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Bioorganic & Medicinal Chemistry 12 (2004) 4769–4781
Bioorganic & Medicinal Chemistry

Synthesis of ethyleneoxide modified 3-carboranyl thymidine analogues and evaluation of their biochemical, physicochemical, and structural properties

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Received 22 May 2004; revised 8 July 2004; accepted 16 July 2004
Available online 7 August 2004

Abstract—Eleven 3-carboranyl thymidine analogues (3CTAs) containing highly hydrophilic and flexible ethyleneoxide moieties were synthesized as potential agents for boron neutron capture therapy (BNCT) and their biochemical and physicochemical properties were evaluated. Based on specific structural features, this library of 3CTAs was divided into three subgroups. The first group contained 3CTAs with 1–4 ethyleneoxide units between the thymidine (Thd) scaffold and a carborane cluster. The second group of 3CTAs contained a pentylene spacer between Thd and the carborane and 2–4 ethyleneoxide units additionally attached to the carborane cluster. The third group contained three 3CTAs all with pentylene spacers and four ethylene units but with different carborane cages. The ethyleneoxide modified 3CTAs were good substrates of thymidine kinase 1 (TK1) and poor substrates of human mitochondrial thymidine kinase 2 (TK2) as determined in phosphoryl transfer assays. In the first group of 3CTAs, all the compounds were efficiently phosphorylated regardless of varying spacer lengths (37–42% of the activity of Thd). The second group of 3CTAs was less effectively phosphorylated (17–26% of the activity of Thd) probably due to a less favorable sterical orientation of Thd within the active site of TK1 and/or an increased lipophilicity compared with the first group. In the third group of structural isomers, no significant differences in phosphorylation rates were observed (17–25%). A structure–function hypothesis explaining these results is presented.

1. Introduction

Boron neutron capture therapy (BNCT) is a chemo-radio therapeutic technique for the treatment of cancer.[1,2] For successful BNCT, a minimum of 20–30 μg of nonradioactive boron-10 per gram of tumor tissue is required. Irradiation of intratumoral boron-10 with low energy (thermal) neutrons triggers a nuclear fission reaction yielding cytotoxic α-particles and lithium nuclei, which are capable of destroying tumor cells. Boronated thymidine (Thd) analogues have been considered as suitable candidates for BNCT because of their potential metabolic pathways, which could result in their selective incorporation into the tumor cells.[3] To be activated, they must be substrates of cytosolic thymidine kinase 1 (TK1), which has elevated activity in proliferating tumor cells.[4] Therefore, conversion of boronated Thd analogues to the corresponding 5′-monophosphates may result in their selective intracellular entrapment in tumor cells.

Abbreviation: ATP, Adenosine triphosphate; BNCT, boron neutron capture therapy; 3CTAs, 3-carboranyl thymidine analogues; CCIC, Campus Chemical Instrument Center; MM+, molecular mechanics force field; DMSO, dimethylsulfoxide; DMF, dimethyl formamide; DTT, dithiothreitol; dUrd, deoxyuridine; HR-FAB-MS, high resolution fast atom bombardment mass spectrometry; HR-ESI, high-resolution electrospray mass spectrometry; HRMS, high resolution mass spectrometry; IPTG, isopropyl-beta-D-thiogalactopyranoside; NMR, nuclear magnetic resonance spectrometry; Ni-NTA, Ni-nitrilotriacetic acid; PEI, polyethyleneimine; R_f, retention factor; RP-HPLC, reversed phase high performance liquid chromatography; PTA, phosphoryl transfer assay; THF, tetrahydrofuran; TBAF, tetrabutylammonium fluoride; Thd, thymidine; TK1, thymidine kinase 1; TK2, thymidine kinase 2; rt, room temperature; TLC, thin-layer chromatography; TBDPS, *tert*-butyldiphenylsilane; TBDMS, *tert*-butyldimethylsilane; UV, ultraviolet spectrometer

Keywords: Boron neutron capture therapy (BNCT); 3-Carboranyl thymidine analogues (3CTAs); Thymidine kinase 1; Thymidine kinase 2; Phosphorylation.

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doi:10.1016/j.bmc.2004.07.032

A large number of boronated nucleoside analogues were synthesized as potential BNCT agents.[5–29] Among deoxyuridines (dUrd) and Thd analogues modified at the 3′-, 5-, and 3-positions with carborane clusters,[8,4] only the later designated here as 3CTAs (3-carboranyl Thd analogues), showed good TK1 substrate characteristics with phosphorylation rates approaching 75% that of Thd.[6–8,22,30] The dUrds with carboranyl substituents at the 5-position were, if at all, poor substrates of TK2, but not of TK1, and those substituted at the 3′-position with carboranes were moderate substrates of TK1 and only poor substrates of TK2. In general, boron-containing substrates of TK2 are probably not suitable as BNCT agents because this kinase is equally active in both normal and proliferating cells.[3] In vitro, a 3CTA designated N5–2OH demonstrated selective uptake and retention only in TK1 containing tumor cells.[6,31] The same compound also showed substantial tumor uptake in rodents carrying implantations of various TK1 positive tumors.[31] In previous studies, we have observed that the degree of hydrophilicity of 3CTAs improved their TK1 phosphorylation rates.[7,32] Hydrophilicity increasing modifications included additional hydroxyl and amino groups attached to the carborane cages[7,30,32] as well as conversion of neutral and highly lipophilic *closo*-carboranes to negatively charged *nido*-carboranes.[30] Carboranyl groups were attached to Thd through hydrocarbon spacers in previously synthesized 3CTAs.[7,22] The concept of introducing spacers has been proven useful in the purification of kinases by affinity chromatography, which exploits the binding of kinases to substrates covalently linked to a solid support.[20,21]

In this manuscript, the synthesis of a novel class of 3CTAs, with hydrophilicity increasing ethyleneoxide spacers and substituents, as well as their bio- and physico- chemical evaluation is described. A structure-based hypothesis for the obtained results is presented.

2. Methods

Proton and carbon-13 NMR spectra were obtained on Bruker (250 or 400 MHz) FT-NMR instruments at The Ohio State University College of Pharmacy. Chemical shifts are reported in parts per million (ppm) from an internal tetramethylsilane standard. The coupling constants are reported in hertz (Hz). High resolution electronspray mass spectra (HR-ESI) were recorded on a Micromass QTOF-Electrospray mass spectrometer and a 3-Tesla Finnigan FTMS-2000 Fourier Transform mass spectrometer at The Ohio State University Campus Chemical Instrumentation Center (OSU-CCIC) and The Ohio State University Department of Chemistry by members of these institutions including Dr. Kari Green-Church, Robin Gates, and Professor Christopher M. Hadad. For ESI analysis, most compounds were dissolved in micromolar concentrations in typical matrixes such as tetrahydrofuran/CH_3OH containing small amounts of NaCl. This process generated sodium-complexed molecular ions (usually as the singly charged species) denoted as $(M+Na)^+$. The theoretical exact mass was provided by The Ohio State University CCIC and was verified with ChemDraw Ultra 7.0 (CambridgeSoft Corporation, Cambridge, MA, USA). Compound visualization on Silica gel 60 F_{254} precoated TLC plates (0.25 mm layer thickness) (Merck, Darmstadt, Germany) was attained by UV light and $KMnO_4$ spray. Carborane-containing compounds were selectively visualized by spraying a solution of 0.06% $PdCl_2$/1% aqueous HCl on TLC plates and subsequent heating to ~120 °C, which caused the slow formation (15–45 s) of gray spots due to the reduction of Pd^{2+} to Pd^0. Reagent grade solvents were used for column chromatography using Silica gel 60, particle size 0.040–0.063 mm (Merck, New Jersey). Analytical HPLC data of the target compounds were obtained with a reversed phase (RP-18) LiChrosphere 100 Å [5 μm] column (Merck,) using Rainin HPLC instrument equipped with a Dynamax DA controller, HPXL pumps, and a Dynamax UV-1 detector (Rainin Instrument Company Inc., Woburn, MA, USA). HPLC grade water and methanol were used as solvents. A water/methanol gradient (100:0 to 50:50 over 5 min and from 50:50 to 0:100 over 30 min) with a flow rate of 1 mL/min was applied. The target compounds were repurified on a semi-preparative 10 μm Discovery® HS C18 (25 cm × 10 mm) (Supelco, Supelco Park, Bellefonte, PA) column. A water/methanol gradient (100:0 to 0:100, over 40 min) with a flow rate of 10 mL/min was used. All chemical syntheses were carried out under argon atmosphere to maintain inert reaction condition unless mentioned otherwise. Anhydrous acetonitrile, anhydrous DMF, anhydrous THF, and anhydrous toluene were purchased from VMR Scientific Products. Acetonitrile was dried over 4 Å molecular sieves before use. Compounds **12**–**16** were purchased from Sigma–Aldrich Fine Chemicals. Structures **1**–**11** were minimized using HyperChem 7.5 (Hypercube Inc., Gainesville, Florida) using molecular mechanics (MM+) force field and Columbic charges until a minimum energy gradient of 0.005 kcal/mol was reached. The Van der Waals surface volumes of structures **1**–**11** were calculated using the *compute* option in HyperChem7.5.

2.1. Log *P* values

The log *P* values of all target compounds were determined by HPLC according to a procedure described previously by Teijeiro et al.[33] The chromatographic analyses were performed on a reversed phase {RP-18 (5 μm)}, LiChrosphere 100 Å (250 mm/4 mm) column, using a Rainin HPLC instrument with an UV detection at $\lambda = 254$ nm. Samples were injected in 20 μL methanol solution and retention times of each compound were measured at 3–4 different methanol–water mixtures (60%, 70%, 80%, and 90%) at a flow rate of 1 mL/min. For each compound, a plot of retention time against composition of mobile phase was generated. The intercept of the plot (k'_w) corresponded to the retention time of the compound in 100% water. All the measurements were carried out at ambient temperature. Finally the log *P* was calculated using the following equation: $\mathrm{Log}P_{o/w} = 1.882 \log k'_w - 1.346$, where, $k'_w = (t_R - t_0)/t_0$; t_0—retention time of methanol (1.78 min); t_R—retention time of the solute; k'_w—extrapolated '*k*' value at 100% water.

2.2. Expression and purification of recombinant human TK1 and TK2

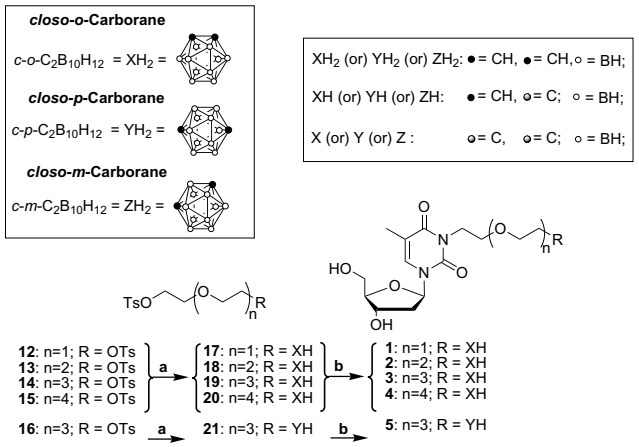
Expression and purification of enzymes were carried out as described previously, with minor modifications.[5,6,22] Briefly, *E. coli* expressing recombinant human TK1 or TK2 under the control of pET vector systems (Novagen) were grown in NZB-M9 medium containing 50 μg/mL carbacillin and 50 μg/mL chloramphenicol. After 4 h incubation at 37 °C, the expression of the enzymes was induced with 1 mM isopropyl-β-D-thiogalactopyranoside (IPTG). The bacteria were centrifuged and the pellet was resuspended in extraction buffer containing 20 mM Tris–HCl, pH 7.6, 500 mM KCl, 10% glycerol, 20 mM imidazole, 0.1% NP-40, and 0.5 mM PMSF. Proteins were purified by affinity chromatography on Ni-NTA His bound resin (Novagen). The His-tag was cleaved from purified proteins with Thrombin protease (10 units/mg protein) at rt. The enzyme extract was concentrated using a Millipore Ultra filter with a 30 kDa cut-off membrane (Millipore) and aliquots were frozen at −70 °C until used.

