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Synthesis, EPR and biological evaluation of four and five co-ordinate heterocyclic base adducts derived from 5-chloro-2-hydroxy acetophenone thiosemicarbazone

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ABSTRACT

Heterocyclic base adducts of copper (II) complexes have been synthesized by the reaction of copper (II) chloride with 5-chloro-2-hydroxy acetophenone thiosemicarbazone in presence of heterocyclic base like pyridine (py), 2,2'-bipyridine (bipy), 1,10-phenanthroline (Phen), α/β-picoline. Thiosemcarbazone has been characterized by ^{13}C, ^{1}H NMR as well as IR, electronic spectra. The magnetic and spectroscopic data indicate a square planner geometry for the four coordinate and a distorted square pyramidal for five coordinate complexes. The thiosemicarbazone and its copper (II) complexes show growth inhibitory activity against Pseudomonas Putida, Escherichia Coli, Aspergillus Niger and Candida Albicans. Thiosemicarbazone and its copper (II) complexes have also been found antioxidant.

Keywords: Thiosemicarbazone, Bioactive metal complexes, antimicrobial, antioxidant activity.

INTRODUCTION

Thiosemiarbazones are sulfur-donor Schiff base ligands that are useful for transition metal ions.The biological activities of thiosemicarbazones are related to their metal complexing ability.thiosemicarbazone Schiff bases are important class of compounds in the medicinal and pharmaceutical fields [1]. In coordination chemistry, Schiff bases have been used as chelating ligands and their metal complexes have been important for researchers.N and S as donor atoms play a key role in the coordination of metals at the active sites of many metallobiomolecules [2]. The importance of metal ions in biological systems is well established. Among the biological important metal ions,Cu (II) ion involved in a large number of distorted complexes [3]. Considerable attention has been paid to metal complexes of Schiff bases containing nitrogen and other donor atoms in past two decades [4,5]. The metallic complexes and their biological applications have been studied in Bioorganometallic chemistry [6]. Many metal complexes may serve as models for biologically important species and because of this the development of the field of bioinorganic chemistry has increased the interest in cchiff base complexes [7-10]. Antioxidants are studied for their capacity to protect organisms and cells from damage induced by oxidative stress. Scientists have become interested to synthesize or obtain new compounds from natural sources which could provide active components to prevent or reduce the impact of oxidative stress on cells [11].

Copper is an essential element for life.It is associated with number of copper-dependent enzymes that play key role in biological processes [12,13]. In plasma elevated copper levels can be important for the etiology of some illness [14]. Copper ions are closely involved in neurodegenerative disorders [15-17] especially in Parkinson's disease [18,19]. Copper complexes have been found to possess varies activites such as antiulcer [18], antiamoebic [19], antidiabetic [20], anticonvulsant [21], anti-inflamatory [22-24], antimicrobial [25] and antitumor [26]. Sulfonamide copper complexes show antimicrobial activity against both types,Gramm (+) (*Staphylococcus Aureus, Bacillus*

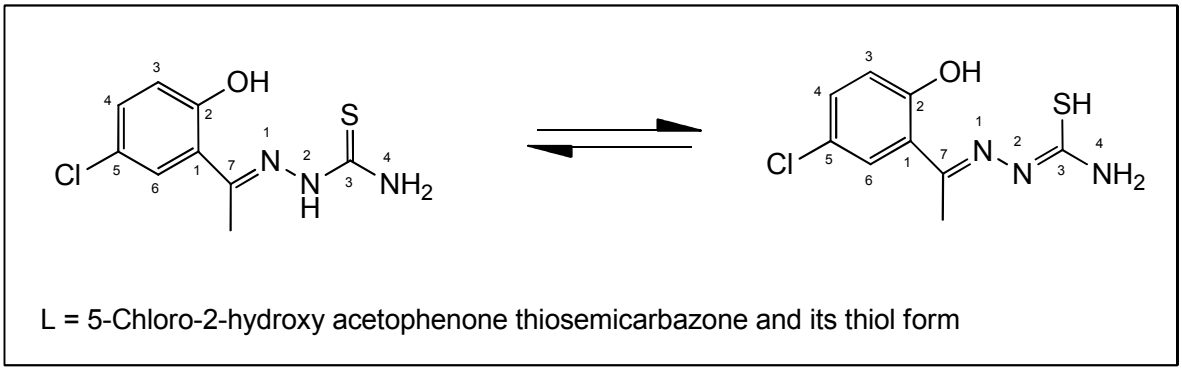
Subtilis) and Gramm (-) (*Escherichia Coli, Pseudomonas Euruginosa*) [27]. A slightly higher activity is found in Gramm (-) bacteria [28].

Here we know report synthesis, spectral characterisation and biological studies of four and five coordinate complexes of copper (II) with 5-chloro 2-hydroxy acetophenone thisemicarbazone.

MATERIALS AND METHODS

Materials and instrumentation

The thiosemicarbazone was synthesized by refluxing 5-chloro 2-hydroxy acetophenone and thiosemicarbazide in the mole ratio 1:1 for 3-4 hours, 2-3 drops of conc. H_2SO_4 was added as a dehydrating agent. The product obtained was filtered and washed with cold ethanol and then diethyl ether. It was recrystalised by hot ethanol and dried over P_2O_5 in vacuum [29].



