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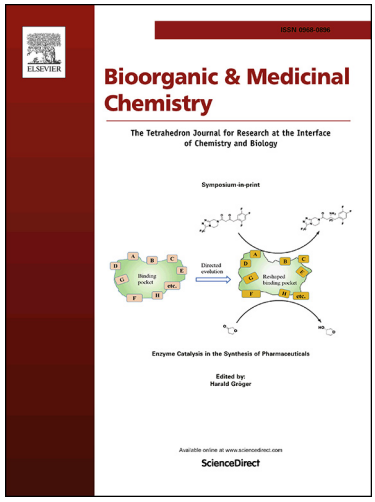

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Structure-based drug design of novel carborane-containing nicotinamide phosphoribosyltransferase inhibitors

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Abstract

A series of carborane-containing NAMPT inhibitors were designed and synthesized based on the structure of compounds **1** and the NAMPT inhibitory activity was evaluated using NAMPT Colorimetric Assay. Among the compounds synthesized, compounds **2b** and **2c** showed significant NAMPT inhibitory activity with IC_{50} values of 0.098 ± 0.008 and 0.057 ± 0.001 μM, respectively. Docking simulation of compound **2** toward NAMPT using the crystal structure of the FK866-NAMPT complex (PDB code: 2GVJ) with replacing the boron atom type by the C3 atom type of carboranes predicted that the NAMPT inhibitory activity of **2c** was improved by the hydrogen bond formation between the carborane amide and H191 of NAMPT. Although dicarborane compounds **38**, **50**, **51**, and **55** were synthesize aiming to two hydrophobic pockets present in the binding pocket of NAMPT, their inhibitory activity was moderate.

Keywords

Carborane, nicotinamide phosphoribosyltransferase, inhibitor, structure-based drug design, docking simulation

1. Introduction

Dicarba-*closo*-dodecaborane (carborane) is an icosahedral cluster containing two carbon atoms, ten boron atoms (one for each vertex), and ten hydrogen atoms. Depending on the position of the two carbon atoms, the three structural isomers of carborane are labeled *o*-, *m*-, and *p*-. Because of its characteristic size and hydrophobicity, being comparable to that of hydrocarbons, carboranes have been used as hydrophobic pharmacophores for drug design over the past 20 year.[1,2] Various bioactive carborane derivatives have been reported including: an estrogen receptor agonist,[3] a transthyretin amyloidosis inhibitor,[4] a HSP60 inhibitor,[5] a LNCaP inhibitor,[6] a carbonic anhydrase 2 inhibitor,[7] and a cyclooxgenase-2 inhibitor.[8] In addition to hydrophobic interactions, carboranes can bind strongly with biomolecules through a unique hydrogen bonding mechanism.[9] Interestingly, the strength of this interaction is different among the carborane isomers. Lee and coworkers reported the synthesis of carborane-containing nicotinamide phosphoribosyltransferase (NAMPT) inhibitors **1a-c** and compared the dihydrogen bonding interactions among the three carborane isomers (*o*-, *m*-, and *p*-, Figure 1).[10] They found that compound **1b**, containing the *m*-carborane, was the most active NAMPT inhibitor.

NAMPT is the first rate-limiting enzyme in the mammalian nicotinamide adenine dinucleotide (NAD^+) recycling pathway, which converts nicotinamide to nicotinamide mononucleotide (NMN). It has recently been elucidated that NAMPT plays a central role in metabolism, cell proliferation, cell survival, and inflammatory responses. Inhibitors of this enzyme are novel and useful for the treatment of many diseases, including cancer, Alzheimer's disease, diabetes, and arthritis. Therefore, NAMPT is an attractive target for new drug discovery.[11,12]

Various NAMPT inhibitor scaffolds have been (Figure 1).[13] For example, compound **X**, having a 1*H*-pyrrolo[3,2-*c*]pyridine moiety, was found to be a highly potent, amide-containing, NAMPT inhibitor.[14] Compound **Y**, having a 1,2,3-triazole ring, showed activity in xenograft and allograft models, strengthening the potential of NAMPT inhibitors to act as anti-tumor drugs.[15] FK866 is the first known specific and highly potent inhibitor of NAMPT: it is now in clinical trials.[16] Although the superimposition of compounds **1a-c** in the hydrophobic site of NAMPT was demonstrated based on the crystal structure of the FK866-NAMPT complex,[17,18] their detailed binding modes to NAMPT have not been elucidated. In this paper, we developed several carborane-containing NAMPT inhibitors using a structure-based drug design model supported by the Autodock vina calculation program.[19]

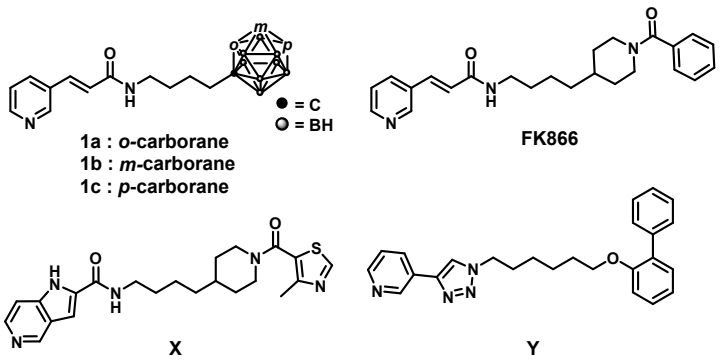


Figure 1. Structures of reported NAMPT inhibitors

The crystal structure of NAMPT/FK866 (PDB code: 2GVJ) was used as the template for the docking simulations. However, the docking studies of carborane derivatives are trivial due to the lack of a carborane forcefield. Although vigorous studies have been carried out for the docking simulations of carborane derivatives using QM/MM modeling[20] or MD simulations[21], these methods require extensive computation time and few compounds can be subjected to these calculation methods. Therefore, carboranes are often approximated by substituting the boron atom for a C3-type atom and boron clusters can be artificially treated as clusters with only carbon atoms.[22,23]

2. Results and Discussion

We designed carborane-containing NAMPT inhibitors based on the structure of compounds **1**. We divided compounds **1** into three moieties: head group, linker, and carborane moiety, as shown in Figure 2. Based on the structures of NAMPT inhibitors FK866, **X**, and **Y** in Figure 1, three skeletons were selected as the head group: pyridinylacrylamide skeleton A, pyrrolopyridine skeleton B, and pyridinyltriazole skeleton C, respectively (Figure 2).[13] For the linker, four and five carbon chains were introduced between the head group and the carborane because these linkers will likely be located in the tubular hydrophobic site of NAMPT. Finally, *o*-carborane was selected as the first carborane moiety to employ for the expected ease of preparation. Additionally, methylene (CH_2), piperidyl carbonyl (Pip-CO), and amide (NHCO) groups were selected for the connection point between the carborane and the linker. Both methylene and piperidyl carbonyl connections were observed in compounds **1** and FK866, respectively. The amide group was selected based on our docking simulation. As shown in Figure 3, the docking study of compound **2** suggested the formation of a hydrogen bond interaction between the amide carbonyl group of compound **2** and histidine 191 (H191) of NAMPT (calculated as ~2.2 Å). The H191 residue is known to be an important amino acid residue for the enzymatic activity of wild-type NAMPT: In fact, the mutation of H191R yields a resistant cell line to FK866.[24]

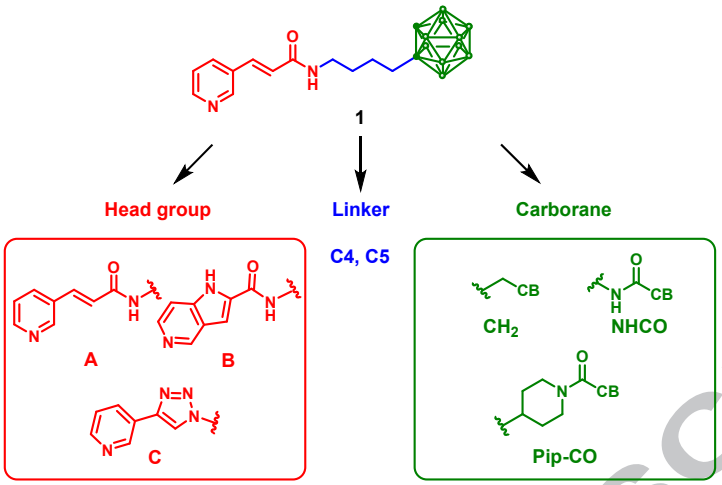


Figure 2. Design of carborane-containing NAMPT inhibitors based on compound **1**

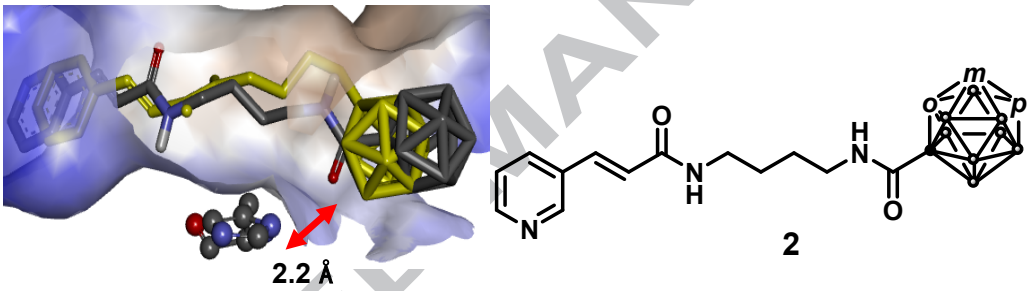
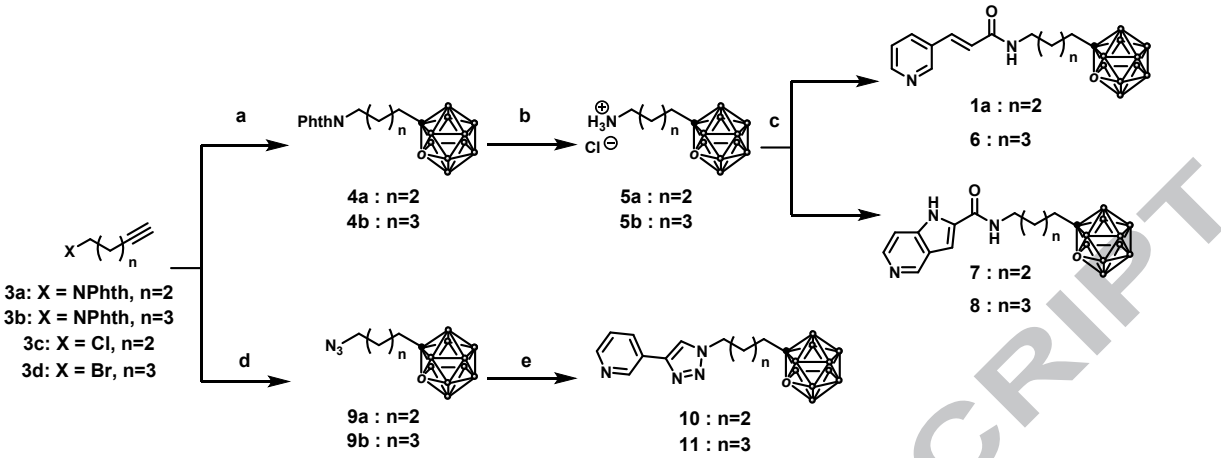


Figure 3. Docking simulation of compound **2** with the enzymatic site of NAMPT.

Compounds **1a, 2, 6-8, 10**, and **11** were synthesized from alkynes **3** via the decaborane coupling reaction according to Scheme 1. **1a** was synthesized according to literature procedures.[10] Next, alkynes **3a-b** were treated with decaborane in chlorobenzene under microwave irradiation[25] to form *o*-carborane derivatives **4a-b**. Reduction with $NaBH_4$ followed by quenching with HCl yielded the corresponding ammonium salts **5a-b**. Ammonium salts **5a-b** were treated with (*E*)-3-(pyridin-3-yl)acrylic acid or 1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid to affording **6-8**. For alkynes **3c-d**, they were treated with decaborane in chlorobenzene under microwave irradiated conditions at 130 ℃ to form the *o*-carborane derivatives. Treatment thereafter with NaN_3 yielded the corresponding azides **9a-b**. Hüisgen-type click reaction of the azide **9a-b** was carried out with 3-ethynyl pyridine in the presence of CuI catalyst to afford the corresponding pyridinyltriazoles **10** and **11**, respectively.

