Synthesis , Evaluation of the Biological Activity and Anti-Oxidant for Some Heterocyclic Compounds Seven-membered Rings Derived from Schiff Bases

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Abstract

In this study, Some new Compounds have been Synthesized including the preparation of some Schiff bases **(P1,P2,R4)** from the reaction Benzdine , 2-aminoanthracine-9,10-dione compounds with two moles of various aldehydes The second stage includes preparation of new heterocyclic compounds seven membered rings (Oxazepine, Oxazepane)(**P1C1,P1C2,P1C3,P2C1,P2C2,P2C3,R4C1,R4C2,R4C3)** using the microwave method . The prepared compounds were characterized by FT-IR, 1H-NMR, and 13C-NMR spectra in addition melting points were measured for all compounds and reactions was followed by TLC (Thin Layer Chromatography).Finally, the synthesized compounds are tested against Gram-positive***(Staphylococcus aureus)*** and Gram-negative bacteria ***(Escherichia Coli)*** to study their biological activity, the results showed high biological effectiveness of some derivatives **(P1,P2,R4,P1C1,P1C2,P1C3,P2C1,P2C2,R4C1)** compared with Ciprofloxacin drug and study anti-oxidant for the **R4C2** compound which gave good results. .

Key Words : Benzidine , Schiff bases, Oxazepine, Oxazepane , anti-bacterial activity, anti-oxidant

1. Introduction

Schiff bases are formed by the condensation of primary (aromatic) amines with aldehydes or ketones that contain the azomethine (imine) moiety (-CR=N-)[1,2] They are regarded as versatile pharmacophores for a variety of pharmacological activities[3] in which the azomethine group has been shown to be critical to bioactivit [4,5] ,Schiff bases, for example, whether natural or synthetic have shown promising antibacterial, antitubercular, antifungal, antiparasitic, antiviral,

antioxidant, and anticancer properties[6-8]. German chemist and physicist (Hugo Schiff) was the first to prepare them in 1864. Their name was derived from his name [9] since they contain in their composition the azomethine group (-C=N-) [10 -12] or the so-called imine, which is a very effective functional group as expected for a double covalent bond, as well as its ability to react reversibly through the process of rapid hydrolysis [13]. These bases are usually prepared by condensing primary amines with active carbonyl groups such as aldehydes and ketones [14] where they are linked the carbon atom is double bonded to nitrogen [15] . Heterocyclic compounds are a sort of organic compounds in which some or all of the atoms within the molecule are linked together in rings that contain at least one atom of an element other than carbon, utilized as intermediates in the production of other important heterocyclic rings which are normally distributed in nature[16]. The biological activity of some heterocyclic rings, such as nitrogen and sulfur, have made them important for a long time in the healthcare industry[17] anti-tumor, anti-inflammatory, etc[18] and antibacterial [19] ,anti-HIV [20] ,antidiabetic [21] ,analgesic [22] .

Oxazepine is a heterocyclic unsaturated ring consisting of one oxygen atom and one nitrogen atom in addition to five carbon atoms[23-25]. There are three isomers (1, 2), (1, 3), and (1,4) [26]. This numbering depends on the position of the oxygen and nitrogen atoms in the seven-ring [27-29]. Derivatives of 1,3-0xazepine were prepared by reaction of Schiff bases with anhydrides. Oxazepine compounds are important because they have a wide range of biological and pharmacological activity[25] including antibacterial[26] antifungal [27] and anticancer.

2.Experimental:

2.1Materials and Instruments :

Reagents and reactants are used as obtained from commercial suppliers without further purification. The solvents were previously purified. The purity of the derivatives and the course of the reaction were monitored using Thin layer chromatography on silica gel G (Merck grade) with a mixture of ethanol and benzene as the mobile phase. Melting points were measured in open capillaries, with the help of a melting point (Stuart) apparatus (SMP30, England) pronounced in °C and uncorrected. The infrared (IR) spectra were recorded on a Shimadzu Prestige-21 spectrophotometer using potassium bromide (KBr pellets) and the values in cm^{-1}, 1- H NMR, and 13- CNMR derivative spectra were recorded on a Bruker (Avance III, Bruker 300MHz NMR

Spectrophotometer using TMS as an internal standard and values are expressed in ppm at University of Tehran – Iran.

2.2. General Synthesis of Schiff base (P1,P2)[28]

Dissolve (0.006mol) of 4-Bromobenzaldehyde , 4-Chlorobenzaldehyde , 4-methylbenzaldehyde) was dissolved in ethanol absolute added (2-3) drops of glacial acetic acid and added (0.003 mol) of different amine (Benzdine , 2-aminoanthracine-9,10-dione) the homogenized mixture is then placed in a ceramic eyelid. Insert a ceramic cover into the microwave oven and irradiate it at 280 w for 8-12 minutes . Then the mixture was allowed to cool at room temperature and the solid product was filtered and recrystallized from ethanol. The physical properties were listed in **Table (1)**.

2.3 General Synthesis of (Oxazepine & Oxazepane) compounds[29]

(0.004 mol) Schiff bases were mixed with various anhydrides (0.008 moles) (maleic anhydride , phthalic anhydride & succinic anhydride) mixture was thoroughly crushed with a mortar until a powder was obtained. The homogenized mixture is then placed in a ceramic eyelid. Insert a ceramic cover into the microwave oven and irradiate it at 280 w for 20-25 minutes after which the precipitate is cooled to laboratory temperature 25°C . The resultant material was washed with benzene, then the precipitate was separated by filtration and recrystallized from Absolute ethanol, dried, The reaction was validated using TLC technology; the physical parameters are reported in **Table 1.**

Table(1): physical properties for synthesized compounds (P1,P2,P1C1,P1C2,P1C3,P2C1,P2C2,P2C3,R4,R4C1,R4C2,R4C3)

NO. COMP	Name of compound	M.F	M.W(g\mol)	M.P (°C)	R*f* (2:4) (Ethanol: Benzene)	Color	Yield %
P1	N,N'-([1,1'-biphenyl]-4,4'-diyl)bis(1-(4-bromophenyl)methanimine)	$C_{26}H_{18}Br_2N_2$	518.25	126-128	0.88	Orange	79
P2	N,N'-([1,1'-biphenyl]-4,4'-diyl)bis(1-(4-chlorophenyl)methanimine)	$C_{26}H_{18}Cl_2N_2$	429.34	>310 Dec	0.69	Red	80

P1 C1	3,3'-([1,1'-biphenyl]-4,4'-diyl)bis(2-(4-chlorophenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{34}H_{22}Cl_2N_2O_6$	625.46	140-142	0.66	Light red	80
P1 C2	4,4'-([1,1'-biphenyl]-4,4'-diyl)bis(3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione)	$C_{42}H_{26}Cl_2N_2O_6$	725.58	175-177	0.84	Reddish brown	89
P1 C3	3,3'-([1,1'-biphenyl]-4,4'-diyl)bis(2-(4-chlorophenyl)-1,3-oxazepane-4,7-dione)	$C_{34}H_{26}Cl_2N_2O_6$	629.49	129-131	0,83	Yellow	84%
P2 C1	N,N'-([1,1'-biphenyl]-4,4'-diyl)bis(1-(4-bromophenyl)methanimine)	$C_{26}H_{18}Br_2N_2$	518.25	144-146	0,75	brown	87%
P2 C2	3,3'-([1,1'-biphenyl]-4,4'-diyl)bis(2-(4-bromophenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{34}H_{22}Br_2N_2O_6$	714.37	154-156	0,86	Brown	71%
P2 C3	4,4'-([1,1'-biphenyl]-4,4'-diyl)bis(3-(4-bromophenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione	$C_{42}H_{26}Br_2N_2O_6$	814.49	133-135	0,71	Dark brown	82%
R4	3,3'-([1,1'-biphenyl]-4,4'-diyl)bis(2-(4-bromophenyl)-1,3-oxazepane-4,7-dione)	$C_{34}H_{26}Br_2N_2O_6$	718.40	180-182	0,73	Orange	78%
R4 C1	2-((4-methylbenzylidene)amino)anthracene-9,10-dione	$C_{22}H_{15}NO_2$	325.37	170-172	0.66	Yellow	69
R4 C2	3-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(p-tolyl)-2,3-dihydro-1,3-oxazepine-4,7-dione	$C_{26}H_{17}NO5$	423.42	160-162	0.78	Light Yellow	75
R4 C3	4-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-3-(p-tolyl)-3,4-	$C_{30}H_{19}NO_5$	473.48	190-192	0.80	Red	73

	dihydrobenzo[e][1,3]oxazepine-1,5-dione						
R4 C4	3-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-(p-tolyl)-1,3-oxazepane-4,7-dione	$C_{26}H_{19}NO_5$	425.44	111-113	0.85	Light red	77

