Supporting Information

Preparation and activities of macromolecule conjugates of the CCR5 antagonist Maraviroc

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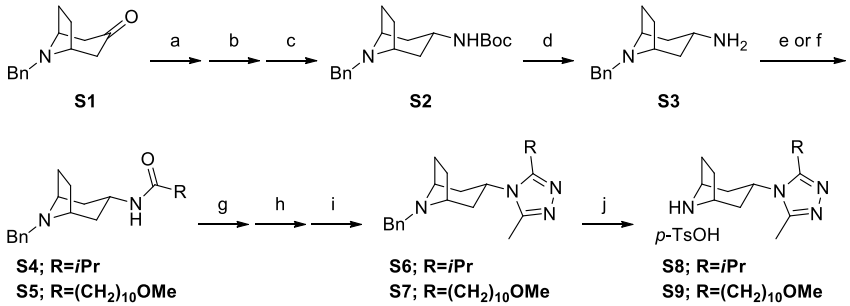
1. Synthetic Procedures for Maraviroc Derivatives

General information

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-600 (600 MHz), DRX-500 (500 MHz), or Varian Inova-400 (400 MHz) spectrometers in the stated solvents using tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (ppm) on the δ scale from an internal standard (NMR descriptions: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Coupling constants, *J*, are reported in Hertz. Mass spectroscopy was performed by The Scripps Research Institute Mass Spectrometer Center. Analytical thin-layer chromatography and flash column chromatography were performed on Merck Kieselgel 60 F254 silica gel plates and Silica Gel ZEOprep 60 ECO 40-63 Micron, respectively. Visualization was accomplished with UV light (254 nm) or $KMnO_4$. LCMS ESI analysis was performed on Agilent 1100 with SB C-18 column, using 1-100% acetonitrile gradient for 20 min method. HPLC was performed using a HITACHI ELITE LaChrom system. The sample was dissolved in acetnitrile solution, applied on a Luna 10u C18 column (250 x 10.00 mm, 5 µm), and eluted at 1 mL/min with a 30 min gradient from 10% to 90% solvent B, where solvent A is water (0.1% TFA solution) and solvent B is acetonitrile. The purity of all compounds used in bioassays was determined by this method to be >90%. Unless otherwise noted, all the materials were obtained from commercial suppliers, and were used without further purification. All solvents were commercially available grade. All reactions were carried out under argon atmosphere unless otherwise mentioned.

Scheme S1. Synthesis of Compounds **S8** and **S9**



[a]Reagents and Conditions: (a) hydroxylamine hydrochloride, NaOH, H_2O, EtOH, reflux, 20 h; (b) Na, toluene, reflux, 12h; (c) Boc_2O, THF, room temp, 3 days, 50%; (d) 4M HCl/dioxane, MeOH, room temp, 2 h, 100%; (e) *i*PrCOCl, Na_2CO_3, H_2O, CH_2Cl_2, room temp, overnight, 79%; (f) $MeO(CH_2)_{10}CO_2H$, WSC HCl, HOBt, Et_3N, DMF, room temp, overnight, 84%; (g) PCl_5, CH_2Cl_2, room temp, 2 h; (h) $AcNHNH_2$, *t*Amyl alcohol, room temp, overnight; (i) AcOH, AcOEt, 80 ˚C, 30 min, **S6** 37%, **S7** 82%; (f) 10% Pd/C, H_2 (50 psi), *p*-TsOH H_2O, MeOH, 1—3 h, **S8** 86%, **S9** 84%.

Synthesis of Compound S2. To a solution of **S1** (4.3 g, 0.020 mol) and hydroxylamine hydrochloride (2.78 g, 0.040 mol) in ethanol (60 mL) was added NaOH (1.6 g, 0.040 mol) and H_2O (15 mL) solution dropwise over 15 minutes, and the reaction was stirred at reflux for 20 h. The mixture was filtered through Celite, and the solvent was removed in vacuo. The mixture was extracted with dichloromethane (x4), and dried over anhydrous sodium sulfate, filtered, and the solvent was removed in vacuo. Sodium (5.83 g) was added to toluene (72 mL) at room temperature, and the mixture was heated to 100 ˚C. To the solution was added dropwise a solution of the above residue in toluene (50 mL) and 1-propanol (30 mL), and the reaction was stirred at reflux for 12 h. After cooling to 80 ˚C, 2-propanol was added to the reaction solution, and the solution was cooled to ambient temperature. The solution was diluted with water (160 mL) and acidified to pH 1 with concentrated hydrogen chloride solution, and the mixture was extracted with ethyl acetate. The aqueous layer was basified to pH 12 with sodium hydroxide solution, and the mixture was extracted with ethyl acetate, dried over

anhydrous sodium sulfate, filtered, and the solvent was removed in vacuo. To a solution of the residue in THF (50 mL) was added Boc_2O (4.8 g, 0.022 mol), and the reaction was stirred at room temperature for 3 days. After concentration under reduced pressure, the residue was triturated with diethylether, and filtered to afford the title compound as a white crystal (2.89 g, 46%). The solvent of the filtrate was removed in vacuo, and the residue was purified by column chromatography on silica gel. The solvent was removed in vacuo, the residue was triturated with diethylether, and filtered to afford compound **S2** as a second crystal (0.27 g, 4%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.43 (9H, s), 1.48 (2H, m), 1.68 (2H, m), 1.81 (2H, m), 2.01 (2H, m), 3.20 (2H, m), 3.53 (2H, s), 3.81 (1H, m), 4.33 (1H, d, J = 8.6 Hz), 7.22–7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 26.5, 28.4, 38.7, 42.8, 56.1, 58.7, 79.2, 126.7, 128.2, 128.5, 140.0, 155.3.

***Synthesis of Compound S3*.** To a solution of **S2** (3.13 g, 9.90 mmol) in methanol (30 mL) was dissolved in 4M HCl dioxane solution (30 mL), and the reaction was stirred at room temperature for 2 h. The solvents were removed in vacuo, and the residue was diluted with dichloromethane, washed with 1M NaOH solution, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo to afford compound **S3** as a brown oil (2.43 g, 100%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.59 (2H, m), 1.69 (2H, m), 1.77 (2H, m), 2.02 (2H, m), 3.13 (1H, m), 3.25 (2H, m), 3.61 (2H, s), 3.70 (2H, brs), 7.22–7.41 (5H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 26.7, 39.5, 43.5, 55.4, 58.4, 127.0, 128.3, 128.7, 139.2.

***Synthesis of Compound S4*.** To a solution of **S3** (649 mg, 3.00 mmol) in dichloromethane (4.5 mL) and H_2O (7.5 mL) was added sodium carbonate (478 mg, 4.50 mmol) and isobutyl chloride (377 μL, 3.60 mmol) at 0 ˚C, and the reaction was stirred at room temperature for overnight. The reaction was quenched by adding water, the mixture was extracted with dichloromethane, washed with brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S4** as a white solid (675 mg, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12 (6H, d, J = 6.9 Hz), 1.48 (2H, m), 1.71 (2H, m), 1.80 (2H, m), 2.02 (2H, m), 2.25 (1H, m), 3.21 (2H, m), 3.52 (2H, s), 4.14 (1H, m), 5.20 (1H, d, J = 8.5 Hz), 7.22–7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 19.6, 26.4, 35.7, 38.7, 41.2, 56.4, 58.9, 126.8, 128.2, 128.5, 140.0, 176.2.

***Synthesis of Compound S5*.** To a solution of **S4** (432 mg, 2.00 mmol) in *N,N*-dimethylformamide (6.0 mL) was added 11-methoxyundecanoic acid (475 mg, 2.20 mmol), 1-**e**thyl-3-(3-**d**imethyl**a**minopropyl)**c**arbodiimide hydrochloride (421 mg, 2.20 mmol), 1-hydroxybenzotriazole (297 mg, 2.20 mmol), and triethylamine (418 μL, 3.00 mmol), and the reaction was stirred at room temperature for overnight. The reaction was quenched by adding saturated sodium bicarbonate solution, the mixture was extracted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S5** as a pale-yellow oil (698 mg, 84%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25–1.33 (12H, m), 1.47–1.60 (6H, m), 1.72 (2H, m), 1.81 (2H, m), 2.04 (2H, m), 2.10 (2H, t, J = 7.6 Hz), 3.21 (2H, m), 3.33 (3H, s), 3.36 (2H, t, J = 6.7 Hz), 3.53 (2H, s), 4.15 (1H, m), 5.23 (1H, d, J = 8.5 Hz), 7.23–7.38 (5H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 25.8, 26.1, 26.4, 29.2, 29.3, 29.4, 29.5, 29.6, 37.0, 38.6, 41.2, 56.3, 58.5, 58.9, 73.0, 126.8, 128.2, 128.6, 139.8, 172.3.

***Synthesis of Compound S6*.** To a solution of pentachloride (542 mg, 2.60 mmol) in dichloromethane (4.0 mL) was added dropwise a solution of **S5** (573 mg, 2.00 mmol) in dichloromethane (6.0 mL) at 0 ˚C, and the reaction was stirred at room temperature for 2 h. To a reaction solution was added a solution of acetylhydrazine (237 mg, 3.20 mmol) in *tert*-amyl alcohol (7.0 mL) at 0 ˚C, and the reaction was stirred at room temperature for overnight. The solution was cooled to 0 ˚C, basified to pH 9 with 2M NaOH solution, and the mixture was extracted with dichloromethane, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo. To a solution of the residue in ethyl acetate (1.5 mL) was added acetic acid (200 μL), and the reaction was stirred at 80 ˚C for 30 minutes. The solution was basified to pH 12 with 4M NaOH solution, and the mixture was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column

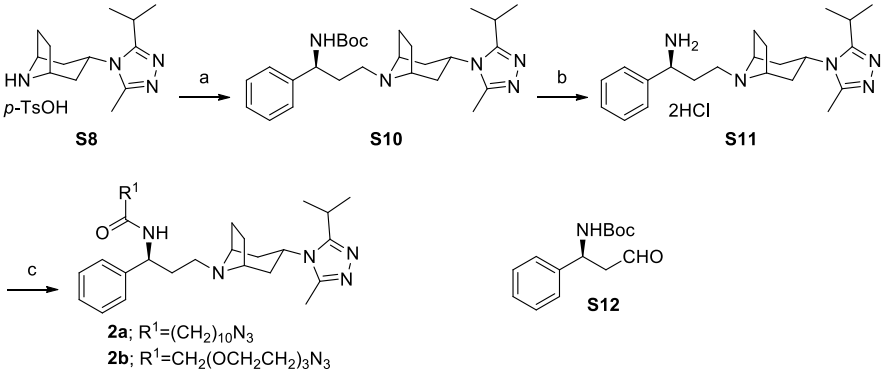
chromatography on silica gel to afford compound **S6** as a white solid (241 mg, 37%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (6H, d, J = 6.8 Hz), 1.67 (4H, m), 2.19 (2H, m), 2.28 (2H, m), 2.59 (3H, s), 3.03 (1H, m), 3.36 (2H, m), 3.59 (2H, s), 4.32 (1H, m), 7.26–7.40 (5H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.2, 21.7, 25.9, 26.5, 37.2, 47.4, 56.7, 58.8, 127.1, 128.3, 128.4, 139.6, 150.8, 159.1.

Synthesis of Compound S7. Compound **S7** was prepared from **S5** in a manner similar to that described for compound **S6** with a yield of 82% as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.32–1.43 (10H, m), 1.48 (2H, m), 1.61 (2H, m), 1.68–1.76 (4H, m), 1.81 (2H, m), 2.24 (2H, m), 2.33 (2H, m), 2.61 (3H, s), 2.81 (2H, t, J = 7.9 Hz), 3.38 (3H, s), 3.41 (4H, m), 3.64 (2H, s), 4.31 (1H, m), 7.31 (1H, m), 7.39 (2H, m), 7.44 (2H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.0, 26.1, 26.2, 26.5, 29.3, 29.46, 29.49, 29.5, 29.7, 37.1, 47.9, 56.6, 58.6, 58.8, 73.0, 127.1, 128.4 (2), 139.6, 150.8, 154.8.

Synthesis of Compound S8. Compound **S6** (220 mg, 0.678 mmol) and *p*-toluenesulfonic acid monohydrate (129 mg, 0,678 mmol) were dissolved in methanol (2.0 mL), and 10% palladium on carbon (50% wet, 88 mg) was added. The reaction was stirred under an atmosphere of hydrogen at 50 psi at room temperature for overnight. The mixture was filtered through Celite, and the solvent was removed in vacuo, and the residue was dissolved in hot 2-propanol (1 mL). The solution was allowed to granulated at room temperature for 1 h and then at 0 ˚C for 3 h. The white solid was filtered to afford compound **S8** as the tosylate salt (238 mg, 86%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.24 (6H, d, J = 6.7 Hz), 1.96–2.09 (6H, m), 2.28 (2H, m), 2.29 (3H, s), 2.44 (3H, s), 3.28 (1H, m), 4.14 (2H, m), 4.31 (1H, m), 7.14 (2H, m), 7.49 (2H, m), 8.83 (2H, brs); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 12.1, 20.8, 22.0, 24.4, 25.3, 32.9, 45.2, 54.3, 125.5, 128.1, 137.8, 145.4, 150.0, 158.7.

Synthesis of Compound S9. Compound **S9** was prepared from **S7** in a manner similar to that described for compound **S8** with a yield of 84% as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.26–1.32 (10H, m), 1.39 (2H, m), 1.47 (2H, m), 1.71 (2H, m), 2.02 (2H, m), 2.06-2.16 (4H, m), 2.29 (3H, s), 2.43 (2H, m), 2.76 (3H, s), 3.08 (2H, t, J = 7.6 Hz), 3.29 (2H, t, J = 6.5 Hz), 4.16 (2H, m), 4.49 (1H, m), 7.13 (2H, d, J = 7.8 Hz), 7.49 (2H, d, J = 7.8 Hz), 9.19 (1H, brs), 9.62 (1H, d, J = 10.4 Hz); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 11.4, 20.8, 25.1, 25.7, 28.3, 28.7, 28.9 (2), 29.0 (2), 31.7, 48.3, 53.9, 57.8, 71.9, 125.5, 128.1, 137.8, 145.4, 152.5, 155.6.

Scheme S2. Synthesis of Compound **2a** and **2b**[a]



[a]Reagents and Conditions: (a) **S12**, $NaBH(OAc)_3$, AcOH, 1,2-Dichloroethane, room temp, 3 h, 89%; (b) 4M HCl/dioxane, MeOH, room temp, 3 h, 100%; (c) RCO_2H, WSC HCl, HOBt, Et_3N, DMF, room temp, 3 h, **2a** 61%, **2b** 55%.

Synthesis of Compound S10. To a solution of **S8** (122 mg, 0.300 mmol) in 1,2-dichloroethane (2.5 mL) was added *(S)-tert*-butyl (3-oxo-1-phenylpropyl)carbamate **S12**[1] (90 mg, 0.360 mmol), which was prepared by 2 steps, acetic acid (25.8 μL, 0.450 mmol), and sodium triacetoxyborohydride (76.3 mg, 0.360 mmol) at 0 ˚C, and the reaction was stirred at

[1] Sarah J. Haycock-Lewandowski, Alexander Wilder, and Jens Åhman. Development of a bulk enabling route to maraviroc (UK-427,857), a CCR-5 receptor antagonist. *Org. Process Res. Dev.* **2008**, *12*, 1094–1103.

room temperature for 3 h. The reaction was quenched by adding saturated sodium bicarbonate solution, and the mixture was extracted with dichloromethane, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S10** as a pale-yellow amorphous (125 mg, 89%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.38–1.42 (15H, m), 1.63–1.69 (4H, m), 1.84–2.10 (4H, m), 2.28 (2H, m), 2.39 (2H, m), 2.57 (3H, s), 2.99 (1H, m), 3.35 (1H, m), 3.43 (1H, m), 4.30 (1H, m), 4.86 (1H, brs), 6.27 (1H, brs), 7.24–7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.7, 21.7, 25.9, 26.5, 26.6, 28.6, 35.0, 36.4, 47.3, 48.9, 58.9, 59.4, 79.5, 126.2, 127.2, 128.7, 142.9, 151.0, 155.6, 159.2.

Synthesis of Compound S11. To a solution of **S10** (103 mg, 0.220 mmol) in methanol (2.0 mL) was added 4M HCl/dioxane solution (2.0 mL), and the reaction was stirred at room temperature for 3 h. The solvents were removed in vacuo to afford compound **S11** as a pale-yellow solid (106 mg, 100%). ^{1}H NMR (DMSO-d_6, 600 MHz) δ 1.28 (6H, d, J = 6.8 Hz), 2.14–2.26 (5H, m), 2.35 (1H, m), 2.54 (1H, m), 2.63 (1H, m), 2.71–2.80 (2H, m), 2.83 (3H, s), 2.94 (1H, m), 3.26 (1H, m), 3.99 (1H, m), 4.14 (1H, m), 4.26 (1H, m), 4.44 (1H, m), 4.53 (1H, m), 7.39 (1H, m), 7.44 (2H, m), 7.61 (2H, m), 8.95 (3H, s); ^{13}C NMR (DMSO-d_6, 151 MHz) δ 11.4, 21.2, 24.4, 29.4, 32.5, 48.2, 52.0, 59.9, 61.9, 66.4, 127.5, 128.8, 128.9, 137.5, 152.4, 160.2.

Synthesis of Compound 2a. To a solution of **S11** (44.0 mg, 0.100 mmol) in *N,N*-dimethylformamide (1.0 mL) was added 11-azideundecanoic acid[2] (27.2 mg, 0.120 mmol), 1-**e**thyl-3-(3-dimethylaminopropyl)**c**arbodiimide hydrochloride (23.0 mg, 0.120 mmol), 1-hydroxybenzotriazole (16.2 mg, 0.120 mmol), and triethylamine (48.7 μL, 0.350 mmol), and the reaction was stirred at room temperature for 3 h. The reaction was quenched by adding saturated sodium bicarbonate solution, the mixture was extracted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **2a** as a pale-yellow oil (35.2 mg, 61%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.25–1.32 (10H, m), 1.35 (2H, m), 1.38 (3H, d, J = 6.8 Hz), 1.39 (3H, d, J = 6.8 Hz), 1.98 (2H, m), 2.07 (2H, m), 2.18 (3H, m), 2.25 (1H, m), 2.42 (2H, t, J = 6.8 Hz), 2.52 (3H, s), 2.99 (1H, m), 3.25 (2H, t, J = 7.0 Hz), 3.39 (1H, m), 4.30 (1H, m), 5.15 (1H, dt, J = 7.0, 7.0 Hz), 6.67 (1H, d, J = 7.0 Hz), 7.25–7.30 (3H, m), 7.34–7.36 (2H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.2, 21.7, 25.7, 25.9, 26.6, 26.7, 28.8, 29.1, 29.31, 29.34, 29.4, 34.6, 35.7, 35.8, 37.0, 47.3, 48.1, 51.5, 52.3, 58.5, 58.8, 126.4, 127.4, 128.7, 142.0, 150.6, 159.1, 172.2; HRMS (ESI) *m/z* Calcd for $C_{33}H_{52}N_8O$ 577.4337; Found 577.4326 (Δ = 1.9 ppm); HPLC: 91.8% pure, t_R=20.64 min.

Synthesis of Compound 2b. Compound **2b** was prepared from **S11** in a manner similar to that described for compound **2a** with a yield of 55% as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.38 (6H, d, J = 6.8 Hz), 1.62 (4H, m), 2.00 (2H, m), 2.07 (2H, m), 2.25 (2H, m), 2.42 (2H, m), 2.51 (3H, s), 3.00 (1H, m), 3.34–3.39 (4H, m), 3.62–3.69 (10H, m), 3.97 (1H, d, J = 15.6 Hz), 4.04 (1H, d, J = 15.6 Hz), 4.27 (1H, m), 5.21 (1H, dt, J = 7.0, 7.0 Hz), 7.27 (1H, m), 7.34–7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.1, 21.6, 25.8, 26.55, 26.63, 29.7, 35.5, 35.8, 35.9, 47.3, 48.4, 50.6, 51.1, 58.6, 59.0, 70.0, 70.4, 70.45, 70.54, 70.7, 71.0, 126.7, 127.5, 128.7, 141.9, 150.8, 159.1, 169.1; HRMS (ESI) *m/z* Calcd for $C_{30}H_{46}N_8O_4$ 582.3715; Found 582.3723 (Δ = 1.4 ppm); HPLC: 92.4% pure, t_R=15.77 min.

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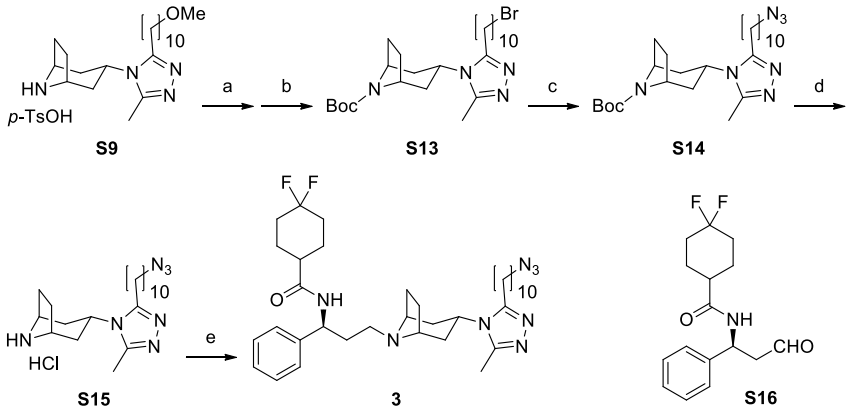
[2] Cyrus A. Anderson, Phillip G. Taylor, Mary A. Zeller and Steven C. Zimmerman. Room temperature, copper-catalyzed amination of bromonaphtyyridines with aqueous ammonia. *J. Org. Chem.*, **2010**, *75*, 4848–4851

Scheme S3. Synthesis of compound **3**[a]



[a]Reagents and Conditions: (a) 48% HBr solution, 100 ˚C, 2 h; (b) Boc_2O, NaOHaq, CH_2Cl_2, room temp, overnight, 100%; (c) NaN_3, EtOH, reflux, 4 h, 39%; (d) 4M HCl/dioxane, room temp, 3 h, 100%; (e) **S16**, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, room temp, 3 h, 69%.

Synthesis of Compound S13. Compound **S9** (86.6 mg, 0.162 mmol) was dissolved in 48% HBr solution (1.0 mL), the reaction was stirred at 100 ˚C for 2 h. The reaction solution was cooled to 0 ˚C, and to the reaction solution was basified to pH 12 with NaOH solution, and added a solution of Boc_2O (70.7 mg, 0.324 mmol) in dichloromethane (3.0 mL) dropwise. The reaction was stirred at room temperature for overnight. The reaction was diluted with water, and the mixture was extracted with chloroform (x2), washed with brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S13** as a pale-yellow oil (91.3 mg, 100%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24–1.45 (12H, m), 1.51 (9H, s), 1.73–1.76 (6H, m), 1.83 (2H, m), 2.14 (3H, m), 2.33 (1H, m), 2.45 (3H, s), 2.71 (2H, t, J = 7.8 Hz), 3.40 (2H, t, J = 7.8 Hz), 4.33–4.50 (3H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 12.8, 26.1, 27.9, 28.1, 28.5, 28.7, 29.2, 29.29, 29.31, 32.8, 34.0, 35.1, 36.2, 47.3, 52.6, 53.2, 80.1, 150.4, 153.2, 154.5.

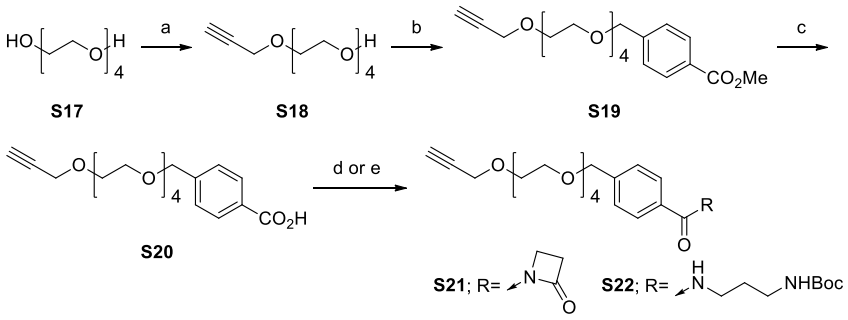
Synthesis of Compound S14. To a solution of **S13** (76.7 mg, 0.150 mmol) in ethanol (2.0 mL) was added sodium azide (29.2 mg, 0.450 mmol), and the reaction was stirred at 100 ˚C for 4 h. The reaction was quenched by adding water, and the mixture was extracted with chloroform (x2), dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S14** as a colorless oil (27.4 mg, 39%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.25–1.42 (12H, m), 1.51 (9H, s), 1.59 (2H, m), 1.70–1.79 (6H, m), 2.16 (3H, m), 2.35 (1H, m), 2.46 (3H, s), 2.70 (2H, t, J = 7.8 Hz), 3.26 (2H, t, J = 7.8 Hz), 4.32–4.49 (3H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 12.9, 26.2, 26.8, 28.0, 28.6, 29.2, 29.38, 29.44, 29.5, 29.8, 35.2, 36.3, 47.4, 51.6, 52.7, 53.3, 80.3, 150.6, 153.4, 154.6.

Synthesis of Compound S15. Compound **S14** (23.4 mg, 0.0494 mmol) was dissolved in 4M HCl/dioxane (0.5 mL), and the reaction was stirred at room temperature for 3 h. The solvent was removed in vacuo to afford compound **S15** as a white solid (22.0 mg, 100%). ^{1}H NMR (DMSO-d_6, 600 MHz) δ 1.25–1.32 (10H, m), 1.39 (2H, m), 1.51 (2H, m), 1.70 (2H, m), 2.01–2.11 (6H, m), 2.49 (2H, m), 2.78 (3H, s), 3.10 (2H, t, J = 7.6 Hz), 3.30 (2H, t, J = 6.9 Hz), 4.13 (2H, m), 4.47 (1H, m), 9.49 (1H, brs), 10.11 (1H, m); ^{13}C NMR (DMSO-d_6, 151 MHz) δ 11.5, 24.4, 25.2, 26.0, 26.2, 28.3, 28.6, 28.7, 28.86, 28.91, 31.6, 48.4, 50.6, 53.7, 66.4, 152.4, 155.5.

Synthesis of Compound 3. To a solution of **S15** (20.6 mg, 0.0502 mmol) in dichloromethane (1.0 mL) was added

(S)-4,4-difluoro-*N*-(3-oxo-1-phenylpropyl)cyclohexanecarboxamide **S16**[31] (17.8 mg, 0.0603 mmol), which was prepared by 3 steps, acetic acid (4.3 μL, 0.0754 mmol), and sodium triacetoxyborohydride (12.8 mg, 0.0603 mmol), and the reaction was stirred at room temperature for 3 h. The reaction was quenched by adding saturated sodium bicarbonate solution, and the mixture was extracted with chloroform, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **3** as a colorless oil (22.7 mg, 69%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.26–1.41 (12H, m), 1.58–2.25 (23H, m), 2.44 (2H, m), 2.49 (3H, s), 2.71 (2H, t, J = 7.8 Hz), 3.25 (2H, t, J = 6.9 Hz), 3.40 (2H, m), 4.24 (1H, m), 5.13 (1H, dt, J = 7.1, 7.1 Hz), 6.77 (1H, d, J = 7.1 Hz), 7.27–7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.2, 26.1 ($J^{13}C$–^{19}F = 10 Hz), 26.2 ($J^{13}C$–^{19}F = 10 Hz), 26.8, 26.9, 27.0, 28.1, 29.0, 29.3, 29.4, 29.5, 29.54, 29.55, 32.9 ($J^{13}C$–^{19}F = 25, 4 Hz), 33.1 ($J^{13}C$–^{19}F = 25, 4 Hz), 34.8, 35.2, 35.3, 43.0, 51.6, 52.2, 58.2, 59.0, 122.8 ($J^{13}C$–^{19}F = 241, 241 Hz), 126.6, 127.7, 128.9, 142.0, 150.8, 154.9, 173.6; HRMS (ESI) *m/z* Calcd for $C_{36}H_{54}F_2N_8O$ 653.4461; Found 653.4457 (Δ = 0.6 ppm); HPLC: 97.6% pure, t_R=22.26 min.

Scheme S4. Synthesis of compounds **S21** and **S22**[a]



[a]Reagents and Conditions: (a) propargyl bromide, NaH, THF, room temp, overnight, 76%; (b) methyl 4-(bromomethyl)benzoate, NaH, THF, room temp, 2 h, 89%; (c) 2M NaOH solution, EtOH, room temp, 2 h, 74%; (d)(1) $SOCl_2$, room temp, 3 h; (2) *n*BuLi, 2-azetidinone, THF, -78 ˚C, 3 h, 57%; (e) *N*-Boc-1,3-propanediamine, WSC-HCl, HOBt, Et_3N, DMF, room temp, overnight, ??%.

Synthesis of Compound S18. To a solution of **S17** (17.3 mL, 0.100 mol) in THF (50 mL) was added NaH (60% oil dispersion, 2.60 g, 0.0650 mol) portionwise at 0 ˚C, and the reaction was stirred at 0 ˚C for 1 h. Propargyl bromide (5.95 g, 0.0500 mol) was added to the reaction solution, and the reaction was stirred at room temperature for overnight. The reaction was quenched by adding ice cold water, and the mixture was extracted with dichloromethane (x2), washed with brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S18** as a colorless oil 8.84 g, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.44 (1H, t, J = 2.4 Hz), 2.72 (1H, brs), 3.62 (2H, m), 3.67–3.70 (14H, m), 4.21 (2H, d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 58.5, 61.8, 69.2, 70.4, 70.5, 70.6, 70.67, 70.72, 72.6, 74.6, 79.7.

Synthesis of Compound S19. To a solution of **S18** (5.81 g, 0.0250 mol) in THF (100 mL) was added NaH (60% oil dispersion, 1.26 g, 0.0300 mol) portionwise at 0 ˚C, and the reaction was stirred at 0 ˚C for 30 minutes. A solution of methyl (bromomethyl)benzoate (6.88 g, 0.0300 mol) in THF (25 mL) was added to the reaction solution at 0 ˚C, and the reaction was stirred at room temperature for 2 h. The reaction was quenched by adding saturated ammonium chloride, and the mixture was extracted with ethyl acetate (x2), washed with brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford

[3] Jens Åhman, Melissa Birch, Sarah J. Haycock-Lewandowski, James Long, and Alexander Wilder. Process research and scale-up of a commercialisable route maraviroc (UK-427,857), a CCR-5 receptor antagonist. *Org. Process Res. Dev.* **2008**, *12*, 1104-1113.

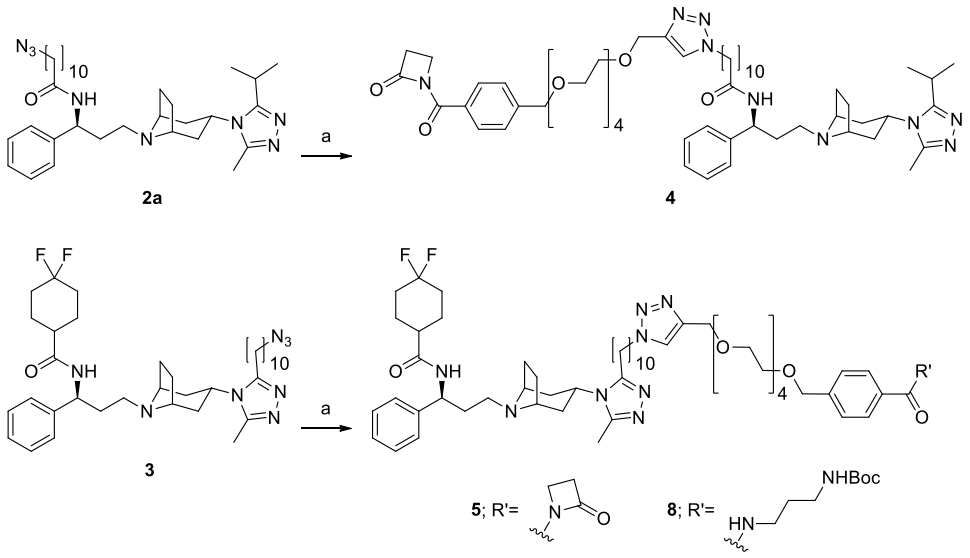
compound **S19** as a colorless oil (8.47 g, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (1H, t, J = 2.4 Hz), 3.66–3.69 (16H, m), 3.91 (3H, s), 4.20 (2H, d, J = 2.4 Hz), 4.62 (2H, s), 7.43 (2H, m), 8.01 (2H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 52.2, 58.5, 69.2, 70.0, 70.5, 70.68, 70.71 (2), 70.8, 72.7, 74.6, 77.4, 79.8.

Synthesis of Compound S20. To a solution of **S19** (7.61 g, 0.0200 mol) in ethanol (40 mL) was added 2M NaOH solution at 0 ˚C, and the reaction was stirred at room temperature for 2 h. Ethanol was removed in vacuo, and the residue was acidified to pH 1 with 1M HCl solution. The mixture was extracted with dichloromethane (x2), dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S20** as a colorless oil (5.41 g, 74%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.41 (1H, t, J = 2.4 Hz), 3.49–3.56 (12H, m), 3.59 (4H, m), 4.14 (2H, d, J = 2.4 Hz), 4.58 (2H, s), 7.45 (2H, m), 7.93 (2H, m); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 57.5, 68.5, 69.4, 69.5, 69.75, 69.78, 69.79, 69.81, 69.9, 71.4, 77.1, 80.3, 127.1, 129.3, 129.7, 143.7, 167.2.

Synthesis of Compound S21. Compound **S20** (1.10 g, 3.00 mmol) was dissolved in thionyl chloride (10 mL), and the reaction was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with dichloromethane. The solution was washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo to afford 4-(2,5,8,11,14-pentaoxaheptadec-16-yn-1-yl)benzoyl chloride as a colorless oil (1.15 g, 100%). To a solution of 2-azetidinone (234 mg, 3.29 mmol) in THF (10 mL) was added 2.5M *n*BuLi/hexane solution (1.31 mL, 3.29 mmol) dropwise at -78 ˚C, and the reaction was stirred at -78 ˚C for 45 minutes. A solution of 4-(2,5,8,11,14-pentaoxaheptadec-16-yn-1-yl)benzoyl chloride (1.15 g) in THF (6.0 mL) was added to the reaction solution at —78 ˚C, and the reaction was stirred at —78 ˚C for 3 h. The reaction was added by adding 10% citric acid solution, and the mixture was extracted with ethyl acetate, washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S21** as a colorless oil (7.19 g, 57%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.44 (1H, t, J = 2.4 Hz), 3.11 (2H, t, J = 5.5 Hz), 3.66–3.69 (16H, m), 3.78 (2H, t, J = 5.5 Hz), 4.20 (2H, d, J = 2.4 Hz), 4.63 (2H, s), 7.45 (2H, m), 7.97 (2H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 35.1, 36.8, 58.4, 69.2, 69.9, 70.5, 70.6, 70.67 (2), 70.73, 72.6, 74.6, 79.7, 127.0, 130.0, 131.0, 144.1, 164.0, 166.0.

