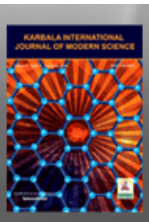

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Synthesis, Characterisation and Biological Evaluation of Tyramine derived Schiff base Ligand and Its Transition Metal(II) Complexes

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University of Kerbala

Synthesis, Characterisation and Biological Evaluation of Tyramine derived Schiff base Ligand and Its Transition Metal(II) Complexes

Abstract

In this study, a new tyramine derived Schiff base ligand (L) (L=1,3-phenylene-bis-4-aminoantipyrinyl-4-aminoethylphenol) and its derived transition metal(II) complexes $[Cu(L)Cl_2]$(1), $[Ni(L)Cl_2]$(2), $[Co(L)Cl_2]$ (3) and $[Zn(L)Cl_2]$ (4) have been synthesized and well characterized by the way of different spectroscopic and analytical techniques. Analytical and spectroscopic studies result suggests that metal(II) complexes more probably have octahedral geometry. DNA binding tendency of L and metal(II) complexes 1-4 have been assessed by probing their ability to bind with Calf Thymus DNA (CT-DNA) via electronic absorption and cyclic voltammetry titration methods. The results clearly reveal that the metal(II) complexes may interact with DNA through intercalation mode of binding and their binding constant value K_b was found to be in the range of 11.2 – 23.7 $\times 10^5$ M^{-1}. The DNA damage study has also been investigated by gel electrophoresis technique. Interestingly, it was found that all the complexes could cleave the circular plasmid pBR 322 super coiled (SC) DNA efficiently in the presence of activators. The complexes showed enhanced antifungal (MIC, 2.7 – 6.9 µg/mL) and antibacterial (MIC, 3.1 – 3.9 µg/mL) activities compared to the free ligand.

Keywords

Schiff base ligand, metal(II) complexes, DNA binding, DNA cleavage, Biological activity.

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Cover Page Footnote

The authors express their sincere thanks to the Principal and the Management of HKRH College, Uthamapalayam for their constant encouragement. We extent our hearty thanks to the Management of The Madura College, Madurai for providing research facilities.

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1. Introduction

Schiff base ligands, have been playing a significant role in the progress of co-ordination chemistry as they tend to form stable co-ordination complexes with transition metal(II) ions. Further the metal(II) complexes have also played a vital role in the development of co-ordination chemistry, ranging from physicochemical to biochemical relevant studies of metal complexes [1]. Substantial anti-cancer drugs are embedded in Schiff bases. These Schiff base metal(II) complexes reveals significant anticancer activity than the free ligands [2,3]. 4-aminoantipyrine derived Schiff base ligands and their metal(II) complexes expose a significant biological activity such as fungicide, anti-tumour, bactericide, anti-inflammatory, and anti-viral activities [4−6]. Schiff base metal complexes efficient of riving biomolecules of DNA and RNA in physiological circumstances by oxidative or hydrolytic mechanisms hold essential position in chemotherapy. In recent past, the combined studies of transition metal(II) complexes received significant currency in the field of chemotherapeutics [7−9]. Researchers have synthesized and sought many varieties of complexes, with the aim seeking anticarcinogenic agents, that can identify and also rive DNA. These Schiff base metal complexes under critical circumstances can support and manifest in the development of separate applications [10,11]. The number of metal(II) complexes derived from 4-aminoantipyrine based Schiff base derivatives is limited [12−17]. The current research work describes the synthesis and characterization of some metal(II) complexes of $[Cu(L)Cl_2]$ (1), $[Ni(L)Cl_2]$ (2), $[Co(L)Cl_2]$ (3) and $[Zn(L)Cl_2]$ (4) synthesized from tyramine derived Schiff base ligand (L) (L = 1,3-phenylene-bis-4-amino-antipyrinyl-4-aminoethylphenol). The DNA binding studies were carried out to better comprehend the preferential mode of binding of these metal(II) complexes 1−4 against Schiff base ligand L. Metal(II) complexes 1−4 and free ligand L were also tested for their *in vitro* anti-bacterial activity and antifungal activity using Broth dilution method [18]. Besides, DNA cleavage study have also been studied for L and metal(II) complexes 1−4.

2. Experimental section

2.1. Materials and methods

Isophthalaldehyde, 4-aminoantipyrine, tyramine, metal(II) salts and Tris-HCl were acquired from Merck company (Darmstadt, Germany). Calf Thymus (CT) DNA was purchased from GENEI (Bangalore, India). Elemental analyses were recorded on an Elementar Vario EL III analyser. The UV−Visible spectra were recorded on UV-1800 (Shimadzu) spectrophotometer. FT-IR and ^{1}H NMR spectra were recorded on FT IR (IR affinity-1, Shimadzu) instrument and Bruker (400 MHz) spectrometer using SiMe4 as the internal standard. The mass spectra were attained by ESI-MS spectrometer and ESR spectra were recorded at IIT, Mumbai using TCNE (tetracyanoethylene) as the g-marker.

2.2. Synthesis

2.2.1. Synthesis of 1, 3-phenylene-bis-4-aminoantipyrine

Isophthalaldehyde (0.01 M) in ethanol was added dropwise into an ethanolic solution of 4-amino-antipyrine (0.02 M) with gentle heating and stirring. The resultant reaction mixture was refluxed for 4 h. The yellow solid was obtained as product, washed thoroughly with cold ethanol, dried and recrystallized from ethanol and dried *in vacuo*. (Scheme 1). Yield: 86%.

