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Synthesis and characterization of thiazolidine-4-one and thiazine-4-one derived from 2-aminoterephthalic acid by microwave method

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

Malath Khalaf Rasheed
Department of Chemistry, College of Education, University of Samarra, Samarra, Iraq

***Abstract*---**The Schiff bases (A1 - A5) were produced from the reaction of the 2-aminoterephthalic acid with a variety of aldehydes by microwave method. Thiazolidine-4- one compoundes (A_6 - A_{10})were of the reaction of the prepared schiffbases with thioglycolic acid in equal molar proportions. Thiazine-4- one compounds (A_{11} - A_{15}) were prepared from the prepared schiff bases with the amino acid (cysteine). The prepared compounds were diagnosed by Spectroscopic methods (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 ciprofloxacin drug. The results proved that the prepared compounds are effective against these bacteria.

***Keywords*---**Schiff base, thiazolidine-4-one, thiazine-4-one, antibacterial.

Introduction

Schiff bases are derived from an amino compound and a carbonyl compound that coordinate with metal ions through an azomethic nitrogen atom, azomethine (C=N) has antibacterial biological activities[1]. Schiff bases have antibacterial, antifungal, herbicide and clinical properties largely attributed to their azomethine binding, and also possess catalytic and photochromic properties [2]. Ship bases of aliphatic aldehydes are less stable and susceptible to polymerization, while aromatic aldehydes have a strong bond and stability [3]. Thiazolidine is one of the heterocyclic compounds that contain sulfur and nitrogen, and when they contain a carbonyl group in the 4-site called thiazolidine-4-one, these systems appear

more stable than thiophene, as they are stable towards acid at moderate temperatures [4]. Thiazolidine 4-on derivatives have a broad biological activity such as antimicrobial, antiviral, antifungal, anticancer and antioxidant action. Today, the trend in the development and synthesis of drugs has more than one biologically active site. Thus, the current work aims to combine pharmacophore 1,2,3-triazole, furan and thiazolidine-4-on-moieties in the same matrix to produce compounds for the development of new drugs[5-8].Thiazine compounds are heterocyclic compounds containing one atom each of nitrogen, sulfur and four carbon atoms. The molecular formula is C_4H_5NS and when it contains a high carbonyl group, it becomes 1,3-thiazine-4-one [9]. 1,3-thiazine derivatives have recently been reported as cholecystokinin antagonists, anti-mycobacterial agents, cannabinoid receptor agonists, and inhibitors of NO synthase (NOS) As antibacterial, anti-heat, anti-inflammatory, analgesic, anti-tumor, antioxidant and as calcium channel modulators [10-12].

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".

Preparation of compoundes

1. Synthesis of Schiff bases derivatives (A_1-A_5).
2. aminoterephthalic acid (0.5 gm, 0.003 mol) dissolves in, 25 ml methanol in concave vial, stirring for 5 minutes at room temperature. Added to the reaction mixture (0.003mol) of different aldehydes with continuous stirring with the addition of a spray of glacial acetic acid. The reaction mix, bounced in the microwave for 6-8 minutes (425 W). The expiration of the reaction was confirmed by TLC (ethanol: Tuluene,2:3 v/v). The reaction mix was cooled, the product was deposited, the contents filtered and the product washed with water twice and dried to give a pure product. Table1: A few physical properties of the synthesized compoundes (A_1-A_5).

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

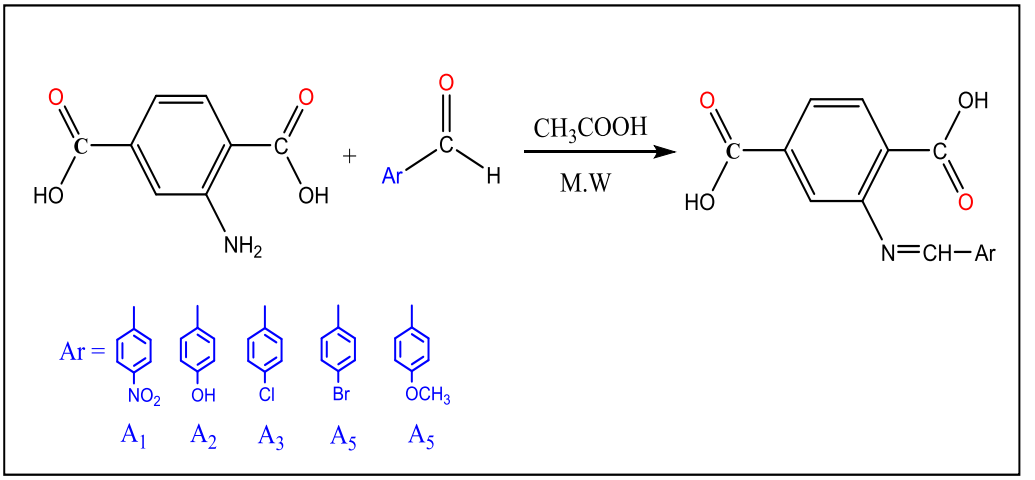


Table 1 : Physical properties of Schiff's manufactured bases (A1 - A5)

