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Synthesis, spectral and biological characterization of Schiff base transition metal complexes derived from L-tyrosine

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ABSTRACT

Schiff bases are important class of organic ligand, which played an integral role in the expansion of coordination chemistry and various aspects of biocoordination chemistry. Four new mononuclear Schiff base transition metal complexes $[ML^aL^bX]$*, (where M = Cu(II), Ni(II), Zn(II) and Co(II);* L^a *= Schiff base ligand derived from L-tyrosine and 2'-hydroxyacetophenone;* L^b *= N,N,N',N'-tetramethylethylene-1,2-diamine; X =* H_2O*) have been synthesized. The synthesized transition metal complexes were characterized by molar conductance, elemental analyses and spectral studies such as UV-Vis., FTIR and EPR. Non-electrolytic nature of the complexes was confirmed by molar conductance. Tridentate coordination nature of the Schiff base ligand was confirmed by FTIR spectra. In vitro antimicrobial studies were carried out against bacterial strains such as S. aureus, Bacillus, E. coli, and P. aeruginosa and fungal strains such as A. flavus, Rhizopus and Mucor. The mosquito larvicidal activity was performed against Culex quinquefasciatus for the Schiff base ligand and the synthesized metal complexes.*

Keywords: Schiff base, transition metal complexes, spectral studies, *in vitro* antimicrobial and larvicidal activities.

INTRODUCTION

Schiff bases are one of the most important organic compounds having an integral characteristic and are widely used in the synthesis of therapeutic agents [1]. The chemistry of Schiff base metal complex is undergoing rapid growth due to their significant roles in biological systems and chemical industries. Recently, considerable attention has been paid to the chemistry of the metal complexes of Schiff bases containing nitrogen and other donors [2, 3]. This may be attributed to their stability, biological activity and potential applications in many fields such as oxidation catalysis, electrochemistry etc [4]. Transition metal complexes derived from amino acid Schiff bases were reported to exhibit interesting biological properties like antimicrobial, antioxidant and DNA cleavage [5-7].

The main target of this paper is to synthesize new Schiff base transition metal complexes derived from L-tyrosine and *o*-hydroxyacetophenone with N,N,N',N'-tetramethylethylene-1,2-diamine and to characterize the synthesized complexes by physico-chemical and spectral studies. In addition, antimicrobial and larvicidal activities of the synthesized compounds were carried out.

EXPERIMENTAL SECTION

Materials and Physical measurements

All the reagents and chemicals were procured from commercial sources and were used without purification. Molar conductance of the complexes was measured in DMF (10^{-3} M) solution using a direct digital conductometer. Magnetic susceptibility of the metal complexes were measured by the Gouy method at room temperature using a K-roy magnetic susceptibility balance and the effective magnetic moments were calculated using the relation $\mu_{eff} = 2.824\ (\chi_m \times T)^{1/2}$ B.M., where χ_m is the molar susceptibility corrected using Pascal's constants for diamagnetism. FTIR spectra of solid complexes were recorded using KBr pellet in the region of 4000–400 cm^{-1} on AVATAR 330 spectrophotometer. UV-Vis. spectra of the complexes were recorded in the region of 200–800 nm using a HitachiU-2800 spectrophotometer in DMF. EPR spectrum was recorded in solid state at room temperature using Bruker EMX -10/2.7 spectrometer.

Synthesis

To an aqueous solution of L-tyrosine (0.19 g, 1 mmol) and KOH (2 mmol), an ethanolic solution of *o*-hydroxyacetophenone (0.15 mL, 1mmol) was added. The reaction mixture was stirred for about 1 h in a magnetic stirrer at 333 K. The solution turned yellow. To this an ethanolic solution of respective hydrated metal acetates [1 mmol, M = copper(II), cobalt(II), nickel(II) and zinc(II)] was added. The reaction mixture was stirred for 1 h. Then, N,N,N'N'- tetramethylethylene-1,2-diamine (0.15 mL, 1 mmol) was added in drops and the mixture was stirred for another 2 h at the same temperature. The resultant product was filtered, washed with ethanol and dried.

