

Synthesis, Structural Characterization and Biological Studies of Metal Complexes with (E)-4-oxo-4-(thiazol-2-ylamino)but-2-enoic Acid

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Abstract. Carboxylate functionalized ligand (LH) was synthesized as a result of reaction between maleic anhydride and 2-aminothiazole. This ligand was further reacted with Co(II), Ni(II), Cu(II), Zn(II) and Bi(III) ions to yield respective metal complexes. The structural aspects were studied using FTIR, UV-Visible and ¹H-NMR spectroscopy. Non-electrolytic behavior was revealed by the conductivity measurements. Except Bi(III) being octahedral, all other complexes prepared are tetrahedral in geometry. Ligand (LH) and its metal complexes were also investigated for their in vitro antibacterial and antifungal activities. All the complexes exhibited significant antibacterial activity but non-significant antifungal activity.

Keywords: Aminothiazole, Metal complexes, Spectroscopic characterization, Antibacterial, Antifungal

1. Introduction

An important heterocyclic compound thiazole, is biologically active in many drug structures, for example ritonavir (anti-HIV drug) [1], nitazoxanide (antiparasitic agent) [2], nizatidine (antiulcer agent) [3], etc. It is well reported in literature that thiazole is an important core moiety in the development of drugs and therapeutic agents [4]. A number of aminothiazole such as benzothiazoles [5], phenolic thiazoles [6] and tetrahydrobenzothiazoles [7] are reported as neuroprotective. Moreover, some of thiazole derivatives (pyrimidyl thiazole and ethynyl thiazole) behave as good glutamate receptors against anxiety complaints [8,9].

2-Aminothiazole derivatives have been reported since years for diverse purposes such as dischargeable monoazo dyes [10,11], drugs against peptic ulcer [12], dermatomycoses [13], bronchitis, pneumonia, sinusitis, frangitis [14] and bipolar disorder [15], etc. Considering structure and biological significance of 2-aminothiazole, its reaction with maleic anhydride was carried out to produce ligand (LH), which was further reacted with Co(II), Ni(II), Cu(II), Zn(II) and Bi(III) ions to yield respective metal complexes, whose structural, antibacterial and antifungal activities are part of this manuscript.

2. Materials and methods

2-Aminothiazole (Sigma Aldrich), acetic acid, maleic anhydride (M and B Chem.), methanol, CoCl₂·6H₂O (Uni Chem.), NiCl₂·6H₂O (United Lab.), CuCl₂·2H₂O (Fluka Chemika),

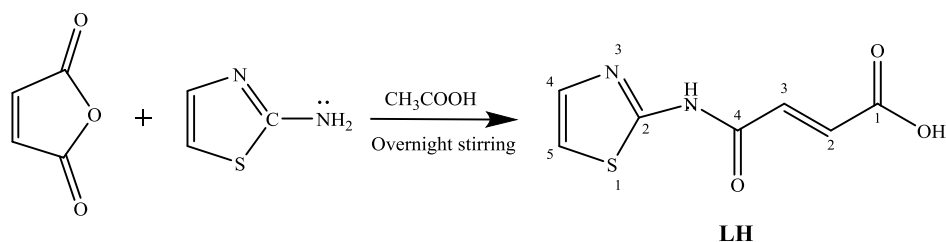
ZnCl₂ (Riedel-de-Haen), BiCl₃ (Beijing Chem.), were purchased and used as such. The use of preoven dried glassware (Make; Pyrex) was ensured for synthetic and screening process.

Synthesis

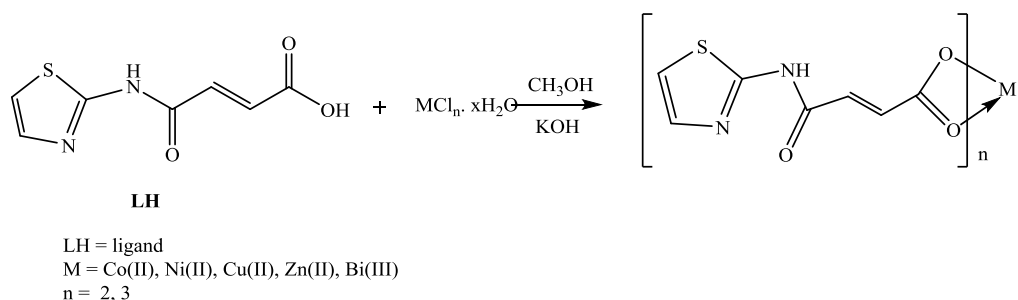
Ligand (LH) was synthesized by following a reported method [16, 17] with minor modifications. The reactants *i.e.* maleic anhydride (4.903 g/5 × 10⁻² mol) and 2-aminothiazole (5.007 g/5 × 10⁻² mol)

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were separately dissolved in glacial acetic acid (10 mL). Then both the solutions were mixed and made to stir overnight at 25°C. Precipitation of pale yellow color occurred and was filtered, washed with glacial acetic acid, n-pentane and subsequently dried for further use.



