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Synthesis, characterization and anticancer activity of mono- and binuclear Ni(II) and Co(II) complexes of a Schiff base derived from *o*-vanillin

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ABSTRACT

A Schiff base ligand, 6,6'-dimethoxy-2,2'-[o-phenylenebis(nitrilomethylidyne)]diphenolato (LA), and its mononuclear and dinuclear Ni(II) and Co(II) complexes were synthesized. Structural elucidation was carried out via elemental analysis, molar conductivity, IR, NMR, UV-Visible spectroscopy, TGA and magnetic susceptibility data. Single crystal X-ray diffraction of the Ni(LA) complex revealed a square planar geometry of the Ni(II) centre, with the ligand acting as a tetradentate *ONNO* chelate. Upon coordination to the metal centers, the v(C=N) and v(C-O) peaks shifted to lower frequencies, with appearance of new peaks assignable to v(M-N) and v(M-O) in the ranges 535-560 and 421-460 cm⁻¹, respectively. Ni(LA) and Ni₂(LA) complexes are diamagnetic, whereas the Co(LA) and Co₂(LA) complexes are paramagnetic with 3 unpaired electrons each. All the complexes display low molar conductivities in acetonitrile indicating non-electrolytic behavior. Anticancer screening against human colorectal cancer HCT116 cell lines revealed that both dinuclear complexes were more active than their mononuclear counterparts.

 $Ni_2(LA)$ showed the highest potency with an IC₅₀ value of 0.81 μ M.

Keywords: mononuclear, dinuclear, complexes, Schiff base, HCT116, anticancer, o-vanillin.

1. Introduction

Since the introduction by Hugo Schiff in 1864, Schiff bases, also known as imines or azomethines, have gained phenomenal popularity mainly due to their ease of synthesis, air stability and relatively cheap starting materials. They are good chelating agents, especially those with potentially coordinating functional groups such as S-H or O-H near the site of condensation [1]. Their ability to chelate metal cations is greatly enhanced by introducing donor atoms at strategic positions in the molecule, allowing a huge array of metal complexes with interesting structural architectures [2-4] such as binuclear and polynuclear.

The presence of nitrogen and oxygen donor atoms renders these compounds effective and stereospecific as catalysts for bond formation, oxidation, reduction, hydrolysis and other transformation of inorganic and organic compounds [5-8]. Fine tuning of molecular electronic properties can be achieved by placing electron withdrawing or donating substituents in the molecules, making them extremely attractive for investigation for various applications such as antimicrobial agents [9], sensor materials [10], pharmacological and electrochemical agents [11].

Schiff bases and their complexes have been reported to show significant bioactivity [12] owing to the azomethine linkage and/or hetero atoms and metals present in their structures. The assessment of novel synthetic Schiff bases as cytotoxic and cytostatic agents has irrefutably been growing exponentially because of their proven effectiveness as attractive frontrunner structures [13]. Anticancer properties are commonly observed to increase upon coordination of these ligands with transition metals, such as zinc, copper, cobalt and nickel [14]. This enhanced bioactivity may be explained by Overton's concept and chelation theory [15] that are based on lipophilicity and penetration of the complexes through the lipid membrane. However, there were isolated reports of ligands displaying higher bioactivity than their metal complexes [16], indicating the potency of the organic compounds by themselves.

Cancer has been ranked among the most fatal diseases of the 21st century. A wide range of cytotoxic drugs with different mechanisms of action are used to treat this disease, either alone or in combination [17]. The main drawback of these drugs is the side effects that are caused mainly by their indiscriminate action against both cancerous and healthy cells. There is an urgent need to find new and improved anticancer agents to fight this disease.

This paper describes the synthesis, structure elucidation and anticancer screening of a Schiff base ligand, LA, derived from *ortho*-vanillin and *ortho*-phenylenediamine, together with its mononuclear and binuclear nickel(II) and cobalt(II) complexes, annotated as Ni(LA), Ni₂(LA), Co(LA) and Co₂(LA), respectively. The ligand and complexes were characterized via their physicochemical and spectral properties, and X-ray crystallography for Ni(LA). The activity of the compounds against human colorectal cancer HCT116 is also reported.

2. Experimental part

2.1. Synthesis

The chemicals used in this investigation were of analytical grade. *Ortho*-vanillin (OVan), *ortho*-phenylenediamine (OPD), nickel(II) acetate tetrahydrate and cobalt(II) acetate tetrahydrate were purchased from Sigma Aldrich (St Louis, US). All chemicals and solvents were used as purchased without prior purification.

2.1.1. Synthesis of the ligand LA

The ligand synthesis is depicted in Scheme 1. OVan (30 mmol, 4.56 g) and OPD (15 mmol, 1.62 g) were dissolved in ethanol (20 mL), separately. Both solutions were mixed in a round-bottomed flask and refluxed for an hour, after which an orange precipitate appeared. The mixture was left to cool at room temperature before the precipitate was filtered off, washed with cold ethanol and dried in a desiccator overnight.

