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DESIGN, ANALYSIS, AND ANTIMICROBIAL EXPLORATION OF TRANSITION METAL COMPLEXES WITH TRIDENTATE SCHIFF BASES

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ABSTRACT
The hydrazone Schiff base ligand, 1-(2,5-dihydroxyphenyl) propylidene) pyrazine-2-carbohydrazide, was synthesized by condensing equimolar amounts of 2,5-dihydroxypropiophenone and pyrazine-2-carbohydrazide in ethanol. This ligand was then reacted with various metal chlorides to form complexes with Fe (III), Ti (III), Cr (III), Th (IV), VO (IV), MoO_2(VI), and WO_2(VI). The synthesis followed an established protocol. These metal-ligand complexes exhibited notable antimicrobial activity. Scanning Electron Microscopy (SEM) was used to study their shape, while X-ray diffraction (XRD) confirmed the structure of the complexes as nano-crystalline.
Keywords: Hydrazone, Metal Complexes, Antimicrobial Activity, SEM Analysis, XRD Analysis.
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INTRODUCTION

Aroyl hydrazone is derived from metal complexes that have been widely studied for their enzyme-inhibitory properties and their broad applications in organic synthesis, analytical chemistry, and medical fields. Schiff-based hydrazones have garnered significant interest due to their potent biological activities.[1,2,3] These synthesized compounds show strong donating abilities, facilitated by azomethine nitrogen, enolate/amide oxygen, and phenolate oxygen, which interact with metal centers. In the present work, we synthesized and screened the biological activity of metal complexes with hydrazone schiff base, focusing on their antimicrobial effects. The unique biological and structural features of these complexes motivated us to explore the potential of 1-(2,5-dihydroxyphenyl) propylidene) pyrazine-2-carbohydrazide-based metal complexes. After, the literature review indicates that these specific metal complexes have not been previously investigated for antimicrobial activity. This work also includes a comprehensive characterization of the synthesized complexes using advanced techniques such as XRD and SEM.

EXPERIMENTAL

Material and Methods

All chemicals and solvents used in this study are of analytical reagent (AR) grade and sourced from local suppliers. The metal complexes were synthesized following well-established procedures from the literature. The crystallinity of the newly synthesized compounds was analyzed using a Bruker AXS-D8 Advance XRD diffractometer equipped with a Si (Li) PDS detector. Scanning electron microscopy (SEM) images were captured using a JEOL Model JSM-6390 LV microscope at the SAIF facility in Jalgaon, India. The XRD and SEM analyses provided comprehensive information about the structural and morphological properties of the metal complexes.

General Procedure

The complexes were synthesized using analytical-grade reagents, following standard procedures. The synthesizing compounds were characterized using X-ray diffraction (XRD) and Scanning Electron Microscopy (SEM). The ligand (H_2L) as 1-(2,5-dihydroxyphenyl) propylidene) pyrazine-2-carbohydrazide, was prepared by refluxing 2,5-dihydroxypropiophenone with pyrazine-2-carbohydrazide. Metal complexes

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were then obtained by refluxing the ligand with corresponding metal salts in a solvent mixture of dichloromethane (DCM) and methanol (MeOH). The antimicrobial activity of the complexes was assessed against various bacterial and fungal strains using the disc diffusion method, with Ciprofloxacin and Clotrimazole as reference drugs.

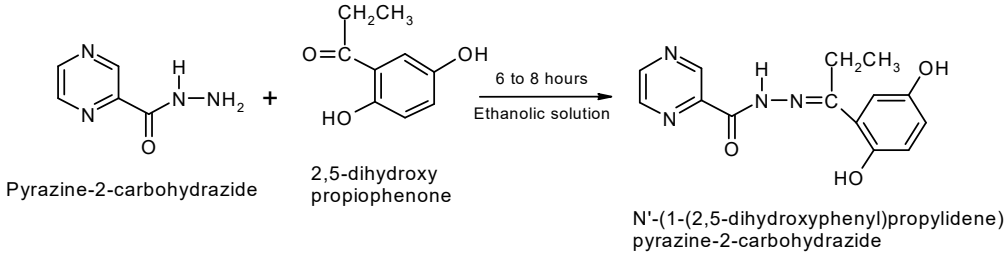
Preparation of Ligand (H_2L) 1-(2,5-dihydroxyphenyl) propylidene) pyrazine-2 carbohydrazide[4]

