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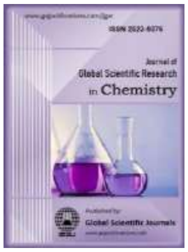

Synthesis, Study of Their Liquid Crystal, Laser Properties of New Binary 1,3-Oxazepine-4,7-dione Derivatives and Evaluation of the Antibacterial Activity of Some of Them

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ABSTRACT

The research included preparing a number of new 1,3- Oxazepine derivatives [B1-B5] were prepared from the reaction of Schiff bases prepared with malic anhydride using dry benzene as a solvent. After purifying the product, the synthetic compounds were characterization with some spectral methods such as [UV], [FTIR], [1H-NMR] and [13C-NMR], in addition to determining the melting and purity levels of the prepared compounds and monitoring the progress of the reactions using TLC thin layer chromatography. The effect of some prepared compounds on the growth of two types of bacterial isolates, known to be resistant to antibiotics, one negative for Gram stain [Gr-ve], which is Pseudomonas aeruginosa, and the second positive for Gram stain [Gr + ve], which is Staphylococcus aurous, were used antibiotics Amoxicillin and Ampicillin. Some of the prepared compounds showed high inhibitory efficacy against the used bacteria in addition, the conformation of prepared compounds at the lower energy level was studied.1,3 -Oxazepine compounds showed the Nematic phase (N) and the Smectic phase (S) because the presence of succession along the molecular system in addition to linearity for the presence of nitro ,chloro and methoxy groups (NO2,Cl,OCH3). The (SEM) for compound [B1,B2,B3] showed the dimensions in which the nanoparticles are aligned, as well as the clusters formed with few interstitial distances for compound [B1,B2,B3]. It is noted that snow balls stacked one above the other appear on the nanoplate (A). The images also showed that the thickness of the layer of the nanoparticles is 87.77 nm and 93.02 nm (B). It is also noted that there are small agglomerated nanoballs as in (C) with the presence of extended plates with a moon in the middle of it on a full moon night on the surface of the nanoplate as in (D).

1. Introduction

1,3-Oxazepine compounds in 1965 used in relief of psychoneurosis characterized by anxiety and tension, oxazepine is a seven-membered ring that includes a nitrogen atom and an oxygen atom in its structure **(1)**. Oxazepines have been found to use as antibacterial**(2),** antifungal**(3)**, antihistamine**(4),** and anti-inflammatory **(5)**. Chemical compounds: such as, azo compounds are used in most scientific research**(6),** and as a result highly rich attention. The aim of this research, synthesized and characterized of seven-membered heterocyclic that bear azo compounds as 1,3-oxazepine rings with different aromatic moieties **(7-11).** These

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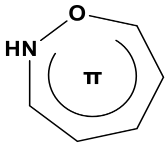
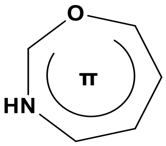
compounds have also been studied and characterized and then test their effectiveness against bacterial pathogenesis.



tetrahyro-1,2-oxazepine



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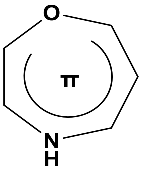


tetrahyro-1,4-oxazepine

Liquid crystals are substances that have the appearance of a liquid. However, their particles are arranged in certain levels, such as crystals **(12)**. It is an intermediate state between a stable liquid state and a stable crystalline solid state. and liquid crystals are considered the fourth state of matter **(13)** 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 **(14)**

Materials:

All chemicals were commercially supplied and used without further purification

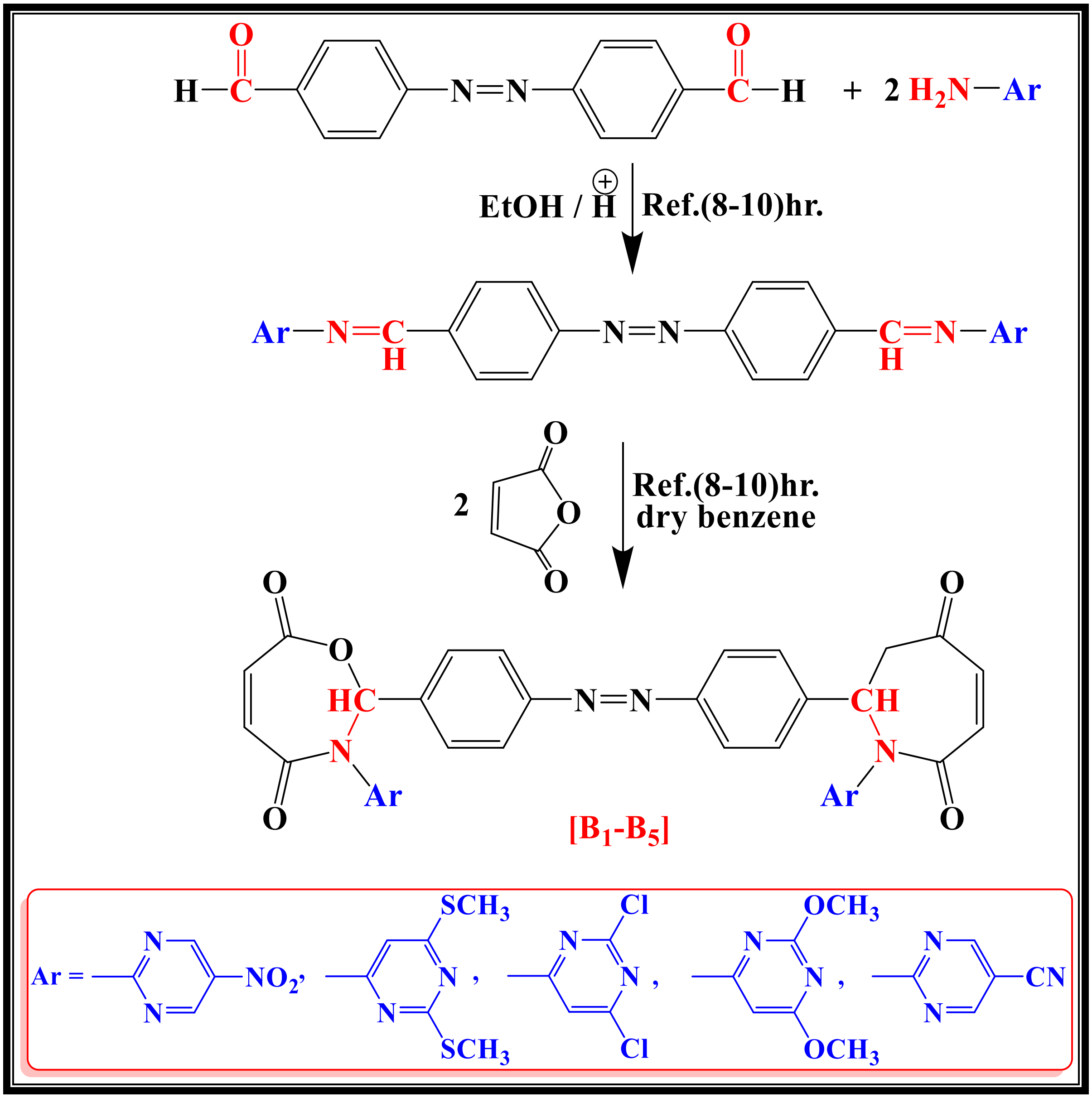
Physical measurements:

Melting Points were obtained on Electro thermal 9300 and are uncorrected. IR spectra were recorded on FTIR 8400 as Shimadzu spectrometer in the range 400- 4000 cm^{-1} as KBr disc. Electronic spectra were measured between 200-400 nm with 10^{-3}M solutions in DMSO Solvent (spectroscopic grade) at 25°C using Shimadzu, UV-Vis 1800PC spectrophotometer. NMR spectra (^{1}H &^{13}C-NMR) were Performed in DMSO-d^{6} solutions using Brukeravance 400 MHz spectrometers .Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard.

2. Synthesis Methods

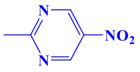
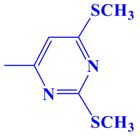
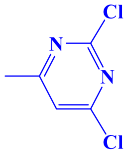
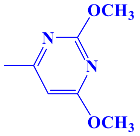
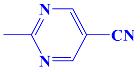
2-1 Synthesis of 1,3 Oxazepine derivatives [B_1-B_5](15)

A mixture of Schiff bases derivatives (0.004mol) ***(Prepared in our previous research***)*(16)* with (0.0008mol,1.82gm Malic anhydride respectively in (30 ml) of dry benzene (C_6H_6) was refluxed for (18-20) hour for compounds [B_1-B_5] .The crude product was dried, recrystallized from absolute ethanol (Scheme1).The physical properties of compounds [B_1-B_5] Table(1). FTIR and UV. data see Table (1).



Scheme (1) Rout of prepared compounds[B_1-B_5].

Table 1- The physical properties of the compounds [B_1-B_5]

Comp. No.	R	Molecular Formula/ M.Wt g/mol	Color	M.P. (^{o}C)	Yield (%)	R_f	T.R hour
*B_1		$\mathbf{C_{30}H_{18}N_{10}O_{10}}$ **678**	**Light yellow**	**151-182**	**62**	**0.92**	18
B_2		$\mathbf{C_{32}H_{22}Cl_2N_8O_6\ S_2}$ **748**	**White**	**139-141**	**50**	**0.97**	19
*B_3		$\mathbf{C_{30}H_{16}Cl_4N_8O_6}$ **723**	**Off White**	**249-265**	**70.14**	**0.97**	18
*B_4		$\mathbf{C_{34}H_{28}N_8O_{10}}$ **708**	**yellow**	**Oilly**	**63.55**	**0.79**	20
B_5		$C_{32}H_{18}N_{10}O_6$ 638	Off White	267-269	82.60	0. 9	20

Note: Compounds[B_1,B_3,B_4] whose liquid crystal properties have been studied.

3- Anti-bacterial Activity (17)

Were screened for their in vitroelementary antibacterial activity against the type of Gram-positive bacteria including (***Pseudomonas aeruginosa***)and the type of Gram-negative bacteria including (***Staphylococcus aureus***) by well agar diffusion method using nutrient agar as medium tested compounds were prepared with different concentration using 100mg/ml in dimethyl sulfoxide (DMSO) as solvent. Each solution of the prepared concentration was added to test tubs contains 5ml of the nutrient broth. Two test tubs were left one without addition to the other tube, DMSO was added only as control, the bacterial suspension was diluted and 1ml of the diluted suspension to the tubes including the control. Disks of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation left at 37^{o}C for one day. The evaluation was carried out by measuring the diameter of inhibition zones in mm. Ampicillin trihydrate and amoxicillin were used as reference standard for all the tested compounds.

4. Results and Discussion

The UV-Vis spectrum of the compounds[B_1-B_5] prepared using ethanol as a solvent was studied at a concentration of [10^{-4}-10^{-5}] M, and all compounds gave absorption peaks in the range (219-261) nm into the $\pi\rightarrow\pi^*$ transitions, and absorption peaks in the range from (343-375) nm into the $n\rightarrow\pi^*$ shown in Figure (1,2).