Scheme 1. Synthesis of **1a, 2, 6-8, 10**, and **11**

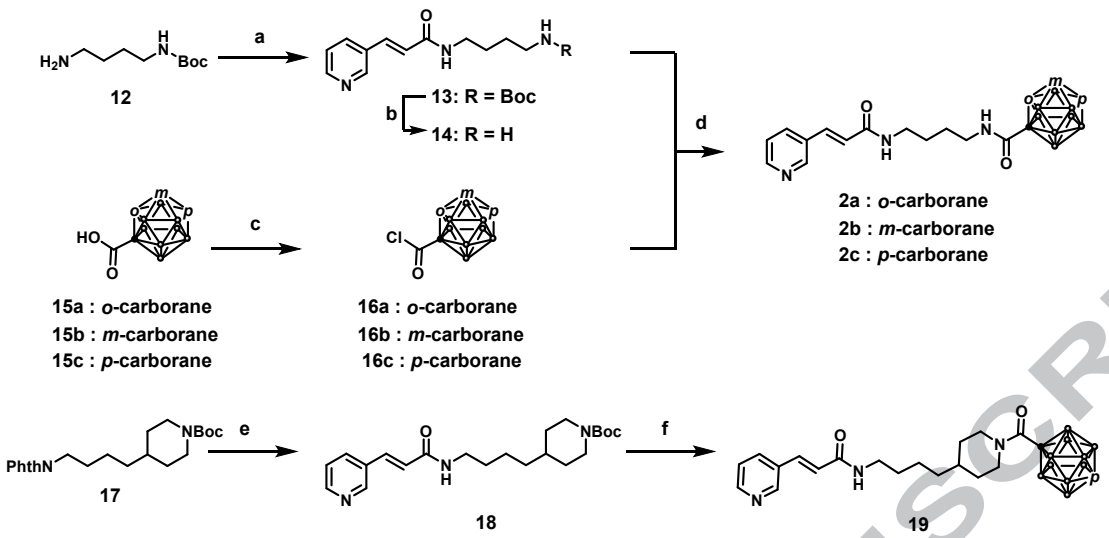


(a) $B_{10}H_{14}$, *N,N*-dimethylaniline, chlorobenzene, MW, 130 ℃, 86%-quant.; (b) (i) $NaBH_4$, IPA/H_2O, r.t.; (ii) HCl, 80 ℃; (c) RCOOH, HATU, DIPEA, DMF, r.t. 26-81% 2 steps; (d) (i) $B_{10}H_{14}$, *N,N*-dimethylaniline, chlorobenzene, MW, 130 ℃; (ii) NaN_3, DMF, 80 ℃, 61–79% 2 steps; (e) 3-ethynylpyridine, CuI, Na ascorbate, DMF/H_2O, 34-40%.

Next, the synthesis of compounds **2a-c** and **19** from carborane carboxylic acids **15a-c** was performed according to Scheme 2. Amine **12** was prepared according to literature procedures.[26] **12** was treated with (*E*)-3-(pyridin-3-yl)acrylic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt), and *N*,*N*-diisopropylethylamine (DIPEA) to afford compound **13**. After deprotection of the *tert*-butoxycarbonyl (Boc) group on **13**, the resulting **14** was treated with acid chlorides **16a-c** (which were prepared from the carborane carboxylic acids **15a-c**).[27] Although the corresponding *m*- and *p*-carborane derivatives **2b** and **2c** were obtained in good yields (43% and 63%, 2 steps, respectively), *o*-carborane derivative **2a** was unstable and readily decomposed, probably due to deboronation of *o*-carborane. It is known that *o*-carborane is highly polarized in comparison with the other isomers. Furthermore, the boron atom at the 3-position was likely activated by the electron withdrawing amide group, thus enhancing the electrophilicity of *o*-carborane in compound **2a**. In fact, the deboronation reaction could be monitored by ^{11}B NMR over time.

Compound **17** was prepared according to literature procedures[28] and was reacted with (*E*)-3-(pyridin-3-yl)acrylic acid in a similar manner to the preparation of compound **13**. The resulting **18** was treated with *p*-carborane carboxylic acid **15c**, after Boc deprotection, to afford the piperidyl carbonyl *p*-carborane **19**.

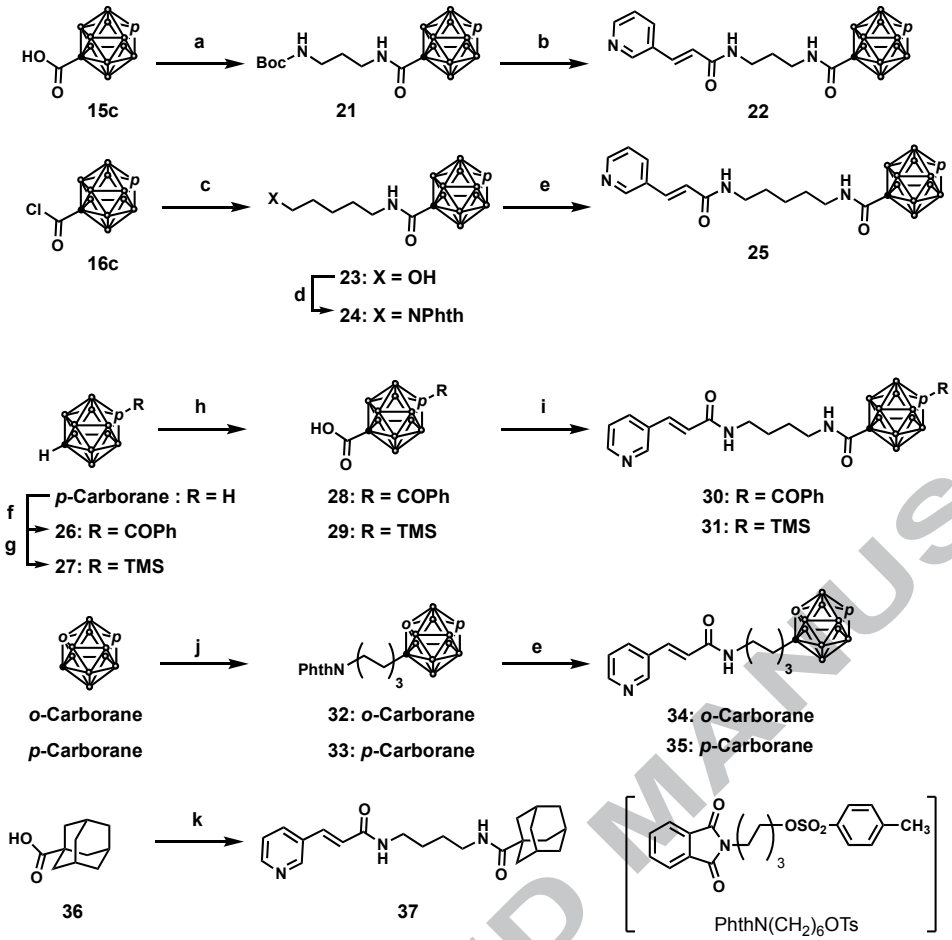
Scheme 2. Synthesis of **2** and **19**



(a) (*E*)-3-(pyridin-3-yl)acrylic acid, EDCI, HOBt, DIPEA, THF, r.t., 82%; (b) HCl, dioxane, r.t.; (c) $(COCl)_2$, toluene, reflux; (d) TEA, DCM, r.t., 43-63% 2 steps; (e) (i) NH_2NH_2-H_2O, EtOH, reflux; (ii) (*E*)-3-(pyridin-3-yl)acrylic acid, EDCI, HOBt, THF, r.t. quant. 2 steps; (f) (i) HCl, dioxane, r.t.; (ii) **15c**, HATU, DIPEA, THF, r.t. 3.6%.

For further investigation, we designed and synthesized compound **2c** derivatives according to Scheme 3. Compound **22** is one carbon shorter and compound **25** is one carbon longer type than **2c**, respectively. Compounds **30** and **31** have benzoyl and trimethylsilyl (TMS) substituents, respectively, at the *p*-position of *p*-carborane. Compounds **34** and **35** are *m*- and *p*-carborane derivatives with a hexyl linker instead of a butylamide linker (**2c**). Furthermore, to compare the stereoelectronic properties of carborane and adamantane, compound **37** was also synthesized from the corresponding adamantylcarboxylic acid **36**.

Scheme 3. Synthesis of **2c** derivatives



(a) **20**, HATU, DIPEA, THF, r.t.; (b) (i) HCl, dioxane, r.t.; (ii) (*E*)-3-(pyridin-3-yl)acrylic acid, HATU, DIPEA, THF, r.t., 41%, 3 steps; (c) 5-aminopentan-1-ol , TEA, DCM, r.t.; (d) Phthalimide, PPh_3, DIAD, THF, r.t.; (e) (i) NH_2NH_2-H_2O, EtOH, reflux; (ii) (*E*)-3-(pyridin-3-yl)acrylic acid, HATU, DIPEA, DMF, r.t. (**25**: 11%, 4 steps, **34**: 10% 3 steps, **35**: 12%, 3 steps); (f) *n*-BuLi, PhCOCl, THF, -78 ℃ to 0 ℃, quant.; (g) *n*-BuLi, TMSCl, Et_2O, -78 ℃ to 0 ℃; (h) diisopropylamine, *n*-BuLi, CO_2, THF, -78 ℃ to 0 ℃; (i) **14**, HATU, DIPEA, DMF, r.t. (**30**: 43% 2 steps and **31**: 25%, 3 steps); (j) *n*-BuLi, PhthN$(CH_2)_6$OTs,[29] THF, -78 ℃ to 0 ℃; (k) **14**, HATU, DIPEA, DMF, r.t., 30%.

NAMPT enzymatic activity was evaluated using the CycLex® NAMPT colorimetric assay kit according to the manufacturer's protocols. The results are summarized in Table 1. Surprisingly, **6-11** did not exhibit higher inhibitory activity toward NAMPT than **1a** and **1b**. When designing the carborane-containing NAMPT inhibitor, to the docking calculations indicated selecting a pyridyl acrylamide head group (A) was optimal. Notably, the IC_{50} value of **1b** was 0.37 ± 0.03 μM, which was a little higher than the reported value.[10] Next, the IC_{50} values of **2b**, **2c**, and **19**, having a carborane amide, was significantly lower than **1a**, **1b**, or FK866. In particular, **2c** had the best NAMPT inhibitory activity: 10-fold higher than that of FK866. These results could be explained by the hydrogen bonding interaction between His191 and the carborane amide, as suggested by the docking simulations (Figure 3). Also, unlike the previous studies, compounds having a *p*-carborane

group were more effective than the *m*-carborane derivative by 2-fold. Therefore, the dihydrogen bonding, caused by polarization of carborane, may contribute further to the effectiveness of the *p*-carborane.

On the other hand, compound **19**, in which the phenyl group of FK866 was replaced by *p*-carborane, exhibited significant inhibition of NAMPT, in a level similar to that of **1b** (IC_{50} = 0.32 ± 0.05 μM), which was about twice as high as FK866. These results suggested that the three-dimensional volume, in addition to hydrophobicity, of the carborane skeleton was more suitable for the hydrophobic pocket of NAMPT.

Next, the NAMPT inhibitory activity among the compounds with carborane amide linkages, like **2b** or **2c**, were compared. First, the NAMPT inhibitory activity was markedly affected by linker length because the IC_{50} value of **22**, which had a shorter linker, was significantly increased while that of **25**, which had a longer linker, did not increase. We believe the binding site in NAMPT has a cylindrical shape, and when the linker was short (**22**), the head group could not reach the active site so that little inhibitory activity was observed. For **30**, the longer linker could be contained within the binding site; however, the distance between the carborane amide of **30** and H191 was too long for creating a hydrogen bond. Thus, the affinity of **30** with NAMPT was lower than that of **2c**.