A solution of 2,5-dihydroxypropiophenone (12 g, 0.0724 moles) in ethanol was combined with an ethanol solution of pyrazine-2-carbohydrazide (10 g, 0.0724 moles) in a 1:1 molar ratio, with the addition of 2-3 drops of concentrated sulfuric acid (H_2SO_4) as a catalyst. The mixture was stirred continuously with a magnetic stirrer and refluxed for 6 to 8 hrs. After the reaction was complete, the solution was cooled to room temperature and stored in a refrigerator overnight. A pale-yellow solid formed which was collected by filtration washed with distilled water and ethanol and then dried in a desiccator using silica gel to remove any remaining moisture. The final yield was 73%, with a melting point of 253°C.

Spectral Data of Ligand (H_2L)

- **^{1}H-NMR (DMSO-d_6, 400 MHz):** δ 9.28 (d, 1H, C2-H), 9.28 (d, 1H, C2-H), 12.25 (d, 1H, O-H), 11.33 (d, 1H, N-H), 9.28 (s, 1H, O-H), 6.78 (s, 1H, C12-H), 6.75 (s, 1H, C10-H), 8.94 (d, 1H, C5), 8.89 (d, 1H, C6-H), 7.01 (d, 1H, C9-H), 1.19 (s, 3H, CH_3), 2.92 (s, 2H, CH_2).
- **^{13}C-NMR (DMSO-d_6, 400 MHz):** δ 147.95 (C2), 144.03 (C3), 143.37 (C5), 149.30 (C6), 117.97 (C7), 119.17 (C8), 113.51 (C9), 151.87 (C12), 19.37 (CH_2), 10.78 (CH_3), 162.83 (C=N), 159.51 (C=O).
- **IR (KBr disc, cm^{-1}):** 3328 (O-H), 3025 (N-H), 1572 (C=N), 1057 (N-N), 1685 (C=O), 1319 (C-O).

The synthesis of the (H_2L) ligand is illustrated as follows:



Reaction to Synthesis of Ligand H_2L[4]

Preparation of Fe (III), Ti (III), Cr (III), Th (IV), and VO(IV) Complex

Metal complexes of Fe (III), Ti (III), Cr (III), Th (IV), and VO(IV) were synthesized following a standard procedure. Equimolar amounts of the (2.91 g, 0.01 mol) ligand H_2L and the corresponding (0.01 mol) metal salt were dissolved separately in a (v/v) 50:50 mixture of dichloromethane (DCM) and methanol (25 mL). After filtration, the two solutions were mixed together with continuous stirring under gentle heating. The resulting mixture was refluxed for 5 hours in an oil bath. The pH was then adjusted to 7.0 using a methanolic solution of sodium acetate (0.5 g), followed by an additional hour of refluxing. After, at room temperature, the reaction mixture was cooled, a precipitate (ppt) formed, which was filtrated and collected the precipitate. A precipitate was thoroughly washed with using cold DCM, methanol, and petroleum ether, then dried under a vacuum over $CaCl_2$. The yields of the complexes ranged from 55% to 68%.

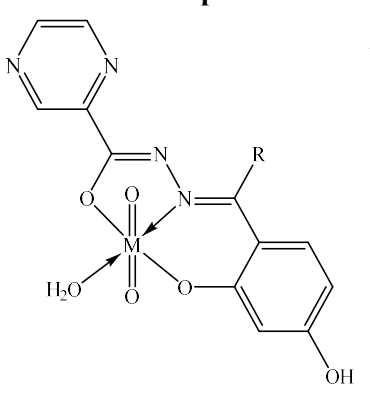
Preparation of MoO_2 (L)H_2O and WO_2 (L)H_2O Complex

To synthesize the $MoO_2(L)H_2O$ complex, a methanolic solution (hot) (25 mL) of [$MoO_2(acac)_2$] (0.44 g, 1.0 mmol) was gradually added to an ethanolic solution (hot) of the (0.1 mmol) ligand H_2L while stirring vigorously. After filtering the resulting cloudy mixture, it was refluxed for 4 hours with continuous stirring in a water bath. The volume of the solution was then reduced to 10 mL and the mixture was cooled to 10°C overnight, resulting in the formation of a colored precipitate. This product was filtered, washed with ethanol and petroleum ether, and dried over anhydrous $CaCl_2$ in a desiccator, yielding the $MoO_2(L)H_2O$ complex at 65%. Using similar conditions, the $WO_2(L)(H_2O)$ complex was obtained by reacting [$WO_2(acac)_2$] with H_2L, achieving a yield of 63%. All the synthesized complexes showed limited solubility in water and common organic solvents but dissolved in DMF and DMSO. Table-1 summarizes the proposed compositions, molecular weights, and elemental analyses of these complexes.