Synthesis of Compound S22. To a solution of **S20** (366 mg, 1.00 mmol) in *N,N*-dimethylformamide (6.0 mL) was added *tert*-butyl (3-aminopropyl)carbamate (192 μL, 1.10 mmol), 1-**e**thyl-3-(3-dimethylaminopropyl)**c**arbodiimide hydrochloride (211 mg, 1.10 mmol), 1-hydroxybenzotriazole (148 mg, 1.10 mmol), and triethylamine (167 μL, 1.20 mmol), and the reaction was stirred at room temperature for overnight. The reaction was quenched by adding saturated sodium bicarbonate solution, and the mixture was extracted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel to afford compound **S22** as a colorless oil (522 mg, 100%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46 (9H, s), 1.71 (2H, m), 2.43 (1H, t, J = 2.4 Hz), 3.24 (2H, dt, J = 6.3, 6.3 Hz), 3.50 (2H, dt, J = 6.2, 6.2 Hz), 3.67 (16H, m), 4.19 (2H, d, J = 2.4 Hz), 4.61 (2H, s), 5.00 (1H, brs), 7.25 (1H, brs), 7.41 (2H, d, J = 7.9 Hz), 7.83 (2H, d, J = 7.9Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 28.5, 30.4, 36.2, 37.2, 58.5, 69.2, 69.8, 70.5, 70.70, 70.73 (3), 70.8, 72.8, 74.7, 79.6, 79.8, 127.2, 127.6, 133.9, 142.0, 157.1, 167.4.

Scheme S5. Synthesis of compound **4**, **5**, and **8**[a]



[a]Reagents and Conditions: (a) **S21** or **S22**, THPTAaq, $CuSO_4$aq, sodium ascorbate, H_2O, *t*BuOH, room temp, 2 h, **4** 100%, **5** 67%, **8** 82%.

Synthesis of Compound 4. To a solution of **2a** (20.0 mg, 0.0347 mmol) in *tert*-butanol (1.56 mL) was added **S21** (17.4 mg, 0.0416 mmol), 50 mM solution of tris(3-hydroxypropyltriazolylmethyl)amine (THPTA) (347 μL, 0.0174 mmol), 50 mM solution of $CuSO_4$ (347 μL, 0.0174 mmol), and 50 mM solution of sodium ascorbate (347 μL, 0.0174 mmol), and the reaction was stirred at room temperature for 2 h. The mixture was extracted with chloroform (x2), washed with brine, dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo, the residue was purified by preparative thin-layer chromatography (PTLC) to afford compound **4** as a colorless oil (39.7 mg, 100%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.24–1.29 (12H, m), 1.38 (6H, m), 1.59–1.67 (6H, m), 1.87 (2H, m), 1.99 (2H, m), 2.07 (2H, m), 2.18 (3H, m), 2.26 (1H, m), 2.42 (2H, m), 2.51 (3H, s), 3.00 (1H, m), 3.10 (2H, t, J = 5.4 Hz), 3.40 (2H, m), 3.63–3.70 (16H, m), 3.76 (2H, t, J = 5.4 Hz), 4.29 (1H, m), 4.31 (2H, t, J = 7.2 Hz), 4.62 (2H, s), 4.67 (2H, s), 5.15 (1H, dt, J = 7.1, 7.1 Hz), 6.99 (1H, d, J = 7.1 Hz), 7.25 (1H, m), 7.29–7.34 (4H, m), 7.43 (2H, d, J = 7.9 Hz), 7.57 (1H, s), 7.95 (2H, d, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 14.0, 22.5, 26.5, 26.6, 27.2, 27.41, 27.44, 29.7, 30.06 (2), 31.1, 35.5, 35.9, 36.5, 36.6, 37.6 (2), 48.1, 49.0, 51.1, 53.0, 59.4, 59.7, 65.5, 70.5, 70.7, 71.3, 71.35, 71.37 (2), 71.4, 71.5, 73.3, 123.3, 127.3, 127.7, 128.1, 129.4, 130.7, 131.8, 143.1, 144.8, 145.8, 151.4, 160.0, 164.8, 166.8, 173.2; HRMS (ESI) *m/z* Calcd for $C_{55}H_{81}N_9O_8$ 996.6281; Found 996.6278 (Δ = 0.3 ppm); HPLC: 96.6% pure, t_R=19.93 min.

Synthesis of Compound 5. Compound **5** was prepared from **3** and **S21** in a manner similar to that described for compound **4** with a yield of 67% as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.25–1.32 (10H, m), 1.39 (2H, m), 1.57–2.29 (23H, m), 2.44 (2H, m), 2.49 (3H, s), 2.71 (2H, t, J = 7.8 Hz), 3.11 (2H, t, J = 5.4 Hz), 3.37–3.42 (2H, m), 3.65–3.69 (16H, m), 3.78 (2H, t, J = 5.4 Hz), 4.24 (1H, m), 4.31 (2H, t, J = 7.2 Hz), 4.63 (2H, s), 4.67 (2H, s), 5.13 (1H, m), 6.67 (1H, d, J = 6.2 Hz), 7.28 (3H, m), 7.35 (2H, m), 7.45 (2H, d, J = 7.8 Hz), 7.56 (1H, s), 7.95 (2H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.0, 25.9 ($J^{13}C–^{19}F$ = 9 Hz), 26.0 ($J^{13}C–^{19}F$ = 9 Hz), 26.4, 26.79, 26.84, 27.9, 28.9, 29.2, 29.25, 29.28, 29.31, 29.7, 30.3, 32.79 ($J^{13}C–^{19}F$ = 24, 5 Hz), 32.81 ($J^{13}C–^{19}F$ = 24, 5 Hz), 34.7, 34.97, 35.05, 35.1, 36.8, 42.9, 47.7, 50.3, 52.1, 58.0, 58.8, 64.7, 69.7, 69.9, 70.5, 70.55, 70.57 (2), 70.59, 70.6, 72.5, 122.4, 122.6 ($J^{13}C–^{19}F$ = 242, 242 Hz), 126.4, 126.9, 127.5, 128.8, 129.9, 131.0, 141.8, 144.0, 145.1, 150.6, 154.7, 164.0, 166.0, 173.3; HRMS (ESI) *m/z* Calcd for $C_{58}H_{83}F_2N_9O_8$ 1072.6405; Found 1072.6402 (Δ = 0.3 ppm); HPLC: 95.8% pure, t_R=20.87 min.

Synthesis of Compound 8. Compound **8** was prepared from **3** and **S22** in a manner similar to that described for compound **4** with a yield of 82% as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.26–1.39 (12H, m), 1.45 (9H, s),

1.59–2.26 (23H, m), 2.44 (2H, m), 2.49 (3H, s), 2.70 (2H, t, J = 7.8 Hz), 3.23 (2H, m), 3.37–3.41 (2H, m), 3.50 (2H, m), 3.63–3.69 (16H, m), 4.24 (1H, m), 4.31 (2H, t, J = 7.3 Hz), 4.60 (2H, s), 4.66 (2H, s), 5.12 (1H, m), 5.17 (1H, brs), 6.73 (1H, brs), 7.28 (3H, m), 7.34 (2H, m), 7.40 (2H, d, J = 8.0 Hz), 7.49 (1H, brs), 7.57 (1H, s), 7.83 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.0, 25.9, 26.0 ($J_{^{13}C-^{19}F}$ = 10 Hz), 26.4, 28.4, 28.9, 29.18, 29.23, 29.26, 29.28, 29.7, 30.1, 30.2, 32.7 ($J_{^{13}C-^{19}F}$ = 24, 5 Hz), 32.8 ($J_{^{13}C-^{19}F}$ = 24, 5 Hz), 34.6, 35.0, 35.2, 36.1, 37.0, 42.8, 47.6, 47.8, 50.3, 51.9, 58.1, 58.9, 64.6, 69.66, 69.70, 70.47, 70.54, 70.56, 70.59, 70.61, 72.6, 79.4, 122.5, 122.6 ($J_{^{13}C-^{19}F}$ = 241, 241 Hz), 124.2, 126.4, 127.2, 127.7, 128.5, 133.8, 141.7, 141.9, 145.0, 150.7, 154.7, 156.9, 167.4, 173.5; HRMS (ESI) *m/z* Calcd for $C_{63}H_{96}F_2N_{10}O_9$ 1175.7402; Found 1175.7403 (Δ = 0.1 ppm); HPLC: 96.8% pure, t_R=21.67 min.

2. Time Dependency of Conjugation Reaction with mAb 38C2

A mixture of 125 µL of mAb 38C2, 10.6 µL of PBS (pH 7.4), and 2.75 µL of the compound **5** (10 mM DMSO solution, 4 eq) was incubated at 23 ˚C for 120 min. The reaction conversion at 0, 3, 10, 30, 60, and 120 min was verified by loss of catalytic activity mAb 38C2 as monitored by methodol-based assay.[4]

Scheme S6. Conjugation reaction of compound **5** with mAb 38C2

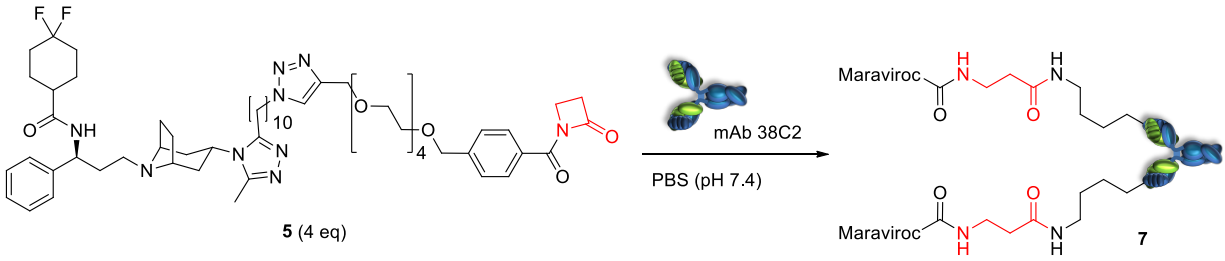
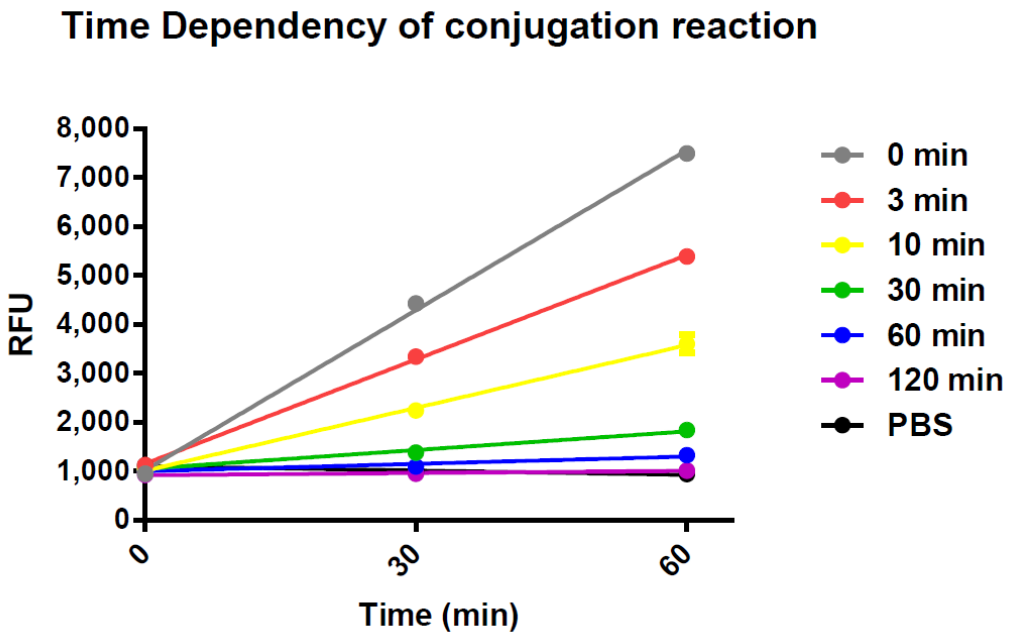


Figure S1. Result of methodol assay

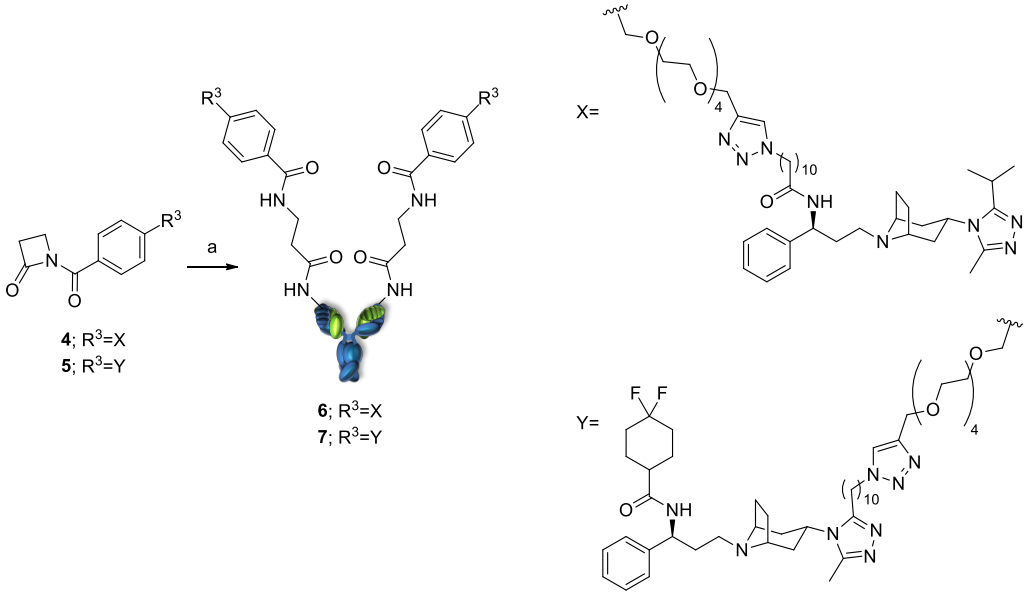


[4] Sinha, S. C.; Das, S.; Li, L. S.; Lerner, R. A. Barbas III, C. F. *Nat. Protoc*. **2007**, *2*, 449-456.

3. Preparation of Chemically Programmed Antibodies 6 and 7

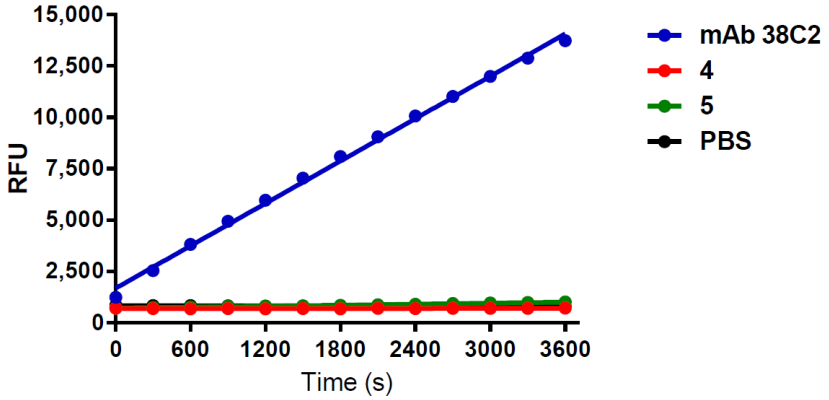
A mixture of 125 μL of mouse mAb 38C2, 10.6 μL of PBS (pH 7.4), and 2.75 μL of the compound **4** or **5** (10 mM DMSO solution, 4 eq) was incubated at 23 ˚C for 2 h. Complete conversion of the reaction was verified by loss of catalytic activity mAb 38C2 as monitored by methodol-based assay.[5] The reaction mixture was purified by gel filtration using Micro Bio-Spin column (BIO-RAD) to remove excess small molecules to obtain the conjugates **6** and **7**. The concentration was measured by nano-drop, and the molecular weights of **4** and **5** were analyzed by MALDI-TOF and ESI mass analysis.

Scheme S7. Synthesis of compound 6 and 7[a]



[a]Reagents and Conditions: (a) mAb 38C2, 100 mM PBS solution (pH 7.4), room temp, 2 h.

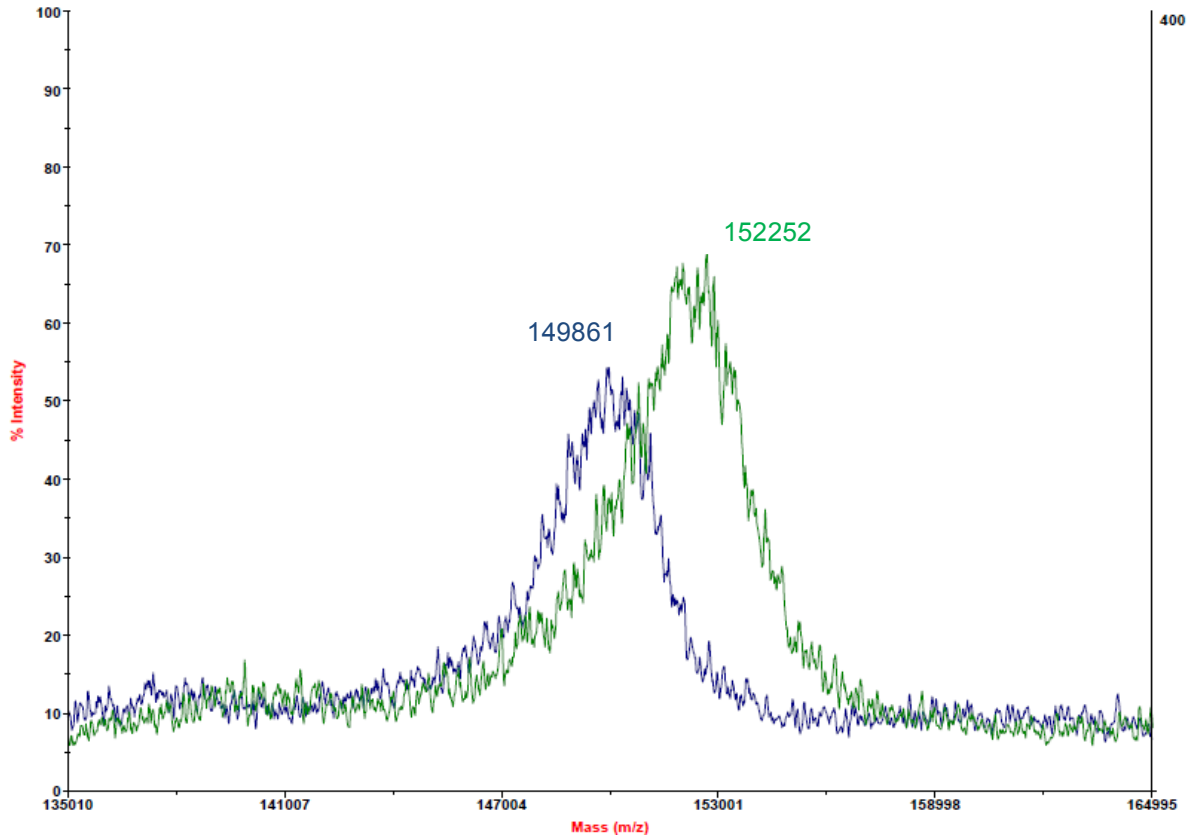
Figure S2. Result of methodol assay



[5] Sinha, S. C.; Das, S.; Li, L. S.; Lerner, R. A. Barbas III, C. F. *Nat. Protoc*. **2007**, *2*, 449-456.

Figure S3. MALDI-TOF mass analysis

Overlay of MALDI mass spectra of mAb 38C2 (blue, MW_{ave} = 149861) and conjugate **6** (green, MW_{ave} = 152252)



Overlay of MALDI mass spectra of mAb 38C2 (blue, MW_{ave} = 149861) and conjugate **7** (green, MW_{ave} = 152182)

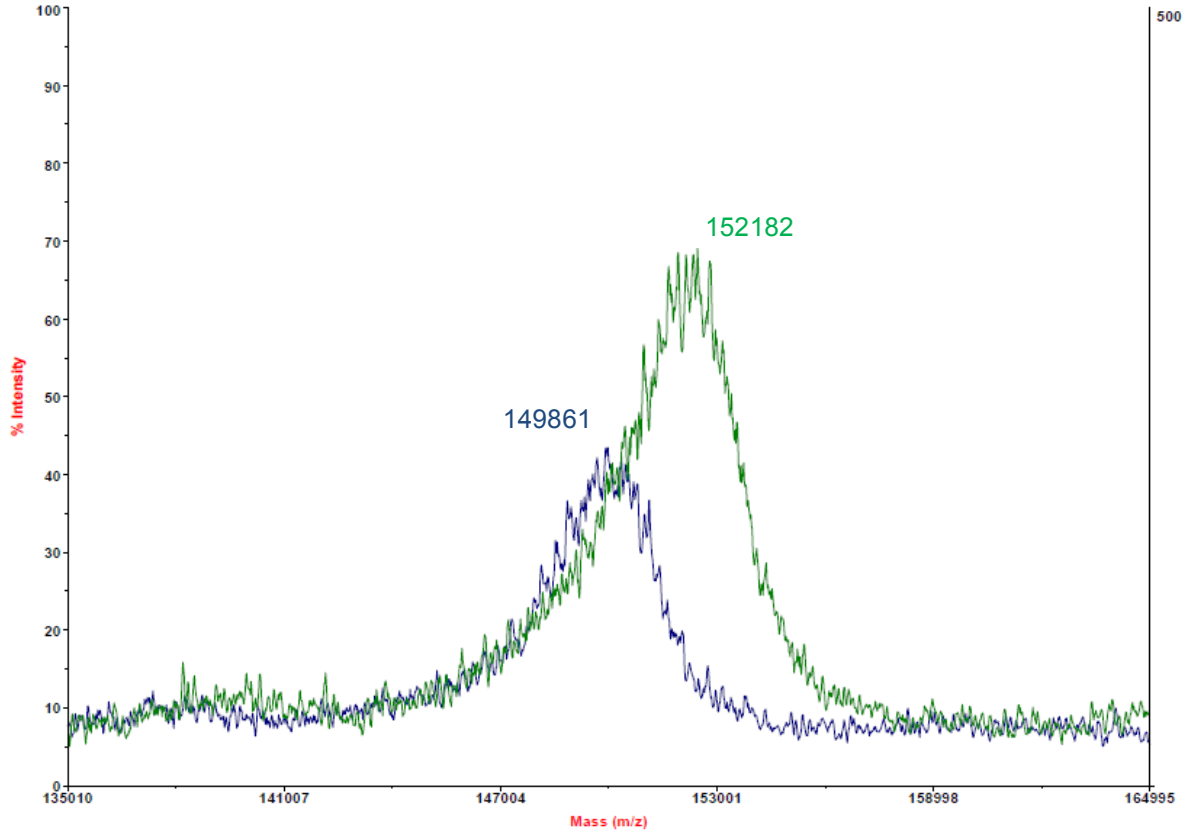
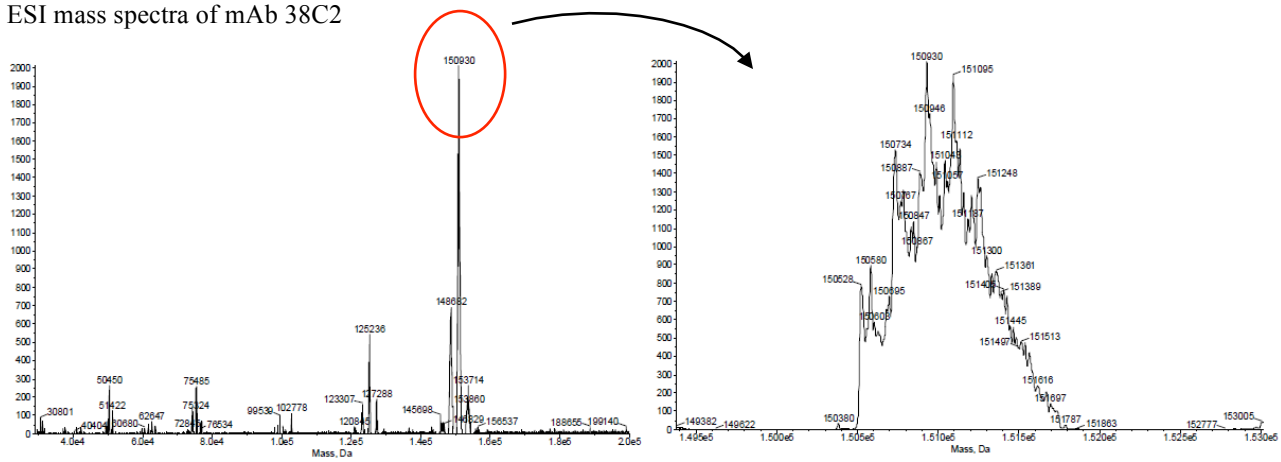
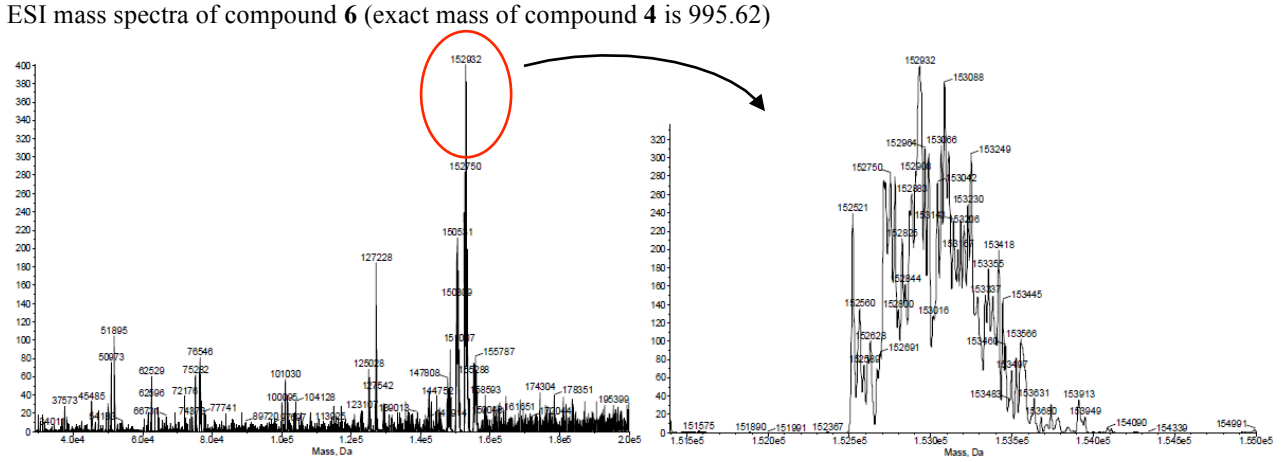


Figure S4. ESI mass analysis

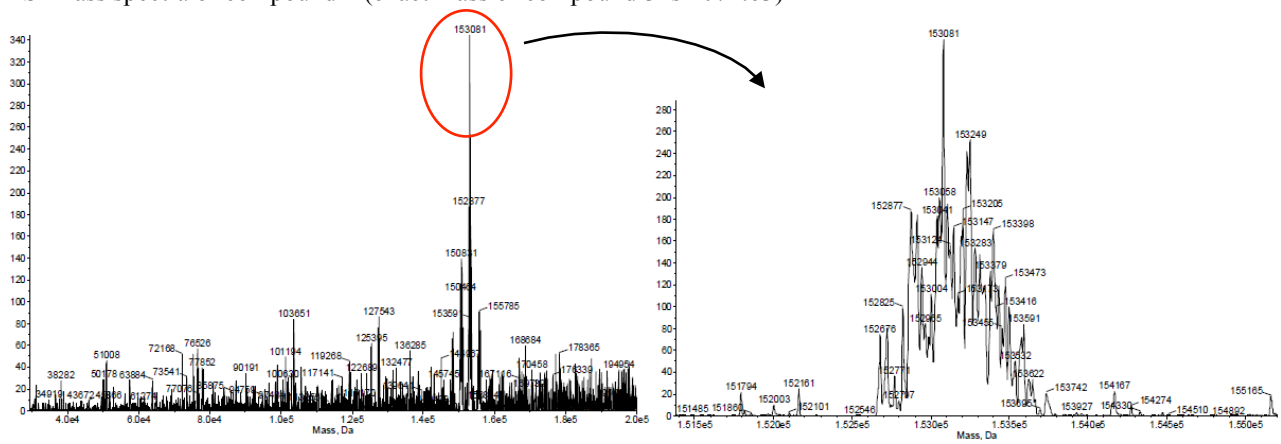
ESI mass spectra of mAb 38C2



ESI mass spectra of compound **6** (exact mass of compound **4** is 995.62)

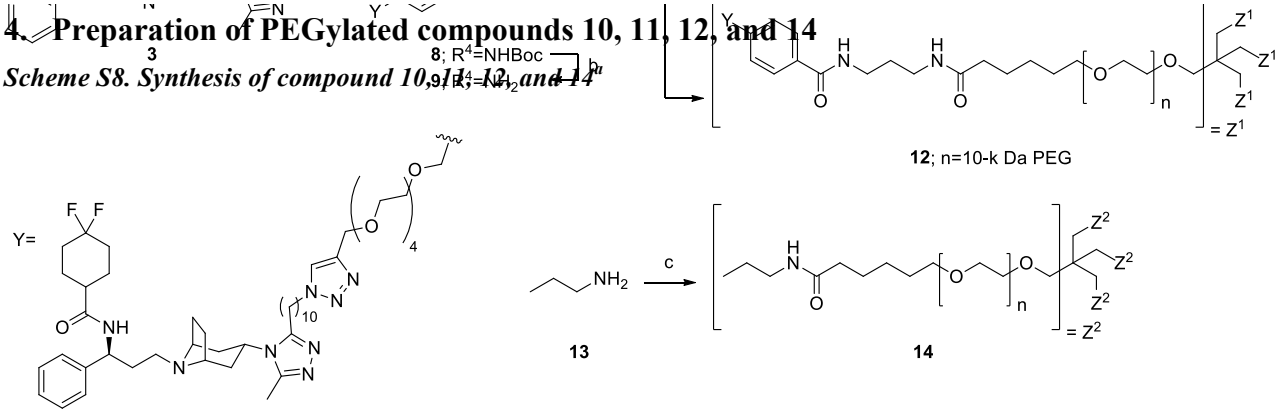


ESI mass spectra of compound **7** (exact mass of compound **5** is 1071.63)



4. Preparation of PEGylated compounds 10, 11, 12, and 14

Scheme S8. Synthesis of compound 10, 11, 12, and 14



[a]Reagents and Conditions: (a) TFA, CH_2Cl_2, room temp, 1 h, quant; (b) SUNBRIGHT ME-050AS or ME-400AS, DMF, room temp, 3 h, **10** 46%, **11** 82%, **12** 92%, **14** 92%.

Synthesis of Compound 9. To a solution of **8** (15.8 mg, 0.0134 mmol) in CH_2Cl_2 (0.8 mL) was added TFA (0.4 mL) at room temperature, and the reaction was stirred for 1 h. The mixture was concentrated, and then the residue was filtered by TFA removal column (PL-HCO_3 MP-SPE) to get free base. The filtrate was concentrated to afford compound **9** as a colorless oil (14.5 mg, 100%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.23–1.38 (12H, m), 1.57–2.23 (23H, m), 2.44 (2H, m), 2.49 (3H, s), 2.70 (2H, m), 2.90 (2H, brs), 3.37 (2H, m), 3.50 (2H, m), 3.50 (2H, m), 3.62–3.68 (16H, m), 4.22 (1H, m), 4.29 (2H, t, J = 7.3 Hz), 4.57 (2H, s), 4.63 (2H, s), 5.12 (1H, m), 6.93 (1H, m), 7.25–7.35 (7H, m), 7.59 (1H, s), 7.80 (2H, d, J = 8.0 Hz), 8.20 (1H, brs); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 12.9, 25.9, 26.0, 26.4 ($J^{13}C$–^{19}F = 10 Hz), 26.7, 27.9, 28.9, 29.15, 29.20, 29.23, 30.2, 32.77 ($J^{13}C$–^{19}F = 24, 5 Hz), 32.81 ($J^{13}C$–^{19}F = 24, 5 Hz), 34.8, 35.1, 35.2, 37.7, 42.7, 47.79, 47.82, 50.3, 52.0, 58.1, 58.8, 64.5, 69.58, 69.62, 70.38, 70.40, 70.44, 70.49, 70.51, 72.6, 122.62, 122.66 ($J^{13}C$–^{19}F = 241, 241 Hz), 126.4, 127.3, 127.4, 127.5, 128.7, 128.8, 133.6, 141.6, 142.0, 144.8, 154.7, 167.7, 173.5; HRMS (ESI) *m/z* Calcd for $C_{58}H_{88}F_2N_{10}O_7$ 1075.6878; Found 1075.6865 (Δ = 1.2 ppm).

Synthesis of Compound 10. To a solution of **9** (1.6 mg, 1.49 μmol) in DMF (1.0 mL) was added SUNBRIGHT ME-050AS (6.7 mg, 1.34 μmol) at room temperature, and the reaction was stirred for 3 h. The mixture was concentrated, and then the residue was recrystallized with Et_2O. The precipitation was filtered and washed with Et_2O to afford compound **10** as a white solid (3.6 mg, 46%). The molecular weight of **10** was analyzed by MALDI-TOF mass analysis.

