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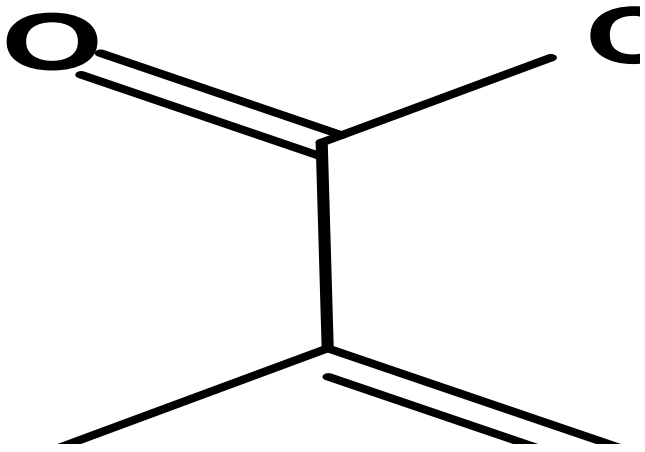
Spectroscopic characterization and Bioactivty studies of new Co(II), Ni(II), Cu(II), Au(III) and Pt(IV) complexes with didentate (NO) donar azo dye ligand

HUDA ABBAS [1], REHAB AL-HASSANI[2]

[1,2]*Department of Chemistry, Al-Mustansyah University, College of Science*

*** HUDA ABBAS**

Abstract : The newligand(5-((4-(1-(p-tolylimino)ethyl)phenyl)diazenyl)pyrimidine -2,4,6(1H, 3H, 5H) -trione (R_2) have been synthesized and characterized by micro elemental analysis ,(^{1}H-^{13}C) NMR, FT-IR, and UV-Vis spectroscopic techniques. (R_2) acts as a ligand coordinating with some metal ions Co(II), Ni(II), Cu(II), Au(III) and Pt(IV) generated fife mononuclear metal complexes, represented as $[CoR_2Cl_2(H_2O)_2]$ (a) ,$[NiR_2Cl_2]$ (b),$[CuR_2Cl_2]$ (c),$[Pt(R_2)_2\ Cl_2\ ]\ Cl_2$ (d) , $[Au(R_2)_2]Cl_3$(e) .The Structures of the new compounds were characterized by elemental , FT-IR and UV-Vis Spectra. The magnetic properties and electrical conductivities of metal complexes were also determined. The anticancer activity for (R_2) and its metal complexes complexes have been extensively studied on **AMGM cancer** cell line.



Scheme (S1) Synthesis of the ligand (R_2)and its metal complexes

Keywords - ***Azo Schiff complexes,AzoBarbituric complexes , barbituric complexes , Pyrimiden complexes , anticancer activity , MTT assay.***

I. INTRODUCTION

Azo dyes compounds are highly colored containing –N=N– group as a characteristic chromophore, and mainly obtained in diazotization and coupling reaction [1]. It is well known that azo compounds are the most widely class of industrial synthesized organic dyes because of their excellent thermal and optical properties in applications in various fields, such as dyeing textile NVDEfiber, biological-pharmacological activities, and advanced application in organic synthesis [2-4]. Barbituric acid, chemically 2,4,6-trioxohexahydropyrimidine, a cyclic amide used as the parent compound to produce barbiturates that act as central nervous system depressants[4]. It self does not give sedative and hypnotic effects but the substituted derivatives with alkyl or aryl group at position 5 provide effects [5,6] . Because of their ability to coordinate with transition metals through carbonyl oxygen and one or both deprotonated oxygen atoms, and also because of their wide use in medicine, the synthesis of their metal complexes has received great interest [7,8]. In this work, we synthesized new azo dye ligand (R_2) in an attempt to introduce the azo (-N=N-) moiety in the structure of 2,4,6-trioxohexahydropyrimidine ring to investigate the coordination behavior of the new (R_2) ligand. Towards some metal ions Cu(II), Ni(II), Co(II), Au(III) and Pt(IV), which have been chosen to react with (R_2)

II. MATERIAL AND METHODS

Melting points were recorded on a Gallen kamp MF B600.For ligand and their metal complexes (C.H.N.S) Elemental analyses were obtained using EA-034 mth Metal contents of complexes were estimated spectrophotometrically using Flame atomic absorption Shimadzu-670 AA Spectrophotometer. Infrared spectra were recorded using FT-IR-8300 Shimadzu in the range of (4000-350) cm^{-1}, samples were measured as (CsI) disc. Magnetic susceptibilities of samples in the solid state were measured by using Balance Magnetic Susceptibility of Sherwood Scietifi. The molar conductivity was measured by using Electrolytic Conductivity Measuring set Model MC-1-Mark V by using Platinum electrode (EDC 304) with Cell constant (1 cm^{-1}),conce nitration (10^{-3} M) in dimethyl formmide as a solvent at room temperature. Electronic spectra were obtained using UV-1650PC-Shimadzu Spectrophotometer at room temperature, the measurement were recorded using a concentration of (10^{-3} M) of the ligand and its metal complexes.

1. Preparation of starting material (Schiff base) (SB):

Schiff base (SB) was prepared by condensation reaction of (4-methyl aniline) with compound (4 – aminoacetophenone) ,by dissolving (1.35g, 0.01 mol) of (4 – aminoacetophenone) in (20 ml) absolute ethanol. Then mixed with a solution (1.07g , 0.01mol) of (4-methylaniline) dissolved in (20 ml) of the same solvent with the addition of four drops of glacial acetic acid followed by reflux for (6) hours [9] Scheme(2).