The 1,3-Oxazepine derivatives [B_1-B_5] were prepared from the reaction of one mole of the prepared Schiff bases with two moles of Malic anhydride in dry benzene (C_6H_6) as showed in Scheme (1). FTIR spectrum of 1,3-Oxazepine derivatives [B_1-B_5] the disappearance of the stretch band of the azomethine group (C=N) and the emergence of two strong bands at the frequency (1747-1781) $cm^{-1}$and (1685-1694) cm^{-1}, due to the stretching of the carbonyl bond (C=O) of the lactone and lactam, respectively. And the emergence of a medium band at the range (1494-1432) cm^{-1} belonging to the group (N=N). FTIR data see Table(2). shown in Figures (3).

^{1}H-NMR spectrum of the compound [B_1] (400 MHz, DMSO) δ 4.58ppm (s , 2H,C-$H_{oxazpene}$) , 6.48-6.52ppm(d,2H,C=$C_{oxazpene}$), δ 6.75-6.78(d,2H,C=$C_{oxazpene}$) , 7.91 (s,2H ,CH=N $_{pyrimidine}$) , δ 7.20-7.22, (d , 4H,C-H-Ar, ddd, *J* = 8.4, 1.6 Hz), δ 7.38-7.39ppm (d , 4H,C-H-Ar ,*J* = 10.7 Hz), ,shown in Fig.(4). Table 3 shows the values of the chemical displacements of the proton for some of the synthesized 1,3-Oxazepine derivatives [$B_{1,}B_2$].

The^{13}C-NMR spectrum of the compound [B_5] is shown δ94.01(C_5,s), 99.55 ppm (C_{13},s),116.83ppm(C_{12},s),123.03(C_1,s),125.58(C_2,s),131.23ppm(C_8,s),134.60(C_7,s),138.13(C_4,s),153.53(C_{11},s) ,164.71(C_{10},s) ,173.78(C_9,s),180.31(C_6,s) shown in Figure (5). Table 4 shows the values of the carbon chemical displacements for the synthetic compound[B_5].

Table 2: FT-IR & UV-Vis spectral data for 1,3-Oxazepine [B_1-B_5].

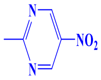
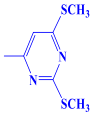
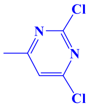
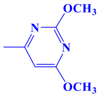
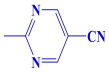
Comp. No.	λ max$_1$ λ max$_2$ EtOH nm	R	IR (KBr) cm^{-1}					
			ν (C-H) ν Arom. νAliph. Sym. /asy.	**ν (C=N)py. ν (C=O)A ν (C=O)B**	**ν (C=C) Arom.**	**ν (N=N)**	**ν(C-N) ν (C-O)**	Others
B_1	**246 375**		3024 2839 2945	1642 1767 1694	1523 1597	1452	1278 1332	NO_2 υ (Smy.) 1333 υ (Asmy.) 1550
B_2	**219 365**		3080 2850 2918	1640 1780 1685	1566 1592	1494	1290 1333	(1032) υ (C-S)
B_3	**232 357**		3030 2868 2949	1643 1747 1691	1539 1566	1479	1257 1336	(844) υ (C-Cl)
B_4	**227 372**		3014 2874 2914	1642 1768 1688	1573 1594	1432	1289 1321	C-O-C υ (Smy.) 1303 υ (Asmy.)1513
B_5	**261 343**		3020 2850 2922	1644 1781 1689	1512 1576	1438	1298 1325	(2470) υ (CN)

Table 3: shows the values of the chemical displacements of the proton for the 1,3-Oxazepine [B_1, B_2 , B_4].

Comp. No.	Chemical Shift (ppm)	No. of protons and signals	Group
B_1	**4.58**	**(s , 2H,C-$H_{Oxazpene}$)**	c
	6.48-6.52	**(d , 2H,*CH=CH)**	d
	6.75-6.78	**(d , 2H, CH=*CH)**	e
	7.20-7.22	**(d , 4H,C-H-Ar)**	b
	7.38-7.39	**(d , 4H,C-H-Ar)**	a
	7.91	**(s , 4H,CH=N pyrimidine)**	f
S =singlet , d=doublet			

Table 4: shows the values of the chemical displacements of carbon for the prepared compounds [B_5].

Comp. No.	Chemical Shift (ppm)	Number
B_5	**94.01**	5
	99.55	13
	116.83	12
	123.03	1
	126.58	2
	131.23	8
	134.60	7
	138.13	4
	148.96	3
	153.53	11
	164.71	10
	173.78	9
	180.31	6

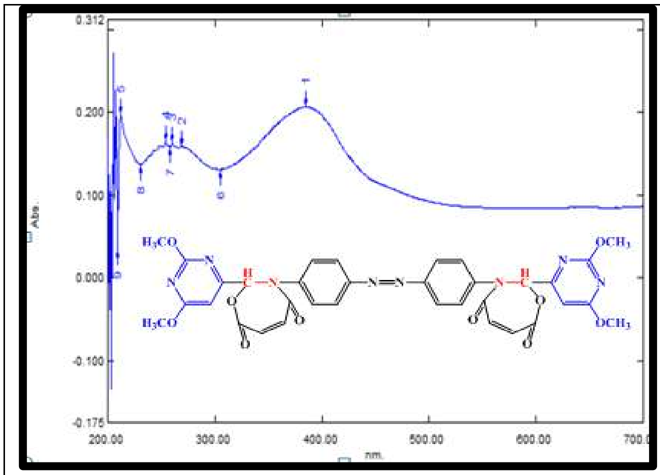


Fig.(1) Uv-vis spectrum the compound [B_4]

