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Synthesis, Characterization and Antibacterial Activity of Some New Oxazepine compounds

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Abstract

Four new 1,3-oxazepine compounds have been prepared by cycloaddition of synthesized bis-Schiff bases with maleic anhydride in toluene. The Schiff bases were prepared by the condensation of ethylene diamine with two equivalents of some aldehydes. The structure of the oxazepines were confirmed via elemental analysis,FT-IR and, ^{1}H-NMR spectra. The compounds were screened for their antibacterial activity against gram negative bacteria (*Escherichia coli)* and gram positive *(Staphylococcus aureus)*. The results showed that the examined compounds exhibited varied antibacterial activity in comparison with the standard drugs.

Keywords:1,3-oxazepine, Schiff base, cycloaddition, and antibacterial activity.

تحضير وتشخيص ودراسة الفعالية المضادة للبكتريا لبعض مركبات اوكسازيباين الجديدة

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الملخص

تم تحضير اربعة من مركبات 1،3-اوكسازيباين بتفاعلات اضافة الحلقة لمركبات ثنائية قواعد شف مع انهيدريد الماليك في مذيب التلوين. حضرت قواعد شف بتفاعلات التكثيف لمركب الاثلين ثنائي الامين مع بعض الالديهيدات. تم تشخيص المركبات المحضرة باستخدام التحليل العنصري الدقيق بالاضافة لمطيافيتي الاشعة تحت الحمراء والرنين النووي المغناطيسي. تم ايضا دراسة الفعالية البيولوجيةللمركبات المحضرة ضد نوعين من البكتريا السالبة والموجبة لصبغة كرام. اظهرت النتائج بان المركبات المحضرة امتلكت فعالية جيدة ضد البكتريا مقارنة بالمركبات الدوائية القياسية المستخدمة في البحث.

1. Introduction

[1,3]oxazepine-diones is a seven-membered ring containing nitrogen, oxygen and two carbonyl groups. Many researchers have investigated the molecular properties of the 1,4-, 4,1-, and 1,5-benzoxazepines. These compounds constitute an important class of heterocyclic compounds which have many biological uses [1-10]. Many methods were used to synthesize oxazepine compounds[11,12]. However, convenient and efficient way to form the oxazepine rings is still preferred owing to its importance as pharmaceutical drugs and active substances in biological systems. Other interesting is modification of oxazepine core as liquid-crystalline compounds which reported in reported in earlier publication [13]. There are different methods to prepare 1,3-oxazepine. One of these ways involves direct addition of maleic anhydride to the (C=N) double bond of Schiff bases and a number of 2,3-diaryl-2,3dihydro-1,3-oxazepine-4,7-diones were prepared and characterized[14].

Pyryliumtetrafluroborate underwent ring expansion on treatment with excess sodium azide in anhydrous 1,4-dioxane to give 58-96% substituted 1,3-oxazepine[15]. Furthermore, thermal rearrangement of ketovinylazirines gave substituted 1,3-oxazepines[16]. In the present work, four compounds containing 1,3-oxazepine moiety were synthesized by the reaction of four bis-imines with maleic anhydride. The four oxazepine compounds were characterized by different spectroscopic methods. The biological activity of the synthesized compounds was tested.

2. Experimental part

Melting points were determined by open capillary and are uncorrected. The CHN analysis measurements for the synthesized compounds were performed using EuroVector model EA3000A (Italy) and 1H-NMR spectra were scanned using Bruker model ultra-shield 400MHz (Switzerland), at TehranUniversity, Iran. DMSO-d6 was used as a solvent and TMS as an internal standard. IR spectra were recorded using KBrdisc on Shimadzu FT-IR model 8400 Spectrophotometer at Chemistry Department, College of Education of Pure Sciences, Basrah University.

