



Synthesis, Characterization, Antimicrobial and Antioxidant Activity of 2-Hydroxy-3-Methoxybenzaldehyde-4-Phenylthiosemicarbazone and its Pd(II) Complex, Ni(II) Mixed Ligand Complex and Cu (II) Complex having Heterocyclic Bases

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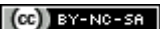
ABSTRACT

The New four complexes of Pd(II), [Ni(II)dppm], [Cu(II)bipyridyl] and [Cu(II)phenanthroline] were synthesized with 2-hydroxy-3-methoxybenzaldehyde-4-phenylthiosemicarbazone HMBPTSC (L). The FT-IR spectral data indicated the coordination of sulphur and azomethine nitrogen atoms with the central metal ion. The EPR spectra of absorptions were observed for complexes Cu (II) bipy the $g_{\perp} = 2.070$, $g_{\parallel} = 2.348$ and Cu(II)phen $g_{\perp} = 2.0705$, $g_{\parallel} = 2.364$ respectively. The g values are found in both the complexes had suggested elongated tetragonal geometry. The ligand and its complexes were evaluated for their antibacterial, antifungal activity, that [Ni(II)dppm-L] shows excellent activity. All the compounds showed good antioxidant activities.

Key words: Antibacterial, antifungal and antioxidant activities, 2-hydroxy-3-methoxybenzaldehyde-4-thiosemicarbazone and Electronic, FT-IR, NMR and EPR spectral studies.

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INTRODUCTION

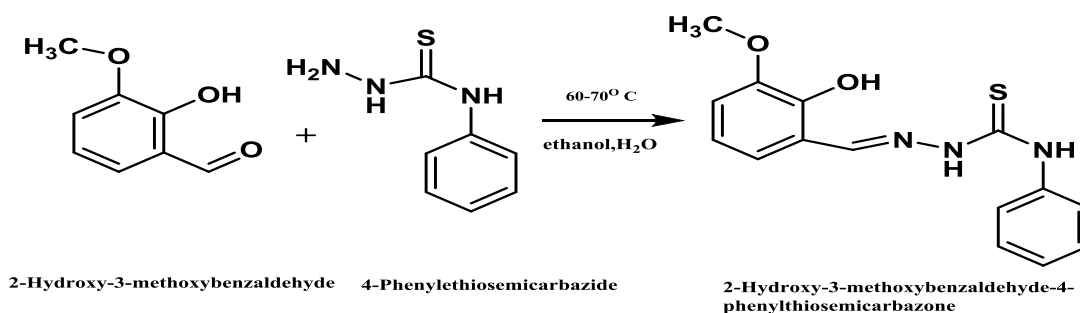
In recent years thiosemicarbazones and their transition metal complexes have been of continuous interest in the coordination chemistry of thiosemicarbazones. These compounds are predominantly showing biological activities such as antituberculosis, antitumours, antibacterial, antifungal and antioxidant activities [1-11]. These thiosemicarbazones have containing S and N donors atoms have been studied in thoroughly due their flexibility, selectivity and sensitivity towards the central metal ion, their structural similarities with natural biological substances and also due to the presence of an imine group (-N=CH-) that imparts biological activity [12]. In some cases the metal thiosemicarbazone complexes are associated with the high in vitro activity than the ligand and decreasing the side effects after complexation [13-15]. The in-depth literature survey has indicated that the biological activities depend upon parent aldehyde or ketone. The coordination of the thiosemicarbazone ligands with transition metal complexes has increased the lipophilicity and decreased some of the side effects [16]. In the present study, the synthesis and spectroscopic characterization of Pd(II), [Ni(II)dppm], [Cu(II) bipy] and [Cu(II)phen] of 2-hydroxy-3-methoxybenzaldehyde-4-phenylthiosemicarbazone ligand by using ^1H NMR, LC-MS, FT-IR, UV-Vis and EPR spectra. In vitro antibacterial and

antifungal and antioxidant activity of these compounds were also extensively evaluated.

MATERIAL AND METHODS

All the chemicals used were of analytical grade. 2-Hydroxy-3-methoxybenzaldehyde, 1,10-phenanthroline, bis(diphenylphosphino)methane and palladium (II) chloride were procured from Sigma-Aldrich. 4-Phenyl-3-thiosemicarbazide was purchased from Alfa Aesar chemicals. Copper (II) Acetate, nickel (II) chloride and 2,2 bipyridyl purchased from SD-Fine chemicals. These chemicals were used without further purification for the preparation of the free ligand as well as metal complexes.

Synthesis of ligand: To 20 mL of hot ethanolic solution containing 2-hydroxy-3-methoxybenzaldehyde (2.12 g, 0.01 mol), 5 mL of hot ethanolic solution of 4-phenyl-3-thiosemicarbazide (1.67 g, 0.01 mol) was added and the mixture was refluxed for an hour. To this mixture 2 drops of glacial acetic acid was added, stirred for 6 h at 60-70 °C and then cooled to room temperature. This reaction was monitored by thin layer chromatography (TLC). The obtained pale yellow coloured precipitate was filtered washed with ethanol and then dried under vacuum with anhydrous P_4O_{10} . The synthesis **Scheme-1** is shown in below.



Scheme-1: Synthesis of 2-hydroxy-3-methoxybenzaldehyde-4-phenylthiosemicarbazone.

