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Synthesis, Identification of Some New Derivatives of Oxazpine, Thiazinone and Hydroquinazoline and Evaluation of Antibacterial Activity.

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Abstract

This work includes synthesis of some new derivatives of Schiff bases as intermediate compounds. Through the reaction 1,4- phen ylene diamine with different aromatic aldehydes substituted by many different groups in acidic medium and absolute ethanol as a solvent to obtain the Schiff bases (1a-5a). These compounds are reacted with substituted aromatic carboxylic acids and anhydride to give three types of heterocyclic compounds. The first line includes direct reaction with maleic anhydride under certain conditions to give new derivatives of oxazpine(6b-10b). The second line includes reaction of compounds (1a-5a) with 2-mercapto benzoic acid in the presence of triethyl amine as a catalyst and dry benzene as a solvent to give new derivatives of thiazinone(11c-15c). While the third line involved reaction the Schiff bases (1a-5a) with anthranilic acid in dioxane as solvent to give new derivatives of hydroquinazoline (16d-20d). The structures of these new synthesized compounds were identified by spectral methods their [FTIR, ^{1}HNMR, ^{13}C-NMR] and measurements of some physical properties and some specific reactions. Furthermore the effects of synthesized compounds on some strains of bacteria were studied.

Keywords: Schiff base, oxazpines, thiazinone, hydroquinazoline, antibacterial.

تحضير وتشخيص بعض المشتقات الجديده للأوكسازبين، ثايازينون وهايدروكوينازولين وتقييم الفعاليه المضاده للبكتيريا.

زينا غني جاسم الركابي ، رضاب عبد الحسين جاعد الفريجي*، سعاد محمد حسين الماجدي
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الخلاصة

تضمن البحث تحضير بعض المشتقات الجديده لمركبات قواعد شيف كمركبات وسطيه من خلال تفاعل 4,1-فنيلين داي أمين مع الديهايدات اروماتيه معوضه بمجاميع مختلفه في وسط حامضي والايثانول المطلق كمذيب للحصول على قواعد شيف (1a-5a). تفاعل هذه المركبات مع حوامض كاربوكسيليه معوضه ومع أنهيدريد الماليك تعطي ثلاثة انواع من المركبات الحلقيه غير المتجانسه: الخط الاول تضمن تفاعل مباشر مع أنهدريد الماليك تحت ظروف معينه لتعطي مشتقات جديده من الاوكسازبين (6b-10b). وتضمن الخط الثاني تفاعل المركبات (1a-5a) مع اورثومركبتوحامض البنزويك بوجود تراي اثيل امين كعامل مساعد والبنزين الجاف كمذيب لتعطي مشتقات جديده من الثايازينون(11c-15c). بينما تضمن الخط الثالث تفاعل قواعد شيف (1a-5a)مع حامض الانثرانيلك باستخدام الدايوكسان كمذيب لتعطي مشتقات جديده من الهيدروكوينازولين(16d-20d). شخصت تراكيب المركبات المحضره الجديده بأستعمال الطرق الطيفيه

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[^{13}C–NMR, ^{1}HNMR, FTIR] وقياس بعض خواصها الفيزياويه بالاضافه لذلك تمت دراسة تأثير بعض المركبات المحضره على بعض سلالات البكتيريا.

1. Introduction

General heterocyclic compounds having nitrogen, oxygen and sulphur as hetero atoms have been reported as common denominator of pharmacological and biochemical activities[1]. These compounds have been studied more thoroughly than those involving other elements, this importance of these compounds are apparent from the wealth and variety of their derivatives that occur naturally or are prepared by the industries. Among the large numbers of such compounds oxazpines, thiazines and quinazolin are of considerable biological and physiological functions in plants and animals [2]. Oxazpines is a seven membered heterocyclic which contains two hetero atoms (N and O). Oxazpines heterocyclic have been shown that they possess many types of biological properties like analgesic [3] antibacterial [4] anticancer [5] and anticoagulant [6]. Other types of compounds are thiazines which are heterocyclic compounds having one nitrogen, one sulphur atom and four carbon atoms at various positions in the six member ring and exist as 1,2 , 1,3 and 1,4 isomers [7-9]. However their derivatives having (N-C-S) linkage have been used in the fields of pharmaceutical chemistry and medicinal and reported to exhibit a variety of biological activities such as antitubercular [10], antimicrobial [11], antitumor [12], fungicidal [13] and anti-inflammatory activities [14]. Quinazoline derivatives are an important class of fused heterocycles that display a wide range of pharmacological and medicinal properties involving anti-inflammatory [15], antibiotic, antipyretic, antihypertonic and diuretic activities [16]. All these new compounds were prepared from Schiff bases derivatives with anhydride, o-mercapto benzoic acid and o-amino benzoic acid by many different methods.

2. Experimental

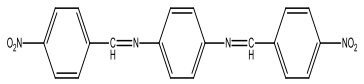
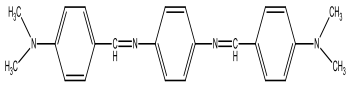
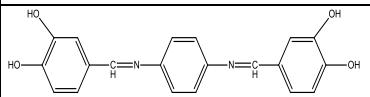
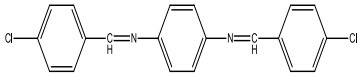
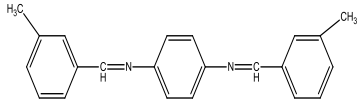
2.1 Materials and Instruments

Chemicals used are provided by Merck, BDH, Sigma Aldrich and Fluka companies. Melting points were measured using digital Stuart scientific SMP3 melting point apparatus. The FTIR spectra have been recorded on Shimadzu FTIR-8400 Fourier transform Infrared spectrophotometer using KBr discs in the (4000-600) cm^{-1} spectral range. ^{1}HNMR and ^{13}CNMR spectra were recorded on Burker 500MHz instrument using DMSO-d_6 as solvent and TMS as internal reference in Sanati Sheriff University-Tehran-Iran.

2.2 Preparations of Schiff base (1a-5a) [17]

To a stirred solution of aromatic aldehydes substituted by different groups (0.022 mol.) in absolute ethanol (18 mL) added (2-3 drops) of glacial acetic acid, 1,4-phenylene diamine (1.08 gm, 0.01 mol.) in (7 mL) of absolute ethanol was slowly added and refluxed in water bath for different period depending on the type of aldehyde. After completion of reaction cooling the mixture and filtering the precipitate. The product was recrystallized from mixture of ethanol and water (2:4) as shown in Table-1.