2.1. Synthesis of compounds

2.1.1. Synthesis of imine (1-4)

The compounds, N,N'-Dibenzylidene-ethane-1,2-diamine (**1**), N,N'-Bis-(4-methoxy-benzylidene)-ethane-1,2-diamine (**2**), N,N'-Bis-(3-methoxy-4-hydroxy-benzylidene)-ethane-1,2-diamine(**3**) and N,N'-Bis-(2-hydroxy-benzylidene)-ethane-1,2-diamine (**4**), were prepared by the same method[17].A mixture of 0.02 mole of aldehyde (benzaldehyde, anisaldeehyde, vanillin and salicylaldehyde), (0.01 mole) ethylene diamine and few drops of glacial acetic acid in 50ml of absolute ethanol was reflux for 1-2 hrs. After cooling, the precipitate was filtered off and recrystallized from ethanol. The physical properties and the elemental analysis are listed in Table 1.

2.1.2. Synthesis of the oxazepines (5-8)

The compounds, 2-(phenyl)-3-{2-[phenyl)-4,7-dioxo-[1,3] oxazepine-3-yl]-ethyl}2,3-dihydro-[1,3] oxazepine-4,7-dione (**5**), 2-(3-methoxyphenyl)-3-{2-[3-methoxy-phenyl)-4,7-dioxo-[1,3] oxazepine-3-yl]-ethyl}2,3-dihydro-[1,3] oxazepine-4,7-dione (**6**), 2-(3-methoxy-4-hydroxyphenyl)-3-{2-[3-methoxy-4-hydroxy-phenyl)-4,7-dioxo-[1,3] oxazepine-3-yl]-ethyl}2,3-dihydro-[1,3] oxazepine-4,7-dione (**7**) and 2-(2-hydroxyphenyl)-3-{2-[2-hydroxy-phenyl)-4,7-dioxo-[1,3] oxazepine-3-yl]-ethyl}2,3-dihydro-[1,3] oxazepine-4,7-dione (**8**), were prepared by the same method[18].To a solution of the imine (0.01 mole) of imine in dry toluene, a solution of maleic anhydride (0.02 mole) in ethanolic solution was added drop wise with stirring then refluxed for 3-4 hr. The progress of the reaction was followed by TLC technique. The solid precipitate of desired product was filtered off, recrystallized from methanol and dried under vacuum.The physical properties and the elemental analysis are listed in Table 1.

Table 1: The characterization of the prepared tetrazole compounds

Compd.	Molecular formula	Molecular weight (g/mole)	m.p. (°C)	Yield (%)	Elemental analysis Found (Calcd.)		
					C%	H%	N%
1	$C_{16}H_{16}N_2$	236.31	116-118	87	80.97 (81.32)	6.54 (6.82)	12.12 (11.85)
2	$C_{18}H_{20}N_2O_2$	296.36		77	73.21 (72.95)	6.66 (6.80)	9.31 (9.45)
3	$C_{18}H_{20}N_2O_4$	328.36		92	64.98 (65.84)	6.32 (6.14)	8.21 (8.53)
4	$C_{16}H_{16}N_2O_2$	268.31		94	70.96 (71.62)	6.45 (6.01)	10.61 (10.44)
5	$C_{24}H_{20}N_2O_6$	432.43	121-123	65	67.02 (66.66)	4.86 (4.66)	6.16 (6.48)
6	$C_{26}H_{24}N_2O_8$	492.48		71	62.75 (63.41)	4.92 (4.91)	5.49 (5.69)
7	$C_{26}H_{24}N_2O_{10}$	524.48		77	59.16 (59.54)	4.69 (4.61)	5.48 (5.34)
8	$C_{24}H_{20}N_2O_8$	464.42		62	62.17 (62.07)	4.51 (4.34)	6.18 (6.03)

