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STUDIES ON DNA CLEAVAGE, ANTIMICROBIAL SCREENING AND ANTICANCER ACTIVITY OF Zr(IV) AND Th(IV) METAL COMPLEXES OF DFMPM AND GLYCINE

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ABSTRACT

The Zr(IV) and Th(IV) Schiff base complexes with di-α-formylmethoxybis(3-pentadecenylphenyl)methane (DFMPM) and glycine were synthesized and characterized by elemental analysis, conductivity measurements, electronic, IR, 1HNMR spectral measurements, Powder XRD and SEM. The conductance measurements indicate that all the complexes are non electrolytes. Infrared spectra indicate the coordination of imino nitrogen and carboxylato oxygen. The electronic 1HNMR spectral results indicate that both Zr(IV) and Th(IV) ions are octacoordinated and ligand is tetradentate. The Zr(IV) and Th(IV) complexes have better antimicrobial activity, DNA cleavage ability and anticancer activity.

INTRODUCTION

Schiff bases are useful chelators because of their ease of preparation, structural varieties, varied denticities and subtle steric and electronic control on their framework (Qin W *et al*., 2013, Kumar S *et al*., 2013, Katwal R *et al*., 2013, Pattanaik S *et al*., 2011, Malik S *et al*., 2011). Recently a great deal of interest have developed in the synthesis and characterization of transition metal complexes containing Schiff bases as ligands due to their applications as catalysts for many reactions and relation to synthetic and natural oxygen carriers. The biocidal effect of Schiff bases as well as its metal complexes is of interest due to their pharmacological activities (Bakir M *et al*., 2009, Emam SM *et al*., 2009, Sumathi S *et al*., 2011, Tharmaraj P *et al*., 2009). Keeping the above facts in mind and in continuation of our recent work (Issa M *et al*., 2009, Sheela CD *et al*., 2010, Agwara MO *et al*., 2010, Pandey VK *et al*., 2010, Sharma AK *et al*.,2011, Subramanian P *et al*., 2013) on Schiff bases and their metal complexes, in our present endeavour, we have chosen to synthesis of a Schiff base and its Zr(IV) and Th(IV) metal complexes. The ligand and its metal complexes were also screened for in vitro antimicrobial activity, DNA cleavage and anticancer activity.

MATERIALS AND PHYSICAL MEASUREMENTS

Cardanol was obtained from M/S Satya Cashew, Chennai, India. Formaldehyde (37% solution) hydrochloric acid, epichlorohydrin, glycine, sodium hydroxide and other chemicals used were of AR grade quality obtained from Merk Chemicals. All the solvent used was purified by standard methods. The micro analytical data (C, H, N) were collected using Perkin Elmer 2400 instrument. The metal ion intake were estimated by standard methods. IR spectra were obtained using PE IR spectrum instrument model: system 2000. 1HNMR spectra were obtained using AMX–300 MHz, FT NMR Spectrometer. Conductance measurements were obtained using systronics–305 conductivity meter. Electronic spectra of the ligands and its complexes was obtained using Perkins Elmer Lamda–25 UV-visible spectrometer in the range of 200-1100 nm. Surface morphological studies was obtained using JSM–5610 scanning electron microscope.

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Synthesis

Synthesis of bis(3-pentadecenyl) phenylmethane (BPPM), diglycidylether of bis (3-pentadecenylphenyl) methane (DEBPPM), di-αformylmethoxybis (3-pentadecenyl) methane(DFMPM) were prepared as per the earlier methods (Isac Sobana Raj C *et al* (2016) a). Synthesis of Schiff base ligands with DFMPM and glycine. The synthesis of Schiff base ligand was carried out by reported methods (Isac Sobana Raj C *et al* (2016) b). Ethanolic solution of DFMPM and glycine in ethanol containing KOH were taken in RB flask in 1:2 molar ratios and refluxed for an hour. The reaction mixture was poured in ice, an yellow compound of Schiff base ligands was obtained (Scheme 1). The precipitated yellow compound was filtered, washed with water and dried over anhydrous calcium chloride. The crude sample was recrystalised from 50% absolute alcohol. Yield = 61% Melting point = 229oC.

