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Synthesis, characterization and antimicrobial activities of some mixed ligand complexes of Co(II) with thiosemicarbazones and N-protected amino acids

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Abstract

The reaction of cobalt(II) chloride with a new class of thiosemicarbazones *viz*; *cis*-3,7-dimethyl-2,6-octadienthiosemicarbazone(CDOTSC; L_1H) and 3,7-dimethyl-6-octenethiosemicarbazone (DOTSC; L_2H) and N-phthaloyl derivative of DL-glycine(A_1H), L-alanine(A_2H) or L-valine(A_3H) in 1:1:1 molar ratio in dry refluxing ethanol have been studied. All the isolated complexes have the general composition [Co(L)(A)]. Tentative structures are proposed for these complexes based upon elemental analysis, electrical conductances, magnetic moment, molecular weight determination and spectral (IR, electronic) studies.The ligands and Co(II) complexes have been tested for their antibacterial and antifungal activities against three bacterial strains *S. aureus*, *B. subtilis*, *E. coli* and two fungal strains *F. moniliformae* and *M. phaseolina.* Attempts have been made to establish a correlation between the antibacterial and antifungal activity and the structures of products.

Keywords: *Thiosemicarbazone, N-phthaloyl amino acids, antibacterial, antifungal activity, Co(II) complexes*

Introduction

The synthesis and biological activities of complexes of thiosemicarbazones continue to attract attention, since Domgk first reported the anticancer activity of thiosemicarbazones [1–3]. The potential biological activity of compounds containing N and S may be responsible for this increased interest. The transition metal complexes with N, O and S donor ligands have remarkable potential for inhibiting the growth of various pathogenic microorganisms [4–12] and this property has been exploited in pharmacological applications.

West et al. in their attempts to establish structure-biological activity relationship have studied numerous transition metal complexes with heterocyclic thiosemicarbazones [13]. Although there has been considerable interest in transition metal complexes derived from heterocyclic thiosemicarbazones and other related thiosemicarbazones but there has been little interest in terpenoid thiosemicarbazones [14] and their metal complexes [15]. Recently some Cu(II) and Ni(II) complexes of citronellal thiosemicarbazones have been reported for their property of inhibition of cell proliferation and apoptosis test on human leukemia cell line U937.

In continuation of our previous work on the synthesis, spectroscopic characterization and antimicrobial studies of binary complexes of some transition metals with semi/-thiosemicarbazone of citral and mixed ligand complexes containing amino acids or N-protected amino acids [16–19], here we reported the preparation, spectral characterization and antimicrobial screening of mixed ligand complexes of Co(II) with thiosemicarbazone of citral (CDOTSC) and citronellal (DOTSC) and N- phthaloyl amino acids (N-phthaloyl glycine, N-phthaloyl alanine and N-phthaloyl valine).

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Materials and methods

All the chemicals used were of AR grade. Solvents were purified by known methods [20]. The triethylamine was distilled over KOH pellets. The complexes were analysed for their cobalt content employing standard literature procedure [21] after destroying the organic matter first with aqua regia and then with concentrated sulphuric acid. Sulfur was estimated gravimetrically as $BaSO_4$. Elemental analyses were carried out on a Elemental Vario EL III Carlo Erba 1108 analyzer. The IR spectra were recorded with KBr pellets in the 4000-225 cm^{-1} range on Nicolet Megna 550 FT-IR spectrometer, electronic spectra were recorded on a Varian Cary 50 Bio Uv/Visible spectrometer. Molecular weights of ligands and complexes were measured by cryoscopic method using Beckmann's thermometer and magnetic moments were measured by Gouy method. Molar conductivities of 10^{-4} M DMF solutions were measured on a μp based conductivity meter model 1601/E.

Synthesis of ligands

Preparation of thiosemicarbazones. The *cis*-3,7-dimethyl-2,6-octadienthiosemicarbazone (citral thiosemicarbazone; CDOTSC), 3,7-dimethyl-6-octene-thiosemicarbazone (citronellal thiosemicarbazone; DOTSC) were synthesized as previously reported method [17] by the reaction of citral or citronellal with thiosemi- carbazide (1:1 molar ratio) in absolute ethanol in the presence of few drops of glacial acetic acid.

Preparation of N-phthaloyl amino acids. The N-phthaloyl amino acids (N-phthaloyl glycine, N-phthaloyl alanine, and N-phthaloyl valine) were synthesized by a published procedure [22].

