



## Synthesis, characterization and anti-microbial activity of transition metal(II) complexes with bidentate (N & S donor) thioamide ligand

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### ABSTRACT

*The bidentate (NS donor) ligand N-(2-pyrimidyl)-quinoline-2-thioamide (L) and its different mixed ligand complexes with transition metal(II) having specific formula  $[ML_2Cl_2]$  have been synthesized under environmentally benign manner using microwave irradiation which is simple, mild and ecofriendly from green chemistry point of view. The investigated complexes have been characterized by elemental analysis, magnetic and conductance measurements, IR and UV-visible spectral studies. All the synthesized complexes were non-electrolyte having octahedral geometry. Antimicrobial study suggests that the metal complexes are better antibacterial agents as compared to the ligand and the antimicrobial activity trend of the investigated complexes is: Cu-complex > Ni-complex > Co-complex > Ligand*

**Keywords:** *anti-bacterial activity, bivalent ligand, Green synthesis, transition metals*

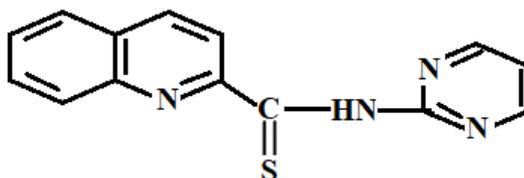
### 1. INTRODUCTION

The synthesis and structural investigations of the transition metal complexes of various ligands are of considerable centre of attention because of their potentially beneficial pharmacological properties and a wide variation in their mode of bonding. To achieve an appropriate balance between the electronic and steric environment around the metal and in order to control their activity, stability and chemo-selectivity, many of these novel metal complexes have been involved with specific ligands. The metal complexes of transition element with heterocyclic ligands, especially those containing nitrogen and sulphur have diverse applications in various fields including biology and anti-herbicidal activities of thioamide ligands and their metal complexes are well known and get more attraction recently. Sulphur and nitrogen donor ligands are also used as powerful pesticides. It is well known fact that N, S and O donor atoms play a prominent key role in the coordination of metal at the activity sites of numerous metallo-biomolecules. Many investigations have proved that binding of drugs to a metallo-element enhances its activity and in some cases complex possess even more healing properties than the parent drugs. Metal complexes offer a platform for the design of novel therapeutic compounds.

The chemistry of thioamides and their derivatives continues to be of interest due to their interesting structural features and also due to their biological importance. Thioamide (rarely named thionamide) is a functional group with the general structure  $R-CS-NR_1R_2$  (H), where R,  $R_1$ ,  $R_2$  are organic groups. These are used in the synthesis of different heterocyclic compounds such as triazoles, thiadiazoles, quinazolines, benzothiazines, benzodiazocines, benzotriazocines, benzothiadiazocines etc. [1-4]. Because of their versatile properties, thioamides are used in rubber vulcanization as accelerators, as inhibitors of metal corrosion, and in electroplating industries as polyolefin stabilizers [4-6]. The thioamide derivatives have shown significant activities such as antibacterial, antifungal, anti-tuberculosis drug, antitumor activity, anti-helminthic activity, thyrotoxic activity; central nervous system depressant etc [7-8].

All these facts motivate our interest in the complex compounds with these heterocyclic ligand. Here we report the synthesis, characterization and antibacterial activities of Co(II), Ni(II) and Cu(II) with the N-(2-pyrimidyl)-quinoline-2-thioamide, (L).

The structure of the N-(2-pyrimidyl)-quinoline-2-thioamide, (L) is given in figure-1.



