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## FULL PAPER



## New heterocyclic Schiff base-metal complex: Synthesis, characterization, density functional theory study, and antimicrobial evaluation

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A new series of heterocyclic Schiff base complexes derived from the condensation of nicotinohydrazide with different heterocyclic aldehyde, followed by metalation with Co (II) and Cu (II) metal ions. The chemical structures of the synthesized compounds have been characterized by elemental analysis, Fourier transform infrared spectroscopy, proton nuclear magnetic resonance, ultraviolet-visible spectroscopy, and magnetic susceptibility. The spectral and magnetic data confirmed their chemical structures, furthermore, the geometry of Cu (II) and Co (II) complexes were square-planar or distorted tetrahedral. X-ray diffraction measurements supported the crystalline structures of the metal complexes rather than the amorphous form of the parent Schiff bases. Thermogravimetric analysis revealed the upgrading of the thermal stability of metal complexes compared to their Schiff base ligands. Antimicrobial efficacies of the Schiff base ligands and their corresponded metal complexes were screened against Staphylococcus aureus and Bacillus subtilis as Gram-positive bacteria, Escherichia coli, and Proteus vulgaris as Gram-negative bacteria, and fungi Aspergillus flavus, Candida albicans. The antimicrobial inhibitory data revealed higher antimicrobial activities of metal complexes compared to their Schiff base ligands. Density functional theory module by Gaussian 09 W software proved the chemical reactivity of the prepared Schiff base ligands based on the total energy, energy gap, E<sub>HOMO</sub>, and E<sub>LUMO</sub> energies.

#### K E Y W O R D S

biological studies, DFT calculations, nicotinic acid, Schiff base, transition metal (II) complexes

## **1** | INTRODUCTION

In the past decades, the problem of multi-drug resistant microorganisms has reached an alarming level around the world. Therefore, the synthesis of new compounds that are used for the effective treatment of microbial infections without side effects is a biomedical problem. Nicotinic acid derivatives are naturally occurring compounds. Low amount of nicotinic acid present in all living cells, liver, yeast, and corn. Many nicotinic acid derivatives have great importance in organic synthesis for their anti-bacterial and anti-mycotic activities.<sup>[1-3]</sup> On the other hand, Schiff

base compounds attract considerable research due to their pharmacological activity and the tendency toward the formation of complexes with almost all the transition metals.<sup>[4,5]</sup> These metal complexes of Schiff bases possess high inspect in medicinal chemistry, such as antiviral, anticancer, antibacterial, antifungal, antioxidant anticonvulsant, and anti-inflammatory activities.<sup>[6,7]</sup> It was reported that Schiff base compounds formed from amine of carbohydrazide with heterocyclic aldehyde are more stable and have high abilities to coordinate with the transition metal ions.<sup>[8]</sup> The chelating ligands containing O and N donor atoms show broad biological activity and have a special interest in bonding to metal ions.<sup>[1,9]</sup> These compounds have unique properties such as photochromic properties, the ability to reversibly bind oxygen, and complexing activity toward toxic metals.<sup>[10,11]</sup> It was investigated that the Co (II), Cu (II), and Zn (II)metal complexes have a potential biological application such as antibacterial, antifungal, anti-inflammatory, total antioxidant, antidiabetic, and DNA binding studies.<sup>[12]</sup> Based on this view, the presented work aims to use nicotinic acid hydrazide for the synthesis of new Schiff base with different heterocycle aldehydes, followed by complexion with Co (II) and Cu (II) as transition metal ions using a new simple procedure. The chemical structure of the produced complexes was elucidated with different techniques and studying their biological activities.

## 2 | EXPERIMENTAL

## 2.1 | Materials and techniques

All chemicals were analytical grade and were purchased from Sigma-Aldrich. They were used as received from the sources without further purification. All melting points are uncorrected and measured on a Gallen Kamp electric melting point apparatus. The elemental analysis was conducted using a Varia Elementary device. The IR spectra recorded using potassium bromide disks on an Fourier transform infrared spectroscopy (FTIR) Thermo Electron Nicolet 7600 (USA) IR-spectrophotometer at the Central Laboratory of Faculty of Science, Ain Shams University. <sup>1</sup>H-NMR spectra run at 300 MHz on a GEMINI 300 BB NMR spectrometer using tetramethyl silane as an internal standard in deuterated dimethyl sulfoxide (DMSO-d6) at Faculty of Pharmacy, Ain Shams University. Electronic spectral changes in electron distribution between ligand-metal in complexes were recorded in the wavelength range of 200-700 using UV-Visible at the Egyptian Petroleum Research Institute. TLC was performed on Merck Kissel gel 60 F254 aluminum backed plates. Powder X-ray diffraction was recorded by Malvern

