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IRON(III), GOLD(III), PLATINUM(IV) AND PALLADIUM(II) TRIMETHOPRIM DRUG COMPLEXES: SYNTHESIS, SPECTROSCOPIC, MORPHOLOGICAL AND ANTICANCER ASSESSMENTS

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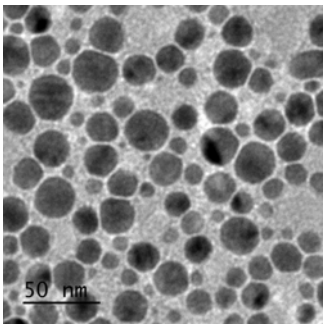
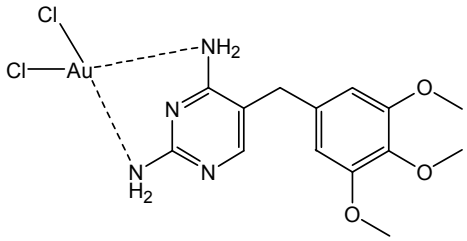
Iron(III), gold(III), platinum(IV) and palladium(II) complexes of trimethoprim (TMP) drug were synthesized and well characterized using elemental analysis, conductance measurements, (UV-Vis, FTIR, ^{1}HNMR and X-ray powder diffraction) spectroscopy. The Au(III), Pt(IV) and Pd(II) complexes have a four coordinate geometry comprising one molecules of the TMP drug and two coordinated chloride ions, while, iron(III) complex has an octahedral geometry containing one TMP, three chloride and one coordinated water molecules. The TMP drug acts as a bi-dentate chelate towards the metal ions through the nitrogen atoms of the two amino groups attached with pyrimidine ring, this was confirmed by spectroscopic analyses with the molecular formulas $[Fe(TMP)Cl_3(H_2O)].4H_2O$, $[Au(TMP)Cl_2]Cl{\cdot}2H_2O$, $[Pt(TMP)Cl_2]Cl_2{\cdot}2H_2O$ and $[Pd(TMP)Cl_2]$. The transmission electron microscopy (TEM) and XRD analyses deduced that the gold(III) complex has a nano-scale range at ~ 10 nm. The $[Au(TMP)Cl_2]Cl{\cdot}2H_2O$ complex was screened for its cytotoxicity evaluation against hepatocellular carcinoma (HepG2) and colon carcinoma (HCT-116) cell lines. It is showed that the IC_{50} of gold(III) complex are 7.46 µg/mL and 9.30 µg/mL against HepG2 and HCT-116 cancer cell lines, respectively.



$Cl.2H_2O$



INTRODUCTION

Trimethoprim is one of an important drug which has an anti-biotic and anti-parasitic activities.[1] It can be used as a good chelating agent towards metal ions through the nitrogen atoms of pyrimidine ring.[2–4] The mixed ligand complexes formed between trimethoprim and isoniazid towards some of transition metal ions were synthesized.[5] These complexes have a coordination sites through nitrogen of pyrimidine ring of TMP and the nitrogen atom of amino group of isoniazid.[5] The silver(I) complexes of trimethoprim and pyrimethamine mixed ligands have been prepared and characterized using microanalytical and spectroscopic analyses. The trimethoprim and pyrimethamine ligands act as a monodentate ligand towards Ag(I) metal ion through the nitrogen atom of pyrimidine ring.[6] Silver(I) complexes of trimethoprim show stronger antibacterial activity compared to free drugs. While Pt(II) and Pd(II) complexes with both TMP and pyrimethamine

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ligands have a square planar geometry.[7] Copper(II), zinc(II) and Ti(IV) complexes of TMP drug have been synthesized and characterized by ^{13}C-NMR, elemental analysis, electronic spectra and showed good antibacterial activity, the titanium(IV) and copper(II) complexes have an excellent anticancer activity.[8] The Cu(II), Zn(II), Pt(II), Ru(III) and Fe(III) complexes of trimethoprim were prepared and characterized using elemental analysis, spectroscopic and morphology.[3] The biological activity of these complexes determined by binding to calf-thymus DNA with UV-spectroscopy and cyclic voltmeter, antimicrobial activity of these complexes and antifungal activity have been evaluated and compared with TMP drug. Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Pb(II) and La(III) complexes of TMP derivative were prepared and the speculated coordination were designed using different physical and chemical tool of analyses. The geometry of these complexes confirmed that the TMP derivative ligand act as a bidentate ligand.[9] In this study, the synthesis and characterization of Fe(III), Au(III), Pt(IV) and Pd(II) complexes with TMP ligand and the anticancer studies of gold(III) trimethoprim complex are presented.