Antimicrobial studies (*in vitro*)

All the synthesized metal complexes and the Schiff base ligand were tested for their antimicrobial studies by *in vitro* method against the four bacterial strains and three fungal strains. The Gram-positive bacteria such as *Staphylococcus aureus* (MTCC 3160), Gram-negative bacteria such as *Escherichia coli* (MTCC 581), *Bacillus sps.*, (MTCC 1272), *Pseudomonas aeruginosa* (MTCC 4673) and three fungal strains such as *Aspergillus flavus, Rhizophus sps.*, and *Mucor sps.*, were used as test microorganism. Antimicrobial activities of the Schiff base transition metal complexes was carried out by previously optimized procedure using Mueller Hilton agar for bacterial strains and Sabouraud dextrose agar for the fungal strains [2]. The tests were carried out in triplicates. The minimum inhibitory concentration (MIC) is the lowest concentration at which the growth of a microorganism is inhibited [8] was measured by serial dilution, using the stock solutions of synthesized compounds (1mg/mL) in DMSO. GraphPad 5.0 version was used to present the graphical representation of antimicrobial studies.

Larvicidal studies

Culex quinquefasciatus larvae were collected from Zonal Entomological Research Centre, Vellore, Tamil Nadu. Mosquito larvicidal activities of the Schiff base ligand and the synthesized metal complexes were carried out by previously optimized procedure [2]. The numbers of dead larvae were counted after 24 h of exposure and the percentage of mortality was reported from the average of triplicates.

RESULTS AND DISCUSSION

Solubility

The synthesized transition metal complexes are freely soluble in DMSO, DMF, ethanol and partially soluble in water, chloroform and acetonitrile at room temperature.

Molar conductance and Melting point

The synthesized Schiff base transition metal complexes were dissolved in DMF and the molar conductivities of 10^{-3} M solution were measured at 25 °C. The analytical data of metal complexes are given in table 1.

Table 1. Analytical data of the Schiff base metal complexes

Complex	Molecular Formula	Molecular Weight	Melting/ decomposition point °C	Colour	Molar conductance Ohm^{-1} cm^{-2} mol^{-1}	Elemental analyses found (calculated) %		
						C	H	N
[CoL^{a}L^{b}X]	$C_{23}H_{33}O_5N_3Co$	490.46	184	Dark brown	3.41	56.41 (56.32)	6.75 (6.78)	8.63 (8.57)
[NiL^{a}L^{b}X]	$C_{23}H_{33}O_5N_3Ni$	490.22	160	Dark green	3.41	56.38 (56.35)	6.81 (6.79)	8.59 (8.57)
[CuL^{a}L^{b}X]	$C_{23}H_{33}O_5N_3Cu$	495.07	196	Dark green	4.56	55.83 (55.80)	6.65 (6.72)	8.53 (8.49)
[ZnL^{a}L^{b}X]	$C_{23}H_{33}O_5N_3Zn$	496.92	130	Pale yellow	3.41	57.69 (55.59)	6.63 (6.69)	8.48 (8.46)

where, L^a = Schiff base derived from o-hydroxyacetophenone and L-tyrosine; L^b = N,N,N'N'- tetramethylethylene-1,2-diamine; X = H_2O.

The lower molar conductivity values in the range of 3.41 to 4.56 Ohm^{-1}cm^{-2}mol^{-1} suggested the non-electrolytic nature of the complexes [9]. The elemental analyses of the complexes support the absence of the counter ions. The analytical results are in good agreement with the general molecular formula for the Schiff base metal complexes.

The Co(II) complex showed a magnetic moment of 4.45 BM, suggesting high spin octahedral arrangement [10]. The nickel(II) complex showed magnetic moment of 2.93 B.M. corresponding to two unpaired electrons [11]. It suggests octahedral geometry of Ni(II) complex. The Cu(II) complex showed magnetic moment of 1.91 BM observed for a d^9 system with an unpaired electron. The Zn(II) complex is diamagnetic as expected for a d^{10} configuration.

UV-Visible spectra

The electronic absorption spectra of Schiff base ligand and its transition metal complexes were recorded in DMF (10^{-3} M) at room temperature and the data are summarized in the table 2.

