Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(21):86-93
(http://www.derpharmachemica.com/archive.html)

Synthesis, Characterization and Study Antibacterial Activity of some New 1,3-oxazepine and 1,3-diazepine Derivatives

Iman K. Naeem, Ezzat H. Zimam*

Department of Chemistry, Faculty of Science, University of Kufa, Iraq

ABSTRACT

In this research some new derivatives of 1,3-Oxazepine and 1,3-Diazepine with sulfadiazine moiety has been synthesized. At the first we prepared the azo derivatives of O-tolidine [A] by the coupling reaction of the dizaonium slat of sulfadiazine with O-tolidine, then different compounds of Schiff base [B1-B5] were prepared by the reaction of compound [A] with benzaldehyde derivatives. 1,3-oxazepine derivatives [C1-C5] and [C6-C10]were synthesized by the cycloaddition reaction of compounds [B1-B5] with the malic anhydride and phthalic anhydride respectively. In the last step compounds [C1-C10] were converted to diazepene derivative [D1-D10] by reaction with sulfadiazine. All the prepared compounds were characterized by FT-IR spectrophotometer and some of their by mass and ^{1}H-NMR spectrophotometers as well as C, H, N and S analysis. All the reactions were monitored by Thin Layer Chromatography (TLC) and some of physical properties like melting point and retention factor was recorded for the prepared compounds. Finally, Biological activity of some prepared compounds were tested as antibacterial agents for two different types of bacteria Klebsiella pneumonia (Gram-negative) and Streptococcus aureus (Gram positive).

Keywords: 1,3-oxazipine, 1,3-diazepine, Sulfadiazine, Schiff bases, *O*-tolidine

INTRODUCTION

Heterocyclic play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells are based on aromatic heterocyclic [1]. Azo compounds constitute one of the largest classes of industrially synthesized organic compounds [2]. Azo compounds of Schiff bases and their derivatives have been used to prepare different Heterocyclic compounds such as 1,3-oxazepine and 1,3-dizepine derivatives [3]. *o*-Tolidine is a commercially important aromatic amines used mainly for dye production [4].

Sulfadiazine is one of sulfonamide class of antibiotics that is widely used as a veterinary medicine. By combining of sulfadiazine with antitumor agent in one compound this will lead to formation new antitumor agent with different activity [5]. Many chemotherapeutically important sulfa drugs like sulfadiazine (silver sulfadiazine), sulfathiazole, sulfamerazine and so forth, possess (-SO_2NH-) Moiety, which is an important toxophoric functional group [6]. Schiff bases are well known in the pharmaceutical industry and medicinal field they have been shown to possess a broad spectrum of biological activities [7]. 1,3-Oxazepine is non-homologous seven member ring that contains two heteroatom (Oxygen and nitrogen) [8]. The discovery of the activity of 1,3-oxazepine on the CNS. Diazepine is an analogue to oxazepine and thiazepine but the difference is nitrogen, oxygen, sulpher atom, diazepam (valium) is a substituted benzodiazepine introduced in 1964 which was used for the control of anxiety and tension states, the relief of muscle spasm and for the management of acute agitation during with drawal from alcohol [9]. This research involved synthesized new derivatives of heterocyclic compounds (1,3-Oxazepine and diazepine derivatives) and tested it as antibacterial agents.

MATERIALS AND METHODS

All the solvents and other chemicals used are of either analytical grade or high purity supplied by Merck and BDH. Distilled water is used in some of experiments.

Equipment's

Elemental analyses of the synthesized compounds are carried out by Perkin-Elmer elemental analyzer. Fourier Transform Infra-Red (FTIR) spectra of the prepared compounds are recorded on using Alpha-Bruker FTIR spectrometer within the range 4000-450 cm^{-1}. ^{1}H-NMR spectra of the prepared compounds are obtained from Bruker AV III 300 MHZ FT-NMR spectrometer using Tetramethylsilane (TMS) as reference.

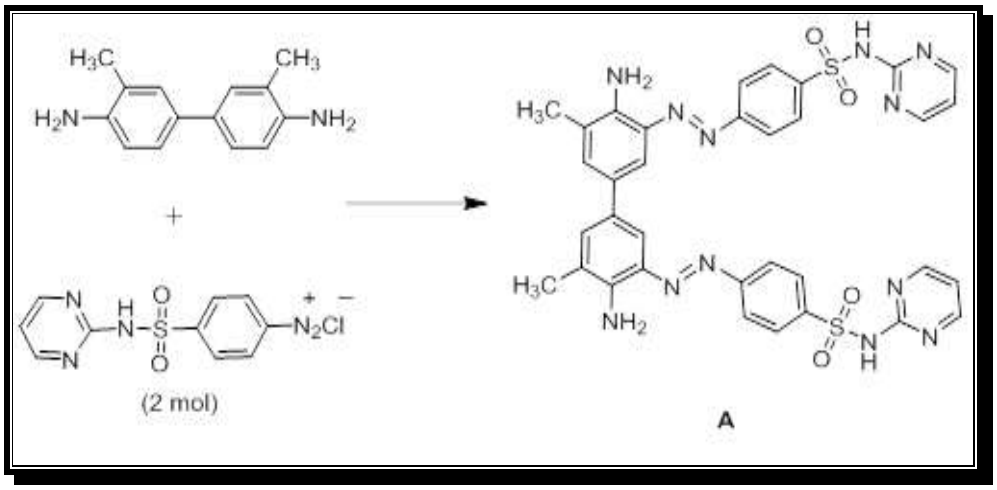
Biological activity

The prepared compounds are screening as anti-bacterial agent against two type of bacteria *Kelebsiella pneumonia* (Gram-negative) and

Streptococcus aureus (Gram-positive). By well diffusion method in Mueller-Hinton agar medium.