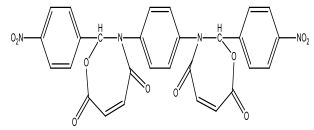
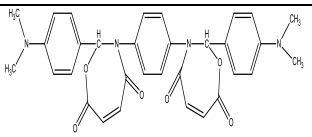
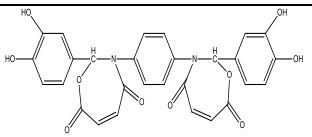
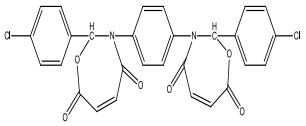
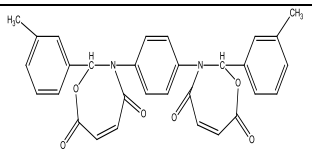
Table 1 - Physical properties and FTIR spectral data (cm^{-1}) of Schiff bases (1a-5a)

Com .No.	Physical Properties				Major FTIR Absorptions cm^{-1}				
	Structures	M. P. C.	Yield %	Color	ν(C-H) Arom.	ν(C-H) aliph.	ν(C=C) arom.	ν(C=N)	Others
1a		228-230	93	yellow	3070	-	1596 1556	1627 1650	ν(NO_2) Sym 1342 Asym 152 ν(=CH) 3080
2a		262-264	72	Deep yellow	3005	2891 2852	1593 1552	1649 1668	ν(=CH) 3080
3a		270-273	76	Green	3005	-	1544 1514	1612 1668	ν(O-H) 3525-3377
4a		225-228	67	Black	3058	-	1512 1461	1612 1643	ν(C-Cl) 1120
5a		88-90	65	Yellow	3010	2891 2850	1595 1550	1652 1672	-

2.3 Preparation of 2, 2'-substituted phenyl (1, 4-phenylene)-2, 3-dihydro-1, 3-oxazepine-4, 7-dione (6b-10b) [18]

Schiff bases (1a-5a) (0.012 mol.) reacted with (1.96 gm, 0.024 mol.) of maleic anhydride after dissolved in (18 mL) of dry benzene, (3mL) of DMF was added to the mixture and refluxed in water bath for (5 hrs.). The excess of solvent was evaporated then cooled to give crystalline solid product (6b-10b) as shown in Table- 2.

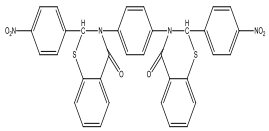
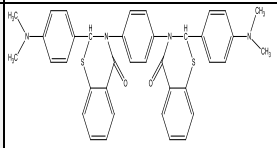
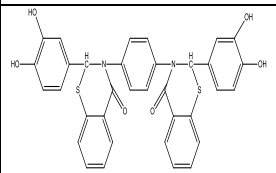
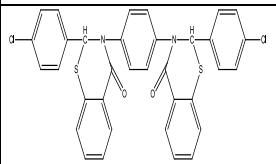
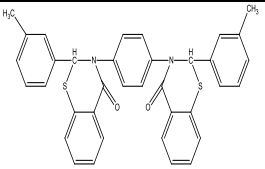
Table 2 - Physical properties and FTIR spectral data (cm^{-1}) of the synthesized compounds (6b-10b)

Com.No.	Physical Properties				Major FTIR Absorptions cm^{-1}					
	Structures	M. P. C	Yield %	Color	ν(C-H) Arom.	ν(C-H) aliph.	ν(C=O)	ν(C=C) arom.	ν(C=C) Olef.	Others
6b		237-238	60	Yellow	3087	2920 2891	1701 1685	1508 1539	1627	ν(NO_2) Sym 1323 Asym 1402
7b		241-242	58	Red	3080	2990	1701 1689	1510 1542	1622	-
8b		238-240	63	Black	3033	2921	1699 1680	1539 1510	1622	ν(O-H) 3531-3282
9b		180-182	67	Black	3087	2850 2678	1705 1685	1542 1510	1622	ν(C-Cl) 1091
10b		>300	55	Yellow	3089	2918	1701 1678	1539 1508	1627	-

2.4 Preparations of 2, 2'-substituted phenyl (1, 4-phenylene) bis (3-(alkyl) -2H-benzo [1, 3] thiazine-4-(3H-one) (11c-15c) [19]

A mixture of Schiff base (0.011 mol.) and 2-mercapto benzoic acid (3.08 gm, 0.02 mol) were dissolved in mixture of (22 mL) dry benzene and (3 mL) of DMF. (A few drops) of triethyl amine was added, then the mixture was refluxed for (4hrs.), after that the solvent was removed under vacuum. The remains was transferred to separatory funnel and extracted by sodium bicarbonate solution (10%), filtered and recrystallized from dioxane, as shown in Table- 3.

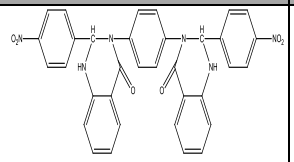
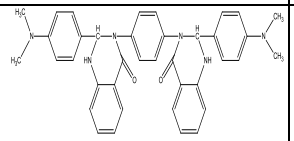
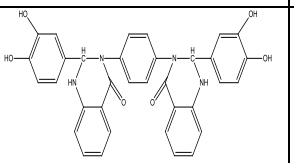
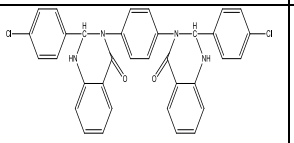
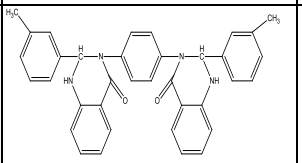
Table 3 - Physical properties and FTIR spectral data (cm^{-1}) of the synthesized compounds (11c-15c)

Com .No.	Physical Properties				Major FTIR Absorptions cm^{-1}						
	Structures	M. P. C.	Yield %	Color	ν(C-H) Arom.	ν(C-H) aliph.	ν(C=O) amide	ν(C=C) arom.	ν(C-S)	ν(C-N)	Others
11c		210 - 212	65	Red	3085	2885	1668	1595 1562	688	1342	ν(NO_2) Sym 1342 Asym 1519
12c		247 - 249	60	Yellow	3040	2852	1668	1525 1550	601	1361	-
13c		123 - 124	81	Off white	3055	2925 2854	1660	1514 1556	619	1392	ν(O-H) 3442-3342
14c		290 - 292	84	Black	3060	2931	1662	1515 1456	622	1227	ν(C-Cl) 1035
15c		>300	53	Brown	3060	2923 2852	1660	1550 1490	698	1288	--

2.5 Preparations of 2, 2'-substituted phenyl (1, 4-phenylene) bis (3-alkyl)-2, 3dihydroquinazoline-4-(1H) one) (16d-20d) [20]

A solution of 2-amino benzoic acid (2.74 gm, 0.02 mol.) in dioxane was added to Schiff bases (0.01 mol.) with a few drops of DMF. This solution was heated under reflux for (20 hrs.) in water bath. The solvent was evaporated under reduced pressure and neutralized the remains with 10% sodium bicarbonate then filtered and recrystallized from the mixture of ethanol/water (1:2), as shown in Table- 4.

