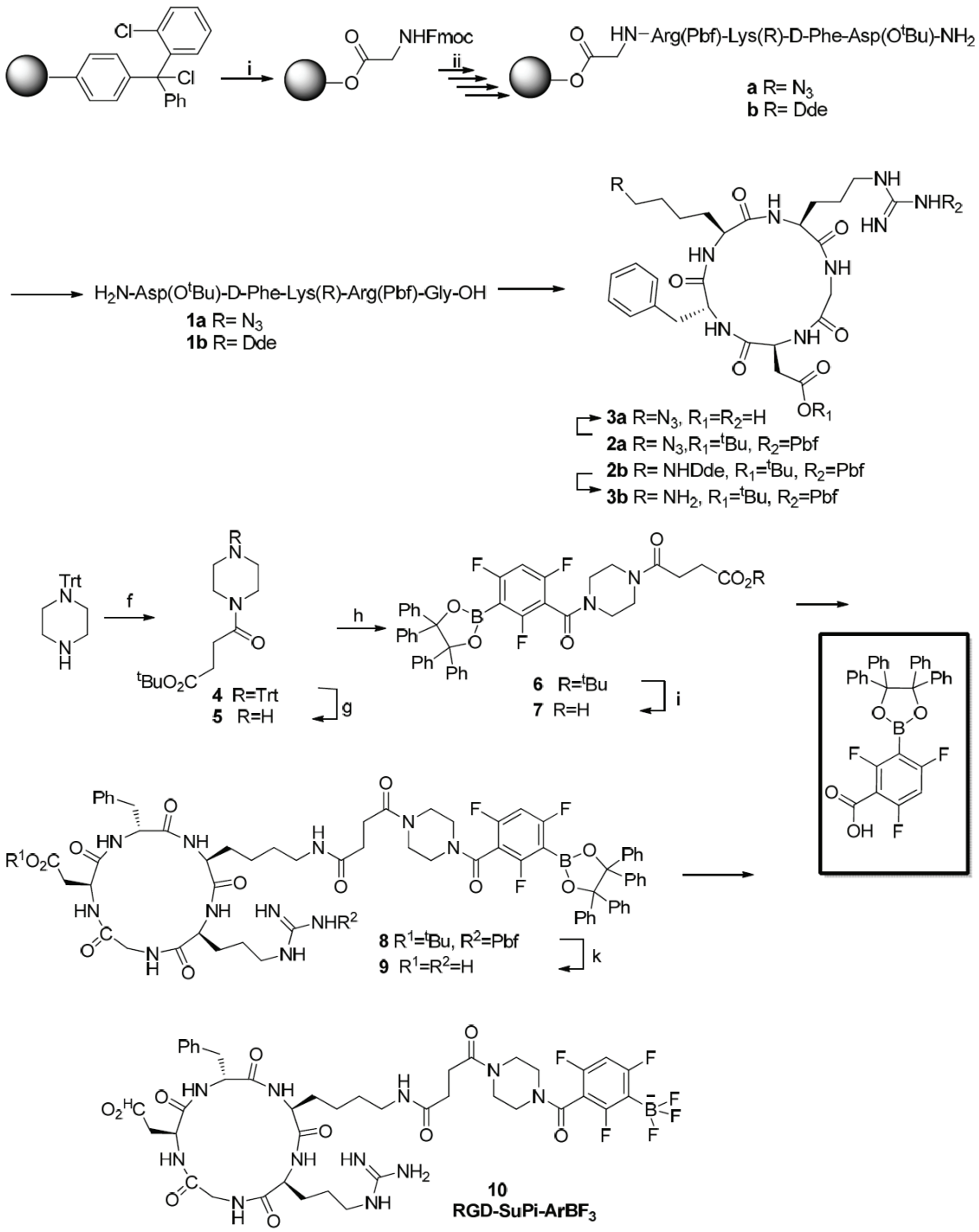


Peptide syntheses: In general, the linear precursors of the RGD peptides, where the lysine ε-amino group was either protected with the Dde group or first converted to the azide, were prepared via solid phase peptide synthesis. Linear peptides were then cyclized to provide the cyclo-RGD whereupon the lysine residue was further acylated with boronate.

H-Asp(O^{t}Bu)-*D*-Phe-Lys(R)-Arg(Pbf)-Gly-OH (1a/b): The linear peptide was prepared following the standard Fmoc solid phase peptide synthesis with 2-chlorotrityl chloride resin. [59, 60] Briefly, Fmoc-Gly-OH (1.00 g, 3.38 mmol) and DIPEA (2.35 mL, 13.52 mmol) were suspended in anhydrous CH_2Cl_2 (20 mL) in

a flame-dried round bottom flask under an Ar atmosphere. DMF (6 mL) was added to assist to dissolve the amino acid prior to the addition of the 2-Cl-trityl chloride resin (2.00 g, 2.60 mmol). The mixture was stirred at room temperature for 90 min. and the solution was filtered. The capping solution (MeOH:DIPEA:CH_2Cl_2 2:1:17, 3 × 20 mL) was mixed thoroughly with the resin and slowly filtered off by gravity. Then the resin was washed with CH_2Cl_2 (3 × 20 mL), DMF (3 × 20 mL), and CH_2Cl_2 (6 × 20 mL), and dried thoroughly over high vacuum. The Fmoc-Gly-attached resin was directly used without further treatment. The resin loading of the Fmoc-Gly-resin was tested based on the DBU/DMF/CH_3CN method and the reported extinction coefficient (7624 M^{-1}·cm^{-1}) for 9-methylene-*9H*-fluorene at 304 nm was used. Then the resin was swollen in DMF (1.5 volumes of the resin) for 30 min. prior to the synthesis in a spin column (5 mL or 10 mL) sealed with a plastic pipette tip. The DMF was filtered and Fmoc was removed with 20% piperidine/DMF (1.5 volumes of the resin) 3 times with each time for 5 min.. Then the resin was thoroughly washed with DMF (3 × 10 mL), CH_2Cl_2 (3 × 10 mL), and DMF (3 × 10 mL). Fmoc-Arg(Pbf)-OH (4 equivalents) and HBTU (4 equivalents) in DMF (1.5 volumes of the resin) was added to the resin followed by the addition of DIPEA (8 equivalents). The spin column was capped and shaken at room temperature for 2 hr. Then the solution was directly filtered through the spin column and the resin was washed with DMF (3 × 10 mL), CH_2Cl_2 (3 × 10 mL), and DMF (3 × 10 mL) before the next cycle of the addition of the next amino acid (Fmoc-Lys(R)-OH, Fmoc-*D*-Phe-OH, and the last Fmoc-Asp(O^{t}Bu)-OH). After the fifth amino acid (Fmoc-Asp(O^{t}Bu)-OH) was attached, the Fmoc group was removed following the same procedure and the resin was thoroughly washed with DMF (3 × 10 mL), CH_2Cl_2 (3 × 10 mL), DMF (3 × 10 mL), and CH_2Cl_2 (5 × 10 mL), and dried over vacuum to remove the residual solvent. Then the resin was transferred to a round bottom flask and treated with 20% HFIP/CH_2Cl_2 (10 volumes of the resin). The mixture was incubated at room temperature for 20 min. and then filtered off. The filtrate was concentrated under reduced pressure and the residue was triturated with MeOH/Et_2O to give a whitish solid. The peptides were used for cyclization without further purification. Peptides **1a**/**b** were analyzed with RP-HPLC in Agilent 1100 series with Column I, using HPLC Program 1: gradient: solvent A: 0.1% TFA in H_2O, solvent B: 0.05% TFA in CH_3CN, 0 min. to 2 min., 10% B, 2 min. to 20 min., 10% B to 50% B, 20 min. to 25 min., 50% B to 100% B, 25 min. to 28 min., 100% B, 28 min. to 30 min., 100% B to 10% B, 30 min. to 32 min., 10% B, column temperature 50 °C, flow rate: 1 mL/min. The desired peptide was characterized with ESI mass spectrometry. H-Asp(O^{t}Bu)-*D*-Phe-Lys(N_3)-Arg(Pbf)-Gly-OH **1a** t_R = 25.4 min.; ESI-HRMS: calcd. for $C_{44}H_{66}N_{11}O_{11}S^+$: 956.4664, found: 956.4639; H-Asp(O^{t}Bu)-*D*-Phe-Lys(Dde)-Arg(Pbf)-Gly-OH **1b** t_R = 25.2 min.; ESI-HRMS: calcd. for $C_{54}H_{80}N_9O_{13}S^+$: 1094.5596, found: 1094.5588.

***Cyclo*[Arg(Pbf)-Gly-Asp(O^{t}Bu)-*D*-Phe-Lys(N_3)] (2a):** The linear peptide H-Asp(O^{t}Bu)-*D*-Phe-Lys(N_3)-Arg(Pbf)-Gly-OH **1a** (100 mg, 0.105 mmol) and DIPEA (54.7 µL, 0.314 mmol) in CH_3CN (105 mL) was added with HBTU (119 mg, 0.314 mmol). The resulting mixture was stirred at room temperature for 24 hr and concentrated under reduced pressure. Then the residue was suspended in EtOAc (100 mL) and H_2O (100 mL) was added to wash the EtOAc layer. The aqueous layer was further extracted with EtOAc (2 × 100 mL). The organic layers were combined, washed with brine (2 × 100 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to give colorless oil. The residue was then dissolved in minimum MeOH (~ 5 mL) and Et_2O (300 mL) was added to precipitate the peptide. The solid was filtered off, washed thoroughly with Et_2O, dried over high vacuum, and used directly without further purification. Yield: 74.5 mg, 76%. The quality of the peptide was determined by RP-HPLC with HPLC Program 1 and Column I in Agilent 1100 series, t_R = 26.2 min.. ^{1}H NMR (400 MHz, d_4-MeOD, rt): δ(*ppm*) 1.06 (m, 2 H), 1.45 (m, 20 H), 1.68 (m, 2 H), 1.84 (m, 1 H), 2.09 (s, 3 H), 2.51 (m, 4 H), 2.57 (s, 3 H), 2.75 (m, 1 H), 2.98 (m, 1 H), 3.02 (s, 3 H), 3.20 (m, 4 H), 3.99 (m, 1 H), 4.23 (m, 2 H), 4.55 (m, 1 H), 4.75 (m, 1 H), 7.21-7.32 (m, 5 H), 7.90 (m, 1 H), 8.21 (m, 1 H), 8.42 (m, 1 H); ESI-HRMS: calcd. for $C_{44}H_{64}N_{11}O_{10}S^+$: 938.4558, found: 938.4542.

