Preparation of Boronated Heterocyclic Compounds Using Intramolecular Cyclization Reaction

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A method for synthesizing *o*-carborane substituted tetrahydroisoquinolines containing a polar functional group such as sulfamide, sulfonic, or phosphoric acid on the nitrogen atom of the piperidine ring, starting from arylethylamine, *N*-(2-arylethyl)sulfamide, *N*-(2-arylethyl)sulfamic acid or 2-arylethylamidophosphate, is described. In vitro studies showed the desired compounds **10**, **15**, **19**, and **25** synthesized accumulate to high levels in B-16 melanoma cells with low cytotoxicity.

Key Words : Brain cancer therapy, Boronated heterocyclic compounds, Cytotoxicity

Introduction

Isoquinoline alkaloids, which are widely distributed in the plant and animal kingdoms, have received much attention because of their important biological activities.[1] For example, 1,2,3,4-tetrahydroisoquinolines present in the mammalian brain play a major role in the therapy of variety of neurological disorders.[2] In particular, 1-arylmethyl-1,2,3,4-tetrahydroisoquinoline (THIQ, Figure 1) has been reported to be a potent dopamine antagonists with respect to neuroleptic agents.[3] This property makes the *o*-carboranyl substituted tetrahydroisoquinolines promising candidates for delivering boron atoms for the treatment of brain tumors. Boron neutron capture therapy (BNCT) was first proposed as a potential cancer therapy in 1936,[4] based on the thermal neutron captured by ^{10}B atoms then produces a ^{4}He (α-particle) and a ^{7}Li ion. However, its successful application in the treatment of cancer patients still presents a challenge in medical research.[5] A major challenge in designing boron-containing drugs for BNCT of cancer is the selective delivery of ^{10}B to the tumor as well as water solubility.[6]

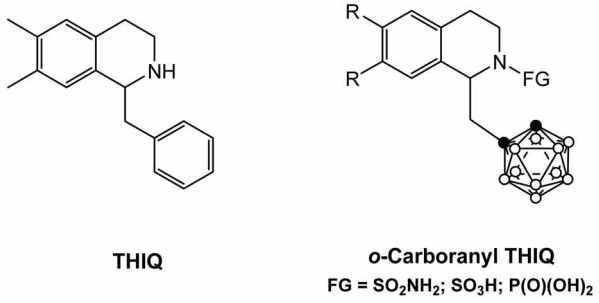


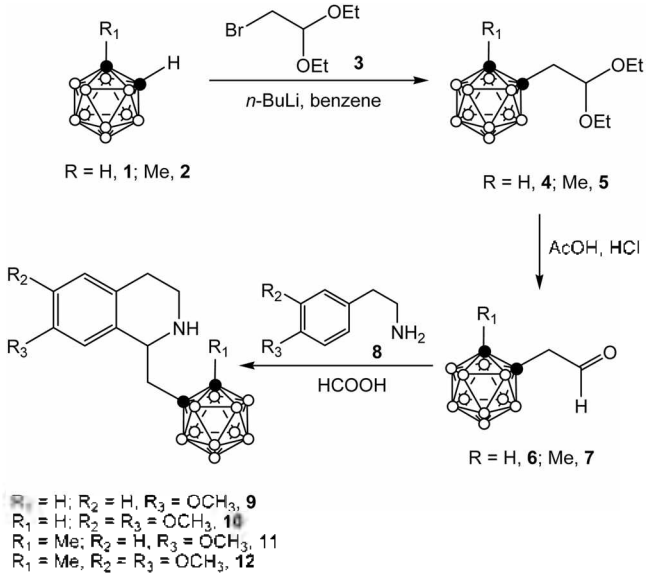
Figure 1. 1,2,3,4-Tetrahydroisoquinolines (THIQ) and *o*-Carboranyl THIQ.

Our synthetic strategy was to use tetrahydroisoquinoline as a boron delivery system, the target molecules being the tetrahydroisoquinolines in which the boron functionality was present as a carborane, known as $C_2B_{10}H_{12}$, an icosahedron cage of ten boron atoms and two carbon atoms. The large number of boron atoms has a clear advantage for BNCT.[7] The synthetic utility and the potent pharmacological activity of tetrahydroisoquinolines have attracted the attention of synthetic chemists in recent years, and consequently, several efficient synthetic procedures have been explored.[8] A convenient method for the synthesis of these types of compounds is an intramolecular electrophilic aromatic substitution of the iminium ion intermediate *in situ* generated from arylethylamine, containing polar functional group, and aldehyde under acidic condition.[9] Thus, the intramolecular cyclization has been applied to the use of *o*-carboranylaldehyde or *o*-carboranylaldehyde diethyl acetal in this study. We herein report the synthesis of tetrahydroisoquinolines **9-12**, **14-17**, **19**, **20**, and **22-25** in which the benzyl groups of THIQ are replaced by the *o*-carboranyl methyl unit.

Results and Discussion

The general synthetic strategy for the preparation of the starting materials used to prepare the reported *o*-carboranylacetaldehydes (**6** or **7**) relied on the methods developed by Rudolph.[10] The synthesis of **9-12** was accomplished in two steps (Scheme 1).

