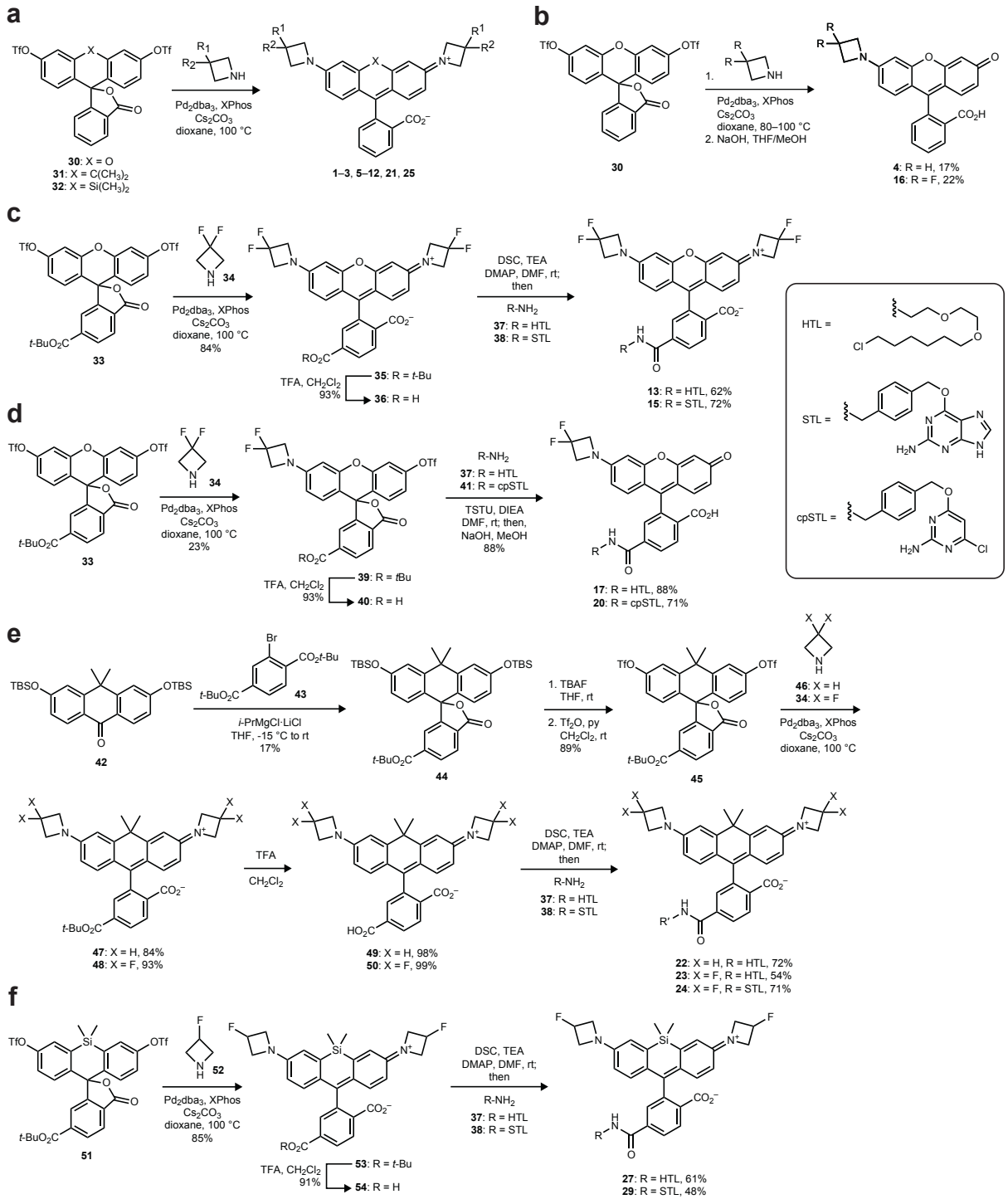
SUPPLEMENTARY NOTE: SYNTHESIS AND CHARACTERIZATION OF NEW COMPOUNDS

GENERAL EXPERIMENTAL INFORMATION FOR SYNTHESIS

General experimental information. Commercial reagents were obtained from reputable suppliers and used as received. All solvents were purchased in septum-sealed bottles stored under an inert atmosphere. All reactions were sealed with septa through which a nitrogen atmosphere was introduced unless otherwise noted. Reactions were conducted in round-bottomed flasks or septum-capped crimp-top vials containing Teflon-coated magnetic stir bars. Heating of reactions was accomplished with a silicon oil bath or an aluminum reaction block on top of a stirring hotplate equipped with an electronic contact thermometer to maintain the indicated temperatures.

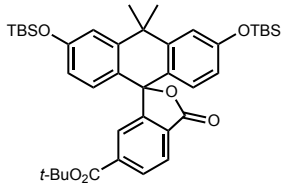
Reactions were monitored by thin layer chromatography (TLC) on precoated TLC glass plates (silica gel 60 F_{254}, 250 μm thickness) or by LC–MS (Phenomenex Kinetex 2.1 mm × 30 mm 2.6 μm C18 column; 5 μL injection; 5–98% MeCN/H_2O, linear gradient, with constant 0.1% v/v HCO_2H additive; 6 min run; 0.5 mL/min flow; ESI; positive ion mode). TLC chromatograms were visualized by UV illumination or developed with *p*-anisaldehyde, ceric ammonium molybdate, or $KMnO_4$ stain. Reaction products were purified by flash chromatography on an automated purification system using pre-packed silica gel columns or by preparative HPLC (Phenomenex Gemini–NX 30 × 150 mm 5 μm C18 column). Analytical HPLC analysis was performed with an Agilent Eclipse XDB 4.6 × 150 mm 5 μm C18 column under the indicated conditions. High-resolution mass spectrometry was obtained by the Mass Spectrometry Center in the Department of Medicinal Chemistry at the University of Washington and the High Resolution Mass Spectrometry Facility at the University of Iowa.

NMR spectra were recorded on a 400 MHz spectrometer. ^{1}H and ^{13}C chemical shifts (δ) were referenced to TMS or residual solvent peaks, and ^{19}F chemical shifts (δ) were referenced to $CFCl_3$. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR spectra are reported by chemical shift (δ ppm) with hydrogen multiplicity (C, CH, CH_2, CH_3) information obtained from DEPT spectra.

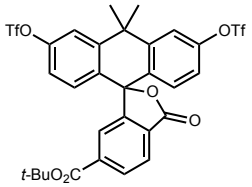


Scheme SN1. Synthesis of Janelia Fluor dyes and ligands. (**a**) Cross-coupling strategy for the synthesis of azetidinyl rhodamines. (**b**) Synthesis of azetidinyl rhodols **4** and **16**. (**c**) Synthesis of JF_{525} ligands **13** and **15** from triflate **33**. (**d**) Synthesis of JF_{503} ligands **17** and **20** from triflate **33**. (**e**) Synthesis of JF_{608} and JF_{585} ligands **22**–**24** from ketone **42**. (**f**) Synthesis of JF_{635} ligands **27** and **29** from triflate **51**.

SYNTHESIS OF DITRIFLATE 45



6-*tert*-Butoxycarbonylcarbofluorescein bis-(*tert*-butyldimethylsilyl ether) (44): A vial was charged with di-*tert*-butyl 2-bromoterephthalate (**43**; 1.48 g, 4.14 mmol, 2 eq), sealed, and flushed with nitrogen. After dissolving the bromide in THF (7 mL) and cooling the reaction to −15 °C, *i*-PrMgCl·LiCl (1.3 M in THF, 3.19 mL, 4.14 mmol, 2 eq) was added. The reaction was warmed to −10 °C and stirred for 4 h. A solution of 3,6-bis((*tert*-butyldimethylsilyl)oxy)-10,10-dimethylanthracen-9(10*H*)-one[1] (**42**; 1.00 g, 2.07 mmol) in THF (4 mL) was then added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h. It was subsequently quenched with saturated NH_4Cl, diluted with water, and extracted with EtOAc (2×). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and evaporated. Silica gel chromatography (0–10% Et_2O/hexanes, linear gradient) provided 245 mg (17%) of **44** as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.02 (dd, *J* = 8.0, 0.6 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.09 – 7.05 (m, 2H), 6.64 – 6.57 (m, 4H), 1.81 (s, 3H), 1.72 (s, 3H), 1.54 (s, 9H), 0.99 (s, 18H), 0.22 (s, 12H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.9 (C), 164.4 (C), 156.5 (C), 155.5 (C), 147.0 (C), 138.1 (C), 130.3 (CH), 129.7 (C), 129.3 (CH), 125.1 (CH), 125.0 (CH), 124.0 (C), 119.2 (CH), 117.8 (CH), 87.0 (C), 82.5 (C), 38.2 (C), 35.0 (CH_3), 33.2 (CH_3), 28.2 (CH_3), 25.8 (CH_3), 18.4 (C), -4.17 (CH_3), -4.19 (CH_3); HRMS (ESI) calcd for $C_{40}H_{55}O_6Si_2$ $[M+H]^+$ 687.3537, found 687.3533.

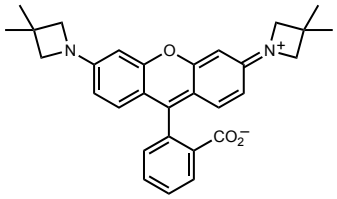


6-*tert*-Butoxycarbonylcarbofluorescein ditriflate (45): To a solution of silyl ether **44** (170 mg, 0.247 mmol) was added TBAF (1.0 M in THF, 990 µL, 0.990 mmol, 4 eq). The reaction was stirred at room temperature for 10 min. It was subsequently diluted with saturated NH_4Cl and extracted with EtOAc (2×). The organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated to provide an orange residue. The crude intermediate was taken up in CH_2Cl_2 (5 mL) and cooled to 0 °C. Pyridine (160 µL, 1.98 mmol, 8 eq) and trifluoromethanesulfonic anhydride (167 µL, 0.990 µmol, 4 eq) were added, and the ice bath was removed. The reaction was stirred at room temperature for 2 h. It was then diluted with water and extracted with CH_2Cl_2 (2×). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (0–20% EtOAc/hexanes, linear gradient) afforded 159 mg (89%) of **45** as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.11 (dd, *J* = 8.0, 0.6 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.56 (d, *J* = 2.5 Hz, 2H), 7.10 (dd, *J* = 8.8, 2.5 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 1.91 (s, 3H), 1.81 (s, 3H), 1.56 (s, 9H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ

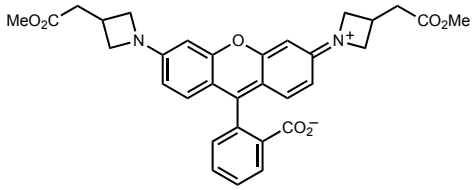
-73.20 (s); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.8 (C), 163.9 (C), 153.9 (C), 150.4 (C), 147.2 (C), 138.9 (C), 131.4 (CH), 131.1 (C), 130.3 (CH), 128.8 (C), 125.9 (CH), 124.7 (CH), 120.6 (CH), 119.8 (CH), 118.9 (q, $^1J_{CF}$ = 320.9 Hz, CF_3), 84.3 (C), 83.1 (C), 39.0 (C), 34.8 (CH_3), 33.2 (CH_3), 28.2 (CH_3); HRMS (ESI) calcd for $C_{30}H_{25}F_6O_{10}S_2$ $[M+H]^+$ 723.0793, found 723.0797.

C–N Cross-coupling Products

General procedure for preparation of rhodamines via C–N cross-coupling of fluorescein ditriflates (Method A): The following procedure for **5** is representative. A vial was charged with fluorescein ditriflate (**30**; 150 mg, 251 μmol), 3,3-dimethylazetidine hydrochloride (73 mg, 604 μmol, 2.4 eq), Pd_2dba_3 (23 mg, 25.1 μmol, 0.1 eq), XPhos (36 mg, 75.4 μmol, 0.3 eq), and Cs_2CO_3 (393 mg, 1.21 mmol, 4.8 eq). The vial was sealed and evacuated/backfilled with nitrogen (3×). Dioxane (2 mL) was added, and the reaction was flushed again with nitrogen (3×). The reaction was then stirred at 100 °C for 4 h. It was subsequently cooled to room temperature, diluted with MeOH, deposited onto Celite, and concentrated to dryness. Purification by silica gel chromatography (0–10% MeOH (2 M NH_3)/CH_2Cl_2, linear gradient; dry load with Celite) afforded **5** (101 mg, 86%) as a purple solid.

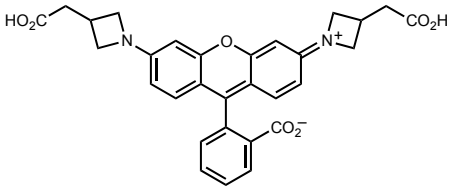


2-(3,6-Bis(3,3-dimethylazetidin-1-yl)xanthylium-9-yl)benzoate (5): (86%, purple solid) ^{1}H NMR (CD_3OD, 400 MHz) δ 8.11 – 8.06 (m, 1H), 7.67 – 7.57 (m, 2H), 7.23 – 7.20 (m, 1H), 7.19 (d, *J* = 9.2 Hz, 2H), 6.56 (dd, *J* = 9.1, 2.2 Hz, 2H), 6.49 (d, *J* = 2.2 Hz, 2H), 3.92 (s, 8H), 1.39 (s, 12H); ^{13}C NMR (CD_3OD, 101 MHz) δ 173.1 (C), 160.2 (C), 158.7 (C), 158.2 (C), 140.8 (C), 134.9 (C), 132.9 (CH), 130.82 (CH), 130.77 (CH), 130.74 (CH), 130.2 (CH), 115.0 (C), 113.1 (CH), 95.5 (CH), 64.4 (CH_2), 33.0 (C), 27.1 (CH_3); Analytical HPLC: t_R = 15.6 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{30}H_{31}N_2O_3$ $[M+H]^+$ 467.2329, found 467.2341.

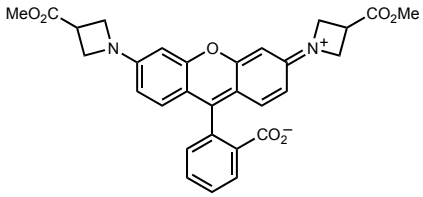


2-(3,6-Bis(3-(2-methoxy-2-oxoethyl)azetidin-1-yl)xanthylium-9-yl)benzoate (55): Method A was used to prepare the title compound from **30** and methyl 3-azetidineacetate trifluoroacetate (67%, purple solid). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.10 – 8.05 (m, 1H), 7.67 – 7.57 (m, 2H), 7.21 – 7.18 (m, 1H), 7.16 (d, *J* = 9.1 Hz, 2H), 6.54 (dd, *J* = 9.1, 2.2 Hz, 2H), 6.48 (d, *J* = 2.2 Hz, 2H), 4.41 – 4.32 (m, 4H), 3.97 – 3.88 (m, 4H), 3.69 (s, 6H), 3.26 – 3.13 (m,

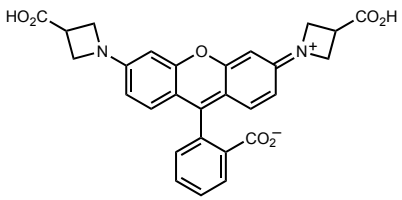
2H), 2.80 (d, J = 7.7 Hz, 4H); ^{13}C NMR (CD_3OD, 101 MHz) δ 173.7 (C), 173.0 (C), 158.3 (C), 157.5 (C), 154.9 (C), 140.1 (C), 136.3 (C), 132.7 (CH), 131.1 (CH), 130.8 (CH), 130.4 (CH), 129.8 (CH), 114.5 (C), 112.7 (CH), 95.7 (CH), 57.5 (CH_2), 52.2 (CH_3), 38.5 (CH_2), 27.3 (CH); HRMS (ESI) calcd for $C_{32}H_{31}N_2O_7$ $[M+H]^+$ 555.2126, found 555.2132.



