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ORIGINAL ARTICLE

SYNTHESIS AND CHARACTERIZATION OF NEW AZO-SCHIFF BASES AND STUDY BIOLOGICAL ACTIVITY

Hamid Hussein Eissa
Assistant Professor in Physical organic Chemistry, Chemistry Department, Education and Applied College Sciences, University of Hajah, Yemen

ABSTRACT: The present study includes synthesis of Aso derivative were prepared by coupling reaction between diazonium salt and salicylaldehyde. Aso-schiff bases were prepared by the condensation by 3-formyl-4-hydroxy phenylazo benzene with 1,3-Docarbonylphenyl dihydrazide, Pyridine-2,6-Dicarbohydrazide and 2,4-diamino -6-methyl -1,3,5-triazine. The Schiff base ligands were checked by different spectral technique (GC-MS, ^{1}H-NMR, IR, Elemental Analysis, and UV-Vis). The second part of this work includes studding the effect of the some bacteria. The results show that disappearance of amine group, carbonyl group and appearance imino group. As results show too that their activities were found to vary from moderate to very strong.

KEYWORDS: Synthesis, Characterization, Azo Schiff base, spectral technique, Biological Activity.

INTRODUCTION

Azo dyes constitute one of the largest and most varied groups of synthetic organic dyes in use today (Zollinger, 1991). Azo compounds are highly important, well known and widely used substances in the textile, paper, and coloring agents for foods and cosmetics industries. Other applications include merging technologies like liquid crystals, organic photoconductors and non-linear optics (Hamon *et al.*, 2009; Gordon, 1990). Azo compounds serve as important analytical tools by providing a strongly chromophoric label, the concentration of which is easily determined by colorimetric, spectrophotometric or spectrofluorimetric methods. Besides, azo compounds are important analytical aid compounds serving as pH indicators, complexometri indicators and to a lesser extent, preconcentration reagents (Patai, 1997). The pharmacological use of azo compounds originates from the discovery of the antibacterial action of Prontosil on streptococcal infections by Dogmagk (Carey, 2000). Furthermore, azo compounds were reported to show a variety of biological activities including antibacterial (Pathak *et al.*, 2000), antifungal (Xu and Zeng, 2010), pesticidal (Samadhiya and Halve, 2001), antiviral (Tonelli *et al.*, 2009), and anti-inflammatory (Rani et al., 2004) activities. Recently heterocyclic azo compounds have been used in the Mitsunobu reaction (Iranpoor *et al.*, 2008). Usually, azo compounds were synthesized by diazotization of the amine in mineral acid at about 0°C (Antonov *et al.*, 2010; Park and Koh, 2009; Zollinger, 1994; Ylldiz and Boztepe, 2002). Schiff bases are used as substrates in the preparation of a large amount of bioactive and industrial compounds (Jarrahpour and Alvand, 2007; Jarrahpour and Zarei, 2010; Jarrahpour and Zarei, 2009a; Jarrahpour and Zarei, 2009b; Zarei and Mohamadzadeh, 2011). In addition, Schiff bases are well-known to have biological activities such as antibacterial (Panneerselvam *et al.*, 2009; Singh *et al.*, 2006), antifungal (*Panneerselvam et al.*, 2005; Sridhar *et al.*, 2001), antitumor (Walsh et al., 1996; Hodnett and Dunn, 1970), antiviral (Kumar *et al.*, 2010; Jarrahpour *et al.*, 2007), anti-HIV-1 (Vicini *et al.*, 2003), antiproliferative (Cheng *et al.*, 2010), herbicidal (Holla *et al.*, 2000) and anti-influenza A virus (Zhao *et al.*, 2011) activities. It has been suggested that azomethine linkage (C=N) might be responsible for the biological activities of Schiff bases (*Raoa et al.*, 2011). Also, Schiff base ligands have been recognized as "privileged ligands" and they are able to coordinate with various metals and stabilize them in various oxidation states, enabling the applications of Schiff base metal complexes in a large variety of useful catalytic transformations (Khatri *et al.*, 2011; Raman *et al.*, 2009; Canpolat and Kaya, 2005). Some Schiff bases have been reported as effective corrosion inhibitors for metal alloys in acidic media (Khaled, 2006; Aytac *et al.*, 2005; Asan *et al.*, 2005). Perhaps the most common method for preparing Schiff bases is the reaction of aldehydes and ketones with primary amines (Tidwell, 2008). The reaction is generally carried out by refluxing the

