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Synthesis and Identification of New Derivatives of Bis-1,3-Oxazepene and 1,3-Diazepine and Assess the Biological and Laser Efficacy for Them

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ABSTRACT
In this study, new schiff bases [A_1-A_2] compounds were prepared by the reaction of terephthalaldehyde with different substituted aniline (4-methoxyaniline and 4-methylaniline) in absolute ethanol, then schiff bases were converted into 1,3-oxazepine derivatives [A_3-A_4] by reacted with 3-bromophthalic anhydride in dry benzene.1,3-Oxazepine derivatives were converted into 1,3-diazepine derivatives [A_5-A_6] through reaction with aniline. The prepared compounds were characterized by physical properties, UV-Vis, FT-IR and ^{1}H-NMR spectral and C.H.N analysis. TLC checked the purity for these compounds. The antibacterial activities were studied against different kinds of bacteria, namely ***Eschershia coli*** **and** ***Klebislla Pneumonia*** **Gram (-) ve,** ***Staphylococcus aureus*** and ***Staphylococcus epidermidis*** **Gram (+) ve.** In addition, evaluation of laser efficacy is showed for the compounds [A_1-A_6] were radiated by laser for (10, 20, 30) seconds. It was found that all the prepared compounds did not have an effect and did not decompose or polymerize when color and the melting point were measured. The stereoisomers of the prepared compounds [A_1-A_6] were also studied at the lowest layer level using the Chem Draw Professional 16.0 program. Heat of formation of the prepared compounds [A_1-A_6] were also studied using the Chem3D 16.0 program.

Key words: *Schiff Bases, Oxazepine, Diazepine, Biological Activity, Laser Effectiveness*.

1. Introduction
Schiff's organic compounds are based on the azomethine group (-CH=N-), named after the Schiff world, which first participated in a simple reaction of aldehydes or ketones with primary amines in 1864. [1, 2]. Schiff bases have achieved wild ranges of biological activities [3-5]. Heterocyclic compounds represent an important branch in pharmaceutical chemistry. Schiff bases are used as substrates in the preparation of a numerous commercial and biologically active compounds via condensation of carbonyl compounds with amines [6]. Recently, the chemistry of unsaturated seven-membered heterocyclic compounds especially 1,3-oxazepine has attracted attention due to their reactivity and showed various biological activities such as antibacterial [7, 8]. Oxazepine, an un-saturated non-homologous seven-membered heterocycle including 1st position oxygen and 3rd position nitrogen, is prepared from reaction of schiff bases with anhydride (succinic imide, phthalic imide, and 3-nitophthalic) [9]. 1,3-oxazepine is of great importance due to its use as an anticonvulsant [10]. Diazepines can be defined as heterocyclic compounds that contain two nitrogen atoms at sites (1,2 or 1,3 or 1,4) and they may also contain a carbonyl group [11]. They are considered one of the most important medical and biological compounds since they show some effects against types of cancer [12] and hepatitis [13], and used in the treatment of epilepsy, malignant gliomas, and amyotrophic lateral sclerosis [14]. In this study we described the preparation of new schiff bases,1,3-oxazepine-4,7-dione and 1,3-diazepine-4,7-dione derivatives (Scheme1) in high yields, and characterized by spectroscopic methods. In addition, derivatives were screened for biological activity against four bacterial strains. Furthermore, study the heat of formation some prepared compounds.

2. Experimental
2.1. Material: All chemicals had been used as supplied by (Alfa Aesar and Aldrich).
2.2. Devices instrument: The melting points were determined by Electro thermal Melting Apparatus 9300 in open capillary tubes that were uncorrected. Thin layer chromatography (TLC) was used for monitory the reaction and to check purity. The FT-IR spectra were recorded using FT-IR 8400S Shimadzu spectrophotometer Scale (4000-400) cm^{-1}. The UV-Vis. spectra was measured in ethanol using Shimadzu

800UV in rang (200-400) nm. ^{1}H-NMR and ^{13}C-NMR Spectrum was recorded on Varian operating at 400 MH_2 instrument using DMSO-d^6 and chloroform as a solvent. Quantitative analysis of the spectrophotometer elements determined using C.H.N analysis. The prepared compounds were irradiated with helium-neon laser beam (visible laser) of 1 milliwatt and wavelength 600-700 nanometers, 2010 model.

2.3. Synthesis methods

2.3.1. Synthesis of Schiff's bases [A_1 –A_2]: Terephthalaldehyde (0.01 mol, 1.34 g) was dissolved in (50 ml) of absolute ethanol. After complete dissolving, (0.02 mol) of substituted aniline (4-methoxyaniline and 4-methylaniline) was added. After adding (4 drops) of glacial acetic acid, the mixture was then refluxed for (3-4) hours, and cooled to room temperature, filtered, dried and recrystallized in absolute ethanol [15, 16]. Physical properties are given in table (1).

2.3.2 Synthesis of 1,3-oxazepine-4,7-dione [A_3 – A_4]: Schiff bases [A_1-A_2] (0.003 mol) was mixed with (0.006 mole, 1.36 g) of 3-bromophthalic anhydride in (20 ml) of dry benzene was refluxed for (6-8) hours. The solvent evaporated and formed precipitate collected and re-crystallized from absolute ethanol [17]. Physical properties are given in table (1).

