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Original Scientific Article

Palladium Complexes with 3-Substituted Derivatives of 5-Methyl-5-(4-pyridyl)hydantoins. Synthesis, Study and *in vitro* Cytotoxicity

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Abstract. Six palladium(II) and palladium(IV) complexes with 3-ethyl-5-methyl-5-(4-pyridyl)hydantoin, 3-propyl-5-methyl-5-(4-pyridyl)hydantoin and 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin were synthesized. The complexes were identified and characterized by elemental analysis, IR, ^{1}H, ^{13}C NMR spectra etc. On the data obtained the molecular formulae of the new palladium complexes were proposed. The cytotoxicity of the complexes was evaluated *in vitro* using a panel of human tumour cell lines. The results demonstrate that the Pd(II) complex with 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin exerts cytotoxicity as compared to the other studied Pd(II) complexes in all tested cell lines.

Keywords: Pd(II) and Pd(IV) complexes, 3,5-disubstituted hydantoins, cytotoxicity

INTRODUCTION

In recent years much research efforts have been focused upon the design and development of innovative antineoplastic transition metal complexes with superior antiproliferative activity than cisplatin. Cisplatin is a widely used drug in cancer chemotherapy,[1–4] but a wide range of side effects[5] have limited its clinical usefulness. For this reason research has been extended to other metal complexes. On the basis of the structural analogy between platinum(II) and palladium(II) complexes, a variety of studies on palladium(II) complexes as potential anticancer drugs have been carried out.[6]

Among the first to be used for clinical trials against tumors, were the analogous to cisplatin, complexes of Pd(II), *cis*-[Pd(En)Cl_2] and *cis*-[Pd(DACH)$_2Cl_2$] because Pd(II) has a very similar coordination chemistry to Pt(II), capable of forming square planar complexes. But these complexes have lower antitumor activity when compared to the analogous Pt(II) complexes, as well as their high toxicity.[7] In general the use of Pd(II) complexes in medicine is limited. However, Pd(II) N, S chelates with inert ligands (*e.g.* sulfur or nitrogen) were suggested by Das and Livingstone[8] to be more effective antitumor agents than those of other metals, they possess the proper lability to bring the metal to the target (DNA) and allow it to interact with it. Palladium(II) complexes are much more labile than corresponding platinum(II) complexes, the lability of central palladium(II) may be much lower because of the shielding effect.[9] Palladium(II) compounds might materialize the concept of tumor targeting, which would result in drugs with other spectrum of activity and a lack of cross-resistance as compared with platinum drugs.[10]

The present study represents the synthesis, physicochemical evaluation and pharmacological investigation of Pd(II) and Pd(IV) complexes with 3-ethyl-5-methyl-5-(4-pyridyl)hydantoin, 3-propyl-5-methyl-5-(4-pyridyl)hydantoin and 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin**.** As a part of our drug discovery program to develop more effective palladium based anticancer drugs, here we report the antiproliferative activity of some Pd(II) and Pd(IV) complexes.

EXPERIMENTAL

Materials and Physical Measurements

Potassium tetrachloropalladate(II) and potassium hexachloropalladate(IV) were purchased from Aldrich - USA. All other chemicals were of analytical grade.

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The ligands 3-ethyl-5-methyl-5-(4-pyridyl)-hydantoin (**L1**), 3-propyl-5-methyl-5-(4-pyridyl)-hydantoin (**L2**) and 3-benzyl-5-methyl-5-(4-pyridyl)-hydantoin (**L3**) were prepared by alkylation of 5-methyl-5-(4-pyridyl)-hydantoin, according to the published method [11]. The obtained compounds are new substances with the following melting points: **L1 -** 126−127 ºC, **L2 -** 85−86 ºC and **L3 -** 158−159 ºC. Their Pd(II) complexes were synthesized using reported procedure with minor revisions.[12,13]

CHN analysis was performed by "EuroEA EuroVector apparatus in the Inorganical Services Laboratory in the Faculty of Pharmacy of the Medical University of Sofia, Bulgaria.

The IR spectra were recorded on Thermo Scientific Nicolet iS10 spectrophotometer in the range of 4000−400 as pellets KBr and on IFS 113 v Bruker FTIR spectrophotometer in the range of 400−150 cm^{-1} in polyethylene.

