

Synthesis, Characterization and Evaluation of the Biological Activity of Some 1, 3-Oxazepine-4, 7-Dione Derivatives and Study of their Liquid Crystal Properties

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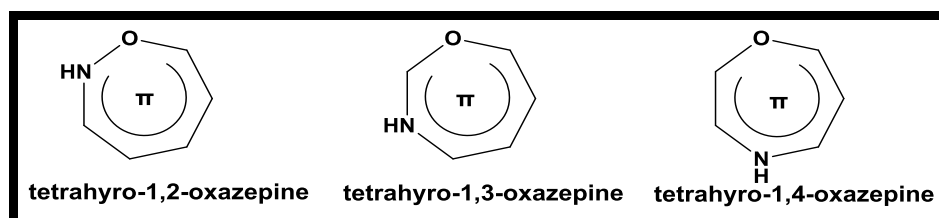
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Abstract: This research included the preparation of Schiff bases from the reaction of (4, 4-sulfonyldianiline) with benzaldehyde derivatives, and then converted to 1,3-Oxazepine-4,7-dione derivatives from the reaction of Schiff bases with maleic anhydride. Using physical and spectroscopic methods (mp, color, proton nuclear magnetic resonance spectroscopy (¹H-NMR, ¹³C-NMR and FT-IR) to confirm the compounds' structure and evaluate their biological activity on two types of bacteria, *Escherichia coli* and *Staphylococcus aureus*. Studying the liquid crystal phases and determining the nature of the transitions that occur in those phases using a polarized light microscope equipped with a heater.

Key words: Schiff bases, Oxazepine, Biological activity, Liquid crystal.

1. Introduction

Oxazepine they are compounds with a heterogeneous and unsaturated seven-ring in most cases called oxazepine [1] and may be saturated and called oxazpane containing five carbon atoms and two heterogeneous atoms, an oxygen atom and a nitrogen atom [2], and there are also three isomers of oxazepins, and these isomers depend on numbering according to the location of the oxygen and nitrogen atoms in the heptagonal ring, which are: 1, 2, 3 (1, 4-oxazepin) and as follows[3]:



The large size of the seven-ring of oxazepine makes it uneven when compared to the hexagonal aromatic ring of benzene, and as a result of its large size, the seven ring takes the shape of a boat in the spatial distribution of atoms, to be more stable and to reduce the ring tension, so it is non-aromatic [4]. The seven rings received wide interest in the field of pharmacology, as it showed high biological activity as anticancer [5], anti-inflammatories [6], anxiolytic [7], antioxidant [8], antiviral [9],

antifungal [10], antibacterial [11], antimalarial [12], also shown to be effective against depression [13], **Liquid crystals** are substances that have the appearance of a liquid. However, their particles are arranged in certain levels, such as crystals [14]. It is an intermediate state between a stable liquid state and a stable crystalline solid state. Liquid crystals are considered the fourth state of matter [15]. Liquid crystals show an intermediate state between a solid phase in which the movement of particles is restricted and has an integrated molecular organization in a position and direction and the isotropic phase or liquid phase in which the movement of particles is free [16].

2. Experimental

2.1. Material: All chemicals were used through this work purchased from Fluka, BDH Companies.

2.2. Devices used: Melting points are uncorrected and were recorded in an open capillary tube on Stuart melting point apparatus. Infrared spectra have been recorded on a Shimadzo FTIR-8100 spectrophotometer using KBr discs—and ¹H-NMR Spectra have been measured on a MHz spectrometer using (DMSO-d⁶) as solvent. reaction monitoring and verification of the purity of the compounds was done by TLC on silica gel-percolated alumina sheets (type 60 F254 Merck, Darmstadt, Germany).