**Figure-1:** Structure of ligand (L)

## 2. EXPERIMENTAL

### 2.1: Materials and Methods

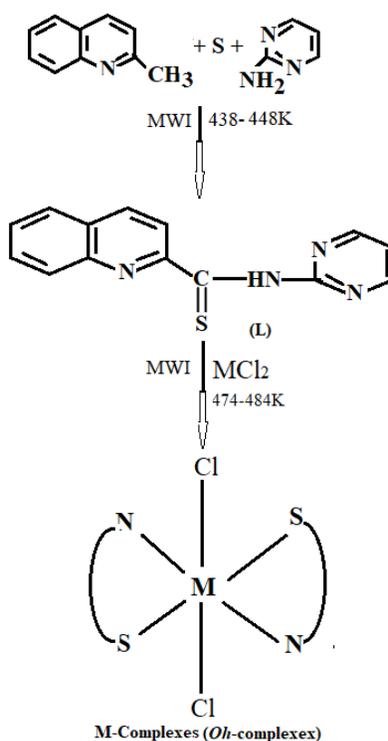
All the chemicals and solvents used for the synthesis were of analytical grade. The solvents were purified by standard methods. The infrared spectra of the ligands and metal complexes were run as KBr discs in the range  $4000-400\text{ cm}^{-1}$  on a Shimadzu Infrared Spectrophotometer. Electronic spectra in the solid state as well as in solution were recorded on a Shimadzu UV-160, UV-visible spectrophotometer. Conductivity measurements of the metal complexes were done in DMF bridge model PW 9501 using Philips PW 9515/10 conductivity cell. Melting points were measured on an Electro-thermal 9100 apparatus and are uncorrected. Elemental analyses were recorded on a Carlo-Erba EA1110CNNO-S analyzer. Magnetic susceptibility of the complexes was carried out by Gouy's method using  $\text{Hg}[\text{Co}(\text{NCS})_4]$  as standard. Microwave assisted synthesis were carried out in open glass vessel on a modified microwave oven model 2001 ETB with rotating tray and a power source 230 V, at output energy of 800W and 2450 MHz frequency. A thermocouple device was used to monitor the temperature inside the vessel of the microwave. The microwave reactions were performed using on/off cycling to control the temperature.

### 2.2: Green Synthesis of Ligand

Ligands were prepared by treating ethanolic solution of 2-aminopyrimidine, pure sulphur and ethanolic solution of quinaldine under microwave irradiation for 5 min. The reaction was completed in a short time (3-5 min) with higher yields showing clear coloured solution. The resulting ligand was then recrystallized with DMF and finally dried under reduced pressure over anhydrous  $\text{CaCl}_2$  in a desiccator. The progress of the reaction and purity of the products were monitored by TLC using silica gel G (yield: 85%)(**Scheme-1**).

### 2.3: Green Synthesis of Metal Complexes

The ethanolic solution of ligand and the M(II) salts were mixed thoroughly in 1:2 (metal: ligand) ratio and then irradiated in the microwave oven by taking 3-4 ml solution. The reaction was completed in a short time (3-5 min.) with higher yields. The resulting coloured products were then recrystallized with ethanol and DMF and finally dried under reduced pressure over anhydrous  $\text{CaCl}_2$  in a desiccator. The progress of the reaction and purity of the product was monitored by TLC using silica gel G (yield: 81-89%) (**Scheme-1**).



**Figure-1:** Green Synthesis of Ligand & Metal Complexes

### 2.4: Biological Evaluation

The *in vitro* biological activity of the investigated ligand (L) and their metal complexes were tested against two bacteria *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Staphylococcus typhi* by disc



diffusion method [9] using nutrient agar as medium. The bacteria were sub-cultured in the agar medium and were incubated for 24h at 37 °C. Standard antibacterial drug (Chloramphenicol) was used for comparison. The discs having a diameter of 4 mm were soaked in the test solutions and were placed on an appropriate medium previously seeded with organisms in petri plates and stored in an incubator at the above mentioned period of time. The inhibition zone around each disc was measured and the results have been recorded in the form of inhibition zones (diameter, mm) showed in Table 4. In order to clarify any effect of DMF on the biological screening [10], separate studies were carried out with solutions alone of DMF and they showed no activity against any microbial strains. The stock solution (1 mg/ml) of the test compounds was prepared in DMF. Each test was performed in triplicate in individual experiments and the average is reported.

### 3. RESULTS AND DISCUSSION

As a result of microwave assisted synthesis, it was observed that the reaction was completed in a short time with higher yields compared to the conventional method. In the microwave method homogeneity of reaction mixture was increased by the rotating of reaction platform tray. The confirmation of the results was also checked by the repeating of the synthesis process. Comparative study results obtained by microwave assisted synthesis; versus conventional heating method is that some reactions which required 2-3 h. by conventional method, was completed within 2-5 min. by the microwave irradiation technique, yields have been improved from 37- 48% to 73- 89%.