Synthesis of Pd(II) complex: The general procedure was developed for the synthesis of Pd(II) thiosemicarbazones was applied for the Pd(II)-HMBPTSC in the present synthesis. To 10 mL of HMBPTSC (L) (0.0602 g, 0.0002 mol) and palladium (II) chloride (0.0177 g, 0.0001 mol) were slowly dissolved separately in limited volumes of hot methanol and mixed together slowly under constant stirring. This mixture was refluxed at 80 °C for about 6-7 h to get brown coloured solution. This solution was further slow evaporation of the solution resulted in the formation of brown coloured solid, washed with methanol and ether then dried under vacuum with P_4O_{10} . The obtained brown coloured precipitate is

checked further purity by TLC, elemental (%) and chemical analysis data are shown in **Table 1**.

Synthesis of [Ni(II)dppm] complex: To 10 mL of ligand in acetonitrile solution (0.574 g, 0.002 mol), 10 mL of acetonitrile solution containing $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ salt (0.474 g, 0.002 mol) was added slowly under stirring, to the reaction mixture 3 mL of Et_3N base were added and stirred for an 1h. After to this mixture solid $\text{PPh}_2\text{-CH}_2\text{-PPh}_2$ (0.768 g, 0.002 mol) was added and further stirred for 4-5 h. The obtained clear red colour solution was allowed to evaporate at room temperature to yield afforded red coloured solution of [Ni(II)dppm] along with the formation of $\text{Et}_3\text{NH}^+\text{Cl}^-$ salt.

Synthesis of [Cu(II) bipy/phen] complexes: The new Copper (II) mixed ligand complexes were synthesized as mentioned here under. To 10 mL of the ligand (0.602 g, 0.002 mol) in hot ethanol solution was added an ethanolic solution of Cu (OAc)₂·H₂O (0.398 g, 0.002 mol) with continuous stirring for 4-5 h. To this mixture, the heterocyclic base (0.002 mol, bipy/phen) was added in solid form and stirring was continued for about one hour. The obtained green coloured compound that formed was filtered, washed with cold ethanol and ether finally dried in vacuume.

Physical measurement: NMR spectrum of the HMBPTSC (L) was recorded with Bruker Bio spin AG-400 MHz (School of Chemistry, University of Hyderabad) using DMSO-d₆ as a solvent. Mass spectrum of the ligand was recorded in a Quattro LC-Micro mass. Elemental analyses (CHN) were performed by using FLASH 1112 series. FT-IR spectra (KBr pellet) were recorded in the region of 4000-400 cm⁻¹ on a FT-IR spectrum. Thermo scientific nicolet-380 spectrophotometer. The electronic spectra were recorded in DMF solution on a UV Shimadzu 3600 spectrometer. The EPR spectra was recorded as polycrystalline samples at 298 K on a Bruker-ER073 instrument equipped with an EMX micro X source.

Biological studies

Collection of microorganisms: The microorganisms such as Bacillus faecalis (B. faecalis), Escherichia coli (E.coli), Salmonella typhimurium (S.typhimurium), Staphylococcus aureus (S. aureus) were obtained from Institute of Microbial Technology (IMTECH), Chandigarh and Dept of Biochemistry, S.V. University, Tirupati, India, and fungal development of Candida albicans was obtained from the Department of Microbiology, RIMS Medical College, Kadapa, India. These were used for testing antimicrobial organisms in the present study. The bacteria were maintained on nutrient broth (NB) at 37°C and fungus was maintained on Potato dextrose agar (PDA) at 28 °C. C. albicans was cultured in YEPD broth with the composition of yeast extract 1 % (w/v), peptone 2 % (w/v) and dextrose 2 % (w/v) at 30°C.

Antimicrobial activity: The antimicrobial activity of different compounds were described using agar diffusion method described by Goni et.al. (2009) with modifications. Each sterile Petri plate (90 mm) was prepared with 20 mL of nutrient agar in PDA medium. After solidifying, 100 µl of bacterial suspension was spread on the plates. After 5 minutes, a sterile filter paper disc (6 mm) containing 5 µl of compound was placed on the

surface of each plate. Afterwards the microbial plates were incubated at 37 °C for 24 hours for bacterial growth and at 28 °C for 48 hours for fungal growth. The antimicrobial activity of different compounds were expressed by measuring the diameter of inhibition zone (DIZ) in mm. The zone of inhibition was measured (Diameter in mm)

Antioxidant activity: The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple coloured methanol solution of 1,1-diphenyl-1-picrylhydrazyl (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. 1 mL of each of various concentrations of the test compounds (25, 50, 75 and 100 µg/mL) in methanol was added to different 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbances of these solutions were read against blank at 517 nm. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation

$$\% \text{ of scavenging} = \frac{(\text{A control} - \text{A sample})}{(\text{A control})} \times 100$$

Where A control is the absorbance of the control reaction (containing all reagents except the test compound) and A sample is the absorbance of the test compound. Vitamin C was used as positive control and the tests were carried out in triplicate.

