Synthesis, molecular docking and computational studies of novel hydrazone complexes

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ABSTRACT
In this study, a hydrazone ligand complexes based on p-anisidine and acetylacetonate derivatives with transition metals like Ni, Cu, Fe, and Zr were prepared. The structure of the prepared compounds was confirmed using Nuclear magnetic resonance (1H-NMR and 13C-NMR), Distortionless enhancement by polarization transfer (DEPT), heteronuclear single quantum coherence (HSQC-NMR), Correlated Spectroscopy (COSY-NMR), Fourier-transform infrared spectroscopy (FT-IR) and Electrospray ionization mass spectrometry (ESI-MS). The x-ray single crystal of the ligand was studied and the results showed that an intramolecular N – H …. O = C hydrogen bond (1.87Å) exists that stabilizes the geometrical structure of the ligand. Also, the magnetic properties for the prepared complexes were studied using Gouy’s method of susceptibility measurement. In addition, there in silico docking and in vitro antibacterial activities were investigated and the results showed that Fe complex has the highest antimicrobial activity. The expected structures and conformers for the prepared ligands and complexes were examined and fully optimized using the level B3LYP/6-31G*.

1. Introduction
Aryl azocompounds (AACs) have ubiquitous motifs in heterocyclic chemistry and are widely utilized as azo dyes, pH-indicators, pigments, food additives, initiators for some radical reactions, therapeutic agents, etc. (He, Qiu, Cheng, Liu, & Wu, 2018; Murase, Moritomo, Goto, Sugamoto, & Yoshikawa, 2005; Salah, El-Wahab, Farag, & Mostafa, 2014). Due to the intensive development of the bio coordination science in recent years (Shul’gin et al., 2011), the coordination science of AACs has been extensively studied through the last decades on account of potential combination of important functional properties with a diversity of molecular structure of their complexes (Adak et al., 2017; Roztoczk, Matoga, & Szklarzewicz, 2015; You et al., 2018). Thereby, these complexes have attracted attention in various fields, (Bekheit, El-Shobaky, & Gad Allah, 2017; Philip, Antony, Eeettinilkunnathil, Kurup, & Velayudhan, 2018) such as manufacturing of magnetic equipments, light-by-light scattering equipments, supramolecular chemistry, biological activity, catalysis and bioinorganic chemistry (Ayyannan et al., 2016; El-Sherif, Fetoh, Abdulhamed, & Abu El-Reash, 2018; Mandewale et al., 2018). On the other hand, aryl hydrazones with active methylene (AHMACs) represent a promising type of ligand toward the formation of novel coordination compounds. For instance, a particular representative of the AHMAC family, aryl hydrazones of diketones (AHBD), esters and dinitriles are drastically differed in physicochemical, analytical, biological, optical and coordination properties from diketones; the possibility to include – OH, – AsO3H2, – SO3 H, – COOH, -CN, -COOR or – NO2 groups at the ortho and para-positions of the aromatic ring increases the stability of AHBD complexes in comparison with ‘simple’ AHBD and diketones. Moreover, the coordination and organo-metallic compounds of AHBD possess catalytic properties and biological activities, photoluminescence, can also be used in thin films as optical recording media, in high-density recordable optical storage components and spin-coating films.

2. Experimental
The IR spectra of the prepared ligands and their complexes were recorded using the Perkin-Elmer spectrophotometer model 10.54 covering the frequency range 4000–400 cm–1, by the ATR Sample base plate diamond method. 1H and 13C NMR spectra were obtained using a Bruker Advance 300 MHz spectrometer, at ambient temperature. All chemical shifts are reported in δ (ppm). All spectra were internally referenced to residual protio-solvent resonance and are reported relative to SiMe4. Electrospray mass spectra (ESI-MS) were obtained on a Varian 500- MS LC Ion Trap Mass spectrometer equipped with an electrospray ion source. For electrospray ionization, the flow rate and drying gas were adjusted according to the specific sample with 35psi nebulizer pressure. The scanning was done from m/z 100–1200 in the CH3OH solution. The ligand and complexes were observed in the positive and negative modes (capillary voltage = 80–105 V).

