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Synthesis, physicochemical and biological evaluation of Co (II) complexes derived from 5-chloro-2-hydroxy acetophenone *N*(4) methyl thiosemicarbazone

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ABSTRACT

Heterocyclic base adducts of cobalt (II) complexes have been synthesized by the reaction of cobalt (II) chloride with 5-chloro-2-hydroxy acetophenone N(4) methyl thiosemicarbazone in presence of heterocyclic base like pyridine (py), 2,2'-bipyridine (bipy), 1,10-phenanthroline (Phen), α/β-picoline. The synthesized thiosemcarbazone has been characterized by ^{13}C, ^{1}H NMR as well as IR, electronic spectra. The magnetic and spectroscopic study show octahedral geometry for six coordinate, square planner geometry for the four coordinate and a distorted square pyramidal for five coordinate complexes. The thiosemicarbazone and its cobalt (II) complexes exhibit growth inhibitory activity against Pseudomonas Putida, Escherichia Coli, Aspergillus Niger and Candida Albicans. Thiosemicarbazone and its cobalt (II) complexes have also been found antioxidant.

Keywords: Thiosemicarbazone, Bioactive metal complexes, Antimicrobial, Antioxidant activity.

INTRODUCTION

Thisemicarbazone moiety is planar and adopts an extended (*E*) configuration. This planar configuration is due to extensive electron delocalization throughout the moiety. The ability of thiosemicarbazones and thiosemicarbazides to form metal chelates is due to *N,S* donors [1]. The total charges smearing on the sulfur atom due to electron delocalization helps in complexation with positively charged metal ions. Another electron rich hydrazine *N* atom is also involed in the complex formation with metal ions. *S* and *N* atoms chelates to metal ion of the biological molucal and possess the pharmaceutical activity of this molecule. Thisemicarbazones also possess second order nonlinear optical properties which have applications such as optical frequency conversion [2,3] and optical parameter oscillator.

Thiosemicarbazones are the compounds used in the treatment of many diseases, for example cancer and its development is in progress [4,5]. The utility of thiosemicarbazones includes antineoplastic,antibacterial,antiviral and antifungul activity [6]. Thiosemicarbazones as ligands allow them to give rise to a great variety of coordination modes [7]. Thiosemicarbazones are typically excellent chelators of transition metals, such ability for metal chelation is an attractive strategy in developing anticancer drugs because of high requirement of neoplastic cells for essential metals needed in groth and proliferation [8]. Ligands with soft donors such as sulfur and nitrogen lead to compounds that can redox cycle and induce a "double punch", namely, marked chelation and redox activity [9]. High spin

octahedral Fe (III) complexes with peridoxal semi-, thiosemi- and *S*-methylisothiosemicarbazones were reported [10]. Thiosemicarbazones are versatile tridentate ligands having the ability to bind transition metal ions by bonding through sulfur and thdrazinic terminal nitrogen atoms [11]. The complexes of hinikithiol, 4-isopropyl tropolone with Co(II) metal ion appeared actie than Cu(II) complexes [12]. The octahedral Co(II) complexes showed activity against Gram(+) and Gram(-) bacteria but less than free ligand alone [13]. Co (II) complexes of imidazole-2-carbaldehyde semicarbazone were found active against yeast S, cerevisiae, tropicalis, Alternaria or selerotinia [14]. The Co(II) 2-methylthionicotinate complexes of N-heterocyclic ligands were found antibacterial and antifungul. The complexation of the nicotinate derivatives led to an increase of their biological activity [16]. Research has been done in developing Co(II) complexes of cshiff bases for their antimicrobial [17-19] and antifungul properties [20].

We know report synthesis, spectral characterization and biological studies of four and five and six coordinate complexes of Co (II) with 5-chloro 2-hydroxy acetophenone *N*(4) methyl thisemicarbazone.