Synthesis of *o*-Carboranylacetaldehyde Diethyl Acetal (4, 5) and *o*-Carboranylacetaldehyde (6, 7). As shown in Scheme 1, the synthesis was initiated by the monolithiation of the *o*-carborane derivatives [R_1 = H (**1**), Me (**2**)]. When *o*-carborane was reacted with an equimolar quantity of *n*-



Scheme 1. Synthesis of *o*-Carboranylmethyl-1,2,3,4-tetrahydroisoquinolines.

butyllithium in benzene, followed by its reaction with bromoacetaldehyde diethyl acetal (**3**), the *o*-carboranylacetaldehyde diethyl acetal [R_1 = H (**4**), Me (**5**)] was formed in 77% yield. The resultant acetals, **4** and **5**, were hydrolyzed with acetic acid in the presence of concentrated HCl to give the corresponding aldehyde [R_1 = H (**6**), Me (**7**)] in 71% yield.

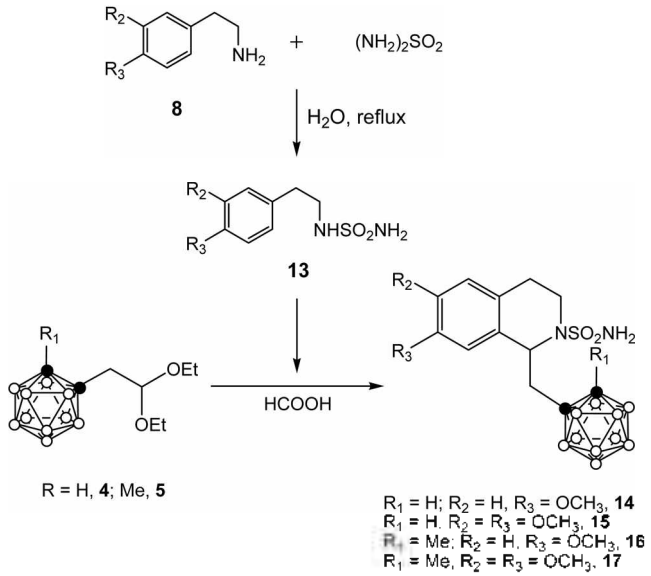
Synthesis of *o*-Carboranylmethyl-1,2,3,4-tetrahydroisoquinolines (9-12). With this *o*-carboranylacetaldehyde (**6**, **7**) now available, the Pictet-Spengler intramolecular cyclization reaction[11] with the arylethylamine (**8**) was investigated as a route to the target compounds **9-12** (Scheme 1). Intramolecular cyclization using the arylethylamine and aldehyde was investigated as a route to the target tetrahydroisoquinoline compounds. Thus, this condensation was finally achieved in 41-58% yield by heating the mixture of **6** and **7** at reflux in formic acid (Table 1). In this case, no color change was observed and the disappearance of the starting material was detected by TLC after 12 h of vigorous stirring with heating at reflux. By replacing *o*-carboranylacetaldehyde (**6**) with 1-methyl-*o*-carboranylacetaldehyde (**7**), the cyclization generated the corresponding product in moderate yield. In particular, the *o*-carborane cage was relatively stable under the acidic reaction condition.[12] All of the isolated products **9-12** were identified with the aid of infrared, ^{1}H and ^{13}C NMR, and elemental analysis.

Synthesis of *N*-Aminosulfonyl-*o*-carboranylmethyl-1,2,3,4-tetrahydroisoquinolines. As an extension of these studies, the reaction of the aminosulfonyl functionalized arylethylamine (**13**) with *o*-carboranylacetaldehyde diethyl acetal (**4**, **5**) was investigated in order to evaluate the effect of placing a sulfonyl group on the amine functionality. It has been noted that the sulfamide moiety is widely represented in many natural products and plays an important role in biological activities.[13] The synthesis of the aminosulfonyl tetrahydroisoquinoline skeleton was performed based on the α-sulfamidoalkylation procedure[14] previously reported by us (Scheme 2). The requisite aminosulfonyl functionalized arylamines (**13**) could be conveniently prepared by aminosulfonylation of the nitrogen atom of **14-17** according to established synthetic protocols.[15]

When the sulfamide **13** was treated with acetal (**4** or **5**) in formic acid, the cyclized *N*-aminosulfonyl-1-(*o*-carboranylmethyl)-1,2,3,4-tetrahydroisoquinoline (**14-17**) was obtained in 70-87% yield. In this case, the cyclization to **14-17** are faster and the reaction is nearly complete in 6 h at room temperature while the cyclization to **9-12** required a heating overnight at reflux. Having the sulfonyl group in the arylamine undoubtedly facilitates cyclization of the initially formed iminium ion. The aforementioned synthesis of **9-12**,

Table 1. Summary of Selected Physical and Spectral Properties of the *o*-Carboranyl-1,2,3,4-Tetrahydroisoquinoline Derivatives **9-12**, **14-17**, **19**, **20**, and **22-25**

