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Synthesis and Characterization of New Schiff Bases and Biological Studies

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ABSTRACT

A new Schiff bases compound has been synthesized by reaction ethylene diamine, with three new types of diketone compounds synthesized from condensation reactions of benzaldehyde, furan-2-carbaldehyde, and pyridine-2-carbaldehyde. The chemical composition and functional group identification of the synthesized compounds were confirmed by mass spectroscopy and 1HNMR spectroscopy.

Preparation of Schiff base compounds (A2en, B2en, and C2en) in absolute ethanol using a solution of 0.2mole ethylene diamine in 25 ml methanol. Melting point, FT-IR, EI-Mass, H-NMR, and ^{13}C-NMR spectroscopy, have been used to classify these compounds. Schiff base compounds (A2en, B2en, and C2en) were used for antibacterial activity in this study. The results proved that all Schiff base compounds provided good inhibition zones against gram-positive and gram-negative bacteria, especially in concentrations 300mg/ml of Schiff base compound B2en with diameter inhibition zone 19-20 mm against gram-negative bacteria and C2en with diameter inhibition zone 15-19mm against gram-positive and gram-negative bacteria respectively.

Keywords: Schiff base; Benzaldehyde; Furan-2-carbaldehyde; Pyridine-2-Carbaldehyde; Antibacterial activity.

INTRODUCTION

The Schiff base is an organic compound consisting of the union of the nitrogen atom in the primary amine with the carbonyl group in various aldehydes or ketones to form an azomethine group C=N-R R2 [1] which is generally prepared from the reaction of the aldehyde or ketone with the primary amine and according to the following reaction **(Scheme 1)**.

Scheme 1: Reaction of the aldehyde or ketone with the primary amine

Schiff bases, which were first obtained by the German chemist Hugo Schiff in 1864 [2]. A Schiff base is derived from aniline, where R_3 is a phenyl or a substituted phenyl [3, 4]. Schiff bases are formed when any primary amine reacts with an aldehyde (RHC=O) or ketone (R 2 C=O), under specific conditions.

Aldehydes react very easily with primary amines to form Schiff bases, but this process is not so easy for ketones. In order to obtain Schiff bases from ketones, it is necessary to pay attention to factors, such as the choice of catalyst, the appropriate pH range, the selection of a solvent that can form an azeotrope mixture with the water to be formed in the reaction, and the appropriate reaction temperature [5, 6]. The carbon-nitrogen double bond in Schiff bases formed as a result of the reaction of primary amines with aldehydes is called azomethine or aldimine, while the bond formed as a result of the reaction with ketone is called imine or ketimine.

Schiff bases are the most widely used organic compounds. They have been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, anti-proliferative, anti-inflammatory, antiviral, and antipyretic properties [7]. The current study includes preparing a number of aromatic Schiff bases derived from Benzaldehyde, furan-2-carbaldehyde, and Pyridine-2-carbaldehyde compounds and studying their applications in biological fields.

MATERIALS AND METHODS

All reagents were used without purification and supplied by Merck. Benzaldehyde, furan-2-carbaldehyde, Pyridine-2-carbaldehyde, ethane-1,2-diamine, sodium cyanide, sodium cyanide, potassium cyanide, ammonium nitrate,. Melting points were determined in an electro-thermal fisher apparatus. The 1HNMR spectrum of the compound was determined in DMSO (internal standard TMS), using an Agilent Technologies 5975C mass spectrometer, the compound's mass spectrum was estimated at 70e.

General Synthesis of (A1) benzoin (B1) furoin and (C1) Condensation reaction (2.1)

In a 250-ml round-bottomed flask place 5 g of pure starter material (Benzaldehyde, furan-2-carbaldehyde, Pyridine-2-carbaldehyde) and a solution of 1 g of sodium cyanide (96-98%) 1 in 10 ml of water. Attach a reflux condenser (preferably of the double surface type) and boil the mixture gently for half an hour. Cool the contents of the flask (preferably in an ice bath). Filter and wash it with cold water, drain well, and dry [8].

Synthesis of benzil (A2) (2.2)

2 g (0. 94mol) of pure benzoin (A1) and 10 ml of concentrated nitric acid in a 25ml round-bottomed flask. Heat on a boiling water bath (in the fume cupboard) with occasional shaking until the evolution of oxides of nitrogen has ceased (about 1.5 hours). Pour the reaction mixture into 30-40 ml of cold water contained in a beaker, and stir well until the oil crystallizes completely as a yellow solid. Filter the crude benzil at the pump, and wash it thoroughly with water to remove the nitric acid. Recrystallize from ethanol or rectified spirit [9].

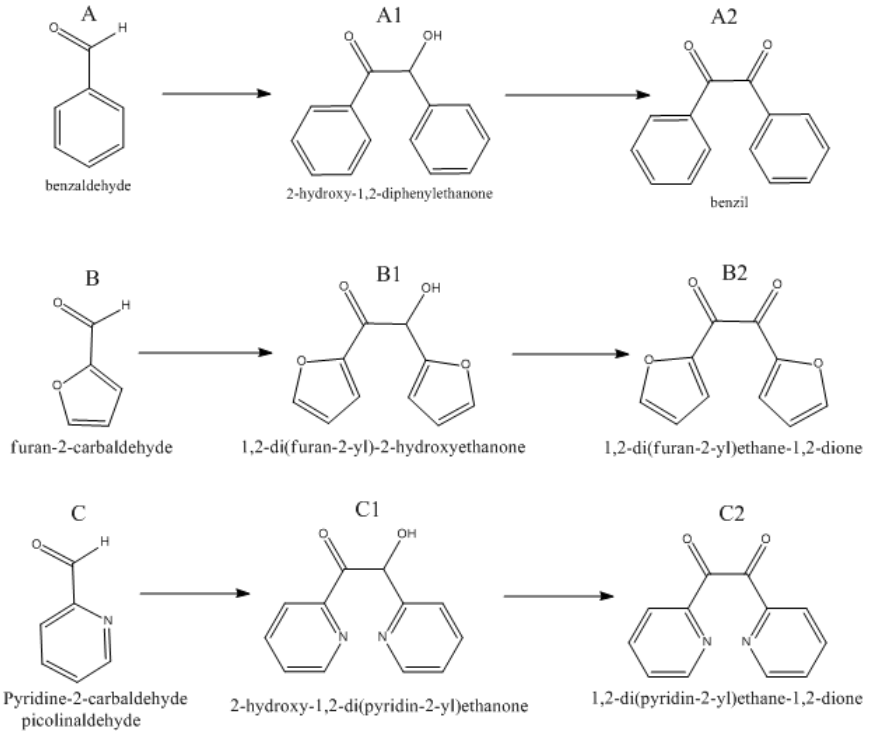
Synthesis of 1, 2-Di(furan-2-yl)ethane-1,2-dione (B2) (2.3)

A mixture of $CuSO_4$ (1.3ml 2%), NH_4NO_3 (0.02 mol, 1g), and 6.5ml glacial acetic was heated to 70 -75 ˚C in an oil bath with stirring. When the homogeneously blue solution, furoin (B1) (0.01 mol, 1.92 g) is added and refluxed for 1.5 hr at 95-100˚C. The product is separated by filtration. The filter cake is washed with 150 ml (5 x 30 ml) of cold water and then recrystallized from 95% ethanol. The product obtained is a brilliant yellow needle crystal (3.05 g, 84% yield). M.p.165~166 C˚ [10]

Synthesis of 1, 2-di (pyridin-2-yl) ethane-1,2-dione (C2) (2.4)

1.5 g (0. 8mol) of pure (C1) and 10 ml of concentrated nitric acid in a 25ml round-bottomed flask. Easy heating on a boiling water bath (60-50C˚)

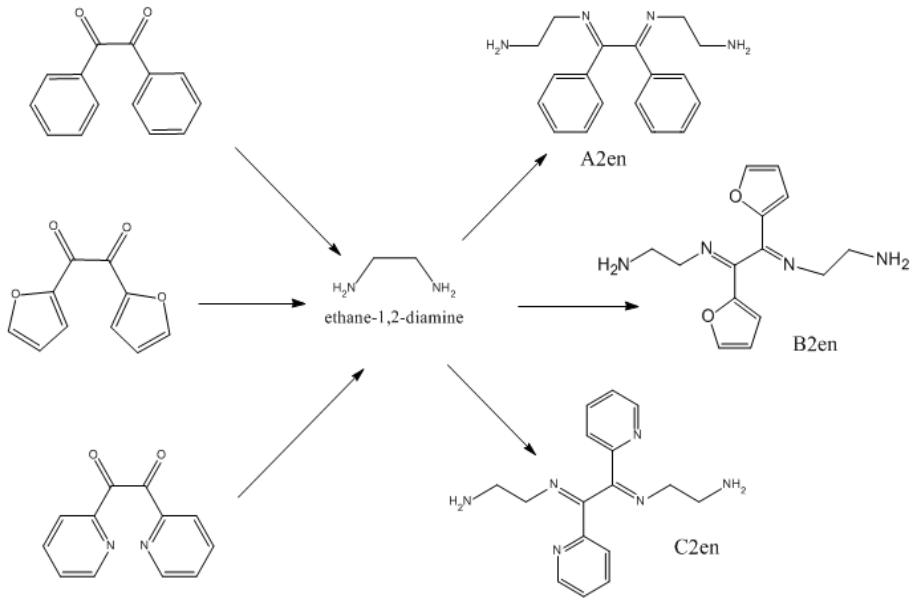
with occasional shaking until the evolution of oxides of nitrogen has ceased (about 10 min). Pour the reaction mixture into 30-40 ml of cold water contained in a beaker, and stir well until the oil crystallizes completely as a yellow solid. Filter at the pump, and wash it thoroughly with water to remove the nitric acid. Recrystallize from methanol. **(Scheme 2)** shows the chemical structure of the prepared diketone compounds.