Scheme (2) Preparation of the Schiff base (SB)

2. General procedure of diazotization reaction of Azo-Schiff ligand (R_2)

The ligand (R_2) was synthesized according to the general method [10] by dissolving (2.24 g, 0.01mol) from (SB) in a mixture (10ml) hydrochloric acid and (10ml) of distilled cold water. In addition, diazotized below 5°C with (0.80 g, 0.01mol) of sodium nitrite dissolved in (10 ml) of distilled water, then the solution was added dropwise with stirring in order to obtain the diazonium salt solution. The solution was mixed with barbituric (1.28 g, 0.01mol) dissolved in a mixture consisting of (150 ml) Ethanol and sodium hydroxide (10%). After leaving in

the refrigerator for 24 hrs, the precipitate was filtered off , recrystallized from hot ethanol and dried the yield was (87%) ,the melting point was (350 C^0) Scheme (3) describessynthesis of the ligand(R_2) .

Scheme (3) Synthesis of (R_2)

III. Synthesis of the metal Complexes of (R_2)

3.1 CoR , NiR and CuR)Complexes

Ethanolic solution of each metal ion salt (0.001mol)($CoCl_2$.$6H_2O$, $NiCl_2$.$6H_2O$ and $CuCl_2$.$2H_2O$) in (M:L) ratio (1:1) was added to an ethanolic solution (0.363gm , 0.001mol) of (R) . The mixture was heated under reflux for three hours , which was filtered ,washed with ethanol and dried under vacuum ,table (1) show some analytical and physical data of ligand (R_2) and their metal complexes.

3.2 (AuR and PtR_2) Complexes

Ethanolic solution of each metal ion salt (0.001mol) ($PtCl_6$.$6H_2O$ and $AuCl_4$.$4H_2O$) in (M:L) ratio (1:2) was added to an ethanolic solution (0.363gm , 0.002 mol) of (R_2) . The mixture was heated under reflux for three hours . which was filtered ,washed with ethanol and dried under vacuum , table (S1) show Some analytical and physical data of ligand (R_2) and their metal complexes.

IV. RESULTS AND DISCUSSION

Elemental Analyses

The physical and analytical data of the ligand (R_2) and metal complexes are given in Table(1).The results obtained from elemental analysis are in satisfactory agreement with the calculate d value.The suggested molecular formula was also supported by spectral measurement as well as magnetic moment. The complexes are thermally stable and unaffected by atmospheric oxygen and moisture.

Table (1) some analytical and physical data of ligands (R_2) and their metal complexes

Comp. symbol	Emprical formula	Yield%	M.P $^0C^{(*)}$	Color	Metal analyses % Found(calc.)			
					C	H	N	M
R_2	$C_{19}H_{17}N_5O_3$	87	350	Yellow	62.81 (62.94)	4.68 (4.84)	19.28 (19.65)	……..
CoR_2	$[CoRCl_2(H_2o)_2]$	83	350<	Brown	43.28 (43.11)	4.08 (3.97)	13.74 (13.23)	10.93 (14.92)
NiR_2	$[NiR_2\ Cl_2\ ]$	77	350<	Green	46.69 (46.28)	3.83 (3.43)	14.70 (14.21)	11.79 (11.91)
CuR_2	$[CuRCl_2].2C_2H_5OH$	75	350<	Dark Green	47.03 (46.02)	5.11 (4.92)	12.14 (11.87)	9.96 (10.78)
PtR_2	$[\ Pt(R)_2\ Cl_2\ ]\ Cl_2\ .H_2o$	70	350<	Dark Orang	42.66 (42.18)	3.96 (3.33)	13.21 (12.95	18.45 (18.04)
AuR_2	$[\ Au\ (R)_2]\ Cl_3$	68	350<	Orang	44.57 (44.29)	3.64 (3.30)	13.76 (13.59)	19.38 (19.13)

(*) =All complexes were decomposed and the ligand was melted.

5.Nuclear Magnetic Resonance (NMR) Spectra of the Ligands (R_2)

The important chemical shifts and their assignments related to (^{1}H and ^{13}C) NMR spectra of ligands (R_2) listed in Tables (2) **[11 ,12,13]**.

Table (2): (^{1}H-NMR,^{13}C-NMR)spectral data, chemical shifts and assignments of (R_2) in DMSO-d_6 as a solvent

LIGAND SYMBOL	*ASSIGNMENT*	*CHEMICAL SHIFTS (PPM) (NO. OF PROTONS AND CARBONS)*
R_2		$\delta H_{(1)}$ =1.10 ppm douplet $\delta H_{(2)}$ =2.47 $\delta H_{(3)}$ =3.31 $\delta H_{(4,5)}$ = 11.68 singlet due to NH of Barbituric ring $\delta H_{(ring)}$ =7.25-8.02 ppm multiplate due to the aromatic protons.
R_2		$\delta C_{(1)=}$ 27 due to CH_3 $\delta C_{(2)=}$ 20 due to CH_3 $\delta C_{(3)=}$165 due to C=N $\delta C_{(4)=}$ 78 due to C_{ring} $\delta C_{(5,7)=}$195 due to C=O $\delta C_{(6)=}$150 due to C=O $\delta C_{(8)=}$96-120 due to C of aromatic ring

6. FTIR Spectra of ligand (R_2) and their metal complexes

FT-IR gave good informations about the complex behavior of the ligands (R_2) with various metal ions. The characteristic frequencies of the free ligands, (R_2) and their metal complexes were readily assigned based on comparison with literature values [14-18], Table(S3). The free ligand (R_2) showed a strong bands located at (1780,1751 and 1707) and (1462) cm^{-1} corresponding to υC=O groups and υN=N stretching frequency respectively, table (2). In all complexes, the ligand (R) behaved as a bidentate coordinating to metal ion through nitrogen of N=N and oxygen of carbonyl group, therefor, these bands were shifted to a lower frequencies, as shown in Table 3. The strong and broad bands at (3246) cm^{-1} and (1656) cm^{-1} in the spectrumof the ligand (R_2) may be attributed to the (υNH) of pyrimidine ring and (υC=N) of imine group. This bands remains in the same position in complexation,. thus the remaining of amine hydrogen and imine groups in act in solid complexes, indicating its non-involvement in coordination of the ligand to the metal ions.

