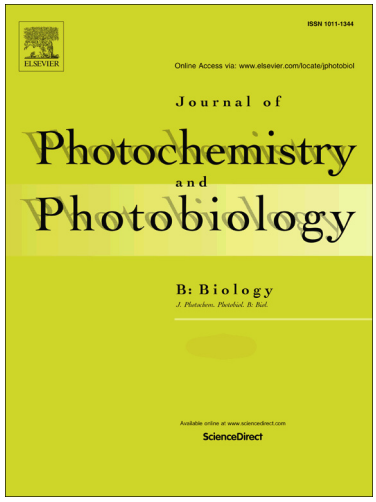

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PII: S1011-1344(15)00129-3
DOI: http://dx.doi.org/10.1016/j.jphotobiol.2015.04.006
Reference: JPB 10003

To appear in: *Journal of Photochemistry and Photobiology B: Biology*

Received Date: 6 January 2015
Revised Date: 30 March 2015
Accepted Date: 12 April 2015

Please cite this article as: S. Packianathan, T. Arun, N. Raman, DNA interaction and efficient antimicrobial activities of 4N chelating metal complexes, *Journal of Photochemistry and Photobiology B: Biology* (2015), doi: http://dx.doi.org/10.1016/j.jphotobiol.2015.04.006

DNA interaction and efficient antimicrobial activities of 4N chelating metal complexes

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Abstract

A new series of metal(II) complexes using a symmetric Schiff base ligand, obtained by the condensation reaction of 4-formyl-N,N-dimethylaniline with benzene-1,2-diamine were synthesized and characterized. The various physico-chemical data indicate that the complexes have octahedral geometry. The intrinsic binding constant of the complexes with DNA is explored. The UV-Vis., circular dichorism, fluorescence emission spectral data and the viscosity measurements indicate that the complexes bind to calf thymus DNA (CT DNA) by intercalative mode. The intrinsic binding constants of Cu(II), Ni(II), Co(II) and Zn(II) complexes are found to be 7.1×10^4, 5.2×10^4, 1.8×10^5 and 6.3×10^4 M^{-1}, respectively. The cleavage studies of these complexes are investigated by gel electrophoresis method in the presence of peroxide. The complexes exhibit enhanced biological activities compared to the free ligand.

Keywords: Octahedral; Fluorescence; Intercalation; Gel electrophoresis; DNA binding

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1. Introduction

Schiff bases are one of the most widespread and important class of ligands due to their simple preparation, selectivity and coordination towards the central metal ions. They are considered as most 'privileged ligands' containing an azomethine group (-CH=N) [1]. These ligands are able to coordinate with various metal ions to form Schiff base metal complexes which increase their application in different fields such as catalysis [2] and pharmacology [3]. The efficiency of the Schiff bases as therapeutic agents has often been enhanced upon coordination to a metal. Over the years there has been a continuous curiosity of the biological activity in metal complexes [4]. 4-acetylpyrazolone and thiazole Schiff base complexes have been found a variety of biological applications including antitumor, antihistaminic and anti-inflammatory activities [5]. The search for new alternative drugs to the eminent cisplatin and its derivatives, which are still used in more than 50% of the treatment regimes for patients depression from cancer, is extremely needed [6,7]. Consequently, efforts are being made to substitute cisplatin with appropriate alternatives and numerous metal-based complexes have been synthesized and tested for their anticancer activities [8, 9].

Schiff bases imply opportunities for inducing substrate chirality, tuning the metal centered electronic factor, enhancing solubility and either performing homogeneous or heterogeneous catalyzes and includes diversified subjects comprising their various aspects in bio-coordination and bio-inorganic chemistry [10-18].

Transition metal Schiff base complexes are multifaceted tools to probe the structure and dynamics of DNA. DNA is the primary intracellular target of anticancer drugs due to the interaction between small molecules and DNA, which cause DNA damage in cancer cells, blocking the division of cancer cells and resulting in cell death [19-22]. In recent years, binding studies of these complexes have become very important in the growth of DNA molecules probes and chemotherapeutics [23-25]. Many transition metal complexes are known to bind to DNA *via* both covalent and non-covalent interactions. In covalent binding, the labile ligand of the complexes is replaced by a nitrogen base of DNA. On the other hand, the non-covalent DNA interactions include intercalative, electrostatic and groove (surface) binding of cationic metal complexes along the outside of the DNA helix and the major or minor groove. 4-formyl-N,N-dimethylaniline, a bioactive ligand, is used as a reagent to detect urobilinogen in urine. Hence, we are tempted to design and synthesize transition metal Schiff base complexes using this ligand to study the impact on biological effect. We herein report the synthesis and characterization of a Schiff base ligand, obtained by the condensation reaction of the above 4-formyl-N,N-dimethylaniline with benzene-1,2-diamine, and its

transition metal(II) complexes. The DNA binding and antimicrobial activities have also been explored.

2. Experimental protocol

The materials and methods, DNA binding, cleavage and antimicrobial procedures are given in the Supplementary file (S1).

2.1. Preparation of Schiff base ligand (L)

An ethanolic solution of 4-formyl-N,N-dimethylaniline (2.98 g, 0.02 M) was added drop wise to an ethanolic solution of benzene-1,2-diamine (1.08 g, 0.01 M). Few drops of glacial acetic acid were added to the reaction mixture and were refluxed for 3 h. It was poured in crushed ice, wherein orange colored precipitate was obtained. The solid product formed was filtered, washed, dried and recrystallized from ethanol, dried in vacuum at room temperature. [L] Yield: 74%. Anal.Calc. (%): C (77.8), H (7.1) and N (15.2); Found (%): C (77.3) H (6.9) and N (14.9); FT-IR (KBr) (cm^{-1}): 1610 (C=N), 2900-2950 (C-H) and 1400-1600 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.7-7.7 (m, aromatic); UV-Vis. in DMSO, (transition) cm^{-1}: 40,485 (π-π*) and 29,293 (n-π*).

2.2. Preparation of metal complexes

To an ethanolic solution of 0.001 M of metal(II) chloride was stirred with twice the amount of an ethanolic solution of the above ligand (0.74 g, 0.002 M) and the resultant mixture was stirred for 2 h and refluxed for *ca.* 3 h. Then the solution was reduced to one-third on a water bath. The precipitated metal complexes were isolated and washed with distilled water. They were recrystallized from ethanol and dried in vacuum at room temperature.

$[CuL_2Cl_2].H_2O$ Yield: 68 %; Anal.Calc. for $[C_{48}H_{52}N_8CuCl_2]$ $.H_2O$: C 64.51; H 6.09; N 12.54; Cl 7.94; Cu 7.11; Found (%); C 64.34; H 5.97; N 12.48; Cl 7.85; Cu 7.0; FT-IR (KBr) (cm^{-1}): 1604 (C=N) and 435 (M-N); Λ_m ($\Omega^{-1}mol^{-1}cm^2$) 11.13; μ_{eff} (BM) 1.78; UV-Vis. in DMSO, (transition) cm^{-1}: 28,683, 41,666 (LMCT) and 11,778 (d-d).

