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SYNTHESIS, CHARACTERIZATION AND *IN VITRO* BIOLOGICAL STUDIES: Cu (II) COMPLEXES OF N-(2-HYDROXYBENZYL) -AMINO ACID LIGANDS AND 4, 4'-BIPYRIDINE

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ABSTRACT

Currently, coordination chemistry occupies a larger area of inorganic research. Copper (II) complexes derived from Schiff bases have attracted attention of the researchers for their preparative, accessibilities and structural varieties. Copper (II) complexes containing Schiff bases and heterocyclic compounds were reported to show very good biological activities. In the present work, a series of five Schiff base Cu (II) complexes derived from N-(salicylidene)-L-aminoacids [L-valine, L-tryptophan, L-leucine, L-alanine and L-cysteine] and 4,4'-bipyridine were designed, synthesized and tested for biological activities. All the complexes were characterized by physicochemical and spectral studies such as UV-Visible, FTIR, EPR, TGA and CV. In vitro antimicrobial studies were carried out against bacterial strains such as S. aureus, E. coli and P. aeruginosa and fungal strains such as A. flavus, A. fumigates and Rhizopus. In addition, in vitro larvicidal and antioxidant studies were also performed. The FTIR spectra confirmed that the Cu (II) ion is coordinated to imine nitrogen, phenolic oxygen and one of the oxygen anion of carboxylate group present in the Schiff base ligand and confirms that the Schiff base acted as a tridentate ligand. The cyclic voltammogram of all the complexes suggested two one electron transfer with quasi-reversible redox reactions. The biological activity data of the Cu (II) complex showed the better antimicrobial, antioxidant and larvicidal activity.

KEY WORDS

Schiff base Cu (II) complexes, spectral studies, in vitro antibacterial, antifungal, larvicidal and antioxidant studies.

INTRODUCTION:

Today metal complexes play an essential role in the drug industries and in agronomy. [1] In the case of metalloproteins, copper (II) complexes act as an active site and plays an important role in biological systems. [2] Recently, many researchers have been focusing their work on synthesis and characterisation of copper complexes due to their ease of preparation, structural varieties and biological applications. The Schiff base copper complexes have wide applications in many fields such as food industry, dye industry, analytical chemistry, catalysis, agrochemical, anti-inflammable activity, antiradical activities and biological activities. [3-5] Further, Schiff base copper complexes are promising agents in pharmaceuticals. [6, 7]

Schiff bases are considered to be privileged ligand in the field of Coordination chemistry [8] which was first reported by Hugo Schiff. [9-10] The nucleophilic attack of amines on electrophilic carbon of aldehydes or ketones end with the result of forming a compound in which C=O

double bond is replaced by a C=N double bond. This type of compound is known as imine, azomethine or a Schiff base. [11, 12] Schiff base ligand derived from salicylaldehyde is a significant component in enlightening the ideal coordination geometries of copper complexes and its derivatives, which are found to possess attractive biological activities. [13] Today, a number of diseases in the world such as malaria, dengue and filariasis are generated by Mosquitoes. To prevent mosquito borne diseases and to improve public health it is necessary to control the larvae of mosquitoes. Copper complexes have been shown to possess better larvicidal activity. [14,15] Till now, there is a lack in the preparations of Schiff base copper complexes as pharmaceuticals agents. Based on these backdrops, an attempt was made to synthesise Schiff base Cu (II) complexes and to investigate their biological properties by *in vitro* method.

In the present work, a series of Schiff base Cu (II) complexes were synthesised using N-(salicylidene)-L-aminoacids [L-valine, L-tryptophan, L-leucine, L-alanine and L-cysteine] and 4,4'-bipyridine. The synthesized Cu (II) complexes were characterised by physicochemical, spectral and *in vitro* antimicrobial, antioxidant and larvicidal studies.

MATERIALS AND METHODS:

All common laboratory chemicals and reagents used were of analytical grade. The electronic absorption spectra of the complexes were recorded on a SYSTRONICS 2201 spectrometer at room temperature with the sample concentration of (10^{-3} M) in DMSO. The FITR spectra were recorded on SHIMADZU spectrometer between 4000-400 cm^{-1} range, using KBr pellet. The EPR spectra were recorded in solid state at room temperature using Bruker EMX -10/2.7 spectrometer. The electrochemical activity of the Cu (II) complexes were studied in DMSO (10^{-3} M) on a cyclic voltammetry model CHI617C electrochemical analyser with the scan rate of 0.1 V/s in the potential range +2 to −2 V using TBAP (Tetrabutylammonium perchlorate) as supporting electrolyte. Thermal stability of complex **1** was carried out on the instrument SDT Q600 V20.9 Build 20 model from room temperature to 800 °C under a nitrogen atmosphere at the heating rate of 20°C/min.

