



## Antimicrobial applications of Cadmium (II) complexes derived from substituted 1, 8- Naphthyridines: Synthesis, Characterization and effect on Bacterial strains

Sunkari Jyothi\* and B. Radhika

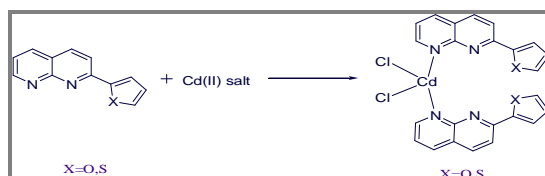
Department of Chemistry, Kakatiya University, Warangal-506 009, **INDIA**  
Email: [jyothisri97@yahoo.co.in](mailto:jyothisri97@yahoo.co.in)

Accepted on 9<sup>th</sup> May, 2019

### ABSTRACT

Two new monomeric Cd(II) complexes of Substituted 1, 8-Naphthyridines with general formula  $[Cd(L)_2Cl_2]$  have been synthesized (where  $L=L_1$  or  $L_2$ ). The structural assignment of complexes thus prepared was based on Elemental analysis, IR, Mass, UV, NMR spectra and thermal analysis. The above studies revealed the tetrahedral geometry around the metal centre. The current compounds were screened for their *in vitro* antimicrobial activity against *Bacillus* and *Pseudomonas* strains, the obtained results shows that complexes exhibit better activity compared to that of free ligand.

### Graphical Abstract



**Keywords:** 1, 8 Naphthyridine derivatives, Cd(II) complexes, spectral studies, Antimicrobial activity.

### INTRODUCTION

1, 8 Naphthyridines (Nap) have received wide attention since being part of many naturally isolated heterocyclics and also exhibit remarkable broad spectrum of biological activities like antibacterial, antitumour, anti-inflammatory activity [1]. Nap and its derivatives are serving in the fertile research field as anti-bacterial agents [2, 3]. Nalidixic acid (1-ethyl-3-carboxy-7- methyl-1,8-naphthyridine-4-one) is the first of its kind being approved as an antibacterial drug [4]. Further Gemifloxacin which belongs to the same group is used to treat acute bacterial chronic bronchitis [5]. Metal ions have a key role to play in different biological processes. Literature survey reveals complexation studies of metals with different Nap containing antibiotic drugs like Enoxacin, Gemifloxacin, cinoxacin, Nalidixic acid etc., enhanced their activity [6-8]. In spite of the toxicity of Cd metal, it is screened for bacteriostatic activity with various quinolones and Nap containing antibiotic drugs since the soft-acid containing metal complexes are more potent antibacterial agents compared to others [9]. Cadmium being a soft

metal ion we have synthesized and characterized new metal complexes from analogues of Nap and evaluated for their anti microbial activity.

## MATERIALS AND METHODS

**Materials and Physical Measurements:** Cadmium metal salt was purchased from Finar and all solvents are of analytical grade and used directly. Elemental analysis was carried out on Elementar Micro Cube instrument. IR spectrum was recorded using PerkinElmer 100S spectrometer ranging from 400-4000  $\text{cm}^{-1}$  with KBr pellets. Electronic Spectra was recorded using DMSO solvent on Cary 5000 UV-Vis-NIR Spectrophotometer from Agilent Technologies. Thermo Gravimetric Analysis was performed using Netzsch STA 2500 Regulus instrument. Nuclear Magnetic Resonance spectra-Proton NMR was recorded using 400 MHz Bruker Avance Resonance Spectrometer.

## RESULTS AND DISCUSSION

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### Synthesis:

**Preparation of Ligand:** The two ligands 2-(furan-2-yl)-1,8-naphthyridine ( $L_1$ ) and 2-(thiophen-2-yl)-1,8-naphthyridine ( $L_2$ ) were synthesized according to the literature procedure [10] by Friedlander condensation of 2- Amino Nicotinaldehyde with corresponding acyl derivatives.