Synthesis of complexes. A weighed amount of corresponding thiosemicarbazone of citral or citronellal (5 mmol) was mixed with cobalt chloride (1.18 g, 5 mmol) solution in anhydrous ethanol (50 mL) followed by the addition of corresponding N-phthaloyl derivative of glycine, alanine or valine (5 mmol). After shaking the reaction mixture, triethylamine (1.4 mL, 10 mmol) was added dropwise with constant stirring. The reaction mixture was stirred with hot plate for 8 h and resulting solid was filtered off, washed with anhydrous ethanol and diethylether. Finally dried under reduced pressure. All the mixed ligand complexes were synthesized by the same method. The analytical data are given in Tables I and II.

Antimicrobial screening

(a) Evaluation of antibacterial activity by inhibition zone technique. The ligands and the mixed ligand Co(II) complexes were evaluated against three bacterial strains *Staphylococcus aureus, Bacillus subtilis,* Gram (+ ve) and *Escherichia coli* Gram (− ve), using the paper disc method [23]. For this purpose pure culture of bacteria were dissolved in distilled water and then uniformly seeded on the nutrient agar plate (composition: peptone 0.5%, beaf extract 3%, NaCl 5%, agar-agar 15% and distilled water 1000 mL). The paper discs of Whatman's paper No. 1 of 5 mm diameter were prepared for the purpose of making bacteriostatic slices. *Ca.* 2 mg of test compound was dissolved in 10 cm^3 DMSO (1%) to make a concentration of 0.2 mg/cm^3. The paper discs were soaked in the test solution and then such 5 paper discs were placed on Petri-dish at almost equal distance on the surface of medium preseeded with bacterial strain. One sample was inoculated in parallel on three medium plates. These Petri-dishes were incubated at 35 ± 1°C. After three days (72 h), the zone of inhibition (bacteriostatic diameter) thus formed around each disc containing the test compound was measured accurately in mm (Table III). The relative antibacterial activity of ligands and complexes are shown in Bar graph (Figure 1).

(b) Evaluation of antifungal activity by food poison technique. The ligands and complexes were screened for their antifungal activity against two fungal strains, *Fusarium moniliformae* and *Macrophomina phaseolina* using radial growth method [24–26]. In this method the medium used was potato dextrose agar medium (composition: dextrose 15 g, agar-agar 20 g and distilled water 1000 mL). The solution of test compound was prepared by dissolving 1 mg in 1 mL of DMSO and added to known amount of medium so as to get desired concentrations (100 and 400 ppm). The flasks were shaken several times to ensure proper and uniform distribution of the test compound. The warm medium was poured in sterilized Petri-dishes and allowed to solidify. The spores of fungi were placed on the medium with the help of a sterilized inoculum needle and the Petri-dishes were placed in an incubator at 25 ± 1°C. Medium with DMSO only incubated with pathogen served as control and three replicates used in each case. The linear growth of the fungus was obtained by measuring the fungal colony after 72 h and percent inhibition was calculated (Table IV) according to Vincent's formula (1927) [27].

$$\%\ \text{inhibition} = ((C - T)/C)\cdot 100$$

Where C = diameter of fungal colony in control plate
T = diameter of fungal colony in test plate.

Table I. Analytical data for thiosemicarbazones, N-phthaloyl amino acids and Co(II) complexes.

