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SYNTHESIS, CHARACTERIZATION AND ANTIFUNGAL ACTIVITY OF 2-[(8-HYDROXYQUINOLINYL)-5-AMINOMETHYL]-3-(4-CHLOROPHENYL)-6-BROMO-3(H)-QUINAZOLIN-4-ONE LIGAND AND ITS TRANSITION METAL CHELATES

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ABSTRACT

Synthesis and characterization of 2-[(8-hydroxyquinolinyl)-5-aminomethyl]-3-(4-chlorophenyl)-6-Bromo-3(H)-quinazolin-4-one ligand called HAMQ (HL_{10}) was studied. To prepare this ligand anthranilic acid was converted into 5-bromo–N-Chloroacetyl anthranilic acid then into 2-[(8-hydroxyquinolinyl) -5-aminomethyl] -3-(4-chrolophenyl) -6-bromo- 3(H)-quinazolin-4-one. This compound was prepared by condensation with 5-amino-8-hydroxyquinoline. New transition metal chelates of Cu^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+} and Co^{2+} of this ligand HAMQ were prepared and characterized by reflectance, ^{1}H-NMR as well as IR spectroscopy, elemental analysis molar conductance and magnetic measurements. The stoichiometry of the complexes has been found to be 1: 2 (Metal: ligand). The data suggested an octahedral geometry around Co^{2+}, Ni^{2+} and Mn^{2+} complexes, a distorted octahedral geometry around Cu^{2+} and a tetrahedral geometry around Zn^{2+} have been proposed. The metal complexes were screened for the antifungal activity.

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

1. INTRODUCTION

The chemistry of heterocyclic compounds continuously to be an explore field in the organic chemistry.

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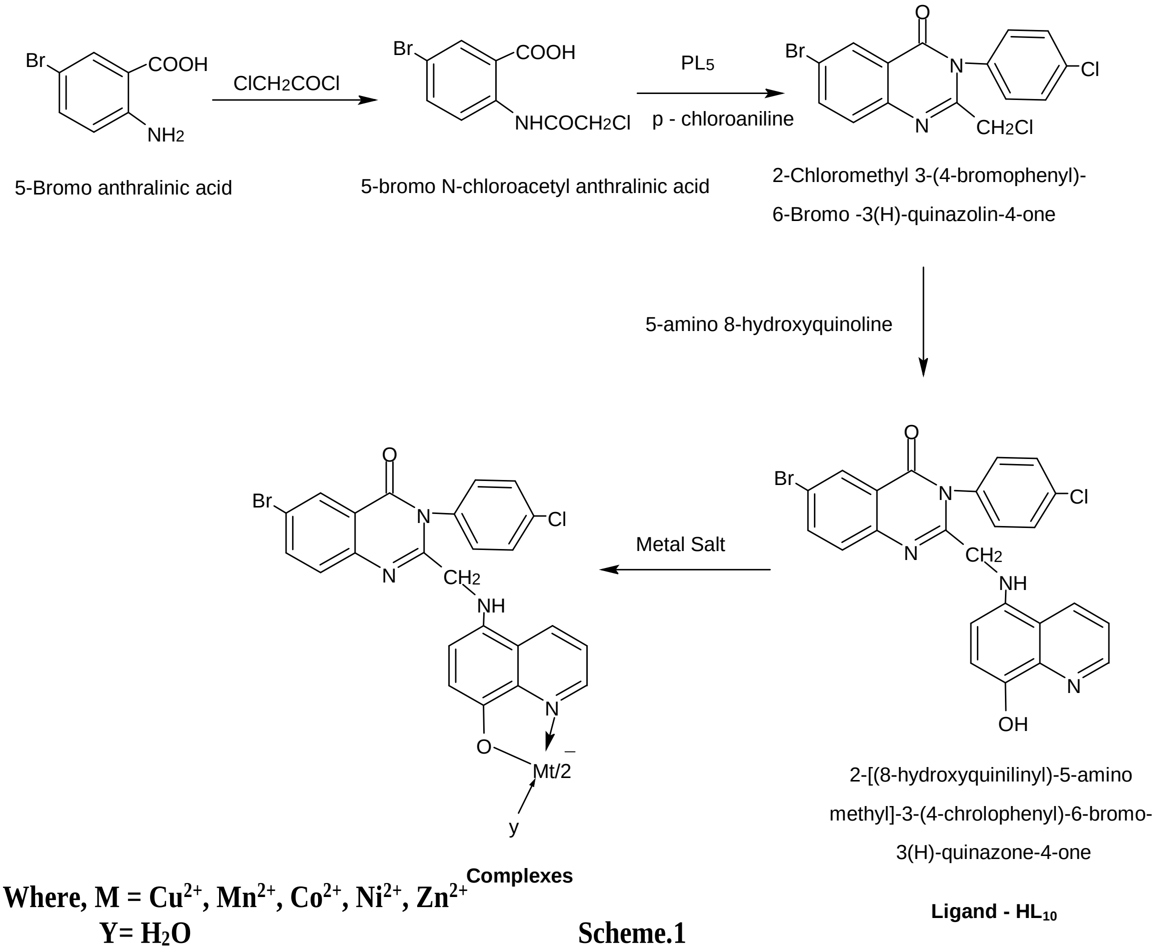
Infectious diseases caused by micro and macro organisms; viz. bacteria, fungi, viruses and parasites are still a major threat to human health, despite tremendous inventions in drug chemistry. The emergence of wide spread drug resistance, particularly multi-drug resistance [1] against gram-positive bacteria is a major concern.

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs [2]. A Quinazolin-4-one derivative possesses biological activities such as antifungal [3-4]. 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 out [5]. Thus in the extension of this work [5] present communication comprises the synthesis, characterization and chelating properties of novel qunazolin-4-one-8-hydroxyquinoline derivatives. The whole work is summarized in scheme-1.



Where, M = Cu^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}
Y= H_2O

Scheme.1

2. EXPERIMENTAL

All the chemicals used were of pure grade (Merck and B.D.H). The melting points of ligand HL_{10} was determined by DSC method and was uncorrected.

Synthesis of ligand HL_{10} (HAMQ) : A mixture of 5-bromo N-chloroacetyl anthranilic acid (3.32 g, 0.1 M) and p-chroloaniline (1.28 g, 0.01 M) and PCl_5 (1.86 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 HL_{10} was 228°C (Uncorrected).

Synthesis of Chelates: A dried ligand sample HL_{10} 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. The resultant pH 4.5 (for Cu^{+2}), pH 6.0 (for Ni^{+2} and Co^{+2}) and pH 5.6 (for Mn^{+2} and Zn^{+2}) were maintained by adding of sodium acetate. A dark 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, dried. The percentage yield of chelates was in the range of 68-82 %. All the complexes were powdered well and dried at 70°C over a period of 24 h.

Measurements: The C, H and N contents of metal complexes were determined on elemental analyzer Thermofiniggan 1101 Flash EA (ITALY). The metal contents were estimated using standard methods [6]. ^1H NMR spectra of ligand was recorded on Bruker NMR spectrophotometer (300 MHz) using TMS as an internal standard in $CDCl_3$/DMSO-d_6. 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. The Infrared spectra (KBr) were recorded in the range 4000-600 cm^{-1} with 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 method [7] at room temperature (300 K) using Hg $[Co(CNS)_4]$ as calibrant [8], and the effective magnetic moment from relation [9], $\mu_{eff} = 2.84\sqrt{Xm \times T}$, 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 method [10]. 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,

Percentage of Inhibition = 100 (X-Y) / X
Where X = area of colony in control plate (without sample)
and Y = area of colony in test plate.

3. RESULT 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 HL_{10}.

Ligand / Complexes	Molecular Formula	M.W. (g/mol)	Yield (%)	Elemental Analysis (%) Found (Calcd.)			
				C	H	N	M
HL_{10}	$C_{24}H_{16}N_4O_2Cl,Br$	507.5	68	56.70 (56.80)	3.10 (3.15)	11.00 (11.03)	-
$(HL_{10})_2\ Cu^{+2}$	$C_{48}H_{30}N_8O_4Cl_2\ Br_2Cu^{+2}.2H_2O$	1112.54	78	55.30 (55.36)	3.00 (3.27)	10.60 (10.76)	6.0 (6.11)
$(HL_{10})_2\ Ni^{+2}$	$C_{48}H_{30}N_8O_4Cl_2\ Br_2Ni^{+2}.2H_2O$	1106.69	69	55.50 (55.62)	3.00 (3.28)	10.70 (10.81)	5.6 (5.67)
$(HL_{10})_2\ Mn^{+2}$	$C_{48}H_{30}N_8O_4Cl_2\ Br_2Mn^{+2}.2H_2O$	1102.93	71	55.70 (55.82)	3.10 (3.29)	10.50 (10.85)	5.2 (5.32)
$(HL_{10})_2\ Co^{+2}$	$C_{48}H_{30}N_8O_4Cl_2\ Br_2Co^{+2}.2H_2O$	1106.93	82	55.50 (55.60)	3.00 (3.28)	10.60 (10.81)	5.6 (5.69)
$(HL_{10})_2\ Zn^{+2}$	$C_{48}H_{30}N_8O_4Cl_2\ Br_2\ Zn^{+2}.2H_2O$	1113.39	70	55.10 (55.26)	3.10 (3.26)	10.60 (10.74)	6.1 (6.27)

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 8.10 to 23.11 $ohm^{-1}cm^2\ mol^{-1}$ 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 cations [11]. The electrical conductivity of these chelates found in the order: Co > Mn > Cu > Zn >Ni.

Table 2. Magnetic moment and electronic spectral data of chelates of Ligand HL_{10}

Sample	**Observed μ_{eff} (B.M) (Expected)**	**Λ_M (Ohm^{-1} cm^2 mol^{-1})**	**Electron Transition**	**Absorption band (cm^{-1})**	**υ_2 / υ_1**
$(HL_{10})_2\ Cu^{2+}$	1.77 (1.7-2.2)	9.31	Charge Transfer Transition	23890	1.55
			$^2B_{1g}$ ----> $^2A_{1g}$	15400	
$(HL_{10})_2\ Ni^{2+}$	3.21 (2.9-3.4)	8.10	$^3A_{2g}$ (F) ----> $^3T_{1g}$ (F)	15630	1.44
			$^3A_{2g}$ (F) ----> $^3T_{1g}$ (P)	22465	
$(HL_{10})_2\ Co^{2+}$	4.55 (4.4-5.2)	23.11	$^4T_{1g}$ (F) ----> $^4T_{1g}$ (F)	8120	2.36
			$^4T_{1g}$ (F) ----> $^4A_{2g}$ (F)	19162	
			$^4T_{1g}$ (F) ----> $^4T_{1g}$ (P)	24900	
$(HL_{10})_2\ Mn^{2+}$	5.24 (5.2-6.0)	10.20	$^6A_{1g}$ ----> $^4T_{1g}$ (^4G)	16895	1.11
			$^6A_{1g}$----> $^4T_{2g}$ (^4G)	18900	
			$^6A_{1g}$ ----> ^4E_g, $^4A_{1g}$ (^4G)	23700	
$(HL_{10})_2\ Zn^{2+}$	-	8.19	-	-	-

NMR spectra: The ^1H NMR spectra of ligand HL_{10} (Fig.1) gave the multiplate between 6.88-7.8 δ ppm for aromatic protons, signal at 5.74-5.98 δ ppm for phenolic –OH group, 3.35-3.77 δ ppm due to CH_2 bridge, 2.5-2.51 δ ppm due to $–OCH_3$ group and 11.1-11.35 δ ppm due to –NH group. The non-aqueous conductometric titration of ligand gave the proton of $–CH_2$ and –OH group in ligand.

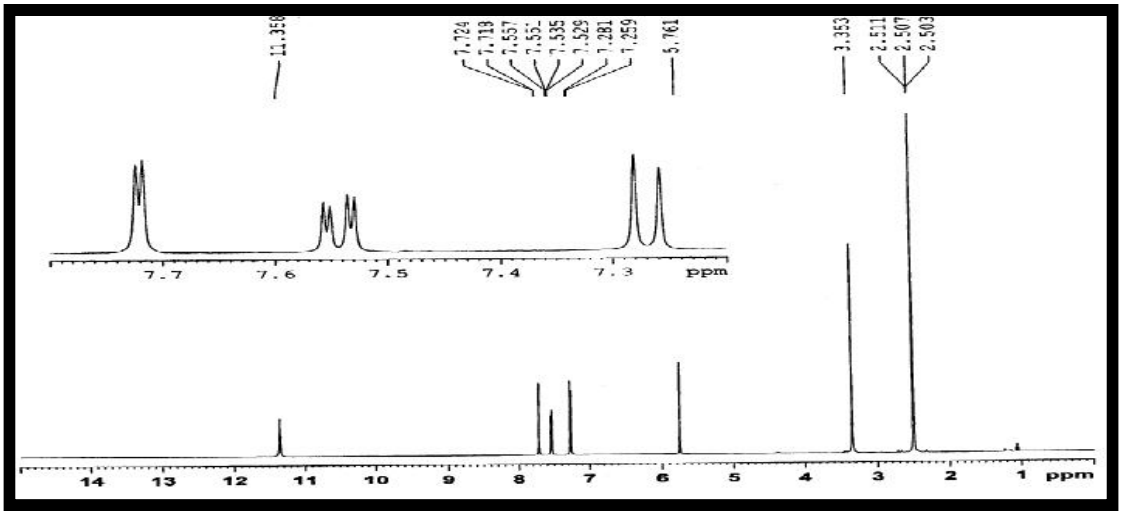


Fig.1. NMR spectrum of ligand HL_{10}

Infrared spectra: The significant IR bands for the ligand HAMQ(HL_{10}) as well as for its metal complexes and their tentative assignments as compiled and represented below.IR spectrum of ligand HL_{10} 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 moieties [12]. The inflextious at 2920, 2850 and 1470 cm^{-1} are due to aromatic $-CH_2-$ and methylene group of bridge [13-16]. The strong band at 1705 cm^{-1} is attributed to -C=O of quinazoline 4-one moiety. Several bands appeared between 1500 and 1600 cm^{-1} region may arised 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 HL_{10} ligand shifted to higher frequency side ~1595 cm^{-1} in the spectra of the metal complexes indicating involvement of nitrogen in the complexes formation [12,17]. 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 $\upsilon_{\text{c-o}}$ of C-O-M bond formation. All the complexes show additional bands at 840-830 cm^{-1} indicating the presence of coordinated water [18].

Electronic spectra and magnatic properties: The magnetic moment, molar conductance and reflectance spectral data were presented in Table-2. The room temperature μ_{eff} value for the Co^{+2} chelate 4.55 B.M. suggest high spin octahedral geometry, which is further supported by the electronic spectral data (Table-2). The value of transition ratio υ_2 / υ_1 is 2.36 providing further evidences for octahedral geometry for the Co^{2+} chelate.

In the Ni^{+2} chelate, μ_{eff} values at room temperature is 3.21 B.M. as expected for six coordinated spin free Ni^{+2} species [19]. 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 earlier [20].

The Cu^{+2} chelate possesses amgnetic moments 1.77 B.M. corresponding to one unpaired electron indicating the distorted octahedral geometry, which is in agreement with data reported by other research worker [21]. 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 ^2E_g ----> $^2T_{2g}$ account for John-teller effect suggesting thereby a distorted octahedral geometry for this chelate [22].

Zn^{+2} chelate 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 d^{10} systems and may have tetrahedral geometry [23]. There is no evidence for the characteristic bands of coordinated water in IR spectra. The observed magnetic moment of the Mn^{2+} chelate are 5.24 B.M. corresponding to five unpaired electrons indicates high spin octahedral environment [24].

Antifungal activity: Ligand and its metal chelates were found more or less toxic against fungi. The antifungal activity of the metal chelate was shown in Table-3 which indicates the order: Cu (II) > Zn (II) > Ni (II) Co(II) > Mn (II). Out of all the chelates copper chelates werw more toxic than other [25]. Hence such type of chelate may find as agricultural and garden fungicides.

Table 3. Antifungal activity of ligand HL10 and its metal chelates.

Sample	Zone of inhibition at 1000 ppm (%)				
	EP	*NS*	*TS*	*AN*	***CL***
HL_{10}	90	85	77	69	74
$(HL_{10})_2\,Cu^{2+}$	86	75	78	87	85
$(HL_{10})_2\,Mn^{2+}$	62	58	64	68	68
$(HL_{10})_2\,Zn^{2+}$	81	71	73	71	72
$(HL_{10})_2\,Co^{2+}$	69	69	54	59	79
$(HL_{10})_2\,Ni^{2+}$	77	74	79	79	78

EP: Erysiphe pisi , NS: Nigrospora Sp., TS : Trichoderma sp.

AN: *Aspergillus niger, CL: Curvularia lunata*

4. CONCLUSION

- The ligand molecule acts as a hexadentate ligand in all the studied cases of chelate. Bonding either among N (4) depending upon the nature of the metal ions.
- Octahedral structures for Ni^{2+}, Co^{2+} and Mn^{2+} chelate, tetrahedral polymeric structure for Zn^{2+} and distorted octahedral for Cu^{2+} chelate have been tentatively proposed.
- Present work will contribute in the field of new antifungal for some plant pathogenic organisms.

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