2.3.3. Synthesis of 1,3-diazepine-4,7-dione [A_5 – A_6]: Aniline (0.002 mol, 0.18 g) was mixed with (0.001 mol) of the prepared 1,3-oxazepine derivatives [A_3-A_4] in (20 ml) dry benzene and placed in a round bottom with two holes, the first in which the condenser is placed for reflux and the second in which the $CaCl_2$ is placed. Refluxed for (5-8) hours. The formed precipitate was collected and recrystallized from ethanol [18, 19]. Physical properties are given in table (1).

Table (1): Physical properties and elemental analysis of prepared compounds [A_1-A_6]

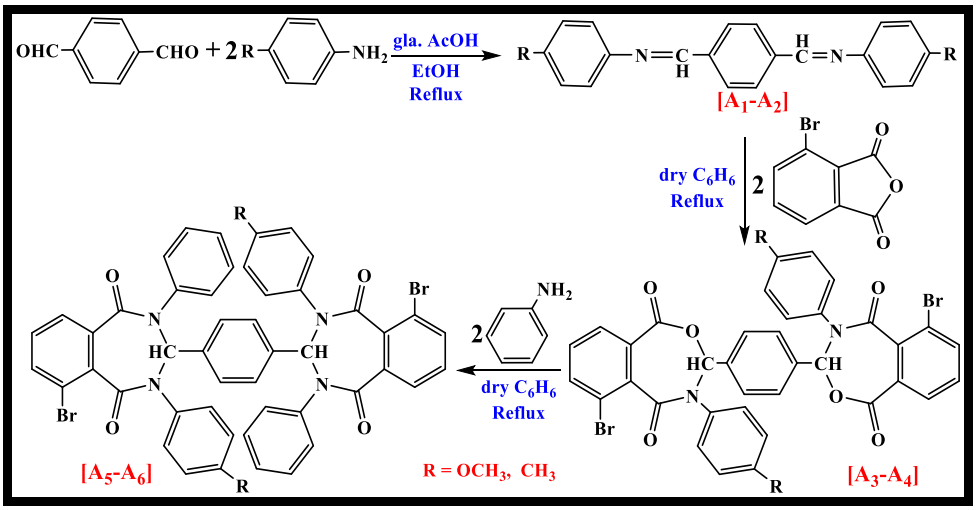
Comp. No.	R	Molecular Formula M. Wt.	Color	M.P (C^0)	T. Ref. (hr.)	Yield (%)	R.f. MeOH	found / (calc.) %		
								C%	**H%**	**N%**
A_1	OCH_3	$C_{22}H_{20}N_2O_2$ 344.41	Yellow	145-147	4	82	0.57	76.64 (76.72)	5.86 (5.85)	8.11 (8.13)
A_2	CH_3	$C_{22}H_{20}N_2$ 312.42	Light green	166-168	3	84	0.69	84.49 (84.58)	6.49 (6.45)	8.93 (8.97)
A_3	OCH_3	$C_{38}H_{26}N_2O_8Br_2$ 798.44	Gray	182-184	7	80	0.91	57.21 (57.16)	3.34 (3.28)	3.46 (3.51)
A_4	CH_3	$C_{38}H_{26}N_2O_6Br_2$ 766.44	Yellow	244-246	6	79	0.73	59.45 (59.55)	3.40 (3.42)	3.67 (3.66)
A_5	OCH_3	$C_{50}H_{36}N_4O_6Br_2$ 948.67	Light orange	249-251	6	70	0.38	63.24 (63.30)	3.84 (3.83)	5.88 (5.91)
A_6	CH_3	$C_{50}H_{36}N_4O_4Br_2$ 916.67	Light red	288-289	5	85	0.71	65.56 (65.51)	3.98 (3.96)	6.07 (6.11)

2.4. Antibacterial Activity

The antibacterial activity of compounds [A_1-A_6] were measured against two types of bacteria namely ***Eschershia coli*** **and** ***Klebislla Pneumonia*** **Gram (-) ve,** ***Staphylococcus aureus*** **and** ***Staphylococcus epidermidis*** **Gram (+) ve**, using the disk deployment method. The disks were full in DMSO. It was then dried in an incubator and then placed placed in the farms of bacteria. It should be noted that the DMSO control sample did not show any inhibition. Then the dishes were incubated at 37 ° C for 48 hours. The region of maximum inhibition was observed and measured against each type of bacterium used for the test. **Ampicillin**, **amoxicillin**, and **Ciprofloxacin** were used as control samples at three concentrations [20, 21].

3. Results and Discussion

In this research many compounds were prepared including Schiff bases, 1,3-oxazepine-4,7-dione and 1,3-diazepine-4,7-dione as in the scheme (1) and characterized by UV-Vis, FT-IR, ^{1}H-NMR Spectra and C.H.N analysis.



Scheme (1): Route of prepared compounds [A_1-A_6]

3.1. Characterization of Schiff bases [A_1-A_2]

The Schiff bases [A_1-A_2] were prepared by the reaction terephthaledyde with 2 mole of substituted aniline (4-methoxyaniline and 4-methylaniline) in absolute ethanol.

The FT-IR spectrum for Schiff bases showed the disappearance of two band due to amino group, beside new bands which appear at (1633-1650) cm^{-1} attributed to the azomethine (C=N) also the appearance of bands at (1458-1475) cm^{-1}, and (1580-1596) cm^{-1} due to (C=C) of aromatic ring. In addition, a band at (3041-3068) cm^{-1} attributed to (C-H) aromatic also the appearance of bands at (1098-1110) cm^{-1} due to (C-N) [22, 23], as shown in Fig. (1). U.V and FT-IR Spectrum are given in table (2).

