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Synthesis and characterization of some 1, 3-oxazepine derivatives containing pyrimidine ring and study their antibacterial activity

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ABSTRACT

The research included the synthesis and Characterization of some oxazepine derivatives, synthesis of these compounds were performed in three steps: The first step. Reaction of the compound 2-aminopyrimidine with chloroasetohydrazid in presence of absolute ethanol [A_1], The second step. Reaction of [A1] with some benzaldehyde derivatives afforded Schiff bases [A_2-A_6].Step 3: In this step 1, 3 - (oxazepine) - 5, 7 dicarbonil [A_7 -A_{11}] were synthesized through reaction of Schiff bases[A_2-A_6]with 3,4-dimethylfuran-2,5-dioneunder reflux. The synthesized compounds were characterized by spectral and physical with such as UV, FTIR ,^{1}H-NMR, ^{13}C-NMR,Melting point and C.H.N.S. analysis. Antibacterial activity for some synthesized compounds have been tested on four know isolates bacteria, *Escherichia coli, Klebsiella pneumonia, Staphylococcus aurous* and *Staphylococcus Epidermidis*. Some compounds showed a good inhibitory against the bacteria used.

Keywords: ring-closing reaction, 1-3-oxazepine, 2-amino pyrimidine, hydrozones

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INTRODUCTION

Within medicinal chemistry, the rapid generation of a library of products to investigate structure-activity relationships is vital for the synthesis of biologically-active molecules and investigation of a biological hypothesis [1]. Significant additional diversity may be obtained by the late-stage functionalisation of advanced intermediates or complex natural products by exploiting existing functionality, whilst avoiding linear sequences and duplicated synthetic efforts [2]. Two examples extensively used within medicinal chemistry include fluorination [3], to adjust a drug's metabolic profile and properties, and C-H functionalisation [4], to introduce further complexity or add functionality. There are, however, draw-backs to this approach such as a lack of generality, functionalisation of only one site or even the formation intractable mixtures. An alternative less widely-investigated approach is exploitation of existing functionality by metamorphosing one heterocycle into another. Late-stage heterocyclic metamorphosis [5]allows for significant transformation of a molecule's physical properties, for example by altering the basicity, the dipole moment, and any hydrogen-bond affinity, as well as the geometrical configuration [6].

The new molecular scaffold generated, and the subsequent library of derivatives, can be screened for biological activity alongside the original heterocycle, allowing for rapid data generation. One important consideration of late-stage functionalization is that the method should be mild and chemo-selective and we believe that the Flow Photochemical Heterocyclic Metamorphosis (FP-HM) protocol detailed herein fulfils these requirements. We have directed our heterocyclic metamorphosis efforts towards transformations of the quinoline ring system, due to its importance in medicinal chemistry and as a privileged scaffold in the treatment of malaria (Scheme 1) and in anti-cancer drugs (Topotecan) [7]. Kaneko [8], Buchardt [9] and Albini [10] have observed that quinoline N-oxides (3) can be transformed into benzo [1,3]oxazepines (4), in variable yields when irradiated at >300 nminnon-hydrogen-bonding solvents. Benzo [1,3]oxazepines are an unusual heterocyclic system that have not been extensively reported [11] and although formally anti-aromatic, the 2-aryl derivatives are easily isolated and purified. Importantly, the seven-

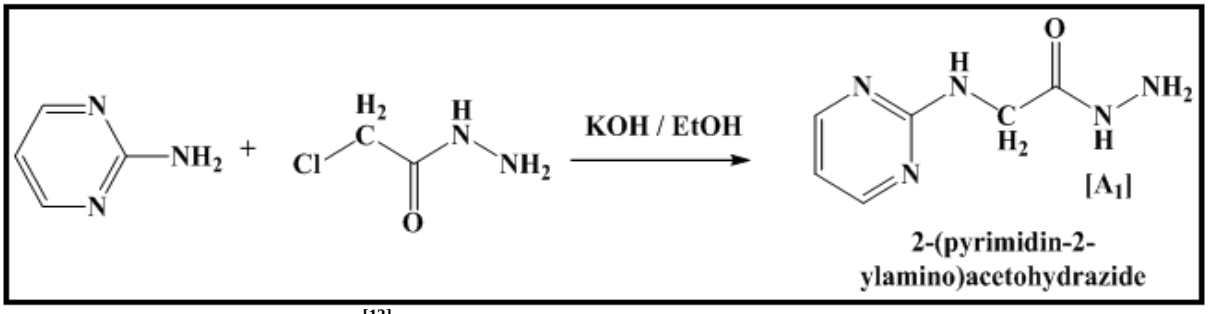
membered [1,3]- oxazepine ring leads to a slight geometrical distortion with respect to the quinoline ring system, and thus offers an interesting counterpoint to the parent quinoline for biological testing.

Experimental
Instruments and Chemicals

All melting points are uncorrected and are expressed in degree(^{0}C), using melting point SMP3. IR spectra were recorded as KBr disks using Shimadzu FT-IR 8400. ^{1}H NMR spectra were recorded using Varian VnmrJ 400 spectrometer (400 MHz) and tetramethylsilane (TMS) as internal standard using DMSO-d^6 as solvent the peaks showed at δ=(2.5-2.4)ppm,^{13}C NMR spectra were recorded using Varian VnmrJ 400 spectrometer (100 MHz) and tetramethylsilane (TMS) as internal standard using DMSO-d^6 as solvent Elemental analysis using Leco CHNS-933 Leco corporation st. Joseph ..

2- Synthesis Methods
Synthesis of compound [A_1][12]2-1

Added(0.001 mmol 11.5gm) 2-chloroacetohydrazide in (30 ml) of absolute ethanol and (0.001 mmol, 10 gm) of 2-amino-pyrimidine dissolved in (15ml) of the absolute ethanol in the presence of potassium hydroxide KOH (2.8gm), the mixture was refluxed for (14-15) hours and the reaction was confirmed by TLC and after the reaction the mixture was left to cool down and filtered precipitated, the product was recrystallized with chloroform and dried at a temperature of 50^{0}C. The output was 81% and melting point (208-210) and the coefficient of obstruction was Rf (0.80 and dark yellow).



Preparation of Schiff bases [A_2-A_6] [13]2-3

Dissolved (10gm, 0.0001mmol) of the compound [A_1] in (15ml) of absolute ethanol was add to (0.0001mmol) of benzaldehyde derivatives and after adding 4 drops of acetic acid the mixture refluxed for (6-5 hours) and the reaction was confirmed using the TLC technique, after the reaction was finished, the resulting mixture was slowly cooled, filtered and collected precipitated, recrystallized from Chloroform and dried at 50^{0}C. (Table1) shows some physical yield properties, percentage and Rf of Schiff base compounds [A_2-A_6], as in the following equation:

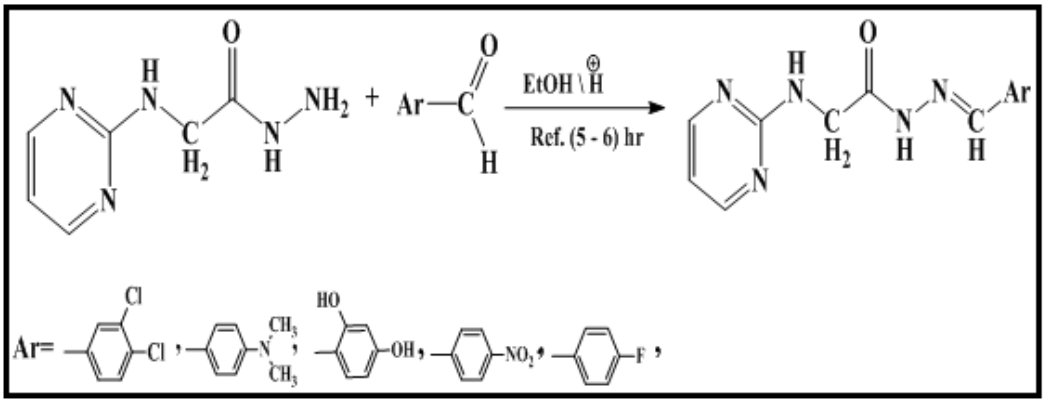
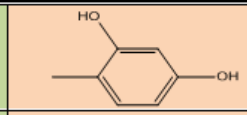
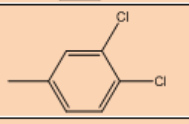
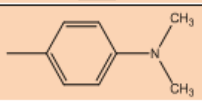


Table 1: Some Physical, yield Percentage and Rf Characteristics of Schiff Base Derivatives [A_2-A_6]

Comp. No.	Ar	Molecular Formula/ M.Wt g/mol	Color	M.P. (^{0}C)	Yield (%)	R f

A_2		$C_{13}H_{13}N_5O_3$ 357.6	Yellow green	244-246	65	0.64
A_3		$C_{14}H_{11}N_5OCl_2$ 324.1	Dark yellow	270-272	84	0.83
A_4		$C_{14}H_{19}N_6O$ 298.1	Red	260-262	62	0.61
A_5		$C_{13}H_{12}N_6O_3$ 300.1	Brown	246-248	79	0.79
A_6		$C_{13}H_{12}N_5OF$ 273.1	Light yellow	225-227	55	0.54

2-4: Synthesis of some 3.1-oxazpine-7, 4-di-one derivatives [A_7-A_{11}] [14].

