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Synthesis, characterization, and biological activity of Cu(II), Ni(II), and Zn(II) complexes of a tridentate heterocyclic Schiff base ligand derived from thiosemicarbazide and 2-benzoylpyridine

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ABSTRACT

Ni(II), Cu(II), and Zn(II) complexes of the tridentate heterocyclic ligand, 2-(phenyl(pyridin-2-yl)methylene)hydrazine-1-carbothioamide (HL) have been synthesized and characterized by various spectroscopic techniques and elemental analyses. Infrared spectroscopy shows that the ligand coordinates to the metal ions through the azomethine and pyridine nitrogen atoms as well as the sulfur atom of the thioamide group to form a tridentate chelate system. *In vitro* screening of metal complexes against four bacterial strains (*Staphylococcus aureus* (ATCC 43300), *Klebsiella pneumoniae* (ATCC 700603), *Methicillin resistant staphylococcus aureus* (ATCC 33591), *Shigella flexneri* (NR 518)) and four fungal strains (*Candida albicans* (NR 29444), *Candida albicans* (NR 29445), *Candida albicans* (NR 29451), *Candida krusei* (HM 1122)) indicate that the Cu(II) complex showed good antibacterial activity on *Methicillin resistant staphylococcus aureus* (ATCC 33591) while the Zn(II) complex showed moderate activity against some of the bacterial and fungi strains. Antioxidant studies reveal that the complexes are more potent than the ligand to eliminate free radicals, with the Ni(II) complex showing the best free radical scavenger.

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1. Introduction

In recent years, heterocyclic Schiff base complexes have received a lot of attention due to their wide range of potential applications [1-3]. Schiff bases, especially those containing O- and/or N-donor atoms, and their metal complexes have been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antioxidant, and anti-inflammatory properties [4-6]. The coordination of the Schiff bases to different metal atoms has been shown to enhance the observed biological activity [7]. The common structural feature of Schiff bases is the presence of the characteristic azomethine functionality, *R*-HC=N-*R'*, which has been shown to account for the observed biological activities [8]. The increasing resistance of microbes to drugs has necessitated the search for new compounds to target these pathogens. The development of systems based on metal ions incorporated into organic molecules is expected to improve the biological properties of these organic molecules (drugs) [9].

Thiosemicarbazones have received a lot of attention due to their structural flexibility, variable binding modes, and ease to form stable chelates with metal ions [10-12]. Thiosemicarbazones containing nitrogen atoms have been the subject of extensive study due to their potential industrial and biological applications [13-15]. Most tridentate donor ligands have been shown to stabilize metal ion centers, forming strain-free five- or six-membered rings [14]. Despite the fact that metal (II) complexes of heterocyclic Schiff base ligands derived from thiosemicarbazone stand out as a promising class of compounds that are considered useful models for bioorganic processes [16], only a few studies have been reported on the use of Ni(II), Cu(II), and Zn(II) complexes of 2-benzoylpyridine thiosemicarbazone as antimicrobial and antioxidant agents. Our group has recently embarked on studies on the antimicrobial and antioxidant activities of complexes of heterocyclic Schiff base ligands [13,17-20]. Some of these heterocyclic Schiff base ligands derived from either isoniazid (Isonicotinic acid hydrazide) [13,17,18] or amino acids [19,20] are generally bidentate or tridentate chelators, forming six-coordinate complexes. We have also used cyclic voltammetry to study the redox properties of some of these systems in an attempt to relate the redox properties to antioxidant activity [13].

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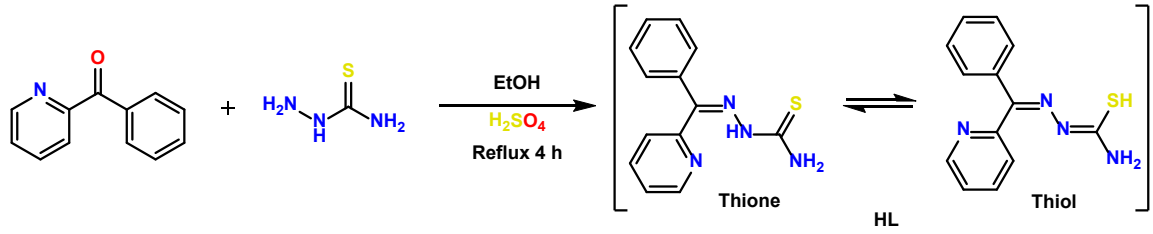

Scheme 1. Synthesis of the ligand, 2-(phenyl(pyridin-2-yl) methylene) hydrazine-1-carbothioamide (HL) and the thione-thiol tautomerism.

In continuation of our studies on metal complexes of heterocyclic Schiff base ligands, we report herein our study on the synthesis, characterization, and antimicrobial and antioxidant activities of metal(II) complexes of a Schiff base ligand, 2-(phenyl (pyridin-2-yl) methylene) hydrazine-1-carbothioamide.