Table 2. The UV-Vis spectral data of the Schiff base and its metal complexes

Compound	Absorption (λ_{max} nm)		
	π-π*	n-π*	d- d
L^a	290	350	-
[CoL^{a}L^{b}X]	260	350	650
[NiL^{a}L^{b}X]	275	350	650
[CuL^{a}L^{b}X]	275	340	600
[ZnL^{a}L^{b}X]	265	350	-

The absorption band appeared at 290 and 350 nm of Schiff base ligand corresponds to π-π* and n- π* transition respectively. The metal complexes exhibited absorption bands in the range of 260 to 275 nm corresponds to π-π* transition of aromatic chromophore [12]. The absorption bands observed at 350, 340, 365 and 350 nm for Co(II), Ni(II), Cu(II), and Zn(II) complexes respectively, are assigned to n-π* transition of lone pair of electrons present in the azomethine moiety [13]. The absorption bands observed at 640, 650 and 600 nm for Co(II), Ni(II), and Cu(II) complexes respectively, are assigned to d-d transition. The Zn(II) complex didn't show any d-d transition due to completely filled d^{10} configuration [14].

FTIR spectra

The assignments of characteristic FTIR spectral bands of the Schiff base metal complexes are given in table 3.

Table 3. FTIR spectral data of the Schiff base metal complexes in cm^{-1}

Complex	C-O	C=N	COO$^-$		$\Delta\upsilon=[\upsilon_{as}-\upsilon_s]$	M-O	M-N
			(υ_{as})	(υ_s)			
[CoL^{a}L^{b}X]	1238	1641	1598	1371	210	435	520
[NiL^{a}L^{b}X]	1249	1579	1573	1369	204	440	524
[CuL^{a}L^{b}X]	1273	1624	1587	1371	216	456	538
[ZnL^{a}L^{b}X]	1246	1556	1514	1344	170	418	512

The FTIR spectra of the Co(II), Ni(II), Cu(II), and Zn(II) complexes displayed a strong absorption bands at 1641, 1579, 1624, and 1556 cm^{-1} respectively, which are assigned to the coordinated imine nitrogen with the metal ions [15-17]. The absorption band observed in 1344 to 1371 cm^{-1} range for the metal complexes are assignable to the symmetric stretching of carboxylate group [18]. The asymmetric stretching ($\upsilon_{as}COO^-$) of the carboxylate group of Schiff base ligand was observed in the range of 1514 to 1598 cm^{-1} for the metal complexes. The separation between asymmetric and symmetric stretching frequencies [$\Delta\upsilon = (\upsilon_{as}COO^- - \upsilon_s COO^-)$] were found to be higher than that of free carboxylate anion (187 cm^{-1}) [19]. This confirmed the monodentate coordination of the carboxylate anion [7, 20] present in the Schiff base ligand. All the complexes showed a broad band around 3200 cm^{-1} which confirms the presence of coordinated or lattice water molecule [22].

The FTIR spectral band found in the range of 1238-1249 cm^{-1} supported the coordinated pheonlic oxygen with the metal ions [23]. The bands appeared between 418- 455 cm^{-1} for the Schiff base metal complexes confirms the formation of M-O coordination [24]. The bands observed at 520, 524, 538, and 512 cm^{-1} for Co(II), Ni(II), Cu(II), and Zn(II) complexes respectively, can be assignable for M-N coordination [25]. FTIR data revealed that the Schiff base acts as a tridentate ligand, via phenolic oxygen, imine nitrogen and oxygen atom present in the carboxylate group.

EPR spectrum

The EPR spectrum of the copper(II) complex recorded at room temperature exhibited unresolved signal with the g_{iso} value of 2.1. The mononuclear nature of the complex was also evident from the absence of a half field signal, due to $m_s = \pm 2$ transitions, ruling out any Cu–Cu interaction [26].

Biological activities

Antibacterial activity

In recent years, researchers focus on the discovery of new drugs for controlling infectious diseases caused by pathogenic microbes. Due to the great flexibility and diverse structural aspects of metal complexes, a wide range of metal complexes have been synthesized and their complexation behavior was studied [27]. The antibacterial activity shown by the Schiff base ligand and its metal complexes are summarized in table 4 and the graphical representation is given in figure 1.