Compound Empirical formula	Yield (%)	M. Pt. (°C)	Analysis Found (Calcd.)% C	H	N	S	Co	Molar Cond.* (Ω^{-1} cm^2 mol^{-1})	μ(B.M.)	Mol. Wt. Found (Calcd.)
L_1H $C_{11}H_{10}N_3S$	92	92	58.65 (58.62)	8.53 (8.49)	18.61 (18.64)	14.20 (14.23)	–	–	–	229 (225)
L_2H $C_{11}H_{21}N_3S$	90	58	57.95 (58.11)	9.25 (9.31)	18.61 (18.48)	14.21 (14.10)	–	–	–	232 (227)
A_1H $C_{10}H_7NO_4$	85	191–192	58.61 (58.55)	3.46 (3.44)	6.80 (6.83)	58.61 (58.55)	–	–	–	201 (205)
A_2H $C_{11}H_9NO_4$	79	161–162	60.30 (60.28)	4.17 (4.14)	6.34 (6.39)	60.30 (60.28)	–	–	–	224 (219)
A_3H $C_{13}H_{13}NO_4$	73	102–103	63.21 (63.16)	5.29 (5.30)	5.60 (5.66)	63.21 (63.16)	–	–	–	250 (247)
$[Co(L_1)(A_1)]$ $[Co(C_{21}H_{24}N_4O_4S)]$	76	278	51.69 (51.75)	4.87 (4.96)	11.53 (11.49)	6.63 (6.58)	12.2 (12.09)	1.32	4.38	480 (487)
$[Co(L_1)(A_2)]$ $[Co(C_{22}H_{26}N_4O_4S)]$	73	282	56.60 (56.69)	5.28 (5.23)	11.21 (11.17)	6.42 (6.39)	11.68 (11.75)	0.97	4.56	495 (501)
$[Co(L_1)(A_3)]$ $[Co(C_{24}H_{30}N_4O_4S)]$	69	262	54.37 (54.44)	6.15 (6.09)	10.62 (10.58)	5.98 (6.05)	11.18 (11.13)	1.33	4.45	520 (529)
$[Co(L_2)(A_1)]$ $[Co(C_{21}H_{26}N_4O_4S)]$	82	269	51.48 (51.54)	5.38 (5.35)	11.40 (11.45)	6.62 (6.55)	12.11 (12.04)	1.42	4.12	493 (489)
$[Co(L_2)(A_2)]$ $[Co(C_{22}H_{28}N_4O_4S)]$	85	262	52.55 (52.48)	5.52 (5.60)	11.18 (11.13)	6.30 (6.36)	11.79 (11.71)	0.89	4.32	498 (503)
$[Co(L_2)(A_3)]$ $[Co(C_{24}H_{32}N_4O_4S)]$	87	267	54.36 (54.23)	6.18 (6.07)	10.64 (10.54)	5.92 (6.03)	11.00 (11.08)	1.38	4.28	523 (531)

*Molar conductance determined at 278 K in 10^{-4} DMF solution.

The relative antifungal activity of ligands and complexes are shown in Bar graphs (Figures 2 and 3).

Results and discussion

Chemistry

Reactions of cobalt(II) chloride with thiosemicarbazones (LH) and N-phthaloyl amino acids (AH) in 1:1:1 molar ratio in refluxing anhydrous ethanol in presence of triethylamine, yielded the complexes of type [Co(L)(A)](Figure 4). The general reaction can be represented by Equation (1).

$$CoCl_2{\cdot}6H_2O + LH + AH \xrightarrow[\Delta]{2Et_3N,EtOH} [Co(L)(A)] + 2Et_3N.HCl \quad (1)$$

{*Where* $LH = CDOTSC, DOTSC$;

$AH = HOOC - CHR' - \overline{NC(O)C_6H_4C(O)}$;

$R' = -H, -CH_3, -CH(CH_3)_2$}

The analytical data of the complexes together with their molar conductances are given in the Table I. The data are consistent with the proposed formula for the complexes. All these complexes are dark green solids, insoluble in water and in common organic solvents but soluble in DMF, DMSO and THF. The molar conductivity data (Table I) suggested the non-ionic nature of these complexes. The molecular weight measurement data indicates that these complexes are mononuclear.

IR spectra. The IR spectra of the thiosemicarbazones shows bands in the regions 3408–3475 cm^{-1} and 3265–3283 cm^{-1} due to the asymmetric and symmetric stretching frequencies for NH_2, while the absorption for NH is present in region 3154–3162 cm^{-1}. An absorption band for CN appears in 1595–1622 cm^{-1} regions. No band due to the SH group is observed between 2600 and 2500 cm^{-1} in agreement with the thione form of thiosemicarbazone and with the presence of a band in 820–836 cm^{-1} region for CS. In the IR spectra of N-phthaloyl amino acids, the carboxylic OH (except for N-phthaloyl glycine) is observed at ~3400 cm^{-1} as a broad band while a ν(OH)deformation appeared as a sharp band at ~900 cm^{-1}. The band observed at ~1750 cm^{-1} may be assigned to $\nu(CO)_{asym}$ (imido) vibration and the band observed at 1700 cm^{-1} is due to the mixing of $\nu(CO)_{sym}$(imido) and $\nu(COO)_{asym}$ vibrations. The $\nu(COO)_{sym}$ band observed at ~1400 cm^{-1} is a weak band. The value of $\Delta\nu = \nu(COO)_{asym} - \nu(COO)_{sym}$

Table II. Main IR spectral vibrations (cm^{-1}) and electronic spectral bands (cm^{-1}) for compounds.

