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Synthesis and screening of bifunctional radiolabelled carborane-carbohydrate derivatives

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ABSTRACT

A new bifunctional carborane ligand was prepared as a platform for the development of targeted molecular radioimaging and therapy agents. The carborane derivative was synthesized bearing a glucose substituent to increase the water solubility of the ligand and a benzoic acid group as a site for linking to amine containing targeting vectors. A convenient method to conjugate the ligand and the non-glycosylated analogue to amino groups was developed using simple active esters which were combined with a model amine generating two new *N*,*N*-diethyl(aminoethyl) benzamide derivatives. These were labelled with ^{125}I in good yield and the log*P* values measured for [^{125}I]-**15** (log*P* = 0.82 ± 0.04) and [^{125}I]-**16** (log*P* = 1.53 ± 0.01). The benzamides were also evaluated for their capacity to bind to B16F10 melanoma cells where the hydrophilic compound showed low binding while [^{125}I]-**16** showed modest uptake (30.7 ± 2.2%) after 24 h.

1. Introduction

Targeted radiopharmaceuticals are typically engineered such that they contain two key components: a vector for achieving high target-to-non-target ratios and a ligand or prosthetic group to ensure that there is a robust covalent linkage between the targeting moiety and the radionuclide. Radiolabelled carboranes are attractive synthons in this regard because they can be readily conjugated to, or incorporated within, targeting vectors using a number of creative strategies and they are conveniently prepared from virtually any suitably protected alkyne [1–7]. 7,8-Dicarba-*nido*-undecaborate(-1) or *nido*-carborane ligands, which can be prepared from the corresponding *closo*-carboranes [1,8–12], have a unique feature in that they can be labelled with both radiometals, including technetium, which is the most widely used radionuclide in diagnostic medicine [13,14] and radiohalogens. *Nido*-carboranes form highly stable η^5-complexes with metals [15–19] and they can be labelled with halogens using electrophilic methods analogous to those currently used to prepare traditional radiopharmaceuticals [20–22]. Iodinated *nido*-carborane derivatives are attractive platforms for developing molecular imaging probes because the B–I bond formed is more robust than aryl C–I bonds, [22–24] thereby curtailing de-iodination *in vivo*. Not surprisingly, there has been an increase in the number of groups developing targeted radiopharmaceuticals using radiohalogenated *nido*-carboranes [21,22,24–35].

One of the limitations associated with carborane-based radiopharmaceuticals is that they are generally lipophilic which can promote non-specific binding. In this paper, we present the synthesis and characterization of a bifunctional carborane-glucose derivative where the hydrophilic nature of the carbohydrate is designed to mask the non-polar carborane group. Several examples for other classes of imaging agents have been reported in which the addition of a carbohydrate reduces non-specific binding and enhances pharmacokinetics (faster clearance from non-target tissues) versus the underivatized counterparts [36–43].

2. Results and discussion

We recently described the preparation and labelling of simple carboranyl glycoside derivatives of glucose with both Tc and iodine [44,45]. Building on the success of the model system, a *nido*-carboranyl glycoside **1** that contains a benzoic acid group for conjugation to targeting vectors such as peptides, proteins, or antibodies was developed (Fig. 1). A non-glycosylated analogue (**2**) was prepared in parallel so that the impact of the sugar on the overall polarity of the compounds (i.e. log*P*) could be determined.

2.1. Preparation of nido-carborane precursors

Compound **1** was prepared in three steps in good overall yield from the known alkyne **3** [46,47]. A Sonogashira type cross-coupling reaction [48] between **3** and methyl 4-iodo-benzoate [49] was used to incorporate the benzoic acid group which would later serve as the location for conjugation to targeting vectors [50–52].

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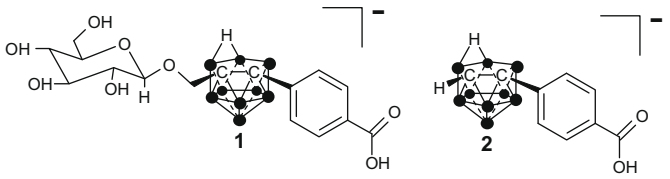


Fig. 1. Functionalized *nido*-carborane derivatives **1** and **2**.

The corresponding carborane was then prepared using a standard decaborane-alkyne insertion reaction. Simultaneous carborane cage degradation and ester saponification was achieved using sodium hydroxide in methanol which, following work-up, gave **1** in 29% overall yield. The non-glycosylated *nido*-carborane-benzoic acid precursor **2** was prepared via a similar route starting with methyl 4-[1,2-dicarba-*closo*-dodecaboranyl] benzoate in excellent yield.

2.2. Preparation of model conjugates

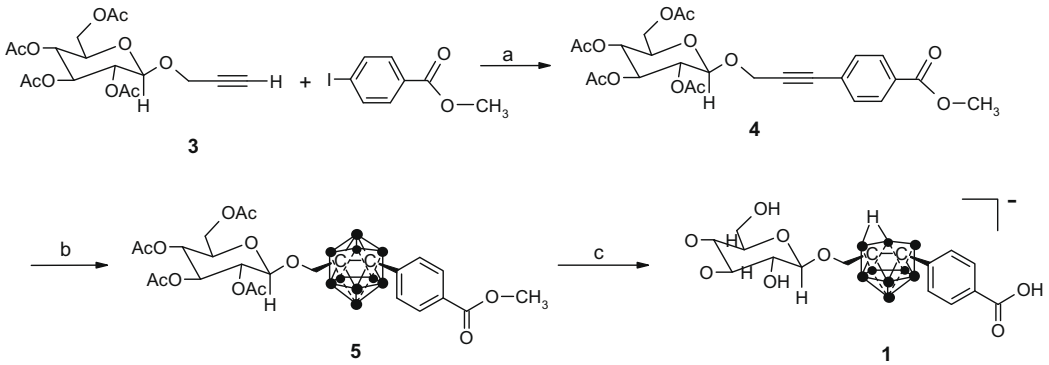
The optimal method for linking **1** and **2** to targeting amines was investigated using a simple alkylamine (*N*,*N*-diethylethylenediamine). This amine was selected to not only probe the reactivity of the benzoic acid group but to also produce two novel benzamides for use in targeting melanoma. There is a wealth of data in the literature indicating that *N*,*N*-dialkyl(aminoalkyl) benzamides have high uptake in melanin positive tumour types [22,53–75]. Moreover, Hawthorne and co-workers have demonstrated the *in vivo* stability and rapid clearance in biodistribution studies of radioiodinated benzamides derived from *nido*-carboranes [22]. The attractive feature of the target carborane-benzamides proposed here over conventional agents containing aryl halides is that the strength of the boron-iodine bond should prevent the premature catabolism while the carbohydrate group should decrease non-specific binding and promote clearance from non-target tissues. If these hypotheses are in fact valid, then the carborane-based agents would not only be useful imaging agents but they would also be attractive compounds for targeted radionuclide therapy which requires robust complexes and high target-to-non-target ratios in order to minimize the radiation dose to healthy tissue (see Scheme 1).

The non-glycosylated *nido*-carboranyl benzamide **7** was prepared from the benzoic acid derivative **2** (Scheme 2) using a convenient active ester coupling strategy. The 2,3,5,6-tetrafluorophenyl active ester **6** was obtained via DIC coupling and isolated by preparative TLC. The benzamide target **7** was then prepared by combining **6** with *N*,*N*-diethylethylenediamine in acetonitrile at room temperature for 12 h; purification by preparative TLC gave the target in 26% yield.

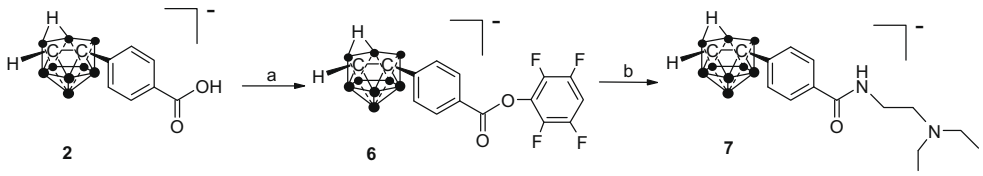
An alternative route was established to prepare the glycosylated target **8** because the polar nature of the compounds complicated the isolation of large quantities of the active ester precursor. To address this issue, the protecting groups were altered such that a benzyl ester was used in place of the methyl ester (Scheme 3). This made it possible to liberate the acid without removing the acetate protecting groups on the carbohydrate, thereby making it simpler to purify the active ester and benzamide. Each step in the synthesis had yields greater than 50% with the exception of the final step which was 35%. This still represents an improvement over the yield obtained when trying to prepare the target directly from *nido*-carboranyl glycoside **1**.

