

SYNTHESIS, CHARACTERIZATION AND ANTIFUNGAL ACTIVITY OF 2-[4-(2,3-DICHLOROPHENYL) PIPERAZINE-1-YL] METHYL]-3-[8-HYDROXY QUINOLINE-5-YL]-3-(H)-QUINAZOLIN-4-ONE LIGAND AND ITS METAL CHELATES

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ABSTRACT

The novel ligand HL₇ was synthesized using 2-Chloromethyl-3-(8-hydroxyquinolin-5-yl)-3(H)-quinazolin-4-one and it was undergo 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 tetra hedral 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

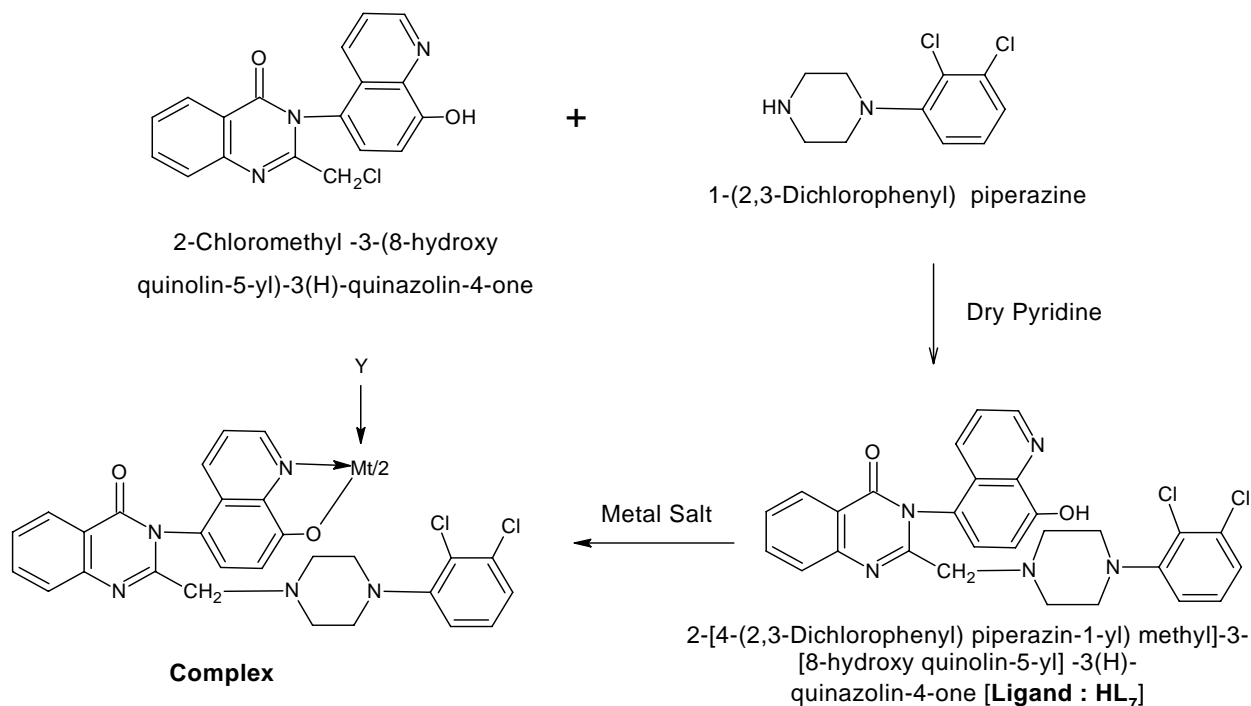
The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs¹. A Quinazolin-4-one derivative possesses biological activities such as antifungal^{2,3}. Ligand 8-hydroxyquinoline is not only act as a compelling agent but also applied for drug synthesis⁴. The 8-hydroxyquinoline and quinazolin-4-one molecules into one

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

Y= H₂O

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 quanzolin-4- one 8-hydroxyquinoline merged molecules as ligand HL₇ with their complexes with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) metal ion. Antimicrobial activities of the ligand and chelates have also been studied.

The whole work is summarized in scheme-1.



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 HL₇: 2-Chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one from Anthranilic acid was prepared according to previous literature⁵. A mixture of 2-Chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one (0.01 mole) and 1-(2,3-Dichlorophenyl) piperazine (0.01 mole) in dry pyridine (20 ml.) was refluxed for 12 h. Pyridine was distilled off as much as possible and the residue was poured into little crushed ice with stirring. The product, HL₇ i.e. 2[4-(2,3-Dichlorophenyl) piperazine-1-yl) methyl]-3-[8-hydroxy quinolin-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 HL₇ was 230 °C.