Table 4 - Physical properties and FTIR spectral data (cm^{-1}) of the synthesized compounds (16d-20d)

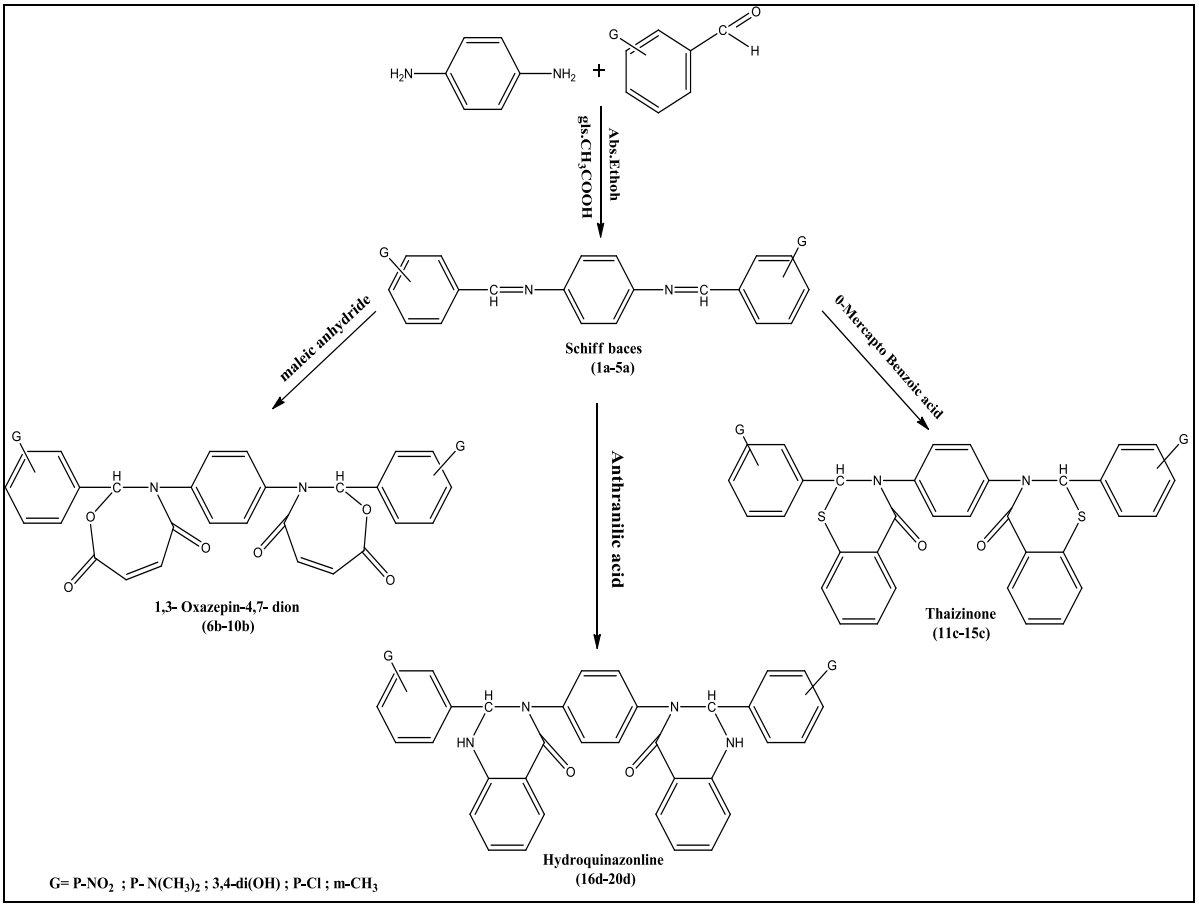
Com .No.	Physical Properties				Major FTIR Absorption cm^{-1}						
	Structures	M. P. C°	Yield %	Color	ν(C-H) Arom.	ν(C-H) aliph.	ν(C=O) amide	ν(C=C) arom.	ν(-NH)	ν(C-N)	Others
16d		238-240	55	Deep Red	3085	-	1681	1577 1614	3348	1257 1321	ν(NO_2) Sym 1344 Asym15 12
17d		210-211	64	Yellow	3147	2852	1668	1525 1550	3352	1250 1396	-
18d		>300	78	Brown	3066	-	1664	1535 1620	3338	1342 1359	ν(O-H) 3417
19d		281-282	85	Black	3060	-	1681	1523 1583	3330	1251 1317	ν(C-Cl) 1014
20d		260-262	62	Deep yellow	3053	2918 2972	1650	1575 1604	3373	1263 1375	-

2.6 Antibacterial activity [21]

The antibacterial evaluation for some of these synthesized compounds was done using disk diffusion process [21]. The results were listed in Table-7.

3. Results and Discussion:

In this work Schiff bases (1a-5a) were prepared by the reaction of 1, 4-phenylene diamine with variety of substituted aromatic aldehydes in acidic medium (glacial acetic acid) as a catalyst and absolute ethanol as a solvent, as shown in scheme 1



Scheme 1- Preparation of new derivatives of oxazpine, thiazinone and hydroquinazoline (6b-20d)

FTIR [22] spectra showed the disappearing of ν (NH_2) group absorption band at (3400) cm^{-1} and appearance of absorption band of ν (-C=N) in the range (1612-1672) cm^{-1} with other value of substituted groups. The other values of FTIR spectral data for compounds (1a-5a) are listed in Table-1 and shown in Figure- 1.

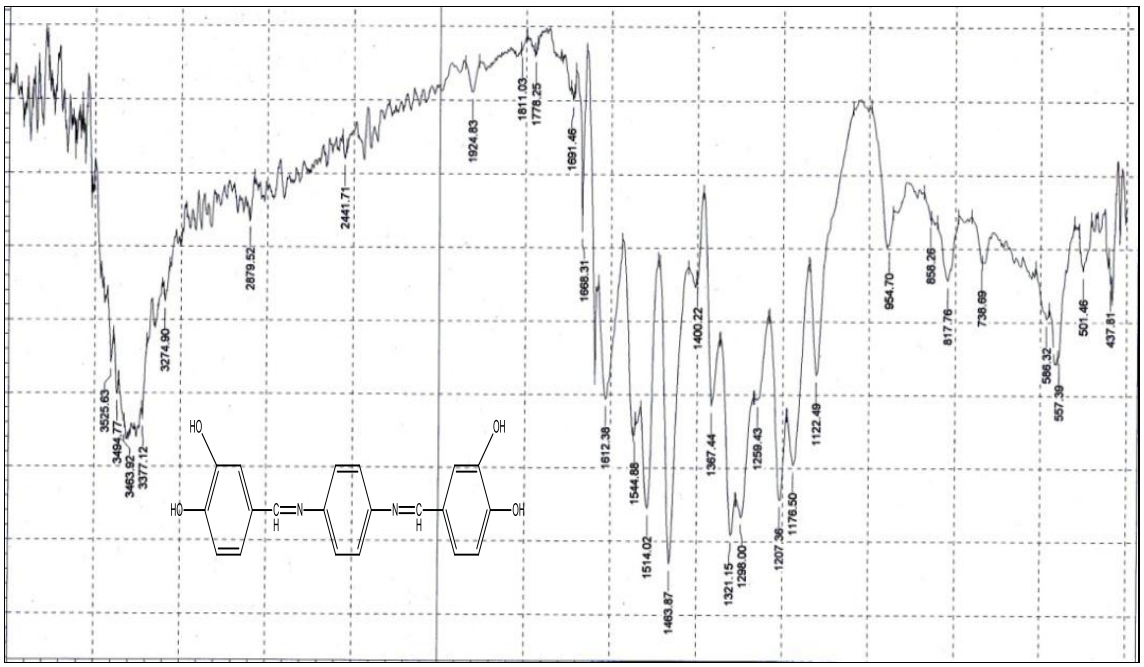


Figure 1 -FTIR spectrum of compound (3a)

The Schiff base obtained from the above step was allowed to react with maleic anhydride in dry benzene and dimethyl formamide produced oxazpine derivatives (6b-10b). These compounds were characterized by FTIR data which showed disappearing of absorption band of ν(C=N) and appearing band of ν(C=C) olfine for maleic anhydride in (1622) cm^{-1}.The other values of FTIR spectral data for compounds (6b-10b) are listed in Table-2 and shown in Figure- 2.