Synthesis of Schiff base metal complexes

The metal complexes were prepared by adding aqueous solution of Zr(IV) nitrate and Th(IV) nitrate to the ligand in ethanol in 1:1 molar ratio and refluxed for about twelve hours at 80oC. (Isac Sobana Raj C *et al* (2016) c) The precipitated solids were filtered, washed with ethanol, diethyl ether and hot water and finally dried under vacuum at 90oC. Yield = 61 – 67%.

RESULTS AND DISCUSSION

All the metal complexes are coloured solids, stable towards air and have high melting points (above 250oC). The complexes are insoluble in water and common organic solvents, but are soluble in DMF, CDCl3 and DMSO.

Elemental Analysis

The analytical data suggest that all the complexes are mono nuclear with the ligands coordinated to the central metal atom. The metal to ligand ratio in all complexes was 1 : 1 and their formulae have been computed and given in Table 1.

Table 1. Physical characteristics and analytical data of the complexes

Compound	Yield %	Colour	Mol. formula	Mol.wt	MP°C	Elemental Analysis			Molar conductance ohm^{-1}cm^{2} mol^{-1}
						C	H	N	
$C_{51}H_{76}N_2O_6$	61	Yellow	$C_{51}H_{76}N_2O_6$	812	228	75.1 (75.3)	9.2 (9.3)	3.3 (3.4)	-
$ZrL(NO_3)_2(H_2O)_2$	67	brown	$ZrC_{51}H_{80}N_4O_{14}$	1063.2	> 259	57.5 (57.6)	7.1 (7.5)	5.1 (5.2)	11
$ThL(NO_3)_2(H_2O)_2$	65	brown	$ThC_{51}H_{80}N_4O_{14}$	1204	> 250	50.5 (50.8)	6.5 (6.6)	4.5 (4.5)	12

Table 2. Selected UV and FTIR frequencies (cm^{-1}) of the ligand and complexes

Ligand/ Complex	ν_{O-H}	ν_{C-H}	ν_{O-C}	$\nu_{C=N}$	$\nu_{assym\ COO^-}$	ν_{symCOO^-}	ν_{M-N}	ν_{M-O}	λ_{max} (nm)		
$C_{51}H_{76}N_2O_6$	3413	3009	2926	1700	1596	1452	-	-	239	278	801
$ZrL(NO_3)_2(H_2O)_2$	3479	2925	2854	1690	1595	1420	774	417	203	272	1203
$ThL(NO_3)_2(H_2O)_2$	3442	2925	2853	1690	1594	1496	774	545	212	270	1202

Molar conductivities of solution of the complexes in DMF are shown in Table 1. All the complexes are non – electrolytes because their conductivity values were low. However, the conductivity value is higher than expected for non- electrolytes probably due to partial solvolysis of complexes in DMF medium.

IR Spectra

Selected IR Spectral bands for the ligand and its complexes are given in Table 2.

