Preparation, Characterization And Antifungal Activity Of Metal Chelates Of 5-(N-Morpholinomethyl)-8-Hydroxyquinoline

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***Abstract*—The 5-chloromethyl-8-hydroxyquinoline (CMQ) hydrochloride reacted with morpholine to yield a novel ligand, 5-(N-morpholinomethyl)-8-hydroxyquinoline (MMQ). The transition metal chelates of MMQ ligand were prepared by using Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+},Zn^{2+} and Cd^{2+} metal salts. The ligand MMQ and its all metal chelates were characterized for elemental content, NMR and IR spectroscopic features, LC-MS, metal: ligand ratio and magnetic properties. The samples were also monitored for antifungal activities.**

Keywords—8-hydroxyquinoline; metal chelates; spectral studies; magnetic properties and Anti-fungal activity.

I. INTRODUCTION

Quinoline and its derivatives have been widely used as metal ion chelating agents, metal extracting agents; corrosive inhibitors and they often show biological activity. 8-hydroxyquinolines (8HQs) are a family of lipophilic metal ion chelators which has a greater coordinating ability and good metal recognition properties. Compounds containing the 8-hydroxyquinoline are widely used in analytical and pharmaceutical applications as antimicrobial, anticancer, anti-HIV, anti-inflammatory, antiviral, anti-diabetic, anti-asthmatic, anti-neurodegenerative and antifungal effects over the last few decades [1-13].

In addition to this, various morpholine derivatives (especially the N-substituted derivatives) have been found to possess diverse pharmacological applications including antioxidants, anticancer, anti-neurodegenerative, anti-viral, antidepressant, anti-parasitic and antifungal and are being used as important component in commercial drug designing since 1955. [14]

Hence, it was thought to bring these two moieties having promising physiological activity within a single framework in order to analyze the additive effects on biological activities.

The chloromethylation of 8HQ was reported. 8HQ metal complexes containing combinations of 5-chloromethyl-8-hydroxyquinoline (CMQ) and Morpholine has not received any attention. We therefore decided to undertake a study of metal complexes from a ligand containing CMQ and morpholine. The correct structural assessment of a ligand was duly made by using 1H NMR spectroscopy, FTIR spectral features and LC-MS. The synthesized complex compounds were characterized by their spectral features and tested against various fungal strains. The details of these procedures and the results obtained are discussed below.

EXPERIMENTAL

All the chemicals used were of laboratory grade. 5-chloromethyl-8-hydroxyquinoline (CMQ) was prepared by reported method.[15,16].

Synthesis of 5-(N-morpholinomethyl)8-hydroxyquinoline (MMQ)

To 5-chloromethyl-8-hydroxyquinoline (CMQ) hydrochloride (0.15 mole) in ethyl acetate, Morpholine (0.15 mole) was added. The mixture was warmed on a steam bath for 1.5 hr. with occasional stirring. The reaction mixture was cooled, morpholine hydrochloride was filtered and washed with ethyl acetate. The filtrate was the concentrated and the residue were extracted with petroleum ether followed by filtration. Concentration of the filtrate gave 76% yield, m.p.92-93° C (uncorrected). Recrystallization from petroleum ether(b.p.60-68°C).

Synthesis of metal chelates of MMQ:

The metal chelates of MMQ with Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, $Zn^{2+}$and Cd^{2+}metal ions were prepared in two steps.

