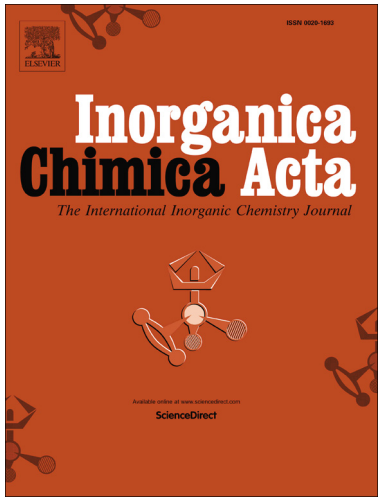

Research paper

Synthesis, Structural Characterization, Antimicrobial and DNA binding studies of homoleptic zinc and copper complexes of NO Schiff bases derived from homoveratrylamine

C.E. Satheesh, P. Raghavendra Kumar, N. Shivakumar, K. Lingaraju, P. Murali Krishna, H. Rajanaika, Amar Hosamani

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Synthesis, Structural Characterization, Antimicrobial and DNA binding studies of homoleptic zinc and copper complexes of NO Schiff bases derived from homoveratrylamine

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Abstract:

Four new homoleptic zinc (**1** and **2**) and copper (**3** and **4**) complexes of two Schiff base ligands (**L^1H** and **L^2H**) derived from 2-(3,4-dimethoxyphenyl)ethan-1-amine (**5**), a dimethyl derivative of dopamine were synthesized. All four complexes were well characterized by elemental analysis, FT-IR and UV-Vis., spectroscopy. Further, the zinc complexes (**1** and **2**) were characterized by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy while the copper complexes (**3** and **4**) by single crystal X-ray diffraction. The characterization data of complexes revealed strong coordination *via* azomethine nitrogen (N) and phenolate oxygen (O) of deprotonated ligands (**L^1** and **L^2**) as NO donors of composition [Zn/Cu(**$L^{1\text{-}2}$**)$_2$] (**1**-**4**). The CT-DNA binding affinity of complexes **1**, **2** and **4** was assessed using electronic absorption titration method which showed avid binding through intercalation mode and the binding constant (***K_b***) was found in the order of 10^5 to 10^6 M^{-1}. The compounds (**1-5**) were screened for dose dependent antimicrobial activity by agar well diffusion method against pathogenic antibacterial strains, *E. coli*, *S. aureus* and antifungal strain, *C. albicans*. The compounds showed significant toxicity to these pathogens.

Key words: Schiff base, Copper, Zinc, DNA binding, Antibacterial activity, Antifungal activity.

1. Introduction:

The discovery of '*cis*-platin' a simple platinum complex but a potential antitumor drug given platform for the design and development of metal-based coordination compounds as metallodrugs [1]. The advantages of metal in metallodrug are: enhancement of biological activity of the organic ligand through a novel mechanism of metallotherapeutic action in comparison to organic ligands, reduced the toxic effects of drug or its metabolites produced in the cell [2]. However, not all metal complexes have been emerged into successful drugs. Because the biological activity of metallodrugs depends on several of their properties such as nature of the metal ion and its

oxidation state(s), number and nature of the ligands, stereochemistry of the metal complex, thermodynamics and kinetics of ligand exchange reactions in bio-environment, electrochemical and photophysical properties [3].

Complexes of platinum metals have been found potential metallodrugs for the treatment of life-threatening diseases such as cancer, inflammatory, tuberculosis, viral, epilepsy, diabetes and cardiovascular [1a,e,4]. However, platinum metals-chelates bear several limitations: these metals are costly, less abundant, more toxic due to severe side effects and most of the complexes are kinetically less-labile, lack of activity for wide range of cancerous cells. Meanwhile biological activity of most of the non-platinum d-block metals complexes particularly Mn, Fe, Co, Ni, Cu, Zn have been explored [1g,h,5] due to their inherent advantages like the metals are more abundant, cost effective and less-toxic, abundant trace essential elements [1g,3c,d,6], these metal ions exhibit excellent bio-coordination chemistry by providing suitable coordination centers in physiological conditions.

Ligands play important roles in metal based drugs. Schiff bases are a special class of ligands because they: can be easily synthesised from low cost raw materials such as aldehydes/ketones and primary amines, exhibit rich coordination and structural chemistry with most of the transition metals, form stable and chelated complexes with additional donors [7]. The azomethine nitrogen play an important role in biological activity hence Schiff bases and their metal complexes have been largely explored in medicine for the treatment of various diseases [5g,8].

The evidence of drug resistance, evolution of new diseases by unknown bacteria and severe toxic effects of existing drugs have been continued to put efforts for designing and development of new, wide spectrum of bio-active and less toxic metal based drugs where the ligands especially derived from synthetic/natural biologically active compounds is of current interest [9]. Such type of drugs may show increased biological potency [9]. Recently, few Cu(II) and Zn(II) [8g,o-p,r-s,10,27a] complexes of Schiff bases especially containing nitrogen (N) and oxygen (O) donors found to show potential biological activity [9c,10a,14b]. We herein report the synthesis and characterization of new homoleptic Zn(II) and Cu(II) complexes (**1-4**) of Schiff bases (**L^1H** and **L^2H**) derived from 2-(3,4-dimethoxyphenyl)ethan-1-amine (**5**) also referred to as homoveratrylamine, which is a dimethyl derivative of dopamine (DA), main structural unit of many drugs used for the treatment of neurological disorders like Parkinson's disease, congestive

heart failure and others [11]. Also reported the studies on antimicrobial and DNA binding activities of above new complexes (**1-4**).

2. Experimental

2.1 Materials

All solvents (EtOH, MeOH, Pet-ether, Hexane, $CHCl_3$ and MDC) and chemicals were of commercial reagent grade and used as received. 2-(3,4-dimethoxyphenyl)ethan-1-amine (**5**) (97%), $Zn(OAc)_2.2H_2O$, $Cu(OAc)_2.H_2O$ and Tris HCl were purchased from Sigma Aldrich, India. 2-Hydroxy benzaldehyde (99.5%) and 2'-hydroxy acetophenone (99%) were purchased from Merck Specialities Pvt. Ind. Ltd. $NiCl_2.6H_2O$ was supplied by S. D. Fine-Chem Ltd., India. The microorganisms such as *Escherichia coli* (*E. coli*) [NCIM-5051] and *Staphylococcus aureus* (*S. aureus*) [NCIM-5022] as pathogenic bacterial strains and *Candida albicans* (*C. albicans*) [NCIM-3100] as pathogenic fungal strains used in this study were purchased from National Chemical Laboratory (NCL), Pune, India. These strains were maintained on nutrient agar slant at 4°C. Standard antibiotics Ciprofloxacin and Fluconazole were purchased from Hi Media, Mumbai, India. *Calf-thymus*-DNA (CT-DNA) was purchased from Genei, Bangalore, Karnataka, India.