Moreover the ^{1}H-NMR spectra of [A_1] Fig. (2) shows a clear singlet signal at δ= 9.00 ppm attributed to (N=C-H) (A) and a multiple signal in the range δ= 7.09-7.66 ppm for the aromatic protons (B,C,D), and singlet signal at δ= 4.02 ppm attributed to (OCH_3) (E) as well as singlet signal at δ= 2.50 ppm attributed to DMSO-d^6 (F) [24, 25].

3.2. Characterization of 1,3-Oxazepin-4,7-dione derivatives [A_3-A_4]

1,3-Oxazepin-4,7-dione derivatives [A_3-A_4]were prepared from the reaction 2 mole of 3-bromophthalic anhydride with Schiff bases [A_1-A_2] in ethanol.

The FT-IR spectrum showed disappearance of band azomethine (C=N) group, beside new bands appear at (2941-2973) cm^{-1} and (2842-2864) cm^{-1} attributed to the (CH) aliphatic as well as the appearance of band at (1722-1729) cm^{-1} and (1657-1658) cm^{-1} due to (C=O) for lactone and lactam compounds respectively. Besides other bands at (1575-1585) cm^{-1} and at (1461-1495) cm^{-1} due to (C=C) aromatic ring, and at (3064-3066) cm^{-1} for aromatic (C-H) as shown in Fig. (3). U.V and FT-IR spectrum are given in table (2) [26, 27].

Moreover, the ^{1}H-NMR spectra of compound [A_4] Fig. (4) showed multiple signal at δ=7.08-8.28ppm due to aromatic rings (A,B,C,D,E,F), and singlet signal at δ= 6.47 ppm due to (C-H) oxazepine ring (G), and singlet signal at δ=2.68 ppm due to (CH_3) (H), as well as singlet signal at δ=2.50 ppm due to DMSOd^6 (I) [28, 29].

3.3. Characterization of 1,3-Diazepin-4,7-dione derivatives [A_5-A_6]

1,3-Diazepin-4,7-dione derivatives [A_5-A_6] were prepared from the reaction of 1,3-oxazeepin-4,7-dione [A_3-A_4] with 2 mole of aniline in dry benzene.

The FT-IR spectrum showed disappearance of band (C=O) lactone, and bands appear at (1639-1661) cm^{-1} due to (C=O) for lactam. Besides other bands at (3053-3076) cm^{-1} for (C-H) aromatic, as well as appear bands at (2929-2990) cm^{-1} and (2826-2842) cm^{-1} due to (C-H) aliphatic, and at (1533-1597) cm^{-1} and at (1473-1476) cm^{-1} due to (C=C) aromatic ring, and as shown in Fig. (5) and Fig. (7). U.V and FT-IR spectrum are given in table (2) [30, 31].

Moreover, the ^{1}H-NMR spectra of compound [A_5] Fig. (6) showed multiple signal δ= 7.09-8.70 ppm due to (CH) aromatic rings (A,B,C,D,E,F,G,H,I), as well as and singlet signal at δ= 6.47 ppm due to (C-H) diazepine ring (J), and singlet signal at δ= 3.70 ppm attributed to (OCH_3) (K), as well as singlet signal at δ= 2.50 ppm due to DMSOd^6 (L).

Moreover, the ^{1}H-NMR spectra of compound [A_6] Fig. (8) showed multiple signal δ= 7.755-8.24 ppm due to (CH) aromatic rings (A,B,C,D,E,F,G,H,I), as well as and singlet signal at δ= 6.50 ppm due to (C-H) diazepine ring (J), and singlet signal at δ= 2.37 ppm attributed to (CH_3) (K), as well as singlet signal at δ= 2.50 ppm due to DMSOd^6 (L) [32, 33].

Table (2): FT-IR and UV/Vis data of prepared compounds [A_1-A_6]

Comp. No.	R	$\lambda_{1\ max}$ nm $_2\lambda_{max}$ nm	IR (KBr) cm^{-1}					
Schiff bases derivatives [A_1-A_2]			**ν (C=N)**	**ν(C-H) Arom.**	**ν (C-C)**	**ν (C=C)**	**ν (C-N)**	**Other**
A_1	OCH_3	241 369	1633	3041	1110	1596 1458	1033	ν(C-H) *asy.,sym.* 2931, 2856
A_2	CH_3	250 388	1650	3068	1098	1580 1475	1046	ν(C-H) *asy.,sym.* 2865, 2818
1,3-oxazepin-4,7-dione derivatives[A_3-A_4]			**ν(C=O) lactone lactam**	**ν(C-H) Arom.**	**ν(C-H) Aliph.**	**ν (C=C)**	**ν (C-O) ν (C-N)**	**Others**
A_3	OCH_3	236 394	1729 1657	3066	2973 2864	1575 1495	1298 1145	ν(C-H) *asy.,sym.* 2973,2831
A_4	CH_3	242 378	1722 1658	3064	2941 2842	1585 1461	1247 1184	ν(C-H) *asy.,sym.* 2941, 2842
1,3-diazepin-4,7-dione derivatives[A_5-A_6]			**ν(C=O) lactam**	**ν(C-H) Arom.**	**ν(C-H) Aliph.**	**ν (C=C)**	**ν (C-N)**	**Others**
A_5	OCH_3	209 360	1639	3076	2929 2842	1533 1473	1191	ν(C-H) *asy.,sym.* 2929, 2842
A_6	CH_3	238 271	1661	3053	2990 2826	1597 1476	1159	ν(C-H) *asy.,sym.* 2990, 2821

3.4. Antibacterial activity

The effect of the prepared compounds **[A_1-A_6]** on the growth of bacteria, namely ***Eschershia coli, Klebsiella Pneumonia*** **Gram (-ve),** ***Staphylococcus aureus*** **and** ***Staphylococcus epidermidis*** **Gram (+ve)**. Antibacterial activity of the prepared compounds were studied and the results showed that some of the prepared compounds possess good antibacterial activity. The results of inhibition zone diameter (IZD) in millimeter are shown in table (3) [34], scheme (2–5).

