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Application of microwave-assisted heating to the synthesis of Pt(II) complexes

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ABSTRACT

The microwave-assisted synthesis of Pt(II) complexes containing several pyridines (i.e., pyridine **L1**, 2-picoline **L2**, 3-picoline **L3**, 4-picoline **L4**, 2,2′-bipyridine **L5**) is reported. For **L1**–**L5**, the reaction was successful in about 50% yield with all the ligands except **L2**. The same method applied to 4,4′-bis(2-morpholinoethoxy)-2,2′-bipyridine (**L6**, a ligand showing interesting antiproliferative properties because of a high DNA affinity), was unsatisfactory. The corresponding complex *cis*-[$PtCl_2$(**L6**)] was obtained only heating at reflux a mixture of [$PtCl_2$(1,5-cyclooctadiene)] and **L6** in acetonitrile for 24 h. Antiproliferative activity of [$PtCl_2$(**L6**)] on four cancer cell lines (ovarian A2780 and its cisplatin-resistant variant A2780cisR, prostate PC3 and breast cancer MDA-MB-231) was compared with that of its ligand and the model complex [$PtCl_2$(**L5**)]. These studies showed that [$PtCl_2$(**L6**)] has just marginal activity towards the tested cells if compared with cisplatin.

1. Introduction

Still today in the third millennium, the "old" Pt-based drugs represent an established class of cancer therapeutics [1]. Successful clinical applications of the prototype complex cisplatin, *cis*-diamminedichloridoplatinum(II), encouraged the search for other molecules in order to reduce the severe side effects associated with cisplatin therapy and to broaden the application spectrum.

The common procedure for the synthesis of the cisplatin-like complexes is the Dhara's method, based on the synthon *cis*-[Pt(amine)$_2$I$_2$] [2]. In alternative, other methods consist in the direct reaction between $K_2[PtCl_4]$ and the ligand upon heating for several hours [3].

In order to improve these procedures, the microwave (MW) synthesis was considered. The employment of MW irradiation has become more and more widespread, in particular in the framework of drug discovery and development, and it is nowadays commonly used in organic reactions [4]. This kind of heating allows to speed up the thermally driven reactions. In the traditional heating, reactants are slowly activated by an external heat source and the heat reaches the substances through the walls of the vessel. On the contrary, MWs interact directly with the molecules of the entire reaction mixture, leading to a rapid and localized rise in temperature of any substance that will respond to dipole rotation or ionic conduction [4].

The MW-assisted heating is rather unexplored in the field of Pt compounds; it has been applied to the synthesis of cisplatin [5,6], although the time saved with this procedure could not fully compensate for the different yield with respect to the Dhara's method [6].

In order to enlarge the application of the MW-based procedures to the synthesis of Pt complexes and to verify whether changing the ligands may lead to better reaction kinetics and yields, this method was applied to the synthesis of a series of Pt(II) complexes with unidentate (pyridine **L1**, 2-picoline **L2**, 3-picoline **L3** and 4-picoline **L4**) and bidentate (2,2′-bipy chelators **L5** and **L6**) pyridyl-based ligands (Fig. 1).

The study of the morpholine-substituted bipyridine **L6** was motivated by the encouraging biological properties reported for a series of mixed bipyridine–terpyridine–Cu^{II} complexes that contain 2,2′-bipy chelators bearing pendant arms with different cyclic amines. All those Cu(II) complexes showed high antiproliferative activity in ovarian carcinoma A2780 and its cisplatin-resistant sub-line A2780R, being three to five times more cytotoxic than

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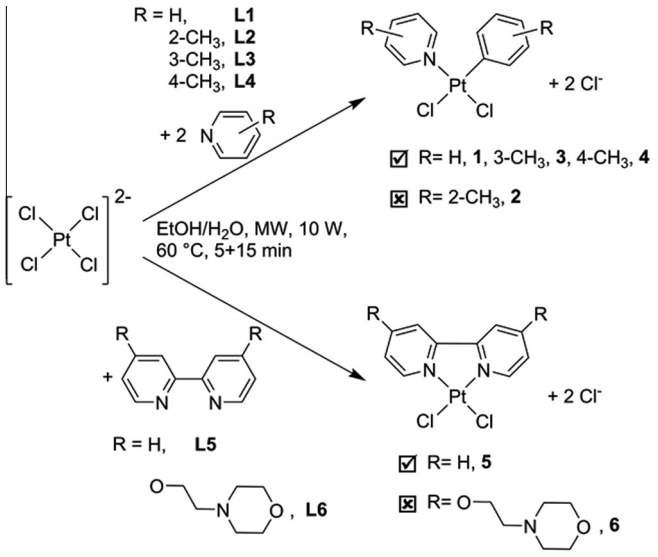

