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Boron-Containing Polyamines as DNA Targeting Agents for Neutron Capture Therapy of Brain Tumors: Synthesis and Biological Evaluation

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Three series of new boron-containing spermidine/spermine (SPD/SPM) analogues have been synthesized: *N*[1]- and *N*[5]-(4-carboranylbutyl) SPD/SPM derivatives (**SPD-1**, **SPD-5**, **SPM-1**, **SPM-5**); *N*[1],*N*[10]-diethyl-*N*[5]-(4-carboranylbutyl)spermidine (**DESPD-5**), *N*[1],*N*[14]-diethyl-*N*[5]-(4-carboranylbutyl)spermine (**DESPM-5**); and *N*[5],*N*[10]-bis(4-carboranylbutyl)spermine (**SPM-5,10**). In vitro studies using rat F98 glioma cells have shown that these polyamines retain the ability to displace ethidium bromide from calf thymus DNA and are rapidly taken up by F98 glioma cells. However, their cytotoxicities, especially those with terminal N-substituted (**SPD-1**, **SPM-1**) boron compounds, are greater than those of SPD/SPM. Nevertheless, the groundwork has been created for a new class of boron-containing compounds that maybe useful for boron neutron capture therapy of tumors.

Introduction

Boron neutron capture therapy (BNCT) is based on the nuclear reaction that occurs when ^{10}B, a stable isotope having a relatively high neutron capture cross section value (σ = 3838 barns), is irradiated with thermal neutrons to produce high linear energy transfer (LET) α particles and recoiling ^{7}Li nuclei (Scheme 1).[1] These particles which have path lengths of 5−9 μm and are capable of destroying those cells containing sufficient quantities of ^{10}B required to sustain a lethal $^{10}B(n,\alpha)^{7}Li$ reaction. The use of BNCT as a cancer treatment modality has been described in several recent reviews[2−4] and monographs.[5,6] For BNCT to be effective, there must be ~20−30 μg ^{10}B per gram of tumor, and low concentration (<5 μg of ^{10}B/g of cell) in surrounding normal cells and blood.[7,8] The boron-containing delivery agent should be nontoxic, should selectively target tumor cells, and should ideally localize within the nucleus. A key question is how can tumor cells be selectively targeted? There has been a concerted effort to synthesize a variety of boron-containing analogues of biologically active compounds such as amino acids,[9−13] peptides,[14] nucleosides/nucleotides,[15−19] and porphyrins[20−22] as well as DNA binders.[14,23−25] Such structures might function in a manner similar to their naturally occurring counterparts and become selectively incorporated into either proliferating or more metabolically active tumor cells. Another potential class of compounds are the polyamines, including putrescine, spermidine (SPD), and spermine (SPM) (Figure 1), which are essential for cell growth and differentiation, especially in rapidly proliferating cells.[26,27] Polyamine depletion has growth inhibitory effects.[28,29] This has been the basis for the preparation of various polyamine synthetase inhibitors[30,31] and synthetic polyamines[32] for cancer treatment. Since cationic polyamines bind ionically to DNA[33] and retain a high degree of freedom within the polyamine cation−DNA complex,[34,35] incorporation of tumoricidal agents into the polyamine scaffold has yielded compounds that have been reported to be more active in cancer control than the parent chemotherapeutic agents.[36−39] On the basis of these observations, we have designed and synthesized three series of *N*-(carboranyl-tethered)polyamine analogues of spermidine and spermine as potential delivery agents for BNCT and have correlated their chemical structure with their in vitro cytostatic/cytotoxic effects, DNA binding properties and cellular uptake. A detailed account of this work is described below.

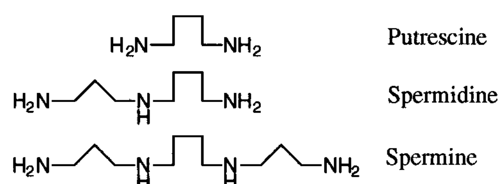


Figure 1. Polyamines.

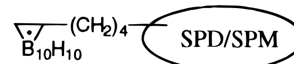
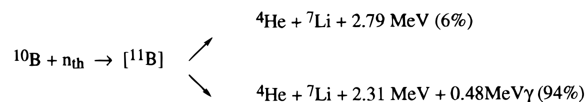


Figure 2. Carboranyl polyamine analogues.

Scheme 1. Boron Nuclear Reaction



Design and Synthesis

Two of the naturally occurring polyamines, spermidine (SPD) and spermine (SPM), were used in the syntheses of these three series of compounds. The boron moiety in these analogues was inserted (1) on the internal N atoms; (2) on the internal N atoms in which the terminal nitrogens carried monosubstituted ethyl groups; and (3) on the terminal nitrogen atoms. The *o*-carborane nucleus was chosen as the boron moiety and was tethered to polyamines by a chain of four methylene groups (Figure 2). The target compounds, whose syntheses are described, are shown in Schemes 2−6. These include *N*[1]- and *N*[5]-(4-carboranylbutyl) SPD/SPM derivatives (**SPD-1**, **SPM-1**, **SPD-5**, **SPM-5**), *N*[1],*N*[10]-diethyl-*N*[5]-(4-carboranylbutyl)spermidine (**DESPD-5**),

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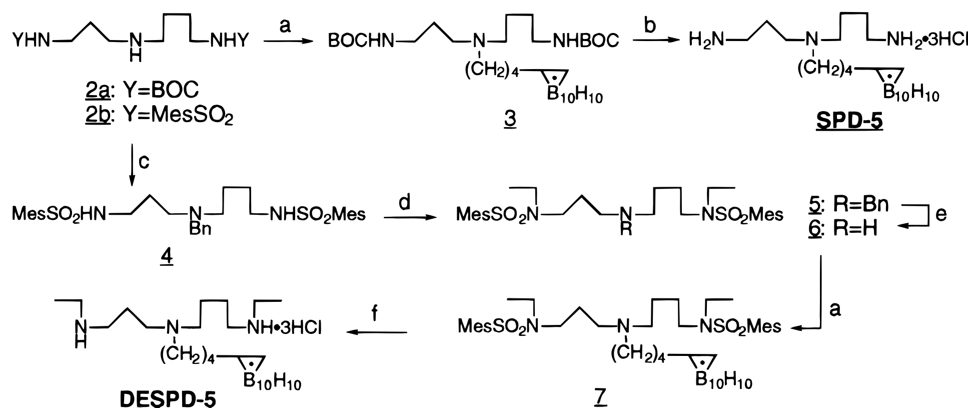
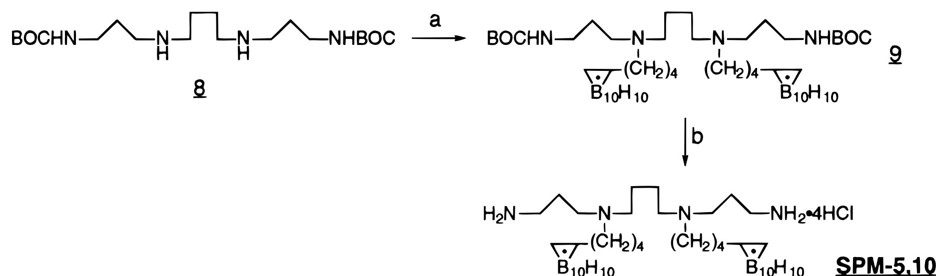
Scheme 2[a]



[a] (a) **1b**, K_2CO_3/DMF, 60−70 °C; (b) 3 N HCl/MeOH, 40−50 °C; (c) BnBr, K_2CO_3/DMF, 60−70 °C; (d) NaH, EtI/DMF; (e) Pd/C, H_2/MeOH; (f) concentrated HCl/EtOH, refluxing.

Scheme 3[a]



[a] (a) **1b**, K_2CO_3/DMF, 60−70 °C; (b) 3 N HCl/MeOH, 40−50 °C.

