



The Metal Complexes of 5-[(benzyloxy) methyl] quinolin-8-ol (BeMQ) and 8-quinolinols mixed Ligand: A New Transition metal Complexes with *In-vitro* Antifungal Activity

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Abstract

5-Chloromethyl-8-quinolinol was condensed stoichiometrically with various alcohols specially benzyl alcohol in presence of sodium carbonate. The resulting 5-[(benzyloxy) methyl] quinolin-8-ol (BeMQ) was characterized by elemental analysis and spectral studies. The transition metal chelates viz. Cu^{2+} , Ni^{2+} , Co^{+2} , Mn^{2+} and Zn^{2+} of BeMQ and 8-quinolinols were prepared and characterized by mixed ligand complexes(L:M:L) ratio, elemental analysis, IR, reflectance spectral studies, magnetic properties and conductivities measurements. The antifungal activity of BeMQ and its metal chelates was investigated against various fungi. The metal complexes exhibit good activity against fungal strains compared with parental compounds.

Keywords: Transition metal complexes, 8-quinolinols, spectral studies, magnetic moment and *In-vitro* antifungal activity.

Introduction

Transition metals have varying utility and interesting chemistry. Coordination compounds are important due to their role in biological and chemical systems in various ways. It has been observed that metal complexes with appropriate ligands are chemically more significant and specific than the metal ions and original¹⁻². It is well known that mixed ligand ternary complexes of some metals play an important role in the activation of enzymes³. It is studied that mixed ligand complexes are biologically active against pathogenic microorganisms⁴⁻⁵; further, metal complexes, which include 8-hydroxyquinoline as a primary ligand, exhibit biological activity⁶. One of the derivative say 5-chloromethyl 8-Quinolinol (CMQ) can be synthesize easily and studied extensively for number of derivatives⁷. CMQ precursor for the synthesis of many coordination polymers, biological active compounds as well as ion-exchanger⁸⁻¹⁰. There has been a tremendous growth of drugs from quinoline family, which began with the discovery of nalidixic acid (Hnal) some 40 years ago. Since then, the exponential growth of this family has produced more than ten thousand analogues¹¹. The complexation of metallic elements with biologically inactive compounds renders them active; and in case the compounds are already active, it makes them more active. The mechanism involved in enhancing this biological activity upon complexation is still needed to be further investigated¹²⁻¹⁵.

As a part of our ongoing work¹⁶⁻¹⁸ on mixed ligand complexes, in this paper we reporting the newly synthesized complexes of Cu (II), Ni (II), Co (III), Mn (II), and Zn(II) ions with 5-(benzyloxy methyl)-8-Quinolinol as primary and heterocyclic bases, viz., Quinoline (Q), 8-hydroxyquinoline (8-HQ) as

secondary ligand. Their antifungal activities investigated to perform primary selection of these complexes as the therapeutic agents.

Material and Methods

Reagent and solvents: All the chemicals and reagents used for the preparation of ligands and complexes were commercial products (E. Merck Ltd, India) and used without further purification. Acetic acid and EDTA were purchased from Sigma Chemical Co., India. The organic solvents were purified by recommended method¹⁹.

