Canadian Journal of Chemistry
Revue canadienne de chimie

**Synthesis, characterization, and anticancer properties of
iminophosphineplatinum(II) complexes containing
boronate esters**

Journal:	<i>Canadian Journal of Chemistry</i>
Manuscript ID	cjc-2016-0570.R1
Manuscript Type:	Article
Date Submitted by the Author:	16-Nov-2016
Complete List of Authors:	St-Coeur, Patrick-Denis; Université de Moncton Kinley, Samantha; Mount Allison University, Chemistry and Biochemistry Vogels, Christopher; Mount Allison University, Chemistry and Biochemistry Decken, Andreas; Department of Chemistry Morin, Pier Jr.; Université de Moncton, Département de chimie et biochimie Westcott, Stephen; Mount Allison University, Chemistry and Biochemistry
Keyword:	anticancer, boron, boronate esters, glioma, platinum

SCHOLARONE™
Manuscripts

Synthesis, characterization, and anticancer properties of iminophosphineplatinum(II) complexes containing boronate esters

Patrick-Denis St-Coeur, Samantha Kinley, Christopher M. Vogels, Andreas Decken, Pier Jr. Morin, and Stephen A. Westcott

P.-D. St-Coeur and P. Jr. Morin. Département de chimie et biochimie, Université de Moncton, Campus de Moncton, Moncton, NB E1A 3E9, Canada.

S. Kinley, C.M. Vogels, and S.A. Westcott. Department of Chemistry and Biochemistry, Mount Allison University, Sackville, NB E4L 1G8, Canada.

A. Decken. Department of Chemistry, University of New Brunswick, Fredericton, NB E3B 5A3, Canada.

Corresponding authors: Stephen A. Westcott (e-mail: swestcott@mta.ca). Corresponding author for anticancer studies: Pier Jr. Morin (e-mail: pier.morin@umoncton.ca); corresponding author for X-ray studies: Andreas Decken (e-mail: adecken@unb.ca).

Abstract: Three new iminophosphines containing pinacol-derived boronate esters have been prepared and ligated to dichloridoplatinum(II) fragments. All compounds have been characterized fully, including an X-ray diffraction study carried out for the platinum complex **8**, which is derived from 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline. These three new platinum complexes, along with the non-boron containing control, have been examined for their initial cytotoxic properties against two glioma cell lines using the MTT method.

Key words: anticancer, boron, boronate esters, glioma, platinum.

Graphical Abstract:

5 B Boron 10.811	88 Ra Radium 226.025	53 I Iodine 126.904	7 N Nitrogen 14.007
20 Ca Calcium 40.078	7 N Nitrogen 14.007	58 Ce Cerium 140.115	R

- 5: $R^1=R^2=R^3=H$
 6: $R^1=Bpin; R^2=R^3=H$
 7: $R^1=R^3=H; R^2=Bpin$
 8: $R^1=R^2=H; R^3=Bpin$

Introduction

Interest in boron pharmaceuticals has rapidly grown in recent years as researchers continue to discover new and remarkable applications for these interesting small molecules.¹ For instance, α -aminoboronic acids are well-recognized as being a unique class of potent enzyme inhibitors with the boro-peptide Velcade® being the first boron-containing small molecule to be approved by the FDA for the treatment of multiple myeloma.² The bioactivity associated with small molecule boron compounds is believed to arise from the electrophilic nature of the three-coordinate boron atom, which contains an empty p-type orbital. The boron atom can readily form dative Lewis acid-base bonds with nucleophiles (i.e. hydroxyl group in serine, bases in DNA, etc) and transform from a neutral trigonal three-coordinate species to a four-coordinate tetrahedral adduct. This dative bonding interaction, which can provide great stability, can also be reversible, unlike the covalent bonds generated when using organic 'suicide inhibitors' and differentiates small molecule boron compounds from traditional pharmaceuticals.

Although there is presently a considerable amount of research focused on designing new organic compounds incorporating boron for potential therapeutic use,¹⁻⁸ much less studied are transition metal complexes containing this remarkable element for possible applications in medicinal chemistry. One area where metal-boron chemistry has attracted considerable attention is in the development of novel anticancer agents.⁹⁻¹³ Indeed,

although cisplatin ($\text{cis-PtCl}_2(\text{NH}_3)_2$) is a well-known antineoplastic agent,¹⁴ severe side-effects limit its use in cancer therapy and new strategies for designing more efficacious metal anticancer compounds are constantly being investigated. Rendina and co-workers have been instrumental in this area and have been examining terpyridineplatinum(II) derivatives containing either carborane (Chart 1, **I**) or boronic acid $[\text{RB}(\text{OH})_2]$ appendages (Chart 1, **II**).⁹ Platinum compounds containing BODIPY groups have also been examined by Weissleder and co-workers for high-resolution *in vivo* cancer imaging.¹⁰ Other metals are also being examined for their potential bioactivities and a considerable body of work has appeared recently on ferrocene-based prodrugs containing boron (Chart 1, **III**).¹¹ More relevant to this present study, however, is a report by Trivedi and co-workers on the *in vitro* anticancer evaluation on a series of iminopyridinepalladium(II) complexes bearing sugar-boronate esters (Chart 1, **IV**).¹² As part of our program developing new metal-boron complexes with potential bioactivities,¹³ we now disclose our findings on the synthesis and characterization of a small family of iminophosphineplatinum(II) compounds and their cytotoxic properties against two glioma cell lines using the MTT method.

Chart 1. Bioactive metal complexes bearing boron groups.

Experimental

Materials and methods

Reagents and solvents used were obtained from Sigma-Aldrich. $[\text{PtCl}_2(\eta^2\text{-coe})]_2$ (coe = *cis*-cyclooctene)¹⁵ and *N*-(2-(diphenylphosphino)benzylidene)aniline (**1**)¹⁶ were prepared as previously reported. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-GSX400 FT NMR (^1H : 400 MHz; ^{11}B : 128 MHz; ^{13}C : 100 MHz; ^{31}P : 162 MHz) spectrometer. Chemical shifts (δ) are reported in ppm [relative to residual solvent peaks (^1H and ^{13}C) or external $\text{BF}_3\cdot\text{OEt}_2$ (^{11}B) and H_3PO_4 (^{31}P)]. Multiplicities are reported as singlet (s), doublet (d), multiplet (m), broad (br) and overlapping (ov) with coupling constants (J) reported in hertz. Melting points were measured uncorrected with a Stuart SMP30 apparatus. Fourier transform infra-red (FT-IR) spectra

were obtained with a Thermo Fisher Scientific Nicolet iS5 FT-IR spectrometer in attenuated total reflections (ATR) mode and are reported in cm^{-1} as strong (s), medium (m) or weak (w). Elemental analyses for carbon, hydrogen, and nitrogen were carried out at Laboratoire d'Analyse Élémentaire de l'Université de Montréal (Montréal, QC). Microwave reactions were performed using a CEM Discover SP system in standard closed vessels with the reaction temperature monitored by the internal IR pyrometer. All reactions were performed under a nitrogen atmosphere in a MBraun LabMaster glovebox.

