SYNTHESIS, SPECTRAL CHARACTERIZATION AND BIOLOGICAL STUDIES OF Cu(II), Co(II) AND Zn(II) COMPLEXES DERIVED FROM QUINOLINE AND QUINAZOLINE MOIETIES

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ABSTRACT

The condensation reaction between 2-methyl-4-oxoquinazoline -3(4H)-carbothihydrazide with 2-hydroxyquinoline-3-carbaldehyde results in the formation of complexes of the type ML_2 and $M'L$ [where M = Cu(II) and Co(II) M' =Zn(II)]. The formation of compounds were characterizations by elemental analysis, spectral (Uv-Visible, IR and NMR) and magnetic data. The synthesized compounds were tested for their antimicrobial activity against Gram positive and Gram negative bacterium as well as against fungi in order to check the biological potency.

KEYWORDS: Quinazoline, quinoline, antimicrobial activity.

INTRODUCTION

In the present era, the search in the discovery of new biologically active compounds which acts as a potential antimicrobial active agents were required, since the microorganism were more resistant to present antibiotics. In context with this, among the various heterocyclic compounds quinazolines and quinazolines are reported to possess divers pharmacological activity such as anti-bacterial, anti-fungal, anti-inflammatory, anti-cancer, anti-convulsant, anti-oxidant, anti-tubercular, anti-HIV and analgesic.[1] Some substituted quinazolines have been found to be potential and highly selective inhibitors of human immunoglobulin E and epidermal growth factor receptor tyrosine kinase, which regulates the cell growth and proliferation, so they work as potent antiallergic or anticancer agents.[2-3]

So, based on above findings we thought of interest to synthesized quinoline and quinazoline Schiff base ligand such as (E)-N-((2-hydroxyquinoline-3-yl)methylene)-2-methyl-4-oxoquinazoline-3(4H)-carbothiohydrazide (HQMMOQC) and its Cu(II), Co(II) and Zn(II) complexes. The synthesized compounds were screen for their antimicrobial activity.

EXPERIMENTAL

PHYSICAL MEASUREMENTS

All the reagents used were of analytical grade and used without further purification. The elemental analyses (CHN) were obtained from Thermo finnigam, Italy, FLASH EA 1112 series. Infrared spectra of the ligand and its metal(II) complexes in KBr pellets were recorded in the spectral range 4000-350 cm^{-1} with Perkin Elmer Spectrum one FT-IR spectrometer.

UV-Visible spectra were recorded on an Elico SL-164 DOUBLE BEAM UV-Vis Spectrophotometer in the range of 200-1200 nm. Magnetic susceptibilities were measured on a Guoy balance at room temperature using $Hg[Co(SCN)_4]$ as calibrant. The molar conductance of the complexes was measured on ELICO CM-82 Conductivity Bridge in DMF solution at a concentration of 10^{-3}M. ^{1}H NMR spectra were recorded on AMX-400 NMR spectrometer, using TMS as internal standard and DMSO as a solvent.

Preparation of (E)-N-((2-hydroxyquinoline-3-yl)methylene)-2-methyl-4-oxoquinazoline-3(4H)-carbothiohydrazide (HQMMOQC).

The Schiff base ligand (HQMMOQC) was prepared by the reaction of 3-amino-2-methylquinazoline-4-one (0.01 mol) with 2-hydroxyquinoline-3-carbaldehyde (0.01 mol) in ethanol by refluxing on water bath for 5-6 hours in the presence of a few drops of acetic acid. The reaction mixture was cooled to room temperature; the separated ligand was filtered, washed and recrystallized from alcohol. The purity of the ligand (HQMMOQC) was checked by TLC.
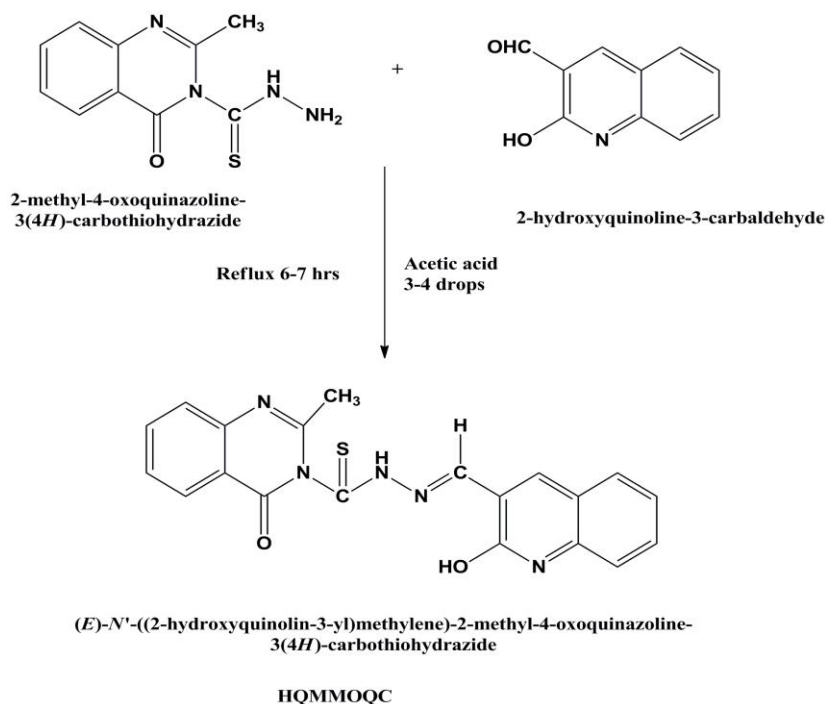
Scheme 1. Synthesis of Schiff base ligand (HQMMOQC).

