

Synthesis and Characterization of Some Bis-1,3 Oxazepine - 4,7- dione and 1, 3 – Diazepine -4,7- dione Derivatives

Saad Salim Jasim

Chemistry Department, College of Education for Pure Sciences ,University of Kirkuk,
Kirkuk, Iraq.

saad9228@yahoo.com

Abstract

In this study, some of the new compounds have been synthesized including some of different Schiff bases (1-6) via the reaction of phenyl-1,4-diamine with substituted benzaldehyde in absolute ethanol and converted into derivatives of 1,3-oxazepine-4,7-dione (7-12) via ring closure reaction [2+5] of Schiff bases with maleic anhydride in dry benzene then the 1, 3- oxazepine -4, 7- compounds (7-12) were reacted with phenylhydrazine to produce 1,3-diazepine-4,7-dione (13-18). The prepared compounds were characterized by determination of melting point, FT-IR and UV-Visspectra, and some of the prepared compounds have been characterized by (¹H-NMR& C.H.N.) techniques.

Keywords : Schiff bases, 1,3-Oaxzpine-4,7-dione, 1,3-Diazepine-4,7-dione.

تحضير وتشخيص بعض من مشتقات ثنائي 3,1-أوكسازيبين-7,4-ثنائي أون و ثنائي 3,1-دايازيبين-7,4-ثنائي أون

سعد سالم جاسم

قسم الكيمياء، كلية التربية للعلوم الصرفة، جامعة كركوك، كركوك، العراق.

saad9228@yahoo.com

المخلص

تم في هذه الدراسة تحضير مركبات جديدة تتضمن بعض من قواعد شيف (1-6) من خلال تفاعل 4,1-ثنائي أمين فنيل مع معوضات البنزليهايد في الايثانول المطلق ومن ثم تحويلها الى مشتقات 3,1-أوكسازيبين-7,4-ثنائي أون (7-12) من خلال تفاعل غلق الحلقة [2+5] لقواعد شيف مع أنهيدريد المالك في البنزين الجاف ومن ثم مفاعلتها مع الفنيل هيدرازين لإنتاج مشتقات 3,1-دايازيبين-7,4-ثنائي أون (13-18). تم تشخيص المركبات الناتجة من خلال تحديد درجة الانصهار ومطيافية الأشعة تحت الحمراء (IR-FI) ومطيافية الأشعة فوق البنفسجية (UV-Vis) وشخصت بعض المركبات المحضرة باستخدام طيف الرنين النووي المغناطيسي للبروتون ($^1\text{H-NMR}$) وتقنية التحليل الدقيق للعناصر (C.H.N).

الكلمات المفتاحية: قواعد شيف, 3,1-أوكسازيبين-7,4-ثنائي أون, 3,1-دايازيبين-7,4-ثنائي أون.

1. Introduction

Schiff bases are one of the most prevalent and important of mixed donor systems in the field of coordination chemistry. The first preparation of imines was reported in the 19th century by Schiff (1884) which were prepared by condensing primary amines with an aldehyde or ketone under specific conditions [1], because of the relative easiness of preparation, synthetic flexibility and special property of C=N group, Schiff bases are considered as an excellent chelating agents and their metal complexes have found to exhibit biological activities [2-7]. Oxazepine – dione is seven-membered ring containing nitrogen, oxygen and two carbonyl group [8-11]. Oxazepine and their derivatives have some important biological pharmacological activities [12] such as Psychoactive drug [13], enzyme inhibitors, [14] and analgesic [15]. Diazepine-dione is seven-membered ring containing two nitrogen atoms at sites 1,2, 1.3 and 1.4 and two carbonyl group [16], diazepine-dione and their derivatives like Oxazepine–diones have some important biological pharmacological actives such as Anti-cancer [17] and hepatitis [18].

2. Experimental:

2.1. Materials and methods

- 1- All chemicals were bought from Fluke and BDH Chemical Ltd. General.
- 2- Melting point were recorded with Stuart melting point apparatus.
- 3- Ultraviolet-visible (UV- Vis) spectra were recorded on Shimadzu (UV–1800) pc Spectrophotometer.
- 4- Infrared spectra (FT-IR) were recorded on Shimadzu FT-IR-3800 Spectrophotometer.
- 5- ^1H -NMR spectra were recorded on a BRUKER ULTRA SHIELD - 400MHz with tetramethyl saline as an internal standard in CDCl_3 and DMSO-d_6 as a solvents.
- 6- C.H.N. analysis were recorded on an EVROV VICTORIA- 3000.