2.2 Analytical methods

Elemental analysis (C, H and N) was performed on a LECO–CHNSO–9320 type elemental analyser. ^1H and $^{13}C\{^1H\}$ NMR spectra of **1** and **2** were recorded in $CDCl_3$ or DMSO-d_6 solution on a Bruker WM-400 spectrophotometer (400 MHz) using TMS as an internal standard. The FT-IR spectra of all the compounds were recorded by scan method in the range of 4000–500 cm^{-1} with Agilent FT-IR spectrophotometer. UV–Visible (UV–Vis.,) spectra were recorded on UNI-CAM-UV 2-100 spectrophotometer. Melting points of all new complexes were determined using Gallenkamp melting point apparatus in an open capillary closed at one end and were reported uncorrected. Single crystal X-Ray diffraction data of **3** and **4** were collected on a Bruker SMART APEX CCD-based X-ray diffractometer with Mo/Kα-radiation (λ, 0.71073 Å, at T 193 K). The molecular structures of **3** and **4** were solved by direct methods and refinement was carried out using SHELXTL-97 [12] package and empirical absorption correction has been applied (SADABS). All refinements were made by full-matrix least-squares on F^2 with anisotropic refinement at calculated positions.

2.3 Synthesis of zinc complexes, [Zn($\mathbf{L^{1\text{-}2}}$)$_2$] (**1**-**2**)

$Zn(OAc)_2.2H_2O$ (100 mg, 0.45 mmol) was dissolved in methanol (20 mL) and the resulting solution was stirred for 10 min. A solution of $\mathbf{L^1H}$ (260 mg, 0.91 mmol)/ $\mathbf{L^2H}$ (273 mg, 0.91 mmol) made in of methanol (10 mL) was added slowly and drop wise to the above solution under vigorous stirring during 10 min. The stirring was continued further for 30 min. A white precipitate was formed, which was filtered, washed with methanol (25 mL X3) and then with diethyl ether (25 mL X3). When the respective precipitates of **1**/**2** was recrystallized from 1:1 mixture of methylene dichloride and hexane at room temperature gave white microcrystals of compound **1**/**2**.

[Zn($\mathbf{L^1}$)$_2$] (**1**): Yield: 490 mg (85%); M.P.: 164-165 °C; Element. Anal. Calcd. (Found) for $C_{34}H_{36}N_2ZnO_6$: C, 60.40 (60.30); H, 5.72 (5.27); N, 4.42 (4.18); FT-IR: (ν, cm^{-1}): 2928, 2835, 1614, 1536, 1516, 1467, 1345, 1284, 1157, 1029, 935, 908, 852, 760, 624, and 560; UV-Vis., (λ_{max} in nm): 275, and 366; ^{1}H NMR ($CDCl_3$, δ ppm): 8.315 (s, 1H, CH=N), 7.214-7.258 (t, 1H, H4), 7.164-7.187 (d, 1H, H3), 6.756-6.736 (d, 1H, H6), 6.509-6.617 (m, 3H, H11, H14, H15), 6.685-6.707 (d, 1H, H5), 3.665-3.701 (t, 2H, NCH_2), 3.628 (s, 3H, OCH_3), 3.562 (s, 3H, OCH_3), 2.691-2.728 (t, 2H, CH_2Ar). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ ppm): 36.140 (C9), 55.749 (OCH_3), 55.931 (OCH_3), 61.835 (C8), 112.375 (C5), 112.982 (C11), 114.394 (C14), 118.621 (C4), 120.943 (C10), 122.825 (C15), 131.089 (C1), 134.936 (C6), 136.424 (C3), 147.769 (C13), 149.059 (C12), 170.421 (C2), 172.295 (C7).

[Zn($\mathbf{L^2}$)$_2$] (**2**): Yield: 483 mg (80%); M.P.: 167-168 °C; Element. Anal. Calcd. (Found) for $C_{36}H_{40}N_2ZnO_6$: C, 65.30 (65.29); H, 6.09 (6.01); N, 4.01 (3.98); FT-IR: (ν, cm^{-1}): 3010, 2932, 2910, 2836, 1615, 1533, 1511, 1466, 1437, 1407, 1318, 1259,1229,1185,1143,1017, 907, 901, 806, 751, 598, and 545; UV-Vis., (λ_{max} in nm): 270, and 365; ^{1}H NMR ($CDCl_3$, δ ppm): 7.211-7.250 (m, 1H, H4), 7.163-7.186 (dd, 1H, H5), 6.734-6.750 (d, 1H, H3), 6.684-6.705 (d, 1H, H6), 6.612-6.616 (d, 1H, H11), 6.508-6.567 (m, 2H, H15, H14), 3.658-3.701 (t, 2H, NCH_2), 3.634 (s, 3H, OCH_3), 3.567 (s, 3H, OCH_3), 2.700-2.738 (t, 2H, CH_2Ar), 2.010 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ ppm): 14.121 (CH_3) 35.818 (C9), 55.208 (OCH_3), 55.419 (OCH_3), 61.558 (C8), 103.313 (C5), 111.842 (C11), 112.364 (C14), 119.834 (C4), 120.467 (C10), 124.667 (C15), 130.559 (C1), 136.450 (C6), 136.964 (C3), 147.275 (C13), 148.543 (C12), 169.004 (C2), 170.733 (C7).

2.2 Synthesis of copper complexes, [Cu($\mathbf{L^{1\text{-}2}}$)$_2$] (**3**-**4**)

$Cu(OAc)_2.H_2O$ (100 mg, 0.5 mmol) was dissolved in 20 mL of methanol and the resulting solution was stirred for 10 min. A solution of ligand **L^1H** (286 mg, 1.0 mmol)/ **L^2H** (300 mg, 1.0 mmol) made in 10 mL of methanol was added slowly and drop wise to the above solution under vigorous stirring during 10-15 min. The stirring was continued further for 30 min during which a greenish-yellow precipitate of **3**/**4** was formed. The precipitate was filtered, washed with methanol (25 mL X3) and then with diethyl ether (25 mL X3).The product was recrystallized from 1:1 mixture of methylene dichloride and hexane gave greenish-yellow single crystals of compound **3**/**4**.

[Cu(**L^1**)$_2$] (**3**): Yield: 571 mg (85%); M.P.: 140-141 °C; Element. Anal. Calcd. (Found) for $C_{34}H_{36}N_2O_6Cu$: C, 64.59 (64.51); H, 5.74 (5.66); N, 4.43 (4.35); FT-IR: (ν, cm^{-1}): 2966, 2925, 2850, 1610, 1507, 1459, 1449, 1322, 1226, 1137, 1017, 904, 901, 835, 808, 753, and 582; UV-Vis. (λ_{max} in nm): 270,307, 361, and 703.

[Cu(**L^2**)$_2$] (**4**): Yield: 575 mg (87%); M.P.: 171-172 °C; Element. Anal. Calcd. (Found) for $C_{36}H_{40}N_2O_6Cu$: C, 65.49 (65.45); H, 6.11 (6.07); N, 4.24 (4.21); FT-IR: (ν, cm^{-1}): 2915, 2835, 1585, 1514, 1440, 1323, 1140, 1022, 858, 815, 752, and 646; UV-Vis. (λ_{max} in nm): 270, 310, 358, and 712.

2.3 DNA binding activity

The DNA binding activity of zinc and copper complexes (**1-4**) of NO Schiff base ligands (**L^1H** and **L^2H**) was assessed using UV–Vis., absorption spectroscopy. CT-DNA was used for the determination of binding capacity of given compounds. The purity of CT-DNA was verified by taking the ratio of absorbance at λ_{260} to λ_{280}, 1.90-2.00 in the buffer 5 mM Tris HCl/ 50 mM NaCl which prepared in double distilled water at pH, 6.90-7.01. A stock solution of CT-DNA was then prepared and its concentration per nucleotide was determined by measuring the absorbance at λ, 260 nm using the molar absorption coefficient ε, 6600 $Lmol^{-1}cm^{-1}$ [21]. The stock solution was stored at 4 ºC and used within 4 days.