2. Experimental

2.1. Materials and measurements

All reagents and solvents used in this work were obtained from commercial sources and used without any further purification. Microanalysis data were obtained using a Euro EA 3000 elemental analyzer. Infrared spectra were obtained using KBr pellets on a Genesis FTIR/TM spectrophotometer (ATI Mattson) equipped with a deuterated triglycine sulphate (DTGS) detector in the transmittance mode. Electronic spectra were obtained using an Ocean Insight FX-VIS-IRS-ES spectrophotometer at room temperature. NMR spectra were obtained using a Bruker Avance II 500 MHz Spectrometer with 5 mm BBO Probe head using DMSO-d_6. Complete assignment of the NMR signals of the compounds was supported by two-dimensional spectral analyses (Heteronuclear multiple bond correlation (HMBC) and heteronuclear single quantum correlation (HSQC)). Conductance measurements were performed at room temperature using a Labtecth Digital AVI-846 conductivity meter.

2.2. Synthesis of 2-(phenyl(pyridin-2-yl)methylene) hydrazine-1-carbothioamide ligand (HL)

The ligand (HL) was synthesized according to the general synthetic procedure reported elsewhere with some slight modifications [5]. The ligand was synthesized by the condensation reaction of 2-benzoylpyridine (0.55 g; 3 mmol) and thiosemicarbazide (0.27 g; 3 mmol) dissolved in hot ethanol, to which two drops of sulphuric acid were added and the reaction mixture maintained under reflux for five hours at 78-80 °C. The volume of the resulting yellow solution was reduced to half by evaporation and the yellow precipitate formed was filtered, washed several times with ethanol, air-dried and the yellow product collected. The reaction equation is represented in Scheme 1. Color: Yellow. Yield: 86%. M.p.: 145-147 °C. FT-IR (KBr, ν, cm^{-1}): 3223-3403 (NH_2, thioamide), 3127 (NH, carbazid), 1592 (C=N) (Azomethine), 1061 (N-N) (Azid), 810 (C=S, thioamide). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 12.60 (s, 1H, N-H), 8.85 (d, 1H, Pyr.), 8.63 (s, 2H, NH_2), 7.99 (d, 1H, Pyr), 7.64 (dd, 1H, Pyr), 7.58 (td, 1H, Pyr), 7.31-7.43 (m, 6H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 178.54 (1C, C=S), 154.40 (1C, C=N), 151.31 (1C, pyr-C-N), 149.01 (1C, pyr-C=N), 143.44 (1C, pyr-C), 126.04 (1C, pyr-C), 124.90 (1C, pyr-C), 138.15 (1C, Ar-C), 131.01 (1C, Ar-C), 128.33-129.44 (Ar-C). UV/Vis ($CHCl_3$, λ_{max}, nm, (ε)): 345 (2.80). Anal. calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86; S, 12.51. Found: C, 61.05; H, 4.72; N, 21.79; S, 12.81%.

2.3. Synthesis of the complexes

2.3.1. Synthesis of Cu(II) complex (1)

A hot methanolic solution of 2-(phenyl(pyridin-2-yl) methylene)hydrazine-1-carbothioamide ligand (3 mmol) was added dropwise to a hot methanolic solution of $Cu(NO_3)_2{\cdot}5H_2O$ (3 mmol) [21]. The mixture was stirred under reflux for 3 h at 78-80 °C. The precipitate obtained was cooled to room temperature, then separated by filtration, and dried to obtain a dark green solid. Yield: 80%. M.p.: 200-202 °C. FT-IR (KBr, ν, cm^{-1}): 3307 (NH_2, thioamide), 1620 (C=N, azomethine), 1133 (N-N, azid), 775 (C-S), 580 (Cu-N), 415 (Cu-S). Anal. calcd. for $C_{13}H_{13}CuN_5O_4S$: C, 39.14; H, 3.29; N, 17.56; S, 8.04. Found: C, 38.41; H, 2.96; N, 18.21; S, 8.44%. UV/Vis ($CHCl_3$, λ_{max}, nm, (ε)): 360 (2.56), 679 (0.37). Λ_m ($S.m^2.mol^{-1}$): 3.9.

2.3.2. Synthesis of Ni(II) complex (2)

This complex was prepared as described for complex **1** using $Ni(NO_3)_2{\cdot}6H_2O$ (3 mmol) dissolved in hot methanol. A hot methanolic solution of 2-(phenyl(pyridin-2-yl)methylene) hydrazine-1-carbothioamide ligand (6 mmol) was added dropwise to the above solution to obtain a green precipitate that was separated by filtration. Yield: 56%. M.p.: 300-302 °C. FT-IR (KBr, ν, cm^{-1}): 3295 (NH_2, thioamide), 3098 (NH, carbazid), 1648 (C=N, azomethine), 1159 (N-N, azid), 840 (C=S, thioamide), 476 (Ni-N), 414 (Ni-S). Anal. calcd. for $C_{26}H_{24}N_{10}NiO_6S_2$: C, 44.91; H, 3.48; N, 20.14; S, 9.22. Found: C, 44.10; H, 3.56; N, 20.18; S, 9.09%. UV/Vis (DMSO, λ_{max}, nm, (ε)): 337 (4.41), 364 (3.58), 407 (4.03), 621 (0.91). Λ_m ($S.m^2.mol^{-1}$): 100.

