

ONE POT SYNTHESIS OF PIPERIDONE BASED TRANSITION METAL COMPLEXES AND THEIR ANTIOXIDANT AND ANTIFUNGAL ACTIVITY STUDIES

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ABSTRACT

Transition metal complexes containing tri-dentate ONO donor ligand i.e., 2,6-bis(2-hydroxyphenyl)piperidin-4-one (BHP) (**2**) have been achieved by one pot multicomponent reaction with salicyaldehyde and acetone in presence of ammonium acetate. The ligand forms complexes (**M₁-M₇**) with different salts of Co(II), Cu(II), Ru(III) in good yield. The newly synthesized ligand and their respective complexes were characterized by elemental analysis, molar conductance measurement and various spectral studies such as infrared (IR), electronic, and NMR (for ligand only)]. The proposed geometries of the complexes are octahedral in nature. The antioxidant and antifungal activity of the synthesized complexes was studied against

DPPH radical and different microbial strains. The study showed that all synthesized ligand and their complexes were exhibits certain degree of antioxidant and antimicrobial activities. Among them Ru(**M₇**) and Co(**M₃**) complexes exhibits effective antioxidant and Cu(**M₄**) and Co(**M₂**) complex showed highest antifungal activity.

KEYWORDS: Piperidone ligand, Metal complexes, Antioxidant, Antifungal.

INTRODUCTION

The introduction of metal ions or metal ion binding components into a biological system for the treatment of diseases is one of the main subdivisions in the field of bioinorganic chemistry.^[1] Nowadays, the bioinorganic chemists target the heterocyclic ligands and their metal complexes to study their pharmacology as the main focus of research.^[2] A wide range

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of biological activities^[3-5] such as antibacterial, antifungal, antitumor and antiviral activities are exhibited by the nitrogen-containing organic compounds and their metal complexes. Transition metal complexes offer two distinct advantages as DNA-binding agents.^[6] First and foremost, transition metal centers are particularly attractive moieties for reversible recognition of nucleic acids research because they exhibit well-defined coordination geometries.

Nitrogen containing heterocycles are one of the most important classes of ligands in coordination chemistry.^[7-10] The ability to readily fit in more than two donor atoms or two or more aromatic nitrogen-containing heterocycles into one molecule, has afforded access to numerous chelating and bridging ligands.^[11] In the latter case, ligands possessing more than one coordination site can link a number of metal atoms. These bridging ligands have attracted in recent years because they enable the formation of multinuclear metallosupramolecular assemblies^[12,13] or coordination polymers^[14-23] with desirable structures and properties. Within such bridging ligands, the additional stabilising effect of chelation to multiple metal atoms can be achieved through the incorporation of bidentate donor groups that form either a five- or six membered chelate ring with each coordinated metal centre. Bridging ligands with the prospective to chelate at both metal centres result in complexes with greater stability and potentially enhance the metal-metal interactions. In view of the importance of nitrogen containing heterocyclic compounds, in the present investigation we have selected one of the nitrogen heterocyclic compounds i.e., piperidone for synthesis metal complexes and studies of their biological relevance.

Heterocyclic compounds carrying piperidine skeleton are attractive targets of organic synthesis owing to their pharmacological activity and their wide occurrence in nature. Specifically, piperidine based chemical entities with aryl substituents at carbons 2 and 6 of the piperidine ring have been documented as potent antimicrobial agent.^[24] Piperidinone derivatives are found to possess diversified pharmacological activity and form an essential part of the molecular structures of some drugs.^[25] Piperidine heterocycles play an important role in the field of medicinal chemistry. Several derivatives of this class such as herbicidal, insecticidal, fungicidal, bactericidal, anti-inflammatory, antihistaminic, hypotensive, anticancer, CNS stimulant and depressant and nerve activities have been found to possess useful biological activities.^[26-28] Based on the above, in the continuation of our work on the metal complexes^[29-30] in the present investigation we synthesized piperidone ligand and its

metal complexes and screened their antioxidant and anti-microbial activity with good potency.