A single crystal of the compound was attached to...
a nylon loop and measured at ambient temperature. Intensity data were collected using a Bruker AXS-KAPPA APEX II PHOTON 100 diffractometer with graphite monochromated Mo-Kα (0.71069 Å) radiation (Mahmoud, Guedes Da Silva, Sokolnicki, Smolen ski, & Pombeiro, 2018; Mahmoud, Martins, Guedes da Silva, & Pombeiro, 2018). Data were collected using phi and omega scans of 0.5° per frame and the full sphere of data was obtained. Cell parameters were retrieved using Bruker SMART software and refined using Bruker SAINT on all the observed reflections. Absorption corrections were applied using the SADABS program. The structures were solved by direct methods using SIR97 and refined with SHELXL-2014. Calculations were performed using the WinGX System-Version 2014–1. The hydrogen atom of the hydrazine group was found in the difference Fourier map and the isotropic thermal parameters were set at 1.5 times the average thermal parameters of the belonging nitrogen atom, frequently with their distances restrained by using the DFIX command. Coordinates of hydrogen atoms bonded to carbon atoms were included in the refinement using the riding-model approximation with the Uiso(H) defined as 1.2Ueq of the parent aromatic atoms, and 1.5Ueq of the parent carbon atoms for methyl. Least square refinements with anisotropic thermal motion parameters for all the non-hydrogen atoms were employed. The Crystallographic data for the structural analysis have been deposited to the Cambridge Crystallographic Data Center (CCDC 1876923). The magnetic moments were measured by the Gouy balance method by measuring the apparent change in the mass of the sample as it is repelled or attracted by the region of the high magnetic field between the poles. The sample is suspended between the magnetic poles through an attached string.

2.1. Synthesis of ligand 3-(2-(4-methoxyphenyl)hydrazono) pentane-2,4-dione ligand (L)

An aqueous solution of 10 mmol of sodium nitrite was added to a 10 mmol solution of p-anisidine dissolved in 20 ml ethanol. The mixture was stirred for 5 min at (0-5°C) followed by dropwise addition of 2 ml of conc. HCl. Another solution of 10 mmol NaOH, 10 ml H2O, 20 ml ethanol and 10 mmol of acetylacetone was added to the previous solution in 3 portions followed by the addition of 0.2g sodium acetate. The orange precipitate formed immediately was filtered, washed with cold ethanol and recrystallized from ethanol.

Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of a methanolic solution at room temperature for 72 h (Mo et al., 2018; Parveen, Govindarajan, Puschmann, & Revathi, 2018).

Figure 1. Scheme for (L) preparation.

Yield%: 83%; m.p.: 92°C. \(\lambda_{\text{max}}\) nm: 417. Anal. Calcd. (found) for (C12H14N2O3): C, 61.53 (62.20); H, 6.02 (5.97); N, 11.96 (11.55).1HNMR,(DMSO-d6) \(\delta\), ppm: 2.38 (s, 3H, CH3), 2.46 (s, 3H, CH3), 3.78 (s, 3H, CH3), 6.99 (2H, Ar-H), 7.51 (2H, Ar-H), 14.38 (s, 1H, NH).13CNMR, (DMSO-d6) \(\delta\), ppm: 26.45 (CH3), 31.15 (CH3), 55.49 (CH3), 114.94 (Ar-CH), 117.95 (Ar-CH), 132.54 (Ar-CH), 135.20 (Ar-CH), 157.48 (C = N), 196.20 (C = O), 196.24 (C = O). FT-IR ATR method cm\(^{-1}\): \(\bar{\nu} (\text{N-H})\) 3664, \(\bar{\nu}(\text{C-H sp})\) 3007, \(\bar{\nu} (\text{C = O})\) 1719 & 1669, \(\bar{\nu}(\text{C = N imine})\) 1616. ESI-Mass (-) m/z: 232.96 [M-H].

