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Synthesis, Characterization and Antifungal Activity of Metal Complexes of 5-((N, N-diphenylamino) methyl)-8-hydroxyquinoline

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ABSTRACT

The novel ligand, 5-((N,N-diphenylamino)methyl)-8-hydroxyquinoline (DPMHQ) was synthesized by reaction of 5-chloromethyl-8-hydroxyquinoline (CMQ) hydrochloride with N,N-diphenylamine. Metal complexes of DPMHQ were synthesized with Cu(II), Co(II), Ni(II), Mn(II), Zn(II) and Cd(II) salts. The ligand DPMHQ and all its metal complexes were further investigated for elemental content, IR-NMR spectral features, metal: ligand ratio and magnetic properties. The samples were also screened for antifungal activities.

Introduction

A large number of nitrogen bearing heterocyclic compounds have displayed various biological as well as pharmacological activities. 8-hydroxyquinoline has attracted the attention of chemists due to its unique physical and chemical properties [1]. 8-hydroxyquinoline (8HQ), a derivative of quinoline, possesses a strong metal chelating property [2,3]. 8-hydroxyquinoline and its derivatives have been known for antibacterial, antifungal and its potency proportional with its ion chelation due to their lipid solubility [4-7]. Antimicrobial, antioxidant, anticancer, anti-inflammatory and anti-alzheimer antineurodegenerative agents, antiviral, anti-tubercular and anti-HIV activities have been reported for 8-HQ derivatives [8-14].

N,N-diphenylamine and its derivatives possess significant therapeutic functions which include antimicrobial, anti-inflammatory, analgesic, anticonvulsant and anticancer activities.[15-17]

Both 8-HQ and DPA, being pharmacologically potent molecules, it was found interesting to analyze the combined effect by bringing both the moieties in a common molecular framework.

In connection with our previous work, the present article displays the synthetic route for the preparation of a novel ligand 5-((N,N- diphenylamino)methyl)-8-hydroxy quinoline (DPMHQ) and its metal complexes. The synthesized compounds were further monitored for antifungal activity.

Experimental

All the chemicals used were of laboratory grade. 5-chloromethyl-8-hydroxyquinoline (CMQ) was prepared by reported method [18, 19].

Synthesis of 5-((N,N-diphenylamino)methyl)-8-hydroxy quinoline (DPMHQ)

N, N-diphenylamine (0.45 mole) was added to 5-chloromethyl-8-hydroxyquinoline (CMQ) hydrochloride (0.15 mole) in ethyl acetate. The mixture was heated on a steam bath for 1.5 hr. with occasional stirring. The reaction mixture was washed with ethyl acetate. The filtrate was concentrated and the residues were extracted with petroleum ether and the solution was filtered. Concentration of the filtrate gave 74% yield, melting point: 108o-109oC (uncorrected). Recrystallization of the ligand was carried out using petroleum ether (b.p.60°-68°C).

Synthesis of metal complexes of DPMHQ

The metal complexes of DPMHQ with Cu(II), Co(II), Ni(II), Mn(II), Zn(II) and Cd(II) salts were prepared in two steps.

Step-I Preparation of DPMHQ solution:

DPMHQ (0.1 mole) was taken in 500 ml beaker and formic acid (85% v/v) was added up to slurry formation. To this slurry, water was added till complete dissolution of DPMHQ. It was then diluted to 100 ml.

Step-II Synthesis of DPMHQ-metal-complexes:

In a solution of metal acetate (0.01 mole) in acetone: water (50:50 v/v) mixture (40 ml) the 20 ml of DPMHQ solution (containing 0.02 M DPMHQ) was added with vigorous stirring at room temperature. The appropriate pH was adjusted by addition of sodium acetate for complete precipitation of metal complex. The precipitates were digested on a boiling water bath. The precipitates of complex were filtered off, washed by water and air-dried.