Synthesis of Chelates: A dried ligand sample HL₇ (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 then diluted to 500 ml. with distilled water and designated as reagent solution. This solution was used for preparation of chelates using ligand with transition metal ions. The reagent solution (100ml.) 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 (each 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 69-84 %. 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 Thermofinigan 1101 Flash EA. The metal contents were estimated using standard methods⁶. 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 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) 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 method⁷ at room temperature (300 K) using Hg [Co(CNS)₄] as calibrant,⁸ and the effective magnetic moment from relation,⁹ μ_{eff} = 2.84 √ χ_m × T, where T is the absolute temperature. Diamagnetic corrections were made by using Pascal's constants.

The ligand and its metal chelates were screen at 1000 ppm concentration in vitro for their antifungal activity against five fungi viz. *Botrydepladia thiobromine*, *Nigrospora sp.*, *Rhizopus nigricans*, *Aspergillus fumigatus* and *Candida albicans*. The antifungal activity of the compounds was measured by plate method¹⁰. 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= 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 and molar conductance data were shown in Table-1. The result indicates that they were less molar in DMF. The molar conductance values found to be 29.69, 10.69, 8.77, 9.92 and 8.68 ohm⁻¹cm²mol⁻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 > Zn > Mn. The very low values of chelates indicates that they are non-electrolytic¹¹ and monomeric in nature. The low conductance values may be attributed to the large cations¹².

FT-IR spectra: The basic features of FT-IR spectra of ligand HL₇ was depicted in table 2.

¹H NMR spectra: The main chemical shifts and its respective probable functional group of ligand, HL₇ are mentioned in table 3. The chemical shift confirmed the formation of HL₇ i.e. 2[(4-(2,3-Dichlorophenyl) piperazin-1-yl) methyl]-3-[8-hydroxyquinolin-5-yl]-3(H)-quinazolin-4-one.

Magnetic moment and electronic spectra

The magnetic moment and molar conductance of complexes were depicted in table 2. The electronic spectral data were shown in table-4. At room temperature the magnetic moment 'μ_{eff}' values for the Co(II) complex is 5.12 B.M suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The values of transition ratio ν₂ / ν₁ were 2.19 providing further evidences for octahedral geometry for the Co(II) complexes.

In the Ni(II) complex, μ_{eff} value at room temperature is observed to be 3.42 B.M. as expected for six coordinated spin free Ni(II) species. The ν₂/ν₁ ratio for the chelate is 1.64 occurs in the usual range (1.60-1.82) for octahedral Ni(II) chelates.¹³ The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier.¹⁴

Table 1: Analytical and physical data of ligand and its metal chelates

Ligand / Mol. Formula	M. W. (g/mole)	Yield (%)	Elemental Analysis (%)				Observed μ _{eff} (B.M) (Expected)	Λ _M (Ohm ⁻¹ cm ² mol ⁻¹)
			Found (Calc.)	C	H	N		
HL ₇	496.5	64	63.00 (63.15)	4.25 (4.32)	13.00 (13.15)	-	-	-
C ₂₈ H ₂₃ N ₅ O ₂ Cl ₂ (HL ₇) ₂ Cu ²⁺	1041.54	70	65.90 (65.91)	4.60 (4.70)	13.70 (13.73)	6.20 (6.23)	2.09 (1.7-2.2)	9.92
C ₅₆ H ₄₈ N ₁₀ O ₆ Cu ²⁺ Cl ₄ (HL ₇) ₂ Ni ²⁺	1036.68	71	66.20 (66.22)	4.60 (4.70)	13.60 (13.79)	5.60 (5.78)	3.42 (2.9-3.4)	10.69
C ₅₆ H ₄₈ N ₁₀ O ₆ Ni ²⁺ Cl ₄ (HL ₇) ₂ Co ²⁺	1036.90	84	66.20 (66.21)	4.70 (4.72)	13.70 (13.79)	5.70 (5.80)	5.12 (4.4-5.2)	29.69
C ₅₆ H ₄₈ N ₁₀ O ₆ Co ²⁺ Cl ₄ (HL ₇) ₂ Mn ²⁺	1032.93	69	66.40 (66.47)	4.70 (4.74)	13.80 (13.84)	5.30 (5.37)	5.78 (5.2-6.0)	8.68
C ₅₆ H ₄₈ N ₁₀ O ₆ Mn ²⁺ Cl ₄ (HL ₇) ₂ Zn ²⁺	1043.39	72	65.70 (65.79)	4.60 (4.69)	13.70 (13.60)	6.30 (6.40)	-	8.77

