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Research Article

SYNTHESIS, CHARACTERIZATION, ANTIOXIDENT AND ANTICANCER HUMAN STUDIES OF NEW METAL ION COMPLEXES OF POLY SCHIFF BASE DERIVED FROM 4-AMINOACETOPHENONE WITH SALICYLALDEHYDE AND 4-BROMOANILINE

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ABSTRACT

Objective: New metal ion complexes of some transition metal ions [Cu(II), Cr(III), Cd(II), Zn(II), and VO(II)] of prepared ligand 2-(((4-(1-((4-bromophenyl) imino)ethyl) phenyl) imino) methyl) phenol were synthesized.

Methods: The method is based on Schiff bases reaction of 4-aminoacetophenone with salicylaldehyde and P-bromoaniline.

Results: The structures of the new metal ion complexes were characterized by elemental microanalysis (C.H.N), Fourier transform infrared, ultra violet-visible spectra, thermal gravimetric analysis-differential thermal gravimetric, flame atomic absorption, molar conductivity, magnetic susceptibility measurement, and mass spectra. According to the obtained data, the probable coordination geometries of these complexes were suggested as octahedral excepted C_5 was pyramidal. All complexes were found to be non-electrolyte.

Conclusion: The anticancer activity was screened against human cancer cell such brain cancer cells (AMJM), cervical cancer cells (HeLa), ovarian cancer cells (SKOV-3), and breast cancer cells (MCF-7). The results indicate that the metal ion complexes show increase cytotoxicity in proliferation to cell lines as compared to the free ligand. Antioxidant activities were shown the ligand, and their complexes have high reactivity.

Keywords: Anticancer, Transition metal ions, Schiff base, Antioxidant.

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INTRODUCTION

Schiff bases have been known since 1864 by Schiff [1]. The Schiff bases are generally prepared by condensation of primary amines (-NH_2) with active carbonyl compounds such as aldehydes and ketones (>C=O). They are also known as imines and azomethine [2], Schiff bases are conceder a weak base and readily hydrolyzed by mineral acids but not by aqueous alkali. Schiff bases derived from formaldehyde exhibit tendency to undergo polymerization [3]. Schiff bases which are effective as coordinating ligands bear a functional group usually OH, sufficiently near the site of condensation that a five- or six-membered chelate ring can be formed by the reaction with a metal ion. The size of the chelate ring formed can be controlled by changing the location of donor atoms and groups to explore the effect of substitution and steric factors. These products have received considerable attention as model compounds for theoretical studies and as a precursor in the following reactions to heterocyclic compounds [4]. The Schiff bases are relatively stable, but Schiff base derived from aromatic compounds is more stable than those derived from aliphatic compounds. The aliphatic aldehydes are relatively unstable and readily polymerizable while those of aromatic aldehydes having effective conjugation which are more stable [5]. The behavior of the azomethine group as a π- accepter is the reason that gives the ligands of Schiff bases ability to form stable complexes in low-oxidation states [6]. Schiff bases are considered a very important class of organic compounds, having wide applications in many biological aspects [7-9]. The mainstays of treatment for advanced cancers are chemotherapy and radiotherapy. However, they are limited due to the resistance of tumor cells to these agents, as well as their narrow therapeutic index. Therefore, combination therapies were invented to overcome cancer cell resistance and to increase the antitumor effect while considering the toxicity for normal tissue. Antitumor chemotherapeutic agents, such as compound derivatives from 4-aminoacetophenone and salicylaldehyde [10], are toxic to the cancer cell and make it dysfunctional. Effective antitumor strategies require a selective response between normal and tumor tissue (i.e., therapeutic index). Replication component oncolytic viruses have important factors contributing to the therapeutic index by the differential destruction of tumor cells with low toxicity to normal cells [11]. Combination strategies involve attacking tumor cells through different mechanisms of action, which can prevent tumor cells from having the time to develop resistance to treatment [12].

