



Synthesis, Characterization, Fluorescence, Electrochemical, Antimicrobial and Cytotoxic studies of Cobalt(II), Nickel(II) and Copper(II) Complexes with N-4-Methylphenyl (2,4-dihydroxyacetophenylideneimine)

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ABSTRACT

N-4-Methylphenyl(2,4-dihydroxyacetophenylideneimine)(NMEPDHAPI) complexes of Co(II), Ni(II) and Cu(II) have been synthesized and characterized. A study on their electrochemical, fluorescence and biological behaviour have also been performed. The complexes have been characterized on account of metal estimation studies, conductance behaviour, magnetic property, IR, UV-Visible, EPR(Liquid nitrogen temperature) spectral studies and thermal analysis. The 1:2 metal : ligand complex formation is authenticated from the analytical data. Based on the various studies, the Co(II) complex has been recommended for octahedral geometry and a square planar geometry has been prompted for Cu(II) and Ni(II) complexes. The electro chemical property of the complexes have been studied by cyclic voltammetry. The Schiff base and its complexes have been scrutinized against bacterial and fungal pathogens. The complexes have been found to be more active than the Schiff base towards most of the pathogens studied. *In vitro* cytotoxicity of the copper complex of NMEPDHAPI has been screened against breast cancer cell lines (MCF-7). The IC_{50} value recommend that the copper complex has notable cytotoxicity against breast cancer cell line (MCF-7).

Keywords: Schiff base, Antimicrobial, Fluorescence, Cyclic voltammetry.

INTRODUCTION

The metal complexes with azo linkage have been explored remarkably during the last few decades.¹⁻³ Biological resemblance of Schiff bases is due to the structural resemblance of peptide bonds in protein.⁴ Such type of metal complexes exhibit many types of applications like catalysis⁵, pharmaceuticals⁶

and molecular based materials⁷. The continuous need for renewed anti-cancer drug has developed chemotherapeutic research depending upon the consume of metallic elements since this must have high potential activity and low side effects.⁸ A well known anticancer drug is cisplatin. Unfortunately cisplatin has number of side effects, which limit the clinical use⁹. Therefore finding a new metal based



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drug with more activity and less side toxicity is a thrust area of research.¹⁰ The present report involves the synthesis of three transition metal complexes based on the Schiff base NMEPDHAPI. All three have been characterized from different spectral studies like IR, UV-Visible and EPR in Liquid nitrogen temperature. The redox behavior from Cyclic voltammetry studies revealed the catalytic application of complexes and fluorescence property indicates the sensor applicability of the complexes. Both the ligand and the complexes have been screened against bacterial and fungal pathogens. Anticancer activity (*In vitro* cytotoxicity) of the copper complex of NMEPDHAPI has been inquired towards breast cancer cell lines (MCF-7).

EXPERIMENTAL

Materials and Methods

IR spectra were performed in KBr medium in FT-IR spectrophotometer (model : Shimadzu IR affinity). Measurements were recorded on powder samples at 298K. Thermal analysis was done by using the instrument (Perkin Elmer Diamond TG/DTA) from 40°C to 740°C at the heating range about 20°C/minute. The EPR spectra were recorded using JEOL model JES FA200 ESR spectrometer in liquid nitrogen temperature. The UV-spectra of the Schiff base and its complexes were taken using Perkin Elmer Spectrometer provided with quartz cells in DMSO medium. The electrical conductance of the synthesized complexes were determined in 10⁻³ M solution of DMSO using a conductivity bridge of Elico make and a dip type conductivity cell. The percentage of metal was estimated by the standard methods. The magnetic susceptibility were ascertained in a Gouy Balance at room temperature. Electrochemical behaviour were measured at room temperature in an air tight three electrode cell by using glassy carbon electrode as a working electrode, a platinum wire served as the counter electrode and a Ag/AgCl in a saturated KCl solution as reference electrode. The electrochemical reactions were carried out using tetrabutylammonium perchlorate (0.11M) as a supporting electrolyte with a scan rate of 0.2V/s. The fluorescence spectra were analysed by using Jasco Spectro Fluorimeter (Model FP-8200) at room temperature by maintaining the concentration at 10⁻⁴M in DMSO.

