

Synthesis of Platinum Complexes from N-Benzyl-1,3-Propanediamine Derivatives, Potential Antineoplastic Agents.

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Abstract: This work describes the synthesis of seven new platinum complexes having N-benzyl 1,3-propanediamine derivatives as ligands. They were prepared by the reaction of $K_2[PtCl_4]$ with the appropriate ligand in water. These complexes are analogs of cisplatin, and are potential antineoplastic agents.

Keywords: Platinum(II) complexes, N-benzyl 1,3-propanediamine, anticancer agents.

Introduction

The discovery of the anticancer activity of the coordination compound *cis*-diaminedichloroplatinum(II) (cisplatin) [1], and its successful clinical use, represents important progress for inorganic medicinal chemistry. Cisplatin has been approved for commercial use in the United States since 1979 [2], being used by itself or in combination with other chemotherapeutic agents to treat several types of cancer, such as testicular, ovarian, head and neck [3-5]. For example, testicular carcinoma, which once had a high mortality rate, can now be cured in 85% of the cases [6].

However, the use of the cisplatin in the clinic is limited by its narrow activity spectrum, cellular resistance, and some serious side effects [7-9], such as nephrotoxicity, ototoxicity and neurotoxicity. Since then, the search for new platinum anticancer drugs has continued, and in 1987 the compound *cis*-diamine(1,1-cyclobutanedicarboxylate)platinum(II), carboplatin [10,11], was approved for commercial purposes. Carboplatin has been shown to be less nephrotoxic and emetogenic than cisplatin, however, it is also active against a limited number of tumors, and it is not effective in cell resistant lines.

Two others compounds have been approved for use in some countries. Oxaliplatin, *trans*-L-(diaminocyclohexane)oxalatoplatinum(II) has been approved for the treatment of colorectal cancer in France, and nedaplatin, *cis*-diamine-glycolateplatinum(II) has received approval for use in Japan. However, they have yet to demonstrate significant advantages over cisplatin or carboplatin [12]. Thus, it is very important to develop new platinum complexes that could effectively act in a larger number of tumors. At the same time those complexes should present less severe side effects and they should be active in resistant cells lines.

