Synthesis, characterization, computational and biological activity of novel hydrazone complexes

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ABSTRACT
In this work, novel hydrazone ligands were prepared by the reaction of chloroanthranilic acid diazonium salt with acetylacetone (L1), ethyl acetoacetate (L2) and diethyl malonate (L3). The prepared compounds were reacted with some transition metals like Ni(II), Cu(II), and Fe(III). The structures of the prepared complexes were 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). Also, the magnetic properties for the prepared complexes were studied using Gouy’s method of susceptibility measurement. Therefore, in silico docking and in vitro antibacterial activities were investigated and the results showed that Ni complexes have 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
The chemistry and biological study of hydrazone compounds represent an important area of chemistry that related to theoretical and computational work on bonding between a metal ion and donor ligands (Akkas, Celik, Ergan, & Levent, 2019; Kopylovich et al., 2011; Murase, Moritomo, Goto, SugaMoto, & Yoshikawa, 2005). Arylhydrazones of 1, 3-diketones (AHBD) are compounds combining in their structure azo- and diketo-function groups and thus providing rich organic chemistry and versatility in complex formation (Kopylovich et al., 2013). On the other hand, the complexes possess significance biological and chemical properties in many attractive applications (Azhari, Salah, Farag, & Mostafa, 2015; Heinrich, Stubbe, & Kulak, 2018; Mohanraj, Ayyannan, Raja, & Jayabalakrishnan, 2016; Salah, ZHa, Farag, & Mostafa, 2014). For example, it was demonstrated that AHBDs can be controllably switched between their (E, Z) enol-azo, keto-azo and (E, Z)-hydrazone forms, that makes them good candidates for molecular switches (Roztocki, Matoga, & Szklarzewicz, 2015; Suzamol, Sindhu, Athira, & Mohanan, 2011). The coordination chemistry of arylhydrazone ligands has also been intensively modified and improved. It was shown that substitution of different donor function groups at the ortho position of the aromatic part of hydrazones creates an additional chelating site with a stabilizing effect on the respective complex leading to a variety of complexes depending on the substituent. For instance (Chowdhury et al., 2018; GurbanoV, Zubkov, Safutdinov, & Fig, 2018; Hadil, Noviany, & Rilyanti, 2018; Kopylovich et al., 2013; Mahmoud, Martins, Guedes Da Silva, & Pombeiro, 2018a; Roztocki, Matoga, & Nitek, 2016), if Cu (II) is used as the metal ion and substitution of sulfonic, carboxylic, hydroxyl or amino groups at the ortho position of the aromatic nuclei of 3-(2-phenylhydrazone)pentane-2,4-dione, monomeric, dimeric and cluster complexes can be synthesized. On the other hand, it would be exciting to discuss the influence of different metal ions on the structure, coordination modes, biological, nuclearities and properties of the formed complexes if the same ligand is used for the synthesis (Ayyannan et al., 2016; He, Qiu, Cheng, Liu, & Wu, 2018; Liu et al., 2017). This work aims to study the biological activity of novel hydrazone complexes.

2. Experimental
2.1. Physical measurements
The IR spectra of the prepared ligands and their complexes were recorded using the Perkin-Elmer spectrophotometer spectrum 10.5.4 covering the frequency range 4000–400 cm−1, by the ATR Sample base plate diamond method. The UV-Visible spectra were measured by Shimadzu UV-vis 160 double beam using DMF as a solvent. 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 35 psi nebulizer pressure. The scanning was done from m/z 100–1200 in the CH$_3$OH solution. All ligands and complexes were observed in the positive and negative modes (capillary voltage = 80–105 V). The magnetic moments were measured by Gouy balance from Johnson Matthey and Sherwood model by measuring the apparent change in the mass of the sample as it is repelled or attracted by the high magnetic field area between the two poles. The sample is forced between the magnetic poles through an attached string.

