Synthesis, Characterization, and Biological Activities of Novel Vanadium(IV) and Cobalt(II) Complexes

Tadewos Damena,* Digafie Zeleke, Tegene Desalegn,* Taye B. Demissie,* and Rajalakshmanan Eswaramoorthy

ABSTRACT: Herein, we report novel Co(II) and V(IV) complexes synthesized from an (E)-2-(((2-((2-hydroxyethyl)amino)quinolin-3-yl)methylene)amino)ethan-1-ol ligand (L), cobalt(II) chloride hexahydrate, and vanadyl(IV) sulfate in methanolic solutions. The ligand and the complexes were characterized by $^1$H NMR spectroscopy, $^{13}$C NMR spectroscopy, UV-visible spectroscopy, fluorescence spectroscopy, FT-IR spectroscopy, powder X-ray diffraction (PXRD), scanning electron microscopy—energy dispersive X-ray spectroscopy (SEM—EDX), mass spectroscopy (MS), thermal analysis, and molar conductance. The FT-IR spectral data showed that the ligand adopted a tridentate fashion when binding with the metal ions via the nitrogen atoms of the imine (C=N) and amine (N−H), and the oxygen atom of the hydroxyl group (O−H). The PXRD and SEM results indicated that the complexes are amorphous in nature. The density functional theory (DFT) calculated absorption and IR spectra agree very well with the corresponding experimental results. The antibacterial activities of the free ligand and its complexes were evaluated using a paper disk diffusion method. The complexes have better percent activity index than the free ligand. The cobalt complex exhibited a more recognizable antibacterial activity than the vanadium complex, specifically against Pseudomonas aeruginosa with a mean inhibition zone of 18.62 ± 0.19 mm, when compared with the positive control, ciprofloxacin, with a mean inhibition zone of 22.98 ± 0.08 mm at the same concentration. Furthermore, the antioxidant activities of the free ligand and its metal complexes were also determined in vitro using 2,2-diphenyl-1-picrylhydrazyl. The ligand exhibited less in vitro antioxidant activity than its transition metal complexes, in which the cobalt complex has a better antioxidant activity with half-inhibitory concentrations (IC$_{50}$ of 16.01 μg/mL) than the ligand and the vanadium complex. Quantum molecular descriptors from the DFT calculations further support the experimental results. Molecular docking analysis also shed more light on the biological activities of the novel cobalt and vanadium complexes.

1. INTRODUCTION

Metal ions are known to combine with many drugs and/or organic ligands to form complexes with enhanced ligand bioactivity.1–5 This made the metal complexes to be widely used in medicinal, pharmaceutical, agricultural, and chemical industries.1,6,7 Recent reports indicate that due attention is being given to the chemistry of metal–organic compounds and their clinical applications for the treatment of various disorders, including both communicable and non-communicable diseases.1–3 Accordingly, researchers’ interest has shifted toward the synthesis of metal complexes that have biological activities, such as antioxidant and antimicrobial activities. In the past few decades, studies have revealed that complexes of metals—such as copper, chromium, cobalt, manganese, vanadium, and zinc—have promising antimicrobial, anti-oxidant, anti-tumor, and anti-diabetic properties.3,5,8–20 The issue of metal-based therapy has witnessed increasing focus with respect to efficient strategies in the design of repository, slow-release, or long-acting drugs.21 In this regard, heterocyclic ligands containing imine are important classes of biologically active molecules that have attracted attention of bioinorganic, pharmaceutical, and medicinal chemists due to their familiar coordination behavior and wide range of pharmacological properties.2,3,13–24

Co(II) and V(IV) play essential roles in biological systems. Cobalt(II) complexes are known for their promising biological activities such as antimicrobial, anticancer, and antiviral activities.3,13,14,24–30 Vanadium can exist in V(IV) and V(V) oxidation states. In this aspect, the oxovanadium complexes attracted the attention of researchers due to their well-known biological activities.2,18,31 There exist reports on the successful synthesis of different vanadium complexes with various ligands and evaluation of their magnetic properties and antidiabetic, anti-inflammatory, and catalytic activities.5 However, the study

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of the antimicrobial activity of vanadium-based complexes is rarely reported.31−33

Quinoline is classified under the alkaloid class of natural products34 and is present in various plants,35 pharmaceuticals, agrochemicals, and dyes. It has been used as a chelating agent due to its N-donor ligands in coordination chemistry to form complexes.36 Quinolines and their derivatives have emerged as compounds with very effective biological and pharmacological activities, which possess wide range of significance such as anticancer,37−39 antimicrobial,38,40 antifungal,41 antiprotozoal,42 anti-inflammatory,42,43 and antioxidant activities.22 The 2-oxo-quinoline, 2-chloro-quinoline, and 2-chloroquinoline-3-carbaldehyde derivatives were also found to exhibit pronounced biological activities, including antimicrobial, anti-inflammatory, antimalarial, anticancer, and antiviral activities.22,35,36,43−45

The structural and biological properties of imine transition metal complexes derived from 2-chloroquinoline-3-carbaldehyde derivatives have not been explored well. This motivated us to synthesize and characterize the quinoline derivative ligand—(E)-2-(((2-(2-hydroxyethyl)amino)quinolin-3-yl)methylene)amino)ethan-1-ol (L), recently reported by our group46—and its coordination complexes with Co(II) and V(IV) metal ions. Even though lots of studies have been performed on the mentioned transition metals,2−5,13−16,47,48 the synthesis of the Co(II) and V(IV) complexes using this ligand and their chemical and biological characterizations are reported for the first time in this work. Hence, we hereby report the synthesis of the two novel complexes of metal salts of cobalt chloride hexahydrate and vanadyl sulfate with the mentioned Schiff base-like ligand containing a N-heterocyclic ring. We also report their antioxidant properties by a 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging method, their antibacterial activity study by a disk diffusion method,20 and their stabilities. Furthermore, density functional theory (DFT) calculations, molecular docking, and ADME calculations were also performed to correlate and interpret the experimental results.

2. RESULTS AND DISCUSSION

2.1. Synthesis of the Ligand and Its Transition Metal Complexes. The schematic representation for the synthesis of the ligand and the corresponding Co(II) and V(IV) complexes is presented in Scheme 1. The ligand (L, (E)-2-(((2-(2-hydroxyethyl)amino)quinolin-3-yl)methylene)amino)ethan-1-ol, was derived from 2-chloroquinoline-3-carbaldehyde.16 The Co(II) and V(IV) complexes were also successfully synthesized, and their physicochemical properties are summarized in Table 1.