3.Biological activity[30]

The study used two types of isolated pathogenic bacteria, Gram-positive ***(Staphylococcus aureus)*** and Gram-negative ***(Escherichia Coli),*** where solutions were prepared for some of the compounds and to be evaluated for their biological effectiveness against two types of bacteria by taking concentrations (0.1mg/ml, 1mg/ml) of each compound and dissolved it in (5ml) of the solvent (DMSO). The sensitivity of the compounds was investigated using the method of spreading bacteria on the surface of the dishes in the culture medium (Agar Mueller-Hinton) using (Lapful), and four holes were made in the dishes with a diameter of 9mm by corkscrew (Cork borer) sterilized with alcohol, with an appropriate distance between one hole and another to avoid the inhibition zones between them overlapping. Where the prepared solutions were applied to these wells in a volume of 0.1 ml using a (Micropipette) and incubated for 24 hours at 37°C. The compounds' inhibitory zones were then measured on a millimeter the results showed high biological effectiveness of some derivatives **(P1,P2,R4,P1C1,P1C2,P1C3,P2C1,P2C2,R4C1)** compared with Ciprofloxacin drug because these derivatives contain heterocyclic rings which include (O,N, S) atoms therefore increased biological activity in these compounds scale are shown in **Table 2.**

Table 2:The biological activity of the compounds

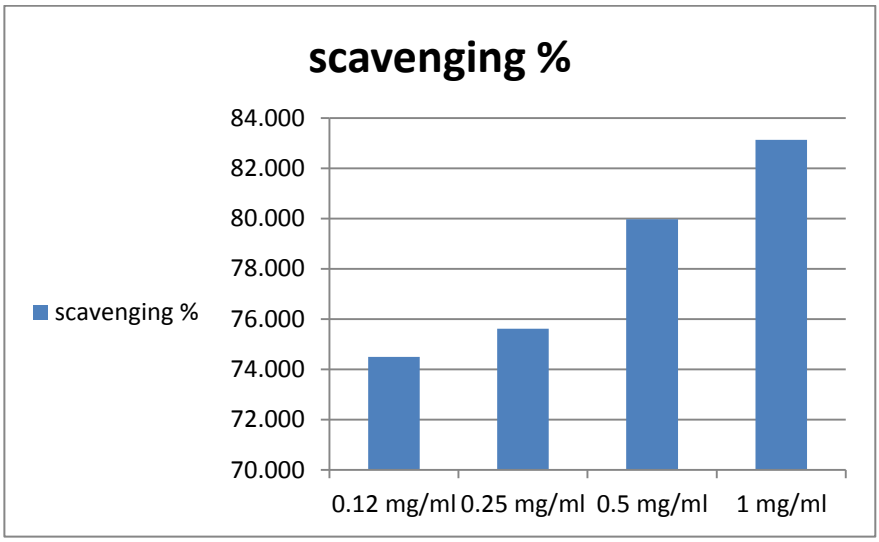
compounds	Anti-Bacterial Activity			
	Escherichia coil		*Staphylococcus aureus*	
	0.1mg/ml	1mg/ml	0.1mg/ml	1mg/ml
P1	12	18	13	21
P2	11	20	14	18
R4	14	23	12	14
P1C1	13	18	11	15

P1C2	**12**	**15**	**10**	**17**
P1C3	**11**	**15**	**10**	**19**
P2C1	**15**	**18**	**11**	**22**
P2C2	**15**	**17**	**12**	**20**
R4C1	**16**	**22**	**14**	**20**
Cipro	**15**	**20**	**14**	**18**

4. Antioxidant:

sample name	concentration	absorbency	scavenging %
1	0.12 mg/ml	0.2576	74.487
2	0.25 mg/ml	0.2462	75.617
3	0.5 mg/ml	0.2023	79.964
4	1 mg/ml	0.1703	83.134
	control	1.0097	

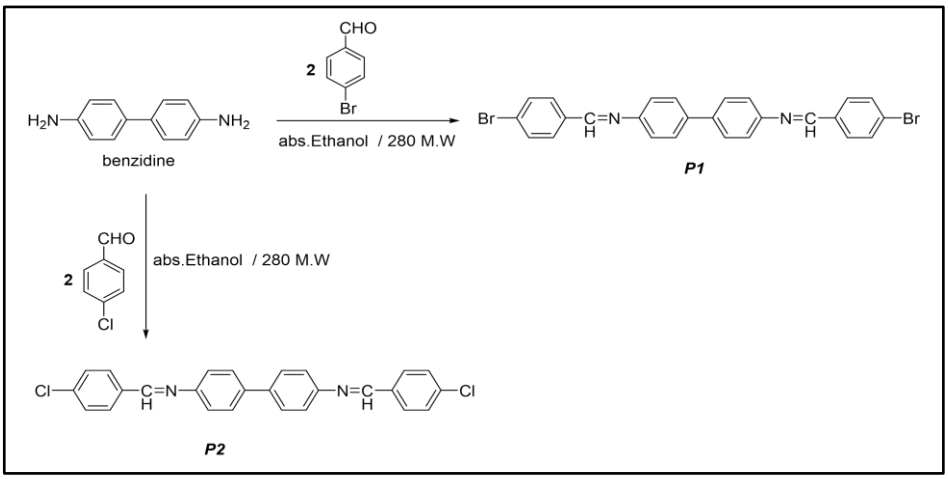
Table-3- Antioxidant of R4C2 Compound



5 .Results &Discussion

The Schiff bases were prepared by reacting (2mole) from(4-Bromobenzaldehyde , 4-Chlorobenzaldehyde , 4-methylbenzaldehyde) and (Benzdine , 2- aminoanthracine-9,10-dione) (1mole) within ethanol absolute. The prepared compounds were characterized by FT-IR spectra, 1H-NMR, and

13C-NMR spectra, The FT-IR spectrum of Schiff bases(P1, P2, R4)of new azomethine (C=N)[31] group at (1625-1610cm^{-1}) and(1587-1550cm^{-1}) for (C=C) aromatic while were characterized 1H-NMR spectra of Schiff bases(P1,P2,R4)showed singlet signal peak at (8.9-8.3 ppm) due to(s N=C-H) proton of an amine group, the spectrum also showed multiple signals at it (6.4-7.8 ppm) belonging to the protons of the aromatic ring of different environments (Ar-H) while were characterized 13C-NMR spectrum of Schiff bases showed signal appeared at the site (158-161 ppm) belonging to the carbon of the imine group (C=N) as well as the spectrum showed multiple signals at the site (116-131 ppm) belonging to the carbon of the aromatic ring of the different environment (C-Ar).**scheme1**