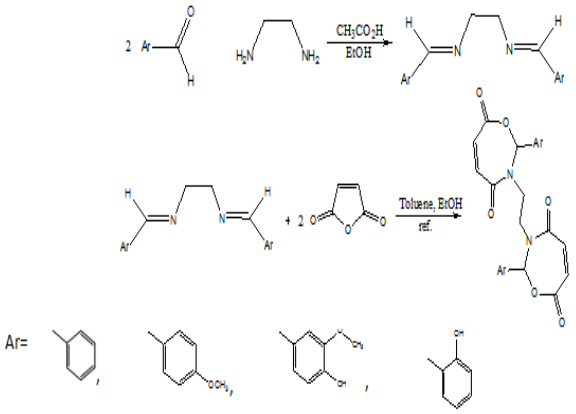
2.2. The biological study[19]

The antibacterial activity of the prepared compounds was investigated by Filter Paper Disc Diffusion Method (Kifby-Bauer Method) using a standard bacterial species, Gram negative *Escherichia coli* (ATCC 25922) and Gram positive *Staphylococcus aureus* (ATCC 25923). A stock solution (1000 □g/ml) of each compound was prepared in dimethyl sulfoxide solvent and stored at 4-8 °C until used. The agar plates (Mueller Hinton agar) in Petri-dishes were inoculated by dipping a sterile cotton swab into the inoculum and evenly streaking the swab in three directions over the entire surface of the plates. Filter paper (6 mm diameter) discs were impregnated with solution (1000 µg/ml) of tested compounds, dried and placed on an agar plate containing lawn cultures of certain bacteria.

The plates were incubated at an optimum growth temperature (37 oC) for 24 hrs and then the zone of microbial growth inhibition around the discs was measured (in mm) and compared with amoxicillin and streptomycin.

3. Results and discussion

The synthetic routes of the compounds **1-8** are illustrated in Scheme 1. The structure of the synthesized compounds **1-8** was conformed via the spectroscopic methods.



Scheme 1

3.1. FT-IR Spectra

The IR spectra for oxazepine compounds were performed by the KBr disc method. Table 2 represents the data of the important bands of the IR spectra of these compounds.These compounds exhibited common bands in the range 1717-1730 $cm^{-1}$and 1651-1672 cm^{-1} attributed to the $\nu_{C=O}$ bond of carbonyl group of ester and amide, respectively. Strong to medium bands in 1490-1600 cm^{-1} related to $\nu_{C=C}$ stretching of aromatic ring, as shown in Figures 1-4. Absorption bands at the range 1319-1390 cm^{-1} and 1182-1197 cm^{-1} are assigned to the existence of asymmetric and symmetric stretching of ν_{C-O-C}, respectively. The compounds **7** and **8** exhibited a broad band at 3254 and 3190 cm^{-1} attributed to O-H band stretching of vanillin and salicylaldehyde fragment which at the lower frequency due to intramolecular H-bonding[20]. As shown in Table 2.

Table 2:FT-IR spectra data of oxazepine compounds

5	*6*	*7*	*8*	*Assignment*
		3254 br	3190 br	O-H stretching
3066w	3062w	3070w	3064 w	C-H stretching aromatic
2975 w	2987w 2920w	2920 w	2977 w 2945 w	C-H stretching aliphatic
1720 s	1726 s	1730 s	1717 s	C=O stretching ester group
1662 s	1665 s	1651 s	1672s	C=O stretching amide group
1595 s 1490 s	1600m 1492 s	1600s 1500 s	1593 m 1514 m	C=C stretching of aromatic rings
1456 s	1442 m	1440 w	1425 m	C-H bending aliphatic
1380 s	1390s	1386s	1319 m	O-C-O C-N asymmetric stretching
1195s	1197 s	1182s	1182 m	O-C-O C-N symmetric stretching
757 s	769 m	827 m	769 s	C-H bending aromatic

