



SYNTHESIS, CHARACTERIZATION AND CHELATING PROPERTIES OF PYRIMIDINE-QUINOLINE COMBINED MOLECULE WITH TRANSITION METALS

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Abstract: The treatment of ethyl-6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidone-5-carboxylate with 5-amino-8-hydroxyquinoline afford a N-(4-hydroxyquinolin-5-yl)-6-methyl-2-oxo-4-phenyl-1,2-dihydro pyrimidine-5-carboxamide(PDHQ). The transition metal complexes of Cu^{2+} , Co^{2+} , Ni^{2+} , Mn^{2+} and Zn^{2+} of PDHQ have been prepared and characterized by elemental analysis, spectral studies, magnetic moment determination, molar conductivity measurement and microbicidal activity.

Keywords: Ethyl-6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidone -5-carboxylate, 5-amino-8-hydroxyquinoline, Antimicrobial activity, Magnetic moment, Metal chelates.

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INTRODUCTION

Pyrimidone belonging to the heterocyclic system prepared by multicomponent chemical reaction from ethyl acetoacetate, an aryl aldehyde and urea are associated with diverse pharmaceutical activities such as antibacterial (Shimoga et al., 2006; Prakash and Desai, 2004), antiproliferative (Primofiore et al., 2003), anticancer (Fahmy et al., 2003; Moukha-Chafiq et al., 2002), antifungal (Patel and Mehta, 2010), antiviral (Rostom et al., 2003), anti-inflammatory (Santagati et al., 2003), etc. Recently the Pyrimidine derivative has been reported with remarkable antimicrobial activity (El-Gaby et al., 1999). The reaction between Pyrimidine derivatives with 8-hydroxy quinoline has not been reported so far. Though 8-hydroxy quinoline is excellent antimicrobial effect (Greenberg et al., 1976; Philips, 1956; Patel and Singh, 2009; Block, 1955; Mohsen and Shawkat, 2003). Thus this may afford good chelating ligand with better microbicidal activity. Hence it was thought interesting to prepare the ligand having Pyrimidine-quinoline moieties. Thus the present communication comprises the studies on Pyrimidine-quinoline combined molecule and its metal chelates. The synthetic approach is shown in Figure 1.

MATERIALS AND METHODS

The 5-Amino-8-hydroxy quinoline were prepared by method reported in literature (Belov and Nichvoloda, 2004) and Ethyl-6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidone-5-carboxylate (Biginelli, 1893). All other chemicals used were of analytical grade.

Synthesis of N-(4-hydroxyquinolin-5-yl)-6-methyl-2-oxo-4-phenyl-1, 2-dihydropyrimidine-5-carboxamide (PDHQ)

A mixture of Ethyl-6-methyl-2-oxo-4-phenyl-1,2-dihydropyrimidone-5-carboxylate (PD) (0.02 mole) and 5-amino-8-hydroxy quinoline (AHQ) (0.02 mole) in ethanol (70 ml) was heated under reflux for 4hrs. Subsequently ethanol was distilled off and the lump mass obtained. It was triturated with petroleum ether (40-60°C). The solid designated as PDHQ was isolated and dried in air. Yield was 87%. It's m.p. was 193-96°C (uncorrected). Elemental Analysis for C₂₁H₁₆O₃N₄ (372), Cal(Found): C%, 67.74(67.72), H%, 4.30 (4.28), N%, 15.05 (15.03). IR(KBr, cm⁻¹): 1638, 1575, 1560, 1475(8-Hydroxy quinoline moiety), 3030, 1520, 1650 (Aromatic C-H), 1685(CO), 2850-3600(OH), 3410(Sec. NH), ¹HNMR(DMSO, ppm): 7.1-7.7(5H, m, Aromatic), 6.5-8.1 (5H, m, Quinoline), 1.6(2H, m, CH₃), 3.8(1H, s, OH), 2.9(1H, s, NH).

Synthesis of metal chelates of PDHQ

The Cu²⁺, Co²⁺, Ni²⁺, Mn²⁺ and Zn²⁺ metal ion chelates of PDHQ have been prepared in a similar manner. The procedure is as follow.