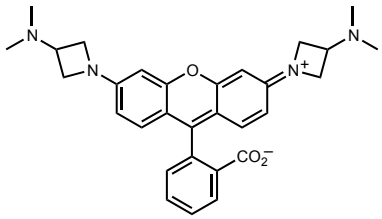
2-(3,6-Bis(3-(carboxymethyl)azetidin-1-yl)xanthylium-9-yl)benzoate (6): Ester **55** (25 mg, 45.1 μmol) was dissolved in MeOH (2 mL), and 1 M NaOH (180 μL, 180 μmol, 4 eq) was added. After stirring the reaction at room temperature for 18 h, it was acidified with 1 M HCl (200 μL) and directly purified by reverse phase HPLC (10–50% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive) to provide 23 mg (80%, TFA salt) of **6** as a red-purple solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.35 – 8.30 (m, 1H), 7.83 (td, J = 7.5, 1.5 Hz, 1H), 7.78 (td, J = 7.6, 1.5 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.07 (d, J = 9.2 Hz, 2H), 6.62 (dd, J = 9.2, 2.2 Hz, 2H), 6.56 (d, J = 2.2 Hz, 2H), 4.43 (t, J = 9.6 Hz, 4H), 4.05 – 3.96 (m, 4H), 3.28 – 3.16 (m, 2H), 2.78 (d, J = 7.7 Hz, 4H); ^{13}C NMR (CD_3OD, 101 MHz) δ 175.1 (C), 167.9 (C), 161.7 (C), 158.8 (C), 158.0 (C), 135.4 (C), 133.8 (CH), 132.5 (CH), 132.3 (CH), 131.41 (CH), 131.40 (CH), 115.1 (C), 113.7 (CH), 95.3 (CH), 57.6 (CH_2), 38.5 (CH_2), 27.3 (CH); Analytical HPLC: t_R = 10.5 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{30}H_{27}N_2O_7$ $[M+H]^+$ 527.1813, found 527.1815.



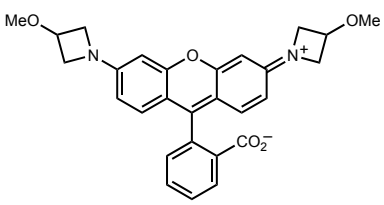
2-(3,6-Bis(3-(methoxycarbonyl)azetidin-1-yl)xanthylium-9-yl)benzoate (56): Method A was used to prepare the title compound from **30** and methyl azetidine-3-carboxylate hydrochloride (79%, purple solid). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.09 – 8.03 (m, 1H), 7.69 – 7.62 (m, 2H), 7.24 – 7.17 (m, 1H), 7.02 (d, J = 8.9 Hz, 2H), 6.48 (dd, J = 8.9, 2.2 Hz, 2H), 6.45 (d, J = 2.1 Hz, 2H), 4.34 (t, J = 9.0 Hz, 4H), 4.25 (dd, J = 9.0, 5.9 Hz, 4H), 3.77 (s, 6H), 3.71 (tt, J = 8.9, 5.9 Hz, 2H); ^{13}C NMR (CD_3OD, 101 MHz) δ 174.4 (C), 172.6 (C), 157.0 (C), 156.5 (C), 141.6 (C), 136.7 (C), 135.8 (C), 132.7 (CH), 131.9 (CH), 130.9 (CH), 129.0 (CH), 128.5 (CH), 113.3 (C), 111.7 (CH), 96.8 (CH), 55.2 (CH_2), 52.9 (CH_3), 34.0 (CH); HRMS (ESI) calcd for $C_{30}H_{27}N_2O_7$ $[M+H]^+$ 527.1813, found 527.1823.



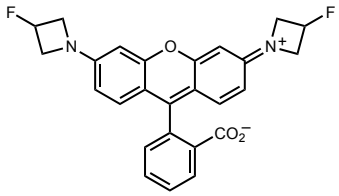
2-(3,6-Bis(3-carboxyazetidin-1-yl)xanthylium-9-yl)benzoate (7): Ester **56** (40 mg, 76.0 μmol) was dissolved in MeOH (2.5 mL), and 1 M NaOH (304 μL, 304 μmol, 4 eq) was added. After stirring the reaction at room temperature for 18 h, it was acidified with 1 M HCl (350 μL) and directly purified by reverse phase HPLC (10–50% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive) to provide 28 mg (60%, TFA salt) of **7** as a red-purple solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.36 – 8.30 (m, 1H), 7.84 (td, *J* = 7.5, 1.6 Hz, 1H), 7.79 (td, *J* = 7.6, 1.5 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.12 (d, *J* = 9.2 Hz, 2H), 6.66 (dd, *J* = 9.2, 2.2 Hz, 2H), 6.61 (d, *J* = 2.2 Hz, 2H), 4.48 (t, *J* = 9.6 Hz, 4H), 4.39 (dd, *J* = 9.9, 5.9 Hz, 4H), 3.72 (tt, *J* = 9.0, 5.8 Hz, 2H); ^{13}C NMR (CD_3OD, 101 MHz) δ 175.2 (C), 168.0 (C), 162.4 (C), 158.9 (C), 157.9 (C), 135.3 (C), 133.9 (CH), 132.6 (CH), 132.5 (CH), 131.5 (CH), 131.4 (CH), 115.4 (C), 113.8 (CH), 95.6 (CH), 55.3 (CH_2), 33.9 (CH); Analytical HPLC: t_R = 11.2 min, >99% purity (10–75% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{28}H_{23}N_2O_7$ $[M+H]^+$ 499.1500, found 499.1507.



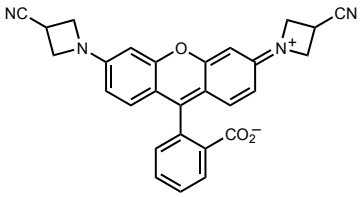
2-(3,6-Bis(3-(dimethylamino)azetidin-1-yl)xanthylium-9-yl)benzoate (8): Method A was used to prepare the title compound from **30** and 3-(dimethylamino)azetidine dihydrochloride (80%, purple solid). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.10 – 8.05 (m, 1H), 7.69 – 7.60 (m, 2H), 7.24 – 7.19 (m, 1H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.56 (dd, *J* = 9.0, 2.2 Hz, 2H), 6.53 (d, *J* = 2.2 Hz, 2H), 4.31 – 4.22 (m, 4H), 4.01 (dd, *J* = 10.5, 5.1 Hz, 4H), 3.39 (tt, *J* = 7.0, 5.1 Hz, 2H), 2.27 (s, 12H); ^{13}C NMR (CD_3OD, 101 MHz) δ 172.8 (C), 157.9 (C), 157.1 (C), 147.7 (C), 138.7 (C), 138.4 (C), 132.5 (CH), 131.8 (CH), 130.8 (CH), 129.9 (CH), 129.3 (CH), 114.1 (C), 112.4 (CH), 96.3 (CH), 57.0 (CH), 56.6 (CH_2), 42.0 (CH_3); Analytical HPLC: t_R = 7.1 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{30}H_{33}N_4O_3$ $[M+H]^+$ 497.2547, found 497.2561.



2-(3,6-Bis(3-methoxyazetidin-1-yl)xanthylium-9-yl)benzoate (9): Method A was used to prepare the title compound from **30** and 3-methoxyazetidine hydrochloride (83%, purple solid). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.00 – 7.94 (m, 1H), 7.77 (td, J = 7.5, 1.2 Hz, 1H), 7.70 (td, J = 7.5, 0.9 Hz, 1H), 7.25 – 7.20 (m, 1H), 6.48 (d, J = 8.6 Hz, 2H), 6.26 (d, J = 2.3 Hz, 2H), 6.19 (dd, J = 8.6, 2.3 Hz, 2H), 4.32 (tt, J = 6.2, 4.2 Hz, 2H), 4.07 (dd, J = 8.0, 6.6 Hz, 4H), 3.66 (dd, J = 8.4, 4.1 Hz, 4H), 3.24 (s, 6H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 168.7 (C), 152.8 (C), 152.5 (C), 151.9 (C), 135.4 (CH), 129.9 (CH), 128.5 (CH), 126.5 (C), 124.5 (CH), 123.9 (CH), 108.2 (CH), 107.2 (C), 97.5 (CH), 84.1 (C), 69.2 (CH), 58.3 (CH_2), 55.4 (CH_3); Analytical HPLC: t_R = 12.2 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{28}H_{27}N_2O_5$ $[M+H]^+$ 471.1914, found 471.1926.

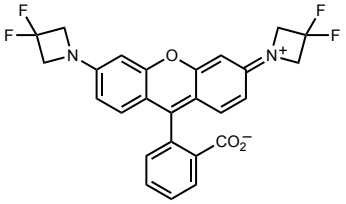


2-(3,6-Bis(3-fluoroazetidin-1-yl)xanthylium-9-yl)benzoate (10): Method A was used to prepare the title compound from **30** and 3-fluoroazetidine hydrochloride (89%, pink solid). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.01 – 7.95 (m, 1H), 7.78 (td, J = 7.5, 1.2 Hz, 1H), 7.71 (td, J = 7.5, 0.9 Hz, 1H), 7.25 – 7.20 (m, 1H), 6.52 (d, J = 8.6 Hz, 2H), 6.33 (d, J = 2.3 Hz, 2H), 6.24 (dd, J = 8.6, 2.3 Hz, 2H), 5.49 (dtt, $^{2}J_{HF}$ = 57.6 Hz, J = 6.0, 3.1 Hz, 2H), 4.26 – 4.13 (m, 4H), 4.00 – 3.88 (m, 4H); ^{19}F NMR (DMSO-d_6, 376 MHz) δ -178.95 (dtt, J_{FH} = 57.4, 24.2, 20.9 Hz); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 168.7 (C), 152.54 (d, $^{4}J_{CF}$ = 1.3 Hz, C), 152.47 (C), 151.8 (C), 135.4 (CH), 129.9 (CH), 128.6 (CH), 126.4 (C), 124.5 (CH), 123.9 (CH), 108.6 (CH), 107.8 (C), 98.0 (CH), 83.8 (C), 83.3 (d, $^{1}J_{CF}$ = 200.3 Hz, CFH), 59.2 (d, $^{2}J_{CF}$ = 23.7 Hz, CH_2); Analytical HPLC: t_R = 12.1 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{26}H_{21}F_2N_2O_3$ $[M+H]^+$ 447.1515, found 447.1525.

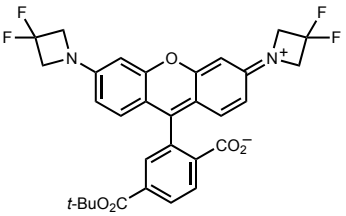


2-(3,6-Bis(3-cyanoazetidin-1-yl)xanthylium-9-yl)benzoate (11): Method A was used to prepare the title compound from **30** and 3-azetidinecarbonitrile hydrochloride (85%, magenta solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 – 7.98 (m, 1H), 7.66 (td, J = 7.4, 1.3 Hz, 1H), 7.60 (td, J = 7.4, 1.1 Hz, 1H), 7.17 – 7.13 (m, 1H), 6.62 (d, J = 8.6 Hz, 2H), 6.25 (d, J = 2.3 Hz, 2H), 6.12 (dd, J = 8.6, 2.4 Hz, 2H), 4.25 – 4.18 (m, 4H), 4.15 – 4.08 (m, 4H), 3.60 (tt, J = 8.5, 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.6 (C), 153.2 (C), 152.5 (C), 151.9 (C), 135.0 (CH), 129.7 (CH), 129.3 (CH), 127.1 (C), 125.1 (CH), 124.0 (CH), 119.7 (C), 109.7 (C), 108.1 (CH), 98.7 (CH), 83.9 (C), 55.2 (CH_2), 18.4 (CH); Analytical HPLC: t_R = 11.0 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with

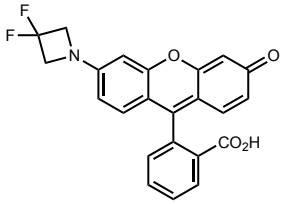
constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{28}H_{21}N_4O_3$ $[M+H]^+$ 461.1608, found 461.1628.



JF_{525} (12): Method A was used to prepare the title compound from **30** and 3,3-difluoroazetidine hydrochloride (91%, pink solid). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 – 7.99 (m, 1H), 7.66 (td, J = 7.4, 1.3 Hz, 1H), 7.60 (td, J = 7.4, 1.1 Hz, 1H), 7.17 – 7.14 (m, 1H), 6.64 (d, J = 8.6 Hz, 2H), 6.30 (d, J = 2.4 Hz, 2H), 6.17 (dd, J = 8.6, 2.4 Hz, 2H), 4.25 (t, $^3J_{HF}$ = 11.7 Hz, 8H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -100.05 (p, $^3J_{FH}$ = 11.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.6 (C), 153.3 (C), 152.6 (C), 151.3 (t, $^4J_{CF}$ = 2.9 Hz, C), 135.0 (CH), 129.7 (CH), 129.3 (CH), 127.2 (C), 125.1 (CH), 124.0 (CH), 115.8 (t, $^1J_{CF}$ = 274.6 Hz, CF_2), 109.7 (C), 108.8 (CH), 99.4 (CH), 83.9 (C), 63.4 (t, $^2J_{CF}$ = 26.3 Hz, CH_2); Analytical HPLC: t_R = 12.7 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 525 nm); HRMS (ESI) calcd for $C_{26}H_{19}F_4N_2O_3$ $[M+H]^+$ 483.1326, found 483.1336.

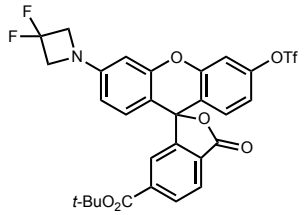


6-*tert*-Butoxycarbonyl-JF_{525} (35): Method A was used to prepare the title compound from 6-*tert*-butoxycarbonylfluorescein ditriflate[2] (**33**) and 3,3-difluoroazetidine hydrochloride (84%, pink solid). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21 (dd, J = 8.0, 1.3 Hz, 1H), 8.04 (dd, J = 8.0, 0.8 Hz, 1H), 7.73 (dd, J = 1.2, 0.8 Hz, 1H), 6.61 (d, J = 8.6 Hz, 2H), 6.30 (d, J = 2.4 Hz, 2H), 6.17 (dd, J = 8.6, 2.4 Hz, 2H), 4.25 (t, $^3J_{HF}$ = 11.7 Hz, 8H), 1.55 (s, 9H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -100.06 (p, $^3J_{FH}$ = 11.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.8 (C), 164.3 (C), 153.3 (C), 152.6 (C), 151.4 (t, $^4J_{CF}$ = 2.9 Hz, C), 138.4 (C), 130.9 (CH), 130.2 (C), 129.3 (CH), 125.1 (CH), 125.0 (CH), 115.7 (t, $^1J_{CF}$ = 274.5 Hz, CF_2), 109.1 (C), 108.9 (CH), 99.4 (CH), 84.3 (C), 82.7 (C), 63.4 (t, $^2J_{CF}$ = 26.3 Hz, CH_2), 28.2 (CH_3); HRMS (ESI) calcd for $C_{31}H_{27}F_4N_2O_5$ $[M+H]^+$ 583.1851, found 583.1859.



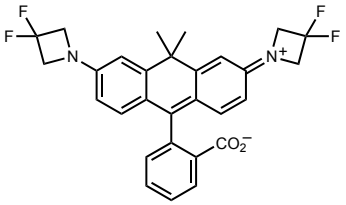
JF_{503} (16): A vial was charged with fluorescein ditriflate (**30**; 100 mg, 168 μmol), 3,3-difluoroazetidine hydrochloride (22 mg, 168 μmol, 1 eq), Pd_2dba_3 (7.7 mg, 8.4 μmol, 0.05 eq), XPhos (12 mg, 25.1 μmol, 0.15 eq), and Cs_2CO_3 (131 mg, 402 μmol, 2.4 eq). The vial was sealed and evacuated/backfilled with nitrogen (3×). Dioxane (1 mL) was added, and the reaction was flushed again with nitrogen (3×). The reaction was then stirred at 100 °C for 1 h. It was subsequently cooled to room temperature, filtered through Celite with CH_2Cl_2, and concentrated to dryness. Purification by silica gel chromatography (0–40% EtOAc/hexanes, linear gradient) afforded JF_{503} triflate (23 mg, 25%) as a white foam.