The ^1H and ^{13}C NMR spectra were registered on a Bruker WM 250 (250 MHz) spectrometer in DMSO-d_6.

Synthesis of Pd(II) Complexes

*Synthesis of cis-[Pd(L1)$_2$Cl$_2$]·H$_2$O (**1**)*

A water-ethanol solution of **L1** (0.1259 g, 0.6112 mmol) was added dropwise to water solution of $K_2[PdCl_4]$ (0.1010 g, 0.3094 mmol). The mixture was stirred for 1−2 hours then the precipitate was filtered off, washed with distilled water and dried under vacuum. The substance is soluble in DMSO, DMF and weakly soluble in water and ethanol. Yield 68 %, m.p.: > 230 ºC (dec.).

IR (KBr disc. and polyethylene, ν / cm^{-1}): 3438, 3301, 1784, 1719, 1658, 1617, 1452, 1427, 369, 318.

^1H NMR (DMSO-d_6, δ / ppm): 9.05 (s,1H, NH-1), 8.77 (d, 2H, J = 7 Hz, H-2 + H-6), 7.66 (d, 2H, J = 7Hz, H-3 + H-5), 3.37 (q, 2H, J = 7Hz, N-**CH$_2$**), 1.69 (s, 3H, CH_3–C-5); 1.06 (t, 3H, J = 7Hz, N-CH_2-**CH$_3$**).

^{13}C NMR (DMSO-d_6, δ / ppm): 173.3 (C=O-4'), 155.3 (C=O-2'), 153.1 (C-2 + C-6), 151.6 (C-4), 122.3 (C-3 + C-5), 62.2 (C-5'), 33.3 (N-**CH$_2$**), 24.6 (CH_3), 13.1 (N-CH_2-**CH$_3$**).

*Synthesis of cis-[Pd(L2)$_2$Cl$_2$] (**2**)*

The complex *cis*-$[Pd(L2)_2Cl_2]\cdot 2H_2O$ **(2)** was synthesized analogously to the procedure for complex **1**. The substance is soluble in DMSO, DMF and weakly soluble in water and ethanol. Yield 68 %, m.p.: > 230 ºC (dec.).

IR (KBr disc. and polyethylene, ν / cm^{-1}): 3302, 1780, 1720, 1618, 1455, 1425, 371, 355.

^1H NMR (DMSO-d_6, δ / ppm): 9.04 (s,1H, NH-1), 8.76 (d, 2H, J = 7Hz, H-2 + H-6), 7.66 (d, 2H, J = 7Hz, H-3 + H-5), 3.32 (q, 2H, J = 7Hz, N-**CH$_2$**), 1.69 (s, 3H, CH_3–C-5); 1.49 (sxt, 2H, J = 7 Hz, N-CH_2-**CH$_2$**), 0.76 (t, 3H, J = 7Hz, N-CH_2-CH_2-**CH$_3$**).

^{13}C NMR (DMSO-d_6, δ / ppm): 173.5 (C=O-4'), 155.4 (C=O-2'), 153.1 (C-2 + C-6), 151.5 (C-4), 122.2 (C-3 + C-5), 62.1 (C-5'), 39.5 (N-**CH$_2$**), 24.6 (CH_3), 20.7 (N-CH_2-**CH$_2$**), 10.9 (N-CH_2-CH_2-**CH$_3$**).

*Synthesis of cis-[Pd(L3)$_2$Cl$_2$]·H$_2$O (**3**)*

The complex *cis*-$[Pd(L3)_2Cl_2].H_2O$ was synthesized analogously to the procedure for complex **1**.

The substance is soluble in DMSO, DMF and weakly soluble in water and ethanol. Yield 74 %, m.p.: > 188 ºC (dec.).

IR (KBr disc. and polyethylene, ν / cm^{-1}): 3282, 1784, 1717, 1616, 1495, 1441.

^1H NMR (DMSO-d_6, δ / ppm): 9.18 (s,1H, N(1)-H), 8.77 (d, 2H, $^3J_{H,H}$ = 7Hz, H-2 + H-6), 7.66 (d, 2H, $^3J_{H,H}$ = 7Hz, H-3 + H-5), 7.30−7.16 (m, 5H, C_6H_5), 4.54 (s, 2H, N-**CH$_2$**), 1.68 (s, 3H, CH_3−C-5).

