

SYNTHESIS, SPECTRAL CHARACTERIZATION AND PHARMACEUTICAL ACTIVITY OF SCHIFF BASE METAL [Cu(II) AND Zn(II)] COMPLEXES DERIVED FROM BENZALDEHYDE DERIVATIVES

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Abstract

A new series of transition metal complexes of Cu(II) and Zn(II) were synthesized from the Schiff base ligands derived from 2-amino-6-nitrobenzothiazole with various aromatic aldehydes such as 4-Methylbenzaldehyde, 4-Ethylbenzaldehyde, 2-Hydroxybenzaldehyde and 4-Hydroxybenzaldehyde. The synthesized ligands and their metal (II) complexes were characterized by AAS studies, magnetic susceptibility, molar conductance measurements, UV-Vis, IR, and NMR spectroscopy techniques. The Schiff bases and their complexes were screened for antimicrobial activity.

Keywords: aldehydes, ligands, metal(II) complexes, Biological activity, AAS

1. INTRODUCTION

Heterocyclic compounds containing 5 and 6 membered ring may be considered as important therapeutic agents¹. Many research studies have been done in the analysis of Schiff bases of heterocyclic ligands in the past three decades. Benzothiazole is a privileged bicyclic ring system with significant biological properties such as antimicrobial²⁻⁶, anticancer⁷⁻¹⁰, anthelmintic¹¹ and anti-diabetic¹². In the 1950s, a number of 2-aminobenzothiazoles were intensively studied, as the 2-amino benzothiazole scaffold is one of privileged structure in medicinal chemistry and reported cytotoxic on cancer cells¹³. In recent years organic materials have been studied for non linear optical property which is used in optical communications. In this context we are interested to synthesize the Schiff bases of 2-Amino 6-Nitrobenzothiazole with various aromatic aldehydes. This work reports the characterization of the Schiff bases and their metal(II) complexes. The antimicrobial activity of the synthesized compounds has been tested and compared.

2. EXPERIMENTAL

All the chemicals used in the present work, viz. 2-amino-6-nitrobenzothiazole, 4-methylbenzaldehyde, 4-ethylbenzaldehyde, 4-hydroxybenzaldehyde, 2-hydroxybenzaldehyde, Copper and Zinc chlorides were of analytical reagent grade. Commercial solvents were distilled and then used for the preparation of the ligands and metal(II) complexes. Molar conductivities in DMSO (10^{-3} mol/dm³) at room temperature were measured on an ELICO CM-180 digital conductivity meter. Magnetic susceptibility measurements of the complexes were realized by a Gouy balance using copper sulfate pentahydrate as the calibrant. The IR spectra were recorded on SHIMADZU FT-IR Affinity-spectrophotometer in the 4000–400 cm⁻¹ range using KBr pellets. The NMR spectra were recorded on a Bruker DRX-300 MHz NMR spectrometer in DMSO(*d*6) and CDCl₃ as solvents with tetramethylsilane (TMS) as the internal reference. The absorption spectra were recorded using a SHIMADZU 1800 spectrophotometer between 200–1100 nm by using suitable solvent.

2.1. Synthesis of ligands (L¹ to L⁴)

An ethanolic solution of 2-amino 6-nitrobenzothiazole (0.050 mol) was added to ethanolic solution of aldehyde (0.050 mol) (4-methyl benzaldehyde, 4-ethyl benzaldehyde, 4-hydroxy benzaldehyde, 2-hydroxy benzaldehyde) and the mixture was stirred. The completion of the reaction mixture was monitored by TLC. The precipitated yellow coloured Schiff bases were filtered, washed and dried. The scheme of the synthesis is shown in Figure 1.

