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ORIGINAL ARTICLE

Palladium(II) complexes incorporating phenylazo arylmethine ancillary ligands: Synthesis, spectral and antitumor activity

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Abstract A series of azoimine palladium(II) complexes of the general type *cis*-[$PdCl_2L$] (**1–6**) {L = PhN═NC(COMe)═NC_6H_4X, where X = H (**L1**), CH_3 (**L2**), Cl (**L3**), Br (**L4**), naphthyl (**L5**) and OMe (**L6**)} have been prepared by the reaction of *cis*-[$PdCl_2(NCPh)_2$] and the ligands (**L**) in acetone at room temperature. These complexes have been characterized by spectroscopic (IR-, UV–Vis and NMR) and electrochemical techniques. In addition, their biological activity has been studied via MTT test and by detecting the inhibition of clonal growth in three tumor cell lines, namely T47D human ductal breast carcinoma, MTLn3 murine mammary adenocarcinoma and RAW 264.7 murine leukemic monocyte macrophage. All of the tested palladium(II) complexes showed a noticeable antitumor activity. Complexes **4** and **5** showed a higher cytotoxic activity against human T47D breast tumor cell line than cisplatin, while comparable activity was observed against murine mammary MTLn3 adenocarcinoma cell line.

1. Introduction

The landmark discovery of cisplatin, *cis*-[$PtCl_2(NH_3)_2$], by Rosenberg et al. (1965) heralded a new area of anticancer drug research. Cisplatin is one of the most effective chemotherapeutic agents in clinical use for the treatment of a testicular and ovarian cancer (Rosenberg et al., 1965; Abu-Surrah and Kettunen, 2006). This anticancer activity stems from the binding of the *cis*-$Pt(NH_3)_2$ fragment with DNA bases. However, cisplatin also interacts with non-cancer cells, through bond formation with –SH group, resulting in nephrotoxicity. Researchers focused on how to reduce the toxicity of *cis*-platinum complexes (nausea, ear damage, vomiting, loss of sensation in hands, and kidney toxicity) and increase their spectrum activity

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against some of the commonest tumors (e.g. colon and breast) to improve the efficiency as antitumor drug (Reedjik, 1996; Reedijk, 1987). This has aroused interests in the design of palladium(II) complexes of improved activity and lower toxicity.

The significant similarity between the coordination chemistry of palladium(II) and platinum(II) compounds has encouraged researchers to use Pd(II) complexes as antitumor drugs (Abu-Surrah etal., 2008). Numerous palladium complexes with promising activity against tumor cell lines have been synthesized (Graham and Williams, 1979; Barton, 1986). Comparing to *cis*-platin which is a commonly used drug, palladium complexes are hydrolyzed 10^5 times faster than their corresponding platinum analogues which make them unable to reach their pharmacological targets (Abu-Surrah et al., 2008). For example, *cis*-[$PdCl_2(NH_3)_2$] and *cis*-[$PdCl_2$(DACH)] (DACH: (1R,2R)-(–)-1,2-diaminocyclohexane (Butour etal., 1997; Zhao et al., 1999) do not show antitumor activity. It is well known that the former undergoes an inactive *trans* isomer. In addition, both compounds hydrolyze very fast and interact in vivo with a lot of proteins molecules which prevent them to reach the DNA target (Butour et al., 1997; Zhao et al., 1999). Mono-dentate ligands can bind in both *cis*- and *trans*-arrangements around a metal center (Abu-Surrah et al., 2002). To prevent hydrolysis and any possible *cis–trans* isomerism for palladium complexes (Mansuri-Torshizi et al., 1992; Abu-Surrah et al., 2010), palladium ion should be stabilized by strongly and non-labile bidentate ligands (Abu-Surrah et al., 2008).