comp.No.	Molecular Formula	Molecular Weight	Color	M.P ^{0}C	Yield %	R_f
A_1	$C_{15}H_{10}N_2O_6$	314.05	Dark yellow	285-286	78	0.65
A_2	$C_{15}H_{10}NO_5$	285.26	Yellow	297-298	93	0.75
A_3	$C_{15}H_{10}NO_4Cl$	303.70	Dark yellow	291-293	96	0.64
A_4	$C_{15}H_{10}NO_4Br$	348.15	Yellow	298-299	95	0.72
A_5	$C_{16}H_{13}NO_5$	299.28	Yellow	262-263	83	0.70

1- Synthesis of thiazolidine-4-one derivatives (A_6-A_{10}).
(0.0001mol) of the rules of the stomach schiff (A1-A5) was dissolved in 25 ml of gasoline with continuous stirring, and after the completion of the dissolution, (0.0002 mol, 0.07 ml) of the added thioglycolic acid. The reaction mix was returned in the microwave for 6-8 minutes (425 W). The completion of the reaction was confirmed by TLC (ethanol:Tuluene,2:3 v/v). The reaction mix was cooled and the product was deposited. It was filtered, washed with water and dried to give the pure product. Table 2:A few physical properties of manufactured compounds (A_6-A_{10}).

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

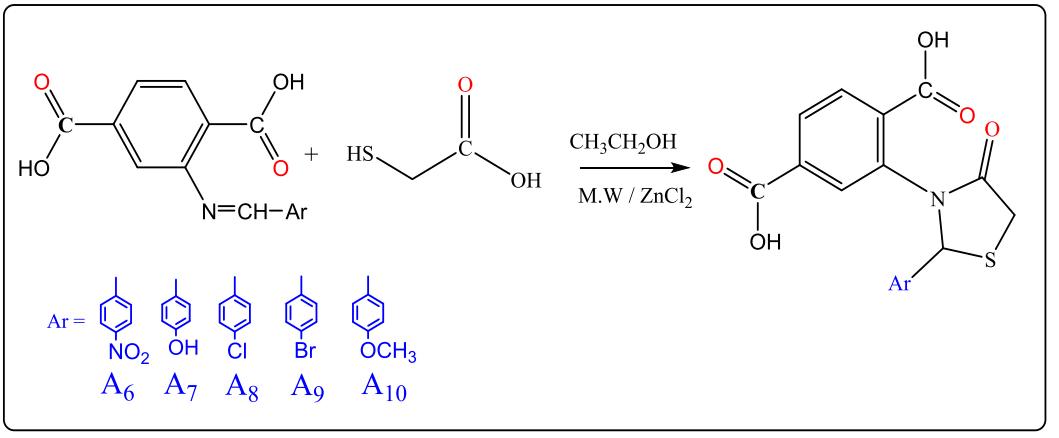


Table 2 : Physical properties of manufactured compounds (A_6-A_{10})

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P ^{0}C	Yield %	R_f
A_6	$C_{17}H_{12}N_2O_7S$	388.35	Dark brown	222-223	62	0.87
A_7	$C_{17}H_{13}NO_6S$	359.35	Orange	291-292	84	0.84
A_8	$C_{17}H_{12}ClNO_5S$	377.80	Orange	262-263	81	0.83
A_9	$C_{17}H_{12}BrNO_5S$	422.25	Orange	274-275	82	0.84
A_{10}	$C_{18}H_{15}NO_6S$	373.38	Dark brown	242-244	78	0.80

2- Synthesis of thiazine-4-one derivatives (A_{11}-A_{15}).
(0.0001mol) of Schiff bases (A1-A5) dissolved in 25 ml Tolwen with continuous stirring, (0.0002 mol) of amino acid (cysteine) added to it. In the microwave, the reaction mixture was heated for 6-8 minutes (425 W). TLC confirmed the completion of the reaction (ethanol: Tuluene 2: 3v/v).The reaction mixture was cold, and the product precipitated. The contents were filteraction, and the product was washed and dried. Table3: Some physical properties of the synthesized compounds (A_{11}-A_{15}).