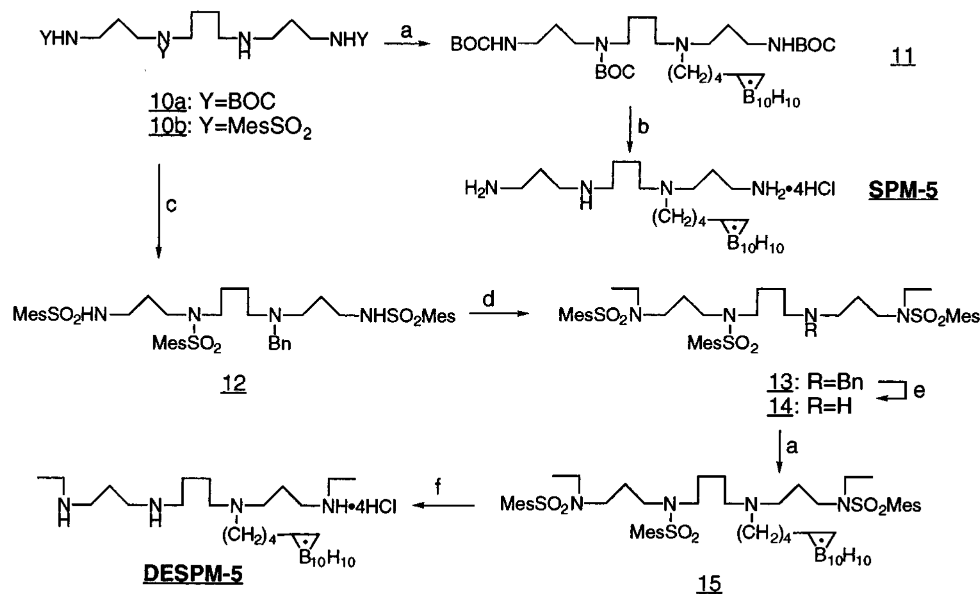
N^1,N^{14}-diethyl-N^5-(4-carboranylbutyl)spermine (**DESPM-5**), and N^5,N^{10}-bis(4-carboranylbutyl)spermine (**SPM-5,10**).

To synthesize internally substituted N-carboranylbutylated derivatives, SPD/SPM were initially protected at both terminal amino groups with the *tert*-butoxycarbonyl (BOC) group.[36] Bis(BOC) intermediates **2a** and **8** were then alkylated with 4-carboranylbutyl iodide, **1b**,[40,41] in DMF in the presence of K_2CO_3, forming the corresponding BOC-protected compounds **3** (Scheme 2) and **9** (Scheme 3) in high yield. Target compounds, **SPD-5** and **SPM-5,10**, were obtained, following removal of the BOC groups by acidic cleavage. With respect to the alkylation of **8**, it was not possible to form any of the mono(carboranylbutylated) species, even when the molar ratio of **8** to **1** was greater than 1:1. We attributed this result to the highly nucleophilic properties of the secondary amines in **8**, precluding the isolation of the monoalkylated analogue by this procedure. To ultimately synthesize target compound **SPM-5**, it was necessary to synthesize the tris-BOC protected derivative of SPM, **10a**. Its alkylation by **1b** generates **11** (Scheme 4), whose subsequent deprotection produces **SPM-5**. Previously, our group reported[40] the synthesis of **3** in two steps from **1b** and **2a**: the secondary amine of **2a** was first protected with the trimethylsilyl (TMS) group and then the TMS amide reacted with **1** in THF, generating **3**. When this same procedure was used for the synthesis of **9**, extremely poor yields of the product were observed. The TMS protecting group reduced the reactivity of the secondary amino group, necessitating longer reaction times, and under these conditions degradation of the carborane function was most probable.[42]

The possibility that toxic metabolites of polyamines could arise from those compounds containing primary amines[43] has led to the synthesis of the N-ethylated derivatives. For this series of compounds, we used the bis(ethylated) derivatives of **2a** as the starting material, but only intractable mixtures of the products were obtained.[44] However, when the BOC group was replaced by a 2-mesitylenesulfonyl ($MesSO_2$) group followed by protection of the internal NH with a benzyl group, the ethylation reactions of **4** and **12** were carried out in excellent yields (Schemes 2 and 4).[45] The bis(N-ethylated) intermediates, **5** and **13**, were then debenzylated by catalytic hydrogenation (H_2, Pd/C), yielding the free secondary amines, **6** and **14**, respectively. These two amines were again alkylated with **1b** under the same conditions as described above and formed the desired target compounds, **DESPD-5** and **DESPM-5**, after removal of the 2-mesitylenesulfonyl group in **7** and **15**, respectively.

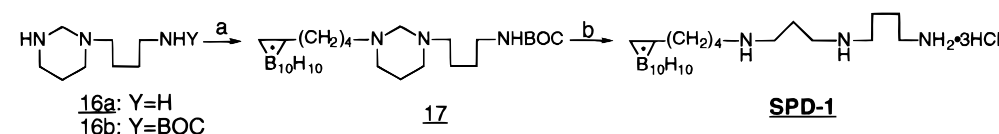
All of the above compounds have the boron moiety on an internal nitrogen. To determine whether terminally substituted analogues have more desirable biological properties, we undertook the syntheses of target compounds **SPD-1** and **SPM-1** shown in Schemes 5 and 6. In both cases, internal nitrogen(s) of SPD/SPM were protected by forming hexahydropyrimidine ring(s) with formaldehyde.[46,47] For the synthesis of **SPD-1**, the primary amine of **16a** was then protected with BOC and subsequently reacted with **1b** to give **17** in moderate yield. Deprotection of both the BOC group and the methylene group of the hexahydropyrimidine ring is achieved with acid, yielding the desired target compound. In the case of **18**, it reacted with 4-carboranylbutyl tosylate, **1a**,[18] to give mono(N-carboranylbutylat-

Scheme 4[a]



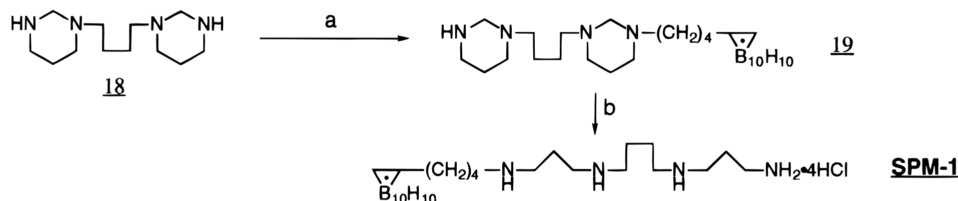
[a] (a) **1b**, K_2CO_3/DMF, 60−70 °C; (b) 3 N HCl/MeOH, 40−50 °C; (c) BnBr, K_2CO_3/DMF, 60−70 °C; (d) NaH, EtI/DMF; (e) Pd/C, H_2/MeOH; (f) concentrated HCl/EtOH, refluxing.

Scheme 5[a]



[a] (a) **1b**, K_2CO_3/DMF, 25 °C; (b) 3 N HCl/MeOH, 40−50 °C.

Scheme 6[a]



[a] (a) **1a**, K_2CO_3/DMF, 25 °C; (b) 3 N HCl/MeOH, 40−50 °C.

ed) compound **19** together with some bis(N-carboranylbutylated) byproduct. The latter can be readily separated from **19** by chromatography. Acid hydrolysis of **19** yielded **SPM-1**.

Biological Studies

Two major questions regarding these boron-containing polyamines were whether these structures behaved biologically similar to SPD/SPM, and whether they possessed the requisite properties for BNCT agents. To determine this, the following properties have been studied: (1) their in vitro growth inhibitory effects using F98 rat glioma cells; (2) their ability to displace ethidium bromide from calf thymus DNA; and (3) the compound's in vitro cellular uptake using the F98 glioma cells.

(1) In Vitro Evaluation of Cytotoxic/Cytostatic Properties. The assay that we have employed quantified the S phase of F98 glioma cells following a 24 h exposure to the test compounds by measuring cellular uptake/incorporation of [^{3}H]TdR and comparing these data to those obtained with cells that were not exposed to the compounds.[48] The results, summarized in Figure 3 for SPD analogues and in Figure 4 for SPM analogues, are expressed as counts per minute (cpm) obtained with cells grown in the presence of the test compound compared to those in the absence of the compound

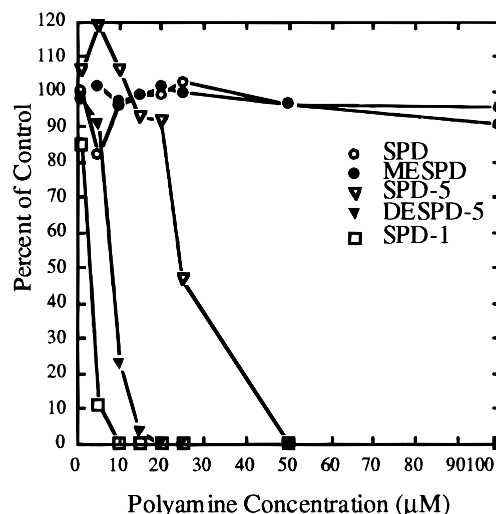


Figure 3. Cytotoxicity/cytostaticity of spermidine analogues.

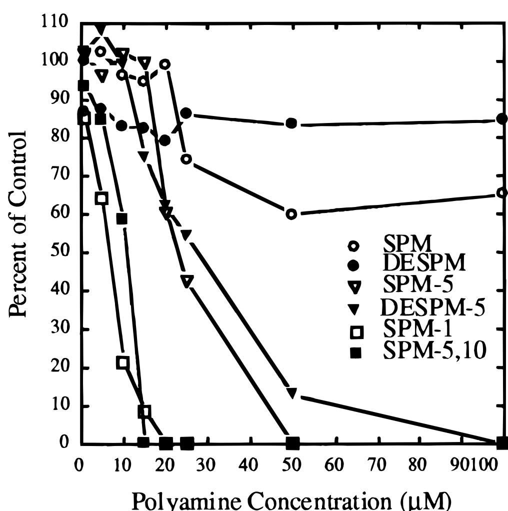


Figure 4. Cytotoxicity/cytostaticity of spermine analogues.

