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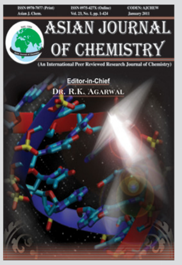

Synthesis, Spectral and Antimicrobial Studies of Metal Complexes of Chlorphenoxamide

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5-Chloromethyl-8-quinolinol hydrochloride was condensed with 2-[(2,2-dichloroethyl)(4-(4-nitrophenoxy)benzyl)amino]ethanol in presence of potassium carbonate. The resulting 5-((2-((2,2-dichloroethyl)(4-(4-nitrophenoxy)benzyl)amino)ethoxy)methyl)quinolin-8-ol was characterized by elemental analysis and spectral studies. The transition metal chelates of this ligand were prepared with Cu^{2+}, Ni^{2+}, Co^{2+}, Mn^{2+} and Zn^{2+} and characterized by IR and electronic spectral studies and magnetic properties. The antimicrobial activity of ligand and its metal chelates were screened against various gram positive (+) and gram negative (–) organism. The results show that all these samples are more or less active agents against various organisms.

Key Words: 2-((2,2-Dichloroethyl)(4-(4-nitrophenoxy)benzyl)amino)ethanol, Antimicrobial activity, Metal chelates.

INTRODUCTION

In continuation of our work of synthesis and characterization of metal complexes of established drugs[1-14], here we report the synthesis and studies of chlorphenoxamide metal complexes.

8-Hydroxyquinoline or 8-quinolinol is well known as an analytical reagent[15,16]. Its various derivatives[17] are also useful in pharmaceuticals more particularly antiprotozoal drug. One of the derivative *i.e.*, 5-chloromethyl-8-quinolinol (CMQ) can be synthesized easily and studied for number of useful compounds and polymers[18-28]. One of the heterocyclic drugs *viz.*, chlorphenoxamide is well known as an important antiamebic drug. If we carried out the formation of chlorphenoxamide-5-chloromethyl-8-quinolinol merged molecule and it's heterochelate, then such molecules may enhance antimicrobial activity. Hence it was thought to study the heterochelate of compound based on chlorphenoxamide and 5-chloromethyl-8-quinolinol. Thus the present paper comprises the synthesis, characterization, chelating properties and antimicrobial activity of 5-((2-((2,2-dichloroethyl)(4-(4-nitrophenoxy)benzyl)-amino)ethoxy)methyl) quinolin-8-ol-CMQ merged molecule). The reaction route is as shown in **Scheme-I**.

