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Synthesis, Characterization of Some New Azo Compounds Containing 1,3-Oxazepine, Anthraquinone Moieties and Studying Their Activity against Pathogenic Bacteria

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Abstract
This research includes design of new derivatives for anthraquinone azo compounds bearing 1,3-oxazepine rings with different saromatic moieties. Diazonium salt of 1-aminoanthraquinone [1] prepared by reaction of 1-aminoanthraquinone with ammonium nitrite in the presence of hydrochloric acid. Then this compound used to prepare of azo derivative [2] through reaction with *o*-Salicyladehyde. Compound [2] then converted into different Schiff bases [3-8] by treating it with different amino benzenes in absolute ethanol. Finally 1,3-Oxazepine compounds [9-14] and [15-20] obtained from reaction of Schiff bases [3-8] with phthalic anhydride and maleic anhydride respectively. Physiochemical properties of synthesized compounds determined by their melting points, FTIR, ^{1}HNMR and ^{13}CNMR spectroscopy. The purity and reaction time were checked by TLC. The new prepared 1,3-oxazepine compounds were evaluated against some pathogenic bacteria for their biological activity testing using three different bacterial species including (*Klebsiella sp., Streptococcus Pneumonia, Proteus sp.*) and compared with (amoxicillin tri hydrate) was used as references drug. The results showed that many of the tested compounds have moderate to good vital activity against the mentioned pathogenic bacteria compared with references drug above.
Keywords: Synthesis, Azo compounds, 1,3-Oxazepine , Anthraquinone, Activity.

1. Introduction
Azo compounds are a highly useful class of chemical compounds receiving attention in most scientific research. They are colored highly and have been used as pigments and dyes (Klaus 2005). Aromatic azo dyes are the important group of organic dyes for their widespread applications in many areas of textile, medicine (Abdolhamid 2015). Azo dyes are determined by the presence of a (R_1–N=N–R_2) functional group. The azo group often assists to stabilize the dyes and form a conjugated system, which absorbs visible frequencies of light producing colored compounds (Michael 2013). Some of azo pigments it has been reported that several bacteria and fungi are capable of mineralize and catabolize azo dyes (Perez-Diaz 2009). Prontosil and some sulfa drugs are also produced using this reaction (Wolff 2003).

Likely 9,10-anthraquinones (9,10-anthracenediones) are a very important class of compounds having some remarkable *in vivo* biological activities, such as antimalarial (Aliasghar 2012), antifungal (Rath 1995), antioxidant (Yen 2000), antibacterial (Younis 2012), antileukemic (Chang 1984), analgesic (Younos 1990), anticancer (Ge 1997), mutagenic functions (Ismail 1997) and hypotensive activity (Koumaglo 1992).

Oxazepines are important unsaturated seven-membered heterocyclic rings due to their wide spectrum of applications. The biological activities of 1,3-Oxazepine compounds were found in the research fields as having antihistaminic and antiallergic agents (Kubota 2011), hypnotic muscle relaxation (Abdel-Hafez 2008) and anti-inflammatory effects (Adnan 2014). Additionally these heterocycles with metals have shown antibacterial and antifungal activity (Serrano-Wu 2002), central depressant (Maysaloon 2014), analgesic (Hallinan 1993) and local anesthetic effects (Vardanyan 2006).

In this respect an attempt has been made to synthesize and characterize a new azo compounds derived from 1-amino anthraquinone and bearing seven membered heterocycles as 1,3-oxazepine rings with different aromatic moieties. These compounds has also been studied and characterized physicochemically and then vital test their effectiveness against bacterial pathogenesis

2. Experimental
2.1. Materials and Methods
All chemical materials, used in this research were supplied from BDH, G.C.C., Hopkins&William, Fluka, Merck, and Sigma-Aldrich companies and were used without further purification. Melting points were recorded by digital melting point equipment (Stuart Scientific SMP30). Fourier Transform Infrared FTIR spectra were recorded on SHIMADZU (8400, Kyoto, Japan) spectrophotometer using KBr discs in the range (400-4000) cm^{-1}. Proton nuclear magnetic resonance ^{1}H-NMR and ^{13}C-NMR spectra were run on Bruker (400MHz) instrument using DMSO-d^6 as a solvent and all chemical shifts, δ were recorded in ppm relative to TMS signal as an

internal standard. Thin layer chromatography (TLC) were performed using Fertigfollen precoated sheets type polygram with 0.25 mm layer Silica gel, GF254 of the Merck and the plates were colored with iodine vapour or sulfuric acid in ethanol (70%)followed by heating. The antibacterial screening was performed in department of Biology, College of Science, Baghdad University.

2.2. Diazotization of 1-Aminoanthraquinone Compound [1].
(0.69 gm., 0.01 mol) sodium nitrite gently added to (5ml.) of concentrated hydrochloric acid (36%) at below 5^{o}C. The reaction temperature rose about 65^{o}C, where no color change observed. The solution cooled to 0-5^{o}C and then (2.32 gm., 0.01 mol) the powder of 1-aminoanthraquinone was added slowly to the solution over 1hr. The reaction mixture was stirred for 5 hrs. (Kamaladin 2007).

