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Synthesis of Some Thiazolidine-4-One Derivatives of Isoniazid by using the Microwave Method and Evaluation of their Antibacterial and Antifungal Activity

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***Abstract*---**In this research, several Schiff bases [A1-A5] were prepared by reacting isoniazid with some aldehydes such as (4-hydroxybenzaldehyde, 3-nitro-4-hydroxybenzaldehyde, 4,3-dichlorobenzaldehyde, 4-hydroxy-3,5-dimethoxybenzaldehyde, pyrrole -2-carbaldehyde) by microwave method. In the same way, some ketones such as (Isatin and 4-aminoacetophenone) were used with Isoniazid to prepare Schiff bases [A6, A7]. Derivatives of thiazolidine-4-one (A8-A14) were prepared through the reaction of Schiff bases [A1-A7] with thioglycolic acid using dry benzene as a solvent and the reaction was done by microwave device. The prepared compounds were identified by infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance spectrometry as well as the change in color and melting point. The results of the biological activity of the prepared compounds showed high inhibitory activity at concentrations of 5, 10, and 15 mg/ml against the fungus Aspergillus sp. and against two types of bacteria isolates, GVe+ Streptococcus pneumonia, and GVe- Pseudomonas aeruginous, and the results were compared with the standard antibiotics Nystatin, Isoniazid l and Sulfamethoxazole.

***Keywords*---**Isoniazid, thiazolidine-4-on, antibacterial, antifungal.

Introduction

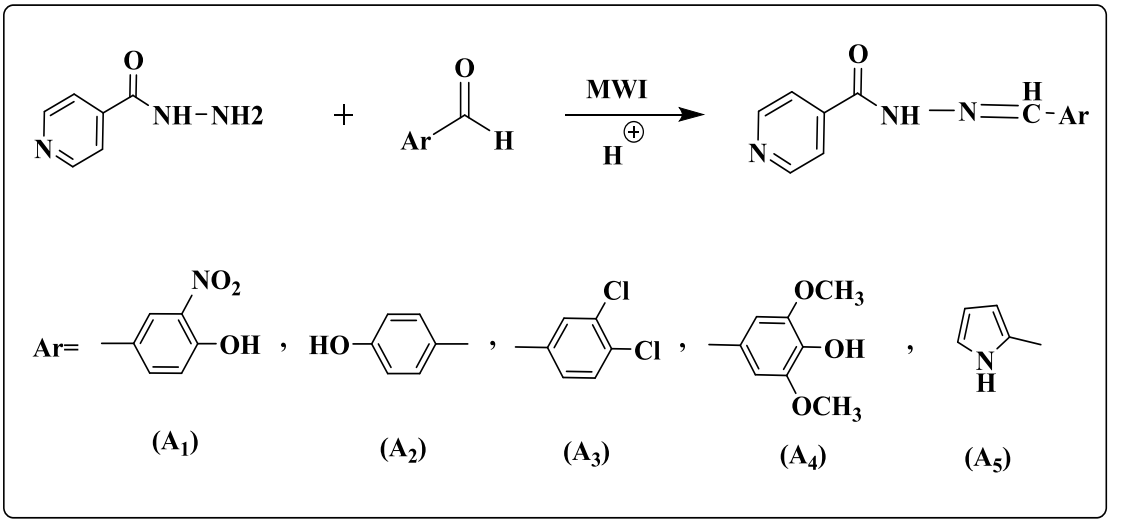
Isoniazid is a hydrazide of isonicotinic acid [(1)]. A white crystal dissolves quickly in water and has a solubility in ethyl alcohol, chloroform, and ether [(2)]. and it is

slowly affected when exposed to light and air. It is one of the most important antibiotics for tuberculosis bacteria [3-6], it has an antidepressant effect [7] and analgesic [8], and it is widely used with Rifampicin and Streptomycin for chemotherapy in tuberculosis [9]. As it was one of the Discovered antidepressants [7]. Schiff's bases have great importance in biological field and contribute a great role in biological activities as in the reactions of enzymatic transport of the amine group and have importance in medicines and medicine, and have important biological effects as they are anti-bacterial, fungi and viruses, especially viral hepatitis in rats, and they are anti-cancer and herbicide [10]. Schiff's bases are also used in industry as they act as corrosion inhibitors [11] and antioxidant [12], in addition to their industrial uses; they are used in the preparation of many condensing polymers. Containing phenolic hydroxyl groups also is of importance in the manufacture of hair dye preparations and in the manufacture of inks used in printing on silk fabric. Some of the complexes of Schiff's bases have an important role in treatment as blood pressure reducers, as well as when preparing the derivative of (sulfa) drugs, as it was found that they work to stop bacteria from Growth and reproduction [13]. Thiazolidine is a pentacyclic that contains nitrogen and sulfur in their composition. These compounds have biological and pharmacological activity. Therefore, they are consider as heterocyclic compounds that have wide application uses. This is because its composition contains a sulfur and nitrogen atom, which makes it an important biological activity [14].

Thiazolidines make a major breakthrough in antidiabetic therapy by increasing sensitivity to insulin [15], so they are also called "insulin sensitizers" when PPARγ is activated by binding to thiazolidine, its receptor where it leaves into DNA to activate a number of specific genes that ultimately enhance sensitivity target tissue [16].

