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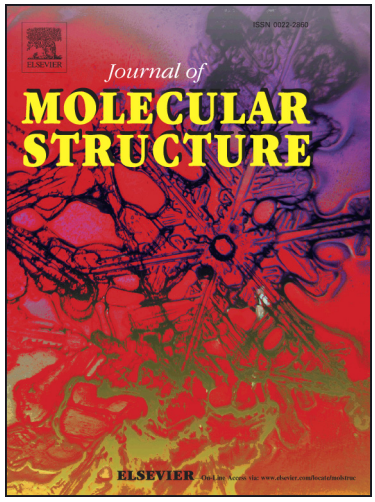

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Spectroscopic, thermal characterization and cytotoxic activity of bi-, tri- and tetra-nuclear Pd(II) and Pt(II) complexes with diSchiff base ligands

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ABSTRACT

In this paper; new di-, tri-, and tetra- nuclear Pd(II) and Pt(II) complexes of N,N'-bis(3,4-dihydroxybenzylidene)ethan-1,2-diamine (EDH_4), N,N'-bis(3,4-dihydroxy-benzylidene)-benzene-1,2-diamine (PDH_4) and N,N'-bis-(3,4-dihydroxybenzylidene)- 4,5-dimethyl-1,2-diamine ($MPDH_4$) ligands were synthesized by two different methods. The first method involve the synthesis of the three ligands from condensation reaction of 3,4-dihydroxybenzaldehyde ($L'H_2$) with ethylenediamine (en), o-phenylenediamine (o-PD), or 4,5-dimethyl-1,2-phenylendiamine (DMPD) in a mole ratio of 2: 1 followed by the reaction of the resulting Schiff bases ligands with Pd(II) or Pt(II) ions in the presence of 2,2'-dipyridyl (L) to form the di- and tri- nuclear metal complexes. The second method involve the condensation of the Pd complex LPd(II)L', (L = 2,2'-dipyridyl, L' = 4-formylbenzene-1,2-bis(olate)) with en, o-PD, or DMPD in a mole ratio of 2: 1, respectively, followed by reaction with $PdCl_2$ to form di-, tri-, and tetra- nuclear palladium(II) complexes, respectively. Structures of ligands and metal complexes are characterized by physical properties, FT-IR spectra and nuclear magnetic resonance. The geometries of metal complexes are suggested according to elemental analysis, electronic absorption spectra, thermal analysis, atomic absorption, magnetic susceptibility and molar conductance. Cytotoxic activity against lung

large cell carcinoma (H460), prostate carcinoma (DU145), breast adenocarcinoma (MCF-7), amelanotic melanoma (M-14), colon adenocarcinoma (HT-29), and chronic myelogenous leukemia (K562) is also reported.

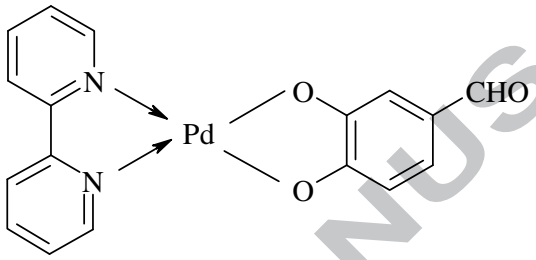
KEYWORDS

Polynuclear complexes, Pd(II) and Pt(II) complexes, Schiff base ligands, Cytotoxicity

1. Introduction

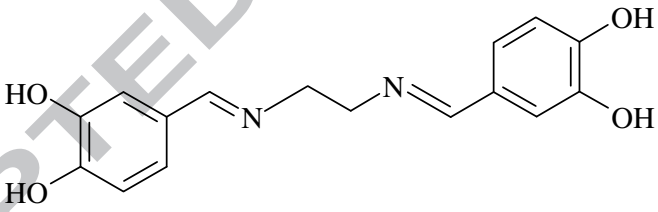
Multinuclear transition metal complexes have become a central theme of current research because of their potential properties. Synthesis and characterization of polynuclear iron, cobalt, nickel, copper and zinc complexes are reported by many researchers [1-7]. The wide range of coordination numbers and geometries, accessible redox states, thermodynamic and kinetic characteristics, and the intrinsic properties of the cationic metal ion and ligand itself offer the medicinal chemist a wide spectrum of reactivities that can be exploited. Biological evaluation of polynuclear complexes of different ligands with Fe(III), Co(II), Ni (II), Cu(II), Pd(II), Ag(I), Pt(II), Hg(II) and diorganotin(IV) are also reported in literature [4,7-16]. The aim of this work is to synthesize di- and tri- nuclear Pd(II) and Pt(II) complexes as synthetic models for multicenter active sites of biological systems by following two methods. The first method (method 1) involves the reaction of metal salts with each of the following three new di-Schiff base ligands: N,N'-bis(3,4-dihydroxybenzylidene)ethan-1,2-diamine (EDH_4) (Figure 2), N,N'-bis(3,4-dihydroxybenzylidene)benzene-1,2-diamine (PDH_4) (Figure 3), and N,N'-bis(3,4-dihydroxybenzylidene)-4,5-dimethyl-1,2-diamine ($MPDH_4$) (Figure 4) prepared from the condensation reaction of 3,4-dihydroxybenzaldehyde with ethylenediamine (en), o-phenylenediamine (o-PD), or 4,5-dimethyl-1,2-phenylendiamine (DMPD), respectively. The second method (method 2) involves the condensation reaction of

mononuclear Pd(II) mixed ligand complex of 3,4-dihydroxybenzaldehyde and 2,2'-dipyridyl (LPd(II)L') (Figure 1) (L = 2,2'-dipyridyl, L' = 4-formylbenzene-1,2-bis(olate)) with (en), o-PD, or DMPD followed by further reaction with the metal salts to form the tri- and tetra-homonuclear metal complexes. The structures of the complexes were elucidated depending on elemental analysis, UV-Vis, ^{1}H NMR, and FT-IR spectra as well as, thermal analysis, atomic absorption, conductivity measurements, and magnetic susceptibility.



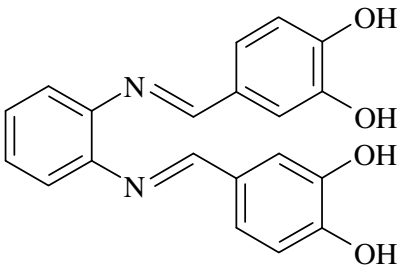
LPd(II)L', (L = 2,2'-dipyridyl, L' = 4-formylbenzene-1,2-bis(olate))

Figure 1



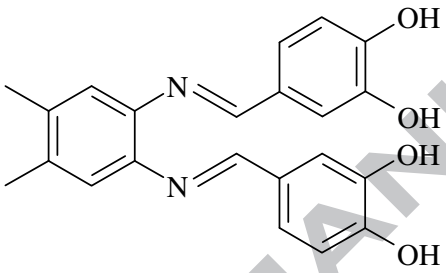
N,N'-bis(3,4-dihydroxybenzylidene)ethan-1,2-diamine (EDH_4)

Figure 2



N,N'-bis(3,4-dihydroxybenzylidene)benzene-1,2-diamine (PDH_4)

Figure 3



N,N'-bis(3,4-dihydroxybenzylidene)-4,5-dimethyl-1,2-diamine ($MPDH_4$)

