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Article

Environmentally Friendly Synthesis, Bioactivity Evaluation and Multi-Faceted Characterization of Bis (5-((1H-Imidazol-4-yl) Methyl) -3- Phenylimidazolidin -4- One) Derivatives

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Abstract: The ecologically friendly synthesis of imidazolidinone derivatives using conventional and microwave-assisted techniques is the main emphasis of this work. The broad-spectrum biological activity of imidazole-based compounds is widely known, yet there are currently no effective or sustainable production techniques available. The research included the preparation of new imidazole derivatives by reacting prepared Schiff bases with the amino acid histidine in the presence of ethanol as a solvent. The reaction was carried out using conventional and microwave methods, and the progress of the reaction was monitored and described by determining the melting point and purity. The Rf values were determined using thin-layer chromatography (T.L.C.), infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (^{1}H-NMR), and quantitative elemental analysis (C.H.N.). The biological activity of the synthesized compounds was evaluated by examining their effect on the growth of four antibiotic-resistant bacterial isolates: Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*). The antibiotic *Amoxicillin* was used as a control sample. The prepared compounds showed good inhibitory activity against the tested bacteria.

Keywords: Green Chemistry, Imidazole, biological activity

Introduction

Imidazole rings are widely found in natural products and pharmaceutical molecules and are one of the most essential nitrogen-containing five-membered heterocyclic structures. In addition, imidazole heterocyclic compounds are essential in medicinal chemistry and are vital in treating various diseases. New medicinal derivatives are being vigorously developed worldwide [1]. Due to the unique structural characteristics of imidazole structure and its electron-rich properties, it is advantageous for

the imidazole group to bind to various receptors and enzymes in biological systems through various weak interactions, thus exhibiting a variety of biological activities.

At present, many imidazole-containing compounds with high medicinal potential have been widely used as clinical drugs for the treatment of various diseases, such as antibacterial [2], antifungal [3], and anti-inflammatory [4]. Due to the critical pharmacological or biological activities and immense medicinal value of imidazole-based molecules, medicinal chemists, and organic synthesis, researchers have found that they have antiviral [5], antiparasitic [6], and anticancer effects [7]. Researchers have long been interested in synthesizing small molecules with imidazole structures. However, a simple and efficient method for constructing imidazole heterostructures is still needed. In recent decades, many classical strategies have emerged for the synthesis of these cyclic compounds in vitro.

Green chemistry is a strategy that uses environmentally friendly and sustainable reaction processes to reduce chemical waste and environmental damage [8]. These techniques are based on several ideas, including reducing the use of harmful solvents and improving the efficiency of the reaction. On the other hand, green chemistry technology emphasizes the use of environmentally safe solvents, the use of environmentally friendly catalysts for catalysis, and reducing the energy used in the reaction process. One of the advanced modern techniques for preparing compounds is microwave technology, which is used in their preparation [9]. It can usually shorten the reaction time and improve the efficiency of the chemical reaction. By heating the compounds with microwave radiation, this method shortens the reaction time and eliminates the need for high temperatures [10]. One of the many benefits of using microwaves to prepare 4-imidazole compounds is that it speeds up the process, allowing it to be completed faster than conventional techniques [18]. Microwave technology helps increase production and improve product purity by enhancing the chemical selectivity of the process to increase the degree of selection. Microwave technology can also significantly reduce energy consumption because it heats food directly and quickly [20]. Waste Reduction This approach makes the process more environmentally friendly by reducing the hazardous chemical waste produced [11].

Materials and Methods

Chemical Used

Chemicals prepared by Aldrich, BDH Thomas, Fluka, and Merck were used.