EXPERIMENTAL

Materials and reagents

All chemicals, reagents and Metal salts (M = Co(II), Cu(II), Ru(III)) were purchased from Merck. Double distilled methanol was used as a solvent for the synthesis. Triple distilled water was used for rinsing the required apparatus and they were dried in the oven before use. All the chemicals used in this research were of analytical reagent grade and used as commercially obtained without further purification.

Instruments

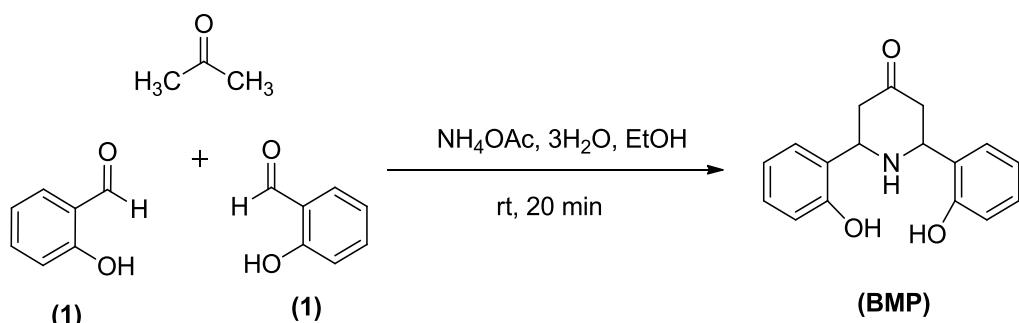
The molar conductance of solid complexes in 10^{-3} (M) DMSO was measured in Labtronics auto digital conductivity meter (LT 16 model). The CHN micro-elemental analysis of the compounds was performed on Elementar Vario EL III model analyzer. The infrared spectra were recorded on a PerkinElmer FT-IR spectrophotometer as a KBr discs in the range of 400–4000 cm^{-1} . The ^1H NMR and spectra were recorded on Bruker Avance III, 400 MHz spectrometer, using DMSO-d₆ as solvent and tetramethylsilane as an internal standard. The electronic spectra of the complexes were recorded on single beam microprocessor Labtronics UV–Vis spectrophotometer (LT-290 model) in the range 200–1000 nm in DMSO solvent. The positive mode ESI-MS spectra of the compounds were analyzed on Agilent Q-TOF mass spectrometer.

Synthesis of ligand (BHP)

Synthesis of 2,6-bis(2-hydroxyphenyl)piperidin-4-one (BHP)

The experimental procedure adopted for the condensations was as follows: a mixture of acetone (2 mmol), salicyaldehyde (4 mmol) and ammonium acetate (2 mmol) in 10 ml of ethanol was heated until the acetate dissolved and a yellow colour developed. After cooling, the reaction mixture was taken in ether (20 ml) then addition of conc. HCl (1 ml) to the clear filtrate afforded the hydrochloride of the 2,6-bis(4-methoxyphenyl) piperidin-4-one (**BMP**). The free base was obtained by treating a suspension of the hydrochloride with aqueous ammonia, followed by dilution with water. The crude solid thus obtained was filtered. Crystallization from ethanol yielded the compound (2) (82%).

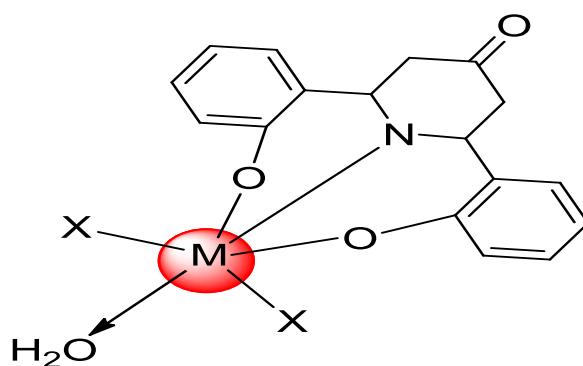
Yield 70% as brown solid, M.p 153–155 °C. IR (KBr) ν max (cm⁻¹): 3126–2972 (Ar–CH), 1615 (C=O), 3632 (N–H). ¹H NMR (300 MHz, DMSO-d₆) δ ppm: 6.89–7.05 (m, 8H, Ar–H), 4.02 (m, 2H, CH), 2.98 (m, 4H, CH₂), 1.91 (s, 1H, NH). Mass (m/z): (M⁺) 311.05.