2.2.2. Synthesis of Schiff base (1,3-phenylene-bis-4-aminoantipyrinyl-4-aminoethyl phenol(L))

1,3- phenylene-bis-4-aminoantipyrine (5.05 g, 0.01 mol) in ethanol was added to an ethanolic solution of tyramine (1.37 g, 0.01 mol) and the resultant mixture was refluxed for 5 h in the presence of anhydrous potassium carbonate. The potassium carbonate was filtered off from the reaction mixture and the solvent was evaporated. The pale orange coloured solid formed as product, separated by filtration and recrystallized from ethanol (Scheme 2). Yield: 82%.

[L]: Yield: 70%; yellowish brown colour; Anal.-Calc.for $C_{46}H_{46}N_8O_2$ (%): C (74.4), H (6.24) and N (15.8); Found (%): C (74.1), H (6.1) and N (15.6); FT-IR (KBr) (cm^{-1}): 1620 ν(C═N) and 3455 ν(-OH); ^{1}H NMR ($CDCl_3$) δppm: 6.9−7.8 (m,Ar-H), 3.2 (s,=C−CH_3), 2.7 (s,N−CH_3).1.6(s,−CH_2)and 9.7 (s,HC═N); UV−vis. in DMSO, cm^{-1} (transition): 39,062 (π-π*) and 29,850 (n-π*)

2.2.3. Synthesis of metal(II) complexes 1-4

An ethanolic solution of metal(II) chlorides (1 mmol) were mixed with Schiff base (1 mmol)

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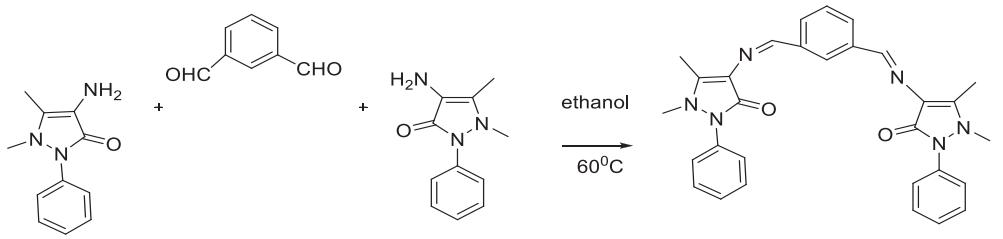
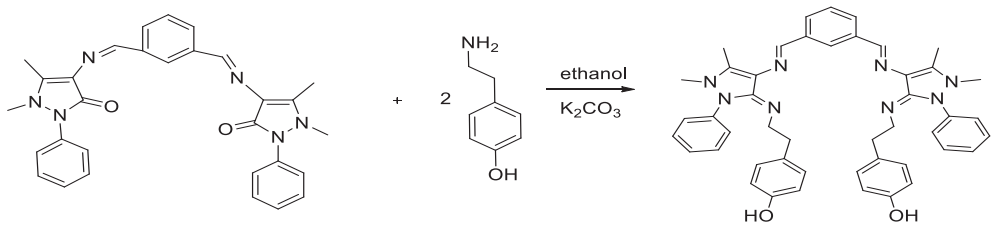


Scheme 1. Synthesis of 1,3-phenylene-bis-4-aminoantipyrine.



Scheme 2. Synthesis of 1,3-phenylene-bis-4-aminoantipyrinyl-4-aminoethyl phenol (L).

dissolved in ethanol. The reaction mixture was stirred for 3 h at room temperature. Then the solution was reduced to one-third on a water bath. The solid complex precipitated, was filtered off, washed thoroughly with ethanol and dried in *vacuo* (Fig. 1).

Complex 1: Yield: 68%; black colour; Anal.Calc.-for $C_{46}H_{46}Cl_2CuN_8O_2$ (%): C (62.9), H (5.3), N (12.8) and Cu (7.24); Found (%): C (62.81), H (5.1), N (12.7) and Cu (7.12); FT-IR (KBr) (cm^{-1}): 1601ν(−C═N), 3410 ν(−OH), 432 ν(M-N) and 350 ν(M-Cl); $\wedge_m(\Omega^{-1}mol^{-1}\ cm^2)$ 20.04; μ_{eff}(BM) 1.87; UV−vis. in DMSO, cm^{-1} (transition): 13,698 cm^{-1} (d-d).

Complex 2: Yield: 66%; pink colour; Anal.Calc.for $C_{46}H_{46}Cl_2CoN_8O_2$ (%): C (63.3), H (5.31), N (12.84) and Co (6.75); Found (%): C (63.1), H (5.11), N (12.62) and Co (6.65); FT-IR (KBr) (cm^{-1}): 1593 ν(−C═N), 3453 ν(-OH), 436 ν(M-N) and 355 ν(M-Cl); $\wedge_m$ $(\Omega^{-1}mol^{-1}cm^2)$ 19.27; μ_{eff}(BM) 4.87; UV−vis. in DMSO, cm^{-1} (transition): 23,419 cm^{-1} (LMCT), 14,814 and 16,949 (d-d).

Complex 3: Yield: 62%: Pale blue colour; Anal.-Calc.for $C_{46}H_{46}Cl_2N_8NiO_2$ (%): C (63.32), H (5.31), N (12.84) and Ni(6.73); Found (%): C (63.12), H (5.1), N (12.6) and Ni (6.7); FT-IR (KBr) (cm^{-1}) 1589 ν(−C═N), 3449 ν(−OH), 440 ν(M-N) and 359 ν(M-Cl);$\wedge_m$ $(\Omega^{-1}mol^{-1}cm^2)$ 21.54; μ_{eff}(BM) 3.19; UV−vis. in DMSO, cm^{-1} (transition): 23,148 cm^{-1} (LMCT), 14,144 and 15,923 (d-d).

