METAL COMPLEX OF BENZIMIDAZOLE CONTAINING QUINOLINONE DERIVATIVE: SYNTHESIS, SPECTROSCOPIC, THERMAL AND ANTIMICROBIAL STUDIES

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Abstract

We have synthesized ligand base approach benzimidazole containing quinolinone compound i.e. 7-hydroxy-4-methyl-1-[(2-thiazol-4-yl)-*1H* benzimidazole-5yl]-quinolin-2-(*1H*)-one and studied their metal complexation with Copper. The synthesized ligand and metal complex were screened for antifungal activity and antibacterial activity against some Gram-positive and Gram-negative bacteria.

Key words: Benzimidazole**,** Thiabendazole**,** Coumarin, Quinolinone and metal complex.

Introduction

Coumarins possess a number of biological activities like anticoagulant, antioxidant and antiviral. Coumarin belongs to a group of benzopyrones in which benzene ring is fused with pyrone. Coumarin also has pharmacological, biochemical and therapeutic applications [1]. Coumarins (2H-1-benzopyran-2-ones) are important oxygen containing fused heterocycles used in drugs and dyes [2,3]**.** Coumarin can be converted into more useful products by incorporation of different groups [4]. Coumarins are also known to have antidiabetic activity [5], as well as antioxidant activity [6].

Cu(II) complexes of some organic drugs have been the subject of a number of studies aimed at establishing the presumed synergy between the Cu(II) ion and the drug [7–10]

In this work, we have prepared a coumarin-derived ligand base compound and their Cu(II) complex and antimicrobial activity of the metal-free ligand and the complex was assessed.

Experimental

Materials/instrumentation

7-hydroxy-4-methyl-1-(2-(thiazol-4-yl)-*1H*-benzimidazole-5-yl) quinolin-2-one (L) ($C_{20}H_{14}N_4O_2S$), The copper chloride dihydrate ($CuCl_2.2H_2O$), ethanol, methanol. All reactions were monitored by ascending Thin Layer Chromatography on 0.2 mm silica gel F-254(Merck) plates using UV light (254 and 366 nm) for detection.IR spectra were recorded on an FTIR spectrophotometer [Shimadzu] using KBr disc method in the range 400 to 4000 cm^{-1} at central instrumentation Centre, KTHM College, Nashik.

LCMS spectra were scanned on Instrument Waters UPLC based LCMS Model: Waters, CHA, SQD-2 with H Class UPLC at Sapala Organics Private Limited, Hyderabad. The C, H, N analysis were carried out on elemental analyzer at Sapala Organics Private Limited, Hyderabad.

^{1}H-NMR and CMR spectra of ligand were recorded on JEOL 500-MHz NMR Spectrometer Model: JEOL, JNM-ECZ500R/S1 at Sapala Organics Private Limited, Hyderabad. Experiments of thermogravimetry were conducted at U. D. C. T., K. B. C. N. M. U., Jalgaon.

Synthesis and characterization of Quinolinone-TBZ ligand L

7-hydroxy-4-methyl-1-[(2-thiazol-4-yl)-*1H*-benzimidazole-5yl]-quinolin-2-(*1H*)-one was synthesized and identified by comparing their spectral data with reported values in the literature[11] or their melting point.

Synthesis and characterization of metal complex of ligand L

It involves synthesis of metal complex from 7-hydroxy-4-methyl-1-(2-(thiazol-4-yl)-*1H*-benzimidazole-5-yl) quinolin-2-one (L) by reaction with Copper metal chloride.