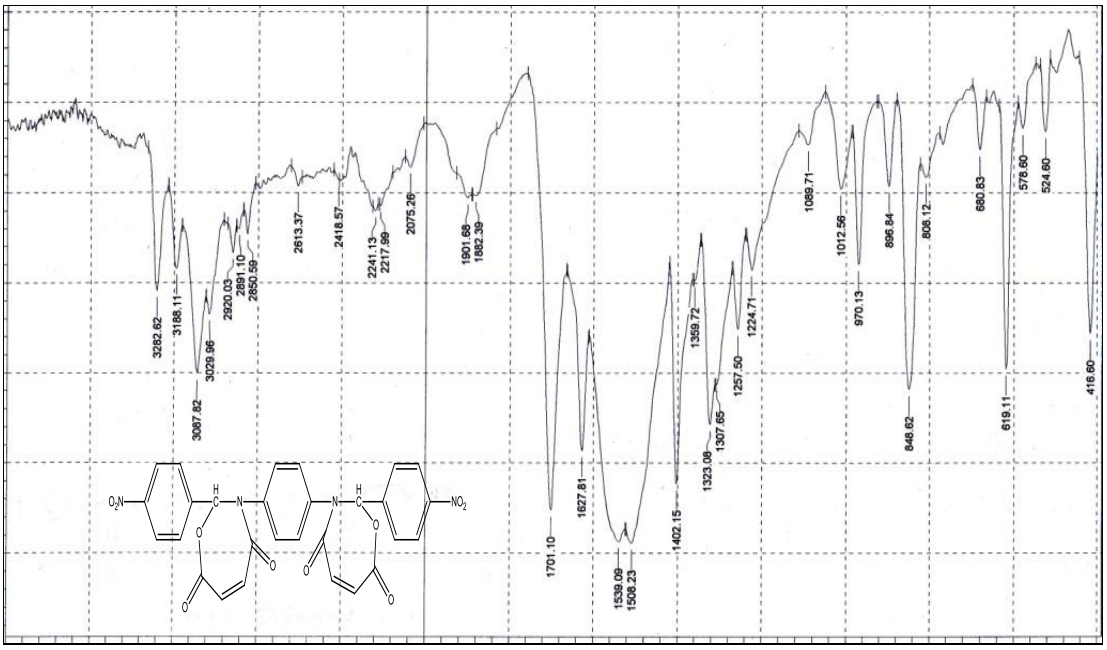


Figure 2 -FTIR spectrum of compound (6b).

^{1}HNMR spectrum for compound (7b) showed singlet signal in δ= (2.8) ppm due to (s,12H,-N(C<u>H</u>$_3$)$_2$)protons ; singlet signal in δ= (3.1) ppm due to(s,2H,N-C<u>H</u>-O) protons; singlet signal in δ= (6.1) ppm due to(s,4H,O=C-C<u>H</u>=C<u>H</u>-C=O) protons and signals in δ= (6.28-7.93) ppm due to aromatic rings protons as listed in Table-5 and shown in Figure- 3.

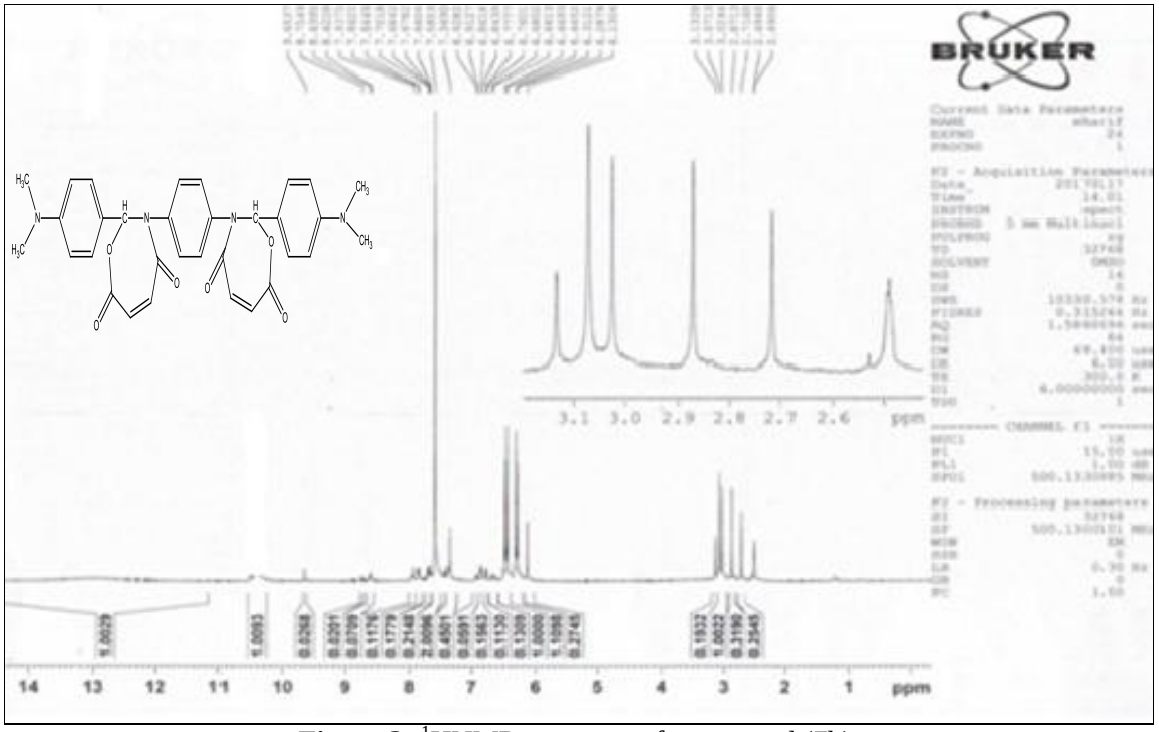


Figure 3 -^{1}HNMR spectrum of compound (7b).

^{1}HNMR spectrum for compound (10b) showed singlet signal at δ= (2.4) ppm due to (s,6H,-Ar-C<u>H</u>$_3$) protons; singlet signal at δ= (3.3) ppm due to(s,2H,N-C<u>H</u>-O) protons; singlet signal at δ= (6.2) ppm due to(s,4H,O=C-C<u>H</u>=C<u>H</u>-C=O) protons and signals at δ= (6.3-7.5) ppm due to aromatic rings protons as listed in Table-5 and shown in Figure- 4.