Absorption titration experiments for compounds, **1-4** were performed for a fixed concentration of each compound (25 µM) against increasing (25–300 µM) amount of CT-DNA. The absorption titration spectra were recorded in the absence and presence with increasing concentration of CT-DNA (0–350 µM). The spectra recorded each time on incremental addition of DNA to the test

solution against blank solution containing same concentration of DNA without the test sample but containing buffer. In order to assess the binding strength of these compounds (**1-4**), the intrinsic binding constant (K_b) was determined from the plot of [DNA]/($\in_A$-$\in_F$) versus [DNA] according to Eq… (1).

$$\frac{[DNA]}{(\in_A - \in_F)} = \frac{[DNA]}{(\in_B - \in_F)} + \frac{1}{K_b(\in_B - \in_F)} \cdots\cdots (1)$$

Where, $\in_A$, $\in_B$ and $\in_F$ are the molar extinction coefficients (A_{obs}/[Conc]) corresponds to the apparent, compound in fully bound form to DNA and free compound respectively. The slope [1/($\in_A$-$\in_F$)] and Y-intercept [1/K_b($\in_B$-$\in_F$)] were determined from the plot for each compound and then K_b was calculated from the ratio of the slope to the intercept.

2.4 Antimicrobial activity studies

The new zinc and copper complexes (**1-4**) of Schiff base ligands (**L^{1}H** and **L^{2}H**) and **5** were screened for antimicrobial activity by agar well diffusion method against a Gram negative (*E. coli*) and a Gram positive (*S. aureus*) bacteria and a fungi (*C. albicans*). Two analytical solutions of all compounds, **1**, **2**, **3**, **4** and **5** were prepared by dissolving 500 and 1000 µg in 50 and 100 µL of DMSO respectively to get 10 µg/µL concentration of each compound in solution and assessed the dose dependent antimicrobial activity.

Nutrient and potato dextrose broths were used to culture the bacteria and fungi respectively. Nutrient agar plates were prepared and swabbed using sterile L-shaped glass rod with 100 µL of 24 h mature broth culture of individual bacterial strains. The wells of 6 mm were crated in to each plate using sterile cork borer. The standard test solutions of compounds (**1-5**) were now added into the wells using sterile micropipettes. These plates were incubated at 37 °C for 36 h. After the incubation period, the zone of inhibition of each well was measured in mm and the values were noted. The measurements were made in triplicate for each compound and their average values were reported. Similarly the zone of inhibition was determined for standard antibiotic drug, ciprofloxacin (5 µg/50 µL) as a positive control.

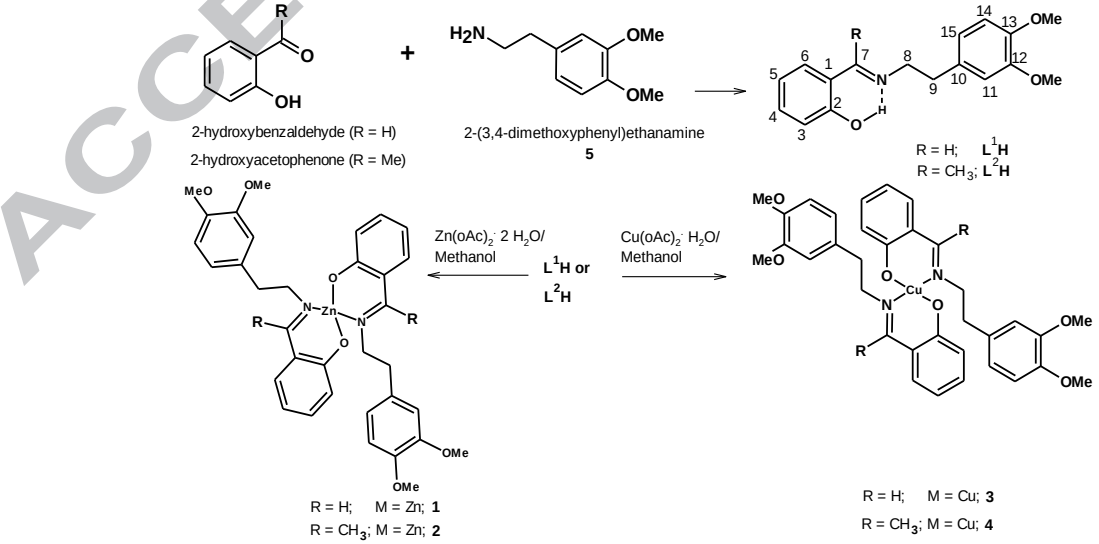
Antifungal activity of the culture strains of fungi (*C. albicans*) performed on potato dextrose agar (PDA) slant at 27 ± 0.2 °C for 48-96 h, till sporulation. Spore of strains were transferred into

5 mL of sterile 1% saline solution. 100 µL of each fungal spore suspension was spread on each sterile PDA plate. Using the sterile cork borer, wells of 6 mm were made in each plate. The standard test solutions of compounds (**1-5**) were now added into the wells using sterile micropipettes. The plates were incubated for 72 h at 27 °C. After the incubation period, the zone of inhibition of each well was measured in mm and the values were noted. Triplicates were maintained for each compound and the average values were reported. Similarly the zone of inhibition was determined for standard antifungal drug, fluconazole (200 µg/50 µL) as a positive control.

3. Results and Discussion

3.1 Synthesis of ligands (**L^1H** and **L^2H**) and complexes, **1** to **4**

The Schiff bases used for the synthesis of homoleptic zinc and copper complexes (**Scheme 1**) were prepared as per our reported procedure [13a] via condensation of 2-(3,4-dimethoxyphenyl) ethan-1-amine (**5**) with 2-hydroxy benzaldehyde (**L^1H**) and 2'-hydroxy acetophenone (**L^2H**) in dry ethanol respectively. These four new complexes (**1-4**) were easily formed at room temperature under magnetic stirring of methanolic solutions containing 2 molar equivalents of ligand (**L^1H** or **L^2H**) and 1 molar equivalents of $[Zn(OAc)_2.2H_2O]$ and $[Cu(OAc)_2.H_2O]$ as metal ion precursors. The precipitate then formed after each reaction was filtered and washed thoroughly with methanol and then recrystallized in 1:1 mixture of methylene dichloride and n-hexane. Zinc complexes were obtained as white microcrystalline and copper ones as greenish-yellow crystalline solids in high yields of about 80-85% and high purity.



Scheme 1 Synthesis of ligands ($\mathbf{L^1H}$ and $\mathbf{L^2H}$) and complexes (**1-4**)

The solubility of these four new complexes (**1-4**) was checked in various solvents and found that they were soluble in MDC, $CHCl_3$, DMSO, DMF and CH_3CN but insoluble in methanol, ethanol, n-hexane, n-heptane and pet-ether.

3.2 Characterisation of complexes, **1** to **4**

The composition of the new zinc (**1-2**) and copper (**3-4**) complexes of Schiff bases derived from veratrylamine was determined by elemental analysis (C, H and N) and was in agreement with their expected molecular formulae $[M(\mathbf{L^{1-2}})_2]$. The complexes were further characterised by FT-IR, UV-Vis., NMR spectroscopy (Zinc complexes) and single crystal X-Ray diffraction (Copper complexes).