Synthesis of *N*-(2-(diphenylphosphino)benzylidene)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2**)**

A mixture of 2-(diphenylphosphino)benzaldehyde (500 mg, 1.72 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (377 mg, 1.72 mmol), and activated molecular sieves (3 Å, 5 g) in toluene (5 mL) was heated at 125 °C under microwave conditions for 3 h. The sieves were removed by suction filtration and the filtrate brought to dryness under vacuum to afford an oily orange solid. Trituration of the solid with cold hexane (1 mL) gave **2** as an off-white solid. Yield: 500 mg (59%); mp 120-122 °C. IR: 3055 (w), 2980 (m), 1625 (m, ν_{CN}), 1591 (m), 1435 (m), 1349 (s), 1310 (m), 1143 (m), 1067 (m), 962 (m), 860 (m), 774 (s), 745 (m), 696 (s). ^1H NMR (CDCl_3) δ : 8.89 (d, $J_{\text{HP}} = 5.0$ Hz, 1H, C(H)=N), 8.31 (dd, $J_{\text{HH}} = 7.8$, $J_{\text{HP}} = 4.1$ Hz, 1H, Ar), 7.70 (d, $J_{\text{HH}} = 7.3$ Hz, 1H, Ar), 7.45 (ov dd, $J_{\text{HH}} = 7.8$, 7.3 Hz, 1H, Ar), 7.34-7.25 (ov m, 12H, Ar), 7.10 (app t, $J_{\text{HH}} = 7.3$ Hz, 1H, Ar), 6.90 (dd, $J_{\text{HH}} = 7.3$, $J_{\text{HP}} = 4.6$ Hz, 1H, Ar), 6.34 (d, $J_{\text{HH}} =$

7.8 Hz, 1H, Ar), 1.28 (s, 12H, pin). ^{11}B NMR (CDCl_3) δ : 30 (br). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 159.0 (d, $J_{\text{CP}} = 23.8$ Hz), 158.0, 140.0 (d, $J_{\text{CP}} = 17.2$ Hz), 138.2 (d, $J_{\text{CP}} = 19.1$ Hz), 136.2 (d, $J_{\text{CP}} = 9.5$ Hz), 135.6, 135 (br, C-B), 134.3 (d, $J_{\text{CP}} = 20.0$ Hz), 133.0, 131.7, 130.7, 129.0, 128.9, 128.8 (d, $J_{\text{CP}} = 6.7$ Hz), 128.2 (d, $J_{\text{CP}} = 4.8$ Hz), 124.5, 118.8, 83.6, 25.0. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) δ : -13.9. This ligand was used as is to make the corresponding platinum complex.

Synthesis of *N*-(2-(diphenylphosphino)benzylidene)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3**)**

A mixture of 2-(diphenylphosphino)benzaldehyde (400 mg, 1.38 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (302 mg, 1.38 mmol) and formic acid (2 drops) in anhydrous MeOH (5 mL) was allowed to react at RT. After 18 h, compound **3** was collected by suction filtration as a pale yellow precipitate. Yield: 625 mg (92%); mp 78-81 °C. IR: 3047 (w), 2975 (w), 1626 (m, ν_{CN}), 1431 (m), 1352 (s), 1314 (s), 1141 (s), 1073 (m), 964 (m), 851 (m), 752 (s), 697 (s). ^1H NMR (CDCl_3) δ : 9.06 (d, $J_{\text{HP}} = 5.0$ Hz, 1H, C(H)=N), 8.15 (dd, $J_{\text{HH}} = 7.8$, $J_{\text{HP}} = 4.1$ Hz, 1H, Ar), 7.61 (d, $J_{\text{HH}} = 7.4$ Hz, 1H, Ar), 7.46-7.42 (ov m, 2H, Ar), 7.36-7.25 (ov m, 12H, Ar), 6.97-6.91 (ov m, 2H, Ar), 1.34 (s, 12H, pin). ^{11}B NMR (CDCl_3) δ : 30 (br). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 159.0 (d, $J_{\text{CP}} = 21.0$ Hz), 151.1, 139.3 (d, $J_{\text{CP}} = 16.2$ Hz), 138.8 (d, $J_{\text{CP}} = 20.0$ Hz), 136.5 (d, $J_{\text{CP}} = 8.6$ Hz), 134.2 (d, $J_{\text{CP}} = 20.0$ Hz), 133.6, 132.3, 130.9, 130 (br, C-B), 129.0 (2C), 128.8 (d, $J_{\text{CP}} = 6.7$ Hz), 128.5, 128.4 (d, $J_{\text{CP}} = 3.8$ Hz), 126.9, 124.2, 83.9, 25.0. $^{31}\text{P}\{^1\text{H}\}$ NMR

(CDCl₃) δ : -12.7. This ligand was used as is to make the corresponding platinum complex.

Synthesis of *N*-(2-(diphenylphosphino)benzylidene)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**4**)

A mixture of 2-(diphenylphosphino)benzaldehyde (400 mg, 1.38 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (302 mg, 1.38 mmol) and formic acid (2 drops) in anhydrous MeOH (5 mL) was allowed to react at RT. After 18 h, compound **4** was collected by suction filtration as a pale yellow precipitate. Yield: 580 mg (86%); mp 98-100 °C. IR: 3050 (w), 2986 (w), 1593 (m, ν_{CN}), 1142 (m), 1087 (m), 964 (w), 841 (m), 693 (s), 654 (s). ¹H NMR (CDCl₃) δ : 8.99 (d, J_{HP} = 5.0 Hz, 1H, C(H)=N), 8.19 (dd, J_{HH} = 7.8, J_{HP} = 4.1 Hz, 1H, Ar), 7.72 (d, J_{HH} = 8.2 Hz, 2H, Ar), 7.44 (ov dd, J_{HH} = 7.8, 7.4 Hz, 1H, Ar), 7.35-7.30 (ov m, 11H, Ar), 6.91 (m, 1H, Ar), 6.81 (d, J_{HH} = 8.2 Hz, 2H, Ar), 1.33 (s, 12H, pin). ¹¹B NMR (CDCl₃) δ : 30 (br). ¹³C{¹H} NMR (CDCl₃) δ : 159.5 (d, J_{CP} = 21.0 Hz), 154.5, 139.0 (d, J_{CP} = 5.7 Hz), 138.9, 136.3 (d, J_{CP} = 9.5 Hz), 135.8, 134.3 (d, J_{CP} = 20.0 Hz), 133.5, 131.1, 129.1, 129.0, 128.8 (d, J_{CP} = 7.6 Hz), 128.2 (d, J_{CP} = 3.8 Hz), 126 (br, C-B), 120.3, 83.8, 25.0. ³¹P{¹H} NMR (CDCl₃) δ : -12.2. This ligand was used as is to make the corresponding platinum complex.

Synthesis of **5**

To a stirred toluene (5 mL) suspension of [PtCl₂(η^2 -coe)]₂ (237 mg, 0.31 mmol) was added a toluene (2 mL) solution of *N*-(2-

(diphenylphosphino)benzylidene)aniline (230 mg, 0.63 mmol). The reaction was allowed to proceed at RT for 18 h, at which point a yellow precipitate was collected by suction filtration. Recrystallization from CH₂Cl₂ (15 mL) at 5 °C afforded **5** as a yellow-orange solid. Yield: 310 mg (79%); mp 255-260 °C. IR: 3055 (w), 2929 (w), 1618 (m, ν_{CN}), 1484 (m), 1436 (m), 1186 (w), 1098 (m), 999 (w), 770 (m), 752 (w), 692 (s). ¹H NMR (CDCl₃) δ : 8.38 (s, $J_{\text{HPt}} = 96.6$ Hz, 1H, C(H)=N), 7.77-7.64 (ov m, 3H, Ar), 7.60-7.54 (ov m, 6H, Ar), 7.49-7.45 (ov m, 4H, Ar), 7.34-7.32 (ov m, 4H, Ar), 7.27 (m, 1H, Ar), 7.10 (m, 1H, Ar). ¹³C{¹H} NMR (CDCl₃) δ : 163.7 (d, $J_{\text{CP}} = 7.6$ Hz), 153.0, 136.9 (d, $J_{\text{CP}} = 13.3$ Hz), 135.9 (d, $J_{\text{CP}} = 8.6$ Hz), 134.3 (d, $J_{\text{CP}} = 11.5$ Hz), 134.2, 133.5 (d, $J_{\text{CP}} = 2.9$ Hz), 132.7, 132.3 (d, $J_{\text{CP}} = 2.9$ Hz), 128.9 (d, $J_{\text{CP}} = 11.4$ Hz), 128.7, 128.5, 125.5, 124.9, 123.8, 123.6, 123.0. ³¹P{¹H} NMR (CDCl₃) δ : 5.7 ($J_{\text{PPt}} = 3680$ Hz). Anal. calc. for C₂₅H₂₀NC₂PPt (631.40 g/mol) (%): C 47.56, H 3.19, N 2.22; found: C 47.79, H 3.32, N 2.15.