Scheme 2: Chemical structure of the prepared diketone compounds

General Procedure for Preparation Schiff bases (A2en) (B2en) (C2en) (2.5)

Schiff bases were prepared by a modification of the reported methods [11, 12]. A typical procedure for the synthesis of Schiff bases is as follows: a solution of 0.2 mol ethylenediamine in (25 ml methanol) was slowly added to a solution of 0.1mol of A2.B2 and C2 (in 50 ml methanol) with the addition of a few drops of glacial acetic acid. After stirring the reaction mixture for 2-3 hours at 80°C, the precipitate was cooled and collected by filtration. The precipitate was washed several times using diethyl ether then, with methanol. Followed by crystallization in methanol and drying at 50°C as shown in **(Scheme 3)**. (**Table 1)** contains the physical properties of these compounds prepared.



Scheme 3: Synthetic procedures of Schiff base compounds

Table 1: Some physical properties of prepared compounds

Compound	Molecular formula (Mol.Wt)	Color and physical state	Time of reaction (hr)	m.P C°	Yield (%)
A1	$C_{14}H_{12}O_2$ 212.08	off-white crystals	15 (min)	135-137ºC	90%
A2	$C_{14}H_{10}O_2$ 210.07	light yellow crystals	1	92-94ºC	85%
A2en	$C_{18}H_{22}N_4$ 294.18	light yellow powder	2	138-140 ºC	72%
B1	$C_{10}H_8O_4$ 192.04	Brown crystals	25 (min)	136-138 ºC	78%
B2	$C_{10}H_6O_4$ 190.03	dark brown crystals	3	166-168 ºC	70%
B2en	$C_{14}H_{18}N_4O_2$ 274.14	light yellow powder	4	131-133 ºC	65%
C1	214.07 $C_{12}H_{10}N2O_2$	yellow crystals	10 (min)	150-152 ºC	92%
C2	$C_{12}H_8N2O_2$ 212.06	light yellow crystals	1	114-116 ºC	80%
C2en	$C_{16}H2_0N_6$ 296.17	light yellow powder	2	182-185 ºC	63%

RESULTS AND DISCUSSION

Spectroscopic analysis (3.0)

FT-IR spectra (3.1)

At room temperature, record the infrared spectra in the range (400–4000) cm-1 of the A2, B2, C2, and Schiff base compounds in the shape of tablets KBr. Figures (1-3) show the most important visible bands in the infrared spectrum for compounds (A2, B2, and C2), which are the two carbonyl groups that appear in the region (1700-1780cm-1)[13,14]. It appeared in all the prepared compounds, as well as the (C-O) band of the furan ring in compound B2 that appears at (1350cm-1) [15] and the (C-N) band in compound C2 that appears at (1537cm-1) [16]. Figures (4-6) show the most important visible bands in the infrared spectrum for compounds (A2en, B2en, and C2 en) which are the bands of the two isomethine groups that appear within the region (1690-1640cm-1) [17] and have appeared in all the prepared compounds, as well as the (C-O) band of the furan ring in the compound (B2en) that appears at (1165cm-1)[15]and the (C-N) band in the compound (C2en) that appears at (1656cm-1) [16].

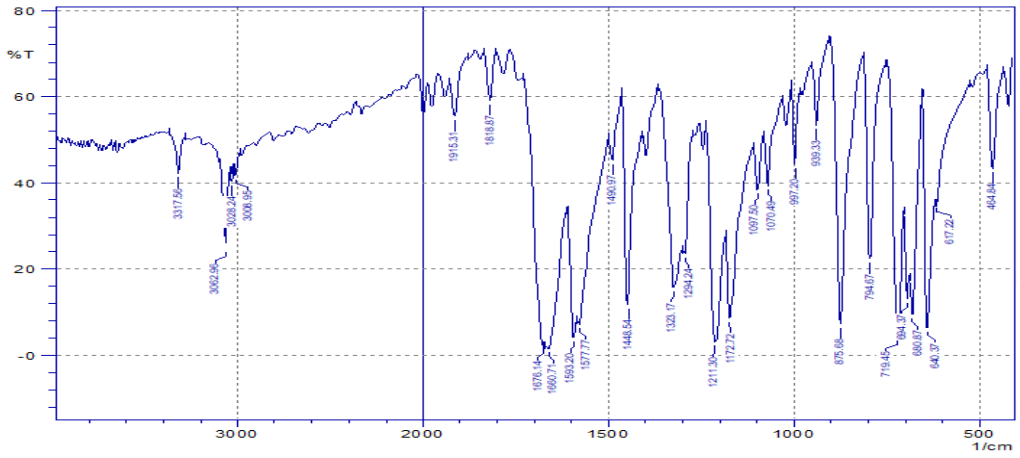


Figure 1: Infrared spectrum of compound A2.

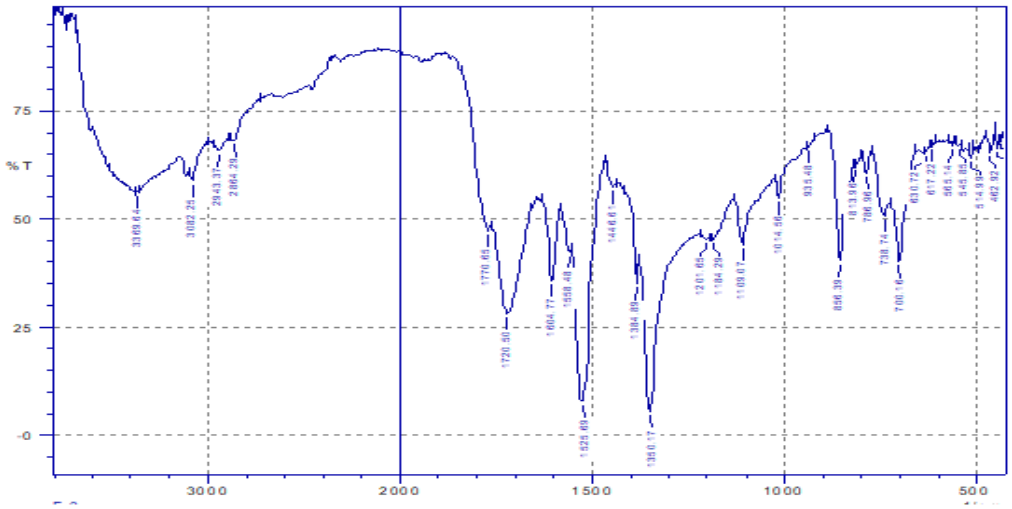


Figure 2: Infrared spectrum of compound B2.

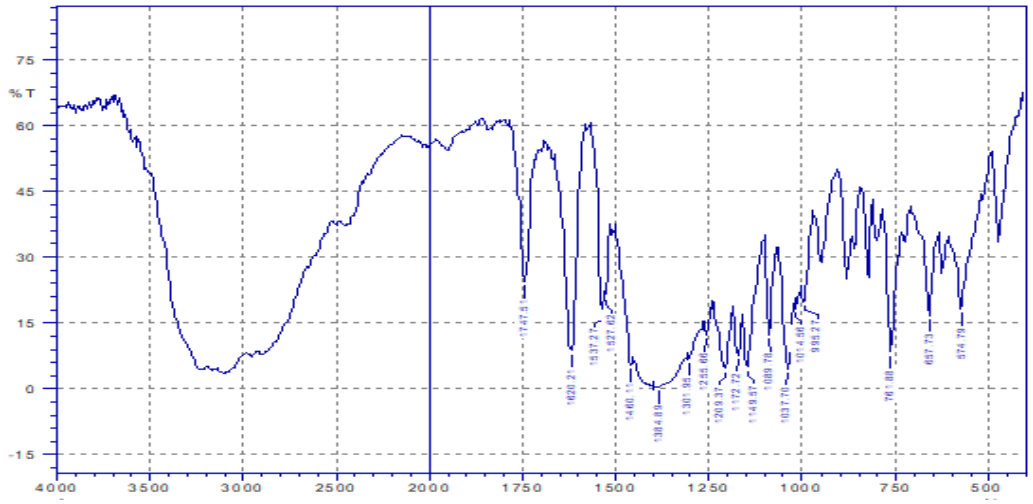


Figure 3: Infrared spectrum of compound C2.