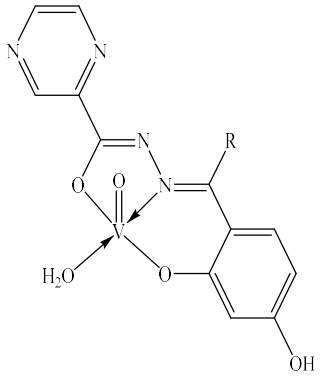
Table-1: Zones of Inhibition of Growth of Microorganisms of Ligand H_2L and its Metal Complexes

Ligand & Metal Complexes	Bacteria		Fungi	
	Escherichia Coli	*Staphylococcus Aureus*	*C. Albicans*	*A. Niger*
H_2L	12	12	11	13
$[Ti(L)(Cl)(H_2O)_2]$	16	13	14	12
$[VO(L)(H_2O)]$	17	15	13	17
$[Cr(L)(Cl)(H_2O)_2]$	15	13	12	12
$[Fe(L)(Cl)(H_2O)_2]$	16	13	11	14
$[MoO_2(L)(H_2O)]$	15	15	11	11
$[WO_2(L)(H_2O)]$	18	12	11	13
$[Th(L)(NO_3)_2(H_2O)]$	16	14	12	12
Streptomycin (standard)	30	40	-	-
Clotrimazole (standard)	-	-	40	25

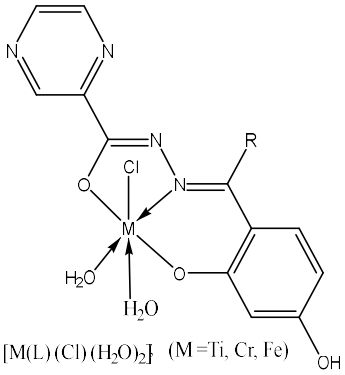
Proposed Structures of the Metal Complexes



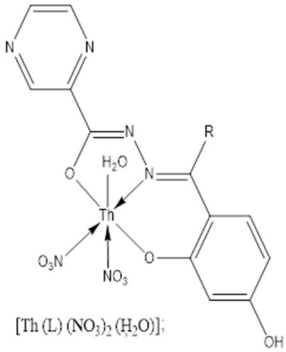
$[MO_2(L)(H_2O)]$; M = (W, Mo)



$[VO(L)(H_2O)]$



$[M(L)(Cl)(H_2O)_2]$ (M = Ti, Cr, Fe)



$[Th(L)(NO_3)_2(H_2O)]$;

Antimicrobial Activity

A study of the biological activity of compounds, especially their antimicrobial properties, has become increasingly significant, particularly in light of the COVID-19 pandemic. In this research, the antimicrobial activity was evaluated for synthesized compounds by using the disc diffusion method, conducted at the Department of Microbiology, Shri Shivaji College, Akola. The activity was tested against both gram-positive and gram-negative bacteria such as *Staphylococcus aureus* (MTCC 96) and *Escherichia coli* (MTCC 443) respectively, as well as fungi, including *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) at a concentration of 1.0 mg/mL.[5] The zone of inhibition was measured after a 24 hrs incubation period. Ciprofloxacin and Clotrimazole are used as reference drugs for antibacterial and antifungal comparisons. The (MIC) Minimum Inhibitory Concentration of the synthesized compounds against the tested microorganisms as bacteria was determined by using the broth micro-dilution method. All screened tests were in triplicate under consistent conditions, with DMSO serving as the negative control.

The activity was quantified by measuring the size diameter of the zone of inhibition, expressed in millimetres.

