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Multinuclear platinum(II)–amine complexes containing bis(aminopropyl)dicarba-*closo*-dodecaborane(12) ligands

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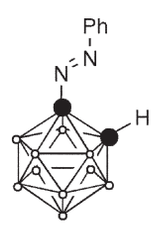
Treatment of the bridging bidentate 1,*Z*-bis(aminopropyl)-1,*Z*-dicarba-*closo*-dodecaborane(12) (1,*Z*-bis(aminopropyl)-1,*Z*-carborane) ligands of the type 1,*Z*-{$H_2N(CH_2)_3$}$_2$-1,*Z*-$C_2B_{10}H_{10}$ (L^1, Z = 7, **5**) or (L^2, Z = 12, **6**) with two equivalents of *trans*-[$PtClI_2(NH_3)$]$^-$, followed by halogen ligand metathesis with AgOTf and $HCl_{(aq)}$ afforded the novel diplatinum(II)–amine species *cis*-[{$PtCl_2(NH_3)$}$_2L^n$] (**7** (n = 1) or **8** (n = 2), respectively). Similarly, the reaction of L^1 or L^2 with the labile *trans*-[$PtCl(dmf)(NH_3)_2$]$^+$ afforded *trans*-[{$PtCl(NH_3)_2$}$_2L^n$]$(OTf)_2$ (**9** (n = 1) or **10** (n = 2), respectively) in good yield and purity. However, isolation of the analogous 1,2-carborane complexes was not possible owing to decomposition reactions that led to extensive degradation of the carborane cage and reduction of the metal centre. The mixed dinuclear complex [*cis*-{$PtCl_2(NH_3)$}–L^1-*trans*-{$PtCl(NH_3)_2$}]OTf (**19**) was prepared by treatment of the Boc-protected amine ligand 1-{$(Boc)_2N(CH_2)_3$}-7-{$H_2N(CH_2)_3$}-1,7-$C_2B_{10}H_{10}$ (L^3, **15**) with *trans*-[$PtCl(dmf)(NH_3)_2$]$^+$ to yield *trans*-[$PtCl(NH_3)_2L^3$]OTf (**16**), followed by acid deprotection of the pendant amine group, complexation with *trans*-[$PtClI_2(NH_3)$]$^-$, and halogen ligand metathesis using AgOTf and $HCl_{(aq)}$. A novel trinuclear species containing **5** was prepared by the addition of two equivalents of **15** to the labile precursor *cis*-[$Pt(dmf)_2(NH_3)_2$]$^{2+}$ followed by acid deprotection of the pendant amine groups. Further complexation with two equivalents of *trans*-[$PtClI_2(NH_3)$]$^-$ followed by halogen ligand metathesis using AgOTf and $HCl_{(aq)}$ afforded the triplatinum(II)–amine species [*cis*-{$Pt(NH_3)_2(L^1)_2$}-*cis*-{$PtCl_2(NH_3)$}$_2$]$(OTf)_2$ (**23**). Complexes **7–10**, **19** and **23** represent the first examples of multinuclear platinum(II)–amine derivatives containing carborane cages. Preliminary *in vitro* cytotoxicity studies for selected complexes are also reported.

Introduction

Boron neutron capture therapy (BNCT) is an experimental cancer treatment that is currently undergoing Phase I/II clinical trials in several countries.[1–4] The key aspect of the therapy is the interaction of slow (thermal) neutrons with ^{10}B-containing drugs that are localised within malignant cells. The resulting nuclear reactions with the ^{10}B nucleus ultimately lead to cell destruction owing to the production of high linear energy transfer (LET) particles that are accompanied by approximately 2.4 MeV of kinetic energy. The effectiveness of the neutron capture reaction is dramatically enhanced if ^{10}B-containing compounds are placed in close proximity to chromosomal DNA,[5–7] and the search for new DNA-binding agents with relevance to BNCT remains a major research objective.[8]

Farrell and co-workers have developed an extensive series of multinuclear platinum(II) complexes bridged by linear or substituted aliphatic linkers that possess a greater affinity for DNA than the archetypal platinum anti-cancer agent cisplatin.[9–14] This class of 'non-classical' DNA-binding agents has been comprehensively studied and extended to include variations in the number of platinum(II) centres, linker lengths, bi-, tri- and tetra-functionality, and coordination geometry that allow a diverse array of unique adducts to be formed with DNA. The study of multinuclear platinum(II) complexes has resulted in the development of a trinuclear platinum(II) complex known as BBR3464, the first representative of the 'non-classical' class of multinuclear platinum(II) anti-cancer drugs to enter clinical trials.[12,15–17] The rapid DNA binding of complexes such as the highly-charged BBR3464 results in high levels of platination.[11,18] The DNA adducts persist over time, implying poor DNA-adduct repair, and thus contribute to a more persistent perturbation of the cell cycle than cisplatin.[12] Indeed, the use of multinuclear complexes as tumour delivery agents for boron clusters may potentially combine the favourable aspects of platinum chemotherapy and BNCT if such complexes are capable of demonstrating persistent DNA-binding within tumour cells in addition to localising adequate concentrations of ^{10}B near chromosomal DNA.

The coordination chemistry of *closo*-carboranes (dicarba-*closo*-dodecaboranes(12)) bearing N-donor groups, *e.g.* phenylazo **1**, *N*,*N*-dimethylamino **2**, and alkylamino **3** (n = 1–3) is an area of increasing interest.[19] Zakharkin and co-workers reviewed the preparation of a series of cyclometallated Group 7 complexes and a dinuclear palladium(II) species containing **1** or **2** in which the carborane derivative acts as a chelating ligand and forms a M–B bond that is stabilised by intramolecular coordination of the nearby N-donor atom.[20] Kang and co-workers have reported the organometallic chemistry of **2** with gallium(III),[21] tin(IV),[22] mercury(II)[22] and



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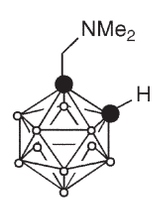

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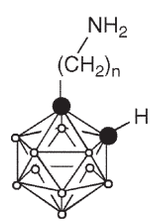

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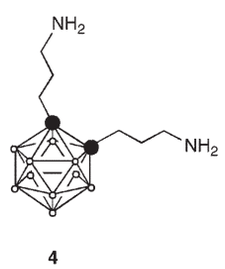
Group 9 and 10 transition metals[23] whereby the carborane is bonded to the metal centre *via* one of the carbon atoms rather than a proximal boron atom. In contrast, the coordination chemistry of **3** had not been explored until recently when the first examples of mononuclear platinum(II)–amine complexes containing this ligand ($n = 1$, 3) were reported.[24] Herein we report the preparation and characterisation of related di- and tri-nuclear platinum(II)–amine complexes containing bridging bidentate diamine ligands that incorporate a *closo*-1,12- or 1,7-carborane entity. A preliminary communication of this work has been reported.[25]

Results and discussion

The bis(aminopropyl)carborane ligands **4** and **5** were prepared from the respective parent carboranes according to the literature procedure established for the corresponding 1,12-carborane isomer **6**.[26] The HCl salts of **4**–**6** were isolated as stable, colourless powders that could be stored at room temperature for indefinite periods of time. The free amines were freshly prepared prior to the complexation reactions by treatment of an aqueous solution containing the corresponding HCl salt with an excess of K_2CO_3 in the presence of CH_2Cl_2.



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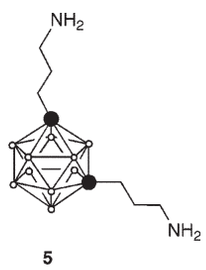

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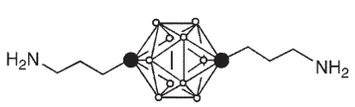

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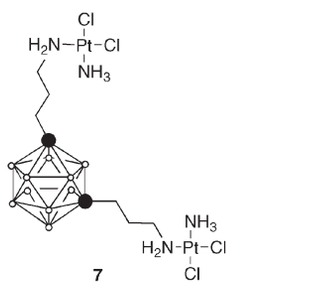
The preparation of a diplatinum(II)–amine species containing a *closo*-1,2-carborane entity was attempted by the reaction of **4** with two equivalents of $K[PtCl_3(NH_3)]$ in DMF–H_2O or MeOH–H_2O solvent mixtures. However, the isolated yellow solid proved to be quite unstable and it discoloured upon purification and/or standing for extended periods of time. $^{11}B\{^1H\}$ NMR spectroscopy confirmed extensive degradation of the *closo*-carborane cage in **4**, a process that was accompanied by reduction of the platinum(II) centre to afford colloidal platinum and/or an unidentified dark material that is soluble in organic solvents and is likely to be a low-valent cluster species containing Pt–Pt bonding. This phenomenon has recently been described in detail for related mononuclear complexes,[24] and the decomposition process is most probably initiated by nucleophilic attack of the amine functionality on the *closo*-1,2-carborane cage to generate the corresponding *nido* species, the rate of which is greatly enhanced by the presence of water.[27] The decomposition of the platinum(II) complex containing **4** was found to be slower than that observed for the related mononuclear complexes,[24] especially under anhydrous conditions, demonstrating that the bifunctionalisation of 1,2-carborane somewhat increases the stability of the platinum(II)–amine derivatives perhaps due to steric factors. It was also found that the degradation process could be retarded significantly by lowering the pH of the solution (pH < 2). However, under such conditions the free amines are fully protonated and the complexation did not proceed to completion.

