Zinc (II) complex of (Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one, a potential antimicrobial agent: Synthesis, characterization, electrochemical, antimicrobial, DFT and docking studies

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Abstract

Herein, the syntheses, characterizations, antimicrobial activities, density functional theory (DFT) predictions, and molecular docking (MD) studies are reported on (Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one (HL) and its Zn (II) complex. The deployed characterization techniques include elemental analysis, solubility and conductivity measurements, TGA, electrochemical studies, FTIR, UV-Vis, ^1H and $^{13}\text{C}\{\text{H}\}$ NMR, HRMS, and PXRD. Antimicrobial activity was studied using some Gram-positive and Gram-negative bacteria. DFT predictions were achieved using B3LYP, WB97XD and M06-2X functionals with 6-31+G(d,p) and LANL2DZ basis sets for nonmetallic and metallic atoms, respectively. The therapeutic potentials of the compounds were evaluated based on protein binding energy, ADME/T and drug-likeness properties. The experimental results revealed the formation of a complex in which two molecules of the ligand are coordinated to the zinc ion in a tetrahedral arrangement that involve the carbonyl and amino portions of the ligand. Both the ligand and the complex displayed a cyclic voltammetric behavior that is indicative of an irreversible one-electron transfer and redox diffusion-controlled process. The results of the antimicrobial study showed that the complex possesses higher antimicrobial potency than the free ligand. The B3LYP emerged as the best performing functional because it yielded the best IR spectra and geometrical parameters relative to the experimental data. The DFT predictions revealed that the complex is more reactive than the ligand, and its formation is thermodynamically feasible and exothermic. However, both the ligand and the complex showed comparable polarity. The MD results revealed the relative binding affinities of the compounds as well as their binding modes, which are in good correlation with the *in-vitro* data. Finally, drug-likeness studies showed that the studied compounds are promising therapeutic candidates.

1.0 Introduction

Schiff bases are important classes of organic compounds with numerous interesting applications [1]. They are generally synthesized via condensation reactions between amino compounds and aldehydes or ketones which produce an imine group [2]. Being one of the most widely used ligands in coordination chemistry, Schiff bases have continued to receive attention due to their facile synthesis, availability, and stability [3–6]. They coordinate with different metals through azomethine nitrogen [7–9] and their coordination chemistry plays a significant role in organic synthesis, analytical chemistry, electrochemistry, pharmaceuticals, etc. [10, 11]. Different Schiff bases present unique properties depending on the component aldehydes or ketone, but their applications remain similar due to their possession of a common (imine) functional group.

Acetylacetonate-based Schiff base ligands and their metal complexes have widespread applications in science and engineering [12–14]. The high affinity of the ligands for transition metals gives them the impetus to form stable and robust complexes with interesting applications. The acetylacetonate Schiff base considered for this study is (Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one (HL), (Fig. 1). This compound which uses acetylacetone and 4-nitro aniline as precursors had previously been reported with its crystal structure [15]. However, to the best of our knowledge after an in-depth exploration of the literature, there is no account of its complexation with Zn (II) ion and/or its biological applications either as a free ligand or in complex with the metal ion. Given the prevalence of microbial resistance to existing antibiotics [16–19], development of stronger antibiotic compounds for combating the menace of dangerous microorganisms becomes imperative. Therefore, we reported in this work the syntheses, characterizations and antimicrobial properties of (Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one (HL) and its Zn (II) complex. The aim is to develop a more potent antimicrobial agent which can be used to overcome the problem of antimicrobial resistance. The relative reactivity, polarity, and thermodynamic stability of the compounds were probed by DFT calculations, while their antimicrobial activities and therapeutic potentials were elucidated via molecular docking, ADME/T and drug-likeness studies.

2.0 Experimental

2.1 Materials

All chemicals and solvents used were of analytical grade (AR) and used without further purifications. Methanol, ethanol, diethyl ether, chloroform, hexane, dimethylformamide, dimethyl sulfoxide and zinc nitrate hexahydrate were source commercially from Sigma Aldrich.

2.2 Synthesis of the ligand: (Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one (HL)

The Schiff base ligand was synthesised using a modified form of the existing procedure [20]. To a hot methanolic (20 mL) solution of 4-nitroaniline (1.3812 g, 10 mmol, 1eq), a hot methanolic (10 mL) solution of acetyl acetone (1.0031 g, 10 mmol, 1eq) was added dropwise with constant stirring, followed by addition of five drops of formic acid to the mixture. The mixture was stirred at room temperature for 24 h, after which a yellow precipitate was formed. The solid product was washed with cold water several times and crystallised in hot methanol to give a yellow needle-like crystal (Scheme 1). Yield: 62.7% (1.36 g), mp: 140–142 °C. ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) = 2.06 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 5.44 (s, 1H, CH), 7.39 (d, 2H, J = 9.2 Hz, Ar), 8.18 (d, 2H, J = 9.2 Hz, Ar), 12.66 (s, 1H, NH); $^{13}\text{C}\{\text{H}\}$ NMR (101 MHz, DMSO- d_6): δ (ppm) = 20.1 (CH₃), 29.4 (CH₃), 100.9(CH), 121.8, 125.1, 142.6, 145.1, (ArC), 157.3 (C-N), 196.9 (C=O); IR_{ATR}: 2970, 1620, 1566, 1481, 1280, 1257, 1188, 1103, 1018, 918, 833, 786, 748, 686, 609, 516, 493 cm⁻¹; CHN Anal. Calculated for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.49; N, 12.72; found C, 59.92; H, 5.49; N, 12.87, HRMS-ESI m/z [M+H]⁺ 224.1103 (Calculated for C₁₁H₁₂N₂O₃ 221.0848).