Dissolved (0.0000069mmol) from some prepared Schiff bases [A_2-A_6] in (10ml) of dry gasoline and add to (0.0000069mmol) of 3,4-dimethylfuran-2,5-dionedissolved in (5ml) of the same solvent then the mixture ascended for (9-8) hours, and the reaction was confirmed using TLC technique. The mixture was cooled, filtered and washed with cold water, recrystallized with absolute ethanol and then dried at 50^0C. The following (Tables7-2) illustrate some of the physical and percentage characteristics (table2): Some Physical, Percentage and Rf properties of the derivatives of 3, 2-dihydro-3.1-oxazbine -7.4-di-on-[A_7-A_{11}] As in the following equation

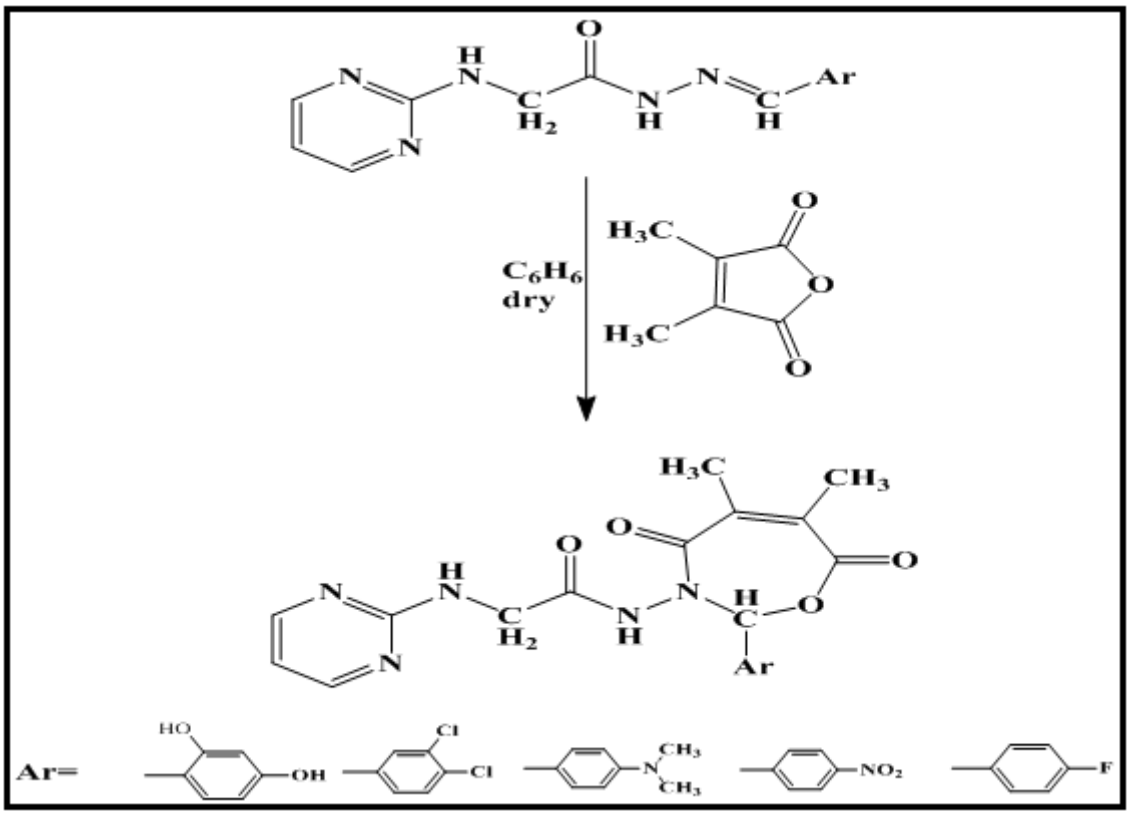
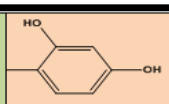
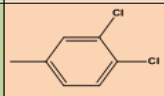
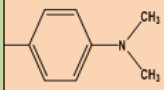
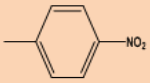
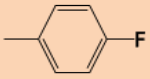


Table (2): Some Physical Properties, Percentage and Rf of Some Derivatives 6,5-Dimethyl-1, 3 -Oxazepine -7,4-Di-On [A_7-A_{11}].

Comp. No.	Ar	Molecular Formula/ M.Wt g/mol	Color	M.P. (^{0}C)	Yield (%)	R_f Solve. 1, 4-Diox.

A_7		$C_{19}H_{19}N_5O_6$ 413	Dark yellow	232-236	77	0.76
A_8		$C_{19}H_{17}C_{l2}N_5O_4$ 450	Light yellow	251-253	92	0.88
A_9		$C_{21}H_{24}N_6O_4$ 424	Orange	244-246	74	0.71
A_{10}		$C_{19}H_{18}N_6O_6$ 426	Brown	179-181	65	0.62
A_{11}		$C_{19}H_{18}N_5O_4F$ 399	Yellow	283-285	75	0.71

The Biological Activity [15]:

The bacteria species used are listed in (Table9). All strains were obtained from College of Education for Women, Tikrit University. They were grown up to the stationary phase nutrient bath at 37°C and a sample of 0.5 ml of each bacterium was spread over a surface of a nutrient agar plate.

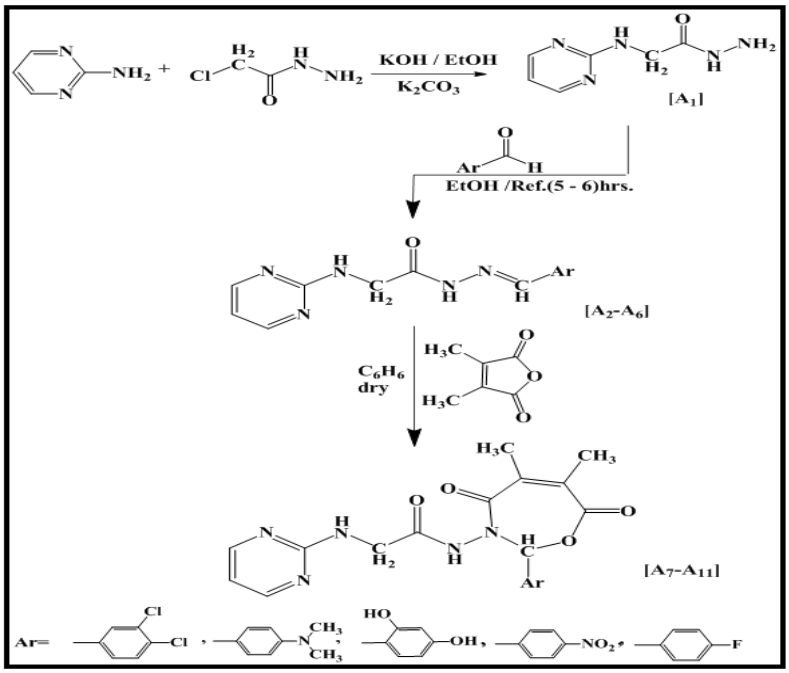
Antibacterial assay [16]:

Disc of filter paper (6 mm diameter) is sterilized at 140 ^{0}C for 1hr., and impregnated with the germs. DMSO was used as a solvent for compounds [A_1-A_{10}]. The same solvent was used for antibiotics (Amoxicillin, Ampicillin). Blank paper discs of DMSO was used as control. The inoculated plates are incubated at 37 ^{0}C for 24 hrs, the inhibition zone was measured. In all experiments the mean of each triplicate was measured.