The triflate (20 mg, 37.1 μmol) was taken up in 1:1 THF/MeOH (1 mL). After adding 1 M NaOH (74 μL, 74.2 μmol, 2 eq), the reaction was stirred at room temperature for 3 h. It was then neutralized with 1 M HCl (74 μL) and concentrated to dryness. Reverse phase HPLC (10–75% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive) afforded 17 mg (88%, TFA salt) of **16** as an orange solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.16 (d, J = 7.5 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.79 – 7.72 (m, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.99 – 6.83 (m, 3H), 6.75 (d, J = 8.6 Hz, 1H), 6.67 – 6.60 (m, 1H), 6.56 (d, J = 8.7 Hz, 1H), 4.49 (t, $^3J_{HF}$ = 11.7 Hz, 4H); ^{19}F NMR (CD_3OD, 376 MHz) δ -75.42 (s, 3F), -100.27 – -100.68 (m, 2F); ^{13}C NMR (DMSO-d_6, 101 MHz, 350 K) δ 168.9 (C), 160.3 (C), 152.7 (C), 152.6 (C), 152.2 (C), 152.1 (t, $^4J_{CF}$ = 2.8 Hz, C), 135.7 (CH), 130.4 (CH), 129.3 (CH), 129.1 (CH), 127.0 (C), 125.2 (CH), 124.6 (CH), 116.9 (t, $^1J_{CF}$ = 273.2 Hz, CF_2), 113.3 (CH), 110.7 (C), 110.1 (CH), 109.8 (C), 102.8 (CH), 99.7 (CH), 63.4 (t, $^2J_{CF}$ = 25.9 Hz, CH_2); Analytical HPLC: t_R = 10.5 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 500 nm); HRMS (ESI) calcd for $C_{23}H_{16}F_2NO_4$ $[M+H]^+$ 408.1042, found 408.1040.

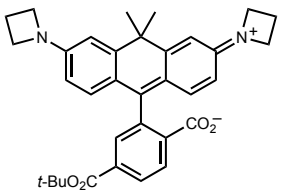


6-*tert*-Butoxycarbonyl-JF_{503} triflate (39): A vial was charged with 6-*tert*-butoxycarbonylfluorescein ditriflate (**33**; 300 mg, 431 μmol), 3,3-difluoroazetidine hydrochloride (56 mg, 431 μmol, 1 eq), Pd_2dba_3 (20 mg, 21.5 μmol, 0.05 eq), XPhos (31 mg, 64.6 μmol, 0.15 eq), and Cs_2CO_3 (337 mg, 1.03 mmol, 2.4 eq). The vial was sealed and evacuated/backfilled with nitrogen (3×). Dioxane (1 mL) was added, and the reaction was flushed again with nitrogen (3×). The reaction was then stirred at 100 °C for 1 h. It was subsequently cooled to room temperature, filtered through Celite with CH_2Cl_2, and concentrated to dryness. Purification by silica gel chromatography (0–40% EtOAc/hexanes, linear gradient) afforded **39** (63 mg, 23%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dd, J = 8.0, 1.1 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.74 (bs, 1H), 7.24 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 8.8, 2.4 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.6 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.22 (dd, J = 8.6, 2.3 Hz, 1H), 4.28 (t, $^3J_{HF}$ = 11.7 Hz, 4H), 1.54 (s, 9H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -73.16 (s, 3F), -100.02 (p, $^3J_{FH}$ = 11.7 Hz, 2F); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.3 (C), 164.1 (C), 152.7 (C), 152.2 (C), 152.0 (C), 151.62 (t, $^4J_{CF}$ = 2.9 Hz, C), 150.2 (C), 138.8 (C), 131.4 (CH), 130.2 (CH), 129.6 (C), 129.2 (CH), 125.3 (CH), 125.0 (CH), 119.5 (C), 118.8 (q,

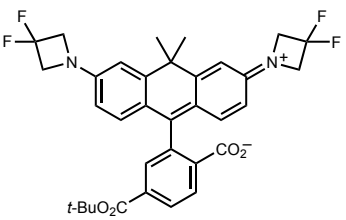
$^{1}J_{CF}$ = 320.8 Hz, CF_3), 116.9 (CH), 115.6 (t, $^{1}J_{CF}$ = 274.6 Hz, CF_2), 110.7 (CH), 109.7 (CH), 108.0 (C), 99.4 (CH), 83.0 (C), 82.4 (C), 63.4 (t, $^{2}J_{CF}$ = 26.6 Hz, CH_2), 28.2 (CH_3); HRMS (ESI) calcd for $C_{29}H_{23}F_5NO_8S$ $[M+H]^+$ 640.1059, found 640.1068.



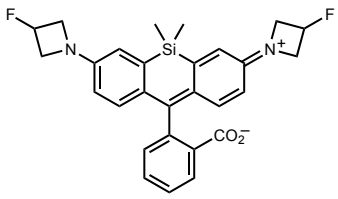
JF_{585} (21): Method A was used to prepare the title compound from carbofluorescein ditriflate[1] (**31**) and 3,3-difluoroazetidine hydrochloride (95%, off-white solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 – 7.98 (m, 1H), 7.60 (td, *J* = 7.3, 1.5 Hz, 1H), 7.56 (td, *J* = 7.3, 1.3 Hz, 1H), 7.04 (s, 1H), 6.64 (d, *J* = 2.8 Hz, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 6.28 (dd, *J* = 8.6, 2.5 Hz, 2H), 4.25 (t, $^{3}J_{HF}$ = 11.8 Hz, 8H), 1.84 (s, 3H), 1.74 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -99.95 (p, $^{3}J_{FH}$ = 11.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6 (C), 155.2 (C), 150.1 (t, $^{4}J_{CF}$ = 2.7 Hz, C), 146.9 (C), 134.8 (CH), 129.3 (CH), 129.2 (CH), 127.0 (C), 125.2 (CH), 123.9 (CH), 122.4 (C), 115.9 (t, $^{1}J_{CF}$ = 274.6 Hz, CF_2), 111.6 (CH), 109.2 (CH), 87.2 (C), 63.4 (t, $^{2}J_{CF}$ = 25.9 Hz, CH_2), 38.6 (C), 35.6 (CH_3), 32.5 (CH_3); Analytical HPLC: t_R = 14.9 min, >99% purity (30–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 600 nm); HRMS (ESI) calcd for $C_{29}H_{25}F_4N_2O_2$ $[M+H]^+$ 509.1847, found 509.1843.



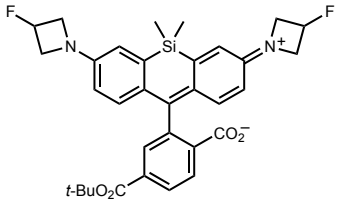
6-*tert*-Butoxycarbonyl-JF_{608} (47): Method A was used to prepare the title compound from ditriflate **45** and azetidine (84%, blue solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.00 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.61 (dd, *J* = 1.3, 0.8 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.54 (d, *J* = 8.6 Hz, 2H), 6.21 (dd, *J* = 8.6, 2.4 Hz, 2H), 3.91 (t, *J* = 7.2 Hz, 8H), 2.38 (p, *J* = 7.2 Hz, 4H), 1.83 (s, 3H), 1.73 (s, 3H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.1 (C), 164.6 (C), 155.6 (C), 152.4 (C), 146.8 (C), 137.8 (C), 130.3 (C), 130.1 (CH), 128.9 (CH), 125.1 (CH), 124.8 (CH), 119.9 (C), 110.5 (CH), 108.0 (CH), 88.8 (C), 82.3 (C), 52.3 (CH_2), 38.5 (C), 35.5 (CH_3), 32.8 (CH_3), 28.2 (CH_3), 17.0 (CH_2); HRMS (ESI) calcd for $C_{34}H_{37}N_2O_4$ $[M+H]^+$ 537.2753, found 537.2768.



6-*tert*-Butoxycarbonyl-JF$_{585}$ (48): Method A was used to prepare the title compound from ditriflate **45** and 3,3-difluoroazetidine hydrochloride (93%, off-white solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (dd, J = 8.0, 1.3 Hz, 1H), 8.02 (dd, J = 8.0, 0.7 Hz, 1H), 7.60 (dd, J = 1.2, 0.8 Hz, 1H), 6.65 (d, J = 2.4 Hz, 2H), 6.62 (d, J = 8.6 Hz, 2H), 6.29 (dd, J = 8.6, 2.5 Hz, 2H), 4.26 (t, $^3J_{HF}$ = 11.7 Hz, 8H), 1.85 (s, 3H), 1.75 (s, 3H), 1.53 (s, 9H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -99.96 (p, $^3J_{FH}$ = 11.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.9 (C), 164.4 (C), 155.3 (C), 150.1 (t, $^4J_{CF}$ = 2.7 Hz, C), 146.8 (C), 138.1 (C), 130.3 (CH), 129.9 (C), 129.2 (CH), 125.1 (CH), 124.9 (CH), 121.7 (C), 115.9 (t, $^1J_{CF}$ = 274.6 Hz, CF_2), 111.8 (CH), 109.3 (CH), 87.5 (C), 82.5 (C), 63.4 (t, $^2J_{CF}$ = 26.0 Hz, CH_2), 38.5 (C), 35.4 (CH_3), 33.0 (CH_3), 28.2 (CH_3); HRMS (ESI) calcd for $C_{34}H_{33}F_4N_2O_4$ $[M+H]^+$ 609.2371, found 609.2384.



JF$_{635}$ (25): Method A was used to prepare the title compound from silafluorescein ditriflate[2] (**32**) and 3-fluoroazetidine hydrochloride (78%, off-white solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (dt, J = 7.6, 0.9 Hz, 1H), 7.65 (td, J = 7.5, 1.2 Hz, 1H), 7.55 (td, J = 7.5, 0.9 Hz, 1H), 7.29 (dt, J = 7.7, 0.8 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 2.6 Hz, 2H), 6.30 (dd, J = 8.7, 2.7 Hz, 2H), 5.41 (dtt, $^2J_{HF}$ = 57.0 Hz, J = 5.9, 3.7 Hz, 2H), 4.25 – 4.14 (m, 4H), 4.04 – 3.91 (m, 4H), 0.62 (s, 3H), 0.60 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -180.48 (dtt, J_{FH} = 57.0, 23.9, 18.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6 (C), 154.1 (C), 150.0 (d, $^4J_{CF}$ = 1.0 Hz, C), 137.2 (C), 133.93 (C), 133.86 (CH), 129.0 (CH), 128.1 (CH), 127.0 (C), 126.0 (CH), 124.7 (CH), 116.3 (CH), 112.9 (CH), 91.6 (C), 82.8 (d, $^1J_{CF}$ = 204.8 Hz, CFH), 59.6 (d, $^2J_{CF}$ = 23.8 Hz, CH_2), 0.5 (CH_3), -1.4 (CH_3); Analytical HPLC: t_R = 14.7 min, 98.7% purity (30–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 650 nm); HRMS (ESI) calcd for $C_{28}H_{27}F_2N_2O_2Si$ $[M+H]^+$ 489.1804, found 489.1810.

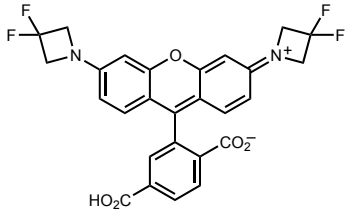


6-*tert*-Butoxycarbonyl-JF$_{635}$ (53): Method A was used to prepare the title compound from 6-*tert*-butoxycarbonylsilafluorescein ditriflate[2] (**51**) and 3-fluoroazetidine hydrochloride (85%, off-white solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (dd, J = 8.0, 1.3 Hz, 1H), 7.97 (dd, J = 7.9, 0.8 Hz, 1H), 7.82 (dd, J = 1.3, 0.8 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 2.6 Hz, 2H), 6.35 (dd, J = 8.7, 2.7 Hz, 2H), 5.41 (dtt, J = 57.0, 5.9, 3.7 Hz, 2H), 4.26 – 4.15 (m, 4H), 4.05 – 3.93 (m, 4H), 1.55 (s, 9H), 0.67 (s, 3H), 0.60 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -180.48 (dtt, J_{FH} = 57.0, 23.9, 18.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.2 (C), 164.4 (C), 155.1 (C), 150.0 (d, $^4J_{CF}$ = 1.2 Hz, C), 137.4 (C), 136.3 (C), 133.5 (C), 130.1 (CH), 129.0 (C), 127.8 (CH), 125.8 (CH), 125.1 (CH),

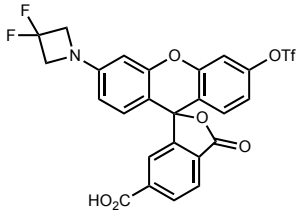
116.3 (CH), 113.3 (CH), 91.4 (C), 82.8 (d, $^{1}J_{CF}$ = 204.8, CFH), 82.5 (C), 59.6 (d, $^{2}J_{CF}$ = 23.8 Hz, CH_2), 28.2 (CH_3), 0.2 (CH_3), -0.7 (CH_3); HRMS (ESI) calcd for $C_{33}H_{35}F_2N_2O_4Si$ $[M+H]^+$ 589.2329, found 589.2335.

HALOTAG AND SNAP-TAG LIGANDS

General procedure for deprotection of *tert*-butyl esters (Method B): The following procedure for **36** is representative. Ester **35** (70 mg, 120 μmol) was taken up in CH_2Cl_2 (2.5 mL), and trifluoroacetic acid (0.5 mL) was added. The reaction was stirred at room temperature for 6 h. Toluene (3 mL) was added; the reaction mixture was concentrated to dryness and then azeotroped with MeOH three times to provide **36** as a dark pink solid (72 mg, 93%, TFA salt). Analytical HPLC and NMR indicated that the material was >95% pure and did not require further purification prior to amide coupling.

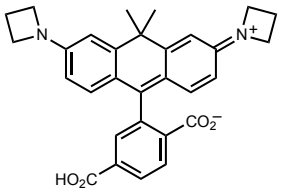


6-Carboxy-JF$_{525}$ (36): (93%, dark pink solid, TFA salt) ^{1}H NMR (CD_3OD, 400 MHz) δ 8.45 (d, *J* = 8.1 Hz, 1H), 8.41 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.01 – 7.97 (m, 1H), 7.24 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 2.2 Hz, 2H), 6.80 (dd, *J* = 9.1, 2.2 Hz, 2H), 4.72 (t, $^{3}J_{HF}$ = 11.6 Hz, 8H); ^{19}F NMR (CD_3OD, 376 MHz) δ -75.59 (s, 3F), -100.90 (p, $^{3}J_{FH}$ = 11.6 Hz, 4F); ^{13}C NMR (CD_3OD, 101 MHz) δ 167.6 (C), 167.3 (C), 159.1 (C), 157.7 (t, $^{4}J_{CF}$ = 3.9 Hz, C), 136.1 (C), 135.8 (C), 135.4 (C), 132.9 (CH), 132.7 (CH), 132.6 (CH), 132.1 (CH), 119.2 (C), 116.5 (t, $^{1}J_{CF}$ = 271.9 Hz, CF_2), 116.1 (C), 115.2 (CH), 97.4 (CH), 64.2 (t, $^{2}J_{CF}$ = 29.1 Hz, CH_2); Analytical HPLC: t_R = 11.2 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 525 nm); HRMS (ESI) calcd for $C_{27}H_{19}F_4N_2O_5$ $[M+H]^+$ 527.1225, found 527.1232.