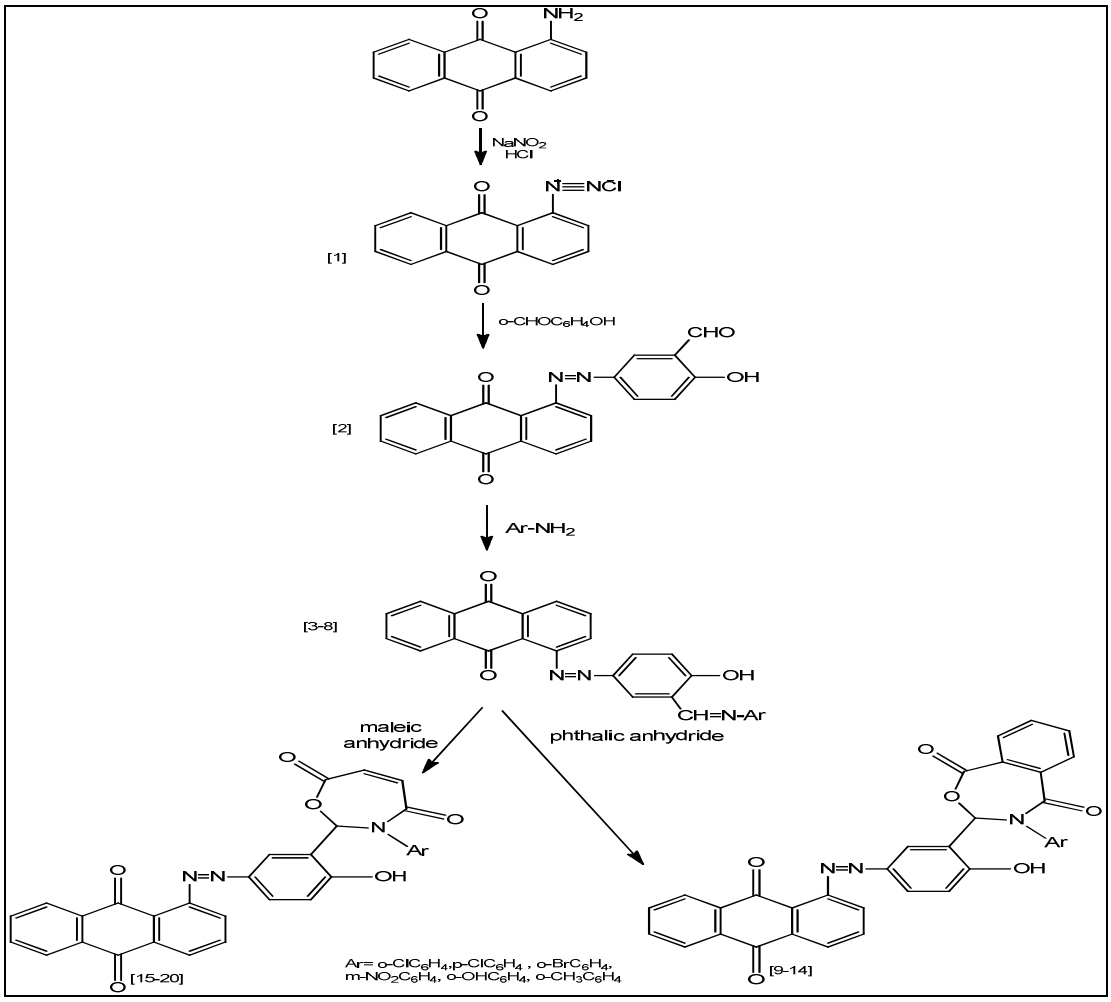
2.3. Coupling of anthraquinone diazonium salt, synthesis of azo compound [2].
(1.22gm, 0.01mol) of the coupling component *o*-salicyladehyde was dissolved in (1 ml) acetic acid. After complete the desolation, the clear solution of diazonium salt was added to these solutions. Mixture of reaction was stirred for (2 hrs.) at below 5^{o}C. Sodium acetate solution was added slowly to make the pH of the solution between four to five, and the mixture stirred continuously for 6 hours at less than 5^{o}C. The products were filtered off, washed with little hot water and dried. The crude azo compound was purified from chloroform (Maryte 2002).

2.4. Synthesis of Schiff bases compounds [3-8].
A mixture of azo compound [II] (3.56gm, 0.01mol), appropriate aromatic amine (0.01 mol), dry benzene (15 ml) and 2 drops of glacial acetic acid was refluxed for 4 hrs. The solvent was evaporated under vacuum and the residue crystallized from suitable solvents (Navin 2011).

2.5. Synthesis of 1,3-oxazepine compounds [9-20].
(0.01mole) of appropriate Schiff bases [3-8] was added to solution of (0.98g, 0.02mole) of maleic anhydride or (1.48g, 0.02mole) phthalic anhydride in (20ml) of dry benzene (benzene was dried with anhydrous calcium chloride). The reaction mixture was refluxed for 5 hrs. The solid formed was collected and recrystallized from suitable solvents (Hanoon 2011).

