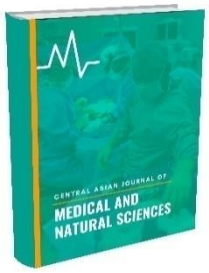
CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES



Volume: 04 Issue: 04 | Jul-Aug 2023 ISSN: 2660-4159

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Synthesis, Characterization, Antibacterial, and Antioxidant Studies of New Schiff Base Ligands Derivative of 4,4-Methylenedianiline and Their Complexes with Copper Ion

1. **Raad Malik Mohammed**
2. **Haider A. Mahdi**

Received 2nd Jun 2023,
Accepted 3rd Jul 2023,
Online 10th Aug 2023

[1,2] Department of Chemistry, College of Science, University of Thi-Qar, Thi-Qar, 64001, Iraq
raadm5108@gmail.com

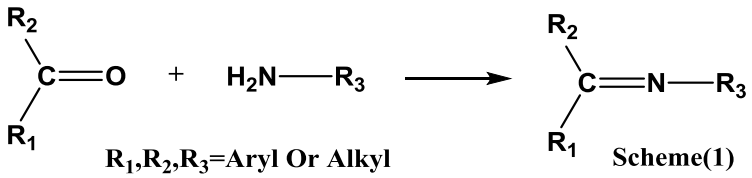
Abstract: The Schiff bases (L1, L2) were prepared by condensation 4,4-methylenedianiline with aromatic aldehyde. These ligands were further complexed with Cu(II) ion. The compounds have been characterization on the basis their spectra of 1H-NMR, mas, Fourier transform infrared (FTIR), as well as magnetic susceptibillty, elemental analysis (CHN) and conductance measurements. Elemental analysis and spectral data of the ligands were found to be in a good agreement with their structures, indicating high purity of all the compounds. The program of Hyperchem 8 have been used for theoretical accounts using PM3 method to study the electrostatic potential that provided good information about the complexity site. Of the result obtained we can suggest tetrahedral geometry for Cu(II) complexes. The antioxidant activity of the syntheses compounds was evaluated by DPPH scavenger and these were showed a good antioxidant activity. All ligands and their complexes were screened for antibacterial activity, and these compounds showed a good antibacterial activity.

Key words: Schiff base, azomethine, ligand, complex, electrostatic, antioxidant, antibacterial.

Introduction:

Schiff bases (imine) are an important class of organic compounds which are formed from primary amines and carbonyl compounds (aldehyde or ketone)[1-3] as shown in (Scheme 1), schiff base was first synthesized in 1869 by the German chemist Hugo Schiff [4]. The bond formed by reaction with aldehyde is called azomethine or aldimine, and the bond formed by reaction with ketone is called imine or ketamine[5]. Schiff bases are known as a good nitrogen donor ligand (-CH=N) [6,7]. Schiff bases are selective toward metal ions and form complexes by transferring electrons from the active ends they contain to the metal[8-10]. During the formation of the coordination compound, one or more electron pairs are donated to the metal ion by these ligands[11]. Schiff bases can form highly stable 4-, 5-, and 6-ring complexes if they donate more than one electron pair[12]. Schiff's bases have also been

shown to exhibit a broad range of biological activities, including antifungal[13,14], antibacterial[15,16], antimalarial[17], antioxidant[18,19], anticancer[20-24], antiviral[25], antiproliferative[26,28], anti-inflammatory[29], and antipyretic properties [30]. many metal complexes of sulfur-nitrogen chelating agents have been revealed to display approved cytotoxic (anticancer) activities[31].



R_1,R_2,R_3=Aryl Or Alkyl Scheme(1)

2. Experimental

All reagents and chemicals used in this study were in the analytical grade and purchased from (Sigma-Aldrich). The melting points of synthesized compounds were measured on the SMP31 melting point apparatus and on the FT.IR affinity (Shimadzu) spectrophotometer using KBr pellets. While their ^{1}H-NMR was recorded in DMSO-d_6 on the Bruker 500MHZ instrument, the internal standard is TMS. Work mass selective Detector 5973 and elemental micro analysis was done on a perkin_Elmer_automatical instruments.

2.1. General procedure for the preparation of Schiff base;

Synthesis 4-(((4-(4-aminobenzyl)phenyl)imino)methyl)benzene-1,3-diol (L1)

A solution of 4,4'-methylenedianiline (0.01 mol, 1.98 g) in ethanol (10 mL) was mixed with a solution of 2-hydroxy-3-methoxybenzaldehyde (0.01 mol, 1.38g), in ethanol (10 mL) and a few drops of acetic acid was added as a catalyst. The mixture was heated in a reflux temperature for 2hours, the reaction was followed by TLC (3 hexane: 7 ethyl acetate). Then, the precipitation was filtered, and the residual was recrystallized from the ethanol to obtain the title compound as a crystal [32]. As shown in scheme (2)

Synthesis 6,6'- (((methylenebis (4,1-phenylene)) bis (azaneylylidene)) bis (methaneylylidene)) bis (2-methoxyphenol) (L2)

A solution of 4,4'-methylenedianiline (0.01 mol, 1.98 g) in ethanol (10 mL) was mixed with a solution of 2-hydroxy-3-methoxybenzaldehyde (0.02 mol, 3.04g), in ethanol (10 mL) and a few drops of acetic acid was added as a catalyst. The mixture was heated in a reflux temperature for 3 hours, the reaction was followed by TLC (3 hexane: 7 ethyl acetate). Then, the precipitation was filtered, and the residual was recrystallized from the ethanol to obtain the title compound as a crystal [33]. As shown in scheme (2)

2.2. Metal complexes synthesis: Copper complex of the obtained Schiff base was prepared using the following approach:

dissolving (0.001 mol) of ligand in 10 mL of MeOH and a drops of DMF. Then, (0.21 g, 0.001 mol) of copper salt (Cu(II) $Cl_2.2H_2O$) were added onto ligand's solution in round flask of 50 mL volume. Thereafter, the mixture was refluxed, heated, and continuously stirred for 2 hours. After completely reflux, mixture was left to perform cooling at room temperature for one hour. After solvent evaporation, the precipitation was filtered and recrystallized by the ethanol [34].

