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Dinuclear bridged biphosphinic and mononuclear cyclopalladated complexes of benzylamines: Synthesis, structural characterization and antitumor activity

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ABSTRACT

Reaction of chloro-bridged dinuclear palladacycles, $[Pd_2\{(C,N)\text{-}C_6H_4CH_2NH(R)\}_2(\mu\text{-}Cl)_2]$ (R = Et (**1a**); R = t-Bu (**1b**)) with pyridine and PPh_3 in the 1:2 M ratio at room temperature was used to prepare the mononuclear complexes, $[Pd(C,N)\text{-}C_6H_4CH_2NH(R)Cl(L)]$ (R = Et and L = Py (**2a**); R = t-Bu and L = PPh_3 (**2b**)). Bridged biphosphinic palladacycle, $[Pd_2(C,N\text{-dmba})_2(\mu\text{-dppe})(Cl)_2]$ (**2c**), (where dmba = *N,N*-dimethylbenzylamine and dppe = 1,2-bis(diphenylphosphino)ethane) has been also synthesized. The complexes were fully characterized by elemental analysis, IR and NMR spectroscopies. In addition, the solid structures of palladacycles **2a** and **2c** were studied by single-crystal X-ray crystallography. In vitro cytotoxicity assays of the cyclopalladated complexes, (**2a**–**2c**) and cisplatin were evaluated against the Hela (human cervix carcinoma), HT-29 (colon cancer cell line), K562 (leukemia cancer cell line) and MDA-MB-468 (human breast carcinoma). The complexes **2a**–**2c** display IC_{50} values in a μM range better than that of the antitumor drug cisplatin.

1. Introduction

Platinum-based antitumor drugs like cisplatin, carboplatin and oxaliplatin are the most active and widely used clinical agents for the treatment of advanced cancer. However, severe side effects such as nephrotoxicity, neurotoxicity, and drug resistance force the limitation of the dose as well as further use of them in clinical treatment [1–4]. Non-platinum metal complexes with potential for the clinical treatment such as those of ruthenium, gallium, and gold have demonstrated impressive antitumor properties in preclinical studies [5]. Palladium(II) complexes are intriguing alternative candidates for metallo-antitumor drugs due to their structural and thermodynamic similarities to platinum(II) complexes [6,7]. Several studies demonstrate that palladium derivates exhibit a noticeable cytotoxic activity, similarly to standard platinum-based drugs used as a reference, and show fewer side effects relative to other heavy metal anticancer compounds [8]. They show ligand-exchange kinetics 10^5 times greater than the Pt(II) analogous [9], which may facilitate the hydrolysis of the leaving groups that dissociate readily in solution, before the complex reaches the pharmacological target [10,11]. To overcome their high lability, chelating ligands have been used to afford high thermodynamically stable and kinetically inert Pd(II) complexes [12–17]. In particular, palladacycles are nowadays attracting attention as potential anticancer agents [18,19] because it is known that their intercalative mode of cytotoxic action is strictly related to the presence of a planar and highly stable aromatic metallacycle [20]. It has been found that some cyclopalladated complexes containing planar structures such as aromatic and aliphatic amines may bind to DNA by means of intercalative or coordinate covalent interactions [21]. Within this context, tertiary amine *N,N*-dimethylbenzylamine (dmba) represents good choice to prepare new ortho-cyclopalladated complexes with promising in vivo and in vitro cytotoxicity [6,22,23]. Some cyclopalladated complexes based on biphosphinic ligands were also reported by Rodrigues et al. [24] and these palladacycle–dppe complexes have been investigated for their antitumor activity in a syngeneic B16F10 murine melanoma model. In our present work, we describe the synthesis, spectroscopic and structural characterization of three cyclopalladated complexes, chloro bridging palladacycle **1a**, mononuclear palladacycle **2a** and biphosphinic palladacycle **2c**. The cytotoxicity of the mononuclear palladacycle **2b**, which was previously characterized [25], was reported here. We have also evaluated the in vitro cytotoxic activity of the compounds **2a**, **2b** and **2c** against the Hela, HT-29, K562 and MDA-MB-468 human cancer cell lines. For comparison purpose, the cytotoxicity of cisplatin, a standard antitumor drug, was evaluated under the same conditions.