Table 4. Antibacterial activity of the Schiff base and its metal complexes

Organism (bacteria)	Zone of inhibition (mm)					
	[CoL^aL^bX]	[NiL^aL^bX]	[CuL^aL^bX]	[ZnL^aL^bX]	L^a	Gentamycin
S. aureus	11	10	11	17	10	17
P. aeruginosa	14	12	12	13	11	18
Bacillus	16	12	11	14	11	20
E.coli	23	22	21	22	10	15

All the synthesized metal complexes have shown moderate to very good activity against the bacteria under investigation. Except Co(II) and Cu(II) complexes against *S. aureus* and Cu(II) complex against *Bacillus,* all the complexes exhibited very good antibacterial activity. The antibacterial activity of the complexes was found to be greater than the corresponding Schiff base ligand. Among the series all the complex showed very good activity against *E. coli* with the zone of inhibition 23 mm, 22 mm, 21 mm, and 22 mm for Co(II), Ni(II), Cu(II), and Zn(II) complexes respectively.

Antifungal activity

The results with reference to *in vitro* antifungal activities (Figure 2) of the Schiff base ligand and the synthesized complexes are summarized in table 5.

Table 5. Antifungal activity of the Schiff base and its metal complexes

Organism (Fungi)	Zone of inhibition (mm)					
	[CoL^aL^bX]	[NiL^aL^bX]	[CuL^aL^bX]	[ZnL^aL^bX]	L^a	Nystatin
A. flavus	16	23	15	15	11	18
Rhizopus	23	26	18	15	13	19
Mucor	18	23	21	14	15	20

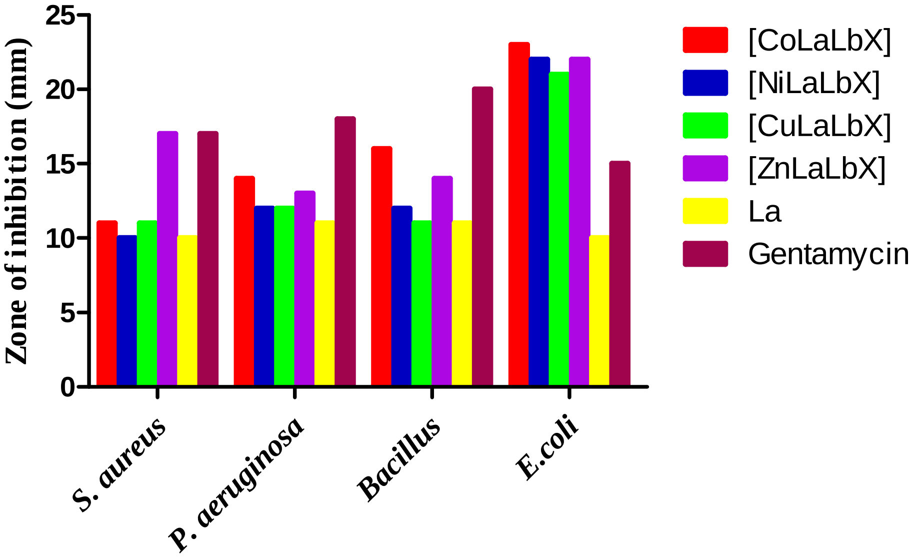

Figure 1. Graphical representation of antibacterial activity of the Schiff base and its metal complexes

All the complexes showed very good antifungal activity against the fungi under investigation. Especially, Ni(II) and Co(II) complexes showed 26 mm and 23 mm zone of inhibition against *Rhizopus* and this is greater than the standard nystatin. In particular, Ni(II) complex exhibited very good anti fungal activity against *Mucor* and *A. flavus* with 23 mm zone of inhibition. The Cu(II) showed very good value of 21 mm zone of inhibition against *Mucor*. Among the series Ni(II) complex showed very good antifungal activity against all the fungi under study. The inhibitory activities of almost all the complexes were greater than the corresponding Schiff base ligand.