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

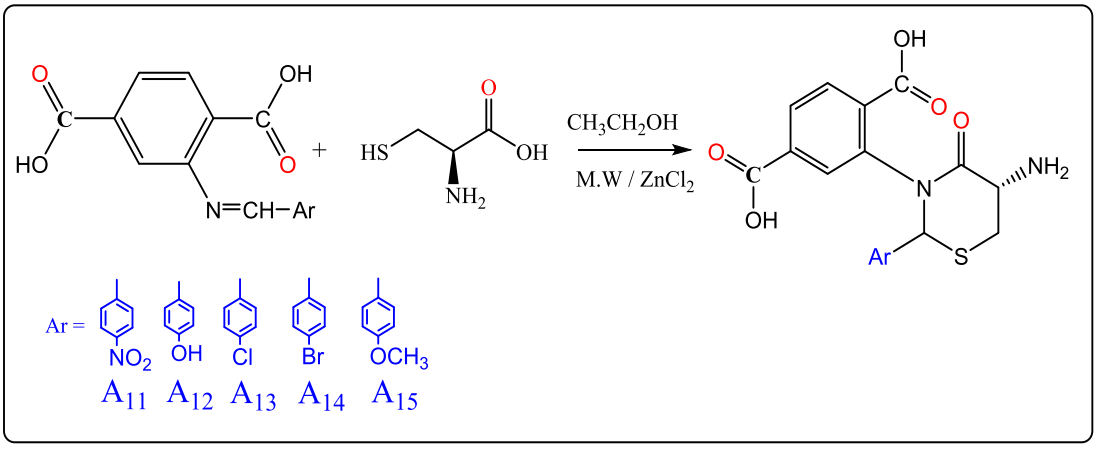


Table 3: physical properties of the synthesized compounds (A_{11}-A_{15})

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	0.81
A_{12}	$C_{18}H_{16}N_2O_6S$	388.39	Orange	240-241	56	0.88
A_{13}	$C_{18}H_{15}ClN_2O_5S$	406.84	Dark brown	258-259	57	0.86
A_{14}	$C_{18}H_{15}BrN_2O_5S$	451.29	Light green	262-263	74	0.89
A_{15}	$C_{19}H_{18}N_2O_6S$	402.42	Dark brown	290-291	79	0.85

Results and discussion

The IR spectrum

The IR spectra of the compounds [A1 - A5] Note that the strong bond resumes at (1623-1678)cm^{-1} return to the azomithin group (C = N)In addition, absorption ranges appeared at the scope (3015 - 3074)cm^{-1} it reverts to the aromatic stretch (C - H)bond. Two bands appear at the range (2855- 2995) and (2913-2890)cm^{-1} refer "to the stretching of the aliphatic (C - H)bond. Appearance of two absorption bands at the range (1514-1579)cm^{-1} and (1529-1492) cm^{-1} due to the stretching of the aromatic(C = C)bond" [13,14]. See Table 4.

