



Synthesis and Antimicrobial Studies of Cu(II), Ni(II) and Zn(II) Schiff Base Complexes Derived from Substituted 1,2,4-Triazoles and Heteroaromatic Aldehydes

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The 1,2,4-triazole containing Schiff base metal complexes were prepared by condensation with some heterocyclic aldehydes. The synthesized Schiff bases and their metal complexes were characterized by elemental analysis, UV-visible, FT-IR, ¹H NMR and physical measurements. The IR spectra indicate the bidentate behaviour of the ligand towards the divalent metal ions *via* one azomethine-N and the sulfur atom of the thiol group. The magnetic moments and electronic spectral data suggest a square-planar geometry for Cu(II) and Ni(II) compounds and a tetrahedral geometry for Zn(II) complexes. Elemental analyses data of the metal complexes indicate 2:1 molar ratio (ligand:metal) and agree with their proposed structures. The antimicrobial screening results showed that the Schiff bases were bacterial and fungal static agents. The antimicrobial activity was enhanced on coordination with the metal ion. The order of complexes activity was Cu(II) > Ni(II) > Zn(II) complexes. The complexes showed more activity against *A. niger* fungus than bacterial strains.

Key Words: Schiff base complexes, 1,2-4-Triazole, Antimicrobial, Heterocyclic aldehydes.

INTRODUCTION

Schiff base complexes with transition metals have played a prominent role in the development of coordination chemistry^{1,2}. They have been amongst the most widely studied coordination compounds³ due to manifestation of novel structural features⁴ and they play an important role in various biological systems, agricultural, pharmaceutical and industrial chemistry^{3,5}.

During the past few decades, considerable attention has been devoted to synthesize Schiff base complexes possessing comprehensive bioactivities⁵⁻⁹. Various Schiff base metal complexes show different antimicrobial activity with different types of bacteria and fungi.

Many studies showed that the presence of heterocyclic ring in the chelating ligand displays additional significant biological and pharmacological properties and increases the potential activity^{10,11}. The Schiff base ligands containing 1,2,4-triazole nucleus have attracted great and growing interest in coordination chemistry and biology due to their wide applications^{9,12-13}. The 1,2,4-triazole containing compounds of numerous substituents have been shown to exhibit a variety of interesting biological actions, including antibacterial, anti-convulsant, antimicrobial, anticancer, antitubercular and anti-fungal activities¹⁴⁻²¹. The alterations in chemical structure of substituted 1,2,4-triazoles strongly change their activities and

affect their interaction with cells and tissues, thereby leading to different biological effects²². Sahoo *et al.*²³ showed that the 1,2,4-triazoles containing chloro, bromo and trichloromethyl groups are responsible for remarkable antimicrobial activity.

Moreover, the literature survey reported that the complexes containing sulfur atom are bacterial and fungal static agents and there are scanty reports on thio-Schiff bases of this class of ligands having N and S donors^{5,24,25}. Moreover, the interesting pharmacological properties of the thio-Schiff bases are believed to be due to the presence of sulfur²⁶. The Schiff base metal complexes containing N and S chelating ligands have attracted considerable attention because of their interesting physio-chemical properties, pronounced biological activities and as models of the metalloenzyme active sites^{5,26-28}.

From these and related observations it has been suggested that an azomethine linkage is perhaps an essential structural requirement for such activity²⁹. Furthermore, coordination of biological active ligands with metals often results into the formation of compounds of enhanced activity^{6,10,13,30-33}. This may be due to chelation that reduces the polarity of the metal ion and increases the hydrophobic character of the metal chelates and favours the penetration through lipid layers of micro-organism membrane^{13,34-35}. In many cases, the pharmacological activity has been found to be highly dependent on the identity of the metal and the donor sequence of the ligands

with different ligands showing widely different biological activities although they may vary only slightly in their molecular structure; however, the mechanism has yet to be determined. Encouraged by the above interesting structures and biological activities, the present investigation aims at synthesis of Cu(II), Ni(II) and Zn(II) complexes of some bioactive Schiff base ligands and assess their activity against representative bacteria and fungi. This study is mainly pertinent to Schiff base ligands derived from the heterocyclic 3-substituted-4-amino-5-mercapto-1,2,4-triazole and five-membered heterocyclic aldehydes (having S or O as a hetero atom) by template condensation. These ligands have two donor sites of N and S atoms and presence of side bromo group. This nature of ligands attracted our attention because of their expected biological activity that may afford potential therapeutic applications.

