

SYNTHESIS , CHARACTERIZATION AND ANTIFUNGAL ACTIVITY OF 2-[(8-HYDROXYQUINOLINYL)-5-AMINOMETHYL]-3-(4- ISOPROPYLPHENYL)-3(H)-QUINAZOLIN-4-ONE LIGAND AND ITS METAL CHELATES WITH Cu(II), Ni(II), Mn(II), Co(II) AND Zn(II) IONS

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ABSTRACT

Synthesis and characterization of 2-[(8-hydroxyquinoliny)-5-aminomethyl]-3-(4-isopropylphenyl)-3(H)-quinazolin-4-one ligand called HAMQ (HL_6) was studied. Anthranilic acid was converted into N-Chloroacetyl anthranilic acid then into 2-Chloromethyl-3-(4-isopropylphenyl)-3(H)-quinazolin-4-one then Product HL_6 prepared. This compound was finally condensed with 5-amino-8-hydroxyquinoline. The transition metal chelets of Cu^{2+} , Ni^{2+} , Zn^{2+} , Mn^{2+} and Co^{2+} of this ligand HAMQ were prepared and characterized by reflectance, NMR and IR spectroscopy, elemental analysis and magnetic measurements. The stoichiometry of the complexes has been found to be 1: 2 (Metal: ligand). The results suggested an octahedral geometry around Co^{2+} , Ni^{2+} and Mn^{2+} chelates, a distorted octahedral geometry around Cu^{2+} and a tetrahedral geometry around Zn^{2+} have been proposed. These chelates have been tested for their antifungal activities.

Keywords: Ligand, 8-hydroxyquinoline, IR and NMR spectral studies, Antifungal activity.

INTRODUCTION

An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi or protozoan. The heterocyclic nitrogen compounds especially quinazolinone derivatives play a important role in many biological processes and as synthetic drugs¹. A Quinazolin-4-one derivative possesses biological activities such as antifungal²⁻⁷. The formation of 8-hydroxyquinoline and quinazolin-4-one molecules into one molecule has not received any attention in spite of well-defined applications of both the molecules. Hence the initial work in this direction has been carried out⁸. Thus in the extension of this work present communication comprises the synthesis, characterization and chelating properties of

novel quazolin-4-one-8-hydroxyquinoline derivatives. The whole work is summarized in scheme-1.

