The IR spectrum:
The IR spectrum of the prepared Schiff base [A_1-A_5] Note that the strong bond resumes at (1623-1678)cm^{-1} belongs to the (C = N) azomithin group. In addition to absorption packages appear when the extent (3008-3097) cm^{-1} it belongs to the stretching of the aromatic (C-H) bond. Two bands appear at the extent (2915-2995) and (2933-2812) cm^{-1} belongs to the stretching of the aliphatic (C-H) bond. Two absorption packages appear in range (1504-1599) cm^{-1} and (1560-1461) cm^{-1} belongs to the expansion of the aromatic bond (C = C) [16,18]. See Table 4.

Table 4
FT-IR spectral data for compounds (A_1-A_5)

Comp. No.	FT-IR (KBr) cm^{-1}						
	R	**ν(C-H) Arom.**	**ν(C-H) Aliph.**	**ν (C=O)**	**ν (C=N)**	**ν (C=C) Arom.**	**Others**
A_1	H	3020	2954 2910	1690	1630	1584 1511	----
A_2	4-NO_2	3011	2963 2924	1687	1626	1573 1512	ν (N=O) 1557-1359
A_3	4-Cl	3067	2915 2857	1693	1644	1572 1500	ν (C-Cl) 759
A_4	4-Br	3066	2912 2845	1677	1632	1531 1496	ν (C-Br) 662
A_5	4-OCH_3	3018	2917 2888	1695	1665	1597 1519	ν (C-O) 1161

(7.00-7.91 ppm) belong to aromatic ring protons, plus a signal at (8.61 ppm) belonging to proton (N = CH) of azomithin. Signal at (9.88 ppm) belonging to alcohol proton (OH), signal at (11.17 ppm) belonging to acid proton (OH) [19-22]. See Figure 4.

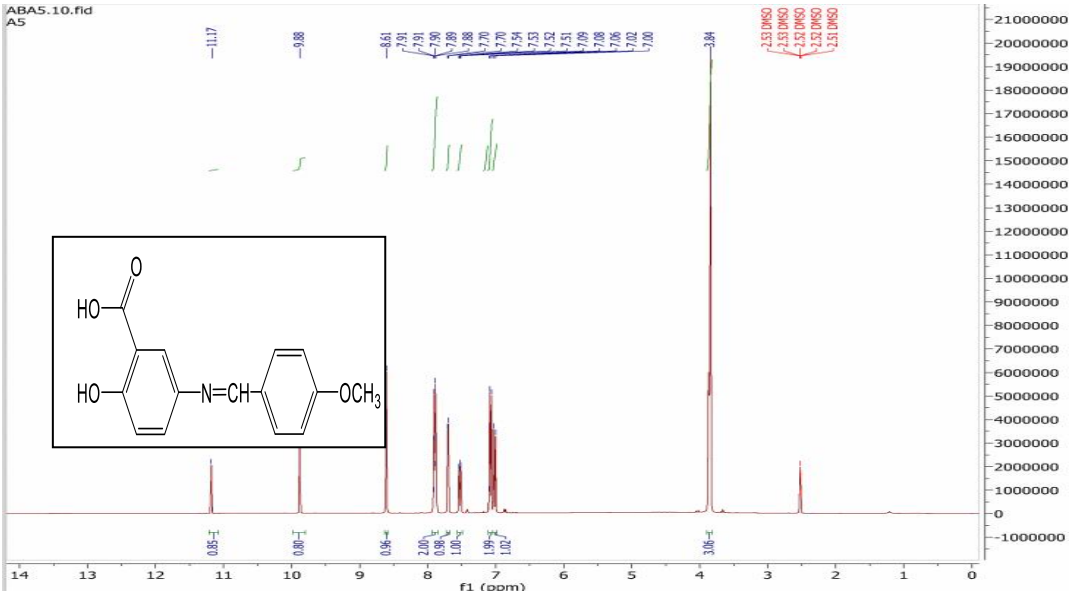

Figure 4: NMR-H[1] Spectrum for compound (A_5)

The IR of the compounds [A_6-A_{10}] Note that the strong bond resumes at (1249-1257) cm^{-1} belongs to (C-N). plus, two absorption packages appear when the extent (3013-3078) cm^{-1} it belongs to the stretching of the aromatic (C-H) bond. Two packages appear in range (2920-2986) and (2845-2931) cm-1 belonging to the extension of the Aliphatic Association (C-H). Appearance Two absorption bundles in range (1574-1593) cm-1 and (1505-1559) cm-1 belonging to aromatic bond expansion (C = C) [16,18]. See Table 5.