The reaction of **5** with two equivalents of $K[PtCl_3(NH_3)]$ afforded the corresponding dinuclear complex **7** with a *cis*-dichloro geometry, as indicated by the characteristic singlet resonance in the $^{195}Pt\{^1H\}$ NMR spectrum at δ −2156 that is consistent with a $PtCl_2N_2$ core.[28] However, a minor impurity signal was sometimes observed at δ −2462. While the identity of this impurity remains unconfirmed, the chemical shift is consistent with a PtN_3Cl complex,[28] *e.g.* a 1 : 1 mononuclear complex containing an *N*,*N*-chelate ring. It proved extremely difficult to purify **7** by recrystallisation methods alone and, in order to increase its purity, $K[PtCl_3(NH_3)]$ was treated with an excess of KI to generate *trans*-$[PtClI_2(NH_3)]^-$ *in situ* prior to the reaction with **5** or **6**. Farrell and co-workers have demonstrated that amine ligands L readily displace either one of the iodo ligands in *trans*-$[PtClI_2(NH_3)]^-$ to give the neutral mixed-halogen complex $[PtClI(NH_3)(L)]$ in which L is located *trans* to the iodo ligand.[29] Thus, treatment of $[PtClI_2(NH_3)]^-$ with **5** followed by the sequential addition of four equivalents of $AgNO_3$ and 0.1 M HCl afforded the desired **7** with a *cis*-dichloro geometry. Under identical conditions, **6** was converted into the corresponding dinuclear platinum(II) species **8**. Once again, the formation of **7** and **8** was confirmed by a characteristic resonance in the $^{195}Pt\{^1H\}$ NMR spectrum at δ −2156 and −2155, respectively.



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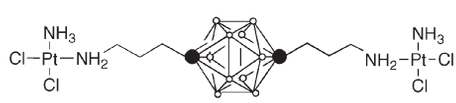

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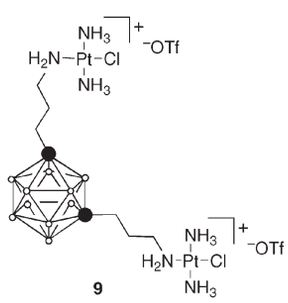

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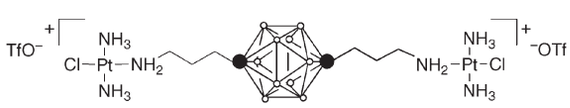

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Treatment of the diamine ligand **5** or **6** with two equivalents of the labile *trans*-$[PtCl(dmf)(NH_3)_2]^+$ afforded the corresponding dinuclear complexes **9** and **10** with characteristic resonances in the $^{195}Pt\{^1H\}$ NMR spectrum at δ −2410 and −2409, respectively. The chemical shifts of these resonances are consistent with a complex possessing a PtN_3Cl core.[28]

The platinum derivatives **7**–**10** display an extensive broadening of the ^{11}B NMR signals (both ^1H-coupled and decoupled) at room temperature which does not allow the determination of ^{11}B–^1H coupling constants, or indeed, adequate resolution of the individual resonances in the case of 1,7-carborane derivatives such as **7** and **9**. This effect is most likely attributed to the slow

tumbling in solution of these large molecular entities containing quadrupolar ^{11}B nuclei which would increase the molecular correlation time (τ_c) and thus shorten T_1.[30]

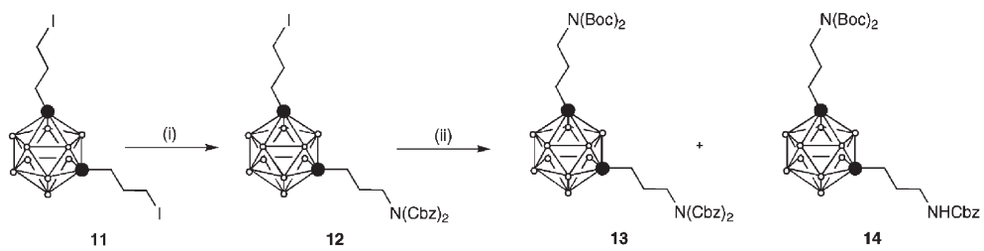
The preparation of di- and tri-nuclear complexes containing mixed platinum(II) centres required that the amine groups in **5** were protected using both Boc (*tert*-butoxycarbonyl) and Cbz (benzyloxycarbonyl) thus allowing their selective removal by means of different deprotection protocols.[26,31–34] The Cbz protecting group can be removed under standard hydrogenation conditions and it is stable in the presence of acid. In contrast, the Boc protecting group can be removed under acidic conditions and it is stable under (non-acidic) hydrogenation conditions. In both cases, the structural integrity of the carborane cage is preserved.

The reaction of the diiodo species **11** with one equivalent of $HN(Cbz)_2$ under phase-transfer conditions gave the Cbz-protected monoamine **12** in moderate yield (Scheme 1). The reaction time was limited to 5 h as longer periods resulted in the dissociation of one of the Cbz groups.[26] Due to the tendency of the Cbz protecting groups to dissociate under phase-transfer conditions, the Boc-protected amine group in **13** was incorporated by gently warming a DMF solution containing **12** with one equivalent of $HN(Boc)_2$ in the presence of K_2CO_3 to afford **13** in moderate yield. If the reaction temperature exceeded 60 °C or the reaction was allowed to proceed for long periods of time (> 48 h), one of the Cbz groups was dissociated to give the mono-Cbz protected amine **14**. However, **13** and **14** were readily separated by flash chromatography and both compounds underwent the sequential deprotection steps outlined as follows.

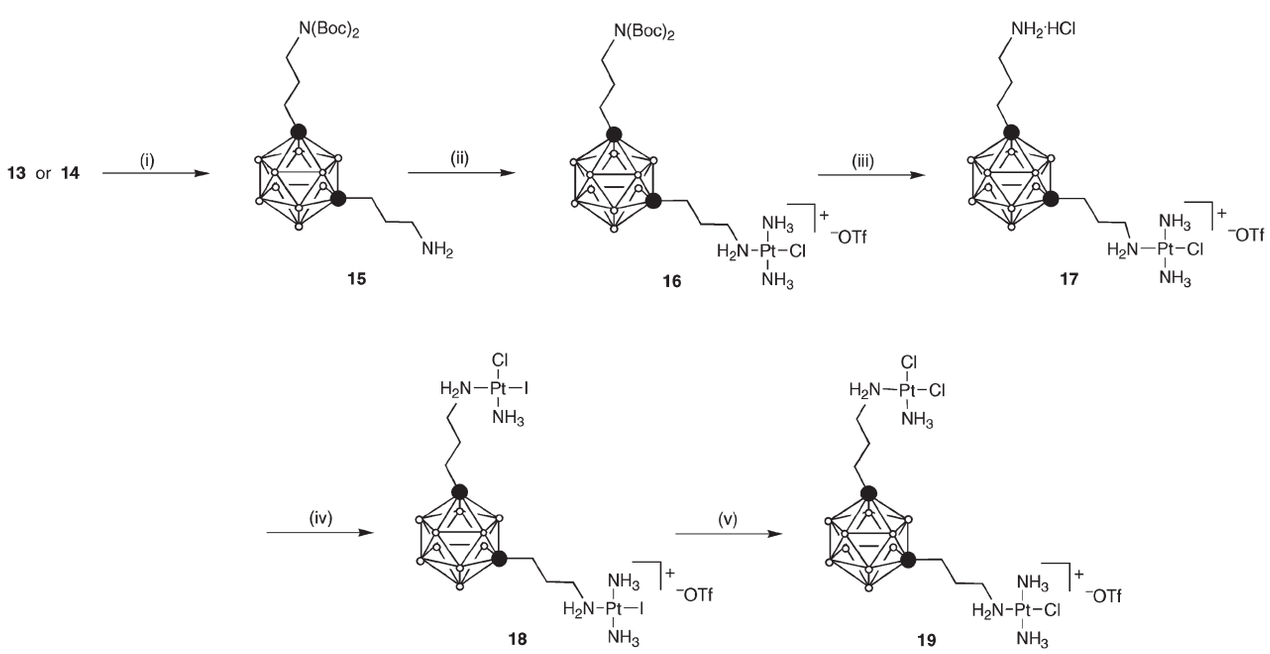
The Cbz protecting group(s) were removed prior to the Boc groups from **13** and **14**. This order of deprotection was chosen in order to eliminate any potential complications that may have occurred if a platinum(II) derivative was subjected to hydrogenation conditions, *e.g.* reduction of the metal centre. Typically, a Cbz group was removed in an acidified polar solvent such as EtOH in the presence of a Pd catalyst under a high-pressure H_2 atmosphere, although acidic conditions would have resulted in the loss of the Boc protecting groups in **13** and **14**. Using related hydrogenation conditions to those described by Sjöberg and co-workers,[31] **15** was successfully obtained in quantitative yield by means of a Pd–C catalyst in a buffered NH_4HCO_2/AcOH solution. Due to the tendency of the free amine to degrade the *closo*-carborane cage,[27] **15** was freshly prepared prior to reaction with the platinum(II) precursors.

The labile species *trans*-$[PtCl(dmf)(NH_3)_2]^+$ readily reacted with **15** to afford the mononuclear platinum(II) species **16** (Scheme 2). The product of this reaction is unusual as it is soluble in solvents such as MeOH and EtOAc, thus allowing the facile separation of any unreacted *trans*-$[PtCl_2(NH_3)_2]$ precursor from solution. The coordination of the primary amine in **15** to the platinum(II) centre was confirmed by a characteristic resonance in the $^{195}Pt\{^1H\}$ NMR spectrum at δ −2409, consistent with a PtN_3Cl core. There was also a marked change in the $^{13}C\{^1H\}$ NMR spectrum with the CH_2NH_2 signal shifting from δ 40.4 to δ 47.4 upon coordination. The Boc protecting groups in **16** were readily removed by treatment of the complex with 3 M HCl affording **17**·HCl which contained a pendant amine group that could be used in further complexation reactions.