2.3. Syntheses of iodinated nido-carborane standards

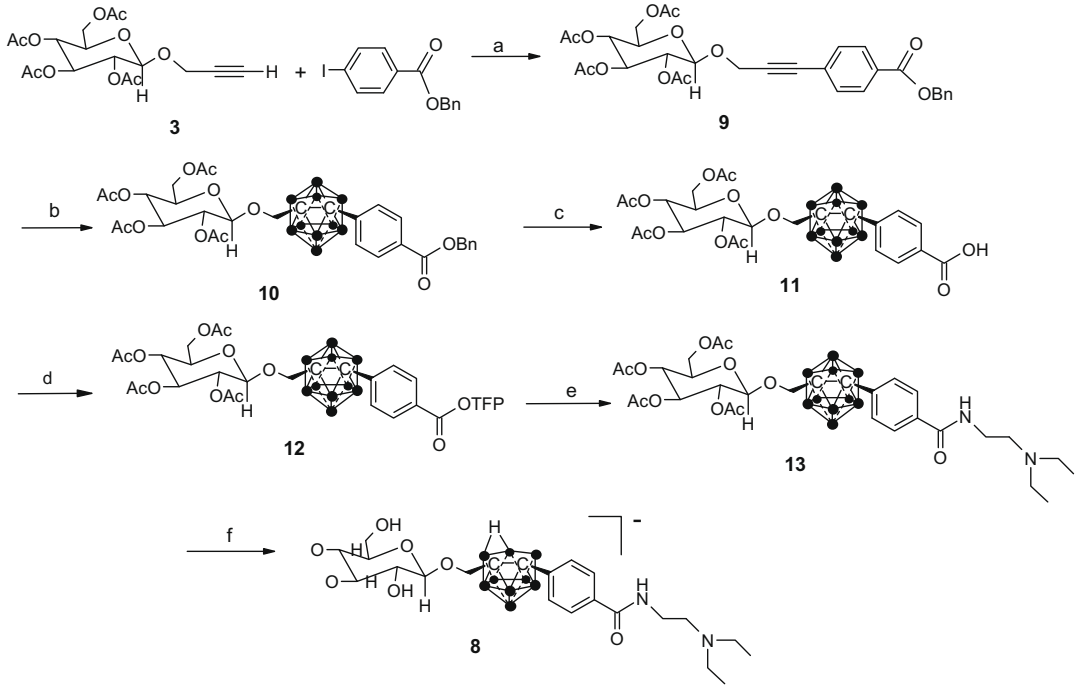
The next step was to isolate the non-radioactive iodinated derivatives **14**–**16** (Scheme 4), for which small quantities are needed as reference standards for the radiolabelled analogues [20]. A sample of **14** was prepared by treating precursor **1** with I_2 in ethanol. Analysis by HPLC and electrospray mass spectrometry indicated complete consumption of the starting material after 2 h at room temperature, as evidenced by the absence of the HPLC and MS signals corresponding to **1**. The HPLC chromatogram of the isolated product contained four peaks (Fig. 2, top), with each peak showing the target anion mass of $m/z = 572$ for **14** in the



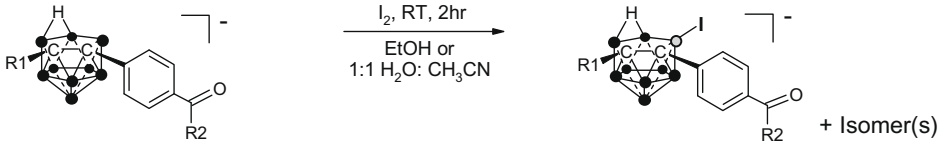
Scheme 1. Reagents and conditions: (a) 5 mol% $(Ph_3P)_4Pd$, 5 mol% CuI, 1:1 THF:NEt_3, reflux, 12 h; (b) $B_{10}H_{14}$ (2.0 equiv.), CH_3CN, reflux, 48 h; (c) (i) NaOH (20 equiv.), MeOH, 60 °C, 12 h; (ii) NaOH(aq), 3 h; (iii) 1 M HCl, pH 4.



Scheme 2. Reagents and conditions: (a) TFP, DIC, 12 h, CH_3CN; (b) *N*,*N*-diethylethylenediamine, 12 h, CH_3CN.



Scheme 3. Reagents and conditions: (a) 5 mol% $(Ph_3P)_4Pd$, 5 mol% CuI, 1:1 v:v THF:NEt_3, reflux, 12 h; (b) $B_{10}H_{14}$, CH_3CN, reflux, 48 h; (c) H_2 (1 atm), 10% Pd/C, EtOH, 1 h; (d) 2,3,5,6-tetrafluorophenol, EDC · HCl, CH_3CN, 2 h; (e) *N*,*N*-diethylethylenediamine, CH_3CN, 12 h; (f) NaOH, EtOH, 60 °C, 12 h.



1: R1 = CH_2-β-D-glucose, R2 = OH
7: R1 = H, R2 = $NH(CH_2)_2N(C_2H_5)_2$
8: R1 = CH_2-β-D-glucose, R2 = $NH(CH_2)_2N(C_2H_5)_2$

14: R1 = CH_2-β-D-glucose, R2 = OH
15: R1 = CH_2-β-D-glucose, R2 = $NH(CH_2)_2N(C_2H_5)_2$
16: R1 = H, R2 = $NH(CH_2)_2N(C_2H_5)_2$

Scheme 4. Synthesis of iodo-*nido*-carborane derivatives **14**–**16**.

LC/MS spectrum. The $^{11}B\{^1H\}$ NMR spectrum of **14** was consistent with the presence of the iodinated carborane cage, with the signal appearing at −29.3 ppm [25,76].

The appearance of four HPLC peaks corresponding to **14** is consistent with the generation of isomers as a result of the iodine reacting with the two boron atoms adjacent to the two carbon atoms on the open face of the *nido*-carborane cage [24,31]. The other two products are formed because the *nido*-carborane exists as a pair of diastereomers. Degradation of mono-substituted *closo*-carboranes results in the formation of enantiomers, and in the case of the carbohydrate derivatives which have fixed stereochemistry, the products are diastereomers [3,77]. As a result, iodination of **1** should result in a total of four species for **14**. Further spectroscopic evidence for this was obtained by the observation of, for example, four distinct anomeric proton signals in the ^1H NMR spectrum, and four distinct anomeric carbon signals in the ^{13}C NMR spectrum of **14**.

The iodinated-*nido*-carboranyl benzamides **15** and **16** were prepared in a manner analogous to that described for **14**. Electrospray mass spectrometry was consistent with exclusive mono-iodination. In the case of both benzamides, multiple HPLC peaks were again observed having the expected target mass, indicating a mixture of four and two isomers for compounds **15** and **16**, respectively. The formation of multiple isomers is not desirable however the peaks can be readily separated by HPLC. Furthermore, in the event that one isomer has higher affinity for the target or preferable pharmacokinetic properties, the *nido*-carborane diastereomers can be separated prior to labelling and HPLC purification. In the case of compound **14**, which is intended for use as a prosthetic group for linking to a larger targeting vector such as a peptide or antibody, we would expect that the presence of multiple isomers at the carborane cage would not influence the affinity of the larger component since it would be located distant to the binding domain of the agent.

2.4. Radiolabelling with ^{125}I

The radiolabelling of compounds **1**, **7**, and **8** was undertaken following methods previously established for radioiodination of the simple carboranyl glycoside derivative [45]. Compound [^{125}I]-**14** was prepared and isolated via HPLC in 50% radiochemical yield. The radiochromatogram for [^{125}I]-**14** displayed a series of four peaks correlating with the non-radioactive standard **14**. The relative intensities of these peaks were consistent with those of the standard (Fig. 2). The slight discrepancy observed may be due to different rates of formation of the various isomers of **14** at the tracer level.

The syntheses of benzamides [^{125}I]-**15** and [^{125}I]-**16** were initially explored by using conditions similar to those described above for **1**. For initial experiments, the non-glycosylated precursor

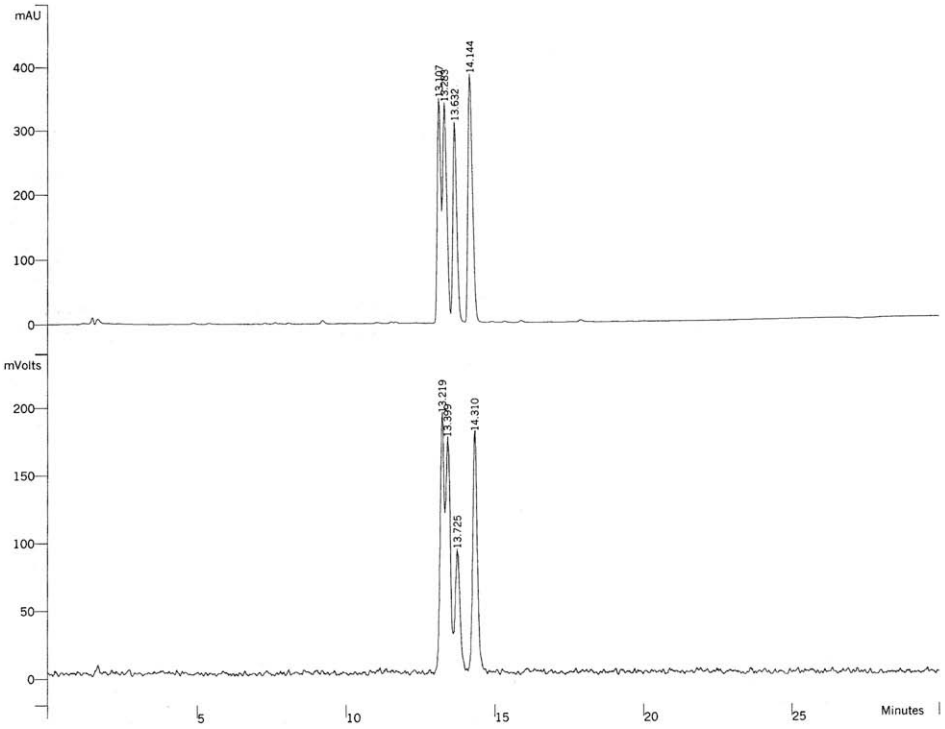


Fig. 2. HPLC analysis for ^{125}I radiolabelling of **1**. Top: UV trace of non-radioactive standard **14**. Bottom: γ-HPLC trace of [^{125}I]-**14**.

