Synthesis, Characterization and Spectral Studies of Some Metal Ions Complexes with New Schiff Base Ligand Derived From 6-Amino Penicillanic Acid And Biological Screening Study For The Pt(II) Complex.

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Abstract

The complexes of Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II) and Pt(II) were prepared from the complexation reaction between the new Schiff base ligand and selected metal ions. Ligand was derived from the condensation reaction of Oxo(4-(pyridin-2-yl)phenyl) methyline, 4-amino antipyrine, and (6-amino Penicillanic acid). The ligand and its complexes were characterized by C.H.N elemental analysis, Uv-Vis, FT-IR, and molar conductivity, Atomic absorption, magnetic moment measurements and mass spectra studies. The results of their studies show the coordination sites for the ligand with the metal ion were to be through oxygen, nitrogen atoms of 6-amino penicillic acid, and the nitrogen atom of 4-amino antipyrine. The complexes were found to have the general formula $[(M)(L)_2]Cl_2$ where M = Co(II), Ni(II), Cu(II), Zn(II), Hg(II), and Cd(II), except the [Pt(L)Cl]Cl. The electronic spectral and magnetic measurement data indicated that the complexes exhibited octahedral geometry, except the Pt(II) complex suggested a square planar geometry around the central metal ion. The ligand forms shape as natural tridentate manner. The biological activity results showed the inhibitory effect for platinum(II) the complex. In this study the cytotoxicity of Pt(II) complex on human colon cancer cell line LS 174 T CRC was investigated and African green monkey kidney cells normal cells were MTT assay. The metal complex showed selective cytotoxicity against colorectal, this metal Complex excelled in halting proliferation of LS 174 T CRC cancer cells line with median inhibitory concentration (IC_{50}) values of Pt(II) complex. The results indicate undoubtedly the possibility of using them as antitumor drugs in the pharmacy colon field cancer.

Keywords: *6-amino penicillic acid; New Schiff base; Transition metal complexes; antitumor (colon cancer).*

Introduction

Schiff base composites have been widely studied in the field of coordination chemistry mainly due to their facile syntheses, easily availability, electronic properties, biological applications and good solubility in common solvents and they easily form stable complexes with most transition metal ions[1,2]. Studies have shown that the azomethine group (-CH=N-) is a donor-acceptor group and is an acceptor through the π- orbital of the double bond, and a doner through the non-acceptor of electrons to the nitrogen atom of this group [3]. In addition to, azomethine of chelating compounds containing a group (CH=N-) with high activity [4], and its derivatives of 6- amino Penicillanic acid and its complexes have wide applications both in the medical field, pharmaceutical [5], as chemical stimulation[6],in addition to their physiological applications as, and impartment as antibacterial and antifungal[7,8].

The aim of this paper is to synthesize, characterize and study the biological screening of the platinum(II) complex as against several organisms of the new tridentate natural Schiff base ligand[6-(((Z)-1,5-dimethyl-2-phenyl-4-(((E)-4-(pyridin-2-yl)benzylidene)amino)-1,2-dihydro-3H-pyrazol-3-ylidene)amino)-3,3-dimethyl-7-oxo-4-thia-1azabicyclo[3.2.0]hept-5-ene-2-carboxylic acid] and some of its transition metal complexes.

Measurement

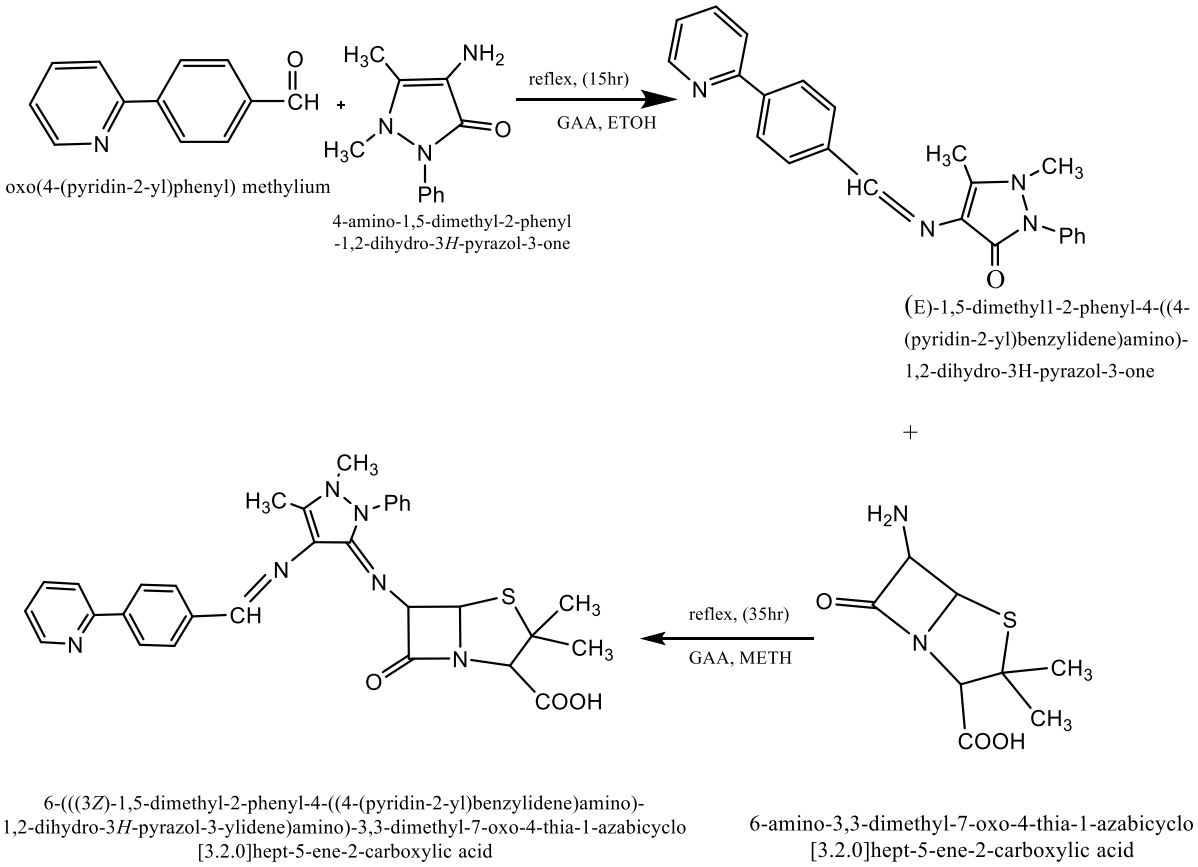
The electro thermal melting point model 9300 was used to measure the melting point of the ligand and its complexes. Elemental analyses were carried out by means of micro analytical unit of 1180 (C.H.N)elemental analyzer. Electronic spectra were recorded on Shimadzu spectrophotometer double beam model 1700 Uv-Vis spectrophotometer-FTIR spectra were recorded in KBr disc on FTIR Shimadzu spectrophotometer model 8400 in wave number(4000-400)cm^{-1}. Magnetic susceptibility were carried out on a balance magnetic(MSB-MKI)using faraday method. The diamagnetic corrections were made by Pascal's constants.