Second, the NAMPT inhibitory activity of **30** and **31** were lower than that of **2c**. This decrease in affinity with NAMPT may have resulted from the steric hindrance of the additional substituent on the carborane.

Third, we elucidated that the hydrogen bond between amide bond of **2c** and H191 of NAMPT could increase the binding affinity. Comparing the IC_{50} value of **2c** with **35**, the NAMPT inhibitory activity of 35 was significantly lower than that of **2c**. Moreover, **34**, in which the *p*-carborane in **35** was changed to an *o*-carborane, showed the same result.

Finally, we elucidated that the carborane moiety increased the NAMPT inhibitory activity from comparing **2c** and **37**. **2c** had a 100-fold stronger inhibitory activity than adamantane-containing **37**.

Thus, **2c** was a potent NAMPT inhibitor because of the appropriate linker length, having a carborane moiety, and the presence of a hydrogen bond between the carborane amide and H191.

Table 1. IC_{50} values of the various carborane-containing derivatives

Compound	NAMPT IC_{50} [μM]
1a	0.61 ± 0.01
1b	0.37 ± 0.03
6	4.9± 0.2
7	> 30
8	> 30
10	> 30
11	> 30
2b	0.098 ± 0.008

2c	0.057 ± 0.001
19	0.32 ± 0.05
22	> 30
25	0.17 ± 0.02
30	0.63 ± 0.04
31	0.18 ± 0.01
34	0.37 ± 0.02
35	0.25 ± 0.06
37	8.0 ± 1
FK866	0.62 ± 0.05

Each compound was mixed with NAMPT in advance and the 1-step assay buffer from the CycLex® kit was added. The absorbance at 450 nm was measured and the inhibition rate of the compound against NAMPT could be calculated (n = 3).

To investigate the anticancer properties of the synthesized compounds, the cell viability of compounds **1a**, **2b**, and **2c**, which showed significant NAMPT inhibition, toward A549 (lung), MDA-MB 468 (breast), and HeLa (cervical) cells was evaluated by a MTT assay. The results are summarized in Table 2. Unfortunately, the synthesized compounds did not show higher cytotoxicity than FK866 for any of the cells tested. We believe that the water solubility of **2b** or **2c** was improved due to the carborane amide, resulting in decreased cell membrane permeability. On the other hand, a comparison between **2b** and **2c** indicated that the cytotoxicity difference between carborane isomers was independent of the specific cell line and the cytotoxicity increased proportionally to the NAMPT inhibitory activity.

Table 2. Cytotoxicity of the synthesized compounds against cancer cell lines.

	A549 [nM]	HeLa [nM]	MDA-MB 468 [nM]
1a	17.8 ± 8	32.3 ± 7	21.2 ± 3
2b	14.4 ± 5	25.6 ± 7	11.8 ± 3
2c	3.77 ± 0.8	14.4 ± 2	7.19 ± 0.6
FK866	1.74 ± 0.5	3.33 ± 0.3	2.83 ± 0.4

Comparing the NAMPT inhibitory activity of **19** with FK866, it was found that the activity was improved by replacing the phenyl group with a carborane. The activity was thought to be improved by the three-dimensional hydrophobicity of carborane. Furthermore, as shown in Figure 5-A, the docking simulation performed with **19** and NAMPT suggested that the carborane of compound **1** would be located at the position of the piperidine moiety of **19**. In addition, the IC_{50} value of **1a**, with a C4-linker, was 0.61 ± 0.01 μM and that of **34**, with a C6-linker, was 0.37 ± 0.02 μM, whereas that

of **6**, with a C5-linker, was 4.9 ± 0.2 μM. This activity cliff was interesting and lead us to believe that there were two potential carborane binding pockets in the active site of NAMPT.

Based on the hypothesis, dicarborane compound **38**, containing two carboranes, was designed. The docking simulation showed good overlap with **19** (Figure 5-C). Each carborane of **38** was located in the carborane binding sites for **1a** and **34** (Figure 5-D). Thus, we decided to synthesize the dicarborane compounds for further study.

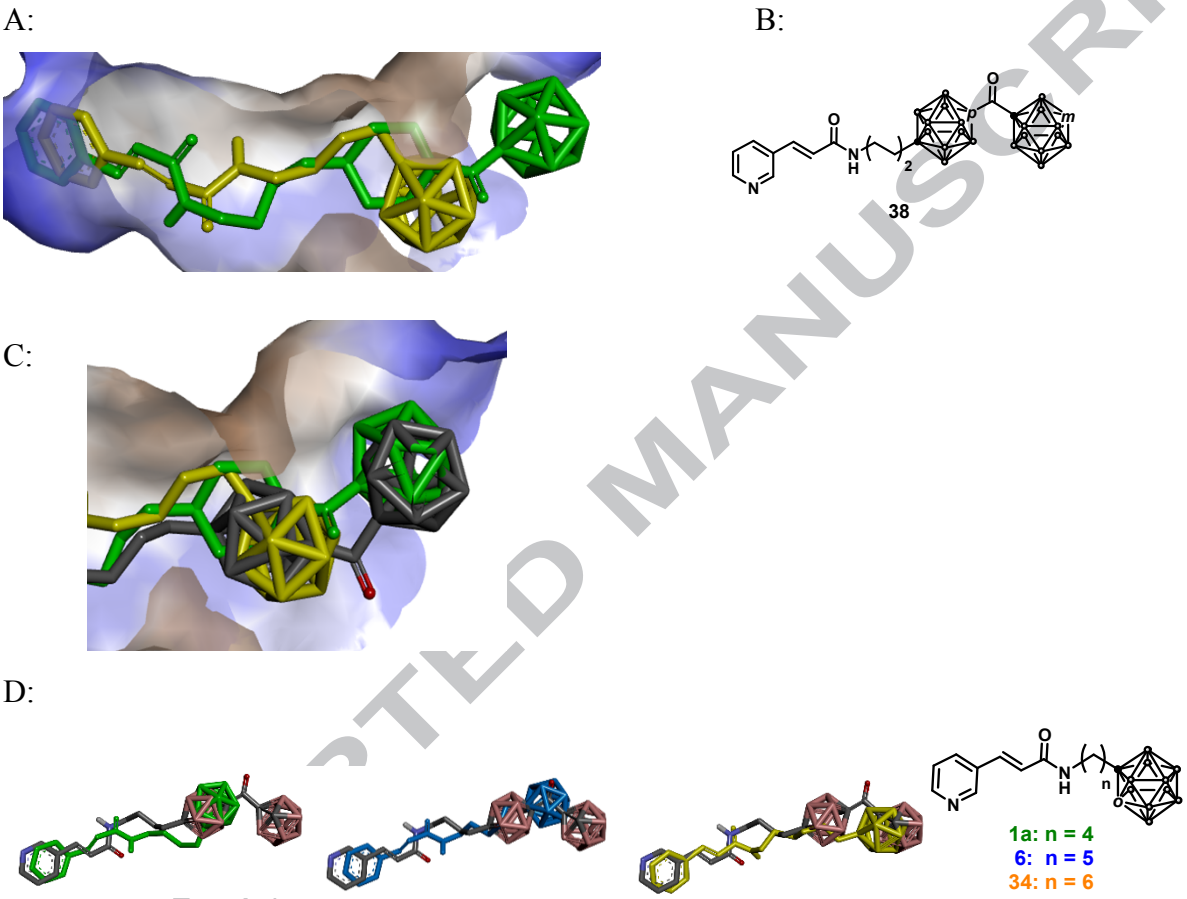
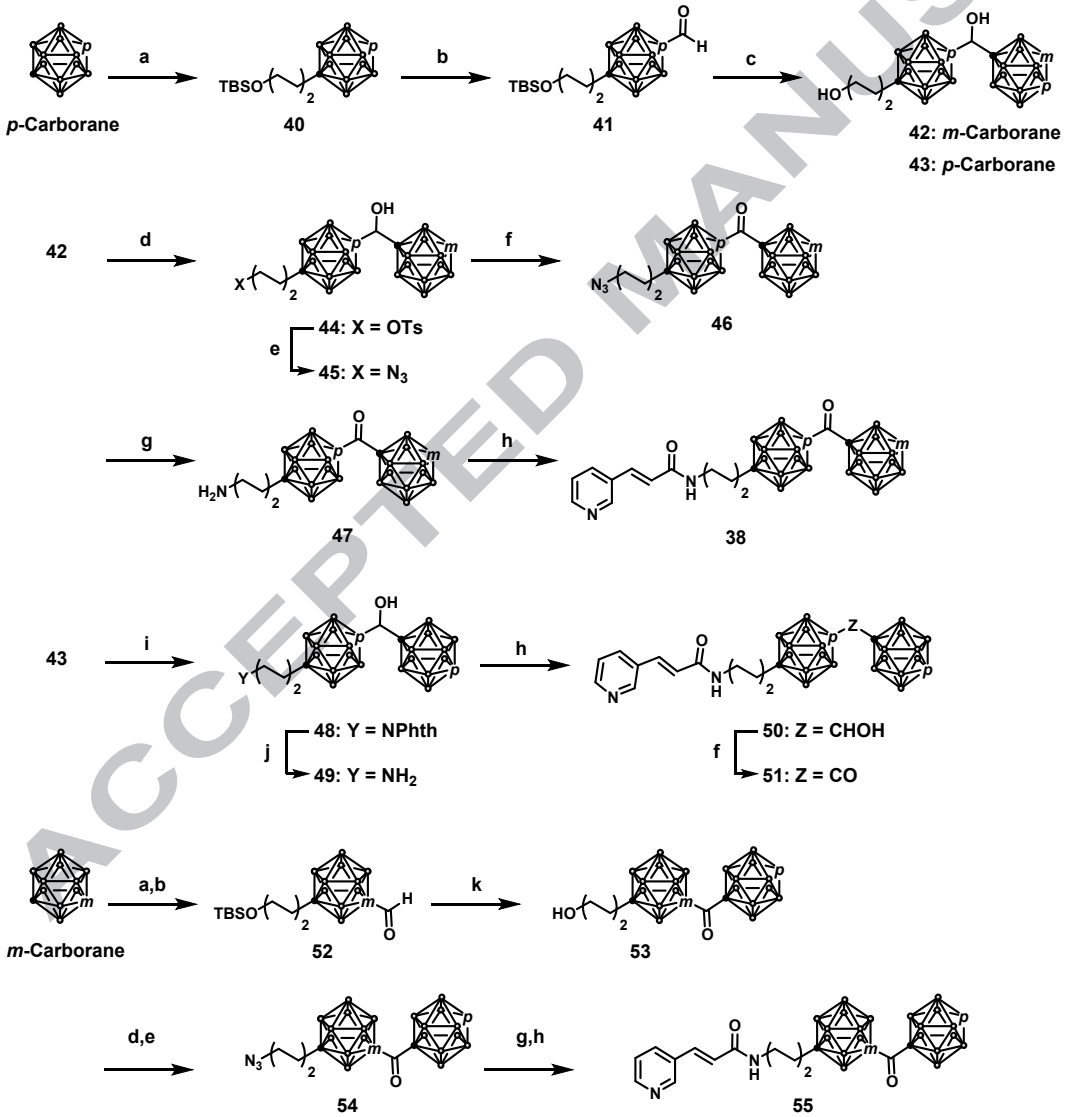


Figure 5. Docking experiments leading to the design of dicarborane compound **38**: (A) Comparisons of the docking models of **1a** (yellow) and **19** (green). (B) Structure of dicarborane compound **38**. (C) Comparisons of the docking models of **1a** (yellow), **19** (green), and **38** (black). (D) Merged images of dicarborane compound **38** with **1a** (green), **6** (blue), and **34** (yellow).