2.3 Synthesis of bis (Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one zinc (II) complex [ZnL₂]

To a 15 mL of a methanolic solution of the ligand (0.44 g, 2 mmol, 2eq.), a 15 mL of methanolic solution of zinc nitrate hexahydrate (0.24 g, 1 mmol, 1eq) was added dropwise with continuous stirring after which three drops of triethylamine was added to adjust the pH of the solution. The mixture was refluxed at 60 °C for 12 h and the progress of the reaction was monitored by thin-layer chromatography (TLC). At the end of the reaction, the yellow solution obtained was cooled overnight in the refrigerator. The pale yellow solid product (complex) formed was filtered, washed with water, methanol, and diethyl ether, and dried in a vacuum desiccator over anhydrous calcium chloride (Scheme 2). Yield: 68.2% (0.16 g); mp: 268 °C. ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) = 1.76 (s, 3H, CH₃), 1.94 (s, 3H, CH₃), 5.09 (s, 1H, CH), 6.89 (d, 2H, J = 8.8 Hz, Ar), 8.14 (d, 2H, J = 9.2 Hz, Ar); $^{13}\text{C}\{\text{H}\}$ NMR (101 MHz, DMSO- d_6): δ (ppm) = 22.8 (CH₃), 27.7 (CH₃),

98.1 (CH), 124.6, 124.8, 143.9, 154.1, (ArC), 171.8 (C-N), 187.1 (C=O); IR_{ATR}: 1558, 1512, 1388, 1334, 1257, 1203, 1103, 1018, 933, 879, 802, 763, 709, 686, 632, 563, 509, 447, 416 cm⁻¹; CHN Anal. Calculated for C₂₂H₂₂N₄O₆Zn: C, 52.45; H, 4.40; ; N, 11.12; found C, 52.33; H, 4.37; N, 11.06. HRMS-ESI *m/z* [M-H]⁻ 501.0876 (Calculated for C₂₂H₂₂N₄O₆Zn 501.0831).

2.4 Measurements

NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts were reported as parts per million (ppm) relative to tetramethylsilane, in DMSO. All NMR analyses were conducted at room temperature. Infrared spectra were recorded on a Tensor 27 Bruker and Perkin-Elmer FT-IR spectrometer BX. Elemental analyses were performed on a VarioElementar III microbe CHN analyzer. Electronic absorption spectra in 200-800 nm range were obtained in DMF (10⁻³ M solution) on a UV-visible spectrometer at room temperature. Molar conductivities were determined in DMF (10⁻³ M solution) at room temperature using a Jenway model 4070 conductivity meter. Powder X-ray diffraction (PXRD) data were collected at 40 KeV, 15 mA on a RigakuMiniFlex 600 Benchtop diffraction using Cu-Kα radiation (λ = 1.5418Å) over 2θ range of 0-80 °C at room temperature. Thermogravimetric analysis (TGA) was carried out on a TGA-Q600 thermoanalyzer with a heating rate of 10 °C min⁻¹ under nitrogen flow. Finally, high-resolution mass spectra (HRMS) were obtained using WatersAcquity UPLC Synapt G2 HD mass spectrometer.

2.5 Electrochemical Studies

The electrochemical measurements were carried out using a Biologic SP-200 Computer-controlled electrochemical measurement device with a potentiostat. A three-electrode system comprising of a glassy carbon working electrode, a platinum wire counter electrode and a saturated Ag/AgCl in KCl reference electrode was used for this study with a 0.01 M phosphate buffer solution (PBS) of pH 7.4 as a supporting electrolyte.

2.6 Biological Evaluation

2.6.1 *In-vitro* Antimicrobial Activity

The synthesized ligand and its complex were evaluated for antimicrobial activity against *Staphylococcus aureus* ATCC-25923 (Sa), *Streptococcus pyogenes* ATCC-19615 (Sp) *Escherichia coli* ATCC-25922 (Ea), and *Klebsiella pneumoniae* ATCC-13883 (Kp), using a modified filter paper disc agar diffusion method [21, 22]. The activities of the compounds towards the selected bacteria were rated relative to a standard (streptomycin). A disc of blotting paper was impregnated with different concentrations of the standard and the synthesized compounds. The disc containing the test compounds were placed on a plate of sensitivity-testing agar after inoculation of the organism and then incubated at 37°C for 24 h. The inhibition zone was recorded in millimetres using a transparent meter rule [23, 24]. The test was conducted in triplicate and the results were presented as mean ± SEM.

2.6.2 Determination of Minimum Inhibitory Concentration (MIC)

The MIC of the compounds was assessed using the broth micro dilution method [25]. Each test compound and the control were dissolved in DMSO (Fisher Chemicals) to give a stock solution. This was serially diluted two-fold in Mueller-Hinton Broth (MHB) to obtain a concentration range of 512 to 0.250 µg.mL⁻¹. 100 µL of each concentration was introduced into a well (96 well micro titre plates) containing 90 µL of MHB and 10 µL of inoculums (1 × 10⁶ CFU.mL⁻¹) of the bacteria were added to obtain a final concentration range of 250 to 0.125 µg.mL⁻¹. The plates were covered and incubated at 37°C for 24 h. MICs were assessed visually after the corresponding incubation period and were taken as the lowest sample concentration at which there was no microbial growth. Streptomycin (Sigma-Aldrich, Steinem, Germany) was used as positive controls, while broth with 20 µL of DMSO was used as a negative control to determine their influence on the biological systems. The assay was repeated thrice.