Entry	No.	Yield (%)	Mp (°C)	IR (cm^{-1}) B–H	^{1}H NMR (δ)				^{13}C NMR (δ)			
					C(1)	C(3)	C(4)	C(α)	C(1)	C(3)	C(4)	C(α)
1	**9**	41	131-133	2578	3.04	4.25, 4.85	3.45, 3.81	2.75	56.7	41.8	38.0	26.9
2	**10**	65	130-131	2585	3.11	4.24, 4.28	3.11, 3.54	2.50	56.8	45.5	37.9	26.0
3	**11**	31	183-185	2586	2.78	4.26, 4.84	3.49, 3.84	2.51	56.7	41.6	38.7	26.2
4	**12**	68	179-181	2581	2.74	4.27, 4.75	3.55, 3.84	2.52	56.8	41.1	39.5	26.3
5	**14**	71	108-110	2586	3.00	3.80, 4.75	3.18, 3.41	2.47	56.8	42.4	38.2	24.4
6	**15**	81	120-122	2582	2.60	3.84, 4.95	3.01, 3.19	2.42	55.0	41.8	38.4	24.9
7	**16**	70	210-212	2578	3.01	3.68, 4.74	3.14, 3.47	2.50	55.6	41.8	38.2	23.7
8	**17**	87	228-230	2579	2.76	3.78, 4.89	3.14, 3.48	2.45	55.5	41.3	38.4	24.0
9	**19**	54	123-125	2583	4.76	3.47, 3.52	3.03, 3.11	2.88	56.6	41.8	39.5	24.9
10	**20**	70	170-177	2589	4.62	3.41, 4.59	2.98, 3.36	2.89	55.3	42.0	40.1	25.2
11	**22**	42	133-135	2604	4.67	3.40, 4.09	3.09, 3.37	2.98	57.7	42.9	36.6	26.7
12	**23**	45	145-147	2591	4.65	3.10, 3.50	2.90, 2.91	2.50	57.5	42.8	36.8	25.9
13	**24**	42	291-294	2583	4.64	3.13, 3.15	2.95, 3.02	2.45	56.4	41.7	40.7	25.9
14	**25**	45	295-296	2591	4.61	3.37, 3.40	2.99, 3.15	2.90	55.3	41.6	39.8	24.8

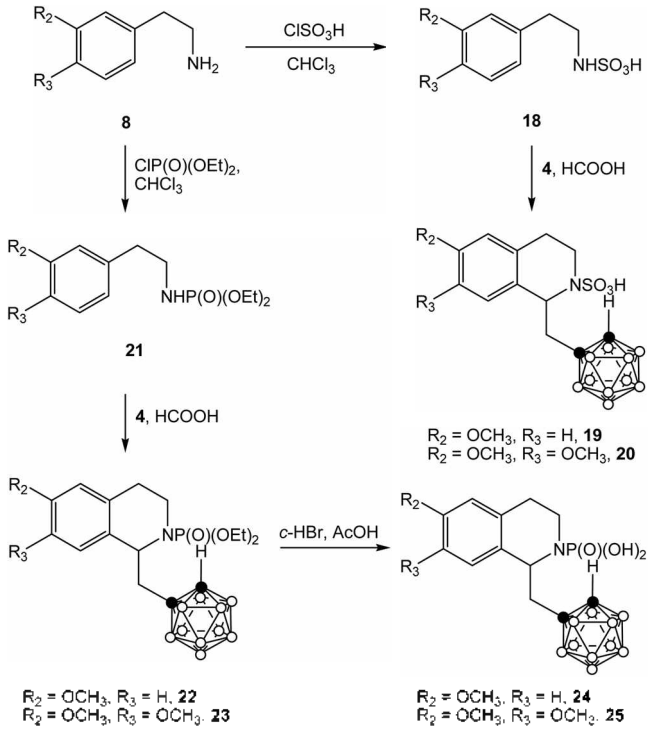


Scheme 2. Synthesis of *N*-Aminosulfonyl-*o*-Carboranylmethyl-1,2,3,4-Tetrahydroisoquinolines.

containing sensitive functional group such as *o*-carborane, is plagued by the harsh experimental conditions required for ring closure which limit their use as precursor compounds. Thus, the cyclization procedure outlined in Scheme 2 represents an efficient and mild approach toward this important class of nitrogen heterocycles. For the *N*-aminosulfonyl tetrahydroisoquinolines **14-17**, elemental analyses confirmed the proposed formulation for this compound. The ^{1}H and ^{13}C NMR data, as well as the IR spectrum of these compounds, provided further confirmation of their identity.