The synthesis of the dicarborane derivatives **38**, **50**, **51**, and **55** are shown in Scheme 4. *p*-Carborane was treated with *n*-BuLi in THF to generate the lithiated *p*-carborane. This was then reacted in situ with *tert*-butyl(4-iodobutoxy)dimethylsilane (**39**) to yield compound **40**. The lithiation of **40** with *n*-BuLi in THF was followed by formylation with methyl formate to afford **41.** This was then treated with lithiated *m*- or *p*-carboranes and followed by a HCl in dioxane work-up to yield the desilylated dicarboranederivatives **42** and **43**, respectively. The primary alcohol of **42** was tosylated

and then substituted with azide, and the resulting azide **45** was oxidized with Dess-Martin periodinane to yield dicarboranyl ketone **46**. After Staudinger reduction of the azide in **46** to an amino group, the resulting amine **47** was treated with (*E*)-4-(pyridin-4-yl)acrylic acid to afford dicarboranyl ketone **38**. On the other hand, *p*-carborane derivative **43** was converted to phthalimide by a Mitsunobu reaction to afford compound **48**, which was then converted to the corresponding amine **49** using hydrazine. Amine **49** was treated with the (*E*)-4-(pyridin-4-yl)acrylic acid to yield dicarborane carbinol **50**. This was then oxidized to dicarboranyl ketone **51**. In a similar manner, dicarboranyl ketone **55**, in which the *m*-carborane was bonded to the linker instead of *p*-carborane, was also synthesized.

Scheme 4. Synthesis of the dicarborane compounds



(a) **39**, *n*-BuLi, THF, 0 ℃; (b) *n*-BuLi, HCO_2CH_3, THF, -78 ℃; (c) (i) Carborane, *n*-BuLi, Et_2O, -78 ℃ to 0 ℃; (ii) HCl, dioxane, r.t.; (d) TsCl, TEA, DMAP, DCM, r.t.; (e) NaN_3, DMF, 80 ℃, 11%, 6 steps; (f) Dess-Martin periodinane, DCM, r.t., 53%; (g) PPh_3, THF/H_2O, r.t.; (h) (*E*)-4-

(pyridin-4-yl)acrylic acid, EDCI, HOBt, DIPEA, THF, r.t., (**38**: 43%, 3 steps, **50**: 29%, 3 steps, **55**: 37%, 7 steps; (i) Phthalimide, PPh_3, DIAD, THF, r.t.; (j) NH_2NH_2-H_2O, EtOH, reflux; (k) (i) *p*-Carborane, *n*-BuLi, Et_2O, -78 ℃ to 0 ℃; (ii) Dess-Martin periodinane, DCM, r.t. (iii) HCl, dioxane, r.t.

Next, we evaluated the NAMPT inhibitory activity of the synthesized compounds (Table 4). First, it was clear that the two hydrophobic pockets were indeed present since the dicarborane compounds showed a NAMPT inhibitory activity on the μM order. However, these compounds were less active than FK866 or **1a** and we believed that correct placement of the two carboranes was critical. In fact, the flexible secondary alcohol linker for the two carboranes was superior to the carbonyl linker in **51** for yielding an activity lower than 10 μM. Compound **55** was the most active diborane compound, so the placement of a terminal carborane was important for NAMPT inhibitory activity. Interestingly, comparing between **38** and **51**, the NAMPT inhibitory activity of **38**, in which the terminal carborane was a *m*-isomer, was higher than that of **51,** in which the terminal carborane was a *p*-isomer. This may suggest a difference in the manner that carborane isomers interact with proteins, specifically through a dihydrogen bond .

Table 4. Inhibition of NAMPT by the dicarborane compounds

Compound	IC_{50} [μM]
1a	0.61 ± 0.01
38	3.76 ± 0.5
50	4.51 ± 0.9
51	> 10
55	2.92 ± 0.5

3. Conclusion

We designed and synthesized a series of carborane derivatives as NAMPT inhibitors. Among the compounds synthesized, **2c** was found to be the most potent NAMPT inhibitor with an inhibitory activity more than 10 times higher than that of FK866. By performing docking simulations, the NAMPT inhibitory activity of **2c** was predicted to be improved because of the formation of a hydrogen bond between the carborane amide in **2c** and H191 in NAMPT. In fact, compound **35**, without a carborane amide, was approximately 4-fold less potent than **2c**, indicating that the carborane amide moiety is important for high NAMPT inhibitory activity. The activity was also believed to have improved by the three-dimensional hydrophobicity of carborane (comparing **2c** and **37**). Using **2c** to further our structure-activity relationship study, the following three issues were critically important: (1) a 4 carbon-chain linker was optimal, (2) a little space around the carborane is needed for flexibility and carborane positioning, and (3) the carborane amide skeleton was needed to establish a hydrogen bond with H191. Although dicarborane compounds **38**, **50**, **51**, and **55**, designed

by docking simulations, showed moderate NAMPT inhibitory activity, they were less effective than **2c**. The findings in this study are not only useful for the further design of NAMPT inhibitors, but also for carborane-based drug development.

4. Experimental Section

General Methods

NMR spectra were recorded on a Bruker biospin AVANCE II (400 MHz for 1H, 100 MHz for 13C) or a Bruker biospin AVANCE III (500 MHz for 1H, 125 MHz for 13C) instrument in the indicated solvent. Chemical shifts are reported in units per million (ppm) relative to the signal (0.00 ppm) for internal tetramethylsilane for solutions in $CDCl_3$ (7.26 ppm for 1H, 77.16 ppm for 13C). Multiplicities are reported using the following abbreviations: s; singlet, d; doublet, dd; doublet of doublets, t; triplet, q; quartet, m; multiplet, br; broad, J; coupling constants in Hertz. Mass spectra were measured using a JMS-700 Mstation. HRMS (EI, 70 eV) was calibrated as perfluorokerosene. All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) with UV light (254 nm) and were visualized using an aqueous alkaline $KMnO_4$ solution, ninhydrin AcOH solution and/or *p*-anisaldehyde EtOH solution. Column chromatography was performed on Silica Gel 60 N, purchased from Fuji Silysia Chemical Ltd. Microwave-assisted synthesis were performed on microwave synthesizer (Biotage, Initiator). Compound **1a** was known and synthesized from **3a** according to the literature procedures.

Synthesis of 1-(Phthalimido-*N*-pentyl)-1,2-dicarba-*closo*-dodecaborane (4b)

To a solution of alkyne **3b** (131 mg, 0.541 mmol) and *N,N*-dimethylaniline (103 μL, 0.812 mmol) in chlorobenzene, was added decaborane (79 mg, 0.649 mmol). The resulting mixture was stirred at 130 ℃ under argon atmosphere for 10 min with microwave synthesizer. The resulting mixture was added 1M HCl and Et_2O after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with Et_2O and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude materials were purified by column chromatography on silica gel (40% EtOAc in hexane) afforded **4b** as a white solid (184 mg, 0.531 mmol, quant.). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.85-7.83 (m, 2H), 7.73-7.71 (m, 2H), 3.67 (t, J = 5.8 Hz, 2H), 3.56 (s, 1H), 2.19 (t, J = 6.0 Hz, 2H), 1.67 (q, J = 6.0 Hz, 2H), 1.51 (q, J = 6.0 Hz, 2H),1.31 (q, J = 6.0 Hz, 2H), 2.5-1.6 (m, 10H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 168.5, 134.1, 132.2, 123.4, 75.2, 61.1, 38.0, 37.6, 28.8, 28.2, 26.2; ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.36, -5.824, -9.35, -11.5, -12.3, -13.2; HRMS (ESI, pos) for $C_{15}H_{25}B_{10}NO_2$ (m/z): calcd 382.2788 $(M+Na)^+$, found 303.2796.

Synthesis of 1-((*E*)-4-(3-(pyridin-3-yl)acrylamido)pentyl)-1,2-dicarba-*closo*-dodecaborane (6)

To a solution of phthalimide **4b** (84 mg, 0.234 mmol) in 2-propanol: water (6:1, v/v), was added

$NaBH_4$ (44 mg, 1.17 mmol). The resulting mixture was reacted at room temperature until the full conversion of a starting material was observed. After which, 12 M HCl aq. was slowly added and stirred at 80 ℃ for 6 h under argon atmosphere. The reaction mixture was concentrated under vacuum. The resulting ammonium salt **5b** was dissolved in water and washed twice with CH_2Cl_2. The aqueous phase was concentrated under vacuum, and the residue was dissolved in ethanol and filtered through a small cotton plug. After removal of ethanol under vacuum, the crude product was used for the next step without further purification. To a solution of the crude **5b**, (*E*)-3-(pyridin-3-yl)acrylic acid (35 mg, 0.234 mmol), and 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (89 mg, 0.234 mmol) in THF was slowly added *N,N*-diisopropylethylamine (DIEA) (102 μL, 0.585 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded **6** as a white solid (20 mg, 0.0554 mmol, 27% from **4b**). m.p. 167-168 ℃; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.75 (s, 1H), 8.58 (d, *J* = 2.2 Hz, 1H), 7.78 (d, *J* = 4.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.33-7.30 (m. 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 5.67 (s. 1H), 3.57 (s. 1H), 3.38 (ddd, *J* = 10, 5.0 Hz, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.61-1.50 (m. 4H), 1.37-1.33 (m. 2H), 2.5-1.9 (br. 10H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 165.3, 150.6, 149.3, 137.8, 134.5, 130.7, 123.8, 122.6, 61.17, 39.6, 38.1, 29.8, 29.5, 29.0, 26.4; ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.29, -5.77, -9.33, -11.5, -12.2, -13.2; HRMS (ESI, pos) for $C_{15}H_{28}B_{10}N_2O$ (m/z): calcd 383.3104 $(M+Na)^+$, found 383.3108.

Synthesis of 1-(5-(1*H*-Pyrrolo[3,2-*c*]pyridine-2-carboxamido)butyl)-1,2-dicarba-closo-dodecaborane (7)

This compound was prepared from compound **4a** (42 mg, 0.123 mmol) and 1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid (20 mg, 0.123 mmol) using the procedure described for **6**. Purification by column chromatography (10% MeOH in CH_2Cl_2) gave **7** in 62% yield as amorphous. ^{1}H NMR (500 MHz; CD_3CN): δ 8.92 (s, 1H), 8.26 (d, *J* = 6.0 Hz, 1H), 7.40 (d, *J* = 5.0 Hz, 1H), 7.06 (s, 1H), 4.12 (s, 1H), 3.34 (t, *J* = 6.0 Hz, 2H), 2.25 (t, *J* = 8.0 Hz, 2H), 1.94-1.91 (m. 2H), 1.53-1.48 (m. 2H), 2.5-1.6 (br. 10H); ^{13}C NMR (125 MHz; CD_3CN): δ161.8, 146.2, 143.0, 140.5, 133.8, 125.9, 108.0, 102.1, 77.4, 63.3, 39.2, 37.7, 29.4, 27.3; ^{11}B NMR (160 MHz; CD_3CN): δ -3.03, -6.31, -9.88, -11.60, -12.02, -13.26; ; HRMS (ESI, pos) for $C_{15}H_{26}B_{10}N_2O_1$ (m/z): calcd 361.3072 $(M+H)^+$, found 361.3070.

Synthesis of 1-(5-(*1H*-Pyrrolo[3,2-*c*]pyridine-2-carboxamido)pentyl)-1,2-dicarba-*closo*-dodecaborane (8)

This compound was prepared from compound **4b** (18 mg, 52.4 μmol) and 1*H*-pyrrolo[3,2-

c]pyridine-2-carboxylic acid (10 mg, 52.4 μmol) using the procedure described for **6**. Purification by column chromatography (10% MeOH in CH_2Cl_2) gave **8** in 26 % yield as a white solid. m.p. 148-149 ℃; ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.83 (bs, 1H), 9.00 (s, 1H), 8.35 (d, *J* = 5.5 Hz, 1H), 7.36 (d, *J* = 6.0 Hz, 1H), 6.91 (s, 2H), 6.36 (s, 1H), 3.57 (s, 1H), 3.52-3.48 (m, 2H), 2.21 (t, *J* = 5.6 Hz, 2H) 1.66 (q, *J* = 7.6 Hz, 2H), 1.53 (q, *J* = 8.0 Hz, 2H), 1.38 (q, *J* = 8.5 Hz, 2H), 2.5-1.9 (br. 10H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 165.4, 150.6, 149.3, 138.0, 134.6, 130.6, 123.9, 122.5, 75.1, 61.4, 39.0, 37.6, 29.2, 26.5; ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.17, -5.60, -9.25, -11.5, -12.2, -13.1; HRMS (ESI, pos) for $C_{15}H_{27}B_{10}N_3O_1$ (m/z): calcd 374.3237 $(M+H)^+$, found 374.3238.