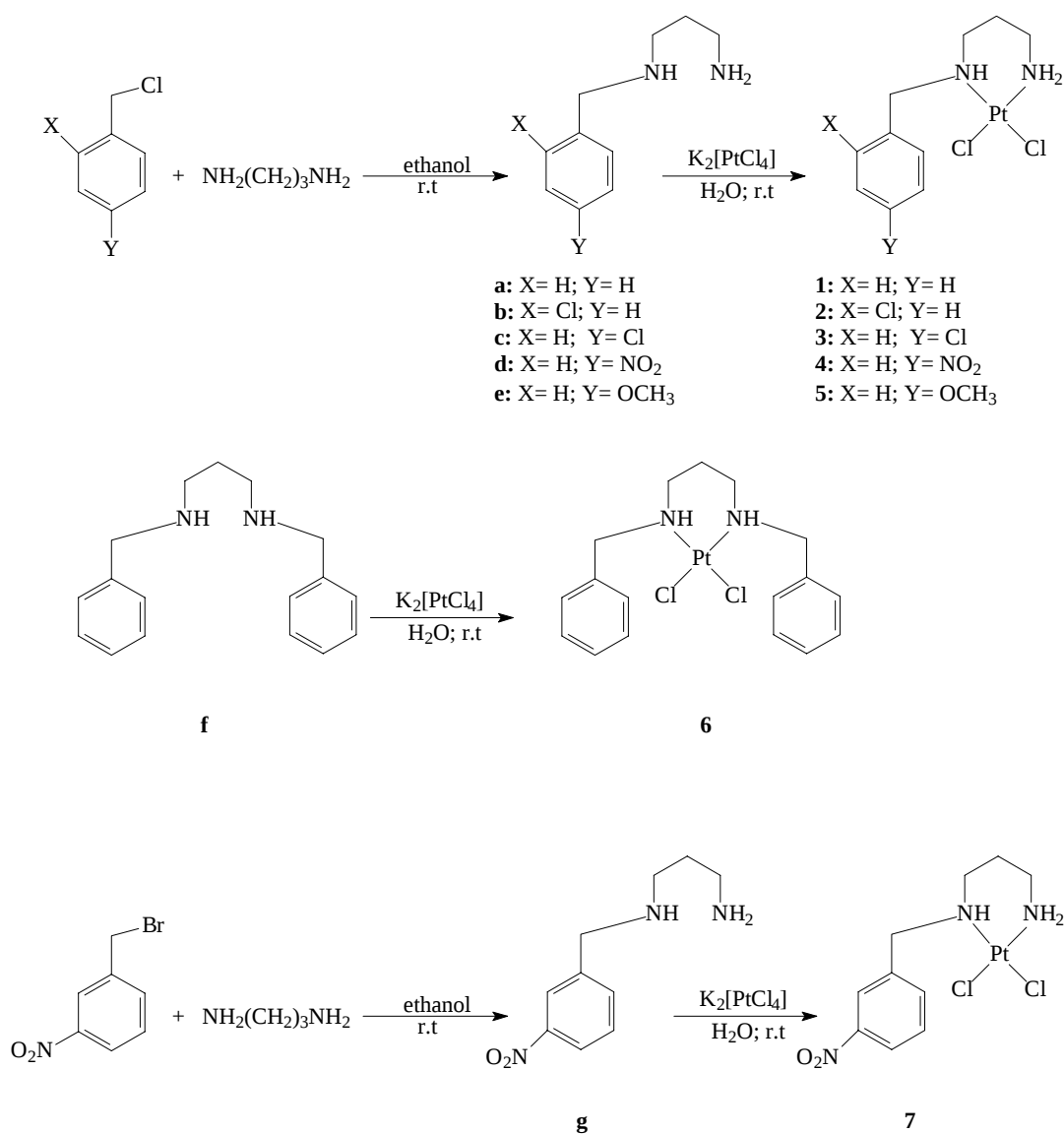
In this context, complexes having N-substituted ethylenediamine ligands have shown activity against several types of tumors [13,14]. Considering the activity displayed by these complexes and since aromatic compounds have shown the possibility of intercalation between DNA bases [15], we have recently reported the synthesis of a series of platinum complexes with ethylenediamine derivatives [16]. In this paper we report the preparation and characterization of analogous complexes having N-benzyl 1,3-propanediamine derivatives as ligands. The synthesis and characterization of these ligands have been recently reported elsewhere [17].

Results and Discussion

We have prepared the required ligands in satisfactory yields by treating 1,3-propanediamine with the corresponding benzyl halide in ethanol at room temperature for 48 h (Scheme 1). In the preparation of these ligands, we have observed the formation of N,N'-dibenzylated compounds as well. Thus, during the purification process of ligand **a**, we have also isolated the corresponding N,N'-dibenzyl 1,3-propanediamine, compound **f**.

The dichloroplatinum(II) complexes **1-7** were obtained by reaction of the corresponding ligands with potassium tetrachloroplatinate(II) in water at room temperature for 48 hours, and were isolated by simple filtration. For these compounds, one may observe in the IR spectra absorptions corresponding to $\nu_{\text{Pt-N}}$ e $\nu_{\text{Pt-Cl}}$ at 550 and 325 cm^{-1} , respectively, in addition to the absorptions observed for the ligand. In the $^1\text{H-NMR}$ spectra one observes that there is a downfield shift for the signals corresponding to NH and NH_2 relative to the free ligands. The $^{195}\text{Pt-NMR}$ spectra for all the complexes show only one signal in the vicinity of δ -2240 for all the complexes. The chemical shift values are expected based on data for similar compounds described in the literature. For instance, the $^{195}\text{Pt-NMR}$ spectrum of $[\text{Pt}(\text{DACH})\text{Cl}_2]$ shows a signal at δ -2287 (DACH=1,2-diaminocyclohexane) [18]. The results of elemental analysis for all complexes prepared are in agreement with the calculated values.

Scheme 1



Conclusions

This work describes the synthesis and characterization of new platinum(II) complexes obtained from derivatives of 1,3-propanediamine, used as ligands. All the complexes were fully characterized and their biological properties are being investigated to determine their possible use as anticancer agents.

