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3-PHENYLIMIDAZOLIDIN-4-ONE: CHARACTERIZATION, GREEN SYNTHESIS, EVALUATION OF BIOLOGICAL AND LASER PERFORMANCE

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Abstract: This study involves the synthesis of 4-imidazolidinone derivatives by reacting Schiff base derivatives with glycine. The reactions were conducted using both conventional and microwave methods and characterized using determining melting points and purity, monitoring reaction progress and Rf values using thin-layer chromatography (TLC), and conducting infrared (FT-IR) spectroscopy, proton nuclear magnetic resonance (1H-NMR) spectroscopy, and quantitative elemental analysis (C.H.N.). The biological activity of the synthesized compounds was evaluated by examining their effects on the growth of four types of antibiotic-resistant bacterial isolates: two Gram-negative strains (Escherichia, Klebsiella pneumoniae) and two Gram-positive strains (Staphylococcus aureus, Staphylococcus epidermidis). The standard antibiotic Ampicillin was used as a control sample. The synthesized compounds exhibited good inhibitory activity against the tested bacteria. Additionally, the laser activity of the synthesized compounds was measured using a helium-neon laser (visible laser). The compounds were irradiated for four different periods (15, 30, 45, and 60) seconds, and their physical properties were re-examined to observe any changes resulting from the laser irradiation. A study of the effect of stereochemistry and the most stable conformation was also conducted using the Chem3D 19.0 program.

Keywords: 4-Imidazolidinone, Green Chemistry, Biological Activity, Laser Effectiveness, Energy Structure.

1. Introduction

Organic molecules known as imidazole compounds have a pentagonal ring with two nitrogen atoms at position (1 & 3) and three carbon atoms overall [1]. 4-Imidazole compounds are a subclass of imidazole compounds where the ring's fourth position has a substituent [2]. Due to their distinct chemical and biological characteristics, which include antibacterial [3], antifungal [4], antioxidant [5], and anti-inflammatory actions [6,] these compounds are very interesting to researchers in organic and pharmaceutical chemistry. 4-Imidazole compounds are a significant area of research and development because of their many biological and industrial uses [7]. Certain 4-imidazole derivatives, for instance, are used in creating medications to treat chronic illnesses, including cancer and inflammatory conditions, and antibacterial and antifungal agents [8]. The occurrence of 4-imidazole compounds in several natural biological systems highlights their biological significance, which raises their worth in chemical and pharmacological research [9]. 4-imidazole compound synthesis using green chemistry techniques. Green chemistry is a strategy that uses ecologically friendly and sustainable reactive processes to minimize chemical waste and environmental harm [10]. These techniques are based on several ideas, including lowering the amount of hazardous solvents used, enhancing reaction efficiency, and cutting down on secondary waste [11]. Creating 4-imidazole compounds using green chemistry techniques is a significant step towards creating industrial

processes that are more ecologically friendly and sustainable [12]. The conventional methods for synthesizing 4-imidazole compounds include using hazardous organic solvents and elevated temperatures, culminating in generating substantial quantities of dangerous chemical byproducts [13].

On the other hand, green chemistry techniques emphasize using safe solvents for the environment, using catalysts that are favorable to the environment for catalysis, and reducing energy used during the reaction process [14]. One of the cutting-edge and contemporary techniques for preparing chemical compounds is microwave technology, which is used to prepare them [15]. It often shortens reaction times and increases chemical reaction efficiency [16]. By heating compounds with microwave radiation, this method shortens reaction times and eliminates the need for high temperatures [17]. Among the numerous benefits of preparing 4-imidazole compounds using microwave technology is that it speeds up the processes, allowing them to be finished much faster than conventional techniques [18]. Increasing the degree of selection by enhancing the chemical selectivity of processes, microwave technology helps to raise yield and improve product purity [19]. Microwave technology also considerably lowers energy usage since it heats food directly and quickly [20]. Cutting down on waste This method makes the process more ecologically friendly by reducing hazardous chemical waste produced [21]. An exceptional illustration of how organic chemistry is progressing towards environmental sustainability and reaction efficiency is the synthesis of 4-imidazole compounds using microwave technology and green chemistry techniques. The chemical industry and scientific research should embrace these contemporary techniques because they provide many chances to improve chemical processes and lessen their effect on the environment [22].