Synthesis of complexes

The Schiff base N-4-methylphenyl-(2,4-dihydroxyacetophenylideneimine) (NMEPDHAPI) has been synthesized, characterized through data from spectral studies. Its structure was established by single crystal XRD analysis by the authors in their previous article.¹¹ The ligand NMEPDHAPI (0.2 mmol) and the metal salt (0.1 mmol) (cobalt acetate, Nickel chloride & copper chloride) were dissolved in 100 ml of ethanol and allowed to react for 6 h at 60°C. The complex formed was filtered, washed with water and dried. The complexes are found to be freely soluble in DMF and DMSO.

[Co(NMEPDHAPI)₂(H₂O)₂]

Yield: 90%, M.p.> 255°C. m.w(g/mol):575.5; Metal percentage found (Calcd.): 9.82(10.24); IR (Solid state, cm⁻¹): ν(O-H) 3439; ν(-C=N-)1655; ν(C-O) 1257; ν(M-O) 604; ν(M-N) 459; UV (In DMSO, λ_{max} /nm): 924 (⁴T_{1g}(F) → ⁴T_{2g}; ⁴T_{1g}(F) → ⁴A_{2g}(F); ⁴T_{1g}(F) → ⁴A_{2g}(P); Conductivity in DMSO(ΔM): 18 ohm⁻¹cm²mol⁻¹.

[Ni(NMEPDHAPI)₂]

Yield:85% , M.p.>260°C m.w(g/mol): 539.2; Metal percentage found (Calcd.): 10.23(10.88); IR (Solid state, cm⁻¹): ν(O-H) 3362; ν(- C=N -) 1641; ν(C-O) 1226; ν(M-O) 626; ν(M-N) 534; UV (In DMSO, λ_{max}/nm): 527 (¹A_{1g} → ³A_{2g}; ¹A_{1g} → ¹A_{2g}; ¹A_{1g} → ¹B_{1g}); Conductivity in DMSO(ΔM): 14 ohm⁻¹cm²mol⁻¹.

[Cu(NMEPDHAPI)₂]

Yield: 86%, M.p.>250°C m.w(g/mol): 544.1; Metal percentage found (Calcd.): 11.08 (11.68); IR (Solid state, cm⁻¹): ν(O-H) 3439; ν(- C=N-) 1607; ν(C-O) 1246; ν(M-O) 623; ν(M-N) 468; UV (In DMSO, λ_{max} /nm): 537nm (²B_{1g} → ²E_g; ²B_{1g} → ²B_{2g} and ²B_{1g} → ²A_{1g}); Conductivity in DMSO(ΔM): 22 ohm⁻¹cm²mol⁻¹.

The biopotency of all the synthesized metal complexes and the Schiff base ligand has been examined by disc diffusion technique employing nutrient agar as medium. The bacterial and fungal pathogens chosen for the study were *staphylococcus aureus*, *klebsiella aerogenes*, *candida albicans* and *aspergillus niger*.

Anticancer activities

The human breast adeno carcinoma cell lines (MCF7) was collected from National Centre for

Cell Science (NCCS), Pune. The MTT assay method was implemented to evaluate the cytotoxicity.^{12,13} The % cell inhibition was inclined by applying the formula % Cell Inhibition = 100- Abs (sample)/Abs (control) x100. Nonlinear regression graph was computed between % Cell inhibition and Log concentration. The IC50 was ascertained by employing GraphPad Prism software.