General procedure for synthesis compound (A) [10]

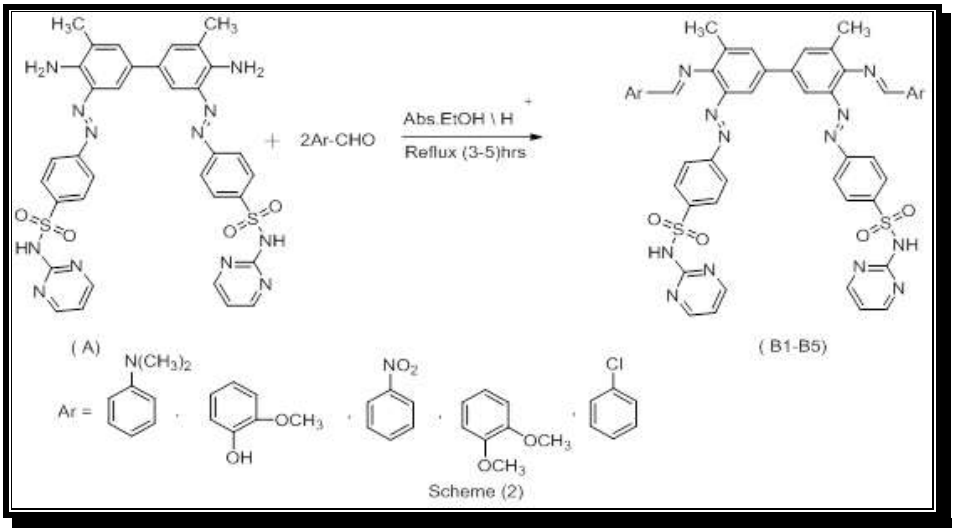
o-Tolidine (2.12 gm, 0.01 mol) was dissolved in (3.5 ml) of concentrated hydrochloric acid and (40 ml) of distilled water. The mixture was cooled at (0°C) in ice-water bath. A solution of sodium nitrite (1.72 gm, 0.02 mol) dissolved in (6 ml) of distilled water. There was added a dropwise to the mixture with stirring. In the other beaker sulphadiazine 5.0 gm, 0.02 mol dissolved in 3 gm of sodium hydroxide and 200 ml of distilled water and place this beaker in ice-water bath at 0°C. The cold diazonium chloride was added to the coupling agent in small portions and stirred after each addition, A completing the addition, the reaction mixture was stirred at 0°C for 15 min (Scheme 1). The pale green product was precipitated and filtered recrystallized from ethanol, yield (6.34 gm, 89%), m.p. 110-112°C and R_f = (0.72) Ethanol: Benzene (1:3).



Scheme [1] Synthesis of compound A

General procedure for synthesis of Schiff base derivatives (B1-B5) [4]

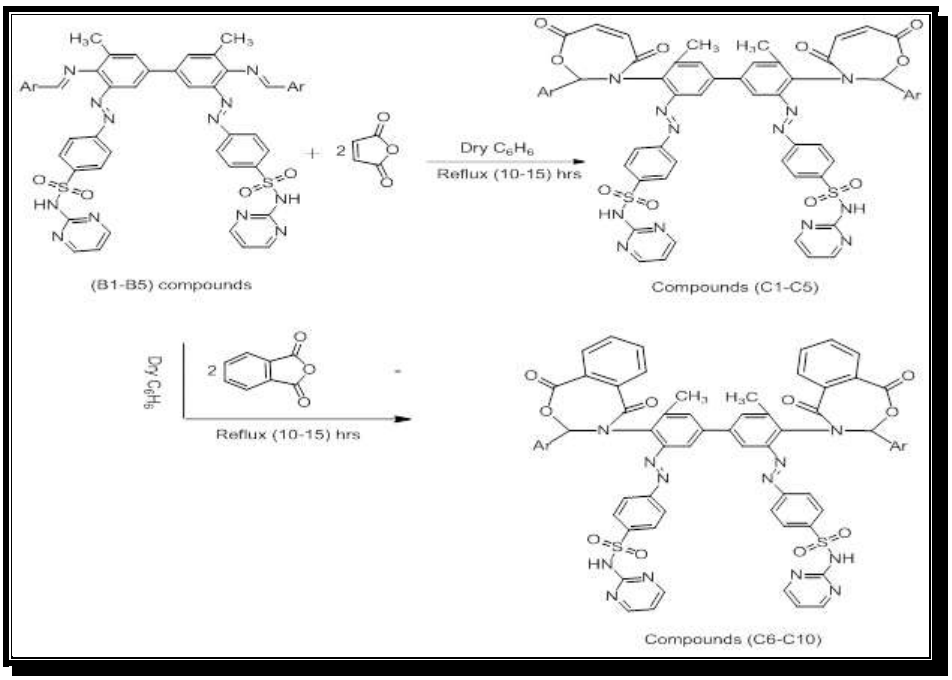
The azo compound [A] (0.01 mol) was added to a solution of appropriate aromatic aldehyde (0.02 mol) in 40 ml of absolute ethanol and two drops of glacial acetic acid were, also added to the above mixture. The mixture was refluxed for 3-5 hr (Scheme 2). The precipitates were formed collected by filtration, dried and recrystallized from ethanol to give compounds (B1-B5) respectively. TLC showed that the reaction was complete by using Ethyl acetate: Toluene (1:4).