Table (3): Antibacterial activity of the prepared compounds [A_1-A_6] and control antibiotic

Comp. No.	*E. Coil* Conc. mg/ml			*K. Pneumonia* Conc. mg/ml			*S. Aureus* Conc. mg/ml			*S. Epidermidis* Conc. mg/ml		
	25	**50**	**100**	**25**	**50**	**100**	**25**	**50**	**100**	**25**	**50**	**100**
A_1	2	5	5	2	4	5	2	3	4	2	4	5
A_2	1	2	3	0	2	2	1	2	4	2	3	5
A_3	2	3	4	1	4	5	2	4	5	0	2	4
A_4	2	3	4	2	2	5	0	1	4	1	3	4
A_5	2	3	5	0	1	2	0	3	4	1	4	5
A_6	1	1	1	2	4	5	1	2	4	0	2	3
Amoxicillin	2	3	4	2	4	4	2	3	4	1	2	3
Ampicillin	2	4	4	2	3	3	2	3	4	2	2	3
Ciprofloxacin	2	3	3	2	2	4	1	2	3	1	3	4
Blank disk	0	0	0	0	0	0	0	0	0	0	0	0

3.5. Influence of lasers on prepared compounds [A_1-A_6]

A laser device with a capacity of (5) milliwatt emits a laser beam in the visible region of the spectrum with a wavelength of (600-700) nanometers in continuous waves. The rays were fired at the prepared organic compounds [A_1-A_6] for periods of time (10, 20, 30) seconds. It was found that all the prepared compounds did not have an effect and did not decompose or polymerize when color and the melting point were measured. This denotes that the laser beams used did not affect the compounds. Since they are stable, as shown in the table (4) [35].

Table (4): The results of the irradiation of the compounds by laser beams

Comp. No.	10 S		20 S		30 S	
	M.P. ^{0}C	**Color**	**M.P. ^{0}C**	**Color**	**M.P. ^{0}C**	**Color**
A_1	145-147	Yellow	145-147	Yellow	145-147	Yellow
A_2	166-168	Light green	166-168	Light green	166-168	Light green
A_3	182-184	Gray	182-184	Gray	182-184	Gray
A_4	244-246	Yellow	244-246	Yellow	244-246	Yellow
A_5	249-251	Light orange	249-251	Light orange	249-251	Light orange
A_6	288-289	Light red	288-289	Light red	288-289	Light red

3.6. Influence of stereochemistry and heat of formation of compounds [A_1-A_6]

The prepared compounds [A_1-A_6] were also studied at the lowest energy level using the Chem Draw Professional 16.0 program at 2016 version, Fig. (9)-(14). Heat of formation of the prepared compounds [A_1-A_6] were also studied using the Chem3D 16.0 program, where schiff bases and the 1,3-diazepine-7,4-dion compounds showed a positive heat formation, indicating that the reactions of their preparation are endothermic while the 1,3-oxazepine -4,7- dione compounds showed negative formation temperature, which indicates that its preparation reactions are exothermic, as shown in the table (5) [36].

Table (5): Heat of formation Kcal/mol of synthesized compounds [A_1-A_6]

Comp. NO.	Heat of Formation KJ/mol
A_1	124.41
A_2	342.21
A_3	-554.05
A_4	-289.61
A_5	153.23
A_6	417.67

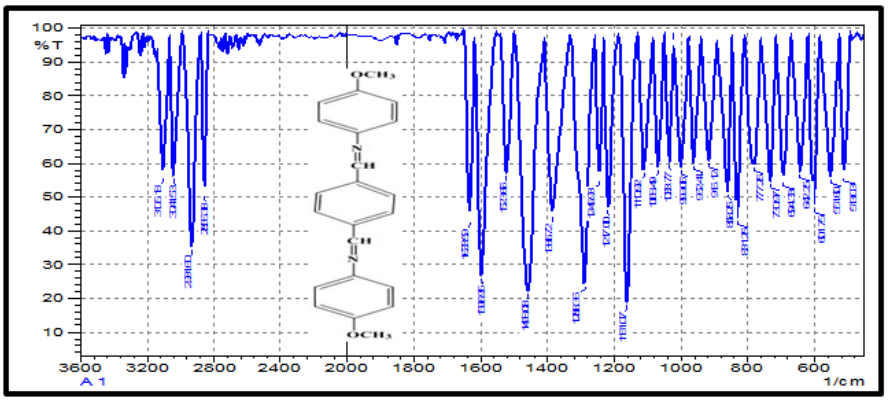


Fig. (1): FT-IR spectrum of compound [A_1]