In an effort to prepare the diplatinum(II) complex **19** containing both *cis*-$[PtCl_2(NH_3)(amine)]$ and *trans*-$[PtCl(NH_3)_2(amine)]^+$ centres, treatment of $K[PtCl_3(NH_3)]$ with **17** was attempted in a mixed DMF–H_2O solvent system, essential for maintaining the solubility of all reactants. However, the slow rate of ligand substitution in $[PtCl_3(NH_3)]^-$, particularly in DMF solution, necessitated the use of iodide ion in order to enhance the rate of reaction. Indeed, the rate was greatly enhanced when *trans*-$[PtClI_2(NH_3)]^-$ was used in the presence



Scheme 1 *Reagents*: (i) $HN(Cbz)_2$, Bu_4NHSO_4, 2 M NaOH, CH_2Cl_2; (ii) $HN(Boc)_2$, K_2CO_3, DMF.



Scheme 2 *Reagents*: (i) H_2/Pd–C catalyst, NH_4HCO_2/AcOH; (ii) *trans*-$[PtCl(dmf)(NH_3)_2]OTf$; (iii) 10 M HCl in EtOAc; (iv) *trans*-$[PtClI_2(NH_3)]^-$, K_2CO_3; (v) AgOTf, 0.1 M HCl.

of K_2CO_3 to afford the dinuclear species **18** containing a mixed-halogen ligand set. The presence of excess KI also resulted in the exchange of the chloro ligand at the remote PtN_3Cl centre to form the corresponding PtN_3I species. The presence of two inequivalent coordination spheres in **18** was confirmed by $^{195}Pt\{^1H\}$ NMR spectroscopy, with resonances appearing at δ −2652 and δ −2851 in a 1 : 1 ratio corresponding to the PtN_2ClI and PtN_3I cores, respectively. Upon treatment of **18** with three equivalents of AgOTf followed by the addition of $HCl_{(aq)}$ afforded **19** as a bright-yellow complex.

Once the synthesis of the key amine **15** was successfully achieved, the synthesis of a novel trinuclear platinum(II) complex containing **5** could also be realised. The methodology employed in this work was adapted from that described by Farrell, Appleton and Hoeschele for the synthesis of (non-boron containing) trinuclear platinum(II) complexes.[35] Treatment of *cis*-$[PtI_2(NH_3)_2]$ with two equivalents of AgOTf in DMF afforded the labile species *cis*-$[Pt(dmf)_2(NH_3)_2]^{2+}$ which upon the addition of two equivalents of **15** resulted in the rapid formation of the platinum(II) species **20** (Scheme 3). The coordination of the primary amine group in **15** to the metal centre was supported by a shift in the $^{13}C\{^1H\}$ NMR signal corresponding to the CH_2NH_2 group from δ 40.4 to δ 46.8 and the appearance of a signal at δ −2663 in the $^{195}Pt\{^1H\}$ NMR spectrum, characteristic of a PtN_4 coordination sphere.[28] The mononuclear complex **20** was sufficiently soluble in EtOAc to allow Boc-deprotection under standard acidic conditions to afford **21**. Removal of the Boc protecting groups in **20** was accompanied by a significant shift in the $^{13}C\{^1H\}$ NMR signal from δ 46.8 to δ 39.6. As expected, no change was observed in the $^{195}Pt\{^1H\}$ NMR spectrum of **21**.

The terminal amine groups in **21** were deprotonated by treatment with K_2CO_3 prior to the reaction with *trans*-$[PtClI_2(NH_3)]^-$. The coordination of each of the free amine groups to platinum(II) was confirmed by a characteristic shift in the $^{13}C\{^1H\}$ NMR signal from δ 39.6 to δ 46.0. The formation of **22** could not be confirmed by $^{195}Pt\{^1H\}$ NMR spectroscopy alone because, coincidentally, both the PtN_4 and $PtICIN_2$ centres characteristically display NMR signals at *ca.* δ −2600.[29] Consequently, only one peak was observed for **22** at δ −2646, and no signals corresponding to the precursor complex or other platinum(II) centres were observed. In order to confirm that the $^{195}Pt\{^1H\}$ NMR spectrum was the result of overlapping signals attributed to two different platinum(II) centres, **22** was treated with four equivalents of AgOTf, followed by an excess of $HCl_{(aq)}$ to afford two new *cis*-$PtCl_2N_2$ centres in **23**. This conversion was confirmed by the observation of two $^{195}Pt\{^1H\}$ NMR signals at δ −2157 and δ −2651 in a 2 : 1 ratio, corresponding to the *cis*-$PtCl_2N_2$ and PtN_4 centres, respectively.

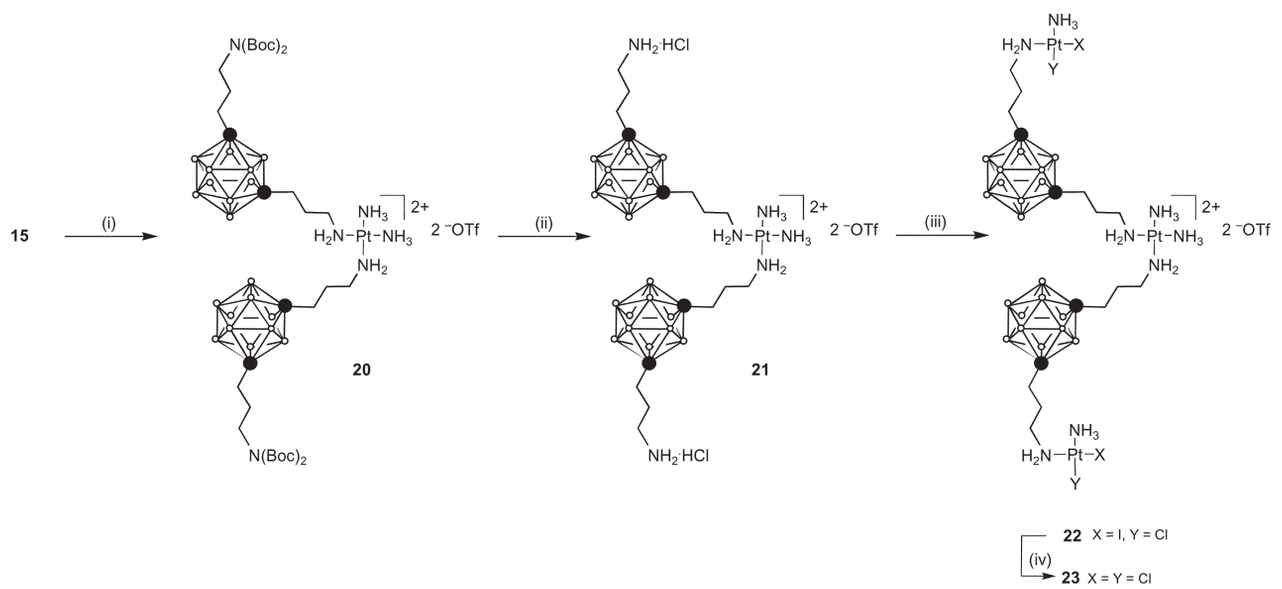
Table 1 IC_{50} values (μM) for **7** and **9** (n = 2). L1210 and L1210/DDP cell lines were assayed by means of a coulter counting (CC) assay. 2008 and C13*5 cell lines were assayed by means of a sulforhodamine B (SRB) assay

Cell Line	**7**	**9**	Cisplatin
L1210	2.0	1.1	0.5
L1210/DDP	2.5	1.4	6.9
2008	13	5.4	0.6
C13*5	13	5.6	10

In vitro cytotoxicity studies

Preliminary *in vitro* cytotoxicity studies were conducted with the dinuclear species **7** and **9** which were screened against a range of tumour cell lines in order to determine whether the complexes exhibited a cytotoxic effect in the absence of neutrons; the low solubility of the 1,12-carborane derivatives **8** and **10** and trinuclear **23** precluded an assessment of their cytotoxicity. The cell lines included L1210 murine leukaemia cells and its cisplatin-resistant variant (L1210/DDP), along with the cisplatin-sensitive (2008) and -resistant (C13*5) human ovarian carcinoma. The concentrations (μM) required to achieve 50% inhibition of cell growth in each cell line (IC_{50}) are presented in Table 1.

The results of the preliminary anti-cancer screening of **7** and **9** are encouraging. Most importantly, the IC_{50} values lie within the same order of magnitude as those observed for cisplatin and appear to indicate that the compounds are able to enter cells without difficulty. This is extremely promising as the achievement of adequate boron uptake by tumour cells is a highly valued goal in BNCT. The IC_{50} values also indicate the compounds are cytotoxic in the absence of neutrons. The mechanism of inducing cell death is unknown at the present time, but it is reasonable to assume that the effects are the result of avid DNA-binding as the complexes are capable of binding to plasmid DNA.[25] The cytotoxic effects of **7** and **9** in the absence of neutrons are not as essential to their proposed application as BNCT agents as is their ability to bind to DNA. A limited cytotoxicity exhibited by the complexes is not necessarily undesirable and could, in some cases, enhance the anti-cancer characteristics of the compounds in the presence of neutrons by an additive or perhaps synergistic effect. Indeed, if the complexes were potent cytotoxic agents (*i.e.* with IC_{50} values in the nM range) their application in BNCT would be limited as this would result in cell death at low platinum(II) concentrations, prior to the accumulation of a sufficient level of boron within the tumour cell.



Scheme 3 *Reagents*: (i) *cis*-$[Pt(dmf)_2(NH_3)_2](OTf)_2$; (ii) 10 M HCl in EtOAc; (iii) *trans*-$[PtClI_2(NH_3)]^-$, K_2CO_3; (iv) AgOTf, 0.3 M HCl.