Scheme [2] synthesis of compounds (B1-B5)

General procedure for synthesis 1,3-oxazepine derivatives (C1-C5) and (C6-C10) [11]

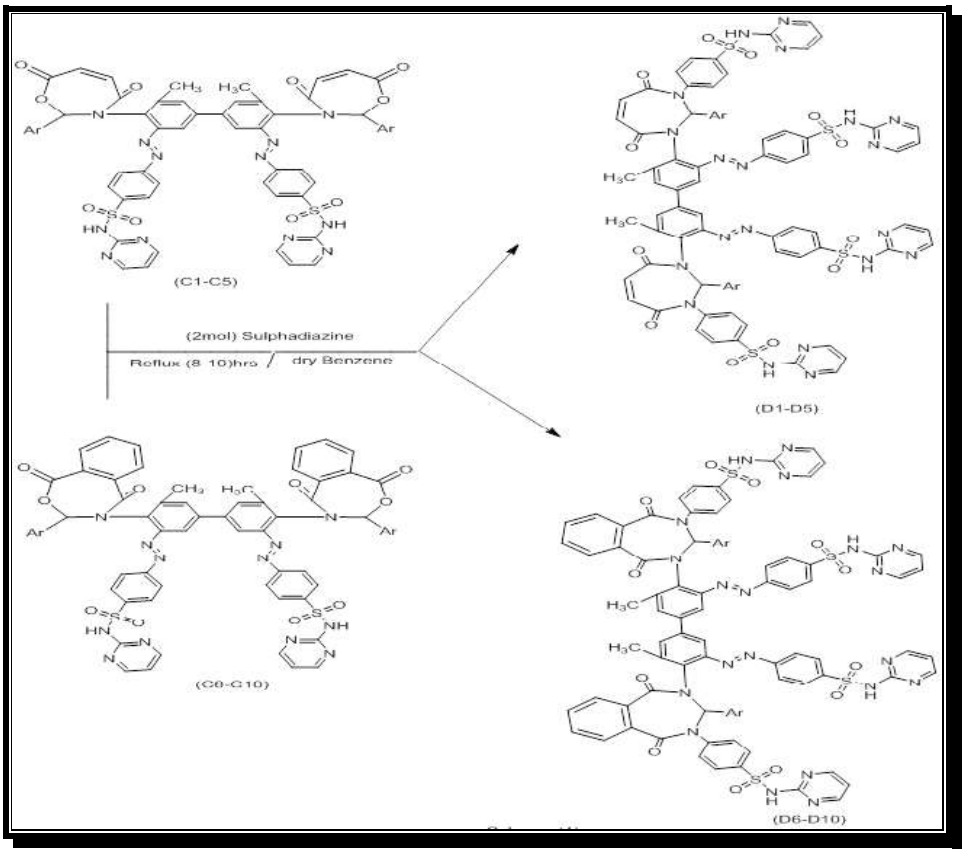
Mixture of azo Schiff bases [B1-B5] (0.01 mol) and appropries acid anhydride (Maleic anhydride or phthalic anhydride) (0.02 mol, 1.96 gm for MA and 2.96 gm for PhA) in dry benzene (250 ml), The reaction mixture was stirred for (10-15 hr) at (55°C for MA and 60°C for PhA), and at the end of the reaction (Scheme 3). The precipitates were collected by filtration and the resulting colored crystalline solid was recrystallized from dry 1,4-dioxan. The TLC showed that the reaction was complete by using Ethyl acetate: Toluene (1:4).



Scheme [3] Synthesis of compounds (C1-C10)

General procedure for synthesis 1,3-dizepene derivatives (D1-D5) [12]

A mixture (0.0001 mol) of oxazepine compounds and (0.0002 mol) of sulfadiazine in (30 ml) of dry benzene was placed round bottom flask. The reaction mixture was refluxed in water bath at 78°C for (10-18 h) then allowed to cool to room temperature and separated crystalline was filtered and re-crystallized from ethanol (Scheme 4). The TLC showed that the reaction was complete by using Ethyl acetate: Toluene (1:4).



Scheme [4] Synthesis of compounds (D1-D10)

RESULTS AND DISCUSSION

All the prepared compounds are colored and stable to air, also these compounds are soluble in polar solvents like Dimethyl Formamide (DMF)

and Dimethyl Sulfoxide (DMSO) and have slightly less solubility in ethanol and methanol. The relatively high melting point of the synthesized compound indicates the thermal stability of these compounds. The first compound (A) was prepared by coupling reaction of *O*-tolidine with a compound that prepared by azotization reaction of sulfadiazine. The product was well identified by some of identification methods like FTIR

spectrum and melting point measurement. FTIR spectrum show a special band related to the absorption of (-N=N-) bond at (1480 cm^{-1}) also the appearance of absorption two bands at (1325 assym.) cm^{-1} and at (1155 sym.) cm^{-1} was due to the (O=S=O) group and is good evidence to formation the desired compound. There are also another bands related to the product like (-N-H-) band of sulfadiazine at (3330 cm^{-1}) and the aliphatic (-C-H) of *o*-toluidine. The reaction was monitored by TLC and the retention factor also measured for the product.