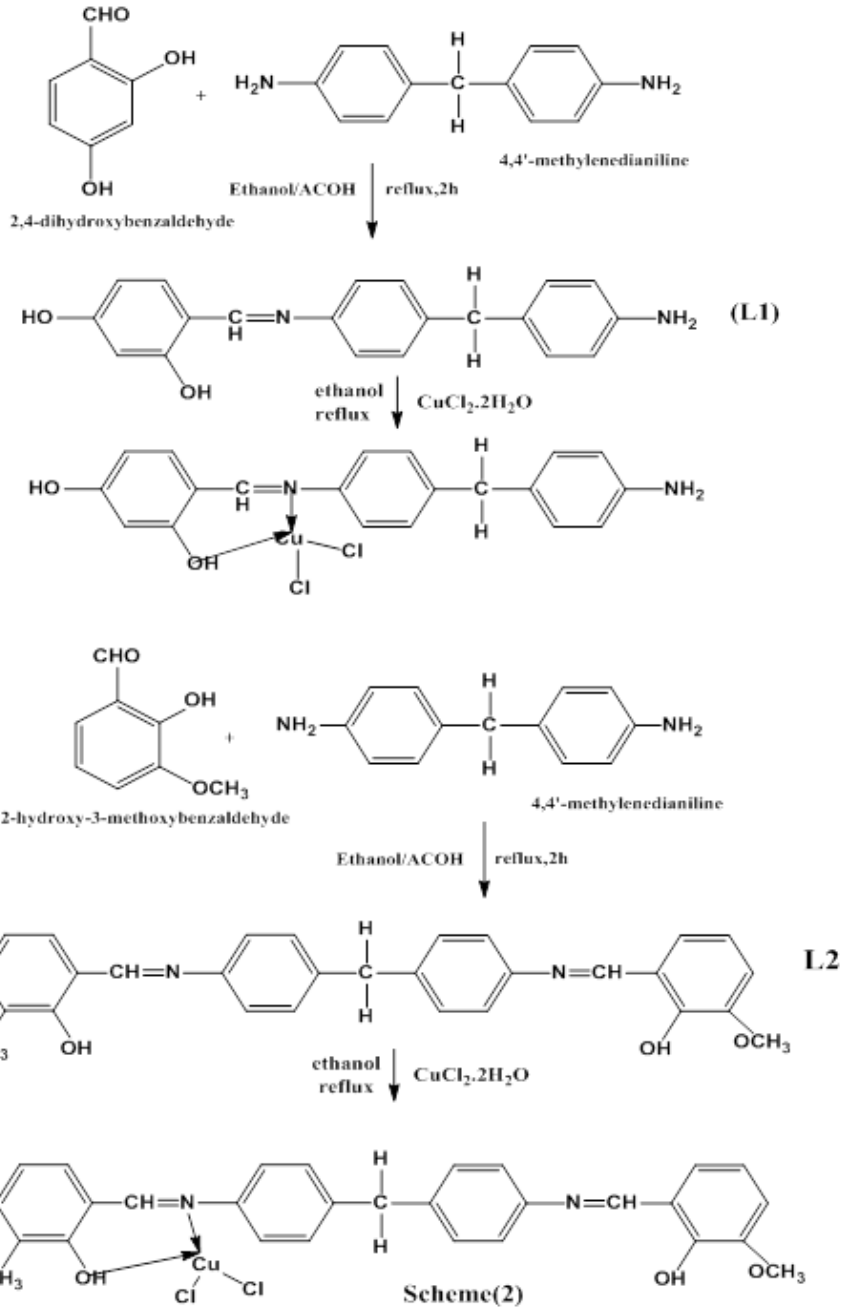
Results and Discussion

The ligands (Schiff base) were synthesized by the condensation of a primary amine with aromatic aldehyde as shown in the scheme (2).

All the physical properties and elemental microanalysis and (CHNS), atomic absorption and the magnetic momentum data of the ligand and its complexes were gathered in the table (1)

Table (1) Physical properties, elemental microanalysis CHN, molar conductance and magnetic susptibility

Compound	Colour	M.P	ʌ.m $s.cm^2.mol^{-1}$	% C Exp. (cal.)	% H Exp. (cal.)	% N Exp. (cal.)	% m Exp. (cal.)	µeff B.M
$C_{20}H_{18}N_2O_2$ (L1)	orange	140-142		74.23 (75.45)	6.15 (5.70)	7.92 (8.80)		
$[Cu(L1)Cl_2]$	Deep green	239-241	19				15.69 (14. 03)	1.65
$C_{29}H_{26}N_2O_4$ (L2)	pale yelloish	149-151		57.24 (57.96)	3.92 (4.36)	5.78 (4.66)		
$[Cu(L2)Cl_2]$	brown	240-242	15				11.89 (10.57)	1.72



Scheme(2)

FT-IR spectral

FT-IR of the synthesized ligand and its complexes were carried out using KBr disc forto ligands and their complexes and all the data of FTIR were gathered in the table (2). The free ligand (L) exhibited the azomethine bands at (1622)- (1658) cm^{-1}, while the azomethine bands of the complex were exhibited at (1642)-(1659) cm^{-1}. New bands were formed Attributed to the (M- N) and (M- O) bonds appeared at the region (446-456) $cm^{-1}$and (556-575) cm^{-1} respectively. This indicates that the coordinate occurred through the (N) and (O) atoms. as shown in the figures (1,2).

