Group 12-Metal Complexes derived from Donor Substituted Carboxylic Acids and 5-Nitro-1,10-Phenanthroline: Spectroscopic and Biological Studies

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DOI **10.2412/mmse.46.5.782** provided by Seo4U.link

Keywords: metal complexes, 5-Nitro-1,10-phenanthroline, Donor Carboxylic acid, Anti-fungal and Anti-Microbial studies.

ABSTRACT. Momeric group 12 metal complexes [M(R-C_6H_4-COO)$_2$(5-NO_2-phen)] [M=Zn, R=NMe_2 **(1)** and M=Cd, R=NH_2 (**2**)] have been synthesized from a reaction between the metal acetate, donor substituted carboxylic acid and 5-nitro-1,10-phenathroline (5-NO_2-Phen) at room temperature. Both complexes were characterized by elemental analysis, FT-IR spectroscopy, ^{1}H NMR and UV-Vis spectroscopy studies. Compound **1** showed more potent anti-fungal activity when compared to standard drug fluconazole and demonstrated MIC at concentration 1.6 µg/ml, 25 µg/ml, 0.4 µg/ml, 3.12 µg/ml against K. pneumonia, Pseudomonas, S. aureus, S. mutans respectively.

Introduction. In the past three decades, transition metal (TM) complexes research has been found applications in the fields like catalysis, material science and biology [1-3]. In particular, group 12 complexes with chelating ligands show interesting biological activity, since zinc plays an importance role in many biological processes[4-6].The synthesis of derivatives of 1,10-phenanthroline and investigations of their properties have become an attractive research area [9]. Furthermore, carboxylate group can bind with metal ion in various modes, such as monodentate, bidentate and bridging which are good source of ligands (O-donor) for the very generous strong bonds that they form [10-12]. The metal complexes based on 5-nitro-1,10-phenanthroline carboxylates and further exploiting the relationship between their structure and biological properties have constituted one of the most attractive research fields in modern bioinorganic chemistry [13]. In particular, the zinc complexes of different substituted carboxylic acids are important substances which have been found to be useful as antimicrobial and antifungal agents and the antimicrobial and antifungal mode of action of these molecules is still not fully understood while the few groups attempted to understand the mechanism of antibacterial and antifungal activity of zinc compounds were done, but still it is unclear [14-15]. The best of our knowledge, there is no report in the literature on antibacterial and antifungal studies based on zinc derivative of aromaticcarboxylates using 5-nitro-1,10-phenanthroline as a co-ligand. Inspired by the aforementioned considerations, we report here,the synthesis and investigation of synthesis, spectral and antimicrobial and antifungal activity of group 12 metal complexes with 5-nitro 1,10-phenanthroline as a co-ligand.

Experimental

Instruments and Methods. Elemental analysis (C, H and N) was performed using LECO-932 CHNS Analyser, IR spectra was recorded using Perkin Elmer Spectrum 100 and recorded from the range 4000 to 650 cm^{-1}, UV-Visible spectra were recorded on a Perkin Elmer Lambda 35 spectrophotometer. Molar extinction coefficients (ε max, M^{-1} cm^{-1}) were determined from absorption maxima obtained in the range 200–800 nm, using a 1 cm quartz cuvette. Samples were prepared in methanol and analysed at room temperature. Melting Point was recorded using Buchi M-565

Instrument, One dimensional NMR spectra was obtained using 400 MHz Bruker spectrometer in d_6-DMSO as solvent.All chemical shifts are reported in parts per million (ppm). d = doublet, dd = doublet of doublets, t = triplet,s = singlet, bs = broad singlet, bd = broad doublet, bt = broad triplet.

Solvents and starting material. Analytical grade solvents were used for the synthesis of the compounds.Zinc acetate, cadmium acetate, 4-aminobenzoic acid and 4-(dimethylamino) benzoicacid were purchased from Sigma Aldrich.The precursor 5-NO_2-phen was synthesized based on already reported synthetic procedure [16].

Antifungal and Antibacterial studies. Antifungal activities of compound 1 were studied against *C albicans.* Results of anti-fungal activity when compared to standard drug Fluconazole. Antibacterial activity for compound 1 were performed towards different microorganisms which was carried out using MIC determination method. Different microorganisms such as, Gram Positive *Staphylococcus aureus* (*S. aureus*), *Staphylococcus mutans* (*S. mutans*), and Gram Negative *Klebsiella pneumoniae* (*K.Pneumoniae*), *Pseudomonas aeruginosa* (*P.aeruginosa*) bacterial strains were used for antibacterial activity of compound 1 and compared with the standard drug Ciprofloxacin.