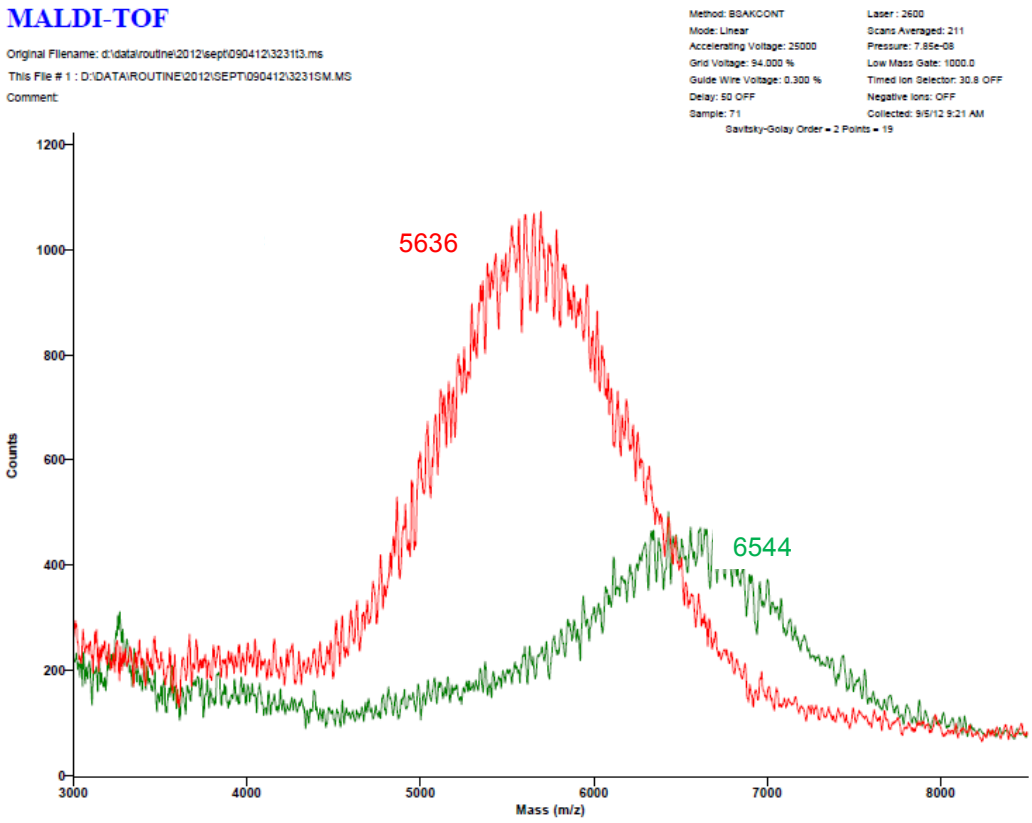
Synthesis of Compound 11. Compound **11** was prepared from **9** and SUNBRIGHT ME-400AS in a manner similar to that described for compound **10** with a yield of 82% as a white solid.

Synthesis of Compound 12. Compound **12** was prepared from **9** and SUNBRIGHT PTE-400HS in a manner similar to that described for compound **10** with a yield of 92% as a white solid.

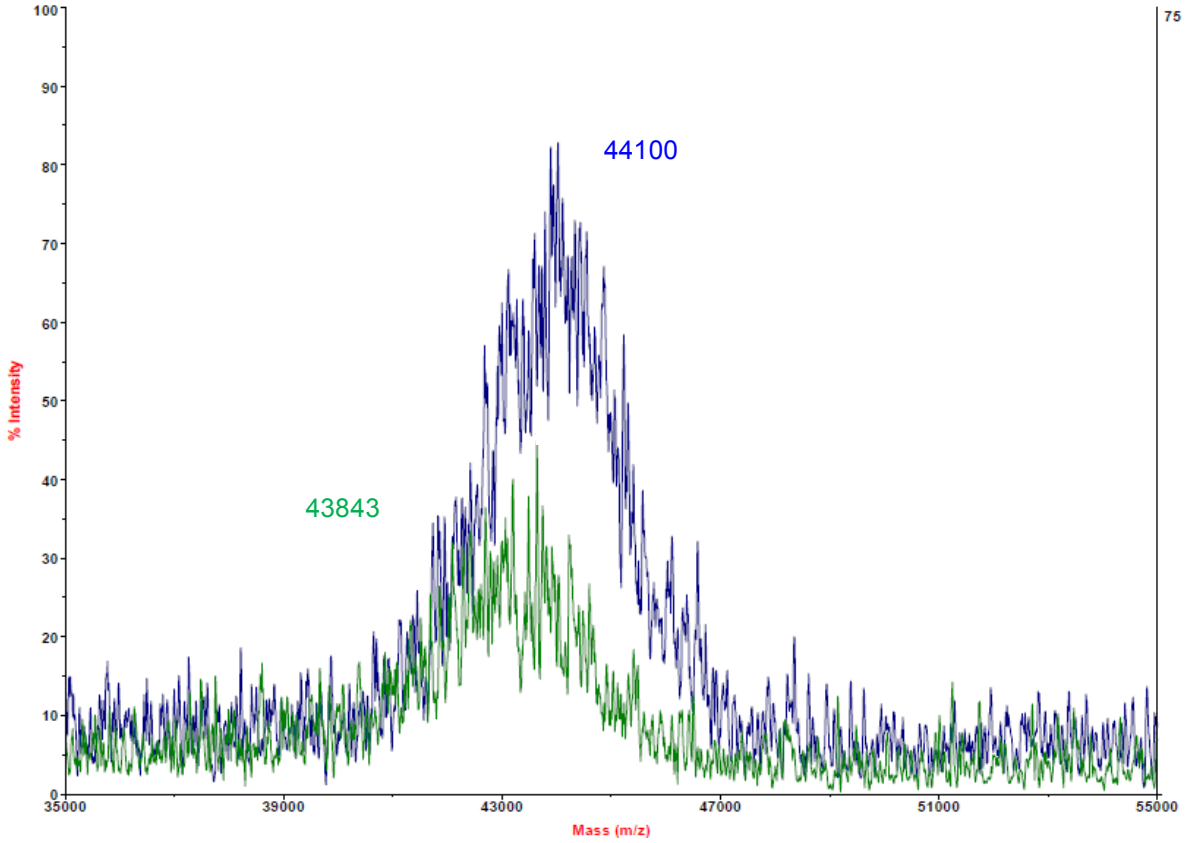
Synthesis of Compound 14. Compound **14** was prepared from *n*-propylamine and SUNBRIGHT PTE-400HS in a manner similar to that described for compound **10** with a yield of 92% as a white solid.

Figure S5. MALDI-TOF mass analysis

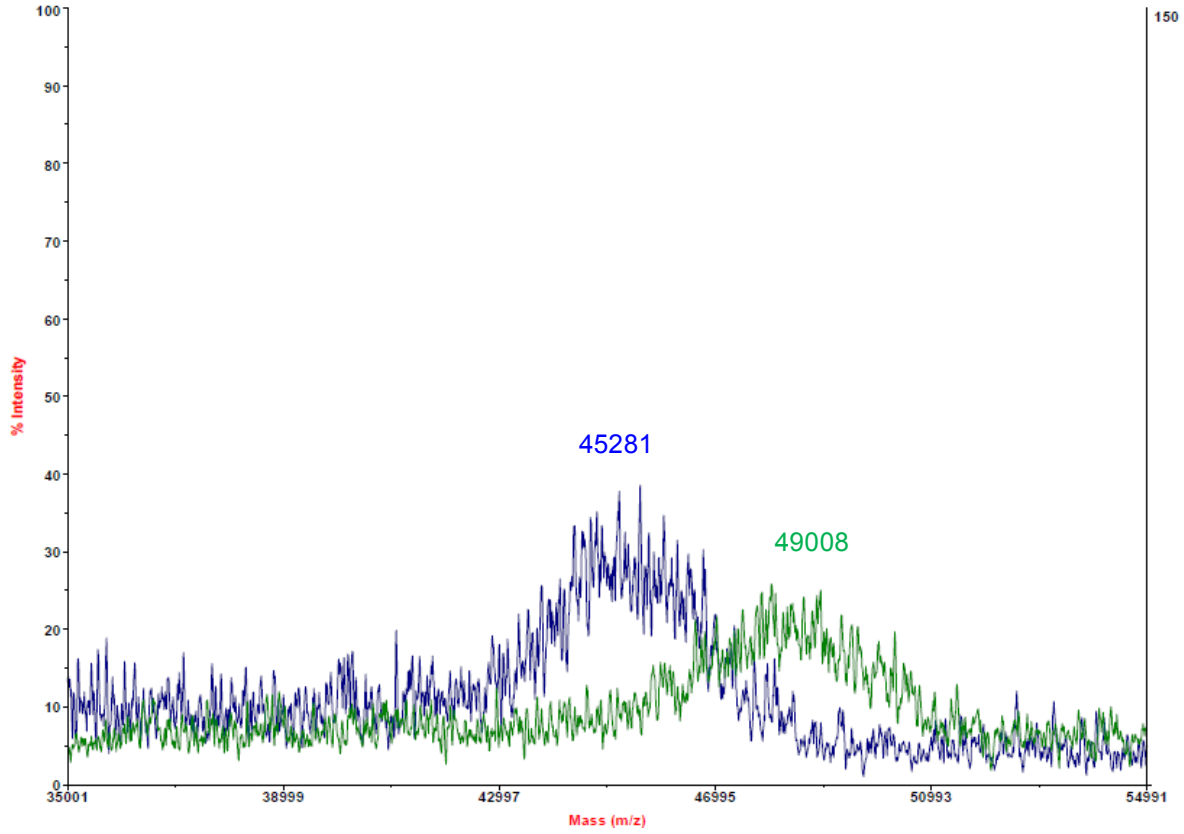
Overlay of MALDI mass spectra of SUNBRIGHT ME-050AS (red, MW_{ave} = 5636) and PEGylated compound **10** (green, MW_{ave} = 6544)



Overlay of MALDI mass spectra of SUNBRIGHT ME-400AS (green, MW_{ave} = 43843) and PEGylated compound **11** (blue, MW_{ave} = 44100)



Overlay of MALDI mass spectra of SUNBRIGHT PTE-400HS (blue, MW_{ave} = 45281) and PEGylated compound **12** (green, MW_{ave} = 49008)



Overlay of MALDI mass spectra of SUNBRIGHT PTE-400HS (blue, MW_{ave} = 45281) and PEGylated compound **14** (green, MW_{ave} = 44894)

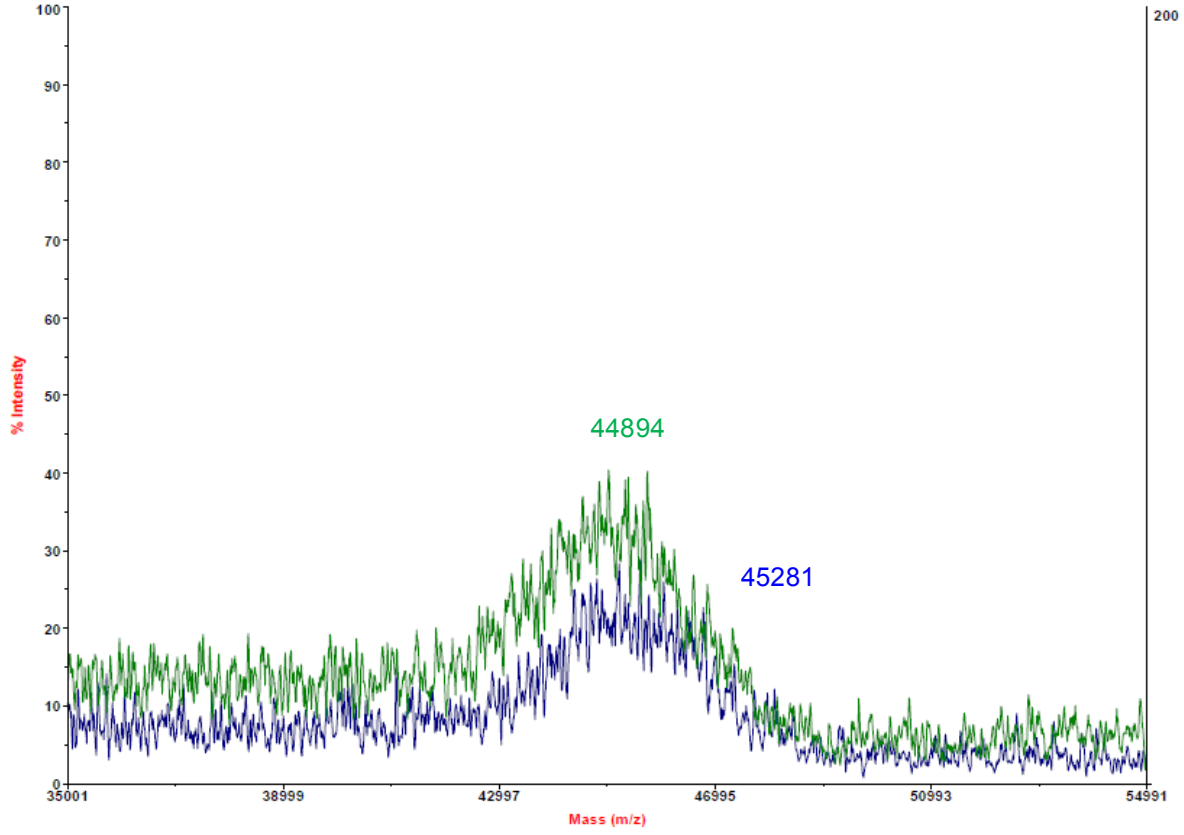
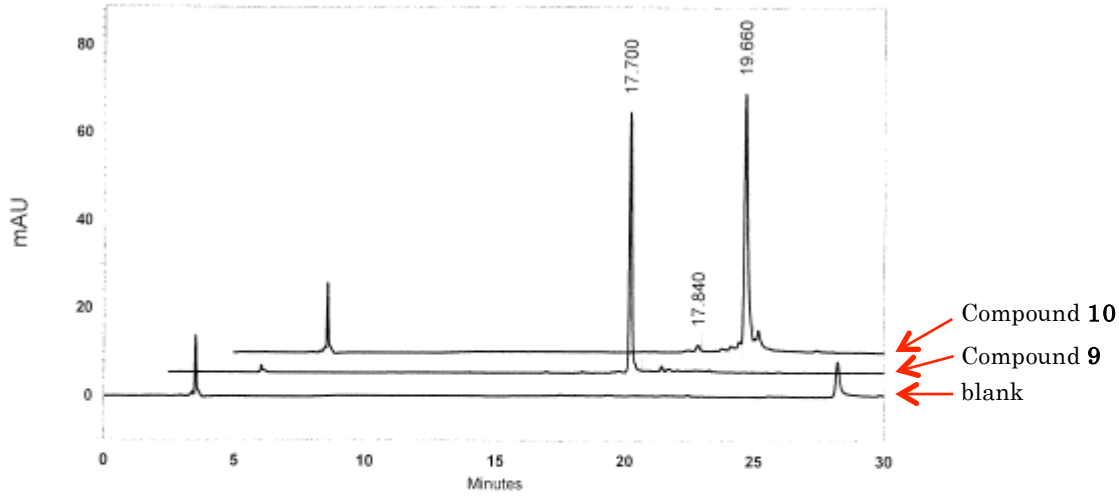


Figure S6. HPLC analysis

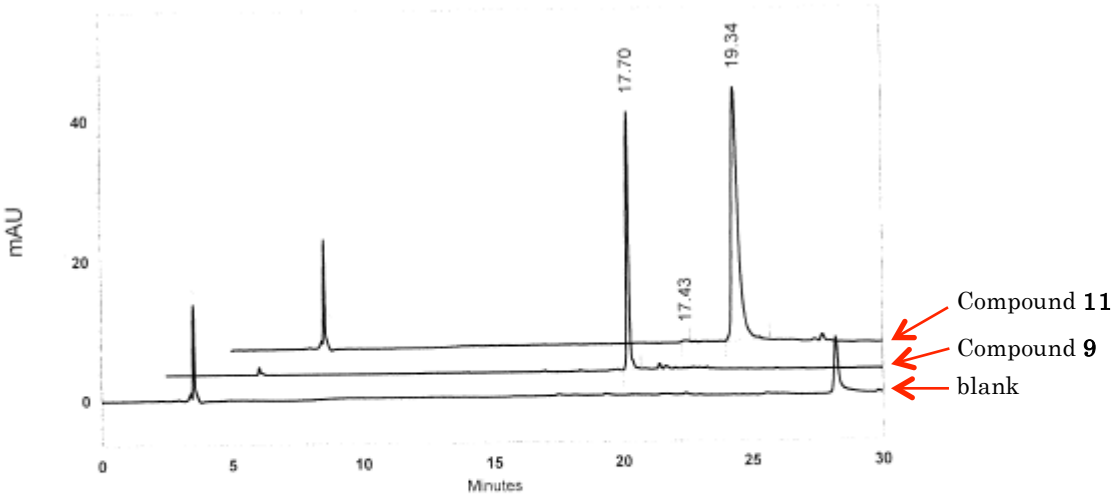
<Compound **10**>



DAD-CH1 254 nm Results

	Pk #	RT	Area
1	17.840	37062	1.8
2	19.660	2040328	98.2
Totals		2077390	100.0

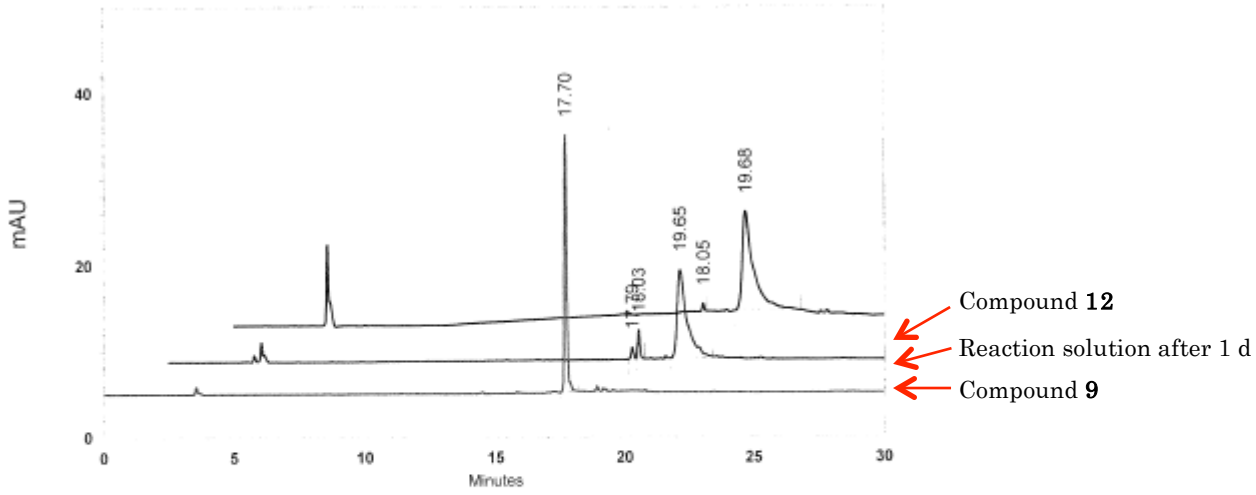
<Compound **11**>



DAD-CH1 254 nm Results

	Pk #	RT	Area
1	17.433	8477	0.3
2	19.340	2610970	99.7
Totals		2619447	100.0

<Compound **14**>



DAD-CH1 254 nm Results

	Pk #	**RT**	Area
1	18.047	19467	1.4
2	19.680	1419546	98.6
Totals		1439013	100.0

5. Neutralization assays of Maraviroc Derivatives

Replication-incompetent HIV-1 enveloped pseudovirus was generated by cotransfection of 293T cells with JR-FL, YU-2, 92RW, and MGC26 HIV-1 Env-expressing plasmid and pSG3ΔEnv as previously described.[6] Serial dilutions of samples (50 µl) along with wt b12, 2D7, 2G12 and an isotype control antibody, DEN3, were added to TZM-bl target cells (50 µl) and preincubated at 37 ˚C for 1 h. Following incubation 250TCID50 of pseudovirus (100 µl) was added to each well and incubated at 37 ˚C. Luciferase reporter gene expression was evaluated 48 h post infection. The percentage of virus neutralization at a given antibody concentration was determined by calculating the reduction in luciferase expression in the presence of antibody relative to virus-only wells (duplicate). The antibody dilution causing 50% reduction (50% inhibitory concentration [IC_{50}]) was calculated by regression analysis using GraphPad Prism.

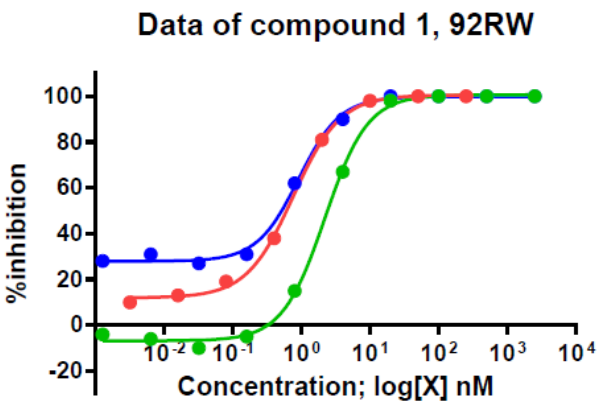
Table S1. IC_{50} (nM) values of compounds **1-8**, **10-12**, **14** and mAb 38C2 for inhibition of HIV-1 virus

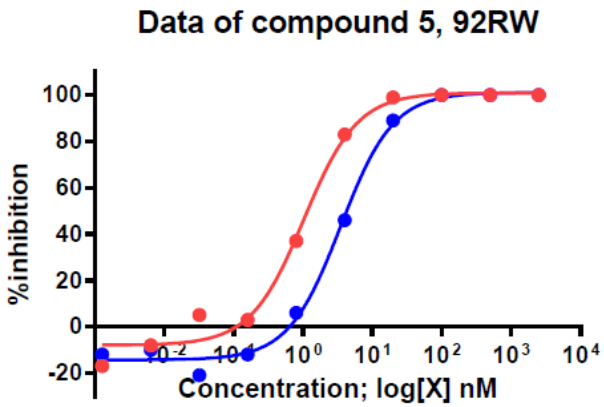
Compound	Inhibition of HIV-1; IC_{50} (nM)			
	Clade A	Clade B		Clade C
	92RW	JR-FL	YU-2	MGC26
1 (Maraviroc)	1.3 ± 0.46	1.6 ± 0.25[a]	0.43 ± 0.070	0.37 ± 0.090
2a		360 ± 34		
2b		>1000		
3		0.96 ± 0.26		
4		27 ± 2.3		
5	2.3 ± 1.2[b]	2.6 ± 0.62	1.1 ± 0.46[b]	0.65 ± 0.086[b]
6		19 ± 2.6		
7	8.1 ± 3.8[b]	7.7 ± 0.50	2.8 ± 0.38[b]	2.7 ± 0.29[b]
8		3.0 ± 0.58		
10		43 ± 9.6		
11		49 ± 13		
12	3.0 ± 0.55[b]	5.6 ± 2.0[c]	2.5 ± 1.1[b]	0.79 ± 0.19[b]
14		>1000		
mAb 38C2	>1000	>1000	>1000	>1000

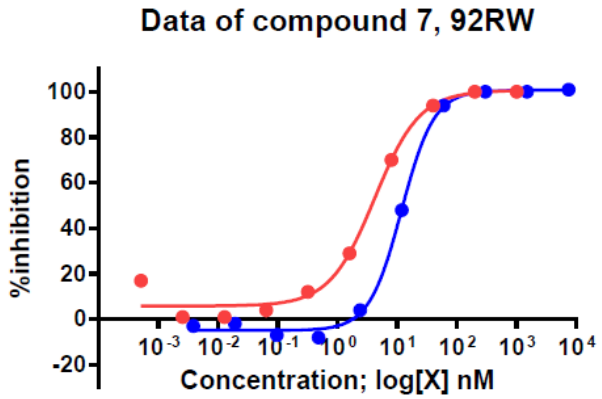
Mean ± SE (N=3), [a] N=12, [b] N=2, [c] N=5

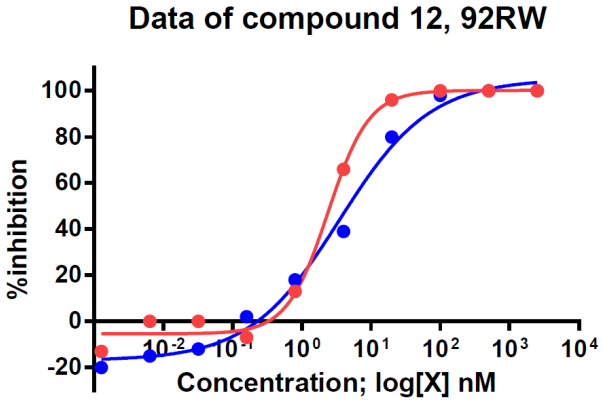
6 Zwick, M. B.; Labrijn, A. F.; Wang, M.; Spenlehauer, C.; Saphire, E. O.; Binley, J. M.; Moore, J. P.; Stiegler, G.; Katinger, H.; Burton. D. R.; Parren, P. W. H. I. *J. Viol.* **2001**, *75*, 10892-10905.

Figure S7. Neutralization Results against HIV-1 92RW Pseudovirus









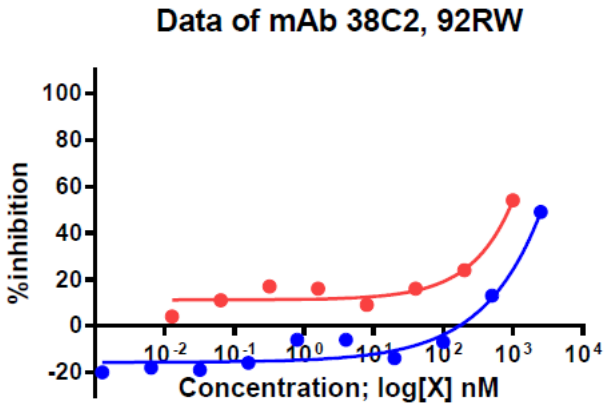
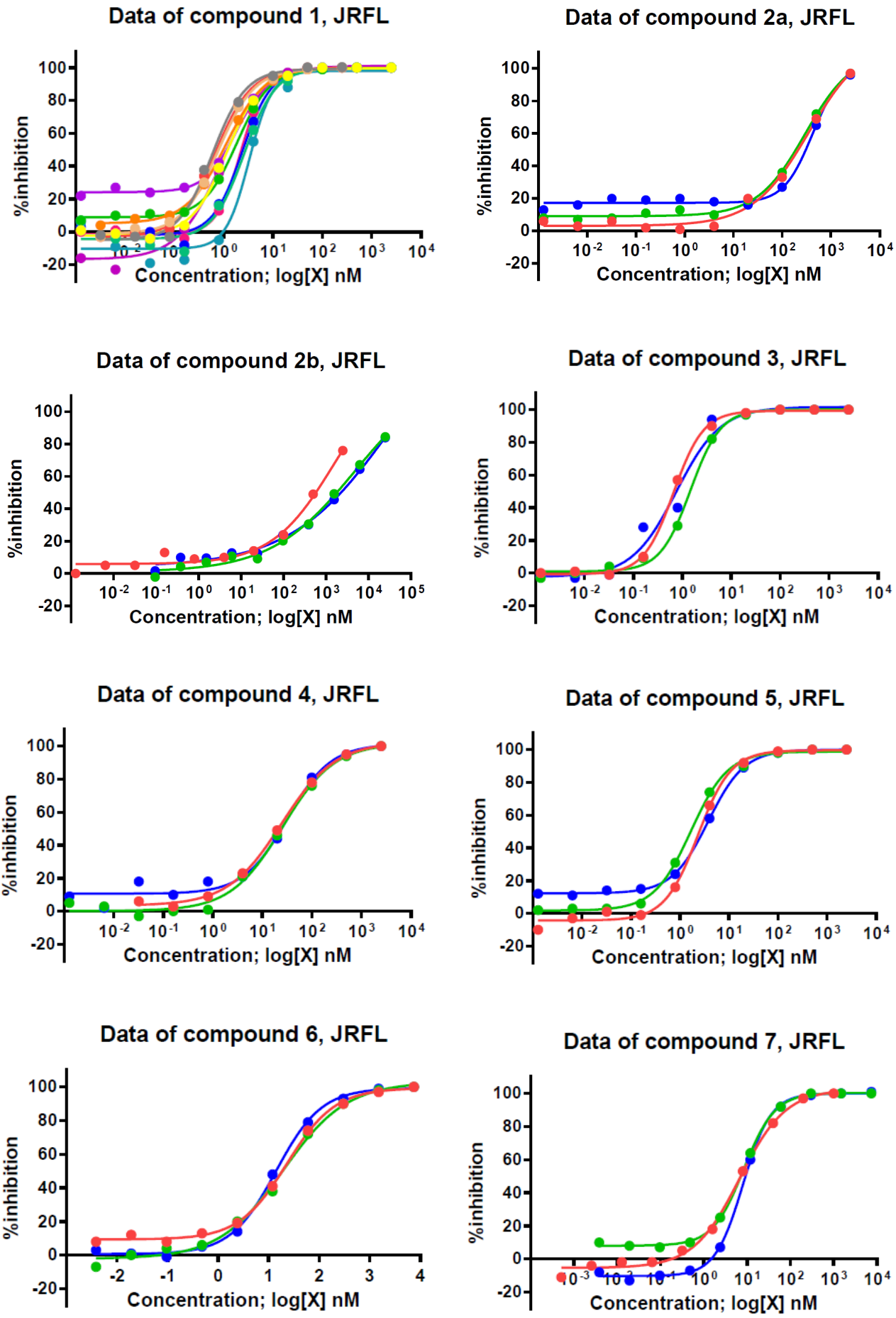


Figure S8. Neutralization Results against HIV-1 JRFL Pseudovirus



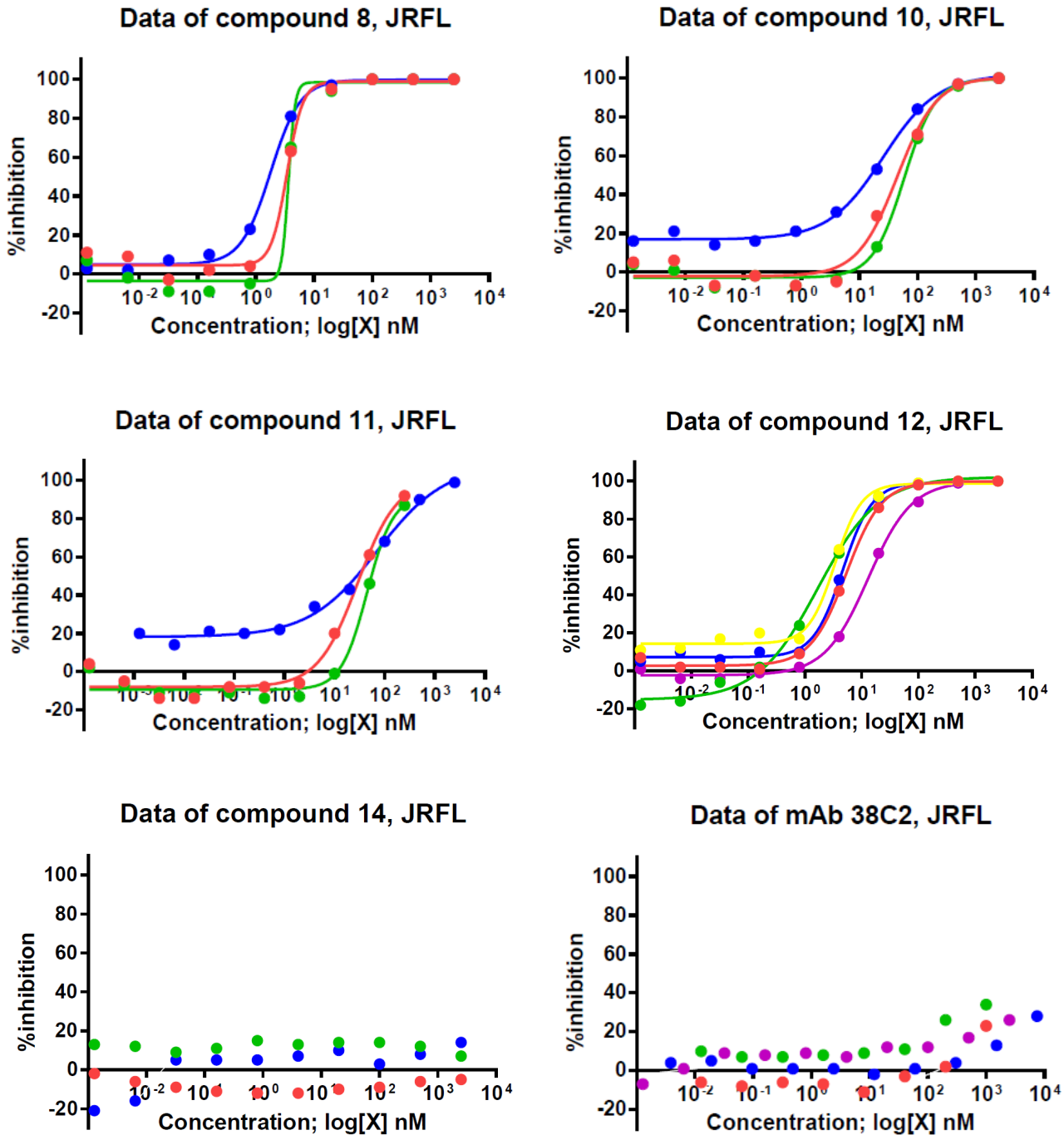
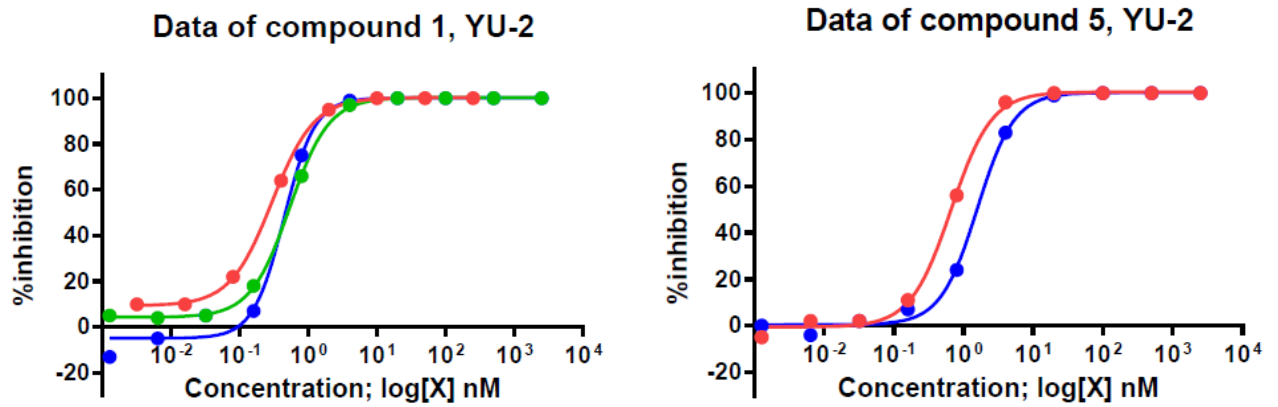


