Synthesis and Characterization of Some Heterocyclic Compounds (Oxazepine, Tetrazole) Derived from Schiff Bases

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Abstract

This work included synthesis of several new Schiff bases by condensation of benzidine and some aldehydes (2-hydroxy benzaldehyde, 4-N, N-dimethyl amino benzaldehyde, Pyridine-3-carboxyaldehyde) to obtain Schiff bases (1-3) and with ketones (4-hydroxy acetophenone, acetophenone, Isatin) to obtain Schiff bases (4-6). Also, new six oxazepines compounds (7-12 compounds) were synthesized through the reaction of phthalic anhydride with the prepared Schiff bases to obtain seven hetrocyclic compounds. Besides, we prepared new tetrazole derivatives from the reaction of the prepared Schiff bases with sodium azide in THF. The prepared compounds were characterized by (FT-IR, and some of them by ^{1}HNMR, ^{13}CNMR spectroscopy), physical properties were recorded and the biological activity was evaluated against two kinds of bacteria gram positive and gram negative.

Keywords: Schiff bases, oxazepine, tetrazole, biological activity.

Introduction

Schiff bases are characterized by the–N=CH- (imine) group which is important in elucidating the mechanism of transformation in biological systems. Due to great flexibility and diverse structural aspects, wide range of Schiff bases have been synthesized and their complexation behavior was studied[1]. Furthermore, Schiff bases are reported to show a variety of interesting biological activities, including antibacterial[2], antifungal[3], anticancer[4], and herbicidal activities[5]. Oxazepam (benzodiazepine) derivative introduced in 1965 for use in relief of the psychoneuroses characterized by anxiety and tension, oxazepam is non-homologous seven membered ring that contains two hetero atoms (oxygen and nitrogen)[6]. Tetrazoles are aromatic five membered ring containing four nitrogen atoms, the first tetrazole was reported over acentury ago[7], but the chemistry of tetrazole remained relatively obscure until the 1960 when the pharmacological and biological properties of tetrazole became known. Tetrazoles have been found to exhibit antibacterial [2], antifungal [3], antihistaimine[8], and anti-inflammatory properties [9].

Material and Methods

General

Melting points were determined in Gallen Kamp melting point apparatus and were uncorrected. FT-IR spectra were recorded on SHIMADZU FTIR –8400 Fourier Transform Infrared spectrophotometer as KBr disc. ^{1}HNMR and ^{13}C NMR spectra were recorded on Bruker specrospin ultra shield magnets 300 MHz instrument using tetramethyl silane (TMS) as an internal standared and DMSO-d_6 as a solvent in Ahl – Albate University in Jordan .

I. Preparation of Schiff bases (1-6)

A series of Schiff bases were prepared from the reaction of benzidine (1 mole), with different aldehydes or ketones (2 moles), in 20ml ethanol absolute and few drops of glacial acetic acid. This mixture was refluxed for 3hrs. The mixture was cooled; Precepitate was obtained then rercystallized from ethanol [10]

II.Preparation of Oxazepine(7-12)

A mixture of Schiff base (0.0012mole) and phthalic anhydride (0.0025mole) was dissolved in (20mL) dry benzene. The mixture was heated for 5hrs in water bath at (70◦C), excess solvent was distilled, the precepitate was filtered and recyrstallized from ethanol [11].

