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Synthesis, Characterization, and Anticancer Activities of Zn^{2+}, Co^{2+}, and Ni^{2+} Complexes Containing Aza Hetero Ligands

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Abstract

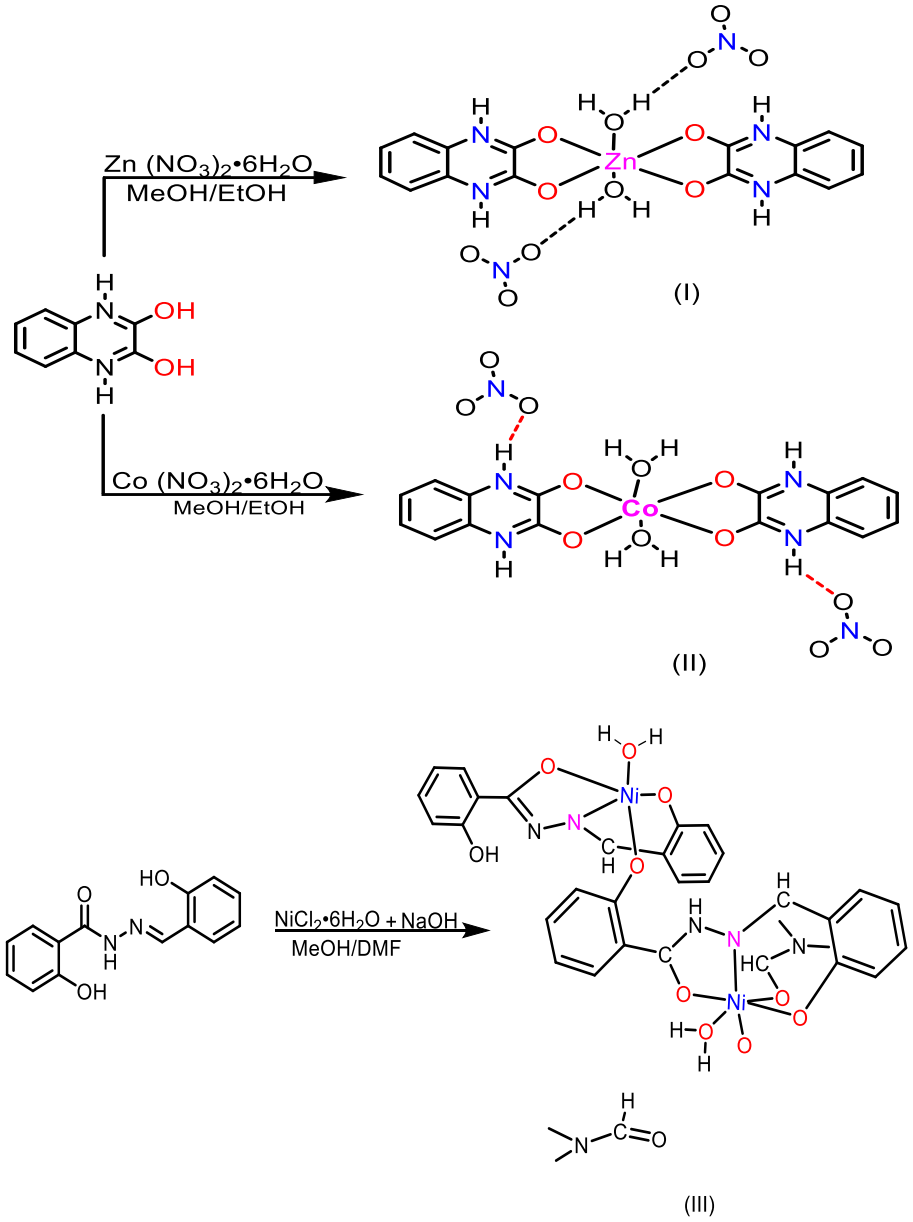
*With numerous uses in synthesis and therapeutics, aza-heterocyclic ligands are an exciting class of coordination chemicals. Three Zn(II), Co(II), and Ni(II) complexes (I-III) such as [$ZnC_{16}H_{16}N_6O_{12}$] (**I**), [$CoC_{16}H_{16}N_6O_{12}$] (**II**), and [$Ni_2C_{34}H_{38}N_6O_{11}$] (**III**) bearing aza-heterocyclic ligands have been synthesized under one-pot self-assembly conditions. The reaction of 2,3 dihydroxyquinoxaline with $Zn(NO_3)_2$•$6H_2O$ and $Co(NO_3)_2$•$6H_2O$ respectively, produced two mononuclear complexes (**I**) and (**II**) while the binuclear complexes (**III**) were synthesized using $NiCl_2$•$_6H_2O$, with salicylidene salicylhydrazide. Then, the complexes were characterized using, MS, FT-IR UV–Vis, and X-ray diffraction to confirm their structures. The synthesized complexes were employed against different human tumor cell lines (SMMC-7721, A549, MDA-MB-231, and SW480). Complex (III) exhibited the best activity against human tumor cell lines MDA-MB-231, which are late-stage breast cancer cells, with an IC_{50} value of 6.57 µM.*

