Original Article

Synthesis of the Derivatives of 1,3-oxazepine-4,7-dione and Investigation of Antibacterial Activity

Ban Hasan Taresh[1]

[1]Department of Clinical Laboratories, College of Applied Medical Sciences, University of Kerbala, Karbala, Iraq.
E-mail: ban.tarsh@uokerbala.edu.iq

Abstract

1,3-oxazepine-4,7-dione derivatives [O1-O4] was synthesized with the [2-5] cycloaddition reaction of malic anhydride and phthalic anhydride with azoimine [S1 – S2]. Synthesis of azo compound [A1 – A2] from 4-aminobenzene sulphonic acid by coupling diazonium salt to 4-hydroxybenzaldehyde phenoxide anion and 4-octylbenzaldehyde phenoxide anion. The aldehyde groups in the azoaldehyde derivatives [A1 – A2] were condensed with 4-nitro aniline in the presence of glacial acetic acid as a catalyst in absolute ethanol to give azoimine derivative [S1 – S2]. The resulting azoimine derivative [S1 – S2] were then introduced into [2-5] the cycloaddition reaction with malic, phthalic of anhydride compounds. The molecules were characterized via FTIR and ^{1}HNMR spectra. Estimate the activity of synthetic compounds as antibacterial.

Keywords: 1,3-Oxazepine, Azo compounds, Schiff's Bases, Biological Activity.

Received date: 11 August 2022 **Accepted: 15 September, 2022** **Published: 07 October, 2022**

DOI: 10.47750/pnr.2022.13.04.051

INTRODUCTION

Oxazepine defined as heterocyclic molecule with two distinguishing oxygen and nitrogen heteroatoms in its structure [1, 2]. Oxazepine molecules have using in a big filled for variety of biological activities, such as anti-convulsants [3], antivirals, antifungals, and other uses our life [4, 5].

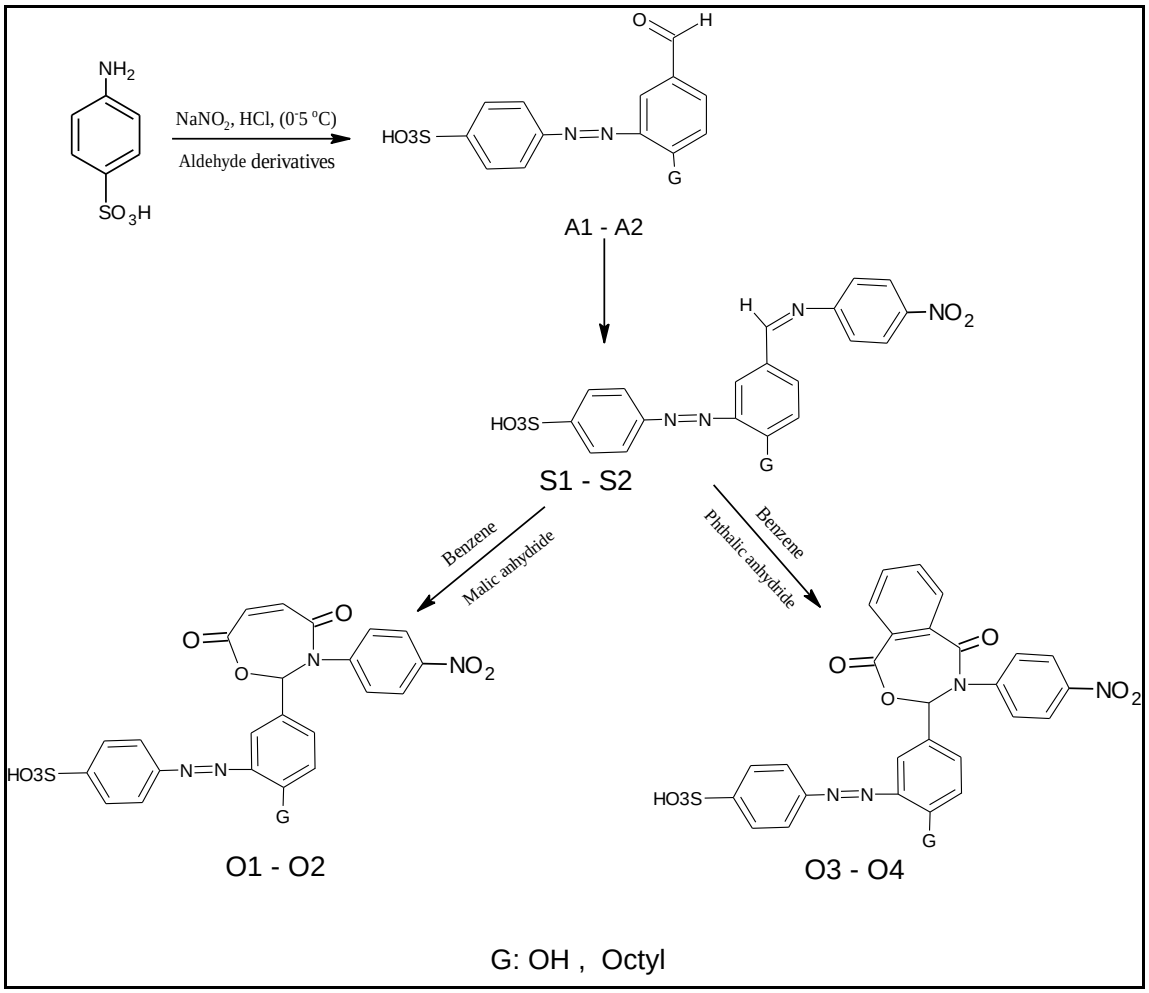
A basic component of the structure is the azo group, which is described as an organic compound with an azo group (N=N) [6]. The imine group defined as active group of schiff base [7].