Table 5
FT-IR spectral data of thiazolidine-4-one derivatives (A_6-A_{10})

Comp. No.	FT-IR (KBr) cm^{-1}						
	R	ν(C-H) Arom.	ν(C-H) Aliph.	ν (C=O)	ν (C=C) Arom.	ν (C-N)	Others
A_6	H	3020	2924 2845	1692	1574 1552	1257	----
A_7	4-NO_2	3028	2964 2851	1681	1581 1505	1245	ν (N=O) 1559-1356
A_8	4-Cl	3013	2920 2868	1687	1589 1506	1250	ν (C-Cl) 750
A_9	4-Br	3061	2939 2856	1673	1593 1559	1256	ν (C-Br) 665
A_{10}	4-OCH_3	3078	2986 2931	1683	1582 1512	1249	ν (C-O) 1169

[1]H-NMR of the compound (A10) it showed a signal at (3.34ppm) belonging to group protons (CH3), and signal at (3.50 ppm) belonging to to the protons of the (CH_2). plus, the signal at (2.51ppm) belonging to the solvent (DMSO-d6). The

signal at (6.48ppm) is belonging to the (C-H) protons and the multiple signals at (6.69-7.45ppm) are belong to aromatic ring protons. a signal at (9.91 ppm) belonging to the alcoholic (OH) proton, plus, the appearancee of a single signal at (11.22 ppm), is belonging to the acidic proton (OH) [19-22]. See figure 5

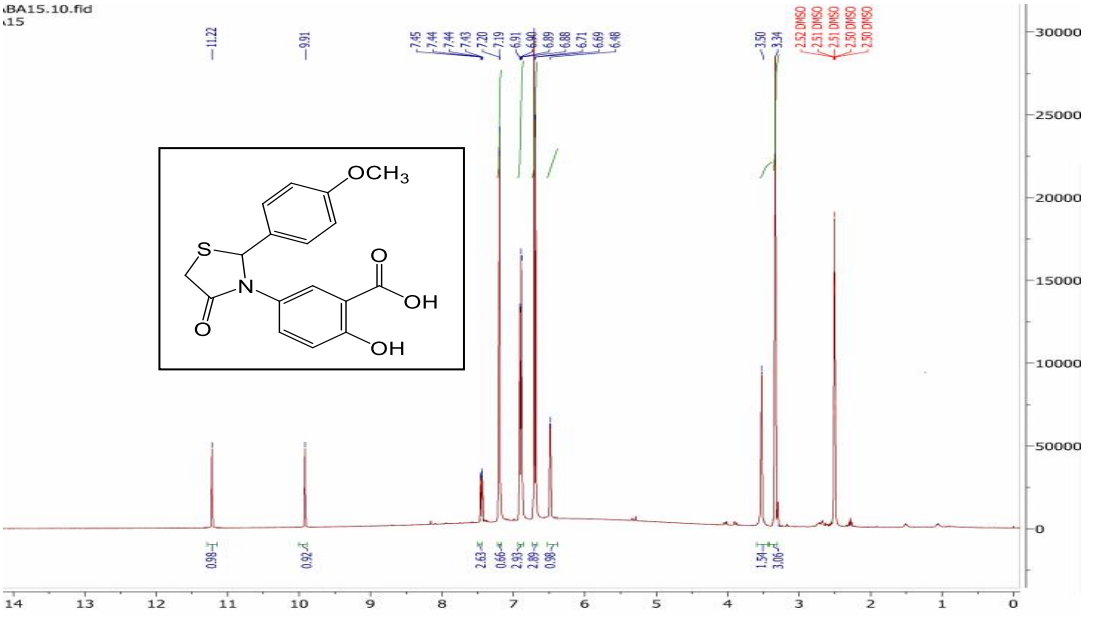

Figure 5: ^{1}H-NMR Spectrum for compound (A_{10})