	IR absorption frequencies (cm^{-1})								
	LH moiety			AH moiety			Non ligand band		Electronic spectral bands (cm^{-1})
Compound	$\nu(NH_2)$	ν(C=N)	ν(CS)	ν(CO)	ν(COO)	ν(Co—N)	ν(Co—O)	ν(Co—S)	
$[Co(L_1)(A_1)]$	3462 as 3292 s	1582	742	1749 as 1710 s	1585 as 1422 s	490	442	375	5,675; 15,225
$[Co(L_1)(A_2)]$	3467 as 3280 s	1594	756	1741 as 1703 s	1568 as 1428 s	482	436	352	5,712; 15,435
$[Co(L_1)(A_3)]$	3458 as 3284 s	1580	759	1750 as 1708 s	1572 as 1429 s	476	422	380	5,619; 15,607
$[Co(L_2)(A_1)]$	3422 as 3262 s	1542	748	1745 as 1709 s	1587 as 1432 s	488	443	358	5,821; 15,427
$[Co(L_2)(A_2)]$	3412 as 3268 s	1555	740	1761 as 1712 s	1578 as 1428 s	465	422	345	5,521; 15,412
$[Co(L_2)(A_3)]$	3460 as 3280 s	1560	755	1755 as 1708 s	1575 as 1425 s	485	447	392	5,670; 15,292

as = asymmetric; s = symmetric

has been found to be in the range 300–320 cm^{-1} for these N-phthaloyl amino acids.

A study and comparison of IR spectra of thiosemicarbazones (CDOTSC, DOTSC), N-phthaloyl amino acids and their mixed ligand cobalt(II) complexes imply that both types of ligands behaves as monobasic bidentate ligand. The ν(C=N) absorption band of thiosemicarbazone moieties shifted towards lower wave number in the complexes, indicates coordination of the azomethine nitrogen [28,29] to cobalt(II) ion. This was further supported by the appearance of a new medium intensity band in the region 465–490 cm^{-1}, assigned to (Co—N) mode. The weak band in the region 928–1092 cm^{-1} in thiosemicarbazone moieties spectra, which has ν(C=S) character, disappears in these complexes owing to the change in the nature of NH—C(=S)—NH_2 on complexation [30,31]. A medium intensity band in the region 820–836 cm^{-1} in the spectra of free thiosemicarbazones, assigned to the thioamide IV band, which has a significant contribution from ν(CS) shift to 740–759 cm^{-1} in complexes, indicating coordination of sulfur atom. In addition, a band in the region 345–392 cm^{-1} was assigned to ν(Co—S) and confirms coordination of the thione/thiolato sulfur atom.

The broad band appearing around ~1700 cm^{-1} due to $\nu(CO)_{sym} + \nu(COO)_{asym}$ in the spectra of N-phthaloyl amino acids is splits into two after complexation [32]. The sharp band at ~1700 cm^{-1} and a medium intensity band at 1568-1587 cm^{-1} may be due to $\nu(CO)_{sym}$ and $\nu(COO)_{asym}$ vibrations, respectively. The magnitude of $\Delta\nu$ [$\Delta\nu = \nu(COO)_{asym} - \nu(COO)_{sym}$] for these complexes found to be in the range 140–163 cm^{-1}, indicates chelating nature of the carboxylic group [33] of N-phthaloyl amino acids and this was further supported by the appearance of a new medium intensity band in the region 422-447 cm^{-1}, assigned to ν(Co—O) mode.

Table III. Antibacterial activity data for ligands and Co(II) complexes after 72 hours.

		Average value of bacteriostatic diameter (mm)*		
Compound	Concentration (μg/Disc)	*S. aureus*	*B. subtilis*	*E. coli*
L_1H	2	13.0	16.0	14.1
L_2H	2	16.4	15.8	14.2
A_1H	2	14.1	13.2	12.6
A_2H	2	12.2	14.6	15.4
A_3H	2	15.2	13.3	13.4
$[Co(L_1)(A_1)]$	2	15.8	18.0	15.9
$[Co(L_1)(A_2)]$	2	16.4	17.4	14.8
$[Co(L_1)(A_3)]$	2	16.7	18.6	15.6
$[Co(L_2)(A_1)]$	2	19.2	17.4	15.2
$[Co(L_2)(A_2)]$	2	18.8	16.9	14.8
$[Co(L_2)(A_3)]$	2	20.2	18.0	15.8

*Average value from three experiments.