Complex **9** was consistently more active than **7** in all cell lines that were examined. This may be due to the di-cationic nature of **9**, which would not only enhance the aqueous solubility of the complex but perhaps also enhance its DNA-binding affinity *via* electrostatic interactions. Additionally, the cationic charge could potentially assist with the internalisation of the dinuclear complex by the cells, thereby balancing out the lipophilicity associated with the carborane cage. In both cisplatin-sensitive cell lines L1210 and 2008, **7** and **9** were not as effective as cisplatin at inhibiting cell growth. This could be attributed to their limited aqueous solubility or perhaps a less efficient mechanism of cellular internalisation by the complexes compared with cisplatin. Indeed, the incorporation of the sterically bulky, lipophilic carborane moiety into the complexes would modulate their biological activity to some degree. Finally, the cytotoxicities of **7** and **9** in the cisplatin-resistant cell lines L1210/DDP and C13*5 were not only greater than that of cisplatin but were also very similar to those observed in the respective parent cell lines, indicating the mechanisms of cisplatin resistance do not adversely affect the biological activities of **7** and **9**. This result is consistent with the observation that DNA-adducts formed by other dinuclear platinum(II) complexes appear to be able to overcome many mechanisms associated with cisplatin resistance.[36,37]

Conclusions

The first examples of multinuclear platinum(II)–amine complexes containing *closo*-1,7- and 1,12-carboranes have been reported in this work. Symmetrical dinuclear platinum(II) complexes containing 1,7- or 1,12-carborane and either the *cis*-$[PtCl_2(NH_3)(amine)]$ (**7** and **8**) or *trans*-$[PtCl(NH_3)_2(amine)]^+$ (**9** and **10**) centres were successfully prepared and characterised. The platinum(II) complexes containing 1,2-carborane could not be isolated due to the degradation of the *closo*-carborane cage with concomitant reduction of the platinum(II) centre. Novel methods for the preparation of mixed di- and tri-nuclear platinum(II) complexes containing 1,7-carborane were also developed. We are currently evaluating the DNA-binding and cell-uptake characteristics of selected complexes in several tumour lines, and the results of these studies will be reported in due course.

Experimental

All reactions were performed under an inert atmosphere of dry N_2 using standard Schlenk techniques. Solvents for recrystallisation and chromatography were distilled prior to use. Tetrahydrofuran (THF) was dried by fresh distillation from sodium benzophenone ketyl, CH_2Cl_2 was freshly distilled from CaH_2, *N*,*N*-dimethylformamide (DMF) was pre-dried over anhydrous $MgSO_4$ followed by distillation under reduced pressure, and EtOH was freshly distilled from Mg/I_2.

All multinuclear 1-D NMR spectra were recorded at 298 K on a Varian Gemini 2000 NMR spectrometer equipped with an Oxford 300 MHz magnet (^1H at 300.10 MHz, ^{13}C at 75.48 MHz, ^{11}B at 96.30 MHz, and ^{195}Pt at 64.38 MHz) or a Varian Gemini 200 NMR Spectrometer equipped with an Oxford 200 MHz magnet (^1H at 199.98 MHz, ^{13}C at 50.29 MHz). ^1H and $^{13}C\{^1H\}$ NMR chemical shifts are reported in ppm relative to TMS. $^{195}Pt\{^1H\}$ and $^{11}B\{^1H\}$ NMR chemical shifts were referenced to a sealed external standard of 0.1 M $Na_2[PtCl_6]$ in D_2O and $BF_3{\cdot}OEt_2$, respectively (0 ppm). Coupling constants are reported in Hz. Melting points were determined using a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected. Thin layer chromatography was carried out on Kieselgel 60 F_{254} silica (Merck) on aluminium-backed plates. Electrospray Ionisation (ESI) mass spectra were obtained by means of a Finnegan LCQ mass spectrometer using 5% (v/v) DMF–MeOH solution. Elemental analyses were performed by Chemical and Microanalytical Services Pty Ltd, Belmont, Victoria (Australia).

Unless otherwise stated, reagents were obtained from Aldrich and were used without further purification. 1,2-, 1,7- and 1,12-carborane (Katchem and Dexsil) and *trans*-$[PtCl_2(NH_3)_2]$ (Strem) were obtained commercially and used without further purification. The compounds **6**·2HCl,[26] $HN(Cbz)_2$,[38] $K[PtCl_3(NH_3)]$,[39,40] and *cis*-$[PtX_2(NH_3)_2]$ (X = Cl, I)[41] were prepared from literature procedures.

Syntheses

1,2-Bis(aminopropyl)-1,2-carborane 4. A solution of **30** (2.35 g, 3.57 mmol) in a homogeneous mixture of 10 M HCl (30 mL) and EtOAc (70 mL) was stirred at room temperature for 6 h. The solvent was removed *in vacuo* to give a pale-yellow solid which was purified by recrystallisation from MeOH–diethyl ether to afford **4**·2HCl as a colourless solid (645 mg, 69%) (Found: C, 28.86; H, 8.61; N, 8.50%. $C_8H_{28}B_{10}Cl_2N_2$ requires C, 29.00; H, 8.51; N, 8.45%). δ_H (199.98 MHz, D_2O) 2.99 (t, 4H, $^3J_{HH}$ = 7.6 Hz, CH_2N), 2.37 (m, 4H, CH_2C_{cage}), 1.93 (m, 4H, CH_2CH_2N); δ_C (50.29 MHz, CD_3OD) 81.0 (C_{cage}), 40.2 (CH_2N), 33.2 (CH_2C_{cage}), 29.0 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, $CDCl_3$) −3.54 (s, 2B), −9.29 (s, 8B).

To a solution of **4**·2HCl (30 mg, 9.06×10^{-5} mol) in H_2O (1 mL) in the presence of CH_2Cl_2 (2 mL) was added saturated $K_2CO_{3(aq)}$ (1 mL) with vigorous stirring. The organic layer was dried over anhydrous Na_2SO_4 and reduced *in vacuo* to give **4** as a colourless, unstable oil (10 mg, 43%).

1,7-Bis(aminopropyl)-1,7-carborane 5. The compound was prepared from **29** in a similar manner to that described for **4** to give **5**·2HCl as a colourless solid (69%) (Found: C, 29.05; H, 8.67; N, 8.42%. $C_8H_{28}B_{10}Cl_2N_2$ requires C, 29.00; H, 8.51; N, 8.45%). δ_H (199.98 MHz, CD_3OD) 3.05 (t, 4H, $^3J_{HH}$ = 7.4 Hz, CH_2N), 2.31 (m, 4H, CH_2C_{cage}), 1.91 (m, 4H, CH_2CH_2N); δ_C (50.29 MHz, CD_3OD) 76.6 (C_{cage}), 40.2 (CH_2N), 34.9 (CH_2C_{cage}), 29.2 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, CD_3OD) −6.05 (s, 2B), −9.77 (s, 6B), −11.78 (s, 2B).

To a solution of **5**·2HCl (59 mg, 0.178 mmol) in H_2O (2 mL) in the presence of CH_2Cl_2 (2 mL) was added saturated $K_2CO_{3(aq)}$ (1 mL) with vigorous stirring. The organic layer was dried over anhydrous Na_2SO_4 and reduced *in vacuo* to give **5** as a colourless oil (27 mg, 58%).

μ-{1,7-Bis(aminopropyl)-1,7-carborane-*N*,*N*′}bis[*cis*-ammine-dichloroplatinum(II)] 7. A solution of KI (108 mg, 0.65 mmol) in H_2O (0.83 mL) was added to a solution of $K[Pt(NH_3)Cl_3]$ (75 mg, 0.21 mmol) in H_2O (1.04 mL), previously adjusted to pH 7 with 0.1 M NaOH and the mixture was stirred for 15 min. A solution of **5** (27 mg, 0.104 mmol) in MeOH (2 mL) was added and stirring was continued for 4 h. The resulting yellow precipitate was collected by centrifugation and washed successively with cold H_2O, MeOH, diethyl ether and dried under vacuum to afford the mixed chloro–iodo complex $[\{Pt(NH_3)ClI\}_2\{1,7\text{-}NH_2(CH_2)_3CB_{10}H_{10}C(CH_2)_3NH_2\}]$ (99 mg, 0.098 mmol, 94%).

To a solution of the mixed chloro–iodo complex (99 mg, 0.098 mmol) in DMF (2 mL) was added a solution of $AgNO_3$ (62 mg, 0.366 mmol) in DMF (2 mL). The solution was stirred in the absence of light for 18 h. AgI and AgCl was removed by filtration through a pad of Celite filter-aid and washed with DMF (1 mL). To the filtrate and washings was added an additional amount of $AgNO_3$ (25 mg, 0.148 mmol) in DMF (1 mL) and the solution was stirred in the absence of light for 9 h. Once again, AgI and AgCl were removed by filtration through a pad of Celite filter-aid. To the filtrate was added 1.0 M HCl (0.20 mL, 0.20 mmol) to precipitate unreacted Ag^+ as AgCl. The solution was left in a refrigerator overnight and AgCl was removed by filtration through a pad of Celite filter-aid. To the filtrate was added 10 M HCl (0.10 mL, 1.0 mmol), followed by 0.1 M HCl (20 mL). The solution was again placed in a refrigerator overnight to precipitate a yellow solid. The precipitate was collected by centrifugation, washed with MeOH, diethyl ether

and air dried. Recrystallisation from DMF–0.1 M HCl gave **7** as a yellow solid (51 mg, 59% overall) (Found: C, 12.33; H, 4.23; N, 6.94%. $C_8H_{32}B_{10}Cl_4N_4Pt_2{\cdot}0.25C_3H_7NO$ requires C, 12.47; H, 4.04; N, 7.06%). δ_H (199.98 MHz, d$_7$-DMF) 4.63 (br s, 4H, NH_2), 3.89 (br s, 6H, NH_3), 2.40 (m, 4H, CH_2N), 1.79 (m, 4H, CH_2C_{cage}), 1.50 (m, 4H, CH_2CH_2N); δ_C (75.48 MHz, d$_7$-DMF) 75.6 (C_{cage}), 45.5 (CH_2N), 33.1 (CH_2C_{cage}), 30.4 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, d$_7$-DMF) −11.40 (br s, 10B). δ_{Pt} (64.38 MHz, d$_7$-DMF) −2156.