Table-1

Comparative results of conventional and microwave methods, analytical and physical data of the compounds under investigation

Complexes (Colour)	(% yield)	MP(°C)	Analysis found (calcd.)					$\lambda_{M*}$ ( $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$ )
			C	H	N	S	M	
Ligand (L) [C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> S] Yellow	89	154	63.45 (63.39)	3.40 (3.39)	21.25 (21.13)	12.10 (12.07)	-	-
[CoL <sub>2</sub> Cl <sub>2</sub> ] [Co(C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> S) <sub>2</sub> Cl <sub>2</sub> ] Brown	86	198	50.95 (50.91)	2.74 (2.73)	16.95 (16.97)	9.72 (9.69)	9.10 (8.93)	15.08
[NiL <sub>2</sub> Cl <sub>2</sub> ] [Ni(C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> S) <sub>2</sub> Cl <sub>2</sub> ] Yellowish brown	84	192	50.95 (50.93)	2.80 (2.73)	16.98 (16.97)	9.72 (9.68)	8.92 (8.89)	14.65
[CuL <sub>2</sub> Cl <sub>2</sub> ] [Cu(C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> S) <sub>2</sub> Cl <sub>2</sub> ] Yellowish green	83	186	50.62 (50.56)	2.74 (2.71)	16.90 (16.85)	9.72 (9.63)	9.60 (9.56)	15.35

\*in 10<sup>-3</sup> DMF solutions at room temperature



All the metal complexes are coloured, solid and stable towards air and moisture at room temperature. They do not possess sharp melting points and decompose on heating at high temperature. The complexes are insoluble in common organic solvents but soluble in DMF and DMSO. The comparative results of conventional and microwave methods, analytical data of the compounds, together with their physical properties are consistent with proposed molecular formula are given in **Table-1**. The micro-analytical data suggest that the composition of all the metal complexes corresponds to 1:2 (metal: ligand) stoichiometry and have one or two water molecules i.e. hydrated. The observed molar conductance values ( $3.5 - 8.4 \text{ ohm}^{-1}\text{cm}^2\text{mole}^{-1}$ ) are too low to account for any dissociation of the complexes in DMF at room temperature, indicating non-electrolytic nature of the complexes [11].

### 3.1: IR Spectral Studies

The data of the IR spectra of investigated Schiff base ligands and their metal complexes are listed in **Table-2**. The IR spectra of the complexes were compared with those of the free ligand in order to determine the involvement of coordination sites in chelation. Characteristic peaks in the spectra of the ligand and complexes were considered and compared. The FT-IR spectra of the investigated complexes contained all the absorption bands from the ligands and some new absorption bands indicative of coordination of the ligands with metal ion through N & S.

In literature it is stated that thioamide forms a complex vibrational group with four characteristic bands in the  $1600 - 600 \text{ cm}^{-1}$  domain [12-13]. In the spectrum of the free ligand the band at  $3452 \text{ cm}^{-1}$  characteristic for  $\nu(\text{NH})$  and at  $1583 \text{ cm}^{-1}$  assigned to  $\delta(\text{NH})$  appear in the spectra of the complexes at lower frequencies. These changes suggest that the nitrogen atom of the -NH- group is involved in the coordination of the ligand to the metallic ion. Changes of the ligand spectrum upon coordination involve a significant perturbation of the characteristic four bands. So, the thioamide I, II and III bands are displaced towards higher frequencies in the complexes spectra and this suggests that nitrogen and sulphur atoms of the thioamide group are involved in coordination. The thioamide IV band is converted from its clearly resolved components in the uncoordinated ligand into a peak with associated shoulders in the complexes. Modest shifts ( $\pm 10 \text{ cm}^{-1}$ ) together with band-splitting also occur with  $\delta(\text{C-S})$  ( $676 \text{ cm}^{-1}$ ) and  $\pi(\text{C-S})$  ( $530 \text{ cm}^{-1}$ ). In this case, the general indication is one of a significant perturbation in the thione region ( $800 - 500 \text{ cm}^{-1}$ ), thus confirming that the sulphur atom participates in bonding [14]. The new bands at  $430 - 415 \text{ cm}^{-1}$  in the spectra of the metal complexes were assigned to  $\nu(\text{M-N})$  stretching vibrations[15]. Therefore, it is concluded that ligand behaves as a bidentate ligand in all the complexes and that the coordination takes place at the sulphur and nitrogen atoms of the thioamide group.

**Table-2**

**IR data ( $4000 - 400 \text{ cm}^{-1}$ ) of the thioamide (L) and its complexes**

Ligand (L) [C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> S]	[CoL <sub>2</sub> Cl <sub>2</sub> ]	[NiL <sub>2</sub> Cl <sub>2</sub> ]	[CuL <sub>2</sub> Cl <sub>2</sub> ]	Assignments
3456	3442	3442	3442	$\nu_{\text{NH}}$



1625	1625	1625	1625	$\nu_{C=Npy}$
1585	1574	1573	1575	$\delta_{NH}$
1498	1512	1508	1510	Thioamide I $\nu(C-N)+\delta(C-H)$
1325	1330	1332	1333	Thioamide II $\nu(C-N)+\delta(CH)+\nu(C=S)$
1049	1064	1061	1063	Thioamide III $\nu(C-N)+\nu(C=S)$
788	812 720	811 714	792 703	Thioamide IV $\nu_s(C-S)+\nu_{as}(C=S)$
678	662 637	662 633	657 636	$\delta(C-S)$
535	510 525	515 530	515 520	$\pi(C-S)$
-	425	415	425	M-N

### 3.2: Magnetic moment and UV-Vis spectra

Electronic spectra and magnetic measurements were performed in order to obtain information about the geometry of the complexes.

