


Synthesis and characterization of iminophosphineplatinum(II) complexes of the type (κ^2 -*P,N*-2-Ph₂PC₆H₄C(H)=NC₆H₄X)PtCl₂ (X = OMe, F)

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Abstract A series of iminophosphineplatinum(II) complexes have been prepared from pro-ligands derived from aniline derivatives containing electron-donating methoxy groups or electron-withdrawing fluorides and [PtCl₂(η^2 -coe)]₂ (coe = *cis*-cyclooctene). All new pro-ligands and metal complexes have been fully characterized, including an X-ray diffraction study for compound **11** (derived from *para*-methoxyaniline). Additionally, the molecular structure of a di-iminophosphineplatinum dication **11a** has been determined. The platinum compounds showed no appreciable cytotoxic properties against two glioma cell lines using the MTT method.

Introduction

The discovery that *cis*-diamminedichloroplatinum(II) (*cis*-platin, or *cis*-DDP) inhibits cellular division in *Escherichia coli* spawned an enormous amount of research into the design and testing of platinum complexes for their potential ability to treat various cancers [1–7]. The mechanism of action of cisplatin is believed to result from the initial loss of the chloride ligands which are readily replaced by a molecule of water to give either *cis*-[(H₃N)₂PtCl(OH₂)]⁺ or *cis*-[(H₃N)₂Pt(OH₂)₂]²⁺. The aqua ligands can readily be

substituted with an *N*-heterocyclic base of DNA such as guanine or purine. The cytotoxic mode of action of cisplatin results from these interactions with DNA, especially intrastrand crosslink adducts, which activate signal transduction pathways such as those involving ATR, p53, p73 and MAPK, whereupon the end result is activation of apoptosis [8, 9]. Serious problems such as cisplatin resistance and side effects arising from cisplatin's poor solubility in physiological media and lack of selectivity for cancer cells have limited its therapeutic use as an anti-cancer agent. As such, much research has focused on designing and testing the second- and third-generation platinum complexes by varying either the inert amine groups of the labile chloride ligands. Notable examples of such derivatives include carboplatin and *cis*-[PtCl₂(1,4-DACH)] (DACH = diaminocyclohexane). Picoplatin is a promising candidate for the treatment of a variety of solid tumours and is unique in that it demonstrates that platinum complexes do not need to contain primary amine groups to have antineoplastic activities [10–13]. Indeed, we [14] and others [15, 16] have shown that complexes containing iminophosphine ligands are also potential candidates for metal-based anticancer therapy. Iminophosphines are a remarkable family of pro-ligands, whereby varying the organic group of the imine appendage allows for fine-tuning of the physicochemical properties of the corresponding platinum complexes. As part of our ongoing research in this area, we have prepared a series of platinum complexes containing iminophosphine ligands and examined their initial cytotoxic properties against two glioma cell lines using the MTT method, the results of which are presented herein.

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Experimental section

Materials and methods

Reagents and solvents used were obtained from Aldrich Chemicals. $[\text{PtCl}_2(\eta^2\text{-coe})_2]$ (coe = *cis*-cyclooctene) [17], *N*-(2-(diphenylphosphino)benzylidene)aniline (**1**) [18], *(E)*-*N*-(2-(diphenylphosphino)benzylidene)-2-methoxyaniline (**2**) [19], *(E)*-*N*-(2-(diphenylphosphino)benzylidene)-4-methoxyaniline (**4**) [20], *(E)*-*N*-(2-(diphenylphosphino)benzylidene)-4-fluoroaniline (**7**) [21] and complex **8** [14] have been synthesized previously, and any additional data have been added below. NMR spectra were recorded on a JEOL JNM-GSX400 FT NMR (^1H : 400 MHz; ^{13}C : 100 MHz; ^{19}F : 376 MHz; ^{31}P : 162 MHz) spectrometer. Chemical shifts (δ) are reported in ppm [relative to residual solvent peaks (^1H and ^{13}C) and external $\text{CF}_3\text{CO}_2\text{H}$ (^{19}F) or H_3PO_4 (^{31}P)]. Multiplicities are reported as singlet (s), doublet (d), triplet (t), multiplet (m) and overlapping (ov) with coupling constants (J) reported in Hz. Melting points were measured uncorrected with a Stuart SMP30 apparatus. FTIR spectra were obtained with a Thermo Fisher Scientific Nicolet iS5 FTIR spectrometer in ATR mode and are reported in cm^{-1} . Elemental analyses for carbon, hydrogen and nitrogen were carried out at Laboratoire d'Analyse Élémentaire de l'Université de Montréal (Montréal, QC). All reactions were performed under a nitrogen atmosphere in a MBraun LabMaster glovebox.

General procedure for the synthesis of pro-ligands 1–6

To a mixture of 2-(diphenylphosphino)benzaldehyde (500 mg, 1.72 mmol) and the appropriate amine (1.81 mmol) was added formic acid (1 drop) in MeOH (5 mL). The reaction was allowed to proceed at RT for 18 h, at which point the iminophosphine pro-ligand was collected by suction filtration as a pale yellow precipitate. Spectroscopic NMR data were collected in CDCl_3 as the pro-ligands decompose in wet DMSO-d_6 . The spectroscopically pure pro-ligands were used as prepared to make the corresponding platinum(II) complexes.

(E)-*N*-(2-(Diphenylphosphino)benzylidene)-2-methoxyaniline (**2**) Yield: 449 mg (66%); m.p.: 108–109 °C.