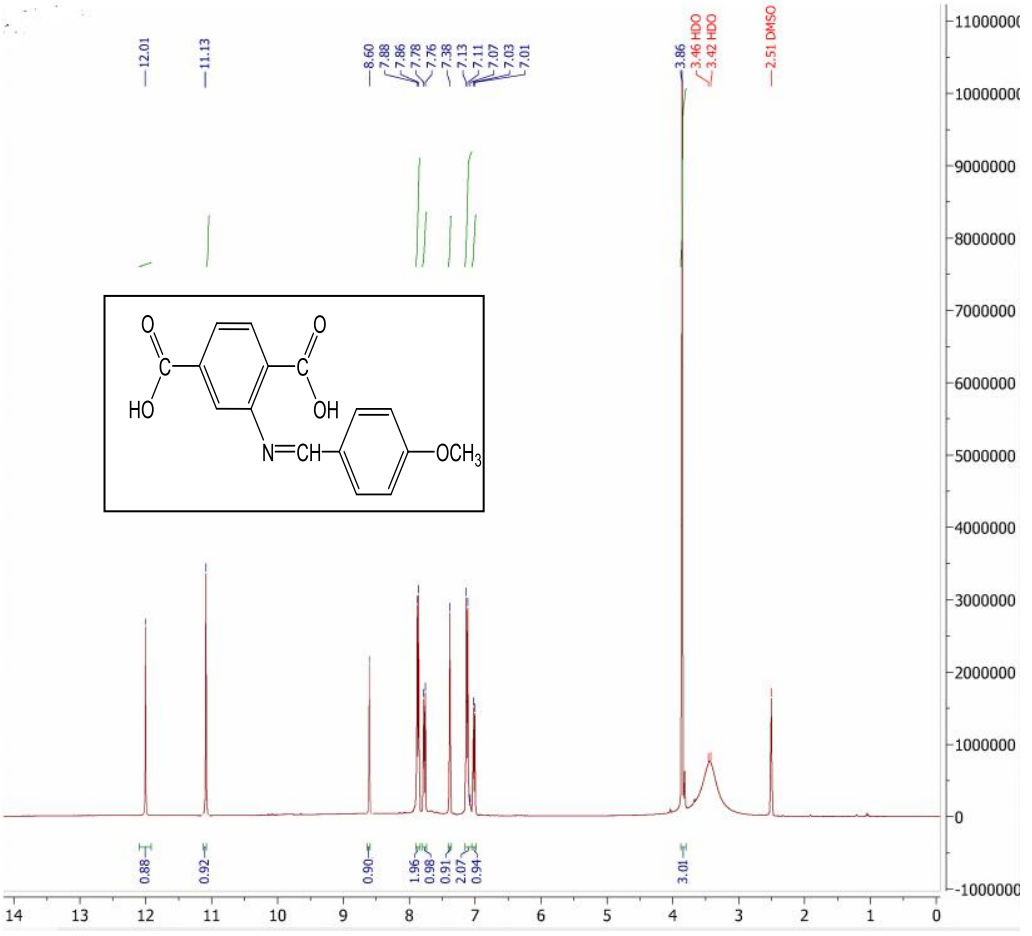
Table 4 : FT – IR Spectral from Schiff base ,derivatives (A_1-A_5)

Comp. NO.	FT- IR (KBr) cm^{-1}						
	R	ν(C-H) Arom.	ν (C-H) Alipha.	ν (C=O)	ν (C =N)	ν (C=C) Ar.	Others
A_1	4-NO_2	3015	2960 2923	1686	1623	1579 1514	ν (N=O) 1550
A_2	4-OH	3024	2941	1691	1631	1587	ν (O-H)

			2912			1517	2443-3320
A_3	4-Cl	3074	2914 2855	1688	1652	1571 1500	ν (C-Cl) 754
A_4	4-Br	3062	2913 2890	1678	1625	1529 1492	ν (C-Br) 667
A_5	4-OCH_3	3017	2995 2886	1690	1678	1599 1532	ν (C-O) 1164

^{1}H-NMR spectrum of compond (A_5) it show one signal in (3.86 ppm) attributed to group protons (CH3). In addition, the signal appears at (2.51 ppm) back to the solvent (DMSO-d6). In addition, multiple signals at (7.01-7.88ppm) it refers to the protones of the aromatic ring, As well as one signal appeared at (8.60 ppm) belonging to a proton (N = CH) of imine. Also a single signal at (11.13 ppm) and (12.01 ppm) return to the acidic (OH) protons [15,17]. See Figure 4 .

Figure 4: ^{1}H -NMR Spectrum for compound (A_5)



