

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

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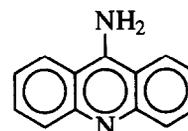
Abstract: An approach to synthesise three different boronated DNA-interacting compounds (**11**, **15** & **19**) is described. Compound **11** is containing both an acridine system and a spermidine residue. The acridine moiety would serve as DNA-intercalating fragment whereas the spermidine residue 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. © 1998 Elsevier Science Ltd. All rights reserved.

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 proposed² 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 [¹⁰B(¹n, ⁴He) ⁷Li] 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 analogues⁴ 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.

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-position⁶ and when *N*-10 in acridine chromophore is protonated (pH = 6), the binding energy into the DNA



9-aminoacridine

Figure: 1

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 et 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, $(\text{CH}_2)_{x=7-10}$.

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 studied *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 has 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**.

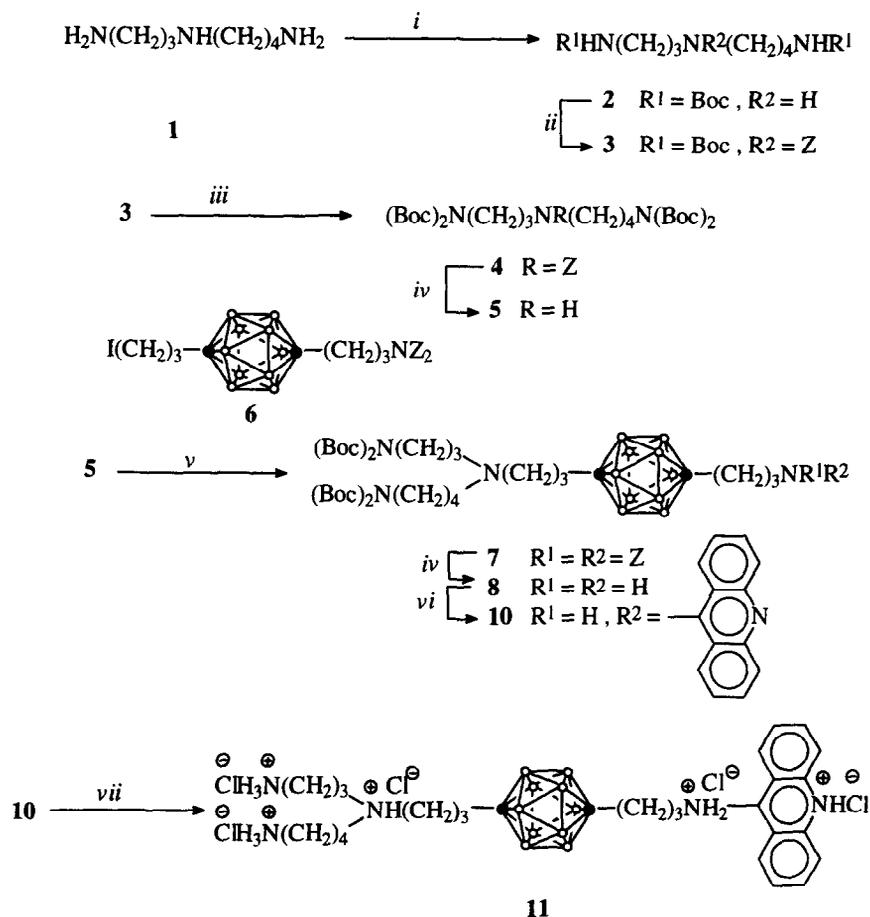
RESULTS AND DISCUSSION

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 alkyl iodide **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 $\text{K}_2\text{CO}_3/\text{DMF}$, resulted in poor yield or undesired product/s. However, 9-phenoxyacridine¹⁷ was prepared by reacting 9-chloroacridine with phenol in potassium carbonate/ DMF. The primary amine **8** was obtained directly before usage by selective 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 alkyl iodide **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 CrO₃ and H₂SO₄ 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 CH₂Cl₂ 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.

