

Synthesis and Characterisation of Novel Hetero Cyclic Compound Having Oxadiazole Ring

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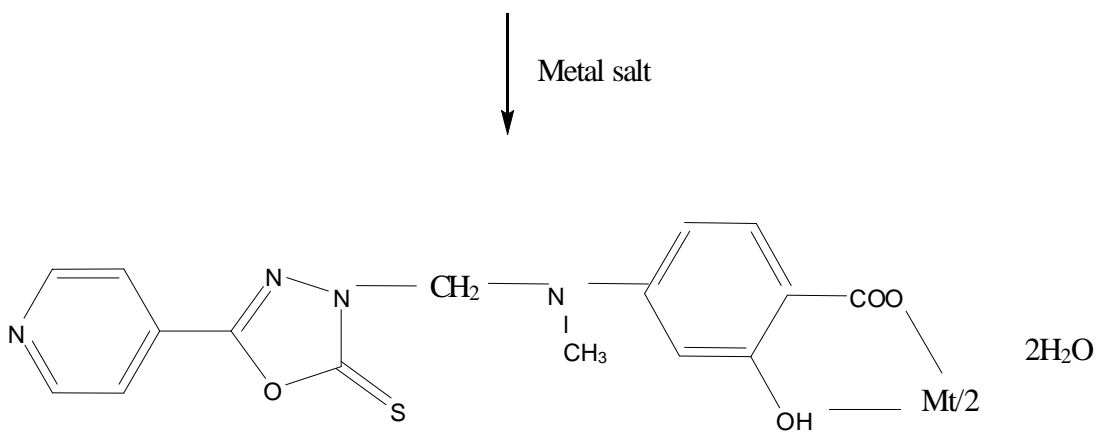
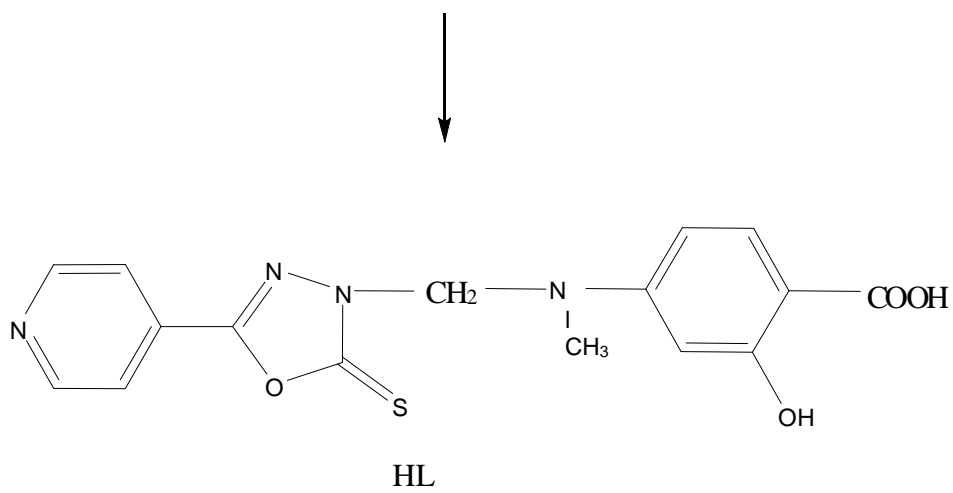
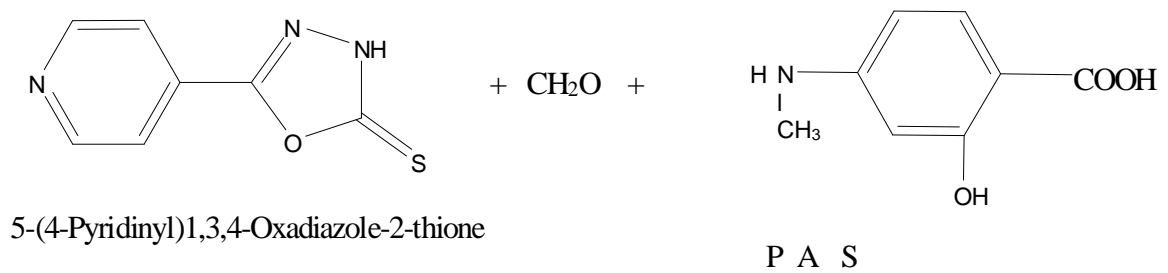
Abstract: Mannich reaction of 5-(4-pyridinyl)-1,3,4-oxadiazole with (N-methyl) 4aminosalicylic acid and formaldehyde in ethanol of 5-(4-Pyridinyl)-3-[4-carboxy-3-hydroxyPhenyl (N-methyl) amino methyl]-1,3,4-oxadiazole-2-thione (HL). The various metal complexes viz Cu^{2+} , Ni^{2+} , Zn^{2+} , Fe^{3+} , and of HL have been prepared. The HL and its metal complexes were characterized by elemental analysis, spectral features, magnetic moment and antimicrobial activity.

