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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF SCHIFF BASE METAL (II) COMPLEXES DERIVED FROM L-METHIONINE AND CUMINALDEHYDE

J. Saranya, R. Bharathi Priyadharsini, Sundaramurthy Santha Lakshmi*

PG and Research Department of Chemistry, D.K.M College for Women (Autonomous), Vellore, Tamil Nadu, India *Corresponding author: santhalakshmi76@gmail.com, saranjothi2019@gmail.com

ABSTRACT

Schiff bases are one of the important class of organic ligands, which are obtained by the condensation of aldehydes/ ketones with primary amines. The metal complexes of Schiff bases are widely studied because they possess very good biological applications such as antimicrobial, larvicidal, antioxidant, antitubercular, antidiabetic, anti-inflammatory and antitumour properties. The present work deals with synthesis and characterization of a series of Schiff base transition metal complexes obtained from amino acid with general formula $[ML^1L^2](ClO_4)$ [where, $M = Co^{2+}$, Cu^{2+} , Ni^{2+} and Zn^{2+} ; $L^1 =$ Schiff base ligand derived from L-methionine and cuminaldehyde; $L^2 = N,N,N',N'$ -tetramethyl-1,3diaminopropane]. The synthesised complexes were characterized by physicochemical and spectral analyses such as UV-Vis., FTIR, GC-MS and ESR. They were also tested for *in vitro* biological activities. The FTIR spectra confirmed the bidentate coordination nature of the Schiff base *via* imine nitrogen and one of the oxygen atom of carboxylate group. The *in vitro* antibacterial studies were carried out against *S. Aureus*, *E. Coli*, *P. aeruginosa*, *Bascillus* as well as antifungal studies against *A. flavus*, *Candida*, *Rhizhopus* and *A. Niger*. Larvicidal activity was performed against *Culex quinquefasciatus* and antioxidant activity of the complexes was studied by H₂O₂ and DPPH method. The results proved that the complexes have good biological activities.

Keywords: Schiff base, L-methionine, in vitro biological activities.

1. INTRODUCTION

A compound containing (>C=N) linkage is generally termed as imines, azomethines or Schiff bases, which has a capability to coordinate with different types of metal ions with various oxidation states to form metal complexes [1]. These complexes occupy large space in coordination chemistry research. The presence of azomethine group (-C=N-) in the Schiff base ligand and its complexes play a huge role in medical field. These complexes possess structural stability and biological activities [2].

Most of the natural products act as a hopeful source for the synthesis of novel drugs. Cuminaldehyde is one of the naturally occurring aldehyde, which is used to synthesize Schiff base metal complexes with effective pharmacological activities [3, 4]. The biological properties of the active constituents are found to be enhanced when they are converted into Schiff base metal complexes [5, 6]. These complexes show remarkable activities on various strains of microorganisms and hence pave the way for the synthesis of effective drug to emerging diseases. Based on these background, a series of Schiff base transition metal complexes with general formula $[ML^{1}L^{2}]$ (ClO₄) [where, $M = Co^{2+}$, Cu^{2+} , Ni^{2+} and Zn^{2+} ; $L^{1} =$ Schiff base ligand derived from L-methionine and cuminal dehyde; $L^{2} = N,N,N',N'$ -tetramethyl-1,3-diaminopropane] has been synthesized and characterised by physicochemical, spectral and *in vitro* antimicrobial, antioxidant and larvicidal studies.

2. MATERIAL AND METHODS

Chemicals and reagents of analytical grade were purchased and used without further purifications. The electronic absorption spectra of the complexes (10^{-3} M) in DMSO were recorded on a Systronics 2201 spectrophotometer at room temperature. The FITR spectra were recorded on SHIMADZU spectrophotometer between 4000-400 cm⁻¹ range, using KBr pellet. The EPR spectrum were recorded in solid state at room temperature using Bruker EMX -10/2.7 spectrometer. The mass spectrum of the complex $[CuL^1L^2](ClO_4)$ was recorded in powdered state using the clarus 680 GC and the fragments recorded from 40 to 600 Da.

2.1. Template synthesis of Schiff base metal complexes

Schiff base metal complexes were synthesised according to the literature [7]. L-methionine (0.447g, 3 mmol), KOH (0.168 g, 3 mmol) and cuminaldehyde (0.45 mL, 3 mmol) were dissolved in ethanol. The reaction mixture was refluxed for 3 hours at 60°C. The solution turned yellow. Then, copper (II) acetate monohydrate (0.61 g, 3 mmol) was added and the reaction mixture was stirred for 3 h at 60°C, followed by addition of N, N, N', N'-tetramethyl-1,3-diaminopropane (0.597 mL, 3 mmol). The mixture was stirred for another 2 h at the same temperature. At the end of the reaction aqueous sodium perchlorate (0.42 g, 3 mmol) was added. The green coloured product was filtered, washed with ethanol and dried.