Preparation of the new Schiff base ligand 6-(((Z)-1,5-dimethyl-2-phenyl-4-(((E)-4-(pyridin-2-yl)benzylidene)amino)-1,2-dihydro-3H-pyrazol-3-ylidene)amino)-3,3-dimethyl-7-oxo-4-thia-1azabicyclo[3.2.0]hept-5-ene-2-carboxylic acid:

The Schiff base ligand was prepared in two steps: In the first step, prepared by condensation of (0.01 mol) of Oxo(4-(pyridin-2-yl)phenyl) methyline with 4-amino antipyrine (0.01mol) in equimolar (1:1) mole ratio in ethanol absolute, Few drops of glacial acetic acid were added to the reaction mixture and refluxed

for (15 h). The product was recrystallized from ethanol and dried over anhydrous $CaCl_2$. The reaction mixture gave one product.

The second step included the preparation of the final Schiff base ligand by reacting a solution (0.01 mol) of the compound prepared in the first step that dissolved in (50mL) of methanol with a solution (0.01 mol) of 6-amino penicillanic acid in the same solvent, then (2-3) drops of (%10 NaOH) were added and the mixture was reflexed for (35 h) with continuous stirring, where it was noticed that the color of the hot mixture solution changed to a dark orange colour, it was recrystallized and its melting point was measured and it was (150-152 ^{0}C). Scheme1 shows of the preparation of (Schiff base) ligand



Scheme.1:preparation of new Schiff base ligands.

Preparation of metal complexes:

Complexes of the ions Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), and Pt(II) were prepared by the mixing of (50 mL) ethanolic solution with (1mmol) From the Schiff base ligand dissolved in (50 mL) from the same solvent in (1:2) (metal: ligand) ratio. except the Pt(II) complex was (1:1) (metal: ligand) ratio. the resulting mixture was refluxed for (1h). The product was isolated after reduced of volume by evaporation. It was filtered off , washed with ethanol and dried under vacuum. The complexes obtained are listed in Table 1.

Biological Part

Cytotoxicity Assay

The anticancer activity of platinum(II) complex with Schiff base ligand in against LS 174T CRC and vero was evaluated by MTT assay, (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazoliun bromide) MTT assay. Chromatography is an established method for determining cell viability and cytotoxicity studies. This assay is based on the cleavage of yellow tetrazolium salt, MTT, to form a soluble blue formazan product by mitochondrial enzymes (growth cells), and the amount of formazan produced is directly proportional to the number of live cells, not dead cells, present during MTT exposure. Since the MTT test is fast, easy and economical, In this method, it has become a very popular method for quantifying live cells. Cell lines were cultured on 96 well plates at a concentration of 1.0 x $l0^5$ cells/ml. After being kept in incubation at 37°C for 48 hrs and once the fused monolayer of HT-29 VERO cells is completed (80% - 100%), the prepared concentrations are added (1 µg/mL,10 µg/mL, 100) µg/mL, 250 µg/mL, 500 µg/mL and 1000 µg/mL) of [Pt(L)Cl]Cl and 5FU to growth cells with a final volume of 100 µl in each hole except for the untreated (form-free) control cells. The plank and tripled three holes for each concentration. The maximum concentration of DMSO (0.01%) was used as a negative control. After 48 hrs incubation at 37 °C in 5% CO_2, the well plates were transferred to a biosafety cabinet with a sterile environment to avoid any contamination. All plate medium used was discarded. The well was washed with PBS solution to remove any residual platinum complex and 5FU solutions that might interact with MTT reagents, then 100 µl of retaining medium was added to all pits containing the treated drug. Cells, drugs, untreated cells and empty pits. Then MTT reagent (20 µl) was added to each plate. After 4 hrs of incubation at 5% CO_2, 37 °C, formazan crystals were observed as a mitochondrial enzymatic process of unaffected organelles were disrupted. Formazan was dissolved by adding 100 µl of solubilization solution Dilute DMSO (1:1 in isopropanol) was formed on each hole including the blank. The

absorbance was read at 490 nm at a reference wavelength of 630 nm by an ELASIS READER. The measurement mechanism of the MTT test is reported in Several sources The average Blank absorption was subtracted from other samples and the pit absorption was adjusted. The same method was performed for VERO normal cells.