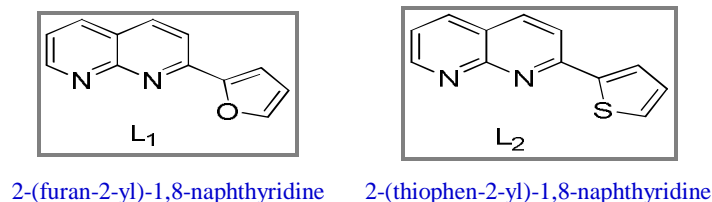
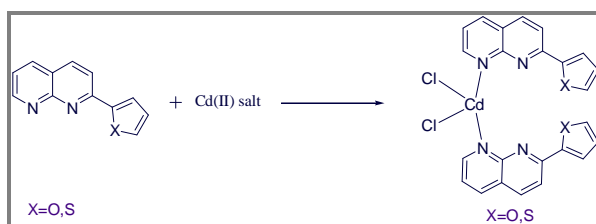


Figure 1. Structures of  $L_1$  and  $L_2$

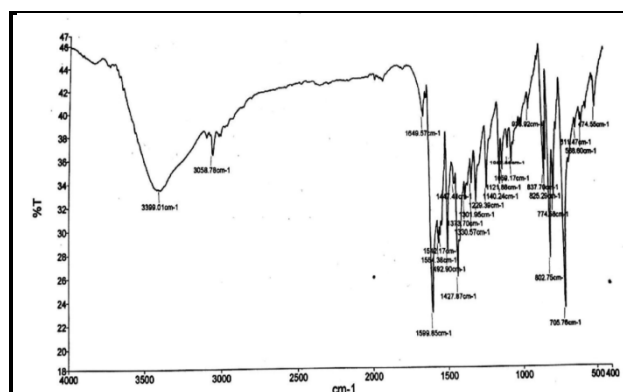
**Preparation of Complexes:**  $[\text{Cd}(L_1)\text{Cl}_2]$  and  $[\text{Cd}(L_2)\text{Cl}_2]$ . The Cd (II) complexes were synthesized by refluxing 0.29 gm (1.5 mmol) methanolic solution of ligand  $L_1$  or 0.31 gm (1.5 mmol) methanolic solution of ligand  $L_2$  with methanolic solution of hydrated cadmium(II) chloride [0.15 gm (0.75 mmol)] in 1:2 molar ratio for 6 h. The solid complexes thus formed were filtered and then washed with hot methanol and dried in vacuo.  $[\text{Cd}(L_1)(\text{Cl})_2]$ :  $\text{C}_{24}\text{H}_{16}\text{N}_4\text{O}_2\text{CdCl}_2$  (**1**): Anal. Found; C, 49.98; H, 2.85; N, 9.69; Cd, 19.60; Calc: C, 50.07; H, 2.80; N, 9.73; Cd, 19.52. ESI MS ( $m/z$ ): 593.11  $[\text{M}+\text{NH}_4]^+$ . IR ( $\text{cm}^{-1}$ ):  $\nu$  3058, 1599, 1554, 1542, 1492, 474. UV-Vis (DMSO)  $\lambda_{\text{max}}$  (nm): 293, 323, 357, 393.  $^1\text{H}$  NMR ( $\delta$ , ppm in DMSO- $d_6$ ): 6.75-6.81 (dd,  $J=1.71, 3.42$  Hz, 2H), 7.47-7.51 (dd,  $J=2.69, 3.67$  Hz, 2H), 7.57-7.64 (dd,  $J=4.15, 8.07$  Hz, 2H), 7.99-8.02 (m, 2H), 8.06 (d,  $J=8.34$  Hz, 3H), 8.44-8.48 (dd,  $J=2.20, 8.07$  Hz, 1H), 8.53 (d,  $J=8.34$  Hz, 3H), 9.05-9.09 (dd,  $J=2.20, 4.40$  Hz, 1H). m.p.  $>300^\circ\text{C}$ ; Yield: 60%.  $[\text{Cd}(L_2)(\text{Cl})_2]$ :  $\text{C}_{24}\text{H}_{16}\text{N}_4\text{S}_2\text{CdCl}_2$  (**2**): Anal. Found; C, 47.46; H, 2.64; N, 9.25; Cd, 18.43; Calc: C, 47.42; H, 2.65; N, 9.22; Cd, 18.49. ESI MS ( $m/z$ ): 630.96  $[\text{M}+\text{Na}]^+$ . IR ( $\text{cm}^{-1}$ ):  $\nu$  2921, 1605, 1555, 1527, 1493, 494. UV-Vis (DMSO)  $\lambda_{\text{max}}$  (nm): 299, 325, 358, 396.  $^1\text{H}$  NMR ( $\delta$ , ppm in DMSO- $d_6$ ): 7.24-7.29 (dd,  $J=3.66, 4.89$  Hz, 2H), 7.57-7.62 (dd,  $J=4.40, 8.31$  Hz, 2H), 7.79-7.84 (dd,  $J=1.22, 4.89$  Hz, 2H), 8.08-8.12 (dd,  $J=1.22, 3.66$  Hz, 2H), 8.24 (d,  $J=8.55$  Hz, 3H), 8.42-8.46 (dd,  $J=2.20, 8.31$  Hz, 1H), 8.50 (d,  $J=8.80$  Hz, 3H), 9.03-9.07 (dd,  $J=1.95, 4.40$  Hz, 1H). m.p.  $>300^\circ\text{C}$ ; Yield: 80%.