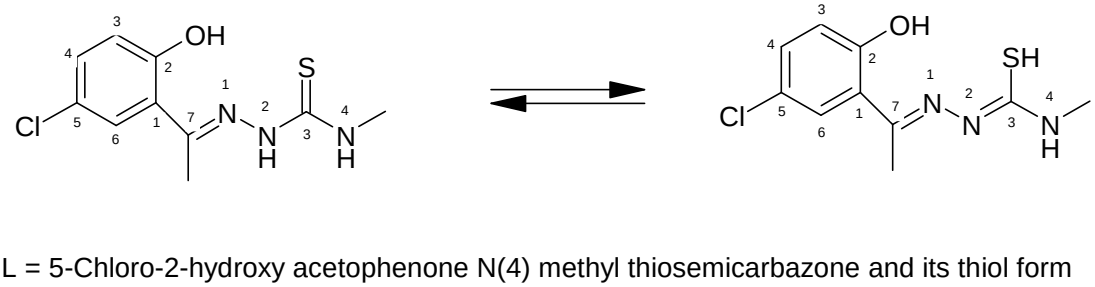
EXPERIMENTAL SECTION

Materials and instrumentation

All the synthetic reagents used are of A.R. grade and solvents were distilled before use. 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 disc. NMR spectra were recorded in the mixture of $CDCl_3$ and DMSO-d_6 (1:1 v/v) with a Bruker AC-300F 300 MHz 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.

Preparation of 5-chloro-2-hydroxy acetophenone *N*(4) methyl thiosemicarbazone (Ligand)

The *N*(4) thiosemicarbazone was synthesized by refluxing 5-chloro 2-hydroxy acetophenone and *N*(4) methyl 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 [21].



L = 5-Chloro-2-hydroxy acetophenone N(4) methyl thiosemicarbazone and its thiol form

Preparation of complex

The complex Co.L.$(H_2O)_3$ (Where, L is 5-Chloro 2-hydroxy acetophenone *N*(4) methyl thiosemicarbazone) was synthesized by refluxing hot ethanolic solutions of $CoCl_2.6H_2O$ 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

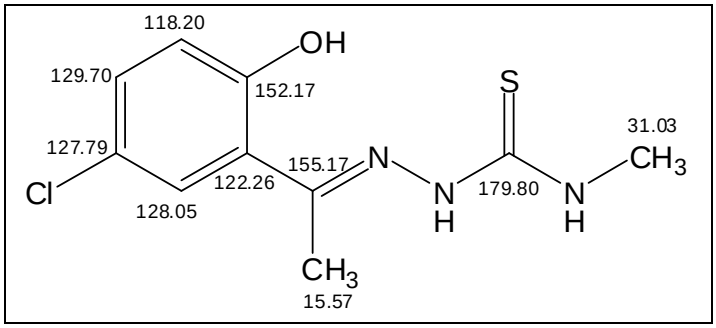
The complex Co.L.B (Where B, is heterocyclic base like pyridine, 2-2'-bipyridine, 1, 10 phenanthroline, α-picoline, β-picoline) was synthesized by refluxing hot ethanolic solutions of $CuCl_2.4H_2O$ and ligand and heterocyclic base in the mole ratio 1:1:1 for 7-8 hours. The adduct obtained was filtered and washed with hot water, cold ethanol and diethyl ether and dried over P_2O_5 in vacuum [22].

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 [23].

Magnetic susceptibility of all complexes was measured in polycrystalline state. The magnetic susceptibility fall in the range 2.59-2.62 for square planer complexes CoLPy, CoL-α-pico, CoL-β-pico [24]. The magnetic moments of CoL bipy and CoLphen are very low and lie in the range 2.68-2.88 B.M. Cobalt complexes with *S* and *N* chelating agents were reported [25, 26]. The high spin octahedral complex $CoL(H_2O)_3$ show magnetic moment 4.54 B.M. [27].

