Synthesis, characterization and antimicrobial activity of transition metal complexes of 5-(propoxymethyl-8-quinolinol) (PMQ)

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ABSTRACT

Mixed ligand complexes of transition metal with 8-quinolinols and 5-Alkoxymethyl-8-quinolinol have been prepared. Structural, spectroscopic and thermal properties have been studied on the basis of infrared spectra, Mass spectra, NMR spectra, electronic spectra, and elemental analyses. The ligands, metal salts, complexes, control and standard drug were tested for their antimicrobial activity. The metal complexes exhibit good activity against Bacterial strains Gram +ve and Gram –ve and fungal strains compared with parental compounds and moderate compared with the standard drugs.

Keywords: Transition metal Heterochelates, Oxine, Spectral studies, Magnetic moment and Antimicrobial activity.

INTRODUCTION

8-Quinolinol (8Q) or its derivatives have been introduced as chelating groups. [1-3].The chelating properties of the compounds of the 8Q series are related to its biological activity [4]. Clioquinol is an antifungal drug and antiprotozoal drug. It is neurotoxic in large doses. It is a member of a family of drugs called hydroxyquinolines which inhibit certain enzymes related to DNA replication. The drugs have been found to have activity against both viral and protozoal infections [5]. Heterocycles containing the quinoline ring constitute a wide variety of biologically active compounds [6]. 8-hydroxyquinoline (8Q) and its metalloquinolates have attracted great interest because their high thermal stability and good electroluminescence properties make them important prototypical electron transport and emitting materials for OLED devices [7-9]. 8-Hydroxyquinoline (8-quinolinol, oxine, 8Q) might be thought to function as a phenol, but of the 7 isomeric hydroxyquinolines only oxine exhibits significant antimicrobial activity, and is the only one to have the capacity to chelate metals. If the hydroxyl group is blocked so that the compound is unable to chelate, as in the methyl ether, the antimicrobial activity is destroyed. The relationship between chelation and activity of oxine has been investigated [10-12]. Copper 8-quinolinolate (copper oxinate), the copper compound of 8-hydroxyquinoline, is employed as an industrial preservative for a variety of purposes, including the protection of wood and textiles against fungus-caused rotting, and interior paints for food plants. It has 25 times greater antifungal activity than oxine [13]. Mixed-ligand chelates serve as suitable models for valuable information in the elucidation of enzymatic processes of biological relevance[14].

We were incited to study the formation of CQ-metal complexes in a media with an ionic composition similar to the brain extracellular environment[15]. Thermal analysis, although an old technique, is now proving useful in the interpretation and determination of different physical parameters such as inorganic and organic thermodynamics and reaction kinetics in different fields of study such as chemistry, polymer science, biology, medicine and pharmaceutics [16].

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In present work, we describes synthetic, characteristic, spectroscopic features of new mixed ligand complexes using different transition metal with 8-Quinolinol(8Q) and 5-Alkoxymethyl-8-quinolinol and also describe antimicrobial activities of newly synthesized compounds.

MATERIALS 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. Clioquinol was purchased from Atul Ltd., Agro Chemical Division, Atul, Valsad (India). Luria broth and agar- agar were purchased from SRL, India. Acetic acid and EDTA were purchased from Sigma Chemical Co., India. The organic solvents were purified by recommended method [17].

Physical measurements
The metal content of the complexes were determined by the EDTA titration technique [18] 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 (χ_g=16.44×10^{-6} c.g.s. units at 20 ^{o}C). Diamagnetic corrections were made using Pascal's constant [19]. 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 ^{o}C min^{-1} under N_2 atmosphere.

Preparation of ligands
Synthesis of 5-(Propoxymethyl-8-Quinolinol) (PMQ).
To a suspension of 2.3 gm. (0.01 mole) of 5-chloromethyl-8-quinolinol (CMQ), propanol (3 times.) and 0.84 gm. (0.01 mole) of sodium bicarbonate ($NaHCO_3$) added. The mixture was warmed on the steam bath with occasional shaking until most of the alcohol had been evaporated. 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 2.0 gm. (85% yield), having m.p- 67°C. (Uncorrected).FT-IR (KBr, cm^{-1}): υ(-OH,) 3368, υ(-CN) 1218, ^{1}H NMR (DMSO-d_6 400 MHz): δ 4,75 (CH$_2$- protons), δ 0.95 (CH$_3$- protons), δ 7.1 to 7.54 (9H, m, aromatic protons), δ 8.5 (1H, s, OH- protons), Elemental analysis found (%):C, 71.75; H, 6.82; $C_{13}H_{15}NO_2$ (217) requires (%): C, 71.88, H, 6.91.