Schiff base derivatives were synthesized by the reaction of compound (A) with different benzaldehyde derivatives to form compounds (B1-B5). Table 1 below show some characteristics properties of the prepared compounds. Spectral information show the mode of bonding of the product, when we compared the FTIR spectrum of the compound (A) with one of (B) compound's we notice the clear difference which disappear of the band relating to the stretching vibration of (-NH_2) at 3330 cm^{-1} and appear new band for imine group at (-N=CH-) at 1550 cm^{-1} as well as the other bands Tables 2 and 3. The reaction was monitored by TLC. Melting point and R_f have been recorded to the products. Also It was found from (C, H, N and S) analysis and comparison with the calculated data for compound [B1-B5] that a good agreement with experimental data.

Table 1: Some physical and chemical properties of prepared compounds (B1-B5)

S. No.	Structural formula	Yield%	Color	M.P (°C)	R_f
B1	$C_{52}H_{48}N_{14}O_4S_2$	78	Brown	(192-194)	0.65
B2	$C_{50}H_{42}N_{12}O_8S_2$	81	Dark Brown	(184-186)	0.81
B3	$C_{48}H_{36}N_{14}O_8S_2$	85	yellow	(210-212)	0.79
B4	$C_{52}H_{48}N_{14}O_8S_2$	94	Dark Black	(200-202)	0.49
B5	$C_{48}H_{36}Cl_2N_{12}O_4S_2$	84	Dark gray	(172-174)	0.78

Table 2: IR data of the investigating compounds

S. No.	υ(-C-H)aliph cm^{-1}	υ(N=N) cm^{-1}	υ(-N=CH)cm^{-1}	υ(-N-H)cm^{-1}	Others cm^{-1}
B1	2892	1550	1585	3357	(N-CH_3): 2810 asym 2736 sym
B2	2864	1550	1579	3351	(C-OH) 3538
B3	2925	1515	1579	3353	(C-NO_2) 1375 assy
B4	2955	1505	1574	3354	(-OCH_3) 1138
B5	2859	1546	1578	3248	(C-Cl) 798

Table 3: C, H, N and S analysis data of compounds (B1-B5)

Compound No.	Molecular formula	Calculated/found			
		C (%)	H (%)	N (%)	S (%)
B1	$C_{52}H_{48}N_{14}O_4S_2$	62.63	4.85	19.67	6.43
		62.28	4.52	19.37	6.21
B2	$C_{50}H_{42}N_{12}O_8S_2$	59.87	4.22	16.76	6.39
		59.27	3.93	16.34	6.11
B3	$C_{48}H_{36}N_{14}O_8S_2$	57.59	3.63	19.59	6.41
		57.38	3.45	19.35	6.34
B4	$C_{52}H_{46}N_{12}O_8S_2$	60.57	4.5	16.3	6.22
		60.32	4.43	15.98	5.94
B5	$C_{48}H_{36}C_{l2}N_{12}O_4S_2$	58.83	3.7	17.15	6.54
		58.63	3.47	16.85	6.36

Table 4: IR data of the investigating compounds (C1-C10)

S. No.	υ(C-O) Str. Lactone (cm^{-1})	υ(-C-H) aliphatic (cm^{-1})	υ(N=N) (cm^{-1})	υ(-N-H) (cm^{-1})	υ(-C=O) (cm^{-1})
C1	1258	2930	1572	3256	1642
C2	1261	2834	1572	3248	1636
C3	1264	2943	1575	3248	1639
C4	1261	2937	1578	3244	1637
C5	1258	2933	1579	3252	1641
C6	1263	2842	1573	3248	1633
C7	1261	2943	1577	3246	1635
C8	1257	2935	1578	3249	1637
C9	1253	2931	1580	3348	1657
C10	1264	2938	1571	3345	1634

Then, the imines results derivatives [B1-B5] were reacted with maleic anhydride and phthalic anhydride in dry benzene to give new 1,3-oxazepine-4,7-dione ring derivatives [C1-C5] and [C6-C10] respectively. These compounds were characterized by FTIR in Table 4, (C, H, N and S) analysis of the calculated data for compound [C1-C10] that a good agreement with experimental data (Figures 1-5). Also ^{1}H-NMR data

for (C1, C2, C4, C6, C7 and C9) showing in Table 5.

Table 5: ^{1}H-NMR data for compounds (C1, C2, C4, C6, C7 and C9)

Compound No.	δ(C-H) aromatic ppm			-NH	Others ppm
C1	6.55-8.32	6.45-6.82	9.71	11.2 11.79	(N-CH_3): δ=2.44
C2	6.54-8.24	6.43-6.85	9.26	11.2 11.79	(O-CH_3): δ=3.14 and (OH): δ=9.52
C4	6.5-8.0	6.46-6.83	9.75	11.2 11.79	(O-CH_3): δ=3.13
C6	6.51-8.12	_	9.62	11.2 11.79	(N-CH_3): δ=2.44
C7	6.56-8.24	-	9.43	11.2 11.79	(O-CH_3): δ=3.12 and (OH): δ=9.72
C9	6.53-8.26	_	9.64	11.2 11.79	(O-CH_3): δ=3.o3