Practical part
1-Preparation of Schiff bases derivatives by microwave method [A1- A5]

(0.002 mol) of Isoniazid was dissolved in 25 ml absolute ethanol. Then (0.002 mol) of different benzaldehyde substitutes (4-hydroxybenzaldehyde, 3-nitro-4-hydroxybenzaldehyde, 4,3-dichlorobenzaldehyde, 4-hydroxy-3,5-dimethoxybenzaldehyde, pyrrole 2-carbaldehyde) were added to it. After the completion of dissolution, 3-4 drops of glacial acetic acid were added. Then it was refluxed in a microwave at a power of (400w) until the completion of the reaction. It was confirmed that the reaction had ended using TLC, and after the reaction was complete, the mixture was cooled, the precipitate was filtered, dried, and recrystallized with absolute ethanol, See Scheme 1 and Table 1.



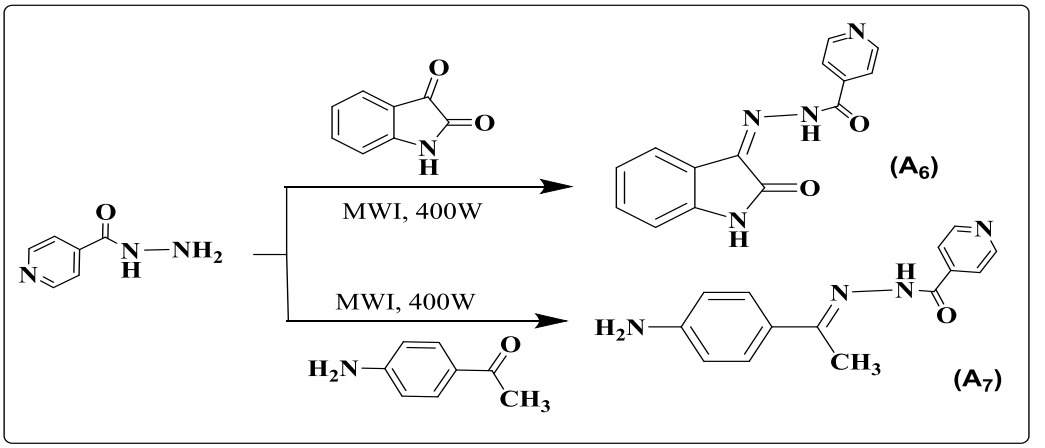
Scheme 1: Equation to prepare Schiff bases [A1- A5]

Table 1: physical properties, percentage, reflux time, and Retardation factor of the Schiff bases compounds [A1-A5].

Comp. No.	Molecular Formula M.Wt g/mol	Color	M.P. (^{0}C)	Ref.T (min)	Yield (%)	R f
A_1	$C_{13}H_{10}N_4O_4$ 286.2	Dark brown	170-172	9	74	0.22
A_2	$C_{13}H_{11}N_3O_2$ 241.3	Light Yellow	190-192	11	82	0.81
A_3	$C_{13}H_9Cl_2N_3O$ 271.29	Dark Yellow	195-197	10	92	0.88
A_4	$C_{15}H_{15}N_3O_4$ 286.3	Yellow	223-225	8	90	0.76
A_5	$C_{11}H_{10}N_4O$ 214.2	Yellow	200-202	6	80	0.76

2-Preparation of Compounds A6 and A7

(0.002 mole) of Izonazide was dissolved in 25ml of absolute ethanol in a round flask of 100ml capacity, then (0.002 mole) of Isatin or 4-aminoacetophenone was added with drops of glacial acetic acid as a catalyst. The termination of the reaction was confirmed using TLC technology. The mixture was then cooled, the precipitate was filtered, dried, and recrystallized with absolute ethanol. See Scheme 2 and Table 2.



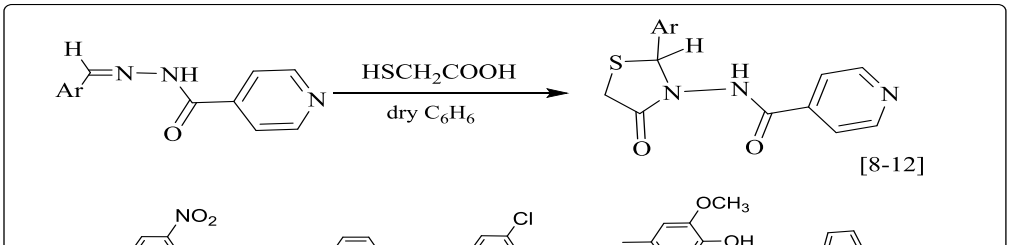
Scheme 2: Equation to prepare Schiff bases [A6, A7]

Table 2: physical properties, percentage, reflux time, and Retardation factor of the Schiff bases [A6,A7].

Comp. No.	Molecular Formula M.Wt g/mol	Color	M.P. (^{0}C)	Ref.T (min)	Yield (%)	R f
A_6	$C_{14}H_{10}N_4O_2$ 266.26	Dark red	231-233	6	81	0.92
A_7	$C_{14}H_{14}N_4O$ 254.29	Brown	294-296	9	80	0.79

3-Preparation of thiazolidine-4-one derivatives compounds [A8-A14] [17]

A mixture of (0.001mole) of the prepared Schiff base derivatives [A1-A7] with (0.001mole) of thioglycolic acid in (10ml) of dry benzene with continuous stirring. The mixture was refluxed on a water bath until the reaction was completed, the mixture was cooled, the precipitate filtered, dried, and recrystallized with absolute ethanol. See Scheme 3 and Table 3.