RESULTS AND DISCUSSION

Characterisation of complexes

FT-IR spectra

In complexes the band assignable to the azomethine linkage is shifted from 1605 cm^{-1} in the Schiff base to 1607-1655 cm^{-1} in their metal complexes. This proves the binding between the metal and azomethine linkage.¹⁴ The nitrogen coordination may be further authenticated by the presence of new band in the order of 467-561 in the complexes corresponding to M-N bond which is absent in the ligand.^{15,16} The another coordination site is phenolic oxygen which is present in the ortho position to the imine group. This is evidenced by the emergence of new band correlating to metal-oxygen bond around 600 cm^{-1} in the complexes.^{17,18} The C-O stretching vibration of phenolic group is noticed at 1282 cm^{-1} in the Schiff base NMEPDHAPI. This band is displaced to lower frequency in the spectra of complexes authenticating metal oxygen coordination.¹⁹

Electronic spectra and magnetic susceptibility

The UV spectrum of the Co(II) complex exhibit the transition at 924 nm assignable to ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}$, ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(P)$ transitions²⁰ and the magnetic moment of 4.65 BM support the octahedral arrangement around Co(II) ion.²¹ The band at 527 nm in Ni(II) complex is designated to the transitions from ${}^1A_{1g} \rightarrow {}^3A_{2g}$, ${}^1A_{1g} \rightarrow {}^1A_{2g}$ and ${}^1A_{1g} \rightarrow {}^1B_{1g}$ respectively²² correlating to the square planar geometry around Ni(II) and is diamagnetic.²³ In the Cu(II) complex the band at 537 nm is ascribed to ${}^2B_{1g} \rightarrow {}^2E_g$, ${}^2B_{1g} \rightarrow {}^2B_{2g}$ and ${}^2B_{1g} \rightarrow {}^2A_{1g}$ transitions²⁴ of Cu(II) with square planar geometry. The magnetic moment of 1.54 BM substantiate the square planar geometry²⁵ around Cu(II). The UV spectra of the complexes are given in supplementary data (Figure S1-S3).