2. Experimental part

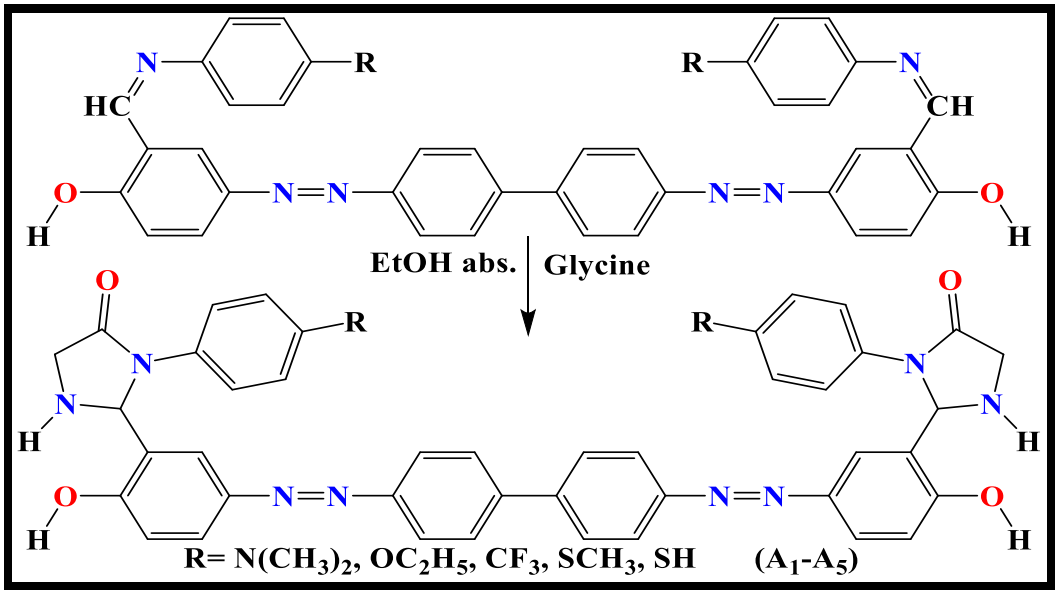
2.1. Materials: All chemicals and reagents used in this study were supplied by companies Fluka.

2.2. Synthesis of a series of 4-imidazolidinone derivatives by the traditional method (A_1-A_5)

Mix (0.001 mol) Schiff bases made in (45 ml) of absolute ethanol with (0.002 mol) glycine dissolved in (10 ml) of pure ethanol. After refluxing the mixture for four to seven hours, the completeness of the reaction was verified using the TLC technique. The mixture was filtered, cleaned, and then recrystallized using ethanol after it had reached room temperature [23, 24]. Table (1) displays some physicochemical properties of the 4-imidazolidinone derivatives (A_1-A_5).

2.3. Synthesis of a series of 4-imidazolidinone derivatives by microwave method (A_1-A_5)

Mix (0.001 mol) of Schiff bases generated in 10 ml of absolute ethanol with 0.002 mol of glycine dissolved in 5 ml of pure ethanol. After placing the mixture in the microwave, set the wattage to 400 W and let it reflux for three to five minutes at 78°C. The completeness of the reaction was confirmed using the TLC technique. The mixture was cooled to a temperature of. It was filtered, chambered, and washed with cold water before being recrystallized with ethanol [25, 26]. Table 1 displays some physicochemical properties of the 4-imidazolidinone derivatives (A_1-A_5).



Scheme (1): Prepared compounds (A_1-A_5)

Table (1): Some physical properties of the 4-imidazolidinone derivatives (A_1-A_5).