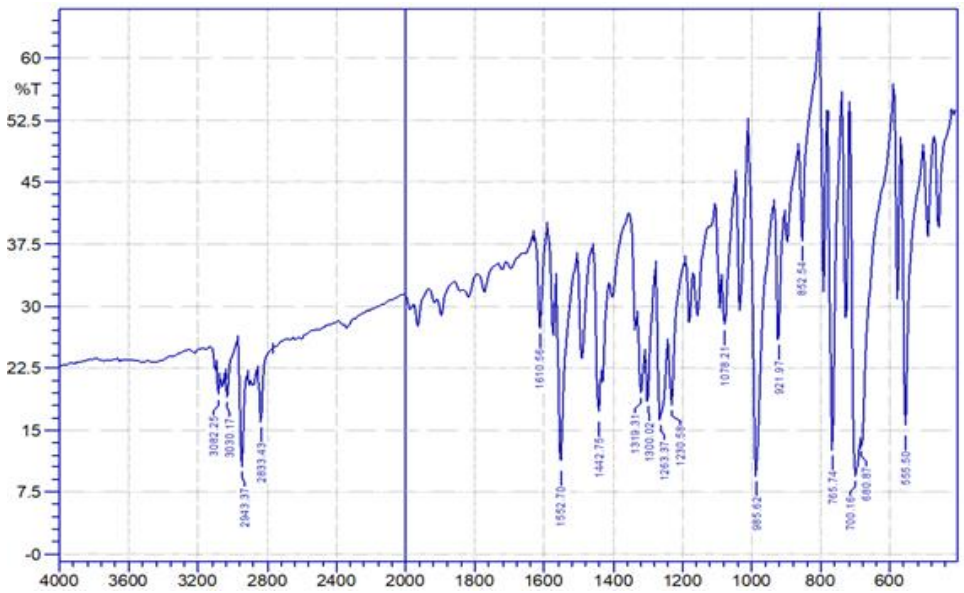


Figure 4: Infrared spectrum of compound A2en.

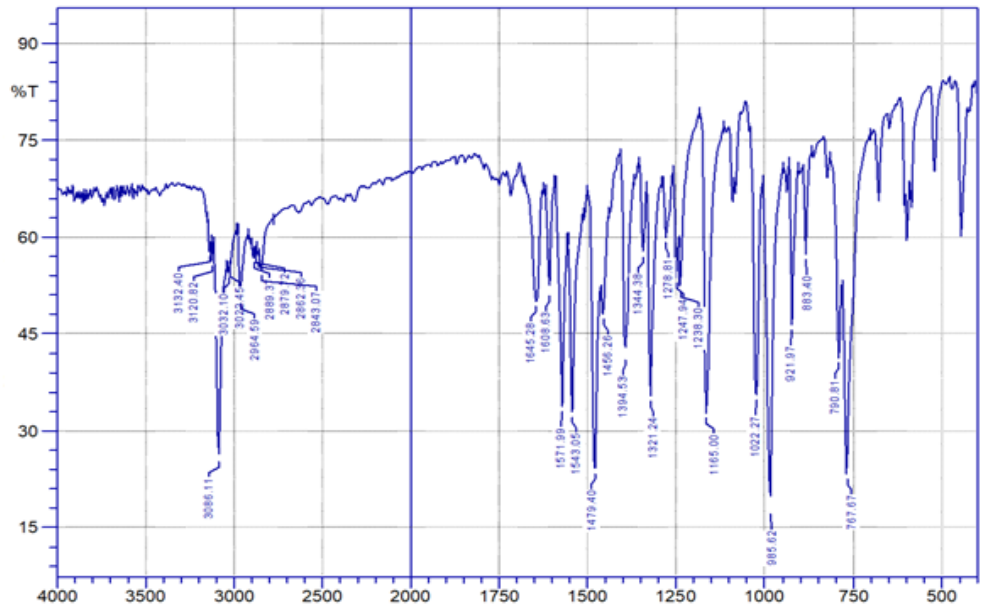


Figure 5: Infrared spectrum of compound B2en.

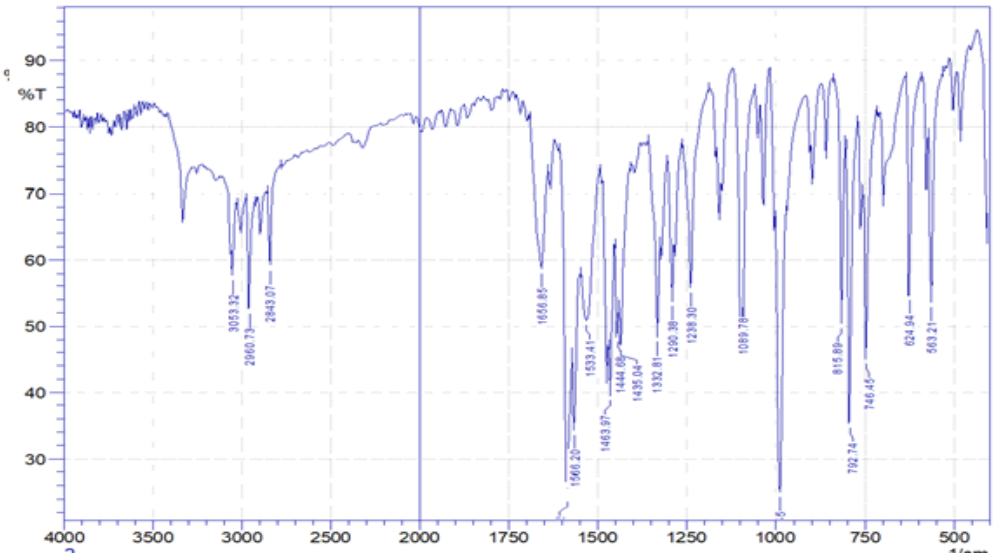


Figure 6: Infrared spectrum of compound C2en.

EI-Mass spectra (3.2)

ESI mass spectra of the prepared compounds were performed using Agilent Technologies-Tehran-Iran-Tarabiyat Modres University. The ESI mass spectra of the prepared compounds showed the molecular ion peak which corresponds to the molecular formula of each compound. **(Table 2)** shows the EI mass spectra of the prepared compounds. It was found that the m/e value is 212.08 for compound A1 **(Figure 7)**, m/e 210.07 for compound A2 **(Figure 8)**, and m/e value is 192.04 for compound B1 **(Figure 9)**, the m/e value of 190.03 for B2 **(Figure 10)**, the m/e value of 214.07 for C1 **(Figure 11)**, and the m/e value of 212.06 for C2 **(Figure 12)**. The Schiff base compounds A2en, B2en**,** and C2en also agree clearly with the mass spectrometric structure, m/e 294.18 for A2en **(Figure 13)**, m/e 274.14 for B2en **(Figure 14)**, and m/e 296.17 for C2en **(Figure 15)**. Through mass spectrometric data, the presence of the compound can be confirmed.

Table 2: EI-Mass spectra of the synthesized compounds.

Compound	Molecular formula (Mol.Wt)
A1	$C_{14}H_{12}O_2$ 212.08
A2	$C_{14}H_{10}O_2$ 210.07
A2en	$C_{18}H_{22}N_4$ 294.18
B1	$C_{10}H_8O_4$ 192.04
B2	$C_{10}H_6O_4$ 190.03
B2en	$C_{14}H_{18}N_4O_2$ 274.14
C1	214.07 $C_{12}H_{10}N2O_2$
C2	$C_{12}H_8N2O_2$ 212.06
C2en	$C_{16}H2_0N_6$ 296.17

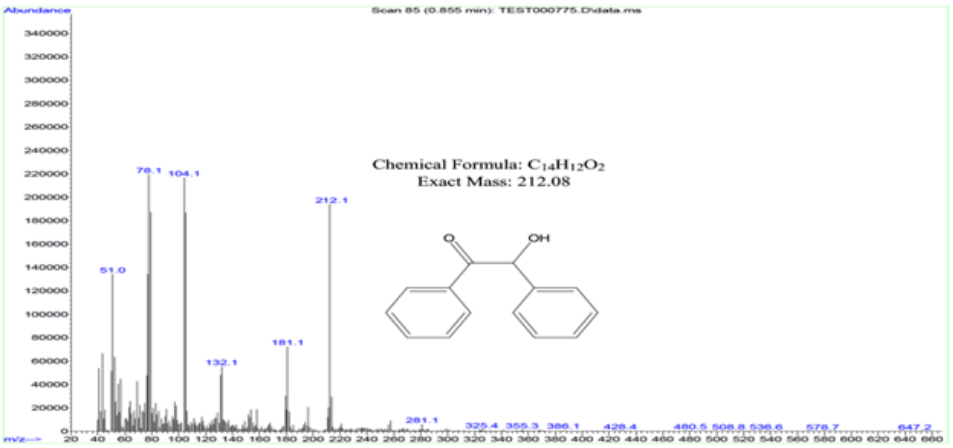


Figure 7: Mass spectra of compound A1.