Table 2: IR spectroscopic data of HL7 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 ^[13]
2	2923, 2852 and 1470	Aromatic CH and methylene group of bridge and piperazine ring ^[14]
3	1700	C=O of quinazoline 4-one moiety
4	1500-1600	Aromatic breathing
5	1580-1600	Nitrogen in the chelate formation [13, 15]
6	1095	New C-O-M bond formation
7	840-830	Coordinated water

Table 3: ¹H NMR data of HL₇ and its justification

Sr. No.	Chemical shift (δppm)	Probable functional group
1	3.47	CH ₂ bridge
2	3.44 to 3.52	Triplet -CH ₂ of piperazine
3	4.82	Singlet of phenolic -OH
4	7.1 to 8.84	Multiplet, quinazoline

The Cu(II) complex exhibit normal magnetic moments (2.09 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research worker.¹⁵ These complex show broad asymmetric bands in the region at 14990 and 23698 cm⁻¹ assignable to ²B_{1g} ----> ²A_{1g} and charge transfer transition respectively.¹⁶ These results reveal the distorted octahedral geometry for these complexes. The former band may be due to ²E_g ---

-> ²T_{2g} accounted due to Jahn Teller effect suggesting thereby a distorted octahedral geometry for these complexes.¹⁷ The value of transition ratio v_2/v_1 was 1.58

Zn(II) complex is diamagnetic as expected for d¹⁰ systems and may have tetrahedral geometry.¹⁸ The observed magnetic moment (5.78 B.M.) for Mn (II) complex indicates high spin octahedral environment¹⁹

Table 4: Magnetic moment and electronic spectra of chelates of ligand HL₇

Samples	Electron transition	Absorption band (cm ⁻¹)	v_2/v_1
(HL ₇) ₂ Co ²⁺	⁴ T _{1g} (F) ----> ⁴ T _{1g} (F)	8536	2.19
	⁴ T _{1g} (F) ----> ⁴ A _{2g} (F)	18745	
	⁴ T _{1g} (F) ----> ⁴ T _{1g} (P)	28965	
(HL ₇) ₂ Ni ²⁺	³ A _{2g} (F) ----> ³ T _{1g} (F)	14962	1.64
	³ A _{2g} (F) ----> ³ T _{1g} (P)	24548	
(HL ₇) ₂ Cu ²⁺	² B _{1g} ----> ² A _{1g}	14990	1.58
	Charge Transfer Transition	23698	
(HL ₇) ₂ Mn ²⁺	⁶ A _{1g} ----> ⁴ T _{1g} (⁴ G)	14546	-
	⁶ A _{1g} ----> ⁴ T _{2g} (⁴ G)	16925	
	⁶ A _{1g} ----> ⁴ E _g , ⁴ T _{1g} (⁴ G)	24987	

Antifungal activity

The ligand and chelates were used for their antimicrobial studies 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) > HL₇ > Mn (II) > Zn (II) > Co (II) > Ni (II).

Table 5: Antifungal activity of ligand HL₇ and its metal chelates

Samples	Zone of inhibition at 1000 pm (%)				
	CA	BT	NS	AF	RN
HL ₇	89	69	68	87	70
(HL ₇) ₂ Cu ²⁺	78	88	82	88	89
(HL ₇) ₂ Ni ²⁺	59	52	56	69	54
(HL ₇) ₂ Co ²⁺	68	62	63	66	67
(HL ₇) ₂ Mn ²⁺	70	75	71	72	73
(HL ₇) ₂ Zn ²⁺	77	69	68	65	63

CA: *Candida Albicans*, BT: *Botrydepladia Thibromine*, NS: *Nigrospora Sp.*, AF: *Aspergillus Fumigatus*, RN: *Rhizopur Nigricums*

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 organisms²⁰.

CONCLUSION

The ligand molecule acts as a hexadentate ligand in all the studied cases of complex. 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. Copper chelate is more toxic to fungus than other chelates studied.

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