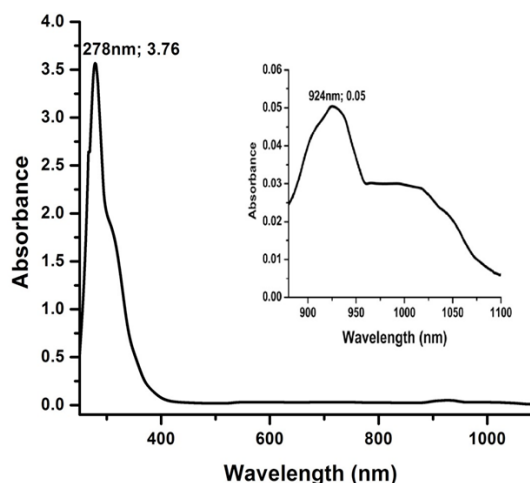


Fig.S1. UV spectra of $[\text{Co}(\text{NMEPDHAPI})_2(\text{H}_2\text{O})_2]$

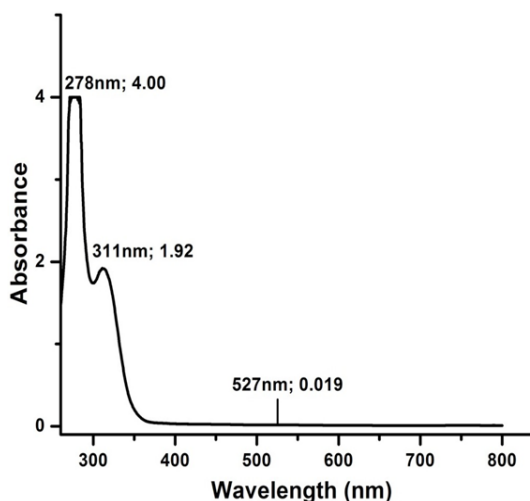


Fig. S2. UV spectra of $[\text{Ni}(\text{NMEPDHAPI})_2]$

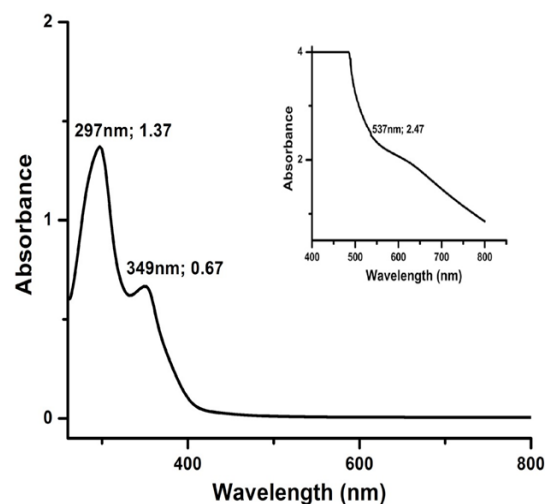


Fig. S3. UV spectra of $[\text{Cu}(\text{NMEPDHAPI})_2]$

EPR spectra

In liquid nitrogen temperature the complex $[\text{Cu}(\text{NMEPDHAPI})_2]$ exhibits well defined peaks. The ground state of Cu(II) complex can be determined from the g value. In square planar complexes the unpaired electron lies in the $d_{x^2-y^2}$ orbital giving ${}^2B_{1g}$ as the ground state with $g_{\parallel} > g_{\perp}$. In our case for $[\text{Cu}(\text{NMEPDHAPI})_2]$, $g_{\parallel} > g_{\perp}$ ($2.30 > 2.03$) which denotes the predominant existence of unpaired electron in $d_{x^2-y^2}$ orbital²⁶ rather than d_z^2 . As a result the screening effect by the d_z^2 electrons is to a greater extent leading to elongation (Jahn teller distortion) finally detachment of two orbitals from the metal ion, resulting in square planor geometry. The epr spectra of the complex is shown in Figure 1.

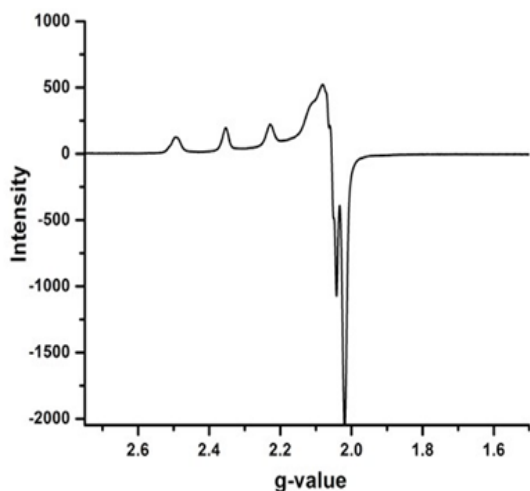


Fig. 1. EPR Spectra of $[\text{Cu}(\text{NMEPDHAPI})_2]$

Conductance measurements

The molar conductance of the complexes were found to be ranging from $14 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$ to $22 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$. This evidences the non-electrolytic quality of the complexes.²⁷ No change in conductance is observed when determined in different solutions. This further substantiate the neutral quality of all three complexes.

Metal estimation studies

The metal percentage of all the complexes were ascertained through standard methods.²⁸ The amount of cobalt in complex was estimated by pyrolytic method. The quantity of nickel calculated by using titrimetric method. The copper percentage were found by colorimetric method. The values obtained are conforming with the values manipulated for the proposed structure of the complexes.

Thermal Analysis

In thermo gravimetric analysis of $[\text{Co}(\text{NMEPDHAPI})_2(\text{H}_2\text{O})_2]$, the first weight loss noticed in the temperature range $101-142^\circ\text{C}$ (observed 5.97%, calculated 6.25%) is correlated with the displacement of two water molecules bound Co(II) ion. Another weight loss is in the temperature range of $156-519^\circ\text{C}$ (observed 83.20%, calculated 83.85%) is suitable to the twofold decomposition of binary molecules of ligand NMEPDHAPI. In $[\text{Ni}(\text{NMEPDHAPI})_2]$ the weight loss ascertained in the temperature range $158-542^\circ\text{C}$ (observed 89.67%, calculated 89.45%) is also due to the double step decomposition of two molecules of ligand. The thermogram of $[\text{Cu}(\text{NMEPDHAPI})_2]$ showed only one weight loss in the temperature range $136-382^\circ\text{C}$ (observed 88.69%, calculated 85.09%) is owed to disintegration of couple of ligand moieties.²⁹ The thermogram of all the complexes finally attains constant mass due to the dissipation of analogous metal oxides. The TGA/DTA curves are given under supplementary data (Figure S4-S6).