Table 1. Physicochemical Properties of the Ligand and Its Co(II) and V(IV) Complexes

| compounds                     | color            | yield (%) | melting point (°C) | conductivity (Ω−1mol−1cm2 at 25 °C) |
|-------------------------------|------------------|-----------|-------------------|--------------------------------------|
| C14H17N3O2 (L)                | yellow           | 2.91 g    | 86                 | 80−85                                 |
| [Co(L)(Cl)(H2O)2] (1)         | brownish purple  | 0.25 g    | 63                 | 215−220 8.47 ± 0.25                   |
| [V(L)(O)(H2O)(SO4)] (2)       | deep green       | 0.19 g    | 59                 | 205−210 13.20 ± 0.59                  |

The solubility test showed that both the synthesized metal complexes were soluble in polar solvents such as methanol, ethanol, DMF, DMSO, acetonitrile, and water but insoluble in non-polar solvents. The conductivity tests revealed their non-electrolytic nature with molar conductance values of 8.47 ± 0.25 Ω−1mol−1cm2 for complex 1 and 13.20 ± 0.59 Ω−1mol−1cm2 for complex 2 at 25 °C in methanol. The changes in the color of the metal complexes to brown color for complex 1 and to deep green color for complex 2 were additional confirmation for the successful synthesis of the intended Co(II) and V(IV) complexes, respectively.

2.2. FT-IR Analysis. The functional groups involved in the ligand and complexes were observed from the FT-IR spectra.
(Table 2 and Figure S2A−C). The FT-IR spectra of the ligand showed a strong stretching band at 1639 cm$^{-1}$, which was attributed to the $\nu(C=N)$ imine group, but this band shifted to a higher frequency in the spectra of both metal complexes to 1687 and 1688 cm$^{-1}$, respectively, which indicated the participation of the nitrogen atom of the imine group $\nu(C=N)$ upon complexation. The characteristic strong stretching frequency of the ligand at 3368 cm$^{-1}$ due to $\nu(O-H)$ disappeared in the cobalt complex, which confirmed that the hydroxyl group participated in dative bond formation. It is clearly observed that the imine substituted end (−OH) coordinated to the metal through deprotonation, which results in the disappearance of the characteristics O–H spectral bands (Figure S2B). Hence, the weak and broad band stretching frequencies that are observed (3687−3236 cm$^{-1}$) could be assigned as the stretching vibrations of the O−H of the two water molecules present in the coordination sphere. However, in the case of V(IV), the stretching frequency has shifted with increased intensity to 3398 cm$^{-1}$, indicative of the overlapping of the non-coordinating hydroxyl $\nu(O-H)$ group of the ligand with $\nu(O-H)$ of water in the coordination sphere. The decrease in the intensity of the characteristic stretching frequency of the ligand at 3275 cm$^{-1}$ $\nu(N-H)$ observed in both the synthesized metal complexes appeared to be a good signal for the involvement of the amine group coordinating to the metals through the nitrogen atom. This interpretation is in line with other previous studies.

Overall, the target ligand consists of two −OH coordinating sites (imine and amine nitrogen atoms). However, from the two potential −OH sites, the one that is found at the side of imine containing end has more electron density due to $\pi$−$\pi$ electron delocalization from the quinoline ring than the other −OH group. Hence, it preferably coordinates to the metal centers through deprotonation. The −OH at the side of the amine containing end is not coordinated to the metals mainly due to electron density and steric hindrance, as it has been clearly confirmed from the spectral data from FT-IR spectra, MS, and elemental composition.

New stretching vibration bands are displayed in the spectra at 546 and 466 cm$^{-1}$ for $\nu(Co-O)$ and $\nu(Co-N)$ bonds of the cobalt complex, respectively, and the bending frequencies at 604 cm$^{-1}$ $\delta(V-O)$ and 459 cm$^{-1}$ $\delta(V-N)$ for the V(IV) complex. These confirm that both metal ions have participated in the coordinate covalent bond formation. The stretching band at 977 cm$^{-1}$ is characteristic of $\nu(V=O)$, in agreement with related studies. The weak band frequency of $\delta(O-H)$ is clearly observed between the range of 1437 and 1449 cm$^{-1}$ for complex 1 and 2, respectively. This indicates the presence of free bending hydroxyl $\delta(O-H)$ groups in the complexes. The DFT calculated IR frequencies are also in good agreement with the corresponding experimental results (Table 2), which further confirms the analysis.

### 2.3. UV−Visible Spectroscopy

The UV−Vis absorption spectra of the free ligand and its complexes are presented in Figure 1, whereas band assignments are presented in Table 3. The UV−Vis spectra of the ligand and its metal complexes were recorded at a wavelength range (200−800 nm) using a 0.1 mM sample solution of methanol at room temperature. The absorption bands of the ligand are due to ($\pi$−$\pi^*$) and (n−$\pi^*$) transitions, which undergo red and blue shifts during metal complexation. The bathochromic and hypsochromic effects confirmed the formation of the title metal complexes when we compared with the free ligand. The free ligand exhibited absorption bands at 231, 258, 300, and 383 nm (Figure 1), which could be attributed to $\pi$→$\pi^*$ and n→$\pi^*$ transitions. The metal complexes of Co(II) and V(IV) exhibited absorption bands in the spectral range of 231−260 nm and 293 and 304 nm, which are assigned to be $\pi$→$\pi^*$ and n→$\pi^*$ transitions, respectively.

Moreover, the broad bands observed at 427 and 409 nm for Co(II) and V(IV) complexes, respectively, are assigned to the ligand to metal charge transfer (LMCT). This could serve as an additional confirmation for the participation of the ligand in complex formation. In these electronic spectra, a d−d transition is not observed due to the dominance of the ligand to metal charge transfer and hence the observed color is mainly due to the pronounced LMCT in both the Co(II) and V(IV) complexes.

To shed more light on the absorption spectra of the ligand and the two complexes, we used TD-B3LYP to calculate the absorption spectra. Comparison of the experimental electronic spectra with the DFT calculated results for the absorption spectra has been carried out, and it was found that the experimental results are in very good agreement with the calculated results, as presented in Figure 1. This further confirms the successful syntheses of the intended complexes.

### 2.4. Fluorescence Spectra

The emission spectra of the ligand (L) showed an emission band at 525.96 nm and the Co(II) and V(IV) complexes showed an emission band at 420.03 nm and 521.03 nm, respectively (Table 4). The formation of metal complexes with the free ligand promotes the hypsochromic (intense) and bathochromic shifts (red shift). The metal complexes showed strong fluorescence intensities compared to their precursor, the ligand (Figure S3). The incorporation of a metal ion in the complex might have increased the conformational rigidity of the ligand and hence increased the fluorescence intensities of the complexes. These results show that the synthesized complexes could have a potential use in photochemical applications.

### 2.5. X-ray Diffraction Analysis

The powder X-ray diffraction (XRD) patterns of the synthesized transition
metal complexes (1 and 2) were studied (Figure 2). The diffraction patterns of both transition metal complexes indicated that the metal complexes 1 and 2 revealed a mixture of polycrystalline and amorphous structures expressed as a broad peak at a range of 2θ = 5–80°.2,3,57

Figure 1. Comparison of the experimental absorption wavelengths of the ligand and complexes 1 and 2 with the corresponding B3LYP-GD3/6-311++G(d,p)/LANL2DZ(PCM/Methanol) calculated results.