Table 1. In Vitro IC_{50} of Polyamine Analogues

compd[a]	IC (μM)[b]	compd[a]	IC (μM)[b]
SPD	>100	**DESPM**	>100
MESPD	>100	**SPM-1**	7.5
SPD-1	3	**SPM-5**	22
SPD-5	22	**DESPM-5**	25
DESPD-5	10	**SPM-5,10**	15
SPM	>100		

[a] Spermidine and its analogues are designated as SPD and spermine and its analogues as SPM. [b] The concentration of the test compound required to produce a 50% reduction in the uptake of [^{3}H]TdR, by F98 glioma cells. These values have been extrapolated from the curves shown in Figures 3 and 4.

(×100). If the compound had no cytotoxic/cytostatic effects, then uptake of [^{3}H]TdR by cells that either were exposed or not exposed to the test compound would be similar. The IC_{50} value was defined as that concentration required to reduce the uptake of [^{3}H]TdR by 50% compared to the controls. All of the carboranyl polyamines were toxic with an $IC_{50} < 25$ μM (Table 1). They were considerably more toxic than both SPD/SPM and their ethylated structures, N^1-ethylspermidine (**MESPD**) and N^1,N^{14}-diethylspermine (**DESPM**). Both classes of internally N-substituted analogues, **SPD-5**, **DESPD-5**, **SPM-5**, and **DESPM-5**, were less toxic than those terminally N-substituted derivatives, **SPD-1** and **SPM-1**. Incorporation of the diethyl group increased the toxicity of the SPD analogue, **DESPD-5**, while the SPM analogue, **DESPM-5**, was slightly less toxic than **SPM-5**. Toxicity also was increased by increasing the number of carborane substituents on the polyamine (**SPM-5,10** vs **SPM-5**). According to these results, as well as those reported by others,[49,50] incorporation of a hydrophobic group into the polyamine scaffold increased the compound's toxicity.

(2) DNA Binding Assay. Due to the high toxicity of many of the carboranyl polyamines, only those two with relatively low toxicity, **SPD-5** and **SPM-5**, were evaluated in the DNA binding assay. The binding of polyamine analogues to DNA was determined by an ethidium bromide displacement assay.[51−53] The C_{50} value was defined as the concentration of the polyamine required to decrease the fluorescence of the ethidium bromide−DNA complex by 50%. The results are summarized in Table 2. SPM analogues, possessing four positively charged ammonium groups, had stronger affinity for DNA than did the corresponding SPD analogues. Insertion of various boron substituents decreased their DNA affinity compared with SPD/SPM. Notably, **SPM-5** was a better DNA binder than SPD. Although the carboranylbutyl group is a bulky substituent and its incorporation reduces the compound's binding potential, our results have demonstrated that polyamine analogues have DNA binding properties that are similar to those of the naturally occurring compounds.

Table 2. DNA Binding Assay[a]

compd	IC_{50} (μM)
SPD	175
SPD-5	245
SPM	17
SPM-5	133

[a] Polyamine displacement of ethidium bromide from calf thymus DNA. Ethidium bromide and DNA concentrations were 1.6 and 10 μg, respectively. IC_{50} values are the concentration of polyamine required to decrease the fluorescence of the ethidium bromide−DNA complex by 50%.

Table 3. In Vitro Cellular Uptake[a]

compd	C_{media} (μg of B/mL)	$C_{cellular}$ (μg of B/g of cells)
	(A) 48 h Incubation	
SPD-5	0.5	43
DESPD-5	0.5	141
SPM-5,10	1.0	101
SPM-5	0.5	64
DESPM-5	0.5	37
	(B) 24 h Incubation	
SPD-5	0.5	65
BSH	570	39
BPA	50	81

[a] (A) F98 cells were incubated for 48 h with 5 μM polyamine analogue (the actual boron concentration, C_{media}, was determined by DCP-AES.) Cells were washed, counted, and digested. Boron was determinated by DCP-AES (10^9 cells ≈ 1 g of cells). (B) F98 cells were incubated for 24 h with boronated compounds and treated as in part A.

(3) In Vitro Cellular Uptake Studies. The in vitro uptake of carboranyl polyamines by F98 glioma cells was determined by measuring cellular boron content by means of direct current plasma atomic emission spectroscopy (DCP-AES) (Table 2).[54] Uptake of the tested compounds was compared with two clinically used agents, sodium undecahydromercapto-*closo*-dodecaborate (BSH) and L-*p*-boronophenylalanine (BPA) (Table 3). On the basis of the boron content in the media, which was 100−1000-fold less for the polyamines than for BSH and BPA, cellular uptake of the carboranyl polyamines was orders of magnitude greater than that obtained for BSH and BPA.

Discussion

The ortho carborane cage is sufficiently stable under neutral and acidic conditions for its incorporation into potential BNCT agents. However, it undergoes degradation under various basic conditions,[42,55−57] and this property has been the major chemical limitation in the synthesis of ortho carborane-containing amines that are very strong bases. This is the case with the polyamines. This problem can be obviated by masking the amino function and generating the final products under acidic conditions as the amine hydrochloride. These salts are very water soluble even with the carboranyl function,

and the resulting aqueous solutions are stable. Difficulties are encountered in alkylating the secondary amino groups of the polyamines since both the starting material and the product have the potential for degrading the cage and generating reduced yields. Using the trimethylsilyl (TMS) group to protect the secondary amine reduces its basicity.[40] However, this derivative also reduces the nucleophilicity of the amino group, and longer reaction times are required to generate the product. Under these conditions, degradation of the carborane cage by the free tertiary amine in the alkylated product becomes more significant. After considering all the factors, direct alkylation without the TMS masking group over a short time period was the optimal way for producing the product. However, in the case of alkylation on cyclic secondary amines (**17**, **18**), a reaction temperature of 60−70 °C was too high. Reactions under ambient conditions gave better, but not very high yields. This result might stem from the fact that such cyclic amines are stronger degrading agents of the carborane nucleus.[42]

The polyamine structure as a scaffold for targeting malignant cells has such a potential only when the polyamine transport system is up-regulated in these cells by contrast with contiguous normal cells. This appears to be especially true for brain tumor cells[31] and has provided the rationale for incorporating boron moieties into the naturally occurring polyamines, spermidine and spermine. The in vitro biological results with carboranyl polyamines show their potential for selectively delivering boron to tumor cells and thereby offer us a new class of BNCT agents. They possess the ability to displace ethidium bromide from calf thymus DNA, as do their natural counterparts, and are rapidly taken up by F98 glioma cells in vitro. This uptake is comparable to that of the clinically used compounds, BSH and BPA, but at a media concentration that is 100−1000-fold less. Accordingly, carboranyl polyamines possess advantages as potential BNCT agents when compared to other boronated compounds such as amino acids,[9−13] nucleosides/nucleotides,[15−19] and other potential DNA-targeting structures.[14,24,25] The high hydrophilic properties of these polyamine salts allow for their direct administration at suitable concentration levels in water. No cosolvents such as DMSO or various alcohols are necessary. The latter can contribute to the compound's toxicity and the inaccuracy of the biological evaluations. Polyamines bind to DNA nonspecifically, and therefore, boronated polyamines may be able to target DNA directly once they penetrate the cell membrane. This is in contrast to amino acids or nucleosides/nucleotides, which must be first incorporated into protein or DNA in order to localize in the cell nucleus. Such incorporation will be definitely limited due to the modification of naturally occurring amino acids and nucleosides/nucleotides by insertion of the boron moiety. However, the major limitation in the use of the present compounds appears to be their cellular toxicity, especially those compounds with terminal N-substituted boron moieties (**SPD-1**, **SPM-1**). Studies currently are in progress (1) to synthesize other boron-containing polyamine analogues with potentially lower toxicity; (2) to correlate their chemical structure with their physiochemical properties, toxicity and DNA binding; (3) to use this information for the design and synthesis of compounds possessing the requisite properties for BNCT delivery agents, i.e., high tumor uptake and retention, low normal tissue and blood content, and sufficiently nontoxic when administered to tumor bearing hosts.