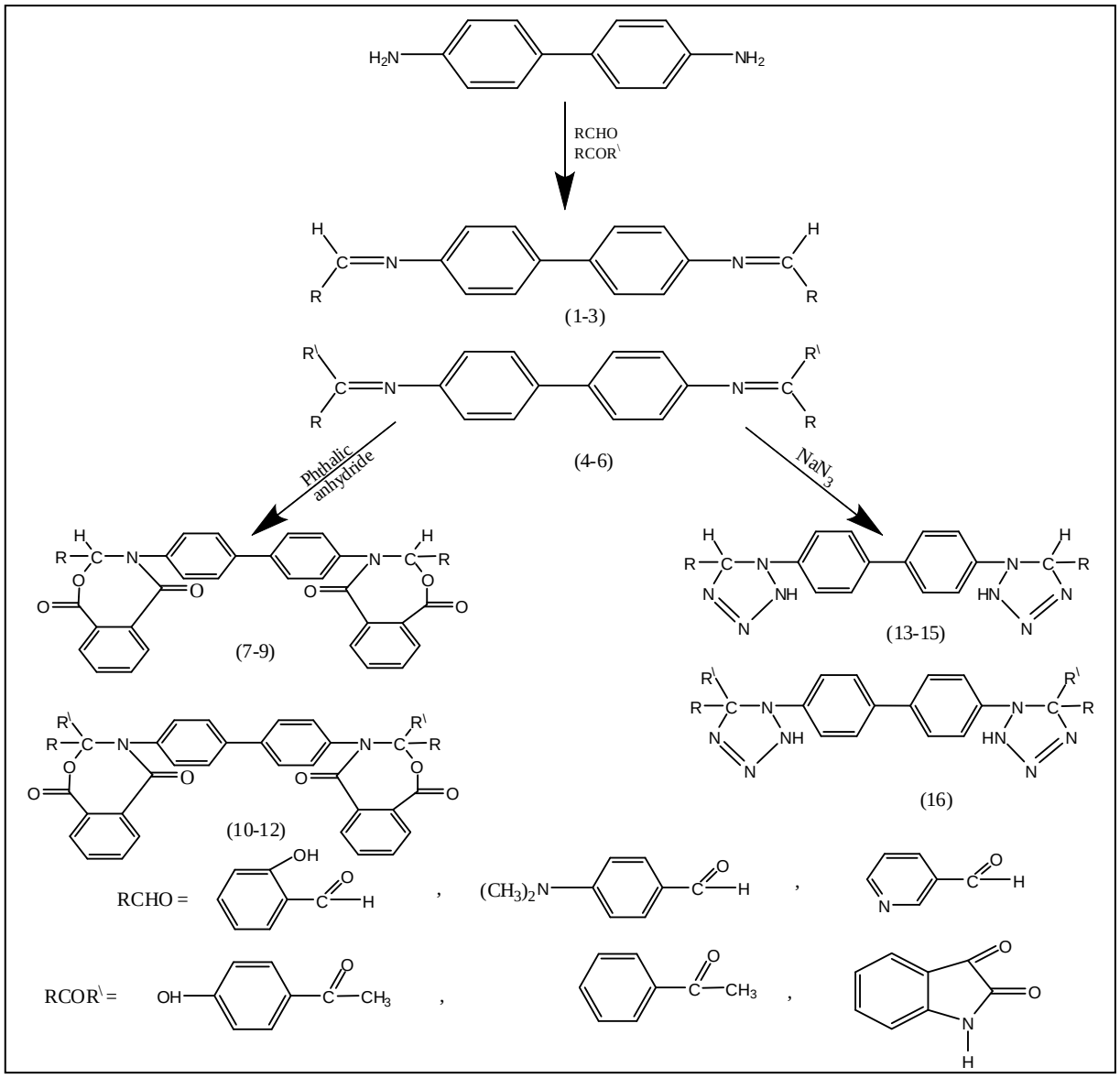
III.Preparation of Tetrazoles (13-16)

Compounds of (1,2,3, and 6) (0.002mole) was dissolved in (20mL) tetrahydrofuran and mixed with (0.004mole) sodium azide. These mixtures were heated in water bath at

T=50-60 ^{0}C. The end of reaction was checked by TLC in methanol [12].

Table (1) lists physical properties of compounds (S, 1-16).

Table (2) FT-IR spectral data of all compounds (S, 1-16).



Scheme (1).

Table (1)
Physical properties for the starting material and new Schiff bases, oxazepine and tetrazole compounds.

Comp.No.	*Formula*	*Colour*	*M.Wt*	*m.p. ^oC*	*yield %*
S	$C_{12}H_{12}N_2$	Pale-yellow	184.24	128	-
1	$C_{26}H_{20}N_2O_2$	Yellow	392	262-265	88
2	$C_{30}H_{30}N_4$	orange	446	296-298	88
3	$C_{24}H_{18}N_4$	Yellow	362	222-225	95
4	$C_{28}H_{24}N_2O_2$	Deep-yellow	420	259-262	60
5	$C_{28}H_{24}N_2$	Pale-yellow	388	198-200	55
6	$C_{28}H_{18}N_4O_2$	Deep-orange	394	Dec.	86.
7	$C_2H_{28}N_2O_8$	Yellow	688	250-253	70
8	$C_{46}H_{38}N_4O_6$	Pale-orange	742	318-320	81
9	$C_{40}H_{26}N_4O_6$	Deep- yellow	658	283-285	85
10	$C_{44}H_{32}N_2O_8$	Pale-yellow	716	Dec.	82
11	$C_{44}H_{32}N_2O_6$	Off white	684	320-322	79
12	$C_{44}H_{26}N_4O_8$	Yellow-orange	690	Dec.	88
13	$C_{26}H_{18}N_4O_2$	Pale-yellow	474	Dec.	96
14	$C_{30}H_{28}N_{10}$	Dark-yellow	526	Dec.	91
15	$C_{24}H_{16}N_{10}$	Pale-yellow	444	Dec.	65
16	$C_{28}H_{20}N_{10}O_2$	Pale-orange	526	Dec.	60

Dec.: Decomposition

Table (2)
FTIR spectra of the starting material and new Schiff bases, oxazepine and tetrazole compounds.