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2. Experimental

2.1. General

Starting materials and solvents were purchased from Sigma–Aldrich or Alfa Aesar and used without further purification. Cisplatin was gifted from Isfahan University of Medical Sciences. Infrared spectra were recorded on a FT-IR JASCO 680 spectrophotometer in the spectral range 4000–400 cm^{-1} using the KBr pellets technique. NMR spectra were measured on a Bruker spectrometer at 400.13 MHz (^1H) and 161.97 MHz (^{31}P) using standard pulse sequences at 298 K. Elemental analysis was performed on a Leco, CHNS-932 apparatus. Palladacycles **1b**, **1c** and [Pd{(*C,N*)-$C_6H_4CH_2$ NH(Et)}(μ-OAc)]$_2$ were obtained using procedure described earlier [25].

2.2. Synthesis of [Pd_2{(C,N)-$C_6H_4CH_2NH(Et)$}$_2$(μ-Cl)$_2$] (**1a**)

To a suspension of the [Pd{(*C,N*)-$C_6H_4CH_2NH(Et)$}(μ-OAc)]$_2$ (0.10 g, 0.17 mmol) in methanol was added excess NaCl and the resulting mixture stirred for 12 h at room temperature. A green precipitate was formed which was filtered and washed with water and then air-dried to give **1a**. Yield: 64%. IR (KBr, cm^{-1}): ν(NH) = 3233, 3194. ^1H NMR (DMSO-d_6, ppm): δ = 1.18 (t, 3H, CH_3, $^3J_{HH}$ = 6.8 Hz), 2.9 (m, 2H, CH_2), 3.78 (dd, H_a, CH_aH, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 2.8 Hz), 4.23 (dd, H_b, CH_bH, $^2J_{HH}$ = 14.8 Hz, $^3J_{HH}$ = 5.2 Hz), 6.18 (sbr, 1H, NH), 6.87–7.64 (m, C_6H_4, $^3J_{HH}$ = 9.2 - Hz). *Anal.* Calc. for $C_{18}H_{24}N_2Cl_2Pd_2$: C, 39.15; H, 4.3; N, 5.07. Found: C, 39.17; H, 4.25; N, 5.02%.

2.3. Synthesis of [Pd(C,N)-$C_6H_4CH_2NH(Et)Cl(Py)$] (**2a**)

To a suspension of palladacycle **1a** (0.05 g, 0.09 mmol) in dichloromethane (15 mL) was added pyridine (14.6 μL, 0.18 mmol). The resulting solution was stirred for 6 h and then filtered through a plug of $MgSO_4$. The filtrate was concentrated to ca. 2 mL and then n-hexane (15 mL) was added to precipitate **2a** as a pale yellow solid, which was collected and air-dried. Yield: 62%. IR (KBr, cm^{-1}): ν(NH) = 3136, 3117. ^1H NMR (DMSO-d_6, ppm): δ = 1.19 (m, 3H, CH_3), 1.24 (m, 3H, CH_3), 2.93 (m br, 4H, CH_2), 3.81 (m, 2H_a, CH_aH), 4.12 (dd, H_b, CH_bH, $^2J_{HH}$ = 15 Hz, $^3J_{HH}$ = 6 Hz), 4.23 (dd, H_b, CH_bH, $^2J_{HH}$ = 14.8 Hz, $^3J_{HH}$ = 5.6 Hz), 5.88 (d, C_6H_4, $^3J_{HH}$ = 7.2 Hz), 6.07 (s br, 1H, NH), 6.19 (s br, 1H, NH), 6.67 (t, Py, $^3J_{HH}$ = 6.8 Hz), 6.86–7.43 (m, C_6H_4), 7.54–8.81 (m, Py). *Anal.* Calc. for $C_{14}H_{17}N_2ClPd$: C, 47.34; H, 4.82; N, 7.88. Found: C, 46.89; H, 4.67; N, 7.67%.