Phosphoryl transfer assays (PTAs) using [$\gamma-^{32}$P] ATP as a phosphate donor were carried out as described previously[7,22] with minor modifications. Thd and 3CTAs (**1**–**11**) were dissolved in DMSO to produce stock solutions of various concentrations (50–150 μM). In TK1 assays, the reaction mixture contained 10 μM compound, 100 μM ATP including a small fraction of 0.0325 μM [$\gamma-^{32}$P] ATP (Amersham, IL, USA), 50 mM Tris–HCl (pH 7.6), 5 mM $MgCl_2$, 125 mM KCl, 10 mM DTT, and 0.5 mg/mL bovine serum albumin (BSA). In all reactions, the final concentration of DMSO was set to 1%. The reaction mixtures were incubated at 37 °C for 20 min in presence of 50 ng of enzyme. Following the incubation period, the enzyme was heat inactivated for 2 min at 95 °C. The reaction mixtures were centrifuged and 1 μL portions were spotted on PEI–cellulose TLC plates (Merck). The TLC plates were developed using the following solvent system: Isobutyric acid/ammonium hydroxide/water (66:1:33). The radiolabeled spots were visualized by a phospho-imager (Fuji Film, Science Lab., Image Gauge V3.3). The TK2 assays were performed in a similar manner as those of TK1, except high concentration (100 μM) of nucleosides were used. At 10 μM nucleoside concentration, TK2 activity was not observed.

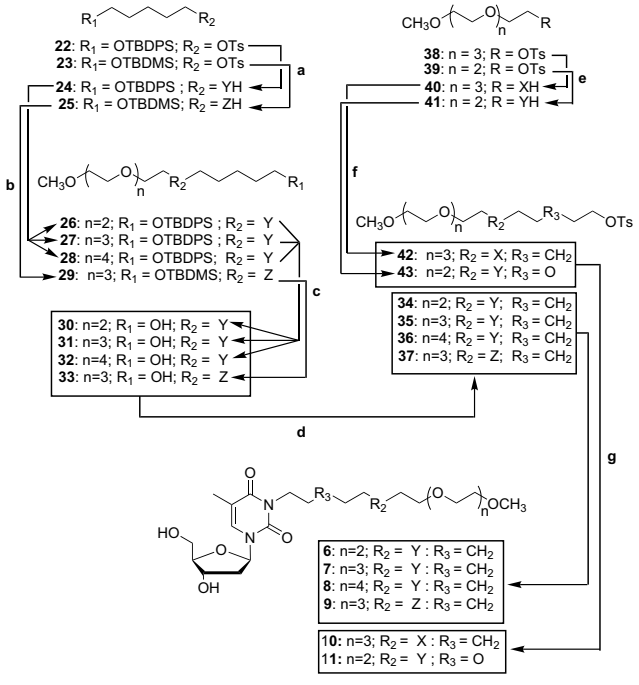
3. Results and discussion

3.1. Chemistry

The synthesis of ethyleneoxide modified 3CTAs was motivated by two important factors: (1) Previous studies with 3CTAs indicated that the degree of their hydrophilicity had a positive impact on their TK1 substrate characteristics[6,7,22] and (2) 3CTAs have to be sufficiently water soluble for application in clinical BNCT.[1,24,31] In order to systematically study the TK1 substrate characteristics of ethyleneoxide modified 3CTAs as well as their physicochemical and structural properties, we have designed a compound library consisting of three subgroups, each of which containing 3CTAs with characteristic structural features. The first group (compounds **1**–**5**, Scheme 1) has 1–4 ethyleneoxide units between the Thd scaffold and either the *o*-(**1**–**4**) or the *p*-(**5**) carbor-ane cluster. The second group (**6**–**10**, Scheme 2) has a pentylene spacer between Thd and a carborane and an ethyleneglycol chain with 2–4 ethyleneoxide units additionally attached to the second carbon atom of a carborane cluster. Compound **11** (Scheme 2) has a



Scheme 1. Reagents and conditions: (a) *o*- or *p*-carborane, *n*-butyl lithium, THF; (b) thymidine, K_2CO_3, DMF/acetone (1:1), 50 °C, 1–2 days.



Scheme 2. Reagents and conditions: (a) *p*- or *m*- carborane, *n*-butyl lithium, THF; (b) **39** or **38** or penta(ethyleneglycol) monomethylether tosylate, *n*-butyl lithium, THF; (c) TBAF, THF, 40 min; (d) *p*-toluene sulfonyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C, 3.5 h; (e) *o*- or *p*-carborane, *n*-butyl lithium, THF; (f) di(ethyleneglycol)-di-*p*-tosylate or 1,5-pentandiol-di-*p*-tosylate, *n*-butyl lithium, THF; (g) thymidine, K_2CO_3, DMF:acetone (1:1), 50 °C, 1–2 days.

diethylether spacer between Thd and *p*-carborane and an additional ethyleneglycol chain with two ethyleneoxide units. This compound could be included in both groups one and two. However, the results of the biochemical and structural analysis of this compound library (see below) justify placement of compound **11** into group two. The third group (compounds **7**, **9**, **10**) has a pentylene spacer between Thd and either the *o*-, *m*-, or *p*-carborane and an ethyleneglycol chain with three ethyleneoxide units. The rational for choosing pentylene or diethylether spacers is based on the results from previous studies, which demonstrated that the TK1 phosphorylation efficiencies of 3CTAs depended strongly on the length of the hydrocarbon spacer between carborane and Thd scaffold.[7,22] 3CTAs with a pentylene spacers consistently showed a higher relative phosphorylation rates (~45%) than their lower ethylene, propylene, and butylene homologues as well as their higher hexylene and heptylene homologues. These compounds also demonstrated high cellular uptake in vitro and selective tumor uptake in in vivo, in both cases combined with a relative low toxicity.[6,31]

3CTAs **1**–**5** were synthesized in two steps as shown in Scheme 1. Reaction of the monolithium salt of *o*-carborane/*p*-carborane with the equimolar quantities of ditosylates (**12**–**16**) in anhydrous THF yielded compounds **17**–**21** (32–54%). The reaction products also contained small quantities of disubstituted carboranes in the range of 10–20%. The formation of disubstituted carboranyl products could be suppressed to some degree by using an excess (1.5 equiv) of ditosylates. Target compounds **1**–**5** were synthesized in 33–78% yield by reacting a 3-fold excess of Thd with **17**–**21** in the presence of K_2CO_3 in a mixture of acetone–DMF (1:1) for 2 days at 45–50 °C. The use of other solvents such as THF, DMF, and other compositions of acetone–DMF as well as reaction temperatures >50 °C caused increased formation of side products. Compounds **1**–**5** were isolated as viscous and hygroscopic materials, which were repurified for biological evaluation by semi-preparative reversed phase (C18) HPLC column chromatography.

Target compounds **6**–**9** were synthesized in six steps as shown in Scheme 2. Compounds **22** and **23** were synthesized by protecting one of the hydroxyl groups of 1,5-pentandiol with either a TBDPS (**22**) or a TBDMS (**23**) group and subsequent introduction of a tosyl group at the remaining hydroxyl function. Synthetic procedures and analytical data for **22**[34] and **23**[35] were reported previously. Compounds **24** and **25** were synthesized by reacting *p*-carborane and *m*-carborane with **22** and **23**, respectively. The crude reaction mixtures contained several unidentified side products. Both **24** and **25** were identified on TLC as distinct UV active and $PdCl_2$ positive spot. Compounds **26**–**28** were synthesized by reacting **24** with ethyleneglycol monomethyl tosylates containing 2–4 ethyleneoxide units and compound **29** was synthesized by reacting **25** with triethyleneglycol monomethylether tosylate in 70–94% yield. The TBDPS/TBDMS protective groups of compound **26**–**29** were removed with tetrabutylammonium fluoride (TBAF) in THF at room temperature. In case of **29**, the reaction was closely monitored by TLC for the disappearance of the UV active spot of **29** and the appearance of the UV inactive/$PdCl_2$ positive spot of **33** since the *m*-carborane cage is known to undergo TBAF-mediated degradation to the corresponding *nido*-*m*-carborane at slightly higher temperatures.[30] Compounds **30**–**33** were reacted with *p*-toluene sulfonyl chloride to obtain the corresponding tosylates **34**–**37**. Finally, target compounds **6**–**9** were obtained in 20–61% yield by reacting **34**–**37** with Thd. Target compounds **10** and **11** were synthesized in three steps using an alternative synthetic scheme (Scheme 2). This synthetic route was subsequently developed in an attempt to increase the overall yields of target compounds involving fewer reaction steps. Compounds **38** and **39** were reacted with the monolithium salt of *o*-carborane and *p*-carborane, respectively, to obtain compounds **40** and **41**. Compounds **40** and **41** were reacted with 1,5-pentanediol-di-*p*-tosylate and di(ethyleneglycol)di-*p*-tosylate, respectively, to obtain **42** and **43**. Reacting **42** and **43** with Thd afforded target compounds **10** and **11** in 83% and 47% yield, respectively. The overall yield of compounds **10**–**11**, obtained by using the later synthetic route, was higher than those of compounds **6**–**9** (20–61%).