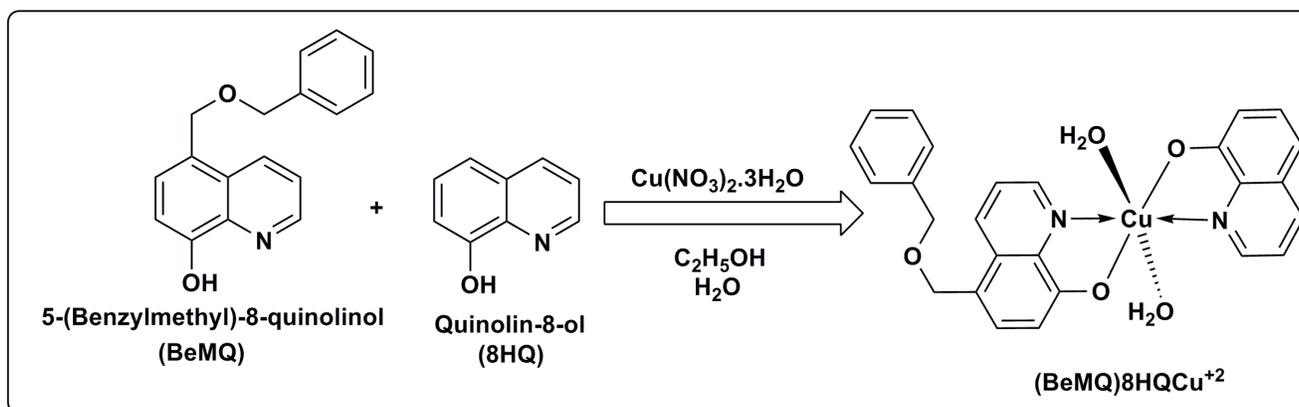
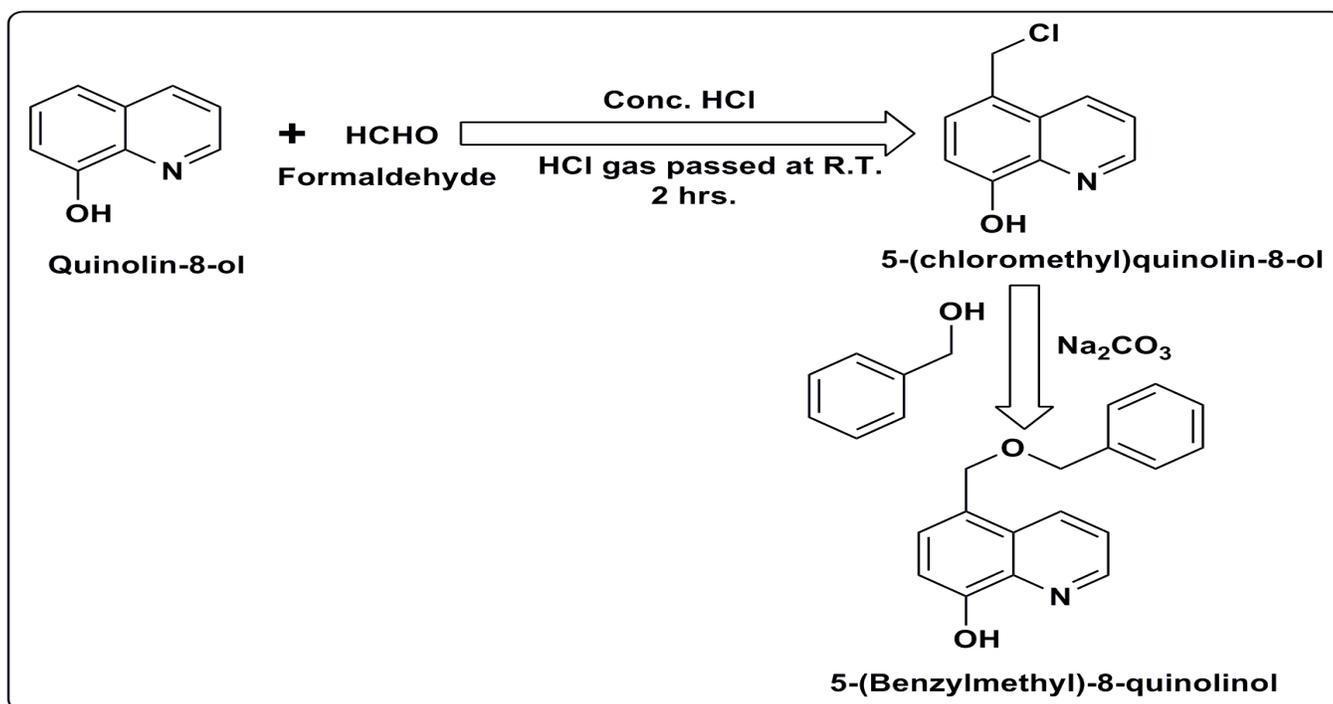
Physical measurements: The metal content of the complexes were determined by the EDTA titration technique²⁰ after treating them with mixture of HClO_4 , H_2SO_4 and HNO_3 (1:1.5:2.5). Elemental analysis was carried out using Perkin Elmer, USA 2400-II CHN analyzer. The magnetic moments were obtained by the Gouy's method using mercury tetrathiocyanatocobaltate (II) as a calibrant ($\chi_g = 16.44 \times 10^{-6}$ c.g.s. units at 20°C). Diamagnetic corrections were made using Pascal's constant²¹. The IR spectra were recorded on a FT-IR Nicolet 400D Spectrophotometer using KBr pellets. NMR spectra were recorded on a model Bruker Avance (400MHz). A simultaneous TG/DTG had been obtained by a model 5000/2960 SDT, TA Instruments, USA at heating rate of 10 °C min^{-1} under N_2 atmosphere. The conductivities of the metal complexes in DMF were measured using conductivity Bridge 305 Systronics and a calibrated conductivity cell at room temperature.