Key words: 5-(4-pyridinyl)-1,3,4-Oxadiazole, p-amino salicylic acid (PAS), metalcomplexes, I R & NMR spectroscopics, magnetic moment, antibacterial activity.

Introduction:

Oxadiazole derivatives are found as important heterocyclic compounds. They found in number of Pharmaceutical applications[1-4]. Their 2-thione derivatives are also found as pharmaceutical applications such as antibacterial, anti-inflammatory, stimulant, pesticidal etc.[4-9]. Having drug moiety i.e. isoniazide for the 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thione is very good pharmaceutical agent [7-9]. If the drug type molecule like p-amino salicylic acid introduced in the molecule of this oxadiazole the end molecule may play good antimicrobial agent. Hence it was thought to study oxadiazole-p-amino salicylic acid combined HL. Thus the present paper comprises the synthesis, characterization, chelating properties and microbial activity of HL molecule. The reaction route is as shown in scheme.

Scheme-1



Mt = Cu²⁺, Ni²⁺, Zn²⁺, Fe⁺³

Experimental:**Materials**

5-(4-pyridinyl) 1, 3, 4, Oxadiazole-2- thione was prepared by method reported in literature. [10]. P –Amino salicylic acid (PAS) (i.e. 4-Aminosalicylic acid) was obtained from local dealer. All other chemicals used were of analytical grade.

Synthesis of 3-(4-carboxy-3 hydroxyphenyl (N-methyl) amino methyl)-5-(4-pyridinyl)-1, 3, 4 -oxadiazole-2-thione: Formation HL.

A mixture of 5-(4-pyridinyl)-1,3,4,-Oxadiazole-2-thione (0.02mole), formaldehyde (0.02 mole), and N-methyl- 4-amino salicylic acid (PAS)(0.02mole) in ethanol(70ml) was refluxed for 4hr. Subsequently ethanol was distilled off and pasty mass obtained. It was triturated with petroleum ether (40-60c). The solid designated as HL was isolated and dried in air. Yield was 75%. It's m.p. was 198⁰ C (uncorrected).

Elemental Analysis

C₁₆H₁₃N₄O₄S (M.W. =357):

	C%	H%	N%	S%
Calculated	53.63	3.94	15.63	8.95
Found	53.61	3.89	15.60	8.91

IR Features :	1480-1520 cm ⁻¹	1,3,4, Oxadiazole
	3030, 1500, 1600 cm ⁻¹	Aromatic
	1680 cm ⁻¹	CO of COOH
	3200-3600 cm ⁻¹	OH
	2850-2920 cm ⁻¹	CH ₂

NMR : (DMSO)	7.2 –7.6 ppm	Multiplate aromatic
	2.56 ppm (1H)	Singlet CH ₂
	12.2 ppm(1H)	Singlet (COOH)
	3.9 ppm (1H)	Singlet (OH)

Synthesis of metal complexes of HL: Formation of HL-metal complexes.

The Cu²⁺, Ni²⁺, Zn²⁺ and Fe³⁺ metal ion complexes of HL have been prepared in similar manner. The procedure is as follow:

To a solution of HL (0.1mole) in ethanol-acetone (1:1) mixture (150ml), 0.1 N KOH solution was added drop wise with stirring. The sticky precipitates were obtained at neutral PH. These were dissolved by addition of water up to clear solution. It was diluted to 250ml. by water and was known as stock solution. 25ml of the stock solution (which contains 0.01 mole(HL)) was added drop wise to the solution of metal salt (0.005 mole for divalent metal ions and 0.0033 mole for Fe³⁺ ion) in water at room temperature. Sodium acetate or ammonia was added up to complete precipitation. The precipitates were digested on water bath at 80⁰ C for 2 hrs. The digested precipitates of complex were filtered washed with water and air-dried. It was amorphous powder. Yield was almost quantitative. The details are given in Table-1.