2.3.3. Synthesis of Zn(II) complex (3)

Complex **3** was prepared using the same method as that for complex **1** and employing $ZnCl_2$ (3 mmol) to obtain a yellow solid. Yield: 52%. M.p.: 250-252 °C. FT-IR (KBr, ν, cm^{-1}): 3264 (NH_2, thioamide), 1638 (C=N, azomethine), 1152 (N-N, azid), 739 (C-S), 484 (Zn-N), 410 (Zn-S). Anal. calcd. for $C_{13}H_{13}ClN_4OSZn$: C, 41.73; H, 3.50; N, 14.97; S, 8.57. Found: C, 41.19; H, 3.18; N, 14.41; S, 8.96%. UV/Vis (DMSO, λ_{max}, nm, (ε)): 404 (2.32). Λ_m ($S.m^2.mol^{-1}$): 9.9.

2.4. Antimicrobial study

Schiff base and its metal complexes were evaluated for antimicrobial screening on four bacterial strains (*Staphylococcus aureus* (ATCC 43300), *Klebsiella pneumoniae* (ATCC 700603), *Methicillin resistant Staphylococcus aureus* (ATCC 33591) and *Shigella flexneri* (NR 518)) and four fungal strains (*Candida albicans* (NR 29444), *Candida albicans* (NR 29445), *Candida albicans* (NR 29451) and *Candida krusei* (HM 1122)). Gentamicin and amphotericin B were used as reference drugs for bacteria and fungi, respectively. Furthermore, ciprofloxacin and fluconazole were used as standards to

determine the inhibition zone of certain bacteria and fungi, respectively.

2.4.1. Determination of the diameters of zone of inhibition

The compounds were dissolved in DMSO at a final concentration of 5 mg/mL. Antimicrobial tests were then performed using the disk diffusion method employing 100 µL of suspension containing 1×10^6 CFU/mL spread on Mueller-Hinton agar medium (MHA). The disks (6 mm in diameter) were impregnated with 50 µL of the compounds (250 µg/disk) at a concentration of 5 mg/mL and placed on the inoculated agar. Negative controls were prepared using the same solvents used to dissolve the plant extracts. Ciprofloxacin (10 µg/disk) and fluconazole were used as a positive reference standard. The inoculated plates were incubated at 30 °C for 24 h for bacterial and fungi strains. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms [22].

2.4.2. Minimum inhibitory concentration (MIC)

Stock solutions of each compound and reference drug (Gentamicin and amphotericin B) were prepared in pure DMSO at a concentration of 2 and 1 mg/mL, respectively. MIC was determined by the broth microdilution method, using the based assay previously reported by Faller *et al.* [23]. Initially, 100 µL of Mueller Hinton Broth (MHB) for bacteria or Sabouraud Dextrose Broth for fungal were introduced into the wells. One hundred µL of each extract was added to the wells in the first line, followed by a serial two-fold dilution of the test samples up to the sixth well. One hundred microliters of standardized bacterial suspension (1×10^6 CFU/mL for bacteria and 1.5×10^3 CFU/mL for fungi) were introduced into the wells to obtain final volumes of 200 µL. MHB and bacteria or SDB with fungi constituted the negative control, while the sterility control contained MHB or SDB alone. Gentamycin and amphotericin B were used as positive controls. The final concentration ranged from 125 to 1.525 µg/mL for the prepared compounds, 40 to 0.3125 µg/mL for gentamycin and 40 to 0.3125 µg/mL for amphotericin B positive control. The final concentration of DMSO was ≤1% and the preliminary test did not inhibit bacterial growth. The plates were incubated overnight at 37 °C for bacteria and 48 hours for fungal. After this time, 10 µL of 0.0015 mg/mL was added to the wells and further incubated at 37 °C for 30 min. The MIC was considered as the lowest concentration where no visible color change was observed after 30 min.

2.5. Antioxidant activities

All compounds were tested for *in vitro* antioxidant activities at 37 °C using both the free radical scavenging assay (DPPH) and the ferric ion reducing antioxidant power assay (FRAP). Ascorbic acid was used as the positive control and was treated in the same way as the DPPH assay. The assay was performed in triplicate.

2.5.1. DPPH free radical trapping assay

The DPPH free radicals method was applied according to the procedure described by Scherer *et al*. [24]. The principle of this method is based on the capacity of compounds in the extracts to supply protons to 2-diphenyl-1-picrylhydrazyl (DPPH) free radicals. DPPH radical is unstable and when it reacts with an antioxidant compound which can donate hydrogen ions, it is reduced and becomes stable. The reducing power of the extract is revealed when the purple-colored DPPH solution becomes colorless. A decrease in absorbance at 517 nm is proportional to the antioxidant potential of the extracts. DPPH was prepared in methanol at a concentration of 0.02%. For this, 20 mg of DPPH was completely dissolved in 100 mL of 100% methanol. The solution was conserved in a closed bottle away from light and any heat source before use. For all antioxidant tests, ascorbic acid was used as a positive control. For the preparation of the initial stock solution at a concentration 2 mg/mL; 2 mg of the acid was completely dissolved in 1 mL of distilled water. Initially, the samples were diluted to obtain final concentrations of 1000, 500, 250, 125, 62.5, 31.25, 15.625, and 7.8125 µg/mL in a 96-well microplate. Twenty-five microliters from each dilution were introduced into a new micro-plate and 75 µL of 0.02% DPPH was added to obtain final concentrations of 250,125, 62.5, 31.25, 15.625, 7.8125, 3.90625, and 1.95325 µg/mL. The reaction mixtures were kept in the dark at room temperature for 30 min, after which the absorbance was measured at 517 nm on a spectrophotometer. The positive control that was made of ascorbic acid was treated in the same way as the extracts, and the assays were performed in triplicate. The percentage (%) of radical scavenging activity of the compounds was calculated using Equation (1).

$$\%\ \text{RSA} = \frac{A0-AS}{A0}\times 100 \quad (1)$$

where RSA: Radical scavenging activity; A_o: Absorbance of the blank (DPPH + methanol); A_s: Absorbance of the DPPH radical + test compound.