Results and Discussion:

All our complexes are freely soluble in DMF, DMSO, methanol and ethanol. Also they are stable in air. The metal complexes were characterized by elemental analysis, molar conductivities, magnetic susceptibility, IR, Uv-Vis, Mass spectra. The analytical data of the complexes are in agreement with the experimental data. The value reveal that the metal to ligand ratio is(1:2).The magnetic susceptibility of the chelate complexes at room temperature were consistent with octahedral geometry, except the Pt (II) complex suggest a square planar geometry around the central metal ion. Most of chelate complexes prepared in this work showed conductivity values of the complexes. This proves that complexes have electrolytic nature.

Micro analysis:

The elemental analysis data of complexes showed that the theoretical values are in a good agreement with the found data, as listed in table (1). The purity of Schiff base ligand and its complexes were tested by TLC technique and C.H.N analysis.

Table.1: Shows the percentages and some physical properties of new Schiff base ligand and its metal complexes

NO.	Chemical formula	M.wt g/mol	M.p	Color	Yield %	*Found (Calc.)%*			
						%C	*%H*	*%N*	*%M*
1	L: $[C_{31}H_{30}N_6SO_3]$	566	150-152	Dark Orange	74	(65.72) 65.11	(5.30) 5.76	(14.84) 13.98	-----
2	$[Co(L)_2]\ Cl_2$	1261.9	>300	Pale Brown	81	(58.95) 58.32	(4.75) 4.65	(13.80) 13.87	(4.66) 4.87
3	$[Ni(L)_2]Cl_2$	1261.7	>300	Brown	75	(58.96) 57.89	(4.75) 4.87	(13.31) 13.76	(4.65) 4.87
4	$[Cu(L)_2]Cl_2$	1266.5	-133 130	Green	78	(58.74) 58.87	(4.73) 4.23	(13.26) 12.46	(5.01) 5.98
5	$[Zn(L)_2]Cl_2$	1268.09	129-	Brown	76	(58.67)	(4.73)	(13.24)	(5.13)

			132			58.98	4.36	12.99	5.34
6	$[Cd(L)_2]Cl_2$	1315.4	230-233	Yellow	80	(56.56) 55.89	(4.56) 4.88	(12.77) 12.62	(8.54) 8.32
7	$[Hg (L)_2]Cl_2$	1403.5	108-112	Brown	76	(53.01) 53.51	(4.27) 4.79	(11.97) 11.42	(14.28) 14.42
8	[Pt(L)Cl]Cl	832.05	195-197	Green	77	(44.70) 44.82	(3.60) 3.71	(10.09) 10.55	(23.44) 23.61

Infrared spectra studies of the ligand and its complexes

The FTIR spectra provided valuable information regarding the nature of the functional group attached to the metal atom. The most important infrared spectral bands that provided conclusive structural evidence for the coordination of the ligand to the central metal ions are given in Table 2. The FI-IR spectrum of the ligand shows characteristic bands at (1698 and 1653) cm^{-1} due to the (C=N) functional group [9]. The (C=N) and band in the free ligand shift to (1666-1597) cm^{-1} for the complex, these shifts confirm the coordination of the ligand via the nitrogen of azomethine group to metal ions [10,11]. The absorption band in ligand Schiff base observed at (1681) cm^{-1} attributed to the υ β(C=O), this band changed in the spectra of their complexes[12]. New bands are attributed to υ(M-N), (M-O) vibrations appearance in all complexes at (592-514) cm^{-1}, (453-414) cm^{-1} respectively [13,14]. It was established that the ligand acted the role of tridentate ligand harmonized to metal ions through O atom of the carbonyl group of β-lactam and N atoms of imine groups for all easily. The spectra data of the new Schiff base ligand and the Cu(II) complex were shown in (Figure 1 and 2).

Table. 2: Characteristic IR absorption bands of the ligand and its complexes.

Compounds Formula	υ(OH) carboxyl group	υ (β(C=O)	υ (C=N)Schiff	υ(C-S)	υ(M-N)	υ(M-O)
L_1: $[C_{31}H_{30}N_6SO_3]$	3435	1681	1653, 1698	1016	-------	------
$[Co(L_1)_2]$ $Cl_2.H_2O$	3441	1765	1666, 1633	1012	590	453
$[Ni(L_1)_2]Cl_2$ $.H_2O$	3402	1700	1633, 1602	1016	567	445
$[Cu(L)_2]Cl_2$	3419	1681	1600, 1639	1022	518	441
$[Zn(L)_2]Cl_2$	3437	1700	1653, 1602	1012	592	414

$[Cd(L)_2]Cl_2$	3441	1676	1600,1633	1014	514	450
$[Hg(L)_2]Cl_2$	3444	1678	1597	1012	592	422
[Pt(L)Cl]Cl	3429	1765	1645,1604	1016	592	422