Scheme 1: Synthetic pathway of 2,6-bis(2-hydroxyphenyl)piperidin-4-one (BHP).

General method for synthesis of metal complexes (M₁–M₇)

Metal salts such as: CoCl₂.5H₂O/Co(SO₄)₂.5H₂O/Co(CH₃COO)₂/CuCl₂.5H₂O/Cu(SO₄)₂.5H₂O/Cu(CH₃COO)₂/RuCl₂.4H₂O/ (1 mmol) was dissolved in 5 ml of ethanol. A 1 mmol of ligand (BMP) is dissolved in methanol separately and this was mixed to the metal solution. It was refluxed 2–3 hrs in on water bath (70–80 °C). Then solvent was evaporated. The complex was obtained were used to further analysis.



$\text{M}=\text{Co(II), Cu(II) and Ru(III)}$
 $\text{X}=\text{Cl, SO}_4, \text{CH}_3\text{COO}$

Fig 1. General structure synthesized metal complexes (M₁(BHP)₂–M₇(BHP)₂).

BIOLOGICAL STUDIES

Antioxidant activity

The newly synthesized ligand and their complexes were screened for their radical scavenging activities using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity.

DPPH radical scavenging assay

The DPPH radical scavenging effect was carried out according to the method first employed by Blois.^[31] ligand and their complexes at different concentrations were prepared in distilled ethanol, 1 mL of each compound solutions having different concentrations (10 μ M, 50 μ M, 100 μ M, 200 μ M and 500 μ M) were taken in different test tubes, 4 ml of a 0.1 mM ethanol solution of DPPH was added and shaken vigorously. The tubes were then incubated in the dark room at RT for 20 min. A DPPH blank was prepared without complex, and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV-visible spectrophotometer and the remaining DPPH was calculated. The percent decrease in the absorbance was recorded for each concentration, and percent quenching of DPPH was calculated on the basis of the observed decreased in absorbance of the radical. The radical scavenging activity was expressed as the inhibition percentage and was calculated using the formula:

$$\text{Radical scavenging activity (\%)} = [(A_o - A_1)/A_o \times 100]$$

Where A_o is the absorbance of the control (blank, without compound) and A_1 is the absorbance of the compound. IC_{50} values were calculated by liner regression algorithm.

Antifungal activity

Antifungal studies of newly synthesized ligand and complexes were carried out against *A. flavus*, *C. keratinophilum* and *C. albicans*. Sabourand's agar media was prepared by dissolving peptone (10 g), D-glucose (40 g) and agar (20 g) in distilled water (1000 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of the corresponding species. 20 mL of agar media was poured into each petridish. Excess of suspension was decanted and plates were dried by placing them in an incubator at 37 °C for 1 hr. Wells were made on these seeded agar plates using sterile cork borer and different concentrations of the test compounds in DMSO were added into each of the labeled wells. A control was also prepared for the plates in the same way using DMSO. The Petri dishes were prepared in triplicate and maintained at 25 °C for 72 hrs. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with fluconazole as standard. Zones of inhibition were determined for compounds.

RESULT AND DISCUSSION

Chemistry

In the present work, one pot multicomponent synthetic strategies was adapted for the synthesis of 2,6-bis(2-hydroxyphenyl)piperidin-4-one (**BHP**). Salicyaldehyde condensed (Mannich reaction) with acetone and ammonium acetate afforded 2,6-bis(2-hydroxyphenyl)piperidin-4-one in 82% yield. Further the ligand (**BHP**) reaction with different metal salts (Co(II), Cu(II), Ru(III)) (M:L 1:1) furnished metal complexes.