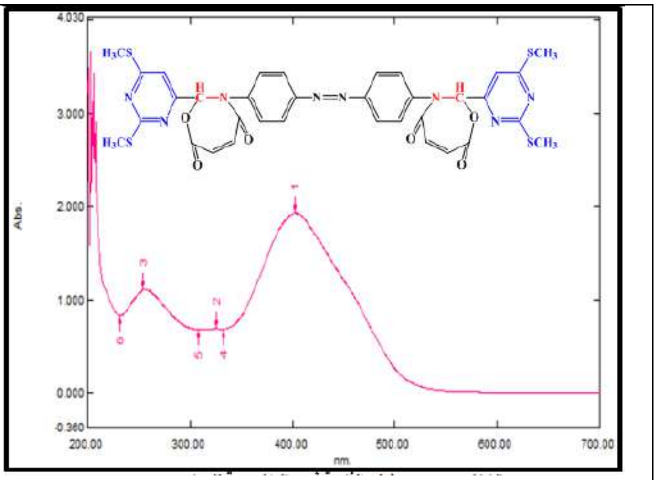


Fig.(2) Uv-vis spectrum the compound [B_2]

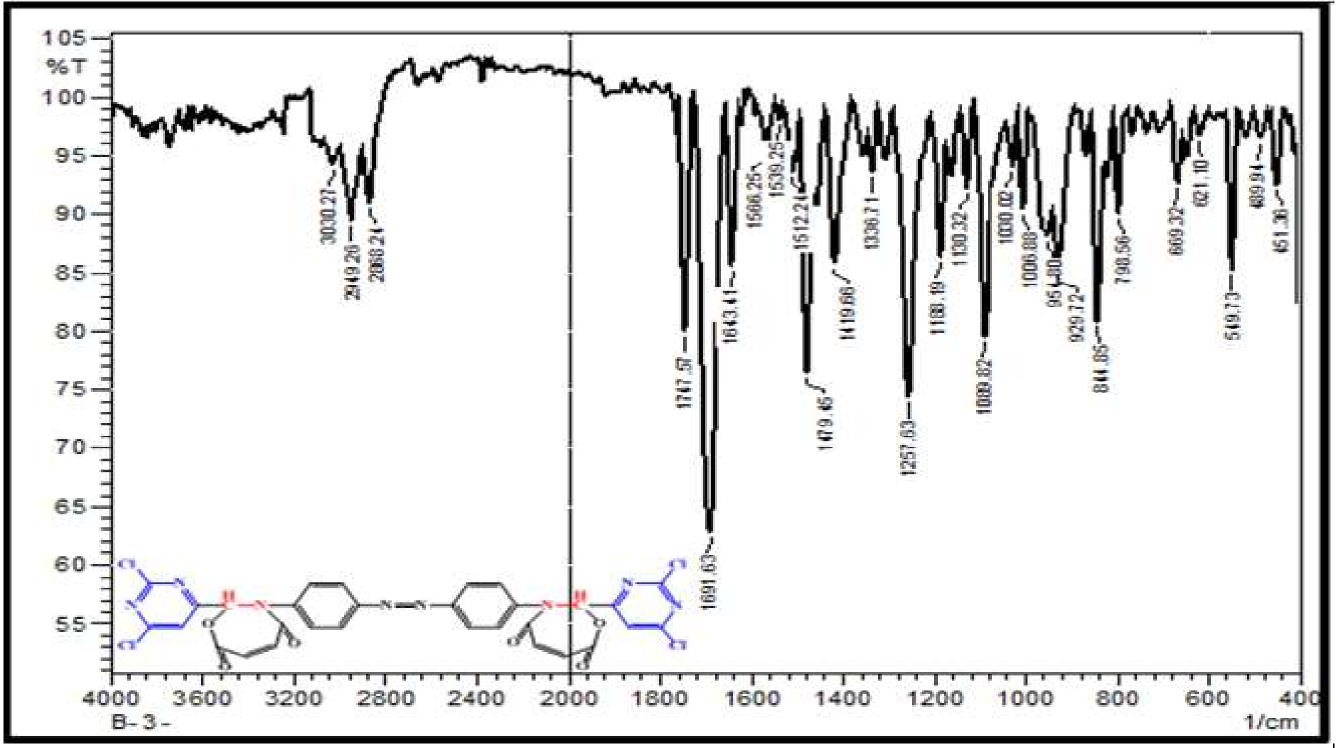


Fig. (3) Infrared spectrum of [B_3]

