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Cobalt (III) Complexes With The *O,N,S*-Tridentate Ligand 5-Chloro-2-Hydroxy Acetophenone Thiosemicarbazone And *N*(4) Methyl Thiosemicarbazone

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ABSTRACT

The synthesis of heterocyclic base adducts of cobalt (III) complexes have been carried out by the reaction of cobalt(II) chloride with 5-chloro-2-hydroxy acetophenone thiosemicarbazone and N(4) methyl thiosemicarbazone in presence of heterocyclic base like 2,2'-bipyridine (bipy), 1,10-phenanthroline (Phen) and 8-amino quinoline (aq). Thiosemcarbazones have been characterized by ^{13}C, ^{1}H NMR as well as IR, electronic spectra. The magnetic and spectroscopic data exhibit octahedral geometry for six coordinate complexes. The thiosemicarbazones and its cobalt (III) complexes show growth inhibitory activity against Pseudomonas Putida, Escherichia Coli, Aspergillus Niger and Candida Albicans. The DPPH assay of thiosemicarbazones and its cobalt (III) complexes show antioxidant nature.

Keywords: Thiosemicarbazone, *N*(4) methyl thiosemicarbazone, Bioactive metal complexes, antimicrobial, antioxidant activity.

INTRODUCTION

Thiosemicarbazones (TSCs) are tridentate ligands having ability to bind transition metal ions by bonding through sulfur and hydrazinnic terminal nitrogen atoms. The hydrazine group combines with aldehydes or ketones to generate the thiosemicarbazone derivatives having biological activities such as antitumour [1], antimalarial [2], antileukemic [3], antiviral [4], antibacterial [5] and antifertility property [6]. Thiosemicarbazone is planar due to the extensive electron delocalization throught the moiety. The N-S donor ligands of thiosemicarbazones and thiosemicarbazides make their ability to form metal chelates [7], non linear optical properties [8] and their reductive capacities [9]. The electron density around sulfur atom due to electron delocalization helps in complexation with positively charged metal ions. Electron rich hydrazinic *N* atom is also involved in the complex formation with metal ions. *S* and *N* atoms chelate to metal ion and possess the pharmaceutical activity. The relationship between metal ions and cancer are controversial. Some antitumour agents also possess the ability to function as chelating agents [10]. The biological activities of heterocyclic thiosemicarbazones depend on the parent aldehydes or ketones [11]. The Co(II) complexes are of limited medical usage.There is interest in Co(III) complexes of bidentate mustards which appear to act as hypoxia-selective agents [12]. Some Co(III) complexses have been found

active not only against leukemia and lymphoma cell lines [13] but also against bacterial strains [14]. Co(II) complexes possess in vivo insulin-like properties [15], antifungal [16] and antioxidant activity [17]. Co (III) complex of drug farmotidine have greater antimicrobial activity against *E.Coli* and *M.Lysodeikticus* than the free drug [18]. Co(III) complexes have been studied as anticancer agents [19]. In 1956 the structures of Co (III) were suggested [20] and these complexes were made to target specific enzymes and the potential of their activity was noted in murine leukemia cells for a complex containing an acetal ligand [21]. The Co-alkyne is highly active against breast cancer lines. The complexes exhibited high intracellular levels of cobalt and were more lipophilic than free ligands [22].

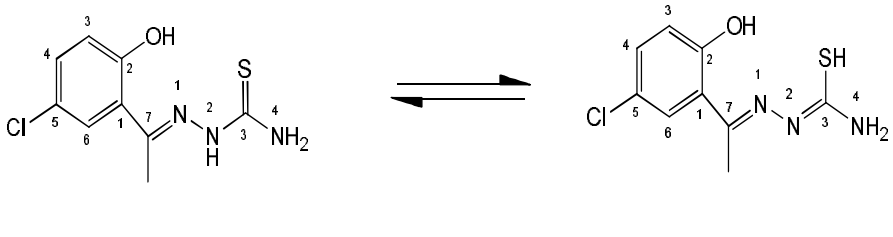
We now report the synthesis, spectral characterization and biological studies of six coordinate complexes of Co(III) with 5-chloro-2-hydroxy acetophenone thiosemicarbazone (L_1) and *N*(4) methyl thisemicarbazone (L_2).