3.2. Biological results

Efficient phosphorylation of target compounds **1**–**11** by TK1 is crucial for their potential application as BNCT agents. Thus, their phosphorylation rates were determined as described under 'Methods' and compared with that of Thd. A TLC β-autoradiogram of the monophosphate products of compounds **1**–**11** (a) as well as Thd-monophosphate 1(a) is shown in Figure 1. In previous studies with similar 3CTAs, combined α/β-autoradiography provided evidence that the observed intense spots with high R_f-values (a) are typical for monophosphate products of 3CTAs.[5,7,22] In the case of several ethyleneoxide modified 3CTAs, faint spots were observed in the β-autoradiogram on the level of Thd monophos-

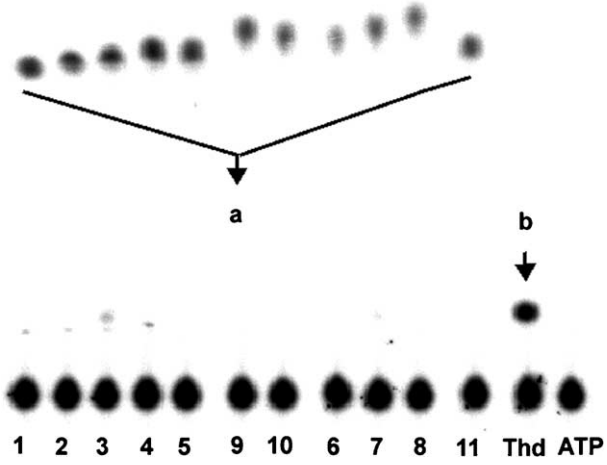


Figure 1. β-Autoradiogram showing the phosphorylation of compounds **1**–**11** and Thd by recombinant TK1. The reaction products were separated by PEI–cellulose TLC. Arrow 'a' indicates monophosphates of compounds **1**–**11** and arrow 'b' indicates thymidine-5′-monophosphate.

phate, which could have been produced by minor Thd impurity probably generated by the removal of N3 substituents during the PTAs.[7]

As shown in Figure 1 and Table 1, all target compounds were effectively phosphorylated by TK1 but not by TK2. All compounds of the first group of 3CTAs (**1**–**5**) showed similar phosphorylation rates (37–42%) regardless of significant differences in spacer lengths. This finding is in contrast to the results of our previous studies, which showed highest TK1 phosphorylation for 3CTAs with pentylene spacers.[7,22] Structural isomers **3**, containing an *o*-carborane cluster, and **5**, containing an *p*-carborane cluster, showed similar phosphorylation. Overall, however, the phosphorylation rates of compounds **1**–**5** were in the same range as those observed for 3CTAs in previous studies.[7,22]

Both the second (**6**–**11**) and third group (**7**, **9**, **10**) of 3CTAs had ~50% lower TK1 phosphorylation rates (17–26%) compared with the first group. Similar to the first group, neither the lengths of the ethyleneglycol substituents nor isomeric alterations due to the nature of the carborane cluster appeared to have significant influence on the phoshorylation rates of the later two groups.

In order to increase their water solubility, ethyleneoxide spacers and substituents were incorporated into 3CTAs **1**–**11**. The degree of lipophilicity was quantified in terms of log *P* values (Table 1). As in the case of the TK1 phosphorylation rates, a distinct pattern emerged separating the 3CTAs of the first group (**1**–**5**) from those of the second and third group (**6**–**11**). The log *P* values of compounds **1**–**5** ranged from 1.31 to 2.07 and those of compounds **6**–**11** from 2.23 to 2.39. Within the first group, the log *P* values clearly increased with increasing lengths of the ethyleneoxide spacers while the log *P* values of the later groups showed only minor variations despite substantial structural differences. As expected, the log *P* values of the *p*-carboranyl 3CTAs **5** (2.07) and **7** (2.37) were higher than those of the corresponding *o*-caboranyl counterparts **3** (1.85) and **10** (2.28). A similar trend was observed in a previous study with series of *o*- and *p*-carboranyl phenol derivatives.[36] Overall, the introduction of ethyleneglycol units to the 3CTAs improved their hydrophilicity in a similar tendency to the dihydroxypropyl groups that were attached to 3CTAs in a previous study.[6,7]

In an attempt to better understand the significant differences in the TK1 phosphorylation rates between the 3CTAs of the first group (**1**–**5**) and those of the second and third group (**6**–**11**) we constructed molecular models of representative members of both groups, as shown in Figures 2 and 3 (compounds **1** and **4**, and compounds **7**, **9**, and **10**, respectively), and calculated the volumes of the compounds **1**–**11** using Hyperchem 7.5. As in the case of the phopshorylation rates and log *P* values, distinct differences between the groups became apparent.

Molecular models of compounds **1** and **4** showed compact structures with relatively large volumes of 1175 and 1585 Å^3, respectively (Fig. 2). This suggests that the large N3-carboranyl ethyleneoxide side chain could be positioned outside the TK1 active site and the Thd

Table 1. Phosphorylation relative to that of Thd, Log *P* values, and Van der Waals surface volumes of compounds **1**–**11**

Compd	TK1	TK2	Log *P* (HPLC)	Volume (Å^3)
	10 μM	100 μM		
Thd	1	1	−1.08	658
1	0.39 ± 0.05	0.005	1.31	1175
2	0.38 ± 0.06	0.000	1.69	1272
3	0.42 ± 0.04	0.001	1.85	1438
4	0.37 ± 0.07	0.000	1.91	1585
5	0.40 ± 0.13	ND	2.07	1438
6	0.19 ± 0.03	0.007	2.39	1744
7	0.21 ± 0.05	0.006	2.37	1859
8	0.17 ± 0.02	0.005	2.28	1915
9	0.26 ± 0.03	0.005	2.28	1845
10	0.26 ± 0.03	0.000	2.28	1852
11	0.25 ± 0.02[a]	0.001	2.23	1687

ND—Not determined. The obtained values for thymidine were set to 1.

The final DMSO concentration in the enzyme assays was 1%.

Mean ± SD values are based on three experiments for recombinant TK1.

[a] In case of compound **11**, two close spots were observed on the level of monophosphorylated 3CTAs, which is not visible in the β-autoradigram displayed in Figure 1. Only the value of the more intense spot is reported.

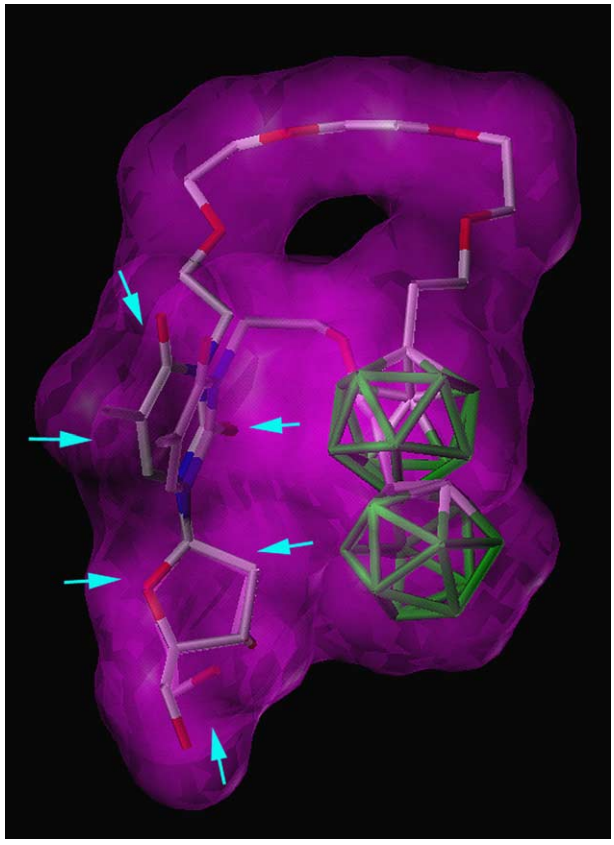


Figure 2. Molecular models of compound **1** and **4**. The presumed active site region of TK1 is marked with arrows.

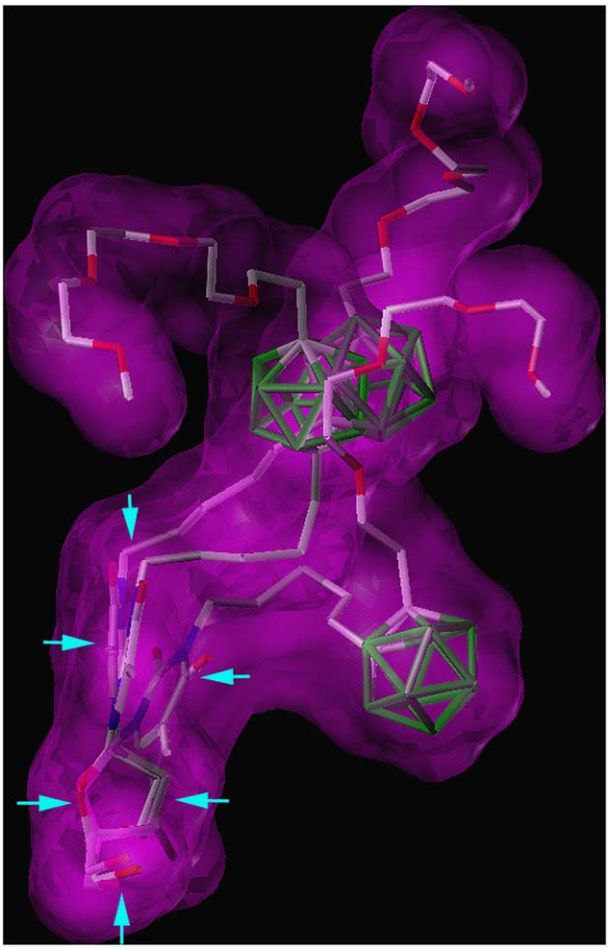


Figure 3. Molecular models of compound **7**, **9**, and **10**. The presumed active site region of TK1 is marked with arrows.

portion of the 3CTAs could be in close proximity to the active site, as indicated by arrows in Figure 2. We hypothesize that the active site of TK1 must be on or close to the surface of the enzyme, which could allow the N3-subtituent to move relative freely outside of the protein. A substantial portion of the N3-substituent located outside of TK1 in combination with a highly flexible ethyleneglycol chain, partially remaining within the active site, could account for the relatively small range in phosphorylation rates observed for compounds **1**–**5**. Unfortunately, neither NMR nor X-ray data of the three-dimensional structure for human TK1 are presently available that would allow computer-aided modeling studies either supporting or dismissing this hypothesis.

Molecular models of compounds **7**, **9**, and **10** (Fig. 3) clearly indicate that their bulky N3 side chains extend much further away form the Thd scaffold, and presumably the active site of TK1, than in the case of compounds **1** and **4**. In addition, the volumes of these compounds, ranging from 1845 to 1859 $Å^3$, are significantly larger than those found for compounds **1** and **4**. We propose that a significant exposure of this large extended N3 side chain to molecular events outside of the active site of TK1 may have a strong impact on the orientation of Thd, including the position 5′-OH, within the active site of TK1, thereby negatively influencing phosphorylation. A certain lack of flexibility of the pentylene spacer in comparison to the ethyleneoxide spacers in compounds **1**–**5** could also contribute to the decreased phosphorylation rates. As already pointed out in the introduction, in previous studies we have observed that the degree of lipophilicity of 3CTAs correlated to some extent negatively with their TK1 phosphorylation rates.[7,32] A similar effect may contribute to the relative low phosphorylation rates observed for compounds **6**–**11**.

4. Summary and conclusions

A small library of 3CTAs hydrophilically enhanced with ethyleneoxide units was synthesized and their TK1 and TK2 phosphorylation activities as well as their log *P* values were investigated to obtain structure–activity correlations. As observed in previous studies,[7,22] N3 modification at Thd was tolerated by TK1 whereas it was not accepted by TK2. TK1 and TK2 phosphorylation rates as well as log *P* values of ethyleneoxide modified 3CTAs were comparable with those obtained previously for structurally different 3CTAs.[6,7,22] The overall volume of ethyleneoxide modified 3CTAs **1**–**11** (1175–1915 $Å^3$), in particular the degree of projection of the N3 side chain away from the active site of TK1, and the level of lipophilicity appeared to influence the TK1 phosphorylation rates. Structural variation that were imposed on isomeric 3CTAs **7**, **9**, and **10** due to the nature of the carborane cluster did not appear to influence TK1 activity.

