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## Synthesis and antifungal activity of 6-bromo-2[(4-pyridinyl)-1-yl] methyl]-3-[8-hydroxy quinolin -5-yl]-3-quinazolin -4-one ligand and its metal chelates

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### ABSTRACT

The novel ligand HL<sub>12</sub> 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.

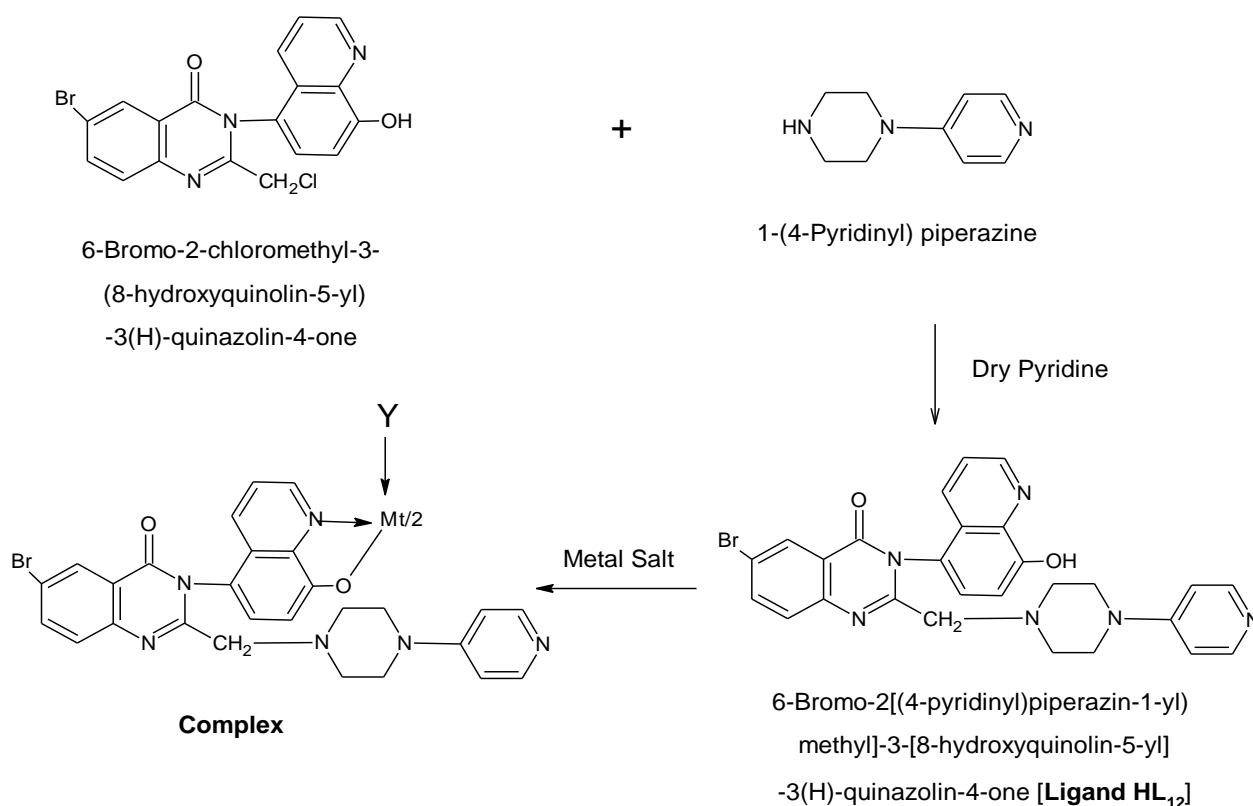
**Key Words:** 8-Hydroxy quinoline ligand, Complexes, Electronic, NMR spectral studies, Antifungal activity

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## 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 [2-4]. 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<sub>12</sub> with their complexes with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) metal ion. Antifungal activities of the ligand and its metal chelates have also been studied.

General structure of formation of chelate was shown in scheme-I.



BPMHQ

Mt: Cu<sup>2+</sup>, Mn<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Zn<sup>2+</sup>

Y = H<sub>2</sub>O

Scheme I

## EXPERIMENTAL PROCEDURE

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 were determined by open capillary method and were uncorrected.

### Synthesis of BPMHQ ligand (HL<sub>12</sub>)

The 6-bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one was prepared as follows: 5-bromoanthranilic acid was prepared by method reported in literature [5]. A mixture of 5-bromo-N-chloroacetyl anthranilic acid (0.1 mol) and 5-amino-8-hydroxy quinoline (0.1 mole) and phosphoric tri chloride (0.1 mol) in dry 1,4-dioxane was refluxed under anhydrous condition for 4 hrs. The reaction mixture was allowed to cool and PCl<sub>3</sub> was decomposed by titrating with cold water. Then 1,4-dioxane was distilled off to get the product. It was filtered, washed first with small portion of sodium bicarbonate solution (10 %) then extensively with cold water. The mixture of 6-bromo-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, HL<sub>12</sub> i.e. 6-Bromo-2-[(4-pyridinyl)piperazin-1-yl] methyl]-3-[8-hydroxyquinolin-5-yl]-3(H)-quinazolin-4-one ligand was separated out, filtered and washed with water and finally with ethanol. The air dried product was quantitative. It decomposed in the range of 230-240 °C.