The purpose of the assays used to evaluate the cytotoxic/cytostatic properties of the boronated polyamines as potential BNCT delivery agents is diametrically opposite to the requirements of the National Cancer Institute in identifying cytoreductive chemotherapeutic agents.[58] The most interesting, and potentially useful compounds for BNCT, would be those that attain high concentration in tumor cells and are minimally toxic to the host and normal cells. In contrast, the most useful cancer chemotherapeutic agents are those demonstrating cytotoxic or growth inhibitory effects on tumor cells, but their cellular uptake and concentration have not been considered relevant. The assay that we have employed measures the uptake of [^{3}H]TdR by F98 glioma cells following their exposure to various boron-containing polyamines. Although it is not a true measure of toxicity since it cannot distinguish between dead and biosynthetically quiescent cells, as measured by cpm, uptake does provide quantitative information on the number of biosynthetically active cells (i.e. S phase) following exposure to the test compound compared to the results obtained with cells grown in the absence of the compound. Since the ideal compounds for BNCT would either have no or minimal effects on the uptake of [^{3}H]TdR by S phase cells, we are screening for those compounds that are *not* cytotoxic. Previous experience with the assay has shown it to be a useful in vitro test for identifying nontoxic compounds that subsequently could be evaluated in vivo.[62]

In conclusion, this report is of the synthesis and evaluation of a group of new boron-containing polyamines that are prototypic of a class of compounds that might be useful as delivery agents for BNCT. The current limitation of these compounds is their toxicity. Recently, however, we have succeeded in synthesizing less toxic analogues, and their DNA binding potential and cellular uptake currently are being evaluated.

Experimental Section

The reagents were purchased from the chemical companies and used directly without further purification unless otherwise specified. Dry DMF was prepared by drying over BaO and then distilling. Dry THF was prepared by refluxing with sodium and distilling the product. Dry ethyl ether was prepared by refluxing over $LiAlH_4$ followed by distillation. Merck silica gel 60 (230−400 mesh) was used as solid phase for flash column chromatograpy. NMR spectra were obtained on a Bruker AC-250 or AC-270 spectrometer. Chemical shifts are reported downfield from TMS in spectra obtained in $CDCl_3$, CD_3OD, and DMSO-d_6 and from DSS in spectra obtained in D_2O. IR spectra were measured on a Laser Precision Analytical 720-XI spectrophotometer. MS were obtained on a VG 70-250S instrument for HR-EI and on a Finnigan MAT-900 instrument for LR-FAB. All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., and Galbraith Laboratories, Inc. All compounds gave elemental analyses within ±0.4% unless otherwise specified. RT (room temperature) is 22−25 °C.

1. Chemical Syntheses. Compounds **2a**, **8**, **10a**, **16**, and **18** were synthesized following the procedures reported in refs 32, 36, 41, and 46.

General Procedure for the Preparation of 2-Mesitylenesulfonamides: *N*[1],*N*[10]-Bis(mesitylenesulfonyl)sper-

midine (2b). 2-Mesitylenesulfonyl chloride (7.97 g, 36.44 mmol) in CH_2Cl_2 (40 mL) was added over 4 h to a mixture of spermidine (2.65 g, 18.24 mmol), 15% NaOH (30 mL), and CH_2Cl_2 (30 mL) at −10 °C under vigorous stirring. After the addition, the reaction mixture was stirred overnight at RT. Layers were separated, and the water layer was extracted with CH_2Cl_2. The organic phase was washed with 1 N NaOH and dried over $MgSO_4$. After filtering and concentrating, the residue was purified by flash column chromatography, eluting with ethyl acetate−MeOH (3:1) to give **2b** (6.7 g, 13.14 mmol, 72%) as a colorless oil: IR (neat, cm^{-1}) 3303 m, 2974 m, 2938 m, 1604 m, 1469 m, 1455 m, 1405 m, 1321 s, 1154 s, 1058 m, 737 m; ^{1}H NMR ($CDCl_3$) δ 7.00 (s, 4H, Ar*H*), 3.00 (t, $J = 7.5$ Hz, 2H, SO_2NCH_2), 2.90 (t, $J = 7.5$ Hz, 2H, SO_2NCH_2), 2.80−2.50 (m, 4H, $N(CH_2)_2$), 2.68 (s, 6H, 2 × $ArCH_3$), 2.66 (s, 6H, 2 × $ArCH_3$), 2.41 (s, 6H, 2 × $ArCH_3$), 1.75−1.60 (m, 2H, $CH_2(CH_2N)_2$), 1.60−1.48 (m, 4H, $NCH_2CH_2CH_2CH_2N$); ^{13}C NMR ($CDCl_3$) δ 141.9 t, 141.8 t, 139.1 t, 139.0 t, 134.0 q, 133.7 q, 132.0 t, 131.8 t, 49.0 d, 48.5 d, 42.4 d, 42.3 d, 27.9 d, 27.6 d, 27.6 d, 27.1 d, 22.9 s, 22.8 s, 20.8 s; MS (HR-EI) for $C_{25}H_{39}N_3O_4S_2$ calcd 509.2416, found 509.2374.

***N*^{1},*N*^{5},*N*^{14}-Tris(mesitylenesulfonyl)spermine (10b).** Compound **10b** (599.4 mg, 0.80 mmol, 37%) was obtained from the reaction of 2-mesitylenesulfonyl chloride (1.42 g, 6.49 mmol) and spermine (439.2 mg, 2.17 mmol). Eluting solvents: ethyl acetate−MeOH (2:1). **10b** was pure enough for use in the next step [IR (neat, cm^{-1}) 3311 m, 2938 m, 1605 m, 1456 m, 1319 s, 1152 s, 712 m; ^{1}H NMR ($CDCl_3$) δ 7.00 (s, 6H, Ar*H*), 3.31 (t, $J = 7.2$ Hz, 2H, SO_2NCH_2), 3.11 (t, $J = 7.2$ Hz, 2H, SO_2NCH_2), 2.95 (t, $J = 7.2$ Hz, 2H, SO_2NCH_2), 2.85 (t, $J = 7.2$ Hz, 2H, SO_2NCH_2), 2.62 (s, 12H, 4 × $ArCH_3$), 2.52 (s, 6H, 2 × $ArCH_3$), 2.52−2.37 (m, $J = 7.2$, 4H, $N(CH_2)_2$), 2.28 (s, 9H, 3 × $ArCH_3$), 1.82−1.22 (m, 8H, 2 × $CH_2(CH_2N)_2$ + $NCH_2CH_2CH_2CH_2N$); ^{13}C NMR ($CDCl_3$) δ 142.5 t, 141.9 t, 141.7 t, 140.0 t, 139.0 t, 138.9 t, 133.9 q, 133.5 q, 133.2 q, 132.0 t, 131.9 t, 131.8 t, 49.4 d, 49.0 d, 45.5 d, 43.2 d, 42.8 d, 39.4 d, 27.7 d, 27.5 d, 27.0 d, 25.1 d, 22.8 s, 20.9 s].

General Procedure for the Alkylation of the Amino Functions of Polyamines. *N*^{1},*N*^{10}-Bis(BOC)-*N*^{5}-(4-*o*-carboranylbutyl)spermidine (3). Compound **1b** (283.8 mg, 0.87 mmol) in DMF (1.5 mL) was added to a mixture of K_2CO_3 (143.5 mg, 1.04 mmol) and **2a** (359.9 mg, 1.04 mmol) in DMF (1 mL) heated to 60−70 °C. The reaction mixture was stirred for an additional hour. After cooling, ice−water and CH_2Cl_2 were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic phase was washed with 1 N NaOH and dried over $MgSO_4$. After filtering and removal of the solvent, the residue was purified by flash column chromatography and eluted with ethyl acetate−MeOH (50:1) to give **3** (421.5 mg, 0.77 mmol, 89%) as a colorless oil. It solidified in the refrigerator: mp 106−8 °C; IR (KBr, cm^{-1}) 3350 m, 2977 s, 2934 s, 2589 s, 1691 s, 1420 s, 1162 s, 723 m; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 1H, $B_{10}CH$), 3.21−3.02 (m, 4H, 2 × $CONCH_2$), 2.50−2.20 (m, 6H, $N(CH_2)_3$), 2.20−2.05 (m, 2H, CH_2CB_{10}), 1.70−1.49 (m, 10H, $CH_2(CH_2N)_2$ + $NCH_2CH_2CH_2$-CH_2N + $CH_2CH_2CH_2CB_2$), 1.48 (s, 18H, 2 × $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 156.0 q, 155.9 q, 79.0 q, 78.9 q, 75.3 q, 61.0 t, 53.6 d, 53.3 d, 52.3 d, 41.4 d, 39.6 d, 37.9 d, 28.4 s, 28.0 d, 27.1 d, 27.0 d, 26.5 d, 24.4d; MS (HR-EI) for $C_{23}H_{55}B_{10}N_3O_4$ (M + 2) calcd 547.5123, found 547.2114. Anal. ($C_{23}H_{53}B_{10}N_3O_4$) C, H, B, N.