MATERIALS AND METHODS

Materials and instrumentation: 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.

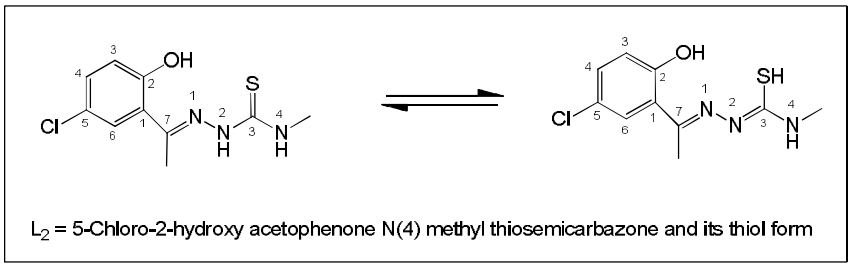
Preparation of Ligands

1.The 5-chloro 2-hydroxy acetophenone thiosemicarbazone (L_1) was synthesized by refluxing 5-chloro 2-hydroxy acetophenone and thiosemicarbazide in the mole ratio 1:1 for 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 [23].



L_1 = 5-Chloro-2-hydroxy acetophenone thiosemicarbazone and its thiol form

2.The 5-chloro 2-hydroxy acetophenone *N*(4) methyl thiosemicarbazone (L_2) was synthesized by refluxing 5-chloro 2-hydroxy acetophenone and *N*(4) methyl thiosemicarbazide in the mole ratio 1:1 for 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 [23].



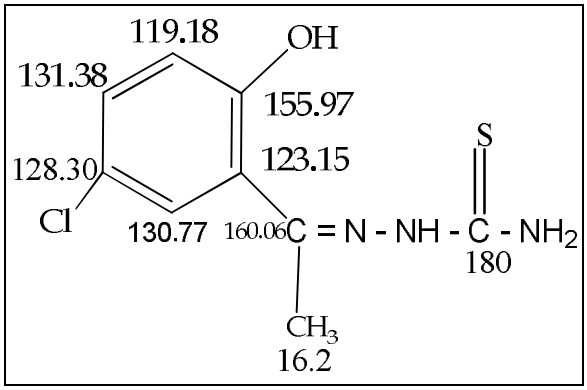
L_2 = 5-Chloro-2-hydroxy acetophenone N(4) methyl thiosemicarbazone and its thiol form

Preparation of complex: Heterocyclic base like, 2-2'-bipyridine, 1, 10 phenanthroline and 8-amino quinoline in solid form (0.5 mmol) was added to thiosemicabazone (0.5 mmol) dissolved in 25 ml of ethanol. The mixture was warmed slightly to ensure complete dissolution of the ligand. Then 10 ml methanolic solution of Co(II) perchlorate (0.5 mmol) was added to the above mixture. The solution turned deep brown in about hour and the product obtained filtered washed with hot water and then with diethyl ether.

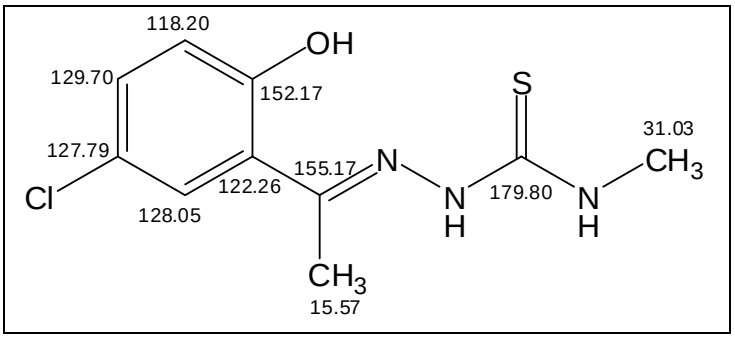
RESULTS AND DISCUSSION

The colours, elemental analysis, stoichiometries of ligand and its complexes are presented in Table 1. Elemental analysis data are consistent with 1:1:1 ratio for metal thiosemicarbazone and heterocyclic base for all adducts. 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 [24].