Figure 4

2. Materials and Methods

All chemicals and solvents (AR) were obtained from Merck except absolute ethanol was (Sigma-Aldrich). ^{1}H and ^{13}C NMR was recorded on Perkin Elmer 283B and 300 MHz Varian XL-300 instruments. IR spectra were recorded on a Perkin Elmer (Spectrum 1000) Fourier-transform infrared (FTIR) spectrometer, using KBr pellets. Elemental analyses were determined at the micro-analytical center, Cairo University, and the results are in agreement with calculated values. Melting points (uncorrected) were determined on Gallenkamp melting point apparatus. Electronic absorptions were recorded in DMF on a Shimadzu UV-1800 automatic spectrophotometer. Thermal analysis were measured under a nitrogen flow rate of 30 cm^3 min^{-1} using a Shimadzu TGA-60H thermo balance from room temperature up to 1000

°C. The metal contents of the complexes were determined by atomic absorption technique using Varian-AA 775 atomic absorption spectrophotometer. Molar conductance A_m, (Ω^{-1} cm^2 mol^{-1}), at 25 °C of freshly prepared (0.001 $mol.dm^{-3}$) metal chelates in DMF was determined using a YSI-32 model conductometer. The magnetic susceptibilities were measured using a Sherwood Scientific Ltd. Magnetic susceptibility balance (England).

2.1. Preparation methods

2.1.1. Method 1

Synthesis of Schiff Bases EDH_4, PDH_4, and $MPDH_4$, General Procedure: To a solution of 0.362 mmol diamine in a minimum amount of absolute ethanol (en, o-PD) or methanol (DMPD) containing 2 drops of piperidine, an ethanolic solution of 0.724 mmol 3,4-dihydroxybenzaldehyde was added. Precipitation took place immediately giving yellow, brown, and orange-yellow products, respectively. The mixtures were heated under reflux with continuous stirring for 1.5 h to allow for complete precipitation. The products were filtered, washed with ethanol, methanol, ether, and vacuum dried.

2.1.1.1. Synthesis of bi- nuclear (C^1, C^2) and tetra- nuclear (C^3) palladium bis(dipyridyl) Schiff base complexes

Di- nuclear palladium complexes C^1 and C^2 were prepared as follows: to a stirred ethanolic solution of Schiff bases (0.166 mmol EDH_4 and 0.143 mmol PDH_4) Pd(II) chloride (59%-Merck) (0.333 and 0.286 mmol, respectively), 2,2'-dipyridyl (0.333 and 0.287 mmol, respectively), and triethylamine (Et_3N) (0.665 and 0.574 mmol, respectively) were added in a minimum amount of ethanol. Precipitation took place immediately. Reflux was continued for 6 h with continuous stirring. The products were filtered off, washed with ethanol, and vacuum dried. C^3 was prepared by treating an ethanolic solution of 0.132 mmol $MPDH_4$ with a

solution mixture of excess 0.586 mmol Pd(II) chloride (59%-Merck), 0.265 mmol 2,2'-dipyridyl, and 0.531mmol Et_3N in ethanol. The mixture was heated under reflux for 6 h. A brown precipitate was formed. The product was filtered off, washed several times with hot ethanol, and vacuum dried.

2.1.1.2. Synthesis of a tri- nuclear palladium bis(dipyridyl) Schiff base Complex (C^4)

To an ethanol solution of 0.06 mmol C^1, 0.06 mmol Pd(II) chloride (59%-Merck) dissolved in a minimum amount of ethanol was added with continuous stirring for 2.5 h during which the color of solution changed to dark brown. The mixture was heated under reflux for 4 h. A brown precipitate was formed. The product was filtered off, washed with ethanol, and vacuum dried.

2.1.1.3. Synthesis of tetra- and tri- nuclear platinum bis- and tris(dipyridyl) complexes of EDH_4 and $MPDH_4$ (C^5 and C^6)

C^5 complex was prepared as follows: a solution of 0.333 mmol 2,2'-dipyridyl and 0.665 mmol Et_3N in a minimum amount of ethanol was added with continuous stirring to a solution of 0.1664 mmol EDH_4 in warm ethanol. Then a solution of 0.669 mmol platinum(II) chloride in ethanol was added. The color of solution changes to brown. The reaction mixture was then heated under reflux for 4 h. A brown precipitate was formed. The product was filtered, washed with hot ethanol, and vacuum dried. The preparation and purification of C^6 complex (dark green) was carried out in the same manner, but the quantities of the reactants are 0.1664 mmol $MPDH_4$, 0.4992 mmol 2,2'-dipyridyl, 0.499 mmol platinum(II) chloride, and 0.665 mmol Et_3N.

2.1.2. Method 2

In this method the metal complexes were prepared from condensation reaction of the Pd(II) complex precursor (LPd(II)L') (L = 2,2'-dipyridyl, L'= 4-formylbenzene-1,2-bis(olate)) with the diamines followed by the reaction with the metal chloride to form tri- and tetra-nuclear complexes.

2.1.2.1. Synthesis of LPd(II)L' complex

This complex was prepared by following a previously published method [17] with modification. A solution of 0.724 mmol Pd(II) chloride (59%-Merck) in ethanol was added to an ethanolic mixture of 0.724 mmol 3,4-dihydroxybenzaldehyde, 0.724 mmol 2,2'-dipyridyl, and 1.448 mmol triethylamine (Et_3N). The reaction mixture was stirred for 30 min. at room temperature during which a brown precipitate was formed. The mixture was heated under reflux for 2 h and the resulting product was separated by filtration, washed with hot ethanol, and dried under vacuum. The complex was characterized by elemental analysis and the FT-IR spectral analysis.

2.1.2.2. Synthesis of bi- nuclear palladium bis(bipyridyl) Schiff base complexes (C^7), (C^8), and (C^9)

An ethanol solution of 0.14 mmol (en, o-PD, and DMPD), was added to a solution of 0.28 mmol LPd(II)L' complex in hot ethanol with stirring for 30 min. The mixture was then heated under reflux for 3 h to allow for complete precipitation. The products were filtered off, washed with ethanol and ether, and vacuum dried.

2.1.2.3. Synthesis of tri- nuclear palladium bis(dipyridyl) Schiff base complexes (C^{10}) and (C^{11})

To a solution of 0.06 mmol (C^7 and C^9) complexes in hot ethanol, 0.06 mmol Pd(II) chloride (59%-Merck) was added in a minimum amount of ethanol with stirring for 1 h. The colors of solutions changed to brown and precipitation of complexes took place. The mixtures were heated under reflux for 6 h and the products were filtered off, washed with ethanol, and vacuum dried.

2.2.1. Biological Activity

2.2.1.1. Cell Culture

The H460 (human lung large cell carcinoma), M-14 (human amelanotic melanoma), DU145 (human prostate carcinoma), MCF-7 (human breast adenocarcinoma), HT-29 (human colon adenocarcinoma), and K562 (human chronic myelogenous leukemia) cell lines were obtained from the National Research Center Dokki, Giza, EGYPT. All the cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal calf serum and 50 $\mu g/cm^3$ gentamycin in humidified 5% CO_2 and 95% air at 37 °C.