2.2. Synthesis of the complexes

A 10 mmol hot methanolic solution of (L) ligand was dropwise added to hot methanolic solutions of equal molar NiCl2.6H2O, Cu(NO3)2.2.5H2O, Fe(NO3)3.9H2O, or ZrCl4 and the progress of reactions was followed by

Figure 1. Scheme for L preparation.
TLC using dichloromethane/methanol. The pH of reactions between ligand with Ni and Cu ions raised up to 9 using drops of 1M NH₄OH. The precipitates formed were filtered, washed with cold methanol and diethyl ether, dried then washed with hot ethanol. The complexes are slightly soluble in dimethylformamide and dimethylsulfoxide. Figure 2. Showed the proposed structures of ligand and complexes.

(1) Ni complex. Yield%: 72%; m.p.: 181°C. \( \lambda_{\text{max}} \), nm: 294. Anal. Calcd. (found) for (C$_{24}$H$_{26}$N$_4$NiO$_6$): C, 54.89 (55.74); H, 4.99 (4.76); N, 10.67 (10.91).$^1$ HNMR, (DMSO-\(d_6\)) \( \delta \): 2.39 (s, 3H, CH$_3$), 2.50 (s, 3H, CH$_3$), 3.77 (s, 3H, CH$_3$), 7.01 (2H, Ar-H), 7.54 (2H, Ar-H).$^1$ CNMR, (DMSO-\(d_6\)) \( \delta \), ppm: 26.40 (CH$_3$), 31.09 (CH$_3$), 55.44 (CH$_3$), 114.89 (Ar-CH), 117.91 (Ar-CH), 132.54 (Ar-CH), 135.18 (Ar-CH), 157.41 (C = N), 196.10 (C = O). FT-IR ATR method cm$^{-1}$: \( \tilde{\nu} \) (C = O) 1670 & 1616, \( \tilde{\nu} \) (C = N (imine)) 1599, and \( \tilde{\nu} \) (Ni-O) 488. (El-Saied, Salem, Shakdofa, Al-Hakimi, & Radwan, 2017; Rashad, Hassan, Nassar, Ibrahim, & Mourtada, 2014; Roztocki, Matoga, & Nitek, 2016). ESI-Mass (+) m/z: 524.81 [M + H$^+$].

(2) Cu complex. Yield%: 67%; m.p.: 159°C. \( \lambda_{\text{max}} \), nm: 398. Anal. Calcd. (found) for (C$_{24}$H$_{34}$CuN$_4$O$_{10}$): C, 47.88 (49.01); H, 5.69 (5.58); N, 9.31 (9.45). FT-IR ATR method cm$^{-1}$: \( \tilde{\nu} \) (OH of H$_2$O) 3316 and \( \tilde{\nu} \) (C = O) 1614. ESI-Mass (+) m/z: 327.62 [M + L+ CH$_3$OH]$^+$. 