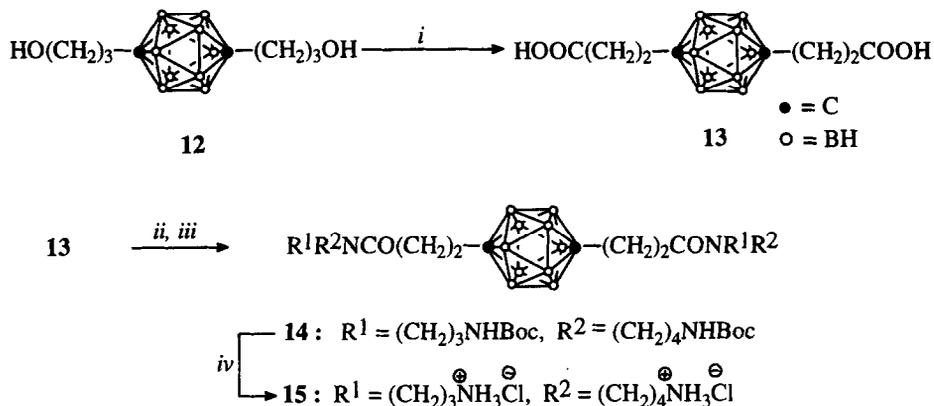


Reagents and conditions: i) Boc-ON, THF, overnight, RT, Ar-atm.; ii) ZCl, 2M Na₂CO₃/dioxane (4:1), 2M NaOH, 4°C, 16 hr; iii) Boc₂O, DMAP, MeCN, RT, 6 hr; iv) ammonium formate, 80% HOAc, 10% Pd-C, RT, 5 hr; v) **6**, K₂CO₃/DMF, 60°C, 24 hr; N₂-atm.; vi) 9-phenoxyacridine (**9**), toluene, reflux, 6 hr; vii) 3M HCl/MeOH, reflux, 3 hr.

Scheme 1

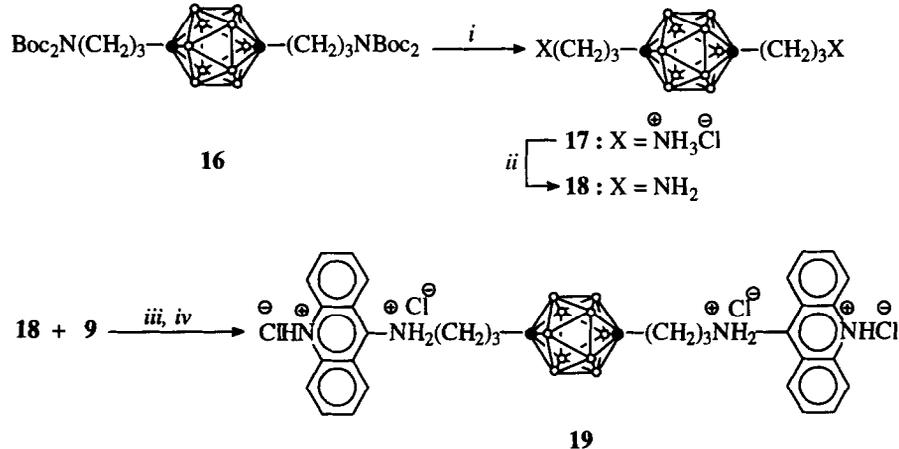
The required diamine for the preparation of diacridine was achieved by the method shown in **Scheme 3**. Aminoalkyl-*p*-carborane **18** was obtained from the corresponding BOC protected aminoalkyl-*p*-carborane **16**^{4b} by acidic deprotection of BOC-groups followed by precipitation of the free amine **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) $\text{CrO}_3/\text{H}_2\text{SO}_4$, acetone, 4 hr, RT; ii) Et_3N , ethyl chloroformate, CH_2Cl_2 , 0°C to RT; iii) **2**, RT, overnight; iv) $\text{HCl}_{(g)}$, 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.