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Experimental

General

IR spectra were obtained on a Bomem FT IR MB-102 spectrometer in KBr pellets. ^1H -NMR (200 and 400 MHz), ^{13}C -NMR (50 and 100 MHz) and ^{195}Pt -NMR (86 MHz) spectra were recorded on Bruker Advance DRX 200 and DRX 400 spectrometers at the Federal University of Minas Gerais, Brazil. Elemental analyses were done at the State University of São Paulo, Brazil. All chemicals were reagent grade and were used without further purification.

Synthesis of ligands: N-Benzylpropane-1,3-diamine (a), N-(2-chlorobenzyl)propane-1,3-diamine (b), N-(4-chlorobenzyl)propane-1,3-diamine (c), N-(4-nitrobenzyl)propane-1,3-diamine (d), N-(4-methoxybenzyl)propane-1,3-diamine (e), N,N'-dibenzylpropane-1,3-diamine (f) and N-(3-nitrobenzyl)propane-1,3-diamine (g).

To 1,3-propanediamine (3.34 mL; 40 mmols) in ethanol (20 mL), the corresponding benzyl halide (20 mmol) was slowly added during 8 h. The reaction mixture was stirred for 48 h at room temperature, after which time, the complete consumption of the starting material was evidenced by TLC (eluent: 8:2 hexane/ethyl acetate). A saturated sodium hydroxide (30 mmol) solution in ethanol was then slowly added. The solvent was evaporated under reduced pressure, and the residue purified on silica gel 60 G (0.2-0.5 mm), using 9:1 dichloromethane/methanol as eluent. Yields: **(a)** 2.65 g (81%); **(b)** 2.89 g (73%); **(c)** 2.81 g (71%); **(d)** 3.26 g (78%); **(e)** 2.67 g (69%); **(g)** 4.9 g (69 %) for compound **g**. The N,N'-dibenzylated compound **(f)** was also isolated in 10% yield in the preparation of compound **a**.

Compound **a**: IR ν_{max} . KBr (cm^{-1}): 3238, 3025, 2982, 2907, 2763, 1599, 1438, 1176, 975, 745; ^1H -NMR (200 MHz; TFA- d_1) δ : 2.12 (m, 2H, CH_2); 3.09 (m, 4H, CH_2N); 4.06 (s, 2H, CH_2Ph); 7.15 (m, 5H, Ph); ^{13}C -NMR (50 MHz, TFA- d_1) δ : 26.17; 40.25; 47.06; 55.60 (CH_2); 108.50; 114.14; 120.77; 125.41 (Ph); MS (m/z, %): 165 (100.00); 148 (1.73); 134 (1.15); 120 (1.00).

Compound **b**: IR ν_{max} . KBr (cm^{-1}): 3285, 3063, 2931, 1573, 1470, 1117, 1050, 751; ^1H -NMR (200 MHz; pyridine- d_5) δ : 1.88 (m, 2H, CH_2); 2.77 (t, 2H, CH_2NH_2); 2.99 (t, 2H, CH_2NH); 4.39 (s, 2H, CH_2Ph); 7.16 (m, 2H, H4, H5); 7.28; 7.59 (2d, 2H, H3, H6, $J_{3-4} = 7.6$ Hz, $J_{6-5} = 7.3$ Hz); ^{13}C -NMR (50 MHz; pyridine- d_5) δ : 32.31; 40.31; 47.57; 51.24 (CH_2); 127.64; 128.48; 129.60; 130.36; 133.71; 138.87 (Ph); MS (m/z, %): 199 (100.00); 182 (6.36); 125 (1.00).

Compound **c**: IR ν_{max} . KBr (cm^{-1}): 3439, 3050, 2934, 2788, 1578, 1498, 1438, 1091, 1018, 805; ^1H -NMR (200 MHz; DMSO- d_6) δ : 2.07 (m, 2H, CH_2); 2.86 (m, 4H, CH_2N); 4.07 (s, 2H, CH_2Ph); 7.48; 7.61 (2d, 4H, Ph); ^{13}C -NMR (50 MHz; DMSO- d_6) δ : 23.91; 36.29; 43.87; 49.46 (CH_2); 128.48; 131.89; 132.05; 133.37 (Ph); MS (m/z, %): 199 (100.00); 182 (12.71); 125 (76.88).