In the IR of compounds [A11-A15], Note that the strong bond resumes at (1244-1257) cm-1 belong to group (C-N). plus, absorption bands appeared in the range (3017-3078) cm-1 he stretching of the aromatic (C-H) bond. Two bands appear in the extent (2910- 2987) and (2844-2955) cm-1 belonging to the extension of the Aliphatic Association (C-H). Appearance of two absorption bands at the range (1564-1596) cm-1 and (1503-1569) cm-1 belong to the stretching of the aromatic (C=C) bond [16-18]. See Table 6.

Table 6
FT-IR spectral data for compounds (A_{11}-A_{15})

Comp. No.	FT-IR (KBr) cm^{-1}						
	R	ν(C-H) Arom.	ν(C-H) Aliph.	ν (C=O)	ν (C=C) Arom.	ν (C-N)	Others
A_{11}	H	3017	2910 2844	1693	1571 1569	1257	----
A_{12}	4-NO_2	3028	2964 2847	1681	1564 1503	1244	ν (N=O) 1559-1354
A_{13}	4-Cl	3019	2919 2852	1689	1596 1507	1249	ν (C-Cl) 750
A_{14}	4-Br	3039	2926	1674	1582	1253	ν (C-Br)

			2869		1555		665
A_{15}	4-OCH_3	3078	2987 2955	1688	1572 1508	1248	ν (C-O) 1169

1H-NMR of compound (A14) it showed a signal at (1.14-1.23ppm) belonging to group protons (CH3), a signal at (2.51ppm) belonging to the solvent (DMSO-d6). plus, the signal at (3.10-3.22ppm) is attributed to the proton (CH) adjacent to the methyl group. In addition, the signal indicates at (5.96 ppm) belonging to the proton (N-CH), and the appearance of multiple signals at (6.66-7.88 ppm) belonging to the aromatic ring protons. A signal at (8.67 ppm) belongs to protons (NH) of the imidazolidin ring, and a signal at (9.31 ppm) belongs to the alcohol proton (OH). In addition to the appearance of a signal at (10.67 ppm) belonging to proton acidity (OH) [19-22]. See figure 6.

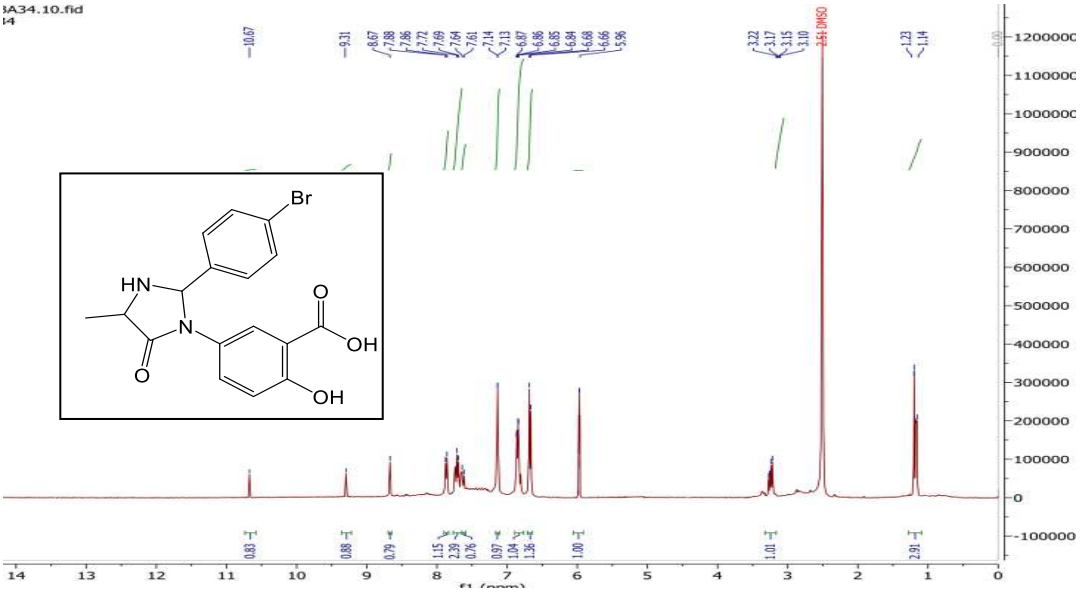

Figure 6: ^{1}H-NMR Spectrum for compound (A_{14})

