Synthesis, Characterization and Antifungal Activity of Novel Quinazolin-4-one Derivatives Containing 8-Hydroxyquinazoline Ligand and its Various Metal Complexes

R. T. VASHI* and S. B. PATEL

Department of Chemistry, Navyug Science College, Rander Road, Surat-395009, India.
vashirajendra@yahoo.co.in

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Abstract: Novel ligands containing quinazoline-4-one-8-hydroxyquinoline (QQ) merged moieties were prepared and characterized. For this anthranilic acid and 5-bromoanthranilic acid were converted respectively into 2-chloromethyl–3-(4-methyl phenyl)-3(\textit{H})-quinazoline-4-one and 2-chloromethyl–3-(methyl phenyl)-6-bromo-3(\textit{H})-quinazoline-4-one. Both these compounds were condensed with 5-amino-8-hydroxyquinoline. The so called resulted compounds were named respectively as 2-[(8-hydroxy-quinolinyl) –5- amino methyl] -3-(4-methylphenyl)- 3(\textit{H})- quinazoline - 4- one and 2-[(8-hydroxyquinolinyl)-5-aminomethyl] -3(methyl phenyl)-6-bromo-3(\textit{H})-quinazoline-4-one. Both the compounds were designated respectively as HL\textsubscript{1} and HL\textsubscript{2} ligands. The transition metal (Cu\textsuperscript{2+}, Ni\textsuperscript{2+}, Zn\textsuperscript{2+}, Mn\textsuperscript{2+} and Co\textsuperscript{2+}) complexes of both these ligands were prepared. The ligands and their complexes as case may be were characterized by elemental analysis, spectral studies and number of hydroxyl groups. The stoichiometry of the complexes has been found to be 1:2 (metal: ligand). An octahedral geometry around Co\textsuperscript{2+}, Ni\textsuperscript{2+} and Mn\textsuperscript{2+}, distorted octahedral geometry around Cu\textsuperscript{2+} and tetrahedral geometry of around Zn\textsuperscript{2+} have been proposed. These complexes also been tested for their antifungal activities.

Keywords: Ligands, 8-hydroxyquinoline, IR spectral studies, Magnetic moment and Antifungal study.

Introduction

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs\textsuperscript{1-3}. Quinazolin-4-one is also well known for many pharmaceutical products\textsuperscript{4-6}. Ligand 8-hydroxyquinoline is not only act as a complexing agent but also applied for drug synthesis\textsuperscript{7}. 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\(^8\). Thus in the extension of this work\(^8\), present communication comprises the synthesis, characterization and chelating properties of novel quinazolin-4-one-8-hydroxyquinoline derivatives. The whole work is summarized in Scheme 1.

![Scheme 1](image)

Where, \(R_1 = \text{H, Br}\)

\(Y = \text{H}_2\text{O or Acetate}\)

\(Mt = \text{Cu}^{2+}, \text{Mn}^{2+}, \text{Co}^{2+}, \text{Ni}^{2+}, \text{Zn}^{2+}\)

**Experimental**

All the chemicals used were of pure grade (Merck and B.D.H). The melting points of both ligands \(HL_1\) and \(HL_2\) were determined by DSC method and were uncorrected.
**Synthesis of ligands HL₁ and HL₂**

For the preparation of ligand HL₁, a mixture of 2-chloromethyl–3-(4-methylphenyl)-3(H)-quinazoline-4-one (0.01 mole) and 5-amino-8-hydroxyquinoline (0.01 mole) and for the preparation of ligand HL₂, a mixture of 2-chloromethyl–3-(methylphenyl)-6-bromo-3(H)-quinazoline-4-one (0.01 mole) and 5-amino-8-hydroxyquinoline (0.01 mole) were taken in dry pyridine (20 mL) and was refluxed for 12 h. Pyridine was distilled off as much as possible and the residue was poured into a little crushed ice with stirring. The products were separated out, filtered, washed with water and finally with ethanol. The air dried products were used. Melting point of HL₁ was ~209 °C and for HL₂ was ~232.2 °C (Uncorrected).

**Synthesis of complexes**

A dried ligand sample HL₁ or HL₂ (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 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 mole) in 100 mL of water respectively with rapid stirring. The resultant pH 4.5 (for Cu²⁺), pH 6.0 (for Ni²⁺ and Co²⁺) and pH 5.6 (Mn²⁺ and Zn²⁺) was maintained by adding of sodium acetate. A dark coloured solid was 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 and dried. The percentage yield of complexes was in the range of 65-82%. All the complexes were powdered well and dried at 70 °C over a period of 24 h.