Scheme 1. Synthetic route of LH



Scheme 2. Synthetic route of -metal complexes

Determination of melting points was done by Gallon Kamp apparatus while UV-visible and FT-IR spectra were obtained by Perkin Elmer multimode T90+ and Cary 630, respectively. Similarly, metal contents were found by Atomic absorption spectrophotometer GBC model 400 XplorAA Dual. Conductivity meter Cond 720 was used to measure electrical conductivity. Five bacterial stains *Bacillus subtilis*, *Staphylococcus aureus* (gram positive), *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* (gram negative), were used to test antibacterial activity of the ligand (LH) and complexes by disc diffusion method. Similarly, fungal stains *i.e.* *Candida albicans*, *Trichophyton rubrum*, *Aspergillus niger*, *Microsporum canis*, *Fusarium lini* were used to find anti-fungal potential of the ligand (LH) and its complexes by agar tube dilution protocol.

3. Results and discussions

The ligand (LH) and its metal complexes were synthesized as outlined in Schemes 1 and 2. Both, the ligand (LH) and metal complexes were obtained in appreciable to good yield and are stable towards air. These are good soluble in common organic solvents but best soluble in DMF and DMSO (Table 1). Conductometric data revealed that all the metal complexes are practically non-electrolyte (low molar electrical conductivity with values in the range $1.6 - 7.5 \Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$) [18, 19].

Generally, the resulting metal complexes exhibited tetrahedral geometry except Bi(III)-complex which exhibited octahedral geometry. The geometry of these complexes (electronic spectra) was proposed on the basis metal/ligand ratio elucidated from the data obtained through ICP-MS/AAS and elemental analyses (Table 2).

**Table 1.** Physical characteristics and molar conductivity values of -lh and its metal complexes

Compound	Melting Point(°C)	Color	Conductance ($\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$)	Solubility
LH	78–82	Pale Yellow	-	water, methanol, ethanol, DMSO, DMF, acetone, acetonitrile
[Co(L) ₂]	54–60	Blue	7.49	water, ethanol, DMSO, DMF, acetone, acetonitrile
[Ni(L) ₂]	~58	Light Green	3.08	DMSO, DMF
[Cu(L) ₂]	65–70	Green	1.66	ethanol, DMSO, DMF
[Zn(L) ₂]	140	White	4.76	water, methanol, DMSO, DMF
[Bi(L) ₃]	72–74	Yellow	3.38	methanol, ethanol, DMSO, DMF
Dimethyl formamide (DMF) Dimethyl sulfoxide (DMSO)				

Table 2. Chemical composition of ligand (LH) and its complexes

Compound	C (%) Calc. (Found)	H (%) Calc. (Found)	N (%) Calc. (Found)	Metal(%) Calc. (Found)
LH	42.42 (41.12)	3.05(2.78)	14.13(12.79)	-
[Co(L) ₂]	37.09(36.17)	2.22(1.89)	12.36(11.31)	13.00(12.76)
[Ni(L) ₂]	37.11(36.65)	2.22(2.01)	12.37(11.76)	12.95(12.62)
[Cu(L) ₂]	36.72(35.22)	2.20(1.76)	12.24(11.56)	13.88(13.23)
[Zn(L) ₂]	36.57(34.88)	2.19(1.97)	12.19(11.09)	14.22(13.57)
[Bi(L) ₃]	31.51(31.11)	1.87(1.67)	10.50(9.21)	26.10(25.30)