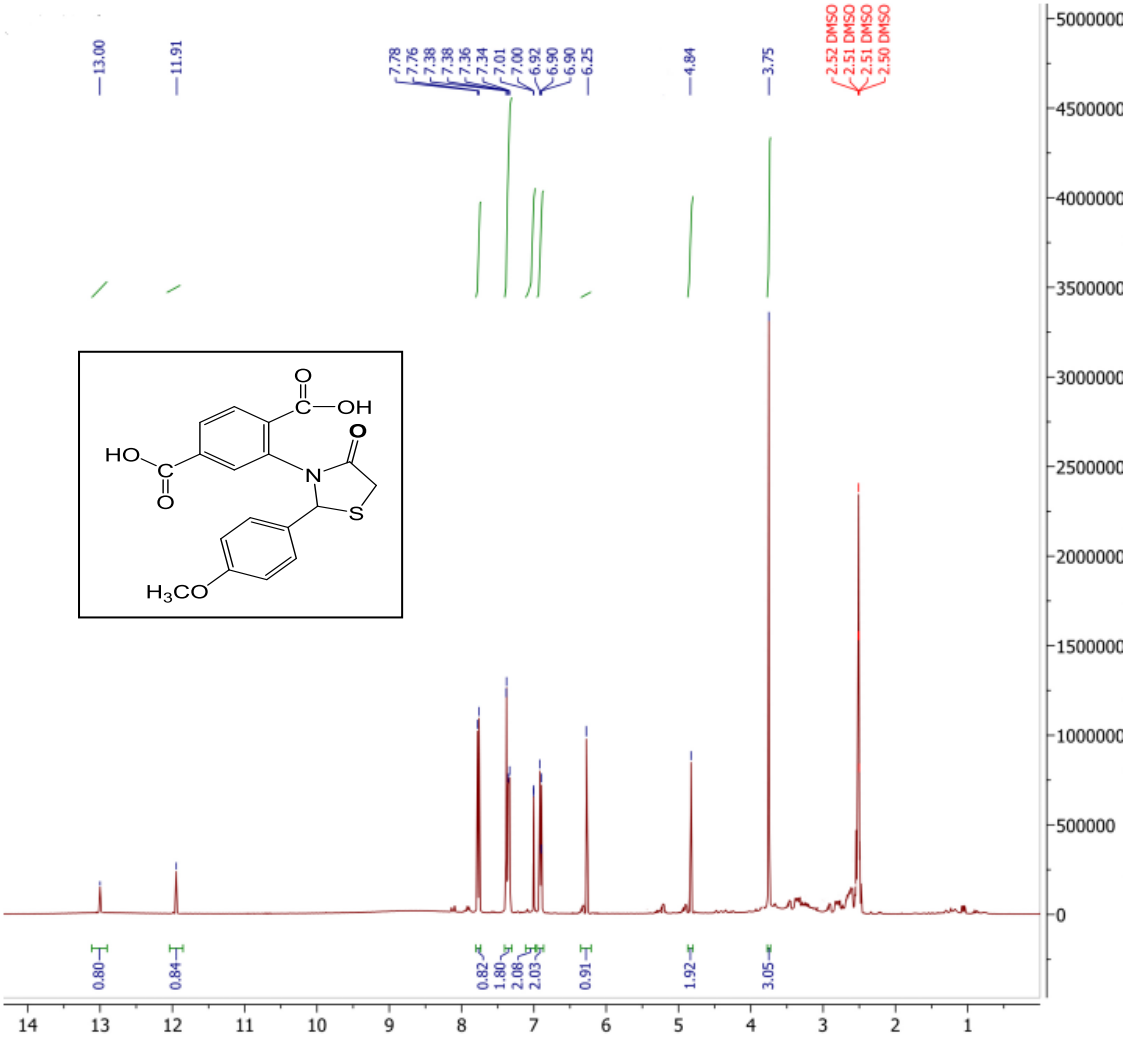
The IR of the compounds [A_6-A_{10}] It was noted that the tape (1245-1255) cm-1 (C-N). In addition, the absorption range appeared in the scope (3016-3080) cm-1 and is return to the extension of the aromatic bond (C-H). Two bands appear in the scope (2916-2985) and (2840-2852) cm-1 indicating the extension of the Aliphatic Association (C-H). Appearance of two absorption bands in the scope (1504-1599) cm-1 and (1502-1471) cm-1 return to aromatic bond expansion (C = C)[13,14]. 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) Alipha.	ν (C=O)	ν (C=C) Ar.	ν (C-N)	Others
A_6	4-NO_2	3029	2960 2846	1685	1569 1500	1248	ν (N=O) 1550
A_7	4-OH	3016	2916 2840	1690	1573 1562	1255	ν (O-H) 2443-3312
A_8	4-Cl	3018	2918 2854	1686	1593 1506	1245	ν (C-Cl) 757
A_9	4-Br	3030	2929 2864	1679	1583 1556	1250	ν (C-Br) 660
A_{10}	4-OCH_3	3080	2985 2952	1684	1571 1502	1247	ν (C-O) 1164