^{13}C NMR (DMSO-d_6, δ / ppm): 173.5 (C=O-4'), 155.3 (C=O-2'), 153.2 (C-2 + C-6), 151.4 (C-4), 136.3 (C-1, benzene), 128.7 (C-2 + C-6, benzene), 127.6 (C-4, benzene), 127.1 (C-3 + C-5, benzene), 122.4 (C-3 + C-5), 62.5 (C-5'), 24.8 (CH_3).

Synthesis of Pd(IV) Complexes

*Synthesis of cis-[Pd(L1)$_2$Cl$_4$] (**1a**)*

A water-ethanol solution of **L1** (0.1110 g, 0.5068 mmol) was added dropwise to water solution of $K_2[PdCl_6]$ (0.1006 g, 0.3082 mmol). The mixture was stirred for 1−2 hours then the precipitate was filtered off, washed with distilled water and dried under vacuum. The substance is soluble in DMSO, DMF and weakly soluble in water and ethanol. Yield 74 %, m.p.: > 275 ºC (dec.).

IR (KBr disc. and polyethylene, ν / cm^{-1}): 3469, 3303, 1784, 1719, 1617, 1452, 1426.

^1H NMR (DMSO-d_6, δ / ppm): 9.05 (s, 1H, N(1)-H), 8.78 (d, 2H, J = 7Hz, H-2 + H-6), 7.67 (d, 2H, J = 7Hz, H-3 + H-5), 3.32 (t, 2H, J = 7Hz, N-**CH$_2$**), 1.70 (s, 3H, CH_3–C-5'), 1.51 (sxt, 2H, J = 7 Hz, N-CH_2-**CH$_2$**), 0.77 (t, 3H, J = 7Hz, N-CH_2-CH_2-**CH$_3$**).

^{13}C NMR (DMSO-d_6, δ / ppm): 173.5 (C=O-4'), 155.4 (C=O-2'), 153.1 (C-2 + C-6), 151.5 (C-4), 122.2 (C-3 + C-5), 62.1 (C-5'), 39.5(N-**CH$_2$**), 24.6 (CH_3–C-5), 20.7 (N-CH_2-**CH$_2$**), 10.9 (N-CH_2-CH_2-**CH$_3$**).

*Synthesis of cis-[Pd(L2)$_2$Cl$_4$] (**2a**)*

The complex *cis*-$[Pd(L2)_2Cl_4]$ (**2a**) was synthesized analogously to the procedure for complex **4**. The substance is soluble in DMSO, DMF and weakly soluble in water and ethanol. Yield 64 %, m.p.: > 185 ºC (dec.).

IR (KBr disc. and polyethylene, ν / cm^{-1}): 3322, 1784, 1719, 1618, 1427.

^1H NMR (DMSO-d_6, δ / ppm): 9.05 (s,1H, N(1)-H), 8.78 (d, 2H, J = 7Hz, H-2 + H-6), 7.67 (d, 2H, J = 7Hz, H-3 + H-5), 3.32 (t, 2H, J = 7Hz, N-**CH$_2$**),

1.70 (s, 3H, CH_3–C-5'), 1.51 (sxt, 2H, J = 7 Hz, N-CH_2-**CH_2**), 0.77 (t, 3H, J = 7Hz, N-CH_2-CH_2-**CH_3**).

^{13}C NMR (DMSO-d_6, δ / ppm): 173.5 (C=O-4'), 155.4 (C=O-2'), 153.1 (C-2 + C-6), 151.5 (C-4), 122.2 (C-3+C-5), 62.1 (C-5'), 39.5 (N-**CH_2**), 24.6 (CH_3–C-5), 20.7 (N-CH_2-**CH_2**), 10.9 (N-CH_2-CH_2-**CH_3**).

*Synthesis of cis-[Pd(L3)$_2$Cl$_4$] (**3a**)*

The complex *cis*-[Pd(L3)$_2$Cl$_4$] **(3a)** was synthesized analogously to the procedure for complex **4**. Yield: 74 %, m.p.: > 172 ºC (dec.).