Comp. No.	R	Molecular Formula/ M.Wt g/mol	Traditional Methods					Microwave Methods				
			Color	M.P. ^{0}C	T. h.	Y.%	R_f	Color	M.P. ^{0}C	T. min.	Y.%	R_f
A_1	$N(CH_3)_2$	$C_{46}H_{44}N_{10}O_4$ 800.92	Light orange	298-299	7	77	0.84	Light orange	298-299	4	91	0.84
A_2	OC_2H_5	$C_{46}H_{42}N_8O_6$ 802.89	Light brown	229-230	7	75	0.72	Light brown	229-230	5	85	0.72
A_3	CF_3	$C_{44}H_{32}N_8O_4F_6$ 850.78	Orange	280-282	4	79	0.55	Orange	280-282	4	89	0.55
A_4	SCH_3	$C_{44}H_{38}N_8O_4S_2$ 806.96	Yellow	240-242	6	71	0.46	Yellow	240-242	3	86	0.46
A_5	SH	$C_{42}H_{34}N_8O_4S_2$ 778.91	Light brown	275-276	5	74	0.57	Light brown	275-276	5	89	0.57

2.4. Evaluation of the Biological Activity of the Synthesized Compounds

Thirty-nine grams of the Muller-Hinton Agar medium were dissolved in one litre of distilled water. The four bacterial isolates assessed were two Gram-negative strains of Escherichia coli and Klebsiella pneumoniae and two Gram-positive strains of Staphylococcus aureus and Staphylococcus epidermidis. Next, chemical solutions for the synthesized compounds were made using DMSO as the solvent, with concentrations of (25, 50, and 100) mg/ml for each solid derivative [27]. The Muller-Hinton Agar (MHA) medium was injected using a sterile cotton swab dipped into tubes containing the diluted bacterial cultures. To ensure that the inoculum was dispersed equally, the medium was streaked in three directions. For five to fifteen minutes, the plates were left to soak and dry [28]. We evaluated the generated compounds using the Agar-well diffusion method. Wells was created using a cork borer and the cylinder metric approach after the bacterial isolates were injected into the agar medium (per the United States Pharmacopoeia USP 35). Each well received 40 µl of the synthesized compounds at the three doses. Twenty-four hours were spent incubating the plates at 37 °C. The compounds' sensitivity was determined by measuring the diameter of the inhibition zones around the wells; the findings were analyzed twice over 24 and 48 hours. The breadth of the inhibitory zones corresponds to an increase in the biological activity of the synthesized compounds. These results were compared to the inhibitory zones of popular antibiotics. Common antibiotics like ampicillin

were employed as control samples by World Health Organization recommendations, which were patterned after those used in Ministry of Health laboratories [29].

2.5. Measurement of Laser Activity of the Compounds

The laser activity of the synthesized compounds was measured using a visible helium-neon laser. Each molecule had four different radiation exposure times (15, 30, 45, and 60 seconds). The laser source, which had a power of 1 mW and a wavelength of 808 nm, was positioned 10 cm away from the sample. The measurements were taken at the Laser Laboratory at the Department of Physics, College of Science, University of Tikrit. Following laser irradiation, the physical properties of the synthesized compounds were reexamined to look for potential alterations [30].

3. Results and Discussion

3.1. Characterization of thiazolidinedione derivatives (A_1-A_5) by using UV-Vis and FT-IR

Ethanol (95%) was utilized as the solvent in the UV-Vis spectra of the synthesized compounds (A_1-A_5), with concentrations ranging from (10^{-4}-10^{-5}) M. The compounds showed long wavelength maxima (λmax) in the range of (290-369) nm, corresponding to (n→π*) electronic transitions, and short wavelength maxima (λmax) at (207-249) nm, corresponding to (π→π*) transitions [31].