Corresponding Author: Hamid Hussein Eissa, Assistant Professor in Physical organic Chemistry, Chemistry Department, Education and Applied College Sciences, University of Hajah, Yemen. **E-mail:** Hamedesia2003@yahoo.com.

carbonyl compounds and amines in organic solvents by separating the water as formed with an azeotroping agent or by anhydrous Na_2SO_4 and $MgSO_4$ (Layer, 1963; Cross *et al.*, 2011; Jarrahpour *et al.*, 2010; Jarrahpour and Zarei, 2007; Jarrahpour and Zarei, 2006).

EXPERIMENTAL METHODOLOGY

2.1. Materials

Sodium nitrite, Aniline, Salicyladehyde, dimethyl ester of isophthalic acid, dimethyl Pyridine-2,6-dicarboxylate, 6-methyl-1,3,5-triazine-2,4-diamine, Methanol, Ethanol, Toluene, Dichloro methane, Na_2SO_4.

All materials obtained from Sigma Aldrich Company. IR spectra were recorded on Jusco 300 FT-IR Spectrometer using compressed KBr discs. Mass spectra of the ligand were measured on a micro mass Quattro LC-MS/MS Spectrometer. ^{1}H-NMR spectra were recorded at ambient Broker DT-400 Spectrometer using $CDCl_3$ with DMSO- DMF as the internal standard.

2.2.1. Synthesis of dihydrazide of isophthalic acid

A mixture of dimethyl ester of isophthalic acid (2.22 g) and hydrazine hydrate (98% 2 cc) in methanol was refluxed for 4-5h. The reaction mixture was allowed to cool to room temperature then, the cooled solution was poured on to ice cold water. The dihydrazide of isophthalic acid thus obtained was filtered and recrystallized from ethanol (Lakshmi *et al.*, 2012).

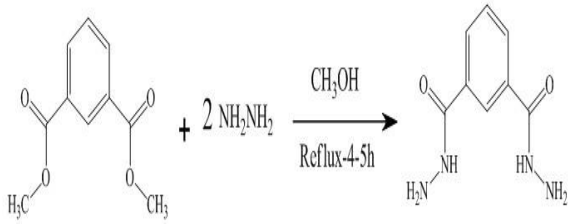
Yield: (80%), m.p=240 C^0

Empirical formula: ($C_8H_{10}N_4O_2$)

M.Wt: (194g)

Mass spectra (m/z):194 (Figure 1)

IR (KBr disk): 3314.66 cm^{-1}



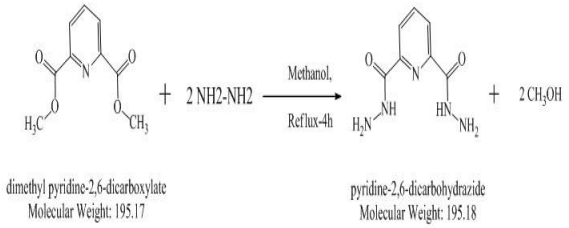
2.2.2. Synthesis of Pyridine-2,6-Dicarbohydrazide

A mixture of dimethyl Pyridine-2,6-dicarboxylate (1.95 g) and hydrazine hydrate (98% 2 cc) in methanol was refluxed for 4-5h. The reaction mixture was allowed to cool to room temperature then, the cooled solution was poured on to ice cold water. The Pyridine -2,6-Dicarbohydrazide thus obtained was filtered and recrystallized from ethanol (Lakshmi *et al.*, 2012).