Transition-metal complexes incorporating azo ligands such as arylazooximes (Casas et al., 2008), arylazophenols (Basuli et al., 1999) and arylazoimines (Mishra et al., 1998) had drawn much attention. These ligands have low-lying π^* orbitals and can stabilize the low valence metal redox state such as Pd(II) by promoting metal-to-ligand charge-transfer (MLCT) transitions (Kaim, 2001). Recently, a new class of azoimine ligands of the general type PhN = NC(R) = NPh has been prepared by us. Previously, we synthesized a family of complexes of the general type *trans*-[Ru^{II}(Y)LCl_2] {L = C_6H_5N=NC($COCH_3$)=NAr, Y = α-diamines} (Al-Noaimi et al., 2007; Al-Noaimi et al., 2008; Al-Noaimi et al., 2010) to study the effect of the substituents of the aromatic ring (Ar) on the electronic properties of the ruthenium center. In this study, we extend our work to prepare a new family of palladium(II) complexes of the general formula, *cis*-[$PdCl_2$L] (**1–6**) {L = PhN=NC(COMe)=NC_6H_4X, where X = H (**L1**), CH_3 (**L2**), Cl (**L3**), Br (**L4**), naphthyl (**L5**) and OMe (**L6**)}. In addition, the in vitro cytotoxic (IC50) and anti-proliferation potential of the complexes (**2–5**) against human T47D breast tumor, murine mammary MTLn3 adenocarcinoma and murine RAW 264.7 leukemia cell lines have also been evaluated.

2. Experimental

2.1. Chemistry

2.1.1. Materials and physical measurements

The reagents: azoimine ligands (**L1–L6**) were prepared according to reported procedures (Al-Noaimi et al., 2008). Tetrabutylammonium hexafluorophosphate (TBAHF), purchased from Aldrich, was recrystallized twice from 1:1 ethanol/water solution and then vacuum dried at 110 °C. *cis*-[$PdCl_2$(PhCN)$_2$] was prepared following the procedure (Evans et al., 1968).

2.1.2. Instrumentation

Micro-analyses (C, H, N) were performed using an elemental analyzer EURO VECTOR model EA3000. IR spectra were obtained by FT-IR JASCO model 420. Electronic spectra were recorded on a Shimadzu 240-UV–visible spectrophotometer. The ^{1}H spectra were measured on a Bruker-Avance 400 MHz spectrometer at 400 MHz using TMS as an internal standard. Electrochemical measurements were performed in 99.8% anhydrous acetonitrile (Aldrich, HPLC grade) using Volta Lab model PGP201 with a platinum working electrode, a platinum wire auxiliary electrode and silver wire pseudo-reference electrode. To control the temperature, a Haake D8-G refrigerated bath and circulator were used to maintain the cell temperature at 25.0 ± 0.1 °C. Tetrabutylammonium hexafluorophosphate (0.1 M) was used as the supporting electrolyte.

2.1.3. General procedure for the synthesis of complexes

A solution of *cis*-[$PdCl_2$(PhCN)$_2$] (0.38 g, 1.0 mmol) in 20 cm^3 acetone was slowly added to a magnetically stirred solution of **L** (1.1 mmol) in 20 cm^3 acetone. The yellow precipitate was filtered after 24 h. The precipitate was washed successively with acetone (3×5 cm^3) diethyl ether (3×5 cm^3), and dried in a vacuum oven at 25 °C.

1: Yield (2.61 g, 52%). Found: C, 42.10%; H, 3.23%; N, 9.92%. Anal. Calc. for $PdC_{15}H_{13}N_3OCl_2$: C, 42.03; H, 3.06; N, 9.80. UV–Vis in acetonitrile: λ_{max} (ε_{max}): 357 (8.83×10^4), 242 (5.24×10^4), 219 (6.90×10^4). IR (KBr, cm^{-1}): ν(N=N) 1496, ν(C=N) 1601, ν(C=O) 1668. ^{1}H NMR (in $CDCl_3$, δ ppm): 7.30 (2H, d, H3, H3′), 7.29 (2H, t, H4, H4′), 7.10 (2H, t, H1, H1′), 6.90 (1H, t, H5), 6.75 (1H, t, X = H), 6.55 (2H, d, H2, H2′), 2.50 (3H, s, $COCH_3$).

2: Yield (3.02 g, 57%). Found: C, 43.10%; H, 3.21%; N, 9.53%. Anal. Calc. for $PdC_{16}H_{15}N_3OCl_2$: C, 43.42; H, 3.42; N, 9.49. UV–Vis in acetonitrile: λ_{max} (ε_{max}): 356 (8.09×10^4), 241 (4.69×10^4), 214 (6.24×10^4). IR (KBr, cm^{-1}): ν(N=N) 1478, ν(C=N) 1599, ν(C=O) 1664. ^{1}H NMR (in $CDCl_3$, δ ppm): 7.27 (2H, d, H3, H3′), 6.95 (2H, d, H2, H2′), 6.45 (2H, d, H1, H1′), 6.2 (3H, m, H4, H4′, H5), 2.59 (3H, s, $COCH_3$), 2.05 (3H, s, CH_3).