2.6. Antibacterial activity test.
The *in vitro* antibacterial activity for twelve 1,3-oxazepine derivatives (9-12) were carried out agar diffusion technique. Stocks samples of were prepare in a 1 mg/mL of Dimethylformamide (DMF) solution. The antibacterial test made against three strains of pathogenic bacteria (*Klebsiella sp., Streptococcus Pneumonia, Proteus sp.*) by agar diffusion technique. Six millimeter diameter wells punched into the nutrient agar with fresh bacteria separately and filled with 100µl of each concentration. The incubation was carried out at 37^{o}C for 48hr., DMF showed zero inhibition zone. The diameter of inhibition zone (mm) was measured and (amoxicillin tri hydrate) for antibacterial activity, was used as references (Al-Rawi 2013).

3. Results and Discussion
3.1. Characterization of anthraquinone diazonium salt and azo compound.
The general method of diazotization of 1-aminoanthraquinone uses hydrochloric acid. This reaction was completed in five hours. The obtained diazonium salts were reacted with coupling component as *o*-salicyladehyde in weak acid media (pH=4-5) (Scheme.1). The analytical data of the synthesized compounds are shown in Table 1. FTIR spectra are shown in Table 2.



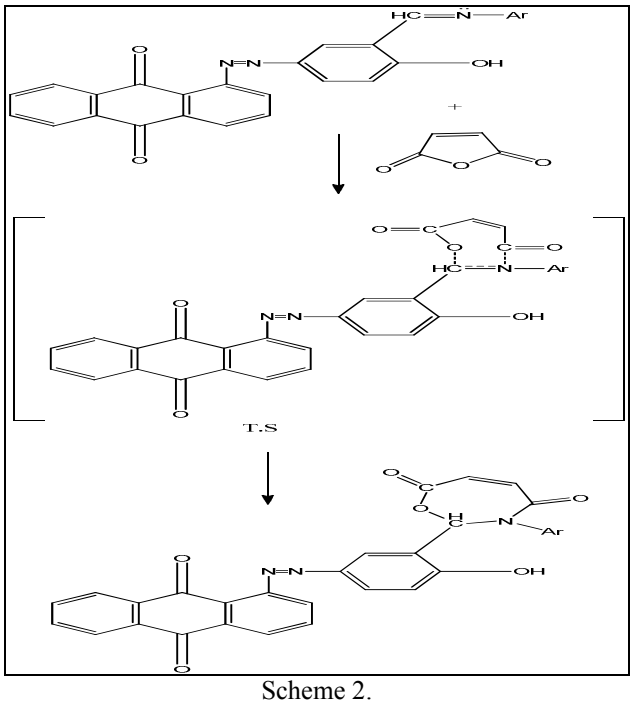
Scheme 1.

3.2. Characterization of Schiff bases

The new Schiff bases [3-8] were synthesized by the refluxing of equimolar quantities azo compound of aromatic aldehyde [2] and appropriate aromatic primary amine in dry benzene with some drops of glacial acetic acid. These Schiff bases were identified by their melting points, FTIR spectra. FTIR absorption spectrum shows the disappearance of absorption bands due to NH_2 and C=O groups of the starting materials together with the appearance of a new absorption band in the region (1596–1604) cm^{-1} which is assigned to C=N stretching. The physical properties of the synthesized compounds [3-8] are shown in Table 1. and FTIR spectra are listed in Table 2.

3.3. Characterization of 1,3-Oxazepine compounds

1,3-Oxazepine derivatives [9-20] have been synthesized by using a pericyclic reaction type [2+5] cycloaddition reaction between imine group (C=N) in compounds [3-8] as two membered component and maleic and phthalic anhydrides as five membered components to give seven- membered 1,3-oxazepine rings [9-20] cycloaddition reaction is a concerted process proceeds via a single cyclic transition state and thus there is no intermediate in the process. Mechanism of 1,3-oxazepine rings formation has been shown in the Scheme 2.



Scheme 2.

FT-IR spectrum of 1,3-oxazepine derivative [9-20] showed disappearance of the strong bands at range (1596–1604) cm^{-1} attributed to the stretching vibration of exocyclic imine group (C=N) and appearance of two strong absorption bands at range (1682-1710) cm^{-1} and at range (1635-1668) cm^{-1} attributed to the υ(C=O) for lactone and lactam structures inside1,3-oxazepine ring respectively.

^{1}H-NMR spectrum of compound [9] displayed signals attributed to proton of (OH) hydroxyl group attached to benzene ring, and also it was found signals belong to aromatic ring protons and (O-CH-N) of 1,3-oxazepine ring respectively. Results of ^{1}H-NMR were listed in Table 3, Figure 1.

^{13}CNMR spectrum of compound [9] showed signals belong to (O-CH-N) of 1,3-oxazepine ring, aromatic carbons, carbons of anthraquinone and benzene rings attached to (N=N) azo group, carbon of benzene ring bearing (OH) group, (C=O) carbonyl group of 1,3-oxazepine ring and (C=O) carbonyl group of anthraquinone ring respectively. Results of ^{13}C-NMR were listed in Table 4, Figure 2.

