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# Co(III) and VO(IV) complexes with a new bidentate Schiff base: Interaction with BSA and antimicrobial studies

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## ABSTRACT

A Schiff base ligand L was prepared from the condensation of 2-amino-3-benzyloxypyridine and 5-chlorosalicylaldehyde. The ligand forms complexes with Co(III) and VO(IV) in good yield. Design, synthesized and characterization of cobalt(III) and oxidovanadium(IV) with (E)-2-((3-(benzyloxypyridinylimino) methyl)-4-chlorophenol (L) are described. The prepared complexes were characterized by different analytical techniques elemental analysis, molar conductance, infrared spectra, $^{1}$H and $^{13}$C NMR, mass, electronic absorption and TGA. The coordination geometry is octahedral in C1 and C2, while complexes C3 and C4 show a square-pyramidal geometry. Numerous biological studies have been conducted on L and Co(III) and VO(IV) complexes. The results of antimicrobial studies indicated that all compounds had antimicrobial activity against bacteria and fungi. The binding of metal complexes with BSA (bovine serum albumin) was reported. The results of these indicated that Co(III) and VO(IV) are significantly quenching fluorescence intensity of BSA, that results in changing its conformation and results in a static quenching.

**Keywords:** *5-chlorosalicylaldehyde Schiff base, Co(III) and VO(IV) complexes, Thermal analysis, antimicrobial activity, BSA binding.*

## 1. INTRODUCTION

Many researchers have studied extensively in the field of coordination chemistry in general and the Schiff bases in particular. Because of widespread applications of metal complexes of Schiff bases in the industry and in biology [1,2]. Imine based ligands have played important role in the development of inorganic biochemistry and optical materials [3,4]. Because of the role of cobalt in biological system, several research papers or monographs involved in the preparation and elucidation of cobalt(III)-Schiff base complexes with one or more bidentate or polydentate ligand are described [5,8]. Bioinorganic chemistry of oxidovanadium complexes [9,10] as well as their catalytic systems [11,14] is highly appreciated.

In binding studies, bovine serum albumin (BSA) has been extensively utilized since of its abundance, stability, ease of purification, medical importance, low cost and of its structural homology with human serum albumin (HAS) [15,16]. BSA is a remarkablewater soluble protein and involved in several biological functions. It mainly control or maintain osmotic pressure, blood pH level and stabilize metal ion concentration in the body [17,19]. In blood circulatory system, it also facilitates excretion and transportation of many small molecules to definite targets [20,21]. *In-vitro* system, BSA was employed to study drug-protein interaction.

In this paper, we explain the synthesis of complexes using a bidentate ligand. Various spectral (FT-IR, UV-Vis, fluorescence) and TGA technique were employed to characterize the prepared complexes. BSA interaction with metal complexes was also confirmed by UV-Vis and fluorescence spectroscopy. The *in-vitro* antimicrobial properties of the complexes were examined against Gram-positive and Gram-negative bacteria and fungi.

## 2. MATERIALS AND METHODS

**2.1.Materials and methods.** Commercially available reagents were purchased and used as such 1,10-phenanthroline, $CoCl_2.6H_2O$, and $VOSO_4.2H_2O$ (Merck Private Limited, Mumbai) were procured. Precision Digital Melting point apparatus for recording Melting point (uncorrected) and Perkin Elmer 240 CHN-analyzer for elemental analysis were used.For recording $^{1}$H and $^{13}$C NMR, Varian-400 MHz spectrometer with TMS (Tetra methylsilane) as a standard was utilized. Mass spectroscopic analysis was performed using a 2010 EV LC-MS Shimadzu spectrometer. FT-IR spectra of the complexes were recorded using a Perkin–Elmer 783 spectrophotometer in 4000–400 $cm^{-1}$ range. Molar conductance in ~$10^{-3}$ M DMSO solution was recorded using an Elico Cm-180 conductometer. An UV-Vis spectrophotometer (DU 730 'Life Science' M/S Beckman coulter, USA) was used to measure the electronic spectra. Thermogram of compounds were measured in nitrogen atmosphere (TGA Q50 instrument) keeping the maximum temperature at 800 °C with the heating rate at 10 °C/min. RF-5301P spectrofluorophotometer (Shimadzu) equipped with a 150-W Xenon lamp, using 96 well plates at a slit width of 5.0 nm was used to record the fluorescence spectra. Bovine Serum Albumin (BSA) was purchased from Sigma-Aldrich and used as supplied.