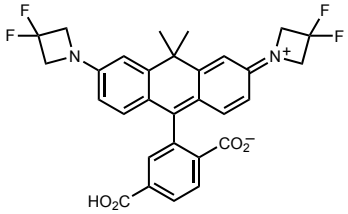


6-Carboxy-JF$_{503}$ triflate (40): Method B was used to convert ester **39** into the title compound (88%, red-orange solid, TFA salt). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.62 (s, 1H), 8.26 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.16 (dd, *J* = 8.0, 0.4 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 6.55 (d, *J* = 2.3 Hz, 1H), 6.39 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.36 (t, $^{3}J_{HF}$ = 12.3 Hz, 4H); ^{19}F NMR (DMSO-d_6, 376 MHz) δ -72.20 (s, 3F), -98.42 (p, $^{3}J_{FH}$ = 12.3 Hz, 2F); ^{13}C NMR (DMSO-d_6, 101 MHz) δ

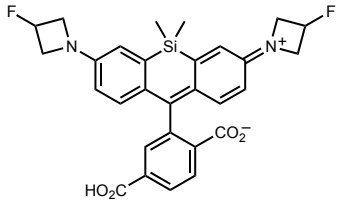
167.6 (C), 166.0 (C), 152.2 (C), 151.8 (t, $^4J_{CF}$ = 2.7 Hz, C), 151.4 (C), 151.1 (C), 149.7 (C), 138.0 (C), 131.3 (CH), 130.7 (CH), 128.9 (CH), 125.5 (CH), 124.5 (CH), 119.4 (C), 118.2 (q, $^1J_{CF}$ = 321.0 Hz, CF_3), 117.1 (CH), 116.4 (t, $^1J_{CF}$ = 273.1 Hz, CF_2), 110.6 (CH), 110.3 (CH), 107.3 (C), 99.3 (CH), 81.7 (C), 62.8 (t, $^2J_{CF}$ = 25.7 Hz, CH_2); HRMS (ESI) calcd for $C_{25}H_{15}F_5NO_8S$ $[M+H]^+$ 584.0433, found 584.0446.



6-Carboxy-JF$_{608}$ (49): Method B was used to convert ester **47** into the title compound (98%, dark blue solid, TFA salt). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.34 (dd, *J* = 8.2, 0.5 Hz, 1H), 8.31 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.84 (dd, *J* = 1.5, 0.5 Hz, 1H), 6.93 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 2.2 Hz, 2H), 6.39 (dd, *J* = 9.1, 2.3 Hz, 2H), 4.33 (t, *J* = 7.6 Hz, 8H), 2.55 (p, *J* = 7.6 Hz, 4H), 1.82 (s, 3H), 1.70 (s, 3H); ^{19}F NMR (CD_3OD, 376 MHz) δ -75.24 (s); ^{13}C NMR (CD_3OD, 101 MHz) δ 167.9 (C), 167.5 (C), 165.4 (C), 158.0 (C), 156.8 (C), 139.3 (C), 137.6 (CH), 136.2 (C), 135.5 (C), 132.5 (CH), 132.4 (CH), 131.5 (CH), 121.8 (C), 111.9 (CH), 109.7 (CH), 52.9 (CH_2), 42.8 (C), 35.6 (CH_3), 32.0 (CH_3), 16.8 (CH_2); Analytical HPLC: t_R = 9.2 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 600 nm); HRMS (ESI) calcd for $C_{30}H_{29}N_2O_4$ $[M+H]^+$ 481.2127, found 481.2120.

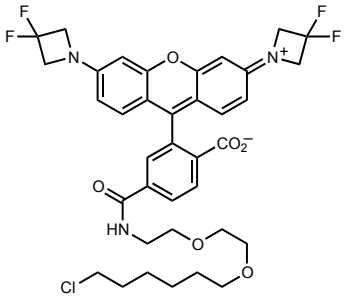


6-Carboxy-JF$_{585}$ (50): Method B was used to convert ester **48** into the title compound (99%, dark blue-purple solid, TFA salt). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.30 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.23 – 8.15 (m, 1H), 7.69 (s, 1H), 6.92 (d, *J* = 2.1 Hz, 2H), 6.79 (d, *J* = 7.6 Hz, 2H), 6.47 (dd, *J* = 8.8, 2.3 Hz, 2H), 4.45 (t, $^3J_{HF}$ = 11.0 Hz, 8H), 1.88 (s, 3H), 1.76 (s, 3H); ^{19}F NMR (CD_3OD, 376 MHz) δ -75.81 (s, 3F), -100.32 (m, 4F); ^{13}C NMR (101 MHz, DMSO-d_6, 350 K) δ 168.3 (C), 165.5 (C), 154.4 (C), 149.9 (t, $^4J_{CF}$ = 2.8 Hz, C), 146.3 (C), 136.8 (C), 129.9 (CH), 128.9 (C), 128.1 (CH), 124.9 (CH), 123.7 (CH), 120.3 (C), 116.2 (t, $^1J_{CF}$ = 273.3 Hz, CF_2), 111.8 (CH), 109.5 (CH), 62.5 (t, $^2J_{CF}$ = 25.6 Hz, CH_2), 37.8 (C), 34.0 (CH_3), 32.8 (CH_3); Analytical HPLC: t_R = 11.9 min, >99% purity (30–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 600 nm); HRMS (ESI) calcd for $C_{30}H_{25}F_4N_2O_4$ $[M+H]^+$ 553.1745, found 553.1741.



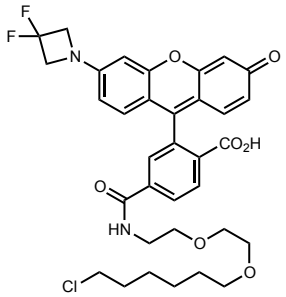
6-Carboxy-JF$_{635}$ (54): Method B was used to convert ester **53** into the title compound (91%, dark blue solid, TFA salt). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.25 (dd, J = 8.0, 1.4 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.84 (dd, J = 1.4, 0.7 Hz, 1H), 6.87 (d, J = 2.6 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.39 (dd, J = 8.9, 2.6 Hz, 2H), 5.43 (dtt, J = 57.3, 6.1, 3.3 Hz, 2H), 4.41 – 4.20 (m, 4H), 4.16 – 4.01 (m, 4H), 0.65 (s, 3H), 0.56 (s, 3H); ^{19}F NMR (376 MHz, CD_3OD) δ -75.92 (s, 3F), -180.00 – -180.61 (m, 2F); ^{13}C NMR (101 MHz, DMSO-d_6, 350 K) δ 168.6 (C), 165.5 (C), 154.6 (C), 149.5 (d, $^4J_{CF}$ = 1.3 Hz, C), 136.3 (C), 135.4 (C), 131.8 (C), 129.6 (CH), 127.8 (C), 127.0 (CH), 125.4 (CH), 123.9 (CH), 115.8 (CH), 113.1 (CH), 83.0 (d, $^1J_{CF}$ = 200.9 Hz, CHF), 58.8 (d, $^2J_{CF}$ = 58.8 Hz, CH_2), -0.6 (CH_3), -1.4 (CH_3); Analytical HPLC: t_R = 11.8 min, 98.1% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 650 nm); HRMS (ESI) calcd for $C_{29}H_{27}F_2N_2O_4Si$ $[M+H]^+$ 533.1703, found 533.1710.

General procedure for preparation of HaloTag and SNAP-tag ligands (Method C): The following procedure for **13** is representative. 6-Carboxy-JF$_{525}$ (**36**; 30 mg, 46.8 μmol) was combined with DSC (26 mg, 103 μmol, 2.2 eq) in DMF (2.5 mL). After adding Et_3N (39 μL, 281 μmol, 6 eq) and DMAP (0.6 mg, 4.7 μmol, 0.1 eq), the reaction was stirred at room temperature for 1 h while shielded from light. HaloTag(O2)amine (HTL-NH_2, **37**; TFA salt; 26 mg, 117 μmol, 2.5 eq, Promega) was then added. The reaction was stirred an additional 2 h at room temperature, then concentrated *in vacuo*. The crude material was purified by reverse phase HPLC (10–90% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive) followed by flash chromatography on silica gel (0–10% MeOH/CH_2Cl_2, linear gradient) to provide 21.3 mg (62%) of **13** as a pink solid.

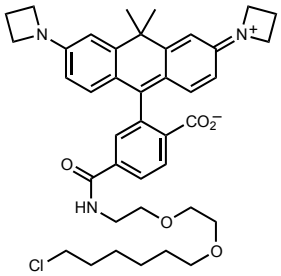


JF$_{525}$–HaloTag ligand (13): (62%, pink solid) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (dd, J = 8.0, 0.8 Hz, 1H), 7.98 (dd, J = 8.0, 1.4 Hz, 1H), 7.55 (dd, J = 1.5, 0.8 Hz, 1H), 6.75 – 6.70 (m, 1H), 6.62 (d, J = 8.6 Hz, 2H), 6.31 (d, J = 2.4 Hz, 2H), 6.17 (dd, J = 8.6, 2.4 Hz, 2H), 4.26 (t, $^3J_{HF}$ = 11.7 Hz, 8H), 3.69 – 3.57 (m, 6H), 3.56 – 3.48 (m, 4H), 3.40 (t, J = 6.6 Hz, 2H), 1.79 – 1.70 (m, 2H), 1.54 – 1.48 (m, 2H), 1.46 – 1.38 (m, 2H), 1.37 – 1.29 (m, 2H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -100.04 (p, $^3J_{FH}$ = 11.8 Hz); Analytical HPLC: t_R = 14.2 min, >99% purity (10–95%

MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{37}H_{39}ClF_4N_3O_6$ $[M+H]^+$ 732.2458, found 732.2457.

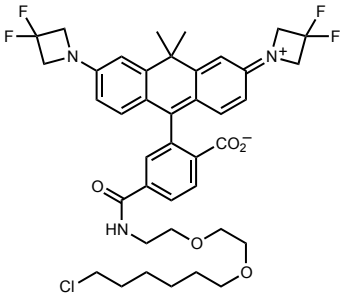


JF_{503}–HaloTag ligand (17): Acid **40** (20 mg, 28.7 μmol) was combined with TSTU (19 mg, 63.1 μmol, 2.2 eq) in DMF (1.5 mL). After adding DIEA (30 μL, 172 μmol, 6 eq), the reaction was stirred at room temperature for 1 h while shielded from light. HaloTag(O2)amine (HTL-NH_2, **37**; TFA salt; 23 mg, 68.8 μmol, 2.4 eq, Promega) was then added, and the reaction was stirred for 1 h at room temperature. After adding MeOH (1 mL) and 1 N NaOH (300 μL) and stirring an additional 3 h at room temperature, the reaction was acidified with 1 N HCl (325 μL) and concentrated to dryness. The crude material was purified by reverse phase HPLC (10–75% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive) to provide 19.4 mg (88%, TFA salt) of **17** as an orange solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.72 (t, *J* = 5.2 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H), 8.19 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.07 – 6.88 (m, 3H), 6.83 – 6.74 (m, 1H), 6.72 – 6.66 (m, 1H), 6.65 – 6.56 (m, 1H), 4.53 (t, *J* = 11.6 Hz, 4H), 3.65 – 3.47 (m, 10H), 3.41 (t, *J* = 6.5 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.56 – 1.27 (m, 6H); ^{19}F NMR (CD_3OD, 376 MHz) δ -75.44 (s, 3F), -100.39 – -100.65 (m, 2F); Analytical HPLC: t_R = 12.7 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 500 nm); HRMS (ESI) calcd for $C_{34}H_{36}ClF_2N_2O_7$ $[M+H]^+$ 657.2174, found 657.2190.

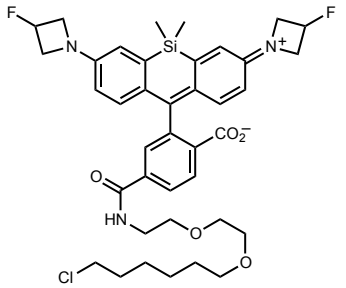


JF_{608}–HaloTag ligand (22): Acid **49** was subjected to Method C to prepare the title compound (72%, dark blue solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (dd, *J* = 8.0, 0.6 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.42 – 7.40 (m, 1H), 6.68 – 6.62 (m, 1H), 6.57 (d, *J* = 2.3 Hz, 2H), 6.52 (d, *J* = 8.6 Hz, 2H), 6.20 (dd, *J* = 8.6, 2.4 Hz, 2H), 3.91 (t, *J* = 7.4 Hz, 8H), 3.64 – 3.56 (m, 6H), 3.55 – 3.48 (m, 4H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.37 (p, *J* = 7.2 Hz, 4H), 1.83 (s, 3H), 1.77 – 1.68 (m, 2H), 1.72 (s, 3H), 1.56 – 1.47 (m, 2H), 1.46 – 1.36 (m, 2H), 1.36 – 1.28 (m, 2H); Analytical HPLC: t_R = 14.2 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20

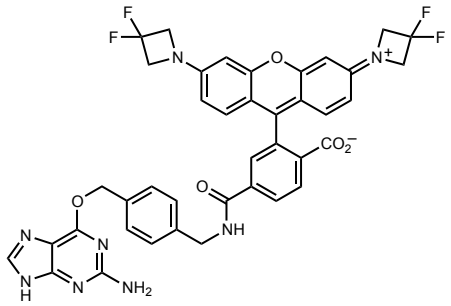
min run; 1 mL/min flow; ESI; positive ion mode; UV detection at 600 nm); HRMS (ESI) calcd for $C_{40}H_{49}ClN_3O_5$ $[M+H]^+$ 686.3361, found 686.3375.



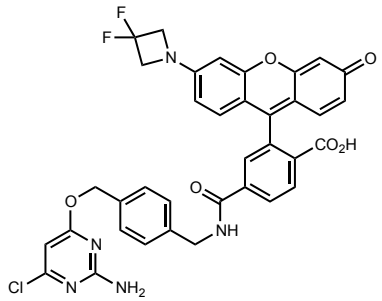
JF_{585}–HaloTag ligand (23): Acid **50** was subjected to Method C to prepare the title compound (54%, off-white/bluish solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (dd, J = 8.0, 0.5 Hz, 1H), 7.93 (dd, J = 8.0, 1.4 Hz, 1H), 7.44 – 7.40 (m, 1H), 6.70 – 6.65 (m, 1H), 6.64 (d, J = 2.4 Hz, 2H), 6.60 (d, J = 8.6 Hz, 2H), 6.28 (dd, J = 8.6, 2.4 Hz, 2H), 4.25 (t, $^3J_{HF}$ = 11.7 Hz, 8H), 3.66 – 3.57 (m, 6H), 3.56 – 3.48 (m, 4H), 3.39 (t, J = 6.6 Hz, 2H), 1.85 (s, 3H), 1.79 – 1.70 (m, 5H), 1.57 – 1.48 (m, 2H), 1.46 – 1.37 (m, 2H), 1.37 – 1.26 (m, 2H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -99.94 (p, $^3J_{FH}$ = 11.8 Hz); Analytical HPLC: t_R = 15.4 min, >99% purity (30–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 600 nm); HRMS (ESI) calcd for $C_{40}H_{45}ClF_4N_3O_5$ $[M+H]^+$ 758.2978, found 758.2989.