(E)-*N*-(2-(Diphenylphosphino)benzylidene)-3-methoxyaniline (**3**) Yield: 490 mg (72%); m.p.: 89–91 °C. ^1H NMR (CDCl_3) δ : 9.04 (d, $J_{\text{HP}} = 5.0$ Hz, 1H, C(H)=N), 8.18 (ddd, $J_{\text{HH}} = 7.8$ Hz, $J_{\text{HP}} = 4.1$ Hz, $J_{\text{HH}} = 1.4$ Hz, 1H, Ar), 7.45 (app t, $J_{\text{HH}} = 7.3$ Hz, 1H, Ar), 7.36–7.28 (ov m, 11H, Ar), 7.18 (t, $J_{\text{HH}} = 7.8$ Hz, 1H, Ar), 6.91 (ddd, $J_{\text{HH}} = 7.8$ Hz, $J_{\text{HP}} = 4.6$ Hz, $J_{\text{HH}} = 0.9$ Hz, 1H, Ar), 6.72

(ddd, $J_{\text{HH}} = 8.2$, $J_{\text{HP}} = 2.7$, $J_{\text{HH}} = 0.9$ Hz, 1H, Ar), 6.50 (dd, $J_{\text{HH}} = 7.8$, 0.9 Hz, 1H, Ar), 6.43 (ov dd, $J_{\text{HP}} = 2.3$, $J_{\text{HH}} = 1.8$ Hz, 1H, Ar), 3.73 (s, 3H, OCH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 160.2, 159.1 (d, $J_{\text{CP}} = 21.0$ Hz), 153.1, 139.1 (d, $J_{\text{CP}} = 16.2$ Hz), 138.7 (d, $J_{\text{CP}} = 20.0$ Hz), 136.5 (d, $J_{\text{CP}} = 9.5$ Hz), 134.3, 134.1, 133.6, 131.0, 129.8, 129.0, 128.8 (d, $J_{\text{CP}} = 6.7$ Hz), 128.3 (d, $J_{\text{CP}} = 3.8$ Hz), 113.0, 112.3, 106.4, 55.4. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) δ : -12.4. IR: 3060 (w), 1619 (s, ν_{CN}), 1577 (m), 1462 (m), 1434 (m), 1263 (m), 1144 (m), 1035 (m), 744 (m).

(E)-*N*-(2-(Diphenylphosphino)benzylidene)-4-methoxyaniline (**4**) Yield: 551 mg (81%); m.p.: 116–118 °C.

(E)-*N*-(2-(Diphenylphosphino)benzylidene)-2-fluoroaniline (**5**) Yield: 422 mg (64%); m.p.: 110–111 °C. ^1H NMR (CDCl_3) δ : 9.17 (d, $J_{\text{HP}} = 5.5$ Hz, 1H, C(H)=N), 8.27 (ddd, $J_{\text{HH}} = 7.8$ Hz, $J_{\text{HP}} = 4.1$ Hz, $J_{\text{HH}} = 1.4$ Hz, 1H, Ar), 7.46 (app t, $J_{\text{HH}} = 7.4$ Hz, 1H, Ar), 7.38–7.28 (ov m, 11H, Ar), 7.13–7.00 (ov m, 3H, Ar), 6.93 (ddd, $J_{\text{HH}} = 7.8$ Hz, $J_{\text{HP}} = 5.0$ Hz, $J_{\text{HH}} = 1.4$ Hz, 1H, Ar), 6.70 (ov ddd, $J_{\text{HH}} = 7.8$ Hz, $J_{\text{HF}} = 7.8$ Hz, $J_{\text{HH}} = 1.4$ Hz, 1H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 161.2 (dd, $J_{\text{CP}} = 23.8$ Hz, $J_{\text{CF}} = 1.9$ Hz), 155.4 (d, $J_{\text{CF}} = 248.0$ Hz), 139.8 (d, $J = 10.5$ Hz), 139.1 (d, $J = 17.2$ Hz), 138.9 (d, $J = 21.9$ Hz), 136.2 (d, $J = 9.5$ Hz), 134.2 (d, $J = 20.0$ Hz), 133.6, 131.4, 129.2, 129.1, 128.8 (d, $J = 7.6$ Hz), 128.2 (d, $J = 3.8$ Hz), 126.9 (d, $J = 7.6$ Hz), 124.5 (d, $J = 3.8$ Hz), 121.8, 116.2 (d, $J = 20.0$ Hz). $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3) δ : -126.6. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) δ : -13.5. IR: 3049 (w), 1619 (s, ν_{CN}), 1578 (m), 1478 (s), 1453 (m), 1279 (m), 1104 (m), 733 (s), 692 (s).

(E)-*N*-(2-(Diphenylphosphino)benzylidene)-3-fluoroaniline (**6**) Yield: 481 mg (73%); m.p.: 103–104 °C. ^1H NMR (CDCl_3) δ : 9.01 (d, $J_{\text{HP}} = 5.5$ Hz, 1H, C(H)=N), 8.17 (ddd, $J_{\text{HH}} = 7.8$ Hz, $J_{\text{HP}} = 4.1$ Hz, $J_{\text{HH}} = 1.4$ Hz, 1H, Ar), 7.46 (ov ddd, $J_{\text{HH}} = 7.4$, 7.4, 0.9 Hz, 1H, Ar), 7.38–7.28 (ov m, 11H, Ar), 7.22 (m, 1H, Ar), 6.93 (ddd, $J_{\text{HH}} = 7.8$ Hz, $J_{\text{HP}} = 4.6$ Hz, $J_{\text{HH}} = 0.9$ Hz, 1H, Ar), 6.85 (ov dddd, $J_{\text{HH}} = 7.8$ Hz, 7.8 Hz, $J_{\text{HF}} = 2.3$ Hz, $J_{\text{HH}} = 1.4$ Hz, 1H, Ar), 6.66 (ddd, $J_{\text{HH}} = 7.8$, 1.8, 0.9 Hz, 1H, Ar), 6.55 (ov ddd, $J_{\text{HF}} = 10.1$ Hz, $J_{\text{HH}} = 1.8$ Hz, $J_{\text{HH}} = 1.8$ Hz, 1H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 163.2 (d, $J_{\text{CF}} = 245.0$ Hz), 159.9 (d, $J_{\text{CP}} = 21.9$ Hz), 153.5 ($J = 8.6$ Hz), 139.0 (d, $J = 20.0$ Hz), 138.8 (d, $J = 16.2$ Hz), 136.3 (d, $J = 8.6$ Hz), 134.2 (d, $J = 20.0$ Hz), 133.6, 131.3, 130.2 (d, $J = 8.6$ Hz), 129.1, 129.0, 128.8 (d, $J = 7.6$ Hz), 128.4 (d, $J = 3.8$ Hz), 116.8 (d, $J = 1.9$ Hz), 112.7 (d, $J = 21.0$ Hz), 108.2 (d, $J = 22.9$ Hz). $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3) δ : -113.2. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) δ : -12.5. IR: 3053 (w), 1597 (s, ν_{CN}), 1583 (m), 1476 (m), 1433 (m), 1252 (m), 945 (m), 695 (s).