Bioactivity, or pharmacological properties, refers to the positive or negative effects a drug has on living organisms. The active component or pharmacophore performs its effect when a drug is a complex organic molecule, although it may be modified by the other components. Among the many properties of chemical compounds, pharmacological and biological activity are important since they show the compounds' medical potential (8, 9). Antibiotics are chemical molecules used to treat or prevent some kinds of bacterial disease. It functions by killing microorganisms or reducing them growth. However, they are not useful in all instances. Antibiotics are useless against all diseases. Antibiotics may be useful against bacteria infections, but they are useless against viruses (10, 11).

In this paper, a novel azo with a seven-membered heterocyclic called 1,3-oxazepine-4,7-dione compounds with several aromatic components, such as 4-hydroxyaniline, was synthesized and characterized. These compounds studied and characterized, physicochemical then via testing their efficacy as insecticide and assess biological activity because their composition contains numerous effective groups.

EXPERIMENTAL

FT-IR instrument in the range (400 to 4000) cm^{-1}, on Bruker. ^{1}HNMR spectra on Brüker ACF 500 spectrometer at 500 MHz, the chemicals have been used were obtained from BDH and Merck chemist companies.



Scheme 1: Synthesis of 1,3-Oxazepine-4,7-dion C1-C3.

Synthesis of Azo compounds (A1 – A2) [12]

0.007 mol of 4-aminobenzene sulphonic acid was dissolved in a mixture of concentrated hydrochloric acid (15 mL) with 15 mL from distilled water. In ice bath, iced the mixture between 0 and 5 degrees Celsius. The solution of $NaNO_2$ (0.47 g, 0.007 mol) was then diluted in 5 mL of distilled water (applied drop-by-drop to the solution) and shaken. The solution was added slowly method to various of P-Alkoxy benzaldyde (0.007 mol) that diluted in 60 mL of 10% NaOH at 0-5 °C and stirred for 30 minutes. The coloured item was filtered, washed with cooled distillation water, and dried with hot steam [7].

Synthesis of schiff`s base compounds (S1-S2) [13, 14]

0.01 mole (A1 – A2) of each molecule synthesized reacts with 0.01 mol of 4-nitroaniline in absolute ethanol as a solvent and three drops from (G.A.A) glacial acetic acid. Refluxed for four hours, the mixture of solution. Finally, the precipitates were produced, dry filtration was used to collect crystals, and they were recrystallized. Table (1) of components.

Table 1: Physicochemical properties of schiff`s bases (A1-A2)

COMP. NO.	G	YIELD %	COLOUR	M.P.℃
S1	Hydroxy	75	Yellow	219 -223
S2	Octyl	71	Dark Yellow	196-200

Synthesis of Oxazepine derivatives (O1-O2) [15]

Each compound includes 0.01 mole of Schiff bases (S1-S2) with 0.01 mole malic anhydride in 15 mL of dry benzene as a solvent. Afterward, the reaction mixture was reflected. Finally, the solution was filtered, the precipitate was collected, and 1,4-dioxan dry was used to recrystallize the resulting coloured crystalline solid.

