



SYNTHESIS, CHARACTERIZATION, BIOLOGICAL ACTIVITY AND METAL COMPLEXING PROPERTIES OF LIGANDS WITH DERIVED FROM HYDRALAZINE DRUG AND CHLORO SUBSTITUTED SALICYLALDEHYDE

Kirti Salame^{1*} And Arun Singh²

^{1*}Research Scholar, Department of Chemistry, Government MLB Girls' PG Autonomous College Bhopal, M.P., India

²Professor, Department of Chemistry, Government MLB Girls' PG Autonomous College Bhopal, M.P., India, Email ID: dr.arunsingh68@gmail.com

***Corresponding Author:** Kirti Salame

*Research Scholar, Department of Chemistry, Government MLB Girls' PG Autonomous College Bhopal, M.P., India, Email ID: m.b.masram@gmail.com

Abstract

Hydrazone ligands viz; 4-chloro-2-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PCP) and 2,4-dichloro-6-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PDP) were prepared by condensation of Hydralazine drug respectively with 5-chlorosalicylaldehyde (CS) and 3,5-Dichloro salicylaldehyde (DCS). The synthesised ligands and their Cu²⁺, Ni²⁺ and Co²⁺ metal complexes have been analysed by elemental content, spectral features, magnetic moment molar conductance and thermo gravimetry. The analytical data show that complexes show 1:1(M:L) ratio, the magnetic moment consistent with predicted structure. All the compounds have been screened for their antimicrobial activity against common microbes.

Keywords: Hydralazine drug, Ligands, Schiff base, Salicylaldehyde, Metal Complexes, Spectral studies, Magnetic and Antimicrobial activity.

Introduction

Because of diverse medicinal application of Schiff's base are synthesised by many organic chemistry researchers nowadays [1-3]. The Schiff's base shows wide array of pharmacological activity like, antiviral, anticancer, anti-inflammatory, antibacterial, antifungal, etc.[4-12]. Schiff's bases have ability to form complexes with metal ions, which accelerate the pharmacological activity of ligands [13-17]. The nanoparticles of Schiff's bases show enhanced antimicrobial activity [18]. In connections of our earlier work [19] the present work comprises the synthesis, Characterization, chelating and microbicidal properties of Schiff's base of chloro substituted salicylaldehyde and hydralazine. The design of synthesis is shown in Figure-1.

EXPERIMENTAL

2.1 Materials

All the chemicals used were of analytical grade.

2.2. Preparation of hydrazone ligands

The hydrazone ligands abbreviated as 4-chloro-2-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PCP) and 2,4-dichloro-6-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PDP) were prepared by mixing an ethanolic solution (20 ml) of 5-chlorosalicylaldehyde (CS) and 3,5-Dichloro salicylaldehyde (DCS) (0.01 mol) with hydralazine (HN) (0.01 mol) in the equal volume of ethanol and add as a buffering agent sodium acetate (0.01 mmol) in 10 ml water. The reaction mixture then refluxed with constant stirring for 3.5-4.0 hrs, respectively. The product was kept for 24hrs, then filtered, washed with distilled water and ethanol. Crystallized them from ethanol.