3: Yield (3.33 g, 57%). Found: C, 41.25%; H, 3.25%; N, 8.12%. Anal. Calc. for $PdC_{15}H_{12}N_3OCl_3{\cdot}C_3H_6O$: C, 41.49; H, 3.48; N, 8.06. UV–Vis in acetonitrile: λ_{max} (ε_{max}): 354 (9.01×10^4), 245 (5.38×10^4), 212 (7.02×10^4). IR (KBr, cm^{-1}): ν(N=N) 1491, ν(C=N) 1599, ν(C=O) 1675. ^{1}H NMR (in $CDCl_3$, δ ppm): 7.27 (2H, d, H2, H2′), 6.98 (1H, t, H5), 7.1 (2H, d, H1, H1′), 7.21 (2H, d, H3, H3′), 7.30 (2H, t, H4, H4′), 2.6 (3H, s, $COCH_3$).

4: Yield (4.02 g, 60%). Found: C, 36.57%; H, 2.88%; N, 7.52%. Anal. Calc. for $PdC_{15}H_{12}BrN_3OCl_2{\cdot}0.5{\cdot}C_3H_6O$: C, 36.49; H, 2.82; N, 7.83. UV–Vis in acetonitrile: λ_{max} (ε_{max}): 358 (8.92×10^4), 243 (5.32×10^4), 214 (6.98×10^4). IR (KBr, cm^{-1}): ν(N=N) 1478, ν(C=N) 1596, ν(C=O) 1675. ^{1}H NMR (in $CDCl_3$, δ ppm): 6.51 (2H, d, H2, H2′), (1H, t, H5), 7.1 (2H, d, H3, H3′), 7.31 (2H, t, H4, H4′), 7.35 (2H, d, H1, H1′), 2.60 (3H, s, $COCH_3$).

5: Yield (3.82 g, 63%). Found: C, 47.43%; H, 3.21%; N, 8.53%. Anal. Calc. for for $PdC_{19}H_{15}N_3OCl_2$: 47.62; H, 3.16; N, 8.78. UV–Vis in acetonitrile: λ_{max} (ε_{max}): 329 (8.80×10^4),

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239 (5.20×10^4), 212 (6.86×10^4). IR (KBr, cm^{-1}): ν(N═N) 1504, ν(C═N) 1600, ν(C═O) 1673. ^{1}H NMR (in $CDCl_3$, δ ppm): 6.34 (1H, d, H(naphthyl proton)), 6.91 (1H, t, H5), 7.04 (2H, d, H(naphthyl proton)), 7.31 (3H, m, H4, H4′, H(naphthyl proton)), 7.6 (3H, m, H3, H3′, H(naphthyl proton)), 7.9 (1H, d, H(naphthyl proton)), 8.1(1H, d, naphthyl proton), 2.60 (3H, s, $COCH_3$).

6: Yield (3.11 g, 55%). Found: C, 41.71%; H, 3.21%; N, 913%. Anal. Calc. for $PdC_{16}H_{15}N_3O_2Cl_2$: C, 41.90; H, 3.30; N, 9.16. UV–Vis in acetonitrile: λ_{max} (ε_{max}): 357 (8.75×10^4), 297 (5.0×10^4), 240 (6.78×10^4). IR (KBr, cm^{-1}): ν(N═N) 1504, ν(C═N) 1618, ν(C═O) 1660. ^{1}H NMR (in $CDCl_3$, δ ppm): 6.62 (2H, d, H1, H1′), 6.80 (2H, d, H2, H2′), 6.92 (1H, t, H5), 7.03 (2H, t, H4, H4′), 7.25 (2H, d, H3, H3′), 3.75 (3H, s, OCH_3), 2.60 (3H, s, $COCH_3$).

2.2. Biology

2.2.1. Cell culture

Human T47D ductal breast epithelial tumor cell line was grown in DMEM-F12 medium (Lonza, Switzerland) supplemented with 10% fetal calf serum (FCS) (Euroclone, Italy). Murine mammary MTLn3 adenocarcinoma cell line was cultured in α-MEM (Gibco Laboratories, USA) supplemented with 5% FCS. Murine RAW 264.7 leukemic monocyte macrophage cell was cultured in RPMI-1640 (Euroclone, Italy) supplemented with 10% FCS. Trypsin–EDTA (Lonza, Switzerland) was routinely used for subcultures. Cell growth was accomplished at 37 °C in a 5% carbon dioxide atmosphere.

