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COMMUNICATION

SYNTHESIS OF NOVEL BORON-CONTAINING POLYAMINES—AGENTS FOR DNA TARGETING IN NEUTRON CAPTURE THERAPY

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Abstract—A new class of carriers for Neutron Capture Therapy, boronated polyamines, are presented that may possess a high affinity for DNA and rapid/specific uptake in brain tumors by comparison with adjacent normal brain. Two first boron-containing polyamines such as 1,8-diamino-4-(4-*o*-carboranylbutyl)-4-azaoctane and 1,8-diamino-4-(3-*o*-carboranylpropyl)-4-azaoctane were synthesized via silylation–alkylation reaction of bis-Boc-protected spermidine with either carboranyl iodides or tosylates.

The treatment of malignant brain tumors by neutron capture therapy[1] is predicated upon the development of boron compounds[2] with the capability for targeting neoplastic cells selectively. To achieve that objective, boron-containing analogues of various cellular building blocks have been synthesized including amino acids,[3,4] nucleosides[5–8] and precursors of membrane lipids.[9] The rationale is that such structures may be conserved and selectively incorporated into proliferating tumor cells in contrast with lower concentrations in normal brain cells.

Another class of naturally-occurring substances important in cell growth and replication are polyamines.[10] Their cellular content in rapidly-dividing malignant cells is significantly greater than normal cells;[11] many of the former possess an active energy-dependent polyamine uptake system that accumulates endogenous and structurally-related polyamines.[12] This observation has led to the use of the polyamine scaffold as a tumor targeting entity for the more selective delivery of cancer chemotherapeutic agents.[13–16] Of special importance is the observation that one polyamine, putrescine, demonstrated rapid and specific uptake in brain tumor in contrast with adjacent normal brain[17] and a polyamine analogue showed significant growth inhibition and decreased colony-forming ability for a number of human brain tumor cells in tissue culture.[18] It would be highly desirable if the boron compounds selectively target tumor DNA since the radiobiological effect is at least twice as great as if the compounds were confined to the cytoplasm.[19] Polyamines do possess a high affinity for DNA[20] and that is the rationale for the development of spermidine targeted chemotherapeutic agents.[14,16]

This communication describes the synthesis of the first boron-containing polyamines: 1,8-diamino-4-(4-*o*-carboranylbutyl)-4-azaoctane and 1,8-diamino-4-(3-*o*-carboranylpropyl)-4-azaoctane as hydrochlorides (**5a** and **5b**, respectively).

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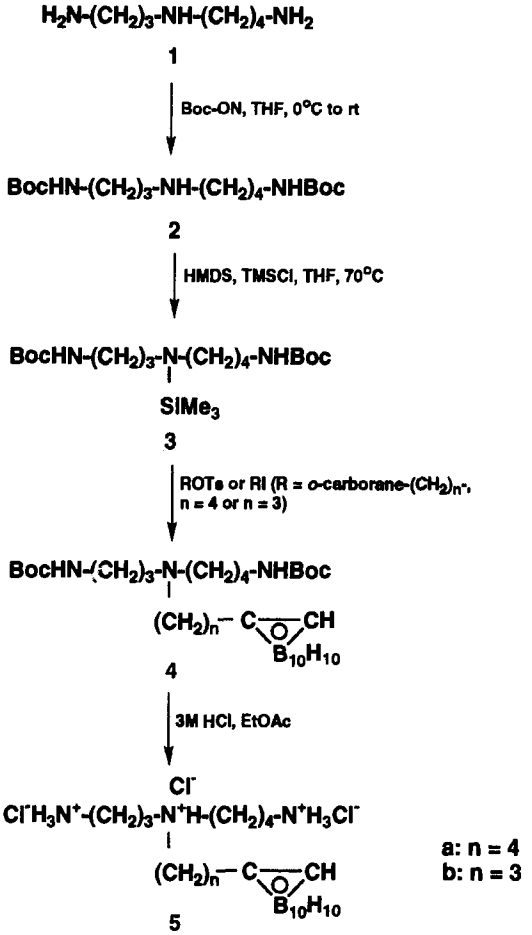