Preparation of 4-Imidazolidinone Derivatives by the Traditional Method (A1-A8)

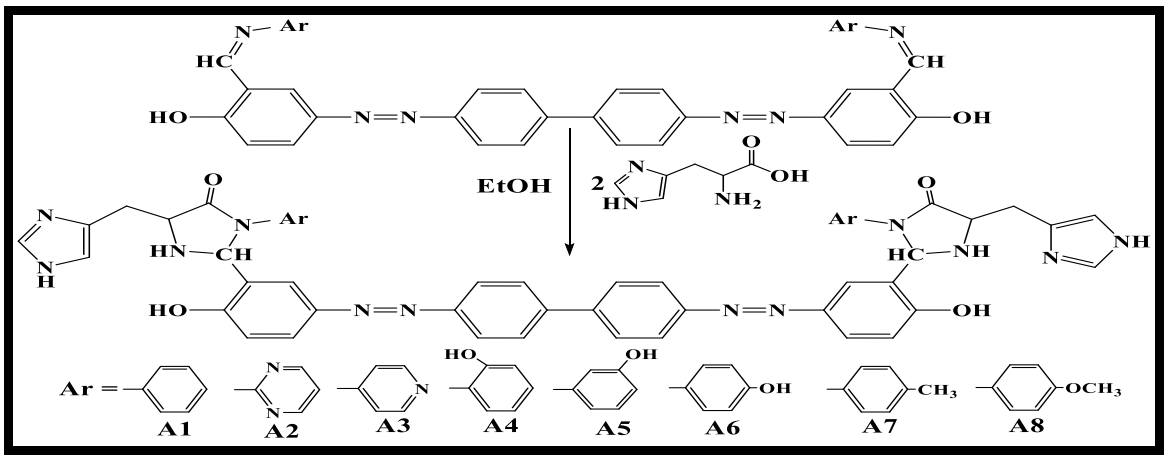
(0.001 mol) of the prepared Schiff bases were mixed in (45 ml) of absolute ethanol with (0.002 mol, 0.31 gm) of histidine dissolved in (10 ml) of absolute ethanol, and the mixture was elevated for (10-7 hours). The completion of the reaction was confirmed using the TLC technique. The mixture was cooled to room temperature and filtered, then washed and recrystallized with ethanol [12, 13]. Table (1) shows some physical properties, percentage, reverse elevation time, and R.f of 4-imidazolidinone derivatives (A1-A8).

Preparation of 4-Imidazolidinone Derivatives by Microwave Method (A1-A8)

Mix (0.001 mol) of the prepared Schiff bases in (10 ml) of absolute ethanol with (0.002 mol, 0.31 gm) of histidine dissolved in (5 ml) of absolute ethanol and put the mixture in the microwave and heated for (5-7) minutes at a temperature of (78 °C) and a power of (400 W). The completion of the reaction was confirmed using the TLC technique. The mixture was cooled to room temperature, filtered, washed with cold water, and recrystallized with ethanol [14, 15]. Table (1) shows some physical properties, percentage, reverse sublimation time, and R.f of 4-imidazolidinone derivatives (A1-A8).

Table 1. Some Physical Properties of the 4-Imidazolidinone derivatives (A1-A8) Prepared by the traditional and microwave methods

Comp.	Traditional method					Microwave method				
No.	Color	Ref. (h.)	M.P. ℃	Y. %	R.f	Color	Ref. (h.)	M.P. ℃	Y. %	R.f
A 1	Yellow	8	205-207	71	0.56	Yellow	5	205-207	71	0.56
A 2	Light red	9	264-266	83	0.72	Light red	7	264-266	83	0.72
A 3	Dark gray	10	230-232	65	0.37	Dark gray	6	230-232	65	0.37
A 4	Light green	8	286-287	86	0.59	Light green	5	286-287	86	0.59
A 5	Red	7	269-271	80	0.67	Red	7	269-271	80	0.67
A 6	Green	10	218-219	77	0.62	Green	6	218-219	77	0.62
A 7	Dark green	7	241-243	76	0.50	Dark green	7	241-243	76	0.50
A 8	Light brown	9	258-260	72	0.42	Light brown	5	258-260	72	0.42



Scheme 1. Prepared compounds (A1-A8)

Biological Activity Study

Mueller-Hinton agar was prepared by dissolving it in 1 litre of distilled water, heating and stirring it with a magnetic stirrer, and then sterilizing it with an autoclave at 121 °C and 1.5 bar pressure [16-19]. For two h, it was cooled to 50 °C, poured into Petri dishes, and frozen at room temperature. Two bacterial isolates were tested: Gram-negative, ***E. coli***, and Gram-positive ***Staphylococcus aureus***. Two colonies of pure bacterial isolates of both Gram-positive and Gram-negative bacteria were transferred from the solid culture medium to test tubes containing (5 ml) distilled water using heat-sterilized holders [16-23]. The tubes were incubated at 30 °C. (37°C) for (20) hours, then diluted with the physiological solution until the turbidity reaches standard turbidity levels to obtain a cell count of approximately (1.5×10^8) cells/ml [24-27]. Chemical solutions of the prepared compounds were prepared using dimethyl sulfoxide (DMSO) solvent at three concentrations (0.01, 0.001, 0.0001) mg/ml of each substance (for each of these solid derivatives) [28-30].

