



Synthesis, characterization and antifungal activity of quinazoline -4-one derivatives containing 8-hydroxy quinazoline ligand and its transition metal chelates

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ABSTRACT

The novel ligand HL₃ was synthesized using 2-Chloromethyl-3-(8-hydroxyquinolin-5-yl)-3(H)-quinazolin-4-one and it undergoes 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 tetrahedral geometry around Zn(II) have been proposed. The antifungal activity of ligand and its metal chelates was conducted against various fungi.

Keywords: Ligand, 8-hydroxyquinoline, IR and NMR spectral studies, magnetic moment, antifungal study.

INTRODUCTION

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs (Patel, 2006). A Quinazolin-4-one derivative possesses biological activities such as antifungal (Vashi, R.T., et al., 2010 & Vashi, 2009 & Vashi, 2010). 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 HL₃ with their complexes with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) metal ion. Antimicrobial activities of both the ligand and chelates have also been studied.

MATERIALS AND METHODS

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 all complexes were determined by open capillary method and were uncorrected.

Synthesis of ligand HL₃: 2-chloromethyl-3-(8-hydroxyquinolin-5-yl)-3(H)-quinazolin-4-one from Anthranilic acid was prepared according to previous literature (Vashi, et al. 2010a). A mixture of 2-Chloromethyl-3-(8-hydroxyquinolin-5-yl)-3(H)-quinazolin-4-one (0.01

mole) and 1-Cyclohexyl piperazine (0.01 M) in dry pyridine (20 ml.) 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, HL₃ i.e. 2-[4-Cyclohexyl piperazine-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. Melting point for HL₃ > 230 °C.

Synthesis of Chelates: A dried ligand sample HL₃ (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 designated as reagent solution. This solution was used for preparation of chelates using ligand with transition metal ions. The reagent solution (100 ml) of ligand was added dropwise to each of solution of Cu(NO₃)₂·6H₂O, Ni(NO₃)₂·6H₂O, Co(NO₃)₂·6H₂O, MnCl₂·6H₂O, Zn(NO₃)₂·6H₂O (0.005 mole) in 100 ml of water with rapid 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 59-76%. 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 Thermo finnigan 1101 Flash EA. The metal contents were estimated using standard methods (Vogel, 1978). 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. ¹H NMR spectra

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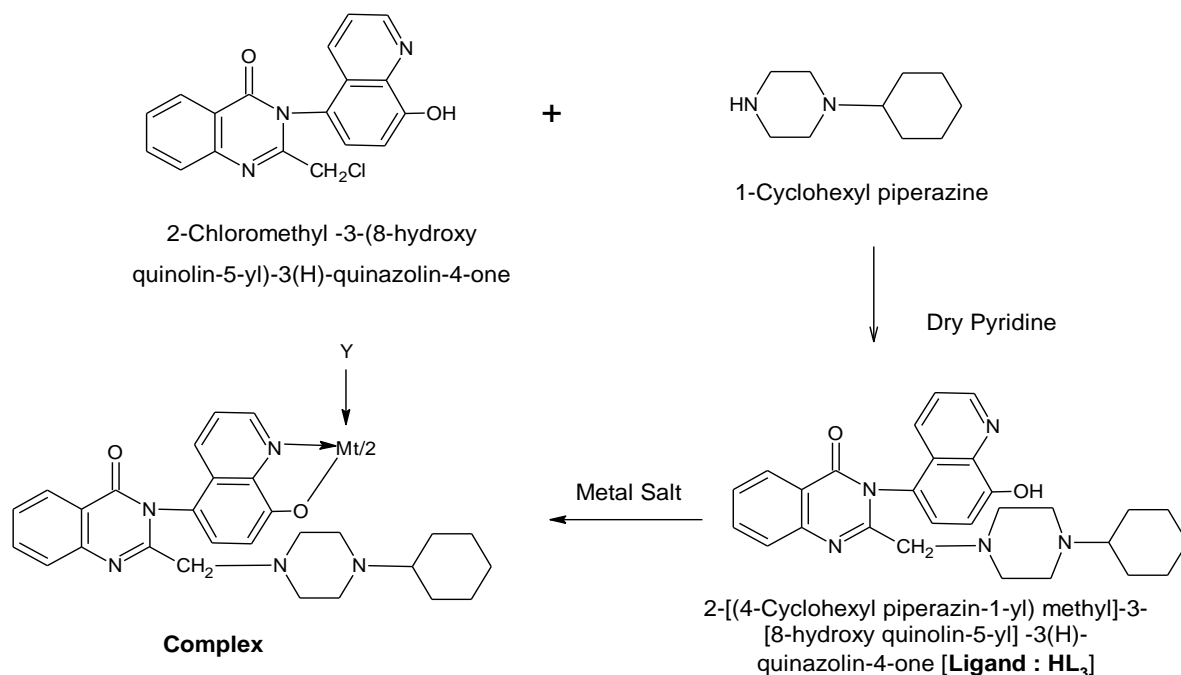
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Where, M = Cu²⁺, Mn²⁺, Co²⁺, Ni²⁺, Zn²⁺