The IR spectrum of the free ligand is characterized mainly by the strong bands at 3009 cm^{-1}, 2926 cm^{-1}, 1596 cm $^{-1}$, 1452 cm^{-1} and 1700 cm^{-1} which are attributed to the stretching frequencies of C - H, O - C, assym COO-, sym coo- and HC = N (azomethine) respectively. The IR Spectrum of the free ligands was compared with the spectra of metal complexes. The characterized absorption bands 3479 cm^{-1} and 3442 cm^{-1} range were attributed to **-**OH group of the lattice water or the coordinated water. The absorption bands in the range 2925 cm^{-1} and 2925 cm^{-1} were assigned to stretching frequencies of C-H. The absorption bands in the range 2854 cm^{-1}and 2853 cm^{-1} were assigned to stretching frequencies of O-C group. The absorption bands in the range. 1595cm^{-1}, 1594cm^{-1} and 1420 cm^{-1}, 1496cm^{-1}, were assigned to asym coo- sym coo- stretching frequencies. The absorption bands in the range 1690 cm^{-1}, and 1690 cm^{-1} were assigned to HC = N stretching frequencies. The imine peak in the metal complexes showed change in shifts compared to the ligand indicating coordination of the imine nitrogen atom to the metal ion due to coordination. Another absorption bands at 774 cm^{-1} and 774 cm^{-1} is assigned to M-N bond and 417 cm^{-1}& 545 cm^{-1} is assigned M - O bonds.

^{1}H NMR Spectra

On examining the ^{1}HNMR spectrum of ligand (Fig 4) it exhibited a multiplet signal at δ = 7.16 ppm - 7.18 ppm for aromatic protons. The presence of HC = N group is indicated by the singlet at δ = 7.2 ppm. Signals at δ = 6. 73 ppm - 6.78 ppm, δ = 4. 10 ppm - 4.17 ppm, 3.32 ppm - 3.39 ppm and 1.2 ppm - 2 ppm indicate the presence of olefinic, - CH2-COO, O - CH2 and -CH2- protons. The ^{1}HNMR spectrum of Th(IV) complex(Fig 5) gave the signals for aromatic protons (δ = 7. 2 ppm - 7.5 ppm, olefinic protons (δ = 4. 12 ppm - 4. 16 ppm), - O CH2 - proton (δ = 3.4 ppm) - CH2 - protons (δ = 1.2 ppm - 2 ppm) and CH = N protons (δ = 7. 7 ppm). There is a down field shift of imine proton after complex formation than in the ligand. Thus ^{1}H NMR study also confirmed the structural information of both ligand and its complexes.

V - Visible Spectra

The UV - visible spectra are often very helpful in the evaluation of results furnished by other methods of structural investigation. The ligands showed a broad band at 239 nm which is assigned to $\pi \rightarrow \pi^*$ transition of the C = N chromophore (Rajasekar K etal., 2013 ,Mohanambal D *et al.*, 2014). On complexation this band was shifted to the lower wavelength suggesting the coordination of imine nitrogen with central metal ion.