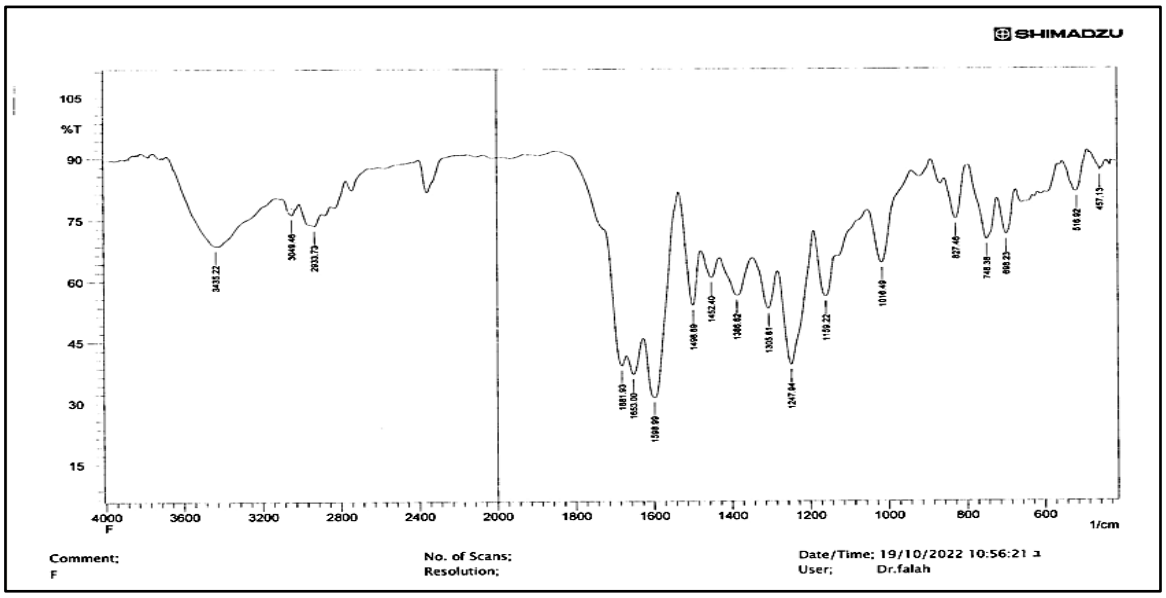


Fig. 1:FTIR spectrum of new Schiff base ligand

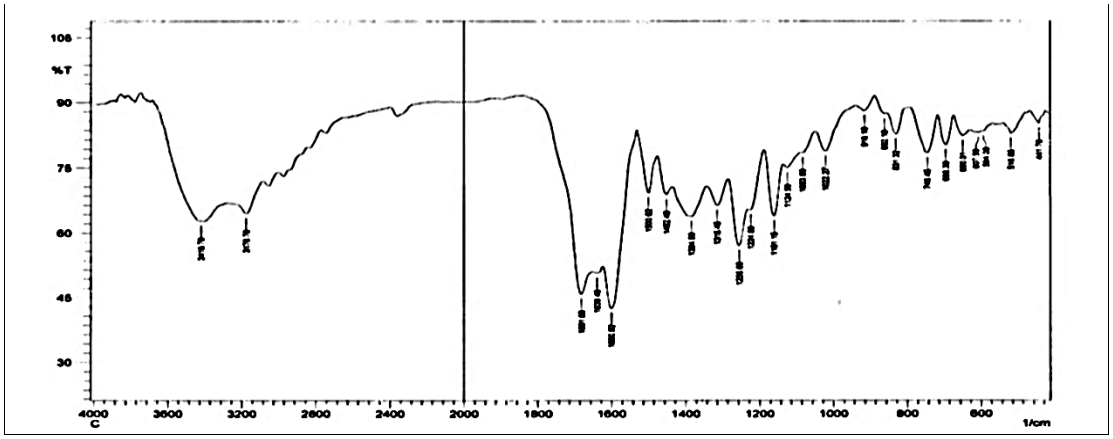


Fig. 2:FTIR spectra of Cu (II) complex.

Electronic spectra

Ultraviolet – visible spectra is one of on important methods used in the field of coordination chemistry, it is studied and compared metal complexes spectra with free ligand spectra .

The electronic absorption spectra of the new Schiff base ligand and its complexes were recorded in freshly ethanol solution (10^{-3}) at room temperature. Their relevant data shown in Table.3

The new Schiff base ligand shows two charge transfer (C.T) absorption bands in the region Uv-Visible at (274) nm (36496) cm^{-1} consigned to ($\pi\rightarrow\pi^*$), and (332) nm (30120) cm^{-1} that has been allocated to($n\rightarrow\pi^*$). In the metal complexes, these absorption bands undergo of charge transfer (LM-CT) transition in the complexes indicating that the Schiff base ligand are coordinated to the metal ions [15,16], suggesting an octahedral geometry around metal(II) in the complexes [17,18], except the Pt(II) complex, which had square planar geometry [19,20]. The UV-Vis spectra of the new Schiff base ligand and Cu(II) complex are shown in (Figure 3).

Magnetic measurements and Conductivity measurement

$\mu S+L=\sqrt{4S(S+1)+L(L+1)}$ B.M **XM=Xg×Mwt (1)**

$\mu s=\sqrt{4(S+1)}$ B.M, S=n/ 2 **XA =XM – D (2)**

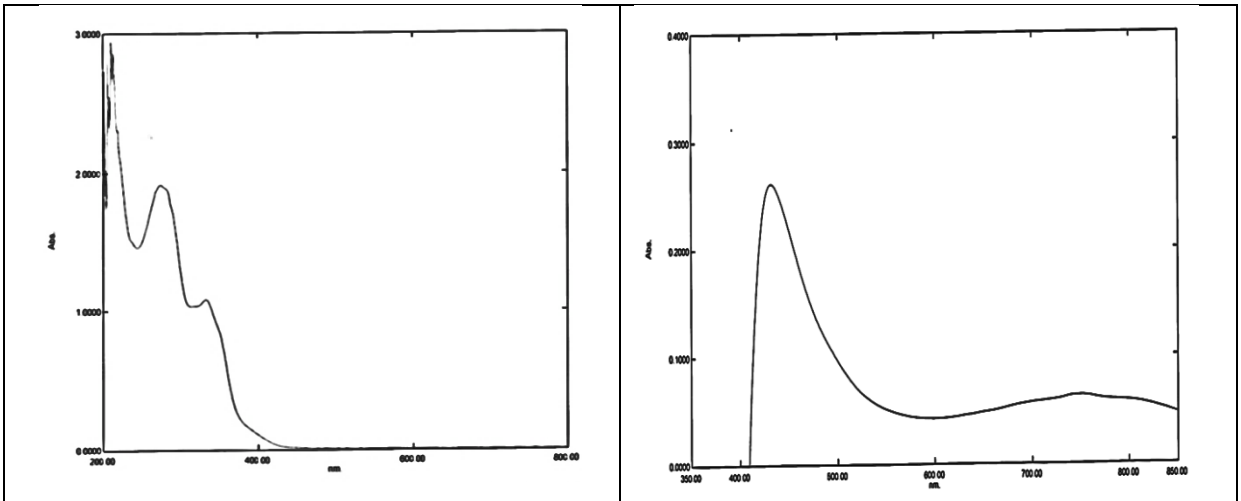
$\mu s=\sqrt{(n+2)}$ B.M **μ eff= 2.82√X A.T (3) B.M**