3.2.1 UV-Vis. spectroscopy

The electronic spectra of zinc (**1-2**) and copper (**3-4**) complexes has been recorded for their solutions of concentration $2.5X10^{-5}$ M made in DMSO.

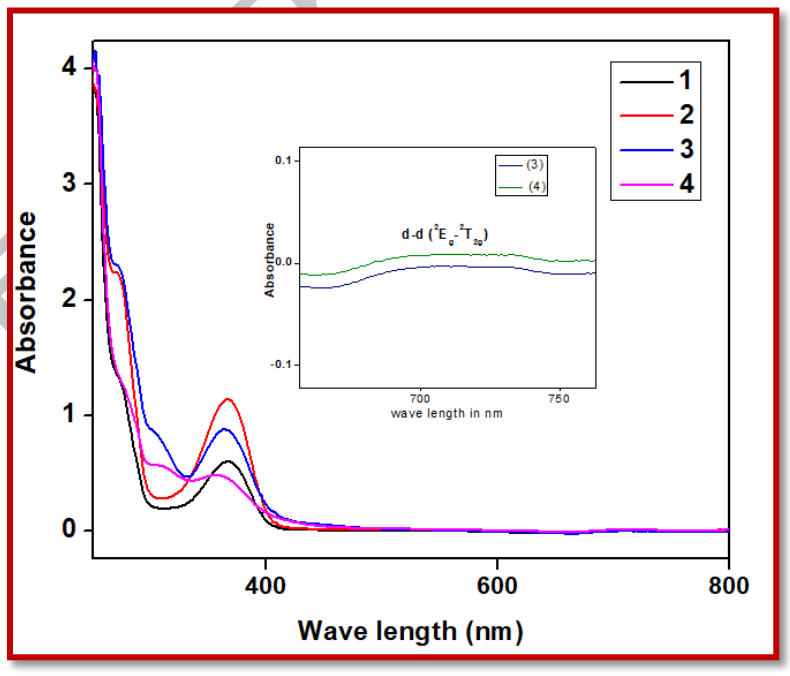


Fig. 1 UV-Vis., spectra of new Zn (**1** – **2**) and Cu (**3** – **4**) complexes of NO Schiff base ligands ($\mathbf{L^{1-2}H}$). (Inset: d-d transition)

In the electronic spectra of all complexes, **1**-**4** represented in **Fig. 1**, an intense high-energy band was observed at λ_{max}, ~270 nm which was attributed to $\pi \rightarrow \pi^*$ intra-ligand charge transfer (ILCT) transition. The bands showed blue shift of about 10-15 nm when compared to these bands in the respective ligands [13a]. A band observed at λ_{max}, 366 $\pm$ 3 nm was due to ligand to metal charge transfer (LMCT) transition [13a]. In the visible domain of absorption spectra, a wide band centered at λ_{max}, ~713 nm was observed only at higher concentration for copper complexes (**3** and **4**) and these bands were attributed to the d-d transition ($^2E_g \rightarrow {}^2T_{2g}$) for a Cu(II) complexes with d^9 configuration which undergo tetragonal distortion due to the John-Teller effect [14].

3.2.2 FT-IR spectroscopy

In the IR spectra of ligands, a strong absorption band observed for ν(O-H) bond stretching at ν, 3400 cm^{-1} was absent in the spectra of their Zn (**1-2**) and Cu (**3-4**) complexes which indicated the coordination of phenolate oxygen to central metal ion. The ν(C=N) stretching band showed a red shift of about 15-20 cm^{-1} in the complexes **1** to **4** in comparison to those bands in the respective ligands [14] indicated the involvement of azomethine nitrogen in complex formation. The ν(C-O) vibrational band in the complexes was shifted to a region of higher wave number [15] and appeared at 1345 and 1330 cm^{-1} in complexes **1** and **2** respectively which showed blue shift of about 30-40 cm^{-1} [13]. In the IR spectra of Cu(II) complexes (**3** and **4**) the ν(C-O^-) stretching vibrational bands were appeared at 1348 and 1323 cm^{-1} respectively which were found very strongly affected on coordination of ligands and they have shown blue shift of about 100 cm^{-1} in the complexes when compared to those bands in respective ligands. The strong absorption bands between 1580 to 1500 cm^{-1} in all ligands and complexes could be reasonably attributed to the presence of the ν(C=C) stretching vibration of the aromatic ring backbone. New bands appeared in the ranges ν, 578-547 cm^{-1} and at 534 cm^{-1} in the all complexes were attributed to the ν(M–N) and ν(M–O) vibrations respectively which they were not present in the spectra of ligands. Coordination of the azomethine nitrogen and phenolate oxygen to the metal ions in the copper complexes has been consistent with X-ray diffraction results [13,16a] those of zinc complexes by NMR studies discussed later in the manuscript. These observations indicated that the coordination of ligands occurred in complexes through the phenoxide (O^-) and imine (C=N) groups to M(II) ions forming chelated complexes [13,16a].

3.2.3 NMR Spectroscopy

The zinc complexes (**1** and **2**) were characterised by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy. In the proton NMR spectra of **1** and **2**, the azomethine proton has shown a downfield shift of 0.14 and 0.12 ppm when compared to the chemical shifts of these protons in the ligands $\mathbf{L^1H}$ and $\mathbf{L^2H}$ respectively [13a,16]. In **1** and **2**, the NCH_2 (0.15 ppm) and CH_2Ar (0.25 and 0.29 ppm) protons were found to be shielded than those protons in their respective ligands $\mathbf{L^1H}$ and $\mathbf{L^2H}$. The methoxy protons were also found to be shielded about 0.3 ppm when compared to proton NMR shifts in the respective ligands as observed in such dimethoxy compounds [13a]. The signal for phenolic proton observed in the proton NMR spectra of $\mathbf{L^1H}$ and $\mathbf{L^2H}$ was disappeared in the spectra of both **1** and **2** [13a].

In the ^{13}C NMR spectra of complex **1** the signals for C2 (-C-O^-), C3 (*ortho* to -CO^-) and azomethine (>C=N-) carbons were found deshielded about 5, 7 and 10 ppm respectively. In the ^{13}C NMR spectra of complex **2** these signals were also found deshielded about 7, 7 and 3 ppm respectively in comparison to these signals in the respective ligands [13a,16].

The observations from NMR spectra of **1** and **2** once again confirmed the coordinated of ligands as deprotonated ($\mathbf{L^1}$ and $\mathbf{L^2}$), monoanionic bidentate (N,O) donors to the central metal ion. The magnitude of NMR shifts also demonstrated that the ligand $\mathbf{L^1}$ was found to be strongly coordinated to zinc ion in **1** than $\mathbf{L^2}$ in **2** due to the steric hindrance of methyl group.

3.2.4 Single crystal X-Ray diffraction

The complexes **1** to **4** were recrystallized in a 1:1 mixture of methylene chloride and n-hexane. The microcrystals obtained for Zn(II) complexes (**1** and **2**) were found not suitable for single crystal X-Ray diffraction studies. The single crystal X-ray diffraction data for Cu(II) complexes (**3** and **4**) was collected and their molecular structures in solid state were determined. The crystal data and structure refinement parameters of **3** and **4** are given in **Table 1** and their selected bond parameters are given in **Table 2**. The molecular structures of **3** and **4** are given in **Fig. 1** and **Fig. 2** respectively.