Table 2: Physicochemical properties of oxazepine derivatives (O1-O2)

COMP. NO.	YIELD %	COLOUR	M.P.℃
O1	78	Orange	263-267
O2	75	Yellowish Orange	231-235

Synthesis of Oxazepine derivatives (O3-O4) [15]

Each compound contains 0.01 mole of Schiff bases (S1-S2) with 0.01 mole phthalic anhydride in 15 ml of dry benzene. Afterward, the resulting mixture was reflected. Finally, the solution was filtered, the precipitate was collected, and 1,4-dioxan dry was used to recrystallize the resulting coloured crystalline solid.

Table 3: Physicochemical properties of oxazepine compounds (O3-O4)

COMP. NO.	YIELD %	COLOUR	M.P.℃
O3	76	Brown	282-286
O4	69	Dark Orange	247- 251

Biological activity of the synthesized compounds O1 and O4

Different kinds of bacteria were cultivated and incubated for 24 hours at 37 °C, then isolated by applying the same gram stain and classified as gram positive and gram negative microorganisms.

In this research, FTIR spectroscopy was used to determine the presence of functional groups in molecules S1 and S2 [17]. These groups: Identify the stretching vibration band of the imine group between 1611 and 1646 cm^{-1}. The vibration of aromatic C–H was noticed at 3024 cm^{-1} and the vibration of aliphatic C–H was identified at 2986 cm^{-1}; the broad band of the hydroxyl group was found at 3307 cm^{-1}. The peaks of the principal bands are shown in table 4.

Table 4: The FT-IR characteristic absorption bands of compounds S1-S2

Compound No.	C-H Aromatic	C-H Alifatic	C=N	N=N	O-H
S1	3307	----	1646	1508	3307
S2	3087	2966	1611	1525	----