EXPERIMENTAL

1. Chemicals

Iron(III) chloride hexahydrate, gold(III) chloride, platinum(IV) chloride and palladium(II) chloride as well as trimethoprim pure drug were received from Sigma-Aldrich Chemical Company, USA and used in the preparation without further purification.

2. Instruments

The type of analyses and their corresponding models can be listed as follows:

Type of analysis	Models
Elemental analyses	Perkin Elmer CHN 2400
Conductance	Jenway 4010 conductivity meter
FTIR spectra	Bruker FTIR Spectrophotometer
^{1}HNMR spectra	Varian Mercury VX-300 NMR spectrometer, 300 MHz
Electronic spectra	UV2 Unicam UV/Vis Spectrophotometer
Magnetic moment	Magnetic Susceptibility Balance
XRD	X 'Pert PRO PANanalytical
TEM	JEOL 100s microscopy

3. Synthesis

The Fe(III), Au(III), Pt(IV) and Pd(II) trimethoprim complexes were synthesized by mixing 1.0 mmol of $FeCl_3.6H_2O$, $AuCl_3$, $PtCl_4$ and $PdCl_2$ in 30 mL methanol with 1.0 mmol TMP in 30 mL methanol. The complex mixtures were refluxed for ~ 4 hrs till the colored precipitates were appeared, the solid products were filtered off and washed several times with little amounts of methanol. The solid precipitates were dried and closed in a vacuum desiccator over anhydrous $CaCl_2$.

4. Anticancer experiment

Human colon carcinoma (HCT-116) and Hepatocellular carcinoma (HepG2) cells were obtained from the American Type Culture Collection (ATCC, Rockville, MD). The cells were grown on RPMI-1640 medium supplemented with 10% inactivated fetal calf serum and 50 µg/mL gentamycin. The cells were maintained at 37 ºC in a humidified atmosphere with 5% CO_2 and were subcultured two to three times a week. A positive control containing doxorubicin drug was also tested as reference drug for comparison. Six wells were used for each concentration of the test sample. Every 24 h the observation under the inverted microscope was made. The number of the surviving cells was determined by staining the cells with crystal violet[10,11] followed by cell lysing using 33% glacial acetic acid and read the absorbance at 590nm using ELISA reader (SunRise, TECAN, Inc, USA) after well mixing. The absorbance values from untreated cells were considered as 100% proliferation. The number of viable cells was determined using ELISA reader as previously mentioned before and the percentage of viability was calculated as [1-(ODt/ODc)]x100% where ODt is the mean optical density of wells treated with the tested sample and ODc is the mean optical density of untreated cells. The 50% inhibitory concentration (IC_{50}), the concentration required to cause toxic effects in 50% of intact cells, was estimated from graphic plots.

RESULTS AND DISCUSSION

1. Elemental analysis and conductance measurements

The yields of the solid Fe(III), Au(III), Pt(IV) and Pd(II) TMP complexes have located within 74-78% range. Trimethoprim has a seven coordination

sites, two pyrimidinic nitrogen atoms, two NH_2 group and oxygen of three methoxyl groups. The elemental analysis of an experimental data is good agreement with calculated values as mentioned in Table 1 and the proposed coordination of TMP complexes are shown in Fig. 1. The molar conductance of $[Fe(TMP)Cl_3(H_2O)]\cdot 4H_2O$, $[Au(TMP)Cl_2]Cl\cdot 2H_2O$, $[Pt(TMP)Cl_2]Cl_2\cdot 2H_2O$ and $[Pd(TMP)Cl_2]$ complexes which were dissolved in DMSO solvent 10^{-3} M have Λ_m = 14, 47, 96, and 17 $ohm^{-1}.cm^2.mol^{-1}$ respectively, these values meaning that, the Au(III) and Pt(IV) complexes indicate there an electrolytic nature while both Fe(III) and Pd(II) complexes have a non-electrolyte properties.[12]

The synthesized complexes are soluble in DMSO and DMF organic solvents but insoluble in most organic solvents and water. The melting points and different colors of the solid complexes were completely different from the TMP ligand which is confirmed from the formation of the new compositions. The single melting point of the solid complexes is an indication of the purity. Elemental analysis and conductivity of the complexes indicate a 1:1 molar ratio (M:L).