L = 5-Chloro-2-hydroxy acetophenone thiosemicarbazone and its thiol form

Preparation of complex

The complex Cu.L.Cl (Where, L is 5-Chloro 2-hydroxy acetophenone thiosemicarbazone) was synthesized by refluxing hot ethanolic solutions of $CuCl_2.4H_2O$ and ligand (L) in the mole ratio 1:1 for 7-8 hours. The complex obtained was filtered and washed with hot water, cold ethanol and diethyl ether and dried over P_2O_5 in vacuum.

Preparation of adducts

The complex Cu.L.B (Where B is heterocyclic base like pyridine, 2-2'-bipyridine, 1,10 phenanthroline, α-picoline, β-picoline) was synthesized by refluxing hot ethanolic solutions of $CuCl_2.4H_2O$ and ligand and heterocyclic base in the mole ratio 1:1:1 for 7-8 hours. The adduct obtained was filtered and washed with hot water, cold ethanol and diethyl ether and dried over P_2O_5 in vacuum [30].

Physical measurements

Magnetic measurements were carried out in the polycrystalline state by Faraday method. High purity $[Co(SCN)_4]$ was used as standard. Diamagnetic corrections were made by Pascal's constants. IR spectra were recorded in the range 4000-200 cm^{-1} range using KBr discs. NMR spectra were recorded in the mixture of $CDCl_3$ and DMSO-d_6 (1:1 v/v) with a Bruker AC-300F 300MHz spectrometer. Conductivity measurements were carried out on Conductivity Bridge, Systonics conductivity meter-304. Refluctance spectra were measured on Systonics UV-visible double beam spectrophotometer-2201.

RESULTS AND DISCUSSION

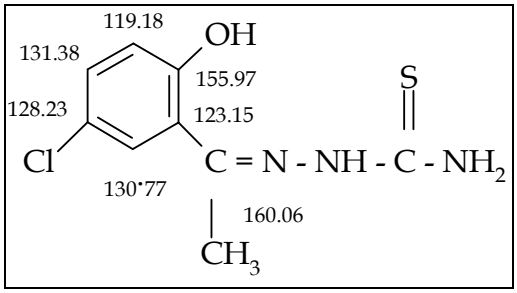
The colours, elemental analysis, stoichiometries of ligand and its complexes are presented in Table 1.1. Elemental analysis data are consistent with 1:1 ratio of metal ion, thiosemicarbazone for complex and 1:1:1 ratio for metal thiosemicarbazone and heterocyclic base for all adducts. The complex and all adducts are insoluble in most of the common polar and non polar solvents. They are soluble in DMF in which conductivity measurements were made (27^0C), showing all complexes to be non electrolyte [31].

The magnetic susceptibility of complex and adducts carried out at room temperature (27^0C) in polycrystalline state fall in the range of 1.80-2.10 B.M (Table 1.1). These are very close to the spin-only value of 1.73 B.M. for d^9. NMR signals at 10.6, 3.39 ppm are assigned to – OH, - CH_3 protons respectively.

L does not show any peak corresponds to S-H proton, indicating it exists in thioketo form. Absence of ^{2}NH proton signal suggests enolisation of ^{2}NH – C = S group to ^{2}N=C-SH. Little low field position of ^{4}NH (7.8 ppm) could be

attributable to the deshielding caused by – N = C< of the system N=CSH = NH. Aromatic protons show multiples at 6.9, 7.25 and 7.50 ppm range.

^{13}C-NMR (DMSO-D_6): δppm 119.18 (C=C); 131.38 (C=C); 128.27 (C=C-Cl); 130.77 (C=C); 123.15 (C=C); 155.97 (C=C-OH), 160.06(C=N); 179.80 (C=S); 31.03 (NH-CH_3)



Anal. Calcd for $C_9H_{10}ClN_3OS$ ESI-MS M/Z, ion 243.70 M^+; C, 44.35 %, H, 4.14 %; N, 17.24 %, S, 13.16 % Found : ESI-MS m/z,ion M^+ 243.80 ;C, 44.03 %; H, 4.36; N, 17.62; S, 13.33 %