2.2. Methods of Preparation

2.2.1. Synthesis of Schiff bases. (1-6)

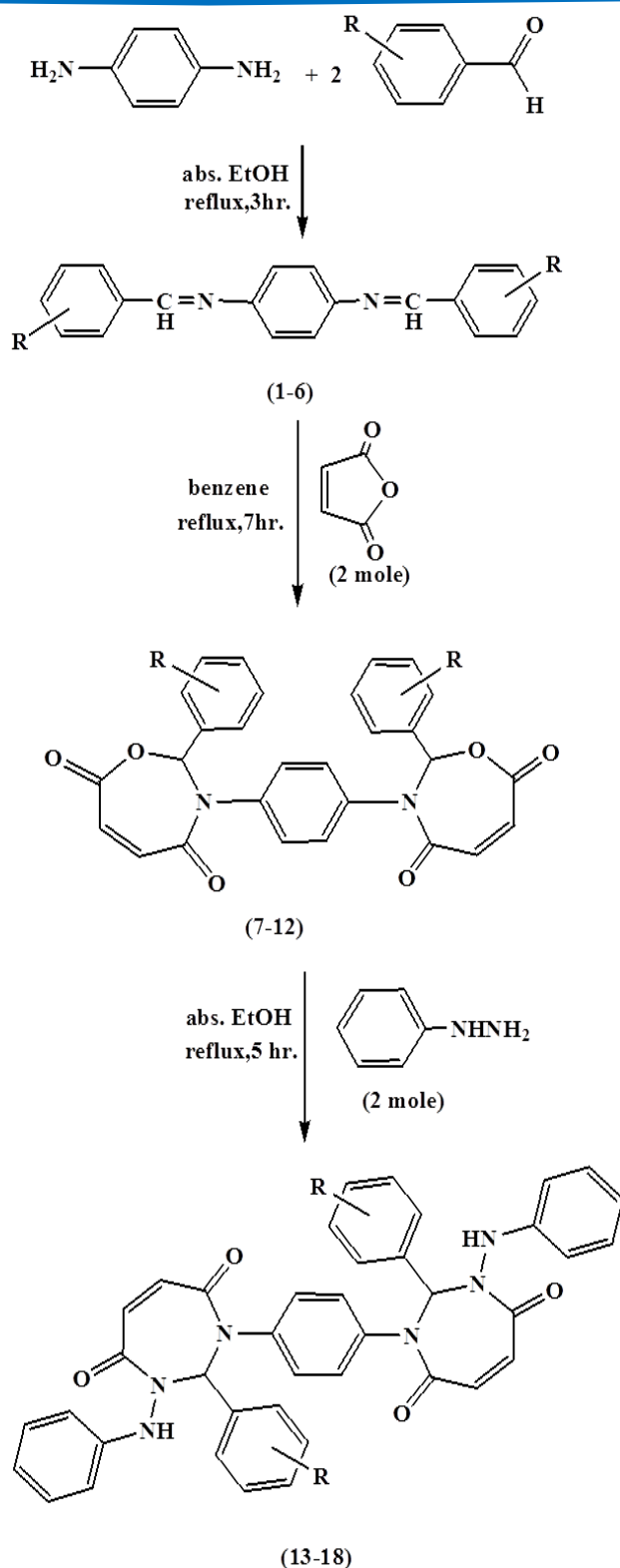
A solution of (0.01mol) of phenyl-1,4-diamine in (40ml) absolute ethanol was added to (0.02mol) of substituted benzaldehyde in (20ml) absolute ethanol, the mixture was refluxed for(3hr.), after that the mixture was cooled to room temperature, filtered, dried and recrystallized from absolute ethanol [19]. Physical properties are given in Table 1.

2.2.2. Synthesis of N,N' -{(1,1- biphenyl)-4,4-diyl} bis {2-(4-substituted)-phenyl-2,3di hydro-1,3-Oxazepine} -4,7-dione. (7-12)

A mixture of Schiff bases (1-6) (0.01mol) and (0.02 mol) of maleic anhydride in (20ml) of dry benzene was refluxed for (7hr.), the solvent was evaporated and the formed precipitate was recrystallized from absolute ethanol [20]. Physical properties are given in [Table 1](#).

2.2.3. Synthesis of N,N' -{(1,1- biphenyl)-4,4-diyl} bis {2-(4-substituted)-phenyl-2,3di hydro-1,3-Diazepine} -4,7-dione. (13-18)

A mixture of 1, 3-oxazepine (7-12) (0.01mol) and (0.02 mol) of phenylhydrazine in (20ml) of absolute ethanol with the addition of sodium carbonate (solution 10%) was refluxed for (5hr.), the solvent was evaporated and the formed precipitate was recrystallized from absolute ethanol [21]. Physical properties are given in [Table 1](#).



R = 4-OH, 4-N(CH₃)₂, 3-NO₂, (3-OCH₃, 4-OH), 4-OCH₃, 2-OH

Scheme (1): Represents the prepared compounds

Table 1: Physical properties of prepared compounds (1-18).

Comp.No.	R	Molecular Formula	Colour	Yield %	M.P ⁰ C
1	4-OH	C ₂₀ H ₁₆ N ₂ O ₂	Yellow	65	277-279
2	4-N(CH ₃) ₂	C ₂₄ H ₂₆ N ₄	Yellow	75	282-284
3	3-NO ₂	C ₂₀ H ₁₄ N ₄ O ₄	Yellow	60	251-253
4	3-OCH ₃ 4-OH	C ₂₂ H ₂₀ N ₂ O ₄	Brown	62	275-276
5	4-OCH ₃	C ₂₂ H ₂₀ N ₂ O ₂	Yellow	69	291-293
6	2-OH	C ₂₀ H ₁₆ N ₂ O ₂	Orange	58	266 dce.
7	4-OH	C ₂₈ H ₁₆ N ₂ O ₈	Brown	75	195-197
8	4-N(CH ₃) ₂	C ₃₂ H ₁₆ N ₄ O ₆	Red	63	198-200
9	3-NO ₂	C ₂₈ H ₁₄ N ₄ O ₁₀	Yellow	59	191-193
10	3-OCH ₃ 4-OH	C ₃₀ H ₂₁ N ₂ O ₈	Orange	75	260-262
11	4-OCH ₃	C ₃₀ H ₂₁ N ₂ O ₈	Red	63	160-162
12	2-OH	C ₂₈ H ₁₆ N ₂ O ₈	Deep Orange	62	199-202
13	4-OH	C ₄₀ H ₃₂ N ₆ O ₆	Brown	69	183-185
14	4-N(CH ₃) ₂	C ₄₄ H ₄₂ N ₆ O ₄	Red	73	212-214
15	3-NO ₂	C ₄₀ H ₃₀ N ₈ O ₈	Deep Brown	68	144-146
16	3-OCH ₃ 4-OH	C ₄₂ H ₃₆ N ₆ O ₈	Deep Red	43	246-248
17	4-OCH ₃	C ₄₂ H ₃₆ N ₆ O ₆	Deep Red	24	205-207
18	2-OH	C ₄₀ H ₃₂ N ₆ O ₆	Deep Orange	71	188-190

3. Results and Discussion

3.1. Schiff bases (1-6)

The Schiff bases were prepared by the reaction of phenyl-1, 4-diamine with substituted benzaldehyde in absolute ethanol. The prepared compounds were characterized by melting point, FT-IR spectra and UV-Vis spectra. The FT-IR spectra of Schiff bases showed the disappearance of bonds at (3317-3392) cm⁻¹ due to amino group, and new bonds appeared

at(1600-1669) cm^{-1} attributed to the azomethene ($\text{C}=\text{N}$) and the appearance of bond at (1429-1523) cm^{-1} and (1500-1581) cm^{-1} due to ($\text{C}=\text{C}$) aromatic and (3000-3135) cm^{-1} attributed to ($\text{C}-\text{H}$) bond in the aromatic ring.