These observations were further indicated by the appearance of υM-O, υM-N and υM-Cl, respectively,table (2).The presence of coordination water in complexes was detected by the appearance of band at(785)cm^{-1} in (CoR_2)complex, as well as a strong broad band at (3555)cm^{-1} attributed to υOH stretching of H_2O.

Table (3): FTIR spectral data (cm^{-1}) of (R_2) ligand and its metal complexes

Comp.	*N-H*	*C=O*	*C=N*	*N=N*	*M-N*	*M-O*	*M-Cl*
R	3246	1780 1751 1707	1656	1462	…….	……..	……..
Co(II)	3244	1670	1655	1450	418	550	398
Ni(II)	3246	1678	1654	1451	492	520	400
Cu(II)	3244	1664	1654	1450	470	587	395
Pt(IV)	3242	1672	1654	1435	452	552	403
Au(II)	3242	1672	1656	1433	474	582	-

7.Electronic absorption spectra, Magnetic susceptibility, and Conductivity measurements

The (U.V-Vis) spectrum of ligand (R_2) in absolute ethanol exhibited three absorption bands at (230 nm, 43478cm^{-1}), (293 nm, 34129cm^{-1}),were assigned to ($\pi\rightarrow\pi^*$),($n\rightarrow\pi^*$) transitions , and band at (388 nm, 2577cm^{-1}) assigned to ($n\rightarrow\pi^*$) intra ligand transitions [19]. Complexation of (R) with metal ions appearance a new bands in the visible and UV. These bands were attributed to M-L charge transfer and to ligand field transitions , describes Bands of maximum absorption of complexes in chloroform with their assignments.

The electronic spectrum of (CuR_2) complex shows one broad band at (660 nm, 15152 cm^{-1}) which corresponds to $^2B_1g \rightarrow {}^2A_1g$ transition, and a shoulder band at (399nm,25063cm^{-1}) which assigned to $^2B_1g\rightarrow {}^2B_2g + {}^2Eg$ transition[20]. The position of these Bands Is In a good agreement with a .square planer configuration. The value of magnetic moment at room temperature Was found to be (1.84B.M), which agree well with distorted octahedral geometry around Cu (II) complexe [21].The conductance measurements in DMF indicate the non ionic behavior of this complex .

The electronic spectrum of .(NiR_2)complex, shows two bands,(494 nm,20243 cm^{-1}) and (435nm , 22989cm^{-1}) assigned to $^1A_1g\rightarrow {}^1A_2g_{(F)}$, and $^1A_1g\rightarrow Eg_{(P)}$ transitions respectively [22] .These bands

indicate a square planer geometry around Ni (II)ion, the calculated values of magnetic moment were (0.03 B.M). This confirm the diamagnetic character of complex and non-conducting behavior [21].

The electronic spectrum of the (CoR_2) complex showed two transitions at (640nm ,15152 cm^{-1}) and (553 nm,18018 cm^{-1}) , which might be assigned to the transition $^4T_1g \rightarrow {}^4A_2g_{(F)}$ (ν_2) and $^4T_1g \rightarrow {}^4T_1g_{(P)}$ (ν_3) respectively [23] , these indicate an octahedral geometry. On the basis of theses assignment it was possible to calculate (ν_1) for d^7 of (Tanaba- Sugano) diagram, the calculated value of (ν_1) to be (7922.3)cm^{-1} due to the transition $^4T_1g \rightarrow {}^4T_2g_{(F)}$. The magnetic susceptibility and molar conductivity Measurement indicated that the complex to be a paramagnetic (4.2 B.M) and non conducting.

The electronic spectrum of (PtR_2) complex, shows Bands , (510 nm, 19608 cm^{-1}), .(425 nm, 23529 cm^{-1}) and (390 nm, 25641 cm^{-1}) assigned to $^1A_1g \rightarrow {}^3T_1g$, $^1A_1g \rightarrow {}^3T_2g$ and ($L \rightarrow Pt_{CT}$) respectively [24]. The complexes may have an octahedral coordination of the central metal ion by the surrounding ligands. The magnetic value (0.20 B.M) for Pt(IV) is observed, this agree with octahedral geometry around Pt(IV)ion[21]. The conductance measurements indicate the ionic behavior of this complex.

The electronic spectrum of (AuR_2) complex, shows two bands, (430 nm,23255cm^{-1}) and (374 nm,26738cm^{-1}) assigned to $^1A_1g \rightarrow {}^1B_1g$ and $^1A_1g \rightarrow {}^1Eg$ transitions respectively [25] .The complex may Have a square-planar Coordination to the central metal ion by the surrounding ligands. The magnetic moment data of Au(III) complex indicate that this complex is diamagnetic .This agree with square-planar geometry around Au(III) ion [26]. The conductance measurements indicate the ionic behavior Of this complex.