IR (KBr disc. and polyethylene, ν / cm^{-1}): 3286, 1780, 1718, 1617, 1497, 1441, 377, 354.

^{1}H NMR (DMSO-d_6, δ / ppm): 9.21 (s,1H, N(1)-H), 8.78 (d, 2H, $^3J_{H,H}$ = 7Hz, H-2 + H-6), 7.68 (d, 2H, $^3J_{H,H}$ = 7Hz, H-3 + H-5), 7.34−7.17 (m, 5H, C_6H_5), 4.55 (s, 2H, N-**CH_2**), 1.72 (s, 3H, CH_3–C-5').

^{13}C NMR (DMSO-d_6, δ / ppm): 173.4 (C=O-4'), 155.3 (C=O-2'), 153.2 (C-2 + C-6), 151.4 (C-4), 136.3 (C-1, benzene), 128.7 (C-2 + C-6, benzene), 127.6 (C-4, benzene), 127.1 (C-3+C-5, benzene), 122.3 (C-3+C-5), 62.5 (C-5'), 24.8 (CH_3).

All the data about molecular formulae, formula weights, colors and the contents of nitrogen, carbon and hydrogen are given in Table 1.

Pharmacology

The present study describes a comparative evaluation of the cytotoxic effects of six newly synthesized Pd(II) and Pd(IV) complexes with some 3,5-disubstituted hydantoins *vs*. the referent antineoplastic agent cisplatin on a panel of human tumor cell lines, using the standard MTT-dye reduction assay for cell viability.

Cell Culture Conditions

The following cell lines were used for the experiments: (i) SKW-3 or a KE-37 derivative (human T-cell leukemia, established from the peripheral blood of a 61-year-old man with T-cell lymphocytic leukemia); (ii) HL-60 (acute myeloid leukemia, established from the peripheral blood of a patient with acute promyelocyte leukemia); (iii) EJ (human urinary bladder carcinoma), (iv) LAMA-84 (human chronic myeloid leukemia, established from the peripheral blood of a 29-year-old woman with chronic myeloid leukemia). The cell lines were maintained as suspension-type (SKW-3, LAMA-84, HL-60) or adherentmonolayer-type cultures (EJ) in cell-culture flasks using RPMI-1640, supplemented with 10 % heat-inactivated fetal calf serum and L-glutamine as a growth medium. The cells were incubated in a controlled environment (37 °C, 5 % carbon dioxide humidified atmosphere).

Cytotoxicity Assessment

Cytotoxicity of the compounds was assessed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] dye reduction assay as described by Mossman[14] with some modifications.[15] Exponentially growing cells were seeded in 96-well microplates (100 μL / well at a density of 3.5×10^5 cells / mL for the adherent and 1×10^5 cells / mL for the suspension cell lines) and allowed to grow for 24 h prior the exposure to the studied compounds. Stock solutions of the palladium complexes were freshly prepared in DMSO and then diluted with corresponding growth medium. At the final dilutions the solvent concentration never exceeded 0.5 %. Cells were exposed to the tested agents for 72 h, whereby for each concentration a set of 8 separate wells was used. Every test was run in triplicate, *i.e.* in three separate microplates. After incubation with the tested compounds MTT solution (10 mg / mL in PBS) aliquots were added to each well. The plates were further incubated for 4 h at 37 ºC and the formazan crystals formed were dissolved by adding 110 μL of 5 % HCOOH in 2-propanol. Absorption of the samples was measured by an ELISA reader (Uniscan Titertec) at 580 nm. Survival fraction was calculated as percentage of the untreated control. The experimental data were processed using GraphPad Prizm software and were fitted to sigmoidal concentration/response curves, using non-linear regression analysis.

