

Synthesis, Spectral Characterization and Biological Evaluation of Schiff Base Metal Complexes Derived from Aniline Derivative

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A new Schiff base ligand (L) N-(4-fluorophenyl)-1-(4-(((4-fluorophenyl)imino)methyl)phenyl)methanimine was prepared by the condensation of terephthalaldehyde with 4-fluoroaniline in 1:2 molar ratio. The mononuclear complexes of Co(II), Ni(II), Cu(II) and Zn(II) (**1-4**) have been synthesized in (2:1) ligand to metal ratio. The composition, geometry and binding sites of ligand with metal complexes were evidenced by various spectral methods like molar conductance, elemental analytical data, magnetic measurements, UV-visible, ¹H & ¹³C NMR, ESI-MS, FT-IR, ESR and thermal analysis. The above studies shows that the ligand is a bidentate and its metal complexes possess an octahedral geometry. Oxidative cleavage of DNA studies of the complexes were monitored by super helix PUC18DNA using a method of agarose gel electrophoresis. Ligand and its metal complexes were screened against gram positive (*Staphylococcus aureus*), gram negative (*Klebsiella pneumoniae*) bacterium and fungus (*Candida albicans*) strains. Antioxidant activities of the metal complexes possess greater activity than ligand.

Keywords: Schiff Base metal(II) complexes, 4-Fluoroaniline, Octahedral geometry, Antimicrobial activities, DNA cleavage studies.

INTRODUCTION

Substituted aniline derivatives of Schiff base complexes have been extensively used as anticancer agents in pharmacological applications and also act as polymeric materials [1-3]. In the fluorinated compounds, fluorine plays vital role in medicinal chemistry is considered by number of drugs being prepared in the pharmaceutical fields [4-6]. The hydrogenation of (CH=N) bond present in Schiff base ligand, form more stable complexes due to enhancing basicity of N atoms and coordinating properties with metal in reduced Schiff base as compared to their former Schiff base reactants [7].

Reactivity of Schiff base depends upon the electron donor, electron acceptor properties and nature of ligands, when coordination sphere contains binding ability in between ligand to metal [8]. The formation of stable Schiff base complexes contain novel therapeutics and biological applications such as antiviral, antimalarial, antibacterial, anti-fungal and anti-inflammatory in coordination chemistry [9,10]. DNA cleavage is an important enzymatic reaction, which concerns in several pharmaceutical

and biological processes. The conventional behavioural changes of DNA, when transition metal chelates hold the approaches in the bioinorganic chemistry [11]. Possible high nuclease activity of DNA in reducing environment, may lead to potential binding nature of the compounds [12]. The aim of present work is to synthesis Schiff base metal complexes with ligand N-(4-fluorophenyl)-1-(4-(((4-fluorophenyl)imino)-methyl)phenyl)-methanimine prepared from terephthalaldehyde and 4-fluoroaniline characterized by various spectral techniques.

EXPERIMENTAL

Terephthalaldehyde, 4-fluoroaniline, hydrated metal(II) chloride, methanol, diethyl ether, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) were used as analytical grade without further purification purchased from Sigma-Aldrich. The elemental analyses of C, H and N were carried out with a model FLASH 1112 SERIES elemental analyzer. The molar conductance of compounds was measured at room temperature using DMF of concentration 1×10^{-3} M. Electro spray ionization of mass spectra in mode of positive (ESI-MS) was performed

with a Q-TOF mass spectrometer. The magnetic moment of powdered samples at room temperature was calculated using the Gouy's method with a calibrant $\text{Hg}[\text{Co}(\text{SCN})_4]$. The ^1H and ^{13}C NMR (300MHz) spectrum were carried with Bruker Avance with CDCl_3 as solvent and TMS as an internal reference. The FT-IR spectra of complexes were recorded as KBr pellets using SHIMADZU model spectrometer in range 4000-400 cm^{-1} . The electronic spectral studies were recorded using Lambda Perkin Elemer spectrometer in the range of 200-800 cm^{-1} . The ESR spectrum of X-band in DMSO was obtained at room temperature JES-FA200 (Japan) ESR spectrometer with tetracyano ethylene using as a standard. Thermal analyses were performed with DSC-TGA Universal V4.5A instrument. The temperature range was 30-800 $^\circ\text{C}$ at heating rate of 20 $^\circ\text{C}/\text{min}$ in oxygen atmosphere.