2.7 Computational Studies

2.7.1 DFT Calculations

The DFT study is primarily focused on predicting the relative reactivity, polarity, and thermodynamic stability of the synthesized complex. For this purpose, the performances of three high-level functional namely: B3LYP, WB97XD, and M06-2X were assessed based on their capacity to reproduce the experimental IR spectra of both the ligand and the complex. B3LYP is a hybrid functional derived from Becke exchange [26] and Lee-Yang-Parr correlation functional [27]. WB97XD is dispersion corrected functional developed by Head-Gordon and co-workers [27, 28], while M062X is a hybrid meta-GGA functional of the Truhlar group [29]. These functional were used in conjunction with 6-31+G(d,p) and LANL2DZ basis sets for describing nonmetallic and metallic atoms, respectively [30]. Solvent phase calculations were performed implicitly in methanol using the integral equation formalism polarizable continuum model (IEFPCM) [31]. All DFT calculations were performed using Gaussian 09 program with GaussView 05 as the visualizer [32].

The geometries of the ligand and the complex were built, refined and fully optimized without symmetry imposition. No imaginary frequency was present in their vibrational frequency data. The predicted IR spectra of the ligand and the complex were obtained, and the absolute deviations (IR_{Dev}) from the experimental data were calculated using Equation 1. Relative reactivity was determined based on HOMO-LUMO energy gap (ΔE) and electro negativity (χ) calculated using Equations 2 and 3 [33, 34]. The polarity hence, the solubility of the compounds was predicted based on their dipole moment magnitudes. Thermodynamic stability was predicted from the change in free energy of complex formation (ΔG) obtained from the changes in enthalpy (ΔH) and entropy (ΔS) at 298.15 K using Equation 4.

$$IR_{Dev} = |IR_{Predicted} - IR_{Expt}| \quad (1)$$

$$\Delta E = E_{LUMO} - E_{HOMO} \quad (2)$$

$$\chi = \frac{1}{2} (E_{LUMO} + E_{HOMO}) \quad (3)$$

$$\Delta G = \Delta H - T\Delta S \quad (4)$$

2.7.2 Molecular docking studies

2.7.2.1 Preparation of the synthesized compounds and the selected bacteria proteins for docking

The molecular docking studies were performed on PyRx software program (version 0.8) installed on a window 10 ultimate PC with Intel Core i5-7200U processor, 8 GB memory, and 64-bit operating system. Open Babel widget, as part of the PyRx software, was used to import the structure of the synthesized compounds (((Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one) and its zinc complex) and the reference drug, streptomycin. The compounds were energy minimized with the Universal Force Field (UFF) geometry using the conjugate gradient optimization algorithm, and the total number of steps was set at 200. Thereafter the minimized structures were converted to a ready-to-dock PDBQT format [35, 36]. To study the binding affinity and interaction profiles of HL and ZnL₂, protein targets representing the key virulence factors in *S. aureus*, *S. pyogenes*, *K. pneumonia*, and *E. coli* were identified as reported by previous studies [37, 38]. The crystal structures of the proteins (Table 1) were retrieved from the protein data bank (<http://www.RCSB.org>) [39], and prepared for docking using the dock prep toolbar on UCSF Chimera (<https://www.cgl.ucsf.edu/chimera/>) [40]. The resultant prepared proteins were saved in PDB format, imported into PyRx software, and converted to a ready-to-dock macromolecule PDBQT file format [35].

Table 1
Description of the selected protein targets in the studied bacteria.

Bacterial	Virulence factor	Target protein	PDB ID
<i>S. aureus</i>	Enterotoxin	Staphylococcal enterotoxin type A	1ESF
<i>S. pyogenes</i>	Surface protein M	Group A streptococcal M protein	6OG4
<i>K. pneumonia</i>	Siderophore	Aerobactin synthetase lucC	6CN7
<i>E. coli</i>	Toxin	Shiga toxin type 2	1R4P

2.7.2.2 Docking

The prepared compounds were docked separately into each protein using the built-in AutoDockVina tool in the PyRx working environment in line with the procedures described by Shaker *et al.* [41]. The AutoDockVina is the choice for this docking study due to its efficient, reliable, and accurate scoring function [42, 43]. The auto generated grid box was adjusted to enclose the active site residues and their surroundings. Docking was run at exhaustiveness of 8, with other parameters kept as default. The conformation with the lowest (i.e., most negative) binding energy (kcal/mol) was selected and analyzed using PyMol (version 2.5) software [44].

2.7.3 ADME-Toxicity and Drug-likeness studies

2.7.3.1 Physicochemical, pharmacokinetics, and drug-likeness analysis

This study was performed using the SwissADME web tool (<http://www.swissadme.ch/>) developed by the Swiss Institute of Bioinformatics [45, 46] and OSIRIS DataWarrior software [45–47]. The two-dimensional structures of the compounds were prepared using ChemDraw [48], converted to SMILES structures, and then pasted into the Swiss ADME webserver. Key physicochemical properties such as molecular weight, lipophilicity, hydrogen bond counts, polar surface area, etc., were calculated while the drug-likeness properties of the compounds were estimated based on the Lipinski's rule of five (RO₅) and Veber's rule as described in previous studies [49, 50]. Finally, the pharmacokinetic parameters namely: absorption, distribution, metabolism, and excretion (ADME), and toxicity (T) of the compounds were determined to predict the fate of the compounds in human subjects [46].

