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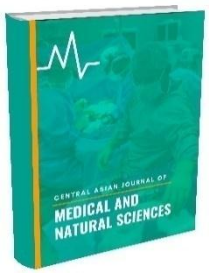

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Synthesis, Characterization and Anticancer Activity Study of New Azo Schiff Base Derivatives and its Complexes with Copper (II) and Nickel (II) Ions

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Abstract: The azo Schiff bases (L1 and L2) were synthesized and characterization on the basis their spectra of 1H-NMR, Fourier transform infrared (FTIR), as well as elemental analysis (CHN). Elemental analysis and spectral data of the ligands were found to be in a good agreement with their structures, and their complexes with Cu (II) and Ni (II) were synthesized. The anticancer activity of the syntheses compound (L1) was evaluated against MCF-7 and WRL68 cell line and it was showed a good anticancer activity.

Key words: Schiff base, azomethine, ligand, complex, anticancer.

1. Introduction:

The first schiff base was created in 1869 by the German chemist Hugo Schiff [1]. Schiff bases are an important class of chemical compounds that are generated from primary amines and carbonyl compounds (aldehyde or ketone) [2-4]. The bond generated by the reaction with the aldehyde is called azomethine or aldimine, while the bond created by the reaction with the ketone is referred to as imines or ketamine [5]. It is well known that Schiff bases are effective nitrogen donor ligands (-CH=N) [6,7]. Schiff's bases have also been shown to exhibit a broad range of biological activities, including antifungal [8,9], antibacterial [10,11], antimalarial [12], antioxidant [13,14], anticancer [15-19], antiviral [20], antiproliferative [21,22], and anti-inflammatory [23]. Azo compounds constitute one of the largest classes of industrially synthesized organic compounds. They are important in dye, drugs and cosmetics and show a variety of interesting biological activities including ntibacterial and pesticidal activities [24]. Compounds containing one or more azo groups (-N=N- linked to two carbon atoms) have a variety of uses. Aliphatic azo compounds, like azobisisobutyronitrile (AIBN), can be as radical initiators in polymerization of alkenes to make plastics. Aromatic azo compounds are used as acid-base indicators, biological stains, and commercial colorants for clothing, plastics, cosmetics, and food beverages. Many azo-dyes, such as methyl red, methyl orange, and congo red, can be used as acid-base indicators due to their ability to function as weak acids or bases [25].

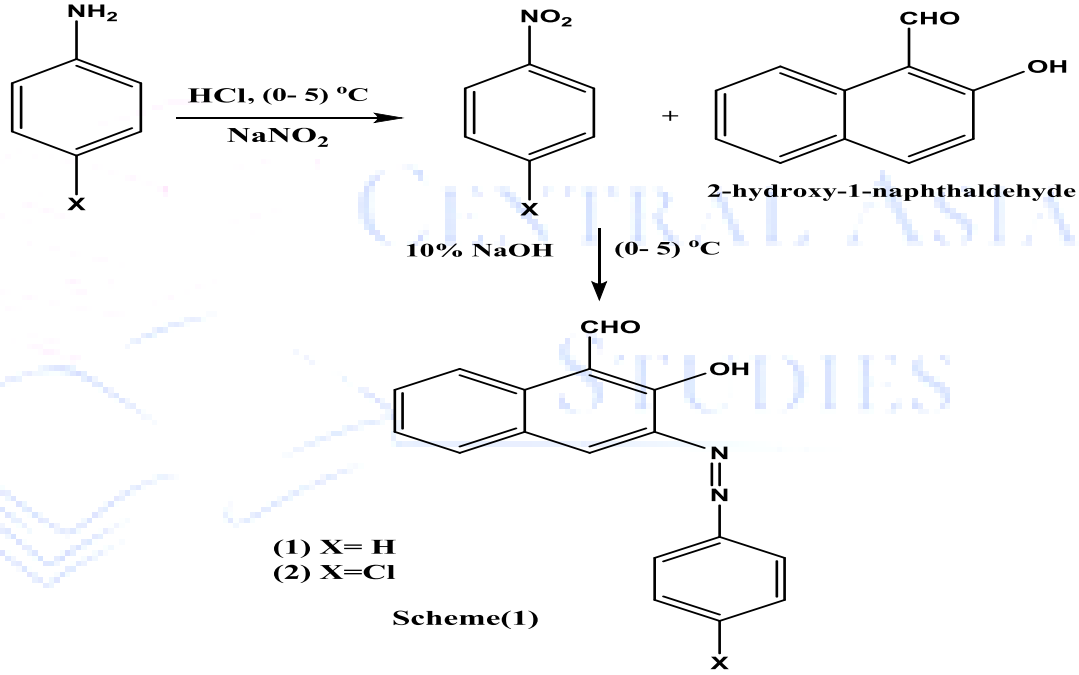
2. Experimental

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: synthesis 2-hydroxy-3-(phenyldiazenyl)-1-naphthaldehyde (1) and 3-((4-chlorophenyl) diazenyl)-2-hydroxy-1-naphthaldehyde (2)