Fig. 1. Structural formulae of the complexes and summary of the MW reactions.

cisplatin. They displayed also an impressive plasmid DNA cleaving ability, triggering double-strand DNA breaks via an oxidative pathway. In particular, the cyclic amines in the pyridine ligands seem to increase the DNA binding affinity of the complexes by electrostatic interactions with the DNA phosphate backbone [7].

2. Experimental

2.1. General procedures

$K_2[PtCl_4]$ (Johnson Matthey and Co.) and all other chemicals (Johnson Matthey and Co. and Sigma Aldrich) were used without further purification. Cisplatin [2], *cis*-$[PtCl_2(COD)]$ [8] and 4,4′-bis (2-morpholinoethoxy)-2,2′-bipyridine, **L6** [6], were synthesized and purified according to literature procedures. The reactions under microwave irradiation were performed by using a CEM Discover® SP System equipped with a focused single mode and self-tuning cavity, an air cooling system, and an automated power control based on temperature feedback, supplying power in 1 W increments from 0 to 300 W. The purity of the compounds was assessed by analytical RP-HPLC (see below), and elemental analysis. Elemental analyses were carried out with a EA3000 CHN Elemental Analyzer (EuroVector, Milano, Italy). For all the compounds, the experimental values of the elemental analyses correspond to calculated values within ±0.4%. The NMR spectra were measured on an NMR Bruker Advance III operating at 500 MHz (^{1}H), 125.7 MHz (^{13}C) and 107.2 MHz (^{195}Pt with a spectral window of 2000 ppm), respectively. ^{195}Pt NMR spectra were recorded using a solution of $K_2[PtCl_4]$ in saturated aqueous KCl as the external reference. The shift for $K_2[PtCl_4]$ was adjusted to −1628 ppm from Na_2PtCl_6 (δ = 0 ppm). RP-HPLC and mass analysis were performed using a Waters HPLC-MS instrument equipped with Alliance 2695 separations module, 2487 dual lambda absorbance detector, and 3100 mass detector. The chromatographic conditions were: silica-based C18 stationary phase (5-μm Phenomenex Phenosphere-NEXT C18 column 250 × 46 mm ID); mobile phase containing 50:50 MeOH:15 mM HCOOH aqueous solution (flow rate = 0.75 mL min^{-1}; isocratic elution, UV–visible detector set at 210 nm). The complexes under study were dissolved in DMSO and then diluted with water to favor the formation of the corresponding cationic solvolyzed species for the following MS analyses. Electrospray ionization mass spectra (ESI-MS) were obtained setting the source and desolvation temperatures to 150 °C and 250 °C, respectively, and using nitrogen both as a drying and as a nebulizing gas. The cone and the capillary voltages were usually 30 V and 2.70 kV, respectively. Quasi-molecular ion peaks $[M+H]^+$ or solvolized $[M-Cl+DMSO]^+$ peaks are assigned on the basis of the *m*/*z* values and of the simulated isotope distribution patterns.

2.2. Synthesis of complexes *1*–*4* by microwave heating

To a solution of $K_2[PtCl_4]$ (60 mg, 0.144 mmol) in a mixture of water (3 mL) and ethanol (1 mL) in a 10-mL microwave vessel, 2 eq. of amine was added (23 μL of pyridine or 28 μL of picoline). The vessel was then capped and introduced into the microwave cavity. The microwave unit was programmed to heat the vessel content to 60 °C over a 5-min ramp period and then hold at this temperature for 15 min; the power was automatically set at 10 W. During this time, the mixture was stirred with a magnetic bar. After heating, the vessel was allowed to cool to room temperature before removing it from the cavity. Some yellow precipitate is formed at this stage. The mixture was then cooled to 0 °C to increase the quantity of final product, which was separated by centrifugation and washed with water, methanol and diethyl ether. The reaction with 2-picoline behaved differently resulting in a complex mixture of by-products in solution. Yields: 30 mg of **1** (49%), 31 mg of **3** (48%) and 32 mg of **4** (52%).

