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Research Article

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Synthesis, characterization and biological studies of tridentate amino acid (L-tryptophan) Schiff base transition metal complexes

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ABSTRACT

Schiff bases plays vital role in various fields especially in industry and biology. In the present study, a series of ternary mononuclear Schiff base transition metal complexes [ML(tmen)], (where M = Cu(II), Ni(II), Zn(II) and Co(II) ions; L = Schiff base ligand derived from L-tryptophan and 2'-hydroxyacetophenone; tmen-N,N,N',N' tetramethylethylenediamine) were synthesized and characterized by molar conductance, elemental analysis and spectral studies such as UV-Vis., and FTIR. Non-electrolytic nature of the complexes were confirmed by molar conductance. Tridentate coordination nature of Schiff base ligand was confirmed on the basis of FTIR spectra. In vitro antimicrobial studies were carried out against bacterial strains such as S. aureus, Bacillus sps., E. coli, and P. aeruginosa and fungal strains such as A. flavus, Rhizopus and Mucor. In addition, in vitro larvicidal and antioxidant studies were also performed for the Schiff base ligand and synthesized metal complexes.

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

INTRODUCTION

Schiff bases are one of the most privileged organic ligand showing integral feature in various fields including medicine and agriculture [1, 2]. The chemistry of Schiff base metal complex is undergoing rapid development due to their essential roles in biological systems and chemical industries. Schiff base ligands which usually contain oxygen and nitrogen donor atoms have played an important role in coordination chemistry [3, 4].

Recently, considerable attention has been paid to the chemistry of Schiff base metal complexes derived from amino acids, containing oxygen and nitrogen donors for their physiological reasons [5, 6]. This may be attributed to their stability, biological activity and potential applications in many fields such as catalysis, electrochemistry etc [7, 8]. Though studies of new kind of Schiff bases are now attracting the attention of researchers for their biological activity and perspective accessibility for pharmaceuticals, only less attention has been given to Schiff bases metal complexes derived from amino acids and *o*-hydroxyacetophenone.

As a part of our research work, herein we report, *in situ* synthesis and spectroscopic characterization of Schiff base transition metal complexes derived from *o*-hydroxyacetophenone and L-tryptophan. *In vitro* biological activities such as antibacterial, antifungal, antioxidant and larvicidal activities have also been reported.

EXPERIMENTAL SECTION

Materials
All chemicals and reagents used were of analytical grade and were used without purification.

Synthesis
The Schiff base metal complexes were prepared by the following procedure:
KOH (0.112 g, 2 mmol) was dissolved in 5 mL of distilled water. To this ethanolic solution of L- tryptophan (0.21 g, 1 mmol) was added slowly with constant stirring. Then, 2'-hydroxyacetophenone (0.15 mL, 1 mmol) was added and the reaction mixture was stirred for about 1 h at 60 °C in a magnetic stirrer. The solution turned yellow. To the above solution, metal(II) acetates [copper(II) acetate monohydrate (0.2 g, 1 mmol), cobalt(II) acetate tetrahydrate (0.25 g, 1 mmol), nickel(II) acetate tetrahydrate (0.25 g, 1 mmol), and zinc(II) acetate dihydrate (0.22 g, 1 mmol)] was added and the reaction mixture was stirred for 1 h, followed by addition of tmen (0.15 mL, 1 mmol). The mixture was stirred for another 2 h at the same temperature. The resultant product was filtered, washed with ethanol and dried.

Molar conductance
The molar conductance of 10^{-3} M (DMF) Schiff base transition metal complexes were recorded at room temperature using Digital conductivity meter, DCM 900 Global electronics. The cell constant of the conductivity cell used was 1.0 cm^{-1}.

CHN analyses
Elemental analyses (C, H & N) were performed with Perkin-Elmer model 2004 series-II CHN analyzer.

UV-Visible spectra
Electronic absorption spectra of the Schiff base transition metal complexes (10^{-3} M) in DMF were recorded using a Systronics-2201 spectrophotometer in the wavelength range of 200-800 nm.

FTIR spectra
The FTIR spectra of all the metal complexes were recorded using Shimadzu spectrometer in the range of 4000-400 cm^{-1} using KBr pellet.

Antimicrobial studies (*in vitro*)
The Schiff base and its metal complexes were screened for antimicrobial activity against bacterial strains such as *Staphylococcus aureus*, *Escherichia coli*, *Bacillus sps.*, *Pseudomonas aeruginosa* and three fungal strains such as *Aspergillus flavus*, *Rhizophus sps.*, and *Mucor sps.*. Antimicrobial activities of the Schiff base transition metal complexes was carried out by previously optimized procedure [9] using Mueller Hilton agar for bacterial strains and Sabouraud dextrose agar for the fungal strains. 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. Stock solutions of synthesized metal complexes were prepared by dissolving 1 mg/mL of the complexes in DMSO. The solutions were serially diluted. Finally the bacterial strains were incubated at 37 °C for 24 h, whereas the fungal strains were incubated at room temperature for 48 h.