Synthesis of *N*-Sulfamic- or Phosphoric-*o*-carboranylmethyl-1,2,3,4-tetrahydroisoquinolines. The starting sulfamic acid **18** and aminophosphates **21** were prepared by treating chlorosulfonic acid or diethyl chlorophosphate with the corresponding 2-arylethylamines **8** at room temperature for 3 h in chloroform, according to established synthetic protocols (Scheme 3).[16]

Intramolecular cyclization of starting materials **18** or **21** with acetal **4** proceeding through an iminium ion intermediate in formic acid gave the desired products **19**, **20** and **22-25** in 42-54% isolated yield. In these processes, an electron-withdrawing substituents were introduced on the nitrogen of **8** to increase the electrophilicity of the iminium intermediate. Deethylation of **22** and **23** by treatment with hydrogen bromide in acetic acid afforded the free acids **24** and **25** in 42-45% yield. Selected spectroscopic properties of the piperidine rings and carborane units of **19**, **20** and **22-25** are given in Table 1. These compounds showed absorption bands in the infrared spectrum at 2583-2606 cm^{-1} characteristic of vibrations of the B-H group. Diagnostic signals were observed at δ 4.09-4.78 in the ^{1}H NMR spectra and at δ 54.1-54.6 in the ^{13}C NMR spectra for the methine (C-1) unit furnished by the acetal **4**. The methine unit signals at δ 4.51-4.56 in the ^{1}H NMR spectra of the starting acetal **4** move downfield upon cyclization.



Scheme 3. Synthesis of *N*-Sulfamic- and Phosphonyl-*o*-Carboranylmethyl-1,2,3,4-Tetrahydroisoquinolines.

Table 2. Cytotoxicity (IC_{50}) of the test compounds towards B-16[a] Cells and boron uptake

Entry	No.	IC_{50} (M)	Boron Uptake (μg B/10^6 cells)[b]	Water Solubility (mol/mL)
1	**10**	5.71×10^{-5}	2.72 ± 0.054	3.45×10^{-6}
2	**15**	2.23×10^{-5}	1.67 ± 0.25	1.49×10^{-6}
3	**19**	4.33×10^{-5}	0.41 ± 0.047	2.84×10^{-5}
4	**25**	4.33×10^{-5}	1.00 ± 0.098	3.88×10^{-5}
5	**BPA**[c]	8.63×10^{-3}	0.083 ± 0.012	

[a]B-16: B-16 melanoma cells. [b]Boron uptake by B-16 cells was determined using the ICP-AES method.[17] Briefly, cells were cultured in Falcon dishes (90 mmϕ) until they grew to fill the dishes (~3.0 10^6 cells/dish). Cells were then incubated for 3 h with Eagle-MEM medium containing one of the test compounds (boron concentration: 10.8 ppm). After 3 h, the cells were washed three times with PBS(−) and processed for determination of the boron concentration by ICP-AES. Each experiment was carried out in triplicate. [c]BPA: *p*-Boronophenylalanine

Conclusions

In conclusion, we have developed a general and versatile method for the preparation of tetrahydroisoquinolines flanked with an *o*-carborane unit at position 1. The intramolecular cyclization of the iminium ion, generated *in situ* from arylethylamine, is demonstrated to be a mild process which has great potential in medicinal chemistry for joining chemically sensitive targeting moieties to pharmacophores for BNCT. Furthermore, it is proved by *in vitro* study that compounds **10**, **15**, **19**, and **25** accumulates highly into B-16 melanoma cells with low cytotoxicity (Table 2). Introduction of other polar substituents on tetrahydroisoquinoline is now under active investigation.

Experimentals

General Methods. IR spectra were recorded on a Biorad FTS-165 spectrophotometer. ^{1}H and ^{13}C NMR spectra were taken on JEOL FT/NMR spectrometer (500 MHz) and Varian Mercury 300 spectrometer. Chemical shifts (δ) in parts per million (ppm) relative to Me_4Si. coupling constant (J value) are in hertz. Elemental analyses were performed with a Carlo Erba Instruments CHNS-O EA1108 analyzer. *o*-Carborane was purchased from Katchem and used without purification. Bromoacetaldehyde diethyl acetal. arylethylamine. sulfamide, sulfamic acid, and diethyl chlorophosphate were purchased from the Aldrich. The solvents and reactants were of the best commercial grade available and were used without further purification. All melting points were uncorrected.

Synthesis of 1-(2,2-Diethoxyethyl)-*o*-carboranes 4. *o*-Carborane **1** (1.44 g, 10.0 mmol) was dissoloved in freshly distilled dry benzene (200 mL) under Ar. *n*-Butyllithium (2.5 M in Hexane, 4.4 mL. 11.0 mmol) was added slowly via syringe through a serum cap at 25 °C. The benzene solution was heated to reflux for 5 min and then placed in an ice bath. When the benzene was cold, bromoacetaldehyde diethylacetal (**3**) (5.0 mL. 10.0 mmol) was added over 10 min. The solution was slowly warmed to room temperature to give a white precipitate. The mixture was stirred overnight. Diethylether was added and the organic layer was washed with water, and dried with anhydrous $MgSO_4$, and then dried *in vacuo* to give **4** of a pale yellow oil. Yield 77% (2.00 g). IR (KBr pellet, cm^{-1}) ν(B-H) 2590. ν(C-H) 3056. ^{1}H NMR (DMSO-d_6) δ 1.12 (t. 6H. J = 2.3 Hz), 2.52 (d. 2H. J = 1.8 Hz), 3.37 (br s. 1H), 3.45-3.56 (m. 4H), 4.51 (t, 1H. J = 1.8 Hz). ^{13}C NMR (DMSO-d_6) δ 15.1. 30.7, 61.3, 61.8, 72.4. 100.2. Compound **5**: Yield. 82% (2.25 g). IR (KBr pellet. cm^{-1}) ν(B-H) 2584, ν(C-H) 3057. ^{1}H NMR (DMSO-d_6) δ 1.12 (t. 6H, J = 2.3 Hz), 2.51 (s, 3H). 2.56 (d, 2H. J = 1.8 Hz), 3.48-3.59 (m. 4H). 4.56 (t. 1H. J = 1.8 Hz). ^{13}C NMR (DMSO-d_6) δ 15.1. 22.7. 32.8, 61.3. 75.6, 76.2. 100.7.