**2.2. Synthesis of ligand and its complexes.**

*2.2.1.* Synthesis of (E)-2-((3-(benzyloxypyridinylimino) methyl)-4-chlorophenol (L). A solution of 2-amino-3-benzyloxypyridine(0.002 mol) in ethanol was mixed with an ethanolic solution of 5-chlorosalicylaldehyde (0.002 mol) and 2-3 drops of glacial acetic acid were added to this. The reaction mixture was refluxed for 7-8 hours at 70-80 °C and cooled to room temperature. The final product was filtered, washed and dried over anhydrous $CaCl_2$ in desiccators (Figure 1). Mass spectrum, $^1$H NMR, $^{13}$C NMR and FT IR spectrum of L are depicted in Figures 2-5.

**Ligand (L):** Yield 93%, mp= 129-131$^o$C. Anal. Calcd for $C_{19}H_{15}ClN_2O_2$ (%) C, 67.36; H, 4.46; N, 8.27; Found C, 67.17; H, 4.31; N, 8.05. MS (m/z): 339.10 [M+1] 342.10 [M+3]; FT IR υ(cm$^{-1}$); ν (OH) 3378, ν (C=N) 1603; $^1$H NMR (400 MHz, $CDCl_3$); 9.36(s, HC=N), 14.19(s, Ph-OH), 6.96-8.0(m, Ar–H), 5.22(-$CH_2$-O); $^{13}$C NMR (400 MHz, $CDCl_3$); 161.717, 161.383, 148.763,147.116, 140.188, 135.969, 133.487, 131.863, 128.706, 128.145, 126.968, 123.705, 123.326, 121.505, 120.010, 119.205, 77.300, 76.982, 76.663. UV-Vis (DMSO): λmax=269, 374nm.

