

Spectral, Magnetic and Biological Studies of Cu^{II} and Zn^{II} Complex of Schiff Base Derived From 4-(4-hydroxy) phenyl-2- Aminothiazole

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Abstract: In the present Cu^{II} and Zn^{II} complexes of Schiff bases derived from ((E)-4-p-hydroxyphenyl-5-((4-phenylthiazol-2-yl)diazanyl)thiazol-2-amine) and p-aminobenzaldehyde were synthesized, characterized and tested for the bioactivity against Gram positive and Gram negative group of organisms. The synthesized complexes were characterized by elemental and spectroscopic methods, UV-Vis, magnetic susceptibility and assayed for biological activities. The complexes showed (1:2)metal: ligand stoichiometry (ML₂) and an octahedral geometry. The complexes showed an increase in the antibacterial and antifungal activity compared to their parent ligand.

Keywords: Substituted thiazole, Schiff bases, metal complexes, antimicrobial screening.

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I. Introduction

The extreme consideration of amalgamating determined wide scope of N and S chelating ligands as thiazole molecule have attracted significant interest of researchers. This is because thiazoles have incredible pharmacological activities. Moreover, these atoms play an important role in the coordination of metals at the active sites of various biomolecules that possess a therapeutic activity or serving as study models for metallo-enzymes.¹⁻³

Thiazoles are very important building blocks in medicinal chemistry and were found in several natural products (e.g. epothilone) and biologically important compounds including the anticancer drug dasatinib, antiviral clinical and antidiabetic drug molecule.^{4,5}

Recently, thiazoles found application in drug advancement for the treatment of hypertension.⁶

Following all these observations and as an aspect to continuing research on the coordination chemistry of multidentate ligands.⁷⁻⁹

We report here the preparation and characterization of a Schiff base ligand derived from condensation of p-aminobenzaldehyde with ((E)-4-p-hydroxyphenyl-5-((4-phenylthiazol-2-yl)diazanyl) thiazol-2-amine). The study has been extended to synthesize Cu(II) and Zn(II) complexes with the prepared ligand. The prepared complexes have been characterized by IR, mass spectra, UV-Vis, in addition to elemental analysis and magnetic susceptibility.

II. Materials And Methods

Analysis and Physical Measurement

Microanalysis (C, H and N) were performed on a elemental-1-Vario-model-III, Carlo Erba 1108 EL III CHNS analyzer. FT-IR spectra were recorded on Bruker spectrophotometer and expressed in wave numbers (cm⁻¹). The mass spectra were recorded on Applied Biosystems 3200 Q-Trap spectrometer. The UV-Visible spectra were recorded on double beam UV-Visible spectrophotometer. All the reagents used for the synthesis of Schiff base ligand (L) and its metal complexes were obtained from Sigma Aldrich and Merck chemical company, India.

Synthesis of Schiff base Ligand (SB-1)

Step 1: Synthesis of 4-(4-hydroxy) phenyl-2-Aminothiazole

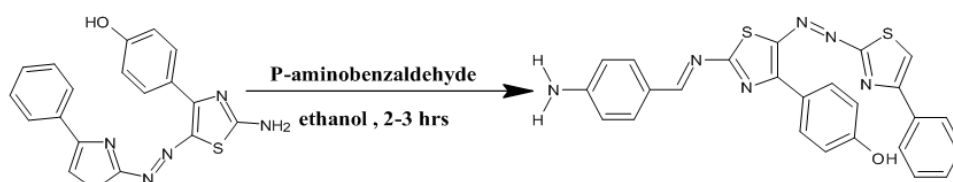
Procedure: An accurately weighed amount of 0.4 mol of thiourea was dissolved in 0.2 mol of 4-hydroxyacetophenone. To the mixture was added 0.2 mol of resublimed iodine and the mixture was heated overnight on an electric mantle. The reaction mixture was cooled to room temperature and the unreacted reactants were washed off with diethyl ether. The residue was dissolved in hot water and filtered. The filtrate was basified with ammonium hydroxide and the obtained precipitate was recrystallized from ethanol.

Step 2: Synthesis of bis-thiazole: ((E)-4-p-hydroxyphenyl-5-((4-phenylthiazol-2-yl)diazenyl)thiazol-2-amine)

Procedure: In a Erlenmeyer flask, 0.02 mol of 4-(4-hydroxy) phenyl-2-aminothiazole and 0.02 mol of sodium acetate were transferred and dissolved in 25 mL of ethanol. In a separate Erlenmeyer flask, 0.02 mol of diazotized thiazole of 4-phenyl-2-aminothiazole, 2-[(E)-chlorodiazenyl]-4-phenyl-1, 3-thiazole synthesized, was dissolved in small amount of glacial acetic acid. To this solution was added the mixture of 4-(4-hydroxy)phenyl-2-aminothiazole and sodium acetate, maintaining the temperature at 0-5°C and stirred for 2h. On completion of the reaction as monitored by TLC, the reaction mixture was diluted with cold water and the solid that separated out was filtered off and recrystallized using a mixture of ethanol and water.