Physical characterization

Micro analytical, molar conductance and other physical properties of the ligand and metal complexes are presented in Table 1. The molar conductance values clearly indicate nonelectrolytic nature of the ligand and its metal complexes. The micro analytical data of the complexes revealed **M(BHP)** type geometry with 1:1 metal ligand ratios. The ligand was soluble in methanol and the metal complexes were soluble only in mild polar organic solvents like DMSO and DMF. They were found insoluble in water. The proposed structure determination and confirmation of the complexes (Fig. 1) is well explained on the basis of the rigorous study of their physical data in combination with spectral results.

Table-1: Molecular formulae, colour, yield, melting point, elemental analysis, magnetic susceptibility and molar conductance data of ligand and their metal complexes.

Compounds	Mol formula	Color	Yield	Melting point(^o C)	Elemental analysis calc. Found (%)				Molar conductance ()	$\mu_{\text{eff}}(\text{BM})$
					C	H	N	M		
L(BHP)	C ₁₇ H ₁₇ NO ₃	Pale yellow	61.05	160	72.80 (72.07)	6.55 (6.05)	4.80 (4.94)	-		
M₁(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] Cl ₂ .H ₂ O	Black	61.15	185	65.88 (65.92)	4.61 (4.56)	4.46 (4.52)	9.47 (9.51)	83.21	3.75
M₂(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] (SO ₄) ₂ .H ₂ O	Grey	66.75	180	65.78 (65.92)	4.71 (4.56)	4.56 (4.52)	9.67 (9.51)	91.13	3.75
M₃(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] (CH ₃ COO) ₂ .H ₂ O	Dark brown	61.20	190	65.99 (65.92)	4.71 (4.56)	4.76 (4.52)	9.87 (9.51)	85.75	3.75
M₄(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] Cl ₂ .H ₂ O	Black	63.35	200	65.76 (65.43)	4.68 (4.52)	4.70 (4.49)	10.90 (10.18)	87.66	1.29
M₅(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] (SO ₄) ₂ .H ₂ O	Light green	67.00	170	65.86 (65.43)	4.98 (4.52)	4.70 (4.49)	10.90 (10.18)	81.35	1.29
M₆(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] (CH ₃ COO) ₂ .H ₂ O	Dark green	64.90	150	65.76 (65.43)	4.58 (4.52)	4.40 (4.49)	10.60 (10.18)	82.37	1.29
M₇(BHP)	[Ru(C ₁₇ H ₁₄ NO ₃)]Cl ₂ .H ₂ O	Black	60.00	200	61.65 (61.72)	4.36 (4.27)	4.45 (4.23)	15.30 (15.28)	76.51	4.49

Infrared spectroscopy

IR spectra of the new metal complexes reveals the following points:

- IR data supports the presence of the carbonyl group in lignad at 1650–1670 cm^{-1}
- The spectra in the region 3125–3350 cm^{-1} is due the presence of –NH functional group in free ligand, which leads the shifting of frequency to lower region of about 50–75 cm^{-1} , indicates that the formation of complexes through NH group of piperidone ring.
- A sharp band appears in the region 3250-3600 cm^{-1} in ligand which is represents the presence of hydroxy group (O-H) group in aromatic ring of ligand. This band frequency was absence in complexes.

Table 2: The important infrared frequencies (in cm^{-1}) of the ligand and its metal complexes.