To a solution of PDHQ (31.3 g, 0.1 mole) in ethanol-acetone (1:1v/v) mixture (150 ml), 0.1N KOH solution was added dropwise with stirring. The pasty precipitates were obtained at neutral pH. These were dissolved by addition of water up to clear solution. It was diluted to 250 ml. by water and was known as stock solution. 25 ml of the stock solution (which contains 0.01 mole PDHQ) was added drop wise to the solution of metal salt (0.005 mole for divalent metal ions) in water at room temperature. Sodium acetate or ammonia was added up to complete precipitation. The precipitates were digested on water bath at 80° C for 2h. The digested precipitates of chelates were filtered washed with water and air dried. It was amorphous powder. Yield was almost quantitative. The detail is given in Table 1.

Measurements

The elemental analysis for C, H and N were carried out on elemental analyzer TF-EA.1101 (Italy). IR spectra of PDHQ and its metal complexes were scanned on a Nicolet 760 FTIR spectrophotometer in KBr. The NMR spectrum of PDHQ was scanned on Bruker NMR spectrophotometer using DMSO solvent. The metal content of the metal chelate were performed by decomposing a weighed amount of each metal complexes followed by EDTA titration as reported in literature (Vogel, 1975). 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 a Beckman DK Spectrophotometer with a solid reflectance attachment, MgO was employed as the reflectance compound. The electrical conductivity of all the complexes was measured in acetonitrile at 10⁻³ M concentration.

Antifungal activity

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro plant pathogenic organisms listed in Table-2. The antifungal activities of all the samples were measured by cup plate method. Each of the plant pathogenic strains on potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200 gms, dextrose 20gms, agar 20gms and water 1 litre. 5 days old cultures were employed. The compounds to be tested were 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 plate. The percentage inhibition for fungi was calculated after 5 days. The fungicidal activity all compounds are shown in Table 2.

RESULTS AND DISCUSSION

The parent ligand PDHQ was an amorphous brown powder, soluble in various solvents like dioxane, DMSO and DMF. The results of elemental analysis of the ligand are reported in experimental part. They are consistent with the predicted structure as shown in Figure-1. Examination of IR spectrum (not shown) of PDHQ reveals that broad band of phenolic hydroxyl stretching is observed at 2850-3600 cm⁻¹ as well as additional absorption bands at 1638, 1575, 1560, 1475 cm⁻¹ are characteristics of the 8-Hydroxy quinoline moiety. The strong bands at 1685 cm⁻¹ for C=O and band at 3410 cm⁻¹ for sec. NH. The NMR

data (shown in experimental part) also confirm the structure of PDHQ. The Metal chelate of PDHQ with ions Cu^{2+} , Co^{2+} , Ni^{2+} , Mn^{2+} and Zn^{2+} vary in colours. On the basis of the proposed structure as shown in Figure-1, the molecular formula of the PDHQ ligand is $\text{C}_{21}\text{H}_{16}\text{O}_3\text{N}_4$. This upon complexation coordinates with one central metal atom at four coordination sites and with two water molecules. Therefore the general molecular formula of the resulting metal chelate is $[\text{C}_{21}\text{H}_{15}\text{O}_3\text{N}_4]_2 \text{M} \cdot 2\text{H}_2\text{O}$ for divalent metal ions. This has been confirmed by results of elemental analysis reported in Table 1. The data are in agreement with the calculated values. Inspection of the IR Spectra (not shown) of metal chelates reveals that all the spectra are identical in all respects. The comparison of IR spectrum of the parent ligand PDHQ with that of its each metal chelates has revealed certain characteristics differences.