Preparation of ligand (L): The ligand N-(4-fluorophenyl)-1-(4-(((4-fluorophenyl)imino)methyl)phenyl)methanimine has been synthesized by mixing 2:1 ratio of methanolic solution (20 mL) of 4-fluoroaniline (2 mmol) with terephthalaldehyde (1 mmol) with constant stirring to 4 h and pale yellow precipitate was obtained. The precipitate was filtered and then washed with methanol followed by diethyl ether, dried in vacuum.

Synthesis of metal(II) chloride complexes: All the metal(II) complexes were synthesized by the following general procedure in 2:1 ratio of ligand with hydrated metal(II) chloride salts. The complexes **1-4** were prepared by the addition of 20 mL methanol solution (1 mmol) of hydrated metal(II) chlorides with ligand (2 mmol) dissolved in methanol and followed by the addition of two drops of triethylamine. The reacting mixture was stirred and refluxed for 3 h at 60 $^\circ\text{C}$. The obtained coloured metal complexes were filtered, washed with methanol and followed by diethyl ether and finally dried in vacuum.

DNA cleavage: The efficiency of super helix PUC18DNA cleavage was promoted by the synthesized metal(II) complexes using agarose gel electrophoresis method. The reaction mixture 20 μL containing PUC18DNA 50Mm, Tris-HCl, pH 7.4, 52 Mm of NaCl, 10 Mm of H_2O_2 were added in a different volume and then adding the millipore water for final volume. The mixed solutions were incubated at 37 $^\circ\text{C}$ for 1 h. After adding 0.5g powdered agarose to 50 mL of buffer solution, it is heated and then cooled, added to ethidium bromide. The gel was examined under ultraviolet light and photographed.

in vitro Antimicrobial activity: *in vitro* Antibacterial activity of ligand and its mononuclear complexes were screened by 1 g positive bacteria (*Staphylococcus aureus*) and gram negative bacteria (*Klebsiella pneumoniae*) maintained at 4 $^\circ\text{C}$ on nutrient agar slants disc of agar well diffusion method. A 100 μL of culture supernatant was loaded into disc and the disc was incubated at 37 $^\circ\text{C}$ for 24 h. The resulting clear inhibition zone was

appeared in surrounding surfaces. Standard antibiotic bacteria strain Tetracycline (10 mg/mL) in DMSO solvent was used. The antifungal activity was tested by the fungi (*Candida albicans*) in potato dextrose agar medium incubated at 37 $^\circ\text{C}$ for 2-3 days. Kanamycin (7.5 mg/mL) in DMSO solvent was used as a standard.

DPPH radical scavenging activity: The free radical scavenging activity of ligand and its metal(II) complexes were measured by using 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay. The complexes were dissolved in DMSO (10 mg/mL) and used as stock solutions. From 1 mL of stock solution at different concentrations were added to 3 mL of DPPH (0.004 %) dissolved in DMSO. The mixtures were vortex-mixed and kept at room temperature under dark condition for 30 min. After that the absorbance of complexes (**1-4**) was taken at 517 nm using UV-VIS spectrometer with BHA (*tert*-butyl-4-hydroxyanisole) used as standard and DPPH solution was used as control without complexes. The radical scavenging activity was calculated as percentage of DPPH decolorization by using the following formula:

$$\text{Scavenging activity (\%)} = \frac{A_0 - A_1}{A_0} \times 100$$

where, A_0 is the absorbance of the control and A_1 is the absorbance of the sample. The IC_{50} (concentration of sample required to scavenge 50 % free radical or to prevent lipid peroxidation by 50 %) was calculated from the regression equation.