Synthesis of 6

To a stirred toluene (3 mL) suspension of [PtCl₂(η^2 -coe)]₂ (100 mg, 0.13 mmol) was added a toluene (1 mL) solution of *N*-(2-(diphenylphosphino)benzylidene)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (134 mg, 0.27 mmol). The reaction was allowed to proceed at RT for 2 h, at which point a yellow precipitate was collected by suction filtration and washed with hexane (5 mL) to afford **6** as a yellow solid. Yield: 132 mg (67%); mp 268-270 °C. IR: 3053 (w), 2982 (w), 1603 (m, ν_{CN}), 1481 (m), 1434 (m), 1347 (s), 1322 (m), 1144 (m), 1099

(m), 1071 (w), 859 (m), 776 (s), 693 (s), 651 (s). ^1H NMR (CDCl_3) δ : 8.27 (s, $J_{\text{HPt}} = 96.7$ Hz, 1H, C(H)=N), 7.84 (d, $J_{\text{HH}} = 6.4$ Hz, 1H, Ar), 7.70-7.47 (ov m, 13H, Ar), 7.31 (ov dd, $J_{\text{HH}} = 7.8, 6.4$ Hz, 1H, Ar), 7.21 (ov dd, $J_{\text{HH}} = 7.3$ Hz, 1H, Ar), 7.09 (dd, $J_{\text{HH}} = 10.4, 7.8$ Hz, 1H, Ar), 6.92 (d, $J_{\text{HH}} = 7.8$ Hz, 1H, Ar), 1.28 (s, 12H, pin). ^{11}B NMR (CDCl_3) δ : 30 (br). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 165.1 (d, $J_{\text{CP}} = 7.6$ Hz), 157.2, 137.1 (d, $J_{\text{CP}} = 12.4$ Hz), 135.8, 135.0 (d, $J_{\text{CP}} = 8.6$ Hz), 134.3 (br), 133.6 (d, $J_{\text{CP}} = 7.6$ Hz), 133.2 (d, $J_{\text{CP}} = 3.8$ Hz), 132.1, 130.9, 129.1, 128.8 (br), 128.3, 127.1, 125.4, 123.6, 123.1, 84.3, 25.1. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) δ : 5.1 ($J_{\text{PPt}} = 3690$ Hz). Anal. calc. for $\text{C}_{31}\text{H}_{31}\text{NBCl}_2\text{O}_2\text{PPt}$ (757.36 g/mol) (%): C 49.16, H 4.13, N 1.85; found: C 49.40, H 4.10, N 1.64.

Synthesis of **7**

To a stirred toluene (4 mL) suspension of $[\text{PtCl}_2(\eta^2\text{-coe})]_2$ (153 mg, 0.20 mmol) was added a toluene (2 mL) solution of *N*-(2-(diphenylphosphino)benzylidene)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (200 mg, 0.41 mmol). The reaction was allowed to proceed at RT for 2 h, at which point a yellow precipitate was collected by suction filtration and washed with hexane (5 mL). The precipitate was recrystallized from CH_2Cl_2 (5 mL) and hexane (5 mL) stored at 5 °C to afford **7** as a yellow solid. Yield: 224 mg (74%); mp 213-216 °C. IR: 3061 (w), 2980 (w), 1609 (m, ν_{CN}), 1433 (m), 1358 (s), 1326 (m), 1144 (s), 1098 (m), 967 (m), 852 (m), 758 (m), 694 (s). ^1H NMR (CDCl_3) δ : 8.35 (s, $J_{\text{HPt}} = 94.8$ Hz, 1H, C(H)=N), 7.77-7.45 (ov m, 16H, Ar), 7.35 (ov dd, $J_{\text{HH}} = 7.8, 7.4$ Hz, 1H, Ar), 7.11 (dd, $J_{\text{HH}} = 10.5, 7.8$ Hz, 1H, Ar), 1.34 (s, 12H, pin). ^{11}B NMR (CDCl_3)

δ : 28 (br). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 163.8 (d, $J_{\text{CP}} = 6.7$ Hz), 152.4, 136.9 (d, $J_{\text{CP}} = 13.4$ Hz), 135.8 (d, $J_{\text{CP}} = 7.6$ Hz), 134.9, 134.4 (d, $J_{\text{CP}} = 11.4$ Hz), 134.1 (d, $J_{\text{CP}} = 7.6$ Hz), 133.3 (d, $J_{\text{CP}} = 2.9$ Hz), 132.6, 132.3 (d, $J_{\text{CP}} = 1.9$ Hz), 130 (br, C-B), 128.9 (d, $J_{\text{CP}} = 11.5$ Hz), 128.6, 128.0, 127.2, 125.4, 124.8, 123.7, 123.2, 84.2, 25.1. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) δ : 6.0 ($J_{\text{PPt}} = 3690$ Hz). Anal. calc. for $\text{C}_{31}\text{H}_{31}\text{NBCl}_2\text{O}_2\text{PPt}$ (757.36 g/mol) (%): C 49.16, H 4.13, N 1.85; found: C 49.06, H 4.29, N 1.73.

Synthesis of 8

To a stirred toluene (5 mL) suspension of $[\text{PtCl}_2(\eta^2\text{-coe})]_2$ (225 mg, 0.30 mmol) was added a toluene (2 mL) solution of *N*-(2-(diphenylphosphino)benzylidene)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (300 mg, 0.61 mmol). The reaction was allowed to proceed at RT for 2 h, at which point a yellow precipitate was collected by suction filtration and washed with hexane to afford **8**. Yield: 304 mg (67%); mp 265-267 °C. IR: 2980 (m), 1588 (m, ν_{CN}), 1356 (s), 1331 (m), 1137 (m), 1089 (m), 962 (m), 851 (m), 694 (s), 654 (m). ^1H NMR (CDCl_3) δ : 8.35 (s, $J_{\text{HPt}} = 95.8$ Hz, 1H, C(H)=N), 7.78 (d, $J_{\text{HH}} = 8.2$ Hz, 2H, Ar), 7.73-7.45 (ov m, 11H, Ar), 7.33 (d, $J_{\text{HH}} = 8.2$ Hz, 2H, Ar), 7.25 (ov dd, $J_{\text{HH}} = 8.3$, 6.4 Hz, 1H, Ar), 7.16 (m, 1H, Ar), 7.10 (dd, $J_{\text{HH}} = 10.5$, 7.8 Hz, 1H, Ar), 1.31 (s, 12H, pin). ^{11}B NMR (CDCl_3) δ : 29 (br). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 163.8 (d, $J_{\text{CP}} = 7.6$ Hz), 155.0, 136.9 (d, $J_{\text{CP}} = 13.4$ Hz), 136.0 (d, $J_{\text{CP}} = 7.6$ Hz), 135.3, 134.3 (d, $J_{\text{CP}} = 11.4$ Hz), 134 (br, C-B), 133.4 (d, $J_{\text{CP}} = 2.9$ Hz), 132.7 (d, $J_{\text{CP}} = 1.9$ Hz), 132.3 (d, $J_{\text{CP}} = 1.9$ Hz), 128.9 (d, $J_{\text{CP}} = 11.5$ Hz), 125.4, 124.8, 123.6, 123.0,

84.1, 25.0. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3) δ : 5.6 ($J_{\text{P-Pt}} = 3670$ Hz). Anal. calc. for $\text{C}_{31}\text{H}_{31}\text{NBCl}_2\text{O}_2\text{PPt}$ (757.36 g/mol) (%): C 49.16, H 4.13, N 1.85; found: C 49.31, H 4.21, N 1.75.