EXPERIMENTAL

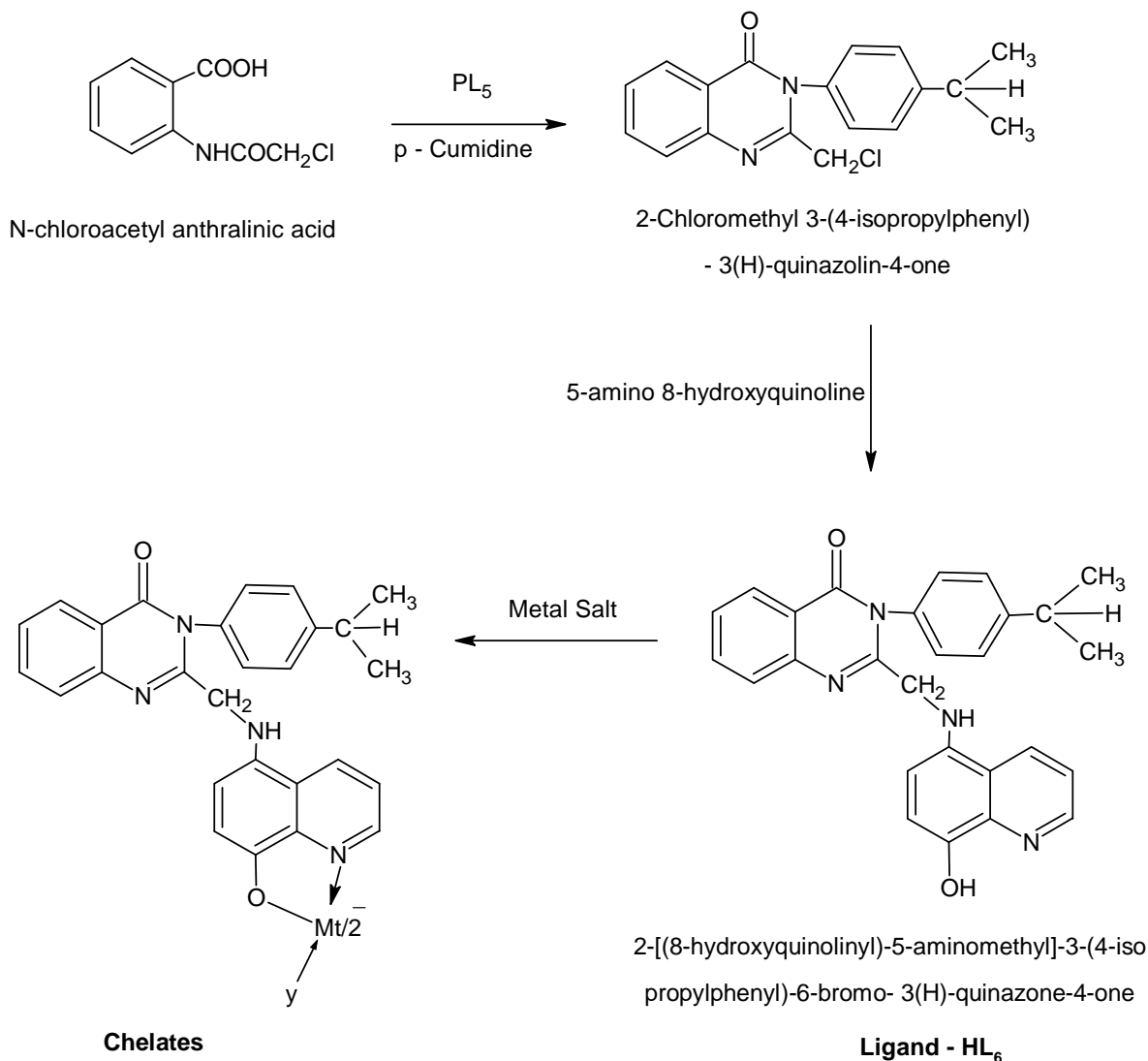
All the chemicals used were of Merck and B.D.H grade. Melting points of ligand HL_6 was determined by DSC method and was uncorrected.

Synthesis of ligand HL_6

A mixture of N-chloroacetyl anthranilic acid (3.32 g, 0.1 M) and p-Cumidine (1.35 g, 0.01 M) and PCl_5 (1.0 g, 0.01 M) in dry 1,4 -dioxane solvent was refluxed under anhydrous condition for 4 h. The reaction mixture was allowed to cool and PCl_5 was decomposed by titrating with cold

water. 1,4 -dioxane was distilled off to get the product. It was filtered, washed with saturated sodium bicarbonate solution and then with cold water and air-dried. A mixture of above mentioned product (2.33 g, 0.01M), 5-amino 8-hydroxy quinoline (1.6 g, 0.01 M) and dry pyridine (20 ml) was refluxed for 12 h. Pyridine was distilled off as much as possible and then

residue was poured into little crushed ice with constant stirring. The product which was separated out was washed with water and finally with ethanol. The product was in form of amorphous dark brown color powder. The air dried products were quantitative. Melting point of HL₆ was 220.91°C.



Where, M = Cu²⁺, Mn²⁺, Co²⁺, Ni²⁺, Zn²⁺
Y = H₂O

Synthesis of Chelates

A dried ligand sample HL₆ was stirred in 85 % (v/v) formic acid and then it was diluted by water until complete dissolution. The resultant solution was designated as reagent solution. This solution was used for preparation of complexes with transition metal ions. The formic acid solution of ligand was added drop wise to a solution of cupric nitrate hexahydrate, nickel nitrate hexahydrate, cobalt nitrate hexahydrate, manganese chloride hexahydrate, Zinc nitrate hexahydrate (0.005 moles) in 100 ml of water respectively with rapid stirring. pH of resultant liquid at 4.5 (for Cu⁺²), 6.0 (for Ni⁺² and Co⁺²) and 5.6 (for Mn⁺² and Zn⁺²) by adding of sodium acetate. A dark brown colored solid precipitated out. It was allowed to settle and digested on water bath at 70°C for about 2 h. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone and, dried. The % yield of chelates was in the range of 65-78 %. All the chelates were powdered and dried at 70°C over a period of 24 h.

Characterization of Ligand and Chelates

The C, H and N contents of metal complexes were determined on elemental analyzer Thermofinigan 1101 Flash EA (ITALY). The metal contents were estimated using standard methods⁹. ¹H NMR spectra of ligand was recorded on Bruker NMR spectrophotometer (300 MHz) using TMS as an internal standard in CDCl₃/DMSO-d₆. The molar conductance of the chelates in DMF (10⁻³ M) solutions were measured at room temperature using Systronics model 305 direct reading conductivity bridge. Infrared spectra (IR) were recorded in KBr pellets on a Nicolet-760

spectrophotometer. Reflectance spectra of complexes were recorded on a Beckman-DK-2A spectrophotometer using MgO as reference. Magnetic susceptibility was measured by Gouy's method¹⁰ at room temperature (300 K) using Hg [Co(CNS)₄] as calibrant¹¹, and the effective magnetic moment from relation¹², $\mu_{\text{eff}} = 2.84 (X_m \times T)^{1/2}$, where T is the absolute temperature. Diamagnetic corrections were made by using Pascal's constants.

The ligand and its metal chelates were screen at 1000 ppm concentration in vitro for their antifungal activity against five fungi viz. *Erysiphe pisi*, *Nigrospora sp.*, *Trichoderma sp.*, *Aspergillus niger*, *Curvularia lunata*. The antifungal activity of the compounds was measured by plate method¹³. Five days old cultures were suspended in potato dextrose agar (PDA) medium and autoclaved at 1200°C for 15 minutes and 15 atmospheric pressure. The percentage inhibition of fungi was calculated after 5 days using the formula given below,

$$\text{Percentage of Inhibition} = 100 (A-B) / A$$

Where A = area of colony in control plate (without sample) and B = area of colony in test plate.

RESULTS AND DISCUSSION

The complexes are microcrystalline colored powders having melting points higher than the ligand. They are stable in air at room temperature. All compounds gave satisfactory elemental analysis, suggesting 1:2 (metal: ligand) stoichiometry. Elemental analysis data of ligand and chelates were shown in Table-1.

Table 1: Analytical and physical data of metal chelates of HL₆

Ligand / Complexes	Molecular Formula	M.W. (g/mol)	Yield (%)	Elemental Analysis (%)			
				Found (Calcd.)			
				C	H	N	M
HL ₆	C ₂₇ H ₂₄ N ₄ O ₂	437.00	69	74.20 (74.31)	5.50 (5.50)	12.70 (12.84)	-
(HL ₆) ₂ Cu ⁺²	C ₅₄ H ₄₆ N ₈ O ₄ Cu ⁺² .2H ₂ O	969.54	67	66.70 (66.84)	5.00 (5.16)	11.40 (11.55)	6.2 (6.55)
(HL ₆) ₂ Ni ⁺²	C ₅₄ H ₄₆ N ₈ O ₄ Ni ⁺² .2H ₂ O	964.69	59	67.10 (67.17)	5.10 (5.18)	11.60 (11.61)	5.9 (6.08)
(HL ₆) ₂ Mn ⁺²	C ₅₄ H ₄₆ N ₈ O ₄ Mn ⁺² .2H ₂ O	960.93	72	67.30 (67.43)	5.10 (5.20)	11.50 (11.66)	5.5 (5.72)
(HL ₆) ₂ Co ⁺²	C ₅₄ H ₄₆ N ₈ O ₄ Co ⁺² .2H ₂ O	964.93	778	67.00 (67.16)	5.00 (5.18)	11.40 (11.61)	6.0 (6.11)
(HL ₆) ₂ Zn ⁺²	C ₅₄ H ₄₆ N ₈ O ₄ Zn ⁺² .2H ₂ O	971.39	65	66.60 (66.71)	5.10 (5.15)	11.20 (11.53)	6.6 (6.73)

The result of molar conductance shown in Table-2 indicates that they are less polar in DMF. Very low molar conductance (Λ_M) values in the range of 4.59 to 25.70 $\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$ in Mn^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} complexes indicates that they are non-electrolytic and monomeric in

nature (ML_2 type complexes). The low Λ_M values may be attributed to the large cations¹⁴. The electrical conductivity of these complexes found in the order: $\text{Co} > \text{Zn} > \text{Ni} > \text{Mn} > \text{Cu}$.