Elemental analysis for LA, analysed as $C_{22}H_{20}N_2O_4$, calc (found): C 70.20 (69.90), H 5.33 (5.36), N 7.44 (7.20)%. IR bands (KBr pellet, cm⁻¹): 1612, 1248, 1205. ¹H NMR (500 MHz, CDCl₃) δ (ppm): 11.20 (s, 1H), 9.93 (s, 1H), 7.29 (1H), 7.20 (dd, J = 7.8, 1.4 Hz, 1H), 7.13 (dd, J= 8.0, 1.4 Hz, 1H), 6.98 (t, J= 7.90 Hz, 1H), 3.93 (s, 3H).¹³C NMR δ (ppm): 164.10 (C-OH), 161.90 (C=N), 142.00-115.00 (Ar-C), 56.00 (-OCH₃)

2.1.2. Synthesis of the mononuclear complexes

The mononuclear complex synthesis is depicted in Scheme 2. The orange LA ligand (0.6 mmol, 0.2511 g) and nickel(II) acetate tetrahydrate (0.6 mmol) were mixed in a round-bottomed flask with ethanol (15 mL), then refluxed for one hour, upon which a change of color to red was observed. After slow cooling, a brick red precipitate was formed. It was filtered off, washed with cold ethanol and air dried. The solid Ni(LA) precipitate was recrystallized in a mixture of chloroform and dimethylsulfoxide (DMSO). The Co(LA) complex was prepared using the same protocol. The reaction of the ligand LA (0.4592 g, 1.22 mmol) with cobalt(II) acetate tetrahydrate (0.3039g; 1.22 mmol) afforded a brown precipitate.

Elemental analysis for Ni(LA), analysed as $C_{22}H_{18}N_2NiO_4(H_2O)$, calc (found): C 58.58 (58.52), H 4.47 (4.27), N 6.21(6.31)%. IR (KBr pellet, cm⁻¹): 1610, 1242, 1195, 550, 437. ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.27 (s, 1H), 7.72 (dd, J = 6.1, 3.3 Hz, 1H), 7.21-7.15 (m, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 6.57 (t, J = 7.8 Hz, 1H), 3.87 (s, 3H), ¹³C NMR δ (ppm): 154.00 (C-OH), 142.00 (C=N), 127.00 -112.00 (Ar-C), 55.00 (-OCH₃). $\mu_{eff} = 0$ BM

Elemental analysis for Co(LA) analysed as $C_{22}H_{18}CoN_2O_4(H_2O)_2$, calc (found): C 56.30 (56.50), H 4.72 (4.37), N 5.97 (5.97)%. IR (KBr pellet, cm⁻¹): 1605(vs), 1244, 1193, 542, 456. $\mu_{eff} = 3.96$ BM

2.1.3. Synthesis of the dinuclear complexes

The dinuclear complex synthesis is depicted in Scheme 3. The $Ni_2(LA)$ complex was obtained by reacting the ligand LA (0.4514 g, 1.2 mmol) with nickel(II) acetate tetrahydrate (0.5972 g, 2.4

mmol). The ligand and metal salt were dissolved in 25 mL of a 4:1 ratio of absolute EtOH:CHCl₃ and refluxed for three hours. The mixture was left to cool to room temperature and the brick red precipitate obtained was filtered off, washed several times with cold EtOH, air dried and stored in a desiccator over blue silica gel. The $Co_2(LA)$ complex was prepared using the same protocol where the ligand LA (0.4514 g, 1.2 mmol) and cobalt(II) acetate tetrahydrate (0.5978 g, 2.4 mmol) were reacted, affording a brown precipitate.

Elemental analysis for Ni₂(LA) analysed as C₂₂H₁₈N₂Ni₂O₄(H₂O)(CH₃CO₂)₂, calc (found): C 49.74 (49.47), H 4.17 (4.18), N 4.46 (4.64)%. IR (KBr pellet, cm⁻¹): 1609, 1244, 1193, 526, 458. ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.30 (s, 1H), 7.74 (dd, J = 6.0, 3.3 Hz, 1H), 7.22 (dd, , J = 6.1, 3.2 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 7.1 Hz, 1H), 6.59 (t, J = 7.8 Hz, 1H), 3.88 (s, 3H).¹³C NMR δ (ppm): 154.00 (C-OH), 142.00 (C=N), 127.00-112.00 (Ar-C), 55.00 (-OCH₃). $\mu_{eff} = 0$ BM

Elemental analysis for Co₂(LA) analysed as C₂₂H₁₈Co₂N₂O₄(H₂O)₃, calc (found): C 48.37 (49.03), H 4.43 (4.57), N 5.13 (4.88)%. IR (KBr pellet, cm⁻¹): 1605, 1243, 1194, 543, 458. μ_{eff} = 3.56 BM

2.2. Physical measurements

Elemental analyses (carbon, hydrogen and nitrogen) were performed on a Thermo Finnigan Flash EA 110 Elemental Analyzer. Infrared spectra were recorded as KBr discs in the range 4000-400 cm⁻¹ on a Perkin-Elmer FT-IR 1600 spectrometer. Molar conductivities were measured on a Mettler Toledo 730 Series conductivity meter using a conductivity standard of 1413 µS/cm. Mgnetic susceptibilities were measured on a Sherwood Auto balance. UV-Visible absorption spectra were recorded as 1 x 10⁻⁵ M acetonitrile solutions on a Perkin Elmer Lambda 35 UV-Vis spectrometer. Thermal analyses were performed in a nitrogen atmosphere using a TA Instruments Q50 TGA analyser. ¹H and ¹³C NMR spectra were recorded in deuterated chloroform on a Bruker Avance 500 MHz spectrometer. All measurements were carried out at room temperature and pressure.