Magnetic moments and electronic spectra. The magnetic moment measurement data (Table I) of representative complexes indicates that these cobalt(II) complexes are paramagnetic and show magnetic moment 4.12–4.56 B.M., corresponding to three unpaired electrons and indicative of tetrahedral geometry [34]. The electronic spectra of these complexes exhibits two bands in the ranges 5521–5821 cm^{-1} and 15225–15607 cm^{-1}, which may be assigned to $^4A_2 \rightarrow {}^4T_1$ (F) and $^4A_2 \rightarrow {}^4T_1$ (P) transitions respectively, which is characteristics of tetrahedral geometry [35–37] of the complexes [Figure 4].

Antimicrobial activity

The antibacterial and antifungal activity results, presented in Tables III and IV and Figures 1–3 respectively, show clearly that all the newly synthesized ligands and Co(II) complexes possess good antimicrobial activity. New derivatives were screened for their antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli* and for antifungal activity against *F. moniliformae* and *M. phaseolina* which exhibited a markedly enhancement of activity on further

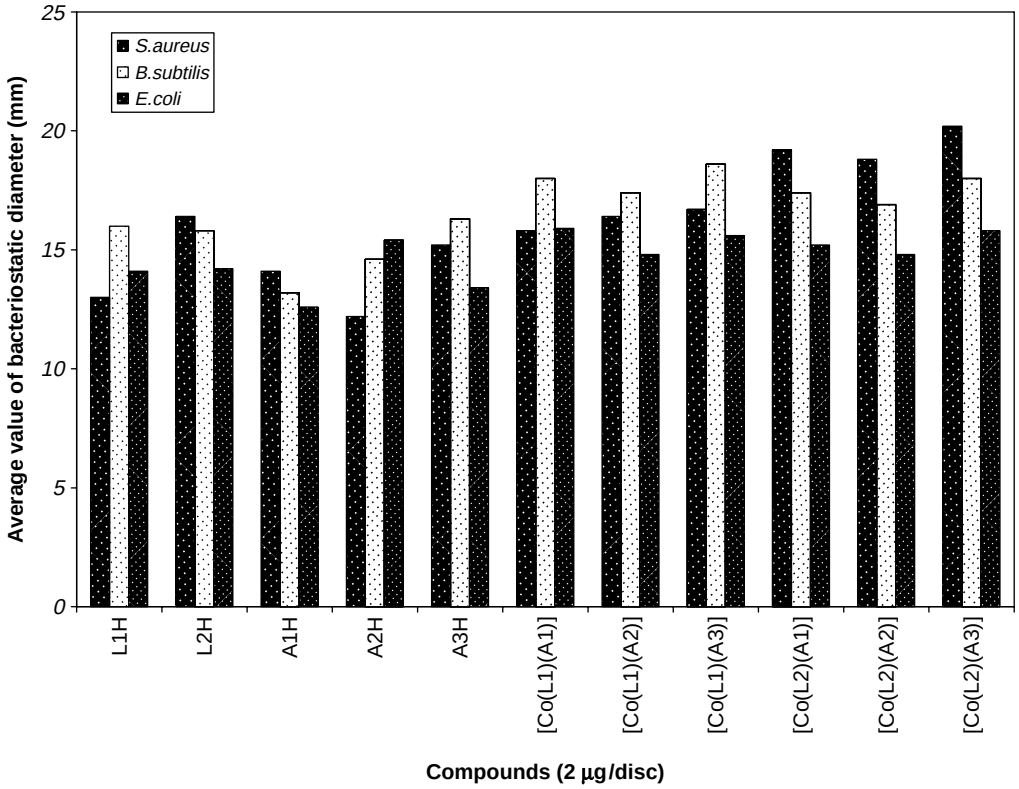


Figure 1. Bar graph showing the relative antibacterial activity of the ligands and Co(II) complexes.

coordination with the cobalt(II) ions against all the test bacteria / fungal strains.