2.4. Synthesis of [Pd_2(C,N-dmba)$_2$(μ-dppe)(Cl)$_2$] (**2c**)

To a suspension of the palladacycle **1c** (0.08 g, 0.14 mmol) in dichloromethane (15 mL) was added dppe (0.06 g, 0.14 mmol). The reaction mixture was stirred for 2 h at room temperature and then filtered through a plug of $MgSO_4$. The filtrate was concentrated to ca. 2 mL and to this concentrated solution, n-hexane (15 mL) was added to precipitate a bright yellow solid, which was collected and air-dried. White crystals of **2c** were obtained from CH_2Cl_2-hexane. Yield: 85%. ^1H NMR ($CDCl_3$, ppm): δ = 1.7 (s br, 2H, CH_2), 2.78 (s br, 12H, CH_3), 4.02 (s br, 4H, CH_2 (dppe)), 6.36–6.9 (m, 8H, C_6H_4), 7.28–7.92 (m, 20H, Ph); ^{31}P-{^1H} NMR ($CDCl_3$, ppm): δ = 37.4 (s). *Anal.* Calc. for $C_{44}H_{48}N_2P_2Cl_2Pd_2$: C, 55.5; H, 5.08; N, 2.94. Found: C, 54.67; H, 5.02; N, 2.90%.

2.5. Crystallography

X-ray diffraction experiments were done at 100 K with the use of Agilent SuperNova single crystal diffractometer (Mo Kα radiation). Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by R.C. Clark & J.S. Reid was made [26]. The structures were solved by direct methods using the Shelxs97 program and refined with the use of Shelxl (Sheldrick 2008) program. Hydrogen atoms were added in the calculated positions and were riding on their respective carbons during the refinement.

2.6. Cell culture and MTT assay

Hela (human cervix carcinoma), HT-29 (colon cancer cell line), K562 (leukemia cancer cell line) and MDA-MB-468 (human breast carcinoma) were purchased from Pasture Institute, Tehran, Iran. They were grown in PRMI 1640 was supplemented with 10% of fetal calf serum, 5 mL of penicillin/streptomycin (50 IU mL^{-1} and 500 μgmL^{-1}, respectively), $NaHCO_3$ (1 g) and 5 mL of L-glutamine (2 mM). Completed media was sterilized through 0.22 μm microbiological filters after preparation and kept at 4 °C before using.

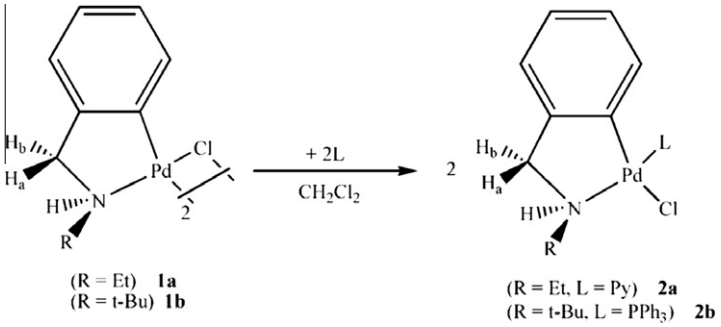
The cytotoxic effects of complexes **2a**–**2c** against Hela, HT-29, K562 and MDA-MB-468 cell lines were determined by a rapid colorimetric assay using 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) for cell growth inhibition and compared with untreated control [27]. The test is based on the reduction of the yellow tetrazolium salt MTT to a violet formazan product via the mithocondrial succinate dehyrogenase in living cells. The color can then be quantified by spectrophotometric means. The am***ount of violet color produced is directly proportional to the number of viable cells. Briefly 200 μL of cells (1×10^5 cells/mL) were seeded in 96-well micro plates and incubated for 24 h (37 °C, 5% CO_2 air humidified). Then, 20 μL of final concentration of each compound was added and incubated for another 72 h in the same condition. To evaluate cell survival, each well was incubated with 20 μL of MTT solution (5 mg/mL in phosphate-buffered saline) for 3 h and afterward, 150 μL of the media of each well was gently replaced with DMSO and mixed to dissolve insoluble formazan crystals. The MTT-formazan absorption was measured at 540 nm using an ELISA plate reader. The percentage of inhibition was calculated using the ratio between the absorbance of treated and untreated cells.

