Synthesis, Characterization and Antimicrobial Activity of Metal Chelates of 5-[4-Chlorophenyl(1, 3, 4)thiadiazol-2-ylaminomethylene]-8-hydroxy quinoline

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Abstract: 5-Chloromethyl-8-quinolinol was condensed stoichiometrically with 5-(4-chlorophenyl)-(1,3,4) thiadiazol-2-ylamine in the presence of sodium bicarbonate. The resulting 5-[4-chlorophenyl-(1,3,4)thiadiazol-2-ylaminomethylene]-8-quinolinol (CTAQ) was characterized by elemental analysis and spectral studies. The transition metal chelates *viz.* Cu^{2+} , Ni^{2+} , Co^{3+} , Mn^{2+} and Zn^{2+} of CTAQ were prepared and characterized by metal-ligand (M:L) ratio, IR and reflectance spectroscopies and magnetic properties. The antifungal activity of CTAQ and its metal chelates was screened against various fungi. The results show that all these samples are good antifungal agents.

Keywords: 1, 3, 4,-Thiadiazol-2-amine, 8-Hydroxyquinoline, IR, NMR, Magnetic moment, Metal Chelates, Antifungal properties.

Introduction

8-Hydroxyquinoline or 8-quinolinol is well known as an analytical reagent^{1,2}. Its various derivatives³ are also useful in pharmaceuticals. Several azo dyes based on 8-quinolinol are also reported for dyeing of textiles as well as their chelating properties⁴⁻⁵. One of the derivative say 5-chloromethyl 8-quinolinol (CMQ) can be synthesized easily and studied extensively for number of derivatives⁶. Some of the ions exchanging resins are also reported with good potentiality⁷⁻¹⁵. The reaction of CMQ with 4-substituted piperazine derivatives has also been reported recently¹⁶. The heterocyclic compound say derivatives of 2-amino-1,3,4-thiadiazole have interesting wide range of biological activity¹⁷. The reaction of these

derivatives with CMQ has not been reported so far. Hence the present paper deals with synthesis, characterization, chelating and microbicidal properties of 5-[4-chlorophenyl-(1,3,4)thiadiazol-2-ylamino methylene]-8-hydroxy quinoline (CTAQ) (Scheme 1).

Scheme 1.

Experimental

5-Chloromethyl-8-quinolinol (CMQ) hydrochloride was prepared according to method reported in literature⁶. 5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl amine was prepared by reported method¹⁷. All other chemicals used were of laboratory grade.

Synthesis of 5-[4-chlorophenyl-(1,3,4-thiadiazol)-2-amino methylene]-8-quinolinol:

In a round bottom flask, to a suspension of 5-chloromethyl-8-quinolinol (CMQ) hydrochloride (23 g, 0.1 mol) in THF (100 mL), 5-(4-chlorophenyl)-1,3,4-thiadiazole-2-amine (17.7 g, 0.12 mol) was added gradually at room temperature. Sodium bicarbonate (16.8 g 0.2 mole) was added in the mixture and the mixture was refluxed on water bath for 3 h. The resulting solid mass was filtered off, washed with boiling water and air dried. It was dark green amorphous powder. It was insoluble in common organic solvent but soluble only in formic acid and DMSO. It did not melt up to 220 °C.

Analysis

		C%	H%	N%	S%
Elemental Analysis	Calculated:	58.61	3.52	15.19	8.68
C ₁₈ H ₁₃ N ₄ O SCl (368.5)	Found :	58.59	3.50	15.15	8.60

IR Spectral Features: 3420 (NH), 2980 (CH₂), 2850, 1630, 1575, 1500, 1470 (aromatic).cm⁻¹)

NMR : δ ppm 5.85-8.3 (m 10H Ar-H), 3.8 (OH) 2.6 (CH₂)

Signals

Synthesis of metal chelates of CTAQ

The metal chelates of CTAQ with Cu²⁺, Co²⁺, Zn²⁺, Mn²⁺ and Ni²⁺ metal ions were prepared in two steps. All the metal chelates were prepared in an identical procedure. The details are given as follows.