7 was reacted with Na[^{125}I] in the presence of Iodogen® in a 1:1 mixture of acetonitrile and water containing 5% acetic acid; the organic solvent was required to dissolve the starting materials which were not soluble in water alone. This initial radiolabelling reaction gave unexpected results, with no radioactive peak observed corresponding to the target. Following this, a non-radioactive experiment was also performed with "cold" sodium iodide under the same conditions. Analysis of the product mixture by HPLC and LC/MS revealed the *N*-dealkylation of the iodinated *nido*-carboranyl benzamide. Degradation of tertiary amines has been reported to occur in the presence of strong oxidants under acidic conditions [78]. Further non-radioactive experiments were conducted which showed that the extent of degradation was reduced when chloramine-T was used as the oxidant. Therefore, this oxidant was used in subsequent preparations involving the benzamide derivatives.

Using chloramine-T (20 μL of a 1 mg/mL solution in water) as the oxidant, the γ-HPLC traces showed two peaks that had retention times that corresponded to those for the non-radioactive standards. Incorporation of activity at the desired target was estimated to be >95% from peak integration of the crude analytical traces. Compound [^{125}I]-**16** was obtained in 73% radiochemical yield following isolation by semi-preparative HPLC. The glycoside [^{125}I]-**15** was prepared in the same manner and isolated in 92% yield. HPLC analysis of the isolated products (Figs. 3 and 4) showed that they were obtained in >99% radiochemical purity, and that their respective precursors had been removed. For the purposes of rapid isolation, it was also possible to use solid phase extraction by employing C18 SepPak™ cartridges. Although the tracers could be obtained in excellent radiochemical purity (>99%) using this method, the specific activity was low, as the SPE method did not separate the radioiodinated benzamides from their non-radioactive precursors. This is not a major issue for the subsequent cell binding studies since the extent of benzamide binding to melanin has been reported to be independent of specific activity [72]. The radioiodinated compounds also showed excellent stability, with 98% of [^{125}I]-**16** remaining intact after 24 h, and >99% of [^{125}I]-**15** remaining intact after 72 h.

With the synthesis and isolation of benzamides [^{125}I]-**15** and [^{125}I]-**16** accomplished, the measurement of their log*P* values was undertaken to assess the impact of the carbohydrate substituent [79]. Following isolation, the solutions containing the products were evaporated by a stream of air and phosphate-buffered saline (pH 7.4) added. As was observed by Wilbur and co-workers, the radioiodinated *nido*-carborane derivatives had a tendency to adhere to glass vessels. In the case of compounds [^{125}I]-**15** and [^{125}I]-**16**, the products adhered to both plastic and glass vessels which could be minimized by silanization of glass vials with Sigmacote™ (Aldrich). The log*P* calculated for compounds [^{125}I]-**15** and [^{125}I]-**16** were 0.82 ± 0.04 and 1.53 ± 0.01, respectively. These results confirm that the addition of the glucose group had a significant impact on the polarity of the compound. The difference of 0.71 log units is in reasonable agreement with differences observed for glycopeptides reported by Haubner and co-workers [37], who noted a difference of approximately 0.5 log units between short peptide sequences and their glycosylated analogues.

The binding of benzamides **7** and **8** to B16F10 mouse melanoma cells was also evaluated. For control purposes, [^{125}I]BZA, which has been shown previously to have high affinity to this particular cell line [53,72], was prepared and its uptake evaluated in parallel. The results showed that the glycosylated benzamide [^{125}I]-**15** bound poorly to the cells with a maximum binding being 0.62 ± 0.11% of the incubated activity after 24 h (Fig. 5). Meanwhile, [^{125}I]-**16** showed improved uptake (30.7 ± 2.2% at 24 h) which was less than that for [^{125}I]BZA (91.6 ± 0.3% at 24 h). These results suggest that the increased hydrophilicity of the carbohydrate conjugate resulted in reduced uptake by the melanoma cells and that perhaps the negative charge on the carborane also had a detrimental impact on binding. This is in agreement with the general observation that uptake of radioiodobenzamides by melanotic melanoma increases with increasing lipophilicity [55].

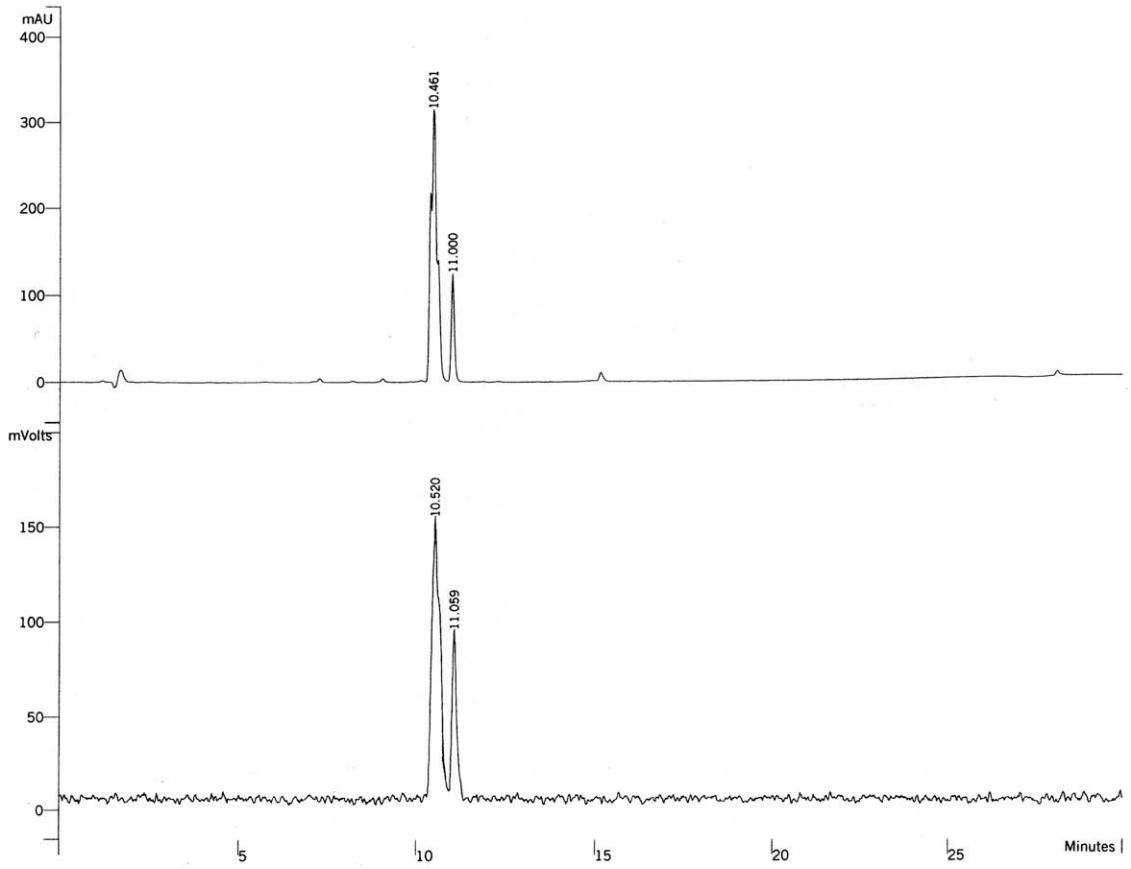


Fig. 3. HPLC analysis for ^{125}I-radiolabelling of **8**. Top: γ-HPLC trace of [^{125}I]-**15**. Bottom: UV trace of non-radioactive standard **15**.

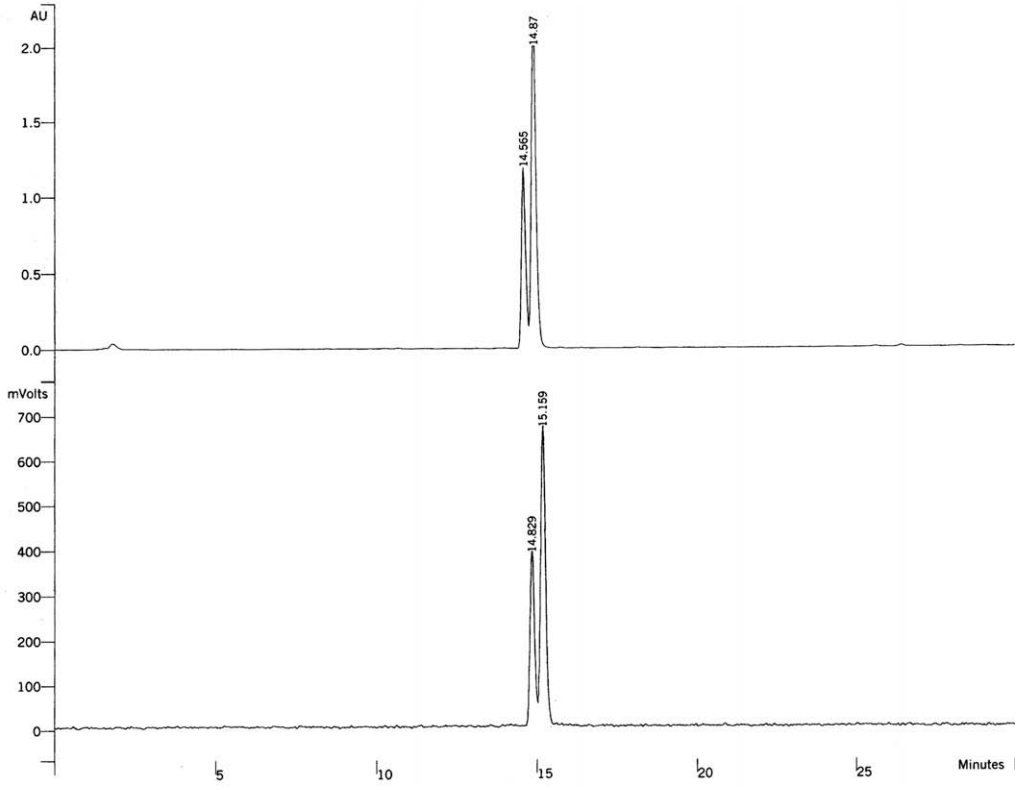


Fig. 4. HPLC analysis for ^{125}I radiolabelling of **7**. Top: UV trace of non-radioactive standard **16**. Bottom: γ-HPLC trace of [^{125}I]-**16**.