Results and Discussion

Characterization of 4-Imidazolidinone Derivatives (A1-A8)

The FT-IR spectrum showed an absorption band due to (C=O) at (1664-1653) cm^{-1}, a band usually for (NH) at (3196-3165) cm^{-1}, a band usually for (C-N) at (1287-1264) cm^{-1}, a band due to (C=N) histidine at (1618-1600) cm^{-1}, two bands due to aliphatic (CH) at (2898-2852 & 2961-2921) cm^{-1}, a typical band for aromatic (CH) at (3055-3004), two bands due to aromatic (C=C) at (1586-1558) cm-1 and (1542-1486) cm^{-1} [31-32]. As in Table 2 and Figures 1, 2.

Table 2. FT-IR absorption results for prepared compounds (A1-A8)

Comp. No.	ν(C-H) Arom.	ν(C-H) Aliph.	ν(NH)	ν(C-N)	ν(C=O)	ν C=N	ν(OH)	ν(C=C) Arom.
A 1	3043	2927, 2852	3186	1286	1664	1618	3413	1575, 1542
A 2	3032	2934, 2883	3196	1274	1657	1607	3387	1558, 1486
A 3	3051	2961, 2898	3184	1279	1658	1606	3401	1565, 1512
A 4	3004	2921, 2856	3166	1284	1662	1618	3340	1571, 1517
A 5	3023	2927, 2877	3193	1270	1659	1610	3345	1568, 1507
A 6	3042	2940, 2874	3165	1278	1660	1612	3331	1586, 1523
A 7	3055	2934, 2884	3190	1285	1653	1600	3390	1572, 1516
A 8	3042	2938, 2881	3187	1276	1663	1609	3379	1563, 1514

^{1}H-NMR spectrum of A3 shows a signal at (11.77) ppm for (NH) histidine, a signal at (10.76) ppm for (OH), a signal at (8.55) ppm for (NH) imidazole, signals at (7.02-8.00) ppm aromatic rings, a signal at (6.01) for (CH) imidazole, a triplet signal at (3.55-3.59) ppm for (CH) imidazole, and a doublet signal at (2.83, 2.85) ppm for (CH_2) histidine [33, 34]. As in Fig. 3.

^{1}H-NMR spectrum of A6 shows a signal for (NH)histidine at (11.50) ppm, two signals at (9.85, 9.53) ppm for (OH) adjacent to the aromatic ring, signal for (NH) imidazole at (8.87), signals for aromatic rings at (6.93-8.05) ppm, signal for (CH)imidazole at (6.24) ppm, triple signal for (CH)imidazole at (3.85-3.91) ppm, double signal for (CH_2) histidine at (2.94, 2.92) ppm. As in Fig. 4.

Elemental Analysis (C.H.N.O.) Measurement

Elemental analysis (C.H.N.O) of the manufactured compounds was performed to verify the accuracy and precision of their structural composition, and the obtained elemental ratios were either consistent with the calculated values or very close to them, confirming the validity of the structures of the manufactured compounds [35, 36], as shown in Table (3).