Results and Discussion

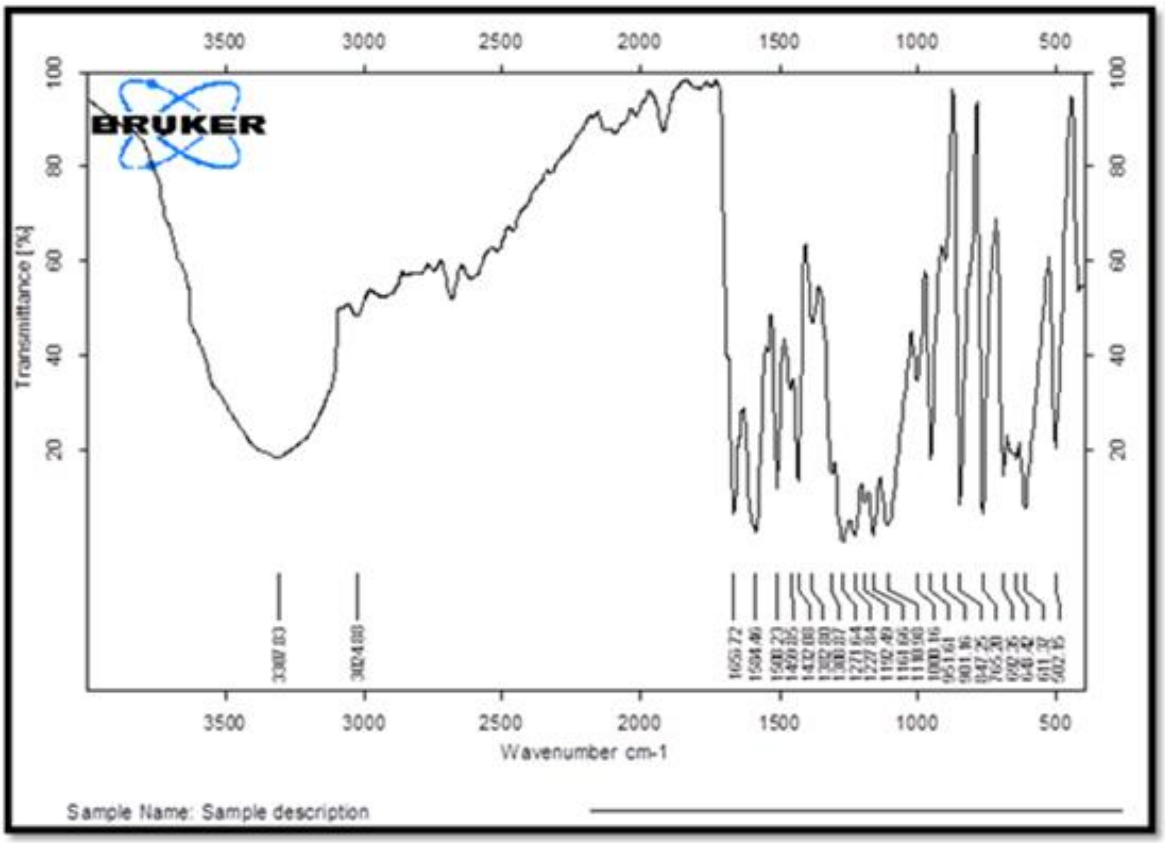


Figure 1: FTIR spectrum of molecule S1

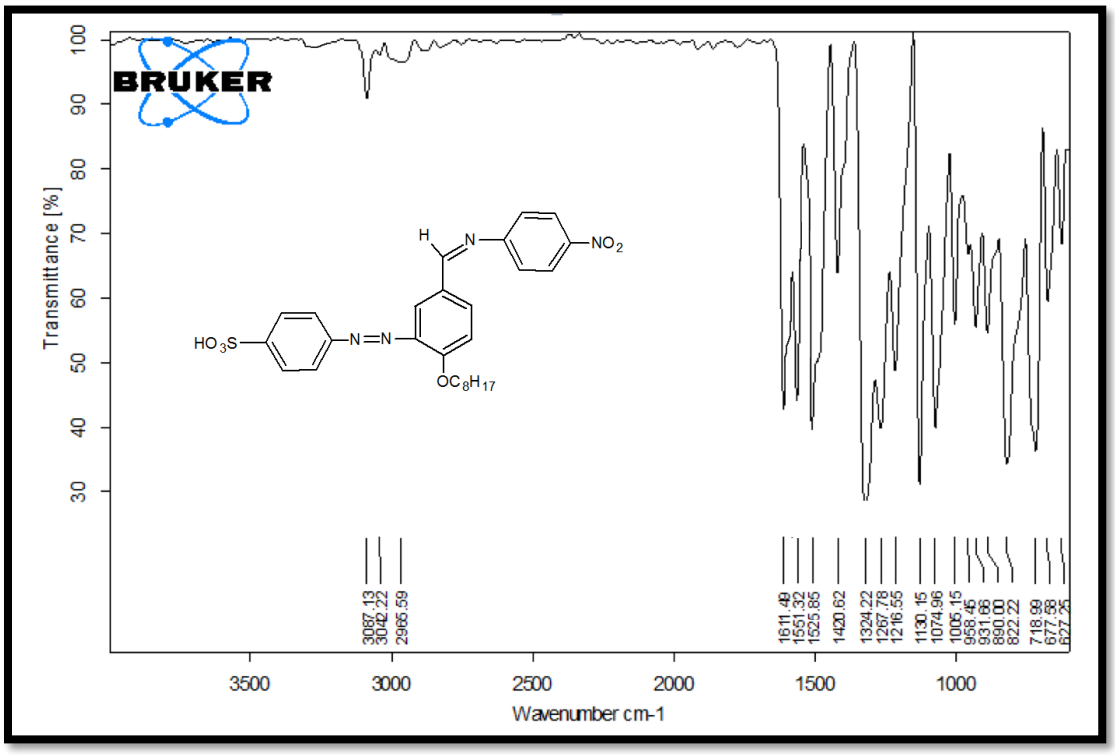


Figure 2: FTIR spectrum of molecule S2

The bands (1722 - 1741) cm^{-1} for (C=O of lactone stretching) [18], (1672 - 1693) cm^{-1} for (C=O of lactam stretching) [19]. The (3074 - 3089) reverted to the (Ar–H) (2987) cm^{-1} value for the (C–H aliphatic stretching).

Table 5: The FT-IR characteristic absorption bands of C1-C3 compounds.

