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Synthesis of novel Boronated Acridines- and Spermidines as possible agents for BNCT

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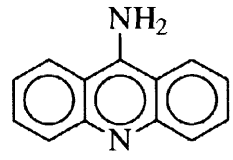
Abstract: An approach to synthesise three different boronated DNA-interacting compounds (**11, 15 & 19**) is described. Compound **11** is containing both an acridine system and a spermidine residue. The acridine moiety would serve as DNA-intercalating fragment whereas the spermidine residue functions both as water-solubilising and DNA-interacting part. 1,12-*p*-Carboranyl bis[(*N*-3-aminopropyl, *N*-4-aminobutyl)-3-propane amide] hydrogen chloride (**15**) was obtained by treating **13** first with ethyl chloroformate and then the secondary amine **2**. Finally, 1,12-Bis(*N*-(9-acridinyl)3-aminopropyl)-*p*-carborane hydrogen chloride (**19**) was accomplished by hydrochloronation of the corresponding free amine which was obtained by the treatment of **18** with **9** in toluene/DMF.

INTRODUCTION

One of the most challenging area of investigation in Boron Neutron Capture Therapy (BNCT)[1] is how to localise selectively boron-containing compounds in tumour cells. It has recently been proposed[2] by our research group that a special tumour delivery system in a two-step targeting principle should be employed in order to reach into the nucleus of the tumour cells. It was found that a higher radiobiological efficiency of the neutron capture reaction [$^{10}B(^{1}n, ^{4}He)^{7}Li$] would be obtained if this reaction occurs in the cell nucleus rather than in the cytoplasm.[3] Thus, boronated DNA-intercalators are potential candidates for BNCT because they could deliver boron-10 into the nuclei of tumour cells.

Earlier, we have synthesised boron-containing analogues[4] of the DNA-intercalator ethidium bromide and herein as a part of an ongoing research program planed to develop new boronated DNA- intercalating/ interacting molecules, we turned our attention to other DNA-affinic agents such as acridine and spermidine.



9-aminoacridine

Figure:1

Acridine as DNA-intercalator: Earlier studies on 9-aminoacridine (**Figure 1**) have shown that this compound intercalates into the DNA. It is assumed that the acridine chromophore with its 9-amino group lies in the minor groove and the 4- and 5-positions of the acridine ring oriented toward the major groove.[5] Furthermore, substitution at the 2-position reduces DNA binding, as do very bulky groups in the 3-position[6] and when *N*-10 in acridine chromophore is protonated (pH = 6), the binding energy into the DNA

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by intercalation increases with a 7-24 Kcal/ mol.[7] Additionally, it has been demonstrated that antitumour activity of any DNA intercalator is associated with high DNA binding affinity, slow drug-DNA dissociation rate, and long drug residence time at individual DNA binding sites.[8] Denny at al.[9] have shown that the average dissociation rates of the complete molecules from the DNA are reduced about 30-fold when two 9-aminoacridine chromophores are linked together by a polyethylene chain, $(CH_2)_{x=7-10}$.

Polyamine cations: Almost all cells contain substantial amounts of at least one of the polyamines, putrescine, spermidine, and spermine. Polyamines are a requirement for the optimum growth and replication of various cell types and are present in higher concentrations in rapidly proliferating cells.[10] The fact that polyamines can be taken up by tissues from the circulation is known, since the metabolism of labelled polyamines has been studies *in vivo*. It is also well established that tissues with a high demand for polyamines, such as prostate, tumours or normal but rapidly dividing cells are taking up polyamines in increased amounts with a specific uptake system.[11] More recently, studies have indicated that polyammonium cations (PACs) have a very "high" DNA affinity but are "loosely" bound and can "read" DNA very rapidly because of their otherwise unconstrained motion. These properties make PACs and related polycations ideal for drug delivery when the drug needs to reach specific sites in the DNA.[12] Finally, it has been shown that a wide variety of *N*-4 substituents on the spermidine molecule do not affect uptake.[13] Therefore, this position have been of interest for introducing substituents with antitumour property.[14] With these considerations in mind, we will describe, in this paper, a method to synthesise the boronated acridine-spermidine **11**, boronated dispermidine **15** and finally boronated diacridine **19**.