METHODS

Apparatus

Fourier transform infrared (FT-IR) spectra were recorded by SHIMADZU 8400s ultraviolet-visible (UV-Vis) spectra for all the studied compounds were recorded on the SHIMADZU 1800. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured on a BRUKER AV 400 Avance-III (400 MHz and 100 MHz). The metal content of the synthesized ligands and complexes was determined using (GBC Avanta Ver. 1.33). The atomic absorption analysis was used to determine the metal contents by Nova 350 spectrophotometer. The percentage of carbon, hydrogen, nitrogen, and sulfur (CHNS elemental analysis) were carried out by CHNS (Elemental Analyzer CHNS-932). The melting points for all the studied compounds were performed by Gallenkamp melting point apparatus. The molar conductivity for metal ion complexes was studied in dimethyl sulfoxide (DMSO) (10^{-3} M) which was determined to hunts capacitors trade mark British made. The magnetic susceptibility of the studied complexes was performed at room temperature by auto magnetic susceptibility balance model Sherwood Scientific. The mass spectra were recorded by liquid chromatography-MS (Perkin–Elmer, USA/Flexer SQ 300 M).

Reagents, chemicals, and supplements

Chemicals and reagents used in this work were of inorganic and bio application grade.

Maintenance of cell cultures (anticancer activity)

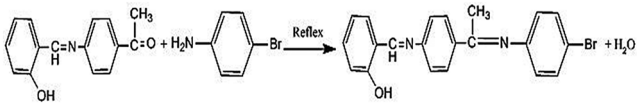
Cell lines were obtained from the Iraq biotech Cell Bank Unit and maintained in RPMI-1640 supplemented with 10% Fetal bovine, 100 units/mL penicillin, and 100 µg/mL streptomycin. Cells were passaged using trypsin-ethylenediaminetetraacetic acid (EDTA) reseeded at 50% confluence twice a week and incubated at 37°C. Trypsin and EDTA from Capricorn (Germany), DMSO from Santacruz (USA) and Roswell Park Memorial Institute (RPMI) 1640 medium from Capricorn (Germany). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) stain from Bio-World, USA. Fetal Bovine Serum (FBS) from Capricorn (Germany).

The chemicals (organic, inorganic, and solvent)

The chemicals used included 4-bromoaniline (Sigma-Aldrich), 4-aminoacetophenone (Sigma-Aldrich), salicylaldehyde (Sigma-Aldrich), $CuCl_2.2H_2O$ (Merck), $CrCl_3.6H_2O$ (BDH), $CdCl_2.2H_2O$ (BDH), $ZnCl_2$ (BDH), and $VOSO_4.5H_2O$. The organic solvents which were used included ethanol 95% (BDH), DMSO (LOBA Chemie), and Petroleum ether (30–60°C) (Fluka).

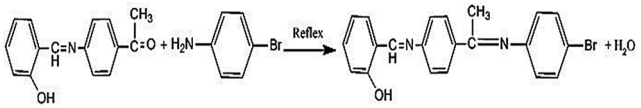
Synthesis of ligand

4-aminoacetophenone (1 mmole), (0.13 g), was dissolved in absolute ethanol (15 mL) then three drops of glacial acetic acid were added. Salicylaldehyde (10 mL), (0.12 g), was added to the solution of 4-aminoacetophenone. The mixture was heated under reflux at temperature 70°C for 10 h. During this period, a yellow solid compound was formed which was collected by washed with ethanol to remove unreacted materials and dried in oven under 70°C giving yellow crystals as shown in the following equation:



(4-(2-hydroxybenzylidene amino)phenyl)ethan-1-one

Step 2: Mixing (1 mmole), (0.23 g), from the derivative recorded above with 1 mmole,. 17 g from 4-bromoaniline in 50 mL ethanol absolute. The mixture was heated under reflux at temperature 70°C for 8 h then let the mixture to cool until the precipitate. The solid precipitate is filtered, washed by absolute ethanol and dried to get the ligand to be prepared pure as shown in the following equation:



Synthesis of ligand

Synthesis of complexes

A solution of 0.786 g and 0.001 mol of the ligand (L) in 8 mL of absolute ethanol was added dropwise to warm solution (0.001mol) of metal salts (0.34 g, 0.532 g, 0.438 g, 0.272 g, and 0.506 g for $CuCl_2.2H_2O$, $CrCl_3.6H_2O$, $CdCl_2$, $ZnCl_2$, and $VOSO_4.5H_2O$, respectively) dissolved in 10 ml absolute ethanol and the mixture was refluxed for 4–8 h. Colored crystalline solid compounds were formed. The products were filtered, washed with ethanol and dried in an oven.