Preparation of Metal Complexes
(I) Formation of Cu^{2+} Complexes
A water solution of $Cu(NO_3)_2.3H_2O$ was added to dimethyl formamide solution of ligand (A^n) followed by addition of 8-HQ 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. A dark green colored crystalline product was obtained. The yield of a purified complex was 74%. The obtained product was washed with ether and dried over vacuum desiccators. The reaction scheme is shown in Fig: 1 and Analytical and physical data are shown in Table 1.

(II) Formation of Ni^{2+} Complexes
Ni^{+2} complexes was synthesized by same method used for Cu^{+2} complexes. A light blue colored crystalline product was obtained. The yield of a purified complex was 70%.

(III) Formation of Co^{2+} Complexes
Co^{+2} complexes was synthesized by same method used for Cu^{+2} complexes. A light brown colored crystalline product was obtained. The yield of a purified complex was 65%.

(IV) Formation of Mn^{2+} Complexes
Mn^{+2} complexes was synthesized by same method used for Cu^{+2} complexes. A light pink colored crystalline product was obtained. The yield of complex was 65%.

(V) Formation of Zn^{2+} Complexes
Zn^{+2} complexes was synthesized by same method used for Cu^{+2} complexes. A pale yellow colored powder product was obtained. The obtained product was washed with ether and dried over vacuum desiccators. The yield was 75%.
Antimicrobial studies

Antifungal activity
The antifungal activity of the standard fungicide (Flucanazone), ligand and complexes were tested for their effect on the growth of microbial cultures and studied for their interaction with *Aspergillus niger and Trichothesium Sp.* using

Czapek's agarmedium 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 [20].

Antibacterial activity
Antibacterial activity was tested against Gram –ve (*Escherichia coli* and *Ps. Aeruginosa, Bacillus subtilis)* and Gram +ve (*Becillus megaterium* and *Staphylococcus aureus*) using the paper disc plate method [21, 22]. Each of the compounds was dissolved in methanol and solutions of the concentrations (500 and 1000 ppm) were prepared separately. Paper discs of Whatman filter paper (No. 42) of uniform diameter (2 cm) were cut and sterilized in an autoclave. The paper discs soaked in the desired concentration of the complex solutions were placed aseptically in the Petri dishes containing nutrient agar media (agar 20 g C beef extract 3 g C peptone 5 g) seeded with *E. coli* and *B. subtilis* bacteria separately. The Petri dishes were incubated at 37 °C and the inhibition zones were recorded after 24 h of incubation. The antibacterial activity of common standard antibiotic Streptomycin was also recorded using the same procedure as above at the same concentrations and solvent. The % Activity Index for the complex was calculated by the formula as under:

% Activity Index = D Zone of inhibition by test compound x 100 /Zone of inhibition by standard

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. The substitution of phenyl rings does not have more effect on the fungicidal activity of complexes. In each series 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 decease in many plants. Cu^{+2} metal complexes are more toxic than others and the order for is $Cu^{+2} > Zn^{+2} > Co^{+2} > Ni^{+2} > Mn^{+2}$.

IR spectra
The important infrared spectral bands and their assignments for the synthesized ligands and complexes were recorded as KBr disks 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}.

In the 8-hydroxyquinoline complexes of divalent metals, the υ (C-O), appeared at 1120 cm^{-1} region and the position of the band slightly varies with the metal. The υ (C-O), observed in the free oxine molecule at 1090 cm^{-1}, shifted to higher frequencies in all the mixed ligand complexes giving a strong absorption band at 1110 cm^{-1}. This clearly indicates the coordination of 8-hydroxyquinoline in these complexes. In the investigated heterochelates, the band observed in the region 3400-3500, 1295-1300, 860-870 and 715-717 cm^{-1} are attributed to –OH stretching, bending, rocking and wagging vibrations, respectively due to the presence of water molecules.[23] The evidence of complexes formation clear by appearance of new bands at 418–432 and 507–516 cm^{-1}, which are assigned to v(M–N) and v(M–O), respectively [24,25].

Reflectance spectra and magnetic measurements
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 ~14600, ~19720 and ~24400 cm^{-1} assignable to $^6A_{1g} \rightarrow ^4T_{1g}$, $^6A_{1g} \rightarrow ^4T_{2g}$ and $^6A_{1g} \rightarrow ^4A_{1g}$, ^4E_g transitions, respectively, in an octahedral environment around the Mn(II) ion. The magnetic moment value of the Mn(II) complex is 6.02 B.M. due to a high-spin d^5-system with an octahedral geometry [26]. For the Co(II) complex, the reflectance spectra exhibits the bands of medium intensity at ~9300, ~18050 and ~18900 cm^{-1}, which may reasonably be assigned to $^4T_{1g}(F) \rightarrow ^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow ^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow ^4T_{1g}(P)$ transitions, respectively, of an octahedral geometry around the metal ion [27] and the magnetic moment value is observed to be of 4.06 B.M. The electronic spectra of the Ni(II) complex exhibits absorption bands at ~10200, ~17650 and ~23800 cm^{-1} assignable to $^3A_{2g}(F) \rightarrow ^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow ^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow ^3T_{1g}(P)$ transitions respectively, in an octahedral geometry. The value of the magnetic moment (2.84 B.M.) may be taken as additional evidence for their octahedral structure [28–31]. The Cu(II) complex display a broad band at ~15440 cm^{-1} due to the $^2E_g \rightarrow ^2T_{2g}$ transition and the

magnetic moment value is 1.78 B.M., which is close to spin-only value (1.73 B.M.) expected for an unpaired electron, which offers the possibility of an octahedral geometry [32].

