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Der Pharma Chemica, 2010, 2(2): 216-222
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Synthesis and antifungal activity of quinazoline-4-one derivatives containing 8-hydroxy quinazoline ligand and its transition metal chelates

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Abstract

The novel ligand PMHQ (HL_5) was synthesized using anthranilic acid and it was undergo the chelating reaction with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) to prepare transition metal chelates. These chelates were characterized by physicochemical methods such as elemental analysis, conductometric studies, magnetic susceptibility, FT-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 tetra hedral geometry around Zn(II) have been proposed. The antifungal activity of ligand and its metal chelates was conducted against various fungi.

Key Words: Ligand, Chelates, Electronic, IR, NMR spectr, 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 quinazolin-4- one 8-hydroxyquinoline merged molecules as ligand HL_5 with their complexes with Cu (II), Ni (II), Co (II), Mn (II) and Zn (II) metal ion. Antifungal activities of the ligand and its chelates have also been studied.

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 and molar conductance data are shown in Table-1. The result indicates that they are less polar in DMF. The molar conductance values found to be 23.99, 10.22, 9.99, 9.79, 6.98 and $\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$ for Co(II), Ni(II), Mn (II), Cu(II), Zn(II) and respectively. So, the electrical conductivity of these metal chelates were found in the decreasing order: Co(II) > Ni(II) > Mn (II) > Cu(II) > Zn(II). The very low values of chelates indicates that they are non-electrolytic [5] and monomeric in nature. The low conductance values may be attributed to the large cations [6].

Infrared spectra: FT-IR spectrum of ligand HL₅ show a broad band extended from 3400 to 2600 cm^{-1} which might be responsible to phenolic group bonded to N atom of 8-hydroxy quinoline moiety [7, 8]. The inflexions at 2923, 2852 and 1470 cm^{-1} are due to aromatic CH and methylene group of bridge and piperazine ring [9]. The strong band at 1705 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 ~ 1580 cm^{-1} (C=N of 8-quinolinol system) of HL₅ ligand shifted to higher frequency side ~1600 in the spectra of the metal chelates indicating involvement of nitrogen in the chelate formation [7, 10, 11]. 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 [12].

NMR spectra: ¹H NMR spectra of ligand was depicted in figure 1, which shows results in δ ppm as follows: 3.44 to 3.52 (triplet -CH₂ of piperazine), 3.47 (-CH₂ bridge), 4.82 (singlet of phenolic -OH), and 7.1 to 8.84 (multiplet, quinazoline).

Magnetic moment and Electronic spectra: At room temperature the magnetic moment ' μ_{eff} ' values for the Co (II) complex is 3.98 B.M (Table-1) suggest high spin octahedral geometry, which was further supported by the electronic spectral data. The electronic spectra of the Co(II) complex display three absorption bands in the range 7999, 17599 and 24156 cm^{-1} , assigned to the transitions ${}^4T_{1g}(\text{F}) \rightarrow {}^4T_{2g}(\text{F}) (\nu_1)$, ${}^4T_{1g}(\text{F}) \rightarrow {}^4A_{2g}(\text{F}) (\nu_2)$ and ${}^4T_{1g}(\text{F}) \rightarrow {}^4T_{1g}(\text{P}) (\nu_3)$ respectively [13]. The values of transition ratio ν_2 / ν_1 is 2.20 providing further evidences for octahedral geometry for the Co (II) complexes.

Nickel (II) complex was found to be paramagnetic with a μ_{eff} value of 3.33 B.M. at room temperature suggesting consistency with it octahedral environment [14]. The reflectance spectra of the Ni(II) complex, exhibit two strong bands at 14969 cm^{-1} and 23568 cm^{-1} , assignable to ${}^3A_{2g}(\text{F}) \rightarrow {}^3T_{1g}(\text{F})$ and ${}^3A_{2g}(\text{F}) \rightarrow {}^3T_{1g}(\text{P})$ respectively. The ν_2/ν_1 ratio for the chelate is 1.57 occurs in the usual range (1.6 –1.82) for octahedral Ni (II) chelates [15] The spectral bands are well within the range observed for hexa coordinate octahedral complexes reported earlier [16].