Comp. No.	*N-H amine*	*C=N*	*C-N*	*C-H alphatic*	*C-H arom*	*C=C*	*O-H*	*C=O*	*C-O-C*	*N=N*
S	3186	-	-	-	3028	1604	-	-	-	-
1	-	1616	-	2989	3051	1570	3444	-	-	-
2	-	1608	-	2854	3030	1550	-	-	-	-
3	-	1620	-	2885	3074	1585	-	-	-	-
4	-	1678	-	2927	3032	1550	3360	-	-	-
5	-	1625	-	2860	3032	1575	-	-	-	-
6	3240	1654	-	2881	3120	1612	3410	1739	-	-
7	-	-	1573	2877	3035	1574	3471	1693	1188	-
8	-	-	1543	2927	3032	1600	-	1712	1188	-
9	-	1627	1553	2885	3055	1566	-	1674	1184	-
10	-	-	1597	2927	3062	1504	3371	1712	1172	-
11	-	-	1593	2873	3008	1500	-	1705	1180	-
12	3244	-	1527	2881	3005	1580	-	1739	1203	-
13	3298	1616	1570	2989	3051	1555	3390	-	-	1454
14	3230	1608	1581	2854	3030	1550	-	-	-	1523
15	3298	1620	1585	2885	3074	1551	-	-	-	1519
16	3244	1654	1523	2881	3120	1612	-	1739	-	1485

Biological activity

Antibacterial activity of these compounds was determind by the ager diffusion method. Using *Echerchia Coli (G-)* and *Bacillus (G+)*, 10mM and 5mM of these compounds were placed on an agar seeded with the test organism. The plate was incubated at the appropriate temperature at 37 °C for 24hrs and the results are listed in Table (5).

Table (5)
Biological activity of benzidine, Schiff bases and Oxazepine compounds.

Comp. No.	G-Echerchia coli		G+Bacillus	
	5mM	10mM	5mM	10mM
S	++	+++	++	++
1	+	++	+	+
2	+	+	+	+
3	+	++	+	+
4	++	++	-	++
5	-	+	-	-
6	+	++	++	+
7	+	+	++	+
8	+	++	+	+
9	+	++	+	+
10	++	-	+	+
11	-	+	-	-
12	++	++	++	++

Key:
(-)Inactive (<5mm)
(+)Slightly active (10-12mm)
(++)Moderatly active (15-20mm)
(+++) Highly active (>20mm)