Y = H₂O

Figure 1: Scheme of synthesis of quinazolin-4-one derivatives

of ligand was recorded on Bruker NMR spectrophotometer (300 MHz). PMR chemical shifts are recorded in δ - value using TMS as an internal standard in CDCl₃/D₆-DMSO. The IR spectra (KBr pellet method) were recorded in the range 4000-600 cm⁻¹ 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 χ_m was measured by Gouy's method (Lewis, 1964) at room temperature (300 K) using Hg[Co(CNS)₄] as calibrant (Figgis, 1960), and the effective magnetic moment from relation (Williams, 1978), $\mu_{\text{eff}} = 2.84 (\chi_m \times T)^{1/2}$, where T is the absolute temperature. Diamagnetic corrections were made by using Pascal's con-

stants.

The ligand and its metal chelates were screened at 1000 ppm concentration in vitro for their antifungal activity against five fungi viz. Botrydella thibromine, Nigrospora sp., Rhizopus nigricans, Aspergillus fumigatus and Candida albicans. The antifungal activity of the compounds was measured by plate method (Barry, 1996). 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:

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

Table 1: Analytical of ligand and its metal chelates

Ligand	Mol. Formula	M. W. (g/mole)	Yield (%)	Elemental Analysis (%)			
				Found (Calc.)			
				C	H	N	M
HL ₃	C ₂₈ H ₃₁ N ₅ O ₂	469.0	78	71.50 (71.64)	6.50 (6.60)	14.80 (14.92)	-
(HL ₃) ₂ Cu ²⁺	C ₅₆ H ₆₄ N ₁₀ O ₆ Cu ²⁺	1035.54	70	65.00 (65.01)	6.00 (6.19)	13.50 (13.54)	6.10 (6.14)
(HL ₃) ₂ Ni ²⁺	C ₅₆ H ₆₄ N ₁₀ O ₆ Ni ²⁺	1030.69	60	65.20 (65.32)	6.20 (6.22)	13.50 (13.60)	5.60 (5.70)
(HL ₃) ₂ Co ²⁺	C ₅₆ H ₆₄ N ₁₀ O ₆ Co ²⁺	1030.90	59	65.30 (65.31)	6.20 (6.24)	13.60 (13.65)	5.20 (5.30)
(HL ₃) ₂ Mn ²⁺	C ₅₆ H ₆₄ N ₁₀ O ₆ Mn ²⁺	1028.90	76	65.50 (65.56)	6.10 (6.22)	13.50 (13.60)	5.70 (5.72)
(HL ₃) ₂ Zn ²⁺	C ₅₆ H ₆₄ N ₁₀ O ₆ Zn ²⁺	1037.39	68	64.80 (64.90)	6.10 (6.18)	13.40 (13.52)	6.30 (6.31)

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 analysis data were shown in Table-1 and molar conductance and magnetic moment data of chelates were shown in Table-4. The result indicates that they are less polar in DMF. The molar conductance values found to be 22.68, 10.02, 8.28, 9.22 and 9.20 $\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$ 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 > Ni > Cu > Mn > Zn. The very low val-

Magnetic moment and Electronic spectra: The magnetic moment, molar conductance and electronic spectral data of complexes were depicted in table 4. At room temperature the magnetic moment ' μ_{eff} ' values for the Co(II) chelate has is 4.88 B.M suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The values of transition ratio ν_2 / ν_1 were 2.18 providing further evidences for octahedral geometry for the Co(II) complexes.

The magnetic moment of Ni(II) chelate is 2.99 B.M. suggesting two unpaired electrons. The ν_2/ν_1 ratio for the chelate is 1.60 occurs in the usual range (1.60–1.82) for octahedral Ni(II) chelates (Syamal, et al., 1986). The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier (Singh, et al., 1997).

Table 2: FT-IR spectroscopic data of HL₃ and its justification

Sr. No.	Group Frequency (cm ⁻¹)	Probable functional group/ Assignment
1	3400 to 2600	Phenolic group bonded to N atom of 8-hydroxy quinoline moiety (Syamal, et al., 1987)
2	2923, 2852 and 1470	Aromatic CH and methylene group of bridge and piperazine ring (Singh, et al., 1997)
3	1710	C=O of quinazoline 4-one moiety
4	1500-1600	Aromatic breathing
5	1580-1600	Nitrogen in the chelate formation (Syamal, et al, 1987 & Reddy, 1987)
6	1095	New C-O-M bond formation
7	840-830	Coordinated water

Table 3: ¹H NMR data of HL₃ and its justification

Sr. No.	Chemical Shift (δ ppm)	Probable Functional group
1	1.4	5-CH ₂
2	2.	-CH
3	3.47	CH ₂ bridge
4	3.44 to 3.52	Triplet -CH ₂ of piperazine
5	4.82	Singlet of phenolic -OH
6	7.1 to 8.84	Multiplet, quinazoline

ues of chelates indicates that they are non-electrolytic (Geary, 1971) and monomeric in nature. The low conductance values may be attributed to the large cations (Upadhyay, 1977).