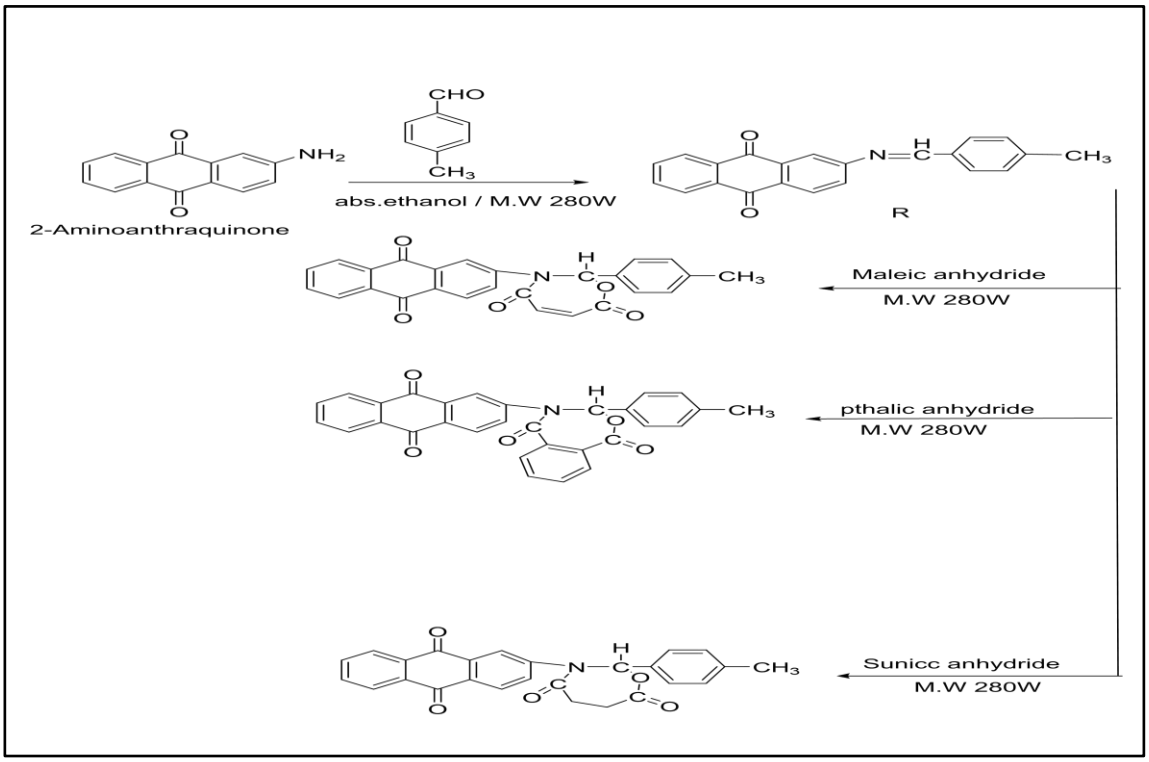


Scheme(1): Synthesis of Schiff bases

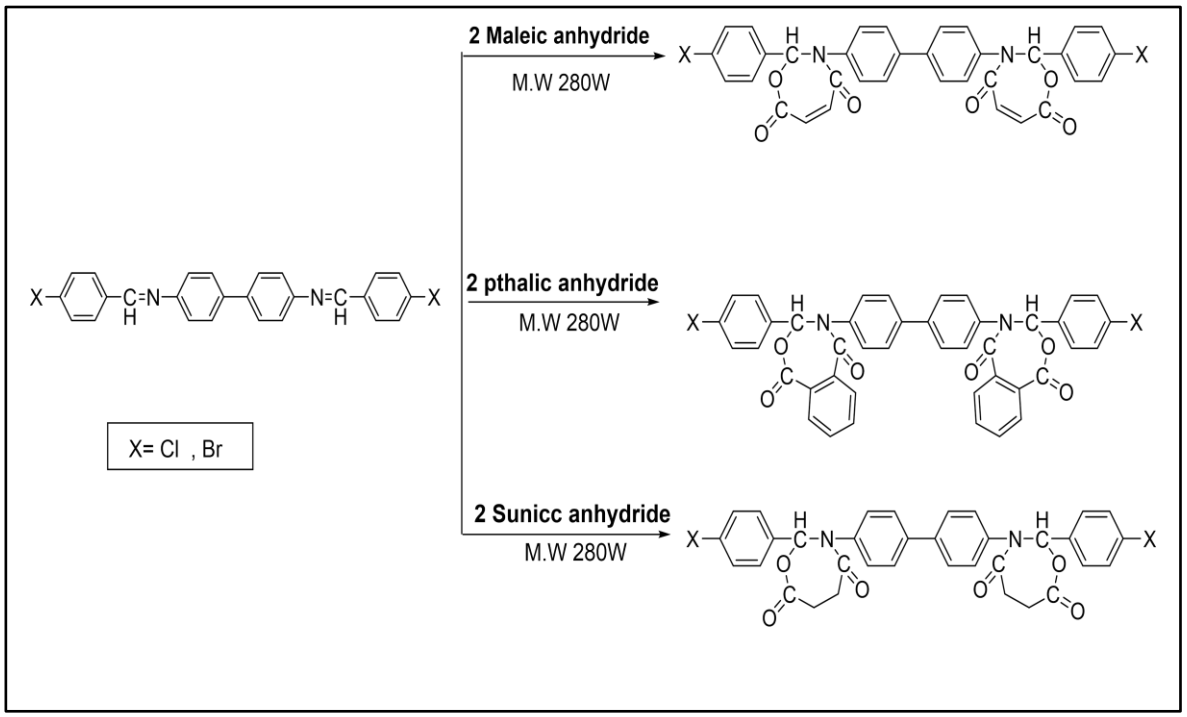
In this study new derivatives of heterocyclic compounds (Oxazepine, Oxazepane)

(P1C1,P1C2,P1C3,P2C1,P2C2,P2C3,R4C1,R4C2,R4C3) were prepared from the reaction of Schiff bases(P1,P2,R4) with different anhydrides. The FT-IR spectrum disappearance of an absorption band belonging to the azomethine group of Schiff bases and the appearance of a stretch band of the bond of the lacton carbonyl group (C=O-O) at the frequency (1732-1701cm^{-1}), while the absorption band of the bond of the amide [32] carbonyl group lactam(N-C=O) at the frequency (1625-1618cm^{-1})due to (C=C) at frequency(1589-1502cm^{-1}) the compound was identified by 1H-NMR spectra, a signal appeared at (2.52 ppm) belonging to the solvent used (DMSO-d*6*) and a signal appeared at (9.6 ppm) due to the proton of the seven ring group (N-CH). It was observed that multiple signals appear at (7.0 -7.9 ppm) due to the protons of the aromatic rings in

different environments (Ar-H). Also, the compound was identified by the (13C-NMR) spectrum, and a signal appeared at the site (40ppm) belonging to the solvent used (DMSO-d*6*), and a signal appeared at the site (176-172ppm) belonging to the carbon atom of the lactone carbonyl group (O-C= O)[33] and at the site (174-168 ppm) it belongs to the carbon of the amide carbonyl group (N-C=O). The position (112-131 ppm) is attributed to the heterocyclic aromatic carbon(C-Ar).**scheme2& scheme 3**