RESULTS AND DISCUSSION

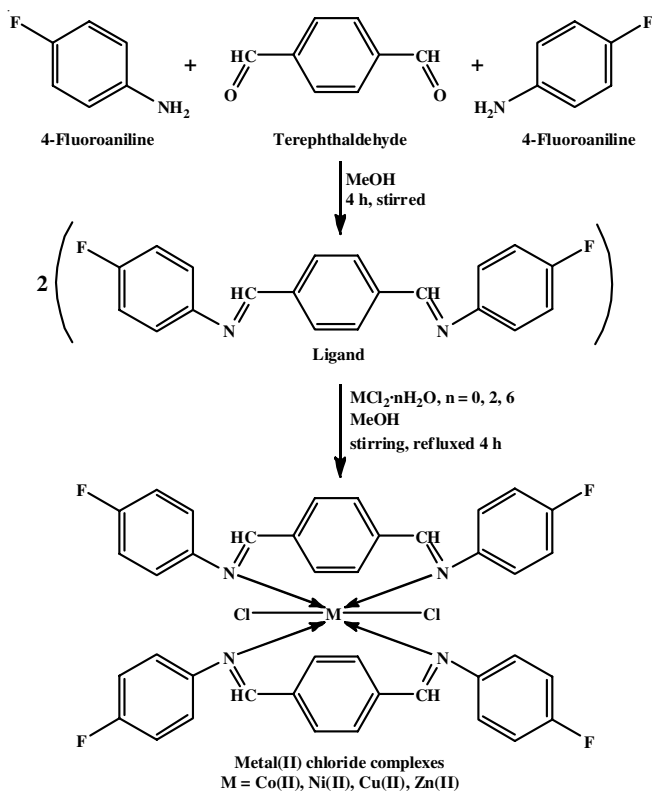
All the synthesized metal complexes **1-4** are coloured powders and stable in air at room temperature. The analytical data of the complexes suggests that all prepared complexes are M:2L ratio (Table-1) and have general formula ML_2Cl_2 as shown in **Scheme-I**. All the complexes are insoluble in common organic solvents (methanol, ethanol, chloroform, etc.) and soluble in DMF and DMSO at ambient temperature.

Molar conductance: The conductance of all the metal complexes in DMF (1×10^{-3} M) solutions are in the range 5.8-12 $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$ (Table-1). The resulting low conductance values revealed all the metal complexes are non-electrolytic in nature [13] and indicates that chloride ions are directly coordinated to metal ions [14].

NMR spectra: ^1H NMR spectra of Schiff base ligand in CDCl_3 exhibited signals of multiplet at δ 7.01-7.27 ppm assigned to aryl protons and other aryl proton is observed at δ 8.001 ppm as a singlet [15]. The protons of two imines (-CH=N-) group appear as singlet at δ 8.50 ppm. The structure of ligand is also supported by ^{13}C NMR spectrum. The carbon of imine group exhibited a peak at δ 159.09 ppm. In ligand, terephthalaldehyde carbon peaks appeared at δ 129.1, 138.5 and 115.8-

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF SCHIFF BASE LIGAND (L) AND 1-4 COMPLEXES

Compound formula	Colour	m.w.	Yield (%)	m.p. ($^\circ\text{C}$)	Elemental analysis (%): Calcd. (Found)				Λ_m ($\Omega \text{cm}^2 \text{mol}^{-1}$)
					C	H	N	Cl	
$\text{C}_{20}\text{H}_{14}\text{F}_2\text{N}_2$ (L)	Pale-yellow	320.10	80	190	74.82 (74.99)	4.01 (4.41)	11.86 (11.21)	–	–
$\text{CoC}_{40}\text{H}_{28}\text{F}_4\text{N}_4\text{Cl}_2$ (1)	Pale-green	770.06	70	290	62.35 (61.64)	3.67 (3.72)	7.28 (7.53)	9.21 (9.34)	4.2
$\text{NiC}_{40}\text{H}_{28}\text{F}_4\text{N}_4\text{Cl}_2$ (2)	Pale-green	769.82	68	245	62.33 (62.01)	3.66 (3.37)	7.27 (7.31)	9.21 (8.91)	8.1
$\text{CuC}_{40}\text{H}_{28}\text{F}_4\text{N}_4\text{Cl}_2$ (3)	Black	774.68	75	294	61.96 (59.97)	3.67 (3.91)	7.23 (7.64)	9.15 (8.75)	5.8
$\text{ZnC}_{40}\text{H}_{28}\text{F}_4\text{N}_4\text{Cl}_2$ (4)	Dirty-yellow	776.54	65	267	61.81 (60.94)	3.63 (3.21)	7.21 (7.14)	9.13 (9.29)	3.2



Scheme-I: Synthesis of ligand and proposed structure of metal(II) complexes

122.5 ppm peaks are due to carbon of substituted aniline. The last singlet peak recorded at δ 163.1 ppm is due to fluorine substituted carbon of aniline in the ligand.