Keywords: *Aza heteroatom ligands, Metal complexes, Crystal structure, Toxicity.*

Introduction

Transition metal complexes, which comprise organic ligands linked to the central metal, have been recognized for their usefulness in various areas, including modern research, medicinal drug synthesis (e.g., anti-cholesterol, anti-HIV, antibacterial, antifungal, analgesic, and anti-cancer), and the development of humanity [1–12]. Organometallic complexes involving N-containing heterocyclic molecules are of significant interest across various fields [13,14] They act as vital organic intermediates in pharmaco-chemistry and organic synthesis [15]. Abdolmaleki et al. (2022) synthesized Ni^{2+} complexes of 2,6-pyridine dicarboxylate, which exhibit promising potential as an anticancer agent, with an IC50 value of 5.13 µM [16]. Gangu et al. (2017) synthesized coordination complexes using 4,5-imidazole dicarboxylic acid as organic ligands. These complexes exhibited notable catalytic activity for environmentally safe chemical transformations, following ecological principles [17]. It is widely accepted that copper complexes have medicinal and catalytic uses. In 2016, Swamy et al. synthesized Cu (II) complex, which was the result of combining imidazole and 2,6-pyridine dicarboxylic acid; in vitro, it exhibited greater antibacterial activity than the respective ligand [18]. In 2014, a novel mixed-ligand binuclear Co^{2+} complex was synthesized by Nfor et al. The complex's magnetic susceptibility measurements indicate the presence of antiferromagnetic interactions among the Co^{2+} ions contained within the dinuclear units [19]. Salama, Ahmed, and Hassan in 2017, synthesized and studied Co^{2+} complexes of amino acid Schiff bases from salicylaldehyde and three amino acids in a basic medium, and also studied their biological activities [20]. Recently, there has been a surge in interest surrounding coordination molecules composed of nitrogen heteroatoms and the initial transitional metals, owing to their efficacy against cancer and their low level of toxicity [21–23].

In this research work, three new compounds were synthesized according to the previously published work using a one-pot synthesis technique [24]. [$ZnC_{16}H_{16}N_6O_{12}$] (I), [$CoC_{16}H_{16}N_6O_{12}$] (II), and [$Ni_2C_{34}H_{38}N_6O_{11}$] (III), which were identified using techniques such as UV–vis spectroscopy, FT-IR, and single-crystal X-ray diffraction. Presently, cancer stands as the most severe disease, and researchers are tirelessly working to develop therapeutic medicines. Our synthetic complexes exhibit admirable cytotoxicity towards different human tumor cell lines (SMMC-7721, A549, MDA-MB-231, and SW480), but negligible toxicity to normal cells.



Scheme 1:[(I)]Synthetic scheme for complex (I), [(II)]Synthetic scheme for complex (II), [(III)]Synthetic scheme for complex (III).

Experimental

Materials and Methods

The reagents and raw materials were utilized in their original state without undergoing any purification or processing. 2,3 dihydroxyquinoxaline, and salicylidene salicylhydrazide, were purchased from J&K Scientific LTD. Metal salts Zn $(NO_3)_2$•$6H_2O$, Co $(NO_3)_2$•$6H_2O$, and $NiCl_2$•$6H_2O$ were bought from Acros while solvents such as methanol and ethanol, DMF and H_2O were purchased from Sinopharm Chemical Reagent Company. The solvent used in combination with tetramethylsilane (TMS) was used as an internal standard, and chemical shifts were recorded in ppm (δ) (residual $CHCl_3$, H 7.26 ppm; $CDCl_3$, C, 77 ppm). Multiples are denoted by the abbreviations s = singlet, d = doublet, t = triplet, and m = multiplet. In cm^{-1}, the peaks are reported for infrared spectra taken with a Mattson Galaxy Series FTIR 3000 spectrometer. A Gemini S Ultra diffractometer was used to determine the crystal structure. Elemental analysis was carried out on an AE-3000 (Elemental Analyser). The Yanaco Micro melting point system MP-J3 and the SYNSYO melting point apparatus SMP-500 were used to measure the melting point, and they were not adjusted.