Scheme(2): Synthesis of Seven membered rings from Schiff bases



Scheme (3) :Synthesis of Seven membered rings from Schiff base compounds

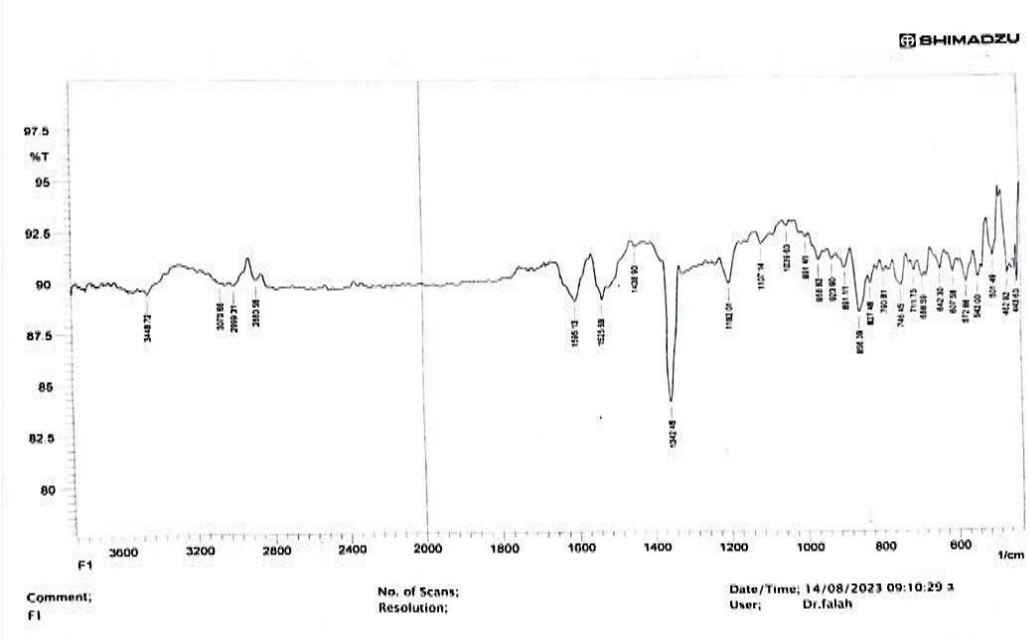


Figure (1): FT-IR spectrum for compound(p1)

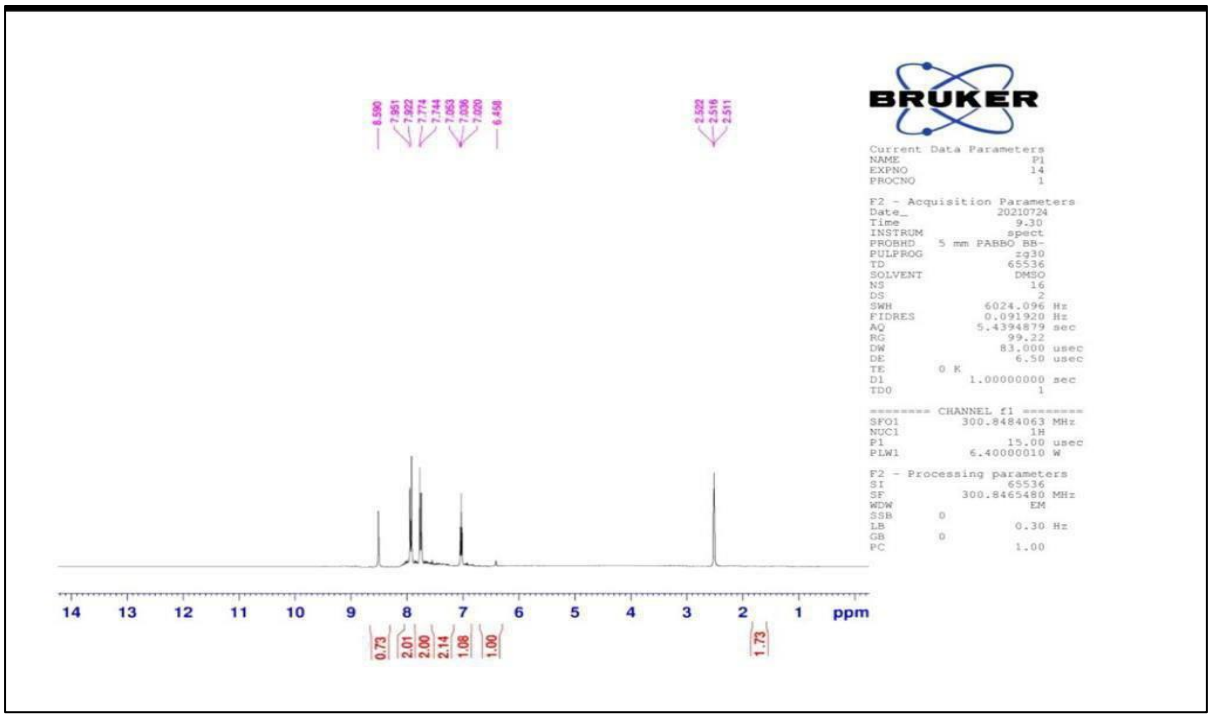


Figure (2):^{1}H-NMR spectrum for compound(p1)

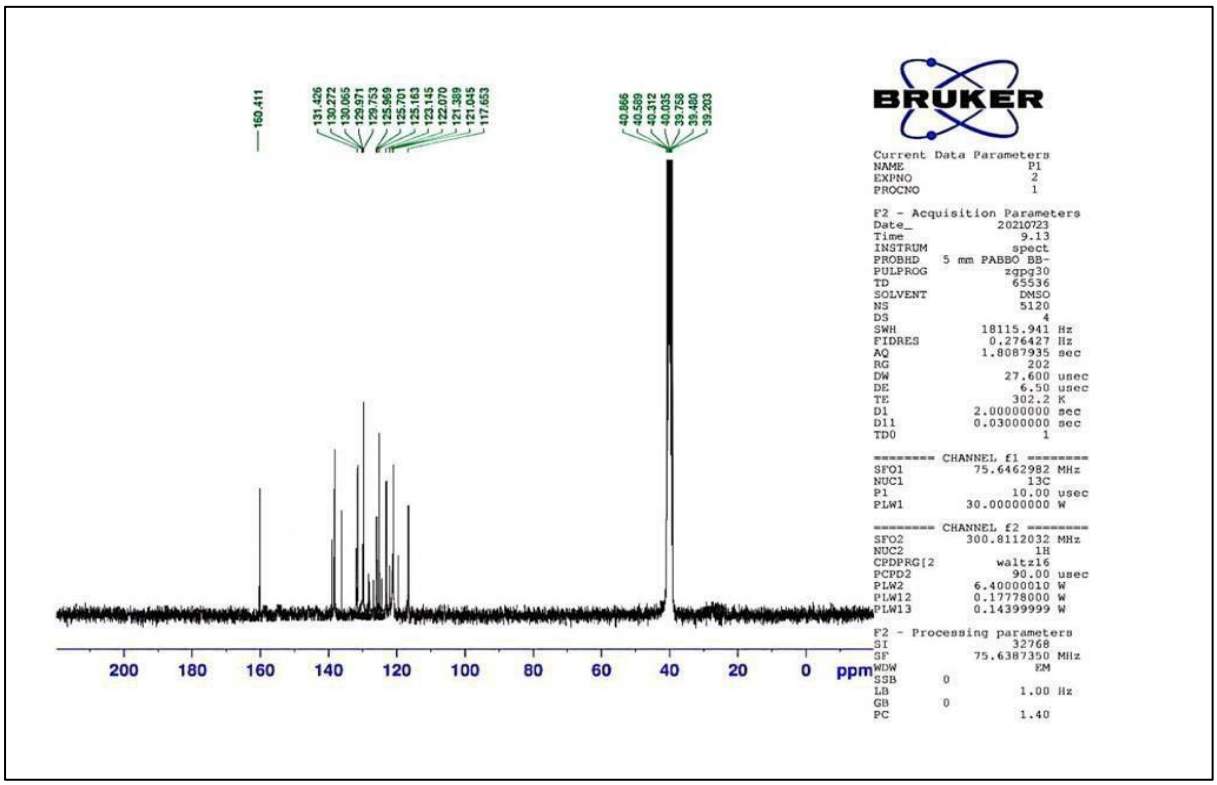


Figure (3):^{13}C-NMR spectrum for compound(p1)