3.0 Results And Discussion

The Schiff base (HL) was synthesized by the condensation of 4-nitroaniline and acetylacetone in methanolic solution at room temperature in a 1:1 mole ratio. The corresponding Zn (II) complex was obtained after the reaction of the ligand with zinc nitrate hexahydrate in a 1:2 mole ratio of metal to the ligand. Both the ligand and the complex gave moderate yield and are stable at room temperature. The ligand and the complex were obtained as yellow and light-yellow compounds, respectively. The ligand is soluble in methanol, ethanol, acetonitrile, DCM, DMF, DMSO while the complex is only soluble in acetonitrile, DMF, and DMSO. Spectroscopic and analytical data obtained are in good agreement with the proposed structures and molecular formula (MF) (Table 2). The positions of the molecular ion peaks in the mass spectra of the ligand and the complex are consistent with their molecular weights (MWt) and formula. The molar conductivity (K) value of 15.3 Ω⁻¹cm²mol⁻¹ obtained for the complex in DMF (Table 2) suggests that the complex is less electrolytic in this solvent [51].

Table 2
The analytical and physical data of the ligand and its Zn (II) complex

Compound	MF (Mwt)	Colour	Yield % (g)	m.p/d.p °C	Elemental analysis (Calc.) found			K($\Omega^{-1}\text{cm}^2\text{mol}^{-1}$)
					C	H	N	
HL	C ₁₁ H ₁₁ N ₂ O ₃ (220.0848)	Yellow	62.7 (1.36)	140–142	59.92 (59.99)	5.47 (5.49)	12.70 (12.72)	–
[ZnL ₂]	C ₂₂ H ₂₂ N ₄ O ₆ Zn (502.0831)	Pale yellow	68.2 (0.16)	238	52.33 (52.45)	4.37 (4.40)	11.06 (11.12)	15.3

3.1 ¹H and ¹³C{H} NMR

The ¹H NMR and ¹³C{H}NMR data obtained for HL and its Zn (II) complex in DMSO-d₆ are presented in Table 3 while the corresponding spectra are provided as Fig. S1-S4 in the Supporting information. The ¹H NMR spectrum of the ligand shows a single broad peak downfield 12.66 ppm, corresponding to the proton of the amine group (N-H). The protons of the methyl substituent in the ligand appear upfield between 2.06 and 2.22 ppm as singlet due to differences in chemical environments as a result of the involvement of the carbonyl group in the formation of β -ketoamine. The vinylic proton appeared as a singlet at 5.44 ppm.

The ¹³C{H}NMR spectrum of the ligand presents a signal for the sp² carbon of the ketone functional group at 196.98 ppm, the sp³ carbon of the amine function at 157.31 ppm, the vinylic carbon at 100.99 ppm and the aromatic carbons of the phenyl ring at 121.84-145.18 ppm. Upon complexation with Zn (II) ion, significant changes in the ¹H NMR spectrum were observed. The methyl protons which initially appeared as singlet at 2.06 and 2.22 ppm shifted to 1.76 and 1.94 ppm, respectively in the complex, and integrating to three protons, each in a different chemical environment. The appearance of these protons upfield as compared to their position in the free ligand suggests that the coordination to the metal ion occurred through the oxygen and nitrogen atoms of the carbonyl and amine. The vinylic proton also shifted upfield at 5.09 ppm due to complexation. The complete disappearance of the amine proton signal from the spectrum of the complex indicates that the ligand is deprotonated before coordination to the metal ion. The aromatic protons appeared upfield as duplets with each integrating into two protons. These changes in the positions of the proton signals confirm the formation of the complex.

Similarly, the ¹³C{H}NMR spectrum of the complex shows substantial changes in the positions of the carbon signals upon complex formation. The carbon atoms of methyl groups appear at 22.8 and 27.7 ppm, the vinyl carbon at 98.0 ppm and the aromatic carbon at 124.6-154.1 ppm. In addition, the sp³ carbon of the imine function shifted downfield to appear at 171.8 ppm against the 157.3 ppm observed for free ligand while the sp² carbon of the ketone functional group shifted upfield to appear at 187.1 ppm as opposed to the 196.9 ppm obtained for the ligand (Table 3). The changes in the positions of these two carbons confirm the involvement of the amine nitrogen and the carbonyl oxygen in coordination.

Table 3
The ¹H and ¹³C{H}NMR data of the ligand and its Zn (II) complex

¹ H NMR data						
HL	^a CH ₃	^b CH ₃	CH	2H–Ar	2H–Ar	1H–NH
Chemical shift (ppm)	2.06	2.22	5.44	7.39	8.18	12.66
[ZnL ₂]	^a CH ₃	^b CH ₃	CH	2H–Ar	2H–Ar	–
Chemical shift (ppm)	1.76	1.94	5.09	6.89	8.14	–
¹³ C{H}NMR						
HL	20.1	29.4	100.9	121.8, 125.1, 142.6, 145.1	157.3	196.9
Chemical shift (ppm)	^a CH ₃	^b CH ₃	CH	Aromatic	C–N	C=O
[ZnL ₂]	22.8	27.7	98.1	124.6, 124.8, 143.9, 154.1	171.8	187.1
Chemical shift (ppm)	^a CH ₃	^b CH ₃	CH	Aromatic	C–N	C=O

3.2 Infrared spectral studies

The most significant IR absorption bands of HL and its Zn (II) complex are listed in Table 4 while the IR spectra of the compounds are depicted in Fig. 2. The presence of a free –NH₂ group in a molecule is signalled by the appearance of an absorption band at 3400 cm^{–1} [52, 53]. However, the absence of this band from the spectra of the ligand and the presence of a new broad band around 3100 cm^{–1} which is assignable to N–H stretching vibration confirm the successful formation of β -ketoamine, not β -ketoimine [54]. Other supporting evidence include the appearance of ν (C=O) band at 1620 cm^{–1}, the ν (C–N) band at 1526 cm^{–1} and the absence of a ν (C=N) band around 1690-1640 cm^{–1}.

