

Synthesis, Characterization and Antimicrobial Activity of Metal Complexes derived from thiazole and 2-naphthaldehyde

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Abstract: The new ligand 2-(naphthalen-2-ylmethylene)-N-(4-(p-tolyl)thiazol-2-yl)hydrazinecarboxamide (**L**) prepared by the condensation of N-(4-(p-tolyl)thiazol-2-yl)hydrazinecarboxamide with 2-naphthaldehyde and its Cu(II), Co(II), Ni(II) and Zn(II) complexes were synthesized and characterized by elemental analysis and various spectral techniques. Spectral analysis indicates octahedral geometry for all the complexes. The complexes have 1:2 stoichiometric ratio of the type $[M(L)_2Cl_2]$. The compounds were screened for their antibacterial and antifungal activities by minimum inhibitory concentration (MIC) method.

Keywords: Antimicrobial, Powder XRD, Schiff base, Thiazole, Transition metal complexes

I. Introduction

The condensation of primary amines with carbonyl compounds yields Schiff bases [1,2]. Schiff base with donors (N, O, S, etc) have structure similarities with neutral biological systems and due to presence of imine group are utilized in elucidating the mechanism of transformation of rasemination reaction in biological system [3]. Thiazole and its derivatives as ligands with potential sulphur and nitrogen bands are interesting and have gained special attention not only the structural chemistry of their multifunctional coordination modes but also of their importance in medicinal and pharmaceutical field. Schiff bases represent an important class of compounds because they are utilized as starting materials in the synthesis of industrial products [4]. Number of thiazole derivatives such as sulfathiazole, ritonavir, abafungin, bleomycine and tiazofurin are well known for their good biological activity [5]. Also, thiazoles are the starting materials for several compounds including biocides, fungicides, sulfur drugs, dyes and chemical reaction accelerators which exhibit several biological activities such as anti-hypertensive, anti-inflammatory, anti-microbial, anti-HIV, antitumor and cytotoxic activity that can be well illustrated by the large number of drugs in the market containing this moiety. The present study describes the coordination behaviour of novel Schiff base derived from the condensation of N-(4-(p-tolyl)thiazol-2-yl)hydrazinecarboxamide with 2-naphthaldehyde towards some transition metal ions, which may help in more understanding of the mode of chelation of Schiff base ligand towards metals. For this purpose the complexes of Cu(II), Co(II), Ni(II) and Zn(II) ions with Schiff base ligand are studied. The structures of the newly synthesized compounds are studied using elemental analyses, IR, MS, ¹H NMR, magnetic moment and molar conductance data and also studied their antimicrobial activity.

II. Material And Methods

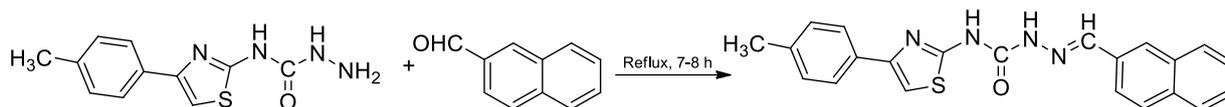
2.1. Analysis and physical measurement

Microanalysis (C, H and N) were performed on a Vario EL III CHNS analyser. IR spectral data were recorded on a Perkin Elmer Spectrum RX-I FTIR spectrophotometer. ¹H NMR spectra 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 source. The UV-Visible spectra were recorded on a ELICO SL-164 double beam UV-Visible spectrophotometer.

All the reagents used for the synthesis of ligand (**L**) were obtained from Sigma Aldrich chemical company, India. Metal salts were purchased from Loba Chemie. The metal and chloride contents of the complexes were determined as per standard procedures [6]. The precursor N-(4-(p-tolyl) thiazol-2-yl)hydrazinecarboxamide was prepared by the literature method [7,8].