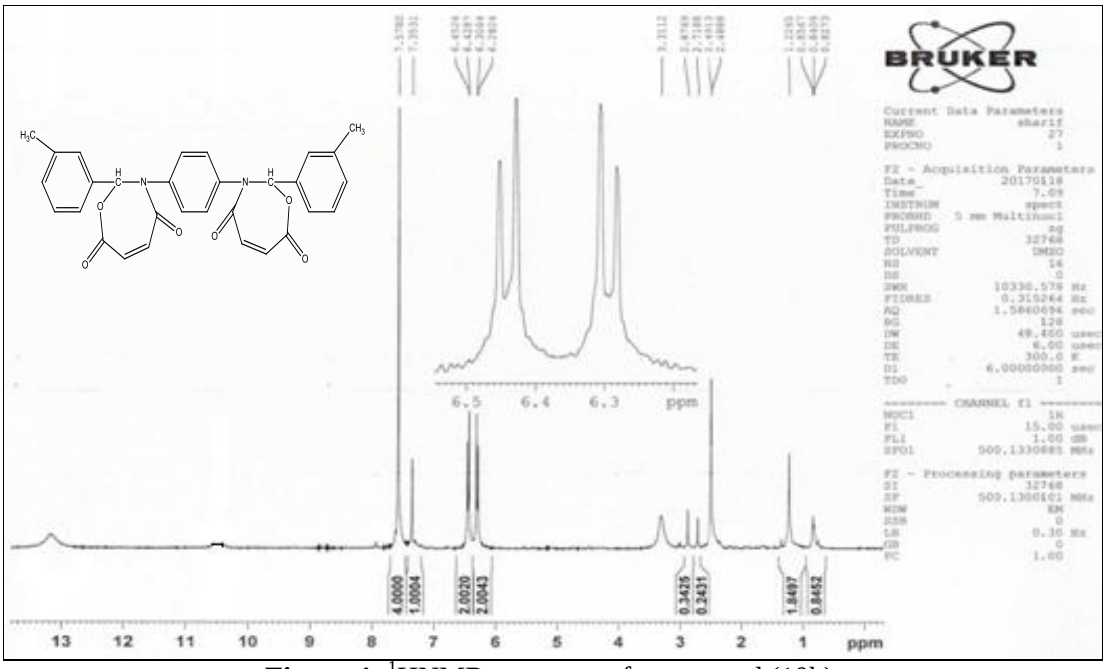


Figure 4 -^{1}HNMR spectrum of compound (10b).

The target product thiazinone derivatives (11c-15c) were obtained by the reaction of Schiff bases with ortho-mercapto benzoic acid in the presence of triethyl amine as a catalyst and dry benzene as a solvent. These compounds also are characterized by FTIR spectra which showed disappearance of ν(C=N) band and appearance of ν(C=O) amide bands in the value (1660-1668) cm^{-1} and ν(C-S) band in (601-698) cm^{-1}. The other values of FTIR spectral data for compounds (11c-15c) were listed in Table-3 and shown in Figure- 5.

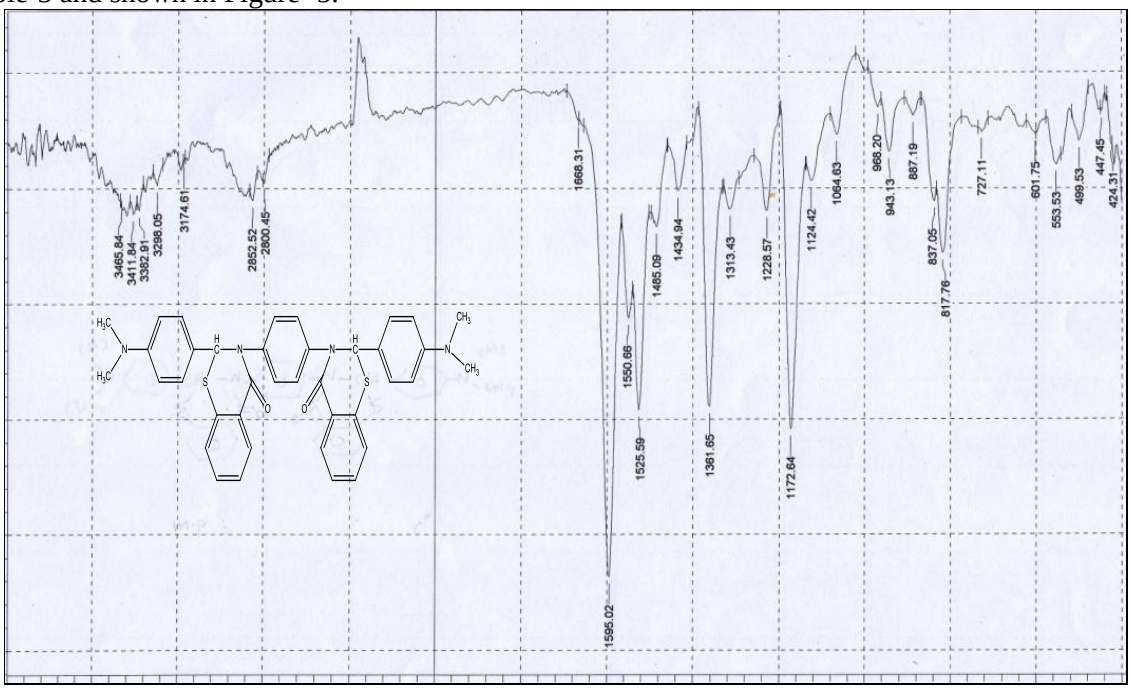


Figure 5-FTIR spectrum of compound (12c).

^{1}HNMR spectrum for compound (12c) showed singlet signal at δ= (2.9) ppm due to (s, 12H,-N ($C\underline{H}_3$)$_2$) protons; singlet signal at δ= (6.2) ppm due to(s, 2H, N-C<u>H</u>-S) protons and signals at δ= (7.04-8.48) ppm due to aromatic rings protons as listed in Table-5 and shown in Figure- 6.