Test the inhibitory activity of some prepared compounds [22,23]

The biological activity of some prepared compounds (A4, A5, A6, A9, A13) was evaluated on two types of bacterial isolates GVe+ Enterococcus faecalis and GVe- Proteus mirabilis. The results showed inhibitory activity of these compounds against bacteria and the results were compared with the stander mesalazine. The results indicated that some For manufactured compounds had ability to inhibit bacteria using different concentrations of compounds (5mg/ml), (10mg/ml), and (15mg/ml). Compared to a standard antibiotic for bacteria. See Table 7

Table 7:
Anti-bacterial activity data from some prepared compounds measured in millimetrs

Comp. No.	*Proteus mirabilis* -GVe			*Enterococcus faecalis* +GVe		
	5 mg/ml	10 mg/ml	15 mg/ml	5 mg/ml	10 mg/ml	15 mg/ml
A4	8	10	12	0	8	10
A5	13	14	15	15	18	20
A6	12	13	14	0	0	10
A13	0	0	13	0	0	0
Mesalazine		14			0	

The following pictures show the inhibition areas of the prepared compounds against two types of bacteria used . See Figure 8 , 9

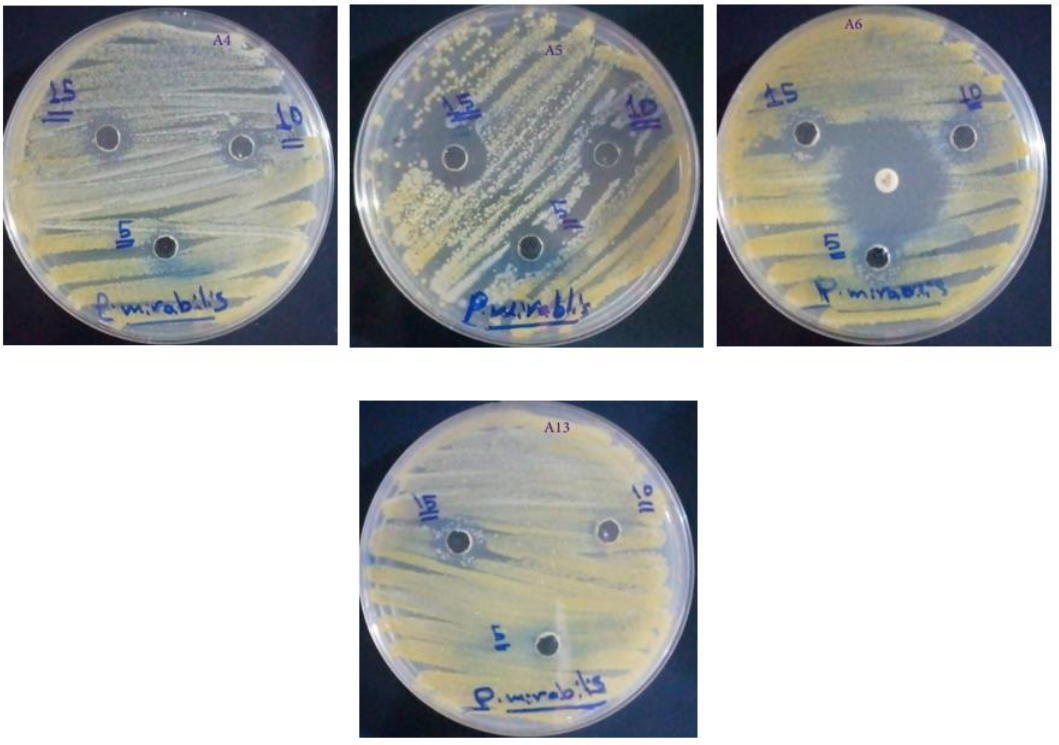

Figure 8: Diameter of inhibition area (mm) on *Proteus mirabilis* GIVe –

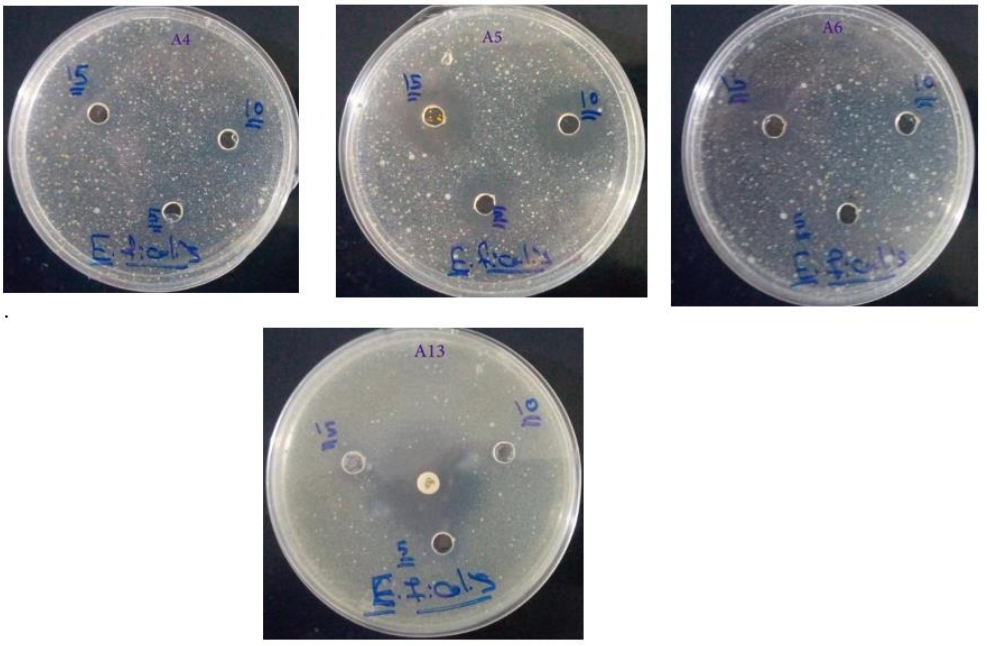

Figure 9: Diameter of inhibition area (mm) on ***Enterococcus faecalis*** GIVe +.

References

1. Joule JA, Mills K, Smith GF. Heterocyclic chemistry. CRC Press; 2020 Nov 25.