UV–Visible electronic spectra

UV–Visible spectrum of Ligand (LH) showed a peak at 280 nm which can be assigned to $\pi\text{-}\pi^*$ transition. The electronic spectrum of the Co(II)-complex suggests tetrahedral configuration for the complex; the spectrum shows a broadband around 17950 cm^{-1} (557 nm) assignable to $^4\text{A}_2(\text{F}) \rightarrow ^4\text{T}_1(\text{P})$ transition of tetrahedral cobalt(II); the magnetic moment value (4.18 B.M.) and the blue color of the cobalt(II) complex, also suggest tetrahedral stereochemistry [20]. The spectrum of the Ni(II) complex, exhibits one band at 15128 cm^{-1} (661 nm) assigned to $^3\text{T}_1(\text{F}) \rightarrow ^3\text{T}_1(\text{P})$ transition in a tetrahedral geometry around Ni(II) ion [21]; the value of magnetic moment (3.72 B.M.) falls in the range reported for tetrahedral geometry around a Ni(II) ion [21]. Cu(II) ions in the tetrahedral ligand

fields do not show any electronic absorption band in the region $20000 - 12500 \text{ cm}^{-1}$; however, the [Cu(L)₂] complex shows broad band at $\approx 25000 \text{ cm}^{-1}$; this can be assigned to charge transfer. Since no spectral bands are present in the range $20000 - 12500 \text{ cm}^{-1}$, the complex Cu(II) is expected to have a distorted tetrahedral stereochemistry; the magnetic moment value of (1.98 B.M.) also supports the tetrahedral geometry of Cu(II) complex [22]. In the spectrum of the [Zn(L)₂] complex is revealed an intense absorption at 24096 cm^{-1} (415 nm); assigned to the charge transfer transition $\text{L} \rightarrow \text{M}$ and the complex is diamagnetic [23]. From the electronic spectrum of the complex the geometry of the metallic ion cannot be precise but taking in consideration the ligand functions in a bidentate form as well as the tendency of the Zn(II) ion for the tetrahedral stereochemistry in the tetra-coordination complexes, we suggest a tetrahedral configuration [23]. The shifting of bands in Bi(III) complex towards bathochromic region when compared with LH indicate the involvement of ligand (LH) in the chelation with Bi(III) ion [24].

FT-IR spectral analysis

Characteristic bond frequencies between the range $4000 - 700 \text{ cm}^{-1}$, were noted for ligand (LH) and its complexes. FT-IR spectrum of ligand (Figure 1) displaying peaks at 3022 cm^{-1} and 1304 cm^{-1} are assigned to N-H group and C-N group respectively. Similarly, the peaks at 1512 cm^{-1} and 1351 cm^{-1} are the depiction of carboxylate moiety in LH, assigned to asymmetric and symmetric vibrations, respectively. The presence of these peaks in (LH) supports its recommended structure. The contribution of COO^- moiety was clearly noted in favor of proposed structures, on comparing the shifts in spectra of LH and its complexes [25]. The difference ($\Delta\nu$) of $\nu(\text{COO})_{\text{asym}}$ and $\nu(\text{COO})_{\text{sym}}$ was observed to be $< 200 \text{ cm}^{-1}$, that supports monoanionic bidentate nature of ligand (LH) [26, 27]. No other significant shift was observed in other functional moieties of ligand like C=O and NH, etc.

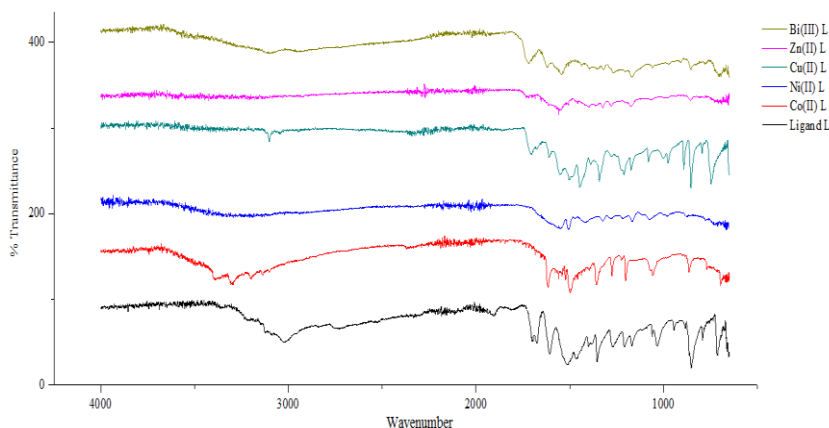
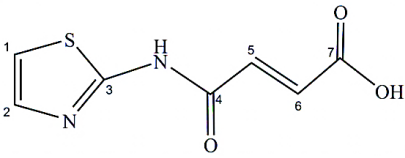