The susceptibility of bacteria towards complex compounds were tested by measuring the bacteriostatic diameter (d) and compared with parent ligands with a concentration of 2.0 µg/disc, $d \geq 20$ mm shows high sensitivity, $14 \leq d < 20$ mm shows medium sensitivity and $9 \leq d \leq 13$ shows slight sensitivity. The antibacterial activity data shows that Gram + ve bacteria, *S. aureus* and *B. subtilis* are more susceptible to test compounds than the Gram − ve bacteria, *E. coli*, which is in accordance with previous studies. The weak antibacterial activity against Gram − ve bacteria was ascribed to the presence of an outer membrane [38], which possessed hydrophilic polysaccharide chains as a barrier to hydrophobic test compound.

All the complexes show high activity against such fungi at the lower concentration and the inhibition

Table IV. Antifungal activity data for ligands and Co(II) complexes after 72 hours.

	F. moniliformae				*M. phaseolina*			
	100(Conc. in ppm)		400(Conc. in ppm)		100(Conc. in ppm)		400(Conc. in ppm)	
Compound	Radial Growth (cm)*	% Inhibition	Radial Growth (cm)*	% Inhibition	Radial Growth (cm)*	% Inhibition	Radial Growth (cm)*	% Inhibition
L_1H	1.86	55.12	1.03	75.15	1.72	65.12	0.76	84.42
L_2H	1.82	56.15	1.12	72.92	1.57	68.16	0.71	85.63
A_1H	2.82	32.12	2.19	47.18	2.66	46.12	1.82	63.15
A_2H	2.73	34.16	2.07	50.05	2.61	47.06	1.72	65.12
A_3H	2.76	33.48	2.08	49.90	2.56	48.12	1.67	66.18
$[Co(L_1)(A_1)]$	1.76	57.60	0.78	81.16	1.65	66.48	0.64	87.12
$[Co(L_1)(A_2)]$	1.68	59.48	0.82	80.14	1.57	68.19	0.62	87.48
$[Co(L_1)(A_3)]$	1.57	62.12	0.65	84.26	1.62	67.15	0.54	88.98
$[Co(L_2)(A_1)]$	1.76	57.52	0.89	78.42	1.51	69.38	0.70	85.78
$[Co(L_2)(A_2)]$	1.74	58.19	0.87	79.07	1.63	67.06	0.68	86.15
$[Co(L_2)(A_3)]$	1.68	59.48	0.81	80.48	1.47	70.14	0.59	88.12
Control (DMSO)	4.15	0.00	4.15	0.00	4.94	0.00	4.94	0.00

* Average value from three experiments.

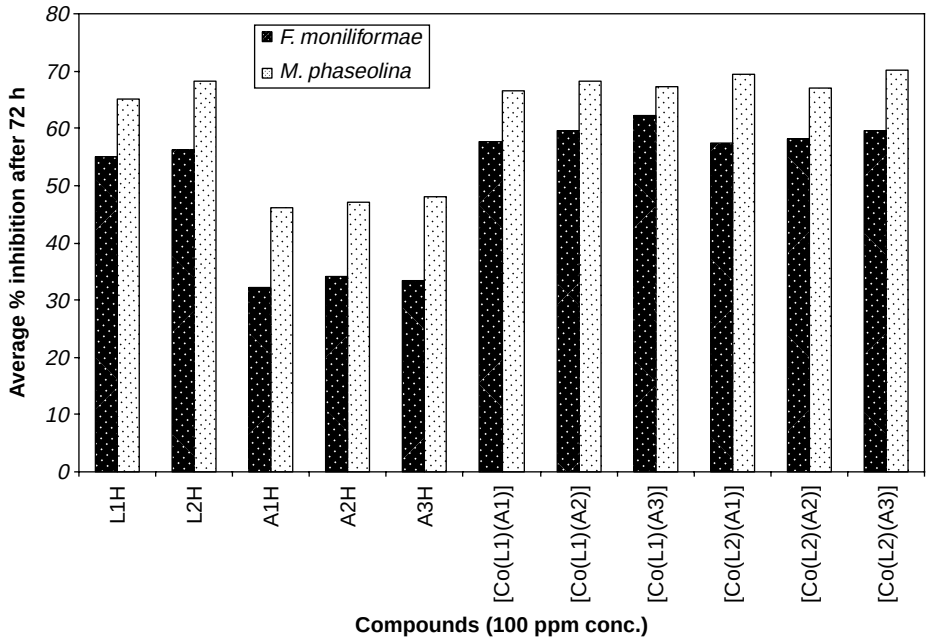


Figure 2. Bar graph showing the relative antifungal activity of the ligands and Co(II) complexes (100 ppm conc.).