(3) Zr complex. Yield%: 60%; m.p.: 152°C. \( \lambda_{\text{max}} \), nm: 429. Anal. Calcd. (found) for (C$_{12}$H$_{18}$Cl$_4$N$_2$O$_5$Zr): C, 28.64 (36.98); H, 3.60 (4.37); N, 5.57 (6.52).$^1$ HNMR, (DMSO-\(d_6\)) \( \delta \): 2.40 (s, 3H, CH$_3$), 2.42 (s, 3H, NH), 2.50 (s, 3H, CH$_3$), 3.77 (s, 3H, CH$_3$), 7.01 (2H, Ar-H), 7.54 (2H, Ar-H).$^1$ 1H NMR, (DMSO-\(d_6\)) \( \delta \): 2.39 (s, 3H, CH$_3$), 2.50 (s, 3H, CH$_3$), 3.77 (s, 3H, CH$_3$), 7.01 (2H, Ar-H), 7.54 (2H, Ar-H).$^1$ 13C NMR, (DMSO-\(d_6\)) \( \delta \), ppm: 26.40 (CH$_3$), 31.09 (CH$_3$), 55.44 (CH$_3$), 114.89 (Ar-CH), 117.91 (Ar-CH), 132.54 (Ar-CH), 135.18 (Ar-CH), 157.41 (C = N), 196.10 (C = O). FT-IR ATR method cm$^{-1}$: \( \tilde{\nu} \) (C = O) 1670 & 1616, \( \tilde{\nu} \) (C = N (imine) 1599, and \( \tilde{\nu} \) (Ni-O) 488. (El-Saied, Salem, Shakdofa, Al-Hakimi, & Radwan, 2017; Rashad, Hassan, Nassar, Ibrahim, & Mourtada, 2014; Roztocki, Matoga, & Nitek, 2016). ESI-Mass (+) m/z: 524.81 [M + H$^+$].
CH$_3$), 3.81 (s, 3H, CH$_3$), 7.00 (2H, Ar-H), 7.58 (2H, Ar-H), 14.36 (s, 1H, NH). $^{13}$CNMR, (DMSO-$d_6$) $\delta$, ppm: 26.82 (CH$_3$), 31.51 (CH$_3$), 55.84 (CH$_3$), 115.29 (Ar-CH), 118.32 (Ar-CH), 132.94 (Ar-CH), 135.61 (Ar-CH), 157.81 (C = N), 196.53 (C = O). FT-IR ATR method cm$^{-1}$: $\tilde{u}$(N-H) 3671, $\tilde{u}$(C = O) 1670, and $\tilde{u}$(C = N imine) 1593. ESI-Mass (+) m/z: 524.74 [M+ Na]$^+$. (4) Fe complex. Yield%: 64%; m.p.: 194°C. $\lambda_{\text{max}}$ nm: 301. Anal. Calcd. (found) for (C$_{26}$H$_{38}$FeN$_{2}$O$_{20}$): C, 36.01 (37.12); H, 4.79 (4.86); N, 12.25 (12.02). FT-IR spectrum showed 3664, 1669 and 1616 for N-H, C = O, and C = N stretching modes.

2.3. Method of calculations

The expected structures and conformers for the prepared ligand, complexes, and their total energy, enthalpy of formation, the free energy of formation, atomic charges, HOMO-LUMO, dipole moment, bond length, bond angle and the dihedral angle at different centers were studied and fully optimized using the level B3LYP/6-31G*.

2.4. Antibacterial docking studies and assessment of antimicrobial assay

The binding sites of the protein were determined using MVD cavities prediction. The predicted cavities having 65.042 Å$^3$ and 55.808 Å$^3$ volumes for Eco SlyD and Sau SlyD, respectively. The binding site was set inside a restriction sphere of 20 Å radius, also using MVD. All other software parameters for docking were set to the default values. The parameters were as follows: the ‘MolDock SE’ searching algorithm was used with the number of runs set to 10 using a maximum of 1500 iterations and a total population size of 50. The energy threshold used for the minimized final orientation was 100. The Simplex evaluation with 300 maximum steps of neighbor distance factor 1 was completed. The chosen cavity was further refined using side-chain minimization by selecting the add-visible option at a maximum (10000) steps of per residue and a maximum (10000) of global steps. The antibacterial activities have been tested under in vitro conditions and in silico against Escherichia coli and Staphylococcus aureus.