^1H , ^{13}C , ^{11}B NMR spectra were recorded in CDCl_3 (7.26 ppm, ^1H , 77.0 ppm, ^{13}C), CD_3OD (3.35 ppm, ^1H , 49.0 ppm, ^{13}C) or DMSO (2.49 ppm, ^1H , 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 F₂₅₄ 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 $\text{C}_{35}\text{H}_{52}\text{O}_{10}\text{N}_3\text{Na}$: 702.3942, Found: 702.3936. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.30 (s, 5H, Ph); 5.08 (s, 2H, CH_2Ph); 3.53 (m, 4H, CH_2NBoc_2); 3.23 (m, 4H, CH_2NZCH_2); 1.79 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$); 1.51 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$); 1.44 (s, 36H, CH_3). $^{13}\text{C-NMR}(\text{CDCl}_3)$: δ 155.83 (COOCH_2Ph); 152.49 (CO); 152.29 (CO); 136.73 (arom.); 127.72 (arom.); 127.61 (arom.); 82.10 (CMe_3); 81.99 (CMe_3); 66.81 (CH_2Ph); 46.68, 45.89, 44.69 and 44.21 (CH_2N); 28.06 (CH_3); 26.22 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$); 25.48 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$). 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 $\text{C}_{27}\text{H}_{51}\text{N}_3\text{O}_8$: 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 $\text{C}_{27}\text{H}_{51}\text{N}_3\text{O}_8$: 546.3755, Found: 546.3763. $^1\text{H-NMR}(\text{CDCl}_3)$: δ 3.62 (t, 2H, CH_2NBoc_2); 3.56 (t, 2H, CH_2NBoc_2); 2.57 (t, 4H, CH_2NHCH_2); 1.71 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$); 1.52 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$); 1.43 (bs, 37H, CH_3 and NH). $^{13}\text{C-NMR}(\text{CDCl}_3)$: δ 152.66 (CO); 152.61 (CO); 82.10 (CMe_3); 81.98 (CMe_3); 49.65 and 47.09 (CH_2N); 46.25 and 44.33 (CH_2NBoc_2); 29.47 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$); 28.05 (CH_3); 27.31 and 26.85 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$). 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. ¹H-NMR(CDCl₃): δ 7.32 (m, 10H, Ph); 5.18 (s, 4H, CH₂Ph); 3.54–3.46 (m, 6H, CH₂NBoc₂(Z₂)); 2.29 (m, 4H, CH₂NCH₂); 2.15 (t, 2H, NCH₂CH₂CH₂C_{cage}); 1.55 (m, 2H, NCH₂CH₂CH₂N); 1.51 (m, 4H, CH₂C_{cage}); 1.49 (s, 36H, CH₃); 1.41 (m, 2H, CH₂CH₂NZ₂); 1.33 (m, 4H, NCH₂CH₂CH₂CH₂N); 1.18 (m, 2H, CH₂CH₂C_{cage}). ¹³C-NMR(CDCl₃): δ 153.07 (COOCH₂Ph); 152.52 (CO); 152.44 (CO); 134.98 (arom.); 128.49 (arom.); 128.30 (arom.); 128.00 (arom.); 81.89 (CMe₃); 81.87 (CMe₃); 79.25 (C_{cage}); 77.92 (C_{cage}); 68.58 (CH₂Ph); 53.39 52.73 and 51.13 (CH₂N); 46.21 (CH₂NZ₂); 45.79 and 44.91 (CH₂NBoc₂); 35.41 and 34.57 (CH₂C_{cage}); 28.66 (CH₂CH₂NZ₂); 28.01 (CH₃); 27.18 (NCH₂CH₂CH₂CH₂N); 26.93 (CH₂CH₂C_{cage}); 26.41 (NCH₂CH₂CH₂N); 24.13 (NCH₂CH₂CH₂CH₂N). ¹¹B-NMR(CDCl₃): δ -13.19. IR-(CDCl₃ 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 CH₂Cl₂/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. ¹H-NMR(CDCl₃): δ 5.19 (bs, 2H, NH₂); 3.52 (m, 4H, CH₂NBoc₂); 2.71 (t, 2H, CH₂NH₂); 2.34 (m, 4H, CH₂NCH₂); 2.18 (t, 2H, NCH₂CH₂CH₂C_{cage}); 1.70–1.60 (m, 6H, NCH₂CH₂CH₂N and CH₂C_{cage}); 1.49 (s, 36H, CH₃); 1.33 (m, 4H, NCH₂CH₂CH₂CH₂N); 1.24 (m, 4H, CH₂CH₂C_{cage}). ¹³C-NMR(CDCl₃): δ 152.60 (CO); 152.53 (CO); 82.18 (CMe₃); 79.30 (C_{cage}); 77.72 (C_{cage}); 53.45 52.74 and 51.20 (CH₂N); 46.31 and 44.93 (CH₂NBoc₂); 39.74 (CH₂NH₂); 35.44 and 34.55 (CH₂C_{cage}); 29.67 (CH₂CH₂NH₂); 28.69 (CH₂CH₂C_{cage}); 28.10 (CH₃); 26.98 (NCH₂CH₂CH₂CH₂N); 26.29 (NCH₂CH₂CH₂N); 24.06 (NCH₂CH₂CH₂CH₂N). ¹¹B-NMR(CDCl₃): δ -13.09. IR-(CDCl₃ 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 K₂CO₃ (8.7g, 63.0mmol) was stirred at 100–110°C in DMF (50 mL) for 24 hr, cooled to room temperature and K₂CO₃ was filtered off and the filtrate was concentrated. The residue was extracted from water with CH₂Cl₂ (3×40 mL). The combined organic layer was dried over MgSO₄ and concentrated. The crude product was purified by column chromatography using CH₂Cl₂/ether (6:1) to obtain **9** (R_f = 0.64) in 94% yield (1.60g). The data were in accordance with published data¹⁷.