Table (2) Infrared spectra of Ligand and its metal complexes (υ cm^{-1})

No.	υ (O-H)	υ (C-H) aromatic	υ (C-H) alaphatic	υ (C=N) azomethane	υ (C=C)	υ (C-O)
L1	3461	3033	2976	1621	1598	1281
$(L1)CuCl_2$	3363	3073	2937	1613	1546	1244
L2	3250	3020	2950	1658	1612	1245
$(L2)_2CuCl_2$	3454	3053	2998	1613	1591	1239

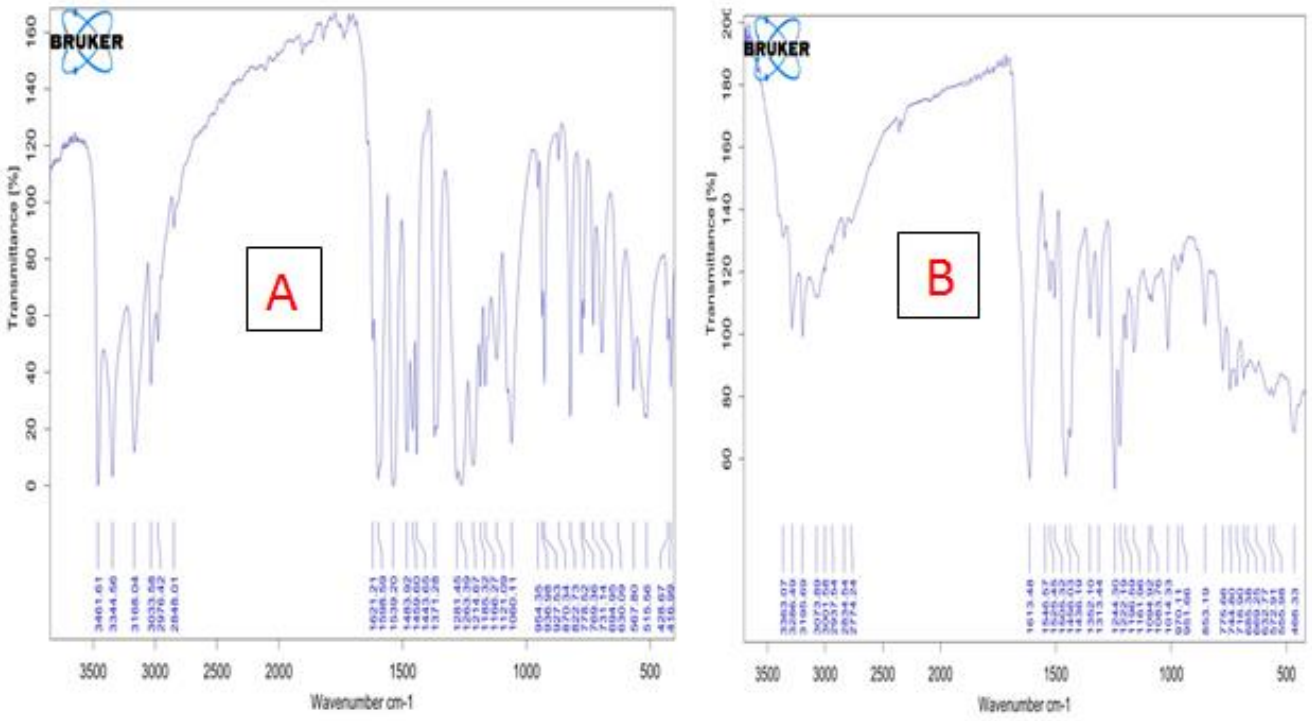


Fig.(1) (A) FTIR of(L1), (B) FTIR of the complex $[Cu(L1)Cl_2]$

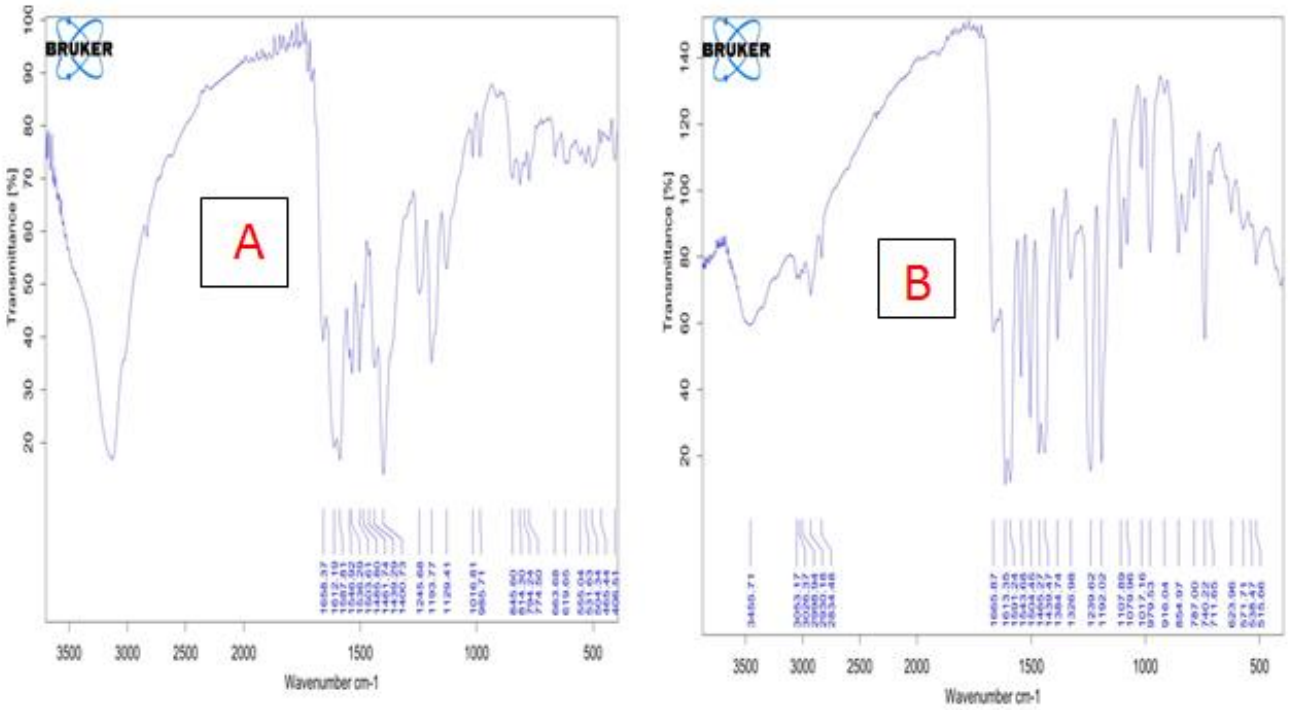


Fig.(2) (A) FTIR of(L2), (B) FTIR of the complex $[Cu(L2)Cl_2]$

Nuclear Magnetic Resonance

The ^{1}H-NMR spectra of the ligands showed two signals at (2.5 and 3.36) ppm due to The solvent (DMSO and H_2O), in the 1H-NMR spectra of the ligands L1 was appeared two signal at (3.96) ppm due to methylene group, melti signals at (6.37-7.97) ppm due to the aromatic group, while signals of the azomethine groups at (8.77) ppm, the two signals of phenolic groups at (13.04) ppm and (10.34) ppm. As shown in the ^{1}H-NMR data and figure (3)