Synthesis of 1-(4-Azidebutyl)-1,2-dicarba-*closo*-dodecaborane (9a)

To a solution of alkyne **3c** (48 μL, 0.400 mmol) and *N,N*-dimethylaniline (76 μL, 0.600 mmol) in chlorobenzene, was added decaborane (57 mg, 0.480 mmol). The resulting mixture was stirred at 130 ℃ under argon atmosphere for 10 min with microwave synthesizer. The resulting mixture was added 1M HCl and Et_2O after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with Et_2O and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The resulting crude material was used for the next step without further purification. To a solution of the crude material in dimethylformamide (DMF), was added sodium azide (78 mg, 1.20 mmol) at room temperature and then the mixture was stirred at 80 ℃ under argon atmosphere for 12 h. The reaction was quenched with water and the mixture was extracted with Et_2O, washed with brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography on silica gel (30% EtOAc in hexane) to afford azide **9a** as color less oil (55 mg, 0.228 mmol, 61%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.57 (s, 1H), 3.30 (s, 2H), 2.25-2.21 (m, 2H), 1.56 (m, 4H), 2.80-1.50 (m, 10H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 75.3, 61.7, 51.4, 38.2, 28.8, 27.0; ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.17, -5.60, -9.28, -11.5, -12.2, -13.1; HRMS (ESI, nega) for $C_6H_{19}B_{10}N_3$ (m/z): calcd 278.2241 $(M+Cl)^-$, found 278.2242.

Synthesis of 1-(5-Azidepentyl)-1,2-dicarba-*closo*-dodecaborane (9b)

This compound was prepared from compound **3d** (100 mg, 0.571 mmol) and decaborane (84 mg, 0.685 mmol) using the procedure described for **9a**. Purification by column chromatography (30% EtOAc in hexane) gave **9b** in 79% yield as a colorless liquid. ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.56 (s, 1H), 3.27 (t, *J* = 6.6 Hz, 2H), 2.21 (dd, *J* = 8.5 Hz, 17 Hz, 2H), 1.61-1.56 (m, 2H), 1.53-1.47 (m, 2H), 1.38-1.34 (m, 2H) ; ^{13}C NMR (125 MHz; $CDCl_3$): δ 75.1, 61.2, 51.2, 38.1, 28.9, 28.6, 26.2; ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.17, -5.60, -9.28, -11.5, -12.2, -13.1; HRMS (ESI, nega) for $C_7H_{21}B_{10}N_3$ (m/z): calcd 254.2658 $(M-H)^-$, found 254.2651.

Synthesis of 1-(4-(4-(Pyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)butyl)-1,2-dicarba-*closo*-dodecaborane (10)

To a solution of 3-ethynylpyridine (17 mg, 0.164 mmol) in DMF:H_2O (4:1, v/v), were added CuI (3.5 mg, 6.85 μmol), sodium ascorbate (7.2 mg, 0.0137 mmol) and azide **9a** (33mg, 0.137 mmol). The mixture was stirred at room temperature under argon atmosphere for 8 h. The reaction was quenched with water and the mixture was extracted with CH_2Cl_2, washed with brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography on silica gel (100% EtOAc) to afford **10** as a white solid (16.1 mg, 0.0467 mmol, 34%). m.p. 150-151 ℃; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.99 (d, *J* = 1.8 Hz, 1H), 8.59 (dd, *J* = 1.8 Hz, 6.0 Hz, 1H), 8.20 (td, *J* = 2.4 Hz, 6.0 Hz, 1H), 7.83 (s, 1H), 7.39 (dd, *J* = 6.0 Hz, 9.6 Hz, 1H), 4.43 (t, *J* = 8.7 Hz, 2H), 3.59 (s, 1H), 2.27 (dd, *J* = 11 Hz, 21 Hz, 2H), 2.00-1.93 (m, 2H), 1.61-1.53 (m, 2H), 3.00-1.50 (m, 10H).^{13}C NMR (125 MHz;$CDCl_3$): δ 149.5, 147.2, 145.1, 133.1, 126.7, 123.9, 119.9, 74.5, 61.3, 49.8, 37.4, 29.6, 26.2; ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.24, -5.65, -9.24, -11.6, -12.2, -13.0; HRMS (ESI, pos) for $C_{13}H_{24}B_{10}N_4$ (m/z): calcd 345.3083 $(M+H)^+$, found 345.3091.

Synthesis of 1-(4-(4-(Pyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)pentyl)-1,2-dicarba-*closo*-dodecaborane (11)

This compound was prepared from azide **9b** (58 mg, 0.198 mmol) and 3-ethynylpyridine (25 mg, 0.238 mmol) using the procedure described for **10**. Purification by column chromatography (100% EtOAc) gave **10** in 40% yield as a white solid. m.p. 85-86 ℃; ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.00 (d, *J* = 1.6 Hz, 1H), 8.60 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 8.22 (td, *J* = 1.9 Hz, 6.0 Hz, 1H), 7.85 (s, 1H), 7.40 (dd, *J* = 4.8 Hz, 8.0 Hz, 1H), 4.44 (t, *J* = 7.0 Hz, 2H), 3.58 (s, 1H), 2.20 (dd, *J* = 8.7 Hz, 17 Hz, 2H), 2.00 (tt, *J* = 7.7 Hz, 7.7 Hz, 2H), 1.57-1.50 (m, 2H), 1.38-1.33 (m, 2H), 3.00-1.60 (m, 10H); ^{13}C NMR (125 MHz;$CDCl_3$): δ 149.4, 147.1, 145.0, 133.1, 126.8, 124.0, 119.9, 74.9, 61.3, 50.3, 37.9, 30.0, 28.8, 26.0; ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.24, -5.65, -9.24, -11.6, -12.2, -13.0; HRMS (ESI, pos) for $C_{14}H_{26}B_{10}N_4$ (m/z): calcd 381.3060 $(M+Na)^+$, found 381.3056.

Synthesis of *tert*-Butyl (*E*)-(4-(3-(pyridin-3-yl)acrylamido)butyl)carbamate (13)

To a solution of **12** (226 mg, 1.20 mmol), carboxylic acid (149 mg, 1.00 mmol), and HATU (380 mg, 1.00 mmol) in THF (3 mL) was slowly added DIEA (261 μL, 1.50 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded **13** (390 mg, quant.) as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.72 (s, 1H), 8.53 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 4.0 Hz, 1H), 7.57-7.49 (m. 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 3.76-3.70 (m, 2H), 3.42-3.37 (m, 2H), 1.63-1.55 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 165.4, 156.4, 150.4, 149.2, 137.1, 134.4, 130.9, 123.8, 123.2, 79.5, 40.1, 39.6, 28.5, 28.0, 28.0, 26.2; HRMS (ESI, pos) for $C_{17}H_{25}N_3O_3$ (m/z): calcd 342.1788 $(M+Na)^+$, found 342.1787.

Synthesis of (*E*)-*N*-(4-(1,7-Dicarba-*closo*-dodecaboranyl)amidebutyl)-3-(pyridin-3-yl)acrylamide (2b)

To a solution of the dicarba-*closo*-dodecaborane-1-acetic acid **15b** (43 mg, 0.221 mmol) in toluene, was slowly added excess oxalyl chloride. After the resulting mixture was stirred at 60 ℃ under argon atmosphere for 12 h, the reaction mixture was concentrated under pressure. The crude materials **16b** were used to the next reaction without further purification.

In another flask, to a solution of **13** (47 mg, 0.147 mmol) in CH_2Cl_2, was slowly added TFA in dioxane. The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. After evaporation of the solvent, **14** was used to the next reaction without further purification.

To a solution of the unpurified amine **14** and triethylamine (60 μL, 0.441 mmol) in CH_2Cl_2, was slowly added dicarba-*closo*-dodecaborane-1-acetyl chloride (**16b**) in CH_2Cl_2 at 0 ℃. After the resulting mixture was stirred 0 ℃ under argon atmosphere for 1 h, the resulting mixture was added NH_4Cl aq. and CH_2Cl_2 after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with CH_2Cl_2 and combined organic layers were dried over sodium sulfate and concentrated under vacuum. Then, the crude materials were purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded **2b** as a white solid (24.4 mg, 0.063 mmol, 43%). m.p. 131-132 ℃; ^{1}H NMR (500 MHz; CD_3OD): δ 8.71 (s, 1H), 8.51 (dd, *J* = 5.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 16 Hz, 1H), 7.47 (dd, *J* = 5.0 Hz, 8.0 Hz, 1H), 6.72 (d, *J* = 16 Hz, 1H), 3.65 (s, 1H), 3.27 (t, *J* = 5.5 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 1.48-1.45 (m, 4H), 1.53-1.52 (m, 4H), 2.87-1.59 (m, 10H); ^{13}C NMR (125 MHz; CD_3OD): δ 167.7, 162.5, 150.7, 149.7, 137.4, 136.2, 132.9, 125.5, 124.8, 77.4, 56.8, 41.3, 40.1, 27.6, 27.5; ^{11}B NMR (160 MHz; CD_3OD): δ -5.61, -7.45, -11.1, -11.6, -13.4, -15.6; HRMS (ESI, pos) for $C_{15}H_{27}B_{10}N_3O_2$ (m/z): calcd 390.3187 $(M+H)^+$, found 390.3195.

Synthesis of (*E*)-*N*-(4-(1,12-Dicarba-*closo*-dodecaboranyl)amidebutyl)-3-(pyridin-3-yl)acrylamide (2c)

Preparation and purification of compound **2c** was carried out according to the procedure of compound **2b** (Yield: 63%). m.p. 173-174 ℃; ^{1}H NMR (500 MHz; CD_3OD): δ 8.70 (d, *J* = 2.0 Hz, 1H), 8.51 (dd, *J* = 1.3 Hz, 4.9 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 16 Hz, 1H), 7.47 (dd, *J* = 1.3 Hz, 8.0 Hz, 1H), 6.70 (d, *J* = 16 Hz, 1H), 3.35 (s, 1H), 3.27-3.25 (m, 2H), 3.27 (t, *J* = 13 Hz, 2H), 3.07 (t, *J* = 13 Hz, 2H), 1.47-1.46 (m, 2H), 2.87-1.59 (m, 10H); ^{13}C NMR (125 MHz; CD_3OD): δ 166.4, 163.5, 149.3, 148.3, 136.0, 134.9, 131.5, 124.2, 123.5, 54.5, 38.9, 38.7, 30.3, 26.2, 26.1; ^{11}B NMR (160 MHz; CD_3OD): δ -13.6, -15.2; HRMS (ESI, pos) for $C_{15}H_{27}B_{10}N_3O_2$ (m/z): calcd 413.2975 $(M+Na)^+$, found 413.2966.

Synthesis of *tert*-Butyl (*E*)-4-(4-(3-(pyridin-3-yl)acrylamido)butyl)piperidine-1-carboxylate (18)

To a solution of **17** (204 mg, 0.528 mmol) in EtOH (6.3 mL) was added hydrazine monohydrate (70 μL, 1.32 mmol). The resulting mixture was stirred at reflux temperature under argon atmosphere until the full conversion of a starting material was observed. After evaporation of the solvent, to the reaction mixture were added water and CH_2Cl_2. The product was partitioned between the aqueous and organic layers. The aqueous layer was washed with CH_2Cl_2 and combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude materials were used to the next reaction without further purification.

To a solution of adamantane-1-carboxylic acid (79 mg, 0.528 mmol), HATU (95 mg, 0.634 mmol) in THF (1.5 mL) was slowly added DIEA (138 μL, 0.792 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2) afforded **18** as a white solid (231 mg, 0.596 mmol, quant.). ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.72 (s, 1H), 8.53 (d, J = 2.2 Hz, 1H), 8.07 (d, J = 4.0 Hz, 1H), 7.57-7.49 (m. 2H), 6.74 (d, J = 8.0 Hz, 1H), 3.76-3.70 (m, 2H), 3.42-3.37 (m, 2H), 1.63-1.55 (m, 4H), 1.44 (s, 9H); HRMS (ESI, pos) for $C_{22}H_{33}N_3O_3$ (m/z): calcd 410.2414 $(M+Na)^+$, found 410.2420.