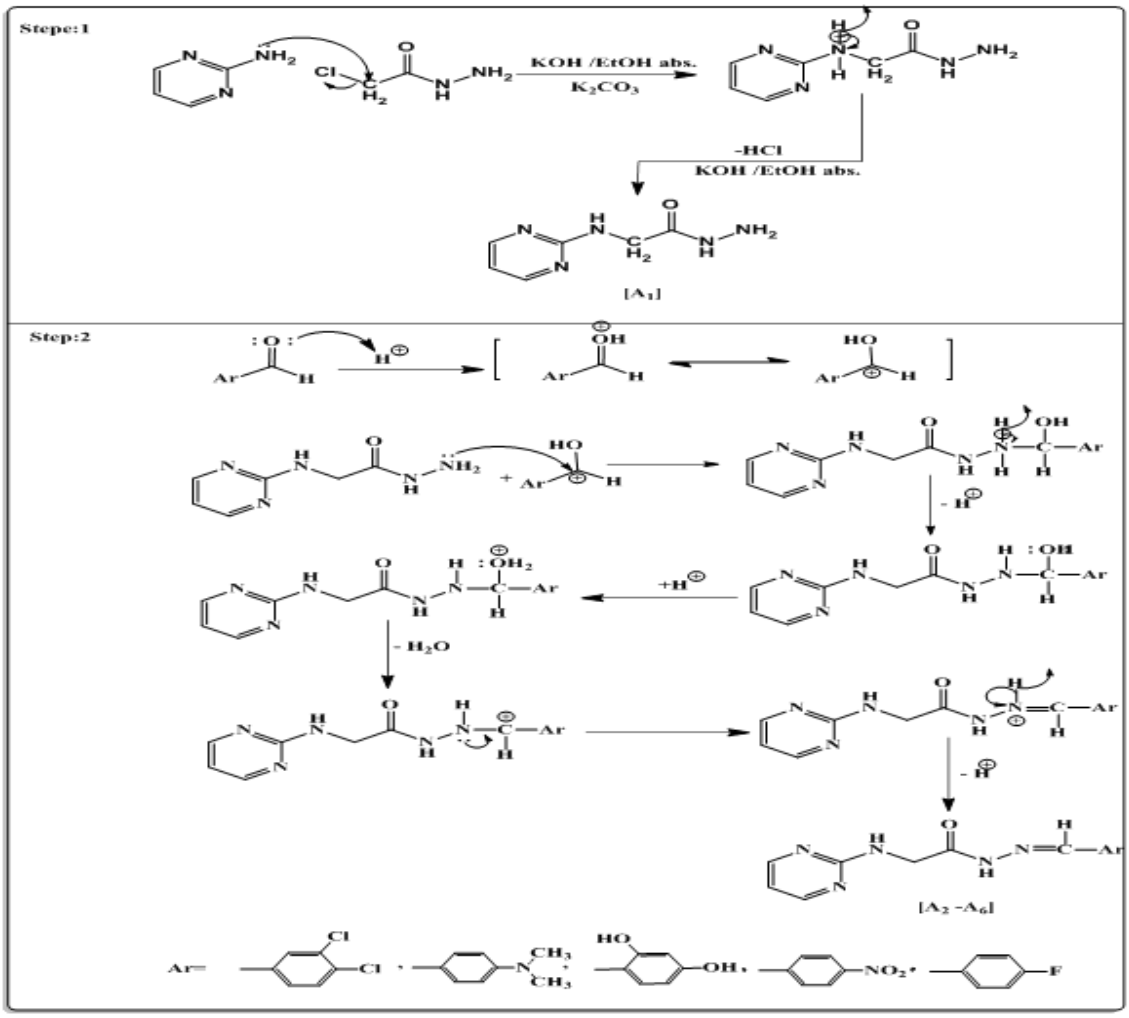
RESULTS AND DISCUSSION

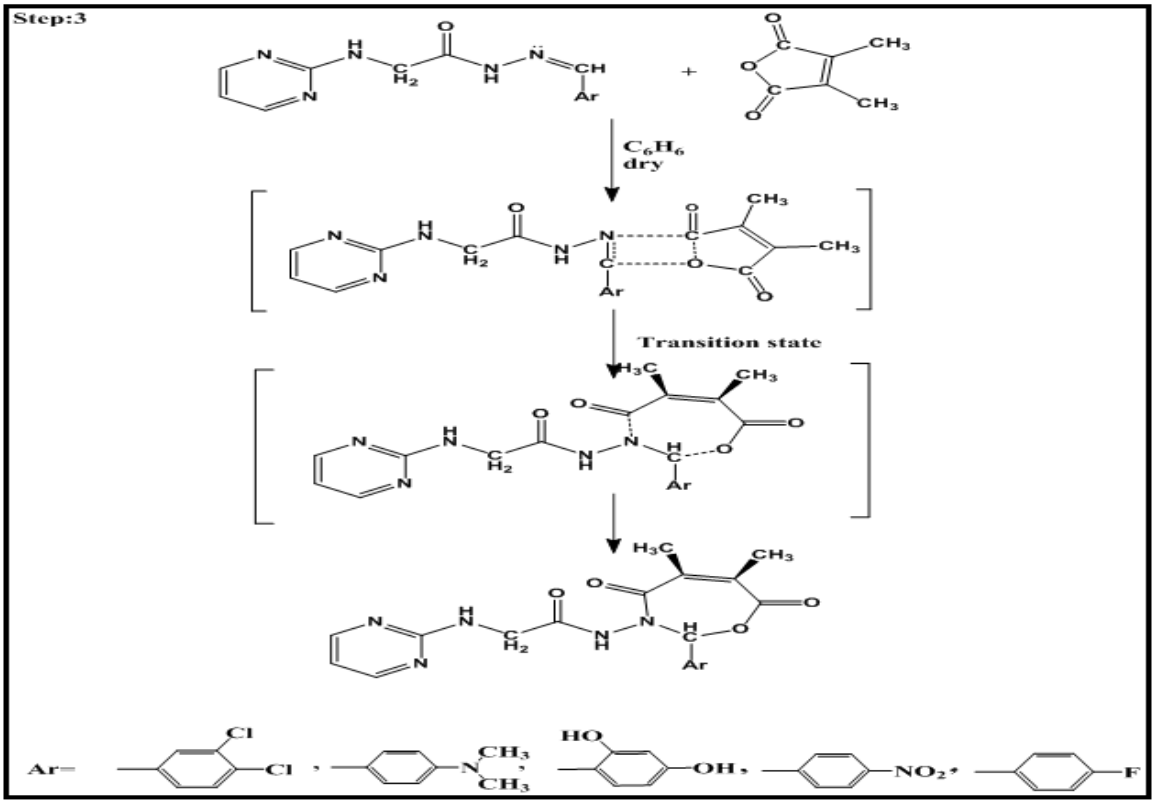
The synthesis of compound [A_1] and Schiff bases and5, 6-Dimethyl-1, 3 -Oxazpine -4, 7 -di-one are described in **(Scheme1):**

(Scheme1): synthesis of compounds [A_1-A_{11}].



(Scheme2): Mechanism [A_1-A_{11}].





Characterization compound [A_1][17].

FT-IR spectral data of novel hydrazide N-H, C=O and NH_2data between 3180-3055, 1662-1680 and3198, respectively. The streching data of C=O were 1734 cm^{-1} for compound 5, 1685 cm^{-1} for compound 6, respectively. In the 1H-NMR spectra of compound 1, for $–CH_2$ moiety 3.06 ppm as signal protons, characteristic signals for –NH-NH2 moiety have been detected 8.46 and 4.32 ppm as signal –NH and –NH2 protons respectively. FT-IR spectrum data are shown in Table (3).beside UV spectra, the transions n-π* and π-π* have confirmed the presence of the un-bonded pair electrons on nitrogen, oxygen atoms and aromatic system (double bond). UV and IR and 1HNMR absorbance spectra were given in table (3) and table (4) see fig (1)(3) (4)(7) and (8).

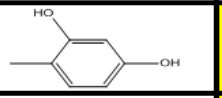
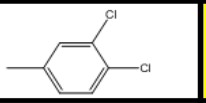
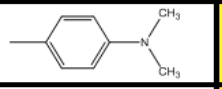
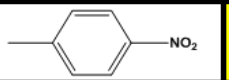
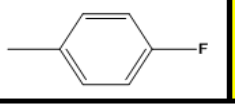
Characterization of Schiff Bases [A_2-A_6][18]

Hydrazones (A_2-A_6) have been characterised through (color, melting point), and the end of the interaction across of the thin layer chromatography (TLC) through emergence of a single spot. FTIR spectrum showed a band at the range (1663-1593) cm-1 for stretching vibration of (C=N) bond. It was noted the disappearance of symmetrical and asymmetrical stretchable absorption packages of the group (NH_2) belonging to hedrazaid at 3477 cm-1 and 3240 cm-1, which was evidence for reaction occur. FT-IR spectrum data are shown in Tables (3& 4). (^{1}HNMR) of compound (10) Showed a single package at (11.84) ppm due to amino group proton (N-H), fourpacks in the range (6.765-8.358) ppm due to protons of aromatic system (Ar-CH)[15]and a single package appeared at (8.397) ppm due to the proton of isomethene group(N = CH) , note (Figure5).