1,8-Bis-(Boc-amino)-4-azaoctane (**2**)[21] was obtained from spermidine (**1**) using 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON) in 70% yield. The alkylation of 1,8-bis-(Boc-amino)-4-azaoctane (**2**) with 1-{4-[(*p*-tolylsulfonyl)oxy]butyl}-*o*-carborane via silyl derivative (**3**) yielded 1,8-bis-(Boc-amino)-4-(4-*o*-carboranylbutyl)-4-azaoctane (**4a**) as yellow oil in 27% overall yield. Replacement of 1-{4-[(*p*-tolylsulfonyl)oxy]butyl}-*o*-carborane with 1-(4-iodobutyl)-*o*-carborane improved the yield of the alkylation to 65%. Similarly, the silylation–alkylation of **2** with 1-(3-iodopropyl)-*o*-carborane afforded 1,8-bis-(Boc-amino)-4-(3-*o*-carboranylpropyl)-4-azaoctane (**4b**) as yellow oil in 60% overall yield. The structures of **4a** and **4b** were confirmed by HRMS, IR, ^{1}H NMR and ^{13}C NMR. Deprotection of **4a** and **4b** *via* acid hydrolysis[22] yielded the corresponding hydrochlorides **5a** and **5b**. Crystallization from ethyl alcohol/ether solution yielded crystalline 1,8-diamino-4-(4-*o*-carboranylbutyl)-4-azaoctane and 1,8-diamino-4-(3-*o*-carboranylpropyl)-4-azaoctane as hydrochlorides (**5a** and **5b**, respectively). Their chemical structures were confirmed by HRMS, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (for **5a**).† Hydrochloride **5b** appeared to be highly hydroscopic. The biological evaluation of **5a** and **5b** is in progress and will be reported separately.

The described procedure is applicable to the synthesis of a variety of different boron-containing polyamines.

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† 1,8-Diamino-4-(4-*o*-carboranylbutyl)-4-azaoctane hydrochloride (**5a**): white powder; MS (HR-EI) for $C_{13}H_{37}N_3B_{10}x2H^+$: Calc. 347.4075, Found 347.4031; for $C_{13}H_{37}N_3B_{10}xH^+$: Calc. 346.3996, Found 346.3960; for $C_{13}H_{37}N_3B_{10}$: Calc. 345.3918, Found 345.3953; ^{1}H NMR (DMSO-d_6) δ 1.2–3.3 (br m, 10H, B—H), 1.47 (quint., 2H, —CH_2—), 1.61 (quint., 2H, —CH_2—), 1.68 (quint., 2H, —CH_2—), 1.79 (quint., 2H, —CH_2—), 2.03 (quint., 2H, —CH_2—), 2.36 (m, 2H, —CH_2—), 2.81 (m, 2H, —CH_2—), 2.89 (m, 2H, —CH_2—), 3.02 (m, 4H, —CH_2—), 3.15 (m, 2H, —CH_2—), 5.28 (br s, 1H, *H*C of carborane), 8.08, 8.19 (2 br s, 6H, 2 NH_3^+), 10.82 (br s, 1H, 4-NH^+); ^{13}C NMR (DMSO-d_6) δ 19.809, 21.033, 21.975, 24.036, 26.018, 35.836, 36.166, 37.978, 48.705, 51.160, 54.811, 63.091 (H*C*— of carborane), 76.141 (—*C*— of carborane); Anal. Found C, 34.56; H, 8.83; N, 9.38. Calc. for $C_{13}H_{37}N_3B_{10}x3HCl$: C, 34.47; H, 8.90; N, 9.28.

1,8-Diamino-4-(3-*o*-carboranylpropyl)-4-azaoctane hydrochloride (**5b**): off-white highly hygroscopic powder; MS (HR-EI) for $C_{12}H_{35}N_3B_{10}$: Calc. 331.3762, Found 331.3769; ^{1}H NMR (DMSO-d_6) δ 1.4–3.5 (br m, 10H, B—H), 1.64 (quint., 2H, —CH_2—), 1.82 (quint., 2H, —CH_2—), 1.89 (quint., 2H, —CH_2—), 2.06 (quint., 2H, —CH_2—), 2.40 (m, 2H, —CH_2—), 2.82 (m, 2H, —CH_2—), 2.92 (m, 2H, —CH_2—), 3.0 (m, 2H, —CH_2—), 3.05 (m, 2H, —CH_2—), 3.20 (m, 2H, —CH_2—), 5.42 (br s, 1H, *H*C— of carborane), 8.20, 8.30 (2 br s, 6H, 2NH_3^+), 10.98 (br s, 1H, 4-NH^+); ^{13}C NMR (DMSO-d_6) δ 19.90 (t, —CH_2—), 21.10 (t, —CH_2—), 23.035 (t, —CH_2—), 24.04 (t, —CH_2—), 33.47 (t, —CH_2—), 36.19 (t, —CH_2—), 38.01 (t, —CH_2—), 48.90 (t, —CH_2—), 50.55 (t, —CH_2—), 51.27 (t, —CH_2—), 62.86 (d, H*C*— of carborane), 75.66 (s, —*C*— of carborane).

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