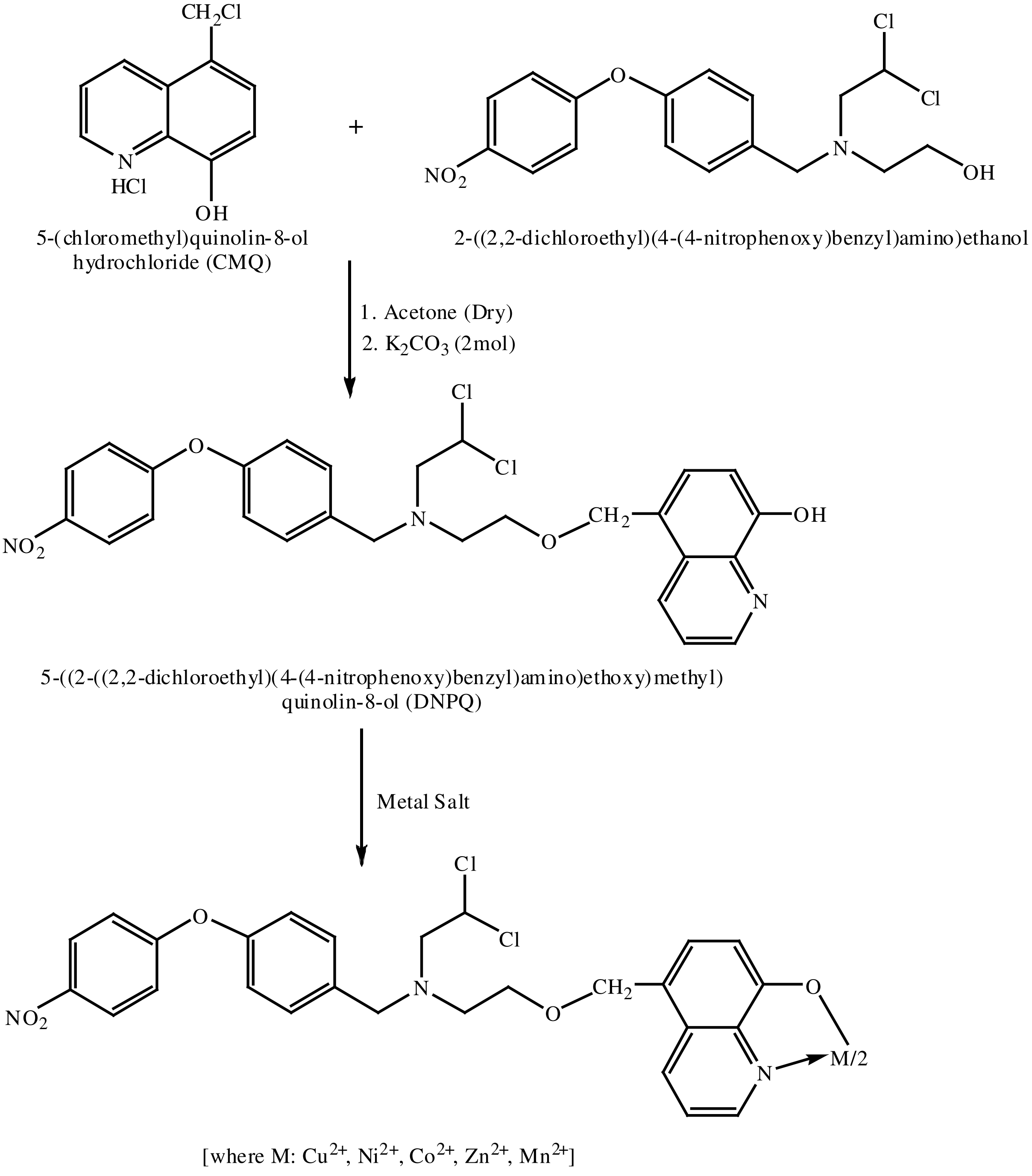
EXPERIMENTAL

5-Chloromethyl-8-quinolinol (CMQ) hydrochloride was prepared according to method reported in literature[18]. Compound based on chlorphenoxamide was obtained from local dealer. All other chemicals used were of laboratory grade.

Synthesis of 5-((2-((2,2-dichloroethyl)(4-(4-nitrophenoxy)benzyl)amino)ethoxy)methyl)quinolin-8-ol (formation of DNPQ): In a round bottom flask, to a suspension of 5-chloromethyl-8-quinolinol (CMQ) hydrochloride (23 g, 0.1 mol) in dry acetone (100 mL), chlorphenoxamide (0.1 mol) was added gradually at room temperature. Potassium carbonate (16.8 g) was added in the mixture and the mixture was refluxed on water bath for 8 h. The resulting solid mass was added into water and the precipitation was filtered off, washed with boiling water and the air-dried. It was dark green amorphous powder. It was insoluble in common organic solvent but soluble only in formic acid and DMSO.

m.f. $C_{27}H_{25}N_3O_5Cl_2$ (m.w. 542), elemental analysis: calcd. (%): C: 59.79, H: 4.65, N: 7.75; found (%): C: 59.62, H: 4.48, N: 7.52. IR (KBr, ν_{max}, cm^{-1}): 2972, 2853, 1465 ($-CH_2$), 1625, 1569, 1490 (8 HQ) 1685 (-CO-), 1672 (carbamide). NMR δ ppm: 7.0-7.6 (8H, Ar-H), 8.2-8.8 (4H, Ar-H attached to $-NO_2$ group), 5.35 (1H, -OH), 5.69 (1H, -CH), 4.80 (2H, $-CH_2$), 2.5-1.66 (8H, four aliphatic $-CH_2$).

Synthesis of metal-chelates of DNPQ: 5-((2-((2,2-Dichloroethyl)(4-(4-nitrophenoxy) benzyl)amino)ethoxy)-methyl)quinolin-8-ol (DNPQ) (0.05 mol) was taken in 500 mL beaker. Formic acid was added up to slurry formation. To this slurry water was added till the complete dissolution of DNPQ. It was diluted to 100 mL.



Scheme-I: Proposed structure of heterochelate

In a solution of metal acetate (0.005 mol) in acetone:water (50:50 v/v) mixture (40 mL) the 20 mL of above mentioned DNPQ solution (*i.e.*, containing 0.01M chlorphenoxamide) was added with vigorous stirring at room temperature. The appropriate pH was adjusted by addition of 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.

