



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

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**ABSTRACT**

Synthesis and characterization of 2-[(8-hydroxyquinolinyl)-5-aminomethyl]-3-(4-bromophenyl)-6-bromo-3(H)-quinazolin-4-one ligand called HAMQ (HL<sub>11</sub>) 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-bromophenyl) -6-Bromo- 3(H)-quinazolin-4-one. This compound was finally condensed with 5-amino-8-hydroxyquinoline. The transition metal complexes of Cu<sup>2+</sup>, Ni<sup>2+</sup>, Zn<sup>2+</sup>, Mn<sup>2+</sup> and Co<sup>2+</sup> of this ligand HAMQ were prepared and characterized by elemental analysis, IR , NMR and reflectance spectral studies 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<sup>2+</sup>, Ni<sup>2+</sup> and Mn<sup>2+</sup> complexes, a distorted octahedral geometry around Cu<sup>2+</sup> and a tetrahedral geometry around Zn<sup>2+</sup> chelates have been proposed. These complexes have been monitored for their antifungal activities.

**KEYWORDS:** Ligand, 8-hydroxyquinoline, IR , NMR and reflectance spectral studies, antifungal study.



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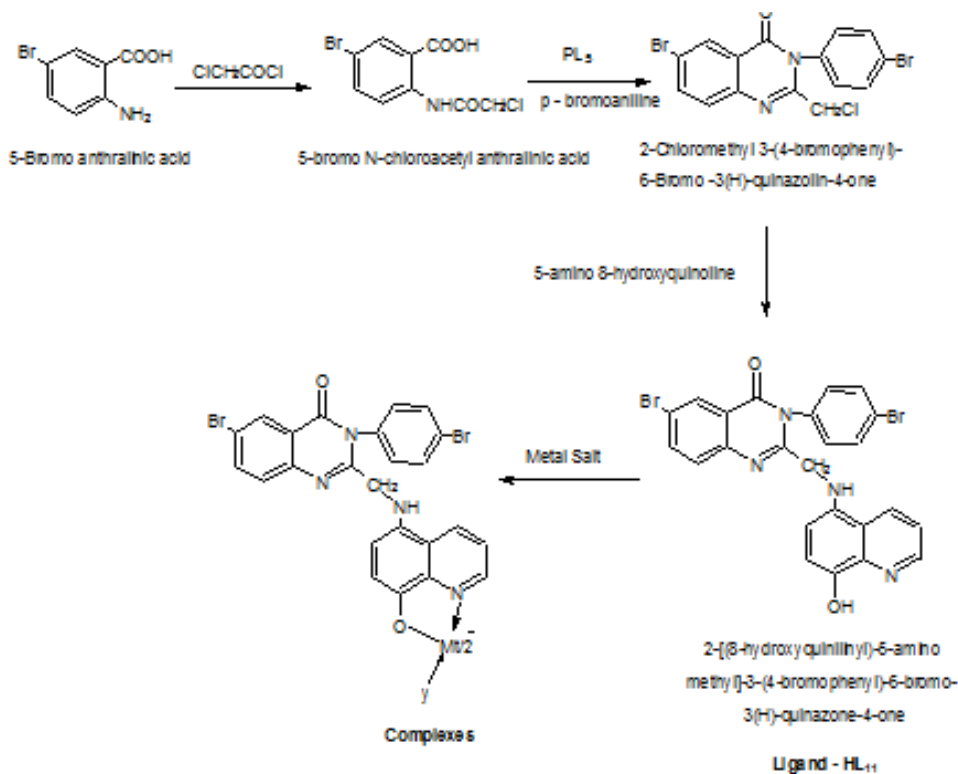
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## INTRODUCTION

The chemistry of heterocyclic compounds continuously to be an explore field in the organic chemistry. Infectious diseases caused by micro and micro 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<sup>1</sup> against gram-positive bacteria is a major concern. The heterocyclic nitrogen compounds especially quinazolin derivatives play a vital role in many biological processes and as synthetic drugs<sup>2</sup>. A Quinazolin-4-one derivative possesses

biological activities such as antifungal<sup>3-4</sup>. 6-bromoquinazolinone derivatives possesses anti-inflammatory, analgesic and anti-bacterial activity<sup>5</sup>. 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<sup>6</sup>. Thus in the extension of this work<sup>6</sup> present communication comprises the synthesis, characterization and chelating properties of novel quazolin-4-one-8-hydroxyquinoline derivatives. The whole work is summarized in scheme-1.