RESULTS & DISCUSSION

¹H NMR and Mass spectra: ¹H NMR spectrum of Ligand was recorded in DMSO-d₆ solution using TMS internal reference compound and it is presented in Fig.1. The analysis of the spectrum of ligand is follows. The peak at 11.39 ppm represents the N-H functionality attached to azomethine. The singlet signal at 9.37 ppm is corresponding to the proton of N-H group present in between phenyl and C=S groups. The phenolic ortho -OH proton shows a singlet at 8.37 ppm. Whereas, the signals appeared in the range of 7.56-6.77 ppm are attributed to nine aromatic protons. ¹H NMR: (400 MHz) δ (ppm) DMSO-d₆: δ 11.39 (1H, s, NH); 9.37 (1H, s, NH), δ 8.37 (1H, s, -OH), 7.56 (2H, d, J= 7.2 Hz, Ar-H) 7.49 (2H, d, J= 6.4 Hz, Ar-H), 7.29 (1H, t, J= 7.8 Hz, Ar-H), 7.14 (1H, d, J= 6.8 Hz, Ar-H), 6.85-6.77 (1H, m, Ar-H). The electronic impact mass spectrum of the ligand shown in Fig. 2. Owed a molecular ion peak at m/z = 302 amu corresponding to species (C₁₅H₁₅N₃O₂S) which confirms structure of the formula.

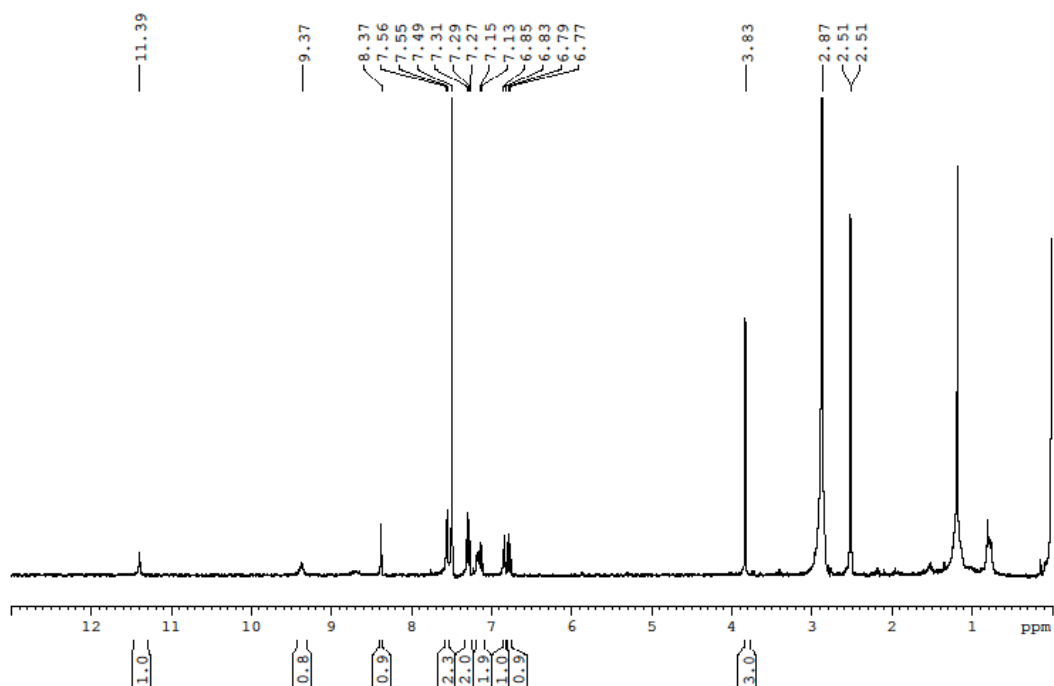


Fig. 1 ¹H NMR spectrum of the ligand

Table 1: Analytical data for the HMBPTSC(L) and its Pd(II)-L, [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes.

Compounds	Color	M.Wt	M.P(°C)	% Yield	Elemental analyses data(%) Experimental (calculated)		
					C	H	N
Ligand	Yellow	302	215	75	59.62 (58.41)	5.08 (4.59)	13.85 (13.47)
Pd(II)-L	Orange	709	>300	62	50.92 (49.35)	4.31 (3.80)	11.76 (11.42)
Ni(II)dppm-L	Redish brown	29.13	>300	65	64.12 (64.16)	4.78 (4.61)	5.69 (5.71)
Cu(II)bipy-L	Green	530.07	>300	61	59.32 (59.18)	4.21 (4.14)	12.76 (12.57)
Cu(II)phen-L	Light Green	506.07	>300	61	57.71 (57.60)	4.38 (4.25)	13.56 (13.11)