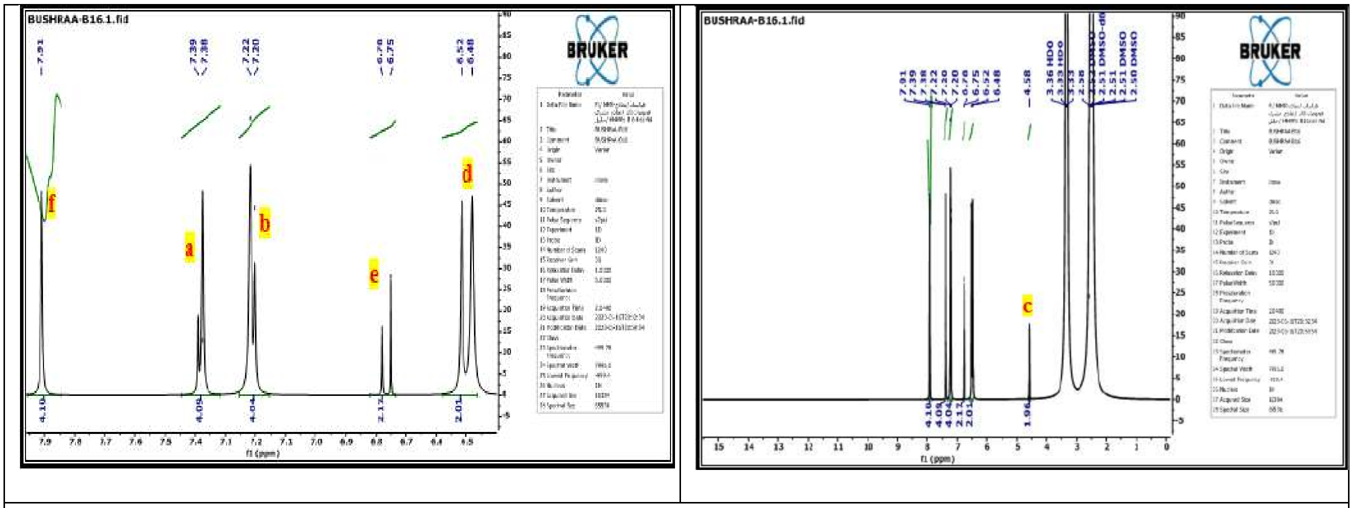
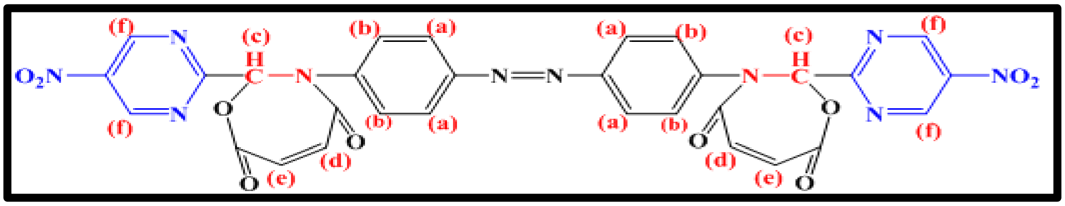


Fig.(4) ^{1}H-NMR spectrum the compound [B_1]



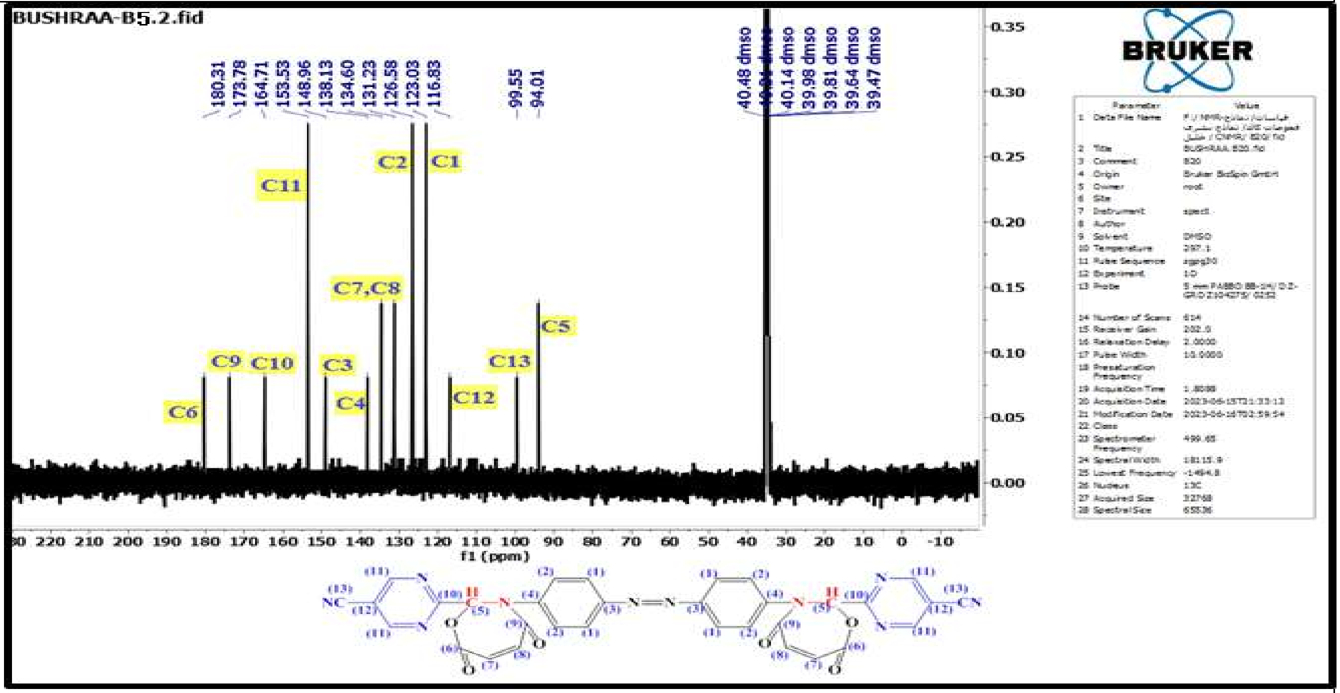


Fig.(5) ^{13}C-NMR spectrum the compound [B_5]

5. Determination of antibacterial activity[18]

Table (5) Illustrates the result of antibacterial activity of 1,3-Oxazepine [B_2,B_3] and are against two types of bacteria ***Pseudomonas aeruginosa*** (gram-negative) and ***Staphylococcus aureus*** (gram-positive). The compounds were evaluated in vitro for their antibacterial activity against the tested bacteria by disc diffusion method the bacterial species. Nutrient agar was used for bacterial screening, DMSO was used as a solvent, Ampicillin, and Amoxicillin ($1x10^{-1}$,$1x10^{-2}$ g/m1) as controls.

The agar well diffusion method was used to detect antibacterial activity compounds 1,3-Oxazepine derivatives of against two pathogenic bacteria species. Young bacterial cultures suspension equivalent of 0.5 tube McFarland turbidity standards (108 μg/ml) were spread on Muller-Hinton agar plates using sterile cotton swabs Wells of 6mm diameter were cut in solidified agar and filled with 50 μl of each concentration. Dimethyl Sulfoxide is also used as a control. The plates were incubated aerobically at 37°C for 24 hours, then inhibition zones diameter (cm) around wells was measured by rule. All tests were applied in triplicate.