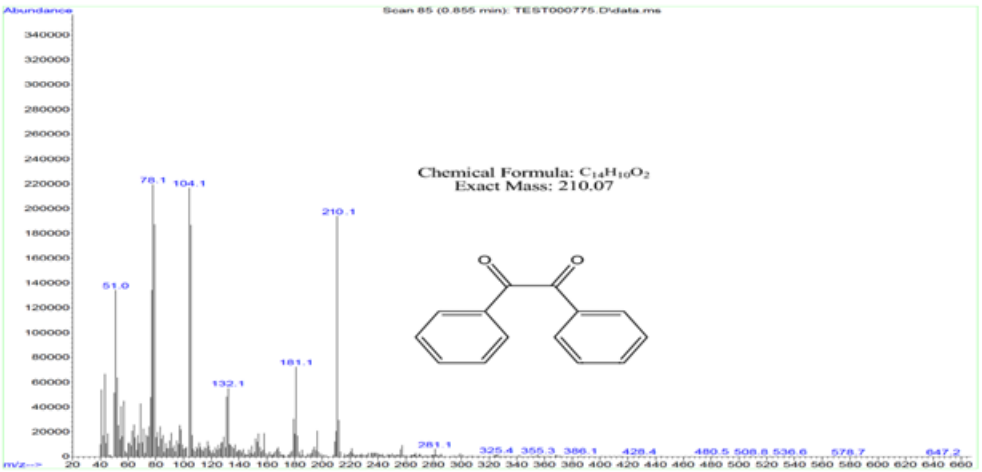


Figure 8: Mass spectra of compound A2.

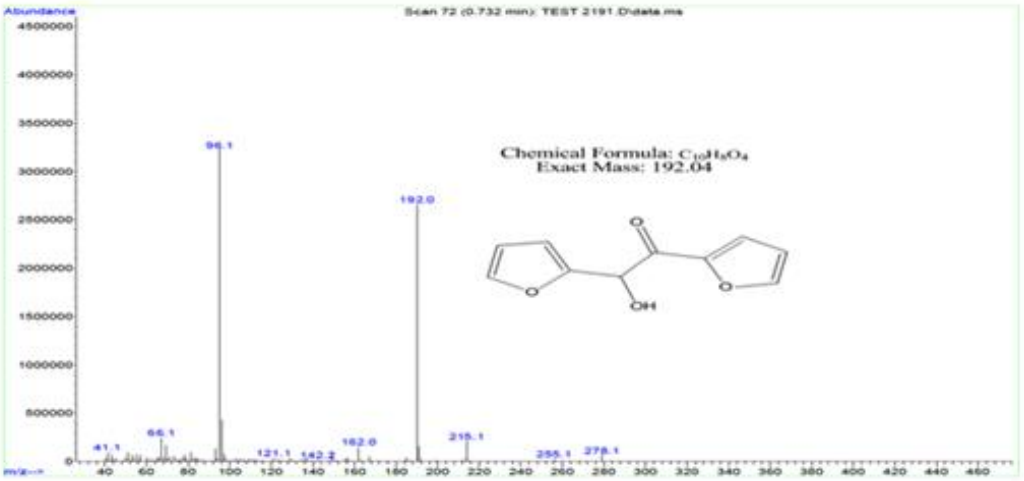


Figure 9: Mass spectra of compound B1.

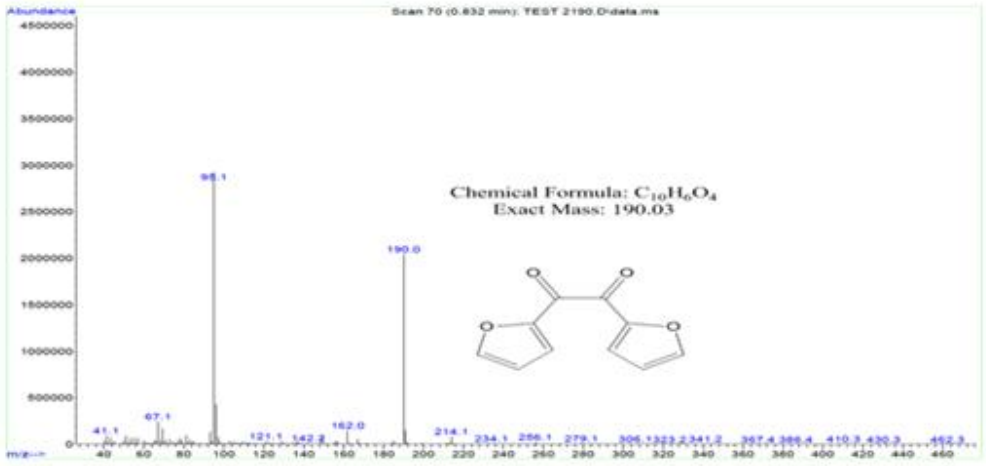


Figure 10: Mass spectra of compound B2.

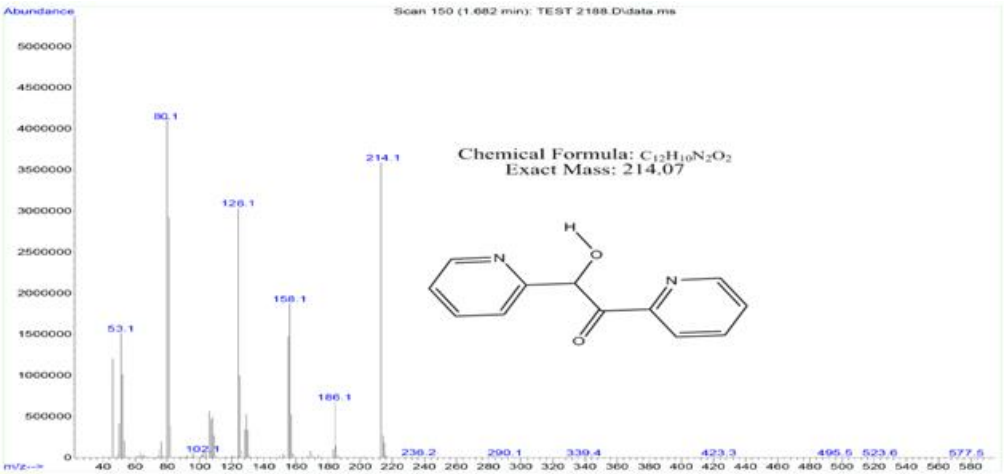


Figure 11: Mass spectra of compound C1.

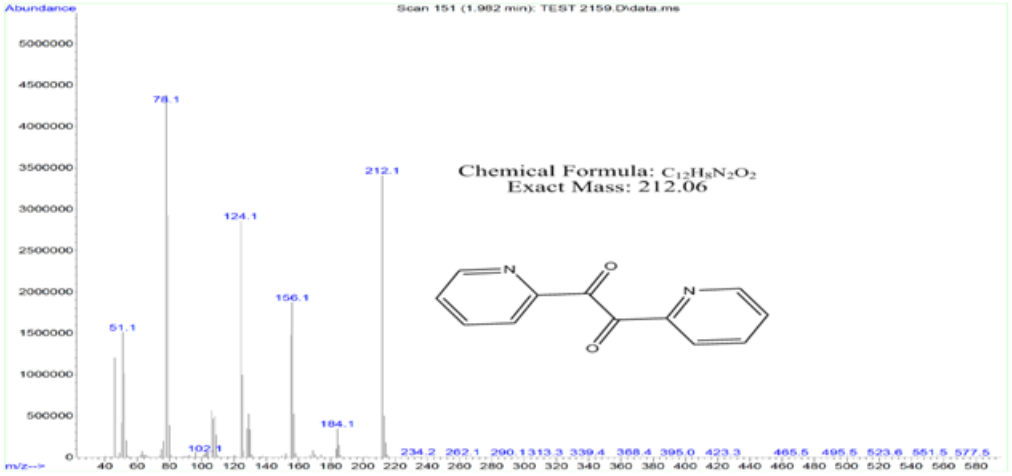


Figure 12: Mass spectra of compound C2.

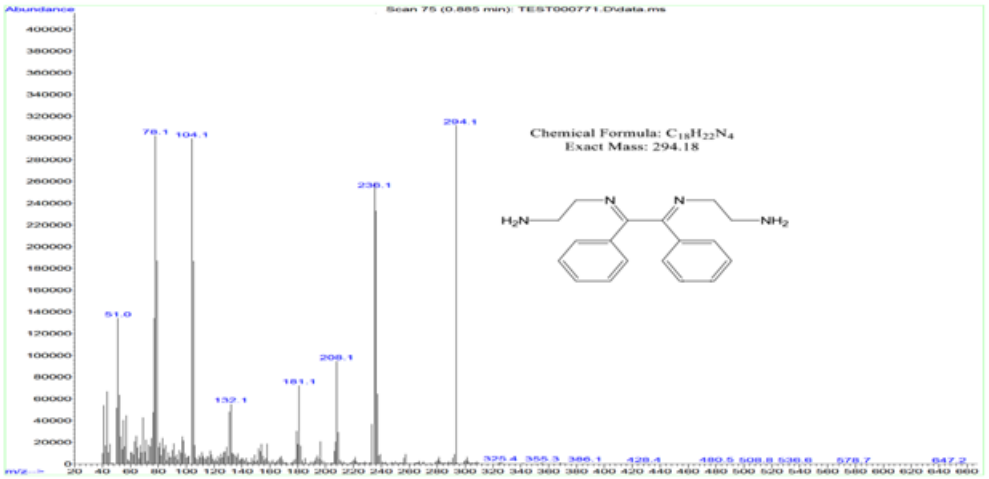


Figure 13: Mass spectra of compound A2en.