1. ESI-MS (positive ion mode): *m*/*z* = 467.3 $[M-Cl+DMSO]^+$, Calcd for $C_{12}H_{16}ClN_2OPtS^+$ 466.87. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.33 (t, 4H, Pt–N–CH–C*H*–CH), 7.84 (t, 2H, Pt–N–CH–CH–C*H*), 8.77 (d, 4H, Pt–N–C*H*–CH–CH) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 126.5 (Pt–N–CH–*C*H–CH), 138.7 (Pt–N–CH–CH–*C*H), 153.0 (Pt–N–*C*H–CH–CH) ppm. ^{195}Pt NMR ($CDCl_3$, 107.2 MHz): δ = −1992 ppm.

3. ESI-MS (positive ion mode): *m*/*z* = 495.3 $[M-Cl+DMSO]^+$, calcd for $C_{14}H_{20}ClN_2OPtS^+$ 494.92. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.33 (s, 6H, Pt–N–CH–C(*CH*$_3$)–CH–CH–CH), 7.18 (t, 2H, Pt–N–CH–C(CH$_3$)–CH–*CH*–CH), 7.60 (d, 2H, Pt–N–CH–C(CH$_3$)–*CH*–CH–CH), 8.51 (d, 2H, Pt–N–CH–C(CH$_3$)–CH–CH–*CH*), 8.67 (s, 2H, Pt–N–*CH*–C(CH$_3$)–CH–CH–CH) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 18.6 (Pt–N–CH–C(*C*H$_3$)–CH–CH–CH), 125.7 (Pt–N–CH–C(CH$_3$)–CH–*C*H–CH), 136.9 (Pt–N–CH–*C*(CH$_3$)–CH–CH–CH) 139.4 (Pt–N–CH–C(CH$_3$)–*C*H–CH–CH), 150.1 (Pt–N–CH–C(CH$_3$)–CH–CH–*C*H), 153.2 (Pt–N–*C*H–C(CH$_3$)–CH–CH–CH) ppm. ^{195}Pt NMR ($CDCl_3$, 107.2 MHz): δ = −1996 ppm.

4. ESI-MS (positive ion mode): *m*/*z* = 495.3 $[M-Cl+DMSO]^+$, calcd for $C_{14}H_{20}ClN_2OPtS^+$ 494.92. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.37 (s, 6H, Pt–N–CH–CH–C(*CH*$_3$)), 7.11 (t, 2H, Pt–N–CH–C*H*–C(CH$_3$)), 8.60 (d, 2H, Pt–N–C*H*–CH–C(CH$_3$)) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 21.3 (Pt–N–CH–CH–C(*C*H$_3$)), 127.3 (Pt–N–CH–*C*H–C(CH$_3$)), 151.0 (Pt–N–CH–CH–*C*(CH$_3$)) 152.2 (Pt–N–*C*H–CH–C(CH$_3$)) ppm. ^{195}Pt NMR ($CDCl_3$, 107.2 MHz): δ = −1996 ppm.

2.3. Synthesis of complex *5* by microwave heating

$K_2[PtCl_4]$ (30.0 mg, 0.072 mmol) was dissolved in 3 mL water in a 10-mL microwave vessel. Ligand **L5** (11.2 mg, 0.072 mmol) was dissolved in 1 mL ethanol and was added to the former solution. The vessel was then capped and introduced into the microwave cavity. The microwave unit was programmed to heat the vessel content to 60 °C over a 5-min ramp period and then hold at this temperature for 5 min. During this time, the mixture was stirred with a magnetic bar. After heating, the vessel was allowed to cool to room temperature before removing it from the cavity. At the end of the reaction, a yellow-orange precipitate was obtained and washed with water and ethanol and dried in vacuo. Yield: 24 mg, 71%. This reaction was successfully scaled-up in a 25-mL flask. ESI-MS (positive ion mode): *m*/*z* = 464.3 $[M-Cl+DMSO]^+$, calcd for $C_{12}H_{14}ClN_2OPtS^+$ 464.02. ^{1}H NMR (DMF-d_7, 500 MHz): δ = 7.93