2.5.2. Ferric ion reducing antioxidant power assay (FRAP)

The ferric ion reducing method was used according to the procedure described by Benzie *et al*. [25]. This method is based on the reduction of Fe^{3+} to Fe^{2+} by components of the extracts which in the presence of 1,10-phenanthroline forms a brown or orange-red colored complex. The complex absorbs at 505 nm and the intensity of the coloration is proportional to the amount of Fe^{3+} converted by the extract. The Fe^{3+} solution was prepared in an Eppendorf tube with 1.2 mg $FeCl_3$ dissolving in 1 mL of distilled water. The samples were dissolved and 25 µL from each dilution was introduced into a new microplate and 25 µL of 1.2 mg/mL Fe^{3+} solution was added. Plates were pre-incubated for 15 min at room temperature. After this time, 50 µL of 0.2% ortho-phenanthroline was added to obtain final extract concentrations of 250, 125, 62.5, 31.25, 15.625, 7.8125, 3.90625, and 1.95325 µg/mL. From the optical density of the products, the relative 50% reducing concentration of the samples was determined using ascorbic acid (positive control) as a 100% reduction.

3. Results and discussion

The ligand, 2-(phenyl(pyridin-2-yl)methylene)hydrazine-1-carbothioamide (HL), was prepared by the condensation reaction between 2-benzoylpyridine and thiosemicarbazide in hot ethanol under reflux as shown in Scheme 1. The corresponding Cu(II) and Zn(II) complexes were synthesized in 1:1 molar ratio of the Schiff base ligand and the metal(II) ions using $Cu(NO_3)_2{\cdot}5H_2O$ and $ZnCl_2$, while, the Ni(II) complex was synthesized in a 1:2 molar ratio of $Ni(NO_3)_2{\cdot}6H_2O$ and the Schiff base ligand, as confirmed by elemental analyses which also confirm the purity of the prepared compounds. All synthesized compounds were obtained in yields greater than 50% indicating that the method is quantitative [26]. The 2-benzoyl pyridine thiosemicarbazone ligand melted at 145-147 °C, while the complexes melted between 200-302 °C indicating that new compounds were formed. The molar conductivities of the complexes were determined in DMSO. The low molar conductivities of Cu(II) and Zn(II) complexes (3.9-9.9 $\Omega^{-1}.cm_2.mol^{-1}$), indicate that they are molecular while the high values of the

molar conductivities for Ni(II) complex (100 $\Omega^{-1}.cm^2.mol^{-1}$) indicate that it is a 1:2 electrolyte in solution [27].

3.1. Infrared spectroscopy

The important IR bands of 2-(phenyl(pyridin-2-yl) methylene)hydrazine-1-carbothioamide ligand and its metal complexes are presented in the Experimental section. On the spectrum of the ligand, the strong and broad band in the 3403-3223 cm^{-1} range is attributed to ν(N-H) of the NH_2 group and the band at 3127 cm^{-1} is attributed to *ν*(N-H) of the carbazid group (N-N*H*-N) [28]. The strong bands at 1592 and 1061 cm^{-1} in the spectrum of the ligand correspond to the presence of *ν*(C=N) of azomethine group [29] and (N-N) of the azide group. The strong band at 810 cm^{-1} is assigned to *ν*(C=S) in the thiosemicarbazone [30]. It is important to note that the ligand can exhibit thione-thiol tautomerism, since it contains a thioamide function (–N*H*-C=S) ⇋ (–N=C–S-*H*) (Scheme 1). Thus, the absence of the band for the S-H moiety in the ligand around 2570 cm^{-1} indicates the thione tautomer of the ligand. The presence of NH and NH_2 bands in the ligand spectrum indicates that in the solid state, the ligand retains the thione tautomer [31].