Preparation of CTAQ solution

CTAQ (0.05 mol) 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 the complete dissolution of CTAQ. It was diluted to 100 mL.

Synthesis of CTAQ-metal-chelates

In a solution of metal acetate (0.005 mol) in acetone: water (50:50 v/v) mixture (40 mL) 20 mL of above mentioned CTAQ solution (*i.e.* containing 0.01 M CTAQ) 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.

Measurements

The elemental contents were determined by Thermo Finigen Flash1101 EA (Italy), the metals were determined volumetrically by Vogel's method¹⁸. To 100 mg chelate sample, each 1 mL of HCl, H₂SO₄ and HClO₄ were added and then 1 g of NaClO₄ 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 Nicolet760 FT-IR spectrometer. NMR spectrum of CTAQ was recorded on 400 MHz NMR spectrophotometer. Magnetic susceptibility measurement of the synthesized complexes was carried out on Gouy Balance at room temperature. Mercury tetrathiocyanatocobalate(II) Hg[Co(NCS)₄] was used as a calibrant. The electronic spectra of complexes in solid were recorded on at room temperature. MgO was used as reference. Antifungal activity of all the samples was monitored against various fungi, following the method reported in literature¹⁹.

Results and Discussion

The synthesis of 5-[4-chlorophenyl-1,3,4-thiazole-2-ylamino methylene]-8-quinolinol (CTAQ) was performed by a simple nucleophilic substitution reaction of 5-(4-chlorophenyl)-1,3,4-thiazole-2-amine and 5-chloromethyl-8-quinolinol hydrochloride (CMQ). The resulted CTAQ ligand was an amorphous dark brown powder. The C,H,N contents of CTAQ (Table 1) are consistent with the structure predicted (Scheme 1). The IR spectrum of CTAQ comprises the important bands due to 8-quinolinol. The bands were observed at 1630, 1575, 1470, and 750 cm^{-1} .

The broad band due to -OH group appeared at 3800-2700 cm^{-1} . In this band the inflections are observed at 2950, 2920 and 2850 cm^{-1} . While the latter two might be attributed to asymmetric and symmetric vibration of CH_2 of CMQ. The NMR spectrum of CTAQ in DMSO indicates that the singlet of 2 H at 2.6 δ ppm of $\text{N-CH}_2\text{-Ar}$ group. While the singlet at 3.8 δ ppm due to -OH group. The aromatic protons are appeared in multiplicity at 7.2 δ . The vigorous oxidations of CTAQ yield 8-hydroxy quinoline-5-carboxylic acid. The melting point²⁰ is 230°C. Thus the structure of CTAQ is confirmed as shown in Scheme 1.

The metal and C,H,N contents of metal chelates of CTAQ Table 1 are also consistent with the predicted structure. The results show that the metal: ligand (M:L) ratio for all divalent metal chelate is 1:2.

The infrared spectra of all the chelates are identical and suggest the formation of all the metalocyclic compound by the absence of band characteristic of free -OH group of parent CTAQ. The other bands are almost at their respectable positions as appeared in the spectrum of parent-CTAQ 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.

Magnetic moments of metal chelates are given in Table 2. The diffuse electronic spectrum of Cu^{2+} chelates shows two broad bands 15780 and 23156 cm^{-1} . The first band may be due to a ${}^2\text{B}_{1g} \rightarrow {}^1\text{A}_{1g}$ 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^{21,22}. 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 22625 and 15166 cm^{-1} , which can be assigned ${}^4\text{T}_{1g} \rightarrow {}^2\text{T}_{2g}$, ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}(\text{P})$ transitions, respectively. These absorption bands and the μ_{eff} value indicate an octahedral configuration of the Co^{2+} metal chelate^{23,24}. The spectrum of Mn^{2+} polymeric chelate comprised two bands at 18241 cm^{-1} and 23720 cm^{-1} . The latter does not have a very long tail. These bands may be assigned to ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g(\text{G})}$ and ${}^6\text{A}_{1g} \rightarrow {}^4\text{A}_{2g(\text{G})}$ transitions, respectively. The 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 distinct bands at 22487 and 15280 cm^{-1} are assigned as ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ and ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ transition, respectively suggested the octahedral environment for Ni^{2+} ion. The observed μ_{eff} values in the range 3.01-3.2 B.M are consistent with the above moiety^{25,26}.