^1H -NMR spectrum for compound (2) showed multiple signals at(6.74-7.65) ppm due to the aromatic system and the signal at(7.86) ppm due to the proton of imine group($\text{N}=\text{C}-\text{H}$). UV-Vis and FT-IR spectral data are given in table (2). FT-IR spectral data of compounds (2) & (4) are shown in figures (1) & (2). ^1H -NMR spectrum of compound (3) is shown in figure (3). C.H.N analysis of compound (3) is shown in table (5).

Table 2: FT-IR & UV-Vis spectral data of Schiff bases (1-6).

Comp. No.	R	λ_{max_1} λ_{max_2} THF	IR (KBr) cm^{-1}				
			$\nu=\text{CH}$ Ar.	$\nu\text{C}=\text{N}$	$\nu\text{C}=\text{C}$ Ar.	1,4-di Sub.	Others
1	4-OH	354 240	3020	1600	1510 1444	833	νOH ,3265
2	4- $\text{N}(\text{CH}_3)_2$	361 205	3035	1595	1525 1481	814	νCH_3 asy.sy. 2976,2852 δ CH_3 asy.sy. 1440,1380
3	3- NO_2	350 284	3090	1605	1581 1523	831	νNO_2 asy.sy. 1523,1360
4	3- OCH_3 4-OH	344 240	3135	1660	1512 1429	823	δOH ,3361 δCH_3 ,asy.sy. 2929,2886 νCH_3 ,asy.sy. 1429,1383
5	4- OCH_3	352 241	3000	1669	1500 1442	814	ν CH_3 asy.sy. 2968,2854 δCH_3 asy.sy. 1454,1365
6	2-OH	350 284	3001	1595	1515 1444	831	νOH 3143

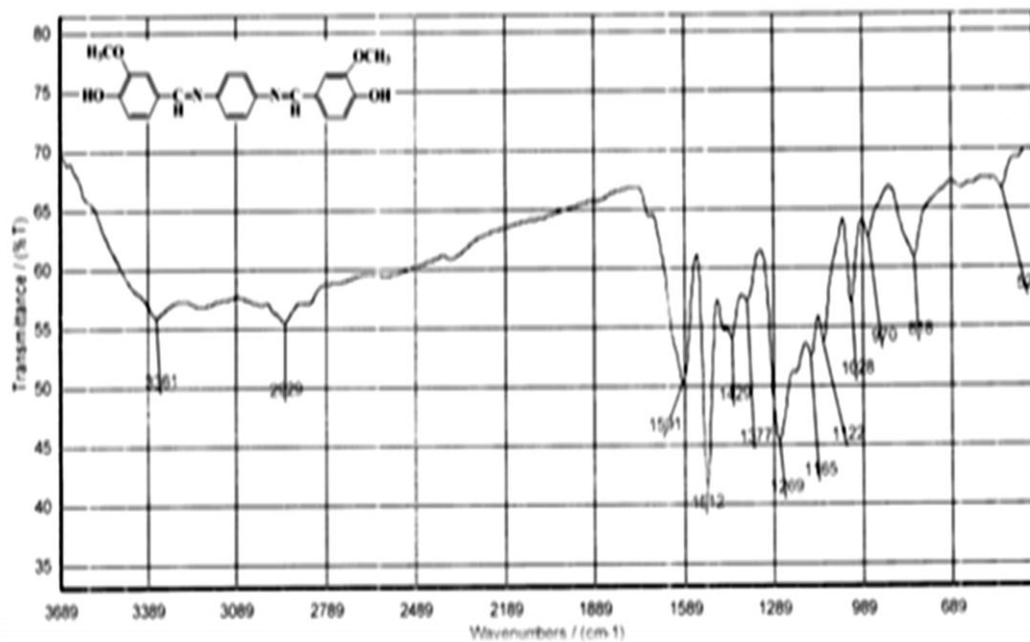


Fig. 2: FT-IR spectrum of compound (4).