Magnetic susceptibility of all complexes was measured in polycrystalline state. All complexes were found diamagnetic. The ^{1}HNMR signals(L_1) at 13.00 and 3.39 ppm are assigned to –OH and –CH_3 protons respectively. L_1 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) L_1: 119.18 (C = C stretching), 131.38 (C = C stretching), 128.30 (C = C – Cl), 130.77 (C = C stretching), 123.15 (C = C stretching), 155.97 (C = C – OH), 160.06 (C = N),180.0 (C=S),16.2 (C-CH_3).



The ^{1}HNMR signals (L_2) at 10.45 and 3.40 ppm are assigned to –OH and –CH_3 protons respectively. The signals at 2.19 and 2.91 corresponds to –^{4}NH and H^{4}N-CH_3 respectively. 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, 7.33, 7.45 ppm range.^{13}C-NMR (DMSO-D_6) L_2: 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), 155.17(C=N); 179.80 (C=S); 31.03 (NH-CH_3); 15.57 (C-CH_3)



ESI-MS ion ligand (L_1) (243.70) , ESI-MS m/z ion ligand (L_2) 257.20 M^+ (257.72), ESI-MS m/z ion $Co.L_1.bipy.ClO_4$ 556.72 M^+ (556.24), ESI-MS m/z ion 580.80 M+ (580.26), ESI-MS m/z ion $Co.L_1.aq.ClO_4$ M^+ 556.92 (556.24),ESI-MS m/z ion $Co.L_2.bipy.ClO_4$ 570.88 M^+ (570.27), ESI MS m/z ion $Co.L_2.phen.ClO_4$ 594.81 M^+ (594.29), ESI-MS m/z ion $Co.L_2.aq.ClO_4$ 570.62 M^+ (570.27). Mass spectra data confirm the structure of ligand as indicated by molecular ion peak (M+1) corresponding to their molecular weight.

Table 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_1	Yellow	$C_9H_{10}N_3OSCl$	-	-	-	44.03 (44.35)	4.36 (4.14)	17.62 17.24)	13.33 (13.16)
L_2	Yellow	$C_{10}H_{12}N_3OSCl$	-	-	-	46.48 (46.81)	5.19 (4.69)	17.15 (16.30)	12.10 (12.44)
$Co.L_1bipy.ClO_4$	Brown	$C_{19}H_{16}N_5O_5SCl_2Co$	40.6	Diamagnetic	10.02 (10.59)	41.89 (41.02)	2.32 (2.90)	12.03 (12.59)	5.25 (5.76)
$Co.L_1phen.ClO_4$	Brown	$C_{21}H_{16}N_5O_5SCl_2Co$	40.6	Diamagnetic	10.82 (10.16)	43.06 (43.46)	2.22 (2.78)	12.52 (12.07)	5.08 (5.53)
$Co.L_1aq.ClO_4$	Brown	$C_{19}H_{16}N_5O_5SCl_2Co$	32.2	Diamagnetic	10.23 (10.59)	41.52 (41.02)	2.42 (2.90)	12.12 (12.59)	5.23 (5.76)
$Co.L_2bipy.ClO_4$	Brown	$C_{20}H_{18}N_5O_5SCl_2Co$	70.8	Diamagnetic	10.80 (10.33)	42.52 (42.12)	3.73 (3.18)	12.83 (12.28)	5.18 (5.62)
$Co.L_2phen.ClO_4$	Brown	$C_{22}H_{18}N_5O_5SCl_2Co$	60.8	Diamagnetic	9.42 (9.92)	44.06 (44.46)	3.73 (3.05)	11.28 (11.78)	5.06 (5.39)
$Co.L_2aq.ClO_4$	Brown	$C_{20}H_{18}N_5O_5SCl_2Co$	50.0	Diamagnetic	10.11 (10.33)	42.72 (42.12)	3.63 (3.18)	12.54 (12.28)	5.24 (5.62)