***Cyclo*[Arg(Pbf)-Gly-Asp(O^{t}Bu)-*D*-Phe-Lys(Dde)] (2b):** The linear peptide H-Asp(O^{t}Bu)-*D*-Phe-Lys(Dde)-Arg(Pbf)-Gly-OH **1b** (200 mg, 0.182 mmol) and DIPEA (96 µL, 0.549 mmol) in CH_3CN (200 mL) was added with HBTU (208 mg, 0.182 mmol). The resulting mixture was stirred at room temperature for 24 hr and then concentrated under reduced pressure. The residue was suspended in EtOAc (100 mL) and H_2O (100 mL) was added to wash the EtOAc layer. The aqueous layer was further extracted with EtOAc (2 × 100 mL). The organic layers were combined, washed with brine (2 × 100 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to give colorless oil. The residue was then

dissolved in minimum MeOH (~ 5 mL) and Et_2O (300 mL) was added to precipitate the peptide. The solid was filtered off, washed thoroughly with Et_2O, dried over vacuum, and used directly without further purification. Yield: 184.3 mg, 94%. The quality of the peptide was determined by RP-HPLC with HPLC Program 1 and Column I in Agilent 1100 series, t_R = 26.0 min.. ESI-HRMS: calcd. for $C_{54}H_{77}N_9O_{12}NaS^+$: 1098.5310, found: 1098.5328.

***Cyclo*[Arg-Gly-Asp-*D*-Phe-Lys(N_3)] (*c*[RGDfK(N_3)]) (3a):** The protected peptide **2a** *cyclo*[Arg(Pbf)-Gly-Asp-*D*-Phe-Lys(N_3)] (74.5 mg, 0.0794 mmol) was dissolved in TFA:H_2O (20:1, 42 mL) and the reaction was stirred at room temperature for 3 hr. Then the solution was concentrated under reduced pressure and toluene (3 × 20 mL) was added to the residue to azeotropically remove the residual TFA and H_2O. The residue was then dissolved in a minimal amount of MeOH (~ 2 mL) and triturated with Et_2O (~ 30 mL) resulting in a white solid. The mixture was filtered. The solid was washed with Et_2O thoroughly and dried over vacuum. Yield: 45.0 mg, 90%. The crude peptide was further purified via semi-preparative HPLC via HPLC Program 2 (gradient: solvent A: 0.1% TFA in water, solvent B: 0.05% TFA in CH_3CN, 0 min. to 1 min., 5% B to 10% B, 1 min. to 10 min., 10% B to 50% B, 10 min. to 13 min., 50% B to 100% B, 13 min. to 14 min., 100% B; column temperature: 50°C; flow rate: 3 mL/min.) with Column II in Agilent 1100 series, t_R = 10.9 min. or analyzed via HPLC Program 1 with Column I in Agilent 1100 series, t_R = 15.1 min.. ^{1}H NMR (400 MHz, d_6-DMSO, rt): δ (*ppm*) 1.06 (m, 2 H), 1.27-1.53 (m, 6 H), 1.54 (m, 1 H), 1.71 (m, 1 H), 2.36 (dd, J_1 = 16.24 Hz, J_2 = 5.60 Hz, 1 H), 2.69 (dd, J_1 = 16.26 Hz, J_2 = 8.70 Hz, 1 H), 2.79 (m, 1 H), 2.91 (m, 1 H), 3.06 (m, 2 H), 3.22 (m, 3 H), 3.93 (m, 1 H), 4.03 (dd, J_1 = 14.18 Hz, J_2 = 7.82 Hz, 1 H), 4.13 (dd, J_1 = 14.14 Hz, J_2 = 7.22 Hz, 1 H), 4.43 (dd, J_1 = 14.16 Hz, J_2 = 7.24 Hz, 1 H), 4.62 (m, 1 H), 6.87 (s, br, 2 H), 7.10-7.29 (m, 7 H), 7.57 (t, *J* = 5.48 Hz, 1 H), 7.69 (d, *J* = 3.92 Hz, 1 H), 8.00-8.16 (m, 3 H), 8.40 (m, 1 H); ^{13}C NMR (100.6 MHz, d_6-DMSO, rt): δ (*ppm*) 23.29, 25.81, 28.18, 28.97, 31.38, 35.66, 37.87, 43.81, 49.48, 51.00, 52.51, 54.92, 126.87, 128.71, 129.70, 137.89, 157.25, 170.11, 170.57, 171.18, 171.70, 172.26, 172.61; ESI-HRMS: calcd. for $C_{27}H_{40}N_{11}O_7^+$: 630.3122, found: 630.3119.

***Cyclo*[Arg(Pbf)-Gly-Asp(O^{t}Bu)-*D*-Phe-Lys] (3b):** The peptide *cyclo*[Arg(Pbf)-Gly-Asp(O^{t}Bu)-*D*-Phe-Lys(Dde)] **2b** (106 mg, 0.099 mmol) in THF (10 mL) was added with $NH_2NH_2{\cdot}H_2O$ (0.4 mL). The resulting mixture was stirred at room temperature for 20 min. and the solution was concentrated under reduced pressure. The residue was dissolved in a minimal volume of MeOH (~ 1.5 mL) and Et_2O (40 mL) was added to precipitate the peptide. The peptide was filtered off, washed with Et_2O, dried over high vacuum, and then used directly in the following step without further purification. Yield: 78.4 mg, 87%. The quality of the peptide was determined by RP-HPLC with HPLC Program 1 and Column I in Agilent 1100 series, t_R = 22.3 min.. ESI-HRMS: calcd. for $C_{44}H_{66}N_9O_{10}S^+$: 912.4653, found: 912.4633.

***N*-Tritylpiperazine:** Trityl chloride (2.0 g, 7.0 mmol) was added in one portion to piperazine (3.0 g, 34.8 mmol) in CH_2Cl_2 (20.0 mL) at 0°C. Then the ice-water bath was removed and the reaction was stirred at room temperature for 0.5 hr. The reaction was then quenched by the addition of H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 layers were combined, washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), and dried over anhydrous Na_2SO_4. The solution was then filtered and concentrated under reduced pressure. The residue was treated with flash chromatography (MeOH: CH_2Cl_2 3:97) to afford a white solid as the desired product (R_f = 0.53 in 1:9 MeOH: CH_2Cl_2). Yield: 1.48 g, 64%. ^{1}H NMR (300 MHz, CD_2Cl_2, rt): δ(*ppm*) 2.15 (s, 2 H), 2.99 (s, 6 H), 7.18 (m, 3 H), 7.29 (d, *J* = 7.73 Hz, 6 H), 7.48 (s, 6 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2, rt): δ(*ppm*) 46.82, 49.87, 77.45, 126.07, 127.55, 129.55.

Mono-*tert*-butyl succinate: Succinic anhydride (3.0 g, 30.0 mmol), *N*-hydroxyl succinimide (1.0 g, 8.7 mmol), DMAP (0.35 g, 2.9 mmol), and NEt_3 (1.25 mL, 9.0 mmol) were dissolved in ^{t}BuOH (5.0 mL) and toluene (50.0 mL). The reaction was heated to reflux for 24 hr. Once cooled to room temperature, the reaction was diluted with EtOAc (50 mL) and washed with 10% aqueous citric acid solution (50 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with 10% aqueous citric acid (2 × 50 mL) and brine (1 × 50 mL), and dried over anhydrous Na_2SO_4. The solution was then filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1:3 EtOAc: hexanes, visualized on TLC by *p*-anisaldehyde stain) to give a white solid as the product (R_f = 0.16 in 1:1 EtOAc:hexanes). Yield: 2.45 g, 47%. ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ(*ppm*) 1.46 (d, *J*= 1.69 Hz, 9 H), 2.54 (m, 2 H), 2.64 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$, rt): δ(*ppm*) 28.16, 29.33, 30.23, 81.16, 171.54, 178.81; ESI-LRMS: $[M+Na]^+$, 197.1 (100%).

***Tert*-butyl 4-oxo-4-(4-tritylpiperazin-1-yl)butanoate (4):** HBTU (493 mg, 1.30 mmol) was added to *N*-tritylpiperazine (330 mg, 1.00 mmol), *tert*-butyl succinate (200 mg, 1.15 mmol), and NEt_3 (0.42 mL, 3.0 mmol) in CH_2Cl_2 (10.0 mL). The reaction was undertaken at room temperature for 2.5 hr. To the reaction was added 10% aqueous citric acid solution (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and washed with H_2O (1 × 50 mL), saturated $NaHCO_3$ (1 × 50 mL), H_2O (1 × 50 mL), and brine (1 × 50 mL). After drying over anhydrous Na_2SO_4, the CH_2Cl_2 solution was concentrated under vacuum. The residue was resuspended in a minimal volume of EtOAc and the product was purified by silica gel flash chromatography (EtOAc:hexanes 1:9 then 1:6) to give a white solid as the desired product (R_f = 0.51 in 1:1 EtOAc:hexanes). Yield: 473.8 mg, 98%. ^{1}H NMR (400 MHz, CD_2Cl_2, rt): δ(*ppm*) 1.40 (s, 9 H), 2.28 (s, br, 2 H), 2.45 (s, 4 H), 3.61 (m, 2 H), 3.72 (s, br, 2 H), 7.21 (m, 3 H), 7.31 (m, 6 H), 7.51 (m, 6 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2, rt): δ(*ppm*) 27.90, 30.50, 42.15, 45.81, 47.98, 48.40, 77.15, 80.07, 126.35, 127.75, 129.40, 169.77, 172.25.

***Tert*-butyl 4-oxo-4-(piperazin-1-yl)butanoate (5):** *Tert*-butyl ester **4** (110.0 mg, 0.227 mmol) and HFIP (1.2 mL, 11.4 mmol) were dissolved in trifluoroethanol (5.0 mL) and stirred at 40°C for 4 hr. The reaction was concentrated *in vacuo* to give oily residue. The residue was then resuspended in a minimal volume of EtOAc and the product was purified by silica flash chromatography (MeOH:CH_2Cl_2 3:97 then 1:9) and colorless oil was obtained as the desired product (R_f = 0.13 in 1:9 MeOH:CH_2Cl_2). Yield: 52.9 mg, 96%. ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ(*ppm*) 1.46 (d, *J* = 1.35 Hz, 9 H), 2.58 (d, *J* = 1.11 Hz, 4 H), 2.90 (d, *J* = 15.88 Hz, 4 H), 3.17 (s, br, 2 H), 3.52 (s, 2 H), 3.63 (s, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$, rt): δ(*ppm*) 28.32, 28.52, 30.85, 42.78, 45.18, 45.91, 46.27, 80.89, 170.34, 172.79; ESI-LRMS: $[M+Na]^+$, 265.1 (100%).