Compounds	Mol formula	γ (N-H) cm^{-1}	γ (C=O) cm^{-1}	γ (M-N) cm^{-1}	γ (M-O) cm^{-1}
L(BHP)	$\text{C}_{17}\text{H}_{17}\text{NO}_3$	3125–3350	1650–1670	-	-
M₁(BHP)	$[\text{Co}(\text{C}_{17}\text{H}_{14}\text{NO}_3)] \text{Cl}_2 \cdot \text{H}_2\text{O}$	3315	1665	610	440
M₂(BHP)	$[\text{Co}(\text{C}_{17}\text{H}_{14}\text{NO}_3)] (\text{SO}_4)_2 \cdot \text{H}_2\text{O}$	3275	1635	623	432
M₃(BHP)	$[\text{Co}(\text{C}_{17}\text{H}_{14}\text{NO}_3)] (\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$	3323	1620	608	410
M₄(BHP)	$[\text{Cu}(\text{C}_{17}\text{H}_{14}\text{NO}_3)] \text{Cl}_2 \cdot \text{H}_2\text{O}$	3295	1685	635	415
M₅(BHP)	$[\text{Cu}(\text{C}_{17}\text{H}_{14}\text{NO}_3)] (\text{SO}_4)_2 \cdot \text{H}_2\text{O}$	3290	1610	605	424
M₆(BHP)	$[\text{Cu}(\text{C}_{17}\text{H}_{14}\text{NO}_3)] (\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$	3325	1638	615	418
M₇(BHP)	$[\text{Ru}(\text{C}_{17}\text{H}_{14}\text{NO}_3)] \text{Cl}_2 \cdot \text{H}_2\text{O}$	3298	1613	610	410

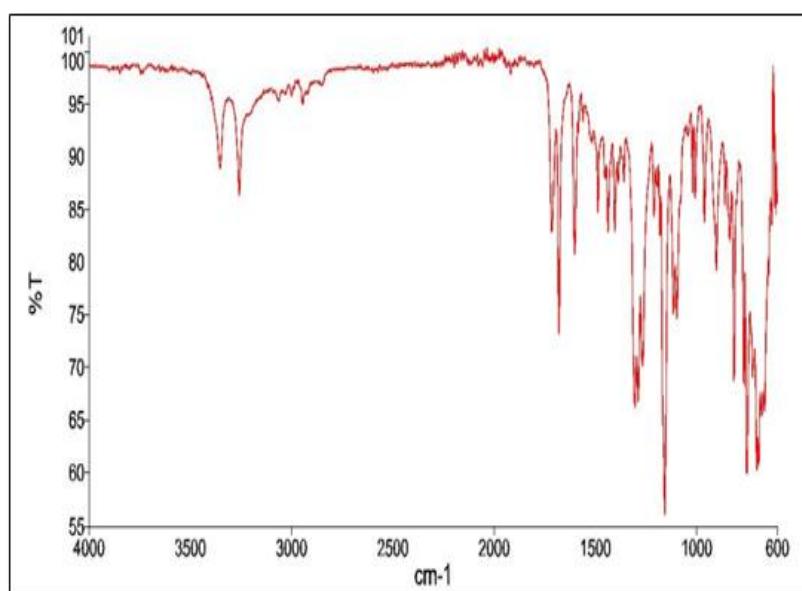


Fig 2. IR spectra of 2,6-bis(2-hydroxyphenyl)piperidin-4-one L(BHP)

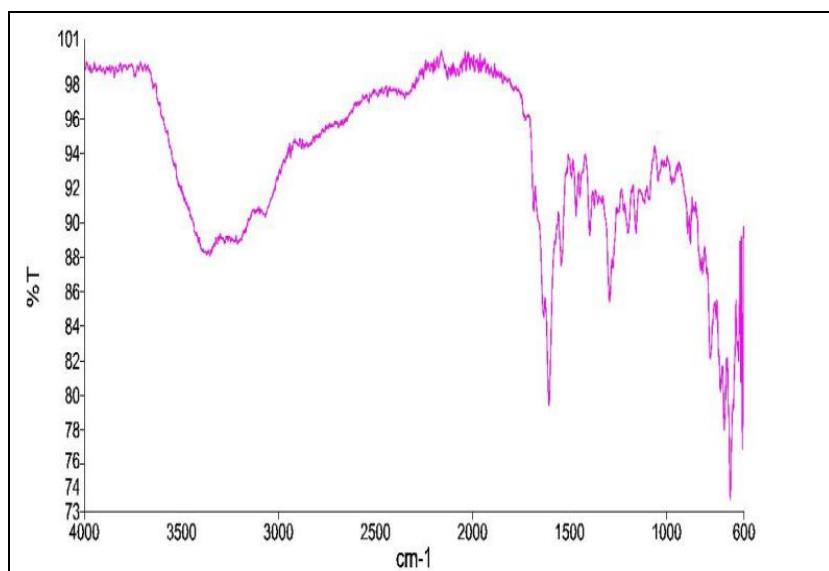


Fig 3: IR spectra of M₇(BHP).