Preparation of ligand: Synthesis of 5-[(benzyloxy) methyl] quinolin-8-ol (BeMQ): To a suspension of 2.3 gm. (0.01 mole)

of 5-chloromethyl-8-quinolinol (CMQ), benzyl alcohol (3 times) and 0.84 gm. (0.01 mole) of sodium carbonate (NaHCO_3) added. The mixture was warmed on the steam bath with occasional shaking until most of the alcohol had been distilled. The pale yellow solid was dissolved in water and made basic with 5 % ammonium hydroxide. The white solid was collected on a filter and dried to give 1.50 gm. (60% yield), having m.p.- 82°C . (Uncorrected). FT-IR (KBr, cm^{-1}): $\nu(\text{-OH})$, 3375-3385, $\nu(\text{-C-N})$ 1285-1298, elemental analysis found (%): C, 76.81; H, 5.66; $\text{C}_{17}\text{H}_{15}\text{NO}_2$ (265) requires (%): C, 76.96, H, 5.70. Scheme represented in below given.

hexahydrate (10 mmol, 2.41 g) was added to dimethyl formamide solution (100 ml) of ligand (BeMQ) (10 mmol, 2.77 g), followed by addition of 8-hydroxyquinoline (10 mmol, 3.05 g) in ethanol; the pH was adjusted to 4.5-6.0 with dilute NaOH solution. The resulting solution was refluxed for 7 h and then heated over a steam bath to evaporate up to half of the volume. The reaction mixture was kept overnight at room temperature. The obtained product was washed with ether and dried over vacuum desiccators. The yield of a purified complex was 67%. The reaction scheme is shown in figure: 2 and physical data are shown in table 1. IR Spectra and IR data are shown in figure: 3 and table 2 respectively.

Preparation of Metal Complexes: Formation of Cu^{2+} Complexes: A water solution (100 ml) of cupric nitrate



Formation of Ni²⁺ complex: Ni²⁺ complex was synthesized by same method used for Cu²⁺ complexes. A dull greenish colored crystalline product was obtained. The yield of a purified complex was 65%.

Formation of Mn²⁺ Complex: Mn²⁺ complex was synthesized by same method used for Cu²⁺ complexes. A light pink colored crystalline product was obtained. The yield of complex was 73%.

Formation of Co²⁺ complex: Co²⁺ complex was synthesized by same method used for Cu²⁺ complexes. A light brown colored crystalline product was obtained. The yield of a purified complex was 61%.

Formation of Zn²⁺ Complex: Zn²⁺ complex was synthesized by same method used for Cu²⁺ complexes. A pale yellow colored powder product was obtained. The obtained product was washed with ether and dried over vacuum desiccators. The yield was 64%.