3. Results and discussion

3.1. Synthesis and characterization of cyclopalladated complexes

We have previously described the formation of five-membered, acetato-bridged dinuclear palladacycles of the general formula [Pd(benzylamine)(μ-OAc)]$_2$ from the reaction of the secondary benzylamines $PhCH_2NH(Et)$ or $PhCH_2N(Me)_2$ with $Pd(OAc)_2$ [25]. Treatment of acetato-bridged complexes with an excess of NaCl in methanol afforded the corresponding chloro-bridged dimers **1a**, **1b** and **1c**. The mononuclear palladacycles **2a** and **2b** [25] were obtained by the reaction of **1a** and **1b** with two equivalents of Py (Pyridine) and PPh_3, respectively (Scheme 1). The complexes were fully characterized by elemental analysis, IR and NMR spectroscopies. The crystal structure of **2a** has been also solved by X-ray diffraction method.

The ^1H NMR spectrum of **1a** shows only one set of signals, which indicates that the dinuclear palladacycle **1a** consists of only one geometrical isomer in the solution phase which we propose to be the *anti* type isomer, as has been reported for most halogen-bridged dimers containing orthopalladated amines [28,29]. In the



Scheme 1. Representation of the cleavage reaction of the dimeric cyclopalladated complexes **1a** and **1b** by pyridine and PPh_3.

IR spectrum of **2a**, the ν(N–H) band (that is sensitive to complexation) is appeared at 3136 and 3117 cm^{-1} for asymmetric and symmetric stretching, respectively, whereas for N-coordination, a lowering of the ν(N–H) bond is expected [30]. In the ^{1}H NMR spectra of the mononuclear complexes **2a** and **2b**, the methylene protons are diastereotopic resulting in formation of two separated signals. Moreover, the ^{1}H NMR spectra show similar patterns for the H_3–H_5 aromatic protons of amine, but H_6 is significantly shifted to lower frequencies for **2a** (5.88 ppm) and **2b** (6.05 ppm) because of the anisotropic shielding from the phenyl or pyridine ring [31]. Concerning the ^{1}H NMR spectrum of **2a**, two sets of signals owing to the two diastreoisomers are observed. The nitrogen atom of benzylamine is a chiral center which can has R and S configurations. The ratio of these stereoisomers is at 1:1 on the basis of the intensity ratio of the corresponding signals.

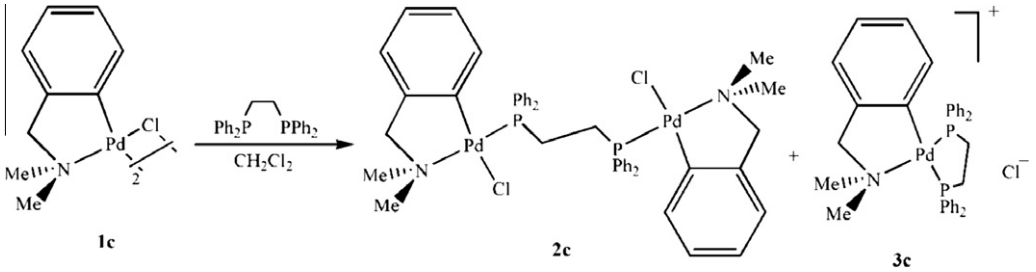
The dimeric palladacycle **1c** reacted with an equivalent of dppe to afford a bright yellow solid. Analysis by ^{1}H and ^{31}P NMR spectroscopies showed the possible presence of a by-product **3c** (Scheme 2). In the ^{1}H NMR spectrum, minor signals for the methylene protons of dppe and chelated benzylamine were observed at 2.60 and 4.25 ppm, which was attributed to **3c**. Moreover, the ^{31}P NMR spectroscopy showed the appearance of a major signal at 37.43 ppm (s), corresponding to the dppe-bridged dimer **2c**, as well as a trace amount of a **3c** displaying doublets centered at 40.7 and 60.6 ppm. The formation of monomeric by-products was observed in the synthesis of the other dppe-bridged complexes [32,33]. The structure of **2c**, which could be isolated in pure form by recrystallization, was confirmed by NMR spectroscopy, elemental analysis, and single crystal X-ray diffraction.

