

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY STUDIES OF QUINAZOLIN-4-ONE -8 HYDROXY QUINOLINE MERGED MOLECULES AND THEIR TRANSITION METAL CHELATES

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ABSTRACT

Novel ligands containing quinazolin-4-one 8-hydroxyquinoline (QH) merged moieties were prepared and characterized. For this anthranilic acid and 5-bromo anthranilic acid were converted respectively in to 2- chloro methyl -3(H)- 8-hydroxyquinolinyl quinazolin-4-one and 2- chloro methyl -3(H)- 8-hydroxyquinolinyl 5- bromo quinazolin-4-one. Both these compounds were condensed with 1- methyl piperazine. The so called resulted compounds were named respectively as 2-(4-methyl piperazin-1-yl) methyl -3(H)- 8-hydroxyquinolinyl quinazolin-4-one and 2-(4-methyl piperazin-1-yl) methyl -3(H)- 8-hydroxyquinolinyl 5- bromo quinazolin-4-one. Both the compounds were designated respectively as HL₁ and HL₂ ligands. The transition metals (Cu⁺², Ni⁺², Zn⁺², Mn⁺² and Co⁺²) chelates of both these ligands were prepared. The ligands and their chelates as case may be were characterized by elemental contents, spectral studies and no of hydroxyl groups. The stoichiometry of the complexes 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. These complexes also been tested for their antimicrobial activities.

Key Words: Ligands, 8-hydroxyquinoline, IR spectral studies, Magnetic moment, Antimicrobial study.

INTRODUCTION

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs¹⁻⁴. Quinazolin-4-one is also well known for many pharmaceutical products⁵⁻⁸. Ligand 8-hydroxyquinoline is not only act as a complexing agent but also applied for drug synthesis⁹⁻¹⁰. 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 it was thought to explore the study of quinazolin-4-one-8-hydroxyquinoline merged molecules designated as ligands HL₁ and HL₂. Hence the present communication comprises the synthesis characterized of chelating properties

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of such quanzolin-4-one-8-hydroxyquinoline derivatives. The whole work is summarized in **fig. 1**

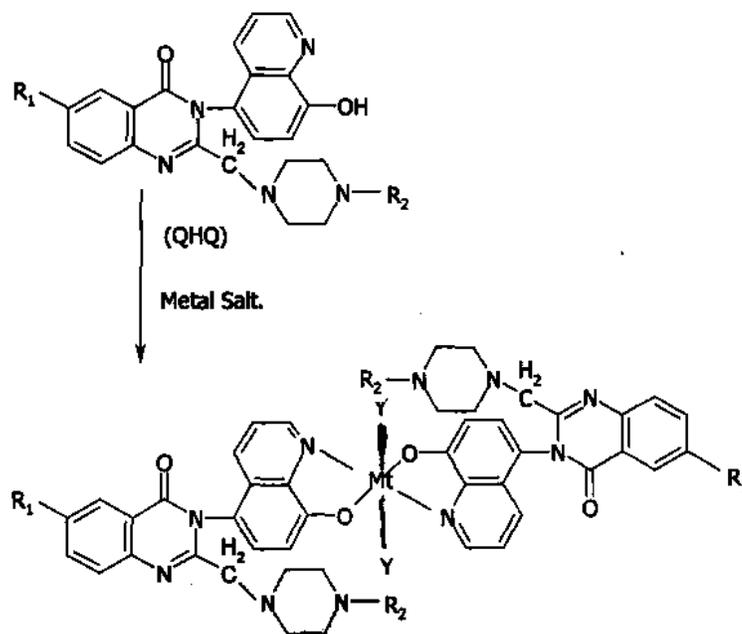


Fig. 1 : QHQ-Metal chelates

Where Mt: Cu^{+2} , Ni^{+2} , Zn^{+2} , Mn^{+2} , Co^{+2} etc.

R_1 : H, Br

R_2 : methyl

Y: H_2O or Acetate.

MATERIAL AND METHODS

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

Synthesis of ligands HL_1 and HL_2 :
For the preparation of ligand HL_1 , a mixture of 2-chloromethyl -3-(8-hydroxyquinolin-5 yl) -3(H) quinazolin-4-one (0.01 mole) and 1-methyl -piperazine (0.01 mole) and for the preparation of ligand HL_2 , a mixture of 6-bromo-2-chloromethyl -3-(8-hydroxyquinolin-5 yl) -3(H) quinazolin-4-one (0.01 mole) and 1-methyl -piperazine (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 quantitative. m.p. $>230^\circ\text{C}$.