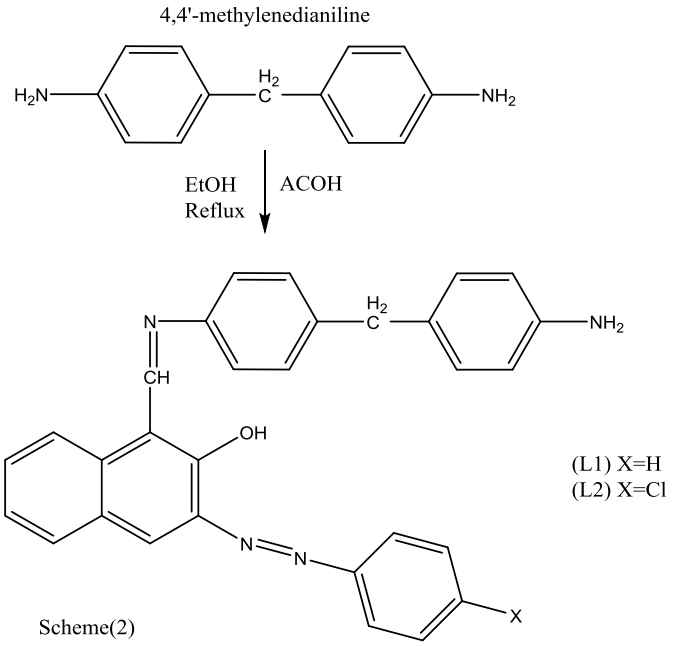
Azo compound was synthesized by dissolving (0.01 moles, 0.94g) of aniline or (0.01mol, 0.60g) of (4-Chloroaniline) in 6 ml concentrated HCl and 14 ml distilled water, then drop by drop, at (0- 5) ^{o}C, a stirring solution of (0.01mol, 0.80 g sodium nitrite in 5 ml distilled water) was added to form diazonium salt. The above diazonium salt was added to an alkaline solution of (0.04 mole, 1.7g) of (2-hydroxy-1-naphthaldehyde) in (10 ml of 10% NaOH). Then, by adding dilute HCl (to maintain a pH value of 6.5 – 7.5), convert the prepared dye from sodium to hydrogen. To remove any remaining un reacted substances. The product was purified by washing with distilled water and recrystallized by using ethanol as solvent and dried in a vacuum at 50°C for several hours [26] as shown in scheme 1



Scheme(1)

2.2:- synthesis 1-(((4-(4-aminobenzyl)phenyl)imino)methyl)-3-(phenyldiazenyl)naphthalen-2-ol(L1) and 1-(((4-(4-aminobenzyl)phenyl)imino)methyl)-3-((4-chlorophenyl)diazenyl)naphthalen-2-ol(L2)

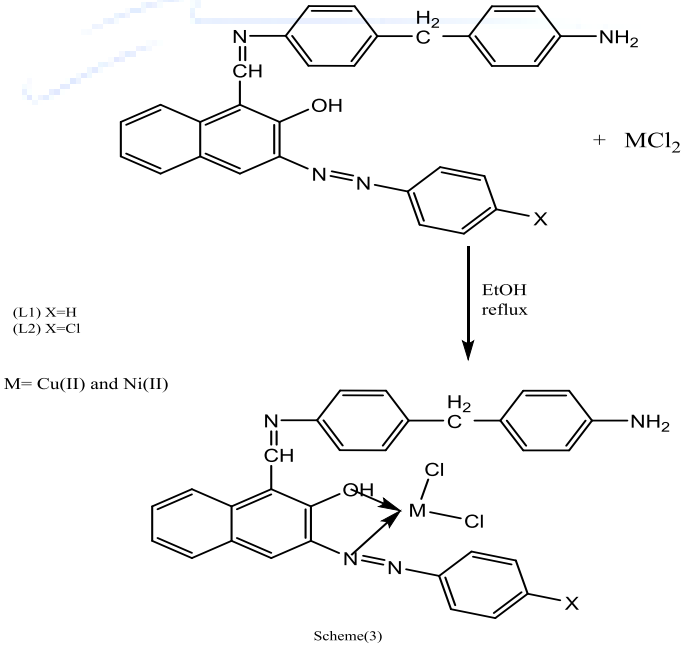
The ligands (L1) and (L2) which synthesized by reaction of 4,4'-methylenedianiline (0.198 g, 0.01 mol) with (0.27g, 0.01 mol) of compound(1) or (0.31g, 0.01) of compound(2) and refluxed the mixture in 20 ml of ethanol with a few drops of glacial acetic acid as a catalyst, The precipitate compound was obtained by filtration, washed with ethanol, and dried. As shown in scheme(2)



Scheme(2)

2.3:- Synthesis of complexes

The complexes were prepared by dissolving (0.001 mol) of ligand (L1) or (L2) in 15 mL ethanol, followed by adding the metal salt $CuCl_2.2H_2O$ (0.001 mol) or (0.001 mol) of $NiCl_2.6H_2O$ as dropwise on the mixture of the ligand; the mixture was refluxed for 3 hrs with continuous stirring at fixed temperature 70-80 °C. The mixture was filtered, and the resulted participate was washed several times with cold ethanol; other complexes were prepared using the same method. Scheme (3) shows the Synthesis route for metal complexes. Melting point of Complexes, colors and yields are all included in Table 1.



Scheme(3)

3: Results and Discussion

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

Table (1) Physical properties

compound	Colour	M.P	% C Exp. (cal.)	% H Exp. (cal.)	% N Exp. (cal.)	%Yeild	%M
$C_{30}H_{24}N_4O$(L1)	Yellow	215-217	77.85 (78.90)	6.15 (5.30)	13.74 (12.27)	78	
Cu(L1)Cl_2	green	253d				80	11.87
Ni(L1)Cl_2	yellow	231-233				70	10.91
$C_{30}H_{23}N_4OCl$	yellow	248-250	68.25 (67.68)	5.69 (6.11)	22.89 (21.71)	67	
Cu(L2)Cl_2	black	257d				55	11.22
Ni(L2)Cl_2	green	252-254				58	10.57

3.1:- FT-IR spectral

FT-IR of the synthesized ligands were gathered in the table (2). The FT-IR spectrum of ligands showed stretching characteristic vibration bands appeared at (3127-3444),(3010-3038),(2830-2980), (1623-1660), (1541-1607) and (1503-1544) cm^{-1} due to the υ (O-H)group, υ (C-H) aromatic group, υ (C-H) alaphtic group, υ (C=N)azomethine group, υ (C=C) and υ (N=N) [27] group respectively, as shown in the figures (1).