Scheme 3: Equation to prepare thiazolidine-4-one derivatives [A8-A14]

Table 3: physical properties, percentage, reflux time, and Retardation factor of the thiazolidine-4-one [A8-A14].

Comp. No.	Molecular Formula M.Wt g/mol	Color	M.P. (^{0}C)	Ref.T (min)	Yield (%)	R f
A_8	$C_{18}H_{15}Cl_2NO_3S$ 396.28	Light Orange	206-208	7	61	0.87
A_9	$C_{20}H_{19}NO_3S$ 353.44	Light brown	108-110	8	85	0.81
A_{10}	$C_{16}H_{20}N_2O_3S$ 320.41	brown	150-152	12	77	0.22
A_{11}	$C_{15}H_{12}N_4O_5S$ 360.34	Light brown	158-160	6	85	0.81
A_{12}	$C_{15}H_{13}N_3O_3S$ 315.35	Light Yellow	198-200	7	82	0.85
A_{13}	$C_{16}H_{12}N_4O_3S$ 340.36	Yellow	270-272	8	82	0.85
A_{14}	$C_{16}H_{16}N_4O_2S$ 328.39	Yellow	184-186	7	72	0.89

Results and Discussion

Infrared (FT-IR) spectrum of the prepared Schiff base compounds [A1-A5] It was observed that a strong band appeared at (1608-1643) cm^{-1} due to azomethine group (C=N). In addition, absorption bands appeared at the range (3008-3097) cm^{-1} it reverts to the stretching of the aromatic (C-H) bond. Two bands appear at the range (2915-2995) and (2933-2812) cm^{-1} refer to the stretching of the aliphatic (C-H) bond. Appearance of two absorption bands at the range (1504-1599) cm^{-1} and (1560-1461) cm^{-1} due to the stretching of the aromatic (C=C) bond [18,19]. See Table 4.

Proton NMR spectroscopy of compound [A1] using solvent (DMSO-d6) and (TMS) as a reference, it was observed that a signal at (2.51) ppm due to the solvent (DMSO-d6), and signal appeared at (3.42) ppm attributed to (H2O) protons. As well as the appearance of multiple signals at (7.22 - 8.80) ppm attributed to the aromatic ring protons. A single signal at (8.43) ppm attributed to a group proton (HC=N), as well as the appearance of a single signal at (9.97) ppm that belongs to the proton of the (NH) group. In addition, the single signal at (12.16) ppm that belongs to the proton of the (OH) group [20,21]. See Figure 1.

^{1}H-NMR spectrum of the compound [A4] observed the appearance of a signal at (2.51) ppm due to the solvent (DMSO-d^6), and signal at the position (3.39) ppm attributed to protons (H_2O). The single signal at (3.83) ppm sites is attributed to the protons of the (OCH_3) group attached to the benzene ring, and the appearance of multiple signals at (6.81 - 8.79) ppm is due to the aromatic ring protons, as well as the appearance of a single signal at (8.34) ppm due to a proton group (HC=N) [20,21]. See Figure 2.

The mass spectrum of the compound (A5) was measured, where it showed a peak at (214 m/z) with a relative abundance (10%) due to the molecular ion of the compound, as well as a base peak at (87 m/z) and with a relative abundance (100%). See Figure 3.

Table 4: Infrared data of Schiff bases derivatives [A1-A5].

(KBr) cm^{-1}) FT-IR (							
Comp. No.	**R**	**ν (C-H) Arom.**	**ν (C-H) Aliph. Asy.sy**	**ν C=O) Amide**	**ν (C=N)**	**ν (C=C) Arom.**	**Others**
A 1	3-NO_2 4-OH	3042	2928 2812	1650	1624	1579 1494	ν (NO_2). *asy.*(1549) *sy.*(1374) ν (O-H) 3370
A 2	4-OH	3080	2941 2879	1669	1626	1581 1470	ν (O-H) 3368
A 3	3,4-Cl	3071	2951 2865	1655	1622	1580 1482	ν (C-Cl) 1143
A 4	3,5-OCH_3 4-OH	3045	2921 2873	1666	1629	1591 1542	ν (O-H) 3352