Step 3: Synthesis of 4-amino) benzylidene)-4-(4-hydroxyphenyl-5-((4-phenylthiazol-2-yl)diazenyl)thiazol-2-amine.

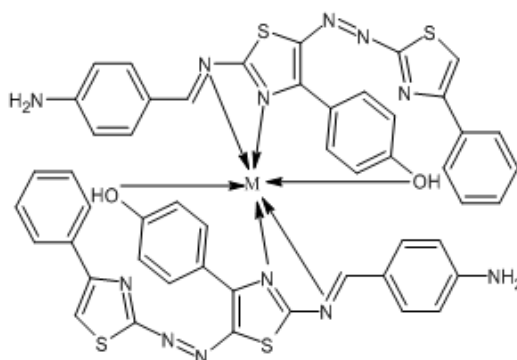
Procedure: An equimolar mixture of ((E)-4-p-hydroxyphenyl-5-((4-phenylthiazol-2-yl)diazenyl)thiazol-2-amine)(10mmol) and p-aminobenzaldehyde (10mmol) in ethanol (25 mL) was refluxed for about 2-3 h on a water bath. The coloured product which separated in was filtered off, washed with hot ethanol, dried and recrystallized from ethanol.



Scheme 1: Synthesis of Schiff base ligand (SB-1)

Synthesis of Metal Cu^{II} and Zn^{II} Complex

To the hot solution of Schiff base ligand (L) (0.002 mol) in ethanol (20 mL) was added a hot ethanolic solution (20 mL) of respective zinc metal chlorides (0.001 mol). The reaction mixture was then refluxed on a water bath for about 5-6 h. The reaction mixture was cooled to room temperature and poured into distilled water. The colored solids separated were collected by filtration, washed with distilled water, then with hot ethanol and finally dried in a vacuum over anhydrous calcium chloride in a desiccator.



$\text{M} = \text{Cu}^{\text{II}}$ and Zn^{II}

Proposed structure of Cu^{II} and Zn^{II} Complex**Biological Evaluation****Antimicrobial Assay**

The newly synthesized compounds were screened for their antibacterial and antifungal activities by the nutrient agar and potato dextrose media respectively by agar well diffusion method. The in vitro antibacterial activity of the test compounds was tested against two Gram-positive bacteria [*Streptococcus mutans* and *Bacillus subtilis*] and one Gram-negative bacteria [*Proteus mirabilis*]. The in vitro antifungal activity was carried out against *Candida albicans* and *Aspergillus niger* fungi. The activity was performed in accordance with the international recommendation provided by the CLSI. The stock solutions of the each test compound and their respective metal chlorides (1 mg/mL) were prepared by dissolving 10 mg of the each test compound in 10 ml of freshly distilled DMSO. Further, the various concentrations of the test compounds (30, 20 and 10 $\mu\text{g/mL}$), were prepared by diluting the stock solutions with the required volume of freshly distilled DMSO.

The MIC of each test compounds was recorded and the average values were calculated. The obtained results of parent ligand and its Zn^{II} complex were compared.

III. Results And Discussion

Chemistry

The newly synthesized metal (II) complexes are colored solids and stable at room temperature

The complexes are insoluble in water and common organic solvents; however these complexes are soluble to a large extent in DMF and DMSO.

Elemental analysis data suggest 1:2 (metal: ligand) stoichiometry (ML₂) for the [Cu(L)₂] complex (Elemental analysis data (Table 1) agree well with the suggested composition of Schiff base ligand and its metal complexes.

IR Spectral Studies

The important IR bands of Schiff base ligand (L) were compared with those of [Cu(L)₂] complex in order to ascertain the bonding mode of the ligand to the metal ion in the complex. The important IR bands for the ligand and its metal complexes together with their assignments are listed in Table 1.

The IR spectrum of Schiff base ligand (L), showed a broad band at 3450.12 cm⁻¹ due to phenolic OH and medium intensity weak bands at 3112.55 cm⁻¹ due to NH₂ attached to the thiazole moiety respectively. The high intensity strong bands observed at 1652.15 cm⁻¹, 1613.27 cm⁻¹ and 1223 cm⁻¹ are due to azomethine function $\nu(\text{C}=\text{N})$, thiazole moiety function $\nu(\text{C}=\text{N})$, and phenolic C-O respectively.