***Tert*-butyl 4-oxo-4-(4-(2,4,6-trifluoro-3-(4,4,5,5-tetraphenyl-1,3,2-dioxaborolan-2-yl) benzoyl)piperazin-1-yl)butanoate (6):** *Tert*-butyl ester **5** (91.1 mg, 0.376 mmol), the tetraphenylpinacolate of 2,4,5-trifluoro-3-carboxy-phenyl-1-boronic acid (238.0 mg, 0.432 mmol), HOBt·H_2O (73.0 mg, 0.475 mmol), and pyridine (0.14 mL, 1.79 mmol) were dissolved in CH_2Cl_2 (15 mL) and added with EDC·HCl (125.0 mg, 0.648 mmol) in one portion. The resulting mixture was reacted at room temperature overnight and then quenched by the addition of 10% aqueous citric acid solution (50 mL). The product was extracted into CH_2Cl_2 (3 × 50 mL). The organic layers were combined, washed with H_2O (1 × 50 mL) and brine (1 × 50 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and the solvent was removed under vacuum. The residue was isolated via silica gel flash chromatography (MeOH:CH_2Cl_2 0:100 to 1:99) to afford a white solid as the desired product (R_f = 0.63 in 1:9 MeOH:CH_2Cl_2). Yield: 241.0 mg, 83%. ^{19}F NMR (282.4 MHz, CD_2Cl_2, rt): δ(*ppm*) -28.75 (s, 1 F), -22.36 (s, 1 F), -17.25 (s, 1 F); ^{1}H NMR (400 MHz, CD_2Cl_2, rt): δ(*ppm*) 1.45 (s, 9 H), 2.58 (m, 4 H), 3.41-3.85 (m, 8 H), 6.91 (t, *J* = 8.80 Hz, 1 H), 7.13 (m, 12 H), 7.21 (m, 4 H), 7.26 (t, *J* = 3.54 Hz, 4 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2, rt): δ(*ppm*) 27.93, 28.00, 30.45, 42.06, 46.80, 80.31, 96.98, 101.26, 127.26, 127.32, 127.45, 128.62, 128.65, 141.82, 142.17, 170.18, 172.12; ESI-HRMS: calcd. for $C_{45}H_{43}BN_2O_6F_3^+$: 775.3166, found: 775.3174.

4-Oxo-4-(4-(2,4,6-trifluoro-3-(4,4,5,5-tetraphenyl-1,3,2-dioxaborolan-2-yl)benzoyl) piperazin-1-yl)butanoic acid (7): TFA (5.0 mL) was added to *tert*-butyl ester **6** (77.3 mg, 0.0998 mmol) in CH_2Cl_2 (10.0 mL) and the mixture was stirred at room temperature for 3 hr. The mixture was then concentrated under vacuum and the residue was purified via silica gel flash chromatography (MeOH:CH_2Cl_2 1:200 to 1:99) to afford white foam as the desired product (R_f = 0.32 in 1:9 MeOH:CH_2Cl_2). Yield: 62.9 mg, 88%. ^{19}F NMR (282.4 MHz, CD_2Cl_2, rt): δ(*ppm*) -28.84 (s, 1 F), -22.47 (s, 1 F), -16.99 (s, 1 F); ^{1}H NMR (400 MHz, CD_2Cl_2, rt): δ(*ppm*) 2.70 (m, 4 H), 3.41-3.89 (m, 8 H), 6.75 (s, br, 1 H), 6.91 (t, *J* = 8.91 Hz, 1 H), 7.08-7.27 (m, 20 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2, rt): δ(*ppm*) 28.07, 29.45, 41.61, 42.00, 42.21, 45.18, 45.71, 97.00, 101.33, 127.28, 127.33, 127.45, 128.62, 128.64, 141.74, 141.82, 142.13, 159.71, 171.03, 175.67; ESI-HRMS: calcd. for $C_{41}H_{34}BN_2O_6F_3Na^+$: 741.2360, found: 741.2346.

***Cyclo*[Arg(pbf)-Gly-Asp(O^{t}Bu)-*D*-Phe-Lys(suc-piperazinyl-boronate)] (8):** EDC·HCl (16.0 mg, 57.5 μmol) was added to the DMF solution (1.5 mL) of **7** (27.7 mg, 38.6 μmol), *cyclo*[Arg(Pbf)-Gly-Asp(O^{t}Bu)-*D*-Phe-Lys] **3b** (23.0 mg, 25.5 μmol), HOBt·H_2O (7.0 mg, 57.5 μmol), and pyridine (24.0 μL, 0.27 mmol). The DMF solution was stirred at room temperature for 36 hr. The reaction mixture was then quenched with 10% aqueous citric acid (20 mL) and extracted with EtOAc (3 × 30 mL). The EtOAc layers were combined,

washed with H_2O (1 × 30 mL) and brine (1 × 30 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure, and the residue was dissolved in a minimal volume of MeOH (~ 1 mL). Et_2O (20 mL) was added to the methanolic solution to precipitate the peptide. The mixture was filtered and the pellet was washed with Et_2O thoroughly to give a whitish solid, which was directly used in the following step without further purification. Yield: 31.7 mg, 77%. The quality of the peptide was determined by RP-HPLC with HPLC Program 1 and Column I in Agilent 1100 series, t_R = 28.2 min.. ESI-HRMS: calcd. for $C_{85}H_{98}BN_{11}O_{15}F_3S^+$: 1612.7010, found: 1612.6984.

***Cyclo*[Arg-Gly-Asp-*D*-Phe-Lys(suc-piperazinyl-boronate)] (9):** The protected peptide **8** (31.7 mg, 0.0197 mmol) was dissolved in TFA (12 mL) and H_2O (0.58 mL). The reaction was incubated at room temperature for 1.5 hr and the solvent was removed under vacuum. The residue was then dissolved in a minimal volume of MeOH (~ 2 mL) whereupon Et_2O (30 mL) was added to precipitate the peptide. The mixture was filtered and the pellet was thoroughly washed with Et_2O to give a whitish powder as the crude product. Yield: 21.1 mg, 82%. The product was analyzed by RP-HPLC via HPLC Program 1 and Column I in Agilent 1100 series, t_R = 26.2 min. The crude peptide (~ 10 mg) was dissolved in CH_3CN containing 10% H_2O (2 mL) and purified by semi-preparative HPLC via HPLC Program 3 (gradient: solvent A: 0.1% TFA in water, solvent B: 0.05% TFA in CH_3CN, 0 min. to 1 min., 20% B to 30% B, 1 min. to 3 min., 30% B to 50% B, 3 min. to 10 min., 50% B to 100% B, 10 min. to 13 min., 100% B, 13 min. to 15 min., 100% B to 50% B, 15 min. to 16 min., 50% B to 20% B; column temperature: 50°C; flow rate: 3 mL/min) and Column II in Agilent 1100 series (t_R = 9.7 min) to give a white solid. Yield: 4.0 mg, 47%. ^{19}F NMR (282.4 MHz, MeOD, rt): δ(*ppm*) -29.73 (s, 1 F), -23.76 (s, 1 F), -17.35 (s, 1 F); ^{1}H NMR (400 MHz, MeOD, rt): δ(*ppm*) 1.04 (m, 2 H), 1.31 (s, 1 H), 1.40-1.47 (m, 3 H), 1.54 (m, 2 H), 1.67 (m, 2H), 1.87 (m, 1 H), 2.34 (s, 2 H), 2.46-2.62 (m, 3 H), 2.64-2.90 (m, 3 H), 2.99 (m, 2 H), 3.03-3.19 (m, 3 H), 3.49 (m, 2 H), 3.55 (m, 1 H), 3.58-3.69 (m, 3 H), 3.72 (m, 2 H), 3.81 (m, 1 H), 3.89 (m, 1 H), 3.94 (m, 1 H), 4.26 (m, 2 H), 4.55 (m, 1 H), 4.76 (m, 1 H), 7.10 (m, 11 H), 7.14-7.31 (m, 15 H), 7.86 (m, 1 H), 8.23 (m, 1 H), 8.43 (m, 1 H). ESI-HRMS: calcd. for $C_{68}H_{74}BN_{11}O_{12}F_3^+$: 1304.5564, found: 1304.5536.

***Cyclo*[Arg-Gly-Asp-*D*-Phe-Lys(suc-piperazinyl-ArBF$_3^-$)] (10, also referred to RGD-SuPi-ArBF$_3^-$):** The crude peptide **9** (~ 8 mg, 4.96 μmol) was dissolved in MeOH (1 mL) to which was added 4 M KHF_2 (200 μL, 0.80 mmol) in a 15 mL Falcon tube. The reaction was then stirred at room temperature overnight and the solvent was removed under vacuum. Et_2O (10 mL) was added to the residue and the mixture was centrifuged after being thoroughly mixed. The Et_2O layer was discarded. The Et_2O wash was then repeated two more times. The residue was then dried over vacuum to remove the residual Et_2O for 5 hr. Then d_6-DMSO (~ 400 μL) was added to extract the product from the crude. ^{19}F NMR (282.4 MHz, d_6-DMSO, rt): δ(*ppm*) -21.13 (s, 1 F), -27.30 (s, 1 F), -40.54 (s, 1 F), -54.91 (s, 3 F). ESI-LRMS: $[M]^-$, 996.4 (100%).

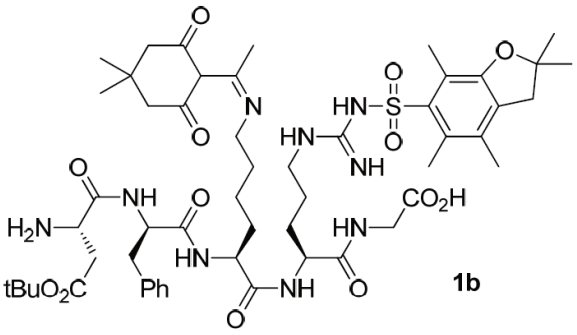
2,4,6-Trifluoro-3-(*1H*-naphtho[1,8-de][1,3,2]diazaborinin-2(*3H*)-yl)benzoic acid (11): 2,4,6-Trifluorobenzoic acid (0.50 g, 2.8 mmol) was dissolved in anhydrous THF (30 mL) and cooled to -78°C under Ar. 1.6 M BuLi in hexanes (4.0 mL, 6.4 mmol) was slowly added to the solution at the same temperature and the resulting mixture was stirred for 10 min. Then $B(OCH_3)_3$ was added in one portion to the mixture and the reaction was incubated at -78°C for another 3 hr. The reaction was quenched by addition of 4 M HCl in dioxane (2.5 mL, 10 mmol). The reaction was continued to stir at -78°C for 0.5 hr and allowed to warm up to room temperature. The reaction crude was then concentrated under vacuum and 1,8-diaminonaphthalene (0.50 g, 3.0 mmol) in THF (30 mL) and toluene (30 mL) was added to the residue. The mixture was then refluxed overnight and concentrated under vacuum. The product was further purified by flash chromatography (0.5% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to yield grey powder as the desired product. Yield: 0.90 g, 94%. ESI-MS: $[M+H]^+$: 343.0; ^{19}F NMR (282.4 MHz, d_4-MeOD, rt): d (*ppm*) -33.84 (s, 1 Ar-F), -26.51 (s, 1 Ar-F), -23.78 (s, 1 Ar-F); ^{1}H NMR (400 MHz, d_4-MeOD, rt): d (*ppm*) 6.42 (dd, J_1= 9.94 Hz, J_2= .85 Hz, 2 H), 6.83 (td, J_1= 8.14 Hz, J_2= 1.54 Hz, 1 H), 6.94 (dd, J_1= 8.29 Hz, J_2= 0.79 Hz, 2 H)), 7.05 (t, J= 7.81 Hz, 2 H); ^{13}C NMR (400 MHz, d_4-MeOD, rt): d (*ppm*) 99.40, 99.70, 99.97, 105.49, 116.99, 120.32, 127.25, 136.57, 141.69.