The examination of antifungal activity of CTAQ ligand and its all chelates Table 3 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.

Table 1. Analysis of CTAQ ligand and its metal chelates.

Empirical Formula	Mol. Cal. g/mole	Yield, %	Elemental Analysis									
			C%		H%		N%		S%		M%	
			Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
C ₁₈ H ₁₃ N ₄ O ₂ SCl	368.5	83	58.61	58.59	3.52	3.50	15.19	15.15	8.68	8.60	----	----
C ₃₆ H ₂₄ N ₈ O ₂ S ₂	834.54	71	51.76	51.70	2.87	2.82	13.42	13.40	7.66	7.62	7.61	7.60
C ₃₆ H ₂₄ N ₈ O ₂ S ₂	829.93	66	52.06	52.00	2.89	8.80	13.49	1.42	7.71	7.70	7.07	7.00
C ₃₆ H ₂₄ N ₈ O ₂ S ₂	829.69	72	52.05	52.00	2.89	2.82	13.49	13.42	7.71	7.70	7.10	7.00
C ₃₆ H ₂₄ N ₈ O ₂ S ₂	825.93	71	52.30	52.10	2.90	2.85	13.56	13.50	7.74	7.71	6.45	6.41
C ₃₆ H ₂₄ N ₈ O ₂ S ₂	836.39	61	51.65	51.62	2.86	2.81	13.39	13.35	7.65	7.61	7.81	7.80

Table 2. Spectral features and magnetic moment of CTAQ metal chelates.

Metal Chelates	μ_{eff} BM	Electronic spectral data cm ⁻¹	Transition	IR spectral features common for all cm ⁻¹	
CTAQ-Cu ²⁺	2.10	23156	Charge transfer	1650	Quinoline moiety
		15780	² B _{1g} → ² A _{1g}	1565	
				1500	
				1460	
CTAQ-Ni ²⁺	3.36	22487	³ A _{1g} → ³ T _{1g} (P)	2920	CH ₂
		15280	³ A _{1g} → ³ T _{1g} (F)	2850	
				1450	
CTAQ-Co ²⁺	4.60	22625	⁴ T _{1g} (F)→ ⁴ T _{2g} (F)	1100	C-O-M & O-M bands
		15166	⁴ T _{1g} (F)→ ⁴ T _{2g}	500	
		8889	⁴ T _{1g} (F)→ ⁴ T _{2g} (P)		
CTAQ-Mn ²⁺	5.48	23720	⁶ A _{1g} → ⁶ A _{2g} ⁴ E _g	710	Ar-Cl
		18241	⁶ A _{1g} → ⁴ T _{2g} (4G)	750	
		16727	⁶ A _{1g} → ⁴ T _{1g} (PG)		
CTAQ-Zn ²⁺	Diamag.		-----	-----	-----

Table 3. Antifungal activity of CTAQ ligand and its metal chelates.

Sample	Zone of inhibition of fungus at 1000 ppm, %						
	BT	N	RN	AN	AF	AA	AK
CTAQ	56	52	55	61	61	65	74
CTAQ-Cu ²⁺	81	71	76	82	80	80	84
CTAQ-Zn ²⁺	74	62	60	76	82	81	85
CTAQ-Ni ²⁺	79	79	77	74	72	82	85
CTAQ-Co ²⁺	60	77	76	72	77	76	84
CTAQ-Mn ²⁺	74	70	79	73	79	74	81

BT= *Botrydeplaia thiobromine* N= *Nigrospora Sp.* RN= *Rhisopus Nigricans*; AN= *Asperginus niger*
 AF= *Aeprogines funigalus* AA= *Anida albicans* AK= *Andida krusegios candida grabrataHO5*

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