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Synthesis, Characterization and Antifungal Activity Studies on Quinazoline-4-one Derivatives Containing 8-Hydroxy Quinazoline Ligand and its Metal Chelates

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The novel ligand HL_4 was synthesized from anthranilic acid. For this quinazoline-4-one 8-hydroxyquinoline (QHQ) condensed molecules were used. The transition metal chelates like Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) with HL_4 have been prepared and characterized by physico-chemical methods such as elemental analysis, conductometric studies, magnetic susceptibility, IR, NMR and electronic spectral data. The stoichiometry of the complex has been found to be 1:2 (metal:ligand). An octahedral geometry around Co(II), Ni(II) and Mn(II), distorted octahedral geometry around Cu(II) and tetrahedral geometry around Zn(II) have been proposed. The antifungal activity of ligand and its metal chelates was screened against various fungi.

Key Words: 8-Hydroxy quinoline ligand, Chelates, Electronic, IR and NMR spectral studies, Antifungal activity.

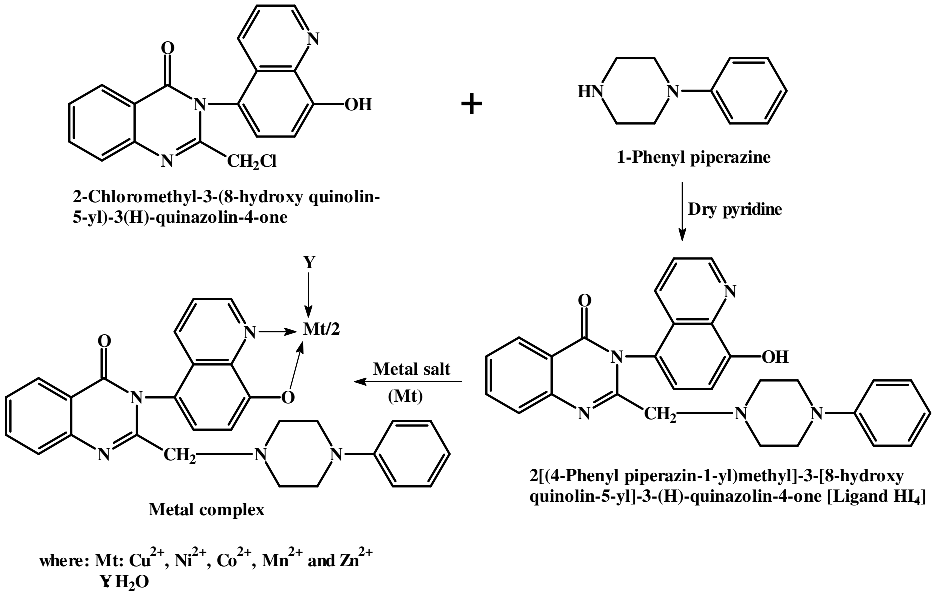
INTRODUCTION

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs[1]. A quinazolin-4-one derivative possesses biological activities such as antifungal[2,3]. Ligand 8-hydroxyquinoline is not only act as a compelling agent but also applied for drug synthesis[4]. The 8-hydroxyquinoline and quinazolin-4-one molecules into one molecule have not received any attention in spite of well-defined applications of both the molecules. Hence it was thought to explore the study of qunazolin-4-one 8-hydroxyquinoline condensed molecules as ligand HL_4 with their complexes with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) metal ion. Antifungal activities of the ligand and metal chelates have also been studied.

EXPERIMENTAL

All the chemicals used were of pure grade (Merck and B.D.H). Double distilled water was used throughout the experiment. The melting points of all complexes were determined by open capillary method and were uncorrected.

Synthesis of ligand HL_4: A mixture of 2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(*H*)-quinazolin-4-one (0.01 mol) and 1-phenyl-piperazine (0.01 mol) were taken in dry pyridine (20 mL) and was refluxed for 12 h. Pyridine was distilled off



Scheme-I

as much as possible and the residue was poured into a little crushed ice with stirring. The product was separated out, filtered, washed with water and finally with ethanol. The air dried product was quantitative. m.p. for HL_4 is 230 °C.

Synthesis of chelates: A dried ligand sample HL_4 (0.01 M) 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 chelates with particular ligand with transition metal ions. The formic acid solution of ligand was added drop wise to a solution of $Cu(NO_3)_2\cdot 6H_2O$, $Ni(NO_3)_2\cdot 6H_2O$, $Co(NO_3)_2\cdot 6H_2O$, $MnCl_2\cdot 6H_2O$, $Zn(NO_3)_2\cdot 6H_2O$ (0.005 mol) in 100 mL of water with rapid stirring. The resultant pH 4.5 [for Cu(II) ion], pH 6.0 [for Ni(II) and Co(II)] and pH 5.6 [for Mn(II) and Zn(II)] were maintained by addition of sodium acetate. A dark coloured solid precipitated out. It was allowed to settle and digested on water bath at 70 ºC for about 2 h. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone then dried. The percentage yield of chelates was in the range of 55-79 %. All the chelates were powdered well and dried at 70 °C over a period of 24 h.

