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Synthesis, Characterization and Study of Microbiological Activity of Copper(II) Complex with 2-(5- Bromo-2- Oxoindolin-3-Ylidene) Hydrazine-1-Carbothioamide

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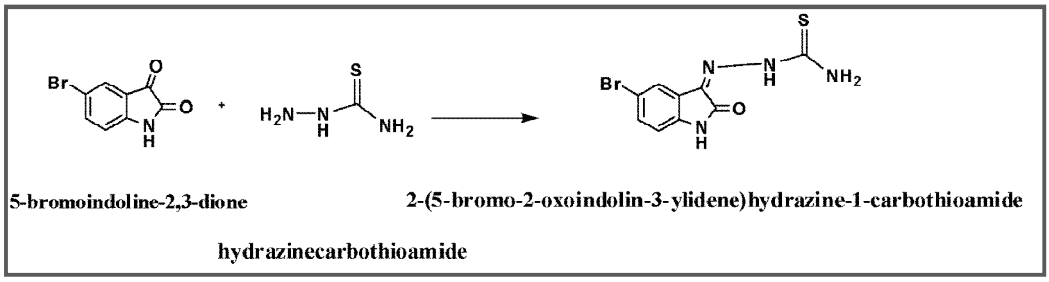
ABSTRACT

5-Bromoisatin and thiosemicarbazide, a Schiff base ligand [2-(5-Bromo -2-Oxoindolin-3-ylidene)-1-Hydrazine Carbothioamide], [HBITSC] is derived and its complex with Cu (II) has been synthesized. The solid metal complex formed is yellow in colour. The characterization was done by electronic spectra elemental analysis, molar conductance, NMR and IR spectroscopy. The Schiff base ligand is bidentate in nature, The Schiff base ligand gets coordinated through azomethine nitrogen and thioketo sulphur to the metal ion. Electronic spectral analysis proposes tetrahedral geometry of complex. Non - electrolytic nature of complex is revealed by the molar conductivity data. Basis of on the above studies ratio of metal to ligand proposed to be 1:2 i.e., two ligands were suggested to be coordinated to copper atom. They are coordinated through thioketo sulphur and azomethine nitrogen to form tetrahedral complexes. The ligand and Cu(II) complex have also been studied by microbiological activity.

Graphical Abstract



Synthesis of 2-(5-Bromo -2-Oxoindolin-3-ylidene)-1-Hydrazine carbothioamide

Keywords: Tetrahedral geometry, Schiff base HBITSC, Microbiological activity.

INTRODUCTION

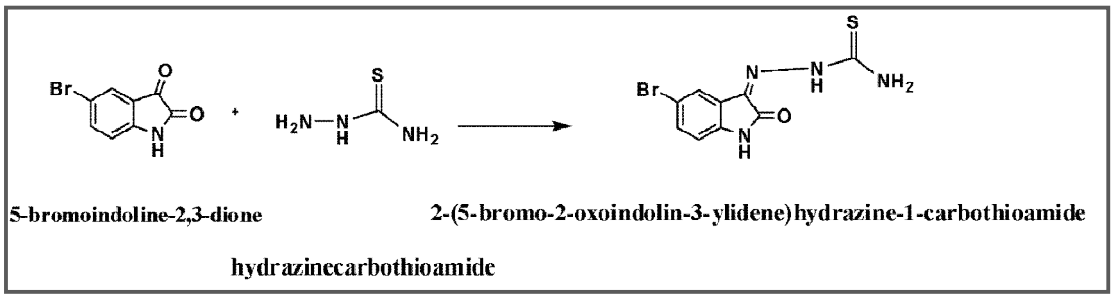
In the field of coordination chemistry, many metal complexes of Schiff bases containing nitrogen and other donor atoms are found and have many applications [**1-5**]. Many Schiff bases and the Cu(II) metal complexes have been found to possess important biological and catalytic activity [**6-8**].

In trace analysis of some metal cations Schiff bases are used as an efficient reagent [**9-10**]. In the present study, we have synthesized a complex of Cu(II), with Schiff base ligand derived from 5-Bromoisatin and thiosemicarbazide, [2-(5-Bromo -2-Oxoindolin-3-ylidene)-1-Hydrazine Carbothio-amide] [HBITSC] Complex was characterized by electronic spectra, elemental analysis, molar conductance, NMR and IR spectroscopy to determine the mode of bonding and geometry. The microbiological activities of the ligand and its metal complex are also studied.