2.2.1.2. Assessment of Cytotoxicity

The assay was performed as described previously [33]. Briefly, 3-5 x 10^3 cells were inoculated in each well of 96-well tissue culture plates and incubated at 37 °C with their corresponding culture medium during 24 h. The ligands (EDH_4, PDH_4 and $MPDH_4$) (10–250 μM), complexes (0.01–10 μM), or cisplatin (1–10 μM) in DMSO were then added and incubated for 48 h at 37 °C with a highly humidified atmosphere, 5% CO_2 and 95% air. After the incubating period, cell monolayers were fixed with 10% trichloroacetic acid and stained for 20 minutes using the sulforhodamine B dye. Then, the excess dye was removed by

washing repeatedly with 1% acetic acid. The protein-bound dye was solubilized with 10 mM Tris buffer (pH 10.5) and the absorbance values were obtained at 510 nm using a microplate reader. The IC_{50} value was defined as the concentration of a test sample resulting in a 50% reduction of absorbance as compared with untreated controls and was determined by linear regression analysis.

2.2.1.3. Antioxidants status assay

Enzyme activities and the level of both reduced GSH and lipid peroxidation (LP) were expressed in cell lysates as a function of total cellular protein [34]. Activities of SOD, CAT, and GSH-Px were determined as described in the literature [35-37]. Levels of reduced GSH and hydrogen peroxide (H_2O_2) were determined using the methods of Ellman and Wolf [38,39].

Table 1: Physical and analytical data for Schiff bases and their metal complexes

Formula	Color	M.p. °C	% Yield	% C found (Calc.)	% H found (Calc.)	% N found (Calc.)	% M found (Calc.)	% Cl found (Calc.)
EDH_4	Yellow	210	63.4	65.04 (65.17)	5.77 (5.42)	9.78 (10.12)	--	--
$PDH_4{\cdot}4H_2O$	brown	239	36.2	57.78 (57.46)	3.84 (4.11)	7.32 (7.27)	--	--
$MPDH_4{\cdot}EtOH$	orange yellow	220	62.7	67.50 (68.11)	6.27 (6.52)	7.72 (7.54)	--	--
C^1: $C_{36}H_{28}N_6O_4Pd_2$	Brown	> 260	69.9	52.63 (51.99)	3.44 (3.31)	10.23 (10.21)	25.91 (26.17)	--
C^2: $[C_{40}H_{28}N_6O_4Pd_2]2H_2O$	Dark brown	> 260	41.1	53.05 (53.14)	3.56 (3.17)	9.28 (9.37)	23.50 (23.62)	--
C^3: $[C_{40}H_{32}N_6O_4Pd_4Cl_4]H_2O$	Brown	> 260	64.6	46.00 (45.54)	3.79 (3.89)	8.25 (7.98)	23.79 (24.18)	12.57 (12.67)
C^4: $C_{36}H_{28}N_6O_4Pd_3Cl_2$	Dark brown	> 260	68.4	43.29 (42.95)	2.83 (3.01)	8.42 (8.33)	31.96 (32.50)	7.10 (6.87)
C^5: $[C_{36}H_{28}N_6O_4Pt_4Cl_4]H_2O$	Dark brown	> 260	28.1	27.91 (28.27)	1.95 (2.13)	5.43 (5.86)	50.39 (50.64)	9.16 (9.18)
C^6: $[C_{52}H_{40}N_8O_4Pt_3]2Cl.Et_3N$	Dark brown	> 260	26.2	43.76 (43.58)	3.71 (3.47)	7.95 (7.89)	36.73 (36.62)	4.81(4.44)
C^7: $C_{36}H_{28}N_6O_4Pd_2$	Dark brown	> 260	68.5	59.50 (60.31)	4.55 (4.63)	11.73 (11.81)	17.93 (18.19)	--
C^8: $[C_{40}H_{28}N_6O_4Pd_2]H_2O$	Brown	> 260	82.1	59.38 (60.20)	4.15 (4.21)	9.61 (9.54)	16.54 (16.57)	--
C^9: $[C_{42}H_{24}N_6O_4Pd_2]3H_2O$	Deep orange	> 260	74.2	58.39 (58.16)	4.12 (3.99)	8.92 (9.24)	15.22 (15.36)	--
C^{10}: $C_{36}H_{28}N_6O_4Pd_4Cl_4]3H_2O$	brown	> 260	54.3	35.15 (34.89)	2.79 (2.82)	6.83 (6.55)	34.60 (34.19)	11.39 (11.53)
C^{11}: $[C_{42}H_{36}N_6O_6Pd_3]2Cl$	brown	> 260	60.7	45.41 (45.66)	3.27 (3.43)	7.59 (7.76)	28.73 (28.79	6.38 (6.15)

Table 2: Significant FT-IR bands (cm^{-1}) for Schiff bases and their metal complexes

Symbol	υOH	υC-H	υC=N (imine)	υC=N (dipy.)	υH_2O Coord.	υM-O	υM-N	υM-Cl
EDH_4	3263	2839	1651 1608	--	--	--	--	--
$PDH_4 \cdot 4H_2O$	3253	2750	1631 1604	--	--	--	--	--
$MPDH_4 \cdot EtOH$	3251	2985	1670	--	--	--	--	--
C^1	--	2860 2760	1654 1608	1519	--	420	370	--
C^2	--	2950	1640 1610	1500	--	460	350	--
C^3	--	2900	1658 1604	1570	--	474	385	297^t 254^b
C^4	--	2800 2750	1643 1604	1543	--	470	385	340^t
C^5	--	2750	1653 1610	1580	--	490	405	312^t 248^b
C^6	--	2980 2870	1640 1610	1560	--	560	395	--
C^7	--	2951 2839	1655	1573	--	478	358	--
C^8	--	2980	1630	1590	--	490	400	--
C^9	--	2823 2754	1651 1608	1570	--	489	389	--
C^{10}	--	2950 2800	1645 1600	1550	--	450	322	304^t 250^b
C^{11}	--	2960 2850	1660 1610	1550	3300 770 650	560	343	--

t = terminal, b = bridged

3. Results and Discussion

3.1. Synthesis

Synthesis by method 1 involves the condensation reaction of the diamines with two molecules of 3,4-dihydroxybenzaldehyde ($L'H_2$) to form the diSchiff bases as a first step for the formation of metal complexes. Whereas, second method involve the condensation reaction between the diamine molecule and two molecules of the mixed ligand palladium complex precursor LPd(II)L'. Although the last method is simpler than the first method to avoid side reactions, the palladium complex precursor is slightly soluble in cold ethanol and therefore reaction with this complex required heating in large amount of solvent. The complexes were non-crystalline which made it difficult to obtain their single crystal structures.