$[NiL_2Cl_2].H_2O$ Yield: 71%; Anal.Calc. for $[C_{48}H_{52}N_8NiCl_2].H_2O$: C 64.88; H 6.13; N 12.61; Cl 7.98; Ni 6.61; Found (%):C 64.6; H 6.02; N 12.52; Cl 7.89; Ni 6.51; FT-IR (KBr) (cm^{-1}): 1604 (C=N) and 433 (M-N); Λ_m ($\Omega^{-1}mol^{-1}cm^2$) 6.58; μ_{eff} (BM) 3.48; UV-Vis. in DMSO, (transition) cm^{-1}: 28,571, 47,846 (LMCT) and 11,185 (d-d).

$[CoL_2Cl_2].H_2O$ Yield: 65%; Anal.Calc. for $[C_{48}H_{52}N_8CoCl_2].H_2O$: C 64.86; H 6.12; N 12.61; Cl 7.98; Co 6.63; Found (%); C 64.79; H 6.03; N 12.54; Cl 7.86; Co 6.52; FT-IR (KBr)(cm^{-1}): 1604 (C=N) and 437 (M-N); Λ_m ($\Omega^{-1}mol^{-1}cm^2$) 9.42; μ_{eff} (BM) 4.55; UV-Vis. in DMSO, (transition) cm^{-1}: 28,901, 45,871 (LMCT) and 11,160 (d-d).

$[ZnL_2Cl_2].H_2O$ Yield: 75%; Anal.Calc. for $[C_{48}H_{52}N_8ZnCl_2].H_2O$: C 64.39; H 6.08; N 12.52; Cl 7.92; Zn 7.30; Found (%) ; C 64.26; H 5.91; N 12.39; Cl 7.8; Zn 7.21; FT-IR (KBr) (cm^{-1}): 1604 (C=N) and 438 (M-N); ^1H NMR (DMSO-d_6) δ(ppm): 6.60-7.90 (phenyl multiplet), 2.90-3.40 (N–CH_3); 3.9–4.2 (C–H); Λ_m ($\Omega^{-1}mol^{-1}cm^2$) 5.63; μ_{eff} (BM) diamagnetic; UV-Vis. in DMSO, (transition) cm^{-1}: 28,571 and 40,816 (LMCT).

3. Results and discussion

All the compounds are air stable for extended periods and the complexes are remarkably soluble in DMSO and DMF. The results of elemental analysis for the metal complexes are in good agreement with the calculated values (Table 1) showing that the stoichiometry of the complexes is $[ML_2Cl_2]$ wherein the ligand acts as a bidentate. The formation of these complexes may proceed according to the equation given below:

$$MCl_2.nH_2O + 2L \rightarrow [ML_2Cl_2].H_2O + nH_2O$$

where, M= Cu(II), Ni(II), Co(II) and Zn(II).

3.1. IR spectra

The IR spectra of the ligand and its corresponding complexes endow with significant information about the metal ligand bonding. The IR spectra of metal complexes and ligand were recorded in the range of 300–4000 cm^{-1}. The characteristic bands for aromatic C=C group are observed in the range of 1400-1600 cm^{-1} (Fig. S1). Significantly, the expected characteristic peak of azomethine (C=N) group is also presented at 1610 cm^{-1} which confirms the formation of the Schiff base. The C=N band is shifted to lower frequency in the complexes (1604 cm^{-1}) as expected. This indicates the coordination of -C=N nitrogen to the metal ion. In the complexes, new peaks formed at 430-440 cm^{-1} and 356-363 cm^{-1} region are assigned to M-N and M-Cl bonds respectively, confirming the complex formation [26].

3.2. Molar conductivity

The molar conductivities (10^{-3} M) of their solution at room temperature were measured. The lower conductance values (5-12 ohm^{-1} cm^2 mol^{-1}) of the complexes support their non-electrolytic nature. The absence of chloride (counter) ion is confirmed from Volhard's

test. It also indicates that the chloride anions bind to the metal ions as ligands and do not ionize. The formation of the Schiff base ligand and its complexes is given in Scheme 1.

3.3. Electronic spectra and magnetic properties of metal(II) chelates

The electronic spectra of complexes were recorded in DMSO solution and are consistent with an octahedral metal(II) environment. In electronic spectra of metal complexes the wide range of bands are due to transition of –CH=N–, charge transfer results from electrons interaction between the metal and the ligand which involves either a metal to ligand or ligand to metal electron transfer. The band observed in 40,485 cm^{-1} is due to π-π* transition of C=N group. It is shifted to higher range, which is due to nitrogen that involved in coordination with metal ion. The absorption band observed at 28,571 cm^{-1} is due to n-π* transition from azomethine group corresponding to the ligand or metal complexes. The Cu(II) complex shows an absorption peak at 11,778 cm^{-1}, due to the d–d transition ($^2E_g \rightarrow {}^2T_{2g}$) of Cu(II) ion (Fig. S2), suggesting that the copper ion exhibits an octahedral geometry [27]. Electronic spectrum of the Ni(II) complex shows a band at 11,185 cm^{-1} which is assigned to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ transition, suggesting an octahedral arrangement for the nickel(II) complex. The electronic spectrum of Co(II) complex exhibits absorptions at 9,425 and 11,160 cm^{-1} which are assigned to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ and $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ transitions respectively, corresponding to Co(II) octahedral complex [28]. In difference, Zn(II) complex does not exhibit any d-d band because of its completely filled d^{10} transition. However, based on its elemental analysis and spectral data, an octahedral geometry is proposed for this complex also.

3.4. ^{1}H NMR spectra

The NMR spectrum is exploiting to determine the identity of prepared ligand and its diamagnetic metal complex. Ligand and its Zn(II) complex are recorded in DMSO-d_6, using tetramethylsilane (TMS) as internal standard (Fig. S3). The proton ^{1}H NMR spectrum of ligand shows a singlet peak at 9.65 ppm (1H, CH=N), multiplet in the range 6.60-7.90 ppm for the aromatic ring protons and a multiplet peak at 2.90-3.40 ppm for (6H, N-CH_3) protons. The proton ^{1}H NMR spectrum of Zn complex shows a singlet peak at 9.55 ppm (1H, CH=N), multiplet in the range 6.60-7.90 ppm for the aromatic ring protons and a multiplet peak at 2.90-3.40 ppm for (6H, N-CH_3) protons. From the above observation, the azomethine group (CH=N) is involved in metal co-ordination.