The IR spectrum of the ligand was compared to that of the metal complexes. The strong band at 1592 cm^{-1} attributed to the azomethine ν(C=N) group in the free ligand was shifted to 1620-1648 cm^{-1} in the spectra of metal complexes, indicating the coordination of the ligand through the nitrogen atom of the imine group [32]. The band at 1061 cm^{-1} assigned to the ν(N–N) group in the ligand, shifted to a higher frequency in the spectra of complexes indicating the coordination of the ligand to the metal through the nitrogen atom of azide group. Also, the band at 810 cm^{-1} corresponding to ν(C=S) vibration mode in the spectrum of the ligand is shifted up field to 840 cm^{-1} in the spectra of Ni(II) complex. The vibration bands for Cu(II) and Zn(II) complexes corresponding to ν(C-S) are observed at 739-775 cm^{-1}. The nitrogen atom of the pyridine ring is also involved in coordination around the metal(II) ion. These vibration modes suggest the involvement of the sulfur atom in coordination, thus confirming the tridentate nature of the 2-(phenyl(pyridin-2-yl)methylene)hydrazine-1-carbothioamide ligand in the complexes [29,33]. This is further supported by the appearance of new bands at 484-580 and 410-415 cm^{-1} in the far-infrared region, assigned to ν(M-N), and ν(M-S), respectively [15]. Furthermore, infrared spectra of Cu(II) complexes show a new absorption band around 1037-1235 cm^{-1}, initially absent in the ligand spectrum, that is assigned to the coordination of the nitrate group with the central metal ion [34,35].

3.2. NMR spectral analysis

A review of the literature revealed that NMR spectroscopy has proven to be useful in establishing the nature of many Schiff bases as well as their complexes in solution. The NMR spectra of Schiff bases were recorded in d_6-dimethylsulfoxide solution and the data is summarized in Experimental section. The ^1H resonances were assigned on the basis of chemical shifts, multiplicities, and, in some cases, by 2D NMR data. The ^1H NMR spectrum of the ligand presents a singlet at δ 12.60 ppm corresponding to the azide N-H proton and the singlet at δ 8.63 ppm is attributed to the thioamide S=C-NH_2 proton. These results are similar to the chemical shifts reported for imidazole-2-carbaldehyde *N*-(4)-substituted thiosemicarbazones, which exist in the *E* isomeric form [15]. On the other hand, the resonance lines of the protons in the multiplet, corresponding to the aromatic ring, were observed at δ 7.31-7.43 ppm. The doublet at δ 8.85 and 7.99 ppm is attributed to the H-C=N (H-1) and H-C=C-N (H-4) protons of the pyridine ring, respectively. This spectrum also shows a doublet at δ 7.64 ppm attributed to the proton at position C-2. The spectrum also reveals a triplet of the doublet corresponding to the H-3 proton at δ 7.58 ppm, in agreement with the chemical shifts of similar compounds derived from pyridine-2-carbaldehyde thiosemicarbazone [36]. NMR spectra of the ligand confirm the presence of the characteristic functional groups and the proposed molecular formulas.

The ^{13}C NMR spectrum of the ligand was recorded in DMSO-d_6 and the spectral signals are in good agreement with the proposed structure. The thiosemicarbazone showed two signals at δ 178.54 and 154.40 ppm assigned to thioamide (C=S) and azomethine carbon (C=N), respectively. Signals at δ 151.31 and 149.01 ppm are attributed to C-N and C=N carbon in the pyridine ring, respectively. The ^{13}C NMR spectrum showed the 13 carbon signals expected for the reported structure, with chemical shifts similar to those described in the literature [37].

Peak assignments were based on 2D NMR data using proton–proton correlated spectroscopy (^1H-^1H COSY), proton-carbon heteronuclear single quantum coherence (^1H-^{13}C HSQC) and proton–carbon heteronuclear multiple-bond correlation (^1H-^{13}C HMBC). The COSY correlation spectroscopy spectrum shows the correlation between the H-1, H-3 nucleus (δ 8.85/8.00 ppm) and H-2, H-4 (δ 8.85 and 7.34/7.60 ppm) of the pyridine ring. The same spectrum shows the correlation between protons H-9, H-11 (δ 7.43 ppm) and H-8, H-10 (δ 7.44 ppm). On this spectrum, we observed the correlation between H-11, H-12 of the aromatic group. Heteronuclear Single-Quantum Correlation Spectroscopy determines the correlations between heteronuclear carbon-proton, so it makes it possible to locate C-1 (δ 149.0 ppm), C-2 (δ 124.9 ppm), C-3 (δ 138.2 ppm), C-4 (δ 126.1 ppm) for the pyridine ring and C-8 (δ 129.44 ppm), C-9 (δ 128.58 ppm), C-10 (δ 129.3 ppm), C-11 (δ 128.9 ppm), respectively, for the aromatic ring. The heteronuclear multiple-bond correlation spectroscopy spectrum shows the correlation of the N-H proton with the quaternary carbon of the thioamide (C=S) function at δ 178.60 ppm, which allows the attribution of the latter to the C-13 carbon. The same spectrum also shows a correlation of proton H-12 with carbon C-7 at δ 136.7 ppm. Dimensional experiments (COSY, HSQC and HMBC) confirmed the proposed structure. The analysis of all IR and NMR data confirms the proposed structure of the Schiff base, as shown in Scheme 1.