3.2. IR spectra

The important vibrational modes of IR spectra for the Schiff bases and their Pd(II) and Pt(II) complexes are described in Table 2. The spectra of the free ligands displayed strong to medium absorption band in the wave number region 3263-3251 cm^{-1} which were assigned to intramolecular hydrogen bonding of the two adjacent OH groups [18]. These bands were absent in the spectra of all complexes which indicates that the phenolic oxygen atoms were bonded to the metal ions [3-5,17]. The spectrum of the mixed ligand palladium(II) complex precursor LPd(II)L' displayed strong absorption bands at 1660 and 1540 cm^{-1} assigned to the stretching vibrations of the C=O and C=N groups of L' and L moieties, respectively [17,19]. The low intensity bands observed at lower wave number region at 440 and 345 cm^{-1} were assignable to stretching vibrations of Pd-O and Pd-N bonds, respectively [3,5]. The strong bands

observed at 1670-1631 cm^{-1} and 1608, 1604 cm^{-1} in the spectra of the Schiff bases were assigned to the asymmetric and symmetric stretching vibration of the azomethine group (υC=N) [2-5]. These bands were shifted to lower frequency in complexes C^3, C^4, C^5, C^6, C^{10} and C^{11} indicating the coordination of the Schiff bases with the metal ions through the azomethine nitrogens [5]. All complexes exhibited strong bands at wave number range 1590-1500 cm^{-1} attributed to υC=N of coordinated dipyridyl ligand [20]. The bands appeared at 3300, 770 and 650 cm^{-1} in the spectra of C^{11} is attributed to vibrational modes of coordinated H_2O [21]. The spectrum of $MPDH_4$ exhibited a strong band at 3251 cm^{-1} attributed to OH stretching vibrations of ethanol embedded in the crystal lattice of the ligand [19,21]. Further bands which appeared at lower frequencies in the spectra of metal complexes were assigned to M-O, M-N and M-Cl stretching vibrations (Table 2).

3.3. NMR spectra

The ^1H NMR spectra of diSchiff bases and their complexes were recorded in DMSO and the chemical shifts and peak assignments are given in Table 3. The spectra of the Schiff base ligands showed a broad peak in the range δ = 8.5-9.9 ppm attributed to phenolic hydroxyl protons [3,4,22]. The absence of this peak in the spectra of complexes (Table 3) confirms the involvement of deprotonated phenolic groups in chelation to the metal ions [22,23]. The peaks displayed by ^1H NMR spectra of Schiff bases in the range δ = 7.9–8.7 ppm were attributed to chemical shifts of the azomethine protons (HC=N) [3,4,22,23]. The spectra of the complexes exhibited the absence of the signals related to OH protons and the appearance of the azomethine proton signals downfield, which confirms the formation of the metal complexes [22,23]. Signals of aromatic and aliphatic protons were observed in the chemical shift

ranges 6.6–8.9 and 0.9–3.5 ppm, respectively [19]. Chemical shifts for ^{13}C NMR of EDH_4 and $MPDH_4$ in DMSO are described in Table 4. The signals assigned to the chemical shifts of methylene and methyl groups for the two ligands, respectively, were observed at 60.99 (CH_2) and at 19.8 and 20.1 (CH_3) ppm [24], while the signals of aromatic carbons were located at 113.6-161.2 and 110.8-146.8 ppm, respectively [24,25]. The signals observed at 167.2 and 150.6-152.7 ppm, respectively, were attributed to the chemical shifts of azomethine carbons, which confirms the formation of the Schiff bases [26-28].

Table 3: ^{1}H NMR data of the three Schiff base ligands and complexes in DMSO

Compound	Chemical shift δ, (ppm)
EDH_4	(8.8-9.9, 4H, b; protons of OH), (8.1, 2H, s; azomethine protons), (6.7-7.4, 6H, m; aromatic protons), (3.9, 4H, s; protons of N-CH_2), (3.0-3.5, 2H, b; protons of H_2O in DMSO), (2.5, 6H, s; protons of DMSO)
PDH_4	(9.6-9.75, 4H, b; protons of OH), (7.9-8.7, 2H, b; azomethine protons), (6.5-7.9, 10H, b; aromatic protons), (3-3.5, 8H, b; protons of H_2O in DMSO), (2.5, 6H, s; protons of DMSO)
$MPDH_4$	(8.5-8.68, 4H, b; protons of OH), (8-8.28, 2H, b; azomethine protons), (6.9-7.6, 10H, b; aromatic protons), (3.0-3.6, 2H, m; protons of H_2O in DMSO), (2.5, 6H, s; protons of DMSO), (1.5-1.7, 6H, m; methyl protons)
C^1	(9.2-9.5, 2H, m; azomethine protons), (6.6-8.9, 22H, b; aromatic and dipyridyl protons), (3.4, 4H, d, $J_{H,H}$ = 7 Hz, protons of $2CH_2$, (2.1-2.4, 6H, m; protons of DMSO)
C^2	(9.5-9.90, 2H, m; azomethine protons), (7.1-8.5, 26H, b; aromatic and dipyridyl protons), (2.35, 4H, m; protons of H_2O), (2.2-2.5, 6H, m; protons of DMSO)
C^3	(9.5-9.8, 2H, b; azomethine protons), (7.2-8.1, 24H, m; aromatic and dipyridyl protons), (2.6, 2H, m; protons of H_2O), (2.15-3.2, 6H, m; protons of DMSO), (1.9, 6H, s; methyl protons)

C^4	(9.45-9.7, 2H, m; azomethine protons), (7.1-8.4, 24H, b; aromatic and dipyridyl protons), (3.5, 4H, d, $J_{H,H}$ = 9 Hz, protons of $2CH_2$, (1.9-2.2, 6H, m; protons of DMSO)
C^5	(8.9-9.3, 2H, m; azomethine protons), (6.9-7.8, 24H, b; aromatic and dipyridyl protons), (3.5, 4H, d, $J_{H,H}$ = 10 Hz, protons of $2CH_2$, (2.85, 2H, m; protons of H_2O) (1.8-2.2, 6H, m; protons of DMSO)
C^6	(9.8-10.45, 2H, b; azomethine protons), (6.6-8.9, 32H, b; aromatic and dipyridyl protons), (2.45-3.1, 12H, b; protons of DMSO and ethyl CH_2), (0.9-1.75, 15H, b; methyl protons)
C^7	(9.3-9.7, 2H, m; azomethine protons), (7.0-8.7, 22H, b; aromatic and dipyridyl protons), (3.3, 4H, $J_{H,H}$ = 7 Hz, protons of $2CH_2$, (2.4-2.6, 6H, m; protons of DMSO)
C^8	(9.1-9.50, 2H, m; azomethine protons), (6.9-7.8, 26H, b; aromatic and dipyridyl protons), (2.35, 2H, m; protons of H_2O), (2.2-2.7, 6H, m; protons of DMSO)
C^9	(10.1-10.98, 2H, b; azomethine protons), (6.7-7.5, 24H, b; aromatic and dipyridyl protons), (3.2, 6H, m; protons of H_2O), (2.4-2.8, 6H, m; protons of DMSO), (0.97-1.85, 6H, b; methyl protons)
C^{10}	(8.9-9.3, 2H, m; azomethine protons), (6.9-7.8, 24H, b; aromatic and dipyridyl protons), (3.5, 4H, $J_{H,H}$ = 10 Hz, protons of $2CH_2$, (2.85, 2H, m; protons of H_2O) (1.8-2.2, 6H, m; protons of DMSO)
C^{11}	(10-10.3, 2H, m; azomethine protons), (7.4-7.9, 24H, b; aromatic and dipyridyl protons), (3.1-3.4, 4H, b; protons of H_2O merged with the DMSO water bands), (2.15-3.2, 6H, m; protons of DMSO), (1.9, 6H, s; methyl protons)