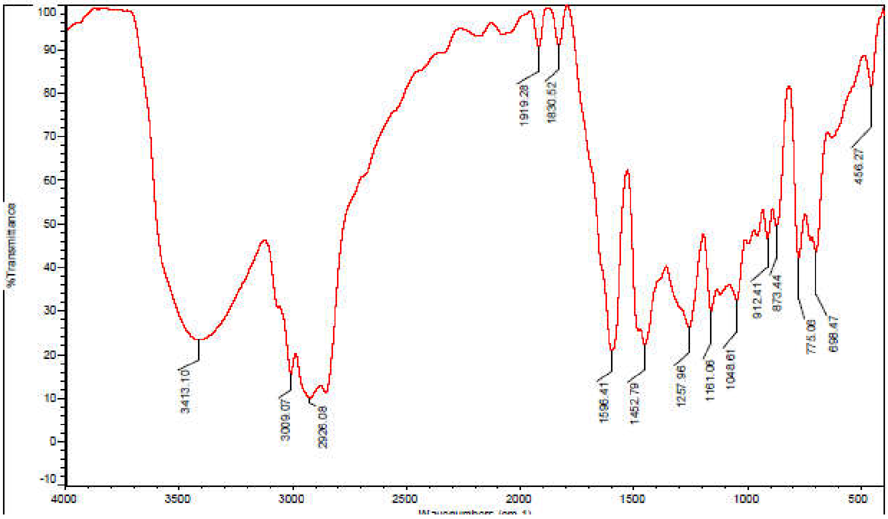


Figure 1. FTIR Spectrum of Schiff base ligand

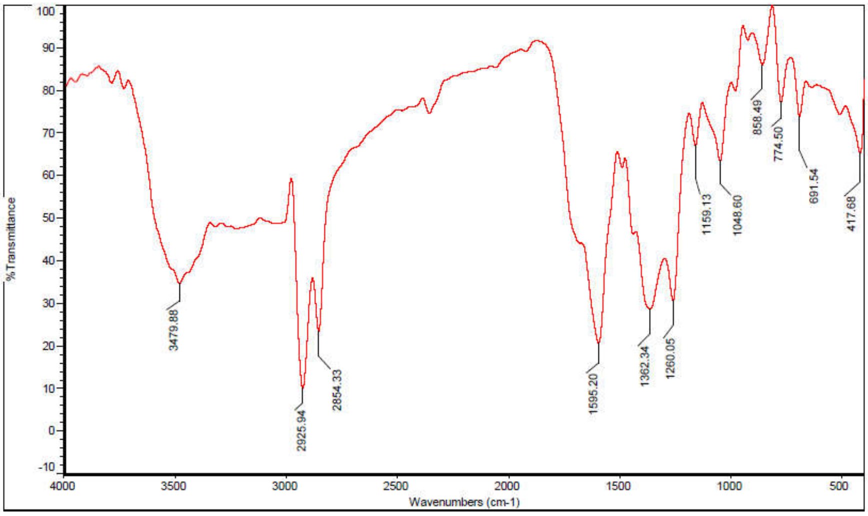


Figure 2. FTIR Spectrum of Zr (IV) complex

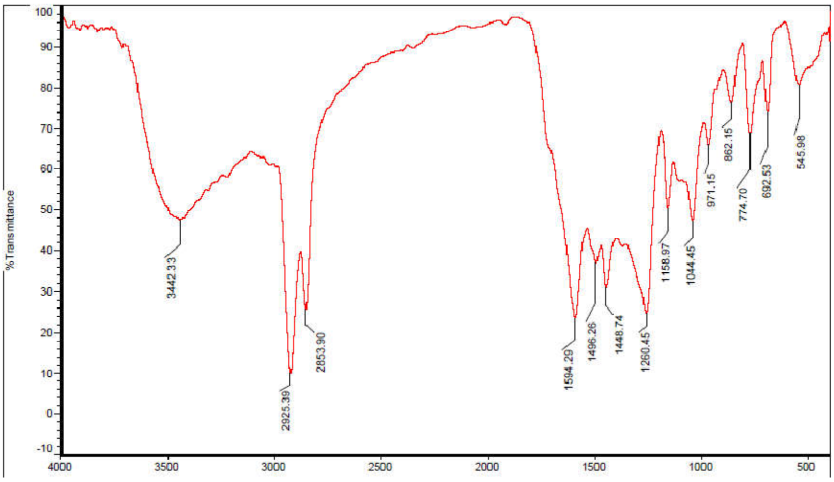


Figure 3. FTIR Spectrum of Th(IV) complex

The UV absorption spectra of the Zr (IV) and Th (IV) exhibit only one extra highly intensive band in the region on 272 nm & 279 nm which may be due to charge transfer band besides ligand bands. However UV- visible spectra could not provide structural details of these complexes. Zr (IV) has the coordination number of 4, 6, 7 and 8. Earlier researchers are indicated the coordination number of Th (IV) is also 6, 8 or 10. The Zr (IV) and Th (IV) formed 1 : 1 complexes. Hence the complexes of Zr (IV) and Th (IV) are believed to have the coordination number of 8. The – NO_3 group is present in the coordination sphere because conductance data showed that the complexes are non–