The Co(II) complex had a magnetic moment of 4.8 BM that is consistent with 3 unpaired electrons, which was in agreement with the reported value for octahedral Co(II) complexes [20]. The present Ni(II) complex showed a magnetic moment value of 3.0 at room temperature that is resultant to 2 unpaired electrons within the range of 2.9-3.3 BM [21], suggesting an octahedral environment. The Cu(II) complex showed a magnetic moment value of 1.73 BM, which was monomeric and consistent with a distorted octahedral geometry [22]. The Zn(II), Cd(II), and Hg(II) were diamagnetic and according to the empirical formulae of complexes for the reason of being diamagnetic in nature (d^{10}) [23]. An octahedral geometry was proposed [24], except the Pt(II) complex suggested a square planar geometry around the central metal ion [25]. Based on the above results, we could deduce the probable.

Most of the chelate complexes prepared in this work showed the conductivity values ranged between (78-54) S cm^2/mol in DMSO at room temperature, which were very low values. This could support the electrolytic nature of the metal complexes[26,27]. According to these results, the structural formulae of these ligand and complexes may be proposed in **Fig. 9**

Table 3: Electronic spectra (nm, cm^{-1}), geometry, hybridization and conductivity.

Compounds Formula	Absorption Bonds (nm)	Absorption Bonds (/cm)	Transition	Conductivity (S cm2/mol)	Geometry	Hybridization
L: $[C_{31}H_{30}N_6SO_3]$	274 332	36496 30120	π– π* n– π*	-----	-----	-----
$[Co(L)_2]\ Cl_2.H_2O$	358	27932cm^{-1}	M→L,C.T	76	Octahedral	sp^3d^2
$[Ni(L)_2]Cl_2\ .H_2O$	435	22988	M→L,C.T	73	Octahedral	sp^3d^2
$[Cu(L)_2]Cl_2$	432	23148	M→L,C.T	76	Octahedral	sp^3d^2
$[Zn(L)_2]Cl_2$	425	23529	M→L,C.T	70	Octahedral	sp^3d^2
$[Cd(L)_2]Cl_2$	433	23094	M→L,C.T	78	Octahedral	sp^3d^2
$[Hg(L)_2]Cl_2$	414	24154	M→L,C.T	78	Octahedral	sp^3d^2
[Pt(L)Cl]Cl	431	23201	M→L,C.T	54	Square-planar	dsp^2



A B

Fig. 3:Electronic spectrum of **(A)** the new Schiff base ligand and **(B)** Cu(II)complex.

Mass spectrum of Schiff base ligand

Mass spectrum of Schiff base ligand is given in Fig.4 The mass spectrum pattern give the expected molecular ion peak at (m/z^+ 566), confirming the proposed formula for preparation ligand and in good agreement with their

formula as expressed from micro analytical data. The mass spectral data fragmentation of the ligand shown in Scheme 2.