Complex 4: Yield: 64%; pale yellow colour; Anal.Calc.for $C_{46}H_{46}Cl_2N_8O_2Zn$ (%): C (62.84), H (5.27), N (12.74) and Zn (7.44); Found (%): C (62.6), H (5.05), N (12.6) and Zn (7.24); FT-IR (KBr) (cm^{-1}): 1585 ν(−CH═N−), 3449 ν(−OH), 440 ν(M-N) and 359 ν(M-Cl); ^1H NMR ($CDCl_3$) δppm: 6.9−7.8 (m,Ar-H), 3.2 (s,=C−CH_3), 2.7 (s,N−CH_3) and 9.3 (s,HC═N); $\wedge_m(\Omega\ ^{-1}mol^{-1}cm^2)$ 21.10; μ_{eff}(BM) diamagnetic;

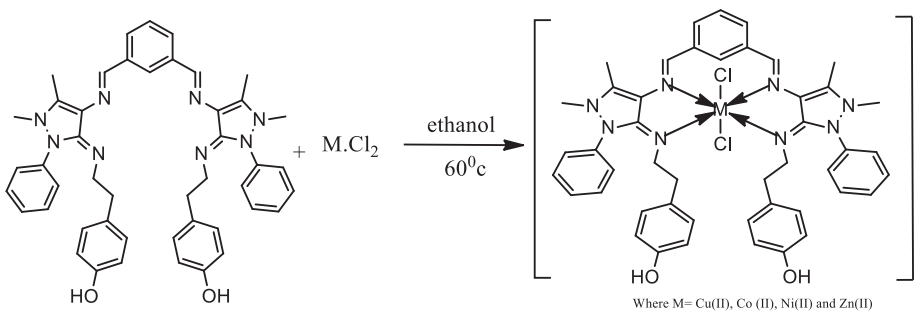


Fig. 1. Proposed structure of the Schiff base metal(II) complexes 1−4.

UV–vis. in DMSO, cm^{-1} (transition): 28,571 (LMCT).

3. Results and discussion

The synthesized L and metal(II) complexes 1–4 were characterized by various physicochemical techniques. These metal(II) complexes are readily soluble in DMF as well as in DMSO. Based on the results of all the analytical studies, metal(II) complexes 1–4 agreed to the proposed general formula of $[MLCl_2]$. Additionally, the lower values of molar conductance of metal(II) complexes 1–4 (19.27–21.54 ohm^{-1} cm^2 $mol^{-}1$) indicates their non-electrolytic properties.

3.1. Physicochemical characterization of L and metal(II) complexes 1-4

FT-IR spectra L and metal(II) complexes 1–4 are shown in Fig. 2. The characteristic phenolic ν(OH) mode due to the hydroxyl group of tyramine moiety of L is observed at 3455 cm^{-1}. The appearance of the same band in all the metal(II) complexes 1–4 indicates that the phenolic –OH group is free from complexation with central metal(II) ion. For Schiff base ligand L, the band observed at 1620 cm^{-1} was shifted to lower frequency by 18–35 cm^{-1} on complexation with central metal(II) ions, suggesting that the coordination occurrs via azomethine nitrogen [19,20].

In the electronic spectra, the free Schiff base ligand L exhibit two intense bands in 39,062 and 29,850 cm^{-1} (256 nm and 335 nm) which are due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively (Fig. 3). In all metal(II) complexes, these absorption bands are shifted to 38,022–38,610 (263–259 nm) and 28,248–28,985 cm^{-1} (354–345 nm). Metal(II) complexes 1–3 display the d–d transition band in the region of 13,698 cm^{-1} - 16,949 cm^{-1} (730-590 nm) [21,22]. This d–d transition band strongly favours a distorted octahedral geometry around the metal(II) ion. It is further supported by the magnetic susceptibility values (1.87–4.87 BM).

The ^1H NMR spectra of L and complex 4 were recorded at room temperature using d6-DMSO as solvent (Figs. 4 and 5). ^1H NMR spectrum of L shows a singlet peak at 11.1 δ, which is attributed to the phenolic –OH group of tyramine moiety. The presence of the same peak complex 4 confirms the phenolic –OH free from complexation with metal(II) ions. L shows the following additional signals of 6.9–7.8δ