Figure S9. Neutralization Results against HIV-1YU-2 Pseudovirus



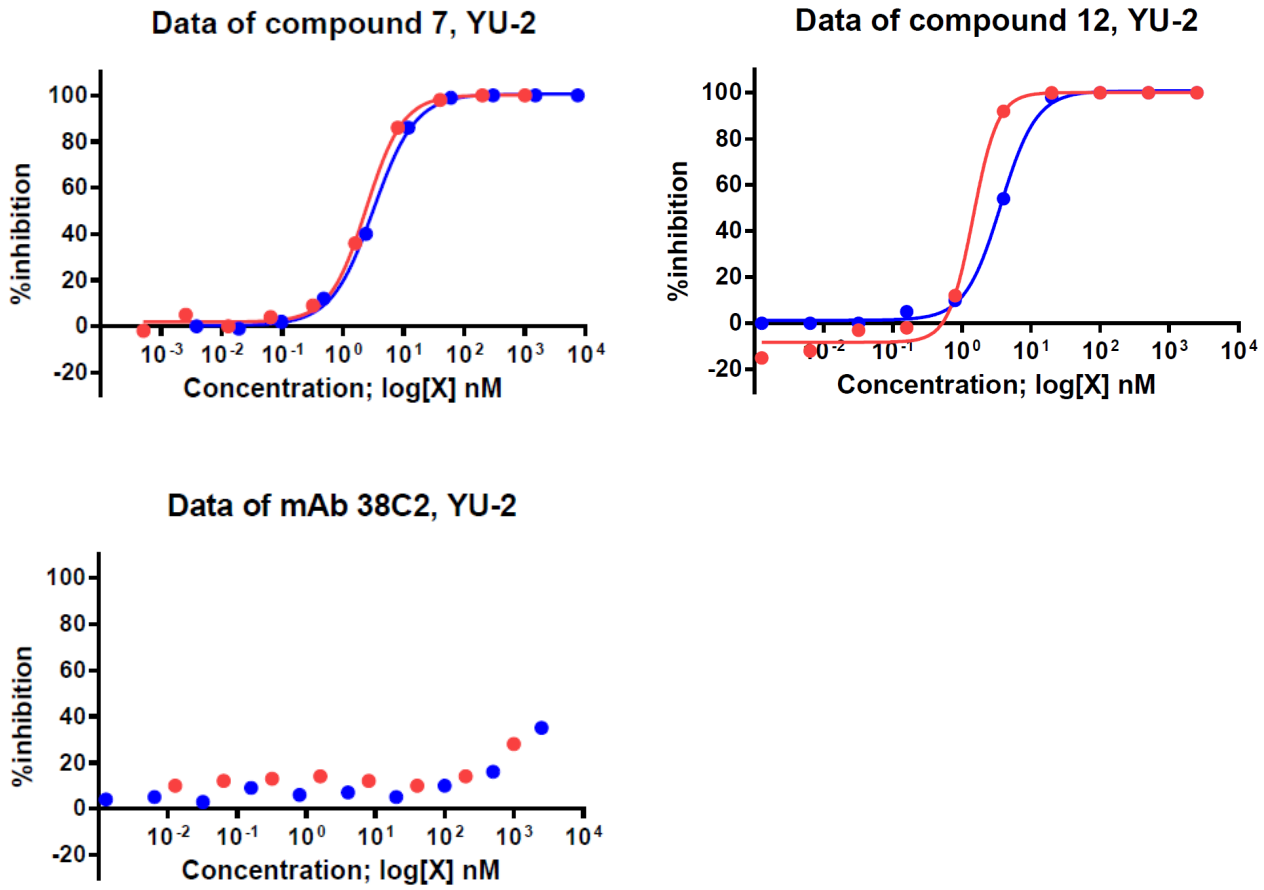
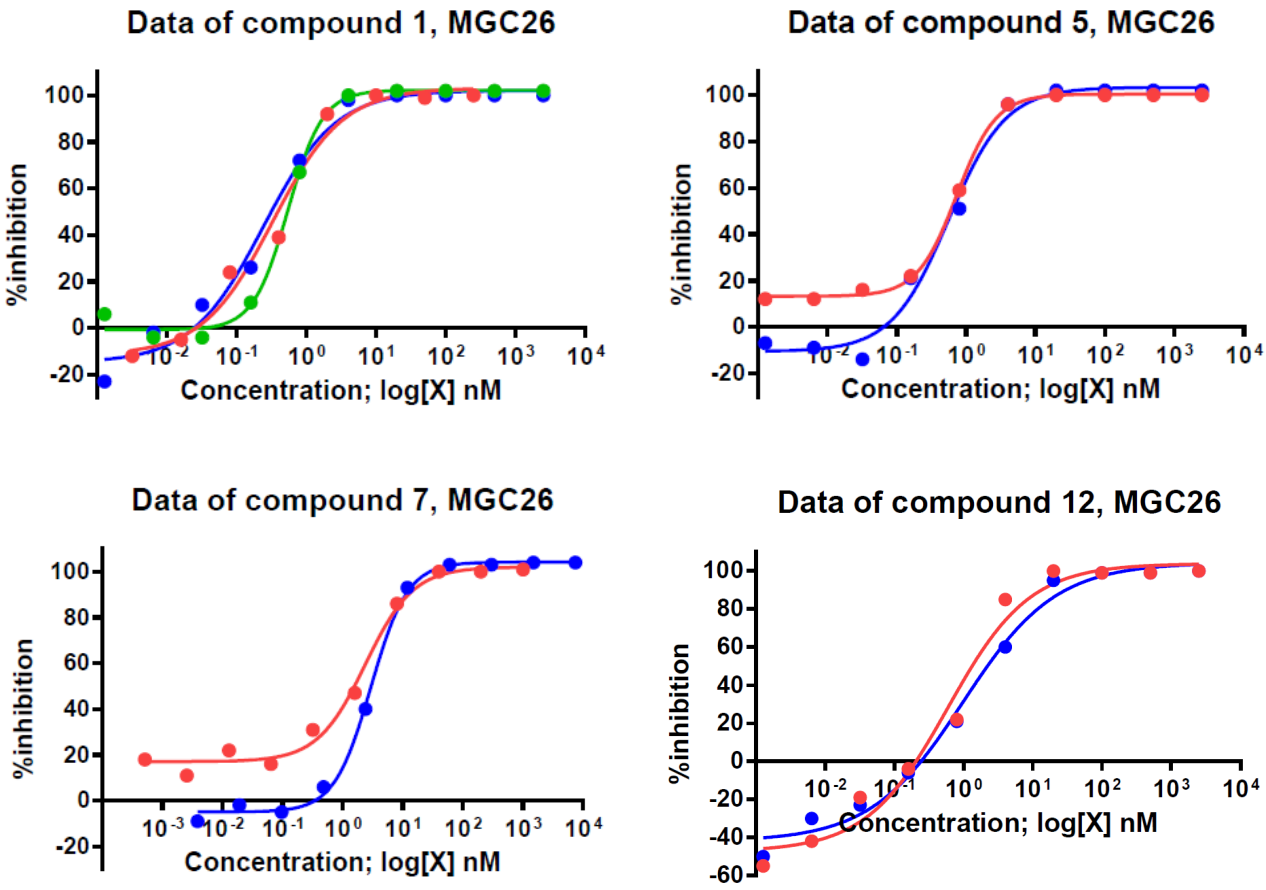


Figure S10. Neutralization Results against HIV-1 MGC26 Pseudovirus



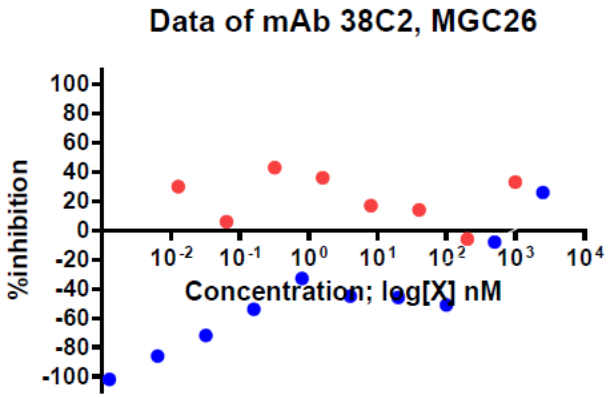
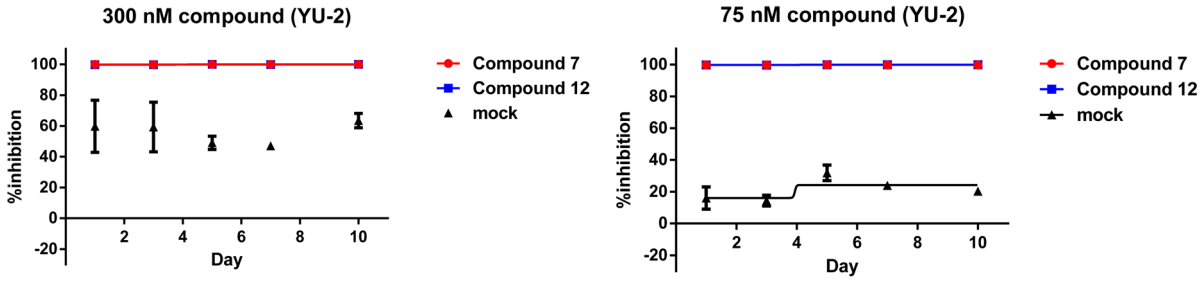


Figure S11. HIV Neutralization Activity of Serum-Incubated Maraviroc Derivatives. Mock indicates Maraviroc.



6. FACS of Chemically Programmed Antibodies 6 and 7

1) Solutions

#1: Compound **6** and **7** (20 μg/mL PBS solution, pH 7.4)

#2: 0.25% trypsin-EDTA solution

#3: Dulbecco's phosphate buffer (DMEM) solution for Hela cells: Cat No. 2013-06 (Life)

#4: FACS buffer solution: 1% BSA/0.01% NaN_3/PBS solution (pH 7.4)

#5: 2^{nd} antibody for 38C2 (PE Donkey anti-mouse $(Fab)_2$) : 1 : 3000 dilution with FACS buffer

2) Preparation of single cell line suspension (HeLa; CCR5-unexpressed, TZM-bl; CCR5-expressed cells)

1. Remove the medium by aspiration.
2. Carefully rinse the cell monolayer with 10 mL of PBS (pH 7.4).
3. Remove PBS by aspiration.
4. Detach the cells by the use of 2.0 mL of 0.25% trypsin-EDTA solution (#2).
5. Add 8.0 mL of DMEM solution (#3). Carefully homogenize the cell suspension by gentle pipetting.
6. Transfer 1 mL of cell suspension into 100 mm dish. Dilute with 9 mL of DMEM solution, and incubate it at 37 ˚C in a CO_2 incubator.
7. Transfer remained cell suspension into 50 mL tube. Wash the disc with 5 mL of DMEM solution (#3).
8. Estimate the concentration by using a counting cell.
9. Centrifuge the suspension.
10. Remove the medium by aspiration.
11. Add 10 mL of cold FACS buffer solution (#4). Carefully homogenize the cell suspension by gentle pipetting.
12. Centrifuge the suspension.
13. Remove the medium by aspiration.
14. Dilute with cold FACS buffer solution (#4), making the end concentration of the solution 6 x 10^6 cells/mL. Carefully homogenize the cell suspension by gentle pipetting.

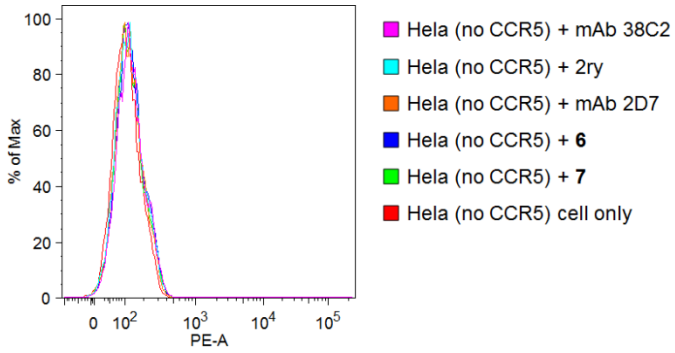
3) Preparation of samples, and Flow Cytometry

1. Add 50μL the samples (compound **6**, **7**, 2D7, mouse mAb 38C2, and FACS buffer) as a duplicate to the V-bottomed wells of a 96 well-plate.
2. Distribute 50 μL aliquots of the cell suspension (6 x 10^6 cells/mL) to the wells.
3. Incubate for 1 hour on ice protected from light.
4. Centrifuge cells as 300 x g for 2 min.
5. Invert and blot away supernatants from cell pellets.

6. Add 150 µL of the cold FACS buffer to the wells, and mix the wells by gentle pipetting.
7. Repeat from step 4 to 6.
8. Centrifuge cells as 300 x g for 2 min.
9. Invert and blot away supernatants from cell pellets.
10. Add 100 µL of 2nd antibody/FACS buffer solution (#5) to each well, and mix the wells by gentle pipetting.
11. Incubate for 40 minutes on ice protected from light.
12. Centrifuge cells as 300 x g for 2 min.
13. Invert and blot away supernatants from cell pellets.
14. Add 150 µL of the cold FACS buffer to the wells, and mix the wells by gentle pipetting.
15. Repeat from step 11 to 14 more 2 times.
16. Centrifuge cells as 300 x g for 2 min.
17. Invert and blot away supernatants from cell pellets.
18. Resuspend with 200 µL of the cold FACS buffer to the wells, and mix the wells by gentle pipetting.
19. Transfer to the filter-top tubes.
20. Analyze stained cell samples by flow cytometry as soon as possible.

Figure S12. Results of Flow Cytometry (Hela cells; CCR5 unexpressed cell)

<1st test>



<2nd test>

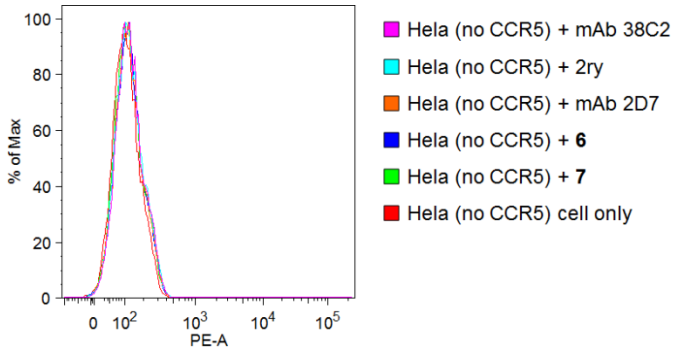


Figure S13. Results of Flow Cytometry (TZM-bl cells; CCR5 expressed cell)

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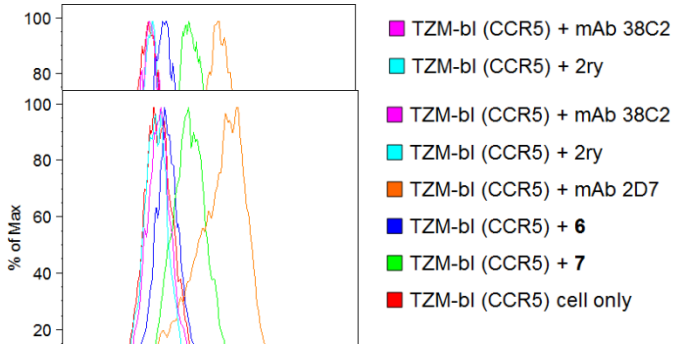
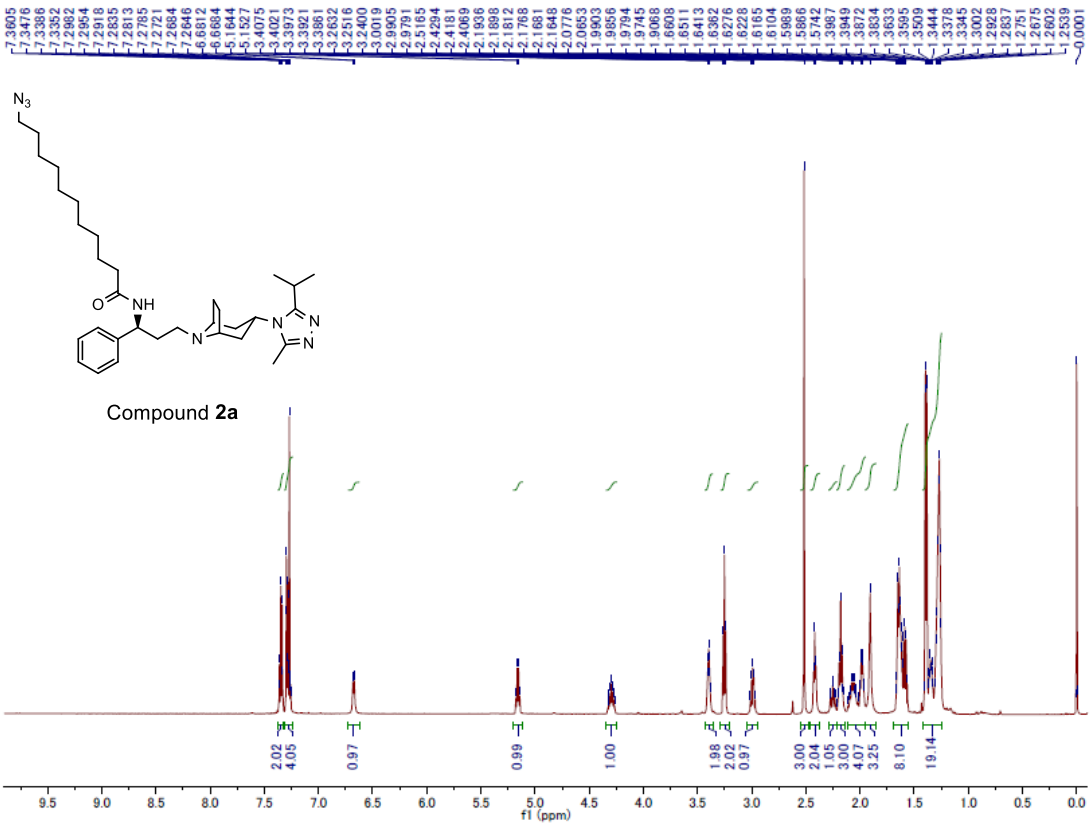
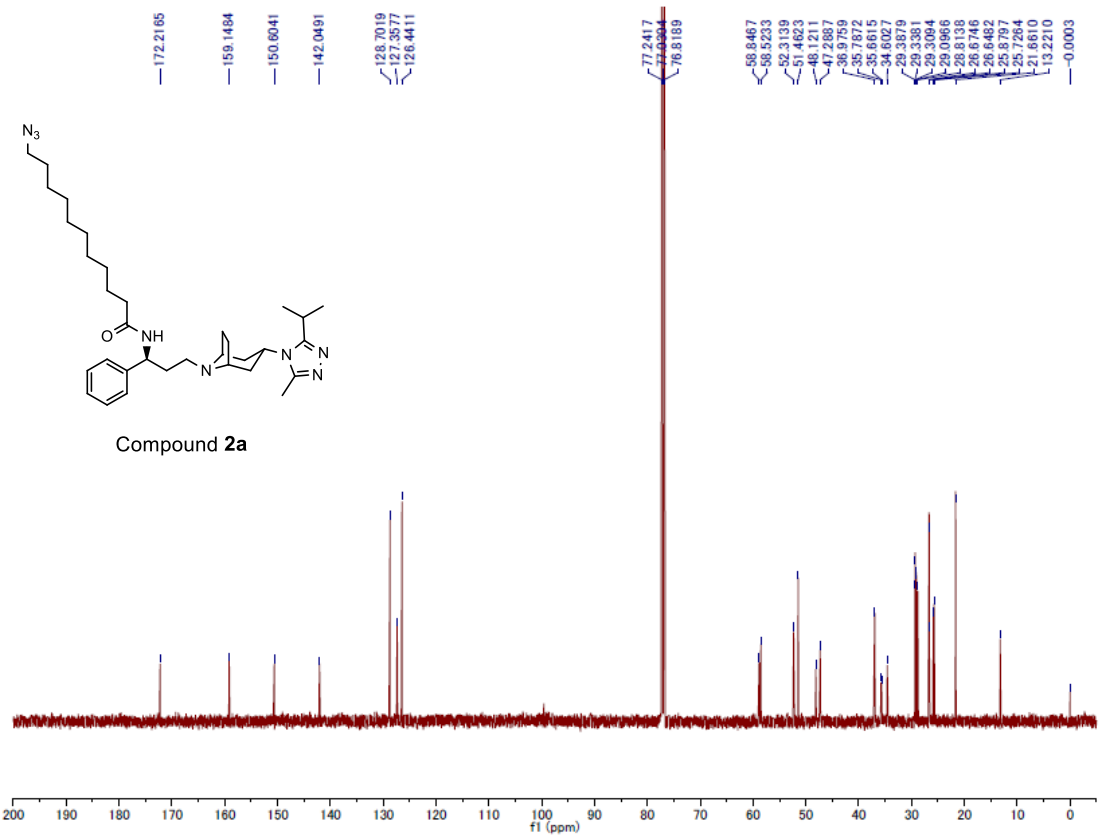


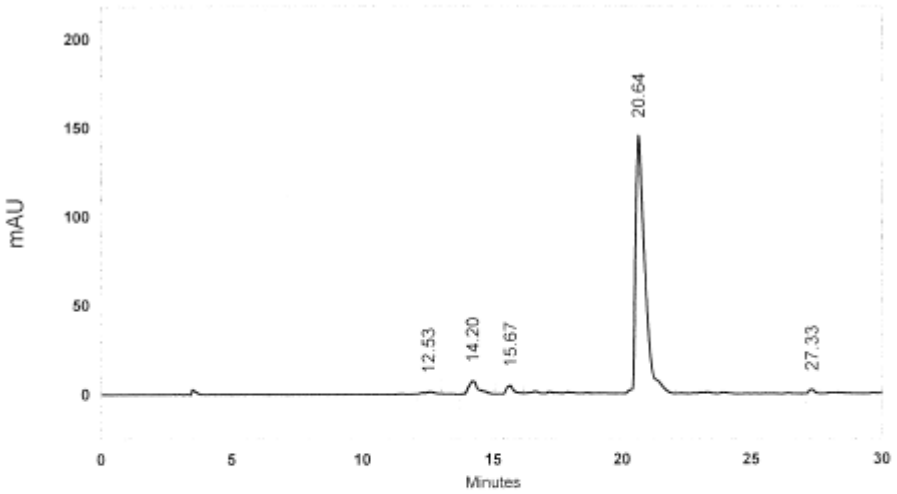
<2nd test>

7. NMR and HPLC charts





Compound **2a**

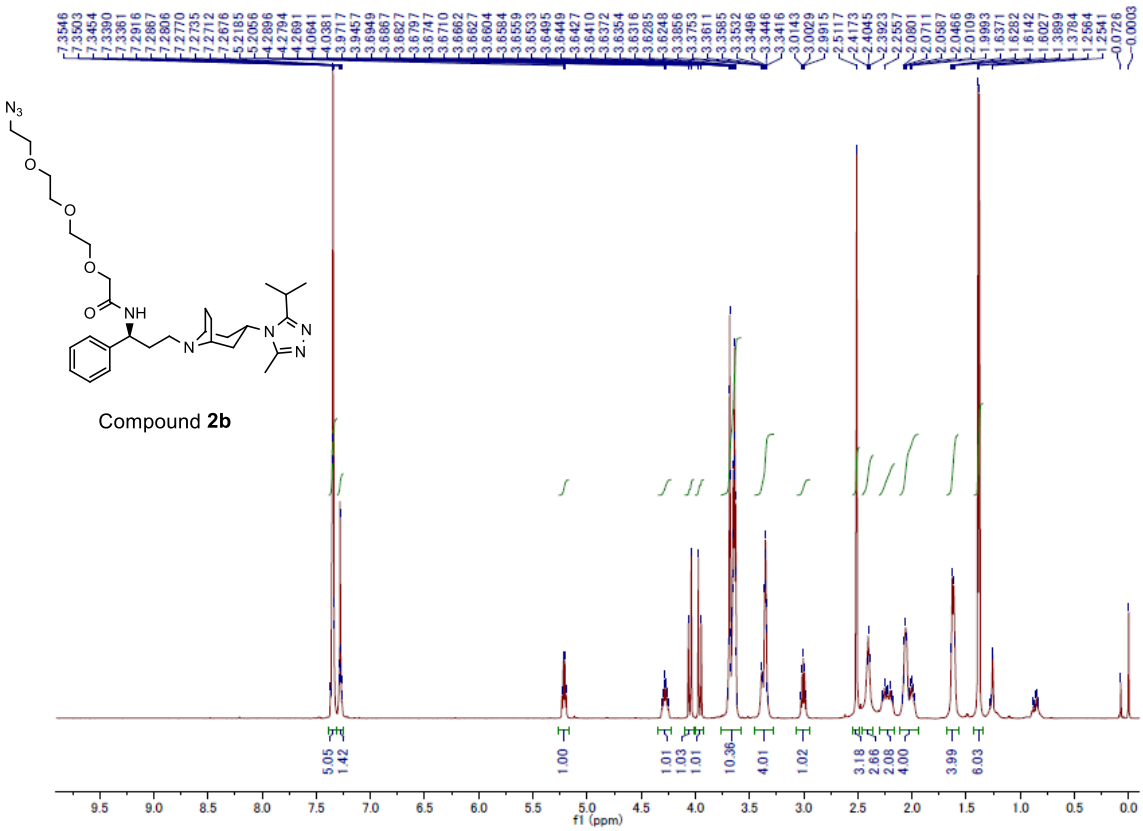


Compound **2a**

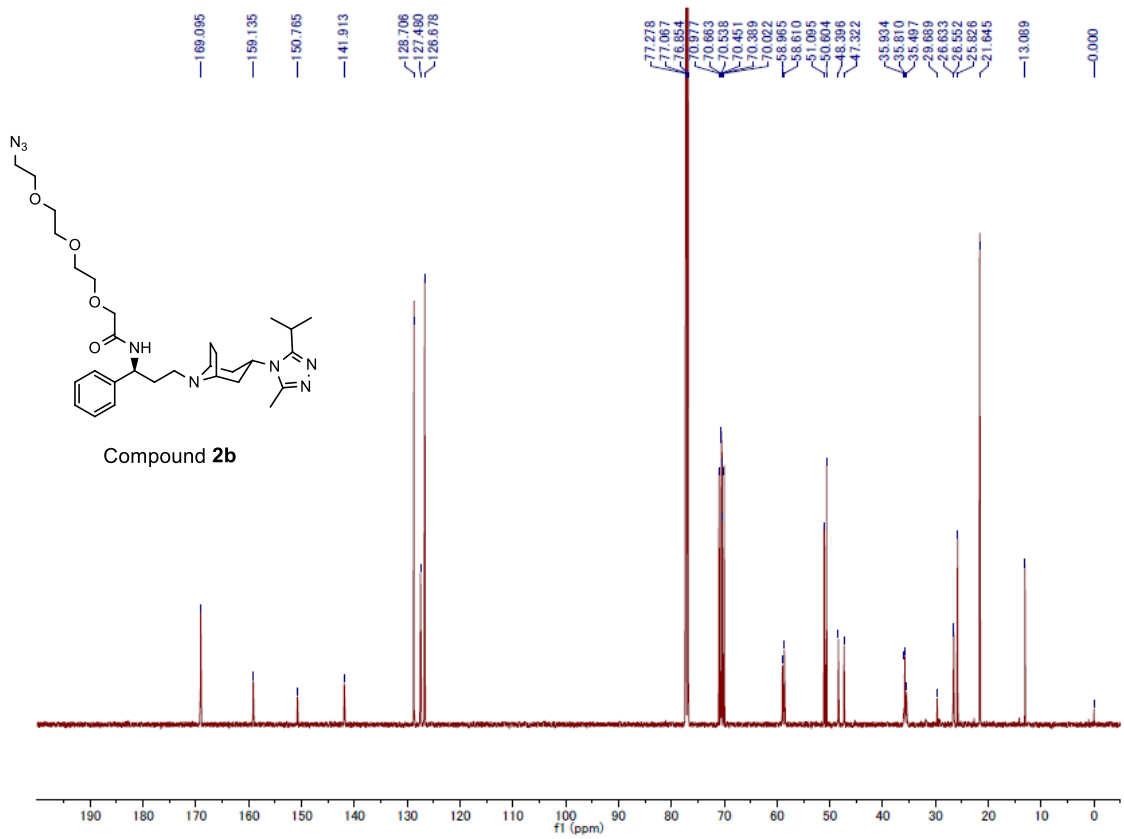
DAD-CH1 254 nm Results

	Pk #	RT	Area
1	12.527	114853	0.7
2	14.200	732574	4.7
3	15.667	307455	2.0
4	20.640	14328924	91.8
5	27.327	120691	0.8

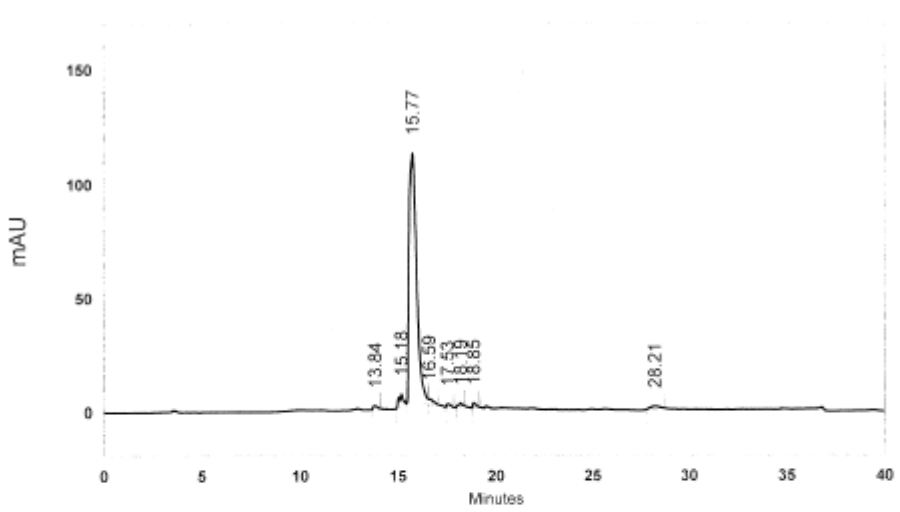
Totals		15604497	100.0

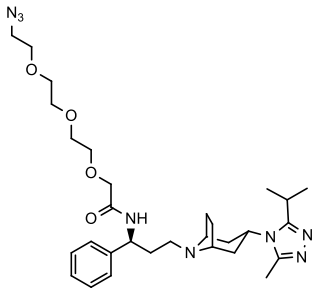


Compound **2b**



Compound **2b**



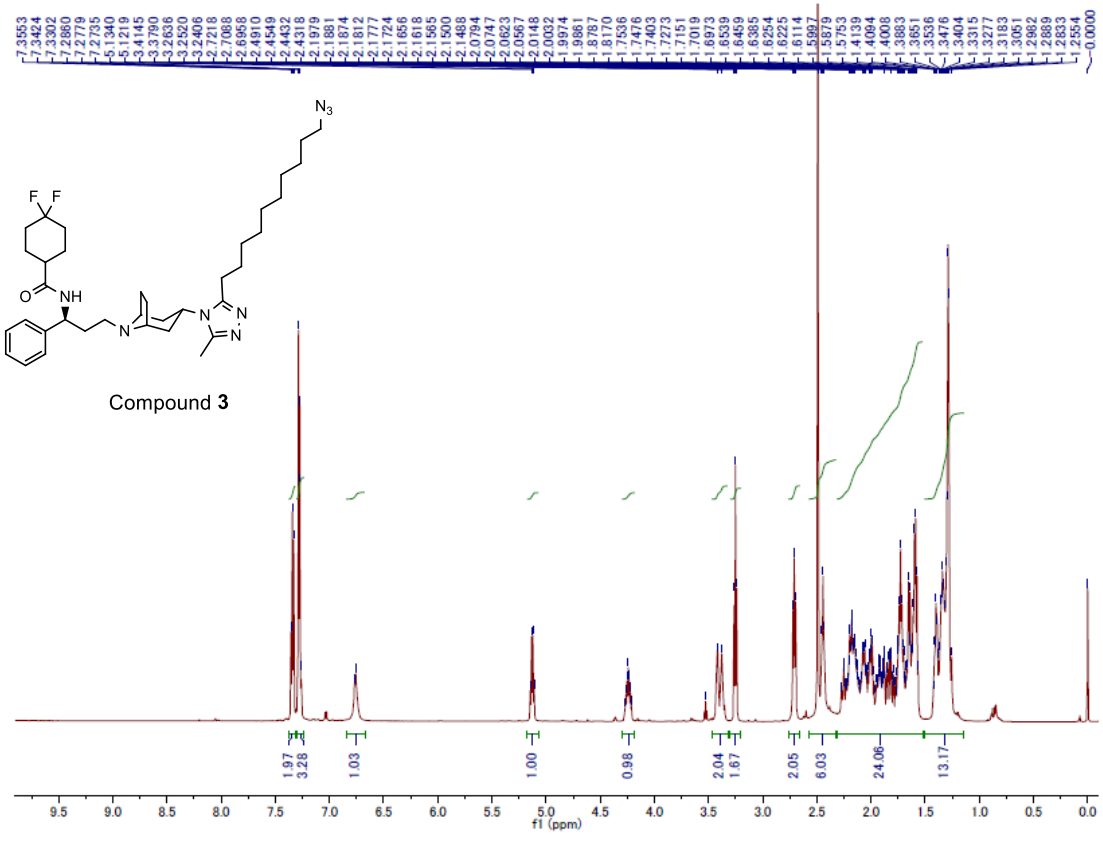


Compound **2b**

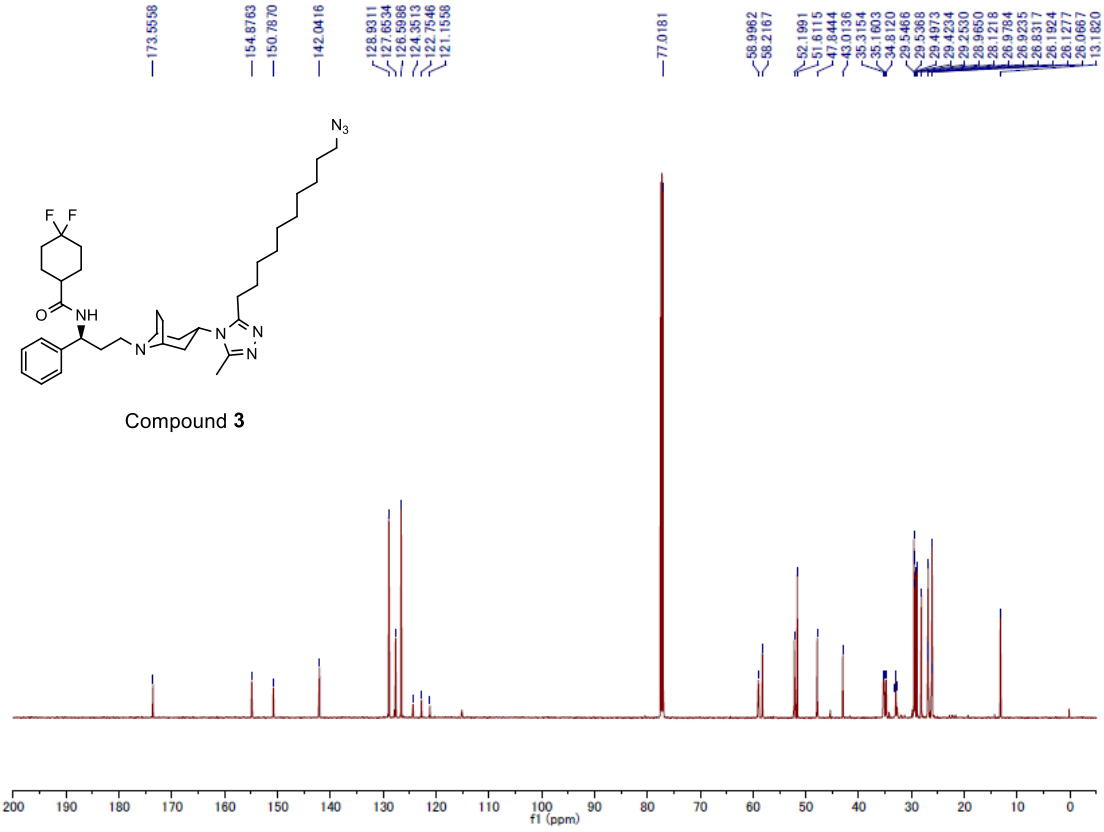
DAD-CH1 254 nm Results

	Pk #	RT	Area
1	13.840	87783	0.7
2	15.180	300328	2.4
3	15.767	11710417	92.4
4	16.593	167113	1.3
5	17.533	70320	0.6
6	18.193	91002	0.7
7	18.853	89712	0.7
8	28.213	162384	1.3