Where,  $M = \text{Cu}^{2+}, \text{Mn}^{2+}, \text{Co}^{2+}, \text{Ni}^{2+}, \text{Zn}^{2+}$ ,  $Y = \text{H}_2\text{O}$

## Experimental

All the chemicals used were of pure grade (Merck and B.D.H). The melting points of ligand HL<sub>11</sub> was determined by DSC method and was uncorrected.

### Synthesis of ligand HL<sub>11</sub>

A mixture of 5-bromo N-chloroacetyl anthranilic acid (3.32 g, 0.1 M) and 4-bromoaniline (2.10 g, 0.01 M) and  $\text{PCl}_5$  (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  $\text{PCl}_5$  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 the 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 a period of 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 the form of amorphous dark brown color powder. The air dried products were quantitative. Melting point of  $\text{HL}_{11}$  was  $\sim 291.87^\circ\text{C}$  (Uncorrected, DSC method).

### Synthesis of Chelates

A dried ligand sample  $\text{HL}_{11}$  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 was 4.5 for  $\text{Cu}^{+2}$ , 6.0 pH for  $\text{Ni}^{+2}$  and  $\text{Co}^{+2}$  while pH 5.6 for  $\text{Mn}^{+2}$  and  $\text{Zn}^{+2}$  were maintained by adding of sodium acetate. A dark colored solid precipitated out. It was allowed to settle and digested on water bath at  $70^\circ\text{C}$  for about 2 h. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone and then dried. The percentage yield

of chelates was in the range of 62-72 %. All the complexes were powdered well and dried at  $70^\circ\text{C}$  over a period of 24 h.

### Measurements

The C, H and N contents of metal complexes were determined on elemental analyzer Thermofinigan 1101 Flash EA (ITALY). The metal contents were estimated using standard methods<sup>7</sup>.  $^1\text{H}$  NMR spectra of ligand was recorded on Bruker NMR spectrophotometer (300 MHz) using TMS as an internal standard in  $\text{CDCl}_3/\text{DMSO-d}_6$ . 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  $4000\text{-}600\text{ cm}^{-1}$  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<sup>8</sup> at room temperature (300 K) using  $\text{Hg}[\text{Co}(\text{CNS})_4]$  as calibrant<sup>9</sup>, and the effective magnetic moment from relation<sup>10</sup>,  $\mu_{\text{eff}} = 2.84\sqrt{Xm} \times T$ , where T is the absolute temperature. Diamagnetic corrections were made by using Pascal's constants.

The ligand and its metal chelates were screened at 1000 ppm concentration in vitro to study their antifungal activity against five fungi viz. *Erysiphe pisi*, *Nigrospora sp.*, *Trichoderma sp.*, *Aspergillus niger* and *Curvularia lunata*. The antifungal activity of the compounds was measured by plate method<sup>11</sup>. Five days old cultures were suspended in potato dextrose agar (PDA) medium and autoclaved at  $1200^\circ\text{C}$  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

and Y

= area of colony in control plate (without sample)

= area of colony in test plate.

## RESULTS AND DISCUSSION

The chelates were 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. The result of molar conductance indicates that they are less polar in DMF (Table-2). Very low

molar conductance ( $\Lambda_M$ ) values in the range of 5.31 to 18.20  $\text{ohm}^{-1}\text{cm}^2 \text{mol}^{-1}$  in  $\text{Mn}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$  and  $\text{Zn}^{2+}$  chelates indicates that they are non-electrolytic and monomeric in nature ( $\text{ML}_2$  type complexes). The low  $\Lambda_M$  values may be attributed to the large cations<sup>12</sup>. The conductivity of these chelates were found in the order:  $\text{Co} > \text{Zn} > \text{Ni} > \text{Mn} > \text{Cu}$ .