Stability testing of platinum compounds

In a NMR tube, compounds **5-8** were dissolved in dimethylformamide (1 mL) and analyzed by $^{31}\text{P}\{^1\text{H}\}$ and ^{11}B NMR spectroscopy. The solutions were stored at 37 °C for 2 d at which point the compounds were reanalyzed by multinuclear NMR spectroscopy.

X-ray crystallography

Crystals of **8** were grown from a saturated acetone solution stored at 5 °C. Single crystals were coated with Paratone-N oil, mounted using a polyimide MicroMount and frozen in the cold nitrogen stream of the goniometer. A hemisphere of data was collected on a Bruker AXS P4/SMART 1000 diffractometer using ω and ϕ scans with a scan width of 0.3° and 30 s exposure times. The detector distance was 5 cm. The data were reduced (SAINT)¹⁷ and corrected for absorption (SADABS).¹⁸ The structure was solved by direct methods and refined by full-matrix least squares on F^2 (SHELXTL).¹⁹ All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms were included in calculated positions and refined using a riding model.

Cell cultures

Human glioma cells Hs683 and T98G were cultured in an incubator at 37 °C and 5% CO₂ in DMEM supplemented with 10% FBS (foetal bovine serum) and antibiotics (Thermo Fisher Scientific) and have been previously characterized.²⁰ 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

10,000 cells were seeded in triplicates in 96-well plates in 200 µL of cell culture medium. Cells were incubated at 37 °C and 5% CO₂ for 24 h. Medium was replaced with medium containing 1 µM, 10 µM or 100 µM of complexes dissolved in DMF. Cells were incubated for an additional 48 h. DMF was used instead of complexes in control wells. Following incubation, 20 µL 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 µL of a 1:24 1M HCl/95% EtOH solution and read at 560 nm on a Varioskan (Scanlab). A similar approach was undertaken for combinatorial treatments of Hs683 and T98G cells with compounds and temozolomide (TMZ). For such treatments, 50 µM of compound and 100 µM of TMZ were used. Experiments were performed as described twice. Data presented are mean ± standard error of the mean (SEM).

LC₅₀ cytotoxicity assays

MTT assays were used to calculate the experimental LC₅₀ values for all four novel organometallic platinum complexes and cisplatin. Hs693 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 control compound cisplatin and the four complexes at final concentrations of 0.1 μ M, 0.5 μ M, 1 μ M, 10 μ M and 100 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 and served as control. Cells were incubated at 37 °C and 5% CO₂ for 48 h following treatment. Cells were then stained with 20 μ L of 5 mg/mL MTT-PBS solution and incubated at 37 °C and 5% CO₂ for 3 h. Cells were re-suspended and absorbance values were 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 and results collected are presented as mean $\pm$ standard error of the mean (SEM).

Results and discussion

Chemistry

Compounds **1–4** have been prepared by a simple condensation reaction between the starting commercially-available aniline derivatives and 2-phosphinobenzaldehyde. Reactions were carried out under an inert-

atmosphere as imines **2–4**, containing the electron-withdrawing boronate ester groups Bpin (pin = pinacolato; 1,2-O₂C₂Me₄), were not stable with respect to water and rapidly converted back to the starting materials. Not surprising, no significant change is observed in either the ³¹P{¹H} or ¹¹B NMR data upon formation of the corresponding imine. However, a significant shift in the ¹H NMR spectra is observed as the aldehyde resonance at 10.50 ppm is replaced with a signal around 9 ppm for the newly generated imines. The same trend is also observed in the ¹³C NMR data as the aldehyde carbon at 191.8 ppm is replaced by a signal at roughly 160 ppm assigned to the new carbon imine.

Addition of iminophosphines **1–4** to toluene suspensions of [PtCl₂(η²-coe)]₂ (coe = *cis*-cyclooctene) afforded the corresponding dichloridoplatinum(II) complexes **5–8** in moderate to good yields (Scheme 1). All new complexes have been fully characterized using a number of physical methods, including multinuclear NMR and FT-IR spectroscopy, as well as elemental analysis. A significant upfield shift in the ¹H NMR spectra from around δ 9 ppm to 8 ppm is observed for the imine proton upon coordination of the ligand to the formally d⁸ metal center. As expected, no peaks are observed for the labile cyclooctene group. Although a singlet for the ligands **1–4** is found at approximately δ -12 ppm in the ³¹P{¹H} NMR spectra, coordination to the platinum(II) metal center shifts this peak to around 5 ppm for complexes **5–8** and platinum satellites are observed with coupling constants ranging from $J_{\text{PPt}} = 3670\text{--}3690$ Hz. These values are well within the range reported for related species.^{21,22} The ¹¹B NMR

data for complexes **6–8** is observed at approximately δ 30 ppm, which is indicative of a three coordinate boron atom in a CBO₂ environment.²³ As late metals such as palladium and platinum are well known to cleave the C-B bond,²⁴ we carried out a single crystal X-ray diffraction study on **8** to confirm that the boronate ester group remained intact, the molecular structure of which is shown in Figure 1.

Scheme 1. Synthesis of iminopyridineplatinum(II) complexes **5–8**.

Fig. 1. The molecular structure of **8** with ellipsoids shown at the 50% confidence level. Hydrogen atoms and molecules of solvent have been omitted for clarity. Selected bond distances (Å) and angles (°): Pt(1)-N(1) 2.044(3), Pt(1)-P(1) 2.2089(9), Pt(1)-Cl(1) 2.2842(9), Pt(1)-Cl(2) 2.3655(9), N(1)-C(19) 1.289(5), B(1)-O(1) 1.360(9), B(1)-O(2) 1.362(8); N(1)-Pt(1)-P(1) 87.33(9), Cl(1)-Pt(1)-Cl(2) 89.29(3), O(1)-B(1)-O(2) 115.1(5), O(1)-B(1)-C(23) 122.4(5), O(2)-B(1)-C(23)

122.4(6).

Crystallographic data are provided in Table 1. The nitrogen–platinum bond distance of 2.044(3) Å is similar to those reported in other platinum systems.^{21,22} The imine C(19)–N(1) distance of 1.289(5) Å is in the range of accepted carbon–nitrogen double bonds. Likewise, the boronate ester group in **8** is roughly coplanar with the aromatic group in order to maximize the donation from the ring $p\pi$ electrons to the empty p -type orbital on boron. The B–O bond distances (1.360(9) and 1.362(8) Å) are also typical for three coordinate Bpin groups.²⁵

[Please Insert Table 1]

Cytotoxicity of complexes on glioma cells

An interesting recent development involves the synergistic use of radiotherapy and platinum chemotherapy for the treatment of glioblastomas.²⁶ This

therapeutic combination of treatments allows for the reduction of the platinum dosage and thereby diminishes side effects. Gliomas are a common and deadly form of brain cancer which are classified into four clinical grades of which glioblastoma multiforme (GBM) is the most aggressive, whereby the median survival period for patients diagnosed with a GBM is a mere twelve months. Unfortunately, tumors infiltrate into regions of the brain that render complete surgical extraction difficult. Although some improvements in the prognosis of GBM patients have been observed using chemotherapeutic agents, such as cisplatin, the search for novel agents to treat GBM is of utmost importance in an effort to improve this combination of cancer treatment. As such, we have examined platinum complexes **5–8** for their cytotoxic properties against two glioma cell lines using the MTT method. The results (Fig. 2A and B) showed that complexes **6–8** displayed detectable cytotoxic effects in one or both cell glioma cell lines. While complexes **7** and **8** displayed appreciable cytotoxic activity in Hs683 cells alone, complex **6** exhibited the most significant impact in both models amongst the four novel compounds tested.