Figure 1. Comparative FT-IR graph of LH complexes

NMR spectra

^1H -NMR spectra of (LH) and $[\text{Zn}(\text{L})_2]$ complex were recorded in DMSO-d_6 (Figures 2 and 3). The ^1H -NMR spectrum of ligand (LH) depicted a broad singlet in the range $12.533\text{--}12.601 \text{ ppm}$ for NH/OH group, two doublets in the range $7.494\text{--}7.503 \text{ ppm}$ and $7.247\text{--}7.256 \text{ ppm}$ that could be attributed to C-H protons (H_1 and H_2) of thiazole ring. Another doublet peak appearing in the range $6.459\text{--}6.466 \text{ ppm}$ can be attributed to the presence of protons H_5 and H_6 in the vicinity of carboxylic group (Table 3). ^1H -NMR spectrum of Zn(II) complex provided fine information about the chemical shifts of protons which is in accordance with proposed monoanionic bidentate mode of ligand. The notable change is the disappearance of $-\text{OH}$ signal at 12.601 ppm indicating its deprotonation and involvement with Zn(II) ion. Similar data were obtained from ^{13}C -NMR spectra. The coordination of metal ion via carboxylate moiety was confirmed by a slight chemical shift shown by its carbon [$\text{C}=\text{O}$, (LH) 176.1 ppm ; $[\text{Zn}(\text{L})_2]$ 174.6 ppm].

Table 3. ^1H -NMR data of ligand (lh) and its zn(ii) complex

Sr. No.	Compound	δ/ppm
1.	Ligand (LH) 	DMSO- d_6 ; AV-400 MHz; $7.494\text{--}7.503$ [(d, 1H, H_1 , (CH-S))]; $7.247\text{--}7.256$ [(d, 1H, H_2 , (CH-N))]; $12.533\text{--}12.583$ [(s, 1H, NH)]; $6.459\text{--}6.466$ [(d, 2H, H_5 and H_6 , (CH=CH))]; 12.601 [(s, 1H, OH)].
2.	$[\text{Zn}(\text{L})_2]$	DMSO- d_6 ; AV-400 MHz; $6.603\text{--}6.612$ [(d, 1H, H_1 , (CH-S))]; $6.923\text{--}6.933$ [(d, 1H, H_2 , (CH-N))]; 7.237 [(s, 1H, NH)]; $6.010\text{--}6.021$ [(d, 2H, H_5 and H_6 , (CH=CH))].

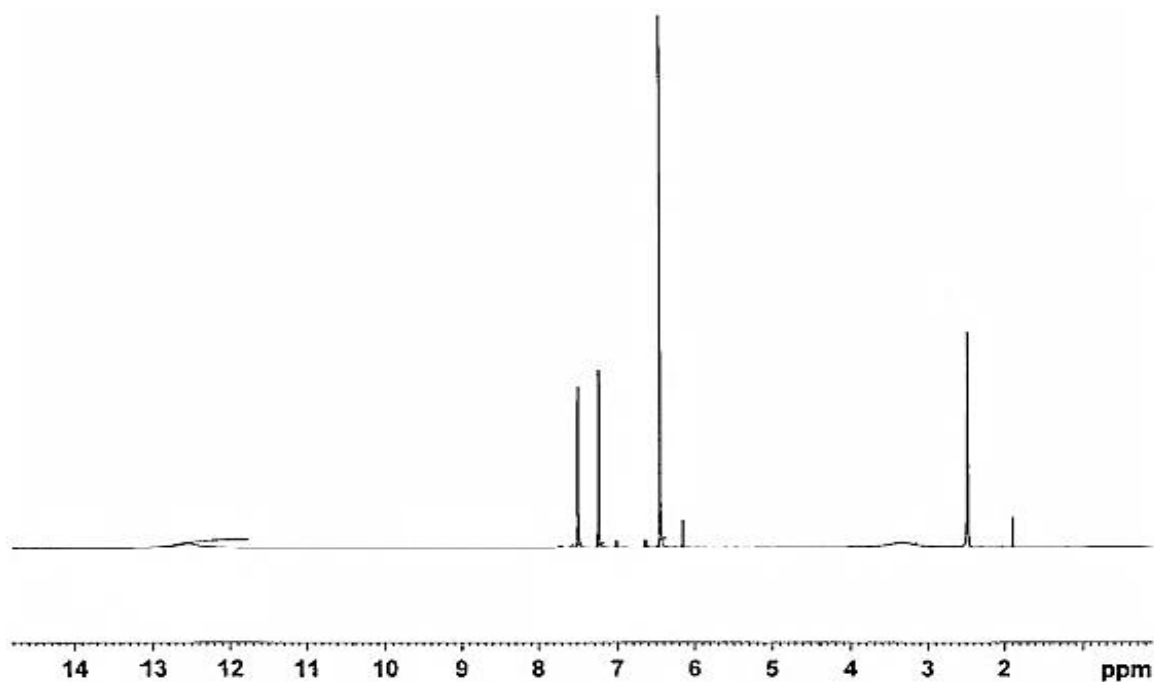


Figure 2. ^1H NMR spectrum of ligand (LH)