The IR spectrum of the complex differs significantly from that of the free ligand (Fig. 2). The $\nu(\text{N-H})$ band initially observed at 3100 cm^{-1} for the free ligand is completely absent in the complex due to deprotonation of the amine group and subsequent coordination to the metal ion through the nitrogen. The shift of $\nu(\text{C-N})$ and $\nu(\text{C=O})$ bands from 1526 cm^{-1} to 1334 cm^{-1} and from 1620 cm^{-1} to 1504 cm^{-1} , respectively confirm the involvement of the carbonyl oxygen and the amine nitrogen atom in the coordination. The presence of two new bands at 428 cm^{-1} and 563 cm^{-1} , assignable to $\nu[\text{M-N}]$ [55–57] and $\nu[\text{M-O}]$ [12, 58–62], respectively, further confirms the involvement of the amine and the carbonyl groups in the formation of the complex. The result of the theoretical IR data correlates well with this experimental data.

Table 4

IR spectral bands (cm^{-1}) of ligand and its Zn (II) complex

Compound	(N-H)	(C=O)	(C-N)	(Zn-O)	(Zn-N)
HL	3101	1620	1526	–	–
[ZnL ₂]	–	1504	1334	563	428

3.3 Electronic absorption spectra

The electronic absorption spectra of the free ligand and the complex are shown as Fig. 3 while the spectral data are presented in Table 5. The ligand displayed two bands at 280 and 320 nm, due to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions. The Zn (II) complex showed two distinct bands at 310 and 380 nm which are assignable to charge transfer from ligand to metal ion (LMCT) in a tetrahedral geometry [63–65]. Zinc complexes are generally diamagnetic due to the filled d-orbital. Hence, a d–d transition possibility is ruled out. The molar extinction coefficients (ϵ) of the ligand and complex were found to be $4000\text{ cm}^{-1}\text{mol}^{-1}$, respectively which correlate well with the observed colours (Table 2).

Table 5

Electronic absorption spectral data of the ligand and its Zn (II) complex

Compound	Wavelength (nm)	Wave number (cm^{-1})	ϵ ($\text{cm}^{-1}\text{mol}^{-1}$)	Band assignment	Geometry
HL	280	35714	4000	$\pi\rightarrow\pi^*$	–
	320	31250		$n\rightarrow\pi^*$	
[ZnL ₂]	310	32258	2000		Tetrahedral
	380	26316			

3.4 Thermal Analysis

Thermal analysis is a useful technique for the determination of the crystal water content of complexes as well as their thermal stability/decomposition pattern under controlled heating. The thermal behaviours of the ligand and its complex as a function of temperature were studied by thermogravimetric analysis (TGA) over a temperature range of 20–800 °C. The profiles obtained which are depicted in Fig. 4 show the weight losses recorded over the studied temperature range. The decomposition profile of the ligand shows a two-step process: loss of $-\text{C}_{11}\text{H}_{12}\text{NO}^*$ radical at 0–280 °C and loss of the inorganic residue containing NO_2 at 300–700 °C. On the other hand, the thermogravimetric profile of the complex shows a three-step process beginning with loss of the moisture content of the complex at 0–100 °C, followed by loss of two ligand molecules at 240–330 °C and finally, the loss of inorganic residue containing NO_2 coupled with the formation of ZnO at 330–700 °C. It can thus be inferred from these results that both the ligand and the complex possess good thermal stability with the latter being more stable.

3.5 X-ray powder diffraction studies

An X-ray powder diffraction study was carried out on the synthesized compounds. The compounds were scanned in the range $2\theta = 0\text{--}80^\circ$ at a wavelength of $15406\text{ \AA}$, and the resulting diffraction patterns are shown in Fig. 5 which suggests that both the ligand and complex are crystalline. However, the peaks of the complex are more clearly resolved compared to the ligand's which might be due to the relatively smaller crystallite size of the complex. Generally in smaller crystallites, there are not enough planes to produce destructive interference hence, broad space exists between their spectral peaks [66].

3.6 Mass Spectra

To further confirm the formation of the Schiff base (HL) and its Zn (II) complex, the compounds were studied using ESI-MS. The proposed molecular formula of the ligand and its complex were ascertained by comparing them with m/z values. In the spectrum of the ligand, the molecular ion peak: $m/z [\text{M}+\text{H}]^+$ was found to be 224.1103 (Fig. S5) while the spectrum of the complex showed molecular ion peak: $m/z [\text{M}-\text{H}]^-$ at 501.0876 (Fig. S6). These data are in good agreement with the proposed molecular formula of the compounds. In addition, the mass spectrum of the ligand shows a single peak, suggesting that the compound is highly stable, while the spectral peaks of the complex confirm its decomposition profile as revealed by thermal analysis.

3.7 Electrochemical studies

To investigate the electrochemical properties of the synthesized compounds and hence predict their bioactivity, the redox behaviors of both the ligand and the complex were studied by cyclic voltammetry (CV) in a 0.01 M PBS electrolyte at scan rates 20, 40, 60, 80 mV/s. The results obtained are displayed as Fig. 7C and 7D for the ligand and the complex, respectively. The single reductive wave observed for the ligand between -0.5 V and 2.0 V potentials (Fig. 7C) is

indicative of a one-electron transfer reduction process involving the amine proton (NH). The reductive wave produced by the complex can be attributed to the reduction of Zn^{2+} to Zn^+ , which is an irreversible one-electron transfer process [66, 67]. The dependence of the peak potential on scan rates indicates that only one electron is transferred, while the linearity of the plots of reduction peak current, I_{pc} against scan rate, v for both the ligand and complex suggests that the electrode process was controlled by adsorption [68]. These results generally revealed that both the ligand and the complex are electrochemically active and will hence show appreciable biological activity.