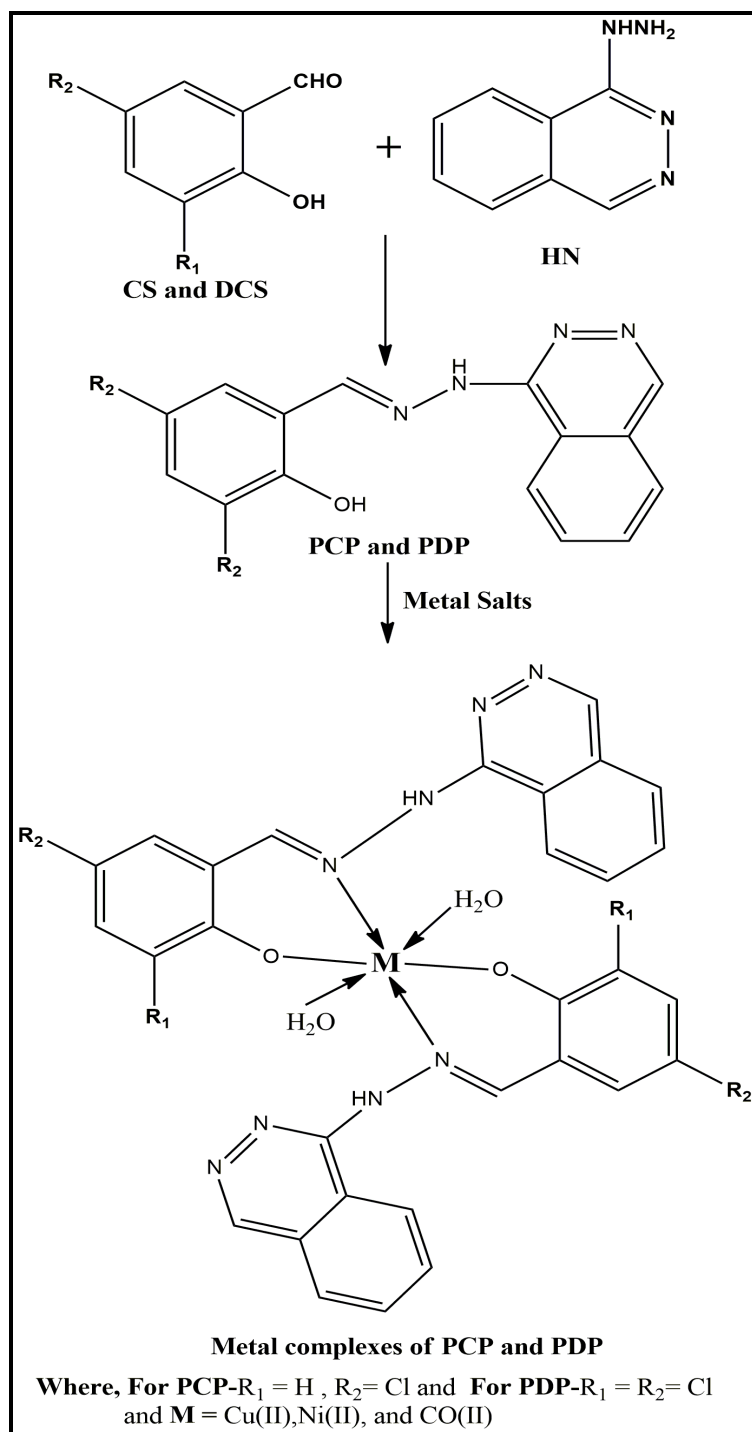


Figure-1 Reaction path of preparation of metal complexes

2.3. Preparation of the metal complexes of 4-chloro-2-((2-(phthalazin-1-yl) hydrazono) methyl)phenol (PCP) and 2,4-dichloro-6-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PDP)

Metal complexes of 4-chloro-2-((2-(phthalazin-1-yl) hydrazono)methyl)phenol (PCP) and 2,4-dichloro-6-((2-(phthalazin-1-yl)hydrazono)methyl)phenol(PDP) were prepared by direct mixing of of metal salt (0.5 mmol) and the corresponding amount of 4-chloro-2-((2-(phthalazin-1-yl) hydrazono) methyl)phenol (PCP) and 2,4-dichloro-6-((2-(phthalazin-1-yl) hydrazono) methyl)phenol (PDP) ligands and sodium acetate. The metal chloride was dissolved in water and ligands was dissolved in ethanol and sodium acetate in the smallest possible volume of water. The mixture was refluxed for 1.0–3.5 hrs. The resultant solid metal complexes were separated by filtration and then washed several times with acetone and then diethyl ether. The solid complexes were dried in vacuum desiccator. The yield ranged from 69% to 80%. The complexes are soluble in ethanol, methanol, DMF and DMSO. The dried complexes were subjected to elemental and spectroscopic analysis.