***N*^{1},*N*^{10}-Bis(MesSO$_2$)-*N*^{5}-benzylspermidine (4).** Compound **4** (0.85 g, 1.42 mmol, 71%) was obtained from the reaction of BnBr (425 mg, 2.49 mmol) with **2b** (1.01 g, 1.98 mmol). The product was eluted with ethyl acetate−hexane (1:1): IR (neat, cm^{-1}) 3308 m, 2939 m, 1604 m, 1453 m, 1405 m, 1322 s, 1154 s, 1077 m, 700 m; ^{1}H NMR ($CDCl_3$) δ 7.45−7.15 (m, 5H, C_6H_5), 6.95 (m, 4H, Ar*H*), 6.47 (s, 1H, N*H*), 5.45 (s, 1H, N*H*), 3.45 (s, 2H, CH_2Ar), 3.05−2.75 (m, 4H, 2 × SO_2NHCH_2), 2.70 (s, 6H, 2 × $ArCH_3$), 2.64 (s, 6H, 2 × $ArCH_3$), 2.52−2.36 (m, 4H, $N(CH_2)_2$), 2.35 (s, 6H, 2 × $ArCH_3$), 1.70−1.51 (m, 2H, $CH_2(CH_2N)_2$), 1.51−1.45 (m, 4H, NCH_2CH_2-CH_2CH_2N); ^{13}C NMR ($CDCl_3$) δ 141.7 t, 139.0 t, 138.3 q, 133.9 q, 133.7 q, 131.8 t, 131.7 t, 128.9 t, 128.1 t, 126.9 t, 58.38 d, 52.9 d, 52.4 d, 42.2 d, 42.0 d, 27.4 d, 25.7 d, 23.7 d, 22.7 s, 20.7 s; MS (HR-EI) for $C_{32}H_{45}N_3O_4S_2$ calcd 599.2885, found 599.2850.

***N*^{1},*N*^{10}-Diethyl-*N*^{1},*N*^{10}-bis(MesSO$_2$)-*N*^{5}-(4-*o*-carboranylbutyl)spermidine (7).** Compound **7** (1.37 g, 1.79 mmol, 69%) was synthesized from the reaction of **1b** (846.9 mg, 2.63 mmol) with **6** (1.47 g, 2.59 mmol). The product was eluted with ethyl acetate−hexane (2:1) containing 2% MeOH: IR (neat, cm^{-1}) 2938 m, 2588 s, 1604 w, 1455 w, 1380 w, 1314 s, 1148 s, 710w; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 4H, Ar*H*), 3.80 (s, 1H, $B_{10}CH$), 3.30−3.14 (m, 8H, 2 × $SO_2NCH_2)_2$), 2.61 (s, 12H, 4 × $ArCH_3$), 2.29 (s, 6H, 2 × $ArCH_3$), 2.35−2.15 (m, 8H, $N(CH_2)_3$ + CH_2CB_{10}), 1.71−1.20 (m, 10H, $CH_2(CH_2N)_2$ + $NCH_2CH_2CH_2$-CH_2N + $CH_2CH_2CH_2CB_2$), 1.08 (t, $J = 7.1$ Hz, 3H, CH_2), 1.06 (t, $J = 7.1$ Hz, 3H, CH_2); ^{13}C NMR ($CDCl_3$) δ 142.1 t, 142.0 t, 139.9 t, 139.8 t, 133.5 q, 131.7 t, 75.5 q, 61.2 t, 53.3 d, 53.0 d, 51.4 d, 45.0 d, 43.6 d, 40.3 d, 39.9 d, 37.7 d, 26.9 d, 26.4 d, 25.5 d, 25.4 d, 24.2 d, 22.6 s, 20.7 s, 12.7 s, 12.6 s; MS (LR-FAB) m/e (calcd, found) for $C_{35}H_{67}B_{10}N_3O_4S_2$: 762 (8, 7), 763 (26, 23), 764 (54, 55), 765 (92, 92), 766 (100, 100), 767 (60, 66), 768 (24, 26), 769 (8, 9); MS (HR-EI) for $C_{35}H_{64}B_{10}N_3O_4S_2$ (M − 1) calcd 764.5302, found 764.5303. Anal. ($C_{35}H_{65}B_{10}N_3$-O_4S_2) C, H, B, N.

***N*^{1},*N*^{14}-Bis(BOC)-*N*^{5},*N*^{10}-bis(4-*o*-carboranylbutyl)spermine (9).** Compound **9** (385.8 mg, 0.48 mmol, 72%) was synthesized from **1b** (436.2 mg, 1.34 mmol) and **14** (538.2 mg, 1.34 mmol). The product was eluted with ethyl acetate−MeOH (6:1): IR (neat, cm^{-1}) 3346 w, 2938 s, 2593 s, 1698 s, 1455 s, 1173 s, 722 w; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, H, 2 × $B_{10}CH$), 3.20−3.07 (m, 4H, 2 × $CONCH_2$), 2.50−2.30 (m, 12H, 2 × $N(CH_2)_3$), 2.30−2.16 (m, 4H, 2 × CH_2CB_{10}), 1.68−1.52 (m, 4H, 2 × $CH_2(CH_2N)_2$), 1.50−1.30 (m, 12H, $NCH_2CH_2CH_2CH_2N$ + 2 × $CH_2CH_2CH_2CB_{10}$), 1.45 (s, 18H, 2 × $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 156.0 q, 77.5 q, 75.4 q, 61.2 t, 54.1 d, 53.4 d, 52.9 d, 39.5 d, 37.9 d, 28.5 s, 27.1 d, 26.6 d, 25.0 d. Anal. ($C_{32}H_{78}$-$B_{20}N_4O_4$) C, H, B, N.

***N*^{5}-(4-*o*-Carboranylbutyl)-*N*^{1},*N*^{10},*N*^{14}-tris(BOC)spermine (11).** Compound **11** (1.44 g, 2.05 mmol, 85%) was synthesized from **1b** (794.3 mg, 2.43 mmol) and **10b** (1468.8 mg, 2.92 mmol). The product was eluted with ethyl acetate−MeOH (8:1): IR (neat, cm^{-1}) 3348 m, 2935 s, 2592 s, 1696 s, 1514 s, 1456 s, 1391 s, 1273 s, 1174 s, 710 w; ^{1}H NMR (CD_3OD) δ 4.49 (s, 1H, $B_{10}CH$), 3.21−3.08 (m, 4H, 2 × $CONCH_2$), 3.07−2.89 (m, 4H, $CON(CH_2)_2$), 2.46−2.28 (m, 6H, $N(CH_2)_3$), 2.27−2.18 (m, 2H, CH_2CB_{10}), 1.68−1.47(m, 12H, 2 × $CH_2(CH_2N)_2$ + $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$), 1.46 (s, 9H, $C(CH_3)_3$), 1.44 (s, 18H, 2 × $C(CH_3)_3$); ^{13}C NMR (CD_3OD) δ 158.3 q, 158.2 q, 157.3 q, 80.8 q, 79.8 q, 77.2 q, 63.5 t, 54.8 d, 54.3 d, 52.7 d, 48.1 d, 45.8 d, 39.8 d, 38.9 d, 38.6 d, 30.0 d, 28.9 s, 28.3 d, 27.9 d, 27.1 d, 24.9 d; MS (HR-EI) $C_{31}H_{70}B_{10}N_4O_6$ (M + 2H) calcd 704.6226, found 704.6218.

***N*^{5}-Benzyl-*N*^{1},*N*^{10},*N*^{14}-tris(MesSO$_2$)spermine (12).** Compound **12** (2.78 g, 3.31 mmol, 75%) was produced from the reaction of BnBr (1.13 g, 6.61 mmol) and **10b** (3.31 g, 4.42 mmol). The product was eluted with ethyl acetate−hexane (2:1): IR (neat, cm^{-1}) 3312 m, 2939 s, 1605 s, 1405 s, 1152 s, 735 s; ^{1}H NMR ($CDCl_3$) δ 7.48−7.12 (m, 5H, C_6H_5), 7.00−6.81 (m, 6H, Ar*H*), 3.43 (s, 2H, CH_2Ar), 3.25 (t, $J = 7.2$ Hz, 2H, SO_2NCH_2), 3.07 (t, $J = 7.2$ Hz, 2H, SO_2NCH_2), 2.98−2.77 (m, 4H, $SO_2N(CH_2)_2$), 2.60 (s, 12H, 4 × $ArCH_3$), 2.54 (s, 6H, 2 × $ArCH_3$), 2.41−2.29 (m, 4H, $N(CH_2)_2$), 2.22 (s, 6H, 2 × $ArCH_3$), 2.20 (s, 3H, $ArCH_3$), 1.73−1.51 (m, 4H, 2 × $CH_2(CH_2N)_2$), 1.48−1.19 (m, 4H, $NCH_2CH_2CH_2CH_2N$); ^{13}C NMR (CD_3OD) δ 142.3 t, 141.8 t, 141.7 t, 139.8 t, 139.0 t, 138.8 t, 138.5 q, 134.0 q, 133.7 q, 133.2 q, 137.9 t, 131.8 t, 131.7 t, 128.8 t, 128.3 t, 128.2 t, 127.0 t, 58.0 d, 53.2 d, 52.7 d, 45.8 d, 42.8 d, 42.1 d, 27.6 d, 25.8 d, 25.2 d, 23.9 s, 22.7 s, 22.6 s, 20.7 s. Anal. ($C_{44}H_{62}N_4$-O_6S_3) C, H, N.