Template synthesis of Schiff base metal complexes:

Schiff base Cu (II) complexes were synthesised as per the literature. [16] L-valine (0.351 g, 3 mmol) and KOH (0.336 g, 6 mmol) were dissolved in water. To this an ethanolic solution (25 mL) of salicylaldehyde (0.3 mL, 3 mmol) was added. The reaction mixture was stirred for an hour 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 2 h, followed by addition of 4, 4'- bipyridine (0.468 g, 3 mmol). The mixture was stirred for another 2 h at the same temperature. The resultant green coloured product was filtered, washed with ethanol and dried.

Similar procedure was adopted for the preparation of the other Cu (II) complexes using the amino acids L-tryptophan (0.6126 g, 3 mmol), L-leucine (0.3935 g, 3 mmol), L-alanine (0.2672g, 3 mmol) and L-cysteine (0.36343 g, 3 mmol).

Antimicrobial studies (*in vitro*):

The synthesised Schiff base Cu (II) complexes were screened for their biological activities to test their bio-efficacy. [17] The copper complexes have been screened for their antimicrobial activities against the bacterial strains of *Staphylococcus aureus, Pseudomonas aeruginosa*, *E. coli* and fungal strains of *Aspergillus flavus, Aspergillus fumigates* and *Rhizopus* using agar well diffusion method. 10^{-3} M test solution in DMSO was used for the study. Ampicillin and polymycin B sulphate were used as a standard for the study of antibacterial and antifungal activities respectively.

Antioxidant activity:

Hydrogen peroxide scavenging activity:

Hydrogen peroxide scavenging activity was carried out as per the literature. [18, 19] 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 spectrophotometer. Synthesized complexes with the concentration of 2 mg /1 mL, 4 mg /1 mL, 6 mg /1 mL in DMF are added to hydrogen peroxide and the absorption at 230 nm was observed after 10 min against blank solution containing phosphate buffer without hydrogen peroxide. The percentage of hydrogen peroxide scavenging activity was calculated using the following equation. [19]

$$\% \text{ scavenged } (H_2O_2) = \frac{A_c - A_s}{A_c} \times 100$$

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

Larvicidal activity:

The eggs and egg rafts of *Culex quinque fasciatus* were procured from Zonal Entomological Unit, Vellore, Tamil

Nadu. *Culex quinque fasciatus* larvae were maintained in the laboratory as per the literature. [20] The larvicidal activity was assessed by the procedure of WHO guidelines with some modification [21] and number of dead larvae, percentage of mortality in each batch were counted for every 24 h exposure period by using various concentration (6 mg, 4 mg, 2 mg and 1mg) of synthesized Cu (II) complexes. The treated larvae were mounted on a slide and examined under a microscope for image capture.

RESULTS:

The analytical data of the synthesized Cu (II) complexes such as molecular formula, molar conductance and colour are shown in Table 1.

Table 1. Analytical data of the Schiff base Cu (II) complexes

Complex Formula	Complex code	Molecular formula	Molecular weight	Melting /Decomposition point °C	Colour	Molar Conductance $Ohm^{-1}cm^{-2}mol^{-1}$
$[Cu_2L_2^1L^2(H_2O)_4]$	**1**	$C_{34}H_{42}O_{10}N_4Cu_2$	794	204	Dark green	8.05
$[Cu_2L_2^3L^2(H_2O)_4]$	**2**	$C_{46}H_{44}O_{10}N_6Cu_2$	966	210	Light green	6.9
$[Cu_2L_2^4L^2(H_2O)_4]$	**3**	$C_{36}H_{46}O_{10}N_4Cu_2$	820	215	Dark green	5.75
$[Cu_2L_2^5L^2(H_2O)_4]$	**4**	$C_{30}H_{34}O_{10}N_4Cu_2$	736	150	Green	9.2
$[Cu_2L_2^6L^2(H_2O)_4]$	**5**	$C_{30}H_{34}O_{10}N_4S_2Cu_2$	800	219	Green	4.6

where, L_2^1-N- salicylidene-L-valine, L_2^3-N- salicylidene-L-tryptophan, L_2^4-N- salicylidene-L-leucine L_2^5-N- salicylidene-L-alanine, L_2^6-N- salicylidene-L-cysteine, L^2-4, 4'-bipyridine.