Metal Complex reaction scheme

$$L + MX_2 \longrightarrow [MLX_2]$$

Where M: L as 1: 1

L = **7**-hydroxy-4-methyl-1-[(2-thiazol-4-yl)-*1H*-benzimidazole-5yl]-quinolin-2-(*1H*)-one ($C_{20}H_{14}N_4O_2S$)
M = Cu
X = Chloride ion

Synthesis of [Cu ($C_{20}H_{14}N_4O_2S$) Cl_2]

The copper chloride dihydrate ($CuCl_2.2H_2O$, 0.400 gm. 2.13 mmol) dissolved in minimum quantity of ethanol was added to 30 ml hot ethanolic solution of L (0.8 gm, 2.13 mmol, 7-hydroxy-4-methyl-1-(2-(thiazol-4-yl)-1*H*-benzimidazole-5-yl)

quinolin-2-one). The reaction mixture was refluxed for 5 hours. The precipitate separated overnight as brown colored solid. The precipitate was thoroughly washed with cold ethanol and finally dried under vacuum to give yield 54 %. Melting point was 259-261 ^{0}C

Table 1: Analytical data for metal complex

Comp.	Molecular Formula	Molecular Weight	Color	Solubility	Melting Point (^{0}C)	Yield (%)
CuL	$[Cu(C_{20}H_{14}N_4O_2S)Cl_2]$	508.87	Brown	Insoluble in water, ethanol, methanol, soluble in DMSO.	259-261	54

UV (λ_{max}, DMSO): 209, 280, 319, 489.
IR (KBr): 3248, 3089 (N-H stretch), 1635 (-C=O stretch), 1481(C=N) $_{imidazole}$), 1442υ (C=N) $_{thiazole}$, 1296 (C-S stretch), 999, 813, 759, 694, 617, 540, 439.
Mass: 507.39, 373.33, 255, 215, 154.The mass spectrum of Cu (II) complex shows molecular ions peak of [Cu ($C_{20}H_{14}N_4O_2S$) Cl_2] [M+1] at *m/z* 507, $[C_{20}H_{14}N_4O_2S]$ at *m/z* = 373, and other important peaks at 343, $[C_{10}H_8N_4S]$ at *m/z* = 215.
Elemental analysis % found (Calcd.): C, 47.64 (47.21); H, 2.39 (2.77); N, 11.45 (11.01) and Cu, 12.11(12.49).

Results and discussion
Table 2 Comparison of IR frequency of ligand L with its metal complex.

IR Band	L cm^{-1}	CuL cm^{-1}
N-H stretch	3093	3089
υ $_{(C=N)imidazole}$	1546	1481
υ $_{(C=N)thiazole}$	1481	1442
C-S stretch	1280	1296
-C=O stretch	1639	1635
-OH stretch	3224	3248

The N-H stretch at 3093 remains same for ligand L and metal complex. The IR associated to υ $_{(C=N)\ imidazole}$, and$\upsilon_{(C=N)\ thiazole}$ have remained same in spectra of complex but have shifted slightly as compare to ligand indicating that ligand is coordinated through imidazole and thiazole nitrogens. The C-S stretches have also remained same in lined and its complex compounds hence sulphur does not coordinated to metal. Carbonyls stretching band as well as –OH stretching band also remain same. **(Table 2)**

Table 3 Molar Conductivity and magnetic moment

Metal Complex	Formula	Molar Conductivity in DMSO Λ_M($ohm^{-1}cm^2mol^{-1}$)	Magnetic moment (B. M.) $\mu_{eff.}$
CuL	$[Cu(C_{20}H_{14}Cl_2N_4O_2S)Cl_2]$	45.97	1.66

Molar conductivity values of complex (CuL) of 0.001 molar solution at room temperature in DMSO solution are listed in **Table 3.** For the complex molar conductivity value is less than expected. This indicates that the complex is non-electrolyte. The molar conductivity value was found in range of 30 to 50 $ohm^{-1}cm^2mol^{-1}$

The magnetic moment of copper complex was 1.66 B. M. Its magnetic moment value indicates that presence of one unpaired electron. Thus, copper is paramagnetic in nature.

Thermo gravimetric analysis of metal complex.