2.3. Synthesis of 1,3-Oxazepine-4,7-dione derivatives(SH₁- SH₅) [17]

(0.0015 mol) of Schiff bases(Prepared in our previous research[18] dissolved in (10 ml) of dry benzene was mixed with (0.003 mol) of maleic anhydride dissolved in (10 ml) of dry benzene, and the mixture was refluxed for (15-18) hours , Precipitates collected and recrystallized from absolute ethanol, were evaporated and formed by the solvent. The physical properties, percentage, reverse sublimation time, and R_f of oxazepine derivatives (S16-S20) are as shown in Table (1).

2.5. Study of the liquid crystal properties of some prepared compounds(SH₁, SH₂) [19]:

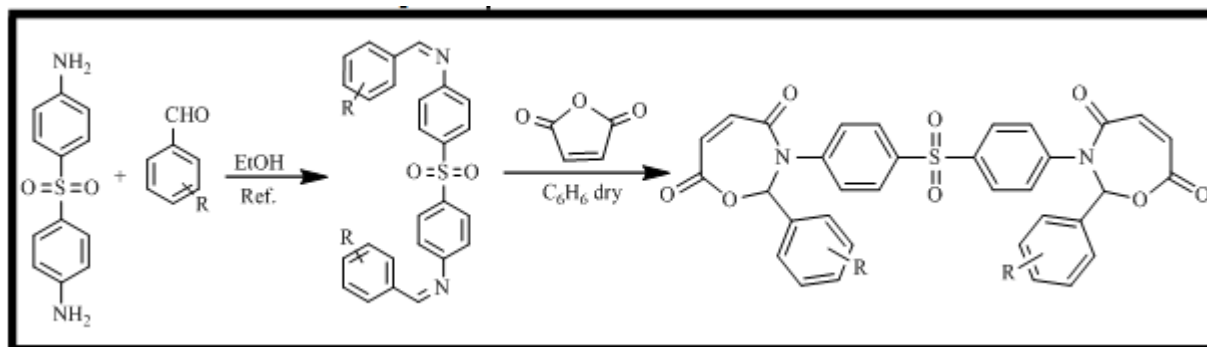
The texture of some of the prepared compounds (SH₁, SH₂) was studied using a polarizing microscope equipped with a hot-stage heater. MEIJI (American origin) with an E-PLAN 10X/0.25 160/0.17 lens with an electronic thermometer to monitor the change in temperature and equipped with a 38MP FHD Camera V6 at 20X magnification. A thin film was prepared from all the compounds under study, and the model was subjected to close observation through a magnifying glass and using an automatic thermal camera, and the texture of the compounds under study was photographed.

2.6. Evaluation of biological activity of (SH₁-SH₃)

The biological activity has been estimated by using the propagation method according the Kirby Bauer movement [20, 21], where 0.1 ml of bacterial suspension has spread to the ager Muller Hinton dishes and left for 5 minutes to absorb the suspension [22, 23]. After that, holes were prepared for each dish using a Cork Porer and a diameter of (5) mm per hole (0.1 ml) of the prepared solutions of the fourth hole using (Ciprofloxacin) as a control sample and incubated the dishes for (24) hours at 37 °C. The inhibition zone diameters around each hole has been measured in miltmeter, depending on the method of Prescott [24].

3. Results and Discussion:

In this research, ten compounds were prepared, five compounds including Schiff bases derivatives (SH₁ - SH₅) were prepared by reacting 4,4'-sulfonaniline with benzaldehyde substituents, and five compounds including Oxazepine derivatives (SH₆ - SH₁₀) were prepared. Through the interaction of the derivatives of Schiff bases with maleic anhydride as in Scheme (1) which is characterized by FT-IR, ¹H-NMR and ¹³C-NMR spectra.