The obtained results may be of crucial importance for general design strategies of 3CTAs that may eventually be used in the clinical BNCT, and they may also have an impact on the design of drugs for use in conventional diagnosis and therapy of cancer and viral diseases.

5. Experimental section

5.1. Synthesis

5.1.1. 2-(1,2-Carboran-1-yl)ethyloxyethyltosylate (17). A solution of 1.2 mL (2.9 mmol) of 2.5 M butyl lithium in hexanes was added dropwise to a solution of 350 mg (2.41 mmol) of *o*-carborane in 5 mL of THF at 0 °C for 30 min. The solution was gradually warmed to rt and stirred for 1 h. Subsequently the solution was cooled again to 0 °C and a solution of 1.00 g (2.41 mmol) of di(ethyleneglycol)di-*p*-tosylate (1.3 equiv) in 5 mL of THF was added over a period of 30 min with constant stirring and keeping the temperature at 0 °C. The reaction mixture was slowly brought to rt, stirred for 5 h, and then quenched with water. The organic layer was extracted with diethylether, washed with brine, dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 0.50 g (54%) of **17** as a colorless liquid. R_f 0.30 (2:1 ethylacetate/hexa-

nes); ^{1}H NMR ($CDCl_3$): δ 2.38–2.52 (m, 5H, CH_2 and CH_3), 3.47–3.59 (m, 4H, CH_2O), 3.82 (m, 1H, CH), 4.10–4.14 (m, 2H, CH_2), 7.60 (dd, $J = 8$ Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 21.69 (CH_3), 37.38 (CH_2), 60.10 (CH), 68.51 (CH_2O), 72.93 ($C_{carborane}$), 127.87 (Ar), 129.93 (Ar), 132.71 (Ar), 145.15 (Ar); MS $C_{13}H_{26}O_4B_{10}SNa$ $(M+Na)^+$ calcd 411.2380, found 411.2372.

5.1.2. 2-[2-(1,2-Carboran-1-yl)ethyloxyethoxy]ethyltosylate (18). The experimental conditions for the synthesis of compound **18** were identical to those described for **17**. The amount of 1.00 g (2.18 mmol) of tri(ethyleneglycol)di-*p*-tosylate yielded 0.40 g (43%) of **18** as colorless liquid. R_f 0.21 (1:1 ethylacetate/hexanes); ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.45–2.50 (m, 2H, CH_2), 3.47–3.55 (m, 6H, CH_2O), 3.64–3.68 (m, 2H, CH_2O), 3.819 (m, 1H, CH), 4.10–4.14 (m, 2H, CH_2), 7.66 (dd, $J = 8$ Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 21.57 (CH_3), 37.21 (CH_2), 60.17 (CH), 68.41 (CH_2O), 68.60 (CH_2O), 69.06 (CH_2O), 69.80 (CH_2O), 70.32 (CH_2O), 73.32 ($C_{carborane}$), 127.82 (Ar), 129.85 (Ar), 132.69 (Ar), 144.96 (Ar); MS $C_{15}H_{30}O_5B_{10}SNa$ $(M+Na)^+$ calcd 455.2642, found 455.2619.

5.1.3. 2-{2-[2-(1,2-Carboran-1-yl)ethyloxyethoxy]ethoxy}ethyltosylate (19). Experimental conditions for the synthesis of **19** were identical to those described for **17**. The amount of 1.31 g (2.60 mmol) of tetra(ethyleneglycol)di-*p*-tosylate yielded 0.51 g (54%) of **19** as a colorless liquid. R_f 0.27 (1:1 ethylacetate/hexanes); ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.47–2.52 (m, 2H, CH_2), 3.50–3.68 (m, 13H, CH_2O and CH), 4.11–4.43 (m, 2H, CH_2), 7.36 (dd, $J = 8$ Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 21.55 (CH_3), 37.20 (CH_2), 60.22 (CH), 68.29 (CH_2O), 68.57 (CH_2O), 69.15 (CH_2O), 69.87 (CH_2O), 70.14 (CH_2O), 70.33 (CH_2O), 70.64 (CH_2O), 73.43 ($C_{carborane}$), 127.83 (Ar), 129.79 (Ar), 132.79 (Ar), 144.83 (Ar); MS $C_{17}H_{34}O_6B_{10}SNa$ $(M+Na)^+$ calcd 499.2904, found 499.2971.

5.1.4. 2-(2-{2-[2-(1,2-Carboran-1-yl)ethyloxyethoxy]ethoxy}ethoxy)ethyltosylate (20). Experimental conditions for the synthesis of **20** were identical to those described for **17**. The amount of 1 g (1.829 mmol) of penta(ethyleneglycol)di-*p*-tosylate yielded 0.30 g (32%) of **20** as a colorless liquid. R_f 0.60 (2:1 ethylacetate/hexanes); ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3) 2.43–2.51 (m, 2H, CH_2), 3.52–3.68 (m, 16H, CH_2O), 4.11–4.15 (m, 2H, CH_2O), 4.18 (1H, CH), 7.36 (dd, $J = 8$ Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 21.65 (CH_3), 37.30 (CH_2), 60.22 ($C_{carborane}$), 68.41 (CH_2O), 68.66 (CH_2O), 69.21 (CH_2O), 70.02 (CH_2O), 70.21 (CH_2O), 70.53 (CH_2O), 70.63 (CH_2O), 70.75 (CH_2O), 73.48 ($C_{carborane}$), 127.96 (Ar), 129.82 (Ar), 132.93 (Ar), 144.82 (Ar); MS $C_{19}H_{38}O_7B_{10}SNa$ $(M+Na)^+$ calcd 543.3166, found 543.3292.

5.1.5. 2-{2-[2-(1,12-Carboran-1-yl)ethyloxyethoxy]ethoxy}ethyltosylate (21). Experimental conditions for the synthesis of **21** were identical to those described for **17**. The amount of 2.7 g (5.3 mmol) of tetra(ethyleneglycol)di-*p*-tosylate and 0.62 g (4.3 mmol) of *p*-carborane, yielded 0.30 g (32%) of **21** as a colorless liquid. R_f 0.46 (2:1 ethylacetate/hexanes); ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3) 2.42–2.51 (m, 2H, CH_2), 3.51–3.67 (m, 12H, CH_2O), 4.11–4.15 (m, 2H, CH_2O), 4.18 (1H, CH), 7.36 (dd, $J = 8$ Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 21.63 (CH_3), 37.32 (CH_2), 60.21 (CH), 68.41 (CH_2O), 68.59 (CH_2O), 69.13 (CH_2O), 69.27 (CH_2O), 69.70, (CH_2O), 70.25 (CH_2O), 70.75 (CH_2O), 73.48 ($C_{carborane}$), 127.95 (Ar), 129.82 (Ar), 132.92 (Ar), 144.82 (Ar); MS $C_{17}H_{34}O_6B_{10}SNa$ $(M+Na)^+$ calcd 499.2785, found 499.3052.

5.1.6. 3-[2-(1,2-Carboran-1-yl)ethyloxyethyl]thymidine (1). A solution of 62 mg (0.26 mmol) of thymidine, 50 mg (0.13 mmol) of **17**, and 56 mg (0.39 mmol) of K_2CO_3 in 5 mL of anhydrous DMF/acetone (1:1) was stirred at 50 °C for 2 days. The reaction mixture was filtered, the solvent was evaporated to dryness, and the product was purified by silica gel column chromatography. The product was dissolved in diethylether and washed with small amount of water after isolation to remove trace amounts of DMF. Subsequently, the product was dried under high vacuum yielding 46 mg (78%) of product as a viscous and hygroscopic liquid. R_f 0.43 (1:12 methanol/dichloromethane); ^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3H, CH_3), 2.34 (t, $J = 6$ Hz, 2H, CH_2), 2.41 (m, 2H, H-2′), 3.47 (m, 4H, CH_2O), 3.59 (m, 3H, CH_2–N and H-3′), 3.79 (m, 2H, H-5′), 3.96 (m, 1H, H-4′), 4.52 (s, 1H, CH), 6.19 (t, $J = 6.5$ Hz, 1H, H-1′), 7.57 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.23 (CH_3), 36.59 (CH_2), 37.38 (CH_2–N), 40.32 (C-2′), 60.26 (CH), 62.17 (C-5′), 67.64 (CH_2O), 68.11 (CH_2O), 71.11 (C-3′), 77.20 ($C_{carborane}$), 86.79 (C-1′), 86.93 (C-4′), 110.07 (C-5), 135.11 (C-6), 150.96 (C-2), 162.68 (C-4); MS $C_{16}H_{32}O_6B_{10}N_2Na$ $(M+Na)^+$ calcd 481.3089, found 481.3146; HPLC retention time: 14.07 min, approx. purity: 99.0%.

5.1.7. 3-{2-[2-(1,2-Carboran-1-yl)ethyloxyethoxy]ethyl}thymidine (2). Experimental conditions for the synthesis of **2** were identical to those described for **1**. The amount of 0.2 g (0.4 mmol) of **18** yielded 120 mg (50%) of **2** as a viscous and hygroscopic liquid. R_f 0.35 (1:12 methanol/dichloromethane); ^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3H, CH_3), 2.30 (t, $J = 6$, 2H, CH_2), 2.45 (m, 2H, H-2′), 3.44–3.65 (m, 11H, CH_2–N, H-3′, and CH_2O), 3.74–3.86 (m, 2H, H-5′), 3.96 (m, 1H, H-4′), 4.52 (s, 1H, CH), 6.17 (t, $J = 6$ Hz, 1H, H-1′), 7.42 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.23 (CH_3), 36.68 (CH_2), 37.13 (CH_2–N), 40.01 (C-2′), 60.35 (CH), 62.22 (C-5′), 67.35 (CH_2O), 68.12 (CH_2O), 69.42 (CH_2O), 69.99 (CH_2O), 73.35 (CH_2O), 71.25 (C-3′), 77.21 ($C_{carborane}$), 86.79 (C-1′), 86.92 (C-4′), 110.12 (C-5), 134.91 (C-6), 150.91 (C-2), 162.83 (C-4); MS $C_{18}H_{36}O_7B_{10}N_2Na$ $(M+Na)^+$ calcd 525.3351, found 525.3403; HPLC retention time: 14.28 min, approx. purity: 99.0%.

5.1.8. 3-(2-{2-[2-(1,2-Carboran-1-yl)ethyloxyethoxy]ethoxy}ethyl)thymidine (3). Experimental conditions for the synthesis of **3** were identical to those described for **1**. The amount of 201 mg (0.526 mmol) of **19** yielded 96 mg (33%) of product as a viscous and hygroscopic liquid. R_f 0.43 (1:12 methanol/dichloromethane); ^{1}H NMR

($CDCl_3$): δ 1.87 (s, 3H, CH_3), 2.29 (t, $J = 6$, 2H, CH_2), 2.47 (m, 2H, H-2′), 3.50–3.65 (m, 12H, CH_2O), 3.80 (m, 2H, H-5′), 3.96 (m, 1H, H-4′), 4.12 (m, 3H, CH_2–N and H-3′), 4.52 (s, 1H, CH), 6.16 (t, $J = 6$ Hz, 1H, H-1′), 7.77 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.25 (CH_3), 36.62 (CH_2), 37.26 (CH_2–N), 40.09 (C-2′), 60.31 (CH), 62.21 (C-5′), 67.44 (CH_2O), 68.40 (CH_2O), 69.78 (CH_2O), 69.94 (CH_2O), 70.10 (CH_2O), 70.48 (CH_2O), 73.39 (CH_2O), 71.17 (C-3′), 77.20 ($C_{carborane}$), 86.96 (C-1′), 87.34 (C-4′), 110.08 (C-5), 134.89 (C-6), 150.94 (C-2), 162.71 (C-4); MS $C_{20}H_{40}O_8B_{10}N_2Na$ $(M+Na)^+$ calcd 569.3613, found 569.3665; HPLC retention time: 14.37 min, approx. purity: 98.0%.