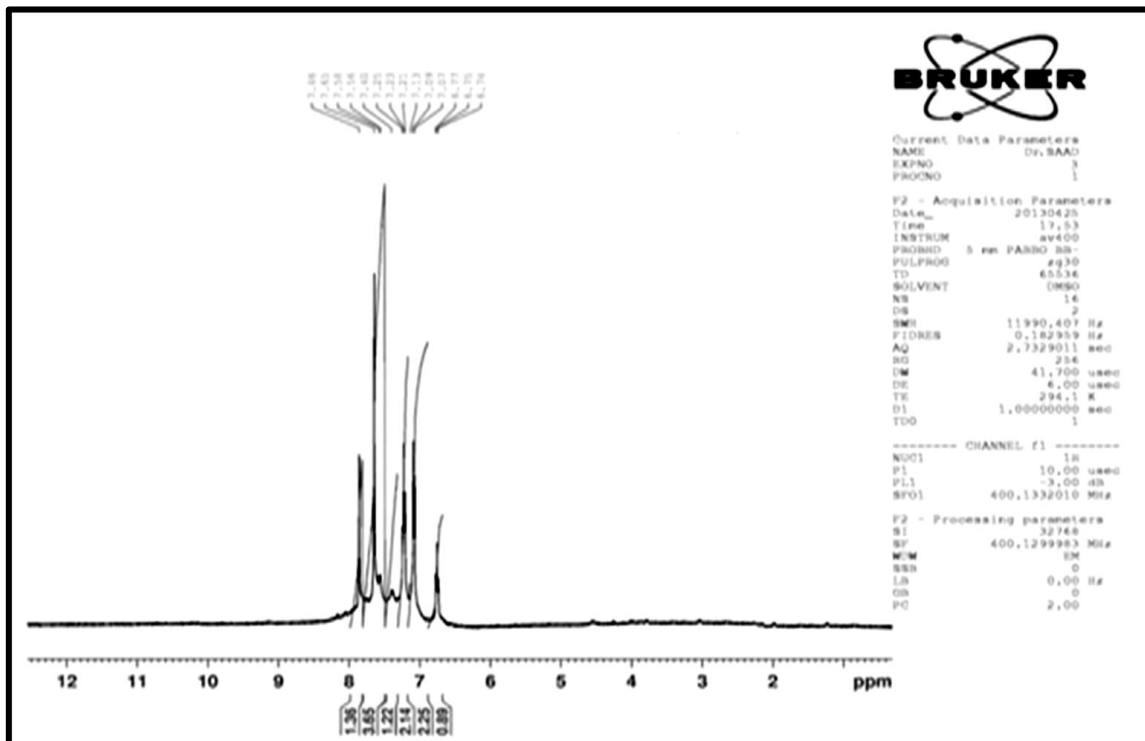
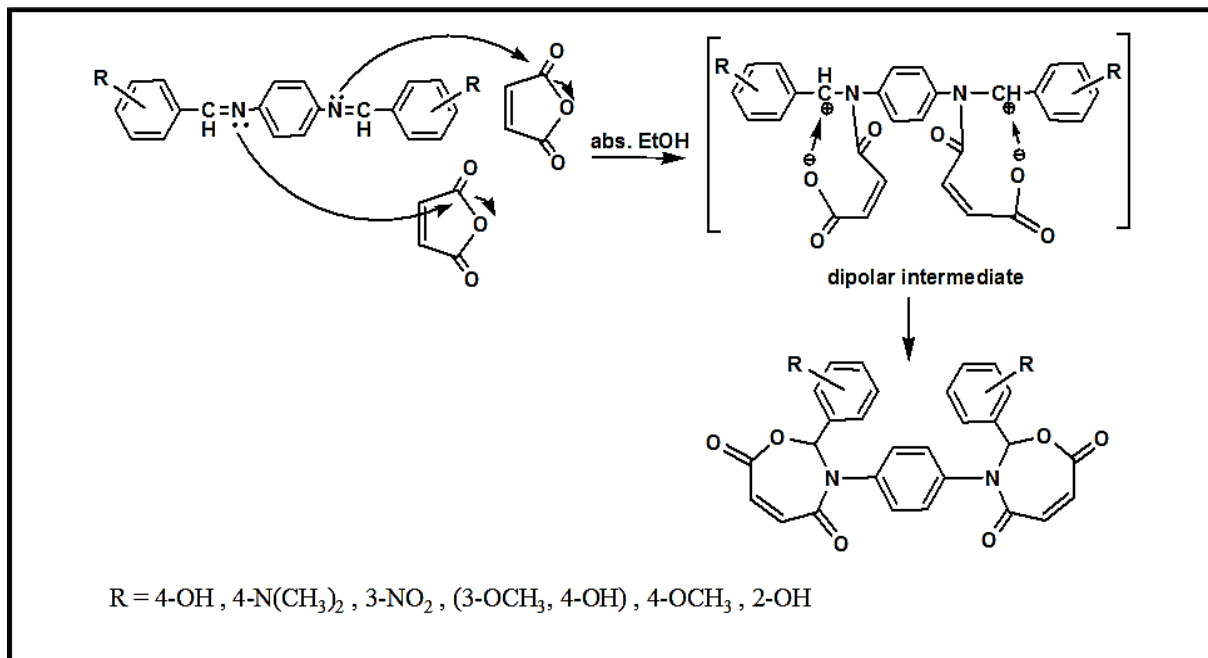


Fig. 3: ¹H-NMR spectrum of compound (3)

3.2. (1,3-Oxazepine-4,7-dione)compounds (7-12):

1,3-Oxazepine-4,7-dione compounds (7-12) were prepared from the reaction of maleic anhydride with Schiff bases (1-6). The reaction follows the following mechanism as shown:



The FT-IR spectra showed the bonds at (1699-1718) cm⁻¹ and (1603-1664) cm⁻¹ due to (C=O) for lactone and lactam compounds respectively besides other two bonds at (1420-1535) cm⁻¹ and (1533-1603) cm⁻¹ due to (C=C) aromatic ring and (1259-1286) cm⁻¹ due to C-O-C bond [22].

¹H-NMR spectrum for compound (10) showed single signal at (3.34) ppm due to protons of (OCH₃) groups besides the multiple signals at (6.74-7.86) ppm due to aromatic system and olefinic protons at C6 and C7 of the Oxazepine ring while the broad single signal at (8.62) ppm it's for the proton at C2 of the Oxazepine ring, finally the single signal at (10.42) ppm due to (OH) proton. The UV-Vis and FT-IR spectral data are given in the table (3). FT-IR spectral data of compounds (9) & (10) are shown in figures (4) & (5). ¹H-NMR spectral data of compound (10) is shown in figure (6). C.H.N analysis of compound (11) is shown in table (5).

Table 3: FT-IR & UV-Vis spectral data for 1,3-Oxazepine-4,7-dione (7-12).