^{1}H NMR (400 MHz, DMSO) δ 13.70 (s, 7H), 10.34 (s, 7H), 8.77 (s, 1H), 7.97 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 6H), 7.29 (s, 23H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.45 (dd, *J* = 8.5, 2.4 Hz, 6H), 6.37 (d, *J* = 2.3 Hz, 6H), 3.96 (s, 2H), 3.77 (s, 2H),

The ^{1}H-NMR spectra of the ligand (L2) showed two signals at (2.5 and 3.36) ppm due to The solvent (DMSO and H_2O), in the ^{1}H-NMR spectra of the ligands L2 were appeared two signal at (3.85) ppm which due to the proton of methoxy groups, and an anthers signal at (4.04) ppm due to methylene group, melti signals at (6.91-7.36) ppm due to the aromatic group, while the signals of the azomethine groups appeared at (8.94) ppm, the signal of phenolic groups appeared at (13.33) ppm. As shown in in the ^{1}H-NMR data and figure (4)

^{1}H NMR (400 MHz, DMSO) δ 13.33 (s,2H), 8.94 (t, *J* = 3.7 Hz, 1H), 7.36 (q, *J* = 5.4 Hz, 4H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.91 (td, *J* = 7.9, 2.9 Hz, 1H), 4.05 (m, 2H), 3.85 (s, 6H).

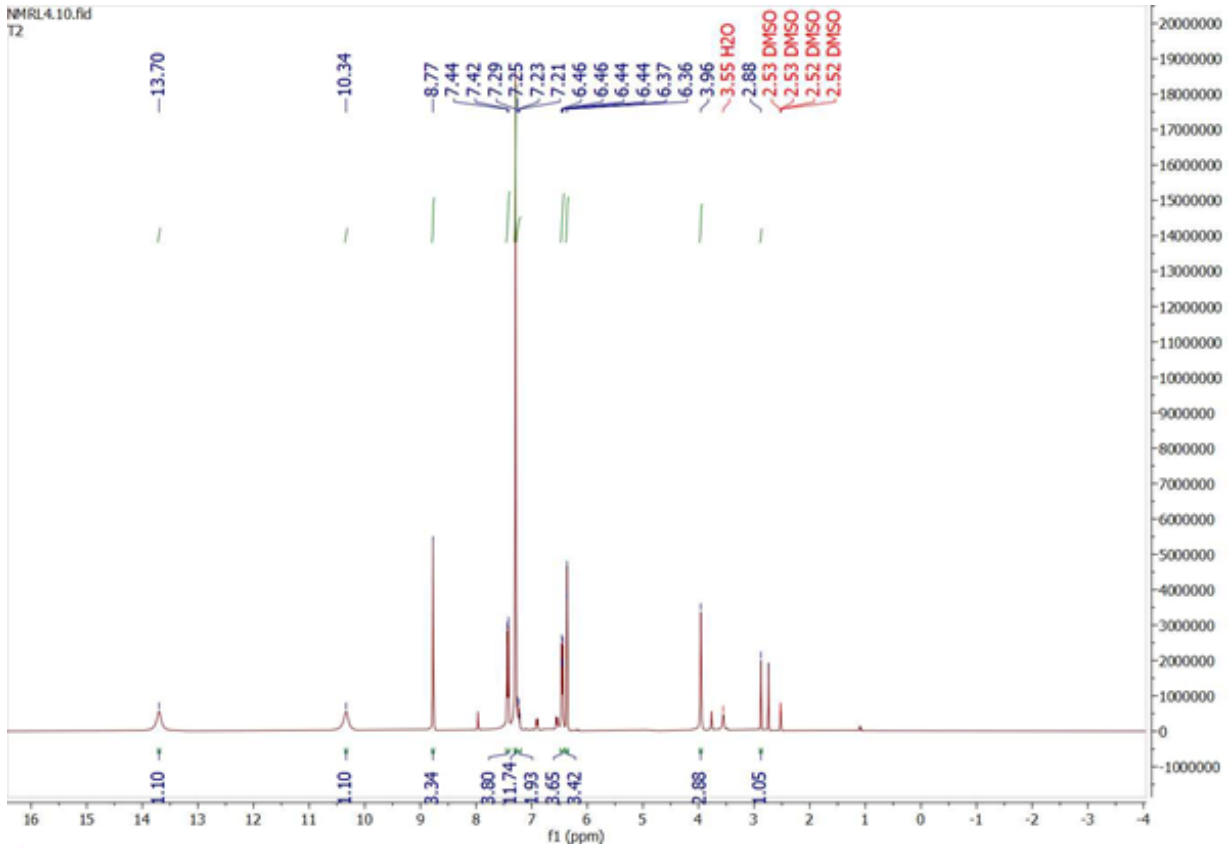


Fig.(3) The ^{1}H-NMR spectra of the ligand (L1)