br = broad, s = strong, m = medium, w = weak

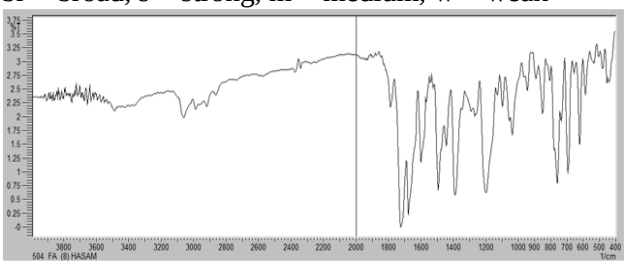


Figure 1: FT-IR spectrum of oxazepine 5

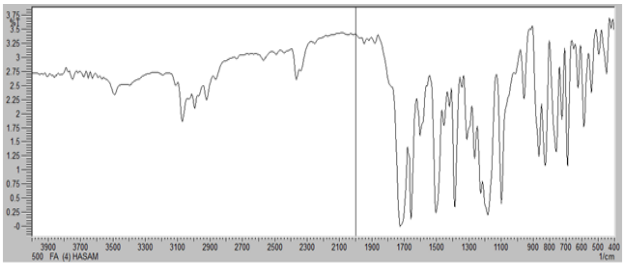


Figure 2: FT-IR spectrum of oxazepine 6

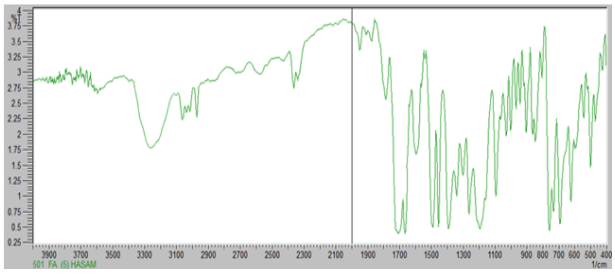


Figure 3: FT-IR spectrum of oxazepine 7

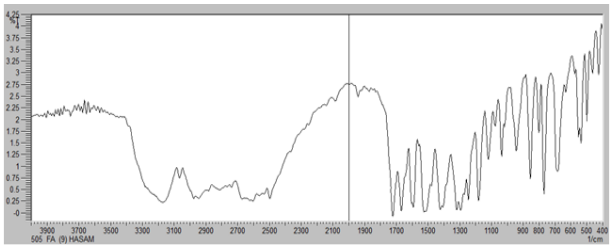
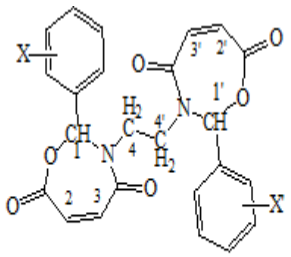


Figure 4: FT-IR spectrum of oxazepine 8

3.2.[1]H-NMR spectra

The [1]H-NMR chemical shift values for compounds **5-8** in $CDCl_3$ solution are listed in Table 3. The [1]H-NMR spectra of these compounds show two doublet signals in the down-field regions 6.980-6.995 ppm and 7.290-7.326 ppm which can be assigned to the heterocyclic ring oxazepine protons H2,2' and H3,3', respectively, with J-coupling constant 7.9-8.4 Hz [21, 22]. All title compounds exhibit singlet signals at the range 9.666-9.880 ppm which can be attributed to the protons H1 and H1'[23]. The hydroxyl protons for the compounds **7** and **8** appeared, in low-field, as a singlet signal at 9.995 ppm and 10.515 ppm, respectively. 1H-NMR spectra of compounds 6 and 7 showed singlet signals at 3.852 ppm and 3.931 ppm, respectively, which can be ascribed to the methoxy group protons. All synthesized compounds as shown in Figures 5-8 exhibited singlet signals at the range 3.438-3.630 ppm attributed to the protons H4 and H4'[21,24,17]. The chemical shift values of the other aromatic protons are listed in Table 3.