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 2). The Co (III) complexes are usually obtained in 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} [25, 26]. 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 ^2A_1g → ^{2} B_3g (dyz → Lπ*) L → M transitions respectively. Co(III) has d^6 configuration. Co(III) complexes generally form low spin complexes with spin allowed transitions $A_{1g}\rightarrow T_{1g}$ and $A_{1g}\rightarrow T_{2g}$. The ground state is A_1g. The high energy charge transfer band due to $A_{1g} \rightarrow T_{2g}$ has been found around 420 nm.The electronic spectra showed bands in the visible region at 470-490 nm.The charge transfer bands are due to S → Co and O → Co charge transitions and hence they are broad [27]
The octahedral geometry of these complexes 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 [28].

Table 2: Electronic spectral assignments (cm^{-1})

Compound	Mode	d-d	L→M	n→π*	π→π*
L_1	DMF	-	-	25974 28571	40860
L_2	DMF	-	9328 20202	25773 32680	37736
Co.L_1.Bipy.ClO_4	DMF	16556	22222	26882,31546	40323
Co.L_1.phen.ClO_4	DMF	16667	22075	26738,31546	40323
Co-L_1-aq.ClO_4	DMF	17241	23474	25641,26954	40161
Co.L_2.Bipy.ClO_4	DMF	16694	23419	25381,30303	39683
Co.L_2.phen.ClO_4	DMF	16556	23256	25381,31250	39526
Co-L_2-aq.ClO_4	DMF	16667	22075	26247,31250	40161

IR Studies: The absence of any band in 2600-2800 cm^{-1} region of the IR spectrum of L_1 and L_2 shows the absence of thiol tautomer in the solid state [29]. The coordination of azomethine nitrogen shifts ν ($^7C = {}^1N$) to lower wave numbers by 20-70 cm^{-1}. The band is shifted from 1624m 1638 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 [30]. The loss of ^{2}NH proton on coordination via thiolate sulphur decreases the n (C = S) bands found at 758, 1311 in L_1 and 795, 1358 cm^{-1} in L_2. The presence of new band at 300 - 330 cm^{-1} is assignable to ν (CoS) [31, 32]. New band at 500-535 cm^{-1} is assignable to ν (CoO) [33]. 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.

Table 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
L1	3147	2943	1281	1624	758,1374	-	1049	-		-	-	-
L2	3225	2925	1288	1638	795,1368	-	1049	-		-	-	-
Co.L_1.bipy.ClO_4	-	-	1232	1604	764,1280	1501	1101	517	282	310	422	1401,1020,671

$Co.L_1.Phen.ClO_4$	-	-	1232	1605	764,1280	1501	1103	519	271	302	452	1462,764,630
$Co.L_1.aq.ClO_4$	-	-	1229	1592	723,1306	1513	1101	526	263	315	447	1230,824,630
$Co.L_2.bipy.ClO_4$	-	-	1239	1593	736,1311	1535	1086	503	268	315	452	1461,1086,736
$Co.L_2.Phen.ClO_4$	-	-	1237	1604	728,1279	1500	1103	516	272	313	450	1404,728,665
$Co.L_2.aq.ClO_4$	-	-	1230	1591	740,1309	1533	1084	533	271	302	452	1310,665,452