Cytotoxicity assay

In the cytotoxic investigation, human tumor cell lines (SMMC-7721, A549, MDA-MB-231, and SW480) were utilized. The cells were acquired from the ATCC in (Manassas, Virginia, USA). Cells were grown in RMPI-1640 or DMEM (Biological Industries, Kibbutz Beit Haemek, and Israel) at 37 ºC in a humid environment with 5% CO_2 and with 10% foetal bovine serum added (Biological Industries). The cytotoxicity experiment was analyzed using an MTS (Promega, Madison, WI, USA) assay. The 3-(4,5-dimethylthiazol-2-yl)-5-(3 carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) assay (Promega, Madison, WI, USA) was used to evaluate the cytotoxicity assay. The cells were seeded into each well of a 96-well cell culture plate. The test reagent (100 M) was added at 37 ºC after 12 h of incubation. After the cells were incubating for 48 hours at 37 ºC, the MTS test was performed. Compound AH106 was rescreened at concentrations of 100, 50, 25, 12.5, and 6.25 M while the remaining compounds were rescreened at

concentrations of 200, 100, 50, 25, and 12.5 M using cisplatin and paclitaxel (Sigma, St. Louis, MO, USA) as positive controls. Compounds at these concentrations that exhibited a 50% growth inhibition rate were further investigated. Using Reed and Muench's approach, the IC_{50} value of each chemical was determined. The findings are provided in (Table 4).

General Experimental Details

Clean and dried glassware was used under normal pressure for all reactions. Reagents were purchased from commercial sources. The temperature was controlled by 'ZNCL-TS Intelligent Magnetic Stirrer' and used a condenser to control evaporation. A Bruker 500 MHz Advance III Spectrometer was used to collect nuclear magnetic resonance (NMR) spectra. To obtain infrared spectra, an FTIR 3000 spectrometer from the Mattson Galaxy Series was used, and peak values were recorded in cm^{-1}. E. A was carried out on VARIO ELIII elemental analyzer. A Gemini S Ultra Diffractometer was used to determine the crystal structure. Chemical shifts of ^1H were recorded in ppm and referenced to DMSO-*daa 6*, 2.50 ppm; for $CDCl_3$, 7.26 ppm. s = singlet, d = doublet, t = triplet, and m = multiplet were used as the shorthand letters to indicate different multiplicities. Both the Yanaco Micro Melting Point System MP-J3 and the SANSYO Melting Point Apparatus SMP-500 were utilized to make accurate measurements of melting points.

General procedure for the syntheses of complexes (I)-(III)

The mixture of ligand and metal slat was heated from and refluxed in a 100 mL round bottom flask. The temperature was controlled by 'ZNCL-TS Intelligent Magnetic Stirrer' and a condenser was used to control evaporation. Rapid filtering occurred after the reaction, and the filtrate was obtained for steady volatilization. Complexes containing Zn^{+2}, Co^{+2}, and Ni^{+2} were successfully synthesized by reacting 2,3 dihydroxyquinoxaline, and salicylidene salicylhydrazide as ligands with Zn $(NO_3)_2$•$6H_2O$, Co $(NO_3)_2$•$6H_2O$, and $NiCl_2$•$6H_2O$, respectively. X-ray diffraction, FTIR, UV, MS, and E.A. were used to examine and characterize the synthesized crystals. The first key was to find the appropriate ligands. After this, reacting the ligands with the proper metal salts yields the filtrate or residue from the reaction, which is then analyzed to determine which solvent is effective for crystal precipitation. Tetrahydrofuran (THF), anhydrous methanol, ethanol, and chloroform are the accessible solvents needed for this stage and are the most important. Crystals can be stored in a refrigerator if these substances cannot precipitate at room temperature.

Synthesis of the complexes (I-III)

(Complex I) Using general procedure (molar ratio 1:5) 2,3 dihydroxyquinoxaline 2.7 mmol (0.44 g) and methanol anhydrous 25 mL was put into 100 mL round bottom flask, 25 mL ethanol was added after 5 minutes to this solution, 4.01 g (13.5 mmol) of Zn $(NO_3)_2$•$6H_2O$ was added. At 80 °C, the mixture was stirred for 24 hours. Following the completion of the reaction, the hot solution was filtered into a 50 mL beaker. After being put in a beaker sealed in plastic wrap which was punctured with a small needle, the solvent evaporated naturally at room temperature within three days, forming white crystals, m.p. 115 °C, single-crystal X-ray analysis was possible with this data. The yield was 80% (0.352 g). IR (KBr, n, cm^{-1}): 3370, 3221 (–NH), 2955 (=C–H), 1654 (–NO_3), 1601, (–C=C–), 1312 (C–N), 1042 (C–O), 647 (–Zn–O). HRMS(m/e) Cal: 549.72 found: 549.0492.