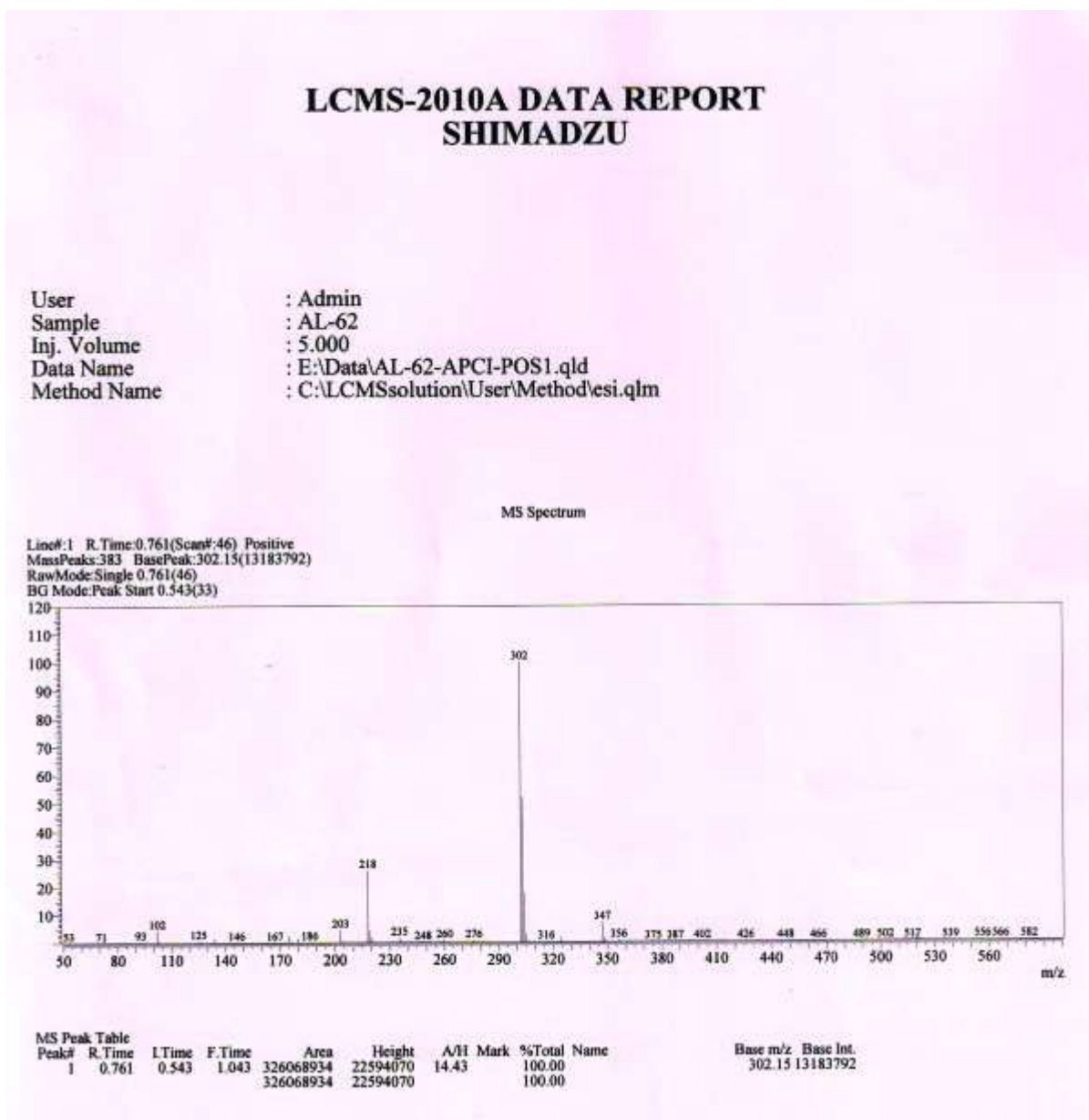


Fig. 2 Mass spectrum of the ligand

FT-IR spectra studies: The significant vibrational bands of ligand and its Pd(II)-L, [Ni(II)dppm-L], [Cu(II)bipy-L] and (Cu(II)phen-L) complexes are presented in the Fig. 3. The impotent significant spectral bands (cm^{-1}) along with assignments compared carefully. The thione form is the free ligand is confirmed on the absence of bands in the range of $2500\text{-}2600\text{ cm}^{-1}$ [17]. The strong IR band present in the spectrum of ligand at 1630 cm^{-1} is corresponding to the azomethine group, $\nu(\text{HC}=\text{N})$. Where as in the spectra of [Cu(II)bipy-L] and [Cu(II)phen-L], Pd(II)-L, [Ni(II)dppm-L], metal complexes the band appears at 1554 cm^{-1} , 1602 cm^{-1} , 1615 cm^{-1} and 1610 cm^{-1}

respectively. The shift of this band to a lower frequencies clearly suggesting the participation of azomethine nitrogen in the coordination to the metal ions [18, 19]. The participation of thione ($\text{C}=\text{S}$) group in the coordination with the central metal ion is observed from the appearance of vibrational band at 849 cm^{-1} , 805 cm^{-1} , 772 cm^{-1} and 855 cm^{-1} , for, [Cu(II)bipy-L], [Cu(II)phen-L], Pd(II)-L and [Ni(II)dppm-L] complexes respectively [20, 21]. In the spectra of complexes the metal – nitrogen bond formation is again confirming the presence of bands observed at 472 cm^{-1} , 475 cm^{-1} , 464 cm^{-1} and 470 cm^{-1} are assigned to $\nu(\text{Cu(II) bipy-M})$, $\nu(\text{Cu(II)phen-M})$ $\nu(\text{Pd(II)-M})$ and $\nu(\text{Ni(II)-(dppm)-M})$, respectively.