Synthesis of (*E*)-*N*-(2-(diphenylphosphino)benzylidene)-4-fluoroaniline (**7**)

A THF (10 mL) solution of 2-(diphenylphosphino)benzaldehyde (500 mg, 1.72 mmol) and 4-fluoroaniline (191 mg, 1.72 mmol) was allowed to react in the presence of activated 3 Å molecular sieves (5 g) over a period of 7 days. The mixture was filtered, and solvent was removed under vacuum to afford an orange oil. The oil was dissolved in hexane (5 mL) and stored at $-30\text{ }^{\circ}\text{C}$. The resulting precipitate was collected by suction filtration to afford **7** as a pale yellow solid. Yield: 514 mg (78%); m.p.: 83–84 $^{\circ}\text{C}$. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 161.3 (d, $J_{\text{CF}} = 243.1$ Hz), 158.7 (d, $J_{\text{CP}} = 21.0$ Hz), 147.7 (d, $J = 2.9$ Hz), 139.1 (d, $J = 16.2$ Hz), 138.7 (d, $J = 20.0$ Hz), 136.5 (d, $J = 8.6$ Hz), 134.2 (d, $J = 20.0$ Hz), 133.7, 131.1, 129.1, 128.8, 128.7, 128.3 (d, $J = 3.8$ Hz), 122.5 (d, $J = 8.6$ Hz), 115.8 (d, $J = 21.9$ Hz).

General synthesis of iminophosphineplatinum(II) complexes **9**–**14**

To a stirred THF (5 mL) suspension of $[\text{PtCl}_2(\eta^2\text{-coe})]_2$ (200 mg, 0.27 mmol) was added a THF (2 mL) solution of the appropriate iminophosphine pro-ligand (0.55 mmol). The reaction was allowed to proceed at RT for 18 h, at which point a yellow–orange precipitate was collected by suction filtration. The final purification steps for each complex are detailed below. Spectroscopic NMR data were collected in DMSO-d_6 due to the poor solubility of the complexes in CDCl_3 .

Synthesis of 9 Washing with hexane (3×5 mL) afforded **9** as a yellow–orange solid. Yield: 296 mg (83%); m.p.: 198–200 $^{\circ}\text{C}$. ^1H NMR (DMSO-d_6) δ : 8.82 (s, $J_{\text{HPt}} = 97.6$ Hz, 1H, C(H)=N), 8.04 (m, 1H, Ar), 7.84 (m, 2H, Ar), 7.62–7.54 (ov m, 6H, Ar), 7.49–7.44 (ov m, 4H, Ar), 7.21 (t, $J = 7.3$ Hz, 1H, Ar), 7.12 (m, 1H, Ar), 7.08 (d, $J = 7.8$ Hz, 1H, Ar), 7.02 (d, $J = 8.2$ Hz, 1H, Ar), 6.91 (t, $J = 7.8$ Hz, 1H, Ar), 3.64 (s, 3H, OCH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 168.0 (d, $J_{\text{CP}} = 6.7$ Hz), 152.2, 142.2, 138.1 (d, $J_{\text{CP}} = 7.6$ Hz), 136.8 (d, $J_{\text{CP}} = 12.4$ Hz), 135.4 (d, $J_{\text{CP}} = 7.6$ Hz), 134.2 (d, $J_{\text{CP}} = 11.4$ Hz), 133.6 (d, $J_{\text{CP}} = 27.7$ Hz), 132.5, 129.3 (d, $J_{\text{CP}} = 11.4$ Hz), 127.2, 126.5, 125.9, 121.5, 120.9, 119.9, 112.6, 56.4. $^{31}\text{P}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 3.8 ($J_{\text{PPt}} = 3720$ Hz). IR: 3061 (w), 1613 (m, ν_{CN}), 1493 (m), 1436 (s), 1258 (m), 1100 (s), 1018 (m), 690 (s). Anal. calcd. for $\text{C}_{26}\text{H}_{22}\text{NCl}_2\text{OPPt}$ (661.42 g/mol) (%): C 47.21, H 3.35, N 2.12; found: C 47.48, H 3.66, N 2.32.

Synthesis of 10 Washing with hexane (3×5 mL) afforded **10** as a yellow solid. Yield: 265 mg (74%); m.p.:

268–270 $^{\circ}\text{C}$. ^1H NMR (DMSO-d_6) δ : 8.83 (s, $J_{\text{HPt}} = 97.1$ Hz, 1H, C(H)=N), 8.11 (m, 1H, Ar), 7.86 (ov dd, $J = 7.8, 7.4$ Hz, 1H, Ar), 7.80 (ov dd, $J = 7.8, 7.4$ Hz, 1H, Ar), 7.62–7.55 (ov m, 6H, Ar), 7.47–7.42 (ov m, 4H, Ar), 7.24 (ov dd, $J = 8.2, 7.8$ Hz, 1H, Ar), 7.02 (app t, $J = 7.8, 7.8$ Hz, 1H, Ar), 6.94 (d, $J = 8.2$ Hz, 1H, Ar), 6.88 (s, 1H, Ar), 6.84 (d, $J = 8.2$ Hz, 1H, Ar), 3.73 (s, 3H, OCH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 167.2 (d, $J_{\text{CP}} = 6.7$ Hz), 159.3, 154.0, 137.9 (d, $J_{\text{CP}} = 8.6$ Hz), 137.1 (d, $J_{\text{CP}} = 13.4$ Hz), 135.2 (d, $J_{\text{CP}} = 7.6$ Hz), 134.2 (d, $J_{\text{CP}} = 11.4$ Hz), 133.4, 133.0, 132.8, 129.5 (d, $J_{\text{CP}} = 11.4$ Hz), 128.7, 125.8, 125.1, 121.9, 121.3, 117.0, 113.7, 110.5, 56.0. $^{31}\text{P}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 5.7 ($J_{\text{PPt}} = 3660$ Hz). IR: 3054 (w), 1598 (m, ν_{CN}), 1479 (m), 1435 (s), 1289 (s), 1273 (m), 1141 (m), 1102 (m), 693 (s). Anal. calcd. for $\text{C}_{26}\text{H}_{22}\text{NCl}_2\text{OPPt}$ (661.42 g/mol) (%): C 47.21, H 3.35, N 2.12; found: C 46.88, H 3.47, N 2.44.