The elemental contents of C, H, N were determined by TF-Flash-1101 EA. The metals contents of metal chelates were determined volumetrically by Vogel's method[29]. 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 spectrometers. NMR spectrum of chlorphenoxamide was recorded on 400 MHz NMR spectrophotometer. Magnetic susceptibility measurement of the synthesized complexes was carried out on Gouy Balance at room temperature. The electronic spectra of complexes in solid were recorded on at room temperature. MgO was used as reference. Antimicrobial activity of all the samples was monitored against various gram positive (+) and gram negative (–) organism, following the method reported in literature[30,31].

RESULTS AND DISCUSSION

The synthesis of 5-((2-((2,2-dichloroethyl)(4-(4-nitrophenoxy)benzyl)amino)ethoxy)methyl)quinolin-8-ol (DNPQ) was performed by a simple nucleophilic substitution reaction of 2-((2,2-dichloroethyl)(4-(4-nitrophenoxy)benzyl)amino)-ethanol and 5-chloromethyl-8-quinolinol hydrochloride (CMQ). The resulted chlorphenoxamide ligand was an amorphous colour powder. The obtained C, H, N contents of chlorphenoxamide and its heterochelates are in good agreement with the calculated one as shown in Table-1.

The IR spectrum shows the important bands due to 8-quinolinol. The bands observed at 1625, 1569, 1490 and 750 cm^{-1}. The broad band in ligand and all the complexes at 3790-2695 cm^{-1} is due to the presence of -OH group. The band at 1685 cm^{-1} is due to -CO- group. The band at 1672 cm^{-1} might be due to carbamide group. In this band the inflections are observed at 2972, 2853 and 1465 cm^{-1}. While the latter two might be attributed to asymmetric and symmetric vibration of -CH$_2$ group of CMQ.

The infrared spectra of all the complexes are identical and suggest the formation of the entire metalocyclic compound by the absence of band characteristic of free -OH group of parent chlorphenoxamide. The other bands are almost at their respectable positions as appeared in the spectrum of parent chlorphenoxamide ligand. However, in the far-IR region, two new bands in the range of 475-440 and 432-413 cm^{-1} in the all the complexes are assigned the binding of metal with oxygen and nitrogen atom of CMQ, respectively.

The ^{1}H NMR spectrum of chlorphenoxamide is carried out in DMSO-d_6 using as solvent indicates that singlet at 2.5-1.66 δ ppm due to the four aliphatic -CH$_2$ group protons, where the singlet at 4.8 δ ppm due to the -CH$_2$ group protons attached to the quinoline ring and oxygen atom, the peak at 5.69 δ ppm indicate the single proton attached to both the chlorine atom, where the broad peak at 5.35 δ ppm indicate the -OH group proton, the range of 7.0-7.6 δ ppm indicate the 8 protons for the aromatic region. Thus the structure of chlorphenoxamide is confirmed as shown in **Scheme-I**.

Magnetic moments of heterochelates are given in Table-2. The diffuse electronic spectrum of Cu^{2+} chelates shows two broad bands around 13000 and 23000 cm^{-1}. The first band may be due to a $^2B_{1g} \rightarrow {}^1A_{1g}$ transition. While the second band may be due to charge transfer. The first band shows structures suggesting a distorted octahedral structure for the Cu^{2+} metal chelates[32,33]. The higher value of the magnetic moment of the Cu^{2+} chelate supports the same. The Co^{2+} metal chelate gives rise to two absorption bands at 23800 and 19040 cm^{-1}, which can be assigned $^4T_{1g} \rightarrow {}^2T_{2g}$, $^4T_{1g} \rightarrow {}^4T_{1g}(P)$ transitions, respectively. These absorption bands and the μ_{eff} value indicate an octahedral configuration of the Co^{2+} metal chelate[34,35]. The spectrum of Mn^{2+} polymeric chelate comprised two bands at 19019 and 23301 cm^{-1}. These bands may be assigned to $^6A_{1g} \rightarrow {}^4T_{2g}(G)$ and $^6A_{1g} \rightarrow {}^4A_{2g}(G)$ transitions, respectively. The