Antioxidant activity by DPPH radical scavenging activity
Antioxidant activity of the Schiff base transition metal complexes was carried out by using previously optimized procedure [9].

Larvicidal studies
Culex quinquefasciatus larvae were collected from Zonal Entomological Research Centre, Vellore, Tamil Nadu. Larvicidal activities of the synthesized metal complexes and the Schiff base ligand was carried out by previously optimized procedure [9]. The percentage of mortality was reported from the average of triplicates.

RESULTS AND DISCUSSION

The synthesized transition metal complexes are freely soluble in DMSO, DMF and ethanol and partially soluble in water at room temperature. 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. The lower molar conductivity value of the complexes indicates their non-electrolytic nature [10]. The elemental analyses of the complexes confirmed that the experimental values are in good agreement with theoretical value.

Table 1. Analytical data of the metal complexes

Complex	Molecular Formula	Molecular Weight	Melting/ decomposition point °C	Colour	Molar conductance $Ohm^{-1} cm^{-2} mol^{-1}$	Elemental analyses calculated (found) %		
						C	H	N
[CoL(tmen)]	$C_{26}H_{34}O_3N_4Co$	508.93	230	Dark brown	4.56	61.31 (61.12)	6.68 (6.40)	11.00 (11.09)
[NiL(tmen)]	$C_{26}H_{34}O_3N_4Ni$	508.65	182	Pale green	3.41	61.34 (61.11)	6.68 (6.38)	11.02 (11.23)
[CuL(tmen)]	$C_{26}H_{34}O_3N_4Cu$	513.54	220	Dark green	4.56	60.75 (60.40)	6.21 (6.26)	10.90 (10.21)
[ZnL(tmen)]	$C_{26}H_{34}O_3N_4Zn$	513.36	140	Pale yellow	4.56	60.78 (60.22)	6.62 (6.13)	10.91 (11.13)

where, L = Schiff base derived from 2'-hydroxyacetophenone and L- tryptophan.

UV-Visible spectra

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

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

Compound	Absorption (λ_{max} nm)		
	π-π*	n-π*	d- d
L	265	350	-
[CoL(tmen)]	270	345	610
[NiL(tmen)]	280	360	650
[CuL(tmen)]	280	360	620
[ZnL(tmen)]	275	350	-

The absorption band appeared at 265 and 350 nm of Schiff base ligand corresponds to π-π* and n-π* transition respectively. The metal complexes of Co(II), Ni(II), Cu(II), and Zn(II) exhibited absorption bands at 270, 280, 280 and 275 nm respectively, corresponds to π-π* transition of aromatic chromophore [11]. The absorption bands observed at 345, 360, 360, and 350 nm for Co(II), Ni(II), Cu(II) and Zn(II) complexes respectively are assigned to n-π* transitions of lone pair of electrons present in the imine moiety [12]. The absorption bands observed at 610, 650 and 620 nm for Co(II), Ni(II) and Cu(II) complexes respectively, are assigned to d-d transition. No d-d transition was observed for Zn(II) complex due to completely filled d^{10} configuration [13].

FTIR spectra

FTIR spectra is an important tool for identifying the coordination nature the ligand with the metal ions. The synthesized complexes were characterized based on C=N (azomethine), COO^-, M-O and M-N absorption bands. The assignments of characteristic infrared bands are represented in table 3.

Table 3. FTIR absorption bands of the metal complexes in cm^{-1}

Complex	C=N	COO^-		$\Delta\upsilon=[\upsilon_{as}-\upsilon_s]$	M-O	M-N
		(υ_{as})	(υ_s)			
[CoL(tmen)]	1604	1525	1338	187	465	565
[NiL(tmen)]	1566	1519	1336	183	460	520
[CuL(tmen)]	1622	1562	1350	212	493	580
[ZnL(tmen)]	1583	1546	1355	191	480	509

The strong absorption band appeared between 1622 to1583 cm^{-1} can be attributed to the coordinated imine moiety with the metal ions [14-16]. Appearance of an absorption band at 1338, 1336, 1350 and 1355 cm^{-1} for Co(II), Ni(II), Cu(II) and Zn(II) complexes respectively, are assignable to the symmetric stretching of carboxylate group [17]. The asymmetric stretching (υ_{as} COO^-) was observed at 1525, 1519, 1562 and 1546 for Co(II), Ni(II), Cu(II) and Zn(II) complexes respectively. The separation between asymmetric and symmetric stretching frequencies [$\Delta\upsilon = (\upsilon_{as}\ COO^- - \upsilon_s\ COO^-)$] were found to be greater than that of free carboxylate anion (177 cm $^{-1}$) [18]. This confirmed the monodentate coordination nature of carboxylate anion [12, 19] present in the Schiff base ligand with the metal ions. The bands appeared in the range 465, 460, 493 and 480 cm^{-1} for Co(II), Ni(II), Cu(II) and Zn(II) respectively, confirms the formation of M-O coordination in complexes [20]. Similarly, the bands observed at 565, 520, 580, and 509 cm^{-1} for Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) complexes respectively, is assignable to M-N coordination [20]. 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.