Preparation of *o*-Carboranylacetaldehyde 6. An acetic acid (20 mL) solution containing the acetal (**4**) (2.7 g. 5.0 mmol) and excess conc. HCl was stirred at room temperature for 8 h. The solution was added to water (30 mL) and extracted with Et_2O (20 mL × 2). The organic layer was washed with water (30 mL × 2). 10% aqueous $NaHCO_3$ solution (20 mL × 2). and saturated aqueous NaCl solution. The organic layer was dried with anhydrous $MgSO_4$. and then dried *in vacuo* to give the desired **6**. Yield. 71% (0.66 g). IR (KBr pellet. cm^{-1}) ν(B-H) 2592. ν(C-H) 3063. ν(C=O) 1739. ^{1}H NMR (DMSO-d_6) δ 3.42 (d. 2H. J = 8.0 Hz), 3.65 (br s, 1H), 9.49 (t. 1H. J = 8.0 Hz). ^{13}C NMR (DMSO-d_6) δ 47.1, 62.7, 69.2. 196.6. Compound **7**: Yield. 73% (0.73 g). IR (KBr pellet. cm^{-1}) ν(C=O) 1740, ν(B-H) 2590. ν(C-H) 3044. ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3H). 3.45 (d, 2H. J = 8.5 Hz). 9.55 (t, 1H. J = 8.5 Hz). ^{13}C NMR (DMSO-d_6) δ 22.6. 45.4. 76.1, 76.8. 196.6.

Synthesis of *o*-Carboranylmethyl-1,2,3,4-tetrahydroisoquinolines 9. A formic acid (15 mL) solution containing arylethylamine (**8**) (0.5 g. 2.0 mmol) and *o*-carboranylaldehyde (**6**) (0.34 g. 2.4 mmol) was heated at reflux for 12 h and then quenched with excess water (20 mL). Ethyl acetate was added and the organic layer washed with water. The organic layer was dried with anhydrous $MgSO_4$. The mixture was purified by flash chromatography ($CHCl_3$) to give the desired **9**. Yield. 41% (0.26 g). mp 131-133 °C. Anal. Calcd for $C_{13}H_{25}B_{10}NO$: C. 48.88; H. 7.89: N, 4.38. Found: C, 48.75: H, 7.91; N, 4.31. IR (KBr pellet. cm^{-1}) ν(B-H) 2578. ν(C-H) 3070, ν(N-H) 3238. ^{1}H NMR (DMSO-d_6) δ 2.75 (m. 2H), 3.04 (m, 1H). 3.28 (br s, 1H). 3.44 (m. 1H), 3.70 (s, 3H). 3.81 (m, 1H), 4.25 (m. 1H). 4.85 (m, 1H), 6.67 (s, 1H). 6.78 (s. 1H). 7.10 (s. 1H). 9.12 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 26.9. 38.0. 41.8. 56.7, 62.3, 73.8. 110.8, 112.7, 113.5, 128.3. 134.8. 145.3. Compound **10**: Yield. 65% (0.45 g). mp 130-131 °C: Anal. Calcd for $C_{14}H_{27}B_{10}NO$: C. 50.43: H, 8.16; N, 4.20. Found: C, 50.31; H. 8.22: N. 4.17. IR (KBr pellet, cm^{-1}) ν(B-H) 2585, ν(C-H) 3220. ν(N-H) 3235. ^{1}H NMR (DMSO-d_6) δ 2.16 (s, 3H), 2.50 (m, 2H), 3.11 (m, 1H). 3.54 (m, 1H). 3.71 (s. 3H). 3.81 (m, 1H), 4.24 (m, 1H), 4.28 (m. 1H). 6.71 (s. 1H). 6.80 (s. 1H), 7.08 (s, 1H), 9.15 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 22.8. 26.0, 37.9. 45.5, 56.8, 76.7. 77.0. 111.6, 112.8, 113.6. 128.5, 135.4. Compound **11**: Yield. 31% (0.21 g). mp 183-185 °C. Anal. Calcd for $C_{14}H_{27}B_{10}NO_2$: C, 48.12; H. 7.79; N, 4.01. Found: C, 48.22: H, 7.68; N. 4.12. IR (KBr pellet. cm^{-1}) ν(B-H) 2586, ν(C-H) 3082, ν(N-H) 3238. ^{1}H NMR (DMSO-d_6) δ 2.51 (m, 2H). 2.71 (m. 1H), 3.27 (br s. 1H), 3.49 (m, 1H). 3.75 (s, 3H). 3.77 (s. 3H). 3.84 (m. 1H). 4.26 (m. 1H). 4.84 (m, 1H), 6.66 (s. 1H). 6.67 (s, 1H), 9.10 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 26.2. 38.7. 41.6. 55.6. 56.7. 62.3. 73.7. 110.4, 112.1. 125.7, 127.6, 147.5. 148.2. Compound **12**: Yield. 68% (0.49 g). mp 179-181 °C. Anal. Calcd for $C_{15}H_{28}B_{10}NO_2$: C, 49.70: H, 7.79: N, 3.86. Found: C, 49.75; H. 7.71; N, 3.79. IR (KBr pellet, cm^{-1}) ν(B-H) 2581, ν(C-H) 3215, ν(N-H) 3235. ^{1}H NMR (DMSO-d_6) δ 2.12 (s, 3H). 2.52 (m, 2H), 2.74 (m, 1H), 3.55 (m. 1H). 3.84 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 4.27 (m, 1H). 4.75 (m, 1H). 6.49 (s, 1H). 6.55 (s, 1H). 9.14 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 23.6. 26.3, 39.5, 41.1, 56.8. 76.0, 76.9, 110.4, 112.1, 125.4, 127.5, 137.5, 142.5.