3.8: In vitro antibacterial activity

The results of antibacterial screening of the ligand, the complex and the reference drug (streptomycin) obtained at concentrations of 10–30 µg/mL using the Agar diffusion method [69] are presented in Fig. 8 while the images of the culture plate are shown in Fig. S7 of the SI file. It is evident from the figures that the complex is more active against the tested organisms than the ligand and the reference drug. The complex appears to be more sensitive to the Gram-positive strains than the Gram-negative ones probably due to the variations in the complexities of the cell walls of the organisms. The zones of inhibition obtained shows that the antibacterial effect of the complex follows the order *S. aureus* > *S. pyogene* > *K. pneumoniae* > *E. coli*. A similar trend is observed for the ligand with reduced zone of inhibition compared to the complex. This suggests that the complexation of the ligand with Zn (II) ion leads to enhanced bioactivity. Finally, the variation in the activity of the complex as a function of microbial strain could be attributed to varying degrees of cell permeability or difference in ribosome [70].

3.8 Minimum inhibitory concentration (MIC)

To further evaluate the antimicrobial potentials of the synthesized compounds, the minimum inhibitory concentrations (MIC) of the compounds were determined and compared with that of streptomycin. The images of the study plates are presented as Fig. S8 in the SI file. The data obtained (Table 6) reveal that the ligand exhibit moderate activity on the tested organisms. The ligand gave MIC of 64 µg/mL for *S. aureus* (Sa) and *S. pyogene* (Sp), and 128 and 256 µg/mL for *K. Pneumoniae* (Kp) and *E. coli* (Ec), respectively. The reference drug yielded MIC values of 8 and 16 µg/mL for Sa and Sp, and 32 and 128 µg/mL for Kp and Ec, respectively. However, the best MIC values were obtained with the complex. This result indicates that complexation increases the activity of the compound.

Table 6 Minimum inhibitory concentrations (MIC) (µg/mL) of the compounds				
Compound	Sa	Sp	Kp	Ec
HL	64	64	128	256
[ZnL ₂]	4	4	16	64
Streptomycin	8	16	32	128

3.9 DFT Calculations

3.9.1 Geometry optimization

The optimized geometries of ZnL₂ obtained with B3LYP, WB97XD and M06-2X functional are shown in Fig. 9. From this figure, the values of a set of equivalent bond angles are listed in Table 7 to compare the relative performances of the functional in predicting the geometry of the complex as proposed experimentally. These include N₂–Zn–O₄ and N₃–Zn–O₅, N₂–Zn–O₅ and N₃–Zn–O₄, and O₄–Zn–O₅ and N₂–Zn–N₃. Comparison of these pairs of bond angles in Table 7 shows that the B3LYP is the best performing functional as it yielded the most perfect geometry with the tetrahedral characteristics of a typical zinc (II) complex. The prediction strengths of the functional follow the order B3LYP > WB97XD > M06-2X.

Table 7 Selected bond angles in ZnL ₂			
Bond angle(°)	B3LYP	WB97XD	M06-2X
∠N ₂ –Zn–O ₄	93.68	92.92	93.14
∠N ₃ –Zn–O ₅	93.71	92.93	93.15
∠N ₂ –Zn–O ₅	113.96	122.88	117.12
∠N ₃ –Zn–O ₄	113.84	122.94	115.52
∠O ₄ –Zn–O ₅	121.28	117.00	122.88
∠N ₂ –Zn–N ₃	122.78	110.68	117.18

3.9.2 Predicted IR spectra

The IR spectra and absorption frequencies obtained from DFT calculations in methanol for both the ligand and the complex are given as Fig. S9 and Table S1, respectively in the Supporting Information file. The absolute deviations from the experimental values given in Table 4 are listed Table 8. On the average, this table clearly shows that the B3LYP model produced the least deviations and the performance strength of the functional follows the order M06-2X < WB97XD < B3LYP.

Table 8
Absolute deviations of predicted frequencies from experimental values in methanol.

Model	N-H	C=O	C-N	Zn-O	Zn-N
HL					
B3LYP/6-31+G(d,p)	138	12	24	–	–
WB97XD/6-31+G(d,p)	264	22	51	–	–
M06-2X/6-31+G(d,p)	279	94	48	–	–
[ZnL₂]					
B3LYP/6-31+G(d,p)	–	65	13	18	2
WB97XD/6-31+G(d,p)	–	52	14	29	10
M06-2X/6-31+G(d,p)	–	54	18	32	24

3.9.3 Reactivity properties of the studied compounds

Based on the outcome of geometry optimization and IR spectra prediction, the best performing functional (i.e. B3LYP) was selected for the reactivity and thermodynamic studies, and the results obtained are presented in Table 9. The HOMO and LUMO charge density graphics are shown in Fig. 10 for both the ligand and the complex. HOMO (i.e. highest occupied molecular orbital) is the orbital through which a molecule gives electron to an acceptor while LUMO is the one used for accepting an incoming electron. The higher the HOMO energy (E_{HOMO}), the greater the ease of giving electron, and the lower the LUMO energy, the higher the likelihood of accepting an incoming electron. Thus, the E_{HOMO} and E_{LUMO} data in Table 9 suggest that the complex will be a better electron donor and a better electron acceptor than the free ligand.

The energy of the LUMO relative to the HOMO gives the overall reactivity/stability of the molecule. The higher the HOMO-LUMO energy gap (ΔE_{HL}), the lower the reactivity and the higher the stability, and *vice versa*. The ΔE_{HL} values in Table 9, therefore suggest that the complex is relatively more reactive than the ligand. However, both of them are predicted to have similar degrees of polarity hence, solubility as informed by their dipole moment (μ) values (Table 9).