2.2.2. In vitro cytotoxicity MTT test

Cytotoxicity of the various palladium complexes on T47D, MTLn3 and RAW 264.7 cells was evaluated by means of MTT (tetrazolium salt reduction) test (Mosmann, 1983; Fotakis and Timbrell, 2006). Briefly, 5×10^4 viable cells (counted using the Trypan Blue Exclusion Test) were added to each well of a 96-well tissue culture plate containing growth media supplemented with FCS (Freshney, 2000). Cells were kept in a humified 5% CO_2 incubator at 37 °C for 24 h. Four complexes (**2**–**5**) were tested and for each complex six concentrations were prepared in growth media: 0.1, 0.5, 2.5, 5, 25, and 50 μg/ml. The complexes were solubilized in 10% DMSO, while complex L5 was solubilized in 50% DMSO. The next morning, the different concentrations were added, and the cells were incubated for 24 h. Freshly prepared MTT salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (5 mg/ml) was added to each well to give a final concentration of 0.5 μg/μl. The plates were incubated for 4 h and the formation of formazan crystals was checked using an inverted microscope. Equal volume of 1:1 (200 μl) of mix of DMSO and isopropanol was added to each well and incubated for 30–45 min. the inhibition of cell growth induced by the various complexes was detected by measuring the absorbance of each well at 570 nm using a Statfax microplate reader. For comparison purposes, the cytotoxicity of cisplatin was evaluated under the same experimental conditions.

2.2.3. Clonogenic assay

2×10^5 cells (counted using a hemocytometer) were seeded in tissue culture dishes containing growth media supplemented with FCS. Cells were kept in a humified 5% CO_2 incubator at 37 °C for 24 h. Afterwards, the medium was replaced and the cells were incubated for 3 h in the presence of an increasing concentration of tested complexes (0.1, 0.5, 2.5, 5, 25, and 50 μg/ml). Aliquots of 200 cells were seeded in growth medium and incubated for 12 days. The colonies were then stained and counted, discarding colonies with less than 50 cells. The surviving fraction (SF) was calculated according to Alverdi et al., 2004 and Franken et al., 2006.

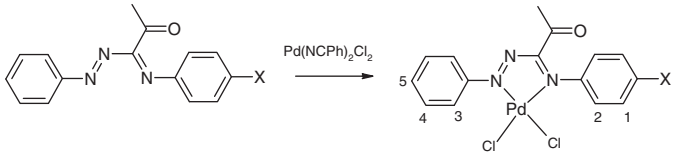
3. Results and discussion

3.1. Chemistry

The ligands (**L1–L6**) {L = C_6H_5N═$NC(COCH_3)$═NC_6H_4X) (Scheme 1) were synthesized by condensation of the corresponding hydrazonyl chloride with aniline derivatives in good yields (Al-Noaimi et al., 2008). These ligands are bidentate chelaters where the active function is the azoimine group (N═N–C═N). The basicity of nitrogen as a donor atom in the ligands was controlled by varying the substituents (X). It is well known that the electron withdrawing substituent diminishes Lewis basicity of the nitrogen donor (Cotton et al., 1995).

The reaction of *cis*-$[PdCl_2(PhCN)_2]$ with the ligands (**L1–L6**) in acetone at room temperature yielded the corresponding *cis*-$[PdCl_2L]$ complexes as a yellow solid. Complexes **1–6** have been characterized by elemental analysis, infrared spectroscopy, ^{1}H-NMR spectroscopy, as well as, and electrochemical (CV) techniques.

Elemental analyses of the complexes (**1–6**) showed that the metal to the azoimine ligand ratio in the dichloro complexes is 1:1. This indicates that the complexes are in the monomer form, the palladium ion is tetra coordinated surrounded by one azoimine ligand and two chloride ligands. The aromatic region in the ^{1}H-NMR spectra of the complexes (**1–6**) consists of several coupled multiplets due to aromatic protons of the



X	H	Me	Cl	Br	Naphtyl	Ome
L	**L1**	**L2**	**L3**	**L4**	**L5**	**L6**
Complex	**1**	**2**	**3**	**4**	**5**	**6**

Scheme 1 The chemical structures of ligands (**L1–L6**) and complexes (**1–6**).