**Table 1**  
**Analytical and physical data of metal chelates of HL<sub>11</sub>**

Ligand / Complexes	Molecular Formula	M.W. (g/mol)	Yield (%)	Elemental Analysis (%)				
				Found (Calcd.)				
				C	H	N	Br	M
HL <sub>11</sub>	C <sub>24</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> Br	552	70	52.00 (52.10)	2.70 (3.89)	10.34 (10.44)	28.80 (28.98)	-
(HL <sub>11</sub> ) <sub>2</sub> Cu <sup>+2</sup>	C <sub>48</sub> H <sub>30</sub> N <sub>8</sub> O <sub>4</sub> Br <sub>4</sub> Cu <sup>+2</sup> .2H <sub>2</sub> O	1201.54	59	47.90 (48.02)	2.60 (2.85)	9.10 (9.34)	26.50 (26.64)	5.00 (5.30)
(HL <sub>11</sub> ) <sub>2</sub> Ni <sup>+2</sup>	C <sub>48</sub> H <sub>30</sub> N <sub>8</sub> O <sub>4</sub> Br <sub>4</sub> Ni <sup>+2</sup> .2H <sub>2</sub> O	1196.69	72	48.10 (48.21)	2.80 (2.85)	9.30 (9.37)	26.6 (26.75)	4.80 (4.91)
(HL <sub>11</sub> ) <sub>2</sub> Mn <sup>+2</sup>	C <sub>48</sub> H <sub>30</sub> N <sub>8</sub> O <sub>4</sub> Br <sub>4</sub> Mn <sup>+2</sup> .2H <sub>2</sub> O	1192.93	62	48.01 (48.37)	2.60 (2.85)	9.20 (9.40)	26.70 (26.84)	4.50 (4.61)
(HL <sub>11</sub> ) <sub>2</sub> Co <sup>+2</sup>	C <sub>48</sub> H <sub>30</sub> N <sub>8</sub> O <sub>4</sub> Br <sub>4</sub> Co <sup>+2</sup> .2H <sub>2</sub> O	1196.93	68	48.00 (48.20)	2.50 (2.85)	9.00 (9.37)	26.5 (26.75)	4.80 (4.93)
(HL <sub>11</sub> ) <sub>2</sub> Zn <sup>+2</sup>	C <sub>48</sub> H <sub>30</sub> N <sub>8</sub> O <sub>4</sub> Br <sub>4</sub> Zn <sup>+2</sup> .2H <sub>2</sub> O	1203.39	62	47.70 (47.94)	2.70 (2.83)	8.90 (9.32)	26.40 (26.60)	5.10 (5.44)

**Table 2**  
**Magnetic moment and electronic spectral data of chelates of ligand HL<sub>11</sub>**

Sample	Observed $\mu_{\text{eff}}$ (B.M) (Expected)	$\Lambda_M$ ( $\text{Ohm}^{-1}\text{cm}^2 \text{mol}^{-1}$ )	Electron Transition	Absorption band ( $\text{cm}^{-1}$ )	$u_2/u_1$
(HL <sub>11</sub> ) <sub>2</sub> Cu <sup>2+</sup>	1.76 (1.7-2.2)	5.31	Charge Transfer Transition ${}^2\text{B}_{1g} \text{----} \rightarrow {}^2\text{A}_{1g}$	24900 14010	1.77
(HL <sub>11</sub> ) <sub>2</sub> Ni <sup>2+</sup>	3.30 (2.9-3.4)	8.01	${}^3\text{A}_{2g}(\text{F}) \text{----} \rightarrow {}^3\text{T}_{1g}(\text{F})$ ${}^3\text{A}_{2g}(\text{F}) \text{----} \rightarrow {}^3\text{T}_{1g}(\text{P})$	15620 22470	1.44
(HL <sub>11</sub> ) <sub>2</sub> Co <sup>2+</sup>	4.25 (4.4-5.2)	18.20	${}^4\text{T}_{1g}(\text{F}) \text{----} \rightarrow {}^4\text{T}_{1g}(\text{F})$ ${}^4\text{T}_{1g}(\text{F}) \text{----} \rightarrow {}^4\text{A}_{2g}(\text{F})$ ${}^4\text{T}_{1g}(\text{F}) \text{----} \rightarrow {}^4\text{T}_{1g}(\text{P})$	8540 19200 22500	2.25
(HL <sub>11</sub> ) <sub>2</sub> Mn <sup>2+</sup>	5.27 (5.2-6.0)	7.41	${}^6\text{A}_{1g} \text{----} \rightarrow {}^4\text{T}_{1g}({}^4\text{G})$ ${}^6\text{A}_{1g} \text{----} \rightarrow {}^4\text{T}_{2g}({}^4\text{G})$ ${}^6\text{A}_{1g} \text{----} \rightarrow {}^4\text{E}_g, {}^4\text{T}_{1g}({}^4\text{G})$	16458 18900 24350	1.15
(HL <sub>11</sub> ) <sub>2</sub> Zn <sup>2+</sup>	-	8.31	-	-	-