Measurement:

The elemental analysis for C, H, and N were carried out on Thermodynamer elemental analyzer. IR spectra of HL and its metal complexes were scanned on a Perkin Elmer FTIR spectrophotometer in KBr. The metal content of the metal chelates were performed by decomposing a weighed amount of each metal complex followed by EDTA titration as reported in literature [11]. Magnetic susceptibility measurement of the entire metal complex

was carried out at room temperature by the Gouy method. Mercury tetrathiocyanatocobaltate(II). Hg [Co(NCS)₄] was used as a calibrant. The diffused reflectance spectra of solid metal complex were recorded on Backman DK Spectrophotometer with solid reflectance attachments, MgO was employed as the reflectance compound.

Anti-fungal activity:

The fungicidal activity of all compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms listed in Table-3 were used. The anti-fungal activity of all the samples was measured by cup plate method [12]. Each of the plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200gms, dextrose 20gms, agar 20gms and water suspended (1000ppm) in a PDA medium and autoclaved at 120 c for 15 min. at 15 atm pressure. These medium were poured into sterile petri plate and the organisms were inoculated after cooling the petri plates. The percentage inhibition for fungi was calculated after 5 days using the formula given below.

$$\text{Percentage of Inhibition} = \frac{100(X-Y)}{X}$$

Where X: Area of colony in control plate
Y: Area of colony in test plate

The fungicidal activity all compounds is shown in Table –3.

Result and Discussion

The parent ligand HL was an amorphous yellow powder, soluble in various solvents like dioxane, DMSO and DMF. The results of elemental analysis of the ligand reported in Table–I are consistent with the predicted structure as shown in Scheme-1. The ligand was synthesized as shown in the scheme-1.

Examination of IR spectrum (not shown) of HL reveals that a broad band of phenolic hydroxyl stretching is observed at 3200-3600 cm⁻¹ as well as additional absorption bands at 3030, 1500 and 1600 are characteristics of the salicylic acid[13,14]. The strong band at 1680 for C=O and band at 3400 for sec. NH. The NMR data (shown in experimental part) also confirm the structure of HL.

The metal complexes of HL with the metal ions Cu²⁺, Ni²⁺, Fe³⁺ and Zn²⁺ vary in colors. On the basis of the proposed structure as shown in scheme-1, the molecular formula of the HL ligand is C₁₆H₁₃N₄O₄S. Which upon complexation coordinates with one central HL atom at four coordination sites and with two water molecules. Therefore the general molecular formula of the resulting metal complex [C₃₂H₂₆N₈O₈S₂] M.2H₂O for divalent metal ions. This has been confirmed by results of elemental analysis of all the seven metal complexes and their parent ligand. The data of elemental analysis reported in Table-1 are in arrangement with the calculated values of C, H, and N based on the above mentioned molecular formula of parent ligand as well as metal complexes..

Inspection of the IR Spectra (not shown) of metal complexes reveals that all the spectra are identical in all respects. The comparison of IR spectrum of the parent ligand HL with that of its each metal complex has revealed certain characteristics differences.

One of the significant difference to be expected between the IR spectrum of the parent ligand and its metal complexes is the presence of more broadened bands in the region of 3200-3600 cm⁻¹ for the metal complexes as the oxygen of the O-H group of the ligand forms a coordination bond with the metal ions. [13-15]. This is explained by the fact that water molecules might have strongly absorbed to the metal chelates sample during their formation. Another noticeable is that the band due to the COO anion at 1600 cm⁻¹ in the IR spectrum of each metal complex. The band at 1400 cm⁻¹ in the IR spectrum of HL assigned to in plane of OH determination [13-15] is shifted towards higher frequency at the spectra of the metal complexes due to the formation of metal oxygen bonds. This has been further confirmed by a weak band at 1105 cm⁻¹ corresponding to C-O-M stretching [12]. Thus all of these characteristics features of the IR studies suggested the structure of the metal complexes as shown in scheme.

Table 1: Analytical and spectral data of HL ligand and its metal chelates.