3.3. Electronic spectra of the Schiff base and its corresponding metal complexes

The UV-Visible electronic data obtained in DMSO are given in Table 1. The spectrum of 2-benzoylpyridine thiosemicarbazone ligand showed one absorption band at 345 nm (28985 cm^{-1}), assigned to the π → π* transition [30]. The band at 345 nm in the spectrum of the Schiff base experienced a higher shift in the spectra of the Cu(II) complex and a lower shift in the spectra of the Ni(II) complex. The spectrum of the Cu(II) complex shows an absorption band at 679 nm (14727 cm^{-1}) attributed to $^2B_{1g} \rightarrow {}^2E_g$ transition of square planar geometry around Cu(II) [38] . The spectrum of the Ni(II) complex shows four absorption bands at 337, 364, 407 and 621 nm. The bands at 407 nm (24570 cm^{-1}) and 621 nm (16103 cm^{-1}) are assigned to Ligand-Metal (L-M) charge transfer in the complex and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ transition, respectively, characteristic of the octahedral geometry around the Ni(II) ion. The bands at 337 nm (29673 cm^{-1}) and 364 nm (27472 cm^{-1}) are attributed to the chromophore of the ligand in the complex. The Zn(II) complex shows a broad absorption band at 404 nm (24752 cm^{-1}) that can be assigned to L-M charge transfer [39] .

Analytical data suggest that the ligand is coordinated in all complexes via the nitrogen atom of the azomethine group (-HC=N-), the 2-benzoylpyridine nitrogen atom, and the sulfur atom of thiosemicarbazone. This confirms the tridentate behavior of the ligand in all complexes.

Table 1. Electronic spectral data of the ligand and its corresponding complexes.

Compounds	λ (nm) and ν (cm^{-1})	Assignments	Geometry
Ligand (HL)	345 (28985)	π → π*	-
$[Cu(L)(NO_3)]\cdot H_2O$	360 (27777)	n → π*	Square-planar
	679 (14727)	$^2B_{1g} \rightarrow {}^2E_g$	
$[Ni(HL)_2](NO_3)_2$	337 (29673)	π → π*	Octahedral
	364 (27472)	n → π*	
	407 (24570)	Charge transfer	
	621 (16103)	$^3A_{2g} \rightarrow {}^3T_{1g}$ (F)	
$[Zn(L)Cl]\cdot H_2O$	404 (24752)	Charge transfer	Tetrahedral

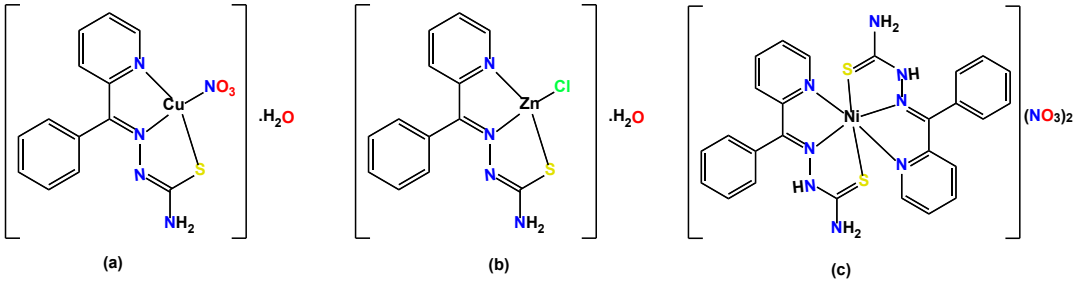

Figure 1. Proposal structure of (a) $[Cu(L)(NO_3)]\cdot H_2O$, (b) $[Zn(L)Cl]\cdot H_2O$, and (c) $[Ni(HL)_2](NO_3)_2$ complexes.

Microanalysis and spectral data indicate the presence of nitrate ion (NO_3^-) in the Cu(II) complex while the presence of chloride ion (Cl^-) is confirmed in the Zn(II) complex. Electronic spectral data suggest square planar geometry for the Cu(II) complex, octahedral geometry for the Ni(II) complex, and tetrahedral geometry for the Zn(II) complex. Molar conductance values indicate that Cu(II) and Zn(II) complexes are molecular while the Ni(II) complex is ionic as represented in Figure 1.

3.4. Biological activity of the compounds

3.4.1. Determination of the diameters of the zone of inhibition

Schiff base and metal complexes were tested against four bacterial strains: *Staphylococcus aureus* (ATCC 43300); *Methicillin resistant staphylococcus aureus* (ATCC 33591); *Klebsiella pneumoniae* (ATCC 700603); *Shigella flexneri* (NR 518)) and four fungi strains: *Candida albicans* (NR 29444), *Candida albicans* (NR 29445), *Candida albicans* (NR 29451), *Candida krusei*. Ciprofloxacin and fluconazole were used as standard. The diameters of the zone of inhibition of the ligand and its metal complexes were determined using the agar well diffusion method [22]. The results revealed that the synthesized compounds did not show visible growth. These results are similar to those obtained by Shubina *et al*. [40]. Low activity of some of the metal complexes, as shown in this study, may be related to their low lipophilicity, which reduces the penetration of the compounds through the lipid membrane and therefore these complexes cannot inhibit the growth of microorganisms [41].

3.4.2. Minimum inhibitory concentration

The minimal inhibitory concentrations of the compounds were determined using microdilution in a liquid environment in 100-well microliter plates. The microbial culture was placed in the presence of the compounds in decreasing order of concentration, in the wells of the microplates. After incubation, the lowest concentration of the antimicrobials in which there was no visible growth of the microorganism represents their minimum inhibitory concentration. In Table 2, 125 µg/mL is the minimal value of the antibacterial and antifungal concentrations in which there is no visible growth of the microorganism. The activities of compounds are considered significant when MIC of antibacterial and antifungal <10 µg/mL, moderate when 10 ≤ MIC ≤ 125 µg/mL, and weak when MIC > 125 µg/mL.