UV-Vis. spectra:

The UV-Visible spectral data are represented in the Table 2.

Table 2. The UV-Vis. spectral data of Schiff base Cu (II) complexes

Complex code	Absorption (λ_{max} nm)		
	π→π*	n→π*	d→d
1	251	389	685
2	240	374	648
3	265	370	703
4	267	375	672
5	269	371	645

FTIR spectra:

The assignments of important infrared spectral data are listed in **Table 3**.

Table 3. Table 3. FTIR spectral data of the Schiff base Cu (II) complexes

Complex	C=N	COO^-		Δυ= [υ_{as} -υ_s]	M-O	M-N
code		υ_{as}	υ_s			
1	1584	1533	1317	216	463	546
2	1628	1593	1348	246	418	549
3	1632	1566	1340	226	480	544
4	1562	1470	1332	138	473	569
5	1593	1535	1389	146	472	538

EPR spectra:

The EPR spectrum is mainly used to analyse the paramagnetic nature and geometry of the metal complexes. The g-value of the Schiff base Cu (II) complexes are given in Table 4.

Table 4. EPR data for Schiff base Cu (II) complexes.

Complex code	g value
1	2.03
2	2.01
3	2.09
4	2.04
5	2.06

Cyclic voltammetry:

The redox potentials of all the complexes of present series are summarised in Table 5.

Table 5. Redox potentials for the Schiff base Cu (II) complexes

Complex code	Epc (V)	Epa (V)	ΔEp (V)	$E_{1/2}$ (V)	Ipc µA	Ipa µA	Ipa/Ipc
1	-1.650	0.180	1.830	-0.735	-0.510	0.595	-1.166
	-1.319	2.870	4.189	0.775	-0.938	0.967	-1.030
2	-1.630	0.395	2.025	-0.617	-0.392	0.323	-0.823
	-1.296	0.847	2.143	-0.224	-0.843	0.919	-1.090
3	-0.741	0.348	1.089	-0.196	-0.750	0.739	-0.985
	-0.567	0.761	1.328	0.097	-0.466	0.678	-1.454
4	-0.704	0.312	-0.392	-0.196	-0.659	0.348	-0.528
	-0.475	0.733	1.208	0.129	-0.503	0.770	-1.530
5	-0.768	0.352	1.120	-0.208	-0.757	0.396	-0.523
	-0.483	0.858	1.341	0.187	-0.537	0.860	-1.601

Epa = anodic peak potential; Epc = cathodic peak potential; Ipa = anodic peak current; Ipc = cathodic current peak; Ipa/Ipc = number of electrons; ΔEp = Epa- Epc; scan rate = 0.1 V/s.

Thermogravimetric analysis:

TGA provides useful information about the thermal stability of the synthesized complexes. The TGA curve of the complex **1** is represented in Fig1.

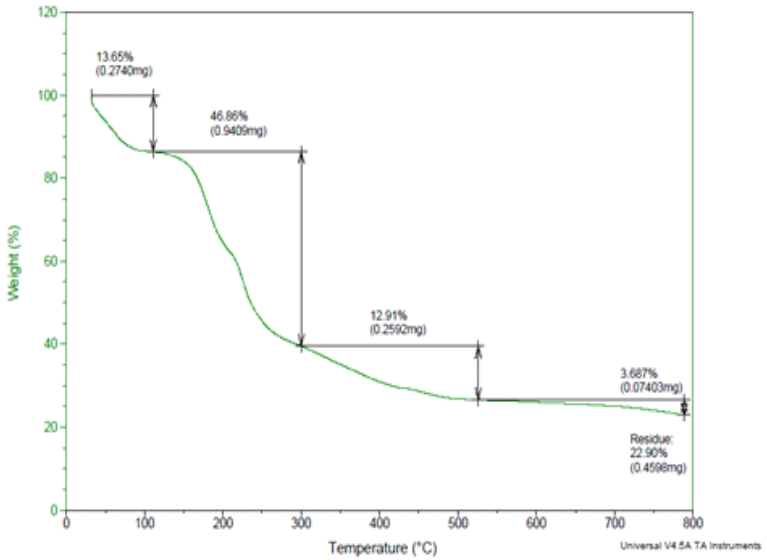

Figure 1. TGA curve of complex 1

Antibacterial and antifungal activity:

The zone of inhibition values of the synthesized metal complexes against the growth of the bacteria and fungi under investigation are measured in mm. The corresponding data are summarized in Tables 6 and 7 and the graphical representation is given in the Fig 2 & 3.