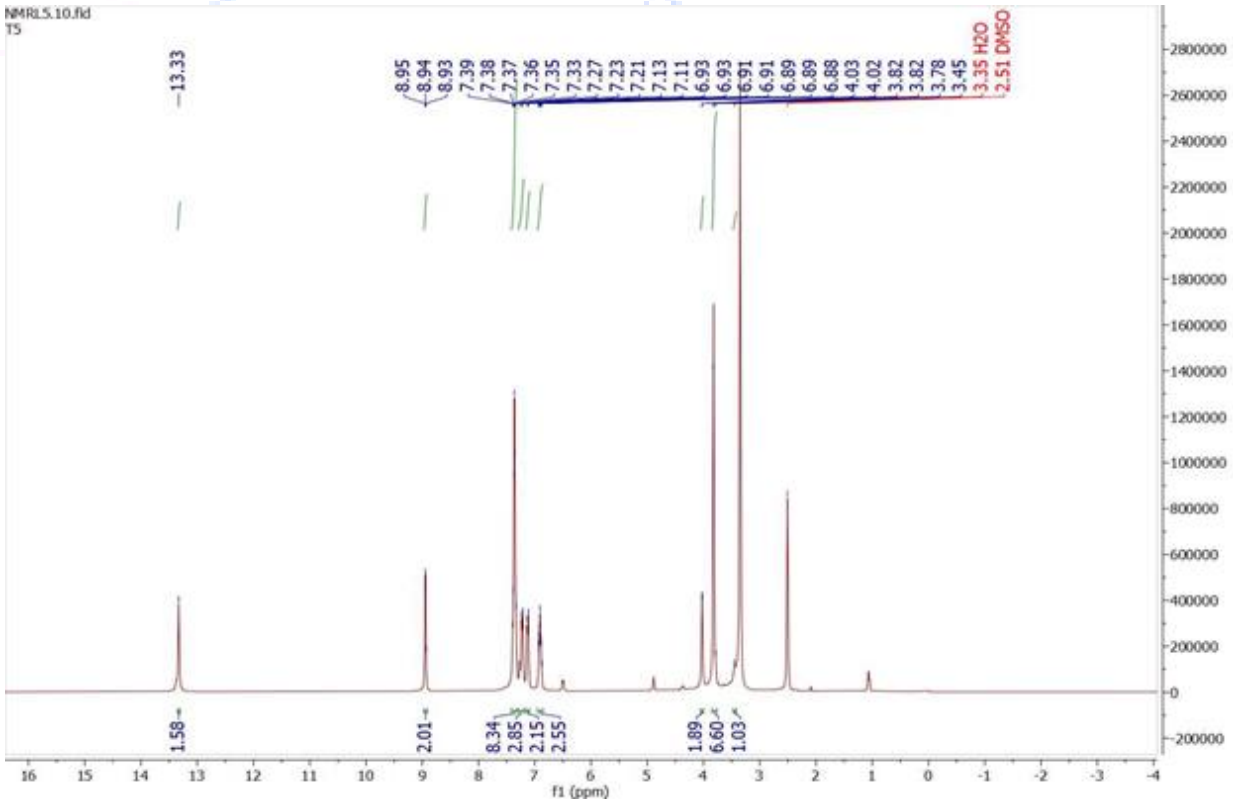


Fig. (4) The ^{1}H-NMR spectra of the ligand (L2)

Mass spectra

The mass spectra of the Copper complexes appeared molecular ion peak at 486 m/z for $[Cu(L1)Cl_2]2H_2O$, 636 m/z for $[Cu(L2)Cl_2]2H_2O$ which is in conformity with the molecular formula $C_{20}H_{22}CuN_2O_4$ and $C_{29}H_{30}CuN_2O_6$ respectively. As shown in fig. (5,6).