MATERIALS AND METHODS

Instrumentation: All solvents and chemicals used were of AR grade hence were not purified further. By using an element analyzer C, H, N, O model Flash EA 1112 series the percentage compositions of the (C,H,N,O) elements of the compounds were determined. To confirm the presence of various functional groups present in ligand and complex the Infrared spectra were recorded using SHIMADZU IR Affinity 1S. By using ELICO SL-159 UV-Vis Spectrophotometer the electronic Spectrum of complex was obtained which was followed by melting point determination of ligand and its Cu(II) complex. To measure the molar conductivity, methanol was used as solvent and measurement was made on ELICO SL-303 model.

Synthesis of 2-(5-Bromo-2-Oxoindolin-3-ylidene)-1-Hydrazine Carbothioamide[HBITSC]: Ethanolic solution of 5-Bromoisatin and thiosemicarbazide in equimolar amount was refluxed for 4-5 hours to prepare Schiff base ligand HBITSC. The reaction mixture was then cooled and a sharp yellow crystalline product obtained was collected by filtration (80%, yield) and purified by recrystallization using aqueous ethanol (procedure recommended by Vogel [**11**]. The pure product was characterized by elemental and spectral analysis.



Scheme 1. Synthesis of 2-(5-Bromo -2-Oxoindolin-3-ylidene)-1-HydrazineCarbothioamide.

Preparation of complex with Schiff base ligand (HBITSC): Aqueous solution of hydrated copper chloride was mixed with ligand (HBITSC) solution prepared in dimethyl formamide, in molar ratio of 1:2 to prepare Cu (II) complex pH was maintained at 5.0 and reaction mixture is refluxed on boiling water bath for 2-3 h on cooling dark brown colored solid separates out. It was filtered, washed with water. Product was purified by recrystallisation and dried in vacuum desicator over anhydrous $CaCl_2$ (yield 60 - 70%).

Biological Studies: 20 mg of compound in methanol was dissolve and the volume was made up to 10 mL with same solvent to prepare the stock solution of Cu (II) complex. The stock solution of 2000 ppm of each compound thus prepared on active ingredient basis and was kept at room temperature till used. Determination of antibacterial and antifungal activity of ligand and its complex was done by cup

plate method. 1 mL of 24 h old, 0.1 O.D. cultures of fungus Candida albicans were used for seeding Sabourauds agar plates and for bacterial test cultures Sterile Mueller Hinton agar plates were used. Wells were punched in the above plates and (50 µL) of test compound was added. After incubation of plates at 37°C/RT for 48 h depending on the cultures the zone of inhibition was seen around the wells. Inhibition zone was measured in millimeters.

RESULTS AND DISCUSSION

The Cu (II) HBITSC complex is brown colored solid. It is stable at room temperature. Molar ratio of Cu (II):Cu (II) HBITSC complex is 1:2. The Analytical and physical data of ligand and Cu (II) HBITSC complex is as follows (Table 1).

Table 1. The Analytical and physical data of ligand and its Cu (II) HBITSC complex

Compounds (Colour)	Mol. Wt	M.P. °C	% Elemental Analysis Found (Calculated)								^mOhm^{-1} cm^{2}mol^{-1}
			C	H	N	Br	O	S	Cl	M	
HBITSC (Yellow)	299.64	278	36.42 (36.10)	2.46 (2.67)	18.5 (18.72)	26.71 (26.7)	4.99 (5.2)	10.92 (10.6)	-	-	-
[Cu (HBITSC)$_2$]Cl$_2$ (Dark Brown)	732.846	269	28.99 (29.46)	2.20 (2.18)	15.32 (15.27)	21.54 (21.79)	4.28 (4.36)	8.62 (8.73)	9.54 (9.68)	8.98 (8.50)	31.42

Infrared Spectral Analysis: Infrared spectra help in identification of important functional groups. SHIMADZU IR Affinity1S Spectrometer (4000-400cm^{-1}) was used to record Infrared spectra of ligand and Cu (II) HBITSC complex. The figure 1 is a IR spectrum of ligand and figure 2 is a IR spectrum of Cu (II) HBITSC complex. Comparison of the spectral data of both was summarized in table 2.

Table 2. The Important IR bands of Ligand and Cu Metal Complexes

Compound	υ(N-N) cm^{-1}	υ(C=N) cm^{-1}	υ(C-S) stretching cm^{-1}	υ(M-N) cm^{-1}	υ(M-S) cm^{-1}
HBITSC	1137.65	1603	856	-	-
[Cu(HBITSC)$_2$]Cl$_2$	1132.96	1609	852	515	441

The IR spectrum of the ligand reveals broad band for (C=N) stretching of azomethine group [**12**], at 1603 cm^{-1}. The same band was shifted at 1609 cm^{-1} i.e., at higher frequency, in Cu (II) complex. This indicates that azomethine nitrogen has donated electron density to metal and is coordinated to metal atom on complexation. [**13-14**].