Synthesis

Compound 1. Sodium methoxide solution (10 mL) is added to 4-(dimethylamino) benzoic acid (0.1651g,1 mmol) and stirred for 30 minutes. To which zinc (II) acetate dihydrate (0.2195g,1 mmol) was dissolved in methanol (10 mL) and clear methanolic solution (20 mL) of 5-NO_2-phen (0.2250g,1 mmol) was added. The resulting solution was stirred for 30 minutes and filtered. The filtrate was kept at room temperature for crystallization. Dark red color crystals were isolated after a few days. Yield: 60 %. mp. 185˚C . Anal. Calcd for $C_{30}H_{27}N_5O_6Zn$: C 58.2; H 4.4; N 11.3. Found: C57.9; H 4.2; N 10.9. IR (KBr, cm^{-1}): 3452(s), 1737(m), 1597(s),1516(s), 1354(broad s), 1193(s), 837(s),783(s), UV-Vis (CH_3OH, nm) 206, 225, 299. ^{1}H NMR (400 MHz, DMSO-d_6) 2.9 (s, $4CH_3$), 6.6 (d, aromatic 4CH), 7.7 (d, aromatic 4H), 8.2 (t, phen 2H), 9.0 (d, phen1H), 9.2 (d, phen 2H), 9.4 (d, phen 2H).

Compound 2. The compound 2 was synthesized in the similar method of Compound 1.Dark Rediish Brown color crystals were isolated after a few days. Yield: 55 %. MP. 198˚C . Anal. Calcd for $C_{26}H_{19}N_5O_6Cd$: C 51.2; H 3.1; N 11.48. Found: C 50.8; H 3.2; N 11.1. IR: 3466(w), 3176(s), 1593(s), 1514(s), 1365(s), 1178(m), 785 (s). UV-Vis (CH_3OH, nm) 206,273. ^{1}H NMR (400 MHz, DMSO-d_6) 5.4 (s, aromatic $2NH_2$), 6.5 (d,aromatic 4CH), 7.6 (d,aromatic 4CH), 8.1 (t, phen 2H), 9.0 (d, phen 1H), 9.1 (d, phen,1H,), 9.2 (s, phen,1H), 9.3 (d, phen,1H), 9.4 (d, phen, 1H).

Results and Discussion

Synthesis. The synthesis of the compound 1and 2 has been achieved by reaction between zinc acetate and sodium methoxide solution is added to 4-(dimethylamino) benzoicacid in the presence of 5-NO_2-phen ligand (Fig. 1). Both are air stable, soluble in common organic solvents like MeOH, DMF and DMSO and the crystalline products was purified by the recrystallization technique by the slow evaporation method. The results of compound 1 and 2 in elemental analysis shows that the products consistentswith the calculated values in the molecular formula of [Zn(Me_2N-C_6H_4-COO)$_2$(5-NO_2-phen)] (1) and [Cd(NH_2-C_6H_4-COO)$_2$(5-NO_2-Phen)] (2).

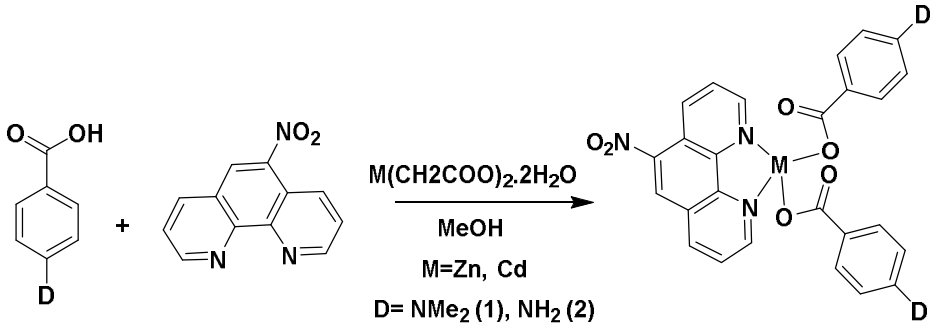

Fig. 1. Scheme of Synthesis.

Spectral Characterization. Compound 1and 2 was characterized by FT-IR spectroscopy. It revealed that monodentate binding mode of aromatic COO^- in compound 1 displays asymmetric stretching vibration band ν_a (COO^-) at 1597 cm^{-1} and wheras for the compound 2 at 1593 cm^{-1}, and symmetric stretching vibration band ν_s (COO^-) at 1365 cm^{-1} for compound 1 and 1354 cm^{-1} for compound 2[17].Addtionally, the C-H bending vibration of Phenanthroline ring occurs at 783 cm^{-1} for compound 1 and 785 cm^{-1} for compound 2.

The ^1H NMR spectrum for the compound 1 and compound 2 in DMSO-d_6, compound 1 shows the presence of resonances at δ = 2.9 ppm which can be assigned to the protons of the $–CH_3$ group in aromatic rings. The resonance appearing at δ = 6.6 and 7.7 ppm can be assigned to the proton attached to aromatic rings, δ = 8.2 ppm can be assigned to –CH proton attached to aromatic rings, δ = 9.0, 9.2 and 9.4 ppm can be assigned to the proton attached to phen ring, whereas compound 2 shows the presence of resonances at δ = 5.4 ppm can be assigned to the $–NH_2$ attached to aromatic rings and δ=6.5 and 7.6 ppm can be assigned to the proton attached to aromatic rings, δ = 8.1 ppm can be assigned to –CH proton attached to aromatic rings, δ = 9.1, 9.2, 9.3 and 9.4 ppm can be assigned to the proton attached to phen ring.