This improvement in activity of complexes is also be rationalized on the basis of their structure activity relationship:
A feasible manner for raise in biocidal activity may be explained on the basis of chelation theory or/and may be due to light of Overtone's concept. Chelation reduces the polarity of the metal ion considerably, mainly because of the partial sharing of its positive charge with donor groups and possible π-electron delocalization on the whole chelate ring. Polysaccharides and lipids are some important constituent of cell wall and membranes, Chelation can considerably reduce the polarity of the metal ion, which in turn increases the lipophilic character of the Chelates. Thus, the interaction between metal ion and the lipid is favored. This may lead to the breakdown of the permeability barrier of the cell, resulting in interference with the normal cell processes. Presence of lypophilic and polar substituents are expected to enhance biocidal activity. Heterocyclic ligand with multifunctionality have greater chance of interaction either with nucleoside bases (even after complexation with metal ion) or with biologically essential metal ions present in the biosystem can be promising candidates as bactericides since they always look to enact especially with some enzymatic functional groups, to achieve higher coordination number. Thus, the antibacterial property of metal complexes can not be ascribed to chelation alone but it is an intricate blend of all the above contributions.

Table -1. Analytical and physical parameters of ligand and complexes

Compounds	Molecular formula	M. wt gm/mole	Yield %	% Metal analysis		Elemental analysis					
				Cal.	Found	% C		% H		% N	
						Cal.	Found	Cal.	Found	Cal.	Found
HL-3	$C_{13}H_{15}NO_2$	217	85	---	---	71.88	71.75	6.91	6.82	6.45	6.39
(HL-3) Cu^{+2}	$C_{22}H_{24}N_2O_5Cu^{+2}$	459.98	74	13.81	13.73	57.44	57.32	5.26	5.16	6.09	6.01
(HL-3)Mn^{+2}	$C_{22}H_{24}N_2O_5Mn^{+2}$	451.37	65	12.17	12.11	58.54	58.18	5.36	5.32	6.21	6.12
(HL-3) Co^{+2}	$C_{22}H_{24}N_2O_5Co^{+2}$	455.36	65	12.94	12.83	58.03	57.92	5.31	5.28	6.15	6.04
(HL-3) Zn^{+2}	$C_{22}H_{24}N_2O_5Zn^{+2}$	461.84	75	14.16	14.03	57.21	57.12	5.24	5.19	6.07	5.94
(HL-3) Ni^{+2}	$C_{22}H_{24}N_2O_5Ni^{+2}$	455.12	70	12.90	12.79	58.06	57.97	5.32	5.27	6.16	6.02

Table 2 FT-IR data of synthesized ligand & complexes

Compounds	Frequencies Cm^{-1}				
	OH	Aromatic	8-HQ Moiety	C-N	CH_2
HL_3	3800-2690	1599 1507 3028	1638,1575, 1698, 1470	1275-1298	2850, 2920, 1450
$HL_3 – M$	3500-2600	1610 1497 2988	1610 1577 1509 1466	1270	2847 2928 1466

$M= Cu^{+2}, Ni^{+2}, Co+2, Mn^{+2}, Zn^{+2}.$

Table 3: Antimicrobial activity of sample

| Sample	Zone of inhibition (in mm)					
	Antifungal activity		Gram + Ve		Gram -Ve	
	Trichothesium Sp.	*A. niger*	*Becillus megaterium*	*S.taphylococcus aureus*	*Ps. aeruginosa*	*E-Coli*
8HQ	45	52	10	13	12	15
HL-3	55	53	11	10	09	10
DMSO	15	16	10	09	10	11
Cu-Salt	15	13	11	10	10	13
Mn-Salt	14	17	13	12	14	15
Co-Salt	15	17	07	06	10	10
Zn-Salt	10	11	10	06	08	08
Ni-Salt	12	17	13	10	11	09
(HL-3) Cu^{+2}	78	81	13	18	18	19
(HL-3) Mn^{+2}	53	57	19	23	22	21
(HL-3) Co^{+2}	63	70	08	08	12	12
(HL-3) Zn^{+2}	67	71	17	14	18	13
(HL-3) Ni^{+2}	63	67	23	11	20	17