Yield: (87%), m.p>280 C^0

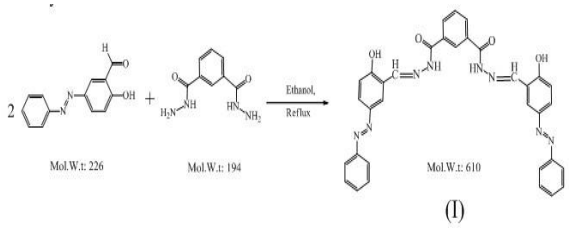
Empirical formula: ($C_7H_9N_5O_2$)

M.Wt: (195 g)



2.2.2. General Method for Synthesis of Azo Schiff bases (I,II,III)

Azo-coupled precursors were prepared as described previously (Khanmohammadi and Darvishpour, 2009; Dinçaple *et al.*, 2007) was added (0.01 mol) of 3-formyl-4-hydroxy phenylazo benzene in 30 ml from absolute ethanol to (dihydrazide of isophthalic acid, Pyridine-2,6-Dicarbohydra-zide, 6-methyl-1,3,5-triazine-2,4-diamino (0.005 mol)in 60 ml ethanol, The reaction mixture was refluxed for 4 h with continue stirrer. A solid mass formatted on hot. The reaction mixture was allowed to cool room temperature, dark yellow precipitated were filtered and recrystallized from mixture (DMF, Ethanol)(1:9), then dried in vacuum.



Bis-N-(5-phenylazo-2-hydroxy-1-benzylidine)-1,3-diamino phthal hydrazide (I)

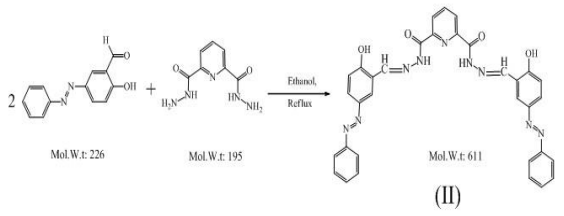
Dark yellow; Yield 80%

UV-Vis: λ_{max} = 335 nm. (Figure 4)

IR (KBr disk): 3414.00-3479.58 cm^{-1}(O-H), 3232.70-3313.17cm^{-1} (N-H, amid), 3051.39 cm^{-1}(C-H), aromatic), 1693.50 cm^{-1} (C=O),1616.35cm^{-1}(C=N),1573.91cm^{-1} (C=C, aromatic), 1442.75–1519.91 cm^{-1} (-N=N-), 1280.73 cm^{-1} (C-O), phenolic).

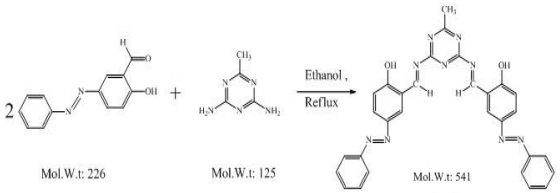
^{1}H-NMR ($CDCl_3$-400MHz) δ=12.399 (s,2H,OH), 11.783(s,2H,N-H), 8.846 (s,2H,CH=N), 7.150 - 8.575 (m,19 H, Ar), 2.257 - 3.353 (Organic solvents, DMSO, H_2O).

Elemental analysis: $C_{34}H_{26}N_8O_4$, Calculated (%):C: 66.88; H: 4.29; N: 18.35; O: 10.48; Found(%).% C:66.94, H:4.19, N:18.40, O:10.47.