Synthesis of 11 Complex **11** was isolated as a yellow solid by recrystallization from a solution of CH_2Cl_2 : hexane (10 mL: 5 mL) stored at 5 $^{\circ}\text{C}$. Yield: 211 mg (59%); m.p.: 262–263 $^{\circ}\text{C}$. ^1H NMR (DMSO-d_6) δ : 8.78 (s, $J_{\text{HPt}} = 87.9$ Hz, 1H, C(H)=N), 8.08 (dd, $J_{\text{HH}} = 6.4$ Hz, $J_{\text{HP}} = 4.1$ Hz, 1H, Ar), 7.84 (ov dd, $J_{\text{HH}} = 7.8, 7.3$ Hz, 1H, Ar), 7.78 (ov dd, $J_{\text{HH}} = 7.8, 7.4$ Hz, 1H, Ar), 7.62–7.54 (ov m, 6H, Ar), 7.47–7.42 (ov m, 4H, Ar), 7.38 (d, $J_{\text{HH}} = 9.2$ Hz, 2H, Ar), 7.03 (dd, $J_{\text{HP}} = 10.5, J_{\text{HH}} = 7.8$ Hz, 1H, Ar), 6.88 (d, $J = 9.2$ Hz, 2H, Ar), 3.73 (s, 3H, OCH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 166.1 (d, $J_{\text{CP}} = 6.7$ Hz), 159.2, 146.4, 137.4, 137.3 (d, $J_{\text{CP}} = 22.0$ Hz), 134.9 (d, $J_{\text{CP}} = 8.6$ Hz), 134.3 (d, $J_{\text{CP}} = 10.5$ Hz), 133.4, 132.8 (2C), 129.5 (d, $J_{\text{CP}} = 11.5$ Hz), 125.7, 125.6, 125.1, 122.0, 121.4, 113.7, 55.9. $^{31}\text{P}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 5.8 ($J_{\text{PPt}} = 3660$ Hz). IR: 3057 (w), 1608 (m, ν_{CN}), 1504 (m), 1437 (s), 1256 (s), 1020 (m), 765 (m), 692 (s). Anal. calcd. for $\text{C}_{26}\text{H}_{22}\text{NCl}_2\text{OPPt}$ (661.42 g/mol) (%): C 47.21, H 3.35, N 2.12; found: C 47.38, H 3.55, N 2.54.

Synthesis of 12 Compound **12** was purified by recrystallization from CH_2Cl_2 (5 mL) stored at 5 $^{\circ}\text{C}$. Yield: 238 mg (68%); m.p.: 241–243 $^{\circ}\text{C}$. ^1H NMR (DMSO-d_6) δ : 9.01 (s, $J_{\text{HPt}} = 85.2$ Hz, 1H, C(H)=N), 8.08 (dd, $J_{\text{HH}} = 8.7$ Hz, $J_{\text{HP}} = 4.2$ Hz, 1H, Ar), 7.84 (dd, $J_{\text{HH}} = 6.8, J_{\text{HF}} = 2.3$ Hz, 2H, Ar), 7.63–7.53 (ov m, 6H, Ar), 7.50–7.45 (ov m, 4H, Ar), 7.30–7.13 (ov m, 5H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 169.6 (d, $J_{\text{CP}} = 6.7$ Hz), 154.8 (d, $J_{\text{CF}} = 246.0$ Hz), 140.7 (d, $J = 11.5$ Hz), 138.6 (d, $J = 8.6$ Hz), 136.4 (d, $J = 13.4$ Hz), 135.9 (d, $J = 7.7$ Hz), 134.3 (d, $J = 10.5$ Hz), 133.8 (d, $J = 2.9$ Hz), 133.6, 132.7, 129.8 (d, $J = 7.7$ Hz), 129.4 (d, $J = 12.5$ Hz), 126.9, 126.6, 125.9, 124.3 (d, $J = 3.8$ Hz), 121.6, 121.0, 116.2 (d, $J = 19.2$ Hz). $^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : -123.4 . $^{31}\text{P}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 4.7

($J_{\text{Pt}} = 3690$ Hz). IR: 3058 (w), 1597 (m, ν_{CN}), 1493 (m), 1435 (m), 1219 (m), 1103 (s), 690 (s). Anal. calcd. for $\text{C}_{25}\text{H}_{19}\text{NCl}_2\text{FPt}$ (649.39 g/mol) (%): C 46.24, H 2.95, N 2.16; found: C 46.52, H 3.14, N 2.45.

Synthesis of 13 Compound **13** was purified by recrystallization from CH_2Cl_2 (5 mL) stored at 5 °C. Yield: 252 mg (72%); m.p.: 253–255 °C. ^1H NMR (DMSO-d_6) δ : 8.88 (s, $J_{\text{HPt}} = 85.2$ Hz, 1H, C(H)=N), 8.11 (dd, $J_{\text{HH}} = 6.4$ Hz, $J_{\text{HP}} = 4.1$ Hz, 1H, Ar), 7.89–7.80 (ov m, 2H, Ar), 7.62–7.55 (ov m, 5H, Ar), 7.49–7.44 (ov m, 3H, Ar), 7.42 (m, 1H, Ar), 7.24 (ov dd, $J_{\text{HF}} = 12.4$ Hz, $J_{\text{HH}} = 8.2$ Hz, 2H, Ar), 7.15–7.05 (ov m, 2H, Ar), 7.03–6.96 (ov m, 2H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 168.2 (d, $J_{\text{CP}} = 6.7$ Hz), 161.7 (d, $J_{\text{CF}} = 244.4$ Hz), 154.3 (d, $J = 9.6$ Hz), 138.3 (d, $J = 8.6$ Hz), 136.8 (d, $J = 12.5$ Hz), 135.5 (d, $J = 8.6$ Hz), 134.3 (d, $J = 11.4$ Hz), 133.5, 133.2 (d, $J = 2.9$ Hz), 132.8, 130.3 (d, $J = 8.6$ Hz), 129.6 (d, $J = 11.5$ Hz), 125.9, 125.2, 121.9, 121.3, 121.1, 115.2 (d, $J = 21.1$ Hz), 112.2 (d, $J = 24.9$ Hz). $^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : –107.6. $^{31}\text{P}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 5.3 ($J_{\text{Pt}} = 3640$ Hz). IR: 3052 (w), 1591 (m, ν_{CN}), 1484 (m), 1436 (m), 1255 (m), 1102 (m), 1079 (s), 693 (s). Anal. calcd. for $\text{C}_{25}\text{H}_{19}\text{NCl}_2\text{FPt}$ (649.39 g/mol) (%): C 46.24, H 2.95, N 2.16; found: C 46.66, H 2.53, N 2.57.