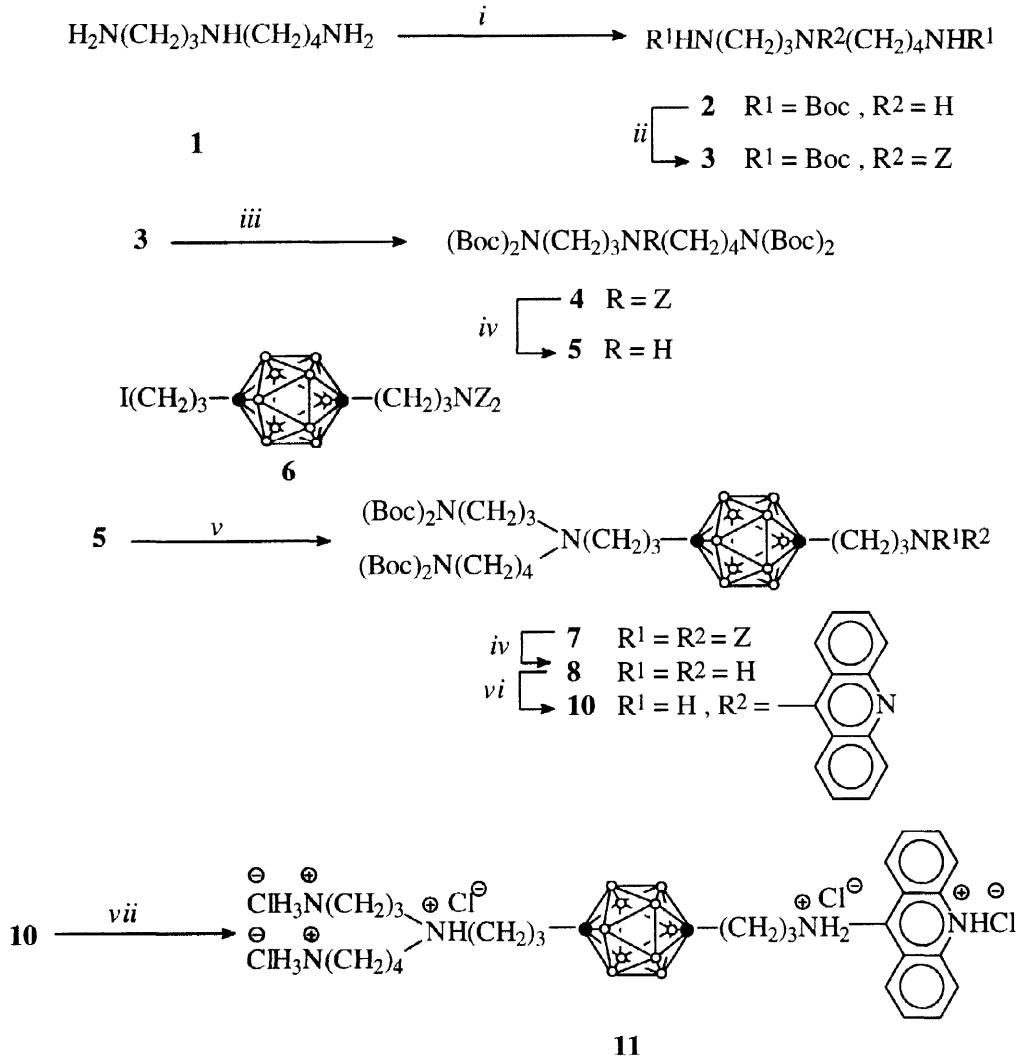
RESULTS AND DISCUSSION

The synthesis of analogues of spermidine, where the secondary amino function is alkylated by a boronated moiety is outlined in **scheme 1**. *N*-1, *N*-8 bis-Boc-spermidine **2**[15] is the key intermediate and was obtained in one step from spermidine (**1**) using 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) in THF. Protection of secondary amine was achieved by introducing the Z group to yield **3** in 88% by reacting **2** with benzyl chloroformate in aqueous 2M sodium carbonate/ dioxane. The di-*tert*-butoxycarbonyl protection of *N*-1 and *N*-8 was accomplished in 74% yield under mild conditions according to the method described by Ragnarsson et al.[16] Purification by column chromatography resulted in the desired compound **4**. The *N*-benzyloxycarbonyl (Z) protecting group was selectively removed by hydrogenolysis over palladium at atmospheric pressure to afford **5** in 90% yield. This compound was next alkylated at the free secondary nitrogen with the boronated alkyliodide **6**[4b] in potassium carbonate/ DMF to produce **7** in 42% yield.

The 9-aminoacridine derivatives were prepared by reaction of the appropriate amine with 9-phenoxyacridine. It was found most satisfactory to use the free amine with phenoxyacridine, other combination of the reagents, e.g. *in situ* treatment of 9 chloroacridine with phenol and subsequent addition of the free amine or when 9-aminoacridine was reacted with 1,12-bis(3-iodopropyl)-*p*-carborane[4b] in K_2CO_3/DMF, resulted in poor yield or undesired product/s. However, 9-phenoxyacridine[17] was prepared by reacting 9-chloroacridine with phenol in potassium carbonate/ DMF. The primary amine **8** was obtained directly before usage by selectively removal of the Z groups according to the same procedure as above (it was found that the colourless oily amine **8** became yellowish during a longer storage time). However, this compound was then reacted with 9-phenoxyacridine in toluene to give **10**. Acidic removal of Boc protecting groups by 3M HCl/ MeOH resulted in the target compound **11** in 80% yield.