Table (4): Magnetic moment , Electronic spectra (B.M) and Conductance in (DMF) for (R_2) complexes

No.	Maximum absorption $\upsilon_{max}(cm^{-1})$	Band assignment	B`	B	10Dq	Molar Cond. $S.cm^2.mol^{-1}$	μeff. B.M	Suggested geometry
(CoR_2)	15625 180083 7922.3	$^4T_1g \rightarrow {}^4A_2g$ (F) $^4T_1g \rightarrow {}^4T_1g$ (P) $^4T_1g \rightarrow {}^4T_2g$ (F) (calc.)	454.2	0.47	7652.41	14.92	4.2	O.h
(NiR_2)	22989 20243	$^1A_1g \rightarrow {}^1Eg$ $^1A_1g \rightarrow {}^1A_2g$				13.56	0.03	S. P
(CuR_2)	25063 15152	$^2B_1g \rightarrow {}^2B_2g + {}^2Eg$ $^2B_1g \rightarrow {}^2A_1g$	----	-----	-----	14.42	1.84	Dist.O.h
(PtR_2)	19608 23529 25641	$^1A_1g \rightarrow {}^3T_1g$ $^1A_1g \rightarrow {}^3T_2g$ LMCT	-----	------	------	163	0.20	O.h
(AuR_2)	23255 26738	$^1A_1g \rightarrow {}^1B_1g$ $^1A_1g \rightarrow {}^1Eg$	-	-	-	225	0.3	S. P

Conclusions

Schiff azo ligand (R_2) obtained from barbituric acid with (SB) (4-aminoacetophenon and 4-methyl). Ligand were reacted with salt of Co(II), Ni(II), Cu(II) , Pt(II) or Au(II) to afford fife mononuclear complexes of formula $[CoR_2Cl_2(H_2O)]$, $[NiR_2Cl_2]$, $[CuR_2Cl_2]$, $[Pt(R_2)_2Cl_2]Cl_2$, $[Au(R_2)_2]Cl_3$. In this work, the detailed study is reported the metal ion is coordinated by chelating ligands (R_2) through the nitrogen of azo and carbonyl oxygen of obarbituric giving octahedral or square planner geometry.

Cytotoxic activity Studies of R_2 metal complexes (AuR_2 and PtR_2)

The cytotoxic effects of (**AuR_2 ,PtR_2**) were studied against AMGM (Ahmed – Majeed-Glioblastoma-Multiform) cell line [27]. This cell line was exposed to concentrations of these compounds ranged from (100-6.25 µg/ml) for 72 hrs only. The optical density was measured under wavelength 490 nm with ELISA reader after their staining with MTT stain. The results showed that these compounds led to decrease the growth of AMGM cancer cell significantly as compared to untreated control cells as estimated by comparison of the optical density of the treated and control cell lines. The results showed of the inhibition rate at 100µg/ml the complex AuR_2 had the lowest inhibition percentage and the other compounds have different inhibition percentage with the order **PtR_2> AuR_2** , as shown in Fig(11) to (14). When the concentration of (**PtR_2 and AuR_2**) increased to 100 µg/ml, the inhibition rates for these concentrations increase andAt 100µg/ml **(AuR_2,PtR_2)** record highest inhibition activity against AMGM cancer cell line compare with the control. this ubiquitous transport system participates in many important cellular functions, such as regulation of intracellular pH, trans cellular movement of acid and base equivalents, cell growth and proliferation, and regulation of cell volume . AMGM cell line is a non polarized epithelial cell which is known to express Na+/H+ exchanger activity. The inhibition caused by ligands and its metal complexes on AMGM is mediated not through their receptors but through direct interaction with the Na+/H+ exchanger and bonded to nucleic acids in DNA. Interaction of complexes and nucleic acids cause conformational changes of DNA and then lead to cell damage. Determination of the interactions between compounds and DNA should be elucidated to help explain the mechanisms of apoptotic events and drug potential of these compounds [28, 29, 30].

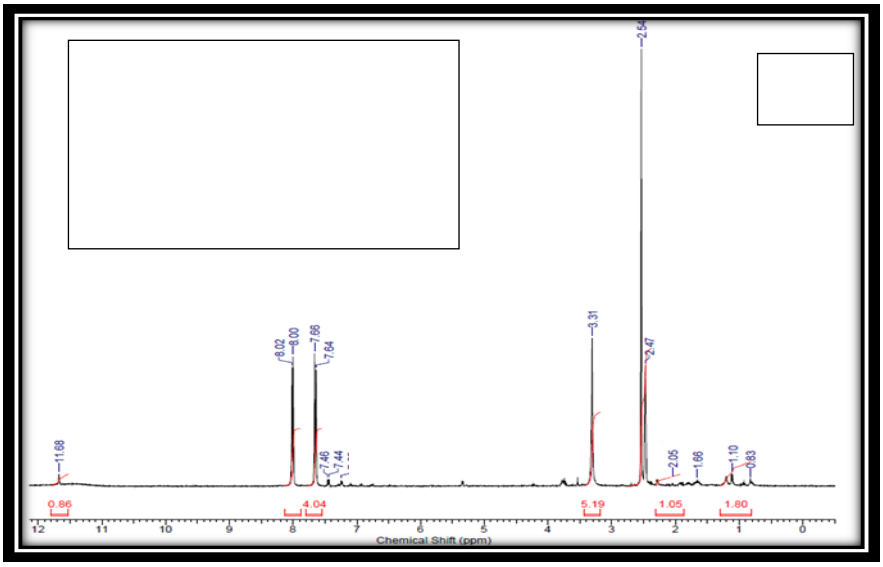
Table(5): Evaluation of cytotoxicity of (AuR_2) complexes against AMGM cancer cell line

CON.	*6.25 µG/ML*	*12.5 µG/ML*	*25 µG/ML*	*50 µG/ML*	*100 µG/ML*
MEAN	28.91	31.78	30.89	32.54	36.77
P VALUE	0.0090	0.0155	0.0022	0.0091	0.0039
SIGNIFICANT	Yes	Yes	Yes	Yes	Yes
(ALPHA=0.05)					

Table(6): Evaluation of cytotoxicity of (PtR_2) complexes against AMGM cancer cell line

CON.	*6.25 µG/ML*	*12.5 µG/ML*	*25 µG/ML*	*50 µG/ML*	*100 µG/ML*
MEAN	43.83	45.85	50.96	57.74	64.56
P VALUE	0.0025	0.0022	0.0005	0.0029	0.0043
SIGNIFICANT	Yes	Yes	Yes	Yes	Yes
(ALPHA=0.05)					

FIGURES :