3.3. Mass spectroscopy

The formation of metal complexes and the speciation of various ionic forms in DMSO solution were studied with ESI–MS. The mass spectrum of the ligand (L) shows molecular ion peak at m/z = 238 corresponding to $[C_{15}H_{15}N_3]^+$ ion. Also the spectrum exhibits peaks for the fragments at m/z 371, 222, 194, 134 and 91 corresponding to $[C_{24}H_{26}N_4]^+$, $[C_{15}H_{15}N_2]^+$, $[C_{13}H_9N_2]^+$, $[C_9H_{11}N]^+$, and $[C_7H_6]$+ respectively (Fig. S4). Besides, the mass spectrum of Cu(II) complex show peaks at m/z 236 [Base peak], 97, 134, 222, 371, 471 and 863 corresponding to $[C_{15}H_{15}N_3]^+$, $[CuCl]^+$, $[CuCl_2]^+$, $[C_{15}H_{15}N_2]^+$, $[C_{24}H_{26}N_4]^+$, $[C_{24}H_{26}N_4CuCl]^+$ and $[C_{48}H_{52}N_8CuCl_2]^+$ respectively (Fig. S5). The m/z of all the fragments of Schiff base ligand and its metal complex confirm the stoichiometry of the type $[ML_2Cl_2]$. Thus, the mass spectral data reinforce the conclusion drawn from the analytical and conductance values.

3.5. Electron paramagnetic spectrum of the Cu(II) complex

The EPR spectrum of Cu(II) complex gives an enough information about the structure of the metal ion environment in the complex. *i.e.*, the geometry, nature of the donating atoms from the ligand and degree of covalency of the Cu(II)–ligand bonds. The EPR spectrum of the Cu(II) complex was recorded in DMSO at liquid nitrogen temperature (LNT) which reveals well resolved peaks in the low filed region (Fig. S6). This is also supported by the magnetic moment of Cu(II) complex (1.78 BM) which confirms the mononuclear nature of the complex. The spin Hamiltonian parameters calculated for the Cu(II) complex are precised in Table 2. The EPR spectrum of the Cu(II) complex exhibits axially symmetric g-tensor parameters with $g_{\parallel} > g_{\perp} > 2.003$ indicating that the copper site has a $dx^2\text{-}y^2$ ground state characteristic of an octahedral stereochemistry [29]. From the values of g factors, the geometric parameter G, representing a measure of exchange interaction between Cu(II) centres in polycrystalline compound can be determined by using the formula :

$$G = (g_{\parallel} - 2.0027) / (g_{\perp} - 2.0027)$$

If G > 4.0, the local tetragonal axes are aligned parallel or only slightly misaligned. If G < 4.0, significant exchange coupling is present and the misalignment is appreciable. The observed value for the exchange interaction parameter for the Cu(II) complex is found to be 4.7 indicating that there is negligible exchange interaction of Cu–Cu in the complex according to Hathaway [30]. This result also indicates that the exchange coupling effects are

not operative in the present complex [31-33]. The isotropic EPR parameters g_{iso} = 2.2064 and A_{iso} = 94 can be calculated from the position spacing of the resonance lines from room temperature solution spectrum of the complex.

The bonding parameters of α^2 and β^2 indicate that the complex has some covalent character and there is interaction in the out-of-plane π-bonding. The lower value of α^2 (0.89) indicates that the complex has some covalent character. The observed β^2 (0.80) [CuL_2Cl_2]) and γ^2 (0.68) [CuL_2Cl_2] indicate that there is interaction in the out of plane π-bonding whereas the in-plane π-bonding is completely ionic. This is further confirmed by orbital reduction factors. For the present case, the observed order is $K_{\|}$ (0.725) > $K_{\perp}$ (0.154) for [CuL_2Cl_2] implying a greater contribution from out-of-plane π-bonding than from in-plane π-bonding in metal-ligand π-bonding. Based on these observations, Cu(II) complex is proposed to have distorted octahedral geometry. The EPR study has provided supportive evidence to obtain the conclusion of electronic spectrum and magnetic moment value.

3.6. Thermal Analysis (TGA/DTA)

The complexes were studied for thermal behavior over the temperature range of 25-300^{o}C under nitrogen atmosphere (Fig S7). The thermograms of Cu(II) and Co(II) complexes are given in supplementary file. In the present investigation, decomposition of copper complex takes place in three stages. The first step of decomposition corresponding to a mass loss of 6.63 % in the region 50-100 $^{\circ}$C, is attributed to the loss of one lattice held water molecule. In the second step, weight loss of 11.32 % in the region 100–250°C, corresponds to the loss of azomethine and two counter chloride ions. Further reduction of mass in the higher temperature range is ascribed to the ligand decomposition and the final product is found to be copper(II) oxide. Further, the cobalt(II) complex shows thermal decomposition in three significant steps. The weight loss of 7.23 % in the first step is attributed to the loss of one coordinated water molecule in the region 70-110°C. In the second stage, the decomposition corresponds to a mass loss of 21.00% in the range 190–270 ◦C, showing the combined loss of two chlorides and the ligand. Further reduction of mass in the higher temperature range is ascribed to the decomposition of remaining part of the ligand and the final product is analyzed and it is cobalt(II) oxide..

3.7. Powder XRD

The powder X-ray diffraction analysis of Cu(II) and Co(II) Schiff base complexes are illustrated in Fig. S8. The Schiff base ligand and its metal complexes were recorded in the

range of 2θ = 0–80 Å. From the experiment, it is found that Cu(II) and Co(II) metal complexes show sharp peaks indicating their crystalline nature. The average crystalline size of the complexes, D was calculated using Scherrer's formula [9] from equation (1)

$$D = 0.89\lambda/(\beta Cos\theta) \quad \text{---------- (1)}$$

where, λ is the wavelength (0.15406 nm), β is the full width at the half- maximum (FWHM) of the ligand, Cu(II) and Co(II) complexes line and θ is the diffraction angle. The ligand and the metal complexes Cu(II) and Co(II) have an average grain size of 49.16, 32.23 and 39.32 nm respectively, suggesting that the ligand and complexes are in a nanocrystalline phase. The crystallite sizes of the Schiff base metal complexes are found to be in the range of 10-100 nm [34].

3.8. DNA binding studies

3.8.1. Electronic absorption spectroscopy

DNA binding activities of metal complexes have been a clue of vital significance for the growth of effective metal based chemotherapeutic drugs. One of the most useful techniques for studying the DNA binding of molecules is electronic absorption spectroscopy [35]. Any change in the UV–Vis absorption spectra of metal complexes upon the addition of DNA serves as a proof for the existence of an interaction between them in particular, hypochromism due to π–π* stacking interaction with a red-shift (bathochromism) may appear in the case of an intercalative binding leading to stabilization of DNA duplex. The increasing concentration of CT DNA results in the bathochromic shift in the range 1.5-2.6 nm and significant hypochromicity lying in the range 17-25 %. The observed hypochromism could be credited to stacking interaction between the aromatic chromophores of the complexes and DNA base pairs consistent with the intercalative binding mode, while the red-shift is an evidence of the stabilization of the CT DNA duplex. UV–Vis spectrum of Cu(II) complex in the absence and presence of CT DNA is shown representatively in Fig. 1. The UV–Vis spectra of Ni(II), Co(II) and Zn(II) complexes are shown in Fig. S9 respectively.