The initial synthetic approach for the synthesis of the reduced **15** (**Scheme 2**) was to treat compound **5** with the corresponding diiodide[4b] of **12** in the presence of catalytic amount of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in acetonitrile. However, this reaction was unsuccessful. It might be due to the presence of four bulky protecting groups at the primary amines in **5**. Next effort was then to treat **2** with either corresponding diiodide or ditosylate of **12** in DMF. No product was isolated. According to our practical knowledge, a basic condition in a polar aprotic solvent is needed to achieve substitution reaction at *N*-4

position of **5** with the boronated alkyliodide **6.** Thus, for compound **2** these conditions could not be applied because of the available hydrogens at *N*-1 and *N*-8 positions. Nevertheless, the *p*-carboranyl propionic acid **13** was required in order to synthesise boronated dispermidine **15**. The propionic acid **13** was prepared by oxidation of 1,12-bis(3-hydroxypropyl)-*p*-carborane (**12**) [18] in acetone using CrO_3 and H_2SO_4 in 96% yield. Compound **14** was obtained according to the method described by Gildersleeve et al.[19] via treatment of **13** with ethyl chloroformate which was then reacted with the secondary amine **2** in CH_2Cl_2 to give the desired analogue **14.** Subsequent removal of BOC-protecting groups in **14** by using hydrogen chloride in anhydrous diethyl ether afforded **15** in 61% yield.

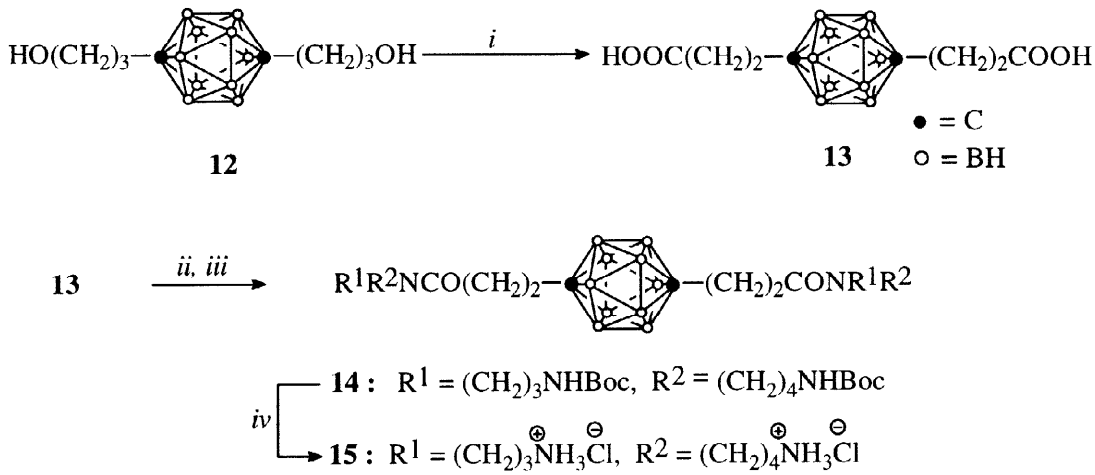


Reagents and conditions: i) Boc-ON, THF, overnight, RT, Ar-atm.; *ii)* ZCl, 2M Na_2CO_3/dioxane (4:1), 2M NaOH, 4°C, 16 hr; *iii)* Boc_2O, DMAP, MeCN, RT, 6 hr; *iv)* ammonium formate, 80% HOAc, 10% Pd-C, RT, 5 hr; *v)* **6**, K_2CO_3/DMF, 60°C, 24 hr; N_2-atm.; *vi)* 9-phenoxyacridine (**9**), toluene, reflux, 6 hr; *vii)* 3M HCl/MeOH, reflux, 3 hr.

Scheme 1

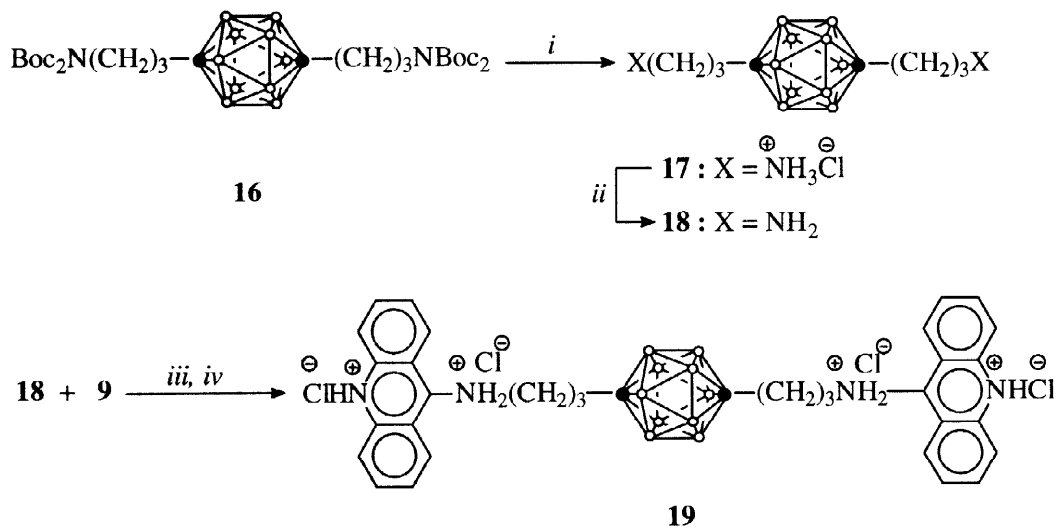
The required diamine for the preparation of diacridine was achieved by the method shown in **Scheme 3**. Aminoalkyl-*p*-carborane **18** was obtained from the corresponding BOC protected aminoalkyl-*p*-carborane **16**[4b] by acidic deprotection of BOC-groups followed by precipitation of the free amine **18** in an aqueous basic

solution. Diacridine **19** was prepared from 9-phenoxyacridine (**9**) and **18** in toluene/DMF which was then protonated by 3M HCl/MeOH. Purification by column chromatography afforded final compound **19** in 61% yield.