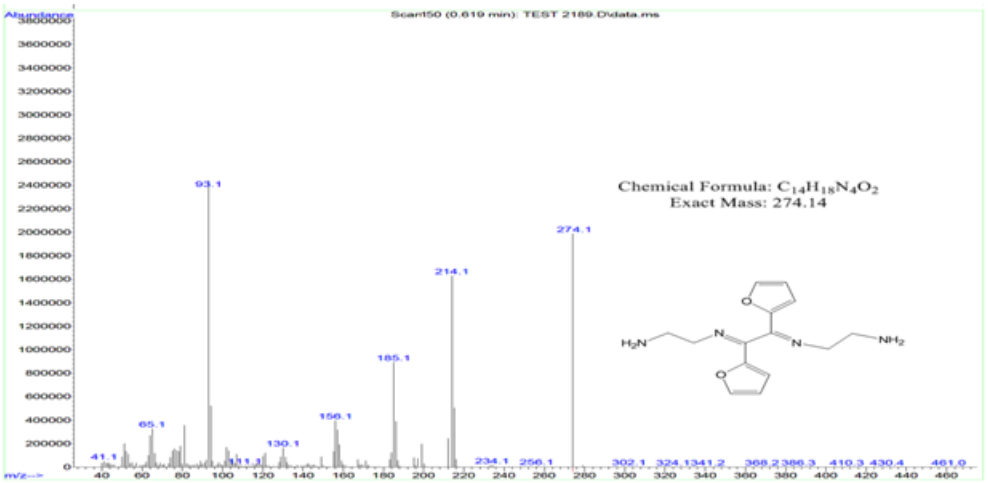


Figure 14: Mass spectra of compound B2en.

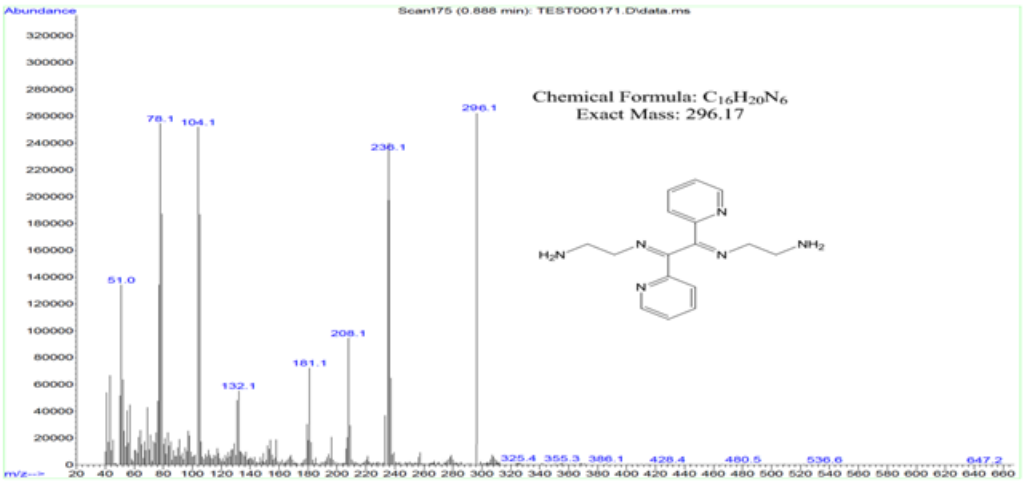


Figure 15: Mass spectra of compound C2en.

H-NMR, 13C-NMR spectra of the compounds prepared (3.3)

The ^{1}H-NMR spectra of the A2, B2, and C2 were recorded in DMSO. Using 400 MHZ, and it appeared many of the characteristic signals of the compounds as shown in **(Table 3) (Figures 16-18)** The signals due to the aromatic protons were observed in the range δ = 7.626 – 8.419 ppm. For A2, δ = 5.8-7.61 ppm. For B2, δ = 7.625-8.962 ppm. For C2. The ^{1}H-NMR spectra of the compounds A2en, B2en, and C2en Several distinctive signs appeared as well of the compounds as shown in **(Table 4) (Figures 19-21)**, olefin protons δ = 3.597-3.340 ppm. NH proton δ = 4.902 ppm, phenyl proton in the range δ = 7.144-7.492 ppm. For A2en olefin protons δ = 2.504-3.340 ppm. NH proton δ = 3.533 ppm, phenyl proton in the range δ = 6.542-8.51 ppm for B2en, olefin protons δ = 1.914-2.999 ppm. NH proton δ = 4.014-4.831 ppm, phenyl proton in the range δ = 7.247-8.8 ppm for C2en

Table 3: Chemical shift of ^{1}H-NMR for compounds (A2, B2, and C2).

protons	Chemical shiftδ (ppm)		
	A_2	B_2	C_2
C_1	7.6	5.8	7.6
C_2	7.8	6.1	8.1
C_3	8.4	6.4	8.5
C_4	-----	7	8.9
C_5	-----	7.6	-----

Table 4: Chemical shift of ^{1}H-NMR for compounds (A2en, B2en, and C2en).

protons	Chemical shift δ (ppm)		
	A_2en	B_2en	C_2en
H-Olefin C_{1-2}	3.34 3.59	2.24 2.50	2.50-2. 99
NH_2-Proton C_3	4.90	3.53	4.01-4.83
H-Phynel C_{4-7}	7.14-7.94	8.25-8.54	7.26-8.8.

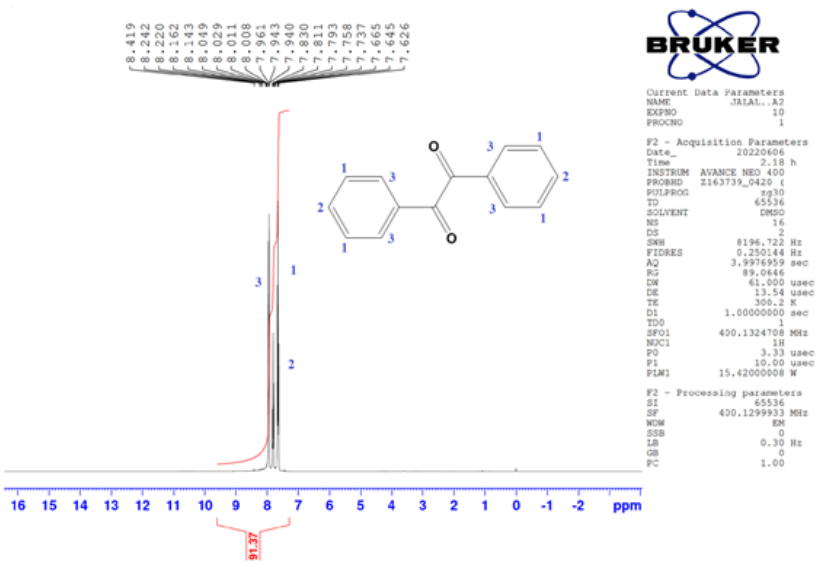


Figure 16: 1H-NMR Spectrum of A2.

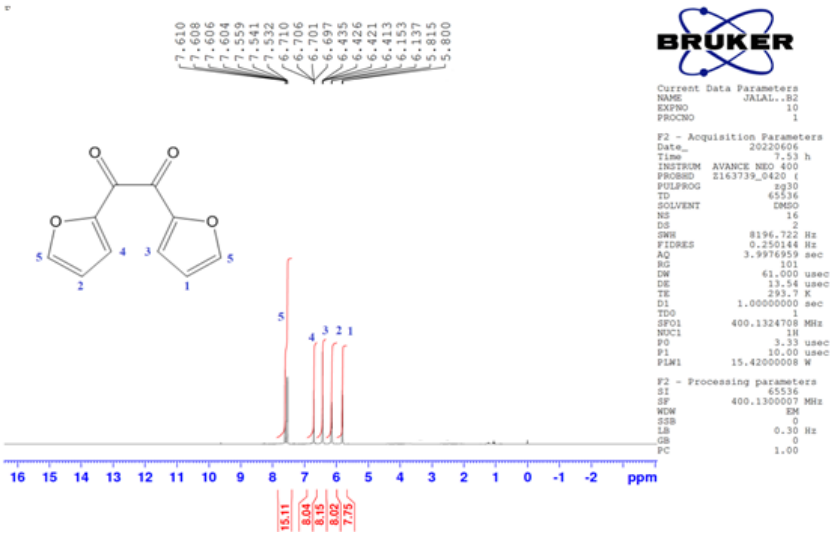


Figure 17: 1H-NMR Spectrum of B2.