3.2. Crystal structure of complexes *2a* and *2c*

To further clarify the coordination environment around the metal center, representative molecular structures of **2a** and **2c** have been ascertained by X-ray diffraction studies. Single crystals of palladacycles **2a** and **2c** were obtained by slow evaporation of a concentrated CH_2Cl_2–hexane solution. The crystal data and structural refinement parameters are listed in Table 1. Both palladacycles crystallize in the monoclinic $P2_1/n$ space group. Fig. 1 shows an ORTEP view of the X-ray molecular structure of **2a** and also gives selected bond lengths and angles. The mononuclear complex **2a** crystallizes with two independent molecules (hereafter called molecule *A* and *B*) in the asymmetric unit. The X-ray molecular structure confirms the structure proposed upon ^{1}H NMR analysis. Each palladium metal is coordinated in a distorted square-planar geometry by a chloride anion, a N atom of a pyridine ligand and a chelating *N*-benzylethylamine-*C*,*N* moiety forming a five-membered cyclopalladated ring through the N1, C3 atoms for molecule *A* and N3, C17 atoms for molecule *B*. The deviations of C3 and C17 from the planes formed by N1, Pd1, N2, Cl1 and N3, Pd2, N4, Cl2 are 0.130 and 0.108 Å for molecules *A* and *B*, respectively.

The angles around each palladium deviate from the ideal value due to the small bite angle of the cyclometalated ligand. For instance, in the molecule *A*, the N1–Pd1–C3 bite angle is 81.32(9)°, while the opposite angle N2–Pd1–Cl1 of 88.95(6)° deviates from the ideal value of 90°. Due to these steric constraints, the other two angles around the Pd center were opened up and were significantly larger than 90°; N1–Pd1–Cl1 = 96.19(6)° and N2–Pd1–C3 = 93.57(9)°. The dihedral angles between the two planes formed by N1, Pd1, C3 and N2, Pd1, Cl1 for molecule *A* and N3, Pd2, C17 and N4, Pd2, Cl2 for molecule *B* are 3.62 and 3.54°, respectively. The Pd–C bond distances (1.982(2) and 1.978(2) Å for *A* and *B*, respectively) are within the range usually reported for five-membered palladacycles [34]. In the crystal, the adjacent molecules are linked by an intermolecular hydrogen bond between the chlorine atom and the NH group (Fig. 2).

Biphosphinic palladacycle **2c** crystallizes with one molecule in the asymmetric unit. Fig. 3 shows an ORTEP view of **2c** and the selected bond lengths and angles. The center of mass of the bridged dimer lies on an inversion center and only half of the molecule is crystallographically unique. The Pd1...Pd1^i distance of 8.1652(4) Å suggests no interaction between the two Pd atoms, so two metal centers in the dimer are not directly bonded. The coordination sphere around the each palladium(II) center is completed by a chloro group *trans*-positioned to the carbopalladated site and a phosphorus atom from the dppe ligand *trans* to the N1



Scheme 2. Synthesis of a dppe bridged palladacycle **2c**.

Table 1
X-ray crystallography data.

	2a	2c
Empirical formula	$C_{14}H_{17}ClN_2Pd$	$C_{44}H_{48}Cl_2N_2P_2Pd_2$
Formula weight	355.15	950.48
T (K)	100(1)	100(1)
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/n$
a (Å)	11.9483(1)	8.7620(7)
b (Å)	16.8268(2)	23.0810(12)
c (Å)	14.0423(1)	10.4370(6)
α (°)	90	90
β (°)	92.391(1)	104.14(1)
γ (°)	90	90
V (Å^3)	2820.77(5)	2046.82(362)
Z	8	2
μ (mm^{-1})	1.49	1.12
D_{cal} (Mg m^{-3})	1.656	1.542
$F(000)$	1396	964
θ ranges (°)	2.95–28.86	2.97–28.81
Independent reflections	6947	3882
Data/restraints/ parameters	6947/0/325	3882/0/235
Goodness-of-fit on F^2	1.098	2.243
Final R indices	R_1 = 0.0264, wR_2 = 0.0622	R_1 = 0.0222, wR_2 = 0.0613
R indices (all data)	R_1 = 0.0281, wR_2 = 0.0630	R_1 = 0.0231, wR_2 = 0.061