Fig. 2. Cytotoxic activities of complexes in Hs683 (A) and T98G (B) glioma cells. Histograms present % Cell Viability $\pm$ SEM.

Complexes **5–8** and cisplatin were also assessed at additional concentrations in both cell lines to assess LC_{50} values. Results are presented in Table 2. Complex **6** displayed the highest cytotoxic activities when compared with the other three complexes and was more cytotoxic than cisplatin in Hs683 cells.

Table 2. LC_{50} values of novel platinum complexes and cisplatin evaluated in Hs683 and T98G glioma cell models.

Complex	Hs683	T98G
Cisplatin	44.3 $\pm$ 22.4 μ M	42.1 $\pm$ 13.4 μ M
5	> 250 μ M	> 250 μ M
6	36.8 $\pm$ 8.0 μ M	65.0 $\pm$ 11.1 μ M
7	106.0 $\pm$ 25.1 μ M	> 250 μ M
8	189.7 $\pm$ 9.8 μ M	> 250 μ M

Complexes **5–8** were further investigated for their impact on glioma cell response to temozolomide (TMZ), an alkylating agent that is part of the

standard therapeutic regimen for GBMs.²⁷ Cytotoxic effects of complexes in combination with TMZ was assessed in Hs683 and T98G cells. Results are shown in Figure 3.

Fig. 3. Cytotoxic activities on Hs683 (A) and T98G (B) cells following treatment with temozolomide (TMZ) and platinum complexes. Results display % Cell Viability $\pm$ SEM.

Cisplatin did not exhibit TMZ-sensitizing characteristics. This is aligned with a recent report showing that neoadjuvant cisplatin in GBM and anaplastic astrocytoma patients did not provide added benefits versus TMZ alone.²⁸ In addition, novel complexes **5–8** did not sensitize cells to TMZ in both glioma models investigated.

Conclusions

Three new iminophosphines containing pinacol-derived boronate esters have been synthesized and ligated to dichloridoplatinum(II) fragments. All compounds have been characterized fully, including an X-ray diffraction study which was carried out for the platinum complex **8**, which is derived from 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline. These three new platinum complexes, along with the non-boron containing control, have been examined for their initial cytotoxic properties against two glioma cell lines using the MTT method. The most promising candidate from this study was complex **6**, where the steric bulk of the boronate ester group may impart enhanced cytotoxic activities. Future work in this area will build on this study in an effort to design a more potent series of metal-based boron compounds with enhanced anticancer activity, the results of which will be disclosed in due course.

Supplemental material

Supplementary material is available with the article through the journal Web site at <http://nrcresearchpress.com/doi/suppl/x/cjc-y>. Crystallographic information has also been deposited with the Cambridge Crystallographic Data Centre (CCDC 1496145). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

Thanks are gratefully extended to Mount Allison University, the Université de Moncton, the Canada Research Chair Program and NSERC for financial support. We also thank Dan Thumbduran (Mount Allison University) for his expert technical assistance and anonymous reviewers are thanked for their very helpful comments.

References

1. General reviews on the therapeutic uses of boron-compounds: (a) Baker, S. J.; Ding, C. Z.; Akama, T.; Zhang, Y.-K.; Hernandez, V.; Xia, Y. *Future Med. Chem.* **2009**, *1*, 1275. (b) Zhang, J.; Zhu, M. Y.; Lin, Y.-N.; Zhou, H.-C. *Sci. China Chem.* **2013**, *56*, 1372. (c) Ellis, G. A.; Palte, M. J.; Raines, R. T. *J. Am. Chem. Soc.* **2012**, *134*, 3631. (d) Soriano-Ursúa, M. A.; Das, B. C.; Trujillo-Ferrara, J. G. *Expert Opin. Ther. Patents* **2014**, *24*, 485. (e) Adamczyk-Woźniak, A.; Cyrański, M. K.; Żubrowska, A.; Sporzyński, A. *J. Organomet. Chem.* **2009**, *694*, 3533. (f) Kahlert, J.; Austin, C. J. D.; Kassiou, M.; Rendina, L. M. *Aust. J. Chem.* **2013**, *66*, 1118. (g) Řezanka, T.; Sigler, K. *Phytochemistry* **2008**, *69*, 585. (h) Armstrong, A. F.; Valliant, J. F. *Dalton Trans.* **2007**, 4240. (i) Ahmet, J. T.; Spencer, J. *Future Med. Chem.* **2013**, *5*, 621. (j) Groziak, M. P. *Am. J. Therap.* **2001**, *8*, 321.
2. Boron-compounds with enzyme-inhibition properties: (a) Touchet, S.; Carreaux, F.; Carboni, B.; Bouillon, A.; Boucher, J.-L. *Chem. Soc. Rev.*

- 2011**, 40, 3895. (b) Baker, S. J.; Tomsho, J. W.; Benkovic, S. J. *Chem. Soc. Rev.* **2011**, 40, 4279. (c) Adachi, S.; Cognetta III, A. B.; Niphakis, M. J.; He, Z.; Zajdlik, A.; St. Denis, J. D.; Cravatt, B. F.; Yudin, A. K. *Chem. Commun.* **2015**, 51, 3608. (d) Troiano, V.; Scarbaci, K.; Ettari, R.; Micale, N.; Cerchia, C.; Pinto, A.; Schirmeister, A.; Novellino, E.; Grasso, S.; Lavecchia, A.; Zappalà, M. *Eur. J. Med. Chem.* **2014**, 83, 1. (e) Matteson, D. S. *Med. Res. Rev.* **2008**, 28, 233. (f) Gallardo-Williams, M. T.; Maronpot, R. R.; Wine, R. N.; Brunssen, S. H.; Chapin, R. E. *Prostate* **2003**, 54, 44. (g) St. Denis, J. D.; Lee, C. F.; Yudin, A. K. *Org. Lett.* **2015**, 17, 5764. (h) Li, A. C.; Yu, E.; Ring, S. C.; Chovan, J. P. *Chem. Res. Toxicol.* **2013**, 26, 608. (i) Shi, J.; Lei, M.; Wu, W.; Feng, H.; Wang, J.; Chen, S.; Zhu, Y.; Hu, S.; Liu, Z.; Jiang, C. *Bioorg. Med. Chem. Lett.* **2016**, 26, 1958. (j) Freund, Y. R.; Akama, T.; Alley, M. R. K.; Antunes, J.; Dong, C.; Jarnagin, K.; Kimura, R.; Nieman, J. A.; Maples, K. R.; Plattner, J. J.; Rock, F.; Sharma, R.; Singh, R.; Sanders, V.; Zhou, Y. *FEBS Lett.* **2012**, 586, 3410. (k) Jagannathan, S.; Forsyth, T. P.; Kettner, C. A. *J. Org. Chem.* **2001**, 66, 6375.
3. Boron-compounds with antimicrobial properties: (a) Dembitsky, V. M.; Al Quntar, A. A. A.; Srebnik, M. *Chem. Rev.* **2011**, 111, 209. (b) Baker, S. J.; Zhang, Y.-K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R. K.; Sanders, V.; Plattner, J. J. *J. Med. Chem.* **2006**, 49, 4447. (c) Fontaine, F.; Hequet, A.; Voisin-Chiret, A.-S.; Bouillon, A.; Lesnard, A.; Cresteil, T.; Jolival, C.; Rault, S. *J. Med. Chem.* **2014**, 57,