Table 6. Antibacterial activity of the Schiff base Cu (II) complexes

Bacteria	Zone of Inhibition (mm)					
	Complex 1	Complex 2	Complex 3	Complex 4	Complex 5	Ampicillin
S. aureus	16	18	15	6	11	10
E. coli	15	13	19	19	12	11
P. aeruginosa	15	18	10	19	12	10

Table 7. Antifungal activity data of the Schiff base Cu (II) complexes

Fungi	Zone of Inhibition (mm)					
	Complex 1	Complex 2	Complex 3	Complex 4	Complex 5	Gentamicin
A. flavus	15	12	23	16	20	20
A. fumigatus	21	19	25	15	24	15
Rhizopus	12	15	21	20	22	15

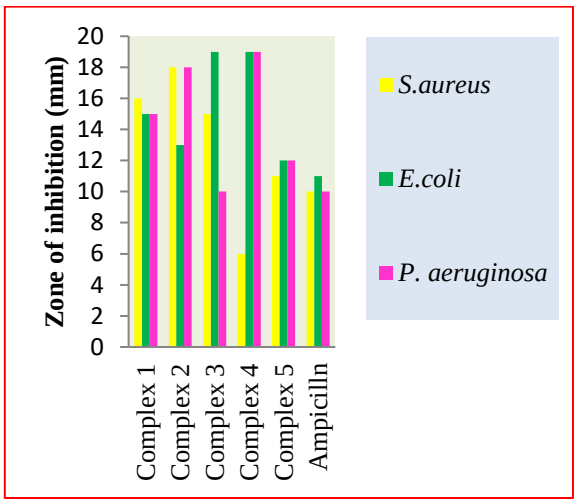

Figure 2. Graphical representation of antibacterial activity of the Schiff base Cu (II) complexes

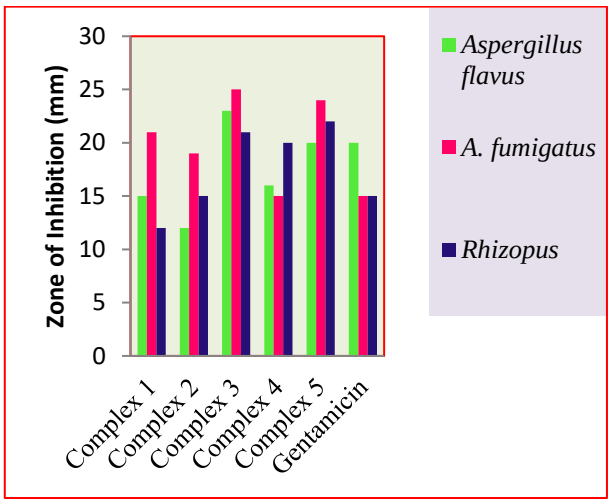

Figure 3. Graphical representation of antifungal activity of the Schiff base Cu (II) complexes

Antioxidant activity:

The antioxidant scavenging activity of the synthesized Schiff base Cu (II) complexes in hydrogen peroxide (H_2O_2) was monitored and the values are listed in Table 8.

Table 8. Antioxidant scavenging activity values of Cu (II) complexes

Complex code	% antioxidant scavenging activity		
	2 mg	4 mg	6 mg
1	90.29	92.23	93.20
2	91.26	92.23	93.20
3	86.40	89.32	90.29
4	85.43	92.23	94.17
5	88.34	89.32	91.26

Larvicidal activity:

The larvicidal activity of synthesized Cu(II) complexes was studied against *C. quinquefasciatus* and the values are depicted in Tables 9 & 10.

Table 9. Larvicidal activity of Schiff base Cu (II) complexes

Complex code	Concentration /Mortality			
	6mg/200mL	4mg/200mL	2mg/200mL	1mg/200mL
1	16	11	7	3
2	17	12	6	3
3	16	10	6	2
4	17	12	7	3
5	17	11	7	4

Table 10. Statistical analysis of larvicidal activity of the Schiff base Cu(II) complexes

Complex code	Concentration /Mortality±SD					
	6mg/200mL	4mg/200mL	2mg/200mL	1mg/200mL	χ2	Df
1	80±6.81	55±6.47	35±7.66	15±6.80	23.75	
2	85±6.91	60±6.62	30±7.81	15±3.26	23.98	
3	80±6.50	50±6.80	30±6.69	10±6.00	21.86	3
4	85±5.93	60±6.29	35±7.22	15±8.21	22.55	
5	85±5.82	55±6.66	35±6.71	20±8.24	18.90	