Table 1.1 : Physicochemical analysis of synthesized compounds

Compounds	Colour	Empirical Formula	Molar conductance $Ohm^{-1}cm^2mole^{-1}$	Magnetic Moment B.M.	Elemental Analysis Found (Calculated) %				
					Metal%	%C	%H	%N	%S
L	Faint yellow	$C_9H_{10}ClN_3OS$			-	44.03 (44.35)	4.36 (4.14)	17.62 17.24)	13.33 (13.16)
Cu-L.Cl	Brown	$C_9H_8N_3SCl_2OCu$	41.6	1.84	18.87 (18.59)	31.13 (31.63)	2.12 (2.65)	12.71 (12.30)	9.21 (9.38)
Cu-L.Py	Brown	$C_{14}H_{13}N_4SClOCu$	93.6	1.89	15.72 (16.53)	43.42 (43.75)	3.34 (3.24)	14.82 (14.62)	8.81 (8.52)
Cu-L.Bipy	Brown	$C_{19}H_{16}N_5OSClCu$	72.8	2.00	13.83 (13.77)	49.14 (49.46)	3.26 (3.50)	15.55 (15.18)	6.72 (6.95)
Cu-L.Phen	Brown	$C_{21}H_{16}N_5SClOCu$	62.4	2.07	13.20 (13.08)	51.72 (51.96)	3.26 (3.32)	14.94 (14.63)	6.32 (6.60)
Cu.L.α-Pico	Brown	$C_{15}H_{15}N_4SClOCu$	41.6	1.86	15.09 (15.95)	45.62 (45.22)	3.34 (3.80)	14.73 (14.06)	8.44 (8.05)
Cu-L.β-Pico	Brown	$C_{15}H_{15}N_4SClOCu$	72.8	1.87	15.72 (15.95)	45.22 (45.22)	3.54 (3.40)	14.51 (14.06)	8.84 (8.05)

UV Studies:

UV-visible spectra of metal complexes in DMF solution and solid state indicate that all complexes have same structure both in solid state and solution state (Table 1.2). The thiosemicarbazone and Cu (II) complexes have band n- π* at 32000 cm^{-1} and π- π*band at 40,000 cm^{-1}. The n- π* band located below 30,000 cm^{-1} in uncomplexed thiosemicarbazone is observed at about 30,000 cm^{-1} in Cu (II) complexes. There are two L-M charge transfer bands are observed at 26,000 and 22000-29000 cm^{-1}. The higher energy band is due to S-Cu (II) transitions [32]. The band 22000-29000 cm^{-1} is due to phenoxy O-Cu (II) transitions [33]. The d-d bands of Cu (II) complexes are observed in the range 13,000-17,000 cm^{-1}. This shows square planer structure [34,35]. The solid electronic spectra of Cu.Lbipy and Cu.LPhen show d-d bands at about 12600 cm^{-1} and 18400 cm^{-1}. These bands show square pyramidal structure [36].

Table 1.2: Electronic spectral assignments (cm^{-1})

Compound	Mode	d-d	L→M	n→π*	π→π*
L	DMF	-	-	2597 28571	40860
Cu-L.Cl	DMF	17825	28169 25641	30864 35461	44843 38610
Cu-L-Py	DMF	17094	27027 25641	31056 34483	44444,40816,38023
Cu-L-Bipy	DMF	18692 15332	25974 22321	30960 35461	45249,40486
Cu-L-Phen	DMF	17544 13699	25641 22989	30581 25641	42553 38023
Cu-L-α Pico	DMF	19194	25907 23585	33113 31250	43478 37736
Cu-L-β Pico	DMF	17391	25641 22727	33333 31056	41667 38023

(absorbance)

IR Studies:

The absence of any band in 2600-2800 cm^{-1} region of the IR spectrum of L shows the absence of thiol tautomer in the solid state [37]. Coordination of the azomethine nitrogen $^{7}C=N^{1}$ shift the frequency to the lower side by 20-40 cm^{-1} [38] as the band shifts from 1624 cm^{-1} in uncomplexed thiosemicarbazone to 1560 cm^{-1} in the spectra of complexes. A new band at 422-463 cm^{-1} confirms the coordination of azomethine nitrogen [39-42]. The increase in frequency of ^{1}N-^{2}N is due to the increase in double bond character off-setting the loss of electron density via donation to the metal. This confirms the coordination of the ligand through the azomethine nitrogen atom. The band ^{2}N-H of thiosemicarbazone disappears in the complexes indicating the deprotonation of the ^{2}N-H proton. A thioamide band which is partly due to C=S found at 1374 and 768cm^{-1} shifted to lower side in complexes indicating coordination through thiolate sulfur [43]. A new band in 309-355 range due to Cu-S is another indication of the involvement of sulfur coordination. The phenolic oxygen occupies the third coordination on loss of OH protons. These causes of shifting of ν(CO) 1281 cm^{-1} in uncomplexed thiosemicarbazone to lower side in the complexes by 50-61 cm^{-1}. The new bands due to Cu-O in complexes in the range 500-525 cm^{-1} confirm coordination through oxygen. The heterocyclic base nitrogen atom(s) occupies fourth (and fifth) coordination site. The band is assigned for ν (Cu-N) due to heterocyclic base in 260-275 cm^{-1} range in the spectra of all complexes [44-46]. The characteristics bands of coordinated heterocyclic bases are also observed in IR spectra of all complexes[47-49] (Table 1.3).