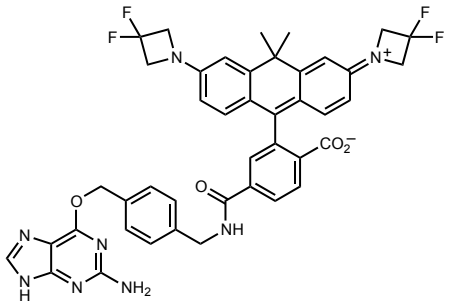
JF_{635}–HaloTag ligand (27): Acid **54** was subjected to Method C to prepare the title compound (61%, blue-green solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (dd, J = 7.9, 0.7 Hz, 1H), 7.89 (dd, J = 8.0, 1.4 Hz, 1H), 7.69 (dd, J = 1.4, 0.8 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.79 – 6.75 (m, 1H), 6.69 (d, J = 2.6 Hz, 2H), 6.31 (dd, J = 8.7, 2.7 Hz, 2H), 5.52 – 5.30 (m, 2H), 4.26 – 4.14 (m, 4H), 4.04 – 3.92 (m, 4H), 3.68 – 3.58 (m, 6H), 3.58 – 3.53 (m, 2H), 3.50 (t, J = 6.6 Hz, 2H), 3.40 (t, J = 6.7 Hz, 2H), 1.77 – 1.68 (m, 2H), 1.54 – 1.48 (m, 2H), 1.44 – 1.36 (m, 2H), 1.35 – 1.27 (m, 2H), 0.66 (s, 3H), 0.59 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -180.49 (dtt, J_{FH} = 56.9, 23.9, 18.2 Hz); Analytical HPLC: t_R = 16.8 min, 98.7% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 633 nm); HRMS (ESI) calcd for $C_{39}H_{47}ClF_2N_3O_5Si$ $[M+H]^+$ 738.2936, found 738.2953.



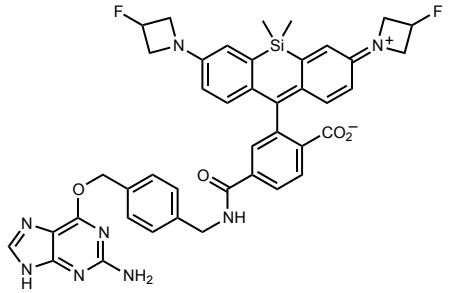
JF_{525}–SNAP-tag ligand (15): Acid **36** and STL-NH_2 (**38**, NEB) were subjected to Method C to prepare the title compound (72%, red-orange solid). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.13 (dd, J = 8.1, 1.4 Hz, 1H), 8.07 (dd, J = 8.0, 0.6 Hz, 1H), 7.80 (s, 1H), 7.65 – 7.60 (m, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 6.46 (d, J = 2.3 Hz, 2H), 6.35 (dd, J = 8.7, 2.4 Hz, 2H), 5.48 (s, 2H), 4.49 (s, 2H), 4.31 (t, $^3J_{HF}$ = 11.9 Hz, 8H); ^{19}F NMR (CD_3OD, 376 MHz) δ -100.07 – -100.32 (m); Analytical HPLC: t_R = 10.8 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 550 nm); HRMS (ESI) calcd for $C_{40}H_{31}F_4N_8O_5$ $[M+H]^+$ 779.2348, found 779.2355.



JF_{503}–cpSNAP-tag ligand (20): Acid **40** and cpSTL-NH_2 (**41**, NEB) were subjected to the same procedure described for **17** to prepare the title compound (71%, orange solid, TFA salt). ^{1}H NMR (CD_3OD, 400 MHz) δ 9.20 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.23 (dd, J = 8.2, 1.6 Hz, 1H), 7.80 (d, J = 1.3 Hz, 1H), 7.36 (AB quartet, ν_A = 2951.5 Hz, ν_B = 2938.7 Hz, J_{AB} = 8.3 Hz, 4H), 7.19 – 7.10 (m, 2H), 7.07 (d, J = 1.9 Hz, 1H), 6.92 (dd, J = 9.0, 2.0 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 6.77 – 6.70 (m, 1H), 6.07 (s, 1H), 5.32 (s, 2H), 4.67 (t, $^3J_{HF}$ = 11.6 Hz, 4H), 4.60 – 4.53 (m, 2H); ^{19}F NMR (CD_3OD, 376 MHz) δ -75.60 (s, 3F), -100.77 (p, $^3J_{FH}$ = 11.7 Hz, 2F); Analytical HPLC: t_R = 12.4 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 500 nm); HRMS (ESI) calcd for $C_{36}H_{27}ClF_2N_5O_6$ $[M+H]^+$ 698.1612, found 698.1627.



JF_{585}–SNAP-tag ligand (24): Acid **50** and STL-NH_2 (**38**, NEB) were subjected to Method C to prepare the title compound (71%, off-white solid). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.07 (dd, J = 8.0, 1.3 Hz, 1H), 8.04 (dd, J = 8.0, 0.7 Hz, 1H), 7.81 (s, 1H), 7.48 – 7.44 (m, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.81 (d, J = 2.4 Hz, 2H), 6.58 (d, J = 8.6 Hz, 2H), 6.39 (dd, J = 8.6, 2.4 Hz, 2H), 5.48 (s, 2H), 4.47 (s, 2H), 4.24 (t, $^3J_{HF}$ = 12.0 Hz, 8H), 1.85 (s, 3H), 1.74 (s, 3H); ^{19}F NMR (CD_3OD, 376 MHz) δ -99.82 (p, $^3J_{FH}$ = 11.9 Hz); Analytical HPLC: t_R = 13.3 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 600 nm); HRMS (ESI) calcd for $C_{43}H_{37}F_4N_8O_4$ $[M+H]^+$ 805.2868, found 805.2876.



JF_{635}–SNAP-tag ligand (29): Acid **54** and STL-NH_2 (**38**, NEB) were subjected to Method C to prepare the title compound (48%, off-white solid). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.02 (dd, J = 8.0, 1.3 Hz, 1H), 8.00 (dd, J = 8.0, 0.8 Hz, 1H), 7.81 (s, 1H), 7.68 – 7.63 (m, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 6.79 (d, J = 2.6 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 6.39 (dd, J = 8.7, 2.7 Hz, 2H), 5.52 (s, 2H), 5.50 – 5.31 (m, 2H), 4.52 (s, 2H), 4.25 – 4.12 (m, 4H), 3.98 – 3.86 (m, 4H), 0.60 (s, 3H), 0.54 (s, 3H); ^{19}F NMR (CD_3OD, 376 MHz) δ -179.91 (dtt, J_{FH} = 57.5, 23.8, 19.3 Hz); Analytical HPLC: t_R = 12.6 min, >99% purity (10–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 633 nm); HRMS (ESI) calcd for $C_{42}H_{39}F_2N_8O_4Si$ $[M+H]^+$ 785.2826, found 785.2828.

REFERENCES

1 Grimm, J. B. *et al.* Carbofluoresceins and carborhodamines as scaffolds for high-contrast fluorogenic probes. *ACS Chem. Biol.* **8**, 1303-1310 (2013).

2 Grimm, J. B. *et al.* A general method to improve fluorophores for live-cell and single-molecule microscopy. *Nat. Methods* **12**, 244–250 (2015).

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
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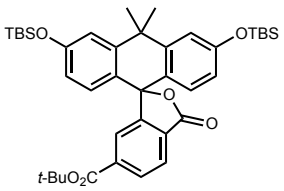
Lowest Frequency	-1646.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



44

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
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Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
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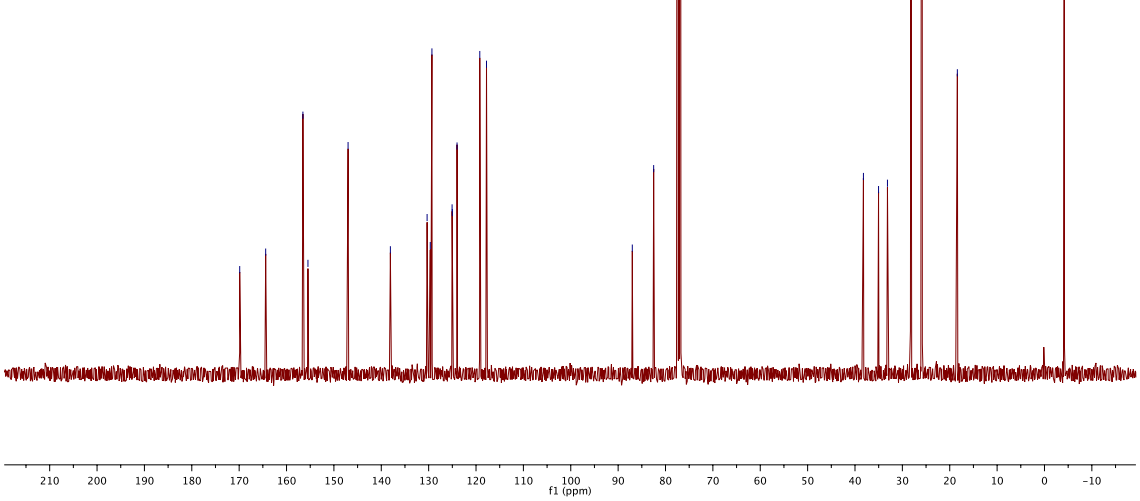
Lowest Frequency	-1942.1
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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Pulse Sequence	zg30
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Nucleus	1H
Acquired Size	32768
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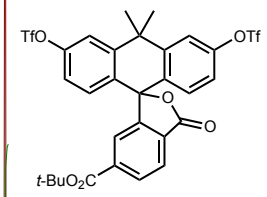

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Nucleus	13C
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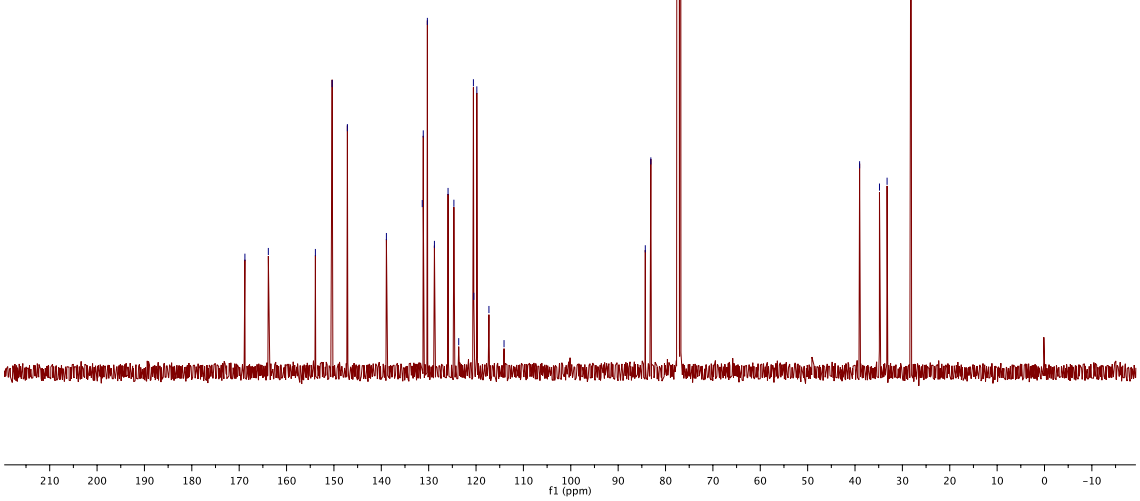
Spectral Size	65536



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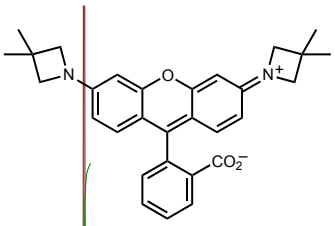
Acquired Size	32768
Spectral Size	65536



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Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
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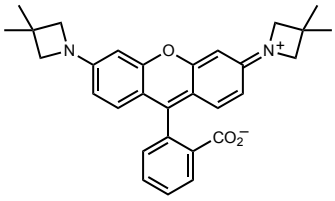
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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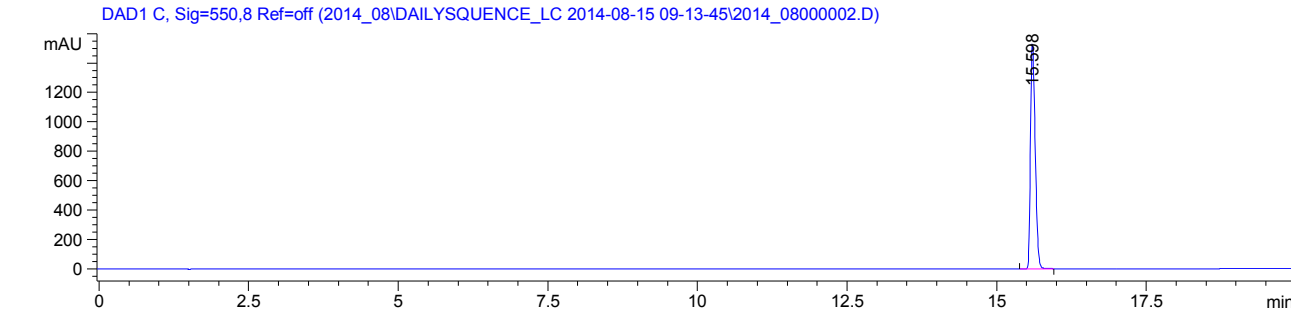
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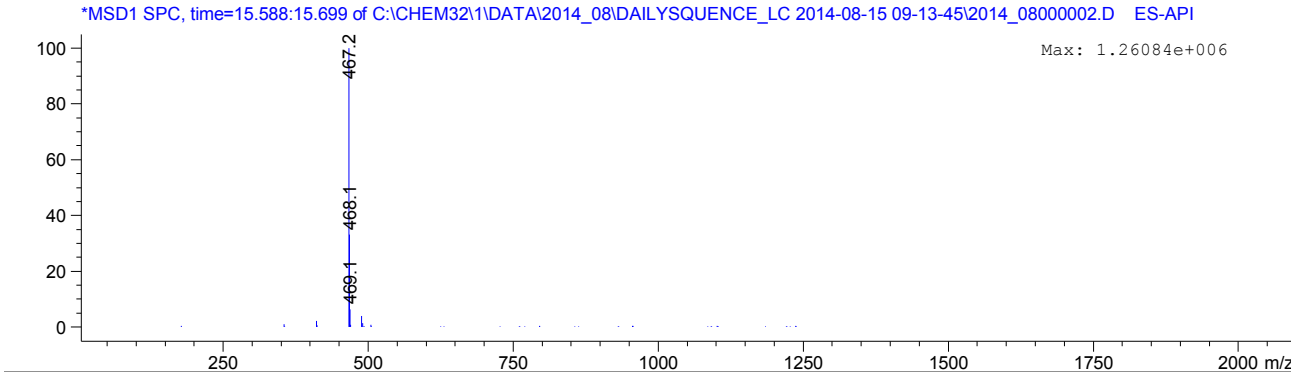
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Pulse Sequence	zg30
Experiment	1D
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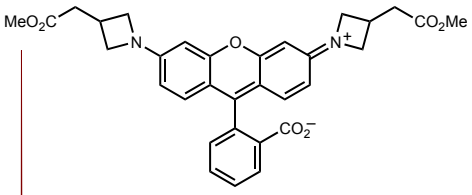
Spectral Size	65536