The TGA curve indicate that metal complex CuL i.e. $[Cu(C_{20}H_{14}N_4O_2S)Cl_2]$ begins to decompose at 420^{0}C and ends at 650^{0}C. The TGA curve for CuL shows single stage of mass loss within the temperature range 200 to 650^{0}C. For CuL the observed mass loss is 85.46 % corresponding to residue CuO. **(Fig. 1)**Thermal decomposition data for the complex CuL is given in the (**Table No 4)**.

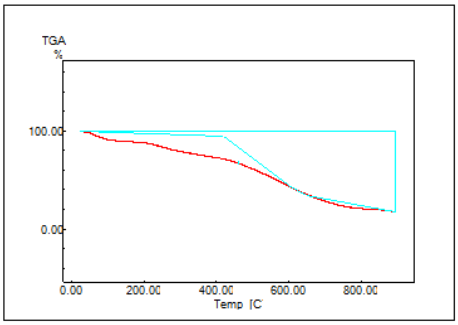

Fig.1 TGA of metal complex CuLi.e. $[Cu(C_{20}H_{14}N_4O_2S)Cl_2]$

Table No 4 TGA data for metal complex CuL, $[Cu(C_{20}H_{14}N_4O_2S)Cl_2]$

Metal Complex	Stages	Temp. range TG (^{0}C)	Mass loss from Thermo gram (%)		Decomposition Pattern
			Expt. loss (%)	Theor. loss (%)	
CuL	1	25 to 700	85.46	85.14	Loss of oxides of sulphur, part of ligand and formation of oxide. $[Cu(C_{20}H_{14}N_4O_2S)Cl_2]$ to CuO

Evaluation of antimicrobial activities

Bioassay is an important and crucial role in evaluation of bio-activity of compounds and helpful to establish structure-activity relationship [12-13]. In the present work ligand as well as metal complex was tested for their antimicrobial potency such as antibacterial and antifungal activities against different grampositive bacteria, gram negative bacteria and fungi using

a) Gram positive bacteria (*Staphylococcus aureus, Bacillus subtilis*).

b) Gram negative bacteria (*Pseudomonas aeruginosa, Escherichia coli).*

***c)* Fungi *(Aspergillus niger, Candida albicans, Fusarium moniliforme)*.**

High media antibiotics disk such as Chloramphenicol (10 microgram/disk, Amphotericin-B (100 units/disk) moistened with water are used as standard.

Stock solution of 1000 µg/ml of each sample ligand L and metal complex CuL was prepared in DMSO. Assay is carried out by taking concentration 100 µg/ disc. Chloramphenicol (10 µg/ disc, amphotericin-B (100 units par disc moistened with water are used as standard. A clear zone of inhibition around the disc demonstrated the relative susceptibility of the bacteria or fungi to the synthesized ligand and metal complex. The fungicidal or bactericidal potency is proportional to the diameter (in mm) of the zone of inhibition. One of inhibition was calculated by Vernier Caliper. The experiments were performed in duplicate and average of the measured zone was considered. The results of antimicrobial activity are summarized in (**Table 5).**

Table 5. Results of antimicrobial activities for ligand $L(C_{20}H_{14}N_4O_2S)$ and its Copper metal complex by disc diffusion assay

Sr. No	Sample Code	Zone of inhibition (Diameter in mm)						
		G^+ bacteria		G^- bacteria		Fungi		
		S. a.	*B. s.*	*E. c.*	*P. a.*	*C. a.*	*A. n*	*F.m.*
1	L	13.70	18.11	14.84	10.08	-----	-----	
4	CuL	10.22	14.03	8.45	-----	-----	-----	-----
6	A	27.90	20.05	26.91	**14.10**	NA	NA	NA
8	B	NA	NA	NA	NA	21.42	7.98	8.10