Panalytical-X-ray diffractometer (XRD)-X'Pert Powder with Cu-K $\alpha$  radiation with wavelength (1.541 Å). The monochromator was adjusted at a voltage (40 kV) and an intensity of 40 mA. Electron spin resonance spectra were also recorded on JES-FE2XG ESR spectrophotometer at room temperature at a microwave frequency 9.1 GHZ and field set 3000 G. Thermogravimetric analysis (TGA) was conducted by SDT Q600 V20.5 Build 15 under a flow of dry nitrogen with 10°C min<sup>-1</sup> of heating rates.

# 2.2 | Synthesis of nicotinic acid hydrazide

The synthesis procedure was performed according to the reported in the literature.<sup>[9]</sup> where a mixture of nicotinic acid (0.03 mol) and phosphorous pentachloride (0.05 mol) in anhydrous carbon tetrachloride (20 ml) was refluxed at 100°C for 2 hr, then the solvent was distilled off to obtained acid chloride as a solid product. The hydrazine hydrate (0.1 mol) was added dropwise at 0°C to the produced solid of acid chloride (0.03 mol) and the resultant mixture was stirred for 5 hr at room temperature. The produced solid was washed with aqueous sodium bicarbonate (10%), dried in a vacuum, and recrystallized using ethanol.

## 2.3 | Synthesis of Schiff bases

A mixture of nicotinohydrazide (0.01 mol) and aromatic heterocyclic aldehyde naming 1H-pyrrole-2-carbaldehyde, 1H-indole-3-carbaldehyde, or 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (0.01 mol) in absolute ethyl alcohol (20 ml) with few drops of glacial acetic acid was heated under reflux for 1 hr. The solid product formed while cooling to room temperature was filtered off and recrystallized from ethanol to give the Schiff bases (**L1–L3**), respectively (Scheme 1).

## 2.3.1 | N'-([1H-pyrrol-2-yl]methylene) nicotinohydrazide (L1)

(Yield 88%); brown crystals; m.p. 204–206°C; UV–Visible (DMSO, nm): 320, 340; IR (KBr) ( $\nu$ , cm<sup>-1</sup>): 3226, 3137 (NH), 3051, (CHarom), 1638 (CO), 1605 (C=N), 1559 (C=C); <sup>1</sup>HNMR (DMSO-d6)  $\delta$ : 6.15–6.93 (m, 3H, CH-pyrrole), 7.53–8.28 (m, 3H, CH-nicotine), 8.75 (s, 1H, CH=NNH), 9.05 (s, 1H, Nicotine [N=CH-CCO]), 11.58 (br.s, 1H, CONHN, exchangeable), 11.71 (br.s, 1H, NH-pyrrole); Anal. Calcd. For C11H10N4O (%): C, 61.67; H, 4.71; N, 26.15; Found (%): C, 61.91; H, 4.84; N, 27.21.

## **SCHEME 1** Synthesis of Schiff base ligands



## $2.3.2 \mid N'-([1H-indol-3-yl]methylene)$ nicotinohydrazide (L2)

(Yield 89%); yellow crystals; m.p.  $210-212^{\circ}$ C; UV–Visible (DMSO, nm): 325,345; IR (KBr) (v, cm<sup>-1</sup>): 3178 (NH), 3047, (CHarom), 1657 (CO), 1600 (C=N), 1575 (C=C); <sup>1</sup>HNMR (DMSO-d6) & 7.13-8.76 (m, 7H, Ar-H + [nicotine ring]), 7.87 (s, 1H, indole-H), 8.63 (s,1H, CH=NNH), 9.09 (s, 1H, Nicotine [N=CH-CCO]), 11.56 (br.s, 1H, CONHN, exchangeable), 11.64 (br.s, 1H, NH-indole); Anal. Calcd. For  $C_{15}H_{12}N_4O$  (%): C, 68.17; H, 4.58; N, 21.20; Found (%): C, C, 68.35; H, 4.19; N, 21.51.

