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Carborane-Derived Local Anesthetics are Isomer Dependent

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Clinically there is a need for local anesthetics with a greater specificity of action on target cells and longer duration. We have synthesized a series of local anesthetic derivatives we call boronicaines in which the aromatic phenyl ring of lidocaine was replaced with *ortho*-, *meta*-, C,C′-dimethyl *meta*- and *para*-carborane clusters. The boronicaine derivatives were tested for their analgesic activity and compared with lidocaine using standard procedures in mice following a plantar injection. The compounds differed in their analgesic activity in the following order: *ortho*-carborane = C,C′-dimethyl *meta*-carborane > *para*-carborane > lidocaine > *meta*-carborane derivative. Both *ortho*-boronicaine and C,C′-dimethyl *meta*-boronicaine had longer durations of analgesia than lidocaine. Differences in analgesic efficacies are rationalized by variations in chemical structure and protein binding characteristics.

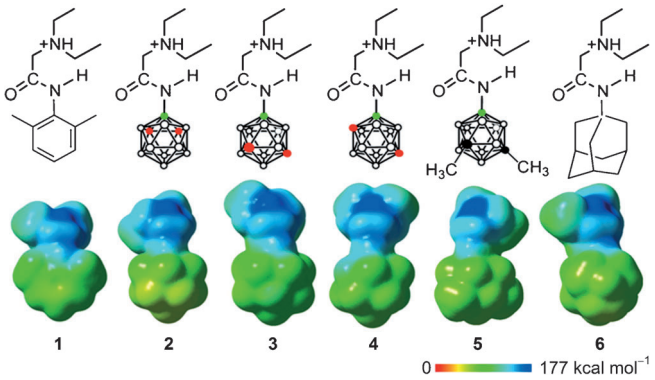

Figure 1. Structures and electron-density distributions mapped with electrostatic potential of lidocaine (**1**), boronicaines **2**–**5**, and an adamantyl derivative (**6**). Color code: B: ●; CH: ●; C: ●; BH: ○.

Since the discovery by Freud and Koller in the 1800s that the natural plant product cocaine has analgesic properties, cocaine and its synthetic congeners have defined the class of drugs called local anesthetics. They decrease pain by blocking voltage-gated sodium channels in peripheral sensory neurons. However, they can also affect these channels in other excitable cells, such as cardiac cells and central nervous system (CNS) neurons and thus are additionally used as antiarrhythmics, anticonvulsants, and antidepressants. Presently, the goals of local anesthetic drug discovery are to develop agents with greater specificity of action on target cells, fewer unwanted side effects, and longer duration.[1,2]

Local anesthetics are typically small, amphiphilic molecules consisting of a hydrophobic, aromatic moiety connected via an amide or ester linkage to a terminal amine. Lidocaine (**1**; Figure 1) belongs to the class of amide local anesthetics. It has a dimethyl substituted phenyl ring attached to the amide side chain. The dependence of anesthetic activity on the presence of a hydrophobic aromatic moiety such as a phenyl ring is well recognized. For example, lidocaine, which contains a phenyl ring, possesses anesthetic activity in man, whereas a lidocaine analogue containing a cyclohexyl group does not.[3] In other studies, compounds containing a phenyl ring were more than an order of magnitude more potent at blocking sodium channels than comparable compounds lacking one.[4] A thiophene ring can substitute for a phenyl ring in the local anesthetic, articaine, which shows comparable anesthetic activity to lidocaine.[5]

Herein, we present a series of local anesthetic derivatives we call boronicaines in which the aromatic phenyl ring of lidocaine has been replaced with an isomeric, carborane cluster. Carboranes are icosahedral, aromatic, dicarba-*closo*-dodecacarboranes with the formula $C_2B_{10}H_{12}$. They are hydrophobic, neutral, moderately polar (contingent upon the position of the carbon atoms), and have a volume of 144 Å^3, somewhat larger than the 102 Å^3 volume of a longitudinally rotated phenyl ring.[6] Carboranes are easily derivatized and have been used as a scaffold in drug design, such as, aspirin analogues,[7] estrogen receptor modulators,[8,9] opioid receptor agonists,[10] transthyretin stabilizers,[11] and antidepressants.[12]

The boronicaines were synthesized by replacing the dimethylphenyl group of lidocaine (**1**), with *ortho*-, *meta*-, *para*-, and C,C′-dimethyl *meta*- carborane clusters yielding *ortho*-boronicaine (**2**), *meta*-boronicaine (**3**), *para*-boronicaine (**4**), and C,C-dimethyl *meta*-boronicaine (**5**), respectively (Figure 1 and Figure S4 in the Supporting Information). Additionally, we synthesized adamantane lidocaine (**6**), in which the phenyl group of lidocaine was replaced with a nonaromatic, hydrophobic, adamantyl group (Figure 1). We found that two of the boronicaines have longer lasting analgesic activity than lidocaine. We

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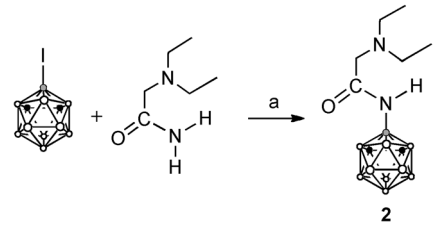
also observed that the boronicaine isomers differ in their analgesic efficacy, a feature rationalized by their structural chemistry and molecular docking characteristics.