Table-1: Analysis of PCP and PDP ligands and its metal complexes

Compound (Designation)	Empirical Formula (Mol. Wt. gm/mole)	Yield (%)	Elemental Analysis				
			% C	% H	% N	% Cl	%M
			Cald Found	Cald Found	Cald Found	Cald Found	Cald Found
PCP	C ₁₅ H ₁₁ N ₄ OCl (298.5)	84	60.31 60.3	3.71 3.7	18.76 18.7	11.87 11.8	-
PCP-Cu ⁺²	C ₃₀ H ₂₀ N ₈ O ₂ Cl ₂ Cu.2H ₂ O (694.54)	80	51.83 51.8	3.46 3.4	16.13 16.1	10.22 10.2	9.15 9.1
PCP-Ni ⁺²	C ₃₀ H ₂₀ N ₈ O ₂ Cl ₂ Ni.2H ₂ O (689.71)	77	52.20 52.1	3.48 3.4	16.24 16.2	10.29 10.2	8.51 8.5
PCP-Co ⁺²	C ₃₀ H ₂₀ N ₈ O ₂ Cl ₂ Co.2H ₂ O (689.94)	75	52.18 52.1	3.48 3.4	16.23 16.2	10.29 10.2	8.54 8.5
PDP	C ₁₅ H ₁₀ N ₄ OCl ₂ (333)	82	54.07 54.0	3.03 3.0	16.82 16.8	21.28 21.2	-
PDP-Cu ⁺²	C ₃₀ H ₁₈ N ₈ O ₂ Cl ₄ Cu.2H ₂ O (763.54)	76	47.15 47.1	2.88 2.8	14.67 14.6	18.60 18.5	8.32 8.3
PDP-Ni ⁺²	C ₃₀ H ₂₀ N ₈ O ₂ Cl ₂ Ni.2H ₂ O (758.71)	73	47.45 47.4	2.90 2.8	14.76 14.7	18.72 18.7	7.74 7.7
PDP-Co ⁺²	C ₃₀ H ₁₈ N ₈ O ₂ Cl ₄ Co.2H ₂ O (758.94)	69	47.43 47.4	2.90 2.8	14.76 14.7	18.71 18.7	7.77 7.7

Measurements:

The elemental contents were determined by Thermo Finigen Flash1101 EA (Italy) the metals were determined volumetrically by Vogel's method [20]. To a 100 mg complex sample, each 1 ml of HCl, H₂SO₄ and HClO₄ were added and then 1 g of NaClO₄ was added. The mixture was evaporated to dryness and the resulting salt was dissolved in double distilled water and diluted to the mark. From this solution the metal content was determined by titration with standard EDTA solution. Infrared spectra of the synthesized compounds were recorded on Nicolet 760 FT-IR spectrometer. NMR spectrum of ligands were recorded on 60 MHz NMR spectrophotometer. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. Magnetic susceptibility measurement of the synthesized complexes was carried out on Gouy Balance at room temperature. Mercury tetrathio cynato cobalate (II) Hg[Co(NCS)₄] was used as a calibrant. The electronic spectra of complexes in solid were recorded on at room temperature. MgO was used as reference. A Shimadzu TGA-50H thermal analyzer was used to record TG curves. The measurements were carried out in N₂ atmosphere (20

ml/min) with a heating rate of 10°C/min in the temperature range 20–1200°C using platinum crucibles, with a TGA-50 Shimadzu instrument. Antifungal activity of all the samples was monitored against various fungi, following the method reported in literature[21].

Results and Discussion

The reaction between 5-chlorosalicylaldehyde (CS) and 3,5-Dichloro salicylaldehyde (DCS) with hydralazine (HN) yielded 4-chloro-2-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PCP) and 2,4-dichloro-6-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PDP). The resulted ligands were an amorphous powder. The C, H, N contents of both ligands (Table-1) are consistent with the structure predicted (Figure-1). The 4-chloro-2-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PCP) ligand gives IR spectra (figure not given) bands at 3400-3250 cm⁻¹ (NH and OH), 3020, 2850, 1630, 1475 cm⁻¹ (C-H), 1590 cm⁻¹ (C=N), 1275 cm⁻¹ (C-N), 1150 cm⁻¹ (C-O), 750 cm⁻¹ (C-Cl) and NMR Signals (δ ppm, figure not given) at 5.40 (s, 1H, OH), 7.00-8.90 (m, 8H, Ar-H), 9.20 (1H, s, CH=N) and 8.10 (1H, s, NH) and M⁺: 299.5. Similarly, 2,4-dichloro-6-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PDP) ligand gives IR spectra (figure not given) bands at 3400-3250 cm⁻¹ (NH and OH), 3020, 2850, 1630, 1475 cm⁻¹ (C-H), 1590 cm⁻¹ (C=N), 1275 cm⁻¹ (C-N), 1150 cm⁻¹ (C-O), 752 cm⁻¹ (C-Cl) and NMR Signals (δ ppm, figure not given) at 5.40 (s, 1H, OH), 7.00-8.90 (m, 7H, Ar-H), 9.20 (1H, s, CH=N) and 8.10 (1H, s, NH) and M⁺: 334.3. The structure of PCP and PDP are confirmed by LC-MS which is consistent with predicted structure. Thus the structure of PCP and PDP are confirmed as shown in Figure-1.