Table 3. Electronic Spectra of the Ligand and Its Co(II) and V(IV) Complexes

| compounds | absorption (nm) | transition                  |
|-----------|-----------------|-----------------------------|
| L         | 231, 258, 300, 383 | (σ–σ*), (π–π*), (n–π*)     |
| 1         | 234, 258, 293, 427 | (σ–σ*), (π–π*), (n–π*), LMCT |
| 2         | 231, 260, 304, 409 | (σ–σ*), (π–π*), (n–π*), LMCT |

Table 4. Absorption, Emission, Wavelength, and Intensity of the Titled Compounds

| compounds | absorption λ_{max} (intensity) | emission λ_{max} (intensity) |
|-----------|-------------------------------|-----------------------------|
| L         | 383 (0.159)                   | 527 (22.610)                |
| 1         | 427 (0.232)                   | 420 (90.120)                |
| 2         | 409 (0.087)                   | 521 (45.850)                |

2.6. SEM–EDX Analysis. The composition of the complexes was obtained from energy dispersive X-ray (EDX) analysis. The spectra are presented in Figure 3. The results showed that the percentage of the experimental atoms is close to the expected (theoretical) values.65,64 The EDX spectrum of complex 1 shows the characteristic signals, which correspond to carbon, oxygen, nitrogen, chlorine, and cobalt. The spectra indicated that the metal complex presents as a CHCoNOCl compound (Figure 3A), whereas the EDX spectrum of complex 2 shows characteristic signals that correspond to carbon, oxygen, nitrogen, sulfur, and vanadium, clearly confirming the formation of a CHVSNO compound (Figure 3B). On the other hand, SEM was used to evaluate the morphology and size of the complexes. The SEM micrographs showed the agglomerate particles of the complexes. Complexes 1 and 2 were shown as mass of agglomeration (Figure 3C,D), in which both the SEM image and the powder XRD data indicated that both complexes have amorphous-like structures.57,63,64

2.7. Mass Spectra. The mass spectra of both complexes were characterized using LC–MS. The mass spectrum of complex 1 exhibits a parent molecular ion peak at m/z = 385.90 (found = 386.03), which is similar to the formula of [C_{14}H_{18}ClCoN_{3}O_{4}]^{+} (M. Wt = 386.70) (Figure S4A). On the other hand, the mass spectrum of complex 2 exhibits a parent molecular ion peak at m/z = 438.11 (found = 439.03), which corresponds to the formula of [C_{14}H_{18}N_{3}O_{8}SV]^{+} (M. Wt = 439.32) (Figure S4B). From these two mass data, it is possible to say that both complexes are hexagonal coordinated systems, inferring that the complexes existed in the form of the Co(II) and V(IV) oxidation state, and this is in line with their elemental composition. There are additional peaks, in which

Figure 2. Powder XRD data of (a) Co(II) and (b) V(IV) complexes.
the complex 1 spectrum also displays another peak at \( m/z = 316.06 \) (34.70%) (found = 316.05), which leads to \([\text{C}_{14}\text{H}_{18}\text{CoN}_{3}\text{O}_{2}]^+\) (M. Wt = 316.22). This spectrum also displayed another peak at \( m/z = 260.14 \) (34.75%) (found = 259.33) assigned to \([\text{C}_{12}\text{H}_{10}\text{N}_{2}\text{O}_{2}]^+\) (M. Wt = 260.31). Similarly, the peaks observed for complex 2 were at \( m/z = 309.05 \) (9.70%) (found = 309.07), leading to \([\text{C}_{14}\text{H}_{18}\text{N}_{3}\text{O}_{2}]^+\) (M. Wt = 309.24), and this spectrum also displayed another peak at \( m/z = 259.33 \) (12.75%) (found = 259.13) assigned to \([\text{C}_{12}\text{H}_{10}\text{N}_{2}\text{O}_{2}]^+\) (M. Wt = 259.30). The MS and elemental composition analyses for both complexes gave results that agree with each other.

2.8. Molar Conductance. The molar conductance of the synthesized free ligand and its transition metal complexes were determined at room temperature in methanol with a concentration of 1 mM of all compounds. The conducting nature of the metal complexes (1 and 2) was measured in triplicate, and the molar conductance values of the complexes were found to be 8.47 and 13.20 \( \Omega^{-1}\text{mol}^{-1}\text{cm}^{2} \), respectively (Table 1). These results indicated the neutrality of the complexes and that the metal cations accepted electron(s) from the ligand and hence the non-electrolytic nature of the complexes 1 and 2 could be due to the relatively low conductivity of the synthesized metal complexes, in agreement with different previous studies. In the case of the Co(II) complex, the chloride ions are coordinated to the metal ion to satisfy the valence and the chloride ions lied in the coordination sphere of the Co(II) complex, which is confirmed by the absence of white precipitates during the chloride test performed using silver nitrate (AgNO₃). Therefore, the synthesized Co(II) complex was formulated as \([\text{Co(L)}-(\text{H}_2\text{O})_2\text{Cl}]^+\). This is also in agreement with the DFT calculated results (vide infra).

2.9. Thermogravimetric Analysis. Thermogravimetric analyses (TGA) of the newly synthesized Co(II) and V(IV) complexes were carried out to get information about their thermal stability and to suggest a general scheme for their thermal decomposition as well as to ensure the nature of the associated water molecules. In this analysis, the heating rate was controlled at 10 °C min⁻¹ under a nitrogen atmosphere and the mass loss was measured from the room temperature to 800 °C.

The TGA and DTA curves are presented in Figures 4A,B, whereas the temperature range values for decomposition along with the corresponding weight loss values for each step of the decomposition reaction are presented in Table 5. The thermogram of the complexes showed that the complexes are stable up to 100 °C and no weight loss occurs before this temperature. This is in agreement with the spectroscopically determined stability constant of both complexes, which did not show any change up to 40 °C (Table S2), and this infers that the metal complexes can be used for different biological applications. The proposed chemical formulas of the complexes are therefore in line with TGA data. Accordingly, the thermal decomposition of the \( \text{C}_{14}\text{H}_{30}\text{ClCoN}_{3}\text{O}_{4} \) complex exhibits three degradation steps (Figure 4A and Figure S5A). The first step of decomposition occurs within a temperature range of 100–130 °C, which shows a mass loss of 9.26% (calcd. = 9.26%) that corresponds to the loss of two water molecules.

The second step of decomposition occurs within a temperature range of 150–510 °C, which is accompanied by a weight loss of 19.89% (calcd. = 20.71%) corresponding to the loss of \( \text{C}_{7}\text{H}_{4}\text{ClO} \) molecules. The third step of degradation occurs in the temperature range of 535–778 °C and is accompanied by a weight loss of 51.43% (calcd. = 51.0%) corresponding to the loss of the \( \text{C}_{12}\text{H}_{2} \) species of the quinoline ring. The actual mass loss from these steps is 80.58%, which is close to the calculated value of 80.97%.

Thereafter, the compound showed a gradual decomposition up to 778 °C with a weight loss of the organic moiety. The weight of the residue corresponds to the respective metal oxide (CoO) about 19.42% (calcd. = 19.03%). Similarly, the thermal decomposition of the \( \text{C}_{14}\text{H}_{18}\text{N}_{3}\text{O}_{5} \) complex exhibits three degradation steps (Figure 4B and Figure S5B). The first step of decomposition occurs in the temperature range of 100
The percentage metal content in both metal complexes obtained from the elemental analysis agrees very well with these thermal studies, and the proposed stepwise thermal decomposition pattern of both complexes with respect to the temperature and formation of respective decomposed molecules are tabulated in Table 5. Overall, the results are in line with the formulæ proposed from the different analytical data. It is possible to conclude that a general decomposition pattern of the complexes occurred in three stages.