In Cu^{II} complex, The absence of ν OH mode (band at 3450.12 cm⁻¹ in the ligands) in the complex suggest the deprotonation of phenolic OH of the ligand and its coordination through O atom. The ν C-O mode for the complexes was observed at ~1211 cm⁻¹ (as against ~1225 cm⁻¹ for the ligand) and ν C=N mode of azomethine and thiazole mode at ~1635 and 1600 cm⁻¹ (as against ~1652 cm⁻¹ and 1613 cm⁻¹ for the ligands). The shifting of ν C-O and ν C=N in the complexes towards lowering frequency as compared to the ligands, suggests that the coordination to the central metal atom takes place through oxygen of the phenolic OH group and nitrogen of the azomethine and thiazole moiety. The coordination of nitrogen to the central metal atom reduces the electron density and thus causes reduction in ν C=N frequency.¹⁰ In the light of above discussion, we propose that coordination to the central metal atom takes place through oxygen of the phenolic OH group, nitrogen of the azomethine group and nitrogen of the thiazole moiety. The ligand thus behave as NNO donor ligands.

The Electronic spectral data of Cu^{II} and Zn^{II} complexes suggested octahedral geometry to both the complexes and the data is tabulated in Table 2.

Important IR frequencies of Cu^{II} complex (cm⁻¹).

Table 1

Complex	ν OH	ν NH	ν C = N azomethine	ν C = N thiazole	ν C = O	ν C = CH aromatic
SB	3450	3112	1652	1613	1225	2932

Table 2

Elemental analysis, Electronic spectra and magnetic susceptibility data of Cu^{II} and Zn^{II} Complexes

Complex	Elemental analysis Calcd./Found	Magnetic susceptibility $\mu_{\text{eff}}(\text{B.M.})$	UV-Vis	Band (nm)	Geometry Suggested
CuL ₂	C (58.38/58.02) N (16.34/16.04) S (12.42/12.17) H (3.53/3.40)	1.6 B.M.	${}^2\text{E}_g \longrightarrow {}^2\text{T}_{2g}$	430	Octahedral
ZnL ₂		Diamagnetic			Octahedral

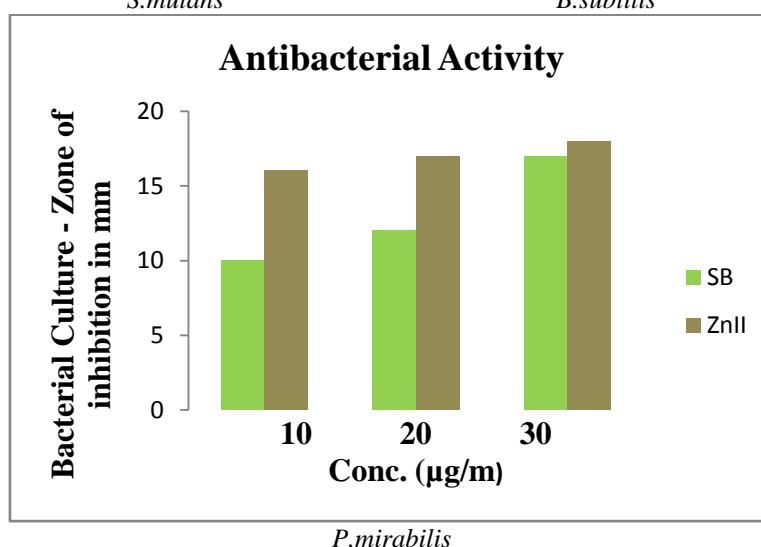
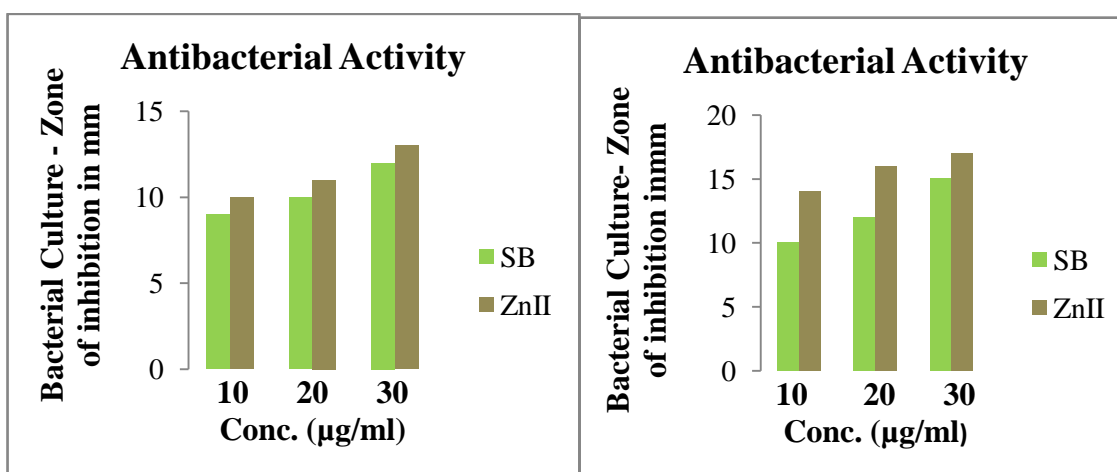
Biological activities

