



Synthesis , Spectral Characterization And Anticancer Studies of Novel Azo Schiff Base And its Complexes with Ag(I), Au(III) And Pt(IV) ions



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Abstract

A novel azo schiff base dye (L) have been Synthesized a reaction of 5- [2-(5-nitro thiazolyl)azo] -2-amino -4-methyl pyridine (NTAPy) with 4-chloro benzaldehyde in alkaline solution . Anew series of complexes with Ag(I), Au(III) and Pt(IV) ions were Prepared forming chelate complexes. The structure of azo schiff base ligand and its metal complexes were characterize by different spectral technique such as ¹H-NMR, ¹³C-NMR, mass spectrum, FT-IR, electronic spectra, C-H.N.S analysis, maganetic susceptibility, atomic absorpotion and molar conductivity. The analytical data suggest the mole ratio [M:L] was [1:1] for Ag(I) and Au(III) ions but [1:2] for Pt(IV) ion. The metal complexes of Au(III) and Pt (IV) was 1:1 and 1:2 electrolyte receptivity while the Ag(I) complex is non electrolyte . In this study the cytotoxicity of Ag(I), Au(III), and Pt (IV) complexes on human (PC₃) breast cancer and normal cells were MTT assay. The metal complexes showed selective cytotoxicit against breast cancer , this metal Complexes excelled in halting proliferation of PC₃ cancer cells with median inhibitory concentration (IC₅₀) values of Mg/ml , µg/ml and µg/ml for Ag(I),Au(III) and Pt(IV) complexes. The results indicate undoubtedly the possibility of using them as antitumor drugs in the field of pharmacy breast cancer.

Key words: Azo,schiff base; Metal complexes; Spectral studies; Anticancer (breast cancer)

1. Introduction

Azo- schiff base they are organic dyes containing two chromophore groups , namely the azo group (-N=N-) and azomethine (-CH=N-) [1]. The azo-schiff compounds are contained on the thiazole and Pyridine are very important class having enormous application in multiple fields such as biological activity, pharmaceutical, industrial, analytical reagents [2-5] some medicines are used in inhibition and killing of bacteria and fungus [6,7]. Azo schiff base compounds are used in optical and electrochemical sensors, inversion schroma to graphic methods and enhance selectivity of the organic reagents [8,9]. The azomethine (C=N) linkage in schiff bases imports in elucidating the mechanism of transamination and resamination reactions biological system[10]. Azo –schiff base dyes were used in applications in multiple field such as polymer paper, paint and coating industries as a dyeing

pigments [11-13]. Also they have been used as antibacterial antifungal, anticancer, intertubercular, hypertensive and hypother reagents [14]. Around a world big number of people are diagno with cancer each rear, and most of a patients die format [15]. Side effect problems of some drugs such as cis- Pt (II) have chemist to develop alternative anticancer drugs based on different metals . Several studies indicated that Ag(I), Pd(II), Au(III), Cu(II), Ni(II) and Pt(IV) complexes had showed some promising results [2,6,16-18]. In this work were port the synthesis, spectral characterization of azo–schiff base ligand and its metal complexes with Ag(I),Au(III) and pt (IV)ions derived from N-(4-chlorobenzylidene)-4-methyl-5-(5-nitro thiazol -2-yl)diazenyl)pyridine-2-amine (L). The cytotoxicity of metal complexes showed higher cytotoxicity against PC₃ Cell. It was also reported that matel complexes displayed antitumor properties and no nephrotoxic side effect. The metal complexes

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of azo-schiff base ligand (L) with Ag(I), Au(III) and Pt (IV) ions evaluated for in vitro anti-cancer activity against human breast cancer MCF₇ by MTT assay