5.1.9. 3-[2-(2-{2-[2-(1,2-Carboran-1-yl)ethyloxyethoxy]-ethoxy}ethoxy)ethyl]thymidine (4). Experimental conditions for the synthesis of **4** were identical to those described for **1**. The amount of 100 mg (0.2 mmol) of **20** yielded 50 mg (42%) of product as a viscous and hygroscopic liquid. R_f 0.77 (1:12 methanol/dichloromethane); ^1H NMR ($CDCl_3$): δ 1.89 (s, 3H, CH_3), 2.33 (m, 2H, H-2′), 2.49 (t, $J = 6$ Hz, 2H, CH_2), 3.51–3.67 (m, 16H, CH_2O), 3.82 (m, 2H, H-5′), 3.86 (m, 3H, CH_2–N and H-3′), 4.14 (m, 1H, H-4′), 4.53 (s, 1H, CH), 6.15 (t, 1H, H-1′), 7.37 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.26 (CH_3), 36.59 (CH_2), 37.32 (CH_2–N), 40.12 (C-2′), 60.36 (CH), 62.35 (C-5′), 67.50 (CH_2O), 68.49 (CH_2O), 69.87 (CH_2O), 70.02 (CH_2O), 70.19 (CH_2O), 70.47 (CH_2O), 70.55 (CH_2O), 71.36 (CH_2O), 71.37 (C-3′), 77.20 ($C_{carborane}$), 86.94 (C-1′), 87.34 (C-4′), 110.18 (C-5), 134.99 (C-6), 151.01 (C-2), 163.38 (C-4); MS $C_{22}H_{44}O_9B_{10}N_2Na$ $(M+Na)^+$ calcd 613.3875, found 613.3904; HPLC retention time: 14.39 min, approx. purity: 98.0%.

5.1.10. 3-(2-{2-[2-(1,12-Carboran-1-yl)ethyloxyethoxy]-ethoxy}ethyl)thymidine (5). Experimental conditions for the synthesis of **5** were identical to those described for **1**. The amount of 0.7 g (1.5 mmol) of **21** yielded 0.5 g (60%) of product as a viscous and hygroscopic liquid. R_f 0.15 (1:12 methanol/dichloromethane); ^1H NMR ($CDCl_3$): δ 1.87 (s, 3H, CH_3), 2.32 (t, $J = 6$ Hz, 2H, CH_2), 2.44 (m, 2H, H-2′), 3.51–3.64 (m, 12H, CH_2O), 3.83 (m, 2H, H-5′), 3.85 (m, 3H, CH_2–N and H-3′), 3.97 (m, 1H, H-4′), 4.51 (s, 1H, CH), 6.15 (t, 1H, H-1′), 7.78 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.24 (CH_3), 36.62 (CH_2), 37.3 (CH_2–N), 40.1 (C-2′), 60.34 (CH), 62.21 (C-5′), 68.40 (CH_2O), 69.78 (CH_2O), 69.94 (CH_2O), 70.13 (CH_2O), 70.48 (CH_2O), 73.39 (CH_2O), 71.2 (C-3′), 77.20 ($C_{carborane}$), 86.96 (C-1′), 87.32 (C-4′), 110.1 (C-5), 134.89 (C-6), 150.91 (C-2), 162.73 (C-4); MS (HR-ESI) $C_{20}H_{40}O_8B_{10}N_2Na$ $(M+Na)^+$ calcd 569.3613, found 569.3669; HPLC retention time: 14.64 min, approx. purity: 97.0%.

5.1.11. 1-(*tert*-Butyldiphenylsilyloxy)-5-(1,12-carboran-1-yl)pentane (24). To a solution of 475 mg (3.30 mmol) of *p*-carborane in 12 mL of anhydrous benzene/ether (2:1) was added a solution of 1.6 mL (3.96 mmol) of 2.5 M butyl lithium in hexanes at 0 °C over a period of 20 min. The reaction mixture was gradually warmed to rt and was allowed to stir for 1 h. Subsequently, the reaction mixture was cooled to 0 °C and a solution of 1.77 g (3.3 mmol) of tosylate (**22**) in 9 mL of anhydrous benzene/ether (2:1) was added dropwise. The reaction mixture was brought to rt, then refluxed for 4 h, cooled, quenched with distilled water (10 mL), and extracted with ethylacetate. The organic layer was washed with brine (15 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using 100% hexanes to obtain 0.99 g (61%) of **24** as a white solid. R_f 0.29 (hexanes); ^1H NMR ($CDCl_3$): δ 0.94–1.50 (m, 13H, CH_2 and CH_3), 1.33–1.46 (m, 4H, CH_2), 2.42 (s, 1H, CH), 3.50 (t, $J = 6.1$ Hz, 2H, CH_2O), 7.24–7.26 (m, 6H, Ar), 7.53–7.55 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 19.09 (C–Si), 22.57 (CH_2), 26.77 (CH_3), 30.74 (CH_2), 31.50 (CH_2), 38.38 (CH_2), 57.94 (CH), 63.44 (CH_2), 84.78 ($C_{carborane}$), 127.51 (Ar), 129.45 (Ar), 135.11 (Ar), 135.42 (Ar); MS $C_{23}H_{40}O_1Si_1B_{10}Na$ $(M+Na)^+$ calcd 492.3733, found 492.3766.

5.1.12. 1-(*tert*-Butyldimethylsilyloxy)-5-(1,7-carboran-1-yl)pentane (25). Experimental conditions for the synthesis of **25** were identical to those described for **24**. The amount of 569.70 mg (3.95 mmol) of *m*-carborane and 1.47 g (3.95 mmol) of **23** yielded 660 mg (48%) of **25** as a white solid. R_f 0.18 (9:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 0.01 (s, 6H, CH_3), 0.86 (s, 9H, CH_3), 1.11–1.50 (m, 6H, CH_2), 1.84–1.93 (m, 2H, CH_2), 2.86 (s, 1H, CH), 3.55 (t, $J = 6.3$ Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ −5.36 (CH_3), 18.20 (C–Si), 25.44 (CH_2), 25.92 (CH_3), 29.75 (CH_2), 32.28 (CH_2), 37.00 (CH_2), 54.73 (CH), 62.74 (CH_2), 75.89 ($C_{carborane}$); MS $C_{13}H_{36}O_1Si_1B_{10}Na$ $(M+Na)^+$ calcd 347.3544, found 347.3529.

5.1.13. 5-(12-{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}carboran-1-yl)pentyloxy-*tert*-butyldiphenylsilane (26). To a solution of 428 mg (0.91 mmol) of compound **24** in 8 mL of anhydrous THF at 0 °C was added dropwise a solution of 0.5 mL (1.1 mmol) of 2.5 M butyl lithium in hexanes over a period of 20 min. The solution was gradually warmed to rt and stirred for 1 h. The reaction mixture was again cooled to 0 °C and a solution of 258.5 mg (0.91 mmol) of tri(ethyleneglycol) monomethylether tosylate in 4 mL of anhydrous THF was added dropwise. After the addition, the solution was warmed to rt and then refluxed for 4 h. The reaction mixture was quenched with distilled water (10 mL) and the organic layer was extracted with ethylacetate (3×20 mL). The organic layer was washed with brine (20 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexanes/ethylacetate (8:2) to obtain 0.16 g (28%) of **26**. R_f 0.48 (1:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 1.00 (s, 9H, CH_3), 1.04–1.18 (m, 4H, CH_2), 1.39–1.55 (m, 4H, CH_2), 1.89 (t, $J = 7.4$ Hz, 2H, CH_2), 3.19 (t, $J = 7.5$ Hz, 2H, CH_2), 3.36 (s, 3H, CH_3), 3.38–3.60 (m, 10H, CH_2), 7.33–7.42 (m, 6H, Ar), 7.59–7.62 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 19.18 (C–Si), 25.33 (CH_2), 26.82 (CH_3), 29.69 (CH_2), 31.99 (CH_2), 36.69 (CH_2), 37.79 (CH_2), 59.02 (CH_3), 63.53 (CH_2), 69.64 (CH_2), 70.16 (CH_2), 70.51 (CH_2), 71.91 (CH_2), 76.68 ($C_{carborane}$), 79.90 ($C_{carborane}$), 127.59 (Ar), 129.52 (Ar), 133.95 (Ar), 135.51 (Ar); MS

$C_{30}H_{54}O_4Si_1B_{10}Na$ $(M+Na)^+$ calcd 639.4620, found 639.4619.

5.1.14. 5-[12-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentyloxy-*tert*-butyldiphenylsilane (27). Experimental conditions for the synthesis of **27** were identical to those described for **26**. The amount of 220 mg (0.47 mmol) of compound **24** and 170 mg (0.47 mmol) of tetra(ethyleneglycol) monomethylether tosylate gave 115 mg (37%) of compound **27** as a viscous liquid. R_f 0.3 (1:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 1.02 (s, 9H, CH_3, 1.08–1.25 (m, 2H, CH_2), 1.40–1.47 (m, 2H, CH_2), 1.54–1.58 (m, 2H, CH_2), 1.90 (t, $J = 7.4$ Hz, 2H, CH_2), 3.20 (t, $J = 7.5$ Hz, 2H, CH_2), 3.37 (s, 3H, CH_3), 3.45–3.48 (m, 2H, CH_2), 3.53–3.64 (m, 14H, CH_2), 7.33–7.42 (m, 6H, Ar), 7.62–7.64 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 19.10 (C–Si), 25.25 (CH_2), 26.77 (CH_3), 29.11 (CH_2), 31.93 (CH_2), 36.68 (CH_2), 37.72 (CH_2), 58.94 (CH_2), 63.43 (CH_3O), 69.54 (CH_2O), 69.99 (CH_2O), 70.08 (CH_2O), 71.41 (CH_2O), 70.43 (CH_2O), 70.53 (CH_2O), 71.84 (CH_2O), 75.63 ($C_{carborane}$), 79.72 ($C_{carborane}$), 127.50 (Ar), 129.44 (Ar), 133.86 (Ar), 135.42 (Ar); MS $C_{32}H_{58}O_5Si_1B_{10}Na$ $(M+Na)^+$ calcd 683.4882, found 683.4885.

