

Synthesis, Characterization, Antimicrobial, DNA cleavage, and Cytotoxicity Studies of Some Metal (II) Complexes of Tridentate Schiff Base Ligand: 2-hydroxy-3-((4-(4-phenylthiazol-2-yl) semicarbazide) methyl) Benzoic Acid

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ABSTRACT

Objective: The main aim of the present work was to synthesize a novel Schiff base ligand 2-hydroxy-3-((4-(4-phenylthiazol-2-yl) semicarbazide) methyl) benzoic acid is obtained by the condensation of N-(4-phenylthiazole-2-yl) hydrazine carboxamide with 3-Aldehydosalicic acid and its Cu(II), Co(II), Ni(II), and Zn(II) complexes and study of their biological activity. **Methods:** The compounds are characterized by elemental analysis and various physicochemical techniques like IR, ¹H NMR, ESI-mass, and molar conductance data. All the compounds were screened for their antibacterial and antifungal activity by MIC method. Further, to study the *in vitro* cytotoxicity properties of all the compounds against Artemia salina and DNA cleavage activity by Agarose Gel Electrophoresis (AGE) method. **Results:** Spectral investigations suggested square pyramidal coordination geometrical arrangement for all the metal (II) complexes, having 1:1 stoichiometric ratio of the type [ML (Cl)₂]. The antimicrobial activity results revealed that the metal complexes were found to be more active than the free ligand. Furthermore, the DNA cleavage activity of the compounds on plasmid DNA *pBR322* molecule showed moderate activity. **Conclusion:** The newly synthesized ligand acts as OON donor tridentate chelate and coordinated through an oxygen of azomethine nitrogen, Phenolic OH and Carboxylic acid (COOH) of 3-Aldehydosalicic acid to the Cu, Co, Ni and Zn metal ions and form square pyramidal geometrical arrangement. All the complexes are found to be non-electrolytic in nature. Further, all the newly prepared compounds showed moderate biological activity.

Key words: Transition metal complexes, Thiazole, Schiff base, Antimicrobial, DNA cleavage.

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INTRODUCTION

Medicinal chemistry has generated important interest in the design of metal complexes as potential diagnostic and therapeutic agents. Thiazoles are one of the most intensively investigated classes of aromatic five-membered heterocyclic and containing three carbons, one sulphur, and one nitrogen atom. Thiazole and its derivatives are very useful compounds in different fields of chemistry including medicine and agriculture. Many

thiazole derivatives such as bleomycin, abafungin, ritonavir, and sulfathiazole are well known potential biologically active compounds.¹ Also, thiazoles are the starting material for several compounds including dyes, fungicides, sulphur drugs, biocides and chemical reaction accelerators which exhibit microbial activity that can be well characterized by a large number of drugs in the market containing this moiety.² Schiff



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base complexes of transition metals are particular attention to inorganic chemists because of their structural, chemical and spectral properties are more strongly dependent on the nature of the ligand structure.³⁻⁶ The coordination chemistry of transition metal complexes derived from Schiff base ligands have been among the majority widely studied coordination compounds in current years.^{7,8} Since they are becoming increasingly important as analytical, biochemical and antimicrobial reagents and Metal complexes of O, S, and N-chelating ligands have more attracted considerable attention because of their interesting Physico-chemical properties, strong biological activities.⁹⁻¹² The fact, copper, calcium, magnesium, zinc, iron, chromium, molybdenum, and vanadium are fundamental metallic elements and exhibit great biological activity when associated with certain metal-protein complexes, participating in oxygen transport the storage of ions or electronic transfer reactions,^{13,14} has created enormous interest in the study of systems containing these metals.¹⁵ Thiazole ring finds applications such as liquid crystals, fluorescent dyes, polymers, insecticides and antioxidants.^{16,17} Therefore it has been found interesting to study the metal complexes containing thiazole moiety. Some of Schiff bases and their transition metal complexes have also been used as drugs as fungicidal, bactericidal, anti-tubercular and antiviral agent.^{18,19} In current years, metal-based drugs have gained much importance in the medicinal field. They are used as medicines for the treatment of cancer, diabetes, cardiovascular diseases and anti-inflammatory.²⁰⁻²² The medical application of the metal complexes compounds of thiazole to impart strength, elasticity, and impermeability of water.²³ Analogous of hetero-aromatic Schiff base derived from 3-aldehydosalicylic acid have been to possess biological activity. Azomethine group ($=C=N-$) which is formed by the condensation of primary amines with aromatic aldehydes. Such Schiff base ligands containing various donor atoms like O, N, and S showed broad biological activities and they are bond to the metal ions of Cu (II), Ni (II), Zn (II), Co (II).²⁴⁻²⁶ Based on these findings and in continuation of our research work on coordination chemistry, we have synthesized the new Schiff base ligand 2-hydroxy-3-((4-(4-phenylthiazol-2-yl) semicarbazide) methyl) benzoic acid containing the carbonyl, azomethine, and hydroxyl groups as potent chelating sites. In order to study the ligation behavior of this ligand, we have prepared a series of its Cu(II), Co(II), Ni(II) and Zn(II) complexes and characterized them by various physicochemical techniques and studied their antimicrobial, DNA cleavage and *In vitro* Cytotoxicity.