**Measurements**

The C, H and N contents of metal complexes were determined on elemental analyzer Thermofinnigan 1101 Flash EA (ITALY). The metal contents were estimated using standard methods⁹. ¹H NMR spectra of ligands were recorded on Bruker NMR spectrophotometer using TMS as an internal standard in CDCl₃/DMSO-d₆¹⁰. 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 method¹¹ at room temperature (300 K) using Hg[Co(CNS)₄] as calibrant¹², and the effective magnetic moment were calculated from relation¹³, \( \mu_{\text{eff}} = 2.84 \sqrt{Xm x T} \), where T is the absolute temperature. Diamagnetic corrections were made by using Pascal’s constants.

The ligands and their 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 at 15 atmospheric pressure. The percentage inhibition of fungi was calculated after 5 days using the formula given below,

\[
\text{Percentage of Inhibition} = 100 \times \frac{(X - Y)}{X}
\]

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

The synthesis of ligands HL₁ and HL₂ was performed by method reported for 2-chloromethyl-3-(4-methylphenyl)-3(4H)-quinazoline-4-one. The C, H and N of both ligands are consistent with predicted structure.

NMR spectra

The ¹H NMR spectra of both ligands gave the multiplet between 6.88-7.8 δ ppm for aromatic protons, signal at 5.74-5.98 δ ppm for singlet of phenolic –OH group, 3.35-3.77 δ ppm due to CH₂ bridge, 1.23 d ppm for –CH₃ group and 11.1-11.35 δ ppm due to –NH group. The non-aqueous conductometric titration at both ligands gave the proton of –CH₂ and –OH group.

The complexes are microcrystalline coloured powders having melting points higher than the ligands. 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 values in the range of 5.11 to 21.72 ohm⁻¹ cm² mol⁻¹ in Mn²⁺, Ni²⁺, Cu²⁺ and Zn²⁺ complexes indicates that they are non-electrolytic and monomeric in nature (ML₂ type complexes). The low Λ_M values may be attributed to the large cations.

Infrared spectra

IR spectrum of ligands HL₁ and HL₂ show a broad band extended from 3700 to 2600 cm⁻¹ which might be responsible to phenolic -OH group bonded to N atom of 8-hydroxyquinoline moieties. The inflexions at 2920, 2850 and 1470 cm⁻¹ are due to aromatic -CH₂ and methylene group of bridge. The strong band at 1700 cm⁻¹ is attributed to -C=O of quinazoline 4-one moiety. Several bands appeared between 1500-1600 cm⁻¹ region may arised from aromatic breathing. The IR band at 1095 cm⁻¹ (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.

Magnetic moment and electronic spectra

At the room temperature, µ_eff values for the Co²⁺ complexes (3.99-4.51 B.M.) suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The electronic spectrum of the Co²⁺ complexes shows three bands at 8960, 18650-18980 and 22590-23710 cm⁻¹, assignable to ⁴T₁g(F) → ⁴T₁g(F) (υ₁), ⁴T₁g(F) → ⁴A₂g(F) (υ₂) and ⁴T₁g(F) → ⁴T₁g(P) (υ₃) transitions, respectively for an octahedral geometry. The values of transition ratio υ₂/υ₁ is 2.08 providing further evidences for octahedral geometry for the Co²⁺ complexes.