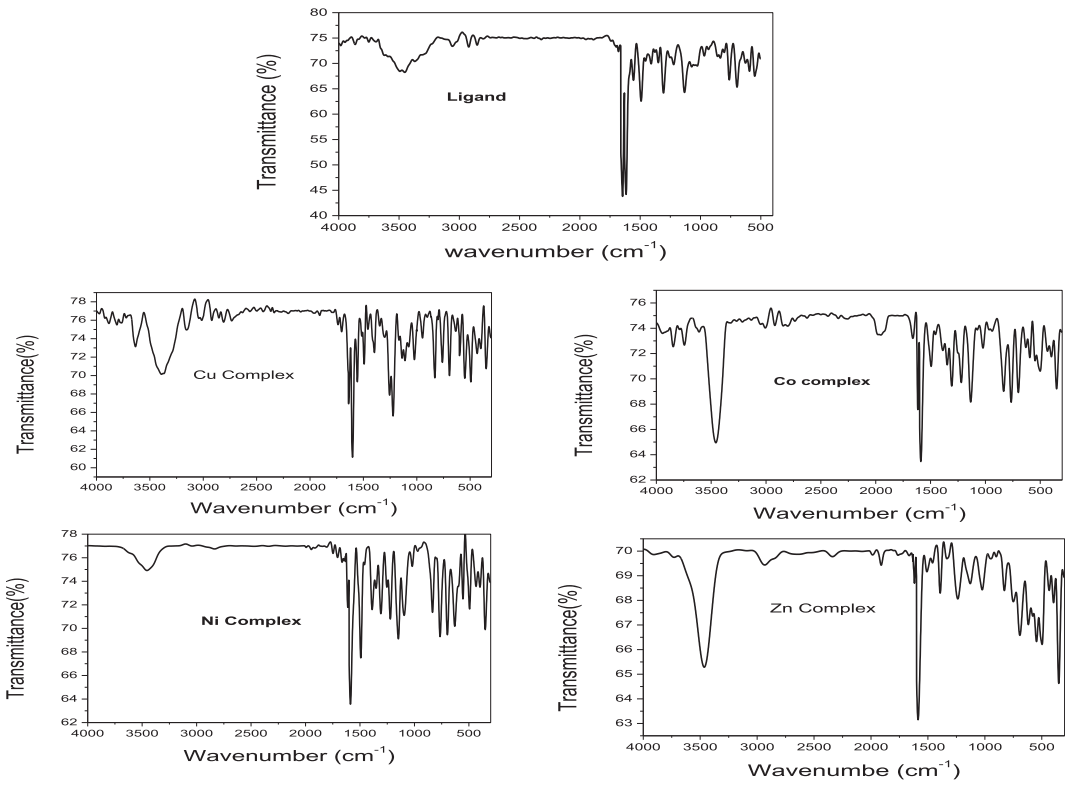


Fig. 2. FT-IR spectra of L and metal(II) complexes 1–4.

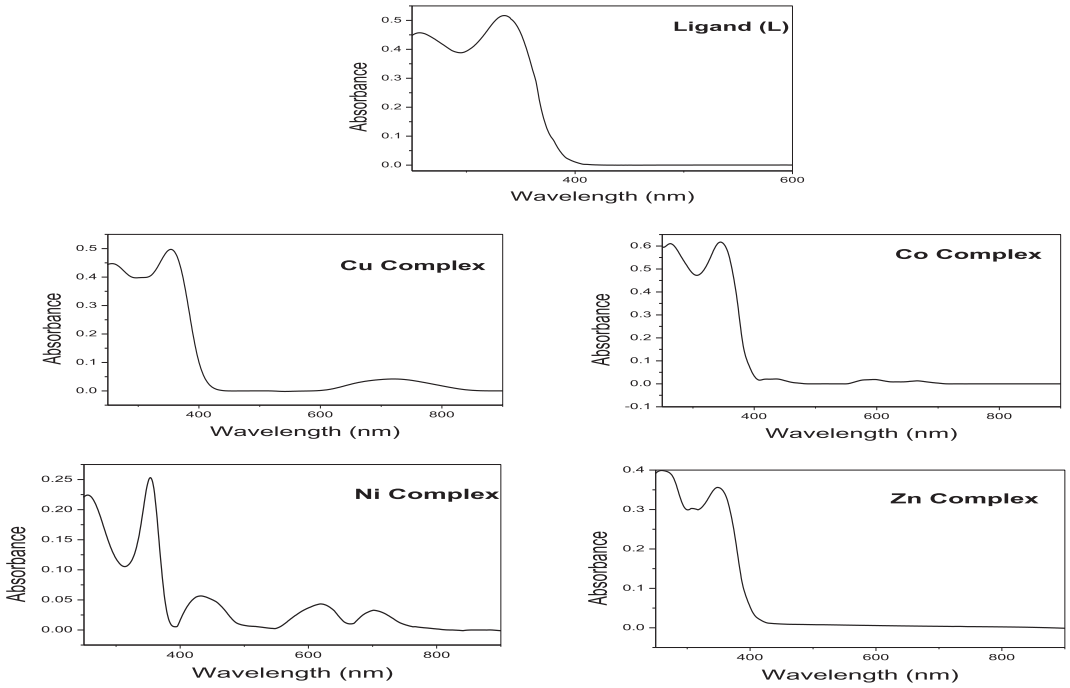


Fig. 3. UV–Vis. spectra of L and metal(II) complexes 1–4.

(aromatic), –CH =N at 9.7δ, –C–CH_3 at 2.7 δ, N–CH_3 at 3.2δ, and –CH_2 at 1.6–2.0 δ. The azomethine proton (–CH= N) signal in the spectrum of complex 4 is shifted to down field region compared to the L, suggesting azomethine group involved in the coordination with Zn(II) ion.

The mass spectrum of L shows a peak at *m/z* 743 corresponding to molecular $[C_{46}H_{46}N_8O_2]$ ion and also exhibits the peaks for the fragments at *m/z* 320,200, 130, 123, 93, and 77 corresponding to $[C_{19}H_{20}N_4O]^+$, $[C_{11}H_{12}N_4]^+$, $[C_8H_{10}O]^+$, $[C_6H_6O]^+$ and $[C_6H_5]^+$ respectively. The mass spectra of complexes 1 and 3 reveal a molecular ion peak [M+] at *m/z* 877 and 872 respectively. Complex 1 gave a fragment ion peak with loss of two chlorine atoms and undergoes de-metallation to yield the species [L+] giving the fragment ion peak at *m/z* 743 (Fig. 6).