Table 1 Cyclic voltammetry and electronic spectroscopy data of *cis*-[$PdCl_2L$], complexes (**1–6**).[a]

Complex	λ_{max} (nm)[b]	L(0/−) (V)[c]
1	357, 242, 219	−0.20
2	356, 241, 214	−0.21
3	354, 245, 212	−0.13
4	358, 243, 214	−0.10
5	329, 239, 212	−0.21
6	361, 240, 215	−0.15

[a] Solvent: acetonitrile; supporting electrolyte: Bu_4NPF_6 (0.1 M); scan rate: 0.1 V s; Pt-disk working electrode, Pt-wire auxiliary electrode, reference electrode Ag at 25 °C.
[b] Solvent: acetonitrile.
[c] Reduction potential.

Table 2 Cytotoxicity data (IC_{50}, μM) of palladium complexes against human T47D, murine MTLn3 and RAW tumor cell lines.

Complex	T47D	MTLn3	RAW
Cisplatin	71.8	38.7	48.3
2	299.3	321.5	249.1
3	269.3	351.9	224.0
4	40.7	81.7	91.1
5	57.5	55.4	102.5

phenyl rings of the azoimine ligands. In their IR-spectra, all complexes show bands in the range of 1660–1712 cm^{-1} assignable to C═O stretching frequency of the acetyl group. The intense bands in the ranges of 1560–1590 and 1430–1500 cm^{-1} were assigned to the C═N and N═N stretching bands of azoimine ligands, respectively.

Electrochemical measurements in the presence of tetrabutylammonium hexafluoro-phosphate as supporting electrolyte were carried out using a Pt-disk working electrode in MeCN solution. The results are given in Table 1, and a representative voltammogram is shown in Fig. 1. *cis*-[$PdCl_2L$] (**1–6**) exhibit one irreversible reduction responses in the potential range

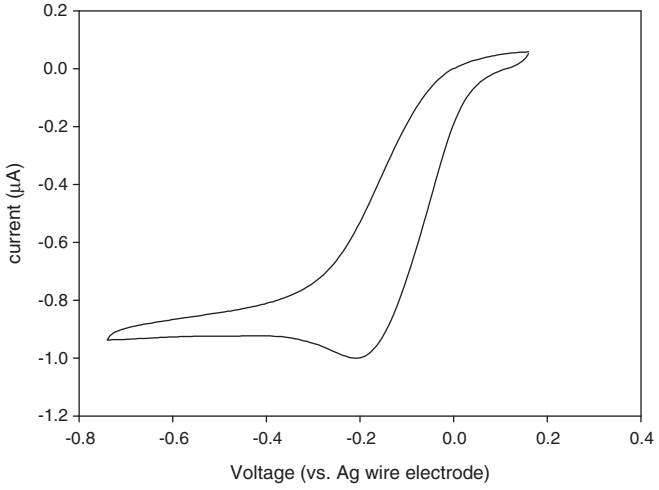


Figure 1 Cyclic voltammogram for **1** in acetonitrile 0.1 M TBAH at 25 °C with scan rate of 0.1 V/s.

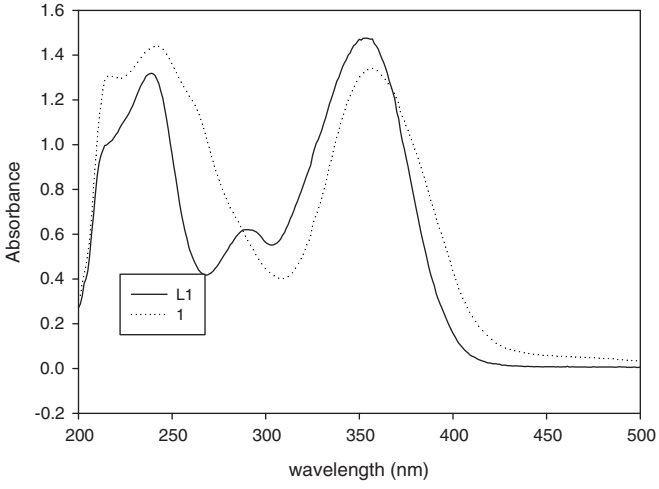


Figure 2 Electronic spectra of **L1** and complex **1** in acetonitrile.