Results and Discussion

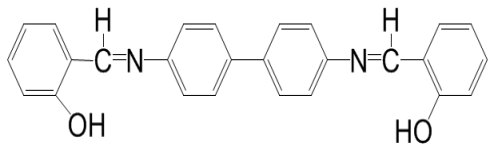
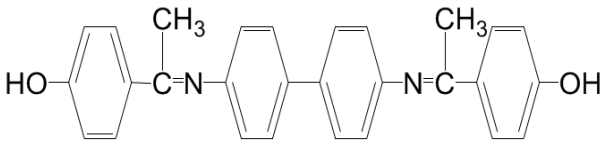
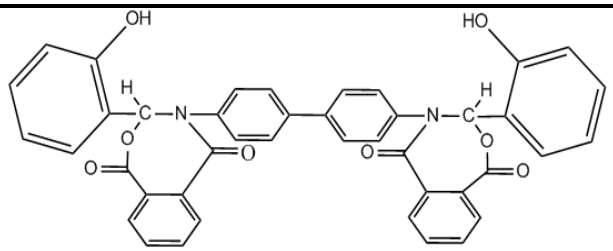
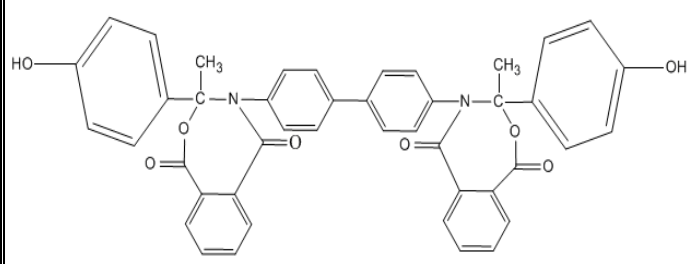
New six Schiff bases were synthesized from the reaction of benzidine with substituted aldehydes and ketones, shown in scheme (1). Some of these Schiff bases posses' good biological activities. Physical properties and the % Yield percentage of the prepared Schiff bases were in the range {55-95} % see (Table (1)) and were identified by FT-IR, and some of them by ^{1}HNMR and ^{13}C NMR spectroscopy. FT-IR spectra of Schiff bases (1-6) showed clear absorption bands at (3120-3030) Cm^{-1}, (2989-2854) Cm^{-1}, (1500-1612) Cm^{-1}, (1585-1654) Cm^{-1} and (1313-1388) Cm^{-1}due to (C-H) aromatic, √ (C-H) alphatic, √ (C=C) aromatic, √ (C=N) and √ (C-N) respectively[14, 15].FT-IR spectra of compounds (1), (4)and (6) showed clear absorption bands at (3360-3444) Cm^{-1} due to √ (O-H), compound (6) showed clear absorption band at (1739) Cm^{1-} due to √ (C=O) imide. Oxazipine compounds (7-12) were synthesized from the reaction of Schiff bases (1-6) with phthalic anhydride in dry benzene shown in scheme (1). These Oxazipine compounds posses good biological activities. The % Yield percentage of the prepared Oxazipine compounds were in the range (70-88) %. These compounds were identified by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. FT-IR spectrum of Oxazipines (7-12) showed clear absorption bands at (1693-1739) Cm^{-1} and (1033-1203) Cm^{-1} due to √(C=O) ketone, imide and ν(C-O-C) respectively. Tetrazoles compound s (13-16) were synthesized from the reaction of Schiff bases (1, 2, 3and 6) with sodium azide in THF. The % Yield percentage of the prepared Tetrazole compounds were in the range (60-96) %. FT-IR spectrum of tetrazoles (13-16) showed clear absorption bands at (1454-1523) Cm^{-1} due to √ (N=N). ^{1}H-NMR spectrum of compound (1) showed singlet signal at 3.5 ppm due to vinylic H, multiplet signals at (7.4 – 7.8 ppm) due to aromatic protons and singlet signal at 9.7 ppm due to O-H group. ^{1}H-NMR spectrum of compound (4) showed singlet signal at 2ppm due to CH_3 group, multiplet signals at (7.1–7.8 ppm) due to aromatic protons and singlet signal at 10ppm due to O-H group. ^{1}H-NMR spectrum of compound (7) showed multiplet signals at (7.5 -7.6ppm) due to aromatic protons, and singlet signal at 10ppm duo to O-H group, and singlet signal at 10.3ppm duo to C-H group. Finally ^{1}H-NMR spectrum of compound (10) showed multiplet signals at (7.2-7.8 ppm) due to aromatic protons, and singlet signal at 10.5ppm due to O-H group, and singlet signal at 10.4ppm duo to C-H group [14, 15]. The results are listed in Table (3). ^{13}C-NMR spectrum of compound (1) showed signals at (123-127ppm) due to aromatic carbons and at 133ppm due to C=N. ^{3}C-NMR spectrum of compound (4) showed signal at 26ppm due to CH_3 group, signals at (115-135ppm) due to aromatic carbons and signal at 149ppm due to C=N. ^{13}C-NMR spectrum of

compound (7) showed signals at (114-134ppm) due to aromatic carbons and signals at (162 -169ppm) due to C=O. ^{13}C-NMR spectrum of compound (10) showed signal at 26.72 ppm due to CH_3 group, signals at (114 - 149ppm) due to aromatic carbons and signals at (162-169ppm) due to C=O [14, 15]. The results are listed in Table (3), ^{1}H-NMR and ^{13}C-NMR spectra for compounds (1, 4, 7, 10) are shown in Figs. (1-8).

Biological activity [16, 17]

The prepared Schiff's bases and oxazepine showed different biological activities against two types of bacteria gram positive and gram negative bacteria including *Bacillus* and *Echerchia Coli*. The test results showed that the most of compounds (Schiff's and oxazepin) showed moderate activity against two types of bacteria, while the compounds (5, 11) showed no activity against two types of bacteria. All these results are shown in Table (5).

Table (3)
^{1}H-NMR and ^{13}C-NMR spectral data for some of the prepared compounds.