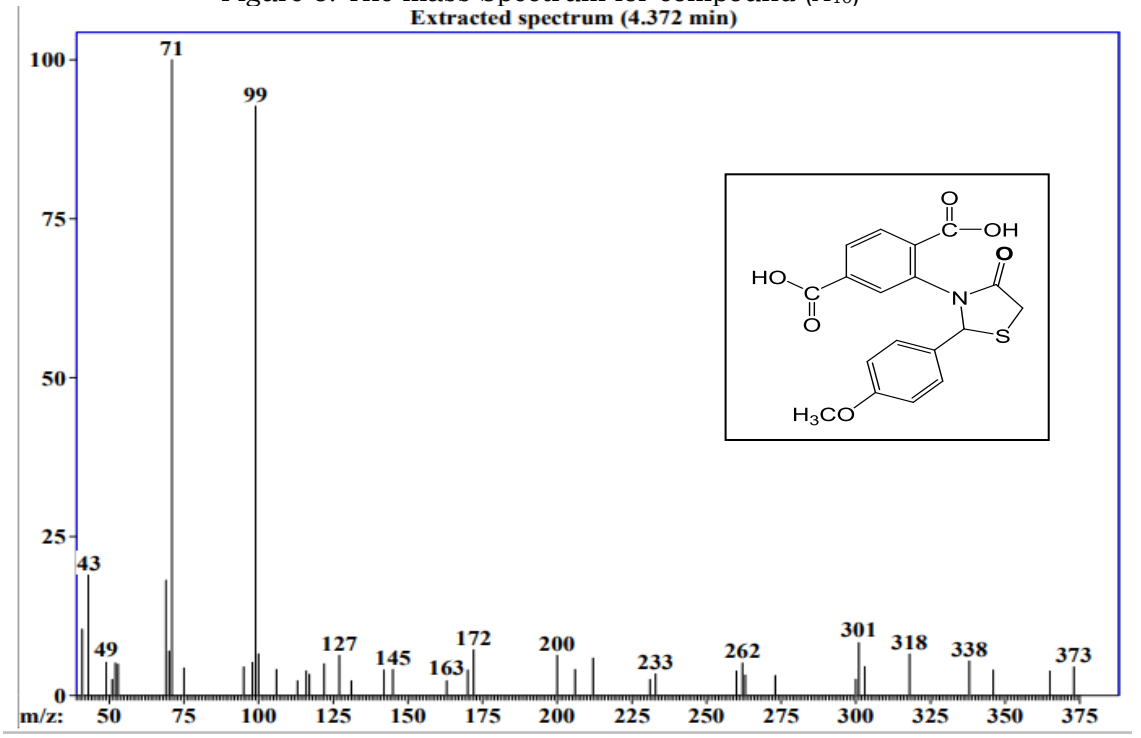
^{1}H-NMR spectrum of compond (A_{10}) It showed a signal at the position (3.75 ppm) attributed to group protons (CH_3), and the signal at (4.84 ppm) attributed to protons (CH_2). In addition to singlet in (2.51 ppm) return to solvent (DMSO-d6), individual appearance in (6.25 ppm) related to protons (C-H) and the appearance of multiplier signals at (6.90-7.78 ppm) related to aromatic ring protons. Individual drag signals at (11.91 ppm) and (13.00 ppm) related to acid protons (OH). [15 - 17]. See figure 5.

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



The mass spectrometry of the compound (A_{10}) was measured and it showed the main peak at (373 m/z) with a relative abundance (10%) due to the molecular ion and a base peak at (71 m/z) with a relative abundance (100%). See Figure 6.

Figure 6: The mass Spectrum for compound (A_{10})



The IR of compounds [A_{11}-A_{15}] It was noted that a strong bond appeared at (1241-1257) cm^{-1} return to group (C – N). In addition, the absorption range appeared at the scope (3015-3084)cm^{-1} it reverts to the starching of the aromatic (C – H) bond. Two bands appear at the range (2917- 2986) and (2842-2952) cm-1 refer to starching of the aliphatic (C - H) bond. What looks like two absorption bonds at the scope (1504-1599) cm^{-1} and (1500-1569) cm^{-1} return to the stretching of the aromatic (C = C)bond [13,14]. See Table 6.