EXPERIMENTAL

All the chemicals used in this study were of analytical grade and were used as received without further purification. The precursor substituted 1,2,4-triazoles (4-amino-5-mercapto-3-methyl-1,2,4-triazole and 4-amino-5-mercapto-3-propyl-1,2,4-triazole) were prepared as by the procedures reported previously in the literature^{23,36,37}. The aldehydes 5-bromo-2-thiophene carboxaldehyde, 5-bromo-2-furaldehyde (purchased from Aldrich) and metal(II) acetates (Qualigens Fine Chemicals, India) were of analytical grade and used without purification.

General procedure for preparation of the Schiff base ligands: The general procedure for preparation of the schiff base ligands is as reported in the literature³⁸. To a solution of triazole compound (0.5 mol) in acetic acid (25 mL) was added the appropriate aldehyde (0.5 mol) and the reaction mixture was heated at reflux temperature for 2 h. After cooling, the formed product was collected by filtration and recrystallized. The yield was between 65-75 %. The synthesized Schiff base ligands are shown in Fig. 1.

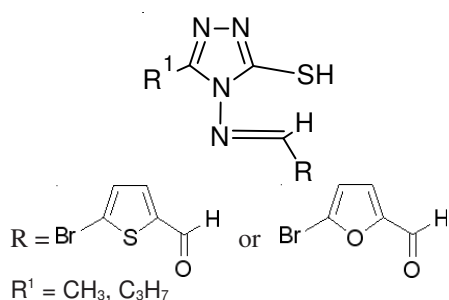


Fig. 1 Schiff base ligands

Preparation of the metal complexes: The general method of preparation of metal complexes used during the course of present investigation is as follows: An ethanolic solution (30 mL) of the corresponding metal acetates (Cu(CH₃COO)₂, Ni(CH₃COO)₂·4H₂O and Zn(CH₃COO)₂·2H₂O) and ethanolic solution (40 mL) of the ligand were reacted in 1:2 (M:L) molar ratio in a round bottom flask. The reaction mixture was refluxed for 5 h with shaking at regular intervals. The coloured products were filtered and being insoluble and non-crystallizable, they were purified by washing thoroughly

with hot water and hot ethanol to remove unreacted metal acetates or the ligand. The percentage of yield was between 60-65 %. The synthesized complexes are shown in Fig. 2.

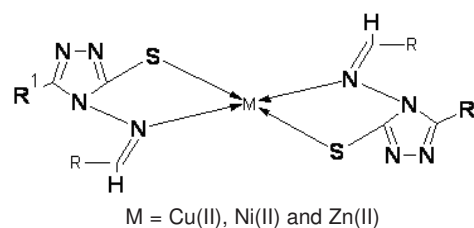


Fig. 2 Schiff base metal complexes

The compounds were analyzed for C, H, N and S using a LECO CHNS-932 and a Perkin-Elmer Plasma 1000 emission spectrometer. The metal contents in the complexes were estimated gravimetrically by standard methods using complexometric titration with EDTA after decomposing with conc. HNO₃ at room temperature³⁹.

IR spectra of the ligands and their metal complexes were recorded on a Perkin-Elmer FTIR spectrophotometer model 1600 using KBr pellets. The Electronic spectra were recorded on a Shimadzu UV-1240 spectrophotometer in using DMSO as solvent. The ¹H NMR spectra were recorded on Hitachi R1200 (60 MHz) NMR spectrometer. Room temperature magnetic susceptibility measurements were made on solid samples, by Gouy method using Hg[Co(SCN)₄] as the calibrant. The molar conductance values of the metal complexes were measured in DMSO solution (10⁻³ M) at room temperature on an Elico digital direct reading conductivity meter model CM-180.