2. Experimental

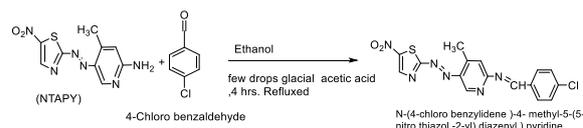
1.1. Materials and measurements

All chemical and solvents used were fluka , sigma , BDH and Aldrich . The azo dye compound 5-[2-(5-nitro thiazolyl)azo]-2-amino-4-methyl pyridine (NTAPy) was synthesized according to the literature procedure (Al-Adilee) [19]. Elemental analysis was carried out at Euro EA 1106 (C.H.N.S) Micro analyzer , ¹H and ¹³C-NMR spectra were determined in DMSO-d₆(internal standard TMS) on Bruker spectrometer (500 MHZ). Mass spectrum of azo-schiff base ligand were recorded on a shimadzu Agilent Technologies 597 ⁰C at 70 ev and MSD energy using a direct insertion probe (ACq method low energy) at 90-110 ⁰C temperatures . The FT-IR spectra of the azo - schiff base ligand (L) and its metal complexes were recorded from a shimadzu 8400S FT-IR spectro- photometer , in the (4000-400) Cm⁻¹ region in CsI discs . The chloride contents of Au (III) and pt (IV) complexes were determine by Mohr method [20]. The electronic spectra of the azo-Schiff base and its metal complexes were recorded on a T80-PG double beam UV-Visible. Spectrophotometer in the rang of 200-1100 nm in absolute ethanol (10⁻⁴ M) solution .The melting point of azo- schiff base and its metal complexes were taken on a stuart melting point apparatus 9300 and are uncorrected. Molar conductivity measurments were recorded on a 31 A digital conductivity meter in dry DMSO (10⁻³ M) solution and the metal contents of complexes were measured by using atomic absorption technique by a shimadzu AA-160.

1.2. Synthesis of novel azo-Schiff base ligand (L)

The azo-schiff base ligand (L) was synthesized according to the Known condensation method [20,21]. A mixture of 2.64 g (0.01 mol) of 5-[2-(5-nitro thiazolyl)azo]-2-amino-4-methyl Pyridine (NTAPY) with equivalent amount of corresponding 4-chloro benzaldehyde (1.49 g, 0.01 mol) in 40 ml of a absolute ethanol with few drops of glacial acetic acid as catalyst . The resulting mixture was left under

reflux for 4 hrs. on awater bath and the solid Product formed was separated by filtration , Purified by recrystallize from hot ethanol , washed with cold distilled water , and then dried . the Purity of the azo-schiff base ligand (L)was checked by TLC, (M.F= C₁₆H₁₁N₆O₂SCl, m.p=143⁰C , yield= 78%, orange crystals). The structure of azo-Schiff base ligand (L) has been Proven by ¹H and ¹³C-NMR, mass spectrum, IR and UV-Visible spectra . The following scheme (1) shows how to Prepare azo-schiff base ligand (L):



Scheme 1. Synthetic route of azo-schiff base ligand (L), N-(4-chloro benzylidene)-4-methyl-5-(5-nitro thiazol -2-yl) diazenyl) pyridine.

1.3. General method for the synthesis of Ag(I), Au(III) and Pt(IV) complexes

The metal complexes were prepared using metal chlorides but Ag(I) used AgNO₃. The mole ratio of metal complexes [M:L] are [1:1] for Ag(I) and Au (III) but 1:2,[M:L] for the Pt(IV) Complex in ethanolic solution (40ml). The metal complexes was refluxed on water bath for about (1hr). .The spertared solid metal compound were filtered off, washed with distilled water. The Ag(I) complex was prepared by using AgNO₃ and azo- schiff base ligand (L) at 1:1, [M:L] mole ratio in (40ml) hot buffer solution (ammonium acetate) at pH =7.0. The resulting solution were refluxed on water bath for about (2 hrs.). The Precipitate was filtered off, washed with distilled water. All metal complexes washed with little warm ethanol to remove any traces of unreacted materials. The metal complexes obtained were finally dried under desiccators over fused CaCl₂. The yield % , color, melting point, molecular wight, and element analysis data of azo-schiff base ligand (L) and its metal complexes are collected in table (1).