Synthesis of (*E*)-*N*-(4-(1-(1,12-Dicarba-*closo*-dodecaboranyl)piperidin-4-yl)butyl)-3-(pyridin-3-yl)acrylamide (19)

To a solution of 4 N HCl in dioxane was added **18** (54.0 mg, 0.139 mmol). The resulting mixture was stirred at room temperature for 12 h under argon atmosphere. The resulting mixture was concentrated under vacuum. It is used to the next step without further purification.

To a solution of the crude material, **15c** (32 mg, 0.167 mmol), and HATU (63 mg, 0.167 mmol) in THF was slowly added DIEA (50 μL, 0.278 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded products as a solid (2.3 mg, 0.0050 mmol, 3.6% 2 steps). m.p. 138-139 ℃; ^{1}H NMR (500 MHz; CD_3OD): δ 8.71 (d, J = 2.0 Hz, 1H), 8.51 (dd, J = 2.0 Hz, 4.9 Hz, 1H), 8.04 (dt, J = 2.0 Hz, 8.0 Hz 1H), 7.53 (d, J = 20 Hz, 1H), 7.47 (dd, J = 4.9 Hz, 8.0 Hz, 1H), 6.72 (d, J = 20 Hz, 1H), 4.35 (d, J = 10 Hz, 2H) 3.45 (s, 1H), 3.30-3.29 (m, 3H), 2.77 (t, J = 12.5 Hz, 2H), 1.72 (d, J = 12.5 Hz, 1H), 1.59-1.51 (m, 3H), 1.42-1.35 (m, 2H), 1.30-1.25 (m, 2H), 1.01-0.93 (m, 2H), 3.10-1.70 (m, 10H).^{13}C NMR (125 MHz; $CDCl_3$): δ 165.3, 159.2, 150.3, 149.1, 137.2, 134.4, 130.9, 123.8, 123.1, 83.8, 64.0, 47.3, 39.8, 35.9, 35.8, 32.6, 29.9, 24.0; ^{11}B NMR (160 MHz; CD_3OD): δ -12.6, -

15.3; HRMS (ESI, pos) for $C_{20}H_{35}B_{10}N_3O_2$ (m/z): calcd 493.3401 $(M+Cl)^-$, found 493.3391.

Synthesis of *tert*-Butyl (1,12-dicarba-*closo*-dodecaboranylamido)propyl)carbamate (22)

To a solution of **15c** (77 mg, 0.408 mmol), **20** (71 mg, 0.408 mmol) HATU (155 mg, 0.408 mmol) in THF (2 mL) was slowly added DIEA (100 µL, 0.612 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. It was used to the next step without further purification.

To a solution of 4 N HCl (100 µL, 0.408 mmol) in dioxane was added the crude material. The resulting mixture was stirred at room temperature for 12 h under argon atmosphere. The resulting mixture was concentrated under vacuum. It is used to the next step without further purification.

To a solution of the crude material, (*E*)-3-(pyridin-3-yl)acrylic acid (61 mg, 0.408 mmol), and HATU (155 mg, 0.408 mmol) in THF was slowly added DIEA (142 µL, 0.816 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded products as amorphous (48.6 mg, 0.129 mmol, 41%, 3 steps). ^{1}H NMR (500 MHz; CD_3OD): δ 8.72 (s, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 20 Hz, 1H), 7.43 (dd, J = 6.1 Hz, 8.6Hz, 1H), 6.67 (d, J = 20 Hz, 1H), 3.36 (bs, 1H), 3.23 (t, J = 10 Hz, 2H), 3.10 (t, J = 10 Hz, 2H), 1.62 (td, J = 5 Hz, 10 Hz, 2H); ^{11}B NMR (160 MHz; CD_3OD): δ -12.6, -15.3; ^{13}C NMR (125 MHz; CD_3OD): δ 168.0, 163.1, 150.7, 149.7, 137.6, 136.2, 132.8, 125.5, 124.6, 63.3, 55.8, 38.9, 37.7, 30.0; HRMS (ESI, pos) for $C_{14}H_{25}B_{10}N_3O_2$ (m/z): calcd 398.2855 $(M+Na)^+$, found 398.2849.

Synthesis of (*E*)-*N*-(4-(1,12-Dicarba-*closo*-dodecaboranyl)amidepentyl)-3-(pyridin-3-yl)acrylamide (25)

To a solution of 5-aminopentan-1-ol (103.2 mg, 1.00 mmo) and triethylamine (340 µL, 2.00 mmol) in CH_2Cl_2, was slowly added carbonic acid chloride in CH_2Cl_2 at 0 ℃. After the resulting mixture was stirred 0 ℃ under argon atmosphere for 1 h, the resulting mixture was added NH4Cl aq. and CH_2Cl_2 after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with CH_2Cl_2 and combined organic layers were dried over sodium sulfate and concentrated under vacuum. It was used to the next step without further purification.

To a solution of PPh3 (262 mg, 1.00 mmol), phthalimide (220 mg, 1.00 mmol) in THF was slowly added 1.9 M diisopropyl azodicarboylate in Toluene (526 µL, 1.00 mmol) at 0 ℃. The resulting

mixture was stirred at room temperature for 1 h under argon atmosphere. To the resulting mixture was added the crude material at 0 ℃. The resulting mixture was stirred at room temperature for 16 h. After evaporation of solvent, it was used to the next step without further purification.

To a solution of the crude material in EtOH was added Hydrazine Monohydrate (125 μL, 2.50 mmol). The resulting mixture was stirred at reflux temperature for 12 h. After evaporation of the solvent, the crude product was resolved in CH_2Cl_2 and filtered. The filtrate was concentrated under vacuum. The crude materials were used as amine to the next reaction without further purification.

To a solution of the crude material, (*E*)-3-(pyridin-3-yl)acrylic acid (149 mg, 1.00 mmol), and HATU (380 mg, 1.00 mmol) in THF (1 mL) was slowly added DIEA (348 μL, 2.00 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded products as a white solid (45.5 mg, 0.113 mmol, 11%, 4 steps). m.p. 85-86 ℃; ^{1}H NMR (500 MHz; CD_3OD): δ 8.71 (d, *J* = 2.0 Hz, 1H), 8.51 (dd, *J* = 6.1 Hz, 2.0 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 20 Hz, 1H), 7.46 (dd, *J* = 6.1 Hz, 8.6 Hz, 1H), 6.73 (d, *J* = 20 Hz, 1H), 3.32 (bs, 1H), 3.28 (t, *J* = 7.0 Hz, 2H), 1.54 (quin, *J* = 7.0 Hz, 2H), 1.44 (quin, *J* = 7.0 Hz, 2H), 1.29-1.23 (m, 2H), 2.97-1.85 (m, 10H); ^{11}B NMR (160 MHz; CD_3OD): δ -12.6, -15.3; ^{13}C NMR (125 MHz; CD_3OD): δ 167.6, 163.0, 150.7, 149.7, 137.3, 136.2, 132.9, 125.5, 124.8, 84.4, 63.2, 41.3, 40.4, 29.9, 29.6, 24.9; HRMS (ESI, pos) for $C_{15}H_{29}B_{10}N_3O_2$ (m/z): calcd 426.3163 $(M+Na)^+$, found 426.3169.

Synthesis of 1-Benzoyl-1,12-dicarba-*closo*-dodecaborane (26)

To a solution of *p*-carborane (200 mg, 1.39 mmol) in Et_2O, was slowly added *n*-BuLi 1.6 M solution in hexane (984 μL, 1.53 mmol) at -78 ℃. After the resulting mixture was stirred -78 ℃ under argon atmosphere for 1 h, benzoyl chloride (176 μL, 1.53 mmol) was added. Then, the resulting mixture was stirred at room temperature for 2 h. After that, the reaction mixture was concentrated under pressure. The resulting mixture was added water and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (10 % Et_2O in hexane) afforded products as white solid (356.4 mg, 1.435 mmol, quant.). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.48-7.44 (m, 3H), 7.36-7.32 (m, 2H), 2.88 (s, 1H), 3.01-1.57 (m, 10H); ^{11}B NMR (160 MHz; $CDCl_3$): δ -12.6, -15.3; ^{13}C NMR (125 MHz; $CDCl_3$): δ 189.7, 136.4, 131.9, 128.3, 87.3, 63.6; HRMS (ESI, pos) for $C_9H_{16}B_{10}O$ (m/z): calcd 271.2101 $(M+Na)^+$, found 271.2093.

Synthesis of (*E*)-*N*-(4-(1-Benzoyl-1,12-dicarba-*closo*-dodecaboran-12-yl)amidebutyl)-3-

(pyridin-3-yl)acrylamide (30)

To a solution of isopropyl amine (18 μL, 0.127 mmol) in Et2O, was *n*-BuLi 1.6 M solution in hexane (71 μL, 0.110 mmol) slowly added at 0 ℃. After the resulting mixture was stirred 0 ℃ under argon atmosphere for 1 h, was added a solution of **26** (21 mg, 0.0846 mmol). Then, the resulting mixture was stirred at room temperature CO_2 atmosphere for 3 h. After that, the reaction mixture was concentrated under pressure. The resulting mixture was added and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane. Then, the aqueous layer was added 6 M HCl and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude materials were used to the next reaction without further purification.

To a solution of the crude material, excess amount of **14** and HATU (48 mg, 0.127 mmol) in THF was slowly added DIEA (44 μL, 0.254 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded products as a solid (18.0 mg, 0.0365 mmol, 43%, 2 steps). m.p. 64-65 ℃; ^{1}H NMR (500 MHz; CD_3OD): δ 8.71 (d, *J* = 2.0 Hz, 1H), 8.51 (dd, *J* = 6.1 Hz, 2.0 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.56-7.40 (m, 7H), 6.70 (d, *J* = 20 Hz, 1H), 3.29-3.26 (m, 2H), 3.09-3.06 (m, 2H), 1.47-1.45 (m, 4H), 3.20-1.88 (m, 10H); ^{11}B NMR (160 MHz; CD_3OD): δ -12.6, -15.3; ^{13}C NMR (125 MHz; CD_3OD): δ 189.3, 166.3, 161.2, 149.3, 148.3, 136.1, 136.0, 134.9, 131.8, 131.5, 127.8, 127.6, 124.1, 123.4, 85.2, 83.4, 39.8, 38.7, 26.2, 26.1; HRMS (ESI, pos) for $C_{22}H_{31}B_{10}N_3O_3$ (m/z): calcd 517.3242 $(M+Na)^+$, found 517.3233.

Synthesis of (*E*)-*N*-(4-(1-Trimethylsilyl-1,12-dicarba-*closo*-dodecaboran-12-yl)amidebutyl)-3-(pyridin-3-yl)acrylamide (31)

To a solution of *p*-carborane (27 mg, 0.185 mmol) in Et2O, was slowly added *n*-BuLi 1.6 M solution in hexane (120 μL, 0.185 mmol) at -78 ℃. After the resulting mixture was stirred -78 ℃ under argon atmosphere for 1 h, TMSCl (23 μL, 0.185 mmol) was added. Then, the resulting mixture was stirred at room temperature for 2 h. After that, the reaction mixture was concentrated under pressure. The resulting mixture was added water and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were dried over sodium sulfate and concentrated under vacuum. It is used to the next step without further purification.

To a solution of the crude material in Et2O, was slowly added *n*-BuLi 1.6 M solution in hexane (120 μL, 0.185 mmol) at -78 ℃. The resulting mixture was stirred at room temperature under argon

atmosphere for 1.5 h. The resulting mixture was stirred at room temperature CO2 atmosphere for 3 h. After that, the reaction mixture was concentrated under pressure. The resulting mixture was added water and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane. Then, the aqueous layer was added 6 M HCl and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was used to the next reaction without further purification.