(2H, td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, N–CH–C*H*–CH), 8.50 (2H, td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, N–CH–CH–C*H*), 8.68 (2H, d, ^3J = 8.5 Hz, N–C–C*H*), 9.68 (2H, dd, ^3J = 5.8 Hz, ^4J = 0.9 Hz, N–C*H*–CH–CH) ppm; ^{13}C NMR (DMF-d_7, 125.7 MHz): δ = 124.2 (N–CH–*C*H–CH), 127.7 (N–C–*C*H), 140.5 (N–CH–CH–*C*H), 148.7 (N–*C*H–CH–CH), 158.4 (N–*C*–CH) ppm; ^{195}Pt NMR (DMF-d_7, 107.2 MHz): δ = −2327 ppm.

2.4. Synthesis of complex **6**

A 10 mL round bottom flask was charged with 0.221 g (1.0 mmol) of **L6**, 0.100 g (1.0 mmol) of cis-[$PtCl_2$(COD)] and 6 mL of acetonitrile then heated at reflux for 24 h. After cooling the mixture to room temperature, solid was separated and rinsed 2 times with acetonitrile to obtain a pale yellow powder. Yield: 0.087 g; 96%. ESI-MS (positive ion mode): calcd for $C_{22}H_{31}Cl_2N_4O_4Pt$ [M+H]$^+$ 681.49 *m/z*, found 681.3 *m/z*. ^{1}H NMR (DMF-d_7, 500 MHz): 2.56 (8H, m, morph –C*H*$_2$–N–C*H*$_2$–), 2.85 (4H, t, ^3J = 5 Hz, Py–O–CH$_2$–C*H*$_2$), 3.62 (8H, m, morph –C*H*$_2$–O–C*H*$_2$–), 4.51 (4H, t, ^3J = 5 Hz, Py–O–C*H*$_2$–CH$_2$), 7.50 (2H, dd, ^3J = 7 Hz, ^4J = 2.5 Hz, N–CH–C*H*), 8.33 (2H, d, ^4J = 2.5 Hz, C–C*H*–C), 9.35 (2H, d, ^3J = 7 Hz, N–C*H*–CH) ppm; ^{13}C NMR (DMF-d_7, 125.7 MHz): δ = 54.25 (morph –*C*H$_2$–N–*C*H$_2$–), 57.20 (Py–O–CH$_2$–*C*H$_2$), 66.96 (morph –*C*H$_2$–O–*C*H$_2$–), 68.00 (Py–O–*C*H$_2$–CH$_2$), 111.16 (N–CH–*C*H–C), 113.60 (N–C–*C*H), 149.66 (N–*C*H–CH–C), 159.00 (N–*C*–CH), 167.32 (N–CH–CH–*C*) ppm; ^{195}Pt NMR (DMF-d_7, 107.2 MHz): δ = −2319 ppm.

2.5. Cell culture and growth inhibition (IC_{50})

The human ovarian cancer cell lines A2780, its cisplatin-resistant sub-line A2870cisR (ECACC, UK), and the prostate cancer cell line PC3 were grown in RPMI 1640 culture medium (Invitrogen) supplemented with 10% FBS and 1% penicillin/streptomycin at 37 °C in a humidified atmosphere of 95% of air and 5% CO_2 (Heraeus, Germany). The human breast cancer cell line MDA-MB-231 were grown in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen) supplemented with 10% FBS and 1% penicillin/streptomycin, in similar conditions as above. The cytotoxicity of the complexes against the different cell lines was evaluated using a colorimetric method based on 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), which is reduced by viable cells to yield purple formazan crystals. Cells were seeded in 96-well plates at a density of 1×10^4 to 1.5×10^4 cells per well in 200 μL of culture medium and left to incubate overnight for optimal adherence. After careful removal of the medium, 200 μL of a dilution series of the compounds (stock solutions freshly prepared) in medium were added and incubation was performed at 37 °C for 72 h. The percentage of DMSO in cell culture medium did not exceed 1%. At the end of the incubation period, the compounds were removed and the cells were incubated with 200 μL of MTT solution (500 μg mL^{-1}). After 3–4 h, the medium was removed and the purple formazan crystals were dissolved in 200 μL of DMSO by shaking. The cell viability was evaluated by measurement of the absorbance at 570 nm using a plate spectrophotometer (Power Wave Xs, Bio-Tek). The cell viability was calculated dividing the absorbance of each well by that of the control wells. Each point was determined in at least 4 replicates, in 3 independent experiments.