55

Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
Acquisition Date	2014-10-08T01:37:00
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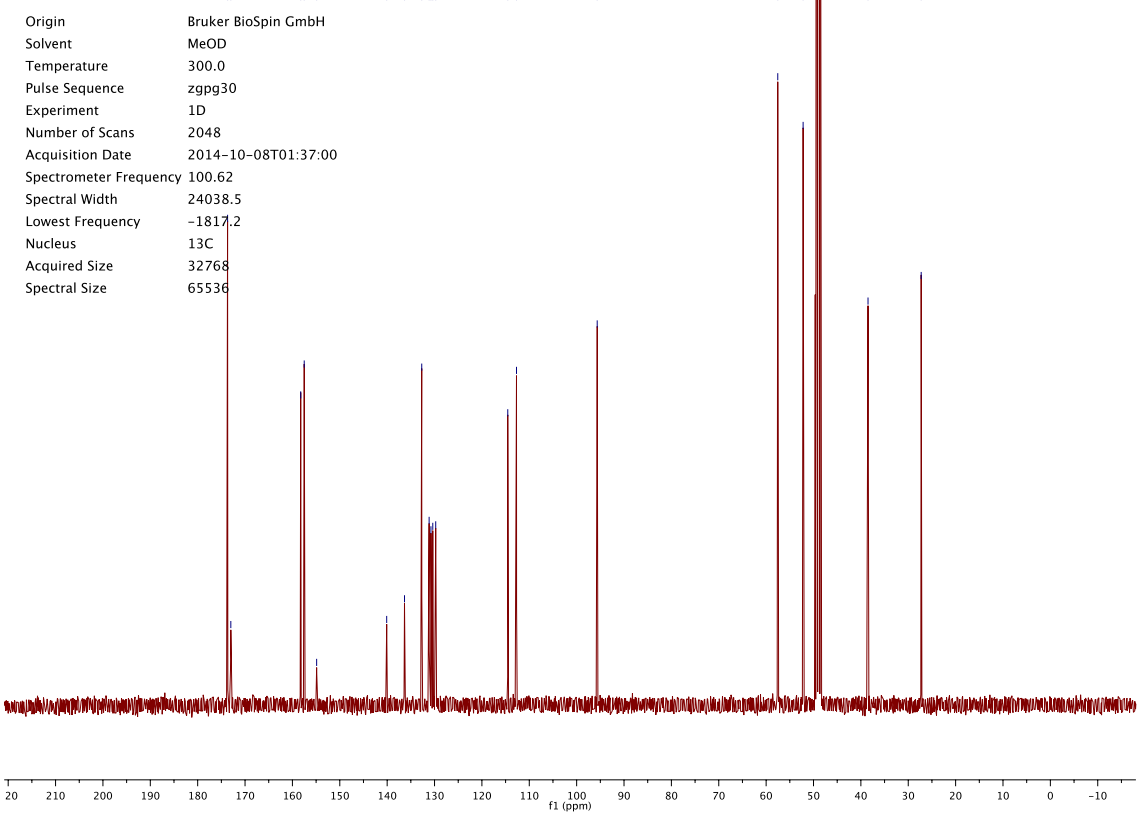
Spectral Width	24038.5
Lowest Frequency	-1817.2
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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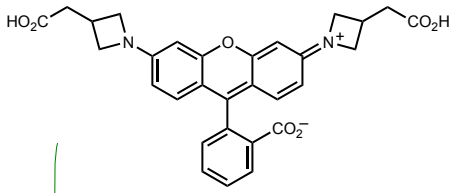
Spectral Size	65536



6

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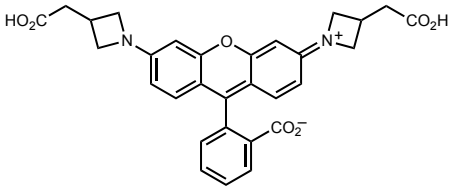
Lowest Frequency	-1816.4
Nucleus	13C
Acquired Size	32768
Spectral Size	65536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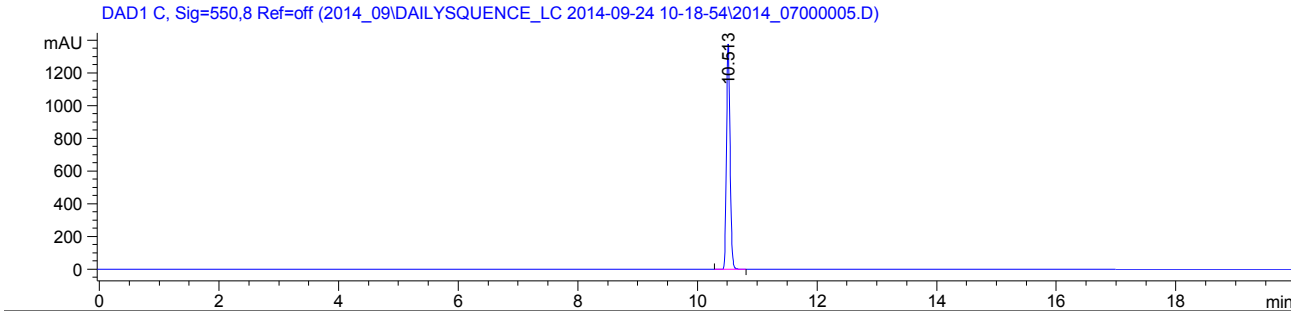
CO2−

6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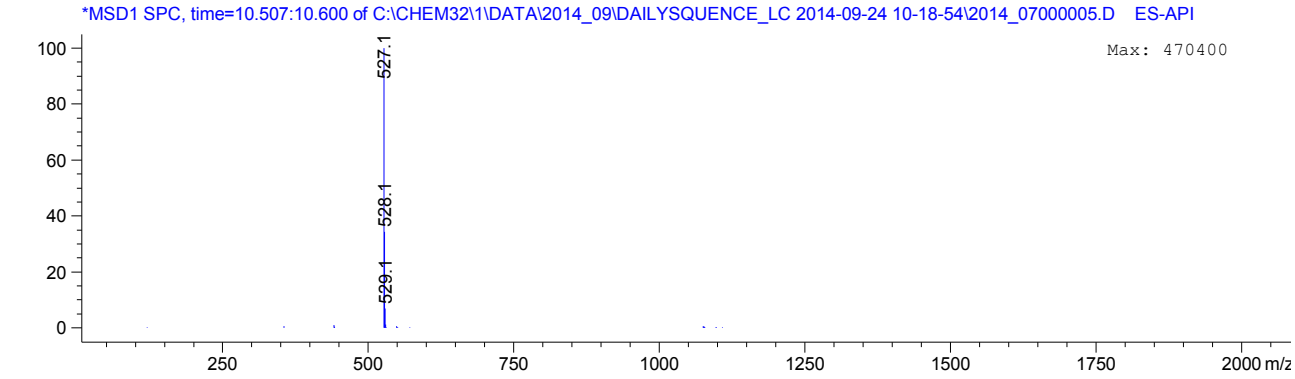
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Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-09-19T11:39:00
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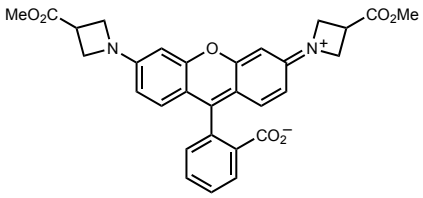
Spectral Size	65536



56

Origin	Bruker BioSpin GmbH
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Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
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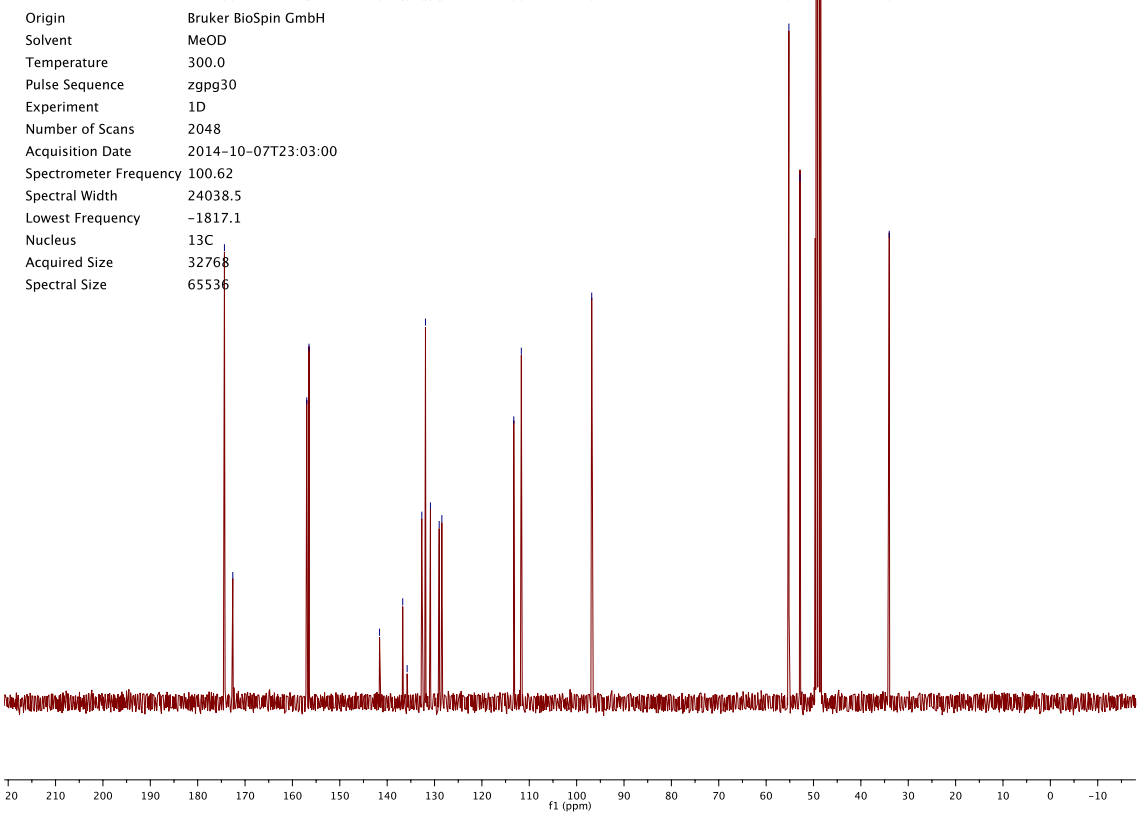
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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Acquired Size	32768
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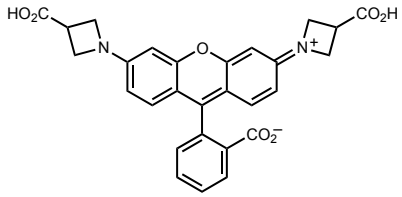

7

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Number of Scans	2048
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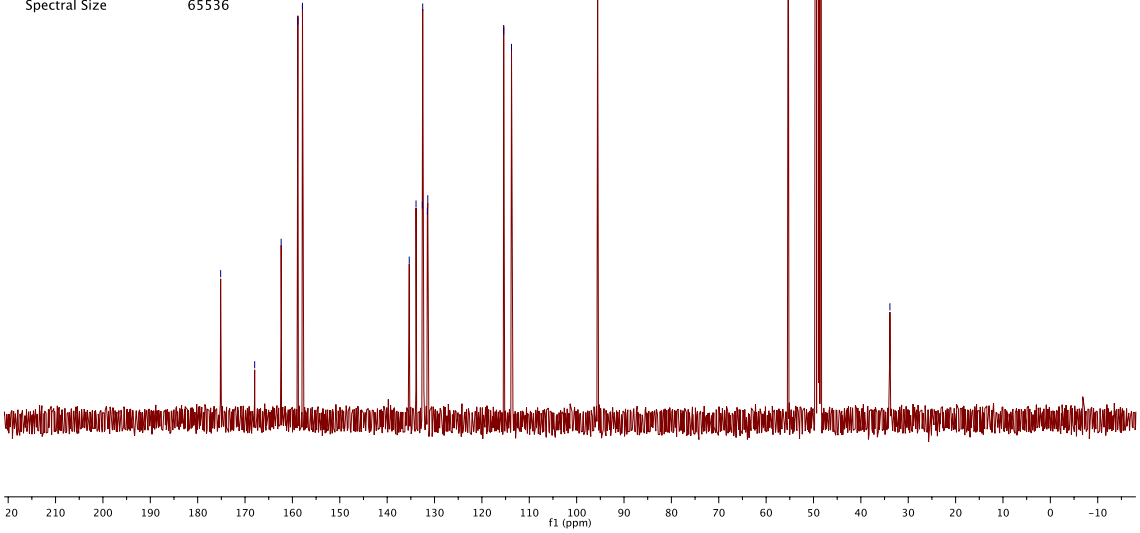

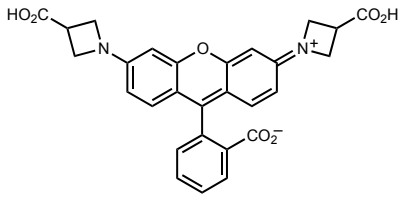
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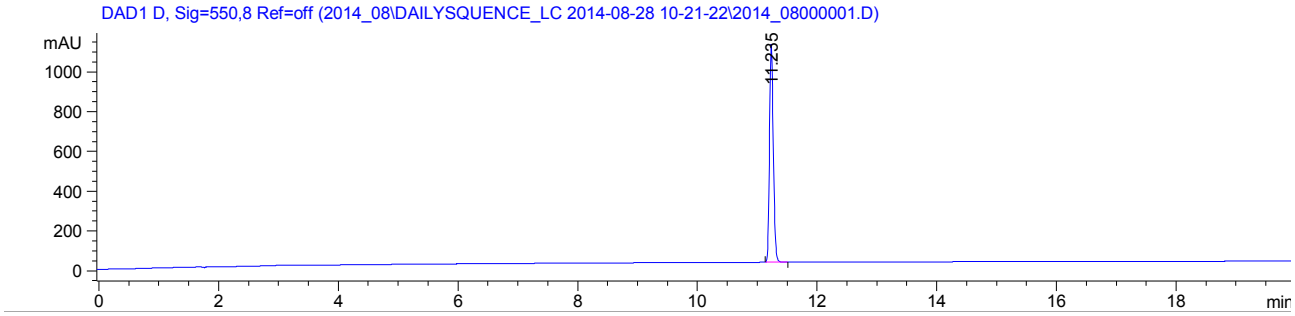
N+
CO2−

7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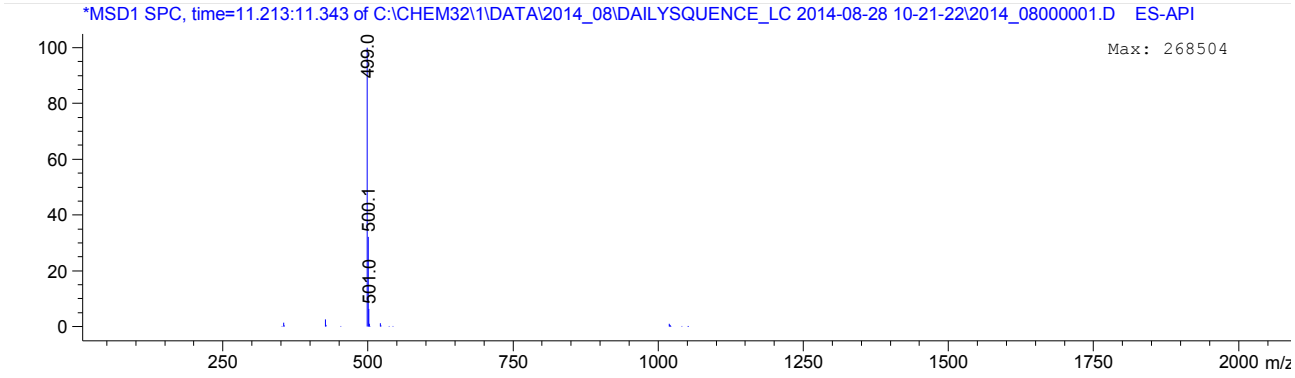
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Acquisition Date	2014-09-05T09:15:00
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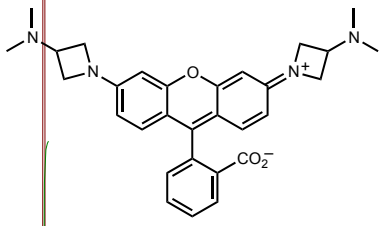

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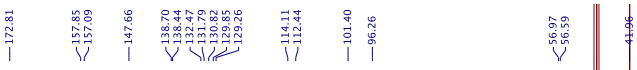