Scheme (1): Route of prepared compounds (SH₁-SH₁₀)

3.1. Characterization of 1,3-Oxazepine-4,7-dione derivatives [SH₁-SH₅]

When studying the ultraviolet-visible (UV-Vis) spectrum of the prepared compounds [SH₁-SH₅] using ethanol (95%) as a solvent and a concentration 1×10^{-4} molar for the prepared compounds, so that short wavelengths (λ_{max}) appeared at (219-261) nm due to the transition ($\pi \rightarrow \pi^*$) with Long wavelengths (λ_{max}) at the range (343 - 375) nm belong to the electronic transmission of the type ($n \rightarrow \pi^*$), and these results were close to what is found in the literature [25], as in Table (2).

When studying the infrared spectrum of Oxazepine derivatives (SH₁-SH₅), it showed absorption bands at the range (3136-3240) cm^{-1} It refers to stretching (CH bonding) oliphines, as well as absorption bands at the range (3014-3080) cm^{-1} It refers to stretching (Ar-H bonding), and band presence at (1761-1780) cm^{-1} and (1685-1720) cm^{-1} due to lactone and lactam compounds (C=O) respectively. with the appearance of (absorption bands) at the range (2914-2989 cm^{-1}) returns to the stretching (CH) bond, with the appearance of absorption bands at the range (1512-1597) cm^{-1} , due to the stretching of the (C=C) aromatic bond, as well as the bands of absorption, at the range (1222-1298) cm^{-1} belonging to the stretching of the (C-N) bond [26], as shown in the tables (2) and figure (1).

The proton nuclear magnetic resonance (¹H-NMR) spectrum of the compound (SH₄) showed a signal at (8.40) ppm belonging to (CH) protons, a signal at (6.48) ppm dating back to a (=CH) proton, a signal at (6.75) ppm dating back to a (=CH) proton, with multiple signals appearing at (7.20-7.92) ppm belonging to protons Aromatic rings (Ar-CH) [27], as shown in figure (2) of compound (SH₄).

The carbon nuclear magnetic resonance (¹³C-NMR) spectrum of the compound (SH₅) also showed a signal at position (85.98) ppm due to carbon (CH), and showed a signal at position (114.55) ppm due to carbon (=CH), and showed a signal at position (118.62) ppm due to carbon (=CH), and a signal at position (188.89) ppm. It refers to a carbon (C=O), and a signal at position (203.99) ppm. It refers to a carbon (C=O), with multiple signals appearing at the position (109.71-147.17). ppm refers to the carbons of the aromatic ring (Ar-CH) [28], as shown in figure (3) of compound (SH₅).

3.3. Evaluation of Biological activity of (SH₁-SH₃):

Some of the synthesized compounds (SH₁-SH₃) were tested against various strains of bacteria: gram-positive bacteria *Staphylococcus aureus*, and gram-negative bacteria *Escherichia coli* by cup plate agar diffusion method [29]. The microbial cultures were incubated at (37 °C for 8 hours) and diluted with 0.8% sterile saline [30]. The solution concentration for used drugs in DMSO was kept at 100 $\mu\text{g}/\text{mL}$. Ciprofloxacin as a negative control was used. The biological activity was measured by measuring the inhibition diameter of the growth of bacteria around the disk in use [31], as shown in Table (3), figures (7) and Scheme (2,3).

3.4. Identification and discussion of liquid crystal phases of (SH₁,SH₂):

The liquid crystalline phases are studied and diagnosed and the nature of the transitions occurring in those phases is determined by using a polarized light microscope equipped with a heater, as shown in Tables (4). The prepared oxazepine derivatives showed the smectic and nematic phases with a high temperature range. The reason for this may be attributed to the presence of four aromatic rings in the molecular structure of these compounds, which give the molecule the appropriate elongation, in addition to the widening of the electronic succession along the axis of the molecule, and this leads to an increase in the variation in the molecular polarity resulting from the forces. The terminal attraction of the dipole-dipole type, which includes the attraction between the nitro groups as well as the methoxy groups, in addition to that the presence of lateral attractive forces represented in the polarization of the group (C = O) and the oliphine group (C = C), and this agrees with what was stated in the literature [32], which confirmed that the presence of more than three aromatic rings in the molecule increases its polarity and thus helps the emergence of liquid crystalline phases. as shown in figure (4,5,6) of compound (SH₁, SH₂).