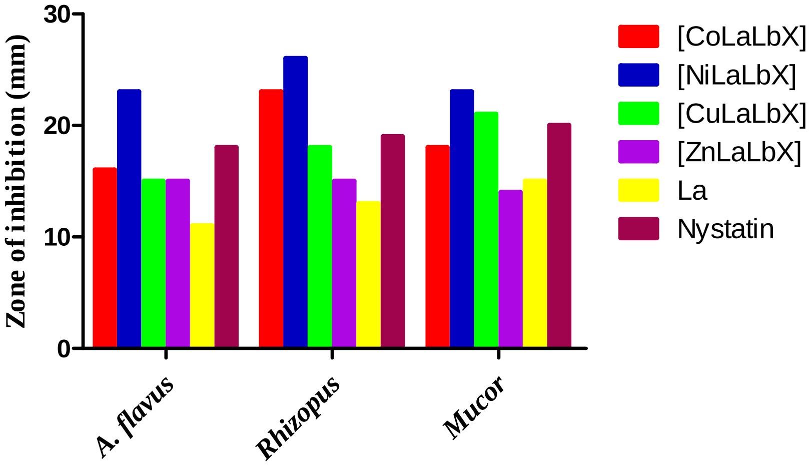

Figure 2. Graphical representation of antifungal activity of the Schiff base and its metal complexes

The results from these studies proved that complexation of metals to Schiff base ligand serves to improve the antimicrobial of the ligand. The higher antibacterial activity of the metal complexes compared to the Schiff base ligand may be due to chelation and hence destroying microbes more forcefully [28]. In the present study low activity of the some metal complexes may be due to the lower penetrating tendency of them through lipid membrane. Hence this could neither block nor inhibit the growth of the microorganisms [17].

Minimum inhibition concentration

Growth of pathogens on each concentration was studied to determine the minimum concentration that inhibits the growth of the microorganism and the values are listed in table 6.

Table 6. MIC values of Schiff base and its metal complexes in µg /mL

Compound	*S. aureus*	*P. aeruginosa*	*Bacillus*	*E. coli*	*A. flavus*	*Rhizopus*	*Mucor*
[CoL^{a}L^{b}X]	5	5	5	2.5	5	5	5
[NiL^{a}L^{b}X]	5	5	5	2.5	5	5	5
[CuL^{a}L^{b}X]	5	5	5	5	5	5	2.5
[ZnL^{a}L^{b}X]	5	5	5	2.5	5	5	5
L^{a}	10	10	10	10	10	10	10

All the synthesized metal complexes showed least minimum inhibitory concentration of 5 µg/mL against Gram-positive bacteria such as *Staphylococcus aureus, Bacillus* and Gram-negative bacteria such as *P. aeruginosa*. Co(II), Ni(II) and Zn(II) complexes showed 2.5 µg/mL MIC value against *E. coli*. The MIC values of the Schiff base metal complexes were found to be less when compared to the corresponding Schiff base ligand. Except Cu(II) complex against *Mucor,* all other metal complexes showed MIC value of 5 µg /mL against *A. flavus, Rhizopus* and *Mucor.*

Larvicidal activity

The larvicidal activity of the Schiff base ligand and the complexes was performed against the larvae of *Culex quinquefasciatus* and the results of mortality values are listed in table 7 and the statistical analysis is shown in table 8. The pictorial representation of larvicidal activity is given figure 3.

Table 7. Larvicidal activity of Schiff base and its metal complexes against *C. quinquefasciatus*

Compound	Concentration / mortality			
	4 mg/200mL	2mg/200mL	1mg/200mL	0.5mg/200mL
[CoL^{a}L^{b}X]	17	10	6	3
[NiL^{a}L^{b}X]	18	13	6	4
[CuL^{a}L^{b}X]	19	17	10	5
[ZnL^{a}L^{b}X]	19	16	11	6
L^{a}	3	2	1	0

Table 8. Statistical analysis of larvicidal activity of Schiff base and its metal complexes against *C. quinquefasciatus*

Compound	Concentration / % Mortality±SD				LC 50 mg/200L	LC 90 mg/200mL	χ^2	df
	4mg/200mL	2mg/200mL	1mg/200mL	0.5mg/200mL				
[CoL^{a}L^{b}X]	85±5.19	50±6.28	30±4.75	15±1.28	2	3.6	21.21	
[NiL^{a}L^{b}X]	90±5.87	65±5.27	30±4.75	20±6.71	1.5	2.7	22.10	
[CuL^{a}L^{b}X]	95±4.56	95±4.56	50±6.28	25±5.45	1.1	1.98	25.50	
[ZnL^{a}L^{b}X]	95±4.56	80±6.92	55±6.19	30±4.75	0.9	1.62	20.93	3
L^{a}	15±1.28	10±2.00	0.5±0.00	-	-	-	-	

LC50: lethal concentration that kills 50% of the exposed larvae.
LC90: lethal concentration that kills 90% of the exposed larvae.
Mean value of triplicates, Control-Nil mortality, df- significant at p< 7.8; χ^2: chi-square.