5.1.15. 5-{12-[2-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethoxy)ethyl]carboran-1-yl}pentyloxy-*tert*-butyldiphenylsilane (28). Experimental conditions for the synthesis of **28** were identical to those described for **26**. The amount of 100 mg (0.21 mmol) of compound **28** and 85.26 mg (0.21 mmol) of pentaethyleneglycol monomethylether tosylate gave 68 mg (36%) of compound **28** as a viscous liquid. R_f 0.15 (6:4 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 1.01 (s, 9H, CH_3), 1.04–1.29 (m, 4H, CH_2), 1.39–1.56 (m, 4H, CH_2), 1.89 (t, $J = 7.4$ Hz, 2H, CH_2), 3.19 (t, $J = 7.5$ Hz, 2H, CH_2O), 3.36 (s, 3H, CH_3), 3.45–3.63 (m, 18H, CH_2O), 7.34–7.36 (m, 6H, Ar), 7.60–7.63 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 19.16 (C–Si), 25.31 (CH_2), 26.79 (CH_3), 29.18 (CH_2), 32.00 (CH_2), 36.69 (CH_2), 37.79 (CH), 59.02 (CH_2), 63.51 (CH_3O), 69.12 (CH_2O), 60.14 (CH_2O), 70.46 (CH_2O), 71.48 (CH_2O), 70.54 (CH_2O), 70.57 (CH_2O), 70.58 (CH_2O), 70.60 (CH_2O), 71.89 (CH_2O), 75.67 ($C_{carborane}$), 79.80 ($C_{carborane}$), 127.59 (Ar), 129.50 (Ar), 133.94 (Ar), 135.44 (Ar); MS $C_{34}H_{62}O_6Si_1B_{10}Na$ $(M+Na)^+$ calcd 727.5144, found 727.5140.

5.1.16. 5-[7-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentyloxy-*tert*-butyldimethylsilane (29). Experimental conditions for the synthesis of **29** were identical to those described for **26**. The amount of 578 mg (1.83 mmol) of compound **25** and 662.40 mg (1.83 mmol) of tri(ethyleneglycol) monomethylether tosylate gave 505 mg (54%) of compound **29** as a viscous liquid. R_f 0.15 (4:5 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ −0.06 (s, 6H, CH_3), 0.79 (s, 9H, CH_3), 1.21–1.41 (m, 6H, CH_2), 1.79–1.83 (m, 2H, CH_2), 2.11 (t, $J = 7.0$ Hz, 2H, CH_2), 3.28–3.33 (m, 5H, CH_2), 3.56–3.54 (m, 14H, CH_2); ^{13}C NMR ($CDCl_3$): δ −5.53 (CH_3), 18.08 (C–Si), 25.24 (CH_2), 25.74 (CH_3), 29.50 (CH_2), 32.07 (CH_2), 36.00 (CH_2), 36.78 (CH_2), 62.53 (CH_3O), 69.44 (CH_2O), 70.01 (CH_2O), 70.09 (CH_2O), 70.32 (CH_2O), 70.41 (CH_2O), 70.40 (CH_2O), 71.79 (CH_2O), 72.70 ($C_{carborane}$), 76.00 ($C_{carborane}$); MS $C_{22}H_{54}O_5Si_1B_{10}Na$ $(M+Na)^+$ calcd 559.4569, found 559.4561.

5.1.17. 5-(12-{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}carboran-1-yl)pentanol (30). To a solution of 156 mg (0.25 mmol) of compound **26** in 2 mL of anhydrous THF at −78 °C was added dropwise 0.3 mL (0.3 mmol) of a 1.0 M TBAF solution in THF for 20 min. The reaction mixture was warmed to rt and monitored by TLC analysis for the disappearance of UV active starting material. After 40 min, the reaction mixture was quenched by the addition of distilled water (10 mL). The organic layer was extracted with ethylacetate, washed with brine (10 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexanes/ethylacetate (6:4) to obtain 85 mg (91% yield) of compound **30** as a colorless material. R_f 0.19 (1:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 1.01–1.23 (m, 4H, CH_2), 1.36–1.41 (m, 2H, CH_2), 1.50–1.55 (m, 2H, CH_2), 1.84 (t, 2H, $J = 7.3$ Hz, CH_2), 3.15 (t, 2H, $J = 7.4$ Hz, CH_2O), 3.31 (s, 3H, CH_3O), 3.41–3.56 (m, 10H, CH_2); ^{13}C NMR ($CDCl_3$): δ 25.11 (CH_2), 29.10 (CH_2), 32.05 (CH_2), 36.56 (CH_2), 37.66 (CH_2), 58.88 (CH_2), 62.26 (CH_3O), 69.50 (CH_2O), 70.00 (CH_2O), 70.33 (CH_2O), 70.36 (CH_2O), 71.75 (CH_2O), 75.56 ($C_{carborane}$), 79.55 ($C_{carborane}$); MS $C_{14}H_{36}O_4B_{10}Na$ (M+Na) calcd 401.3442, found 401.3446.

5.1.18. 5-[12-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentanol (31). Experimental conditions for the synthesis of **31** were identical to those described for **30**. The amount of 115 mg (0.18 mmol) of compound **27** yielded 68 mg (93% yield) of compound **31**. R_f 0.19 (1:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 0.99–1.20 (m, 4H, CH_2), 1.37–1.39 (m, 2H, CH_2), 1.52–1.56 (m, 2H, CH_2), 1.84 (t, 2H, $J = 7.3$ Hz, CH_2), 3.14 (t, 2H, $J = 7.4$ Hz, CH_2O), 3.31 (s, 3H, CH_3O), 3.40–3.57 (m, 14H, CH_2); ^{13}C NMR ($CDCl_3$): δ 25.11 (CH_2), 29.10 (CH_2), 32.07 (CH_2), 36.59 (CH_2), 37.60 (CH_2), 58.88 (CH_2), 62.52 (CH_3O), 69.47 (CH_2O), 69.99 (CH_2O), 70.00 (CH_2O), 70.34 (CH_2O), 70.44 (CH_2O), 70.45 (CH_2O), 71.76 (CH_2O), 75.59 ($C_{carborane}$), 79.57 ($C_{carborane}$); MS $C_{16}H_{40}O_5B_{10}Na$ $(M+Na)^+$ calcd 445.3740, found 445.3720.

5.1.19. 5-{12-[2-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethoxy)ethyl]carboran-1-yl}pentanol (32). Experimental conditions for the synthesis of **32** were identical to those described for **21**. The amount of 192 mg (0.27 mmol) of compound **28** yielded 91 mg (73%) of compound **32** as a viscous material. R_f 0.15 (1:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 1.01–1.21 (m, 4H, CH_2), 1.35–1.39 (m, 2H, CH_2), 1.48–1.52 (m, 2H, CH_2), 1.82 (t, 2H, $J = 7.2$ Hz, CH_2), 3.13 (t, 2H, $J = 7.3$ Hz, CH_2O), 3.30 (s, 3H, CH_3 O), 3.36–3.88 (m, 18H, CH_2); ^{13}C NMR ($CDCl_3$): δ 25.59 (CH_2), 29.06 (CH_2), 31.99 (CH_2), 36.49 (CH_2), 37.54 (CH_2), 58.84 (CH_3O), 62.10 (CH_2), 69.41 (CH_2), 69.93 (CH_2), 70.23 (CH_2), 70.26 (CH_2), 70.32 (CH_2), 70.35 (CH_2O), 70.37

(CH_2O), 70.42 (CH_2O), 71.70 (CH_2O), 75.50 ($C_{carborane}$), 79.49 ($C_{carborane}$); MS $C_{18}H_{44}O_6B_{10}Na$ $(M+Na)^+$ calcd 489.3966, found 489.3966.

5.1.20. 5-[7-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentanol (33). The synthesis of this compound is identical to that described for compound **30**. The amount of 505 mg (0.98 mmol) of compound **29** yielded 390 mg (94%) of compound **23** as a viscous material. R_f 0.11 (4:5 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 0.10–1.46 (m, 6H, CH_2), 1.80–1.86 (m, 4H, CH_2), 2.13 (t, 2H, $J = 6.9$, CH_2), 3.29–3.35 (s, 3H, CH_3), 3.28–3.34 (m, 14H, CH_2O); ^{13}C NMR ($CDCl_3$): δ 25.74 (CH_2), 29.50 (CH_2), 31.97 (CH_2), 35.99 (CH_2), 35.99 (CH_2), 62.01 (CH_2), 69.44 (CH_2O), 69.99 (CH_2O), 70.01 (CH_2O), 70.23 (CH_2O), 70.25 (CH_2O), 70.36 (CH_2O), 71.67 (CH_2O), 72.35 ($C_{carborane}$), 75.94 ($C_{carborane}$); MS $C_{16}H_{40}O_5B_{10}Na$ $(M+Na)^+$ calcd 445.3740, found 445.3715.

5.1.21. 5-(12-{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}carboran-1-yl)pentyltosylate (34). To a solution of 85 mg (0.23 mmol) of compound **30**, 16.9 mg (0.14 mmol) of DMAP, and 2 mL of triethylamine in 5 mL of anhydrous dichloromethane was added a solution of 87 mg (0.46 mmol) of *p*-toluenesulfonyl chloride in 5 mL of dichloromethane for 20 min at 0 °C. The reaction mixture was warmed to rt and allowed to stir for 4 h. The reaction mixture was quenched with water and the organic layer was extracted with dichloromethane. The organic layer was washed with dilute hydrochloric acid (10%), followed by brine (10 mL), and evaporated to dryness. The resulting residue was purified by chromatography on a silica gel column using hexanes/ethylacetate (1:1) to obtain 78 mg (64%) of compound **34** as a viscous material. R_f 0.3 (2:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 0.96–1.14 (m, 4H, CH_2), 1.38–1.51 (m, 4H, CH_2), 1.86 (t, 2H, $J = 7.4$ Hz, CH_2), 2.42 (s, 3H, CH_3), 3.17 (t, 2H, $J = 7.4$ Hz, CH_2), 3.34 (s, 3H, CH_3O), 3.44–3.59 (m, 8H, CH_2O), 3.91 (t, 2H, $J = 6.3$ Hz, CH_2O), 7.31 (d, 2H, $J = 8.1$ Hz, Ar), 7.73 (d, 2H, $J = 8.2$ Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 21.60 (CH_3), 24.76 (CH_2), 28.26 (CH_2), 28.59 (CH_2), 36.67 (CH_2), 37.39 (CH_2), 58.98 (CH_3O), 62.54 (CH_2), 69.99 (CH_2O), 70.10 (CH_2O), 70.46 (CH_2O), 70.52 (CH_2O), 71.85 (CH_2O), 75.78 ($C_{carborane}$), 79.26 ($C_{carborane}$), 127.81 (Ar), 129.75 (Ar), 132.98 (Ar), 144.70 (Ar); MS $C_{21}H_{42}O_6S_1B_{10}Na$ $(M+Na)^+$ calcd 555.3530, found 555.3506.