2.2. Synthesis of Schiff base ligand (**L**)

An equimolar mixture of N-(4-(p-tolyl)thiazol-2-yl)hydrazinecarboxamide (0.001 mol) and 2-naphthaldehyde (0.001 mol) in ethanol (25 mL) was refluxed with a catalytic amount of glacial acetic acid (1-2 drops) for about 5-6 h on a water bath. The pale yellow coloured product which separated in hot was filtered off, washed with hot ethanol, dried and recrystallized from 1, 4-dioxane (**Scheme 1**).



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

2.3. Synthesis of metal (II) complexes

To the hot solution of ligand (**L**) (0.001 mol) in ethanol (20 mL) was added a hot ethanolic solution (20 mL) of respective metal chlorides (0.001 mol). The reaction mixture was then refluxed on a water bath for about 6-7 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.

2.4. Antimicrobial assay

The newly synthesized compounds were screened for their antibacterial and antifungal activities by the Muller-Hinton agar and potato dextrose media respectively by agar well dilution method. The in vitro antibacterial activity of the test compounds was tested against two Gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis* and in vitro antifungal activity was carried out against *Aspergillus flavus* and *Aspergillus niger*. 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⁻¹) 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 (100, 75, 50, 25 and 12.5 µg mL⁻¹), were prepared by diluting the stock solutions with the required volume of freshly distilled DMSO. The MIC of each test compounds was recorded as the lowest concentration of compound with no visible growth. The experiment done in triplicate and the average values were calculated.

III. Results And Discussion

3.1. Chemistry

The metal complexes are colored solids, stable at room temperature and possess high melting point (>300 °C). 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 (**Table 1**) agree well with the suggested composition of ligand and its metal complexes. The results of conductivity measurements are too low to account for any dissociation of the complex in DMF (17-22 ohm⁻¹ cm² mole⁻¹). Hence, the complexes may be regarded as non-electrolytes.

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

Compound	M.W.	M.P. (°C)	Elemental Analysis, found (Calc.) [%]					λ_m	μ_{eff} (BM)
			C	H	N	M	Cl		
C ₂₂ H ₁₈ N ₄ OS (L)	386	263	68.36 (68.24)	4.62 (4.82)	14.24 (14.21)	--	--	--	--
[Cu(L) ₂ Cl ₂]	905.11	>300	58.10 (58.76)	4.36 (4.76)	12.12 (12.04)	7.07 (7.35)	7.85 (7.36)	18	1.81
[Co(L) ₂ Cl ₂]	901.11	>300	58.46 (58.94)	4.80 (4.82)	12.89 (12.11)	6.88 (6.06)	7.24 (7.64)	22	4.74
[Ni(L) ₂ Cl ₂]	900.11	>300	58.91 (58.49)	4.36 (4.78)	12.26 (12.32)	6.39 (6.47)	7.31 (7.41)	19	2.92
[Zn(L) ₂ Cl ₂]	906.11	>300	58.09 (58.65)	3.70 (3.45)	12.18 (12.49)	7.15 (7.34)	7.14 (7.94)	17	Dia.

3.2. IR spectral studies

The IR bands of ligand (**L**) were compared with those of the newly synthesized complexes in order to establish 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 2**.

The IR spectrum of ligand (**L**) showed medium intensity weak bands at 3227 cm⁻¹ and 3051 cm⁻¹ due to amide NH and NH attached to the thiazole moiety respectively. The high intensity strong bands observed at 1681 cm⁻¹ and 1584 cm⁻¹ are due to carbonyl function $\nu(\text{C}=\text{O})$, and azomethine function $\nu(\text{C}=\text{N})$ respectively. The IR spectra of the metal complexes exhibited ligand bands with the appropriate shifts due to complex formation. In the IR spectra of the metal complexes, medium intensity weak bands at 3228-3249 cm⁻¹ and 3049-3056 cm⁻¹ were due to amide NH and NH attached to thiazole moiety respectively, which appeared almost at about the same position as in the case of ligand, thus confirming their non-involvement in coordination. The shift of amide carbonyl $\nu(\text{C}=\text{O})$ to lower frequency side about 28-36 cm⁻¹ and which appeared in the region

1645-1653 cm^{-1} in all the complexes confirms the coordination of oxygen atom of amide $\nu(\text{C}=\text{O})$ with the metal ions as such without undergoing enolization [9]. The absorption frequency due to azomethine $\nu(\text{C}=\text{N})$ function also shifted to lower frequency side about 18-54 cm^{-1} and appeared in the region 1530-1566 cm^{-1} suggesting the involvement of nitrogen atom of azomethine function in complexation with metal ions [10].