Experimental

Analysis and physical measurement

Elemental analysis(C, H, and N) was performed on Vario EL CHNS analyzer. IR spectra of the synthesized Schiff base and its metal complexes were recorded in KBr pellets on a Parkin-Elmer FT-IR instrumental in the range 4000-250 cm^{-1} . ¹HNMR spectra of ligand and its Zn (II) complex were recorded on the FT-NMR spectrometer model Bruker Avance II, 400 MHz using d_6 DMSO as solvent. ESI-MS were recorded on a mass spectrometer equipped with electrospray ionization (ESI) source having mass arranged of 4000 amu in quadruple and 20000 amu in ToF. Molar conductivity measurement were recorded on ELICO (CM-180) conductivity bridge in DMF (10^{-3}) solution using a dip-type conductivity cell fitted with a platinum electrode.

Material and methods

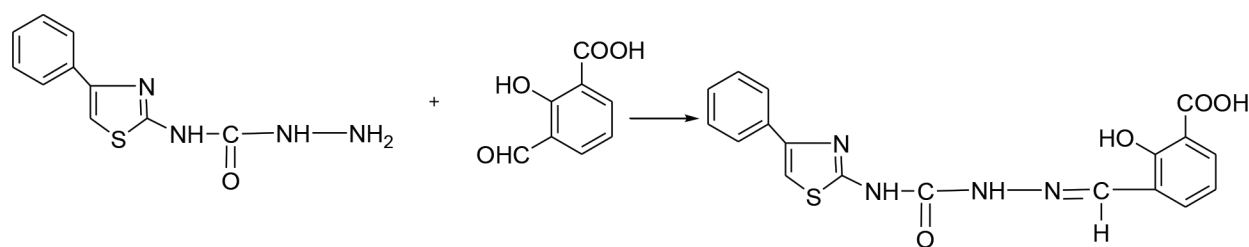
All reagents and chemicals required were AR grade, purchased commercially. All the solvents were purified by distillation and used. Thiourea, bromine, acetophenone, salicylic acid, hexamethylenetetramine, benzene, ammonium hydroxide, barium chloride, sodium hydroxide, hydrochloric acid and pyridine were purchased from S.D. Fine Chemicals, ethylchloroformate and hydrazine hydrate were purchased from Sigma Aldrich chemical company, India. Melting points of the newly synthesized compounds were determined by electro-thermal apparatus using open capillaries and are uncorrected. The metal and chloride contents of the metal complexes were determined as per standard procedures.²⁷ Purity of the compounds was checked by TLC and the spots were observed in iodine vapour. The precursor N-(4-phenylthiazol-2-yl) hydrazinecarboxamide was prepared by the literature method.²⁸

Synthesis of Schiff base ligand (L)

An equimolar mixture of N-(4-phenylthiazol-2-yl) hydrazinecarboxamide (0.001 mol) and 3-Aldehydosalicylic acid (0.001 mol) in ethanol (30 ml) was refluxed with a catalytic amount of glacial acetic (1-2 drops) for about 5-6 hrs on a water bath, the yellow colored product which separated in hot was filtered off, washed with hot ethanol, dried and recrystallized from alcohol (Scheme 1). The reaction was monitored by TLC. Yield: 72% M.P: 267-280°C.