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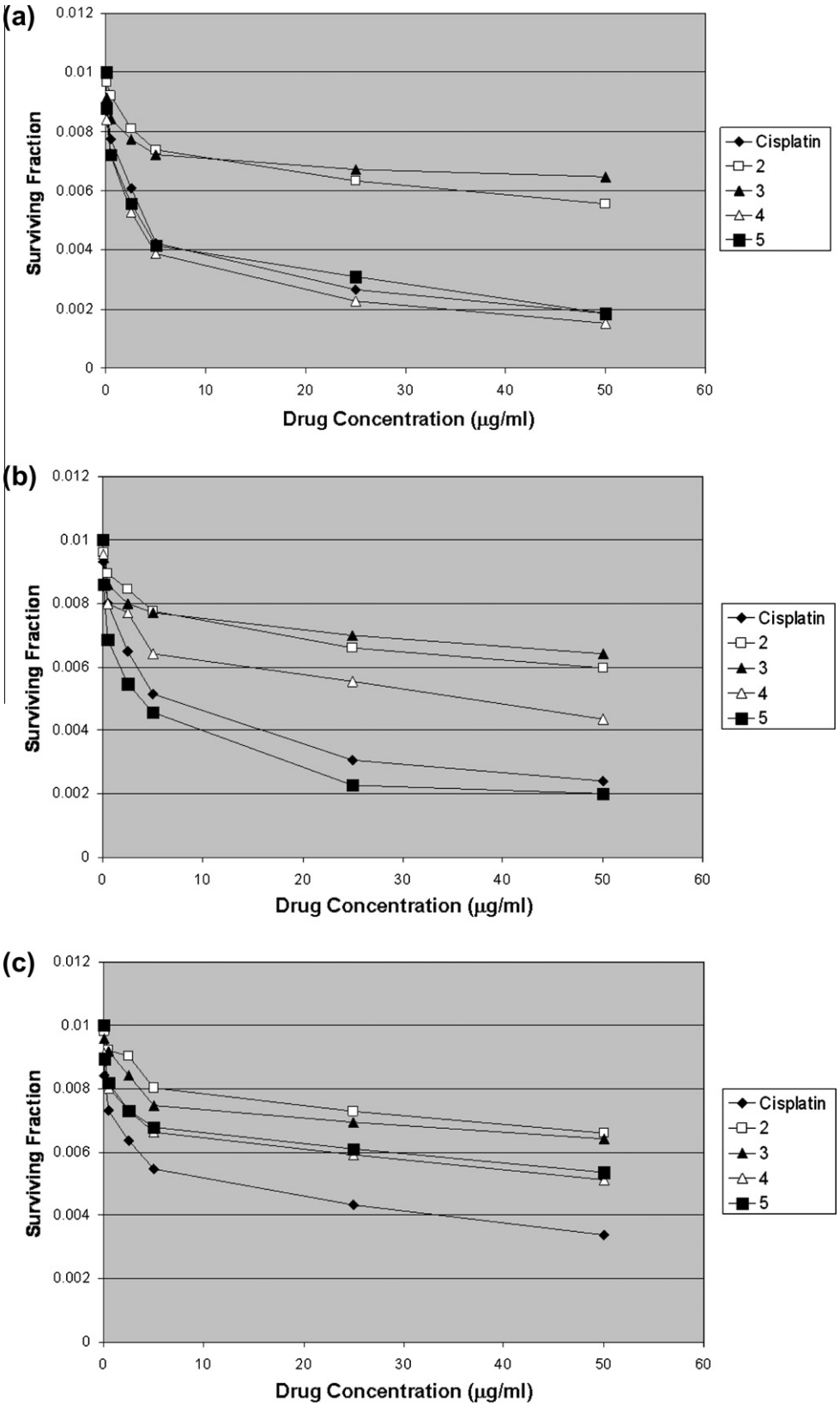

Figure 3 Survival curves of T47D (a), MTLn3 (b) and RAW (c) cells after treatment with palladium(II) complexes and cisplatin.