2.3. X-ray crystallographic analysis

Red crystals of Ni(LA) were grown from a 1:3 mixture of CHCl₃:DMSO. A single crystal was selected, mounted on a glass fiber with epoxy cement and placed in the goniometer prior to data collection. A Bruker D8 QUEST with a photon CCD area-detector diffractometer (Bruker, AXS Inc., Madison, WI, USA) and graphite-monochromated Mo-K α radiation (λ =0.71073 Å) was used for data collection. The data collected were reduced using the program SAINT [18] and an empirical absorption correction was applied using SADABS [19]. The structure was solved by direct methods and refined by using the full- matrix least-squares method using the SHELXTL [20] software package. All non-H atoms were anisotropically refined. The hydrogen atoms bonded to water oxygen atom were located by difference syntheses and refined isotropically. The molecular graphics were created using SHELXTL and MERCURY software. The PLATON program was used for the molecular structure calculation [21]. Atomic scattering factors and anomalous dispersion corrections were taken from the International Tables for X-ray crystallography.

2.4 Cytotoxicity assay

2.4.1 Cell Culture

The human colorectal carcinoma cell line, HCT116 (ATCC® CCL-247[™]), was cultured in the Roswell Park Memorial Institute, RPMI 1640 Medium w/25mM HEPES & L-Glutamine, Biowest, supplemented with 10% heat inactivated fetal bovine serum (FBS)(PAA Laboratories) and 1% penicillin/streptomycin, Sigma Aldrich, (St Louis, US). The cultures were maintained in a humidified incubator at 37 °C in an atmosphere of 5% CO₂.

2.4.2 MTT assay

HCT116 cells were plated at 7,000 cells per well and allowed to incubate at 37 °C for 24 hours. The Schiff base LA and its metal complexes were dissolved in DMSO separately as stock solutions with a concentration of 1000 μ M. Serial dilution with DMSO was carried out before being added to each well. DMSO is a commonly used solvent in bioactivity investigations for metal complexes [22] and being an aprotic solvent, DMSO has small tendency to interact with metal complexes [23]. The cells were treated with the compounds at concentrations ranging between 0.01 and 100 μ M and incubated at 37 °C for 72 hours. The cytotoxicity of the compounds was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide, from Sigma Aldrich, as described by [24], with minor modifications. Briefly, 50 μ L of 0.06 mol/L MTT solution (Sigma) was added to each well and the plates were incubated at 37 °C for 4 hours. All solutions were aspirated and the formazan crystals were dissolved in DMSO (Merck). The plate was read at 450 nm. Data generated were used to plot a dose-response curve from which the concentration of compounds required to kill 50% of the cell population (the IC₅₀ value) was determined. Neat DMSO was used as a negative control.

3. Results and discussion

The physical properties and elemental analyses data for the Schiff base LA and its complexes are presented in Table 1. The experimental percentages of C, H and N were in close accord with the theoretical values, indicating formation of the intended compounds. The melting points of the complexes were higher than that of the ligand (Table 1), a trait commonly reported [25], likely due to increased molecular sizes and to a certain extent, the presence of stronger dative covalent and ionic bonds. The molar conductivity values of the complexes in acetonitrile were very low, in the range $0.03-0.22 \ \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$, indicative of the non-electrolytic nature of the complexes.

3.1. Infrared spectroscopy

The significant infrared bands of the LA ligand and its metal complexes are listed in Table 2. The spectra, as shown in Fig. 1, provide valuable information on the functional groups present in the compounds [26]. The spectrum of the free Schiff base exhibited a high intensity band at 1612 cm⁻¹, attributed to v(C=N) stretching in accordance with the report by Ghani et al. [27]. This band was observed to be shifted slightly to lower frequencies of 1605-1610 cm⁻¹ in the complexes, likely

due to coordination of the metal atom to the imine nitrogen atom through sharing of the N lone pair of electrons in a dative manner. The lowering of the frequency indicated a weakening of the C=N bond upon coordination to the metal center, caused by a decrease in the π -electron density due to an inductive effect.

The involvement of deprotonated phenolic oxygen atom in chelation was indicated by the shifting to lower frequencies of the v(C-O)_{phenolic} peak. The medium intensity v(C-O)_{phenolic} band that was observed at 1248 cm⁻¹ in LA shifted slightly to lower wavenumbers of 1243 cm⁻¹ in Co₂(LA) and 1244 cm⁻¹ in Ni(LA), Ni₂(LA) and Co(LA). There are two bands between 1540 and 1490 cm⁻¹ that are not present in the ligand spectra that can be assigned to coupled v(C=N) + v(C=C) + v(C-C) modes [28-29].

The coordination of the imine nitrogen and phenolic oxygen atoms to the metal centers was supported by the appearance of weak v(M-N) and v(M-O) bands at 526-543 and 456-460 cm⁻¹, respectively. This observation is in good agreement with previous assignments [30-31].