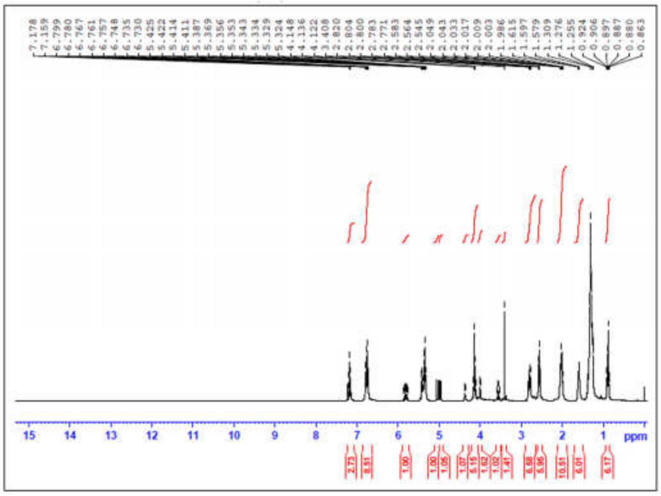


Figure 4. ¹HNMR Spectrum of Ligand

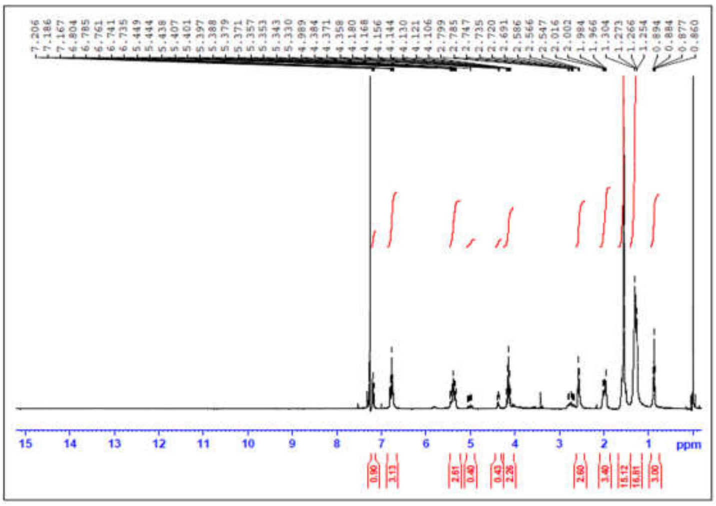
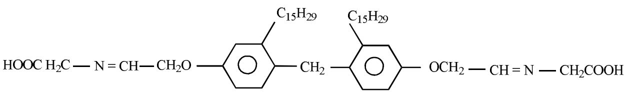
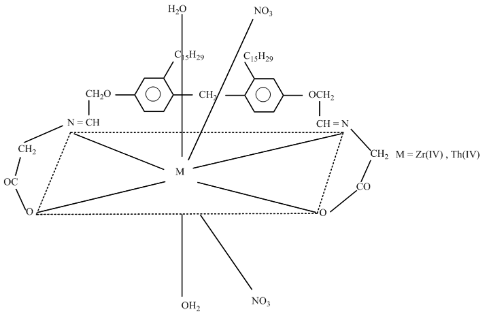


Figure 5. ¹H NMR Spectrum of Th(IV) Complex

electrolytes and NO_3 groups were coordinated with the central Zr (IV) or Th (IV) ion (Lakshmi SS *et al*., 2011). On the basis of forgoing observation the probable structure of ligand and Zr (IV) and Th (IV) complexes may be presented as follows.Earlier researcher also reported the octa coordination of Zr (IV) and Th (IV) Schiff base complexes (Abdul Wajid etal., 2013, Manjula B *et al*., 2013, Anand Prakash Mishra etal., 2012),



Scheme 1. Structure of Schiff base ligand



Scheme 2. Structure of Schiff base complexes of Zr (IV) or Th (IV) ions

SEM Analysis

Surface morphology of the Zr (V) and Th (IV) complexes in this study are shown in Fig. 6,7. From the fig 6, 7 pitted and rough surface is observed in the complex. The particle sizes of the Zr (IV) and Th (IV) complexes were in the diameter range of few microns. Careful examination of the single crystal, clearly indicated the nano scale size of the single crystal of the complexes (Shakir M,*et al*., 2011).