Comp. No.	C-H Arom.	C-H Alif.	O-H	C=O lactone	C=O lactam
O1	3088	---	3298	1722	1672
O2	3089	2987	---	1741	1688
O3	3074	---	3285	1731	1693

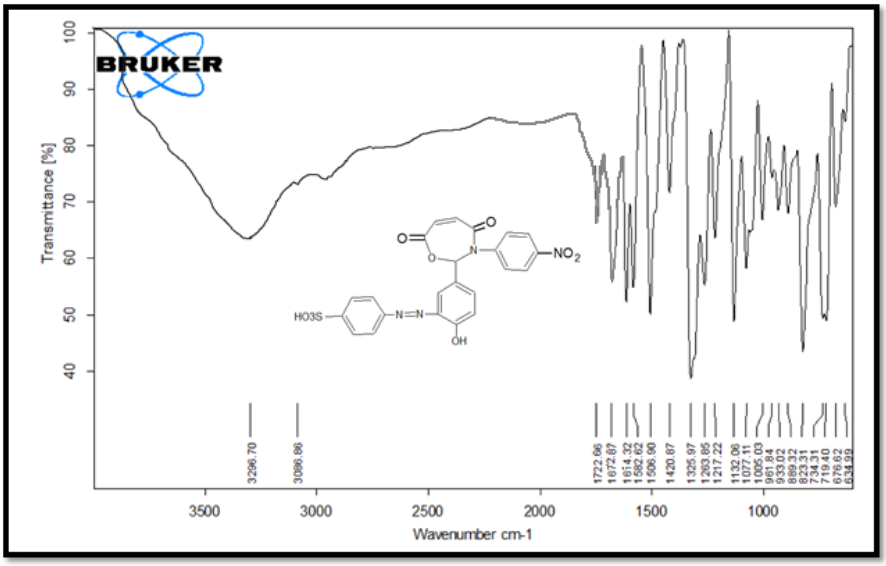


Figure 3: FTIR spectrum of molecule O1

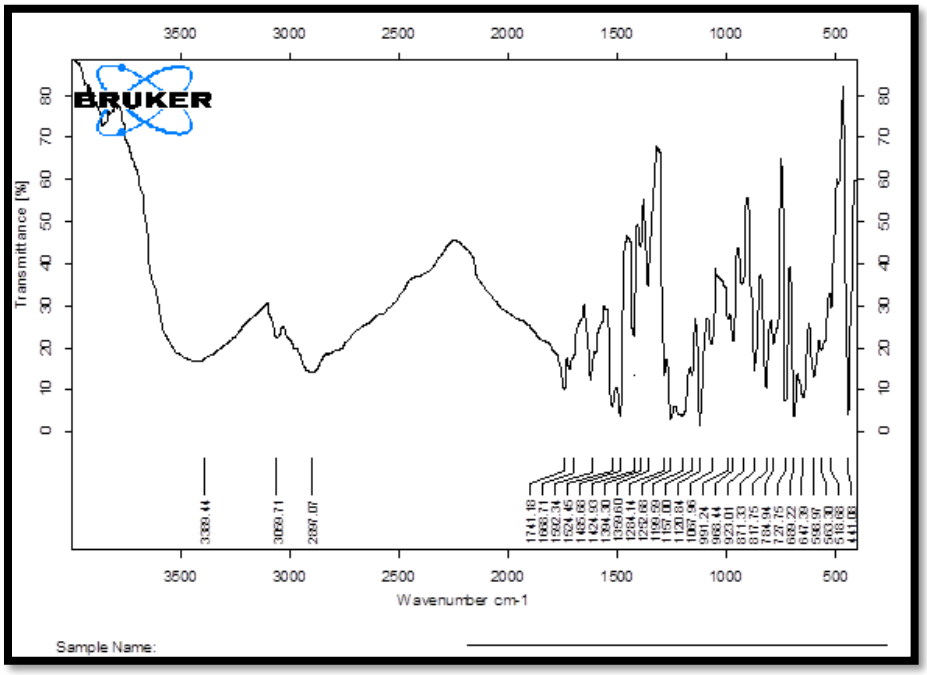


Figure 3: FTIR spectrum of molecule O2

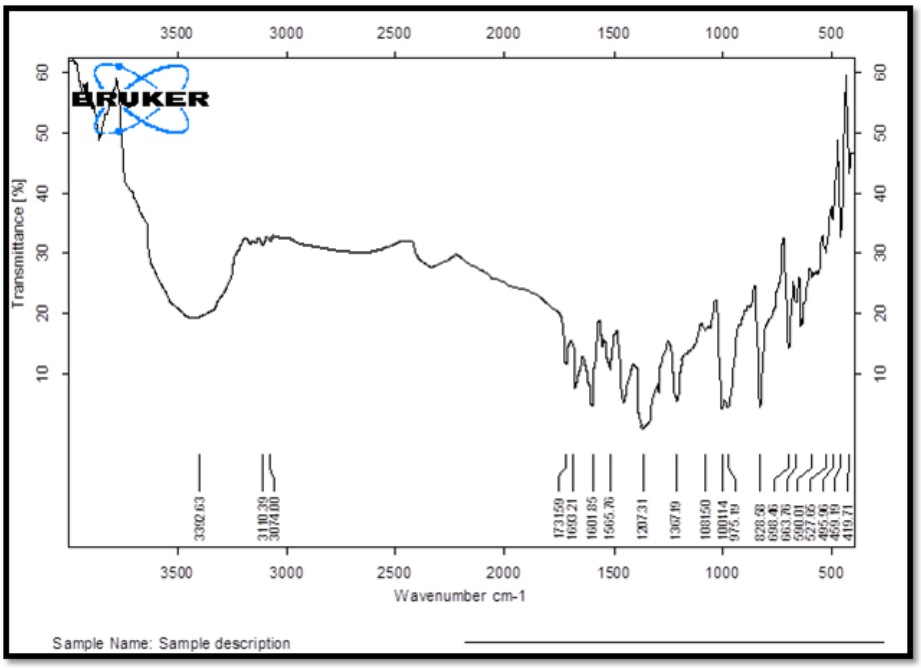


Figure 4: FTIR spectrum of molecule O3

The ^{1}HNMR spectroscopy method was used to determine the collection's structure. Figure 5 below shows the molecule [O2], ^{1}H-NMR spectrum along with its specific chemical shifts (d6-DMSO, ppm): Signals are generated by the aromatic protons between