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

DISCUSSION:

The synthesized Schiff base Cu (II) complexes are freely soluble in DMSO, DMF and ethanol. The lower molar conductivity value of the complexes indicates their non-electrolytic nature. [22] The electronic spectrum of Cu (II) 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 band observed around 270 nm and 300 nm corresponds to π→π* and n→π* transitions respectively. [23] The green colour observed for the Cu (II) complexes are due to the presence of a broad d → d transitions in the visible region of the UV-Visible spectrum.

In the FTIR spectra an intense band appeared around 1590 cm^{-1} for the complexes corresponds to the coordination of imine nitrogen with Cu (II) ions. [24] The difference between asymmetric and symmetric stretching frequencies ($\Delta\upsilon = [\upsilon_{as}\, COO^- - \upsilon_s\, COO^-]$) 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 Cu (II) ions. [25] The bands appeared between 418-480 cm^{-1} and 538-550 cm^{-1} are assigned to the formation of M-O and M-N coordination respectively. [26] FTIR spectral data of all the Schiff base Cu (II) complexes revealed that the Cu (II) ion is coordinated through phenolic oxygen, imine nitrogen and oxygen atom present in the carboxylate group of the Schiff base ligand and act as a tridentate ligand.

ESR spectra of the complexes displayed an isotropic spectrum with the g_{iso} values between 2.01-2.09, indicating an axial symmetry with all the principal axes aligned parallel symmetry i.e., $g_{xx} = g_{yy} = g_{zz}$. Such a spectrum is expected in complexes with octahedral geometry. [27]

All the binuclear Cu (II) complexes undergo two one-electron reduction and oxidation at different potential. Cyclic voltagrams for all the complexes are similar and the cathodic (Ipc) and anodic (Ipa) peak currents are not equal. This indicates the quasi-reversible nature of the electron transfer process. [28] Two reduction waves are obtained in the cathodic region corresponding to stepwise one-electron reductions through a $Cu^{II}Cu^{I}$ intermediate to give a binuclear $Cu^{I}Cu^{I}$ species. All the binuclear copper (II) complexes showed two quasi-reversible reduction waves. [29] The reason for the observation of two reduction waves may be due to electronic change between the copper ions. After the first one-electron reduction some of the electron density is transferred from the reduced copper ion to the other copper ion.

The thermal decomposition of the complex 1 takes place in four stages. The 1st stage takes place in a single step that is between 40 to 120°C with mass loss of 13.65 % it may due to elimination of water molecule. In the 2nd stage the decomposition occurs in the temperature range of 120 to 300° C. This range corresponds to the decomposition of 4, 4'-bipyridine ligand [29] and the maximum range of mass loss was recorded as 46.86 %. The 3rd stage corresponds to the decomposition of Schiff base ligand in the temperature range of 300 to 530°C. The final residue with 22.9 % was probably due to CuO. [29]

Schiff base Cu (II) complexes structure enhances the coordination and chelating which was tends to make more powerful and potent bacteriostatic agents, thus inhibiting the growth of the bacteria also destroying them more forcefully. [30] In the present study, the lower activity of 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 microorganism. [30]

The Schiff base Cu (II) complexes **1** and **2** showed very good antioxidant scavenging activity with 90.29 % and 91.26 % respectively with minimum concentration of 2 mg. The highest mortality of 85 % was obtained for the complexes **2**, **4** and **5**. The complexes **1** and **3** exhibited 80 % of mortality values. The average larval mortality data were subjected to statistical analysis for calculating standard deviation and chi-square values for synthesized Schiff base Cu (II) complexes. The calculated values were lesser than table value hence the results with $p < 7.81$ were considered to be statistically significant.

CONCLUSION:

In the present study, we have designed and synthesized a series of Schiff base Cu (II) complexes using N-(salicylidene)-L-aminoacids [L-valine, L-tryptophan, L-leucine, L-alanine and L-cysteine] and 4,4'-bipyridine. The synthesized Schiff base Cu (II) complexes were characterized by UV-Visible, FTIR, EPR, TGA and CV. The biological activities such as *in vitro* antibacterial, *in vitro* antifungal, antioxidant and larvicidal activity was assayed. All the complexes exhibited significant *in vitro* biological activities. However, further *in vivo* studies are necessary to prove their biological activities.

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