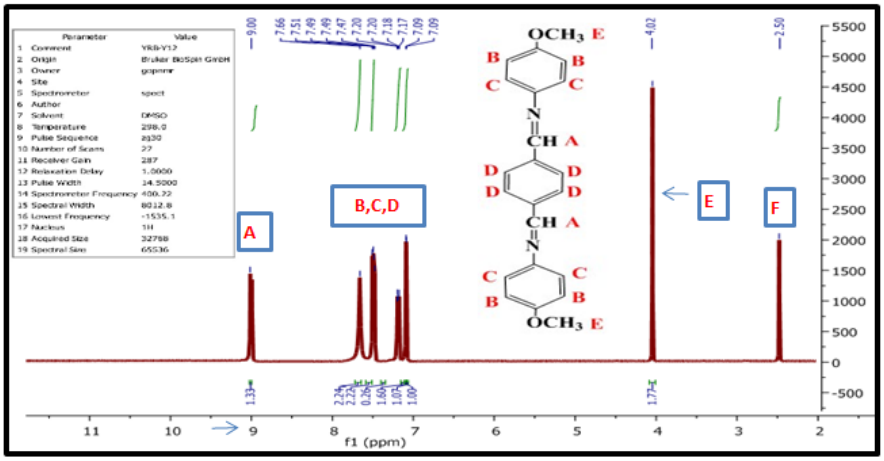


Fig. (2): ^{1}H-NMR spectrum of compound [A_1]

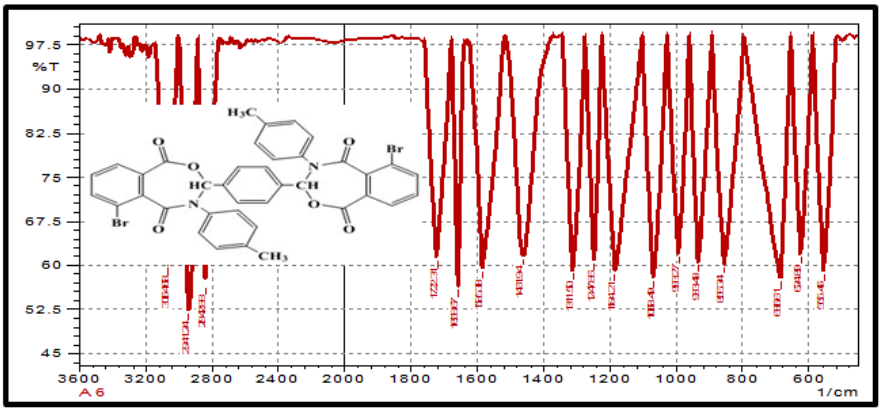


Fig. (3): FT-IR spectrum of compound [A_4]

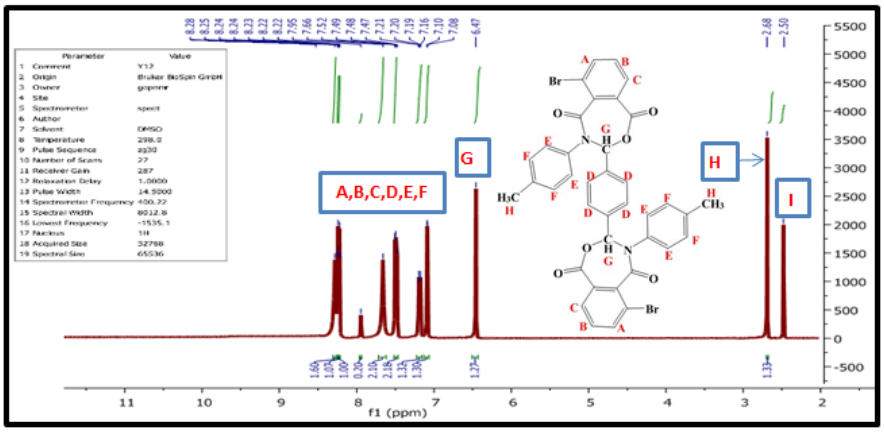


Fig. (4): ^{1}H-NMR spectrum of compound [A_4]

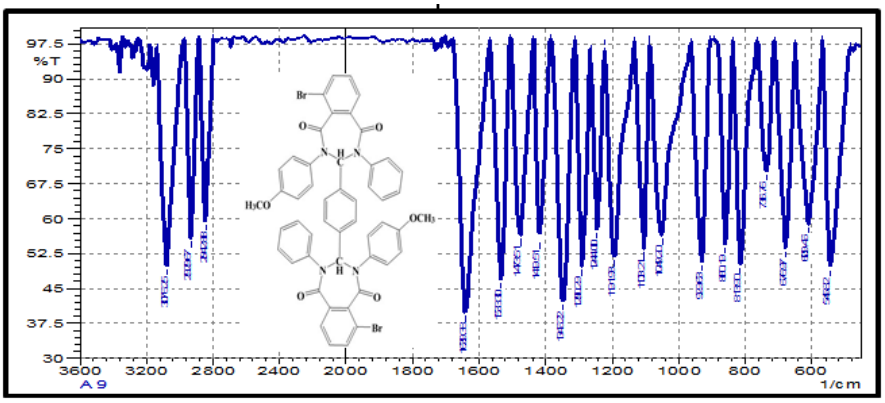


Fig. (5): FT-IR spectrum of compound [A_5]