A_5	Pyrrole	3072	2956 2923	1664	1618	1593 1568	ν (N-H) 3388

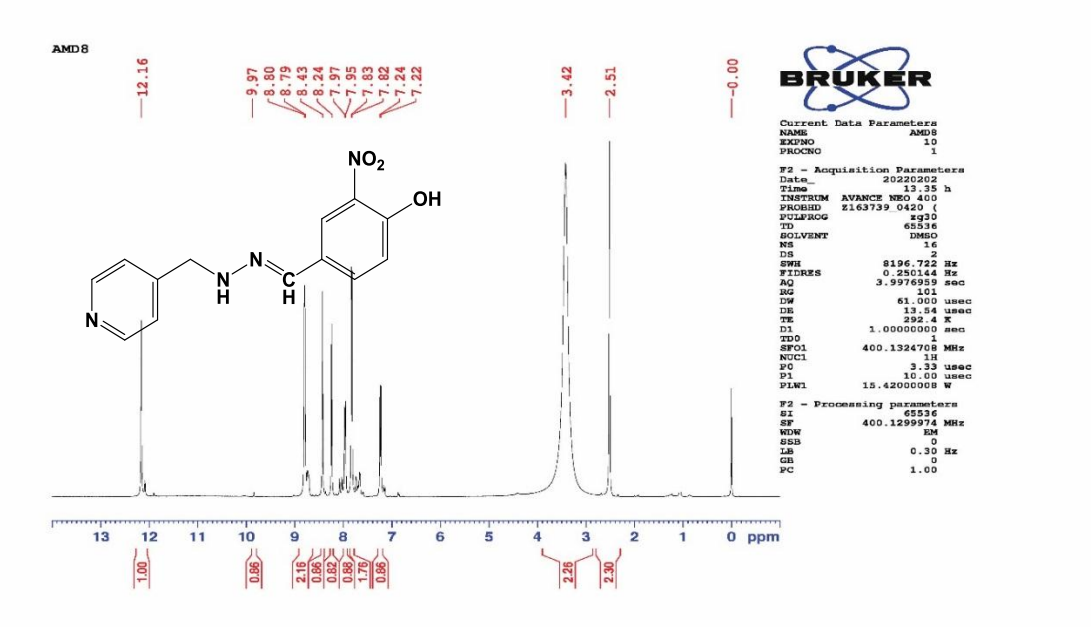


Figure 1: ^{1}H-NMR of Compound (A1)

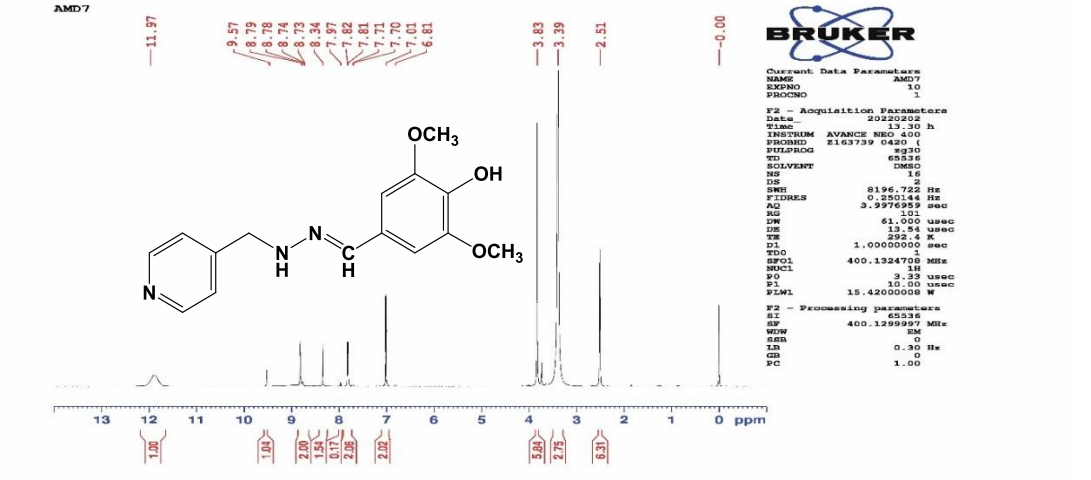


Figure 2: ^{1}H-NMR of Compound (A4)

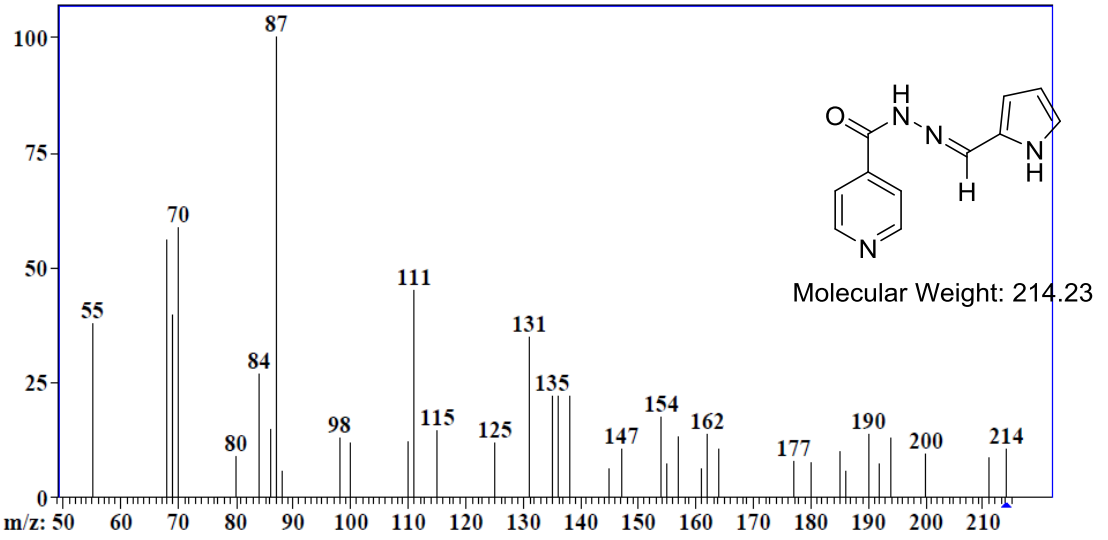


Figure 3: The mass spectrum of the compound (A5)

Table 5: Infrared data of Compounds [A6,A7].