atom, resulting in a slightly distorted square-planar geometry. The Pd atom deviates very slightly (0.055 Å) from the plane containing C16, N1, Cl1 and P1. The dihedral angle between the two planes formed by C15, N1, C16, Pd1 and C15, C14, N1 is 30.50°. The bond angle at Pd1 involving the bidentate ligand N1–Pd1–C16 equals 83.25(7)°, is smaller than the other three bond angles at the palladium center. Other cyclopalladated compounds bearing the *C, N*-chelated dmba ligand exhibit comparable N–Pd–C angles [23,34,35]. In comparison of **2a** and **2c**, the Pd–N distance (2.155(15) Å) for **2c** is longer than the Pd1–N1 (2.076(2) Å) and Pd2–N3 (2.071(2) Å) distances for **2a**, due to the greater *trans* influence of the P atom with respect to the N2 and N4 atoms [36]. The Pd–N distance (2.155(15) Å) for **2c** is also longer than the analogous distances reported in other bridged biphosphinic palladacycles (2.086(5)–2.099(8) Å) [32,37]. These data suggested that the sterically demanding of the benzyl groups at the nitrogen atom increases the Pd–N length. The Pd–$C_{Palladate}$ bond distance in **2c** (2.022(2) Å) also lies within the normal range for palladium dmba complexes [23].

3.3. Cytotoxicity

The cytotoxic activity of cyclopalladated complexes **2a**–**2c** were evaluated by means of the standard MTT-dye reduction assay which is a widely used method in biological evaluation. Recently, new palladium (II) complexes were assessed using this method [38].

The complexes **2a**–**2c** were tested against four human cancer cell lines: Hela, HT-29, K562, and MDA-MB-468. The results of cytotoxic activity in vitro are expressed as IC_{50} – the concentration required to inhibit a 50% of the cell growth when the cells are exposed to the compounds (Table 2). Cisplatin was included in the assay as a positive control. The complexes were not readily soluble in water hence they were first dissolved in DMSO (dimethylsulfoxide) which is effective in accelerating the rate of chloride displacement from a complex [39], so fairly good relationship generally could be seen between activity and solubility of the complexes. Palladacycles **2a**–**2c** have displayed IC_{50} values in a μM range better than that of the antitumor drug cisplatin. Bridged biphosphinic palladacycle **2c** was more effective than mononuclear palladacycles **2a** and **2b**, especially against the K562 cell line with an IC_{50} of 1.4 μM, which maybe partly ascribed to its greater solubility and lipophilicity that may facilitate transport through the cellular membranes. The lipophilicity of the bridged palladacycle **2c** can be related to the presence of two bulky PPh_2 groups from dppe. In addition, the dppe bridge leads to the more flexibility in the structure and makes more interactions with DNA.

Palladacycle **2c** was found to be 24.4, 17.8, 5.9 and 2 times more cytotoxic than cisplatin against the Hela, HT-29, K562 and MDA-MB-468 human cancer cell lines, respectively. In another study bridged biphosphinic palladacycle of 1,4 benzodiazepine was tested against K562 cell [34] and IC_{50} value of 4.3 μM was reported which is in agreement with our result of palladacycle **2c** against the same cell line. A slightly decreasing in the activity of the mononuclear complex **2b** compared to **2a** is probably related to the presence of three bulky phenyl groups in this complex which sterically hinder the metal–DNA interactions and also prevent direct hydrogen bonding with the biological molecules. The IC_{50} values for three palladacycles with different cell lines in our study ranged