### Synthesis of Chelates

A dried ligand sample HL<sub>12</sub> (0.05 M) was stirred in 85 % (v/v) formic acid and then it was diluted by water until complete dissolution. The resultant solution was then diluted to 500 ml. by distilled water and designated as reagent solution. This solution was used for preparation of chelates with particular ligand with transition metal ions. The reagent solution (100 ml. containing 0.01 mole ligand) of ligand was added drop wise to each of solution of Cu(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O (0.005 mole), Ni(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O(0.005 mole), Co(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O (0.005 mole), MnCl<sub>2</sub>.6H<sub>2</sub>O(0.005 mole), Zn(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O (0.005 mole) in 100 ml of water with constant 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 1.0 g 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 69-80 %. 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 [6]. The molar conductance of the complexes in DMF (10<sup>-3</sup> M) solutions were measured at room temperature using Systronics model 305 direct reading conductivity bridge. <sup>1</sup>H NMR spectra of ligand was recorded on Bruker NMR spectrophotometer (300 MHz). PMR chemical shifts were recorded in δ – value using TMS as an internal standard in CDCl<sub>3</sub> /D<sub>6</sub>- DMSO. The IR spectra (KBr) were recorded in the range 4000-600 cm<sup>-1</sup> 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 ‘ $\chi_m$ ’ was measured by Gouy’s method [7] at room temperature (300 K) using Hg [Co(CNS)<sub>4</sub>] as calibrant [8], and the effective magnetic moment from relation [9],  $\mu_{\text{eff}} = 2.84 \sqrt{\chi_m \times T}$ , 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. *Botrydepladia thiobromine*, *Nigrospora sp.*, *Rhizopus nigricans*, *Aspergillus fumigatus* and *Candida albicans*. 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 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 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 were shown in Table-1. The result indicates that they are less ionic in DMF. The molar conductance values found to be 19.20, 8.28, 7.68, 10.02 and 7.12 ohm<sup>-1</sup>cm<sup>2</sup>mol<sup>-1</sup> for Co(II), Ni(II), Zn(II), Cu(II) and Mn(II) respectively. So, the electrical conductivity of these chelates was found in the decreasing order: Co > Cu > Ni > Zn > Mn. The very low values of chelates indicates that they are non-electrolytic [11] and monomeric in nature. The low conductance values may be attributed to the large cations [12].

Ligand / Mol. Formula	M. W. (g/mole)	Yield (%)	Elemental Analysis (%)					Observed $\mu_{\text{eff}}$ (B.M) (Expected)	$\Lambda_M$ (Ohm <sup>-1</sup> cm <sup>2</sup> mol <sup>-1</sup> )
			Found (Calcd.)						
			C	H	N	Br	M		
HL <sub>12</sub> C <sub>27</sub> H <sub>23</sub> N <sub>6</sub> O <sub>2</sub> Br	543.00	72	60.00 (60.11)	4.20 (4.26)	15.48 (15.58)	14.70 (14.84)	-	-	-
(HL <sub>12</sub> ) <sub>2</sub> Cu <sup>2+</sup> C <sub>54</sub> H <sub>48</sub> N <sub>12</sub> O <sub>6</sub> Cu <sup>2+</sup> Br <sub>2</sub>	1183.54	76	54.70 (54.75)	4.00 (4.05)	14.10 (14.19)	13.30 (13.34)	5.30 (5.36)	2.19 (1.7-2.2)	10.02
(HL <sub>12</sub> ) <sub>2</sub> Ni <sup>2+</sup> C <sub>54</sub> H <sub>48</sub> N <sub>12</sub> O <sub>6</sub> Ni <sup>2+</sup> Br <sub>2</sub>	1178.69	78	54.80 (54.97)	4.00 (4.07)	14.25 (14.25)	13.30 (13.40)	4.97 (4.90)	3./2 (2.9-3.4)	8.28
(HL <sub>12</sub> ) <sub>2</sub> Co <sup>2+</sup> C <sub>54</sub> H <sub>48</sub> N <sub>12</sub> O <sub>6</sub> Co <sup>2+</sup> Br <sub>2</sub>	1178.90	69	54.90 (54.96)	3.90 (4.07)	14.25 (14.25)	13.30 (13.40)	4.80 (4.99)	3.99 (4.4-5.2)	19.20
(HL <sub>12</sub> ) <sub>2</sub> Mn <sup>2+</sup> C <sub>54</sub> H <sub>48</sub> N <sub>12</sub> O <sub>6</sub> Mn <sup>2+</sup> Br <sub>2</sub>	1174.90	70	55.10 (55.15)	4.00 (4.08)	14.20 (14.29)	13.40 (13.44)	4.60 (4.62)	5.35 (5.2-6.0)	7.12
(HL <sub>12</sub> ) <sub>2</sub> Zn <sup>2+</sup> C <sub>54</sub> H <sub>48</sub> N <sub>12</sub> O <sub>6</sub> Zn <sup>2+</sup> Br <sub>2</sub>	1185.39	80	54.60 (54.66)	3.90 (4.04)	14.17 (14.17)	13.20 (13.32)	5.40 (5.51)	-	7.68