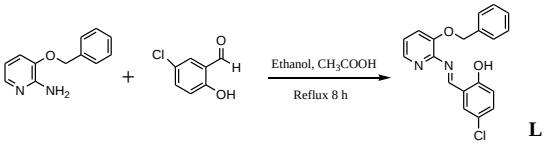


**Figure 1.** Schematic representation of synthesis of Schiff base ligand.

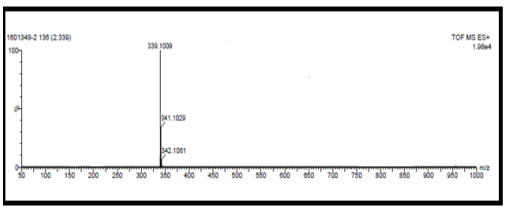

**Figure 2.** MS spectrum of L.

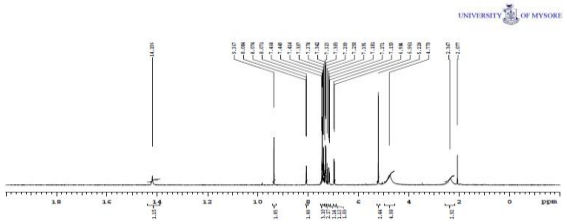

**Figure 3.** $^1$H-NMR of L.

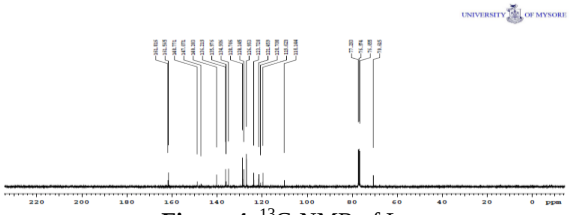

**Figure 4**. $^{13}$C-NMR of L.

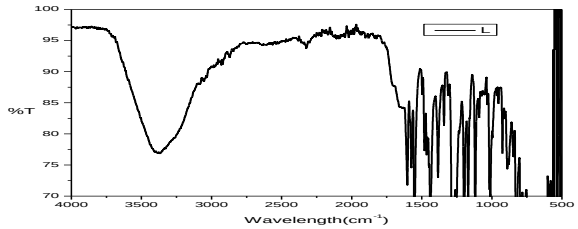


**Figure 5**. FT IR spectrum of L.

*2.2.2.* Synthesis of 1:2 ratio complexes C1 and C3. To a solution of the ligand L (2 mmol) in hot ethanol, was added to an ethanolic solution of metal salts (1 mmol). The mixture was heated for 7 h at 80 °C and cooled. The precipitate obtained was filtered, washed with ethanol and then dried under vacuum over $CaCl_2$.

**Complex C1:** Yield: 75%. Anal. Calcd for [$CoC_{38}H_{30}Cl_3N_4O_5$] (%) C, 55.73; H, 4.20; N, 6.67; Found C, 55.39; H, 4.19; N, 6.57. mp= 282-284 °C. IR ($\upsilon_{max}$. /cm$^{-1}$); (HC=N) azomethine 1589; M-O 459; M-N 535; $H_2O$ 3249

**Complex C3**: Yield: 79%. Anal. Calcd for [$VC_{38}H_{28}Cl_2N_4O_5$] (%) C, 62.19; H, 4.44; N, 7.25; Found C, 61.77; H, 4.11; N, 7.05. mp= 293-295 °C. IR ($\upsilon_{max}$. /cm$^{-1}$); (HC=N) azomethine 1567; M-O 431; M-N 517; $H_2O$ 3318

2.2.3. Synthesis of 1:1:1 ratio complex C2 and C4. To a solution of L (1 mmol) in hot ethanol was added to an ethanolic solution of metal salts (1 mmol) under stirring for 30 min. To this was added 1mmol of phenanthroline monohydrate (Phen) and the resulting solution was stirred for 7 h at 70 °C on water bath and then kept at room temperature. The formed precipitate was separated out, filtered and then washed with ethanol. The obtained complex was dried using $CaCl_2$ in vacuum.

**Complex C2:** Yield: 80%. Anal. Calcd for [$CoC_{31}H_{22}Cl_3N_4O_2$] (%) C, 57.47; H, 3.42; N, 8.65; Found C, 57.23; H, 3.17; N, 8.46. mp= >300 °C. IR ($\upsilon_{max}$. /cm$^{-1}$); (HC=N) azomethine 1573; M-O 455; M-N 529

**Complex C4:** Yield: 83%. Anal. Calcd for [$VC_{31}H_{22}ClN_4O_3$] (%) C, 63.65; H, 3.79; N, 9.58; Found C, 63.52; H, 3.29; N, 9.07. mp= >300 °C. IR ($\upsilon_{max}$./cm$^{-1}$); (HC=N) azomethine 1575; M-O 437; M-N 521

**2.3. *In-vitro* Antimicrobial Screening.** *In-vitro* antimicrobial screening effects of the ligand L and its metal complexes were employed to check their efficacies by disc diffusion method. Gentamicin and fluconazole drugs are used as standards in these experiments. All the measurements were made in triplicate and record the average inhibition zone. To get the required test solutions, the compounds were dissolved in DMSO. The compounds which show significant activities were selected to determine the minimum inhibitory concentration (MIC) using well diffusion technique.

**2.4. BSA interaction studies.** The binding interaction between complexes and BSA has been interpreted employing absorption and fluorescence measurements. The stock solution of BSA was prepared by dissolving it in a buffer solution (containing 5 mM Tris-HCl/50 mM NaCl at pH 7.2) and stored at 4 °C for further use. In a fluorescent method, BSA was excited at 280 nm and the emission was monitored at 300-400 nm with slit width of 5 nm. Fluorescence interaction experiment was performed by keeping the concentration of the BSA constant while varying concentrations of the complexes. BSA concentration was determined by applying UV-Vis spectra [22].

For recording UV-Vis spectra, BSA concentration was kept constant with variable concentration of complex in the range 200-800 nm. BSA solution was prepared freshly before being in used [23].