^{1}H-NMR spectrum of compound [13] which contain signals belong to protons of two (OH) hydroxyl groups attached to benzene rings, aromatic ring protons and (O-CH-N) of 1,3-oxazepine ring respectively. Results of ^{1}H-NMR were listed in Table 3, Figure 3.

^{13}CNMR spectrum of compound [13] showed signals belong to (O-CH-N) of 1,3-oxazepine ring, aromatic carbons, carbons of anthraquinone and benzene rings attached to (N=N) azo group, two carbons of benzene rings bearing (OH) hydroxyl group, (C=O) carbonyl group of 1,3-oxazepine ring and (C=O) carbonyl group of anthraquinone ring respectively. Results of ^{13}C-NMR were listed in Table 4, Figure 4. All results of ^{1}H-NMR and^{13}CNMR data for compounds [14, 19, 20] are were listed in Table 3 and Table 4 respectively.

Table 1. Physical Properties Data of Compounds [1-20].

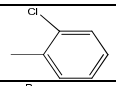
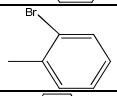
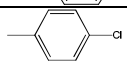
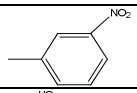
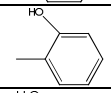
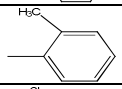
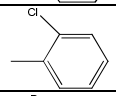
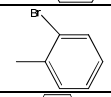
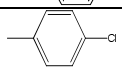
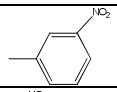
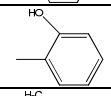
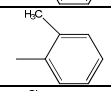
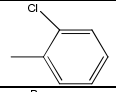
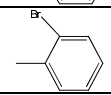
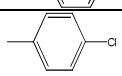
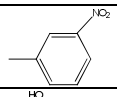
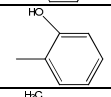
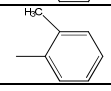
Comp. No.	Ar =	Physical Properties					
		Color	Yield %	M.P. °C	Molecular formula	Solvents of Recryst.	R_f Value
1	-	Yellow	70	158	$C_{14}H_7N_2O_2Cl$	Chloroform	0.72
2	-	White	65	176	$C_{21}H_{12}N_2O_4$	Dioxane	0.61
3		Gray	78	227-229	$C_{27}H_{16}N_3O_3Cl$	Ethanol-water 1:1	0.69
4		Off white	80	234	$C_{27}H_{16}N_3O_3Br$	Methanol -ethanol 1:1	0.68
5		White	85	218-220	$C_{27}H_{16}N_3O_3Cl$	Ethanol	0.70
6		Pale yellow	75	202-205	$C_{27}H_{16}N_4O_5$	Ethanol	0.62
7		Dark brown	80	238	$C_{27}H_{17}N_3O_4$	Dioxane-ethanol 1:1	0.55
8		White	72	245-246	$C_{28}H_{19}N_3O_3$	Ethanol-water 1:1	0.58
9		Brown	75	255-256	$C_{35}H_{20}N_3O_6Cl$	Dioxane	0.77
10		Brown	90	285-287	$C_{35}H_{20}N_3O_6Br$	Dioxane	0.65
11		White	85	273-274	$C_{35}H_{20}N_3O_6Cl$	Dioxane-Ethanol 1:1	0.56
12		Light yellow	88	226	$C_{35}H_{20}N_4O_8$	Ethanol-water 1:1	0.63
13		Brown	80	188	$C_{35}H_{21}N_3O_7$	Water	0.69
14		Green	78	193-195	$C_{36}H_{23}N_3O_6$	Ethanol-water 1:1	0.70
15		Off white	75	198-201	$C_{31}H_{18}N_3O_6Cl$	Water	0.73
16		Dark brown	68	172-175	$C_{31}H_{18}N_3O_6Br$	Dioxane-Ethanol 1:1	0.64
17		Dusty	70	178-180	$C_{31}H_{18}N_3O_6Cl$	Dioxane	0.68
18		Orange	86	169-170	$C_{31}H_{18}N_4O_8$	Ethanol	0.58
19		Brown	88	184-186	$C_{31}H_{19}N_3O_7$	Ethanol	0.59
20		White	84	190-193	$C_{32}H_{21}N_3O_6$	Chloroform	0.62

Table 2. Major FTIR spectral data cm^{-1} of Compounds [1-20]