The intrinsic binding constant values (K_b) for the complexes Cu(II), Ni(II), Co(II) and Zn(II) were found to be 7.1×10^4, 5.2×10^4, 1.8×10^5 and 6.3×10^4 M^{-1} respectively [36]. The binding constant (K_b) values of these complexes were compared to those observed for typical intercalators, ethidium bromide and $[Ru(bpy)_2(dppz)]^{2+}$ whose binding constants are in the order of 1.4×10^6 and $>10^6$ M^{-1} [37, 38]. In order to compare quantitatively the binding strength of the complexes with CT DNA, the intrinsic binding constants (K_b) were obtained by monitoring the changes in the absorbance for the complexes with increasing concentration

of DNA. K_b was obtained from the ratio of slope to the intercept from the plot of [DNA]/(ε_a–ε_f) *versus* [DNA]. The K_b values are shown in Table 3.

3.8.2. Cyclic voltammetry

Electrochemistry has been growing helpful in elucidating the basic chemistry of biological systems. Cyclic voltammetric measurements of Cu(II) complex were carried out. The cyclic voltammograms of Cu(II) complex in the absence and in presence of varying amount of DNA are shown in Fig. 2. The incremental addition of CT DNA to the complex causes shift in the potential of peak in cyclic voltammogram. This result shows that complex stabilizes the duplex (GC pairs) by intercalating way. The ip_c/ip_a ratios of these four redox couples of the complexes are 0.6122, 0.4364, 0.5635 and 0.6571 respectively which indicate that the reaction of the complex on the glassy carbon electrode surface is quasi-reversible redox process. The incremental addition of CT DNA to the complex the redox couples causes a less negative shift in $E_{1/2}$ and decrease of ΔEp. The augmentation addition of CT DNA to the complex causes a positive shift in potential and a decrease in the current intensity. From these data, it is understood that the entire synthesized complexes interact with DNA through intercalating way [39]. The cyclic voltammograms of Ni(II) and Zn(II) are shown in Figs.S10 and S11 respectively.

In differential pulse voltammogram of Cu(II) complex in the absence and presence of varying amount of [DNA] with significant decrease of current intensity (Fig. 3), the shift in potential is related to the ratio of binding constant by the following equation:

$$E_b - E_f = 0.0591 \log (K_{[red]}/K_{[oxd]})$$

where E_b and E_f are peak potentials of the complex in the bound and free form respectively. In the present study Schiff base complexes show one electron transfer during the redox process and its ip_c/ip_a value is less than unity which indicates the reaction of the complex on the glassy carbon electrode surface is quasi-reversible. Other complexes [Co(II), Ni(II) and Zn(II)] show considerable shift in both cathodic and anodic peak potentials in the presence of incremental addition of CT DNA. Most of the synthesized complexes give both the anodic and cathodic peak potential shifts which are either positive or negative (Table 4). It indicates the intercalating mode of DNA binding with the Schiff base complexes.

3.8.3. CD spectroscopy

To further investigate the binding mode and interaction affinity of complexes and DNA, the circular dichorism spectra were carried out. Modifications of the CD signals in the spectral range of 250–400 nm have shown to be useful to predict and confirm the DNA conformational changes, damage and/or cleavage upon interaction with metal complexes. CD spectrum of CT DNA exhibits a positive band at 280 nm due to base stacking and a negative band at 245 nm due to right-handed helicity of B–DNA. It is generally accepted that classical intercalation leads to change in intensities of both positive and negative bands, due to enhancement of base stacking and stabilization of helicity, whereas groove binding and electrostatic interaction of complexes with DNA shows less or no perturbation on the base stacking and helicity bands [40, 41]. As shown in Fig. 4, upon increasing the concentration of complexes to the DNA solution, the intensities of both positive and negative bands changes in few degrees. In the present complex, the DNA intensity has been found to decrease in positive band with 2-5 nm and red shifts are observed. Observed changes in those CD signals of DNA suggest that the stacking mode and the orientation of base pairs in DNA are disturbed with the binding of the complex. The decrease in intensity clearly suggest that the binding of the complex induces certain conformational changes, in which the more B- to more A- conformational changes of DNA could be induced upon the binding of the Cu(II) complex. In addition, a significant broad induced CD signals with negative ellipticity at 315-320 nm is observed which reveals that the compound firmly bind as intercalation to the DNA double helix [42].

3.8.4. Emission spectroscopy

In order to get further facts of the aim, illuminating the binding of the metal(II) complexes to DNA, the fluorescence emission spectrum was studied. In the fluorescence titrations, the concentration of complex is keeping constant, and varying the CT DNA concentration. Fig. 5 shows the fluorescence emission intensity curves of Cu(II) and Co(II) complexes with CT DNA. As seen in both cases, the increasing addition of the CT DNA to the Cu(II) and Co(II) complexes, the fluorescence emission intensity gradually increases which clearly delegates that the complexes expose the strong binding with DNA [43]. This result provides that the binding of complexes with DNA can be intercalation. The fluorescence intensity fabricates that the complex can insert between base pairs of the CT DNA. This strengthening of the fluorescence intensity is invented to be one of the patterns for intercalative binding [44].

3.8.5. Viscosity measurements

To get further evidence and clarifying the binding of the metal(II) complexes to DNA, viscosity measurements were carried out on CT DNA by varying the concentration of the complexes added. The viscosity of DNA is significantly improved by complete or partial intercalation of complexes into the DNA base-pair stack, but it is slightly disturbed by the electrostatic or covalent binding of molecules. A classical intercalation model results in the lengthening of the DNA helix as the base pairs are separated to accommodate the binding molecule, leading to an increase in the DNA viscosity. The changes in the relative specific viscosity of CT DNA in the presence and absence of the complex were plotted against 1/R = [complex]/[DNA]. A classical intercalation mode causes a significant increase in the viscosity of DNA due to an increase in base pair separation at intercalation sites and hence an increase in the overall DNA length [44]. The effects of all the complexes on the viscosity of CT DNA are shown in Fig. 6. A significant increase in the viscosity of DNA on addition of complex results due to the intercalation which leads to the separation among the DNA bases to the increase in the effective size in DNA which could be the reason for the increase in the viscosity [46].