## 3. RESULTS

All the synthesized metal complexes of the respective Schiff base in this study are colored, non hygroscopic solids stable in air and moisture without any kind of decomposition even after several months and remarkable soluble in DMSO and DMF but insoluble in water and many common organic solvents. The donor sites of ligand were confirmed by FTIR spectra, electronic spectra. Analytical data shows that the complexes have the stoichiometry to be 1:2 (metal: ligand) for complexes C1 and C3 whereas 1:1:1 (metal: ligand: phen) for complexes C2 and C4. The concentrations of $10^{-3}$ M solutions of C1-C4 in DMF were used to record their conductance values, that are in the range 6.7-17.79 $Ohm^{-1}$ $cm^2$ $mol^{-1}$ indicate that they are non-electrolytic in nature [24,25]. Many attempts, such as crystalline using a mixture of solvents and different temperatures, were unsuccessful for the growth of a single crystal suitable for X-ray crystallography. However, the analytical, spectroscopic and magnetic data results are consistent with the proposed formula.

**3.1. FTIR spectra.**The important FTIR spectral data containing relevant vibrational bands of the ligand in the range of 4000-400 $cm^{-1}$ and it's Co(III) and VO(IV) complexes are listed in Table 1 and represented in Figure 6. In the spectra, a broad bandappeared in the range 3345–3457 $cm^{-1}$, that is due to –OH groups of intramolecular hydrogen. This peak appeared in all metal complexes, which reveals that –OH group is not involved in complexation. C=N stretching frequency of azomethine was peaked at 1603$cm^{-1}$ in the ligand, that was shifted to 30–40 $cm^{-1}$ lower range upon complexation with metal ion [26]. The band for phenolic oxygen υ (Ph–O) occurs at 1274 $cm^{-1}$, whereas in complexes, this band is shifted to different frequency showing very strong bands around 1263-1271 $cm^{-1}$ region. M-O and M-N modes were in the range 431-459 and 517-535 $cm^{-1}$, respectively. Involvement of oxygen and nitrogen donor atoms in the bonding is again confirmed by far IR spectral bands at around 500–400 $cm^{-1}$ range corresponding to ν(M-O) and ν(M-N), respectively. The IR spectral data confirms, the Schiff base ligand coordinated to Co(III) and VO(IV) ion in a bidentate (N- and O-) manner. In addition, the oxidovanadium complexes C3 and C4 showband at 967-971 $cm^{-1}$ attributed to V=O frequency [27].

**3.2. Electronic spectra.** The UV spectra and magnetic moment values gave sufficient evidence regarding the geometry around the metal ions. The UV-Vis spectra of L showed two bands at 269 and 374 nm as depicted in Figure 7. The first band can be attributed to π→π* transition within an aromatic ring, whereas the second band would be due to n→π* transition within -C=N group. On interaction with metal ion, n→π* transition of new L shifts to a longer wavelength; this reflects the complexation between ligand and metal. The electronic spectra of C1 and C2 complexes shows a broad band at around 247-273, 324-347 and a shoulder at 557-595 nm, which may tentatively be assigned to $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$ and $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$, respectively. The position of bands indicated that Co(III) complexes have an overall octahedral geometry [28]. The electronic spectra of VO(IV) complexes show low intensity d-d bands at 269-287, 317-334 and 500-553 nm assigned to $^2b_2\rightarrow{}^2e$, $^2b_2\rightarrow{}^2b_1$ and $^2b_2\rightarrow{}^2a_1$ transitions, respectively, which are consistent with the square pyramidal geometry around VO(IV) [29,30].