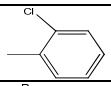
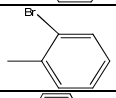
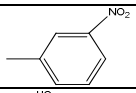
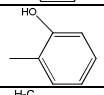
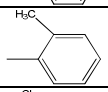
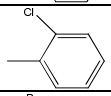
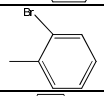
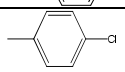
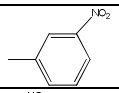
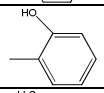
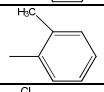
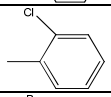
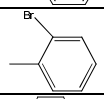
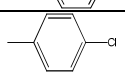
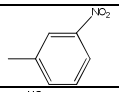
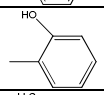
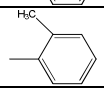
Comp. No.	Ar =	IR spectral data (cm^{-1})					
		v(C-H) Arom.	v(C=O)	v(C=N)	v(N=N)	v(C-O-O) Sym. & Asym.	Others
1	-	3058	1705	-		-	-
2	-	3069	1688	-		-	-
3		3055	1690	1597	1585	-	v(C-Cl) 814
4		3096	1697	1598	1589	-	v(C-Br) 820
5		3070	1703	1596	1588	-	v(C-Cl) 809
6		3078	1701	1602	1580	-	v(NO_2) 1519,1315
7		3049	1695	1601	1578	-	v(OH) 3212
8		3053	1698	1604	1579	-	v(C-H) Aliph. 3066
9		3077	1692, 1662	-	1583	1166, 1066	v(C-Cl) 828
10		3042	1706, 1655	-	1586	1162, 1065	v(C-Br) 816
11		3028	1704, 1660	-	1582	1167, 1060	v(C-Cl) 812
12		3048	1687, 1645	-	1584	1168, 1058	v(NO_2) 1506,1324
13		3056	1685, 1657	-	1581	1167, 1063	v(OH) 3206
14		3031	1703, 1668	-	1580	1169, 1061	v(C-H) Aliph. 3052
15		3082	1690, 1643	-	1587	1165, 1059	v(C-Cl) 834
16		3063	1710, 1635	-	1588	1166, 1061	v(C-Br) 812
17		3062	1708, 1648	-	1577	1164, 1057	v(C-Cl) 828
18		3049	1704, 1659	-	1575	1160, 1069	v(NO_2) 1508,1330
19		3033	1682, 1644	-	1578	1163, 1062	v(OH) 3238
20		3037	1696, 1638	-	1576	1162, 1064	v(C-H) Aliph. 3042

Table 3. [1]HNMR Spectral Data (δ ppm) For Selected Compounds.

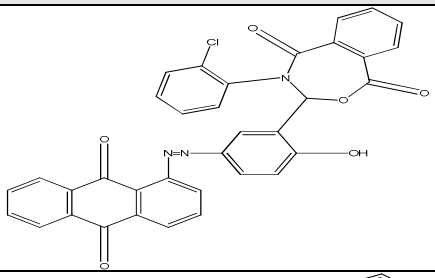
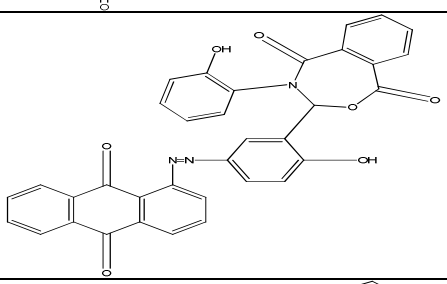
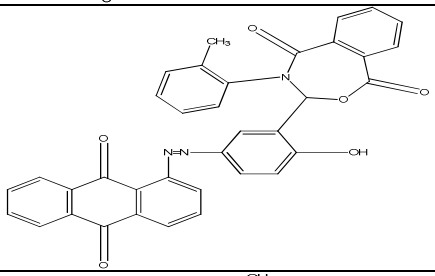
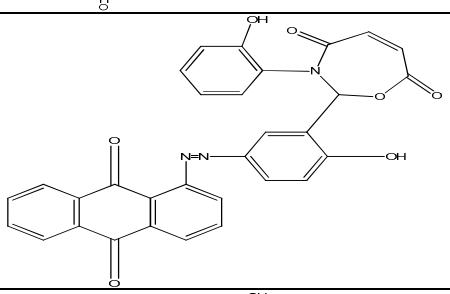
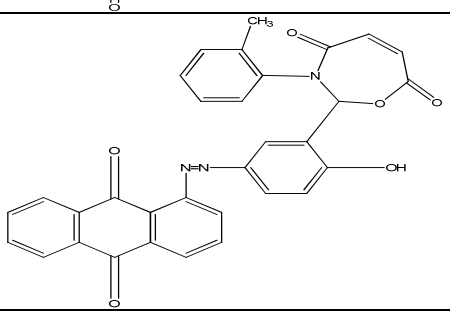
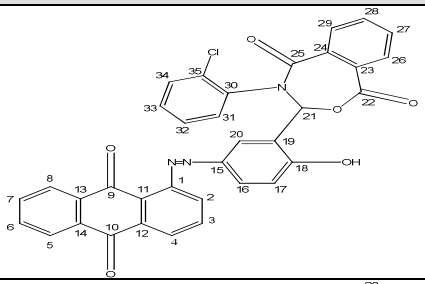
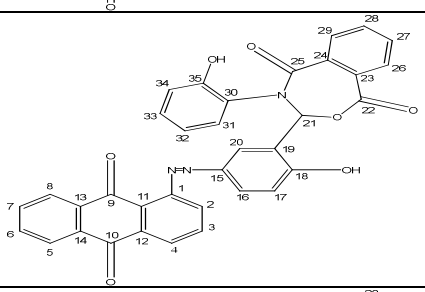
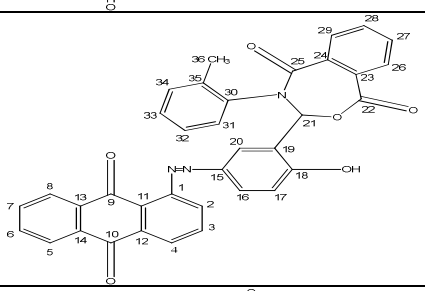
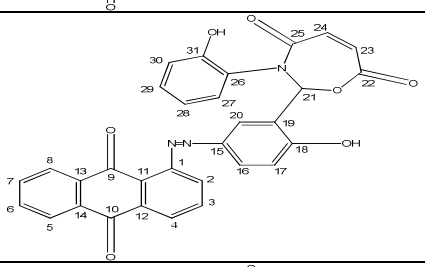
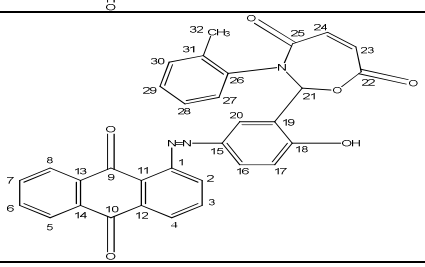
Comp. No.	Compound Structure	[1]HNMR Spectral Data (δ ppm)
9		**4.93 O-H proton,** **(6.83-7.16) aromatic ring protons** **7.39 (O-CH-N) proton.**
13		**5.43 O-H protons,** **(6.60-7.10) aromatic ring protons** **7.38 (O-CH-N) proton.**
14		**2.04 CH_3 protons** **5.30 O-H proton** **(6.65-7.01) aromatic ring protons** **7.42 (O-CH-N) proton.**
19		**5.50 O-H Protons,** **(6.72-7.08) aromatic ring protons** **7.40 (O-CH-N) proton.**
20		**2.18 CH_3 protons** **5.26 O-H proton** **(6.70-7.21) aromatic ring protons** **7.48 (O-CH-N) proton.**