5 (X,X'= H), **6** (X,X'= *p*-OCH_3), **7** (X,X'=*m*-OCH_3, *p*-OH) and **8** (X,X'= *o*-OH)

Table 3: Data of 1H-NMR spectra [δ (ppm), J (Hz)] of the synthesized compounds 5-8

Compound	H1,1'	H2,2'	H3,3'	$J_{2,3}$	H4,4'	-OH	$-OCH_3$	Aromatic
5	9.845	6.980	7.290	8.4	3.552	-----	------	7.193-7.251
6	9.880	6.962	7.174	8.4	3.610	------	3.852	6.858-7.202
7	9.666	7.049	7.310	8	3.631	9.995	3.931	7.722-7.855
8	9.720	6.995	7.326	7.9	4.388	10.515	-----	6.839-7.114

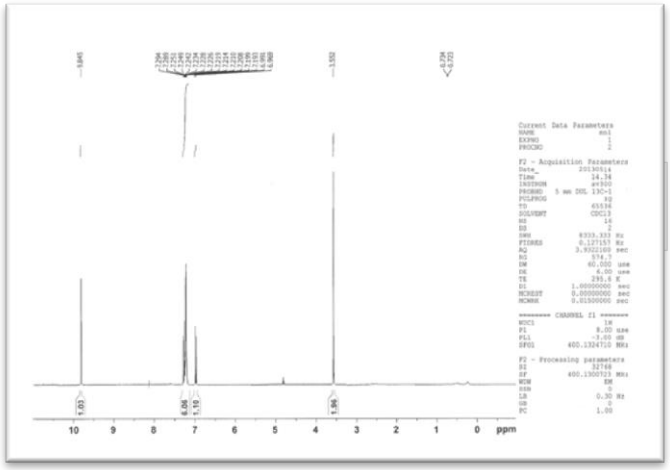


Figure 5: 1H-NMR spectrum of compound 5

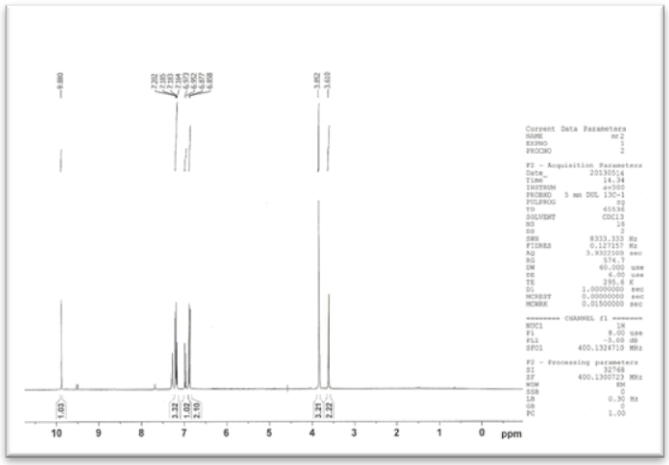


Figure 6: [1]H-NMR spectrum of compound 6

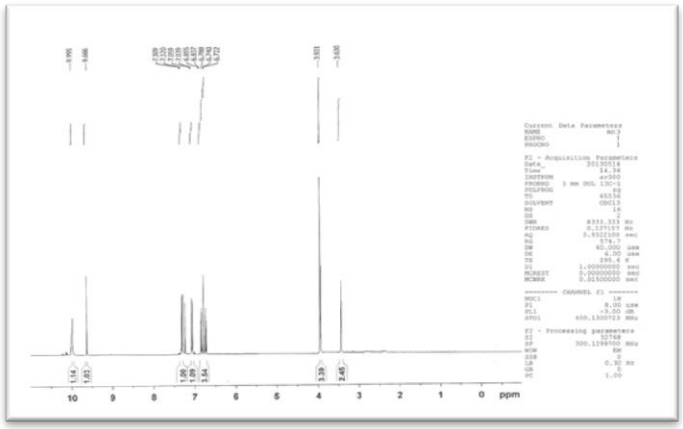


Figure 7: [1]H-NMR spectrum of compound 7

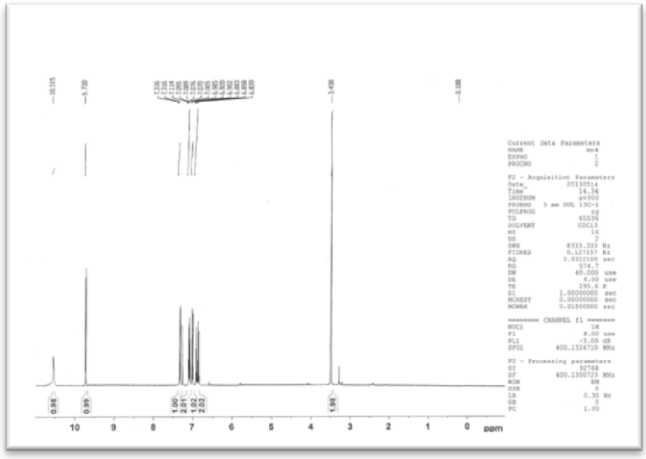


Figure 8: ^{1}H-NMR spectrum of compound 8

3.3. Antibacterial activity

The preliminary results of the antibacterial activity of the prepared compounds indicated that all compounds had good activity against *E. coli* and *S. aureus*, as shown in Table 4, and Figures 9 and 10.Table 4 showed that compound **7** and **8** exhibited the best inhibition zones 25 and 23 mm against *E. coli*, respectively, and 21 and 27 mm against *S. aureus*, respectively, as compared with the other compounds,and these compounds are less active as compared with the standard drugs, as shown in Figure10.In the comparison between oxazepines and imines, we see that oxazepines gave greater