The coordination of metal ions with ligand was further confirmed by the appearance of new weak intensity, non-ligand bands in the region 495-586 cm^{-1} , 436-467 cm^{-1} and 364-396 cm^{-1} in the IR spectra of the complexes are assigned to frequencies of $\nu(\text{M}-\text{O})$, $\nu(\text{M}-\text{N})$ and $\nu(\text{M}-\text{Cl})$ stretching vibration respectively [11].

Table 2: IR spectral data of Schiff base ligand (L) and its metal (II) complexes

Compounds	Amide	Thiazole	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$	$\nu(\text{M}-\text{O})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{Cl})$
	$\nu(\text{NH})$	$\nu(\text{NH})$					
$\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$ (L)	3227	3051	1681	1584	--	--	--
$[\text{Cu}(\text{L})_2\text{Cl}_2]$	3234	3055	1651	1566	495	436	365
$[\text{Co}(\text{L})_2\text{Cl}_2]$	3230	3054	1645	1532	586	456	367
$[\text{Ni}(\text{L})_2\text{Cl}_2]$	3249	3049	1653	1530	498	467	396
$[\text{Zn}(\text{L})_2\text{Cl}_2]$	3228	3056	1651	1541	546	437	364

3.3. ^1H NMR spectral studies

The ^1H NMR spectrum of ligand (L) displayed two singlets each at 11.28 and 10.89 ppm are due to the proton of amide NH and NH attached to thiazole moiety respectively. The signal due to azomethine proton ($\text{CH}=\text{N}$) resonated at 9.15 ppm. The signals due to twelve aromatic protons (ArH) have resonated as multiplets in the region 7.12-7.98 ppm and signal at 3.18 ppm is due to three protons of methyl group of thiazole moiety respectively. In the Zn(II) complex, the signals due to amide NH and NH attached to thiazole are appeared in the region 10.49 ppm and 11.23 ppm respectively. The signal due to azomethine proton ($\text{CH}=\text{N}$) resonated at 9.45 ppm. The signals due to nine aromatic protons (ArH) have resonated as multiplets in the region 7.42-8.14 ppm and signal at 3.34 ppm are due to three protons of methyl group of thiazole moiety respectively.

When compared to the ^1H NMR spectral data of ligand (L) and its $[\text{Zn}(\text{L})_2\text{Cl}_2]$ complex, all the signals due to protons have been shifted towards down field strength confirming the complexation of Zn(II) ion with the ligand. Thus, the ^1H NMR spectral results further supports the IR spectral inferences and complexation of Zn(II) ion with ligand.

3.4. ESI-mass spectral studies

The mass spectra of $[\text{Cu}(\text{L})_2\text{Cl}_2]$, $[\text{Co}(\text{L})_2\text{Cl}_2]$ and $[\text{Zn}(\text{L})_2\text{Cl}_2]$ complexes showed a molecular ion peaks recorded at m/z 905, 907, 909 (7%, 3%, 1%), m/z 901, 903, 905 (20%, 11%, 5%) and m/z 906, 908, 910 (16%, 10%, 6%) respectively which are equivalent to their molecular weights.

3.5. Electronic spectral studies

The $[\text{Cu}(\text{L})_2\text{Cl}_2]$ complex showed a low intensity single broad asymmetric band in the region 16126-17034 cm^{-1} . The broadness of the band designates the three transitions $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$ (ν_1), $^2\text{B}_{1g} \rightarrow ^2\text{B}_{2g}$ (ν_2) and $^2\text{B}_{1g} \rightarrow ^2\text{E}_g$ (ν_3), which are similar in energy and give rise to only one broad absorption band and the broadness of the band may be due to dynamic Jahn-Teller distortion. All of these data suggested a distorted octahedral geometry around the Cu(II) ion [12].