Table 1

Elemental analysis and physical properties of TMP complexes

Complex	Color	Conductance ($ohm^{-1}.cm^2.mol^{-1}$)	Element	Calc.	Found
Fe(III)	Orange	14	%C	30.99	30.92
			%H	5.20	5.14
			% N	10.33	10.21
			%Fe	10.29	10.22
Au(III)	Yellow	47	%C	26.70	26.64
			%H	3.52	3.50
			% N	8.90	8.88
			%Au	31.28	31.21
Pt(IV)	Yellow	96	%C	25.35	25.30
			%H	3.34	3.31
			% N	8.45	8.42
			%Pt	29.41	29.35
Pd(II)	Yellow	17	%C	35.96	35.91
			%H	3.88	3.83
			% N	11.98	11.92
			%Pd	22.76	22.71

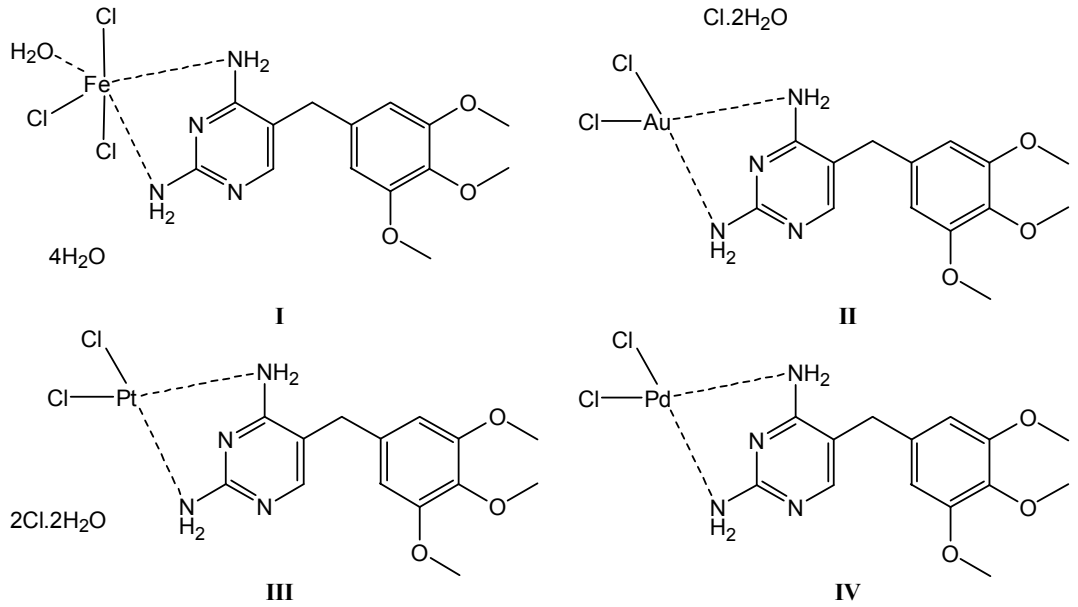

Fig. 1 – Proposed coordination of iron(III), gold(III), platinum(IV) and palladium(II) TMP complexes (I, II, III, IV, respectively).