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 (N=N) azo
L1	3437	3038	2924	1660	1593	1503
Cu(L1)Cl_2	3444	3020	2965	1658	1607	1526
Ni(L_1)Cl_2	3131	3010	2830	1623	1602	1544
L2	3319	3012	2980	1642	1572	1532
Cu(L2)Cl_2	3129	3020	2830	1620	1541	1510
Ni(L2)Cl_2	3127	3015	2830	1624	1602	1543

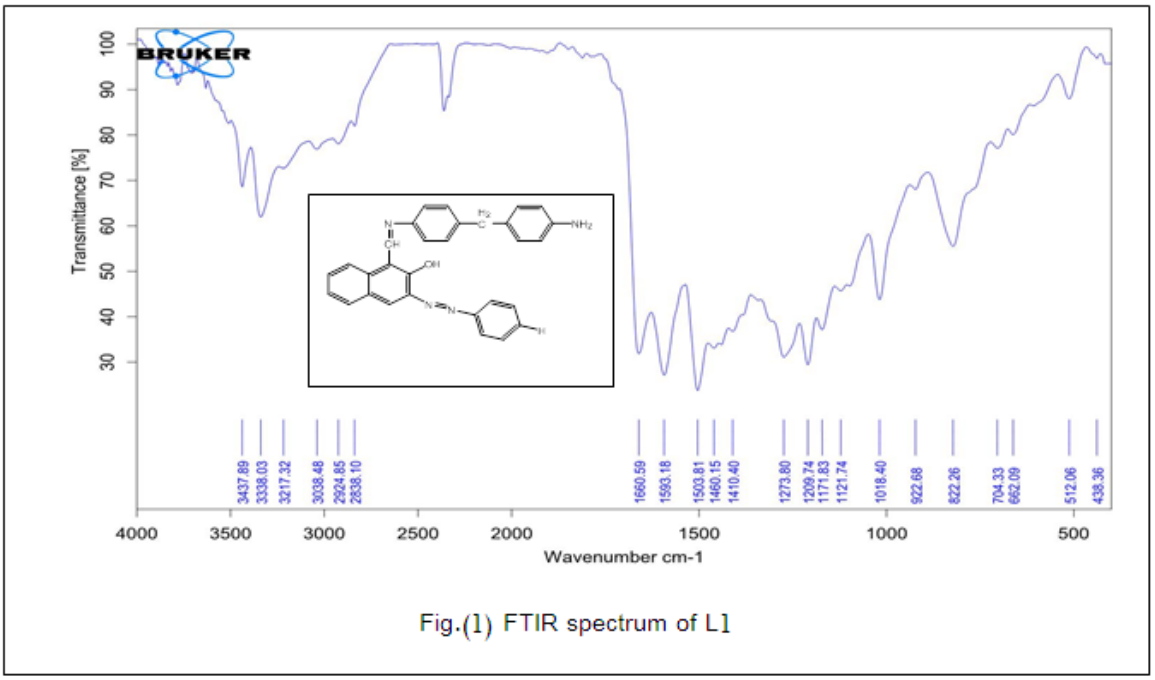


Fig.(1) FTIR spectrum of L1

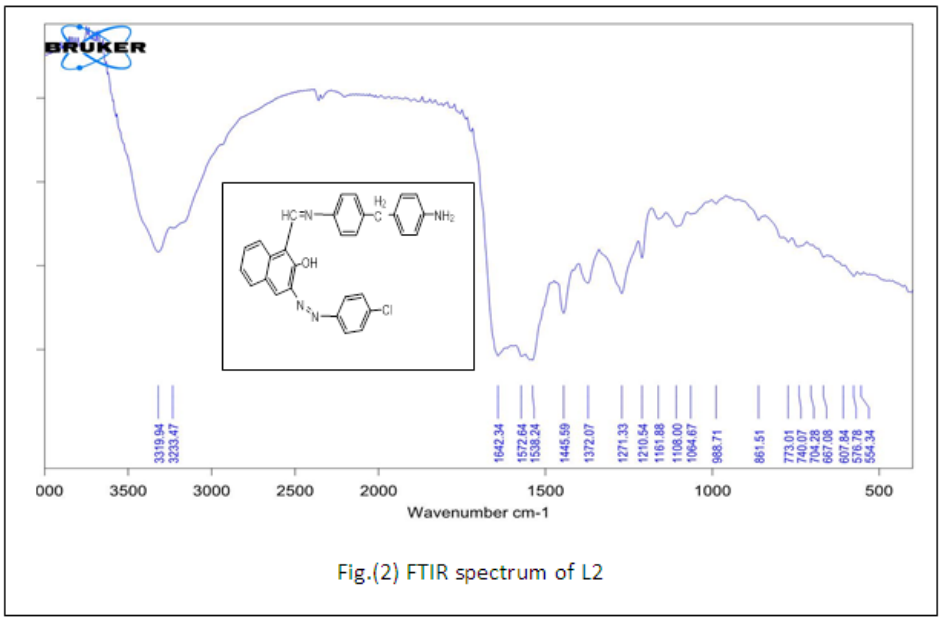


Fig.(2) FTIR spectrum of L2

3.2:- 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)

The ^{1}H-NMR spectrum of the ligand (L1) was appeared two signals at (4.05) ppm and (6.9) ppm due to the proton of (CH_2) and (NH_2) group respectively, melti signals at (7.19-7.95) ppm due to the aromatic group [28], while the signal of the azomethine groups at (8.48) ppm, the signal of phenolic groups at (15.8) ppm. As shown in the figure (2)

The ^{1}H-NMR spectrum of the ligand (L2) was appeared two signals at (4.05) ppm and (4.9) ppm due to the proton of (CH_2) and (NH_2) group respectively, melti signals at (6.51-7.93) ppm due to the aromatic group, while the signal of the azomethine groups at (8.7) ppm, the signal of phenolic groups at (15.8) ppm. As shown in the ^{1}H-NMR data and figure (3)