3. Results and discussion

3.1. Description of the ligand structure

The desired hydrazone fragment was prepared through the coupling of p-methoxy aniline diazonium salt moiety and acetylacetone in the presence of sodium acetate as a catalyst. The crystals of L were obtained by recrystallization from methanol. A summary of the crystal data and refinement details, hydrogen bonding and bond angles for the prepared ligand are given in Tables 1 and 2. There is an intramolecular N – H … O = C hydrogen bond (1.87Å) that stabilizes the geometrical structure of the compound with a dihedral angle of 133°. Figure 3. Showed the intermolecular Hydrogen bond interactions. The crystal system is monoclinic and the geometric parameters of the titled molecule agree well with those reported for similar hydrazone structures (Aradhuya, Joshi, Poluri, & Kollipara, 2018; Yousefi, Sedaghat, Simpson, Motamedi, & Dayer, 2018). The $^1$H-NMR and FT-IR spectra of the compound and its complexes provide significant information's about the metal-ligand bonding modes. The $^1$H-NMR spectrum showed singlet signals at $\delta$ 2.38–2.49 due to the different methyl groups of acetylacetone moiety, while the singlet signal appeared at $\delta$ 3.78 due to highly deshielded methoxy group. Aromatic protons appeared at normal chemical shift $\delta$ 6.99–7.51 and the signal at $\delta$ 14.38 due to hydrogen-bonded N-H. The $^{13}$C-NMR spectrum confirms the previous data obtained, it showed signals at $\delta$ 157.48, 196.20 and 196.24 due to C = N, free carbonyl group, and hydrogen-bonded carbonyl respectively. DEPT spectrum was obtained to identify signals of C, CH, CH$_2$, and CH$_3$. The FT-IR spectrum showed band at $\tilde{\nu}$ 3664, 1669 and 1616 for N-H, C = O, and C = N respectively. ESI-MS (-) showed m/z: 232.96 due to [M-H]$^–$.

3.2. Description of complexes structures

The $^1$H-NMR spectrum of Ni-L did not display the N-H signal, which indicates the coordination of the N to the metal ion. The signals at $\delta$ 2.39–3.77 due to different

| Table 1. Hydrogen bonding distances (Å) and angles (°). |
|--------------------------------------------------------|
| D–H–A | D–H–A | D–H–A | D–H–A |
| N1–H1–O2 | 0.91 | 1.87 | 2.579 | 133 |
| C7–H7–O3$'$ | 0.930 | 2.608 | 3.521 | 167.3 |
| C3–H3–O2$'$ | 0.930 | 2.686 | 3.435 | 138.1 |
| C8–H8B–O3$''$ | 0.960 | 2.631 | 3.385 | 135.7 |
| N3–H3C–O3$''$ | 0.960 | 2.631 | 3.385 | 135.7 |

| Table 2. Crystal data and structure refinement summary. |
|-------------------------------------------------------------|
| Empirical formula | C$_{26}$H$_{38}$FeN$_{2}$O$_{20}$ |
| Formula Weight | 234.25 |
| Crystal system | Monoclinic |
| Space group | P 21/n |
| Temperature/°K | 293(2) |
| a/Å | 8.1900(6) |
| b/Å | 16.660(5) |
| c/Å | 11.099(8) |
| $\alpha^\circ$ | 90 |
| $\beta^\circ$ | 93.71(3) |
| $\gamma^\circ$ | 90 |
| $\tilde{\nu}$ (Å$^3$) | 604.1(9) |
| Z | 2 |
| D$_{calc}$ (g cm$^{-3}$) | 1.288 |
| F000 | 248 |
| $\mu$(Mo Kα) (mm$^{-1}$) | 0.094 |
| R$_{int}$ | 0.117 |
| Final R1 $^a$ | 0.0670, 0.1973 |
| Goodness-of-fit on F$^2$ | 1.127 |