Table 1.3: Infrared Spectroscopic Assignment (cm^{-1})

Compounds	νOH	ν^{2}NH	νCO	νCN	νCS	N (C=N-N=C)	νNN	νMO	νMN.H.B	νMS	$\nu M^{1}N$	Bands due to heterocyclic bases
L	3147	2963	1281	1624	758,1374	-	1049	-		-	-	-
Cu.LCl	-	-	1231	1612	747,1327	1528	1113	525	-	315	424	-
Cu.LPy	-	-	1230	1589	730,1281	1535	1113	500	260	324	464	1281,618,463
Cu.LBi	-	-	1225	1560	750,1310	1559	1100	521	265	332	426	1526,1020,765
Cu.L.Phen	-	-	1223	1619	725,1303	1589	1101	525	266	355	453	1512,725.526
Cu.L.α-Pico	-	-	1230	1596	676,1310	1534	1111	520	270	324	463	1310,676,621
Cu.L.β-Pico	-	-	1230	1577	695,1319	1565	1107	500	274	309	422	1107,695,422

TGA Analysis

The TGA curves of the copper (II) complex and adducts were carried out within a temperature range from room temperature up to 800^{0}C. The data from gravimetric analysis clearly indicated that the decomposition of complex proceed in several steps. Hydrations of water molecules were lost in between 30-110^{0}C. There is no change up to ~ 200^{0}C after that there is break in the curves due to evaporation of 0.5 molecule of organic ligand, the remaining ligand is removed from the coordination sphere at ~ 600^{0}C. Finally the metal oxides were formed above 600^{0}C. The decomposition was complete at ~ 780^{0}C.

It has been found that Cu (II) complex was stable up to 200^{0}C except CuL.phen andCuL.β-pico and decomposition started at this temperature was completed at about 380^{0}C (Table 1.4). The second step temperatures are in the range of 317-407^{0}C. The solid residue was CuO [50].

The complexes prepared with different metals decompose in two steps. It is evaluated that the coordination of metal ion to ligand is responsible for the thermal stabilities of metal complexes [51].

Table 1.4: TGA analysis data

Complex	First step	Mass loss %	Second step	Mass loss %	Residue	Temperature	% (Cal) found
Cu.L.Cl	200	1.23	300.00	45.34	CuO	778	22.92(23.27)
Cu.L.Py	200	2.70	380.76	57.52	CuO	780.76	21.22(20.69)
Cu.L.Bipy	211.54	7.37	319.23	55.02	CuO	776.92	18.00(17.23)
Cu.L.Phen	159.25	6.45	300.00	59.12	CuO	785.18	17.22(16.38)
Cu.Lα.Pico	214.81	25.12	318.51	40.70	CuO	782.10	19.02(19.96)
Cu.L.β-Pico	115.38	1.70	311.53	46.32	CuO	780.76	18.99(19.96)

Table 1.5 EPR analysis

Complex	g_{11}	$g_{\perp}$	g_{av}	**G**	A_{11}	$A_{\perp}$	**R**	**f**	α^2	β^2	K_{II}	K_o
Cu L_1 Cl	2.21	2.14	2.12	1.5	185	50	0.53	119	0.514	0.719	0.370	0.367
Cu L_1 Py	2.20	2.12	2.11	1.67	170	30	0.80	129	0.486	0.766	0.372	0.279
Cu L_1 bipy	2.16	2.09	2.09	1.78	160	20	0.88	135	0.444	0.732	0.325	0.259
Cu L_1 phen	2.18	2.12	2.10	1.50	170	20	0.55	128	0.472	0.730	0.345	0.266
Cu L_1 □–pico	2.20	2.12	2.11	1.67	170	30	0.73	129	0.472	0.812	0.383	0.263
Cu L_1 □–pico	2.20	2.11	2.11	1.82	170	50	0.90	129	0.472	0.812	0.383	0.308

Electron Paramagnetic Resonance Spectra :
EPR spectrum of complexes was carried out in DMF at 77 K. The values of g_{11}, $g_{\perp}$, g_{ar}, A_{11}, $A_{\perp}$ R, f, G, α^2, β^2 and γ^2 are listed in Table No. 1.5