Preparation of complexes

To the hot solution of the Schiff base ligand (HQMMOQC) (0.001 mol) in ethanol (35 ml), a hot ethanolic solution of respective metal chlorides (0.001 mol) in ethanol (15 ml) was added and the reaction mixture was then treated with sodium acetate (0.5 g) and the refluxing was continued further for 2 hours. The resulting reaction mixture was then decomposed by pouring into distilled water (80-100 ml), the colored complex separated out was collected by filtration, washed with distilled water, then with hot ethanol and dried in vacuum over anhydrous calcium chloride. The complexes were analyzed for their metal and chloride contents by standard methods.[4] Elemental analysis data is shown in Table 1.

RESULTS AND DISCUSSION

The prepared complexes were sparingly soluble in common organic solvents but soluble in DMF, DMSO and acetonitrile. The analytical data indicates that the stoichiometry of the complexes are 1:2 (metal to ligand ratio) for Cu(II) and Co(II) and 1:1 (metal to ligand ratio) for Zn(II) complex. The observed molar conductance values measured in DMF solution fall in the range 16-28 Ohm^{-1} cm^2 mol^{-1} indicating that the complexes are non-electrolytic in nature.[5]

Table 1: shows the measured magnetic moment values of Cu(II) and Co(II) complexes in the range of 1.90–2.10 BM and 4.54–4.95 BM respectively and indicates their octahedral geometries.[6]

Table 1 Analytical, magnetic susceptibility and molar conductance data of the Schiff base ligand Schiff base (HQMMOQC) and its complexes

| Ligand / Complex | Mol. wt. (color) | M.P. / ^{0}C [Yield/(%)] | Found /(Calculated) % | | | | | | μ_{eff} (B.M) | $\Lambda_m{}^*$ |
			M	C	H	N	S	Cl		
$C_{20}H_{15}N_5O_2S$	389.43 (Yellow)	271 (75)	–	61.68 (61.87)	3.88 (4.12)	17.89 (18.10)	8.23 (8.52)	–	–	–
$[Cu(C_{20}H_{14}N_5O_2S)_2]$	840.39 (Green)	294 (67)	7.56 (7.63)	57.17 (57.30)	3.36 (3.45)	16.67 (16.75)	7.63 (7.72)	–	1.96	28.50
$[Co(C_{20}H_{14}N_5O_2S)_2]$	835.78 (Light pink)	293 (68)	7.05 (7.11)	57.48 (57.60)	3.38 (3.50)	16.76 (16.85)	7.67 (7.76)	–	4.90	26.15
$[Zn(C_{20}H_{14}N_5O_2S)Cl]$	489.27 (Grey)	291 (70)	13.36 (13.50)	49.10 (49.18)	2.88 (3.02)	14.31 (14.60)	6.55 (6.75)	7.25 (7.55)	Diam	27.45

$\Lambda_m{}^*$ **Molar Conductance, λ_M Ohm^{-1} cm^2 mol^{-1}**

Electronic spectra

The electronic spectral data of Cu(II) and Co(II) complexes of the ligand (HQMMOQC) were recorded in DMF solution at 10^{-3} M concentration and are given in Table 2. They have been studied with a view to obtaining more information on the stereochemistry of the complexes and to procure more support for the conclusion deduced with the help of magnetic data. The Cu(II) complex exhibits a broad asymmetric band in the region 12750-16800 cm^{-1} with a maxima at 14430 cm^{-1} in an distorted octahedral geometry.[7] The broadness of the band may be due to dynamic Jahn-Teller distortion and is assigned to $^2T_{2g} \rightarrow {}^2E_g$ transitions.