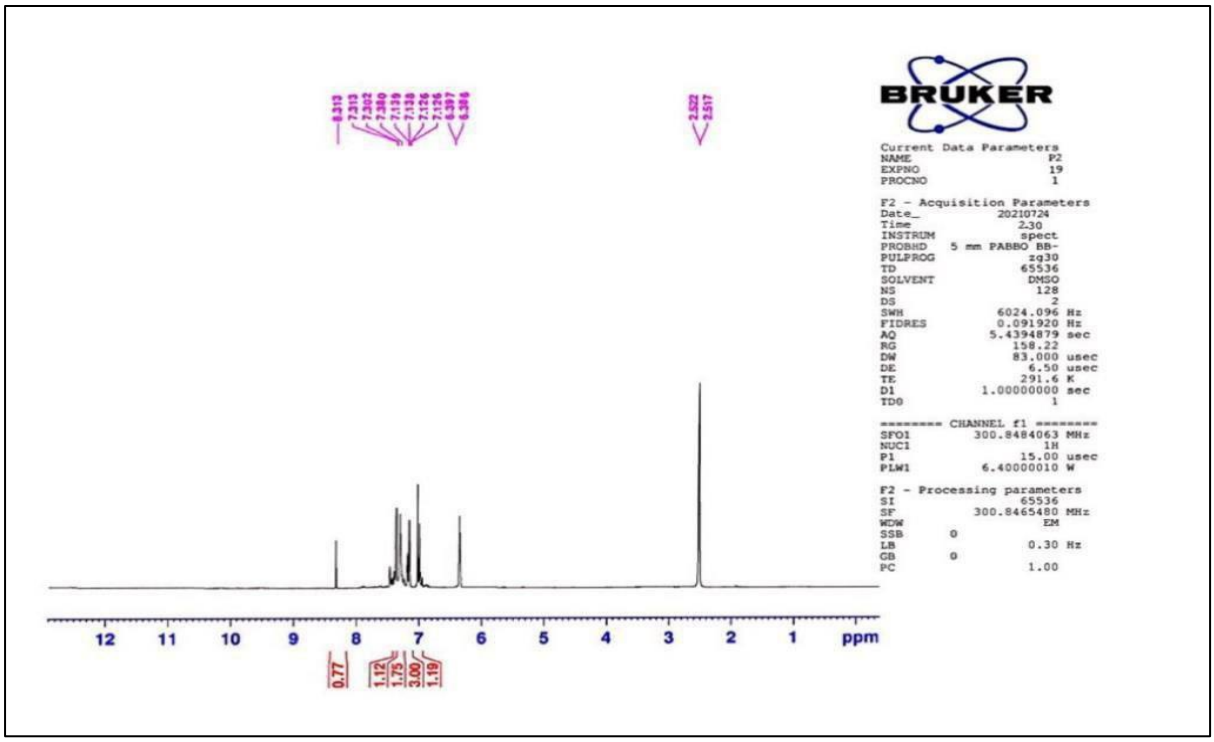


Figure (4) :^{1}H-NMR spectrum for compound(P2)

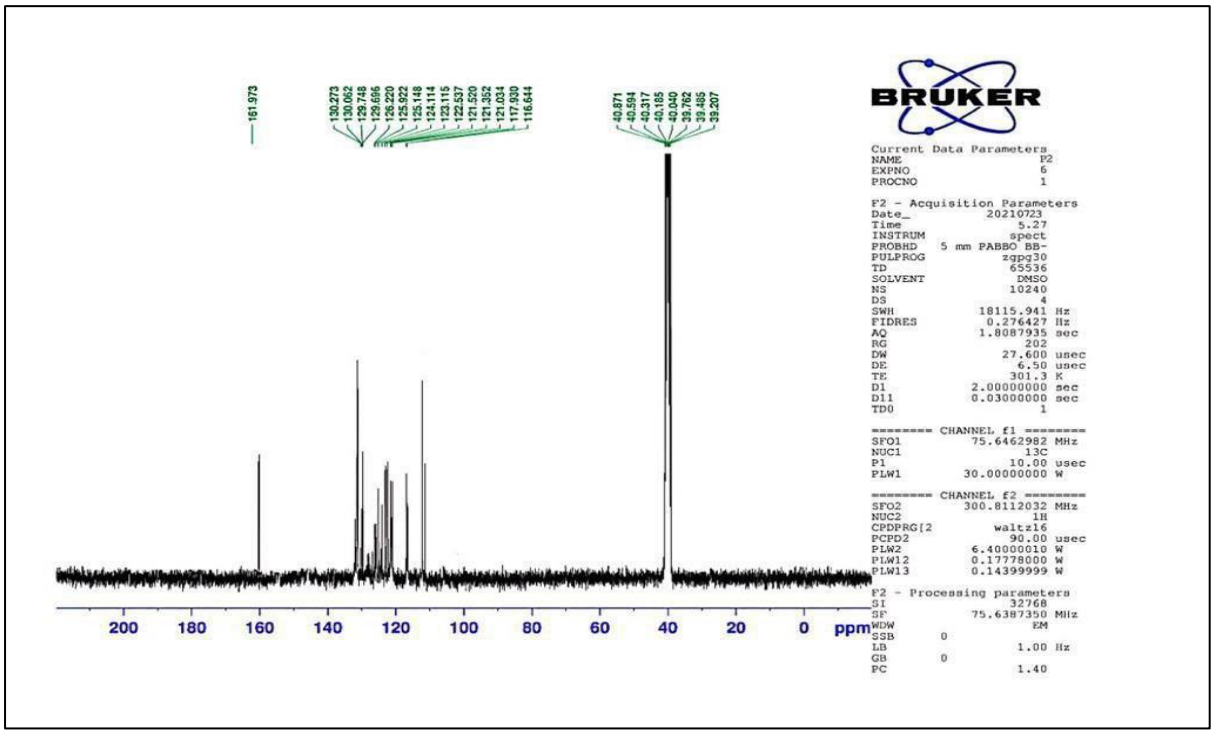
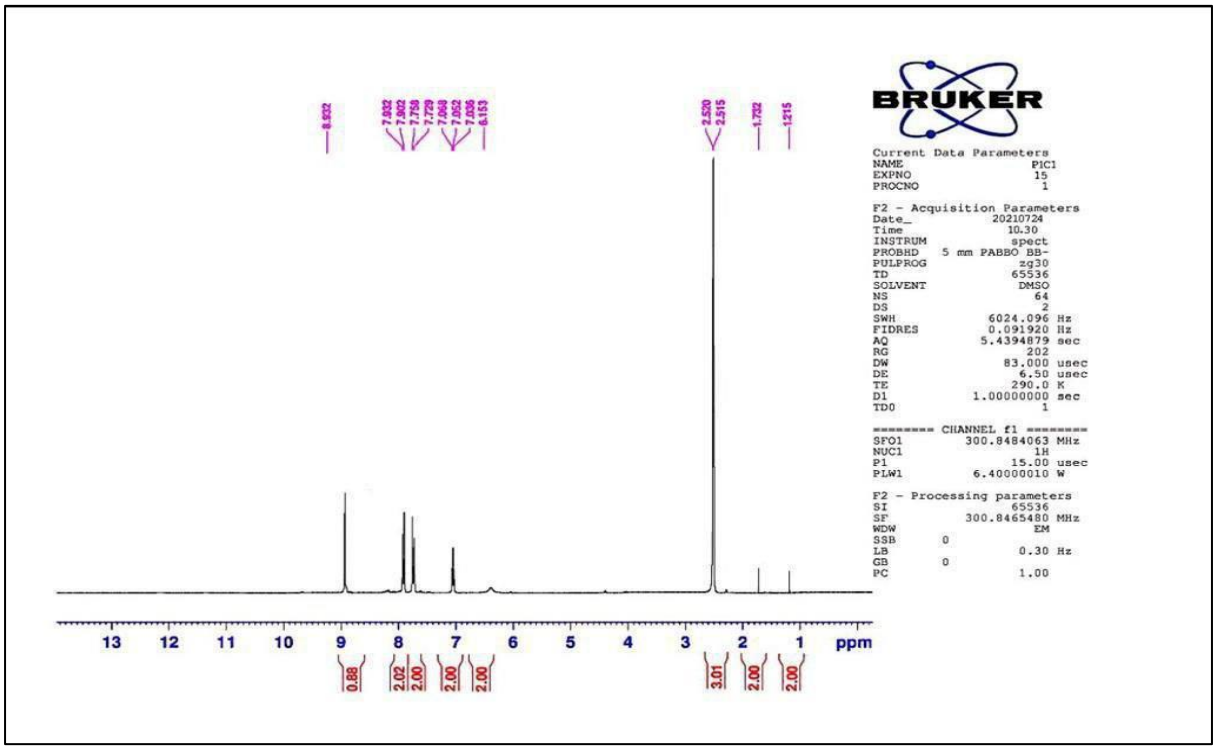


