

Synthesis, Characterization and Antifungal Activity of 6-Bromo-2[(4-Cyclohexyl Piperazine-1-yl) Methyl]-3-[8-Hydroxy Quinolin -5-yl]-3-(H) Quinazolin -4-one Ligand and Its Transition Metal Chelates

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Abstract: The present investigation involved the synthesis of novel ligand HL₁₀ and its chelate complexes with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II). The characterization studies of chelates were conducted using various physicochemical methods such as elemental analysis, conductometric studies, magnetic susceptibility, FT-IR, NMR and electronic spectral data. The stoichiometry of the complex has been carried out and 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 performed against various fungi.

Key Words: 8-Hydroxy quinoline ligand, Complexes, Electronic, NMR spectral studies, Antifungal activity.

Introduction

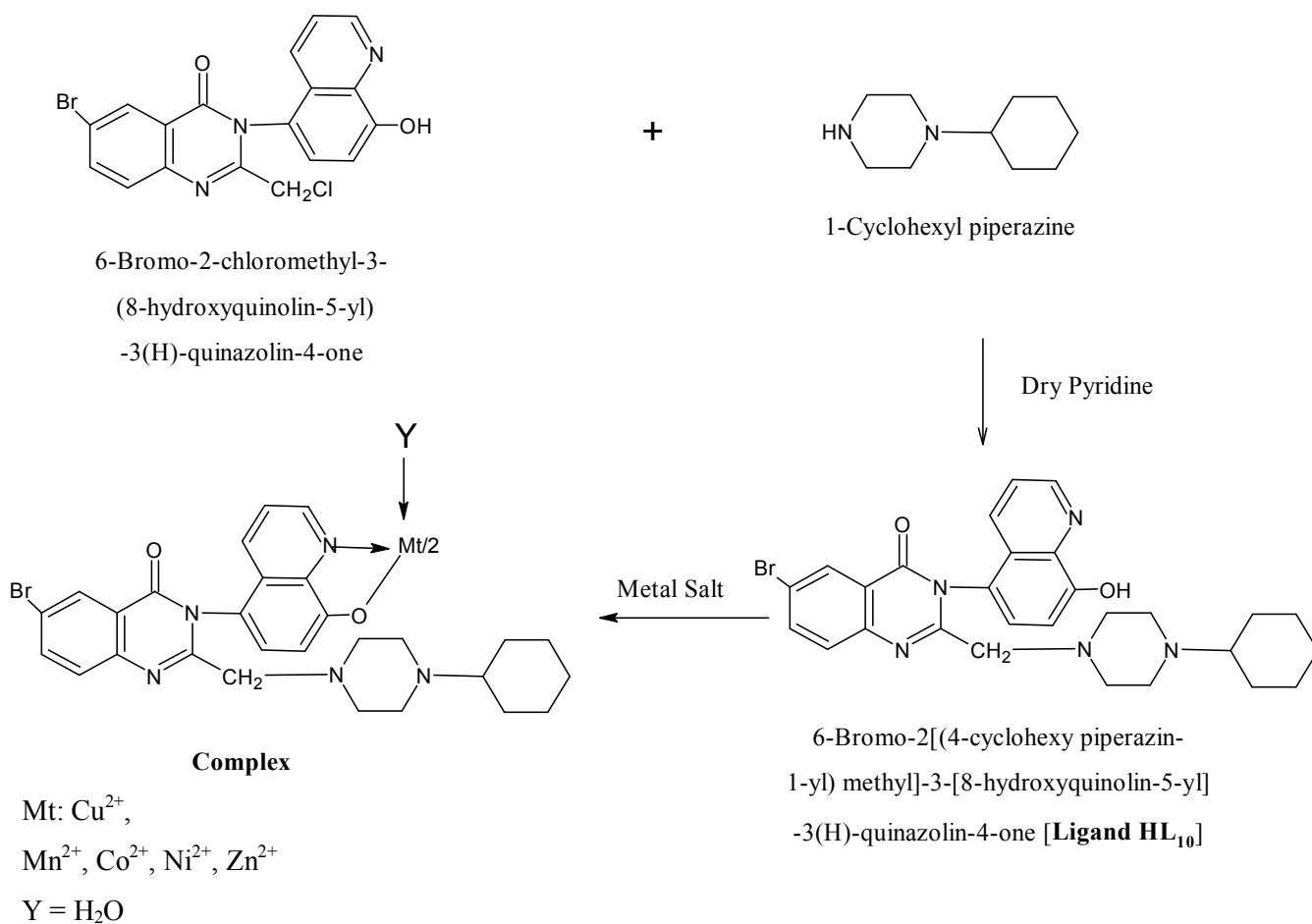
The unique heterocyclic nitrogen compounds especially quinazolinone derivatives are employed in many biological processes and as synthetic drugs¹. The Quinazolin-4-one derivative is exploited in biological activities such as antifungal²⁻⁴. A 8-hydroxyquinoline and quinazolin-4-one molecules into one 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 qunazolin-4- one 8-hydroxyquinoline merged molecules as ligand HL₁₀ with their complexes with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) metal ion. Antifungal activities of the ligand and its metal chelates have also been studied. General structure of formation of chelate was shown in **scheme-I**.