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Solvent	MeOD
Temperature	300.0
Pulse Sequence	zgpg30
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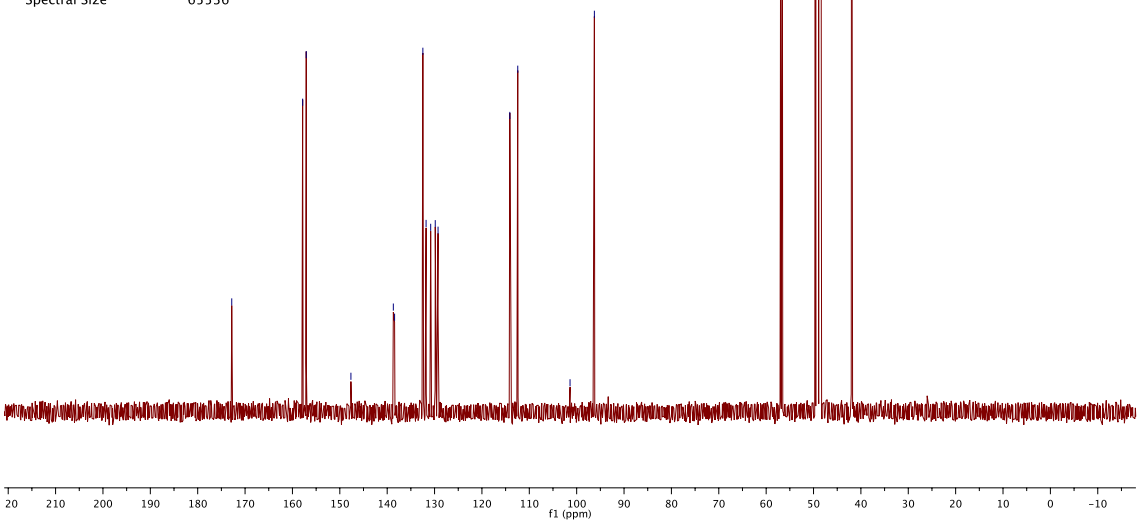
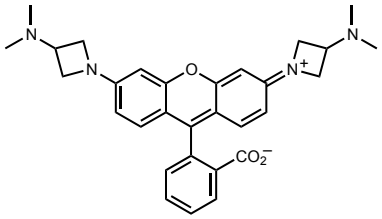
Spectral Size	65536





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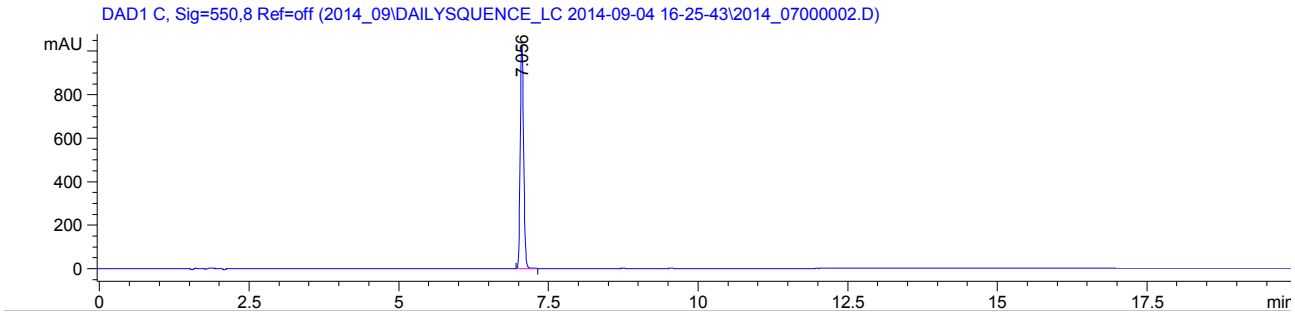
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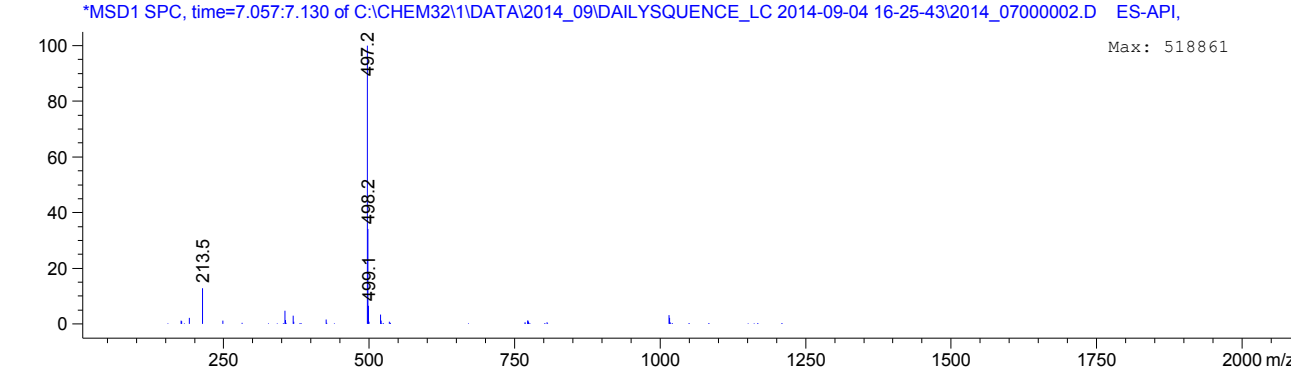
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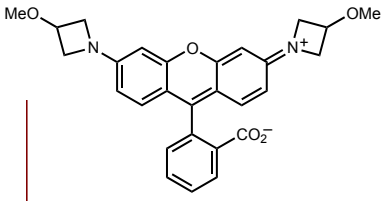
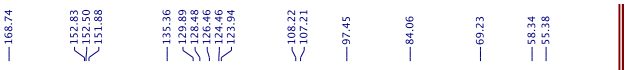
497.2
498.2
499.1
213.5
250
500
750
1000
1250
1500
1750
2000 m/z

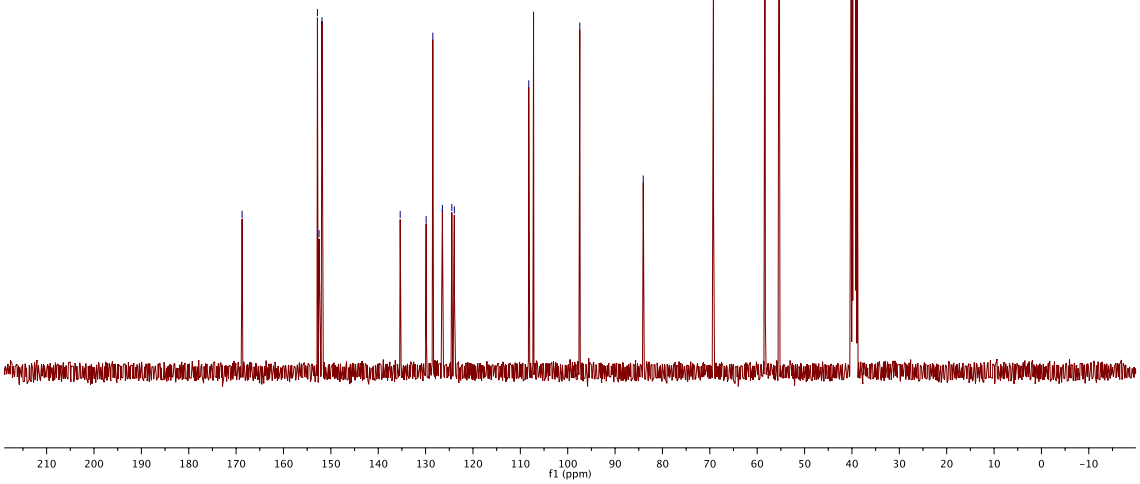
Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-10-07T09:01:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1638.5
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

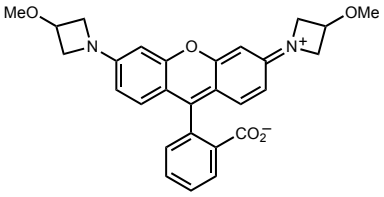


9

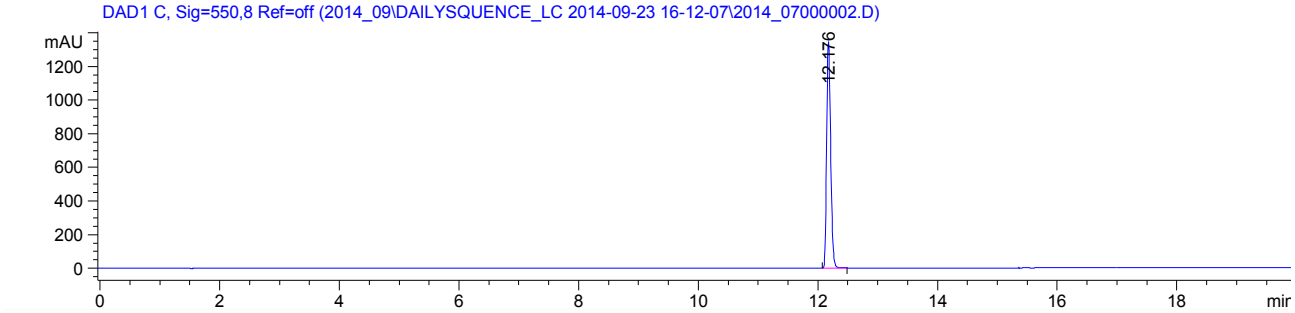


Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
Acquisition Date	2014-10-08T04:11:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-2006.8
Nucleus	13C
Acquired Size	32768
Spectral Size	65536




MeO
OMe
N
O
N+
CO2−

9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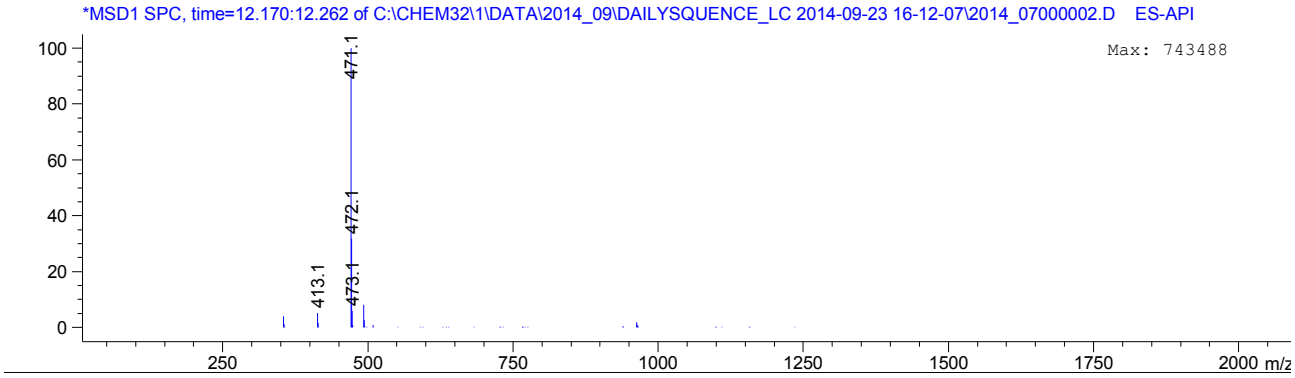
mAU
12.176
min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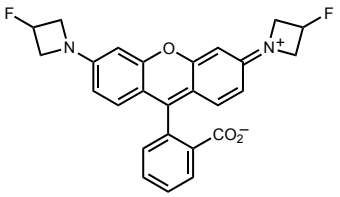
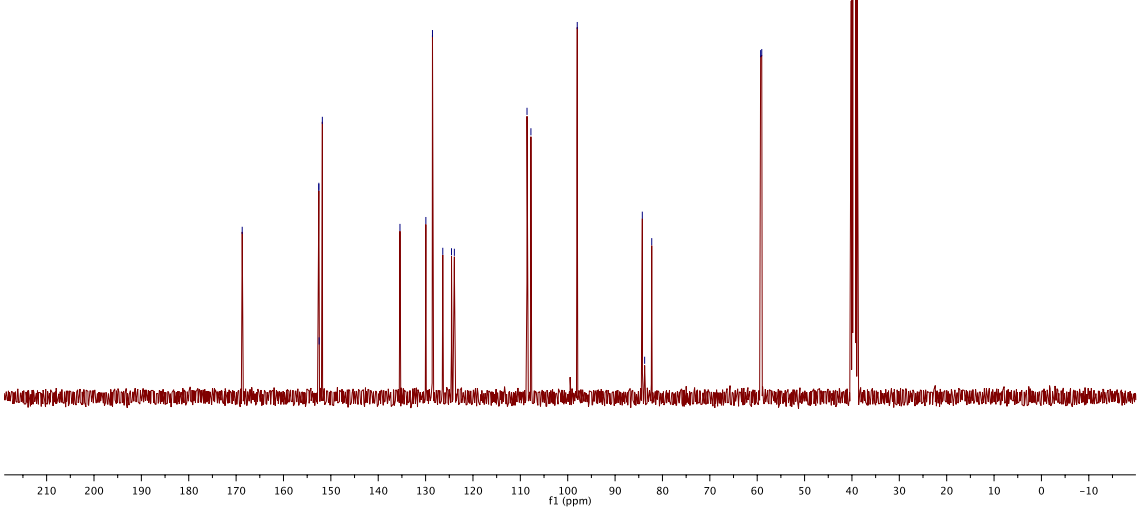
Max: 743488
474.1
472.1
473.1
413.1
m/z

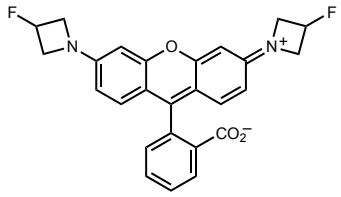
Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-10-09T10:02:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1638.5
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



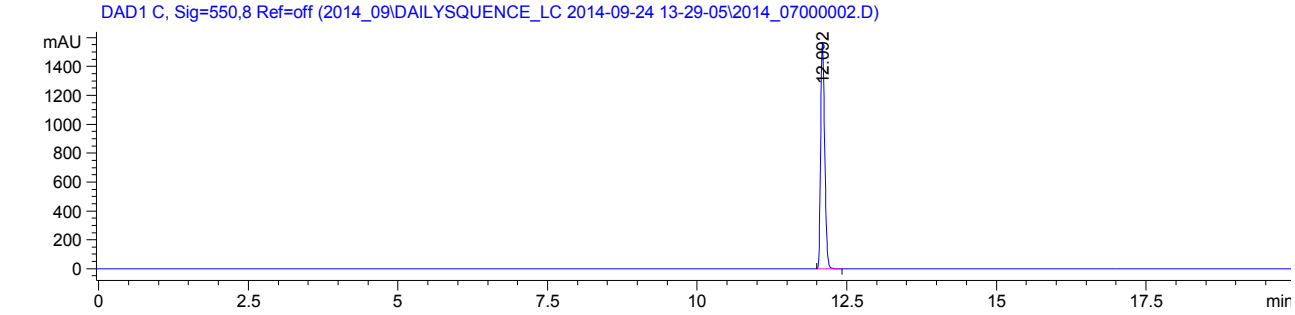
10

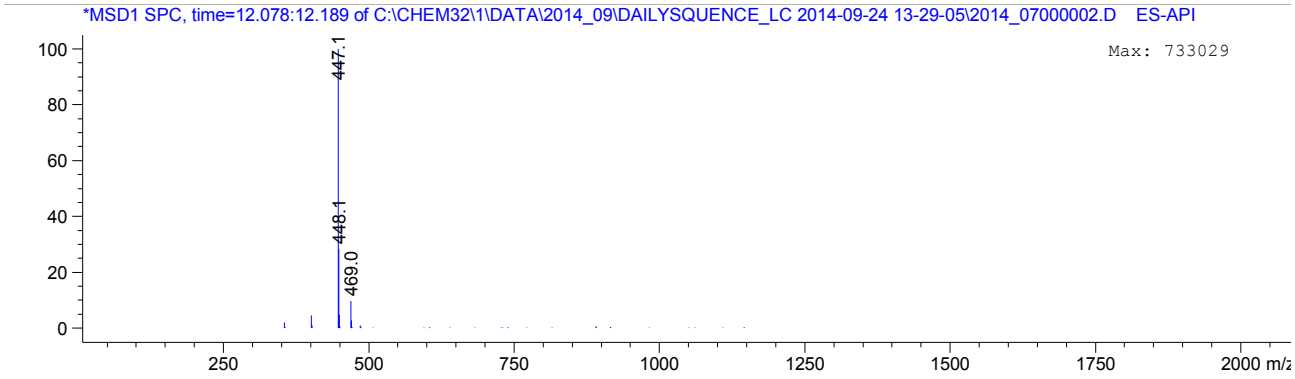
Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
Acquisition Date	2014-10-10T04:37:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-2006.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536