Table 1. Physical properties and elemental analysis of new palladium complexes

Complex	Molecular formula (Formula weight)	Colour	Elemental analysis: Calc. % (Found)		
			C	H	N
cis-[Pd(L1)$_2$Cl$_2$]·H$_2$O	$C_{22}H_{28}N_6O_5Cl_2Pd$ (633.3)	Light yellow	41.69 (41.33)	4.42 (4.50)	13.26 (13.41)
cis-[Pd(L2)$_2$Cl$_2$]	$C_{24}H_{30}N_6O_4Cl_2Pd$ (643.3)	Lemon yellow	44.77 (44.55)	4.66 (4.35)	13.06 (11.23)
cis-[Pd(L3)$_2$Cl$_2$]	$C_{32}H_{32}N_6O_5Cl_2Pd$ (741.3)	Light yellow	50.80 (50.72)	4.32 (4.08)	11.33 (11.32)
cis-[Pd(L1)$_2$Cl$_4$]	$C_{22}H_{26}N_6O_4Cl_4Pd$ (686.2)	Light yellow	38.47 (39.16)	3.79 (4.02)	12.24 (12.56)
cis-[Pd(L2)$_2$Cl$_4$]	$C_{24}H_{30}N_6O_4Cl_4Pd$ (714.2)	Light yellow	40.33 (41.29)	4.20 (4.48)	11.76 (11.75)
cis-[Pd(L3)$_2$Cl$_4$]	$C_{32}H_{32}N_6O_4Cl_4Pd$(812 .2)	Light yellow	47.28 (47.63)	3.94 (3.91)	10.34 (10.61)

RESULTS AND DISCUSSION

Chemical Studies

Complexes (**1**), (**2**) and (**3**) were prepared by adding of water-ethanol solutions of ligands **L1, L2** and **L3** to the water solution of $K_2[PdCl_4]$ in molar ratio 1 : 2. Complexes (**1a**), (**2a**) and (**3a**) were prepared by adding of water-ethanol solutions of ligands **L1, L2** and **L3** to the water solution of $K_2[PdCl_6]$ in the same ratio. The mixtures were stirred for 1−2 hours then the precipitates were filtered off, washed with distilled water and dried under vacuum. The substances are soluble in solvents with pronounced donor properties, such as N,N-dimethyl-formamide, dimethylsulfoxide and weakly soluble in water and ethanol.

IR Spectroscopy

Infrared spectroscopy data confirm the coordination of ligands to the palladium(II) and palladium(IV) ions *via* nitrogen atom from pyridine ring of the ligands. In the spectra of the ligands **L1**, **L2** and **L3** the typical stretching vibrational mode of substituted pyridines, ν(C=N) for the uncoordinated ligands is appeared at 1600 cm^{-1} and were blue shifted to higher wavenumbers - 1658, 1618, 1616, 1617, 1618 and 1617 cm^{-1} in the spectra of the complexes - respectively. The other characteristic bands from the pyridine ring of the metal-free ligands are again blue-shifted upon complexation. These shifts were in agreement with the N-coordination, involving the pyridine N atom of the ligands. New bands in the range of 377–318 cm^{-1} were assigned to the ν(Pt–Cl) stretching vibrations. In the IR spectra of the all complexes two bands for ν(Pt–Cl) stretching vibrations were observed, implying *cis*-location of chloride ligands.[16]

The bands related to the stretching vibrations of the two carbonyl groups in the metal-free ligands did not shift upon coordination of **L1, L2** and **L3** to palladium(II) and palladium(IV) ions, indicating that the C=O groups were not involved in binding to the metals.

NMR Spectroscopy

^{1}H NMR

The ^{1}H NMR spectra of the freshly prepared DMSO-d_6 solutions of the ligands and complexes were recorded. In the spectra of complexes **1**, **2** and **3** the signals of the protons for H-2 and H-6 from the pyridine ring were shifted from 8.61 ppm in the ligands **L1**−**L3** to 8.77, 8.76, 8.77, 8.78, 8.78 and 8.78 ppm in the complexes **1**−**3** and **1a**−**3a**. The differences between the chemical shifts of the protons of the ligands **L1**−**L3** and those of the corresponding complexes are in the range of 0.15–0.17 ppm for all studied complexes**.** The signals of the H-3 and H-5 protons from the pyridine ring were shifted from 7.48 ppm in the ligands **L1**–**L3** to 7.66, 7.66, 7.66, 7.67, 7.67 and 7.68 ppm in the complexes **1**–**3** and **1a**−**3a** respectively. Here the differences are in the range of 0.18–0.20 ppm. All signals for the protons in the pyridine ring were shifted. This shows that the most probable bounding of the ligands with the palladium ions in all complexes is realized through the nitrogen atom from the pyridine ring.