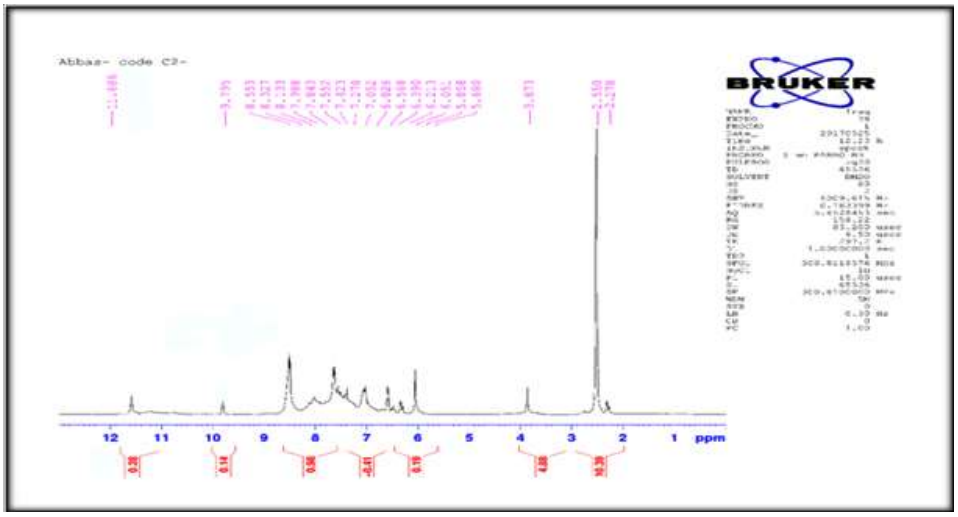


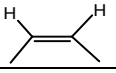
Figure 1: ^{1}H-NMR data for compounds (C2)

Then, 1,3-oxazepine derivatives [C1-C5] and [C6-C10] were reacted with sulphadiazinein dry benzene to give new 1,3-dizepine -4,7-dione ring derivatives [D1-D10]. These compounds were characterized by FTIR some of them were characterized by ^{1}H-NMR spectra and mass spectroscopy.

The FTIR spectra of the compounds [D1-D10] showed appearance of absorption two bands at (1323-1325 assym.) cm^{-1} and at (1153-1155sym.) cm^{-1} was due to the (O=S=O) group, and disappearance of the strong absorption band at (1680-1733) cm^{-1} was due to the stretching vibration of the (C=O) lactone group[(122)], the appearance of the strong absorption band at (1705-1743) cm^{-1} was due to the stretching vibration of the (C=O) lactam group.

^{1}H-NMR spectrum of compounds [D1, D2, D4, D6, D7 and D9] showed the following characteristic signals (DMSO-d_6 as a solvent) the multiplet signal at δ=7.2-8.23 ppm that could be attributed to the aromatic protons for phenyl rings and the doublet signal at δ=6.5-6.8 ppm that could be attributed to the two protons of seven membered ring of diazepine (2H of double bond of diazepine ring) group and singlet signal at δ=7.0-7.3 ppm that could be attributed to the (CH of diazepine ring) group and the two singlet signals at δ=11.27 and 11.76 of (-NH) group of sulphadiazine other data of groups containing protons were showed in Table 6.

Table 6: ^{1}H-NMR Data of compounds (D1, D2, D4, D6, D7 and D9)

Compound No.	δ (C-H) aromatic ppm		CH of Diazepine ring	NH Sulphadiazene	HC=N pyrimidine	δ(C-H) of CH_3 *o*-tolidine	Others ppm
D1	7.6	6.5-6.7	7.3	11.31 11.72	8.34	2.42	(N-CH_3) δ=3.13
D2	7.9	6.6-6.8	7.3	11.23 11.74	8.51	2.51	-OCH_3 δ=3.80 O-H δ=9.70
D4	7.8	6.5-6.7	7	11.33 11.72	8.45	2.5	-OCH_3 δ 3.80
D6	7.6	-	7.1	11.25 11.62	8.35	24.7	N-CH_3: δ3.15
D7	7.7	-	7	11.13 11.82	8.37	2.52	-OCH_3 δ3.80 O-H δ 9.65
D9	7.5	-	7.2	11.26 11.68	8.32	2.61	O-CH_3 δ3.83