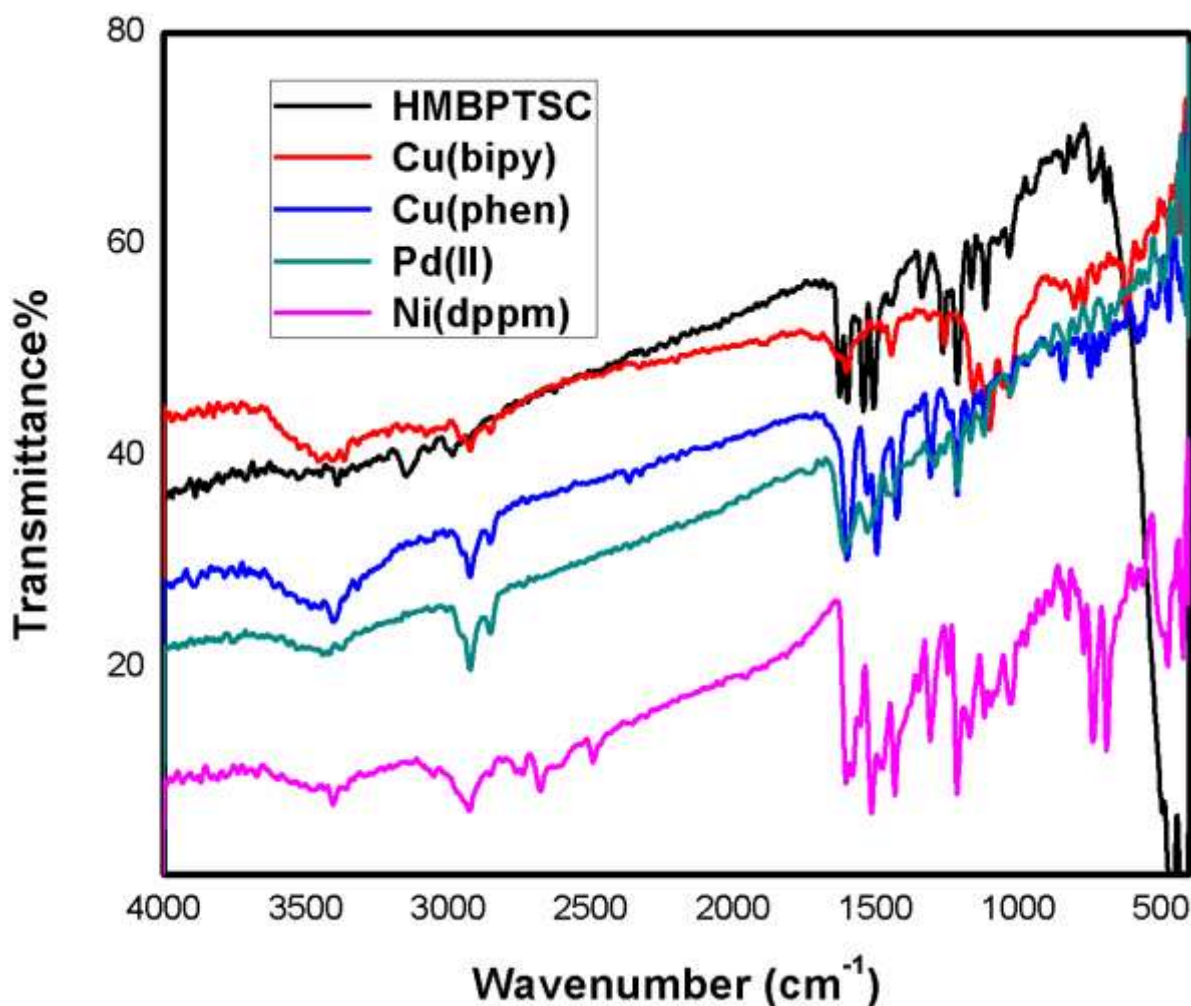


Fig. 3 FT-IR spectra of HMBPTSC(L), [Cu(II)bipy-L] and [Cu(II)phen-L] Pd(II)-L and [Ni(II)dppm-L] complexes.

Electronic absorption spectra: Electronic spectra of ligand and its complexes [Cu(II)bipy-L], [Cu(II)phen-L] and Pd(II)-L were recorded in their methanolic solutions. Whereas, [Ni(II)dppm-L] mixed ligand complex was recorded in acetonitrile solution. The absorption patterns of the ligand is comparable with similar types of thiocarbazonates and display a group of bands at 282 and 330 nm corresponding to $\pi - \pi^*$ transition and observed at 330 nm is attributed to $n - \pi^*$ transition [22]. The complexes display similar bands corresponding to Intra-ligand transitions below 330 nm and an expected blue shift was observed when compared to ligand. The

[Cu(II)bipy-L] and [Cu(II)phen-L] complexes have also shown similar pattern of display a broad band with considerable intensity in the range of 331 – 407 nm corresponding to Ligand to Metal Charge Transfer transitions(LMCT) [23]. The Ni(II) complex with $\text{PPh}_2\text{-CH}_2\text{-PPh}_2$ as ancillary ligand confirms square planar nature of the complex and Pd(II)-L complex suggests a square planar geometry involving in the transition in the spectra and also show a similar kind of absorption bands compared to Cu(II) complexes in the region of 384 – 410 nm, which are also attributed to Ligand to Metal Charge Transfer transitions as shown in Fig. 4 and Fig. 5 respectively.