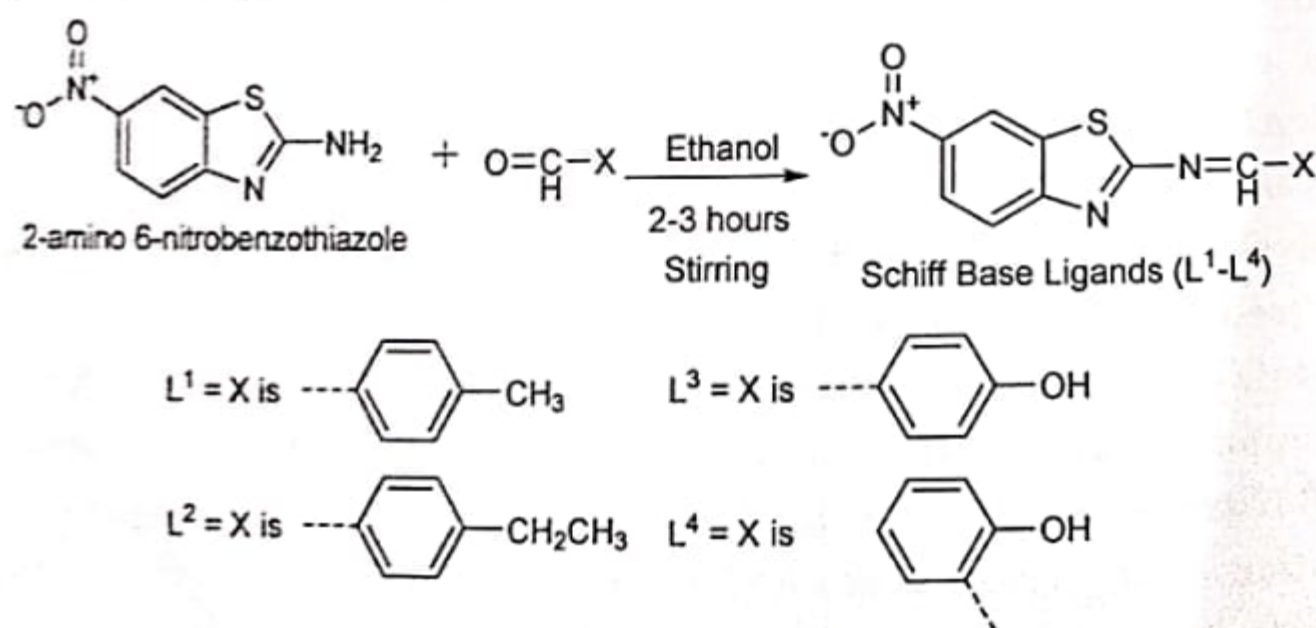


Figure 1. Scheme of the synthesis of ligands L¹ to L⁴

2.2. Synthesis of metal(II) complexes

All the complexes were prepared from hydrated metal salts. To a solution of 20 mmol of Schiff bases (L^1 to L^4) in 25 mL ethanol was added 10 mmol of $MCl_2 \cdot 2H_2O$ ($M = Cu(II)$ and $Zn(II)$). The solution was stirred for 2 h and the resulting solid product was filtered, washed with ethanol and dried under vacuum.

2.3. Estimation of percentage of metal

The percentage of metal in the complexes was estimated by Atomic Absorption Spectroscopy studies at BSR lab, Jayaraj Annapackiam College for Women. 5 mg of the complex was dissolved in 2 ml of DMSO and the solution is made up to 50 mL with Double Distilled water. Standard solutions (1000 ppm, 100 ppm, 10 ppm and 1ppm) of metal salts of Copper and Zinc were prepared in DD water. Different metal filters were used for running the analysis for estimation. Comparing with the amount of metal ion present in the standard solutions, the amount of metal in the metal complexes was estimated graphically.

2.4. Antimicrobial activity screening

Antimicrobial activity of the compounds was tested *in vitro* by the well diffusion method¹⁴ against the bacteria *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* using agar nutrient as the medium. Antifungal activity was evaluated against *Candida albicans* cultured on potato dextrose agar as medium. All the bacterial strains mentioned above were incubated in Nutrient Broth (NB) at 37° C for 24 h and fungal isolates were incubated in PDA broth at 28° C for 2 to 3 days. The well each of 5 mm in diameter was made in Muller Hinton agar using cork borer. The test solution was prepared in 10^{-3} moles litre⁻¹ concentration (DMSO) and then 100 μ L of the solution was transferred into each well. The plates were incubated for 24 h at 37° C and examined for clear inhibition zone around the well.