Table 3. Results of elemental analysis (C.H.N.O) of manufactured compounds

Comp No.	Molecular Formula	Calculated				Found			
		C%	H%	N%	O%	C%	H%	N%	O%
A 1	$C_{50}H_{42}N_{12}O_4$	68.41	4.67	19.25	7.29	68.35	4.43	19.03	7.05
A 2	$C_{46}H_{38}N_{16}O_4$	62.61	4.16	25.65	7.17	62.46	4.00	25.43	7.08
A 3	$C_{48}H_{40}N_{14}O_4$	65.47	4.45	22.58	7.35	62.23	4.31	22.43	7.12
A 4	$C_{50}H_{42}N_{12}O_6$	66.02	4.62	18.67	10.28	66.10	4.46	18.41	10.08
A 5	$C_{50}H_{42}N_{12}O_6$	66.02	4.62	18.67	10.28	66.05	4.01	18.32	9.95
A 6	$C_{50}H_{42}N_{12}O_6$	66.02	4.62	18.67	10.28	65.94	4.44	18.24	10.00
A 7	$C_{52}H_{46}N_{12}O_4$	69.27	5.32	18.54	7.01	66.96	5.08	18.12	6.87
A 8	$C_{52}H_{46}N_{12}O_6$	66.76	4.87	17.76	10.23	69.02	5.00	17.65	9.98

Green Synthesis and Traditional Synthesis

All compounds were synthesized using conventional and microwave methods, and the two methods were compared in terms of solvent usage, catalyst requirement, reaction time, relative yield, melting point, color, and solubility. The microwave method has the advantages of high yield, low solvent consumption, no catalyst, and short time. It is also easier to separate the compounds prepared using microwave technology. The compounds prepared by the two methods are identical regarding physical properties such as color, melting point, and RF value [37, 38].

Evaluation of the Biological Activity of Prepared Compounds

The antibacterial activity of the prepared compounds was tested using the agar diffusion method [39-44]. After inoculating the culture medium with the bacterial isolates, holes were made in the Petri dishes using the cylinder measuring method (according to USP 35) [45-48]. The results are read after 24 hours to indicate the sensitivity of the derivative used, which depends on the inhibitory diameter shown in the culture dish around the well-used [49-51], as an increase in the inhibitory diameter means an increase in the bioavailability of the prepared compound [52-55]. Compare the inhibitory diameter with the diameter of the standard antibiotic, such as amoxicillin [56-59]. As in Table 4 and Scheme 1, 2.

Table 4. Antibacterial activity of the synthesized compounds (inhibition zone in mm)

Comp. No.	E. Coil Conc. mg/ml			Staph. Aureus Conc. mg/ml		
	0.0001	0.001	0.01	0.0001	0.001	0.01
A_1	0	5	14	5	8	13
A_2	6	10	17	4	10	16
A_3	9	9	15	6	11	15
A_4	8	12	15	10	15	24
A_5	10	17	20	8	13	18
A_6	0	5	10	0	0	5
A_7	5	5	9	10	6	10
A_8	6	9	14	5	10	13
Amoxicillin	14	20	30	15	21	30

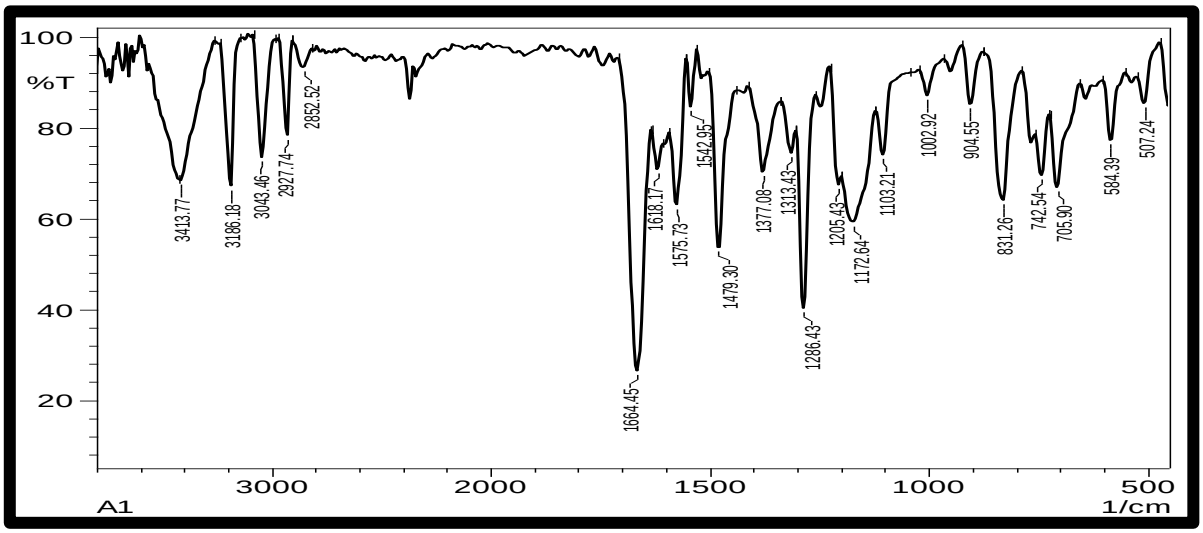


Figure 1. The compound's FT-IR spectra (A1)