Cytotoxicity assays

To determine the cytotoxic effect, the MTT cell viability assay was done using 96-well plates. Cell lines were seeded at 1×10^4 cells/well. After 24 h or a confluent monolayer was achieved, cells were treated with the tested compound. Cell viability was measured after 72 h of treatment by removing the medium, adding 28 µL of 2 mg/mL solution of MTT and incubating the cells for 1.5 h at 37°C. After removing the MTT solution, the crystals remaining in the wells were solubilized by the addition of 130 µL of DMSO followed by 37°C incubation for 15 min with shaking [12]. The absorbency was determined on a microplate reader at 492 nm (test wavelength); the assay was performed in triplicate. The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated as the following equation:

Inhibition rate=A-B/A*100.

Where A and B are the optical density of control and the optical density of test.

RESULTS AND DISCUSSION

Microanalysis

The importance of preparing Schiff base compounds arises from their versatility as starting materials for the synthesis of many compounds. The structures, of the prepared Schiff base with its metal ion complexes, were identified by C.H.N (Table 1), FT-IR (Table 2), UV-Vis (Table 3), ^{1}H-NMR (Table 4) ^{13}C-NMR (Table 5), and thermal gravimetric analysis-differential thermal gravimetric (TGA-DTG) (Table 6) with some other techniques.

FT-IR spectral studies

Important characteristic stretching frequencies of the ligand and its metal ion complexes [13,14] are described in Table 2 and their spectra (L and C_1) are shown in Figs. 1 and 2.

Molar conductance measurement

The molar conductance values of the synthetic complexes obtained in DMSO as a solvent at room temperature were listed in Table 3. The

Table 1: Elemental, microanalysis and some physical properties of the ligand and the prepared complexes

Compounds	M.Wt. g/mol	Yield %	Color	M.P (°C)	Micro elemental analysis Calc. (Found)			M % Cal (found)	Cl % Cal (found)
					C (%)	H (%)	n (%)		
L	393.28	74	Yellow	100–102	64.07 (63.90)	4.32 (4.30)	7.11 (7.34)	-	-
C_1	563.44	65	Dark-Brown	144–146	44.72 (44.31)	3.72 (4.62)	4.96 (4.74)	11.27 (10.98)	12.60 (12.38)
C_2	659.39	69	Green	90–92	38.21 (38.66)	4.39 (4.26)	4.24 (4.73)	7.88 (7.80)	16.15 (16.08)
C_3	612.31	65	Pall-Yellow	200 Dec	41.15 (40.98)	3.42 (3.22)	4.57 (4.56)	18.35 (18.89)	11.59 (11.29)
C_4	621.28	80	Pall-Yellow	130 Dec	48.28 (48.17)	4.66 (4.12)	4.50 (4.28)	10.52 (10.48)	11.42 (11.35)
C_5	645.84	77	Green	200–202	39.01 (39.49)	4.18 (4.29)	4.33 (4.61)	7.8 (-)	-

Table 2: FT-IR spectra of the ligand (L) and the metal ion complexes

Compounds	υ (OH), H2O coordination	υ (C=N)	υ (C-O)	υ (M-N)	υ (M-O)	υ (M-Cl)
L	3411	1566	1236	-	-	-
C_1	3452	1537	1266	545	490	349
C_2	3390	1542	1269	518	486	345
C_3	3352	1535	1265	518	495	372
C_4	3433	1535	1248	501	472	352
C_5	3334	1539	1245	493	455	-

FT-IR: Fourier transform infrared

Table 3: Electronic spectra, spectra parameter and magnetic susceptibility, molar conductance and suggested stereo chemical of the ligand and the metal ion complexes