2.10. Antibacterial Activity. The synthesized Co(II) and V(IV) complexes from the quinoline derivative ligand were evaluated (in vitro) for their bacterial activities against four pathogenic bacteria; two Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa) and two Gram-positive bacteria (Staphylococcus aureus and Streptococcus pyogenes). The results are presented in Table 6 and Figure 5. The inhibition zone values of the studied complexes showed their potential antimicrobial activity when compared to a standard drug.

The results presented in Table 6 also show that complex 1 has a better antibacterial activity against P. aeruginosa, with a mean inhibition zone of 18.62 ± 0.19 mm diameter at 300 μg/mL, compared to the positive control, ciprofloxacin, with a mean inhibition zone of 22.98 ± 0.08. This indicates that metal complex 1 exhibited medium to high antibacterial activities with the range of inhibition zones from 10.78 ± 0.24 to 18.62 ± 0.19 mm diameter at concentrations 150 and 300 μg/mL for all bacterial strains (E. coli, P. aeruginosa, S. pyogenes, and S. aureus), in line with previous reports.

However, complex 2 has low bacterial activities with mean inhibition zone ranges of 7 ± 0.31 to 8 ± 0.52 for Gram-positive bacteria (S. aureus) and 7.32 ± 0.90 to 9.52 ± 0.49 for Gram-negative bacteria (E. coli) at both 150 and 300 μg/mL concentrations, while it has no effect on P. aeruginosa and S. pyogenes. The free ligand has a low mean inhibition zone range of 6.22 ± 0.14 to 7 ± 0.11 for E. coli, P. aeruginosa, and S. pyogenes, while it has no bacterial activity effect for S. aureus, indicating that the free ligand has a lower bacterial activity than its metal complexes (Figure 5).

2.11. Antioxidant Activity. The antioxidant activities of the free ligand and its metal complexes were conducted in terms of their proton-donating ability with UV–visible absorbance using the DPPH assay, which is widely used to assess the ability of compounds as scavengers of free radicals and evaluate the antioxidant activity of the targeted free ligand and metal complexes. Accordingly, compounds that have an antioxidant activity may reduce the absorbance at 517 nm, and metal complexes. Accordingly, compounds that have an antioxidant activity may reduce the absorbance at 517 nm, which is due to the DPPH radical that changes in color in the reaction process (Figure 6).

The radical scavenging activity of the free ligand and its metal complexes was evaluated using DPPH in comparison to 182 °C, which is accompanied by a mass loss of 14.23% (calcd. = 14.34%) corresponding to the loss of one water molecule and C7H5O2 ethanol molecule. The second step of decomposition occurs in the temperature range of 185–450 °C, which is accompanied by a mass loss of 31.35% (calcd. = 31.44%) corresponding to the loss of an ethyl amine unit and a sulfate fragment. The third and final step of decomposition occurs within the temperature range of 455–680 °C, with a mass loss of 22.86% (calcd. = 23.45%), which is due to the loss of the C7H5N fragment of the quinoline ring, leaving other residues of carbon, nitrogen, and VO2+ representing 31.56% (calcd. = 32.52%) of the total complex. From the data, the actual mass loss from these steps is 68.44%, which is close to the calculated value of 69.23%.6,69

### Table 5. Temperature Range Values for Decomposition and Corresponding Weight Loss Values

| complexes | decomposition temp. (°C) | Obsd. (%) | Calcd. (%) | interpretation |
|-----------|--------------------------|-----------|------------|----------------|
| [Co(L)(Cl)(H2O)2] | 100–130 | 9.26 | 9.26 | loss due to two water molecules |
| | 150–510 | 19.89 | 20.71 | loss due to a single coordinated chlorine atom and ethanol moiety |
| | 535–778 | 51.43 | 51.00 | loss due to the C7H5N2 species of a quinoline ring |
| | 100–182 | 14.23 | 14.34 | loss of one water and C7H5O2OH molecule |
| [VO((L)H2O)(OSO3)] | 185–450 | 31.35 | 31.44 | loss of an ethyl amine unit and a sulfate fragment |
| | 455–680 | 22.86 | 23.45 | mass loss of the C7H5N fragment of a quinoline ring |

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| | 455–680 | 22.86 | 23.45 | mass loss of the C7H5N fragment of a quinoline ring |
Table 6. Mean Inhibition Zones of the Synthesized Compounds in mm (Mean ± SD)

| bacterial strains | Conc. (µg/mL) | ligand | complex 1 | complex 2 | ciprofloxacin |
|-------------------|--------------|--------|-----------|-----------|--------------|
| *E. coli*         | 150          | 6.22 ± 0.14 | 10.78 ± 0.24 | 7.32 ± 0.90 | 21.50 ± 0.28 |
|                   | 300          | 6.50 ± 0.36 | 11.91 ± 0.10 | 9.52 ± 0.49 | 22.00 ± 0.50 |
| *P. aeruginosa*   | 150          | 6.00 ± 0.25 | 17.87 ± 0.07 | 0.00       | 20.52 ± 0.40 |
|                   | 300          | 6.24 ± 0.39 | 18.62 ± 0.19 | 0.00       | 22.98 ± 0.08 |
| *S. aureus*       | 150          | 0.00       | 12.11 ± 0.15 | 7.00 ± 0.31 | 19.00 ± 0.92 |
|                   | 300          | 0.00       | 14.63 ± 0.20 | 8.00 ± 0.52 | 20.80 ± 0.37 |
| *S. pyogenes*     | 150          | 6.20 ± 0.15 | 0.00       | 0.00       | 15.90 ± 0.55 |
|                   | 300          | 7.00 ± 0.11 | 0.00       | 0.00       | 17.00 ± 0.94 |

Figure 5. Mean inhibition zones of the bacterial activities of the ligand and metal complexes at 150 µg/mL. n = 3. Error bars indicate the standard deviation.

Figure 6. Absorbance spectra of DPPH, ascorbic acid, the ligand and its complexes at 115 µg/mL concentration.

