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SYNTHESIS, CHARACTERISATION AND BIOLOGICAL SCREENING OF Cu (II) COMPLEXES OF PINCER LIGANDS

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Keywords:

Benzimidazole, Pincer ligand, Tridentate, Octahedral complex, Cytotoxic activity

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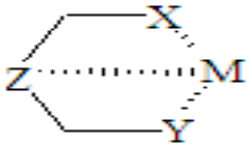
ABSTRACT: The ligands bis-(benzimidazolyl)pyridine (BBIP) and bis-(benzimidazolyl)benzene (BBIB) have been used to synthesize Copper(II) complexes $[Cu(BBIP)_2]Cl_2$ and $[Cu(BBIB)_2]Cl_2$ respectively. The complexes are characterized by analytical and spectral (FTIR, ^1H NMR and electronic) techniques. IR spectra of complexes show that the tertiary nitrogens in the ligand are involved in the co-ordination to the metal ion. An octahedral geometry has been suggested for the complexes and the molar conductance values reveal them to be 1:2 electrolytes. The TGA curves of the complexes$[Cu(BBIP)_2]Cl_2$ and $[Cu(BBIB)_2]Cl_2$ show no mass loss upto 200°C which indicates the absence of lattice as well as co-ordinated water. The ligand BBIP and $[Cu(BBIP)_2]Cl_2$complex exhibit good antifungal and antibacterial activity against *Candida albicans* and *Staphylococcus aureus* (gram positive), *Escherichia coli* (gram negative) respectively, by using modified Kirby-Bauer disc diffusion method. The screening results for anti-proliferative activity for the MCF 7 breast cancerous cells show promising activity. The $[Cu(BBIP)_2]Cl_2$ complex has enhanced growth inhibition in a dose-dependent manner

INTRODUCTION: N-heterocyclic ligands have recently become more and more attractive in homogeneous catalysis and organic synthesis, because their organometallic complexes usually exhibit higher reactivity and better stability than those with phospheneligands [1].

Benzimidazole is an important pharmacophore and chelating ligands containing benzimidazolyl group are receiving attention of the co-ordination chemists. Benzimidazole is also a structural unit of naturally occurring nucleoside due to which it easily interacts with the biopolymers of living system. This character is responsible for its numerous biological aspects like anthelmintic [2], antifungal [3], antimicrobial [4], antineoplastic [3] activities. The incorporation of this nucleus is an important synthetic strategy in studies of antimicrobial drug discovery.

This project is aimed at synthesizing tridentate ligands containing benzimidazole group attached to pyridine/benzene unit. These ligands belong to the class called Pincer ligands and are represented as,



The ligand architecture can be changed by changing the anchoring donor Z or flanking donors or the linkers X and Y. Such modification can alter the physical and electronic properties and hence the reactivity of the complexes.

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- The tridentate nature of the pincer ligands gives high stability to the corresponding metal complexes. The pincer complexes have been employed as catalysts in various bond activation reactions.[5-7]

- They have also been evaluated as efficient anticancer agents through DNA binding studies.[8]

In this project, bis benzimidazolyl ligands with pyridine and benzene as bridging moieties to give NNN and NCN ligands have been prepared. Cu complexes of the ligands have been prepared, characterized and evaluated for their biological applications.

MATERIALS AND METHODS:

Synthesis of ligands:

The ligand was synthesized according to the reported procedure [9]. o-Phenylene diamine (6.34g, 58.7mmol) and pyridine-2,6-dicarboylic acid(4.59g, 27.5mmol)/isophthalic acid (8.1g, 27.5mmol) were suspended in phosphoric acid (55 mL, 85%). The reaction mixture was stirred at 205˚C for about 6 hours. The solution was cooled to room temperature and was poured into a beaker containing 400mL ice water. The precipitate formed was filtered and added 10 % hot aqueous Na_2CO_3 solution. Filtered and added to hot methanol saturated with Na_2CO_3. The solution was diluted with100mL of water and acidified with 15% HCl. The precipitate was extracted with hot methanol and evaporated to produce pure ligand.

Synthesis of complexes:

The hot solution of the ligands BBIP / BBIBin methanol: chloroform mixed solvent (1:1, 20ml, 10mmol) was added to the solution of corresponding metal salt 2:1 (Ligand: metal) in the same solvent. The reaction mixture was stirred well, refluxed for 2h and left overnight. The complexes formed on standing were collected by vacuum filtration, washed several times with cold methanol and then dried in vacuum over anhydrous $CaCl_2$.