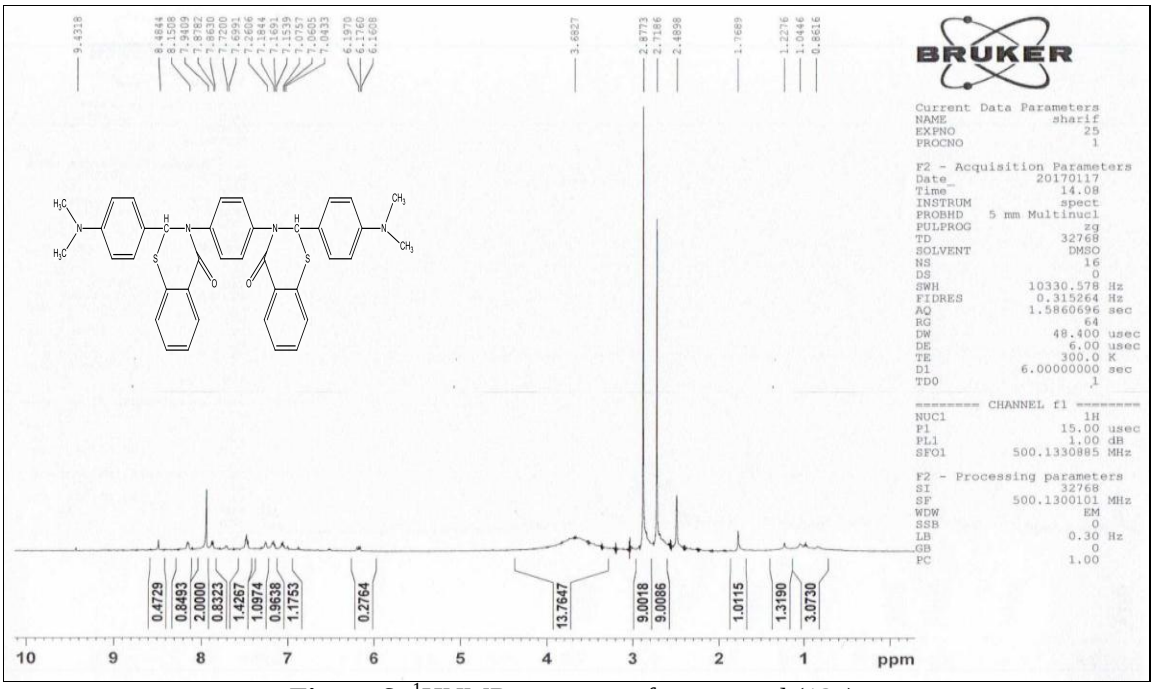


Figure 6 -^{1}HNMR spectrum of compound (12c).

^{13}CNMR spectrum data of compound (12c) were listed in Table-6, and shown in Figure- 7.

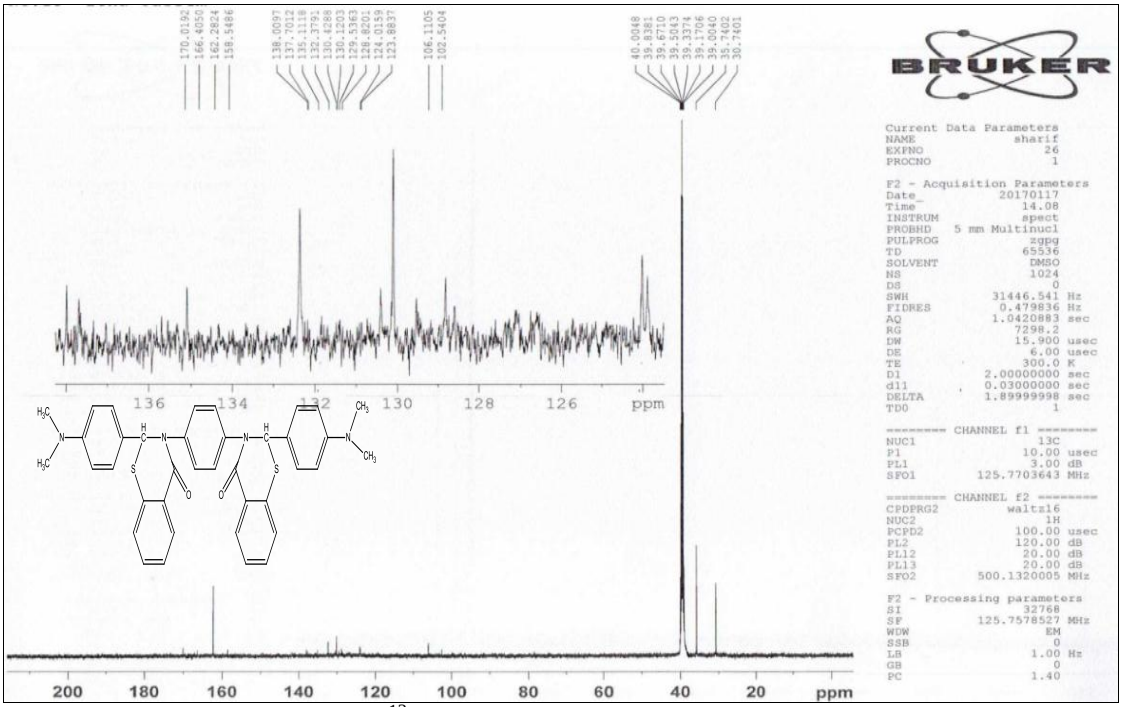


Figure 7-^{13}CNMR spectrum of compound (12c).

On the other hand hydroquinazoline derivatives (16d-20d) were synthesized by the reaction of Schiff bases (1a-5a) with 2- amino benzoic acid in dioxane as a solvent for long period of time about (20 hrs). The FTIR spectral data for compounds (16d-20d) show the disappearance of ν(C=N) band and appearance of ν(C=O) band in the values (1650-1681) cm^{-1} and ν (-NH) absorption band in the

range (3330-3373) cm^{-1}. The other values of FTIR spectral data for compounds (16d-20d) are listed in Table-4 and shown in Figure- 8.

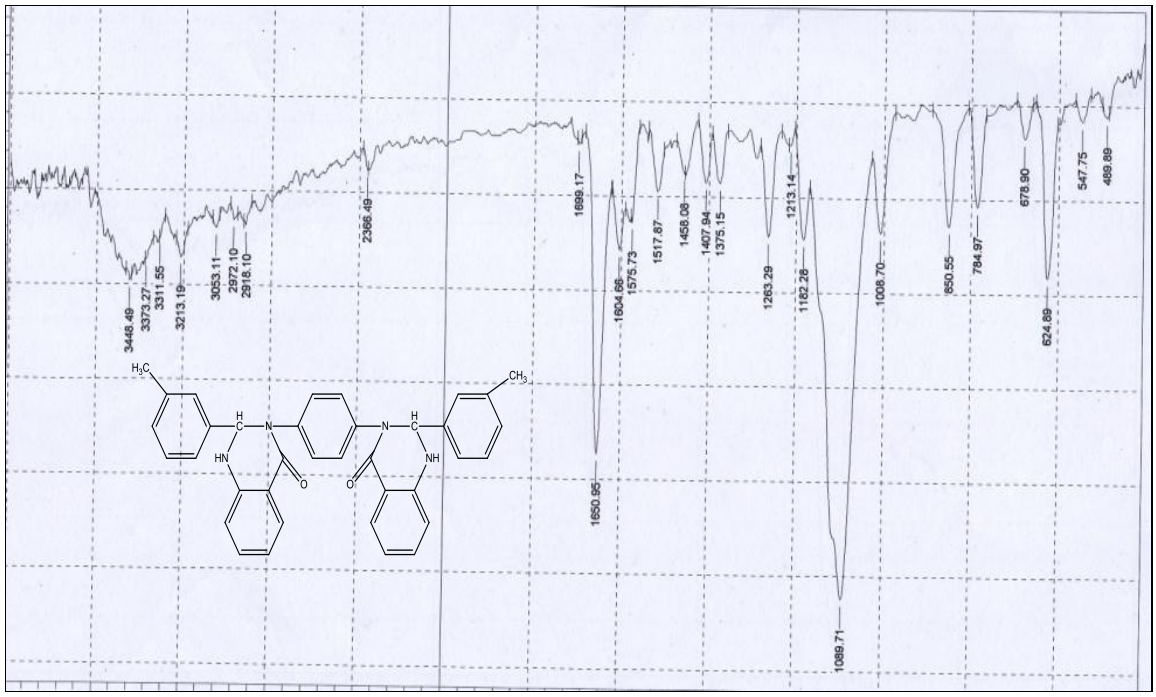


Figure 8-FTIR spectrum of compound (20d).