^{13}C NMR Spectra

In the ^{13}C NMR spectra of the compounds **1**–**3** and **1a**−**3a** the signals for the carbon atoms C-2 and C-6 from the pyridine ring were at 153.1, 153.1, 153.2, 153.1, 153.1 and 153.2 ppm, respectively, compared to 150.0 ppm for the metal-free ligands **L1**−**L3**. The downfield chemical shifts in the range 3.1 to 3.2 ppm indicate that the pyridine nitrogen atom takes part in the coordination to the metal ions. The shifts of the C-3 and C-5 were smaller in according to their remote positions from the binding nitrogen atom.

The resonances of the two C=O groups of the hydantoin ring in metal-free-ligands **L1**, **L2** and **L3** and in their complexes **1**–**3** and **1a**−**3a** were the practically same. This shows that the hydantoin ring is not involved in the coordination with the metal ion.

The elemental analysis and spectroscopic data confirm the following structures of the complexes shown in Figure 1.

Pharmacology

In vitro Cytotoxicity

The tested palladium(II) and palladium(IV) complexes exerted cytotoxic effects after 72 h continuous exposure, whereby the individual chemosensitivity varied among the different cell lines, as evidenced by the IC_{50} values, summarized in Table 2.

The Pd(II) complex with 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin (**3**) proved to be the most active analogue within this series, whose antiproliferative potency in SKW-3 was relative to that of the reference antineoplastic drug cisplatin.

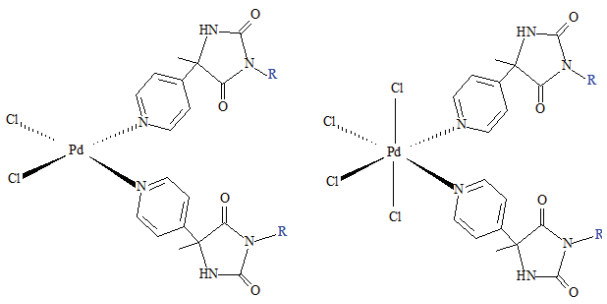

Figure 1. Chemical structures of studied Pd(II) and Pd(IV) complexes.

Table 2. Cytotoxicity of all studied Pd(II) and Pd(IV) complexes **1**–**3** and **1a**–**3a** in comparison to cisplatin in four human tumour cell lines

	IC_{50} values/μM			
Cell line	SKW-3[(a)]	HL-60[(b)]	EJ[(c)]	LAMA-84[(d)]
Complex 1	149.2	>200	162.3	>200
Complex 2	–	>200	137.5	165.8
Complex 3	49.5	134.2	99.7	117.2
Complex 1a	147.7	>200	>200	>200
Complex 2a	–	194.1	125.8	160.8
Complex 3a	139.7	153.0	88.6	119.4
Cisplatin	11.4	8.7	10.2	16.9

[(a)] T-cell leukemia.
[(b)] Acute myeloid leukemia.
[(c)] Urinary bladder carcinoma.
[(d)] Human chronic myeloid leukemia.

CONCLUSION

Six Pd(II) and Pd(IV) complexes with 3-ethyl, 3-propyl- and 3-benzyl-5-methyl-5-(4-pyridyl)hydantoins were synthesized according to procedures described in the literature. All complexes were characterized by elemental analysis, IR, ^{1}H, ^{13}C NMR spectra. The mode of the coordination of the ligands with palladium ions is realized *via* the nitrogen atom of the pyridine ring. The coordination mode is identical to those of Pt(II) and Pt(IV) complexes with the same ligands, described in our preceding reports. The cytotoxicity of the prersented palladium complexes was assessed *in vitro* on a panel of four human tumour cell lines. The results show that the Pd(II) and Pd(IV) complexes with 3-benzyl-5-methyl-5-(4-pyridyl)hydantoin possess higher cytotoxicity in all cell lines than the other Pd(II) and Pd(IV) complexes with 3-ethyl- and 3-propyl-5-methyl-5-(4-pyridyl)hydantoins. This is in keeping with the Pt(II) (where for Pt(II) complexes cytotoxicity was strongly dependent on their calculated log*P* values) and Pt(IV) complexes with the same ligands.

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