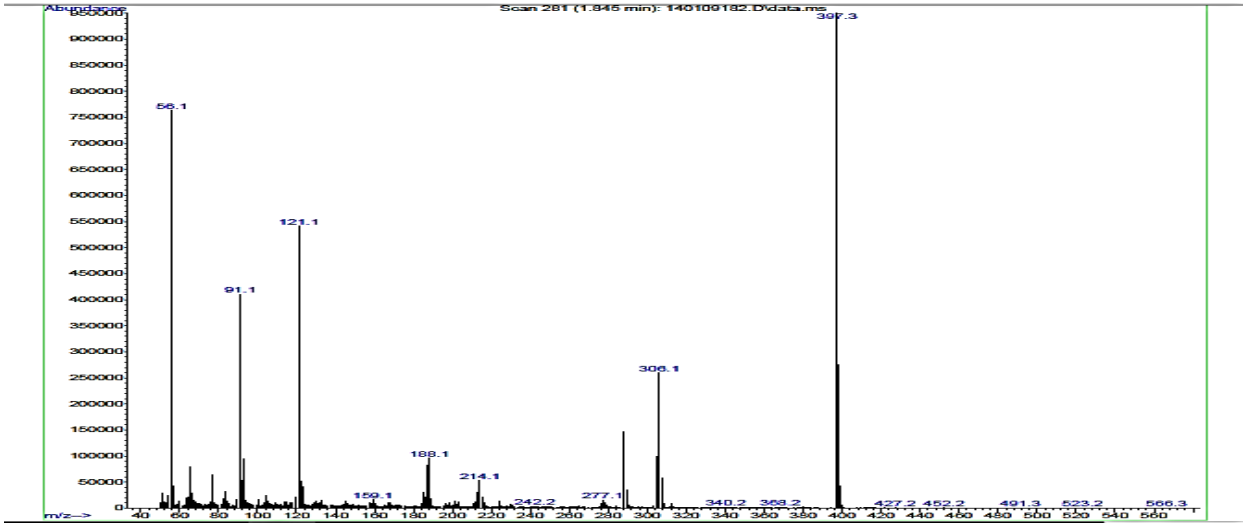
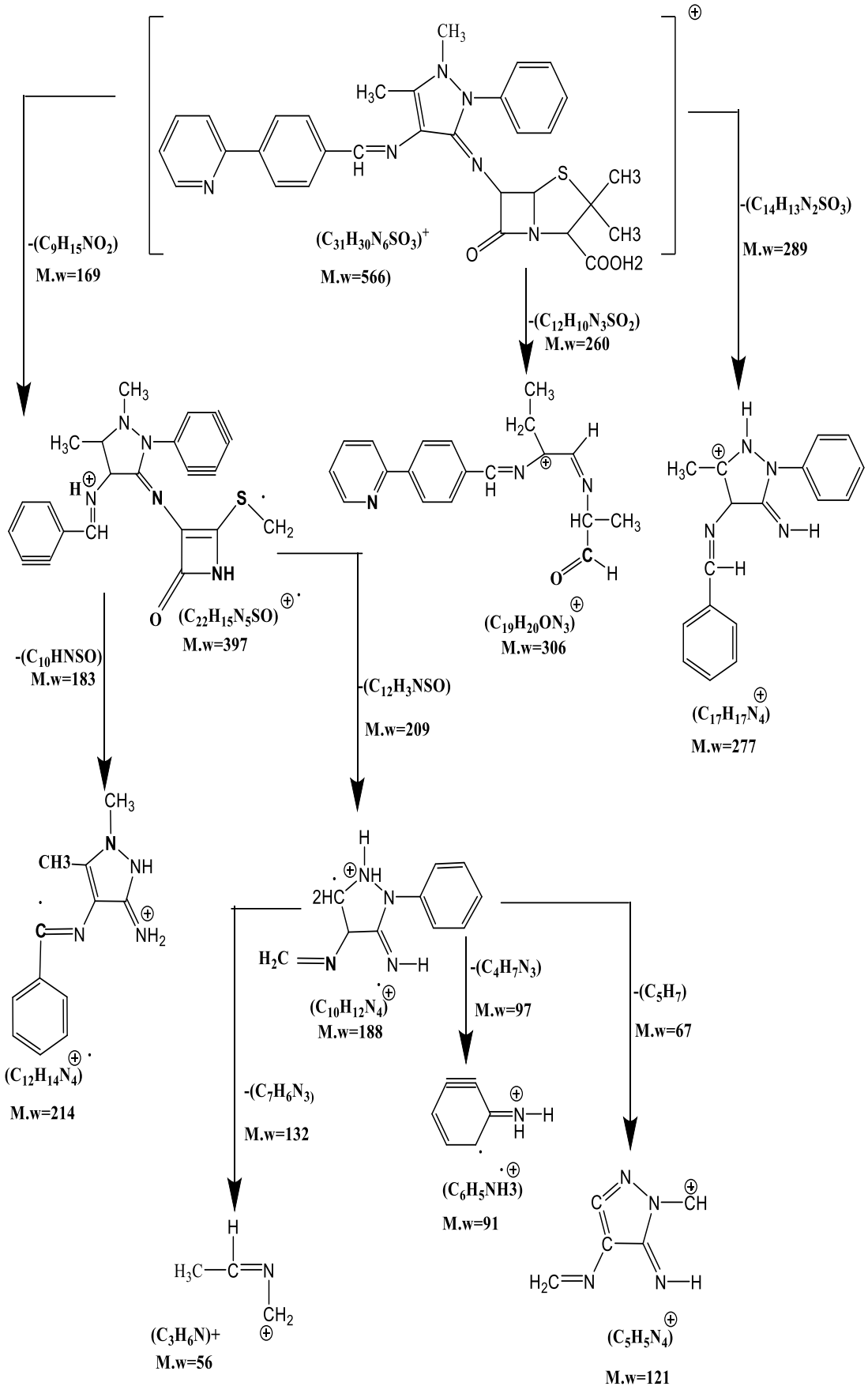


Fig.4:the mass spectrum of the new Schiff base ligand

Table 4: Mass fractionation products of Schiff base

Fragment	M/Z^+ Exacs Mass	Relative Abundance(%)
$[C_{31}H_{30}N_6SO_3]^+$	566.3	1
$[C_{22}H_{15}N_5SO]^{\cdot+}$	397.3	100
$[C_{19}H_{20}N_3O]^+$	306.1	27
$[C_{17}H_{17}N_4]^+$	277.1	2
$[C_{12}H_{14}N_4]^{\cdot+}$	214.1	6
$[C_{10}H_{12}N_4]^{\cdot+}$	188.1	9
$[C_5H_5N_4]^+$	121.1	57
$[C_6H_5N]^{\cdot+}$	91.1	43
$[C_3H_6N]^+$	56.1	81



Scheme 2 :Mass spectrum fragmentation of new Schiff base ligand

The Influence of Platinum Complex on the Growth of LS 174 T CRC Colon Cancer Cell Lines

Evaluation of newly preparation complexes in cancer therapy were studied. In this study the antitumor activities of Pt(II) complex were tested against a human LS 174 T CRC cell line. The results showed that the highest inhibitory effect was reported for Pt(II) complex, giving the IC50 value as of Pt(II) complex is 251.09

The cell cytotoxic effect of the tested Pt(II) complex was calculated. The optical density was measured with the micro plate reader to determine the number of viable cells, and the percentage of viability was calculated as

Cytotoxicity = A-B/A *100
Where A and B are the optical density of control
and the optical density of test.

The relation between surviving cells and drug concentration was plotted to get the survival curve of each tumor cell line after treatment with the specified compounds. The anticancer activity of Pt(II) complex was determined against LS 174 T CRC cell line using different concentrations.

Table 5: The effect of the [Pt(L)Cl]Cl complex on the cells of the colon cancer cell line LS 174 T CRC and its comparison with the normal cell line VERRO.