$^a$R = $\Sigma$|F$_{o}$|−|F$_{c}$|/$\Sigma$|F$_{o}$|; wR(F) = $\Sigma$w(F$_{o}$)$^2$ − (F$_{o}$)$^2$/$\Sigma$w(F$_{o}$)$^2$.
methyl groups, while the aromatic protons appeared at δ 7.00–7.54. The $^{13}$C-NMR and 2D-NMR spectra confirm the proposed structure, a slight shift for C = O δ (196.24 → 196.10) and C = N δ (157.48 → 157.41) due to coordination with the metal ion. The ESI-MS (+) and elemental analysis of Ni-L proved that the ratio of the ligand to metal ion is 1:2. It showed m/z: 524.81 due to [Ni$^{12+}$ + 2L+H$^+$], the complex formed via coordination between carbonyl and negatively charged nitrogen with the metal ion to form a stable 5-membered ring. IR data showed decreasing of their stretching frequencies on coordination (i) C = O 1719 → 1669), (ii) C = N 1573), the complex formed via coordination between carbonyl and imine groups with the metal ion. The ESI-MS (+) of Zr-L proved that the ratio of the ligand to the metal ion is 1:1. It showed m/z: 524.74 due to [Zr$^{14+}$ + L + 4Cl$^-$$^-$$^- + 2H$_2$O+Na$^+$], the complex formed via coordination between carbonyl and imine groups with the metal ion. IR data showed decreasing of stretching frequencies of coordinated groups (i) C = O 1719 → 1670), (ii) C = N 1616 → 1593). The spectral data obtained and magnetic susceptibility measurement proved that the complex structure is octahedral with coordination number 6 and it is diamagnetic.

The broadening of the $^1$H-NMR spectrum of Cu-L due to paramagnetic properties of metal ion which is proved by magnetic susceptibility measurement (1.98 $\mu_B$). The spectrum proved the disappearance of the N-H signal indicating coordination between metal and negatively charged nitrogen. The ESI-MS (+) and elemental analysis of Cu-L proved that the ratio of the ligand to the metal ion is 1:2. It showed m/z: 327.62 due to [Cu$^{12+}$ + L + CH$_3$OH], the complex formed via coordination between carbonyl and negatively charged nitrogen with the metal ion. IR data showed the disappearance of the NH stretching band and a new stretching broad band δ C=O 3316 due to OH moieties, carbonyl stretching frequency is shifted to lower frequency, δ C = O 1719 → 1614. Based on the results obtained and theoretical calculations for the most stable geometry, Cu ion is surrounded by Pentacoordination sites with the expected square pyramid (Radunsky, Kösters, & Müller, 2015).

The $^1$H-NMR spectrum of Zr-L showed that the N-H signal appeared at the same chemical shift on ligand spectrum δ 14.36 indicating no coordination occurs between the metal ion and N-H; the signals appeared at δ 2.40–3.81 due to non-equivalent methyl groups, while signals appeared at δ 7.00–7.58 due to aromatic protons. The $^{13}$C-NMR and DEPT spectra confirm the data obtained, both C = O δ (196.24 → 196.53) and C = N δ (157.48 → 157.81) are shifted to downfield area indicating coordination between them and metal ion. DEPT spectrum was obtained to identify signals of C, CH, CH$_2$ and CH$_3$. The ESI-MS (+) of Zr-L proved that the ratio of the ligand to the metal ion is 1:1. It showed m/z: 524.74 due to [Zr$^{14+}$ + L + 4Cl$^-$$^-$$^- + 2H$_2$O+Na$^+$], the complex formed via coordination between carbonyl and imine groups with the metal ion. IR data showed decreasing of stretching frequencies of coordinated groups (i) C = O 1719 → 1670), (ii) C = N 1616 → 1593). The spectral data obtained and magnetic susceptibility measurement proved that the complex structure is octahedral with coordination number 6 and it is diamagnetic.