Preparation of *N*-Aminosulfonyl Arylethylamines 13. The mixture of **8** (2.5 g. 10.0 mmol). sulfamide (3.0 g. 10.0 mL). and water (10 mL) was heated at reflux for 6 h. The solution was cooled to room temperature and acidified (pH 2) with an aqueous 1 *N* HCl solution. The mixture was permitted to stand at 0-5 °C. The solid that formed was filtered and then washed with to give the desired **13**.

Synthesis of *N*-Aminosulfonyl-*o*-carboranylmethyl-1,2,3,4-tetrahydroisoquinolines 14. A formic acid (15 mL) solution of containing 0.77 g of **13** (2.0 mmol) and *o*-carboranyl diethyl acetal (**4**) 0.32 g (2.4 mmol) was reacted at 25 °C (6 h) and then quenched with excess water (20 mL). The solid that precipitated was filtered. washed with water. and dried *in vacuo* to give the desired **14**. Yield. 71% (0.57 g). mp 108-110 °C. Anal. Calcd for $C_{13}H_{26}B_{10}NO_3S$: C, 39.18: H, 6.58: N, 7.03. Found: C, 39.09; H. 6.47; N, 7.13.

IR (KBr pellet, cm^{-1}) ν(B-H) 2586, ν(C-H) 3271, ν(N-H) 3357. ^1H NMR (DMSO-d_6) δ 2.47 (m, 2H), 3.00 (m, 1H), 3.18 (m, 1H), 3.36 (br s, 1H), 3.41 (m, 1H), 3.70 (s, 3H), 3.80 (m, 1H), 4.75 (m, 1H), 6.64 (s, 1H), 6.77 (s, 1H), 7.04 (m, 1H), 9.42 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 24.4, 38.2, 42.4, 56.8, 60.6, 73.7, 112.6, 113.3, 127.1, 128.4, 136.8, 158.9. Compound **15**: Yield, 81% (0.69 g), mp 120-122 °C. Anal. Calcd for $C_{14}H_{28}B_{10}N_2O_3S$: C, 40.76; H, 6.84; N, 6.79. Found: C, 40.85; H, 6.69; N, 6.85. IR (KBr pellet, cm^{-1}) ν(B-H) 2582, ν(C-H) 3273, ν(N-H) 3353. ^1H NMR (DMSO-d_6) δ 2.04 (s, 3H), 2.42 (m, 2H), 2.60 (m, 1H), 3.01 (m, 1H), 3.19 (m, 1H), 3.71 (s, 3H), 3.84 (m, 1H), 4.95 (m, 1H), 6.69 (s, 1H), 6.77 (s, 1H), 7.07 (s, 1H), 9.40 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 24.8, 24.9, 38.4, 41.8, 54.9, 76.6, 77.1, 112.5, 113.4, 128.1, 128.2, 135.3, 148.1. Compound **16**: Yield, 70% (0.58 g), mp 210-212 °C. Anal. Calcd for $C_{14}H_{28}B_{10}NO_4S$: C, 39.24; H, 6.59; N, 6.54. Found: C, 39.12; H, 6.65; N, 6.39. IR (KBr pellet, cm^{-1}) ν(B-H) 2578, ν(C-H) 3271, ν(N-H) 3355. ^1H NMR (DMSO-d_6) δ 2.50 (m, 2H), 3.01 (m, 1H), 3.14 (m, 1H), 3.35 (br s, 1H), 3.47 (m, 1H), 3.68 (m, 1H), 3.70 (s, 3H), 3.74 (s, 3H), 4.74 (m, 1H), 6.68 (s, 1H), 7.11 (s, 1H), 9.41 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 23.7, 38.2, 41.8, 55.6, 56.7, 60.3, 73.5, 110.5, 111.9, 125.4, 126.7, 147.1, 147.8. Compound **17**: Yield, 87% (0.77 g), mp 228-230 °C. Anal. Calcd for $C_{15}H_{30}B_{10}N_2O_4S$: C, 40.71; H, 6.83; N, 6.33. Found: C, 40.72; H, 6.65; N, 6.37. IR (KBr pellet, cm^{-1}) ν(B-H) 2579, ν(C-H) 3244, ν(N-H) 3335. ^1H NMR (DMSO-d_6) δ 2.12 (s, 3H), 2.45 (m, 2H), 2.76 (m, 1H), 3.14 (m, 1H), 3.48 (m, 1H), 3.72 (s, 3H), 3.74 (s, 3H), 3.78 (m, 1H), 4.89 (m, 1H), 6.67 (s, 1H), 7.12 (s, 1H), 9.40 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 23.6, 24.0, 38.4, 41.3, 51.9, 55.4, 58.5, 76.8, 77.3, 110.3, 112.0, 125.7, 127.5, 147.0, 147.9.