Table 7. Percentage Radical Scavenging Activity of the Synthesized Compounds (Mean ± SD)

| Conc. (µg/mL) | ligand (L) | 1 | 2 | ascorbic acid |
|---------------|------------|---|---|---------------|
| 115           | 55.50 ± 0.32 | 91.68 ± 0.40 | 56.46 ± 0.26 | 97.71 ± 0.39 |
| 100           | 55.39 ± 0.13 | 90.74 ± 0.56 | 55.69 ± 0.45 | 97.23 ± 0.37 |
| 85            | 54.61 ± 0.16 | 85.12 ± 0.18 | 54.81 ± 0.25 | 96.25 ± 0.05 |
| 70            | 53.80 ± 0.32 | 70.91 ± 0.27 | 52.55 ± 0.35 | 91.80 ± 0.34 |
| 55            | 52.74 ± 0.13 | 65.31 ± 0.26 | 50.16 ± 0.20 | 87.85 ± 0.13 |
| 40            | 51.66 ± 0.27 | 61.55 ± 0.20 | 49.70 ± 0.33 | 75.55 ± 0.49 |
| 25            | 48.23 ± 0.18 | 50.45 ± 0.33 | 49.30 ± 0.19 | 60.89 ± 0.92 |
| 10            | 47.07 ± 0.23 | 48.09 ± 0.78 | 48.52 ± 0.05 | 47.35 ± 0.23 |
| 5             | 46.99 ± 0.40 | 47.58 ± 0.25 | 48.19 ± 0.41 | 41.67 ± 0.65 |
| IC₅₀ (µg/mL)  | 35.36       | 16.01       | 34.79       | 4.49         |

with a positive standard, and the findings are presented in Table 7 and Figure 7A. From the results, it has been observed that the complexes have higher antioxidant activities than the free ligand because the metal ions could significantly change the chemical properties of the ligands. This has favored the synthesized complexes to have good radical scavenging activities when compared with ascorbic acid (Figure 7A). In addition, from the data obtained, we can also deduce that complex 2 has insignificant radical scavenging activities as compared with ascorbic acid and complex 1, in which the Co(II) complex has the highest radical scavenging activities with a higher nucleophilicity index (0.192), while the V(IV) complex showed an activity that is comparable with or a bit higher than that of the corresponding ligand. This indicates that the vanadium(IV) did not enhance the radical scavenging activity of the ligand after complexation. This could be mainly due to the sulfate group sitting in the coordination sphere of the V(IV) complex, which potentially decreases the electron-donating ability of the metal center with a lower nucleophilicity index (0.150). This has also been observed in other related studies.

The half-inhibitory concentrations IC₅₀ of the free ligand and its complexes are shown in Figure 7B as a radical eliminator. The higher value of IC₅₀ indicates a lower radical scavenging activity of the compounds. The complexes (1 and 2) and the ligand exhibit half-inhibitory concentrations (IC₅₀) of 16.01, 34.79, and 35.36 µg/mL, respectively, while ascorbic acid (positive control) has a value of 4.49 µg/mL. From the IC₅₀ values, complex 1 has good communication with the positive control, implying that this transition metal complex has a better antioxidant activity than the free ligand.

2.12. Stability Constants, Stoichiometry, and Thermodynamic Parameters. Stoichiometry of the complexes was determined as a 1:1 ratio (metal:ligand) from the linear plot of mole fraction versus absorbance at different temperatures, in which similar results were obtained at all temperatures (Figure S6 and Table S2). The thermodynamic parameters of the complexes are presented in Table S2.
\[ \Delta G = \Delta H - T\Delta S \quad (1) \]

\[ \Delta G = -RT \ln K \quad (2) \]

Gibbs free energy and enthalpy values were found to be negative, which indicated that the metal complexes (1 and 2) were thermally stable at the specified temperatures, and in a way, the lower and negative values of enthalpy change (\( \Delta H \)) indicated the small change in total internal energy and the exothermic nature of transition metals–ligand interaction during complex formation. Similarly, the negative value of Gibbs free energy (\( \Delta G \)) shows the spontaneous formation of both the titled transition metal complexes. The positive values of the change in entropy (\( \Delta S \)) also confirm that the synthesized transition metal complex formations are entropically favored.\(^23,75\)

2.13. Drug-Likeness and ADME Predictions. Drug-likeness is a prediction that determines whether a particular pharmacological agent has properties consistent with being an orally active drug or not, in which this prediction is based on the Lipinski rule of five. The rule predicts that there is likely to be poor absorption or permeation when the specific compounds possess more than five H-bond donors and 10 H-bond acceptors, a molecular weight greater than 500 g/mol, and a calculated LogP greater than 5. In this aspect, the SwissADME predictor has a potential to give information on the numbers of hydrogen donors and acceptors, rotatable bonds, and total polar surface areas of the compounds. The ligand and its metal complexes were subjected to the SwissADME predictor. The analyses of the titled compounds were compared with that of the ciprofloxacin drug used as a standard drug in in vitro bacterial activities during this study, and only the compounds without violation of any of the screenings were used for the molecular docking analysis.\(^74,76\)

The SwissADME calculated results showed that the synthesized free ligand and its metal complexes (1 and 2) satisfy Lipinski’s rule of five with zero violations (Table S3), inferring that the synthesized compounds have a drug-like molecular nature. The ADME lab computed octanol/water partition coefficient (LogP) value revealed that the free ligand and its metal complex 1 have good lipophilicity (0.78; 3 \( \geq \) LogP \( \geq 0 \)), while complex 2 has poor lipophilicity (–0.47; 3 \( \geq \) LogP \( \geq 0 \)).\(^74\) In addition, the SwissADME prediction parameters showed that the synthesized ligand and its complexes 1 and 2 have a high gastrointestinal (GI) absorption and no blood–brain barrier (BBB) permeation and are a substrate of permeability glycoprotein (P-gp). The skin permeability (logKp) values of the ligand and its metal complexes were found to be –7.15 and –8.29 cms\(^{-1}\), deducing low skin permeability.\(^77,78\)

The synthesized compounds were predicted as a substrate of P-glycoprotein (P-gp), a transporter, and a biological barrier responsible for the ADME of drugs.\(^77\) It is inferred that the compounds have no tendency to interact with other drugs.

Table 8. Thermodynamic Parameters of the Transition Metal Complexes at Different Temperatures

| parameters      | 25 °C | 30 °C | 37 °C | 40 °C | 25 °C | 30 °C | 37 °C | 40 °C |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|
| ln K            | 18.52 | 18.51 | 18.51 | 18.50 | 13.60 | 13.54 | 13.53 | 13.53 |
| \(-\Delta G \) (kJ mol\(^{-1}\)) | 45.89 | 46.63 | 47.71 | 48.15 | 33.69 | 34.11 | 34.87 | 35.21 |
| \(-\Delta H \) (kJ mol\(^{-1}\)) | 0.85  |       |       |       | 3.59  |       |       |       |
| \(\Delta S \) (J mol\(^{-1}\)) | 151.10|       |       |       | 101.07|       |       |       |

\( T \) is the temperature in Kelvin (K) and \( K \) is the formation constant.
fingered by the transporter and then could not induce drug—drug interactions. Moreover, the topological polar surface areas (TPSAs) of the ligand and its complexes 1 and 2 were predicted to be 77.74, 78.18, and 95.25 Å², respectively. From these data we can deduce that the free ligand and its transition metal complexes 1 and 2 have a very good intestinal absorption, whereby TPSAs of 140 Å² and above would be poorly absorbed (<10% fractional absorption), while those with a TPSA of 60 Å² would be well absorbed (>90%). The ADME lab predicted descriptors for the physicochemical properties as well as the optimal solubility of the ligand and its transition metal complexes were found to agree very well with the corresponding experimental results.

2.14. Quantum Chemical Analysis. The quantum chemical parameters of the ligand and its metal complexes are tabulated in Table 9. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) analysis was performed to predict the reactivity of the ligand and the complexes. The energy gaps ($E_g = E_{\text{LUMO}} - E_{\text{HOMO}}$) for possible electron transition were calculated to be 3.817, 3.684, and 3.991 eV for the ligand, complex 1, and complex 2, respectively. These results predict the good reactivity of the titled compounds. The energy gap ($E_g$) can also be correlated with various biological aspects like antibacterial, antioxidant, and DNA binding aspects.