Characterization techniques:

Microanalysis of carbon, hydrogen and nitrogen in the synthesized complexes were carried out using Elementar Vario EL III. The percentage of metal in the complexes was estimated gravimetrically as their oxides by fusion with Anala R ammonium oxalate. Molar conductances of 10^{-3} M solutions of the complexes in DMSO were measured on EQ660A digital conductivity meter. Magnetic susceptibility measurements were carried out using Gouy balance at room temperature. The thermograms were recorded in dynamic nitrogen atmosphere (flow rate 20mL/min) with a heating rate of 10 K/min using a Perkin Elmer (TGS-2 model) thermal analyzer in the temperature range of ambient temperature to 900^{o}C under stable air condition.

Spectral techniques:

IR spectra of bis benzimidazolyl pyridine/benzene and their metal complexes were recorded in the range 400to4000 cm^{-1} on a Shimadzu FTIR–8400S spectrophotometer as KBr discs. The electronic absorption spectra were recorded on a UV 3000+ spectrophotometer (cell length, 1 cm) in the 200 – 800 nm range. DMSO (spectral grade) was used as a solvent. The ^{1}H NMR spectra of the samples were carried out in Bruker Avance III model instrument 400MHz in DMSO-d6.

RESULTS AND DISCUSSION:

The complexes are coloured solids and stable in air and moisture. They are soluble in DMSO, but insoluble in water, ethanol, methanol, and chloroform. The physical data of the ligands and complexes are given in **Table 1**.

On the basis of analytical data (**Table 2**) the complexes were found to have 1:2 (metal:ligand) stoichiometry.

Molar Conductance:

In order to determine whether an anion is bonded to the metal (or) simply present in the compound as counter ion, molar conductance measurements are used. The molar conductances of the complexes measured in DMSO solutions are given in table-2.The molar conductance values of Cu(II) complexes were found to be 94.5, 128.4 $ohm^{-1}cm^2mol^{-1}$ which denotes that they are 1:2 electrolytes [10].

TABLE: 1 PHYSICAL DATA OF LIGANDS BBIP, BBIB AND THEIR COMPLEXES

S.No	Compound Name	Colour	Yield (%)	Melting Point (^{O}C)	Solubility
1	BBIP	White	88	261	DMSO
2	BBIB	Violet	89	295	DMSO
3	$[Cu(BBIP)_2]Cl_2$	Dark Green	92	>360	DMSO/Ethanol
4	$[Cu(BBIB)_2]Cl_2$	Dark Green	85	>360	DMSO

TABLE: 2 ANALYTICAL DATA OF BBIP, BBIB AND THEIR COMPLEXES

Compound	Mol. Formula	Mol. Weight	Elemental Analysis (%)				Δm $\Omega^{-1}cm^2mol^{-1}$	μ_{eff} (BM)
			C	H	N	M		
BBIP	$C_{19}H_{13}N_5$	311.34	73.293 (73.599)	4.175 (4.832)	22.483 (22.185)	-	-	-
BBIB	$C_{20}H_{14}N_4$	310.35	77.396 (76.432)	4.511 (4.912)	18.044 (18.854)	-	-	-
$[Cu(BBIP)_2]Cl_2$	$Cu(C_{38}H_{26}N_{10})Cl_2$	757.13	60.278 (59.783)	3.434 (3.628)	18.491 (17.131)	8.42 (8.78)	94.5	1.75
$[Cu(BBIB)_2]Cl_2$	$Cu(C_{40}H_{28}N_8)Cl_2$	755.15	63.617 (58.023)	3.708 (3.098)	14.831 (13.543)	8.39 (8.10)	128.4	1.73

FTIR Spectra:

The binding mode of the ligands BBIP and BBIB to the metal in the complexes has been studied by comparison of IR spectra of the ligands and complexes (**Fig.1**). **Table 3** summarizes the most important IR peaks, the corresponding assignment and the frequencies.

TABLE: 3 INFRARED STRETCHING FREQUENCIES

Compound Name	ν(C=N) cm^{-1}	ν(N-H) cm^{-1}	ν(C=C) cm^{-1}
BBIP	1620	3154.71	1597.13
BBIB	1654.22	3325.75	1440.49
$[Cu(BBIP)_2]Cl_2$	1604.90	3413.43	1473.37
$[Cu(BBIB)_2]Cl_2$	1621.24	3172.07	1458.25

In free ligands (bis benzimidazolyl pyridine (BBIP) and bis benzimidazolyl benzene (BBIB)), band characteristic of benzimidazole ring is observed at 1597 cm^{-1} [11]. A medium to weak band around 3154cm^{-1}, 3325$cm^{-1}$is attributed to NH bonds. The νC=N and νC=C vibrations are very close to each other and occur around 1620 cm^{-1} and 1654 cm^{-1}as weak to medium intensity band in the uncoordinated ligands. The νN-H mode of the ligands remains unaffected on complexation and occur in the range 3500-3100 cm^{-1}.