FT-IR spectra: The basic features of FT-IR spectra of ligand HL₃ was depicted in table 2, which shows the attachment of 1-Cyclohexyl piperazine with 2-Chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one.

¹H NMR spectra: The main chemical shifts and its respective probable functional group of Ligand, HL₃ are mentioned in table 3. The chemical shift confirmed the formation of HL₃ i.e. 2[[4-Cyclohexyl piperazin-1-yl) methyl]-3-[8-hydroxyquinolin-5-yl]-3(H)-quinazolin-4-one.

The Cu (II) chelates possess a magnetic moment value of 2.02 B.M. indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers (Reddy, 1987). These complex show broad asymmetric bands in the region at 14856 and 23871 cm^{-1} assignable to ${}^2B_{1g} \rightarrow {}^2A_{1g}$ and charge transfer transition respectively (Chaudhary, et al., 1997). 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 (Satapathy, et al., 1989). The value of transition ratio ν_2/ν_1 was 1.60

Zn (II) complex is diamagnetic as expected for d^{10} systems and may have tetrahedral geometry (Yidliz, et al., 2004). The observed magnetic moment (5.32 B.M.) for

Table 4: Magnetic moment and electronic spectra of chelates of ligand HL₃

Samples	Observed μ_{eff} (B.M) (Expected)	Λ_M (Ohm^{-1} $\text{cm}^2 \text{mol}^{-1}$)	Electron Transition	Absorption band (cm^{-1})	u_2/u_1
$(\text{HL}_3)_2 \text{Co}^{2+}$	4.88 (4.4-5.2)	22.68	$^4T_{1g}(F) \rightarrow ^4T_{1g}(F)$	8541	2.18
			$^4T_{1g}(F) \rightarrow ^4A_{2g}(F)$	18659	
			$^4T_{1g}(F) \rightarrow ^4T_{1g}(P)$	24856	
$(\text{HL}_3)_2 \text{Ni}^{2+}$	2.99 (2.9-3.4)	10.02	$^3A_{2g}(F) \rightarrow ^3T_{1g}(F)$	13989	1.60
			$^3A_{2g}(F) \rightarrow ^3T_{1g}(P)$	21548	
$(\text{HL}_3)_2 \text{Cu}^{2+}$	2.02 (1.7-2.2)	9.20	$^2B_{1g} \rightarrow ^2A_{1g}$	14856	1.60
			Charge Transfer Transition	23871	
$(\text{HL}_3)_2 \text{Mn}^{2+}$	5.32 (5.2-6.0)	9.20	$^6A_{1g} \rightarrow ^4T_{1g}(^4G)$	15999	
			$^6A_{1g} \rightarrow ^4T_{2g}(^4G)$	17853	
			$^6A_{1g} \rightarrow ^4E_g, ^4T_{1g}(^4G)$	26548	
$(\text{HL}_3)_2 \text{Zn}^{2+}$	-	8.28	-	-	-

Table 5: Antifungal activity of ligand HL₃ and its metal chelates

Samples	Zone of inhibition at 1000 μm (%)				
	CA	BT	NS	AF	RN
HL ₃	88	87	68	81	62
$(\text{HL}_3)_2 \text{Cu}^{2+}$	81	76	78	74	81
$(\text{HL}_3)_2 \text{Ni}^{2+}$	59	68	69	77	70
$(\text{HL}_3)_2 \text{Co}^{2+}$	63	68	69	68	88
$(\text{HL}_3)_2 \text{Mn}^{2+}$	77	68	56	58	59
$(\text{HL}_3)_2 \text{Zn}^{2+}$	77	78	72	73	69

CA: *Candida Albicans*, BT: *Botrydepladia Thibromine*, NS: *Nigrospora Sp.*,

AF: *Aspergillus Fumigatus*, RN: *Rhizopur Nigricums*

Mn (II) complex indicates high spin octahedral environment (Sahu, 1979)

Antifungal activity: The ligand and chelates were studied for their antifungal activity 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-5 inhibition of fungal in following decreasing order: Cu (II) > Mn(II) > Zn(II) > Co(II) > Ni(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 (Patel, 1996).

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. The antifungal activity of all the compounds measured for various plant pathogens. The result shown in Table-5 indicates that all compounds

are good toxic for fungi. Out of all chelates studied copper chelates was more toxic than others. Hence the ligand and produced metal chelates can be employed as garden fungicides.

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