Synthesis of Chelates : A dried ligand sample HL_1 or (HL_2) (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 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 Cu^{+2}), pH 6.0 (for Ni^{+2} and Co^{+2}) and pH 5.6 (Mn^{+2} and Zn^{+2}) was maintained by adding of sodium acetate. A dark coloured solid precipitated out. It was allowed to settle and digested on water bath at 70 °C for about 2h. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone, dried. The percentage yield of chelates was in the range of 65-82 %. All the chelates were powdered well and dried at 70 °C over a period of 24 h.

Measurements: The C, H and N contents of metal chelates were determined on elemental analyzer Thermofinigan 1101 Flash EA (ITALY). The metal contents were estimated using standard methods¹¹. The halogen content was determined by Carius method¹². 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 chelates were recorded on a Beckman-DK-2A spectrophotometer using MgO as reference. PMR spectra of ligands were recorded on Bruner NMR spectrophotometer using TMS as an internal standard in $\text{CDCl}_3/\text{D}_6\text{-DMSO}$. Magnetic susceptibility was measured by Gouy's method¹³ at room temperature (300 K) using $\text{Hg}[\text{Co}(\text{CNS})_4]$ as calibrant¹⁴, and the effective magnetic moment from relation¹⁵, $\mu_{\text{eff}} = 2.84 \sqrt{Xm X T}$, where T is the absolute temperature. Diamagnetic corrections were made by using Pascal's constants.

The ligands and their metal chelates were screen at 1000 ppm concentration in vitro for their antifungal activity against five fungi viz. *Botrydepladia thibromine*, *Nigospora sp.*, *Rhizopus nigricans*, *Aspergillus fumigatus* and *Candida albicans*. 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,

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

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 HL_1 and HL_2 was performed by method reported for 2-chloro methyl-3(H)-quinazolin-4-one. The C, H and N of both ligands are consistent with predicted structure. The IR spectra of both ligands compare the important bands due to ν_{OH} (3200 cm^{-1}), ν_{aromatic} ($1600, 1500, 1080 \text{ cm}^{-1}$), and ν_{CH_2} ($2850, 2920, 1450 \text{ cm}^{-1}$). The NMR spectra of both ligands gave the multiplate between 6.9-7.8 ppm for aromatic protons, signal at 4.5 δ ppm for -OH and doublet at 2.9 δ ppm due to CH_2 of piperazine. The non-aqueous conductometric titration at both ligands gave the proton of - CH_2 and -OH group in ligands.

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 5.20 to 18.19 $\text{ohm}^{-1}\text{cm}^2 \text{mol}^{-1}$ in Mn^{+2} , Ni^{+2} , Cu^{+2} and Zn^{+2} chelates indicates that they are non-electrolytic¹⁶ and monomeric in nature (ML_2 type chelates). The low $\wedge M$ values may be attributed to the large cations¹⁷. The electrical conductivity of these chelates found increases in the order: $\text{Co} > \text{Ni} > \text{Zn} > \text{Mn} > \text{Cu}$.

Infrared spectra: IR spectrum of ligands HL_1 and HL_2 show a broad band extended from 3450 to 2600 cm^{-1} which might