The C=N stretching occurring around 1620, 1654 cm^{-1} in the ligands BBIP and BBIB, undergoes a shift to shorter wavelength and become broad and appears in the range 1600 cm^{-1} and 1620 cm^{-1} which shows that the imidazole tertiary nitrogen is involved in the co-ordination. These results suggest the tridentate NNN and NCN co-ordination of BBIP and BBIB which is in accordance with that reported elsewhere.[12, 13]

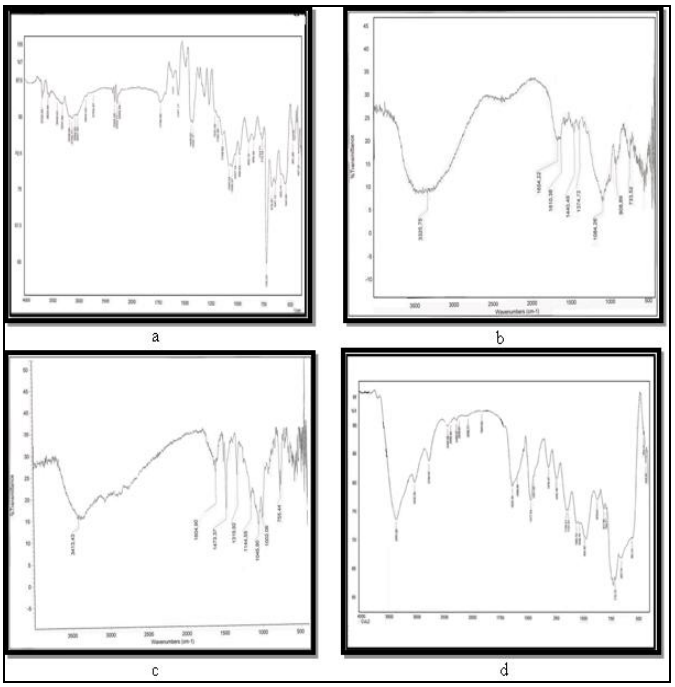


FIG. 1: IR SPECTRUM OF (a) BBIP, (b) BBIB, (c $[Cu(BBIP)_2]Cl_2$ AND (d) $[Cu(BBIB)_2]Cl_2$

Electronic Spectra and Magnetic Moment:

The free ligands (BBIP and BBIB) displayed two absorption bands at 263 nm and 307nm/297nm ranges. The shorter wavelength band is attributed to the high energy π-π* transition in the aromatic

moiety. The longer wavelength band is assigned to the n-π* transition of C=N group. In the spectra of the complexes an intense band is observed around 290 nm and 350 nm. This band may be assigned to $t_2(M) \rightarrow \pi^*(L)$ charge transfer transition.

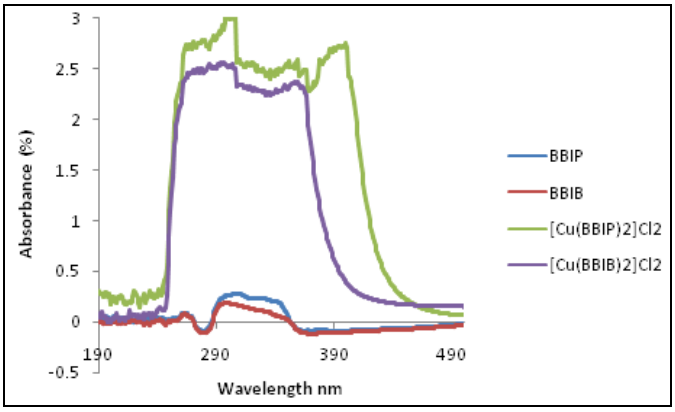


FIG. 2: UV SPECTRUM OF BBIP, BBIB AND THEIR METAL COMPLEXES

The electronic spectra of Cu(II) complexes $[Cu(BBIP)_2]Cl_2$ and $[Cu(BBIB)_2]Cl_2$(**Fig.2**) showed two bands in the range (400nm, 359 nm) and (359 nm , 318 nm) which are assigned to $^2T_{2g}{}^2E_g$ and charge transfer transitions respectively and represent an octahedral geometry around the central metal ion[13] (**Table 4**).