Figure(1) ^{1}H-NMR Spectrum of (R_2) ligand

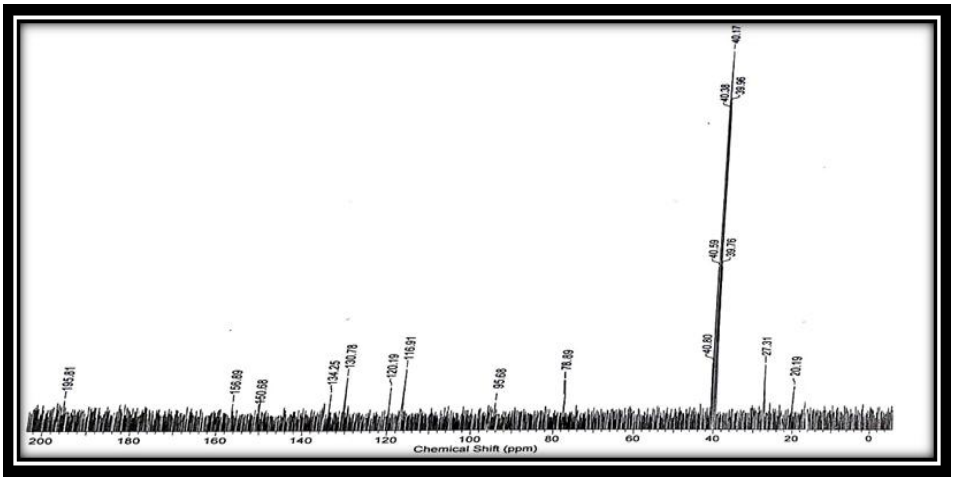


Figure (2) ^{13}C-NMR Spectrum of (R_2) ligand

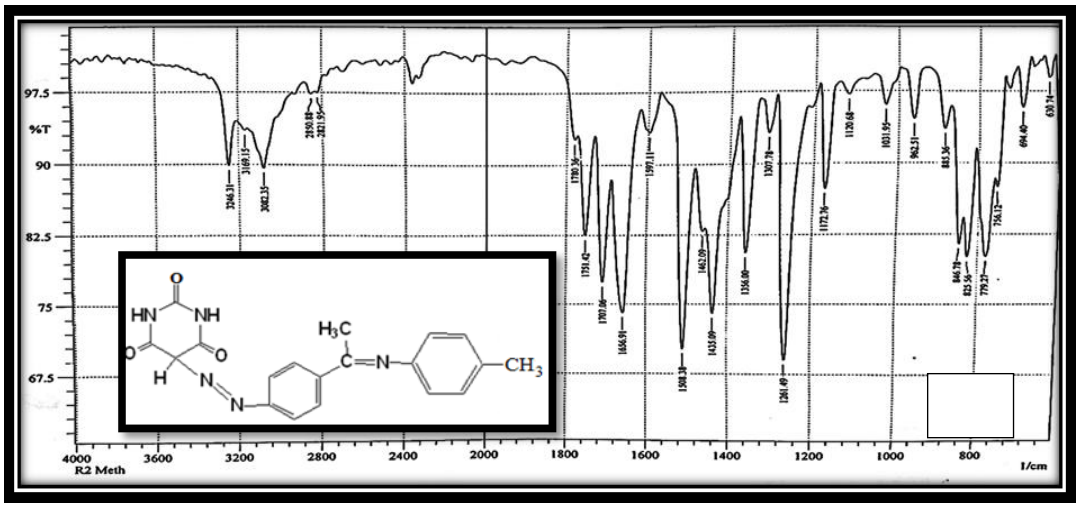


Figure (3) FTIR spectrum of (R_2) ligand

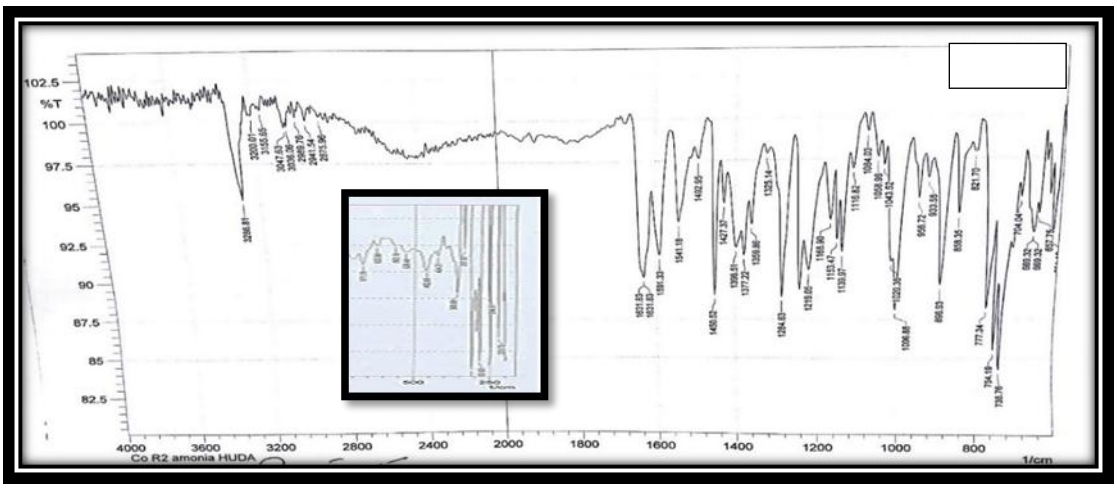


Figure (4) FTIR spectrum of (CoR_2)complex