Compound **d**: IR $\nu_{\max}$. KBr (cm^{-1}): 3380, 3090, 2955, 1603, 1519, 1351, 1107, 850, 740; ^1H -NMR (200 MHz; D_2O) δ : 2.00 (m, 2H, CH_2); 3.00 (m, 4H, CH_2N); 4.21 (s, 2H, CH_2Ph); 7.57; 8.19 (2d, 4H, Ph); ^{13}C -NMR (50 MHz; D_2O) δ : 24.20; 36.58; 44.58; 50.47 (CH_2); 124.11; 130.59; 139.59; 147.86 (Ph); MS (m/z , %): 210 (86.12); 193 (52.60); 179 (10.40); 165 (17.34); 136(34.68).

Compound **e**: IR $\nu_{\max}$. KBr (cm^{-1}): 3244, 3007, 2934, 1614, 1542, 1513, 1479, 1249, 1180, 1030, 811; ^1H -NMR (200 MHz; D_2O) δ : 1.45 (m, 2H, CH_2); 2.39 (m, 2H, CH_2NH_2); 2.55 (m, 2H, CH_2NH); 3.48 (s, 2H, CH_2Ph); 3.59 (s, 3H, OCH_3); 6.73; 7.06 (2d, 4H, Ph); ^{13}C -NMR (50 MHz, D_2O) δ : 28.74; 38.18; 45.07; 51.52 (CH_2); 55.24 (OCH_3); 113.96; 130.10; 130.61; 158.8 (Ph); MS (m/z , %): 195 (94.79); 178 (0.58); 164 (1.73); 150 (1.00); 136 (1.00); 121 (100.00).

Compound **f**: IR $\nu_{\max}$. KBr (cm^{-1}): 3159, 3037, 2981, 1590, 1444, 1280, 1213, 1073, 944, 913, 860, 775, 738, 690, 607; ^1H -NMR (200 MHz; TFA d^1) δ : 2.55 (m, 2H, CH_2); 3.36 (m, 4 H, CH_2NH); 4.30 (sl, 4 H, CH_2Ph); 7.41 (s, 10 H, Ph); 7.81 (sl, 2H, NH); ^{13}C -NMR (50 MHz, TFA d^1) δ : 25.73; 47.34; 55.61 (CH_2); 128.86; 129.78; 131.05; 133.11 (Ph); MS (m/z , %): 255 (100.00); 148 (1.00); 134 (1.00).

Compound **g**: IR $\nu_{\max}$. KBr (cm^{-1}): 3399, 3080, 2944, 1598, 1537, 1462, 1354, 1102, 939, 736; ^1H -NMR (200 MHz; DMSO d^6) δ : 2.01 (m, 2H, CH_2); 2.96 (t, 2H, CH_2NH_2); 3.12 (t, 2H, CH_2NH); 4.24 (s, 2H, CH_2Ph); 7.69 (m, 1H, H5); 8.06; 8.23 (2d, 2H, H4, H6); 8.48 (s, 1H, H2); ^{13}C -NMR (50 MHz; DMSO d^6) δ : 23.93; 36.33; 44.14; 49.33 (CH_2); 123.74; 125.14; 130.21; 134.75; 137.13; 147.73 (Ph); MS (m/z , %): 210 (100.00); 193 (43.93); 179 (1.15); 165 (7.51); 136 (26.01).