The electronic spectra of the Co(II) complex gave two absorption bands at 10500 cm^{-1} and 21250 cm^{-1}, due to $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)(\nu_1)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)(\nu_3)$ transitions.[8] The bands due to the $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)(\nu_2)$ transitions could not be observed because of its very low intensity. The position of ν_2 band has been calculated (15750 cm^{-1}) by using the equation $\nu_2 = \nu_1 + 10Dq$. These transitions suggest octahedral geometry for Co(II) complex. The ligand field parameters such as Dq, B′, β and β% have been calculated by using band-fitting equation given by Billing and Underhill.[9] The crystal field splitting energy (Dq) value of 826 cm^{-1}, is well within the range reported for most of the octahedral Co(II) complexes. The Co(II) complex under present investigation possess Racha parameter B′ 930 cm^{-1}. The Racha parameter B′ is less than free ion value 971cm^{-1}, suggesting a considerable orbital overlap

and delocalization of electrons on the metal ion. The nephelauxetic ratio (β) for the present Co(II) complex is 0.96 cm^{-1}. This is less than one, suggesting partial covalency in the metal ligand bond. The values Dq, β%, LFSE and ν_2/ν_1 suggest the octahedral geometry for Co(II) complex.[10]

Table 2: Electronic spectral data and ligand field parameters of Cu(II) and Co(II) complexes of Schiff base ligand (HQMMOQC) (cm^{-1})

Complexes	ν_1	ν_2	ν_3	Dq	B′	β	β%	ν_2/ν_1	ν_3/ν_2	LFSE kcal mol^{-1}
[Cu(C$_{20}$H$_{14}$N$_5$O$_2$S)$_2$]	-	12750-16800		1430	-	-	-	-	-	25.50
[Co(C$_{20}$H$_{14}$N$_5$O$_2$S)$_2$]	10500	15750	21250	826	930	0.965	16.12	1.50	1.35	14.52

Infrared spectra

In the IR spectra of the ligand a sharp band observed at 1750 cm^{-1} assigned to quinazoline ring ν(C=O), which was shifted to 25-35 cm^{-1} in all complexes, indicating the involvement of carboxyl group of quinazoline ring(C=O) in complexation with metal ion.[11]

The band exhibited at 1645 cm^{-1} is assigned to the azomethine ν(C=N) group in the ligand, but in complexes it has lowered to 50-58cm^{-1} due to the reduction of double bond character in carbon-nitrogen of the azomethine group.[12]

The broad band observed at 3405 cm^{-1} in the ligand (HMQMAMQ) is assigned to ν(OH), which disappeared in all the complexes, thereby indicating the involvement of phenolic oxygen in bonding with metal ions through deprotonation.[13]

The frequency observed at 1245 cm^{-1} of the ligand is attributed to phenolic ν(C-O), but this band is shifted to higher frequency in the region 40-50 cm^{-1} for the complexes, which confirms the involvement of phenolic OH in the complex formation.[14]

The low frequency skeletal vibrations due to M–O and M–N stretching provide direct evidence for complexation. In the present investigation the frequencies observed in the region of 580-585 cm^{-1} are due to ν(M-O), and the frequencies observed in the region of 468-472 cm^{-1} are due to ν(M-N) vibrations. [15, 16] The frequencies observed in the region 355-360 cm^{-1} were due to ν(M-Cl) bonding.[17] These are characteristic of chlorine atom in Zn(II) complex and is further confirmed by quantitative chloride estimation.