Table 1: Analytical and physical data of ligand and complexes

Ligand / Complexes	Molecular Formula	M.W. (g/mole)	Yield (°C)	Elemental Analysis (%)										μ_{eff} (B.M.)	Λ_M ($\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$)	
				Found (Calc.)					M							
				C	H	N	Br	M	C	H	N	Br	M			
HL ₁	C ₂₃ H ₂₃ N ₅ O ₂	402	70	68.4	5.6	17.3	-	-	-	-	-	-	-	-	-	-
HL ₂	C ₂₃ H ₂₂ N ₅ O ₂ Br	480	82	57.6	4.5	14.58	16.5	-	-	-	-	-	-	-	-	-
(HL ₁) Cu ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Cu ⁺²	899	72	61.2	5.3	15.4	-	-	-	7	-	-	-	-	-	-
(HL ₂) Cu ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Cu ⁺² Br ₂	1057	70	52.1	4.3	13.2	14.8	5.9	-	-	-	-	-	-	-	-
(HL ₁) Ni ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Ni ⁺²	895	69	61.6	5.3	15.5	-	-	-	6.4	-	-	-	-	-	-
(HL ₂) Ni ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Ni ⁺² Br ₂	1053	86	52.4	4.2	13.1	14.9	5.4	-	-	-	-	-	-	-	-
(HL ₁) Co ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Co ⁺²	895	65	61.6	5.3	15.6	-	-	-	6.5	-	-	-	-	-	-
(HL ₂) Co ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Co ⁺² Br ₂	1053	72	52.4	4.3	13.2	14.9	5.5	-	-	-	-	-	-	-	-
(HL ₁) Zn ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Zn ⁺²	901	70	61.2	5.2	15.5	-	-	-	7.2	-	-	-	-	-	-
(HL ₂) Zn ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Zn ⁺² Br ₂	1059	72	52	4.3	13.2	14.8	6.1	-	-	-	-	-	-	-	-
(HL ₁) Mn ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Mn ⁺²	890	59	61.2	5.3	15.4	-	-	-	6	-	-	-	-	-	-
(HL ₂) Mn ⁺²	C ₄₆ H ₄₆ N ₁₀ O ₆ Mn ⁺² Br ₂	1049	60	52.6	4.3	13.3	15	5.1	-	-	-	-	-	-	-	-

be responsible to phenolic group bonded to N atom of 8-hydroxyquinoline moiety¹⁸⁻¹⁹. The inflexions at 3030, 2930 and 2850 cm^{-1} are due to aromatic CH and methylene group of bridge and piperazine ring²⁰⁻²³. 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 arise from aromatic breathing. The IR band at 1580 cm^{-1} (C=N of 8-quinolinol system) of HL₁ and HL₂ ligands shifted to higher frequency side -1600 in the spectra of the metal chelates indicating involvement of nitrogen in the chelate formation^{18,24,25}. Most of bands appeared in the spectra of corresponding ligand are observed at their metal chelates. Only a new band at 1094 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 water²⁶.

Magnetic moment and electronic spectra: The room temperature μ_{eff} values for the Co⁺² complexes (3.90- 4.90 B.M.) suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The reflectance spectra bands of the complexes are observed at 7986 – 8965, 18965 -20056 and 22586 -22589 cm^{-1} , assignable to ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{2g}(\text{F})$ (ν_1), ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{A}_{2g}(\text{F})$ (ν_2) and ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{P})$ (ν_3) transitions, respectively²⁷. 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⁺² complexes, μ_{eff} values at room temperature are in the range 3.39 -3.85 B.M. as expected for six coordinated spin free Ni⁺² species. The reflectance spectra of the Ni⁺² complexes, exhibit two strong bands at 14585-14589 cm^{-1} and 24221-24660 cm^{-1} , assignable to ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ and ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$ respectively. The ν_2/ν_1 ratio for the chelate is 1.66 occurs in the usual range (1.6 – 1.82 B.M.) for octahedral Ni⁺²

chelates²⁸. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier²⁹⁻³⁰. The Cu⁺² complexes exhibit normal magnetic moments (1.95-2.18 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers³¹⁻³². These complexes show broad asymmetric bands in the region 14589-14775 cm^{-1} and at 24637 cm^{-1} assignable to ${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_{1g}$ and charge transfer transition respectively³³⁻³⁴. 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 complexes³⁵. Zn⁺² complexes are diamagnetic as expected for d10 systems and may have tetrahedral geometry³⁶⁻³⁷. There is no evidence for the characteristic bands of coordinated water in IR spectra.

The electronic spectra of the Mn⁺² exhibited three spin allowed bands in the region 14523 – 14589 cm^{-1} , 16999 – 18569 cm^{-1} and 24221 – 25896 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 ${}^6\text{A}_{1g} \rightarrow {}^4\text{E}_g$, ${}^4\text{T}_{1g}({}^4\text{P})$ respectively, indicating octahedral geometry^{38,39}. The observed magnetic moment (5.50-5.69 B.M.) of the complexes indicates high spin octahedral environment⁴⁰.

Antimicrobial activity : The result indicates that the Cu II and Zn II exhibits higher activity towards most of the plant pathogenic organisms studied than the ligands. The other metal complexes did not show any significant increase in activity as compared to the ligands. 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 organisms⁴¹.

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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