Reagents and conditions: *i)* CrO_3/H_2SO_4, acetone, 4 hr, RT; *ii)* Et_3N, ethyl chloroformate, CH_2Cl_2, 0°C to RT; *iii)* **2**, RT, overnight; *iv)* $HCl_{(g)}$, diethyl ether, 2 hr.

Scheme 2



Reagents and conditions: *i)* 3M HCl/EtOAc, 5 hr, RT; *ii)* aqueous K_2CO_3; *iii)* toluene/DMF, reflux, 15 hr; *iv)* 3M HCl/MeOH, reflux, 2 hr.

Scheme 3

EXPERIMENTAL SECTION

General Details.

^{1}H, ^{13}C, ^{11}B NMR spectra were recorded in $CDCl_3$ (7.26 ppm, ^{1}H, 77.0 ppm, ^{13}C), CD_3OD (3.35 ppm, ^{1}H, 49,0 ppm, ^{13}C) or DMSO (2.49 ppm,^{1}H, 39.5 ppm, ^{13}C) on a Varian XL-400 spectrometer operating at 400, 100.6 and 128.3 MHz respectively. Boron fluoride etherate was used as external standard for the boron spectra. The IR spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrometer. FAB-Mass spectra were recorded on a SX/SX 102A (JEOL) mass spectrometer. Elemental analyses were performed by Analytische Laboratrien, Lindlar, GERMANY. For column chromatography Merck Silica Gel 60 (230-400 mesh) was used. Merck Silica 60 F_{254} gel plates were used for TLC. Melting points are uncorrected and were obtained using a Buchi capillary melting point apparatus.

1,8-(N,N,N,N-Tetra-tert-butoxycarbonyl)diamino-4-(N-benzyloxycarbonyl)-4-azooctane **(4) :**
To a solution of crude compound **3** (5.06g, 10.55 mmol) and DMAP (0.52g, 4.25 mmol) in dry acetonitrile (100 mL), was added Boc_2O (4.61g, 21.12 mmol) in small portion with stirring during 6 hr at room temperature. The reaction mixture was then left overnight to decompose the excess of Boc_2O. The solvent was evaporated and the residue was extracted from 1M $KHSO_4$ with ether (3×30 mL). The combined organic layer was then washed with 1M $KHCO_3$ and saturated NaCl repeatedly and dried over $MgSO_4$. The crude product was purified by column chromatography using CH_2Cl_2/ether (9:1) to give **5** (R_f=0.50) as a pale yellow oil in 74% yield (5.29g). HR: MS (NBA, FAB^+): Calcd for $C_{35}H_{52}O_{10}N_3Na$: 702.3942, Found: 702.3936. ^{1}H-NMR($CDCl_3$): δ 7.30 (s, 5H, Ph); 5.08 (s, 2H, $C\underline{H}_2Ph$); 3.53 (m, 4H, $C\underline{H}_2NBoc_2$); 3.23 (m, 4H, $C\underline{H}_2NZC\underline{H}_2$); 1.79 (m, 2H, $NCH_2C\underline{H}_2CH_2N$); 1.51 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2CH_2N$); 1.44 (s, 36H, CH_3). ^{13}C-NMR($CDCl_3$): δ 155.83 ($\underline{C}OOCH_2Ph$); 152.49 ($\underline{C}O$); 152.29 ($\underline{C}O$); 136.73 (arom.); 127.72 (arom.); 127.61 (arom.); 82.10 ($\underline{C}Me_3$); 81.99 ($\underline{C}Me_3$); 66.81 ($\underline{C}H_2Ph$); 46.68 , 45.89, 44.69 and 44.21 ($\underline{C}H_2N$); 28.06 ($\underline{C}H_3$); 26.22 ($NCH_2\underline{C}H_2C\underline{H}_2CH_2N$); 25.48 ($NCH_2\underline{C}H_2CH_2N$). IR-($CDCl_3$ solution): 2981.8, 2935.5, 1778.6, 1735.4, 1690.4, 1477.2, 1368.8 and 1132.8 cm^{-1}.