Table 4.^{13}CNMR Spectral Data (δ ppm) For Selected Compounds.

Comp. No.	Compound Structure	^{13}CNMR spectral data (δ ppm)
9		**95.84 C_{21}, 120.10-139.16 (C_2-C_8),(C_{11}-C_{14}), (C_{16},C_{17},C_{19},C_{20},C_{23},C_{24}),(C_{26}-C_{35}), 151.94 (C_1, C_{15}), 158.36 C_{18}, 168.56 (C_{22}, C_{25}), 179.82 (C_9, C_{10}).**
13		**92.34 C_{21}, 120.24-140.06 (C_2-C_8),(C_{11}-C_{14}), (C_{16},C_{17},C_{19},C_{20},C_{23},C_{24}),(C_{26}-C_{34}), 150.01 (C_1,C_{15}), 159.22 (C_{18}, C_{35}), 166.55 (C_{22},C_{25}), 175.29 (C_9, C_{10}).**
14		**23.67 C_{36} 90.77 C_{21} 122.51-141.39 (C_2-C_8),(C_{11}-C_{14}), (C_{16},C_{17},C_{19},C_{20},C_{23},C_{24}), (C_{26}-C_{35}) 152.87 (C_1,C_{15}), 157.92 (C_{18}), 169.61 (C_{22},C_{25}), 176.45 (C_9, C_{10}).**
19		**91.74 C_{21}, 122.37-140.18 (C_2-C_8),(C_{11}-C_{14}), (C_{16},C_{17},C_{19},C_{20},C_{23},C_{24}),(C_{26}-C_{30}), 153.12 (C_1,C_{15}), 155.34 (C_{18}, C_{31}), 167.61 (C_{22},C_{25}), 173.31 (C_9, C_{10}).**
20		**22.41 C_{32}, 89.38 C_{21} 123.62-140.51 (C_2-C_8),(C_{11}-C_{14}), (C_{16},C_{17},C_{19},C_{20},C_{23},C_{24}), (C_{26}-C_{31}) 150.11 (C_1,C_{15}), 158.46 (C_{18}), 170.08 (C_{22},C_{25}), 180.27 (C_9, C_{10}).**