Synthesis of metal (II) complexes

To the 2-hydroxy-3-((4-(4-phenylthiazole-2-yl) semicarbazido) methyl) benzoic acid (0.001 mol) in ethanol (25 ml) was added hot ethanolic solution (20ml) of respective metal chlorides (0.001 mol). The reaction



2-hydroxy-3-((4-(4-phenylthiazol-2-yl)semicarbazido)methyl)benzoic acid

Scheme 1: Synthesis of Schiff Base Ligand (L)

Scheme 1: Synthesis of Schiff base ligand (L).

mixture was then refluxed on water bath for about 4-5 hrs, pH of the reaction mixture adjusted Ca. 7 to 7.5 by adding alcoholic solution of sodium acetate (0.5 gm) and refluxing continued for about an one hr more. The reaction mixture was cooled to room temperature and poured into distilled water. The colored solids separated were collected by filtration, washed with sufficient quantity of distilled water, then with hot ethanol to remove any traces of unreacted starting materials and finally dried in a vacuum over anhydrous calcium chloride in desiccator.

Biological activities

Antimicrobial assays

The biological activities of the newly synthesized ligand and their Cu (II), Co (II), Ni (II) and Zn (II) complexes were screened for their antibacterial and antifungal activities by disc and well diffusion method respectively.²⁹

The *in vitro* antibacterial activities of the compounds were tested against two Gram-negative [*Escherichia coli* and *Salmonella typhi*] and two Gram-positive [*Bacillus subtilis* and *Staphylococcus aureus*] bacteria. The *in vitro* antifungal activities were carried out against *Candida albicans*, *Cladosporium oxy-sporum* and *Aspergillus Niger fungi*. The stock solutions of the test chemicals (1 mg mL⁻¹) were prepared by dissolving 10 mg of the each test compound in 10 mL of freshly distilled DMSO. The different concentrations of the test compounds (100, 50, 25 and 12.5 µg mL⁻¹), were prepared by diluting the stock solution with the required amount of distilled DMSO. The lowest concentration that inhibited microbial growth was called as the MIC value. Further the dilutions for the metal chlorides were prepared by using distilled water and control experiments were carried out by using DMSO solvent alone.

Antibacterial screening

Muller–Hinton agar media was used for the antibacterial studies. The pure dehydrated Muller–Hilton agar (38 g) was dissolved in 1000 mL distilled water. The pure cultures of the bacterial strains *E. coli*, *S. aureus*, *B. subtilis*

and *S. typhi* were sub cultured by inoculating them in the nutrient broth and they were incubated at 37°C for about 18 h. The agar plates were prepared by using the above media. Each plate were inoculated with 18 h old bacterial culture (100 µL) using a micropipette and spread uniformly using bent glass rod. Wells were dug with the help of 6 mm sterile metallic cork borer. The drug *gentamycin* is used as standard. Different concentration of the test compounds and their respective metal chloride solutions were incorporated into the wells using micropipette and the plates were kept for incubation at 37°C for 24 h. Soon after the completion of incubation period, the diameter of the inhibition zone generated by each test compound against bacterial growth were measured using antibiogram zone measuring scale.

Antifungal screening

Potato dextrose agar (PDA) media was used for the antifungal studies. The following ingredients were used to prepare the media i.e. potatoes (sliced washed unpeeled) 200 g, dextrose 20 g, agar 20 g in 1000 mL distilled water. The pure cultures *C. albicans*, *C. oxysporum* and *A. niger* were inoculated on PDA slants. These slants were incubated at 32°C for 7 days. To these 7 days old slants of fungal strains, 10 mL of 0.1% tween-80 solution was added and the culture were scraped with sterile inoculating loop to get uniform spore suspension. The agar plates were prepared by using the above potato dextrose agar media. Each plate were inoculated with 7 days old spore suspension of each fungal culture (100 µL) using a micropipette and spread uniformly using bent glass rod. Wells were dug with the help of 6 mm sterile metallic cork borer. Each well was incorporated with the test compound solution of different concentrations and their respective metal chloride solution. The drug *Fluconazole* is used as standard. All the inoculated plates were incubated at 32 °C for about 48 h. Soon after the completion of incubation period the diameter of the inhibition zone generated by each

test compound against fungal growth were measured using antibiogram zone measuring scale.