Table-1
Characterization of metal complexes of Ligand (BeMQ+8-HQ+M)

Metal complexes	Molecular formula	M. wt gm/mole	Yield %	% Metal analysis		Elemental analysis					
				Cal.	Found	% C		% H		% N	
						Cal.	Found	Cal.	Found	Cal.	Found
(BeMQ)8HQCu ⁺²	C ₂₆ H ₂₄ N ₂ O ₅ Cu ⁺²	508.03	67	12.51	12.45	61.47	61.45	4.76	4.75	5.51	5.49
(BeMQ)8HQNi ⁺²	C ₂₆ H ₂₄ N ₂ O ₅ Ni ⁺²	503.17	65	11.66	11.65	62.06	62.03	4.81	4.78	5.57	5.51
(BeMQ)8HQMn ⁺²	C ₂₆ H ₂₄ N ₂ O ₅ Mn ⁺²	499.42	73	11.00	10.96	62.53	62.49	4.84	4.80	5.61	5.55
(BeMQ)8HQCo ⁺²	C ₂₆ H ₂₄ N ₂ O ₅ Co ⁺²	503.41	61	11.71	11.65	62.03	62.00	4.81	4.77	5.56	5.51
(BeMQ)8HQZn ⁺²	C ₂₆ H ₂₄ N ₂ O ₅ Zn ⁺²	509.89	64	12.83	12.79	61.24	61.19	4.74	4.69	5.49	5.45

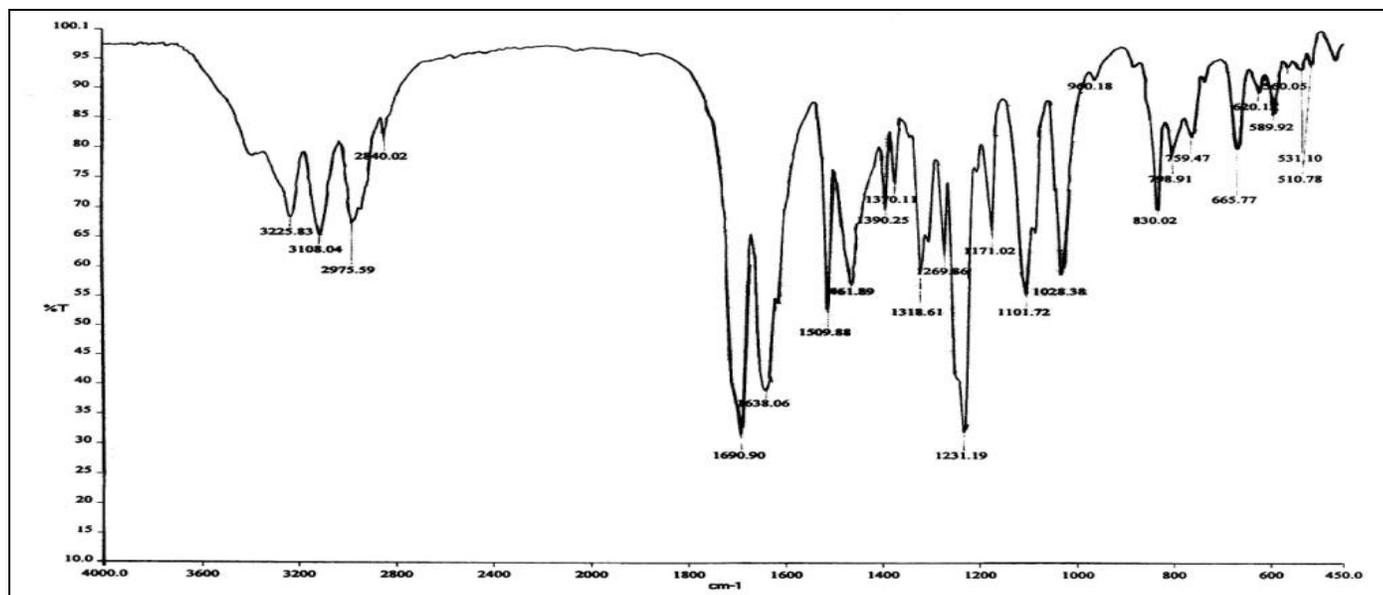


Figure-3
IR Spectra of Cu (II) Complex.