Antibacterial activity

In vitro antibacterial activity of the Schiff base ligand and its metal complexes were screened against Gram-positive bacteria such as *Staphylococcus aureus* and Gram-negative bacteria such as *Pseudomonas aeruginosa, Bacillus sps.,* and *E. coli* using well diffusion method. The zone of inhibition values against the growth of the selected bacteria were measured in mm. The zone of inhibition value less than 10 mm is considered as resistant against the corresponding microorganism. The standard gentamycine was used as a positive control and DMSO was used as negative control. The antibacterial activities exhibited by synthesized compounds are summarized in table 4.

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

Organism (bacteria)	Zone of inhibition (mm)					
	[CoL(tmen)]	[NiL(tmen)]	[CuL(tmen)]	[ZnL(tmen)]	L	Gentamycin
S. aureus	11	10	11	10	10	17
P. aeruginosa	11	12	16	15	10	18
Bacillus	12	13	15	16	10	20
E.coli	12	15	20	24	10	15

All the metal complexes exhibited very good zone of inhibition when compared to the Schiff base ligand against the bacteria under study. Cu(II) and Zn(II) complexes showed good zone of inhibition against *P. aeruginosa, Bacillus* and *E.coli.* Zn(II) and Cu(II) complexes showed 24 mm and 20 mm zone of inhibition against *E.coli*, and the values are greater than the corresponding Schiff base ligand as well as the positive control, gentamycine.

Antifungal activity

The Schiff base ligand and its metal complexes were assessed for their *in vitro* antifungal activity by well diffusion method against fungi such as *Rhizopus*, *Aspergillus flavus* and *Mucor.* The standard nystatin was used as positive control and DMSO was used as negative control. The results with reference to *in vitro* antifungal activities of synthesized complexes are summarized in table 5. The antimicrobial activity exhibited by the Schiff base and its metal complexes is depicted in figure 1.

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

Organism (Fungi)	Zone of inhibition (mm)					
	[CoL(tmen)]	[NiL(tmen)]	[CuL(tmen)]	[ZnL(tmen)]	L	Nystatin
A. flavus	17	14	18	15	11	18
Rhizopus	16	15	17	14	13	19
Mucor	18	16	20	19	13	20

The *in vitro* antifungal activity of metal complexes showed very good inhibition activity than the Schiff base ligand against the fungal strains under investigation. Cu(II) complex exhibited very good inhibition against *A. flavus, Rhizopus,* and *Mucor* showing 18 mm, 17 mm, and 20 mm values respectively. The MIC values of the metal complexes against the microbial species is shown in the table 6.

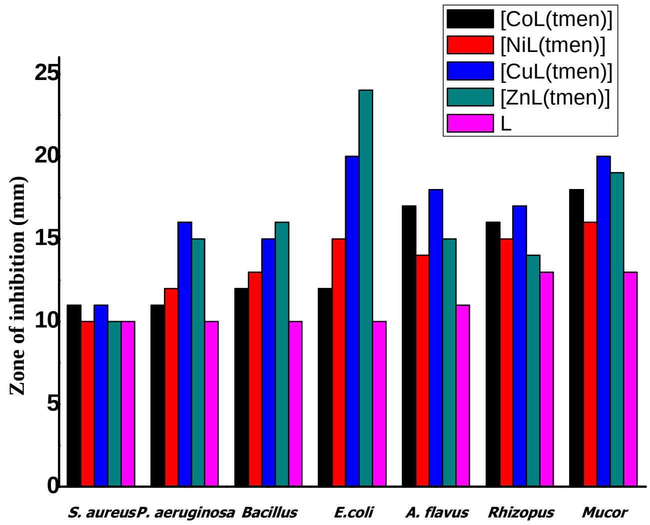

Figure 1. Pictorial representation of zone of inhibition exhibited by Schiff base and its metal complexes

Table 6. MIC values of Schiff base ligand and its metal complexes (µg /mL)