**Table 1.** FTIR spectral data of the Schiff base ligand [L] and its metal complexes.

| Compound | ν(C=N) | ν(Ph-O) | ν(V=O) | ν(M-O) | ν(M-N) |
|---|---|---|---|---|---|
| **HL** | 1603 | 1274 | — | — | — |
| **C1** | 1589 | 1263 | — | 459 | 535 |
| **C2** | 1573 | 1270 | — | 455 | 529 |
| **C3** | 1567 | 1271 | 967 | 431 | 517 |
| **C4** | 1575 | 1269 | 971 | 437 | 521 |

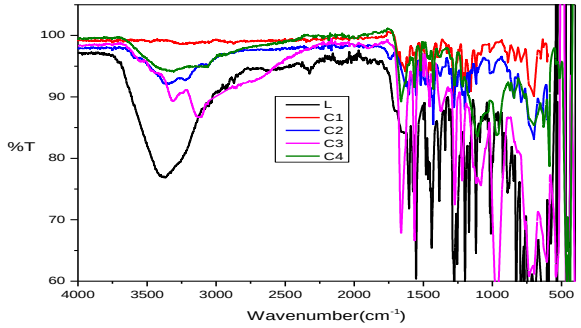


**Figure 6**. IR spectra of **L**, **C1**,**C2, C3 and C4.**

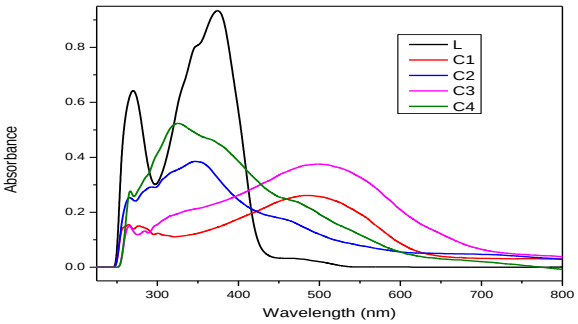


**Figure 7**. The Electronic spectra of L, C1, C2, C3 and C4 in DMSO.

**3.3. Thermal analysis.** Thermal decomposition of complexes has been investigated using thermal gravimetric analysis (TGA) (Figure 8).

The representative TG spectrum of Co(III) shows that, the thermal decomposition took place in two steps in the region 149-197 °C and 347-515 °C corresponding to the mass of loss of coordinated water and chloride ion with the percentage mass loss of 7.89 (calcd. 7.91%), loss of ligand moieties with the percentage mass loss of 87.65 (calcd. 88.07) and 1, 10-phenanthroline moiety were decomposed at 570-667 °C with the mass loss of 27.68 (calcd. 27.71%) respectively. In case of VO(IV) complexes two-step of condensation in the thermogram took place where phenanthroline decomposition occurred at a temperature (113-136 °C) that is lower than that of the ligand (325-377 °C). The formed metal oxide was confirmed at above 670 °C. Thus TG results prove the stability of synthesized complexes and the presence of coordinated water [31].

On the basis of the above facts, the proposed structure of metal complexes is presented in Figure 9.