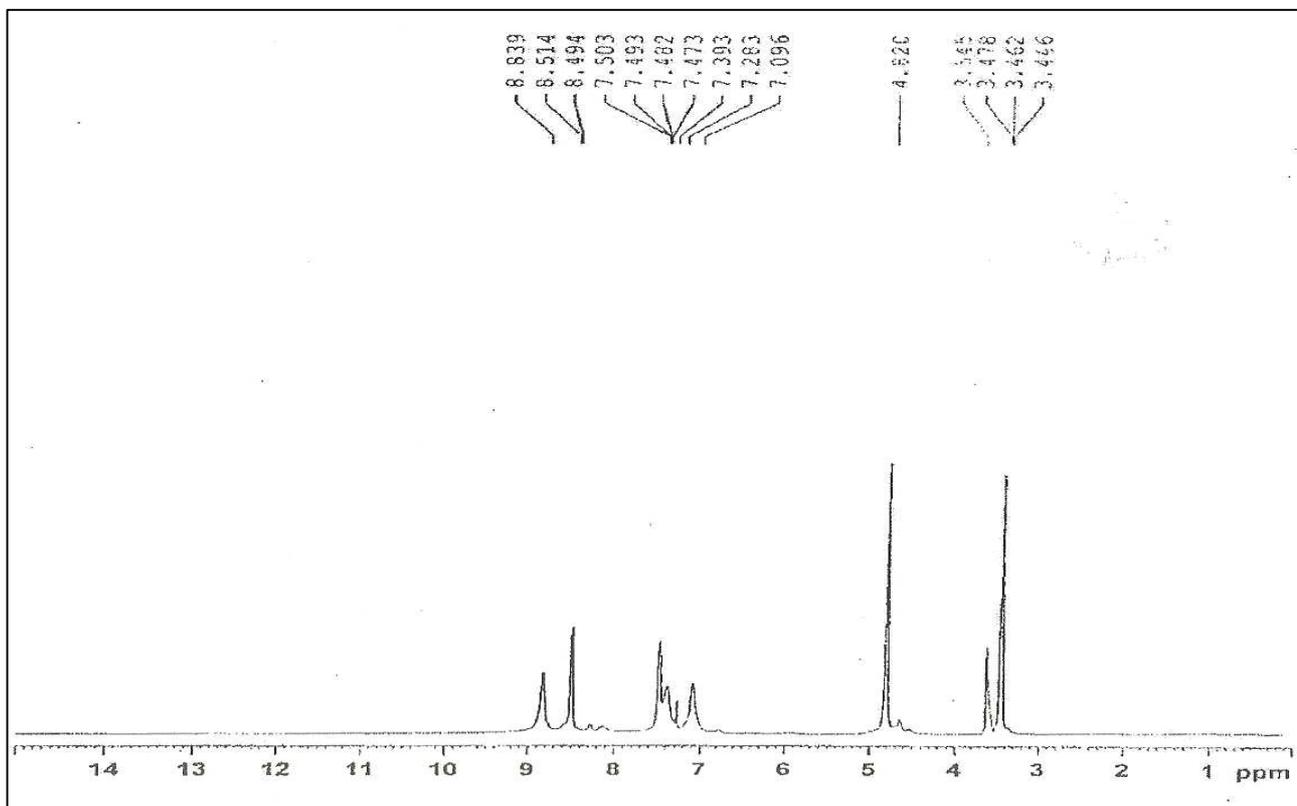


Fig.1 ^1H NMR spectra of ligand HL_5

Copper (II) complex exhibit normal magnetic moment value of 2.12 B.M slightly higher than spin only value (1.73 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers [17, 18]. These complex show broad asymmetric bands in the region 15888 cm^{-1} and at 23859 cm^{-1} assignable to $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$ and charge transfer transition respectively [19, 20]. These results reveal the distorted octahedral geometry for these complexes. The former band may be due to $^2\text{E}_g \rightarrow ^2\text{T}_{2g}$ accounted due to Jahn Teller effect suggesting thereby a distorted octahedral geometry for these complexes [21]. The value of transition ratio ν_2/ν_1 is 1.50.

The electronic spectra of the Mn(II) exhibited three spin allowed bands in the region 16987 , 18523 and 24963 cm^{-1} assigned to the transitions $^6\text{A}_{1g} \rightarrow ^4\text{T}_{1g} (^4\text{G})$, $^6\text{A}_{1g} \rightarrow ^4\text{T}_{2g} (^4\text{G})$ and $^6\text{A}_{1g} \rightarrow ^4\text{E}_g, ^4\text{T}_{1g} (^4\text{G})$ respectively, indicating octahedral geometry [22]. The observed magnetic moment (5.88 B.M.) of the complexes indicates high spin octahedral environment [23]. Zinc (II) complex was found diamagnetic as expected for d^{10} configuration, according to the empirical formula of the complex, a tetrahedral geometry [24, 25]. There is no evidence for the characteristic bands of coordinated water in IR spectra.