The syntheses of boronicaine isomers **2**–**5** were accomplished using palladium-catalyzed coupling of boron-substituted mono-iodo-carboranes, 3-iodo-*ortho*-carborane, 9-iodo-*meta*-carborane, 2-iodo-*para*-carborane, with 2-diethylaminoacetamide to yield **2**–**5**, respectively.[13] Scheme 1 illustrates the synthesis of **2** from 3-iodo-*ortho*-carborane.



Scheme 1. Palladium-catalyzed coupling of boron-substituted, mono-iodo carborane with 2-diethylaminoacetamide. *Reagents and conditions*: a) K_3PO_4, DavePhos ligand, $Pd_2(dba)_3$, toluene, reflux, 3 h, 45%. Color code: CH: ●; B: ●; BH: ○.

The positions of the positive charges on the tertiary amine are indicated in Figure 1 by the dark blue regions in the electron density distributions of **1** and **2**. The positive charge on the tertiary amine is an important factor in the access and binding of the local anesthetic to the target in the inner pore of the sodium channel.[14] The natural bond orbital (NBO) charge distributions of the protonated tertiary amine groups of compounds **2**–**5** were not affected by the replacement of the phenyl ring with the carborane cage (Table S3 in the Supporting Information).

The molecular basis of the interaction of local anesthetics with sodium channels involves interactions between the drugs and specific aromatic amino acids lining the channel pore. Two types of mechanisms have been proposed. One mechanism, suggested by amino acid substitution experiments, involves the protonated amine of the local anesthetic molecule forming cation–π interactions with the electron-rich π face of the aromatic side chain of a phenylalanine residue in the sodium channel pore.[15,16] The presence of carborane clusters should not preclude cation–π interactions between the boronicaines and their receptor sites. Another type of mechanism was suggested in studies of voltage-gated sodium channels and model channel peptides. This involved π–π stacking between local anesthetic phenyl groups and amino acid phenyl groups in the channel pore.[17,18] However, our experiments with boronicaines suggest that π–π stacking is not a significant driving force for sodium channel block since the replacement of the phenyl ring of **1** with a three-dimensional, highly symmetric carborane cage, incapable of comparable π interactions, resulted in molecules with analgesic activity.

The crystal structure of **3** (CCDC 964297) along with the atom numbering is shown in Figure S1 in the Supporting Information. The carborane framework displayed no distortion upon functionalization with the 2-diethylaminoacetamide group. The B–N bond length of 1.480(2) Å was within the range of distances reported for other carboranylamides.[13] Crystallographic details are given in Tables S1 and S2 in the Supporting Information.

The analgesic properties of **2**–**6** were tested and compared with **1** using the hot plate test as described in the Supporting Information. We injected anesthetics in to the upper hindlimb near the sciatic nerve as well as the hindlimb plantar region.[19,20] Even though injections in the upper hindlimb gave the desired results, we found that plantar injections were more consistent (for details, see Supporting Information). Anesthetics were dissolved at 10 mM in saline at pH 5.2 since **2**–**6** were not soluble at 10 mM in a pH 7.4 solution. All carborane analogues of lidocaine showed analgesic activity (Figure 2). The onset of analgesia was rapid since the plantar injections deposit the anesthetics in close proximity to the sensory nerves in the foot touching the hot plate. However, the compounds had quite different analgesic characteristics. Figure 2a shows that both **2** and **5** had analgesic activity of much longer duration than **1**, while **3** had a shorter duration than **1**. The kinetics of **4** looked very similar to **1**. As expected, analgesia was seen with neither the saline control nor **6** (data not shown). Since the boronicaines were not soluble at 10 mM in a pH 7.4 buffer solution, there was the possibility of them precipitating out in the mouse interstitial fluid which has a pH of 7.4. Therefore, we investigated a unilamellar liposome formulation of compounds **1**–**4** at pH 7.4 for the upper hindlimb experiments. The overall trend remained similar to nonliposomal experiments, but we found that the kinetics of the analgesic effect were slower than nonliposomal formulations (for details, see Supporting Information). The transient nature of the analgesic responses to **1**–**5** might be explained by the complex pharmacokinetics of local anesthetics.[21] For example, the short analgesic duration of lidocaine is likely due to its vasodilator properties.[22] Boronicaines **2** and **5** might be lesser vasodilators than lidocaine and thus have longer durations.