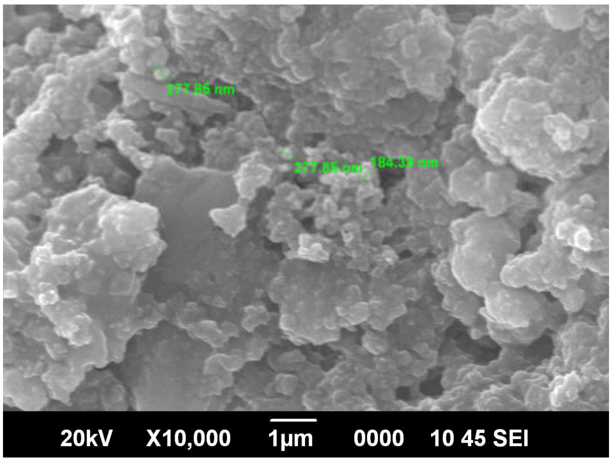


Figure 6. SEM image of Schiff base complex of Zr (IV)

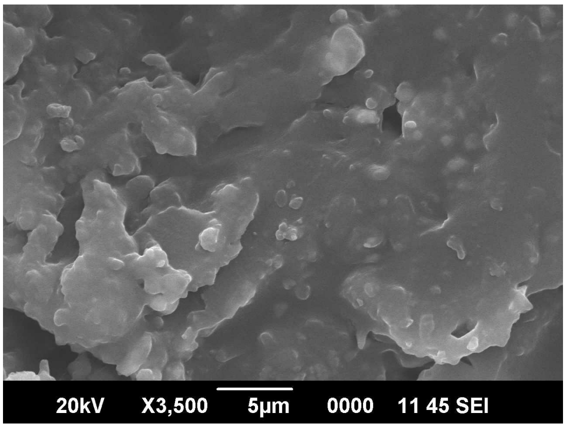


Figure 7. SEM image of Schiff base complex of Th(IV)

Powder XRD

Powder XRD patterns of Zr (IV) and Th (IV) complexes recorded in the range (2θ= 0 – 180o) were shown in Fig 8 and 9. XRD patterns of the metal complexes show the sharp crystalline peaks indicating their crystallite phase. The average crystalline size (dXRD) of the complexes was calculated using Scherrer's formula (Jayaseelan P *et al*., 2013). The Zr (IV) and Th (IV) complexes have an average crystallite size of 2.85 nm & 1.39 nm.