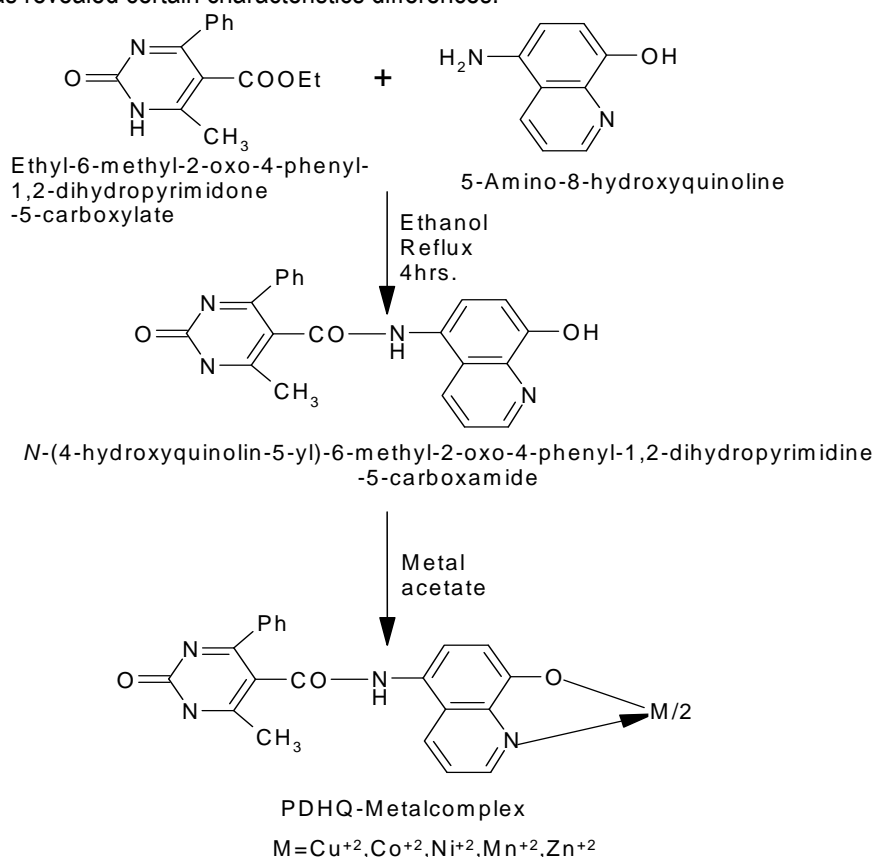


Figure 1. Synthesis of PDHQ

One of the significant differences to be expected between the IR spectrum of the parent ligand and its metal chelates is the presence of more broadened bands in the region of $3200\text{--}3600\text{ cm}^{-1}$ for the metal chelates as the oxygen of the O-H group of the ligands forms a coordination bond with the metal ions (Charles et al., 1956; Mamdouh et al., 2008). This is explained by the fact that water molecule might have strongly absorbed to the metal chelates samples during their formation. Another noticeable difference is that the bands due to the CO at 1730 cm^{-1} in the IR spectrum of the each metal chelates. The band at 1400 cm^{-1} in the IR Spectrum of HL assigned to inplane OH determination is shifted towards higher frequency in the spectra of confirmed by a weak bands at 1095 cm^{-1} corresponding to C-O-M (Satpathy et al., 1991). Thus all of these characteristics features of the IR studies suggested the structure of the metal chelates as shown in scheme. Examination of data of the metal content in each compound revealed a 1:2 metal: ligand (M: L) stoichiometry in all of the chelate of divalent metal ions. Magnetic moment (μ_{eff}) of each of the metal chelates is given in Table-3. Examination of these data reveals that all chelates other than that of Zn^{2+} , are Para magnetic while those of Zn^{2+} are diamagnetic.

The diffuse electronic spectrum of the $[\text{CuHL}(\text{H}_2\text{O})_2]$ metal complex shows broad bands at 15960 and 22797 cm^{-1} due to the ${}^2\text{T} \rightarrow {}^2\text{T}_{2g}$ transition and charge transfer, respectively suggesting a distorted octahedral structure (Lever, 1968; Figgis, 1976; Carlin and Van Dyneveldt, 1997) for the $[\text{CuHL}(\text{H}_2\text{O})_2]$ complex. Which is further confirmed by the higher value of μ_{eff} of the $[\text{CuHL}(\text{H}_2\text{O})_2]$ complex. The $[\text{NiHL}(\text{H}_2\text{O})_2]$ and $[\text{CuHL}(\text{H}_2\text{O})_2]$ complex gave two absorption bands respectively at 14785, 23089 and 15960, 22797 cm^{-1} corresponding to ${}^4\text{T}_{1g} \rightarrow {}^2\text{T}_{1g}$ and ${}^4\text{T}_{1g}$ (p) transitions. Thus absorption bands at the diffuse, reflectance spectra and the value of the magnetic moments μ_{eff} indicate an octahedral configuration for the $[\text{NiHL}(\text{H}_2\text{O})_2]$ and $[\text{CuHL}(\text{H}_2\text{O})_2]$ complex. The spectra of $[\text{MnHL}(\text{H}_2\text{O})_2]$ shows weak bands at 15478, 17756 and 23054 cm^{-1} assigned to the transitions ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{1g}$ (4G), ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}$ (4G) and ${}^6\text{A}_{1g}$ (F) $\rightarrow {}^4\text{T}_{1g}$, respectively suggesting an octahedral structure for the $[\text{MnHL}(\text{H}_2\text{O})_2]$ chelate. 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 $[\text{ZnHL}(\text{H}_2\text{O})_2]$ polymer is not well resolved, it is not interpreted but its μ_{eff} value shows that it is diamagnetic as expected. Conductivities of all the complexes were measured in acetonitrile solvent and all the complexes were found to be electrolytic in nature of 1:2 type and molar conductivity values are in the range of 36.2-37.8 $\text{Ohm}^{-1} \text{Cm}^{-1}$.