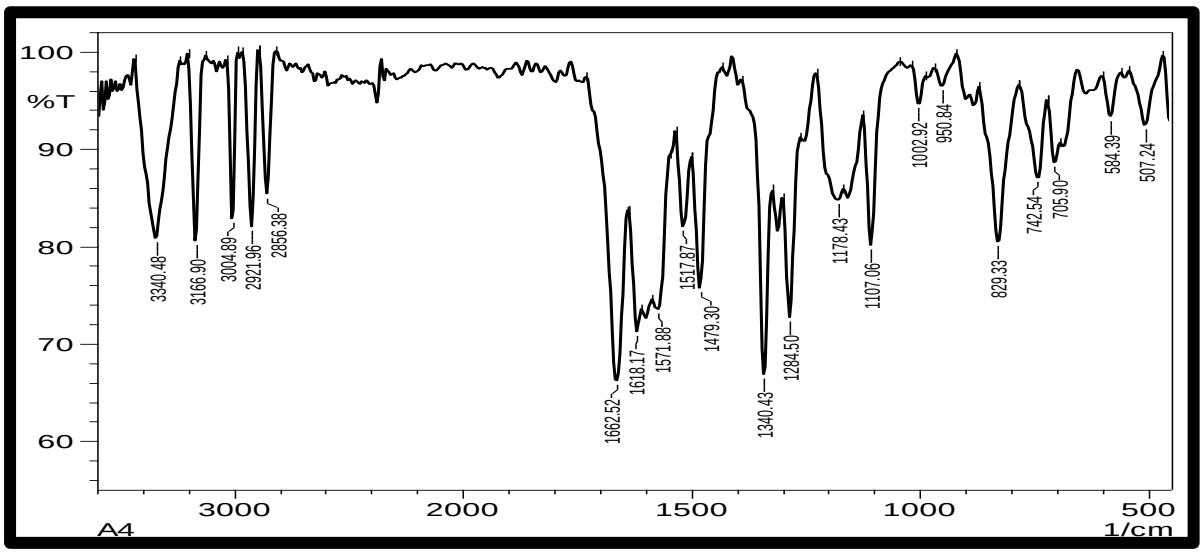


Figure 2. The compound's FT-IR spectra (A4)