2. FTIR spectra

The FTIR spectra of the TMP ligand and its iron(III), gold(III), platinum(IV) and palladium(II) complexes were scanned (Fig. 2) and assigned (Table 2). The TMP free drug has different distinguish frequencies at 3470, 3319, 2933, 2833, 1464, 1333, 1635 and 1594 cm^{-1} attributed to $\nu_{as}NH_2$, ν_sNH_2, $\nu_{as}CH_3$, ν_sCH_3, $\delta_{as}CH_3$, δ_sCH_3, νC=N, νC=C stretching frequencies of pyrimidine ring and trimethoxy groups respectively. The two bands of $\nu_{as}NH_2$ and ν_sNH_2 were shifted to lower wavenumber in the spectra of the synthesized complexes and presence in the region of (3408–3184 cm^{-1}), this results confirmed the coordinated of nitrogen atoms of amino group to central metal ions.[2-4] The weak to medium bands within at around of ~ 3400 cm^{-1} are assigned to the stretching vibration bands of water molecules. The new absorption band detected in the spectra of complexes in the region of 520−530 cm^{-1} was assigned to ν(M—N) and.[3] FTIR spectral data of all TMP synthesized complexes indicated that the chelating of the TMP drug towards metal ions exhibited as a bidentate ligand via the nitrogen atoms of the amino groups.

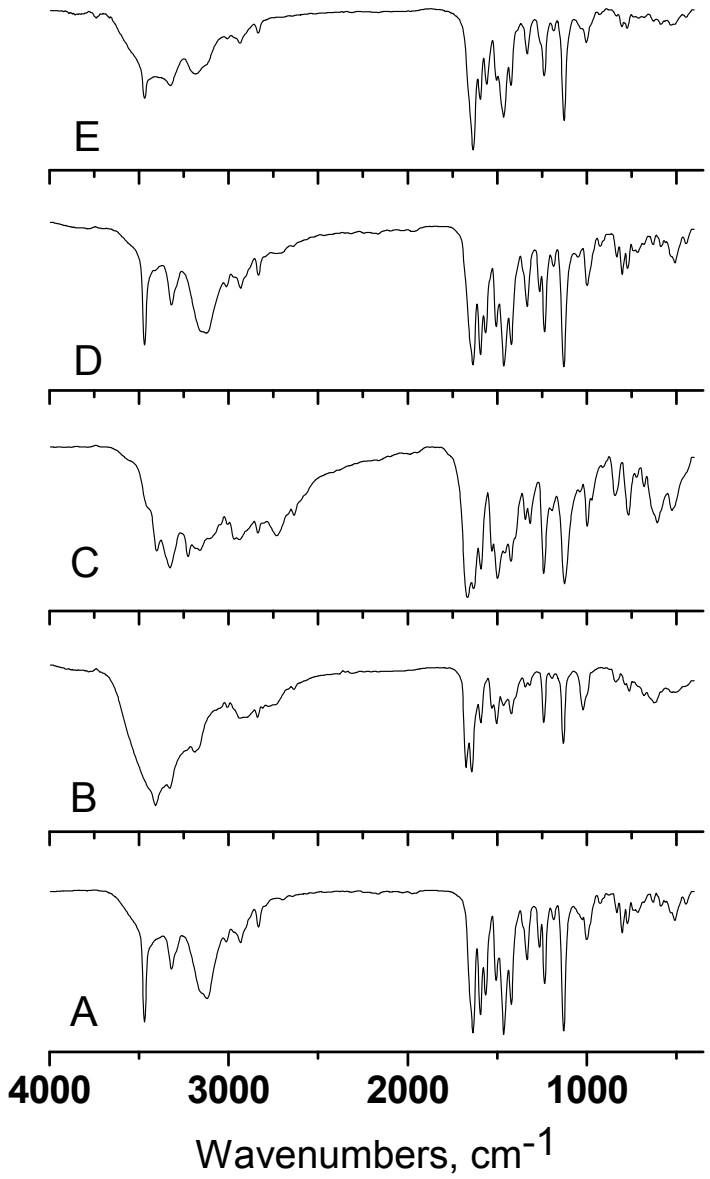

Fig. 2 – Infrared spectra of TMP free ligand and its iron(III), gold(III), platinum(IV) and palladium(II) complexes (A, B, C, D, and E, respectively).