All the synthesized complexes show moderate to stronger toxic effect against *Culex quinquefasciatus.* The percentage mortality was found for the synthesized metal complexes after 24 h of exposure period. The average larval mortality data were subjected to statistical analysis for calculating standard deviation and chi-square values for synthesized metal complexes. The calculated values were lesser than table value hence the results with $p < 7.81$ were considered to be statistically significant. The order of % of mortality of the synthesized complexes is given below:

[CuL^{a}L^{b}X] = [ZnL^{a}L^{b}X] > [NiL^{a}L^{b}X] > [CoL^{a}L^{b}X] > L^{a}

The highest mortality of 95% was obtained for Cu(II) and Zn(II) complexes. The % moratality for Co(II) and Ni(II) complexes was 90% and 85% respectively.

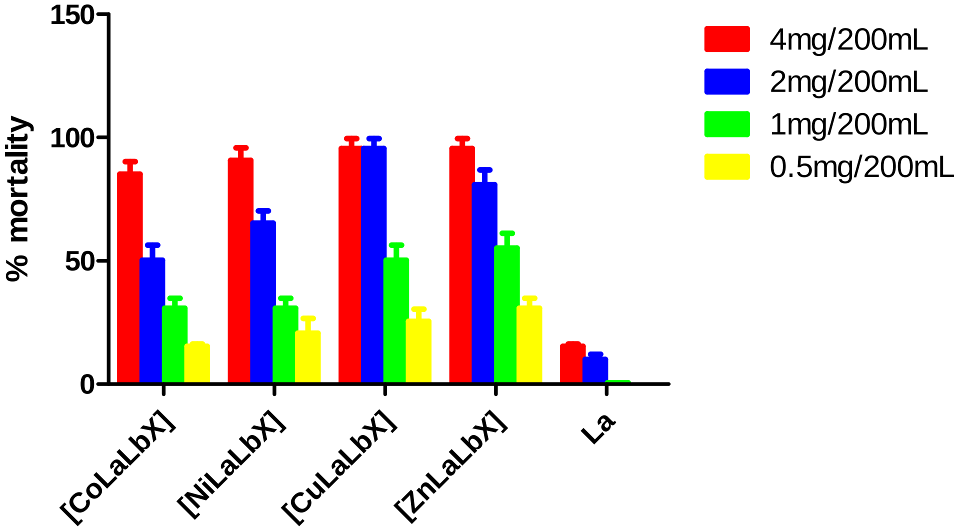

Figure 3. % mortality of Schiff base and its metal complexes against the larvae of *Culex quinquefasciatus*

CONCLUSION

In the current study, four Schiff base transition metal complexes have been synthesized and characterized by physicochemical and spectral techniques. The lower molar conductance value indicates that all the complexes are non-electrolytes. FTIR spectra revealed the tridentate coordinating mode of the Schiff base ligand. Based on physicochemical and spectral studies an octahedral geometry has been proposed for all the complexes. All the synthesized complexes against *E. coli* and Zn(II) complex against *S. aureus* showed very good antibacterial activity. Ni(II) complex against *A. flavus*, Co(II) and Ni(II) complexes against *Rizopus* and Co(II), Ni(II) and Cu(II) complexes against *Mucor* showed very good antifungal activities when compared with the Schiff base ligand and the standard drug nystatin. The larvicidal activity against *Culex quinquefasciatus* emphasized that the metal complexes are highly potent than the free Schiff base ligand. Cu(II) and Ni(II) complexes showed higher mortality of 95% against the larvae *C. quinquefasciatus*. Hence, these preliminary studies showed that these compounds can serve as good targets to design antimicrobial as well as larvicidal agents.

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