Comp. No.	IR (KBr) cm^{-1}						
	ν (C-H) Arom.	ν (N-H)	ν (C-H) Aliph.	ν (C=O) Amid	ν (C=C) Arom.	ν (C=N)	ν (C-N)
A_6	3055	3285	2983 2875	1658	1596 1490	1618	1277
A_7	3097	3280	2933 2882	1672	1580 1493	1626	1244

The mass spectrometry of the compound (A6) was measured and it showed the main peak at (260 m/z) with a relative abundance (10%) due to the molecular ion and a base peak at (119 m/z) with a relative abundance (100%).See Figure 4.

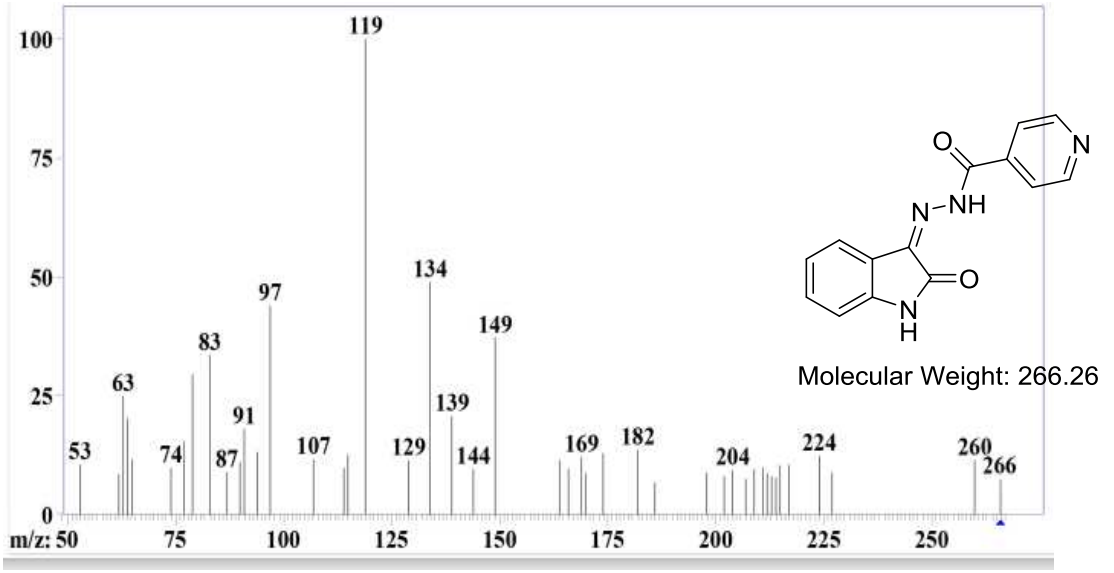


Figure 4: The mass spectrum of the compound (A6)

The infrared spectrum of the prepared compounds [A8-A14] observed the disappearance of the stretching band of the imine group (C = N), and the appearance of a strong band at the frequency (1645 - 1680) cm-1 due to the stretching of the carbonyl bond (C = O) of the thiazolidine ring. See Table 7.

The proton nuclear magnetic resonance spectrum of the compound [A8] was observed a signal at (2.50) ppm due to the protons of the solvent (DMSO-d6). The appearance of a signal at (3.44) ppm due to (H_2O) protons, and a single signal in the position (3.61) ppm is attributed to the protonation of (CH_2) of the thiazolidine ring protons. Multiple signals at (6.97 - 8.88) ppm are due to the aromatic ring protons. As well as the single signal at (11.09) ppm belonging to a proton the (NH) group in Isoniazid, and single signal at (11.45) ppm belongs to the (NH) group proton in Isatine. See Figure 5.

The mass spectrum of the compound (A12) where it showed a main peak at (288 m/z) and with a relative abundance (7%) due to the molecular ion of the compound, as well as a base peak at (108 m/z) and with a relative abundance (100%) as in Figure 6.

Mass spectrum of the compound (A13) where it showed a main peak at (340 m/z) and with a relative abundance (8%) due to the molecular ion of the compound, as well as a base peak at (111 m/z) and with a relative abundance (100%) See Figure 7.

Table 6: Infrared data of thiazolidine-4-one derivatives [A8-A14]

(KBr) cm^{-1}) FT-IR(							
Comp. No.	**R**	**ν (C-H) Arom.**	**ν (C-H) Aliph.**	**ν(C=O) Amide**	**ν(C=C) Arom.**	**ν (C-N)**	**Others**
A_8	3-NO_2 4-OH	3051	2962 2920	1668 1674	1510 1489	1222	ν (NO_2) *asy.*(1539) *sym.*(1358) ν (O-H)

							3532
A_9	4-OH	3059	2968 2930	1668 1641	1610 1489	1213	ν (O-H) 3591
A_{10}	3,4-Cl	3035	2978 2860	1693 1660	1583 1527	1257	ν (C-Cl) 728
A_{11}	3,5-OCH_3 4-OH	3093	2902 2867	1749 1664	1587 1469	1230	ν (O-H) 3372
A_{12}	Pyrrole	3055	2939 2856	1751 1670	1569 1479	1282	ν (N-H) 3263
A_{13}	Isoniazid	3033	2921 2871	1712 1650	1591 1456	1249	ν (N-H) 3321
A_{14}	Isoniazid	3082	2990 2815	1695 1680	1579 1471	1260	ν (N-H) 3279