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



Sr. No.	Chemical Shift (ppm)	Probable functional group
1	3.47	CH <sub>2</sub> bridge
2	3.44 to 3.52	Triplet -CH <sub>2</sub> of piperazine
3	4.82	Singlet of phenolic -OH
4	7.1 to 8.84	Multiplet, quinazoline

Table 3: <sup>1</sup>H NMR data of HL<sub>12</sub> and its justification

### Magnetic moment and Electronic spectra:

At room temperature the magnetic moment ' $\mu_{\text{eff}}$ ' values for the Co (II) complex is 3.99 B.M (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 8562, 19549 and 24859 cm<sup>-1</sup>, assigned to the transitions <sup>4</sup>T<sub>1g</sub> (F) ----> <sup>4</sup>T<sub>2g</sub> (F) ( $\nu_1$ ), <sup>4</sup>T<sub>1g</sub> (F) ----> <sup>4</sup>A<sub>2g</sub> (F) ( $\nu_2$ ) and <sup>4</sup>T<sub>1g</sub> (F) ----> <sup>4</sup>T<sub>1g</sub> (P) ( $\nu_3$ ) respectively [17]. The value of transition ratio

$\nu_2 / \nu_1$  was 2.28 providing further evidences for octahedral geometry for the Co(II) complexes.

In the Ni (II) complex,  $\mu_{\text{eff}}$  value at room temperature is observed to be 3.12 B.M. as expected for six coordinated spin free Ni(II) species. The reflectance spectra of the Ni(II) complex, exhibit two strong bands at 15888 and 23809 cm<sup>-1</sup>, assignable to <sup>3</sup>A<sub>2g</sub> (F) ----> <sup>3</sup>T<sub>1g</sub> (F) and <sup>3</sup>A<sub>2g</sub> (F) ----> <sup>3</sup>T<sub>1g</sub> (P) respectively. The  $\nu_2/\nu_1$  ratio for the chelate is 1.50 occurs in the usual range (1.6 –1.82) for octahedral Ni (II) chelates [18]. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier [19].

The Cu (II) complex exhibit normal magnetic moments (2.19 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers [20]. These complex show broad asymmetric bands in the region at 13984 and 23859 cm<sup>-1</sup> assignable to <sup>2</sup>B<sub>1g</sub> ----> <sup>2</sup>A<sub>1g</sub> and charge transfer transition respectively [21]. These results reveal the distorted octahedral geometry for these complexes. The former band may be due to <sup>2</sup>E<sub>g</sub> ----> <sup>2</sup>T<sub>2g</sub> accounted due to Jahn Teller effect suggesting thereby a distorted octahedral geometry for these complexes [22]. The value of transition ratio  $\nu_2 / \nu_1$  was 1.71.

Zn (II) complexes are diamagnetic as expected for d<sup>10</sup> systems and may have tetrahedral geometry [23]. The electronic spectra of the Mn(II) exhibited three spin allowed bands in the region 15545, 18552 and 23568 cm<sup>-1</sup> assigned to the transitions <sup>6</sup>A<sub>1g</sub> ----> <sup>4</sup>T<sub>1g</sub> (<sup>4</sup>G), <sup>6</sup>A<sub>1g</sub> ----> <sup>4</sup>T<sub>2g</sub> (<sup>4</sup>G) and <sup>6</sup>A<sub>1g</sub> ----> <sup>4</sup>E<sub>g</sub>, <sup>4</sup>T<sub>1g</sub> (<sup>4</sup>G) respectively, indicating octahedral geometry [24]. The observed magnetic moment (5.35 B.M.) of the complexes indicates high spin octahedral environment [25].

### 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 its metal chelates shown in Table-4 inhibition of fungal in following decreasing order:

Samples	Zone of inhibition at 1000 ppm (%)				
	Candida Albicans	Botrydepladia Thibromine	Nigrospora Sp.	Aspergillus Fumigatus	Rhizopur Nigricums
HL <sub>12</sub>	88	87	80	81	82
(HL <sub>12</sub> ) <sub>2</sub> Cu <sup>2+</sup>	79	76	78	80	73
(HL <sub>12</sub> ) <sub>2</sub> Ni <sup>2+</sup>	59	68	69	77	70
(HL <sub>12</sub> ) <sub>2</sub> Co <sup>2+</sup>	63	68	69	68	88
(HL <sub>12</sub> ) <sub>2</sub> Mn <sup>2+</sup>	77	69	56	58	59
(HL <sub>12</sub> ) <sub>2</sub> Zn <sup>2+</sup>	77	78	72	73	69

**Table 4: Antifungal activity of ligand HL<sub>12</sub> and its metal chelates**

HL<sub>12</sub> > Cu (II) > Zn (II) > Co (II) > Ni (II) > Mn (II).

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].

### 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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