Synthesis of 14 Complex **14** was isolated as a yellow solid by recrystallization from a solution of CH_2Cl_2 : hexane (10 mL: 5 mL) stored at 5 °C. Yield: 295 mg (84%); m.p.: 260 °C. ^1H NMR (DMSO-d_6) δ : 8.85 (s, $J_{\text{HPt}} = 98.3$ Hz, 1H, C(H)=N), 8.10 (dd, $J_{\text{HH}} = 6.4$ Hz, $J_{\text{HP}} = 4.1$ Hz, 1H, Ar), 7.86 (app t, $J_{\text{HH}} = 7.3$ Hz, 1H, Ar), 7.81 (app t, $J_{\text{HH}} = 7.3$ Hz, 1H, Ar), 7.63–7.54 (ov m, 6H, Ar), 7.48–7.42 (ov m, 6H, Ar), 7.21 (app t, $J = 8.7$ Hz, 2H, Ar), 7.06 (dd, $J_{\text{HP}} = 10.1$, $J_{\text{HH}} = 7.8$ Hz, 1H, Ar). $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 167.5 (d, $J_{\text{CP}} = 6.7$ Hz), 161.6 (d, $J_{\text{CF}} = 243.1$ Hz), 149.5, 138.0 (d, $J = 8.6$ Hz), 137.0 (d, $J = 13.4$ Hz), 135.2 (d, $J = 8.6$ Hz), 134.3 (d, $J = 10.5$ Hz), 133.4, 133.1 (d, $J = 2.9$ Hz), 132.8 (d, $J = 1.9$ Hz), 129.5 (d, $J = 11.4$ Hz), 126.5 (d, $J = 8.6$ Hz), 125.9, 125.3, 121.9, 121.3, 115.4 (d, $J = 22.9$ Hz). $^{19}\text{F}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : –113.0. $^{31}\text{P}\{^1\text{H}\}$ NMR (DMSO-d_6) δ : 5.5 ($J_{\text{Pt}} = 3650$ Hz). IR: 3061 (w), 1609 (m, ν_{CN}), 1502 (s), 1436 (m), 1238 (m), 1160 (m), 1103 (s), 835 (m), 690 (s). Anal. calcd. for $\text{C}_{25}\text{H}_{19}\text{NCl}_2\text{FPt}$ (649.39 g/mol) (%): C 46.24, H 2.95, N 2.16; found: C 46.18, H 2.52, N 2.34.

Stability of compounds in dimethyl formamide

Solutions of the compounds in wet DMF were monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy over a period of 2 days at 37 °C. Evidence of 2-diphenylphosphinobenzaldehyde was observed in solutions of the pro-ligands (demonstrating

decomposition to starting materials); therefore, they were not included in the biological testing. As no decomposition of the platinum complexes **8–14** was observed, biological studies of these compounds were initiated.

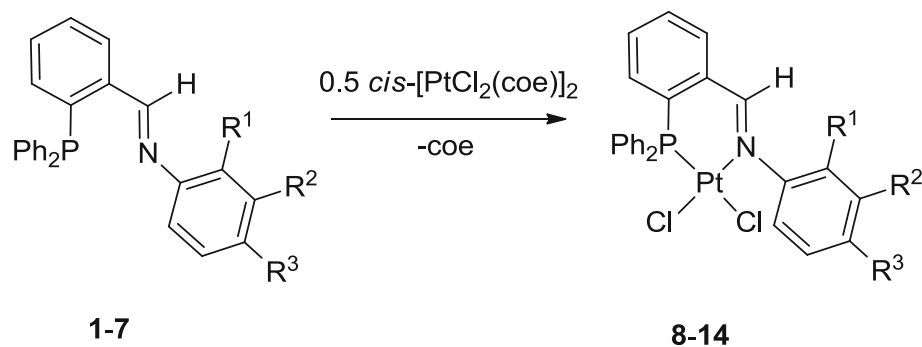
X-ray crystallography

Crystals of **11** and **11a** were grown from a $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{Cl}$: hexane solution stored at RT. Crystals were attached to the tip of a 400 μm MicroLoop with Paratone-N oil. Measurements were made on a Bruker APEXII CCD equipped diffractometer (30 mA, 50 mV) using monochromatic Mo-K α radiation ($\lambda = 0.71073$ Å) at 125 K. The initial orientation and unit cell were indexed using a least-squares analysis of a random set of reflections collected from three series of 0.5° wide scans, 10 s per frame and 12 frames per series that were well distributed in reciprocal space. For data collection, four ω -scan frame series were collected with 0.5° wide scans, 5 (**11**) or 30 (**11a**) second frames and 416 frames per series at varying ϕ angles ($\phi = 0^\circ, 90^\circ, 180^\circ, 270^\circ$). The crystal to detector distance was set to 6 cm, and a complete sphere of data was collected. Cell refinement and data reduction were performed with the Bruker SAINT software, which corrects for beam inhomogeneity, possible crystal decay, Lorentz and polarization effects. Data processing and a multi-scan absorption correction were applied using the APEX2 software package [22]. The structure was solved using direct methods [23]. All non-hydrogen atoms were refined anisotropically. In general, hydrogen atoms were included at geometrically idealized positions with coupled isotropic temperature factors and were fixed (C-H, Ar-H), or in the case of methyl groups, the dihedral angle of the idealized tetrahedral CH_3 fragment was allowed to refine. There was a molecule of dichloromethane that was co-crystallized with **11**. Figures were made using Ortep-3 for Windows [24].