^{1}HNMR spectrum for compound (16d) showed singlet signal at δ= (6.3) ppm due to (s, 1H, N-C<u>H</u>-NH) proton; signals at δ= (6.4-8.8) ppm due to aromatic rings protons and singlet signal at δ= (10.00) ppm due to(s, 2H, NH) proton as listed in Table-5 and shown in Figure- 9.

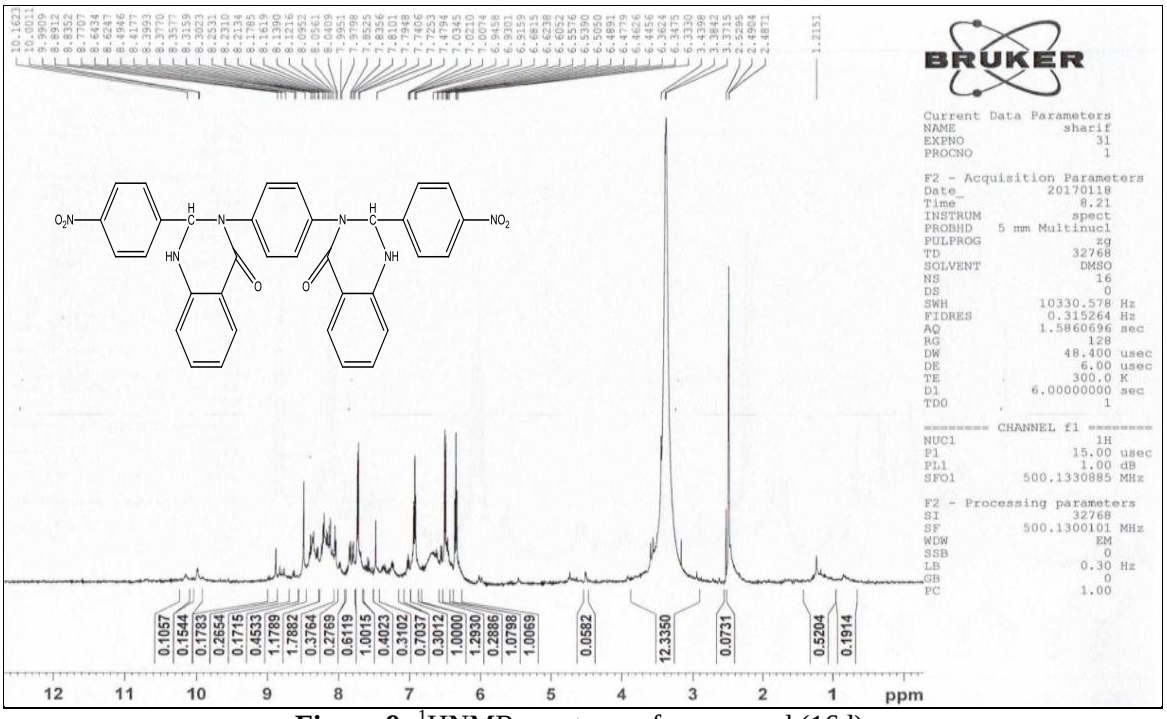


Figure 9 -^{1}HNMR spectrum of compound (16d).

^{13}CNMR spectral data of compound (16d) were listed in Table-6, and shown in Figure- 10.

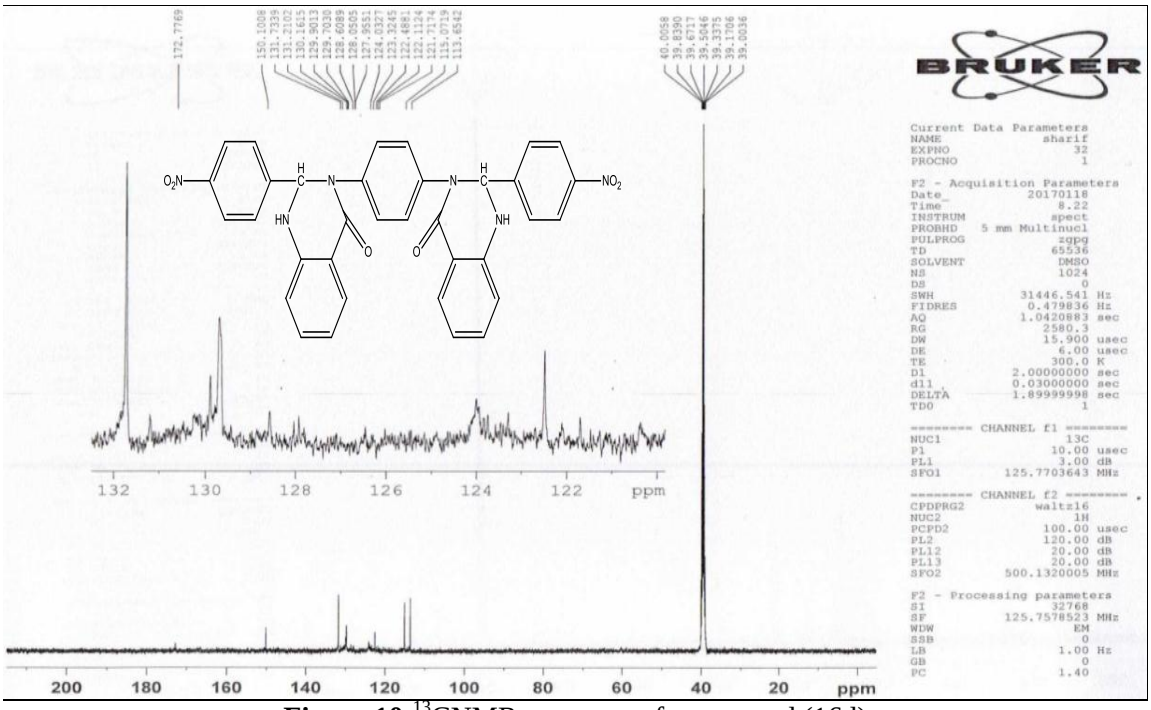


Figure 10-^{13}CNMR spectrum of compound (16d)

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^{13}CNMR spectral data of compound (19d) were listed in Table-6, and shown in Figure- 11.