Table 1: Physical Properties and analytical data of azo- schiff base ligand (L) and its metal complexes.

Compound	Color	m.p °C	Yield %	Molecular formula (Mol.Wt)	Found(Calc.)%				
					C	H	N	S	M
Ligand=(L)	Orange	143	78	C ₁₆ H ₁₁ N ₆ O ₂ SCl (386.82)	(50.15) 49.68	(2.95) 2.78	(22.12) 21.73	(7.92) 8.29
[Ag(L)(ONO)(H ₂ O)]	Red	179	64	C ₁₆ H ₁₃ N ₇ O ₅ SClAg (572.73)	(34.92) 34.39	(2.37) 2.34	(18.16) 17.55	(6.61) 5.74	(19.79) 19.31
[Au(L)Cl ₂]Cl.H ₂ O	Yellowish Purple	185	81	C ₁₆ H ₁₃ N ₆ O ₃ SCl ₄ Au (708.15)	(27.65) 27.14	(1.89) 1.85	(12.45) 11.87	(4.92) 4.53	(28.37) 27.81
[Pt (L) ₂ Cl ₂]Cl ₂ .H ₂ O	Greenish blue	206	73	C ₃₂ H ₂₄ N ₁₂ O ₅ S ₂ Cl ₆ Pt (1128.54)	(34.53) 34.05	(2.24) 2.14	(15.51) 14.90	(6.21) 5.68	(17.74) 17.28

3. Result and Discussion

Characterization of novel azo-schiff base ligand and its metal complexes. The novel azo- schiff base dye (L) was orange crystals, but the prepared chelate metal complexes were powder and crystals with different colour depend on the metal ion. The azo-schiff base ligand and its metal complexes are stable to air at room temperature and insoluble in water but soluble in most organic solvents, including ethanol, methanol, acetone, DMF and DMSO. Electron attracting substituents such as nitro group (-NO₂) in the coupler increase the polarizability. This leads to a decrease in the energy gap between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), thus ($\pi \rightarrow \pi^*$). Electronic with lower frequency photon results in a bathochromic shift of the visible band for azo-schiff base ligand [22].

3.1. Metal : Ligand Ratio

The metal ligand ratio [M:L] of metal complexes were determined by mole ratio method [23-25]. The azo- schiff base ligand (L) was found [1:1], [M:L] mole ratio with Ag(I) and Au(III) ions but [1:2], [M:L] with Pt(IV) ion suggested the formation of metal complexes to give one five-membered ring with Ag(I) and Au(III) ions and two five membered chelate ring with Pt (IV) ion.

Table 2: Selected IR absorption bands (4000-400) cm⁻¹ for novel azo- Schiff base ligand (L) and its metal complexes (KBr disc).

Compound	ν (H ₂ O)	ν (-N=CH)	ν (C=N)	ν (NO ₂)	ν (C=C)	ν (C-Cl)	M-N
Ligand=(L)	-----	1620 s.	1615 m.	1520m. 1373 S.	1373 s. S	753 m.	-----
[Ag(L)(ONO)(H ₂ O)]	3354 m.br	1623 s.	1598 m.	1514m. 1356m.	1351 m.	756 m.	512 w.
[Au(L)Cl ₂]Cl.H ₂ O	3453 m.br	1621 s.	1610 m.	1524 S. 1367 m.	1328 m.	749 w.	536 w.
[Pt (L) ₂ Cl ₂]Cl ₂ .H ₂ O	3487 W.br	1620 s.	1596 m.	1528m. 1364S.	1321 m.	754 m.	517 w.

S= strong, m = medium, w= weak, br = shoulder

3.2. Conductivity measurements

The molar conductance values of metal complexes (table 2) in DMSO (10⁻³ M) medium indicate the Ag(I) complex is non-electrolyte but Au(III) and Pt(IV) Complexes is 1:1 and 1:2 electrolytes respectively indicate these complexes possess an electrolytic nature [26,27].