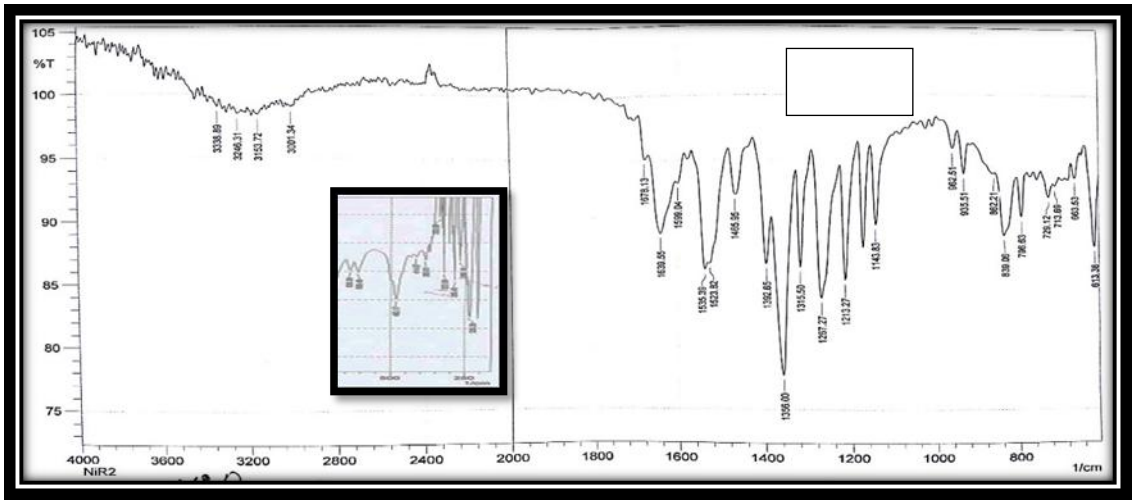


Figure (5) FTIR spectrum of (NiR_2)complex

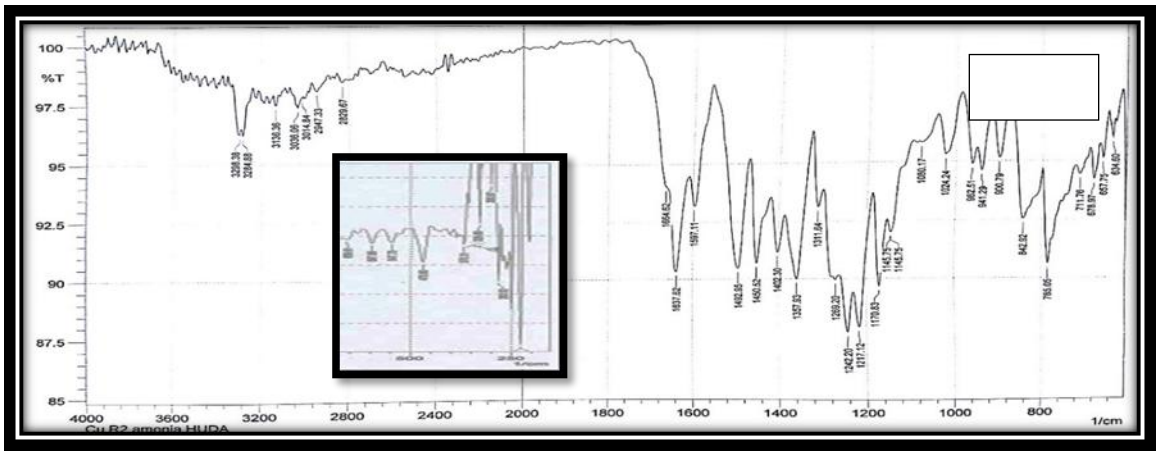


Figure (6) FTIR spectrum of (CuR_2)complex

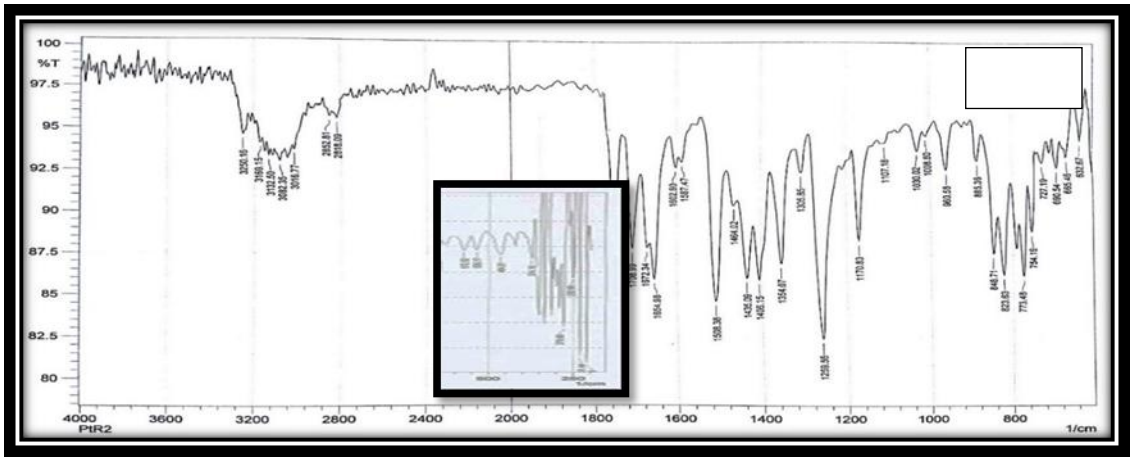


Figure (7) FTIR spectrum of (PtR_2)complex

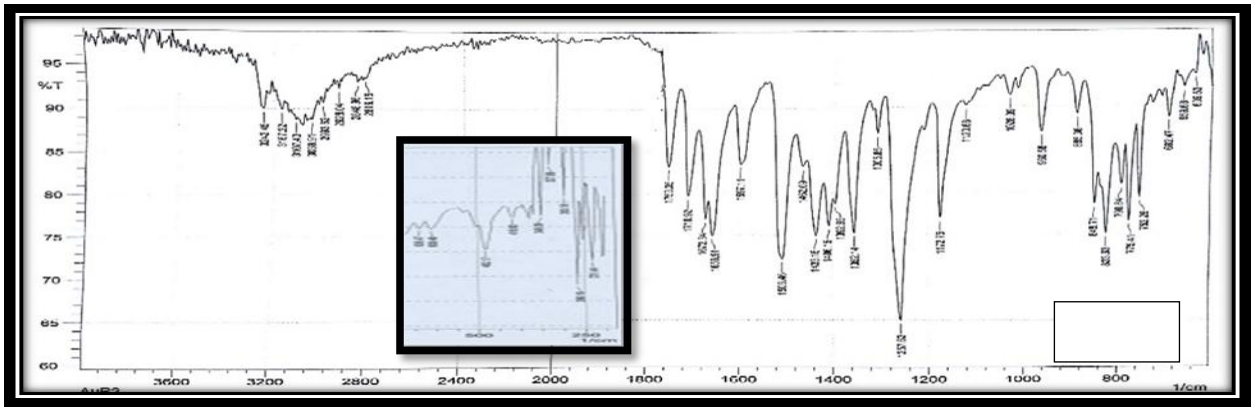