The electronic spectra of $[\text{Co}(\text{L})_2\text{Cl}_2]$ complex displayed two absorption bands at 17390 cm^{-1} and 19928 cm^{-1} . These bands are assigned to be $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{A}_{2g}(\text{F})$ (ν_2) and $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{T}_{2g}(\text{P})$ (ν_3) transitions respectively, which are in good agreement with the reported values [13]. The lowest band, ν_1 could not be observed due to the limited range of the instrument used, but it could be calculated using the band fitting procedure suggested by Underhill and Billing [14]. The obtained transition values of ν_1 , ν_2 and ν_3 suggest the octahedral geometry of the Co(II) complex.

The $[\text{Ni}(\text{L})_2\text{Cl}_2]$ complex under present study exhibited two absorption bands in the region 14965 cm^{-1} and 25382 cm^{-1} , which are assigned to $^3\text{A}_{2g} \rightarrow ^3\text{T}_{1g}(\text{F})$ (ν_2) and $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{P})$ (ν_3) transitions respectively in an octahedral environment. The transition value of band ν_1 was calculated by using a band fitting procedure [14].

3.6. Magnetic susceptibility studies

For $[\text{Cu}(\text{L})_2\text{Cl}_2]$, $[\text{Co}(\text{L})_2\text{Cl}_2]$ and $[\text{Ni}(\text{L})_2\text{Cl}_2]$ complexes, the magnetic susceptibility measurements were carried out and they were found to be paramagnetic in nature. The observed magnetic moment value for $[\text{Cu}(\text{L})_2\text{Cl}_2]$ complex is 1.81 BM. The observed value is slightly higher than the spin-only value due to one unpaired electron 1.73 BM, suggesting the octahedral geometry [15]. Thus, in the present $[\text{Co}(\text{L})_2\text{Cl}_2]$ complex is devoid of any spin interaction with distorted octahedral geometry. In octahedral $[\text{Co}(\text{L})_2\text{Cl}_2]$ complex the ground state is $^4\text{T}_{1g}$. A large orbital contribution to the singlet state lowers the magnetic moment values for the various

[Co(L)₂Cl₂] complexes which are in the range 4.12-4.70 for tetrahedral and 4.70-5.20 BM for octahedral geometry of the complexes respectively [16]. In the current study the observed magnetic moment value for [Co(L)₂Cl₂] complex is 4.74 BM which suggests the octahedral geometry. The observed magnetic moment value for [Ni(L)₂Cl₂] complex is 2.92 BM, which is well within the expected range of 2.83 - 3.50 BM, suggesting the consistency with its octahedral environment of [Ni(L)₂Cl₂] complex [17].

3.7. ESR spectral study of [Cu(L)₂] complex

In the present study the observed measurements for [Cu(L)₂Cl₂] complex is $g_{||}$ (2.23) > g_{\perp} (2.26) > 2.0023 indicate that the complex is axially symmetric and copper site has a $d_{x^2-y^2}$ ground state characteristic of octahedral geometry [18]. The $g_{||}$ value is an important function for indicating the metal-ligand bond character, for covalent character $g_{||} < 2.3$ and for ionic character $g_{||} > 2.3$ respectively [19]. In the present study the $g_{||}$ value of [Cu(L)₂Cl₂] complex is less than 2.3, indicating an appreciable covalent character for the metal-ligand bond. The geometric parameter (G) is the measure of extent of exchange interactions and is calculated by using g -tensor values by the expression $G = g_{||} - 2.0023/g_{\perp} - 2.0023$. According to Hathaway and Billing [20], if the G value is greater than 4, the exchange interaction between the copper centres is negligible, whereas if its value is less than 4 and the exchange interaction is noticed. In present observations the calculated G value for the [Cu(L)₂Cl₂] complex is 5.23, indicate the exchange coupling effects are not operative in [Cu(L)₂Cl₂] complexes.