3.9. DNA cleavage efficacy

Gel electrophoresis experiments were performed using ligand and complexes in presence of H_2O_2. Complexes exhibit cleavage ability at low concentration. The ligand exhibits no major activity in the presence of oxidant. The activity was much higher for the complexes in presence of H_2O_2. When CT DNA is subjected to electrophoresis, relatively fast migration will be observed for the intact super coil form (Form I). If scission occurs on one strand (nicking), the super coil will relax to generate a slower moving open circular form (Form II). If both strands are cleaved, a linear form (Form III) that migrates between Forms I and II will be generated [47, 48]. The complexes show more activity in the presence of oxidant which may be due to the reaction of hydroxyl radical with DNA. The results of DNA cleavage studies have been shown in Fig. 7. Further, $[CuL_2Cl_2]$ and $[NiL_2Cl_2]$ complexes have shown greater cleavage potential compared to ligand and other complexes studied.

3.10. Antimicrobial activity

Biological activity of the ligand and a series of its metal complexes [Cu(II), Ni(II), Co(II) and Zn(II)] were screened for anti-bacterial activity against *P. putida* (Gram-negative bacteria), *N.asteroides* and *L. lactis* (Gram-positive bacteria) and anti-fungal activity against the fungi *A.flavus, C.ablicans* and *A.niger*. The minimum inhibitory concentration (MIC)

was determined by assaying at serial dilution of concentrations along with standards at the same concentrations. The antimicrobial results of Schiff base and its metal complexes are systematized in Tables 5 and 6. The remarkable activity of Schiff base ligand may arise from the presence of azomethine group which may be one of the reasons for impart in elucidating the mechanism of transformation reaction in biological systems [49]. The results indicate that the complexes show more activity and the ligand has less activity against the same microorganisms under identical experimental conditions.

As previously mentioned, the metal complexes show improved antimicrobial activity than their corresponding ligand. According to the Overtone′s concept of cell permeability, the lipid membrane surrounding the cell favors the passage of only lipid-soluble materials and therefore, liposolubility is an important factor which controls the antimicrobial activity. On chelation, polarity of the metal ion is reduced to a greater extent due the overlapping of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. The increased lipophilicity enhances the penetration of the complexes into the lipid membranes and blocks the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism [50].

4. Conclusion

A novel biological important Schiff base ligand and its metal complexes of Cu(II), Co(II), Ni(II) and Zn(II) have been synthesized and characterized. The complexes have been employed to bind CT DNA and such binding ability has been explored using diverse techniques. The above data have proved the CT DNA binding of the complexes through the intercalation mode. Among the synthesized metal complexes Co(II) complex has the strongest DNA binding affinity. The biological screening data reveal that the complexes have higher antimicrobial activity than the free ligand. The collective biological activities of the complexes may be helpful for the designing of metal based drugs.

Acknowledgments

The authors express their heartfelt thanks to the College Managing Board, Principal and Head of the Department of Chemistry, VHNSN College for providing necessary research facilities. IIT Bombay and CDRI, Lucknow, are gratefully acknowledged for providing instrumental facilities.

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Figure Captions

Scheme 1. Schematic route for synthesis of metal complexes.

Fig. 1. Absorption spectrum of Cu(II) complex in buffer pH =7.2 at 25 ^{0}C in presence of increasing amount of DNA. Arrow indicates the changes in absorbance upon increasing the DNA concentration.

Fig. 2. Cyclic voltammograms of Cu(II) complex in buffer (pH = 7.2) at 25 ^{0}C in presence of increasing amount of DNA.

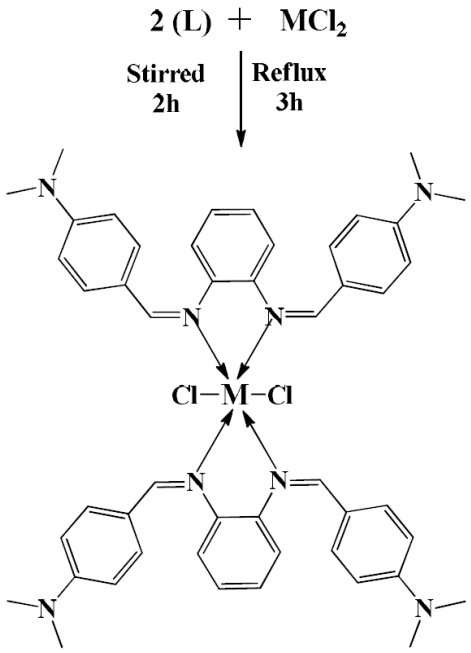
Fig. 3. Differential pulse voltammograms of Cu(II) complex in buffer (pH = 7.2) at 25 ^{0}C in the presence of increasing amount of DNA.

Fig. 4. CD spectra of DNA in buffer pH =7.2 at 25 ^{0}C in presence of increasing amount of Cu(II) complex. Arrow indicates the changes in ellipticity upon increasing the DNA concentration.

Fig. 5. Emission spectrum of Cu(II) complex in buffer pH =7.2 at 25 ^{0}C in presence of increasing amount of DNA.

Fig. 6. Effect of increasing amounts of $[CuL_2Cl_2]$ ( ), $[NiL_2Cl_2]$ ( ), $[CoL_2Cl_2]$ ( ), $[ZnL_2Cl_2]$ (X), and [EB] (X) on the relative viscosity of CT DNA *vs* [complex]/[DNA] (1/R) ratio.

Fig. 7. The gel electrophoretic separation of plasmid pUC19 DNA treated with $[ML_2Cl_2].H_2O$ complexes. Lane 1; DNA control; Lane 2: DNA + ligand + H_2O_2; Lane 3: DNA + Cu + H_2O_2; Lane 4: DNA + Co + H_2O_2; Lane 5: DNA + Ni + H_2O_2; Lane 6: DNA + Zn + H_2O_2.



M= Cu(II), Ni(II), Co(II) and Zn(II)

Scheme 1. Schematic route for the synthesis of metal complexes.

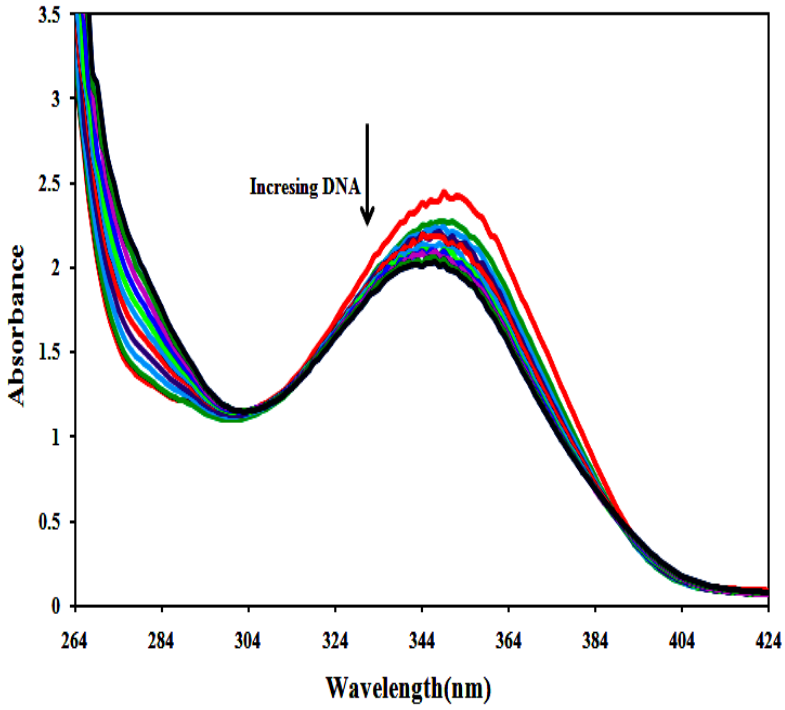


Fig. 1. Absorption spectrum of Cu(II) complex in buffer pH=7.2 at 25 ^{0}C in presence of increasing amount of DNA. Arrow indicates the changes in absorbance upon increasing the DNA concentration.