The wave function analysis (Figure 8) of the ligand revealed that the electron density of the molecule is circulating between the secondary amine substituent nitrogen and the quinoline ring amine from HOMO to LUMO and throughout the molecule due to $\pi$-bond delocalization. The wave function analysis showed that the electron density of the HOMO and LUMO of the cobalt(II) complex is very close to that of the ligand. However, in the case of the V(IV) metal complex, the HOMO and LUMO are localized over the coordinated system. Both HOMO and LUMO are the main orbitals that take part in chemical stability, whereas the negative values of $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ point to the stability of the molecules, and the selected quantum chemical parameters had been derived from $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ and used to evaluate the chemical reactivity of the complexes. The chemical reactivity of the complexes increases with a decrease in the energy gap ($\Delta E$) values. Based on this, it is deduced that complex 1 is more reactive than complex 2. In general, the complexation between the metal ions and the ligand has reduced the HOMO–LUMO energy gap, which can be considered as an indication for better biological activities.

Accordingly, from the band gap and dipole moment analyses, the metal complexes were predicted to have better biological activities than the free ligand, in good agreement with the experimental biological activities.

The biological activity of the complexes toward appropriate molecules can be discussed with the hard—soft—acid—base (HSAB) principle, which states that soft acids prefer to bind with soft bases and hard acids prefer to bind with hard bases. Accordingly, the biological structures of enzymes, which are commonly soft, prefer to bind with soft complexes. Therefore, the biological activity increases with the increase in softness. Complex 1 is softer than complex 2, which confirms that complex 1 is more reactive with biological molecules. This agrees well with the results obtained from the experimental biological activities (Table 9).

Chemical potential is used to determine the chemical reactivity, which is directly proportional with the Gibbs free energy that is related with the spontaneity of the reactions. The chemical reactivity increases with a decrease in the chemical potentials; hence, complex 1 has a stronger reactivity than complex 2. This is also in agreement with the experimentally determined negative change in Gibbs free energy for the complexes, inferring that the chemical reaction is spontaneous (Table 8).

Other important parameters predicted are the electrophilicity and nucleophilicity indexes. The electrophilicity index implies the ability of the complexes to accept electrons, while the nucleophilicity index displays the ability to donate electrons. In this aspect, complex 1 has a stronger nucleophilicity index while complex 2 has a higher electrophilicity index (Table 9).

2.15. Molecular Docking Analysis. We studied the molecular interaction between the synthesized ligand and the complexes against *E. coli* DNA gyrase (PDB ID: 6F86) to

| compounds | HOMO | LUMO | $E_g$ | $\chi$ | $\mu$ | $\eta$ | $\sigma$ | $\omega$ | Nu |
|-----------|------|------|-------|-------|-------|-------|--------|--------|----|
| L         | −5.901 | −2.0843 | 3.817 | −3.993 | 3.993 | 1.908 | 4.177 | 0.239 |
| 1         | −6.2394 | −2.5357 | 3.684 | −4.378 | 4.378 | 1.842 | 5.202 | 0.192 |
| 2         | −7.1581 | −3.1670 | 3.991 | −5.163 | 5.163 | 1.996 | 6.678 | 0.150 |

**Figure 8.** (a) HOMO and LUMO of the ligand and its metal complexes. (b) Spin density plots of the metal complexes.
understand the mechanism of action. The ligands interacted with the key amino acids by making hydrogen bonds with Asp-73, Gly-77, and Thr-165 and having a hydrophobic interaction with Ile-78, Ile-94, Glu-50, and Pro-79 within the active site (Table S4 and Figure 9). Both the complexes showed interaction profiles like the ligand. The results clearly showed that the free hydroxyl chain in the complexes interacts with the amino acids within the active sites of the protein. The cobalt complex showed a better docking score compared to the vanadium complex. This docking analysis is also in good agreement with the in vitro antibacterial analysis results.

3. CONCLUSIONS

In the present study, novel Co(II) and V(IV) metal complexes were prepared with the oxygen and two nitrogen atoms (ONN) donor (E)-2-(((2-((2-hydroxyethyl)amino)quinolin-3-yl)methylene)amino)ethan-1-ol ligand (L). The ligand and the complexes were characterized using 1H NMR, 13C NMR, FTIR, EDX–SEM, powder XRD, UV–vis spectroscopy, fluorescence, thermal analysis, and mass spectroscopy. From these various spectroscopic analyses, it is possible to conclude the successful synthesis of the Co(II) and V(IV) complexes under the specified reaction conditions. The in vitro antibacterial activities of the free ligand and its metal complexes were identified with the paper disk diffusion technique against two Gram-positive and two Gram-negative bacteria, in which the metal complexes showed better activities against the bacterial strains than the free ligand. The cobalt complex showed maximum percent activity index (AI = 80%) against P. aeruginosa compared to the V(IV) complex and the positive control. Overall, the results indicated that the cobalt complex exhibited from medium to high antibacterial activities with the range of inhibition zones from 10.78 ± 0.24 to 18.62 ± 0.19 mm diameters at concentrations 150 and 300 μg/mL for all bacterial strains (E. coli, P. aeruginosa, S. pyogenes, and S. aureus). In addition, the synthesized complexes were evaluated for their antioxidant activities using DPPH. The results indicated that the Co(II) complex has a higher antioxidant activity (IC50 = 16.01 μg/mL) than the V(IV) (IC50 = 34.79 μg/mL) complex. The stability of the metal complexes was determined spectroscopically (KCo(II) = 1.10 × 10^8 and KV(IV) = 8.06 × 10^5). Both metal complexes were stable at the specified temperatures, and the thermodynamic parameters indicated that the reactions are spontaneous with the exothermic nature of metal–ligand interactions. The in silico (drug-likeness, DFT, and molecular docking) studies of the synthesized compounds were performed. The results indicated that both complexes fulfill Lipinski’s rule of five. The results of the molecular orbital analysis and the binding modes of these compounds against E. coli DNA gyrase B are in good agreement with the experimental biological activities. Overall, the newly synthesized cobalt(II) and vanadium(IV) complexes have potential biological activities, where the Co(II) complex showed a much better activity than the free ligand and the V(IV) complex.