Compounds	Wavelength λ (nm)	Wave No. ῡ/cm	Assignment	Molar Cond. S.cm²/moL	μ eff. (B.M)	Geometry suggested
L	322	31055	n→π*			
C_1	513	19493	2Eg→2T2g	1.25	1.89	Distorted octahedral
C_2	890	10204	4A2g→4T2g	4.71	4	Octahedral
	508	19685	4A2g→4T1g (F)			
	409	24449	4A2g→4T1g (P)			
C_3	451	22172	C.T (M→L)	3.41	Diam.	Octahedral
C_4	449	22271	C.T (M→L)	2.03	Diam.	Octahedral
C_5	719	12642	2B1g→2Eg	2.58	1.73	Pyramidal
	515	19417	2B1g→2B1g			

Table 4: ^{1}H-NMR data of the ligand (L) and the metal ion complexes

Compounds	O-H	N=CH	C-H aromatic	H_2O	CH_3 proton
L	13.04	8.62	6.98–7.55	-	1.60
C_1	13.60	8.73	6.58–8.08	3.55	1.92
C_2	13.11	9.00	6.69–8.05	3.62	1.23
C_3	13.16	8.96	6.57–7.65	3.74	1.76
C_4	13.40	9.44	6.57–7.67	-	1.80
C_5	13.19	8.73	6.06–8.08	3.79	1.61

Table 5: ^{13}C-NMR data of ligands (L) and some of the metal ion complexes

Compounds	HC=N	C-O	C-N	C-H aromatic	CH_3 proton
L	164.46	151.17	147.50	112.89–136.87	15.13
C_1	168.49	152.63	150.20	111.72–139.22	15.62
C_2	166.80	153.72	149.40	108.71–139.65	15.64
C_3	167.35	154.07	149.96	111.22–139.50	15.99
C_4	165.57	154.85	150.72	108.46–137.39	16.05
C_5	167.48	154.06	146.09	108.19–136.65	15.60

results which are given in this table were showed that all complexes have non-electrolytic nature [15].

Electronic spectra (UV-Vis) studies

The UV-Vis spectrum of the ligand (L) was showed the intense band at 31055 cm^{-1} which were belong to n→π∗ [13]. Ligand and its metal ion complexes [16] are described in Table 3 and their spectra (L and C_2) are shown in Figs. 3 and 4. The electronic spectra of the ligand and its metal ion complexes were recorded for their solution in DMSO at room temperature (10^{-4} M).

^{1}H-NMR/and ^{13}C-NMR spectra

The ligand was characterized by ^{1}H-NMR and ^{13}C-NMR spectroscopic methods, in addition of all complexes using DMSO d^6 as a solvent [17]. The ^{1}HNMR spectra results were listed in Table 4 and shown (L and C_3) in Figs. 5 and 6. The ^{13}C-NMR spectra results were listed in Table 5 and shown (L and C_4) in Figs. 7 and 8.

Thermal analysis of the ligand and their metal ion complexes

TGA and DTG of complexes were studied under nitrogen gas at heating range 25–600°C and heating rate (10°C/min). The thermal analysis was performed to proof the suggested structures and studied the thermal stability of the complexes. The results were listed in Table 6 and shown (C_5) in Fig. 9.

MS

MS has been successfully used to investigate molecular species in solution. The Schiff base (L) and its complexes were compared with their molecular formula weight. The MS of ligand and its complexes were shown a molecular ion peak at m/z=(393, 576, 661, 613, 620, and 646) for the ligand and its complexes, respectively. These data are good agreement with the proposed molecular formula for ligand and