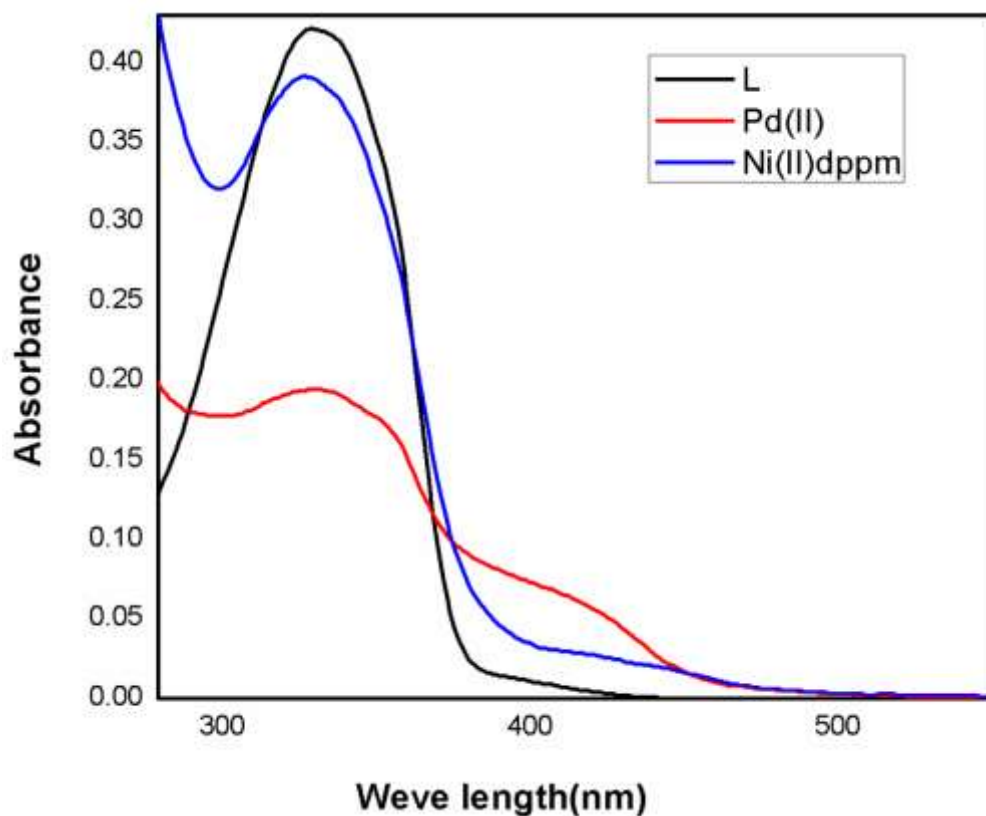


Fig. 4 Electronic spectra of the ligand, Pd(II)-L and [Ni(II)dppm-L] complexes.

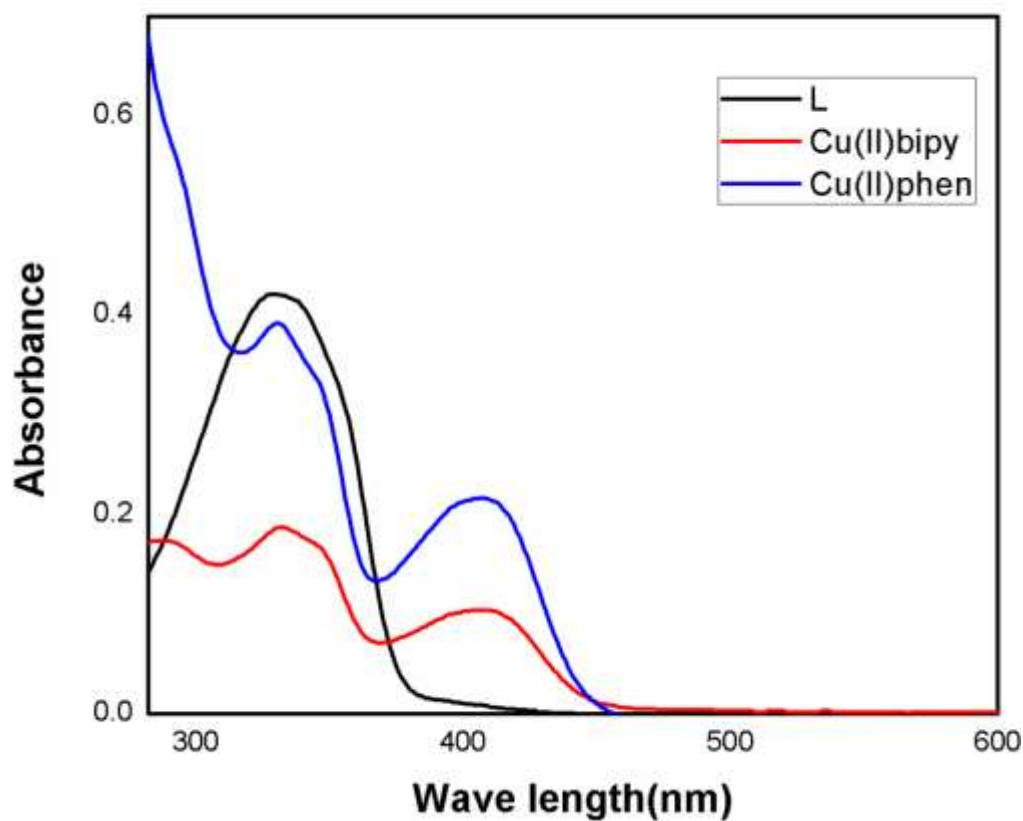


Fig. 5 Electronic spectrum of the ligand, [Cu(II)bipy-L] and [Cu(II)phen-L] complexes.

Electron paramagnetic resonance (EPR) spectrum:

EPR spectra for Cu(II) complexes of 2-hydroxy-3-methoxybenzaldehyde-4-Phenyl thiosemicarbazone were recorded in polycrystalline form, on X band at frequency of 9.68 GHz under the magnetic field strength of 3200 G room temperature X-band EPR spectra of [Cu(II)bipy-L] and [Cu(II)phen-L] complexes are presented in Fig. 6 and Fig. 7 respectively. The spectrum of [Cu(II)bipy-L] complex is a superposition of a very broad component due to strong dipole-dipole interactions. From the EPR spectrum of [Cu(II)bipy-L] complex it is observed that the characteristic of mononuclear copper complexes with axial symmetry, and lacks the hyperfine splitting like concentrated solid Cu(II) complexes. The analysis of spectra gives $g_{\perp}=2.070$, $g_{\parallel}=2.348$, and $g_{\perp}=2.070$ $g_{\parallel}=2.364$ values for the [Cu(II)bipy-L] and [Cu(II)phen-L] complexes respectively