4. MATERIALS AND METHODS

4.1. Materials and Instrumentation. The chemicals and reagents that were used for this study are 2-chloroquinoline-3-carbaldehyde, ethanolamine, N,N-dimethyl formamide, methanol, triethylamine, cobalt chloride hexahydrate, vanadyl sulfate, dimethyl sulfoxide (DMSO), and 2,2-diphenyl-1-picyrylhydrazyl (DPPH); all chemical reagents, including salts and solvents, were of analytical grade and used without further purification. Morphology and elemental compositions were

Figure 9. Binding interactions of the (a) ligand and (b) Co(II) and (c) V(IV) complexes against E. coli DNA gyrase (PDB ID: 6F86).
analyzed using a FESEM-EDX (CARL ZE 15S, OXFORD Instruments, USA). Fluorescence spectra measurements were performed using an Agilent: MY-18490002/PC spectrophotometer. Mass spectra were recorded using a SHIMADZU LC-MS (8030). The UV–visible spectral data were recorded on an SM-1600 double beam spectrophotometer at the wavelength range 200–800 nm, whereas the powder XRD data were recorded on a diffractometer (X-ray tube target: Cu-Kα (λ = 1.5406 nm)) and FT-IR was recorded with a Perkin-Elmer BX spectrometer (4000–400 cm⁻¹) in KBr pellets. Conductivity was measured using an electrical conductivity meter (AD8000). Melting points were measured using capillary tubes with a digital melting point apparatus, and thermogravimetric analysis (TGA) and differential thermal analysis (DTA) were performed under a N₂ atmosphere (20 mL/min) using a DTG-60H Shimadzu thermal analyzer with detectors. The rate of heating of the sample was set at 10 °C/min; TGA/DTA techniques were performed with an NETZSCH STA 409 PC/PG, in which a heating rate of 10 °C/min was used between room temperature and 800 °C. Thin layer chromatography (TLC) was run on a 0.2 mm silica gel GF254 (Merck) on an aluminum plate, and spots were detected and visualized using UV light with 254 and 366 nm wavelengths.

4.2. Synthesis of the Ligand (E)-2-((2-((2-Hydroxyethyl)amino)quinolin-3-yl)methylene)amino)ethan-1-ol (L). The ligand (L) was synthesized based on our previous report with slight modifications, where 2-chloroquinoline-3-carbaldehyde (2.5 g, 0.013 mol) was added to 15 mL of 2-aminoethanol-1-ol in a 250 mL two-neck round-bottom flask and heated to 90–95 °C for 2 h in an oil bath. The progress of the reaction was monitored with thin layer chromatography. Once the reaction was completed, the resulting product was cooled to room temperature and then put into 200 mL of cold ice water and then the resulting precipitate was separated using suction filtration, washed with 100 mL of ice cold water to remove the excess amount of ethanolamine, which served both as a solvent and reagent, and then dried at room temperature.

The ligand (E)-2-((2-((2-hydroxyethyl)amino)quinolin-3-yl)methylene)amino)ethan-1-ol (L) has formula C₁₄H₁₉N₃O₈SV; C, 38.19; H, 4.35; N, 9.54; O, 29.07; S, 7.28; and V, 11.57%. Found C, 38.1; H, 4.3; N, 9.5; O, 29.0; S, 7.3; and V, 11.6%. FTIR (KBr cm⁻¹): 3368 ν(O-H), 3275 ν(N-H), 1647 ν(C=N), 1639 ν(imine C=N), 1620 ν(quinoline C=C). ¹H NMR (400 MHz, DMSO-d₆): δH 3.65 (8H, d, H-11, H-12, H-15, and H-16), 4.72 (1H, s, H-13), 4.92 (1H, s, H-17), 7.19 (1H, t, J = 7.25 Hz, H-6), 7.55 (2H, m, H-5, H-8), 7.72 (1H, d, J = 8.36 Hz, H-7), 8.21 (1H, s, H-4), 8.51 (1H, s, H-9), and 9.55 (1H, s, NH) (Figure S1A). ¹³C NMR (100 MHz, DMSO-d₆): δC 43.4(C-14), 60.5(C-12), 61.2(C-15), 63.7(C-11), 117.2(C-3), 121.9(C-8), 122.4(C-4a), 125.7(C-5), 128.9(C-6), 131.5(C-7), 143.0(C-4), 148.3(C-8a), 155.4(C-2), and 163.8(C-9) (Figure S1B); DEPT-135 δC 43.4 (C-14 negative), 60.5 (C-12 negative), 61.2 (C-15 negative), 63.7 (C-11 negative), 121.9 (C-8), 125.7 (C-5), 128.9 (C-6), 131.5 (C-7), 143.0 (C-4), and 163.8 (C-9) (Figure S1C). Additional results are presented in Figure S1 of the Supporting Information (SI).

4.3. Synthesis of the Metal Complexes. Under constant stirring at room temperature, a drop of triethylamine was added to the methanolic solution of the ligand (0.25 g, 0.96 mmol) in 10 mL of CoCl₂·6H₂O (0.23 g) and VOSO₄ (0.16 g) was added dropwise to the solution under continuous stirring and then all mixtures were refluxed for 3.5 and 4 h at 80 °C in a water bath. The progress of the reaction was monitored with TLC, and after the completion of the reaction, the mixture was cooled to room temperature and then washed repeatedly using cold absolute methanol to remove the unreacted metal and ligand, in which dry samples were collected for analysis.

4.3.1. Complex 1. Complex 1 has a molecular formula [Co(L)(H₂O)₂Cl]. Brownish purple non-hygroscopic amorphous solid, Yield: 63%; melting point: 215–220 °C; soluble in methanol, ethanol, and water. Molar conductance: 8.47 ± 0.25 Ω⁻¹ mol⁻¹ cm² at 25 °C (Table 1). Anal. Calc. for C₁₄H₁₉N₃O₈SV: C, 38.19; H, 4.35; N, 9.54; O, 29.07; and V, 11.57%. Found C, 38.1; H, 4.3; N, 9.5; O, 29.0; S, 7.3; and V, 11.6%. FTIR (KBr cm⁻¹): 1647 ν(C=N), 1059 ν(C=O), 546 ν(C=O), 466 ν(C=N) (Figure S2B). UV–vis (nm): 234 (π-π⁺), 258 (π-π⁺), 293 (n-π⁺), 427 (LMCT) (Figure 1 and Table 2).

4.3.2. Complex 2. Complex 2 has a molecular formula [V(L)(O)(H₂O)(SO₄)]⁻. Deep green amorphous-like powder and non-hygroscopic; Yield: 59%; melting point: 205–210 °C; soluble in methanol, ethanol, DMSO, DMF, and water. Molar conductance (MeOH): 13.20 ± 0.59 Ω⁻¹ mol⁻¹ cm² at 25 °C (Table 1). Composition: Calc. for C₁₄H₁₉N₃O₈SV; C, 38.19; H, 4.35; N, 9.54; O, 29.07; S, 7.3; and V, 11.57%. Found C, 37.96; H, 4.68; N, 9.66; O, 28.91; S, 6.71; and V, 12.08%. FTIR (KBr cm⁻¹): 1688 ν(imine C=N), 1070 ν(C=O), 977 ν(V=O), 604 δ(V–O), 459 δ(V–N) (Figure S2C). UV–vis (MeOH, nm): 231 (π-π⁺), 260 (π-π⁺), 304 (n-π⁺), 409 (LMCT) (Figure 1 and Table 2). The structure of this complex is also in agreement with previous studies.