The Cu-O and Cu-N bond lengths in **3** and **4** were found in the range of 1.878(4) - 1.888(3) Å and 2.003(4) - 2.044(4) Å respectively. The Cu-N bonds are slightly stretched in **4** due to the steric hindrance of bulky methyl group than H in **3**. These bond lengths are in agreement with those shown by the copper(II) complexes of similar Schiff base ligands [13b]. The O-Cu-O/ N-Cu-

N (180°) and O-Cu-N (90°) bond angles in both **3** and **4** revealed that they have square planar geometry around central copper ion [13b]. These observations also strongly confirmed the coordination of ligands $\mathbf{L^1H}$ and $\mathbf{L^2H}$ as deprotonated ($\mathbf{L^1}$ and $\mathbf{L^2}$) bidentate (NO^-) donors forming homoleptic 6-membered chelated complexes.

Further in the crystals of **3** and **4** the molecules were found to held by C-H···O type intermolecular hydrogen bonding (2.50 - 2.59 Å) resulting in supramolecular assemblies as shown in **Fig. S9** and **Fig. S10** respectively (ESI). These secondary interactions were slightly weaker than those found in copper complexes of similar type of ligands [14b].

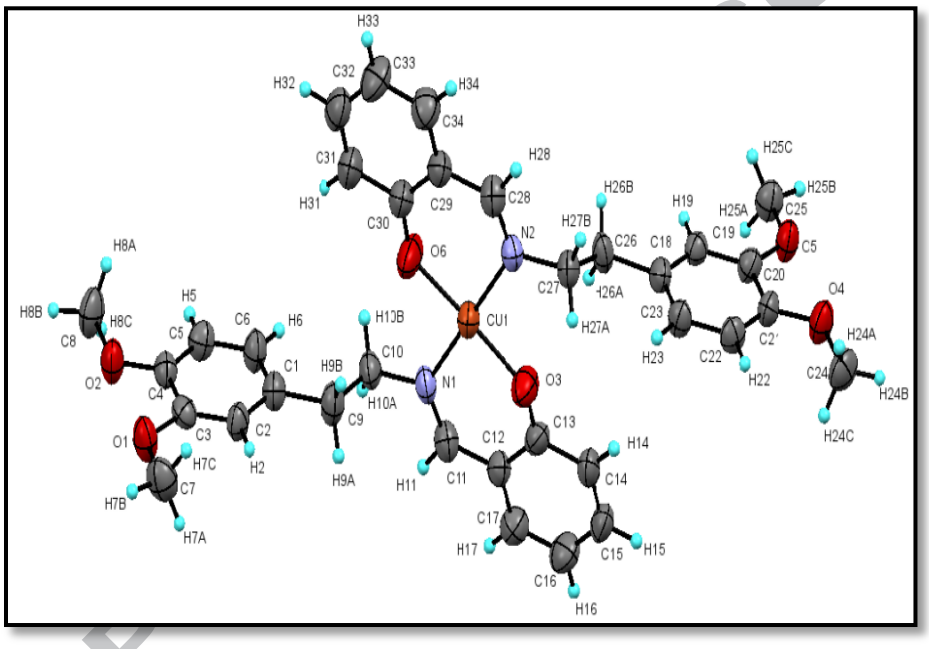


Fig. 1 Molecular structure of $[Cu(\mathbf{L^1})_2]$ (**3**).

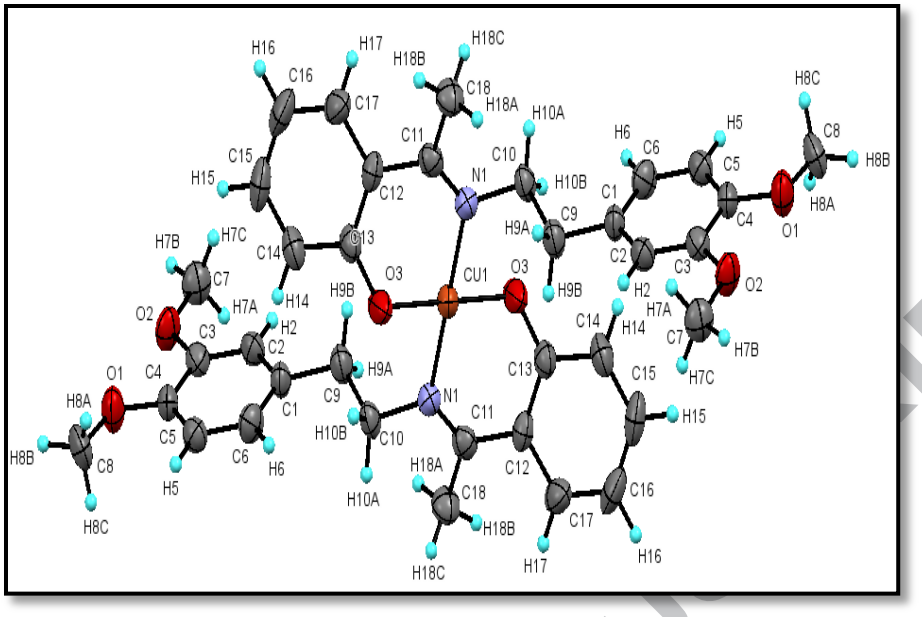


Fig. 2 Molecular structure of [Cu($\mathbf{L}^2$)$_2$] (**4**).

Table 1 Crystal data and structure refinement for of [Cu($\mathbf{L}^1$)$_2$](**3**) and [Cu($\mathbf{L}^2$)$_2$](**4**).

Complex	[Cu($\mathbf{L}^1$)$_2$] (**3**)	[Cu($\mathbf{L}^2$)$_2$] (**4**)
Empirical formula	$C_{34}H_{36}N_2O_6Cu$	$C_{36}H_{40}N_2O_6Cu$
Formula weight	632.19	660.24
Temperature/K	298(2)	289(2)
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$
a/Å	21.3711(12)	10.8183(12)
b/Å	5.7236(4)	6.2205(7)
c/Å	24.8756(16)	23.431(2)
α/°	90	90
β/°	98.172(6)	99.609(10)
γ/°	90	90
Volume/Å^3	3011.9(4)	1554.7(3)
Z	4	2
ρ_{calc} g/cm^3	1.394	1.410
μ/mm^{-1}	0.774	0.753
F(000)	1324.0	694.0
Crystal size/mm^3	0.24 × 0.23 × 0.15	0.23 × 0.22 × 0.21
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.062 to 50.046	5.614 to 49.994
Index ranges	$-25 \le h \le 25$, $-6 \le k \le 4$, $-22 \le l \le 29$	$-12 \le h \le 5$, $-4 \le k \le 7$, $-25 \le l \le 27$
Reflections collected	10956	5468
Independent reflections	5310 [R_{int} = 0.0632,	2745 [R_{int} = 0.0816,

	R_{sigma} = 0.0909]	R_{sigma} = 0.1285]
Data/restraints/parameters	5310/0/392	2745/0/208
Goodness-of-fit on F^2	1.041	0.968
Final R indexes [I>=2σ (I)]	R_1 = 0.0621, wR_2 = 0.1557	R_1 = 0.0690, wR_2 = 0.1478
Final R indexes [all data]	R_1 = 0.0947, wR_2 = 0.1897	R_1 = 0.1116, wR_2 = 0.1757
Largest diff. peak/hole / e $Å^{-3}$	0.30/-0.43	0.55/-0.42
CCDC No.	1569503	1569610

Table 2 Selected bond lengths and bond angles of [Cu ($\mathbf{L^1}$)$_2$] (**3**) and [Cu ($\mathbf{L^2}$)$_2$] (**4**).