3.2. NMR spectroscopy

The ¹H and ¹³C NMR data for LA and Ni(LA) are listed in the Tables 3 and 4, respectively. The ¹H NMR spectra (Fig. 2) showed integrations and multiplicities consistent with the proposed structures. The peak at δ 9.94 ppm for LA represented the signal for the -OH hydrogen atom. In the spectrum of Ni(LA), deprotonation of OH upon complexation was observed by the disappearance of the -OH hydrogen atom signal.

The chemical shift of the azomethine hydrogen atom (-HC=N-) was shielded in the spectrum of Ni(LA) at δ 8.27 ppm compared to the free Schiff base at δ 8.66 ppm, inferring coordination of the Ni(II) ion to the LA ligand through the azomethine nitrogen atom [32]. The spectra of the ligand and Ni(LA) show aromatic hydrogen atom chemical shifts in the ranges of δ 6.87-7.29 and 6.56-7.73 ppm, respectively. The non-equivalent aromatic hydrogen atoms interact with each other to produce spin-spin splitting patterns indicative of *meta* and *ortho* interactions, with J coupling values of 1.4-3.3 Hz and 6.1-8.0 Hz, respectively. The methoxy signals appeared unsplit and stand out as tall sharp singlets in the upfield region of δ 3.87 ppm in LA and Ni(LA).

The ¹³C NMR spectra recorded signals of sharp peaks representing the chemically non-equivalent carbon atoms in the compound (Table 4). The ¹³C peak for C-O was observed at δ 154 ppm, C=N at δ 142 ppm, aromatic C atoms in the range δ 112-127 ppm and –OCH₃ at δ 55 ppm.

3.3. UV-Visible spectroscopy

The UV-Visible data and band assignments are listed in Table 5. The spectra of the free ligand and its complexes exhibited a high intensity band in the region 200-300 nm, assignable to $\pi - \pi^*_{(C=C)}$ of the aromatic benzene and $\pi - \pi^*_{(C=N)}$ of the azomethine groups. Upon complexation, the metal complexes showed a hypsochromic shift (blue shift) to lower wavelengths for both electronic transition bands, likely due to the possible occurrence of a significant amount of π -backbonding from the metal to the ligand, enriching the C=N bond with electrons and strengthening it.

The peaks attributed to $n-\pi^*$ were observed in the range 330-377 nm. In the electronic spectra of the metal complexes, except for that of Co(LA), the bands showed hypsochromic shifting to lower wavelengths, indicating strengthening of the C=N bond. All the complexes exhibited a weak broad band in the region 432-494 nm due to a ligand to metal charge transfer (LMCT) from the HOMO of the ligand to the hybrid orbitals of the metal atoms.

3.4. Thermogravimetric analysis

The elemental microanalysis of the compounds, shown in Table 1, indicate that Ni(LA), Ni₂(LA), Co(LA) and Co₂(LA) contained one, one, two and three molecules of water, respectively. TGA was performed to investigate the nature of the bonding of the water molecules in these complexes. The compounds were analysed in a platinum pan under nitrogen over the temperature range 30-450 °C with 10 °C/minute increments. The temperature intervals and the percentage mass loss are listed in Table 6, presenting the summary of the thermal decomposition of the water molecules throughout the analysis. Ni(LA), Ni₂(LA) and Co(LA) showed a mass degradation at temperatures below 160 °C, indicating that water moieties are present as solvation molecules.

The thermogram of $Co_2(LA)$ showed two stages of thermal degradation below 250 °C. An equivalence of two water molecules were lost between 36 and 125 °C, and one at a higher temperature of 125-210 °C. This observation indicates that there are two lattice and one coordinated water molecule in $Co_2(LA)$. It is therefore noted that one of the Co(II) centres might have a coordination number of 5 to account for this coordinated H₂O molecule, which is likely to be the one that is bonded to the –OCH₃ molecules, taking steric factors into account.

3.5. Magnetic susceptibility

The magnetic moment values for the metal complexes furnish information on the geometry of the central metals. There are two possible geometries for four-coordinate complexes, namely square planar and tetrahedral [33]. Both Ni(LA) and Ni₂(LA) showed diamagnetism, indicating that the compounds assume a square planar geometry, as expected for a Ni(II) $3d^8$ species [34]. The Co(II) complexes revealed a μ_{eff} value of 3.88 B.M., very close to the spin only magnetic moment, μ_{so} , of 3.87 B.M. for 3 unpaired electrons. It is therefore suggested that the Co(II) d^7 centre in Co(LA) assumes a tetrahedral geometry. For Co₂(LA), one of the Co(II) centres is proposed to have tetrahedral geometry whereas the other Co(II) ion, bonded to the fifth ligand of H₂O, takes a distorted square pyramidal geometry.