Differencial scaning colorimetry (DSC): 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. **Co L_1 bipy ClO_4** : Endothermic; on set temperature 260.12 °C, Peak, 263.28, ΔH, - 35.66 Jg^{-1}, End set temperature, 270.00 °C, Exothermic; onset temperature, 273.75 °C, Peak, 277.5 °C, End set temperature, 285.06 °C.
2. **Co L_1 phen ClO_4** : Endothermic; on set temperature 178.22 °C, Peak, 180.24, ΔH, - 3.68 Jg^{-1}, Tg 226.25 °C, End set temperature, 183.54 °C, Exothermic; onset temperature, 250.0 °C, Peak, 271.25 °C, End set temperature, 287.5 °C.
3. **Co L_1 aq ClO_4** : Endothermic; on set temperature 169.28 °C, Peak, 179.34 °C, ΔH, - 53.42 Jg^{-1}.
4. **Co L_2 bipy ClO_4** : Endothermic; on set temperature 236.61 °C, Peak, 240.97 °C, ΔH, - 8.34 Jg^{-1}, Exothermic; onset temperature, 281.33 °C, Peak, 282.10 °C, End set temperature, 290 °C.
5. **Co L_2 phen ClO_4** : Endothermic; on set temperature 238.59 °C, Peak, 239.03 °C, ΔH, - 0.23 Jg^{-1}, Tg 250 °C, Exothermic; onset temperature, 290.0 °C, Peak, 297.5 °C, End set temperature, 303.75 °C.
6. **Co L_2 aq ClO_4** : Endothermic; on set temperature 136.26 °C, Peak, 136.64 °C, ΔH, - 0.11 Jg^{-1}, Tg, 256.25 °C, Exothermic; onset temperature, 287.5 °C, Peak, 293.75 °C, End set temperature, 306.25 °C.

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

APPLICATIONS

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°C for 24 hours for bacterial activity and 50 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 [34]. The diameters of the inhibition zones for all tested compounds are presented in table .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 [35]. Out of these seven compounds tested, Ni.L.phen was found more active against four cultures. The 5-chloro-2-hydroxy acetophenone N(4) Methylthiosemicarbazone 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 [36]. In gram negative bacteria *(Pseudomonas Putida, Escherichia Coli)* the outer membrane. So 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. .% Activity Index of Co (III) complexes is given in table 5 and shown in figures 1A-1D.

Table 4: Antimicrobial activity of synthesized compounds

Compounds	*Pseudomonas Putida* 10^{-3}M	10^{-4}M	*Escherichia Coli* 10^{-3}M	10^{-4}M	*Aspergillus Niger* 10^{-3}M	10^{-4}M	*Candida Albicans* 10^{-3}M	10^{-4}M
L1	10	09	11	10	10	09	11	10
L2	12	10	09	08	12	10	10	09
CoL_1 bipy ClO_4	15	16	12	13	13	11	13	11
CoL_1 phen ClO_4	18	17	14	14	12	10	12	10
Co L_1 aq ClO_4	14	15	13	12	15	12	15	12
CoL_2 bipy ClO_4	16	17	13	13	16	13	16	13
CoL_2 phen ClO_4	17	18	14	14	15	14	14	12
Co L_2 aq ClO_4	15	16	11	12	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)

Table 5.% Activity Index of Co (III) complexes

Compound	*Pseudomonas Putida* 10^{-3}M	10^{-4}M	*Escherichia Coli* 10^{-3}M	10^{-4}M	*Aspergillus Niger* 10^{-3}M	10^{-4}M	*Candida Albicans* 10^{-3}M	10^{-4}M
L_1	29.41	25.00	42.31	32.26	55.55	47.37	64.71	50.00
L_2	35.29	27.78	34.62	25.81	66.67	52.63	58.82	45.00
CoL_1 bipy ClO_4	44.12	44.44	46.15	41.94	72.22	57.89	76.47	55.00
CoL_1 phen ClO_4	52.94	47.22	53.85	45.16	66.67	52.63	70.59	50.00
Co L_1 aq ClO_4	41.18	41.67	50.00	38.71	83.33	63.16	88.24	60.00
CoL_2 bipy ClO_4	47.06	47.22	50.00	41.94	88.89	68.42	94.12	65.00
CoL_2 phen ClO_4	50.00	50.00	53.85	45.16	83.33	73.68	82.35	60.00

Co L_2 aq ClO_4	44.12	44.44	42.31	38.71	66.67	63.16	88.24	60.00
Std	100	100	100	100	100	100	100	100
$CoCl_2.6H_2O$	64.71	69.44	76.92	70.97	172.22	157.89	164.71	135.00