Bis-N-(5-phenylazo-2-hydroxy-1-benzylidine)-2,6-pyridyl hydrazide (II)

Dark yellow; Yield 89%;
UV-Vis: Λ_{max} = 350 nm (Figure 8)
IR (KBr disk):3414.00 -3471.87 cm^{-1}(O-H), 3228.84 cm^{-1}(N-H,amid), 3062.96cm^{-1}(C-H), aromatic), 1651.07 cm^{-1} (C=O), 1616.35 cm^{-1} (C=N), 1573.91cm^{-1} (C=C , aromatic), 1442.75–1489.05 cm^{-1}
(-N=N-), 1280.73 cm^{-1} (C-O), phenolic).
^{1}H-NMR($CDCl_3$-400MHz) δ=12.558 (s,2H,OH), 11.642(s,2H,N-H), 9.095 (s,2H,CH=N), 7.184 - 8.426 (m,19 H, Ar), 2.259 - 3.338 (Organic solvents,DMSO,H_2O).
Elemental analysis:) $C_{33}H_{25}N_9O_4$, Calculated (%):C: 64.80; H: 4.12; N: 20.61; O: 10.46.; Found(%).C:64.81, H:4.17, N:20.73, O:10.29.



(III)

Bis-N-(5-phenylazo-2-hydroxy-1-benzylidine)-2,4-diamino -6-methyl -1,3,5-triazine.(III)
Yellow; Yield 70%;
UV-Vis: Λ_{max} = 375 nm (Figure 12).
IR (KBr disk): 3419.58 cm^{-1} (OH), 3080.82 cm^{-1} ((C-H), aromatic), 1662.64 cm^{-1} (C=N), 1624.06cm^{-1}(C=C, aromatic), 1454.33-1554.63cm^{-1}(-N=N-), 1284.59 cm^{-1} (C-O), phenolic).
^{1}H-NMR ($CDCl_3$-400MHz) δ=10.383 (s,2H,OH), 9.183 (s,2H,CH=N), 6.575 -8.197 (m,16 H, Ar), 2.068 (s,3H,CH_3), 2.507-3.422(DMSO,H_2O).
Elemental analysis: $C_{30}H_{23}N_9O_2$, Calculated (%):C:66.53, H, 4.28, N, 23.28, O, 5.91; Found(%). C:66.59 , H:4.32 ,N:23.18 ,O, 5.91.

2.2.3. Biological Activity
The ligands were tested for their antimicrobial activity against four species of bacteria (Klebcella, Escherichia coli, Staphylococcus aureus, Salmonella typhi) using filter paper disc method (Zainab, 2005). The screened compounds were dissolved individually in dimethyl sulfoxide (DMSO) in order to make up a solution of 10^{-3}, 10^{-4}, 10^{-5} M concentration for each of these compounds. Filter paper discs (Whitman No.1 filter paper, 5 mm diameter) were saturated with the solution of these compounds. The discs were placed on the surface of solidified Nutrient agar dishes seeded by the tested bacteria. The diameters of inhibitions zones (mm) were measured at the end of an incubation zones period, with was 24 h at 37^{0}C for bacteria. Discs saturated with DMSO are used as solvent control. Ampicillin 10^{-5} M was used as reference substance for bacteria (Ibrahim *et al.*, 2006).

RESULT AND DISCUSSION

The prepared organic compounds (I, II, III) were soluble in DMF, DMSO and partially soluble in acetone, Dichloro methane, Benzene, Methyl izo butyl ketone, chloroform, Dimethyl forma amide. All the compounds are characterized by GC-MS, LC-MS, IR, ^{1}H-NMR spectra, which help in elucidating their empirical formula (Table 1).

Table 1: Color, molecular weight, melting point and Elemental Analysis of (I, II, III)

Elemental Analysis Found (Calculated %)				Λ_{max} nm	Color	Yield %	M.Wt	Melting point C^0	Ligand
C	H	N	O						
64.81 (64.80)	4.17 (4.12)	20.73 (20.61)	10.29 (10.46)	350	Dark Yellow	% 89	611	Δ300 <	**I**
66.94 (66.88)	4.19 (4.29)	18.40 (18.35)	10.47 (10.48)	335	Dark Yellow	% 80	610	Δ300 <	**II**
66.59 (66.66)	4.32 (4.28)	23.18 (23.28)	5.91 (5.91)	375	Yellow	% 70	541	278	**III**

dec = decomposition

3.1. IR Spectra of Ligands
The IR Spectral data are shown in table 2 of and 8.3 ppm are assigned to the prepared Schiff bases The four bands at 1616.35, 1616.35, 1662.64 cm^{-1} are attributed to imine group (-HC=N-) for (I, II, III) (Figures 1, 6, 10), respectively.