3. RESULTS AND DISCUSSION

The Schiff base ligands were obtained as low melting solids and stored in vacuum desiccators. The ligands form stable complexes in ethanol medium. The percentage of metal in the complexes was estimated by Atomic Absorption Spectroscopy technique. The analytical data of the ligands and the complexes together with their physical

properties are given in the Table 1. All the ligands coordinate in bidentate fashion. The metal (II) complexes are partially soluble in ethanol, chloroform and acetonitrile but soluble in polar solvents such as DMF and DMSO. The low values of conductance in DMSO indicate that the complexes are non-electrolytes¹⁵. The estimated percentage data of metal ion (II) in the complexes were in good agreement with the calculated data for the 1:2 (M:L) ratio.

Table 1. Physical characterization and molar conductance of the ligands and metal(II) complexes

Compounds	FW g/mol ⁻¹	% of metal calculated (observed)	Color	Δ_M (mho cm ² mol ⁻¹)
L¹	297	-	Yellow	-
[Cu(L ¹) ₂ Cl ₂]	728.4	8.72 (8.06)	Brown	07
[Zn(L ¹) ₂ Cl ₂]	730.6	9.00 (8.51)	Yellow	04
L²	311	-	Yellow	-
[Cu(L ²) ₂ Cl ₂]	756.4	8.40 (7.92)	Brown	05
[Zn(L ²) ₂ Cl ₂]	758.6	8.67 (8.11)	Yellow	04
L³	299	-	Yellow	-
[Cu(L ³) ₂ Cl ₂]	732.4	8.67 (8.12)	Brown	10
[Zn(L ³) ₂ Cl ₂]	734.6	8.95 (8.21)	Yellow	07
L⁴	299	-	Yellow	-
[Cu(L ⁴) ₂]	661.5	9.60 (9.11)	Brown	07
[Zn(L ⁴) ₂]	663.7	9.91(9.53)	Yellow	05

3.1. IR Spectra

In IR spectrum of the free ligands, (L¹ to L⁴) the frequencies at 1653-1649 cm⁻¹ are assigned to azomethine group (ν (CH=N)). The bands at 1523 -1517 cm⁻¹ are attributed to stretching vibration of C=N group of thiazole ring (ν (C=N)). In the spectra of the metal (II) complexes of L¹ to L³ the frequencies at 1653-1649 cm⁻¹ and 1523-1517 cm⁻¹ are shifted to lower values (1651 to 1504 cm⁻¹ and 1517-1493 cm⁻¹) confirming the coordination of the azomethine nitrogen and ring nitrogen¹⁶ of benzothiazole group respectively to the metal ion. In the spectra of metal (II) complexes L¹ to L⁴ the stretching frequencies 653-516 cm⁻¹ are assigned to M-N mode¹⁷⁻¹⁹. The spectrum of the

ligand L^4 shows a band at 3454 cm^{-1} due to phenolic OH group. The absence of this band in the spectrum of metal complexes evidences the coordination of deprotonated phenolic group to the metal(II) ion. In the spectra of metal (II) complexes of L^4 , the stretching frequencies $712\text{--}742\text{ cm}^{-1}$ are assigned to M-O vibrations²⁰.

3.2. $^1\text{H-NMR}$ spectra

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6 , δ/ppm) spectrum of the Schiff base ligands exhibited the following signals: The $^1\text{HNMR}$ spectrum of L^1 : $8.35\text{ }\delta$ (s, 1H, azomethine proton), $7.46\text{--}6.93\text{ }\delta$ (m, aromatic protons), 1.63 (s, 3H, methyl protons) L^2 : $8.41\text{ }\delta$ (s, 1H, azomethine proton), $7.40\text{--}6.94$ (m, 7H, aromatic protons), $1.89\text{ }\delta$ (q, 2H, methylene protons), 1.63 (t, 3H, methyl protons), L^3 : $8.45\text{ }\delta$ (s, 1H, azomethine proton), $7.26\text{--}6.95\text{ }\delta$ (m, aromatic protons), 11.23 (s, phenolic proton), L^4 : $8.40\text{ }\delta$ (s, 1H, azomethine proton), $7.36\text{--}6.94\text{ }\delta$ (m, aromatic protons), 11.34 (s, phenolic proton).