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

Ligand / Mol. Formula	M. W. (g/mole)	Yield (%)	Elemental Analysis (%)				Observed μ_{eff} (B.M) (Expected)	Λ_{M} (Ohm^{-1} $\text{cm}^2 \text{mol}^{-1}$)
			Found (Calc.)					
			C	H	N	M		
HL ₅ C ₂₇ H ₂₄ N ₆ O ₂	464.0	80	69.70 (69.18)	5.10 (5.17)	18.10 (18.14)	-	-	-
(HL ₅) ₂ Cu ²⁺ C ₅₄ H ₅₀ N ₁₂ O ₆ Cu ²⁺	1025.54	65	63.10 (63.18)	4.80 (4.87)	16.30 (16.38)	6.10 (6.19)	2.12 (1.7-2.2)	9.79
(HL ₅) ₂ Ni ²⁺ C ₅₄ H ₅₀ N ₁₂ O ₆ Ni ²⁺	1020.69	80	63.40 (63.48)	4.80 (4.89)	16.30 (16.45)	5.70 (5.75)	3.33 (2.9-3.4)	10.22
(HL ₅) ₂ Co ²⁺ C ₅₄ H ₅₀ N ₁₂ O ₆ Co ²⁺	1020.90	79	63.40 (63.47)	4.80 (4.89)	16.40 (16.45)	5.70 (5.76)	3.98 (4.4-5.2)	23.99
(HL ₅) ₂ Mn ²⁺ C ₅₄ H ₅₀ N ₁₂ O ₆ Mn ²⁺	1016.93	72	63.60 (63.72)	4.90 (4.91)	16.50 (16.52)	5.30 (5.34)	5.88 (5.2-6.0)	9.99
(HL ₅) ₂ Zn ²⁺ C ₅₄ H ₅₀ N ₁₂ O ₆ Zn ²⁺	1027.39	70	63.00 (63.07)	4.80 (4.56)	16.30 (16.35)	6.30 (6.36)	-	6.98

Antifungal activity: The ligand and chelates were used for their antimicrobial studies by means of fungi, such as *Candida Albicans*, *Botrydepladia Thibromine*, *Nigrospora Sp*, *Aspergillus Fumigatus* and *Rhizopur Nigricums*. Antifungal activity of ligand and chelates (Table-2) show antifungal activity in following decreasing order:

Cu (II) > Zn (II) > Ni (II) > Co (II) > Mn (II).

Table 2. Antifungal activity of ligand HL₅ and its metal chelates

Ligand/ Chelates	Zone of inhibition at 1000 pm (%)				
	<i>Candida Albicans</i>	<i>Botrydepladia Thibromine</i>	<i>Nigrospora Sp.</i>	<i>Fumigatus Aspergillus</i>	<i>Rhizopur Nigricums</i>
HL ₅	88	57	57	81	62
(HL ₅) ₂ Cu ²⁺	79	76	75	74	73
(HL ₅) ₂ Ni ²⁺	59	68	69	77	70
(HL ₅) ₂ Co ²⁺	63	68	69	68	88
(HL ₅) ₂ Mn ²⁺	77	69	56	58	59
(HL ₅) ₂ Zn ²⁺	77	78	72	73	69

The substitutions of phenyl rings by chlorine have much more effect on the fungicidal activity. The results suggest 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 [26].

MATERIAL AND METHODS

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 ligand was determined by open capillary method and were uncorrected.

Synthesis of ligand PMHQ (HL₅): The anthranilic acid was converted into N-Chloroacetyl anthranilic acid by means of chloroacetyl chloride then it refluxed with 5-amino-8-hydroxy quinolin and phosphorous trichloride in dry 1, 4-dioxone under anhydrous condition for 4 hrs.

The reaction mixture was allowed to cool and phosphorous trichloride was decomposed by titrating with cold water. Then, 1, 4-dioxone was distilled off to get the product, 2-chloromethyl -3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one. It was filtered and washed with small portion of sodium bicarbonate solution (10 %) after then extensively with cold water. The mixture of 2-Chloromethyl -3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one and 1-(4-pyridinyl)-piperazine in dry pyridine was refluxed for 12 hrs. Pyridine was distilled off as much as possible and the residue was poured into little crushed ice with stirring. The product, HL₅ was separated out, filtered and washed with water and finally with ethanol. The air dried product was quantitative. Melting point of HL₅ was 230 °C.

Synthesis of Chelates: A dried ligand sample HL₅ (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 (NO₃)₂.6H₂O, Ni(NO₃)₂.6H₂O, Co(NO₃)₂.6H₂O, MnCl₂.6H₂O, Zn(NO₃)₂.6H₂O (0.005 mole) in 100 ml of water with rapid stirring. The resultant pH 4.5 [for Cu(II), 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 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 then dried. The percentage yield of chelates was in the range of 65-80 %. All the chelates were powdered well and dried at 70 °C over a period of 24 h.