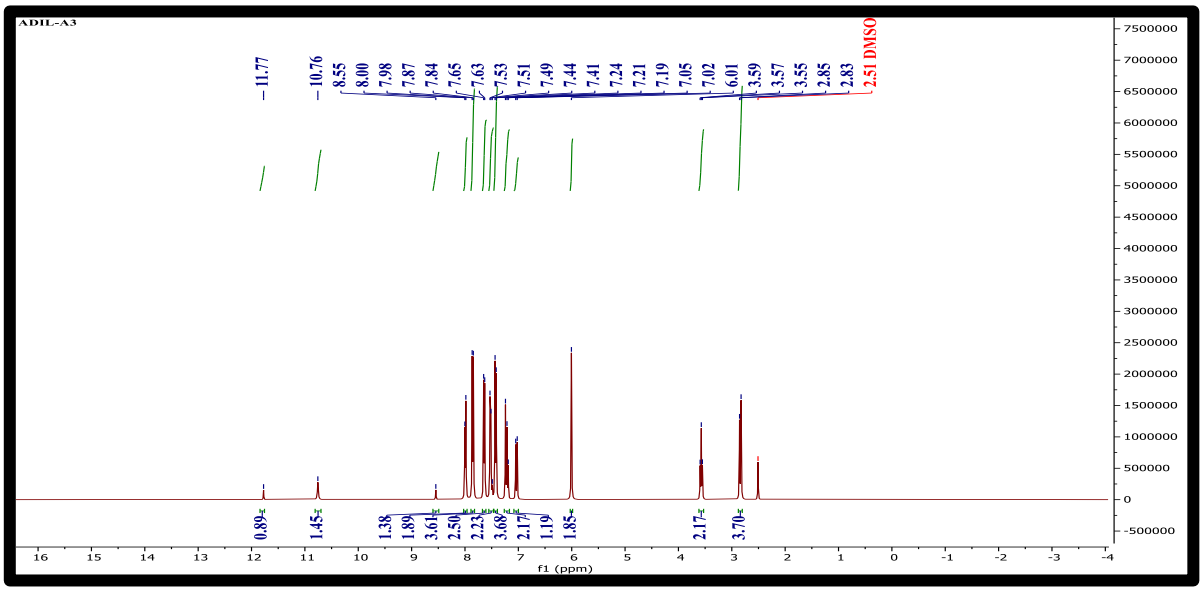


Figure 3. 1-H NMR spectra of the substance (A3)

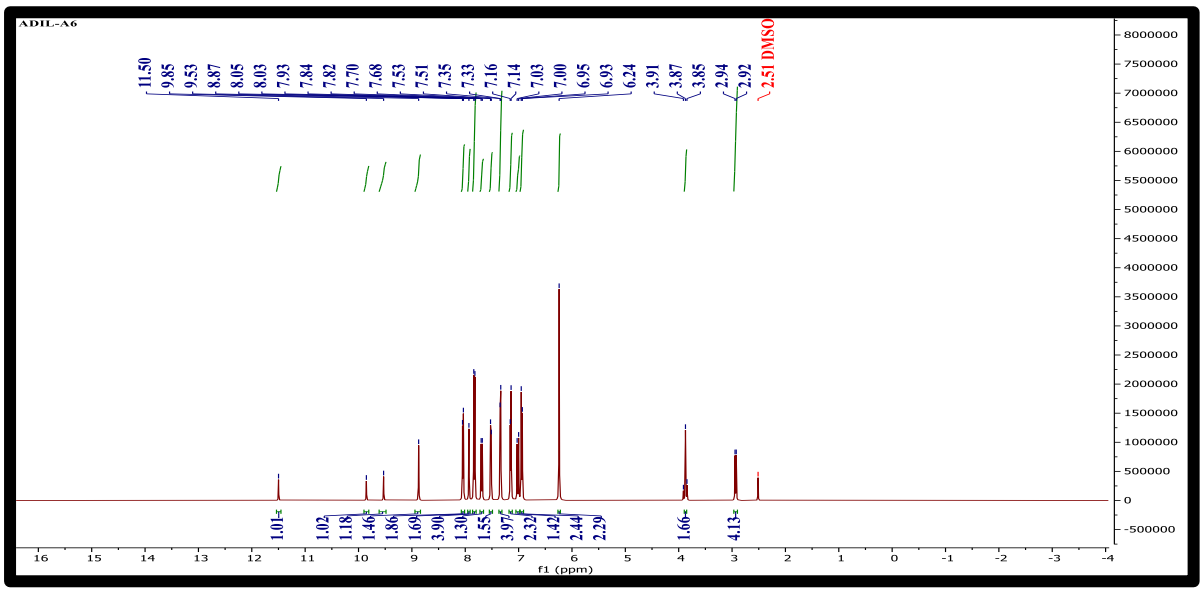
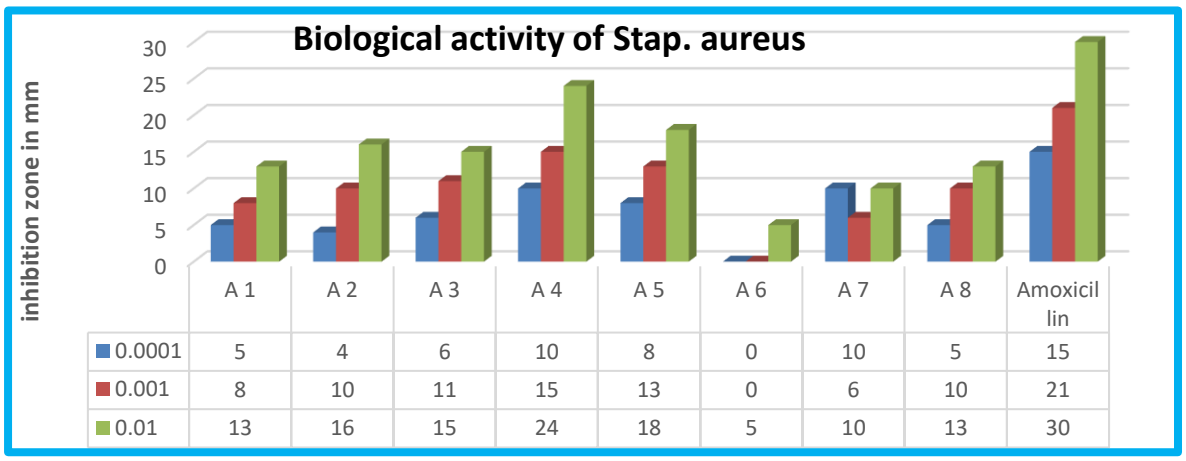
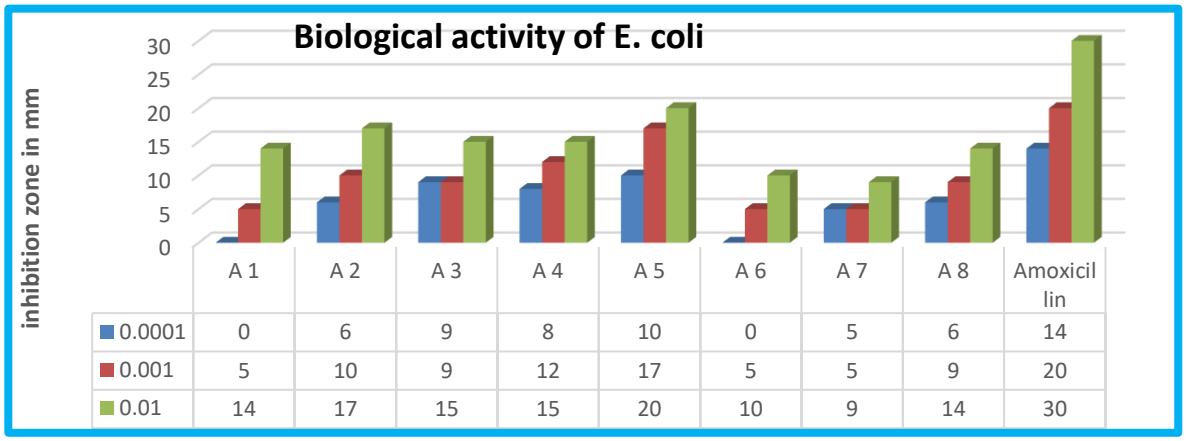