Alkyneborimidine (12): 2,4,6-Trifluoro-3-(*1H*-naphtho[1,8-de][1,3,2]diazaborinin-2(*3H*)-yl)benzoic acid (0.17 g, 0.50 mmol), propargylamine (35 μL, 0.55 mmol), HOBt·H_2O (0.10 g, 0.65 mmol), and pyridine (0.65 mL, 8.0 mmol) in DMF (10 mL) was added with EDC·HCl (0.15 g, 0.80 mmol). The resulting mixture

was stirred at room temperature overnight and then concentrated under vacuum. The residue was purified via flash chromatography (10% EtOA in hexanes to 20% EtOAc in hexanes) to give pale green solid. Yield: 93 mg, 49%. ESI-MS: $[M+H]^+$: 380.3; ^{19}F NMR (282.4 MHz, *d*-$CDCl_3$, rt): d (*ppm*) -29.33 (s, 1 Ar-F), -24.98 (s, 1 Ar-F), -19.62 (s, 1 Ar-F); ^{1}H NMR (300 MHz, *d*-$CDCl_3$, rt): d (*ppm*) 2.35 (s, 1 H), 4.31 (*dd*, J_1= 4.91 Hz, J_2= 2.44 Hz, 2 H), 6.14 (s, br, 1 H), 6.40 (*d*, *J*= 7.10 Hz, 2 H), 6.81 (*d*, *J*= 12.0 Hz, 1 H), 7.10 (*m*, 4 H).

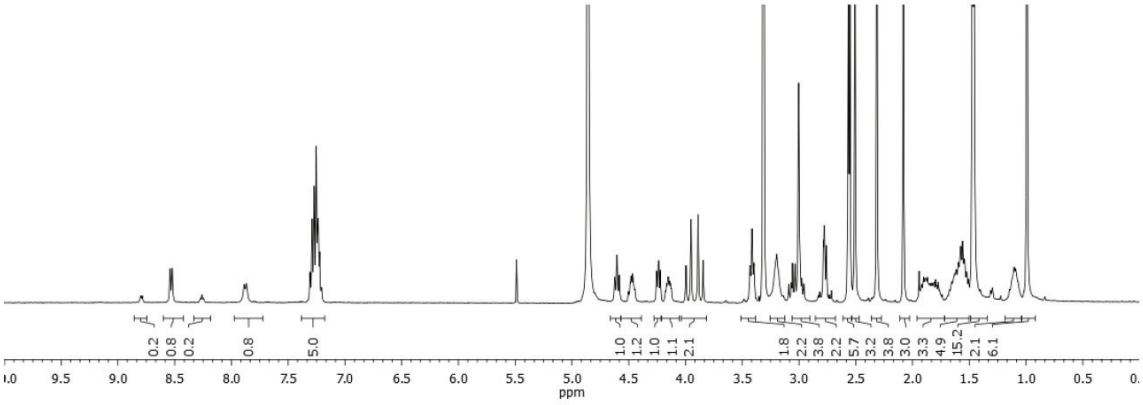
NMR spectra

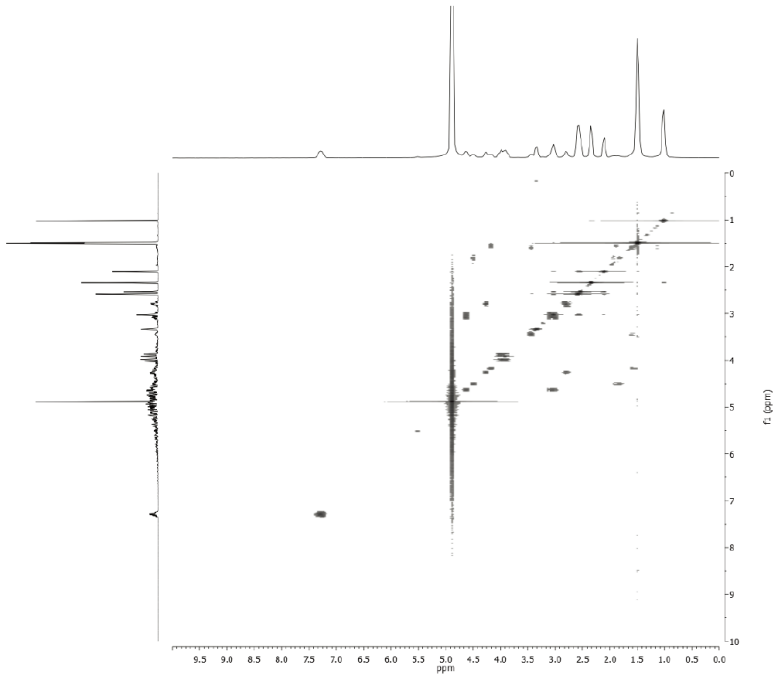
H-Asp(O^{t}Bu)-*D*-Phe-Lys(Dde)-Arg(Pbf)-Gly-OH (1b)



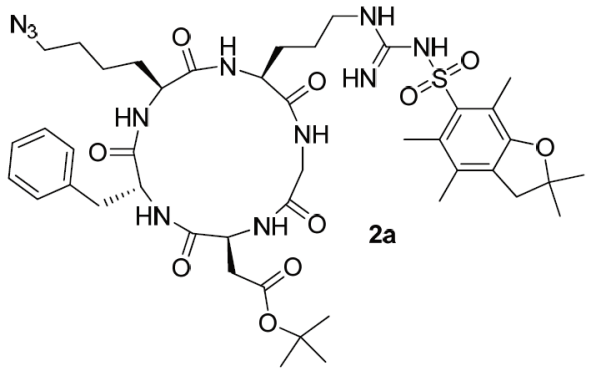
Chemical Formula: $C_{54}H_{79}N_9O_{13}S$
Exact Mass: 1093.5518
Molecular Weight: 1094.3226

^{1}H NMR 400 MHz, ^{1}H-^{1}H-COSY, d_4-MeOD



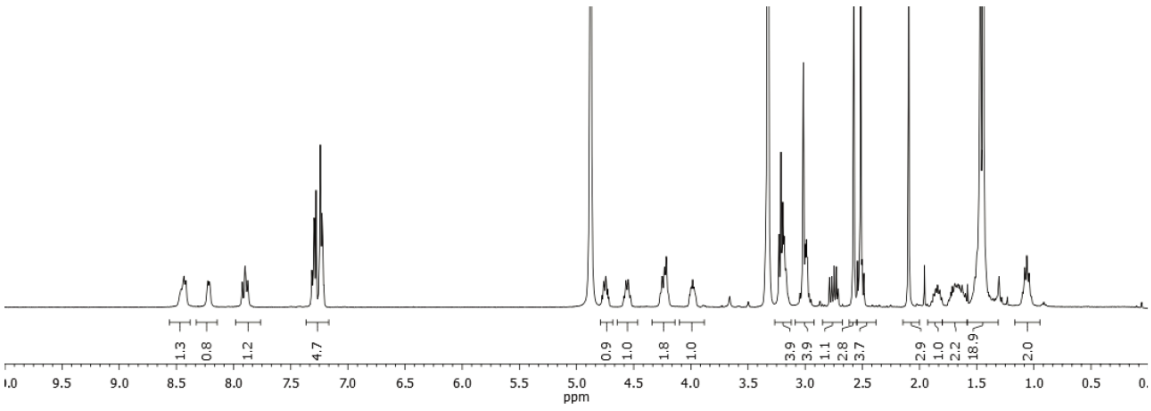


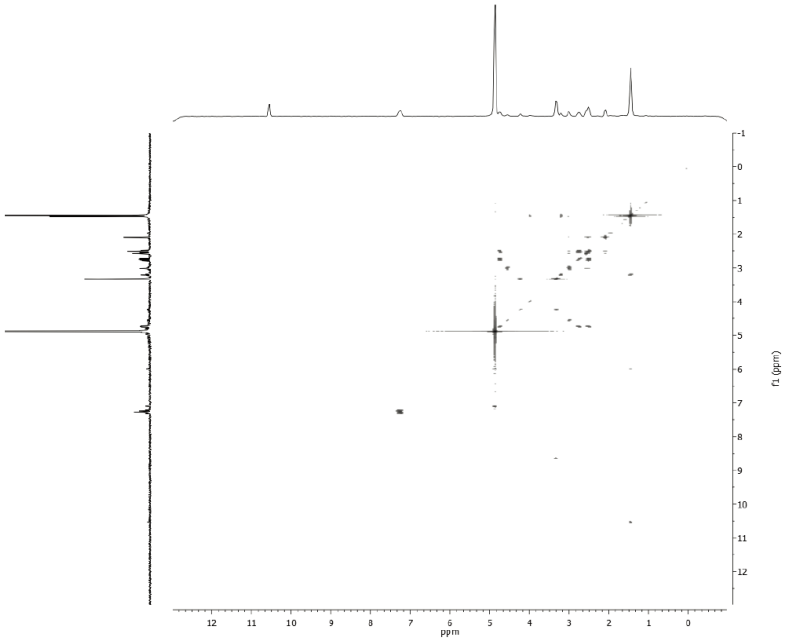
***Cyclo*[Arg(Pbf)-Gly-Asp(O^{t}Bu)-*D*-Phe-Lys(N_3)] (2a)**



Chemical Formula: $C_{44}H_{63}N_{11}O_{10}S$
Exact Mass: 937.4480
Molecular Weight: 938.1037

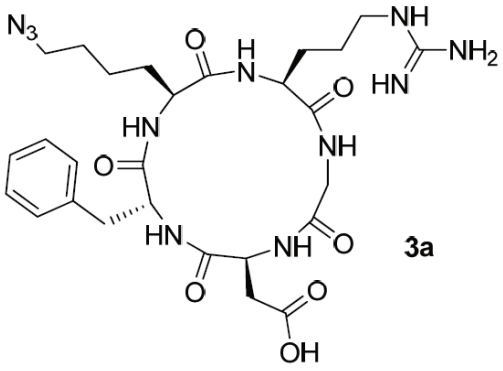
^{1}H NMR 400 MHz, ^{1}H-^{1}H-COSY, d_4-MeOD