The EPR parameters of Cu (II) complexes obtained in DMF at liquid nitrogen temperature (LNT) and presented in Table No.1.5. In frozen DMF four coordinate complexes show well resolved four copper hyperfine lines, characteristic of monomeric Cu (II) complexes and nine superhyperfine lines due to azomethine nitrogen and nitrogen atom of the coordinated heterocyclic base. Since superhyperfine coupling by nitrogen of the heterocyclic base is observed, the coordinated heterocyclic base is found to be coplanar with the ONS bichelate rings [52]. So a square planar structure can be assigned for CuL . B (B = py, α/β – pico) complexes. $g_{11} > g_{\perp}$ suggests a distorted square pyramidal structure and rules out the possibility of a trigonal bipyramidal structure which would be expected to have $g_{\perp} > g_{11}$. Thus the coordination in CuL B, (B = 1, 10 phen, bipy) comprises one phenanthroline/ bipyridyl nitrogen, the azomethine nitrogen, the thiolate sulphur, the phenolate oxygen of the thiosemicarbazone form the base of the pyramid and the remaining phenanthroline/2-2' bipyridyl nitrogen occupies the axial position. The variations in g values indicate that the geometry of the compound which is affected by the nature of the coordinating gegenions. The geometric parameter G is calculated by the relation $G = (g_{11-2}/g_{\perp-2})$ is a measure of the exchange interaction between copper centres in the polycrystalline compound. If G > 4, the exchange interactions is negligible and if it is less than 4 exchange interaction is indicated in the complex. All complexes have values $g_{11} > g_{\perp} > 2$ and G values falling within this range 1 to 3 are consistent with a $dx^2 – y^2$ ground state corresponding to square planer or square pyramidal geometry. For all complexes the lowest g value is 2.01 indicating a rhombic square coplanar or distorted square based pyramidal geometries. The rhombic spectral values R is calculated by the relation $R = g_2 – g_1/g_3 – g_2$. If R > 1, a predominant $dx^2 – y^2$ ground state is present and when R= 1 then the ground state is an approximately equal mixture of dz^2 and $dx^2 – y^2$, the structure is intermediate between square planar and trigonal bipyramidal geometries. For all complexes R < 1 suggests a distorted square pyramidal or square planar geometry with a $dx^2 – y^2$ ground state. The empirical factor $f = g_{11}/A_{11}$ (cm) is an index of tetragonal distortion. The value may vary from 110 to 135 for square planer complexes. In presence of tetragonally distorted structures the values can be higher. The orbital reduction factor K11 was calculated by the relation $K11 = \alpha^2 \beta^2$. According to Hathway [53] for pure σ bonding $K_{11} = K_{\perp} = 0.77$. For all compounds $K_{11} \approx 0.32 \sim 0.40$. The contribution of s electrons to the hyperfine interaction can be estimated by the value of Fermi contact hyperfine interaction term (K_0). K_0 is a dimensionless quantity and is generally found to have a value of 0.3. the values calculated for all complexes are in the range of 0.25 to 0.36. The bonding parameters α^2, β^2 are regarded as measures of the covalency of the in plane σ bonds, in plane π bonds α^2, β^2 values are much less than 1.0 which is expected for 100 % ionic character of the bonds, and become smaller with increasing covalent bonding. The evaluated values of α^2, β^2 of the complexes are consistent with both strong in plane σ and in–plane π bonding. For all complexes, the g_{11} values are nearly same indicating that the bonding is dominated by the thiosemicarbazone moiety rather than the heterocyclic bases. The g_{11} values are less than 2.3, is an indication of significant covalent bonding in the complexes [54, 55].

Biological activity (Agar well diffusion method)
The antibacterial activity was determined using the agar well diffusion method. The well was dug in the media with a sterile borer and eight-hour bacterial inoculums containing ca. 104 - 106 colony-forming units (CFU)/ml was spread on the surface of the nutrient agar using a sterile cotton swab. The recommended concentration of the best sample (2 mg/ml in DMSO) was introduced into respective wells. Other wells containing DMSO and the reference antibacterial drug served as negative and positive controls, respectively. The plates were incubated immediately at 37°C for 20 h. The activity was determined by measuring the diameter of the inhibition zone (in mm) showing by the hanging drop method. Biological activity was measured in two different molar concentrations (10^{-3}M, 10^{-4} M). The chelate Cu.L.phen showed maximum activity against bacterial and fungal species than free ligand. The results of antibacterial and antifungal studies are given in Table 1.5. Out of these seven compounds tested, Cu.L.phen was found more active against four cultures. The 5-chloro 2-hydroxy acetophenone thiosemicarbazone was found less active than its copper complex and adducts. Thus increase in coordination number from four to five in copper complexes increases microbial activity [56].

The [Cu (L)(Phen)] chelate exhibited high activity against all the bacteria and fungi. Thus it is evaluated that the coordination of metal ion to ligand is responsible for high biological activity. It has ben observed that the % activity index increases on dilution.

Table 1.6 % Activity index of L , Cu (II) complexes and standered

Compounds	*Pseudomonas Putida*		*Escherichia Coli*		*Aspergillus Nigar*		*Candida Albicans*	
	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M
L	29.41	25.00	42.30	32.26	55.56	47.36	64.71	50.00
Cu L.Cl	44.12	38.89	50.00	38.71	72.22	63.16	82.35	65.00
Cu LPy	50.00	44.44	50.00	38.71	72.22	63.16	82.35	65.00
CuLbipy	41.18	36.11	53.85	41.94	83.33	73.68	88.23	70.00
CuLPhen	47.06	41.67	61.54	48.39	88.89	78.95	94.12	75.00
CuL α-pico	38.24	33.33	46.15	35.48	66.67	57.89	70.59	55.00
CuL β-pico	41.18	36.11	46.15	35.48	61.11	52.63	76.47	60.00
Standered	100	100	100	100	100	100	100	100
$CuCl_2.4H_2O$	79.41	66.67	92.31	83.87	138.89	126.32	123.53	111.11

(Std-amphiciline,bicip)