Figure 3. ^1H NMR spectrum of $\text{Zn}(\text{L}_2)$ complex

Biological studies

Antibacterial and antifungal studies

Tests against five bacterial strains were conducted for the antibacterial potency of prepared ligand LH and complexes made, using disc diffusion method [27-30]. Among these bacterial strains two were gram positive bacteria such as *Bacillus subtilis*, *Staphylococcus aureus* and three were gram negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi*. Generally metal complexes exhibited non-significant action against most of the bacterial strains except $[\text{Co}(\text{L})_2]$ and $[\text{Zn}(\text{L})_2]$ complexes which exhibited significant activity against *Staphylococcus aureus* (Table 4).

**Table 4.** Data presenting antibacterial potential of LH and its metal complexes

Name of Bacteria	Percent (%) inhibition of drug	Percent (%) inhibition of compound					
		Ligand (LH)	[Co(L) ₂]	[Ni(L) ₂]	[Cu(L) ₂]	[Zn(L) ₂]	[Bi(L) ₃]
<i>Escherichia Coli</i>	86.2	17.5	–	11	–	10	–
<i>Bacillus Subtilis</i>	95.6	15.5	–	–	16.7	–	12.6
<i>Staphylococcus Aureus</i>	93.7	17.0	47.5	–	–	70.5	–
<i>Pseudomonas Aeruginosa</i>	95.5	11.00	–	–	–	–	11
<i>Salmonella Typhi</i>	96.7	13.5	–	7.5	14.5	–	–
Ligand (LH) is (E)-4-oxo-4-(thiazol-2-ylamino)but-2-enoic acid; sign - means No inhibition							

Antifungal potential of ligand (LH) and its metal complexes was investigated against five fungal strains *i.e.* *Fusarium lini*, *Trichophyton rubrum*, *Aspergillus niger*, *Candida albicans* and *Microsporum canis* via agar tube 'dilution' protocol [30]. Preliminary screening of in vitro antifungal bioassay was carried out using 400 µg/mL concentration of each compound (in DMSO) by Agar Tube Dilution Protocol. Minimum inhibitory concentration (MIC) of two drugs was also calculated against each of the five fungi through this protocol. Dilution plates (containing solution of each compound and melted agar) were incubated at 27°C for 7 days in order to ensure growth of fungus. Inhibitory action was determined (as percentage) for each sample against each of the five fungi. The MIC values as determined for LH and metal complexes were in the range 5.6 to 13.5 (Table 5). When compared with MIC values of reference drugs, almost all the metal complexes displayed insignificant activity against several fungal strains.

Table 5. Data presenting antifungal potential of LH and metal complexes

Fungus name	Drug (Standard)	MIC (µg/mL)	Percent (%) inhibition of compound					
			Ligand (LH)	[Co(L) ₂]	[Ni(L) ₂]	[Cu(L) ₂]	[Zn(L) ₂]	[Bi(L) ₃]
<i>Candida albicans</i>	Miconazole	97.8	10.0	–	–	–	–	–
<i>Trichophyton rubrum</i>	„	113.5	–	–	8.5	–	–	13.5
<i>Microsporum canis</i>	„	98.1	5.8	–	11	–	–	5.6
<i>Fusarium Lini</i>		73.50	–	–	–	–	9.5	–
<i>Aspergillus niger</i>	Amphotericin B	20.70	–	–	–	–	12.4	–
The minimum inhibitory concentration (MIC) Ligand (LH) means (E)-4-oxo-4-(thiazol-2-ylamino)but-2-enoic acid; Sign - means No inhibition								

4. Conclusions

Ligand (LH) and its five metal complexes containing carboxylate moiety were prepared and characterized. Ligand (LH) behaved in a monoanionic bidentate manner that results into one octahedral and four tetrahedral complexes. Co(II) and Zn(II) complexes exhibited significant antibacterial activity. The incorporation of thiazole moiety in the system together with Co(II) and Zn(II) complexes can be investigated *in-vivo* for further model studies, a step towards development of metal based drugs.



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