3. Results and discussion

3.1. Synthesis and characterization of the platinum complexes

Before applying the MW-assisted synthesis to **L6**, the simple ligands **L1**–**L5** were used to set up the reaction conditions (Fig. 1). A water solution of $K_2[PtCl_4]$ was mixed with an ethanol solution of each ligand, and the MW unit was programmed to heat the vessel content to 60 °C over a 5 min ramp period and then hold at this temperature for 15 min (see Section 2). A pale yellow precipitate of **1** and **3**–**5** was obtained in about 50% yield, without further purification steps. The synthesis of **1** [9], **3** and **4** with the traditional thermal approach has been already reported with higher yields. However, it is worthwhile to mention that for **3** the traditional synthesis led also to the formation of Magnus' salt type impurities (i.e., [PtCl(**L3**)$_3$]$^+$[$PtCl_3$(**L3**)]$^-$) [10]. In the case of **2**, several by-products (e.g., [PtCl(**L2**)$_3$]$^+$ and Magnus' salt type species [PtCl(**L2**)$_3$]$^+$[$PtCl_3$(**L2**)]$^-$ among others) were present in the reaction mixture that resulted from the MW irradiation, and no precipitation of the desired product was observed. Probably, the steric hindrance of the methyl group in position 2 did not allow to obtain the final product. All attempts to improve the MW-assisted reaction (longer reaction time and/or different temperature) were unsuccessful. Interestingly, the traditional synthesis of **2** was previously reported with a yield of 20%, but with the formation of various rotamers [14]. Since the heating can promote the formation of the *trans* isomers, the isomeric purity of complexes **1**, **3** and **4** was spectroscopically verified. In particular, the ^{195}Pt NMR chemical shifts of *cis* and *trans* complexes are usually different and the data for complexes **1**, **3** and **4** in $CDCl_3$ (i.e., δ = −1992 ppm for **1** and δ = −1996 ppm for both **3** and **4**) confirmed that these complexes were obtained as *cis* isomers, in agreement with the observations of Rochon et al. [14]. In fact, the ^{195}Pt NMR chemical shifts of their *trans* analogues in the same solvent are observed at higher frequency ($\Delta\delta \approx 50$ ppm).

The above reported MW-assisted procedure, while successful for the synthesis of complex **5**, required some modification to be applied to **L6**, such as the exclusion of ethanol and/or lower temperatures, in order to avoid extensive degradation (i.e., formation of insoluble dark brown solid). Unfortunately, none of the attempts was satisfactory giving rise to mixtures of several products, including also complex **6** but in low percentage.

The usual Dhara's method [2] and the direct coordination of **L6** to $K_2[PtCl_4]$ ($K_2[PtCl_4]$:bipyridine = 1:1 in water, 75 °C, excess Cl^- [3]) improved neither yields nor purity of the final complex (Fig. 2). On the contrary, the direct coordination of **L5** to $K_2[PtCl_4]$ was successful for the synthesis of complex **5**.

Finally, the typical synthesis starting from the precursor *cis*-dichlorido(1,5-cyclooctadiene)platinum(II), [$PtCl_2$(COD)] [10] (i.e., heating at 40–70 °C for 15 min in water suspension [11]) was ineffective to give high yield and/or pure products. Nevertheless, changing the solvent (from water to acetonitrile) and refluxing the mixture of [$PtCl_2$(COD)] and **L6** for 24 h [12], complex **6** was successfully synthesized (Fig. 2).

Compounds **1** and **3**–**6** were characterized by means of RP-HPLC, ESI-MS, and multinuclear NMR spectroscopy. Since the complexes are barely soluble in water and/or alcohols, and are not so easily ionized into the mass spectrometer, HPLC-MS analysis were carried out on solutions of the complexes in DMSO, which promotes the Cl/DMSO exchange forming the corresponding solvated cationic species. The NMR analyses, carried out in $CDCl_3$ or DMF-d_7, confirmed the identity of the different compounds. In particular, it is worth noting that the ^{195}Pt NMR chemical shifts are compatible with a "PtN_2Cl_2" core, i.e. in the −1990/−2330 ppm region [10,13].