DNA cleavage experiment

The extent to which the newly synthesized ligands and their metal complexes could function as DNA cleavage agents was examined using supercoiled plasmid *DNA pBR 322* (Bangalore Genei, Bengaluru, Cat. No.105850) as a target molecule. The electrophoresis method was employed to study the efficiency of cleavage by the synthesized compounds. Each test compounds (100 µg) were added separately to the 225 mg *pBR 322 DNA* sample and these samples mixtures were incubated at 37 °C for 2 h. The electrophoresis of the test compounds was done according to the literature method.³⁰ Agarose (600 mg) was dissolved in hot tris-acetate-EDTA (TAE) buffer (60 mL) (4.84 g Tris base, pH – 8.0, 0.5 M EDTA L⁻¹) and heated to boil for few minutes. When the gel attains approximately 55 °C, it was then poured into the gel cassette fitted with comb. Slowly the gel was allowed to solidify by cooling to room temperature and then carefully the comb was removed. The solidified gel was placed in the electrophoresis chamber containing TAE buffer. The DNA sample (20 µL) initially treated with the test compounds were mixed with bromophenol blue dye in equimolar ratio along with standard DNA marker containing TAE buffer was loaded carefully into the wells and the constant 50 V of electricity was supplied for about 30 min. Later, the gel was removed, stained with Ethidium bromide solution (10 µg mL⁻¹) for 15–20 min and then the bands were observed and photographed under UV-illuminator.

In vitro Cytotoxicity

Brine shrimp nauplii (*Artemia salina*) be used in the *in vitro* cytotoxicity analyze, according to the protocol of Meyer *et. al.*³¹ with some modifications. This is a rapid, efficient, inexpensive test and has a good relationship with cytotoxic activity. *Brine shrimp* (*A. salina*) eggs was hatch in a shallow rectangular plastic dish (22 x 32 cm) packed with artificial seawater, which was prepared with a mixture of commercial salt and double distilled water. An unequal partition was made in the plastic dish with the help of a perforated apparatus. Approximately 50 mg of eggs are sprinkled into the large compartment, which has darkened while the small compartments were open to ordinary light. Two days after nauplii were collected by pipette by lighted side. Samples of the test compound were prepared by dissolving 20 mg of each compound in 2 ml of DMSO. From the stock separate vials and the volume of each vial made up to 10ml with artificial sea water to obtain the desired final concentra-

tions. The negative control was prepared in the same manner, omitting the sample. After two days, when shrimp larvae were ready, 10 shrimp nauplii were then placed in each vial. After 24 hrs incubation, the vials were observed using a magnifying glass, and the number of survivors in each vial was counted. Tests were performed in triplicate and the resulting data were analyzed by a Finney computer program to determine the LD₅₀ values.³² The results for test compounds were compared with positive control bleomycin.

Results and discussion

The newly synthesized metal complexes are colored solids, stable at room temperature and possess high melting point (>278°C). The metal complexes are insoluble in water and common organic solvents but completely soluble in DMF and DMSO. The evidence for the formation of tridentates OON donor nature of the Schiff base ligand (L) was confirmed by using various spectral techniques. Elemental analysis and analytical data (Table 1) agree well with the proposed composition of Schiff base ligand and its metal complexes. These data of metal complexes suggest that the metal to ligand ratio of the complexes is 1:1 stoichiometry of the type [M (L) (Cl)₂] for Cu (II), Co (II), Ni (II) and Zn (II) complexes. The measured molar conductance values of the metal complexes were too low to account for any dissociation of the complexes in DMF (18–36 ohm⁻¹ cm² mole⁻¹), indicating their non-electrolytic behavior.³³

IR spectral studies

Infrared spectra helps in getting on idea on how is the ligand coordinate to metal ion. The characteristics frequencies of the expected functional groups are depicted in Table 2. IR spectrum of the ligand showed a high intensity band at 1727 cm⁻¹ due to carbonyl function (C=O) and two absorption bands at 3259 cm⁻¹, 3119 cm⁻¹ due to amide NH and NH attached to thiazole moiety respectively. A high intensity band observed at 1628 cm⁻¹ is attributed to the azomethine (C=N) vibration. IR spectrum of Schiff base ligand showed a broad band at 3176 cm⁻¹ and 3480 cm⁻¹ due to phenolic OH and COOH respectively Figure 1.