# 2.3.3 | N'-([1,3-diphenyl-1H-pyrazol-4-yl] methylene)nicotinohydrazide (L3)

(Yield 96%); white crystals; m.p. 220–222°C; UV–Visible (DMSO, nm): 330, 350; IR (KBr) ( $\upsilon$ , cm<sup>-1</sup>): 3216 (NH), 3058, (CHarom), 1671 (CO), 1613 (C=N), 1598 (C=C); <sup>1</sup>HNMR (DMSO-d6) & 7.37–8.27 (m, 13H, Ar-H + [nicotine ring]), 8.57 ((s,1H, CH=NNH), 8.76 (s, 1H, CH-Pyrazole), 9.07 (s, 1H, Nicotine [N=CH-CCO]), 11.90 (br. s, 1H, NH, exchangeable); Anal. Calcd. For C<sub>22</sub>H<sub>17</sub>N<sub>5</sub>O (%): C, 71.92; H, 4.66; N, 19.06; Found (%): C, 71.63; H, 4.81; N, 19.23.

## 2.4 | Synthesis of metal complexes

The metal complexes have been prepared by addition of the ethanolic solution of Copper (II) acetate or cobalt (II) nitrate (0.01 mol) dropwise to the stirring ethanolic solution of the Schiff bases (**L1–L3**) (0.02 mol) at room

temperature. The resulting mixture was then refluxed at 70°C for 1 hr on a water bath. A colored product appeared on standing and cooling the above solution. The complexes were filtered, washed with ether, and dried under reduced pressure over anhydrous  $CaCl_2$  in a desiccator. All formed metal complexes are colored solids crystals, with high melting points >300°C.

## 2.4.1 | $[Co(L1)_2(NO_3)_2]$

Yield (88%); reddish brown solid, Anal. Calcd. for  $C_{22}H_{20}CoN_{10}O_8$  (%): C, 43.22; H, 3.30; Co, 9.64; N, 22.91. Found (%): C, 43.32; H, 3.52; Co, 9.93; N, 23.12.; IR (KBr) (v, cm<sup>-1</sup>): 1614 (C=O), 1537 (C=N), 1357, 1014 (NO<sub>3</sub><sup>-</sup>), 570 (Co-O), 490 (Co-N), UV-Visible (DMSO, nm): 250 ( $\pi$ - $\pi$ \*), 380 (n- $\pi$ \*).

## 2.4.2 | $[Co(L2)_2(NO_3)_2]$

Yield (95%); reddish brown solid, Anal. Calcd. for  $C_{30}H_{24}CoN_{10}O_8$  (%): C, 50.64; H, 3.40; Co, 8.28; N, 19.69.; Found (%): C, 50.43; H, 3.67; Co, 8.78; N, 19.79; IR (KBr) (v, cm<sup>-1</sup>): 1590 (C=O), 1540 (C=N), 1332, 1025 (NO<sub>3</sub><sup>-1</sup>), 540 (Co-O), 481 (Co-N), UV-Visible (DMSO, nm): 240 ( $\pi$ - $\pi$ \*), 385 (n- $\pi$ \*).

## 2.4.3 | $[Co(L3)_2(NO_3)_2]$

Yield (89%); reddish brown solid, Anal. Calcd. for  $C_{44}H_{34}CoN_{12}O_8$  (%):C, 57.58; H, 3.73; Co, 6.42; N, 18.31Found (%):C, 57.93; H, 3.84; Co, 7.12; N, 18.62.; IR

(KBr) (v, cm<sup>-1</sup>): 1596 (C=O), 1550 (C=N), 1346, 1012 (NO<sub>3</sub><sup>-</sup>), 525 (Co-O), 472 (Co-N), UV–Visible (DMSO, nm): 230 ( $\pi$ - $\pi$ \*), 360 (n- $\pi$ \*).

## 2.4.4 | $[Cu(L1)_2(OCOCH_3)_2]$

Yield (93%); brownish green solid, Anal. Calcd. for  $C_{26}H_{26}CuN_8O_6$  (%): C, 51.19; H, 4.30; Cu, 10.42; N, 18.37; Found (%): C, 51.37; H, 4.62; Cu, 10.98; N, 18.64; IR (KBr) (v, cm<sup>-1</sup>): 1600 (C=O), 1519 (C=N), 1442, 1210 (<sup>-</sup>OAc), 531 (Cu-O), 463 (Cu-N), UV-Visible (DMSO, nm): 290 ( $\pi$ - $\pi$ \*),370 (n- $\pi$ \*).

## 2.4.5 | $[Cu(L2)_2(OCOCH_3)_2]$

Yield (85%); green solid, Anal. Calcd. for C34H30CuN8O6 (%): C, 57.50; H, 4.26; Cu, 8.95; N, 15.78; Found (%): C, 57.87; H, 4.41; Cu, 9.13; N, 15.65; IR (KBr) (v, cm<sup>-1</sup>): 1605 (C=O), 1580 (C=N), 1456, 1225 (<sup>-</sup>OAc), 520 (Cu-O), 492 (Cu-N), UV–Visible (DMSO, nm): 260 ( $\pi$ - $\pi$ \*), 385 (n- $\pi$ \*).