In the Ni²⁺ complexes, µ_eff values at room temperature are in the range 2.97-3.12 B.M. as expected for six coordinated spin free Ni²⁺ species. The reflectance spectra of the Ni²⁺ complexes, exhibit two strong bands at 15620-15625 cm⁻¹ and 22470-22478 cm⁻¹, assignable to ³A₂g(F) → ³T₁g(F) (υ₁) and ³A₂g(F) → ³T₁g(P) (υ₂) respectively. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier. The Cu²⁺ complexes exhibit normal magnetic moments (1.70-1.81 B.M.) corresponding to one unpaired electron indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers.
<table>
<thead>
<tr>
<th>Ligand / Complexes</th>
<th>Mol Formula</th>
<th>M.W. g/mol</th>
<th>Yield %</th>
<th>Elemental Analysis, % Found (Calcd.)</th>
<th>( \mu_{\text{eff}} ) B.M.</th>
<th>( \Lambda_{\text{M}} ) ohm(^{-1}) cm(^2) mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL(_1)</td>
<td>C(<em>{25})H(</em>{20})N(_4)O(_2)</td>
<td>408</td>
<td>72</td>
<td>C 73.50 (73.52) H 4.80 (4.90) N 13.70 (13.72) Br - - -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HL(_2)</td>
<td>C(<em>{23})H(</em>{19})N(_4)O(_2)Br</td>
<td>487</td>
<td>75</td>
<td>C 61.50 (61.61) H 3.80 (3.90) N 11.40 (11.49) Br 16.30 (16.42)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(HL(_1)) Cu(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(_4)Cu(^{2+})2H(_2)O</td>
<td>913.54</td>
<td>72</td>
<td>C 65.60 (65.68) H 4.10 (4.60) N 12.20 (12.26) Br 6.90 (6.96)</td>
<td>1.81</td>
<td>8.10</td>
</tr>
<tr>
<td>(HL(_2)) Cu(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(<em>4)Br (</em>{2}) Cu(^{2+})2H(_2)O</td>
<td>1073.54</td>
<td>77</td>
<td>C 54.20 (54.42) H 3.50 (3.63) N 10.00 (10.16) Br 11.40 (11.49)</td>
<td>1.70</td>
<td>5.11</td>
</tr>
<tr>
<td>(HL(_1)) Ni(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(_4)Ni(^{2+})2H(_2)O</td>
<td>908.69</td>
<td>69</td>
<td>C 66.00 (66.03) H 4.10 (4.62) N 12.30 (12.33) Br -</td>
<td>2.97</td>
<td>9.31</td>
</tr>
<tr>
<td>(HL(_2)) Ni(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(<em>4)Br (</em>{2}) Ni(^{2+})2H(_2)O</td>
<td>1068.69</td>
<td>79</td>
<td>C 54.50 (54.66) H 3.40 (3.64) N 9.80 (10.20) Br 14.80 (14.99)</td>
<td>3.12</td>
<td>17.20</td>
</tr>
<tr>
<td>(HL(_1)) Mn(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(_4)Mn(^{2+})2H(_2)O</td>
<td>904.93</td>
<td>79</td>
<td>C 66.00 (66.30) H 4.10 (4.64) N 12.30 (12.38) Br -</td>
<td>5.13</td>
<td>6.10</td>
</tr>
<tr>
<td>(HL(_2)) Mn(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(<em>4)Br (</em>{2}) Mn(^{2+})H(_2)O</td>
<td>1064.93</td>
<td>82</td>
<td>C 54.70 (54.85) H 3.40 (3.66) N 10.00 (10.24) Br 14.90 (15.05)</td>
<td>5.11</td>
<td>7.12</td>
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<tr>
<td>(HL(_1)) Co(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(_4)Co(^{2+})2H(_2)O</td>
<td>908.93</td>
<td>76</td>
<td>C 66.00 (66.01) H 4.10 (4.62) N 12.30 (12.32) Br -</td>
<td>3.99</td>
<td>21.72</td>
</tr>
<tr>
<td>(HL(_2)) Co(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(<em>4)Br (</em>{2})Co(^{2+})2H(_2)O</td>
<td>1068.93</td>
<td>66</td>
<td>C 54.50 (54.65) H 3.50 (3.64) N 9.90 (10.20) Br 14.80 (14.99)</td>
<td>4.51</td>
<td>18.10</td>
</tr>
<tr>
<td>(HL(_1)) Zn(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(_4)Zn(^{2+})2H(_2)O</td>
<td>915.39</td>
<td>70</td>
<td>C 65.50 (65.55) H 4.10 (4.59) N 12.20 (12.24) Br -</td>
<td>7.10</td>
<td>9.80</td>
</tr>
<tr>
<td>(HL(_2)) Zn(^{2+})</td>
<td>C(<em>{50})H(</em>{38})N(_8)O(<em>4)Br (</em>{2}) Zn(^{2+})2H(_2)O</td>
<td>1075.39</td>
<td>65</td>
<td>C 54.20 (54.33) H 3.40 (3.62) N 10.00 (10.14) Br 14.70 (14.90)</td>
<td>-</td>
<td>8.22</td>
</tr>
</tbody>
</table>

Table 1. Analytical and physical data of ligand and complexes.
Electronic spectra of the complexes show broad asymmetric bands in the region 14980–15490 cm\(^{-1}\) and at 23690-24650 cm\(^{-1}\) assignable \(^2B_{1g} \rightarrow ^2A_{1g}\) and charge transfer transition respectively\(^{27}\). 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\(^{28}\). \(\text{Zn}^{2+}\) complexes are diamagnetic in nature and their 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\(^{29}\). There is no evidence for the characteristic bands of coordinated water in IR spectra.

The electronic spectra of the Mn\(^{2+}\) complexes exhibited three spin allowed bands in the region 14589-15896 cm\(^{-1}\), 18570-19000 cm\(^{-1}\) and 24220-24350 cm\(^{-1}\) assigned to the transitions \(6A_{1g} \rightarrow 4T_{1g} (^4G)(\nu_1)\), \(6A_{1g} \rightarrow 4T_{2g} (^4G) (\nu_2)\) and \(6A_{1g} \rightarrow 4E_g, 5T_{1g} (^4P) (\nu_3)\) respectively, indicating octahedral geometry\(^{30-31}\). The observed magnetic moment of the Mn\(^{2+}\) complexes are 5.11-5.13 B.M. corresponding to five unpaired electrons indicates high spin octahedral environment\(^{32}\).

**Antifungal activity**

All the ligands and their complexes are found toxic more or less against fungi. HL\(_2\) was more toxic than HL\(_1\). Off all the complexes Copper complex exhibit more toxicity than other metal complexes against fungi. These results are in agreement with the result obtained by the work of Patel I. J and Vohra I. M\(^{33}\). Hence such type of complexes may find 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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**References**

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