The EPR spectrum of complex 1 was recorded in DMSO at room temperature (Fig. 7). Complex 1 exhibits the $g_{||}$ value of 2.24 and $g_{\perp}$ value of 2.05, which indicate that unpaired electron lies predominantly in the d^2_{x-y} orbital [23]. The observed value for the exchange interaction parameter for complex 1 (G = 4.8) indicates that the local tetragonal axes are aligned

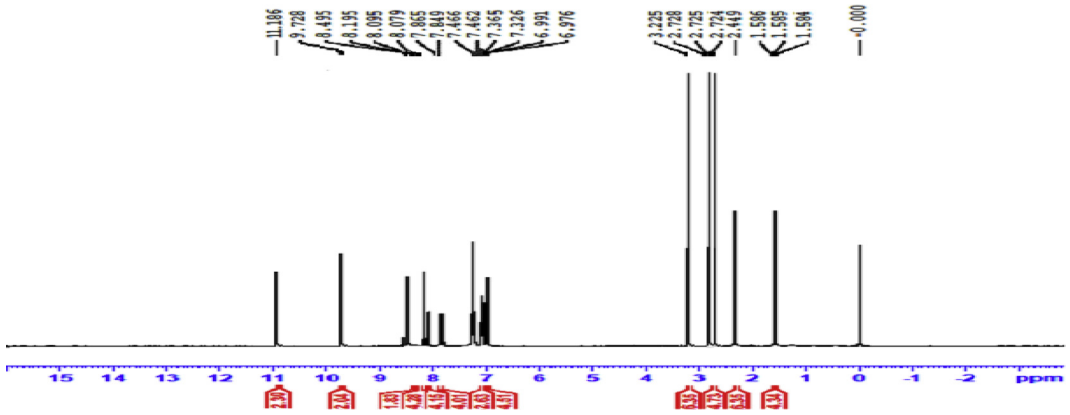


Fig. 4. ^{1}H NMR spectrum of ligand L.

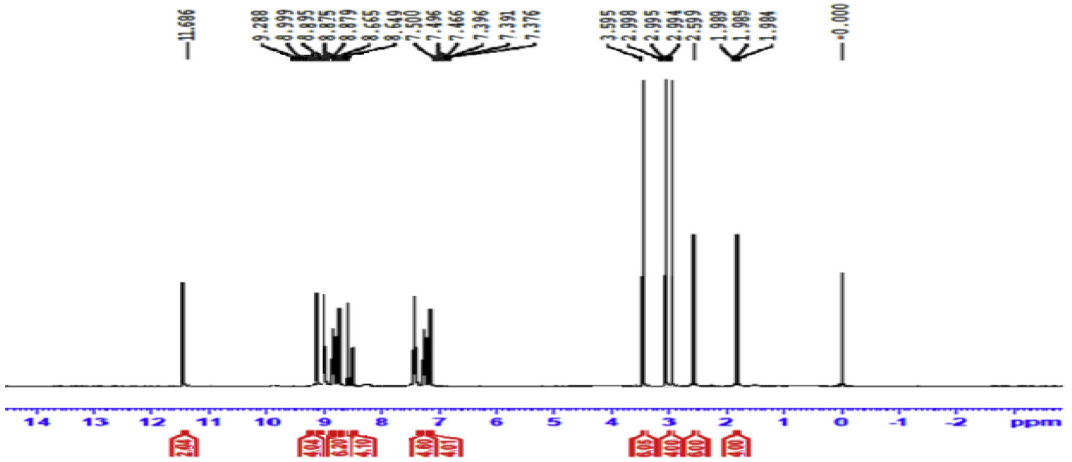


Fig. 5. ^{1}H NMR spectrum of complex 4.