The metal and C, H, N contents of metal complexes of PCP and PDP (Table-1 and 2) are also consistent with the predicted structure. The results show that the metal: ligand (M:L) ratio for all divalent metal complex is 1:2.

The infrared spectra of all the complexes are identical and suggest the formation of the entire metalocyclic compound. The bands are almost at their respectable positions as appeared in the spectrum of parent-ligand expect the absent of band for -OH, which indicates the formation of M-O band for metal complexation with shifting of C-O bands at 1260 cm⁻¹. However, the band due to (M-O) band could not be detected as it may appear below the range of instrument used.

The observed μ_{eff} values in the range 2.50-4.61 B.M are consistent with the above moiety. The value of magnetic moments and reflectance spectral data of each complexes co-relates with structure assigned as the octahedral geometry. [20-23]

Table-2: Spectral features and magnetic moment of PCP and PDP metal complexes

Metal Complexes	μ_{eff} (BM)	Electronic spectral data (cm ⁻¹)	Transition
PCP-Cu ⁺²	2.50	23445 15876	Charge transfer $^2B_{1g} \rightarrow ^2A_{1g}$
PCP-Ni ⁺²	3.63	22582 15372	$^3A_{1g} \rightarrow ^3T_{1g}(P)$ $^3A_{1g} \rightarrow ^3T_{1g}(F)$
PCP-Co ⁺²	4.60	22723 15263 8940	$^4T_{1g}(F) \rightarrow ^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow ^4T_{2g}$ $^4T_{1g}(F) \rightarrow ^4T_{2g}(P)$
PDP-Cu ⁺²	2.52	23450 15874	Charge transfer $^2B_{1g} \rightarrow ^2A_{1g}$
PDP-Ni ⁺²	3.62	22580 15375	$^3A_{1g} \rightarrow ^3T_{1g}(P)$ $^3A_{1g} \rightarrow ^3T_{1g}(F)$
PDP-Co ⁺²	4.61	22725 15261 8943	$^4T_{1g}(F) \rightarrow ^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow ^4T_{2g}$ $^4T_{1g}(F) \rightarrow ^4T_{2g}(P)$

The data of electronic transitions and magnetic moments of metal complexes are summarized in Table-2.

The thermogravimetric (TG) plots of Cu^{+2} -complex are shown in Figure.3. In Table-2 shows the stepwise decomposition of metal complexes with corresponding weight loss.