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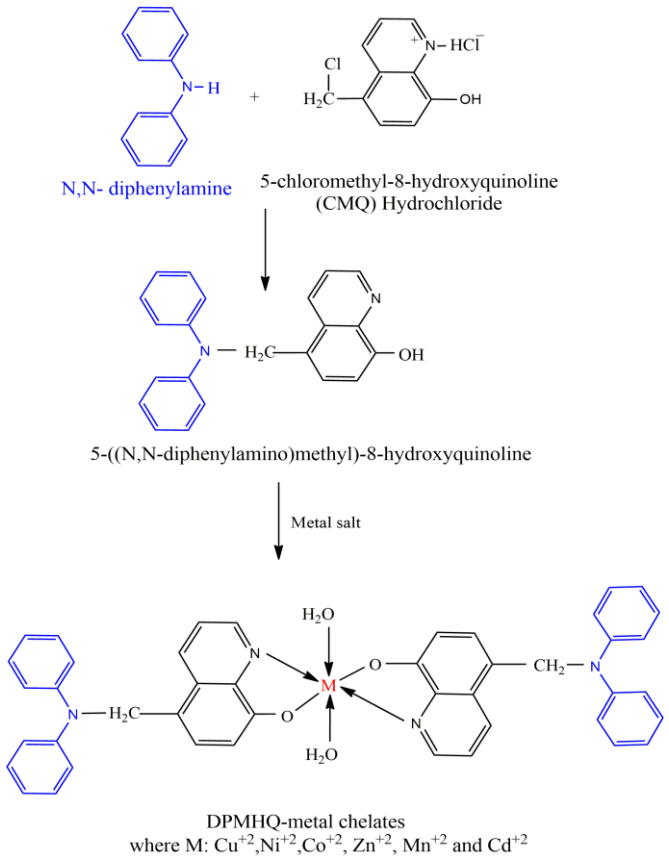

Scheme-1

Anal. Calcd. for $C_{22}H_{18}N_2O$(326):%C,80.96; %H, 5.56; %N, 8.58.**Found:**%C, 80.9; %H, 5.5; %N,8.5. IR Spectral Features (cm^{-1}) shows at 3302 (OH), 3026, 2872, 1599, 1478(C-H), 1624, 1580, 1456 and 740 (8-Hydroxy quinoline), 1280(C-N), 1150(C-O) NMR Signals (δ ppm) at 4.82 (s,1H,-OH), 6.65-8.92(m, 15H, Quinoline and aromatic), 3.58(2H,s,N-CH_2-).LC-MS (m/z): 327.60

Measurements

Metals and elemental contents were determined volumetrically by Vogel's method and Thermo Finigen Flash1101 EA (Itally), respectively [20].To a 100 mg complex sample, each 1 ml of HCl, H_2SO_4 and $HClO_4$ were added followed by addition of 1 g of $NaClO_4$. 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 DPMHQ 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 cobaltate (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 a reference. Antifungal activity of all the samples was monitored against various fungi, following the method reported in literature[21]. The standard open capillary method is used for detection of melting point.

Results and Discussion

5-((N,N-diphenylamino)methyl)-8-hydroxyquinoline (DPMHQ) was prepared by condensation of 5-chloromethyl-8-hydroxyquinoline (CMQ) hydrochloride with N,N-diphenylamine. The resulted DPMHQ ligand was an amorphous yellow powder. The C, H, N contents of DPMHQ (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 DPMHQ ligand and its metal complexes.

Empirical Formula Mol. Wt. gm/mole	Yield (%)	Elemental Analysis			
		% C	% H	% N	% M
		Cald Found	Cald Found	Cald Found	Cald Found
$C_{22}H_{18}N_2O$ 326	74	80.96 80.9	5.56 5.5	8.58 8.5	-
$C_{44}H_{34}N_4O_2Cu^{+2}2H_2O$ 749.54	70	70.44 70.4	5.07 5.0	7.47 7.4	8.48 8.4
$C_{44}H_{34}N_4O_2Co^{+2}2H_2O$ 744.94	72	70.88 70.8	5.10 5.0	7.52 7.5	7.91 7.9
$C_{44}H_{34}N_4O_2Ni^{+2}2H_2O$ 744.71	71	70.90 70.8	5.10 5.0	7.52 7.5	7.88 7.8
$C_{44}H_{34}N_4O_2Mn^{+2}2H_2O$ 740.94	68	71.26 71.2	5.13 5.1	7.56 7.5	7.41 7.3
$C_{44}H_{34}N_4O_2Zn^{+2}2H_2O$ 751.38	73	70.27 70.2	5.06 5.0	7.45 7.4	8.70 8.6
$C_{44}H_{34}N_4O_2Cd^{+2}2H_2O$ 798.4	69	66.13 66.0	4.76 4.7	7.01 7.0	14.08 14.0

The IR spectrum of DPMHQ comprises the important bands due to 8-hydroxyquinoline. The bands were observed at 1624, 1580, 1456 and 740cm^{-1}. The broad band due to –OH group appeared at 3302 cm^{-1}.