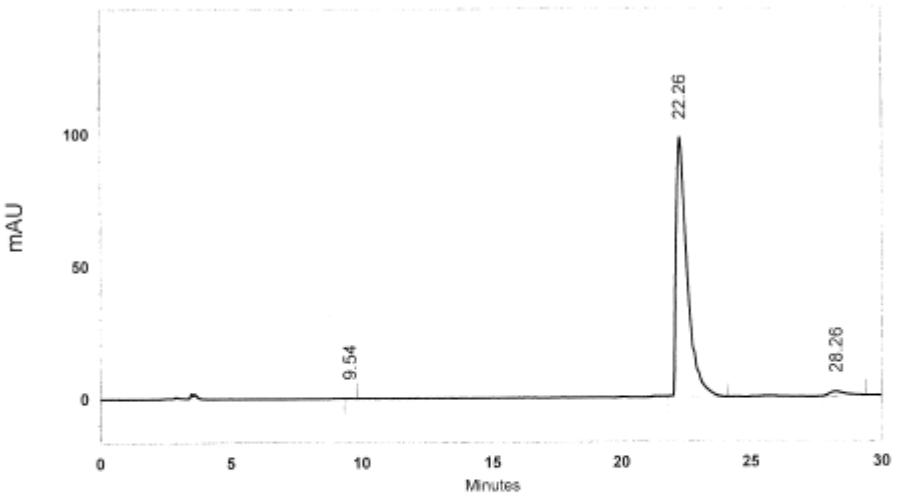
Totals			
		12679059	100.0

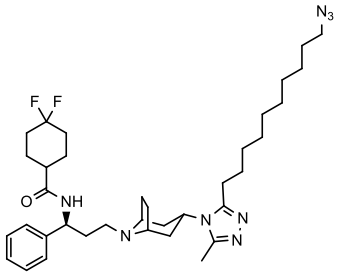


Compound **3**



Compound **3**



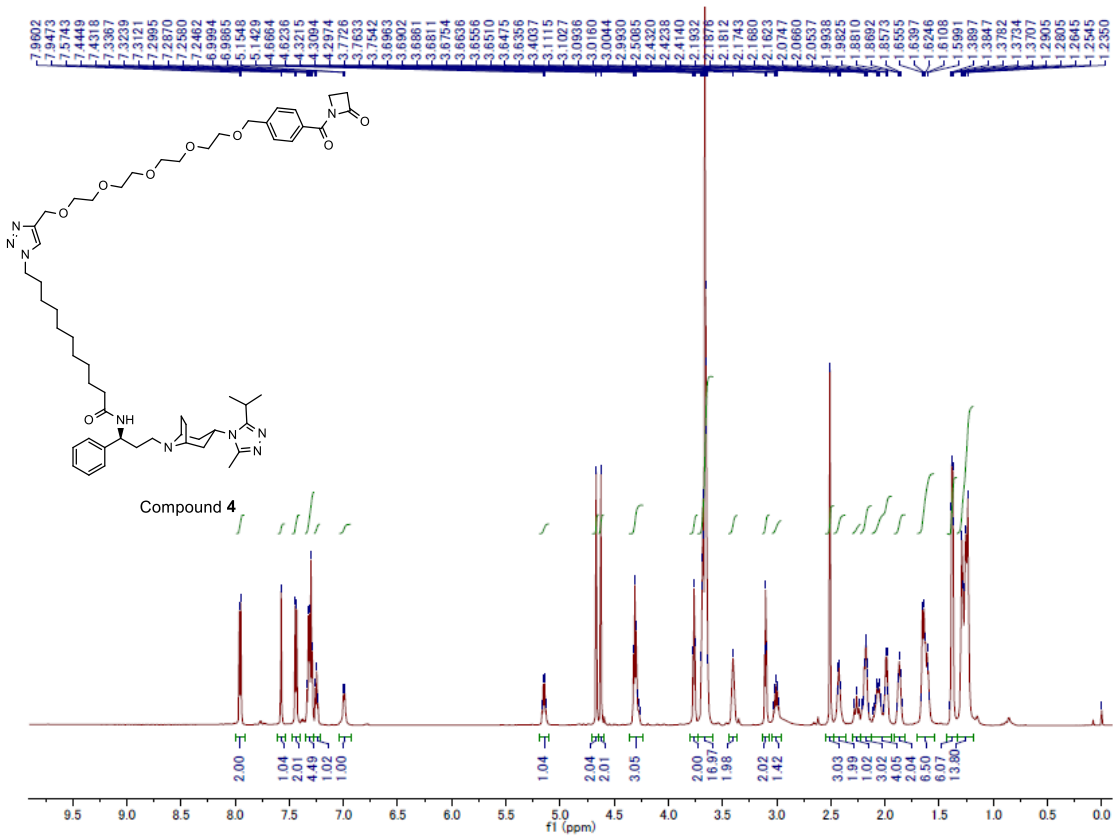


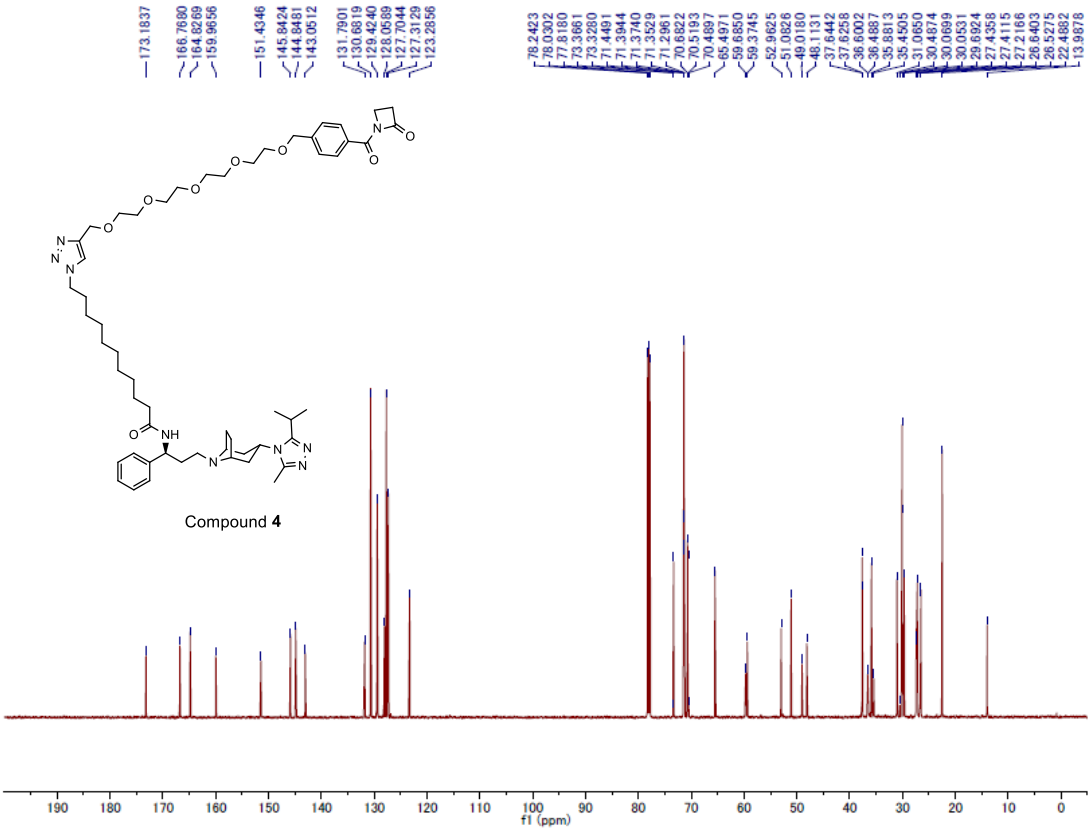
Compound **3**

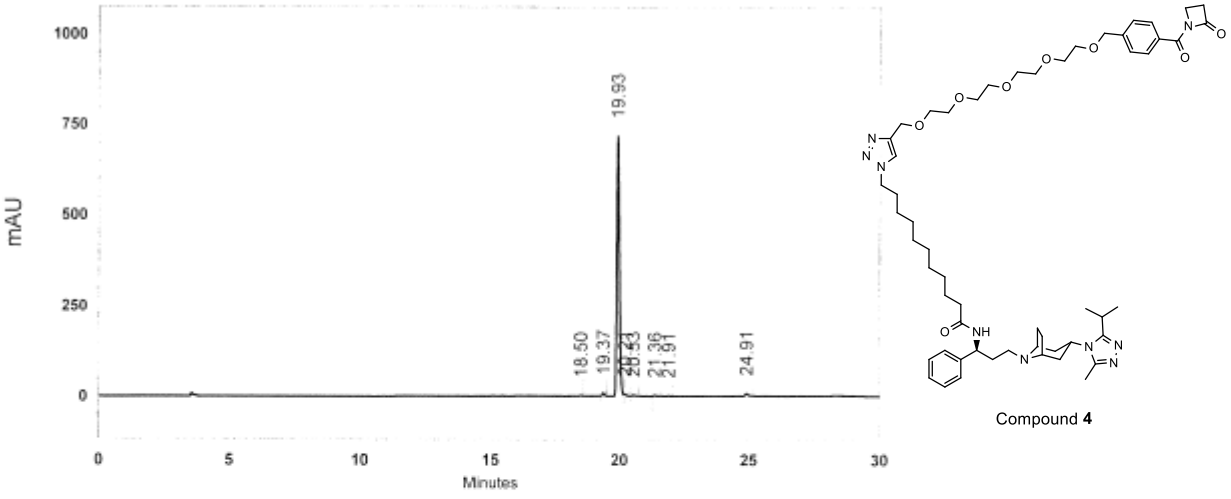
DAD-CH1 254 nm Results

	Pk #	RT	Area
1	9.540	4612	0.0
2	22.260	11590533	97.6
3	28.260	282740	2.4

Totals			
		11877885	100.0


Compound 4
f1 (ppm)

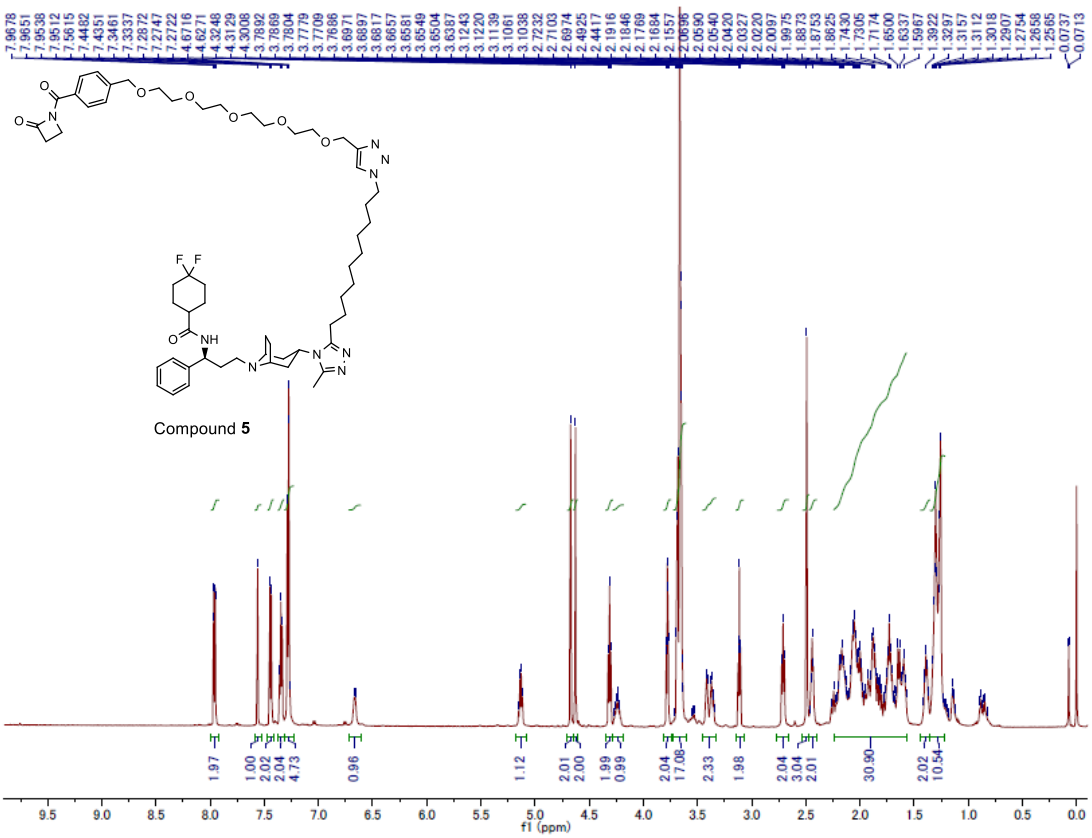




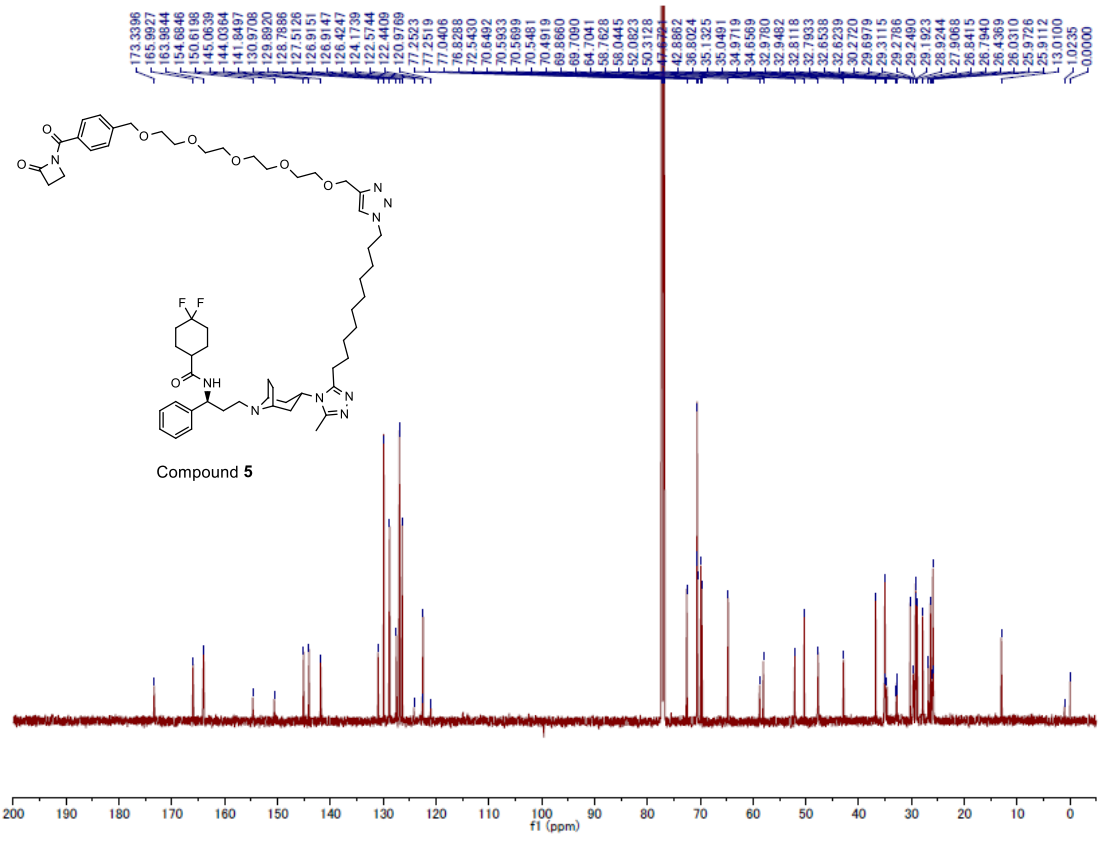
DAD-CH1 254 nm Results

	Pk #	RT	Area
1	18.500	39885	0.2
2	19.373	198277	0.9
3	19.927	20485182	96.6
4	20.207	136356	0.6
5	20.533	66289	0.3
6	21.360	73659	0.3
7	21.907	24970	0.1
8	24.913	178805	0.8

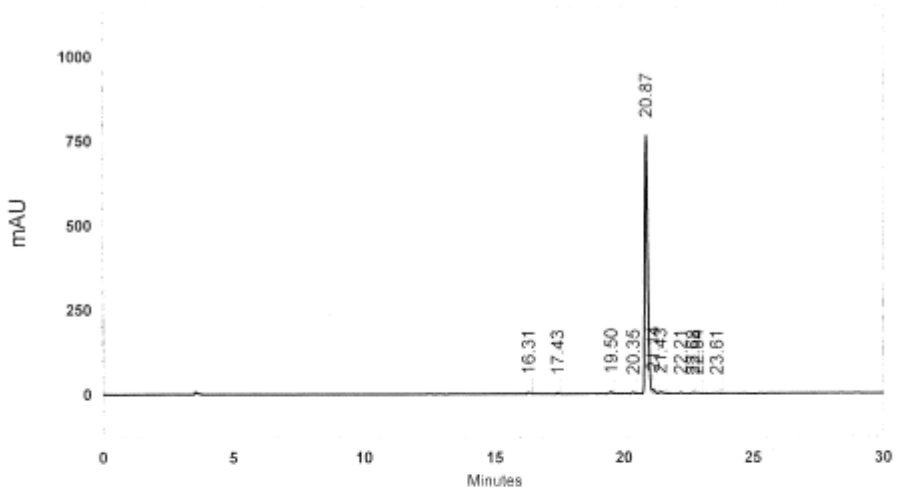
Totals			
		21203423	100.0

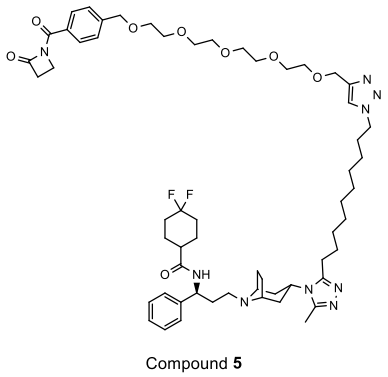


Compound **5**



Compound **5**

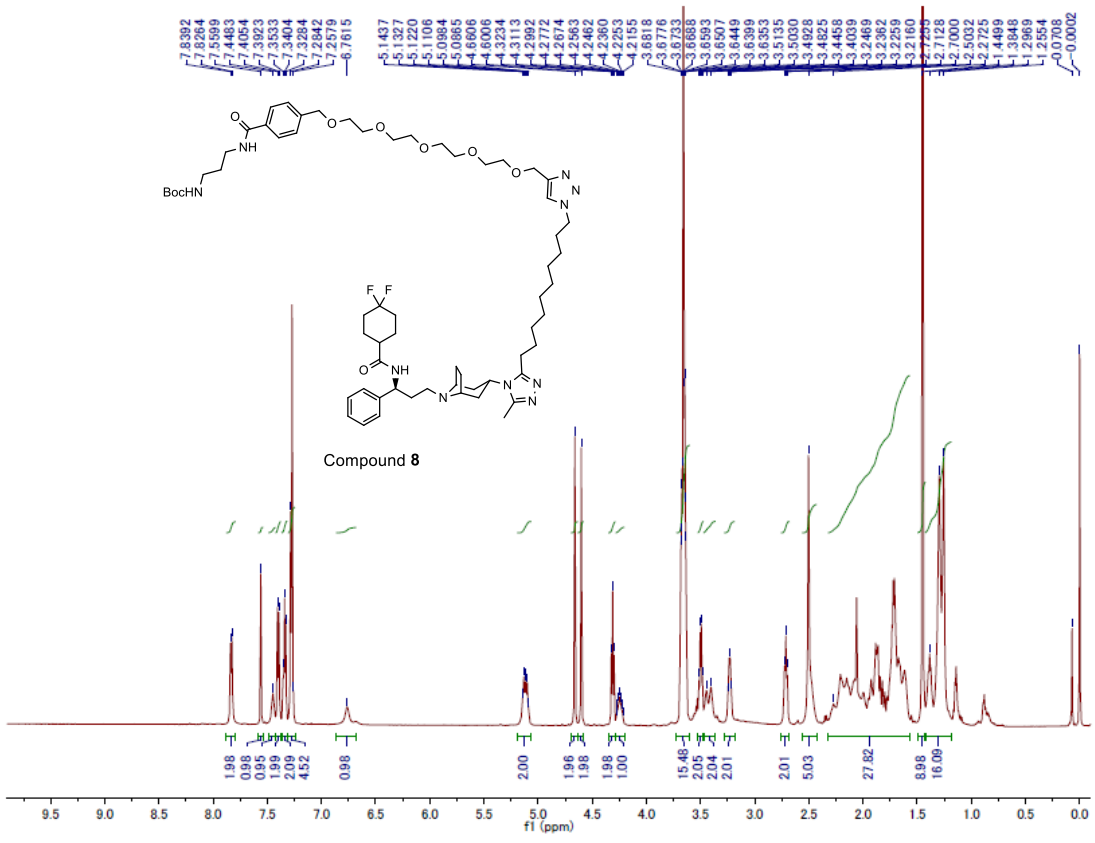


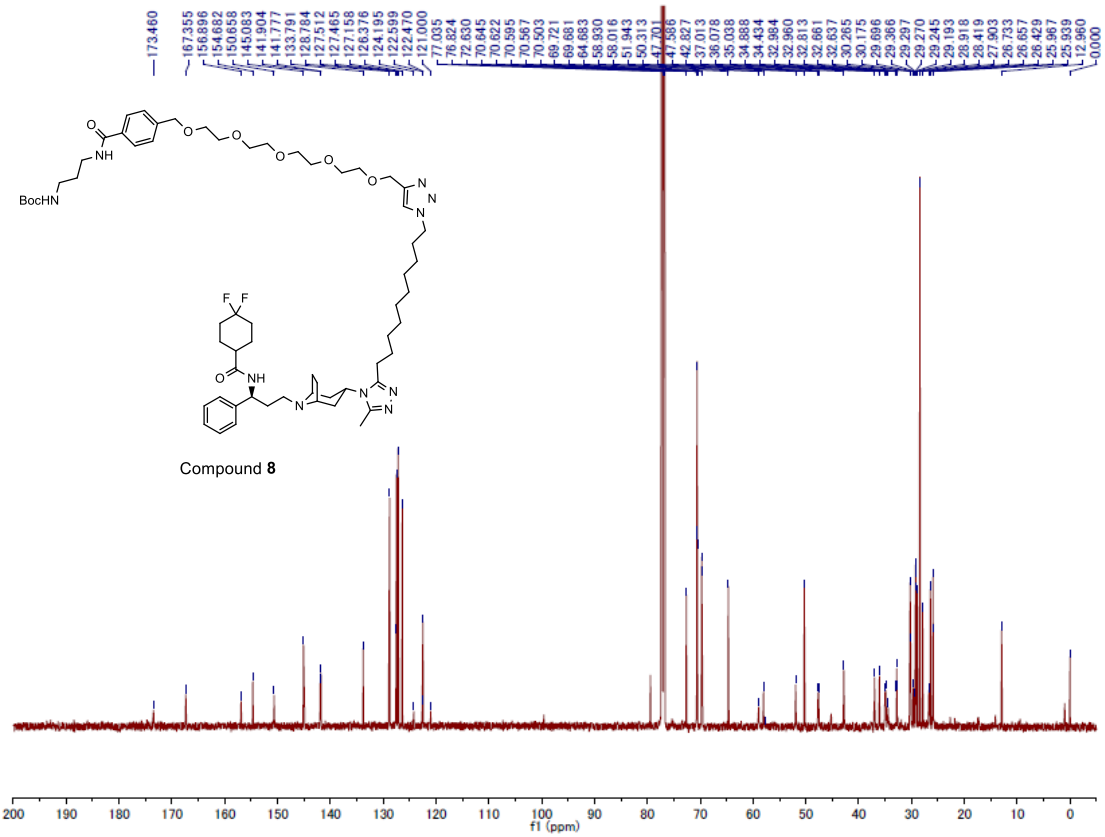


Compound **5**

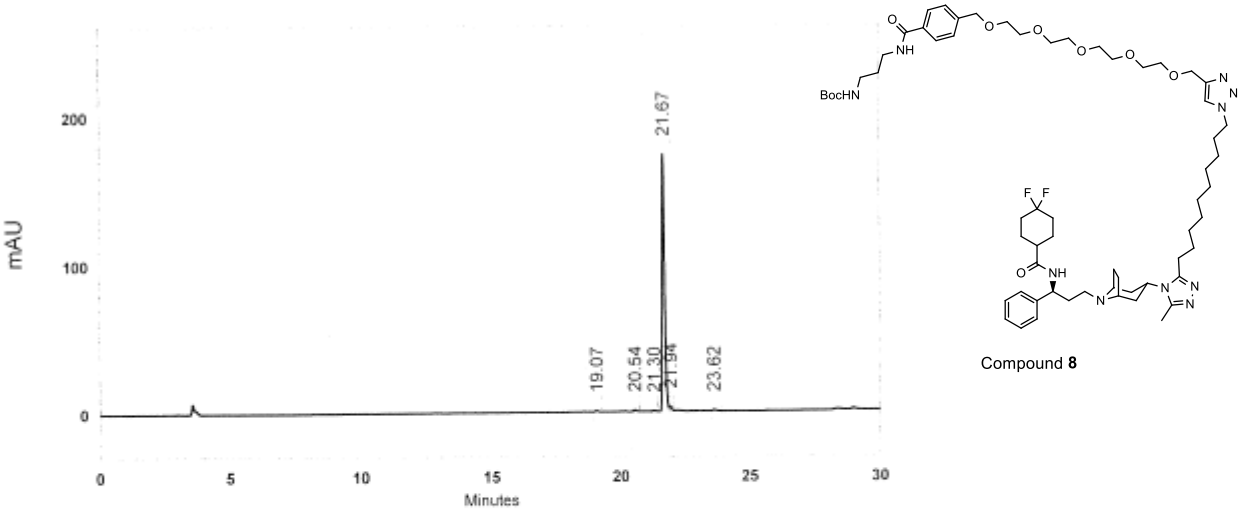
DAD-CH1 254 nm Results

	Pk #	RT	Area
1	16.307	90903	0.4
2	17.427	54945	0.2
3	19.500	157289	0.7
4	20.353	85660	0.4
5	20.867	22740690	95.8
6	21.140	302676	1.3
7	21.427	121947	0.5
8	22.207	69470	0.3
9	22.680	39768	0.2
10	22.840	42943	0.2
11	23.607	32523	0.1
Totals		23738814	100.0