The areas under the curve (AUC) values, which are measures of analgesic efficacy, are shown in Figure 2b. The compounds differed in their analgesic efficacy in the following order: **2** = **5** > **4** > **1** > **3** > **6**. Boronicaine derivatives **2** and **5** had significantly greater analgesic efficacy than **1** and did not significantly differ from each other. In the literature, differences in measured activities have been observed with other isomeric carborane-based compounds. For example, carborane-derived bisphenols had an estrogenic activity ranking of *para* > *ortho* > *meta*.[23] In another example, *ortho*- but not *meta*-carborane derivatives of indomethacin-inhibited cyclooxygenase.[24]

Studies of the binding of local anesthetics to mammalian voltage-gated sodium channels have been hampered by the absence of channel crystal structures. However, crystallization studies of human serum albumin (HAS) complexed with lidocaine (PDB code 3JQZ[25]) have been useful in understanding local anesthetic–protein binding geometry since albumin and the channel binding sites both have similar cation–π and hydrogen-bonding interactions with lidocaine.[25]

In order to investigate the differences in binding of the boronicaine anesthetics, we docked lidocaine and compounds **2**–

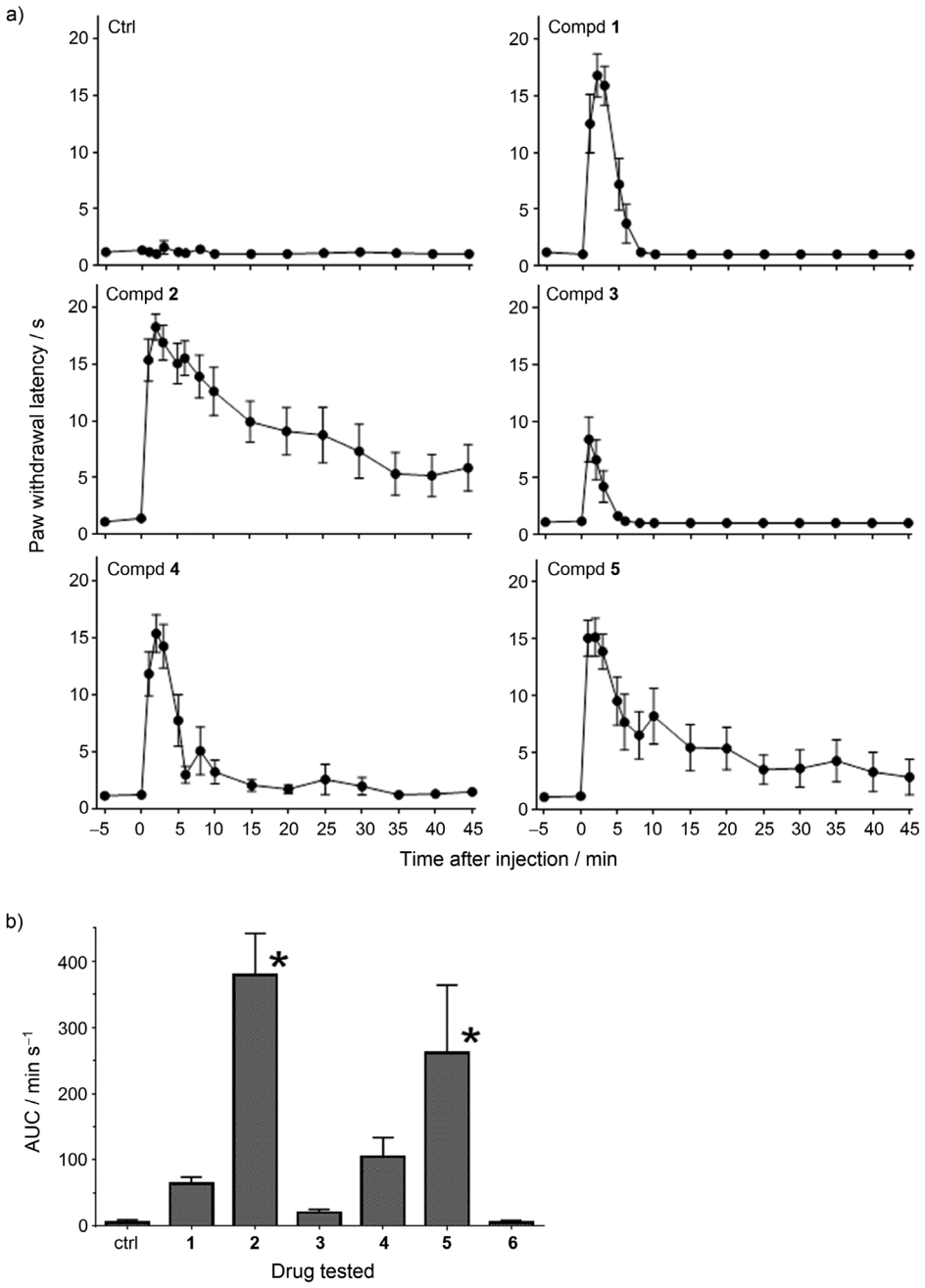


Figure 2. Time courses of the analgesic effects of saline-dissolved drugs **1**–**5** and saline control (ctrl). Analgesia was measured in mice as paw withdrawal latency in seconds in the hot plate test after a single hindlimb plantar injection of 50 μL of a 10 mM solution, equivalent to 0.5 μmols of drug. A) Time courses of analgesia are shown from 5 min before to 45 min after injection. Data represent the mean ± SEM for 10–13 animals. b) Areas under the curve (AUC) were calculated from the experiments summarized in panel a). Data are the mean, and error bars represent ± SEM. An asterisk denotes a significant difference ($p < 0.05$, ANOVA) between **2** and **1**, and between **5** and **1**. There is no significant difference between the results of compounds **2** and **5**.