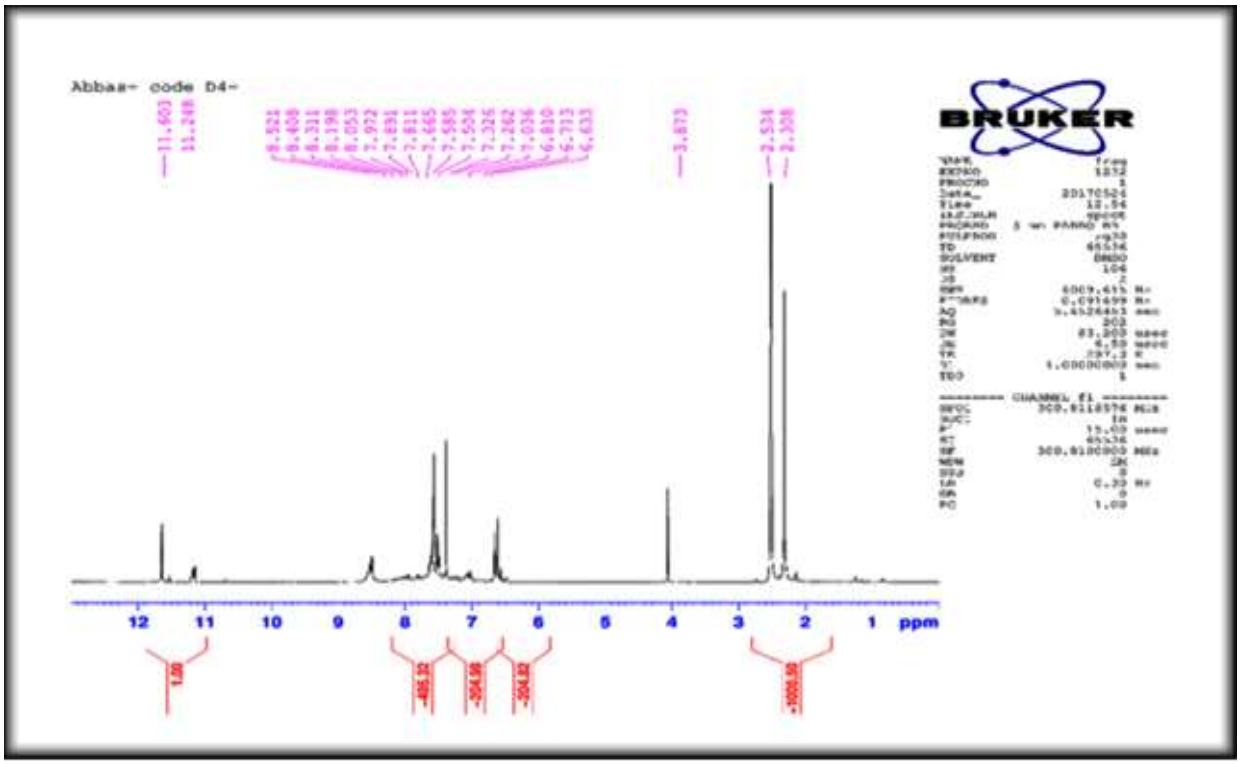


Figure 2: ^{1}H-NMR spectrum of the compound [D4]

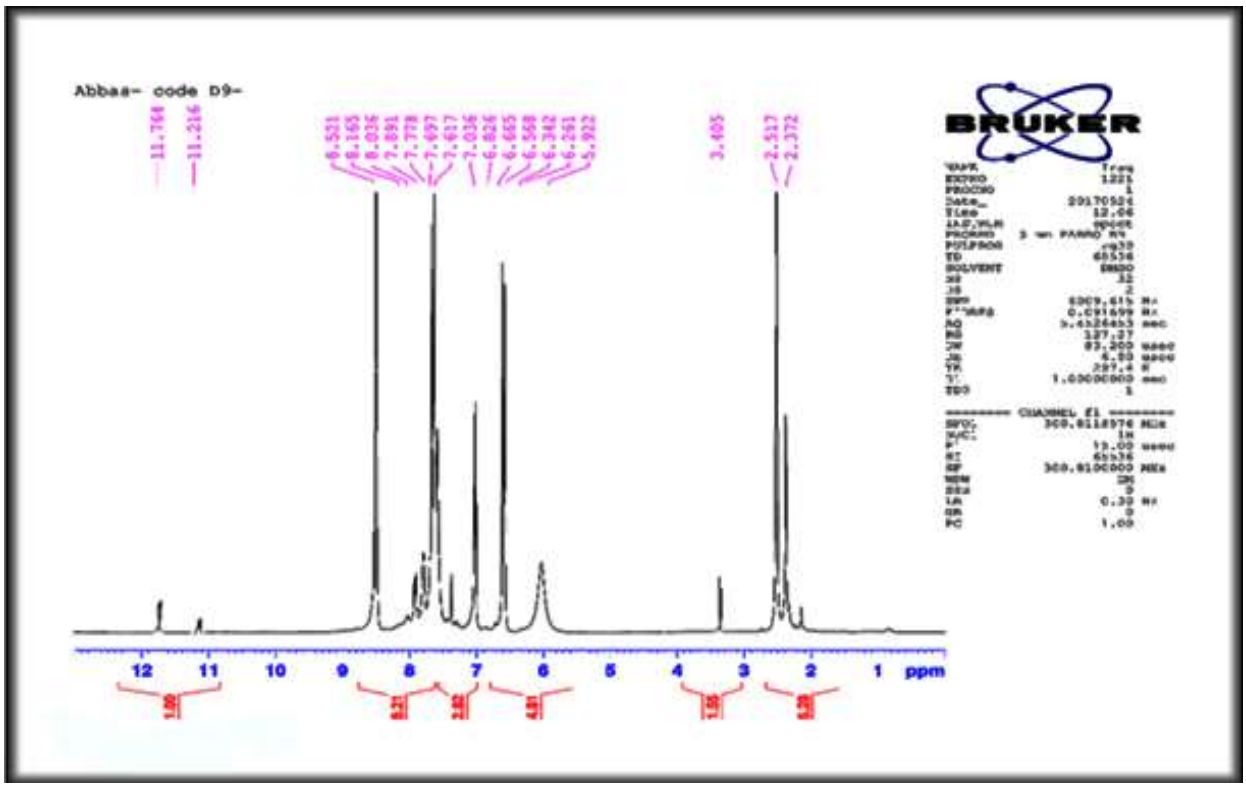


Figure 3: ^{1}H-NMR spectrum of the compound [D9]

Mass spectrum of compounds (D3, D5, D8 and D10) gives a good result for detection compounds [(D3) m/z: 1660.31 (100.0%), 1661.32 (82.2%), (D5) m/z: 1638.26 (100.0%), 1639.27 (82.2%) (D8) m/z: 1760.34 (100.0%), 1761.35 (90.9%) and (D10) m/z: 1738.30 (100.0%), 1739.30 (90.9%)].