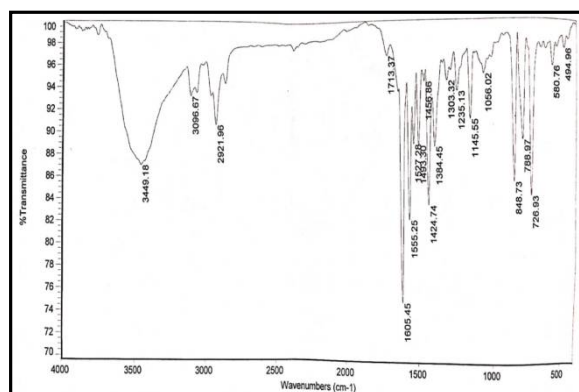
**Scheme 1.** Preparation of Cd(II) complexes.

The synthesized Cd (II) complexes are pale orange colored and non-hygroscopic. They are soluble in DMSO and DMF. The elemental analysis supports the formation of complexes in 1:2 metal, ligand ratio with molecular formulae  $[Cd(L)_2Cl_2]$ , where L may be  $L_1$  and  $L_2$ . From the analytical and spectral data tetrahedral geometry of the complexes is confirmed.

**FTIR, Electronic, NMR and Mass spectral studies:** IR spectrum of ligand and its metal complexes gives information regarding possible sites of ligand co-ordination with metal. IR spectrum has shown several bands for both the ligands in the region of  $1606-1448\text{ cm}^{-1}$  which are attributed to characteristic C=N and C=C ring stretching vibrations where as in the complexes these vibrations occur at  $1605-1492\text{ cm}^{-1}$ . The characteristic aromatic C-H stretching bands appeared at  $3051$  and  $3048\text{ cm}^{-1}$  of  $L_1$  and  $L_2$  were moved to  $3058$  and  $2921\text{ cm}^{-1}$  in the complexes. The formation of complexes was further confirmed by the presence of M-N bands around  $474\text{ cm}^{-1}$  in complex 1 and  $494\text{ cm}^{-1}$  in 2 which were not seen in the ligand spectrum [11] (Figure 2 and 3).

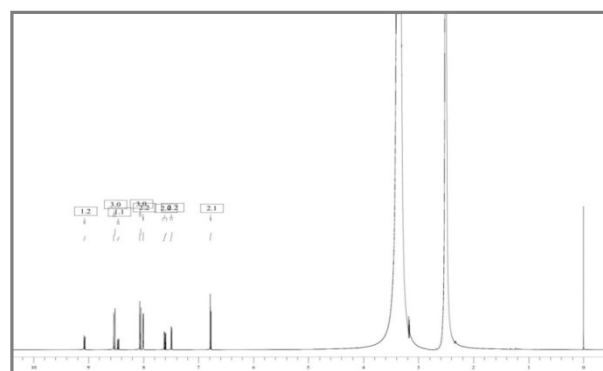


**Figure 2.** IR spectrum of  $[Cd(L_1)Cl_2]$ .

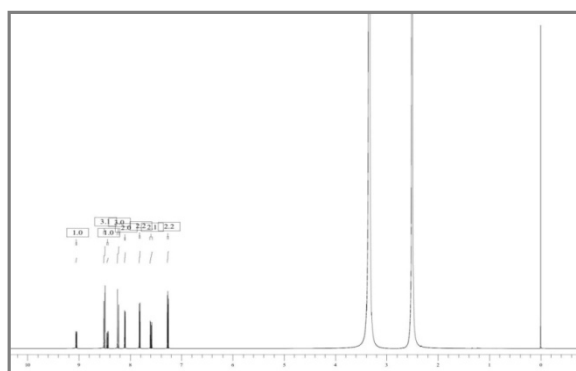


**Figure 3.** IR spectrum of  $[Cd(L_2)Cl_2]$ .

The  $^1H$  NMR spectra of both the Cd(II) complexes 1 and 2 were recorded in DMSO- $d_6$ . Characteristic signals of aromatic protons in complexes shows down field shift when compared to that of ligand protons due to increased conjugation upon coordinating with metal [12].