6 in the active site of the HSA using molecular docking software FlexX[26] (for details, see Supporting Information). The top ranking docking pose is the one with the lowest root mean square deviation (RMSD) of coordinates against the reference structure. The corresponding values of the FlexX total docking scores (TS), which include contributions from the protein–ligand interactions, clash penalty, and ligand rotation entropy are shown in Figure S8 in the Supporting Information. The best docking score among carborane derivatives was obtained for **2** with the TS value of −3.3568 with a RMSD value of 1.8859 Å, followed by **4** (TS = −2.1059, RMSD = 1.5153 Å), **5** (TS = +0.3402, RMSD = 0.7050 Å) and finally **3** (TS = +3.3496, RMSD = 1.5744 Å). The TS value for the adamantyl derivative (**6**) was −3.6990 (RMSD = 0.7050 Å). The ranking for boronicaines based on TS has a direct correlation with the analgesic responses we observed experimentally in mice. The unfavorably high TS value for compound **3** is due to the nearly three times higher clash score compared with the corresponding value for **1**.

Figure 3 shows lidocaine and boronicaines **2**–**5** aligned inside the active site of HSA. The following hydrogen bonds were observed for all analyzed compounds: Asp 187–COO^-···HN^+–amine and Lys 190–HN^+N···O=C–NH–R (R = phenyl for **1**, carborane for **2**–**5**, adamantyl for **6**). The amide–amine sections of the compounds resided in identical regions of the cavity, but the spatial displacement of hydrophobic moiety and the positions of the mildly acidic C–H groups[27] in the carborane cage differed among the isomers. Their position relative to the boron-substituted amide linkage would determine their exposure to the amino acids on the surrounding protein. As shown in Figure 1, two or one of the C–H protons in **2** and **4**, respectively, are shielded by the B-amido substituent, while both C–H protons in **3** are positioned away from the amide substituent and exposed to the surrounding protein for hydrogen-bonding interactions. The analgesic effects shown in Figure 2 led us to believe that hydrogen-bonding interactions of C–H protons with the amino acid residues of the surrounding protein play an important role in the efficacy of these derivatives. To further study the role of C–H protons of carborane derivatives in the analgesic activity, we synthesized a C,C′-dimethyl *meta*-carbor-

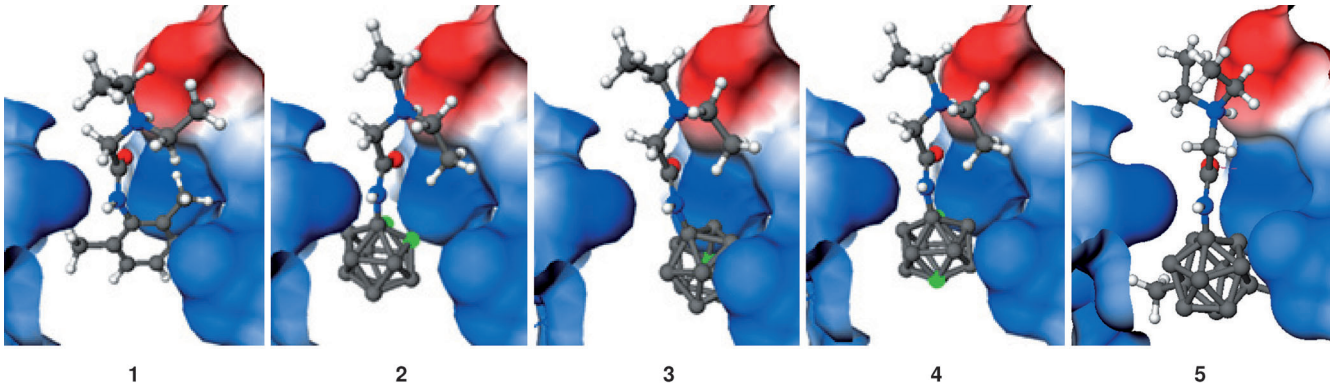


Figure 3. Results of FlexX docking in HSA. The view of the human serum albumin (HSA) active site (PDB code 3JQZ[25]) with compounds **1**–**5** (balls and sticks). Surface charge color code: negative, positive.