To a solution of the crude material, excess amount of **14** and HATU (70 mg, 0.185 mmol) in THF (1 mL) was slowly added DIEA (64 µL, 0.370 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded products as a solid (21.0 mg, 0.0455 mmol, 25%, 3 steps). m.p. 65-66 ℃; ^{1}H NMR (500 MHz; CD_3OD): δ 8.72 (d, *J* = 2.0 Hz, 1H), 8.53 (dd, *J* = 6.1 Hz, 2.0 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 20 Hz, 1H), 7.49 (dd, *J* = 6.1 Hz, 8.6 Hz, 1H), 6.72 (d, *J* = 20 Hz, 1H), 3.33-3.22 (m, 2H), 3.09-3.08 (m, 2H), 1.49-1.47 (m, 4H), 2.95-1.71 (m, 10H), 0.01 (s, 9H) ; ^{11}B NMR (160 MHz; CD_3OD): δ -12.6, -15.3; ^{13}C NMR (125 MHz; CD_3OD): δ 166.3, 161.7, 149.3, 148.3, 148.3, 136.0, 134.9, 131.5, 124.2, 123.4, 85.8, 71.6, 39.7, 38.7, 26.2, 26.1, -2.69; HRMS (ESI, pos) for $C_{18}H_{35}B_{10}N_3O_2Si$ (m/z): calcd 485.3374 $(M+Na)^+$, found 485.3376.

Synthesis of 1-((*E*)-4-(3-(Pyridin-3-yl)acrylamido)hexyl)-1,2-dicarba-*closo*-dodecaborane (34)

To a solution of *o*-carborane (40 mg, 0.277 mmol) in THF (2 mL) was slowly added *n*-BuLi 1.6 M solution in hexane (179 µL, 0.277 mmol) at 0 ℃. The resulting mixture was stirred at 0 ℃ for over 1 h under argon atmosphere. Then $PhthN(CH_2)_6OTs$[29] (111 mg, 0.277 mmol) was added at 0 ℃. After the resulting mixture was stirred for 12 h at room temperature, the resulting mixture was added water and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel afforded products. The crude material was used to the next reaction without further purification.

To a solution of the crude material in 2-propanol:water (2.0 mL, 6:1, v/v), was added NaBH4 (52 mg, 1.39 mmol). The resulting mixture was stirred at room temperature. After 2 h, conc.HCl (200 µL) was added after which was reacted at 80 ℃ for 6 h under argon atmosphere. The reaction mixture was dried by repeated co-concentration with methanol. The product was dissolved in water and washed twice with CH2Cl2. The aqueous phase was concentrated in vacuo, dissolved in ethanol and

filtered through a small cotton plug. The crude material was used without further purification.
To a solution of the crude material, (*E*)-3-(pyridin-3-yl)acrylic acid (41 mg, 0.277 mmol) and HATU (105 mg, 0.277 mmol) in THF (500 µL) was slowly added DIEA (97 µL, 0.554 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2) afforded products as a solid (10.5 mg, 0.028 mmol, 10%, 3 steps). m.p. 125-126 ℃; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.71 (d, *J* = 2.0 Hz, 1H), 8.51 (dd, *J* = 6.1 Hz, 2.0 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 20 Hz, 1H), 7.46 (dd, *J* = 6.1 Hz, 8.6 Hz, 1H), 6.73 (d, *J* = 20 Hz, 1H), 4.52 (bs, 1H), 2.27 (m, 2H), 1.58-1.46 (m, 4H), 1.40-1.29 (m, 6H), 2.97-1.85 (m, 10H); ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.24, -5.65, -9.24, -11.6, -12.2, -13.0; ^{13}C NMR (125 MHz; $CDCl_3$): δ 167.6, 150.7, 149.6, 137.3, 136.2, 132.9, 125.5, 124.8, 86.0, 59.7, 40.4, 40.0, 30.4, 30.2, 29.7, 27.5; HRMS (ESI, pos) for $C_{16}H_{30}B_{10}N_2O$ (m/z): calcd 374.3476 $(M+H)^+$, found 374.3463.

Synthesis of 1-((*E*)-4-(3-(Pyridin-3-yl)acrylamido)hexyl)-1,12-dicarba-*closo*-dodecaborane (35)
To a solution of *p*-carborane (40 mg, 0.277 mmol) in THF (2 mL) was slowly added *n*-BuLi 1.6 M solution in hexane (179 µL, 0.277 mmol) at 0 ℃. The resulting mixture was stirred at 0 ℃ for over 1 h under argon atmosphere. Then $PhthN(CH_2)_6OTs$ (111 mg, 0.277 mmol) was added at 0 ℃. After the resulting mixture was stirred for 12 h at room temperature. The resulting mixture was added water and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel afforded products. The crude material was used to the next reaction without further purification.
To a solution of the crude material in EtOH (1 mL) was added hydrazine monohydrate (19 µL, 0.277 mmol). The resulting mixture was stirred at reflux temperature for 6.5 h under argon atmosphere. After evaporation of solvent, to the reaction mixture were added water and CH_2Cl_2. The product was partitioned between the aqueous and organic layers. The aqueous layer was washed with CH_2Cl_2 and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude material was used without further purification.
To a solution of the crude material, (*E*)-3-(pyridin-3-yl)acrylic acid (41 mg, 0.277 mmol) and HATU (105 mg, 0.277 mmol) in THF (500 µL) was slowly added DIEA (97 µL, 0.554 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and

concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2) afforded products as a white solid (12 mg, 0.033 mmol, 12%, 3 steps). m.p.147-148 ℃; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.71 (s, 1H), 8.51 (s, 1H), 8.04 (s, 1H), 7.57-7.47 (m, 2H), 6.71 (m, 1H), 3.27 (m, 2H), 3.10 (bs. 1H), 1.64 (s. 2H), 1.51 (m, 2H), 1.30 (bs, 2H), 1.18 (m, 4H), 2.5-1.9 (br. 10H); ^{11}B NMR (160 MHz; CD_3OD): δ -13.0, -15.9; ^{13}C NMR (125 MHz; $CDCl_3$): δ 167.6, 150.7, 149.6, 137.3, 136.2, 132.9, 125.5, 124.8, 86.0, 59.7, 40.4, 40.0, 30.4, 30.2, 29.7, 27.5; HRMS (ESI, pos) for $C_{16}H_{30}B_{10}N_2O$ (m/z): calcd 397.3261 $(M+Na)^+$, found 397.3268.

Synthesis of (3*r*,5*r*,7*r*)-*N*-(4-((*E*)-3-(pyridin-3-yl)acrylamido)butyl)adamantane-1-carboxamide (37)

To a solution of adamantane-1-carboxylic acid (30 mg, 0.166 mmol), excess amount of **14**, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (34 mg, 0.177 mmol), 1-hydroxybenzotriazole (HOBt) (34 mg, 0.249 mmol) in THF was slowly added DIEA (87 µL, 0.498 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until the full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2) afforded **37** as a white solid (19.2 mg, 0.0503 mmol, 30%). m.p. 194-195 ℃; ^{1}H NMR (400 MHz; CD_3OD): δ 8.71 (d, *J* = 1.6 Hz, 1H), 8.51 (dd, *J* = 6.0 Hz, 1.6 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 20 Hz, 1H), 7.47 (dd, *J* = 6.0 Hz, 8.0 Hz, 1H), 6.72 (d, *J* = 20 Hz, 1H), 3.34-3.22 (m, 2H), 3.09-3.08 (m, 2H), 2.00 (s, 3H), 1.86-1.71 (m, 12H), 1.56 (t, *J* = 3.2 Hz, 4H); ^{13}C NMR (125 MHz; CD_3OD): δ 181.0, 167.7, 150.7, 149.7, 137.4, 136.2, 132.9, 125.5, 124.9, 41.8, 20.3, 40.3, 40.2, 40.0, 37.6, 29.7, 28.0, 27.7; HRMS (ESI, pos) for $C_{23}H_{31}N_3O_2$ (m/z): calcd 404.2308 $(M+Na)^+$, found 404.2328.

Synthesis of (4-(4-Azidobutyl)-1,12-dicarba-*closo*-dodecaboranyl) (1,7-dicarba-*closo*-dodecaboranyl)methanol (45)

To a solution of *p*-carborane (72 mg, 0.50 mmol) in THF (4 mL) was slowly added *n*-BuLi 1.6 M solution in hexane (318 µL, 0.50 mmol) at -78 ℃. The resulting mixture was stirred at 0 ℃ for over 1 h under argon atmosphere. Then **39** (157 mg, 0.50 mmol) was added at -78 ℃. After the resulting mixture was stirred for 12 h at room temperature, the resulting mixture was added water and hexane after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel afforded products. Then, the crude material **40** was used to the next reaction without further purification.

To a solution of the crude material **40** in THF (2 mL), was slowly added *n*-BuLi 1.6 M solution in

hexane (318 μL, 0.50 mmol) at 0 ℃. After the resulting mixture was stirred at 0 ℃ under argon atmosphere for 1 h, the resulting mixture was cooled to -78 ℃. Methyl formate (62 μL, 1.00 mmol) was slowly added the resulting mixture was stirred at the same temperature for 2 h. After that, the resulting mixture was quenched by NH_4Cl aq. and concentrated under pressure. The resulting mixture was added water and hexane, after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were dried over sodium sulfate and concentrated under vacuum. Then, the crude material **41** was used to the next reaction without further purification.

To a solution of *m*-carborane (72 mg, 0.50 mmol) in Et_2O (2 mL), was slowly added *n*-BuLi 1.6 M solution in hexane (318 μL, 0.50 mmol) at 0 ℃. After the resulting mixture was stirred at -78 ℃ under argon atmosphere for 1 h, the resulting mixture was cooled to -78 ℃. The crude material **41** in Et_2O was slowly added the resulting mixture was stirred at the same temperature for 2 h. After that, the resulting mixture was quenched by NH_4Cl aq., the resulting mixture was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined organic layers were dried over sodium sulfate and concentrated under vacuum. Next, to a solution of 4M HCl in Dioxane (500 μL) was added the crude material at room temperature. After the resulting mixture was stirred for 12 h, and concentrated under vacuum. Then, the crude material **42** was used to the next reaction without further purification.

To a solution of the crude material **42**, triethylamine (205 μL, 1.50 mmol), and DMAP (6.1 mg, 0.050 mmol) in dichloromethane, was slowly added *p*-toluenesulfonylchloride (191 mg, 1.00 mmol) at room temperature. After the resulting mixture was stirred at room temperature under argon atmosphere until full conversion of a starting material was observed. The resulting mixture was added water and CH_2Cl_2 after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with CH_2Cl_2 and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material **44** was used to the next reaction without further purification.

To a solution of the crude material **44** in dimethylformamide, was added sodium azide (162 mg, 2.50 mmol). After the resulting mixture was stirred at 80 ℃ under argon atmosphere until full conversion of a starting material was observed. The resulting mixture was added water and Et_2O after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with Et_2O and combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel afforded **45** as a colorless oil (23.8 mg, 0.0570 mmol, 11%, 6 steps).

^{1}H NMR (400 MHz; $CDCl_3$): δ3.84 (d, J = 8.0 Hz, 1H), 3.20 (t, J = 10.8 Hz, 2H), 3.10-1.60 (m, 20H), 2.85 (s, 1H), 2.23 (d, J = 8.0 Hz, 1H), 1.67-1.62 (m, 2H), 1.44-1.37 (m, 2H), 1.26-1.23 (m, 2H); ^{11}B NMR (160 MHz; $CDCl_3$): δ –3.99, -6.94, -11.2, -13.2, -15.6; ^{13}C NMR (125 MHz; $CDCl_3$): δ 84.4, 82.6, 74.5, 66.0, 51.1, 37.5, 28.5, 26.2; HRMS (ESI, pos) for $C_9H_{31}B_{20}N_3O$ (m/z): calcd 436.4367 $(M+Na)^+$, found 436.4367.