The ^{1}HNMR signals at 10.45 and 3.40 ppm are assigned to –OH and $–CH_3$ protons respectively. The signals at 2.91 corresponds to H^4N-CH_3. Absence of ^{2}NH protons signal suggests enolization of ^{2}NH-C=S group to ^{2}N=C-SH. The aromatic protons show multiplet at 6.9, 7325, 7.45 ppm range. ^{13}C-NMR (DMSO-D_6): δppm 118.20 (C=C); 129.70 (C=C); 127.79 (C=C-Cl); 128.05 (C=C); 122.26 (C=C); 152.17 (C=C-OH), 155.39(C=N); 179.80 (C=S); 31.03 (NH-CH_3)



ESI-MS m/z ion ligand (L) 257.72 M^+, ESI-MS m/z ion Co.L.$(H_2O)_3$ 367.80 M^+, ESI-MS m/z Co.L.py 394.99 M^+, ESI-MS m/z ion Co.L.bipy 470.53 M^+, ESI-MS m/z ion Co.L.phen 493.84 M^+, ESI-MS m/z ion Co.L.α-pico 407.57 M^+, ESI-MS m/z ion Co.L.β-pico 407.57 M^+. Mass spectra data confirm the structure of ligand as indicated by molecular ion peak (M+1) corresponding to their molecular weight.

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					-	44.03 (44.35)	4.36 (4.14)	17.62 17.24)	13.33 (13.16)
Co-L.$(H_2O)_3$	Dark brown	$C_{10}H_{16}N_3O_4SClCo$	41.6	4.62	15.17 (15.98)	32.03 (32.55)	4.62 (4.37)	11.18 (11.40)	8.32 (8.70)
Co-L.Py	Brown	$C_{15}H_{15}N_4OSClCo$	41.6	2.61	15.16 (14.96)	45.37 (45.82)	4.55 (3.84)	14.34 (14.23)	8.64 (8.14)
Co-L.Bipy	Brown	$C_{20}H_{18}N_5OSClCo$	31.2	2.73	13.84 (13.36)	50.11 (50.52)	3.48 (3.82)	14.42 (14.73)	6.60 (6.74)
Co-L.Phen	Brown	$C_{22}H_{18}N_3OSClCo$	72.8	2.68	13.21 (12.72)	52.07 (52.90)	4.51 (3.63)	13.51 (14.02)	7.24 (6.42)
Co.L.α-Pico	Brown	$C_{16}H_{17}N_4OSClCo$	62.8	2.60	15.09 (15.40)	46.27 (46.60)	4.51 (4.16)	13.51 (13.59)	7.24 (7.77)
Co-L.β-Pico	Brown	$C_{16}H_{17}N_4OSClCo$	52.0	2.59	15.09 (15.40)	46.27 (46.60)	4.62 (4.16)	13.21 (13.59)	7.24 (7.77)

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 Co (II) complexes are usually obtained in tetrahedral and octahedral environments and less frequently in planer environment. In planer coordination low spin complexes show narrow band near 8,500 cm^{-1} and second stronger broader band near 20,000 cm^{-1} [28, 29]. The observed absorption bands in CoL.Py, Co.L α-pico/ β-pico indicate D_2h symmetry for d^7 planer stereochemistry [30]. The absorption bands at 22,500 cm^{-1} and 24,500 cm^{-1} are assigned to the $^2A_1g \rightarrow {}^2B_2g$ (dxz → Lπ*) and $^2Ag \rightarrow {}^2B_3g$ (dyz → Lπ*) L → M transitions respectively. The electronic spectra of CoL Phen and CoL bipy resemble the spectra of other five coordinate Cobalt (II) complexes (Roy et al. 1984, Lever et al. 1968), and square pyramidal structure may be assigned for these complexes [31].

The ground term of Co (II) is ^4T_1g or ^4Eg in octahedral coordination depending on whether the complex is high spin or low spin. The electronic spectrum of CoL $(H_2O)_3$ complex shows three bands due to spin allowed transitions at 9346, 18868 and 20,080 cm^{-1} which correspond to $^4T_1g\ (F) \rightarrow {}^4T_2g\ (F)\ (\nu_1)$, $^4T_1g(F) \rightarrow {}^4A_2g\ (F)\ (\nu_2)$ and $^4T_1g(F) \rightarrow {}^4T_1g\ (P)\ (\nu_3)$ respectively expected for d^7 system in octahedral field. The appearance of these bands suggests octahedral geometry around Co(II) [32]. The octahedral geometry of this complex is further supported by the value of ν_2/ν_1 and ν_3/ν_1 which comes out to be 2.02 and 2.15 respectively [27].