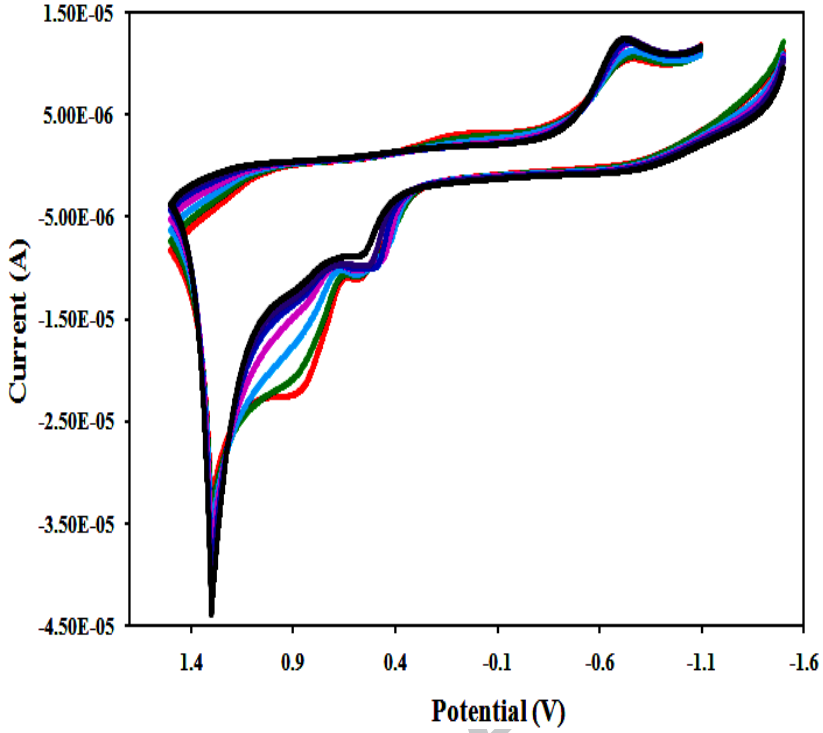


Fig. 2. Cyclic voltammograms of Cu(II) complex in buffer (pH = 7.2) at 25 ^{0}C in presence of increasing amount of DNA.

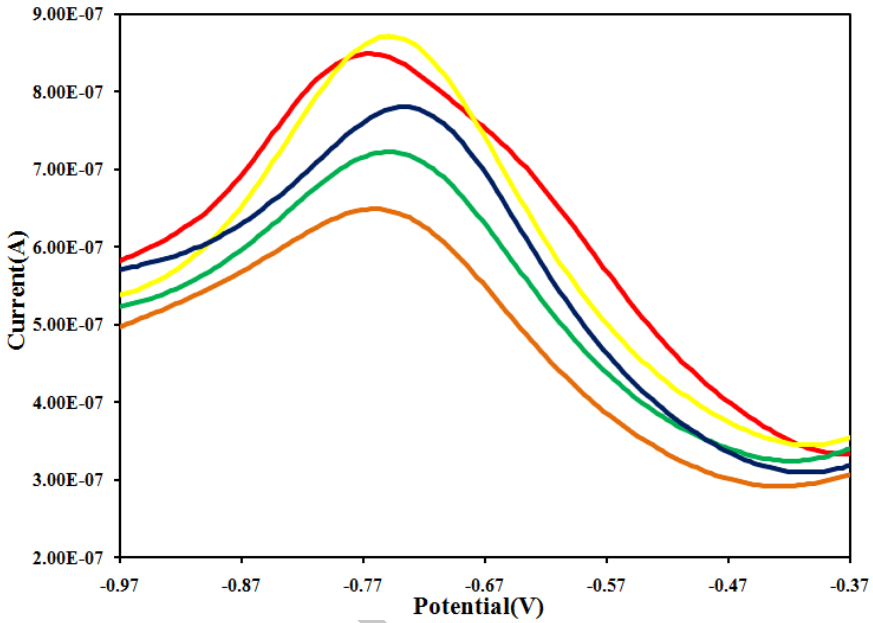


Fig. 3. Differential pulse voltammograms of Cu(II) complex in buffer (pH = 7.2) at 25 ^{0}C in the presence of increasing amount of DNA.

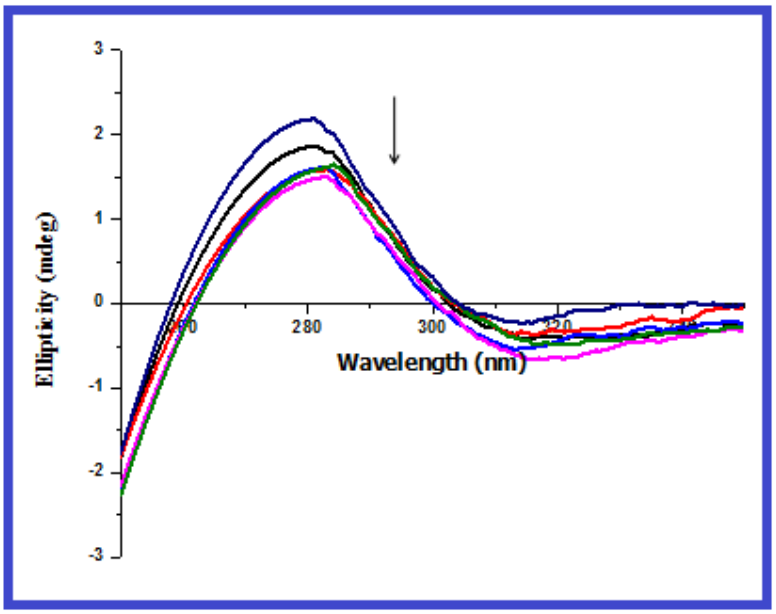


Fig. 4. CD spectra of DNA in buffer pH =7.2 at 25 ^{0}C in presence of increasing amount of Cu(II) complex. Arrow indicates the changes in ellipticity upon increasing the DNA concentration.