5.1.22. 5-[12-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentyltosylate (35). Experimental conditions for the synthesis of **35** were identical to those described for **34**. The amount of 68 mg (0.16 mmol) of compound **31** gave 78 mg (64%) of compound **35** as a viscous material. R_f 0.4 (1:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 1.16–1.21 (m, 4H, CH_2), 1.51–1.58 (m, 4H, CH_2), 1.74–1.80 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 3.14–3.22 (m, 2H, CH_2O), 3.34 (s, 3H, CH_3O), 3.43–3.59 (m, 12H, CH_2O), 3.91 (t, 2H, $J = 6.1$ Hz, CH_2O), 7.30 (d, 2H, $J = 8.1$ Hz, Ar), 7.72 (d, 2H, $J = 8.2$ Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 21.58 (CH_3), 24.74 (CH_2), 28.26 (CH_2), 28.58 (CH_2), 36.69 (CH_2), 37.39 (CH_2), 58.96 (CH_2), 61.52 (CH_3O), 70.00 (CH_2O), 70.01 (CH_2O), 70.40 (CH_2O), 70.44 (CH_2O), 70.50 (CH_2O), 70.53 (CH_2O), 71.85 (CH_2O), 75.71 ($C_{carborane}$), 79.71 ($C_{carborane}$), 127.77 (Ar), 129.78 (Ar), 133.01 (Ar), 144.69 (Ar); MS $C_{23}H_{46}O_7S_1B_{10}Na$ $(M+Na)^+$ calcd 599.3792, found 599.3798.

5.1.23. 5-{12-[2-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethoxy)ethyl]carboran-1-yl}pentyltosylate (36). Experimental conditions for the synthesis of **36** were identical to those described for **34**. The amount of 48 mg (0.10 mmol) of compound **32** gave 20 mg (30%) of compound **36** as a viscous material. R_f 0.35 (1:1 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 0.93–1.14 (m, 4H, CH_2), 1.38–1.54 (m, 4H, CH_2), 1.85 (t, 2H, $J = 7.4$ Hz, H_2C), 2.42 (s, 3H, CH_3), 3.18 (t, 2H, $J = 7.4$ Hz, CH_2), 3.35 (s, 3H, CH_3O), 3.43–3.60 (m, 16H, CH_2), 3.91 (t, 2H, $J = 6.2$ Hz, CH_2O), 7.31 (d, 2H, $J = 8.1$ Hz, Ar), 7.72 (d, 2H, $J = 8.2$ Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 21.61 (CH_3), 24.75 (CH_2), 28.27 (CH_2), 28.60 (CH_2), 36.66 (CH_2), 37.30 (CH_2), 59.00 (CH_2), 62.54 (CH_3O), 69.99 (CH_2O), 70.11 (CH_2O), 70.40 (CH_2O), 70.43 (CH_2O), 70.49 (CH_2O), 70.50 (CH_2O), 70.54 (CH_2O), 70.56 (CH_2O), 71.86 (CH_2O), 75.75 ($C_{carborane}$), 79.25 ($C_{carborane}$), 127.81 (Ar), 129.78 (Ar), 132.96 (Ar), 144.72 (Ar); MS $C_{25}H_{50}O_8S_1B_{10}Na$ $(M+Na)^+$ calcd 643.4055, found 643.4061.

5.1.24. 5-[7-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentyltosylate (37). Experimental conditions for the synthesis of **37** were identical to those described for **34**. The amount of 390 mg (0.93 mmol) of compound **33** yielded 325 mg (66%) of compound **37** as a viscous material. R_f 0.3 (2:3 hexanes/ethylacetate); ^1H NMR ($CDCl_3$): δ 1.16–1.21 (m, 4H, CH_2), 1.51–1.58 (m, 2H, CH_2), 1.74–1.80 (m, 2H, CH_2), 2.13 (t, 2H, $J = 7.1$ Hz, CH_2), 2.39 (s, 3H, CH_3), 3.31–3.36 (m, 5H, CH_2O and CH_3O), 3.48–3.58 (m, 12H, CH_2O), 3.91 (t, 2H, $J = 6.2$ Hz, CH_2O), 7.28 (d, 2H, $J = 8.1$ Hz, Ar), 7.70 (d, 2H, $J = 8.2$ Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 21.46 (CH_3), 24.74 (CH_2), 28.20 (CH_2), 28.97 (CH_2), 36.03 (CH_2), 36.46 (CH_2), 58.82 (CH_3O), 69.45 (CH_2), 69.90 (CH_2O), 70.05 (CH_2O), 70.10 (CH_2O), 70.32 (CH_2O), 70.43 (CH_2O), 70.51 (CH_2O), 71.74 (CH_2O), 72.47 ($C_{carborane}$), 75.63 ($C_{carborane}$), 127.64 (Ar), 129.70 (Ar), 133.88 (Ar), 144.62 (Ar); MS $C_{23}H_{46}O_7S_1B_{10}Na$ $(M+Na)^+$ calcd 599.3792, found 599.3793.

5.1.25. 1-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)-1,2-carborane (40). To a solution of 393 mg (2.8 mmol) of *o*-carborane in 5 mL of anhydrous benzene/ether (2:1) at 0 °C was added dropwise a solution of 1.3 mL (3.36 mmol) of 2.5 M butyl lithium in hexanes over a period of 20 min. The reaction mixture was gradually warmed to rt and stirred for 1 h. Subsequently, the reaction mixture was cooled to 0 °C and a solution of 1.01 g (2.77 mmol) of **38** in 5 mL of anhydrous benzene/ether (2:1) was added. The reaction mixture was warmed to rt, refluxed for 10 h, cooled, and then quenched with distilled water. The organic layer was extracted with ethylacetate, washed with brine (15 mL), dried over magnesium sulfate, and evaporated under re-

duced pressure. The resulting residue was purified by silica gel column chromatography using hexanes/ethylacetate (7:3) yielding 520 mg (55%) of compound **40** as a colorless liquid. R_f 0.25 (1:1 hexanes/ethylacetate); ^{1}H NMR ($CDCl_3$) δ 2.50 (t, 2H, J = 5.4 Hz, CH_2), 3.36 (s, 3H, CH_3O), 3.46–3.61 (m, 14H, CH_2O), 4.18 (s, 1H, CH); ^{13}C NMR δ 37.31 (CH_2), 55.31 ($C_{carborane}$), 59.03 (CH_3O), 60.20 (CH_2O), 68.42 (CH_2O), 70.01 (CH_2O), 70.19 (CH_2O), 70.53 (CH_2O), 70.61 (CH_2O), 71.89 (CH_2O), 100.97 ($C_{carborane}$); MS $C_{11}H_{30}O_4B_{10}Na$ $(M+Na)^+$ calcd 359.2972, found 359.2965.

5.1.26. 1-{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}-1,12-carborane (41). The synthetic conditions for **41** were similar to that described for compound **40**. The amount of 1.4 g (4.4 mmol) of **39** and 625 mg (4.4 mmol) of *p*-carborane yielded, 0.95 g (70%) of **41** as a viscous material. R_f 0.15 (1:1 hexanes/ethylacetate); ^{1}H NMR ($CDCl_3$): 2.49 (t, J = 6 Hz, 2H, CH_2), 3.35 (s, 3H, CH_3O), 3.47–3.62 (m, 10H, CH_2O), 4.19 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 37.33 (CH_2), 59.05 (CH_3O), 60.19 (CH), 68.40 (CH_2), 69.97 (CH_2O), 70.22 (CH_2O), 70.52 (CH_2O), 71.87 (CH_2O), 73.40 (CH_2O); MS $C_9H_{26}B_{10}O_3Na$ $(M+Na)^+$ calcd 315.2710, found 315.2803.

5.1.27. 5-[2-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}-ethyl)carboran-1-yl]pentyltosylate (42). To a solution of 220 mg (0.63 mmol) of compound **40** in 5 mL of dry THF was added 0.4 mL (0.9 mmol) of 2.5 M butyl lithium in hexanes at 0 °C for 20 min. The reaction mixture was brought to rt and stirred for 1 h. A solution of 441.31 mg (1.07 mmol) 1,5-pentanediol-di-*p*-tosylate in 5 mL of anhydrous THF was added dropwise at 0 °C and stirred for 4 h at rt prior to quenching with water (5 mL). The organic layer was extracted with ethylacetate, washed with brine, dried over anhydrous magnesium sulfate, and evaporated to dryness. The residue was purified by silica gel column chromatography to obtain 104 mg (29%) of compound **42** as a viscous liquid. R_f 0.3 (1:1 hexanes/ethylacetate); ^{1}H NMR ($CDCl_3$): δ 1.22–1.33 (m, 2H, CH_2), 1.39–1.47 (m, 2H, CH_2), 1.59–1.65 (m, 2H, CH_2), 2.01–2.13 (m, 2H, CH_2), 2.38–2.41 (m, 5H, CH_2O and CH_3), 3.33 (s, 3H, CH_3O), 3.49–3.61 (m, 14H, CH_2O), 3.99 (t, 2H, J = 6.2 Hz, CH_2O), 7.33 (d, 2H, J = 8.3 Hz, Ar), 7.74 (d, 2H, J = 8.2 Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 21.58 (CH_3), 25.01 (CH_2), 28.34 (CH_2), 29.06 (CH_2), 34.68 (CH_2), 34.80 (CH_2), 58.95 (CH_3O), 69.25 (CH_2), 70.32 (CH_2O), 70.40 (CH_2O), 70.43 (CH_2O), 70.45 (CH_2O), 70.50 (CH_2O), 70.52 (CH_2O), 71.83 (CH_2O), 77.16 ($C_{carborane}$), 79.40 ($C_{carborane}$), 127.79 (Ar), 129.81 (Ar), 133.82 (Ar), 144.08 (Ar); MS $C_{23}H_{46}O_7S_1$-$B_{10}Na$ $(M+Na)^+$ calcd 599.3792, found 599.379.

5.1.28. 2-[2-(12-{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}-carboran-1-yl)ethoxy]ethyltosylate (43). The experimental procedure for the synthesis of **43** was similar to that described for compound **42**. The reaction mixture of 0.75 g (2.6 mmol) of **41** and 1.7 g (2.67 mmol) of di(ethyleneglycol)-di-*p*-tosylate yielded 1.2 g (75%) of **43** as viscous liquid. R_f 0.12 (dichloromethane); ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H,CH_3), 2.44–2.58 (m, 4H, CH_2), 3.34 (s, 3H, CH_3O), 3.44–3.64 (m, 14H, CH_2O), 4.08–4.15 (m, 2H, CH_2O), 7.66 (dd, J = 8 Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$): δ 21.62 (CH_3), 34.59 (CH_2), 34.79 (CH_2), 58.99 (CH_3O), 68.31 (CH_2O), 68.83 (CH_2O), 69.21 (CH_2O), 70.27 (CH_2O), 70.44 (CH_2O), 70.49 (CH_2O), 71.86 (CH_2O), 77.11 ($C_{carborane}$), 127.88 (Ar), 129.87 (Ar), 132.86 (Ar), 144.94 (Ar); MS $C_{20}H_{40}B_{10}O_7SNa$ $(M+Na)^+$ calcd 557.3323, found 557.3325.