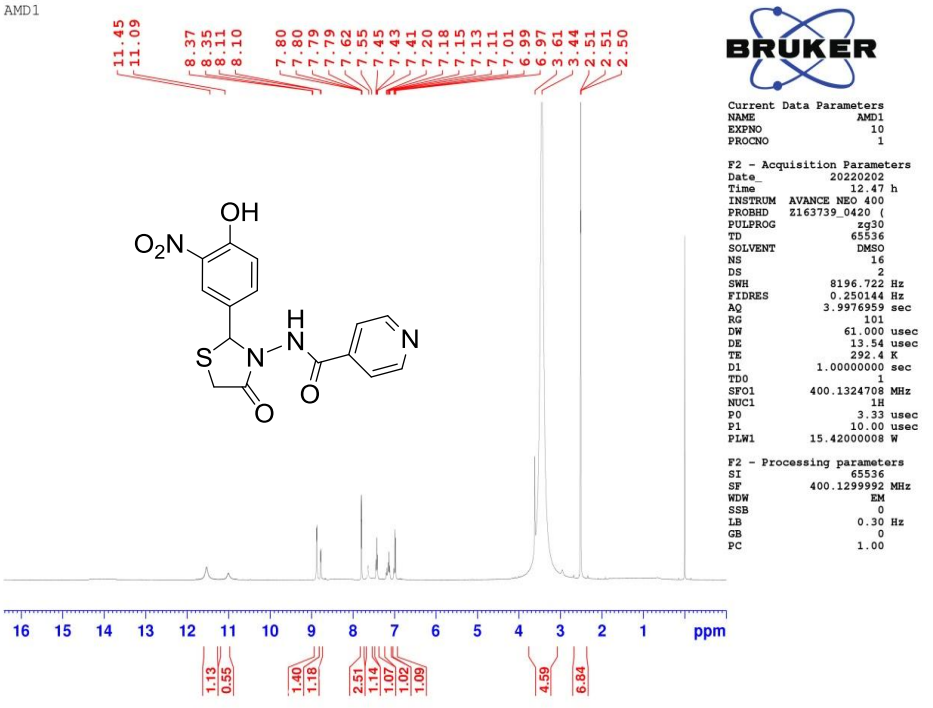


Figure 5: ^{1}H-NMR of Compound (A8)

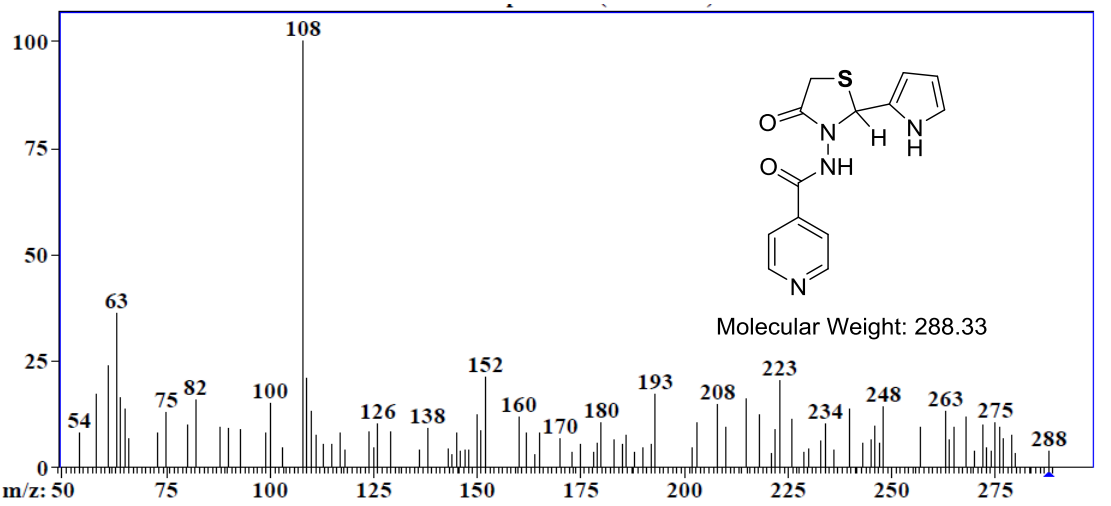


Figure 6: The mass spectrum of the compound (A12)