(−0.1 to −0.20) V. We suggest that this couple is due to reduction of the azoimine ligand L(−/0). These complexes are easy to reduce due to the fact that azoimine is a good π-acceptor ligand. However, *cis*-[$PdCl_2L$] (**1–6**) does not exhibit redox

response in the positive side because Pd(II) is redox-inactive. Among the six complexes, the potential of the L(0/−) couple is slightly affected by variations in the substituent Y on the azoimine ligand, being shifted to more positive potentials upon replacing the donating group with the more withdrawing groups.

The absorption spectra were recorded in a MeCN solution in the wavelength range 250–800 nm. The bands in the UV–visible spectra of complexes **1–6** were assigned upon comparison with spectrum of the free ligands (**L1**–**L6**) (Fig. 2). For the free ligands, the absorption between 200–300 nm and 300–400 bands for **L1** (as representative example) are assigned to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, respectively. These bands are shifted to lower energy upon complexation. The structured absorption bands between 250–350 and 350–450 nm for complex **1** (as representative example) are assigned to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, respectively. A tail extending into 500 nm may arise from metal-orbital to ligand-orbital charge transition: $d\pi(Pd^{10}) \rightarrow \pi^*$(ligand) state of the azoimine.

3.2. Biological investigations

The cytotoxic activities of selected palladium(II) complexes incorporating ligands with electron withdrawing (X = Cl (**3**) and Br (**4**)) and electron releasing groups (X = CH_3 (**2**) and naphthyl (**5**)) have been evaluated against human T47D breast tumor cell line, murine mammary MTLn3 adenocarcinoma cell line and murine RAW 264.7 leukemia cell line. The results are shown in Table 2 in terms of IC_{50} values (the concentration needed to inhibit 50% of the cellular proliferation). For comparison purposes, the cytotoxicity of cisplatin, a standard antitumor drug, was tested under the same conditions. As listed in Table 2, the complexes 4 and 5 exerted cytotoxic effects against the three cell lines, T47D, MTLn3 and RAW 264.7. Moreover, they have selectivity against tested tumor cell lines.

Palladium(II) complex with X = Br (**4**) showed the highest cytotoxic activity against human T47D breast tumor cell line compared with other complexes (**2**, **3**, and **5**). It also exhibited a higher cytotoxicity (IC_{50} = 40.7 μM) than cisplatin (IC_{50} = 71.8 μM) (Table 2). It can be also seen that the complex with X = naphthyl (**5**) was more active (IC_{50} = 57.5 μM) than cisplatin against the same tumor cell line (Table 2). Complex **5** which contains azoimine ligand with naphthyl group demonstrated a higher cytotoxicity (IC50 = 55.4 μM) than the corresponding complexes **2** (321.5 μM), **3** (351.9 μM) and **4** (81.7 μM) against murine mammary MTLn3 adenocarcinoma cell line, but comparable with that of cisplatin (IC50 = 38.7 μM). Similar trend was also observed in the cytotoxic properties of the complexes against murine RAW 264.7 leukemia cell line, but the complexes were less active than cisplatin.

In general, the more the electronegativity of the substituent (X) on the azoimine ligand the more it enhances the cytotoxicity of the complexes against the above cell lines (Br ⩾ naphthyl > Cl ⩾ CH_3). Based on the cytotoxic activity results above, both electronic properties and bulkiness of the substituent have a noticeable influence on the activity of the palladium(II) complexes. The antiproliferative activity of the new complexes was also evaluated by studying the effect on clonal growth capacity of cells (Fig. 3a–c). The obtained data suggest that all palladium derivatives show a significant activity similar to that of the reference drug (cisplatin).

4. Conclusions

Azoimine palladium(II) complexes of the general type *cis*-[$PdCl_2L$] (**1–6**) {L = PhN═NC(COMe)═NC_6H_4X, where X = H (**L1**), CH_3 (**L2**), Cl (**L3**), Br (**L4**), naphthyl (**L5**) and OMe (**L6**)} have been synthesized and characterized by elemental analysis, spectroscopic and electrochemical (CV) techniques. Cyclic voltammetric studies show one irreversible responses negative to silver wire electrode which is assigned to L(−/0) couple. These complexes are easy to reduce due to the fact that azoimine is a good π- acceptor ligand. However, *cis*-[$PdCl_2L$] (**1–6**) does not exhibit redox response in the positive side because Pd^{II} is redox-inactive. The in vitro cytotoxic potential (IC_{50}) studies against T47D, MTLn3 and RAW tumor cell lines show a satisfactory inhibitory effect on cells comparable to that of cisplatin.

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