Table 4: ^{13}C NMR chemical shifts of Schiff bases EDH_4 and $MPDH_4$ in DMSO

Schiff base	Chemical shift δ (ppm)	Assignments
EDH_4	60.99	Carbon of CH_2
	113.6–161.2	Aromatic carbons
	167.2	Carbon of HC=N

$MPDH_4$	19.8, 20.1	Carbon of methyl group
	110.8–146.8	Aromatic carbons
	150.6, 152.7	Carbon of HC=N

3.4. Electronic Spectra, Conductivity and Magnetic Susceptibility Measurements

The results of electronic spectra of the ligands and their metal complexes in DMF are described in Table 5. The three ligands exhibited high intensity bands, which appeared at wave number region 405-300 nm, and low intensity bands at 480-361 nm that were assigned to $\pi \rightarrow \pi*$ and $n \rightarrow \pi*$ transitions, respectively [19]. The spectra of metal complexes exhibited hypsochromic shifts of the ligand $\pi \rightarrow \pi*$ band, which refers to complex formation with the metal ions [24]. The spectra of complexes exhibited additional medium intensity bands in the near UV to visible region at 430-354 nm, which are attributed to charge transfer transitions [29]. The palladium and platinum complexes displayed bands in the regions 832-771 nm, 653-531 nm, and 502-461 nm assigned to $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, and $^1A_{1g} \rightarrow {}^1E_{1g}$ transitions, respectively, of square planar Pd(II) and Pt(II) complexes [29-31]. The energies of υ_1 as well as the values of the spectral parameters Dq/B', B', 10Dq, and nephelauxetic ratio β for the Pt(II) complexes C^5 (7083 cm^{-1}, 0.9, 787 cm^{-1}, 7080 cm^{-1}, and 0.811, resp.), and C^6 (6456 cm^{-1}, 0.7, 807 cm^{-1}, 5740 cm^{-1}, and 0.831, resp.), were calculated by applying the band ratio υ_3/υ_2 on Tanabe-Sugano diagram of d^8 complexes. The values of β indicate a covalent bonding character of both complexes [19]. Conductivity measurements in DMF showed non-electrolytic nature for all complexes (Table 3) except C^6 and C^{11} which were electrolytes with ionic ratio (1: 2) [32]. Magnetic susceptibility measurements at room temperature showed that all complex are diamagnetic that agrees with square planar geometry. According to the

aforementioned results in addition to elemental analysis and FT-IR and NMR spectra the chemical structures of the studied complexes were suggested as is illustrated in Scheme 1.

Table 5. Electronic transitions and molar conductance of ligands and complexes

Symbol	Band positions (nm)	Assignment	molar conductance (Ω^{-1} cm^2 mol^{-1})
EDH_4	301, 405	$\pi \rightarrow \pi*$	0.0018
PDH_4	301, 360	$\pi \rightarrow \pi*$	0.011
	480	$n \rightarrow \pi*$	
$MPDH_4$	301	$\pi \rightarrow \pi*$	0.0007
	361	$n \rightarrow \pi*$	
C^1	315	$\pi \rightarrow \pi*$ (Intraligand)	2.47
	354	C.T	
	786, 607, 461	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^2	322	$\pi \rightarrow \pi*$ (Intraligand)	6.42
	359	C.T	
	818, 641, 482	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^3	309	$\pi \rightarrow \pi*$ (Intraligand)	1.78
	387	C.T	
	832, 593, 476	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^4	345	$\pi \rightarrow \pi*$ (Intraligand)	0.56
	410	C.T	
	809, 577, 483	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^5	321	$\pi \rightarrow \pi*$ (Intraligand)	3.40
	379	C.T	
	827, 531, 500	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^6	365	$\pi \rightarrow \pi*$ (Intraligand)	154.12
	427	C.T	
	786, 653, 499	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^7	346	$\pi \rightarrow \pi*$ (Intraligand)	7.06
	430	C.T	
	771, 648, 470	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^8	348	$\pi \rightarrow \pi*$ (Intraligand)	6.15

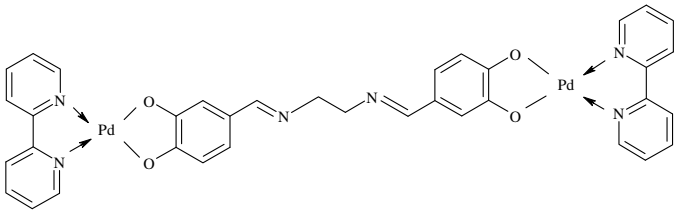
	420	C.T	
	776, 650, 468	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^9	317	$\pi \rightarrow \pi*$ (Intraligand)	9.21
	406	C.T	
	782, 581, 475	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^{10}	361	$\pi \rightarrow \pi*$ (Intraligand)	2.55
	397	C.T	
	790, 619, 481	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	
C^{11}	327	$\pi \rightarrow \pi*$ (Intraligand)	141.56
	358	C.T	
	801, 562, 502	$^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_{1g}$	

3.5. Thermal Analysis.

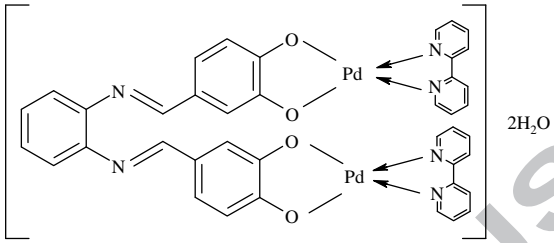
The decomposition temperature range and the % weight losses for the two complexes C^6 and C^{10} are described in Table 6. The loss of solvent molecules embedded in the crystal lattice of the complexes as well as uncoordinated water molecules took place at the first stage at temperature range 73-180 °C with peak temperatures at 100 and 98 °C, respectively. The loss of dipyridyl and chloride ligands took place at temperature range 400-900 °C. The DTG of C^6 showed three peaks at 412, 620, and 822 °C for this stage. The high percentage of the remaining residues at 1000 °C indicates that the two complexes are very stable and require a higher temperature range for complete decomposition that is quite common for poly nuclear metal complexes [5]. Suggested structures of the synthesized complexes according to elemental analysis, electronic absorption spectra, thermal analysis, atomic absorption, magnetic susceptibility and molar conductance are given in Scheme 1.