## 2.4.6 | $[Cu(L3)_2(OCOCH_3)_2]$

Yield (91%); green solid, Anal. Calcd. for  $C_{48}H_{40}CuN_{10}O_6$ (%): C, 62.91; H, 4.40; Cu, 6.93; N, 15.28; Found (%): C, 63.21; H, 4.65; Cu, 7.32; N, 15.41; IR (KBr) (v, cm<sup>-1</sup>): 1610 (C=O), 1520 (C=N), 1481, 1231 (<sup>-</sup>OAc), 518 (Cu-O), 475 (Cu-N), UV-Visible (DMSO, nm): 290 ( $\pi$ - $\pi$ \*), 370 (n- $\pi$ \*).

#### 2.5 | Antimicrobial studies

Invitro antimicrobial activities of the synthesized ligands (Schiff Bases) and related metal complex were screened against Gram-positive bacteria (Staphylococcus aureus RCMB010010), (Bacillus subtilis RCMB 015 [1]), Gram-negative bacteria (Escherichia coli RCMB 010052), (Proteus vulgaris RCMB 004 [1]) and fungi (Aspergillus flavus RCMB 002002), (Candida albicans RCMB 005003 [1]) by disc diffusion method in DMSO as a solvent.<sup>[13]</sup> Gentamycin and Ketoconazole were used as standard antibacterial and antifungal, respectively. The resulting inhibition zone for each compound was measured in mm for the growth of bacterial or fungal around the discs were measured and summarized in Table 3. The mean value obtained for three individual replicates was used to calculate the average value of inhibition zone of each sample.

#### 2.6 | Density functional theory studies

Chemical reactivity and other properties of the prepared compounds were identified by density functional theory (DFT) using Becke three-parameter hybrid exchange and Lee–Yang–Parr correlation functional (B3LYP/3-21G) for ligand and B3LYP/LANL2DZ for metal complexes using GAUSSIAN09 program<sup>[14,15]</sup>. The Gaussian files obtained through this method were visualized using Gauss-View 05 molecular visualization program.

### 3 | RESULTS AND DISCUSSION

#### 3.1 | Chemistry

The condensation reaction of nicotinocarbohydrazide with different heterocyclic aldehyde naming *1H*-pyrrole-2-carbaldehyde, *1H*-indole-3-carbaldehyde, or 1,3-diphenyl-*1H*-pyrazole-4-carbaldehyde affording Schiff base compounds (L1–L3) (cf. Scheme 1). The suggested structures of the synthesized compounds are elucidated from Their spectral data. The IR spectrum showed



SCHEME 2 Synthesis of the Schiff base metal complexes



FIGURE 1 Fourier transform infrared spectroscopy (FTIR) spectra of ligands and their Co and Cu complexes



FIGURE 2 UV-visible spectra of ligands and their Co and Cu complexes in  $10^{-3}$  M DMF solution

absorptions characteristic for NH, CN, and C=O groups. The <sup>1</sup>H-NMR spectrum exhibited multiplet signals in the range  $\delta$ 7–9 ppm for aromatic protons as well as broad singlet signal in the downfield region attributable to NH

proton. Further evidence was gained from their elemental analysis was in good agreement with the calculated values (cf. experimental). The prepared Schiff bases (L1-L3) are used as a reactive chelating agent to form new metal complexes with Co (II) and Cu (II) (Scheme 2). The chemical structure of the obtained complexes was elucidated with different techniques including elemental analysis, FTIR, UV–Vis, XRD, TGA, and magnetic susceptibility.

#### 3.2 | Structure analysis

## 3.2.1 | Fourier transform infrared spectroscopy spectral studies

WILEY Organometallic Chamietry

6 of 14

The FTIR spectra of the ligand and its copper and cobalt complexes are represented in Figure 1. The IR spectra of the metal complexes were compared with those of the free ligand to determine the involvement of coordination sites in the complexes. Characteristic peaks in the spectra of the ligand and complexes were considered and compared. The absorption band in the spectra of the ligands L1–L3 at 1638–1671 cm<sup>-1</sup> has been assigned to v(C=O).<sup>[16]</sup> This band was shifted to a lower wavelength