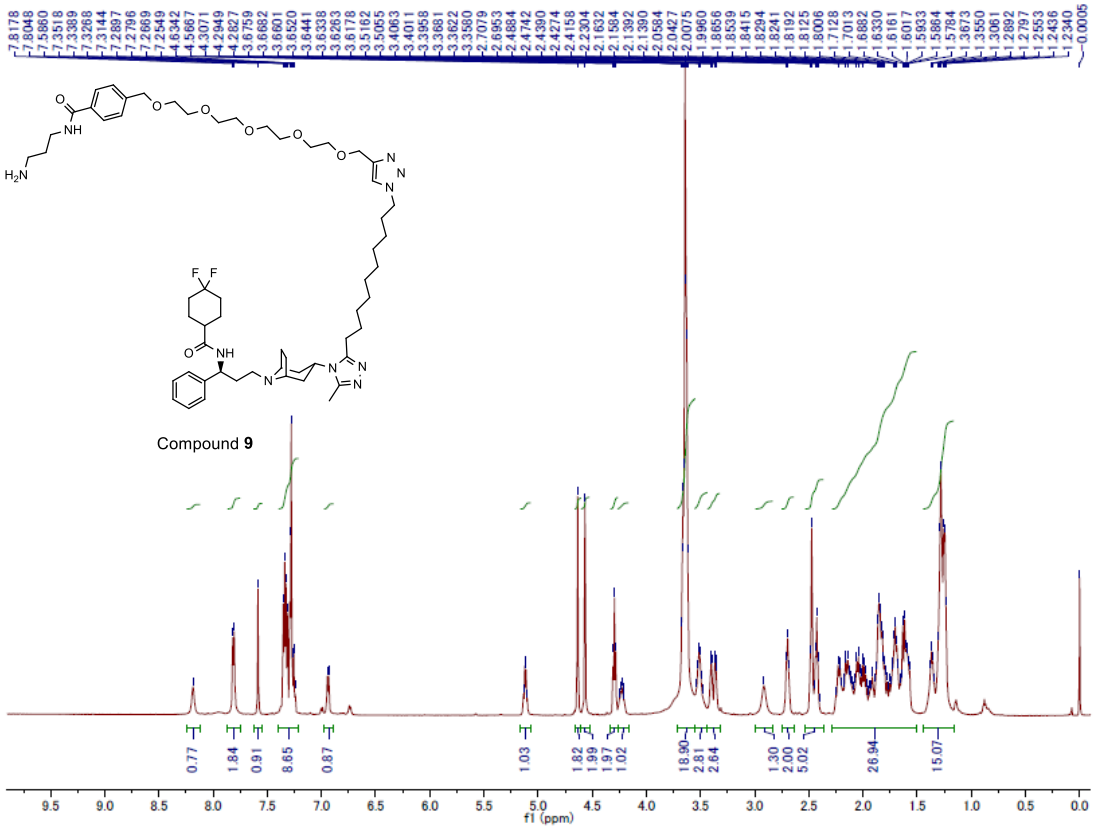
Compound **8**

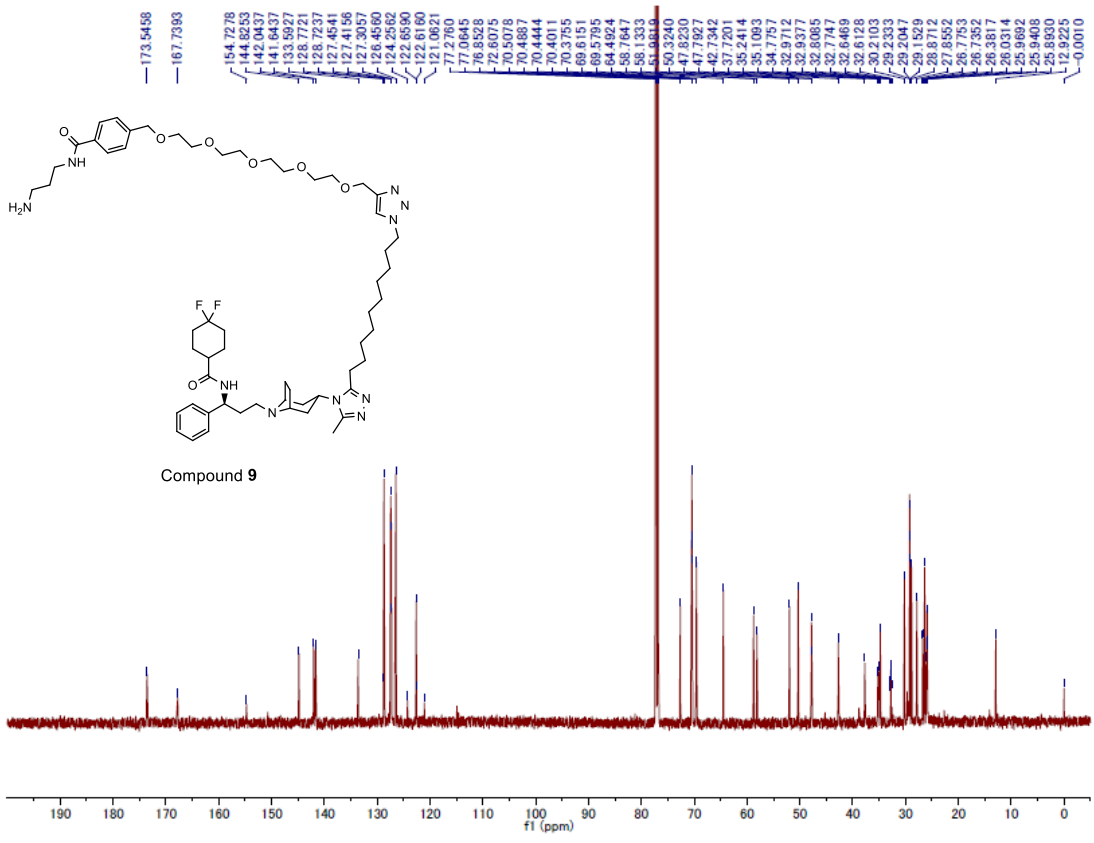


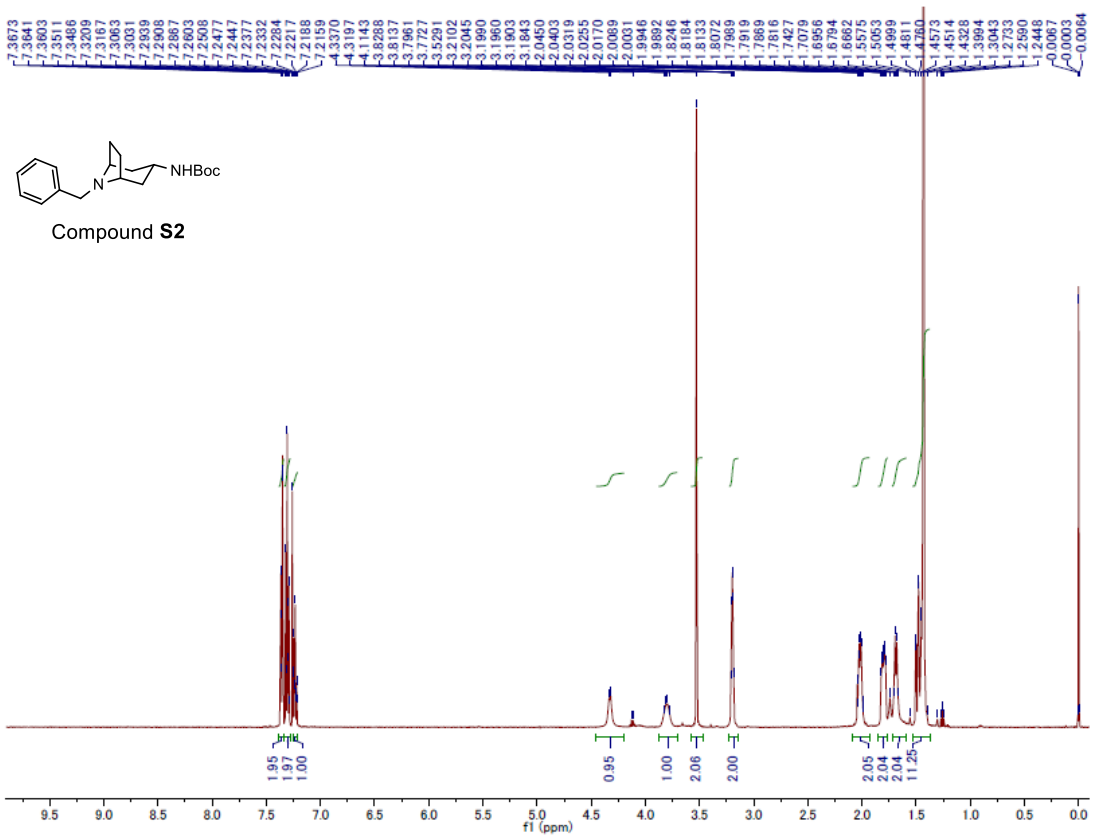
Compound **8**

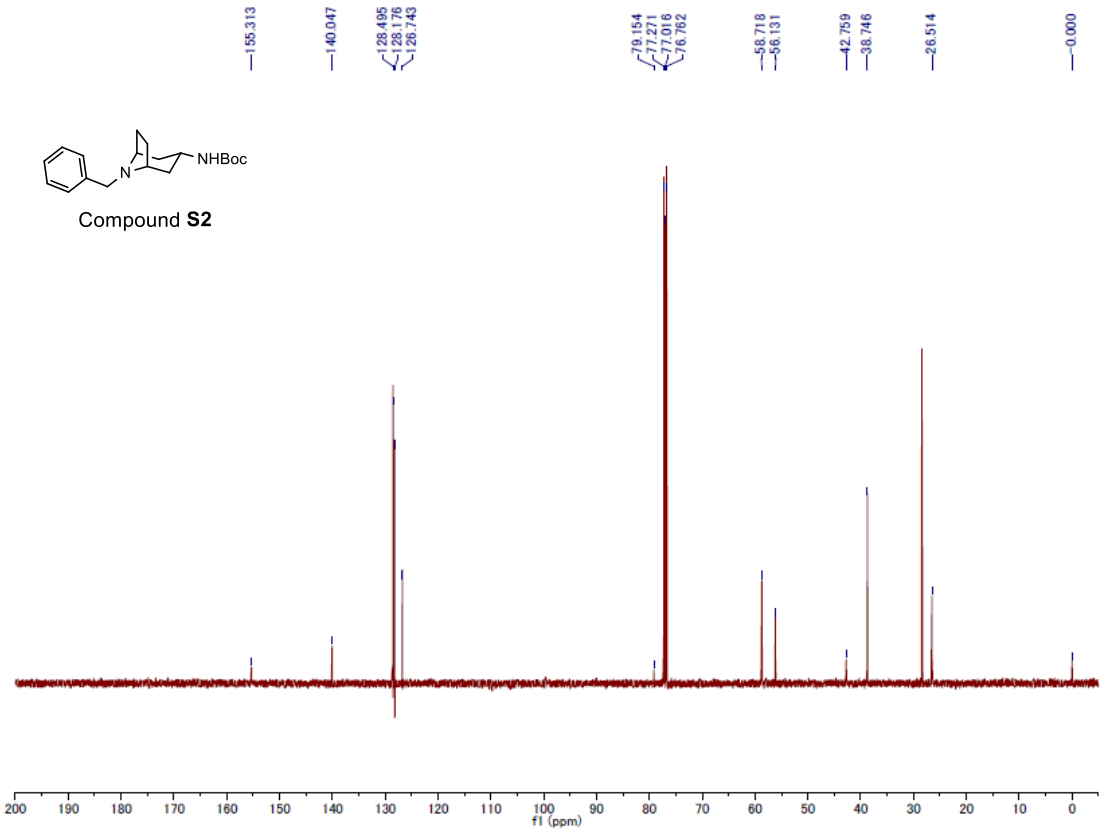
DAD-CH1 254 nm Results

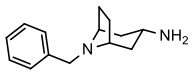
	Pk #	RT	Area
1	19.067	20160	0.4
2	20.540	28390	0.6
3	21.300	12876	0.3
4	21.673	4788735	96.8
5	21.940	66463	1.3
6	23.620	32016	0.6
Totals		4948640	100.0


Compound 9
f1 (ppm)

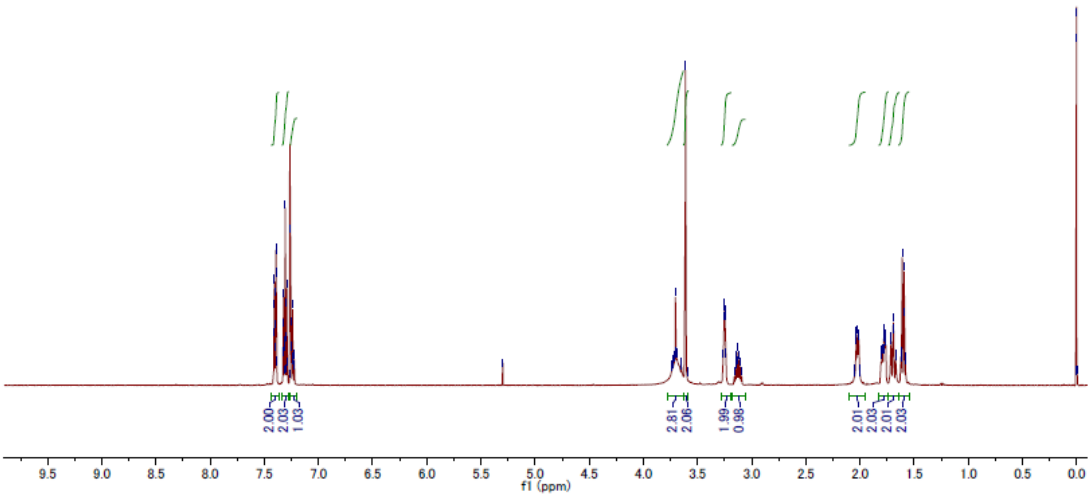

Compound 9
f1 (ppm)

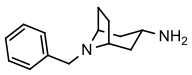

NHBoc
N
Compound S2
f1 (ppm)


NHBoc
N
Compound S2
f1 (ppm)

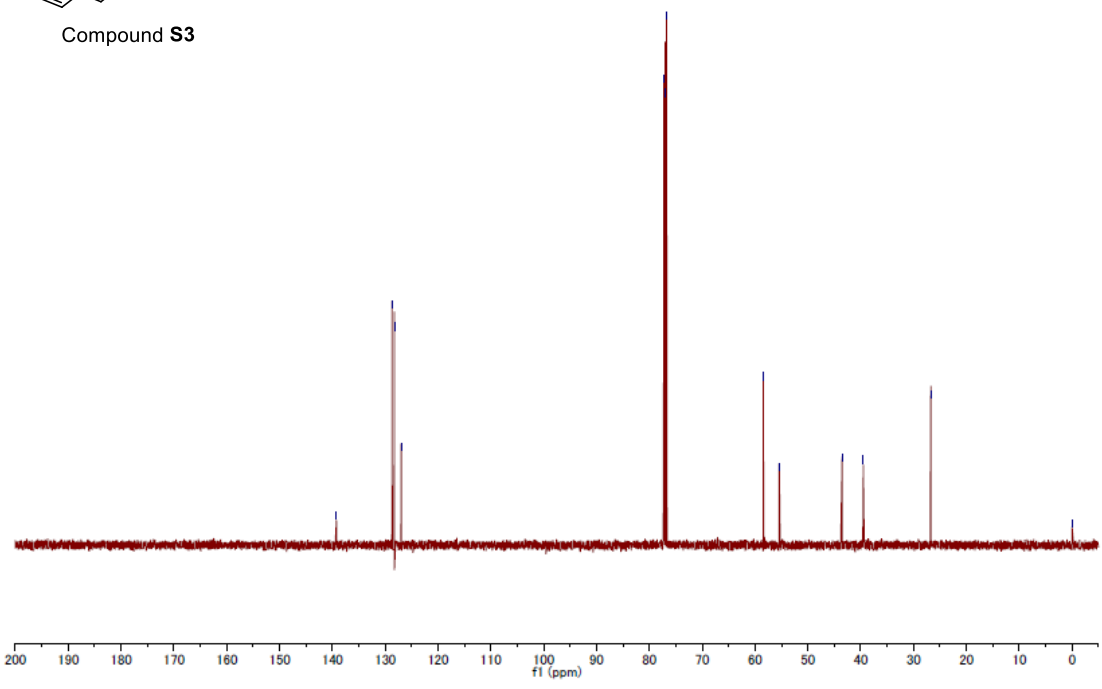


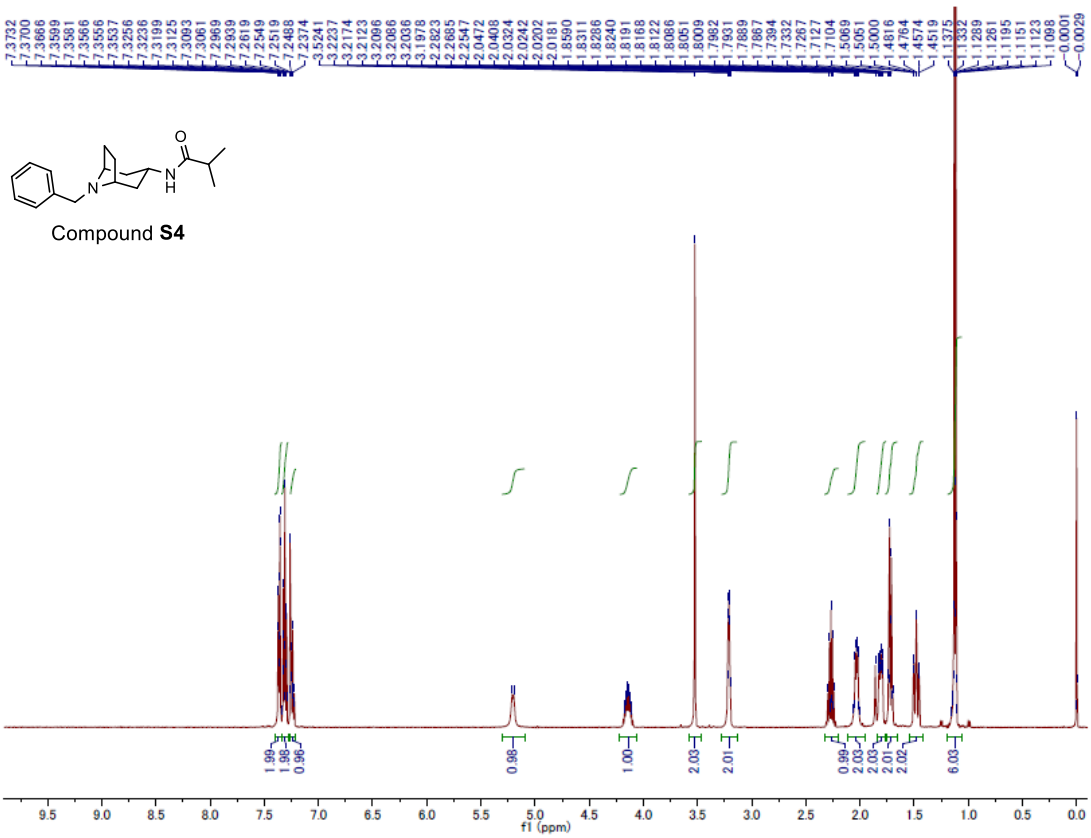
Compound **S3**



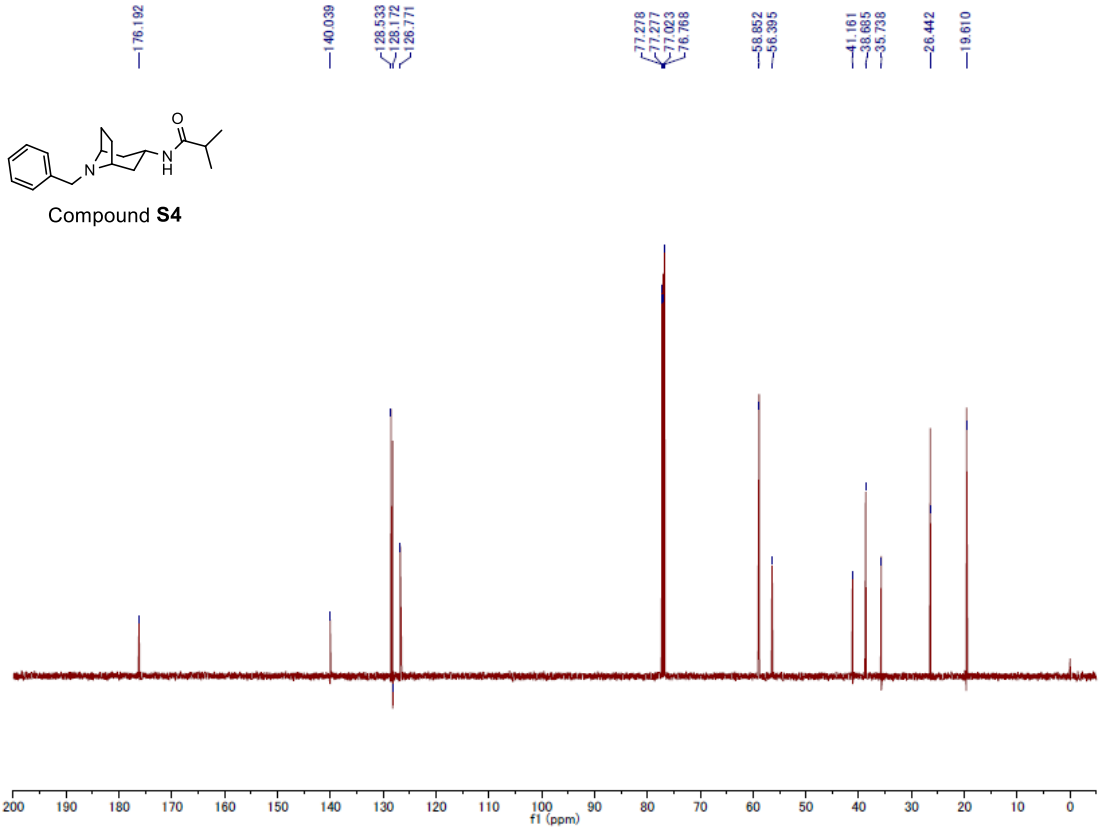


Compound **S3**

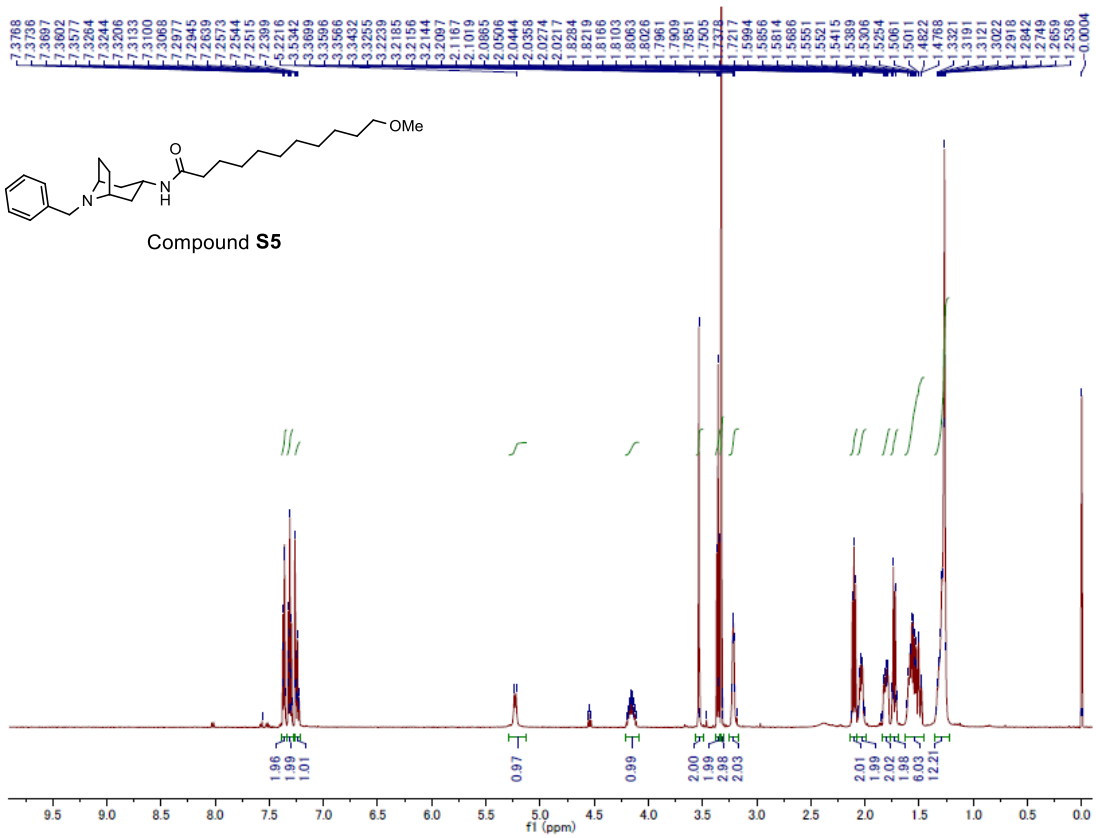


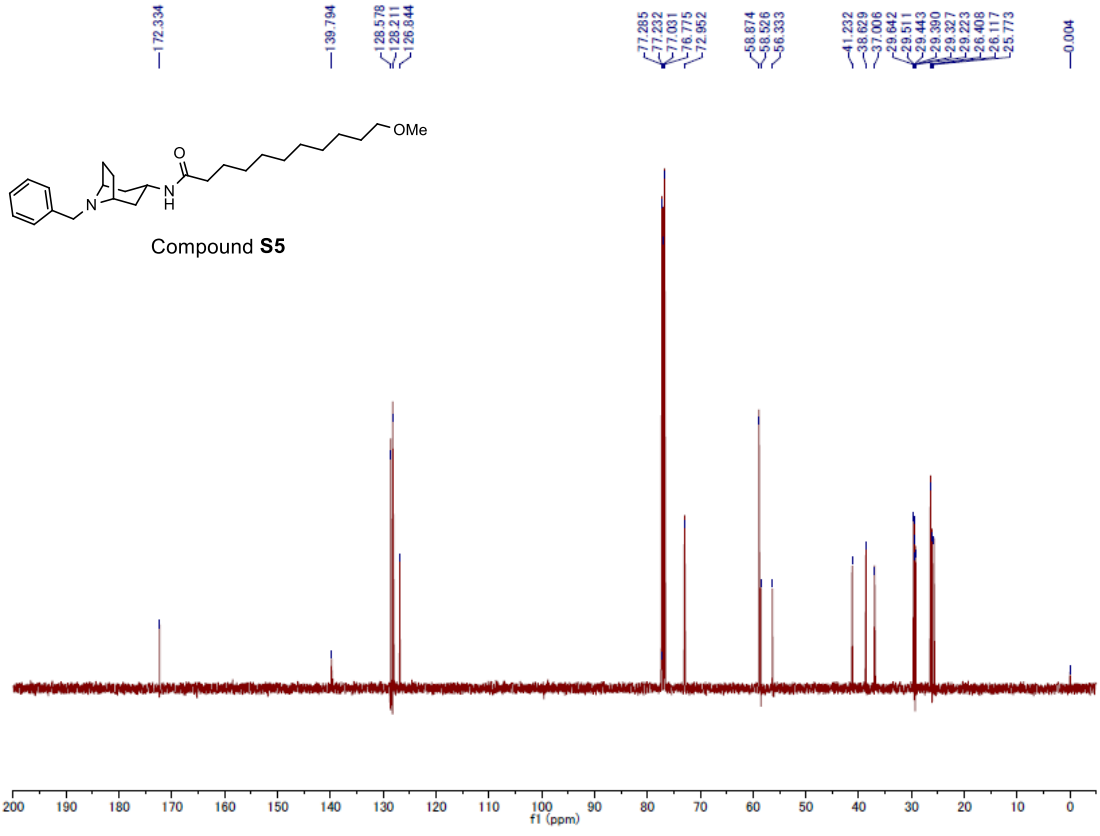


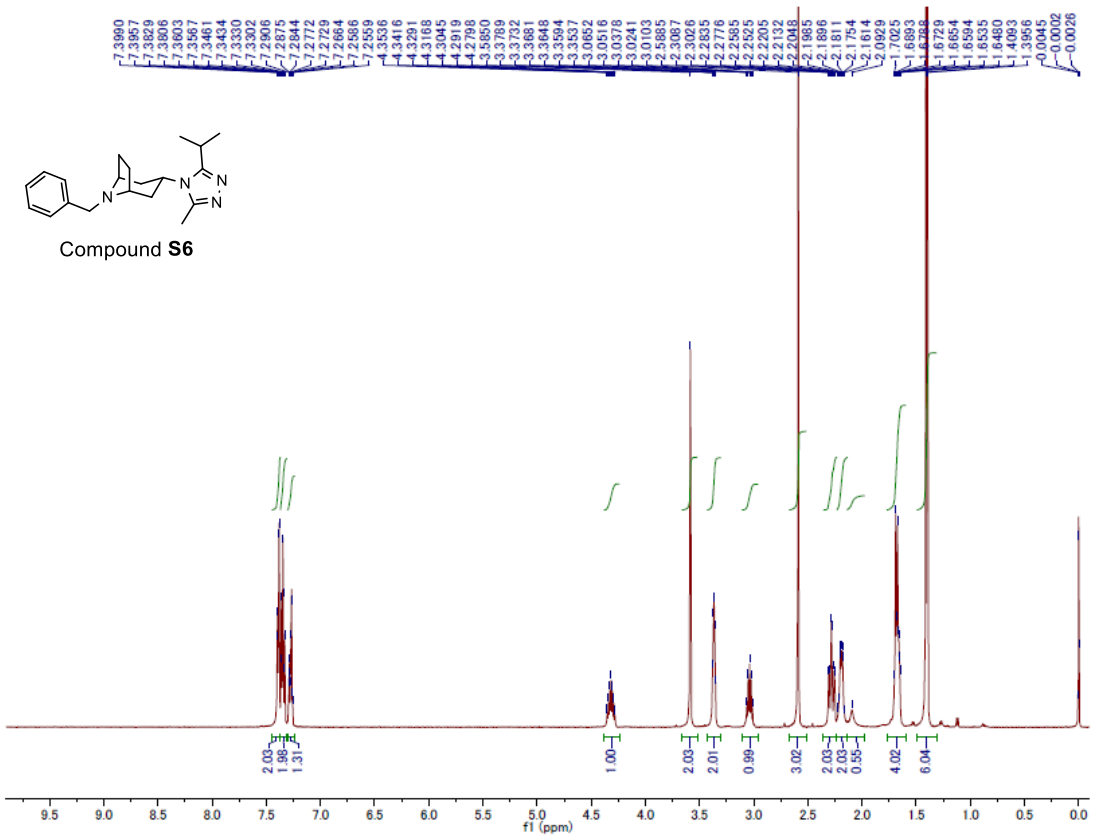
Compound **S4**



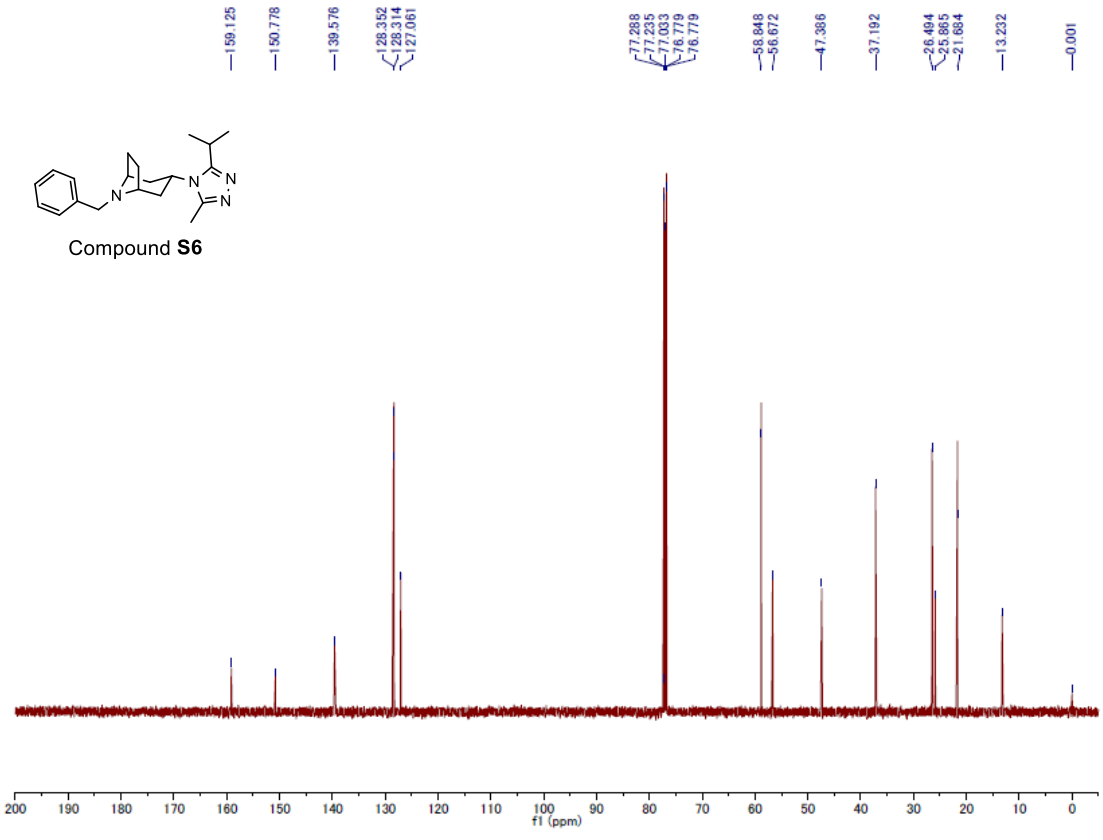
Compound **S4**


OMe
O
N
H
N
Compound S5
f1 (ppm)

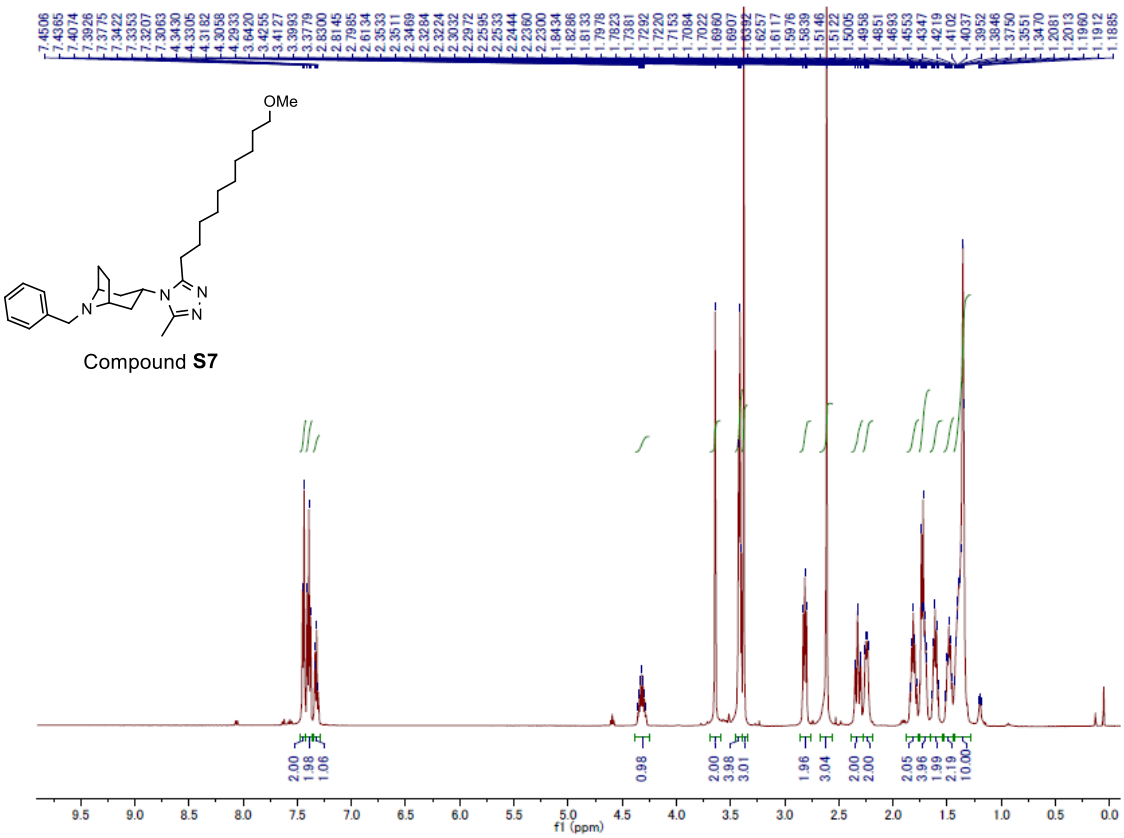

OMe
O
N
H
N
Compound S5
f1 (ppm)