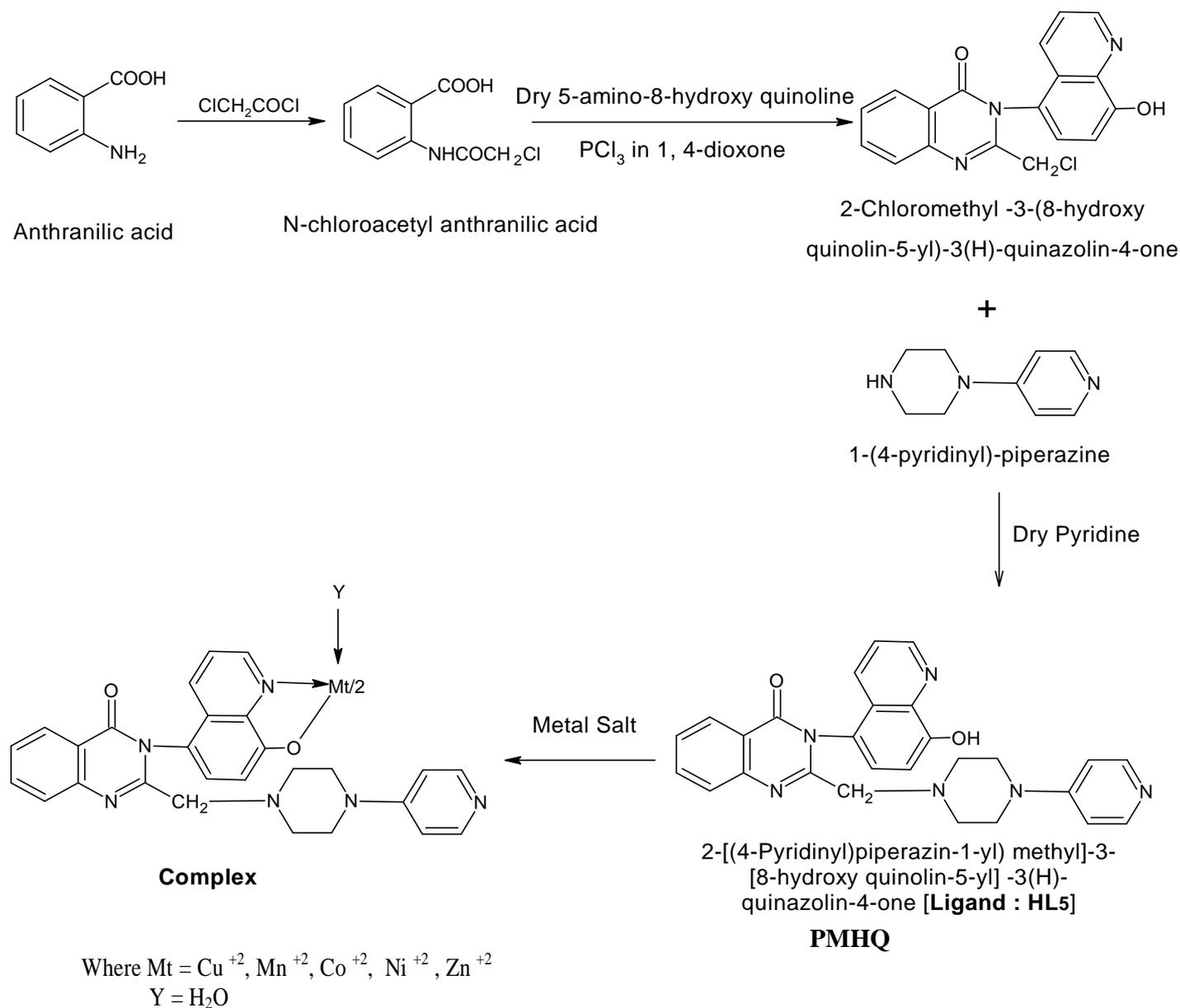
The C, H and N contents of metal chelates were determined on elemental analyzer Thermofinigan 1101 Flash EA. The metal contents were estimated using standard methods [27]. The molar conductance of the complexes in DMF (10⁻³ M) solutions were measured at room temperature using Systronics model 305 direct 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 CDCl₃ /D₆- DMSO. The IR spectra (KBr) were 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 [28] at room temperature (300 K) using Hg [Co(CNS)₄] as calibrant [29], and the effective magnetic moment from relation [30], μ_{eff} = 2.84 √ χ_m x 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. *Botrydepladia thiobromine*, *Nigrospora sp.*, *Rhizopus nigricans*, *Aspergillus fumigatus* and *Candida albicans*. The antifungal activity of the compounds was measured by plate method [31]. 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:

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

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

General structure of formation of chelates was shown in Scheme-I

Scheme-I**CONCLUSION**

The ligand molecule acts as a hexa dentate 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 study will contribute in the field of new antifungal for some plant pathogenic organisms.

Acknowledgements

The authors are thankful to Department of Chemistry, Navyug Science College, Surat for providing laboratory facilities.

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