(Complex II) In accordance with the general procedure (molar ratio 1:5), the synthetic method of complex (II) is the same as for complex (I), the only difference is metal salt. 25 mL methanol anhydrous and 2,3 dihydroxyquinoxaline 3.2 mmol (0.53 g) were put into a 100 mL round bottom flask. After a few minutes, 25 mL ethanol was added, and then 4.67 g (16.0 mmol) of Co $(NO_3)_2$•$6H_2O$ was added. The reaction was refluxed for 24 hours at 80 °C. The hot solution was passed into a 50 mL beaker after the reaction. The liquid evaporated naturally at room temperature for three days After being put in a beaker sealed with plastic wrap which was perforated with a small needle. It formed brownish crystals with a melting point of 120 °C. These crystals could be used for single-crystal X-ray analysis. The yield was 78% (0.414 g). IR (KBr, n, cm^{-1}): 3337, 3228 (–NH), 2960 (=C–H), 2321 (–CH), 1643 (–NO3), 1615, (–C=C–), 1320 (C–N), 895 (C–O), 622 (–Co–O). HRMS(m/e) Cal: 543.28 found: (M+H)544.033.

(Complex III) Using general procedure (molar ratio 1:1), complex (III) was synthesized and characterized using a salicylidene salicylhydrazide 2.34 mmol (0.6 g), and 30 mL methanol anhydrous was put into a 100 mL round bottom flask, 20 mL DMF was added after 5 minutes to this solution, $NiCl_2$•$6H_2O$ 2.34 mmol (5.56 g) was added. NaOH 1.5 mmol (0.06 g) was added (dissolved in 15ml H_2O) after 5 minutes of refluxing at 90 °C, the purpose of adding a strong base to the reaction was to activate the active cites, the mixture was then stirred for 36 hours. Following the completion of the reaction, the hot solution was filtered into a 50 mL beaker. The solvent naturally evaporated at room temperature after 7 days of covering the beaker with plastic wrap and making pores in it with a small needle, yielding dark green crystals, The yield was 83% (0.498 g). m.p. 155 °C, single-crystal X-ray analysis was possible with the abovementioned data. IR (KBr, n, cm^{-1}): 3728 (–OH), 3333 (–NH), 2928 (=C–H), 1664 (–C=C–), 1517, (–C=C), 1463 (C=C), 1403 (C–C), 953 (C–N), 886 (C–O) 660 (–Co–N). HRMS(m/e) Cal: 824.10 found: 824.4008.

X-ray structure

Monochromatic Ga Kα radiation (λ= 1.34139 Å) was utilized in a Bruker D8 Venture diffractometer in order to generate X-ray crystal data. SHELXT [25] and SHELXL-2018/3 [26] were used to solve and revise the structures of complexes (**I**)-(**III**), respectively. OLEX2 [27] and MERCURY [28] were used to generate the molecular graphics. All atoms other than H were purified using anisotropic thermal parameters. Theoretical calculations were used to locate all the hydrogen atoms, which were subsequently adjusted using position parameters from the riding model and isotropic thermal settings. For a complete set of crystallographic data, see (Table 1).

Complex	(I)	(II)	(III)
Empirical formula	$ZnC_{16}H_{16}N_6O_{12}$	$CoC_{16}H_{16}N_6O_{12}$	$Ni_2C_{34}H_{38}N_6O_{11}$
Formula mass	549.72	543.28	824.10
Temp (K)	200.0	200.0	100(2)
Wavelength (Å)	1.34139	1.34139	1.34139
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/n$	$P2_1/n$	P-1
a (Å)	5.0921(4)	5.0752(4)	10.0957(3)
b (Å)	15.3433(11)	15.3303(13)	12.5513(4)
c (Å)	12.9483(9)	12.9546(10)	13.5639(4)
β (°)	93.450(3)°	92.839(3)	85.4240(10)
Volume (Å^3)	1009.81(13)	1006.69(14)	1702.15(9)
Z	2	2	2
D_{calcd} (g cm^{-3})	1.808	1.792	1.577
μ (mm^{-1})	1.603	5.168	6.419
F (000)	560	544	840
θ range (°)	5.015-61.564	3.889-60.385	2.843-72.462
Total relfec.	9459	12410	39900
Unique reflections	2324	2245	9855
R_1, wR_2 [$I > 2\sigma$(I)]	0.0436, 0.1199	0.0579, 0.1459	0.0355, 0.0941
R_1, wR_2 [all data]	0.0488, 0.1236	0.0724, 0.1526	0.0432, 0.0968
Residuals (e.Å^3)	0.487, -0.474	0.448, -0.627	0.389, -0.613

Table 1: Cell parameters and crystallographic data for complexes **(I)**–**(III)**.