In the IR spectra, the disappearance of the azomethine group (C=N) and the appearance of a strong band at (1649-1672) cm^{-1}, attributed to the (C=O) bond, was observed [32]. Additionally, appears package (O-H) at (3350-3402) cm^{-1}, appears package (C-H aromatic) at (3013-3097) cm^{-1}, while appears package (C-H aliphatic) at (2920-2987) cm^{-1} [33]. Furthermore, appears package (C=C) at (1581-1598 and 1470-1499) cm^{-1}, appears package (N=N) at (14331-1447) cm^{-1} [34]. Other appears package (C-N) at (1242-1280) cm^{-1}, and appears package (C-S) at (741-789) cm^{-1} [35]. Table (2) which shows UV and IR absorption results (cm^{-1}).

Table (2): UV/Vis., and FT-IR data of prepared compounds (A_1-A_5)

Comp No.	λmax1 λmax2 EtOH	IR (KBr) cm^{-1}							
		ν O-H	ν C-H Arom., Aliph.	ν C=O	ν C=C	ν N=N	ν C-N	ν C-S	Others
A_1	249, 369	3382	3053, 2920	1670	1586, 1492	1439	1254	767	.....
A_2	241, 290	3399	3013, 2987	1665	1595, 1490	1431	1242	789	.....
A_3	232, 327	3359	3019, 2942	1672	1581, 1470	1447	1280	741	.....
A_4	221, 345	3402	3097, 2957	1649	1583, 1479	1445	1275	755	.....
A_5	207, 313	3950	3078, 2961	1660	1598, 1499	1438	1263	770	.....

3.2. Characterization of 4-imidazolidinone derivatives (A_3, A_5) by used ^{1}H-NMR

When studying the ^{1}H-NMR spectrum of (A_3), it was observed that a single signal appears at δ= (3.66) ppm due to two groups (CH_2) in the 4-imidazolidinone ring, a single signal appeared at δ= (3.95) ppm is attributed to two groups (NH) in the 4-imidazolidinone ring, a single signal appeared at δ= (6.86) ppm is attributed to two groups (CH) in the 4-imidazolidinone ring, a multiple signal in the δ= (7.15-7.92) ppm is attributed to the aromatic rings, a single signal appeared at δ= (8.96) ppm is attributed to two groups (OH), and a signal appears at δ= (7.50) ppm is attributed to (Chloroform-d) [36].

Studying the ^{1}H-NMR spectrum of (A_5), it was observed that a single signal appears at δ= (3.57) ppm due to two groups (CH_2) in the 4-imidazolidinone ring, a single signal appeared at δ= (3.78) ppm is attributed to two groups (NH) in the 4-imidazolidinone ring, a single signal appeared at δ= (4.30) ppm is attributed to two groups (SH), a single signal appeared at δ= (6.88) ppm is attributed to two groups (CH) in the 4-

imidazolidinone ring, a multiple signal in δ= (7.04-7.81) ppm is attributed to the aromatic rings, a single signal appeared at δ= (8.48) ppm is attributed to of two groups (OH), and a signal appears at δ= (7.50) ppm is attributed to (Chloroform-d) [37].

3.3. Elemental Analysis (C.H.N.S.) Measurement

Elemental analysis (C.H.N.) was done on a number of the synthesized compounds to verify the accuracy and precision of their structural makeup. The obtained elemental percentages, as shown in Table (3), were either consistent with or very close to the expected values, demonstrating the accuracy of the synthetic chemical structures [38].

Table (3): Elemental Analysis (C.H.N.) Results for Selected Synthesized Compounds (A_1-A_5)

Comp. No.	Molecular Formula	Calculated				Found			
		C%	H%	N%	S%	C%	H%	N%	S%
A_1	$C_{46}H_{44}N_{10}O_4$	68.98	17.49	5.54	---	68.82	17.42	5.65	---
A_2	$C_{46}H_{42}N_8O_6$	68.81	5.27	13.96	---	68.93	5.21	14.02	---
A_3	$C_{44}H_{32}N_8O_4F_6$	62.12	3.79	13.17	---	62.20	3.70	13.15	---
A_4	$C_{44}H_{38}N_8O_4S_2$	65.49	4.75	13.89	7.95	65.37	4.80	13.76	7.91
A_5	$C_{42}H_{34}N_8O_4S_2$	64.77	4.40	14.39	8.23	64.67	4.43	14.33	8.18