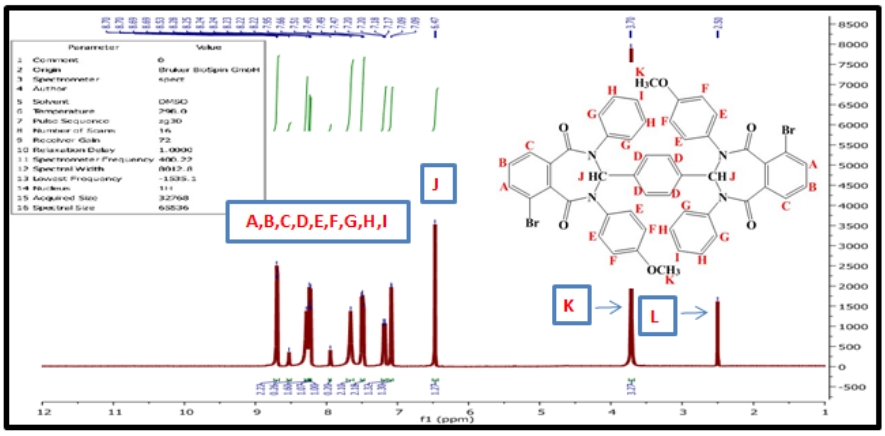


Fig. (6): ^{1}H-NMR spectrum of compound [A_5]

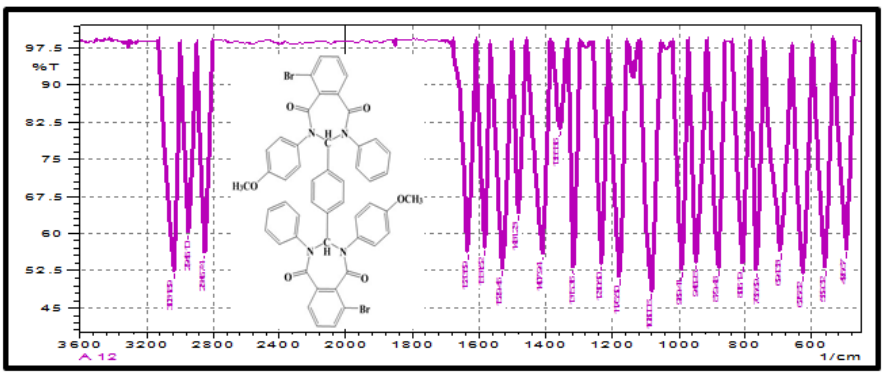


Fig. (7): FT-IR spectrum of compound [A_6]

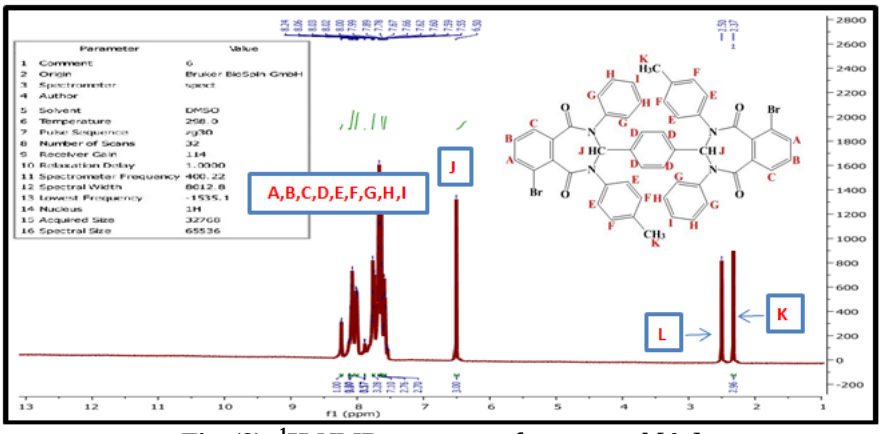
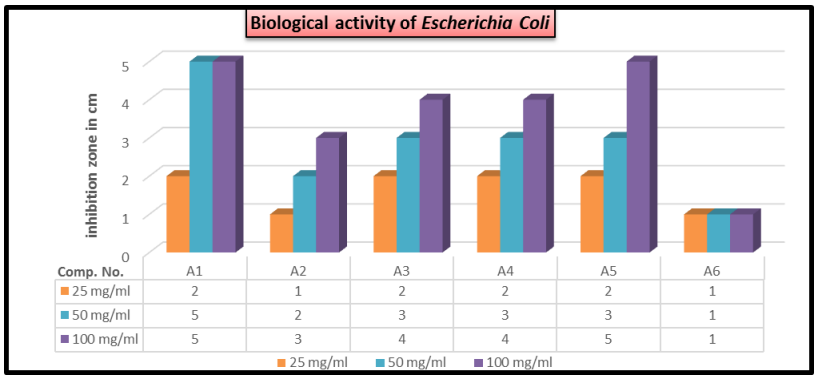
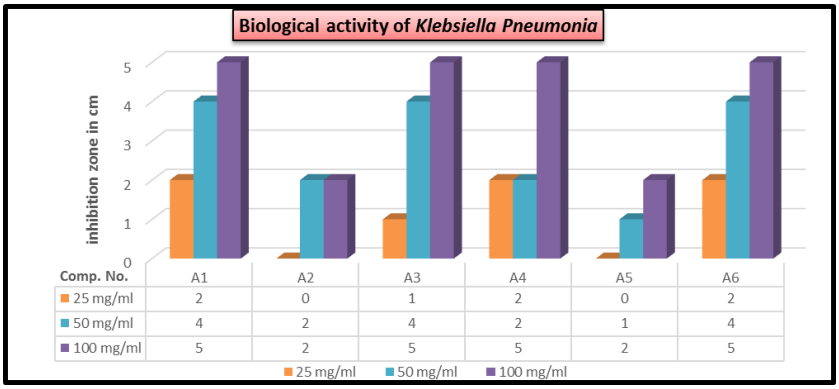