Molar conductance studies

The molar conductivity values in the range 15.25– 22.00 ohm's mol⁻¹ cm² in DMSO denote that all the complexes behave as 1:2 electrolytes in these solvents^[32] and all metal complexes shows non-electrolytic characteristic property.

Electronic spectra

Electronic spectra of the ligand is shown in the (Figs. 4) and the metal complexes **M₂(BHP)** in the (Figs. 6), these spectra's were depicted that the bands below ~340 nm are attributed to intraligand transition.^[33] A small shift should be observed for the second band in all complexes, these π - π^* /transitions probably involving metal and ligand orbital's. Bands above ~340 nm are ascribed to charge transfer process, probably from ligand to metal and mainly associated with the NH and OH group.

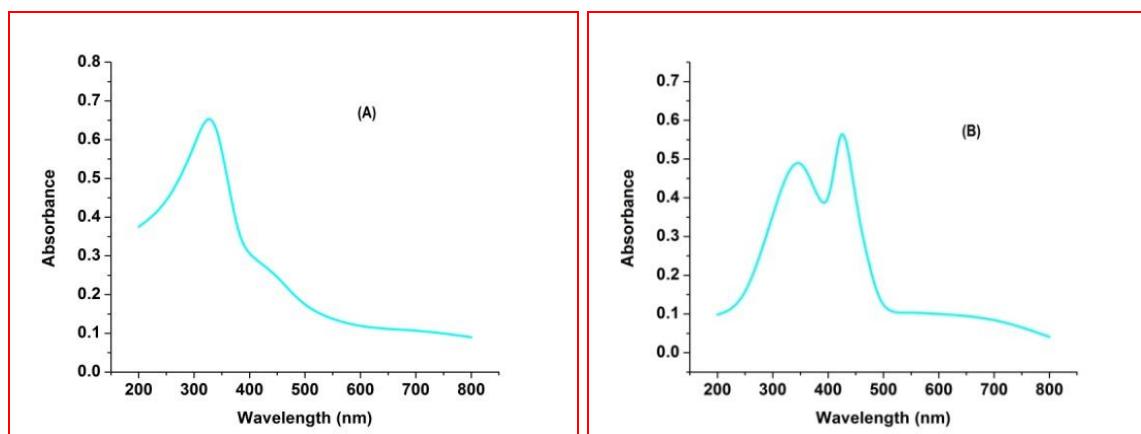


Fig 4. UV-visible spectra of ligand BHP (A) and M₂(BHP) (B).

¹H NMR spectral study of ligand

The ¹H NMR spectra were recorded in DMSO-d₆ in a multiplet from δ 6.85 to 7.30 ppm for aromatic protons (Ar-H). In piperidone ring the signals within the range of δ 2.73 to 2.98 ppm are attributable to CH₂ protons on the piperidone ring. The signal of the two CH protons on piperidone ring showed triplet at δ 4.30 ppm in ¹H NMR spectrum. The signals observed as a singlet at δ 1.91 (NH), and δ 5.20 ppm (OH) respectively.^[34]

BIOLOGICAL ACTIVITY

Antioxidant activity

DPPH Radical Scavenging Activity. The antioxidant activity of ligand as well as metal complexes showed moderate to high activity (Table 3). At the different concentration of 10, 25, 50, 100, 200 and 500 μ M, few complexes such as Ru (**M₇(BHP)**) and Co (**M₃(BHP)**) showed a much stronger radical scavenging activity compared to ascorbic acid (65%). The antioxidant activity of ligand [BHP] and metal complexes (**M₁(BHP)**) and (**M₂(BHP)**) were showed moderate activity comparison with complexes (**M₇(BHP)**) and (**M₇(BHP)**), could be due to the coordination of metal after complexation of the system, increasing its capacity to stabilize unpaired electrons and thereby, to scavenge free radicals. Remain complexes of (**M₄(BHP)**), (**M₅(BHP)**) and (**M₆(BHP)**) shows moderate activity of scavenging property.