**Infrared spectral study**

IR spectrum of ligand HL<sub>11</sub> show a broad band extended from 3700 to 2600 cm<sup>-1</sup> which might be responsible to phenolic -OH group bonded to N atom of 8-hydroxyquinoline moieties<sup>13</sup>. The inflexions at 2925, 2855 and 1465 cm<sup>-1</sup> are due to aromatic -CH<sub>2</sub>- and methylene group of bridge<sup>14-17</sup>. The strong band at 1710 cm<sup>-1</sup> is attributed to -C=O of quinazoline 4-one moiety. Several bands appeared between 1500 and 1600 cm<sup>-1</sup> region may arise from aromatic breathing. Band at 3400 cm<sup>-1</sup> is confirms the presence of -NH group. The IR band at 1580 cm<sup>-1</sup> (C=N of 8-quinolinol system) of HL<sub>11</sub> ligand shifted to higher frequency side ~1595 cm<sup>-1</sup> in the spectra of the metal complexes indicates involvement of nitrogen in the complexes formation<sup>13</sup>. Most of the bands appeared in the spectra of corresponding ligand are observed at their metal complexes. Only a new band at 1095 cm<sup>-1</sup> had appeared in the spectra of metal complexes. This may be assigned to  $\nu_{C-O}$  of C-O-M bond formation. All the complexes show additional bands at 840-830 cm<sup>-1</sup> indicating the presence of coordinated water<sup>18</sup>.

**NMR spectral study**

The <sup>1</sup>H NMR spectra of ligand HL<sub>11</sub> gave the multiplet between 6.88 and 7.8  $\delta$  ppm for aromatic protons, signaling at 5.74-5.98  $\delta$  ppm for phenolic -OH group, 3.35-3.77  $\delta$  ppm due to CH<sub>2</sub> bridge, 2.5-2.51  $\delta$  ppm due to -OCH<sub>3</sub> group and 11.1-11.35  $\delta$  ppm due to -NH group. The non-aqueous conductometric titration of ligand gave the proton of -CH<sub>2</sub> and -OH group in ligand.

**Reflectance spectral study**

The magnetic moment, molar conductance and reflectance spectral data were presented in Table-2. The room temperature  $\mu_{\text{eff}}$  value for the Co<sup>+2</sup> chelate 4.25 B.M. suggests high spin octahedral geometry, which is further

supported by the electronic spectral data (Table-2). The value of transition ratio  $u_2 / u_1$  is 2.24 providing further evidences for octahedral geometry for the Co<sup>2+</sup> chelate. In the Ni<sup>+2</sup> complexes,  $\mu_{\text{eff}}$  values at room temperature is 3.30 B.M. as expected for six coordinated spin free Ni<sup>+2</sup> species<sup>19</sup>. The reflectance spectral data of Ni<sup>+2</sup> chelate is shown in Table-2. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier<sup>20</sup>. The Cu<sup>+2</sup> chelate possesses magnetic moments 1.76 B.M. corresponding to one unpaired electron indicating the distorted octahedral geometry, which is in agreement with data reported by other research workers<sup>21</sup>. 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  ${}^2E_g \rightarrow {}^2T_{2g}$  account for Jahn-teller effect suggesting thereby a distorted octahedral geometry for this chelate<sup>22</sup>. Zn<sup>+2</sup> 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<sup>10</sup> systems and may have tetrahedral geometry<sup>23</sup>. There is no evidence for the characteristic bands of coordinated water in IR spectra. The observed magnetic moment of the Mn<sup>2+</sup> complexes are 5.27 B.M. corresponding to five unpaired electrons indicating high spin octahedral environment<sup>24</sup>.

**Antifungal Activity**

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

**Table 3**  
**Antifungal activity of ligand HL<sub>11</sub> and its metal chelates**

Sample	Zone of inhibition at 1000 ppm (%)				
	EP	NS	TS	AN	CL
HL <sub>11</sub>	87	81	80	68	65
(HL <sub>11</sub> ) <sub>2</sub> Cu <sup>2+</sup>	78	83	83	87	77
(HL <sub>11</sub> ) <sub>2</sub> Mn <sup>2+</sup>	73	74	74	71	75
(HL <sub>11</sub> ) <sub>2</sub> Zn <sup>2+</sup>	75	67	67	65	63
(HL <sub>11</sub> ) <sub>2</sub> Co <sup>2+</sup>	68	59	61	65	65
(HL <sub>11</sub> ) <sub>2</sub> Ni <sup>2+</sup>	61	55	55	67	57

CA: *Erysiphe pisi*, NS: *Nigrospora Sp.*, TS : *Trichoderma sp.*  
 AN *Aspergillus niger*, CL: *Curvularia lunata*

## CONCLUSION

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

## ACKNOWLEDGEMENT

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

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