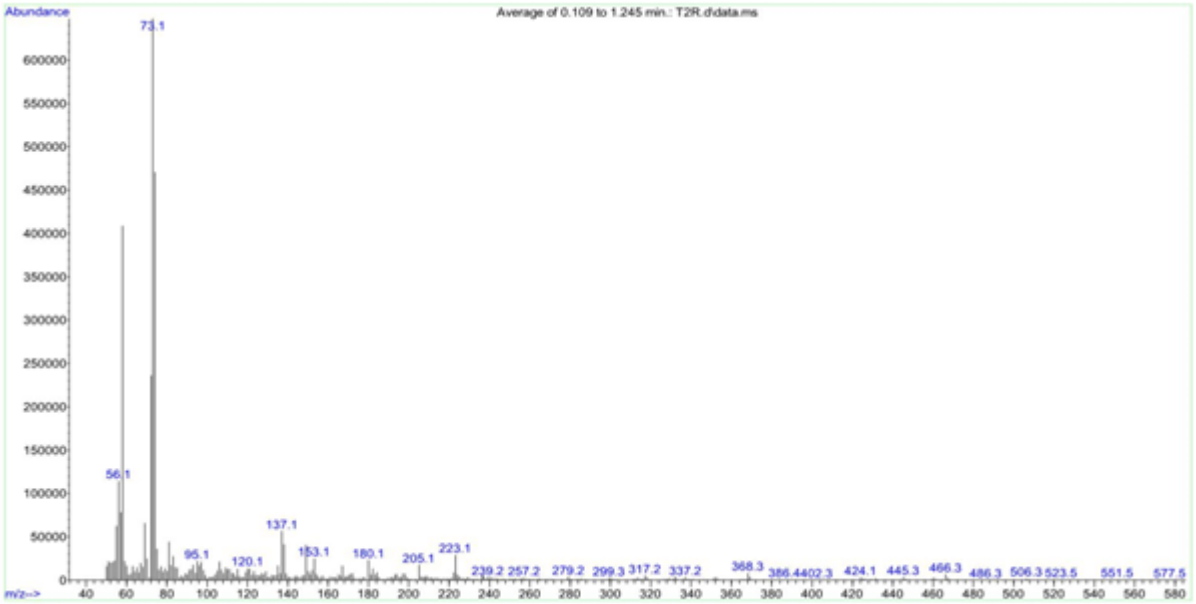


Fig. (5) The mas spectra of the complex $[Cu(L1)Cl_2]2H_2O$

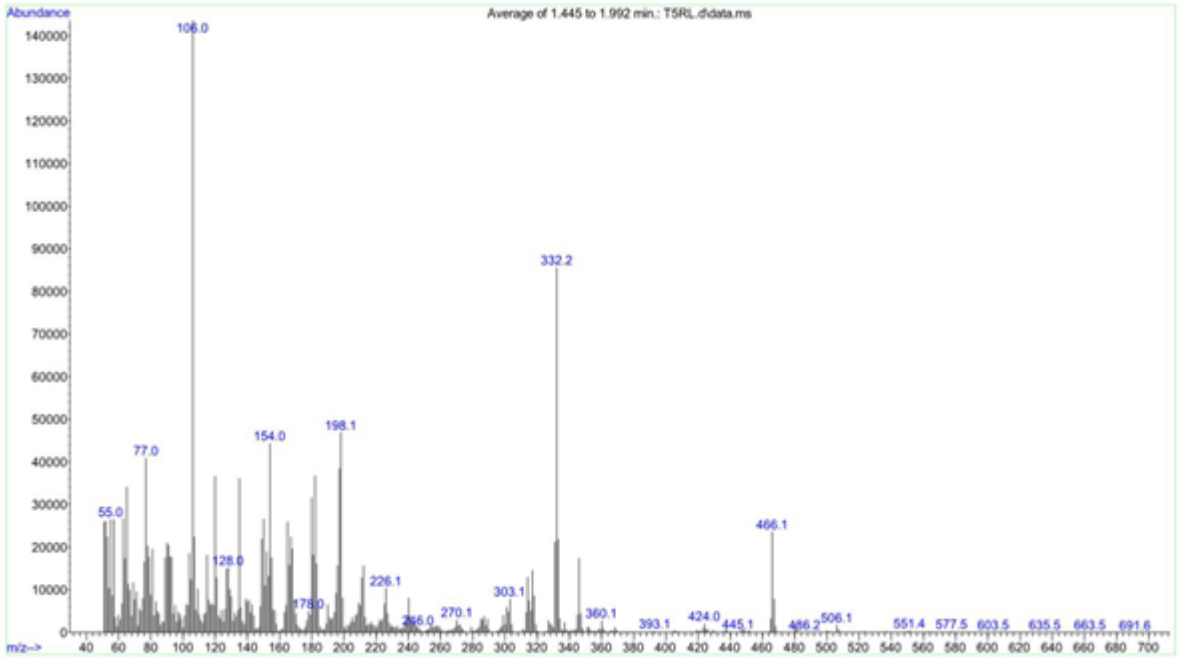


Fig. (6) The mas spectra of the complex $[Cu(L2)Cl_2]$

Conductivity Measurements.

The molar conductance values of the synthesized compounds in 10^{-3}M DMSO were measured at room temperature. The conductance values of the synthesized compounds were below (17-20)

$Ohm^{-1}\cdot cm^{2}\cdot mol^{-1}$, indicating their nonelectrolyte nature. This suggested that there were no anions present outside the coordination sphere of the complexes.

Spectrophotometric determination of DPPH radical scavenging activity

DPPH radical scavenging activity evaluation is a standard assay used in antioxidant activity studies. The antioxidant. The 1mL of an ethanolic solution had 100 µg of synthesized compounds. It was added with an equal concentration of ethanolic solution of DPPH. The prepared solution settled for incubation at room temperature for 30 min and 60 min. The decreases in the concentration of DPPH were measured by noting the absorbance at 517nm. A similar test was performed with ascorbic acid, as an internal standard, instead of Schiff's base. The percentage scavenging of DPPH free radical for each of test compounds had calculated the absorbance of negative control using Eq. (1) [35,36]. All the synthesized compound is less antioxidant activity than vitamin C, and the complexes were less activity than Schiff base as shown in the fig. (1). The ligands and their metal complexes contain several hydrogen atoms that can be donated. The donating ability of the hydrogen atoms in the complexes was determined by the decolorization of the DPPH reagent. DPPH produces a violet/purple color in a methanol solution, which changes to a yellow color in the presence of antioxidants.