The antibacterial activity of the synthesized compounds (B_2,B_3) were examined by the agar diffusion method using two different bacterial species, ***Pseudomonas aeruginosa***, ***Staphylococcus aureus***. The results indicated that some of the assayed compounds showed a microbial activity against the used bacteria. Antibacterial activity of compounds (B_1,B_3). Evaluation of the inhibitory activity of compounds prepared are given in fig. (6).

Table 5: Growth inhibition zone diameter(mm)of six heterocyclic compounds against two pathogenic bacteria species

Compounds NO.	*Conc. Mg per ml*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
B_1	***0.1***	***2.8***	***2.0***
	0.01	***2.8***	***1.5***
B_3	***0.001***	***1.5***	***1.0***
	0.1	***3.0***	***1.5***
	0.01	***2.7***	***1.5***
B_3	***0.001***	***0.4***	***0.5***
	0.1	***3.0***	***1.8***
	0.01	***2.4***	***1.0***
B_4	***0.001***	***1.0***	***0.8***
	0.1	***3.5***	***3.0***
	0.01	***1.6***	***1.5***
B_5	***0.001***	***0.8***	***1.0***
	0.1	***3.5***	***2.5***
	0.01	***3.5***	***2.5***
	0.001	***1.0***	***2.0***
DMSO (Control)	***0.0***	***0.0***	***0.0***
Ciprofloxacin	***10mg***	***1.5***	***2.0***
Amoxicillin	***10mg***	***0.5***	***1.0***

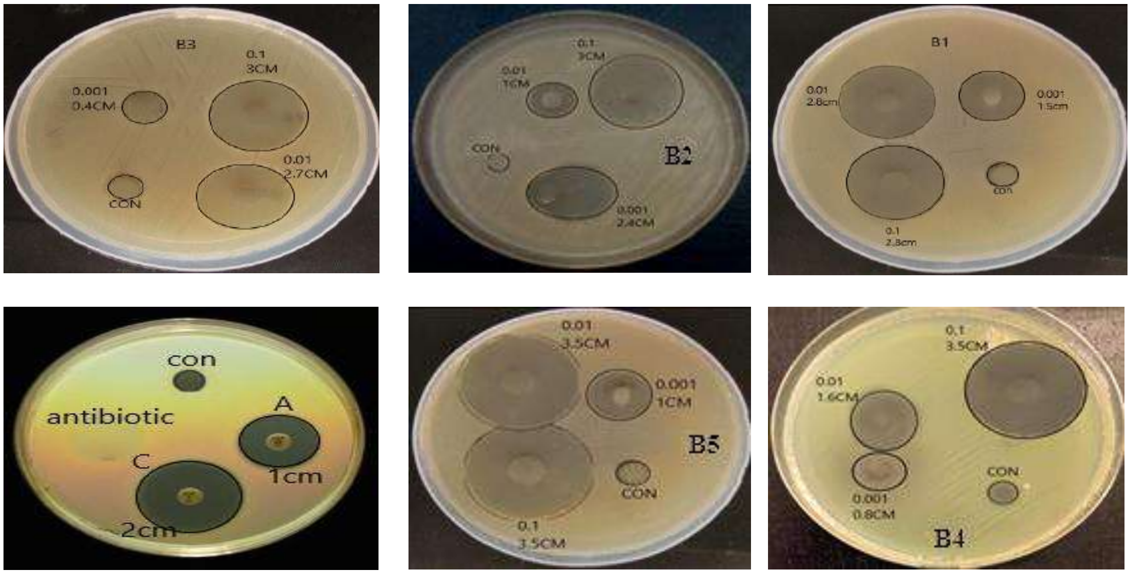


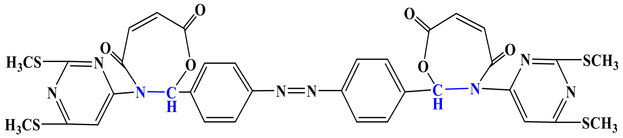
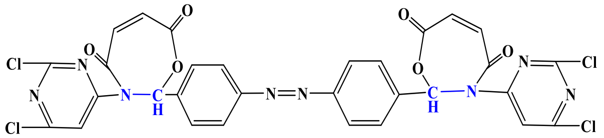
Fig. 6: Biological effect and sensitivity test of compounds against Staphylococcus aureus & Pseudomonas aeruginosa and showing the inhibition zone for compounds [B_1- B_5]

6. Discussion of liquid crystal phases (19)

Thermal transition values were calculated heating with a polarized microscope was diagnosed the liquid crystals and it was found that the microscope values were similar, as seen in Tables(6).

The1,3-Oxazepine derivatives compounds [B_2] showed three transitions in the liquid crystalline phases, the first transition is due to the melting point, the second transition is due to the transition from the crystalline phase to the Smectic crystalline phase (S), and the third transition is attributed to the transition from the Smectic phase (S) to the Nematic phase (N), As in the figure (7). As for the compound [B_3], it did not show any of the liquid crystalline phases. This may be due to the fact that the ratio between the length of the molecule to its average width does not fall within the range (4.0-6.4) , which represents the ratio of compounds that appear in a liquid crystalline state, which was indicated by the researcher Flory in his theoretical study of compounds that exhibit such properties.

(Tables: 6) Liquid crystal phase transitions of the prepared compounds[B_2,B_3].