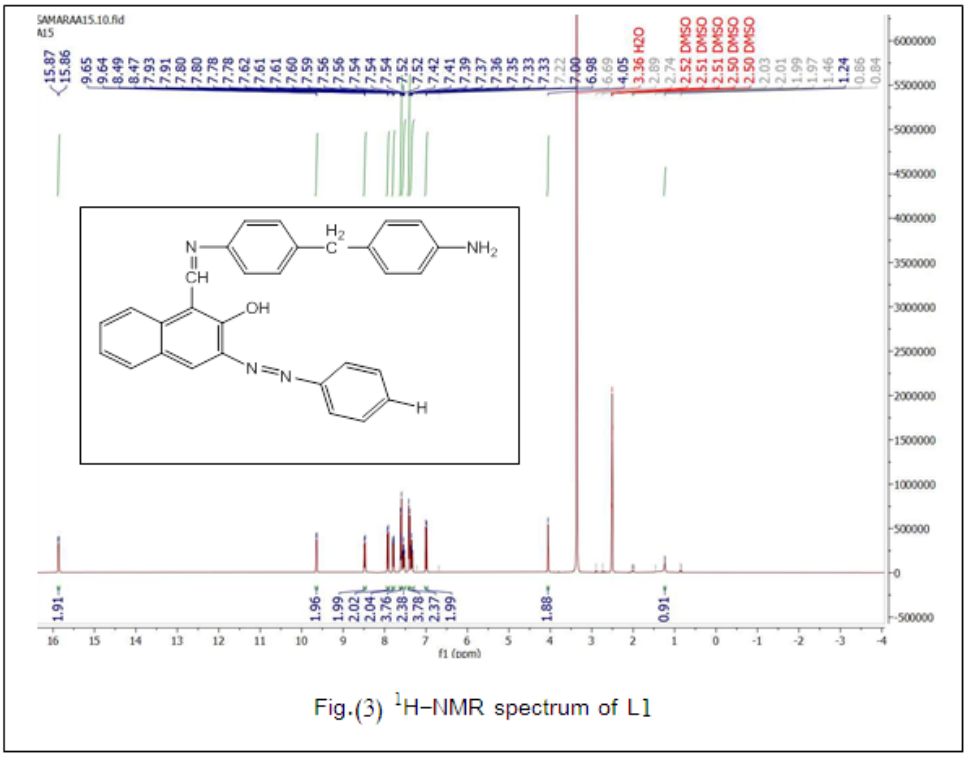


Fig.(3) ^{1}H–NMR spectrum of L1

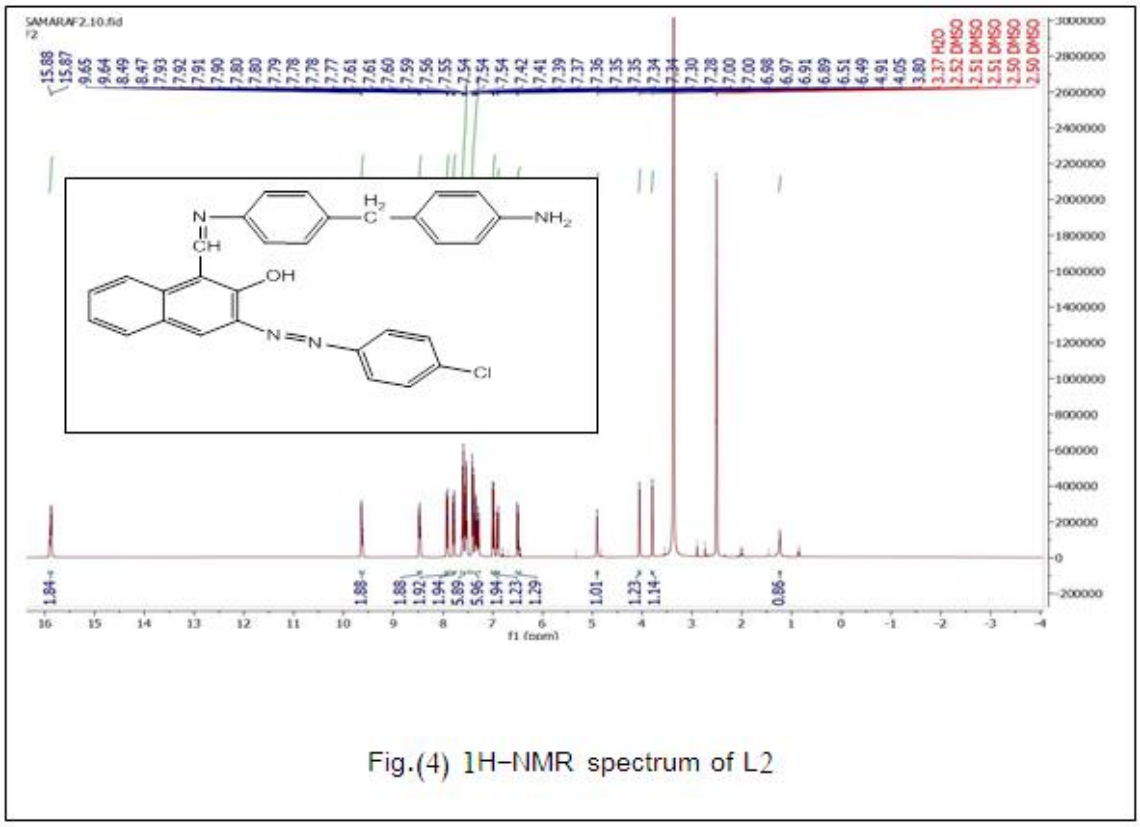


Fig.(4) 1H–NMR spectrum of L2

3.3: The mass spectra

Mass spectrometry has been successfully used to investigate molecular species; The pattern of mass spectrum gives an impression of the successive degradation of the target compound with the series of peaks corresponding to the various fragments. Their intensity gives an idea of the stability of Fragments [29], the stoichiometry of compounds was compared using mass spectra obtained at room temperature (21) °C in Table (3) and figures (5-10). Each synthesized compounds matched the molecular ion fragment and supported the proposed structure.