3.6. Structure description of Ni(LA)

The nickel complex crystallized in the monoclinic system with the space group P 21/n, a = 8.8525(4) Å, b = 19.061(8) Å, c = 11.8339(5) Å, β = 99.546(2)°, Z = 4 and V = 1969.91(15) Å³. The crystal system and refinement parameters are shown in Table 7. The ORTEP diagram of the complex, along with the atomic labelling scheme, is shown in Fig. 3. The Ni(II) atom is coordinated within an *ONNO* square planar donor set, provided by the tetradentate Schiff base ligand, LA. Selected bond lengths and bond angles are listed in Table 8. The Ni1—O2 and Ni1—O3 distances are 1.8385(14) and 1.8419(14) Å, respectively, slightly shorter than the Ni1—N2 (1.8532(16) Å) and Ni1—N1 (1.8564(16) Å) bond lengths, as expected. Both phenolic hydroxyl groups in the ligand are deprotonated upon complexation. The square planar geometry of the complex is distorted as evidenced by the O2—Ni1—O3 and O2—Ni1—N2 bond angles of 84.18(6) and 175.35(7)°, respectively. The presence of a water molecule of crystallization in the

crystal structure is consistent with the results obtained from the micro-elemental analysis data (Table 1) and the TGA investigations (Table 6). A similar crystal structure of the analogous $[Ni(C_{20}H_{14}N_2O_2)]$.H₂O, without the presence of methoxy groups, has been reported by Ghaemi et al. [35].

In the crystal structure, the complex molecules are linked by a C7--H7A...O3 intermolecular hydrogen bond, the symmetry code of which is given in Table 9, to form a zigzag chain along the c axis (Figure 4). In addition, the solvated water molecule also forms hydrogen bonds with the oxygen atoms O1, O2, O3 and O4 of the ligand, as listed in Table 9.

3.7. Cytotoxicity assay against HCT 116 cell line

Fig. 5 shows the dose-response curves of LA and its complexes, from which their respective IC_{50} was derived as illustrated in Fig. 6 and listed in Table 10. The relative cytotoxicity of LA and its complexes against HCT116 is in the order of Ni₂(LA) > Ni(LA) > LA > Co₂(LA) > Co(LA). The ligand, LA, yielded IC_{50} at 29.40 ± 5.90 µM indicating that even without the presence of any metal, the ligand itself has the ability to interact and alter the DNA present in HCT116, hence retarding its growth. Ni₂(LA) complex, on the other hand, exhibited the most potent anticancer activity with IC_{50} recorded at 0.81 ± 0.22 µM. It is interesting to note that contrary to the nickel(II) complexes, both the cobalt(II) complexes have lower anticancer activities than their parent ligand.

While nickel(II) complexes exhibited much higher anticancer activities than their analogous cobalt(II) complexes, both dinuclear complexes out-performed their mononuclear counterparts. This observation indicates that to a certain extent, the anticancer potency of these compounds is also metal-dependent.

4. Conclusion

The Schiff base LA acts as a tetradendate ligand and coordinates to metal centers through its phenolic O and azomethine N donor atoms. The appearance of new M-N and M-O peak in IR spectra evidenced the involvement of azomethine N and phenolic O in complexation and the disappearance of phenolic OH peak in ¹H NMR spectra supported the coordination of the metal

ion *via* phenolic O. Ni(LA) single crystal x-ray diffraction data shows a distorted square planar geometry with one solvated water molecule. With regard to cytotoxicity against HCT116, dinuclear Ni₂(LA) was the most potent bioactive agent, followed by it mononuclear counterpart, the parent ligand LA and the cobalt(II) compounds.

Appendix A. Supplementary data

CCDC 1533932 contains the supplementary crystallographic data for Ni(LA). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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Table 1

The physical properties and elemental analyses data for Schiff base ligand, LA and it complexes series

Compound	Color	Molecular Formula (RMM)	Yield (%)	Melting Point	Molar Conductivity	Eleme	ntal Percen d (Calcula	tages ted)
p		()	(, .,	(°C)		C (%)	H (%)	N (%)
LA	Orange	C ₂₅ H ₂₆ N ₂ O ₄ (418.49)	89.8	170	N/A	69.90 (70.20)	5.36 (5.33)	7.20 (7.44)
Ni(LA)	Brick red	C ₂₂ H ₁₈ N ₂ Ni O ₄ (H ₂ O) (451.10)	88.5	>300	0.03	58.52 (58.58)	4.27 (4.47)	6.31 (6.21)
Ni ₂ (LA)	Brick red	$\begin{array}{c} C_{22}H_{18}N_2Ni_2O_4(H_2O)\\ (CH_3CO_2)_2\\ (627.89) \end{array}$	83.1	>300	0.04	49.47 (49.74)	4.18 (4.17)	4.64 (4.46)
Co(LA)	Brown	C ₂₂ H ₁₈ CoN ₂ O ₄ (H ₂ O) ₂ (469.36)	94.57	>300	0.22	56.50 (56.48)	4.37 (4.54)	5.97 (5.49)
Co ₂ (LA)	Brown	$\begin{array}{c} C_{22}H_{18}Co_2N_2O_4(H_2O)_3\\ (546.31)\end{array}$	98.44	>300	0.15	49.03 (48.37)	4.57 (4.43)	4.88 (5.13)

Table 2

Selected IR data of LA ligand and metal complexes in cm⁻¹

Compound	v(C=N)	v(C-O) Phenolic	v(C-O) Methoxy	v(M-N)	ν(M-O)
LA	1612	1248	1205	-	-
Ni(LA)	1609	1244	1195	535	460
Ni ₂ (LA)	1609	1244	1193	526	458
Co(LA)	1605	1244	1193	542	456
Co ₂ (LA)	1605	1243	1194	543	458

Table 3

¹H chemical shifts for LA, Ni(LA) and Ni₂(LA)