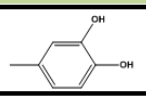
Characterization of 1, 3 –Oxazpine[A_7-A_{11}][19]

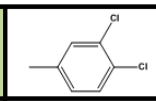
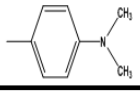
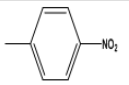
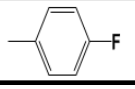
FT-IR spectrum sat the range (1704-1740) cm-1 for stretching vibration of lactone carbonyl (C=O) bond [16] , another vibration at (1678-1597) cm-1 due to stretching of lactam bond (–N–CO–). The other packages appeared in their expected position. FT-IR spectrum data are shown in Table (4&3).(^{1}HNMR) of compound (10) showed a multiple packages within the range (6.803 - 8.025) ppm attributable to protons of aromatic rings (Ar-CH), also noted the emergence of two single packages at (10.33-8.506) ppm due to amino group proton (NH)), a single package at (2.994) ppm, with the emergence of a single package at (6.753) ppm attributable to the proton of oxazepine group, as well as the compound showed a package at (11.34) ppm due to proton of implied hydrogen bond which formed by proton transfer from the amino group (N-H) to oxygen of carbonyl group[17],note (Figure6).

Table (3): FT-IR, UV/Vis. data of the prepared compounds [A_2-A_6].

Comp. No.	Ar	λ_1 max λ_2 max EtOH	IR (KBr) cm^{-1} ν (N-H)	ν (C=N) Sheiff	ν (C-H) Arom. Aliph.	ν (C=C) Arom.	ν (C=N) Pyi.	ν (C=O) Amid	Others
A_2		239 305	3184	1653	3009 2860	1622	1566	1662	ν (OH)3475
A_3		218 390	3184	1647	3090 2941	1620	1570	1666	ν (C-Cl)813
A_4		217 342	3178	1642	3053 2993	1606	1556	1674	νCH3 asy.sy.1500,1357
A_5		216 320	3201	1627	3051 2924	1527	1575	1666	$νNO_2$ asy.sy. 1520,1355
A_6		224 370	3149	1624	3045 2955	1527	1572	1680	ν (C-F)979

(Table4): FT-IR, UV/Vis. data of the prepared compounds [A_7-A_{11}].

Comp. No.	Ar	λ_1 max λ_2 max	IR (KBr) cm^{-1} ν (N-H)	ν(C-H) Arom.	ν(C-H) Aliph.	ν(C=N) Pyi. Lactone Lactam	ν (C=C) Arom.	ν (C-O)	ν (C-N)	Others
A_7		216 322	3178	3041	2964 2864	1587 1730 1685	1587 1468	1342	1263	ν (OH).(3488)

A_8		230 392	3190	3078	2970 2812	1587 1718 1679	1592 1491	1313	1247	ν (C-Cl) 811
A_9		242 315	3193	3053	2921 2882	1587 1718 1691	1578 1499	1315	1231	ν N (CH_3) *asy.*(1473) *sym.*(1367)
A_{10}		208 344	3195	3035	2921 2840	1569 1718 1674	1580 1475	1357	1277	ν (NO_2). *asy.*(1525) *sym.*(1394)
A_{11}		260 390	3190	3041	2981 2854	1564 1726 1668	1591 1474	1301	1280	ν (C-F) 815

(Table5): ^{1}H-NMR Data Compound [$A_1$and A_4]

Comp. No.	δ(C-H) Aromatic ppm m ,nH	δ(N=CH) Imine ppm s , 1H	δ(CH=N) pyrimidine ppm d , 2H	δ(CH=C) pyrimidine ppm t , 1H	δ(CH_2) ppm s , 1H	δ(NH-C=O) ppm s , 1H	Others ppm
A_1	……	……	6.79	7.95	3.56	8.46	(s,1H,NH-Pyi) 6.22(s,2H,NH_2) 4.15
A_4	7.55-7.93	8.49	6.87	7.95	3.96	10.43	(s,1H,NH-Pyi)5.89 (s,6H,CH_3)3.00

(Table6): ^{1}H-NMR Data Compounds [A_{10}].

Comp. No.	δ(C-H) Aromatic ppm m ,nH	δ(N=CH) Imine ppm s , 1H	δ(CH=N) pyrimidine ppm d , 2H	δ(CH=C) pyrimidine ppm t , 1H	δ(CH_2) ppm s , 1H	δ(NH-C=O) ppm s , 1H	δ(CH) oxazepineppm s , 1H	Others ppm
A_{10}	7.52-7.82	……..	8.84	6.57	3.57	10.16	8.85	(s,1H,NH -Pyi)5.89

(Table7): ^{13}C-NMR Data Compounds [A_1, A_4,A_5,A_7, and A_{10}].

A_1	^{13}C NMR (100 MHz, δ 40.58 (DMSO-d^6 solvent), δ (4CPyi.) 162.28, 157.33, 110.36, δ (CH_2)42.07. δ(C=O) 170.22
A_4	^{13}C NMR (100 MHz, δ 40.58 (DMSO-d^6 solvent) δ (4CPyi.) 162.28, 157.33,110.36, δ(C=O) 163.66, 1 δ($6C_{ar}$), 129.59, 127.31, 118.56, 111.50, 111.33,δ (CH_2)42.07 δ (=CH)149.44,δ($2CH_3$)39.93
A_5	^{13}C NMR (100 MHz, δ 40.58 (DMSO-d^6 solvent) δ(C=O)163.86, δ (4CPyi.)162.33, 157.33, δ ($6C_{ar}$),148.24, 146.04, 127.82, 123.03, 115.50, 114.86, 111.50, δ(CH_3) 56.06.
A_8	^{13}C NMR (100 MHz, δ 40.58 (DMSO-d^6 solvent) δ(2C=O) 169.64,168.81, δ (4CPyi.)166.69, 162.28,110.36, δ ($6C_{ar}$),148.24, 146.04, 127.82, 123.03, 115.50, 114.86, 111.50, δ($2CH_3$) 17.26,15.84, δ (CH_2)42.73
A_{11}	^{13}C NMR (100 MHz, δ 40.58 (DMSO-d^6 solvent) δ(2C=O) 169.64,168.81, δ (4CPyi.)166.69, 162.28,110.36, δ ($6C_{ar}$),148.24, 146.04, 127.82, 123.03, 115.50, 114.86, 111.50, δ($2CH_3$) 17.26,15.84, δ (CH_2)42.73

(Table 8): Elemental analysis of some of the prepared compounds.

Comp. No.	Molecular Formula	Found				Calculated			
		C%	H%	N%	S%	C%	H%	N%	S%
A_1	$C_6H_9N_5O$	43.11	5.43	41.89	……	43.6	5.35	41.79	……
A_4	$C_{16}H_{19}N_5O$	64.63	6.44	23.55	……	64.63	6.50	23.36	……
A_{10}	$C_{19}H_{18}N_6O_6$	53.52	4.26	19.71	……	53.45	4.33	19.70	……

Biological activity [14]:

The antimicrobial activity of the synthesized compounds [A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8, A_9, A_{10}] were examined by the agar diffusion method using four different bacterial species ***Escherichia coli, Klebsiella pneumoniae, Staphylococcus aurous*** and ***Staphylococcus Epidermidis***. The results indicated that some of the assayed compounds showed a microbial activity against the used bacteria. Antibacterial activity of compounds [A_1, A_2, A_7, A_8] were given in fig (10) and (11). Evaluation of inhibitory activity of compounds prepared is given in fig (**12-15**).

(Table9): Antibacterial activity of some of the prepared compounds.

Comp. No.	Conc. mg/ml	*E. Coil*	*K. Pneumonia*	*S. Aureus*	*S. Epidermidis*	Inhibition distance
A_1	25 50 100	+ ++ +++	++ +++ +++	- + ++	- + +	0 1-2 1-4
A_2	25 50 100	+ ++ +++	++ +++ +++	+ ++ +++	+ +++ +++	1-2 1-5 4-5
A_3	25 50 100	+ +++ +++	+ ++ +++	++ ++ +++	+ +++ +++	1-4 2-5 4-5
A_4	25 50 100	+ +++ +++	+ ++ +++	- + ++	++ +++ +++	0-2 1-5 2-5
A_5	25 50 100	- ++ ++	- + ++	- ++ ++	- ++ ++	0 1-4 2-4
A_6	25 50 100	++ ++ +++	- + +++	- + ++	- ++ ++	0 1-4 2-4
A_7	25 50 100	- ++ +++	- + +	- + ++	+ ++ ++	2 1-4 2-4
A_8	25 50 100	- + +++	- + ++	- ++ ++	- ++ ++	0 1-3 2-4
A_9	25 50 100	- + ++	- ++ ++	- + ++	- + ++	0 1-4 2-4
A_{10}	25 50 100	- + ++	- + ++	- + ++	- + ++	0 1-2 2-4

(-) = No inhibition **(+) = Inhibition zone (1-2) cm**
(++) = Inhibition zone (2-4) cm **(+++) = Inhibition zone (4-5) cm**

Table (8): Antibacterial efficacy of control treatments (antibiotics) in the growth of a number of negative and positive bacteria (diameter of the inhibition circuit measured by cm).