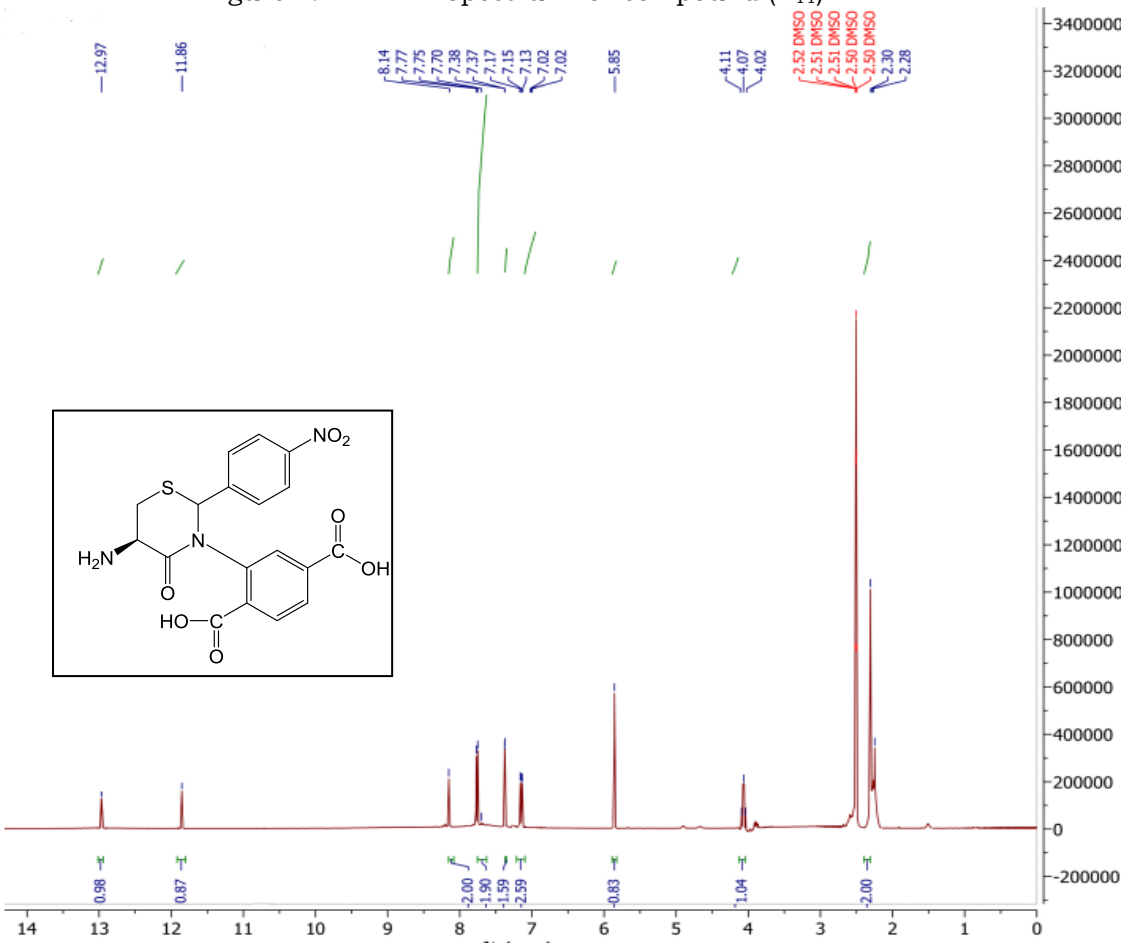
Table 6: FT-IR spectral data of thiazine-4-one derivatives (A_{11}-A_{15})

Comp. NO.	FT- IR (KBr) cm^{-1}						
	R	ν(C-H) Arom.	ν (C-H) Alipha.	ν (C=O)	ν (C=C) Ar.	ν (C-N)	Others
A_{11}	4-NO_2	3022	2960 2847	1685	1569 1500	1249	ν (N=O) 1553
A_{12}	4-OH	3016	2917 2844	1690	1573 1562	1257	ν (O-H) 2443-3321
A_{13}	4-Cl	3015	2918 2854	1686	1593 1506	1241	ν (C-Cl) 753
A_{14}	4-Br	3031	2929 2873	1679	1588 1556	1250	ν (C-Br) 664

A_{15}	4-OCH_3	3084	2986 2952	1684	1571 1502	1243	ν (C-O) 1167

^{1}H-NMR spectrum of compond" (A_{11}) It showed a doubling signal, in situ (2.28 ppm) attributed to protons (CH_2) of the thiazine ring. signal at (2.51 ppm) return to solvent (DMSO-d6), and triple signal at (4.02-4.11 ppm) attributable to proton (CH) adjacent to the NH_2 group. In addition to an individual signal at (5.85 ppm) attributed to proton (N-CH), signals at (7.02-7.77 ppm) refer to aromatic ring protons. In addition to an individual signal at (8.14 ppm) belonging to protons (NH_2), individual signals at (11.86 ppm) and (12.97 ppm) belonging to acid protons (OH).[15-17]. Shown figure 7.

Figure 7: ^{1}H-NMR Spectrum for compound (A_{11})



Test the inhibitory activity of some prepared compounds [18-20]

The biological activity of some prepared compounds (A4, A5, A10, A14, A15) was evaluated on two types of bacterial isolates namely GVe + *Enterococcus faecalis* and GVe - *Proteus mirabilis* .The results showed the inhibitory activity of the prepared compounds against bacteria and the results were compared with the

antibacterial ciprofloxacin. The results indicated that the prepared compouds had the ability to inhibit bacteria using different concentrations of the compounds (5mg/ml), (10mg/ml) and (15mg/ml). Especially compound A_{15}, which showed high efficacy at concentrations (10 mg/ml) compared to the standard antibiotic. See Table 7

Table 7: Anti-bacterial activity data of some prepared compounds measured in millimeters