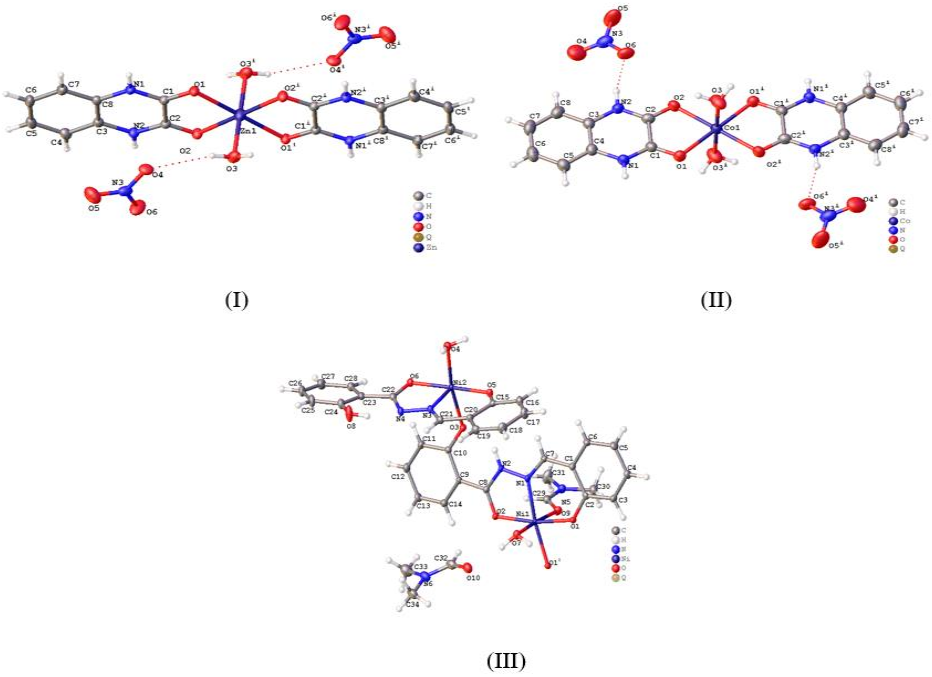
D–H···A	d_{D-H}	$d_{H\cdots A}$	$d_{D\cdots A}$	∠ DHA
For complex (I)				
N(1)-H(1)...O(6)#2	0.88	1.99	2.778(3)	148.3
O(3)-H(3A)...O(2)#3	0.88	2.47	3.152(2)	135.3
O(3)-H(3A)...O(4)	0.88	2.42	3.167(3)	143.3
N(2)-H(2)...O(4)#4	0.88	1.90	2.749(2)	160.2
For complex (II)				
N(1)-H(1)...O(5)#2	0.88	1.96	2.763(4)	150.9
N(2)-H(2)...O(6)	0.88	1.89	2.742(4)	161.8

Symmetry codes: For (I), $^{\#1}$ = - x + 2, - y +1,- z + 1, $^{\#2}$ = x + 3/2, - y + 1/2 , z + 1/2; for (II), $^{\#1}$ = - x, - y +1, - z +1, $^{\#2}$ = x +1/2, - y +1/2, z +1/2, $^{\#3}$ = x +1, y, z, $^{\#4}$ = x -1, y, z.

Results and discussion

Overview of the crystal structures for complexes (I)-(III)

Fig. 1 displays the stereogram and crystal structure of the complexes (**I**)-(**III**). Under specific experimental conditions, all the complexes from (**I**)-(**III**) crystallize in centrosymmetric space groups, i.e., $P2_1/n$ for (**I**)/(**II**), and P-1 for (**III**) (Table 1). Complexes (**I**) and (**II**) are mononuclear metal complexes, which contain one complete neutral coordination molecule in their asymmetric units. Complexes (**III**) is dinuclear metallic coordination compound. The asymmetric unit of complex (**III**), contains dinuclear Ni(II) coordination molecules and one half of DMF solvent. However, the apical positions of the two Ni(II) coordination are different. First, the axial positions were occupied by water molecule; second, the axial positions were furnished by each one water and DMF molecules.



(I) (II)

(III)

Figure 1: The ORTEP molecular structures of all three complexes, (I), (II), and (III), depicted as 30% thermal ellipsoid probability In more detail, complex (**I**) contained a zinc ion, two 2,3 dihydroxyquinoxaline ligands, two nitrate ions, and two water molecules. Complex **(II)** contains one cobalt ion, two 2,3 dihydroxyquinoxaline ligands, two water molecules, and one nitrate ion. Both (complexes (I) and (II)) have a 5:1 ratio and octahedral geometry but have distinct center metal ions. Complex (**III**) contains two nickel ions, two salicylidene salicylhydrazide ligands, two DMF, and two water molecules.