TABLE 4: ELECTRONIC SPECTRAL DATA OF BBIP, BBTP AND THEIR COMPLEXES

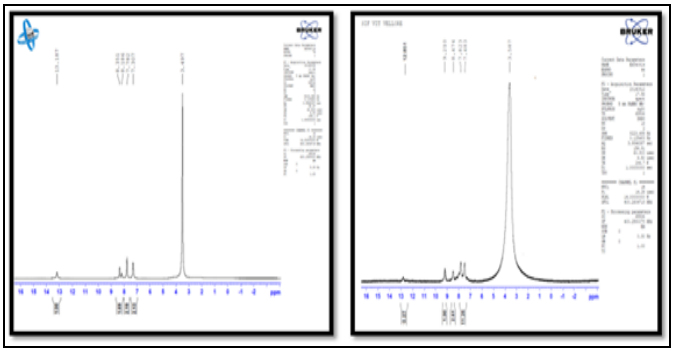
Compound	Amax (Absorption region in nm)	Band assignments	Geometry
BBIP	263 307	π-π* charge transfer transition	
BBIB	263 297	π-π* charge transfer transition	
$[Cu(BBIP)_2]Cl_2$	400 359	$2T_{2g} \rightarrow 2E_g$ Charge transfer transition	Octahedral
$[Cu(BBIB)_2]Cl_2$	359 318	$2T_{2g} \rightarrow 2E_g$ charge transfer transition	Octahedral

The room temperature μ_{eff} was found to be 1.75-1.73 BM confirming the presence of one unpaired electron for the d^9 system of copper (II).

^{1}H NMR Spectra:

The ^{1}H NMR spectra were recorded for one of the ligands - bis-(benzimidazolyl) pyridine and for its copper complex in DMSO-d^6 as solvent.

The ^{1}H NMR spectrum of the ligand (**Fig.3a**) shows signals at δ (ppm) 8.186 (s, 1H); 8.351 (s, 2H); 7.782 (s, 4H); 7.307 (s, 4H); 13.187 (s,1H, NH).



(a) (b)

FIG. 3: ^{1}H NMR SPECTRUM OF (A) BBIP AND (B) $[Cu(BBIP)_2]Cl_2$

It is observed that the NH proton signal does not disappear in the copper complex (**Fig.3b**) and all other proton signals still exist at the same positions which shows that the -NH group of the benzimidazole ring is not involved and no deprotonation and bonding of NH- nitrogen occurs with the Cu^{2+} ion

Thermal analysis:

From thermal analysis, the properties, nature of intermediates and final products of thermal decomposition of co-ordination compounds can be obtained. From TGA curves of the chelates, mass loss was calculated for the different steps and compared with those calculated theoretically for the proposed formulae based on analytical, spectral and molar conductance measurements. The observed and calculated mass losses of residues and temperatures observed in each step based on TGA and DTA curves are given in **Table 5.**

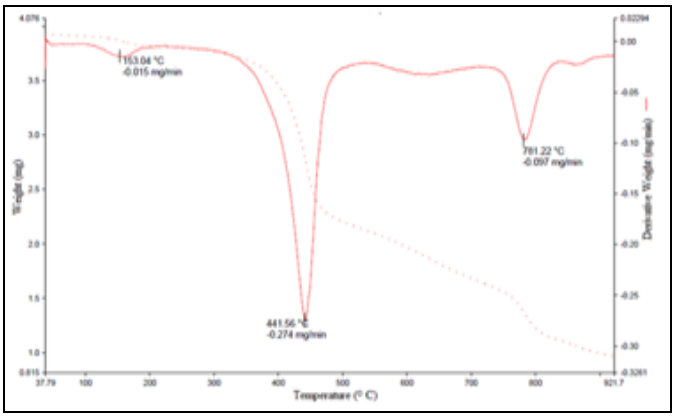


FIG.4: TGA CURVE OF $[Cu(BBIB)_2]Cl_2$

TABLE 5: THERMO GRAVIMETRIC ANALYSIS

Compound Name	Step	TGA		Assignments	Stable Product CuO(%)	Peak
		Temperature range (°C)	Mass loss (%)			
$[Cu(BBIP)_2]Cl_2$	1	220-250	11(9.364)	Chloride ions		
	2	300-350	32(30.906)	Benzimidazolyl groups	10	Endo
	3	500-540	21(20.34)	Pyridine ring	(10.506)	
$[Cu(BBIB)_2]Cl_2$	1	200-260	45(40.376)	Benzimidazolyl groups + Chloride ions	10	Endo
	2	280-320	19(20.393)	Pyridine rings	(10.534)	

The TGA curves (**Fig.4**) of the complexes show no mass loss upto 200°C which indicates the absence of lattice as well as co-ordinated water.