Comp. No.	R	$\lambda_{\max_1}$ $\lambda_{\max_2}$ THF	IR- (KBr) –cm ⁻¹					
			ν =CH Ar.	ν C=O Lactone, Lactam	ν C=C Ar.	ν C-O- C	1,4-di Sub.	Others
7	4-OH	282 219	3111	1707 1658	1601 1514	1259	837	ν OH 3210
8	4-N(CH ₃) ₂	282 217	3102	1703 1664	1603 1545	1270	816	CH ₃ vasy.sy. 2951,2810 δ CH ₃ asy.sy. 1444,1394
9	3-NO ₂	350 282	3099	1709 1626	1533 1420	1261	822	NO ₂ vasy.sy. 1533,1352
10	3-OCH ₃ 4-OH	280 225	3097	1701 1631	1545 1512	1167	840	δ OH ,3398 ν CH ₃ asy.sy. 2952,2854
11	4-OCH ₃	361 226	3118	1718 1608	1568 1506	1281	847	ν CH ₃ asy.sy. 2910,2828 δ CH ₃ asy.sy. 1402,1323
12	2-OH	284 224	3076	1699 1603	1516 1501	1286	833	ν OH,3380

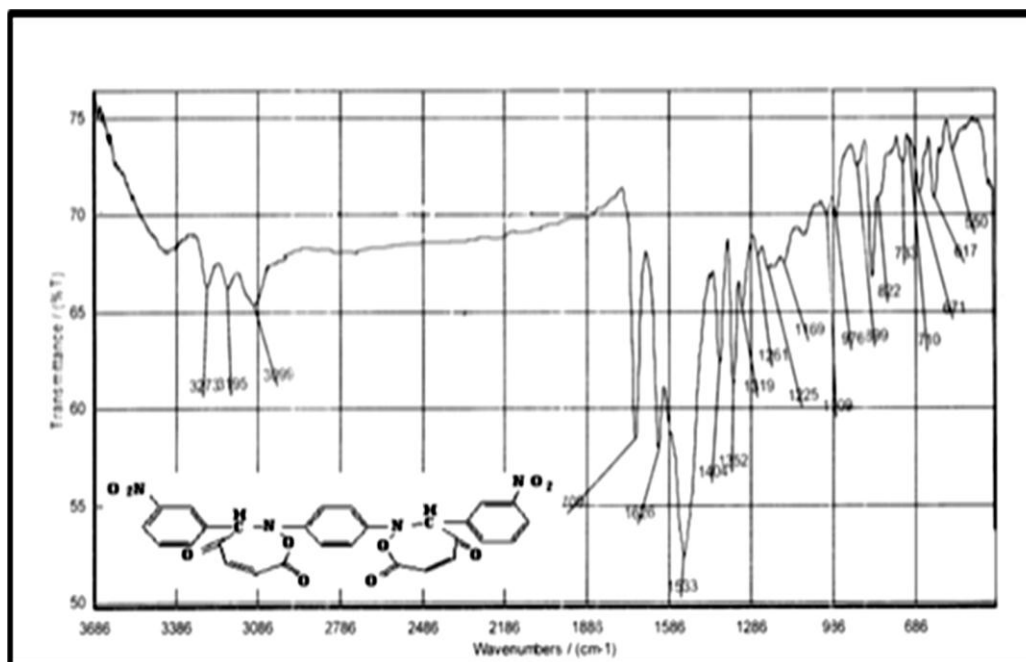


Fig 4: FT-IR spectrum of compound (9).

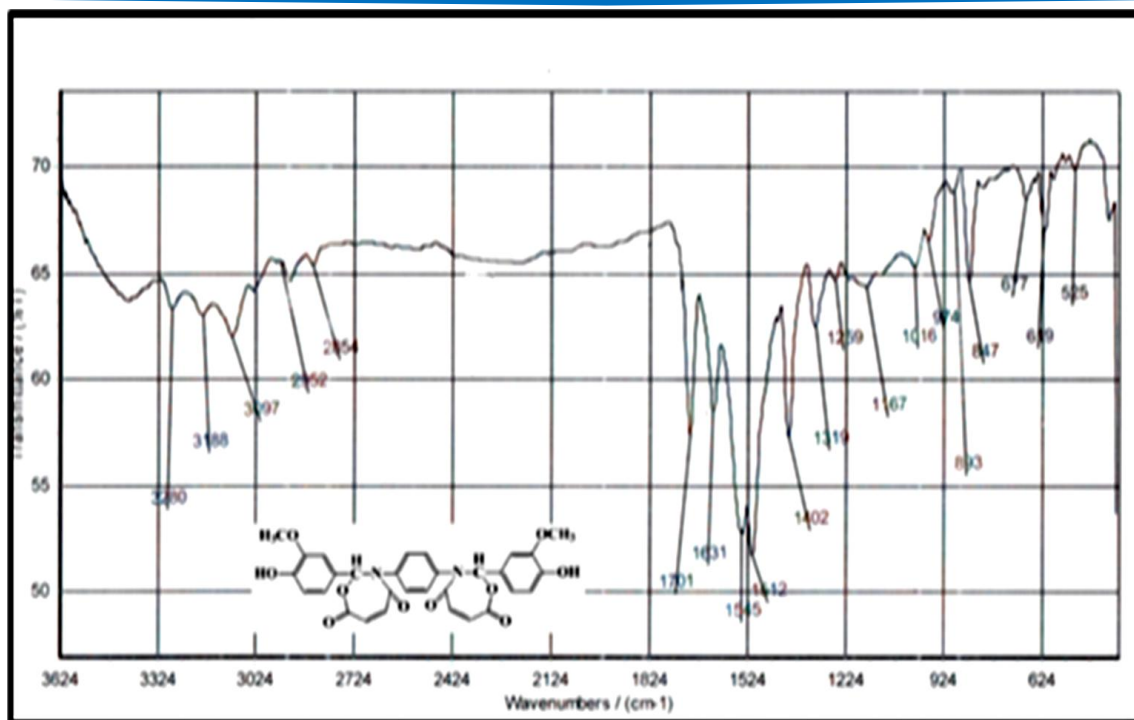


Fig. 5: FT-IR spectrum of compound (10).