Similar procedure was carried out for the preparation of other complexes using nickel (II) acetate tetrahydrate (0.744 g, 3 mmol), cobalt (II) acetate tetrahydrate (0. 747g, 3 mmol) and zinc (II) acetate dehydrate (0.657g, 3 mmol). The final product was filtered and dried.

2.2. In vitro antimicrobial studies

The standard process was followed to study bio efficiency of the synthesised complexes [8]. The bacterial strains *S. aureus*, *E. coli*, *P. aeruginosa*, *Bascillus* and fungal studies against *A. flavus*, *Candida*, *Rhizhopus* and *A. Niger* were taken for the investigation. The synthesized complexes with the concentration 10^{-6} M in DMSO was used as stock solution for the study. 50 µL test solution was used for this study. Ampicillin and Polymyxin B sulphate were taken as reference for the study of antibacterial and antifungal activities respectively.

2.3. Larvicidal activity

Zonal Entomological Unit, Vellore, has provided the eggs and egg rafts of *Culex quinquefasciatus*. The standard procedure was followed to maintain the procured larvae. The procedure of WHO guidelines with some modification has been used to study the larvicidal activity [9] and number of dead larvae, percentage of mortality in each batch were counted for every 24 h exposure period by using various concentration (6 μ g, 4 μ g, 2 μ g and 1 μ g) of synthesized complexes.

2.4. Antioxidant activity

2.4.1. Hydrogen peroxide scavenging activity

A solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (50 mM, pH 7.4). The concentration of hydrogen peroxide is determined by adsorption at 230 nm using a UV-Vis. Spectrophotometer. Complexes with the concentration of 4 μ g /mL in DMSO were added to hydrogen peroxide and the absorption was observed at 230 nm after 10 min against blank solution containing phosphate buffer without hydrogen peroxide [10]. The radical scavenging activity was calculated using following equation.

% of radical scavenging activity $(H_2O_2) = \frac{A_c - A_s}{A_c} \times 100$

where, A_c is the absorbance of the control solution; A_s is the absorbance of the sample solution.

2.4.2. DPPH method

The free radical scavenging effects of all complexes with the DPPH radical were evaluated using concentrations 4 μ g / mL of the complex in DMSO with 2 mL of 0.05 M methanol solution of DPPH. After 30 minutes incubation period at room temperature, the antiradical scavenging ability of synthesized metal complexes was determined by measuring the decrease in the absorbance of DPPH at 517 nm. DPPH solution without sample was taken as control. The percent of inhibition (I %) of free radical production from DPPH was calculated as like H₂O₂ method [11].

3. RESULTS AND DISCUSSION

All the synthesized complexes are stable at room temperature. All the complexes are insoluble in benzene and toluene but soluble in DMF, DMSO, CH₃CN, C₂H₅OH, CH₃OH and partially soluble in H₂O. The synthesised complexes (10^{-3} M) are found to be 1:1 electrolytes since the molar conductance value of the complexes fall in the range 58-80 in DMF [12, 13].

3.1. FTIR spectra

FTIR absorption band appeared around 1504 cm⁻¹ confirms the formation of imine linkage in the ligand [14]. This imine absorption band is shifted to higher frequency when it is coordinated to metal ions. The absorption band appeared around 1622 cm⁻¹, 1581 cm⁻¹, 1616 cm⁻¹ and 1606 cm⁻¹ corresponds to coordination of imine nitrogen to metal ions of Co(II), Ni(II), Cu(II) and Zn(II) in the complexes respectively [15].

The difference between asymmetric and symmetric stretching frequencies ($\Delta \upsilon = [\upsilon_{as} \text{ COO}^{-} - \upsilon_{s} \text{ COO}^{-}]$) of the carboxylate group in the Schiff base transition metal complexes were found to be higher than the corresponding free carboxylate anion. This confirmed the monodentate coordination of the carboxylate anion

present in the Schiff base ligand with the metal ions [16].

The bands appeared around 440 cm^{-1} and 580 cm^{-1} are assigned to the formation of M-O and M-N coordination respectively [17]. FTIR spectral data of all the Schiff base metal complexes revealed that the metal ion is

coordinated through imine nitrogen and oxygen atom present in the carboxylate group of the Schiff base ligand. Hence, the Schiff base ligand is bidentate in nature. The stretching frequency appeared around 1100 cm⁻¹ confirmed the uncoordinated nature of the perchlorate ion [18].