3			
Cu(1)-O(3)	1.888(3)	O(3)-Cu(1)-N(1)	91.80(15)
Cu(1)-O(6)	1.878(4)	O(3)-Cu(1)-N(2)	88.09(15)
Cu(1)-N(1)	2.003(4)	N(1)-Cu(1)-N(2)	177.81(15)
Cu(1)-N(2)	2.004(4)	O(6)-Cu(1)-O(3)	176.9(2)
N(1)-C(11)	1.301(6)	O(6)-Cu(1)-N(1)	88.10(16)
N(2)-C(28)	1.298(6)	O(6)-Cu(1)-N(2)	92.13(16)
N(2)-C(27)	1.481(6)		
N(1)-C(10)	1.479(5)		
4			
Cu(1)-O(3)^1	1.878(4)	O(3)^1-Cu(1)-O(3)	180.0
Cu(1)-O(3)	1.878(4)	O(3)^{1}Cu(1)N(1)	89.17(16)
Cu(1)-N(1)	2.044(4)	O(3)-Cu(1)-N(1)	90.83(16)
Cu(1)-N(1)^1	2.044(4)	O(3)^1-Cu(1)-N(1)^1	90.83(16)
N(1)-C(11)	1.310(6)	O(3)-Cu(1)-N(1)^1	89.17(16)
N(1)-C(10)	1.490(6)	N(1)-Cu(1)-N(1)^1	180.0
		^{1}1-x,1-y,-z;	

Table 3 C-H···O secondary interactions in [Cu($\mathbf{L^1}$)$_2$] (**3**) and [Cu($\mathbf{L^2}$)$_2$] (**4**)

	D-H…A	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
3	C(15)-H(15)···O(2)^{i}	0.93	2.58	3.4745	162
	C(32)-H(32)···O(5)^{ii}	0.93	2.50	3.3750	156

4	C(9)-H(9A)···O(2)[iii]	0.97	2.56	3.4772	157
	C(18)-H(18C)···O(3)[iv]	0.96	2.59	3.4637	151

i = 1/2+x, 3/2-y, 1/2+z; ii = -1/2+x, 1/2-y, -1/2+z; iii=1-x,-1/2+y,1/2-z; iv= x,1+y,z

3.2.5 DNA binding activity

The UV–Vis., spectroscopy has been a widely used technique to study the nature of interaction and binding ability of ligands and their metal complexes with DNA [18,19]. In the present study, the DNA binding interaction of each compound (**1**, **2**, and **4**) was determined by performing electronic absorption titration experiments using the protein free *calf thymus*-DNA (CT-DNA) [20]. The compound **3** was precipitated on addition of buffer hence, its absorption titration spectra was not recorded.

The changes in absorbance at λ_{max}, 270 and 310 nm was monitored for a fixed concentration (25 µM) of metal complexes (**1, 2** and **4**) against the increasing concentration (0-350 µM) of CT-DNA. The resulted absorption titration spectra are shown in **Fig. 5** to **Fig. 7** respectively.

The results of absorption titration experiments of new complexes **1** and **4** showed hyperchromism whereas that of **2** showed hypochromism along with minor blue shift or no shift [22]. The DNA binding affinity of the above compounds with CT-DNA was determined quantitatively from the calculation of the intrinsic binding constant, K_b using Eq. (1) [23]. The extent of hyperchromism or hypochromism and K_b values obtained are given in **Table 4**.

Table 4 Effect of concentration of CT-DNA on the absorbance bands and binding constant of **1**, **2** and **4**

Sl. No.	**Compound**	**λ_{max} (nm)**		**$\Delta\lambda_{max}$ (nm)**	**H(%)** [a,b]	**K_b (M^{-1})**
		Free	**Bound**			
1	**1**	249	248	1	1.075	$24x10^5$
2	**2**	244	243	1	-1.189	$2x10^5$
3	**4**	236	235	1	2.330	$39x10^5$

H(%)[a] = $[\varepsilon_{free} - \varepsilon_{bound}/\varepsilon_{free}]x100$, [b] '-' Hypochromism and '+' Hyperchromism

The high intrinsic binding constant (K_b, 10^5 - 10^6 M^{-1}) of **1**, **2** and **4** suggested their strong binding affinity for CT-DNA. The compounds were expected to bind with the CT-DNA bases through non-covalent π–π stacking interaction [23b] as the complexes contain planar aromatic rings. The results demonstrated that the complexes of salicylaldehyde Schiff base bind stronger than 2-hydroxy acetophenone and further the copper complex exhibited strong binding capacity than zinc as shown by their binding constants. These findings are due to the steric hindrance of 2-hydroxy acetophenone Schiff base and the geometry of copper complexes is square planar whereas the zinc complexes is tetrahedral.

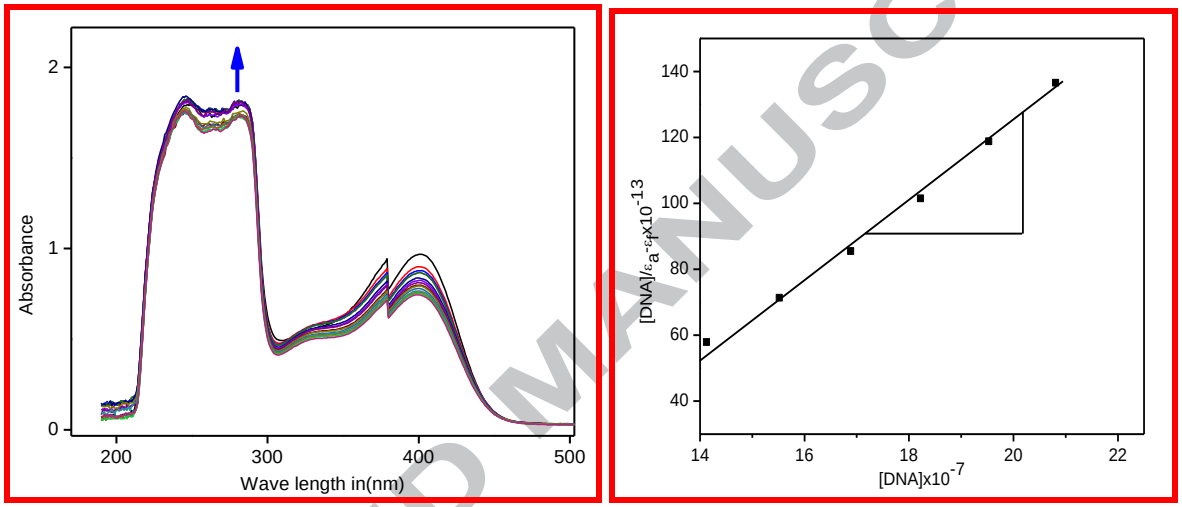


Fig. 5 (a) Electronic absorption spectra of [Zn($\mathbf{L}^1$)$_2$] (**1**) in 5 mM Tris HCl/50 mM NaCl buffer at pH 6.90-7.01 in the absence (- - -) and presence (—) of increasing amount of DNA. The [**1**] =25 μM; [DNA] = 0 - 350 μM. The incubation period is 10 min at room temperature; (b) Plot of [DNA]/(ε_a–ε_f) versus [DNA].