2536. (d) Kanichar, D.; Roppiyakuda, L.; Kosmowska, E.; Faust, M. A.; Tran, K. P.; Chow, F.; Groziak, M. P.; Sarina, E. A.; Olmstead, M. M.; Silva, I.; Xu, H. H. *Chem. Biodivers.* **2014**, *11*, 1381. (e) Irving, A. M.; Vogels, C. M.; Nikolcheva, L. G.; Edwards, J. P.; He, X.-F.; Hamilton, M. G.; Baerlocher, M. O.; Baerlocher, F. J.; Decken, A.; Westcott, S. A. *New J. Chem.* **2003**, *27*, 1419. (f) Printsevskaya, S. S.; Reznikova, M. I.; Korolev, A. M.; Lapa, G. B.; Olsufyeva, E. N.; Preobrazhenskaya, M. N.; Plattner, J. J.; Zhang, Y. K. *Future Med. Chem.* **2013**, *5*, 641. (g) Hernandez, V.; Crépin, T.; Palencia, A.; Cusack, S.; Akama, T.; Baker, S. J.; Bu, W.; Feng, L.; Freund, Y. R.; Liu, L.; Meewan, M.; Mohan, M.; Mao, W.; Rock, F. L.; Sexton, H.; Sheoran, A.; Zhang, Y.; Zhang, Y.-K.; Zhou, Y.; Nieman, J. A.; Anugula, M. R.; Keramane, E. M.; Savarirak, K.; Reddy, D. S.; Sharma, R.; Subedi, R.; Singh, R.; O'Leary, A.; Simon, N. L.; De Marsh, P. L.; Mushtaq, S.; Warner, M.; Livermore, D. M.; Alley, M. R. K.; Plattner, J. J. *Antimicrob. Agents Chemother.* **2013**, *57*, 1394. (h) Wieczorek, D.; Lipok, J.; Borys, K. M.; Adamczyk-Woźniak, A.; Sporzyński, A. *Appl. Organomet. Chem.* **2014**, *28*, 347. (i) Gozhina, O. V.; Svendsen, J.-S.; Lejon, T. *J. Pept. Sci.* **2014**, *20*, 20. (j) Brzozowska, A.; Ćwik, P.; Durka, K.; Kliś, T.; Laudy, A. E.; Luliński, S.; Serwatowski, J.; Tyski, S.; Urban, M.; Wróblewski, W. *Organometallics* **2015**, *34*, 2924. (k) Baldock, C.; de Boer, G.-J.; Rafferty, J. B.; Stuitje, A. R.; Rice, D. W. *Biochem. Pharmacol.* **1998**, *55*, 1541. (l) Rock, F. L.; Mao, W.; Yaremchuk, A.; Tukalo, M.; Crépin, T.; Zhou, H.; Zhang, Y.-K.

- Hernandez, V.; Akama, T.; Baker, S. J.; Plattner, J. J.; Shapiro, L.; Martinis, S. A.; Benkovic, S. J.; Cusack, S.; Alley, M. R. K. *Science* **2007**, *316*, 1759. (m) Vilchis, M.; Velasco, B.; Penierres, G.; Cruz, T.; Miranda, R.; Nicolás, I. *Molbank*, **2009**, M600, doi:10.3390/M600. (n) Trivedi, R.; Reddy, E. R.; Kumar, C. K.; Sridhar, B.; Kumar, K. P.; Rao, M. S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3890. (o) Reddy, E. R.; Trivedi, R.; Kumar, B. S.; Sirisha, K.; Sarma, A. V. S.; Sridhar, B.; Prakasham, R. S. *Bioorg. Med. Chem. Lett.* **2016**, doi:10.1016/j.bmcl.2016.06.049.
4. Boron-compounds with antimycobacterial properties: (a) Alam, M. A.; Arora, K.; Gurrapu, S.; Jonnalagadda, S. K.; Nelson, G. L.; Kiprof, P.; Jonnalagadda, S. C.; Mereddy, V. R. *Tetrahedron* **2016**, *72*, 3795. (b) Campbell-Verduyn, L. S.; Bowes, E. G.; Li, H.; Vallée, A. M.; Vogels, C. M.; Decken, A.; Gray, C. A.; Westcott, S. A. *Heteroatom Chem.* **2014**, *25*, 100. (c) Gorovoy, A. S.; Gozhina, O. V.; Svendsen, J.-S.; Tetz, G. V.; Domorad, A.; Tetz, V. V.; Lejon, T. *J. Pept. Sci.* **2013**, *19*, 613. (d) Gorovoy, A. S.; Gozhina, O. V.; Svendsen, J.-S.; Domorad, A.; Tetz, G. V.; Tetz, V. V.; Lejon, T. *Chem. Biol. Drug Des.* **2013**, *81*, 408. (e) Adamska, A.; Rumijowska-Galewicz, A.; Ruszczynska, A.; Studzińska, M.; Jabłońska, A.; Paradowska, E.; Bulska, E.; Munier-Lehmann, H.; Dziadek, J.; Leśnikowski, Z. J.; Olejniczak, A. B. *Eur. J. Med. Chem.* **2016**, *121*, 71. (f) Wardell, J. L.; de Souza, M. V. N.; Wardell, S. M. S. V.; Lourenço, M. C. S. *J. Mol. Struct.* **2011**, *990*, 67.

5. Boron-compounds with signal transduction and optical properties: (a) Hofer, A.; Kovacs, G.; Zappatini, A.; Leuenberger, M.; Hediger, M. A.; Lochner, M. *Bioorg. Med. Chem.* **2013**, 21, 3202. (b) Morera, E.; Di Marzo, V.; Monti, L.; Allarà, M.; Schiano Moriello, A.; Nalli, M.; Ortar, G.; De Petrocellis, L. *Bioorg. Med. Chem. Lett.* **2016**, 26, 1401. (c) Chung, M.-K.; Lee, H.; Mizuno, A.; Suzuki, M.; Caterina, M. J. *J. Neurosci.* **2004**, 24, 5177. (d) Hu, H.-Z.; Gu, Q.; Wang, C.; Colton, C. K.; Tang, J.; Kinoshita-Kawada, M.; Lee, L.-Y.; Wood, J. D.; Zhu, M. X. *J. Biol. Chem.* **2004**, 279, 35741. (e) Barbon, S. M.; Staroverov, V. N.; Boyle, P. D.; Gilroy, J. B. *Dalton Trans.* **2014**, 43, 240. (f) Kumbhar, H. S.; Deshpande, S. S.; Shankarling, G. S. *Dye Pigm.* **2016**, 127, 161.
6. Boron-compounds with anticancer properties: (a) Jiang, Q.; Zhong, Q.; Zhang, Q.; Zheng, S.; Wang, G. *ACS Med. Chem. Lett.* **2012**, 3, 392. (b) Moreira, V. M.; Salvador, J. A. R.; Simões, S.; Destro, F.; Gavioli, R. *Eur. J. Med. Chem.* **2013**, 63, 46. (c) Achilli, A.; Jadhav, S. A.; Guidetti, G. F.; Ciana, A.; Abbonate, V.; Malara, A.; Fagnoni, M.; Torti, M.; Balduini, A.; Balduini, C.; Minetti, G. *Chem. Biol. Drug Des.* **2014**, 83, 532. (d) Nizioł, J.; Zieliński, Z.; Leś, A.; Dąbrowska, M.; Rode, W.; Ruman, T. *Bioorg. Med. Chem.* **2014**, 22, 3906. (e) Xu, W.; Ding, J.; Li, L.; Xiao, C.; Zhuang, X.; Chen, X. *Chem. Commun.* **2015**, 51, 6812. (f) Canturk, Z.; Tunali, Y.; Korkmaz, S.; Gulbaş, Z. *Cytotechnology* **2016**, 68, 87. (g) Barranco, W. T.; Eckhert, C. D. *Br. J. Cancer* **2006**, 94, 884. (h) Scorei, R.; Ciubar, R.; Ciofrangeanu, C. M.; Mitran, V.; Cimpean, A.; Iordachescu, D. *Biol. Trace*