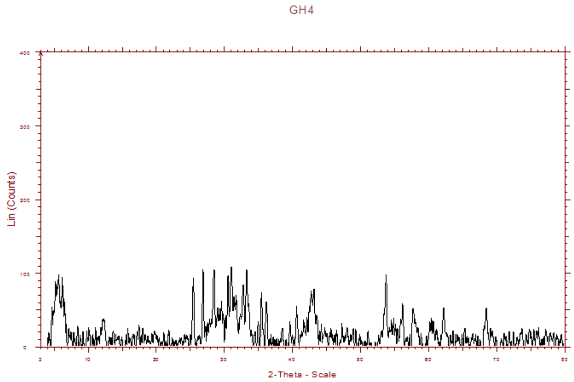


Figure 8: XRD Spectrum of Zr (IV) Complex

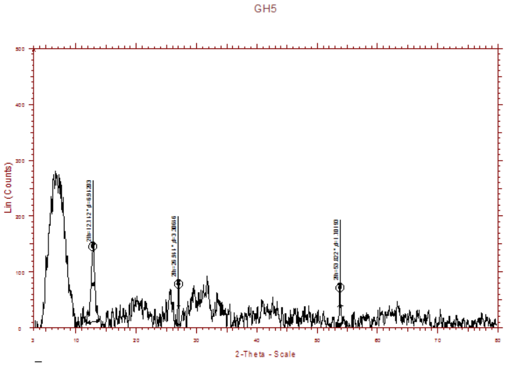


Figure 9. XRD Spectrum of Th (IV) Complex

Antimicrobial Activity

In the present investigation, biological activity of the ligands and their complexes` with Zr (IV) and Th (IV), have been screened for antimicrobial activity against bacteria (Klebsiella sps, E.coli, P.aeruginosa and S. aureus) and fungi (Candida sps and Aspergillus sps) by disc diffusion method. The concentration for these samples was maintained as 1mg/mL in DMSO. The results thus obtained were explained on the basis of Overtone's concept and Chelation theory (Ramachandran E *et al*., 2012), Raman N *et al*., 2011 a.). The mode of action of the compounds may involve formation of a hydrogen bond through the azomethine group with the active centers of cell constituents, resulting in a interference with the normal cell process (Singh S *et al*., 2013). The variation in the activity of different complexes against different organisms depends either on impermeability of the cells of the microbes or difference in ribosome of microbial cell. A composition of the biological activity of the synthesized compounds with some known antibiotics (Chloramphenicol and Nystatin is presented in Table.3 & 4. It is observed that the Schiff base metal complexes exhibit better activity than the corresponding ligand.

DNA Cleavage Studies

The DNA cleavage activities of Schiff base ligand and its metal complexes at a 1 μM concentration were studied using pUC18 DNA (2μg) in H_2O_2 (10 μL) in 30 mM Tris Buffer (pH-7.4) and upon irradiation with uv light. The reaction is modulated by metallo complexes bound hydroxyl radical or a peroxo species generated from the co-reactant H_2O_2. It is evident from Fig.9, that the Zr (IV) and Th (IV) complex cleave DNA more efficiently in the presence of an oxidant than the ligand. This may be hydroxyl free radicals, which can be produced by metal ions reacting with H2O2 to produce the diffusible hydroxyl radical or molecular oxygen, which may damage DNA through Fenton type Chemistry. This hydroxyl radical participates in the oxidation of the deoxyribose moiety, followed by hydrolytic cleavage of sugar - phosphate back bone(Raman N *et al*.,2011 a, Raman N *et al*.,2011 b, Ramachandran E *et al*., 2012). . Further, the presence of a smear in the gel diagram indicated the presence of radical cleavage.

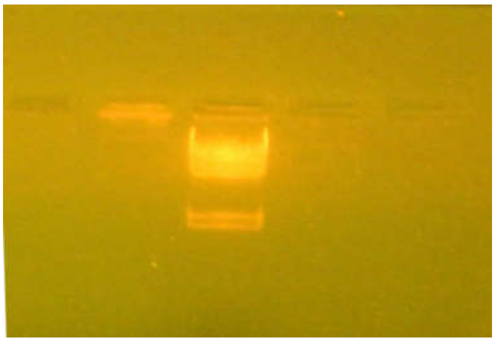


Figure 9. Gel electrophoresis diagram of the Schiff base metal complexes

Lane 1: Control DNA
Lane 2: Marker
Lane 3: DNA + L + H_2O_2
Lane 4: DNA + $[ZrL(NO_3)_2 (H_2O)_2] + H_2O_2$
Lane 5: DNA + $[ThL(NO_3)_2 (H_2O)_2] + H_2O_2$

Anticancer Activity

The result of anticancer activities are presented in Table 5 & 6. The colon carcinoma (HT-20) cells, were sensitive to the Th(IV) complex with an IC_{50} value of 80.06 μM. The cytotoxic activity may be assigned to that the positive charge of the metal increased the acidity of coordinated ligand that bears protons, leading to stronger hydrogen bonds which enhanced the biological activity.