5.1.29. 3-[5-(12-{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}-carboran-1-yl)pentyl]thymidine (6). Experimental conditions for the synthesis of **6** were identical to those described for **1**. The amount of 78 mg (0.15 mmol) of compound **34** yielded 52 mg (61%) of compound **6** as viscous material. R_f 0.3 (25:1 dichloromethane/methanol); ^{1}H NMR ($CDCl_3$): δ 1.03–1.06 (m, 4H, CH_2), 1.34–1.50 (m, 4H, CH_2), 1.80–1.86 (m, 5H, and H-2′), 3.13 (t, 2H, J = 7.5 Hz, CH_2O), 3.30 (s, 3H, CH_3O), 3.40–3.56 (m, 12H, CH_2O and H-5′), 3.77–3.80 (m, 2H, CH_2–N), 3.91 (q, 1H, J = 3.2 Hz, H-3′), 4.51–4.53 (m, 1H, H-4′), 6.17 (t, J = 6.6 Hz, 1H, H-1′), 7.45 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.13 (CH_3), 31.35 (CH_2), 36.55 (CH_2), 36.71 (CH_2), 40.18 (CH_2), 40.75 (CH_2), 40.87 (C-2′), 58.88 (CH_3O), 61.95 (CH_2), 62.52 (C-5′), 69.87 (CH_2O), 70.20 (C-3′), 70.37 (CH_2O), 70.80 (CH_2O), 71.15 (CH_2O), 71.77 (CH_2O), 75.68 ($C_{carborane}$), 79.54 ($C_{carborane}$), 86.89 (C-1′), 87.25 (C-4′), 110.18 (C-5), 134.78 (C-6), 150.80 (C-2), 163.28 (C-4); MS $C_{24}H_{48}O_8N_2B_{10}Na$ $(M+Na)^+$ calcd 625.4277, found 625.4249. HPLC retention time: 13.84 min, approx. purity: 99.0%.

5.1.30. 3-{5-[12-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentyl}thymidine (7). Experimental conditions for the synthesis of **7** were identical to those described for **1**. The amount of 62 mg (0.12 mmol) of compound **35** yielded 19.3 mg (21%) of compound **7** as a viscous material. R_f 0.35 (25:1 dichloromethane/methanol); ^{1}H NMR ($CDCl_3$): δ 1.01–1.07 (m, 4H, CH_2), 1.33–1.54 (m, 4H, CH_2), 1.77–1.88 (m, 5H, CH_3 and H-2′), 3.15 (t, J = 7.4 Hz, 2H, CH_2O), 3.33 (s, 3H, CH_3O), 3.39–3.58 (m, 16H, CH_2O and H-5′), 3.78–3.81 (m, 2H, CH_2–N), 3.92–3.96 (m, 1H, H-3′), 4.50–4.53 (m, 1H, H-4′), 6.16 (t, J = 6.7 Hz, 1H, H-1′), 7.43 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.20 (CH_3), 29.93 (CH_2), 36.51 (CH_2), 36.75 (CH_2), 40.20 (CH_2), 40.85 (C-2′), 41.02 (CH_2), 58.89 (CH_3O), 62.07 (CH_2), 62.51 (C-5′), 69.63 (CH_2O), 69.91 (CH_2O), 70.21 (C-3′), 70.33 (CH_2O), 70.38 (CH_2O), 70.48 (CH_2O), 70.75 (CH_2O), 71.73 (CH_2O), 71.13 (CH_2O), 71.73 (CH_2O), 75.65 ($C_{carborane}$), 79.61 ($C_{carborane}$), 86.81 (C-1′), 87.20 (C-4′), 110.15 (C-5), 134.71 (C-6), 150.81 (C-2), 163.29 (C-4); MS $C_{26}H_{52}O_9N_2B_{10}Na$ $(M+Na)^+$ calcd 669.4501, found 669.4053. HPLC retention time: 14.85, approx. purity: 98.0%.

5.1.31. 3-(5-{12-[2-(2-{2-[2-(2-Methoxyethoxy)ethoxy]-ethoxy}ethoxy)ethyl]carboran-1-yl}pentyl)thymidine (8). Experimental conditions for the synthesis of **8** were identical to those described for **1**. The amount of 20 mg (0.032 mmol) of compound **36** yielded 18 mg (83%) of compound **8** as viscous material. R_f 0.32 (25:1 dichloromethane/methanol); ^{1}H NMR ($CDCl_3$):

δ 1.05–1.11 (m, 4H, CH_2), 1.36–1.54 (m, 4H, CH_2), 1.72–1.88 (m, 5H, CH_3 and H-2′), 3.17 (t, $J = 7.4$ Hz, 2H, CH_2O), 3.35 (s, 3H, CH_3O), 3.51–3.54 (m, 20H, CH_2O and H-5′), 3.78–3.82 (m, 2H, CH_2–N), 3.90–3.96 (m, 1H, H-3′), 4.51–4.53 (m, 1H, H-4′), 6.15 (t, $J = 6.6$ Hz, 1H, H-1′), 7.43 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.27 (CH_3), 29.65 (CH_2), 40.13 (CH_2), 36.66 (CH_2), 37.54 (CH_2), 40.07 (C-2′), 41.14 (CH_2), 58.99 (CH_3O), 62.32 (CH_2), 62.48 (C-5′), 69.59 (CH_2O), 69.95 (CH_2O), 70.20 (C-3′), 70.38 (CH_2O), 70.41 (CH_2O), 70.49 (CH_2O), 70.50 (CH_2O), 70.52 (CH_2O), 70.61 (CH_2O), 71.85 (CH_2O), 75.61 ($C_{carborane}$), 79.66 ($C_{carborane}$), 86.83 (C-1′), 87.26 (C-4′), 110.26 (C-5), 134.71 (C-6), 150.82 (C-2), 163.28 (C-4); MS $C_{29}H_{56}N_2O_{10}B_{10}Na$ $(M+Na)^+$ calcd 713.4807, found 713.4804. HPLC retention time: 16.39 min, approx. purity: 99.0%.

5.1.32. 3-{5-[7-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentyl}thymidine (9). Experimental conditions for the synthesis of **9** were identical to those described for **1**. The amount of 325 mg (0.62 mmol) of compound **37** yielded 193.5 mg (47%) of compound **9** as a viscous material. R_f 0.4 (25:1 dichloromethane/methanol); ^{1}H NMR ($CDCl_3$): δ 1.16–1.22 (m, 2H, CH_2), 1.26–1.34 (m, 2H, CH_2), 1.49–1.52 (m, 2H, CH_2), 1.81–1.86 (m, 5H, CH_3 and H-2′), 2.14 (t, $J = 6.9$ Hz, 2H, CH_2), 2.25–2.28 (m, 2H, CH_2), 3.32–3.38 (m, 5H, CH_3O and CH_2O), 3.47–3.59 (m, 14H, CH_2 and H-5′), 3.78–3.84 (m, 2H, CH_2–N), 3.92–3.94 (m, 1H, H-3′), 4.50–4.52 (m, 1H, H-4′), 6.18 (t, $J = 6.7$ Hz, 1H, H-1′), 7.43 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.28 (CH_3), 29.45 (CH_2), 35.98 (CH_2), 36.62 (CH_2), 40.13 (CH_2), 40.87 (C-2′), 41.02 (CH_2), 58.86 (CH_3O), 62.50 (C-5′), 62.13 (CH_2), 69.93 (CH_2O), 70.05 (CH_2O), 70.22 (C-3′), 70.29 (CH_2O), 70.31 (CH_2O), 70.40 (CH_2O), 70.43 (CH_2O), 70.56 (CH_2O), 71.13 (CH_2O), 71.73 (CH_2O), 72.73 ($C_{carborane}$), 76.01 ($C_{carborane}$), 86.81 (C-1′), 87.19 (C-4′), 110.03 (C-5), 134.60 (C-6), 150.77 (C-2), 163.32 (C-4); MS (HR-ESI) $C_{26}H_{52}O_9N_2B_{10}Na$ $(M+Na)^+$ calcd 669.4501, found 669.4535. HPLC retention time: 13.85 min, approx. purity: 98.0%.

5.1.33. 3-{5-[2-(2-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}ethyl)carboran-1-yl]pentyl}thymidine (10). Experimental conditions for the synthesis of **10** were identical to those described for **1**. The amount of 100 mg (0.17 mmol) of compound **42** yielded 27.32 mg (36%) of compound **10** as a viscous material. R_f 0.4 (25:1 dichloromethane/methanol); ^{1}H NMR ($CDCl_3$): δ 1.16–1.35 (m, 2H, CH_2), 1.40–1.63 (m, 4H, CH_2), 1.89 (s, 3H, CH_3), 2.08–2.19 (m, 2H, H-2′), 2.37–2.28 (m, 2H, CH_2), 2.43 (t, $J = 7.0$ Hz, 2H, CH_2), 3.35 (s, 5H, CH_3O and CH_2O), 3.52–3.62 (m, 14H, CH_2O and H-5′), 3.86–3.90 (m, 2H, CH_2–N), 3.95–3.97 (m, 1H, H-3′), 4.52–4.54 (m, 1H, H-4′), 6.17 (t, $J = 6.7$ Hz, 1H, H-1′), 7.43 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.27 (CH_3), 28.95 (CH_2), 34.66 (CH_2), 35.02 (CH_2), 36.16 (CH_2), 40.16 (CH_2), 40.81 (C-2′), 58.96 (CH_3O), 62.34 (CH_2), 62.49 (C-5′), 69.35 (CH_2O), 69.68 (CH_2O), 70.21 (C-3′), 70.31 (CH_2O), 70.43 (CH_2O), 70.49 (CH_2O), 70.50 (CH_2O), 71.86 (CH_2O), 77.05 ($C_{carborane}$), 79.75 ($C_{carborane}$), 86.87 (C-1′), 87.21 (C-4′), 110.21 (C-5), 134.74 (C-6), 150.88 (C-2), 163.32 (C-4); MS $C_{26}H_{52}O_9N_2B_{10}Na$ $(M+Na)^+$ calcd 669.4501, found 669.4479. HPLC retention time: 14.70, approx. purity: 95%.

5.1.34. 3-{2-[2-(12-{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}carboran-1-yl)ethoxy]ethyl}thymidine (11). Experimental conditions for the synthesis of **11** were identical to those described for **1**. The amount of 0.55 g (1.03 mmol) of compound **43** yielded 0.1 g (20%) of compound **11** as viscous material. R_f 0.92 (25:1 dichloromethane/MeOH); ^{1}H NMR ($CDCl_3$): δ 1.9 (s, 3H, CH_3), 2.25 (m, 2H, CH_2), 2.40 (t, $J = 6$ Hz, 2H, H-2′), 2.46 (t, $J = 6$ Hz, 4H, CH_2), 3.35 (s, 3H, CH_3O), 3.5–3.72 (m, 16H, OCH_2 and H-5′), 4.15 (t, 2H, CH_2–N), 6.14 (t, $J = 7$ Hz, 1H, H-1′), 7.34 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$): δ 13.28 (CH_3), 34.66 (CH_2), 34.77 (CH_2), 40.11 (C-2′), 58.96 (CH), 62.42 (C-5′), 68.50 (CH_2O), 69.33 (CH_2O), 70.46 (CH_2O), 71.84 (CH_2O), 72.21 (CH_2O), 71.37 (C-3′), 77.19 ($C_{carborane}$), 86.80 (C-1′), 87.55 (C-4′), 110.18 (C-5), 135.20 (C-6), 151.04 (C-2), 163.37 (C-4); MS $C_{23}H_{46}B_{10}O_9N_2Na$ $(M+Na)^+$ calcd 627.4032, found 627.4037; HPLC retention time: 13.49, approx. purity: 98.0%.

Acknowledgements

This work was supported by the US Department of Energy Grant DE-FG02-90ER60972 and grants from the Swedish Research Council to S.E. The results described in this paper were partially presented at the 227th ACS National Meeting, Anaheim, CA, United States, March 28–April 1, 2004.

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