3.3. ¹H-NMR spectrum of azo- schiff base

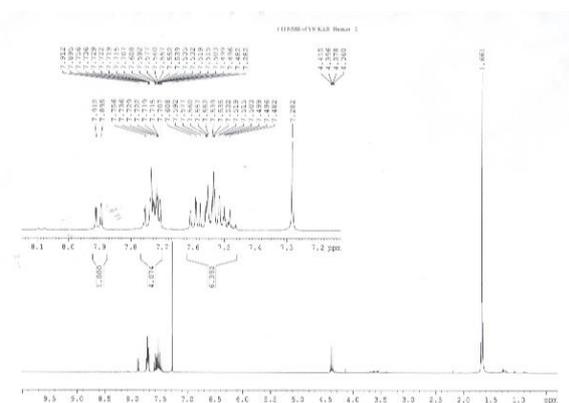
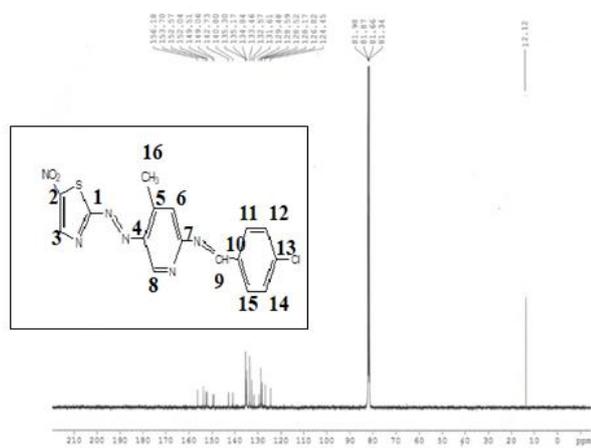
The ¹H-NMR (500MHz) spectrum of novel azo- schiff base ligand (L) (figure 1) was measured in DMSO-d₆ solvent with TMS as an internal reference. The ¹H-NMR spectrum ligand (L) shows a signal at $\delta = 1.66$ ppm (S,3H) due to the presence of -CH₃ groups a signal at 7.28 ppm (S,1H) due to the presence of proton H₄ of thiazole ring. Also, the same spectrum displays a signals at $\delta = 7.48-7.60$ ppm (m,4H,Ar-H) and $\delta = 7.71-7.76$ ppm (m,3H,Py-ring) due to the presence of aromatic protons. A signal at $\delta = 7.89-7.9$ ppm (D,1H) attributed to the presence of azomethine (-N=CH) proton, a signal at $\delta = 4.36-4.41$ ppm due to DMSO -d₆ solvent protons [19,28-30].

3.4. ¹³C-NMR spectrum of azo-schiff base ligand (L)

The ¹³C-NMR spectrum of novel azo-schiff base ligand (L) figure (2), was measured by using DMSO as solvent. The ¹³C-NMR spectrum provide further support the structural characterization of the azo-schiff base. The ¹³C-NMR spectrum of azo

Table 3: Electronic spectral data (nm, cm⁻¹), conductivities, proposed structure and hybridization of prepared metal complexes

Compound	λ_{Max} (nm)	Absorption Band (cm ⁻¹)	Assignment	Proposed structure	Hybridization ion	Λ_m S.cm ² . mol ⁻¹	M_{eff} (BM)
Ligand=(L)	401	24937	n \rightarrow π^*	-----	-----	-----
[Ag(L)(ONO)(H ₂ O)]	480	20833	d π (Ag ⁺¹ \rightarrow π^* (L)(C.T)	Tetrahedrol	SP ³	12.28	Diamag
[Au(L)Cl ₂]Cl.H ₂ O	568	17605	¹ A _{1g} \rightarrow ¹ B _{1g}	Square Planer	d sp ²	40.39	Diamag
[Pt (L) ₂ Cl ₂]Cl ₂ .H ₂ O	719	13908	¹ A _{1g} \rightarrow ¹ T _{1g(F)}) ₀₁	Octahedral (Regular)	d ² sp ³ (Low spin)	82.12	Diamag
	483	20704	¹ A _{1g} \rightarrow ¹ T _{2g(F)}) ₀₂				