**FIGURE 3** Powder X-ray diffraction analysis of the prepared Schiff bases (L1) and their Cu (II) and Co (II) complexes; 4,6,8 = Co (II) complexes of L1-L3, respectively; 5,7,9 = Cu (II) complexes of L1-L3, respectively

on the complexes, indicating the involvement of the carbonyl group in the bonding to metal. The absorption band correlated to the imine group, v(C=N) appeared at 1600–1613  $\text{cm}^{-1}$  for the free ligand (L1–L3) and shifted lower to 1519, and 1580 cm<sup>-1</sup> for the Co and Cu metal complexes. This agreed with the involvement of the nitrogen atom of the v(C=N) in the bonding with the metal (II) ions. The stretching vibrations of nitrate  $(NO_3^{-})$ , and acetate (CH<sub>3</sub>COO<sup>-</sup>) ions for Co and Cu complexes were observed at 1332–1357 and 1441–1482  $\text{cm}^{-1}$ , respectively. This indicates that nitrate and acetate ions were involved in the inner sphere coordination of the metal complex. FT-IR spectra showed an absorption band for v N-H stretching at 3178–3226 cm<sup>-1</sup> region for the ligands (L1– L3). The stretching v (NH) of the ligand is not shifted in the spectra of the metal complexes indicate the nonparticipation of the nitrogen atom of v (NH) in the chelation.<sup>[17]</sup> Hence, it is concluded that Schiff base ligands (L1-L3) act as a neutral bidentate ligand. Furthermore, IR spectra of the metal complex showed two new stretching bands in the lower wavelength region ranging 518-570 and 463-492 which correlated to the M (II)-O and M (II)-N cm<sup>-1</sup>, respectively.<sup>[18-20]</sup>

## 3.2.2 | Electronic spectral and magnetic susceptibility studies

The electronic absorption spectra of all ligands and related copper and cobalt complexes were recorded in  $10^{-3}$  M DMF solution at room temperature over the wavelength range of 200 to 800 nm (Figure 2). Ligands (L1–L3) exhibit two intense absorption bands at short wavelengths, the first absorption bands at (320–330) due to  $\pi \to \pi^*$  transition of the aromatic ring and the second shoulder absorption bands appear at (340–350 nm) which are assigned to  $n \to \pi^*$  transition.<sup>[21]</sup> Copper and Cobalt complexes exhibited two bands at a shifted wavelength within (230–290) and (360–385) attributable to ( $\pi \to \pi^*$  transition) and ( $n \to \pi^*$  transition), respectively, confirming coordination of the oxygen and nitrogen atoms of ligands (L1–L3) to the metal centers.<sup>[4]</sup> Cu (II) and Co



**FIGURE 4** Thermogravimetric analysis of: (a) L1 (representative for L1-L3); (b) metal complexes 4–9

(II) complexes show an absorption band at 650 nm and 640 nm, respectively, which were attributed to  ${}^{2}B_{1g} \rightarrow {}^{2}A_{1g}$  transition. That was compatible with the square-planner or distorted octahedral structures.<sup>[22]</sup> The magnetic moments of the complexes were measured for the coordination mechanism. As expected, the prepared Schiff bases based-on azomethine group is a strong ligand with multi-dentate that they squeezed to d-orbital electrons of the metal ions. The magnetic moment of Cu (II) complexes was found in the range of 1.7-1.8 B. M which corresponds to a single unpaired electron in the final *d*-orbital contribution, which confirms the squareplanar geometry of the Cu (II) complexes. While the Co (II) complexes reported herein are high spin at room temperature with the magnetic moment in the range of 4.1-4.3 B. M, which indicates that the complexes of Co (II) have a six-coordinate with a square planner or octahedral geometrical structure.<sup>[23]</sup>

#### 3.2.3 | X-ray diffractometer spectroscopy

During powder X-ray diffraction analysis (Figure 3), the synthesized Schiff base ligands L1-L3 showed two types of peaks, two peaks at 2theta = 3°, and 17°; while a broad peak was appeared for the three Schiff bases L1–L3 in the entire range of 2 theta. That indicates the Schiff bases are amorphous in nature with a minor crystallinity (Figure 3 SC, representative profile for the prepared Schiff bases L1-L3). On the other hand, the metal complexes showed high crystallinity compared to the diffractogram of the parent ligands due to the appearance of several peaks. Cobalt complexes of L1-L3 showed characteristic XRD peaks at:  $2\theta = 7$ , 9, 11, 12, 15, 17, 20, and  $22^{\circ}$ . While copper complexes of L1-L3 represented several XRD peaks at:  $2\theta = 12.5$ , 15, 16, 18, 24, 26, and  $28^{\circ}$ .<sup>[24,25]</sup>