2.2. Synthesis of 4-chloro-2-(2-(2,4-dioxopentan-3-ylidene) hydrazinyl) benzoic acid ligand (L$_1$)

A 10 mmol of an aqueous solution of chloroanthranilic acid sodium salt and 10 mmol of an aqueous solution of NaNO$_2$ were mixed at (0–5°C) followed by the addition of 2 ml conc. HCl. Another solution of 10 mmol NaOH, 10 ml H$_2$O, 20 ml ethanol, and 10 mmol of acetylacetone was added to the previous solution in three portions followed by the addition of 0.2 g sodium acetate. The yellow precipitate formed immediately was filtered, washed with cold ethanol and recrystallized from ethanol. Figure 1. Scheme for L$_1$ preparation. Yield%: 79%; m.p.: 206°C. $\lambda_{\text{max}}$ nm: 391. Anal. Calcd. (found) for (C$_{12}$H$_{10}$ClN$_2$NaO$_4$): C, 47.31 (46.42); H, 3.31 (4.01); N, 9.19 (8.93). $^1$HNMR (DMSO-d$_6$) $\delta$, ppm: 2.43 (s, 6H, 2CH$_3$), 7.11 (1H, Ar-H), 7.74 (1H, Ar-H), 7.95 (1H, Ar-H), 16.06 (s, 1H, NH), $^{13}$CNMR (DMSO-d$_6$) $\delta$, ppm: 26.64 (CH$_3$), 31.17 (CH$_3$), 113.62 (Ar-CH), 122.84 (Ar-CH), 133.57 (Ar-CH), 134.82 (Ar-CH), 135.61 (Ar-CH), 144.69 (Ar-CH), 161.48 (C = N), 194.97 (C = O), 196.97 (C = O). FT-IR, ATR method cm$^{-1}$: $\tilde{\nu}$(N-H) 3680, $\tilde{\nu}$(C-H sp$^2$) 3087, $\tilde{\nu}$(C = O) 1674, $\tilde{\nu}$(C = N imine) 1637. ESI-Mass (-) m/z: 280.92 [M-Na]$^-$. 

2.3. Synthesis of (E)-4-chloro-2-(2-(1-ethoxy-1,3-dioxobutan-2-ylidene) hydrazinyl) benzoic acid ligand (L$_2$)

A 10 mmol of an aqueous solution of chloroanthranilic acid was reacted with 10 mmol of sodium hydroxide to produce the corresponding acid salt, then the salt produced was reacted with (10 mmol) of an aqueous solution of NaN$_2$ at ice medium followed by dropwise addition of 2 ml conc. HCl. Another solution of 10 mmol NaOH, 10 ml H$_2$O, 20 ml ethanol, and 10 mmol of ethyl acetoacetate was added to the previous solution in three portions followed by the addition of 0.2 g sodium acetate. The dark yellow precipitate formed was filtered, washed with cold ethanol and recrystallized from ethanol. Figure 2. Scheme for L$_2$ preparation. Yield%: 75%; m.p.: 228°C. $\lambda_{\text{max}}$ nm: 432. Anal. Calcd. (found) for (C$_{13}$H$_{12}$ClN$_2$NaO$_5$): C, 46.65 (47.01); H, 3.61 (3.71); N, 8.37 (8.96). $^1$HNMR (DMSO-d$_6$) $\delta$, ppm: 1.29 (t, 3H, CH$_3$), 2.42 (s, 3H, CH$_3$), 4.29 (q, 2H, CH$_2$), 7.08 (1H, Ar-H), 7.65 (1H, Ar-H), 7.94 (1H, Ar-H), 15.45 (s, 1H, NH). $^{13}$CNMR (DMSO-d$_6$) $\delta$, ppm: 13.93 (CH$_3$), 25.64 (CH$_3$), 61.25 (CH$_3$), 113.03 (Ar-CH), 121.75 (Ar-CH), 132.94 (Ar-CH), 133.31 (Ar-CH), 136.85 (Ar-CH), 145.55 (Ar-CH), 161.91 (C = N), 168.24 (C = O), 193.74 (C = O). FT-IR, ATR method cm$^{-1}$: $\tilde{\nu}$(N-H) 3680, $\tilde{\nu}$(C-H sp$^2$) 3087, $\tilde{\nu}$(C = O) 1683, $\tilde{\nu}$(C = N imine) 1620. ESI-Mass (+) m/z: 334.89 [M + H]$^+$. 

Figure 1. Scheme for L$_1$ preparation.
2.4. Synthesis of 4-chloro-2-(2-(2,4-dioxopentan-3-ylidene) hydrazinyl)benzoic acid ligand (L₃)