1,8-(N,N,N,N-Tetra-tert-butoxycarbonyl)diamino-4-azooctane **(5):**
To a solution of **4** (5.12g, 7.53 mmol) in aqueous 80% HOAc (60 mL) was added ammonium formate (3.94g, 62.48 mmol). When everything was dissolved, a slurry of Pd-C (10%, 1.28g) in 80% HOAc (15 mL) was added in small portion under nitrogen with vigorous stirring at room temperature. After 5 hr the reaction was completed. The catalyst was filtered off and rinsed with 80% HOAc. Evaporation of solvent afforded an oily residue which was extracted from saturated K_2CO_3 with ether (3×60 mL). The combined organic layer was then washed with saturated NaCl (2×30 mL), dried over $MgSO_4$ and purified by column chromatography using CH_2Cl_2/MeOH (1:1) to give **5** (R_f =0.6) in 90% yield (3.68g). The analytical sample was obtained by recrystallisation from n-hexane. Mp: 93-94°C. Anal. Calcd for $C_{27}H_{51}N_3O_8$: C, 59.4; H, 9.4; N, 7.7. Found: C, 59.55; H, 9.57; N, 7.83. HR: MS (NBA, FAB^+): Calcd for $C_{35}H_{57}O_{10}N_3Na$: 546.3755, Found: 546.3763. ^{1}H-NMR($CDCl_3$): δ 3.62 (t, 2H, $C\underline{H}_2NBoc_2$); 3.56 (t, 2H, $C\underline{H}_2NBoc_2$); 2.57 (t, 4H, $C\underline{H}_2NHC\underline{H}_2$); 1.71 (m, 2H, $NCH_2C\underline{H}_2CH_2N$); 1.52 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2CH_2N$); 1.43 (bs, 37H, $C\underline{H}_3$ and $N\underline{H}$). ^{13}C-NMR($CDCl_3$): δ 152.66 ($\underline{C}O$); 152.61 ($\underline{C}O$); 82.10 ($\underline{C}Me_3$); 81.98 ($\underline{C}Me_3$); 49.65 and 47.09 ($\underline{C}H_2N$); 46.25 and 44.33 ($\underline{C}H_2NBoc_2$); 29.47 ($NCH_2\underline{C}H_2CH_2N$); 28.05 ($\underline{C}H_3$); 27.31 and 26.85 ($NCH_2\underline{C}H_2C\underline{H}_2CH_2N$). IR-($CDCl_3$ solution): 2934.7, 2823.4, 1775.3, 1735.6, 1686.7, 1456.2, 1368.7 and 1126.3 cm^{-1}.

1,8-(N,N,N,N-Tetra-tert-butoxycarbonyl)diamino-4-N-3-[12-(N,N-di-benzyloxycarbonyl-3-aminopropyl)-p-carborane-1-yl]propyl-4-azooctane **(7):**
5 (0.32g, 0.586 mmol), 12-(3-iodopropyl)-N,N-dibenzyloxycarbonyl-1-(3-aminopropyl)-*p*-carborane **6** (0.34g, 0.533 mmol) and K_2CO_3 (0.74g, 5.35 mmol) were dissolved in freshly distilled DMF (25 mL). The mixture was stirred at 60°C under nitrogen atmosphere for 24 hr. K_2CO_3 was then filtered off and the filtrate was concentrated. Purification by column chromatography using ether/pentane (1:1) gave compound **7** (R_f =0.38) as a

colourless oil in 42% yield. Anal. Calcd for $C_{51}H_{86}B_{10}N_4O_{12}$: C, 58.0; H, 8.20; N, 5.30. Found: C, 58.23; H, 8.36; N, 5.43. HR: MS (NBA, FAB^+): Calcd for $C_{51}H_{87}O_{12}N_4{}^{11}B_{10}$: 1057.7251, Found: 1057.7344. ^{1}H-NMR($CDCl_3$): δ 7.32 (m, 10H, Ph); 5.18 (s, 4H, $C\underline{H}_2Ph$); 3.54-3.46 (m, 6H, $C\underline{H}_2NBoc_2(Z_2)$); 2.29 (m, 4H, $C\underline{H}_2NC\underline{H}_2$); 2.15 (t, 2H, $NC\underline{H}_2CH_2CH_2C_{cage}$); 1.55 (m, 2H, $NCH_2C\underline{H}_2CH_2N$); 1.51 (m, 4H, $C\underline{H}_2C_{cage}$); 1.49 (s, 36H, $C\underline{H}_3$); 1.41 (m, 2H, $C\underline{H}_2CH_2NZ_2$); 1.33 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2CH_2N$); 1.18 (m, 2H, $C\underline{H}_2CH_2C_{cage}$). ^{13}C-NMR($CDCl_3$): δ 153.07 ($\underline{C}OOCH_2Ph$); 152.52 ($\underline{C}O$); 152.44 ($\underline{C}O$); 134.98 (arom.); 128.49 (arom.); 128.30 (arom.); 128.00 (arom.); 81.89 ($\underline{C}Me_3$); 81.87 ($\underline{C}Me_3$); 79.25 ($\underline{C}_{cage}$); 77.92 ($\underline{C}_{cage}$); 68.58 ($\underline{C}H_2Ph$); 53.39 52.73 and 51.13 ($\underline{C}H_2N$); 46.21 ($\underline{C}H_2NZ_2$); 45.79 and 44.91 ($\underline{C}H_2NBoc_2$); 35.41 and 34.57 ($\underline{C}H_2C_{cage}$); 28.66 ($\underline{C}H_2CH_2NZ_2$); 28.01 ($\underline{C}H_3$); 27.18 ($NCH_2\underline{C}H_2CH_2CH_2N$); 26.93 ($\underline{C}H_2CH_2C_{cage}$); 26.41 ($NCH_2\underline{C}H_2CH_2N$); 24.13 ($NCH_2\underline{C}H_2\underline{C}H_2CH_2N$). ^{11}B-NMR($CDCl_3$): δ -13.19. IR-($CDCl_3$ solution): 2981.3, 2603.5, 1778.4, 1737.9, 1691.3, 1455.9, 1368.9 and 1130.7 cm^{-1}.