The C, H and N contents of metal chelates were determined on elemental analyzer Thermofiniggan 1101 Flash EA. The metal contents were estimated using standard methods[5]. 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. ^1H NMR spectra of ligand was recorded on Bruner NMR spectrophotometer. PMR chemical shifts are recorded in δ-value using TMS as an internal standard in $CDCl_3$/DMSO-d_6. The IR spectra (KBr) of ligand was recorded in the range 4000-600 cm^{-1} on a Nicolet-760 spectrophotometer. Electronic spectra of the metal chelates were recorded on a Beckman -DK-2A spectrophotometer using MgO as reference. Magnetic susceptibility 'χ_m' was measured by Gouy's method[6] at room temperature (300 K) using Hg $[Co(CNS)_4]$ as calibrant[7] and the effective magnetic moment from relation[8], $\mu_{eff} = 2.84\sqrt{\chi_m \times T}$, where T = 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. Botrydepladia thiobromine*, *Nigrospora* sp., *Rhizopus nigricans*, *Aspergillus fumigatus* and *Candida albicans*. The antifungal activity of the compounds was measured by plate method[9]. Five days old cultures were suspended in potato dextrose agar (PDA) medium and autoclaved at 1200 ºC for 15 min at 15 atmospheric pressure. The percentage inhibition of fungi was calculated after 5 days using the formula given below:

$$\text{Percentage of inhibition} = 100\ (X - Y)/X$$

where X = area of colony in control plate (without sample) and Y = area of colony in test plate.

RESULTS AND DISCUSSION

The complexes are microcrystalline coloured 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. The low molar conductance values in the range of 8.22-23.09 $ohm^{-1}\ cm^2\ mol^{-1}$ in Mn(II), Ni(II), Cu(II) and Zn(II) chelates indicates that they are non-electrolytic[10] and monomeric in nature (ML_2 type chelates). The low conductance values may be attributed to the large cations[11]. The electrical conductivity of these chelates was found in the decreasing order: Co > Zn > Cu > Ni > Zn.

Infrared spectra: IR spectrum of ligand HL_4 show a broad band extended from 3400-2600 cm^{-1} which might be responsible to phenolic group bonded to N atom of 8-hydroxy quinoline moiety[12,13]. The inflextious at 2923, 2852 and 1470 cm^{-1} are due to aromatic CH and methylene group of bridge and piperazine ring[14]. The strong band at 1710 cm^{-1} is attributed to C=O of quinazoline 4-one moiety. Several bands appeared between 1500-1600 cm^{-1} region may arise from aromatic breathing. The IR band at *ca.* 1580 cm^{-1} (C=N of 8-quinolinol system) of HL_4 ligands shifted to higher frequency side *ca.* 1600 in the spectra of the metal chelates indicating involvement of nitrogen in the chelate formation[12,15,16]. Most of bands appeared in the spectra of corresponding ligand are observed at their metal chelates. Only a new band at 1095 cm^{-1} had appeared in the spectra of metal chelates. This may be assigned to ν(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[17].

TABLE-1
ANALYTICAL AND PHYSICAL DATA OF LIGAND AND ITS METAL CHELATES

Ligand/molecular formula	m.w. (g/mol)	Yield (%)	Elemental analysis (%): Found (calcd.)				Observed μ_{eff} (BM)	Λ_M (Ohm^{-1} cm^2 mol^{-1})
			C	H	N	M		
HL_4 ($C_{28}H_{25}N_5O_2$)	463.53	69	72.40 (72.57)	5.30 (5.40)	15.00 (15.11)	–	–	–
$(HL_4)_2Cu^{2+}$ ($C_{56}H_{54}N_{10}O_6Cu^{2+}$)	1025.54	70	65.60 (65.65)	5.00 (5.08)	13.60 (13.67)	6.10 (6.20)	2.00	8.88
$(HL_4)_2Ni^{2+}$ ($C_{56}H_{54}N_{10}O_6Ni^{2+}$)	1014.69	55	65.80 (65.96)	5.00 (5.10)	13.60 (13.74)	5.70 (5.76)	3.09	8.22
$(HL_4)_2Co^{2+}$ ($C_{56}H_{54}N_{10}O_6Co^{2+}$)	1014.90	65	65.90 (65.95)	5.00 (5.10)	13.70 (13.74)	5.70 (5.78)	5.00	23.09
$(HL_4)_2Mn^{2+}$ ($C_{56}H_{54}N_{10}O_6Mn^{2+}$)	1016.90	79	66.20 (66.21)	5.10 (5.12)	13.75 (13.79)	5.30 (5.35)	5.90	7.68
$(HL_4)_2Zn^{2+}$ ($C_{56}H_{54}N_{10}O_6Zn^{2+}$)	1024.39	72	65.30 (65.53)	4.90 (5.07)	13.60 (13.65)	6.30 (6.37)	–	9.02