3.9. Powder X-ray diffraction studies (Powder-XRD)

The newly synthesized metal complexes were soluble in some polar organic solvents like DMSO and DMF, crystals that are suitable for single crystal studies are not obtained. The powder X-ray diffraction pattern of [Cu(L)₂Cl₂] complex is scanned in the range 3-60° (θ) at wave length 1.54 Å. The diffractogram and associated data depict the 2θ value for each peak, relative intensity and inter-planar spacing (d-values). Powder X-ray diffraction pattern of [Cu(L)₂Cl₂] complex displayed a 7 reflections with maxima at $2\theta = 32.129^\circ$ corresponding to d value 2.125 Å. The inter-planar spacing (d) has been calculated by using Bragg's equation, $n\lambda = 2d \sin\theta$. The unit cell calculations have been calculated for the entire complex from the entire important highly intense peaks and $h^2 + k^2 + l^2$ values were determined. The observed inter-planar d-spacing values have been compared with the calculated ones and it was found to be in good agreement with observed values. The $h^2+k^2+l^2$ values of [Cu(L)₂Cl₂] complex are 1, 5, 8, 12, 1, 28 and 32. The calculated lattice parameter for [Cu(L)₂Cl₂] complex is $a=b=c=13.451$. It was observed that the presence of forbidden number 15 indicates that the complex may belong to hexagonal or tetragonal systems.

3.10. In vitro antimicrobial results

The antimicrobial activity was found to be enhanced on coordination with metal ions. This enhancement in the antimicrobial activity of the complexes over the free ligand can be explained on the basis of chelation theory [21, 22]. The enhancement in the antimicrobial activity may be rationalized on the basis that ligands mainly possess azomethine (C=N) bond. More over in metal complex, the positive charge of the metal ion is partially shared with the hetero donor atoms (N and O) present in the ligand and there may be π -electron delocalization over the whole chelating system [23]. Hence the increase in the lipophilic character of the metal chelates favour its permeation through the lipid layer of the bacterial membranes and blocking of the metal binding sites in the enzymes of microorganisms. In general, metal complexes are more active than the ligands because metal complexes may serve as a vehicle for activation of ligands as the principal cytotoxic species [24, 25]. The minimum inhibitory concentration (MIC) values of the compounds against the respective bacterial and fungal strains are summarized in **Table 5**.

Table 5: MIC values of Schiff base ligand (L) and its metal (II) complexes

Compounds	Bacteria		Fungi	
	S. aureus	B. subtilis	A. flavus	A. niger
C ₂₂ H ₁₈ N ₄ O ₅ (L)	50	75	75	50
[Cu(L) ₂ Cl ₂]	50	50	50	25
[Co(L) ₂ Cl ₂]	50	25	75	50
[Ni(L) ₂ Cl ₂]	25	25	50	25
[Zn(L) ₂ Cl ₂]	50	50	25	75
Gentamicin	12.50	12.50	--	--
Fluconazole	--	--	12.50	12.50

IV. Conclusion

A series of Cu(II), Co(II), Ni(II) and Zn(II) complexes were prepared with bidentate ON donor Schiff base ligand (L) derived from N-(4-(p-tolyl)thiazol-2-yl)hydrazinecarboxamide and 2-naphthaldehyde and characterized them by various spectral techniques. Spectral analysis indicates octahedral geometry for all the

complexes. The antimicrobial activity results showed that all the newly synthesized metal (II) complexes have exhibited good activity when compared to the free ligand. From all these general observations, it was resolved that the ligand (L) and its metal complexes provided the valuable information of coordination compounds.

Acknowledgements

Authors are thankful to Chairman BVV Sangha's Bagalakot, Principal and HOD, Department of Chemistry, Basaveshwar Science College Bagalakot and UGC New Delhi for financial assistance. Authors are also thankful to SAIF Punjab University, IIT Bombay, STIC Cochin University, for providing spectral data.