CuL $[Cu(L)Cl_2]$ **A** Chloramphenicol **B** Amphotericin B

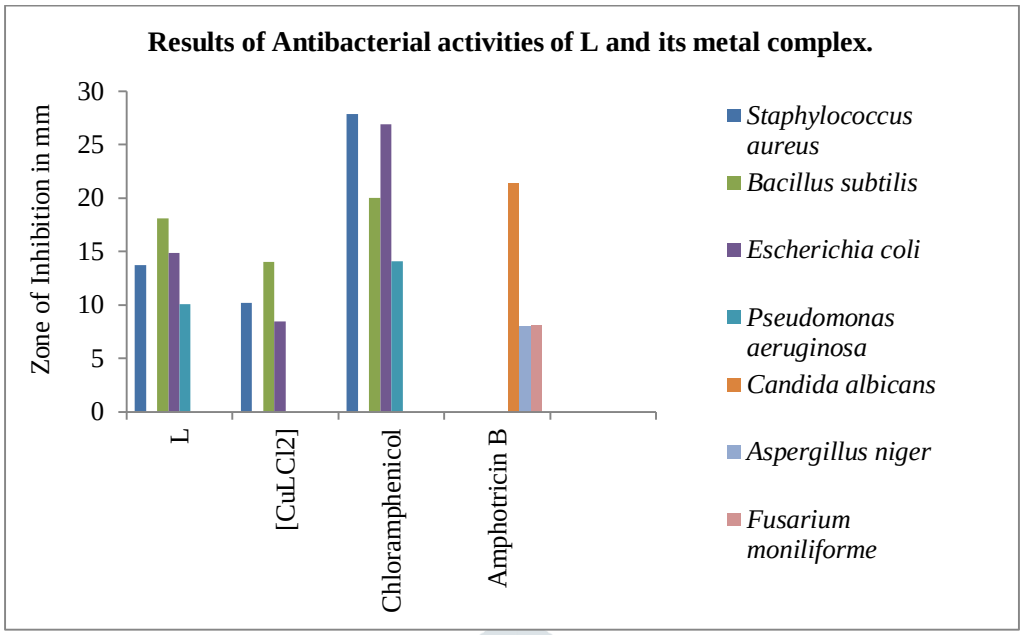

Fig. 2: Antimicrobial activities of L and its metal complex

Antibacterial activity:

Staphylococcus aureus: In antibacterial efficacy against *S. aureus* the ligand L exhibited moderate antibacterial activity. The metal complex CuL i.e. $[Cu(L)Cl_2)]$ shows poor antibacterial activity.

Bacillus subtilis: Metal free ligand L exhibit excellent antibacterial activity against *Bacillus subtilis* with zone of inhibition 18.11 mm compare to standard drug Chloramphenicol is 20.05 mm. The metal complex CuL shows moderate antibacterial activity.

Escherichia coli: Ligand L shows better antibacterial activity against *E. Coli.*with zone of inhibition 18.11 mm. The metal complex CuL metal complex shows poor efficacy against *E. Coli.*

Pseudomonas aeruginosa: Ligand L shows moderate antibacterial activity against *P. aeruginosa.* Metal complex CuL are inactive against *P. aeruginosa*.

Antifungal activity:

Candida albicans: L is inactive against antifungal species *C. albicans.* Metal complex CuL is inactive due to no zone of inhibition.

***Aspergillus niger*:** L is inactive against antifungal species *Aspergillus niger*while CuL are inactive**.**

Fusarium moniliforme: CuL is inactive against *F. moniliforme*.

Conclusion

Cu(II) complex of **7**-hydroxy-4-methyl-1-[(2-thiazol-4-yl)-*1H* benzimidazole-5yl]-quinolin-2-(*1H*)-one (L) characterized based on elemental analyses, infrared, magnetic moment, molar conductance, mass spectra, UV-Vis analysis and thermogravimetric analysis (TGA).

From the elemental analysis, it is found that the complex have formula $[M(L)(Cl)_2]$. The molar conductance data reveal that metal chelate is non-electrolytes. From the magnetic and solid reflectance spectra, it is found that the structure of these complex is square planer. The synthesized ligand and metal complex were screened for antimicrobial activity, such a non-toxic compound as might have potential use as a therapeutic agent.

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