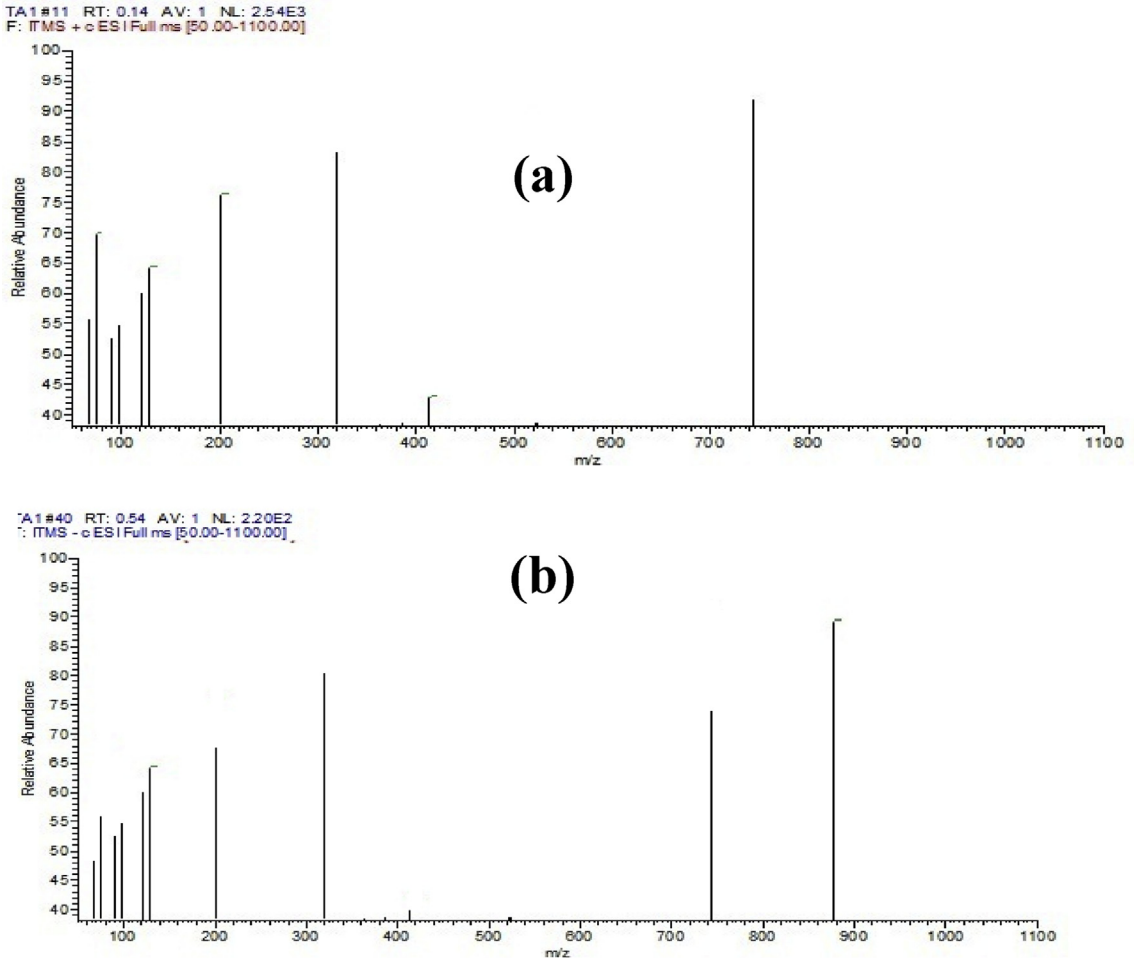


Fig. 6. ESI-Mass spectra of (a) L and (b) complex 1.

parallel or slightly misaligned and the unpaired electron is present in the d^2_{x-y} orbital (Table 1).

3.2. DNA binding studies

3.2.1. Electronic absorption titration

Electronic absorption titration was exploited to study the binding behaviour of the synthesized L and metal(II) complexes 1–4 with CT-DNA. The absorption spectral titration experiments were executed by adding incremental amount of CT-DNA to the constant concentration of L and metal(II) complexes 1–4 in 5 mM/50 mM Tris–HCl buffer (pH 7.4). The absorption spectra of synthesized L and metal(II) complexes 1 and 3 in the presence and absence of CT-DNA were shown in Fig. 8 and increase in the amount of CT-DNA resulted in decrease in the peak intensity (The percentage of observed hypochromism are 15.6%, 10.8%, 10.2% and 13.5% for the complexes 1 (424 nm), 2 (426 nm), 3 (338 nm) and 4 (265 nm), respectively) reveals the intercalative mode of binding with CT-DNA [24].

The calculated K_b values (Table 2) for metal(II) complexes 1–4 are found to be higher than that of cisplatin ($5.73 \times 10^4\ M^{-1}$) [25,26] and relatively lower than the metallo intercalator $[Ru(bpy)_2(HBT)]^{2+}$ ($5.71 \times 10^7\ M^{-1}$) [27].

3.2.2. Cyclic voltammetry

Cyclic voltametry is an another method to prove the DNA binding behaviour of metal(II) complexes with CT-DNA. These experiments were done in the presence and absence of CT-DNA with complexes 1 and 4. The cyclic voltametric behaviour of complexes 1 and 4 in the presence and absence of excess DNA are given in Fig. 9. The concentration of CT-DNA increases towards the voltammetric current. This coupled with positive shift in $E_{1/2}$ is observed to decrease significantly (Table 3). This result confirms the binding ability of complexes 1–4 with CT-DNA. Moreover, the positive shift of Ep_c or Ep_a indicates that the complex intercalates into DNA double helix [28,29].

Table 1
The spin Hamiltonian parameters of the Cu(II) complexes in DMSO solution at room temperature.

Complex	g-tensor			$A \times 10^{-4}$ (cm^{-1})			G
	$g_{\|\|}$	$g_\perp$	g_{iso}	$A_{\|\|}$	$A_\perp$	A_{iso}	
1	2.24	2.05	2.11	128	142	70.6	4.8

3.3. DNA cleavage efficacy

The efficacy of the metal(II) complexes 1–4 to act as artificial nucleases is monitored by subjecting the super coiled plasmid DNA pBR322 to agarose gel electrophoresis [30]. Fig. 10 displays the cleavage pattern of pBR322 DNA in the presence of metal(II) complexes 1–4 and H_2O_2. Complexes 1, 2 and 4 showed significant nuclease activity by cleaving into distinctive nicked (open circular) and linear form. Complex 3 has low K_b value compared to other metal complexes. It is also reflected in the DNA cleavage activity. The double strand cleavage of the plasmid DNA was prominent with the increase in the concentration of the metal(II) complexes suggesting their strong nuclease activity [31].