^{1}H NMR spectra

In the ^{1}H NMR spectrum of ligand L[1], a sharp peak is observed at δ 12.2 (s, 1H,-OH) due to -OH at 2-position of quinoline moiety has resonated, but in the case of Zn(II) complex of ligand L[1] has been disappeared, indicating the involvement of phenolic oxygen in the coordination via deprotonation.[18] The peak appeared at δ 10.6 (s, 1H, -NH) is due to the amide proton group in ligand L[1], but in Zn(II) complex the peak is observed at δ 10.4 (s, 1H, -NH). The nine aromatic protons due to the quinazoline and quinoline rings have been observed in the region δ 7.3-8.8 (m, 9H, Ar-H) as a multiplet in Zn(II) complex. This lower shift confirms the complex formation. The data suggests the coordination of the phenolic -OH with the metal ion via deprotonation.[19]

Antimicrobial activity

The antimicrobial activity of synthesized ligand (HQMMOQC) and its Cu(II), Co(II) and Zn(II) complexes were tested by cup-plate method. [20] The antimicrobial activity results of the screened compounds are given in the Table-3. Antibacterial activity against *E. coli* and *S. aureus* and antifungal activity against *A. niger* and *A. flavous* at 1000μg/ ml concentration[21] were carried out.

The standard drugs *Streptomycin a*nd *Clotrimazole* were also tested for their antibacterial and antifungal activity at the same concentration under the conditions similar to that of the test compounds.

The comparative antimicrobial activity results revealed that the ligand (HQMMOQC) and its complexes show weak to good activity. In other words, antimicrobial activity the ligand (HQMMOQC) was enhanced upon complex formation with Cu(II), Co(II) and Zn(II) ions.

The enhanced activity of the Schiff base and its complexes were explained based on chelation theory. On chelation the positive charge of metal is partially shared with the donor atoms present in the ligands, there may be π- electron delocalization over the whole chelating. This increases the lipophilic character of the metal chelate and favors its penetration through the lipid layer of the bacterial membranes. Chelation is not only the criterion for antibacterial activity it is expected to be a function of steric, electronic and pharmacokinetic factors along with mechanistic pathway.[22] Other factors such as solubility, conductivity, dipole moment, size of metal ions, stability constants of the complexes and their magnetic moments are also reported to affect the microbial activity of the complexes.[23]

Table 3: Antimicrobial activity data of the Schiff's base ligand (HQMMOQC) and its metal complexes.

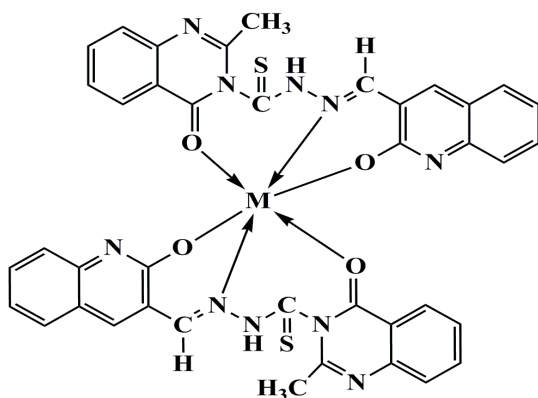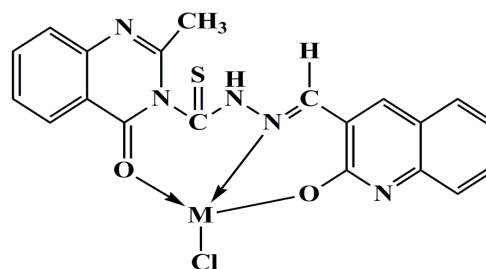| Sr. No.	Test Compound	Antibacterial activity of zone of inhibition (in mm)		Antifungal activity of zone of inhibition (in mm)	
		E. coli	*S. aureus*	*A. niger*	*A. flavous*
1	$C_{20}H_{15}N_5O_2S$	12	13	13	11
2	$[Cu(C_{20}H_{14}N_5O_2S)_2]$	20	19	18	19
3	$[Co(C_{20}H_{14}N_5O_2S)_2]$	19	18	16	15
4	$[Zn(C_{20}H_{14}N_5O_2S)Cl]$	20	19	19	18
5	*Streptomycin*	24	25	-	---
6	*Clotrimazole*	-	-	26	25

Figure 1. M = Cu(II) and Co(II)

Figure 2. M = Zn(II)

Figure 1 and 2. Proposed structure of the synthesized complexes

CONCLUSIONS

In conclusion, the elemental analysis, conductivity data, magnetic susceptibility, electronic, IR, ^{1}H NMR spectral observations reveal the mononuclear nature of all the complexes. The non-electrolytic behavior of the complexes confirms the presence of chlorides within the coordination sphere. The Cu(II) and Co(II) complexes exhibit octahedral geometry, whereas Zn(II) complex exhibit tetrahedral geometry (Figure 1 and 2). All the complexes show higher activity than the Schiff base ligand (HQMMOQC).

ACKNOWLEDGEMENTS

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