From the above analytical data it is may be concluded that the cobalt complex is having octahedral geometry with two coordinated water molecules and nickel and copper complexes are in square planar geometry. The structure assigned for the complexes is depicted in Figures 2 and 3.

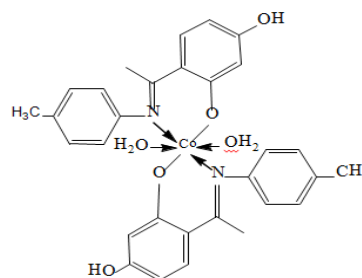


Fig. 2. $[\text{Co}(\text{NMEPDHAPI})_2(\text{H}_2\text{O})_2]$

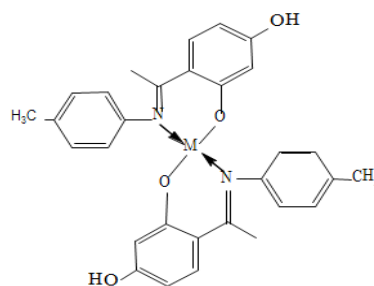


Fig. 3. $[\text{M}(\text{NMEPDHAPI})_2]$, M=Ni(II) and Cu(II)

Study on Redox Property

The cyclic voltammogram of $[\text{Co}(\text{NMEPDHAPI})_2(\text{H}_2\text{O})_2]$ exhibits two well defined quasi-reversible peaks. First reduction peak found in $E_{p_c} = -0.680\text{V}$ with an associated oxidation peak placed at $E_{p_a} = -0.338\text{V}$ and second reduction peak appearing in $E_{p_c} = 0.132\text{V}$ is associated with oxidation peak situated at $E_{p_a} = 0.673\text{V}$. The value of ΔE_p is 0.342V and 0.541V for first and second redox couples respectively and the ratio between oxidation and reduction peak current indicative of simple quasi-reversible one electron redox processes.³⁰ The voltammogram of $[\text{Ni}(\text{NMPDHAPI})_2]$ also shows one well denoted redox process. The reduction peak is viewed at $E_{p_c} = -0.994\text{V}$ and the oxidation peak is noted at $E_{p_a} = 0.730\text{V}$. This couple is quasi-reversible and ratio between oxidation and reduction current suggests the process to be simple one-electron transfer³¹. The voltammogram of $[\text{Cu}(\text{NMPDHAPI})_2]$ displays one oxidation peak at $E_{p_a} = -0.715\text{V}$ and the corresponding reduction peak at $E_{p_c} = -1.224\text{V}$. The another oxidation peak found in $E_{p_a} = 0.603\text{V}$ and the respective reduction peak placed at $E_{p_c} = 0.120\text{V}$. The ΔE_p values 0.509V and 0.483V shows that the redox processes are quasi-reversible. The correlation of oxidation to reduction peak height suggest that the the process is simple one electron process.³² The cyclic voltammograms are given in Fig 4. The redox property of the complex may find the application in catalytic studies.

Fluorescence Property

The fluorescence spectra of all the synthesized compounds are shown in Fig. 5. The emission peaks are noticed in the range of $357\text{-}359\text{ nm}$. Quenching of emission was observed in all the three complexes. This may be due to the predominance of PET process over CHEF effect.³³ This quenching may lead to the chemo sensor utility of the Schiff base.