The broadening of $^1$H-NMR and magnetic susceptibility measurement for Fe-L indicating the paramagnetic properties of metal ion (6.05 $\mu_B$) but it showed that the N-H signal appeared at the same chemical shift on ligand spectrum indicating no coordination occurs between the metal ion and the N-H. The ESI-MS (+) and elemental analysis of Fe-L proved that the ratio of the ligand to the metal ion is 1:2 with m/z: 641.85 due to [Fe(NO$_2$)$_2$ + L + 2H$_2$O+6CH$_3$OH]$^+$, The complex formed via coordination between carbonyl and imine groups with the metal ion. IR data showed decreasing of stretching vibration frequencies of donating groups (i) C = O 1719 → 1604), (ii) C = N 1616 → 1573), the broad band around 3300 due to OH of water moiety coordinated with Fe with expected octahedral structure (Azhari, Salah, Farag, & Mostafa, 2015).

### 3.3. Computational details

The structure and geometry of ligand were confirmed by x-ray single crystal, due to the absence of a single crystal structure of complexes and to get the molecular...
Table 3. Calculated parameters for L, Ni-L, and Cu-L using B3lyp/6-31G*.

| Parameters                  | L             | Ni-L          | Cu-L          |
|-----------------------------|---------------|---------------|---------------|
| structure                   |               |               |               |
| $E_{\text{HOMO}}$, a.u.     | −0.2033       | −0.2154       | −0.4370       |
| $E_{\text{LUMO}}$, a.u.     | −0.1303       | −0.2154       | −0.3441       |
| $E_{\text{HOMO}}$, a.u.     | −0.1295       | 0.0851        | 0.0929        |
| Sum of $\Delta H$           | −800.8327     | −3229.4770    | −2746.3840    |
| Sum of $\Delta G$           | −800.5675     | −3229.2019    | −2746.0044    |
| $\Delta E_{\text{g}}$, a.u. | 0.1295        | 0.0851        | 0.0929        |

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geometry of complexes, energy minimization studies were carried out using Gaussian 09W software package. The geometries of the studied structures were fully optimized in the gas phase without any symmetry constraints.

### 3.3.1. Ligand geometry

The computational results showed that the structure \( L \) has the total energy \(-800.8327\) a.u. The atomic charge on \( N_1, N_2, O_5, O_8 \) and \( O_{19} \) atoms in the most stable \( L \) structure are \(-0.497889, -0.230365, -0.525026, -0.441305 \) and \(-0.504654 \) respectively, which are the highest negatively charged atoms, therefore they are the most expected chelating centers. The dipole moment is 3.3415 Debye and it is highly polar and stabilized in polar solvents Table 3: summarized the calculated parameters for \( L, Ni-L, \) and \( Cu-L \). (Kurbah et al., 2018).

### 3.3.2. Complexes geometry

The computational data proved that the best geometrical structure for Ni-L (1:2) is square planar geometry with coordination number 4, while the best geometrical structure for Cu-L (1:2) is that with coordination number 5 to form a square pyramid structure. The Cu ion completes its coordination number by solvent molecules. The computed results revealed that the octahedral structure for Cu-L was not located as a minimum point. To confirm the previous structures, the thermodynamic parameters were calculated at 25°C using the same level. The calculated \( E_{\text{HOMO}} \) and \( E_{\text{LUMO}} \) values of the ligand are \(-0.2033\) and \(-0.0738\) a.u., while those for Ni and Cu complexes become more negative leading to stabilization of the HOMO and LUMO after complexation. The calculated bond distances and angles around the central Ni(II) and Cu(II) metal ions are in good agreement with that obtained experimentally and theoretically for analogous complexes (Abdel-Latif & Mohamed, 2017).

### 3.4. Antibacterial docking results and antimicrobial activity

The compound 3-(2-(4-methoxyphenyl) hydrazinediene)pentane-2,4-dione and its Cu(II), Fe(III), Zr(IV), and Ni(II) complexes were synthesized, characterized and their antibacterial activities have been tested under in vitro conditions and in silico. Table 4: Summarized the In silico docking study and In vitro antibacterial activities. The complex (Fe-L) showed the highest antibacterial activity.