A solution of 10 mmol NaOH, 10 ml H₂O, 20 ml ethanol, and 10 mmol of diethyl malonate was added to 10 mmol of diazonium chloride solution of chloroanthranilic acid sodium salt at (0–5°C) followed by the addition of 0.2 g sodium acetate. The red precipitate formed was filtered, washed with cold ethanol and recrystallized from ethanol. Figure 3. Scheme for L₃ preparation. Yield%: 76%; m.p.: 261°C. \( \lambda_{\text{max}} \) nm: 416. Anal. Calcd. (found) for (C₁₄H₁₂ClN₂NaO₆): C, 46.10 (46.63); H, 3.87 (3.59); N, 7.68 (7.61).¹HNMR (DMSO-\( d_6 \)) \( \delta \), ppm: 1.35 (t, 6H, 2CH₃), 4.31 (q, 4H, 2CH₂), 7.11 (1H, Ar-H), 7.68 (1H, Ar-H), 7.99 (1H, Ar-H), 14.65 (s, 1H, NH). ¹³CNMR (DMSO-\( d_6 \))
δ, ppm: 14.38 (CH$_3$), 14.57 (CH$_3$), 61.36 (CH$_2$), 61.83 (CH$_2$), 113.65 (Ar-CH), 122.17 (Ar-CH), 124.32 (Ar-CH), 133.82 (Ar-CH), 137.39 (Ar-CH), 145.65 (Ar-CH), 161.09 (C = N), 162.97 (C = O), 168.36 (C = O). FT-IR, ATR method cm$^{-1}$: $\tilde{u}$(C-H sp$^2$) 3084, $\tilde{u}$(C = O) 1717, $\tilde{u}$(C = N imine) 1569. ESI-Mass (+) m/z: 364.90 [M+ Na]$^+$. 

2.5. Synthesis of the complexes

A 10 mmol hot methanolic solution of (L$_1$, L$_2$, and L$_3$) ligands was dropwise added to hot methanolic solutions of equal molar NiCl$_2$.6H$_2$O, Cu(NO$_3$)$_2$.2.5H$_2$O and Fe(NO$_3$)$_3$.9H$_2$O, then the progress of reactions was followed by TLC using dichloromethane/methanol. The pH of reactions between ligand with Ni and Cu ions was raised to nine using drops of 1M NH$_4$OH. The precipitates formed were filtered, washed with cold methanol and diethyl ether, dried then washed with hot ethanol. Figure 4. Proposed structures for the prepared complexes.

(1) L$_1$Ni.3H$_2$O complex. Yield%: 68%; m.p.: 288°C. $\lambda_{\text{max}}$ nm: 440. Anal. Calcd. (found) for (C$_{12}$H$_{15}$ClNiN$_2$O$_7$): C, 36.64 (35.71); H, 3.84 (4.16); N, 7.12 (6.85). FT-IR, ATR method cm$^{-1}$: $\tilde{u}$(O-H) 3331, $\tilde{u}$(C = O) 1622, $\tilde{u}$(C = N imine) 1573. ESI-Mass (+) m/z: 370.52 [Ni+(L-H)+CH$_3$OH]$^+$. 

(2) L$_1$Cu.2H$_2$O complex. Yield%: 71%; m.p.: 269°C. $\lambda_{\text{max}}$ nm: 300. Anal. Calcd. (found) for (C$_{12}$H$_{13}$ClCuN$_2$O$_6$): C, 37.90 (38.44); H, 3.45 (3.59); N, 7.37 

Figure 4. Proposed structures for the prepared complexes.
(7.62). FT-IR, ATR method cm⁻¹: \(\tilde{\nu}(\text{O-H})\) 3316, \(\tilde{\nu}(\text{C} = \text{O})\) 1670 and \(\tilde{\nu}(\text{C} = \text{N})\) 1622. ESI-Mass (+) m/z: 375.45 [Cu+L-H+CH₃OH]⁺.

(3) \(\text{L}_2\text{Fe.4H}_2\text{O.N}_2\text{O}_5\) complex. Yield%: 65%; m.p.: 301° C. \(\lambda_{\text{max}}\), nm: 400. Anal. Calcd. (found) for (C₂₄H₂₈C₂₄FeN₂O₇): C, 38.27 (37.88); H, 3.75 (3.81); N, 9.30 (9.17). FT-IR, ATR method cm⁻¹: \(\tilde{\nu}(\text{O-H})\) 3377, \(\tilde{\nu}(\text{C} = \text{O})\) 1679 and \(\tilde{\nu}(\text{C} = \text{N})\) 1599. ESI-Mass (+) m/z: 399.26 [Fe+L+ NO₃]⁺.

(4) \(\text{L}_2\text{Ni.4H}_2\text{O}\) complex. Yield%: 77%; m.p.: 332°C. \(\lambda_{\text{max}}\), nm: 295. Anal. Calcd. (found) for (C₁₉H₁₉C₁₅N₂O₄): C, 35.37 (36.09); H, 4.34 (4.65); N, 6.35 (6.82). FT-IR, ATR method cm⁻¹: \(\tilde{\nu}(\text{O-H})\) 3330, \(\tilde{\nu}(\text{C} = \text{O})\) 1621, \(\tilde{\nu}(\text{C} = \text{N} \text{ imine})\) 1557. ESI-Mass (+) m/z: 405.05 [Ni+L-H+CH₃OH+H⁺].