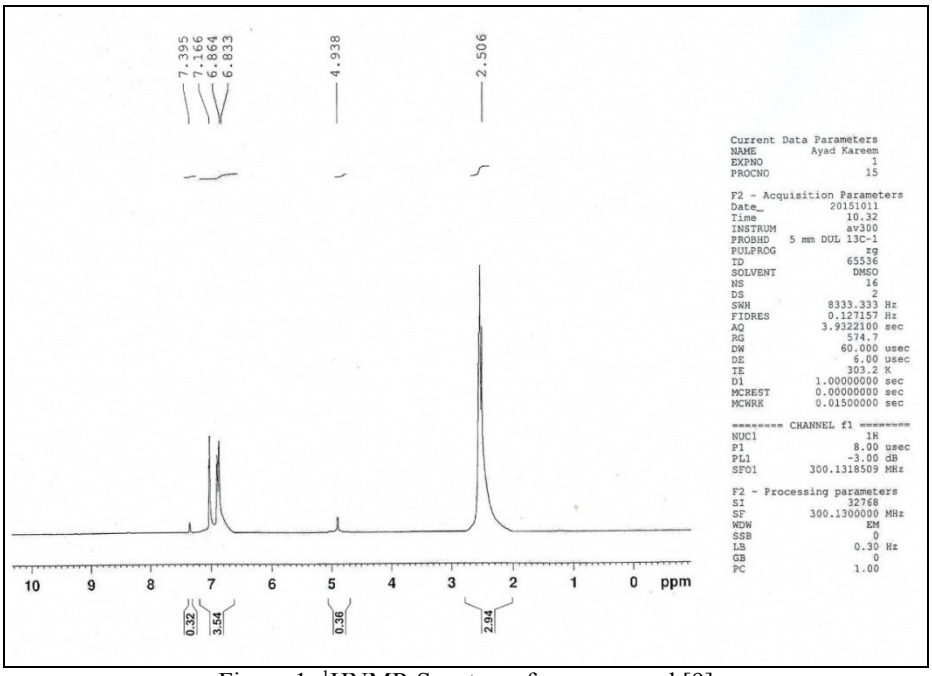


Figure 1. [1]HNMR Spectrum for compound [9]

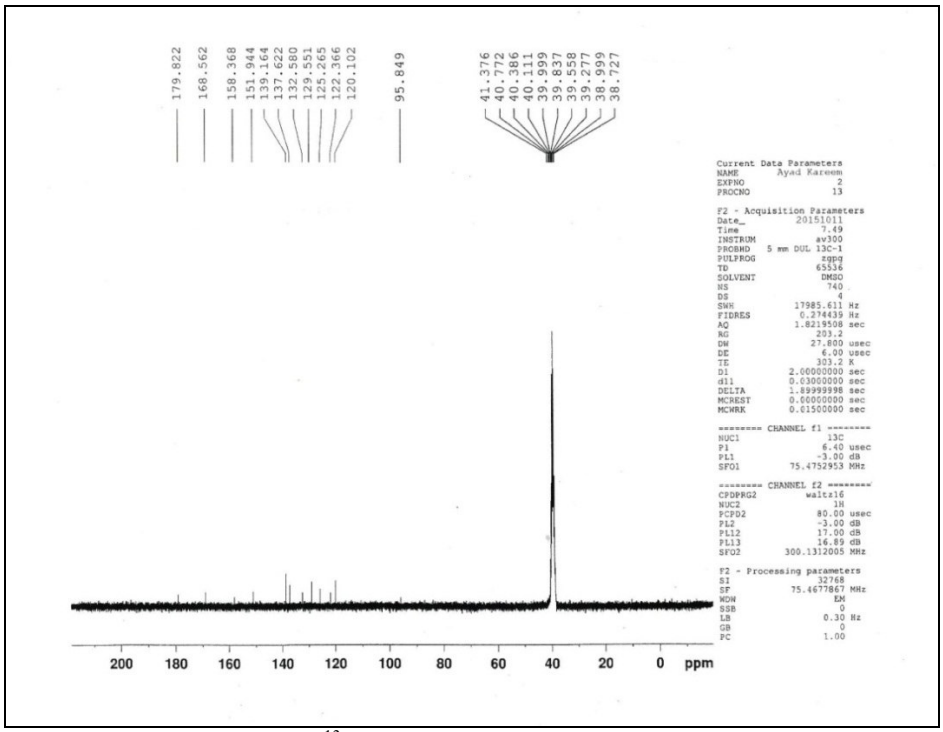


Figure 2. [13]CNMR Spectrum for compound [9]