Organism	[CoL(tmen)]	[NiL(tmen)]	[CuL(tmen)]	[ZnL(tmen)]	L
S. aureus	5	5	5	5	5
P. aeruginosa	5	5	5	2.5	10
Bacillus	5	5	2.5	5	5
E.coli	5	5	5	5	10
A. flavus	5	5	5	5	5
Rhizopus	5	5	5	2.5	5
Mucor	5	2.5	2.5	5	5

The Cu(II) complex showed least MIC value of 2.5 µg /mL against *Bacillus* and *Mucor*. Zn(II) complex showed 2.5 µg /mL MIC value against *P. aeruginosa* and *Rhizopus.*

Antioxidant activity

The main characteristic of an antioxidant is its ability to trap free radicals. Research evidences suggests that antioxidants reduce the risk for chronic diseases including cancer and heart disease. Literature shows that the study of antioxidant property of Schiff base metal complexes [21, 22] has been increased recently. To study the antioxidant potential through free radical scavenging by the metal complexes, the change in optical density of DPPH radical were monitored.

The antioxidant scavenging activity of the synthesized metal complexes studied by DPPH method are summarized in table 7. α-tocopherol with 89.45 % of scavenging activity [23] was used as positive control and DMF was used as negative control. All the complexes exhibited moderate antioxidant scavenging activity when compared with the standard α-tocopherol.

Table 7. Antioxidant scavenging activity of metal complexes

Complex	Scavenging activity %
[CoL(tmen)]	32.00
[NiL(tmen)]	39.00
[CuL(tmen)]	40.00
[ZnL(tmen)]	37.00
α-tocopherol	89.45

All the complexes, exhibited 30-40% of scavenging activity. Among the series Cu(II) complex showed higher scavenging activity with 40% by DPPH scavenging method, whereas the Co(II) complex showed lower antioxidant activity with 32%. The order of scavenging activity shown by the metal complexes is given below.
[CuL(tmen)] > [NiL(tmen)] > [ZnL(tmen)] > [CoL(tmen)]

Larvicidal activity

Mosquitoes are the major vector of transmitting harmful diseases such as malaria, yellow fever, filariasis, and dengue fever *Culex quinquefasciatus*, the southern house mosquito, transmits diseases such as lymphatic filariasis and malaria. Hence, it is important to find new agents to control mosquito vectors of disease [24]. In the present study, the larvicidal activity of the synthesized compounds was performed against *Culex quinquefasciatus* and the mortality values of complexes are listed in tables 8 and 9.

Table 8. Larvicidal activity of Schiff base ligand and its metal complexes

Compound	Concentration / mortality			
	4 mg/200 mL	2mg/200mL	1mg/200mL	0.5mg/200mL
[CoL(tmen)]	16	11	7	3
[Ni L(tmen)]	17	12	8	5
[Cu L(tmen)]	19	16	9	6
[Zn L(tmen)]	18	10	6	3
L	3	2	1	0

Table 9. Statistical analysis of Larvicidal activity of Schiff base ligand and its metal complexes

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(tmen)]	80±6.92	55±6.19	35±6.90	15±1.88	1.8	3.24	12.83	
[Ni L(tmen)]	85±5.19	60±5.88	40±5.63	25±15.45	1.5	2.7	16.56	
[Cu L(tmen)]	95±6.56	80±6.92	45±6.86	30±4.75	1.9	3.42	24.18	
[Zn L(tmen)]	90±5.28	50±6.28	30±4.75	15±1.88	1.8	3.24	24.09	3
L	15±1.28	10±2.00	0.5±0.00	-	-	-	-	

Mean value of triplicates, Control-Nil mortality, df- significant at p< 7.81

All the synthesized metal complexes showed moderate to stronger toxic effect against *Culex quinquefasciatus*. The highest mortality was obtained for Cu(II) complex with 95%. Co(II), Ni(II) and Zn(II) complexes exhibited 80%, 85% and 90% of mortality respectively. The average larval mortality data were subjected to statistical analysis for calculating standard deviation and chi-square values for synthesized metal complexes. The order of % of mortality of the synthesized complexes is given below.

[CuL(tmen)] > [ZnL(tmen)] > [NiL(tmen)] > [CoL(tmen)] > L

CONCLUSION

In the current study four new Schiff base transition metal complexes derived from 2'-hydroxyacetophenone and L-tryptophan has been synthesized and characterized by spectral studies. The lower molar conductivity values of the metal complexes revealed the non-electrolytic nature. FTIR spectra proved the tridentate nature of the Schiff base ligand. All the complexes showed very good antimicrobial activities against the microbes under study. Among the synthesized metal complexes Cu(II) and Zn(II) complexes exhibited higher zone of inhibition against *E. coli* and *Mucor*. All the metal complexes showed moderate antioxidant activity. The larvicidal studies against *C. quinque fasciatus* suggested that Zn(II) and Cu(II) complexes showed highest mortality of 90% and 95% respectively.

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