1,8-(N,N,N,N-Tetra-tert-butoxycarbonyl)diamino-4-N-3-[12-(3-aminopropyl)-p-carborane-1-yl] propyl-4-azooctane **(8):**

Compound **8** was synthesised by the same procedure as for **5**. The crude product was purified by column chromatography using CH_2Cl_2/MeOH (4:1) as mobile phase giving **8** (R_f =0.53) in a sticky yellow oil in 90% yield. This compound decomposes during the course of chromatography and a longer storage time. HR: MS (NBA, FAB^+): Calcd for $C_{35}H_{75}O_8N_4{}^{11}B_{10}$:789.6515, Found: 789.6563. ^{1}H-NMR($CDCl_3$): δ 5.19 (bs, 2H, $N\underline{H}_2$); 3.52 (m, 4H, $C\underline{H}_2NBoc_2$); 2.71 (t, 2H, $C\underline{H}_2NH_2$); 2.34 (m, 4H, $C\underline{H}_2NC\underline{H}_2$); 2.18 (t, 2H, $NC\underline{H}_2CH_2CH_2Ccage$); 1.70-1.60 (m, 6H, $NCH_2C\underline{H}_2CH_2N$ and $C\underline{H}_2C_{cage}$); 1.49 (s, 36H, $C\underline{H}_3$); 1.33 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2CH_2N$); 1.24 (m, 4H, $C\underline{H}_2CH_2C_{cage}$). ^{13}C-NMR($CDCl_3$): δ 152.60 ($\underline{C}O$); 152.53 ($\underline{C}O$); 82.18 ($\underline{C}Me_3$); 79.30 ($\underline{C}_{cage}$); 77.72 ($\underline{C}_{cage}$); 53.45 52.74 and 51.20 ($\underline{C}H_2N$); 46.31 and 44.93 ($\underline{C}H_2NBoc_2$); 39.74 ($\underline{C}H_2NH_2$); 35.44 and 34.55 ($\underline{C}H_2C_{cage}$); 29.67 ($\underline{C}H_2CH_2NH_2$); 28.69 ($\underline{C}H_2CH_2C_{cage}$); 28.10 ($\underline{C}H_3$); 26.98 ($NCH_2\underline{C}H_2\underline{C}H_2CH_2N$); 26.29 ($NCH_2\underline{C}H_2CH_2N$); 24.06 ($NCH_2\underline{C}H_2\underline{C}H_2CH_2N$). ^{11}B-NMR($CDCl_3$): δ -13.09. IR-($CDCl_3$ solution): 2981.4, 2603.9, 1774.6, 17336.1, 1686.8, 1456.2, 1131.3 and 908.3 cm^{-1}.

9-Phenoxyacridine **(9):**

A mixture of phenol (1.00g, 10.6mmol), 9-chloroacridine (1.34g, 6.3mmol) and K_2CO_3 (8.7g, 63.0mmol) was stirred at 100-110°C in DMF (50 mL) for 24 hr, cooled to room temperature and K_2CO_3 was filtered off and the filtrate was concentrated. The residue was extracted from water with CH_2Cl_2 (3×40 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography using CH_2Cl_2/ether (6:1) to obtain **9** (R_f =0.64) in 94% yield (1.60g). The data were in accordance with published data[17].

1,8-Diamino-4-N-3-[12-(N-9-acridinyl-3-aminopropyl)-p-carborane-1-yl]propyl-4-azooctane hydrogen chloride **(11):**

9-Phenoxyacridine (**9**) (0.5g, 1.84mmol) and **8** (1.44g, 1.83mmol) was refluxed in toluene for 6 hr under nitrogen atmosphere. Cooled to room temperature and concentrated. Purification of the crude product by column chromatography using CH_2Cl_2/MEOH (9:1) afforded **10** (R_f =0.25) which was then refluxed in 3M HCl/MeOH for 3 hr. The solvent was evaporated and the crude product was recrystallised from isopropanol. Filtered off and washed with cold iospropanol, acetone and finally ether to give **11** in 80% yield (1.10g). Mp: 250-255°C. Anal. Calcd for $C_{28}H_{54}B_{10}Cl_5N_5$: C, 45.77; H, 7.83; N, 9.23. Found: C, 45.10; H, 7.30; N, 9.40. HR: MS (NBA, FAB^+): Calcd for $C_{28}H_{50}N_5{}^{11}B_{10}$:566.4996, Found: 566.5004. ^{1}H-NMR(D_2O, TMS as external standard): δ 7.73 (m, 2H, H-1 and H-8 in acridine ring); 7.65 (m, 2H, H-4 and H-5 in acridine ring); 7.25 (m, 4H, H-2, H-3, H-6 and H-7 in acridine ring); 3.47 (m, 2H, $C\underline{H}_2N_{in\ acridine\ ring}$); 3.07 (m, 4H, $C\underline{H}_2N$); 2.90 (m, 6H, $C\underline{H}_2NH_3Cl$ and $NC\underline{H}_2CH_2CH_2C_{cage}$); 1.94 (m, 2H, $NCH_2C\underline{H}_2CH_2N$); 1.59 (m, 4H, $C\underline{H}_2C_{cage}$); 1.47 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2CH_2N$); 1.44 (m, 4H, $C\underline{H}_2CH_2C_{cage}$). ^{13}C-NMR($D_2O$, TMS as external standard): δ 157.00,135.26, 126.18, 123.91 and 118.22 (arom.); 76.68 (C_{cage}); 52.45, 52.17 and 49.97 ($\underline{C}H_2N$); 47.65 ($\underline{C}H_2N_{in\ acridine\ ring}$); 38.86 and 36.56 ($\underline{C}H_2NH_3Cl$); 33.96 and 33.48 ($\underline{C}H_2C_{cage}$); 29.07 ($\underline{C}H_2CH_2N_{in\ acridine\ ring}$); 23.98 ($NCH_2\underline{C}H_2\underline{C}H_2CH_2N$); 23.54 ($\underline{C}H_2CH_2C_{cage}$); 21.73 ($NCH_2\underline{C}H_2CH_2N$); 20.63 ($NCH_2\underline{C}H_2\underline{C}H_2CH_2N$). ^{11}B-NMR($D_2O$): δ -13.13. IR-(KBr disk): 3404.5, 2926.2, 2595.5, 1634.9, 1588.3, 1466.6, 1271.3 and 746.1 cm^{-1}.