In the initial models in the case of **11a**, there was significant excess electron density around the dichloromethane molecules. After running a variety of models, it was deduced that the electron density was part of a water molecule. In the case of the co-crystallized water molecule, the O-H bonds were fixed at 0.90 Å and the H-H 1,3-distance was set to 1.40 Å and the H atoms were positioned to have a hydrogen bond interaction with Cl of dichloromethane. Attempts to provide a disorder model to account for the excess electron density near the Cl atoms of the dichloromethane molecules were unsuccessful and were thus left as is.

Cell cultures

Human glioma cells Hs683 and T98G were cultured in an incubator at 37 °C and 5% CO_2 in DMEM supplemented



Scheme 1 Synthesis of iminophosphineplatinum(II) complexes **8–14**. **1**: $R^1=R^2=R^3=H$; **2**: $R^1=OMe, R^2=R^3=H$; **3**: $R^1=R^3=H, R^2=OMe$; **4**: $R^1=R^2=H, R^3=OMe$; **5**: $R^1=F, R^2=R^3=H$; **6**: $R^1=R^3=H, R^2=F$;

7: $R^1=R^2=H, R^3=F$; **8**: $R^1=R^2=R^3=H$; **9**: $R^1=OMe, R^2=R^3=H$; **10**: $R^1=R^3=H, R^2=OMe$; **11**: $R^1=R^2=H, R^3=OMe$; **12**: $R^1=F, R^2=R^3=H$; **13**: $R^1=R^3=H, R^2=F$; **14**: $R^1=R^2=H, R^3=F$

with 10% FBS (foetal bovine serum) and 1% antibiotics (Thermo Fisher Scientific) and have been previously characterized [25]. Hs683 cells were originally provided by Dr. Adrian Merlo (Basel, Switzerland), while T98G cells were purchased from American Type Culture Collection (ATCC, #CRL-1690).

MTT assays

A total of 10,000 cells were seeded in triplicates in 96-well plates in 200 μ L of cell culture medium. Cells were incubated at 37 $^{\circ}$ C and 5% CO_2 for 24 h. Medium was replaced with medium containing 1, 10 or 100 μ M of the required complex dissolved in DMF. Cells were incubated for an additional 48 h. DMF was used instead of complexes in control wells. Following incubation, 20 μ L of 5 mg/mL

MTT in PBS was added to each well. Cells and MTT were incubated for 3 h and subsequently removed. Stained cells were re-suspended in 100 μ L of a 1:24 1 M HCl/95% EtOH solution and read at 560 nm on a Varioskan (Scanlab). Experiments were performed as described twice.

LC₅₀ cytotoxicity assays

MTT assays were used to calculate the experimental LC₅₀ values for the compounds. Hs683 or T98G cells were seeded at a density of 10,000 cells per well in 96-well plates and cultured as above for 24 h. Cells were then treated with the complexes at final concentrations of 0.1, 0.5, 1, 10 and 100 μ M, 150 and 250 μ M. DMF was used to dissolve the compounds at the appropriate concentrations. Each compound, at each final concentration, was assessed in triplicate wells. DMF-only treatment was also assessed in triplicate wells. DMF-only treatment was also assessed in triplicate and served as a control. Cells were incubated at 37 $^{\circ}$ C and 5% CO_2 for 48 h following treatment. Cells were then stained, incubated, re-suspended and absorbance values collected as above. Data were converted to the percentage of cell viability compared to solvent control (DMF only) wells from the same experiment. LC₅₀ values were calculated via the GraphPad Prism 6 software. LC₅₀ experiments were repeated twice.

Results and discussion

In order to overcome some of the limitations inherent within cisplatin therapy, a considerable amount of research has recently focused on the synergistic use of radiotherapy and platinum chemotherapy for the treatment of glioblastomas [26–33]. This unique combination allows for reduction in the platinum dosage, and thereby alleviates some of the problematic side effects. Gliomas are a common and deadly form of brain cancer which are typically classified into four clinical grades, of which glioblastoma multiforme (GBM) is the most aggressive. The median

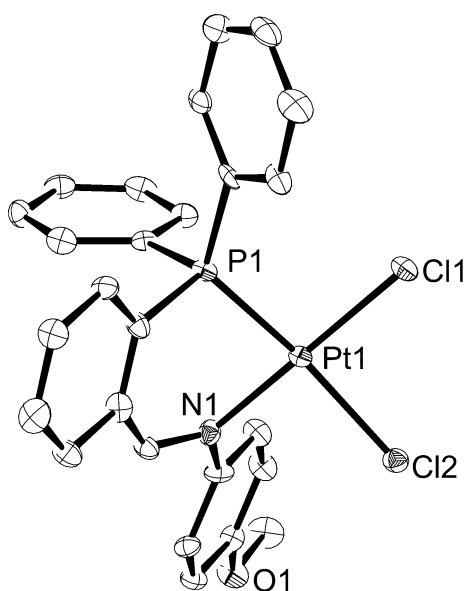


Fig. 1 The molecular structure of **11** drawn with 50% probability ellipsoids and hydrogen atoms and a molecule of solvent removed for clarity

Table 1 Crystallographic data collection parameters

Complex	11	11a
Formula	C ₂₇ H ₂₄ Cl ₄ NOPPt	C ₁₁₂ H ₁₀₆ Cl ₂₀ N ₄ O ₅ P ₄ Pt ₂
Molecular weight	746.33	2811.06
Crystal system	Triclinic	Monoclinic
Space group	<i>P</i> – 1	<i>P2/c</i>
<i>a</i> (Å)	9.8615(17)	12.2694(8)
<i>b</i> (Å)	10.6792(19)	13.2083(8)
<i>c</i> (Å)	14.457(3)	18.5323(12)
α (°)	74.828(2)	90
β (°)	71.841(2)	99.4020(10)
γ (°)	70.9912(2)	90
<i>V</i> (Å ³)	1345.3(4)	2963.0(3)
<i>Z</i>	2	1
ρ_{calc} (Mg m ⁻³)	1.842	1.575
Crystal size (mm ³)	0.217 × 0.122 × 0.076	0.530 × 0.313 × 0.252
Temp (K)	125(2)	125(2)
Radiation	Mo- <i>K</i> _α (λ = 0.71073 Å)	Mo- <i>K</i> _α (λ = 0.71073 Å)
μ (mm ⁻¹)	5.694	2.916
Total reflections	9040	23648
Total unique reflections	4808	7239
No. of variables	317	339
θ range (°)	2.256–25.242	2.228–28.864
Largest difference peak/hole (e/Å ⁻³)	3.48 and –2.40	1.899 and –1.258
S (goodness-of-fit) on F ²	0.995	1.197
<i>R</i> 1 ^a (<i>I</i> > 2 <i>s</i> (<i>I</i>))	0.0604	0.0290
<i>wR</i> 2 ^b (all data)	0.1407	0.0713