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	11	13	15	0	8	10
A5	10	11	15	0	0	0
A10	14	16	16	0	10	11
A14	13	15	20	13	15	17
A15	16	22	22	12	14	15
Ciprofloxacin		20			20	

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

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

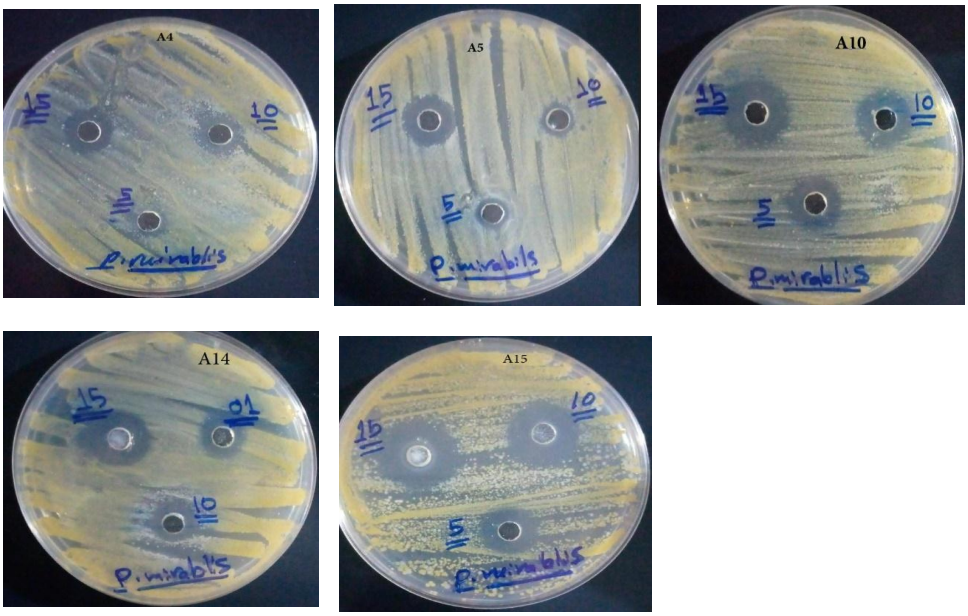
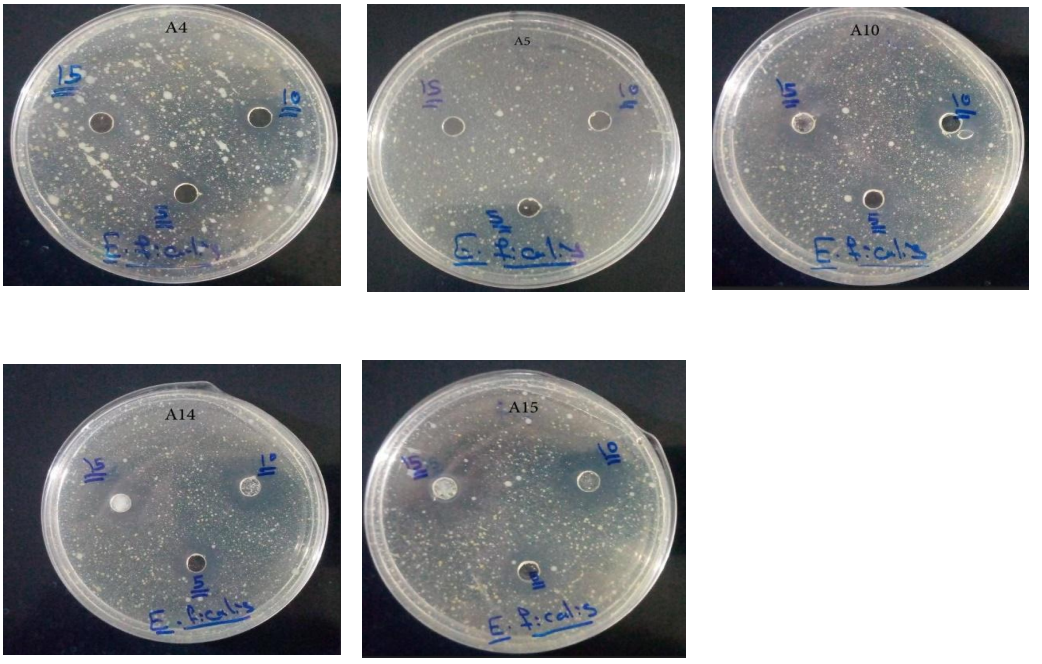


Figure 9: Diameter of inhibition area (mm) on Enterococcus faecalis + GIVe.



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