1,12-p-Carboranyl bis(3-propionic acid) **(13):**
1,12-Bis(3-hydroxypropyl)-*p*-carborane **(12)**[16] (2.0 g, 7.68 mmol) was dissolved in acetone (50 mL) and the solution was cooled to 0°C. A solution of CrO_3 (6.15 g, 61,5 mmol) in 3M H_2SO_4,(40 mL) was added dropwise over a period of 0.5 hr. The solution was stirred at RT for 4 hr, until the colour of the solution turned to a greenish-black, and water (50 mL) was added. The acetone was evaporated and the residue was extracted with CH_2Cl_2 (3×100 mL). The CH_2Cl_2 was stripped off and the solid residue was dissolved in 10% NaOH and extracted with diethyl ether (3×100 mL). Conc. HCl was added dropwise to the basic aqueous solution in order to precipitate the acid, filtered and washed with water to give 96% acid **13** (2.14 g). The analytical sample was recrystallised from acetone: diethyl ether(1:2). Mp: 279-285°C. Anal. Calcd for $C_8H_{20}B_{10}O_4$: C, 33.30; H, 7.00; Found: C, 33.41; H, 6.83. HR: MS (Glyc+PEG, FAB$^-$): Calcd for $C_8H_{19}O_4{}^{11}B_{10}$:289.2214, Found: 289.2313. ^{1}H-NMR(CD_3OD): δ 2.20 (m, 4H, C$\underline{H}_2$COOH); 2.02 (m, 4H, C$\underline{H}_2C_{cage}$). ^{13}C-NMR(CD_3OD): δ 174.95 (C$\underline{O}$); 79.47 (C_{cage}); 34.43 ($\underline{C}H_2C_{cage}$); 33.56 ($\underline{C}H_2COOH$). ^{11}B-NMR(CD_3OD): δ -12.43. IR-(KBr disk): 3029.9 , 2952.0, 2602.6, 1835.5, 1439.1, 1363.1, 1274.0 and 1038.1 cm^{-1}.

1,12-p-Carboranyl bis[(N-3-aminopropyl, N-4-aminobutyl)-3-propane amide] hydrogen chloride **(15):**
A stirred solution of **13** (50.0 mg, 0.173 mmol) in dry CH_2Cl_2 (20 mL) was treated with triethylamine (58 μL, 0.416 mmol) and cooled to 0°C. To this mixture ethylchloroformate (40 μL, 0.416 mmol) was added and stirred at RT for 2 hr. The secondary amine **2** (180 mg. 0.521 mmol) was then added and stirring continued overnight at ambient temperature. Removal of the solvent afforded an oil which was partitioned between ethyl acetate (15 mL) and saturated aqueous Na_2CO_3 (15 mL). The organic layer was removed and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layer was washed with water (20 mL) and dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography using diethyl ether as mobile phase to give **14** (R_f =0.26). **14** was then dissolved in dry diethyl ether (20 mL) and was kept saturated with dry hydrogen gas at ambient temperature for 2 hr. Concentrated to half of its original volume by bubbling nitrogen through the solution and the fluffy white crystals was filtered off and washed with dry diethyl ether (3×10 mL) to give 73.0 mg (61%) of **15**. Sublim.: 202°C at 760 mmHg. Anal. Calcd for $C_{22}H_{58}B_{10}Cl_4N_6O_2$: C, 38.4; H, 8.50; N,12.20. Found: C, 38.62; H, 8.68; N, 11.94. HR: MS (NBA, FAB$^+$): Calcd for $C_{22}H_{55}O_2N_6{}^{11}B_{10}$: 545.5317, Found: 545.5341. ^{1}H-NMR(CD_3OD): δ 3.48-3.36 (m, 8H, C$\underline{H}_2$NCO); 3.04-2.90 (m, 8H, C$\underline{H}_2NH_3Cl$); 2.32 (m, 4H, C$\underline{H}_2$CO); 2.06 (t, 4H, C$\underline{H}_2C_{cage}$); 1.93 (t, 4H, NCH$_2$C$\underline{H}_2$CH$_2$N); 1.70 (m, 8H, NCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$N). ^{13}C-NMR(CD_3OD): δ 172.65 (C$\underline{O}$); 79.75 ($\underline{C}_{cage}$); 43.60 ($\underline{C}H_2N$); 40.45 and 38.14 ($\underline{C}H_2NH_3Cl$); 33.83 ($\underline{C}H_2C_{cage}$); 33.54 ($\underline{C}H_2CH_2C_{cage}$); 26.79 (NCH$_2\underline{C}H_2\underline{C}H_2CH_2$N); 26.73 (NCH$_2\underline{C}H_2CH_2$N); 25.88 (NCH$_2\underline{C}H_2\underline{C}H_2CH_2$N). ^{11}B-NMR($CD_3OD$): δ -12.34. IR-(KBr-disk): 3420.7, 2976.0, 2601.5, 1623.6, 1466.1, 1386.5, 1157.1 and 739.8 cm^{-1}.