		· •		Chemical shif	t, (ppm)			
Assign.		N-C8 U	С ³ -Н	C ⁴ -H	C ⁵ -H	C ¹⁰ -H	C ¹¹ -H	C ² -
	С-ОП	№–С*-П	(Ar.)	(Ar.)	(Ar.)	(Ar.)	(Ar.)	OCH ₃

	11.20	9.93	7.29	7.20	7.13	6.98		3.93
LA	(s)	(s)	(s)	(dd;7.8,1.4)	(dd; 8.0,1.4)	(t;7.9)	-	(s)
	(1H)	(1H)	(1H)	(1H)	(1H)	(1H)		(3H)
		8.27	7.72	7.21-7.15	6.95	6.72	6.57	3.87
Ni(LA)	-	(s)	(dd; 6.1,3.3)	(m)	(d;7.6)	(d;7.3)	(t;7.8)	(s)
		(1H)	(1H,)	(1H)	(1H)	(1H)	(1H)	(3H)
		8.30	7.74	7.22	6.95	6.72	6.59	3.87
Ni ₂ (LA)	-	(s)	(dd; 6.1,3.3)	(dd; 6.1, 3.2)	(d; 7.9)	(d;7.1)	(t;7.8)	(s)
		(1H)	(1H)	(1H)	(1H)	(1H)	(1H)	(3H)

Note: Ar.=Aromatic, s=singlet, d=doublet, dd=doublet of doublet, t=triplet, m=multiplet

Table 4

¹³C NMR chemical shifts for LA, Ni(LA) and Ni₂(LA)

					Chem	ical shift, ((ppm)				
Assıgn.	C ¹ -OH	N=C ⁸ -	C ² -H	C ⁶ -H	C ³ -H	C ⁵ -H	C ⁴ -H	С ¹¹ -Н	C ¹⁰ -H	С9-Н	OC ⁷ H
		H	(Ar.)	(Ar.)	(Ar.)	(Ar.)	(Ar.)	(Ar.)	(Ar.)	(Ar.)	3
LA	196.61	151.65	148.30	127.69	124.53	121.96	121.89	120.81	119.58	117.99	56.30
Ni(LA)	157.85	154.19	142.79	127.75	127.27	124.16	119.41	115.10	114.85	112.80	55.29
Ni ₂ (LA)	186.62	179.65	166.37	139.46	130.53	127.31	124.08	119.42	115.16	112.82	55.30
Note: Ar.=	=Aromat	tic									
Table 5 The UV-V	/isible d	ata									

Table 5

The UV-Visible data

	Transition assignment	Wavelength (nm)	Molar absorptivity, (ε)
	$\pi - \pi^*_{\text{benzene}}$	250	26094
LA	$\pi - \pi^{*}_{(C=N)}$	306	19668
	n- n *	337	5237
	$\pi - \pi^*_{\text{benzene}}$	215	4764
$N_{i}(\mathbf{I}, \mathbf{A})$	$\pi - \pi^{*}_{(C=N)}$	283	2564
NI(LA)	n-π*	330	2636
	LMCT	432	1392
	$\pi - \pi^*_{\text{benzene}}$	254	5058
$Ni_{\rm e}(LA)$	$\pi - \pi^*_{(C=N)}$	300	1957
$N_2(LA)$	n -π*	369	2977
	LMCT	480	755
	π – π^*_{benzene}	219	34240
$C_{\alpha}(\Gamma \Lambda)$	π - $\pi^*_{(C=N)}$	269	15634
CO(LA)	$n-\pi^*$	358	21150
	LMCT	489	5667
	π – π^*_{benzene}	256	12739
$C_{2}(I,\Lambda)$	π - $\pi^*_{(C=N)}$	290	5309
$CO_2(LA)$	$n-\pi^*$	377	6012
Ŧ	LMCT	494	1708

Table 6

The temperature intervals and the percentage of water loss

		Decomposition	Weight loss (<u>(%)</u>
Compound	Molecular formula	temperature (°C)	Found Ca	Lost species