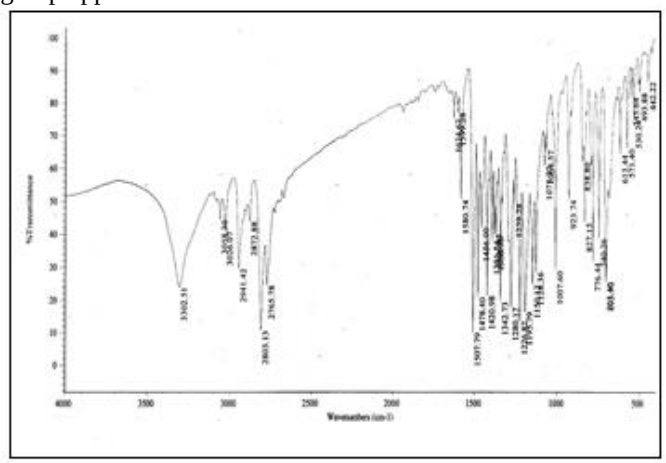

Fig 1. IR spectrum of DPMHQ

The absence of band characteristic of free –OH group of parent DPMHQ in the infrared spectra of all the complexes suggest the formation of the entire metalocyclic compound. The other bands are almost at their respectable positions as appeared in the spectrum of parent-DPMHQ ligand. However, the band due to (M-O) band could not be detected as it may appear below the range of instrument used. The important IR Spectral data are shown in Table-2.

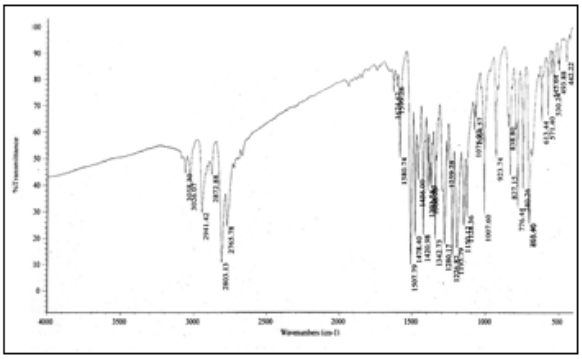

Fig 2 . IR of DPMHQ-Cu(II)

Table 2. IR data of DPMHQ metal chelates.

IR data of	-OH	C-H	8-HQ	C-N	C-O
DPMHQ	3302	3026, 2872, 1599, 1478	1624, 1580, 1456, 740	1280	1150
DPMHQ metal chelates	---	3058, 2941, 2803, 1599, 1456	1624, 1580, 1507, 776	1239	1128

The NMR spectrum of DPMHQ in DMSO indicates that the singlet at 4.82 δ ppm due to –OH group. The quinoline protons are appeared in multiplicity at 6.65-8.92 δ and methylene proton shows singlet at 3.58 δ.

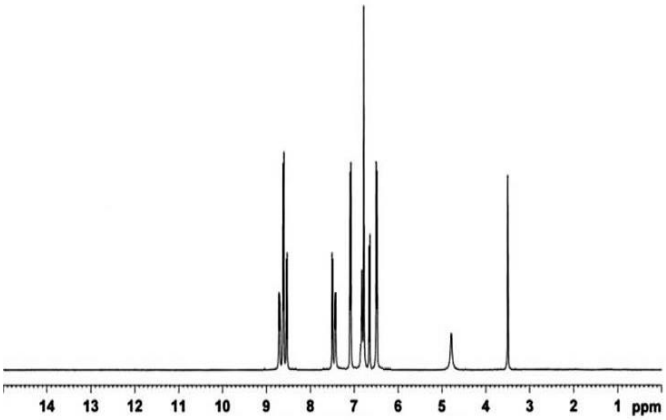

Fig 3. NMR spectrum of DPMHQ

The structure of DPMHQ is confirmed by LC-MS which is consistent with predicted structure. Thus the structure of DPMHQ is confirmed as shown in Scheme-I.