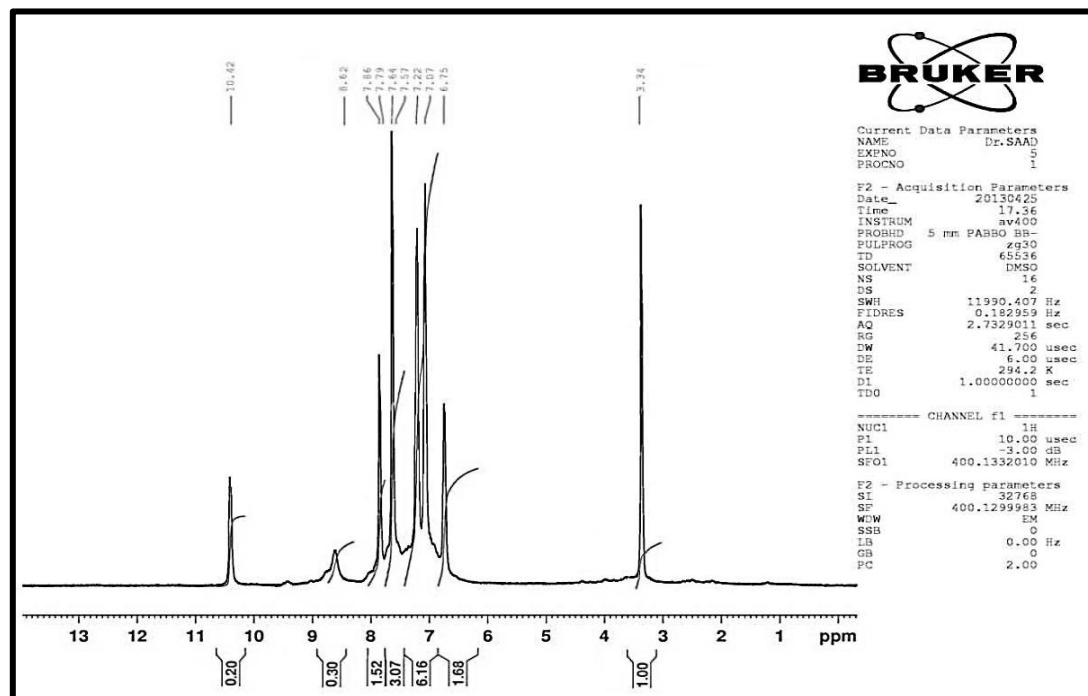
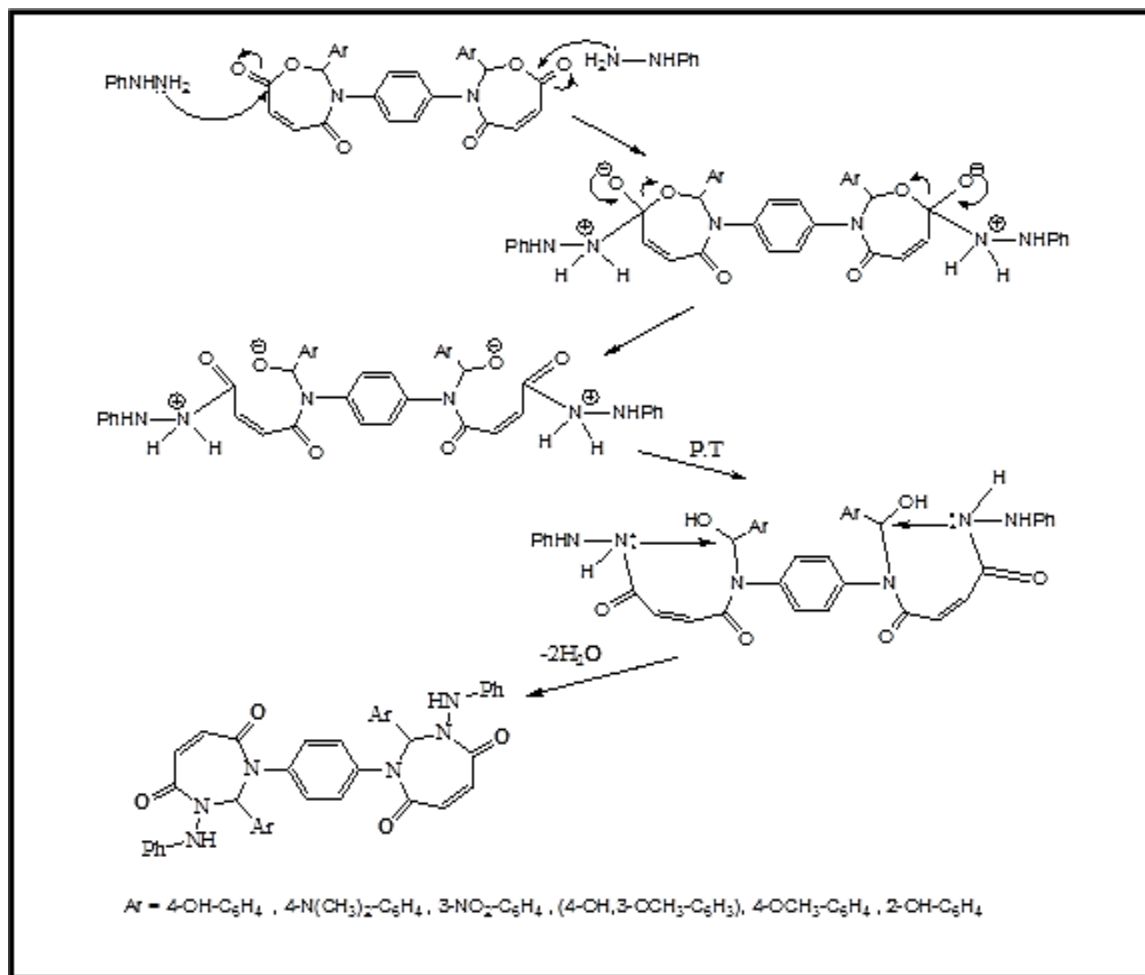


Fig. 6: ¹H-NMR spectrum of compound (10)

3.3. (1,3-Diazepine-4,7-dione) compounds (13-18)

1,3-Diazepine-4,7-dione compounds (13-18) were prepared from the reaction of phenylhydrazine with 1,3-Oxazepine-4,7-dione (13-18). The reaction follows the following mechanism as shown:



The FT-IR spectra showed the bonds at (1609-1689) cm⁻¹ due to (C=O) of lactam compounds besides other two bonds at (1497-1567) cm⁻¹ and (1533-1610) cm⁻¹ due to (C=C) aromatic ring.