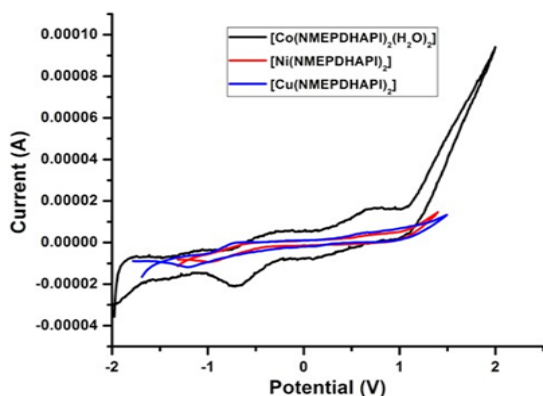


Fig. 4. Cyclic voltammogram of complexes

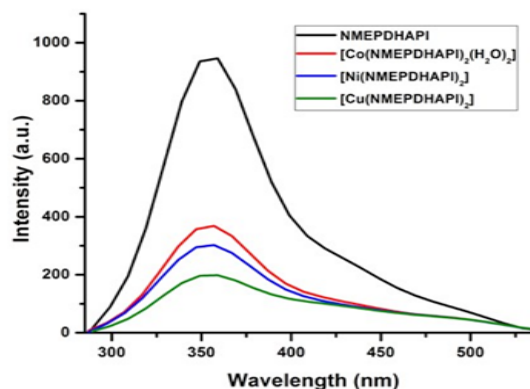


Fig. 5. Fluorescence spectra of NMEPDHAPI and its complexes

Antimicrobial activities

Antimicrobial activities of NMEPDHAPI and their complexes are given in Table 1. It is ascertained that the complexes are more active than the Schiff base towards almost all pathogens studied, which can be elucidated by Tweedy's chelation theory.³⁴ Lipophilic nature of the metal ion increases by chelation, which could facilitates to cross the lipid layer of the cell membrane. The coordination of metal ion to the Schiff base influence the magnetic property and conductance which may also be a cause for the extensive biological characteristics of the complexes. The azomethine bond also extend contribution for activity of the complexes³⁵. The maximum sensitiveness of the complexes is observed with the fungal pathogen candida albicans. The antimicrobial activity images are shown in Figures 6 and 7.