Table 2

Infrared spectral data (cm^{-1}) of TMP and its complexes

Compounds	Frequencies, cm^{-1}						
	ν_{as}(NH)	ν_s(NH)	$\nu(CH_3)$	$\delta(CH_3)$	ν(C=N)	ν(C=C)	ν(M-N)
TMP	3470	3319	2933 2833	1464 1333	1635	1594	--
Fe(III)	3408	3190	3007 2839	1465 1343	1643	1592	526
Au(III)	3401	3227	2940 2836	1458 1343	1632	1591	525
Pt(IV)	3405	3220	2930 2832	1455 1340	1637	1590	520
Pd(II)	3407	3184	2936 2833	1464 1333	1635	1595	530

3. Electronic spectra and magnetic susceptibility

The diamagnetic complexes of $[Au(TMP)Cl_2].Cl.2H_2O$, $[Pt(TMP)Cl_2].Cl_2.2H_2O$ and $[Pd(TMP)Cl_2]$ have a square planar geometry. The electronic absorption spectrum of orange iron(III) complex contains a bands at 275, 285, 330 nm, these bands are assigned to charge transfer transition from $t_{2g}\rightarrow\pi^*$ and $\pi\rightarrow e_g$. The effective magnetic moment of iron(III) complex is (μ_{eff} = 5.26 B.M), this meaning that the Fe(III) complex formed with an octahedral geometry.[13] The electronic absorption spectrum of Au(III) yellow complex has three absorption bands at 325, 290 and 280 nm attributed to $^1A_{1g}\rightarrow{}^1A_{2g}$, $^1A_{1g}\rightarrow{}^1B_{1g}$, $^1A_{1g}\rightarrow{}^1E_g$ and charge transfer transitions, respectively. These bands were assigned to the low-spin square planar configuration.[14] The yellow color of platinum(IV) and palladium(II) complexes can be revealed to the d-d transition bands.[13] These complexes display high energy absorption band around 290 nm which can be traced to a typical charge transfer transitions in the complexes[13] confirming the square planar geometry.

4. ^{1}HNMR spectra

^{1}H-NMR spectra and the assignments for TMP free drug and $[Au(TMP)Cl_2]Cl{\cdot}2H_2O$ complex are displayed in Table 3 and Fig. 3. The peaks at δ 3.40, 3.52 & 3.72, 5.71 & 6.10 and 6.55 & 7.51 ppm attributed to protons of the CH_2, two methoxy OCH_3 groups, two NH_2 groups and two protons of Ar-H group in case of trimethoprim ligand respectively.[3] The protons of the two NH_2 groups exhibited downfield shift to 6.20 ppm and the other proton at 5.71 ppm is disappeared in case of gold(III) complex. This is slightly shifted from 6.10 ppm in the ligand to 6.20 ppm in the complex due to the coordination of the nitrogen atoms of the two NH_2 groups to the gold(III) metal ion.

5. X-ray powder diffraction and TEM analyses

X-ray powder diffraction spectrum of gold(III) TMP complex within 5-90° 2θ range is presented as shown in Fig. 4, the diffraction patterns has a crystalline behavior. The Scherrer equation[15] was utilized to calculate the particle size of the synthesized gold(III) complex based on the full-width at half-maximum. Transmission electron microscopy image of the $[Au(TMP)(Cl)_2]Cl{\cdot}2H_2O$ complex is shown in Fig. 5, the complex show a black spherical spots with ~ 10 nm nano-scale.

Table 3

^{1}HNMR spectral data (cm^{-1}) of TMP and its gold(III) complex

Assignments	Compounds	
	TMP	Gold(III) complex
CH_2	3.40	3.48
OCH_3	3.52, 3.72	3.59, 3.74
NH_2	5.71, 6.10	6.20
Ar-H	6.55, 7.51	6.62, 7.46