The  $\mu_{eff}$  values of Co(II) and Ni(II) complexes were found to be 5.20 and 3.05, indicating an octahedral geometry around the metal ions and 1.96 B.M. for Cu(II) complex respectively, indicating a distorted octahedral geometry [16-17].

The electronic spectrum of the free ligand contains three absorption bands of different intensities at 34480  $cm^{-1}$ , 29840  $cm^{-1}$  and 26800  $cm^{-1}$ . The first band placed in the UV region is due to a  $\pi \rightarrow \pi^*$  type electronic transition from the aromatic cycles. The remainder absorption bands are due to  $n \rightarrow \pi^*$  electronic transitions. These absorption bands appear in the electronic spectra of metal complexes but at higher frequencies, which means that the ligand is coordinated to the central metallic ion.

The electronic spectrum of Co(II) complex showed bands at 10520 and 19230  $cm^{-1}$  assignable to  ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ , and  ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$  transitions, respectively, which are characteristic to the octahedral configuration [17].

Ni(II) complex exhibited two transitions at 18800 and 21200  $cm^{-1}$  assignable to  ${}^1A_{1g} \rightarrow {}^1A_{2g}$ , and  ${}^1A_{1g} \rightarrow {}^1B_{1g}$  transitions, respectively, which correspond to the octahedral geometry [17].

The UV-Vis spectrum of Cu(II) complex displays a broad band at 18691  $cm^{-1}$  attributable to  ${}^2B_{1g} \rightarrow {}^2A_{1g}$  transition, which favours the distorted octahedral geometry around the central metallic ion [17].



### 3.3: Antibacterial activity

The ligand and its metal complexes were screened for their antibacterial activity and the results are presented in table-3. Comparing the biological activity of the thioamide and its metal complexes with the standard (ciprofloxacin), the following results were obtained: the biological activity of the thioamide was less than that of streptomycin; the biological activity of the metal complexes was higher than that of the free ligand while the biological activity of the metal complexes was less than that of the standard; the biological activity of the complexes follows the order: Cu-complex > Ni-complex > Co-complex > Ligand

. A possible explanation for the increased activity upon chelation is that in the chelated complex, the positive charge of the metal ion is partially shared with the donor atoms of the ligand and a  $\pi$ - electron delocalization occurs over the whole chelate ring, increasing in this way the lipophilic character of the metal chelate and favouring its permeation through the lipid layers of the bacterial membranes and blocking the metal binding sites in the enzymes or microorganism [18]. Other factors such as solubility, conductivity and dipole moment (influenced by the presence of metal ions) may also be the possible reasons for increasing this activity.

**Table-3**

**Anti-microbial activity of ligand (L) and their metal complexes (1-3)**

Compounds	Zone of inhibition in (mm)			
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus typhi</i>
L	19	20	19	20
[CoL <sub>2</sub> Cl <sub>2</sub> ]	21	20	19	20
[NiL <sub>2</sub> Cl <sub>2</sub> ]	22	21	20	21
[CuL <sub>2</sub> Cl <sub>2</sub> ]	22	22	20	21
Ciprofloxacin	23	23	21	22

## 4. CONCLUSIONS

Some new transition metal complexes with a thioamide ligand N-(2-pyrimidyl)-quinoline-2-thioamide (L) were prepared in environmentally benign manner and characterized. The complexes have the following molecular formulae: [ML<sub>2</sub>Cl<sub>2</sub>] where M = Co(II), Ni(II) and Cu(II). The IR spectra indicate ion that the ligand acts in bidentate fashion by bonding to the central metal through the nitrogen and sulphur atoms. Electronic spectra and magnetic measurements gave information about the octahedral geometry of the Co(II) and Ni(II) complexes and Cu(II) complex have a distorted octahedral geometry. The biological activity of all the complexes is higher than that of the free thioamide ligand and follow the order: Cu(II) > Ni(II) > Co(II) > Ligand. This means that the metal chelation significantly affects the antimicrobial behaviour of the organic ligand.



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