Ni(LA) C22H18N2NiO4(H2O) 70-120 3.90 3.99 One lattice water molecule Ni2(LA) C22H18N2Ni2O4(H2O) 70-100 3.34 2.87 One lattice water molecule Co(LA) C22H18CON2O4(H2O)2 36-175 7.80 7.67 Two lattice water molecule Co2(LA) C22H18CON2O4(H2O)3 36-125 7.6 6.5 Two lattice water molecule Co2(LA) C22H18Co2N2O4(H2O)3 125-210 3.8 3.29 One coordinated water molecule	Ni(LA) C22H18N2NiQ(H2O) 70-120 3.90 3.99 One lattice water molecule Ni2(LA) C22H18N2NiQ(H2O) 70-100 3.34 2.87 One lattice water molecule Co(LA) C22H18CoN2Q(H2O) 36-175 7.80 7.67 Two lattice water molecule Co(LA) C22H18CoN2Q(H2O) 36-175 7.80 7.67 Two lattice water molecule Co2(LA) C22H18Co2N2Q(H2O) 36-125 7.6 6.5 Two lattice water molecule Co2(LA) C22H18Co2N2Q(H2O) 125-210 3.8 3.29 One coordinated water molecule	Ni(LA) C22H ₁₈ N ₂ NiO ₄ (H2O) 70-120 3.90 3.99 One lattice water molecule Ni ₂ (LA) C22H ₁₈ N ₂ NiO ₄ (H2O) 70-100 3.34 2.87 One lattice water molecule Co(LA) C22H ₁₈ Co ₃ D ₂ (H ₂ O) 36-175 7.80 7.67 Two lattice water molecule Co ₂ (LA) C22H ₁₈ Co ₃ D ₂ O ₄ (H ₂ O) 36-125 7.6 6.5 Two lattice water molecule Co ₃ (LA) C22H ₁₈ Co ₃ N ₂ O ₄ (H ₂ O) 36-125 7.6 6.5 Two lattice water molecule Co ₃ (LA) C22H ₁₈ Co ₃ N ₂ O ₄ (H ₂ O) 36-125 7.6 6.5 Two lattice water molecule	Ni(LA) C ₂₂ H ₁₈ N ₂ NiO ₂ (H ₂ O) 70-120 3.90 3.99 One lattice water molecule Ni ₃ (LA) C ₂₄ H ₁₈ N ₂ NiO ₂ (H ₂ O) 70-100 3.34 2.87 One lattice water molecule Co(LA) C ₂₂ H ₁₈ CO ₂ O ₄ (H ₂ O) 36-175 7.80 7.67 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) 36-125 7.6 6.5 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) 36-125 7.6 6.5 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) 125-210 3.8 3.29 One coordinated water molecule	Ni(LA) Ni ₂ (LA) Co(LA)	C ₂₂ H ₁₈ N ₂ NiO ₄ (H ₂ O)				
Ni ₂ (LA) C ₂₂ H ₁₈ N ₂ Ni ₂ O ₄ (H ₂ O) (CH ₃ CO ₂) 70-100 3.34 2.87 One lattice water molecule Co(LA) C ₂₂ H ₁₈ CoN ₂ O ₄ (H ₂ O) 36-175 7.80 7.67 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) 36-125 7.6 6.5 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) 125-210 3.8 3.29 One coordinated water molecule	Ni ₂ (LA) C ₂₂ H ₁₈ N ₅ N ₂ O ₄ (H ₂ O) 70-100 3.34 2.87 One lattice water molecule Co(LA) C ₂₂ H ₁₈ Co ₂ O ₄ (H ₂ O) 36-175 7.80 7.67 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) 125-210 3.8 3.29 One coordinated water molecule One coordinated water molecule	Ni ₂ (LA) C ₂₂ H ₁₈ CN ₂ O ₄ (H ₂ O) 70-100 3.34 2.87 One lattice water molecule Co(LA) C ₂₂ H ₁₈ CoN ₂ O ₄ (H ₂ O) 36-175 7.80 7.67 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) 36-125 7.6 6.5 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) 125-210 3.8 3.29 One coordinated water molecule	Nig(LA) C2HinNON(O(H2O)) 70-100 3.34 2.87 One lattice water molecule Co(LA) C2HinCON2O(H2O) 36-175 7.80 7.67 Two lattice water molecule Cog(LA) C22HinCON2O(H2O) 36-125 7.6 6.5 Two lattice water molecule 125-210 3.8 3.29 One coordinated water molecule	Ni ₂ (LA) Co(LA)		70-120	3.90	3.99	One lattice water molecule
Co(LA) C ₂₂ H ₁₈ CoN ₂ O ₄ (H ₂ O) ₂ 36-175 7.80 7.67 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) ₃ 36-125 7.6 6.5 Two lattice water molecule 125-210 3.8 3.29 One coordinated water molecule	Co(LA) C ₂₂ H ₁₈ CoN ₂ O ₄ (H ₂ O) ₂ 36-175 7.80 7.67 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) ₃ 125-210 3.8 3.29 Two lattice water molecule One coordinated water molecule	Co(LA) C ₂₂ H ₁₈ Co ₂ O ₄ (H ₂ O) ₂ 36-175 7.80 7.67 Two lattice water molecule Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) ₃ 125-210 3.8 3.29 One coordinated water molecule One coordinated water molecule	Co(LA) C ₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) ₂ 36-175 7.80 7.67 Two latice water molecule Co ₂ (LA) C ₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) ₅ 125-210 3.8 3.29 One coordinated water molecule One coordinated water molecule	Co(LA)	$C_{22}H_{18}N_2Ni_2O_4(H_2O)$ (CH ₂ CO ₂)	70-100	3.34	2.87	One lattice water molecule
Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) ₃ 36-125 7.6 6.5 Two lattice water molecule One coordinated water molecule	Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) ₃ 36-125 7.6 6.5 Two lattice water molecule One coordinated water molecule	Co ₂ (LA) C ₂₂ H ₁₈ Co ₃ N ₂ O ₄ (H ₂ O) ₃ 36-125 7.6 6.5 Two lattice water molecule 125-210 3.8 3.29 One coordinated water molecule	Co ₂ (LA) C ₂₂ H ₁₈ Co ₂ N ₂ O ₄ (H ₂ O) ₃ 36-125 7.6 6.5 Two lattice water molecule One coordinated water molecule		$C_{22}H_{18}CoN_2O_4(H_2O)_2$	36-175	7.80	7.67	Two lattice water molecule
Coger() Coger(1903) 125-210 3.8 3.29 One coordinated water molecule				$Co_{\alpha}(I \Lambda)$	$C_{22}H_{12}C_{22}N_2O_2(H_2O)_2$	36-125	7.6	6.5	Two lattice water molecule
			ACCERTIFIC						Scale
						0	P		
				P					
				P					
				P					