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 CH₂Cl₂/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 isopropanol, 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. ¹H-NMR(D₂O, 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, CH₂N_{in acridine ring}); 3.07 (m, 4H, CH₂N); 2.90 (m, 6H, CH₂NH₃Cl and NCH₂CH₂CH₂C_{cage}); 1.94 (m, 2H, NCH₂CH₂CH₂N); 1.59 (m, 4H, CH₂C_{cage}); 1.47 (m, 4H, NCH₂CH₂CH₂CH₂N); 1.44 (m, 4H, CH₂CH₂C_{cage}). ¹³C-NMR(D₂O, 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 (CH₂N); 47.65 (CH₂N_{in acridine ring}); 38.86 and 36.56 (CH₂NH₃Cl); 33.96 and 33.48 (CH₂C_{cage}); 29.07 (CH₂CH₂N_{in acridine ring}); 23.98 (NCH₂CH₂CH₂CH₂N); 23.54 (CH₂CH₂C_{cage}); 21.73 (NCH₂CH₂CH₂N); 20.63 (NCH₂CH₂CH₂CH₂N). ¹¹B-NMR(D₂O): 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 CrO₃ (6.15 g, 61.5 mmol) in 3M H₂SO₄ (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 CH₂Cl₂ (3×100 mL). The CH₂Cl₂ 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 C₈H₂₀B₁₀O₄: C, 33.30; H, 7.00; Found: C, 33.41; H, 6.83. HR: MS (Glyc+PEG, FAB⁺): Calcd for C₈H₁₉O₄¹¹B₁₀: 289.2214, Found: 289.2313. ¹H-NMR(CD₃OD): δ 2.20 (m, 4H, CH₂COOH); 2.02 (m, 4H, CH₂C_{cage}). ¹³C-NMR(CD₃OD): δ 174.95 (CO); 79.47 (C_{cage}); 34.43 (CH₂C_{cage}); 33.56 (CH₂COOH). ¹¹B-NMR(CD₃OD): 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 CH₂Cl₂ (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 Na₂CO₃ (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 MgSO₄ 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 C₂₂H₅₈B₁₀Cl₄N₆O₂: 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 C₂₂H₅₅O₂N₆¹¹B₁₀: 545.5317, Found: 545.5341. ¹H-NMR(CD₃OD): δ 3.48-3.36 (m, 8H, CH₂NCO); 3.04-2.90 (m, 8H, CH₂NH₃Cl); 2.32 (m, 4H, CH₂CO); 2.06 (t, 4H, CH₂C_{cage}); 1.93 (t, 4H, NCH₂CH₂CH₂N); 1.70 (m, 8H, NCH₂CH₂CH₂CH₂N). ¹³C-NMR(CD₃OD): δ 172.65 (CO); 79.75 (C_{cage}); 43.60 (CH₂N); 40.45 and 38.14 (CH₂NH₃Cl); 33.83 (CH₂C_{cage}); 33.54 (CH₂CH₂C_{cage}); 26.79 (NCH₂CH₂CH₂CH₂N); 26.73 (NCH₂CH₂CH₂N); 25.88 (NCH₂CH₂CH₂CH₂N). ¹¹B-NMR(CD₃OD): 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 K₂CO₃ 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 C₈H₂₇N₂¹¹B₁₀: 261.3105, Found: 261.3105. ¹H-NMR(CD₃OD): δ 2.79 (t, 4H, CH₂NH₃Cl); 1.80 (m, 4H, CH₂C_{cage}); 1.55 (m, 4H, CH₂CH₂C_{cage}). ¹³C-NMR(CD₃OD): δ 79.62 (C_{cage}); 39.86 (CH₂NH₃Cl); 35.34 (CH₂C_{cage}); 28.05 (CH₂CH₂C_{cage}). ¹¹B-NMR(CD₃OD): 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 CH₂Cl₂. The residue was washed from the column by MeOH:CH₂Cl₂ (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 CH₂Cl₂: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 K₂CO₃ (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 C₃₄H₄₁N₄¹¹B₁₀: 615.4261, Found: 615.4280. ¹H-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, CH₂NH₂); 1.77 (m, 4H, CH₂C_{cage}); 1.73 (m, 4H, CH₂CH₂C_{cage}). ¹³C-NMR(DMSO): δ 157.01, 134.50, 126.07, 123.00 and 118.45 (arom.); 78.71 (C_{cage}); 47.52 (CH₂NH₂); 33.89 (CH₂C_{cage}); 28.84 (CH₂CH₂C_{cage}). ¹¹B-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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