The IR spectra of the metal complexes exhibited ligand bands with the appropriate shifts due to complex formation. In the IR spectra of all the metal complexes it was observed that, the absence of band at 3176 cm⁻¹ and 3480 cm⁻¹ due to phenolic OH and COOH of ligand indicates the formation of coordination bond between the metal ions. IR spectrum of the metal complexes, medium intensity weak bands at 3240-3180 cm⁻¹ and 3104-3080 cm⁻¹ were due to amide NH and NH

The ESI mass spectra of the Schiff base ligand (L) and its Cu (II), and Co (II) complexes have been studied for their mass spectral studies. The ESI-mass spectra of the compounds exhibited molecular ion peaks equivalent to their molecular weight along other fragment peaks Figure 6. The ESI mass spectrum of the Schiff base ligand (L) showed a molecular ion peak recorded at m/z 382 which is equivalent to its molecular weight. Similarly, the ESI mass spectra of Cu (II) and Co (II) complexes

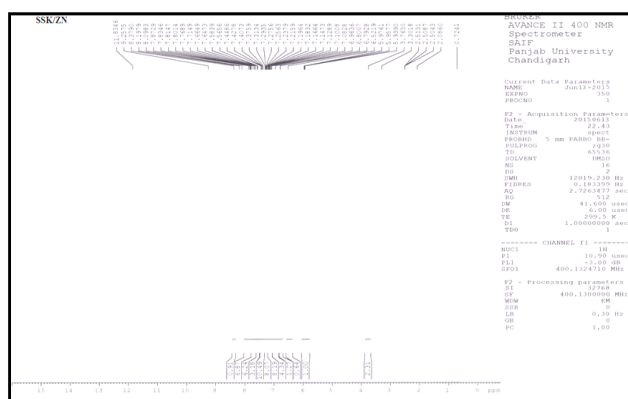


Figure 5: ^1H NMR spectrum of Zn (II) complex

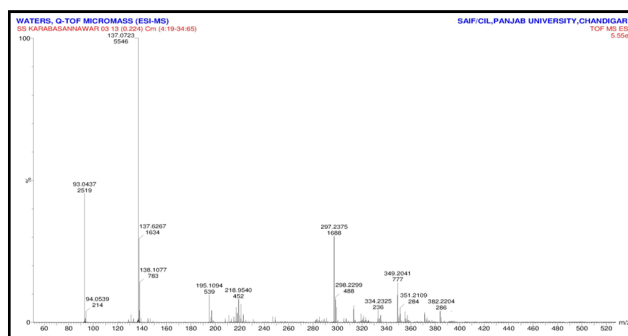


Figure 6: ESI Mass Spectrum of Schiff Base Ligand

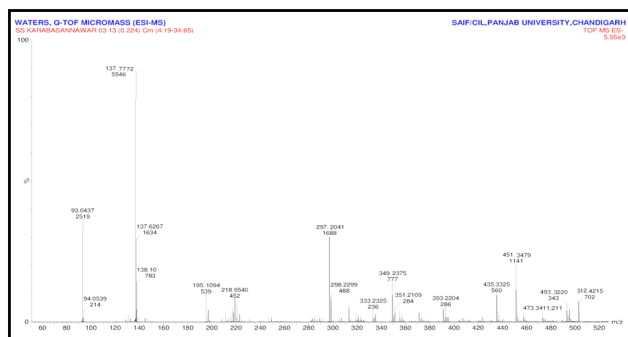


Figure 7: ESI Mass Spectrum of Cu (II) complex

showed a molecular ion peaks recorded to m/z 512 and 508 respectively which are equivalent to their molecular weights Figure 7.

Biological Activities

In vitro antimicrobial activity

The synthesized ligand and their metal complexes have been screened for their antimicrobial activity. The antimicrobial activities were carried out against *Escherichia coli*, *Salmonella typhi*, *Bacillus subtilis* and *Staphylococcus aureus* bacterial strains and anti fungal activity against *Candida albicans*, *Cladosporium oxysporum* and *Aspergillus niger* fun-