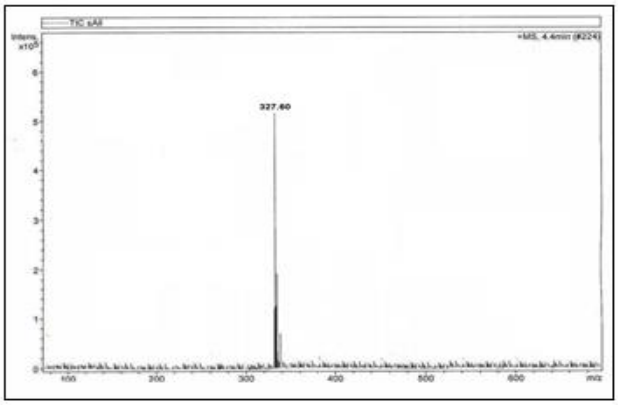

Fig 4. LC-MS spectrum of compound DPMHQ.

The data of electronic transitions and magnetic moments of metal complexes are summarized in Table-3.

Table 3. Spectral featrues and magnetic Moment of DPMHQ metal complexes.

Metal Complexes	μ_{eff} (BM)	Electronic spectral data (cm^{-1})	Transition
DPMHQ-Cu(II)	2.51	23452 15872	Charge transfer $^2B_{1g} \rightarrow {}^2A_{1g}$
DPMHQ-Ni(II)	3.69	22584 15376	$^3A_{1g} \rightarrow {}^3T_{1g}(P)$ $^3A_{1g} \rightarrow {}^3T_{1g}(F)$
DPMHQ-Co(II)	4.62	22725 15260 8940	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$
DPMHQ-Mn(II)	5.54	23862 18349 16824	$^6A_{1g} \rightarrow {}^6A_{2g}\,{}^4E_g$ $^6A_{1g} \rightarrow {}^4T_{2g}$ (4G) $^6A_{1g} \rightarrow {}^4T_{1g}$(PG)
DPMHQ-Zn(II)	Diamag.	-	-
DPMHQ-Cd(II)	Diamag.	-	-

The observed μ_{eff} values in the range 2.51-5.54 B.M are consistent with the above moiety.The value of magnetic moments and reflectance spectral data of each complexes corelates with structure assigned as the octahedral geometry. [22,23].

The screening of antifungal activity of DPMHQ ligand and its all complexes (Table-4) reveals that the ligand is moderately toxic against fungi, while all the complexes are more toxic than ligand. Among all the complexes the Cu(II) complex has shown more toxicity against fungi.

Table 4. Antifungal Activity of DPMHQ Ligand and its Metal Complexes.

Sample	Zone of inhibition of fungus at 1000 ppm (%)			
	AN	***BT***	***NS***	***FO***
DPMHQ	63	64	61	65
DPMHQ-Cu(II)	78	80	75	79
DPMHQ-Ni(II)	76	76	72	74
DPMHQ-Co(II)	75	77	74	78
DPMHQ-Mn(II)	72	74	75	76
DPMHQ-Zn(II)	72	75	77	77
DPMHQ-Cd(II)	73	72	71	75

AN=Aspergillus Niger; BT=Botrydepladia Thiobromine; NS= Nigrospora Sp.; FO=Fusarium oxyporium

Conclusions

A novel ligand is sythesised by condensation of CMQ and N,N-diphenylamine and its metal complexes were prepared in good yield and were duly characterized. In the metal complexes, the ligand coordinates with one central metal atom at four coordination sites, with two water molecules. Structure proposed for the ligand and its metal complexes are consistent with results from elemental and spectral analysis. The geometry of the central metal ion was confirmed by electronic spectra and magnetic susceptibility measurements. All the data provide good evidence of complex formation. The complexes exhibited good antifungal activity.

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