#### Table 4. In silico docking study and In vitro antibacterial activity of selected 11C, 11E, 13B and Ciprofloxacin (Cip) with DNA Gyrase B chain.

| Bacteria          | Name | MolDock Score | Rerank Score | Inhibition zone (mm) |
|-------------------|------|---------------|--------------|----------------------|
| *Escherichia coli* | Cu-L | -85.1636      | -2.68517     | 11                   |
| (PDB ID)          | Fe-L | -116.589      | -8.97727     | 13                   |
|                   | Ni-L | -85.7575      | -56.4619     | 11                   |
|                   | Zr-L | -66.7845      | 17.3705      | 8                    |
| *Staphylococcus Aureus* | Cu-L | -76.2451      | 24.7959      | 11                   |
| (PDB ID)          | Fe-L | -117.639      | 10.9352      | 15                   |
|                   | Ni-L | -82.0171      | -49.9671     | 12                   |
|                   | Zr-L | -66.0151      | -39.1062     | 7                    |

Figure 4. Binding interaction of Ni-L with SlyD of (A) *E. coli* (A) *S. aureus*.

Figure 5. Binding interaction of Fe-L with SlyD of (A) *E. coli* (A) *S. aureus*. 
activity against *Escherichia coli* and *Staphylococcus aureus* with inhibition zone diameter of 13 and 15mm, respectively. Fe-L showed the highest inhibitory activity against *E. coli* SlyD and *S. aureus* SlyD with \(-116.58\) and \(-117.63\) MolDock Score, respectively. It can form 5 H-bonds with Tyr 13 and Tyr 38 *E. coli* SlyD and 5 H-bonds with Tyr 13 & Tyr 68 *S. aureus* SlyD. Figure 5: showed the binding interaction of Fe-L with SlyD of (A) *E. coli* (A) *S. aureus*.

The complexes (Ni-L) and (Cu-L) showed good antibacterial activities against both *E. coli* and *S. aureus*. Also, having a high MolDock Score against *E. coli* SlyD and *S. aureus* SlyD, The MolDock Score of them against *E. coli* SlyD and *S. aureus* SlyD were \((-85.75)\), \((-82.01)\),
(−85.16) and (−76.24) respectively. They can form 3 H-bonds with Ser 26, Ser 40, Tyr 13, Tyr 34, Tyr 40 and Tyr 68 E. coli SlyD and 3 H-bonds with Ile 42, Tyr 13 & Tyr 68 S. aureus SlyD (Cao, Liu, Zhang, & Jia, 2018; Liu et al., 2017). Figures 4, 6: showed the binding interaction of Cu-L and Ni-L with SlyD of (A) E. coli (A) S. aureus.

The complex (Zr-L) showed low antibacterial activity against E. coli and S. aureus and having the lowest MolDock Score against E. coli SlyD and S. aureus SlyD. It can form 1 H-bonds with Ile 42 E. coli SlyD. Figure 7: Showed the binding interaction of Zr-L with SlyD of (A) E. coli (A) S. aureus. Figure 8: showed the antimicrobial effect of Fe-L and Ni-L complexes against (A) E. coli (A) S. aureus.

4. Conclusion

Four transition metals complexes based on p-anisidine hydrazone ligand have been successfully synthesized and characterized by different spectral methods. The structure of the prepared hydrazone ligand was confirmed by x-ray single-crystal study. Ni complex has a square planar geometry, Cu complex has a square pyramid structure and both Zr and Fe have octahedral structures. The theoretical calculations were used to confirm their structures and studying of some thermodynamic parameters using the level B3LYP/6-31G*. The antibacterial disk diffusion data agree with those obtained from docking studies. Fe-L has the highest antimicrobial activities against E. coli and S. aureus, while Zr-L has the lowest biological activities.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The data used to support the findings of this study are included within the supplementary information file(s).

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