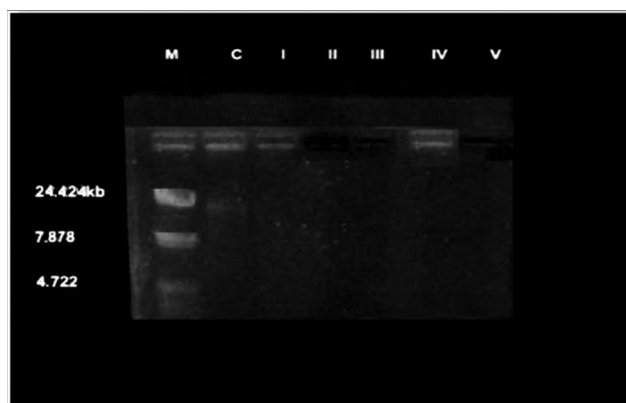


Figure 8: DNA cleavage of super coiled plasmid DNA pBR322. M, standard molecular weight marker; C, control. Ligand (Lane I) and its Cu (II), Co (II) and Ni (II) (Lane II, III and IV) were treated plasmid DNA pBR322 with respective compounds.

gal strains. The antimicrobial activity results and minimum inhibitory concentration values of the compounds against respective strains are summarized in Table 4. the antimicrobial activity results of all the synthesized compounds exhibit antimicrobial properties and it is important to note that the metal complexes exhibited more inhibitory effect compared to their respective ligands and their metal chlorides. The enhanced antimicrobial activity of the complexes over the ligands and their metal chlorides can be explained on the basis of chelation theory.^{36,37} It is known theory chelation enhances the ligand to act as more powerful potent bacterial agents, thus killing more of the bacteria than the ligand. The enhancement in the activity may be rationalized on the basis that ligands mainly possess azomethine ($\text{C}=\text{N}$) bond. It has been suggested that the ligands with hetro donor atoms (nitrogen and oxygen) inhibit enzyme activity, since the enzymes which require these groups for their activity appear to be especially more susceptible to deactivation by metal ion on coordination. It is observed that, in a complex, the positive charge of the metal ion is partially shared with the ligand and there may π -electron delocalization over the whole chelating system.³⁸ Thus the increase in the lipophilic character of the metal chelates and favors its permeation through the lipid layer of the bacterial membranes and blocking of the metal binding sites in the enzymes of microorganisms. The factors namely solubility, conductivity and bond length between the metal ion and the ligand also increases the activity. The increase in the activity of metal complexes against the fungi is due to the formation of a hydrogen bond the azomethine nitrogen atom and active centers of the cell constituents, resulting in the interference with the normal cell process.

DNA cleavage activity

The ligand and its Cu(II), Co(II), Ni(II) and Zn(II) complexes were studied for their DNA cleavage activity by agarose gel electrophoresis method against supercoiled DNA pBR 322 (Bangalore Genei, Bengaluru, Cat.No.105850) as a target molecule and the gel picture showing cleavage is depicted in Figure 8. The characterization of DNA recognition by transition metal complex has been aided by the DNA cleavage chemistry associated with redox active or photo-activated metal complex.³⁹ The electrophoresis analysis clearly revealed that the ligand and its metal complexes have acted on DNA because of a difference in molecular weight between the control and the treated DNA samples. The difference was observed in the bands of lanes of complexes compared with the control DNA (lane C) of pBR322 due to the relaxation of circu-

lar DNA into linear form. This shows that the control DNA alone does not show any apparent cleavage, whereas the ligand and its metal complexes do show. In the present case, the ligand (Lane I) and its Cu (II), Co (II) and Ni (II) (Lane II, III and IV) complexes showed complete cleavage of supercoiled DNA whereas Zn (II) complex showed partial cleavage of supercoiled DNA. It can be concluded that all the compounds under present study inhibited the growth of pathogenic organisms by DNA cleavage as has been observed on the DNA cleavage of supercoiled plasmid DNA pBR322.

In vitro Cytotoxicity

The brine shrimp bioassay is an excellent tool to be used for monitoring the biological activity in order to predict the ability to kill cancer cells.⁴⁰ A summary of the cytotoxic assay results of the Schiff base ligand (L)

Table 1: Physical, Analytical and Molar conductance data of Schiff base ligand (L) and its metal complexes

Compounds	M.W. ^a	M.P (°C) ^b	Elemental analysis found [%]							λ (cm ² Ω ⁻¹ mol ⁻¹)	Color
			M	C	H	N	O	S	Cl		
C ₁₈ H ₁₄ N ₄ O ₄ S	382.4	274-280	-----	56.54	3.69	14.65	16.74	8.39	-----	-----	Yellow
[Cu(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	498.8	286	12.74	43.34	2.42	11.23	9.62	6.43	14.21	24	Green
[Co(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	494.2	290	11.92	43.74	2.45	11.34	9.71	6.49	14.35	18	Brown
[Ni(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	494	285	11.34	43.77	2.45	11.34	9.72	6.49	14.35	36	Brown
[Zn(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	500.7	287	13.06	43.18	2.42	11.19	9.59	6.40	14.16	30	Pale Yellow