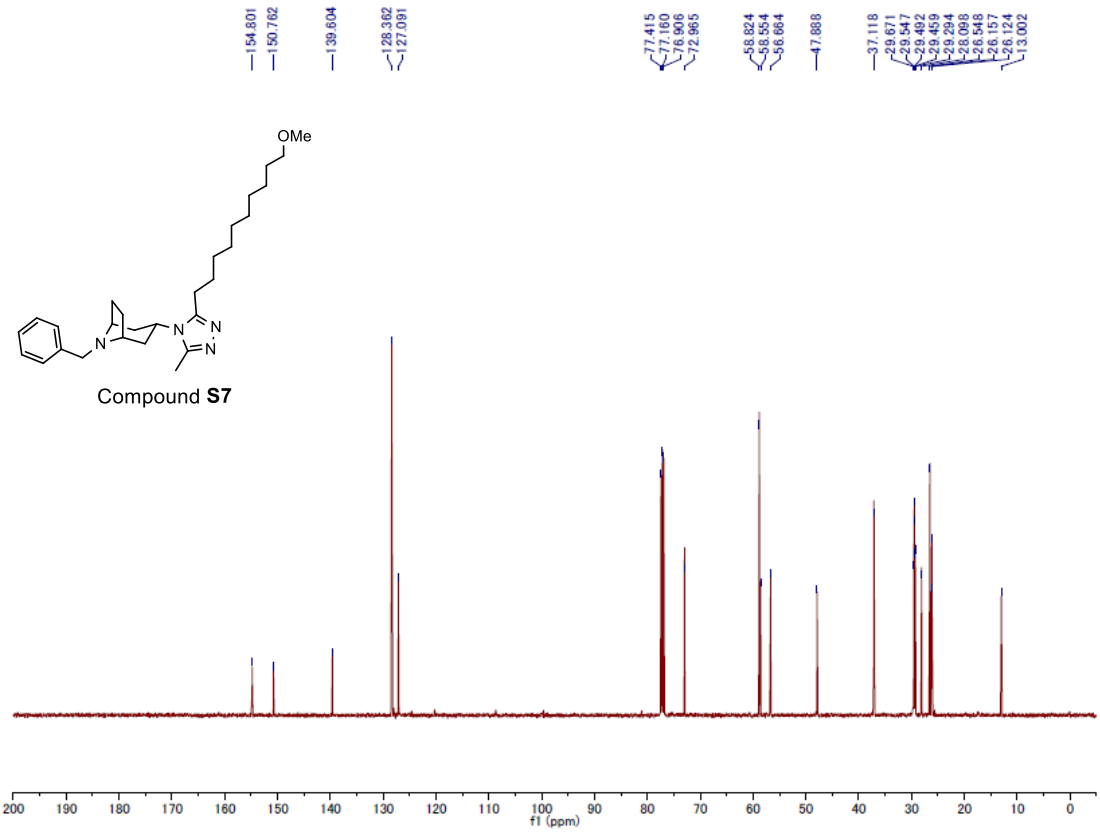
Compound **S6**



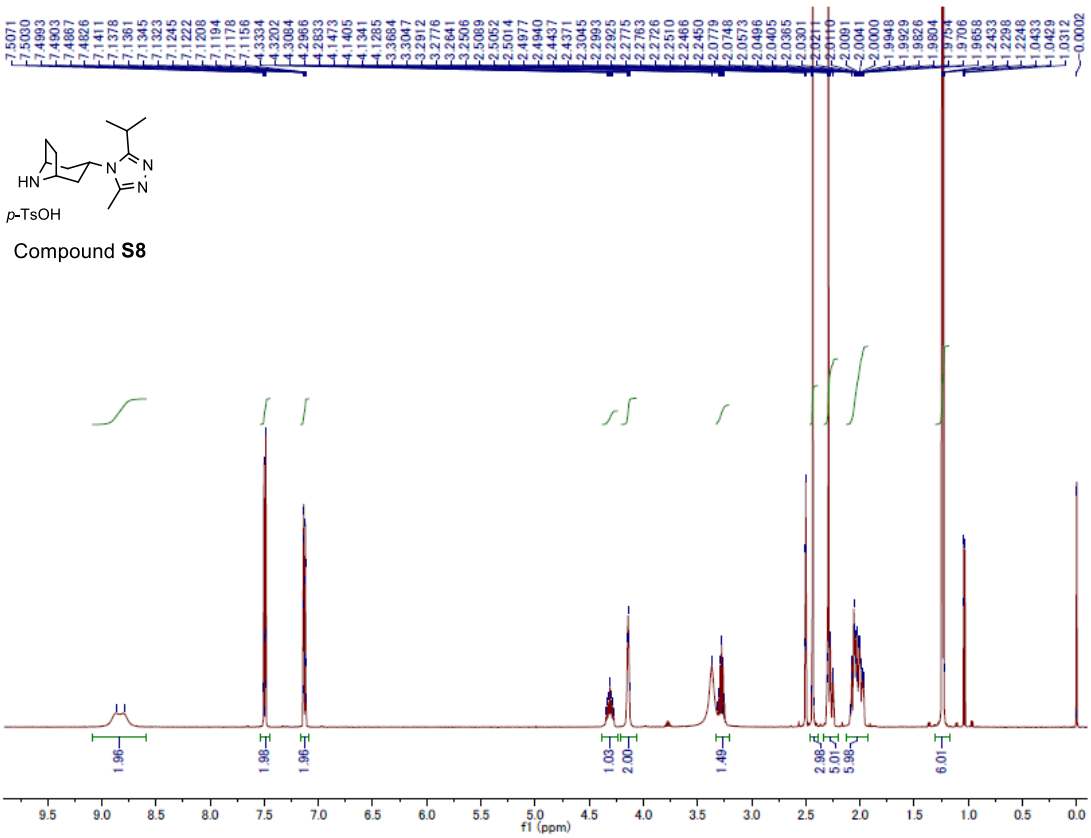
Compound **S6**



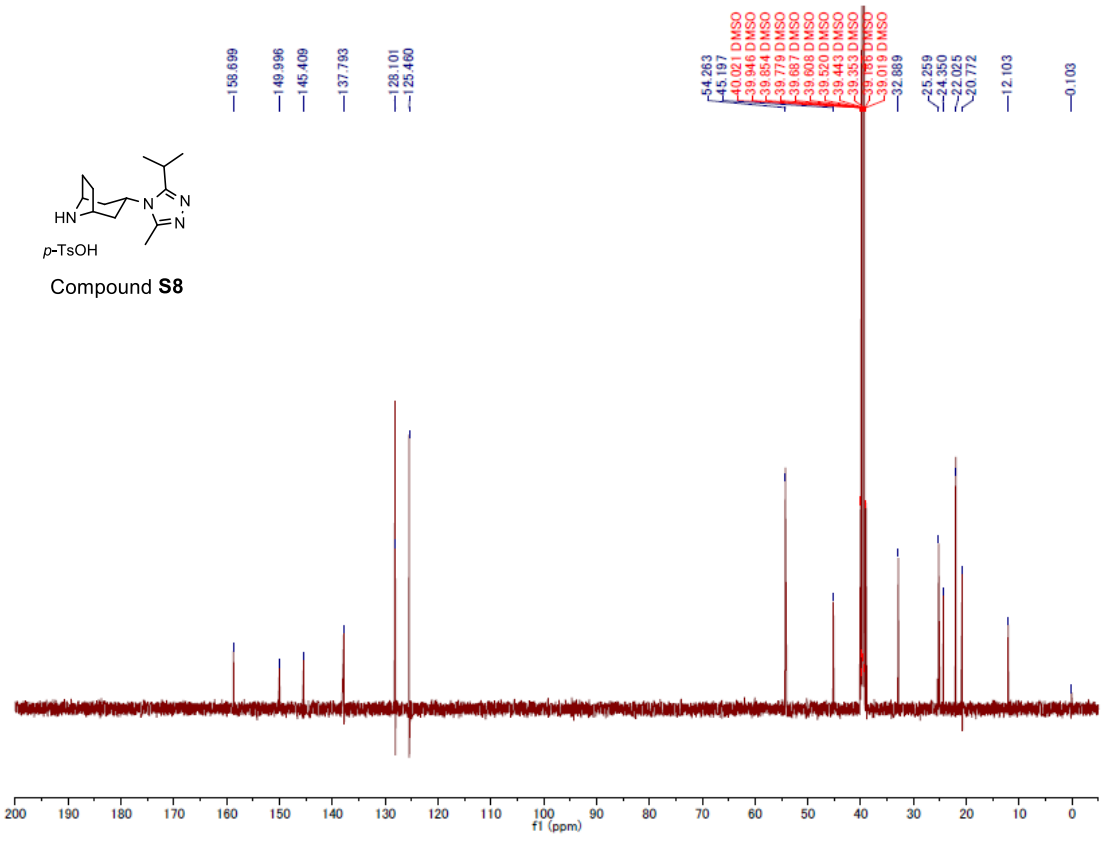
Compound **S7**



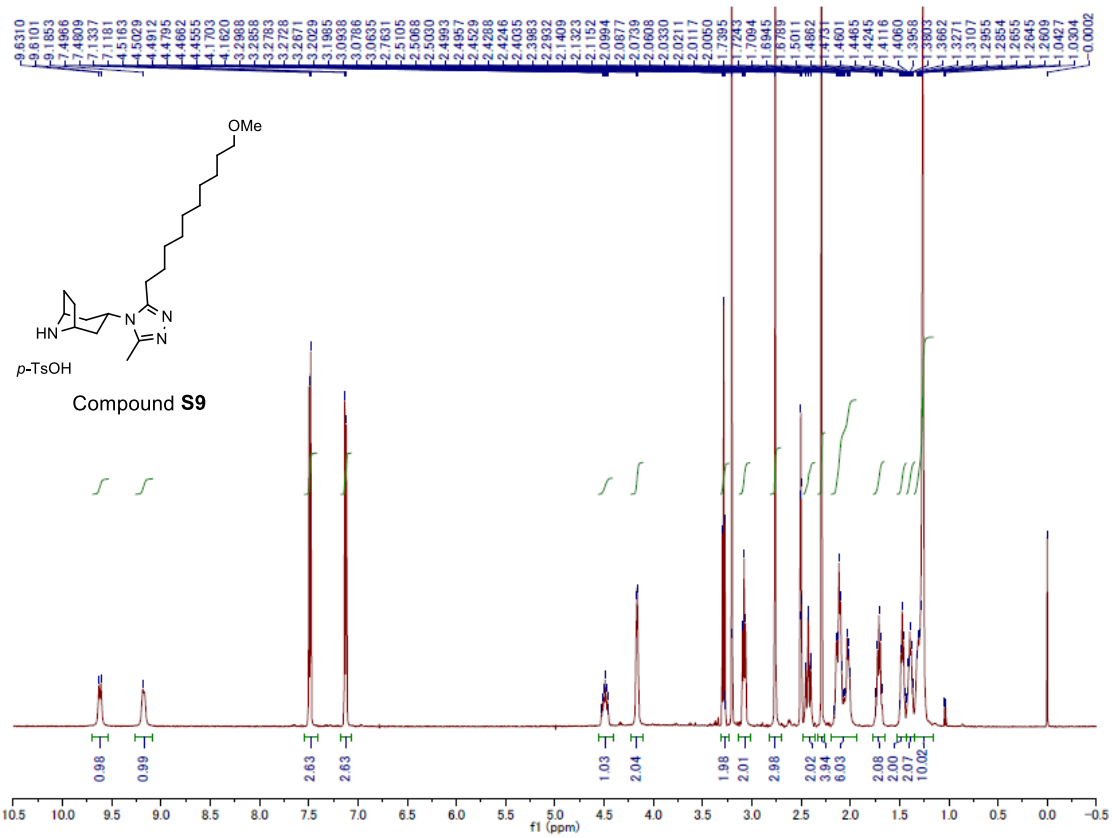
Compound **S7**



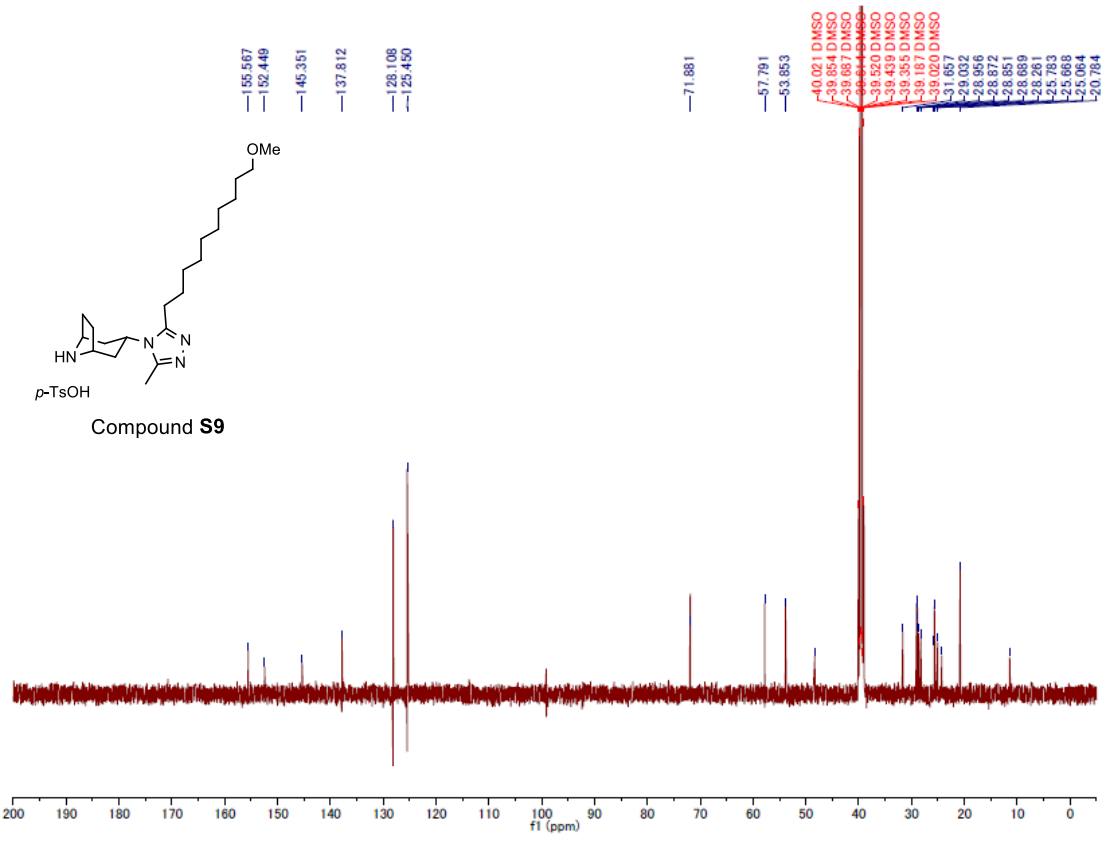
Compound **S8**



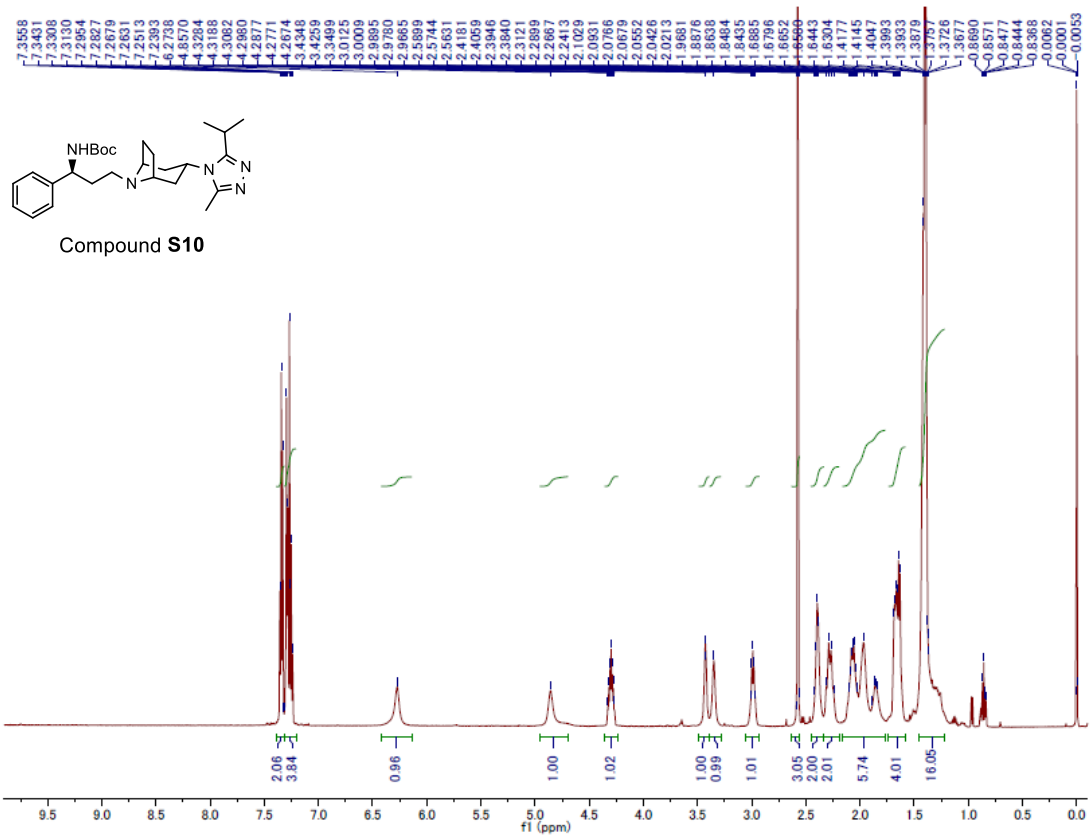
Compound **S8**



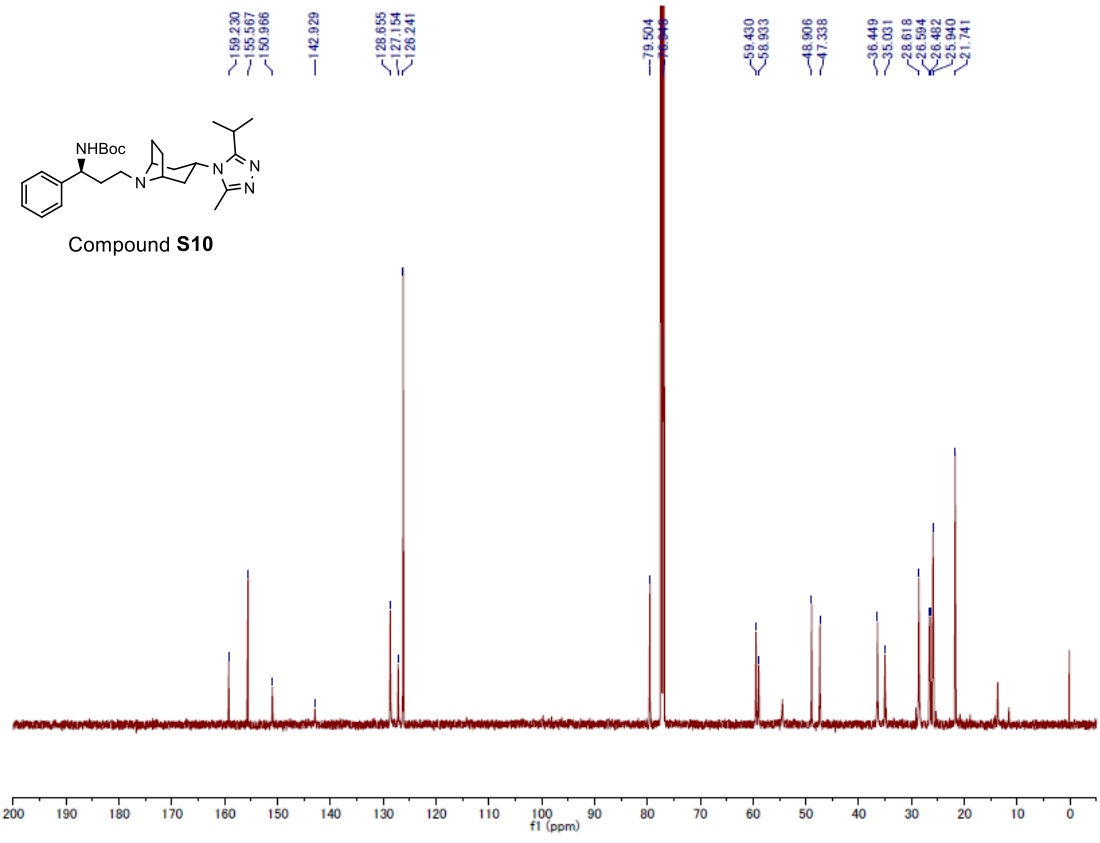
Compound **S9**



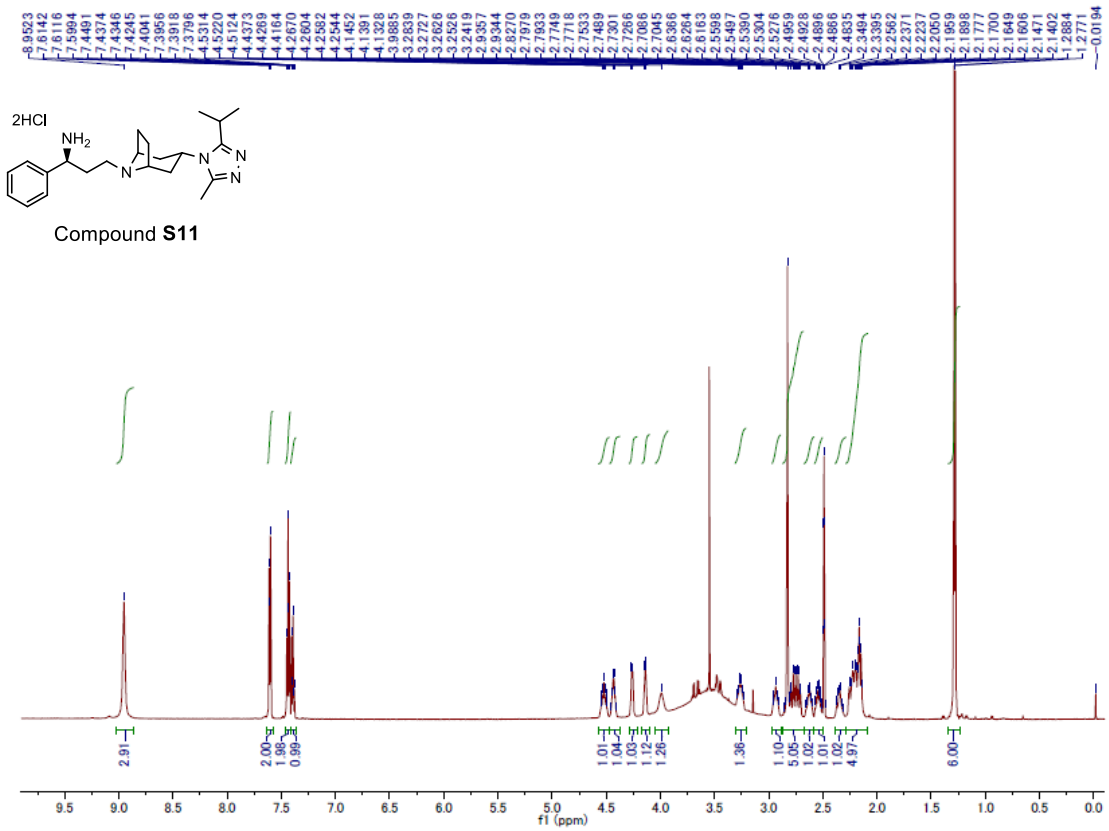
Compound **S9**



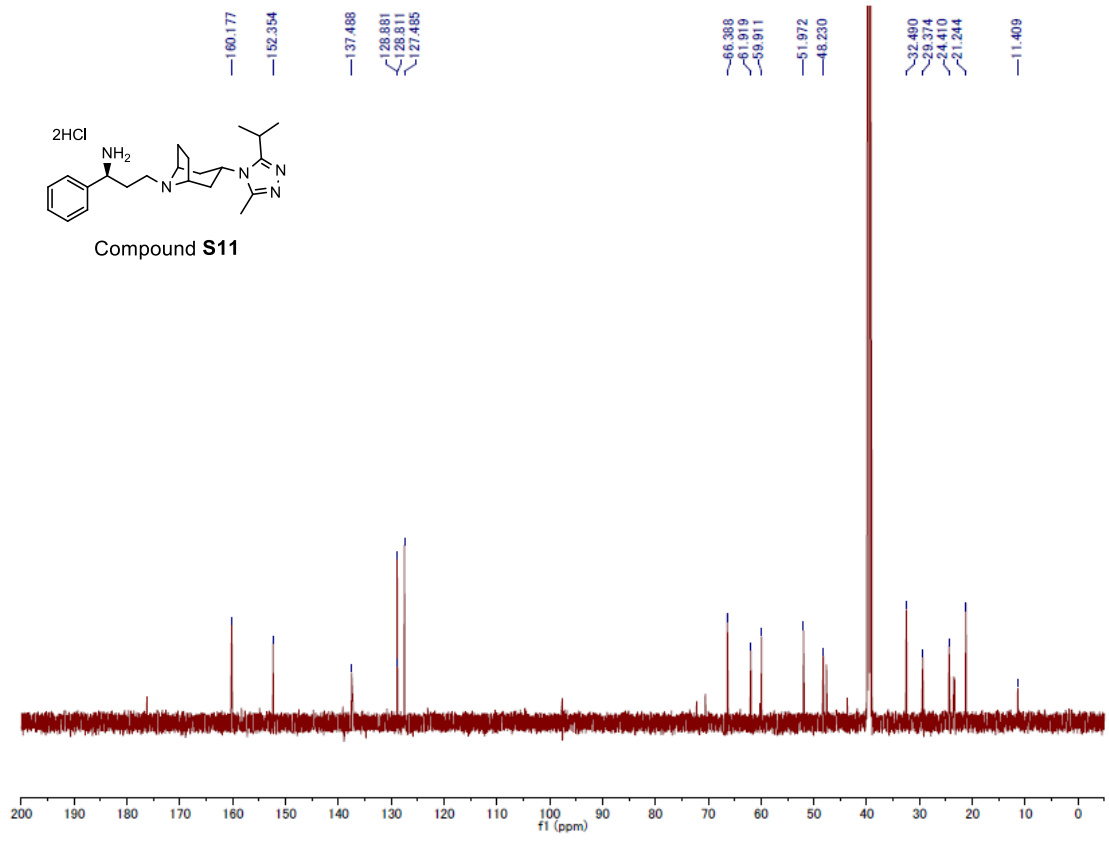
Compound **S10**



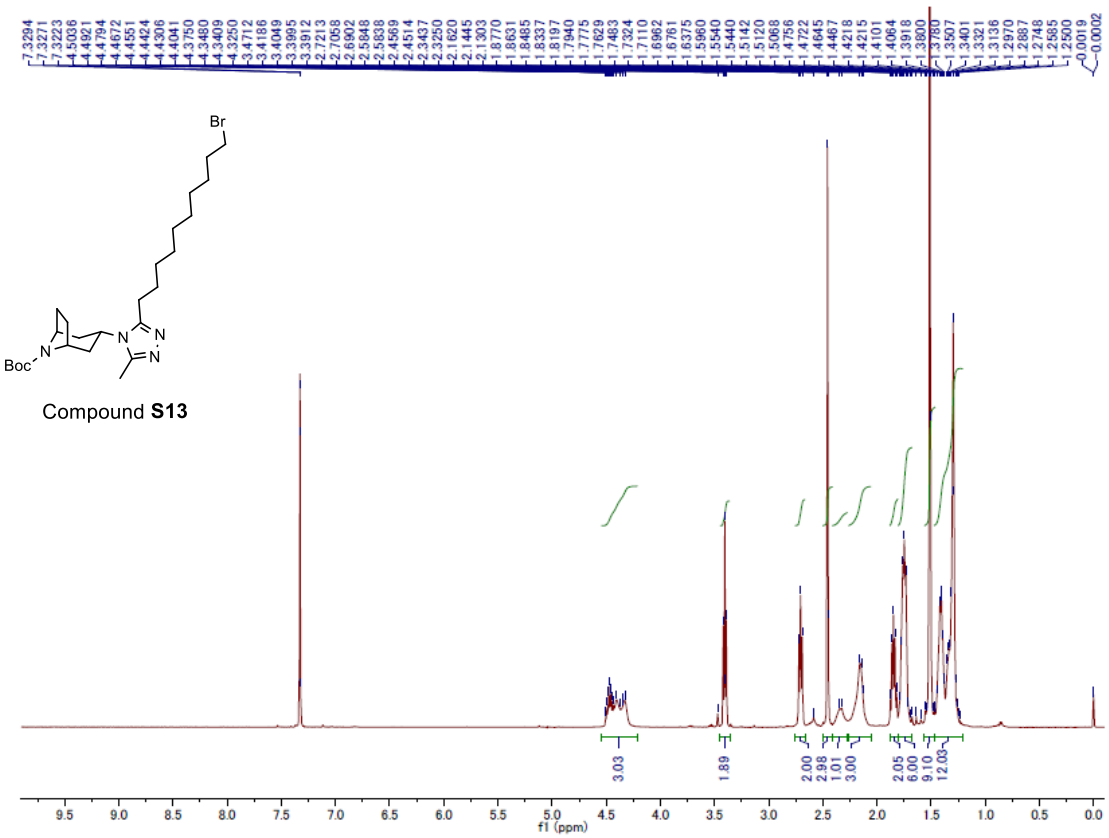
Compound **S10**



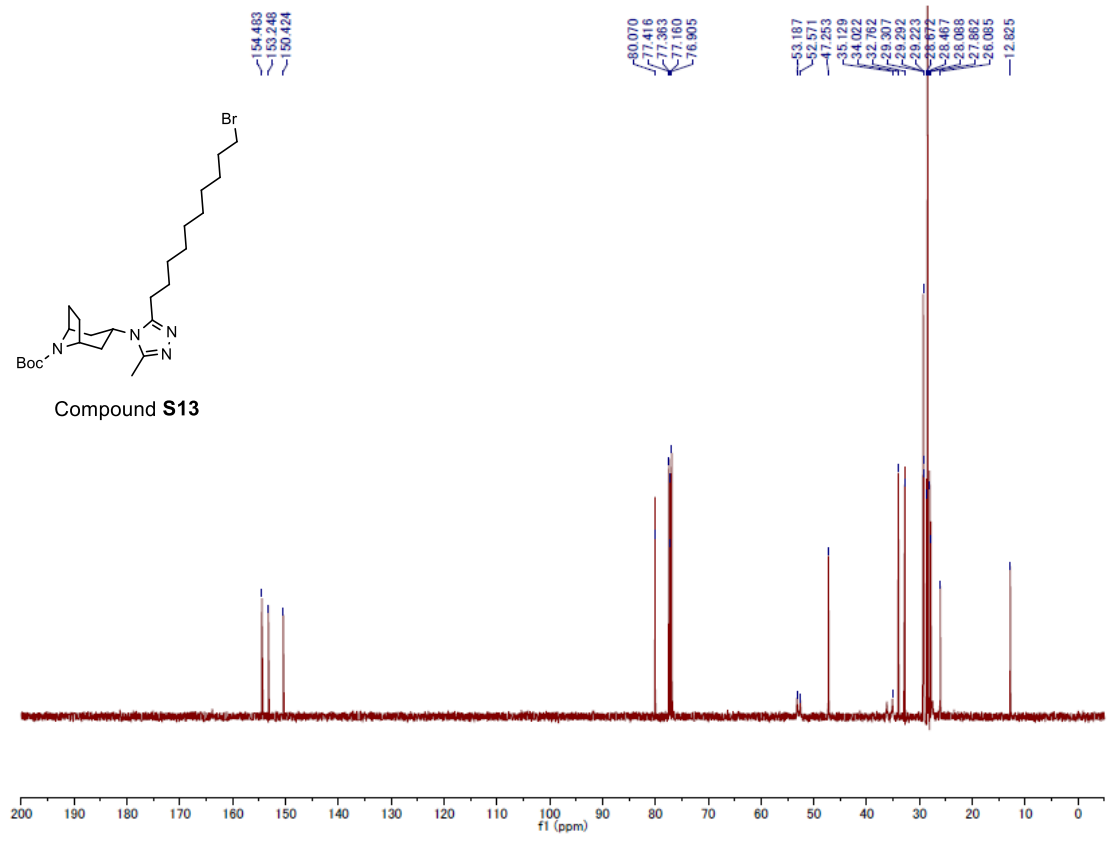
Compound **S11**



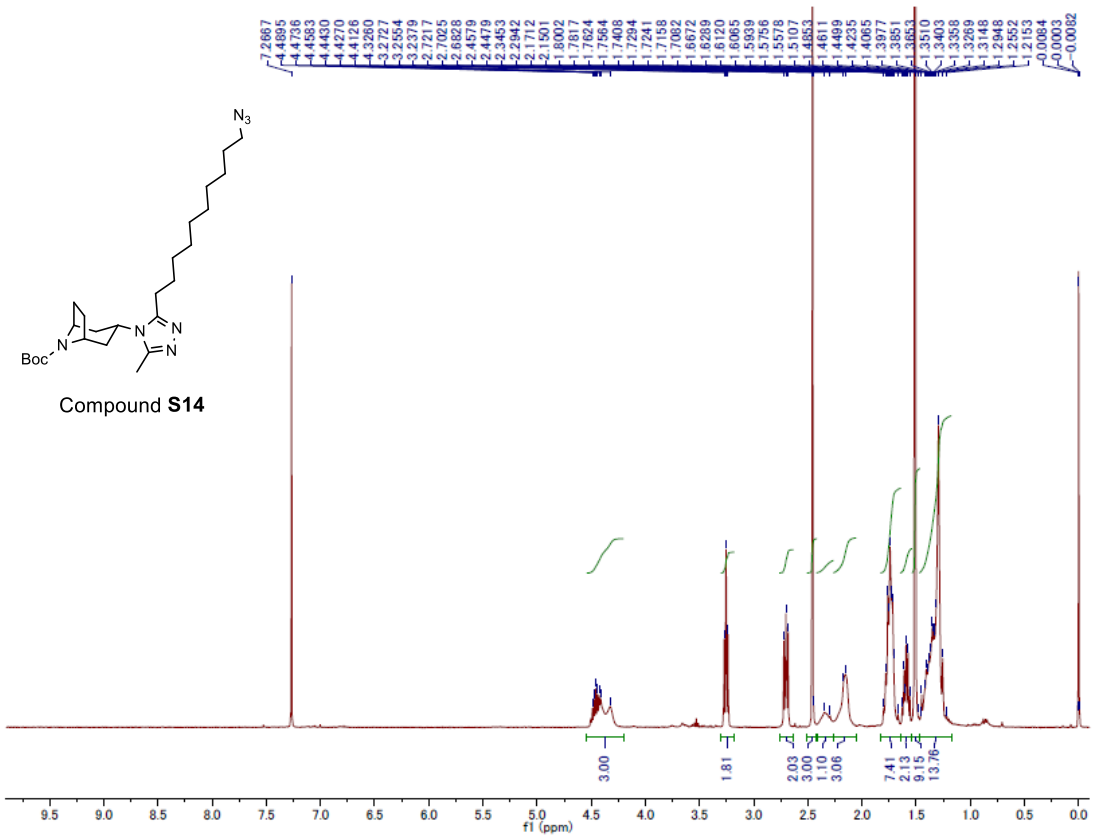
Compound **S11**



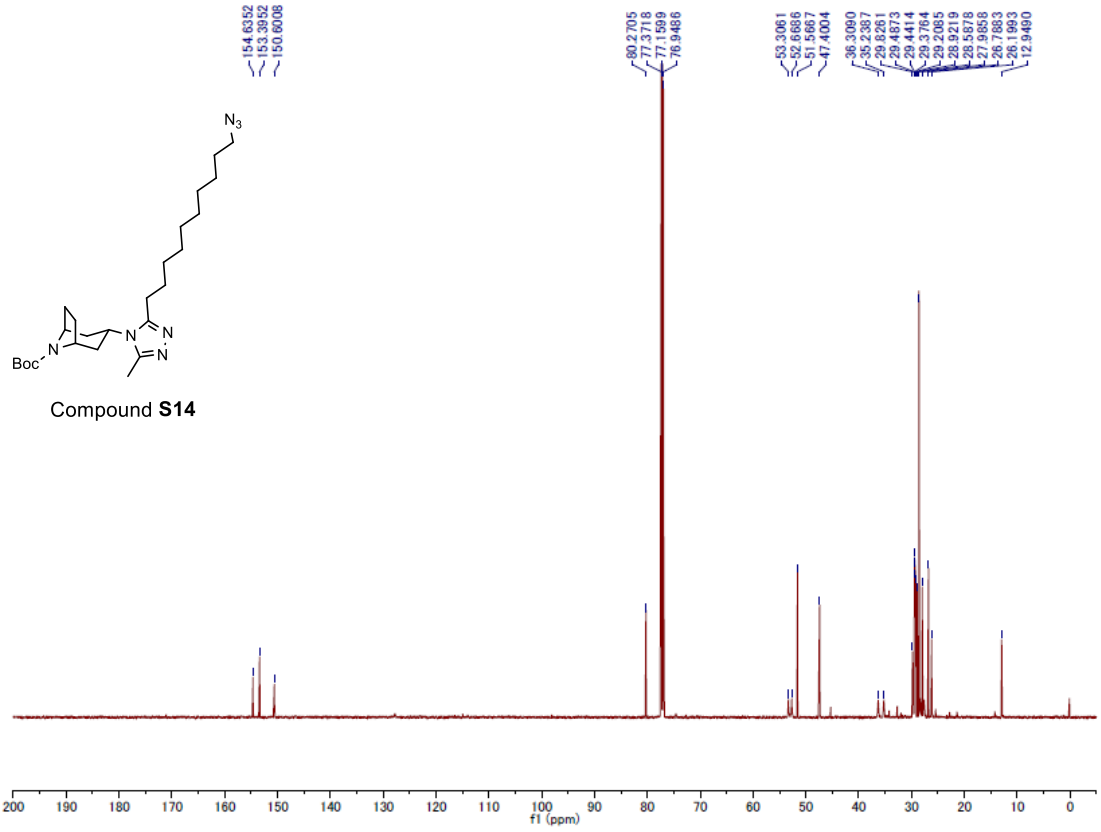
Compound **S13**



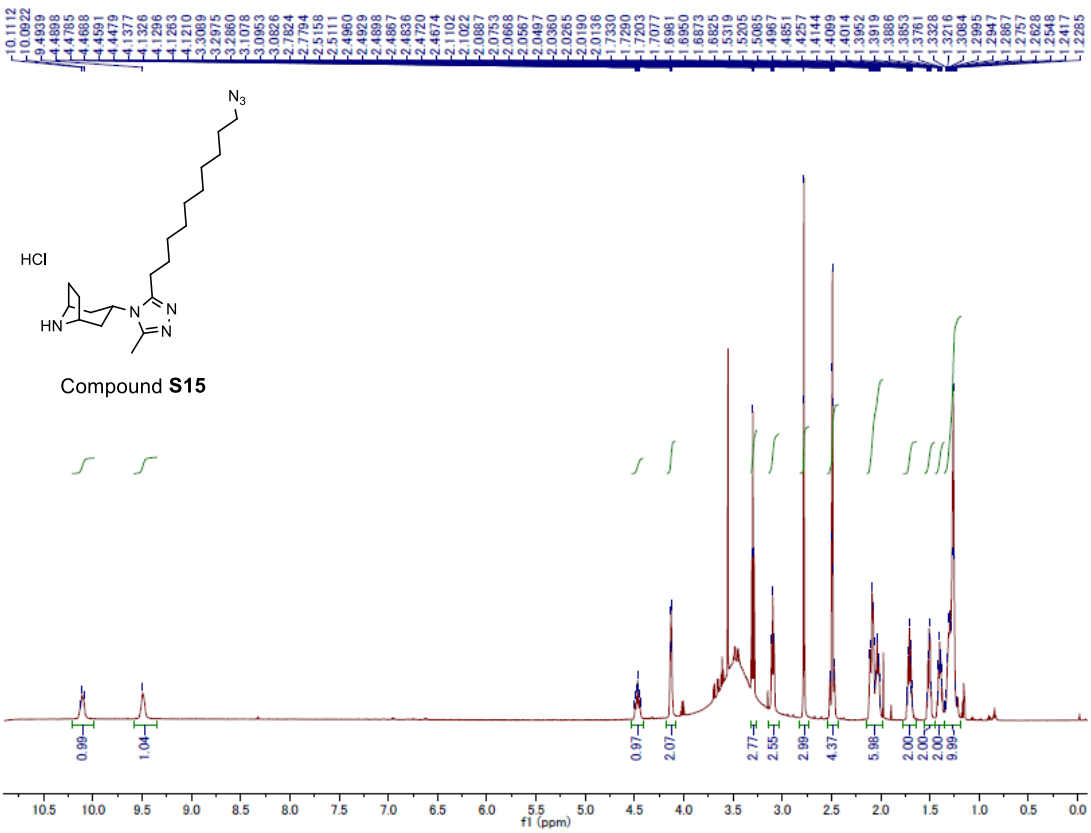
Compound **S13**

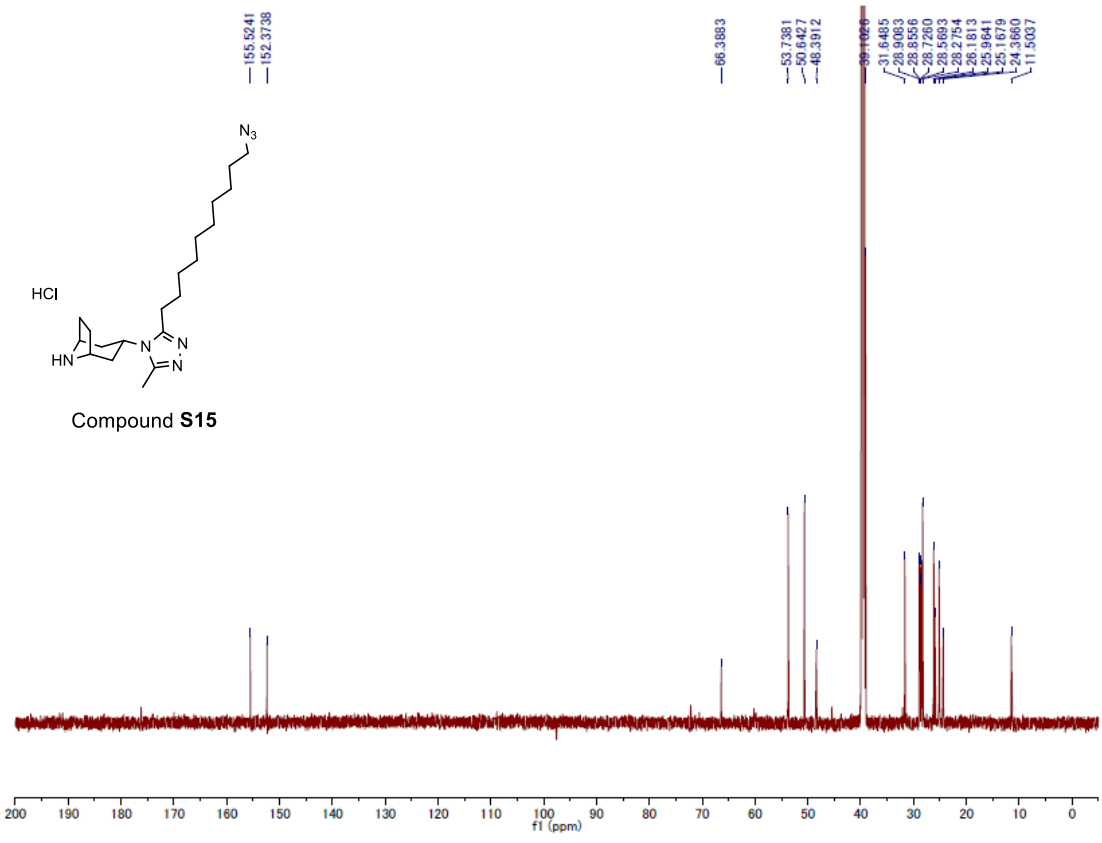


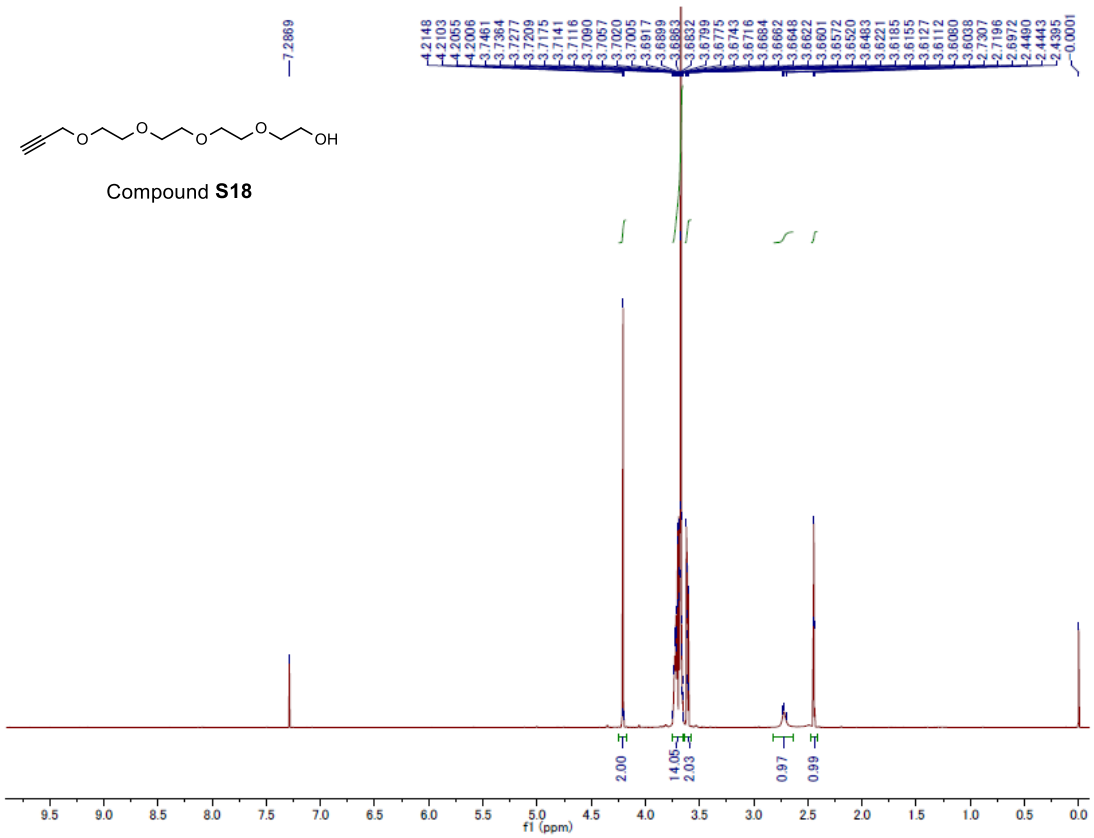
Compound **S14**

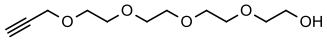


Compound **S14**