Figure (5):^{13}C-NMR spectrum for compound(P2)



Figure(6) : ^{1}H-NMR spectrum for compound(P1C1)

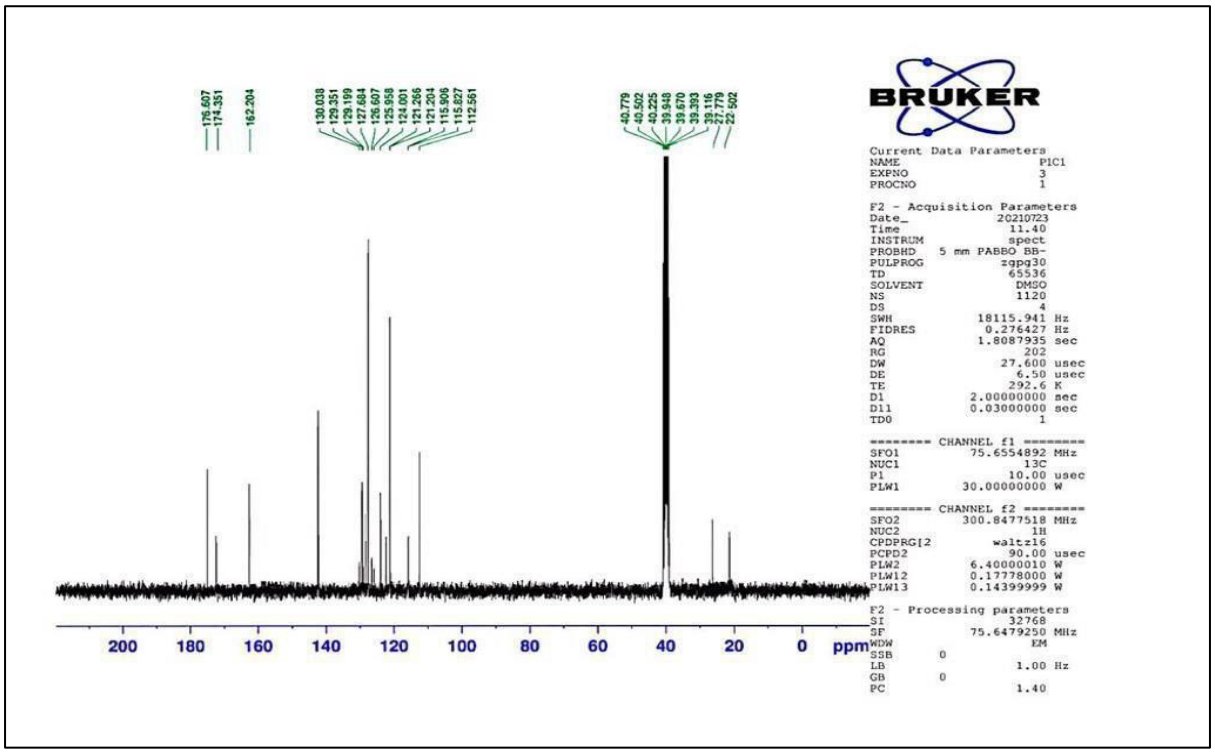


Figure (7) :^{13}C-NMR spectrum for compound(P1C1)

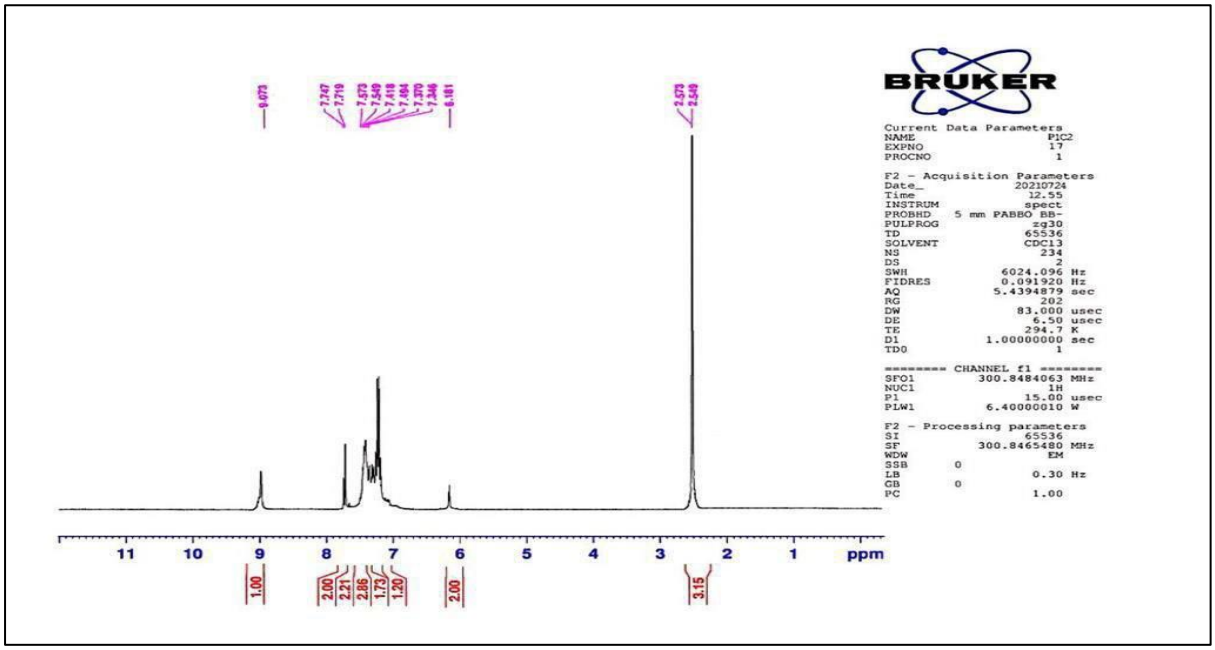


Figure (8) : ^{1}H-NMR spectrum for compound(P1C2)