^a molecular weight of the compounds

^b melting point if the compounds at their decomposition

Table 2: IR spectral data of Schiff base ligand and its metal complexes

Compounds	Amide NH	Thiazole NH	C=O	C=N	OH	COOH	M-O	M-N	M-Cl
C ₁₈ H ₁₄ N ₄ O ₄ S	3259	3119	1727	1628	3176	3480	-----	-----	-----
[Cu(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	3229	3104	1726	1591	-----	-----	542	495	368
[Co(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	3221	3096	1727	1594	-----	-----	533	489	360
[Ni(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	3220	3096	1726	1593	-----	-----	536	497	337
[Zn(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	3225	3063	1726	1556	-----	-----	546	496	326

Table 3: ¹H NMR data of Schiff base ligand (L) and its Zn (II) metal complexes

Ligand / complex	¹ H NMR data (ppm)
C ₁₈ H ₁₄ N ₄ O ₄ S	13.59 (s, 1H, Carboxylic acid) 12.2 (s, 1H, Phenolic OH) 10.70 (s, 1H, NH attached to thiazole) 8.93 (s, 1H, CONH) 8.38 (s, 1H, CH=N) 7.39-8.40 (m, 9H, ArH).
[Zn(C ₁₈ H ₁₂ N ₄ O ₃ S) Cl ₂]	9.23(s, 1H, NH attached to thiazole) 8.38 (s, 1H, CONH) 8.20 (s, 1H, CH=N) 7.07-8.10 (m, 9H, ArH)

Table 4: Minimum inhibitory concentration (MIC $\mu\text{g mL}^{-1}$) of Schiff base ligand and its metal complexes

Compounds	Bacteria				Fungi		
	S.aureus	B.Subtilis	E.coli	S.typhi	C.albicans	C.oxysporum	A.niger
$\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_4\text{S}$	50	75	75	50	75	75	50
$[\text{Cu}(\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3\text{S}) \text{Cl}_2]$	50	25	50	25	50	25	50
$[\text{Co}(\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3\text{S}) \text{Cl}_2]$	25	50	25	50	25	50	25
$[\text{Ni}(\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3\text{S}) \text{Cl}_2]$	50	25	50	50	50	25	50
$[\text{Zn}(\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3\text{S}) \text{Cl}_2]$	50	50	50	50	25	50	25
Gentamicin	12.50	12.50	12.50	12.50	--	--	--
Fluconazole	--	--	--	--	12.50	12.50	12.50

Table 5: Brine shrimp bioassay data of the Schiff base ligand (L) and its metal complexes

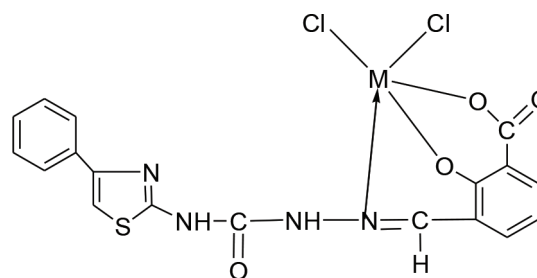
Compounds	LD ₅₀ (M/mL)
$\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_4\text{S}$	2.276×10^{-4}
$[\text{Cu}(\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3\text{S}) \text{Cl}_2]$	2.187×10^{-4}
$[\text{Co}(\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3\text{S}) \text{Cl}_2]$	1.104×10^{-4}
$[\text{Ni}(\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3\text{S}) \text{Cl}_2]$	2.321×10^{-4}
$[\text{Zn}(\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3\text{S}) \text{Cl}_2]$	1.145×10^{-4}

and its metal complexes is presented in Table 5. The standard anticancer drug bleomycin showed the LD₅₀ value 0.51×10^{-4} . Among all the compounds tested Co (II) complex showed the highest cytotoxicity with LD₅₀ value of 1.108×10^{-4} which is indicative of its potent cytotoxicity than other coordination complexes in this experiment showed followed by Zn (II) complex with LD₅₀ value of 1.156×10^{-4} . On the other hand, ligand (L), Cu (II) and Ni (II) complex were found to be inactive against A.salina.