Compd. No.	*Compd. Structure*	*^{1}H-NMR spectra data*	*^{13}C-NMR spectra data*
1		δ =3.5ppm vinylic Hδ = 7.4-7.6ppm C-H aromatic, δ =9.7ppm O-H.	δ =123-127ppm aromatic carbons, δ = 133ppm C=N
4		δ =2ppm CH_3, δ =7. 1 - 7.8ppm H-aromatic, δ = 10ppm O-H.	δ =26ppm CH_3, δ =115-135ppm aromatic carbons, δ = 149ppm C-OH, δ = 165ppm C=N.
7		δ=7.5-7.6 ppmH-aromatic, δ =10.5ppm O-H, C-H Proton δ=10.3ppm.	δ =114-134ppm aromatic carbons , δ =162-169ppm C=O
10		δ =7.2-7.8ppm H-aromatic, δ =10.5ppm O-H, C-H Proton δ=10.4ppm.	δ =26.72ppm CH_3, δ =114-149ppm aromatic carbons , δ = 162-169ppmC=O.

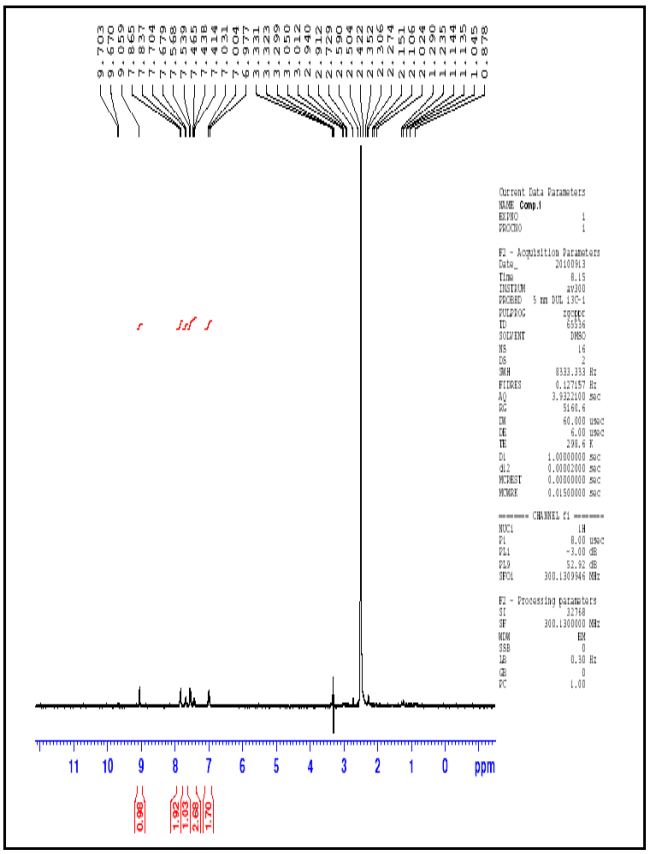


Fig. (1) HNMR spectrum of compound (1).

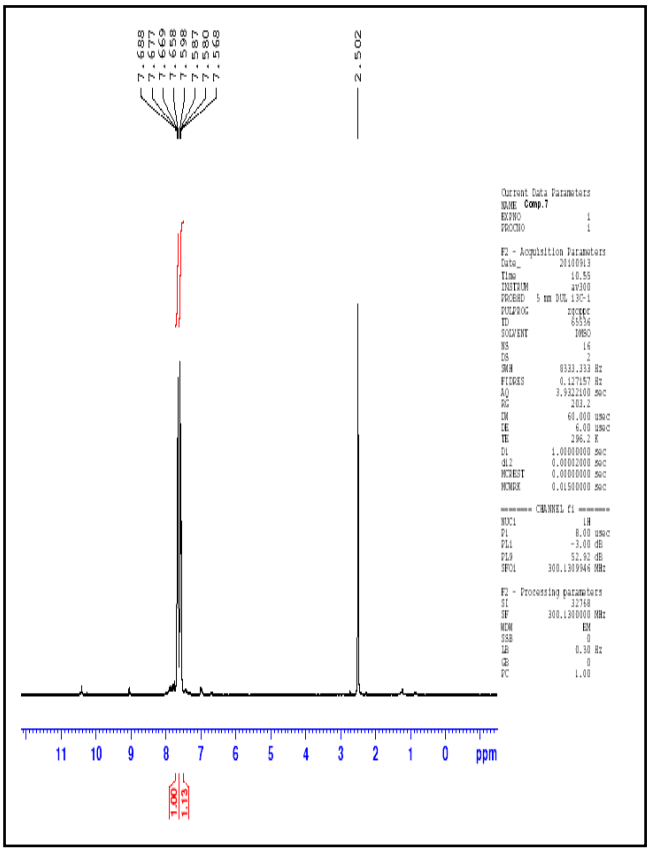


Fig. (3) HNMR spectrum of compound (7).

