



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 .

R. T. VASHI* , S. B. PATEL AND HIMANSHU PATEL

Department of Chemistry, Navyug Science College, Rander Road, Surat-395009, India.

ABSTRACT

Synthesis and characterization of 2-[(8-hydroxyquinolinyl)-5-aminomethyl]-3-(4-bromophenyl)-6-bromo-3(H)-quinazolin-4-one ligand called HAMQ (HL₁₁) 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 Cu²⁺, Ni²⁺, Zn²⁺, Mn²⁺ and Co²⁺ 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 Co²⁺, Ni²⁺ and Mn²⁺ complexes, a distorted octahedral geometry around Cu²⁺ and a tetrahedral geometry around Zn²⁺ 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.



R. T. VASHI

Department of Chemistry, Navyug Science College, Rander Road, Surat-395009, India.

*Corresponding author

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 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 HL_{11} was $\sim 291.87^\circ\text{C}$ (Uncorrected, DSC method).

Synthesis of Chelates

A dried ligand sample 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 Cu^{+2} , 6.0 pH for Ni^{+2} and Co^{+2} while pH 5.6 for Mn^{+2} and 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°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°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 methods⁷. ^1H 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 method⁸ at room temperature (300 K) using $\text{Hg}[\text{Co}(\text{CNS})_4]$ as calibrant⁹, and the effective magnetic moment from relation¹⁰, $\mu_{\text{eff}} = 2.84\sqrt{Xm} \times T$, 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 method¹¹. 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

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 (Λ_M) values in the range of 5.31 to 18.20 $\text{ohm}^{-1}\text{cm}^2 \text{mol}^{-1}$ in Mn^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} chelates indicates that they are non-electrolytic and monomeric in nature (ML_2 type complexes). The low Λ_M values may be attributed to the large cations¹². 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 HL₁₁

Ligand / Complexes	Molecular Formula	M.W. (g/mol)	Yield (%)	Elemental Analysis (%) Found (Calcd.)				
				C	H	N	Br	M
HL ₁₁	C ₂₄ H ₁₆ N ₄ O ₂ Br	552	70	52.00 (52.10)	2.70 (3.89)	10.34 (10.44)	28.80 (28.98)	-
(HL ₁₁) ₂ Cu ⁺²	C ₄₈ H ₃₀ N ₈ O ₄ Br ₄ Cu ⁺² .2H ₂ 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 ₁₁) ₂ Ni ⁺²	C ₄₈ H ₃₀ N ₈ O ₄ Br ₄ Ni ⁺² .2H ₂ 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 ₁₁) ₂ Mn ⁺²	C ₄₈ H ₃₀ N ₈ O ₄ Br ₄ Mn ⁺² .2H ₂ 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 ₁₁) ₂ Co ⁺²	C ₄₈ H ₃₀ N ₈ O ₄ Br ₄ Co ⁺² .2H ₂ 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 ₁₁) ₂ Zn ⁺²	C ₄₈ H ₃₀ N ₈ O ₄ Br ₄ Zn ⁺² .2H ₂ 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 HL₁₁

Sample	Observed μ_{eff} (B.M) (Expected)	Λ_M ($\text{Ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$)	Electron Transition	Absorption band (cm^{-1})	u_2/u_1
(HL ₁₁) ₂ Cu ²⁺	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 ₁₁) ₂ Ni ²⁺	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 ₁₁) ₂ Co ²⁺	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 ₁₁) ₂ Mn ²⁺	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 ₁₁) ₂ Zn ²⁺	-	8.31	-	-	-

Infrared spectral study

IR spectrum of ligand HL₁₁ 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 moieties¹³. The inflexions at 2925, 2855 and 1465 cm⁻¹ are due to aromatic -CH₂- and methylene group of bridge¹⁴⁻¹⁷. The strong band at 1710 cm⁻¹ is attributed to -C=O of quinazoline 4-one moiety. Several bands appeared between 1500 and 1600 cm⁻¹ region may arise from aromatic breathing. Band at 3400 cm⁻¹ is confirms the presence of -NH group. The IR band at 1580 cm⁻¹ (C=N of 8-quinolinol system) of HL₁₁ ligand shifted to higher frequency side ~1595 cm⁻¹ in the spectra of the metal complexes indicates involvement of nitrogen in the complexes formation¹³. Most of the bands appeared in the spectra of corresponding ligand are observed at their metal complexes. Only a new band at 1095 cm⁻¹ had appeared in the spectra of metal complexes. 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 water¹⁸.

NMR spectral study

The ¹H NMR spectra of ligand HL₁₁ gave the multiplet between 6.88 and 7.8 δ ppm for aromatic protons, signaling at 5.74-5.98 δ ppm for phenolic -OH group, 3.35-3.77 δ ppm due to CH₂ bridge, 2.5-2.51 δ ppm due to -OCH₃ group and 11.1-11.35 δ ppm due to -NH group. The non-aqueous conductometric titration of ligand gave the proton of -CH₂ 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 μ_{eff} value for the Co⁺² 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 Co²⁺ chelate. In the Ni⁺² complexes, μ_{eff} values at room temperature is 3.30 B.M. as expected for six coordinated spin free Ni⁺² species¹⁹. The reflectance spectral data of Ni⁺² chelate is shown in Table-2. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier²⁰. The Cu⁺² 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 workers²¹. 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 chelate²². Zn⁺² 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 d¹⁰ systems and may have tetrahedral geometry²³. There is no evidence for the characteristic bands of coordinated water in IR spectra. The observed magnetic moment of the Mn²⁺ complexes are 5.27 B.M. corresponding to five unpaired electrons indicating high spin octahedral environment²⁴.