Figure 4. 1-H NMR spectra of the substance (A6)



	A 1	A 2	A 3	A 4	A 5	A 6	A 7	A 8	Amoxicillin
0.0001	5	4	6	10	8	0	10	5	15
0.001	8	10	11	15	13	0	6	10	21
0.01	13	16	15	24	18	5	10	13	30

Scheme 2. Inhibitory activity of (A1-A8) for Staph. aureus



	A 1	A 2	A 3	A 4	A 5	A 6	A 7	A 8	Amoxicillin
0.0001	0	6	9	8	10	0	5	6	14
0.001	5	10	9	12	17	5	5	9	20
0.01	14	17	15	15	20	10	9	14	30

Scheme 3. Inhibitory activity of (A1-A8) for E. coli

Conclusion

Compared with conventional methods, microwave methods have achieved better results in obtaining organic compounds. This technology has proven to be economical as it saves time, effort, solvents and catalysts while providing higher product yields. Therefore, it can be concluded that the microwave method is superior, especially for small reactions. In addition, the microwave method uses fewer reactants and causes less pollution to the laboratory environment and the wider ecosystem, making it an environmentally friendly technique. Reactions of Schiff base derivatives with compounds containing suitable functional groups usually produce five-membered heterocycles. Biological studies have shown that the synthesised compounds have antimicrobial activity and can inhibit the growth of bacteria. These compounds exhibit higher biological activity than the parent material, which is important since the starting material is a drug used in the medical field.

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