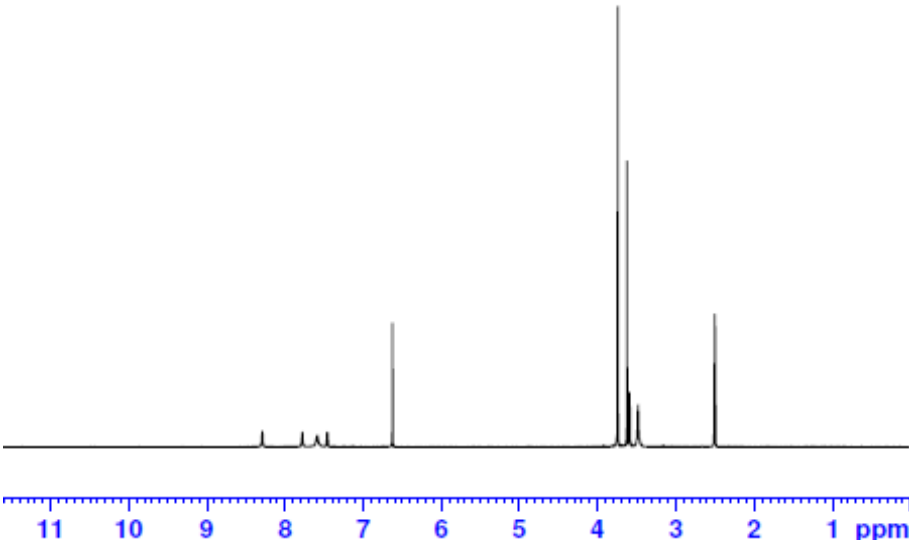

Fig. 3 – ^{1}HNMR spectrum of gold(III) TMP complex.

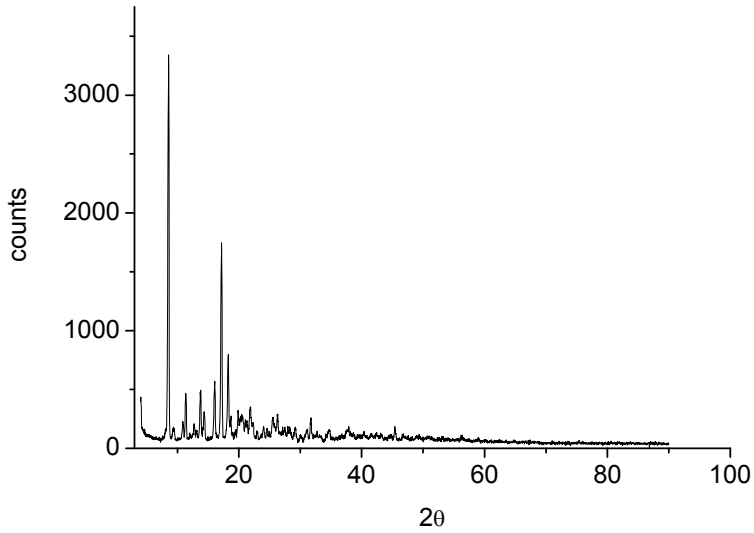

Fig. 4 – XRD spectrum of gold(III) TMP complex.

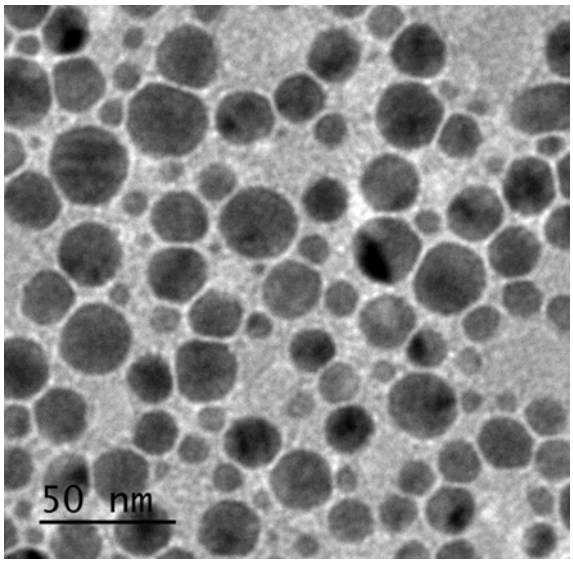

Fig. 5 – TEM image of gold(III) TMP complex.