3.4. Green synthesis and traditional synthesis

The usage of solvents, catalyst needs, reaction times, percentage yield, melting points, colors, and solubility were compared between the two methods [34]. Every chemical was created using both conventional and microwave techniques. The microwave method uses minimal solvent and no auxiliary ingredient to get a significant yield in a short amount of time. Using microwave technology, it was also simple to isolate the prepared compounds. Compounds produced by both processes had comparable physical properties, such as color, melting point, and Rf values [35].

3.5. Solubility test for prepared compounds (A_1-A_5)

The produced compounds are thermally stable at room temperature because, as Table (3) illustrates, (A1-A5) are completely dissolved in MeOH, EtOH, acetone, THF, DMSO, DMF, $CHCl_3$, and mix benzene with EtOH. They are also poorly soluble in solvents like CCl_4, hexanol, and 1,4-dioxane, and they are not soluble in solvents like H_2O, diethyl ether, benzene, and 1,4-dioxane [36].

Table (4): Solubility test for (A_1-A_5), (+) soluble, (-) Insoluble, (÷) Poorly soluble

Comp. No.	MeOH	EtOH	H_2O	CCl_4	Acetone	Diethyl ether	Hexanol	Benzene	1,4-Dioxane	THF	DMSO	DMF	$CHCl_3$	Benzene + EtOH 1:1
A_1	+	+	-	÷	+	-	÷	-	-	+	+	+	+	+
A_2	+	+	-	÷	+	-	÷	-	-	+	+	+	+	+
A_3	+	+	-	÷	+	-	÷	-	-	+	+	+	+	+
A_4	+	+	-	÷	+	-	÷	-	-	+	+	+	+	+
A_5	+	+	-	÷	+	-	÷	-	-	+	+	+	+	+

3.6. Evaluation of the Biological Activity of Synthesized Compounds

The biological activity of many synthesized compounds was assessed as heterocyclic compounds, known to have distinct biological activities against Gram-positive and Gram-negative bacteria [37]. In this study, the

effects of the synthesized compounds were evaluated using four more species of bacteria: ***Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, and Staphylococcus epidermidis***. These bacteria were selected due to their significance to medicine since they are responsible for various ailments and exhibit different levels of antibiotic resistance [38]. The results show that the synthesized compounds have varying inhibitory effects on the growth of Gram-positive and Gram-negative bacteria, as shown in Table (5), Schemes (2, 3).

Table (5): Antibacterial activity of the synthesized compounds (inhibition zone in mm).

Comp. No.	*E. Coil* mg/ml			*K. Pneumonia* mg/ml			*S. Aureus* mg/ml			*S. epidermidis* mg/ml		
	25	**50**	**100**	**25**	**50**	**100**	**25**	**50**	**100**	**25**	**50**	**100**
A_1	8	18	24	7	16	21	8	17	23	7	17	22
A_2	10	20	24	8	18	22	7	16	21	8	18	22
A_3	9	17	25	10	19	25	9	19	25	9	20	25
A_4	9	19	22	8	16	22	8	17	22	9	20	25
A_5	10	19	25	9	19	24	10	20	25	7	17	21
Ampicillin	9	19	23	10	18	24	8	19	24	8	19	24
Blank disk	0	0	0	0	0	0	0	0	0	0	0	0

3.7. Results of Laser Activity Measurement for Some Synthesized Compounds

This study used a helium-neon source to generate laser radiation to evaluate several synthesized substances' laser activity. The physical properties of the compounds, such as color, melting point, and flow rate (Rf), were then evaluated once again to check for any alterations. The investigation's findings demonstrated that the chemical compounds' physical properties remained unchanged for 15, 30, or 45 seconds [39]. These compounds did not show any effects from laser light during these periods, keeping their physical properties and structural integrity. However, throughout the 60 seconds, significant changes in the physical properties were observed, such as observable changes in the melting points and changed (Rf) values in thin-layer chromatography (TLC) [40]. Additionally, some color differences were noted. These alterations are most likely the result of specific bonds within the compounds breaking after prolonged exposure to high-energy laser irradiation for 60 seconds, which might create new compounds [41]. The results of the laser activity measurement for certain synthesized compounds are shown in Table (6).