NMR spectra: ^{1}H NMR spectra of ligand shows results in δ ppm as follows: 1.4 (-CH_2), 2.0 (-CH), 4.82 (singlet of phenolic -OH), 3.44-3.52 (triplet -CH_2 of piperizine), 3.47 (-CH_2 bridge) and 7.1-8.84 (multiplet, quinazoline).

Magnetic moment and electronic spectra: At room temperature the magnetic moment 'μ_{eff}' values for the Co(II) complex is 5.0 BM (Table-1) suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The electronic spectra of the Co(II) complex display three absorption bands in the range 7895, 18745 and 23258 cm^{-1}, assigned to the transitions $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1), $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (ν_2) and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (ν_3), respectively[18]. The values of transition ratio ν_2/ν_1 is 2.37 providing further evidences for octahedral geometry for the Co(II) complexes.

In the Ni(II) complex, μ_{eff} value at room temperature is observed to be 3.09 BM as expected for six coordinated spin free Ni(II) species. The reflectance spectra of the Ni(II) complex, exhibit two strong bands at 13845 and 25489 cm^{-1}, assignable to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$, respectively. The ν_2/ν_1 ratio for the chelate is 1.84 occurs in the usual range (1.60-1.82) for octahedral Ni(II) chelates[19]. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier[20,21]. The Cu(II) complex exhibit normal magnetic moments (2.0 BM) indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers[2,22,23]. These complex show broad asymmetric bands in the region 14896 cm^{-1} and at 25896 cm^{-1} assignable to $^2B_{1g} \rightarrow {}^2A_{1g}$ and charge transfer transition, respectively[24]. These results reveal the distorted octahedral geometry for these complexes. The former band may be due to $^2E_g \rightarrow {}^2T_{2g}$ accounted due to Jahn Teller effect suggesting thereby a distorted octahedral geometry for these complexes[25]. The values of transition ratio ν_2/ν_1 is 1.60.

Zn(II) complexes are diamagnetic as expected for d^{10} systems and may have tetrahedral geometry[26,27]. There is no evidence for the characteristic bands of coordinated water in IR spectra. The electronic spectra of the Mn(II) exhibited three spin allowed bands in the region 14965, 18654 and 24856 cm^{-1} assigned to the transitions $^6A_{1g} \rightarrow {}^4T_{1g}$ (^4G), $^6A_{1g} \rightarrow {}^4T_{2g}$ (^4G) and $^6A_{1g} \rightarrow {}^4E_g$, $^4T_{1g}$(^4G), respectively, indicating octahedral geometry. The observed magnetic moment (5.90 BM) of the complexes indicates high spin octahedral environment[28].

Antifungal activity: The complexes show inhibition of fungal in following decreasing order: Cu(II) > Ni(II) > Co > Mn(II) > Zn(II).

The substitutions of phenyl rings by chlorine have much more effect on the fungicidal activity. The results were shown in Table-2, suggests that variation in structure on coordination affects the growth of micro organisms and may result in to inhibitory or reduction in toxicology of metal ions towards some organisms[29].

TABLE-2
ANTIFUNGAL ACTIVITY OF LIGAND (HL_4) AND ITS METAL CHELATES

Samples	Zone of inhibition at 1000 pm (%)				
	Candida albicans	*Botrydepladia thibromine*	*Nigrospora Sp.*	*Aspergillus fumigatus*	*Rhizopur nigricums*
HL_4	80	59	55	82	79
$(HL_4)_2Cu^{2+}$	89	88	74	75	78
$(HL_4)_2Ni^{2+}$	89	87	54	65	69
$(HL_4)_2Co^{2+}$	59	58	81	86	54
$(HL_4)_2Mn^{2+}$	67	69	65	61	60
$(HL_4)_2Zn^{2+}$	59	49	59	56	63

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(II), Co(II) and Mn(II) complexes, tetrahedral polymeric structure for Zn(II) and distorted octahedral for Cu(II) complex have been tentatively proposed. Present work will contribute in the field of new antifungal for some plant pathogenic organisms.

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