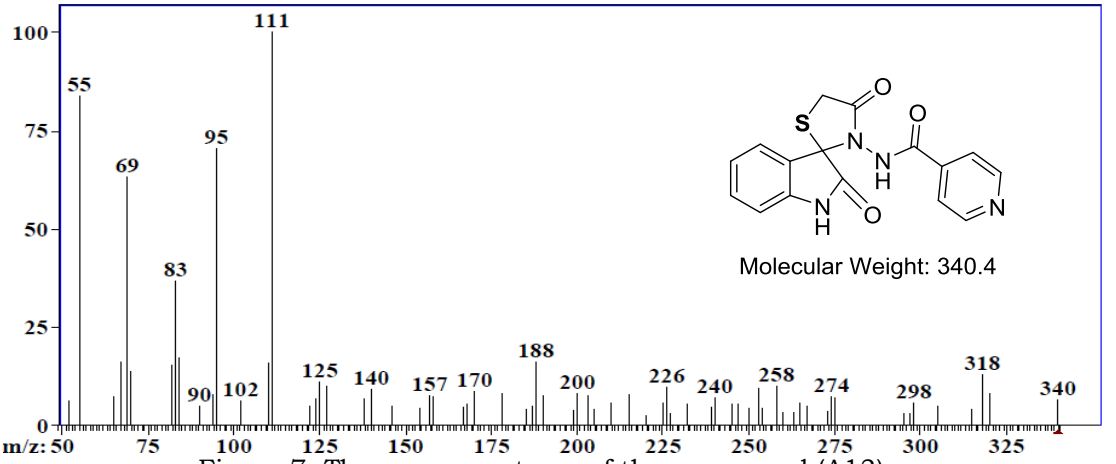


Figure 7: The mass spectrum of the compound (A13)

Evaluation of the biological activity of some prepared compounds [22]

The biological activity of some prepared compounds (A2, A7, A11, A12 and A14) was evaluated on a type of yeast of the class of yeasts, *Aspergillus sp*. In addition, on two types of bacterial isolates of the class of Bacillus, which are GVe+ *Streptococcus pneumonia*, and GVe- *Pseudomonas aeruginous*. The results showed inhibitory activity of the prepared compounds against the fungus and the results were compared with the standard antifungal Nystatin. As well as the results showed inhibitory activity against bacteria and the results were compared with the antibacterial Isoniazid and Sulfamethoxazole for bacteria. The results indicate that the prepared compounds have the ability to inhibit fungi and bacteria by using different concentrations of compounds (5 mg/ml), (10 mg/ml), and (15 mg/ml) compared to inhibition with standard antibiotics for fungal and bacteria. See Table 7.

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

Comp.No.	*Streptococcus pneumonia* +GVe			*Pseudomonas aeruginosa* -GVe			*Aspergillus sp.*		
	5 mg/ml	10 mg/ml	15 mg/ml	5 mg/ml	10 mg/ml	15 mg/ml	5 mg/ml	10 mg/ml	15 mg/ml
A2	6	8	12	8	11	14	8	10	12
A7	8	8	16	9	11	14	8	12	18
A11	10	15	22	8	12	16	9	11	15
A12	6	9	11	7	9	14	8	10	12
A14	7	10	13	8	11	19	11	15	20
Isoniazid		2			5			-	
Sulfamethoxazole		5			7			-	
Nystatin		-			-			8	

The concentration of Isoniazid, sulfamethoxazole, and nystatin is only 10mg/ml. The following pictures show the inhibition areas of the prepared compounds against two types of bacteria used and one type of fungus. See Figure 8 , 9 and 10.

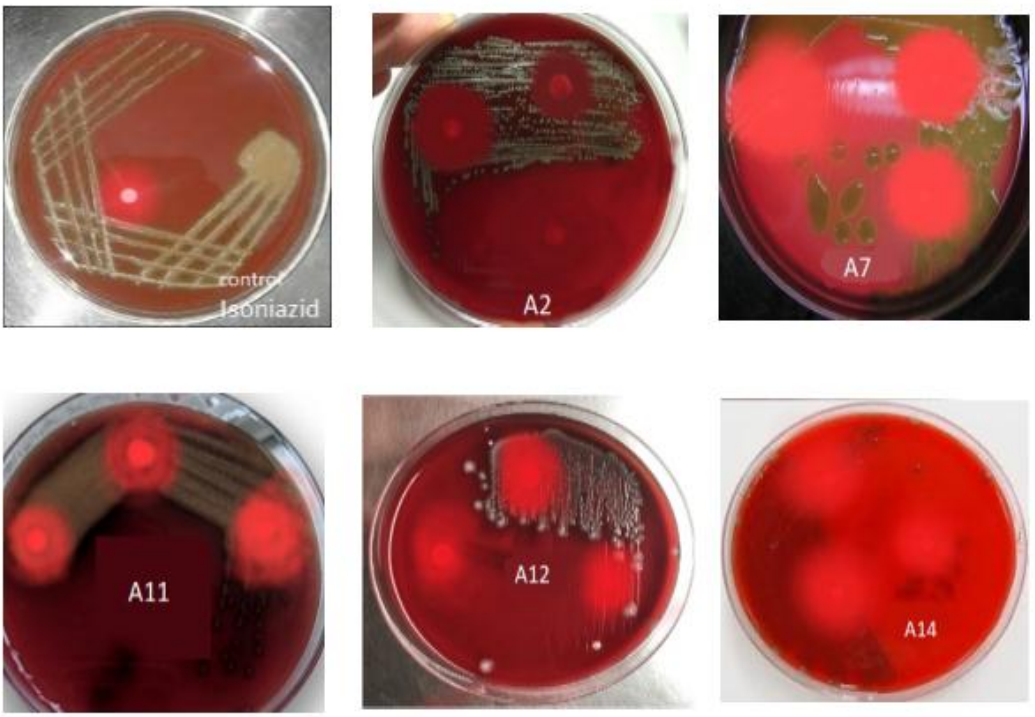


Figure 8: Inhibition zone diameter (mm) on *Streptococcus pneumoniae* GIVe+ growth on blood agar.