Comp. No.	*Name*	*E. Coil*	*K. pneumonia*	*S. Aureus*	*S. Epidermidis*	*Conc. gm /ml*
1	Amoxicillin	2.8	2.7	3.0	2.5	0.1 0.01 0.001
2	Ampicillin	3.7	2.5	2.5	2	0.1 0.01 0.001
3	Blank disk	0	0	0	0	0.1 0.01 0.001

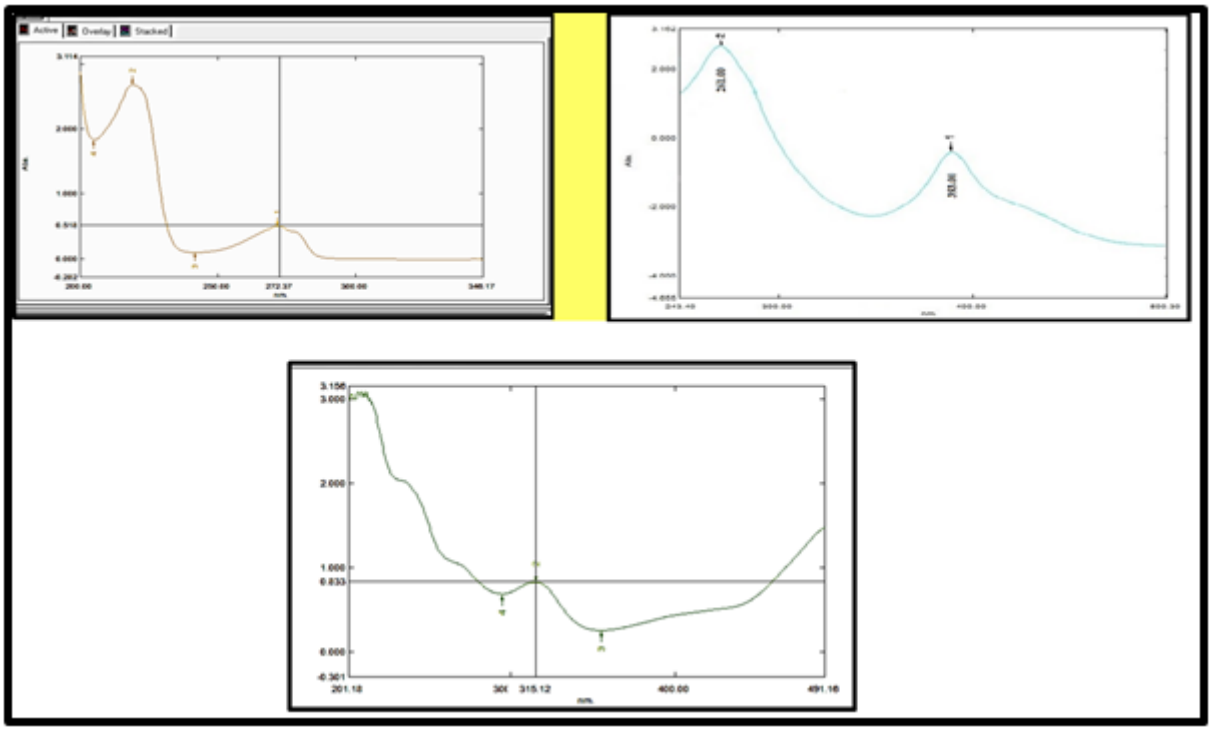


Fig (1): UV/Vis spectrum of compound [A_1,$A_{4and}A_{10}$].

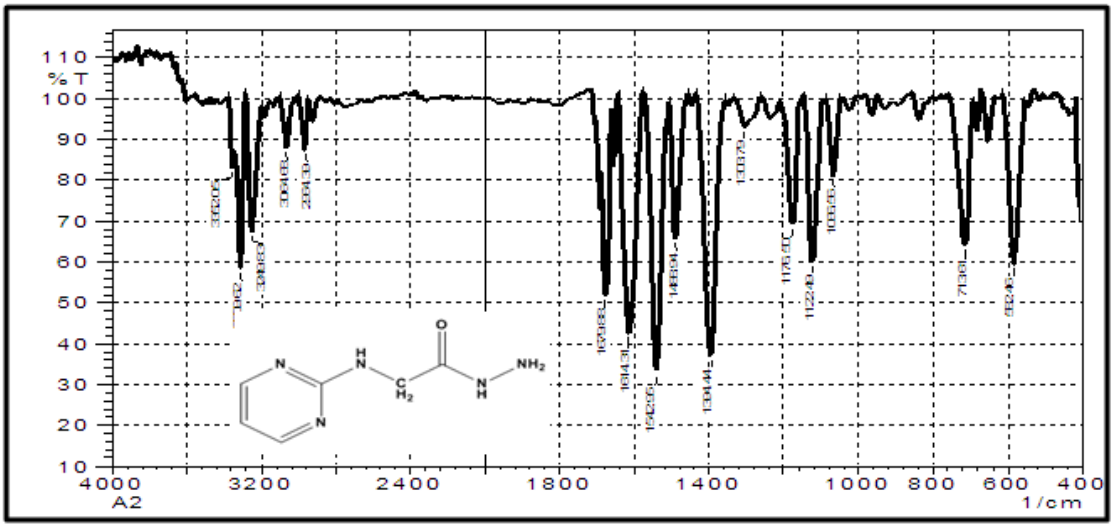


Fig (2): FT-IR spectrum of compound [A_1].

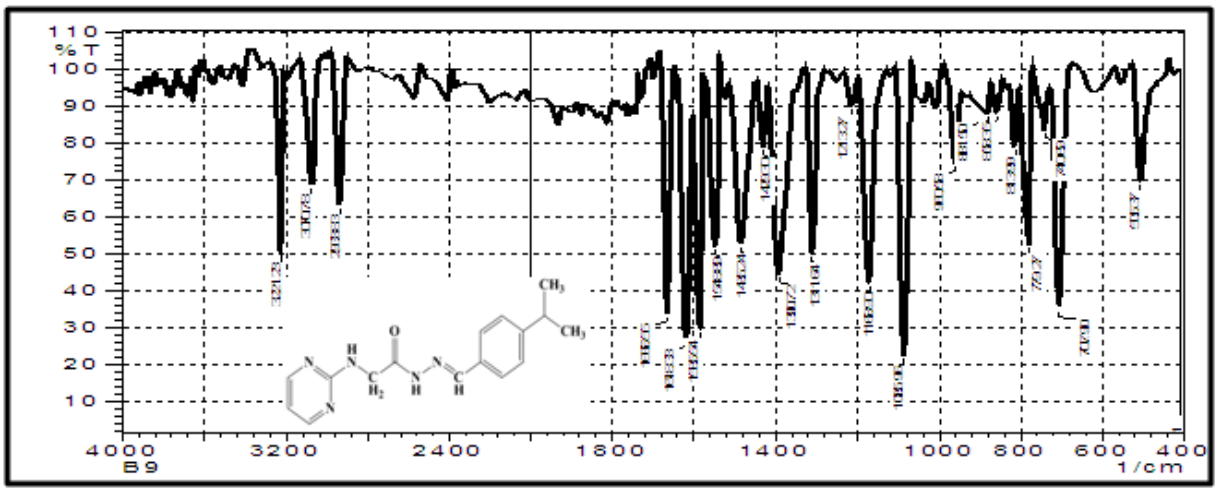


Fig (3): FT-IR spectrum of compound [A_4].

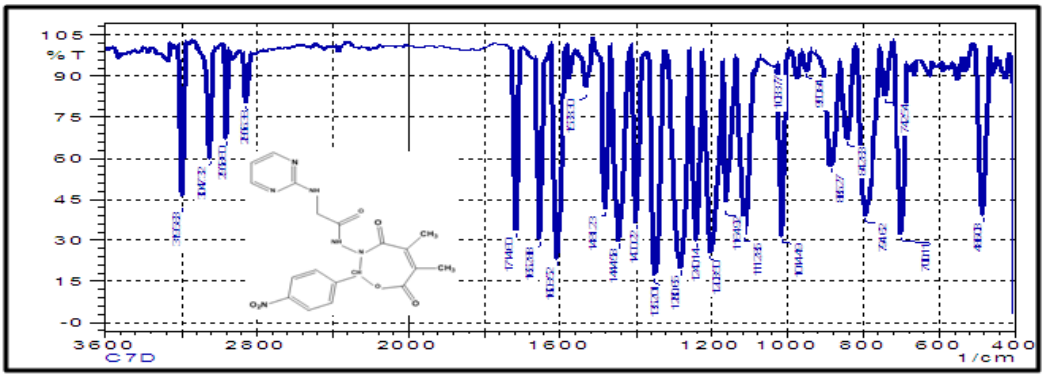


Fig (3): FT-IR spectrum of compound [A_{10}].