(5) \(\text{L}_2\text{Cu.2H}_2\text{O}\) complex. Yield%: 67%; m.p.: 359°C. \(\lambda_{\text{max}}\), nm: 416. Anal. Calcd. (found) for (C₁₃H₁₁C₁₃CuN₂O₇): C, 39.81 (39.16); H, 3.34 (3.51); N, 7.14 (7.82). FT-IR, ATR method cm⁻¹: \(\tilde{\nu}(\text{O-H})\) 3329, \(\tilde{\nu}(\text{C} = \text{O})\) 1656 and \(\tilde{\nu}(\text{C} = \text{N})\) 1625. ESI-Mass (+) m/z: 405.09 [Cu+L-H+CH₃OH]⁺.

(6) \(\text{L}_2\text{Ni.3H}_2\text{O}\) complex. Yield%: 70%; m.p.: 355°C. \(\lambda_{\text{max}}\), nm: 400. Anal. Calcd. (found) for (C₁₉H₁₉C₁₅N₂O₄): C, 37.08 (38.15); H, 4.22 (3.82); N, 6.18 (6.53). FT-IR, ATR method cm⁻¹: \(\tilde{\nu}(\text{O-H})\) 3359, \(\tilde{\nu}(\text{C} = \text{O})\) 1602, \(\tilde{\nu}(\text{C} = \text{N} \text{ imine})\) 1557. ESI-Mass (+) m/z: 430.34 [Ni+L-H+CH₃OH]⁺.

(7) \(\text{L}_2\text{Cu.2H}_2\text{O}\) complex. Yield%: 67%; m.p.: 379°C. \(\lambda_{\text{max}}\), nm: 406. Anal. Calcd. (found) for (C₁₂H₁₁C₁₃CuN₂O₇): C, 36.56 (35.29); H, 2.81 (2.72); N, 7.11 (6.99). FT-IR, ATR method cm⁻¹: \(\tilde{\nu}(\text{O-H})\) 3325, \(\tilde{\nu}(\text{C} = \text{O})\) 1622 and \(\tilde{\nu}(\text{C} = \text{N})\) 1673. ESI-Mass (+) m/z: 397.93 [Cu+L-H+H⁺ CH₃OH]⁺.

(8) \(\text{L}_2\text{Fe.2H}_2\text{O.N}_2\text{O}_5\) complex. Yield%: 64%; m.p.: 347° C. \(\lambda_{\text{max}}\), nm: 298. Anal. Calcd. (found) for (C₂₄H₂₆N₄N₂O₁₀): C, 40.16 (41.37); H, 3.85 (3.56); N, 8.36 (8.49). FT-IR, ATR method cm⁻¹: \(\tilde{\nu}(\text{O-H})\) 3316, \(\tilde{\nu}(\text{C} = \text{O})\) 1623 and \(\tilde{\nu}(\text{C} = \text{N})\) 1571. ESI-Mass (+) m/z: 458.94 [Fe+L+ NO₃]⁺.

2.6. Method of calculations

The expected structures and conformers for the ligand (L₁), some of its complexes and their total energy, enthalpy of formation, free energy of formation, atomic charges, HOMO-LUMO, dipole moment, bond length, bond angle, and dihedral angle at different centers were studied and fully optimized using the level B3LYP/6-31G*.

2.7. 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 Å³ and 55.808 Å³ 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 (Lanez & Lanez, 2016). 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 (Kamboj, Chaudhary, Paliwal, & Jindal, 2015). The chosen cavity was further refined utilizing side-chain minimization by choosing the add-visibility option at a limit (10,000) of steps per residue and a maximum (10,000) of global steps.

3. Results and discussions

3.1. Description of ligands structures

The desired hydrazone fragments were prepared through the coupling of chloroantranilic acid diazoniun salt moiety with acetylacetone, ethyl acetocetate and diethyl malonate in the presence of sodium acetate as a catalyst. The ¹H-NMR spectra showed triplet, quartet and singlet signals at δ 1.29–4.31 due to different methyl and methylene groups of acetylacetone, ethyl acetocetate, and diethyl malonate moieties. The three aromatic protons appeared at the normal chemical shift δ 7.06–7.98 and the signals appeared at δ 14.78–16.06 due to hydrogen-bonded N-H. The ¹³C-NMR spectra confirmed the previous data obtained, they showed signals at δ 161.09–196.79 due to different C = N and carbonyl groups. DEPT spectra were obtained to identify signals of C, CH, CH₂, and CH₃. The FT-IR spectra showed a set of bands for N-H, C = O, and C = N at their normal wavenumbers.