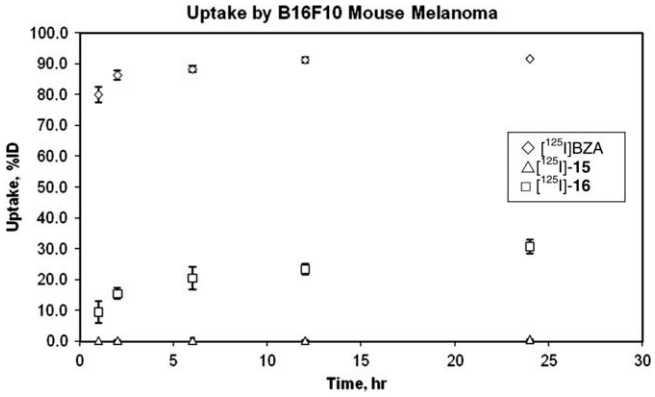


Fig. 5. Binding of [^{125}I]BZA, [^{125}I]-**15** and [^{125}I]-**16** to B16F10 melanoma cells as a function of time.

3. Experimental

3.1. Materials and instruments

All reagents used were purchased from Aldrich, except for decaborane [14], which was purchased from Katchem (Czech Rep.). Solvents were purchased from Caledon and dried using a PureSolv drying apparatus (Innovative Technology). No-carrier-added ^{125}I was obtained from the McMaster Nuclear Reactor as Na[^{125}I] in 0.1 N NaOH. NMR spectroscopy was performed on either a Bruker DRX-500 (^{1}H frequency = 500.13 MHz, ^{13}C = 125.77 MHz, ^{11}B = 160.46 MHz) or Avance AV-600 (^{1}H = 600.13 MHz, ^{13}C = 150.90 MHz, ^{11}B = 192.55 MHz) spectrometer. Proton and carbon assignments were made with the assistance of COSY, HSQC and HMBC spectra. The residual signal of the NMR solvent relative to tetramethylsilane was taken as the internal reference for ^{1}H and ^{13}C spectra. ^{11}B spectra were referenced using a $BF_3 \cdot Et_2O$ external standard. The numbering scheme used for NMR assignments can be found in Supplementary material. Infrared spectra were recorded on a BioRad FTS-40 FT-IR instrument. Mass spectra were obtained using a Micromass Quattro-LC Triple Quadrupole mass spectrometer. Radioactivity measurements were made using either a Capintec CRC-15W dose calibrator or a Perkin–Elmer Wizard gamma counter. High-performance liquid chromatography was performed with a Varian ProStar HPLC system fitted with an IN/US γ-RAM Model 3 detector. For analysis of compounds, either a Varian Nucleosil 4.6 × 250 mm C18 or Phenomenex Gemini 4.6 × 100 mm C18 column was used. For semi-preparative HPLC, a Varian Dynamax 10 × 250 mm C18 column was used. Elution conditions: Method A: 80:20 A:B to 20:80 A:B; 0–20 min, 20:80 A:B to 100% B; 20–25 min, 100% B; 25–30 min (A = H_2O containing 0.05% TFA, B = CH_3CN containing 0.05% TFA), Nucleosil column; Method B: 80:20 A:B to 20:80 A:B; 0–20 min, 20:80 A:B to 100% B; 20–25 min, 100% B; 25–30 min (A = H_2O containing 0.05% TFA, B = CH_3CN containing 0.05% TFA), Gemini column. Analytical flow rate was 1.0 mL/min; semi-preparative flow rate was 4.7 mL/min. Thin-layer chromatograms (Merck F_{254} silica gel on aluminum plates) were visualized using 0.1% $PdCl_2$ in 3 M HCl.

3.2. Cell culture

The murine B16F10 melanoma cell line was purchased from ATCC (Manassas, VA) and maintained in monolayer in DMEM (11995; Gibco, Burlington, ON, Canada) supplemented with 10% fetal bovine serum (SH30071.03; Hyclone Laboratories, Logan, UT) and 1% antibiotic/antimycotic (AB/AM) (15240-062; Invitrogen, Burlington, ON). All cells were maintained at 37 °C in 5% CO_2.

3.3. Methyl 4′-(2-propynyl-2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyloxy)-3-benzoate (**4**)

Methyl 4-iodo-benzoate (2.53 g, 9.6 mmol) was placed in a 2-neck round-bottom flask (equipped with a condenser and magnetic stir bar) under an atmosphere of nitrogen, and dissolved in dry THF (50 mL). To this was added $Pd(PPh_3)_4$ (560 mg, 0.5 mmol), CuI (111 mg, 0.6 mmol) and triethylamine (50 mL). A solution of compound **3** (3.42 g, 8.8 mmol) in dry THF (40 mL) was added dropwise to the reaction vessel. The reaction mixture was stirred at reflux for 12 h, during which time the solution changed from colourless, to light yellow, to dark brown with a white suspended solid. The solution was filtered through a pad of Celite, concentrated on a rotary evaporator and subsequently re-dissolved in 100 mL of dichloromethane and placed in a separatory funnel. The organic solution was shaken twice with 250 mL of 0.1 M HCl, followed by 250 mL of brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated to a dark orange-brown oil on the rotary evaporator. Silica gel column chromatography (10–50% ethyl acetate/hexanes) was used to isolate the target compound as an orange oil that was dissolved in a mixture of diethyl ethyl acetate and hexanes to crystallize the desired product. The target compound was obtained in 64% yield (2.93 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, 2H, $^3J_{2',3'} = 8.3$ Hz, H-2′), 7.50 (d, 2H, H-3′), 5.27 (dd, 1H, $^3J_{2,3} = 9.4$ Hz, $^3J_{3,4} = 9.4$ Hz, H-3), 5.12 (t, 1H, $^3J_{4,5} = 10.0$ Hz, H-4), 5.04 (dd, 1H, $^3J_{1,2} = 8.0$ Hz, H-2), 4.84 (d, 1H, H-1), 4.61 (s, 2H, H-7), 4.29 (dd, 1H, $^2J_{6a,6b} = -12.3$ Hz, $^3J_{5,6a} = 4.6$ Hz, H-6a), 4.17 (dd, 1H, $^3J_{5,6b} = 2.3$ Hz, H-6b), 3.93 (s, 3H, H-11), 3.77 (ddd, 1H, H-5), 2.08, 2.04, 2.03, 2.01 (4s, 12H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.2, 169.3, 166.3, 131.6, 130.1, 129.5, 126.8, 98.5, 86.4, 86.3, 72.8, 72.0, 71.2, 68.4, 61.8, 56.7, 52.2, 20.6, 20.5. IR (KBr): ν 1758, 1722 cm^{-1}. ESI-MS: m/z = 538.6 $[M+NH_4]^+$. HRMS (ESI): Calculated for $C_{25}H_{28}O_{12}NH_4$: 538.1925. Observed: 538.1915. M.P.: 80–83 °C. TLC (2:1 hexanes:ethyl acetate): R_f = 0.24.

3.4. Methyl 4′-(1-methyl-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyloxy)-1,2-dicarba-closo-dodecaboranyl)-2-benzoate (**5**)

$B_{10}H_{14}$ (1.35 g, 11.0 mmol) was dried under vacuum for 2 h in a flame-dried round-bottom flask. Under nitrogen, dry acetonitrile (50 mL) was added via syringe through a septum, and the resulting solution stirred at room temperature for 12 h. Compound **4** (2.57 g, 4.94 mmol) was added, and the solution heated to reflux and stirred for a further 48 h. The solution was cooled to room temperature and concentrated on a rotary evaporator, yielding an orange-brown oil. Column chromatography (10–50% ethyl acetate/hexanes) resulted in the isolation of a slightly yellow solid which was re-crystallized from ethyl ether and hexanes to give the desired compound as a white solid in 60% yield (1.89 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, 2H, $^3J_{2',3'} = 8.5$ Hz, H-3′), 7.70 (d, 2H, H-2′), 5.13 (t, 1H, $^3J_{2,3} = 9.5$ Hz, $^3J_{3,4} = 9.5$ Hz, H-3), 4.99 (t, 1H, $^3J_{4,5} = 9.9$ Hz, H-4), 4.95 (dd, 1H, $^3J_{1,2} = 7.8$ Hz, H-2), 4.31 (d, 1H, H-1), 4.11 (dd, 1H, $^2J_{6a,6b} = -12.4$ Hz, $^3J_{5,6a} = 4.7$ Hz, H-6a), 3.95 (dd, 1H, $^3J_{5,6b} = 2.3$ Hz, H-6b), 3.94 (s, 3H, OCH_3 H-11), 3.83 (d, 1H, $^2J_{7a,7b} = -12.6$ Hz, H-7a), 3.69 (d, 1H, H-7b), 3.52 (ddd, 1H, H-5), 2.12, 2.03, 2.01, 1.99 (4s, 12H, CH_3) 1.70–3.20 (br m, B-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.1, 169.2, 169.0, 165.7, 134.3, 132.4, 131.2, 129.9, 100.2, 81.3, 79.4, 72.3, 72.0, 70.7, 68.1, 67.9, 61.5, 52.5, 20.6, 20.5. ^{11}B{^{1}H} NMR (160 MHz, $CDCl_3$): δ −3.7, −11.0. IR (KBr): ν 2587, 1758, 1730 cm^{-1}. ESI-MS: m/z = 657.8 $[M+NH_4]^+$. HRMS (ESI): Calculated for $C_{25}H_{38}B_{10}O_{12}NH_4$:

657.3696. Observed: 657.3715. TLC (2:1 hexanes:ethyl acetate): R_f = 0.27. M.P.: 167–170 °C.

3.5. 4′-(Sodium[7-methyl-β-D-glucopyranosyloxy-7,8-dicarba-nido-undecaboranyl])-8-benzoic acid (**1**)

Compound **5** (1.57 g, 2.5 mmol) and NaOH (1.03 g, 26 mmol) were dissolved in methanol (40 mL), and stirred with mild heating (~50 °C) for approximately 12 h. The methanol was removed by rotary evaporation, and the resulting white solid re-dissolved in 10 mL of distilled water, to which was added 2.5 mL of 1.0 M NaOH (2.5 mmol). The resulting solution was stirred at room temperature for 3 h whereupon the pH was adjusted to 4 using 1 M HCl. The solution was dried by rotary evaporation, yielding a white solid which was dissolved in a minimum amount of methanol and cooled in a freezer for 2 h. The resulting precipitate was removed on a pad of Celite on top of a fine glass frit. The filtrate was subsequently concentrated by rotary evaporation to give an off-white solid. This crude product was purified using silica gel column chromatography (1:4 MeOH:CH_2Cl_2 to 2:3 MeOH:CH_2Cl_2). The fractions containing the desired product were concentrated by rotary evaporation, re-dissolved in a minimum quantity of methanol, and allowed to stand in a freezer overnight. The resulting precipitate was removed as described above. The solvent was removed by rotary evaporation yielding the desired product as a white solid (0.88 g, 76%). The signals attributed to the second isomer are denoted with *. ^{1}H NMR (600 MHz, CD_3OD): δ 7.76 (d, 2H, $^3J_{2'^*,3'^*}$ = 8.4 Hz, H-2′*), 7.74 (d, 2H, $^3J_{2',3'}$ = 8.4 Hz, H-2′), 7.43 (d, 2H, H-3′*), 7.38 (d, 2H, H-3′), 3.95 (d, 1H, $^3J_{1,2}$ = 7.7 Hz), 3.81 (d, 1H, $^2J_{7a^*,7b^*}$ = −10.9 Hz, H-7a*), 3.71 (dd, 1H, $^2J_{6a^*,6b^*}$ = −12.1 Hz, $^3J_{5^*,6a^*}$ = 2.4 Hz, H-6a*), 3.66 (dd, 1H, $^2J_{6a,6b}$ = −11.9 Hz, $^3J_{5,6a}$ = 2.5 Hz, H-6a), 3.60 (dd, 1H, $^3J_{5^*,6b^*}$ = 5.1 Hz, H-6b*), 3.52 (m, 3H, H-1*, H-7a, H-6b), 3.44 (d, 1H, $^2J_{7a,7b}$ = −11.1 Hz, H-7b), 3.24 (m, 4H, H-3,3*,4,4*), 3.18 (dd, $^3J_{1^*,2^*}$ = 7.7 Hz, H-2*), 3.10 (dd, 1H, H-2), 3.02 (ddd, $^3J_{4,5}$ = 9.3 Hz, $^3J_{5,6b}$ = 5.4 Hz, H-5), 2.94 (ddd, 1H, H-5*), 2.92 (d, 1H, H-7b*), 2.50 to −0.30 (br m, 18H, B-H), −2.20 (br s, 2H, B-H-B). ^{13}C NMR (151 MHz, CD_3OD): δ 179.0, 174.2, 147.1, 147.0, 133.5, 132.7, 132.6, 129.2, 129.0, 103.9, 103.5, 77.7, 77.5, 77.4, 75.7, 75.3, 75.0, 74.8, 71.5, 71.5, 66.6, 66.1, 63.3, 62.9, 62.5, 62.3. ^{11}B{^{1}H} NMR (192 MHz, CD_3OD): δ −8.3, −10.0, −14.0, −16.8, −33.1, −36.6. IR (KBr): ν 3433, 2530, 1592 cm^{-1}. TLC (1:3 CH_3OH:CH_2Cl_2 + 0.1% HOAc): R_f = 0.38. HPLC: t_R = 12.6 min (Method **A**); 11.5 min, 11.7 min (Method **B**). ESI-MS: m/z = 446.4 [M]$^-$. HRMS (ESI): Calculated for $C_{16}H_{28}B_9O_8$: 446.2671. Observed: 446.2681.

3.6. 4′-(Sodium [7,8-dicarba-nido-undecaboranyl]-7-benzoic acid (**2**)

Methyl 4-[1,2-dicarba-*closo*-dodecaboranyl] benzoate [80] (1.10 g, 4.0 mmol) and sodium hydroxide (0.86 g, 21.4 mmol) were combined in a round-bottom flask, and dissolved in methanol (75 mL). The flask was heated overnight (approximately 12 h) in an oil bath at 65 °C. The reaction was cooled to room temperature, and the solvent removed by rotary evaporation. The solid residue was re-dissolved in distilled water (10 mL) and the resulting solution stirred at room temperature for 4 h, whereupon the pH was adjusted to 3 using 1.0 M HCl (14.6 mL). The solution was diluted with acetonitrile and concentrated to dryness on a rotary evaporator, giving a white solid. The target compound was isolated via silica gel column chromatography (5–25% CH_3OH/CH_2Cl_2), giving a thick, light yellow oil. Yield: 1.02 g (93%). ^{1}H NMR (600 MHz, acetone-d_6): δ 7.78 (d, 2H, $^3J_{2,3}$ = 8.1 Hz, H-2), 7.25 (d, 2H, H-3), 2.27 (br s, C_{cage}-*H*), −0.30–2.60 (br m, B-H), −2.42 (br, B-H-B). ^{13}C NMR (150 MHz, acetone-d_6): δ 171.0, 151.9, 129.6, 126.7, 62.2, 45.1. ^{11}B{^{1}H} NMR (192 MHz, acetone): δ −7.9, −9.5, −12.9, −15.7, −17.3, −19.1, −22.3, −32.0, −34.9. IR (KBr): ν 3576, 2526, 1606. TLC (1:9 CH_3OH:CH_2Cl_2 + 0.1% CH_3COOH): R_f = 0.15. HPLC: t_R = 17.4 min (Method **A**). ESI-MS: m/z = 254.0 [M]$^-$. HRMS (ESI) Calculated for $C_9H_{16}B_9O_2$: 254.2031. Observed: 254.2025.

3.7. 2″,3″,5″,6″-Tetrafluorophenyl-4′-(sodium[7,8-dicarba-nido-undecaboranyl])-7-benzoate (**6**)

Compound **2** (0.1138 g, 0.41 mmol) and 2,3,5,6-tetrafluorophenol (0.15 g, 0.90 mmol) were dissolved in 1 mL of dry acetonitrile. To this solution was added diisopropylcarbodiimide (100 μL, 0.65 mmol), and the reaction stirred overnight at room temperature during which time a white precipitate formed. The precipitate was removed by filtration, and the filtrate solution concentrated by rotary evaporation. The target compound was isolated by preparative TLC (15% CH_3OH/CH_2Cl_2), and used without further purification. ^{11}B{^{1}H} NMR (160 MHz, acetone): δ −7.4, −9.2, −12.6, −15.4, −17.0, −19.0, −22.2, −31.8, −34.6. ESI-MS: m/z = 402.1 [M]$^-$. HRMS (ESI): Calculated for $C_{15}H_{16}B_9O_2F_4$: 402.1971. Observed: 402.1985.

3.8. N,N-Diethyl(aminoethyl)-4′-(sodium[7,8-dicarba-nido-undecaboranyl])-7-benzamide (**7**)

N,*N*-Diethylethylenediamine (45.5 μL, 0.32 mmol) was added to compound **6** (0.13 g, 0.30 mmol) in 1 mL dry acetonitrile. After stirring overnight the desired product was isolated via preparative TLC (20% CH_3OH/CH_2Cl_2 + 1%NEt_3) using acetone to extract the product from the plate (0.03 g, 26%). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.25 (br, 1H, amide N-H, H-12), 7.64 (d, 2H, $^3J_{2,3}$ = 8.5 Hz, H-2), 7.29 (d, 2H, H-3), 3.78 (m, 2H, $^3J_{8,9}$ = 5.4 Hz, H-8), 3.39 (m, 2H, H-9), 3.31 (q, 4H, $^3J_{10,11}$ = 7.2 Hz, H-10), 2.27 (br s, H-6), 1.33 (t, 6H, H-11), −0.30 to −2.80 (br, B-H). ^{13}C NMR (125 MHz, acetone-d_6): δ 170.5, 152.3, 129.9, 127.3, 127.1, 62.3, 55.4, 49.0, 44.9, 37.8, 10.2. ^{11}B{^{1}H} NMR (160 MHz, acetone-d_6): δ −7.7, −9.4, −12.8, −15.7, −17.0, −19.0, −22.1, −31.9, −34.9. IR (KBr pellet): ν 3407, 2527, 1640. TLC (20% CH_3OH/CH_2Cl_2 + 1%NEt_3): R_f = 0.50. HPLC: t_R = 13.3 min (Method **B**). ESI-MS: m/z = 352.4 [M]$^-$. HRMS (ESI) Calculated for $C_{15}H_{30}B_9ON_2$: 352.3242. Observed: 352.3251.