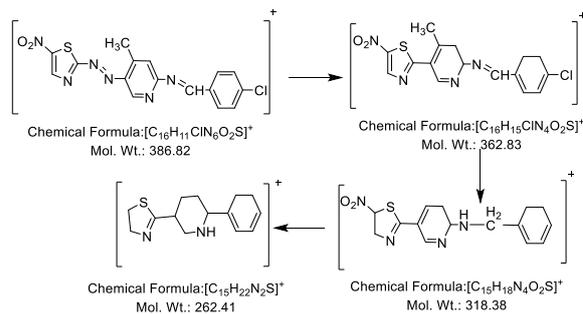
Fig. 1. ¹H-NMR spectrum of azo-schiff base ligand (L)Fig. 2. ¹³C-NMR spectrum of azo-schiff base ligand (L)

Schiff base ligand (L) show $\delta=12.12$ PPM (C₁₆), $\delta=165$ PPM(C₁), $\delta=153$ PPM(C₄), $\delta=152.5$ PPm (C₆), $\delta=152.0$ PPM (C₂), $\delta=149$ PPM(C₁₃) and $\delta=124-142$ PPM(C_{Aromatic}) [19,31,32]. The aromatic carbon present in the structure of azo-schiff base ligand were assigned by comparing the experimental chemical

shifts with those calculated from the increment method [33].

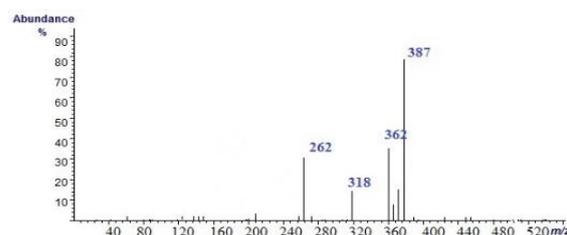
3.5. Mass spectrum of azo-schiff base ligand (L)

The mass spectrum fragmentation of novel azo-schiff base ligand (L) shown in scheme (2), figure (3). The mass spectrum of azo-schiff base ligand showed a molecular ion peak at $m/z = 387$ is due to the original molecular weight of ligand (C₁₆H₁₁N₆O₂SCl), 386.82. Other peaks like equivalent to its weight and correspond to various fragment. The intensity of these peaks gives the idea of the stability of fragments [19,34].



Scheme 2

Fig. 3. Mass spectrum of azo-schiff base ligand(L).



3.6. IR Spectra

Infrared spectral data of prepared novel azo-schiff base ligand (L) and their metal complexes with Ag(I), Au(III) and Pt (IV) (KBr disc, ν cm⁻¹) are Presented in table (2). The spectra of all metal complexes show abroad band around at (3456-3487)

cm^{-1} indicates the Presence of a water molecule ν (H_2O) . Two weak absorption bands had been observed at 3093 cm^{-1} and 2969 cm^{-1} in spectrum of free ligand (L) which are due to ν (C-H) aromatic and aliphatic ν ($-\text{CH}_3$) respectively . These bands have not change in position and intensity for both ligand (L) and metal complexes. IR spectrum of free azo- schiff base exhibited a band at 1620 cm^{-1} was attributed to ν ($-\text{N}=\text{CH}$) stretch of the azomethine group [35]. This band no shifted in position or change in the shape of the metal complexes. A medium intensity band at 1489 cm^{-1} in the free ligand was attributed to azo group, ν ($-\text{N}=\text{N}-$) stretch [36,37]. This band shifts to lower wave number side ($1446\text{-}1472$) cm^{-1} in all metal complexes indicating the coordination of the azo group with metal ions suggest that the ligand behaves a bidentate N,N donor molecule chelating agent trough the nitrogen of atom of thiazole ring and nitrogen of azo group nearest to pyridine ring to give five membered metalo ring [19,37].