δ 6.33 and 8.81 ppm. protons appeared as triplets at δ 0.89 ppm, which might be linked to -CH_3 [20]. δ 1.80 ppm for sulphonic hydroxyl. The -CH_2 appeared at δ 0.9 to 1.79 ppm.

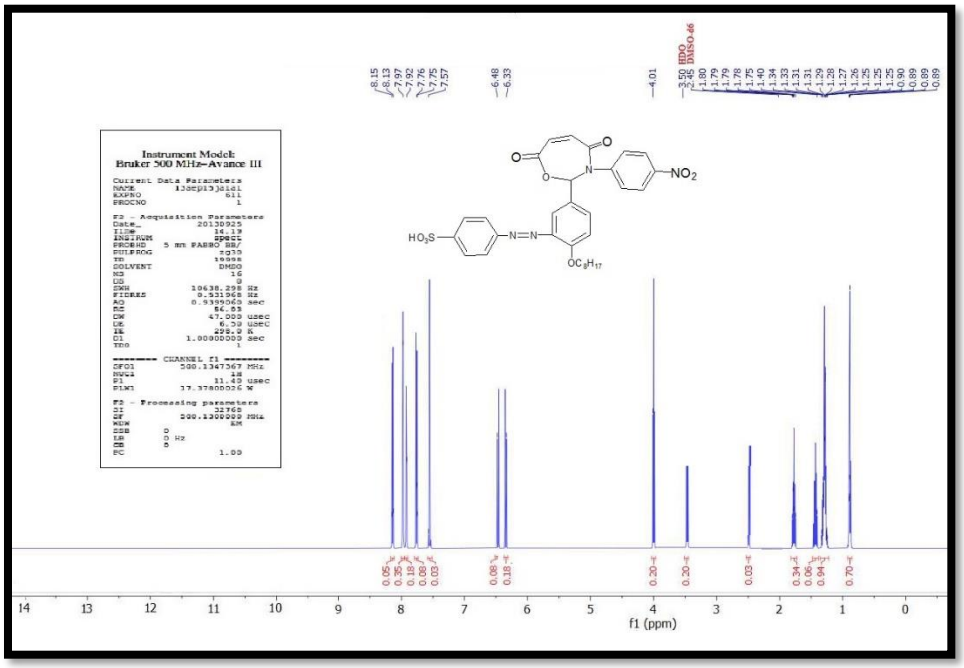


Figure 4: [1]HNMR spectrum of molecule O2

The [1]HNMR spectroscopy method was used to determine the structures. Figure 5 shows the [1]H-NMR spectrum of compound [O4], with the distinctive chemical shifts (d6-DMSO, ppm) as follows: The aromatic protons emit signals between 7.40 and 8.15 ppm. At 4.91 ppm, it was identical that the proton in the –OH group [(20)]. OH proton concentration in sulphonic is 2.11 ppm.