3.9. Benzyl 4′-(2-propynyl-2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyloxy)-3-benzoate (**9**)

2-Propynyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (2.01 g, 5.20 mmol), benzyl 4-iodobenzoate (1.94 g, 5.73 mmol), tetrakis(triphenylphosphine) palladium(0) (0.321 g, 0.28 mmol) and copper(I) iodide (0.053 g, 0.28 mmol) were combined in a round-bottom flask and dissolved in 100 mL of a 1:1 solution of dry THF and freshly distilled triethylamine. The resulting mixture was heated to reflux and allowed to stir overnight (~12 h), during which time a white precipitate was formed, and the solution became amber-brown in colour. The solid was removed by filtration, and the filtrate concentrated by rotary evaporation giving an amber-brown oil. The crude material was dissolved in chloroform (50 mL) and extracted three times with 50 mL of 0.01 M HCl, followed by washing three times with 50 mL of distilled water. The organic layer was dried over Na_2SO_4 before filtering through a pad of silica gel, washing with 100 mL $CHCl_3$, followed by 300 mL of ethyl acetate. The filtrate was concentrated by rotary evaporation. The resulting oil was re-dissolved in the minimum amount of ethyl acetate and the target compound isolated via silica gel column chromatography (10–40% ethyl acetate/hexanes). The fractions containing the product were concentrated to an amber oil by rotary evaporation. The desired product was crystallized from the oil using ether/hexanes to give an off-white solid (2.02 g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, 2H, $^3J_{2',3'}$ = 8.4 Hz, H-2′), 7.49 (d, 2H, H-3′), 7.39 (m, 5H, OBn Aryl H), 5.37 (s, 2H,

$OCH_2C_6H_5$H-11), 5.26 (t, 1H, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4}$ = 9.8 Hz, H-3), 5.12 (t, 1H, $^3J_{4,5}$ = 10.0 Hz, H-4), 5.04 (dd, 1H, $^3J_{1,2}$ = 8.0 Hz, H-2), 4.83 (d, 1H, H-1), 4.61 (s, 2H, H-7), 4.29 (dd, 1H, $^2J_{6a,6b}$ = −12.3 Hz, $^3J_{5,6a}$ = 4.7 Hz, H-6a), 4.17 (dd, 1H, $^3J_{5,6b}$ = 2.4 Hz, H-6b), 3.76 (ddd, 1H, H-5), 2.08, 2.04, 2.02, 2.01 (s, 12H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.2, 169.4, 165.7, 135.8, 131.6, 130.1, 129.7, 128.6, 128.4, 128.2, 126.9, 98.5, 86.5, 86.3, 72.8, 72.0, 71.2, 68.4, 67.0, 61.8, 56.8, 20.7, 20.6. IR (KBr pellet): ν 1757, 1725. TLC (1:2 ethyl acetate:hexanes): R_f = 0.19. ESI-MS: m/z = 655.3 $[M+CH_3COO]^-$. HRMS (ESI): Calculated for $C_{31}H_{32}O_{12} + CH_3COO$: 655.2027. Observed: 655.2026.

3.10. Benzyl 4′-(1-methyl-2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl-1,2-dicarba-closo-dodecaboranyl)-2-benzoate (**10**)

$B_{10}H_{14}$ (0.49 g, 4.0 mmol) was dried under vacuum for 2 h prior to addition of 20 mL dry acetonitrile. The resulting solution was stirred at room temperature overnight. Alkyne **9** (0.79 g, 1.3 mmol) was added, and the solution heated to reflux for 48 h, giving a deep yellow solution from which a precipitate formed on cooling. The precipitate was removed by gravity filtration, and the filtrate concentrated by rotary evaporation, giving a yellow solid which was dissolved in a minimum quantity of ethyl acetate, and the desired product isolated silica gel column chromatography (1:2 ethyl acetate:hexanes). The fractions containing the desired product were concentrated by rotary evaporation, giving a light yellow oil which crystallized slowly at room temperature. The product was re-crystallized from ethyl acetate and hexanes, giving a white, crystalline solid. (0.48 g, 50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, 2H, $^3J_{2',3'}$ = 8.4 Hz, H-2′), 7.69 (d, 2H, H-3′), 7.39 (m, 5H, OBn aryl H), 5.38 (s, 2H, H-11), 5.12 (dd, 1H, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4}$ = 9.6 Hz, H-3), 4.99 (dd, 1H, $^3J_{4,5}$ = 10.0 Hz, H-4), 4.95 (dd, 1H, $^3J_{1,2}$ = 7.8 Hz, H-2), 4.31 (d, 1H, H-1), 4.10 (dd, 1H, $^2J_{6a,6b}$ = −12.3 Hz, $^3J_{5,6a}$ = 4.7 Hz, H-6a), 3.96 (dd, 1H, $^3J_{5,6b}$ = 2.4 Hz, H-6 b), 3.82 (d, 1H, $^2J_{7a,7b}$ = −12.7 Hz, H-7a), 3.69 (d, 1H, H-7 b), 3.52 (ddd, 1H, H-5), 2.10, 2.00, 1.99 (4 s, 12H, CH_3), 1.70–3.40 (br, B-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 170.1, 169.2, 165.1, 135.6, 134.4, 132.4, 131.2, 130.0, 128.7, 128.5, 128.3, 100.3, 81.4, 79.4, 72.3, 72.0, 70.7, 68.1, 67.9, 67.2, 61.5, 20.6, 20.5. ^{11}B{^{1}H} NMR (160 MHz, $CDCl_3$): δ −3.0, −10.3. IR (KBr pellet): ν 2594, 1758, 1726. TLC (1:1 ethyl acetate:hexanes): R_f = 0.67. ESI-MS: m/z = 714.4 $[M-H]^-$. HRMS (ESI): Calculated for $C_{31}H_{41}B_{10}O_{12}$: 714.3586. Observed: 714.3588.

3.11. 4′-(1-Methyl-2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosylozy-1,2-dicarba-closo-dodecaboranyl)-2-benzoic acid (**11**)

Compound **10** (0.55 g, 0.77 mmol) was dissolved in 100 mL of absolute ethanol in a round-bottom flask. To this solution was added slowly 0.11 g of 10 wt% Pd/C. The flask was purged twice with hydrogen from a balloon, using a long, stainless steel needle to bubble the gas through the solution. After 1 h, the product mixture was filtered through pad of Celite and the filtrate concentrated to dryness by rotary evaporation. The solid residue so obtained was re-dissolved in DCM and filtered through a plug of glass wool to remove the last residue of catalyst, and the solution concentrated to dryness by rotary evaporation, giving a white solid (0.47 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.39 (br s, 1H, H-10), 8.09 (d, 2H, $^3J_{2',3'}$ = 8.4 Hz, H-2′), 7.74 (d, 2H, H-3′), 5.14 (t, 1H, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4}$ = 9.7 Hz, H-3), 5.00 (t, 1H, $^3J_{4,5}$ = 9.9 Hz, H-4), 4.96 (t, 1H, $^3J_{1,2}$ = 7.8 Hz, H-2), 4.34 (d, 1H, H-1) 4.11 (dd, 1H, $^2J_{6a,6b}$ = −12.3 Hz, $^3J_{5,6a}$ = 4.6 Hz, H-6a), 3.95 (dd, 1H, $^3J_{5,6b}$ = 2.4 Hz, H-6b), 3.82 (d, 1H, $^2J_{7a,7b}$ = −12.6, H-7a), 3.73 (d, 1H, H-7b), 3.54 (ddd, 1H, H-5), 2.12, 2.04, 2.01, 1.99 (4s, 12H, CH_3), 1.80–3.30 (br, B-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.1, 169.9, 169.3, 169.1, 135.0, 134.8, 131.3, 130.4, 100.1, 81.2, 79.3, 72.3, 71.9, 70.7, 68.1, 67.9, 61.7, 20.6, 20.5. ^{11}B{^{1}H} NMR (160 MHz, $CDCl_3$): δ −2.8, −10.4. IR (KBr pellet): ν 3245, 2593, 1758. TLC (ethyl acetate + 0.1% HOAc): R_f = 0.85. ESI-MS: m/z = 624.4 $[M-H]^-$. HRMS (ESI): Calculated for $C_{24}H_{35}B_{10}O_{12}$: 624.3113. Observed: 624.3114.