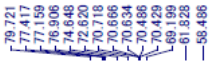

HCl
HN
N
N
N
N3
Compound S15
f1 (ppm)


HCl
HN
N
N
N
N3
Compound S15
f1 (ppm)

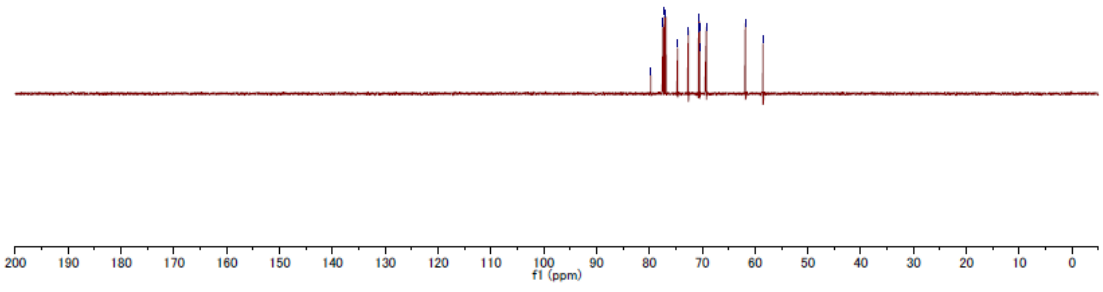


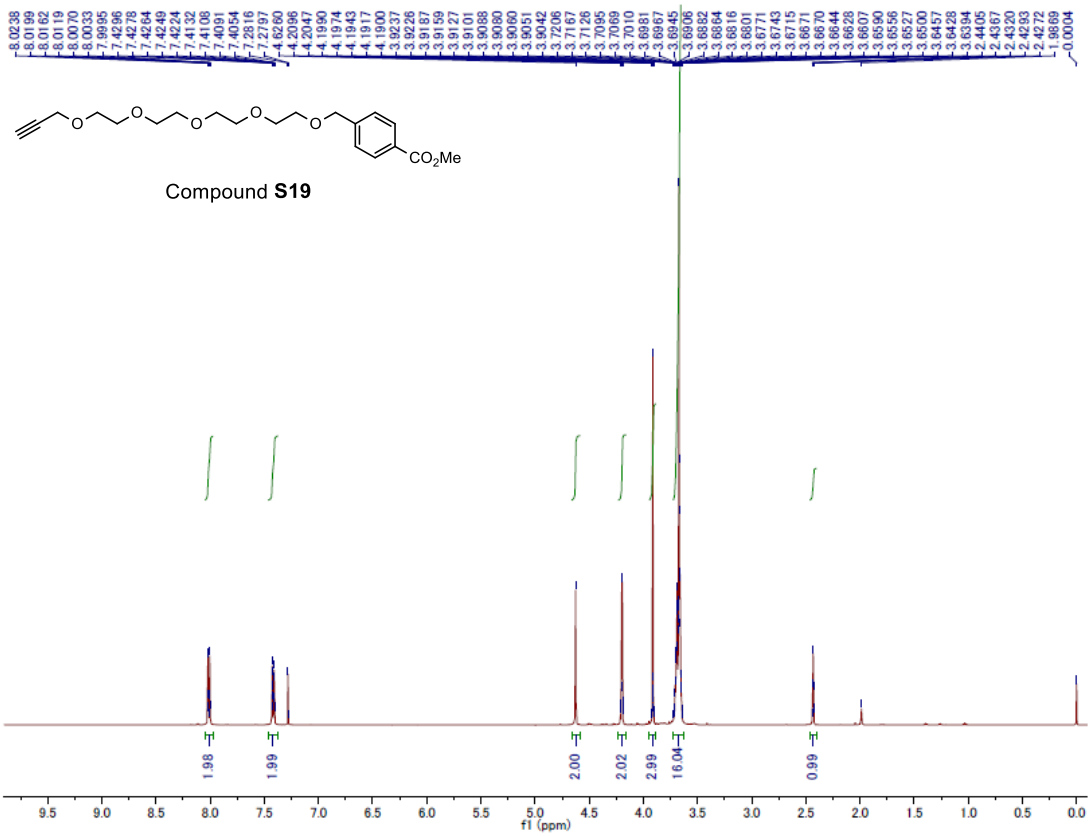


Compound **S18**

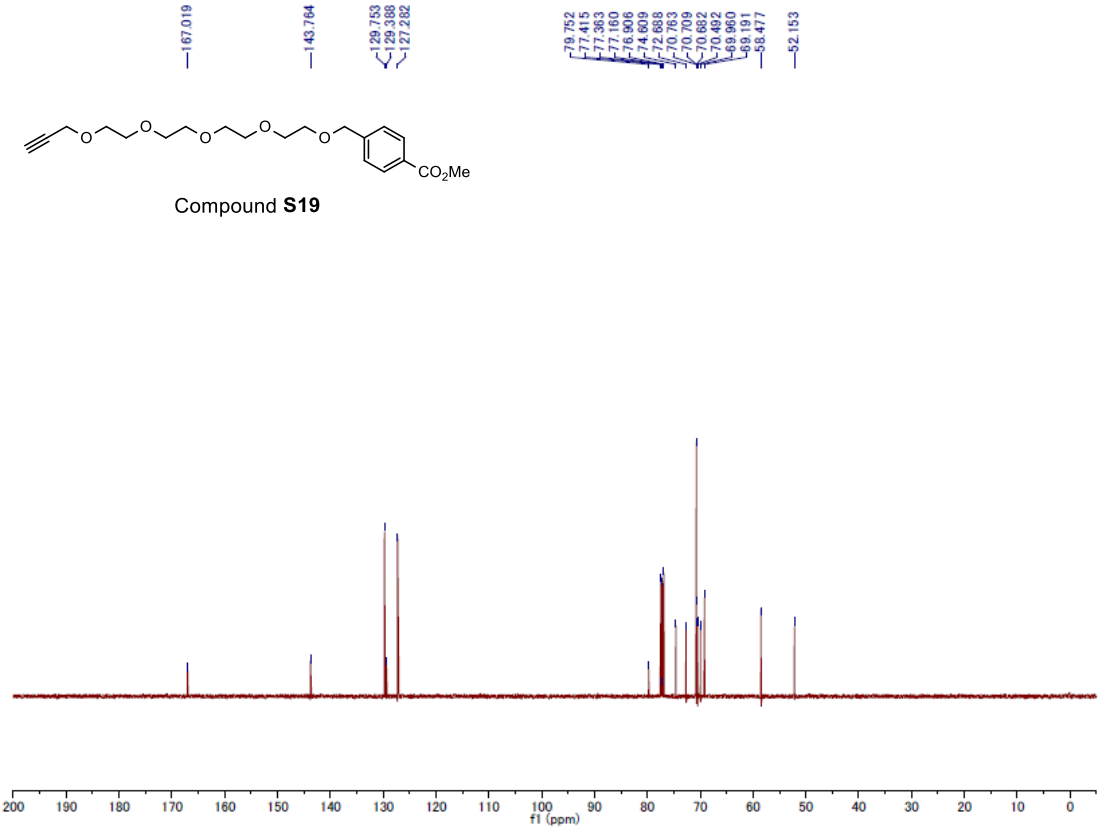


Compound **S18**

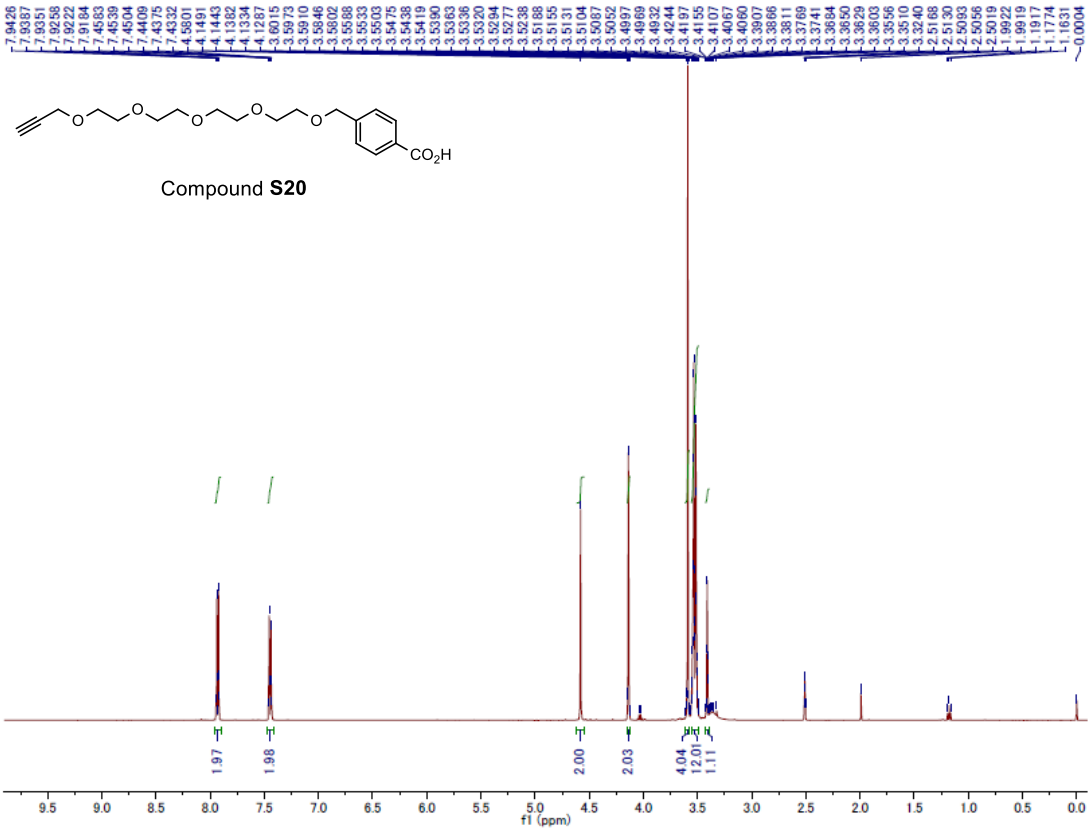




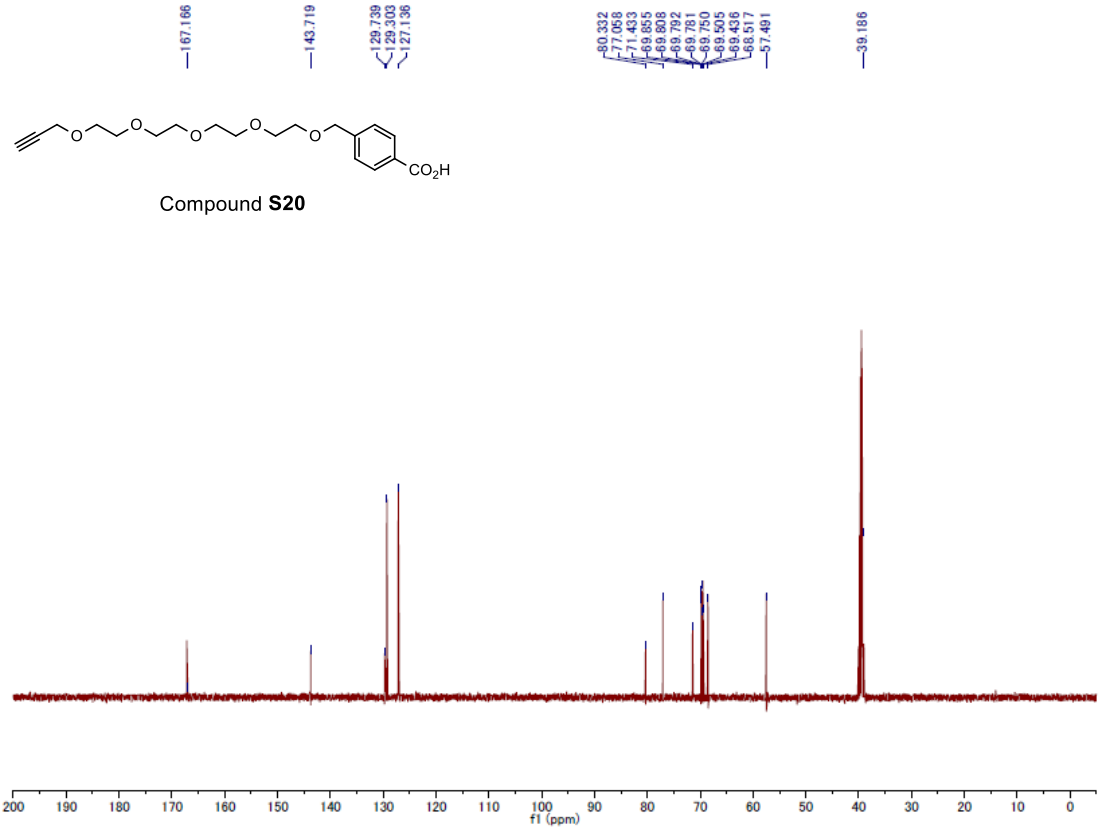
Compound **S19**



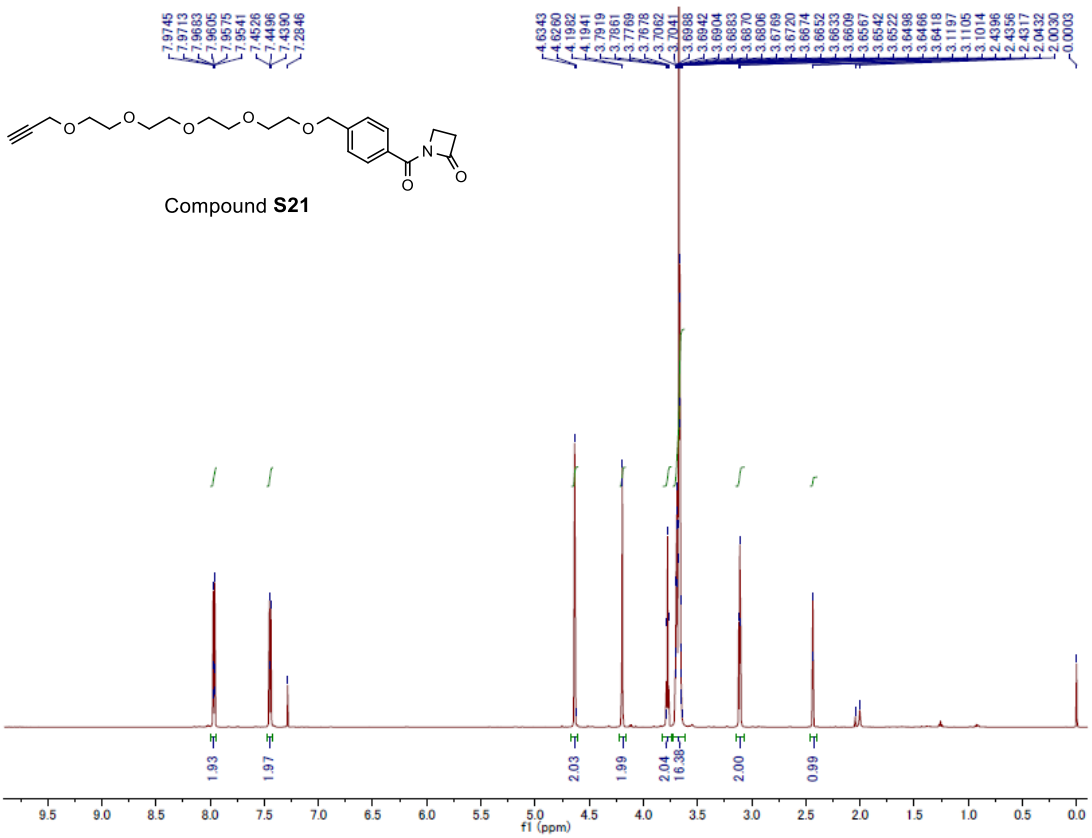
Compound **S19**



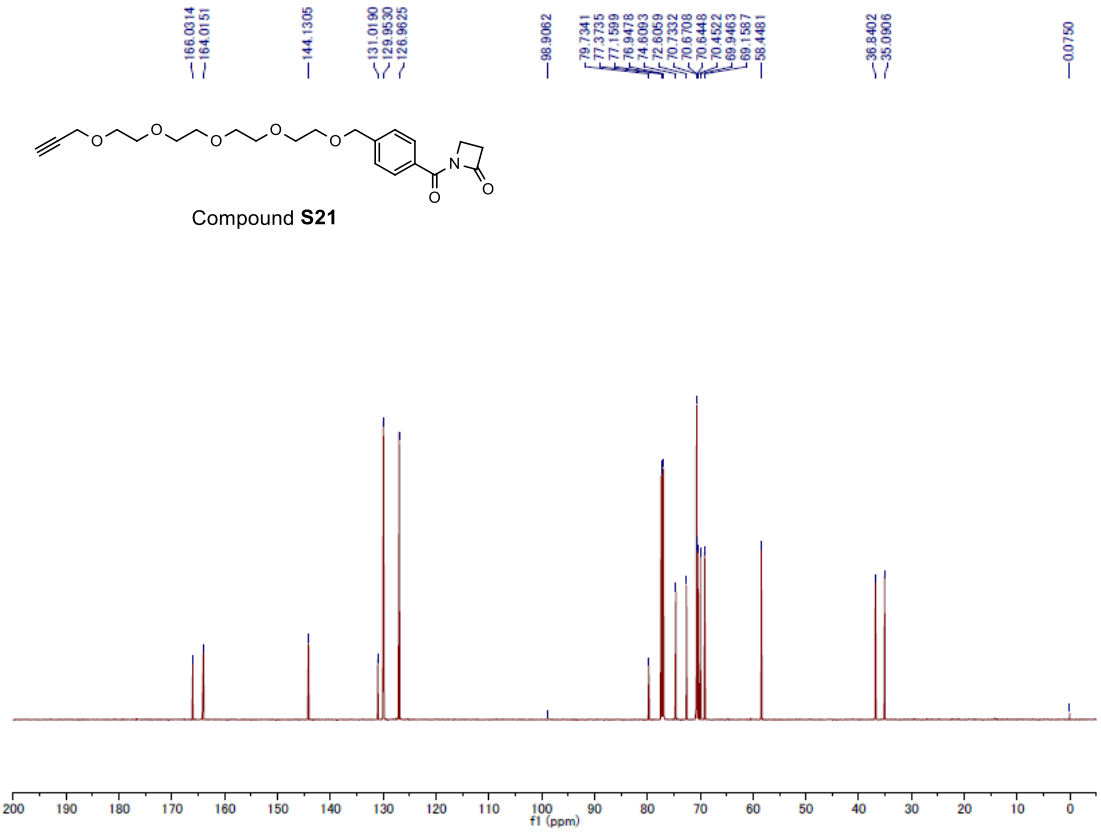
Compound **S20**



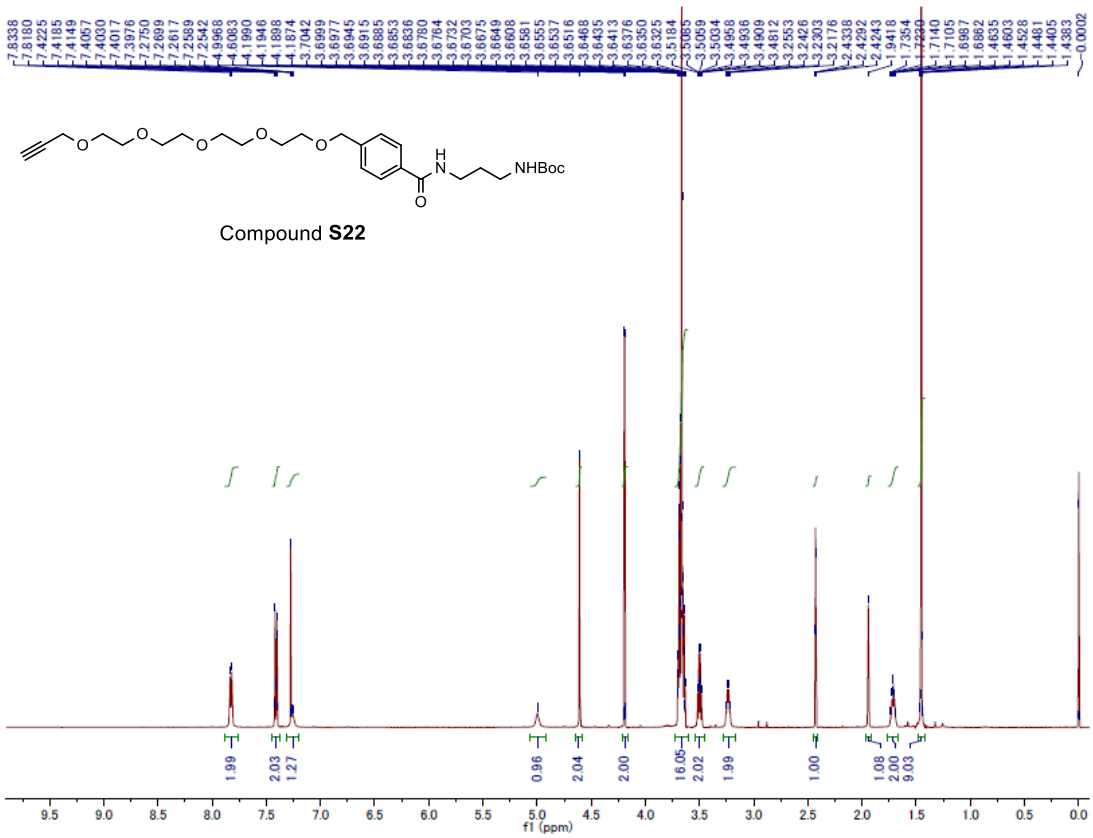
Compound **S20**



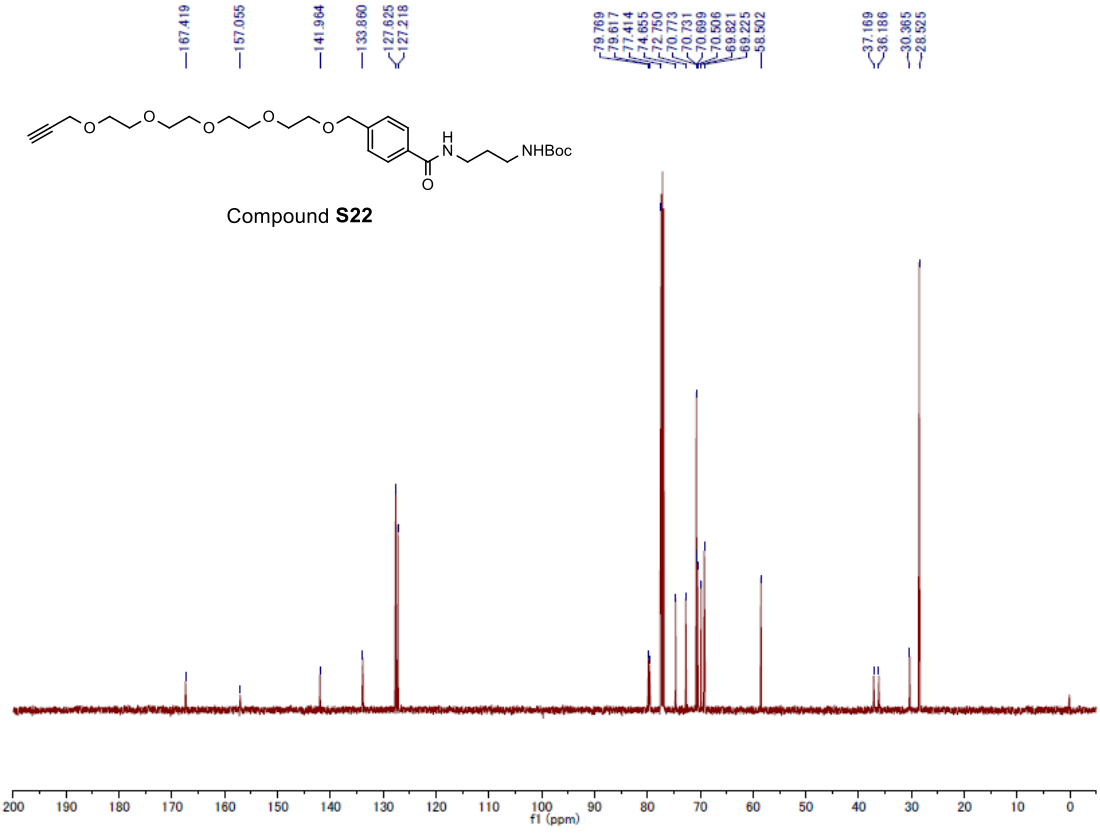
Compound **S21**



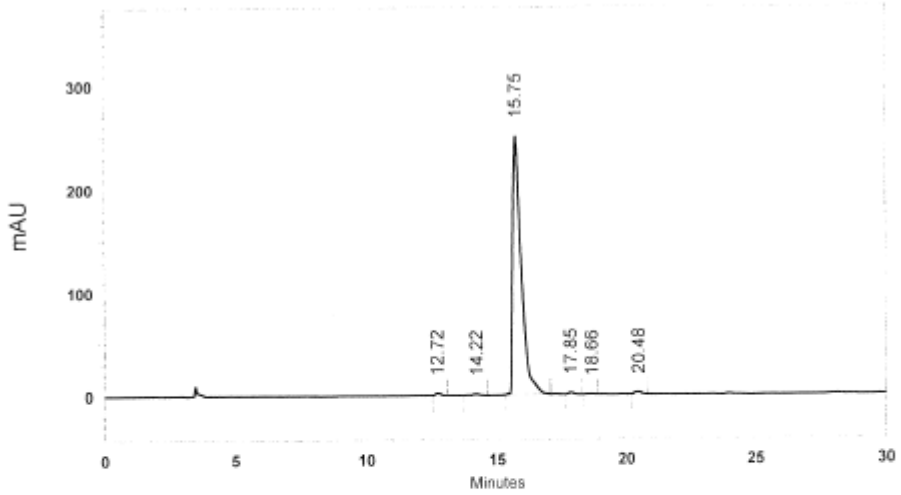
Compound **S21**

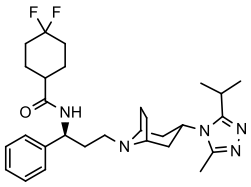


Compound **S22**



Compound **S22**





Compound **1** (Maraviroc)

DAD-CH1 254 nm Results

	Pk #	RT	Area
1	12.720	115484	0.5
2	14.220	112735	0.5
3	15.753	22744709	97.8
4	17.847	103753	0.4
5	18.660	37207	0.2
6	20.480	150453	0.6
Totals		23264341	100.0