In the crystal packing of complex (**I**), the coordination sphere of the central metal zinc ion adopted octahedral geometry by coordinating with four oxygen (O1, O2, $O1^i$ and $O2^i$) from two 2,3 dihydroxyquinoxaline ligands and two water molecules coming with metal salt $Zn(NO_3)_2$•$6H_2O$. Both the water molecules are further connected with two nitrate ions (NO_3) via hydrogen bonding i.e. O(3)–H(3A)···O(4) and $O(3^i)$–$H(3A^i)$···$O(4^i)$ making complex (**I**). Each ligand has two nitrogen atoms (N1, N2 and $N1^i$, $N2^i$) inside the ring that do not take part in coordination with CMA which may be because of high bond distance from the center metal ion as well as the inter-delocalized bonding effect resonating hetero-cyclic alkenes rings. both 2,3 dihydroxyquinoxaline ligands had strong electron-donating groups (-O), which were involved in coordination with zinc. The six bond lengths are $d_{Zn1–O2}$ = 2.0549(15) Å, $d_{Zn1–O2i}$ = 2.0549(15) Å, $d_{Zn1–O1}$ = 2.0990(15) Å, $d_{Zn1–O1i}$ = 2.0991(15) Å, $d_{Zn1–O3}$ = 2.1296(17) Å, and $d_{Zn1–O3i}$ = 2.1296(17) Å.

For the molecular structure of **(II)**, the coordination sphere of the core metal cobalt ion took on an octahedral shape by combining with four oxygen (O1, O2, O1i, and O2i) from two 2,3 dihydroxyquinoxaline ligands and two water molecules resulting from the metal salt $Co(NO_3)_2$•$6H_2O$. Furthermore, each ligand has two nitrogen atoms (N1, N2 and $N1^i$, $N2^i$) inside the ring are not take part in coordination with CMA which may be because of the high bond distance from the center metal ion as well as the inter-delocalized bonding effect resonating hetero-cyclic alkenes rings, although forming hydrogen bonding with nitrate ions (NO_3^-) i.e. N(2)–H(2)···O(6) and $N(2^i)$–$H(2^i)$···$O(6^i)$ in the coordination sphere of complex (**II**), this is just because of the symmetry operation which can be used to generate the omitted nitrate anion. The six bond lengths are d_{Co1-O2} = 2.077(2) Å, $d_{Co1-O2i}$ = 2.077(2) Å, d_{Co1-O3} = 2.091(3) Å, $d_{Co1-O3i}$ = 2.091(3) Å, d_{Co1-O1} = 2.096(2) Å, and $d_{Co1-O1i}$ = 2.096(2) Å.

The dark green colored complex (**III**) is crystallized under a certain experimental condition, i.e., *P*-1. A di-nuclear nickel complex with two core nickel ions, two salicylidene salicylhydrazide ligands, two DMF, and two water molecules makes up the compound. It's interesting to observe that, both central nickel ions are not coupled to the same number of atoms. Octahedral geometry is formed by the connection of Ni1 to five oxygen (O1, 01^i, O2, O7, O9) in which one oxygen each comes from water and DMF molecules, and one nitrogen atom (N1) from ligand. Furthermore, Ni2 is connected to four oxygens (O3, O4, O5, O6) in which O4 is coordinated from water while O3 is coming from the fist ligand, and one nitrogen atom makes trigonal bipyramidal geometry. The six bond lengths for Ni (1) are d_{Ni1-N1} = 1.9944(13) Å, d_{Ni1-O1} = 1.9972(11) Å, $d_{Ni1-O1i}$ = 2.0324(11) Å, d_{Ni1-O2} = 2.0487(11) Å, d_{Ni1-O7} = 2.0873(12) Å, and d_{Ni1-O9} = 2.1121(12) Å. For Ni (2), the five bond lengths are d_{Ni2-N3} = 1.9691(14) Å, d_{Ni2-O5} = 2.0386(11) Å, d_{Ni2-O6} = 2.0411(11) Å, d_{Ni2-O3} = 2.0925(11) Å and d_{Ni2-O4} = 2.2049(12) Å.

IR analysis of complexes (I)-(III)

Several peaks were in the IR analysis that occur in all IR spectra **(Fig. 2)**. Typically, infrared spectroscopy reveals that the vibrations of O–H groups are more affected by the surrounding environment. Consequently, the O–H group displayed an atypical infrared absorption peak. Generally, when there is no hydrogen bonding occurs between the free O–H groups, the O–H stretching vibrations typically produce strong absorption peaks with peaks in the 3750–3000 cm^{-1} range. An OH (hydroxyl groups) was observed in our investigated compounds **(III)** for the infrared absorption vibration peak at 3728 cm^{-1}.

Additionally, the peak produced by the stretching vibrations of N–H groups falls between 3500–3100 cm^{-1}. This can be seen in all three complexes from 3370–3221 cm^{-1}. Since the stretching vibrations of the C=C bonds in the rings were observed by the absorption peaks from 1601 and 1664 cm^{-1}, the presence of aromatic structures was confirmed. The absorption peaks for C–N, C–O, and C–C vibrations were found in complexes (**I**)–(**III**) at 1403 to 886 cm^{-1}. There are stretching vibration peaks at 647 cm^{-1}, 622 cm^{-1}, 660 cm^{-1}, and 590 cm^{-1} for Zn–O, Co–O, Ni–N, and Ni–O, [29], respectively, that exemplifies the connection between metal and ligand interactions (Fig. 2).