- Elem. Res.* **2008**, 122, 197. (i) Marepally, S. R.; Yao, M.-L.; Kabalka, G. W. *Future Med. Chem.* **2013**, 5, 693. (j) Wang, L.; Xie, S.; Ma, L.; Chen, Y.; Lu, W. *Eur. J. Med. Chem.* **2016**, 116, 84.
7. Boron-compounds with anti-inflammatory properties: (a) Maeda, D. Y.; Peck, A. M.; Schuler, A. D.; Quinn, M. T.; Kirpotina, L. N.; Wicomb, W. N.; Fan, G.-H.; Zebala, J. A. *J. Med. Chem.* **2014**, 57, 8378. (b) Baker, S. J.; Akama, T.; Zhang, Y.-K.; Sauro, V.; Pandit, C.; Singh, R.; Kully, M.; Khan, J.; Plattner, J. J.; Benkovic, S. J.; Lee, V.; Maples, K. R. *Bioorg. Med. Chem. Lett.* **2006**, 16, 5963. (c) Akama, T.; Baker, S. J.; Zhang, Y.-K.; Hernandez, V.; Zhou, H.; Sanders, V.; Freund, Y.; Kimura, R.; Maples, K. R.; Plattner, J. J. *Bioorg. Med. Chem. Lett.* **2009**, 19, 2129.
8. Boron-compounds with other bioactivities: (a) Gray, Jr., C. W.; Walker, B. T.; Foley, R. A.; Houston, T. A. *Tetrahedron Lett.* **2003**, 44, 3309. (b) Sarker, T.; Selvakumar, K.; Motiei, L.; Margulies, D. *Nat. Commun.* **2016**, 7, 11374. (c) Jacobs, R. T.; Plattner, J. J.; Keenan, M. *Curr. Opin. Infect. Dis.* **2011**, 24, 586. (d) Cal, P. M. S. D.; Vicente, J. B.; Pires, E.; Coelho, A. V.; Veiros, L. F.; Cordeiro, C.; Gois, P. M. P. *J. Am. Chem. Soc.* **2012**, 134, 10299. (e) Feeney, R. E.; Osuga, D. T.; Yeh, Y. *J. Protein Chem.* **1991**, 10, 167. (f) Groziak, M. P.; Chen, L.; Yi, L.; Robinson, P. D. *J. Am. Chem. Soc.* **1997**, 119, 7817. (g) Duggan, P. J.; Houston, T. A.; Kiefel, M. J.; Levonis, S. M.; Smith, B. D.; Szydzik, M. L. *Tetrahedron* **2008**, 64, 7122. (h) Wu, G.-F.; Xu, M. *BioResources* **2014**, 9, 4173. (i) Zhang, Y.-K.; Plattner, J. J.; Easom, E. E.; Zhou, Y.; Akama, T.; Bu, W.; White, W. H.;

- Defauw, J. M.; Winkle, J. R.; Balko, T. W.; Guo, S.; Xue, J.; Cao, J.; Zou, W. *Bioorg. Med. Chem. Lett.* **2015**, 25, 5589.
9. (a) Woodhouse, S. L.; Rendina, L. M. *Dalton Trans.* **2004**, 3669. (b) Woodhouse, S. L.; Ziolkowski, E. J.; Rendina, L. M. *Dalton Trans.* **2005**, 2827. (c) Ching, H. Y. V.; Clegg, J. K.; Rendina, L. M. *Dalton Trans.* **2007**, 2121. (d) Hosseini, S. S.; Bhadbhade, M.; Clarke, R. J.; Rutledge, P. J.; Rendina, L. M. *Dalton Trans.* **2011**, 40, 506.
10. Miller, M. A.; Askevold, B.; Yang, K. S.; Kohler, R. H.; Weissleder, R. *ChemMedChem* **2014**, 9, 1131.
11. (a) Schikora, M.; Reznikov, A.; Chaykovskaya, L.; Sachinska, O.; Polyakova, L.; Mokhir, A. *Bioorg. Med. Chem. Lett.* **2015**, 25, 3447. (b) Daum, S.; Chekhun, V. F.; Todor, I. N.; Lukianova, N. Y.; Shvets, Y. V.; Sellner, L.; Putzker, K.; Lewis, J.; Zenz, T.; de Graaf, I. A.; Groothuis, G. M.; Casini, A.; Zozulia, O.; Hampel, F.; Mokhir, A. *J. Med. Chem.* **2015**, 58, 2015. (c) Yadav, S.; Singh, R. V. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2011**, 78, 298. (d) Reddy, E. R.; Trivedi, R.; Giribabu, L.; Sridhar, B.; Kumar, K. P.; Rao, M. S.; Sarma, A. V. S. *Eur. J. Inorg. Chem.* **2013**, 5311.
12. Reddy, E. R.; Trivedi, R.; Sarma, A. V. S.; Sridhar, B.; Anantaraju, H. S.; Sriram, D.; Yogeeswari, P.; Nagesh, N. *Dalton Trans.* **2015**, 44, 17600.
13. (a) Zhang, H.; Norman, D. W.; Wentzell, T. M.; Darwish, H. A.; Irving, A. M.; Edwards, J. P.; Wheaton, S. L.; Baerlocher, F. J.; Vogels, C. M.; Decken, A.; Westcott, S. A. *Trans. Met. Chem.* **2005**, 30, 63. (b) Scales, S.

- J.; Darwish, H. A.; Horton, J. L.; Nikolcheva, L. G.; Zhang, H.; Vogels, C. M.; Saleh, M.; Ireland, R. J.; Decken, A.; Westcott, S. A. *Can. J. Chem.* **2004**, 82, 1692.
14. (a) Johnstone, T. C.; Wilson, J. J.; Lippard, S. J. *Inorg. Chem.* **2013**, 52, 12234. (b) Patra, M.; Johnstone, T. C.; Suntharalingam, K.; Lippard, S. J. *Angew. Chem. Int. Ed.* **2016**, 55, 2550. (c) Vaughan, T. F.; Koedyk, D. J.; Spencer, J. L. *Organometallics* **2011**, 30, 5170. (d) Johnstone, T. C.; Suntharalingam, K.; Lippard, S. J. *Chem. Rev.* **2016**, 116, 3436. (e) Dilruba, S.; Kalayda, G. V. *Cancer Chemother. Pharmacol.* **2016**, 77, 1103.
15. Shaver, M. P.; Vogels, C. M.; Wallbank, A. I.; Hennigar, T. L.; Biradha, K.; Zaworotko, M. J.; Westcott, S. A. *Can. J. Chem.* **2000**, 78, 568.
16. Chen, X.; Femia, F. J.; Babich, J. W.; Zubieta, J. *Inorg. Chim. Acta* **2001**, 315, 147.
17. SAINT 7.23A; Bruker AXS, Inc., Madison, Wisconsin, USA, 2006.
18. Sheldrick, G. M. *SADABS 2008*; Bruker AXS, Inc., Madison, Wisconsin, USA, 2008.
19. Sheldrick, G. M. *Acta Crystallogr.* **2008**, A64, 112.
20. Ishii, N.; Maier, D.; Merlo, A.; Tada, M.; Sawamura, Y.; Diserens, A. C.; Van Meir, E. G. *Brain Pathol.* **1999**, 9, 469.
21. (a) Chiririwa, H.; Moss, J. R.; Hendricks, D.; Smith, G. S.; Meijboom, R. *Polyhedron* **2013**, 49, 29. (b) Chiririwa, H.; Meijboom, R. *Acta Cryst.* **2011**, E67, m1497. (c) Motswainyana, W. M.; Onani, M. O.; Madiehe, A.