Table (1) Physical properties of the prepared compounds (SH₁-SH₅)

Comp. No.	R	Molecular formula	m.p. °C	Yield%	Color
SH ₁	4-CH ₃ O	C ₃₆ H ₂₈ O ₁₀ N ₂ S	Gume	55	Yellow
SH ₂	3-CH ₃	C ₃₆ H ₂₈ O ₈ N ₂ S	Gume	94	Dark Brown
SH ₃	3-OH, 4-CH ₃ O	C ₃₆ H ₂₈ O ₁₂ N ₂ S	Gume	63	Brown
SH ₄	2-Br	C ₃₄ H ₂₂ Br ₂ N ₂ O ₈ S	122-150	51	Golden
SH ₅	2-Cl	C ₃₄ H ₂₂ O ₈ N ₂ Cl ₂ S	Gume	87	Brown

Table (2): FT-IR data of prepared compounds (SH₁-SH₅) cm⁻¹

Comp. No.	λ max ₁ λ max ₂ EtOH Nm	R	ν (C-N)	νC-H Arom.	νC-H Aliph.	νC=O νC=O	ν C=C Arom.	Others
SH ₁	246 375	4-CH ₃ O	1278	3024	2945	1767 1694	1597	ν (C-O-C) 1310
SH ₂	219 365	3-CH ₃	1290	3080	2918	1780 1685	1566	-----
SH ₃	232 357	3-OH, 4-CH ₃ O	1222	3041	2989	1761 1720	1550	ν (OH) 3480
SH ₄	227 372	2-Br	1289	3014	2914	1768 1688	1573	ν (C-Br) 1030
SH ₅	261 343	2-Cl	1298	3020	2922	1781 1689	1512	ν (C-Cl) 819

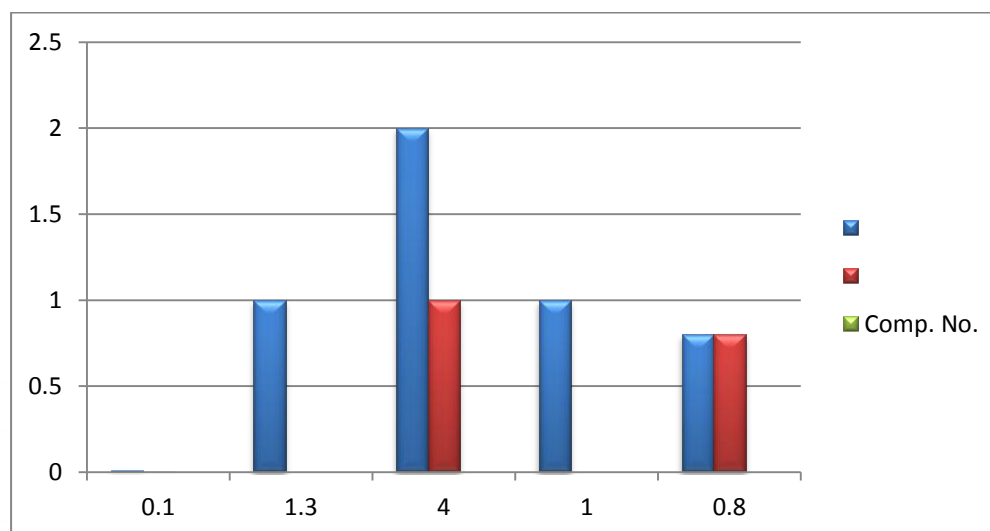
Table (3): Inhibitory effectiveness of some prepared compounds (SH₁-SH₃) and control treatments (antibiotics) on the growth of a number of positive and negative bacteria