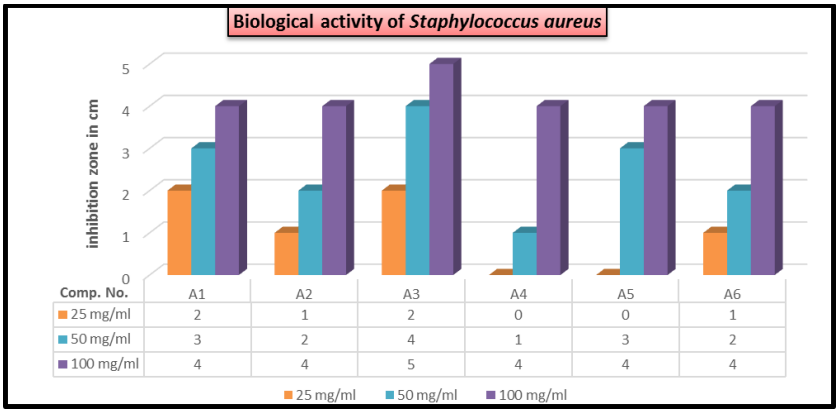
Fig. (8): ^{1}H-NMR spectrum of compound [A_6]



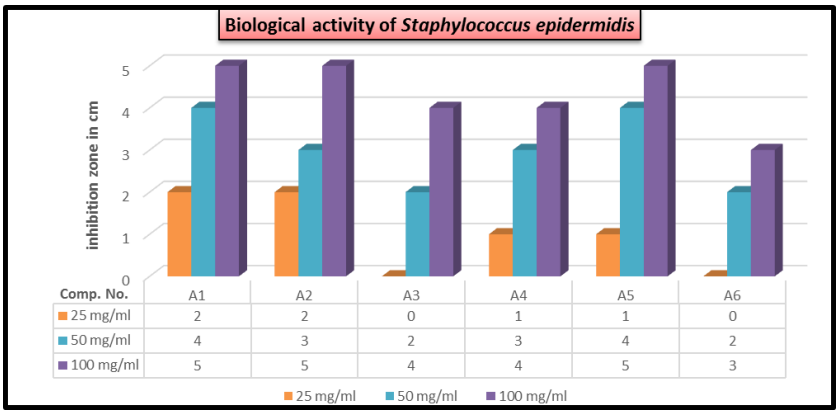
Scheme (2): Assess of inhibitory activity of [A_1-A_6] for *Escherichia Coli*



Scheme (3): Assess of inhibitory activity of [A_1-A_6] for *K. Pneumonia*



Scheme (4): Assess of inhibitory activity of [A_1-A_6] for *S. Aureus*



Comp. No.	A1	A2	A3	A4	A5	A6
25 mg/ml	2	2	0	1	1	0
50 mg/ml	4	3	2	3	4	2
100 mg/ml	5	5	4	4	5	3

Scheme (5): Assess of inhibitory activity of [A_1-A_6] for *S. Epidermidis*

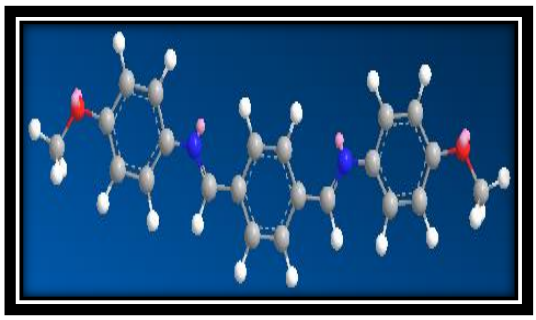


Fig. (9): Stereochemistry of compound [A_1]

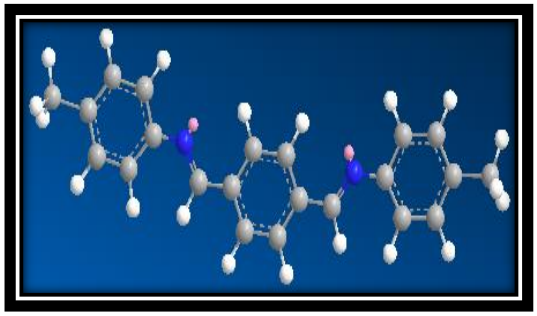


Fig. (10): Stereochemistry of compound [A_2]

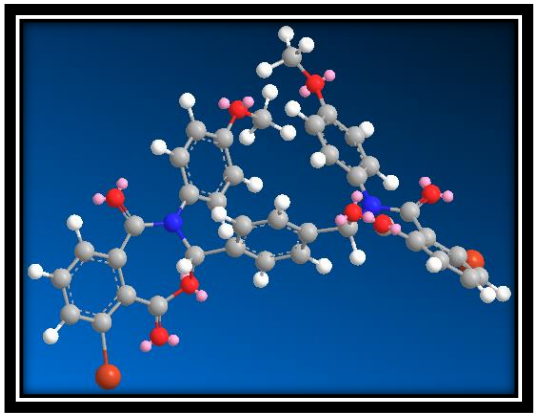


Fig. (11): Stereochemistry of compound [A_3]