- M.; Saibu, M.; Thovhogi, N.; Lalancette, R. A. *J. Inorg. Biochem.* **2013**, 129, 112.
22. (a) Henderson, W.; Alley, S. R.; *Inorg. Chim. Acta* **2001**, 322, 106. (b) Quiroga, A. G.; Ramos-Lima, F. J.; Álvarez-Valdés, A.; Font-Bardía, M.; Bergamo, A.; Sava, G.; Navarro-Ranninger, C. *Polyhedron* **2011**, 30, 1646. (c) Dalla Via, L.; García-Argáez, A. N.; Agostinelli, E.; Dell'Amico, D. B.; Labella, L.; Samaritani, S. *Bioorg. Med. Chem.* **2016**, 24, 2929. (d) Fourie, E.; Erasmus, E.; Swarts, J. C.; Jakob, A.; Lang, H.; Joone, G. K.; Van Rensburg, C. E. J. *Anticancer Res.* **2011**, 31, 825. (e) Villarreal, W.; Colina-Vegas, L.; de Oliveira, C. R.; Tenorio, J. C.; Ellena, J.; Gozzo, F. C.; Cominetti, M. R.; Ferreira, A. G.; Ferreira, M. A. B.; Navarro, M.; Batista, A. A. *Inorg. Chem.* **2015**, 54, 11709. (f) Medrano, M. A.; Álvarez-Valdés, A.; Perles, J.; Lloret-Fillol, J.; Muñoz-Galván, S.; Carnero, A.; Navarro-Ranninger, C.; Quiroga, A. G. *Chem. Commun.* **2013**, 49, 4806. (g) Řezníček, T.; Dostál, L.; Růžicka, A.; Vinklársek, J.; Řezáčová, J. R. *Appl. Organomet. Chem.* **2012**, 26, 237. (h) Bergamini, P.; Bertolasi, V.; Marvelli, L.; Canella, A.; Gavioli, R.; Mantovani, N.; Mañas, S.; Romerosa, A. *Inorg. Chem.* **2007**, 46, 4267. (i) Guerrero, E.; Miranda, S.; Lüttenberg, S.; Fröhlich, N.; Koenen, J.-M.; Mohr, F.; Cerrada, E.; Laguna, M.; Mendiá, A. *Inorg. Chem.* **2013**, 52, 6635. (j) Ramos-Lima, F. J.; Quiroga, A. G.; García-Serrelde, B.; Blanco, F.; Carnero, A.; Navarro-Ranninger, C. *J. Med. Chem.* **2007**, 50, 2194. (k) Shi, J.-C.; Yueng, C.-H.; Wu, D.-X.; Liu, Q.-T.; Kang, B.-S. *Organometallics* **1999**, 18, 3796.

23. Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer-Verlag: Berlin, 1978.
24. Maluenda, I.; Navarro, O. *Molecules* **2015**, *20*, 7528.
25. (a) Hawkeswood, S.; Stephan, D. W. *Dalton Trans.* **2005**, 2182. (b) Hawkeswood, S.; Wei, P.; Gault, J. W.; Stephan, D. W. *Inorg. Chem.* **2005**, *44*, 4301.
26. (a) Margiotta, N.; Denora, N.; Ostuni, R.; Laquintana, V.; Anderson, A.; Johnson, S. W.; Trapani, G.; Natile, G. *J. Med. Chem.* **2010**, *53*, 5144. (b) Maksimović-Ivanić, D.; Mijatović, S.; Mirkov, I.; Stošić-Grujičić, S.; Miljković, D.; Sabo, T. J.; Trajković, V.; Kaluđerović, G. N. *Metallomics* **2012**, *4*, 1155. (c) Mihajlović, L. E.; Savić, A.; Poljarević, J.; Vučković, I.; Mojić, M.; Bulatović, M.; Maksimović-Ivanić, D.; Mijatović, S.; Kaluđerović, G. N.; Stošić-Grujičić, S.; Miljković, D.; Grgurić-Šipka, S.; Sabo, T. J. *J. Inorg. Biochem.* **2012**, *109*, 40. (d) Gwak, H.-S.; Shingu, T.; Chumbalkar, V.; Hwang, Y.-H.; DeJournett, R.; Latha, K.; Koul, D.; Yung, W. K. A.; Powis, G.; Farrell, N. P.; Böglér, O. *Int. J. Cancer* **2011**, *128*, 787. (e) Charest, G.; Paquette, B.; Fortin, D.; Mathieu, D.; Sanche, L. *J. Neurooncol.* **2010**, *97*, 187. (f) Soares, M. A.; Mattos, J. L.; Pujatti, P. B.; Leal, A. S.; dos Santos, W. G.; dos Santos, R. G. *J. Radioanal. Nucl. Chem.* **2012**, *292*, 61. (g) Patole, J.; Padhye, S.; Moodbidri, M. S.; Shirsat, N.; *Eur. J. Med. Chem.* **2005**, *40*, 1052. (h) Yildirim, H.; Köçkar, F.; Nakıboğlu, C. *Afr. J. Biotech.* **2012**, *11*, 12422. (i) Biston, M.-C.; Joubert, A.; Charvet, A.-M.; Balosso, J.; Foray, N. *Radiat. Res.* **2009**,

- 172, 348. (j) Billecke, C.; Malik, I.; Movsisyan, A.; Sulghani, S.; Sharif, A.; Mikkelsen, T.; Farrell, N. P.; Böglér, O. *Mol. Cell. Proteomics* **2006**, 5, 35.
- (k) Stanzione, S.; Cimoli, G.; Debernardis, D.; Michelotti, A.; Conte, P.; Parodi, S.; Russo, P. *Mutat. Res.* **1995**, 348, 131.
27. Stupp, R.; Mason, W. P.; van den Bent, M.J.; Weller, M.; Fisher, B.; Taphoorn, M. J.; Belanger, K.; Brandes, A. A.; Marosi, C.; Bogdahn, U.; Curschmann, J.; Janzer, R. C.; Ludwin, S. K.; Gorlia, T.; Allgeier, A.; Lacombe, D.; Cairncross, J. G.; Eisenhauer, E.; Mirimanoff, R. O. *New Engl. J. Med.* **2005**, 352, 987.
28. Capdevila, L.; Cros, S.; Ramirez, J. L.; Sanz, C.; Carrato, C.; Romeo, M.; Etxaniz, O.; Hostalot, C.; Massuet, A.; Cuadra, J. L.; Villà, S.; Balañà, C. *J. Neurooncol.* **2014**, 117, 77.

Table 1. Crystallographic data collection parameters for **8**.

Complex	8
Formula	C ₃₄ H ₃₇ BCl ₂ NO ₃ PPt
Molecular weight	815.42
Crystal system	Orthorhombic
Space group	Pbca
<i>a</i> (Å)	10.5021(14)
<i>b</i> (Å)	23.362(3)
<i>c</i> (Å)	27.406(4)
α (°)	90
β (°)	90
γ (°)	90
<i>V</i> (Å ³)	6724.0(15)
<i>Z</i>	8
$\rho_{\text{calc.}}$ (mg/m ⁻³)	1.611
Crystal size (mm ³)	0.20 x 0.10 x 0.05
Temp (K)	173(1)
Radiation	Mo- <i>K</i> _α (λ =0.71073 Å)
μ (mm ⁻¹)	4.414
Total reflections	44505
Total unique reflections	7607
No. of variables	394
θ Range (°)	1.49-27.50
Largest difference peak/hole (e/Å ⁻³)	1.614 and -0.577
S (goodness-of-fit) on <i>F</i> ²	1.072
<i>R</i> ₁ [<i>I</i> >2 <i>s</i> (<i>I</i>)] ^a	0.0265
<i>wR</i> ₂ (all data) ^b	0.0692

$$^a R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|.$$

$$^b wR_2 = (\sum [w(F_o^2 - F_c^2)^2] / \sum [wF_o^4])^{1/2}, \text{ where } w = 1 / [\sigma^2(F_o^2) + (0.0270P)^2 + (11.6591P)], \text{ where } P = (\max(F_o^2, 0) + 2F_c^2) / 3.$$