Table (4)- Mass spectra of synthesized compound

Compound	Calculated mass	Obtain mass (m/z)	Peak assigned
$C_{30}H_{24}N_4O$ (L1)	456	456	M^+
$Cu(L1)Cl_2$	590	592	$[M+2H]^+$
$Ni(L1)Cl_2$	585	587	$[M+2H]^+$
$C_{30}H_{23}ClN_4O$	490	490	M^+
$Cu(L2)Cl_2$	624	622	$[M-2H]^+$
$Ni(L2)Cl_2$	619	621	$[M-2H]^+$

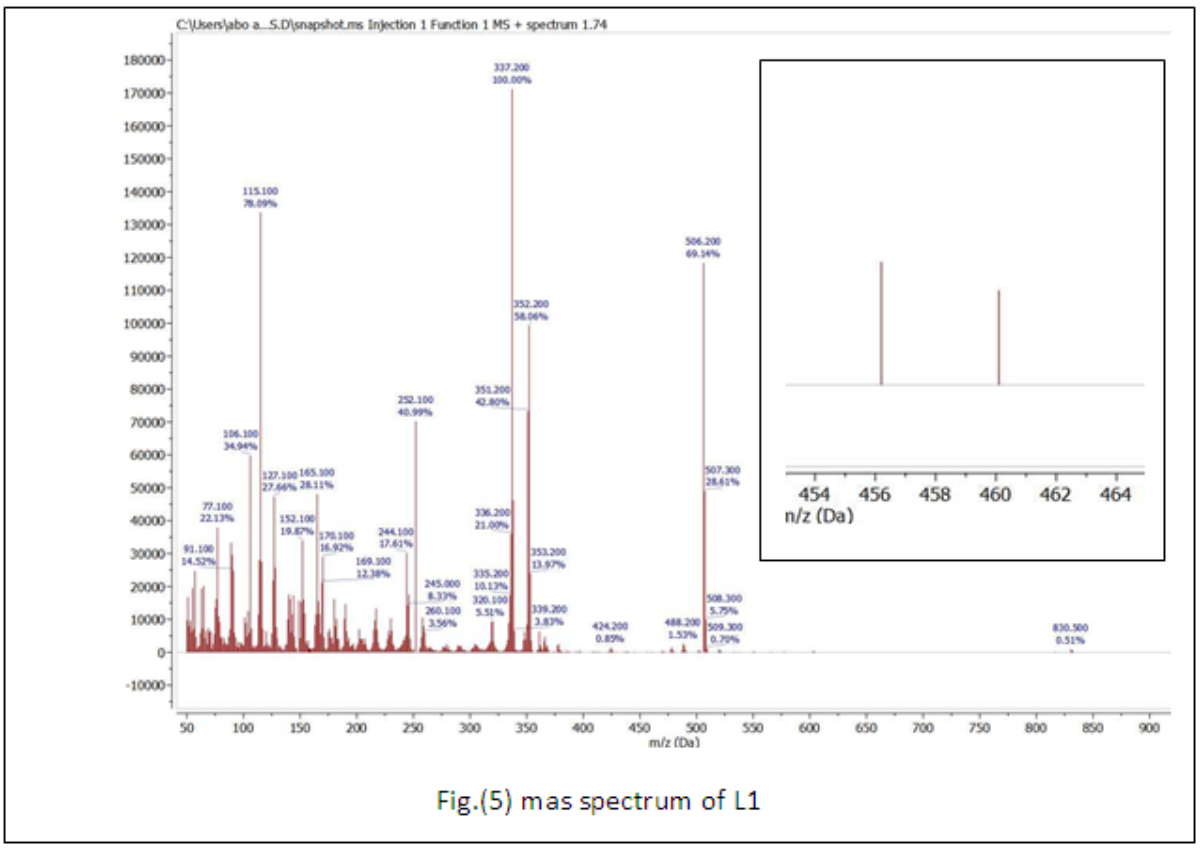


Fig.(5) mas spectrum of L1

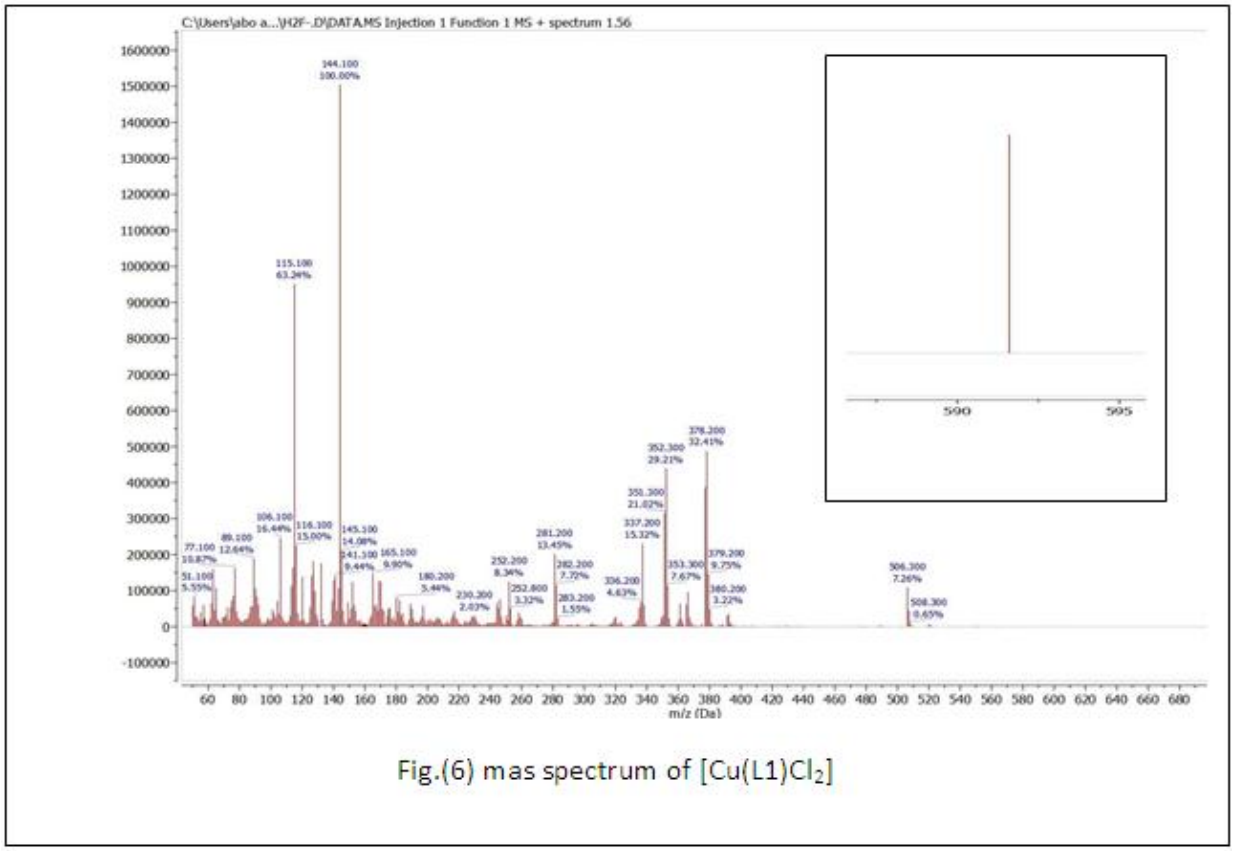


Fig.(6) mas spectrum of $[Cu(L1)Cl_2]$

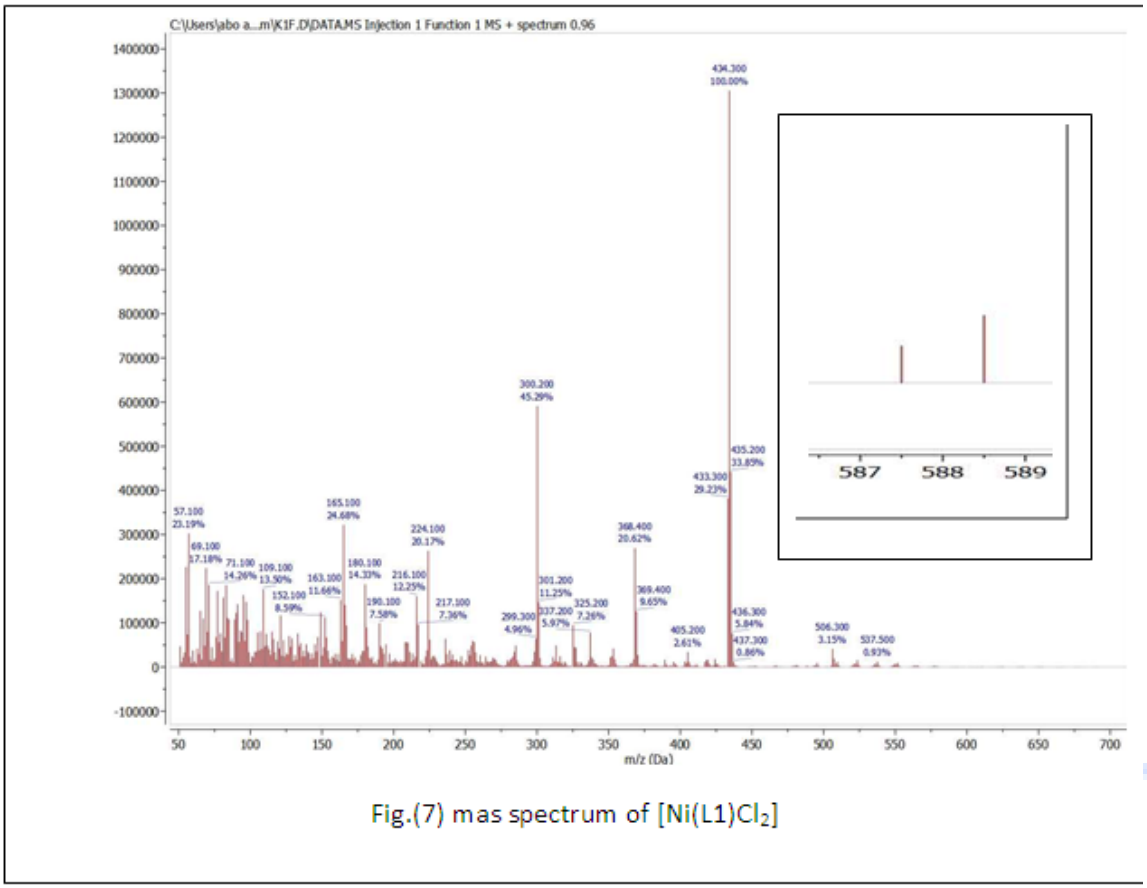