#### 3.2.4 | Thermogravimetric analysis

TGA study was carried out up to 800 °C for the prepared compounds (Figure 4). The TGA thermograms of the prepared ligands (L1–L3) and their metal complexes (4–9) showed gradual weight loss, indicating decomposition by fragmentation with increase in temperature. For all the ligands, there was a gradual increase in the weight loss in the temperature range of 80–275°C reached about 85%. Then a sudden decrease in the weight loss reached to complete decay of the compounds was observed in the temperature range of 275–400°C. That indicate the prepared ligands have moderate thermal stability up to 270°C. For all the complexes, similar stages were observed, including a small weight loss in the range of

180°C, assignable to the loss of water of crystallization. Then, gradual increase in the weight loss of the complexes reached to the semi-decay. The metal complexes showed higher thermal stability than the parent ligands.

#### 3.2.5 | Electron spin resonance

Electron spin resonance is one of the most powerful techniques for studying the electronic structure of many species including organic free radical, biradical, and most transition metals. The ESR spectra of copper (II) complexes provide information of important in studying the metal ion environment. The X-band ESR spectrum of three cupper complexes [Cu(L1)2(OCOCH3)2], [Cu(L2)2(OCOCH3)2], and [Cu(L3)2(OCOCH3)2] were recorded in the polycrystalline form at room temperature at a microwave frequency 9.1 GHZ and field set 3000 G. The spectrum has been studied and depicted in Figure 5. All these cupper complexes are similar and display a resolved axial dx2-y2 ground state spectrum consistent with tetragonally elongated octahedral or square planar configuration around copper (II).<sup>[24]</sup> In addition to the hyperfine structure of copper (II) complexes in the gll region. The (g) values and the nuclear hyper line coupling constant (A) have been calculated from the center of the each of the hyperfine lines and the spacing between the two consecutive lines, respectively, of the spectrum.<sup>[24]</sup> The values of gll and  $g \perp$  were calculated by using the formula

$$g = \frac{71.4484 \times v(in GHz)}{B(in mT)}$$

where g is proportionality factor, v is frequency of the Xband (in GHz) and B is magnetic field (in mT). The



**FIGURE 5** ESR spectrum of Cu (II) complexes of Schiff base ligands

8 of 14 WILEY Organometallic

various Spin-Hamiltonian parameters for the copper (II) complexes were calculated and recorded in Table 1.

According to calculation data, all the g-tensor value follows the rule:  $gll > g \perp > g$  where g was (A free electron in vacuum has a g value = 2.00232). This trend observed in these complexes suggests that the unpaired electron lies predominantly in the dx2-y2 and implying 2B1g orbital of the copper (II) ion and that the spectral features are characteristic of axial symmetry.<sup>[25]</sup> Kivelson

**TABLE 1** Powder ESR parameters for copper (II) complexes at room temperature

Compound	$\mathbf{g}\parallel$	g⊥	g <sub>iso</sub>	G
[Cu(L1)2(OCOCH3)2]	2.249	2.019	2.1540	1.113
[Cu(L2)2(OCOCH3)2]	2.0341	2.0681	2.1245	3.751
[Cu(L3)2(OCOCH3)2]	2.2261	2.0360	2.1001	3.600

and Neiman suggested that when g-value for copper (II) complexes is greater than 2 indicating to present of Cu-O and Cu-N bonds in the molecules. The  $g_{iso}$  value has been calculated by using

$$g_{iso} = \frac{(gll + 2g \perp)}{3}$$

The  $g_{iso}$  in the range of 2.100 and 2.154 which was less than 2.3 indicating covalent character of the metal-ligand bond of solid polycrystalline cupper complexes and suggested the presence of elongated tetragonal axes.<sup>[26]</sup> The G factor is indicative of exchange interaction between the copper (II) centers in polycrystalline solids and can be calculated using formula

$$G = \frac{(gll - 2.00232)}{(g \perp -2.00232)}$$



FIGURE 6 Optimized geometrical structure of ligands (L1-L3) and M-complex

the G value of all copper (II) complexes is less than 4 (Table 1) indicating the presence of very weak exchange coupling in the polycrystalline solids.<sup>[27]</sup> This suggests that the distorted octahedral geometry for Cu (II) complex of Schiff base ligand L and acetate ion.<sup>[28]</sup>