3.2. Description of complexes structures

The ¹H-NMR spectra of L₁Ni, L₂Ni, and L₃Ni did not display the N-H signal which indicates the coordination of the N to the metal ion. The ESI-MS (+) of L₁Ni, L₂Ni, and L₃Ni showed m/z: 370.52, 400.50 and 430.34, respectively, complexes formed via coordination between carboxyl, carboxylate group and negatively charged nitrogen with the metal ion to form stable 6-membered rings. IR spectra showed decreasing of their stretching vibration frequencies on coordination (δ C = O 1674–1717 → 1602–1622) (δ C = N 1620–1637→ 1558–1581) (Dhande, Badwaik, & Aswar, 2007; Mahmoud et al., 2018a; Mandewale, Kokate, Thorat, Savant, & Yamgar, 2016; Popov et al., 2017). Based on magnetic susceptibility results and spectroscopic data obtained, the proposed structures of the complexes are octahedral formed by the combination of metal ion with one ligand molecule and completed...
their coordination geometry by water molecules. The broadening of $^1$H-NMR spectra of L$_1$Cu, L$_2$Cu, and L$_3$Cu due to paramagnetic properties of metal ion which were proved by magnetic susceptibility measurement. Spectra showed the disappearance of the N-H signal indicating coordination between metal and negatively charged nitrogen. The elemental analysis of L$_1$Cu, L$_2$Cu, and L$_3$Cu proved that the ratio of ligand and metal ion was 1:1. They showed m/z: 375.45, 405.09 and 374.04, respectively, complexes formed via coordination between carbonyl, carboxylate group and negatively charged nitrogen with the metal ion. IR spectra showed the disappearance of the N-H stretching band and a new stretching broadband $\nu$O-H around 3316 for water moieties, carbonyl stretching frequencies were shifted to a lower frequency, $\nu$C = O (1674-1717→ 1623–1670). Based on the results obtained (Philip, Antony, Eeettinilkunnathil, Kurup, & Velayudhan, 2018; Sergienko et al., 2014; Tamayo et al., 2017), Cu ion is surrounded by penta and tetra-coordination sites with the expected square pyramid and tetrahedral structures.

The broadening of $^1$H-NMR spectra and magnetic susceptibility measurement for L$_1$Fe and L$_3$Fe indicating the paramagnetic properties of metal ion, the spectra showed that the N-H signal appeared at the same chemical shift on ligand spectrum indicating no coordination occurs through N-H group. The elemental analysis of L$_1$Fe and L$_3$Fe proved that the ratio of the ligand and metal ion is 2:1 with m/z: 399.26 and 458.94 due to [Fe+L+ NO$_3^-$]$.^+$. The complexes formed via coordination of the carboxylate groups to the metal ion. IR spectra showed decreasing of stretching frequencies of donating groups ($\nu$C = O 1683-1717→ 1623–1679) (Simonov et al., 2009), the broadband around 3316 due to OH of water moiety coordinated to Fe with expected octahedral and tetrahedral structures.

### 3.3. Theoretical modeling of the structure

The computational analyses were performed to get the molecular geometry of complexes and energy minimization studies using the Gaussian 09W software package. The expected geometries of the studied ligand and some of its complexes were fully optimized in the gas phase without any symmetry constraints.

#### 3.3.1. The geometry of the ligand

The computational results showed that the structure L$_1$ has the total energy $-1333.94$ a.u, Table 1. Calculated parameters for L$_1$ and L$_1$Cu square planar using B3lyp/6-31G*. The atomic charge on N$_1$, N$_2$, O$_5$, O$_6$, and O$_{18}$ atoms in the most stable L$_1$ structure are $-0.484526$, $-0.190864$, $-0.543205$, $-0.431758$, and $-0.594054$, respectively, which are the highest negatively charged atoms; therefore, they are the most expected chelating centers (Abdel-Latif & Mohamed, 2017; Sreejith, Nair, Table 1. Calculated parameters for L$_1$ and L$_1$Cu square planar using B3lyp/6-31G*.

| Parameters       | L$_1$ (I) | L$_1$ (II) | L$_1$ (III) | L$_1$Cu (I) square planar |
|------------------|-----------|------------|-------------|---------------------------|
| $E_{total}$, a.u.       | $-1333.94736$ | $-1333.93678$ | $-1333.93624$ | $-3050.06120$          |
| Sum of $\Delta H$, a.u. | $-1333.72326$ | $-1333.71267$ | $-1333.71099$ | $-3049.81613$          |
| Sum of $\Delta G$, a.u. | $-1333.79021$ | $-1333.78003$ | $-1333.77765$ | $-3049.89177$          |
| $E_{HOMO}$, a.u.       | $-0.09672$ | $-0.07703$ | $-0.06536$ | $-0.22602$             |
| $E_{LUMO}$, a.u.       | $0.03307$ | $0.03618$ | $0.03443$ | $-0.10016$             |
| $\Delta E_g$, ev.     | $0.12979$ | $0.11321$ | $0.09979$ | $0.32618$              |

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Table 2. Calculated parameters for L₁Ni and L₁Cu complexes using B3lyp/6-31G*. The dipole moment is 10.1252 Debye and it is highly polar and stabilized in polar solvents.