Table (6): Laser Activity Measurement Results for Some Synthesized Compounds.

Comp No.	15 S			30 S			45 S			60 S		
	Color	**M.P ^{0}C**	**R*f***	**Color**	**M.P ^{0}C**	**R*f***	**Color**	**M.P ^{0}C**	**R*f***	**Color**	**M.P ^{0}C**	**R*f***
A_1	Light orange	298-299	0.84	Light orange	298-299	0.84	Light orange	298-299	0.84	Light brown	167-170	0.61
A_2	Light brown	229-230	0.72	Light brown	229-230	0.72	Light brown	229-230	0.72	Light yellow	190-195	0.84
A_3	Orange	280-282	0.55	Orange	280-282	0.55	Orange	280-282	0.55	Yellow	202-209	0.77
A_4	Yellow	240-242	0.46	Yellow	240-242	0.46	Yellow	240-242	0.46	Orange	187-189	0.68
A_5	Light brown	275-276	0.57	Light brown	275-276	0.57	Light brown	275-276	0.57	Yellow	221-224	0.32

3.8. Study of the most stable and lowest energy structure

Using the Chem3D 19.0 programme, the influence of stereochemistry was investigated. The collision process between hydrogen atoms, which results in a rise in energy and instability, is the source of this sort of vacuum shape instability. Friction drops as the hydrogen atoms are separated, which subsequently causes a drop in power and stability [42]. As a result, the molecule is most stable and has the lowest energy in its

stereoscopic form [43]. Additionally, it was shown that the synthesized compounds' energy of formation is positive, indicating that their preparation processes are endothermic. This is compatible with the functional findings [44], as displayed in Table (7).

Table (7): The lowest energy for the structure of synthesized compounds (A_1-A_5)

Comp. No.	A_1	A_2	A_3	A_4	A_5
Energy Minimization kcal/mol	93.311	182.016	121.137	122.663	122.463