Material 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 point of ligand

was determined by open capillary method and was uncorrected.

Synthesis of BPMHQ ligand (HL₁₀): 6-bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one from 5-bromoanthranilic acid was prepared according to previous literature⁵. A mixture of 6-bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one (0.01 mole) and 1-Cyclohexyl piperazine (20 ml) 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, HL₁₀ i.e. 6-Bromo-2[(4-(2cyclohexyl piperazin-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 HL₁₀ > 230 °C.

**Scheme I****Synthesis of Chelates:**

A dried ligand sample HL₁₀ (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 particular ligand with transition metal ions. The formic acid solution of ligand was added drop-wise to a 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 constant 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 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 69-80 %. 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. PMR chemical shifts were 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 calibrant⁸, and the effective magnetic moment from relation, μ_{eff} = 2.84 (χ_m × T)^{1/2}, where T is the absolute temperature⁹. 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 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.

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

Ligand	Mol. Formula	M. W. (g/mole)	Yield (%)	Elemental Analysis (%)				
				Found (Calcd.)				
				C	H	N	Br	M
HL ₁₀	C ₂₈ H ₃₀ N ₅ O ₂ Br	548.00	65	61.20 (61.31)	5.40 (5.47)	12.77 (12.70)	16.50 (16.60)	-
(HL ₁₀) ₂ Cu ²⁺	C ₅₆ H ₆₂ N ₁₀ O ₆ Cu ²⁺ Br ₂	1193.54	76	56.20 (56.30)	5.10 (5.19)	11.70 (11.72)	13.20 (13.23)	5.30 (5.32)
(HL ₁₀) ₂ Ni ²⁺	C ₅₆ H ₆₂ N ₁₀ O ₆ Ni ²⁺ Br ₂	1188.69	69	56.40 (56.53)	5.10 (5.22)	11.60 (11.78)	13.20 (13.29)	4.80 (4.96)
(HL ₁₀) ₂ Co ²⁺	C ₅₆ H ₆₂ N ₁₀ O ₆ Co ²⁺ Br ₂	1188.90	80	56.50 (56.52)	5.20 (5.21)	11.70 (11.77)	13.20 (13.28)	4.90 (4.95)
(HL ₁₀) ₂ Mn ²⁺	C ₅₆ H ₆₂ N ₁₀ O ₆ Mn ²⁺ Br ₂	1184.90	78	56.71 (56.60)	5.20 (5.23)	11.80 (11.81)	13.30 (13.33)	4.50 (4.58)
(HL ₁₀) ₂ Zn ²⁺	C ₅₆ H ₆₂ N ₁₀ O ₆ Zn ²⁺ Br ₂	1195.39	72	56.20 (56.21)	5.10 (5.18)	11.70 (11.71)	13.10 (13.21)	5.40 (5.47)

Table 2: FT-IR spectroscopic data of HL₁₀ 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	1709	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: ¹ H NMR data of HL₁₀ and its justification

Sr. No.	Chemical Shift (δppm)	Probable Functional group
1	1.4	5 -CH ₂
2	2.0	-CH
3	3.47	CH ₂ bridge
4	3.44 to 3.52	Triplet -CH ₂ of piperizine
5	4.82	Singlet of phenolic -OH
6	7.1 to 8.84	Multiplet, quinazoline