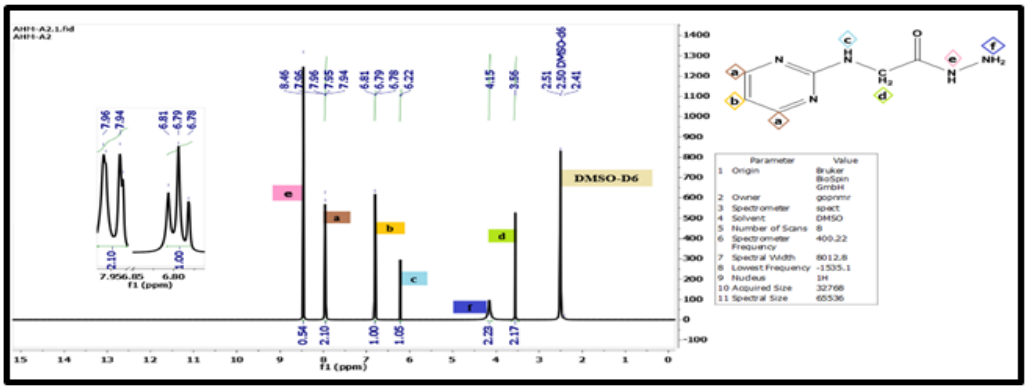


Fig (4): ^{1}H-NMR spectrum of compound [A_1].

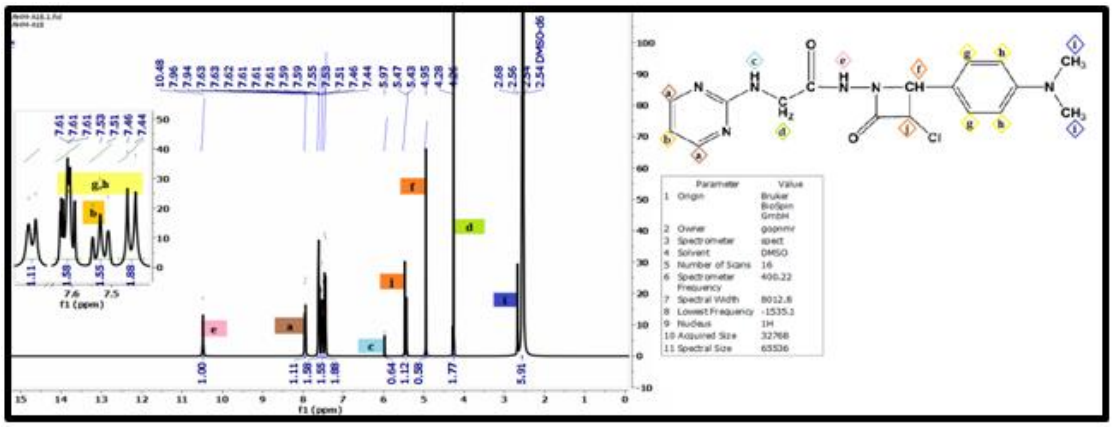


Fig (5): ^{1}H-NMR spectrum of compound [A_4].

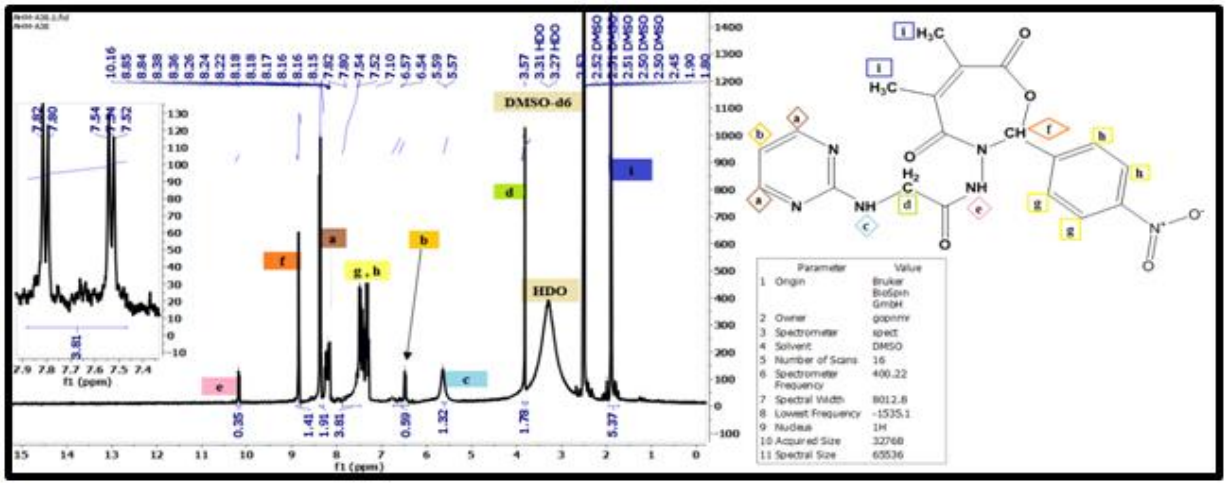


Fig (6): ^{1}H-NMR spectrum of compound [A_{10}].

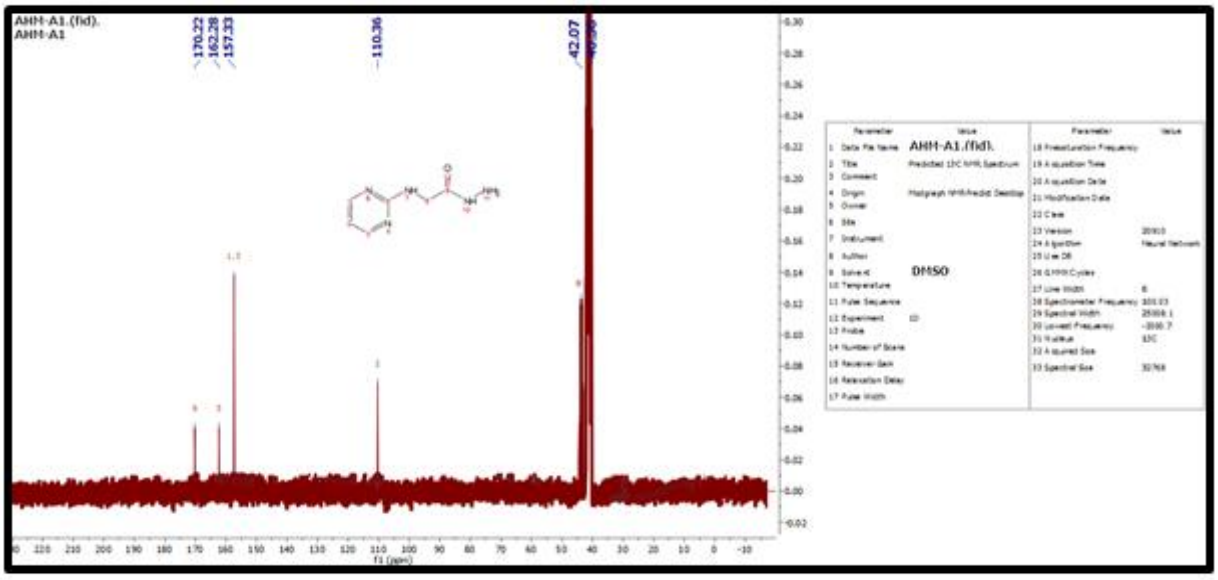


Fig (7): ^{13}CNMR spectrum of compound [A_1].

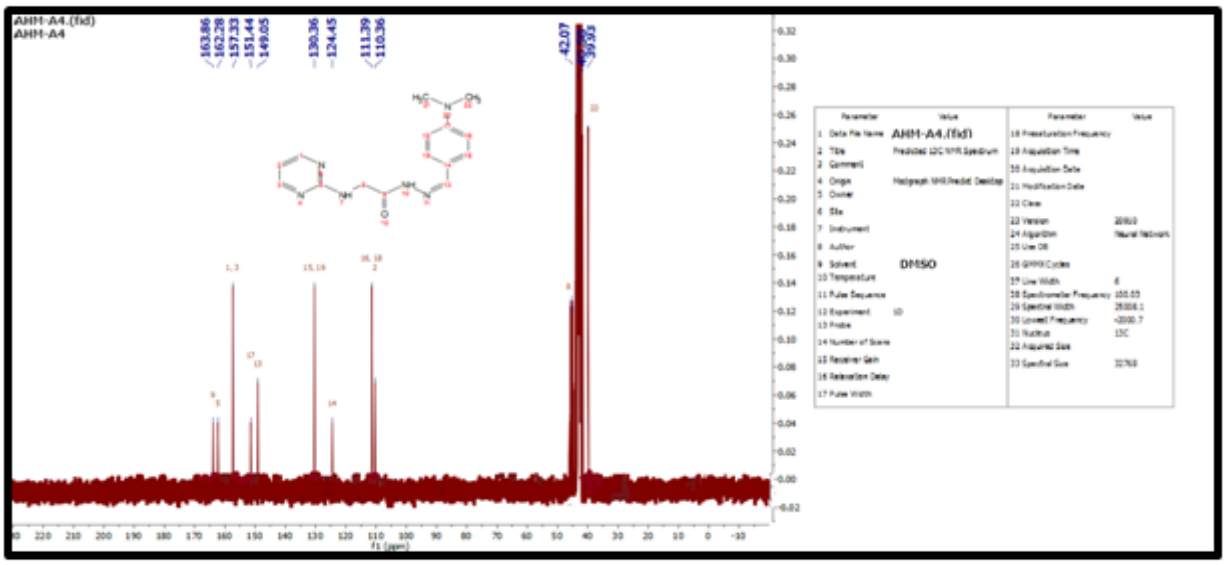


Fig (8): ^{13}CNMR spectrum of compound [A_4].