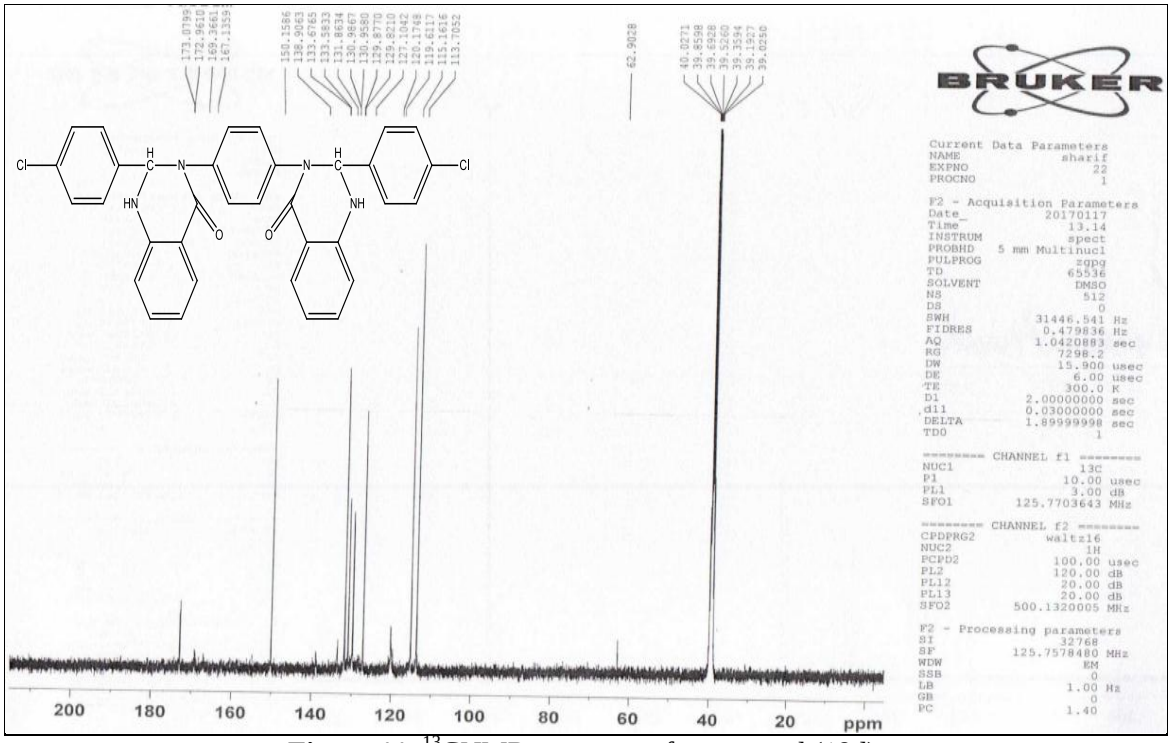


Figure 11- ^{13}CNMR spectrum of compound (19d).

Table 5- ^{1}H-NMR spectral data (δ ppm) for some synthesized compounds

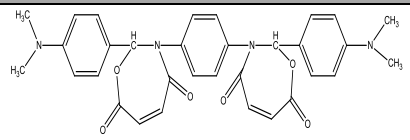
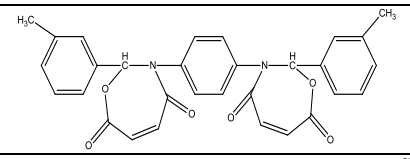
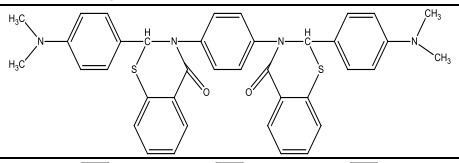
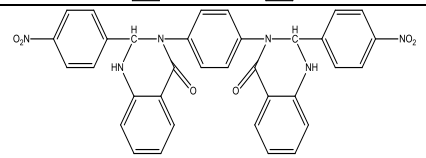
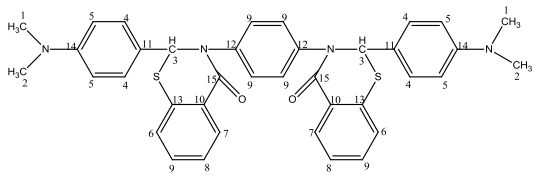
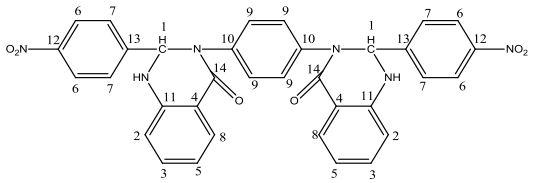
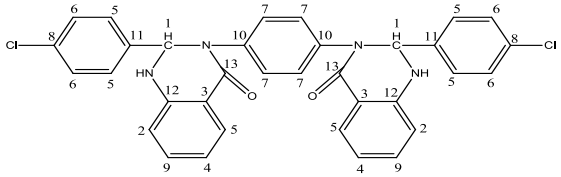
Comp. No.	Compound Structures	^{1}HNMR Spectral data ($^{\delta}$ppm)
7b		2.8(s,12H,N-(C<u>H</u>$_3$)$_2$); 3.1(s,2H,N-C<u>H</u>-O); 6.1(s,4H,O=C-C<u>H</u>=C<u>H</u>-C=O); 6.28-7.93 (m,12H,Ar-<u>H</u>)
10b		2.4(s,6H,C<u>H</u>$_3$-Ph); 3.3(s,2H,N-C<u>H</u>-O); 6.2(s,4H,O=C-C<u>H</u>=C<u>H</u>-C=O); 6.3-7.5 (m,12H,Ar-<u>H</u>)
12c		2.9(s,12H,-N(C<u>H</u>$_3$)$_2$) ; 6.2(s,2H,N-C<u>H</u>-S); 7.04-8.48(m,18H,Ar-<u>H</u>)
16d		6.3(s,2H,N-C<u>H</u>-NH); 6.4-8.8(m,20H,Ar-<u>H</u>); 10.00(s,2H,N<u>H</u>)

Table 6- ^{13}CNMR spectral data (δ ppm) for some synthesized compounds

Comp. No.	Compound structure	^{13}CNMR spectral data (δppm)
12c		30.7-35.7(C1-C2); 102.5-138(C3-C13); 158.5(C14); 162.2(C15).
16d		113.6-128.6(C1-C11) ;129.7(C12);130.1 (C13);172.77 (C14)
19d		62.9(C1); 113.7-138.9 (C2-C12): 167.1(C13).

3.1 Antibacterial activity

The information about antibacterial activity was listed in Table-7. The results indicate that all synthesized compounds having strong effect against certain types of bacteria while it did not possess any effect against others. Compounds (4a, 8b, and 9b) having strong activity against pseudomonas sp. while compounds (11c, 15c and 20d) having specific strong effect against the same bacteria.

Compounds (2a and 9b) having moderate activity against E.coli. while compound (8b) possess specific strong effect against the same bacteria. Compounds (2a, 4a, 8b, 9b and 11c) possess strong effect against proteus sp. while compounds (15c and 20d) showed no inhibition against E.coli and proteus sp., at the last compounds (4a, 8b and 20d) possess specific strong activity against staphylococcus aureus.

Table 7- Antibacterial activity of some of the prepared compounds.

Comp. No.	*Pseudomonas Spp*	*Escherichia coli*	*Proteus*	*Staphylococcus aureus*
2a	-	8	11	-
4a	15	-	15	20
8b	15	20	12	19
9b	14	8	15	-
11c	22	-	15	-
15c	18	-	-	-
20d	20	-	-	22

Solvent: Dimethyl sulfoxide; 800µg/mL concentration.
Zone of inhibition: (-) no inhibition zone; (3-6) mm weak; (7-10) mm moderate; (11-15) mm strong

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