5.7. Stimulation of chloride

Chloride was determined gravimetrically as silver chloride [38]. The sample was acidified with 5 N of HNO_3 and 1% silver nitrate solution was added , till the Precipitation was complete. The Precipitate was filtered through a G-4 sintered glass crucible, dried at 110°C and weighed as silver chloride [39].

5.8. Electronic Spectral Studies

The electronic absorption spectra of azo- schiff base ligand (L) and their metal complexes with Ag(I), Au(III) and Pt(IV) were recorded in freshly Prepared ethanol solution (10^{-3} M) at room temperature in the UV-Visb. region (200-1100) nm. The spectral data of free ligand and its metal complexes are presented in table (3). UV-Visb. spectral studies of the metal complexes exhibit transition at higher transitions than

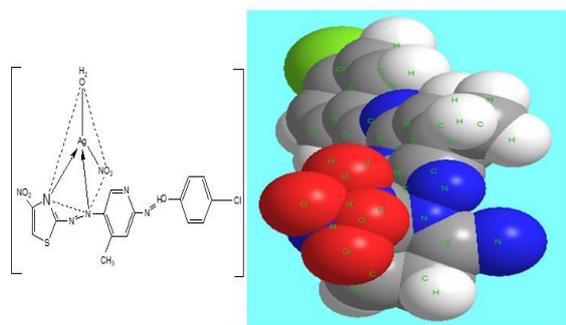


Fig. 4. The Proposed chemical structure of Ag(I) –Complex

400 nm corresponding to Intramolecular ($n \rightarrow \pi^*$) and ($\pi \rightarrow \pi^*$) transitions of azo-schiff base ligand (L) [40]. Intense absorption bands appear in the range (480-719) nm for the metal complexes which may be assigned to ($M \rightarrow \pi^*$) (ligand) charge transfer transitions [40,41].

According to these spectral and analytical results and discussed the data through different techniques suggest the geometrical structures for the Prepared metal

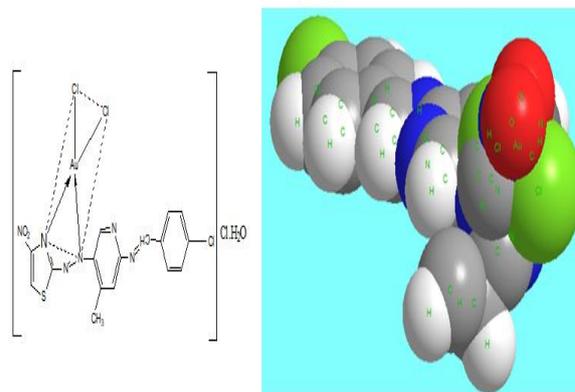


Fig. 5. The Proposed chemical structure of Au(III)-Complex.

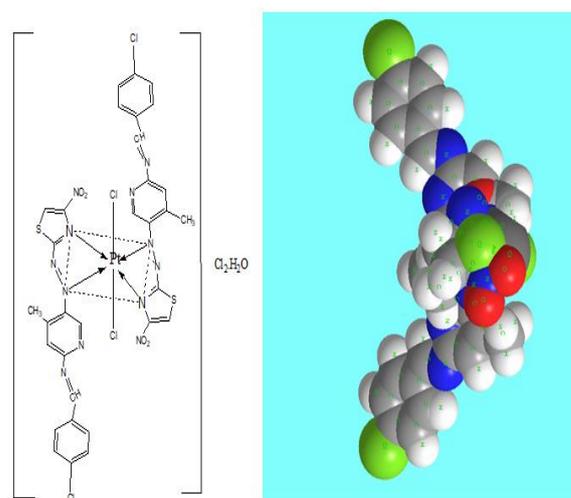


Fig. 6. The Proposed Chemical Structure of Pt(IV)- Complex

complexes may be proposed in figures 4,5 and 6.