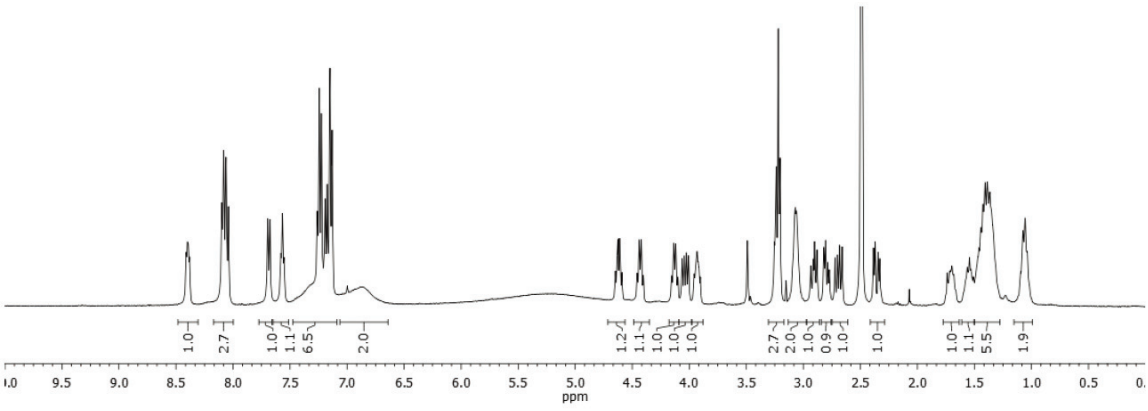
***Cyclo*[Arg-Gly-Asp-*D*-Phe-Lys(N_3)] (3a)**

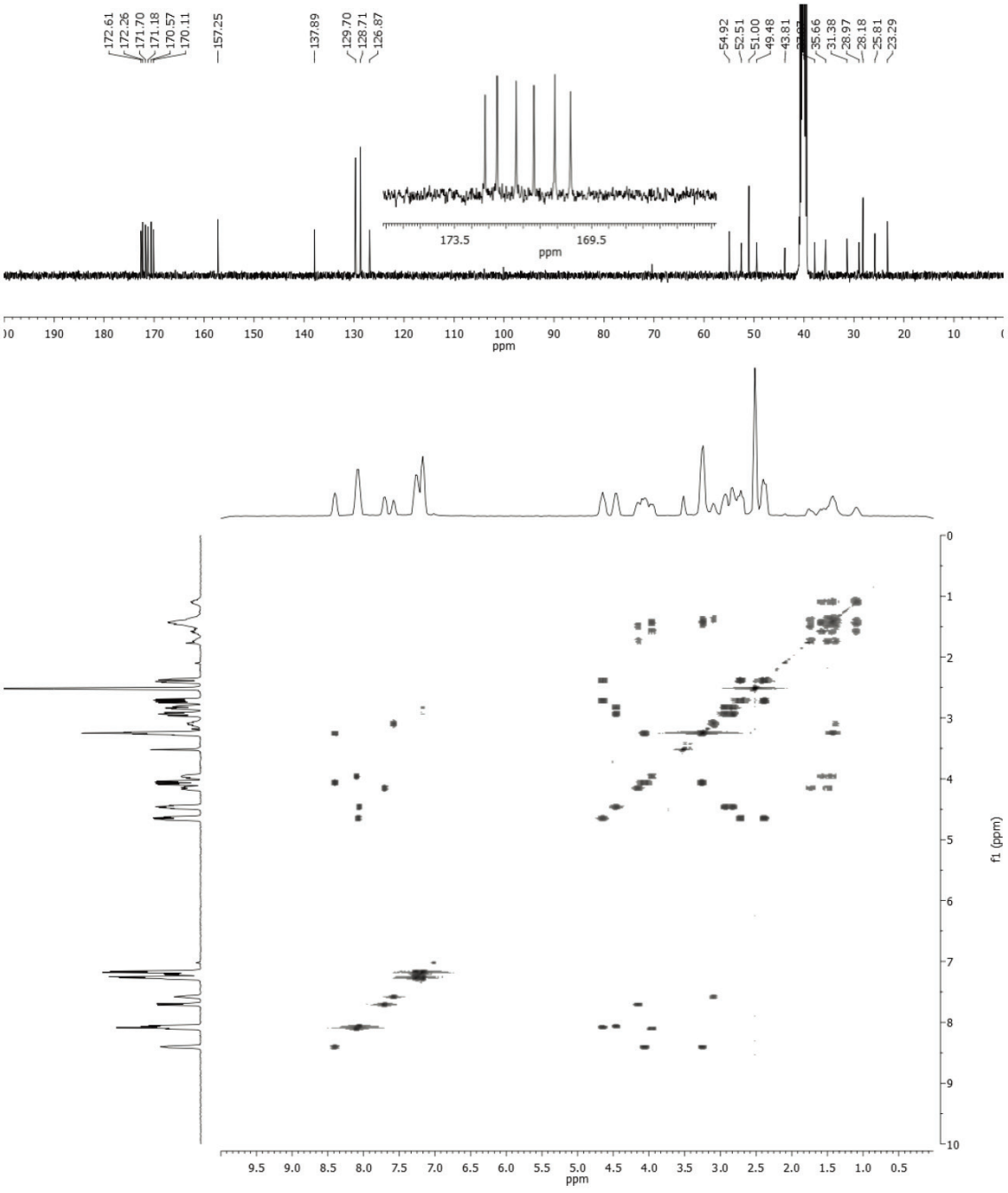
^{1}H NMR 400 MHz, ^{13}C NMR 100.6 MHz, ^{1}H-^{1}H-COSY, d_6-DMSO



3a

Chemical Formula: $C_{27}H_{39}N_{11}O_7$
Exact Mass: 629.3034
Molecular Weight: 629.6681

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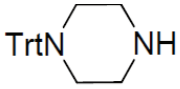
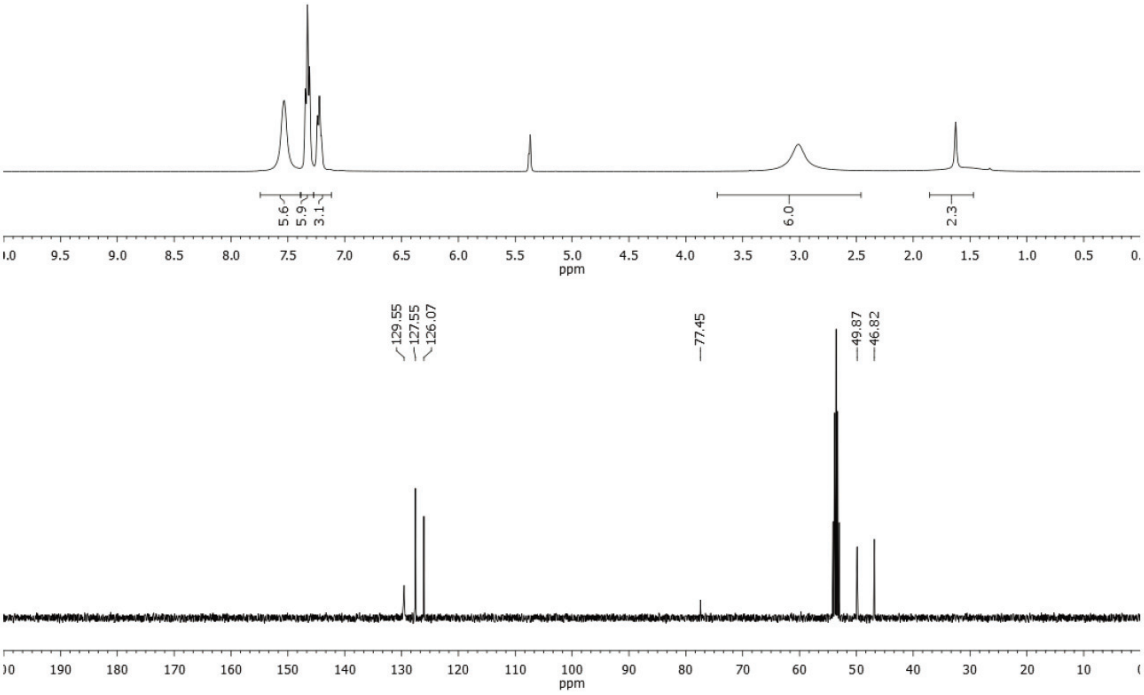
ppm
ppm
f1 (ppm)

***N*-Tritylpiperazine**

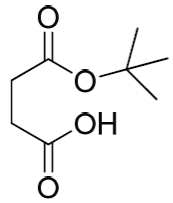


Chemical Formula: $C_{23}H_{24}N_2$
Exact Mass: 328.1939
Molecular Weight: 328.4501