activity than imines which may be attributed to the presence of oxazepine ring. From Figures9 and 10, we see that the activity affected directly by the substituents on the aromatic ring, where the activity of compound **1** is less than the other imines and the activity of compound **5** is less than other oxazepines, as shown in Table 4.

Table 4: Inhibition zone of imines, oxazepines and standard drugs at 1000 g/ml against E coli and S. aureus

imine	Inhibition zone (mm)		oxazepine	Inhibition zone (mm)	
	E. coli	*S. aureus*		*E. coli*	*S. aureus*
1	10	NI	**5**	15	13
2	13	10	**6**	15	14
3	15	20	**7**	25	21
4	19	21	**8**	23	27
Amoxicillin	39	40	Streptomycin	29	35

NI = No inhibition

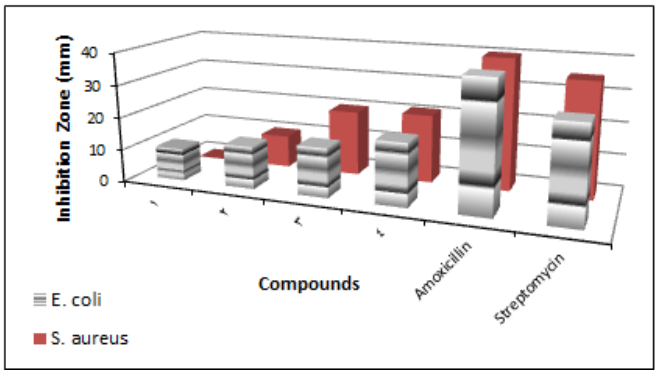


Figure 9: Inhibition zone of imine compounds and drugs against the two bacterial stains

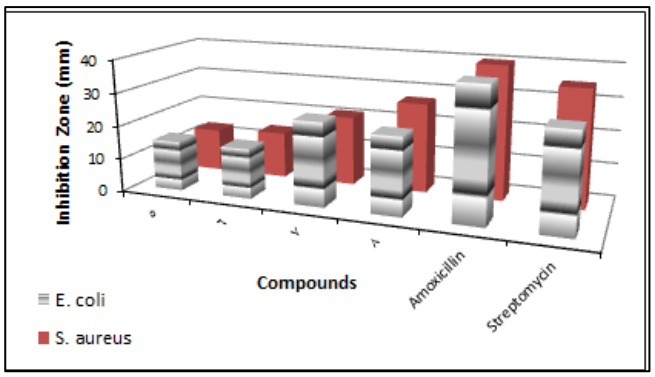


Figure 10: Inhibition zone of oxazepine compounds and drugs against the two bacterial stains

4. Conclusions

The antibacterial activity of synthesized compounds against *E. coli* and *S. aureus* was evaluated using disc diffusion method. The antibacterial activity of the newly synthesized compounds **7** and 8 gave the highest activity as compared with other synthesized compounds and less activity than the standard drugs. The activity of oxazepines was greater than the activity of imines which may be attributed to the presence of the oxazepine ring.