Biological screening activity: The *in vitro* antibacterial activities were tested against Gram positive bacteria *Staphylococcus aureus* and Gram negative *Escherichia coli* as test organism. *Aspergillus niger* fumigate were used for antifungal activities. All the synthesized Schiff bases and their corresponding metal complexes dissolved in DMSO (at concentration of 1 mg/mL) were screened *in vitro* for their biological activity using Agar-well distribution method^{7,40}.

The bacteria were sub-cultured in nutrient agar medium and the fungi were sub-cultured in potato dextrose agar medium. Inoculation of the test strain was done by the Pour-plate technique. Recommended concentration 0.1 mL of the synthetic compounds (1 mg/mL in DMSO) was added into the wells using micropipette. The plates were incubated at 37 °C for the bacteria (24 h) and at 27 °C for the fungi (72 h). The controls were maintained (for each bacterial strain, fungus and each solvent), where 0.1 mL of the pure solvent was inoculated into the well. At the end of the period, the antibacterial and antifungal activity were indicated by the presence of clear inhibition zones around the wells. The complete inhibition zone diameter (mm) was measured using a scale and are summarized in Table-2.

RESULTS AND DISCUSSION

Preparation of the ligands and the complexes: Condensation of the 4-amino-5-mercapto-3-substituted 1,2,4-triazoles with the corresponding aldehydes readily gives rise to the

corresponding Schiff base (Fig. 1). The imines formed were dark orange colour and in nearly low quantitative yields (65-75 %) and are stable at room temperature in solid state. The ligands were soluble in common organic solvents.

Condensation of the ligands-produced in the first step-with the metal salts of Cu(II), Ni(II) and Zn(II) for nearly 5 h give rise to the metal complexes (Fig. 2). The yields (50-65 %) of the complexes were lower than those of the ligands. Further stirring and heating did not increase the yield of the complexes. The low yield of the complexes may be due to the steric hindrance around the coordination center. The complexes were stable at room temperature, non-hygroscopic, insoluble in water and in common organic solvents, but they were soluble in DMF and DMSO solvents.

The results of the elemental analysis are given in Table-1. Elemental analyses of all the ligands and their metal complexes are in very good agreement with calculated values. The data agree well with the formation of (2:1) (ligand:metal) stoichiometry of the type (ML₂). The bidentate nature of the ligands is expected, as the (2:1) ratio of ligand to the metal allows for saturation of the coordination number.

Solution conductivity measurements were performed to establish the charge of the complexes. The molar conductance measurements of the complexes at the concentration of 10⁻³ M in anhydrous DMSO solution were very low and lie within the range of 3.5-11.5 ohm⁻¹ cm² mol⁻¹ (Table-1). These low values indicate that these complexes are non-electrolytes, suggesting that the two molecules of the Schiff base ligands were bonded with the metal ions and the ligand anion moieties are not dissociated in solution⁴¹⁻⁴³.

The IR spectra of the free ligands show characteristic bands in the region 1615-1625 cm⁻¹ due to azomethine group $\nu(\text{C}=\text{N})$. Upon complexation this frequency were shifted to lower region frequencies in all metal complexes by 24-51 cm⁻¹ and appears in the region 1591-1574 cm⁻¹. This shift in the spectra of the complexes indicates the reduction of double bond character of the C=N bond and expected to reduce the electron density on the azomethine link^{5,41}. In addition, it indicates the participation of azomethine nitrogen in the coordination to metal ions and the (M-N) bond formation. The presence of non-ligand band in the far IR spectra of all metal complexes in the region 518-465 cm⁻¹ due to $\nu(\text{M-N})$ is another

indication of the involvement of nitrogen in azomethine group coordination⁵.

The IR spectra of the free ligand shows the presence of a medium-intense band around 2560 cm⁻¹ which is assigned to $\nu(\text{S-H})$ ^{5,14}. Another band at 1160 cm⁻¹ indicates the thione form of the ligand and the presence of $\nu(\text{C}=\text{S})$ ⁴⁴⁻⁴⁵.