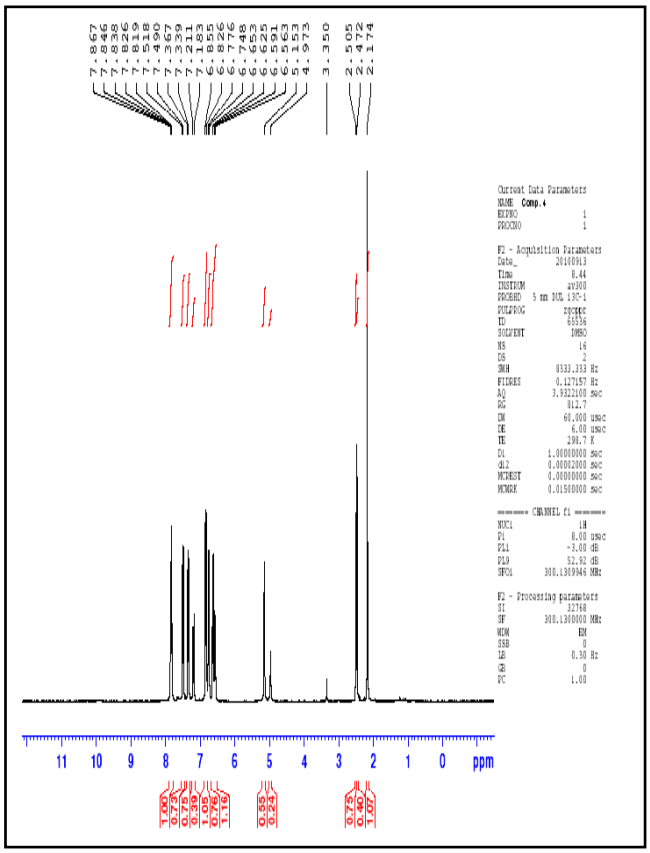


Fig. (2) HNMR spectrum of compound (4).

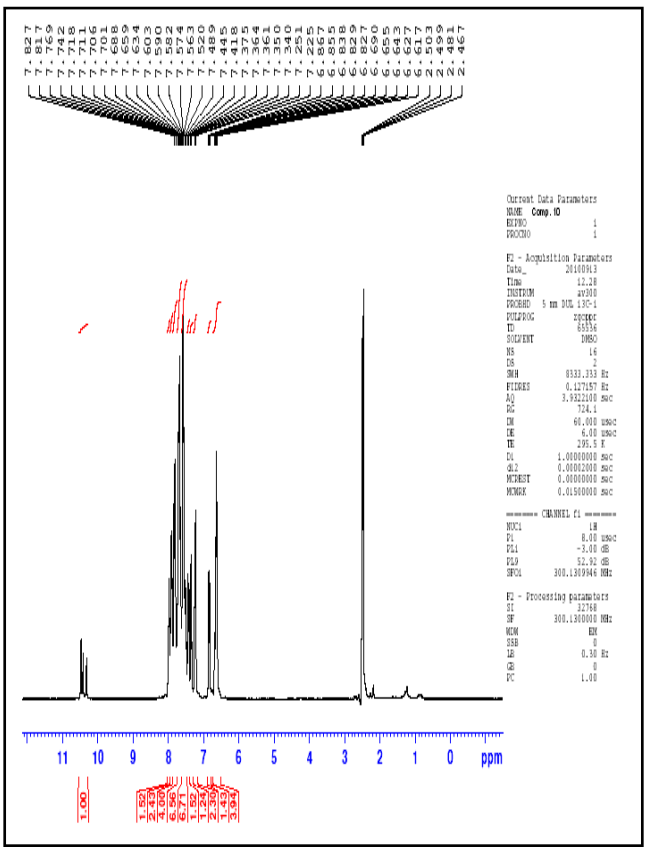


Fig. (4) HNMR spectrum of compound (10).