3.4. Antimicrobial screening

3.4.1. Antibacterial activity

The synthesized ligand L and metal(II) complexes 1–4 were tested for their *in vitro* anti-microbial

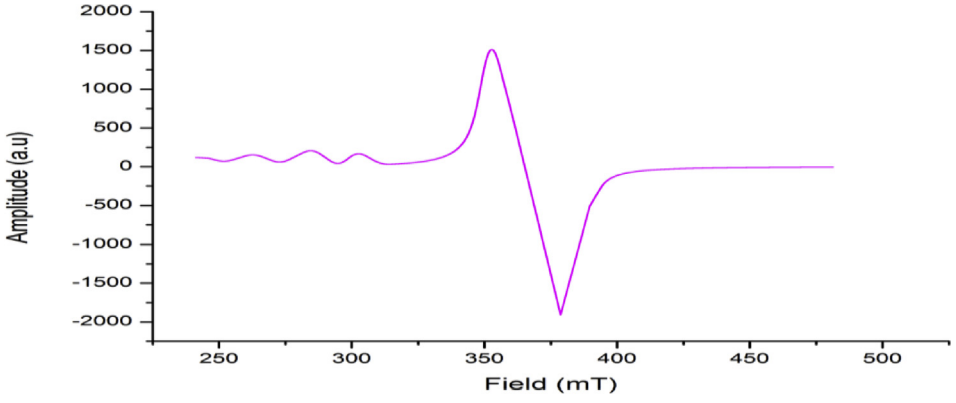


Fig. 7. EPR spectrum of complex 1 at room temperature.

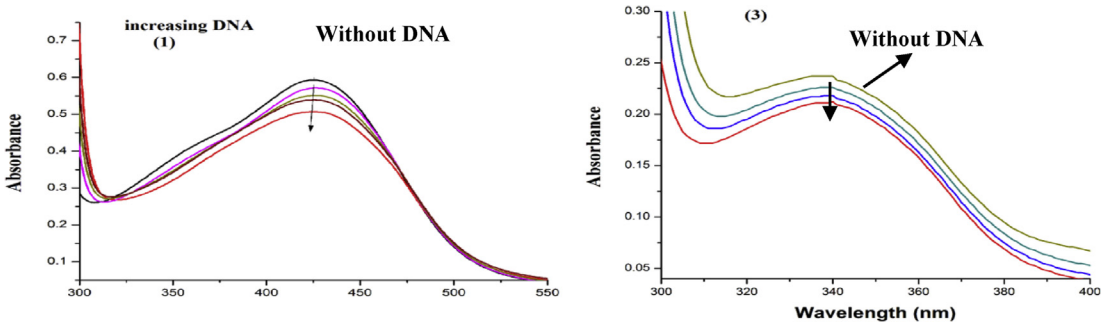


Fig. 8. Absorption spectra of complexes 1 and 3 in buffer pH = 7.4 at 25 °C in presence of increasing amount of DNA (25 µl/addition). Arrow indicates the changes in absorbance upon increasing the DNA concentration.

Table 2
Electronic absorption parameters for the interaction of DNA with metal(II) complexes 1–4.

Complex	λ_{max} (nm)		Δλ (nm)	[a]H%	$K_b \times 10^5$ (M^{-1})
	Free	Bound			
1	424	427	3.0	15.6	23.7
2	426	427	1.0	10.8	14.5
3	338	340	2.0	10.2	11.2
4	265	263	3.0	13.5	16.5

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

Table 3
Electrochemical parameters for the interaction of DNA with metal(II) complexes 1–4.

Complex	$E_{1/2}$(V)		ΔEp(V)		Ip_a/Ip_c
	Free	Bound	Free	Bound	
Cu	−0.406	0.021	−0.545	0.293	0.91
Co	−0.285	0.451	1.025	2.244	0.88
Ni	−0.452	0.156	1.356	1.865	0.82
Zn	−0.489	−0.291	0.583	1.025	0.62

activity against the bacteria *Staphylococcus aureus*, *Bacillussubtilis*, *Escherichia coli*, *and Salmonella typhi* by Broth dilution method. The antibacterial activity of L and metal(II) complexes 1–4 is presented in Table 4 and Fig. 11.

The results indicate that L exhibits moderate antibacterial activity with respect to the complexes 1–4 against the same micro-organisms under identical experimental conditions. L exhibits MIC in the range of (14.5–16.9 µg/mL) against all the pathogens. Metal(II) complexes 1–4 shows better antibacterial activity than free Schif base ligand and their MIC value is found to be in the range of 2.1–3.9 µg/mL. Higher electro negativity and large atomic radius decreases the effective positive charges on the metal complex molecules which facilitates their interaction with the highly sensitive cellular membranes towards the charged particle [32]. Here, streptomycin is used as the standard.

3.4.2. Antifungal activity

The Schiff base ligand L and metal(II) complexes 1–4 were screened for their antifungal activity against *A.niger*, *C.lunata*, *R.Bataicola and C.albicans*. The minimum inhibitory concentration (MIC) values of the

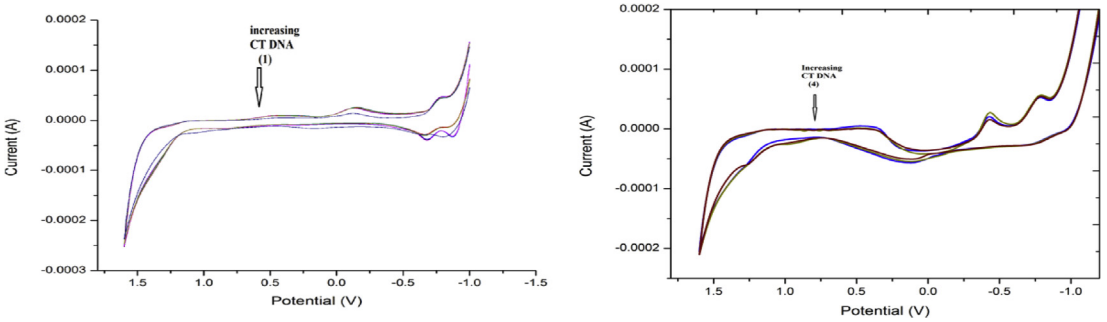


Fig. 9. Cyclic voltammogram of complexes 1 and 4 in buffer (pH = 7.4) at 25 °C in presence of increasing amount of DNA (0–100 µl). For complex 1, the amount of DNA increases in the order red < violet < blue. For complex 4, DNA increases in the order olive < blue < red.