ane derivative (**5**), where hydrogens on the carbons were replaced with methyl groups. This modification resulted in a satisfactory docking in the HAS crystal structure (Figure 3) and improved analgesic activity over *meta*-boronicaine **3** (Figure 2).

The docking of **6** in HSA was successful (for details, see Supporting Information); however, the experimental studies show that the replacement of the lidocaine aromatic phenyl with adamantyl ceases the analgesic activity. Thus we hypothesize that there are three factors that contribute to the analgesic activity of our carborane derivatives: 1) the presence of delocalized electron density in the hydrophobic part of the molecule; 2) exposure of hydrophobic B–H vertices to the protein; 3) the presence or absence of acidic C–H groups in the vicinity of the substituent.

The relative potencies of **1** and **2** were established by measuring the analgesic responses of animals injected with varying concentrations of the compound. Data were fitted to the Hill equation with a four-parameter (top, bottom, EC_{50} and Hill slope), nonlinear regression curve. Figure 4 shows that the potencies of **1** and **2**, calculated from experiments similar to those in Figure 2, were not significantly different. The EC_{50} value for **1** was 6.3 mM (range: 4.4–8.9 mM, with 95% confidence interval) and for **2** was 5.3 mM (range: 3.0–9.5 mM, with 95% confidence interval). Hill coefficients (mean ± SEM) were 1.6 ± 0.4 for **1** and 4.5 ± 2.2 for **2**. The analgesic efficacy of **2** was significantly greater than **1** at both 10 and 20 mM.

In summary, to the best of our knowledge, we have synthesized the first carborane-based local anesthetics and studied their structure–activity relationships. Analgesic studies in mice showed that two of the carborane isomers, *ortho*- (**2**) and C,C′-dimethyl *meta*- (**5**), had longer durations and greater efficacies of analgesic effects than the parent lidocaine (**1**). The adamantyl derivative (**6**) had minimal analgesic activity. The potencies of **1** and **2** were not significantly different from each other, but **2** was more efficacious than **1**. The analgesic activity differed among the compounds in the following order: **2** = **5** > **4** > **1** > **3** > **6**. The variation in boronicaine analgesic activity can partially be explained by molecular docking studies, which show differences in the exposure of acidic C–H protons of the carborane cage to the surrounding proteins with more exposure correlating with less analgesic activity.

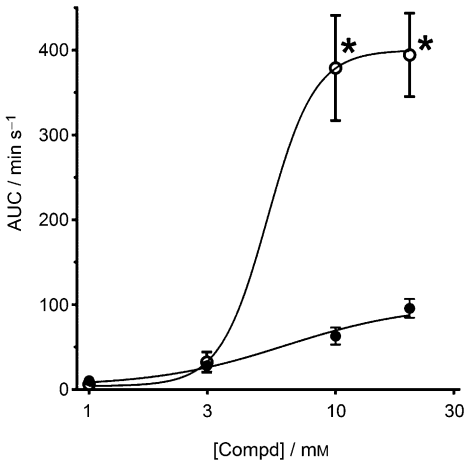


Figure 4. Analgesia log concentration–response curves for **1** (●) and **2** (○). Single hindlimb plantar injections were made with 50 µL of drug at the designated concentration. The equivalent molar amounts of compound injected were 0.05, 0.15, 0.5, and 1.0 µmols, respectively. Data represent the mean ± SEM for 6–13 animals. An asterisk denotes statistically different ($p < 0.05$ ANOVA) mean values between the compounds.