### 3.3 | Computational analysis

For further approaches to the examined properties of the prepared Schiff base compounds and metal complexes, theoretical studies using DFT calculations at the B3LYP/3-21G and B3LYP/LANL2DZ level of theory were executed in the gas phase. Figure 6 shows the optimized geometrical structure of the synthesized Schiff base compounds and their metal complexes. The molecular electrostatic potential MEP delivers an important idea regarding the nucleophilic and electrophilic reactivity of the ligands. The negative and positive electrostatic potential areas in MEP map was represented in the form of color-coding. Red color indicates the electrophilic attack (maximum negative region) and the blue color indicates the nucleophilic (maximum positive region). The potential reduces in the order of blue > green > yellow >

orange > red. In the presented maps for the prepared ligands (Figure 7), the most negative electrostatic potential area is localized in the region of the O and N atoms. It is clear that C = O and C=N, groups are the most favored region for an electrophilic attack. Additionally, the frontier molecular orbitals (FMOs) energy gap of the ligand and its metal complex affords valuable electronic properties regarding the dynamic stability and chemical reactivity. In the Schiff base ligand, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are mainly placed overall molecular system which supports the  $\pi$ - $\pi$ \* electron transfer on the ligand molecule. While, in the L-M complex, HOMO and LUMO orbitals are mainly placed on the donor site of the ligand and surrounding the metal center (Figure 8). The frontier molecular orbital energy gap of the ligands was higher than the metal complex. These results are strongly in agreement with the complexation of transition metal to the ligand Schiff base.

Additional parameter such as global softness (S), chemical hardness ( $\eta$ ), which indicate the molecular reactivity and stability of the molecules. Electronegativity (X), chemical potential ( $\mu$ ), and electrophilicity value ( $\omega$ ) which reflect the biological activity of the molecules are



FIGURE 7 (a) Computed molecular electrostatic potential MEP (b) electrostatic potential plot for the prepared Schiff bas L1–L3



**FIGURE 8** The frontier molecular orbital frontier molecular orbital (FMO) structure of Ligand 1–3 and related metal complexes by DFT/B3LYP method

calculated utilizing reported equations in the literature.<sup>[29–31]</sup> The results of these parameters are summarized in Table 2 and showed that all prepared Schiff bases have good chemical reactivity and soft. The higher  $\omega$ 

value of the metal complexes agrees with biological results which showed that the metal complex has a higher antimicrobial effect than ligand Schiff base. The lower energy gap for ligands may be related to low kinetic stability, which performs electronic charge transfer interaction and high chemical reactivity, increasing the contribution to metal ions.<sup>[32,33]</sup>

### 3.4 | Antimicrobial activity

Antibacterial activities of the synthesized ligands (Schiff Bases) and related metal complexes were screened against Gram-positive bacteria (S. aureus RCMB010010), (B. subtilis RCMB 015 (1)), gram-negative bacteria (E. coli RCMB 010052), (P. vulgaris RCMB 004 (1)) and fungi (A. flavus RCMB 002002), (C. albicans RCMB 005003 (1)) by disc diffusion method in DMSO as a solvent. The antibacterial activity of a common standard antibiotic Gentamycin and antifungal Ketoconazole were also recorded. The results of study are given in Table 3 and Figure 9. The ligands 1, 2, and 3 have little activity against all the bacterial pathogens, compared to their metal complexes. The observed activity of ligand may be arise from the interference in the normal cell process of an organism caused by the formation of a hydrogen bond through the azomethine group with the active center of cell constituents.<sup>[34]</sup> Further, the uncoordinated heteroatom of aromatic heterocyclic aldehyde naming 1H-pyrrole-2-carbaldehvde. 1H-indole-3-carbaldehvde. or 1,3-diphenyl-1H-pyrazole-4-carbaldehyde moiety also contributes to microbial growth inhibition. Moreover, the metal complexes showed better antibacterial activity than those of the ligands, which can be explained based on overtone's concept and chelation theory. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups.<sup>[35]</sup> Chelation Also enhanced activity of the complexes may be attributed to chelation of Schiff base with metal ions that provide stability and more susceptibility against the bacterial pathogens. It has been suggested that possessing azomethine group (C=N), as well as nitrogen and oxygen donor systems inhibit enzyme activity through their deactivation by metal coordination. That also facilitates its efficient permeation through the organism's lipid layer and destroys their activity. The chelation process rises the lipophilicity of metal complexes by increasing the delocalization of  $\pi$  electrons over the full chelate ring. The improved lipophilicity helps the metal complexes to penetrate the lipid membranes and block the metal-binding sites of enzymes of microorganisms. The metal complexes also affect the protein synthesis and further growth of