3.3. Electronic absorption spectra

The UV-Vis spectra of the complexes were recorded in DMSO solution. The copper(II) complexes of L^1 to L^3 exhibit a d-d band in the region $10,000\text{--}9,267\text{ cm}^{-1}$. This band may be assigned to $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$ transition, characteristic for a distorted octahedral structure²¹. The copper(II) complex of L^4 shows a band at 12650 cm^{-1} assignable to the $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$, transition, characteristic for a distorted square-planar geometry²². The zinc(II) complexes of L^1 to L^3 exhibits intraligand charge transfer bands in the region 28329 cm^{-1} and 26178 cm^{-1} which are attributed to $\pi\text{-}\pi^*$ and $n\text{-}\pi^*$ transitions respectively. The zinc(II) complex of L^4 shows bands 29670 cm^{-1} and 26235 cm^{-1} assigned to intraligand charge transfer bands.

3.4. Magnetic moments of metal(II) complexes

Magnetic susceptibility measurements give sufficient data to characterize the structure of the metal complexes. Magnetic moment measurements of compounds were carried out at 25°C .

The magnetic moment value of copper (II) complex of L^4 is 1.75 BM suggesting square planar environment²³. The magnetic moment values of copper(II) complexes of L^1 to L^3 are in the range $1.81\text{--}2.08$ BM indicating the octahedral coordination. The higher magnetic moment value than the spin only value (1.73 BM) might be due to orbital

contribution. The zinc complexes are found to be diamagnetic due to d-10 configuration. The proposed structures of the complexes are shown in the Figure 2.

On the basis of above discussion the following structures are proposed for the complexes.