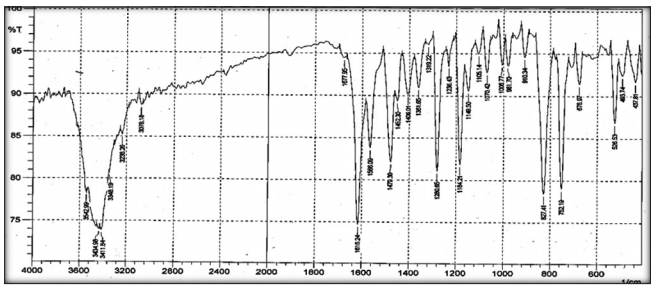


Fig. 1: Fourier transform infrared spectrum of ligand

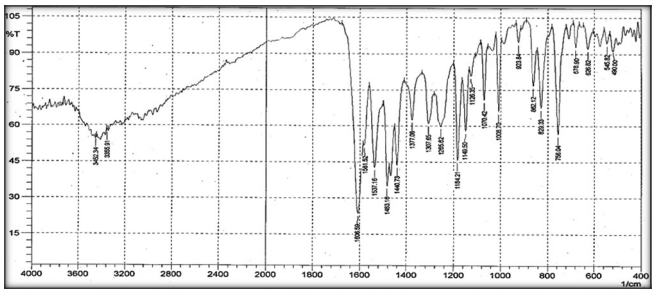


Fig. 2: Fourier transform infrared spectrum of C_1 complex

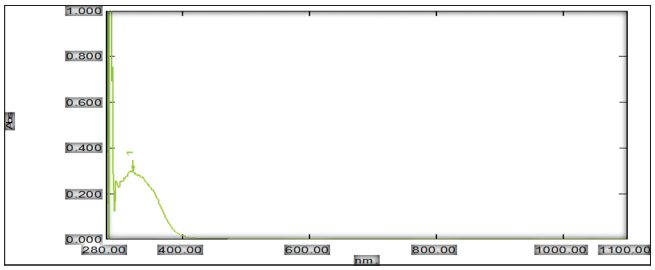


Fig. 3: Ultraviolet-visible spectrum of ligand

complexes. It also shows series of some peaks corresponding to various fragments. The intensities of these peaks give the idea of the stabilities of the fragments (supplementary material).

Cytotoxicity assays (anticancer activity)

The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated as the following equation:

Inhibition rate=A-B/A*100.

Where A and B are the optical density of control and the optical density of test.

The toxicity of many anticancer agents is partially due to the inability to distinguish between normal and tumor cells. We selected the compound for their primary anticancer assay [18]. To eliminate

Table 6: Thermal decomposition data of the ligand and complexes

Compounds	Molecular formula	Step	Temp. rang of the decomposition C°	Suggested formula of loss	Mass loss% Cal.	found
L	$C_{21}H_{17}N_2OBr393.28$	1	150–325>600	$C_{20}H_{14}BrN_2O$	96.34	96.08
				Residue (CH_3)	3.66	3.81
C_1	[Cu (L_2) $Cl_2.2H_2O$]	1	120–594>600	$2H_2O$,2Cl, Br, OH, CH_3	39.26	38.85
	563.44			Residue (Cu,3(C_6H_4) 2CN,CH)	60.74	61.15
C_2	[Cr (L_2) $Cl_3.H_2O$] $5H_2O$	1	110–595>600	$6H_2O$,3Cl, Br	44.88	44.64
	659.39			Residue (Cr, C_6H_4N, $CCH_3C_6H_4NCHC_6H_4OH$)	55.12	55.35
C_3	[Cd (L_2) $Cl_2.2H_2O$]	1	120–366>600	$2H_2OC_{21}H_{17}N_2OBr$	81.25	81.62
	612.41			Residue (Cd)	18.75	18.35
C_4	[Zn (L_2) $Cl_2.2EtOH$]	1	100–349	2EtOH, Cl,C_6H_4Br	46.17	45.61
	621.28	2	350–594>600	$C_6H_4NCCH_3C_6H_4NCHC_6H_4$)	34.80	35.41
				Residue (Zn,Cl,OH)	19.02	19.05
C_5	[VO (L_2) $SO_4.H_2O$] $4H_2O$	1	100–299	$5H_2O,SO_4$,OH	32.00	31.43
	645.84	2	300–427	CH_3,C_6H_4	13.98	14.09
		3	428–594>600	C_6H_4Br,CH	25.97	26.15
				Residue (VO,NC_6H_4CN)	28.05	28.32