¹H-NMR spectrum for compound (14) showed a single signal at (3.25) ppm due to protons of (CH₃) groups besides the multiple signals at (6.72-8.37) ppm due to the aromatic system and olefinic protons at C6 and C7 of the diazepine ring and a signal at (8.38) ppm for the proton at C2 of the diazepine ring, the single signal at (9.50) ppm due to amine protons. UV-Vis and FT-IR spectral data are given in the table (4). ¹H-NMR spectral data of

compound (14) is shown in Fig. 7. C.H.N analysis of compounds (11, 13, 15) is shown in Table 5.

Table 4: FT-IR & UV-Vis spectral data for 1,3-Diazepine-4,7-dione (13-18).

Comp. No.	R	$\lambda_{\max 1}$ $\lambda_{\max 2}$ THF	IR- (KBr) –cm ⁻¹				
			ν =CH Ar.	ν C=O Lactam	ν C=C Ar.	1,4-di Sub.	Others
13	4-OH	286 217	3176	1634	1610 1567	825	ν OH 3265
14	4-N(CH ₃) ₂	284 218	3123	1689	1578 1532	819	ν CH ₃ asy.sy. 2978,2834 δ CH ₃ asy.sy. 1476,1326
15	3-NO ₂	345 279	3089	1634	1589 1497	837	ν NO ₂ asy.sy. 1598,1324
16	3-OCH ₃ 4-OH	286 219	3107	1652	1587 1509	852	OH ,3352 δ ν CH ₃ asy.sy. 2965,2854 ν C-O-C,1137
17	4-OCH ₃	354 227	3112	1610	1598 1520	850	ν CH ₃ asy.sy. 2987,2823 δ CH ₃ asy.sy. 1416,1347 ν C-O-C,1245
18	2-OH	279 226	3135	1609	1542 1510	823	ν OH,3392

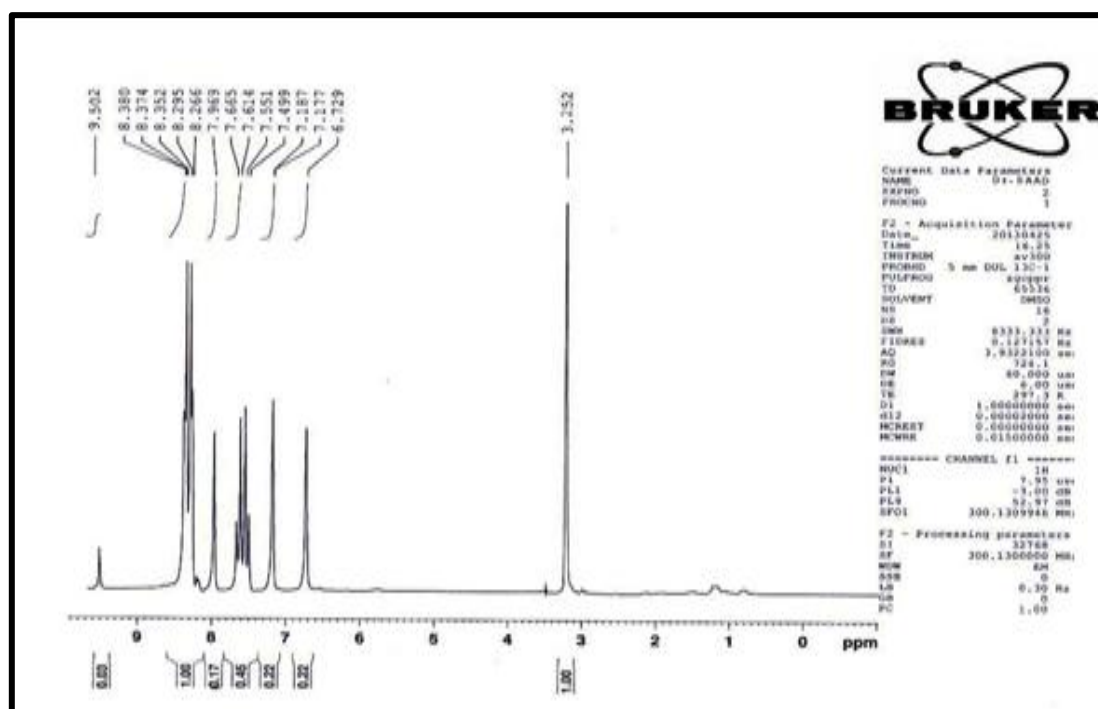


Fig 7: ¹H-NMR spectrum of compound (14).

Table 5: C.H.N Results of a careful analysis of the elements (2, 11, 13, 15 & 18).

Comp. No.	Molecular Formula	Found			Calculated		
		C%	H%	N%	C%	H%	N%
2	C ₂₄ H ₂₆ N ₄	77.80	7.10	15.11	77.80	7.07	15.12
11	C ₃₄ H ₂₆ N ₄ O ₁₀	66.68	4.50	5.20	66.66	4.48	5.18
13	C ₄₀ H ₃₂ N ₆ O ₆	66.39	4.64	12.14	69.36	4.62	12.13
15	C ₄₀ H ₃₀ N ₈ O ₈	64.03	4.02	14.94	64.00	4.00	14.93
18	C ₄₀ H ₃₂ N ₆ O ₆	69.38	4.64	12.15	69.36	4.62	12.13

4- Conclusions

In this study, new substituted 1,3- oxazepine-4,7-dione and 1,3- diazepine-4,7-dione derivatives were synthesized by using different substituted starting materials. The results of characterization were in agreement with structures, this type of compounds have a various biological activity as shown in introduction, due to the importance of these compounds, we worked on preparing some of them as a first stage and the study their biological effects may be studied by other researchers.