Table 6. Thermal decomposition of complexes C^6 and C^{10}

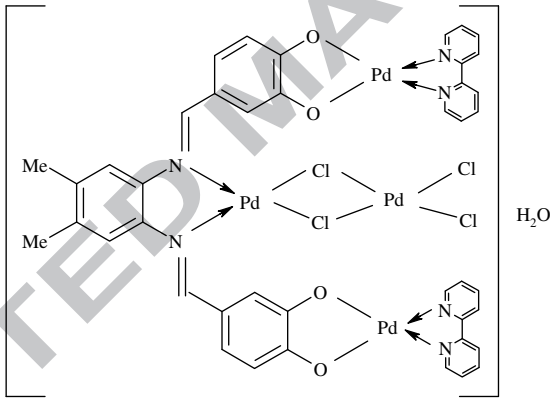
C^6 stable phase $[MPD(Pt)_3(dipy)_3]2Cl.\ Et_3N$ M.wt. = 1598.31	Decomposition temp. range °C	% Weight loss found (calc.)
↓ 0.4 Et_3N	82-209	2.44 (2.53)
↓ 0.6 Et_3N + Cl	210-423	6.26 (6.02)
↓ $2CH_3$ + 2 dipy + C_6H_2	424-661	26.18 (26.06)
↓ Cl + dipy + HCN	662-998	13.70 (13.68)
$C5H_4NO_2Pt_2 + C_6H_4O_2Pt$ (residue)	--	50.29 (51.77)
C^{10} stable phase $[ED(Pd)_4(dipy)_2Cl_4].3H_2O$ M.wt. = 1230.09	Decomposition temp. range °C	% Weight loss found (calc.)
↓ $3H_2O$	73-116	4.27 (4.39)
↓ C_2H_4	262-365	2.34 (2.28)
↓ C_5H_4N + dipy	366-542	18.44 (18.72)
↓ 4Cl	543-761	11.19 (11.53)
↓ C_5H_4N	762-998	5.99 (6.35)
$C_{14}H_{12}N_2O_4Pd_4$ (residue)	--	57.16 (56.73)



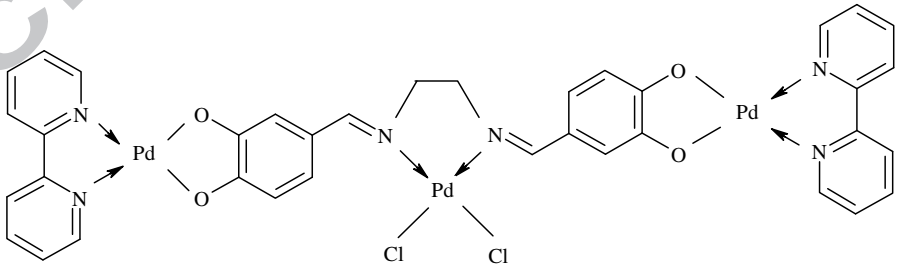
C^1



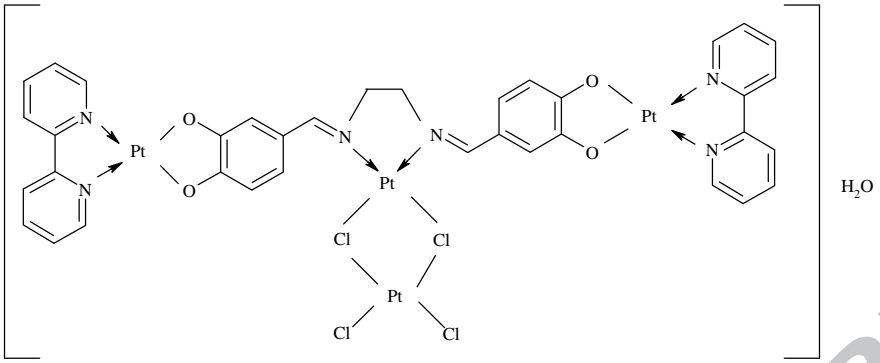
C^2



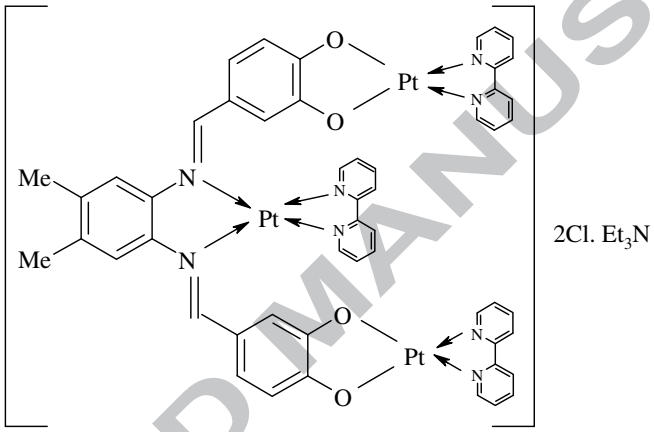
C^3



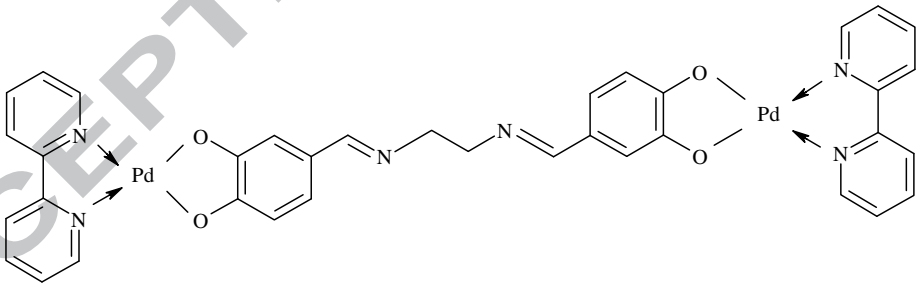
C^4



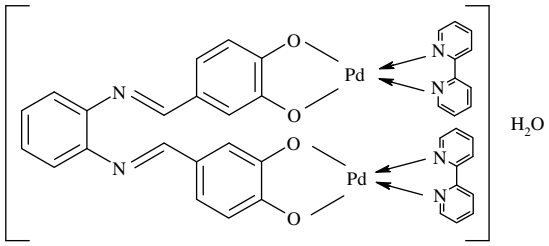
C^5



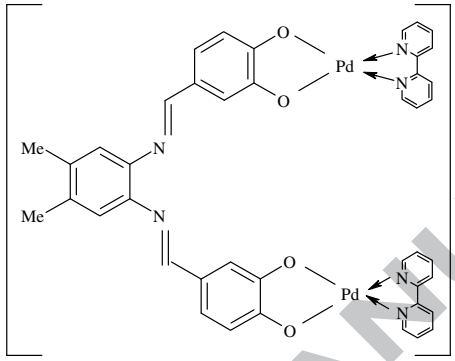
C^6



C^7



C[8]



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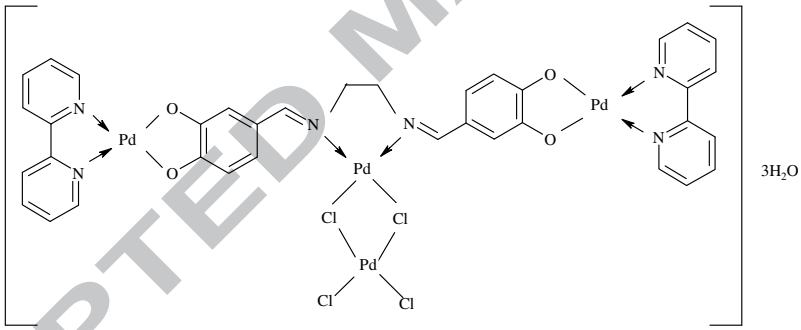
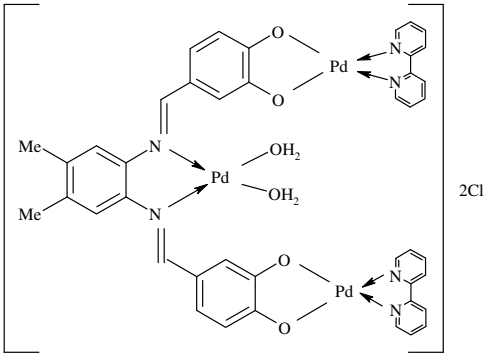