Figure1.6 A

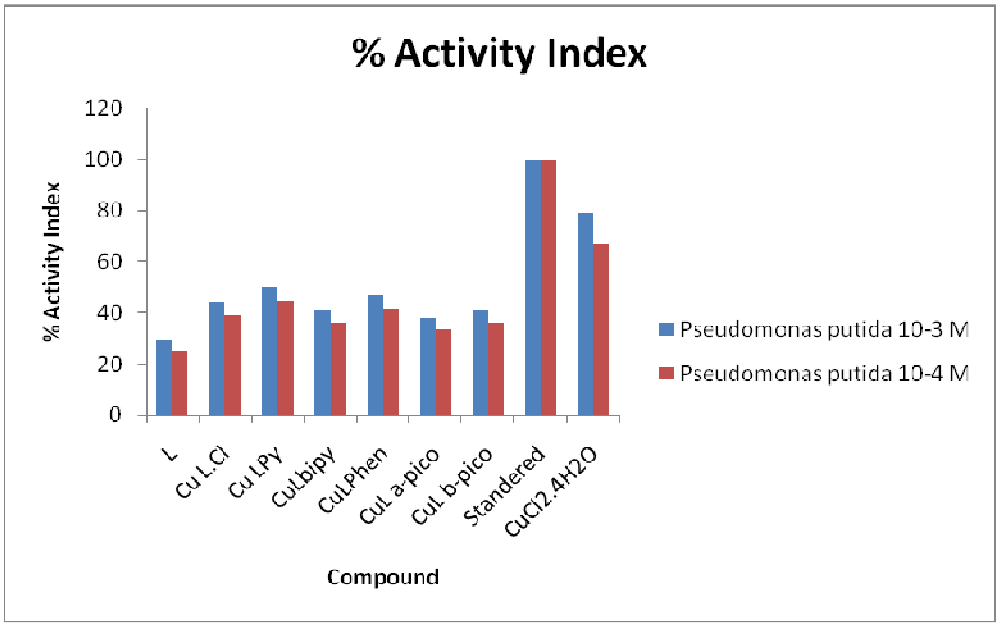


Figure 1.6 B

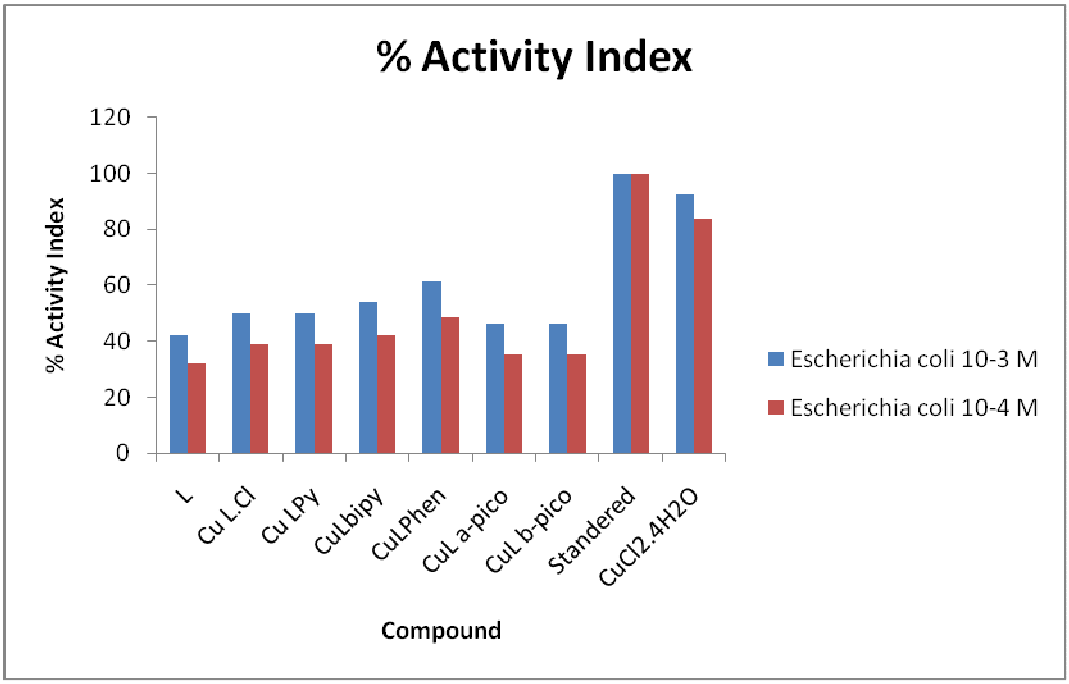


Figure 1.6 C