Table 4: Magnetic moment and electronic spectra of chelates of ligand HL₁₀

Sample	Observed μ_{eff} (B.M) (Expected)	Λ_M (Ohm ⁻¹ cm ² mol ⁻¹)	Electron Transition	Absorption band ν_2/ν_1 (cm ⁻¹)	ν_2/ν_1
(HL ₁₀) ₂ Co ²⁺	5.10 (4.4-5.2)	23.10	⁴ T _{1g} (F) ----> ⁴ T _{1g} (F) ⁴ T _{1g} (F) ----> ⁴ A _{2g} (F) ⁴ T _{1g} (F) ----> ⁴ T _{1g} (P)	8125 19562 25896	2.41
(HL ₁₀) ₂ Ni ²⁺	3.09 (2.9-3.4)	8.20	³ A _{2g} (F) ----> ³ T _{1g} (F) ³ A _{2g} (F) ----> ³ T _{1g} (P)	14856 24691	1.66
(HL ₁₀) ₂ Cu ²⁺	2.08 (1.7-2.2)	9.10	² B _{1g} ----> ² A _{1g} Charge Transfer Transition	15300 23871	1.56
(HL ₁₀) ₂ Mn ²⁺	5.49 (5.2-6.0)	10.20	⁶ A _{1g} ----> ⁴ T _{1g} (⁴ G) ⁶ A _{1g} ----> ⁴ T _{2g} (⁴ G) ⁶ A _{1g} ----> ⁴ E _g , ⁴ T _{1g} (⁴ G)	16895 17856 21548	-
(HL ₁₀) ₂ Zn ²⁺	-	8.10	-	-	-

Table 5: Antifungal activity of ligand HL₁₀ and its metal chelates

Sample	Zone of inhibition at 1000 pm (%)				
	CA	BT	NS	AF	RN
HL ₁₀	73	76	75	74	72
(HL ₁₀) ₂ Cu ²⁺	75	75	78	89	87
(HL ₁₀) ₂ Ni ²⁺	78	75	79	82	80
(HL ₁₀) ₂ Co ²⁺	69	68	59	58	77
(HL ₁₀) ₂ Mn ²⁺	56	58	69	68	67
(HL ₁₀) ₂ Zn ²⁺	77	75	72	72	73

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

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

Results and Discussion

The chelates 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 molecular weight data were shown in Table-1 while molar conductance and magnetic moments data were shown in table-4. The result indicates that they are less molar in DMF. The molar conductance values found to be 23.10, 8.20, 8.10, 9.10, and 10.20 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 > Mn > Cu > Ni > Zn. The very low values of conductance of chelates indicates that they are non-electrolytic¹¹ and monomeric in nature. The low conductance values may be attributed to the large cations¹².

Infrared spectra: The basic features of FT-IR spectra of ligand HL₁₀ was depicted in table 2, which indicates the attachment of 1-Cyclohexyl piperazine into 6-

bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one.

NMR spectra: The main chemical shifts and its respective probable functional group of Ligand, HL₁₀ are mentioned in table 3. The chemical shift confirmed the formation of HL₁₀ i.e. 6-Bromo-2[(4-Cyclohexyl piperazine piperazin-1-yl)methyl]-3-[8-hydroxyquinolin-5-yl]-3(H)-quinazolin-4-one.

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) complex is 5.10 B.M suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The value of transition ratio ν_2 / ν_1 was 2.41 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 3.09 B.M. as expected for six coordinated spin free Ni(II) species. The ν_2/ν_1 ratio for the chelate was 1.66 occurs in the usual range

(1.60–1.82) for octahedral Ni(II) chelates¹³. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier¹⁴.

The Cu(II) complex exhibit normal magnetic moments (2.08 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research worker¹⁵. These complex show broad asymmetric bands in the region at 15300 and 23871 cm⁻¹ assignable to ²B_{1g} ----> ²A_{1g} and charge transfer transition respectively¹⁶. 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 complexes¹⁷. The value of transition ratio ν_2/ν_1 was 1.56.

Zn(II) complex is diamagnetic as expected for d¹⁰ systems and may have tetrahedral geometry¹⁸. The observed magnetic moment (5.49 B.M.) for Mn(II) complex indicates high spin octahedral environment¹⁹.

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 fungi were found in the following decreasing order: Cu(II) > Ni(II) > Zn(II) > Co(II) > Mn(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 organisms²⁰.

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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