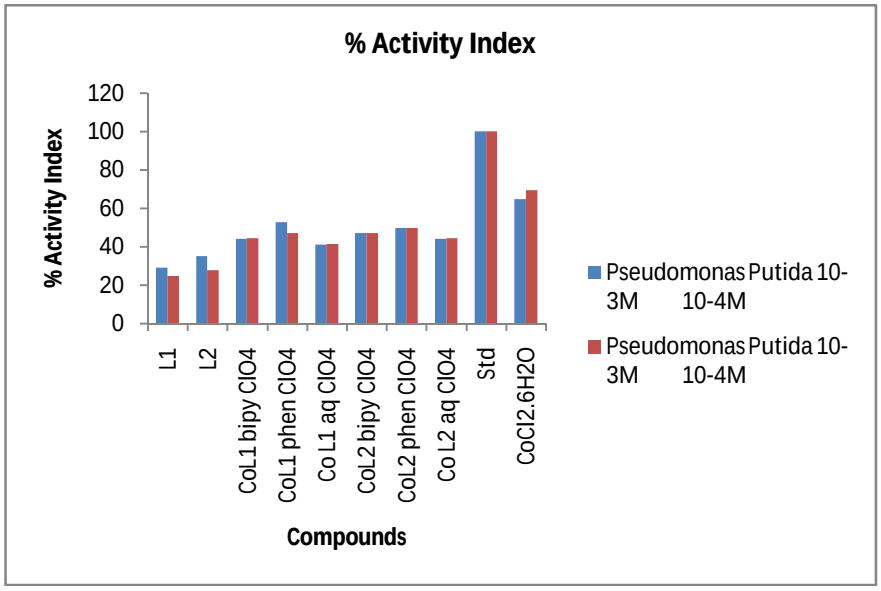


Fig. 1A Antimicrobial Assay

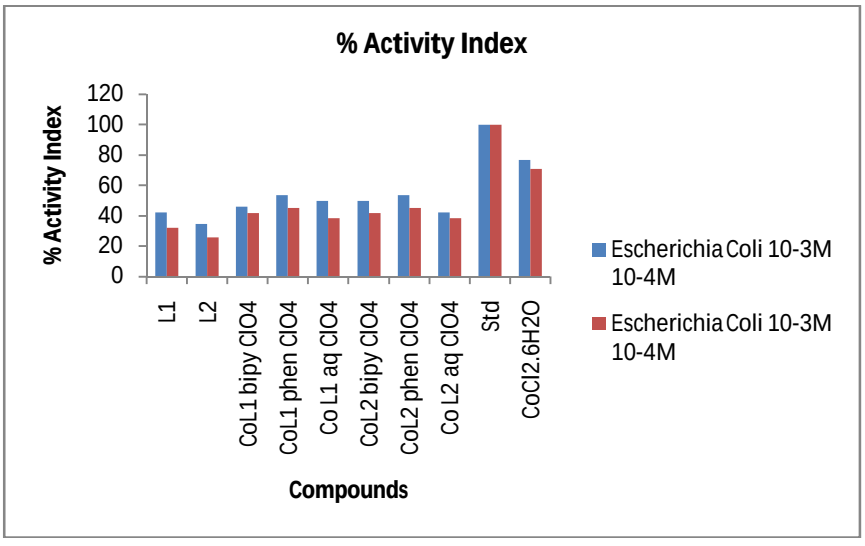


Fig.1B Antimicrobial Assay

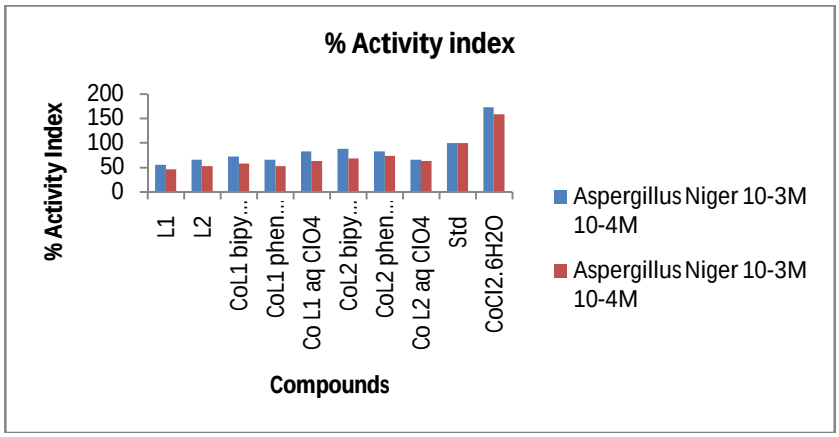


Fig.1C. Antimicrobial Assay

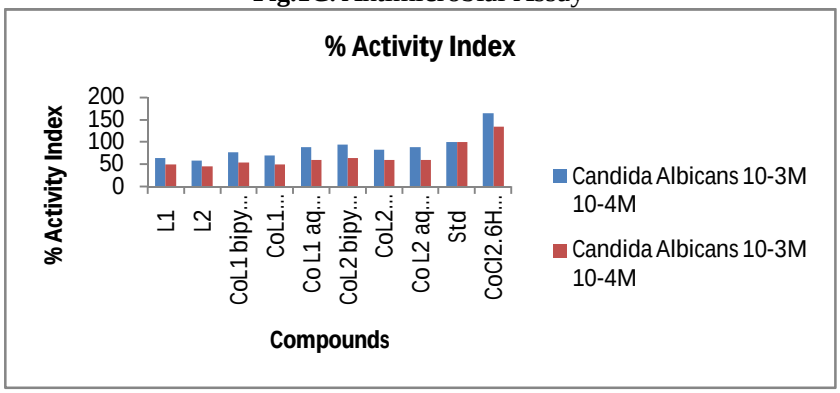


Fig.1D Antimicrobial Assay

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 6 and fig 2). About 100 _l of each concentration or standard (from 21 mg/ml to 21_g ml^{-1}) 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 [37].

Table 6: Antioxidant activity data (%Radial scavenging)

µg/ml	$CoL_1bipyClO_4$	$CoL_1phenClO_4$	CoL_1aqClO_4	$CoL_2bipyClO_4$	$CoL_2phenClO_4$	CoL_2aqClO_4	Vit C Std	L_1	L_2
20	19.51	13.82	17.88	72.09	58.13	69.76	39.53	69.76	72.09
40	22.76	17.88	19.51	75.58	63.95	74.41	46.51	76.74	74.41
60	26.01	21.95	21.96	76.74	66.27	76.74	58.13	79.06	76.74
80	29.26	27.64	25.20	80.23	72.09	79.06	60.46	79.06	76.74
100	32.52	32.52	30.08	84.88	77.90	82.59	65.11	81.39	79.06
IC_{50}	153.75	153.75	166.22	13.87	17.20	14.33	51.00	14.33	13.87