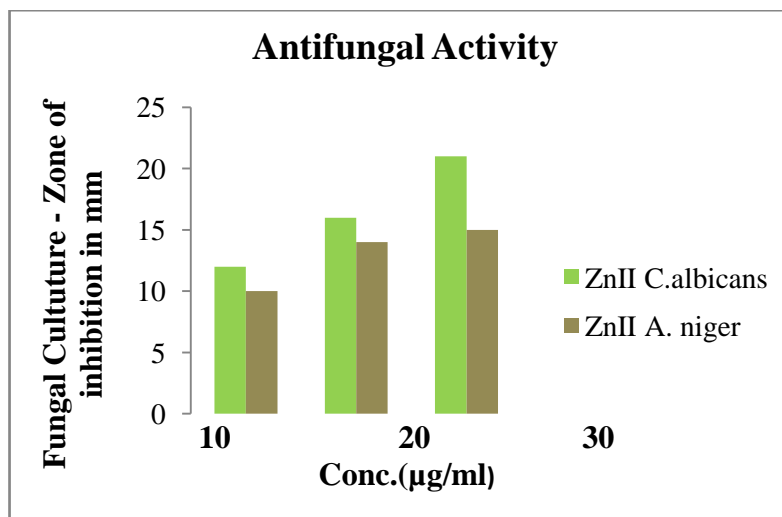
Literature survey reveals that aminothiazole, Schiff bases and their complexes exhibits anti-quorum sensing antibiofilm, antibacterial, antifungal, anticancer and anti-tubercular activities.¹¹⁻¹³ In present studies we have tested the Zn^{II} complex of thiazole Schiff base for the evaluation of antibacterial activity against two gram positive bacteria (*S.mutans* and *Bacillus subtilis*) and one gram negative bacteria *P.mirabilis*. Also we have tested this complex for the evaluation of antifungal activity against two fungi (*Aspergillus niger* and *Candida albicans*).

The antimicrobial activity of the metal complexes can be explained on the basis of chelation theory. Chelation reduces the polarity of the metal ion, because positive charges of the metal are partially shared with the donor atoms present in the ligands and there maybe π -electron delocalization over the whole chelation. This phenomenon increases the lipophilic character of the metal chelate and favors its permeation more efficiently through the lipid layer of the microorganism, thus destroying them more forcefully. The other factors like solubility, conductivity and bond length between the metal and ligand also increase the biological activity. The MIC results are given in Table 3. As seen the Zn^{II} complex of SB-1 showed increase in antimicrobial activity against all the selected microbial strains.

Table 3:
Diameter of Zone of Inhibition by Zn^{II} complexes of SB-1

Conc.(μ g/ml)	Diameter of Zone of Inhibition (mm)									
	Zn^{II} complex SB-1									
	Bacteria						Fungi			
	S.mutans		B.subtilis		P.mirabilis		C.albicans		A.niger	
	SB	Zn^{II}	SB	Zn^{II}	SB	Zn^{II}	Zn^{II}	Zn^{II}	Zn^{II}	
10	9	10	10	14	10	16	12		10	
20	10	11	12	16	12	17	16		14	
30	12	13	15	17	17	18	21		14	





IV. Conclusion

The Cu^{II} and Zn^{II} complexes of thiazole Schiff base under study are coloured crystalline solids. They are soluble in chloroform, DMSO, DMF etc. solvents. Elemental analysis data suggested 1:2 metal-ligand stoichiometry (CuL₂) for the complexes. Electronic spectral data and magnetic measurements suggested that the complexes are diamagnetic and supports the octahedral geometry for Cu^{II} and Zn^{II} complexes.

Whereas zone of inhibition of Zn^{II} complex was observed against bacterial strains *S. mutans*, *B. subtilis*, *P. mirabilis* and fungal strains *C. albicans* and *A. niger*. It was observed that Zn^{II} complex showed an enhanced in the antimicrobial activity against all the bacterial and fungal strains due to action of Zn metal ions compared to the parent Schiff base ligand.

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