[24]. The observed g_{\perp} values for the complexes are less than 2.3 indicate the covalent character of the metal ligand bond. The calculated g values provide valuable information on the electronic ground state of the ion. For g values, $g_{\parallel} > g_{\perp} > g_e$, the ground state of the ion is $d_{x^2-y^2}$ which suggest an elongated tetragonal symmetry. The exchange coupling interaction between two copper ions is obtained from the expression given by Hathaway.

$$G = (g_{\parallel} - 2.0023) / (g_{\perp} - 2.0023).$$

According to Hathaway, if $G > 4$, the exchange interaction is negligible, but $G < 4$ indicates considerable exchange interaction the solid complexes. The complexes reported in this paper, given the “G” value is 1.255 and for [Cu(II)bipy-L] and [Cu(II)phen-L] complexes respectively, i.e. $G < 4$ indicating the exchange interaction in the prepared both copper complexes.

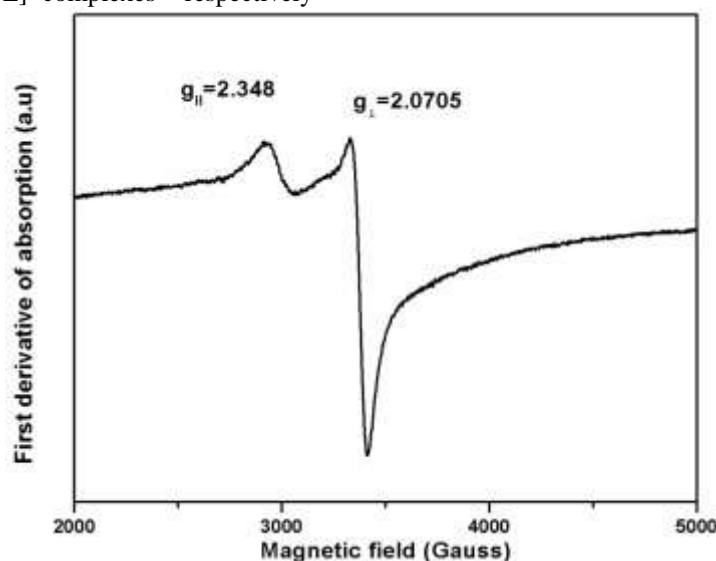


Fig. 6 EPR Spectrum of [Cu(II)bipy-L] complex.

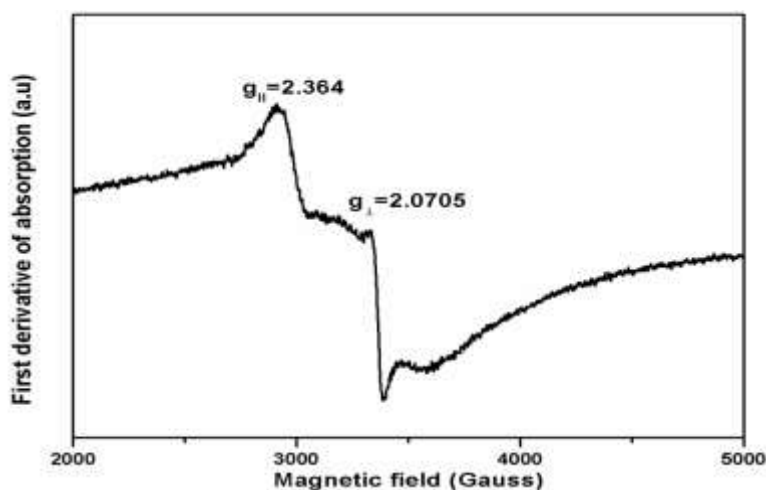


Fig.7 EPR Spectrum of [Cu(II)phen-L] complex.

BIOLOGICAL STUDIES

Antibacterial activity: Antibacterial activity of the ligand and its Pd(II), [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes were tested against different gram positive and negative bacteria. The minimum inhibitory concentration (MIC) is the lowest concentration of visible growth after overnight incubation. MICs are important in diagnostic laboratories to confirm the resistance of microorganisms to antimicrobial agents also to monitor the activity of the new microbial drugs. We used modified agar well diffusion method to measure the MIC values are presented in **Table 2**. The result of antibacterial activity of ligand and its complexes showed moderate to significant effect against all bacterial strains in a concentration dependent manner. At 100 µg/ml concentration all

the compounds showed maximum effect. The reason for greater activity of complexes could be explained by the chelation theory [25]. According to the chelation theory, the polarity of the metal ion is determined to be minimized to an advanced level, due to the responsibility of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups, especially with sulphur and nitrogen donors. The other factors like solubility, conductivity and bond length between the metal and ligand also incise the activity. The results clearly show that Ni(II)dppm metal chelates present effective antibacterial activity. Finally, the growth of antibacterial activity of all the compounds following the order of [Ni(II)dppm-L] > [Pd(II)-L] > ligand.

Table 2: Antibacterial activity of HMBPTSC (L) and its [Pd(II)-L], [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes.