Metal complexes	Molecular formula	Mol.Wt. gm/mol	Yield %	Elemental analysis.								%Metal analysis	
				C%		H%		N%		S%			
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Cu(HL) ₂ 2H ₂ O	C ₃₂ H ₂₆ N ₈ O ₈ S ₂ Cu ²⁺ 2H ₂ O	813.54	77	47.20	47.1	3.68	3.6	13.76	13.7	3.94	3.8	7.81	7.8
Ni(HL) ₂ 2H ₂ O	C ₃₂ H ₂₆ N ₈ O ₈ S ₂ Ni ²⁺ 2H ₂ O	808.69	67	47.48	47.4	3.70	3.6	13.84	13.7	3.97	3.9	7.25	7.2
Fe (HL) ₂ 2H ₂ O	C ₃₂ H ₂₆ N ₈ O ₈ S ₂ Fe ²⁺ 2H ₂ O	805.85	59	47.47	47.4	3.70	3.6	13.84	13.7	3.96	3.9	7.28	7.2
Zn (HL) ₂ 2H ₂ O	C ₃₂ H ₂₆ N ₈ O ₈ S ₂ Zn ²⁺ 2H ₂ O	815.39	64	47.09	47.0	3.67	3.6	13.73	13.6	3.93	3.8	8.01	7.9

Examination of data of the metal content in each compound revealed a 1:2 metal: ligand (M: L) stoichiometry in all of the complexes of divalent metal ions and 1:3 metal: ligand stoichiometry for Fe³⁺ ions.

Magnetic moment (μ_{eff}) each of the metal complex is given in Table-2. Examination of these data reveals that all complexes other than that of Zn²⁺ is para-magnetic while those of Zn²⁺ are diamagnetic.

The diffuse electronic spectrum of the [Cu HL(H₂O)₂] metal complexes shows broad bands at 15873 and 24691 cm⁻¹ due to the ²T → ²T_{2g} transition and charge transfer, respectively suggesting a distorted octahedral structure [16-18] for the [Cu HL(H₂O)₂] complex. Which is further confirmed by the higher value of μ_{eff} of the [CuHL(H₂O)₂] complex. The [NiHL (H₂O)₂] and [Cu HL(H₂O)₂] complexes gave two absorption bands respectively at 15603,22998 and 15384,22727 cm⁻¹ corresponding to ⁴T_{1g} → ²T_{1g} and ⁴T_{1g} (p) transitions. Thus absorption bands at the diffuse, reflectance spectra and the value of the magnetic moments (μ_{eff}) indicate and octahedral configuration for the [NiHL (H₂O)₂] and [Cu HL(H₂O)₂] complexes. The spectrum of Fe³⁺ complex has not been adequately characterized. The spectrum comprises the band ground 1900 cm⁻¹ and other weak band ground 2300 cm⁻¹. The latter has not very long tail. These may have the transitions ⁶A_g → ⁴T₂ (4G) and ⁶A₁ → ⁴T₁ (4G). The high intensities of the bands suggests that they might be charge transfer in origin- μ_{eff} is found to be lower than normal range. In the absence of low temperature moments it is difficult to give any significance. As the spectrum of the [Zn HL (H₂O)₂] polymer is not well resolved, it is not interpreted but its μ_{eff} value shows that it is diamagnetic as expected.

The antifungal activity of all the compounds measured for various plant pathogens. Inspection of the result shown in Tabel-2 indicates that all compounds are good toxic for fungi. Out of all the compounds copper chelate is more toxic than others. These compounds almost inhibit the fungi about 70%. Hence produced metal chelates can be employed as garden fungicides. Further work in direction is in progress.

Table 2: Reflectance Spectral Data of ML₁, Chelates (cm⁻¹).

Metal chelates	Absorption band(Cm ⁻¹)	Transitions	Magnetic moment(BM)
Cu- (HL) ₂ .2H ₂ O	23,687	C.T	2.10
	15,485	² B _{1g} → ² A _{1g}	
Ni- (HL) ₂ .2H ₂ O	23,458	³ A _{2g} → ³ T _{1g} (p)	2.80
	13,589	³ A _{1g} → ³ T _{1g} (f)	
Fe- (HL) ₂ .2H ₂ O	22,742	⁶ A _{1g} (f) → ⁴ T _{2g} (f)	5.8
	18,247	⁶ A _{1g} (f) → ⁴ T _{2g}	
Zn- (HL) ₂ .2H ₂ O	-	--	

Zn- L₁ is diamagnetic in nature.

Table 3: Antifungal activity of Ligand CHPOT and its Metal complexes

Sample	Zone of inhibition of fungus at 1000 ppm(%)					
	Botrydepladia thiobromine	Nigrospora Sp.	Rhizopus Nigricans	Aeperginus niger	Amdida Albicans	Amdida Kruseigos candida glabrata405
HL	57	60	71	72	68	61
HL-Ni ²⁺	72	75	72	76	69	67
HL-Cu ²⁺	60	78	80	82	80	75
HL-Fe ³⁺	76	67	64	77	75	76
HL-Zn ²⁺	64	73	63	76	73	80

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