ESI-Mass spectra: The stoichiometric composition of ligand and its metal complex **3** was determined using ESI mass spectrum. The molecular ion peak of ligand M^+ observed at $m/z = 320.7$ amu and various fragmentation (L) peaks appeared at 320.7, 227.8, 216.8, 111.9 amu (Fig. 1a). This observed molecular ion peak confirms the formula of ligand ($C_{20}H_{14}N_2F_2$). The complex **3** exhibited the molecular ion peak at ($M^+ + 2H$) which is coincident with $m/z = 776.3$ amu value. The various fragmentations showed the thermal stability of complex. This value was further supported by other synthesized complexes of mass spectra (Fig. 1b).

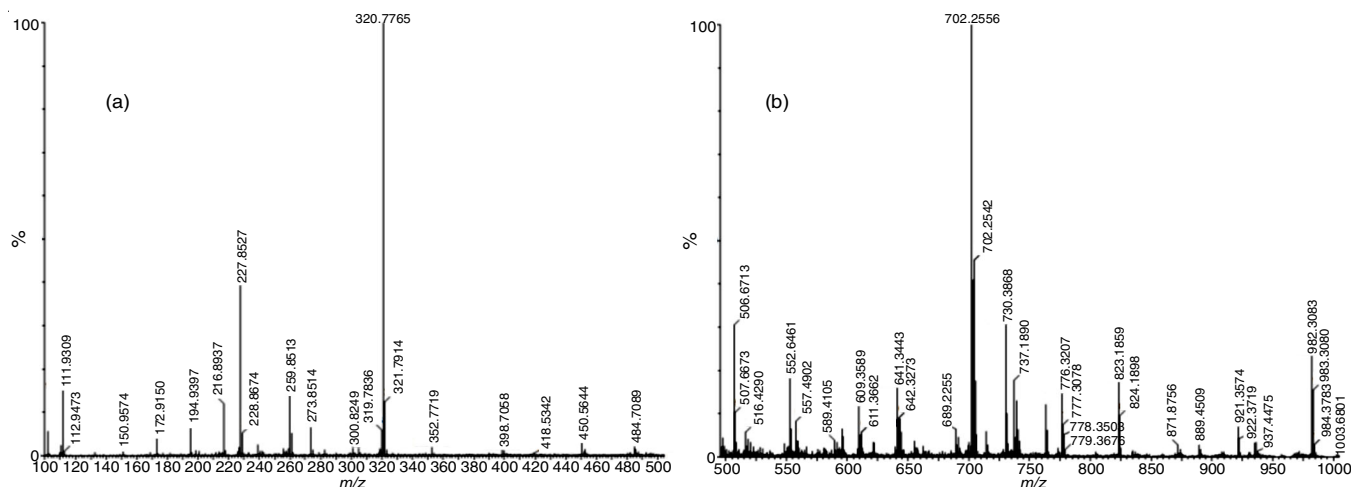


Fig. 1. Mass spectra (a) ligand L (b) Cu(II) complex

Electronic spectra and magnetic moments: The electronic spectrum of ligand exhibited three bands (intra-ligand) at 243, 293 and 350 nm. The first two bands are assigned to $\pi \rightarrow \pi^*$ transition and final band at 350 nm is assigned to $n \rightarrow \pi^*$ transition [16]. The charge transfer (L \rightarrow M) transitions of complexes displayed between 371-413 nm is due to ligand coordinated to metal(II) ion. The complex **1** displayed $d-d$ transitions of weak band at 608 nm and broad band at 672 nm with $T_{1g} \rightarrow A_{2g}$ (F) and ${}^4T_{1g} \rightarrow {}^4T_{2g}$ (F) transitions respectively. The magnetic moment value 4.7 B.M. which confirm that complex **1** possess a regular octahedral geometry [17]. The electronic absorption spectra of complex **2** attributed medium bands at 556 and 702 nm which may assign to ${}^3A_{2g}$ (F) \rightarrow ${}^3T_{1g}$ (P) and ${}^3A_{2g}$ (F) \rightarrow ${}^3T_{1g}$ (F), respectively. The magnetic moment of complex is 2.6 B.M, which is an evidence of octahedral environs around the Ni(II) ions [18]. The complex **3** exhibits a broad band at 573 nm and a medium band at 751 nm which is due to ${}^2E_g \rightarrow {}^2T_{2g}$ and ${}^2B_{1g} \rightarrow {}^2A_{2g}$ transitions, respectively. The magnetic measurement value is 1.87 B.M and this may be given a distorted octahedral stoichiometry of Cu(II) complex [19]. The diamagnetic nature of complex **4** shows the charge transfer transitions and has no $d-d$ absorptions, probably due to an octahedral geometry.