C[10]



C[11]

Scheme 1 Suggested structures of the synthesized complexes

3.6. Antitumor Evaluation

The cytotoxic potential of the ligands (EDH_4, PDH_4 and $MPDH_4$) and their respective complexes were investigated *in vitro* against six human tumor cell lines: H460, DU145, MCF-7, M-14, HT-29, and K562. For comparison purposes, the cytotoxicity of cisplatin was evaluated under the same experimental conditions. The results are expressed in Table 7 as IC_{50} values (median inhibitory concentration 50% cell growth). All complexes show cytotoxic activity more than ligands. The antitumor activity of tri- and tetra- nuclear complexes are higher than that of binuclear complexes. Figure 5 shows representative cytotoxic activity of promising complexes against DU145, MCF-7, M-14 and HT-29. Platinum complexes C^5 and C^6 are highly cytotoxic even more than cisplatin against the six human tumor cell lines expressed. Palladium complex C^{11} has cytotoxic activity higher than cisplatin against DU145, MCF-7, M-14 and HT-29 whereas C^{10} has cytotoxic activity higher than cisplatin against DU145 and MCF-7. All other complexes have IC_{50} close to that of cisplatin.

To elucidate the mechanism by which the prepared complexes exert their antitumor activities, we estimated the activities of the free radical-metabolizing enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), as well as the levels of glutathione (GSH) and H_2O_2 in HT-29 cells. As shown in Table 8, treatment of the cells with the complexes C^6, C^{10} and C^{11} increased the activity of SOD and the level of H_2O_2 (in a dose-dependent manner) as compared with the control. In addition, our results revealed that treatment with the complexes leads to decrease in the activity of CAT and GSH-Px as well as the level of GSH (in a

dose-dependent manner). These results indicate that the antitumor effect of the present complexes may be exerted at least partly by production of H_2O_2. The antitumor activities are accompanied by dose-dependent increases in SOD activities of treated cells compared with the control group. This means that complexes can cause H_2O_2 production. The H_2O_2 produced should be rapidly removed through the activation of CAT and GSH-Px. The present results show that activities of CAT and GSH-Px and the level of reduced GSH are lowered in groups treated with the complexes (in a dose-dependent manner) compared with the control group (Table 8). Consequently, the excess H_2O_2 produced in tumor cells with complexes cannot be removed. In other words, the accumulation of H_2O_2 in tumor cells should be partly the cause of tumor cell death. Thus, the results of the present study are consistent with the hypothesis that the prepared complexes exert their antitumor effects through production of reactive oxygen species (ROS) so they are capable of inducing apoptosis and oxidative damage to DNA, proteins, and lipids [40]. Probably, complexes of square planar geometry act as intercalating agents between the pyrimidine and guanine bases of the DNA tumor cells, inducing conformational changes on the DNA double helix specific that finally produce tumor cell death [41,42].

Table 7. IC_{50} (μm) values* of the ligands and complexes against the different human tumor cell lines**

Symbol	H460	DU145	MCF-7	M-14	HT-29	K562
EDH_4	36.15	38.05	34.00	35.18	29.51	34.08
PDH_4	28.17	27.76	31.06	28.74	29.13	33.89
$MPDH_4$	32.71	35.65	34.91	29.99	38.46	30.27
C[1]	10.32	11.54	17.10	12.75	9.65	7.49

C^2	8.54	13.01	15.87	10.88	17.54	12.21
C^3	3.65	6.98	8.28	3.54	12.40	6.74
C^4	4.21	8.46	9.34	8.98	6.54	4.65
C^5	0.94	1.37	1.99	2.03	4.54	1.76
C^6	1.32	3.24	4.21	2.80	6.32	2.87
C^7	6.98	9.13	9.87	8.16	9.43	6.77
C^8	8.17	13.21	16.09	6.87	9.29	20.21
C^9	6.32	11.26	16.45	8.19	12.36	10.98
C^{10}	3.15	4.65	6.87	3.94	8.87	5.61
C^{11}	6.14	5.65	7.08	2.91	7.55	4.54
Cisplatin	2.85	6.50	7.20	2.95	7.60	3.20

*IC_{50} corresponds to the concentration required to inhibit 50% of the cell growth when the cells are exposed to the compounds during 48 h.

**Lung large cell carcinoma (H460), prostate carcinoma (DU145), breast adenocarcinoma (MCF-7), amelanotic melanoma (M-14), colon adenocarcinoma (HT-29), and chronic myelogenous leukemia (K562).

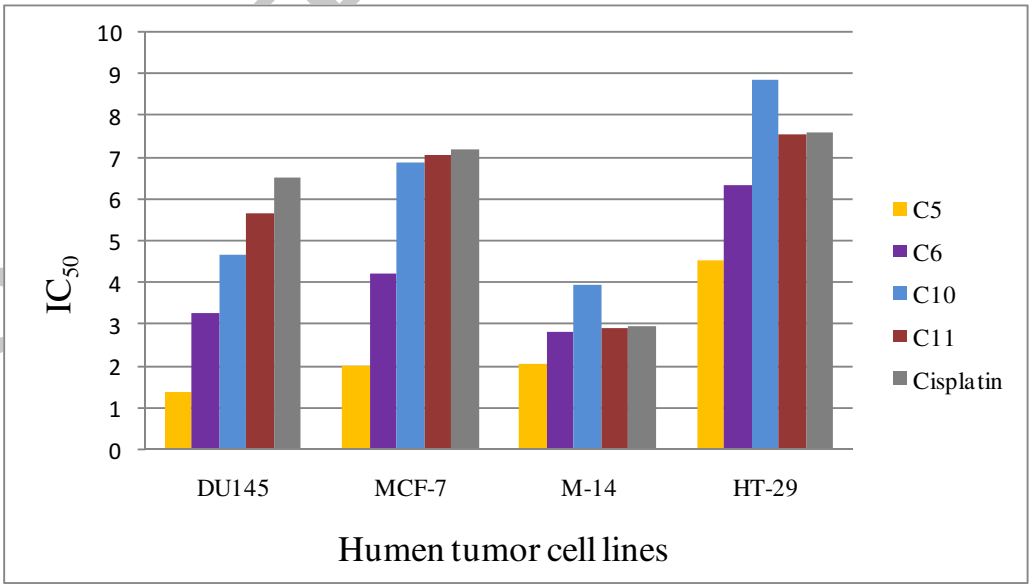


Figure 5. Representative cytotoxic activity expressed as IC_{50} of some complexes compared with cisplatin

4. CONCLUSION

The bi-, tri-, and tetra- nuclear bis- and tris- (dipyridyl) palladium(II) and platinum(II) mixed ligand complexes of three diSchiff base ligands derived from 3,4-dihydroxybenzaldehyde and three diamines in a stoichiometric ratio of 2:1 were successfully synthesized by two different methods. The structures of the ligands were confirmed by elemental and spectral analysis. Coordination of the metal ions to form tri- nuclear and tetra- nuclear complexes took place through the two imino nitrogens and phenolic dianionic oxygen atoms of each ligand molecule as was indicated by FT-IR spectra. The formation of bi- nuclear diSchiff base palladium bis(dipyridyl) complexes was achieved by reacting the mononuclear palladium(II) mixed ligand complex LPd(II)L' with the diamines in a 2: 1 ratio, respectively, as was confirmed by the NMR spectrum, while tri- nuclear bis- and tris(dipyridyl) and tetra- nuclear complexes of the three ligands were achieved by reacting the synthesized Schiff bases