The second important band observed in the IR spectrum of ligand is at 856.00 cm^{-1} (strong band). This is due to the (C=S) stretching vibration. This band is also found to be shifted but at lower frequency 852 cm^{-1} in spectra of complex. The shifting in position of band from 856.00cm^{-1} to 852 cm^{-1} confirms the coordination of thioketo Sulphur to metal atom [**13-15**].

After studying both spectrums in detail it was observed that two new bands have appeared in the region of 441-600 cm^{-1} in the complex, and were absent in the spectrum of ligand. One band corresponding to υ(M-S) stretching frequencies 441cm^{-1} region and the other band between 515cm^{-1} which is because of stretching frequencies υ(M-N) respectively [**15-18**].

After studying above spectral details, we suggest that ligand behaves as bidentate ligand and get coordinated to metal ion through azomethine nitrogen and thioketo Sulphur.

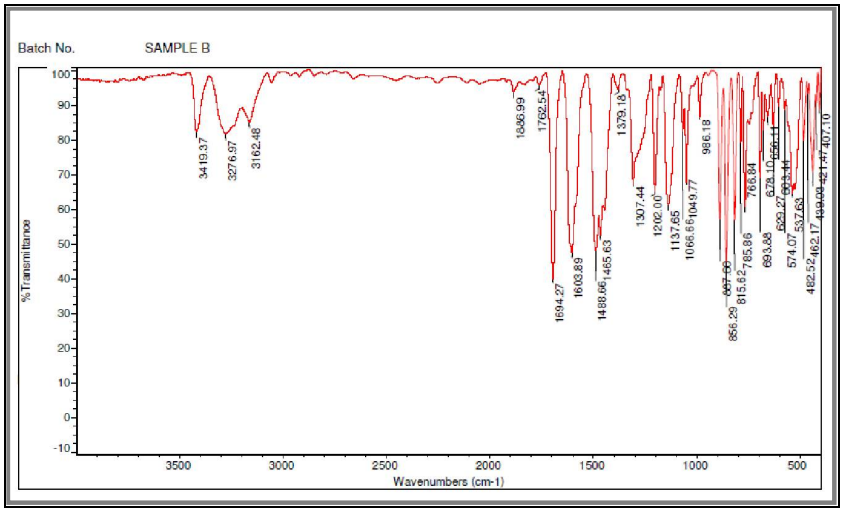


Figure 1. IR spectrum of Ligand [HBITSC].

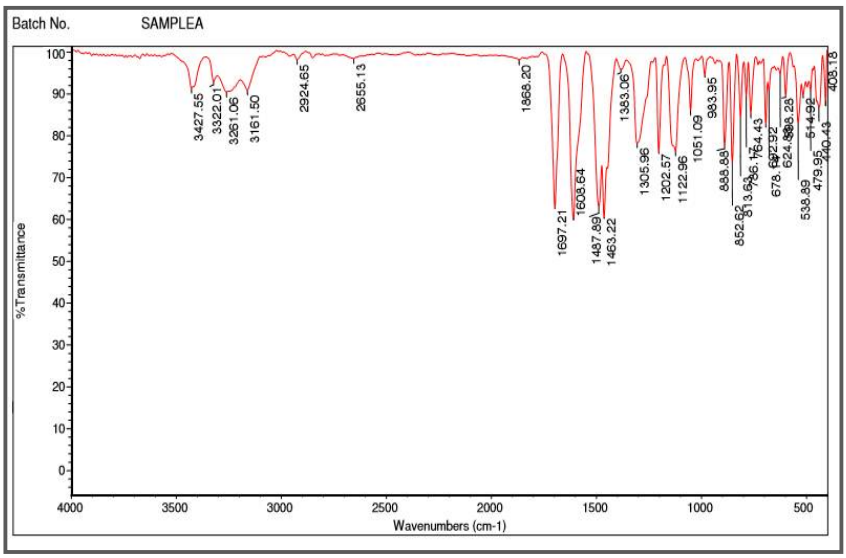


Figure 2. IR Spectra of Cu (II)-{HBITSC] Complex.

Molar Conductance: To measure molar conductance of Cu (II) complex ELICO Conductivity meter (cell constant 1.0 cm^{-1}) is used. Measurement was carried out at room temperature and $1x10^{-3}$M solution of Cu (II) complex in methanol was used (Table 1). The non-electrolytic nature of the complex was revealed by comparing this value with known molar conductivities [**19-21**].