Table 3. Antimicrobial activity for Bacteria

S.No	Samples	Media	Zone of Inhibition (mm)			
			Klebeiella	E.coli	aeruginosa	S.aureus
1	$C_{51}H_{76}N_2O_6$		6.0	6.0	6.0	6.0
2	$ZrL(NO_3)_2(H_2O)_2$	Muller	6.0	6.0	11.0	6.0
3	$ThL(NO_3)_2(H_2O)_2$	Hinton	12.0	6.0	10.0	6.0
4	PC (Chlorampheninol)	Agar	25.0	26.0	24.0	25.0
5	NC		6.0	6.0	6.0	6.0

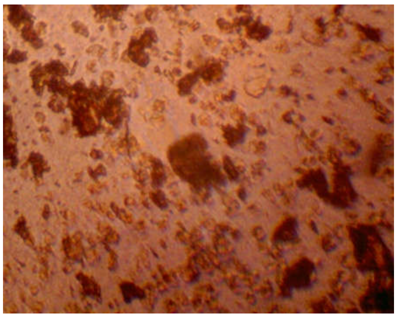
Table 4. Antimicrobial Activity for fungi

S.No	Samples	Media	Zone of Inhibition (mm)	
			Candida sps	Aspergillus sps
1	$C_{51}H_{76}N_2O_6$		6.0	6.0
2	$ZrL(NO_3)_2(H_2O)_2$	Muller	10.0	6.0
3	$Th\ L\ (NO_3)_2(H_2O)_2$	Hinton	6.0	10.0
4	PC (Nystatin)	Agar	25.0	26.0
5	NC		6.0	6.0

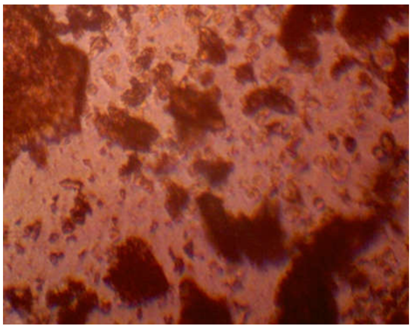
Table 5. % viability of Th(IV) complex

Sample Concentration (µg/ml)	Average OD at 570nm	Percentage Viability
Control	0.617	
6.25	0.607	98.37
12.5	0.591	95.78
25	0.542	87.84
50	0.403	65.31
100	0.230	37.27

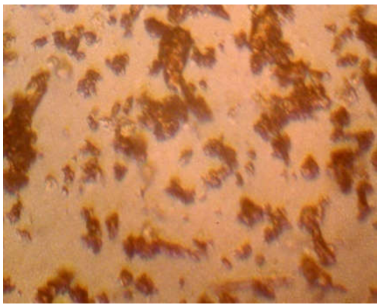
IC_{50} = 80.06 µM



a)Th (IV) Complex at 25 µM



b) Th (IV) Complex at 50 µM



c)Th (IV) Complex at 100 µM

Figure 10. Microscopic observation of anticancer activity

It seems that changing the anion, coordination sites, and the nature of the metal ion has a pronounced effect on the biological behavior by altering the binding ability of DNA. Gaetke and Chow had reported that metal has been suggested to facilitate oxidative tissue injury through a free radical mediated pathway analogous to the Fenton reaction. (Fig. 10 a, b and c). Schiff base complexes of Zr(IV) and Th(IV) were synthesized from DFMPM using glycine were clearly described and characterized on the basis of analytical and spectral data. The SEM & XRD analysis indicate that the crystals of Schiff base metal complexes are nano crystalline in nature. Anti microbial study showed that the complexes have higher anti microbial activity than the ligand. The DNA cleavage studies show that the Zr(IV) and Th(IV) complexes cleave DNA more efficiently. The in-vitro anti cancer studies reveal that the Th(IV) complex had better anticancer activity against HT-29(colon carcinoma) cell with IC_{50} value of 80.06 µM.

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