TABLE-1
ANALYSIS OF DNPQ LIGAND AND ITS HETEROCHELATES

Empirical formula	m.w. (g/mol)	Yield (%)	Elemental analysis (%) calcd.(found)			
			C	H	N	M
$C_{27}H_{25}N_3O_5Cl_2$	542	90	59.79 (59.62)	4.65 (4.48)	7.75 (7.52)	–
$C_{54}H_{48}N_6O_{10}Cl_4Cu^{2+}\cdot 2H_2O$	1182	88	54.85 (53.13)	4.43 (4.44)	7.11 (14.15)	5.37 (8.11)
$C_{54}H_{48}N_6O_{10}Cl_4Ni^{2+}\cdot 2H_2O$	1177	83	55.08 (54.99)	4.45 (4.41)	7.14 (7.11)	4.98 (4.92)
$C_{54}H_{48}N_6O_{10}Cl_4Co^{2+}\cdot 2H_2O$	1177	79	55.07 (54.85)	4.45 (4.39)	7.14 (7.09)	5.00 (4.91)
$C_{54}H_{48}N_6O_{10}Cl_4Mn^{2+}\cdot 2H_2O$	1173	82	55.26 (55.10)	4.47 (4.45)	7.16 (7.10)	4.68 (4.65)
$C_{54}H_{48}N_6O_{10}Cl_4Zn^{2+}\cdot 2H_2O$	1184	85	54.77 (54.71)	4.43 (4.38)	7.10 (7.07)	5.52 (5.49)

TABLE-2
SPECTRAL FEATURES AND MAGNETIC MOMENT OF DNPQ LIGAND AND ITS HETEROCHELATES

Heterohelates	$\mu_{eff.}$ (BM)	Electronic spectral data (cm^{-1})	Transition	IR spectral features common for all (cm^{-1})	
(DNPQ)-Cu^{2+}	2.05	23178 15779	Charge transfer $^2B_{1g} \rightarrow {}^2A_{1g}$	1625 1569 1490	Quinoline moiety
(DNPQ)-Ni^{2+}	3.13	22536 15385	$^3A_{1g} \rightarrow {}^3T_{1g}(P)$ $^3A_{1g} \rightarrow {}^3T_{1g}(F)$	2972 2853 1465	CH$_2$
(DNPQ)-Co^{2+}	4.39	22645 15220 8895	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$	1110 455	C-O-M & O-M bands
(DNPQ)-Mn^{2+}	5.25	23778 18322 16731	$^6A_{1g} \rightarrow {}^6A_{2g}\ {}^4E_g$ $^6A_{1g} \rightarrow {}^4T_{2g}$ (4G) $^6A_{1g} \rightarrow {}^4T_{1g}$(PG)	712 743	Ar-Cl
(DNPQ)-Zn^{2+}	Diamag.	–	–	–	–

high intensity of the bands suggests that they may have some charge transfer character. The magnetic moment is found to be lower than normal range. In the absence of low temperature measurement of magnetic moment it is difficult to attach any significance to this. As the spectrum of the metal chelate of Ni^{2+} show two bands at 11961-11490 and 17701-17400 cm^{-1} are assigned as $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ transition, respectively suggested the octahedral environment for Ni^{2+} ion. The observed μ_{eff} values in the range 3.01-3.20 BM are consistent with the above moiety[36,37].

To assess the biological potential of the ligands and their macrocyclic complexes, laboratory experiments have been conducted. The following techniques have been used for the antimicrobial activities of these compounds. In this technique sterilized hot nutrient agar medium and 5 mm diameter paper discs of Whatman were used. The agar medium was poured into the petri dishes. After solidifications, the petri dishes were stored in inverted position so that there was condensation of water in the upper lid. Solutions of test compounds in DMSO in 500 and 1000 ppm concentrations were prepared in which discs were dipped in solution of the test sample placed on seeded plates. The petri dishes having these discs on the seeded agar should first be placed at low temperature for 2 or 4 h to allow for the diffusion of chemicals before being incubated at suitable optimum temperature 28 ± 2 °C for 24-30 h. After the expiry of their incubation period, the zone of inhibition associated with the treated disc was measured in mm. The compounds were tested against *Pseudomonas aeruginosa*, *Escherichia coli* gram positive (+) and *Serratiamarcescens*, *Bacillus substilis* gram negative (–) organism.

The examination of antimicrobial activity of chlorphenoxamide ligand and its all heterochelates (Table-3) reveals that the ligand is moderately more or less active against various organisms, while all the heterochelates are more active than ligand. Among all the heterochelates the Cu^{2+} chelate is more active against organism used.

TABLE-3
ANTIMICROBIAL ACTIVITY OF DNPQ LIDAND AND IT'S HETEROCHELATES

Compound	*P. aeruginosa*	*E. coli*	*Serratiamarcescens*	*B. substilis*
Ligand	10	15	13	16
(DNPQ)-Cu^{2+}	26	23	29	26
(DNPQ)-Ni^{2+}	19	16	27	24
(DNPQ)-Co^{2+}	23	20	20	24
(DNPQ)-Mn^{2+}	17	18	25	15
(DNPQ)-Zn^{2+}	22	21	22	17

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