Table 9
Reactivity and thermodynamic parameters obtained for the ligand and the complex

Compound	Reactivity indices				Thermodynamic properties		
	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE_{HL} (eV)	μ (Debye)	ΔH (kJmol ⁻¹)	ΔS (kJmol ⁻¹)	ΔG (kJmol ⁻¹)
HL	-6.385	-2.875	3.510	6.96	-	-	-
ZnL₂	-6.204	-2.903	3.301	6.95	-1083.3	-348.72	-979.33

The HOMO and LUMO electron density isosurfaces reveal the parts of a molecule which are involved in donation and acceptance of electrons, respectively. The HOMO isosurfaces of the ligand (Fig. 10A) therefore indicates that donating molecular orbital is distributed over the entire ligand structure with the exception of the methyl substituent, while the LUMO isosurfaces shows that the accepting orbital is mainly concentrated around the nitro phenyl portion of the molecule (Fig. 10B). On the other hand, the HOMO isosurfaces of the complex is centered on the delocalized pi network between the carbonyl and the pseudo imine group of the attached ligand while the LUMO isosurfaces is spread over the nitro phenyl portions of the complex.

3.9.4 Predicted thermodynamic properties of the complex at 298.15 K

Inspection of the thermodynamic parameters in Table 9 shows that the formation of ZnL₂ is exothermic since it involves the formation of new bonds between Zn (II) ion and two molecules of HL as indicated by the negative change in the enthalpy of formation (ΔH). The negative change in entropy (ΔS) implies that the complex formation is an associative process that resulted in a decrease in disorderliness in the system. The negative change in Gibb's free energy suggests that the formation of ZnL₂ from Zn (II) ion and HL is highly spontaneous as it leads to increased stability.

3.10 Molecular docking

The combination of *in silico* and *in vitro/in vivo* experimental processes has been described as an interesting strategy in the design and development of drug candidates [71]. In this study, the newly synthesized compounds were docked against key representative proteins in all the studied bacteria to predict their therapeutic potentials. Their free binding energies and conformations were determined and compared with that of the known antibacterial drug, streptomycin. The result presented in Table 10 shows that ZnL₂ might be a promising therapeutic candidate as revealed by its highest negative binding energy (ranging from -6.3 to -7.5 kcal/mol) for the different proteins. The compound, HL showed docking scores ranging from -5.4 to -7.1 kcal/mol, which was better than the interaction of streptomycin particularly in 6CN7.

Table10: The binding affinities of the compounds with the studied proteins.						
HL			ZnL ₂		Streptomycin	
PDB ID	BE (kcal/mol)	H-bond forming residue	BE (kcal/mol)	H-bond forming residue	BE (kcal/mol)	H-bond forming residue
1ESF	-5.4	Thr145, Asn146, Thr88	-6.3	Asn195	-5.6	Asn195, Gly200, Asp197
6OG4	-5.3	Lys223, Ala105, Ser112	-7.0	Val78	-5.9	Asn207, Lys208, Glu172, Glu103
6CN7	-7.1	Gln356, Arg145	-7.5	Gln424	-6.6	His422, Trp550, Asn425, Ser257, Arg259
1R4P	-6.7	Trp202, Gly203, Thr114	-7.3	Lys233	-6.6	Glu259, Asp94, Tyr77, Leu200, Asp111, Try114

The result for the binding interaction as displayed in Figure 11 shows that the oxygen atoms of the nitro group of the HL shared at least one hydrogen bond with the residues of the various proteins.

Similarly, Figure 12 also shows that the oxygen atoms of both nitro and carbonyl groups of the ZnL₂ participated in the sharing of at least two hydrogen bonds with the amino acids of the various studied proteins. There was no comparable interaction observed between the standard drug molecule (Fig. 13) and the synthesized compounds except for ASN195 residue of 1ESF which participated in the complex formed with both ZnL₂ and streptomycin. Overall, the binding mode and interactions of the synthesized compounds across the proteins were different and stronger than the standard drug molecule (Fig. 13). The involvement of different residues in the interactions could also suggest that the synthesized compounds might have a different mechanism of action from the known drug, streptomycin.

3.11 Drug-likeness and pharmacokinetic properties of the compounds

The calculated physicochemical properties and drug-likeness parameters of the synthesized compounds are enlisted in Table 11. Lipinski's requirements that an orally active molecule should not violate any two of the physicochemical parameter range of MW ≤ 500, cLog P ≤ 5, HBDs ≤ 5, and HBAs ≤ 10. Veber also described that TPSA and nRTBs values not more than 140 Å² and 10 respectively as efficient and selective criteria for oral bioavailability [48].

Table 11
Selected molecular and physicochemical properties of the synthesized compounds

Ligands	MW (≤500)	cLogP (≤ 5)	HBAs (≤ 10)	HBDs (≤ 5)	TPSA (≤ 140 Å ²)	nRTBs (≤ 10)	LogS	SA	RO ₅ rule	Veber rule
HL	220.22	1.6093	3	1	74.92 Å ²	4	-2.78	2.40	Yes	Yes
ZnL ₂	503.81	2.5486	6	0	132.26 Å ²	4	-5.67	5.38	Yes	Yes
MW: Molecular weight, cLogP: calculated log of octanol/water partition coefficient, HBAs: Hydrogen bond acceptors, HBDs: Hydrogen bond donors, TPSA: Total polar surface area nRTBs: Number of rotatable bonds, Log S: log of solubility. RO ₅ ; Rule of five.										