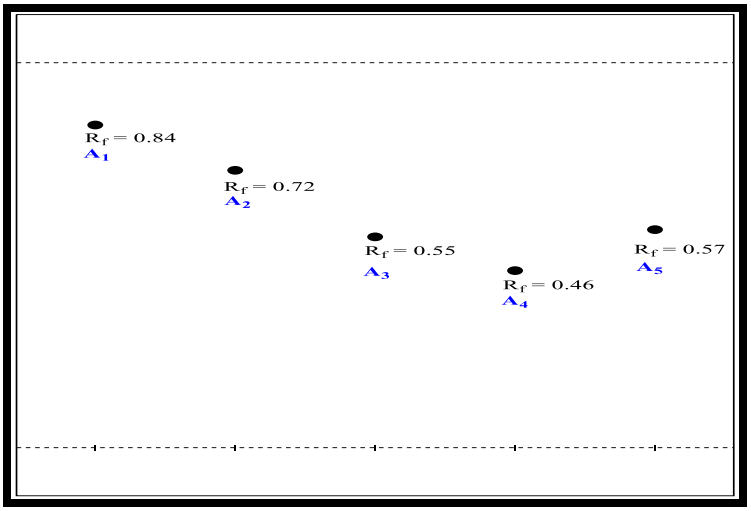
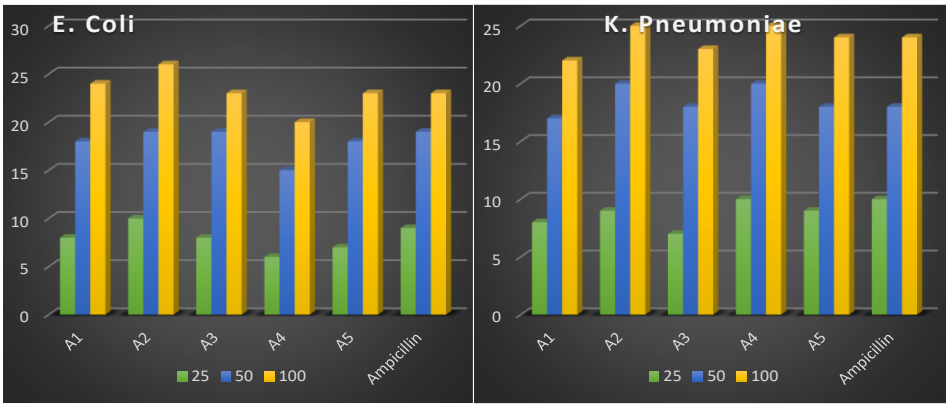
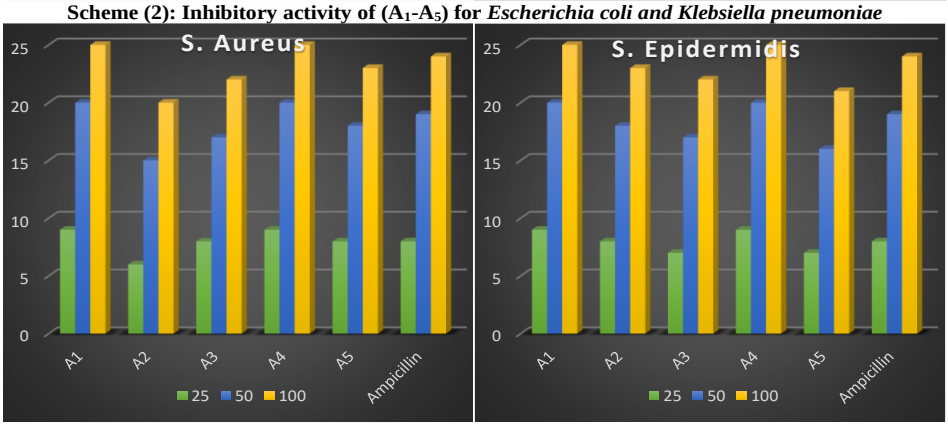


Figure (1): TLC spots and R_f of (A_1-A_5).



Scheme (2): Inhibitory activity of (A_1-A_5) for *Escherichia coli and Klebsiella pneumoniae*



Scheme (3): Inhibitory activity of (A_1-A_5) for *Staphylococcus aureus & Staphylococcus epidermidis*

4. Conclusions

When compared to the conventional approach, the organic compounds obtained by the microwave-assisted method produced superior outcomes. This method yielded greater product yields at a lower cost since it required less time, efforts, solvents, and catalysts. Therefore, microwave-assisted synthesis is a better technique, especially for small-scale processes. Furthermore, since the microwave approach employs fewer reactants, it is an ecologically beneficial technology that pollutes the laboratory environment and the larger ecosystem. Also, the produced compounds demonstrated high solubility in a variety of solvents. When Schiff base derivatives combine with appropriate functional group-containing chemicals, heterocyclic five-membered rings are often the result. According to the biological investigation, the produced chemicals have antibacterial action and may stop the development of germs. Compared to their parent materials, these compounds showed more biological activity, which is noteworthy since the original materials were pharmaceuticals employed in the medical industry. When the synthetic compounds were subjected to Helium-Neon laser radiation, they demonstrated excellent stability. Measurements using physical and spectroscopy verified the legitimacy and correctness of the produced nanostructures. The derivatives of imidazoline-4-one were discovered to create positive heat at the lowest energy step, indicating that their production procedures are endothermic.

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