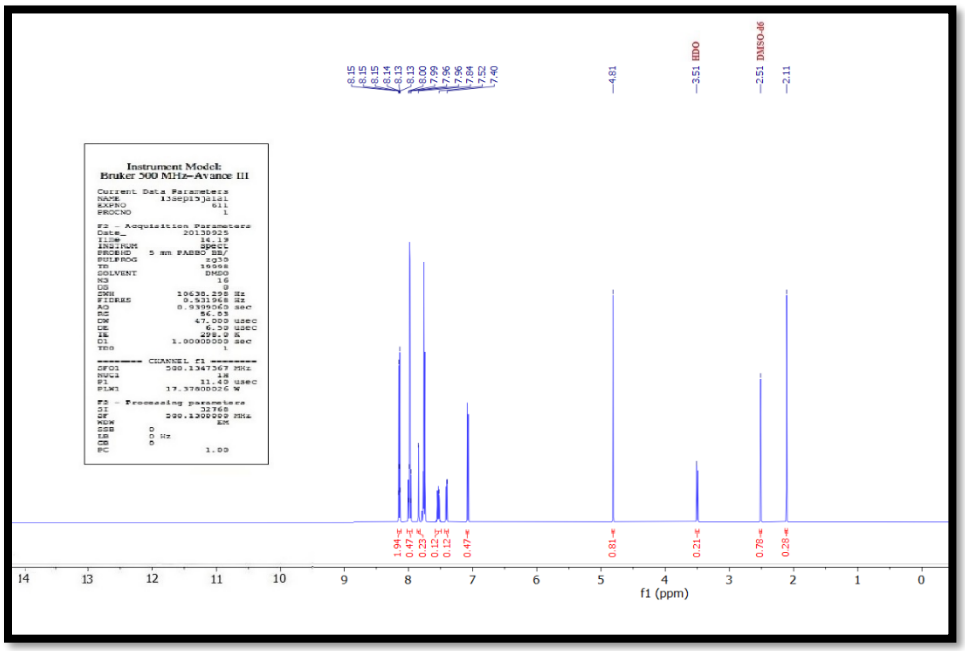


Figure 5: [1]HNMR spectrum of molecule O4

Biological Activity of synthesized compounds O1, O4.

The synthesized oxazepine compounds have already been tested against gram positive and gram negative bacteria, including *Staphylococcus, bacillus subtilis, pseudomonas aerug, and escherichia coli*, supplied the microorganism as

ready bacterial cultures at concentrations of 25, and 50 g/ML by using the Agar well Diffusion technique [21]. A ruler was used to measure the inhibitory diameter of each pore. The zone of inhibition is the transparent region that surrounds the disc (including the diameter of the disc that is free of bacterial growth). The mechanism of action for new oxazepine compounds involved formation of hydrogen bonding with the active centers of the cell constituents resulting in the interference with the normal cell process. Table 6 shows all of these results.

Table 6. Antibacterial activities of the compounds (O1, O4).

Bacteria name	Zone of inhibition (mm)			
	Compound O1		Compound O4	
	[con. 25 mg/ml]	[con. 50 mg/ml]	[con. 25 mg/ml]	[con. 50 mg/ml]
Staphylococcus	39	42	32	35
Bacillus subtilis	37	43	31	33
Pseudomonas aerug	31	39	27	28
Escherichia coli	36	38	32	39

The hydroxyl, chain series, aromatic ring, azo group and carbonyl groups in the seven ring of oxazepine structure in compounds O1 and O4 play a big role in inhibiting DNA gyrase and topoisomerase IV activities. The hydroxyl group plays a role in inhibiting protein synthesis by preventing binding of t-RNA to the A site of the ribosome [22, 23]. Other groups play a role in the inhibition of growth bacteria.

CONCLUSION

We have synthesized a new 1,3-oxazepine-4,7-dione derivatives O1 – O4 using a schiff's bases synthesis. In addition, the newly synthesized compounds (O1, O4) played a big role as inhibitors to growth bacterial, which include bacteria, because these compounds have different active groups that bonded via cell wall of bacteria.

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