Apparatus	NO.	Crystal	S	N	ΔT_S	ΔT_N	Structure
	B_2	**139**	**150**	**160**	**11**	**10**	
	B_3	**149**	**------**	**------**	**-----**	**------**	

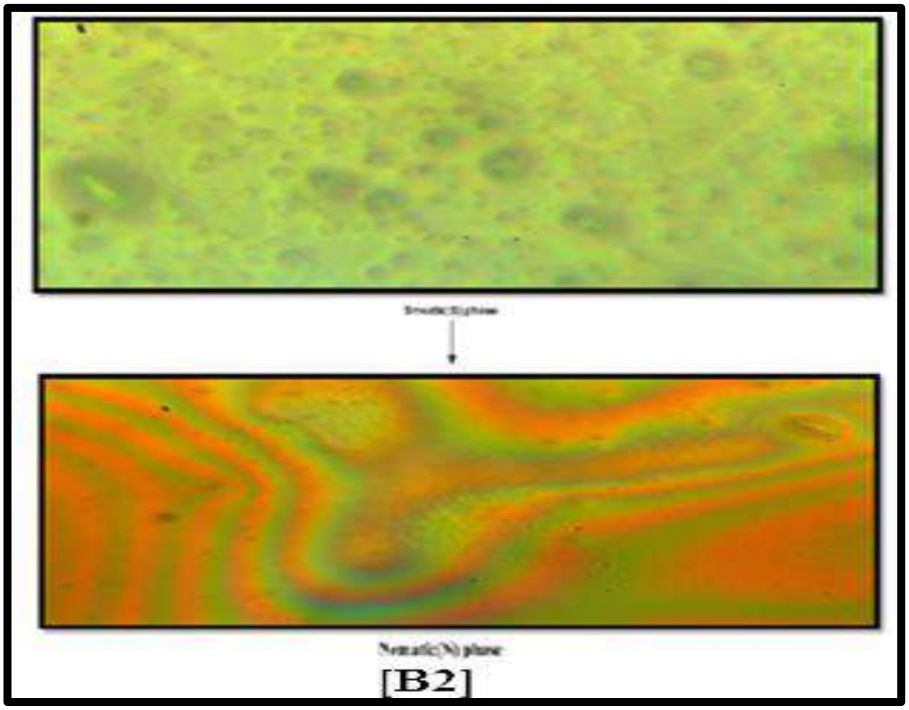


Fig. (7) : Liquid crystal phase transitions of compound [B_2]

7. Discussion of SEM, AFM (20)

The morphological images recorded with a scanning electron microscope **(SEM)** of compound [B_2] showed that the nanoparticles were aligned with it, as well as the formed clusters with few interstitial distances, as in compound [B_2]. It resembles a mountain chain with different heights (B), and the images showed the appearance of broken longitudinal plates as in (C). In addition, the thickness of the nanoplates is 32.82 mm (D), as in Figure (8).

Morphological images recorded with an atomic force microscope (AFM) for compound [B_1] showed clear roughness in the surface of the sample at a peak of 35 nm (A) with the presence of chains of united and parallel peaks (B) with the presence of shiny bubbles along the area of the nanoplate as in the figure (C) as in Figure (8).

The morphological images recorded with a scanning electron microscope **(SEM)** of compound [B_5] showed that the nanoparticles were aligned with it, and formed clusters with few interstitial distances, as in compound B5. The images showed the presence of structural clusters on all nanoplates (A) with the presence of clouds in the form of buds with deep openings. Inside the surface of the nanoplate (B), the images also showed the appearance of dense and broken longitudinal plates along the layer (C). In addition, the thickness of the nanoplates is 77.87 nm and 02.93 nm as in (D) as in Figure (9).

The morphological images recorded with an atomic force microscope (AFM) for compound [B_5] showed clear roughness in the surface of the sample with the presence of clusters of peaks such as hills at a value of 140 nm (A) with protrusions in the form of rock blocks spread along the plate (B). Clear nanoparticles as in (C) as in Figure (9).

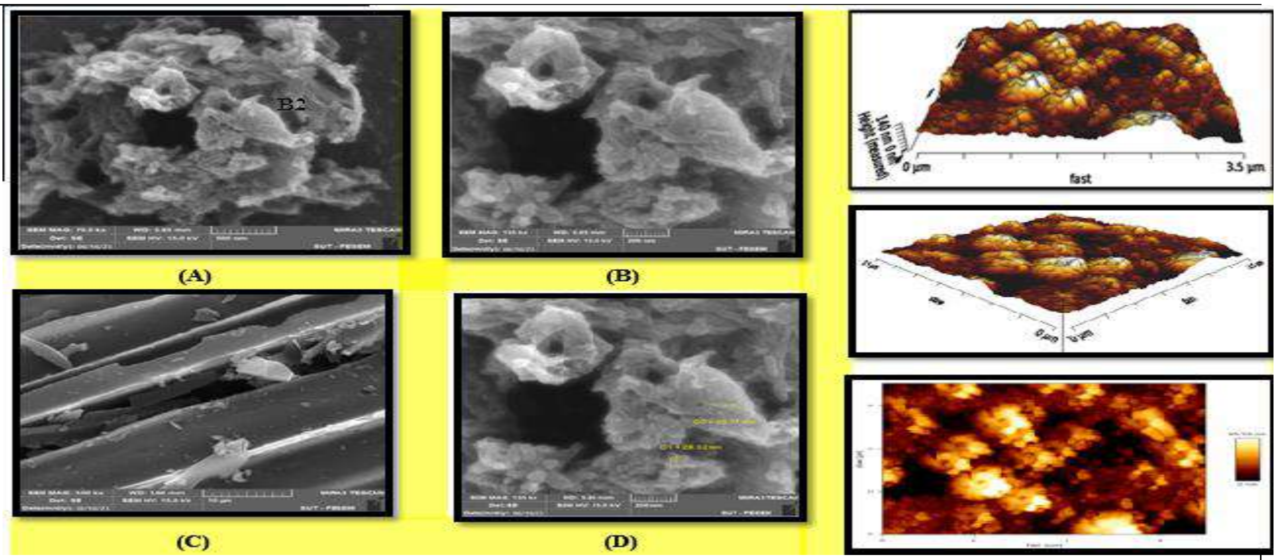


Fig.(8) SEM,AFM the compounds[B_2,B_1]