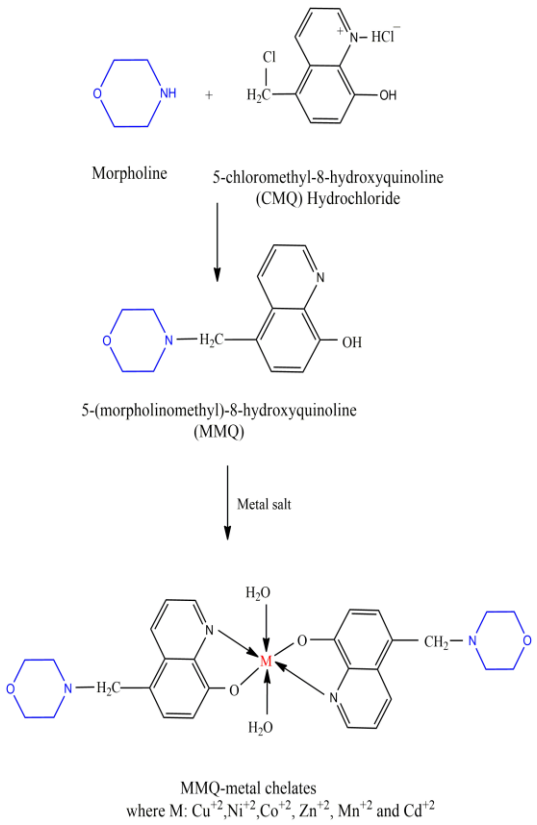
Step-I Preparation of MMQ solution:

MMQ (0.1 mol) was taken in 500 ml beaker and formic acid (85% v/v) was added upto slurry formation. To this slurry water was added till the complete dissolution of MMQ and diluted to 100 ml.

Step-II Synthesis of MMQ-metal-chelates:

In a solution of metal acetate (0.01 mol)in acetone: water (50:50 v/v) mixture (40 ml) the 20 ml of MMQ solution (containing 0.02 M MMQ) was added with vigorous stirring at room temperature. The appropriate pH was adjusted by adding sodium acetate for complete precipitation of metal chelate. The precipitates were digested on a boiling water bath. The

precipitates of chelate were filtered off, washed by water and air-dried.



Scheme-1

Anal. Calcd. for $C_{14}H_{16}N_2O_2$(244.30): %C, 68.83; %H, 6.60; %N, 11.47. **Found:** %C, 68.8; %H, 6.6; %N,11.4. **IR Spectral Features (cm^{-1})**shows at 3500-2750 (OH),3020, 2850, 1630,1470(C-H),1640, 1580, 1475 and 755(8-hydroxyquinoline),1275(C-N), 1150 (C-O) and **NMR Signals (δ ppm)** at 4.82 (s, 1H, -OH), 6.98–8.92 (m, 5H, Quinoline), 3.58 (s, 2H, N–CH_2-), 2.60 (t, 4H, –CH_2–), 3.82 (t, 4H, –CH_2–).

III. MEASUREMENTS:

The elemental contents were determined by Thermo Finigen Flash1101 EA (Itally) and the metals were determined volumetrically by Vogel's method [17].To a 100 mg chelate sample, each 1 ml of HCl, H_2SO_4 and $HClO_4$ were added and then 1 g of $NaClO_4$ was added. The mixture was evaporated to dryness and the resulting salt was dissolved in double distilled water and diluted to the mark. From this solution the metal content was determined by titration with standard EDTA solution. Infrared spectra of the synthesized compounds were recorded on Nicolet 760 FT-IR spectrometer. NMR spectrum of MMQ was recorded on 60 MHz NMR spectrophotometer. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. Magnetic susceptibility measurement of the synthesized complexes was carried out on Gouy Balance at room temperature. Mercury tetrathio cynato cobalatate (II) $Hg[Co(NCS)_4]$ was used as a calibrant. The electronic spectra of complexes in solid were recorded at room temperature. MgO was used as reference. Antifungal activity of all the samples was monitored against various fungi, following the method reported in literature[18].

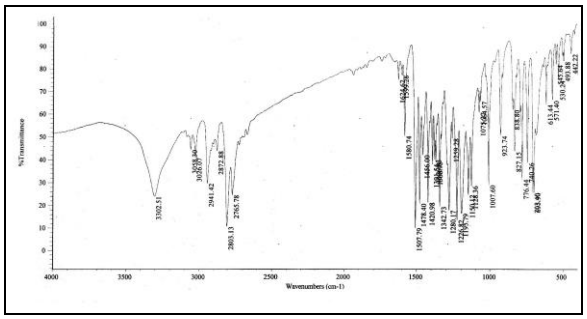
IV. RESULTS AND DISCUSSION:

5-(N-morpholinomethyl)-8-hydroxyquinoline (MMQ) was prepared by condensation of 5-chloromethyl-8-hydroxyquinoline (CMQ) hydrochloride with morpholine. The resulted MMQ ligand was an amorphous brown powder. The C, H, N contents of MMQ (Table-1) are consistent with the structure predicted (Scheme-1). The results show that the metal: ligand (M:L) ratio for all divalent metal chelate is 1:2.