Comp. No.	<i>Escherichia coli</i>			<i>Staphylococcus aureus</i>		
	0.001	0.01	0.1	0.001	0.01	0.1
SH ₁	1	0.9	0.9	0	1	1.3
SH ₂	1,8	2,2	2	1	2	4

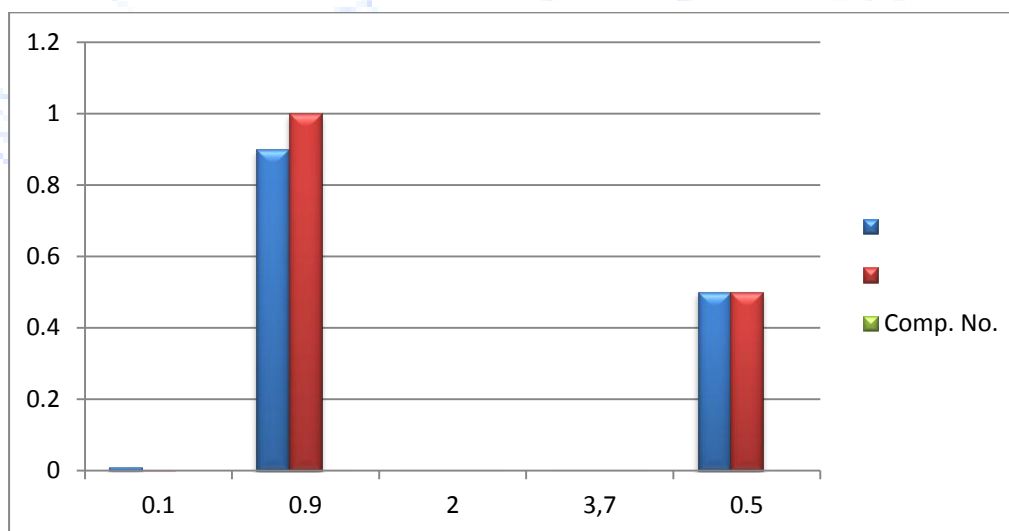
SH ₄	1,7	1,8	3,7	0	1	1
Ciprofloxacin	0.5	0.5	0.5	0.8	0.8	0.8

Table (4): The nature of the transitions of the liquid crystalline phases of some prepared compounds