μ-{1,12-Bis(aminopropyl)-1,12-carborane-*N*,*N*′}bis[*cis*-amminedichloroplatinum(II)] 8. A solution of KI (76 mg, 4.58×10^{-4} mol) in H_2O (1.0 mL) was added to a solution of K[Pt(NH_3)Cl_3] (54.4 mg, 1.52×10^{-4} mol) in H_2O (1.0 mL), previously adjusted to pH 7 with 0.1 M NaOH and the mixture was stirred for 15 min. A solution of **6** (19.5 mg, 7.54×10^{-4} mol) in MeOH (4 mL) was added and the stirring was continued for 2 h. The yellow precipitate was collected by centrifugation, washed successively with H_2O, MeOH, diethyl ether and dried under vacuum to give the mixed iodo–chloro complex [{Pt(NH_3)ClI}$_2${1,12-$NH_2(CH_2)_3CB_{10}H_{10}C(CH_2)_3NH_2$}] (70 mg, 91%).

To a solution of the mixed iodo–chloro complex (70 mg, 6.9×10^{-4} mol) in DMF (2 mL) was added a solution of AgOTf (70 mg, 2.72×10^{-4} mol) in DMF (2 mL). The solution was stirred overnight in the absence of light. AgI and AgCl were removed by filtration through a pad of Celite filter-aid. To the filtrate was added a second portion of AgOTf (23 mg, 8.95×10^{-5} mol) in DMF (1 mL) and the solution was stirred in the absence of light for 12 h. Once again, AgI and AgCl were removed by filtration through a pad of Celite filter-aid and to the filtrate was added 1.0 M HCl (0.20 mL) to precipitate unreacted Ag^+ as AgCl which was removed by filtration through a pad of Celite filter-aid. To the filtrate and washings was added 0.1 M HCl (20 mL) and the solution was cooled to 4 °C overnight. The yellow precipitate **8** was collected by centrifugation, washed with MeOH, diethyl ether and dried *in vacuo* (29 mg, 46% overall) (Found: C, 12.50%; H, 4.15; N, 7.00%. $C_8H_{32}B_{10}Cl_4N_4Pt_2{\cdot}0.25C_3H_7NO$ requires C, 12.47; H, 4.04; N, 7.06%). δ_H (300.10 MHz, d$_7$-DMF) 4.87 (s, NH), 4.19 (s, NH), 2.62 (m, 4H, CH_2N), 1.76 (m, 4H, CH_2C_{cage}), 1.56 (m, 4H, CH_2CH_2N); δ_C (75.48 MHz, d$_7$-DMF) 80.3 (C_{cage}), 47.2 (CH_2N), 35.5 (CH_2C_{cage}), 31.7 (CH_2CH_2N); δ_B (96.30 MHz, d$_7$-DMF) −8.8 (br s, 10B). δ_{Pt} (64.38 MHz, d$_7$-DMF) −2155.

μ-{1,7-Bis(aminopropyl)-1,7-carborane-*N*,*N*′}bis[*trans*-diamminechloroplatinum(II)] bis(triflate) 9. A solution of AgOTf (48 mg, 0.187 mmol) in DMF (0.50 mL) was added dropwise to a suspension of *trans*-[$PtCl_2(NH_3)_2$] (50 mg, 0.167 mmol) in DMF (0.50 mL). The solution was stirred in the absence of light for 18 h. AgCl was removed by filtration through a pad of Celite filter-aid. To the filtrate was added a solution of **5** (19 mg, 0.074 mmol) in DMF (0.50 mL) and stirring was continued for 48 h. 0.1 M HCl (3 mL) was added to the solution and it was cooled to 4 °C overnight. A colourless precipitate was collected by centrifugation, washed with H_2O, EtOH and diethyl ether and dried under vacuum to afford **9** (18 mg, 22%) (Found: C, 10.96; H, 4.09; N, 8.11%. $C_{10}H_{38}B_{10}Cl_2F_6N_6O_6Pt_2S_2$ requires C, 11.06; H, 3.53; N, 7.74%). ESI-MS (5% DMF–MeOH): *m*/*z* 393.9 ([M − 2OTf]$^{2+}$); δ_H (300.10 MHz, CD_3OD + drop d$_7$-DMF) 2.74 (t, 4H, $^3J_{HH}$ = 7.5 Hz, CH_2N), 2.10 (m, 4H, CH_2C_{cage}), 1.78 (m, 4H, CH_2CH_2N); δ_C (75.48 MHz, d$_7$-DMF) 75.6 (C_{cage}), 46.0 (CH_2N), 33.4 (CH_2C_{cage}), 30.6 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, d$_7$-DMF) −11.0 (br s, 10B); δ_{Pt} (64.38 MHz, d$_7$-DMF) −2410.

μ-1,12-Bis(aminopropyl)-1,12-carborane-*N*,*N*′-bis[*trans*-diamminechloroplatinum(II)] bis(triflate) 10. A solution of AgOTf (36 mg, 1.40×10^{-4} mol) in DMF (2.0 mL) was added dropwise to a suspension of *trans*-[$PtCl_2(NH_3)_2$] (44 mg, 1.47×10^{-4} mol) in DMF (3 mL). The solution was stirred overnight in the absence of light. AgCl was removed by filtration through a pad of Celite filter-aid. To the filtrate was added a solution of **6** (19 mg, 7.35×10^{-5} mol) in DMF (3 mL) and stirring was continued overnight. The solution was reduced to dryness *in vacuo* and the residue was recrystallised from DMF–0.1 M HCl to give **10** as a colourless solid (57 mg, 71%) (Found: C, 10.50; H, 4.35; N, 8.23%. $C_{10}H_{38}B_{10}Cl_2F_6N_6O_6Pt_2S_2$ requires C, 11.06; H, 3.53; N, 7.74%). ESI-MS (5% DMF–MeOH): *m*/*z* 394.0 ([M − 2OTf]$^{2+}$); δ_H (300.10 MHz, CD_3OD + drop d$_7$-DMF) 2.64 (t, 4H, $^3J_{HH}$ = 7.5 Hz, CH_2N), 1.76 (m, 4H, CH_2C_{cage}), 1.56 (m, 4H, CH_2CH_2N); δ_C (50.29 MHz, d$_7$-DMF + CD_3OD) 78.3 (C_{cage}), 49.4 (CH_2N), 34.0 (CH_2C_{cage}), 30.7 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, d$_7$-DMF) −9.15 (br s, 10B); δ_{Pt} (64.38 MHz, d$_7$-DMF) −2409.

1,7-Bis(iodopropyl)-1,7-carborane 11. A solution of **26** (483 mg, 1.25 mmol) and NaI (1.05 g, 7.01 mmol) in acetone (20 mL) was heated to reflux for 24 h. The solvent was removed *in vacuo* from the cooled solution to afford a mixture containing both yellow and orange solids. The solids were dissolved in diethyl ether (20 mL) and H_2O (20 mL). The aqueous layer was extracted with diethyl ether (20 mL) and the combined organic layers were washed with H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give **11** as a yellow oil (551 mg, 92%) (Found C, 20.04; H, 4.52%. $C_8H_{22}B_{10}I_2$ requires C, 20.01; H, 4.62%). δ_H (300.10 MHz, $CDCl_3$) 3.01 (t, 4H, $^3J_{HH}$ = 6.0 Hz, CH_2I), 1.98 (m, 4H, CH_2C_{cage}), 1.78 (m, 4H, C$H_2CH_2C_{cage}$); δ_C (50.29 MHz, $CDCl_3$) 74.5 (C_{cage}), 37.6 (CH_2C_{cage}), 33.1 ($CH_2CH_2C_{cage}$), 4.12 (CH_2I); δ_B (96.30 MHz, $CDCl_3$) −7.48 (s, 2B), −11.30 (s, 6B), −13.86 (s, 2B).

7-(Iodopropyl)-*N*,*N*-dibenzyloxycarbonyl-1-(aminopropyl)-1,7-carborane 12. To a stirred solution of Bu_4NHSO_4 (790 mg, 2.33 mmol) and 2 M NaOH (2.4 mL, 5.00 mmol) in CH_2Cl_2 (50 mL) was added a solution of dibenzyl iminodicarboxylate (664 mg, 2.33 mmol) in CH_2Cl_2 (20 mL). After stirring for 30 min, a solution of **11** (1.12 g, 2.32 mmol) in CH_2Cl_2 (25 mL) was added dropwise to the mixture. The reaction was then heated to reflux for 6 h. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were reduced *in vacuo* to afford a yellow residue, which was stirred with diethyl ether (100 mL) for 30 min to precipitate the Bu_4NI, which was removed by vacuum filtration. The filtrate was dried over anhydrous Na_2SO_4 and reduced *in vacuo* to afford a yellow oil that was purified by flash chromatography on silica. Elution with 10–25% diethyl ether in *n*-hexane (R_f = 0.35) gave **12** (660 mg, 44%) (Found: C, 45.19; H, 5.73; N, 2.20%. $C_{24}H_{36}B_{10}INO_4$ requires C, 45.21; H, 5.69; N, 2.20%). δ_H (300.10 MHz, $CDCl_3$) 7.36 (s, 10H, Ph), 5.24 (s, 4H, CH_2Ph), 3.61 (t, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2N), 3.07 (t, 2H, $^3J_{HH}$ = 6.6 Hz, CH_2I), 2.04 (m, 2H, $ICH_2CH_2CH_2$), 1.83 (m, 4H, $(Cbz)_2NCH_2CH_2CH_2$, ICH_2CH_2), 1.62 (m, 2H, NCH_2CH_2); δ_C (75.48 MHz, $CDCl_3$) 153.3 (CO), 135.1 (Ph), 128.7 (Ph), 128.5 (Ph), 128.2 (Ph), 75.0 (C_{cage}), 74.5 (C_{cage}), 68.8 (CH_2Ph), 45.9 (CH_2N), 37.6 ($CH_2CH_2CH_2I$), 33.9 ($CH_2CH_2CH_2N$), 33.1 (CH_2CH_2I), 29.2 (CH_2CH_2N), 4.2 (CH_2I); δ_B (96.30 MHz, $CDCl_3$) −7.72 (s, 2B), −11.24 (s, 6B), −13.97 (s, 2B).