3.12. 2‴,3‴,5‴,6‴-Tetrafluorophenyl-4′-(1,2-dicarba-closo-dodecaboranyl-1-methyl-2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-2-benzoate (**12**)

Compound **11** (0.22 g, 0.35 mmol) and tetrafluorophenol (0.12 g, 0.75 mmol) were dissolved in 2 mL dry acetonitrile, followed by EDC · HCl (0.082 g, 0.43 mmol). The reaction was allowed to stir at room temperature for 2 h until TLC indicated consumption of starting material. The solution was concentrated to dryness, then re-dissolved in 4 mL CH_2Cl_2 and added to a separatory funnel. The dichloromethane solution was extracted three times with 0.01 M HCl (4 mL), and washed three times with distilled water (4 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to a light yellow oil by rotary evaporation. The oil was re-dissolved in a minimum volume of ether, cooled in an ice bath and hexanes added to induce crystallization, yielding a white solid (0.19 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, 2H, $^3J_{2',3'}$ = 8.6 Hz, H-2′), 7.82 (d, 2H, H-3′), 7.07 (m, 1H, TFP H-11), 5.15 (t, 1H, $^3J_{2,3}$ = 9.6 Hz, $^3J_{3,4}$ = 9.5 Hz, H-3), 5.01 (t, 1H, $^3J_{4,5}$ = 10.0 Hz, H-4), 4.97 (dd, 1H, $^3J_{1,2}$ = 7.8 Hz, H-2), 4.36 (d, 1H, H-1), 4.15 (dd, 1H, $^2J_{6a,6b}$ = −12.4 Hz, $^3J_{5,6a}$ = 4.6 Hz, H-6a), 4.00 (dd, 1H, $^3J_{5,6b}$ = 2.4 Hz, H-6b), 3.86 (d, 1H, $^2J_{7a,7b}$ = −12.8 Hz, H-7a), 3.77 (d, 1H, H-7b), 3.56 (ddd, 1H, H-5), 2.12, 2.02, 2.01, 2.00 (4 s, 12H, CH_3), 1.70–3.30 (br, B-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.0, 169.2, 169.0, 161.4, 147.1, 145.1, 141.7, 139.7, 136.0, 131.6, 130.9, 129.6, 129.4, 103.6, 100.3, 80.7, 79.5, 72.3, 72.0, 70.7, 68.1, 68.0, 61.4, 20.6, 20.5, 20.4. ^{11}B{^{1}H} NMR (192 MHz, $CDCl_3$): δ −2.8, −10.3. IR (KBr pellet): ν 2596, 1758. TLC (1:2 ethyl acetate:hexanes): R_f = 0.31. ESI-MS: m/z = 885.4 $[M+TFA]^-$. HRMS (ESI): Calculated for $C_{30}H_{36}B_{10}O_{12}F_4 + CF_3COO$: 886.2982. Observed: 886.2977.

3.13. N,N-Diethyl(aminoethyl)-4′-(1,2-dicarba-closo-dodecaboranyl-1-methyl-2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-2-benzamide (**13**)

Compound **12** (0.25 g, 0.32 mmol) was dissolved in 2.5 mL dry acetonitrile. To this solution was added 47 μL (0.33 mmol) of *N*,*N*-diethylethylenediamine. After stirring overnight, the solvent was removed by rotary evaporation, and the resulting off-white foam re-dissolved in a minimum volume of DCM. The target was isolated via silica gel column chromatography (1:4 acetone:DCM containing 1% (v/v) triethylamine). The target fractions were combined and concentrated by rotary evaporation yielding a colourless oil which formed a white solid upon drying under vacuum (0.20 g, 86%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, 2H, $^3J_{2',3'}$ = 8.4 Hz, H-2′), 7.68 (d, 2H, H-3′), 7.08 (br, 1H, amide N-H, H-15), 5.13 (t, 1H, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4}$ = 9.4 Hz, H-3), 5.01 (t, 1H, $^3J_{4,5}$ = 10.0 Hz, H-4), 4.96 (dd, 1H, $^3J_{1,2}$ = 7.8 Hz, H-2), 4.32 (d, 1H, H-1), 4.13 (dd, 1H, $^2J_{6a,6b}$ = −12.4 Hz, $^3J_{5,6a}$ = 4.6 Hz, H-6a), 3.99 (dd, 1H, $^3J_{5,6b}$ = 2.3 Hz, H-6b), 3.83 (d, 1H, $^2J_{7a,7b}$ = −12.8 Hz, H-7a), 3.68 (d, 1H, H-7b), 3.54 (ddd, 1H, H-5), 3.49 (m, 2H, $^3J_{11,15}$ = 5.3 Hz, H-11), 2.67 (t, 2H, $^3J_{11,12}$ = 5.8 Hz, H-12), 2.59 (q, 4H, $^3J_{13,14}$ = 7.1 Hz, H-13), 2.13, 2.03, 2.01, 2.00 (4s, 12H, OAc CH_3), 1.05 (t, 6H, H-14), 1.60–3.10 (br, B-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.5, 170.1, 169.3, 169.1, 165.8, 137.1, 132.7, 131.3, 127.4, 100.4, 81.7, 79.5, 72.3, 71.9, 70.7, 68.1, 61.5, 51.1, 46.7, 37.3, 20.7, 20.6, 20.5, 11.9. ^{11}B{^{1}H} NMR (160 MHz, $CDCl_3$): δ −2.0, −9.4. IR (KBr pellet): ν 3406, 2592, 1758, 1652. TLC (1:2 acetone:CH_2Cl_2 + 1%NEt_3): R_f = 0.70. ESI-MS: m/z = 724.3 $[M+H]^+$, 782.6 $[M+CH_3COO]^-$. HRMS

(ESI): Calculated for $C_{30}H_{50}B_{10}O_{11}N_2 + CH_3COO$: 782.4542. Observed: 782.4537.

3.14. N,N-Diethyl(aminoethyl)-4′-(sodium[(7-methyl-β-D-glucopyranosyl-7,8-dicarba-nido-dodecaboranyl])-8-benzamide (**8**)

Compound **13** (0.19 g, 0.26 mmol) was dissolved in 5 mL of absolute ethanol. To this solution was added 775 μL (1.6 mmol) of a 80 mg/mL solution of NaOH in 17% H_2O/ethanol, and the reaction stirred overnight with heating in an oil bath at 60 °C. The reaction was cooled to room temperature and $CO_{2(g)}$ passed through the solution to precipitate excess NaOH as Na_2CO_3. The solid was removed by filtration, washed with ethanol, and the filtrate concentrated to a colourless oil by rotary evaporation. Re-dissolution in methanol, filtration through a plug of glass wool and rotary evaporation gave a white solid. The crude material was dissolved in a minimum volume of methanol and the target compound isolated via silica gel column chromatography (gradient 10–20% CH_3OH:CH_2Cl_2 containing 1% (v/v) NEt_3) in 35% yield (0.052 g). ^{1}H NMR (500 MHz, CD_3CN): δ 7.89, 7.84 (br, 2H, H-15), 7.65, 7.62 (d, 4H, H-2′), 7.53, 7.47 (d, 4H, H-3′), 3.94 (d, 1H, $^3J_{1,2}$ = 7.7 Hz, H-1), 3.77 (d, 1H, $^2J_{7a,7b}$ = −10.9 Hz, H-7a), 3.65 (m, 4H, H-11), 3.61 (dd, 1H, H-6a), 3.54–3.40 (m, 6H, H-1, H-6a, H-6 b, H-7), 3.25–3.14 (m, 16H, 2H-3, 2H-4, H-12, H-13), 3.07 (m, 1H, H-2), 3.00 (m, 2H, H-2, H-5), 2.94 (m, 1H, H-5), 2.90 (d, 1H, H-7b), 1.26 (t, 12H, $^3J_{13,14}$ = 7.2 Hz, H-14), −0.40–2.60 (br, B-H), −2.20 (br, B-H-B). ^{13}C NMR (125 MHz, CD_3CN) δ 171.3, 147.9, 147.7, 133.0, 131.3, 131.2, 127.3, 127.1, 103.1, 102.9, 77.4, 76.9, 76.6, 74.9, 74.8, 74.0, 71.7, 71.3, 67.2, 62.7, 62.6, 61.6, 61.3, 55.4, 49.2, 49.0, 37.4, 37.3, 9.6. ^{11}B{^{1}H} NMR (160 MHz, CD_3CN): δ −7.1, −10.0, −14.8, −18.0, −19.7, −32.9, −36.4. IR (KBr pellet): ν 3431, 2526, 1641. TLC (15% CH_3OH/CH_2Cl_2 + 1%NEt_3): R_f = 0.55. HPLC: t_R = 8.87 min (Method **C**). ESI-MS: m/z = 544.3 [M]$^-$. HRMS (ESI): Calculated for $C_{22}H_{42}B_9O_7N_2$: 544.3879. Observed: 544.3882.