The antifungal activity of all the compounds measured for various plant pathogens. Inspection of the result shown in Table 2, indicates that all compounds are good toxic for fungi. Out of all the compounds copper chelates is more toxic than other. These compounds almost inhibit the fungi about 78%. Hence produced metal chelates can be employed as garden fungicides. Further work in the direction is in progress.

Table 1. Analytical Data of the Metal Chelates of HL i.e. PDHQ

S.No.	Compounds	Yield (%)	N% Cald	N% Found	M% Cald	M% Found
1.	HL (PDHQ)	87	15.05	15.02	--	--
2.	$(\text{L})_2\text{Cu}^{2+} \cdot 2\text{H}_2\text{O}$	83	13.30	13.26	7.55	7.52
3.	$(\text{L})_2\text{Co}^{2+} \cdot 2\text{H}_2\text{O}$	84	13.38	13.33	7.04	7.01
4.	$(\text{L})_2\text{Ni}^{2+} \cdot 2\text{H}_2\text{O}$	78	13.38	13.36	7.01	6.95
5.	$(\text{L})_2\text{Mn}^{2+} \cdot 2\text{H}_2\text{O}$	80	13.44	13.38	6.59	6.54
6.	$(\text{L})_2\text{Zn}^{2+} \cdot 2\text{H}_2\text{O}$	76	13.27	13.22	7.75	7.69

Table 2. Antifungal Activities of Metal Chelates of PDHQ Ligand

S. No.	Compounds	Zone of inhibition of fungus at 1000ppm (%)						
		PE	BT	N	T	RN	AN	TL
1	HL (PDHQ)	67	58	68	67	64	64	65
2	$(\text{L})_2\text{Cu}^{2+} \cdot 2\text{H}_2\text{O}$	85	73	77	78	76	81	79
3	$(\text{L})_2\text{Co}^{2+} \cdot 2\text{H}_2\text{O}$	78	77	75	74	76	75	77
4	$(\text{L})_2\text{Ni}^{2+} \cdot 2\text{H}_2\text{O}$	82	74	78	79	73	77	78
5	$(\text{L})_2\text{Mn}^{2+} \cdot 2\text{H}_2\text{O}$	74	72	76	73	67	74	73
6	$(\text{L})_2\text{Zn}^{2+} \cdot 2\text{H}_2\text{O}$	78	72	72	73	72	80	74

PE: *Penicillium expansum*; BT: *Botrydepladia thiobromine*; N: *Nigrospra sp.*; T: *Trichothesium sp.*; RN: *Rhizopus nigricans*; AN: *Aspergillus niger*; TL: *Trichoderma lignorum*

Table 3. Magnetic Moment and Reflectance Spectral data of Metal Chelates of PDHQ ligand

S. No.	Metal chelates	Magnetic Moment μ_{eff} (B.M.)	Molar Conductivity $\Omega\text{m ohm}^{-1}\text{ cm}^2\text{ mol}^{-1}$	Absorption band (cm^{-1})	Transitions
1	Cu-HL	1.92	37.6	22797 15960	C.T ${}^2T \rightarrow {}^2T_{2g}$
2	Ni-HL	3.87	36.8	14785 23089	3 A _{2g} → 3T _{1g} (p) 3 A _{1g} → 3T _{1g} (F)
3	Co-HL	4.54	35.4	15474 22823	4 T _{1g} (F) → 4T _{2g} (F) 4 T _{1g} (F) → 3A _{2g}
4	Mn-HL	5.13	37.2	15478 17756 23054	6 A _{1g} → 4T _{1g} (4E _g) 6 A _{1g} → 4T _{2g} (4G) 6 A _{1g} → 4T _{1g} (4G)

CONCLUSION

The novel N-(4-hydroxyquinolin-5-yl)-6-methyl-2-oxo-4-phenyl-1,2-dihydro pyrimidine-5-carboxamide (PDHQ) and its octahedral metal(II) oxinates (1:2 metal to ligand ratio) were synthesized and characterized. They showed moderate to good antibacterial and antifungal activities. This might be due to the additive biological effect of parent molecules and/or due to the metal chelating properties. Among the oxinate of Cu⁺² chelate showed better activity.

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CONFLICT OF INTEREST : Nothing