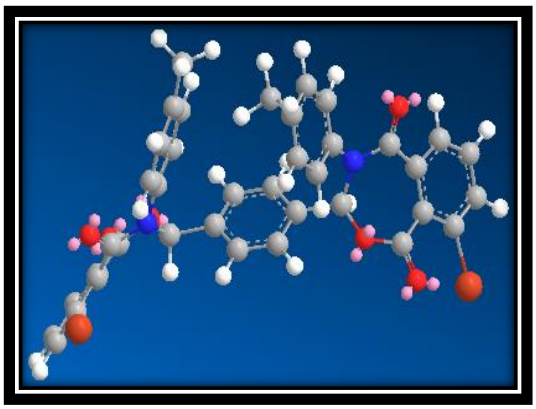


Fig. (12): Stereochemistry of compound [A_4]

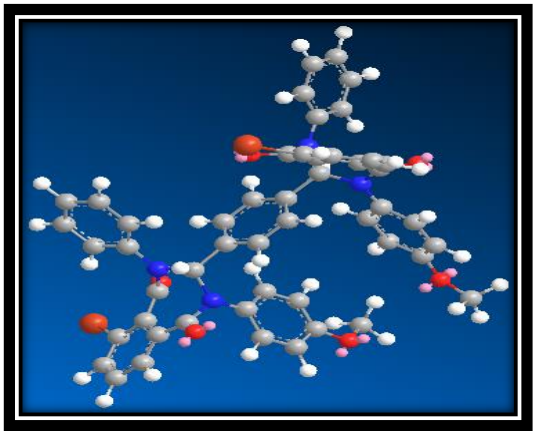


Fig. (13): Stereochemistry of compound [A_5]

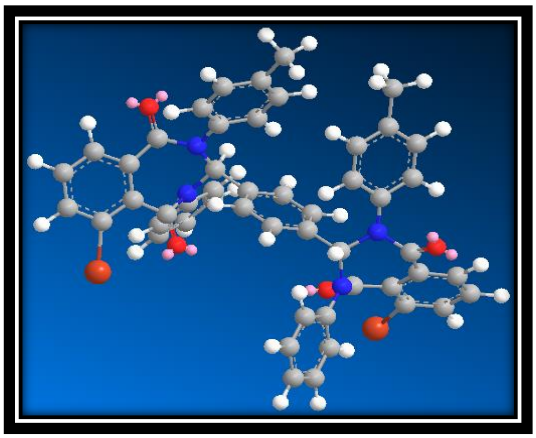


Fig. (14): Stereochemistry of compound [A_6]

4. Conclusions

The spectroscopic measurements used showed the accuracy of the compounds prepared. In addition, some of the prepared compounds showed good antibacterial activity against the antibacterial such as ***Eschershia coli, Klebislla Pneumonia*** **Gram (-ve),** ***Staphylococcus aureus*** **and** ***Staphylococcus epidermidis*** **Gram (+ve)**. The compounds [A_1-A_6] were radiated by laser for (10, 20, 30) seconds. It was found that all the prepared compounds did not have an effect and did not decompose or polymerize when color and the melting point were measured. This denotes that the laser beams used did not affect the compounds. Since they are stable.

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Credit authorship contribution statement

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تحضير وتشخيص مشتقات جديدة من 3,1- أوكسازبين و3,1- ديازبين وتقييم فعاليتها البايولوجية والليزرية

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الملخص

تم في هذا البحث تحضير بعض مشتقات قواعد شيف الجديدة [A_1-A_2] من خلال تفاعل مركب التريفثالديهايد مع معوضات بارا أنيلين (4- ميثوكسي أنيلين و4- مثيل أنيلين) بالإيثانول المطلق، ثم حولت قواعد شيف الى مشتقات 3,1- اوكسازبين [A_3-A_4] المقابلة من خلال تفاعلها مع 3- برومو فثاليك إنهيدريد ثم حولت الى مشتقات 3,1- ديازبين [A_5–A_6] المقابلة بتفاعلها مع الأنلين، بعد ذلك شخصت المركبات العضوية المحضرة بالطرائق الطيفية من أطياف الرنين النووي المغناطيسي للبروتون (^{1}H-NMR) والاشعة تحت الحمراء (FT-IR) والاشعة فوق البنفسجية (UV) والتحليل الدقيق للعناصر (C.H.N)، كما تم تقييم الفعالية المضادة للبكتريا للمركبات المحضرة [A_1-A_6] على أربعة أنواع مختلفة من البكتريا، وهي المكورات العنقودية الذهبية ***Staphylococcus aureus*** والعنقودية البشروية ***Staphylococcus epidermidis*** الموجبة لصبغة كرام Gram (+) ve واشريشيا القولون ***Eschershia Coli*** وكلبسيلا الرئوية ***Klebsiella Pneumonia*** السالبة لصبغة كرام Gram **(-)** ve والتي اظهرت فعالية جيدة تجاه انواع البكتريا قيد الدراسة، كما وتم تقييم الفعالية الليزرية للمركبات المحضرة [A_1-A_6] بتشعيعها بالليزر لمدة (10، 20، 30) ثانية، ولوحظ أنها لم تتأثر إذ لم تتحلل أو تتبلمر أو تتغير درجة انصهارها أو يتغير لونها. وتمت دراسة الهيئات الفراغية للمركبات المحضرة [A_1-A_6] عند أدنى مستوى للطبقة باستعمال برنامج ChemDraw Professional 16.0. فضلا عن دراسة حرارة تكوين المركبات المحضرة [A_1-A_6] باستخدام برنامج Chem3D 16.0.