^{1}H NMR 400 MHz, ^{13}C NMR 100.6 MHz, CD_2Cl_2

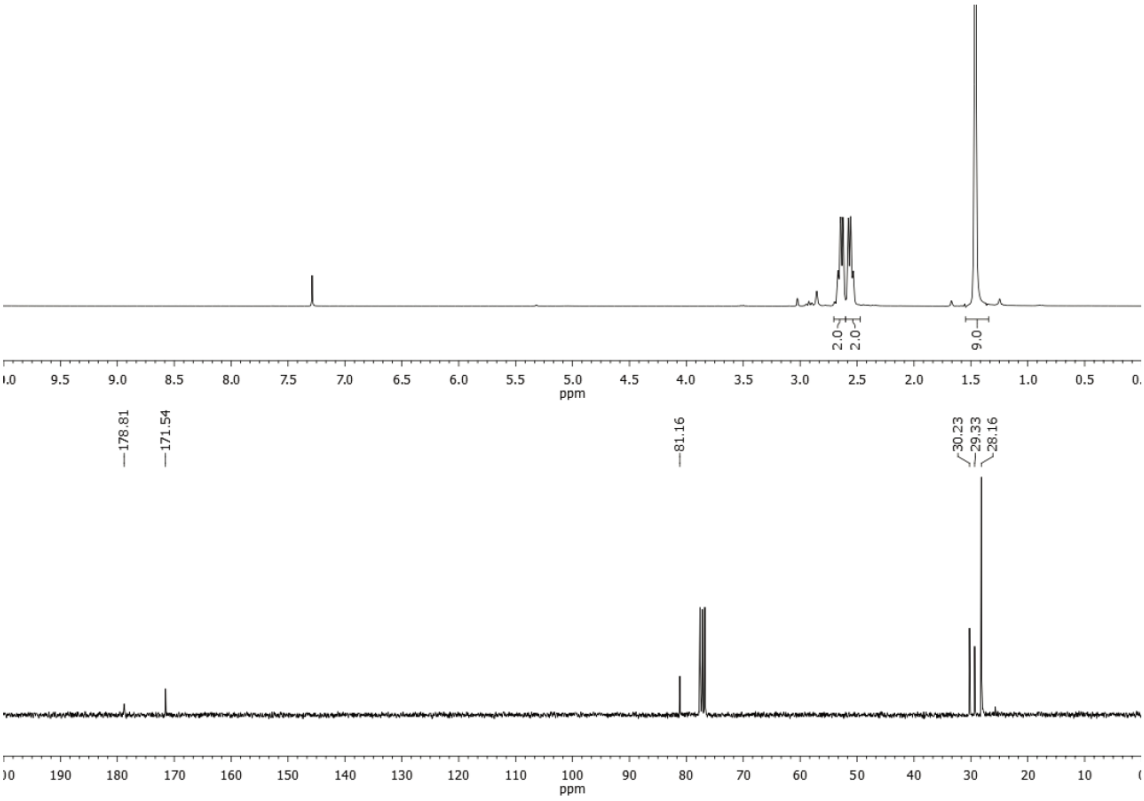


Mono-*tert*-butyl succinate

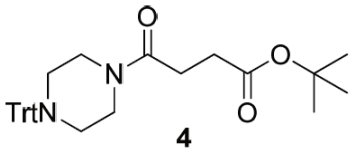


Chemical Formula: $C_8H_{14}O_4$
Exact Mass: 174.0892
Molecular Weight: 174.1944

^{1}H NMR 300 MHz, ^{13}C NMR 75.5 MHz, $CDCl_3$



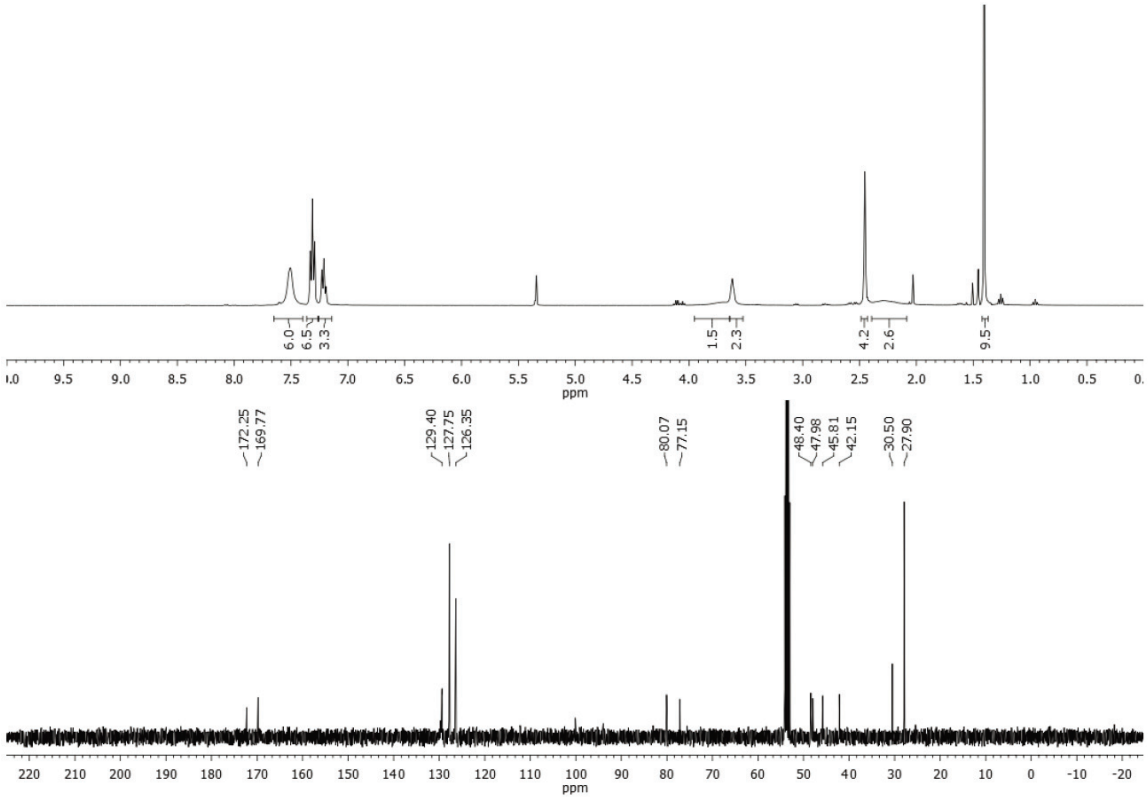
***Tert*-butyl 4-oxo-4-(4-tritylpiperazin-1-yl)butanoate (4)**



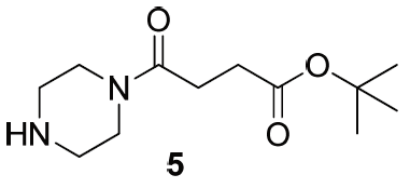
4

Chemical Formula: $C_{31}H_{36}N_2O_3$
Exact Mass: 484.2726
Molecular Weight: 484.6291

^{1}H NMR 400 MHz, ^{13}C NMR 100.6 MHz, CD_2Cl_2



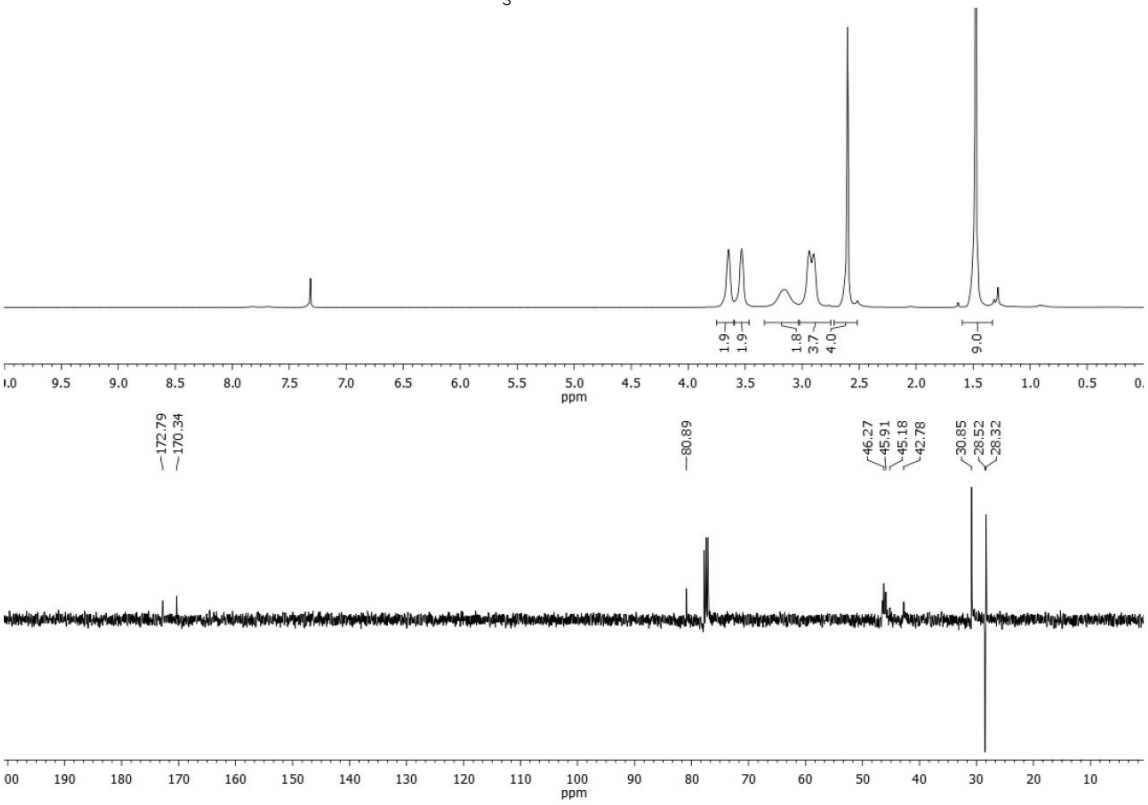
***Tert*-butyl 4-oxo-4-(piperazin-1-yl)butanoate (5)**



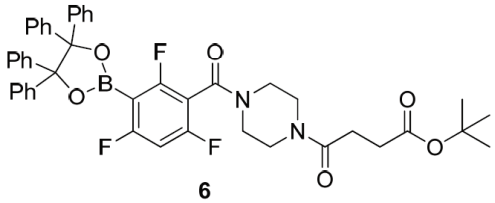
5

Chemical Formula: $C_{12}H_{22}N_2O_3$
Exact Mass: 242.1630
Molecular Weight: 242.3147

^{1}H NMR 400 MHz, ^{13}C NMR 100.6 MHz, $CDCl_3$



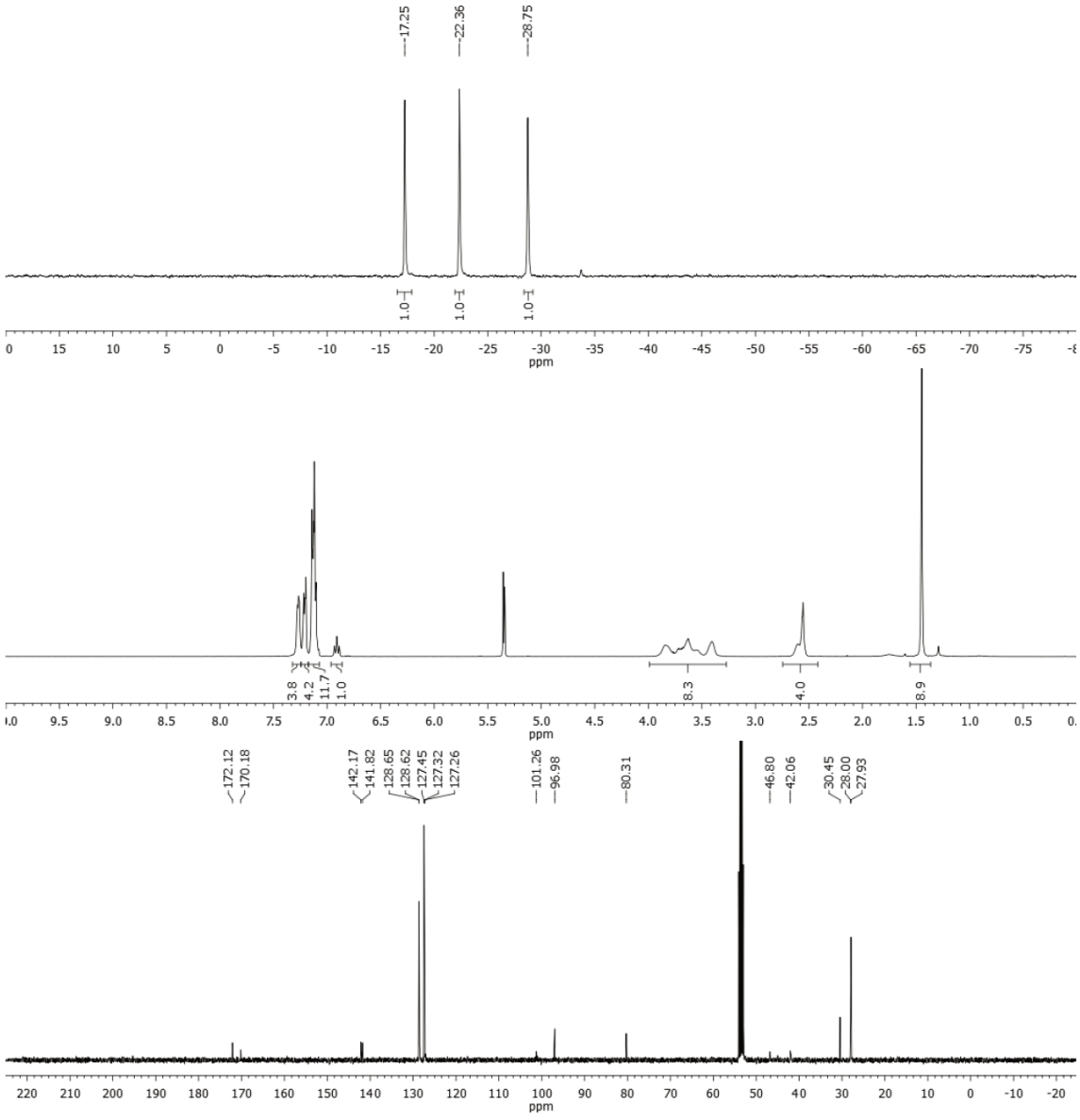
***Tert*-butyl 4-oxo-4-(4-(2,4,6-trifluoro-3-(4,4,5,5-tetraphenyl-1,3,2-dioxaborolan-2-yl) benzoyl)piperazin-1-yl)butanoate (6)**