M=Cu(II),Ni(II),Co(II),Mn(II),Zn(II)
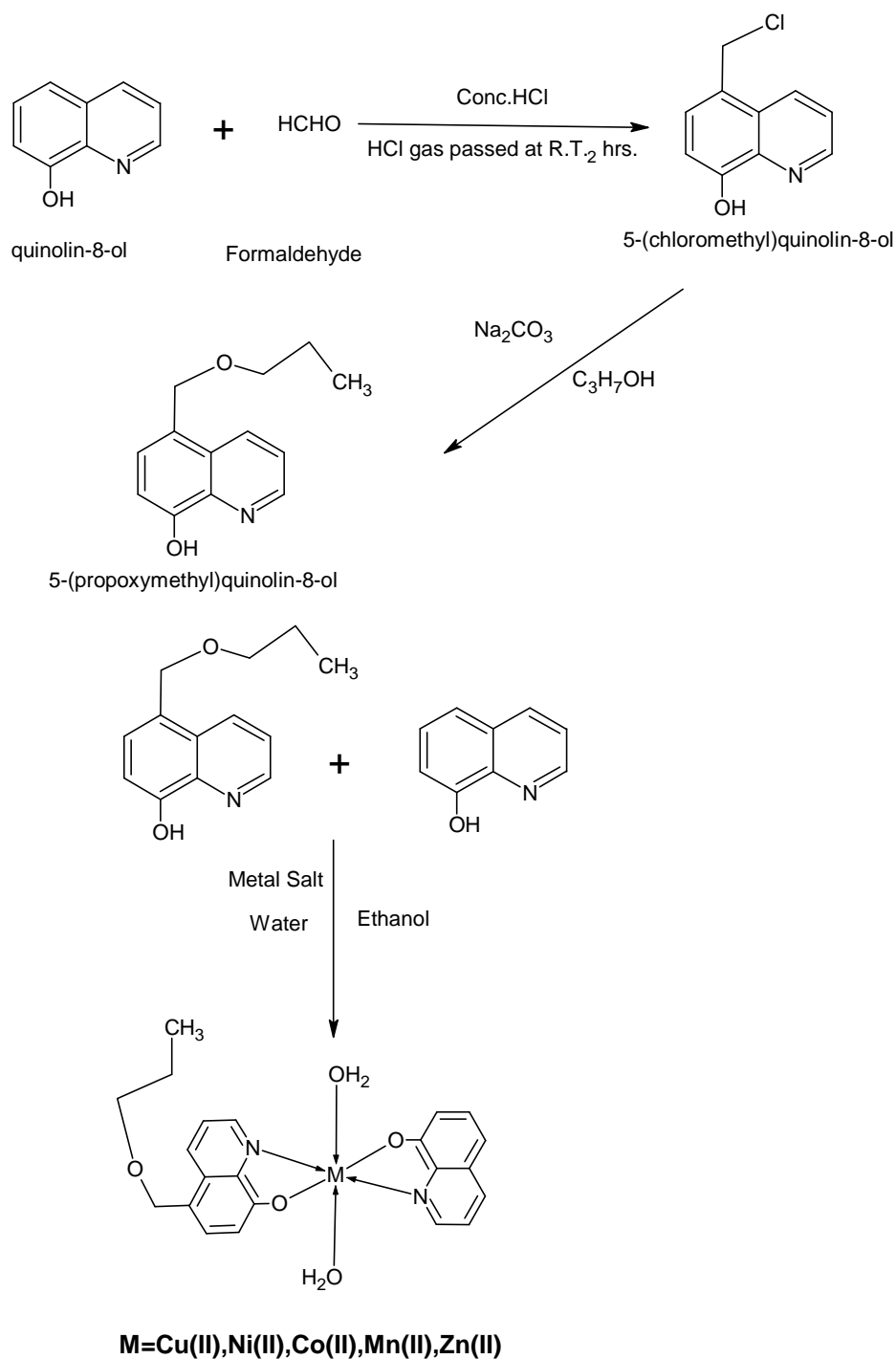
Fig . 1

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 antimicrobial activity data, it is observed that the complexes exhibit higher activity than the free ligands, metal salt, and the control (DMSO). The increase in antimicrobial 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 biocidal than the ligand. The zone of inhibition was measured (in mm) around the disc and the results are represented in Table 3. It is clear that Cu(II) is highly active among the complexes of the

respective metal, this may be due to presence of propoxy group of ligand whereas Cu(II) is most active among all which may be due to combine effect of Cu(II) and functional groups on the ligand.

Abbreviation
8HQ = 8- Hydroxy Quinoline
HL$_3$ = 5-(Propoxymethyl-8-Quinolinol) (PMQ).
D.D.Water = Double distilled water
LB = Luria broth

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