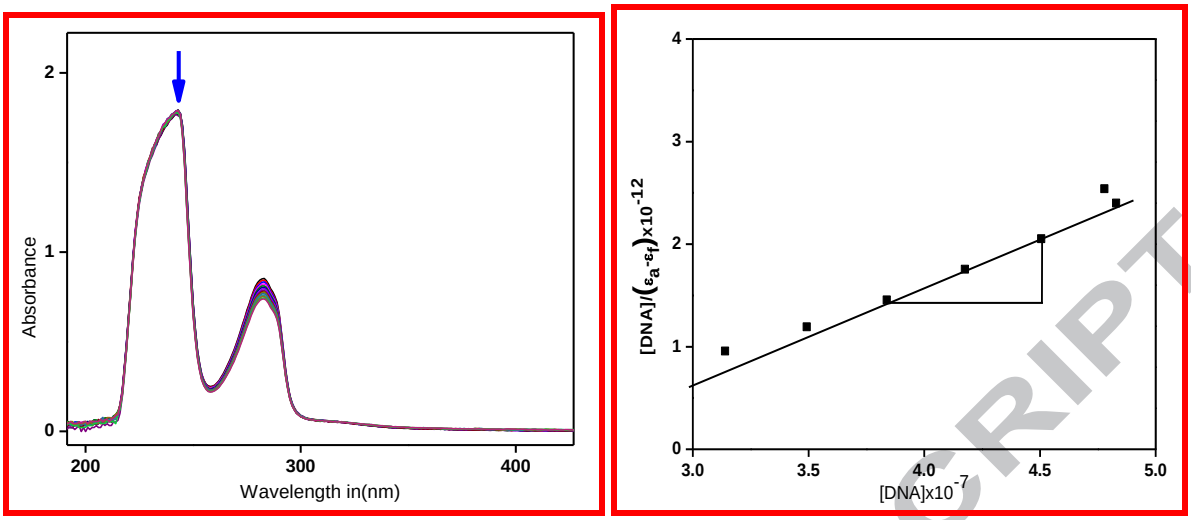


Fig. 6 (a) Electronic absorption spectra of [Zn($\mathbf{L}^2$)$_2$] (**2**) in 5 mM Tris HCl/50 mM NaCl buffer at pH 6.90-7.01 in the absence (- - -) and presence (—) of increasing amount of DNA. The [**2**] =25 μM; [DNA] = 0 - 350 μM. The incubation period is 10 min at room temperature; (b) Plot of [DNA]/(ε_a–ε_f) versus [DNA].

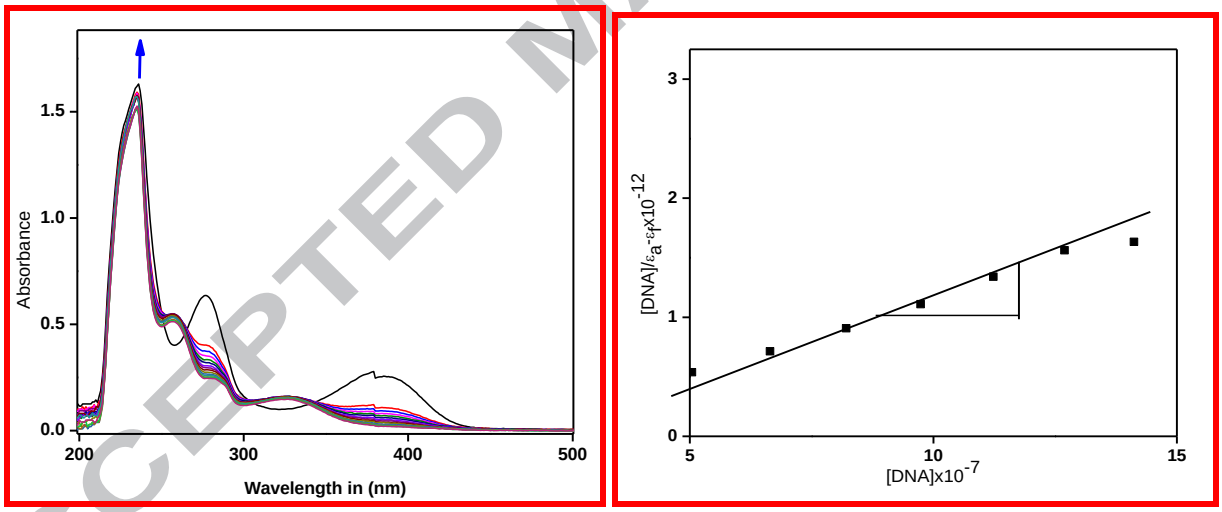


Fig. 7 (a) Electronic absorption spectra of [Cu($\mathbf{L}^2$)$_2$] (**4**) in 5 mM Tris HCl/50 mM NaCl buffer at pH 6.90-7.01 in the absence (- - -) and presence (—) of increasing amount of DNA. The [**4**] = 25 μM; [DNA] = 0 - 350 μM. The incubation period is 10 min at room temperature; (b) Plot of [DNA]/(ε_a–ε_f) versus [DNA].

3.2.6 Antimicrobial activity

The antimicrobial activity of new homoleptic zinc **(1-2)** and copper **(3-4)** complexes of NO donor Schiff base ligands (**L^1H** and **L^2H**), and their precursor dimethyl derivative of dopamine (**5**) was investigated by agar well diffusion method [24,8n] against the selected bacteria like *E. coli* (Gram negative) and *S. aureus* (Gram positive) and fungi such as *C. albicans*. Nutrient and potato dextrose agars were used to culture the bacteria and fungi respectively. The experimental details and zone of antimicrobial inhibition in respect of both antibacterial and antifungal activity of compounds (**1-5**) against the above pathogenic microbial strains are given in **Table 5** and **Table 6** respectively. The results of antimicrobial activity of **1-5** are also represented diagrammatically in **Fig. 8** and **Fig. 9** respectively. Effectiveness of an antimicrobial agent will be evaluated based on their respective zones of inhibition.

The results of antimicrobial activity studies demonstrated that the synthesized complexes have got the capacity to inhibit the metabolic growth of the investigated bacteria and the toxicity increases with dosage of any of the above tested compounds. The complexes found superior antibacterial and antifungal agents than the corresponding Schiff base ligands [13a] as well as dimethyl derivative of dopamine (**5**) under identical experimental conditions. The enhanced biological activity of the chelated metal complexes is due to the presence of the metal ion. This can be explained according to the Tweedy's chelation theory, which states that chelation reduces the polarity of the central metal atom because of partial sharing of its positive charge with the ligand which favors the permeation of the complexes through the lipid layer of cell membranes [24g]. Among the selected antibacterial pathogens, these complexes showed more toxicity towards *E. coli* than *S. aureus*. Among the complexes the copper complexes showed higher antimicrobial activity than zinc and which is due to difference in geometrical structures of complexes as revealed by the literature reports [24].