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

Compound	Mode	d-d	L→M	n→π*	π→π*
L	DMF	-	-	25974(4.05) 28571(3.85)	40860(3.35)
Co-L.$(H_2O)_3$	DMF	18939(1.85)	9328(3.95) 20202(4.01)	25773(3.90) 32680(4.18)	37736(4.72)
Co-L-Py	DMF	15198(1.49)	23753(3.95) 24938(4.02)	26954(3.91) 33898(4.28)	37037(4.74)
Co-L-Bipy	DMF	15848(2.74) 16393(2.46) 18485(2.71) 14815(1.80)	23529(4.12) 24272(4.14)	26954(4.16) 34965(4.41)	37313(4.66)
Co-L-Phen	DMF	17361(2.54) 14641(1.84) 13947(2.51)	24390(2.31) 23981(2.38)	26316(2.31) 34722(4.41)	37453(4.96)
Co-L-α Pico	DMF	15361(1.44)	23923(3.91) 24096(4.17) 22779(4.12)	29240(3.91) 32051(4.22)	37736(4.71)
Co-L-β Pico	DMF	15015(1.46)	23148(2.35) 24272(2.31) 22727(4.15)	29070(3.94) 31746(4.21)	37175(4.73)

(Absorbance)

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

Compounds	νOH	ν^2NH	νCO	νCN	νCS	ν(C=N-N=C)	νNN	νMO	νMN.H.B	νMS	νM^1N	Bands due to heterocyclic bases
L	3225	2925	1288	1638	795,1368	-	1049	-		-	-	-
Co.L.H_2O	-	-	1227	1598	733,1309	1579	1102	520	-	305	458	-
Co.L.Py	-	-	1229	1592	780,1309	1510	1101	510	287	319	468	1306,665,534
Co.L.Bipy	-	-	1239	1593	736,1311	1535	1086	503	268	315	452	1461,1086,736
Co.L.Phen	-	-	1237	1604	728,1279	1500	1103	516	272	313	450	1404,728,665
Co.L.α-Pico	-	-	1230	1591	740,1309	1533	1084	533	271	302	452	1310,665,452
Co.L.β-Pico	-	-	1228	1591	750,1310	1560	1100	520	275	305	458	1310,613,458

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 [33]. The coordination of azomethine nitrogen shifts $\nu(^7C = {}^1N)$ to lower wave numbers by 20-70 cm^{-1}. The band is shifted from 1624 cm^{-1} in uncomplexed thiosemicarbazones spectra to Ca 1534 cm^{-1} in the spectra of complexes. The shifting of ν (NN) to higher wave numbers in the spectra of complexes confirms the coordination of azomethine nitrogen. The new band appeared at 420-468 cm^{-1} confirms the coordination of azomethine nitrogen [34]. The loss of ^{2}NH proton on coordination via thiolate sulphur decreases the ν (C = S) bands found at 795, 1358

cm^{-1} in L. The presence of new band at 300-330 cm^{-1} is assignable to ν (CoS) [34, 35]. New band at 500-535 is assignable to ν (CoO) [36]. The coordination of *N* atom(s) of heterocyclic base is confirmed by ν (CoN) band in 260-290 cm^{-1} range. The bands of coordinated heterocyclic bases are also observed in IR spectra of all complexes.

TGA Analysis

The TGA curves of $CoL_2(H_2O)_3$ complex were carried out between the temperature 30^0C to 800^0C.

$CoL(H_2O)_3$: First step, 114.28 ^{0}C, Mass loss 9.52 % second step, 132.14 ^{0}C, Mass loss, 13.52 % Third Step 225 ^{0}C, Mass loss, 20.02 % Fourth Step, 364.29 ^{0}C, Mass loss, 55.01 %, Residue, 753.57 ^{0}C, % of CoO.

The coordinated water molecules were eliminated from their complexes at relatively higher temperature than those in the case of the lattice water molecules. The coordinated water molecules in $CoL(H_2O)_3$ were removed in two steps. In the $CoL(H_2O)_3$ two water molecules were removed at a temperature >115^0C and one water molecule was >140^0C. The TGA data of CoL $(H_2O)_3$ indicated that the decomposition of the complex proceed in several steps. There are two breaks after the removal of three water molecules, first at a temperature >230^0C and second >365^0C. The decomposition was complete and CoO formed at a temperature >801^0C.