2. Sell CS. Chemistry and the Sense of Smell. John Wiley & Sons; 2014 Mar 26.
3. MOHAMMED AM, AL-SHEMARY RK. Metal complexes with heteroscorpionate ligand founded on the pyridinamine group: cyclin-dependent kinase 2 inhibitor antimicrobial, antioxidant, and in vitro cytotoxicity, notional studies. International Journal of Pharmaceutical Research. 2021 Jan;13(1).
4. Hanna. H, Juncheng .Z, Zude .O, Zhou.B, Meiying.L and Liu.Y, ",Journal of Natueal Science", Wuhan University, 1, 15, 7177, (2010).
5. Al-Khyaat AD. Preparation and identification of some new thiazolidine-4-one compounds from Schiff base derivatives. JOURNAL OF EDUCATION AND SCIENCE. 2020 Sep 1;29(3):142-56.
6. Wang SQ, Yan XW, Hu BL, Zhang XG. Transition-metal and base-free thioannulation of propynamides with sodium sulfide and dichloromethane for the selective synthesis of 1, 3-thiazin-4-ones and thiazolidine-4-ones. Tetrahedron. 2020 Mar 20;76(12):131021.
7. Gummidi L, Kerru N, Ebenezer O, Awolade P, Sanni O, Islam MS, Singh P. Multicomponent reaction for the synthesis of new 1, 3, 4-thiadiazole-thiazolidine-4-one molecular hybrids as promising antidiabetic agents through α-glucosidase and α-amylase inhibition. Bioorganic Chemistry. 2021 Oct 1;115:105210.
8. Pitta.I.R ; Mourao.R.H and Silva.T.G. Synthesis and Biological Activity of Novel Acridinylidene and Benzylidene thiazolidinediones. Eur. J. Med. Chem., 40, 1129- 1133, 2005.