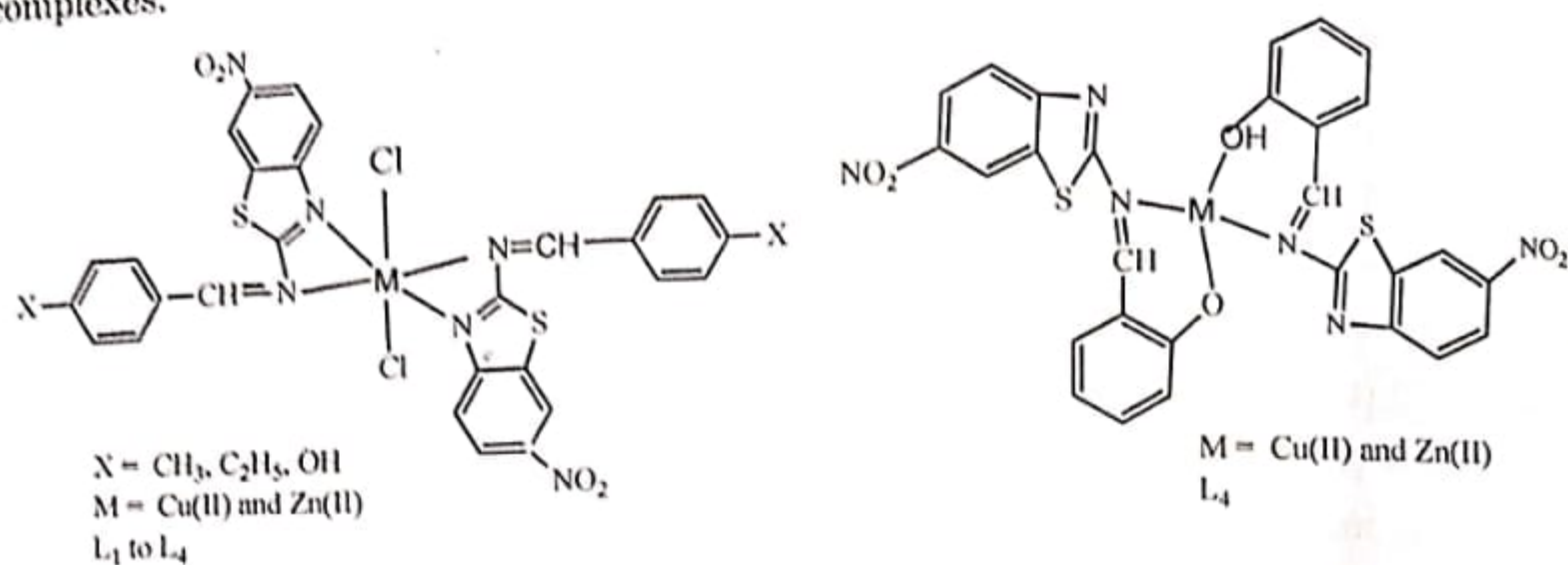


Figure 2. Proposed geometry of the complexes

3.5. Antimicrobial screening

The ligands and the complexes exhibit antifungal activity. From the zone of inhibition it is shown that the some of the ligands and complexes are resistant to *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Some metal complexes are found to be more potent than the ligands against bacterial and fungal strains. The different substituents in the Schiff bases have very lesser effect in the antimicrobial activity. The metal complexes of L^2 have no antifungal activity. The data showing the zone of inhibition is given in the Table 2.

Table 2. Antimicrobial activity data of the ligand and metal(II) complexes (Zone of inhibition in mm)

Compounds	<i>E.Coli</i>	<i>P.Aeruginosa</i>	<i>S.Aureus</i>	<i>C.Albicans</i>
L^1	04	05	03	10
$[\text{Cu}(L^1)_2\text{Cl}_2]$	R	10	12	12
$[\text{Zn}(L^1)_2\text{Cl}_2]$	R	-	13	12
L^2	R	R	R	R
$[\text{Cu}(L^2)_2\text{Cl}_2]$	R	R	R	10
$[\text{Zn}(L^2)_2\text{Cl}_2]$	R	R	10	R

Compounds	<i>E.Coli</i>	<i>P.Aeruginosa</i>	<i>S.Aureus</i>	<i>C.Albicans</i>
L^3	R	R	12	12
$[Cu(L^3)_2Cl_2]$	R	12	10	14
$[Zn(L^3)_2Cl_2]$	R	R	10	15
L^4	R	R	12	12
$[Cu(L^4)_2]$	R	12	14	14
$[Zn(L^4)_2]$	R	R	15	14
Standard	17	17	18	19

It is observed that, in a complex, the positive charge of the metal is partially shared with the donor atoms present in the ligand and there may be π -electron delocalization over the whole chelating system²⁴⁻²⁶. This increases the lipophilic character of the metal chelate and favors its permeation through the lipid layer of the bacterial membranes. So the metal complex can become more active than the free ligand. Therefore, the metal complexes show greater antifungal activities than the uncoordinated ligand and free metal ion.

4. CONCLUSIONS

In this work the Cu(II) and Zn(II) complexes of Schiff bases of 2-amino-6-nitrobenzothiazole are synthesized and characterized. The ligands and their metal complexes are studied by various physicochemical techniques such as metal estimation by AAS, UV-vis, NMR and IR. All the synthesized ligands and complexes have been screened for antimicrobial activity. All the metal [Cu(II) and Zn(II)] complexes of synthesized ligands (L^1 to L^3) show octahedral geometry. Distorted square planar geometry is proposed for the copper complex of L^4 . The Zinc(II) complex of L^4 coordinate in a tetrahedral fashion. Ligands and complexes possess lesser antimicrobial activity than the standard drugs. The synthesized compounds possess very less antibacterial activity and appreciable antifungal activity.

Acknowledgements

The authors express their sincere thanks to the College Management, Principal and Head of the Department of Chemistry, Jayaraj Annapackiam College for Women, Periyakulam, India, for providing the necessary research facilities.

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