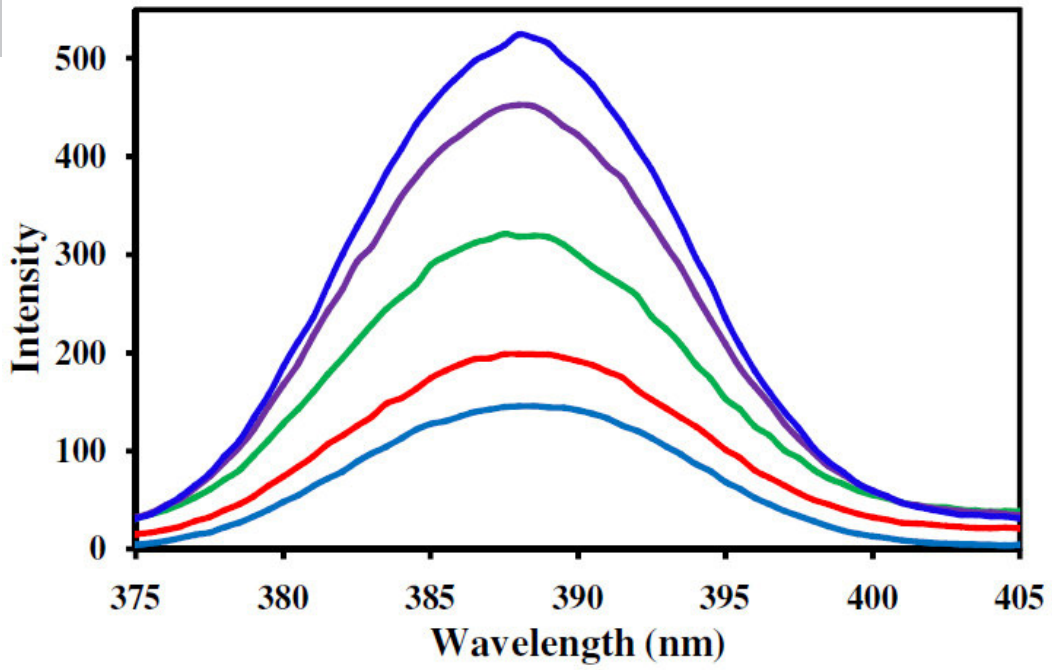


Fig. 5. Emission spectrum of Cu(II) complex in buffer pH =7.2 at 25 ^{0}C in presence of increasing amount of DNA.

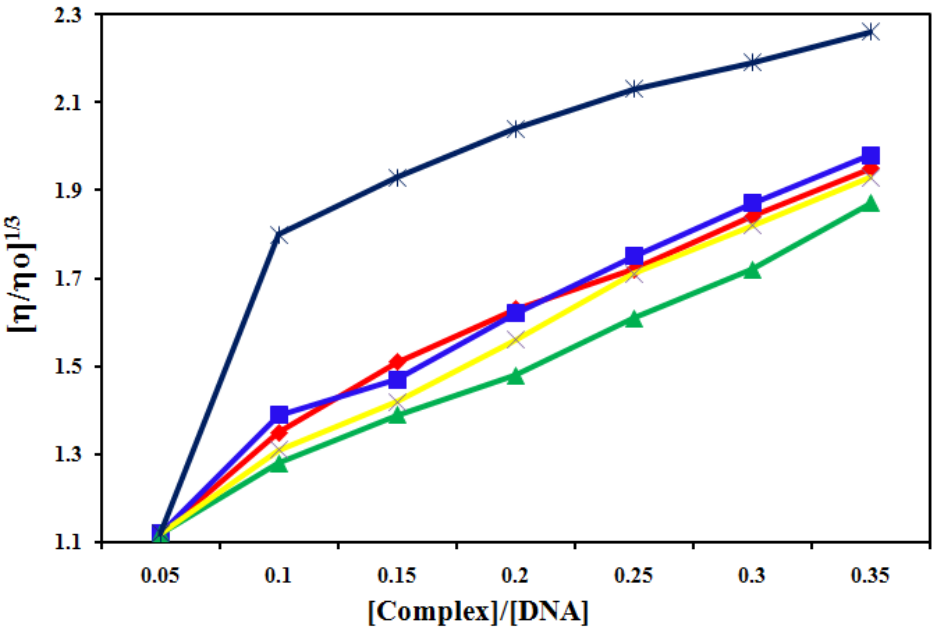


Fig. 6. Effect of increasing amounts of $[CuL_2Cl_2]$ (◆), $[NiL_2Cl_2]$ (▲), $[CoL_2Cl_2]$ (■), $[ZnL_2Cl_2]$ (X), and [EB] (✕) on the relative viscosity of CT DNA *vs* [complex]/[DNA] (1/R) ratio.

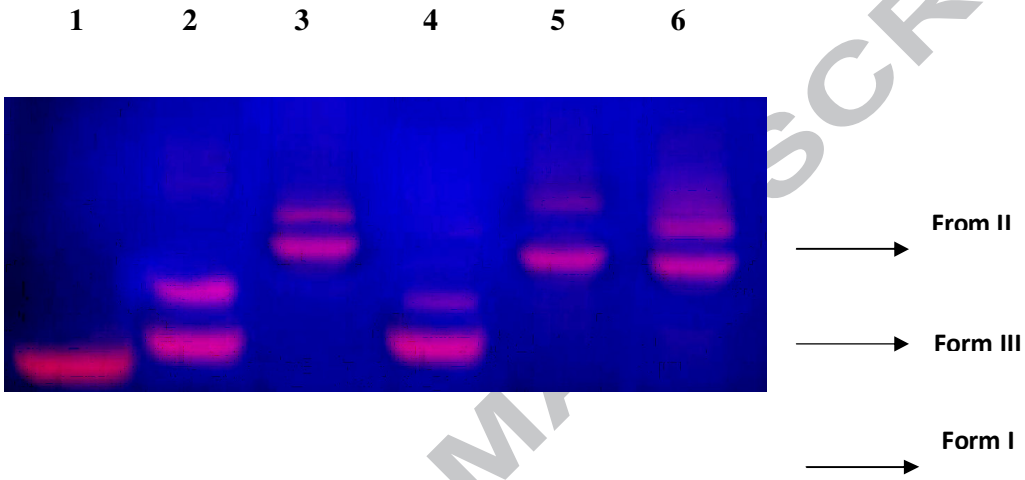


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Table Captions

Table 1. Elemental and physical data of Schiff base ligand (HL) and its metal(II) complexes

Compound	Calculated(Found) %				$\wedge_m$ (ohm^{-1} cm^2mol^{-1})	μ_{eff} (BM)
	M	C	H	N		
L	-	77.8 (77.3)	7.1 (6.9)	15.2 (14.9)	-	-
Cu(II)	7.11 (7.01)	64.51 (64.34)	6.09 (5.97)	12.54 (12.48)	11.13	1.78
Ni(II)	6.61 (6.51)	64.88 (64.66)	6.13 (6.02)	12.61 (12.52)	6.58	3.48
Co(II)	6.63 (6.52)	64.86 (64.79)	6.12 (6.03)	12.61 (12.54)	9.42	4.55
Zn(II)	7.30 (7.21)	64.39 (64.26)	6.08 (5.91)	12.52 (12.39)	5.63	Diamagnetic