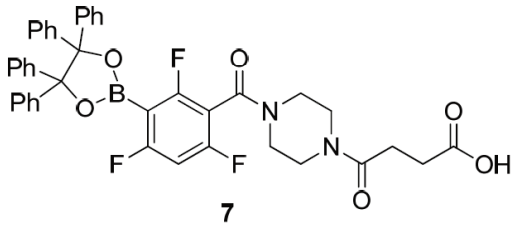
6

Chemical Formula: $C_{45}H_{42}BF_3N_2O_6$
Exact Mass: 774.3088
Molecular Weight: 774.6310

^{19}F NMR 282.4 MHz, ^{1}H NMR 400 MHz, ^{13}C NMR 100.6 MHz, CD_2Cl_2



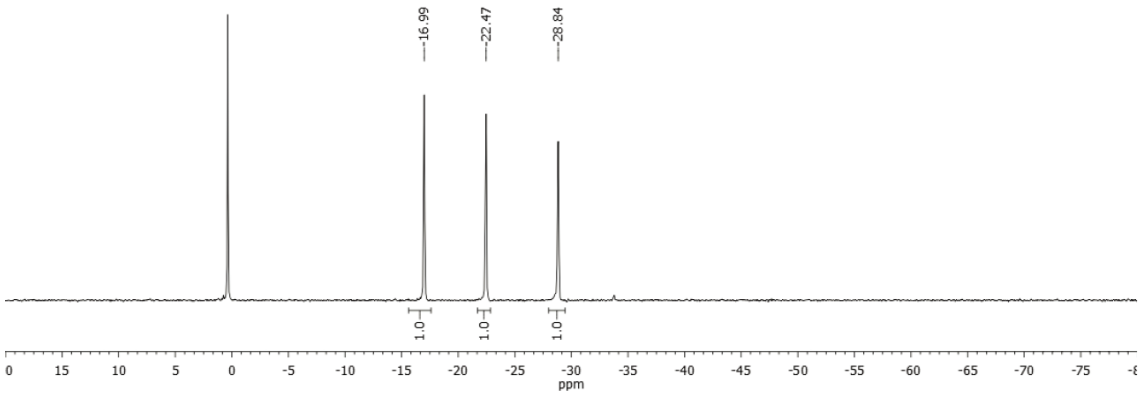
4-Oxo-4-(4-(2,4,6-trifluoro-3-(4,4,5,5-tetraphenyl-1,3,2-dioxaborolan-2-yl)benzoyl) piperazin-1-yl)butanoic acid (7)

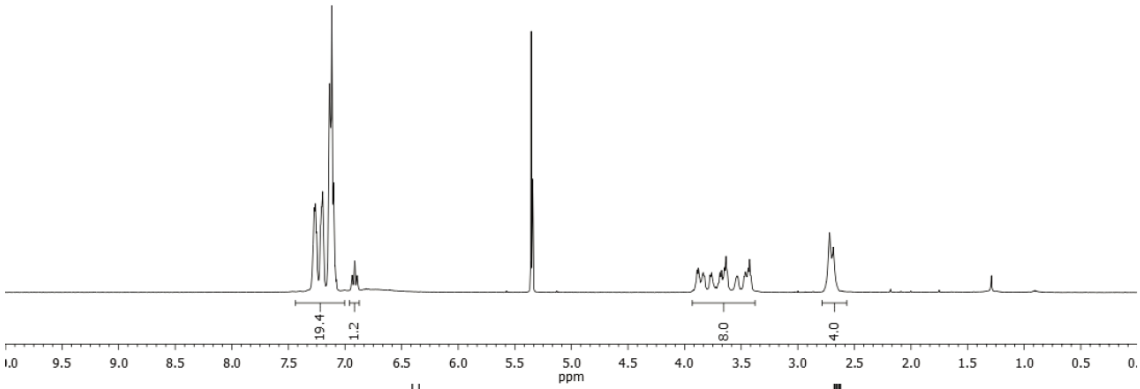


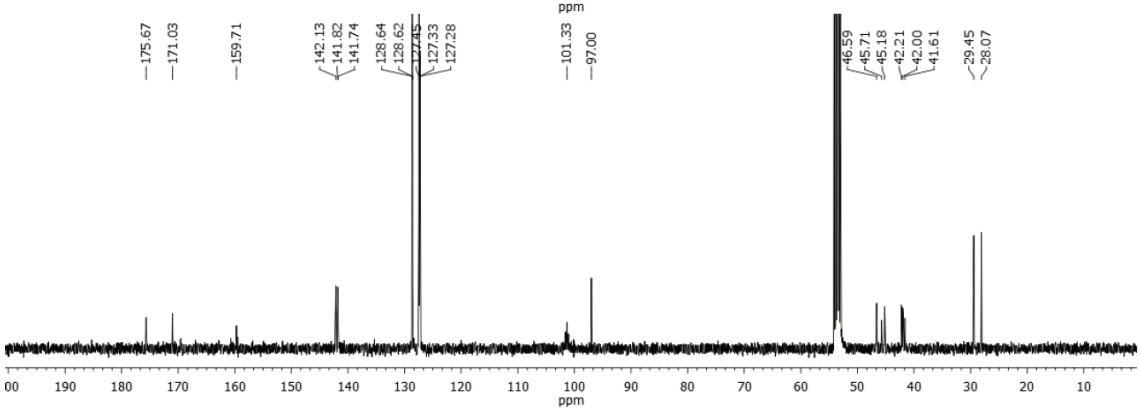
7

Chemical Formula: $C_{41}H_{34}BF_3N_2O_6$
Exact Mass: 718.2462
Molecular Weight: 718.5247

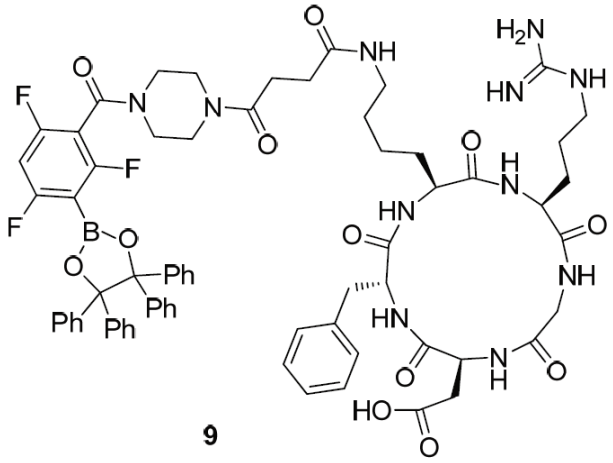
^{19}F NMR 282.4 MHz, ^{1}H NMR 400 MHz, ^{13}C NMR 100.6 MHz, CD_2Cl_2







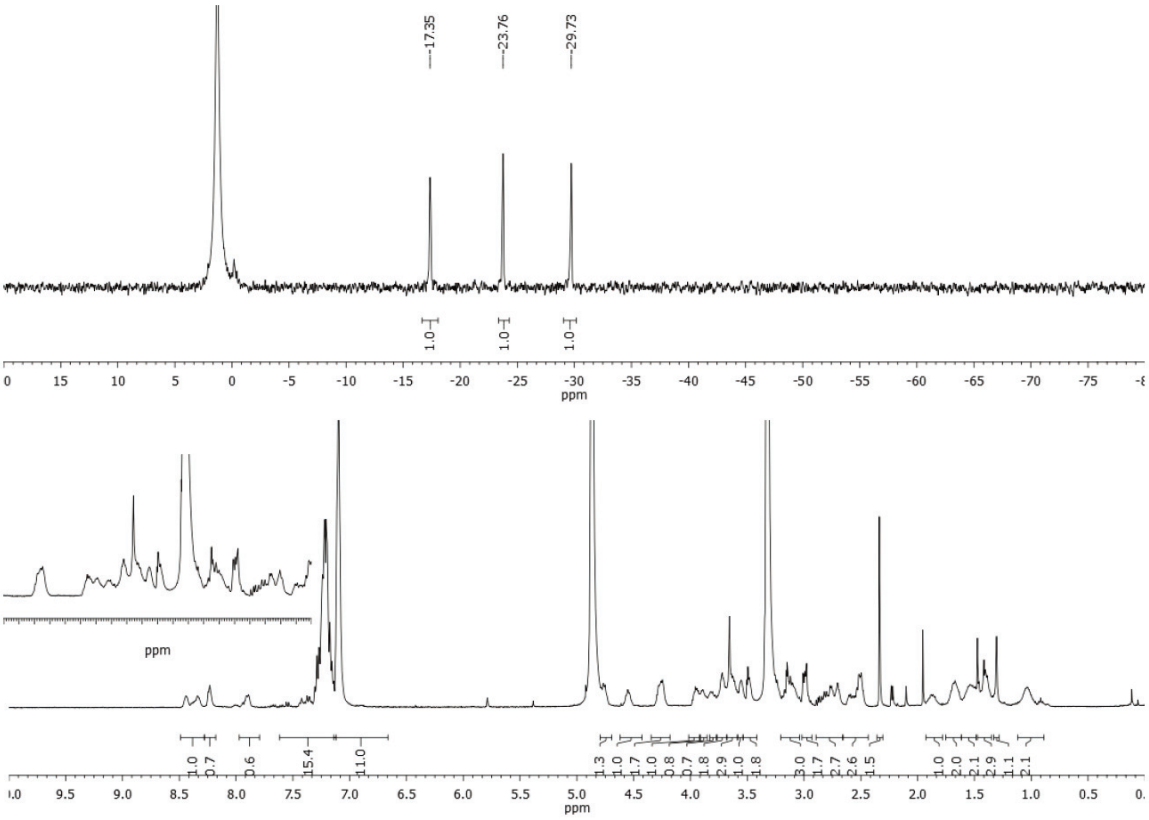
***Cyclo*[Arg-Gly-Asp-*D*-Phe-Lys(piperazinyl-boronate)] (9)**