DSC (Differencial scaning colorimetry):

The thermal stability, melting, crystallisation, decomposition desolvation, sublimation and glass transition temperature of complexes can be studied by carrying out differential scanning calorimetry (DSC). This technique also detects any reaction or transformation involving absorption or release of heat. Thermograms gave thermal characteristic data, melting point corresponding to endothermic peak and decomposition temperature. The results of DSC are summarised.

1. **CoL $(H_2O)_3$** : Endothermic; on set temperature 257.29^{0}C, Peak, 258.22^{0}C, ΔH, -35.66 Jg^{-1}, End set temperature, 261.21^{0}C, Exothermic; onset temperature, 273.75^{0}C, Peak, 277.5^{0}C, End set temperature, 282.5^{0}C.
2. **Co L Py** : Endothermic; on set temperature 175.24^{0}C, Peak, 177.27^{0}C, ΔH, -3.68 Jg^{-1}, Tg 226.25^{0}C, End set temperature, 183.54^{0}C, Exothermic; onset temperature, 250.0^{0}C, Peak, 271.25^{0}C, End set temperature, 287.5^{0}C.
3. **Co L Py** : Endothermic; on set temperature 169.28^{0}C, Peak, 179.34^{0}C, ΔH,-53.42 Jg^{-1}.
4. **Co L Phen** : Endothermic; on set temperature 236.61^{0}C, Peak, 240.97^{0}C, ΔH, -8.34 Jg^{-1}, Exothermic; onset temperature, 281.33^{0}C, Peak, 282.10^{0}C, End set temperature, 290^{0}C.
5. **Co L α-pico** : Endothermic; on set temperature 238.59^{0}C, Peak, 239.03^{0}C, ΔH, -0.23 Jg^{-1}, Tg 250^{0}C, Exothermic; onset temperature, 290.0^{0}C, Peak, 297.5^{0}C, End set temperature, 303.75^{0}C.
6. **Co L β-pico** : Endothermic; on set temperature 136.26^{0}C, Peak, 136.64^{0}C, ΔH, -0.11 Jg^{-1}, Tg, 256.25^{0}C, Exothermic; onset temperature, 287.5^{0}C, Peak, 293.75^{0}C, End set temperature, 306.25^{0}C.

DSC curves presented a melting process for all complexes followed by decomposition presented by exothermic process. The Co (II) complexes are thermally stable to the temperature >240^0C. The complexes start to decompose at a relatively higher temperature >300^0C. All complexes melted at a temperature >262^0C. The endothermic peak corresponds to melting process and exothermic peak corresponds to decomposition process. All complexes decomposed completely at a temperature >330^0C.

Biological activity (Agar well diffusion method)

The antibacterial activity was determined using the agar well diffusion method. The prepared culture plates were inoculated with different bacteria and fungus by using plate method. Wells were made on the agar surface with 6 mm cork borer, the solutions of complexes were poured into the well using sterile syringe.the plates were incubated at 37±2^{o}C for 24 hours for bacterial activity and 48 hours for fungul activity. The plates were observed for the zone formation around the wells. The zone of inhibition was calculated by measuring the diameter of the inhibition zone around the well (in mm) including the well diameter. The activity was determined using two different concentrations 10^{-3} M and 10^{-4} M. In order to compare activity of the synthesized complexes, followed the same procedure with metal chlorides. The activity index was calculated to express the activity in comparison to the antibiotics [37]. The diameters of the inhibition zones for all tested compounds are presented in Table No. 1.4. The results showed that the complexes showed better activity than free ligand. The adducts with bipyridine and 1,10 phenanthroline showed better activity. The most probable reason for this difference might be due to chelation which reduces the polarity of the central metal atom because of the partial sharing of its partial positive charge with donor groups and possible Π-

electron delocalization within the whole chelating ring. As a result of this,the lipophilic nature of the central metal atom increases,which favours the permeation of the complexes through the lipid layer of the cell membrane [38]. Out of these seven compounds tested, Ni.L.phen was found more active against four cultures. The N(4) substituted 5-chloro 2-hydroxy acetophenone methyl thiosemicarbazone was found less active than its Ni(II) complex and adducts. Thus increase in coordination number from four to five in copper complexes increases microbial activity [39]. In gram negative bacteria (*Pseudomonas Putida and Escherichia Coli*) due to the outer membrane, it might not be ease for the complexes to diffuse inside the bacterial cell. The metal ion chloride salts were more effective than complexes. This shows free metal ions are more effective than binded in complexes.