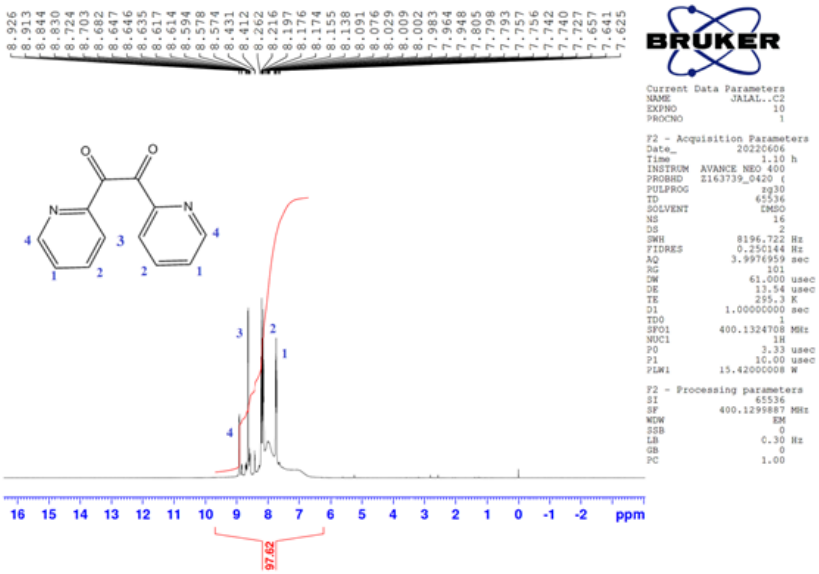


Figure 18: 1H-NMR Spectrum of C2.

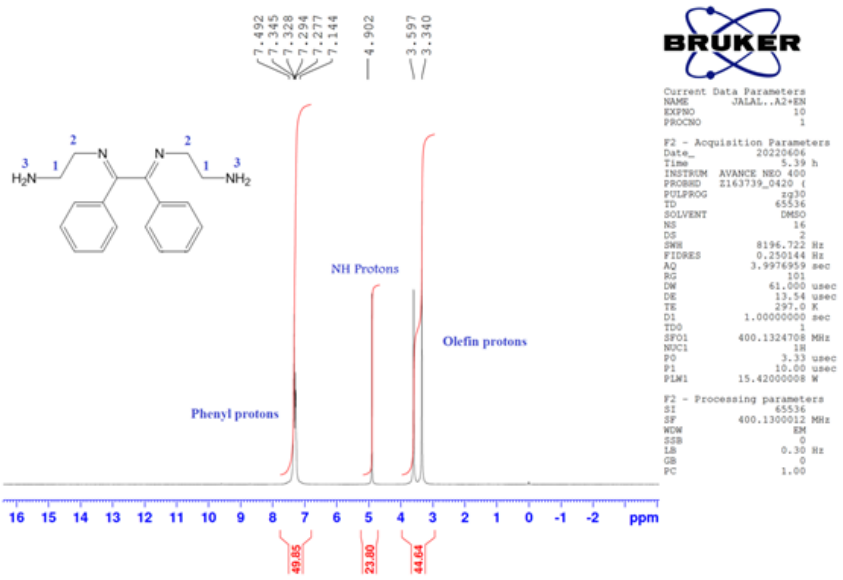


Figure 19: 1H-NMR Spectrum of A2en.

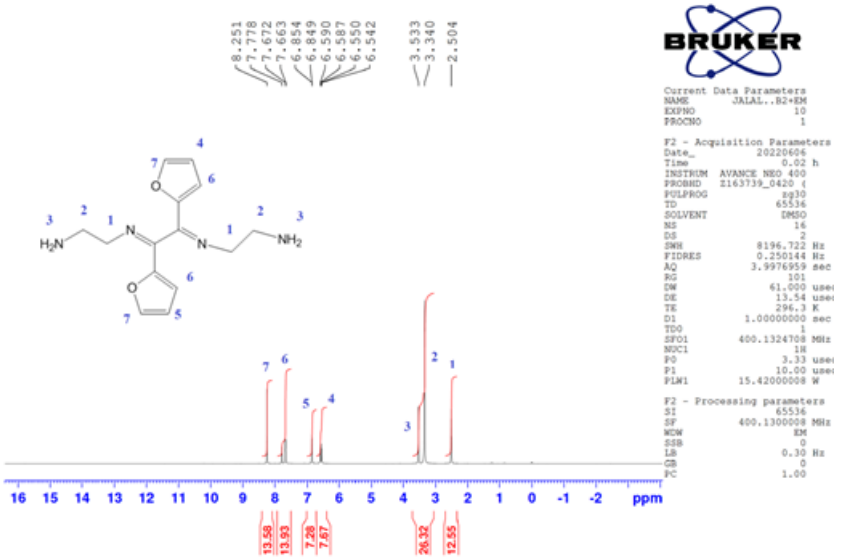


Figure 20: 1H-NMR Spectrum of B2en.

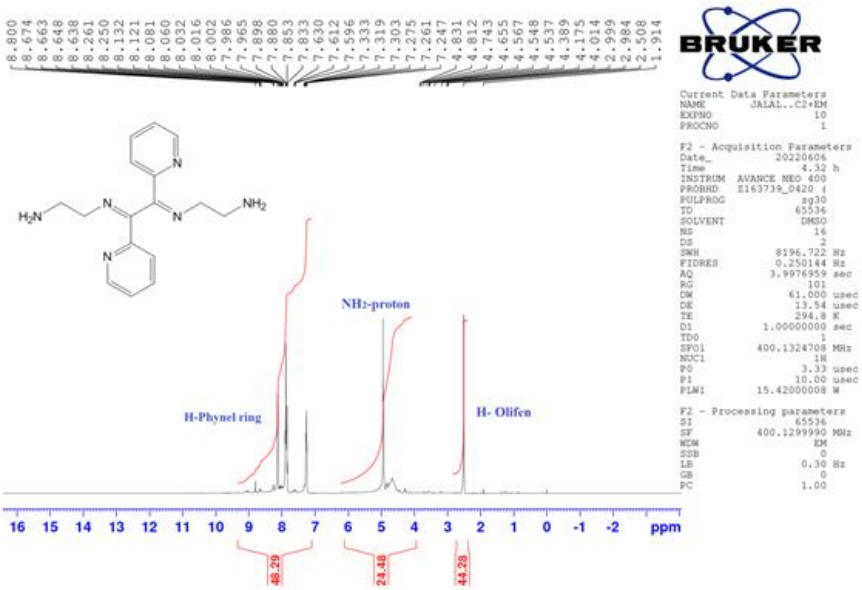


Figure 21: 1H-NMR Spectrum of C2en.

^{13}C – NMR data of compounds correspondent with 1H – NMR data indicated above as shown in **(Tables 5, 6)** and **(Figures 22-27)**, and that confirms the proposed structure of the compounds.

Table 5: Chemical shift of ^{13}C-NMR for compounds (A2, B2, and C2).

Carbon atom	Chemical shift δ (ppm)		
	A_2	B_2	C_2
C_1	129	109	122
C_2	132	111	129
C_3	135	113	138
C_4	195	120	150
C_5	-----	143	151
C_6	-----	148	-----
C_7	-----	150	-----
C_8	-----	152	-----
C_9	-----	185	-----

Table 6: Chemical shift of ^{13}C-NMR for compounds (A2en, B2en, and C2en).

Carbon atom	Chemical shift δ (ppm)		
	A_2en	B_2en	C_2en
C_1	128.10	40.82	45.86
C_2	128.49	48.82	54.46
C_3	129.91	122.25	121.68
C_4	138.17	113.29	124.16
C_5	157.76	114.07	138.21
C_6	-----	125.34	147.90
C_7	-----	145.25	156.68
C_8	-----	149.31	160.49
C_9	-----	150.90	-----
C_{10}	-----	151.43	-----