Table 2. The spin Hamiltonian parameters of Cu(II) complex in DMSO solution at 77 K

Complex	Hyperfine constant $\times 10^{-4}$ cm^{-1}			$g_{\parallel}$	$g_{\perp}$	g_{iso}	α^2	β^2	γ^2	G
	$A_{\perp}$	$A_{\parallel}$	A_{iso}							
$[CuL_2Cl_2]$	90	104	94	2.4319	2.0937	2.064	0.89	0.80	0.68	4.7

Table 3. Electronic absorption spectral properties of Cu(II), Co(II), Ni(II) and Zn(II) complexes with DNA

Compound	λ max		$\Delta\lambda$	[a]H%	[b]K_b
	Free	Bound	(nm)		(M^{-1})
Cu(II)	349.5	346.8	2.7	35	7.1 X 10^4
Ni(II)	346.7	344.3	2.4	19	5.2 X 10^4
Co(II)	348.2	346.3	1.9	25	1.8 X 10^5
Zn(II)	347.8	346.2	1.6	27	6.3 X 10^4

[a]H%= $[(A_{free} - A_{bound}) / A_{free}] \times 100\%$

[b]K_b = Intrinsic DNA binding constant determined from the UV – Vis., absorption spectral titration

Table 4. Electrochemical parameters for interaction of DNA with Cu(II), Ni(II), Co(II) and Zn(II) complexes

Compound	$^{a}E_{1/2}$ (V)		$^{b}\Delta Ep$(V)		$Ip_c / Ip_a^{\#}$	$K_{[red]}/K_{[oxd]}$
	Free	Bound	Free	Bound		
Cu(II)	-0.126	-0.250	0.542	0.458	0.6122	0.8128
Ni(II)	-0.298	-0.228	0.698	0.521	0.4364	1.1253
Co(II)	-0.243	-0.269	0.224	0.317	0.5635	1.1051
Zn(II)	-0.202	-0.061	0.627	0.479	0.6571	0.7158

$^{\#}$Error Limit: ± 5%

Data from cyclic voltammetric measurements: $^{a}E_{1/2}$ is calculated as the average of anodic (E_{Pa}) and cathodic (Ep_c) peak potentials; $^{a}E_{1/2} = Ep_a + Ep_c / 2$; $^{b}\Delta Ep = Ep_a - Ep_c$

Table 5. Minimum inhibitory concentration of the synthesized compounds against the growth of bacteria (μg/mL)

S.No.	Compounds	Minimum inhibitory concentration (MIC) ($\times 10^4$ μM)		
		N.asteroide	*P.putida*	*L.lactis*
1	Schiff base	20.1	19.3	19.2
2	Cu(II)	13.8	15.5	14.3
3	Ni(II)	14.3	16.1	17.3
4	Co(II)	13.1	14.6	15.8
5	Zn(II)	15.1	17.5	16.3
6	Gentamicin	3.1	3.4	3.9

Table 6. Minimum inhibitory concentration of the synthesized compounds against the growth of fungi (μg/mL)

S.No	Compounds	Minimum inhibitory concentration (MIC) ($\times 10^4$ μM)		
		A.flavus	*C.ablicans*	*A.niger*
1	Schiff base	19.5	18.6	19.1
2	Cu(II)	12.8	14.1	13.3
3	Ni(II)	13.7	15.1	16.4
4	Co(II)	13.2	14.3	15.8
5	Zn(II)	15.3	16.2	16.9
6	Fluconazole	3.2	2.9	2.4

DNA interaction and efficient antimicrobial activities of 4N chelating metal complexes

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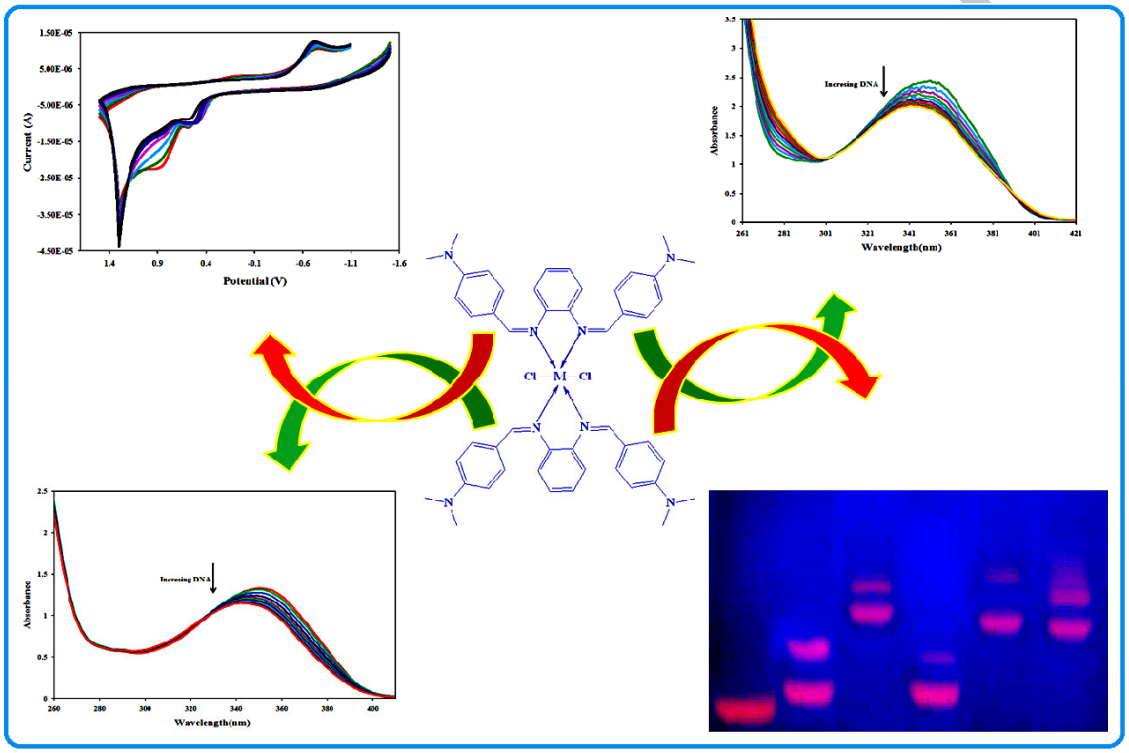
Pictogram



Research Highlights

- Synthesis of new and efficient DNA targeting chelates.
- Synthesis of good metallointercalators.
- Excellent DNA binding behavior of Co(II) complex.
- Efficient antimicrobial effect of complexes against various pathogens.