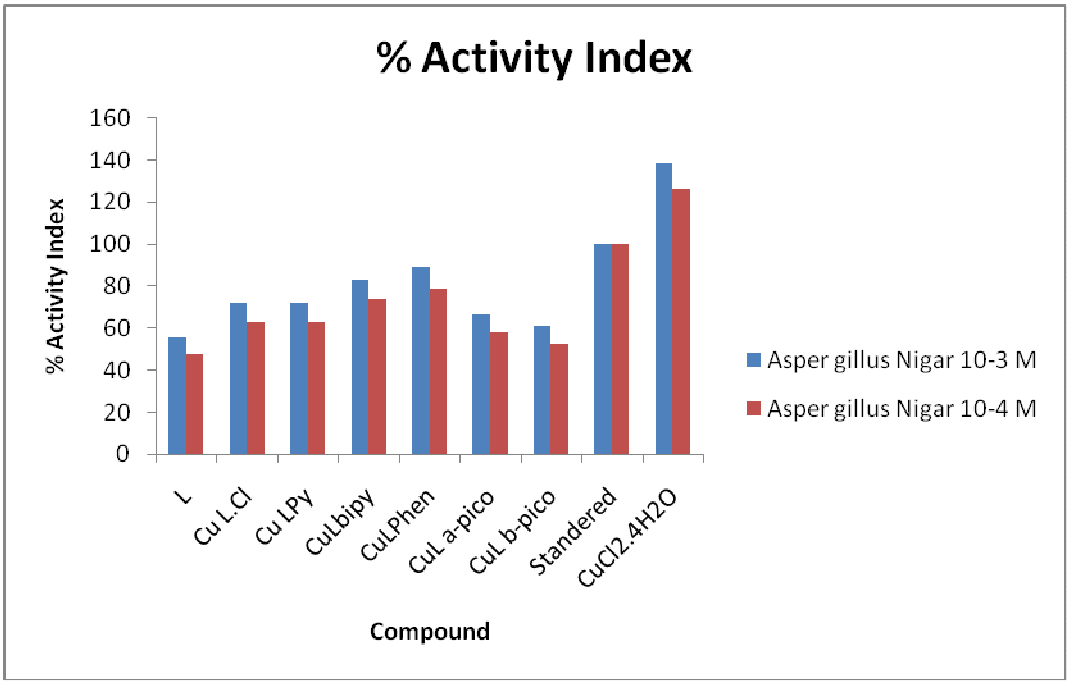
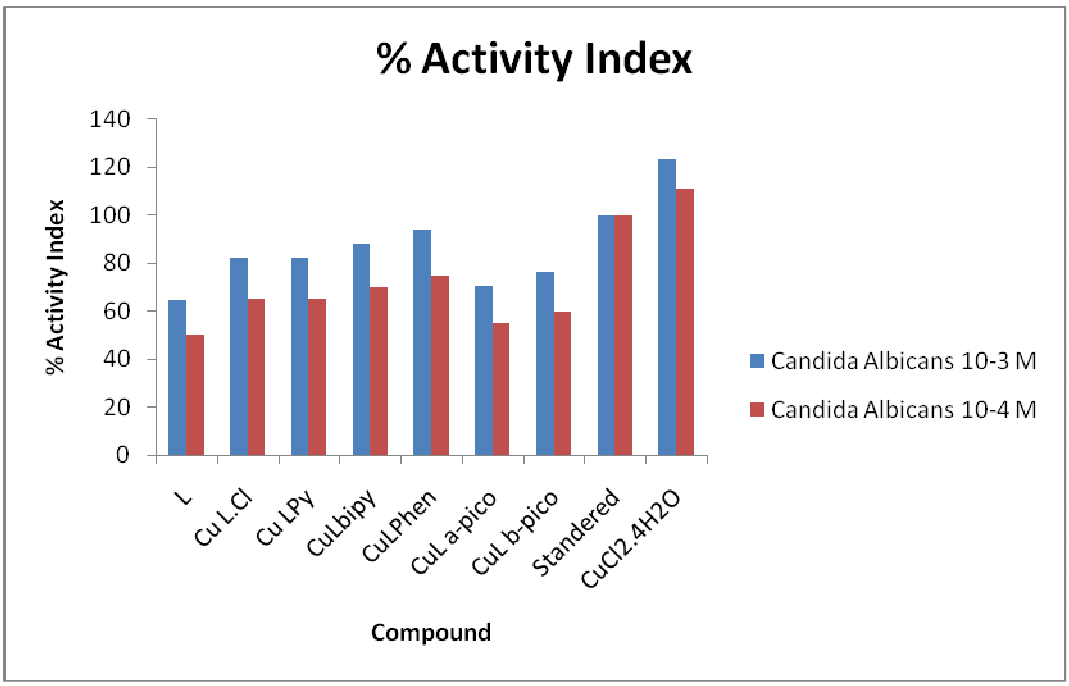


Figure 1.6 D



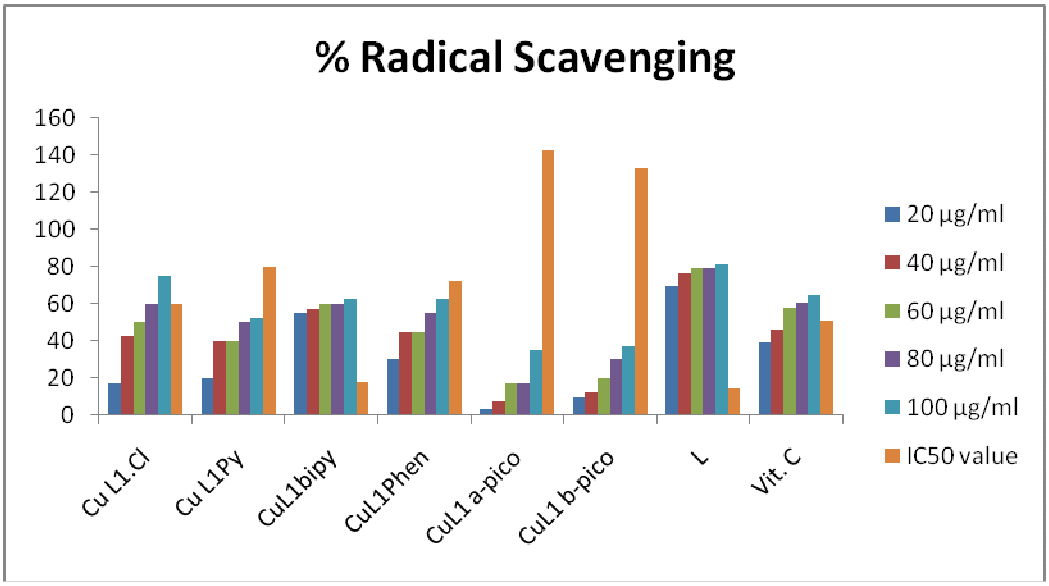
Antioxidant activity:

The antioxidant activity of ligand and complexes was assessed on the basis of the radical scavenging effect of the stable DPPH free radical (Table 1.7). About 100 _l of each solution and standard (from 21 mg/ml to 21_g/ml) was added to 2 ml of DPPH in methanol solution (100_M) in a test tube. After incubation at 37 ^{0}C for 30 min, the absorbance of each solution was determined at 517 nm using spectrophotometer. The corresponding blank readings were also taken and the remaining DPPH was calculated. IC_{50} value is the concentration of the sample required to scavenge 50% DPPH free radical. Lower the absorbance of the reaction mixture indicated higher free radical scavenging activity [57].

Table 1.7 % Radical scavenging exhibited Cu (II) complexes

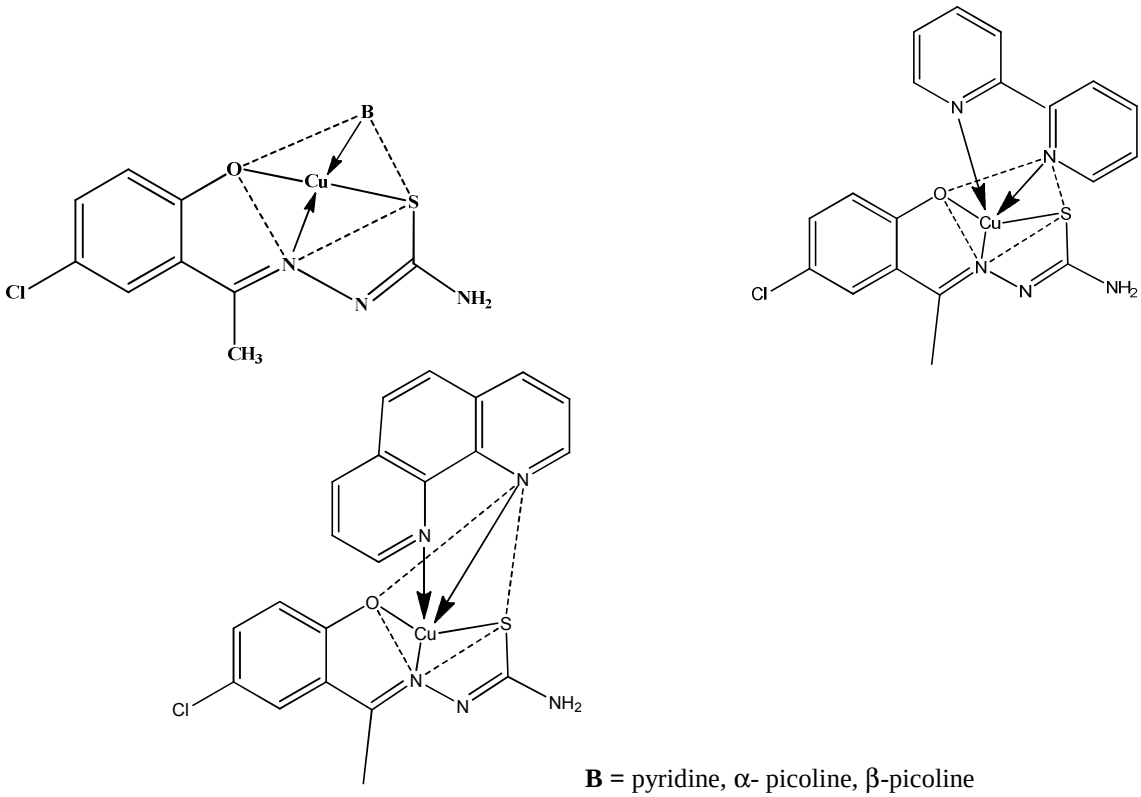
Complex	20 µg/ml	40 µg/ml	60 µg/ml	80 µg/ml	100 µg/ml	IC_{50} value
Cu L.Cl	17.50	42.50	50.00	60.00	75.00	60.00
Cu LPy	20.00	40.00	40.00	50.00	52.20	80.00
CuLbipy	55.00	57.50	60.00	60.00	62.50	18.18
CuLPhen	30.00	45.00	45.00	55.00	62.50	72.72
CuL α-pico	3.33	7.50	17.50	17.50	35.00	142.85
CuL β-pico	10.00	12.50	20.00	30.00	37.50	133.33
L	69.76	76.74	79.06	79.06	81.39	14.33
Vit. C (standard)	39.53	46.51	58.13	60.46	65.11	51.00

Figure 1.7



Effect of synthesized compounds on DPPH assay

Expected structure :



B = pyridine, α- picoline, β-picoline

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