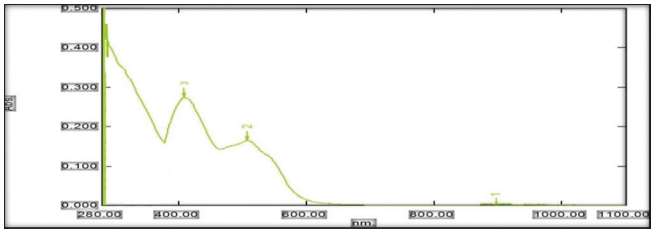


Fig. 4: Ultraviolet-visible spectrum of C_2 complex

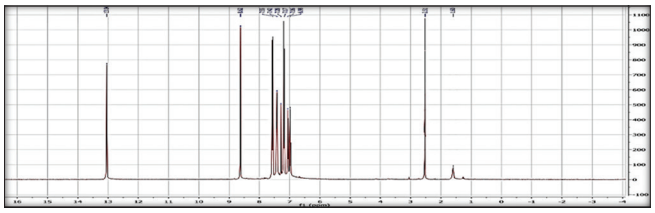


Fig. 5: ^{1}H-nuclear magnetic resonance spectrum of ligand

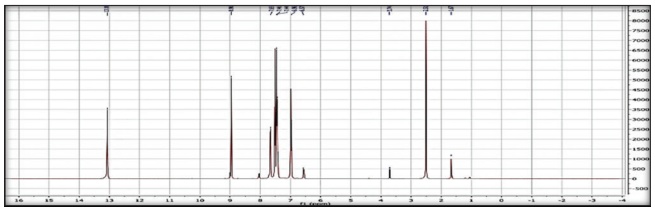


Fig. 6: ^{1}H-nuclear magnetic resonance spectrum of C_3 complex

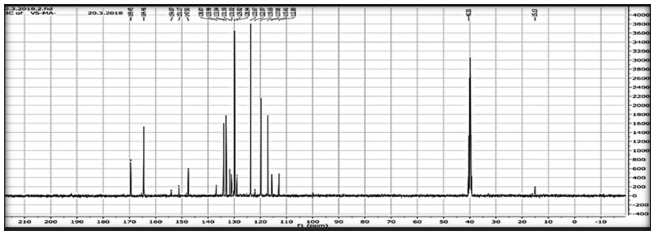


Fig. 7: ^{13}C-nuclear magnetic resonance spectrum of ligand

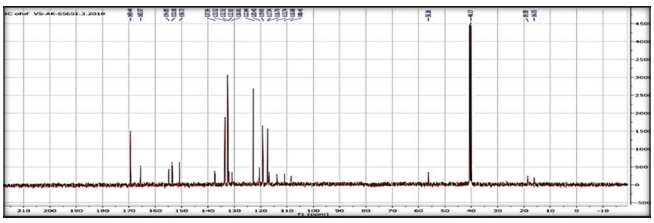


Fig. 8: ^{13}C-nuclear magnetic resonance spectrum of C_4 complex

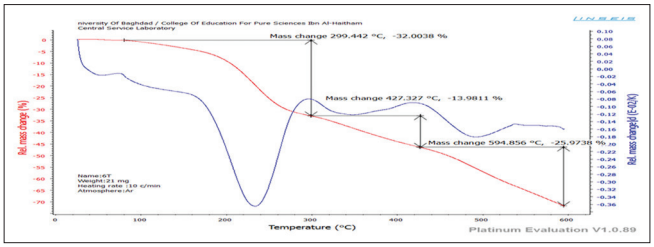


Fig. 9: The thermogram of C_5 complex

toxicity, it is necessary to identify some specific properties of cancer cells different from normal cells; numerous transition metal complexes have been synthesized and screened for their anticancer properties. In order to study the action of the ligand and its complexes to cancer cells. First measured the antiproliferation activity of these ligands and complexes by the MTT assay, and found that most compounds in most concentrations have the ability to kill human brain cancer cells, cervical cancer cells, ovarian cancer cells, and breast cancer cells in a concentration-dependent manner [19], also found that Schiff base ligand improves the anticancer properties of the complex. The increase in the percentage of cell inhibition may be due to the presence of Schiff base, but the mechanics are unknown, another suggestion of kill cancer cells that Schiff base azomethine linkage (–C=N) is an essential structural requirement for biological activities including antibacterial, antifungal, and antitumor activities. Cytotoxicity assays of ligand and its complexes are shown in Table 7 and Figs. 10 and 11 for L and C_1.