Fig (8): FTIR spectrum of (AuR_2) **complex**

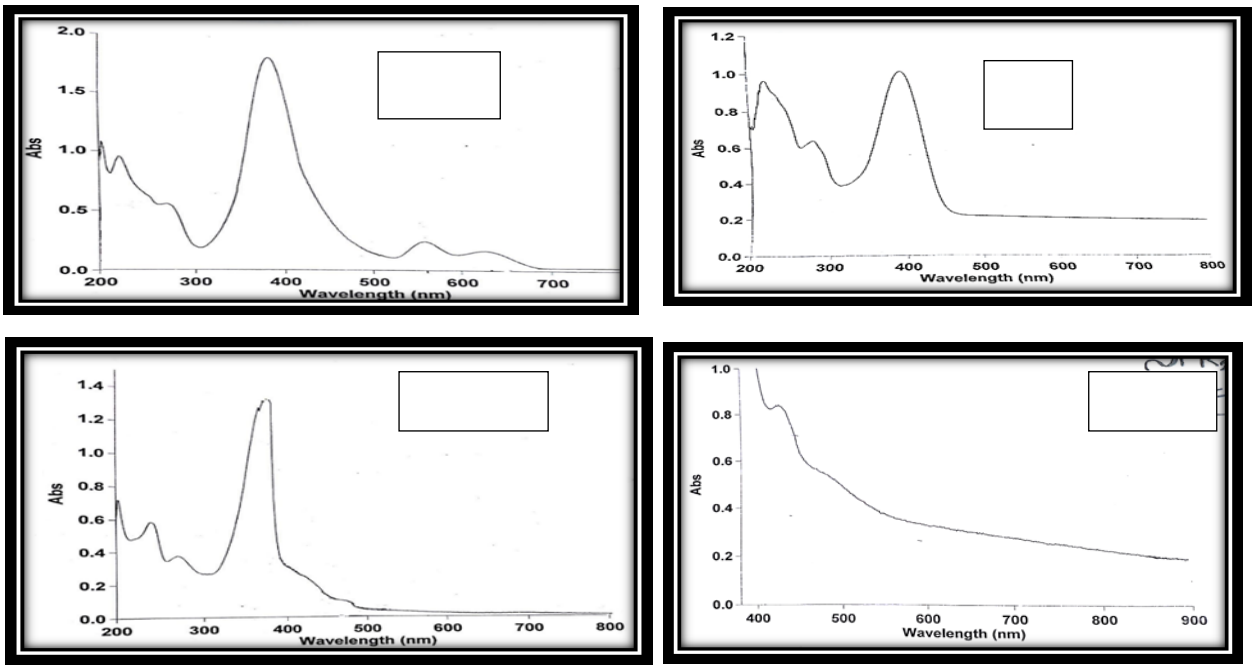


Figure (9) The UV-Vis spectra of R_2 **ligand** *(CoR_2,NiR_2(a,b),)complexes*

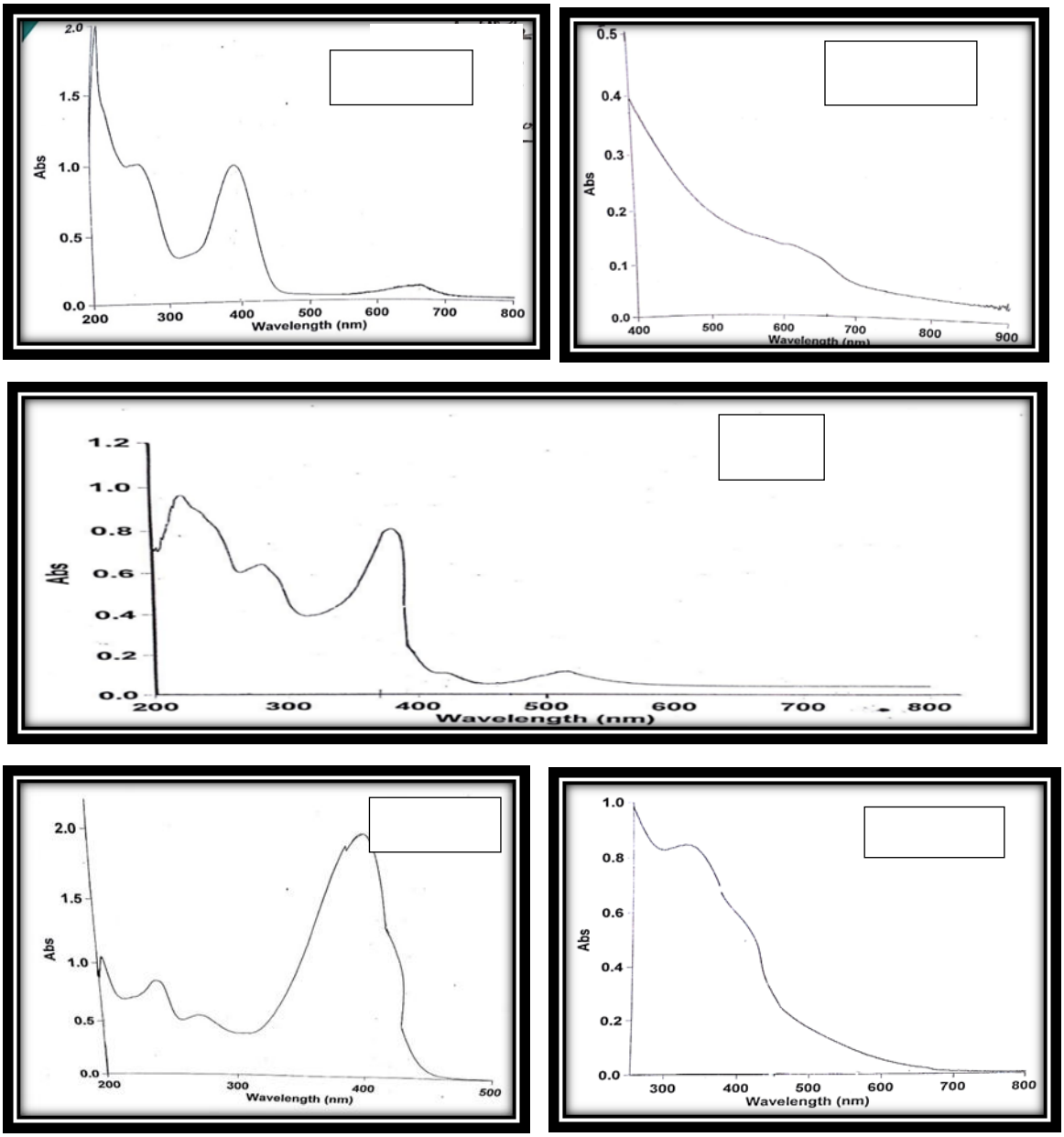


Figure (10) The UV-Vis spectra of(CuR_2(a,b),PtR_2 and AuR_2(a,b)) complexes