. % scavenging = [(absorbance of control - absorbance of test sample) /
absorbance of control)] *100

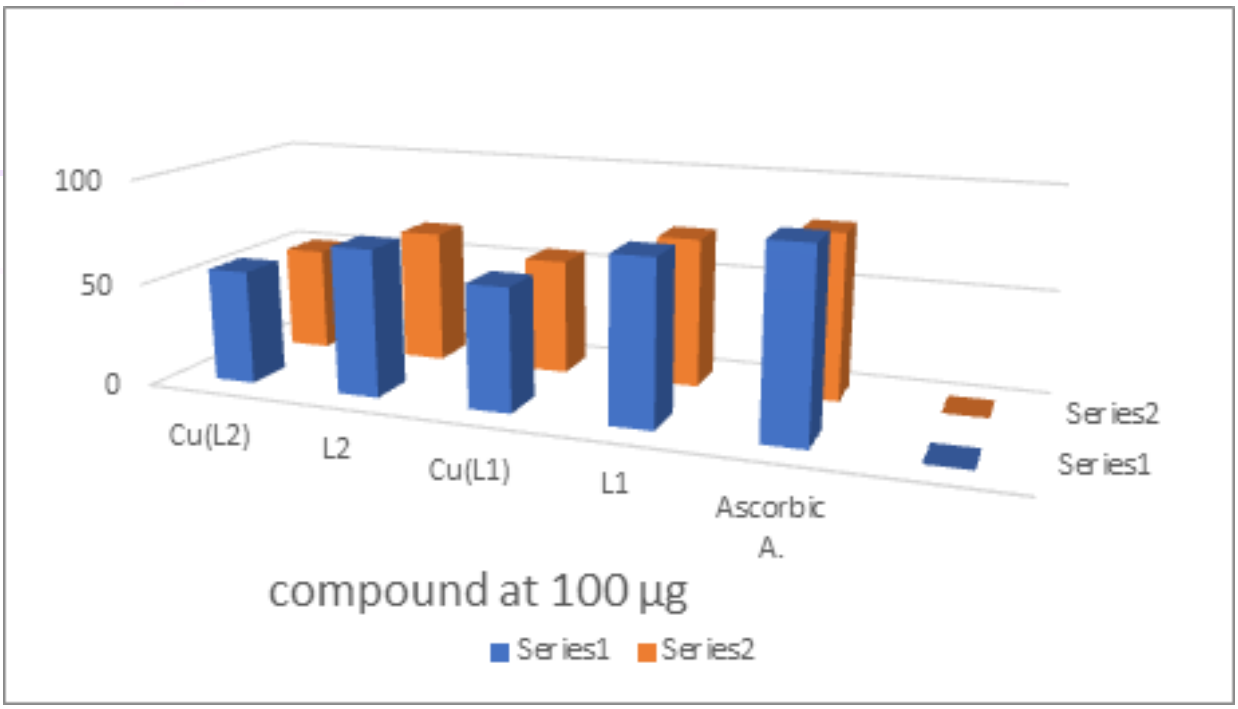


Fig. (7) the antioxidant of the ligands and their complexes with Copper ions

Biological Activity

All the synthesized compounds were screened for them in vitro antibacterial activity against (Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus) bacterial strains by the filter paper disc method [37]and recorded in Table (4). Small portion (10 mL) of nutrient broth was inoculated with the test organisms and incubated at 37◦C for 24h.Using a sterile pipette, 0.6mL of the broth culture of the test organism was added to 60 mL of molten agar which had been cooled to 45◦C, mixed well, and poured into a sterile petri dish. Duplicate plates of each organism were prepared. The agar was allowed to set and harden and the required numbers of holes were cut using a sterile cork borer ensuring proper distribution of holes on the border and one in the center. Agar plugs were

removed. Different cork borers were used for different test organisms. Using a 0.1mL pipette, 100 μL of the test sample dissolved in an appropriate solvent was poured into appropriately labelled cups and the solvents control were used. The plates were left at room temperature for 2 h to allow diffusion of the sample and incubated face upwards at 37∘C for 24 h. The diameter of the zones of inhibition was measured to the nearest mm. All the compound gave a good activity against the tested bacterial. As shown in Fig. (8)

Table (4). Antibacterial data of ligands and their metal(II) complexes (zone of inhibition in mm).

NO	Type	L1	L2	M1	M2
1	Pseudomonas	14	15	22	12
3	E.coli	12	13	10	6
5	staph arues	27	14	16	16