Preparation of Arylethylsulfamic Acid 18 and Arylethylphosphate 21. A solution of arylethylamine **8** (10.0 mmol) and 1.2 equivalent of triethylamine (1.67 mL, 12.0 mmol) in 30 mL of $CHCl_3$ was stirred at −5 °C and chlorosulfonic acid (0.66 mL, 10.0 mmol) or diethyl chlorophosphate (1.45 mL, 10.0 mmol) was added dropwise so as to maintain the temperature below 0 °C. The solution was acidified with 1 *N* HCl solution to pH 2. The solid that precipitated was filtered to give the desired product **18** or **21**.

Synthesis of *N*-Aminosulfonyl-*o*-carboranylmethyl-1,2,3,4-tetrahydroisoquinolines 19. A formic acid (15 mL) solution of containing **18** (2.0 mmol) and *o*-carboranyl diethyl acetal (**4**) 0.32 g (2.4 mmol) was reacted at 25 °C (6 h) and then quenched with excess water (20 mL). The solid that precipitated was filtered, washed with water, and dried *in vacuo* to give the desired **19**. Yield, 54% (0.43 g), mp 123-125 °C. Anal. Calcd for $C_{13}H_{25}B_{10}NO_4S$: C, 39.08; H, 6.31; N, 3.51. Found: C, 39.07; H, 6.42; N, 3.49. IR (KBr pellet, cm^{-1}) ν(B-H) 2583, ν(C-H) 3271. ^1H NMR (DMSO-d_6) δ 2.88 (m, 2H), 3.03 (m, 1H), 3.11 (m, 1H), 3.47 (m, 1H), 3.52 (m, 1H), 3.70 (s, 3H), 4.76 (m, 1H), 4.82 (br s, 1H), 6.67 (s, 1H), 6.80 (s, 1H), 7.03 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 24.9, 39.5, 41.8, 54.5, 56.6, 64.0, 72.6, 111.8, 117.2, 129.3, 133.2, 136.2, 142.7. Compound **20**: Yield, 70% (0.60 g), mp 170-177 °C. Anal. Calcd for $C_{14}H_{27}B_{10}NO_5S$: C, 39.15; H, 6.34; N, 3.26. Found: C, 39.16; H, 6.40; N, 3.31. IR (KBr pellet, cm^{-1}) ν(B-H) 2589, ν(C-H) 3153. ^1H NMR (DMSO-d_6) δ 2.89 (m, 2H), 2.98 (m, 1H), 3.09 (m, 1H), 3.36 (m, 1H), 3.41 (m, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 4.59 (m, 1H), 4.62 (m, 1H), 5.33 (br s, 1H), 6.82 (m, 1H), 7.13 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 24.3, 25.2, 40.1, 42.0, 54.6, 55.3, 64.6, 73.7, 112.5, 113.9, 127.1, 130.1, 135.5, 158.9. Compound **22**: Yield, 42% (0.38 g), mp 133-135 °C. Anal. Calcd for $C_{17}H_{34}B_{10}NO_4P$: C, 44.82; H, 7.52; N, 3.07. Found: C, 44.87; H, 7.54; N, 3.11. IR (KBr pellet, cm^{-1}) ν(B-H) 2604, ν(C-H) 3197. ^1H NMR (DMSO-d_6) δ 2.89 (m, 2H), 2.98 (m, 1H), 3.09 (m, 1H), 3.21 (t, 3H), 3.37 (m, 1H), 3.40 (m, 1H), 3.70 (s, 3H), 3.82 (q, 2H), 4.09 (m, 1H), 4.67 (m, 1H), 5.49 (br s, 1H), 6.71 (s, 1H), 6.77 (s, 1H), 6.91 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 22.8, 26.7, 36.6, 42.9, 53.4, 57.7, 63.2, 72.8, 112.5, 112.9, 126.1, 127.8, 147.3, 147.7. Compound **23**: Yield, 45% (0.44 g), mp 145-147 °C. Anal. Calcd for $C_{18}H_{36}B_{10}NO_5P$: C, 44.52; H, 7.47; N, 2.88. Found: C, 44.54; H, 7.48; N, 2.87. IR (KBr pellet, cm^{-1}) ν(B-H) 2591, ν(C-H) 3144. ^1H NMR (DMSO-d_6) δ 2.50 (m, 2H), 2.90 (m, 1H), 2.91 (m, 1H), 3.10 (m, 1H), 3.20 (t, 3H), 3.50 (m, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 3.80 (q, 2H), 4.65 (m, 1H), 5.46 (br s, 1H), 6.69 (s, 1H), 7.01 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 22.1, 25.9, 36.8, 42.8, 53.6, 53.6, 57.5, 63.1, 72.9, 112.3, 112.7, 127.7, 128.3, 147.5, 147.9.