Table-1: ANALYSIS OF MMQ LIGAND AND ITS METAL CHELATES

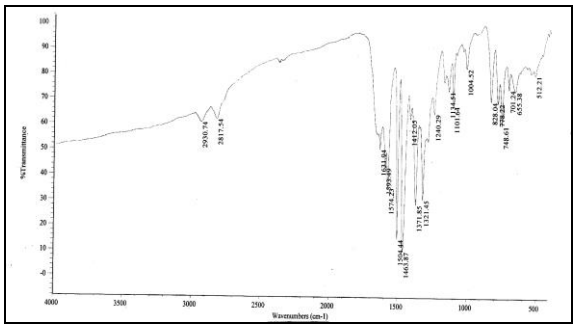
Empirical Formula	Mol. Wt gm/mole	Yield (%)	Elemental Analysis			
			% C	% H	% N	% M
			Cald Found	Cald Found	Cald Found	Cald Found
$C_{14}H_{16}N_2O_2$	244.30	76	68.83 68.8	6.60 6.6	11.47 11.4	- -
$C_{28}H_{30}N_4O_4Cu^{+2}2H_2O$	585.54	73	57.38 57.3	5.81 5.7	9.56 9.5	10.85 10.8
$C_{28}H_{30}N_4O_4Co^{+2}2H_2O$	580.94	74	57.8 57.8	5.85 5.8	9.64 9.6	10.15 10.1
$C_{28}H_{30}N_4O_4Ni^{+2}2H_2O$	580.71	69	57.86 57.8	5.85 5.8	9.64 9.6	10.11 10.1
$C_{28}H_{30}N_4O_4Mn^{+2}2H_2O$	576.94	73	58.24 58.2	5.89 5.8	9.71 9.6	9.52 9.5
$C_{28}H_{30}N_4O_4Zn^{+2}2H_2O$	587.38	74	57.20 57.1	5.79 5.7	9.53 9.5	11.13 11.1
$C_{28}H_{30}N_4O_4Cd^{+2}2H_2O$	634.4	70	52.96 52.9	5.36 5.3	8.83 8.8	17.72 17.7

The IR spectrum of MMQ comprises the important bands due to 8- hydroxyquinoline. The bands were observed at 1640, 1580, 1475 and 755 cm^{-1}. The broad band due to –OH group appeared at 3500-2750 cm^{-1}.



IR of MMQ

The infrared spectra of all the chelates are identical and suggest the formation of the entire metalocyclic compound by the absence of band characteristic of free –OH group of parent MMQ. The other bands are almost at their respectable positions as appeared in the spectrum of parent-MMQ ligand. However, the band due to (M-O) could not be detected as it may appear below the range of the instrument used.



IR of MMQ-Cu^{+2}

The important IR Spectral data are shown in Table-2.

Table-2: IR DATA OF MMQ LIGAND AND ITS METAL CHELATES

IR data of	-OH	C-H	8-HQ	C-N	C-O
MMQ	3500-2750	3020,2850 1630,1470	1640, 1580, 1475, 755	1275	1150
MMQ metal chelates	---	2930, 2817 1593,1463	1631, 1574, 1504,748	1240	1134

The NMR spectrum of MMQ in DMSO indicates the triplet at 2.60 δ and 3.82 δ for 8 H of four methylene protons of morpholine, the singlet at 4.82 δ ppm due to –OH group. While the quinoline protons are appeared in multiplicity at 6.98-8.92 δ and methylene proton (N-CH_2-) shows singlet at 3.58 δ. Thus, the structure of MMQ as shown in Scheme-I is confirmed.