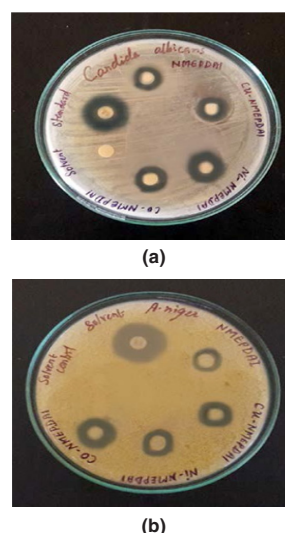


Fig. 6. (a) Activity against *C. Albicans* and (b) Activity against *A. Niger*

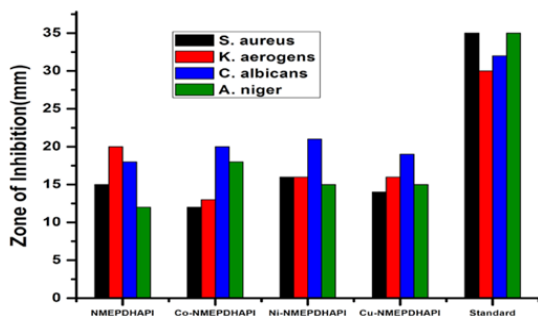


Fig. 7. Antimicrobial activity of Schiff base and its metal complexes

Anticancer activities

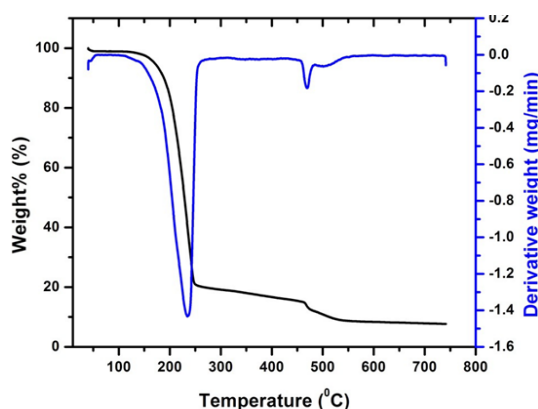
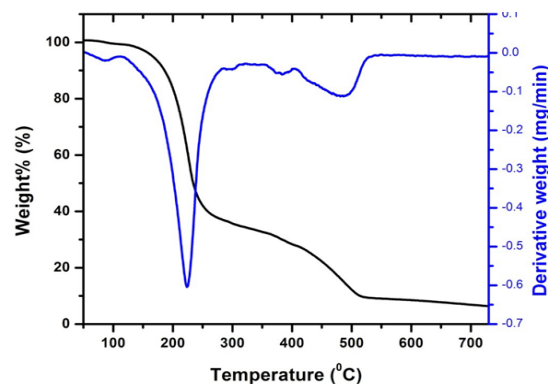
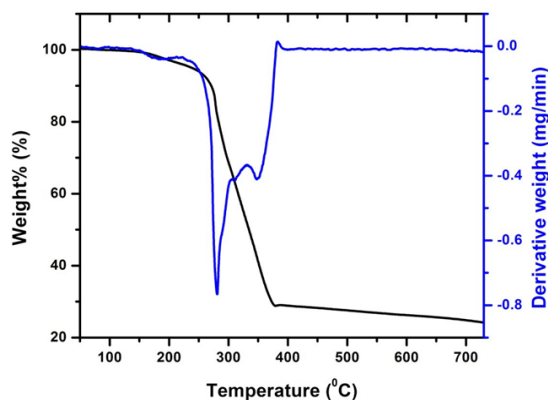
The *in vitro* cytotoxicity of copper complex were examined against breast cancer cell line (MCF-7) by MTT assay. The % of cell inhibition in different concentration shown in the Fig. 7 and Table 2. The IC_{50} value of copper complex ($27.61\mu M$) compared with cis platin ($4.5\mu M$). From the IC_{50} value, it may be accomplished that the copper complex possess considerable cytotoxicity for breast cancer cell line (MCF-7).

Table 1: Antimicrobial activity of the ligand and its complexes

Compound /Complex	Zone of Inhibition in mm			
	<i>G</i> -positive		<i>G</i> -negative	
	SA	KA	CA	AN
NMEPDHAPI	15	20	18	12
$[Co(NMEPDHAPI)_2(H_2O)_2]$	12	13	20	18
$[Ni(NMEPDHAPI)_2]$	16	16	21	15
$[Cu(NMEPDHAPI)_2]$	14	16	19	15
Standard	35	30	32	35

Table 2: % Cell inhibition of $[Cu(NMEPDHAPI)_2]$ towards breast cancer cell line(MCF-7)

S. No	Conc(μM)	% Cell Inhibition
1	0.25	1.053864
2	2.5	4.800937
3	25	37.00234
4	50	96.01874
5	100	100

Fig. S5. TGA/DTA curve of $[Ni(NMEPDHAPI)_2]$ Fig. S4. TGA/DTA curve of $[Co(NMEPDHAPI)_2(H_2O)_2]$ Fig. S6. TGA/DTA curve of $[Ni(NMEPDHAPI)_2]$

CONCLUSION

The ligand NMEPDHAPI has been complexated with Cobalt(II), Nickel (II) and Copper (II). Analytical data exhibited that there is formation of 2:1 ligand to metal complexes. The low conductivity values intimated that the complexes are of neutral in nature. From various studies Co(II) complex has been suggested an octahedral geometry and a square planar geometry has been proposed for Ni(II) and Cu(II) complexes. The study of redox property and fluorescence property indicate that the complexes may find application as catalysts and chemosensors. The complexes are found to possess remarkable biopotency towards most of the pathogens studied which could be explained by chelation theory. The copper complex exhibits

considerable cytotoxic behaviour towards breast cancer cell line (MCF-7).

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