Table 2: IR Spectra of Ligands (I, II, III)

v(C-O) Cm^{-1}	v(N=N) Cm^{-1}	v(C=C) Cm^{-1}	v(C=N) Cm^{-1}	v(C-H) aliph.	v(C-H)arom. Cm^{-1}	v(OH) Cm^{-1}	Ligand
1276.88	1442.75 – 1489.05	1573.91	1616.35	--------	3062.96	3414.00 -3471.87	**I**
1280.73	1442.75 – 1519.91	1573.91	1616.35	--------	3051.39	3414.00 -3479.58	**II**
1284.59	1481.33-1554.63	1624.06	1662.64	2873.94	3080.82	3419.58	**III**

The bands in the spectra at 1573.91, 1573.91, and 1624.06 cm^{-1} is due to (C=C) of aromatic rings. The v (OH) stretching frequencies are observed at 3414.00 -3471.87, 3414.00 -3479.58, 3419.58 cm^{-1} for (I, II, III), respectively. The IR spectra of (I,II,III) show characteristic absorption bands at 1442.75-1489.05, 1442.75-1519.91, and 1481.33-1554.63cm^{-1} due to v(-N=N-) stretching vibrations, respectively. The bands which observed for all compounds at 1276.88, 1280.73, and 1284.59cm^{-1} were due to v(C-O) vibration. While the band at 2873.94 cm^{-1} was attributed to C-H alkanes for (III). Also, the bands at 3062.96, 3051.39 and 3080.82 cm^{-1} are attributed to (C-H aromatic) for (I, II, III) respectively (Salih and Hamid, 2008).

3.2. ^{1}H-NMR Spectra of Ligands

The data of ^{1}H-NMR Spectra of prepared compounds are shown in table 3. The ^{1}H-NMR spectra of (I,II,III) ligands in d6-$CDCl_3$ (Figures 3,7,11) shows a singlet signal at 12.558, 12.399 and 10.383 ppm assigned to the protons OH groups of the Ligands (I,II,III), respectively. The multiple signals 8.426 - 7.184, 8.575 - 7.150, and 8.197-6.575 ppm are due to the aromatic protons for (I, II, III) respectively. Also the signals at 9.095, 8.846and 9.183 ppm are assigned to the 2H, (HC=N) protons of the Ligands (I,II,III), respectively. The signals at 11.642 and 11.783 ppm are assigned to the 2H, (HC=N) protons of the Ligands (I,II), respectively.

Table 3: ^{1}H-NMR Spectra of Ligands (I, II, III)

Chemical Shifts δ (ppm)				Ligand
OH	CO-NH-	CH=N	C-H Aromatic	
12.558 (s,2H)	11.642 (s,2H)	9.095 (s,2H)	8.426 - 7.184 (m,19 H)	I
12.399 (s,2H)	11.783 (s,2H)	8.846 (s,2H)	8.575 - 7.150 (m,19 H)	II
10.383 (s,2H)	--------	9.183 (s,2H)	8.197 - 6.575 (m,16 H)	III

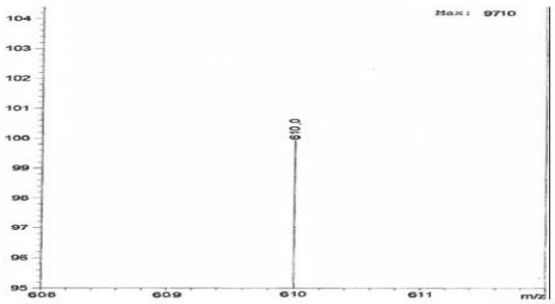


Figure 1: MS spectra of ligand (I)