FTIR spectra: The sharp band appeared at 1620 cm^{-1} is due to the stretching vibration of azomethine ($-\text{CH}=\text{N}-$) group of Schiff base ligand [20]. For all the synthesized metal complexes **1-4**, the intensity of absorption bands at $1622-1618\text{ cm}^{-1}$ is shifted to lower or higher wavelengths indicates formation of (M-N) coordination. This is further confirmed with small intensity bands exhibited at $428-413\text{ cm}^{-1}$ of (M-N) vibrations [21]. The stretching vibrations of ($-\text{C}=\text{C}-$) aromatic ring in ligand appears as medium intensity band at 1594 cm^{-1} [22]. These vibrations shifted to lower wavelengths by $11-86\text{ cm}^{-1}$ for all the complexes **1-4** when compared to ligand.

ESR spectra: The ESR spectrum of X-band of polycrystalline solid complex **3** was recorded in powder form at room temperature (77 K) in DMSO solution. It exhibits g -tensor parameter g_{\parallel} (2.21) $>$ g_{\perp} (2.15) $>$ g_e (2.002) which indicates that the complex **3** has an unpaired electron present in $d_{x^2-y^2}$ ground state [23]. This complex displayed that the spectra is axially symmetrical with no hyperfine splitting. Commonly

six coordinated complex **3** displayed high g_{\parallel} value with ligand having N and O hard donors [24]. It concluded that the presented complex have high g_{\parallel} value of four N donors sites, which consist of a six coordinated complex **3** has a distorted octahedral Cu(II) ion. The G value is calculated following expression $G = (g_{\parallel} - 2.002)/(g_{\perp} - 2.002)$, where G measures the considerable exchange interaction of copper centre ion in the polycrystalline compound. The g_{av} is also calculated by the following relation $g_{av} = 1/3(g_{\parallel} + 2g_{\perp})$. The g_{\parallel} value also predicts the ionic and covalent environment in metal-ligand bond. The g_{\parallel} value is less than 2.3 which indicates the covalent nature present in metal-ligand bonding [25].

Thermal analysis: The ligand decomposed completely without impurity at 347 °C, with loss of weight 100 % (calc. 100 %). Decomposition of ligand is single stage process. All the metal complexes of decomposition takes places in three degradation stages. The synthesized metal complexes **1-4**, first stage start decomposing at 73-169 °C with a weight loss of 9.13-9.21 %. This is in good agreement with the calculated (9.13-9.21 %) values and the percentage of weight indicating the loss of two chlorine atoms in the coordination sphere [26].

Thermal decomposition of complex **1** consisted temperature range 161-347 °C corresponded by mass loss of 51.30 %, which is in good results with calculated (51.74 %) values and contributed to loss of $C_{24}H_{16}N_2F_2$ moiety. The third stage decomposition occurs from 345-644 °C by a weight loss of 20.42 %. It is good agreement with the calculated (20.55 %) value by assigned to removal of $C_9H_{10}+2HF$ moiety and the remaining product $5C+CoO$ as a residue. For complex **2**, second stage thermal decomposition occurs at 162-339 °C, which corresponds to the loss of $C_{24}H_{16}N_4F_4$ organic moiety. The weight loss of (55.81 %) is in good agreement with calculated (56.65 %) value. The third stage starts at 339-700 °C assigned by weight loss of 19.12 %, which is related to calculated (19.32 %) value corresponding to elimination of $C_{10}H_{12}$ and the final residue was $6C+NiO$ (Fig. 2).