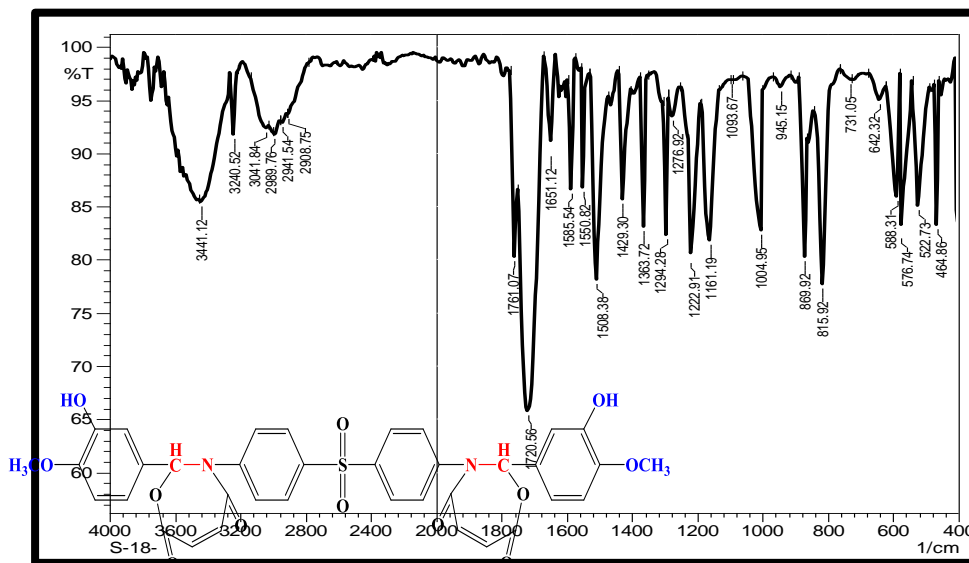
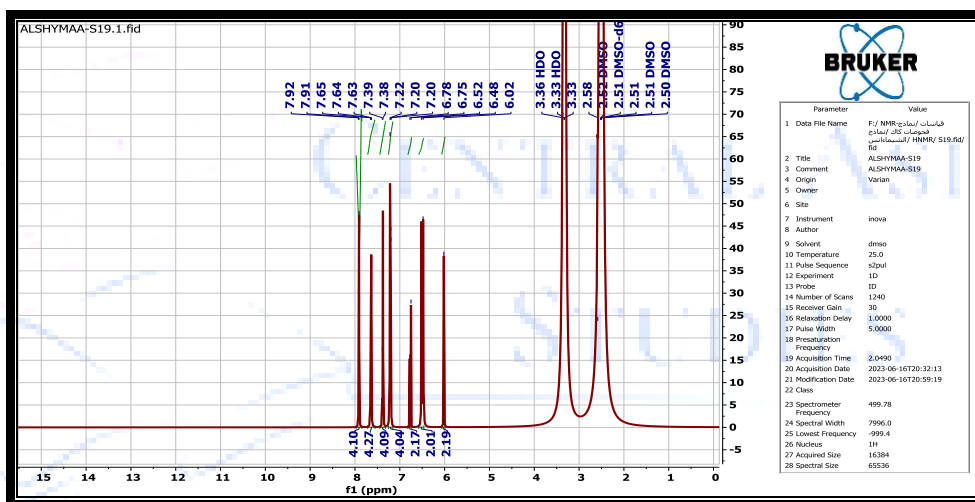
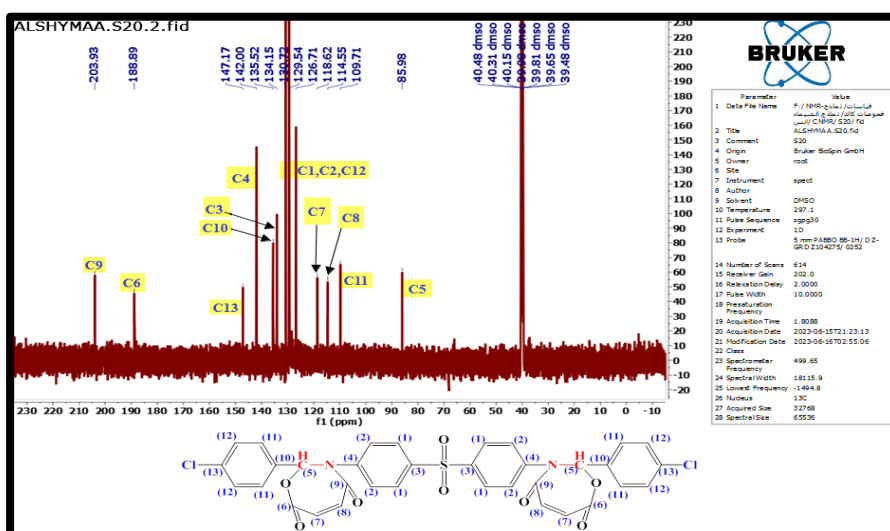
NO.	Crystal	S	N	ΔT_S	ΔT_N
SH ₁	Gum	120	150	-----	30
SH ₂	Gum	-----	300	-----	-----



Scheme (2): Values of inhibitory activity measured in cm for some prepared compounds against *Staphylococcus aureus*



Scheme (3): Values of inhibitory activity measured in cm for some prepared compounds against *Escherichia coli*

Figure (1): The infrared spectrum of compound (SH₃)Figure (2): The ¹H-NMR spectrum of compound (SH₄)Figure (3): The ¹³C-NMR spectrum of compound (SH₅)