Table 1: Analyt	tical data of the	synthesized	complexes
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Compound	Molecular Formula	Molecular Weight	Decomposition Point	$\begin{array}{c} \text{Molar Conductance} \\ (\Omega^{^{-1}} \text{cm}^2 \text{mol}^{^{-1}}) \end{array}$
L^1	$C_{14}NO_2SH_{19}K$	403	>240°C	-
$[\operatorname{Co} L^1 L^2] \operatorname{ClO}_4$	$C_{22}H_{38}CoN_3O_6SCl$	568	>300°C	58
[Ni $L^1 L^2$] ClO ₄	$C_{22}H_{38}NiN_3O_6SCl$	569	>300°C	65
[Cu L1 L2] ClO4	$C_{22}H_{38}CuN_3O_6SCl$	570	>300°C	72
$[\operatorname{Zn} L^1 L^2] \operatorname{ClO}_4$	$C_{22}H_{38}ZnN_3O_6SCl$	571	>300°C	80

 $L^{i} =$ Schiff base ligand derived from L-methionine and cuminal dehyde; $L^{2} = N, N, N', N'$ -tetramethyl-1,3-diaminopropane

Table 2: FTIR spectral data of the synthesized compounds

Compound	$C-N$ ClO_4^-		COO			MN	M-O
compound	C-N		v_{as}	v_{s}	$-\Delta \mathbf{U} - [\mathbf{U}_{as} \mathbf{U}_{s}]$		
L^1	1504	-	-	-	-	-	-
$[\operatorname{Co} L^1 L^2] \operatorname{ClO}_4$	1622	1122	1523	1379	144	580	486
[Ni $L^1 L^2$] ClO ₄	1581	1147	1514	1334	178	582	478
[Cu L1 L2] ClO4	1616	1143	1567	1388	179	584	468
$[\operatorname{Zn} L^1 L^2] \operatorname{ClO}_4$	1606	1107	1423	1338	146	576	449

Table 3: UV-Visible spectral data of the syn-thesized compounds

Compound	Absorption (λ_{max} nm)			
compound	π-π*	n-π*	d- d	
L^1	276	318	-	
$[\operatorname{Co} L^1 L^2] \operatorname{ClO}_4$	230	335	536	
[Ni $L^1 L^2$] ClO ₄	240	350	560	
[Cu L1 L2] ClO4	253	347	543	
$[\operatorname{Zn} L^1 L^2] \operatorname{ClO}_4$	260	345	-	

The electronic spectrum of complexes were shifted to longer wave length with increasing the intensity which may be attributed to the donation of lone pair of electron present in the nitrogen atom of the Schiff base to the metal ions. The absorption maximum observed around 270 nm and 300 nm corresponds to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions due to presence of aromatic chromophore and imine moiety respectively [19]. The broad absorption maximum appeared around 500 nm are due to the $d \rightarrow d$ transitions in the visible region of the UV-Visible spectrum [20]. Due to lack of unpaired electrons, $d \rightarrow d$ transitions was not observed for the zinc complex.

3.2. EPR spectra

The EPR spectrum of the Cu(II) complex has been recorded at room temperature (Fig. 1). The EPR spectrum of polycrystalline Cu(II) complex shows an isotropic peak with the g_{iso} value at 2.08. This confirmed the paramagnetic behaviour of the Schiff base Cu(II) complex. The g_{iso} values of the complex indicate an axial symmetry with all the principal axes aligned parallel. This type of spectrum expected for symmetrical environment like octahedral, square planar and square pyramidal geometry of the complexes [21].

3.3. Mass Spectra

The GC-MS of copper (II) complex shown in Fig. 2 and have been recorded in DMSO. The spectrum displayed a peak at m/z 569.9 amu, corresponding to the molecular ion (M^{+1}), which is agreement with the proposed structure of the complex. The peak observed at 147, 133 and 45 amu, are assignable to the loss of various fragments such as $C_{11}H_{15}^+$, $C_{10}H_{13}^+$ and $C_2H_5O^+$ respectively. This spectral data confirms that all the compounds present in copper (II) complex were 1:1:1 ratio [22].



Fig. 1: EPR spectrum of Cu(II) complex

3.4. Antimicrobial activity

The Schiff base ligand, its metal complexes as well as the standard drug Ampicllin were screened for their antimicrobial activity against the bacteria such as *S. aureus, P. aeruginosa, Bacillus* and *E. coli.* The results of the antibacterial study of the synthesised compounds are given in Table 4. From the data, it is evident that the metal complexes showed significant activity against the bacterial strains under investigation except *E. coli.*

From the graphical representation, we conclude that synthesized copper (II) complex exhibits enhanced antimicrobial activity than other complexes and the ligand. This enhanced activity may be due to effective chelation of the metal to the ligand which inhibits the growth of the selected bacteria [23].