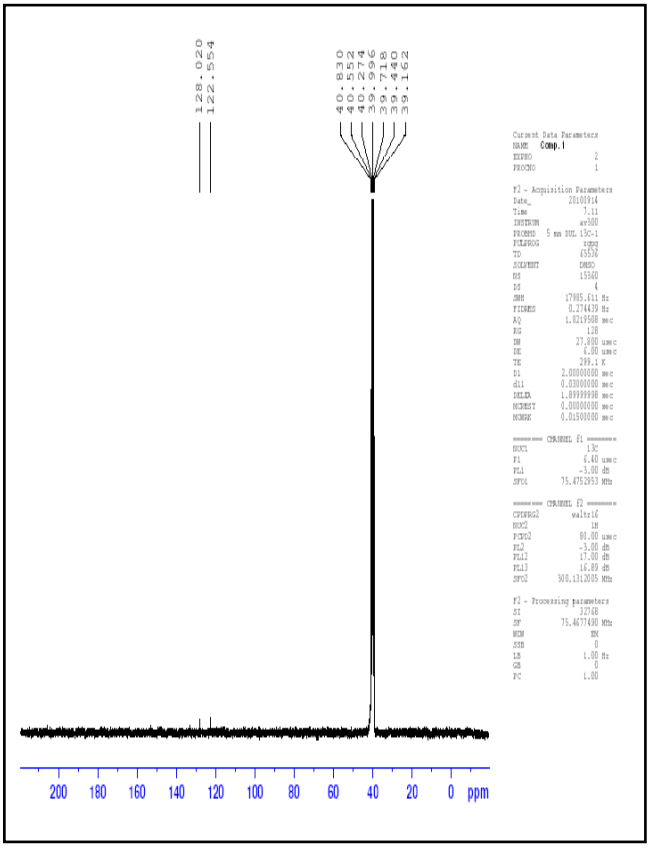


Fig.(5) 13CNMR spectrum of compound (1).

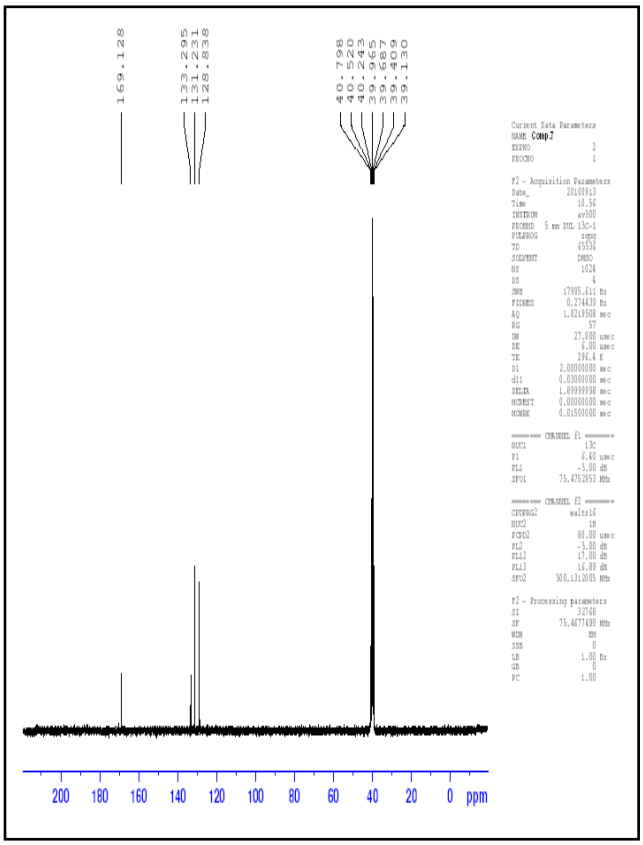


Fig.(7) 13CNMR spectrum of compound (7).