The disappearance of the $\nu(\text{S-H})$ band at 2560 cm⁻¹ and the $\nu(\text{C}=\text{S})$ band (1160 cm⁻¹) from the spectra of the complexes and the presence of the new band at nearly 720 cm⁻¹ assigned to $\nu(\text{C-S})$ which confirms coordination through mercapto sulfur atom⁴⁶. Moreover, it indicates the thione \rightleftharpoons thiol tautomerism followed by deprotonation of the thiol group prior to co-ordination and consequent coordination of the sulfure atom^{5,45}. Thus, these ligands behave as NS donor bidentate ligands.

The possible structures of complexes of Cu(II), Ni(II) and Zn(II) ions are presumed by element analysis. The complexes contains two chelating ligand with a ratio of 1:2 (M:L) and no H₂O or solvent, so it is expected to be a tetrahedral or planar structure for the complexes.

The magnetic moment (μ_{eff}) of the Cu(II) complexes was observed in the range of 1.75-1.81 BM (Table-1) are closer to the expected value (1.73 BM) for a simple mononuclear Cu(II) complex. This corresponds to a single unpaired electron with a very slight orbital distribution above spin only value for Cu(II) suggest square-planar geometry^{7,47,48}.

The electronic spectra of the Cu(II) complexes exhibited weak bands in the region 17870-18930, 14960-16230 cm⁻¹ and a strong high energy band at 23865 cm⁻¹ which can be assigned to d-d transitions of the metal ions ${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_{1g}$, ${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_{2g}$ and charge transfer spectra, respectively. This is an indicative of square-planar geometry for the Cu(II) Schiff base complexes^{45,49}.

The electronic spectrum of Ni(II) complexes shows bands at 14720, 20820 and 25160 due to ${}^1\text{A}_{1g} \rightarrow {}^1\text{A}_{2g}$, ${}^1\text{A}_{1g} \rightarrow {}^1\text{B}_{1g}$ and ${}^1\text{A}_{1g} \rightarrow {}^1\text{E}_g$ transitions, respectively, which is consistent with expected square-planar geometry for Ni(II) complexes^{49,50}. The magnetic susceptibility measurements of Ni(II) complexes show that these complexes are diamagnetic. This indicate a singlet ground state term characteristic of square-planar Ni(II) complexes and confirms the square-planar environment around Ni(II) ion⁴².

TABLE-1
ELEMENTAL ANALYSIS OF Cu(II), Ni(II) AND Zn(II) COMPLEXES, MAGNETIC MOMENT AND THEIR MOLAR CONDUCTANCE DATA

Compd. m.f.	Elemental analysis (%): Calcd. (found)					Molar conductance (ohm ⁻¹ cm ² mol ⁻¹)	Magnetic moment (μ_{eff}) (BM)
	M	C	N	H	S		
CuC ₁₂ H ₁₂ N ₈ S ₄ Br ₂	10.25 (9.70)	23.25 (23.70)	18.08 (17.85)	1.94 (2.25)	20.67 (20.90)	9.30	1.75
NiC ₁₂ H ₁₂ N ₈ S ₄ Br ₂	9.55 (9.12)	23.43 (22.90)	18.22 (17.80)	1.95 (2.15)	20.83 (21.20)	6.50	Diamagnetic
ZnC ₁₂ H ₁₂ N ₈ S ₄ Br ₂	10.47 (10.25)	23.20 (23.45)	18.04 (18.25)	1.93 (2.20)	20.62 (20.25)	3.50	Diamagnetic
CuC ₁₂ H ₁₂ N ₈ O ₂ S ₂ Br ₂	10.81 (10.50)	24.52 (25.00)	19.07 (20.24)	2.04 (2.32)	10.89 (11.12)	11.00	1.81
NiC ₁₂ H ₁₂ N ₈ O ₂ S ₂ Br ₂	10.07 (10.45)	24.72 (24.23)	19.23 (19.56)	2.06 (2.40)	10.99 (11.35)	8.50	Diamagnetic
ZnC ₁₂ H ₁₂ N ₈ O ₂ S ₂ Br ₂	11.04 (11.30)	24.45 (24.82)	19.02 (19.15)	2.04 (2.52)	10.87 (11.10)	4.30	Diamagnetic
CuC ₁₆ H ₂₀ N ₈ S ₄ Br ₂	9.40 (9.96)	28.43 (28.20)	16.58 (16.85)	2.96 (3.20)	18.95 (19.22)	10.00	1.78
NiC ₁₆ H ₂₀ N ₈ S ₄ Br ₂	8.75 (9.12)	28.63 (28.55)	16.70 (16.36)	2.98 (2.68)	19.09 (19.63)	7.50	Diamagnetic
ZnC ₁₆ H ₂₀ N ₈ S ₄ Br ₂	9.60 (9.25)	28.36 (28.30)	16.55 (17.14)	2.95 (3.36)	18.91 (19.42)	3.70	Diamagnetic
CuC ₁₆ H ₂₀ N ₈ O ₂ S ₂ Br ₂	9.87 (10.26)	29.84 (30.35)	17.41 (17.55)	3.11 (3.36)	9.95 (10.28)	11.50	1.80
NiC ₁₆ H ₂₀ N ₈ O ₂ S ₂ Br ₂	9.19 (9.43)	30.07 (30.64)	17.54 (17.42)	3.13 (3.25)	10.02 (9.68)	8.00	Diamagnetic
ZnC ₁₆ H ₂₀ N ₈ O ₂ S ₂ Br ₂	10.08 (10.47)	29.77 (30.24)	17.37 (17.76)	3.10 (3.23)	9.92 (10.22)	5.00	Diamagnetic