***N*^{1},*N*^{14}-Diethyl-*N*^{5}-(4-*o*-carboranylbutyl)-*N*^{1},*N*^{10},*N*^{14}-tris(MesSO$_2$) spermine (15).** Compound **15** (2.08 g, 2.08 mmol, 78%) was formed from **1b** (875.1 mg, 2.68 mmol) and **14** (2.16 g, 2.68 mmol). The product was eluted with ethyl acetate−hexane (2:1) containing 2% MeOH: IR (neat, cm^{-1}) 2939 m, 2593 m, 1605 w, 1457 w, 1314 s, 1149 s, 910 s, 733 s; ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 6H, Ar*H*), 3.25 (s, 1H, $B_{10}CH$), 3.30−2.95 (m, 12H, 6 × SO_2NCH_2), 2.59 (s, 6H, 2 × $ArCH_3$), 2.56 (s, 6H, 2 × $ArCH_3$), 2.53 (s, 6H, 2 × $ArCH_3$), 2.40−2.12 (m, 17H, 3 × $ArCH_3$ + $N(CH_2)_3$ + CH_2CB_{10}), 1.75−1.18 (m, 12H, 2 × $CH_2(CH_2N$-$)_2$ + $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$), 1.04

(t, J = 7.1 Hz, 3H, CH_3), 0.88 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 142.3 t, 142.2 t, 140.0 t, 133.6 q, 133.4 q, 131.9 t, 131.8 t, 75.5 q, 61.2 t, 53.4 d, 53.1 d, 51.5 d, 45.8 d, 43.6 d, 43.2 d, 42.8 d, 40.36 d, 40.2 d, 37.9 d, 27.0 d, 26.5 d, 25.6 d, 25.3 d, 24.2 d, 22.7 s, 20.8 s, 12.8 s, 12.6 s; MS (LR-FAB) m/e (calcd, found) for $C_{47}H_{82}B_{10}N_4O_6S_3$ 1001 (6, 8), 1002 (20, 24), 1003 (51, 56), 1004 (87, 90), 1005 (100, 100), 1006 (74, 72), 1006 (36, 33), 1007 (5, 4). Anal. ($C_{47}H_{82}B_{10}N_4O_6S_3$) C, H, N; B: calcd, 10.77; found, 8.52.

***N*¹-(4-BOC-amidobutyl)-*N*³-(4-*o*-carboranylbutyl)hexahydropyrimidine (17).** Compound **17** (184.9 mg, 0.41 mmol, 44%) was formed by reacting **1b** (303.3 mg, 0.93 mmol) and **16b** (239.3 mg, 0.93 mmol) at 25 °C. The product was eluted with ethyl acetate−MeOH (4:1): ^1H NMR (CD_3OD) δ 3.72 (s, 1H, $B_{10}CH$), 3.19−3.05 (m, 4H, $CH_2(N)_2$ + $CONCH_2$), 2.55−2.41 (m, 4H, $CH_2(CH_2N)_2$), 2.30−2.40 (m, 4H, 2 × CH_2N), 2.29−2.18 (m, 2H, CH_2CB_{10}), 1.66 (quint, J = 3 Hz, 2H, $CH_2(CH_2N)_2$), 1.52−1.40 (m, 17H, $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_2$ + $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 155.8 q, 78.5 t, 75.8 d, 75.2 q, 60.9 t, 54.4 d, 52.1 d, 52.0 d, 40.1 d, 37.5 d, 28.2 s, 27.7 d, 26.9 d, 26.2 d, 24.1 d, 23.0 d; MS (HR-EI) $C_{19}H_{45}B_{10}N_3O_2$ calcd 457.4442, found 457.4432.

1-((4-*o*-Carboranylbutyl)hexahydro-3-pyrimidyl)-4-(hexahydro-3-pyrimidyl)butane (19). Compound **19** (154.5 mg, 0.36 mmol, 36%) was formed by the reaction of **1a** (370.5 mg, 1.00 mmol) with **18** (249 mg, 1.10 mmol) at 25 °C. The product was eluted with MeOH containing 2% concentrated ammonium hydroxide: ^1H NMR ($CDCl_3$) δ 3.66 (s, 1H, $B_{10}CH$), 3.39 (s, 2H, $CH_2(N)_2$), 3.06 (s, 2H, $CH_2(N)_2$), 2.90−2.70 (m, 2H, NCH_2), 2.70−2.15 (m, 14H, 6 × CH_2N + CH_2CB_{10}), 1.81−1.61 (m, 4H, 2 × $CH_2(CH_2N)_2$), 1.58−1.30 (m, 8H, $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$); ^{13}C NMR (CD_3OD) δ 76.2 d, 75.1 q, 69.7 d, 60.8 t, 55.1 d, 55.0 d, 54.3 d, 52.8 d, 52.2 d, 44.9 d, 37.7 d, 27.0 d, 26.8 d, 26.3 d, 25.1 d, 23.3 d. Anal. ($C_{18}H_{44}B_{10}N_4$) H, N; C: calcd, 50.91; found, 49.95.

General Procedure for the Ethylation of the Amido *N* of Polyamines and Debenzylation: *N*¹,*N*¹⁰-Diethyl-*N*¹,*N*¹⁰-bis(MesSO₂)spermidine (6).[45] A solution of **4** (2.59 g, 4.32 mmol) in dry DMF (15 mL) was added slowly to a suspension of NaH (60%, 518.4 mg 12.96 mmol) in dry DMF (25 mL) at −5 °C. The reaction mixture was stirred for 45 min at RT and then cooled to 0 °C. To the mixture was added slowly a solution of EtI (2.03 g, 13.08 mmol) in dry DMF (1 mL). The solution was stirred for 30 min at 0 °C and for an additional 2 h at RT. Ice−water was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2, and the organic phase was washed with 1 N NaOH and dried over $MgSO_4$. After filtering and removal of the solvent, the residue was purified by flash column chromatography and eluted with ethyl acetate−hexane (1:1). The intermediate, compound **5** (2.7 g, 4.12 mmol, 96%), was obtained as a colorless oil. A mixture of **5** (2.7 g, 4.12 mmol) and 10% Pd/C (249 mg) in MeOH (40 mL) was stirred under a H_2 atmosphere overnight at RT. The Pd/C was removed by filtration and the methanol by a rotary evaporator. The residue was dried in high vacuum to give **6** (2.31 g, 4.08 mmol, 99%) as a colorless oil: IR (neat, cm^{-1}) 2937 m, 1604 m, 1457 m, 1382 m, 1315 s, 1148 s, 710 sl ^1H NMR (CD_3OD) δ 6.95 (s, 4H, ArH), 3.39−3.11 (m, 8H, 4 × SO_2NCH_2), 2.60 (s, 12H, 4 × $ArCH_3$), 2.52−2.48 (m, 4H, $N(CH_2)_2$), 2.40 (s, 6H, 2 × $ArCH_3$), 1.78−1.61 (m, 2H, $CH_2(CH_2N)_2$), 1.60−1.28 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 1.05 (t, J = 7.1 Hz, 6H, 2 × CH_3); ^{13}C NMR (CD_3OD) δ 142.1 t, 142.0 t, 140.0 t, 133.5 q, 131.9 t, 131.6 t, 49.1 d, 46.8 d, 44.9 d, 43.0 d, 40.1 d, 40.0 d, 27.8 d, 27.1 d, 25.3 d, 22.6 s, 20.9 s, 12.8 s, 12.7 s; MS (HR-EI) $C_{29}H_{48}N_3O_4S_3$ calcd 566.3120, found 566.3125.