Bacterial Species	Compounds	Zone of Inhibition in mm				
		Concentration in µg/ml				
		25	50	75	100	Std.30 µg/ml
Escherichia coli	Ligand	8	10	14	18	23
	Pd(II)	7	10	13	17	22
	Ni(II)dppm	10	13	17	22	24
	Cu(II)bipy	8	11	14	17	21
	Cu(II)phen	6	8	12	15	19
Bacillus faecalis	Ligand	9	11	13	17	21
	Pd(II)	8	10	13	18	23
	Ni(II)dppm	11	15	19	22	25
	Cu(II)bipy	9	14	16	20	23
	Cu(II)phen	10	13	14	19	22
Salmonella typhimurium	Ligand	11	14	16	22	24
	Pd(II)	9	14	17	19	23
	Ni(II)dppm	12	15	19	24	25
	Cu(II)bipy	10	13	15	21	22
	Cu(II)phen	8	14	17	19	21
Staphylococcus aureus	Ligand	11	16	19	20	25
	Pd(II)	13	18	20	22	24
	Ni(II)dppm	14	19	21	24	23
	Cu(II)bipy	12	17	22	24	21
	Cu(II)phen	10	15	20	22	24

Antifungal activity: Antifungal activity of the ligand and its Pd(II)-L, [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes were tested against *Candida albicans* fungal strains. The activities of the ligand and its complexes were compared with *Candida albicans* given in Table 3. All the complexes showed good activity against *C. albicans*. Moreover, [Ni(II)dppm-L] showed the

very efficient inhibition. The way of action may involve the formation of a hydrogen bond through the azomethine nitrogen atom with the active centers of the cell constituents. The resulting fungal effect in interference with the common cell process [26, 27]. All the compounds show fungal growth inhibition in the following order Ni(II)dppm > Cu(II)bipy > Pd(II) > ligand.

Table 3: Antifungal activity of HMBPTSC (L) and its [Pd(II)-L], [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes.

.Compounds	Ligand	[Pd(II)-L]	[Ni(II)dppm-L]	[Cu(II)bipy-L]	[Cu(II)phen-L]	Fluconazole
<i>Candida albicans</i>	1.2	1.6	1.9	1.8	0.7	2.1

Antioxidant activity: The synthesized Pd(II)-L, [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes are subjected to antioxidant activity test by using DPPH radical scavenging method. The DPPH method is a rapid, simple and reliability. This method is a rapid and inexpensive method measure antioxidant capacity of neutral or synthesized compound *in vitro*. The principal for the reduction in DPPH free radicals was that the antioxidant reacts with stable free radical DPPH radical and converts it to 1,1-diphenyl-2-picrylhydrazine. The ability to Scavenging the

stable free radical DPPH radical is measured by decrease in the absorbance at 517 nm [28]. The free ligand exhibited comparative activity in DPPH scavenging as seen in the case of standard antioxidant Vitamin-C. All the complexes showed good antioxidant activity properties in a concentration dependent manner. Moreover, [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes showing the best antioxidant activity any given concentration than Vitamin-C as shown in the Fig. 8.

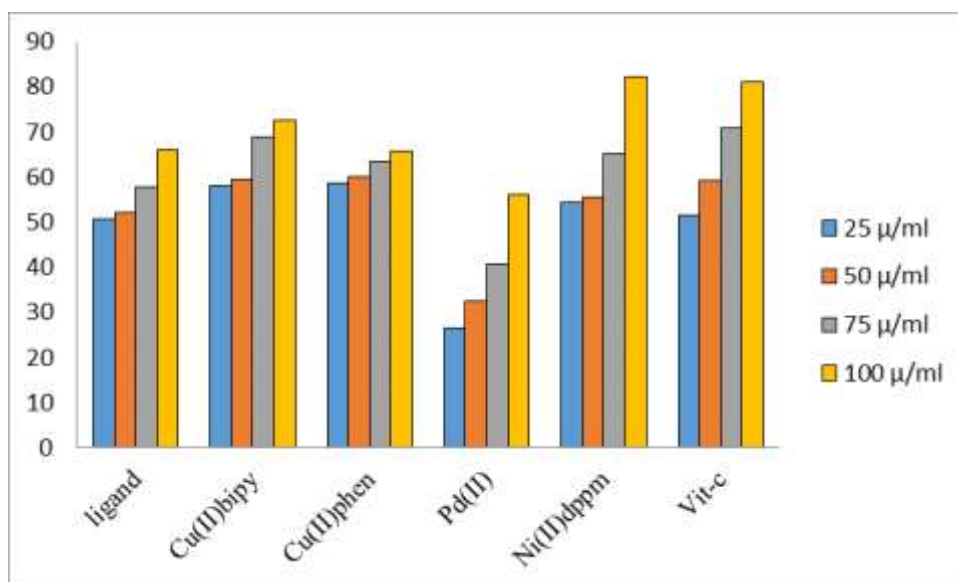


Fig.8. DPPH Scavenging activity of ligand and its Pd(II)-L, [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes.

CONCLUSION

Finally, to conclude that the [Pd(II)-L], [Ni(II)dppm-L], [Cu(II)bipy-L] and [Cu(II)phen-L] complexes of tridentate 2-hydroxy-3-methoxybenzaldehyde-4-

phenylethiosemicarbazone were prepared and characterized. The IR spectra of the complexes have suggested the strong bonding with thione functional of ligand with the metal complexes. Infrared and electronic spectral studies reveal on

square planar geometry for [Pd(II)-L] and [Ni(II)dppm-L] complexes. NMR spectroscopy supports the structure of the synthesized ligand. The antibacterial activity of ligand and its metal complexes are shows good activity, among the all compounds [Ni(II)dppm-L] shown more activity ,The results of fungal activity shows [Ni(II)dppm-L] best activity and antioxidant activity studies that all compounds shows good antioxidant activity.

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