The Zn(II) complexes show a diamagnetic properties and do not display any *d-d* transitions. The Zn(II) complexes gave only bands in the electronic spectra region, which is attributed to charge transfer⁴². Moreover, based on stoichiometry of these complexes and elemental analysis, they are four coordinated, which could be either tetrahedral or square-planar. However, tetrahedral geometry is the more preferred stereochemistry for these Zn(II) complexes.

The square-planar geometry is preferred by Cu(II) and Ni(II) complexes, because the square-planar geometry is less symmetrical than the tetrahedral geometry and it offers more possibilities for isomerism (*cis*- and *trans* isomers) (Fig. 3). It is worth noting that *cis-trans* isomerism is not possible in the case of tetrahedral complexes. Theoretically, two isomeric forms are possible for the complexes. In the C_{2v} point group, the sulphur atom and the nitrogen of the azomethine assume a *cis* orientation with respect to their counterparts on the second coordination ligand. The orientation of these atoms is *trans* in the form designated as C_{2h} . It is hypothesized that electron-electron repulsion involving lone pairs make the *cis* isomer less energetically favoured and subsequently promote the formation of the more stable *trans* chelate. The examination of IR spectra of the complexes indicate the presence of single stretching bands for M-N vibrations and the M-S bonds in the complexes. Single frequencies would be expected for the symmetrical *trans* isomer, while multiple vibrations would be anticipated for these molecular perturbations in the *cis* form.

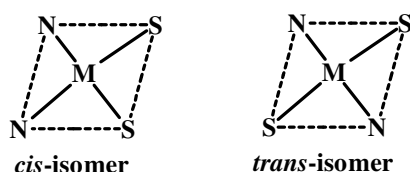


Fig. 3. *cis-trans*-Isomers of the metal complexes

¹H NMR spectra: ¹H NMR spectra of the free Schiff bases and their metal complexes were taken in DMSO. By comparing the chemical shifts of the uncoordinated Schiff bases with those of their corresponding metal complexes, it was found that some of the resonance signals experienced shifting upon coordination. ¹H NMR spectra of the free Schiff base ligands, show a peak in the range 8.12-8.40 ppm assigned for azomethine group (C=N). This was shifted (0.7-1.0 ppm) downfield in the ¹H NMR spectrum of the metal complexes suggesting the shielding of azomethine group due to the coordination with metal ions^{46,51,52}. The ¹H NMR data shows a signal at 9.88 ppm accounted for the -SH protons in the spectrum of the ligands. This signal was absent in all of the complexes indicating the removal of the -SH protons and the formation of M-S bonds^{12,46,53}.