Synthesis of complexes: (N-Benzylpropane-1,3-diamine)dichloroplatinum(II) (1), [N-(2-chlorobenzyl)propane-1,3-diamine]dichloroplatinum(II) (2); [N-(4-chlorobenzyl)propane-1,3-diamine]dichloroplatinum(II) (3); [N-(4-nitrobenzyl)propane-1,3-diamine]dichloroplatinum(II) (4); [N-(4-methoxybenzyl)propane-1,3-diamine]dichloroplatinum(II) (5); (N,N'-dibenzylpropane-1,3-diamine)dichloroplatinum (II) (6) and [N-(3-nitrobenzyl)propane-1,3-diamine]dichloroplatinum(II) (7):

To $\text{K}_2[\text{PtCl}_4]$ (0.415 g; 1 mmol) in water (5 mL), the appropriate ligand (1 mmol) dissolved in water (5 mL) was slowly added. After stirring for 48 h at room temperature, the product was isolated by filtration and dried. Yields: 0.22 g (52 %) for compound **1**; 0.31 g (66 %) for compound **2**; 0.17 g (37 %) for compound **3**; 0.14 g (67 %) for compound **4**; 0.17 g (38 %) for compound **5**; 0.17 g (34 %) for compound **6** and 0.25 g (53 %) for compound **7**.

Compound **1**: IR $\nu_{\max}$. KBr (cm^{-1}): 3207, 3135, 3031, 2946, 2879, 1598, 1456, 1048, 748, 701, 517, 328; ^1H -NMR (400 MHz; DMSO- d_6) δ : 1.63 (m, 2H, CH_2); 2.50; 2.63 (2m, 4H, CH_2NH_2 , CH_2NH); 4.00; 4.41 (2dd, 2H, H7, H7', $J_{7-7'} = 13$ Hz, $J_{7-\text{NH}} = 3$ Hz, $J_{7'-\text{NH}} = 4$ Hz); 5.12; 6.00 (2sl, 3H, NH_2 , NH); 7.58 (m, 5H, Ph); ^{13}C -NMR (100 MHz, DMSO- d_6) δ : 23.45; 42.41; 46.74; 55.78 (CH_2); 128.24; 128.62; 129.50; 130.55; 131.20 (Ph); ^{195}Pt -NMR (86 MHz, DMSO- d_6) δ : - 2254; Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{Cl}_2\text{Pt} \cdot 2\text{HCl}$: C: 23.85; H: 3.57; N: 5.56; found: C: 23.35; H: 3.43; N: 5.56.

Compound 2: IR $\nu_{\max}$. KBr (cm^{-1}): 3238, 3211, 3134, 3067, 2993, 2940, 1601, 1447, 1180, 1054, 1035, 860, 748, 551, 435, 315; ^1H -NMR (200 MHz; $\text{DMSO}-d_6$) δ : 1.96 (m, 2H, CH_2); 2.37 (m, 2H, CH_2NH_2); 2.79 (sl, 2H, CH_2NH); 4.09; 4.84 (2m, 2H, H7, H7'); 5.78; 6.63 (2m, 3H, NH_2 , NH); 7.42; 7.44 (2d, 2H, H3, H6); 7.51; 8.22 (2t, 2H, H4, H5); ^{13}C -NMR (50 MHz, CDCl_3) δ : 22.99; 41.81; 51.20; 54.21 (CH_2); 127.28; 129.57; 131.03; 132.16; 133.86; 135.19 (Ph); ^{195}Pt -NMR (86 MHz, $\text{DMSO}-d_6$) δ : - 2250; Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{Cl}_3\text{N}_2\text{Pt}$: C: 25.85; H: 3.25; N: 6.03; found: C: 26.26; H: 3.48; N: 5.71.

Compound 3: IR $\nu_{\max}$. KBr (cm^{-1}): 3244, 3207, 3135, 3030, 2934, 2879, 1596, 1575, 1492, 1180, 1092, 1013, 848, 815, 527, 493, 320; ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ : 1.75 (m, 2H, CH_2); 2.49; 2.70 (2m, 4H, CH_2NH_2 , CH_2NH); 3.92; 4.33 (2dd, 2H, H7, H7', $J_{7-7'} = 12$ Hz, $J_{7-\text{NH}} = 4$ Hz, $J_{7'-\text{NH}} = 4$ Hz); 5.20; 6.16 (2sl, 3H, NH_2 , NH); 7.44; 7.52 (2d, 4H, Ph); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 23.10; 42.39; 47.70; 55.07 (CH_2); 128.13; 128.42; 131.89; 132.03 (Ph); ^{195}Pt -NMR (86 MHz, $\text{DMSO}-d_6$) δ : - 2248; Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{Cl}_3\text{Pt}$: C: 25.85; H: 3.25; N: 6.03; found: C: 26.37; H: 3.27; N: 5.91.