Furthermore, LogS has been described as one of the key parameters that facilitate the developmental activities of orally administered drugs [72, 73]. In this study, both HL and ZnL₂ complied with the RO₅ and Veber's rule. The LogS values also showed that both compounds might be soluble in water. The results, therefore, imply that they have the prospect for good absorption and permeability across the membrane. Furthermore, the synthetic accessibility scores, 2.40 and 5.38 for HL and ZnL₂, respectively revealed that their molecular fragment might be easily obtainable.

The pharmacokinetic properties of the compounds are described in Table 12. The results suggest that HL might be well absorbed while both compounds were predicted as non-P-substrates and they both showed the potential to penetrate the BBB. The compound, ZnL₂ showed inhibition of most of the CYP450 isozymes including CYP1A2, 2C19, and CYP3A4 while only CYP1A2, and CYP2C19 isozymes were inhibited by HL. Toxicity profiling showed that HL and ZnL₂ possess the risk of reproductive effects. This result implies the need for a more in-vitro assessment of the safety of these compounds.

Table 12
Selected pharmacokinetic properties of the synthesized compounds

Compounds	GI absorption	P-gp substrate	BBB permeant	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Mutagenic	Tumorigenic	Reproductive effects
HL	High	No	Yes	Yes	Yes	No	No	No	No	High	No
ZnL ₂	Low	No	Yes	No	Yes	Yes	No	Yes	No	High	No
GI: Gastrointestinal, P-gp: p-glycoproteins, BBB: Blood-brain barrier, CYP: Cytochrome P450											

4.0 Conclusion

(Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one (HL) and its Zn (II) complex have been successfully synthesized, characterized and screened for antibacterial activity and therapeutic property. The following is the summary of the key findings:

1. The parts of the ligand responsible for coordination with the zinc ion are the nitrogen atom of the amine group and the oxygen atom of the carbonyl.
2. Electronic absorption spectra favors a tetrahedral geometry around the metal ion, and this is supported by evidence from DFT calculations.
3. The complex has low molar conductivity value hence, it is a weak electrolyte.
4. Cyclic voltammetric measurement revealed that both the ligand and the complex undergo an irreversible one-electron transfer and redox diffusion-controlled process.
5. *In vitro* antibacterial study revealed that the complex is more biologically active than the ligand and the reference drug (streptomycin).
6. The complex is predicted to be more reactive than the ligand and its formation is exothermic and thermodynamically feasible.
7. B3LYP emerged as the best DFT method for calculating the properties of the synthesized compounds.
8. The results of the docking studies revealed that the complex had the highest binding energies across the bacteria proteins, supporting the *in vitro* activities.
9. The drug-likeness properties of the compounds also showed good compliance with the criteria for selecting oral drugs.
10. Finally, these compounds can be utilized for the development of multi-targeted antimicrobial agents.

Declarations

Authors' contribution statement

All authors participated in the Conceptualization, Data curation, Formal analysis, Interpretation, Review and Editing. Mala G., Nasir H. and Waziri I.: Material preparation, Data collection, Analysis, Writing, Review and Editing - original draft. Wahab O.O.: Computational software, DFT calculations, Data collection, Analysis, Validation, Writing, Review and Editing - original draft. Oselusi S.O. and Egieyeh S.A.: Molecular docking, Writing, Review and Editing - original draft.

Declaration of competing interest

The authors declare no conflict of interest.

Supporting information

The supporting data associated with this article can be found in the online version at.....

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Scheme

Scheme 1 & 2 is available in the Supplementary Files section.

Figures

Figure 1

The structure of ((Z)-4-((4-nitrophenyl) amino) pent-3-en-2-one) (HL)

Figure 2

Plot of FTIR spectra of the ligand and its complex

Figure 3

Plot of the electronic absorption spectra of the ligand and the complex

Figure 4

Plots of the TGA spectra of HL (A) and ZnL_2 (B).

Figure 5

The PXRD spectra of the ligand and its complex.

Figure 6

Proposed structure of the complex

Figure 7

Cyclic voltammograms of HL (C) and ZnL_2 (D). Inset: calibration curve of I_{pc} versus v at scan rates 20, 40, 60, and 80 mV/s in 0.01 M PBS, pH 7.4.

Figure 8

Comparison of *in vitro* antimicrobial activities of the ligands, the complex and the control drug on the studied Gram-positive and Gram-negative bacteria at a concentration of 10 µg/mL (A), 20 µg/mL (B), and 30 µg/mL (C); Sa: *S. aureus*, Sp: *S. pyogenes*, Ec: *E. coli*, and Kp: *K. pneumoniae*.

Figure 9

The optimized geometries of ZnL_2 . Hydrogen, zinc, carbon, nitrogen and oxygen are coloured white, purple, grey, blue and red, respectively.

(A)

(B)

Figure 10

Charge density isosurfaces of the HOMO (A) and the LUMO (B) of both the ligand (left) and the complex (right) as obtained from B3LYP calculation.

Figure 11

The interaction diagrams of HL with the different proteins. Figures a, b, c, and d present the polar (blue lines) and non-polar (pink lines) residues of 1ESF, 6OG4, 6CN7, and 1R4P, respectively that were involved in the interaction. The yellow lines within the complexes represent hydrogen bonds and their respective distance.

Figure 12

The binding modes and interactions of ZnL_2 with the proteins. Figures a, b, c, and d present the polar (blue lines) and non-polar (pink lines) residues of 1ESF, 6OG4, 6CN7, and 1R4P, respectively that were involved in the interaction. The yellow lines within the complexes represent hydrogen bonds and their respective distance.