3.9. Maintenance of Cell Cultures

MCF-7 Cell line were maintained in RPMI-1640 supplemented with 10% Fetal bovine , 100 units/mL Penicillin , and 100µg / mL streptomycin. Cells were passaged using trypsin -EDTA reseeded at 80% confluence twice a week and incubated at 37 °C.

3.10. Cytotoxicity Assays

To determine the cytotoxic effect of x-substances, the MTT cell viability assay was done using 96-well Plates. cell lines were seeded at 1×10^4 Cells / well, after 24 hrs or a confluent monolayer was achieved, cells were treated with tested compounds . Cell viability was measured after 72 hrs. of treatment by removing the medium, adding 28ml of 2 mg/ml solution of MTT and incubating the cells for 2.5 h at 37 °C. After removing the MTT solution , the crystals remaining in the wells were solubilized by the addition of 130 mL of DMSO (Dimethyl Sulphoxide) followed by 37 °C incubation for 15 min with shaking [42]. The absorbency was determined o amicroplate 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:

$$\text{Cytotoxicity} = \frac{A-B}{A} * 100$$

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

3.11. Biologic Study on Cancer Cells

After studying the biologic activity of the ligand Prepared one type of cells and identifying the most effective ligand of the biological ligand (L), with Au (I), Ag(III) and Pt(IV) ions the pharmacology efficacy of the enzyme as well as its pharmacological efficacy on the infected carcinoma this study showed that this ligand has a high pharmacological efficacy. The effect of this ligand Anticancer cells was studied in five different concentrations. The results showed that when the concentration of 100 µg /ml cells infected the response rate(70%) to ligand(L) and its metal complexes with Ag (I), Au(III) and Pt(IV) ions as shown in figures (7,8 and 9).

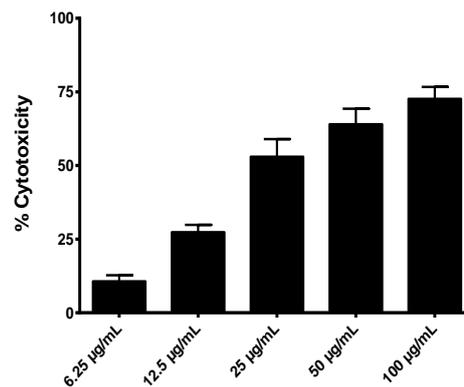


Fig.7. Cytotoxicity effect of Ag(I)- complex in MCF-7 cell line, IC50=22.14 µg/ml.

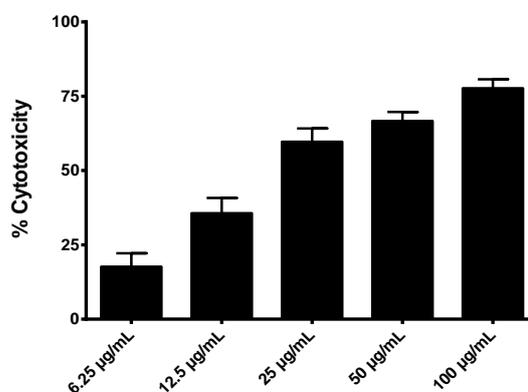


Fig. 8. Cytotoxicity effect of Au(III)- complex in MCF-7 cell line, IC50=16.81 µg/ml .