3.4.2.1. Antibacterial activity

The antibacterial activities of the compounds were tested on four bacterial strains (*Staphylococcus aureus* (ATCC 43300)), *Methicillin resistant staphylococcus aureus* (ATCC 33591), *Klebsiella pneumoniae* (ATCC 700603), *Shigella flexneri* (NR 518)) using gentamicin as standard. The MIC values of the Schiff base and its complexes were determined using the broth micro-dilution method and all the results are summarized in Table 2. The ligand, Ni(II) and Zn(II) complexes exhibited weak antimicrobial activity on bacteria strains. It is important to note the moderate activity of Zn(II) complex on *Methicillin resistant Staphylococcus aureus* (ATCC 33591) when compared to the standard. The Cu(II) complex showed moderate activities on *Staphylococcus aureus* (ATCC 43300) and *Klebsiella pneumoniae* (ATCC 700603) and very strong activity (higher than the reference antibiotic) on *Methicillin resistant Staphylococcus aureus* (ATCC 33591). The significant activity of Cu(II) complex compared to that of the ligand can be explained on the basis of the chelation [42], where chelation reduces the polarity of the metal atom mainly because of partial sharing of its positive charge with donor groups and possible delocalized π-electron within the whole chelate ring, resulting in interference with the normal cell process. In addition, such a chelation could enhance the lipophilic character of the central metal atom, which subsequently favors its permeation through the lipid layer of the cell membrane. The results showed that the copper complex showed higher antimicrobial activity [43].

3.4.2.2. Antifungal activity

The antifungal activities of the compounds were tested on four fungal strains (*Candida albicans* (NR 29451), *Candida albicans* (NR 29444), *Candida albicans* (NR 29445) and *Candida krusei* (HM 1122)) using amphotericin B as a standard. The MIC values of the Schiff base and their complexes were determined using the broth micro-dilution method and all results are shown in Table 2. The results reveal that Ni(II) and Cu(II) complexes exhibited less antimicrobial activities than the Schiff base on all fungal strains. It is important to note that only the Zn(II) complex exhibited high activities on *Candida albicans* (NR

Table 2. Minimum inhibition concentration (MIC, µg/mL) of the Schiff base ligand and its complexes.

Compounds	*S. aureus* ATCC 43300	*K. pneumoniae* ATCC 700603	*S. aureus* ATCC 33591	*S. flexneri* NR 518	*C. albicans* NR 29451	*C. albicans* NR 294444	*C. albicans* NR 29445	*C. krusei* HM 1122
HL	125	>125	>125	125	62.5	31.25	15.625	62.5
$[Cu(L)(NO_3)]\cdot H_2O$	31.125	31.25	3.9	125	>125	>125	>125	>125
$[Ni(HL)_2](NO_3)_2$	>125	>125	>125	>125	>125	>125	>125	>125
$[Zn(L)Cl]\cdot H_2O$	>125	125	62.25	>125	62.5	125	31.125	>125
Gentamicin	4	2	8	4	-	-	-	-
Amphotericin B	-	-	-	-	2.5	0.625	0.625	2.5

Table 3. IC_{50} values of Schiff base and its complexes against DPPH radicals.

Compounds	DPPH radical scavenging activity, IC_{50}±SD (µg/mL)
HL	8.72±0.72
$[Ni(HL)_2](NO_3)_2$	1.52±0.02
$[Zn(L)Cl]\cdot H_2O$	5.74±0.15
$[Cu(L)(NO_3)]\cdot H_2O$	-
Vitamin C	0.47±0.01

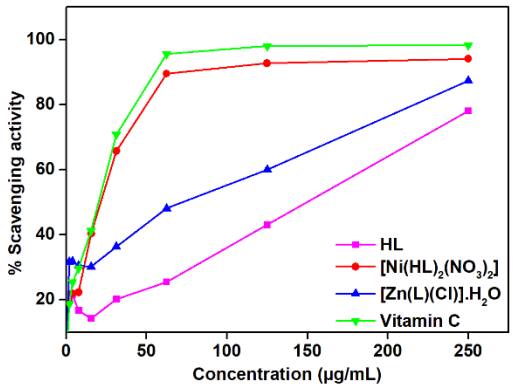

Figure 2. DPPH· radical scavenging activity of the ligand and its metal complexes.

29451) and *Candida albicans* (NR 29445) compared to the other complexes. The significant activity of the ligand and Zn(II) complex may be attributed to the mode of action of the compound; this may involve the formation of a hydrogen bond through the azomethine group with the active center of cell constituents [43]. The activities of compounds are considered significant when MIC values of antifungal < 10 µg/mL, moderate when 10 ≤ MIC ≤ 125 µg/Ml and weak when MIC > 125 µg/ML.