$$^a R1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$$

$$^b wR2 = \frac{(\sum [w(F_o^2 - F_c^2)^2])^{1/2}}{(\sum wF_o^4)^{1/2}}, \text{ where } w = 1/[\sigma^2(F_o^2) + (0.0767P)^2] \text{ (11)} \text{ and } w = 1/[\sigma^2(F_o^2) + (0.0208P)^2 + (9.0344P)] \text{ (11a)}, \text{ where } P = (\max(F_o^2, 0) + 2.F_c^2)/3$$

Table 2 Selected bond distances (Å) and angles (°) for **11**

Bond distances		Bond angles	
Pt(1)-N(1)	2.045(9)	N(1)-Pt(1)-P(1)	86.4(3)
Pt(1)-P(1)	2.204(3)	N(1)-Pt(1)-Cl(1)	175.9(3)
Pt(1)-Cl(1)	2.294(3)	N(1)-Pt(1)-Cl(2)	90.1(3)
Pt(1)-Cl(2)	2.365(3)	Cl(1)-Pt(1)-Cl(2)	89.41(10)
N(1)-C(19)	1.321(15)	P(1)-Pt(1)-Cl(1)	94.63(10)
N(1)-C(20)	1.445(14)	P(1)-Pt(1)-Cl(2)	171.77(10)
P(1)-C(1)	1.814(12)	N(1)-C(19)-C(6)	126.7(10)

survival period for patients diagnosed with GBM is only 12 months. The tumours that infiltrate into regions of the brain complicate surgical extraction so it is understandable that the quest for efficacious chemotherapeutic agents to treat GBM is of utmost importance in an effort to improve this combination of cancer treatment. As mentioned

previously, we have found that platinum(II) complexes bearing iminophosphine ligands containing boronate ester groups showed moderate anticancer activity against two glioma cell lines [14]. With this in mind, we have prepared iminophosphineplatinum complexes **9–14** containing electron-donating methoxy derivatives and electron-withdrawing fluoride groups along with the aniline derivative **8** and examined these species for their cytotoxic properties against two glioma cell lines using the MTT method.

The synthesis of pro-ligands **1–7** was performed under an atmosphere of dinitrogen, since the resulting iminophosphines readily decompose back to the starting materials in the presence of water. Formation of the pro-ligands was confirmed by multinuclear NMR spectroscopy where the aldehyde proton at 10.50 ppm disappears and a new peak is observed at *ca.* 9 ppm for the imine proton in the ¹H NMR spectra. Imine formation is further confirmed by ¹³C{¹H} NMR data, since the aldehyde C=O resonance at 191.8 ppm for 2-diphenylphosphinobenzaldehyde

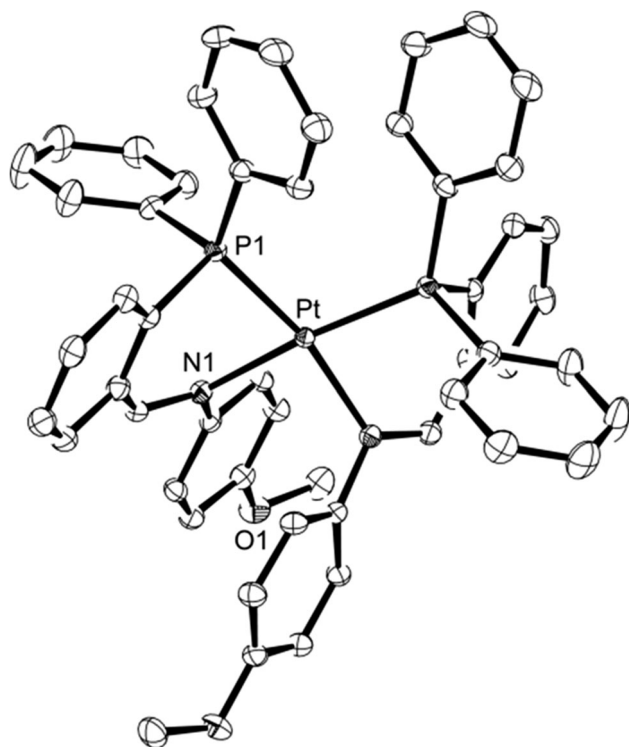


Fig. 2 The molecular structure of the dication **11a** drawn with 50% probability ellipsoids and hydrogen atoms and solvent molecules removed for clarity

Table 3 Selected bond distances (Å) and angles (°) for **11a**

Bond distances		Bond angles	
Pt(1)–N(1)	2.121(2)	N(1)–Pt(1)–P(1)	83.38(7)
Pt(1)–N(1)#	2.121(2)	N(1)#–Pt(1)–P(1)	168.16(7)
Pt(1)–P(1)	2.2509(7)	N(1)–Pt(1)–P(1)#	168.16(7)
Pt(1)–P(1)#	2.2509(7)	N(1)#–Pt(1)–P(1)#	83.38(7)
N(1)–C(19)	1.292(4)	P(1)–Pt(1)–P(1)#	106.35(4)
N(1)–C(20)	1.438(4)	N(1)–Pt(1)–N(1)#	87.84(13)
P(1)–C(1)	1.821(3)	N(1)–C(19)–C(6)	125.1(3)

disappears as the appearance of a new peak at *ca.* 160 ppm for the C=N bonds is observed.