Detection Method

The crystallinity of the newly synthesized samples was analyzed using a Bruker X-ray diffractometer with Si (Li) PDS. Scanning Electron Microscopy (SEM) images were captured using a JEOL JSM-6390 LV microscope at SAIF, Jalgaon University. Antimicrobial activity was evaluated using the disc diffusion method against *S. aureus*, *E. coli*, *C. albicans*, and *A. niger*. The MIC was determined via the broth micro-dilution method, with ciprofloxacin and clotrimazole as standard reference drugs.

RESULTS AND DISCUSSION

The complexes were synthesized are colored stable solids at room temperature. They exhibit poor solubility in some common organic solvents (i.e. ethanol, methanol, chloroform, benzene, cyclohexane, acetone, and diethyl ether), but are sparingly soluble in DMSO and DMF. The data like analytical and physical, along with elemental analyses, indicate a 1:1 metal-to-ligand stoichiometry for all the complexes[4] consistent with the proposed structures and geometries.

SEM Analysis

SEM analysis of the ligand H_2L and its representative complexes revealed details about morphology and particle size distribution. The micrographs of the Fe (III), Ti (III), and Th (IV) complexes, as shown in Fig.-1 to 4, display a smooth yet irregular surface morphology with particle sizes exceeding 10 μm. The SEM images also indicated that the crystallites are agglomerated and polycrystalline, lying within the nano-range. These findings are consistent with the XRD patterns.[6]

XRD Analysis of H_2L Ligand and its Complexes

The X-ray diffraction (XRD) patterns of the H_2L ligand and its metal complexes (Fig.-5) display sharp peaks, indicative of their crystalline nature. The observed 2θ values and indexed X-ray diffraction data correspond to prominent peaks, confirming the crystalline structure. The data of unit cell and crystal lattice parameters for the H_2L ligand and its complexes are as follows:

- The H_2L ligand exhibits the parameters are given bellow: a = 12.349 Å, b = 13.4266 Å, c = 15.7404 Å, α = 72.92°, β = 67.39°, γ = 76.82°, with a unit cell volume (V) of 2282.650 Å³, placing it in the triclinic crystal system.
- For the $[Ti(L)(Cl)(H_2O)_2]$ complex, the parameters are: a = 8.6370 Å, b = 20.3460 Å, c = 9.7847 Å, α = 90°, β = 90°, γ = 90°, V = 1719.450 Å³, indicating an orthorhombic system.
- The $[VO(L)(H_2O)]$ complex has parameters: a = 7.7820 Å, b = 10.6360 Å, c = 5.9930 Å, α = 90°, β = 90°, γ = 90°, V = 496.037 Å³, also orthorhombic.
- The $[WO_2(L)(H_2O)]$ complex is characterized by: a = 7.3000 Å, b = 27.8720 Å, c = 9.9500 Å, α = 90°, β = 109.005°, γ = 90°, V = 1914.129 Å³, fitting within the monoclinic crystal system.
- The $[Th(L)(NO_3)_2(H_2O)]$ complex displays cubic parameters: a = 5.6650 Å, b = 5.6650 Å, c = 5.6650 Å, α = 90°, β = 90°, γ = 90°, V = 181.302 Å³.
- The average particle sizes of crystallite for H_2L ligand and its metal complexes, including $[Ti(L)(Cl)(H_2O)_2]$, $[VO(L)(H_2O)]$, $[WO_2(L)(H_2O)]$, and $[Th(L)(NO_3)_2(H_2O)]$, were calculated by using full width at half maximum (FWHM) from XRD patterns, applying Scherrer's formula. The resulting sizes are 27.35 nm, 30.49 nm, 29.30 nm, 27.36 nm, and 30.46 nm, respectively, hence indicating that these materials are nanocrystalline.

Antimicrobial Activity

An antimicrobial property of the synthesized [7,8,9] transition metal complexes (Fig.-6) were tested for gram-positive and gram-negative bacteria, as well as fungi. The results are compared with standard antibacterial and antifungal drugs. The Table-1 data demonstrates that the biological activity of the ligands significantly increases upon complexation with transition metals. The complexes exhibited moderate activity against all tested bacterial and fungal strains.[10-14]