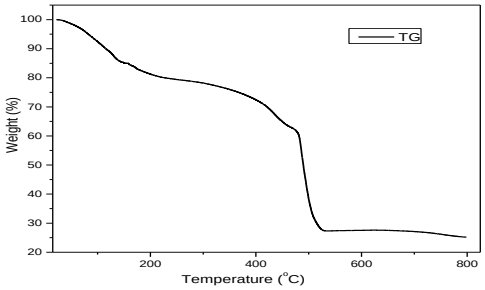


**Figure 8**.Thermogram of complex C3.

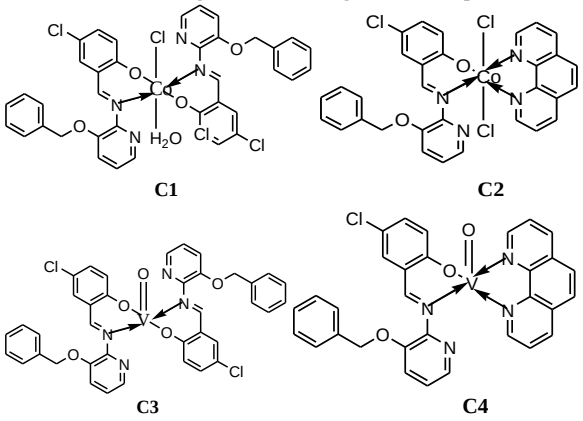


**Figure 9.**Proposed structure of the Schiff base complexes.

**3.4. Antimicrobial activity.** Newly prepared Schiff base complexes of cobalt and oxidovanadium were subjected to find their antibacterial efficacies against two Gram-positive bacteria (*B. subtilis*, *S. aureus*) and Gram-negative bacteria (*S. typhi* and *E. coli*) and antifungal activities against *C. albicans* and *A. niger* by disc diffusion method on nutrient agar medium. A series of Petri plates were filled with sterile nutrient agar along with cultured microorganism (bacteria and fungi). The studied compounds were dissolved in DMSO and make the concentration of stock is $10^{-3}$ M. For each, three determinations were made. Each plate was incubated (37 °C for 24 h) inhibition zone was recorded. Gentamicin and fluconazole were used as standards drugs for the comparison of the results. The results achieved from these studies are enlisted in Table 2 and Table 3. The enhanced antibacterial efficacy was observed in the compounds containing halides or phenyl groups [32].

Comparison of MIC values (in µg/mL) of metal complexes and standard drugs against different bacteria and fungi are presented in Table 3. The data of the antifungal and antibacterial activity indicated that the metal complexes are more active than ligand, L. Based on Overtone's and chelation theory concept, one can predict the biological activity of metal complexes are more than its ligand L [33,34].

**3.5. BSA binding studies.**

*3.5.1.* Fluorescence quenching of BSA. Interactions of complexes with BSA were studied by recording the fluorescence emission spectra of BSA with increasing concentration of complexes [35]. In presence of variable concentrations of studied metal complexes, the emission and excitation of BSA were recorded at 300-400 nm and at 280 nm, respectively. These spectra are depicted in Figure 10, the spectra reveals that a strong emission peak was observed at 342 nm for BSA. The addition of the complexes to the solution of BSA resulted in a significant decrease in the fluorescence intensity, accompanied by a bathochromic shift for complexes C1-C4, respectively. The observed changes indicating that the metal complexes and BSA have strong interaction to form binary complexes. The fluorescence quenching is described by Stern-Volmer relation:

$$F_0/F = 1 + K_{SV}[Q]$$

where $F_0$ is the emission intensity in the absence of quencher, F is the emission intensity in the presence of quencher, $K_{SV}$ is the Stern-Volmer quenching constant, and [Q] is the quencher concentration. The $K_{SV}$ value is obtained as a slope from the plot of $F_0/F$ versus [Q]. The fluorescence quenching of BSA is in accord with the Stern-Volmer equation (Figure 10). From the linear plot of $F_0/F$ vs [Q] were calculated to be $3.55\times10^5$ $M^{-1}$, $6.37\times10^5$ $M^{-1}$, $2.69\times10^5$ $M^{-1}$ and $5.27\times10^5$ $M^{-1}$ corresponding to the respective complexes C1, C2, C3 and C4. The observed linearity in the plots supported the fact that the quenching of BSA by the test complex is in good agreement with the linear Stern-Volmer equationThe calculated $K_{SV}$ values for the test compounds exhibit their strong protein binding ability.

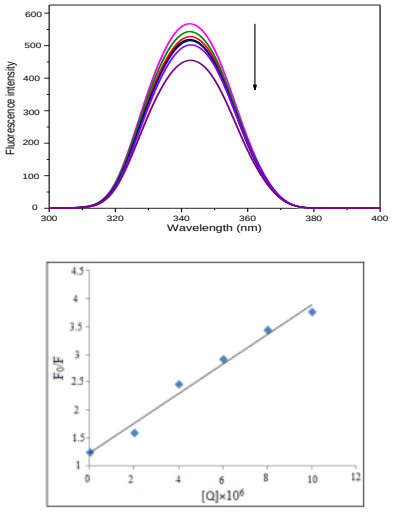


**Figure 10.** Emission spectra of BSA ($\lambda_{ex}$ =280 nm; $\lambda_{em}$ =342 nm) as a function of concentration of the complex C3. Arrow indicates the effect of metal complex C3 on the fluorescence emission of BSA. Insert: shows the Stern-Volmer plot.