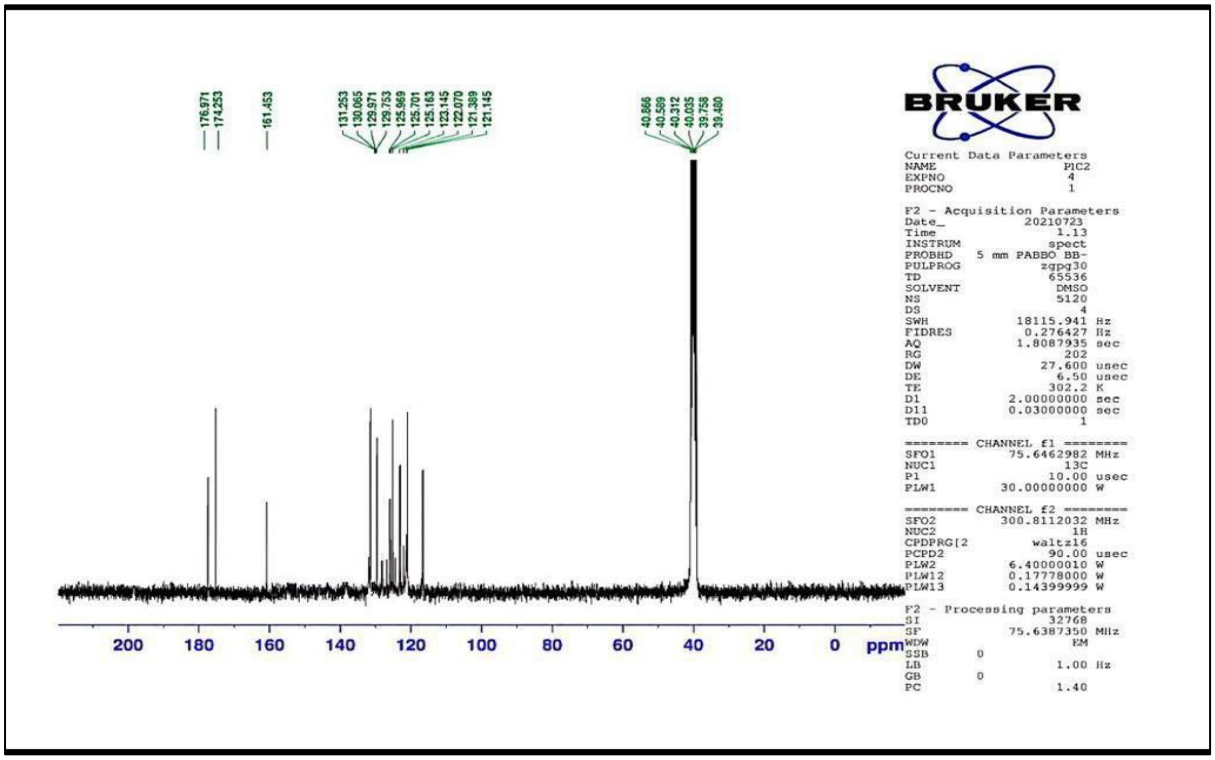


Figure (9): ^{13}C-NMR spectrum for compound(P1C2)

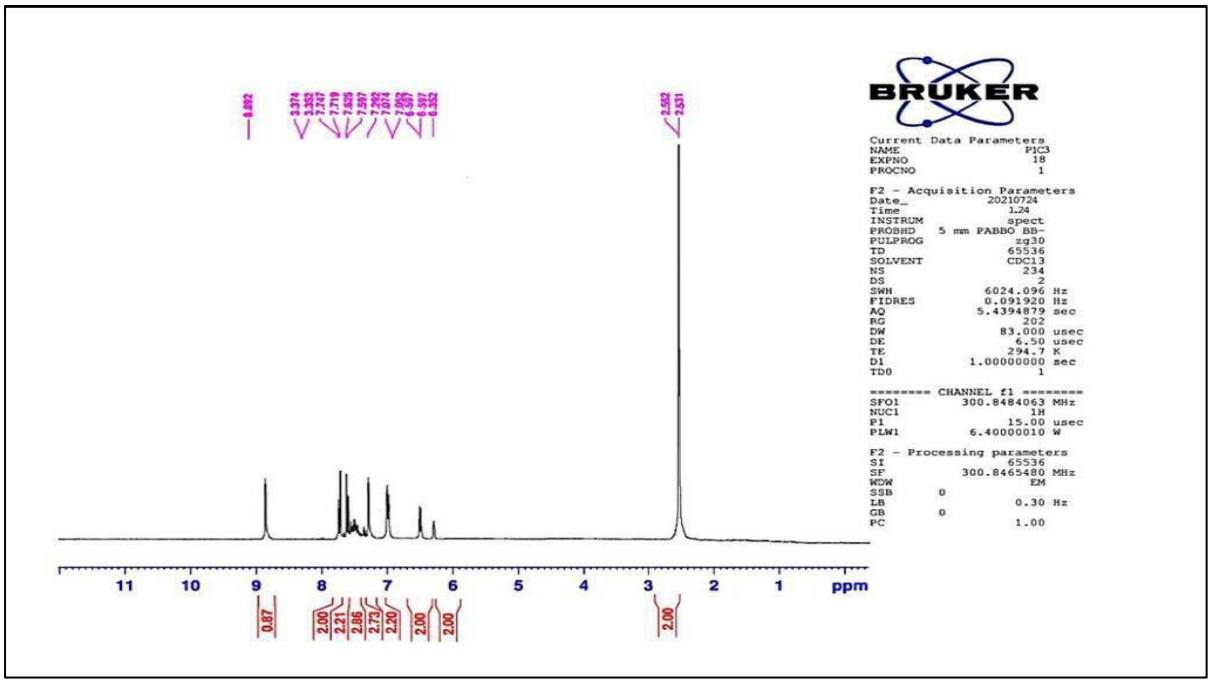


Figure (10):^{1}H-NMR spectrum for compound(P1C3)

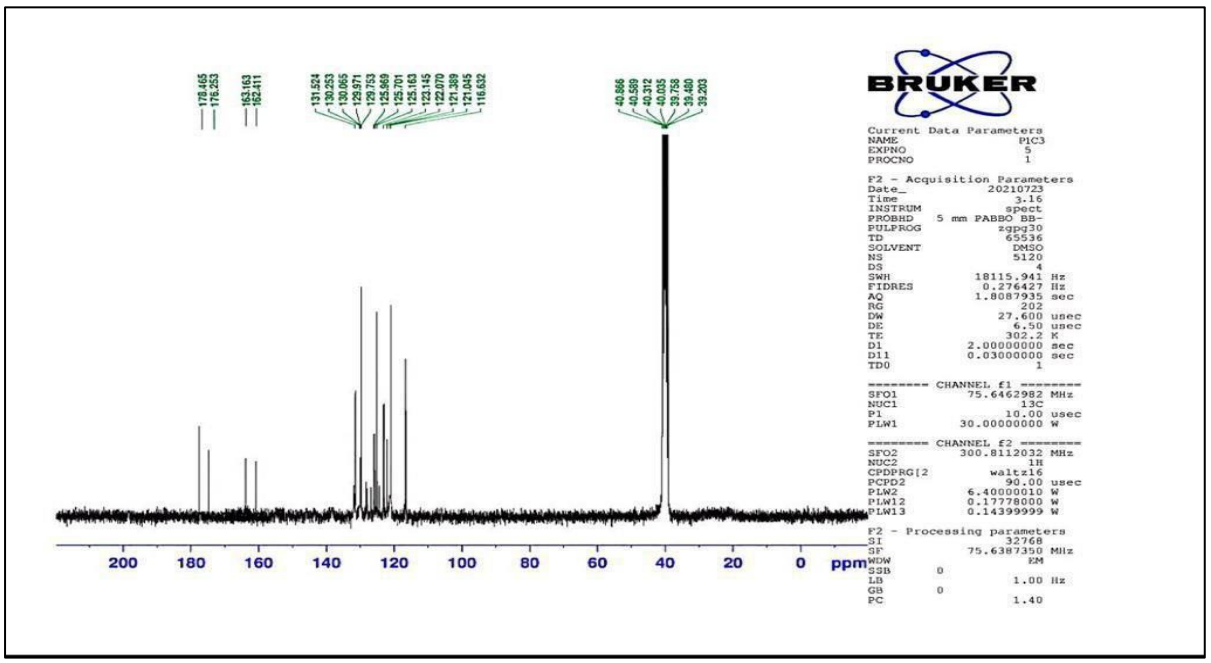


Figure (11) :^{13}C-NMR spectrum for compound(P1C3)