Table-3: Thermal degradation of PCP and PDP metal complexes

Metal Complexes (Mol. Wt.)	TG range (°C)	Weight Loss %Calcd. (%Found)	Predicted intermediates and final products	Metallic residue %Calcd. (%Found)
PCP-Cu^{+2} (694.54)	45-102	5.18 5.22	H_2O	CuO 11.45 (11.48)
	102-250	10.22 10.26	$1/2\text{Cl}_2$	
	400-550	20.73 20.75	$2\text{N}_2 + \text{CH}_4$	
	550-680	50.10 50.16	C_{14}H_6	
PCP-Ni^{+2} (689.71)	40-120	5.21 5.25	H_2O	NiO 10.83 (10.88)
	150-550	31.17 31.23	$1/2\text{Cl}_2$, $2\text{N}_2 + \text{CH}_4$	
	550-680	50.45 50.49	C_{14}H_6	
PCP-Co^{+2} (689.94)	35-120	5.21 5.25	H_2O	CoO 10.86 (10.92)
	150-570	31.16 31.22	$1/2\text{Cl}_2$, $2\text{N}_2 + \text{CH}_4$	
	570-690	50.43 50.47	C_{14}H_6	
PDP-Cu^{+2} (763.54)	45-102	4.71 4.76	H_2O	CuO 10.41 (10.45)
	102-250	18.59 18.63	$1/2\text{Cl}_2$	
	400-550	18.85 18.94	$2\text{N}_2 + \text{CH}_4$	
	550-680	45.57 45.66	C_{14}H_6	
PDP-Ni^{+2} (758.71)	40-120	4.74 4.79	H_2O	NiO 9.84 (9.90)
	150-550	37.69 37.76	$1/2\text{Cl}_2$, $2\text{N}_2 + \text{CH}_4$	
	550-680	45.86 45.94	C_{14}H_6	
PDP-Co^{+2} (758.94)	35-120	4.74 4.80	H_2O	CoO 9.87 (9.96)
	150-570	37.68 37.77	$1/2\text{Cl}_2$, $2\text{N}_2 + \text{CH}_4$	
	570-690	45.85 45.93	C_{14}H_6	

The TGA curve of the PCP-Cu⁺² complex shows four stages of decomposition within the temperature range (45–680°C). The first step of decomposition due to the loss of water molecule, the second step between 102–250°C due to the loss of two chlorine atoms. The third step due to the loss of 4N₂ + 2CH₄ molecules with mass loss 20.75% (calcd. 20.73%). The fourth step due to the loss of two C₁₄H₆ molecule with mass loss 50.16% (calcd. 50.10%). The total mass loss up to 690°C is in agreement with the formation of CuO as the final residue (TG 11.48%, calcd. 11.45%). Similarly, results are shown in Table-3.

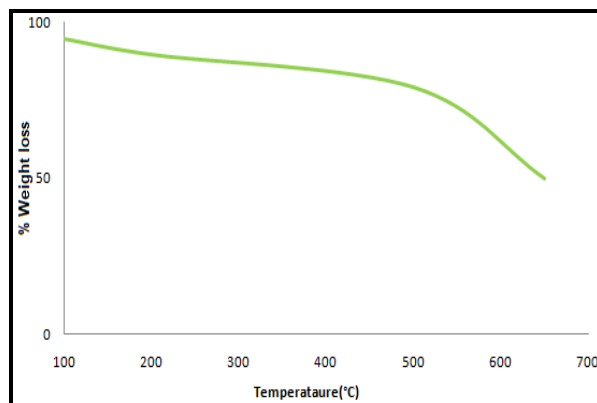


Figure-3 thermogravimetric (TG) plots of Cu⁺²-complex

The examination of antibacterial and antifungal activity of PCP and PDP ligands and their all complexes (Table-4 and 5) reveals that the ligands are moderately toxic against bacteria and fungi. The result of antibacterial and antifungal activity of PCP and PDP ligands and their all complexes (Table-4 and 5) reveals that all the complexes are more toxic than ligands. Among all the complexes the Cu⁺² complex is more toxic against bacteria and fungi.

Table-4: Antibacterial activity of ligands and its metal complexes

Compound (Designation)	Zone of Inhibition (in mm)			
	Gram positive		Gram negative	
	<i>B.megaterium</i>	<i>S.Aureus</i>	<i>E.Coli</i>	<i>Ps.Aeruginosa</i>
PCP	7	9	8	10
PCP-Cu ⁺²	14	16	15	17
PCP-Ni ⁺²	13	14	12	14
PCP-Co ⁺²	10	11	12	13
PDP	9	9	10	11
PDP-Cu ⁺²	16	17	16	19
PDP-Ni ⁺²	14	15	14	17
PDP-Co ⁺²	12	13	14	15
Tetracycline	18	19	18	21