### 3.3.2. Geometry of complexes

The calculated data proved that the best geometrical structure for L₁Ni (1:1) is octahedral geometry with coordination number 6, while the best geometrical structure for L₁Cu (1:1) is that with coordination number 5 to form a square pyramid structure. Ni and Cu ions complete their coordination number by solvent molecules. The computed results revealed that the octahedral structure of L₁Ni was located as the 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 $-0.09672$ and $0.03307$ au, while those for Ni and Cu complexes become more negative leading to stabilization of the HOMO and LUMO after complexation (more negative)(Abdel-Latif & Mohamed, 2018). 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.

### 3.3.3. Antibacterial docking results

The compounds 4-chloro-2-(2,4-dioxopentan-3-ylidene)hydrazinyl)benzoic acid, (E)-4-chloro-2-(1-ethoxy-1,3-dioxobutan-2-ylidene)hydrazinyl)benzoic acid and 4-chloro-2-(1,3-diethoxy-1,3-dioxopropan-2-ylidene)hydrazinyl)benzoic acid, and their Cu(II), Fe(III), and Ni(II) complexes were synthesized and characterized and their antibacterial activities have been tested under in vitro conditions and in silico. Sodium 4-chloro-2-(2,4-dioxopentan-3-ylidene)hydrazinyl)benzoate nickel (II) (L₁Ni) and sodium (E)-4-chloro-2-(1-ethoxy-1,3-dioxobutan-2-ylidene)hydrazinyl)benzoate nickel (II) (L₂Ni) complex showed higher antibacterial activity against E. coli and Staphylococcus aureus and having the highest MolDock Score against Eco SlyD and Sau SlyD. The MolDock Scores of L₁Ni against Eco SlyD and Sau SlyD was $(-133.192)$ and $(-128.77)$, respectively. It can form 4 H-bonds with lle 42, Ser 40 & Tyr 68 Eco SlyD and 4 H-bonds with Tyr 13, Tyr 34 & Tyr 68 Sau SlyD (Yousef, Sedaghat, Simpson, Motamedei, & Dayer, 2018). Figure 5. Ligand interaction of L₁Ni complex with SlyD of (a) E. coli (b) S. aureus.

Table 3. Showed in silico docking study and in vitro antibacterial activity of selected 11C, 11E, 13B and Ciprofloxacin (CIP) with DNA Gyrase B chain. The MolDock Score of L₁Ni against Eco SlyD and Sau SlyD were $(-126.462)$ and $(-129.92)$ with Eco SlyD and Sau SlyD, respectively. It can form 4 H-bonds with Asp 24, Ile 42, Tyr 13 & Tyr 68 Eco SlyD and 7 H-bonds with Asp
In conclusion, some ligands based on chloroanthranilic acid hydrazone have been successfully synthesized and characterized by different spectroscopic methods. The complexes of Ni, Cu, and Fe have been synthesized and characterized, and then the theoretical calculations for some complexes were performed to confirm their structures and study their thermodynamic parameters using the level B3LYP/6-31G*. The magnetic moments for the complexes were calculated using Gouy’s method. The antibacterial activity was evaluated for the suggested compounds using the disc diffusion method and the results were in good agreement with those obtained from docking studies. The experimental results showed that Ni complexes have the highest biological activities against both *E. coli* and *S. aureus.*
Disclosure statement
No potential conflict of interest was reported by the authors.

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References
Abdel-Latif, S. A., & Mohamed, A. A. (2017). Synthesis, structure, spectroscopic properties and DFT studies on some 7-hydroxy-4-methyl-b-(arylazo)-2H-1-benzopyran-2-one and their complexes with some divalent transition metal ions. Journal of Molecular Structure, 1134, 307–318.

Abdel-Latif, S. A., & Mohamed, A. A. (2018). Synthesis, spectroscopic characterization, first order nonlinear optical properties and DFT calculations of novel Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes with 1,3-diphenyl-4-phenylazo-5-pyrazolone ligand. Journal of Molecular Structure, 1153, 248–261.

Akbas, E., Celik, S., Ergan, E., & Levent, A. (2019). Synthesis, characterization, quantum chemical studies and electrochemical performance of new 4,7-dihydrotrazo[1,5-alpyrimidine derivatives. Journal of Chemical Sciences, 131, 30.