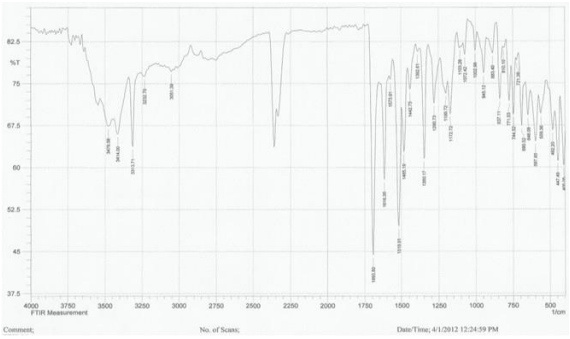


Figure 2: IR spectra of ligand (I)

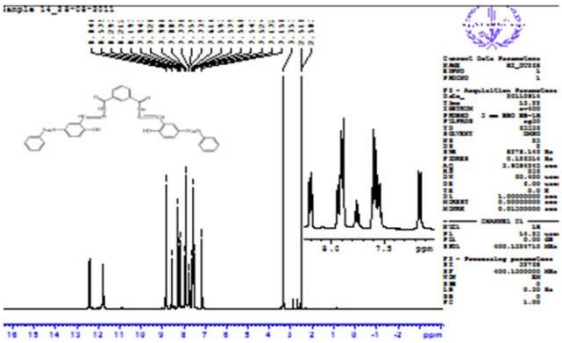


Figure 3: ^{1}-H-NMR spectra of ligand (I)

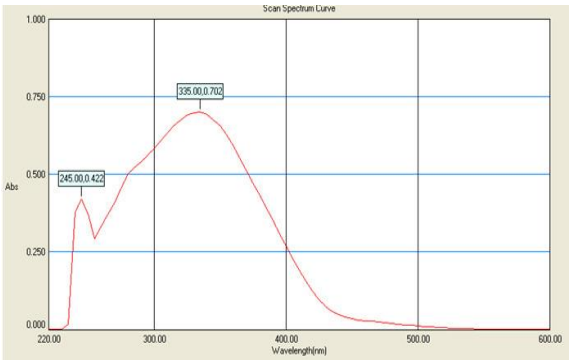


Figure 4: Λ_{max} of ligand (I)

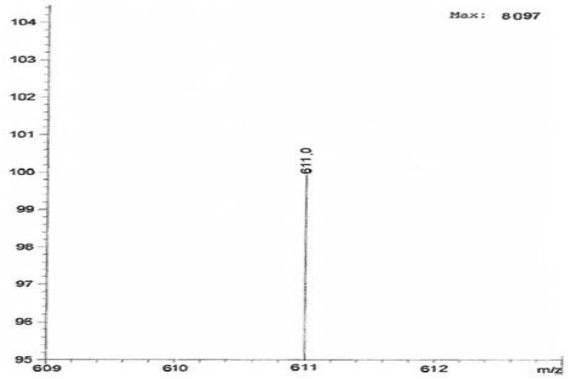


Figure 5: MS spectra of ligand (II)

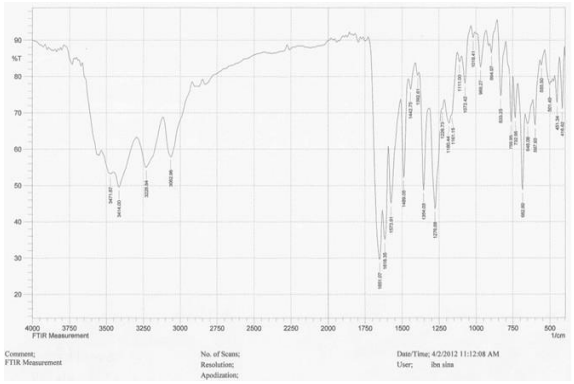


Figure 6: IR spectra of ligand (II)