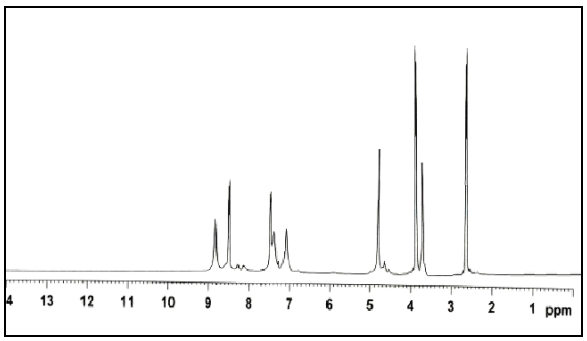
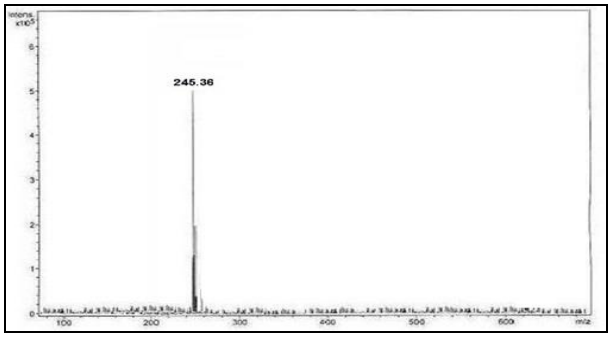


Fig. 3 NMR of MMQ

The recorded LC–MS spectrum and molecular ion peak for ligand (MMQ) was used to confirm their molecular formula. Peak at 245.36 m/z values represents the molecular ion peak of ligand. LC–MS mass spectrum of ligand is shown in (Fig. 4).



LC-MS spectrum of MMQ

TABLE-3: SPECTRAL FEATRUES AND MAGNETIC MOMENT OF MMQ METAL CHELATES

Metal Chelates	μ_{eff} (BM)	Electronic spectral data (cm^{-1})	Transition
MMQ-Cu^{+2}	2.53	23449 15875	Charge transfer $^2B_{1g} \rightarrow {}^2A_{1g}$
MMQ-Ni^{+2}	3.68	22581 15374	$^3A_{1g} \rightarrow {}^3T_{1g}(P)$ $^3A_{1g} \rightarrow {}^3T_{1g}(F)$
MMQ-Co^{+2}	4.65	22726 15262 8938	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$
MMQ-Mn^{+2}	5.51	23859 18346 16822	$^6A_{1g} \rightarrow {}^6A_{2g}\ {}^4E_g$ $^6A_{1g} \rightarrow {}^4T_{2g}$ (4G) $^6A_{1g} \rightarrow {}^4T_{1g}$(PG)
MMQ-Zn^{+2}	Diamag.	-	-
MMQ-Cd^{+2}	Diamag.	-	-

The data of electronic transitions and magnetic moments of metal chelates are summarized in Table-3. The observed μeff values in the range 2.53-5.51 B.M are consistent with the octahedral geometry of above moiety.The value of magnetic moments and reflectance spectral data of each chelates co-relates with structure assigned as the octahedral geometry. [19,20].

TABLE-4: ANTIFUNGAL ACTIVITY OF MMQ LIGAND ANDITS METAL CHELATES

Sample	Zone of inhibition of fungus at 1000 ppm (%)			
	Aspergillus Niger	*Botrydepladia Thiobromine*	*Nigrospora Sp.*	*Fusarium oxyporium*
MMQ	65	66	63	67
MMQ-Cu^{+2}	81	83	78	80
MMQ-Ni^{+2}	79	78	73	76
MMQ-Co^{+2}	78	80	76	78
MMQ-Mn^{+2}	77	76	77	78
MMQ-Zn^{+2}	75	77	78	79
MMQ-Cd^{+2}	74	75	73	77

The examination of antifungal activity of MMQ ligand and its all chelates (Table-4) reveals that the ligand is moderately toxic against fungi, while all the chelates are more toxic than ligand. Among all the chelates the Cu^{+2} chelate is more toxic against fungi.

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