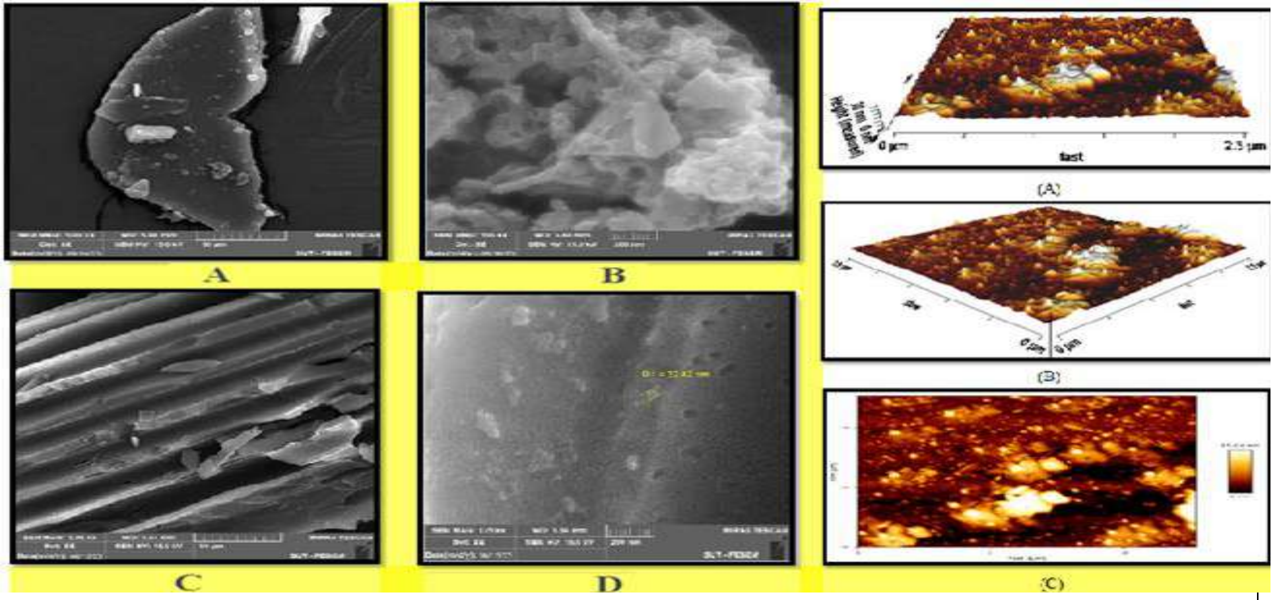
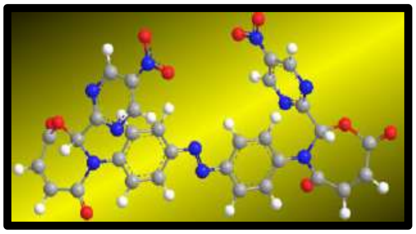


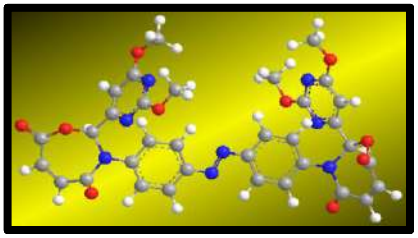
Fig.(9) SEM,AFM the compounds[B_5]

8.The most stable stereochemistry form of some synthesized compounds

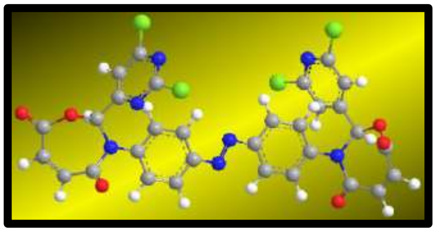
Some of the prepared compounds [B_1-B_5] were studied at the lowest energy level using the chem Draw professional 16.0 program in the 2016 version, Fig. (10).



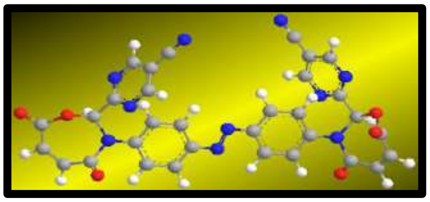
B$_1$



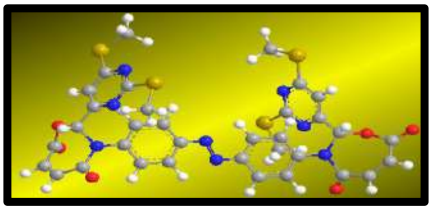
B$_2$



B$_3$



B$_4$



B$_5$

9. Conclusion

Treatment of Schiff bases with malic anhydride, give the corresponding 1,3-Oxazepine derivatives. The prepared showed high activity against the two types of Gram-positive and Gram-negative bacteria used in the study. The derivatives of the prepared 1,3-Oxazepine showed liquid crystalline properties, as they showed Nematic and Smectic phases, according to the nature of the molecule composition and the substituent terminal groups in it. The morphological images of the scanning electron microscope and the atomic force microscope of the prepared Schiff bases derivatives and the 1,3-Oxazepine showed nanostructures with dimensions, structures, and nanoparticles depending on the lamellar structure of the crystals within the molecular structure of the prepared derivatives.

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