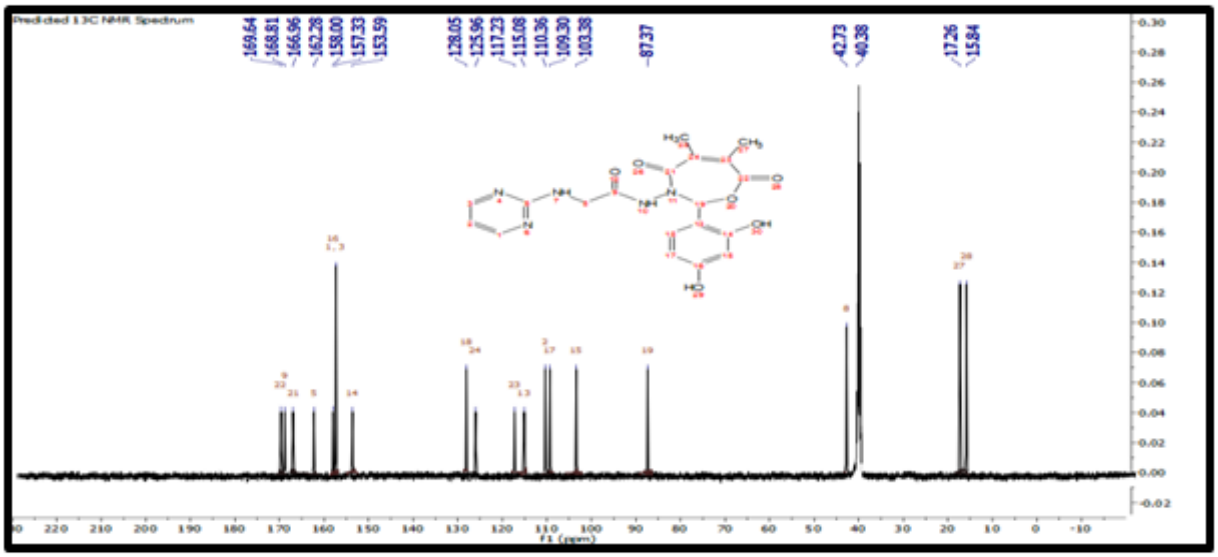


Fig (9): ^{13}CNMR spectrum of compound [A_8].

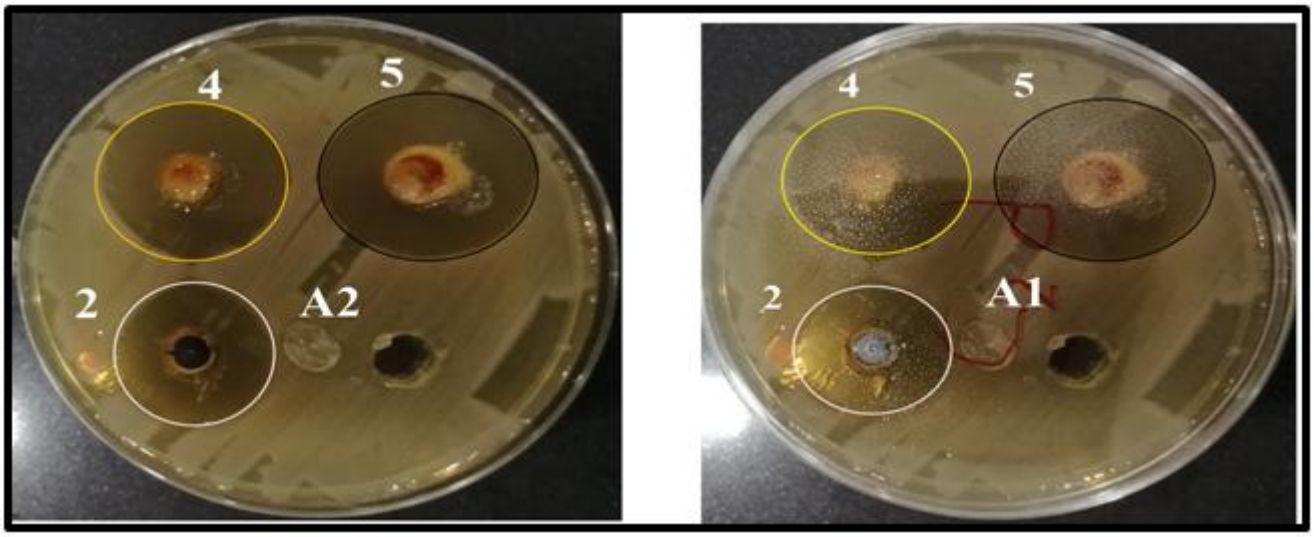


Fig (10): Antibacterial activity of compounds [A_1, A_2] against *Escherichia coli*.

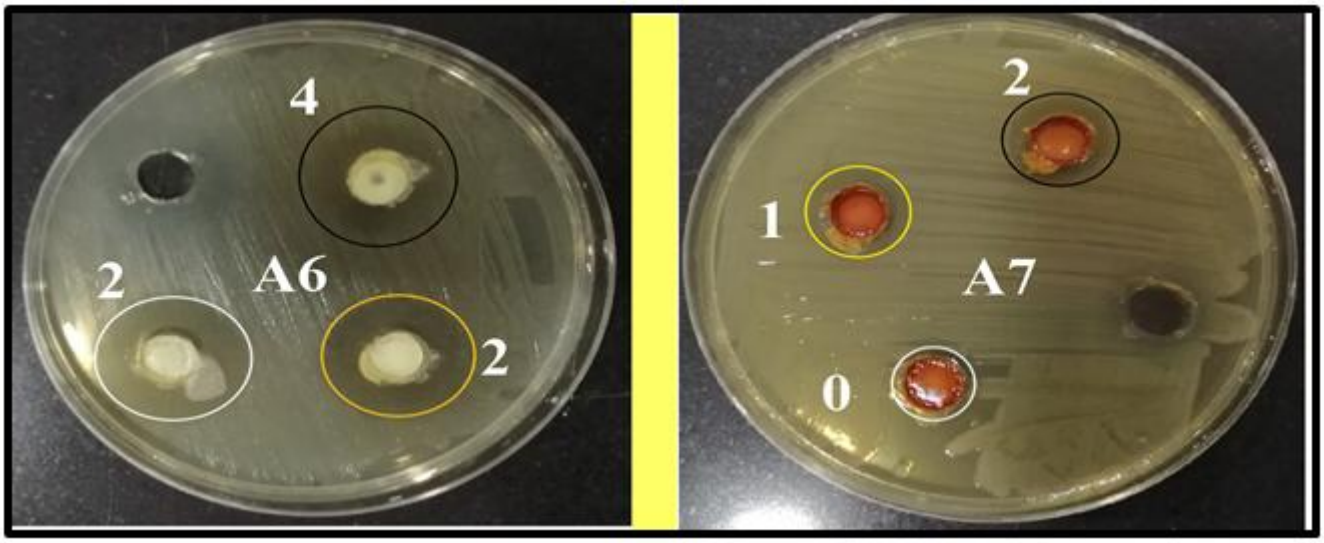


Fig (11): Antibacterial activity of compounds [A_6 , A_7] against *Klebsiella pneumonia*.