(x) =Conc . µg / ml	1	10	100	250	500	1000
Log x	0	1	2	2.4	2.7	3
Inhibition % Colon Cell Line	29.3	33.2	35.3	35.8	35.9	60.2
Inhibition % VERR Cell Line	39.4	46.1	43.1	47.5	62.6	75.7
Colon LS 174 T CRC Cell Line IC50= 251.09*µg/ml*			VERRO Cell Line IC50 = 697.59 *µg/ml*			

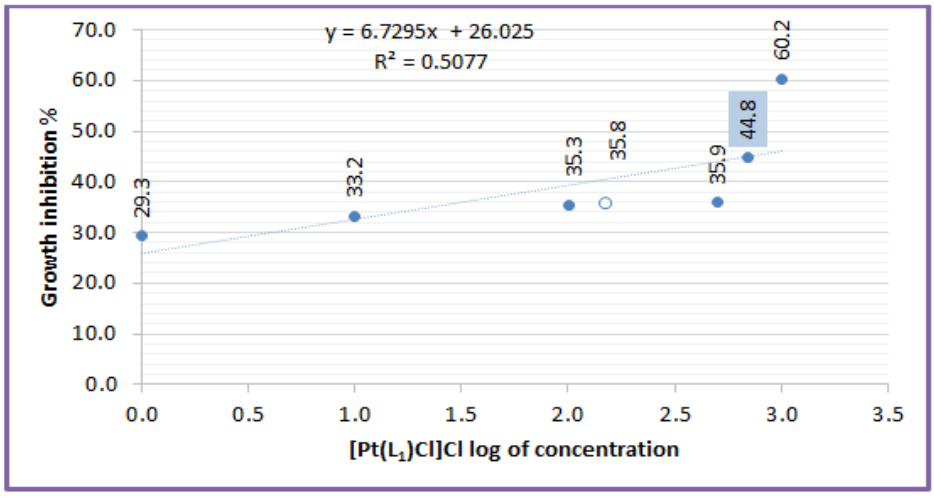


Fig. 5: Percentage of inhibition in LS 174 T CRC colon cancer line cells vs. logarithm of complex [Pt(L)Cl]Cl concentration

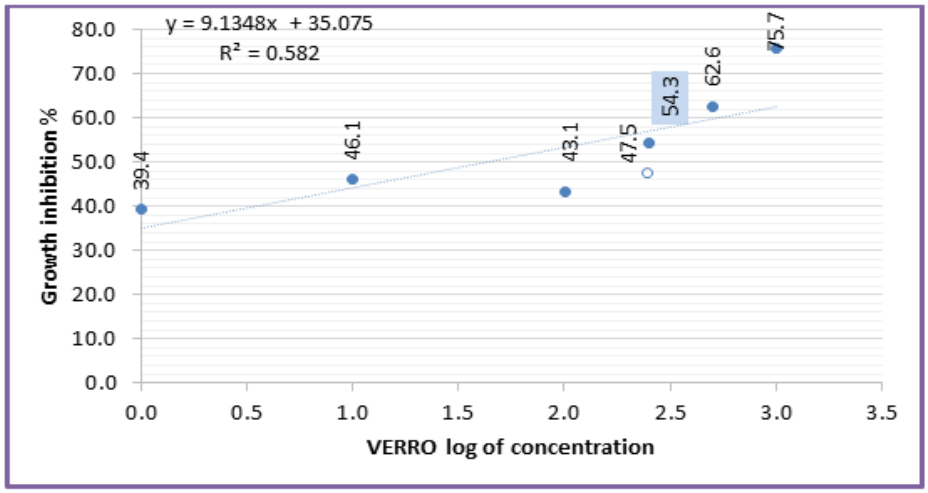


Fig. 6: Percentage of inhibition in cells of the normal line VERO against the logarithm of the concentration of the complex [Pt(L)Cl]Cl when concentrations up to 1000 are adopted.

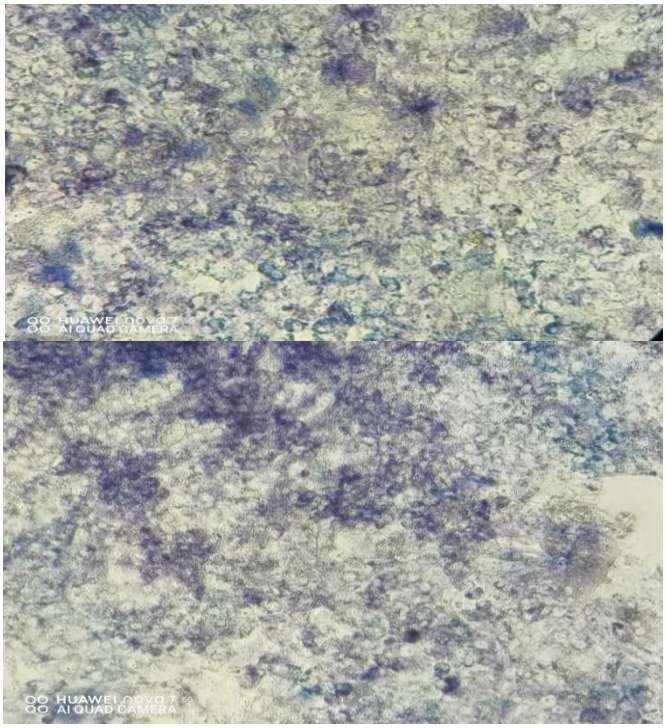


Fig. 7: Untreated cancer cells without MTT and cancer cells untreated with MTT.