Table 3: Antioxidant activity (ic₅₀) of the ligand and its metal complexes.

Compounds	Mol formulae	IC ₅₀
L(BHP)	C ₁₇ H ₁₇ NO ₃	315 \pm 0.18
M₁(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] Cl ₂ .H ₂ O	143 \pm 0.07
M₂(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] (SO ₄) ₂ .H ₂ O	135 \pm 0.13
M₃(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] (CH ₃ COO) ₂ .H ₂ O	32 \pm 0.05
M₄(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] Cl ₂ .H ₂ O	165 \pm 0.28
M₅(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] (SO ₄) ₂ .H ₂ O	159 \pm 0.19
M₆(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] (CH ₃ COO) ₂ .H ₂ O	148 \pm 0.31
M₇(BHP)	[Ru(C ₁₇ H ₁₄ NO ₃)]Cl ₂ .H ₂ O	24 \pm 0.04
Standard	Ascorbic acid	19 \pm 0.05

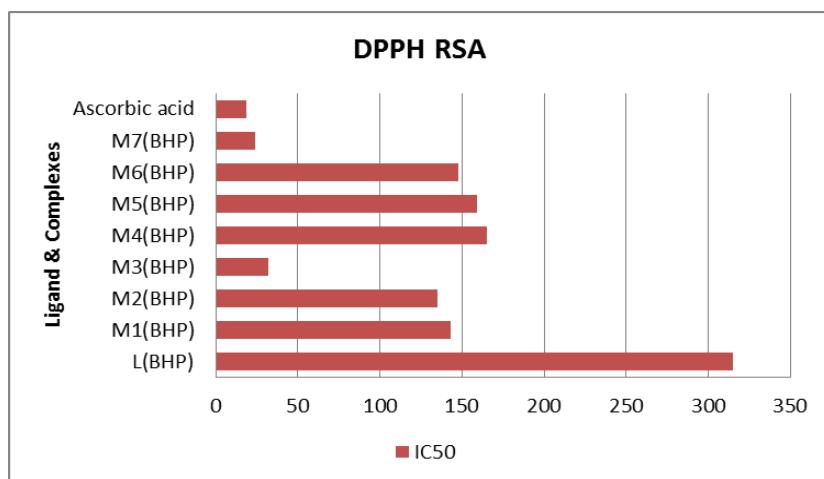


Fig 5: Graphical representation of DPPH Radical scavenging activity ligand their metal complexes.

Antifungal activity

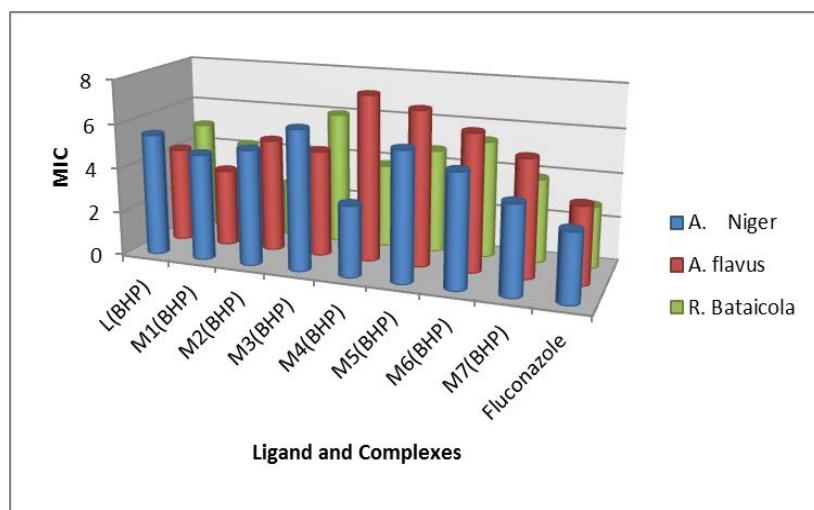
The minimum inhibitory concentration (MIC) values of the compounds against the respective strains are summarized in table-4, figure-10. The antifungal screening results of all the synthesized ligand and their metal complexes exhibited antimicrobial properties.