Fig.(7) mas spectrum of $[Ni(L1)Cl_2]$

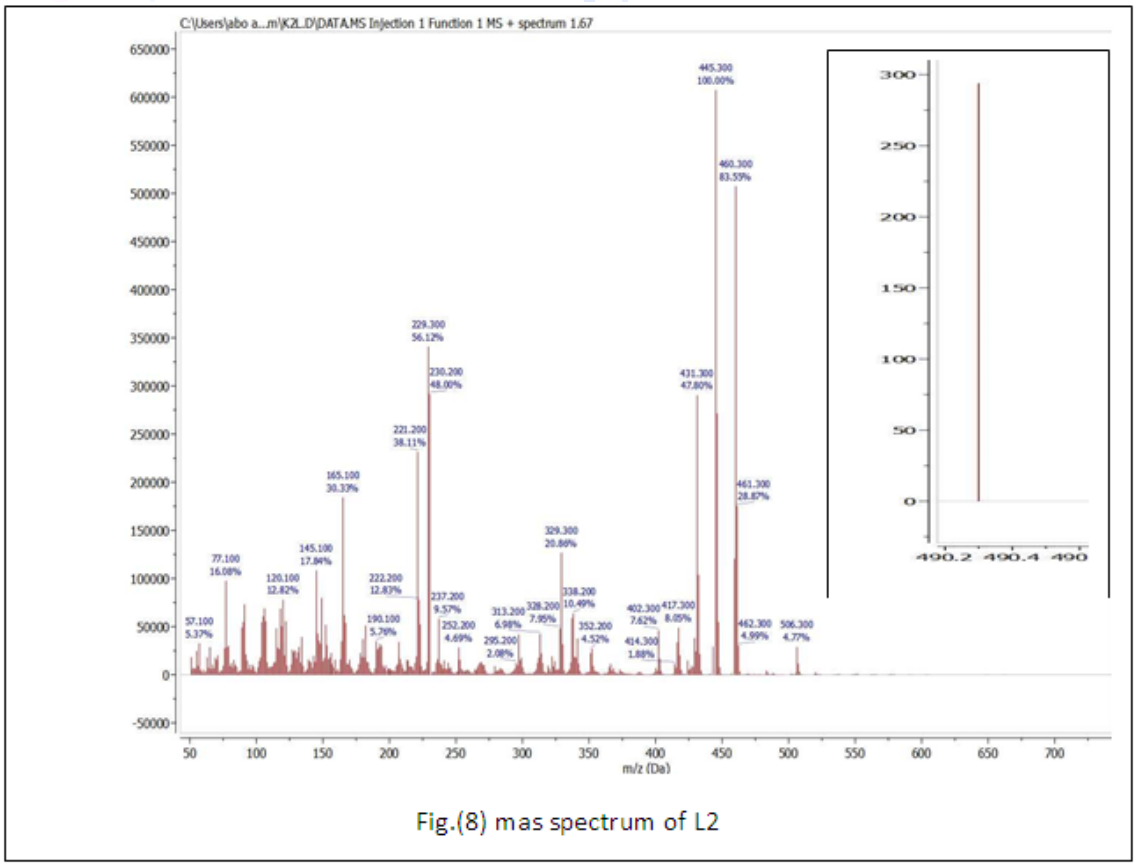


Fig.(8) mas spectrum of L2

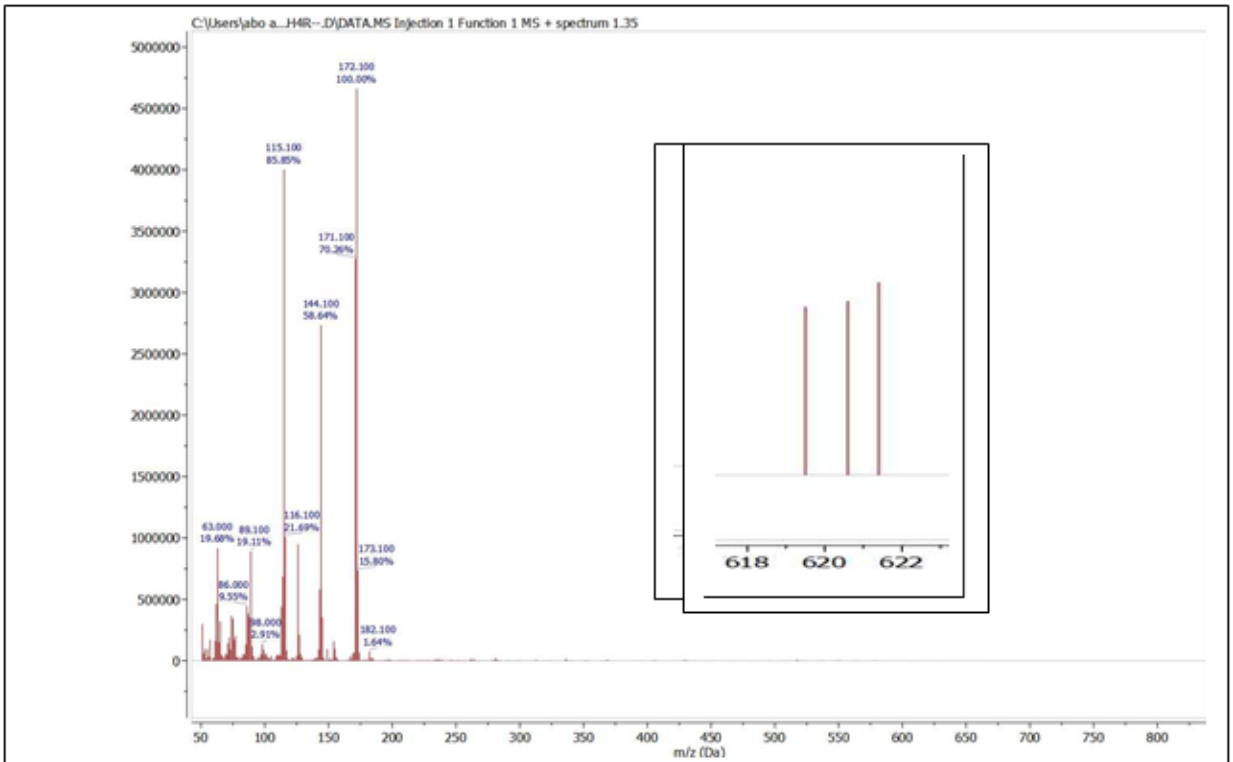


Fig.(9) mas spectrum of $[Cu(L2)Cl_2]$

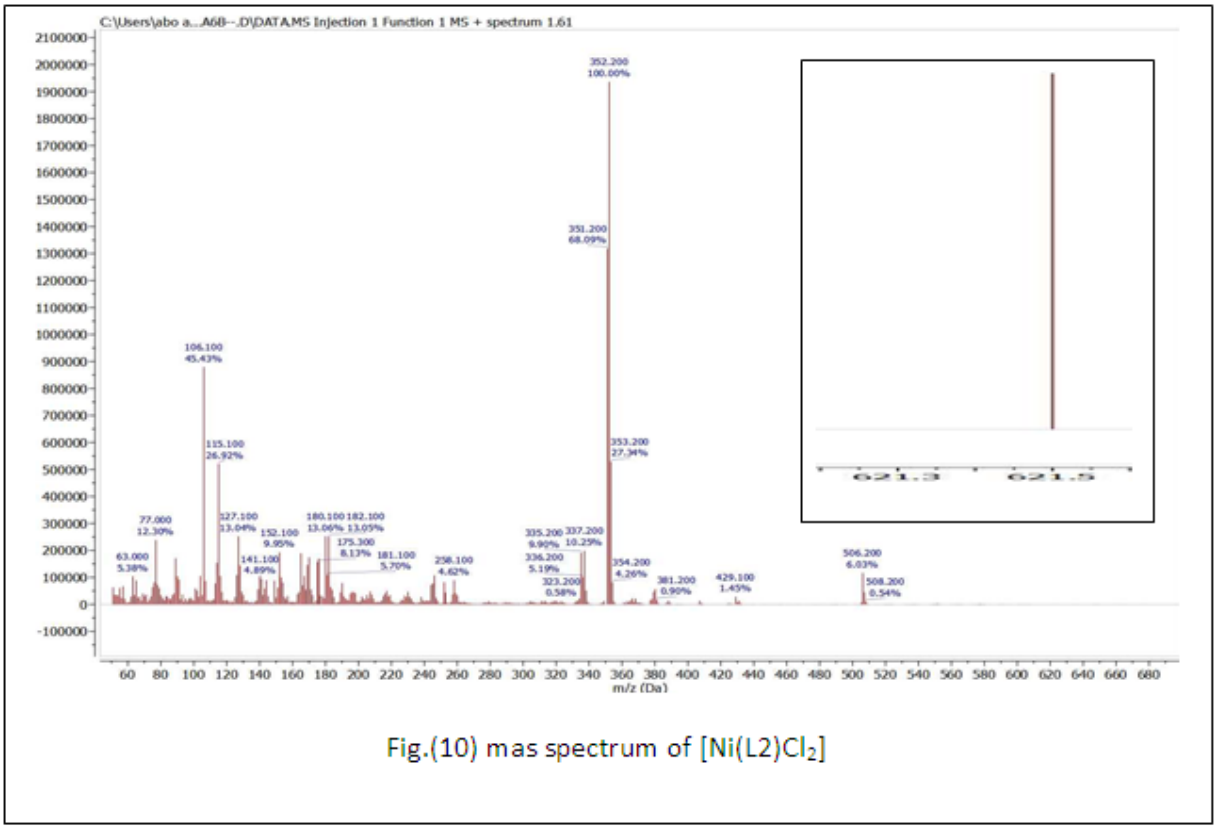


Fig.(10) mas spectrum of $[Ni(L2)Cl_2]$

3.4:- Evaluation of cytotoxic activity

The cytotoxic ability of the ligand (L1) was screened against the MCF-7 and WRL68 cell line (breast carcinoma cells), which was one of the most common