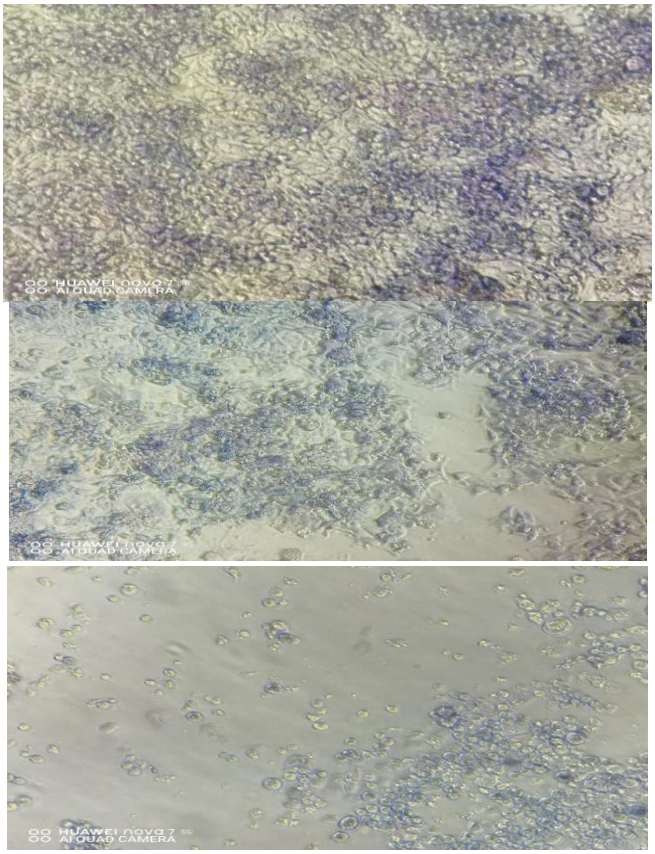


Fig. 8: Cancer cells treated with [Pt(L)Cl]Cl at different concentrations after adding MTT

Conclusions

This work described the preparation and characterzation of a new series of Co(II), Ni(II), Cu(II), Zn(II) Cd(II), Hg(II) and Pt(II) Schiff base ligand derived from 6-amino penicillanic acid. These chelate complexes with ligand were characterized by using different physiochemical techniques. The spectrum revealed that ligand behaves as neutral tridentate ligand coordinated to the metal ions through Schiff base-nitrogen, oxygen (β-lactam) donor atoms. The spectral and magnetic studies of the prepared metal complexes of Schiff base ligand reveals that all ligand chelate complexes are having octahedral geometry. except the complex Pt(II) suggested a square planar geometry around the central metal ion, also from the above studies it can be concluded that the preparation ligand and Pt(II) complex has been appeared Anti proliferative activity of LS 174 T CRC

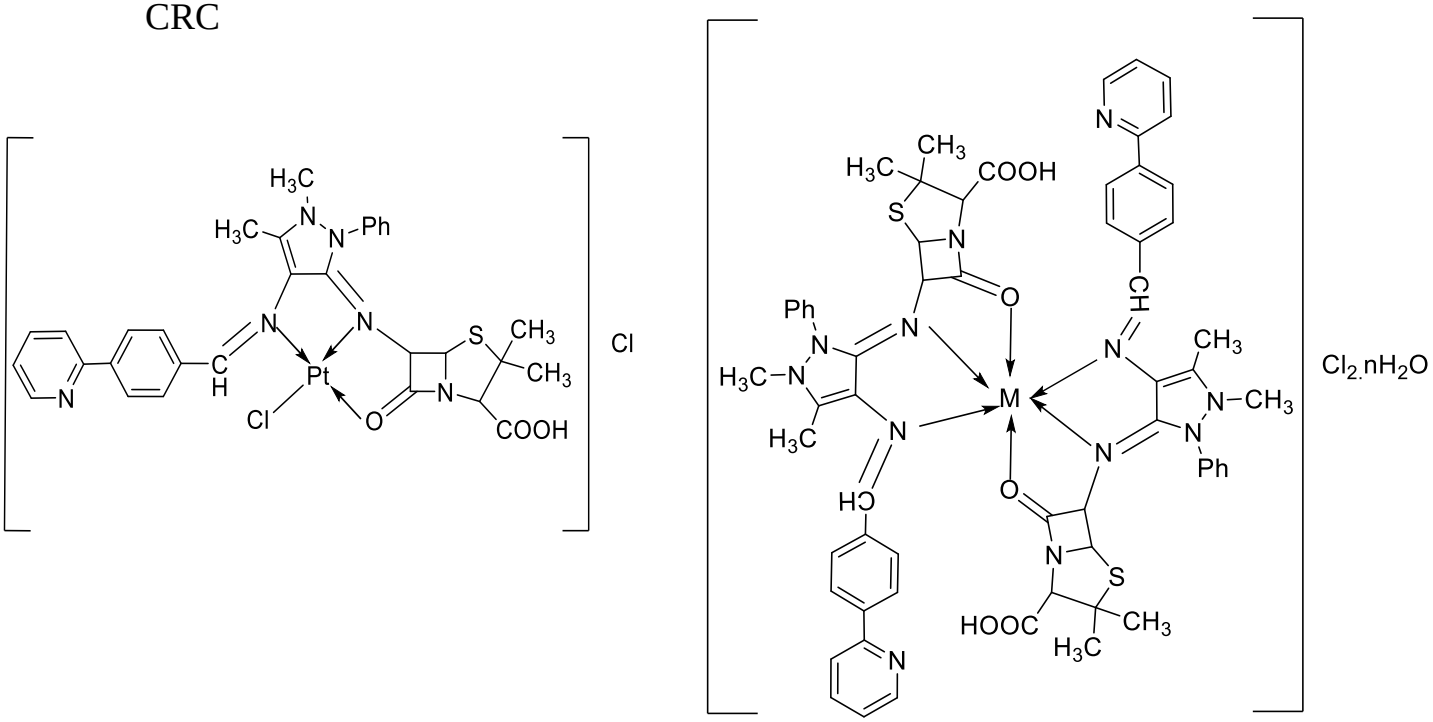


Fig. 9: The Proposed chemical structure of Complexes

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