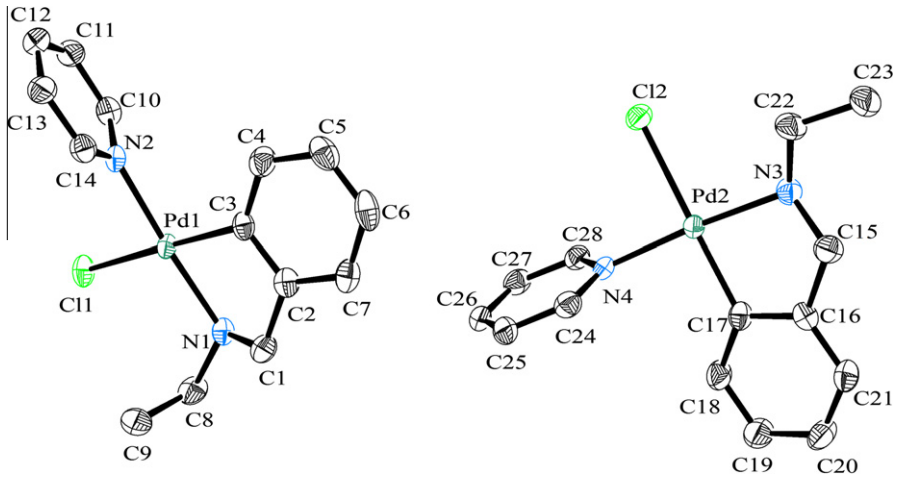


Fig. 1. ORTEP diagram for palladacycle **2a** with ellipsoids drawn at the 70% probability level. The hydrogen atoms have been omitted for clarity. Selected bond lengths (Å), and angles (°): Pd1–Cl1 2.429(6), Pd1–N2 2.052(2), Pd1–N1 2.076(2), Pd1–C3 1.982(2), C3–Pd1–N1 81.32(9), C3–Pd1–N2 93.57(9), N2–Pd1–Cl1 88.95(6), N1–Pd1–Cl1 96.19(6), N1–Pd1–N2 174.84(8), C3–Pd1–Cl1 175.70(7) (molecule *A*); Pd2–Cl2 2.430(6), Pd2–N4 2.041(2), Pd2–N3 2.071(2), Pd2–C17 1.978(2), C17–Pd2–N3 82.81(9), C17–Pd2–N4 93.05(9), N4–Pd2–Cl2 87.69(6), N3–Pd2–Cl2 96.52(6), N3–Pd2–N4 174.70(8), C17–Pd2–Cl2 178.67(8) (molecule *B*).

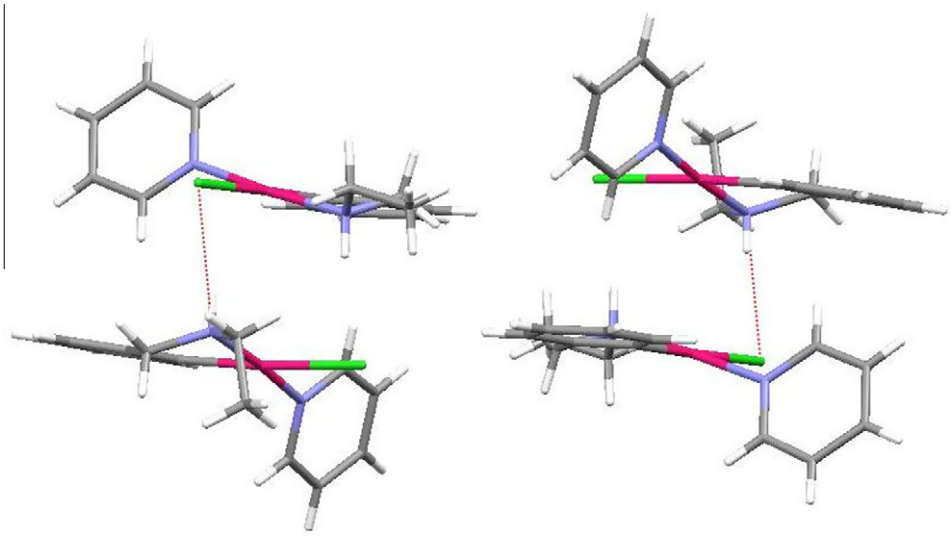


Fig. 2. Part of the crystal packing of **2a**. The adjacent molecules are linked through intermolecular N–H···Cl hydrogen bonds (dotted lines).