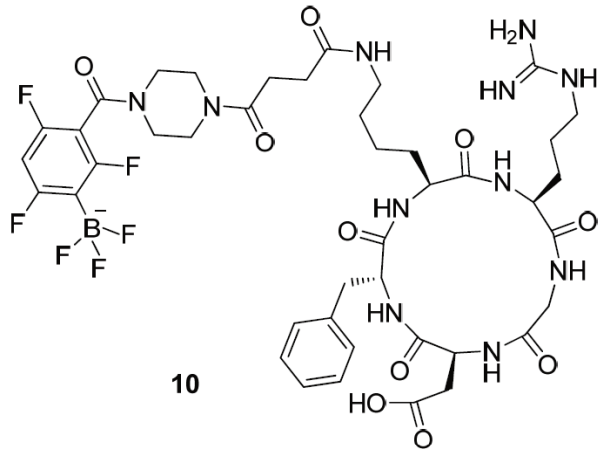
9

Chemical Formula: $C_{68}H_{73}BF_3N_{11}O_{12}$
Exact Mass: 1303.5485
Molecular Weight: 1304.1799

^{19}F NMR 282.4 MHz, ^{1}H NMR 400 MHz, ^{13}C NMR 100.6 MHz, d_4-MeOD



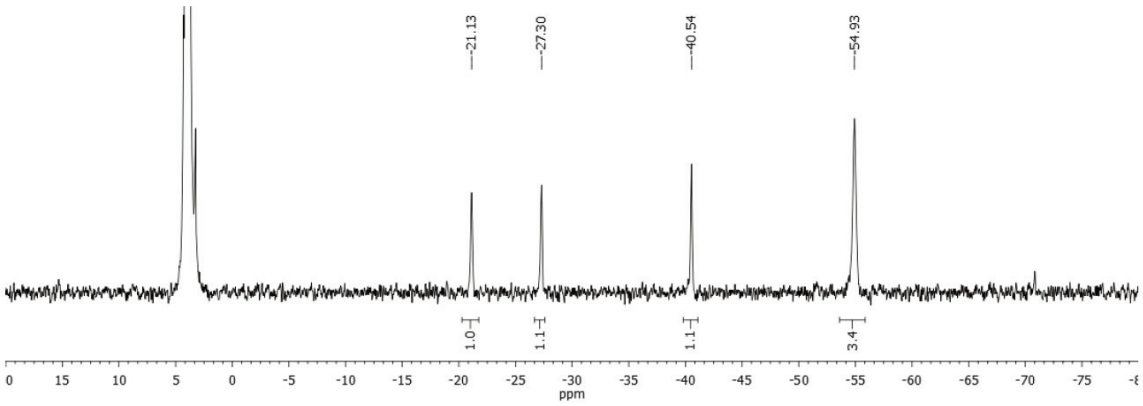
***Cyclo*[Arg-Gly-Asp-*D*-Phe-Lys(suc-piperazinyl-ArBF$_3$)] (10)**



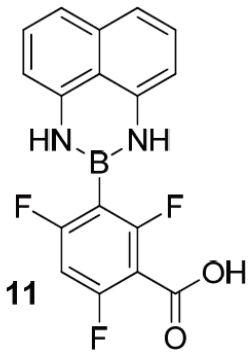
10

Chemical Formula: $C_{42}H_{53}BF_6N_{11}O_{10}^-$
Exact Mass: 996.3980
Molecular Weight: 996.7399

^{19}F NMR 282.4 MHz, d_6-DMSO

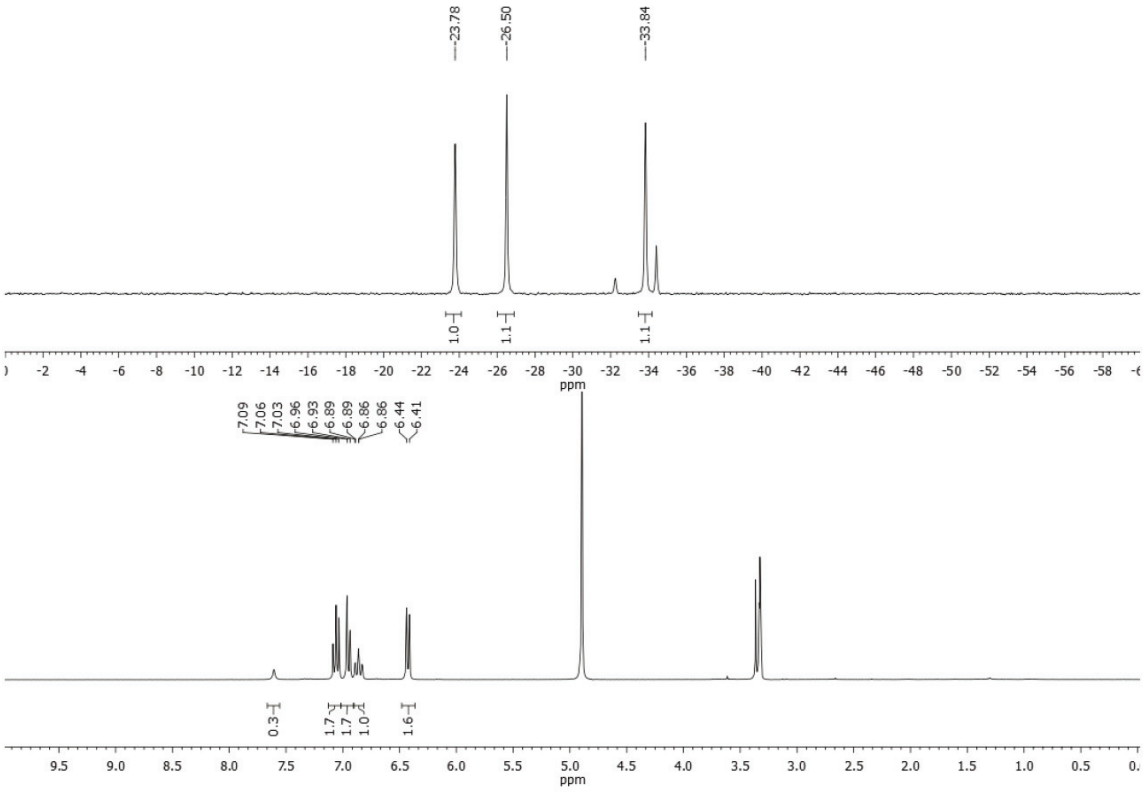


2,4,6-Trifluoro-3-(1*H*-naphtho[1,8-de][1,3,2]diazaborinin-2(3*H*)-yl)benzoic acid (11)

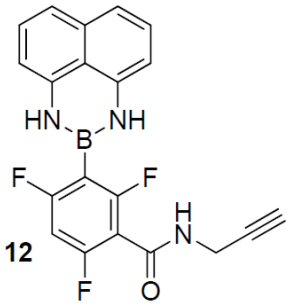


11

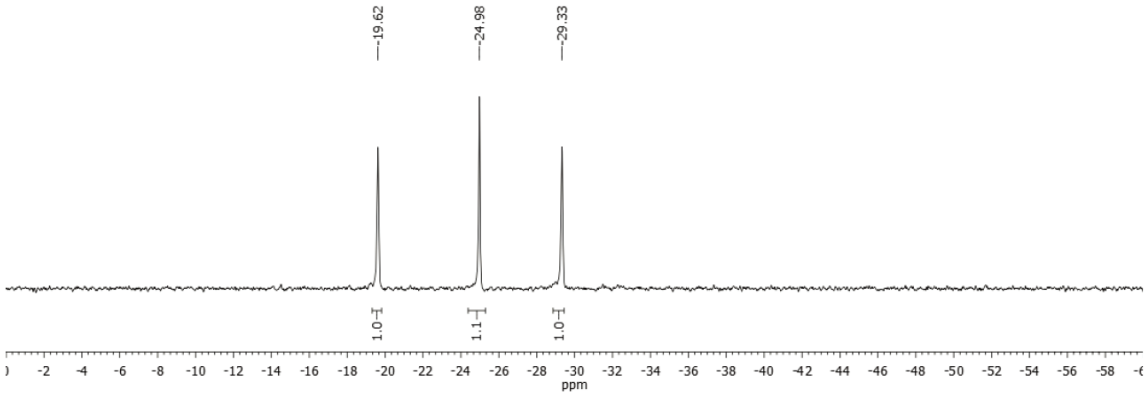
Chemical Formula: $C_{17}H_{10}BF_3N_2O_2$
Exact Mass: 342.0787
Molecular Weight: 342.0797

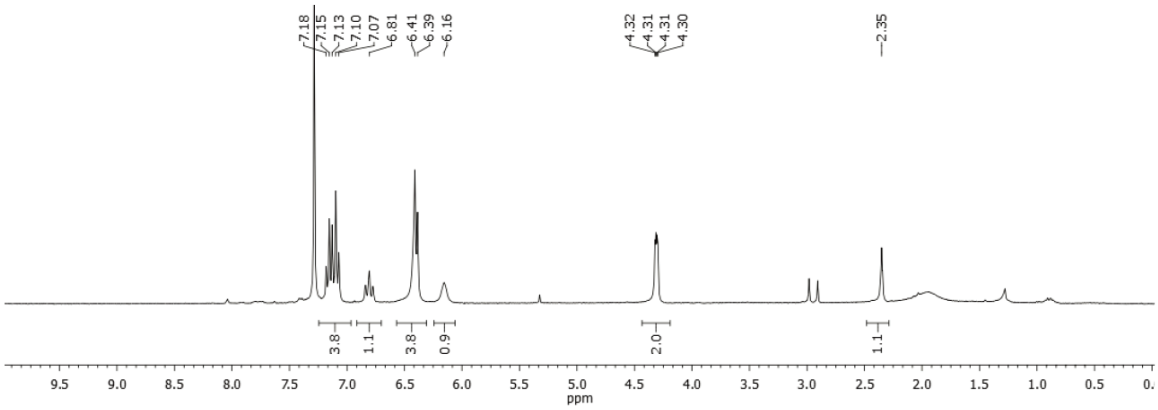


Alkynylborimidine (12)



Chemical Formula: $C_{20}H_{13}BF_3N_3O$
Exact Mass: 379.1104
Molecular Weight: 379.1429

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2.35
3.8
1.1
3.8
0.9
2.0
1.1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm