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Synthesis, Characterization and Biological Investigations on Metal Chelates of 2-[(8-hydroxyquinolinyl)-5-aminomethyl]-3-(4-chlorophenyl)-3(H)-quinazolin-4-one

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ABSTRACT:2-[(8-hydroxyquinolinyl)-5-aminomethyl]-3-(4-chlorophenyl)-3(H)-quinazolin-4-one ligand called HACQ (HL_4) was studied. Anthranilic acid was converted into N-chloroacetyl anthranilic acid and then to 2-chloromethyl–3(4-chloro phenyl)-3(H)-quinazoline-4-one. This compound was finally condensed with 5-amino-8-hydroxyquinoline for the preparation of this HACQ ligand. The transition metal chelates of Cu^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+} and Co^{2+} of this ligand HACQ were prepared and characterized by Metal-Ligand (M:L) ratio, reflectance spectral studies, NMR, IR spectroscopy, elemental analysis and magnetic properties. 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. These complexes have been tested for their antifungal activities. The results show that all these samples are good antifungal agents.

Keywords: 8-hydroxyquinoline, IR and NMR, spectral studies, magnetic properties, antifungal properties.

INTRODUCTION

8- Hydroxyquinoline or 8-quinolinol is well known as an analytical reagent[1-2]. Its various derivatives[3] are also useful in pharmaceuticals. Several azo dyes based on 8-quinolinol are also reported for dying of textiles as well as their chelating properties[4]. One of the derivatives, viz 5-Amino-8-hydroxy quinoline can be Synthesis facilely and studied extensively for number of derivatives[5].

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs[6]. A Quinazolin-4-one derivative possesses biological activities such as antifungal[7-8]. 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[9]. Thus in the extension of this work[9] 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.

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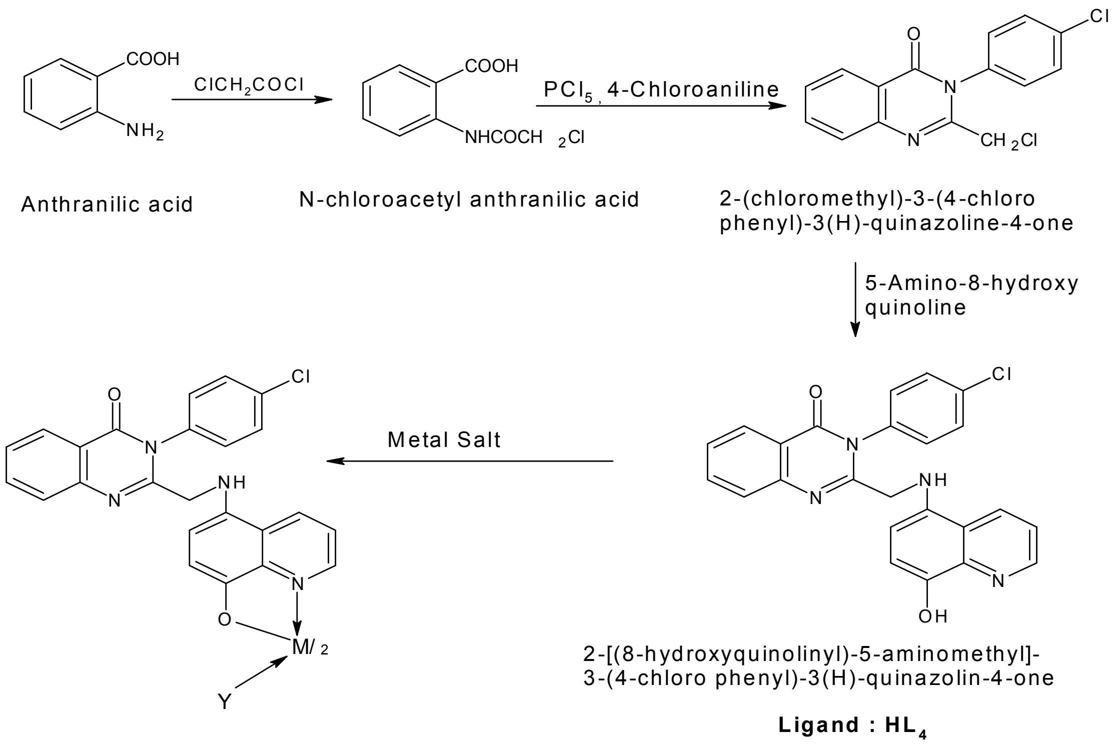

Complexes **[SCHEME -1]** **HACQ**

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

Y= H_2O

MATERIAL AND METHODS

All the chemicals used were of pure grade (Merck and B.D.H). The melting points of ligand HL_4 was determined by DSC method and was uncorrected.

Synthesis of ligand HL_4 : A mixture of N-chloroacetyl anthranilic acid (2.13 g, 0.1 M) and 4-chloroaniline (1.28 g, 0.01 M) and PCl_5 (1.86 g, 0.01 M) in dry 5-Amino-8-hydroxy quinoline solvent was refluxed under anhydrous condition for 4 hrs. The reaction mixture was allowed to cool and PCl_5 was decomposed by titrating with cold water. 5-Amino-8-hydroxy quinoline was distilled off to get the product. It was filtered, washed with saturated sodium bicarbonate solution and then with cold water and air-dried. The product was in form of amorphous dark brown color powder. The air dried products were quantitative. Melting point of HL_4 was 224°C (Uncorrected).

Synthesis of Metal Chelates: A dried ligand sample HL_4 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 hrs. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone, dried. The percentage yield of complexes was in the range of 59-82 %. All the complexes were powdered well and dried at 70°C over a period of 24 hrs.

Measurements: The elemental contains of C, H and N metal chelates were determined by TF-Flash-1101 EA (ITALY). The metal contents were determines volumetrically by Vogel's methods[10]. ^{1}H NMR spectra of ligand was recorded on Bruker NMR spectrophotometer using TMS as an internal standard in $CDCl_3$/DMSO-d_6[11]. The molar conductance of the complexes 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[12] at room temperature (300 K) using Hg $[Co(CNS)_4]$ as calibrant1z[13], and the effective magnetic moment from relation[11], $\mu_{eff} = 2.84\sqrt{Xm}$ x T, where T is the absolute temperature. Diamagnetic corrections were made by using Pascal's constants.

The ligand and its metal complexes 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. 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)
Y = area of colony in test plate.

RESULTS AND DISCUSSION

The synthesis of Ligand HL_4 was performed by method reported for 2-chloromethyl–3-(4-chlorophenyl)-3(H)-quinazoline-4-one. The C, H and N of ligand are consistent with predicted structure.

NMR spectra: The ^1H NMR spectra of ligand HL_4 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 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. 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 and molar conductance data are shown in Table-1.

The result indicates that they are less polar in DMF. Very low molar conductance (Λ_M) values in the range of 8.33 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[14]. The electrical conductivity of these complexes found in the order: Co > Zn > Cu > Ni >Mn.

IR spectra: IR spectrum of ligand HL_4 show a broad band extended from 3300 to 2600 cm^{-1}which might be responsible to phenolic -OH group bonded to N atom of 8-hydroxyquinoline moieties[15]. The inflextious at 2920, 2850 and 1470 cm^{-1} are due to aromatic $-CH_2$- and methylene group of bridge[16-19]. The strong band at 1716 cm^{-1} is attributed to -C=O of quinazoline 4-one moiety. Several bands appeared between 1500 and1600 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_4 ligand shifted to higher frequency side ~1595 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 υc-o of C-O-M bond formation. All the complexes show additional bands at 840-830 cm^{-1} indicating the presence of coordinated water[21].

Magnetic moment and electronic spectra: The room temperature μ_{eff} value for the Co^{+2} complexes 3.87 B.M. suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The electronic spectrum of the Co^{2+} complex shows three bands at 7890, 18740 and 23278 cm^{-1}, assignable to $^4T_{1g}(F) \rightarrow {}^4T_{1g}(F)$ (υ_1), $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (υ_2) and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (υ_3) transitions, respectively for an octahedral geometry[22]. The value of transition ratio υ_2 / υ_1 is 2.37 providing further evidences for octahedral geometry for the Co^{2+} complex.

In the Ni^{+2} complexes, μ_{eff} values at room temperature are in the range 3.20 B.M. as expected for six coordinated spin free Ni^{+2} species[23]. The reflectance spectra of the Ni^{2+} complex, exhibit two strong bands at 15621 cm^{-1} and 22420 cm^{-1}, assignable to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ (υ_1) and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ (υ_2) respectively. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier[24-25].

The Cu^{+2} complexes exhibit normal magnetic moments 1.98 B.M. corresponding to one unpaired electron indicating the distorted octahedral geometry, which is in agreement with data reported by other research worker[26]. Electronic spectra of these complex show broad asymmetric bands in the region 15000 cm^{-1} and at 24900 cm^{-1} assignable $^2B_{1g} \rightarrow {}^2A_{1g}$ and charge transfer transition respectively[27]. These results reveal the distorted octahedral geometry for this complex. The former band may be due to ${}^2E_g \rightarrow {}^2T_{2g}$ accounted due to John Teller effect suggesting thereby a distorted octahedral geometry for these complexes.