It is important to note that the metal complexes exhibited a more inhibitory effect compared to parent ligand. The enhanced activity of the complexes over the ligand can be explained on the basis of chelation theory.^[35] It is known that chelation makes the ligand a more powerful and potent fungicidal agent, thus killing more of the fungi than the ligand.

It has been suggested that ligand with hetero donor atoms (nitrogen and oxygen) showed the fungal activity, since the enzymes that require these groups for their activity appear to be especially more susceptible to deactivation by metal ions on coordination. It is observed that, in a complex, the positive charge of the metal ion is partially shared with the hetero donor atoms (nitrogen and oxygen) present in the ligand, and there may be π -electron delocalization over the whole chelating system.^[36] Thus the increase in the lipophilic character of the metal chelates favors their permeation through the lipoid layer of the fungal membranes and blocking of the metal binding sites in the enzymes of microorganisms. Other factors, namely solubility, conductivity and bond length between the metal ion and the ligand, also increase the activity. Among these complexes, compound (**M₄(BHP)**) against *A. Niger* and (**M₂(BHP)**) *R. Bataicola* exhibited the highest antifungal activity. Remaining compounds showed considerable to moderate activity compared to the standard.

Table 4: Antifungal activity of the ligand and its metal complexes (minimum inhibitory concentration $\times 10^{-2}$ m).

Compounds	Mol formula	A. Niger	A. Flavus	R. Bataicola
L(BHP)	C ₁₇ H ₁₇ NO ₃	5.5	4.3	5.0
M₁(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] Cl ₂ .H ₂ O	4.8	3.5	4.2
M₂(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] (SO ₄) ₂ .H ₂ O	5.2	5.1	2.5
M₃(BHP)	[Co(C ₁₇ H ₁₄ NO ₃)] (CH ₃ COO) ₂ .H ₂ O	6.3	4.8	6.0
M₄(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] Cl ₂ .H ₂ O	3.2	7.5	3.8
M₅(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] (SO ₄) ₂ .H ₂ O	5.8	7.0	4.7
M₆(BHP)	[Cu(C ₁₇ H ₁₄ NO ₃)] (CH ₃ COO) ₂ .H ₂ O	5.1	6.2	5.3
M₇(BHP)	[Ru(C ₁₇ H ₁₄ NO ₃)]Cl ₂ .H ₂ O	4.0	5.3	3.8
Standard	Fluconazole	3.1	3.5	2.8

**Fig 6: Graphical representation of antifungal activity ligand their metal complexes.**

CONCLUSION

In this research article, we have synthesized a new piperidone ligand and its metal complexes. The formation of the compounds has been confirmed by the analytical data, IR, electronic, mass, ¹H NMR spectral studies, magnetic susceptibility, and molar conductance data. The above studies reveal that the piperidone ligand acts as neutral tridentate coordinating through nitrogen and hydroxyl oxygen atoms to the metal ions. The results displayed that Ru (**M₇(BHP)**) and Co (**M₃(BHP)**) complexes exhibit higher antioxidant activity and complexes (**M₄(BHP)**) and (**M₂(BHP)**) exhibited the highest antifungal activity compared to other complexes. It is well noticed that the synthesized metal complexes exhibited more inhibitory effects than the parent piperidone ligand as the efficacy of the organic compound is positively modified upon coordination with the metal ions. Thus, the present study gives valuable information to the bioinorganic chemists and contributes better knowledge to the field of bioinorganic chemistry.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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