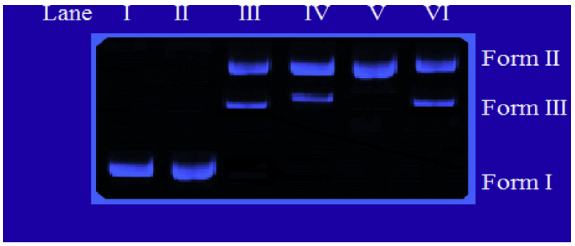


Fig. 10. Gel electrophoresis pattern showing cleavage of pBR 322 DNA treated with metal complexes. Lane I; DNA control; Lane II: DNA + L + H_2O_2; Lane III: DNA + complex 1 + H_2O_2; Lane IV: DNA + complex 2 + H_2O_2; Lane V: DNA + complex 3 + H_2O_2 and Lane VI: DNA + complex 4 + H_2O_2.

Table 4
The *in vitro* anti-bacterial activity of Schiff base ligand L and its metal complexes 1–4 (MIC in μg/mL).

Compound	Minimum inhibitory concentration (MIC)			
	S. aureus	*B. subtilis*	*E. coli*	*S. typhi*
L	15.9	14.6	15.5	15.2
1	2.1	2.6	2.8	2.5
2	3.2	3.0	3.1	2.7
3	3.9	3.1	3.5	3.6
4	3.6	3.9	3.2	3.9
Streptomycin	1.2	1.4	1.8	1.5

investigated compounds are summarized in Table 5 and Fig. 11.

A comparative study of MIC values of L (12.2–16.4 μg/mL) and its metal(II) complexes 1–4 (2.7–7.0 μg/mL) indicates that metal(II) complexes exhibit higher antifungal activity than the free ligand L. Such increased activity on metal chelation can be explained on the basis of Tweedy's chelation theory [33]. Here, nystatin is used as the standard.

Table 5
The *in vitro* anti-fungal activity of Schiff base ligand L and its metal complexes 1–4 (MIC in μg/mL).

Compound	Minimum inhibitory concentration (MIC)			
	A. niger	*C. lunata*	*R. bataticola*	*C. albicans*
L	13.2	15.5	12.2	16.4
1	2.7	3.3	4.3	6.2
2	4.4	4.9	4.5	5.8
3	5.2	6.3	6.7	7.0
4	5.8	6.5	6.9	6.7
Nystatin	1.5	2.1	1.6	2.2

4. Conclusions

Four new metal(II) complexes were prepared from tyramine derived Schiff base ligand L and well characterized by conventional analytical and different physicochemical spectral methods. The results of FT-IR, electronic transition and g-tensor data led to the conclusion that the metal(II) complexes 1–4 assumed a distorted octahedral geometry. The electronic absorption and cyclic voltammetry titration results revealed that the metal(II) complexes interacts with DNA through intercalation mode of binding. Metal(II)

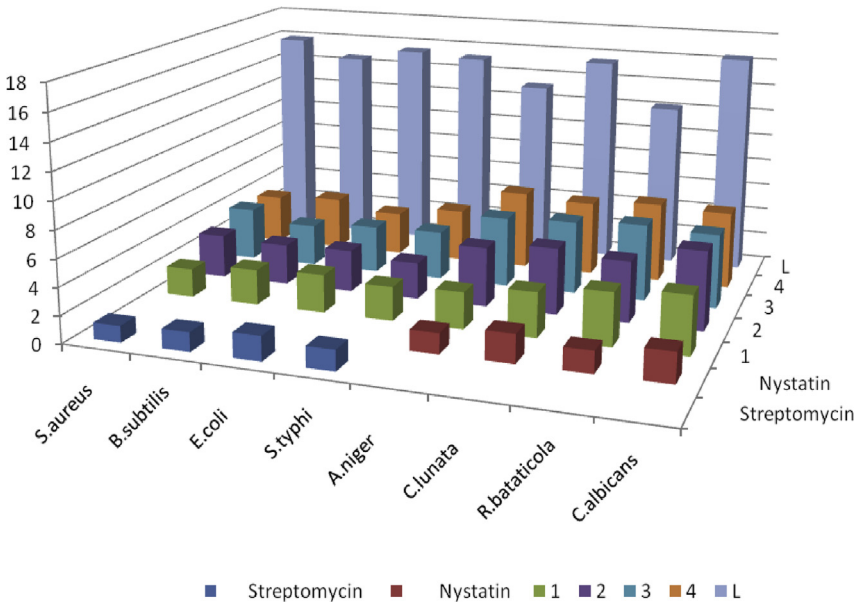


Fig. 11. Antimicrobial activity of L and metal(II) complexes 1–4.

complexes 1–4 showed better DNA cleavage and antimicrobial abilities than free ligand L. These preliminary experimental report on significant DNA binding and antimicrobial activity of metal(II) complexes against some conventional pathogens warranted further extensive cellular level *in vivo* studies.

Declaration of Competing Interest

There are no conflicts to declare.

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