**Figure 4.**  $^1H$  NMR spectrum of  $[Cd(L_1)Cl_2]$



**Figure 5.**  $^1H$  NMR spectrum of  $[Cd(L_2)Cl_2]$

The UV-Visible absorption spectra of complexes were recorded in DMSO at room temperature. The absorption bands at 293 and 323 in complex 1 and 299 and 325 in 2 are attributed to intra ligand  $\pi-\pi^*$  transitions of the aromatic ring [13] and the bands at 393 in 1 and 396 in 2 are due to charge transfer transitions. The absence of appreciable transitions above 450 indicate that there are no d-d transitions since Cd(II) ion is diamagnetic with  $d^{10}$  configuration [14].

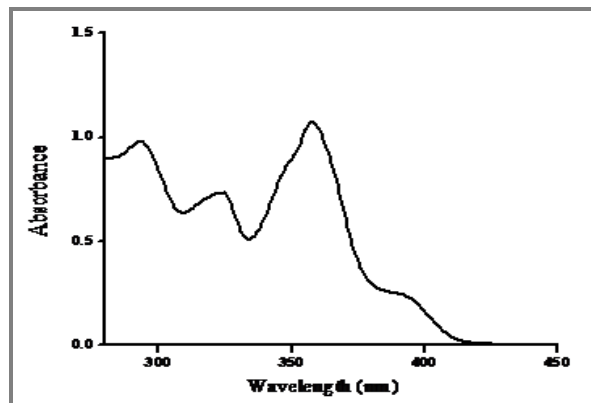


Figure 6. Electronic Spectrum of  $[Cd(L_1)Cl_2]$ .

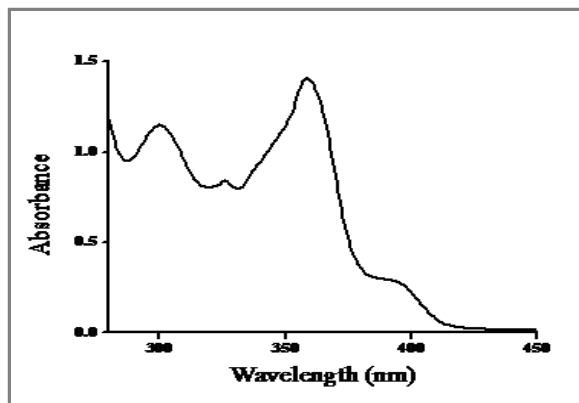


Figure 7. Electronic Spectrum of  $[Cd(L_2)Cl_2]$ .

The recorded ESI mass spectrum of complexes exhibit mass peak at  $m/z$  593.11 for complex 1 corresponds to  $[M+NH_4]^+$  and at  $m/z$  630.96 for complex 2 which corresponds to  $[M+Na]^+$ . The Thermo gravimetric analysis of complexes was carried out under inert atmosphere of Nitrogen using  $Al_2O_3$  pan at a range of  $27^\circ C$   $10\text{ min}^{-1}$  resulted in a three stage decomposition curve. The decomposition of first complex started around  $228^\circ C$  while the second is at  $248^\circ C$  indicating there are no water molecules in the synthesized complexes. In the second step weight loss of organic moiety is associated with loss of chlorides. The percentage weight loss for both the complexes up to this stage is 76-77%. The final residue above  $725^\circ C$  for Complex 1 (found 22.15%; Calc. 22.31%) is CdO and for complex 2 at  $904^\circ C$  the left over residue was CdS (found 23.07%; 23.77%) [15].

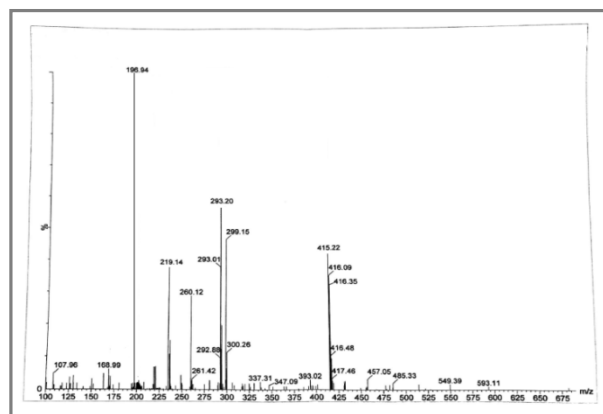


Figure 8. Mass spectrum of  $[Cd(L_1)Cl_2]$ .