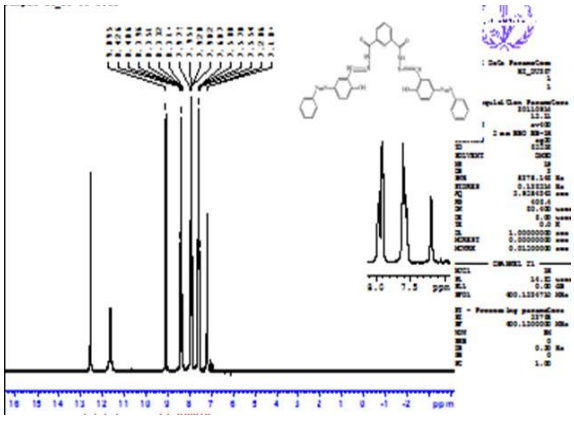


Figure 7: ^{1}-H-NMR spectra of ligand (II)

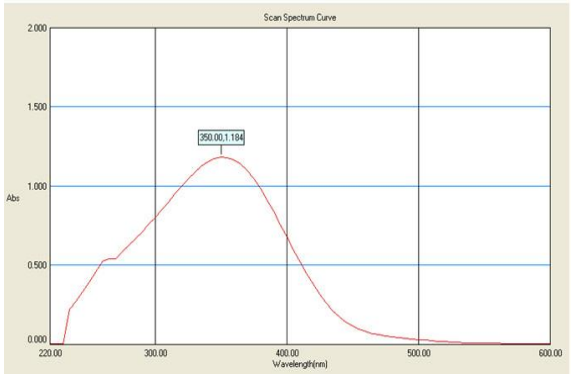


Figure 8: λ_{max} of ligand (II)

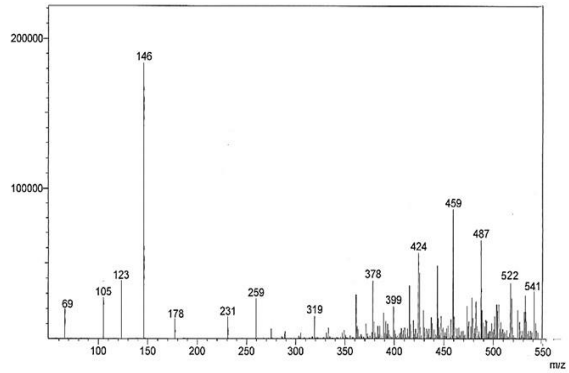


Figure 9: MS spectra of ligand (III)

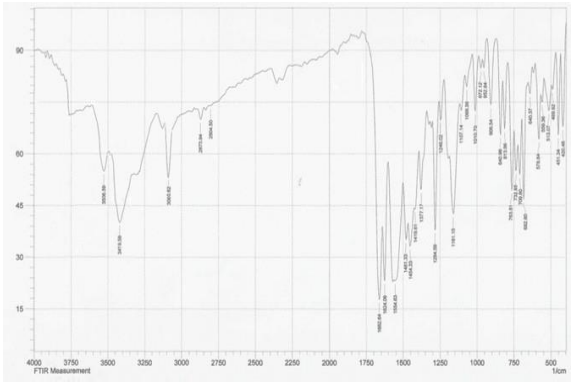


Figure 10: IR spectra of ligand (III)

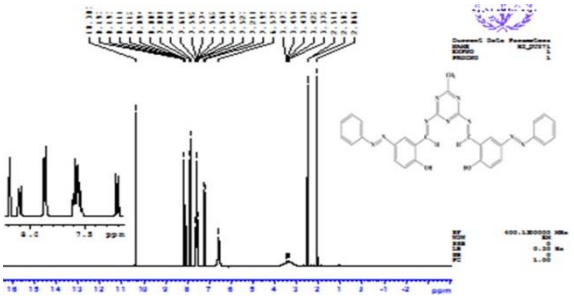


Figure 11: ^{1}-H-NMR spectra of ligand (III)