3.2. Antiproliferative activity

The antiproliferative properties of **6** and the corresponding ligand **L6** were assayed by monitoring their ability to inhibit cell growth. Cisplatin, complex **5** and its ligand **L5** were also evaluated for comparison purposes. The cytotoxic activity was determined on four different human cancer cell lines (namely, ovarian A2780 and

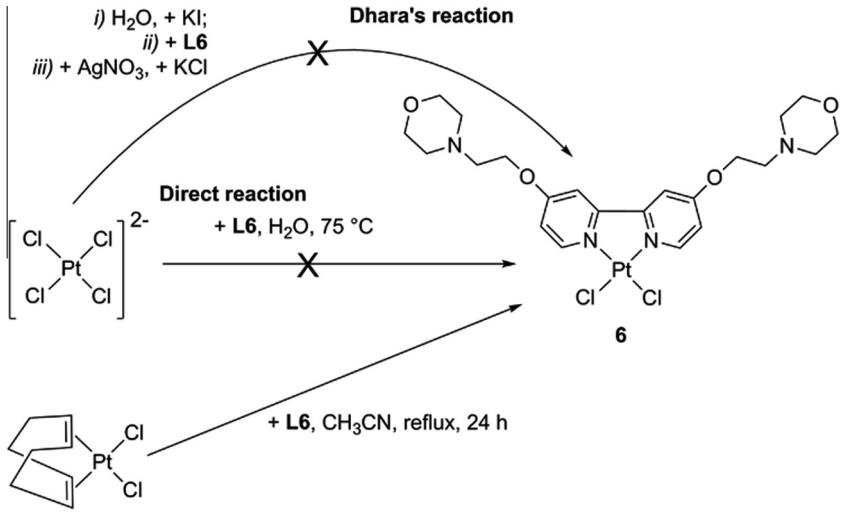

Fig. 2. General scheme of the syntheses of complex **6**.

Table 1
IC_{50} values for 72 h treatment of four different human tumour cell lines.

Compound	IC_{50} [μM]			
	A2780	A2780cisR	MDA-MB-231	PC3
Cisplatin	1.3 ± 0.5	16 ± 1.2	8.5 ± 1.2	51 ± 7
L5	94 ± 1.5	126 ± 6.2	–	–
5	65 ± 1.4	173 ± 1.3	>200	182 ± 1.7
L6	90 ± 2.0	174 ± 1.1	–	–
6	113 ± 1.3	169 ± 2.2	>200	167 ± 2.2

its cisplatin-resistant variant A2780cisR, prostate PC3, and breast MDA-MB-231), by the colorimetric MTT assay. The dose–response curves, after 72 h exposure, were used to calculate the half-maximal inhibition concentrations (IC_{50}) (Table 1).

The analyzed Pt complexes show low cytotoxicity against the different cell lines if compared with the reference drug cisplatin. In addition, their cytotoxicity did not significantly increased from that of the corresponding ligands. Complex **5** exhibited the lowest IC_{50} value, which was found in the sensitive A2780 cell line.

4. Conclusions

A new Pt(II) complex with the morpholino-bipyridine **L6** was designed and biologically evaluated, as inspired by the important DNA binding affinity and cytotoxicity showed by Cu(II) complexes with the same ligand. However, complex **6** showed lower cytotoxicity than that of the congener without morpholino substituents (complex **5**). This result may be related to a lower cell uptake of **6** *vs.* **5**. In fact, the logarithm of the partition coefficient (log *P*, directly related to the ability of a compound to cross cell membrane by passive diffusion) estimated with ALOGPS 2.1 [14] shows that **L5** is more lipophilic than **L6** (1.85 *vs.* 1.60). Assuming that the contribution of the "$PtCl_2$" moiety to the final log *P* of the complexes is similar [15], this difference in the ligands is expected to be reflected on the final complexes. Therefore, complex **6** must be less lipophilic than complex **5**, which can justify its minor cell uptake.

Despite the poor biological performance of the reported Pt complexes, the present work corroborates the possibility of the application of microwave heating to the synthesis of Pt complexes.

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