Experimental Section

General: All coupling reactions were carried out under argon using Schlenk techniques. Toluene was freshly distilled from CaH_2 prior to use. Tetrahydrofuran (THF) was dried by passage through a solvent purification system to give the solvent with a water content of less than 25 ppm as determined by a coulometric KF titrator (Mettler, Toledo, USA). All other solvents were used as purchased from commercial sources. 2-Dicyclohexylphosphino-2-(*N*,*N*-dimethylamino) biphenyl (DavePhos), Et_2NH, 2-bromoacetamide and $Pd_2(dba)_3$ were used as purchased (Sigma–Aldrich, St. Louis, MO, USA). *ortho*-, *meta*- and *para*-carboranes were obtained from Katchem Ltd (Prague, Czech Republic). Starting materials 2-iodo-*para*-carborane, 9-iodo-*meta*-carborane,[28] 3-iodo-*ortho*-carborane,[29] 1,7-dimethyl-*meta*-carborane,[30] and diethylaminoacetic acid hydrochloride[31] were prepared using literature procedures. All iodo-carboranes were azeotropically dried with benzene to remove any trace of water. K_3PO_4 was ground to a fine powder and then dried thoroughly by heating in vacuo at 105 °C. All solids were stored in an argon-filled glove box. Silica gel was used as purchased (63–200 µm, Sorbent Technologies, Inc.). Analytical thin-

layer chromatography (TLC) for carborane identification was performed by using pre-coated silica gel XHL plates (Sorbent Technologies, Inc.) and visualized by dipping into an acidified (HCl) solution of $PdCl_2$ followed by heating.

^1H, ^{13}C and ^{11}B NMR spectrometry was performed on Bruker Avance 400 and Avance 500 spectrometers. ^{11}B NMR spectra were externally referenced to $BF_3{\cdot}Et_2O$; the peaks upfield of the reference were designated as negative. ^1H and ^{13}C NMR chemical shifts (δ) are given in parts per million (ppm) relative to residual solvent signals ($CDCl_3$: $\delta = 7.24$ ppm for ^1H NMR and $\delta = 77.0$ ppm for ^{13}C NMR). High-resolution mass spectra (HRMS) were obtained on an ABI QSTAR and Mariner Biospectrometry Workstation (PerSeptive Biosystems). Melting points (mp) were obtained using an automated melting point system OptiMelt (Stanford Research Systems). Measurements were conducted in open-end Kimble Chase capillary tubes from borosilicate glass ($L = 90$ mm). The melting point range is defined as the interval between the onset and clear points using a 0.5 °C min^{-1} ramp rate, and values are uncorrected.

2-Diethylaminoacetamide: A Schlenk tube containing 2-bromoacetamide (2.6 g, 18.9 mmol), Et_2NH (1.38 g, 18.9 mmol), K_2CO_3 (2.8 g, 20.3 mmol), and KI (3.14 g, 18.9 mmol) was evacuated and then refilled with argon. Dry CH_3CN (50 mL) was added to the tube. The mixture was stirred at reflux for 4 h. The solvent was evaporated, the solid residue was redissolved with EtOAc (70 mL), and the solution was filtered. The filtrate was washed with water, dried with $MgSO_4$, and then the solvent was evaporated. A white solid product was obtained without any further purification steps (73%): ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.19$ (br s, 2H, NH_2), 3.01 (s, 2H, CH_2), 2.56 (q, $J = 7.2$ Hz, 4H, NEt_2), 1.04 ppm (6H, t, $J = 7.3$ Hz, NEt_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 175.6$ (C=O), 57.4 (CH_2), 48.6, 12.3 ppm (NEt_2); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_6H_{15}N_2O$: 131.1184, found: 131.0907.

2-(Diethylamino)-*N*-(1,2-dicarba-*closo*-dodecaboran-3-yl)acetamide (2): The following were added to a dry 25 mL Schlenk flask in an argon-filled glove box: 3-iodo-*o*-carborane (300 mg, 1.10 mmol), 2-diethylaminoacetamide (432 mg, 3.32 mmol), K_3PO_4 (1.13 g, 5.35 mmol), DavePhos ligand (42 mg, 0.1 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol) and a Teflon-coated magnetic stir bar. To this mixture, dry toluene (4 mL) was added by syringe at the Schlenk line. The reaction mixture was heated at reflux for 3 h, after which time it was filtered. The filtrate was evaporated to leave a yellow oily residue, which was purified by column chromatography using silica gel ($MeOH/Et_2NH/CH_2Cl_2$, 0:0:100→ 1.43:0.075:98.5). Further purification was carried out by treating a solution of the product with active charcoal to give the desired compound as a white crystalline solid (130 mg, 45%): ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.04$ (s, 1H, CONH), 4.52 (s, 2H, $C_{carborane}$–H), 3.04 (s, 2H, CH_2), 2.66 (q, $J = 6.7$ Hz, 4H, NEt_2), 1.12 (t, $J = 7.5$ Hz, 6H, NEt_2), 3.0–1.3 ppm (m, 9H, BH); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 176.7$ (C=O), 57.7, 54.6 (CH_2+$C_{carborane}$), 48.9, 12.2 ppm (NEt_2); ^{11}B NMR (160.5 MHz, $CDCl_3$): $\delta = -4.8$ (d, $J = 148$ Hz, 2B), −6.7 (s, 1B), −11.1 (d, $J = 151$ Hz, 1B), −13.0 (d, $J = 167$ Hz, 2B), −15.1 ppm (d, $J = 141$ Hz, 4B); HRMS (ESI): m/z $[M+H]$ calcd for $C_8H_{25}N_2OB_{10}$: 273.2970, found: 273.2799.