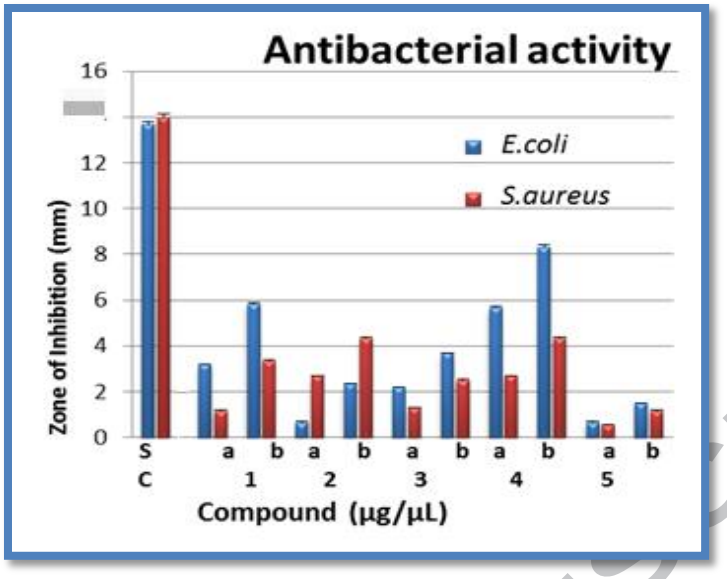


Fig. 8 Antibacterial activity of standard Ciprofloxacin and new compounds: **1**, **2**, **3**, **4** and **5**

Table 5 Antibacterial activity of standard Ciprofloxacin and new compounds: **1**, **2**, **3**, **4** and **5**

Sample	Treatment	*E. coli* (Mean±SE)	*S. aureus* (Mean±SE)
Ciprofloxacin	5 µg/50 µL	13.67±0.03	14.00±0.00
1	500 µg/50 µL	3.17±0.17	1.17±0.17
	1000 µg/100 µL	5.83±0.33	3.33±0.33
2	500 µg/50 µL	0.67±0.33	2.67±0.33
	1000 µg/100 µL	2.33±0.33	4.33±0.33
3	500 µg/50 µL	2.17±0.17	1.30±0.06
	1000 µg/100 µL	3.67±0.03	2.50±0.29
4	500 µg/50 µL	5.67±0.3	2.67±0.33
	1000 µg/100 µL	8.33±0.33	4.33±0.33
5	500 µg/50 µL	0.67±0.33	0.53±0.00
	1000 µg/100 µL	1.50±0.29	1.17±0.29

Values are the mean ± SE of inhibition zone in mm.

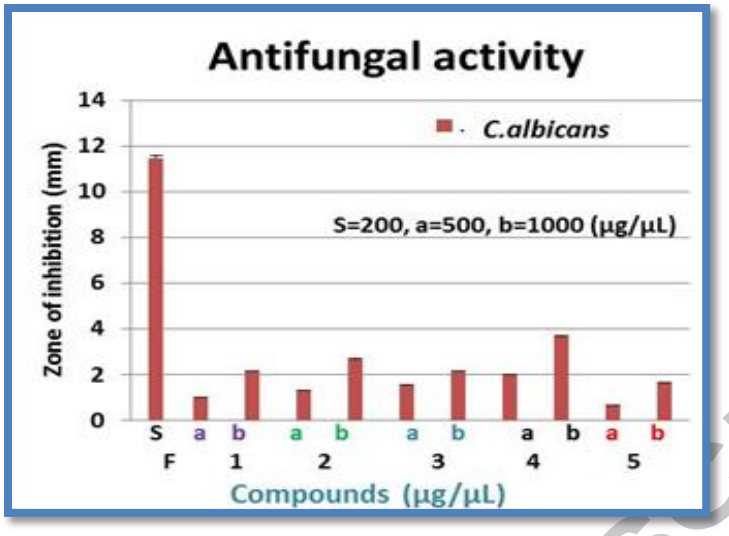


Fig. 9 Antifungal activity of fluconazole and new compounds: **1**, **2**, **3**, **4** and **5**

Table 6 Antifungal activity of fluconazole, and new compounds: **1**, **2**, **3**, **4** and **5**

Sample	**Treatment**	***C. albicans*** **(Mean±SE)**
Fluconazole	(200 µg/50 µL)	11.50±0.06
1	(500 µg/50 µL)	1.00±0.00
	(1000 µg/100 µL)	2.17±0.00
2	(500 µg/50 µL)	1.33±0.33
	(1000 µg/100 µL)	2.67±0.33
3	(500 µg/50 µL)	1.53±0.03
	(1000 µg/100 µL)	2.17±0.03
4	(500 µg/50 µL)	2.00±0.58
	(1000 µg/100 µL)	3.67±0.33
5	(500 µg/50 µL)	0.67±0.33
	(1000 µg/100 µL)	1.67±0.17

Conclusions

In conclusion, this paper contributed to the synthesis, characterization, CT-DNA binding affinity and antimicrobial activity of four new zinc (**1** and **2**) and copper (**3** and **4**) complexes of two Schiff base ligands (**L^1H** and **L^2H**) of homoveratrylamine (**5**). The composition and structural characteristics of **1-4** were confirmed by elemental analysis, FT-IR and UV-Vis., spectra. The zinc complexes (**1** and **2**) showed characteristic ^{1}H and ^{13}C{^{1}H} NMR spectra. The molecular structures of copper complexes (**3** and **4**) was confirmed by single crystal X-ray diffraction studies. In all the complexes the deprotonated ligands (**L^1** and **L^2**) coordinated as monobasic, bidentate NO donor systems resulting in homoleptic tetracoordinate

complexes. The results of CT-DNA binding affinity studies assessed using electronic absorption titrations demonstrated that they bind *via* π-π stacking mode and exhibited strong binding capacity as revealed by their binding constant (K_b) values found in the order of 10^5 to 10^6 M^{-1}. The compounds (**1-5**) also found to act as potential antimicrobial agents and the activity increases with increasing dosage of the respective compounds.

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Appendix A. Supplementary Information (SI)

CCDC Nos.1569503 and1569610 contain the supplementary crystallographic data for **3** and **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Synthesis, Structural Characterization, Antimicrobial and DNA binding studies of homoleptic zinc and copper complexes of NO Schiff bases derived from homoveratrylamine

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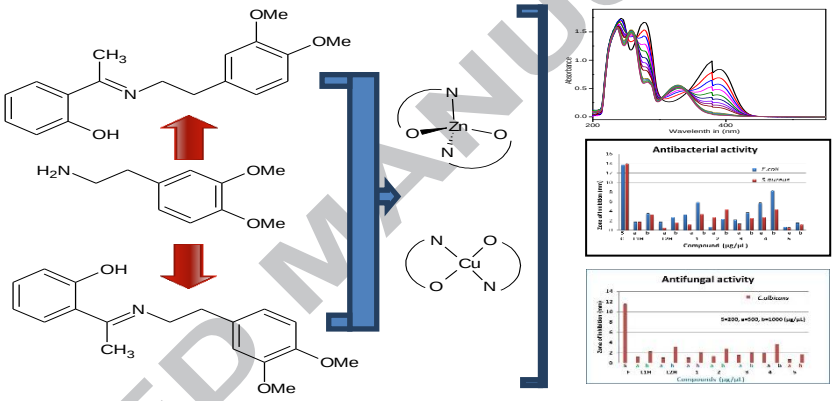
Graphical Abstract:



DNA binding and antimicrobial studies of zinc and copper complexes of NO Schiff bases

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Highlights:

- Synthesized and characterised homoleptic Zn and Cu complexes of Schiff bases of homoveratrylamine.
- Single crystal structures of two Cu complexes were solved which contain C-H···O secondary interactions.
- The complexes showed significant antimicrobial activity and strong DNA binding capacity.