Iminophosphineplatinum(II) complexes (**8–14**) were prepared in moderate to good yields (Scheme 1) by the addition of pro-ligands **1–7** to THF suspensions of $[\text{PtCl}_2(\eta^2\text{-coe})]_2$ (coe = *cis*-cyclooctene). The platinum compounds have been characterized using a number of physical methods, including multinuclear NMR and FTIR spectroscopy, as well as elemental analysis. Coordination of the iminophosphine to the metal centre was confirmed by ^1H NMR spectroscopy where an upfield shift is observed for the imine proton from around 9 ppm to *ca.* 8.4 ppm (in CDCl_3) with associated ^{195}Pt satellites (avg.

$J_{\text{HPt}} = 92$ Hz). Upon coordination, a significant shift is also observed in the $^{31}\text{P}\{^1\text{H}\}$ spectra, from roughly -13 ppm for the free pro-ligands to around 5 ppm for complexes **8–14**. Furthermore, the ^{195}Pt satellites observed with these resonances display coupling constants ($J_{\text{PPt}} = 3640$ to 3720 Hz) which are well within the range reported for related species. The decrease in the $\nu_{\text{C=N}}$ stretching vibration band in the IR spectra from ~ 1619 cm^{-1} for the free iminophosphines to ~ 1603 cm^{-1} is indicative of coordination of the imine moiety to a metal centre [34, 35]. We carried out a single-crystal X-ray diffraction study on the *para*-methoxy derivative **11** in order to confirm the solid-state structure of these complexes, the molecular structure of which is shown in Fig. 1. Crystallographic data are provided in Table 1 and selected bond distances and angles in Table 2. The molecule assumes a distorted square planar geometry about the platinum atom as is evidenced by the bond angles N(1)–Pt(1)–Cl(1) and P(1)–Pt(1)–Cl(2) which are $176.0(2)^\circ$ and $171.54(7)^\circ$, respectively, and are significantly less than 180° . The ligand coordinates to the metal in a $\kappa^2\text{-P,N}$ fashion where the stronger *trans*-effect of the diphenylphosphino group over the amine is observed, as the Pt(1)–Cl(1) distance of $2.293(2)$ Å is noticeably shorter than that of the Pt(1)–Cl(2) distance of $2.372(2)$ Å [36]. The nitrogen–platinum and phosphorus–platinum bond distances of $2.051(7)$ Å and $2.197(2)$, respectively, are similar to those reported in other platinum systems [37–39]. For instance, the nitrogen–platinum and phosphorus–platinum bond distances in the related complex ($\kappa^2\text{-P,N-2-Ph}_2\text{PC}_6\text{H}_4\text{C(H) = N-2,6-}i\text{Pr}_2\text{C}_6\text{H}_3\text{)PtCl}_2$ are $2.0421(18)$ and $2.2128(6)$ Å, respectively [15]. The corresponding N(1)–Pt–P(1) bond angle in this related complex is $89.80(5)^\circ$, whereas the same angle in **11** is $86.4(3)$. The imine N(1)–C(1) distance of $1.287(11)$ Å in **11** is in the range of accepted carbon–nitrogen double bonds. A single crystal of the minor product **11a** was also solved by an X-ray diffraction study. The molecule structure consists of two ligands coordinated to the platinum dication surrounded by two outer-sphere Cl^- anions and solvent molecules (CHCl_3 , CH_2Cl_2 and H_2O). The molecular structure of the dication is presented in Fig. 2, with crystallographic data in Table 1 and selected bond lengths and angles in Table 3. The Pt(1)–N(1) distance of $2.121(2)$ is similar to that of **11**, and the C(19)–N(1) distance of $1.292(4)$ is indicative of a carbon–nitrogen double bond. The platinum centre exists in a slightly distorted square planar configuration, as demonstrated by the sum of angles around Pt of $360.95(34)^\circ$. The ligands are arranged so that the phosphine and imine fragments are *trans* to one another. The Pt–N and Pt–P bond lengths are $2.120(2)$ and $2.2509(7)$ Å, respectively, and are much longer than observed in **11**, presumably due to either the steric effects of the two iminophosphine ligands, or due

to differing *trans*-effects when compared to the Cl ligands in **11**. Related *cis*-diaminophosphineplatinum(II) complexes have been reported previously [40–46]. For instance, the disparate Pt–N and Pt–P bond lengths in [Pt{(NC₅H₄)(Ph₂PNH)C(=NH)-4}{(NC₅H₄)(Ph₂PNH)C(=N)-4}][BF₄] [44] are 2.07(2)/2.03(2) and 2.218(6)/2.246(6) Å, respectively. The coordination chemistry of a wide array of *P,N*-ligands with late metals is an area of considerable interest [47–49].

We then decided to examine the anticancer potential of compounds **8–14** against two glioma cell lines using the MTT method, but not one of these derivatives showed any appreciable bioactivity. These results are in contrast to our previous study, wherein complexes of the type (κ^2 -*P,N*-2-Ph₂PC₆H₄C(H)=NC₆H₄X)PtCl₂ (X = Bpin, pin = 1,2-O₂C₂Me₄) showed moderate anticancer activities, suggesting it is the boron group that imparts bioactivity [14].

Conclusion

Seven iminophosphine compounds were prepared from the condensation of 2-diphenylphosphinobenzaldehyde and aniline, and its derivatives containing electron-donating methoxy groups and electron-withdrawing fluorides. The corresponding platinum(II) complexes were formed by addition of the pro-ligands to [PtCl₂(η^2 -coe)]₂ (coe = *cis*-cyclooctene). All new pro-ligands and metal complexes were fully characterized by multinuclear NMR and FTIR spectroscopy, and elemental analysis for the platinum species. A single-crystal X-ray diffraction study was performed for **11**, the platinum complex containing the *para*-methoxy iminophosphine ligand. The structure of the unique *cis*-diiminophosphineplatinum(II) dication **11a** was also determined through a single-crystal X-ray diffraction study. Platinum compounds **8–14** showed minimal cytotoxic effects against two glioma cell lines.

Supplemental material

Full supplemental crystallographic data in CIF format have been deposited with the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk) and are available on request, quoting deposition numbers 1557055 (**11**) and 1557056 (**11a**).

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