CONCLUSION

The newly synthesized Schiff base ligand 2-hydroxy-3-((4-(4-phenylthiazol-2-yl) semicarbazide) methyl) benzoic acid behaves as tridentate OON donor and the complexes of square pyramidal coordination type $[\text{ML}(\text{Cl})_2]$. The help of various physicochemical and spectroscopic methods such as IR, ^1H NMR, the square pyramidal coordination geometries of Cu (II), Co (II), Ni (II), and Zn (II) complexes have been proposed (scheme 2). The non-electrolyte nature of the complexes was confirmed on the basis of their molar conductance values. The newly synthesized metal complexes having good antimicrobial activity when compared to Schiff base ligand. The DNA cleavage activity of all the newly synthesized compounds showed the cleavage of plasmid DNA cleavage. In addition to that, cytotoxicity of Co (II) and Zn (II) complexes indicate potent cytotoxic agents that might become potent anticancer agent in

clinical trials. Hence from all these extensive observations; it was concluded that the Schiff base ligand (L) and its metal complexes give the significant, adaptable and valuable information of coordination compounds and also they may be used as potent biological agents with reduced toxicity and higher efficiency.



M= Cu (II), Co (II), Ni (II), and Zn (II)

Scheme 2: Proposed structure of the complexes.

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CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATION USED

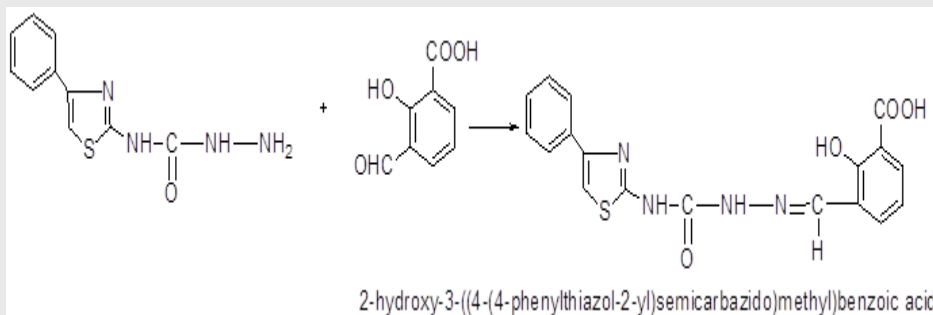
FT-IR: Fourier Trans- form Infrared; **¹H NMR:** Proton Nuclear Magnetic Resonance; **ESI mass:** Electrospray Ionization Mass Spectrometry; **DNA:** Deoxyribonucleic acid; **TLC:** Thin-layer chromatography; **DMSO:** Dimethyl sulfoxide; **TMS:** Tetramethylsilane; **DMF:** Dimethylformamide; **MTCC:** Microbial Type Culture Collection and Gene Bank; **PDA:** Potato dextrose agar; **EDTA:** Ethylene diamine tetraacetic acid; **MIC:** Minimum inhibitory concentration; **LD50:** Lethal Dose; **ETBr:** Ethidium bromide.

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PICTORIAL ABSTRACT



SUMMARY

- The newly synthesized Schiff base ligand 2-hydroxy-3-((4-(4-phenylthiazol-2-yl) semicarbazide) methyl) benzoic acid behaves as tridentate OON donor and the complexes of square pyramidal coordination type [ML (Cl)₂]. The help of various physicochemical and spectroscopic methods such as IR, ¹H NMR, the square pyramidal coordination geometries of Cu (II), Co (II), Ni (II), and Zn (II) complexes have been proposed. The non-electrolyte nature of the complexes was confirmed on the basis of their molar conductance values. The newly synthesized metal complexes having good antimicrobial activity when compared to Schiff base ligand. The DNA cleavage activity of all the newly synthesized compounds showed the cleavage of plasmid DNA cleavage. In addition to that, cytotoxicity of Co (II) and Zn (II) complexes indicate potent cytotoxic agents that might become potent anticancer agent in clinical trials. Hence from all these extensive observations; it was concluded that the Schiff base ligand (L) and its metal complexes give the significant, adaptable and valuable information of coordination compounds and also they may be used as potent biological agents with reduced toxicity and higher efficiency

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