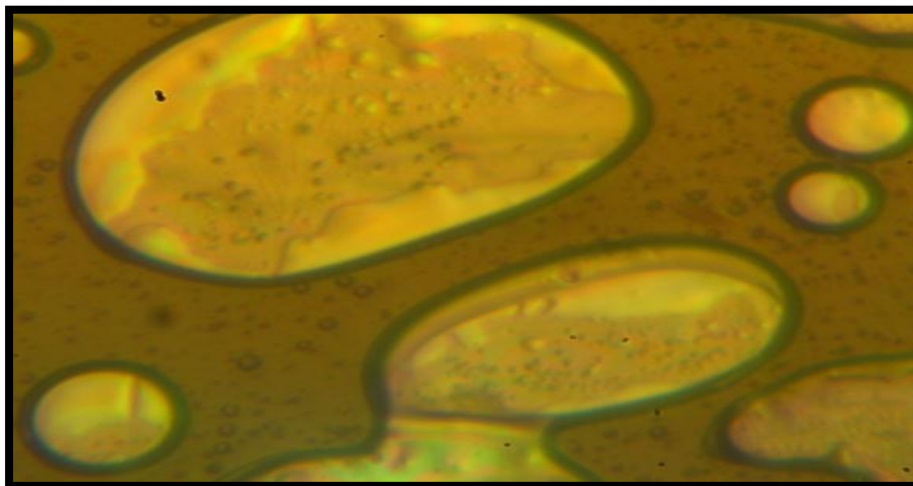


Figure (5): Smectic phase S of compound [SH₁]

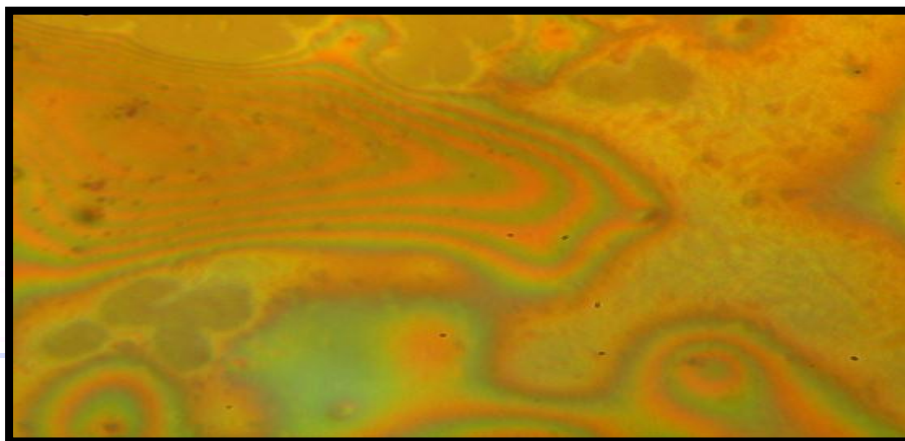


Figure (6): Nematic phase N of compound [SH₁]