***N*,*N*-Di-*tert*-butoxycarbonyl-7-(aminopropyl)-*N*,*N*-dibenzyloxycarbonyl-1-(aminopropyl)-1,7-carborane 13 and *N*,*N*-Di-*tert*-butoxycarbonyl-7-(aminopropyl)-*N*-benzyloxycarbonyl-1-(aminopropyl)-1,7-carborane 14.** A solution of **12** (1.40 g, 2.20 mmol), K_2CO_3 (666 mg, 4.82 mmol) and di-*tert*-butyliminodicarboxylate (528 mg, 2.43 mmol) in DMF (20 mL) was warmed to 60 °C for 24 h and then reduced to dryness *in vacuo*. The colourless solid was dissolved in CH_2Cl_2 (100 mL) and H_2O (100 mL) and the aqueous solution was extracted with another portion of CH_2Cl_2 (100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$ and reduced *in vacuo* to give a yellow oil. Flash chromatography on silica (10–50% diethyl ether in *n*;-hexane) gave **13** (270 mg, R_f = 0.23, 16%) and **14** (783 mg, R_f = 0.12, 60%) as colourless oils.

13: (Found: C, 56.11; H, 7.33; N, 3.90%. $C_{34}H_{54}B_{10}N_2O_8$ requires C, 56.18; H, 7.49; N, 3.85%). δ_H (300.10 MHz, $CDCl_3$) 7.35 (s, 10H, Ph), 5.23 (s, 4H, CH_2 Ph), 3.60 (t, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2N(Cbz)$_2$), 3.47 (t, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2N(Boc)$_2$), 1.86 (m, 4H, (Cbz)$_2$NCH$_2$CH$_2$CH_2, (Boc)$_2$NCH$_2$CH$_2$CH_2), 1.62 (m, 4H, (Cbz)$_2$NCH$_2$CH_2, (Boc)$_2$NCH$_2$CH_2), 1.50 (s, 18H, C(CH$_3$)$_3$); δ_C (75.48 MHz, $CDCl_3$) 153.3 (CO), 152.5 (CO), 135.1 (Ph), 128.7 (Ph), 128.5 (Ph), 128.2 (Ph), 82.5 (*C*(CH$_3$)$_3$), 75.3 (C$_{cage}$), 75.0 (C$_{cage}$), 68.8 (*C*H$_2$ Ph), 45.9 (*C*H$_2$N(Cbz)$_2$), 45.5 (*C*H$_2$N(Boc)$_2$), 34.2 (*C*H$_2$C$_{cage}$), 34.0 (*C*H$_2$C$_{cage}$), 29.3 (NCH$_2$*C*H$_2$), 29.2 (NCH$_2$*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$); δ_B (96.30 MHz, $CDCl_3$) −7.84 (s, 2B), −11.29 (s, 6B), −13.82 (s, 2B).

14: (Found: C, 52.69; H, 8.10; N, 4.81%. $C_{26}H_{48}B_{10}N_2O_6$ requires C, 52.68; H, 8.16; N, 4.73%). δ_H (300.10 MHz, $CDCl_3$) 7.35 (m, 5H, Ph), 5.09 (s, 2H, CH_2Ph), 4.70 (br s, 1H, NH), 3.46 (t, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2N(Boc)$_2$), 3.11 (q, 2H, $^3J_{HH}$ = 6.6 Hz, CH_2NH(Cbz)), 1.86 (m, 4H, (Cbz)$_2$NCH$_2$CH$_2$CH_2, (Boc)$_2$NCH$_2$CH$_2$CH_2), 1.62 (m, 4H, (Cbz)$_2$NCH$_2$CH_2, (Boc)$_2$NCH$_2$CH_2), 1.50 (s, 18H, C(CH$_3$)$_3$); δ_B (96.30 MHz, $CDCl_3$) −7.82 (s, 2B), −11.36 (s, 6B), −13.77 (s, 2B).

***N*,*N*-Di-*tert*-butoxycarbonyl-7-(aminopropyl)-1-(aminopropyl)-1,7-carborane 15.** A solution of **13** or **14** (0.413 mmol) in EtOAc was added to an NH_4HCO_2 solution (15 mL, 1.02 M in 80% aqueous AcOH). A slurry of Pd–C (10%, 47 mg) in NH_4HCO_2 solution (2 mL) was added with stirring. The mixture was stirred for 15 h under a H_2 atmosphere. The catalyst was removed by filtration through Celite filter-aid. The filtrate was reduced *in vacuo* to give a colourless residue that was dissolved in EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with dilute $NaHCO_{3(aq)}$, dried over Na_2SO_4, and reduced *in vacuo* to give **15** as a colourless oil (150 mg, 79%) (Found: C, 47.69; H, 9.58; N, 5.78%. $C_{18}H_{42}B_{10}N_2O_4$ requires C, 47.14; H, 9.23; N, 6.11%). δ_H (300.10 MHz, $CDCl_3$) 3.47 (t, 2H, $^3J_{HH}$ = 6.6 Hz, CH_2N(Boc)$_2$), 2.86 (t, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2NH$_2$), 2.06 (m, 2H, NH$_2$CH$_2$CH$_2$CH_2C$_{cage}$), 1.92 (m, 2H, (Boc)$_2$NCH$_2$CH$_2$CH_2C$_{cage}$), 1.75 (m, 2H, NH$_2$CH$_2$CH_2CH$_2$C$_{cage}$), 1.61 (m, 2H, (Boc)$_2$NCH$_2$CH_2CH$_2$C$_{cage}$), 1.50 (s, 18H, C(CH_3)$_3$); δ_C (75.48 MHz, $CDCl_3$) 152.5 (CO), 82.5 (C(*C*H$_3$)$_3$), 75.4 (C$_{cage}$), 75.0 (C$_{cage}$), 45.5 (*C*H$_2$N(Boc)$_2$), 40.4 (CH$_2$NH$_2$), 34.2 (*C*H$_2$CH$_2$-CH$_2$N(Boc)$_2$), 34.0 (*C*H$_2$CH$_2$CH$_2$NH$_2$), 31.1 (CH$_2$*C*H$_2$CH$_2$N-(Boc)$_2$), 29.3 (CH$_2$*C*H$_2$CH$_2$NH$_2$), 28.1 (C(*C*H$_3$)$_3$); δ_B (96.30 MHz, $CDCl_3$) −7.86 (s, 2B), −11.24 (s, 6B), −13.67 (s, 2B).

***trans*-[Diammine{1-(*N*,*N*-di-*tert*-butoxycarbonylaminopropyl)-7-aminopropyl-1,7-carborane}chloroplatinum(II)] triflate 16.** To a suspension of *trans*-[$PtCl_2(NH_3)_2$] (46.6 mg, 0.155 mmol) in DMF (1 mL) was added a solution of AgOTf (38.4 mg, 0.149 mmol) in DMF (2 mL). The solution was stirred overnight in the absence of light. AgCl was removed by filtration through a pad of Celite filter-aid and the filtrate was added dropwise to a solution of **15** (68.2 mg, 1.49×10^{-4} mol) in DMF (4 mL). After stirring the solution for 12 h, the solvent was removed *in vacuo* to give a pale-yellow residue. The residue was extracted with MeOH and the supernatant was reduced *in vacuo* to give **16** as a pale-yellow oil (126 mg, 97%) (Found: C, 25.77; H, 5.03; N, 5.66%. $C_{19}H_{48}B_{10}ClF_3N_4O_7PtS{\cdot}H_2O$ requires C, 25.63; H, 5.66; N, 6.29%). δ_H (199.98 MHz, d$_7$-DMF) 5.69 (s, 2H, NH$_2$), 4.20 (s, 6H, NH$_3$), 3.52 (t, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2N(Boc)$_2$), 3.22 (s, 2H, CH_2NH$_2$Pt), 2.15 (m, 2H, CH$_2$C$_{cage}$), 2.05 (m, 2H, CH$_2$C$_{cage}$), 1.84 (s, 2H, CH_2CH$_2$C$_{cage}$), 1.70 (m, 2H, CH_2CH$_2$C$_{cage}$), 1.53 (s, 18H, C(CH$_3$)$_3$). δ_C (75.48 MHz, d$_7$-DMF) 153.4 (CO), 83.0 (*C*(CH$_3$)$_3$), 76.9 (C$_{cage}$), 47.4 (*C*H$_2$NH$_2$Pt), 46.1 (*C*H$_2$N(Boc)$_2$), 34.7 (C$_{cage}$*C*H$_2$), 34.4 (C$_{cage}$*C*H$_2$), 32.2 (C$_{cage}$CH$_2$*C*H$_2$), 30.3 (C$_{cage}$CH$_2$*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$). δ_B (96.30 MHz, d$_7$-DMF) −6.15 (br s, 10B). δ_{Pt} (64.38 MHz, d$_7$-DMF) −2409.

***trans*-Diammine{1,7-bis(aminopropyl)-1,7-carborane-*N*}-chloroplatinum(II) triflate hydrochloride 17.** To a solution of **16** (126 mg, 0.144 mmol) in EtOAc (2 mL) was added a homogenous mixture of 10 M HCl (3 mL) and EtOAc (7 mL). The solution was stirred at room temperature for 3 h and the solvent was removed *in vacuo* to give **17** as a colourless solid (96 mg, 99%) (Found: C, 15.88; H, 4.89; N, 7.99%. $C_9H_{33}B_{10}Cl_2F_3N_4O_3PtS$ requires C, 15.26; H, 4.69; N, 7.91%). δ_C (75.48 MHz, d$_7$-DMF) 76.5 (C$_{cage}$), 76.1 (C$_{cage}$), 47.0 (*C*H$_2$NH$_2$Pt), 39.1 (*C*H$_2$NH$_2$·HCl), 34.0 (C$_{cage}$*C*H$_2$), 33.7 (C$_{cage}$*C*H$_2$), 31.5 (*C*H$_2$CH$_2$NH$_2$Pt), 27.9 (*C*H$_2$CH$_2$NH$_2$·HCl); δ_B (96.30 MHz, d$_7$-DMF) −7.3 (br s, 10B); δ_{Pt} (64.38 MHz, d$_7$-DMF) −2408.