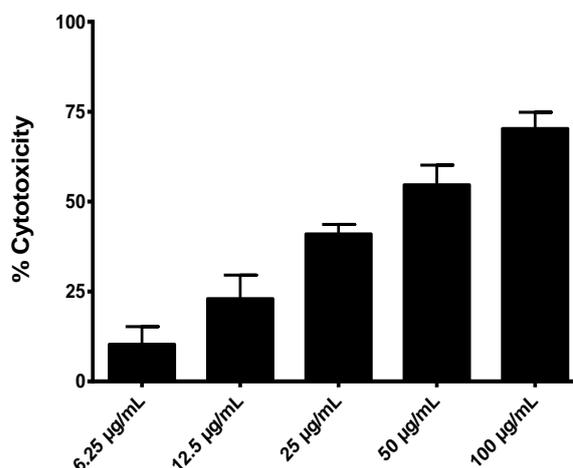


Fig. 9. Cytotoxicity effect of Pt (IV)- complex in MCF-7 cell line , IC50=39.22 µg/ml.

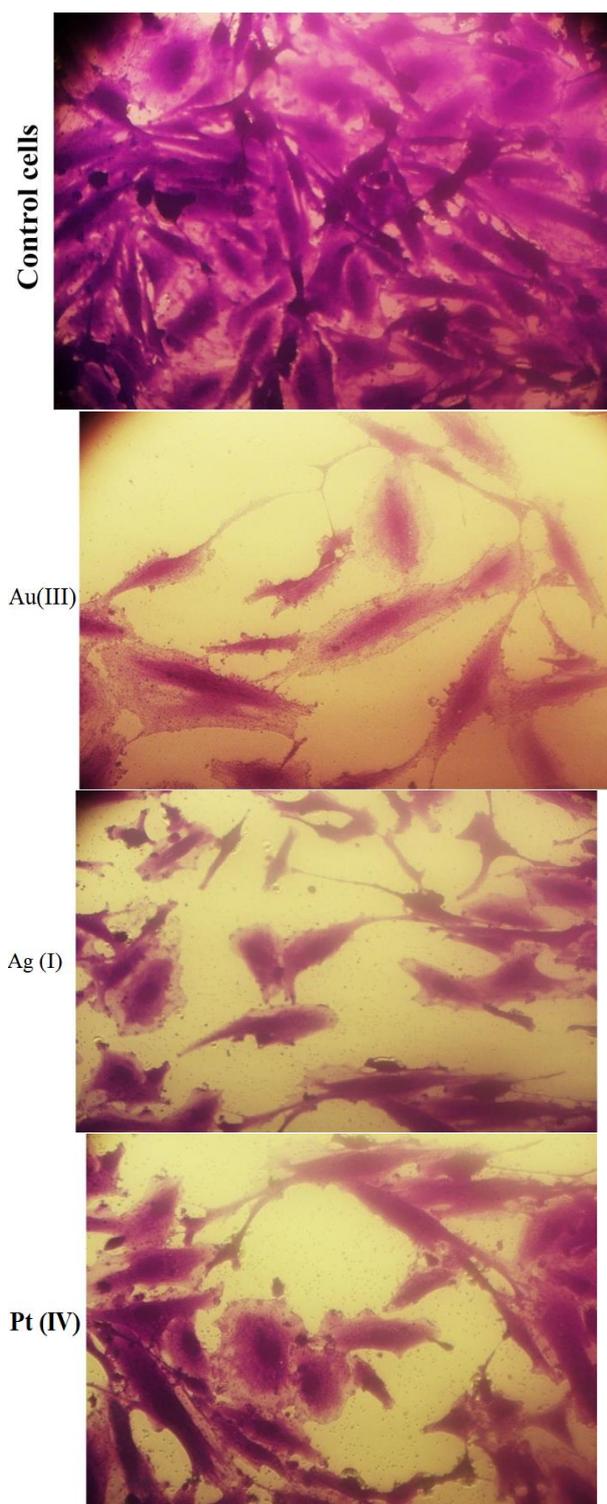


Fig. 10. Anti proliferative activity of metal complexes in MCF-7 cell.

4. Conclusions

From the above studies it can be concluded that the synthesized ligand (L) and its metal complexes with Ag (I) , Ag(III) and,Pt(IV)the ligand

that appeared Anti proliferative activity of in MCF-7 cell. Shown in the fig. (10).

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