Zn^{+2} 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 d^{10} systems and may have tetrahedral geometry[28]. There is no evidence for the characteristic bands of coordinated water in IR spectra.

The electronic spectra of the Mn^{2+} complex exhibited three spin allowed bands in the region 14965 cm^{-1}, 18650 cm^{-1} and 24300 cm^{-1} assigned to the transitions ${}^6A_{1g} \rightarrow {}^4T_{1g}({}^4G)(\upsilon_1)$, ${}^6A_{1g} \rightarrow {}^4T_{2g}({}^4G)(\upsilon_2)$ and ${}^6A_{1g} \rightarrow {}^4E_g, {}^4T_{1g}({}^4P)(\upsilon_3)$ respectively, indicating octahedral geometry[29]. The observed magnetic moment of the Mn^{2+} complexes are 5.30 B.M. corresponding to five unpaired electrons indicates high spin octahedral environment[30].

Antifungal activity: The study of antifungal activity of HACQ ligand and its all chelates (Table-2) reveals that the ligand is moderately toxic against fungi while all the chelates are more toxic than ligand. Among all the chelates the Cu^{+2} chelates is more toxic against fungi. These compound almost inhibit the fungi about 85 %. The antifungal activity of the metal chelates was found to be in the order: Cu (II) > Co (II) > Ni (II) >Mn (II) > Zn. Hence produce metal chelates can be employed as agricultural and garden fungicides.

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 Ni^{2+}, Co^{2+} and Mn^{2+} complexes, tetrahedral polymeric structure for Zn^{2+} and distorted octahedral for Cu^{2+} complex have been tentatively proposed.
- Present work will contribute in the field of new antifungal for some plant pathogenic organisms.

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Table – 1 Analytical and physical data of ligand and its metal chelates .

Compound/ Molecular Formula	M.W. (g/mol)	Yield (%)	Elemental Analysis (%) Found (Calcd.)					μ_{eff} (B.M.)	Λ_M ($ohm^{-1} cm^2 mol^{-1}$)
			C	H	N	Cl	M		
HL_4 $C_{24}H_{17}N_4O_2Cl$	428.50	89	67.20 (67.21)	3.90 (3.96)	13.010 (13.06)	8.49 (8.52)	-	-	-
$(HL_4)_2\ Cu^{+2}$ $C_{48}H_{32}N_8O_4Cl_2$ $Cu^{+2}.2H_2O$	954.54	66	60.2 (60.34)	3.5 (3.79)	11.60 (11.73)	7.60 (7.65)	6.50 (6.66)	1.98	8.76
$(HL_4)_2\ Ni^{+2}$ $C_{48}H_{32}N_8O_4Cl_2$ $Ni^{+2}.2H_2O$	948.69	72	60.5 (60.65)	3.60 (3.79)	11.50 (11.79)	7.50 (7.69)	6.00 (7.18)	3.20	8.33
$(HL_4)_2\ Mn^{+2}$ $C_{48}H_{32}N_8O_4Cl_2$ $Mn^{+2}.2H_2O$	945.93	65	60.6 (60.89)	3.70 (3.81)	11.60 (11.84)	7.60 (7.72)	5.70 (5.81)	5.30	7.80
$(HL_4)_2\ Co^{+2}$ $C_{48}H_{32}N_8O_4Cl_2$ $Co^{+2}.2H_2O$	948.93	52	60.5 (60.64)	3.5 (3.79)	11.70 (11.79)	7.5 (7.68)	6.1 (6.20)	3.98	23.11
$(HL_4)_2\ Zn^{+2}$ $C_{48}H_{32}N_8O_4Cl_2$ $Zn^{+2}.2H_2O$	956.39	66	60.1 (60.23)	3.60 (3.76)	11.60 (11.71)	7.5 (7.63)	6.8 (6.84)	-	9.05

Table-2 Antifungal activities of ligand HL_4 (HACQ) and its metal chelates

Sample	Zone of inhibition at 1000 ppm (%)				
	EP	NS	TS	AN	C
HL_4	80	80	75	68	65
$(HL_4)_2Cu^{+2}$	86	88	77	74	75
$(HL_4)_2Mn^{+2}$	65	68	63	65	62
$(HL_4)_2Zn^{+2}$	60	51	61	57	64
$(HL_4)_2Co^{+2}$	59	60	83	88	57
$(HL_4)_2Ni^{+2}$	87	89	55	66	68

EP = Erysiphepisi, NS = Nigrospora sp., TS = Trichoderma sp.,

AN = Aspergillus niger, C = Curvularialunata.

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