{μ-1,7-Bis(aminopropyl)-1,7-carborane}-*N*-[amminechloroiodoplatinum(II)]-*N*′-[*trans*-diammineiodoplatinum(II)] triflate 18. To a solution of K[$PtCl_3(NH_3)$] (45.4 mg, 1.27×10^{-4} mol) in H_2O (0.20 mL) was added a solution of KI (63 mg, 3.79×10^{-4} mol) in H_2O (0.60 mL). The brown solution was stirred at room temperature for 15 min, and then added to a solution of **17** (89 mg, 1.25×10^{-5} mol) in DMF (5 mL) containing K_2CO_3 (17 mg, 1.23×10^{-4} mol). The mixture was stirred overnight at room temperature, reduced *in vacuo* to approx. 1 mL and filtered off to remove the insoluble inorganic salts. The filtrate was evaporated *in vacuo* to give **18** as an orange solid (92%) (Found: C, 8.77; H, 3.69; N, 6.52%. $C_9H_{35}B_{10}ClF_3I_2N_5O_3Pt_2S{\cdot}1.5H_2O$ requires C, 9.28; H, 3.29; N, 6.01%). δ_{Pt} (64.38 MHz, d$_7$-DMF) −2652, −2851.

***cis*-Diamminebis{1-(*N*,*N*-di-*tert*-butoxycarbonylaminopropyl)-7-aminopropyl-1,7-carborane-*N*}platinum(II) bis(triflate) 20.** To a solution of *cis*-[$PtI_2(NH_3)_2$] (33 mg, 6.8×10^{-5} mol) in DMF (2 mL) was added a solution of AgOTf (35 mg, 1.36×10^{-4} mol) in DMF (1 mL). The solution was stirred in the absence of light at room temperature for 30 min. AgI was removed by filtration through a pad of Celite filter-aid. The filtrate was added to a solution of **15** (62 mg, 1.35×10^{-4} mol) in DMF (2 mL). The solution was stirred overnight and the solvent was removed *in vacuo* to yield **20** as a colourless oil (98 mg, 99%) (Found: C, 31.83; H, 6.07; N, 5.36%. $C_{38}H_{90}B_{20}F_6N_6O_{14}PtS_2$ requires C, 31.60; H, 6.28; N, 5.82%). δ_C (75.48 MHz, d$_7$-DMF) 153.4 (CO), 82.9 (*C*(CH$_3$)$_3$), 76.9 (C$_{cage}$), 76.8 (C$_{cage}$), 46.8 (*C*H$_2$NH$_2$Pt), 46.1 (*C*H$_2$N(Boc)$_2$), 34.7 (C$_{cage}$*C*H$_2$), 34.3 (C$_{cage}$*C*H$_2$), 32.2 (*C*H$_2$CH$_2$NH$_2$Pt), 30.3 (*C*H$_2$CH$_2$N(Boc)$_2$), 28.3 (C(*C*H$_3$)$_3$); δ_{Pt} (64.38 MHz, d$_7$-DMF) −2664.

***cis*-Diamminebis{1,7-bis(aminopropyl)-1,7-carborane-*N*}-platinum(II) hydrochloride bis(triflate) 21.** To solution of **20** (98 mg, 6.8×10^{-5} mol) in EtOAc (2 mL) was added a homogenous mixture of 10 M HCl (0.5 mL) and EtOAc (2 mL). The reaction mixture was stirred for 2 h at room temperature during which time the product separated as a yellow oil. After the solvent was removed by decantation, the residue solidified. The residue was dried *in vacuo* to give **21** as a pale-yellow solid (56 mg, 74%) (Found: C, 19.48; H, 5.87; N, 7.31%. $C_{18}H_{60}B_{20}Cl_2F_6N_6O_6PtS_2$ requires C, 19.36; H, 5.41; N, 7.52%). δ_C (75.48 MHz, d$_7$-DMF) 77.1 (C$_{cage}$), 76.7 (C$_{cage}$), 46.9 (*C*H$_2$NH$_2$Pt), 39.6 (*C*H$_2$NH$_2$·HCl), 34.5 (*C*H$_2$C$_{cage}$), 34.4 (*C*H$_2$C$_{cage}$), 32.3 (*C*H$_2$CH$_2$NH$_2$Pt), 28.6 (*C*H$_2$CH$_2$NH$_2$·HCl); δ_{Pt} (64.38 MHz, d$_7$-DMF) −2642.

[*cis*-Bis{μ-1,7-bis(aminopropyl)-1,7-carborane-*N*,*N*′}-diammineplatinum(II)] bis[ammine(chloro)iodoplatinum(II)] bis(triflate) 22. A solution of KI (49 mg, 2.95×10^{-4} mol) in H_2O (0.20 mL) was added to a solution of K[$Pt(NH_3)Cl_3$] (36 mg, 1.01×10^{-4} mol) in H_2O (0.5 mL). The solution was stirred for 15 min and then it was added to a stirred solution of **21** (56 mg, 5.01×10^{-5} mol) in DMF (5 mL), followed by the addition of K_2CO_3 (15 mg, 1.09×10^{-4} mol). After stirring the mixture for 2 h, the solvent was removed *in vacuo* to give a orange solid. The crude residue was recrystallised from DMF–0.1 M HCl to give **22** as an orange solid (41 mg, 46%) (Found: C, 12.05; H, 3.77; N, 5.98%. $C_{18}H_{64}B_{20}Cl_2F_6I_2N_8O_6Pt_3S_2$ requires C, 12.06; H, 3.60; N, 6.25%). δ_C (75.48 MHz, d$_7$-DMF) 77.0 (C$_{cage}$), 76.8 (C$_{cage}$), 46.8 (*C*H$_2$NH$_2$Pt), 46.0 (*C*H$_2$NH$_2$Pt), 34.6 (C$_{cage}$*C*H$_2$), 34.4 (C$_{cage}$*C*H$_2$), 32.0 (*C*H$_2$CH$_2$NH$_2$), 31.6 (*C*H$_2$CH$_2$NH$_2$);

δ_B (96.30 MHz, d_7-DMF) −7.35 (br s, 10B); δ_{Pt} (64.38 MHz, d_7-DMF) −2646.

[*cis*-Bis{μ-1,7-bis(aminopropyl)-1,7-carborane-*N*,*N*′}diammineplatinum(II)]bis[*cis*-amminedichloroplatinum(II)] bis(triflate) 23. A solution of **22** (72 mg, 4.02×10^{-5} mol) in DMF (4 mL) was added a solution of AgOTf (41 mg, 1.60×10^{-4} mol) in DMF (1 mL). The solution was stirred in the absence of light for 3 h. AgI and AgCl were removed by filtration through a pad of Celite filter-aid and the filtrate was stirred overnight with 0.3 M HCl (2 mL, 0.6 mmol). HCl (0.1 M) was added to precipitate **23** as a yellow solid (10 mg, 15%) (Found: C, 12.96; H, 4.36; N, 6.25%. $C_{18}H_{64}B_{20}Cl_4F_6N_8O_6Pt_3S_2{\cdot}2H_2O$ requires C, 13.13; H, 4.16; N, 6.81%). δ_C (75.48 MHz, d_7-DMF) 76.7 (C_{cage}), 76.5 (C_{cage}), 46.7 (CH_2NH_2Pt), 46.4 (CH_2NH_2Pt), 34.2 (CH_2C_{cage}), 34.1 (CH_2C_{cage}), 31.9 ($CH_2CH_2C_{cage}$), 31.4 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, d_7-DMF) −7.4 (br s, 10B); δ_{Pt} (64.38 MHz, d_7-DMF) −2162 (s, $[PtCl_2N_2]$), −2653 (s, $[PtN_4]$).

1,7-Bis(hydroxypropyl)-1,7-carborane 24. A solution of 1,7-carborane (860 mg, 5.96 mmol) in THF (30 mL) was stirred at −78 °C. A solution of *n*-BuLi (2.5 M, 6 mL, 15 mmol) in THF (25 mL) was added dropwise over 10 min and the mixture was stirred for a further 40 min at −78 °C and slowly warmed to room temperature. Oxetane (1.1 mL, 16.9 mmol) was added and the mixture was heated to reflux for 4 h. The addition of 2 M HCl (15 mL, 30 mmol) quenched the reaction. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with H_2O (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to afford a colourless solid. Purification by flash chromatography on silica (67% EtOAc in *n*-hexane, $R_f = 0.31$) gave **24** (963 mg, 62%) (Found: C, 36.84; H, 9.18%. $C_8H_{24}B_{10}O_2$ requires C, 36.90; H, 9.29%). δ_H (300.10 MHz, $CDCl_3$ + drop d_6-acetone) 3.56 (t, 4H, $^3J_{HH}$ = 6.3 Hz, CH_2OH), 2.03 (m, 4H, CH_2C_{cage}), 1.62 (m, 4H, $CH_2CH_2C_{cage}$); δ_C (75.48 MHz, $CDCl_3$ + drop d_6-acetone) 75.5 (C_{cage}), 61.4 (CH_2OH), 33.4 (CH_2C_{cage}), 32.7 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, $CDCl_3$ + drop d_6-acetone) −7.66 (s, 2B), −11.45 (s, 6B), −13.84 (s, 2B).