References

- [1] Badma Priya D. and Santha Lakshmi S., "*Synthesis, Spectral and Antimicrobial Investigation of some Ternary Schiff Base Transition Metal Complexes*", International Journal of ChemTech Research, 6(1), 87 (2014).
- [2] Rathelot P, Vanelle P, Gasquet M, Delmas F, Crozet MP, Timon-David P, et al. "*Synthesis of novel functionalized 5-nitroisoquinolines and evaluation of in vitro antimalarial activity*", Eur. J. Med. Chem., 30(6), 503 (1995).
- [3] Martins CVB, da Silva DL, Neres ATM, Magalhães TFF, Watanabe GA, Modolo LV, et al. "*Curcumin as a promising antifungal of clinical interest*", J. Antimicrob Chemother, 63(2), 337 (2009).

-
- [4] Martins CVB, de Resende MA, da Silva DL, Magalhães TFF, Modolo LV, Pilli RA, et al, "***In vitro studies of anticandidal activity of goniothalamine enantiomers***", J. Appl Microbiol, 107(4), 1279 (2009).
- [5] De Souza AO, Galetti FCS, Silva CL, Bicalho B, Parma MM, Fonseca SF, et al, "***Antimycobacterial and cytotoxicity activity of synthetic and natural compounds***", Quim Nova, 30(7), 1563 (2007).
- [6] Pandeya SN, Sriram D, Nath G, de Clercq E., "***Synthesis and antimicrobial activity of Schiff and Mannich bases of isatin and its derivatives with pyrimidine***", IL Farmaco, 54(9), 624 (1999).
- [7] Wang PH, Keck JG, Lien EJ, Lai MMC. Design, "***Synthesis testing and quantitative structure–activity relationship analysis of substituted salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate as new antiviral agents against coronavirus***", J. Med Chem, 33(2), 608 (1990).
- [8] Guan-Yeow Yeap, Abdul Karim-Talaq Mohammad, Hasnah Osman, "***Synthesis, spectroscopic and mesomorphic studies on heterocyclic liquid crystals with 1,3-oxazepine-4,7-dione, 1,3-oxazepane-4,7-dione and 1,3-oxazepine-1,5-dione cores***", Journal of Molecular Structure, 982 (1–3), 33 (2010).
- [9] Kalid Fahad A. Al. Jobary "***decarboxylation of 9,10- anthraquinone iminoacetic acid Their Spiro oxazepin derivative***", Ph.D Thesis, University of Tikrit, Iraq, (2005).
- [10] Guan YeowYeap, AbdulKarim Talaq Mohammad, Hasnah Osman, "***Synthesis, spectroscopic and mesomorphic studies on heterocyclic liquid crystals with 1,3-oxazepine-4,7-dione, 1,3-oxazepane-4,7-dione and 1,3-oxazepine-1,5-dione cores***", Journal of Molecular Structure, 982 (1–3), 33 (2010).

- [11] Fawzi. H. Jumaa, Nashwan Omar Tapabashi and Omar Abdullah Abd, "**Synthesis and Characterization of some 5, 5--Ethyl Bis- (4-Amino-4H-1, 2, 4-Triazole-3-Thiol) Derivatives**" Journal of Scientific and Engineering Research, 4(8), 98 (2017).
- [12] Zainab Amer Sallal and Hasan Thamer Ghanem, "**Synthesis of New 1,3-Oxazepine Derivatives Containing Azo Group**", Journal of Kufa for Chemical Science, (2), 11 (2011).
- [13] Basavaraju, H. S. B. Naik and M. C. Prabhakara, "**Transition Metal Complexes of Quinolino[3,2-b]benzodiazepine and Quinolino[3,2-b]benzoxazepine: Synthesis, Characterization, and Antimicrobial Studies**", Bioinorganic Chemistry and Applications, 1(10), 1155/42587, 1 (2007).
- [14] Patent Evaluation, "**Tricyclic Antihistamines with Potent Anti-Allergic Activity**", Journal of Current Opinion on Therapeutic Patents 2(1), 11 (1992).
- [15] Martin Kratzel, "**Synthesis of 5a,11b-propanonaphtho[1,2-e][1,2]oxazepines as potential opioid analgesics**", J. Chem. Soc., Perkin Trans. 1, 0, 1541 (1994).
- [16] G.W.H. Chesman and S.G Gremberg, "**Synthesis and characterization of -5,6-dihydro 7h-pyrol[1,2-d][1,4]benzodiazepine-6-one**", J. Heterocyclic Chem.,16, 241 (1979).
- [17] Min Xie, Ren G. Lapidus, Mariola Sadowska, Martin J. Edelman, Ramachandra S. Hosmane, "**Synthesis, anticancer activity, and SAR analyses of compounds containing the 5:7-fused 4,6,8-triaminoimidazo[4,5-e][1,3]diazepine ring system**". Bioorganic & Medicinal Chemistry, 24(12), 2595 (2016).
- [18] Peng Zhang, Ning Zhang, Brent E. Korba, Ramachandra S.Hosmane. "**Synthesis and in vitro anti-hepatitis B and C virus activities of ring-expanded ('fat') nucleobase analogues containing the imidazo[4,5-e][1,3]diazepine-4,8-dione ring system**". Bioorganic & Medicinal Chemistry, 15(24), 5397 (2005).

-
- [19] Sawsan Hydar Haji *"Preparation of Some Schiff Bases, Azo, Oxazepine Compounds, Identification, and Avdreation of Biological Activity"*, M.Sc. Thesis, Tikrit University, Iraq (2010).
- [20] Gazwan H. Al-Somaidaie, Fawzi H. Al-Obaidy, Bushra A. Khear Allah, *"Synthesis and Characterization of Some New 1,3-Oxazepine-4,7-dione Derivatives and Study their Antibacterial Activity"*, Tikrit Journal of Pharmaceutical Sciences, 7(1), 15 (2011).
- [21] Iman K. Naeem, Ezzat H. Zimam. *"Synthesis, Characterization and Study Antibacterial Activity of some New 1,3- oxazepine and 1,3-diazepine Derivatives"*. Der Pharma Chemica., 9(21), 86 (2017).
- [22] R. M. Silverstein. *"Spectrometric Identification of Organic Compounds"*. 7th Ed., Jon Wiley and Son Ltd, (1998).