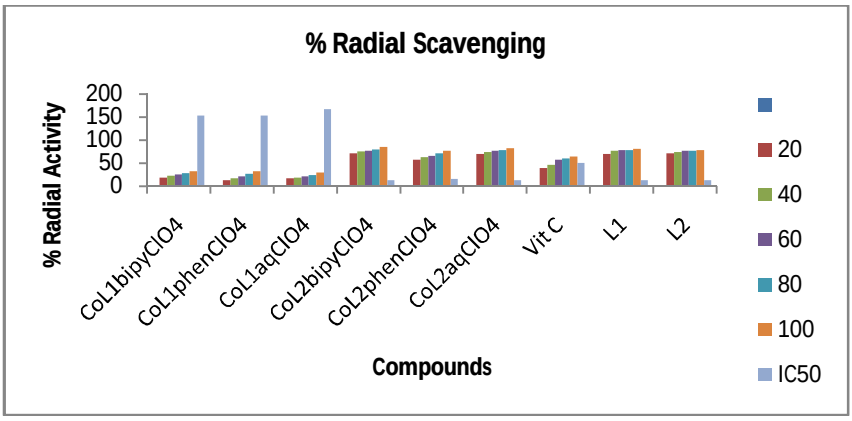
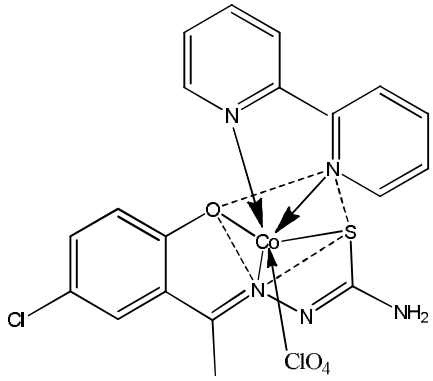
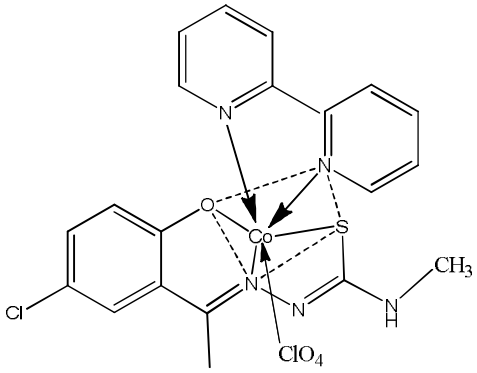
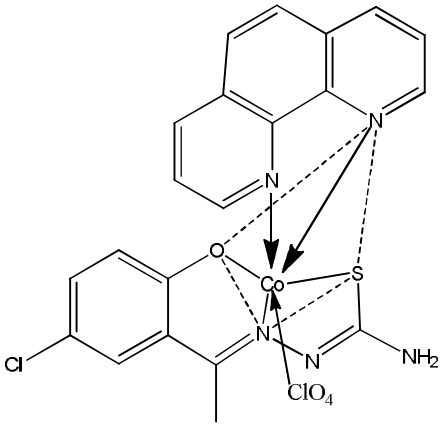


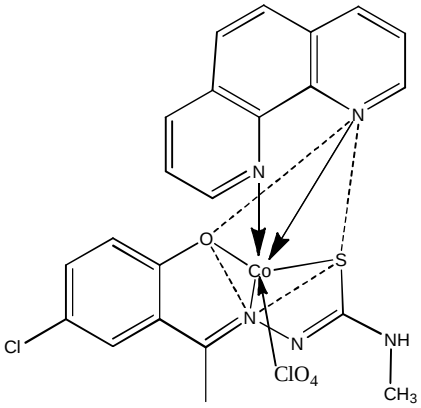
Fig 2. DPPH Assay

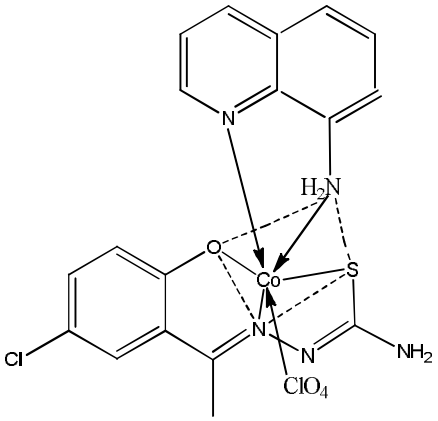
Expected Structures

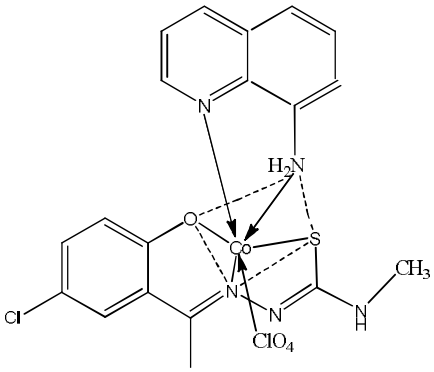












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