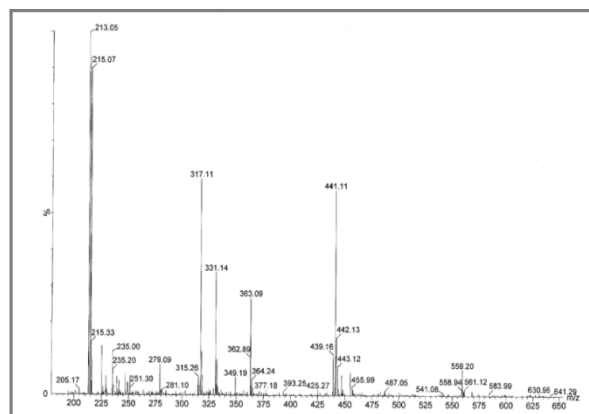


Figure 9. Mass spectrum of  $[Cd(L_2)Cl_2]$ .

## APPLICATION

The ligand and its metal complexes were screened for assaying of *in vitro* antibacterial activity against Gram-positive strains *Bacillus sphaericus* and *subtilis* and Gram-negative strain *Pseudomonas aeruginosa* using nutrient agar medium by paper disc method at  $400\ \mu\text{g mL}^{-1}$  concentration, using streptomycin as the standard drug. Discs impregnated with sample solution are introduced onto culture plates and incubated at  $30^\circ C$  for 24 h. Standard discs of Streptomycin were used as positive

control and blank disc soaked in DMSO is used as a negative control where the zone of inhibition values is measured in millimeters. All the synthesized complexes have exhibited better activity than ligands against all the strains except complex 1 with *B. subtilis* has shown decreased activity than that of ligand as shown in Figure 6. The higher activity of complexes than ligands can be explained using Tweedy Chelation Theory which states that chelation of ligand with metal ion decreases polarity of metal ion and the increased  $\pi$  electron delocalization increases the lipophilicity due to which the permeability into the lipid layer was made easy thus blocking the enzyme active sites of the organisms [16-18].

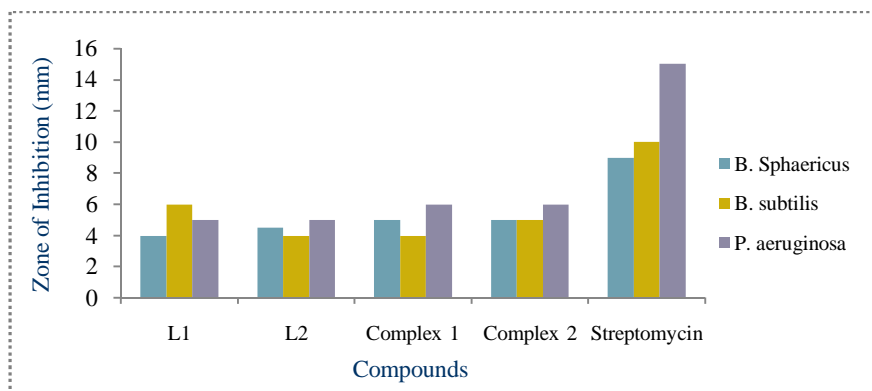


Figure 9. Graph showing Zone of inhibitions for ligands and complexes.

## CONCLUSION

The current work emphasizes the synthesis and characterization of Cd(II) complexes of substituted 1,8-Naphthyridine. Based on analytical and spectral studies it is understood that L1 and L2 acts as neutral mono dentate ligands and the synthesized metal complexes are mononuclear. Four coordinated tetrahedral geometry was proposed for the complexes. The *in vitro* antibacterial assay of screened compounds shows higher antibacterial activity of complexes than free ligand which signifies the fact that coordination increases the activity.

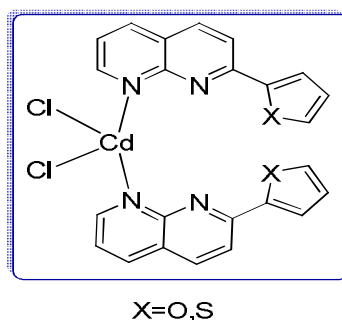


Figure 11. Proposed structure of the complexes.

## ACKNOWLEDGEMENTS

Author B. Radhika acknowledges UGC, New Delhi, India for providing financial assistance as research fellowship.

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