The $[Cu(BBIP)_2]Cl_2$ complex decomposed in three steps. First step appeared in the temperature range 220-250°C may be due to elimination of the chloride ions. The second step observed in the temperature range 300-350°C was associated with an endothermic peak, may be due to the decomposition of organic species corresponding to 32% mass loss of two benzimidazole moieties. The third step of decomposition observed between 500-540°C may be attributed to the loss of two pyridine rings with the mass loss of 21% as against the theoretical value of 20.34%. Finally the complex undergoes complete decomposition of the organic portion resulting in the formation of CuO as final stable product with residual mass of 10% (Calculated 10.501%).

The Cu(II) complex with BBIB ligand undergoes decomposition by two steps. First step occurring in the temperature range of 400-460^{O}C which may be due to the loss of two benzimidazole rings + two chlorine. The second stage of dissociation accounts for the loss of pyridine unit around 780^{O}C with a mass loss 11% as against the calculated value 10.197%. The complex then undergoes slow decomposition of the remaining ligand parts to give the metal oxide CuO with a mass of 10%.

Antimicrobial Activity*:*

The ligand BBIP and its complex $[Cu(BBIP)_2]Cl_2$ were tested for their *in-vitro* antibacterial and antifungal activities. The bacterial sub culture *Staphylococcus aureus* (gram positive) and *Escherichia coli* (gram negative) were used for antibacterial test whereas *Candida albicans* was used for antifungal test using modified Kirby-Bauer disc diffusion method [14]. The medium used is Muller-Hinton agar with 2% glucose. The diameter of the zone of inhibition was measured 24 hours after incubation at 37°C. Antibacterial and antifungal activities were estimated on the basis of the diameter of the zone of inhibition formed around the paper discs on the seeded agar plates.

TABLE 6: ANTIMICROBIAL ACTIVITY OF METAL COMPLEXES

Micro organisms		Zone of Inhibition (mm)		
		Std	BBIP	$[Cu(BBIP)_2]Cl_2$
Bacteria	*Staphylococcus aureus*	28	11	12
	Eschericia coli	13	07	09
Fungi	*Candida albicans*	18	09	12

The activities of the compounds were compared with those of standards such as ciprofloxacin for antibacterial and clotrimazole for antifungal activity (**Table 6**).

Compared with ciprofloxacin the ligand and the complex showed lesser activity against both the bacterial strains. The complex showed better activity than the ligand (**Fig.5** and **6**).

The complex showed moderate antifungal activity compared with clotrimazole whereas the ligand showed only 50 % activity.

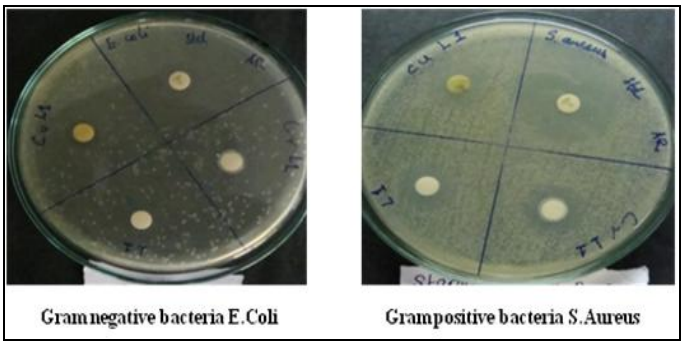


FIG. 5: ANTIBACTERIAL ACTIVITY OF (BBIP), $[Cu(BBIP)_2]$ Cl_2

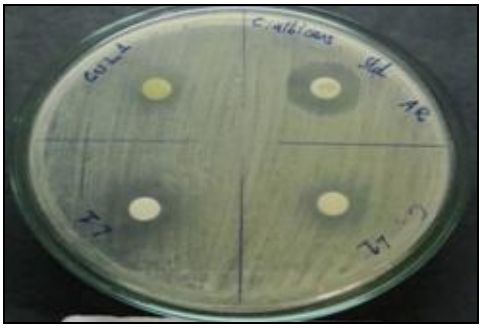


FIG. 6: ANTIFUNGAL ACTIVITY OF (BBIP), $[Cu(BBIP)_2]Cl_2$ Complexes

Anticancer Activity:

In this study the $[Cu(BBIP)_2]Cl_2$ complex was evaluated for its cytotoxic activity against breast cancer cells by MTT assay method.[15]

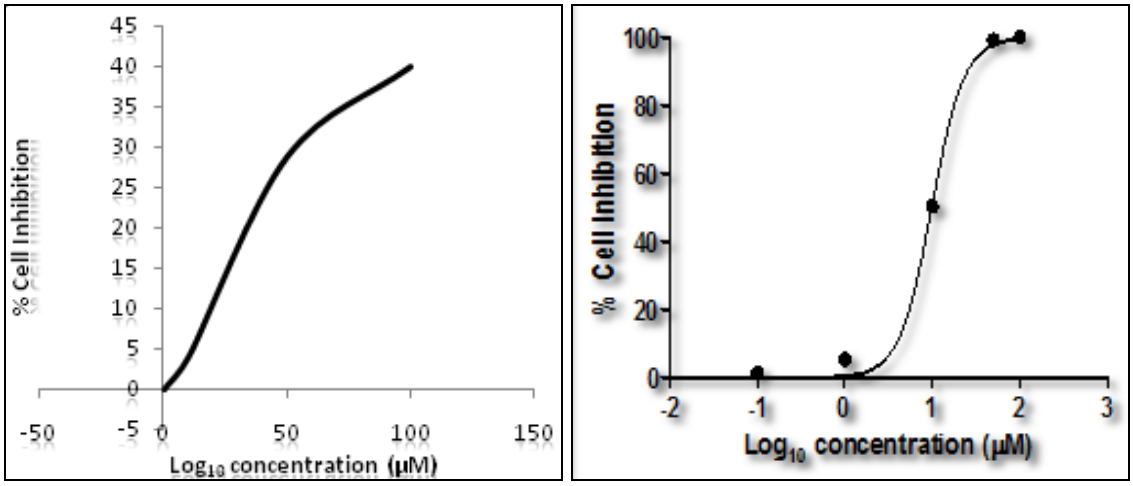
The MTT cell proliferation assay has been widely accepted as a reliable way to measure the cell proliferation rate. The data obtained by the MTT assay show that the copper(II) complex has inhibitory effects on the growth of MCF-7 breast cancer cells in dose- dependent manner as shown in **Table 8**. The metal complex has much more pronounced antiproliferative activity towards the cancer cells than the normal cells(NIH-3T3) and show IC_{50} values of 9.9 and 158.9 µg for cancer and normal cells respectively.

TABLE 7: MINIMUM INHIBITORY CONCENTRATION FOR ANTIMICROBIAL ACTIVITY

Sample name	Microorganisms		500 µg/ml	250 µg/ml	125 µg/ml	62.5 µg/ml	31.25 µg/ml	15.62 µg/ml
BBIP	Bacteria	*E.coli*	-	-	+	+	+	+
		Staphylococcus aureus	-	-	+	+	+	+
	Fungi	*C.albicans*	-	-	+	+	+	+
$[Cu(BBIP)_2]Cl_2$	Bacteria	*E.coli*	-	-	-	+	+	+
		Staphylococcus aureus	-	-	-	+	+	+
	Fungi	*C.albicans*	-	-	-	-	-	+

TABLE 8: ANTICANCER ACTIVITY OF THE SYNTHESIZED COPPER COMPLEX

Conc (µM)	% Cell Inhibition		IC 50 (µg/ml)		
	MCF 7	NIH 3T3	MCF 7	NIH 3T3	
0.1	1.386322	0.05623			
1	5.360444	0.39845			
10	50.36969	4.05781			
50	99.16821	28.78232	**9.9**	**158.9**	**R^2= 0.997**
100	100	39.85653			



(a) **(b)**

FIG. 7: GRAPHICAL REPRESENTATION OF (a) NORMAL CELL LINE NIH 3T3 (b) BREAST CANCER CELL MCF 7

Breast cancer cells have been shown to be very sensitive to additional oxidative stress produced by the complex due to their down-regulated antioxidant defense enzymes leading generally to apoptotic death [16]. The graphical representation is given in **Fig.7**.

SUMMARY AND CONCLUSION: From the spectral and analytical data an octahedral geometry has been proposed for the complexes with 1:2 metal:ligand stoichiometry. The complexes showed good cytotoxic activity against MCF 7 breast cancer cell.

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