Electronic Spectra of Complex: The electronic structures of transition metal ions are extremely varied since they occur in variable structural environments which can be been identified with UV-Visible spectroscopy. The electronic spectra were recorded on ELICO SL-159 UV-Visible Spectrophotomer. The electronic spectra help to deduce the nature of ligand field around the metal ion and the geometry of complex. Tetrahedral geometry is confirmed for the Cu (II) complex [**22-23**]. as it displays band at 19607.00 cm^{-1} (510nm) .

^{1}H NMR: ^{1}H NMR spectra further confirms coordination of thiosemicarbazones in the Cu (II) complexes (Table 3) The proton peaks of N−H group at δ 11.321ppm and 12.25 ppm in complex remains same as in the ligand, it suggested that deprotonation do not occur and it has also shown keto form of the ligands [**15, 22**] The multiplet as strong band in the region 6.87-7.88 ppm of aromatic ring protons, was also shifted downfield in the complex [**15, 22, 23**].

Table 3. NMR spectral data (δ, ppm) of the thiosemicarbazones and the Cu complexes

Compound	δ(N-H)	δ(N–H)	δ(Ar–H)
HBITSC	12.25	11.321	6.87-7.88
$[Cu(HBITSC)_2]Cl_2$	12.25	11.321	6.88-7.9

Proposed Structure of Complexes: The probable structure of the complex under investigation on the basis of the above experimental evidence can be shown as figure 3. The present study clearly indicates that the ligand forms stable coordination compound with the Copper(II), under investigation which is evidenced by micro-analytical and spectroscopic data.

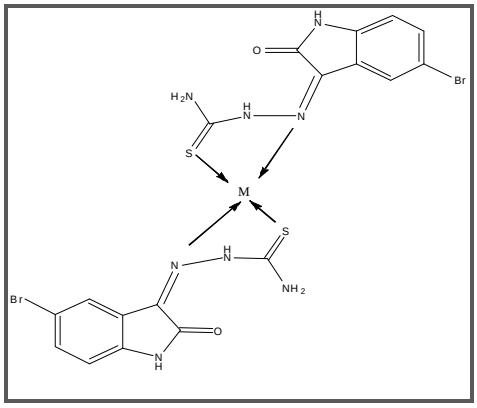


Figure 3. Proposed Structure of Complexes.

APPLICATION

Biological Activity: Antibacterial activity of Schiff base ligand and its Cu (II)-HBITSC complex were studied. Study was conducted for antibacterial activity against gram positive bacteria (*staphylococcus aureus*), gram negative bacteria (*Escherichia coli* and *Klebsiella pneumonia*). Even antifungal activity against (*Candida albicans*) was studied. Cup plate method was used for same [24]. From the above study following facts are revealed.

Table 4. Zone of inhibition of growth in millimeters after 48 h of incubation

Complexes	Cultures			
	S. *aureus*	E. *coli*	*K. pneumonia*	C. *albicans*
HBITSC	12	08	10	13
$[Cu\ (HBITSC)_{2]}Cl_2$	22	15	14	16
SOLVENT	-	-	-	-

A comparative study of the ligand and the Cu (II)-HBITSC complexes indicates that Cu (II) chelate exhibited higher antibacterial and antifungal activity than that of the free ligand recorded in table 4. The increase in the biological activity of Cu(II) chelate was explained on the basis of overtones concept and chelation theory. On chelation as there is overlap of the ligand orbital with metal orbitals and partial sharing of positive charges of Cu (II) with donor groups the polarity of the Cu (II) reduced to a greater extent. Also the lipophillicity of the complex increases because of delocalization of electrons over the whole chelate ring. As lipophillicity [25-30] increases it enhanced the penetration of the complex into lipid membrane and it leads to blocking of the metal sites on enzymes of microorganism**.** The activity was compared with zone of inhibition which was measured in millimeters.

CONCLUSION

From the results of above study, it can be concluded that Schiff base ligand 2-(5-Bromo -2-Oxoindolin-3-ylidene)-1- Hydrazine Carbothioamide, [HBITSC] acts as a very good bidentate complexing agent towards Cu (II) during complexation. Analytical data of complex is in good agreement with its molecular formula. By comparing electronic, IR and NMR spectral data of the ligand with that of its Cu (II)- HBITSC complex, the involvement of azomethine (N), thioketo (S) of the bidentate Schiff base to the Cu (II) was confirmed. The appearance of new bands due to ν(M—N) and ν(M—S) in the Cu (II)- HBITSC complex further confirms the coordination of this Schiff-base with Cu (II). The geometry of Complex of Cu (II) with HBITSC was proposed to be tetrahedral in nature on the basis of the electronic spectra. On the basis of these findings the structures have been proposed for the complexes which are in good agreement with theoretical consideration.

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