2-(Diethylamino)-*N*-(1,7-dicarba-*closo*-dodecaboran-9-yl)acetamide (3): To a dry 25 mL Schlenk flask in an argon-filled glove box were added 9-iodo-*m*-carborane (500 mg, 1.85 mmol), 2-diethylaminoacetamide (722 mg, 5.54 mmol), K_3PO_4 (1.96 g, 9.23 mmol), DavePhos ligand (44 mg, 0.11 mmol), $Pd_2(dba)_3$ (42 mg, 0.05 mmol). To this mixture, dry THF (20 mL) was added by syringe at the Schlenk line. The reaction mixture was heated at reflux for 3 days, after which time it was filtered, and the filtrate was evaporated to give a yellow crude solid. The crude product was purified by column chromatography using silica gel ($MeOH/Et_2NH/CH_2Cl_2$, 0:0:100→5.7:0.3:94) to give a yellowish solid. Washing the solid with Et_2O gave the desired product as a white crystalline powder (432 mg, 86%): mp: 127.9–129.2 °C; ^1H NMR (400 MHz, [D_6]DMSO): $\delta = 7.05$ (s, 1H, CONH), 3.82 (s, 2H, $C_{carborane}$–H), 2.80 (s, 2H, CH_2), 2.42 (q, $J = 7.1$ Hz, 4H, NEt_2), 0.88 (t, $J = 7.2$ Hz, 6H, NEt_2), 3.2–1.1 ppm (m, 9H, BH); ^{13}C NMR (100.6 MHz, [D_6]DMSO): $\delta = 173.6$ (C=O), 58.0, 52.9 ($CH_2+C_{carborane}$), 48.1, 12.2 ppm (NEt_2); ^{11}B NMR (128.4 MHz, [D_6]DMSO): $\delta = -0.5$ (s, 1B), −7.7 (d, $J = 139$ Hz, 2B), −11.6 (d, $J = 146$ Hz, 1B), −14.2 (d, $J = 184$ Hz, 2B), −15.8 (d, $J = 167$ Hz, 2B), −18.8 (d, $J = 173$ Hz, 1B), −22.2 ppm (d, $J = 148$ Hz, 1B); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_8H_{24}N_2OB_{10}$: 273.2970, found: 273.2508.

2-(Diethylamino)-*N*-(1,12-dicarba-*closo*-dodecaboran-2-yl)acetamide (4): To a dry 25 mL Schlenk flask in an argon-filled glove box were added 2-iodo-*p*-carborane (1.0 g, 3.69 mmol), 2-diethylaminoacetamide (630 mg, 4.85 mmol), K_3PO_4 (3.91 g, 18.45 mmol), DavePhos ligand (71 mg, 0.18 mmol), $Pd_2(dba)_3$ (169 mg, 0.18 mmol). To this mixture, dry THF (20 mL) was added by syringe at the Schlenk line. The reaction mixture was heated at reflux for 2 days, after which time it was filtered, and the red colored filtrate was evaporated to give a reddish-brown residue. The crude product was purified by column chromatography over silica gel gel (100% CH_2Cl_2) to give the desired compound as a yellowish solid (940 mg, 93%). The product was further purified by recrystallization from MeOH/ Et_2O. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$ (br s, 1H, CONH), 3.71 (s, 1H, $C_{carborane}$–H), 2.93 (s, 2H, CH_2), 2.68 (s, 1H, $C_{carborane}$–H), 2.55 (q, $J = 7.2$ Hz, 4H, NEt_2), 1.03 (t, $J = 7.2$ Hz, 6H, NEt_2), 3.1–1.1 ppm (m, 9H, BH); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 175.9$ (C=O), 64.7, 60.5 ($C_{carborane}$), 58.4 (CH_2), 49.0, 12.5 ppm (NEt_2); ^{11}B NMR (128.4 MHz, $CDCl_3$): $\delta = -5.1$ (s, 1B), −13.9 (d, $J = 190$ Hz, 2B), −15.5 (d, $J = 161$ Hz, 4B), −16.5 (d, $J = 139$ Hz, 2B), −19.9 ppm (d, $J = 162$ Hz, 1B); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_8H_{24}N_2OB_{10}$: 273.2970, found: 273.2803.