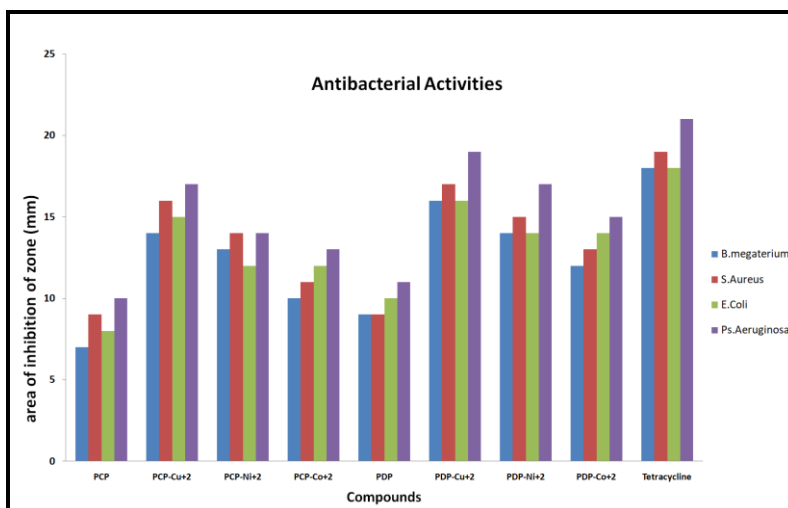


Fig-3. Histogram of antibacterial activity of ligands and its metal complexes

Table-5: Antifungal activity of ligands and its metal complexes

Sample	Zone of inhibition of fungus at 1000 ppm (%)			
	<i>Aspergillus Niger</i>	<i>Botrydepladia Thiobromine</i>	<i>Nigrospora Sp.</i>	<i>Fusarium oxyporium</i>
PCP	62	62	61	63
PCP-Cu ⁺²	78	79	76	76
PCP-Ni ⁺²	76	74	71	72
PCP-Co ⁺²	75	76	74	74
PDP	67	65	66	65
PDP-Cu ⁺²	80	79	79	76
PDP-Ni ⁺²	79	75	80	76
PDP-Co ⁺²	77	76	81	77

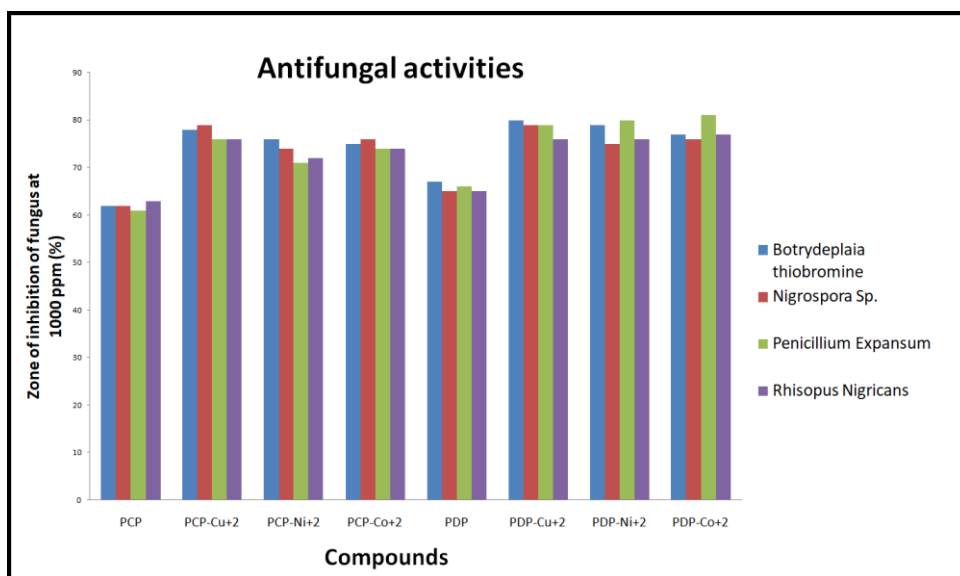


Fig-4. Histogram of antifungal activity of ligands and its metal complexes

Conclusions:

The novel ligands namely, 4-chloro-2-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PCP) and 2,4-dichloro-6-((2-(phthalazin-1-yl)hydrazono)methyl)phenol (PDP) synthesised and characterized. The

structures of all the synthesised ligands and its all metal complexes were confirmed by elemental analysis, spectroscopic analysis and magnetic properties. All the synthesised ligands and its all metal complexes also were shows moderate to good antimicrobial activity.

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Conflict of Interest

Authors of this manuscript declare that there is no any conflict of interest between Authors.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors have used no any AI tool to generate the report.

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