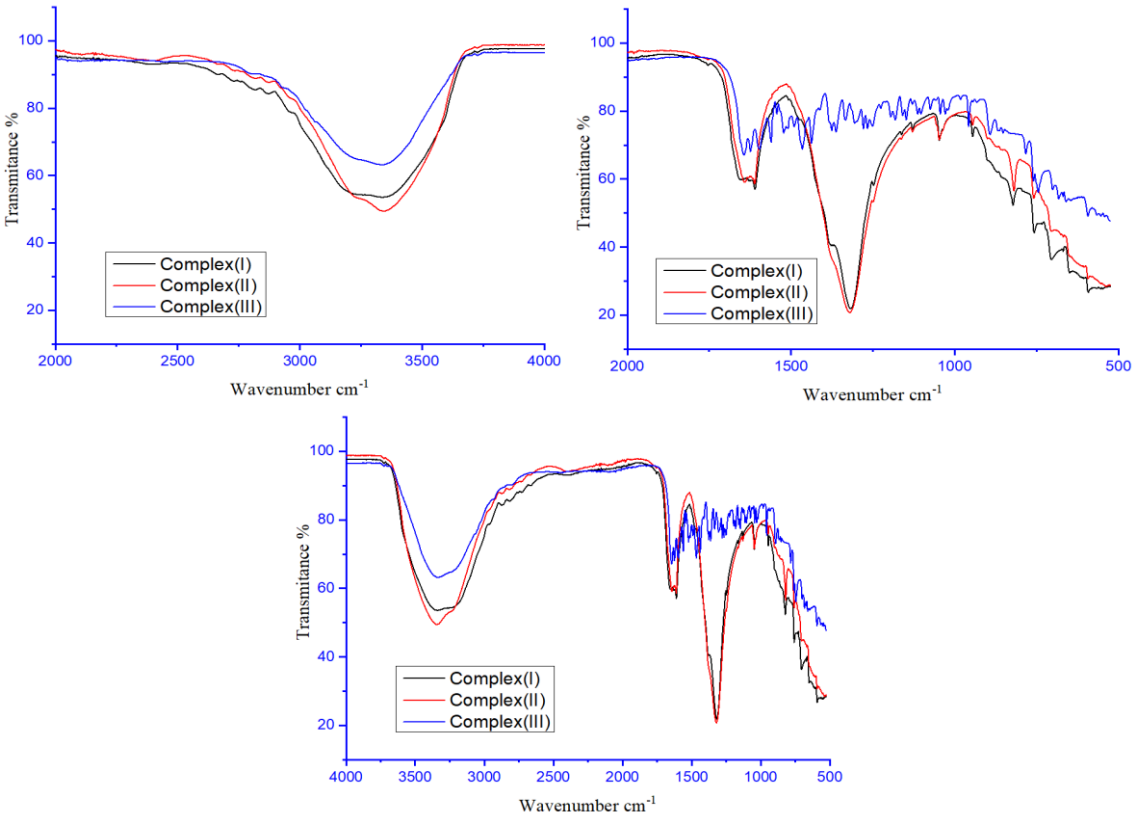


Figure 2: FTIR spectra of complexes (I)-(III)

UV–vis spectral analysis of complexes (I)-III)

The coordination complex exhibits vibrant colours as a result of the presence of vacant d orbitals, which undergo d-d transitions upon interaction with light. This process leads to the absorption of specific wavelengths of light, resulting in complimentary colours being observed. The synthesized complexes were also characterized via UV–Vis (200-800 nm) because of their d-d transition and different peaks as compared to those of the raw material. All the complexes were dissolved in methanol and their characteristic peaks were analyzed [30,31]. The shift of lower to higher d-d transitions in the complexes that were absent from the ligand was due to the high electron density provided by the ligands and d-d transitions (Fig 3). Complexes (I/II) produced a sharp peak at 250–380 nm while complex (III) at 210–240 nm and 300–325 nm had an absorption peak. This could be caused by the n→σ* transition of the C-O/C-N groups in the complex or by the n→π* transition of the C=O group. Perhaps, the central metal of complex (III) is Ni^{2+}, which is green and has a strong absorbance, A broad and wide peak from ultraviolet to visible region 373-438 nm is because of the d-d transition in complex (III) for C=C, C-O Transition. For complexes (II), the central Co^{2+} which forms a brownish colour complex, having small absorption peaks at 460-540 nm.