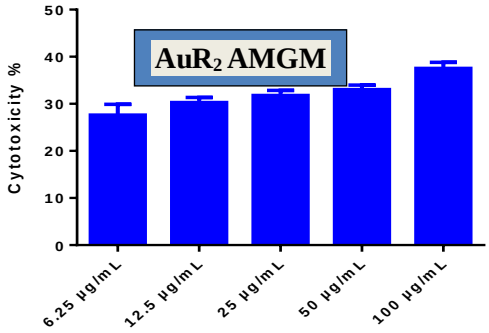
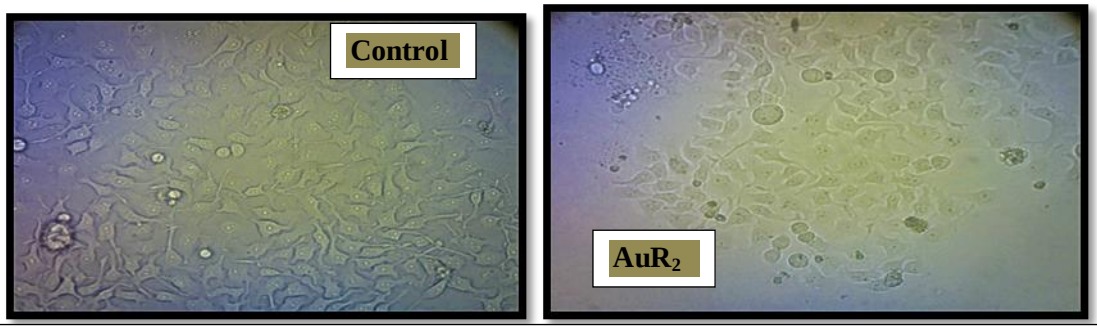
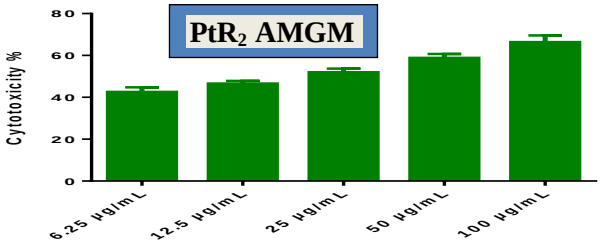
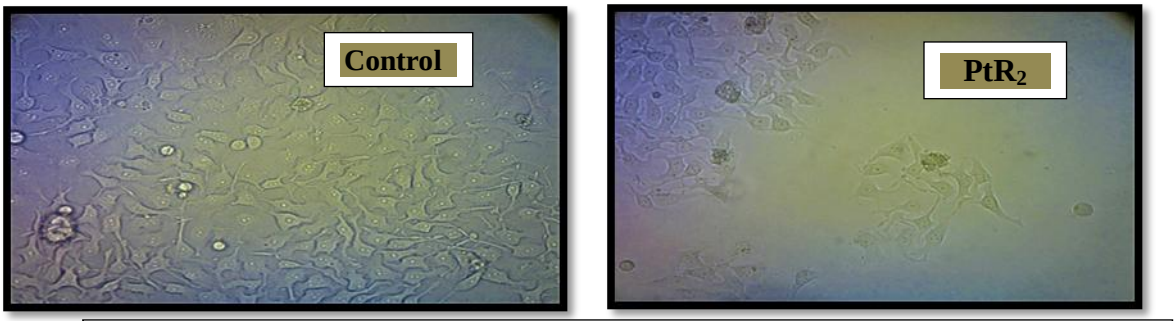


Figure: (11) Cytotoxic effect on AMGM cell line





Figure(13): Cytotoxic effect on AMGM cell line



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