Table 2: Magnetic moment and electronic spectral data of chelates of ligand HL₆

Sample	Observed μ_{eff} (B.M) (Expected)	Λ_M ($\text{Ohm}^{-1}\text{cm}^2\text{mol}^{-1}$)	Electron Transition	Absorption band (cm^{-1})	u_2/u_1
$(\text{HL}_6)_2\text{Cu}^{2+}$	2.01 (1.7-2.2)	4.59	Charge Transfer Transition	24958	1.71
			${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_{1g}$	14600	
$(\text{HL}_6)_2\text{Ni}^{2+}$	2.93 (2.9-3.4)	9.82	${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$	15630	1.44
			${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$	22470	
			${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{F})$	8450	
$(\text{HL}_6)_2\text{Co}^{2+}$	4.23 (4.4-5.2)	25.70	${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{A}_{2g}(\text{F})$	19610	2.32
			${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{P})$	23220	
$(\text{HL}_6)_2\text{Mn}^{2+}$	4.88 (5.2-6.0)	8.12	${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{1g}({}^4\text{G})$	15896	1.14
			${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}({}^4\text{G})$	18200	
			${}^6\text{A}_{1g} \rightarrow {}^4\text{E}_g, {}^4\text{T}_{1g}({}^4\text{G})$	24100	
$(\text{HL}_6)_2\text{Zn}^{2+}$	-	8.30	-	-	-

NMR spectra

The ${}^1\text{H}$ NMR spectra of ligand HL₆ gave the multiplet between 6.88-7.8 δ ppm for Quinazoline and benzene ring, signal at 5.74-5.98 δ ppm for singlet of phenolic -OH group, 3.35-3.77 δ ppm due to CH_2 bridge, 2.2-2.5 δ ppm due to - CH_3 group, 11.1-11.35 δ ppm due to -NH group and 3.72-3.82 δ ppm due to -CH group.

Infrared spectra

IR spectrum of ligand HL₆ (Figure 1) show a broad band extended from 3700 to 2600 cm^{-1} which might be responsible to phenolic -OH group bonded to N atom of 8-hydroxyquinoline moieties¹⁵. The inflexions at 2925, 2855 and 1470 cm^{-1} are due to aromatic - CH_2 - and methylene group of bridge¹⁶⁻¹⁹. The strong band at 1705 cm^{-1} is attributed to -C=O of quinazoline 4-one moiety. Several bands appeared between 1480 and 1600 cm^{-1} region may arise from aromatic breathing. Band at 3400 cm^{-1} for -NH group. The IR band at 1580 cm^{-1} (C=N of 8-quinolinol system) of HL₆ ligand shifted to higher frequency side $\sim 1595\text{ cm}^{-1}$ in the spectra of the metal complexes indicating involvement of nitrogen in the complexes formation^{15,20}. Most of bands appeared in the spectra of corresponding ligand are observed at their metal complexes. Only a new band at 1095 cm^{-1} had appeared in the spectra of metal complexes. This may be

assigned to uc-o of C-O-M bond formation. All the complexes show additional bands at 840-830 cm^{-1} indicating the presence of coordinated water²¹

Magnetic moment and Electronic spectra

The magnetic moment, molar conductance and reflectance spectral data were presented in Table-2. The μ_{eff} value for the Co^{+2} chelate was found 4.23 B.M. (Table-2) which suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The value of transition ratio u_2 / u_1 is 2.32 providing further evidences for octahedral geometry for the Co^{2+} chelate.

In Ni^{+2} chelates, μ_{eff} values at room temperature is 2.93 B.M. as expected for six coordinated spin free Ni^{+2} species²². The reflectance spectral data of Ni^{+2} chelate shown in Table-2. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier²³.