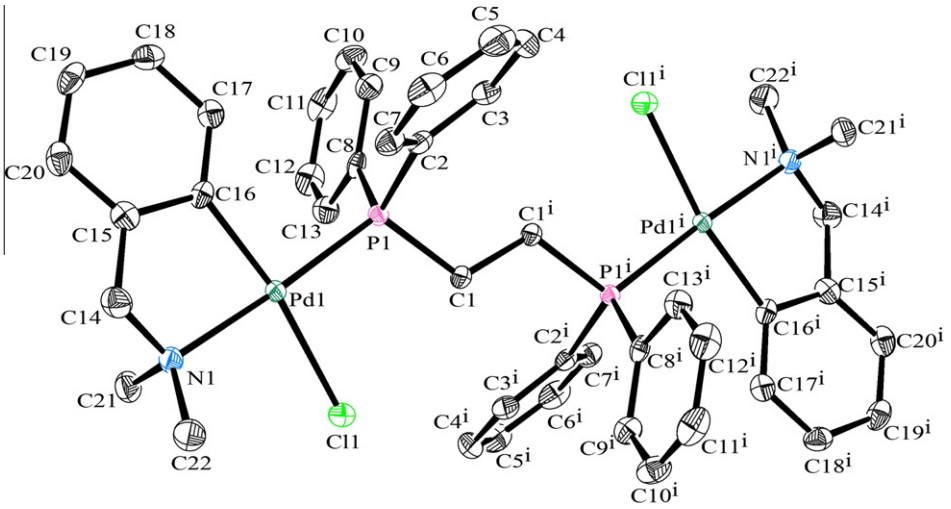


Fig. 3. ORTEP diagram for palladacycle **2c** with ellipsoids drawn at the 70% probability level. The hydrogen atoms have been omitted for clarity. The center of mass of the dimeric molecule lies on an inversion center. The symmetry transformation used to generate equivalent atoms is: (i) $-x, -y, -z$. Selected bond lengths (Å), and angles (°): Pd1–Cl1 2.424(5), Pd1–P1 2.255(5), Pd1–N1 2.155(15), Pd1–C16 2.022(2), P1–C1 1.842(2), C1–C1^{i} 1.525(3), C16–Pd1–N1 83.25(7), C16–Pd1–P1 93.4(5), P1–Pd1–Cl1 93.7(17), N1–Pd1–Cl1 89.7(5), N1–Pd1–P1 176.4(5), C16–Pd1–Cl1 170.09(5), C1–P1–Pd1 110.6(6), P1–C1–C1^{i} 116.63(17), C14–N1–Pd1 106.9(11), C22–N1–Pd1 115.5(12), Pd1–N1–C14–C15 32.16(17), Pd1–C16–C15–C14 12.9(2), P1–Pd1–C16–C17 13.2(18).

Table 2
Cytotoxicity data (IC_{50}) of the complexes **2a**, **2b**, **2c** and control compound (cisplatin) against Hela, HT-29, K562 and MDA-MB-468 cancer cell lines.

Complex	IC_{50} value (μM ± SD)			
	Hela	HT-29	K562	MDA-MB-468
2a	7.5 ± 0.6	4.3 ± 0.04	3.7 ± 0.04	2.4 ± 0.05
2b	7.7 ± 0.4	5.3 ± 0.28	3.3 ± 0.04	3.3 ± 0.05
2c	2.1 ± 0.05	2.2 ± 0.04	1.4 ± 0.06	2.3 ± 0.01
Cisplatin	51.3 ± 2.8	39.2 ± 3.1	8.3 ± 0.6	4.8 ± 0.07

from 1.4 to 7.7 μM, which are clinically achievable doses. Thus, **2a**–**2c** are considered as agents with potential antitumor activity, and can therefore be candidates for further stages of screening in vitro and/or in vivo.

4. Conclusion

Herein, the synthesis and characterization of new palladacycles were reported. The structure of cyclopalladated complexes **2a** and **2c** was confirmed by the single-crystal X-ray diffraction. In the structures, the palladium atom shows a slightly distorted square-planar geometry. The biological properties of the complexes **2a**–**2c** were investigated by evaluation of their antitumor activity. The results suggested that the three complexes exhibit noticeable cytotoxic activity towards the all cell lines. They show inhibitory effect against tumor cell lines in low μM ranges which are comparable with a standard metal-based chemotherapeutical drug, cisplatin. Further studies of the DNA binding properties of these complexes will be necessary to understand the mechanism of action.

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