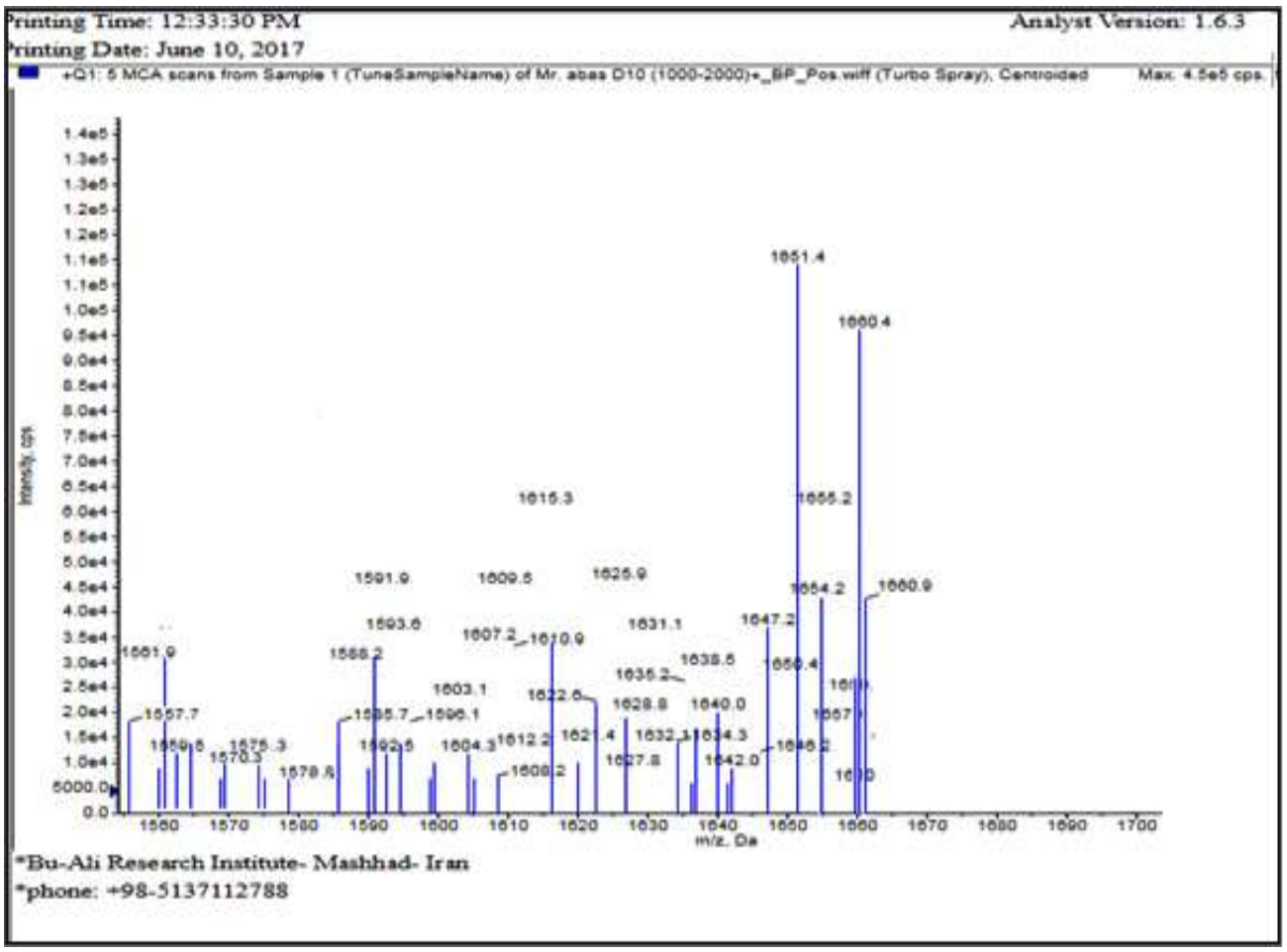


Figure 4: Mass spectrum of the compound [D2]