***N*¹,*N*¹⁴-Diethyl-*N*¹,*N*¹⁰,*N*¹⁴-tris(MesSO₂)spermine (14).** The intermediate, compound **13** (2.75 g, 3.07 mmol, 93%), was first prepared from **12** (2.78 g, 3.31 mmol), NaH (60%, 397.5 mg, 9.94 mmol), and EtI (1.56 g, 10.0 mmol). Then **13** (2.62 g, 2.93 mmol) was then converted to compound **14** (2.21 g, 2.74 mmol, 94%) by hydrogenation with 10% Pd/C (250 mg) in MeOH: IR (neat, cm^{-1}) 2937 m, 1606 m, 1457 m, 1316 s, 1149 s, 735 m; ^1H NMR (CD_3OD) δ 6.90 (s, 6H, ArH), 3.31−3.18 (m, 4H, 2 × SO_2NCH_2), 3.11−2.96 (m, 8H, 4 × SO_2NCH_2), 2.58 (s, 6H, 2 × $ArCH_3$), 2.53 (s, 12H, 4 × $ArCH_3$), 2.50−2.33 (m, 4H, $N(CH_2)_2$), 2.26 (s, 9H, 3 × $ArCH_3$), 1.78−1.54 (m, 4H, 2 × $CH_2(CH_2N)_2$), 1.51−1.12 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 1.08 (t, J = 7.1 Hz, 3H, CH_3), 0.98 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 142.3 t, 142.2 t, 141.9 t, 140.0 t, 122.3 q, 133.2 q, 131.9 t, 131.8 t, 49.2 d, 46.9 d, 45.6 d, 43.3 d, 43.1 d, 42.8 d, 40.2 d, 40.1 d, 28.0 d, 27.2 d, 25.6 d, 25.1 d, 22.7 s, 22.6 s, 22.6 s, 20.8 s, 12.7 s, 12.6 s; MS (LR-FAB) $C_{41}H_{64}N_4O_6S_3$ (M^+) 895.

General Procedure for Deprotection of BOC and the Methylene Group of Hexahydropyrimidine. A mixture of the protected carboranyl SPD/SPM in 3 N HCl (2−3 mL) and EtOH (5 mL) was stirred for 10−16 h at 50−60 °C. The reaction mixture was concentrated, and EtOH was added and removed twice. The solid residue was purified by (A) recrystallization or by (B) boiling in EtOH (1−2 mL) for 30 min and allowing to stand for 1 day at RT. The solid was collected by filtration and dried in high vacuum.

***N*⁵-(4-*o*-Carboranylbutyl)spermidine·3HCl (SPD-5).** Compound **SPD-5** (542.4 mg, 1.20 mmol, 73%) was obtained from **3** (888.8 mg, 1.63 mmol), using method A MeOH−ethyl acetate (1:1): mp 255 °C dec; IR (KBr, cm^{-1}) 3424 m, 2963 s, 2588 s, 1601 m, 1465 m, 1396 m, 1066 m, 722 m; ^1H NMR (CD_3OD) δ 4.61 (s, 1H, $B_{10}CH$), 3.38−3.08 (m, 6H, $N(CH_2)_3$), 3.08−2.78 (m, 4H, 2 × NCH_2), 2.38−2.25 (m, 2H, CH_2CB_{10}), 2.20−2.01 (m, 2H, $CH_2(CH_2N)_2$), 1.81−1.40 (m, 8H, $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$); ^{13}C NMR (CD_3OD) δ 76.8 q, 63.7 t, 53.9 d, 53.6 d, 40.0 d, 37.9 d, 27.4 d, 25.5 d, 24.1 d, 23.1 d, 21.9 d, 20.9 d; MS (LR-FAB) m/e (calcd, found) for $C_{13}H_{38}B_{10}N_3$: 341 (9, 9), 342 (28, 29), 343 (64, 67), 344 (100, 100), 345 (95, 81), 346 (44, 44), 347 (6, 5). Anal. ($C_{13}H_{40}B_{10}Cl_3N_3$) C, H, N.

***N*¹-(4-*o*-Carboranylbutyl)spermidine·3HCl (SPD-1).** Compound **SPD-1** (140.6 mg, 0.31 mmol, 77%) was obtained from **17** (180 mg, 0.40 mmol) using method B: mp 233−5 °C; ^1H NMR (CD_3OD) δ 4.57 (s, 1H, $B_{10}CH$), 3.18−2.81 (m, 10H, 5 × NCH_2), 2.43−2.20 (m, 2H, CH_2CB_{10}), 2.20−2.0 (m, 2H, $CH_2(CH_2N)_2$), 1.90−1.40 (m, 8H, $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$); ^{13}C NMR (CD_3OD) δ 76.8 q, 63.7 t, 48.4 d, 45.8 d, 40 d, 38 d, 27.4 d, 26.5 d, 25.5 d, 24.2 d, 24; MS (LR-FAB) m/e (calcd, found) for $C_{13}H_{38}B_{10}N_3$ 341 (8, 9), 342 (28, 29), 343 (64, 63), 344 (100, 100), 345 (95, 88), 346 (46, 42), 347 (6, 5). Anal. ($C_{13}H_{40}B_{10}Cl_3N_3$) C, H, N; B: calcd, 23.87; found, 23.04.

***N*⁵-(4-*o*-Carboranylbutyl)spermine·4HCl (SPM-5).** Compound **SPM-5** (1010.0 mg, 1.85 mmol, 98%) was obtained from **11** (1.32 g, 1.88 mmol) using method B: mp 110−3 °C; IR (KBr, cm^{-1}) 3429 m, 2961 s, 2597 s, 1604 w, 1468 w, 721 w; ^1H NMR (CD_3OD) δ 4.52 (s, 1H, $B_{10}CH$), 3.25−2.87 (m, 14H, 7 × NCH_2), 2.35−2.20 (m, 2H, CH_2CB_{10}), 2.15−1.90 (m, 4H, 2 × $CH_2(CH_2N)_2$), 1.88−1.40 (m, 8H, $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$); ^{13}C NMR (DMSO-d_6) δ 76.2 q, 63.2 t, 51.4 d, 51.2 d, 48.9 d, 45.9 d, 43.8 d, 36.2 d, 36.1 d, 35.8 d, 26.0 d, 23.4 d, 22.5 d, 22.1 d, 21.0 d, 20.1 d; MS (LR-FAB) m/e (calcd, found) for $C_{16}H_{45}B_{10}N_4$ 398 (8, 8), 399 (27, 24), 400 (63, 62), 401 (100, 100), 402 (97, 85), 403 (49, 39), 404 (8, 7). Anal. ($C_{16}H_{48}B_{10}Cl_4N_4 \cdot H_2O$) C, H, N.

***N*¹-(4-*o*-Carboranylbutyl)spermine·4HCl (SPM-1).** Compound **SPM-1** (174.9 mg, 0.32 mmol, 80%) was obtained from **19** (168.4 mg, 0.39 mmol) using method B: mp 255−7 °C; IR (KBr, cm^{-1}) ^1H NMR (D_2O) δ 4.24 (s, 1H, $B_{10}CH$), 3.20−2.87 (m, 14H, 7 × NCH_2), 2.30−2.21 (m, 2H, CH_2CB_{10}), 2.19−1.19 (m, 4H, 2 × $CH_2(CH_2N)_2$), 1.80−1.40 (m, 8H, $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$); ^{13}C NMR (D_2O, 500 MHz) δ 76.6 q, 63.3 t, 48.3 d, 48.1 d, 48.0 d, 45.5 d, 37.6 d, 37.4 d, 26.9 d, 25.9 d, 24.7 d, 23.7 d, 23.4 d; MS (LR-FAB) m/e (calcd, found) for $C_{16}H_{45}B_{10}N_4$ 398 (8, 7), 399 (27, 24), 400 (63, 61), 401 (100, 100), 402 (97, 96), 403 (49, 24), 404 (8, 5). Anal. ($C_{16}H_{48}B_{10}Cl_4N_4$) C, H, N.

***N*⁵,*N*¹⁰-Bis(4-*o*-carboranylbutyl)spermine·4HCl (SPM-5,10).** Compound **SPM-5,10** (260.4 mg, 0.35 mmol, 92%) was obtained from **9** (300 mg, 0.38 mmol) using method B: mp 151−3 °C; IR (KBr, cm^{-1}) 3423 m, 2960 s, 2590 s, 1607 m, 1468 s, 1066 m, 722 m; ^1H NMR (CD_3OD) δ 4.52 (s, 2H, 2 × $B_{10}CH$), 3.42−2.90 (m, 16H, 8 × CH_2N), 2.38−2.26 (m, 4H, 2 × CH_2CB_{10}), 2.22−1.98 (m, 4H, 2 × $CH_2(CH_2N)_2$), 1.90−1.41 (m, 12H, $NCH_2CH_2CH_2CH_2N$ + 2 × $CH_2CH_2CH_2CB_2$); ^{13}C NMR (CD_3OD) δ 76.8 q, 63.8 t, 54.2 d, 53.6 d, 51.4 d, 38.1 d, 27.5 d, 24.3 d, 23.2 d, 22.2 d; MS (LR-FAB) m/e (calcd, found)

for $C_{22}H_{64}B_{20}N_4$ 596 (9, 12), 597 (22, 24), 598 (46, 49), 599 (76, 80), 600 (99, 94), 601 (100, 100), 602 (74, 68), 603 (38, 37), 604 (12, 12). Anal. ($C_{22}H_{66}B_{20}Cl_4N_4 \cdot H_2O$) C, H, N.