Table 7

Summary of crystal data and structure refinement parameters for Ni(LA) complex

Compound	Ni(LA)
CCDC	1533932
Identification code	Ni(LA)
Empirical formula	C22 H20 N2 Ni O5
Formula weight	451.11
Temperature	0(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/n
Unit cell dimensions	a = 8.8525(4) Å
$\alpha = 90^{\circ}$.	
	b = 19.0681(8) Å
$\beta = 99.546(2)^{\circ}.$	
	c = 11.8339(5) Å
$\gamma = 90^{\circ}$.	
Volume	1969.91(15) Å ³
Z	4
Density (calculated)	1.521 Mg/m ³
Absorption coefficient	1.023 mm ⁻¹
F(000)	936
Crystal size	0.500 x 0.320 x 0.270 mm ³
Theta range for data collection	2.759 to 28.417°.
Index ranges	-11<=h<=11, -25<=k<=25, -15<=l<=15
Reflections collected	67732
Independent reflections	4928 [R(int) = 0.0525]
Completeness to theta = 25.242°	99.9 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4928 / 3 / 279
Goodness-of-fit on F^2	1.066
Final R indices [I>2sigma(I)]	R1 = 0.0356, $wR2 = 0.0766$
R indices (all data)	R1 = 0.0544, WR2 = 0.0869
Extinction coefficient	n/a

Largest diff. peak and hole

0.424 and -0.354 e.Å⁻³

Table 8

Selected bond lengths (Å) and bond angles (°)

Bond lengths (Å)		
Ni1 O2	1.8385 (14)	
Ni1 O3	1.8419 (14)	
Ni1 N2	1.8532 (16)	
Ni1 N1	1.8564 (16)	
Bond angles (°)		
O2 Ni1 O3	84.18 (6)	
O2 Ni1 N2	175.35 (7)	
O3 Ni1 N2	95.32 (7)	
O2 Ni1 N1	94.88 (7)	
O3 Ni1 N1	173.34 (7)	
N2 Ni1 N1	86.14 (7)	

Table 9

Intermolecular hydrogen bonds (Å, °)

DHA	DH (Å)	HA (Å)	DA (Å)	DHA (°)
O1WH1WAO3 ⁱ	0.83 (3)	2.28 (3)	2.990 (2)	145(3)
O1WH1WAO4 ⁱ	0.83 (3)	2.39 (3)	3.114 (3)	147(3)
O1WH1WBO1 ⁱ	0.83 (2)	2.20 (19)	3.001 (3)	163(3)
O1WH1WBO2 ⁱ	0.83 (2)	2.47 (3)	3.034 (3)	127(3)
C9H9AO2 ⁱⁱ	0.95	2.47	3.201 (3)	134

(symmetry codes; i = -x, 2-y, 1-z, ii = -1/2+x, 3/2-y, -1/2+z)

Table 10

IC₅₀ of the investigated compounds against HCT116

Compound	Ni ₂ (LA)	Ni(LA)	LA	Co ₂ (LA)	Co(LA)
IC ₅₀ , μΜ	0.81 ± 0.22	1.46 ± 0.56	29.40 ± 5.90	45.50 ± 11.39	60.25 ± 5.50
Each data represents mean \pm standard deviation of quadruplicates.					



CAPTION TO THE FIGURES

Fig. 1. IR spectra of LA, Ni(LA), Ni₂(LA), Co(LA) and Co₂(LA)

Fig. 2. ¹H NMR spectra of LA, Ni(LA)and Ni₂(LA)

Fig. 3. ORTEP diagram of the Ni(LA) complex with the atom labelling scheme, drawn at 50% probability ellipsoids

Fig. 4. The crystal packing of the Ni(LA) viewed along a axis. All non-hydrogen bonded hydrogen atoms are omitted for clarity. The hydrogen bonds are indicated by dashed lines.

Fig. 5. IC₅₀ dose-response curves for LA and its complexes

Fig. 6 IC₅₀ for LA and its complexes

FIGURE 1



FIGURE 2



C8

C10

C12 C11

FIGURE 4





FIGURE 6

ACC

The Schiff base ligand LA was reacted with nickel(II) acetate and cobalt(II) acetate in different L:M ratios and under different reaction conditions, resulting in mononuclear and dinuclear complexes of both metals. Characterization was carried out via physicochemical and spectral techniques, including single crystal X-ray crystallography for Ni(LA). The Ni(II) centre has a distorted square planar geometry, with the ligand acting as a tetradentate *ONNO* chelate. There are 4 asymmetric units, each containing one water molecule of crystallization and one Ni(LA) complex, in a unit cell. All the compounds were screened for anticancer activity against HCT116 cell lines and Ni(LA) emerged as the most potent compound with the lowest IC₅₀ value of 0.81 mM. The order of anticancer potency was Ni₂(LA) > Ni(LA) > LA > Co₂(LA) > Co(LA).

Synopsis of the graphical abstract







R