3.15. 4′-(Sodium[7-methyl-β-D-glycopyranosyl-(iodo-7,8-dicarba-nido-undecaboranyl])-8-benzoic acid (**14**)

To a solution of compound **1** (37.5 mg, 80.2 μmol) in ethanol (500 μL) was added 2 mL of I_2 in EtOH (82.7 μmol) gradually over 1 h. After addition of the iodine solution was complete, the reaction was stirred at room temperature for a further hour, followed by addition of 1.7 mL of 0.1 M $Na_2S_2O_5$ to quench the reaction. The resulting mixture was concentrated to dryness by rotary evaporation. The resulting residue was re-dissolved in 0.5 mL H_2O and loaded onto a pre-conditioned C18 SepPak® cartridge (Waters), which was subsequently eluted with 7 mL H_2O, 3 mL 1:1 H_2O:CH_3CN, and 5 mL CH_3CN giving a total of 15 × 1 mL fractions. Fractions 10 and 11 contained a single, UV and Pd-active product, which was confirmed by mass spectrometry to be the desired product. These were combined, concentrated by rotary evaporation, and lyophilized giving a light white solid (15 mg, 32%). Signals for the other 3 isomers are denoted by *, + and ×. ^{1}H NMR (600 MHz, CD_3OD): δ 7.81–7.75 (m, 8H, H-2′), 7.51 (d, 2H, ^3J = 8.3 Hz, H-3′), 7.46 (d, 5H, ^3J = 8.3 Hz, H-3′), 3.99 (d, 1H, ^2J = −11.0 Hz, H-7), 3.97 (d, 1H, ^3J = 7.7 Hz, H-1), 3.93 (d, 1H, ^2J = −10.9 Hz, H-7), 3.86 (d, 1H, ^3J = 7.6 Hz, H-1), 3.74 (dd, 1H, ^2J = −12.0 Hz, ^3J = 2.4 Hz, H-6$^{(*)}$), 3.70–3.66 (m, 3H, H-7, H-6, H-6$^{(+)}$), 3.63 (d, 1H, ^3J = 7.6 Hz, H-1), 3.62–3.52 (m, 7H, 3 H-7, H-6, H-6$^{(*)}$, H-6$^{(\times)}$, H-6$^{(+)}$), 3.41 (dd, 1H, ^2J = −11.8 Hz, ^3J = 5.6 Hz, H-6$^{(\times)}$), 3.36 (d, 1H, ^3J = 7.5 Hz, H-1), 3.30–3.09 (m, 13H, H-7, H-2, H-3, H-4), 3.03 (ddd, 1H, H-5), 2.99 (ddd, 1H, H-5$^{(*)}$), 2.95 (ddd, 1H, H-5$^{(\times)}$), 2.88 (ddd, 1H, H-5$^{(+)}$), 2.87 (d, 1H, ^2J = −10.8 Hz, H-7), 2.80–0.10 (br, B-H), −2.30, −2.44 (br, B-H-B). ^{13}C NMR (150 MHz, CD_3OD) δ 173.0, 147.0, 146.9, 145.9, 145.8, 133.4, 132.5, 132.3, 129.5, 129.2, 129.1, 129.0, 104.1, 104.0, 103.7, 103.3, 77.8, 77.5, 77.4, 76.0, 75.5, 75.4, 75.2, 75.1, 75.0, 71.3, 71.7, 71.6, 71.5, 67.6, 62.7, 62.6, 62.5, 62.4, 60.0, 57.5, 56.9. ^{11}B{^{1}H} NMR (192 MHz, CD_3OD): δ −4.6, −14.1, −24.1, −29.3, −36.4. IR (KBr): ν 3433, 2542, 1607. ESI-MS: m/z = 572.1 [M]$^-$. HRMS (ESI): Calculated for $C_{16}H_{27}B_9O_8I$: 572.1638. Observed: 572.1639. HPLC: t_R = 12.34, 12.50, 12.84, 13.36 (Method **B**).

3.16. N,N-Diethyl(aminoethyl)-4′-(sodium[7-methyl-β-D-glucopyranosyl-(iodo-7,8-dicarba-nido-undecaboranyl])-8-benzamide (**15**)

Compound **8** (9 mg, 15.9 μmol) was dissolved in 1200 μL of a 5:1 mixture (v/v) of ethanol and acetonitrile. To this was added dropwise 544 μL of a 0.03 M solution of I_2 (16.1 μmol) in ethanol and the reaction stirred at room temperature for 2 h. A 0.1 M solution of $Na_2S_2O_5$ (322 μL) was added and the mixture concentrated to dryness by rotary evaporation, giving a clear, colourless residue which was re-dissolved in 400 μL of a 3:1 (v/v) water:acetonitrile solution. The mixture was loaded onto a C18 SepPak® cartridge and the desired product isolated following elution with 6 mL H_2O, and 3 mL CH_3CN that were collected in 1 mL fractions. The product was found in the acetonitrile fractions, which were combined and lyophilized giving a white solid (2 mg, 18%). ^{11}B{^{1}H} NMR (192 MHz, CD_3CN): δ −5.0, −14.0, −14.2, −19.0, −23.9, −29.2, −36.3. ESI-MS: m/z = 670.1 [M$^-$]. HRMS: Calculated for $C_{22}H_{41}B_9O_7N_2I$: 670.2849. Observed: 670.2830. HPLC (Method C): t_R = 10.5 min, 11.0 min.

3.17. N,N-Diethyl(aminoethyl)-4′-(sodium[iodo-7,8-dicarba-nido-undecaboranyl])-7-benzamide (**16**)

Compound **7** (4 mg, 10.7 μmol) was dissolved in 500 μL of a 1:1 mixture of water and acetonitrile. To this solution was added 366 μL of a 0.0295 M solution of I_2 in ethanol (10.8 μmol) gradually over 1 h. After all the iodine solution was added, the reaction was allowed to stir a further hour at room temperature before quenching with 216 μL of 0.1 M $Na_2S_2O_5$, and concentrating to dryness by rotary evaporation. The crude material was re-dissolved in 200 μL of 1:1 water:acetonitrile, which was loaded onto a pre-conditioned C18 SepPak® cartridge. The SPE cartridge was eluted first with 5 mL of H_2O, then 5 mL CH_3CN, into 10 × 1 mL fractions where the desired product was in fractions 7 and 8. These fractions were combined and concentrated by rotary evaporation and lyophilized giving a white film (1 mg, 19%). ESI-MS: m/z = 478.1 [M]$^-$. HRMS (ESI): Calculated for $C_{15}H_{29}B_9ON_2I$: 478.2209. Observed: 478.2208. HPLC: t_R = 13.96, 14.30 (Method C).

3.18. Radiolabelling

A 1.0 mg/mL solution of each ligand was prepared in H_2O containing 5% acetic acid (**1**), or in the case of the benzamides **7** and **8**, a 1:1 solution of 5% HOAc/H_2O:CH_3CN. To a 2 mL reaction vial, were added 100 μL of the ligand solution and 20 μg of an appropriate oxidant (**1**: Iodogen®, **7** or **8**: chloramine-T as 20 μL of a 1.0 mg/mL solution in water). To these solutions were added Na[^{125}I] (20–150 μCi, 0.74–5.6 MBq) in 0.1 N NaOH. The solutions were stirred for five minutes before addition of 10 μL 0.1 M $Na_2S_2O_5$ to reduce any oxidized forms of radioiodine. Products were isolated via semi-preparative HPLC (Method **B**, Dynamax 10 × 250mm C18 column at 4.7 mL/min). The radioiodinated compounds were characterized by correlation of their HPLC retention times with those of the non-radioactive analogues (Method **B**).

3.19. Log*P* calculations

Log*P* measurements were made using the "shake-flask" method described by Wilson and co-workers [79]. Radioiodinated com-

pounds [^{125}I]-**15** and [^{125}I]-**16** were concentrated to dryness and reconstituted in 1 mL of phosphate-buffered saline. The saline was added to a vial containing 2 mL phosphate buffer and 3 mL of 1-octanol. The flask was shaken on a vortex mixer for 3 min, and the respective layers separated. The octanol layer was taken, and divided (0.5 mL) among four "partitioning" vials containing 1.5 mL phosphate buffer (pH 7.4) and 1.0 mL 1-octanol. These vials were shaken on a vortex mixer for 10 min, followed by centrifugation for a further 5 min. Aliquots (0.5 mL) of each layer were transferred to pre-weighed vials, counted for activity, and counts/mL calculated from the weight of solution transferred. Log*P* was calculated as log {[counts/mL(1-octanol)]/[counts/mL(buffer)]}. The reported values correspond to the average of four measurements ± standard deviation.

3.20. Cell binding studies

Following similar methods to those reported by Dittmann and co-workers [72], cells were seeded at a density of 2×10^5 cells in 25 cm^3 vented cap cell culture flasks (430639, Corning) 2 days prior to the experiment. L-tyrosine (Sigma, Oakville, ON) was added to the media to a final concentration of 2 mM. Each time-point had three replicate flasks, as well as a control flask not receiving radioactive compound. After 48 h, the ^{125}I-labelled compound (~25 kBq) was added to each flask in a volume of 50 μL and cells were incubated for 1, 2, 6, 12 or 24 h at 37 °C and 5% CO_2. At each time-point, media was removed from cells and saved for counting. Cells were washed twice with PBS (each wash being retained for analysis) and then trypsinized. Once cells had lifted from flask, they were collected for analysis. The activity in the cells, media and the wash from each sample were counted for 60 s using the Perkin–Elmer Wizard Pro gamma counter. Counts per minute (cpm) were analyzed as percentage of total counts from cells and wash supernatants. Uptake values represent the percentage of the initial activity added to the cells and are the average of three measurements ± standard deviation.

4. Conclusion

A bifunctional *nido*-carborane ligand containing a carbohydrate group and a benzoic acid substituent for linking the cluster to amine-bearing targeting vectors was prepared. Benzamide derivatives of the *nido*-carborane ligand and its non-glycosylated analogue were synthesized as model conjugates, and subsequently labelled with ^{125}I. Lipophilicity measurements confirmed the increase in hydrophilicity associated with the presence of a carbohydrate group. The carbohydrate had a detrimental impact on the uptake of the benzamides by melanoma cells relative to both the control compound, [^{125}I]BZA, and the non-glycosylated *nido*-carborane-benzamide analogue. The general utility of the reported ligands for preparing targeted molecular imaging probes by conjugating to more specific bio-vectors remains work in progress.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.12.063.

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