forms of cancer. Therefore, the synthesized compound was investigated against single-dose concentration (100 µg/ml) of MCF-7 cell line. The *in-vitro* screening of the compound indicated that the azo Schiff base had good anticancer activity, The half-inhibitory concentration (IC50)(113.3) as shown in (Fig. 11), by using various concentrations (5, 12.5, 25 and 50 µg/ml) [30]. The data obtained were illustrated in (Table 5)

Table (5) Anti-breast cancer activity of (L1)

Conc.(µg/ml)	Mean viability (%) ± SD	
	WRL68	MCF-7
400	73.148±1.13	39.9 ±2.7
200	± 1.2 84.02	49.7± 6.6
100	92.2± 0.99	70.7± 5.2
50	± 0.40 96.3	89.7±4.8
25	96.2±0.6	94.3 ±0.6

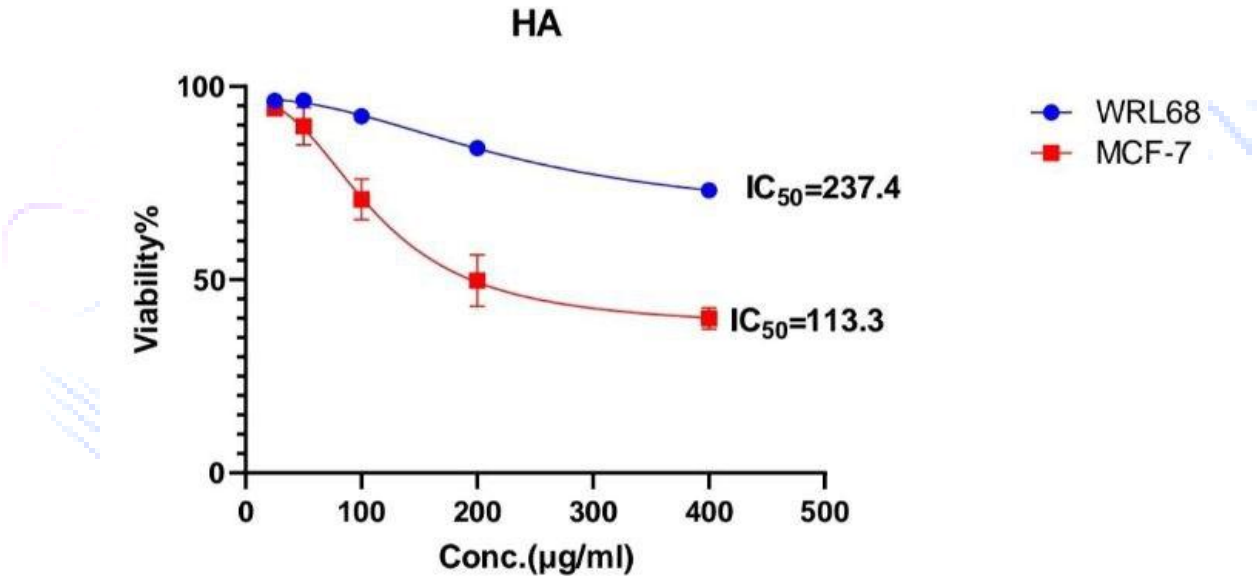


Fig. (11) effective of the ligand (L1) on cell line of MCF-7 and WRL68

Conclusions

The compounds were synthesised, characterised, and ligand(L1) was tested for anti-tumour activity against the MCF-7 and WRL68 cell lines.

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