Compound 4: IR $\nu_{\max}$. KBr (cm^{-1}): 3258, 3228, 3111, 2951, 2935, 1609, 1516, 1459, 1350, 1190, 1109, 848, 706, 530, 327; ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ : 1.88 (m, 2H, CH_2); 2.75 (sl, 2H, CH_2NH_2); 2.85 (t, 2H, CH_2NH); 4.00; 4.46 (2m, 2H, H7, H7'); 5.17; 6.37 (2sl, 3H, NH_2 , NH); 8.04; 8.28 (2d, 4H, Ph); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 23.17; 42.53; 49.05; 55.22 (CH_2); 123.10; 131.69; 132.55; 147.03 (Ph); ^{195}Pt -NMR (86 MHz, $\text{DMSO}-d_6$) δ : - 2236; Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{Cl}_2\text{O}_2\text{Pt}$: C: 25.27; H: 3.18; N: 8.84; found: C: 25.05; H: 3.38; N: 8.56.

Compound 5: IR ν KBr (cm^{-1}): 3245, 3216, 3168, 3144, 3004, 2938, 1611, 1513, 1460, 1253, 1177, 1030, 817, 554, 329; ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ : 1.49 (m, 2H, CH_2); 2.40; 2.49 (2m, 4H, CH_2NH_2 , CH_2NH); 3.72 (s, 3H, OCH_3); 3.92; 4.33 (2dd, 2H, H7', H7'); 5.12; 5.85 (2sl, 3H, NH_2 , NH); 6.88; 7.32 (2d, 4H, Ph); ^{13}C -NMR (100 MHz, CDCl_3) δ : 23.06; 42.43; 47.05; 55.14 (CH_2); 55.22 (OCH_3); 113.58; 131.07; 131.87; 132.45; 158.86 (Ph); ^{195}Pt -NMR (86 MHz, $\text{DMSO}-d_6$) δ : - 2256; Anal. Calcd. for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{Cl}_2\text{OPt}$: C: 28.71; H: 3.94; N: 6.09; found: C: 28.77; H: 4.03; N: 5.93.

Compound 6: IR ν KBr (cm^{-1}): 3159, 3012, 2980, 1576, 1498, 1453, 1433, 1211, 994, 748, 697, 523, 325, 315; ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ : 2.08 (m, 2H, CH_2); 3.03 (sl, 4H, CH_2NH); 4.14 (sl, 4H, CH_2Ph); 7.44; 7.56 (2d, 10H, Ph); Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{Cl}_2\text{Pt}\cdot 4\text{H}_2\text{O}$: C: 34.46; H: 5.10; N: 4.72; found: C: 34.60; H: 4.67; N: 4.84.

Compound 7: IR ν KBr (cm^{-1}): 3229, 3208, 3127, 3049, 2953, 1596, 1529, 1450, 1352, 1140, 1048, 813, 736, 702, 472, 324; ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ : 1.71 (m, 2H, CH_2); 2.64; 2.66 (2t, 4H, CH_2NH_2 , CH_2NH); 3.94; 4.44 (2sl, 2H, H7, H7'); 5.15; 6.42 (2sl, 3H, NH_2 , NH); 7.68 (sl, 1H, H5); 8.08; 8.22 (2d, 2H, H4, H6, $J_{4-5} = J_{5-6} = 6.8$ Hz); 8.51 (s, 1H, H2); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 23.10; 42.52; 49.19; 58.13 (CH_2); 122.74; 125.24; 125.26; 129.46; 137.25; 147.38 (Ph); ^{195}Pt -NMR

(86 MHz, DMSO- d_6) δ : - 2241; Anal. Calcd. for $C_{10}H_{15}N_3Cl_2O_2Pt \cdot H_2O$: C: 24.34; H: 3.44; found: C: 24.46; H: 2.94.

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Sample availability: Samples of ligands **a-f** and compounds **1**, **3** and **5** are available from MDPI