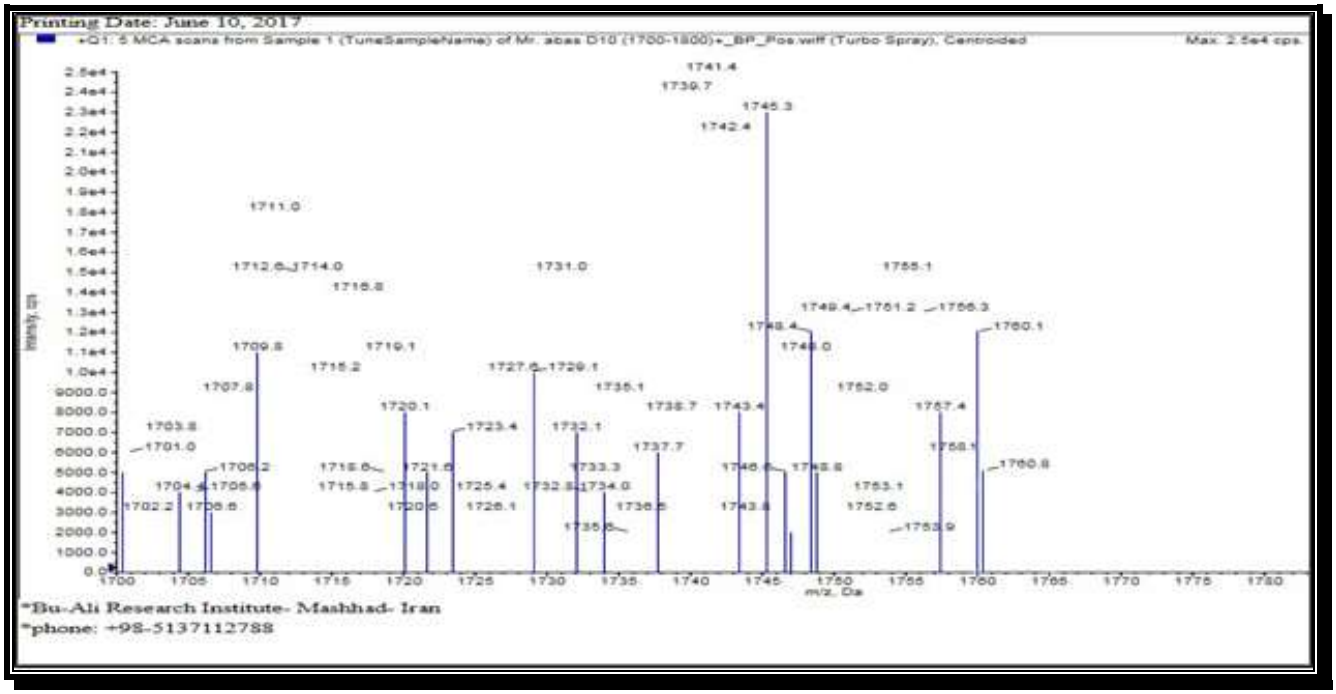


Figure 5: Mass spectrum of the compound [D2]

Biological activity

The prepared compounds (C2, C8, D2, D3, D7 and D10) were examined for antibacterial activity against *S. aureus* (Gram-positive) and *K. pneumonia* (Gram-negative) by well diffusion method in Mueller-Hinton agar medium. After 24 h zone of inhibition around each disc. The test results presented in Table 7.

Table 7: Antibacterial activity of compounds (C2, C8, D2, D3, D7 and D10)

Compound No.	Zone of inhibition (mm)	
	Staphylococcus aureous	***Klebsiella pneumonia***
C2	17.3	16.5
C8	20.5	19.4
D2	28.3	26.3
D3	22.7	21.6
D7	28.5	27.8
D10	18.2	19.4
Ciprofloxacin	27.2	27.6

CONCLUSION

The electron-donating and the electron-withdrawing groups affect the determination of the time of the reaction. The electron-donating group increases the rate of the reaction, therefore the time of the reaction decreases. While the electron-withdrawing group decreases, the rate of the reaction, therefore, the time of the reaction was increases. All synthesized compounds were stable by resonance and having high melting points relatively; this is evidence in relation to stability. The synthesized compounds have a biological activity against some type of bacteria, also it compared with traditional antibiotic and some of it were showed higher zone of inhibition than traditional antibiotic

ACKNOWLEDGMENT

I would like to thank Mr. Abbas Almulla for his help to do this work and also many thanks to everyone who contribute even with words to do this research.

REFERENCES

[1] A.S. Anees, M.I. Hamad, M.I. Hasan, *Der Pharmacia Lettre.*, **2011**, 3(1), 228-236.
[2] L. Pereira, M.M. Alves, In: A. Malik, E. Grohmann (Eds.), Protection Strategies for Sustainable Development, Springer, Dordrecht, **2012**, 111.
[3] Z. Heinrich, Color Chemistry: Syntheses, properties and applications of organic dyes and pigments, 2nd Rev. Edi., Weinheim; New York: VCH, **1991**, 498.
[4] G. Gangadhar, *Chemoshere*., **1996**, 32(2), 267.
[5] A.F. Abbass, E.H. Zimam, *Int. J. ChemTech Res.*, **2016**, 9(11), 206-217.
[6] E.H. Zimam, *Int. J. Chem. Nat. Sci*., **2014**, 2(4), 109-115.
[7] C.U. Dueke-Eze, T.M. Fasina, N. Idika, *African J. Pure Appl. Chem.*, **2011**, 5(2), 13-18.
[8] K. Tong, *Tetrahedron*., **2013**, 69(10), 2369-2375.
[9] Y. Deng, C. Pei, H. Arman, K. Dong, X. Xu, M.P. Doyle, *Org. Lett.*, **2016**, 18(22), 5884-5887.
[10] G.M.A. College, S. Odisha, *Der Pharma Chemca*., **2016**, 8(3), 254-272.
[11] R.W. Adam, E.H. Zimam, *Kerbala J. Pharmac. Sci*., **2014**, 7, 195-217.
[12] C. Guo, B. Sahoo, C.G. Daniliuc, F. Glorius, *J. Am. Chem. Soc*., **2014**, 136(50), 17402-17405.