Ayyannan, G., Mohanraj, M., Raja, G., Bhuvanes, N., Nandhakumar, R., & Jayabalakrishnan, C. (2016). Design, synthesis, structure and biological evaluation of new palladium(II) hydrazone complexes. Inorganica Chimica Acta, 453, 562–573.

Azhari, S. J., Salah, S., Farag, R. S., & Mostafa, M. M. (2015). Comparative studies, synthesis, spectroscopic and characterization of N-methylsatin-3-Girard’s T and P hydrazone complexes. Spectrochim Acta - Part A Mol Biomol Spectrosc, 136, 1903–1911.

Chowdhury, B., Bhowmik, B., Sahu, A., Joshi, M., Paul, S., Choudhury, A. R., et al. (2018). Phenoxazinonine synthase and antimicrobial activity by a bis(1,3-diamino-2-propenolate) cobalt(III) complex. Journal of Chemical Sciences, 130, 1–12.

Dhande, V. V., Badwaik, V. B., & Aswar, A. S. (2007). Hydrazine as complexing agent: Synthesis, structural characterization and biological studies of some complexes. Russian Journal of Inorganic Chemistry, 52, 1206–1210.

Gurbanov, A. V., Maharramov, H. A. M., Zubkov, B. F., Saijufudinov, A. M., & Fig, F. (2018). Cyanosilylation of aldehydes catalyzed by Iron (III) Arylhydrazone- b-diketone complexes. Australian Journal of Chemistry, 71(3) 190–194. doi:10.1071/CH17595

Hadi, S., Noviary, N., & Rilyanti, M. (2018). In vitro antimalarial activity of some organovin(VI)-2-nitrobenzoate compounds against plasmodium falciparum. Macedonian Journal of Chemistry and Chemical Engineering, 37, 185–191.

He, L. Y., Qiu, X. Y., Cheng, J. Y., Liu, S. J., & Wu, S. M. (2018). Synthesis, characterization and crystal structures of vanadium(V) complexes derived from halido-substituted tridentate hydrazone compounds with antimicrobial activity. Polyhedron, 156, 105–110.

Heinrich, J., Stubbe, J., & Kulak, N. (2018). Cu(II) complexes with hydrazone-functionalized phenanthrolines as self-activating metallonucleases. Inorganica Chimica Acta, 481, 79–86.

Kamboj, R. C., Chaudhary, A., Paliwal, D., & Jindal, P. (2015). Chemical science review and letters in vitro cytotoxicity evaluation and docking studies of benzofurooxepines’ derivatives against human cancer cell lines. Chemical Science Review and Letters, 2015, 502–508.

Kopylovich, M. N., Guedes Da Silva, M. F. C., Martins, L. M. D. R. S., Kuznetsov, M. L., Mahmudov, K. T., & Pomeiro, A. J. L. (2013). Synthesis, structure and electrochemical behaviour of Na, Mgly, Mnnl, Znll, Cdlland Nill complexes of 3-(2-carboxyphenylhydrazone)pentane-2,4-dione. Polyhedron, 50, 374–382.

Kopylovich, M. N., Mahmudov, K. T., MFCG, D. S., Figiel, P. J., Karbach, Y. Y., & Kuznetsov, M. L. (2011). Ortho-hydroxyphenylhydrazone-β-diketones: Tautomer. Coordination ability, and catalytic activity of their copper(II) complexes toward oxidation of cyclohexane and benzylic alcohols. Inorganic Chemistry, 50, 918–931.

Lanex, T., & Lanex, E. (2016). A molecular docking study of N-FerroenylmethylNitroanilines as potential anticancer drugs. International Journal of Pharmacology, Phytochemistry and Ethnomedicine, 2, 5–12.

Liu, K., Yan, H., Chang, G., Li, Z., Niu, M., & Hong, M. (2017). Organotin(IV) complexes derived from hydrazone Schiff base: Synthesis, crystal structure, in vitro cytotoxicity and DNA/BSA interactions. Inorganica Chimica Acta, 464, 137–146.

Mahmoud, A. G., Martins, L. M. D. R. S., Guedes Da Silva, M. F. C., & Pomeiro, A. J. L. (2018a). Copper complexes bearing C-scorpionate ligands: Synthesis, characterization and catalytic activity for azide-alkyne cycloaddition in aqueous medium. Inorganica Chimica Acta, 483, 371–378.