Table 1.4: Antimicrobial activity of synthesized compounds

Compounds	*Pseudomonas Putida*		*Escherichia Coli*		*Aspergillus Niger*		*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	12	10	9	8	12	10	10	9
Co-L.H_2O	15	12	11	09	13	11	13	11
Co-L-Py	18	13	13	11	12	10	12	10
Co-L-Bipy	16	14	15	12	15	12	15	12
Co-L- Phen	16	12	17	14	16	13	16	13
Co-L.α-Pico	10	09	09	08	15	14	14	12
Co-L.β-Pico	11	09	10	09	12	11	15	12
Std	34	36	26	31	18	19	17	20
$CoCl_2.6H_2O$	22	25	20	22	31	30	28	27

(Zone in mm, Std-Amphicilin,Bicip)

% Activity Index of Co (II) complexes:

Compounds	*Pseudomonas Putida*		*Escherichia Coli*		*Aspergillus Niger*		*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	35.29	27.78	34.62	25.81	66.67	52.63	58.82	45.00
Co.L.H2O	44.12	33.33	42.31	29.03	72.22	57.89	76.47	55.00
Co.L.Py	52.94	36.11	50.00	35.48	66.67	52.63	70.59	50.00
Co.L.Bipy	47.06	38.89	57.69	38.71	83.33	63.16	88.24	60.00
Co.L.Phen	47.06	33.33	65.38	45.16	88.89	68.42	94.12	65.00
Co.L.α-Pico	29.41	25.00	34.62	25.81	83.33	73.68	82.35	60.00
Co.L.β-Pico	32.35	25.00	38.46	29.03	66.67	57.89	88.24	60.00
Std	100	100	100	100	100	100	100	100
$NiCl_2.6H_2O$	64.71	69.44	76.92	70.97	172.22	157.89	164.71	135.00

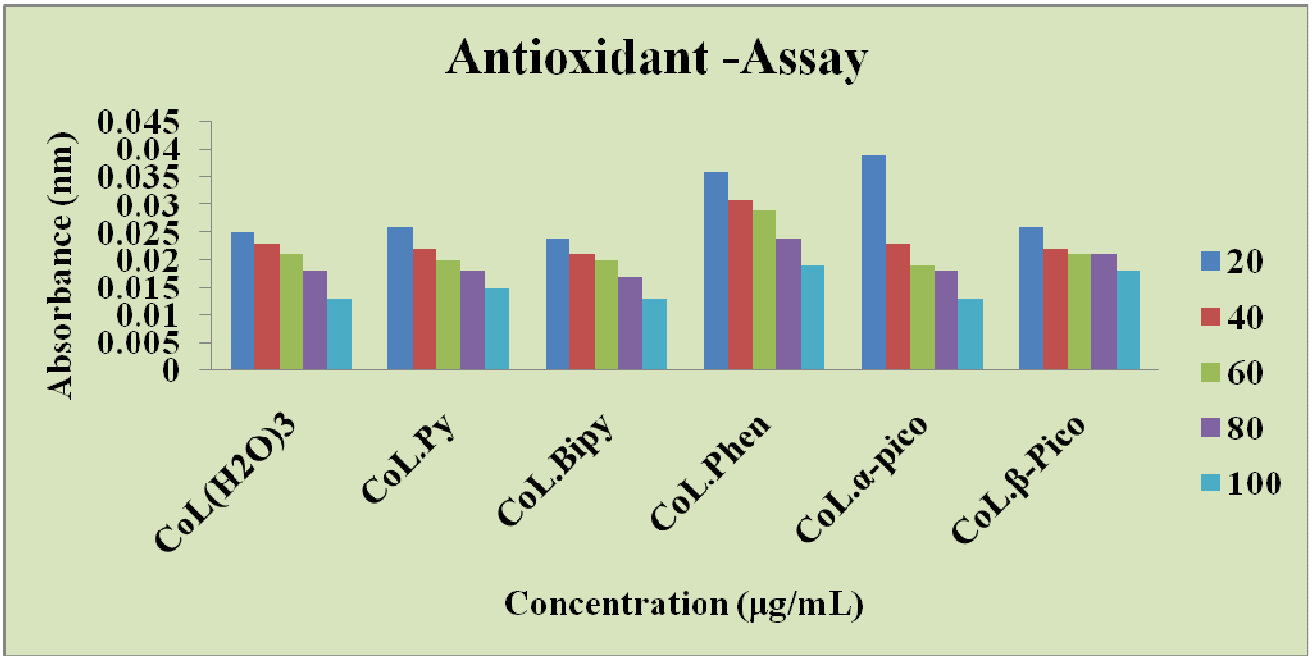
Antioxidant activity:

The antioxidant activity of ligand and complexes was assessed on the basis of the radical scavenging effect of the stable DPPH free radical (Table 1.6). About 100 _l of each concentration 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 [40].

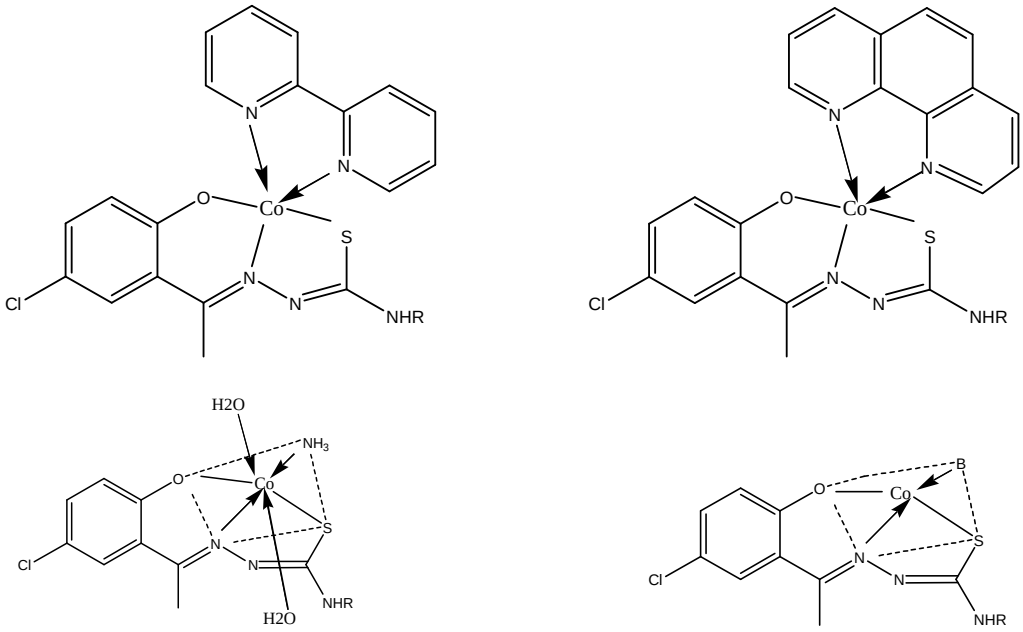
Table 1.6: Antioxidant activity data (%Radial scavenging)

µg/ml	Co-L.H_2O	Co-L-Py	Co-L-Bipy	Co-L. Phen	CoL.α-Pico	Co-L. β-Pico	Vit C Std
20	70.93	69.76	72.09	58.13	54.65	70.93	39.53
40	73.25	74.41	75.58	63.95	73.25	74.71	46.51
60	75.58	76.74	76.74	66.27	77.90	75.58	58.13
80	79.06	79.06	80.23	72.09	79.06	75.58	60.46
100	84.88	82.59	84.88	77.90	84.88	79.06	65.11
IC_{50}	14.09	14.33	13.87	17.20	18.29	14.09	51.00

Figure 1.1: Effect of synthesized compounds on DPPH assay



Expected Structure



(Where R= CH_3)

B = pyridine, α-picoline, β-picoline

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