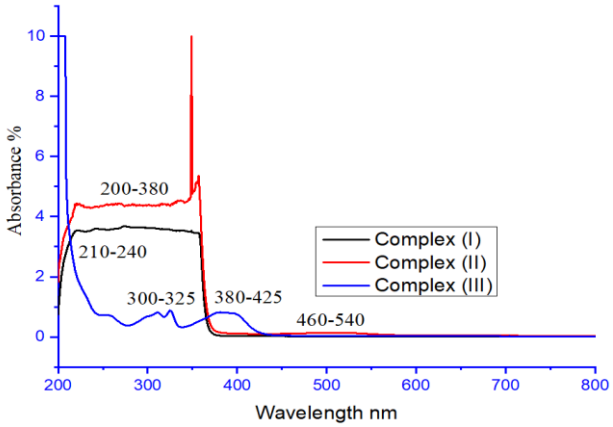


Figure 3: UV–vis spectra of complexes (I)-(III) in the range 200-800 nm.

Cytotoxicity assays of complexes (I)-(III)

The anticancer activity of complexes (I)–(III) and cisplatin were assessed, and the values of each compound were calculated using Reed and Muench's method [32], which demonstrated cytotoxic activity towards a variety of human cancer cell lines (SMMC-7721, A549, MDA-MB-231, and SW480). Complex (III) was the most effective, with an IC_{50} value of 6.57 μM, against the human tumor cell line MDA-MB-231.

In pursuit of understanding the correlations between the structure and activity of the metal complexes under investigation, the physical and chemical characteristics of the ligands and metal ions were taken into account throughout the research process. Structurally, we found that the reported activities were linked to the central ions of the metal coordination spheres, the features and coordination modes of the ligands, and the properties of the auxiliary ligands [33,34].

It was found that Complex (II) exerted the least cytotoxic effect on all the cell lines. On the other hand, complex (III) (8.90 μM) and (I) (35.77 μM) were comparatively more cytotoxic to the SMMC-7721 cell line. Similarly, Complex (III) (6.57 μM) was preferable to the other two complexes for its ability to treat the cell line MDA-MB-231. The best activity for cell lines SW480 and A549 was also shown by Complex (III) which are 10.16 μM and 19.3 μM, respectively. These findings led us to conclude that complex (III) produced the most potent cytotoxic effects against the four cancer cell lines (SMMC-7721, A549, MDA-MB-231, and SW480). Despite a high structural similarity of compounds (I) and (II), the anticancer activity of the compound (I) is more effective than that of compound (II), which indicates that the metal zinc ions are more beneficial in improving its anticancer activity. The relatively better activity of complex (III) compared to complexes (I and II) is likely attributed to the presence of coordinated DMF and water molecules, which can readily dissociate from the core metal and Ni(II) ion. This could enhance the interaction between metal ions and cancer cells. The ligands generated from organic hydrazides in complex (III) may also have a certain anticancer activity. In our laboratory, we are currently investigating other connections between the coordination environment of a metal atom and how it behaves.

Complex	SMMC-7721	SW480	MDA-MB-231	A549
	Cell Inhibition (%)			
I	99.01	90.62	8.98	9.06
II	39.80	14.81	1.84	1.64
III	98.67	76.36	84.91	92.07

Table 3: Cell Inhibition (%) of complexes (I)-(III) to the different human tumor cell lines.

Complex	SMMC-7721	SW480	MDA-MB-231	A549
	IC_{50} (μM) [a]			
I	35.77	47.88	---	---
II	---	---	---	---
III	8.90	10.16	6.57	19.3
cis	16.90	15.30	18.01	8.49

Table 4: Cytotoxicities of complexes (I)-(III) to the different human tumor cell lines.

[a]Each cell line's cytotoxicity was reported as an IC_{50} value using the SRB assay; this value represents the concentration of the complex that resulted in a 50% reduction in cell number when compared to untreated cells. The drug cisplatin served as a control in these studies.

Conclusion

In conclusion, the crystal structures of two mononuclear (Zn(II) and Co(II)) **I–II** and one binuclear Ni(II) complex **III** were reported using a simple method and were employed in contradiction of different human tumor cell lines. All complexes crystallized in the chiral space groups ($P2_1/n$ for (I)/(II) and P–1 for (III). Currently, research is underway on these complexes in various chemical processes, such as the coupling of amides with olefins and aldehydes.

Disclosure

Author Contributions: M. Luo designed the research and revised the article; Amir Nazeer performed the experiments, analysed the data, and wrote the manuscript; Qasim Umar helped in experiments and also performed the research work; Zhang Li and Yanting Yang aslo performed the research work; all the authors read and approved the final manuscript.

Data Availability Statement

Accession codes: complete crystallographic information files for all compounds have been deposited with the Cambridge Crystallographic Data Center as supplementary publications CCDC 2341288 (complex 1), 2341289 (complex 2) and 2341293 (complex 3). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_reque st/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. Provided in the manuscript.

Supporting Information: Bond lengths and angles, crystal stacking, infrared data.

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Declarations

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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