Table-2
IR Spectral data of complex

Metal complex	Frequencies cm ⁻¹ (ν)				
	8-HQ	Aromatic	C-N	CH ₂	OH
(BeMQ)-Cu(II)-8HQ	1638	1598	1269	2840	3500-
	1690	1461		2975	2600
	1509	3108		1469	broad
	1390				

Antifungal activity: The antifungal activity of the standard fungicide (Clioquinol), ligand and complexes were tested for their effect on the growth of microbial cultures and studied for their interaction with *Penicillium Expansum*, *Botrydepladia Thiobromine*, *Nigras Pora Sp Aspergillus Niger* and *Trichothesium Sp.* using Czapek's agar medium having the composition, glucose 20 g, starch 20 g, agar-agar 20 g and distilled water 1000 ml. To this medium was added requisite amount of the compounds after being dissolved in methanol so as to get the certain concentrations (50, 100 and 200 ppm). The medium then was poured into petri plates and the spores of fungi were placed on the medium with the help of inoculum's needle. These petri plates were wrapped in polythene bags containing a few drops of alcohol and were placed in an incubator at 30°C. The controls were also run and three replicates were used in each case. The linear growth of the fungus was recorded by measuring the diameter of the fungal colony after 96 h and the percentage inhibition was calculated by the equation: % Inhibition D (C – T/C) 100

Where C and T are the diameters of the fungal colony in the control and the test plates, respectively.²²

% Activity Index = D Zone of inhibition by test compound x 100 / Zone of inhibition by standard. Results are shown in Below given table 3.

Results and Discussion

The toxic effect of all the complexes on fungi is shown in table 3. The results give the following conclusions. All the complexes are toxic more or less to fungi. In all complexes the Cu-complexes have much toxicity. This is expected because the copper salts are mostly used as fungicides. Most of the complexes inhibit the growth of the above organisms which cause decrease in many plants. Cu⁺² metal complexes are more toxic than others and the toxicity is in order of Cu⁺² > Zn⁺² > Co⁺² > Ni⁺² > Mn⁺².

IR spectra: The important infrared spectral bands and their assignments for the synthesized ligands and complexes were recorded as KBr discs and are presented in table 2. The IR data of the free ligands and its metal complexes were carried out within the IR range 4000–400 cm⁻¹.

A broad band was observed in the region between 3460 and 3431 cm⁻¹ due to asymmetric and symmetric O–H stretching modes and a band in the range 1600–1585cm⁻¹ due to H–O–H bending vibrations indicating the presence of coordinated water molecules further confirmed by thermal studies. The ν(CO) band is observed at ~1120 cm⁻¹. The position of this band undergoes variation depending on metal complex under study²³. A strong ν(CO) band observed in the range between 1106 and 1105 cm⁻¹ indicates the presence of oxine moiety in the complexes coordinated through its nitrogen and oxygen atoms as uninegative bidentate ligand²⁴. In the investigated heterochelates, the band observed in the region 3420–3500, 1290–1305, 865–875 and 714–716 cm⁻¹ are attributed to –OH stretching, bending, rocking and wagging vibrations, respectively due to the presence of water molecules²⁵. The evidence of complexes formation clear by appearance of new bands at 416–430 and 508–517 cm⁻¹, which are assigned to ν (M–N) and ν(M–O), respectively^{26,27}.

Reflectance spectra, magnetic measurements and conductivity:

In order to shed some light on the geometrical structure of the complexes, the reflectance spectra of the complexes were recorded in the solid phase at room temperature. The reflectance spectra of the Mn(II) complex shows absorption bands at ~16202, ~17985 and ~22102 cm⁻¹ assignable to ⁶A_{1g}→⁴T_{1g}, ⁶A_{1g}→⁴T_{2g} and ⁶A_{1g}→⁴A_{1g}, ⁴E_g transitions, respectively, in an octahedral environment around the Mn (II) ion. The magnetic moment value of the Mn (II) complex is 5.55 B.M. due to a high-spin d⁵-system with an octahedral geometry.²⁸ For the Co (II) complex, the reflectance spectra exhibits the bands of medium intensity at ~8748 ~18979, and ~24120 cm⁻¹, which may reasonably be assigned to ⁴T_{1g}(F) →⁴T_{2g}(F), ⁴T_{1g}(F) →⁴A_{2g}(F) and ⁴T_{1g}(F) →⁴T_{2g}(P) transitions, respectively, of an octahedral geometry around the metal ion²⁹ and the magnetic moment value is observed to be of 4.65 B.M. The electronic spectra of the Ni (II) complex exhibits absorption bands at ~13254 and ~22570 cm⁻¹ assignable to ³A_{2g}(F) →³T_{1g}(F) and ³A_{2g}(F) →³T_{1g}(P) transitions respectively, in an octahedral geometry. The value of the magnetic moment (2.97 B.M.) may be taken as additional evidence for their octahedral structure³⁰⁻³³. The Cu (II) complex display a broad band at ~15715 cm⁻¹ due to the ²B_{1g}→²A_{1g} transition and the magnetic moment value is 1.92 B.M., which is close to spin-only value (1.93 B.M.) expected for an unpaired electron, which offers the possibility of an octahedral geometry³⁴.

Table-3
Antifungal activity of ligand (BeMQ) and their metal complexes

Sample	Zone of inhibition at 1000 ppm (%)				
	Penicillium expansum	Botrydepladia thiobromine	Nigras pora Sp.	Trichothesium Sp.	A. niger
Clioquinol	64	63	72	67	62
8-HQ	59	61	69	55	57
(BeMQ)	66	63	69	57	53
(BeMQ)8HQCu ⁺²	82	83	79	81	85
(BeMQ)8HQMn ⁺²	55	56	55	59	55
(BeMQ)8HQCo ⁺²	69	69	65	66	69
(BeMQ)8HQZn ⁺²	81	80	71	71	73
(BeMQ)8HQNi ⁺²	60	63	60	60	59

Table-4
Experimental data of magnetic moment and conductivity of metal complexes

Metal complexes	$\chi_g \times 10^{-6}$ (cgs)	$\chi_m \times 10^{-6}$ (cgs)	Magnetic moment μ_{eff} (BM)	$\mu_{\text{eff}} = \sqrt{n(n+2)}$ BM	μ_{eff} (BM) Expected	\wedge_M^a
(HL-9)8HQMn ⁺²	20.50	12693	5.55	5.91	5.2-6.0	7.98
(HL-9)8HQCo ⁺²	14.30	8910	4.65	3.87	4.4-5.2	2.20
(HL-9)8HQNi ⁺²	5.83	3634	2.97	2.82	2.9-3.4	11.02
(HL-9)8HQCu ⁺²	2.42	1519	1.92	1.93	1.7-2.2	7.80
(HL-9)8HQZn ⁺²	-	-	-	-	D(*)	9.20

The conductivity of 0.001 M each solution of each complex was measured twice or thrice and the constant value observed was used in further calculations. From the measured conductivity, specific and molar conductivities were calculated using following formula:

Sp. Conductivity = cell constant X conductivity

Molar conductivity = Sp. Conductivity X $\frac{1000}{M}$

Where, M is the molarity of the solution. Results are tabulated in table: 4.

Conclusion

The complexes were obtained as colored powdered materials and were characterized using IR spectra, electronic spectra, and magnetic measurements. The compounds were insoluble in ethanol, methanol, DMF, acetone, ether, hexane, chloroform, THF, and dichloromethane, and soluble in DMSO. The elemental analyses were in good agreement with the complexes. From the *In-vitro antifungal activity* data, it is observed that the complexes exhibit higher activity than the free ligands, metal salt, and the control (DMSO). The increase in *antifungal activity* of the complexes may be due to the metal chelation. From comparative analysis as shown in Table 3, it is observed that all the metal complexes are more potent therapeutic than the ligand. The zone of inhibition was measured (in %). It is clear that Cu(II) complex is highly active among all the complexes of the respective metal, this may be due to presence of benzyloxy group of ligand whereas Cu(II) is most active or because of combine effect of Cu(II) and functional groups on the ligand.

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Abbreviation

8HQ = 8- Hydroxy Quinoline

BeMQ=5-[(benzyloxy) methyl] quinolin-8-ol

D. D. Water = Double distilled water

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