References

1- F.Aiello, A. Brizzi, A. Garofalo, F. Grande, G. Ragno, R. Dayam and N. Neamati, ***Bio. Med. Chem.***,12, 4459, (2004).

2- K.Audouze, E.Q. Nielsen and D. Peters, ***J. Med. Chem.***, 47, 3089, (2004).

3- P.P.M.A.Dols, B.J.B. Folmer, H., Kuil, C.W. Hamersma, H. Lucas, L. Ollero, J.B.M. Rewinkel and P. H.H. Hermkens, Chem.Lett., 18, 1461, (2008).

4- R.G.Franzen,.J. Combin. Chem., 2, 195(2000).

5- M.Ichikawa, Y. Igarashi and Y. Ichikawa, Tetrahedron Lett., 36, 1767, (1995).

6- S.Kaneko, M. Arai, T. Uchida, T. Harasaki, T. Fukuoka and T. Konosu, Bio. Med. Chem. Lett., 12,1705, (2002).
7- Y.Liao, B.J. Venhuis, N. Rodenhuis, W. Timmerman and H. Wikstrom, J. Med. Chem., 42, 2235, (1999).
8- I.Ott, B. Kircher, G. Heinisch and B. Matuszczak,J. Med. Chem., 47, 4627, (2004).
9- M.H. Serrano, D.R.S. Laurent, C.E. Mazzucco, T.M. Stickle, J.F. Barrett, D.M. Vyas and B.N.Balasubramanian,Bioorganic. Med. Chem. Lett., 12, 943, (2002).
10- L.Smith, W.C. Wong, A.S. Kiselyov, S.B. Wizemann, Y. Mao, Y. Xu, M.A.J. Duncton, K. Kim, E.L. Piatnitski, J.F. Doody, Y. Wang, R.L. Rosler, D. Milligan, J. Columbus, C. Balagtas, S.P. Lee, A. Konovalov and Y.R. Hadari, Bioorganic. Med. Chem. Lett., 16, 5102, (2006).
11- K.Bajaja, Archana and A. Kumar, Eur. J. Med. Chem., 39, 369, (2004).
12- A.Kamal, V. Tekumalla, P.Raju, V.G.M. Naidu, P.V. Diwan and R. Sistla, Bioorganic. Med. Chem. Lett., 18, 3769, (2008).
13- Y.G.Yeap, A.T. Mohammad and H. Osman, J. Mol. Struc., 982, 33, (2010).
14- F.A Hussein, Iraqi J. Chem., 26, 42, (2000).
15- J. R. Dyer, Angew. Chem. Internt., 7,321, (1968).
16- W. F.Al-hiti and M. A.Al-hadithy, National J. chem., 23, 405, (2005).
17- N. M.Aljamali, J. Scientific & Innovative Res., 2, 53(2013).
18- N. M. Al-Jamali and R. A. Khdur, J. Chem. &Cheml. Sci., 3, 97, (2013).
19- M. A. M-Ali, Ph. D. Thesis, Basrah University, (2008)
20- D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", 6th Edition, Tata McGrow-Hill, New Delhi, (2006).
21- G-Y Yeap, A. Mohamad and H. Osman, J. Molec. Struc., 3, 32, (2010)
22- A. Hameed, J. Al-Nahrain Univ., 4, 47, (2012)
23- A-T, H. Osman and G-Y Yeap, Inter. J. Spectro., ID945216, 7, (2011)
24- Z. H. Abood, H. D. Hanoon and R. T. Haiwal, J. Kerbala Univ., 3, 267, (2012)