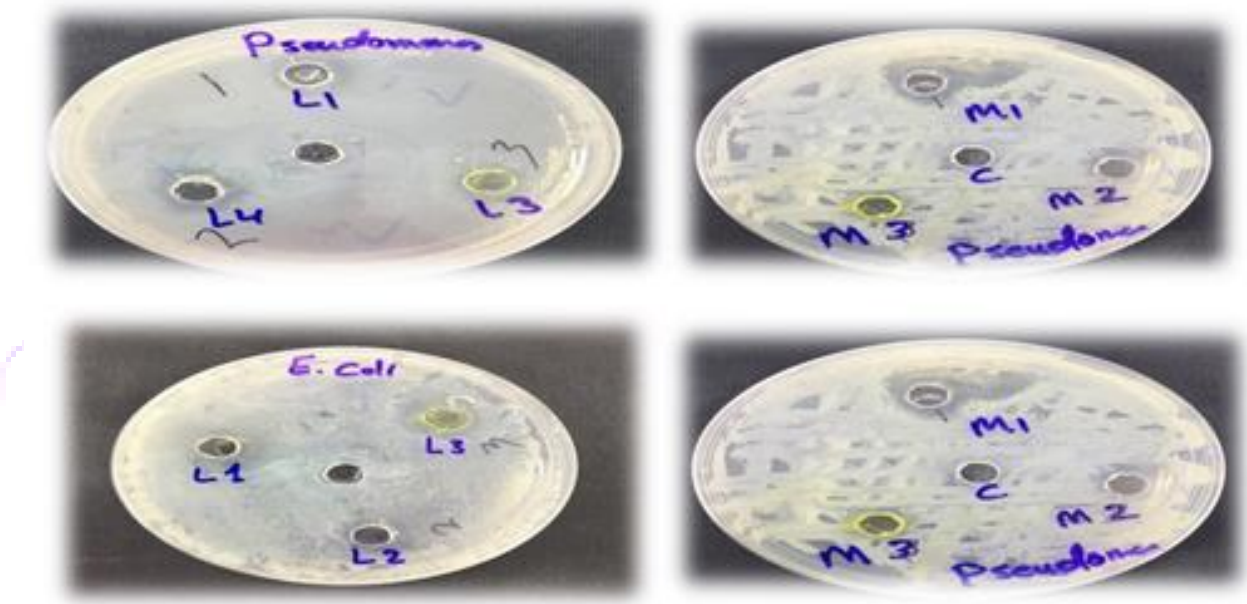


Fig. (8) antibacterial of the ligands and their complexes with Copper ion

Electrostatic potential(MEP) Molecular

Electrostatic potential is an important in finding the active sites in the molecule system with a positive point charge. Electrostatic potential of free ligand was measured and plotted as 2D contour to find the active site of molecule, as shown in figures [38]. The electrostatic potential of the ligands and the geometric of the ligands and their complexes were calculated by using semiemerical-PM3 method by hyperchem program.

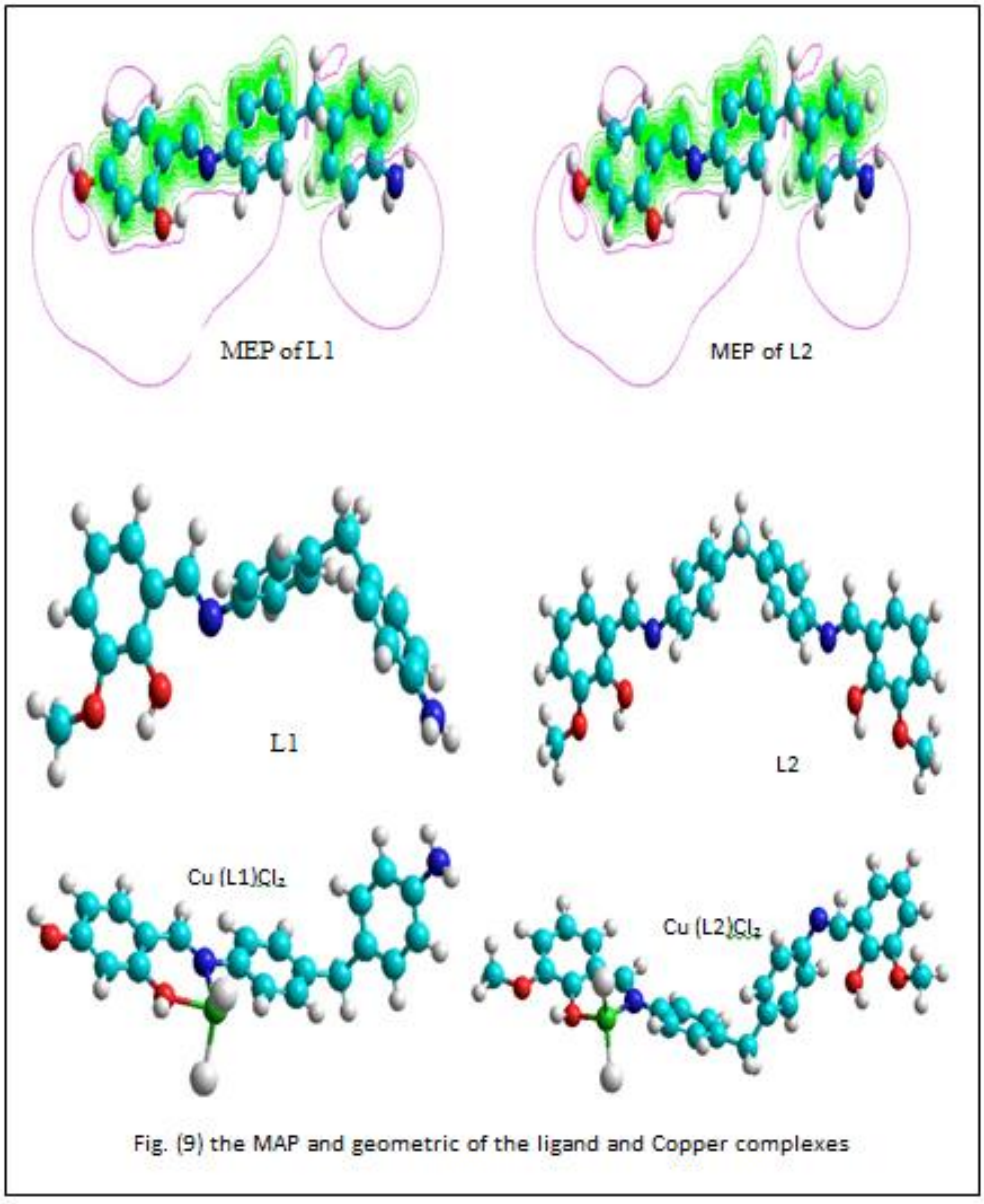


Fig. (9) the MAP and geometric of the ligand and Copper complexes

Conclusions

The Schiff base ligands and their complexes, were successfully synthesized and characterized. The Schiff base ligand coordinated to the Cu (II) ion via the azomethine nitrogen and phenolic oxygen resulting in the formation of a stable six-membered chelate ring. A tetrahedral geometry has been proposed for Cu (II) complexes based on the magnetic susceptibillty measurements which agreement with the theoretical calculation. The complexes formed are neutral with no free anions outside the coordination sphere. The compounds exhibited a good antioxidant and antibacterial properties.

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