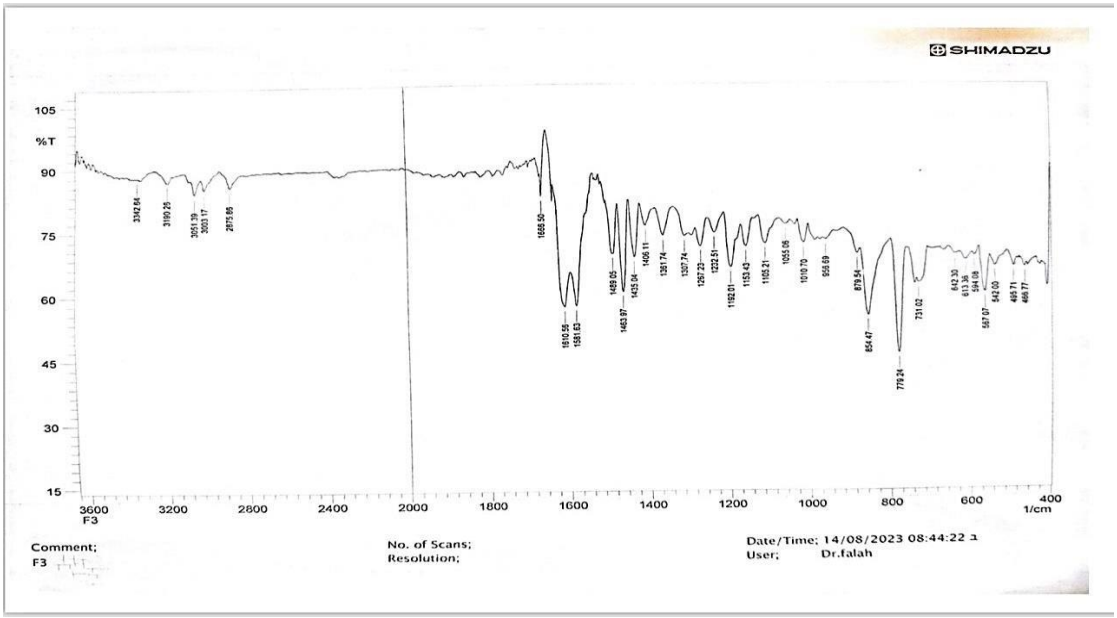


Figure (12) : FT-IR spectrum for compound(R4)

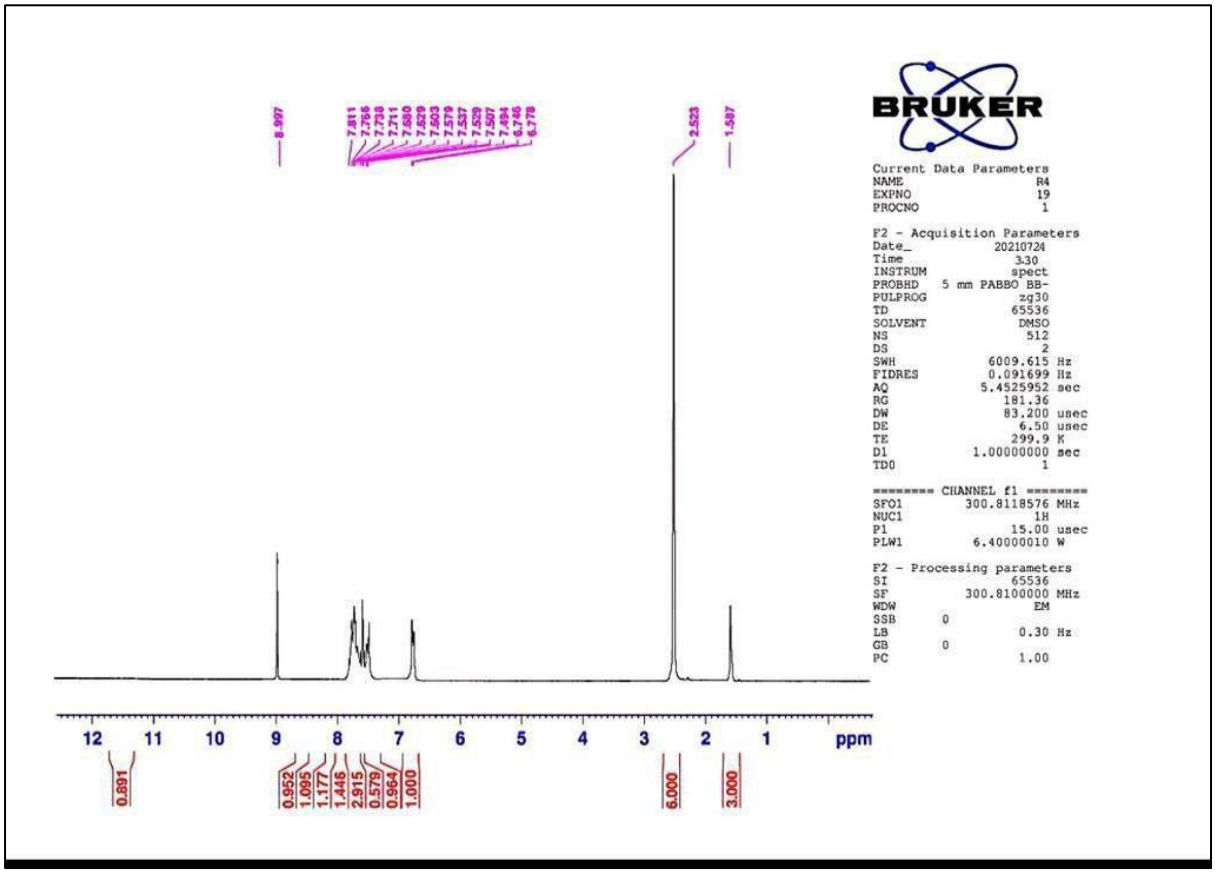


Figure (13):^{1}H-NMR spectrum for compound(R4)

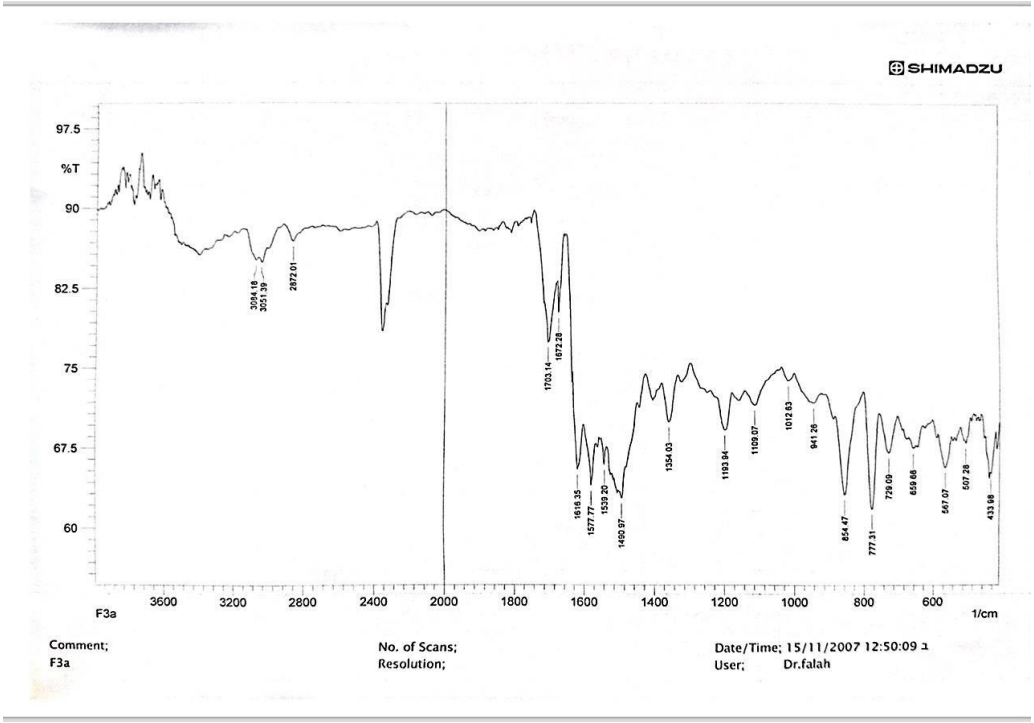


Figure (14): FT-IR spectrum for compound(R4C1)

5.Conclusion

The synthesis of the designed chemicals has been completed successfully. Physical characteristics, FT-IR spectroscopy, 1H-NMR, and 13C-NMR spectra were used to corroborate the characterization and identification of the target compounds. Following that, the compounds were tested for antibacterial activity against gram-positive and gram-negative bacteria strains. The majority of the produced compounds exhibit extremely promising antibacterial action against some bacteria strains, whereas others exhibit no activity against specific bacterium strains.

6.Acknowledgement:

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