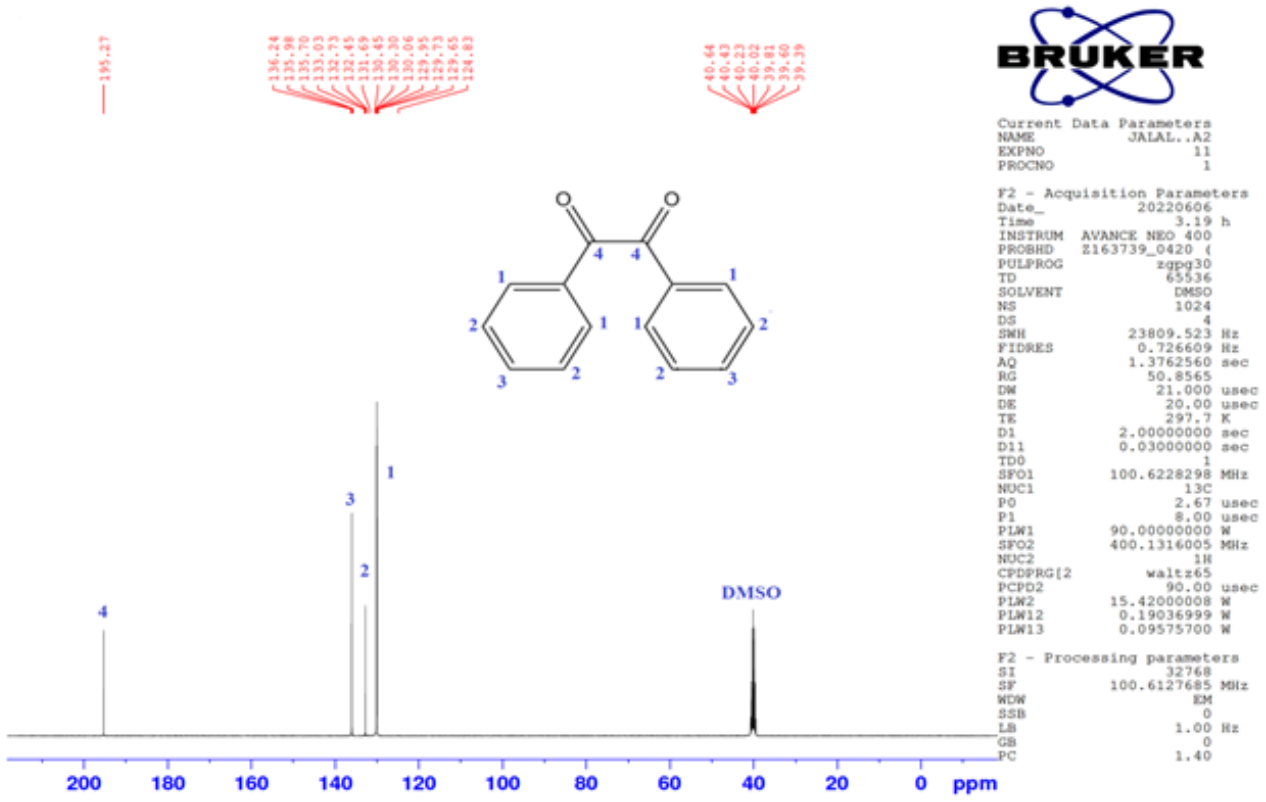


Figure 22: ^{13}C-NMR Spectrum of A2.

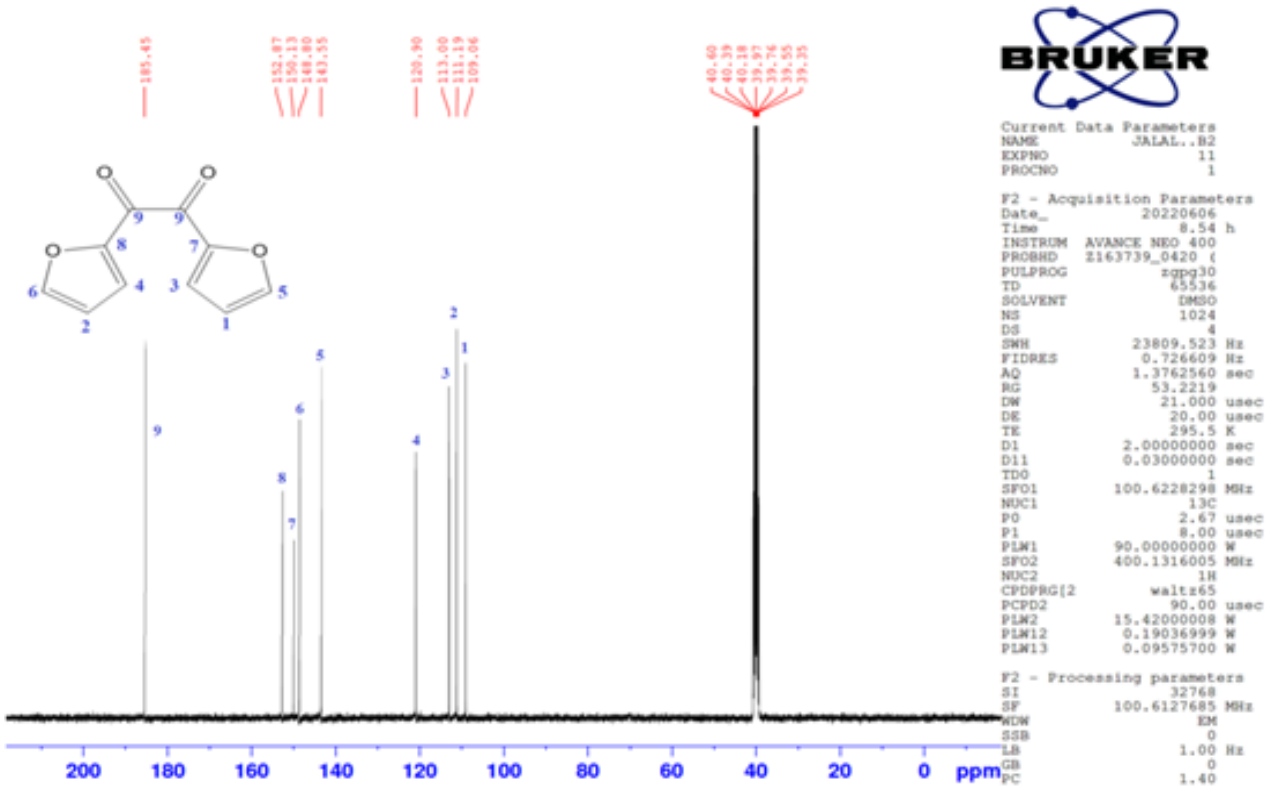


Figure 23: ^{13}C-NMR Spectrum of B2.

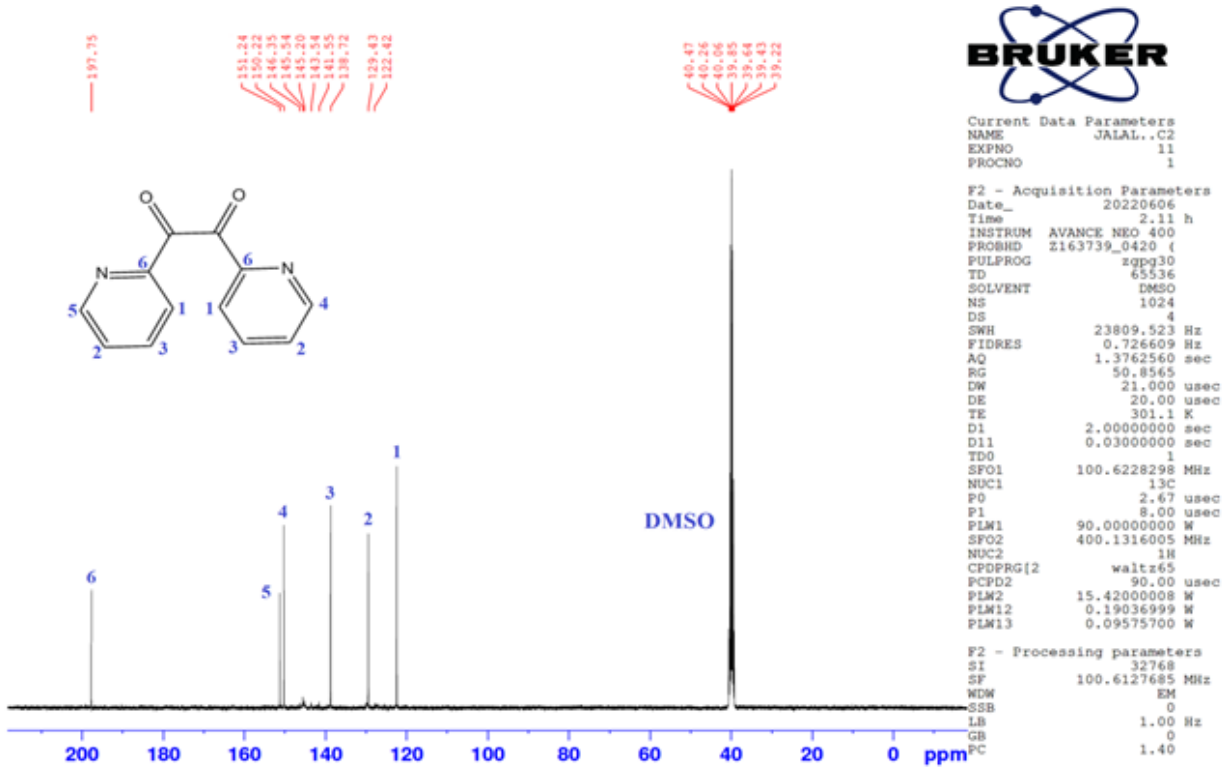


Figure 24: ^{13}C-NMR Spectrum of C2.