9. Dr. Ning Xi , Dr. Longbin and Dr. Qi Huang, "Int. Comprehensive Heterocyclic Chemistry III :Volume 4, 2008, Pages 143-364.
10. HASSAN HA, ALHEETY KA, HASSAN DF. Synthesis and identification of novel 2 thioxo imidazolidin 4 one derivatives containing azo and ester groups. International Journal of Pharmaceutical Research. 2019 Jul;11(3).
11. Mahmood RM, Ghafil RA. Synthesis and Characterization some Imidazolidine Derivatives and Study the Biological Activity. Annals of the Romanian Society for Cell Biology. 2021 Mar 20:569-84.
12. Arif IA, Ahamed A, Kumar RS, Idhayadhulla A, Manilal A. Cytotoxic, larvicidal, nematicidal, and antifeedant activities of piperidin-connected 2-thioxoimidazolidin-4-one derivatives. Saudi journal of biological sciences. 2019 May 1;26(4):673-80.
13. Rodriguez F., Rozas I., Ortega J.E., Erdozain A.M., Meana J.J., Callado L.F.: J. Med. Chem. 52, 601 (2009).
14. Shaker RM, Abd El-Naby HA, Ahmed EK, Ibrahim MA, Gedamy SA. One-pot synthesis, theoretical study and antimicrobial activity of 5, 5′-(1, 4-phenylenebis-(methanylylidene)) Bis (3-Aryl (Alkyl)-2-thioxoimidazolidin-4-one) derivatives. Phosphorus, Sulfur, and Silicon and the Related Elements. 2019 Feb 1;194(1-2):147-55.
15. Arif IA, Ahamed A, Kumar RS, Idhayadhulla A, Manilal A. Cytotoxic, larvicidal, nematicidal, and antifeedant activities of piperidin-connected 2-thioxoimidazolidin-4-one derivatives. Saudi Journal of Biological Sciences. 2019 May 1;26(4):673-80.
16. Elmi F, Movaghar AF, Elmi MM, Alinezhad H and Nikbakhsh N. Application of FT-IR spectroscopy on breast cancer serum analysis. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2017 Dec 5;187:87-91.
17. Ozaki Y, Huck C, Tsuchikawa S, Engelsen SB, editors. Near-Infrared Spectroscopy: Theory, Spectral Analysis, Instrumentation, and Applications. Berlin/Heidelberg, Germany: Springer; 2021.
18. Kanoun O. Impedance spectroscopy advances and future trends: A comprehensive review. Impedance Spectroscopy. 2018 Dec 17:1-22.
19. Markussen J, Schaumburg K. Reaction Mechanism in Trypsin Catalyzed Synthesis of Human Insulin Studied by 17O-NMR Spectroscopy. In17. Prague, Czechoslovakia, August 29–September 3, 1982 2019 May 20 (pp. 387-394).
20. Emsley JW, Lindon JC. NMR spectroscopy using liquid crystal solvents. Elsevier; 2018 Jan 10.
21. De Graaf RA. In vivo NMR spectroscopy: principles and techniques. John Wiley & Sons; 2019 Mar 11.
22. Raics M, Timári I, Szilágyi L, Gabius HJ, Kövér KE. Introducing 77 Se NMR Spectroscopy to Analyzing Galectin–Ligand Interaction. InGalectins 2022 (pp. 105-123).
23. World Health Organization. WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR): report of the 7th meeting, 17-20 October 2016, Raleigh, United States of America. World Health Organization; 2018.
24. Racovita S, Popa M, Atanase LI, Vasiliu S. Synthetic macromolecules with biological activity. Biological Macromolecules. 2022 Jan 1:305-35.