Fig. 2: GC-MS spectrum of Cu(II) complex



Fig. 3: Proposed structure of the Cu(II) complex

All the synthesized complexes were tested against *A*. *niger, A. flavus, Candida* and *Rhizhopus* in order to evaluate the antifungal

activity. Among the synthesized compounds Cu(II) and Co(II) complexes inhibits the fungi under investigation to a greater extent when compared with the standard drug.

Antifungal activity of all the synthesized complexes exhibits greater activity when compared to the standard which proves that these complexes can act as effective antifungal agent. This effective activity may be due to presence of effective component present in the complex as well as binding nature of the ligand to metal ions [24].

3.5. Antioxidant activity

Antioxidant is the one which inhibits the production of free radicals. Herein we reported the radical scavenging activity of the synthesised compounds by DPPH and H_2O_2 method. The results suggest that all the complexes exhibits good antioxidant activity when compared with the standard α -tocopherol.

Table 4: Antibacterial activity of the synthesized compounds

Compound —	Zone of inhibition (mm)			
	S. aureus	P. aeruginosa	Bacillus	E. coli
$[\operatorname{Co} L^1 L^2] \operatorname{ClO}_4$	26	24	22	12
[Ni $L^1 L^2$] ClO ₄	27	18	<10	10
$[\operatorname{Cu} \operatorname{L}^1 \operatorname{L}^2] \operatorname{ClO}_4$	28	24	20	10
$[\operatorname{Zn} L^1 L^2] \operatorname{ClO}_4$	28	18	10	11
L^1	18	14	12	10
Ampicillin	30	25	11	16

Table 5: Antifungal activity of the synthesized compounds

Compound -	Zone of inhibition (mm)			
	A. niger	A. f lavus	Candida	Rhizhopus
$[\operatorname{Co} L^1 L^2] \operatorname{ClO}_4$	23	20	23	14
[Ni $L^1 L^2$] ClO ₄	22	16	10	13
[Cu L1 L2] ClO4	22	20	18	14
$[\operatorname{Zn} L^1 L^2] \operatorname{ClO}_4$	19	16	16	12
L^1	12	11	12	10
Polymyxin B sulphate	11	11	11	11

Table 6: Antioxidant activity of synthesizedcompounds

Compound	% Scavenging Activity		
compound —	DPPH	H_2O_2	
$[\operatorname{Co} L^1 L^2] \operatorname{ClO}_4$	45	47	
[Ni $L^1 L^2$] ClO ₄	34	38	
[Cu L1 L2] ClO4	52	53	
$[\operatorname{Zn} L^1 L^2] \operatorname{ClO}_4$	62	68	
L^1	10	12	

3.6. Larvicidal activity

All the synthesized compounds were used to test the larvicidal activity against *C. quinquefasciatus*. The percentage of mortality was calculated. The results revealed that Cu(II) complex is more active when compared with the other compounds. It is to be noted that larvicidal activity increases with the increase in concentration.



Fig. 4: Graphical representation of Antibacterial activity



Fig. 5: Graphical representation of Antifungal activity

Compound –	% of Mortality			
	6µg / 50 mL	4µg / 50 mL	2µg / 50 mL	1µg / 50 mL
$[\operatorname{Co} L^1 L^2] \operatorname{ClO}_4$	35	28	20	11
[Ni $L^1 L^2$] ClO ₄	42	32	22	12
[Cu L1 L2] ClO4	56	35	28	20
$[\operatorname{Zn} L^1 L^2] \operatorname{ClO}_4$	53	30	23	20
L^1	06	08	10	09

Table 7: Larvicidal activity of synthesized compounds

4. CONCLUSION

Schiff base metal complexes $[ML^1L^2] ClO_4$ (M = Co⁺², Ni⁺², Cu⁺² and Zn⁺²] have been prepared and characterised. The molar conductivity values revealed 1:1 electrolytic nature of the metal complexes. The FTIR results confirmed the bidentate nature of the

Schiff base ligand *via* imine nitrogen and one of the oxygen atom of carboxylate group. The EPR spectrum of the Cu(II) complex suggests the symmetrical environment around the complex. The *in vitro* antimicrobial activities show very good result. The antioxidant and larvicidal activity against *C*.

quinquefasciatus of the metal complexes are quite promising.

5. REFERENCES

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