3.4.3. Antioxidant activity of the compounds

Schiff base and its metal complexes were screened for free radical scavenging activity by both the DPPH and FRAP method using ascorbic acid (vitamin C) as a standard. The antioxidant activities of these compounds were studied by measuring the radical scavenging effect against DPPH radicals. The results of the free radical scavenging activity of the compounds at different concentrations are presented in Figure 2. The ligand exhibited moderate scavenging activity. The Ni(II) complex showed good scavenging activity compared to that of the ligand. This observation could be due to free electron mobility in the complexes and deprotonation of ligand during chelation [44]. The Zn(II) complex exhibited moderate scavenging activity. Cu(II) complex showed no scavenging activity.

The antioxidant activities of these compounds were also investigated by determining the concentration of substance necessary to reduce 50% of the DPPH· radical (IC_{50} values) of each compound. The results of the determination of the IC_{50} values of the compounds are shown in Table 3. The increased antioxidant activity of this complex can be attributed to the electron-withdrawing effect of the Ni(II) ion, which facilitates the release of hydrogen to reduce the DPPH radical [45]. This release of proton is very pronounced in the Ni(II) complex, with an IC_{50} value of 1.52 µg/mL obtained. Schiff base (8.72 µg/mL) and Zn(II) (5.74 µg/mL) complex showed moderate scavenging activity. This can be due to free electron mobility in the complexes. While Cu(II) complex exhibited no scavenging effect on DPPH free radical. Therefore, the DPPH radical scavenging ability of the test samples can be ranked in the order Vitamin C > Ni(II) complex > Zn(II) complex > Schiff base. It is evident from these results that the Ni(II) complex had the best antioxidant potential compared to the other compounds. Therefore, the IC_{50} values for scavenging free radicals confirm the above statement that the Ni(II) complex is more potent than the ligand and the Zn(II) complex. The enhanced inhibition displayed on the DPPH radical by the test samples shows that the Ni(II) complex is capable of donating electrons to reduce free radicals and, thus, could be promising therapeutic agents for the treatment of pathological diseases and conditions caused as a result of excessive radicals or stress.

The reducing powers of the Schiff base and its metal complexes are associated with their antiradical power. The reducing ability of the synthesized compounds was determined using the FRAP method. This technique determines the ability of the tested compounds to reduce the ferric iron (Fe^{3+}) present in the $K_3[Fe(CN)_6]$ complex to ferrous iron (Fe^{2+}). Only the Ni(II) complex, presented in Table 4, showed the reduction capacity of ferrous iron. It is clear from this result that the reducing capacity of the compounds depends on the concentration. From the result, we find that the reduction of iron by the FRAP method is more pronounced in the $[Ni(HL)_2](NO_3)_2$ complex thus $[Ni(HL)_2](NO_3)_2$ has the capacity to reduce the ferric ion, and therefore $[Ni(HL)_2](NO_3)_2$ has the best anti-free radical scavenging activity compared to all other studies of complexes. It is evident that only $[Ni(HL)_2](NO_3)_2$ complex show the capacity to reduce Fe^{3+} to Fe^{2+}. While Schiff base, Cu(II) and Zn(II) complexes are not able to reduce ferric ions [46]. From all of the above results, it is confirmed that the Ni(II) complex has the best antiradical activity when compared to all the other synthesized compounds.

Table 4. EC_{50} data of Schiff base and complexes.

Compounds	FRAP ion reducing antioxidant, EC_{50} (µg/mL) ± SD
HL	-
$[Ni(HL)_2](NO_3)_2$	17.44±1.69
$[Zn(L)Cl]\cdot H_2O$	-
$[Cu(L)(NO_3)]\cdot H_2O$	-
Vitamin C	12.99±0.73

4. Conclusions

In the present study, we have synthesized and characterized one Schiff base ligand (HL) and used it to synthesize Ni(II), Cu(II), and Zn(II) complexes. The Schiff base ligand coordinates to Cu(II) and Zn(II) ions in a tridentate mode forming square planar and tetrahedral environments around Cu(II) and Zn(II) ions, respectively, and forms an octahedral complex with Ni(II) in which the Schiff base coordinate in a tridentate mode. Antibacterial studies revealed that $[Cu(L)(NO_3)]\cdot H_2O$ complex showed good activity against *Methicillin* resistant *Staphylococcus aureus* (ATCC 33591) strains when compared to the standard. These studies revealed that the synthesized compounds showed moderate antifungal activity. Antioxidant tests revealed that the Ni(II) complex is more potent to prevent the formation of free radicals than the Cu(II) and Zn(II) complexes.

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Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

CRediT authorship contribution statement

Conceptualization: Awawou Gbambie Paboudam, Line Edwige Tsakeng Ngoudjou; Methodology: Line Edwige Tsakeng Ngoudjou, Maurice Kuate, Giscard Doungmo; Formal Analysis: Giscard Doungmo; Investigation: Line Edwige Tsakeng Ngoudjou; Resources: Peter Teke Ndifon; Data Curation: Line Edwige Tsakeng Ngoudjou, Maurice Kuate; Writing - Original Draft: Line Edwige Tsakeng Ngoudjou, Adrien Pamen Yepseu, Maurice Kuate; Writing - Review and Editing: Maurice Kuate, Adrien Pamen Yepseu, Awawou Gbambie Paboudam; Funding acquisition: Peter Teke Ndifon; Supervision: Peter Teke Ndifon; Project Administration: Peter Teke Ndifon.

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