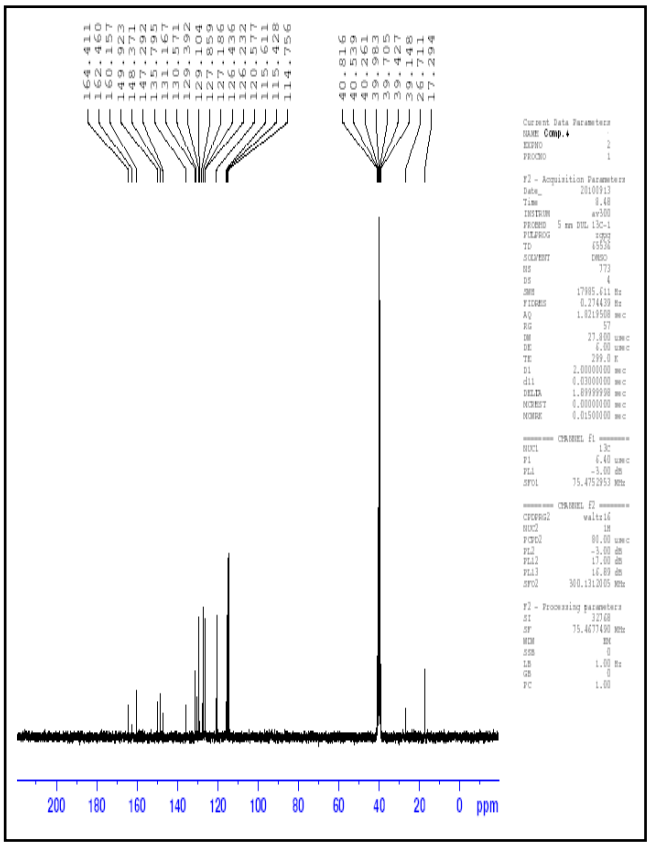


Fig.(6) 13CNMR spectrum of compound (4).

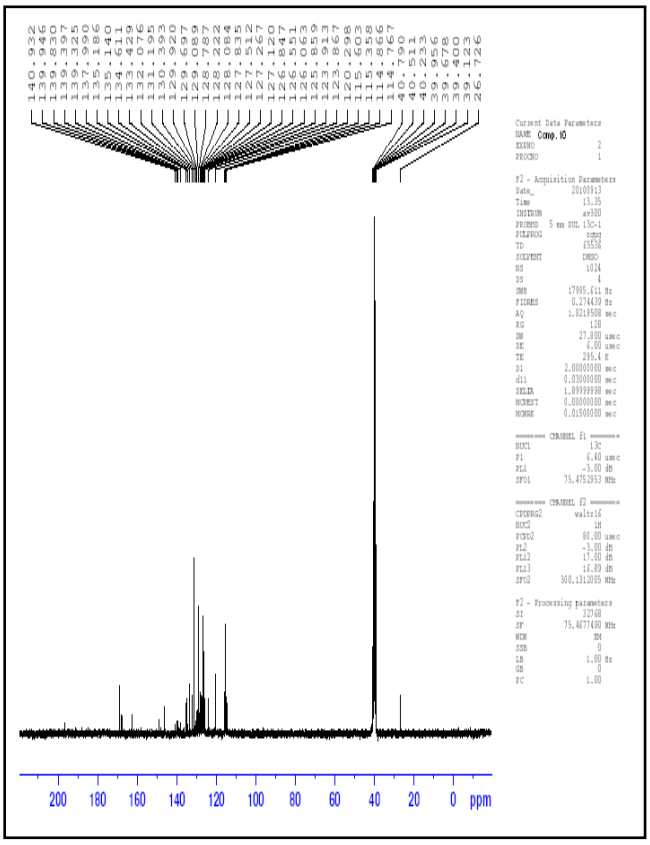


Fig.(8) 13 CNMR spectrum of compound (10).

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الخلاصة

تضمن البحث تحضيرعدد من مركبات قواعد شيف الجديدة لمركب البنزدين من خلال تكثيفه مع بعض الالديهايدات (٢–هيدروكسي بنزالديهايد، ٤–ثنائي مثيل امينو بنزالديهايد، بيردين–٣– كاربوكسي الديهايد) للحصول على نواتج قواعد شيف (١–٣) وكذلك مع الكيتونات (٤–هيدروكسي اسيتوفينون، اسيتوفينون، ايساتين) للحصول على نواتج قواعد شيف (٤–٦)، اضافة الى ذلك تم تحضير ستة من مركبات الاوكسازيين من خلال تفاعل انهدريدفثاليك مع قواعد شيف الستة للحصول على حلقات سباعية غير متجانسة، كما تم تحضيرعدد من مركبات التترازول وذلك نتيجة تفاعل قواعد شيف المحضرة مع الصوديوم ازايد في THF للحصول على حلقات خماسية غير متجانسة. وقد تم تشخيص هذه المركبات بطيف الاشعة تحت الحمراء FT-IR و^{1}H, ^{13}C-NMR بالاضافة الى تعيين الخواص الفيزياوية كما تم تقييم الفعالية البايولوجية ضد نوعين من البكتريا ذات الصبغة السالبة*Echerchia Coil (G$^-$)* وذات الصبغة الموجبة *Bacillus (G$^+$)* وبتركيزين مختلفين وقد اظهرت النتائج بأن اغلب المركبات المحضرة ذات فعالية بايولوجية معتدلة ضد هذه الانواع من البكتريا.