1,12-Bis(3-aminopropyl)-p-carborane **(18):**
N,N-Di-*tert*-butoxycarbonyl-1,12-bis(3-aminopropyl)-*p*-carborane **16** (1.30 g, 1.97 mmol) was stirred in 3M HCl in ethyl acetate (50 mL) for 5 hr at RT. The solvent was evaporated under reduced pressure and the crude hydrochloride salt was recrystallised from MeOH: diethyl ether (1:4), dissolved in water and saturated aqueous K_2CO_3 was added in order to precipitate the free amine. The crude amine was filtered and washed with water to give **18** in 90% (0.46 g).The spectroscopy data was obtained for 1,12-Bis(3-aminopropyl)-*p*-carborane hydrogen chloride (**17**). Mp: >300°C. HR: MS (NBA, FAB$^+$): Calcd for $C_8H_{27}N_2{}^{11}B_{10}$:261.3105, Found: 261.3105. ^{1}H-NMR(CD_3OD): δ 2.79 (t, 4H, C$\underline{H}_2NH_3Cl$);1.80 (m, 4H, C$\underline{H}_2C_{cage}$); 1.55 (m, 4H, C$\underline{H}_2CH_2C_{cage}$). ^{13}C-NMR($CD_3OD$): δ 79.62 ($C_{cage}$); 39.86 ($\underline{C}H_2NH_3Cl$); 35.34 ($\underline{C}H_2C_{cage}$); 28.05 ($\underline{C}H_2CH_2C_{cage}$). ^{11}B-NMR($CD_3OD$): δ -12.39. IR-(KBr disk): 3421.2, , 2964.8, 2605.6, 1609.0, 1498.4, 1406.5, 1027.9 and 738.2 cm^{-1}.

1,12-Bis(N-(9-acridinyl)3-aminopropyl)-p-carborane hydrogen chloride **(19):**
A solution of **18** (105.0 mg, 0.41 mmol) and **9** (240.0 mg, 0.89 mmol) was stirred in toluene/DMF (5:1) (25 mL) at 110°C for 15 hr. Cooled to RT and concentrated. Compound **9** was recovered by column chromatography using CH_2Cl_2. The residue was washed from the column by MeOH:CH_2Cl_2 (2:1), concentrated and refluxed in

3M HCl in MeOH for 2 hr. The solvent was stripped off and the residue was purified by column chromatography using CH_2Cl_2:MeOH:HOAc (78:20:2) in order to separate mono-and disubstituted products. Monosubstituted product (0.034 g, 0.062 mmol) (R_f=0.23) was then reacted with **9** (34.0 mg) and K_2CO_3 (10 eq.) in toluene/DMF (5:1) (15 mL) for 8 hr and worked up as above. The combined product (**19**) was obtained in 61% yield (187.0 mg) R_f =0.48. Mp: >300°C. HR: MS (NBA, FAB^+): Calcd for $C_{34}H_{41}N_4{}^{11}B_{10}$:615.4261, Found: 615.4280. ^{1}H-NMR(DMSO): δ 10.03 (bs, 2H, NH); 8.60 (m, 4H, H-1 and H-8 in acridine ring); 8.06 (d, 4H, H-4 and H-5 in acridine ring); 7.92 (t, 4H, H-2 and H-7 in acridine ring); 7.47 (t, 4H, H-3 and H-6 in acridine ring); 3.93 (t, 4H, CH_2NH_2); 1.77 (m, 4H, CH_2C_{cage}); 1.73 (m, 4H, $CH_2CH_2C_{cage}$). ^{13}C-NMR(DMSO): δ 157.01, 134.50 126.07, 123.00 and 118.45 (arom.); 78.71 (C_{cage}); 47.52 (CH_2NH_2); 33.89 (CH_2C_{cage}); 28.84 ($CH_2CH_2C_{cage}$). ^{11}B-NMR(DMSO): δ -12.59. IR-(KBr disk): 3231.5, 3062.0, 2934.8, 2594.2, 1635.8, 1587.9, 1468.6, 1376.7 and 744.5 cm^{-1}.

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