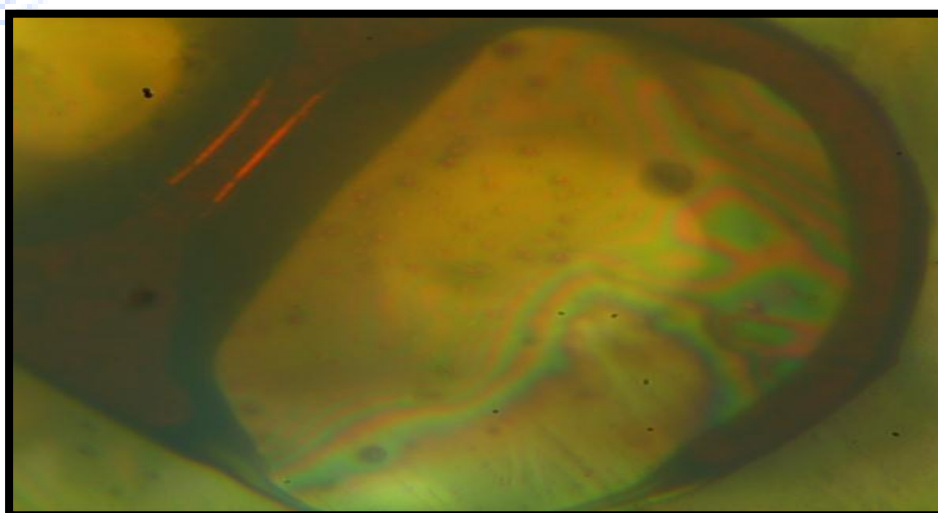


Figure (4): Nematic phase N of compound [SH₂]

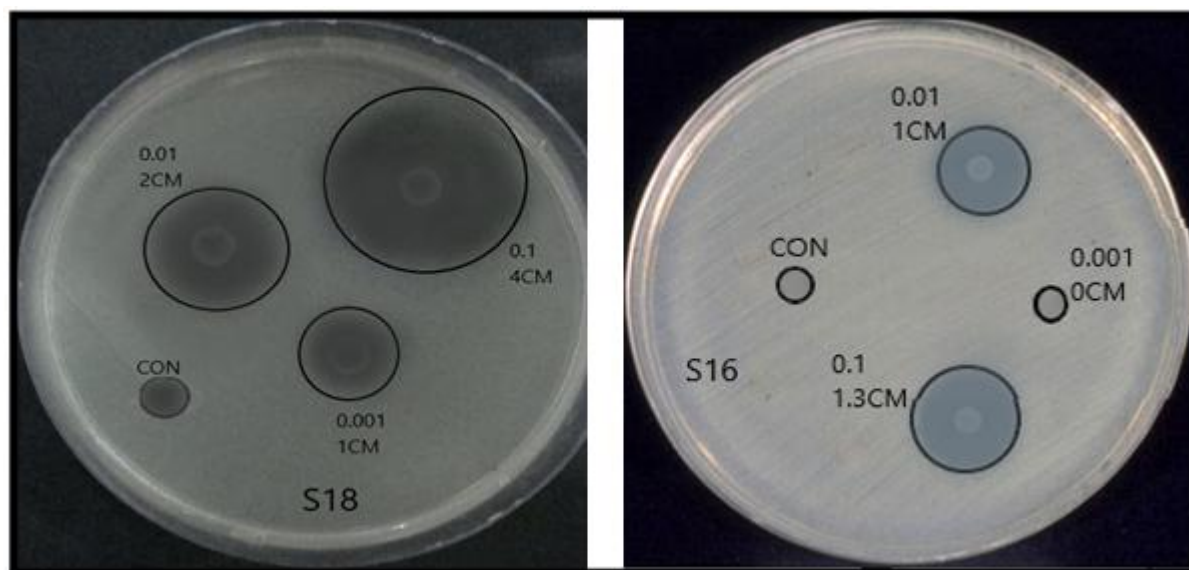


Figure (7): Biological effect and sensitivity test of compounds against bacteria

4. Conclusions: The accuracy and validity of the prepared compounds were confirmed through spectroscopic and physical measurements, as the infrared and ultraviolet spectroscopy proved the presence of active aggregates accurately, and this confirmation increased the nuclear magnetic resonance spectrum of the proton and carbon spectrum, which accurately agreed on its validity. of the structures of the prepared compounds. These compounds are stable at laboratory temperature and do not degrade or change color. The prepared compounds showed high inhibitory activity against gram-positive and gram-negative bacteria, and the results were compared with control samples, which are antibiotics. And the study of the liquid crystals of the compounds of the two phases, the nematic (N) and the smectic (S), proved an indication of the presence of polarized and successive terminal groups along the length of the system.

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