TABLE 2 Electronic energy	calculation valu	ies of synthesized	Schiff base and the	sir metal complex	es				
Different parameters	L1	L2	L3	L1-Cu	L1-C0	L2-Cu	L2-C0	L3-Cu	L3-C0
Total energy (au)	-719.3325	-868.206	-1188.552	-2090.763	-3364.278	-2398.931	-2451.503	-3048.891	-3101.477
Dipole moment (Debye)	4.8131	4.3671	13.1546	6.0464	4.7681	3.8920	2.0891	2.5816	7.0987
$E_{HOMO}$ (eV)	-0.21115	-0.19745	-0.19483	-0.20490	-0.21759	-0.21138	-0.21439	-0.13757	-0.13599
E <sub>LUMO</sub> (eV)	-0.07105	-0.05372	-0.02639	-0.09854	-0.09880	-0.09276	-0.09104	-0.09745	-0.09392
Energy gap $\Delta E$ (eV)	0.1401	0.14373	0.16841	0.10636	0.11879	0.11862	0.12335	0.04012	0.04207
Electronegativity $\chi$ (eV)	-0.1411	-0.1255	-0.11061	-0.15172	-0.15819	-0.15207	-0.152715	-0.11751	-0.114955
Chemical potential $\mu$ (eV)	0.1411	0.1255	0.11061	0.15172	0.15819	0.15207	0.152715	0.11751	0.114955
Chemical hardness η (eV)	0.07005	0.071865	0.084205	0.05318	0.059395	0.05931	0.06167	0.02006	0.021035
Softness S (eV) <sup>-1</sup>	14.2755	13.9149	11.8757	18.8040	16.8364	16.8605	16.2153	49.8504	47.5398
Electrophilicity index $\omega$ (eV)	0.14210	0.10958	0.07264	0.2164	0.2106	0.19495	0.189086	0.34418	0.31411

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**TABLE 3** Antimicrobial studies for the synthesized Schiff base and their metal complexes measured as inhibition zone diameter (mm) by well diffusion agar assay

	Inhibition zone diameter (mm)					
Sample	Gram positive bacteria		Gram negative	bacteria	Fungi	
	S. aureus RCMB010010	B. subtilis RCMB 015	<i>E. coli</i> RCMB 010052	P. vulgaris RCMB 004	A. flavus RCMB 002002	C. albicans RCMB 005003
L1	13	14	11	13	12	15
L2	12	13	10	12	11	13
L3	9	10	9	12	10	12
4	15	17	13	14	16	17
6	17	19	14	15	14	15
8	18	17	13	14	15	16
5	20	22	17	19	18	19
7	19	20	16	18	15	18
9	18	19	14	17	14	17
Gentamycin	24	26	30	25	—	—
Ketoconazole	_	—	—	—	20	24





microorganisms by inhibiting the respiration process of the cell.<sup>[34]</sup> The weak antibacterial activity for Cu-ligand and Co-ligand against gram-negative bacteria was ascribed to the presence of an outer membrane, which poses hydrophilic polysaccharides chains as a barrier to these complexes. Cobalt is not generally considered to be a very toxic element.<sup>[36,37]</sup>

#### 4 | CONCLUSIONS

New Schiff base ligands and their Co (II) and Cu (II) metal complexes were successfully synthesized with bident N and O donor Schiff base ligand derived from nicotinic acid hydrazide. Their chemical structures were confirmed using several spectroscopic tools including IR, UV, XRD, and ESR spectra. It was revealed that all Schiff base ligand act as bident agent in all metal complex through the azomethine nitrogen and carbonyl group of nicotine moiety. Based on the magnetic measurements and ESR results, it was elucidated that all Cu (II) complexes appeared as a square-planar or distorted octahedral geometry. XRD spectroscopy showed that all parent Schiff bases are amorphous structures, and the crystallinity of the metal complexes was raised after complexation. Further elucidation for the metalation of the synthesized Schiff base was performed through DFT theory and calculation of some chemical parameters. In vitro antibacterial activities were studied and demonstrate that the Complexes formation increased their antimicrobial activities toward gram-positive and gram-negative bacteria.

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#### AUTHOR CONTRIBUTIONS

Heba Hashem: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; software; supervision; visualization.
Eslam A. Mohamed: Formal analysis; methodology.
Ahmed Farag: Investigation; visualization.
Negm: Investigation; methodology.
Eman
A.M. Azmy: Methodology; visualization.

#### **CONFLICT OF INTEREST**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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14 of 14 WILEY \_\_\_\_\_\_\_ WILEY \_\_\_\_\_\_ Chemistry

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