Preparation of *N*-Phosphonyl-*o*-carboranylmethyl-1,2,3,4-tetrahydroisoquinolines 24. A acetic acid (15 mL) solution of containing 0.91 g of **22** (2.0 mmol) and 1.2 equivalent of conc. HBr was reacted at 25 °C and then quenched with minimum water. The solid that precipitated was filtered, washed with water, and dried *in vacuo* to give the desired **24**. Yield, 42% (0.34 g), mp 291-294 °C. Anal. Calcd for $C_{13}H_{26}B_{10}NO_4P$: C, 39.09; H, 6.56; N, 3.51. Found: C, 39.10; H, 6.71; N, 3.53. IR (KBr pellet, cm^{-1}) ν(B-H) 2583, ν(C-H) 3191. ^1H NMR (DMSO-d_6) δ 2.45 (m, 2H), 2.95 (m, 1H), 3.02 (m, 1H), 3.13 (m, 1H), 3.15 (m, 1H), 3.70 (s, 3H), 4.64 (m, 1H), 5.40 (br s, 1H), 6.78 (s, 1H), 6.85 (s, 1H), 7.09 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 25.9, 40.7, 41.7, 54.5, 56.4, 64.8, 74.2, 115.2, 118.3, 126.7, 128.2, 134.6, 145. Compound **25**: Yield, 45% (0.39 g), mp 295-296 °C. Anal. Calcd for $C_{14}H_{28}B_{10}NO_5P$: C, 39.15; H, 6.57; N, 3.26. Found: C, 39.18; H, 6.58; N, 3.24. IR (KBr pellet, cm^{-1}) ν(B-H) 2591, ν(C-H) 3262. ^1H NMR (DMSO-d_6) δ 2.90 (m, 2H), 2.99 (m, 1H), 3.15 (m, 1H), 3.37 (m, 1H), 3.40 (m, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 4.61 (m, 1H), 5.44 (br s, 1H), 6.83 (m, 1H), 7.15 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 24.8, 25.1, 39.8, 41.6, 54.6, 55.3, 74.3, 112.1, 112.4, 128.4, 129.2, 136.3, 148.1.

Determination of IC_{50}. The boron compounds (20 mg) was dissolved in 1.0 mL of DMSO, and the resulting solution was diluted with Eagle's MEM (10% FCS), or BPA (*p*-boronophenylalanine) was directly dissolved in the same medium. In Falcon 3072 96-well culture plate, the cells (1×10^3 cells/well) were cultured on five wells with the medium containing boron compounds at various concentrations (1-100 ppm), and incubated for 3 days at 37 °C in CO_2 incu-

bator. It is known that DMSO is non-toxic at the concentration lower than 0.5%. We also confirmed by the control experiment that DMSO was non-toxic at the concentrations shown above. The medium was removed, and the cells were washed three times with PBS (−) (phosphate-buffered saline) and then MTS Assay for counting cells on Microplate reader. The results are presented as the concentration of agents that resulted in 50% of the cell number of untreated cultures (IC_{50}).

***In vitro* Boron Incorporation into B-16 Melanoma Cells** B-16 melanoma cells were cultured in Falcon 3025 dishes (90 mmϕ). When the cells were grown to fill up the dish (3.0×10^6 cells/dish), the boron compounds (1.0×10^{-4} M, 10.8 ppm boron) and BPA (1.0×10^{-3} M, 10.8 ppm boron) were added to dishes. The cells were incubated for 3 h at 37 °C in 20 mL of the medium (Eagle-MEM, 10% FBS). The cells were washed 3 times with Ca-Mg free phosphate buffered saline [PBS (−)], collected by rubber policeman, digested with 2 mL of 60% $HClO_4$-30% H_2O_2 (1:2) solution and then decomposed for 1 h at 75 °C. After filtration with membrane filter (Millipore, 0.22 mm), the boron concentration was determined by using ICP-AES (Shimadzu, ICPS-1000-III). Three replications of each experiment were carried out. The average of boron concentrations of each fraction was indicated in Table 2.

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