Table 8. Effect of treatment with different concentrations of the ligand, C^6, C^{10} and C^{11} complexes on some metabolizing enzymes and hydrogen peroxide (H_2O_2) in colon adenocarcinoma (HT-29) cells

Treatment (µmol)	SOD (U/mg protein)	CAT (U/mg protein	GSH-Px (U/mg protein)	GSH (nmol/mg protein)	H_2O_2 (nmol/mg protein)
Control	30.45 ± 4.11	8.80 ± 0.50	9.50 ± 0.70	37.70 ± 3.20 0	11.70 ± 1.60
Cisplatin					
15	118.55 ± 13.40	3.61 ± 0.40	4.70 ± 0.48	17.46 ± 1.85	31.60 ± 3.61
30	143.33 ± 16.00	2.76 ± 0.30	3.62 ± 0.39	16.70 ± 1.75	53.50 ± 6.10
60	367.60 ± 24.80	2.54 ± 0.23	2.06 ± 0.25	15.61 ± 2.11	68.75 ± 6.51
120	412.80 ± 35.89	1.35 ± 0.11	1.74 ± 0.20	12.20 ± 1.64	84.50 ± 7.60
C^6 Complex					
15	82.65 ± 1.32	5.32 ± 0.30	6.58 ± 0.29	21.40 ± 2.41	20.54 ± 1.70
30	106.21 ± 6.32	3.75 ± 0.25	5.62 ± 0.33	20.37 ± 2.05	36.30 ± 3.71
60	257.21 ± 8.21	2.42 ± 0.15	5.23 ± 0.49	17.69 ± 1.93	57.12 ± 2.57
120	366.30 ± 20.22	2.21 ± 0.31	3.68 ± 0.42	16.29 ± 1.56	64.15 ± 4.11
C^{10} Complex					
15	175.23 ± 5.03	2.65 ± 0.68	4.53 ± 0.60	16.34 ± 0.24	42.89 ± 2.20
30	196.33 ± 8.42	2.23 ± 0.54	3.67 ± 0.58	14.64 ± 0.11	56.33 ± 3.16
60	423.54 ± 11.63	1.64 ± 0.37	3.35 ± 0.30	13.08 ± 0.35	79.40 ± 3.41
120	491.62 ± 15.40	0.91 ± 0.13	2.44 ± 0.42	11.37 ± 0.27	114.74 ± 4.82
C^{11} Complex					
15	117.90 ± 5.94	3.65 ± 0.20	4.94 ± 0.52	18.27 ± 0.21	29.34 ± 3.41
30	144.12 ± 8.52	2.83 ± 0.32	3.70 ± 0.50	16.89 ± 0.20	52.19 ± 2.57
60	359.64 ± 18.11	2.61 ± 0.45	2.42 ± 0.48	15.61 ± 0.28	65.20 ± 3.31
120	399.51 ± 27.19	1.49 ± 0.18	1.73 ± 0.20	12.87 ± 1.68	81.16 ± 4.26

Data are expressed as mean ± standard error (SE) of five separate experiments. All values for ligand, complexes, and cisplatin were significantly different at $p < 0.05$ versus control

with the palladium salts in the presence of 2,2'-dipyridyl. The diamagnetic properties of the complexes made them a good synthetic model for interaction the biological systems. The cytotoxic results show promising chemotherapeutic complexes possessing antitumor activity, higher in many cases or at least comparable in some cases to the activity of the commonly used anticancer drug cisplatin.

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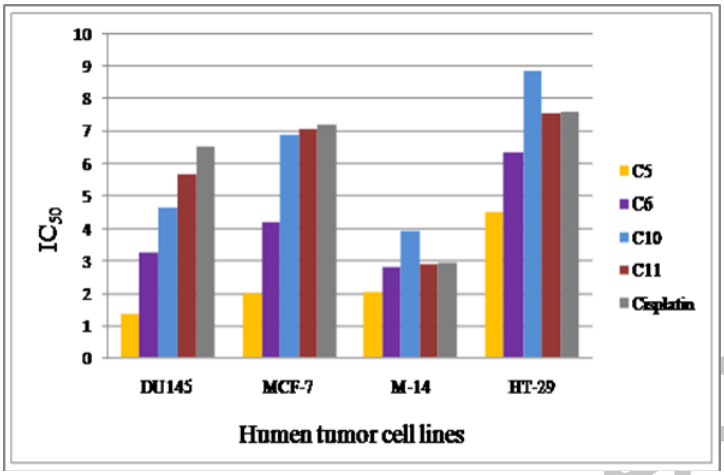
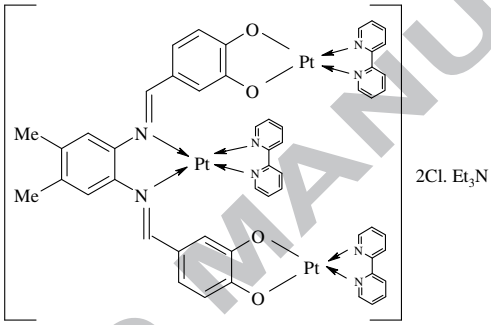
Graphical abstract





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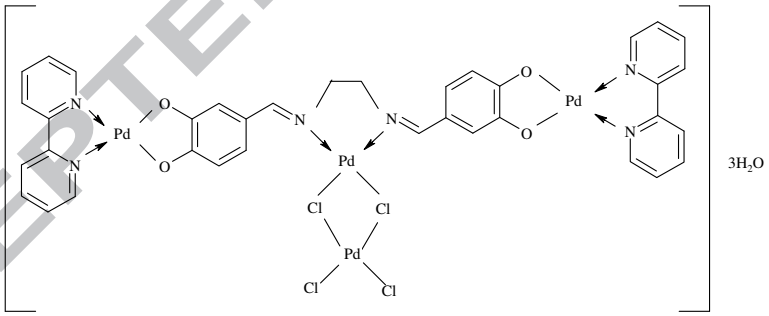

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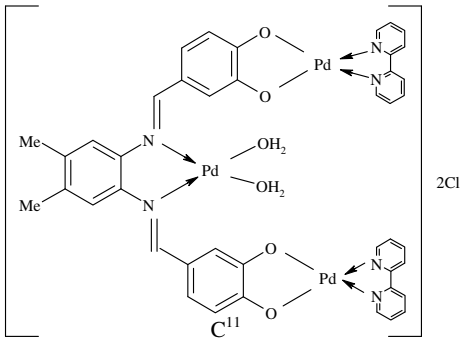

C^{11}

Highlights

- Poly-nuclear Pd(II) and Pt(II) complexes of diSchiff base ligands were synthesized.
- Structures are characterized by different spectroscopic techniques.
- Geometries of metal complexes are suggested using various methods .
- The cytotoxic results show promising chemotherapeutic antitumor activity.