General Procedure for Deprotection of Mesitylenesulfonyl Group. A mixture of the amide in concentrated HCl (1 mL), AcOH (0.5 mL), and EtOH (5 mL) was refluxed for 24 h. The reaction mixture was concentrated under reduced pressure, diluted with water (10 mL), and washed with CH_2Cl_2. The aqueous solution was neutralized with 15% NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and extracted with 3 N HCl (3 × 3 mL). The acidic solution was then concentrated, and EtOH was added and removed twice. The solid residue was purified by boiling in EtOH (1−2 mL) for 30 min and standing for 1 day at RT. The solid was collected by filtration and dried in high vacuum.

***N*^{1},*N*^{10}-Diethyl-*N*^{5}-(4-*o*-carboranylbutyl)spermidine·3HCl (DESPD-5).** Compound **DESPD-5** (406.3 mg, 0.8 mmol, 47%) was obtained from **7** (1.30 g, 1.70 mmol): mp 181−3 °C; IR (KBr, cm^{-1}) 3413 m, 2948 m, 2592 s, 1456 m, 722 w; ^{1}H NMR (CD_3OD) δ 4.52 (s, 1H, $B_{10}CH$), 3.25−2.85 (m, 14H, 7 × NCH_2), 2.35−2.22 (m, 2H, CH_2CB_{10}), 2.21−1.94 (m, 2H, $CH_2(CH_2N)_2$), 1.88−1.37 (m, 8H, $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$), 1.21 (t, J = 7.1 Hz, 3H, CH_3), 1.20 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 76.8 q, 63.8 t, 54.1 d, 53.7 d, 51.2 d, 45.5 d, 44.4 d, 44.2 d, 38.0 d, 27.5 d, 24.4 d, 24.3 d, 22.1 d, 22.0 d, 11.6 s; MS (LR-FAB) *m/e* (calcd, found) for $C_{17}H_{47}B_{10}N_3$ 398 (8, 10), 399 (27, 31), 400 (64, 68), 401 (100, 100), 402 (97, 95), 403 (49, 47), 404 (8, 7). Anal. ($C_{17}H_{48}B_{10}Cl_3N$) C, H, N.

***N*^{1},*N*^{14}-Diethyl-*N*^{5}-(4-*o*-carboranylbutyl)spermine·4HCl (DESPM-5).** Compound **DESPM-5** (83.4 mg, 0.14 mmol, 53.7%) was obtained from **15** (260.0 mg, 0.26 mmol): mp 145−7 °C; IR (KBr, cm^{-1}) 3428 m, 2949 s, 2591 s, 1459 m, 1403 w, 723 w; ^{1}H NMR (CD_3OD) δ 4.56 (s, 1H, $B_{10}CH$), 3.42−2.85 (m, 18H, 9 × NCH_2), 2.35−2.22 (m, 2H, CH_2CB_{10}), 2.21−1.98 (m, 4H, 2 × $CH_2(CH_2N)_2$), 1.92−1.33 (m, 8H, $NCH_2CH_2CH_2CH_2N$ + $CH_2CH_2CH_2CB_{10}$), 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.24 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 76.8 q, 63.7 t, 54.0 d, 53.4 d, 51.1 d, 48.2 d, 45.9 d, 45.4 d, 44.3 d, 44.2 d, 37.9 d, 27.4 d, 24.2 d, 24.1 d, 22.0 d, 11.5 s; MS (LR-FAB) *m/e* (calcd, found) for $C_{20}H_{54}B_{10}N_4$ 455 (8, 11), 456 (27, 32), 457 (63, 67), 458 (100, 100), 459 (99, 99), 460 (52, 34), 561 (10, 9). Anal. ($C_{20}H_{56}B_{10}Cl_4N_4$) C, H, N.

2. Biological Studies. The variations for all of the biological test data were ∼±10%; therefore no error bars were inserted in the figures or tables. All tests were repeated two or three times. For cytotoxicity/growth inhibitory studies, each time six replicates were used for each sample.

a. In Vitro Evaluation of Cytotoxic/Cytostatic Properties. The F98 glioma cell line was derived from an undifferentiated brain tumor induced by administering *N*-ethyl-*N*-nitrosourea to a pregnant inbred CD Fisher 344 rat and has been propagated in vitro and in vivo since 1971. Its morphology and in vitro characteristics have been described in detail,[59,60] and it has been used by us to evaluate a variety of boron compounds as potential delivery agents for BNCT.[48,61,62] The assay that was employed to detect the toxicity and/or growth inhibitory effects has been widely used[63] and is based on the incorporation of tritiated thymidine ([^{3}H]TdR) by biosynthetically active (i.e. S phase) surviving cells following an exposure to the test compound. Ninety-six well plates (Corning Glass Works, Corning, NY) were seeded with 10 000 F98 cells per well and allowed to grow overnight at 37 °C in Dulbecco's minimal essential medium (DMEM) supplemented with 10% fetal bovine serum (FBS) (Hyclone, Logan, UT), 100 units/mL of penicillin, containing 100 μg/mL streptomycin, 2 mM L-glutamine, and 0.1 mM MEM nonessential amino acids (Gibco BRL, Grand Island, NY). This was replaced with media containing varying concentrations (1−100 μM) of spermidine, spermine, or carboranyl polyamines containing 0.1−10 μg/mL boron. After 24 h incubation at 37 °C in a humidified atmosphere containing 5% CO_2, the polyamine-containing media was removed and replaced with polyamine-free DMEM supplemented with FBS, and then pulsed with 0.1 μCi [^{3}H]TdR (specific activity 46 Ci/mmol) (Amersham, Arlington Heights, IL) per well. After an additional 18−24 h, the plates were harvested using a Skatron cell harvester (Skatron, Inc., Sterling, VA). Samples were counted in a LS 7800 beta scintillation counter (Beckman Instruments, Inc., Irvine, CA) using ScintiVerse scintillation fluid (Fisher Scientific, Fair Lawn, NJ). Uptake of [^{3}H]TdR was measured by counts per minute of cells grown in the presence of the test polyamines analogues compared to those of cells grown in media lacking the test compound using six replicates per concentration of compound. Percent uptake was determined by multiplying these values by 100, and that concentration required to produce a 50% reduction in [^{3}H]TdR uptake (i.e. IC_{50}) was calculated for each compound. Results for SPD and its analogues are shown in Figure 3 and for SPM and its analogues in Figure 4.

b. Ethidium Bromide Displacement Assay. The binding of spermidine, spermine, and the polyamine analogues to DNA was determined by an ethidium bromide displacement assay.[51−53] To 10 μg of calf thymus DNA (Sigma, St. Louis, MO) in 2.8 mL of buffer containing 2 mM HEPES, 10 μM EDTA, and 9.4 mM NaCl (pH = 7.0) was added 1.6 μM ethidium bromide (Sigma, St. Louis, MO). Fluorescence was measured on a Model 8000 spectrofluorometer (SLM Instruments, Kankakee, IL). Emission and excitation wavelengths were 598 and 546 nm, respectively. The various polyamine compounds were individually added in 10 μL aliquots. The decrease in fluorescence was recorded, and the C_{50} value was defined as the concentration of the polyamine compound required to reduce fluorescence of the ethidium bromide−DNA complex by 50%. These results and the comparison with SPD and SPM are presented in Table 2.

c. Cellular Uptake. Cellular uptake was determined by culturing F98 glioma cells in the presence of the test polyamines at a concentration that was not toxic or growth inhibitory. To each of four T150 tissue culture flasks (Corning Glass Works, Corning, NY) was added 5 × 10^6 F98 glioma cells in DMEM, supplemented as described above in the toxicity/growth inhibition assay. After 24 h, the tissue culture medium was decanted from the flasks and replaced with medium containing a nontoxic concentration (5 μM) of carboranyl polyamines in DMEM. Boron concentrations in the media (0.5 μg/mL) were confirmed by DCP-AES, as described previously.[54] Cells were incubated at 37 °C in an atmosphere containing 5% CO_2 for 48 h (approximately four doubling times), following which the media was removed and its boron content was determined. Cells were washed three times with phosphate buffer saline (PBS), and the washes also were saved for boron determination. The cells then were disaggregated using trypsin−EDTA (Gibco BRL, Grand Island, NY) and digested in concentrated sulfuric acid−70% hydrogen peroxide,[54] and the boron content was determined. Boron levels are expressed in micrograms per gram of cells, and as previously determined by direct cell counting, 10^9 cells ≈ 1 g. The results of these studies are presented in Table 3A and compared with the values obtained for sodium undecahydromercapto-*closo*-dodecaborate (BSH) and L-*p*-boronophenylalanine (BPA) (Boron Biologicals Inc., Raleigh, NC) in Table 3B.

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