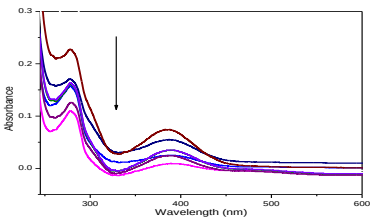


**Figure 11.** Absorption spectrum of BSA in the presence of complex C3 in the concentration range (0–30 µM) at room temperature. An arrow shows the absorbance changes upon increasing BSA concentration.

*3.5.2.* UV-visible absorption studies. Though a simple technique, UV-visible spectral measurement is useful to study the structural changes as well as different quenching [36,37]. Dynamic quenching will be affecting the fluorophore of excited states, whereas static quenching normally affects the absorption peak of the fluorophore along with the formed complex of fluorophore-quencher in the ground state. The UV absorption spectrum of BSA

alone and BSA-complexes are shown in Figure 11. As shown in this figure, the absorption band of BSA appeared at 280 nm has been increased after the addition of complexes. A steady increase of the BSA absorption band with the mixing of a metal complex (C3) to a constant concentration of BSA was observed in the figure. Similar observations were noticed in the case of other complexes C1, C2 and C4. The result implies that an interaction between test compounds and BSA occurs. In other words, the fluorescence quenching between C1-C4 and BSA is mainly due to static quenching [38]. The above results can be rationalized in terms of strong interaction between complexes and BSA may lead to a change in the conformation of BSA.

**Table 2.** Antimicrobial results of Schiff base and their corresponding metal complexes.

| Compound | Zone of inhibition (in mm) | | | | | |
|---|---|---|---|---|---|---|
| | Antibacterial | | | | Antifungal | |
| | Gram-positive bacteria | | Gram-negative bacteria | | | |
| | *B. subtilis* | *S. aureus* | *E. coli* | *S. typhi* | *C. albicans* | *A. niger* |
| **L** | 18 | 17 | 14 | 12 | 9 | 13 |
| **C1** | 24 | 22 | 25 | 23 | 14 | 17 |
| **C2** | 32 | 29 | 27 | 22 | 20 | 16 |
| **C3** | 31 | 27 | 34 | 21 | 23 | 22 |
| **C4** | 29 | 25 | 26 | 24 | 19 | 21 |
| **Gentamicin** | 38 | 33 | 35 | 26 | — | — |
| **Fluconazole** | — | — | — | — | 29 | 27 |

**Table 3.** MIC [μg/ml] values for antimicrobial activity of Schiff base and its corresponding metal complexes.

| Compound | Bacteria | | | | Fungi | |
|---|---|---|---|---|---|---|
| | Gram-positive bacteria | | Gram-negative bacteria | | | |
| | *B. subtilis* | *S. aureus* | *E. coli* | *S. typhi* | *C. albicans* | *A. niger* |
| **HL** | >100 | >100 | >100 | >100 | >100 | >100 |
| **C1** | 67 | 72 | 59 | 64 | 74 | 70 |
| **C2** | 86 | 73 | 78 | 69 | 68 | 63 |
| **C3** | 74 | 80 | 77 | 61 | 65 | 71 |
| **C4** | 71 | 74 | 66 | 60 | 57 | 62 |
| **Gentamicin** | 37 | 37 | 37 | 37 | — | — |
| **Fluconazole** | — | — | — | — | 37 | 37 |

## 4. CONCLUSIONS

The Schiff-base ligand L (E)-2-((3-(benzyloxypyridinylimino) methyl)-4-chlorophenol was synthesized and determined with different spectroscopic techniques like IR, NMR, electronic and thermal, followed by synthesis of cobalt(III) and oxidovanadium(IV) complexes. The metal ligand stoichiometry of these complexes is 1:2 and 1:1:1. With the help of aforementioned techniques, octahedral geometry around the Co(III) complexes and square pyramidal geometry around the VO(IV) complexes have been proposed. Compounds were screened *in vitro* for antimicrobial activities against selected bacterial and fungal strains and binding activity towards BSA hasbeen done using spectroscopic techniques. The spectral result reveals that the interaction between BSA and studied metal complexes are in a static mode.

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