1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity

The percentage activity of solutions of the ligand (L) and their complexes was studied and compared. Initially, the free ligands were showed negligible DPPH activity, however, on linked with metal ions (Cu(II), Cr(III), Cd(II), Zn(II), and VO(II)) the activity was enhanced significantly. All the metal ion complexes were showed comparable or slight less activity to that of standard (ascorbic acid). All the metal ion complexes were showed much better activity than the ligands. The copper ion complexes were showed pronounced reducing power than the other metal ion complexes.

CONCLUSION

In this study, the prepared compounds represent a new group of dentate ligand exhibiting good complexes properties. The presence

Table 7: Cytotoxicity assays (AMJM) cells of ligand (L) and its complexes

Compound	IR% (C) µg/mL	PR% (C) µg/mL	Other effect cytotoxicity% (C) µg/mL		
L	56 (100)	6 (6.125)	38 (50)	32 (25)	27 (12.5)
C_1	87.5 (100)	20 (6.125)	75 (50)	69 (25)	63 (12.5)
C_2	85 (100)	19 (6.125)	64 (50)	37.5 (25)	31.5 (12.5)
C_3	94 (100)	13 (6.125)	59 (50)	63 (25)	69 (12.5)
C_4	82 (100)	9.5 (6.125)	75 (50)	69 (25)	63 (12.5)
C_5	63 (100)	15 (6.125)	50 (50)	25 (25)	25 (12.5)

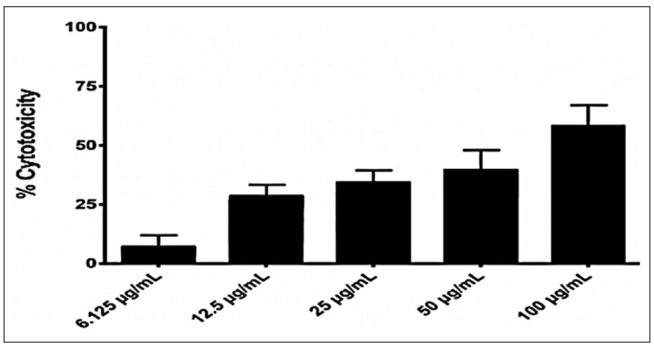


Fig. 10: Cytotoxic effect of ligand in AMJM

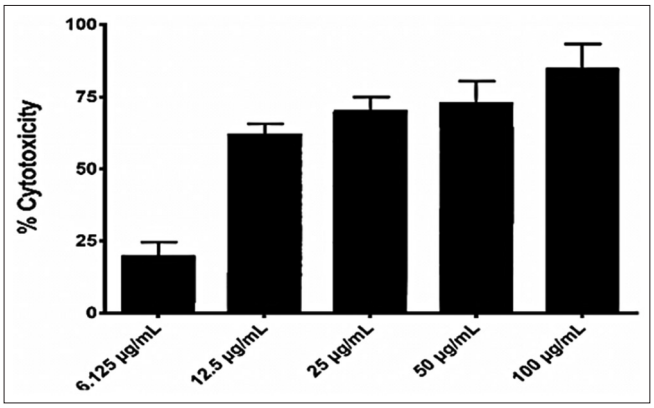


Fig. 11: Cytotoxic effect of C_1 in AMJM

of two donor atoms in this ligand may give various polynuclear metal complexes. In all complexes, the coordination of ligand to the metal ions took place through the nitrogen atom of azomethine and oxygen groups. All complexes found to be octahedral geometry around metal ions expected C_5 was pyramidal. All complexes were tested anticancer human activity. All complexes were tested antioxidant activity and anticancer activity

AUTHORS' CONTRIBUTION

All authors have contributed equally.

CONFLICTS OF INTEREST

Authors have no conflicts of interest.

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