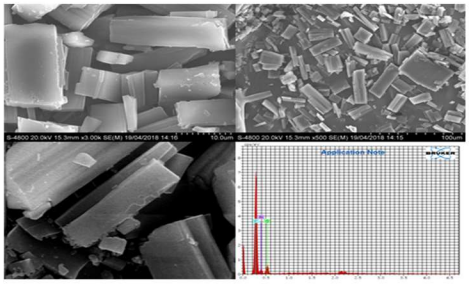


Fig. 1 Scanning electron microscope image of H_2L Ligand

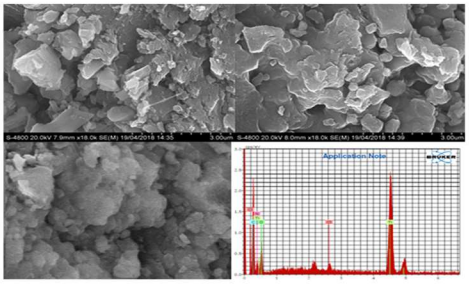


Fig. 2 Scanning electron microscope image of $[Ti(L)(Cl)(H_2O)_2]$Complex

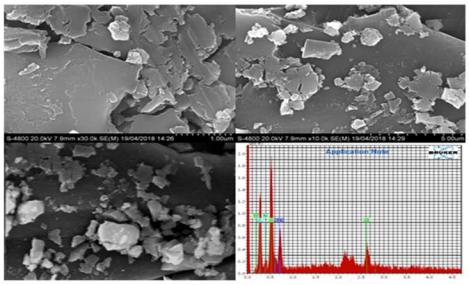


Fig. 3 Scanning electron microscope image of $[Fe(L)(Cl)(H_2O)_2]$ Complex

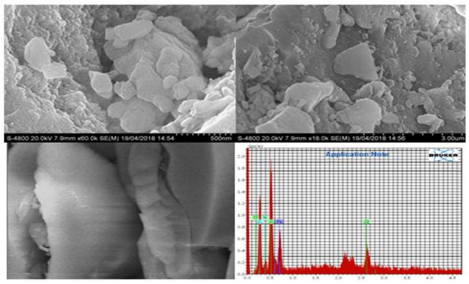


Fig. 4 Scanning electron microscope image of $[Th(L)(NO_3)_2(H_2O)_2]$ Complex

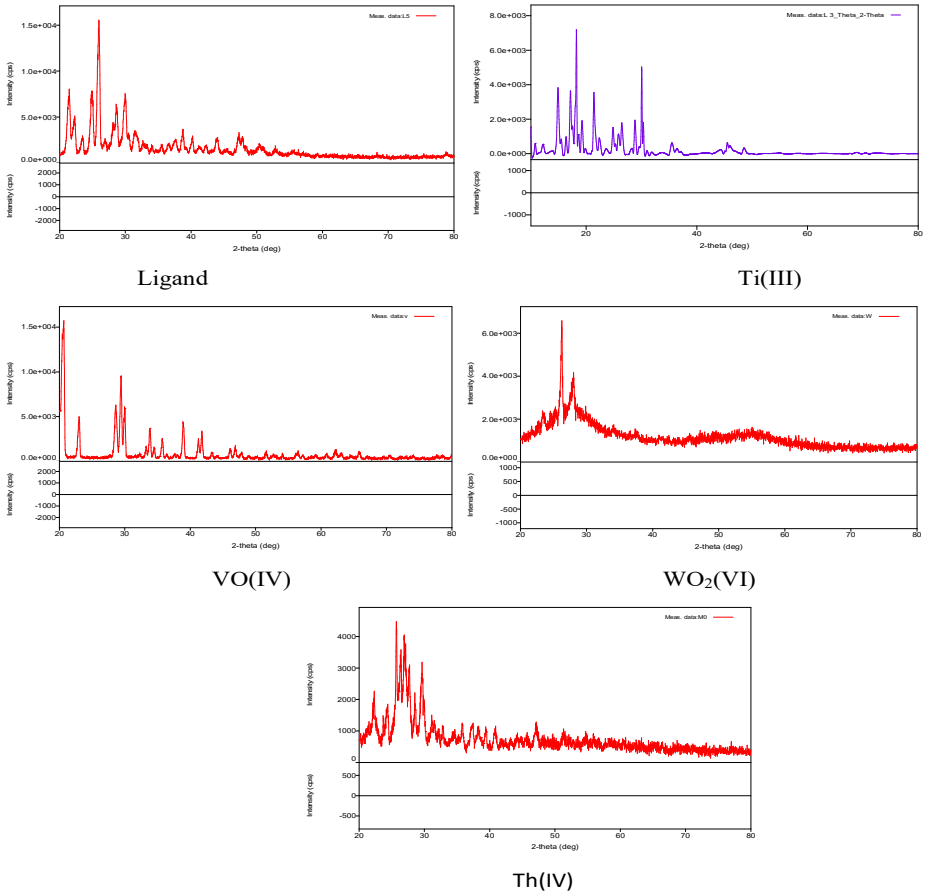


Fig.5 X-ray Diffraction spectra of H_2L Ligand and its complexes

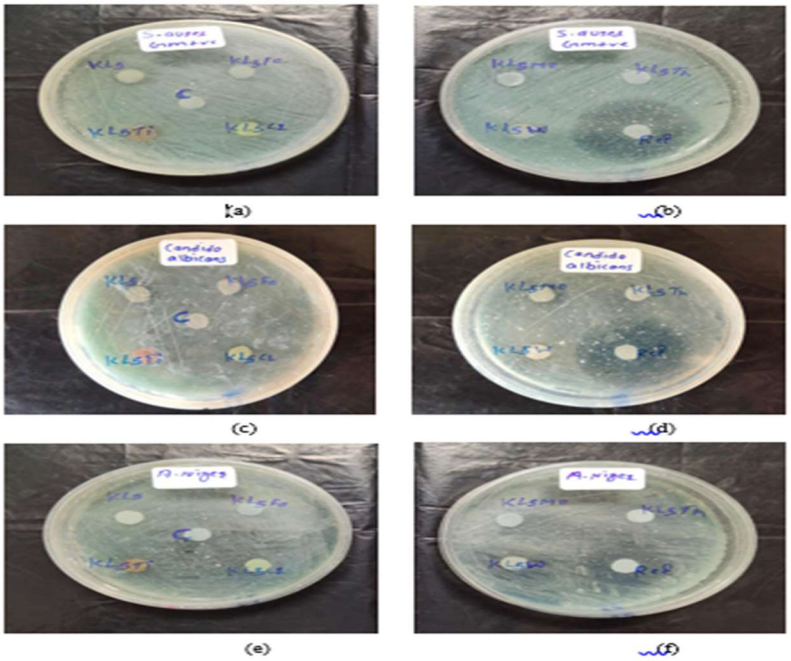


Fig. 6 Antimicrobial Activity of Synthesized Metal Ligand Complexes

Antibacterial Activity

The antibacterial screening revealed that the level of activity varied among the compounds, with gram-positive bacteria showing slightly more susceptibility than gram-negative bacteria. Overall, the metal complexes displayed greater antibacterial activity than the ligand alone. Among the active compounds, the VO (IV) complex demonstrated the highest antibacterial activity, followed by Ti (III), Cr (III), Fe (III), MoO_2 (VI), WO_2 (VI), and Th (IV) complexes.

The [VO (L)(H_2O)] complex exhibited superior activity compared to other complexes, likely due to its distorted geometry.