The second stage thermal decomposition of complex **3** occurs at 169-302 °C, which attributed to the weight loss of 52.88 % and related to calculated (53.65 %) value with a removal of $C_{24}H_{16}N_4F_3$ organic moiety. The third stage occurs at 302-655 °C, assigned to weight loss of 15.21 % is due to the loss of $C_7H_{11}+HF$, which is good results for calculated (14.89 %) value

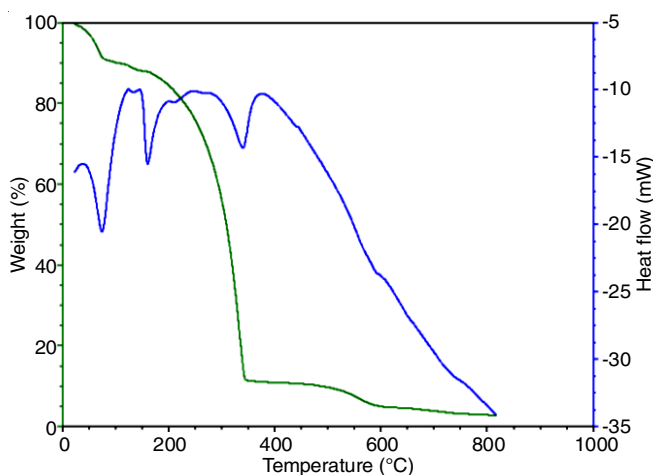


Fig. 2. DSC-TGA curve for complex **2**

and the final product $9C+CuO$ as a residue [27]. The second stage of thermal decomposition in complex **4** exhibited at 167-341 °C accompanied by the weight loss of 55.52 %, which is good agreement with calculated (56.02 %) value. The organic moiety of $C_{24}H_{16}N_4F_4$ was lost. Decomposition occurs in third stage at 341-668 °C, which contributed by loss of $C_{10}H_{12}$ organic moiety with weight loss of 17.04 % and calculated (16.44 %) value. The final residue was $6C+ZnO$. From elemental analysis data and thermal analysis curves related to confirm the structure of ligand and complexes.

DNA Cleavage: DNA cleavages of agarose gel electrophoresis method were performed against PUC18DNA with metal complexes on basis of oxidative mechanisms in being of hydrogen peroxide. DNA cleavage was presided by relaxation of the super helix (plasmid) form of PUC18DNA (Form I) into open circular form (Form II) and linear form (Form III). In Fig. 3, complex **3** cleavage activity showed good efficiency and conversion of open circular form (Form II) to linear form (Form III) with increasing in concentrations (30 and 40 μ M) (lane 3, 4) due to hydroxyl radical ($\cdot OH$), which cause damage to the sugar or base of DNA. In complexes **2** and **4**, the nuclease activity with super helix DNA (Form I) changed to open circular form (Form II) (lane 7, 9). Owing to increasing in concentrations, cleaving activity also increases (lane 8, 10). The complex **3** was completely degraded with DNA (lane 5, 6) due to presence of empty reducible metal centre make it inactive towards the hydroxyl radicals. The control DNA alone (lane 1) and with hydrogen peroxide (lane 2) having no cleaving activity. From this, concluded all the synthesized complexes **1-4** retard the growth of pathogenic organism by cleaving the genome [28].

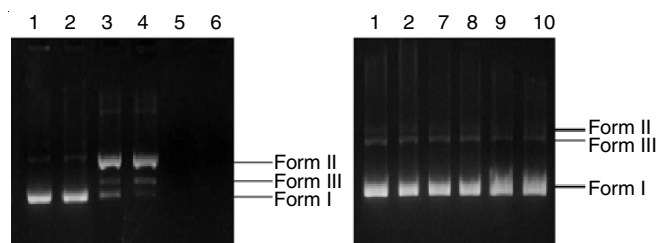


Fig. 3. Agarose-gel electrophoresis method of DNA cleavage of metal complexes in DMSO of various concentrations. Lane 1: PUC18 DNA control; Lane 2: DNA + H_2O_2 (1 mM); Lane 3: DNA + H_2O_2 (1 mM) + Cu (30 μ M); Lane 4: DNA + H_2O_2 (1 mM) + Cu (40 μ M); Lane 5: DNA + H_2O_2 (1 mM) + Co (30 μ M); Lane 6: DNA + H_2O_2 (1 mM) + Co (40 μ M); Lane 7: DNA + H_2O_2 (1 mM) + Ni (30 μ M); Lane 8: DNA + H_2O_2 (1 mM) + Ni (40 μ M); Lane 9: DNA + H_2O_2 (1 mM) + Zn (30 μ M); Lane 10: DNA + H_2O_2 (1 mM) + Zn (40 μ M)

Antimicrobial activity: The synthesized Schiff base ligand and its metal complexes were tested against gram positive *S. aureus* and gram negative *K. pneumoniae* bacterial strains with Tetracycline is used as a standard. All the complexes have shown greater activity than ligand results as given in Table-2. This is explained on the chelating theory [29] and Overton's concept [30]. From this concept mainly noticed that cell permeability and lipophilic character of compound. Owing to cell permeability, the cell is covered by lipid membrane and it allows only lipid soluble compounds, to pass through it. According to lipophilic character, the polarity of metal ion changes positive charge, due to formation of donor group. Cell permeability

TABLE-2
ANTIMICROBIAL ACTIVITY AND IC₅₀ VALUE OF LIGAND (L) AND ITS COMPLEXES (1-4)

Compound	Zone of inhibition (mm) in 100 µL concentration			IC ₅₀ (µg/mL)
	Bacterial activity		Fungal activity	
	<i>S. aureus</i>	<i>K. pneumoniae</i>	<i>C. albicans</i>	
C ₂₀ H ₁₄ F ₂ N ₂ (L)	–	–	9	0.176
CoC ₄₀ H ₂₈ F ₄ N ₄ Cl ₂ (1)	7	11	14	0.147
NiC ₄₀ H ₂₈ F ₄ N ₄ Cl ₂ (2)	7	9	11	0.121
CuC ₄₀ H ₂₈ F ₄ N ₄ Cl ₂ (3)	9	10	11	0.114
ZnC ₄₀ H ₂₈ F ₄ N ₄ Cl ₂ (4)	7	–	10	0.140
Tetracycline (10 mg/ml)	16	19	–	–
Kanamycin (7.5 mg/ml)	–	–	16	–
<i>tert</i> -Butyl-4-hydroxyanisole (BHA)	–	–	–	0.127

increase with lipophilic character, penetrates the complexes more efficient activity by killed micro-organisms.

Among these two bacteria's, gram negative bacteria strain shows more activity than gram positive bacteria. In complex 3, *S. aureus* has greater activity than other complexes. The complexes 1, 2 and 4 exhibited in nearly too moderate activity. Antifungal activity was determined against fungal strain *Candida albicans*, kanamycin using as a standard. All the synthesized complexes shown excellent activity, except complex 4 which has medium activity. The complex 1 has more activity, nearest to standard (kanamycin).

DPPH radical scavenging activity: The DPPH radical scavenging activity is highly considered reliable method to quantify the antioxidant activities of compounds. The antioxidants donate hydrogen to free radical DPPH, leading to non-toxic species and therefore to inhibition of the propagation phase of lipid oxidation. So absorbance decreases indicates the higher free radical scavenging activity was expressed for IC₅₀ values (Table-2) [31]. The IC₅₀ value is inversely related to the radical scavenging activity. The Cu(II) and Ni(II) complexes showed efficient scavenging activity when compared to BHA as standard. The Co(II) and Zn(II) complexes showed the moderate antioxidant activity and the prominent activity showed by ligand. The DPPH radical scavenging activity of complexes may depends on formation of metal ion chelation of complexes.

Conclusion

Newly synthesized Schiff base (L) ligand and its transition mononuclear complexes 1-4 were characterized by various spectral methods. The composition of all the metal complexes is confirmed by molar conductance, elemental analysis, mass, ESR spectral studies. The electronic and IR spectrum suggested the bidentate coordination of ligand with the transition metal(II) ions. The stability of ligand and its metal complexes were determined with the help of DSC-TGA thermal analysis. DNA cleavage activity revealed that complex 3 has good efficiency than the other complexes. Fluorinated aniline group in this complex may responsible for the kind potential copper drugs in reducing environment. All prepared metal complexes are bioactive against bacterial strains and fungal strain whereas complex 4 is inactive against *K. pneumoniae*.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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