1,2-Bis(hydroxypropyl)-1,2-carborane 25. The compound was prepared from 1,2-carborane in a similar manner to that described for **24** to afford **25** as a colourless solid (76%) after stirring the crude material in $CHCl_3$ (4 mL) in order to dissolve the small amount of impurity (Found: C, 36.87; H, 9.35%. $C_8H_{24}B_{10}O_2$ requires C, 36.90, H, 9.29%). Mp 125–126 °C. δ_H (199.98 MHz, $CDCl_3$ + drop d_6-acetone) 3.65 (t, 4H, $^3J_{HH}$ = 5.4 Hz, CH_2OH), 2.35 (m, 4H, CH_2C_{cage}), 1.81 (m, 4H, $CH_2CH_2C_{cage}$); δ_C (50.29 MHz, $CDCl_3$ + drop d_6-acetone) 79.6 (C_{cage}), 61.3 (CH_2OH), 32.4 (CH_2C_{cage}), 31.6 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, $CDCl_3$ + drop d_6-acetone) −5.17 (s, 2B), −11.00 (s, 8B).

1,7-Bis(bromopropyl)-1,7-carborane 26. To a solution of **24** (947 mg, 3.64 mmol) and CBr_4 (3.145 g, 9.48 mmol) in CH_2Cl_2 (40 mL) at 5 °C was added dropwise a solution of PPh_3 (2.89 g, 11.0 mmol) in CH_2Cl_2 (30 mL) over 30 min. The reaction mixture was warmed to room temperature and stirred for a further 2 h. The solvent was removed *in vacuo* to afford an orange residue which was stirred with diethyl ether (20 mL) for 30 min, and the undissolved solid was removed by filtration. The filtrate was reduced to dryness *in vacuo* to give a yellow residue which was purified by squat chromatography on silica (2% diethyl ether in *n*-hexane, $R_f = 0.38$) to give **26** as a pale-yellow oil (1.21 g, 86%) (Found: C, 24.83; H, 5.81%. $C_8H_{22}B_{10}Br_2$ requires C, 24.88; H, 5.74%). δ_H (300.10 MHz, $CDCl_3$) 3.31 (t, 4H, $^3J_{HH}$ = 6.3 Hz, CH_2Br), 2.10 (m, 4H, CH_2C_{cage}), 1.91 (m, 4H, $CH_2CH_2C_{cage}$); δ_C (50.29 MHz, $CDCl_3$) 74.7 (C_{cage}), 35.4 (CH_2Br), 32.5 (CH_2C_{cage}), 31.9 ($CH_2CH_2C_{cage}$); δ_B (96.30 MHz, $CDCl_3$) −7.45 (s, 2B), −11.24 (s, 6B), −13.79 (s, 2B).

1,2-Bis(bromopropyl)-1,2-carborane 27. The compound was prepared from **25** in a similar manner to that described for **26**. Purification of the orange residue by squat chromatography on silica (15% EtOAc in *n*-hexane, $R_f = 0.55$) gave, after removal of the solvent *in vacuo*, **27** (73%) (Found: C, 24.87; H, 5.76%. $C_8H_{22}B_{10}Br_2$ requires C, 24.88; H, 5.74%). Mp 49–50 °C. δ_H (300.10 MHz, $CDCl_3$) 3.42 (t, 4H, $^3J_{HH}$ = 6.0 Hz, CH_2Br), 2.39 (m, 4H, CH_2C_{cage}), 2.10 (m, 4H, $CH_2CH_2C_{cage}$). δ_C (75.48 MHz, $CDCl_3$) 78.7 (C_{cage}), 33.5 (CH_2Br), 32.1 (CH_2C_{cage}), 31.9 ($CH_2CH_2C_{cage}$). δ_B (96.30 MHz, $CDCl_3$) −4.80 (s, 2B), −10.46 (s, 8B).

1,2-Bis(iodopropyl)-1,2-carborane 28. The compound was prepared from **27** in a similar manner to that described for **11** to afford **28** as a yellow solid (73%) (Found: C, 20.02; H, 4.66%. $C_8H_{22}B_{10}I_2$ requires C, 20.01; H, 4.62%). Mp 63–64 °C. δ_H (300.10 MHz, $CDCl_3$) 3.20 (t, 4H, $^3J_{HH}$ = 6.2 Hz, CH_2I), 2.35 (m, 4H, CH_2C_{cage}), 2.03 (m, 4H, $CH_2CH_2C_{cage}$). δ_C (50.29 MHz, $CDCl_3$) 78.5 (C_{cage}), 35.8 (CH_2C_{cage}), 32.6 ($CH_2CH_2C_{cage}$), 4.2 (CH_2I). δ_B (96.30 MHz, $CDCl_3$) −4.79 (s, 2B), −10.55 (s, 8B).

***N*,*N*-Di-*tert*-butyloxycarbonyl-1,7-bis(aminopropyl)-1,7-carborane 29.** To a stirred solution of Bu_4NHSO_4 (4.38 g, 12.9 mmol) and aqueous NaOH (2 M, 13 mL, 26 mmol) in CH_2Cl_2 (80 mL) was added a solution of di-*tert*-butyl iminodicarboxylate (2.81 g, 12.9 mmol) in CH_2Cl_2 (25 mL). After stirring for 30 min, a solution of **11** (3.09 g, 6.45 mmol) in CH_2Cl_2 (50 mL) was added dropwise to the mixture. The reaction was then heated to reflux for 20 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were reduced *in vacuo* to afford a yellow residue that was stirred with diethyl ether (100 mL) for 20 min to precipitate Bu_4NI, which was removed by vacuum filtration. The filtrate was dried over anhydrous Na_2SO_4 and reduced *in vacuo* to afford a yellow oil that was purified by flash chromatography on silica (elution with *n*-hexane followed by gradients up to 30% diethyl ether in *n*-hexane). Recrystallisation of the residue from *n*-hexane gave **29** (2.48 g, 58%). Mp 103 °C (Found: C, 51.20; H, 8.96; N, 4.19%. $C_{28}H_{58}B_{10}N_2O_8$ requires C, 51.04; H, 8.87; N, 4.25%). δ_H (199.98 MHz, $CDCl_3$) 3.47 (t, 4H, $^3J_{HH}$ = 7.0 Hz, CH_2N), 1.87 (m, 4H, CH_2C_{cage}), 1.50 (m, 40H, $C(CH_3)_3$, CH_2CH_2N); δ_C (50.29 MHz, $CDCl_3$) 152.5 (CO), 82.5 ($C(CH_3)_3$), 75.2 (C_{cage}), 45.5 (CH_2N), 34.2 (CH_2C_{cage}), 29.3 ($CH_2CH_2C_{cage}$), 28.1 (CH_3); δ_B (96.30 MHz, $CDCl_3$) −7.61 (s, 2B), −11.18 (s, 6B), −13.90 (s, 2B).

***N*,*N*-Di-*tert*-butyloxycarbonyl-1,2-bis(aminopropyl)-1,2-carborane 30.** The compound was prepared from **28** in a similar manner to that described for **29** to afford a yellow oil that was purified by flash chromatography on silica. Elution with CH_2Cl_2 followed by gradients up to 5% diethyl ether in CH_2Cl_2 gave, after removal of solvent *in vacuo*, **30** (89%) (Found: C, 51.10; H, 8.78; N, 4.17%. $C_{28}H_{58}B_{10}N_2O_8$ requires C, 51.04; H, 8.87; N, 4.25%). δ_H (300.10 MHz, $CDCl_3$) 3.55 (t, 4H, $^3J_{HH}$ = 6.9 Hz, CH_2N), 2.13 (m, 4H, CH_2C_{cage}), 1.84 (m, 4H, CH_2CH_2N), 1.51 (s, 36H, $C(CH_3)_3$); δ_C (50.29 MHz, $CDCl_3$) 152.4 (CO), 82.5 ($C(CH_3)_3$), 82.4 (C_{cage}), 45.2 (CH_2N), 32.3 (CH_2C_{cage}), 28.9 ($CH_2CH_2C_{cage}$), 28.0 (CH_3); δ_B (96.30 MHz, $CDCl_3$) −4.89 (s, 2B), −10.69 (s, 8B).

In vitro cytotoxicity studies

All anti-cancer screening was performed in the Andrew Durant Drug Testing Facility, Peter MacCallum Cancer Institute (Melbourne, Australia).

Coulter counting (CC) assay

Cells are placed into the wells of a culture plate. The drugs are dissolved in DMSO and diluted to a range of concentrations. 5 μL of each drug solution is added to the wells of the plate. Six

wells are used as controls: 5 μL vehicle is added to four wells (solvent controls) and the remaining two wells represent blank controls. The plate is then incubated at 37 °C in a humidified 5% CO_2, 95% air atmosphere for 48 h after which the cells are diluted and counted using a Sysmex particle counter.

The percent cell growth at each drug concentration is determined as the average cell number in the drug treated wells/average cell number of the vehicle control wells × 100. The results are plotted as % cell growth against drug concentration. The IC_{50} (read from the dose response curve) is defined as the drug concentration that results in a 50% reduction in cell growth.

Sulforhodamine (SRB) assay

Cells are placed into the wells of two culture plates and incubated overnight at 37 °C in a humidified 5% CO_2, 95% air atmosphere. One plate is then fixed with TCA (as a measure of cells present at the time of addition of drug). Drugs are dissolved in DMSO to make solutions of concentrations spanning a 4-log range. 100 μL of each drug solution is then added to wells of the second plate. The plate is then incubated for a further 72 h after which viable cells are measured using the sulforhodamine B (SRB) assay.[42,43] Cells are measured by reading the absorbance at 550 nm using an automatic plate reader. The mean absorbance for time zero growth (Tz), control growth (C) and test drug growth (Ti) is determined and the % growth is calculated at each drug concentration as:

$[(Ti - Tz)/(C - Tz)] \times 100$ for concentrations where $Ti \geq Tz$

$[(Ti - Tz)/Tz] \times 100$ for concentrations where $Ti < Tz$

The IC_{50} is the drug concentration that results in a 50% reduction in the net cellular protein increase in control cells following drug incubation.

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