of fungal growth has been found to be dependent on the concentration of compound. The antifungal activity data of test compounds against *F. moniliformae* and *M. phaseolina*, indicates that the test compound are more active against *M. phaseolina* than the *F. moniliformae*. It is observed from these tests that cobalt chelates have a higher activity than the free ligands. Such increased activity of the cobalt chelates can be explained on the basis of Overtone's concept [39] and Tweedy's chelation theory [40]. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid-soluble material due to which liposolubility is an important factor that controls antibacterial activity. On chelation, the polarity of the metal ion is reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor group. Further, it increase the delocalization of π-electrons over the whole chelates ring and enhance the penetration of the

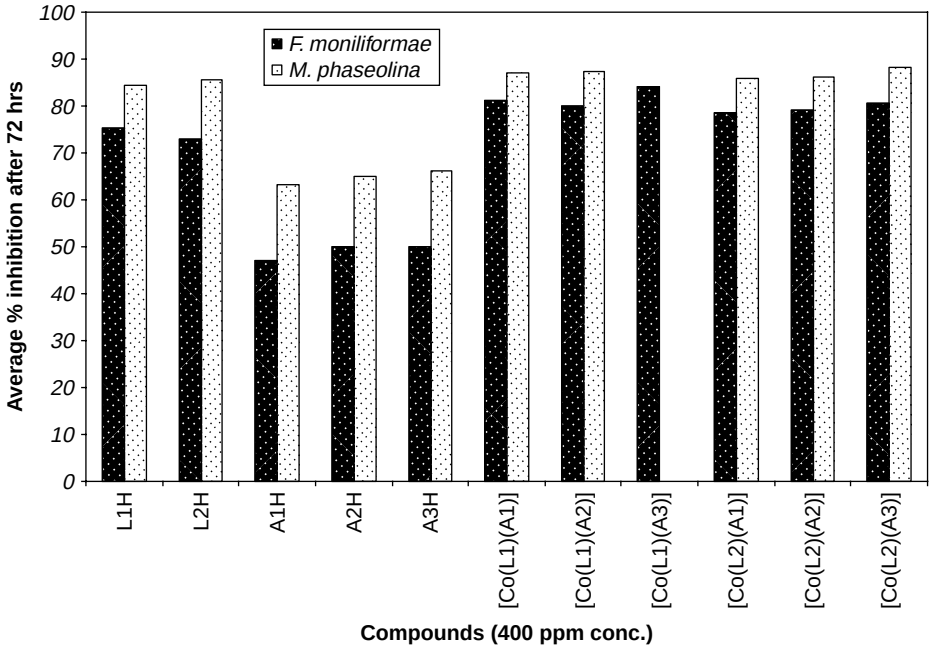
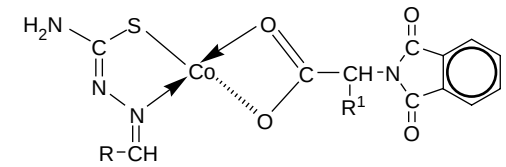


Figure 3. Bar graph showing the relative antifungal activity of the ligands and Co(II) complexes (400 ppm conc.).



{where R= $-CH_2-CH(CH_3)-CH_2-CH_2-CH=C(CH_3)_2$, $-CH_2-CH(CH_3)-CH_2-CH_2-CH=C(CH_3)$; R^1= $-H$,$-CH_3$,$-CH(CH_3)_2$)}

Figure 4. The proposed structure formula for the complexes [Co(L)(A)].

complexes into lipid membranes and blocks the of metal binding sites on the enzymes of the microorganism. These complexes also disturb the respiratory processes of the cell and thus block the synthesis of protein, which restricts further growth of the organism.

Conclusion

The mixed ligand cobalt(II) complexes isolated during the present study demonstrated that the interaction of cobalt(II) chloride with thiosemicarbazone of citral or citronellal and N-phthaloyl amino acids leads to complexes with 1:1:1 stoichiometry and are found to be mononuclear. The bidentate nature of both type of ligands have been suggested on the basis of spectral evidences. All the complexes showed enhanced antimicrobial activity than the parent ligands.

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