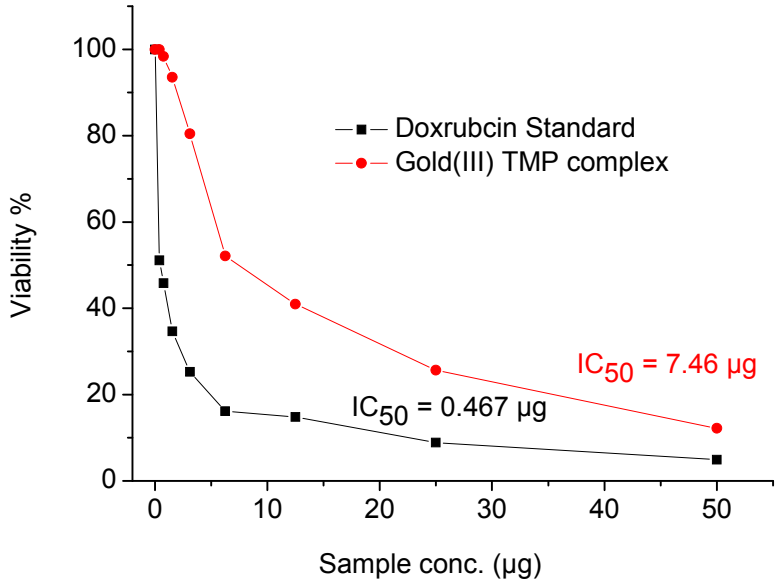

Fig. 6a – Cytotoxicity evaluation of doxorubicin standard and gold(III) TMP complex against HepG2 cell line.

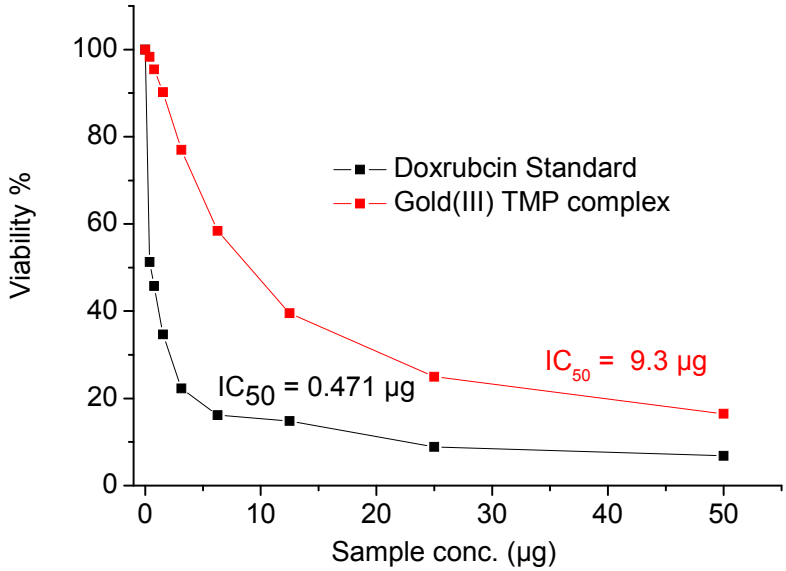

Fig. 6b – Cytotoxicity evaluation of doxorubicin standard and gold(III) TMP complex against HCT-116 cell line.

6. Anticancer assessment

The cytotoxicity activity of the gold(III) complex against HepG2 and HCT-116 cancer cell lines were assessed (Fig. 6a,b). The half maximal inhibitory concentration (IC_{50}) percentage of the gold(III) complex against HepG2 and HCT-116 cancer cell lines are 7.46 µg/mL and 9.30 µg/mL respectively, in comparison with doxorubicin standard drug (0.35 & 0.36 µg/mL against HCT-116 and HepG2 respectively). From this result, it can be concluded that the gold(III) TMP has a potential anticancer agent against HepG2 cell line rather than HCT-116.

CONCLUSIONS

In present investigation synthesis of Fe(III), Au(III), Pt(IV) and Pd(II) complexes of trimethoprim have been reported. These synthesized complexes have been characterized with the help of infrared (FT IR), electronic and ^{1}H-NMR spectra, molar conductance, and magnetic susceptibility measurements at room temperature. Based on the results obtained four coordinated has been proposed for all these complexes except iron(III) complex that has an octahedral geometry. The Au(III) complex was also screened for their anticancer activities against

HepG2 and HCT-116 cancer cell lines and the results obtained are discussed.

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