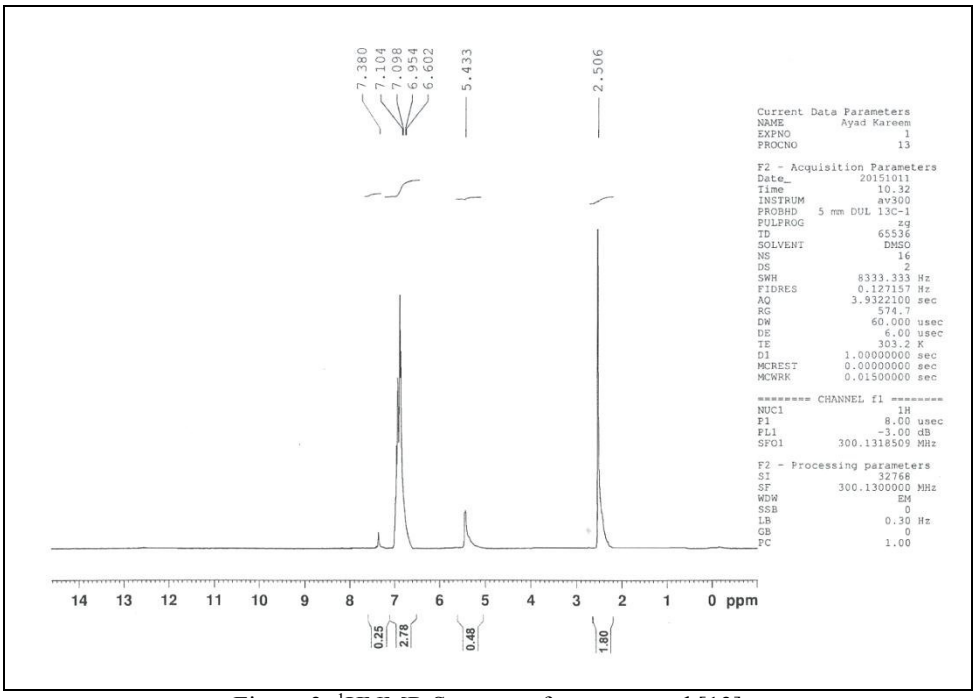


Figure 3. [1]HNMR Spectrum for compound [13]

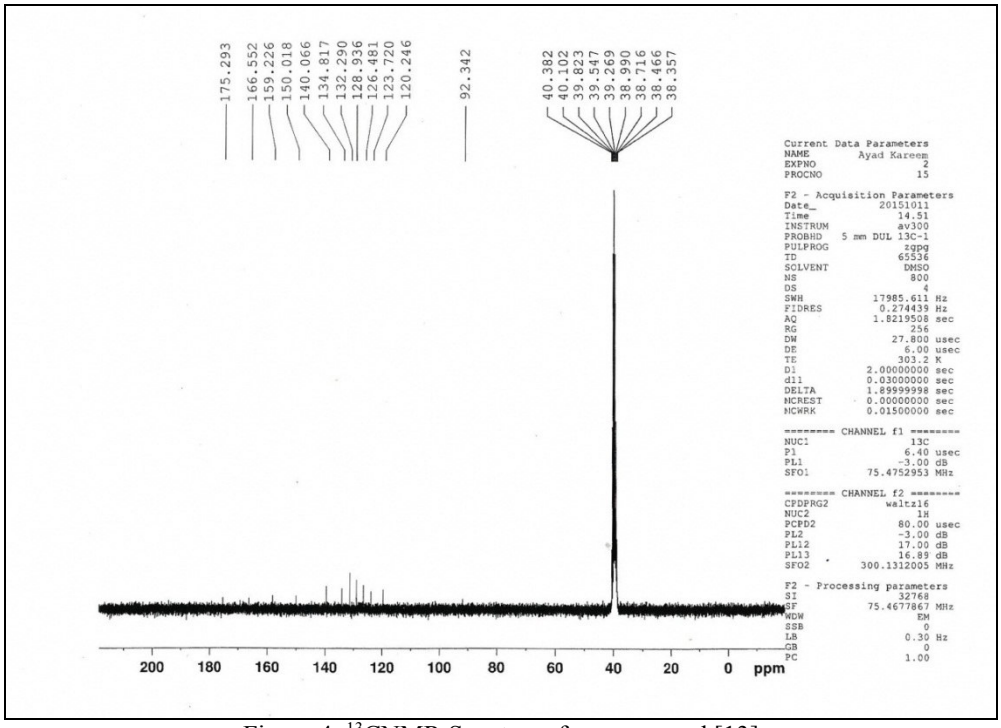


Figure 4. [13]CNMR Spectrum for compound [13]

3.4. Antibacterial activity.

The results of antibacterial activity are shown in Tables 5.

Table 5. Antibacterial activity of synthesized compounds

Comp. No.	*Klebsiella sp.* (Zone of inhibition at 100 µg/ml)	*Streptococcus Pneumonia* (Zone of inhibition at 100 µg/ml)	*Proteus sp.* (Zone of inhibition at 100 µg/ml)
9	**-**	**7**	**6**
10	**-**	**7**	**7**
11	**-**	**8**	**6**
12	**-**	**7**	**8**
13	**6**	**9**	**6**
14	**-**	**8**	**9**
15	**6**	**10**	**11**
16	**6**	**12**	**10**
17	**7**	**11**	**10**
18	**6**	**12**	**11**
19	**6**	**10**	**12**
20	**6**	**10**	**11**
amoxicillin tri hydrate (Ref.)	**9**	**15**	**14**

1,3-oxazepine derivatives [15-20] exhibited good activities against *Streptococcus pneumonia, Proteus sp.,* while it displayed moderate activity against gram negative *Klebsiella sp.* Compounds [9-14] groups were found inactive against *Klebsiella sp.* bacterial species. While it possesses moderate activities against *Streptococcus pneumonia, Proteus sp.*as compared to amoxicillin tri hydrate.

4. Conclusions

Series of new 1,3-oxazepine derivatives attached to anthraquinone azo ring have been synthesized successfully by cycloaddition reactions type [2+5] of Schiff bases. Some of these compounds shown good antibacterial activity. 1,3-oxazepine derivatives [15-20] were found active than 1,3-oxazepine derivatives [9-14].

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