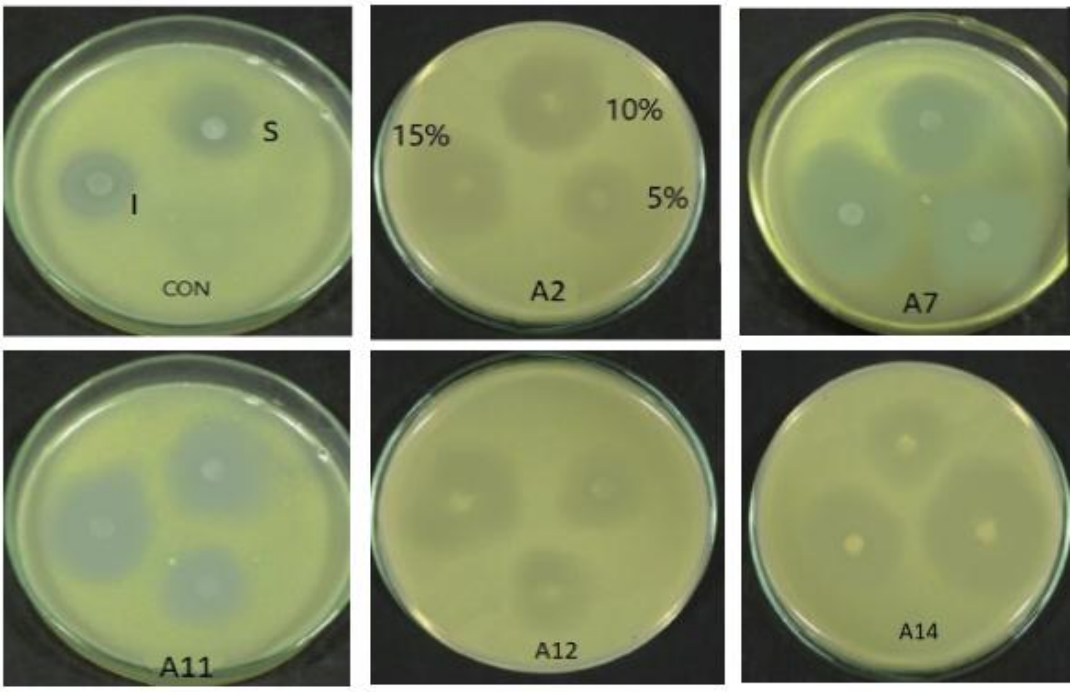


Figure 9: Inhibition zone diameter (mm) on *Pseudomonas aerugenosa* GVe-growth on broth agar.

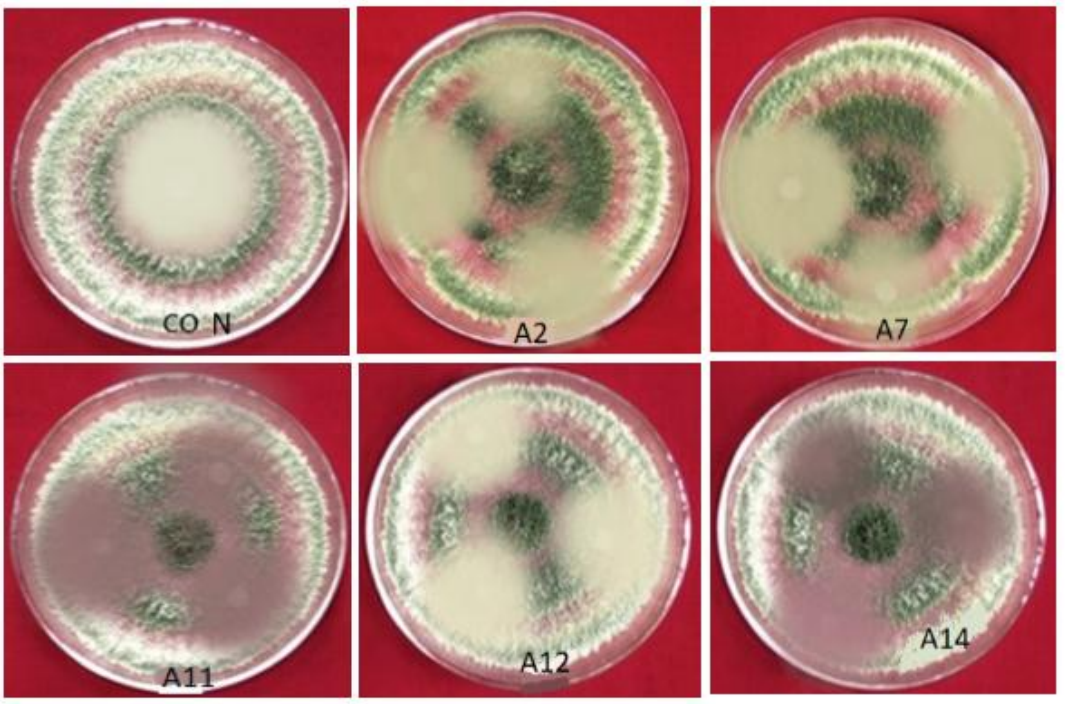


Figure 10: Inhibition zone diameter (mm) on *Aspergillus sp.* specie fungi growth

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