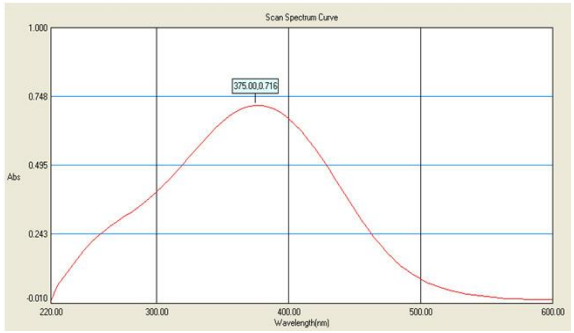


Figure 12: λ_{max} of ligand (III)

3.3. Biological Activity

During the last two or three decades, attention has been increasingly paid to the synthesis of Schiff bases which exhibits various biological activities including antibacterial, fungicidal, tuberculostatic and plant growth regulative properties (Zainab, 2005). It was judicious to investigate the synthesis of various new types of Schiff bases and studied their antibacterial activity against four strains of bacteria (Klebsiella, Escherichia coli, Staphylococcus aureus, and Salmonella typhi). The concentrations used for the screened compounds are 10^{-3}, 10^{-4}, 10^{-5} M. Control discs were performed using DMSO solvent and inhibition zones are measured in mm. The results of antibacterial activity were compared with 10^{-5}M of Ampicillin (Ibrahim *et al.*, 2006). The results of the antibacterial activity are summarized in table 4.

Table 4: Effect of the compounds (I, II, III) on the growth of Bacteria (Zone of inhibition in mm)

Types bacteria				Concen [M]	Ligands
Positive gram	Negative gram				
Staphyllococcus aureus	Klebsiella pneumoniae	Salmonella typhi	Escherichia coli		
---	+++	++	++	[1x10^{-3}]	
---	+	+	+	[1x10^{-4}]	I
---	---	---	---	[1x10^{-5}]	
++	+++	++	+++	[1x10^{-3}]	
-	-	+	++	[1x10^{-4}]	II
---	---	---	---	[1x10^{-5}]	
+++	+++	+++	+++	[1x10^{-3}]	
---	+++	++	++	[1x10^{-4}]	III
---	---	---	---	[1x10^{-5}]	
++	++	++	++	[10^{-5} M]	Ampcilline

- The ligand (I) show high activity against the Klebsiella pneumonia, Also show moderate activity against the Escherichia coli and Salmonella typhi, except (I) don't have significant activity against the Staphylococcus aureus when using the concentration [1x10^{-3}]M. and when using concentration [1x10^{-4}]M was weak activity against the negative gram bacteria. While not shown any Influence against both positive and negative gram negative bacteria when using concentration [1x10^{-5}]M.
- The ligand (II) show high activity against the Klebsiella pneumonia and Escherichia coli, Also show moderate activity against the Salmonella typhi and Staphylococcus aureus when using the concentration [1x10^{-3}]M. while when using concentration [1x10^{-4}]M was moderate against the Escherichia coli. While not shown any Influence against the Klebsiella pneumonia and Staphylococcus aureus, Also, didn't show any Influence against both positive and negative gram negative bacteria when using concentration [1x10^{-5}]M.
- The ligand (III) showed Influence strong against all types of bacteria studied when using the concentration [1x10^{-3}]M. and when using concentration [1x10^{-4}]M was high activity against the Klebsiella pneumonia. While moderate effect against Escherichia coli. While not shown any Influence against the Staphylococcus aureus, Also, didn't show any Influence against both positive and negative gram negative bacteria when using concentration [1x10^{-5}]M.

CONCLUSION

1- The (I,II,III) compounds are new and were prepared for the first time.

2- The new compounds were identified by ^{1}H-NMR, IR, LC-MS, GC-MS, Elemental analysis, and UV-Vis spectral methods.

3- Some of the prepared compounds have been biologically screened i.e. Staphylococcus aureus, Klebsiella pneumonia, Salmonella typhi, Escherichia coli studying their effects against gram-positive, three gram-negative bacteria. The results show that their activities were found to vary from moderate to very strong when using the concentration [1x10^{-3}]M.

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