Synthesis of (*E*)-*N*-(4-(4-(1,7-Dicarba-*closo*-dodecaboranecarbonyl) -1,12-dicarba-*closo*-dodecaboranyl)butyl)-3-(pyridin-3-yl)acrylamide (38)

To a solution of **45** (8.3 mg, 0.020 mmol) in CH_2Cl_2 was added Dess–Martin periodinane (20 mg, 0.040 mmol) at room temperature. The resulting mixture was stirred under argon atmosphere until full conversion of a starting material was observed. The resulting mixture was quenched by $NaHCO_3$ aq., after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with CH_2Cl_2 and combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under vacuum. Then, the crude material is used to the next step without further purification.

To a solution of the crude material in THF : H_2O (500 µL, 10:1, v/v), was added PPh_3 (10 mg, 0.040 mmol). The resulting mixture was stirred at room temperature for 12 h under argon atmosphere. After evaporation of solvent, the crude product **47** was used to the next reaction without further purification.

To a solution of the crude material **47**, (*E*)-3-(pyridin-3-yl)acrylic acid (3.0 mg, 0.020 mmol), EDCI (4.6 mg, 0.024 mmol), HOBt (4.6 mg, 0.030 mmol) in THF was slowly added DIEA (10 µL, 0.060 mmol, 3.0). The resulting mixture was stirred at room temperature under argon atmosphere until full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2) afforded **38** as a white solid (4.4 mg, 8.5 µmol, 43%, 3 steps). m.p. 127-128 ℃; ^{1}H NMR (500 MHz; CD_3OD): δ 8.71 (s, 1H), 8.51 (d, *J* = 5.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 15 Hz, 1H), 7.47 (dd, *J* = 5.0 Hz, 8.0 Hz, 1H), 6.70 (d, *J* = 15 Hz, 1H), 3.72 (s, 1H), 3.22 (t, *J* = 7.0 Hz, 2H), 3.10-1.60 (m, 20H), 1.72 (t, *J* = 8.5 Hz, 1H), 1.41-1.37 (m, 2H), 1.24-1.21 (m, 2H); ^{11}B NMR (160 MHz; $CDCl_3$): δ -4.56, -10.9, -13.1, -14.9; ^{13}C NMR (125 MHz; CD_3OD): δ 181.7, 167.7, 150.7, 149.7, 137.5, 136.3, 132.9, 125.6, 124.7, 79.5, 57.5, 57.1, 54.8, 39.9, 39.0, 29.7, 27.8; HRMS (ESI, pos) for $C_{17}H_{36}B_{20}N_2O_2$ (m/z): calcd 540.4652 $(M+Na)^+$, found 540.4637.

Synthesis of (*E*)-*N*-(4-(4-(1,12-Dicarba-*closo*-dodecaboranyl(hydroxy)methyl) -1,12-dicarba-*closo*-dodecaboranyl)butyl)-3-(pyridin-3-yl)acrylamide (50)

To a solution of *p*-carborane (34 mg, 0.240 mmol) in Et_2O (2 mL), was slowly added *n*-BuLi 1.6 M solution in hexane (151 µL, 0.240 mmol) at 0 ℃. After the resulting mixture was stirred at -78 ℃ under argon atmosphere for 1 h, the resulting mixture was cooled to -78 ℃. The crude material **41** (described above) was slowly added the resulting mixture was stirred at the same temperature for 2 h. After that, the resulting mixture was quenched by NH_4Cl aq., the resulting mixture was partitioned between the aqueous and organic layers. The aqueous layer was washed with hexane and combined

organic layers were dried over sodium sulfate and concentrated under vacuum. Next, to a solution of 4M HCl in Dioxane (500 µL) was added the crude material at room temperature. After the resulting mixture was stirred for 12 h, and concentrated under vacuum. Then, the crude product was used to the next reaction without further purification.

To a solution of PPh_3 (63 mg, 0.240 mmol), phthalimide (35 mg, 0.240 mmol) in THF (1.5 mL) was slowly added 1.9 M diisopropyl azodicarboylate in toluene (126 µL, 0.240 mmol) at 0 ℃. The resulting mixture was stirred at room temperature for 1 h under argon atmosphere. To the resulting mixture was added the crude material at 0 ℃. The resulting mixture was stirred at room temperature for 16 h. After evaporation of solvent, the crude product was used to the next reaction without further purification.

To a solution of the crude material in EtOH, was added hydrazine monohydrate (30 µL, 0.600 mmo). The resulting mixture was stirred at reflux temperature under argon atmosphere until full conversion of a starting material was observed. After evaporation of solvent, to the reaction mixture were added water and CH_2Cl_2. The product was partitioned between the aqueous and organic layers. The aqueous layer was washed with CH_2Cl_2 and combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude materials were used to the next reaction without further purification.

To a solution of the crude material, (*E*)-3-(pyridin-3-yl)acrylic acid (36 mg, 0.240 mmol), EDCI (55 mg, 0.029 mmol), HOBt (55 mg, 0.360 mmol) in THF was slowly added DIEA (126 µL, 0.720 mmol). The resulting mixture was stirred at room temperature under argon atmosphere until full conversion of a starting material was observed. The resulting mixture was added aq. $NaHCO_3$ and EtOAc after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with EtOAc and combined organic layers were dried over sodium sulfate and concentrated under vacuum. Then, the crude material was purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2) afforded **50** as a white solid (36 mg, 0.0686 mmol, 29%, from **41**). m.p. 204-205 ℃; ^{1}H NMR (500 MHz; CD_3OD): δ 8.71 (s, 1H), 8.51 (d, *J* = 5.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 15 Hz, 1H), 7.47 (dd, *J* = 5.0 Hz, 8.0 Hz, 1H), 6.70 (d, *J* = 15 Hz, 1H), 3.44 (s, 1H), 3.25 (s, 1H), 3.21 (t, *J* = 8.0 Hz, 2H), 2.90-1.50 (m, 20H), 1.67 (t, *J* = 8.5 Hz, 1H), 1.40-1.37 (m, 2H), 1.24-1.19 (m, 2H); ^{11}B NMR (160 MHz; $CDCl_3$): δ -12.9, -15.7; ^{13}C NMR (125 MHz; CD_3OD): δ 167.7, 150.7, 149.7, 137.5, 136.3, 132.9, 125.5, 124.7, 90.6, 85.3, 75.6, 64.4, 54.8, 40.0, 38.5, 29.8, 28.0; HRMS (ESI, pos) for $C_{17}H_{38}B_{20}N_2O_2$ (m/z): calcd 542.4809 $(M+Na)^+$, found 542.4813.

Synthesis of (*E*)-*N*-(4-(4-(1,12-Dicarba-*closo*-dodecaboranecarbonyl) -1,12-dicarba-*closo*-dodecaboranyl)butyl)-3-(pyridin-3-yl)acrylamide (51)

To a solution of **50** (16.3 mg, 0.029 mmol) in CH_2Cl_2 (500 µL) was added Dess–Martin periodinane (24.6 mg, 0.058 mmol) at room temperature. The resulting mixture was stirred under argon atmosphere until full conversion of a starting material was observed. The resulting mixture was

quenched by $NaHCO_3$ aq., after which the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with CH_2Cl_2 and combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2) afforded products as a white solid (8.1 mg, 0.0155 mmol, 53%). m.p. 176-177 ℃; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.74 (s, 1H), 8.57 (d, *J* = 4.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 16 Hz, 1H), 7.30 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 6.43 (d, *J* = 16 Hz, 1H), 5.72 (s, 1H), 3.28 (dd, *J* = 7.0 Hz, 14 Hz, 2H), 2.87 (s, 1H), 2.90-1.60 (m, 20H), 1.62 (t, *J* = 8.5 Hz, 1H), 1.41-1.35 (m, 2H), 1.25-1.16 (m, 2H); ^{11}B NMR (160 MHz; $CDCl_3$): δ -13.0, -15.4; ^{13}C NMR (125 MHz; $CDCl_3$): δ 180.5, 165.2, 150.5, 149.2, 137.7, 134.5, 130.7, 123.8, 122.7, 86.6, 85.9, 70.7, 65.2, 39.4, 37.9, 29.2, 26.8; HRMS (ESI, pos) for $C_{17}H_{36}B_{20}N_2O_2$ (m/z): calcd 540.4652 $(M+Na)^+$, found 540.4653.

Synthesis of (*E*)-*N*-(4-(4-(1,12-Dicarba-*closo*-dodecaboranecarbonyl) -1,7-dicarba-*closo*-dodecaboranyl)butyl)-3-(pyridin-3-yl)acrylamide (55)

Preparation and purification of compound **55** was carried out according to the procedure of compound **38** as a white solid (11.8 mg, 0.023 mmol, 37%, 7 steps). m.p. 209-211 ℃; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.74 (d, *J* = 1.5 Hz, 1H), 8.57 (dd, *J* = 1.5 Hz, *J* = 6.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 15 Hz, 1H), 7.31 (dd, *J* = 5.0 Hz, 8.0 Hz, 1H), 6.45 (d, *J* = 15 Hz, 1H), 5.80 (s, 1H), 3.35 (q, *J* = 6.7 Hz, 2H), , 2.91 (s, 1H) 3.10-1.50 (m, 20H), 1.95 (t, *J* = 8.5 Hz, 1H), 1.51-1.42 (m, 2H), 1.41-1.38 (m, 2H); ^{11}B NMR (160 MHz; $CDCl_3$): δ -2.24, -7.24, -11.0, -12.8, -15.3; ^{13}C NMR (125 MHz; $CDCl_3$): δ 180.2, 165.3, 150.5, 149.3, 137.8, 134.5, 130.7, 123.8, 122.7, 85.8, 77.7, 75.6, 65.4, 39.4, 36.7, 29.3, 27.3; HRMS (ESI, pos) for $C_{17}H_{36}B_{20}N_2O_2$ (m/z): calcd 539.4686 $(M+Na)^+$, found 539.4682.

Recombinant NAMPT Inhibition Assay

The assay was performed according to the manufacturers protocol (CycLex NAMPT Colorimetric Assay Kit, MBL International Corp., Woburn, MA). The NAMPT assay was performed according manufacturers protocol. Briefly we used the "1-Step Assay Method" for which following reagents were mixed to make assay buffer and kept at ice before starting the assay: 10 µL each of 10X NAMPT assay buffer, nicotinamide, PRPP, ATP and EtOH; 2 µL each of recombinant NMNAT1, WST-1, ADH, diaphorase and dH_2O. The NAMPT inhibition assay was performed by mixing 2 µL of various concentrations (DMSO as vehicle control) with the following: 2 µL recombinant NAMPT and 36 µL dH_2O. The reaction was initiated by adding 60 µL of 1- Step Assay Buffer to each well and mixed thoroughly followed by incubation at 30 ℃ for 20 mins. After this period, the absorbance at 485 nm was measured and compared with the positive control.

MTT assay

Human epithelioid cervical carcinoma HeLa cells were used for the cell viability assay. The cells

(5×10^4 cells/mL of 96-well plate) were incubated at 37 °C for 72 h in 100 μL of RPMI-1640 medium containing various concentrations of compounds. After the incubation, 10 μL of 3'-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, TCI) in PBS (5 mg/ml) was added into the each well, and the cells were further incubated at 37 ºC for 2 h. After the removal of the medium, 100 μL of DMSO was added and the absorbance at 595 nm was determined by a microplate S6 reader. The drug concentration required to reduce cell viability by 50% (IC_{50}) was determined from semilogarithmic dose-response plots.

Docking study

Ligand structures and geometries were optimized with Discovery Studio 4.1 using CHARMm force field. The crystal structures for NAMPT complexed with the NAMPT- selective inhibitor FK866 (PDB ID: 2GVJ) were downloaded from the Protein Data Bank (PDB). All ligands and water molecules were removed. One monomer of NAMPT was prepared for docking with AutoDock Vina. The optimized geometries of the ligands were prepared for docking. Ligand nonpolar hydrogens (including carborane C−H protons) were merged to conform to the AutoDock atom types, and all of the torsion angles within the carborane clusters were set to nonrotatable. A new atom type (B) was defined for the boron atoms, utilizing the force field parameters reported by Tiwari et al. for docking of carborane-containing ligands. The docking area was defined using AutoGrid, Three-dimensional affinity grid with 1.0 Å grid point spacing was placed around the NAMPT active site. Docking was performed with AutoDock Vina.

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