Complexes [VO (L)(H_2O)], [Th (L)(NO_3)$_2$(H_2O)], [WO_2 (L)(H_2O)], [Fe (L)(Cl)(H_2O)$_2$], and [MoO_2 (L)(H_2O)] showed enhanced activity against *E. coli*.

The [MoO_2 (L)(H_2O)] complex displayed the highest activity against *S. aureus*.

Antifungal Activity

The antifungal activities were evaluated and it revealed that both the ligands and their metal complexes exhibited significant antifungal activity. The activity was enhanced upon complexation with metals. The VO (IV) complex again showed the most significant antifungal activity, followed by Ti (III), Cr (III), MoO_2 (VI), Fe (III), WO_2 (VI), and Th (IV) complexes.

The [VO(L)(H_2O)] complex was particularly effective against *A. niger*.

Metal complexes of the H_2L ligand demonstrated higher inhibitory effects against both *C. albicans* and *A. niger*.

CONCLUSION

The experimental results indicated that the synthesized materials are polycrystalline. Both XRD spectra and SEM images confirm their polycrystalline nature and reveal particle sizes of 27.35 nm, 30.49 nm, 29.30 nm, 27.36 nm, and 30.46 nm. The transition metal complexes demonstrate notable biological activity, showing higher efficacy against gram-positive bacteria compared to gram-negative. Additionally, these complexes exhibit significant antifungal activity.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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