4.4. Stability Constant and Thermodynamic Parameters. The stoichiometric and formation constants or stabilities were determined using Job’s method, which is also known as a continuous variation method. In this method, from transition metal salts of Co(II) and V(IV), the standard solution (1 × 10⁻⁴ M) was prepared and put into 10 50 mL volumetric flasks (0, 1, 2, ..., 10 mL), and similarly, a solution of the ligand (10, 9, 8, ..., 0 mL) was prepared and added, respectively, in order to retain a constant molar ratio; the absorbance values were measured at λmax (427 and 409 nm) and at temperatures of 25, 30, 37, and 40 °C for Co(II) and V(IV) complexes, in which the pH of the solution was adjusted with triethylamine. The stoichiometric calculations were made by varying the molar fraction of the metal ion and the ligand between 0 and 1 at a constant total concentration and then the absorbance values of the solutions of different compositions were measured. The absorbance was then plotted against the molar fraction of the ligand and then “n”, the average bound ligand, has been calculated from the abscissa of the maximum of the curve (Xmax) using eq 3:

\[
n = \frac{X_{\text{max}}}{1 - X_{\text{max}}}
\]

In addition, the stability constants of the titled complexes were calculated (eq S1) by spectrophotometry at the specified temperatures (25, 30, 37, and 40 °C), and from these constants, the thermodynamic parameters (ΔG, ΔH, and ΔS) were determined.
examined using the paper disk diffusion technique in which two Gram-positive bacteria (S. aureus, ATCC25923, and S. pyogenes, ATCC19615) and two Gram-negative bacteria (E. coli, ATCC25922, and P. aeruginosa, ATCC27853) were used to examine their activity. The medium was prepared from molten nutrient and Mueller–Hinton agar. Ciprofloxacin and dimethyl sulfoxide were used as positive and negative controls, respectively. The bacterial strains were tested with 150 and 300 μg/mL concentration using the paper disk diffusion technique. In the process, each of the compounds were dissolved in DMSO at concentrations of 150 and 300 μg/mL and 6 mm diameter Whatman filter paper disks were soaked in a 1 mL solution of the above two concentrations. Then, these saturated paper disks were inactivated at the center of a Petri dish having a bacterial lawn in triplicate. The plates were incubated at 37 °C for 48 h, and then the inhibition zone was determined by measuring the diameter of the inhibition zone.22,46,70

4.6. Antioxidant Activity. The antioxidant studies of the free ligand and its transition metal complexes were performed using a 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay as this free radical scavenging assay is a quick and effective method to examine the antioxidant activity of potential antioxidants.71,72 Different concentrations of the sample compounds (5, 10, 25, 40, 55, 70, 85, 100, and 115 μg/mL) and 4 × 10⁻⁷% concentration of the DPPH solutions were prepared. In the experimental process, 2 mL of this solution was added into each 2 mL of the synthesized compound samples in methanol and the control was prepared by adding 2 mL of the DPPH solution to 2 mL of methanol, while 4 mL of methanol was used as a blank. The resulting samples were shaken vigorously and allowed to stand at 37 °C in a dark incubator (Labfreez: TSI-200) for 30 min, and the absorbance was recorded at 517 nm using a double beam UV–vis spectrophotometer; then, quenching of the absorbance at 517 nm of the DPPH radical was examined at a constant time of 30 min and ascorbic acid was used as a positive control.22,46,70–72 All the activities were performed in triplicate, and the average absorbance was taken for calculating the percentage of inhibition using eq 4:

\[ \text{DPPH}_{\text{Inhibition}}(\%) = \left( \frac{A_C - A_S}{A_C} \right) \times 100\% \]  

(4)

where \( A_C \) is the absorbance of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) solution without the samples and \( A_S \) is the absorbance of the titled complex compounds with DPPH solution.

4.7. Drug-Likeness and ADME Prediction. A free web tool (SwissADME)24 was used to convert the two-dimensional (2D) structures into a simplified molecular input line entry system (SMILES) to estimate the in silico pharmacokinetics parameters and other molecular properties. This approach has been successfully used for related studies.74,76,77 Pharmacokinetics properties, lipophilicity, skin permeation, drug-likeness for Lipinski’s rule of five, and physicochemical properties were also predicted via SwissADME.77,78

4.8. Density Functional Theory Calculations. In order to understand the electronic structure of the ligand and its transition metal complexes, DFT calculations were carried out using the Gaussian 16 program package (version G16 C01).85 The results were visualized using the GaussView 06 software. The geometries of the compounds were optimized using the DFT/B3LYP hybrid functional together with Grimme’s dispersion correction (labeled B3LYP-GD3) and 6-311+ +G(d, p)90 basis sets for the light atoms and the LANL2DZ effective core potential basis set for the metal centers to account for scalar relativistic effects. All the DFT calculations were performed within a continuum solvent model by employing the polarizable continuum model (PCM) in its integral equation formalism variant (IEF-PCM).91 methanol as a solvent. The optimized geometries were confirmed to be real minima without any imaginary vibrational frequency by performing vibrational frequency calculations at the same level of theory. TD-DFT calculations were performed at the same level of theory as the geometry optimizations. A total of 100 states were taken for TD-DFT. The absorption spectra were red-shifted by 25 nm for better comparison with the experimental results. The calculated IR spectra were scaled by 0.975. Similarly, the frontier molecular orbitals (FMOs) of the synthesized compounds were calculated at the same level of theory and are presented in the Supporting Information (SI).

4.9. Molecular Docking Analysis (AutoDock Vina). The molecular docking studies were performed using AutoDock Tools (ADT), which is a free graphic user interface (GUI) for the AutoDock Vina. AutoDock Vina with a standard protocol was used to dock the ligand and its complexes (1 and 2) against the active sites of protein (PDB ID: 6F86 and 2UV0).72 The grid box was constructed using s, s, and 40, pointing in x, y, and z directions, respectively, with a grid point spacing of 0.375 Å. The center grid box dimension was 14.527, 56.689, and −5.122 Å. Nine different conformations were generated for each ligand and its transition metal complexes scored using AutoDockVina scoring functions and ranked according to their binding energies. AutoDock Tools and PyMOL were used for the post-docking analyses. The conformations with the most favorable binding free energies were selected for analyzing the interactions between the target receptor and the compounds using PyMOL.22,46,76

4.10. Statistical Analysis. The antibacterial data analyses generated by triplicate measurements were reported as mean plus standard deviation. GraphPad Prism version 5.00 for Windows was used to perform the Analysis (GraphPad Software, San Diego, California, USA). Groups were analyzed for significant differences using a linear model of variance analysis (ANOVA) test for comparisons with significance accepted for \( p < 0.05 \) (Table S1 of the SI).

■ ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06205.

1H NMR,13C NMR, DEPT-135, FT-IR, fluorescence, and mass spectra of the ligand and the complexes, Job’s curves for stability constants, plot of In K versus 1/T for the determination of thermodynamic parameters, one-way analysis of variance, metal–ligand formation constants and stoichiometric ratios, ADME and drug-likeness descriptors, and molecular docking results (PDF)

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T. Damena and D.Z. conducted the experiments; T. Damena, D.Z., T. Desalegn, T.B.D., and R.E. performed the data analysis; T. Damena, T. Desalegn, R.E., and T.B.D. prepared the methodology; T. Damena and T. Desalegn wrote the original draft; and T. Damena, T. Desalegn, T.B.D., and R.E. participated in reviewing and editing the paper.

Notes

The authors declare no competing financial interest.

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