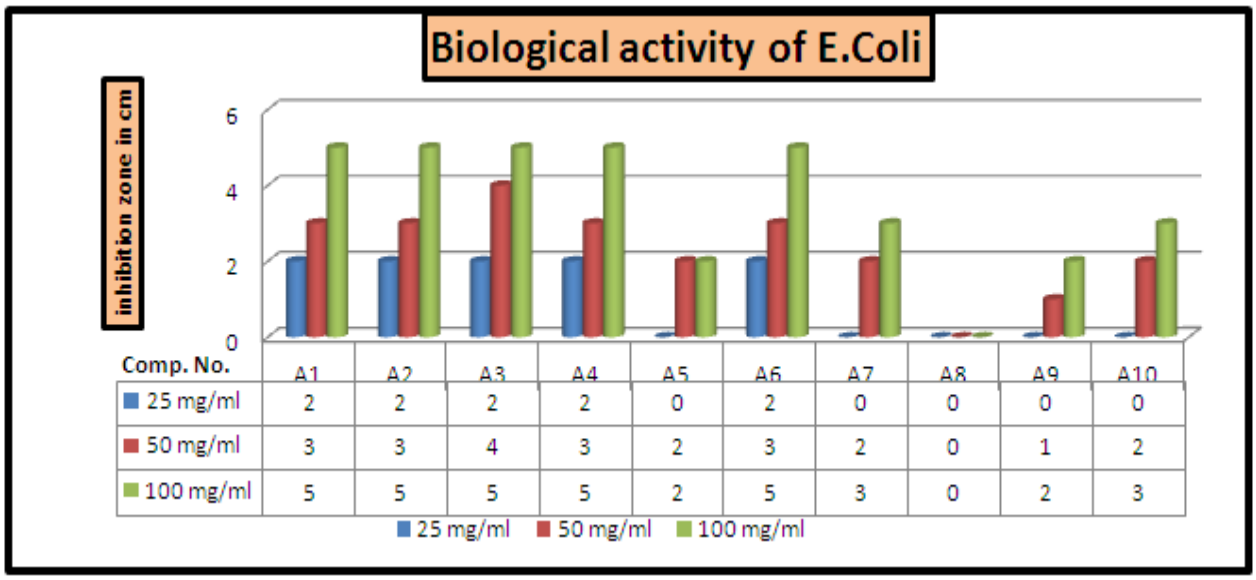


Fig. (12): Evaluation of inhibitory activity of compounds prepared for *Escherichia coli*.

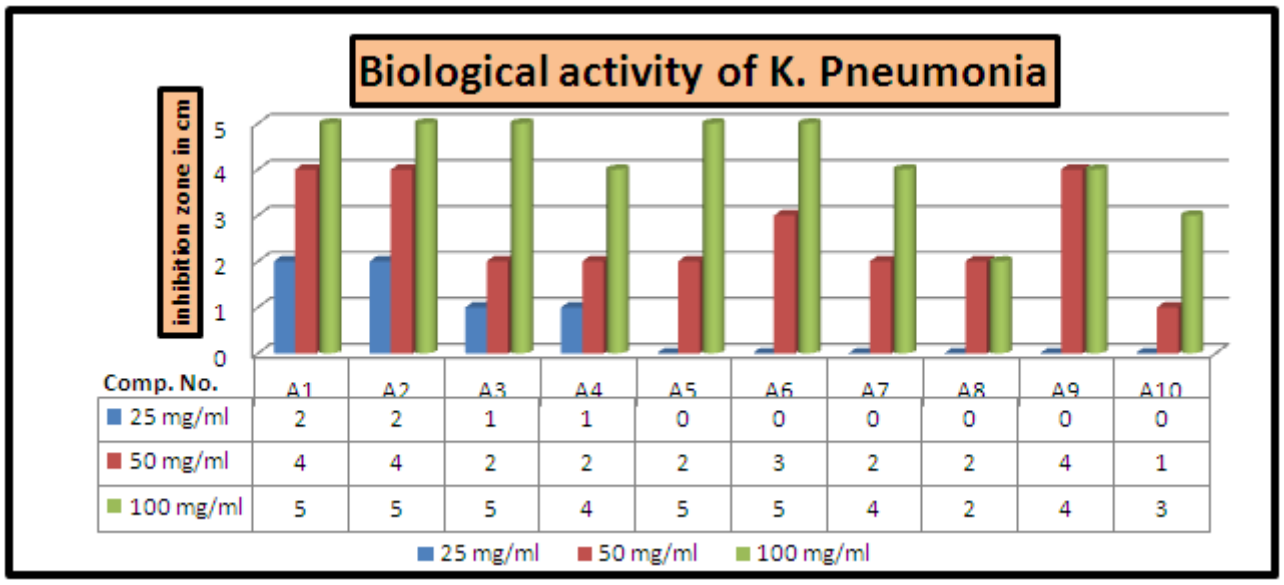


Fig. (13): Evaluation of inhibitory activity of compounds prepared for Klebsiella pneumoniae.

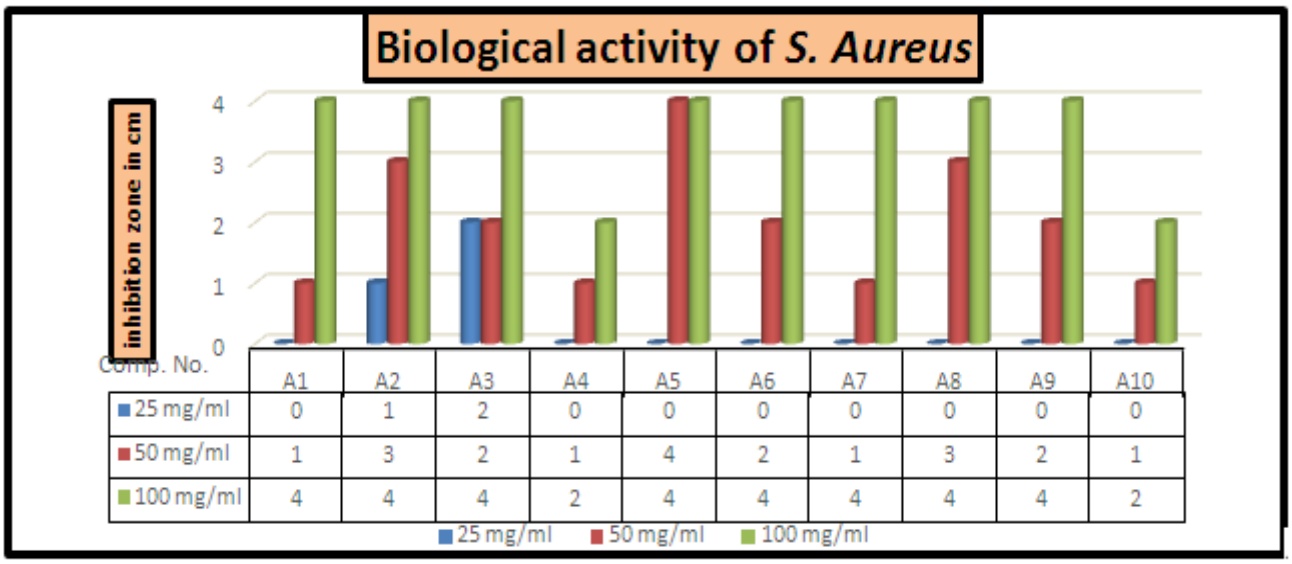


Fig. (14): Evaluation of inhibitory activity of compounds prepared for *Staphylococcus aureus.*

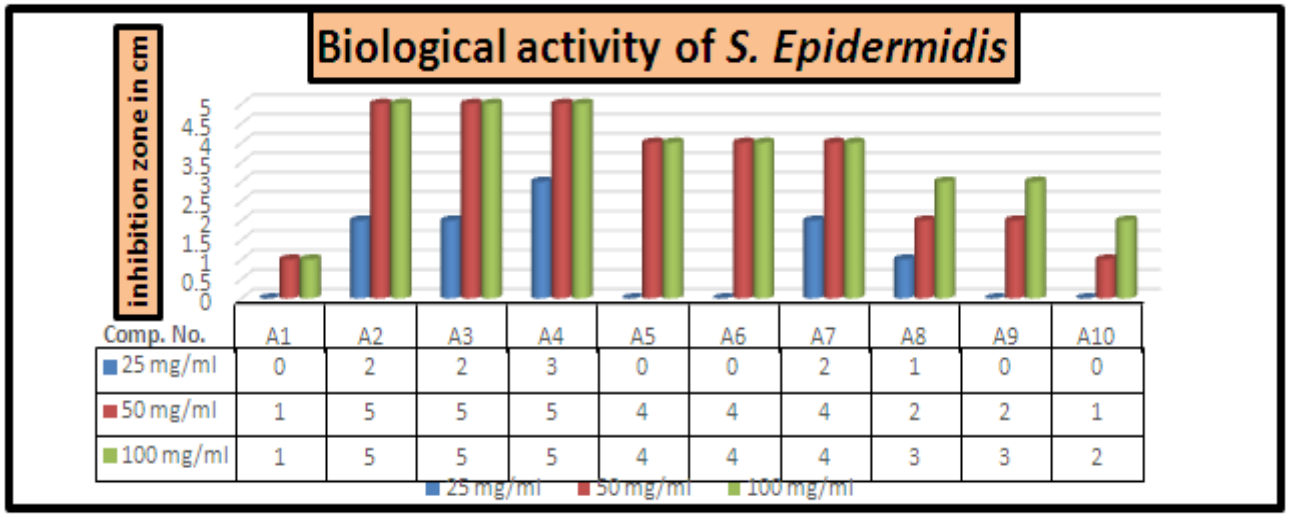


Fig. (15): Evaluation of inhibitory activity of compounds prepared for*Staphylococcus Epidermidis.*

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