The UV-Vis spectrum of compound 1 and 2 in CH_3OH shows absorption maximum band in the region 200-300 nm for high energy π–π* and n– π* transitions (Fig. 2). Compound 1 has absorption maximum at 299, 225 and 206 nm whereas Compound 2 has absorption maximum at 273 and 206 nm [18].

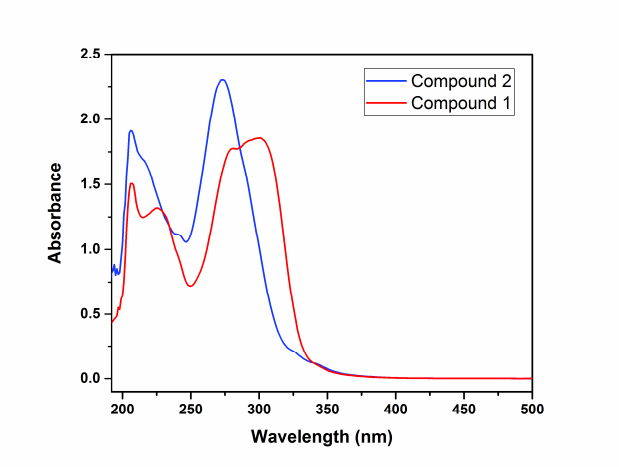

*Fig. 2. UV Vis spectra of compound **1** and **2.***

Antimicrobial and Antibacterial activity of compound 1. The tested bacterial and fungal strains were prepared in the BHI broth and incubated at 37˚C and 200 rpm in an orbital incubator for overnight.Sample solutions were prepared in DMSO for concentration 100, 50, 25, 12.5, 6.25, 3.12, 1.6, 0.8, 0.4 and 0.2 µg/ml. The standard drug solution of Ciprofloxacin (antibacterial drug) and Fluconazole (antifungal drug) were prepared in DMSO. Serial broth micro dilution was adopted as a reference method. 10 µl solution of test compound was inoculated in 5 ml BHI broth for each concentration respectively and additionally one test tubes was kept as control. Each of the test tubes was inoculated with a suspension of standard microorganism to be tested and incubated at 35˚C for 24 hrs. At the end of the incubation period, the tubes were examined for the turbidity.Turbidity in the test tubes indicated that microorganism growth has not inhibited by the antibiotic contained in the medium at the test concentration

Compound **1** demonstrated MIC at concentration 1.6 µg/ml, 25 µg/ml, 0.4 µg/ml, 3.12 µg/ml against *K. pneumonia*, *Pseudomonas*, *S. aureus*, *S. mutans* respectively and was compared with the standard

drug Ciprofloxacin. The results indicate that compound **1** shows moderate antibacterial activity against *K. pneumonia*, *Pseudomonas*, *S. aureus*, *S. mutans* respectively compound **1** was having good activity in *S. aureus*, bacterium due to the role of zinc in complex system, coordination and chelating tends are acting as more powerful and influential bacteriostatic agents, thus inhibiting the growth of the microorganisms.

The compound **1** were exhibited the growth of *C. albicans* at concentration 1.6 µg/ml, whereas the standard anti-fungal drug Fluconazole executed antifungal activity at 16 µg/ml. It can be concluded from this study that the tested compound **1** showed more potent anti-fungal activity when compared to standard drug Fluconazole, whereas antibacterial activity is moderate when compared to standard drug Ciprofloxacin.

*Table 1. Antibacterial and Antifungal activity of compound **1**.*

Drug / Organism	**Concentration of compound 1 (µg/ml)**									
	100	**50**	**25**	**12.5**	**6.25**	**3.12**	**1.6**	**0.8**	**0.4**	**0.2**
K. pneumoniae	S							R	R	R
Pseudomonas	S		R	R	R	R	R	R	R	R
S. aureus	S									R
S. mutans	S						R	R	R	R
Candida albicans	S							R	R	R

Summary. Monomeric group 12 metal complexes have been synthesized and characterized by analytical and spectroscopic studies. Compound **1** possesses showed more potent anti-fungal activity when compared to standard drug fluconazole. Compound **1** demonstrated MIC at concentration 1.6 µg/ml, 25 µg/ml, 0.4 µg/ml, 3.12 µg/ml against K. pneumonia, Pseudomonas, S. aureus, S. mutans respectively against Ciprofloxacin, Hence compound **1** to exhibit more potent anti-bacterial and Antifungal activity.

Acknowledgement. The authors thank the management of VIT University for providing the excellent research facilities (VIT-SAIF). CG acknowledges Sigma Aldrich, subsidiary of Merck Life Sciences for sponsoring my Ph.D. program. Also, the authors are very much thankful to Maratha Mandal Dental College, Belgaum for performing the antibacterial and antifungal activity.

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Cite the paper
Champaka Gurudevaru, Nallasamy Palanisami, (2017). Group 12-Metal Complexes derived from Donor Substituted Carboxylic Acids and 5-Nitro-1,10-Phenanthroline: Spectroscopic and Biological Studies. Mechanics, Materials Science & Engineering, Vol 9. doi 10.2412/mmse.46.5.782