Mandewale, M. C., Kokate, S., Thorat, B., Sawant, S., & Yamgar, R. (2016). Zinc complexes of hydrazone derivatives bearing 3,4-dihydroquinolin-2(1H)-one nucleus as new anti-tubercular agents. Arabian Journal of Chemistry, 2, doi:10.1016/j.arabjc.2016.07.016

Mohanraj, M., Ayyannan, G., Raja, G., & Jayabalakrishnan, C. (2016). Synthesis, spectral characterization, DNA interaction, radical scavenging and cytotoxicity studies of ruthenium(II) hydrazone complexes. Journal of Photochemistry and Photobiology B: Biology, 158, 164–173.

Murase, T., Moritomo, H., Goto, A., Sugamoto, K., & Yoshikawa, H. (2005). Does three-dimensional computer simulation improve results of scaphoid nonunion surgery? Clinical Orthopaedics and Related Research, 147, 143–150.

Philip, J. E., Antony, S. A., Eeettininkunnathil, S. J., Kurup, M. R. P., & Velayudhan, M. P. (2018). Design, synthesis, antimicrobial and antioxidant activity of 3-formyl chromone hydrazone and their metal (II) complexes. Inorganica Chimica Acta, 469, 87–97.

Popov, L. D., Tkachev, V. V., Tupolova, Y. P., Borodkin, S. A., Shilov, G. V., Ugolkova, E. A., … Minin, V. V. (2017). Copper(II), nickel(II), and zinc(II) complexes with o-tozylaminobenzaldehyde 4,6-dimethylpyrimidyl hydrazone. Russian Journal of Inorganic Chemistry, 62, 893–899.

Roztoczk, K., Matoga, D., & Nitek, W. (2016). Cobalt(II) complexes with acetone isonicotinoyl hydrazone tautomers: Syntheses and crystal structures of complexes with free donor atoms. Inorganica Chimica Acta, 448, 86–92.

Roztoczk, K., Matoga, D., & Szklarzewicz, J. (2015). Copper(II) complexes with acetone picolinoyl hydrazones: Crystallographic insight into metalloligand formation. Inorganic Chemistry Communications, 57, 22–25.

Salah, S., ZHA, E-W., Farag, R. S., & Mostafa, M. M. (2014). Synthesis, characterization and modeling structures of isatin-3-Girard T (IGT) and P (IGP) hydrazone complexes. Spectrochim Acta - Part A Mol Biomol Spectrosc, 124, 579–587.

Sergienko, V. S., Ryabov, M. A., Davydov, V. V., Ryabov, M. A., Rychagina, N. V., Strashnov, P. V., & Sergienko, V. S. (2014).
Synthesis, crystal structure, and electronic structure of a copper(II) chloride complex with 9(E)-phenanthrene-9,10-dione(1Z)-3,3-dimethyl-3,4-dihydropyridine-1(2H)-ylidene hydrazone [Cu2(L-H)2Cl2]. Russian Journal of Inorganic Chemistry, 59, 927–934.

Simonov, Y. A., Bourosh, P. N., Gdaniec, M., Revenko, M. D., Palamarchuk, O. V., & Lipkowski, J. (2009). Synthesis and structure of iron(III) complexes with a new ligands based on Girard’s reagent. Russian Journal of Inorganic Chemistry, 54, 1581–1589.

Sreejith, S. S., Nair, A., Smolenski, V. A., Jasinski, J. P., & Prathapachandra Kurup, M. R. (2018). Cd(II) and Ni(II) complexes from aryl hydrazones: Unravelling the intermolecular interactions and electronic, crystal structures through experimental and theoretical studies. Inorganica Chimica Acta, 469, 264–279.

Sujamol, M. S., Sindhu, Y., Athira, C. J., & Mohanan, K. (2011). Synthesis, characterization, thermal decomposition studies and dyeing properties of some novel transition metal complexes of an azo derivative formed from 2-aminothiophene. Russian Journal of Inorganic Chemistry, 56, 1276–1283.

Tamayo, L. V., Da Silva, J. G., Quintão, M. C., Duarte, H. A., Louro, S. R. W., & Beraldo, H. (2017). Investigation on the physicochemical properties of trans- 4- stilbenecoaldehyde- derived hydrazones and their copper(II) complexes. Polyhedron, 134, 199–206.

You, Z., Yu, H., Li, Z., Zhai, W., Jiang, Y., Li, A., … Zhang, C. (2018). Inhibition studies of Jack bean urease with hydrazones and their copper(II) complexes. Inorganica Chimica Acta, 480, 120–126.

Yousefi, M., Sedaghat, T., Simpson, J., Motamedi, H., & Dayer, M. R. (2018). Bis-substituted diphenylamine aryldene hydrazones for the synthesis of new binuclear organotin(IV) complexes: Crystal structure, DNA cleavage and molecular docking. Polyhedron, 155, 153–162.