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 HL₁₁ and its metal chelates

Sample	Zone of inhibition at 1000 ppm (%)				
	EP	NS	TS	AN	CL
HL ₁₁	87	81	80	68	65
(HL ₁₁) ₂ Cu ²⁺	78	83	83	87	77
(HL ₁₁) ₂ Mn ²⁺	73	74	74	71	75
(HL ₁₁) ₂ Zn ²⁺	75	67	67	65	63
(HL ₁₁) ₂ Co ²⁺	68	59	61	65	65
(HL ₁₁) ₂ Ni ²⁺	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 Ni²⁺, Co²⁺ and Mn²⁺ complexes, tetrahedral polymeric structure for Zn²⁺ and distorted octahedral for Cu²⁺ 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.

REFERENCES

1. Okeke N, Laxmaninarayan R, Bhutta ZA., Duse AG, Jenkins P, O' Brien TF, Pablos-endez A and Klugman KP, Antimicrobial resistance in developing countries. Part 1: recent trends and current status, Lancet Infect Dis, 5: 481-491, (2005).
2. Desai P, Naik J, Desai CM and Patel D, Some quinoline, quinazoline and pyrazine derivatives as antitubercular-antibacterial agents, Asian J Chem, 10 (4): 993-994 (1998).
3. Patel NB and Patel JN, Synthesis and biological activity of some new 1,3 thiazolyl-6-bromoquinazolin-4(3H) ones, J Indian Chem Soc, 86: 1231-1236 (2009).
4. Vashi RT and Patel SB, Synthesis, Characterization and Antifungal Activity of Novel Quinazolin -4-one Derivatives Containing 8- Hydroxyquinazoline Ligand and its various Metal Complexes, E-J. Chem., 6 (S₁): S445-S451, (2009).
5. Rajveer CH, Kumaraswamy D, Sudharshini S and Stephen Rathinaraj B, Synthesis of some 6-bromoquinazolinone derivatives for their pharmacological activities., Int. J. of Pharma and Bio Sci., 1(3), 1-14, (2010).
6. Vashi RT and Shelat CD, Transition Metal Complexation Studies on Heterocyclic Ligands, Asian J Chem, 22(3): 1745-1750, (2012).

7. Upadhyay RK, Chemistry of mixed ligand complexes of copper (II) involving ketoanil and thiourea, ammonia or anionic ligands., J Indian Chem Soc, 74: 535-537, (1997).
8. Bellamy LJ, Infrared spectra of complexes molecules, Chapman and Hall, London, (1957).
9. Silvestein RM, Spectrometric identification of organic compounds, 5th Edn., John Wiley, 123, (1991).
10. Vogel AI, A Textbook of Quantitative Chemical Analysis, Revised by J. Bessett, J. H. Feffery and J. Mondhaus, ELBS, London, (1996).
11. Bellamy LJ, The Infrared Spectra of Complex Molecule, Wiley, New York, (1959).
12. Nakamoto K, Infrared Absorption Spectroscopy, Nankando Company Ltd., Tokyo, 45, (1964).
13. Nakamoto K, Infrared spectra of Inorganic and Coordination Compounds", Wiley- Interscience, New York, (1975).
14. Nakamoto K, Infrared and Raman Spectroscopy of Inorganic and Coordination Compounds, 3rd Edn, Wiley, Inter science, New York, (1978).
15. Cotton FA and Wilkinson G, Advanced Inorganic Chemistry, 5th Edn., Wiley, New York, (1988).
16. Singh DP, Shishodia N, Yadav BP and Rana VB, Trivalent transition metal ion directed macrocycles, J Indian Chem Soc, 81: 287-290, (2004).
17. Sulekh C and Archana G, Synthesis, spectral characterization and biological screening of a tetraazamacrocyclic ligand and its complexes with Co(II), Ni(II) and Cu(II), J. Indian Chem Soc, 85: 980-984 (2008).
18. Yildiz M, Dulger B, Koyuncu SY and Yanpici BM, Synthesis and antimicrobial activity of bis (imido) Schiff bases derived from thiosemicarbazide with some 2-hydroxyaldehydes and metal complexes, J Indian Chem Soc, 81: 7-12, (2004).
19. Patel MM and Patel HR, Synthesis, Spectral, Thermal, Electrical and Antimicrobial studies of some complexes derived from 7-(α -phenyl- α m/p-nitroanilinomethyl)-8-quinolinol, J Indian Chem Soc, 73: 313-317, (1996).
20. Vogel AI, A Text book of Quantitative Inorganic Analysis, 3rd Edn, ELBS, London, (1978).
21. Lewis J and Wilkins RG, Modern Coordination Chemistry, Interscience, NewYork, (1964).
22. Figgis BN and Lewis J, The Magneto Chemistry of Complexes in Modern Coordination Chemistry, Inter Science, New York, (1960).
23. Williams JO, Electrical Conduction in Organic Solids, Adv Phys Org Chem, 16:159-237, (1978).
24. Barry AL, Antibiotics in Laboratory Medicine, Williams & Wilkians, Baltimore, 3rd Edn., (1996).