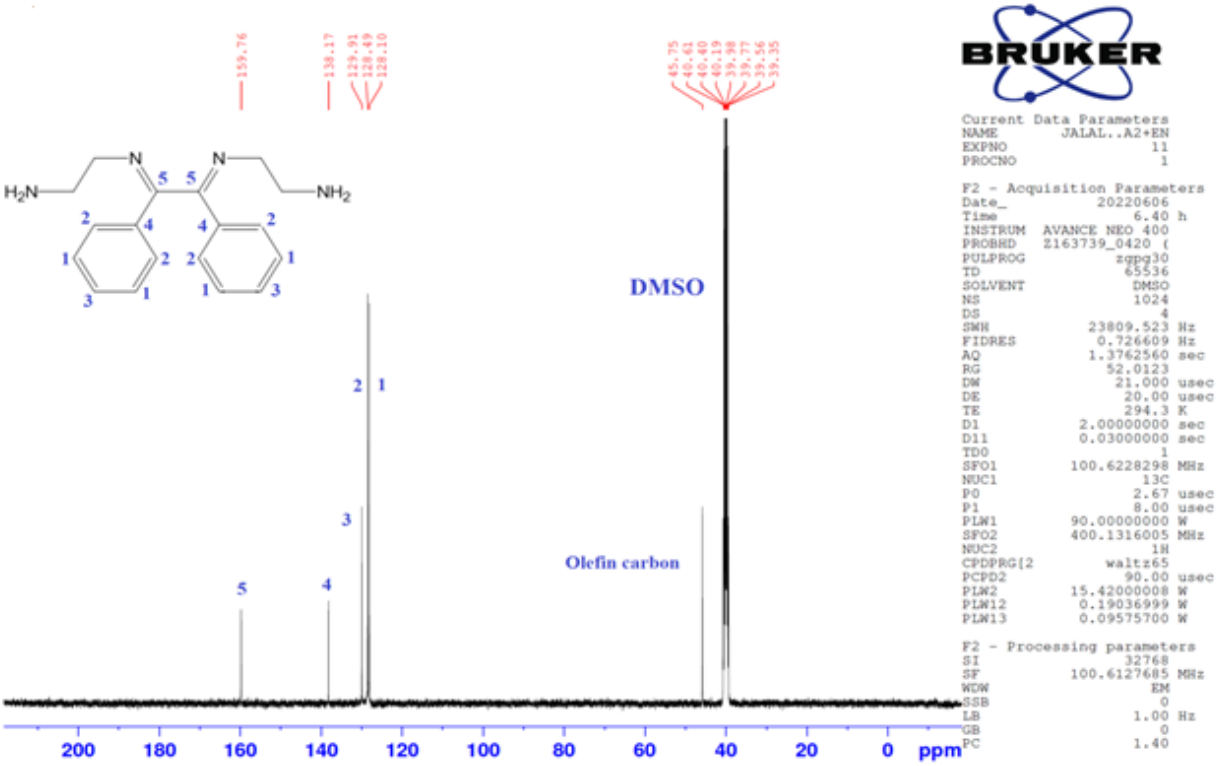


Figure 25: ^{13}C-NMR Spectrum of A2en.

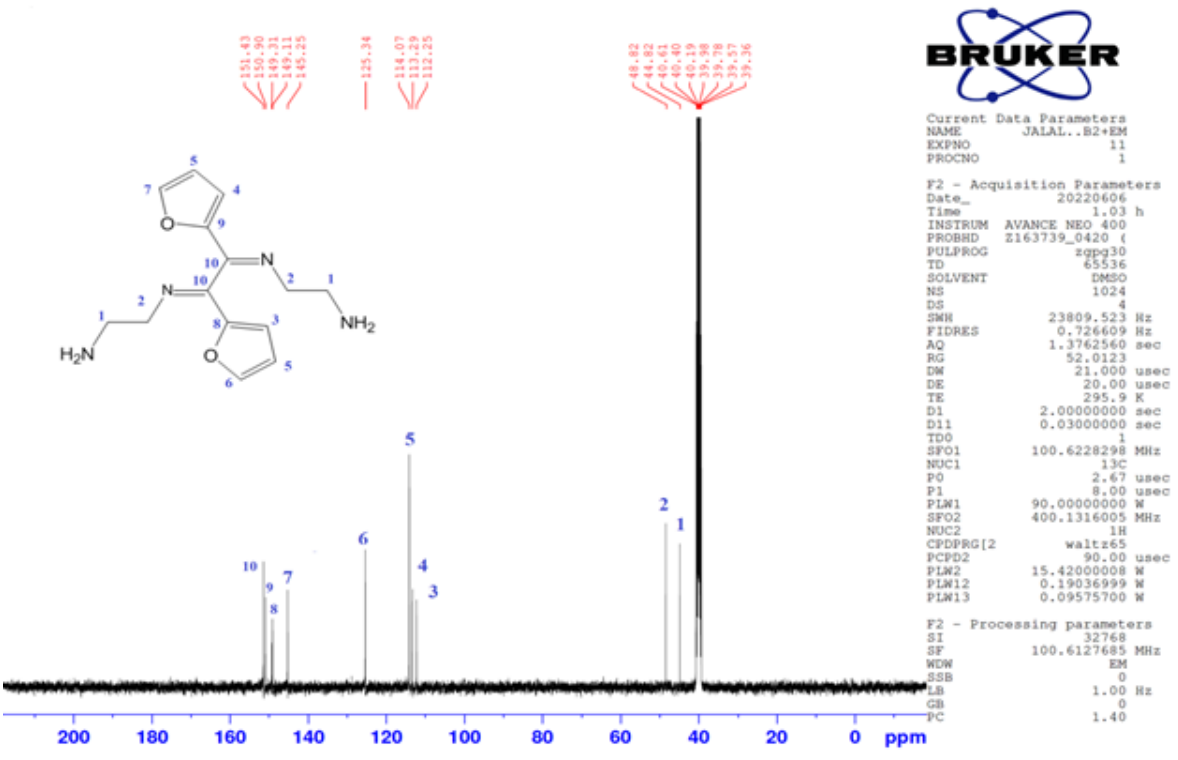


Figure 26: ^{13}C-NMR Spectrum of B2en.

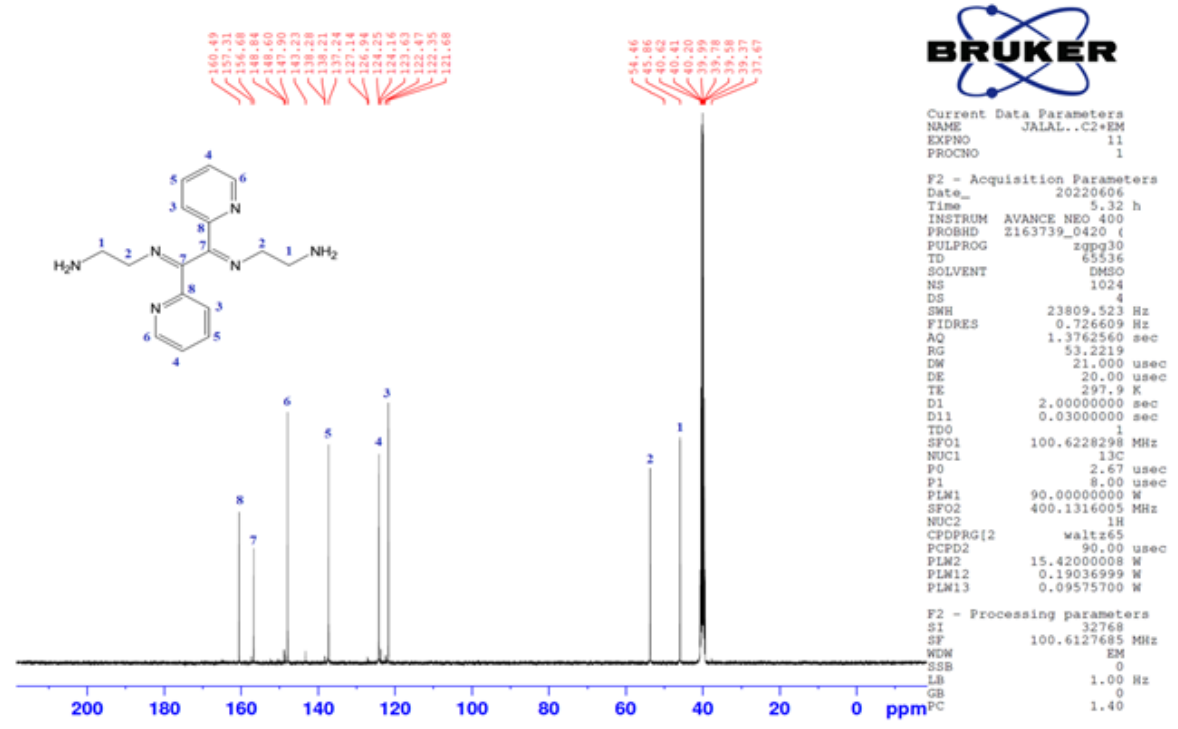


Figure 27: ^{13}C-NMR Spectrum of C2en.

Antibacterial activity of the Schiff base compounds (4)

The antibacterial activity of Schiff base compounds was evaluated against gram-positive and gram-negative bacteria as shown in **(Table 7)**. The data indicated that all compounds showed high activity compared to the prepared compound. These data may be attributed to the biological activity increase with increasing molecular weight and azomethine groups.

Table 7: Biological activity data of the compounds.

Compound	*Gram-positive bacteria*	*Gram-negative bacteria*
DMSO	-	-
A2en	++	++
B2en	++	++++
C2en	+++	+++

Inhibition zone diameter in mm

(-) 0, (+) 7-10, (++) 10-15 (+++) 15-19, (++++) 19-20

CONCLUSION

In this work, the changes in various physical characteristics of the prepared compounds were investigated. The obtained compounds were studied by FT-IR, mass, ^{1}H NMR, and ^{13}C NMR spectroscopy. The prepared Schiff base A2en, B2en, and C2en, which contain two biologically active components, may be able to lead to the discovery of new drugs that fight different bacterial infections or treat microbial diseases.

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