References

- [1]. Y. Shibuya, K. Nabari, M. Kondo, S. Yasue, K. Maedo, F. Uchida, H. Kawaguchi, *J. Chem. Lett.* 37 (2008) 78. *Int. J. Electrochem. Sci.*, 8, 2013 (11876)
- [2]. M. Bera, U. Mukhopadhyay, D. Ray, *Inorg. Chem. Acta* 358, 2008, (437).
- [3]. L. A. Saghatforoush, F. Chalabian, A. Aminkhani, G. Karimnezhad, S. Ershad, *Eur. J. Med. Chem.* 44, 2009 (4490).
- [4]. D.P. Singh, R. Kumar, J. Singh, *Eur. J. Med. Chem.* 44, 2009, (1731).
- [5]. G.Y. Nagesh, U.D. Mahadev and B.H.M. Mruthyunjayaswamy, *Int. J. Pharm. Sci. Rev. Res.*, 31, 2015 (190).
- [6]. J. Mendham, R.C. Denney, J.D. Barnes, M.J.K. Thomas, *Vogel's Quantitative Chemical Analysis*, sixth ed., Prentice Hall, London, 2000.
- [7]. G.Y. Nagesh, K. Mahendra Raj, B.H.M. Mruthyunjayaswamy, *J. Mol. Struct.* 1079, 2015 (423).
- [8]. B.H.M. Mruthyunjayaswamy, S.M. Basavarajiah, *Indian. J. Chem. Sec B.* 48, 2009 (1274)
- [9]. S. Roy, T.N. Mandal, K. Das, R.J. Butcher, A.L. Rheingold, S.K. Kar, *J. Coord. Chem.* 63, 2010 (2146).
- [10]. S. Chandra, L.K. Gupta, *Spectrochim. Acta. Part A.* 62, 2005 (1102).
- [11]. N.G. Yernale, B.H.M. Mruthyunjayaswamy, *Bioinorg. Chem. Appl.* 2014, 2014 (1).
- [12]. H. Liu, H. Wang, F. Gao, D. Niu, Z. Lu, *J. Coord. Chem.* 60, 2007 (2671).
- [13]. R.A. Rai, *J. Inorg. Nucl. Chem.* 42, 1980 (450).
- [14]. A.E. Underhill, D.E. Billing, *Nature*. 210, 1966 (834).
- [15]. D.P. Singh, R. Kumar, V. Malik, P. Tyagi, *Trans. Met. Chem.* 32, 2007 (1051).
- [16]. M.U. Hassan, Z.H. Chohan, C.T. Supuran, *Main. Group. Met. Chem.* 25, 2002 (291).
- [17]. T.R. Rao, P. Archana, *Synth. React. Inorg. Met. -Org. Chem.* 35, 2005 (299).
- [18]. B.T. Thaker, P.K. Tandel, A.S. Patel, C.J. Vyas, M.S. Jesani, D.M. Patel, *Indian J. Chem. Sec. A.* 44A, 2005 (265).
- [19]. D. Kilveson, *J. Phy. Chem. B.* 101, 1997 (8631).
- [20]. B.J. Hathaway, D.E. Billing, *Coord. Chem. Rev.* 5, 1970 (143).
- [21]. Z.H. Chohan, M. Arif, M.A. Akhtar, C.T. Supuran, *Bioinorg. Chem. Appl.* 2006, 2006, (1).
- [22]. G.Y. Nagesh, B.H.M. Mruthyunjayaswamy, *J. Mol. Struct.* 1085, 2015 (198).
- [23]. Z.H.A. Wahab, M.M. Mashaly, A.A. Salman, B.A. El-Shetary, A.A. Faheim, *Spectrochim. Acta. Part A.* 60, 2004 (2861).
- [24]. D.H. Petering, H. Sigel, *Metal Ions in Biological Systems*. Marcel Dekker, New York, 1980.