Biological activity: The *in vitro* biological screening results are summarized in Table-2. Bactericidal activities of the ligands and their metal complexes were tested against *S. aureus* (+ve) and *E. coli* (-ve) bacteria. While, fungicidal activity were tested against *A. niger* fungus. The antibacterial and antifungal results revealed that, all the Schiff bases were found to be active against both bacteria strains especially with *E. coli* and the fungus used. The screening data obtained

showed that the metal(II) complexes showed enhanced antibacterial and antifungal activity. It is, however, known that, chelation tends to make the Schiff bases act as more powerful and potent biological static agents, thus inhibiting the growth of bacteria and fungi more than the parent Schiff bases^{6,33}. It is suspected that cell permeability mechanism (influenced by the presence of metal ions) may be the possible reasons for the increase in activity. The N- and S-donor systems might have inhibited enzyme production, since enzymes that require free thiol groups for their activity appear to be especially more susceptible to deactivation by metal ions on coordination¹³. Moreover, coordination reduces the polarity of the metal ions because of the partial sharing of its positive charge with the donor groups within the chelate ring system⁵⁴. This process increases the lipophilic nature of the metal atom, which facilitate their diffusion through the lipid layer of spore membranes to the site of action ultimately destroying the microorganism^{13,34}. The results indicate that among these metal complexes Cu(II) and Ni(II) complexes exhibit relatively more potency compared to Zn(II) complexes (Cu > Ni > Zn). The maximum zone of inhibition was 24 mm for Cu(II)(L₂)₂ against *A. niger* fungus (Table-2).

TABLE-2
RESULTS OF ANTIBACTERIAL AND ANTIFUNGAL
ACTIVITY OF THE EXAMINED COMPOUNDS

Compd.	Antibacterial and antifungal activity (mm/conc. 1 mg mL ⁻¹)		
	<i>S. aureus</i>	<i>E. coli</i>	<i>A. niger</i>
L ₁	16.0	18.0	22.0
L ₂	15.0	18.5	21.0
L ₃	14.5	16.0	17.5
L ₄	14.0	17.0	20.0
Cu(L ₁) ₂	18.0	21.0	24.0
Cu(L ₂) ₂	18.5	20.0	23.0
Cu(L ₃) ₂	16.0	19.0	19.0
Cu(L ₄) ₂	15.0	18.0	21.0
Ni(L ₁) ₂	18.0	17.0	20.0
Ni(L ₂) ₂	17.5	18.0	18.5
Ni(L ₃) ₂	16.0	17.0	19.0
Ni(L ₄) ₂	16.0	17.0	18.5
Zn(L ₁) ₂	15.0	16.5	16.0
Zn(L ₂) ₂	16.0	17.5	18.0
Zn(L ₃) ₂	15.5	16.0	17.0
Zn(L ₄) ₂	15	15	16

*L₁ (R' = CH₃; R = 5-bromo-2-thiophenecarboxaldehyde); L₂ (R' = C₃H₇; R = 5-bromo-2-thiophenecarboxaldehyde); L₃ (R' = CH₃; R = 5-bromo-2-furaldehyde); L₄ (R' = C₃H₇; R = 5-bromo-2-furaldehyde)

In addition, it was observed that compounds with sulfur as heteroatom shows higher activity against all bacterial and the fungus. The ligands and their metal(II) complexes were more potent against fungus than bacteria strains.

Conclusion

We report successfully synthesis and antimicrobial activity of a new Schiff bases containing 1,2,4-triazole moiety and a heterocyclic ring as ligand and their metal complexes with Cu(II), Ni(II) and Zn(II). All metal complexes are slightly soluble in common organic solvents and soluble in DMF and DMSO. The synthesized Schiff bases act as a bidentate ligand through the coordination of azomethine nitrogen and mercaptide sulfur atom to the metal ion. The bonding of ligand to metal

ion was confirmed by the elemental analysis, IR, electronic, magnetic, NMR, thermal and electrochemical studies. All these observations put together lead us to propose the structures shown in Fig. 2 in which, the complex having the stoichiometry of the type ML_2 ($M = Cu(II), Ni(II)$ and $Zn(II)$). It is suggested that $Cu(II)$ and $Ni(II)$ complexes having square-planar geometry, while, $Zn(II)$ complex is of tetrahedral geometry. In biological results it confirms that, all the Schiff bases are biologically active against the tested organisms and their metal(II) complexes are shown to increase the activity than the Schiff bases.

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