1,7-Dimethyl-9-iodo-1,7-dicarba-*closo*-dodecaborane: To a solution of 1,7-dimethyl-1,7-dicarba-*closo*-dodecaborane (387 mg, 2.25 mmol) in CH_2Cl_2 (50 mL) were added I_2 (600 mg, 2.36 mmol) and $AlCl_3$ (30 mg, 0.22 mmol). The reaction mixture was heated at reflux for 4 h. The solvent was removed in vacuo, and the crude product was purified by column chromatography using silica gel (CH_2Cl_2/hexane, 1:10) to give the desired compound as a white solid (470 mg, 70%): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.8–1.9$ (br m, 9H, BH), 1.71 ppm (s, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 72.5$ (CH), 24.2 ppm (CH_3); ^{11}B NMR (128.4 MHz, $CDCl_3$): $\delta = -6.3$ (d, $J = 167$ Hz, 2B), −8.5 (d, $J = 155$ Hz, 1B), −9.0 (d, $J = 159$ Hz, 2B), −10.0 (d, $J = 165$ Hz, 2B), −12.2 (d, $J = 181$ Hz, 1B), −14.0 (d, $J = 182$ Hz, 1B), −23.5 ppm (s, B–I); HRMS (ESI): m/z $[M]^-$ calcd for C4H15B10I: 298.1221, found: 298.1017.

2-(Diethylamino)-*N*-(1,7-dimethyl-1,7-dicarba-*closo*-dodecaboran-9-yl)acetamide (5): In a 10 mL round bottom flask, 2-diethylaminoacetamide (83 mg, 0.64 mmol) was added to a suspension of NaH (60% dispersion in mineral oil, 26 mg, 0.64 mmol) in dioxane (2 mL). The mixture was stirred at 100 °C for 15 min, and then 1,7-dimethyl-9-iodo-1,7-dicarba-*closo*-dodecaborane (94 mg, 0.32 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (16 mg, 0.015 mmol), and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (20 mg, 0.03 mmol) were added to the reaction mixture. Stirring was continued at 100 °C for another 72 h. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (EtOAc/Hexane, 0:100 arrow 30:70) to give compound **5,** an oil (34 mg, 35%):

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.93$ (s, 2H, CH_2), 2.54–2.49 (q, $J =$ 7.3 Hz, 4H, NEt_2), 1.67 (s, 6H, CH_3), 0.99 (t, $J = 7.3$ Hz, 6H, NEt_2), 3.5–1.5 ppm (m, 9H, BH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 175.2$ (C=O), 67.8 (CH), 58.5 (CH_2), 48.8 (CH_2), 24.3 (CH_3), 12.4 ppm (CH_3); ^{11}B NMR (128.4 MHz, $CDCl_3$): $\delta = -0.5$ (s, 1B, B–N), -8.0 (d, $J =$ 162 Hz, 2B), -10.9 (d, $J = 178$ Hz, 3B), -12.4 (d, $J = 187$ Hz, 2B), -14.1 (d, $J = 186$ Hz, 1B), -17.2 ppm (d, $J = 178$ Hz, 1B); HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{10}H_{28}B_{10}N_2ONa$: 323.3103, found: 323.2695.

The general procedure for preparing hydrochloride salts of compounds 2–5: The compound was dissolved in anhydrous Et_2O (3–6 mL), and anhydrous HCl gas was bubbled through the stirred solution for 20–40 min at a medium rate. The product precipitated as white crystals, which were isolated by filtration and then recrystallized from MeOH/Et_2O to give the hydrochloride salt as shiny white crystals. The yield range was 50–70%.

2-(Diethylamino)-*N*-tricyclo[3.3.1.1^{3,7}]dec-1-ylacetamide (6): To a solution of diethylaminoacetic acid hydrochloride (168 mg, 1 mmol) and 1-aminoadamantane (150 mg, 1 mmol) in CH_2Cl_2 (10 mL) were added at RT 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (233 mg, 1.5 mmol), hydroxybenzotriazole (HOBT) (150 mg, 1.1 mmol) and *N*,*N*′-diisopropylethylamine (DIPEA) (390 mg, 3 mmol). The reaction mixture was stirred at RT for 24 h. The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (EtOAc, 100%) to give compound **6** as a colorless oil (83 mg, 29%): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.17$ (br s, 1H, NH), 2.86 (s, 2H, CH_2), 2.53–2.47 (q, $J = 7.0$ Hz, 4H, NEt_2), 2.07–2.02 (m, 3H, CH), 1.99–1.95 (m, 6H, CH_2), 1.69–1.62 (m, 6H, CH_2), 0.99 ppm (t, $J = 7.0$ Hz, 6H, NEt_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 171.0$ (C=O), 58.5 (CH_2), 51.0 (C–N), 48.8 (CH_2), 41.7 (CH_2), 36.4 (CH_2), 29.4 (CH), 12.6 ppm (CH_3); HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{16}H_{28}N_2ONa$: 287.2099, found: 287.2122.

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