The Cu^{+2} chelate possesses Paramagnetic moments 2.01 B.M. corresponding to one unpaired electron indicating the distorted octahedral geometry, which is in agreement with data reported by other research worker²⁴. Electronic spectra of this chelate were shown in Table-2. These results reveal the distorted octahedral geometry for this chelate. The former band may be due to ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$ account for

John-teller effect suggesting thereby a distorted octahedral geometry for this chelate²⁵.

Zn²⁺ complex is diamagnetic in nature and its electronic spectra do not furnish any characteristic d-d transitions except charge transfer (C.T.) bands as expected for d¹⁰ systems and may have tetrahedral geometry²⁶. There is no evidence for the characteristic bands of coordinated water in IR spectra. The observed magnetic moment of the Mn²⁺ complexes are 4.88 B.M. corresponding to five

unpaired electrons indicates high spin octahedral environment²⁷.

Antifungal Activity

Ligand and its metal chelates were found more or less toxic against fungi. The antifungal activity of the metal complexes was shown in Table-3 which indicates the following decreasing order: Cu < Ni < Zn < Co < Mn. Copper chelate exhibit more toxicity than other metal complexes. Hence such type of complexes may find as agricultural and garden fungicides.

Table 3: Antifungal activity of ligand HL₆ and its metal chelates

Sample	Zone of inhibition at 1000 ppm(%)				
	EP	NS	TS	AN	CL
HL ₆	73	64	72	71	55
(HL ₆) ₂ Cu ²⁺	88	78	74	86	85
(HL ₆) ₂ Mn ²⁺	55	56	72	66	67
(HL ₆) ₂ Zn ²⁺	74	73	67	71	72
(HL ₆) ₂ Co ²⁺	67	68	58	57	74
(HL ₆) ₂ Ni ²⁺	78	74	78	81	79

CA: *Erysiphe pisi*, NS: *Nigrospora Sp.*, TS: *Trichoderma sp.*
AN *Aspergillus niger*, CL: *Curvularia lunata*

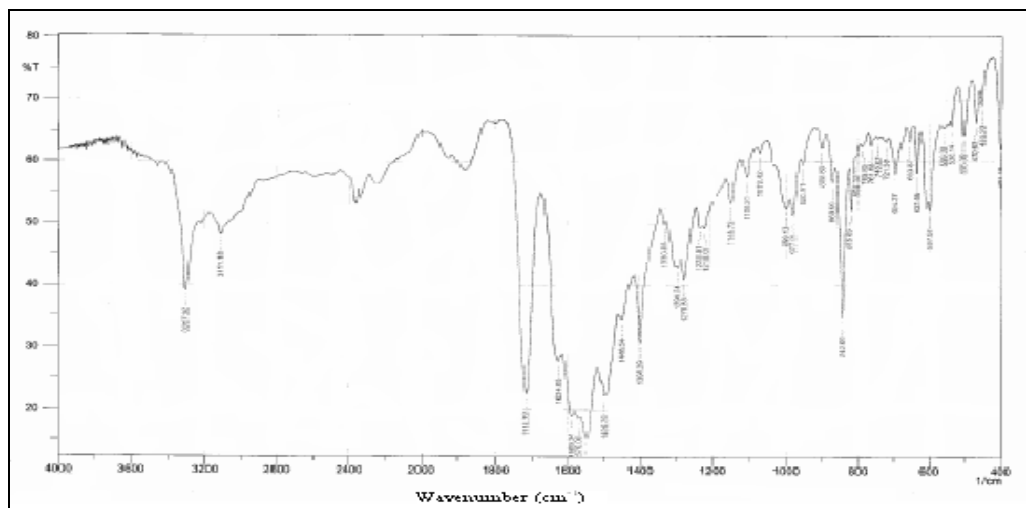


Fig. 1: FT-IR Spectrum of Ligand [HL₆]

CONCLUSION

- The ligand molecule acts as a hexadentate ligand in all the studied cases of complex. Bonding either among N (4) depending upon the nature of the metal ions.
- Octahedral structures for Ni²⁺, Co²⁺ and Mn²⁺ complexes, tetrahedral polymeric structure for Zn²⁺ and distorted octahedral for Cu²⁺ complex have been tentatively proposed.

- Present work will contribute in the field of new antifungal for some plant pathogenic organisms

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