F
N
O
N+
F
CO2−

10


DAD1 C, Sig=550,8 Ref=off (2014_09\DAILYSQUENCE_LC 2014-09-24 13-29-05\2014_07000002.D)
mAU
1400
1200
1000
800
600
400
200
0
12.092
0
2.5
5
7.5
10
12.5
15
17.5
min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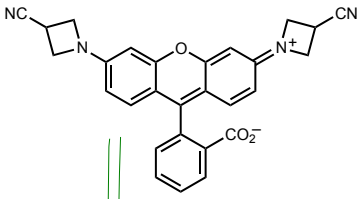
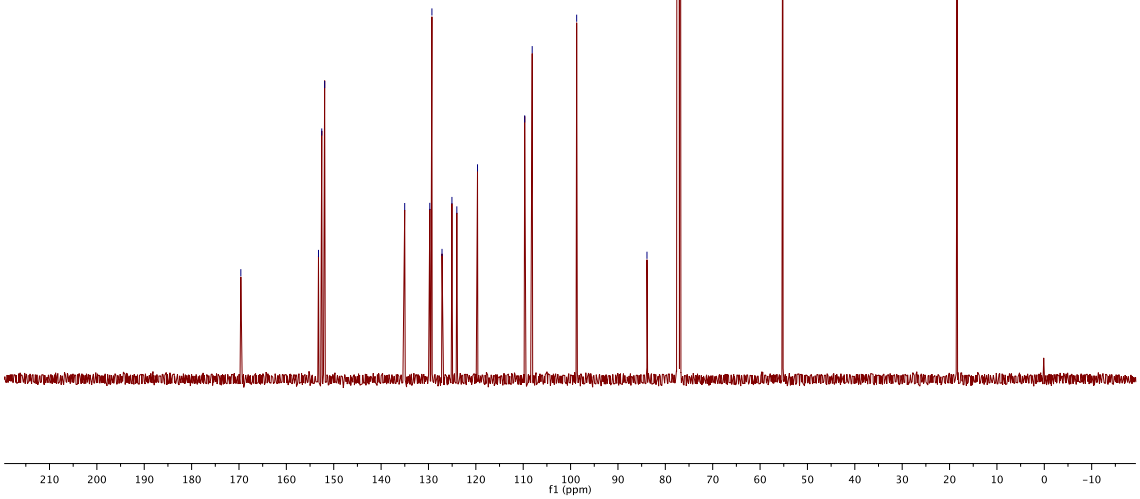
Max: 733029
100
80
60
40
20
0
447.1
448.1
469.0
250
500
750
1000
1250
1500
1750
2000 m/z

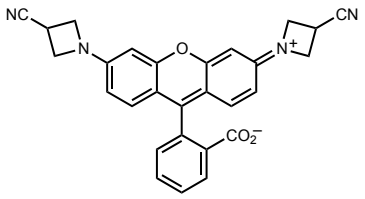
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-09-24T17:01:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1646.7
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



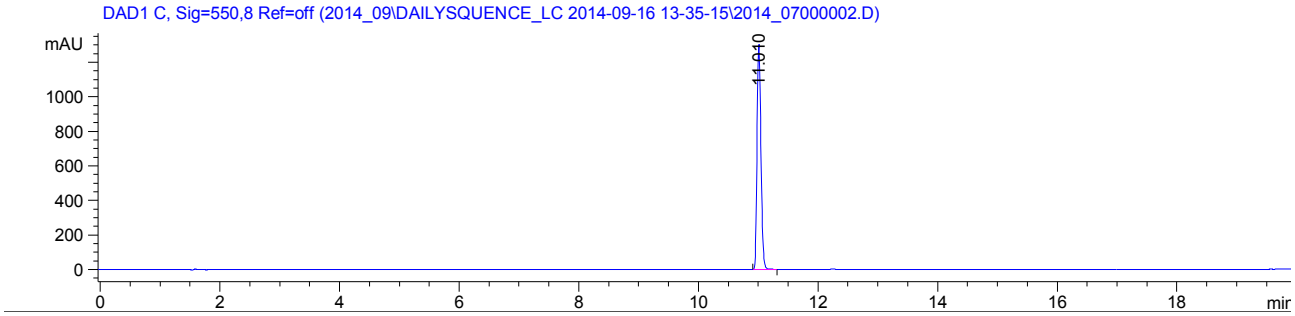
11

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
Acquisition Date	2014-09-25T04:15:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1945.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536




NC
N
O
N+
CN
CO2−

11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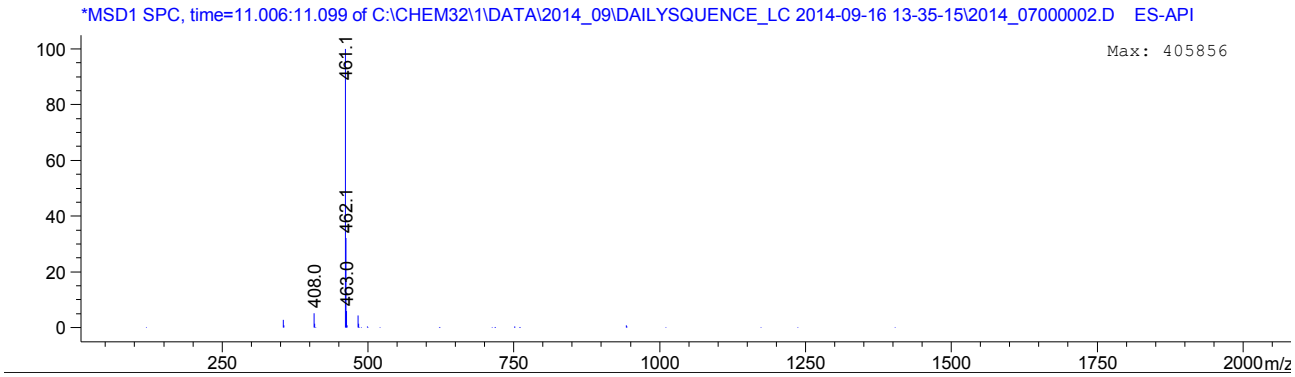
mAU
1000
800
600
400
200
0
11.010
0
2
4
6
8
10
12
14
16
18
min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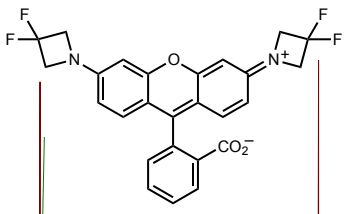
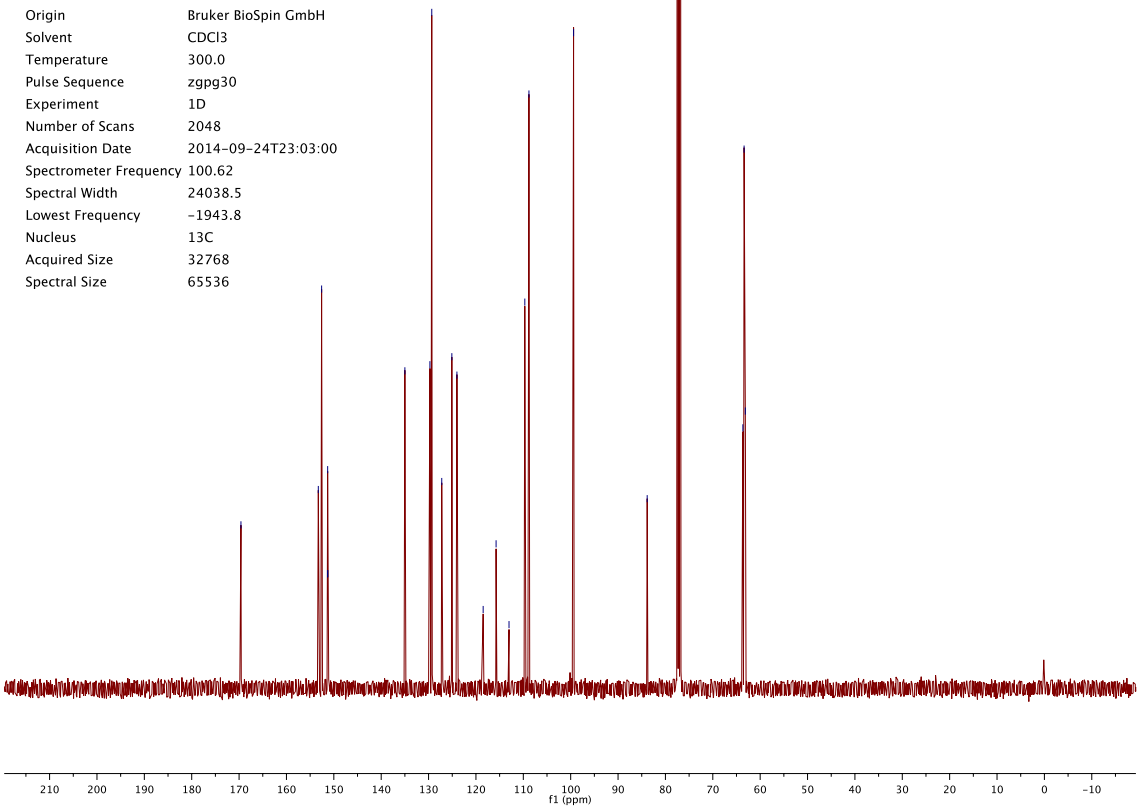
100
80
60
40
20
0
461.1
462.1
463.0
408.0
250
500
750
1000
1250
1500
1750
2000
m/z

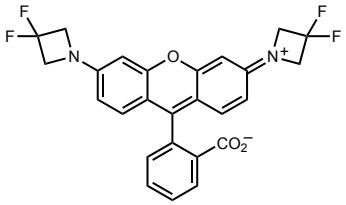
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-09-24T16:50:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1646.9
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



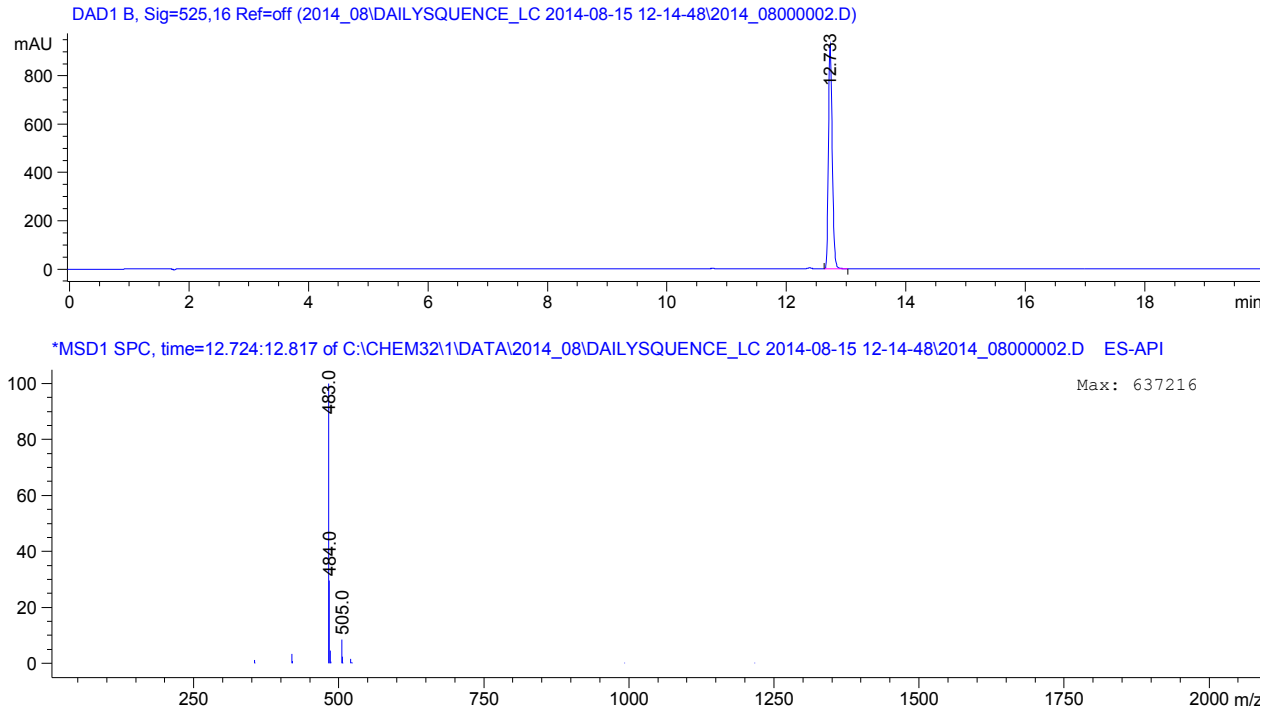
12

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
Acquisition Date	2014-09-24T23:03:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1943.8
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

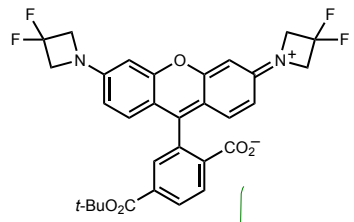



F
F
N
O
N+
F
F
CO2−

12


DAD1 B, Sig=525,16 Ref=off (2014_08\DAILYSQUENCE_LC 2014-08-15 12-14-48\2014_08000002.D)
mAU
800
600
400
200
0
12.733
0
2
4
6
8
10
12
14
16
18
min
*MSD1 SPC, time=12.724:12.817 of C:\CHEM32\1\DATA\2014_08\DAILYSQUENCE_LC 2014-08-15 12-14-48\2014_08000002.D ES-API
Max: 637216
100
80
60
40
20
0
483.0
484.0
505.0
250
500
750
1000
1250
1500
1750
2000 m/z

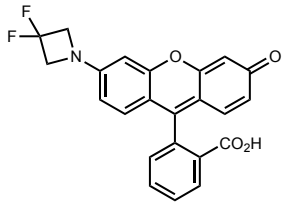
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2015-03-16T13:02:00
Modification Date	2015-03-16T13:02:44
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1617.3
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



35

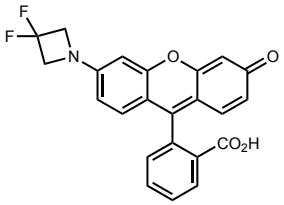
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	1024
Acquisition Date	2015-03-16T14:03:00
Modification Date	2015-03-16T14:03:38
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1677.2
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2016-09-27T09:32:00
Modification Date	2016-09-27T09:32:59
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1543.3
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

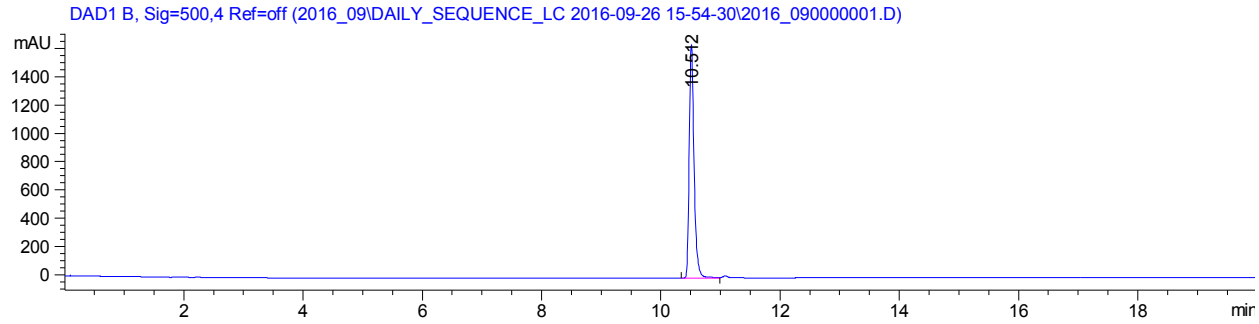


16

Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	350.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	4096
Acquisition Date	2016-10-05T20:43:00
Modification Date	2016-10-05T20:43:12
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1958.4
Nucleus	13C
Acquired Size	32768
Spectral Size	65536


F
F
N
O
O
CO2H

16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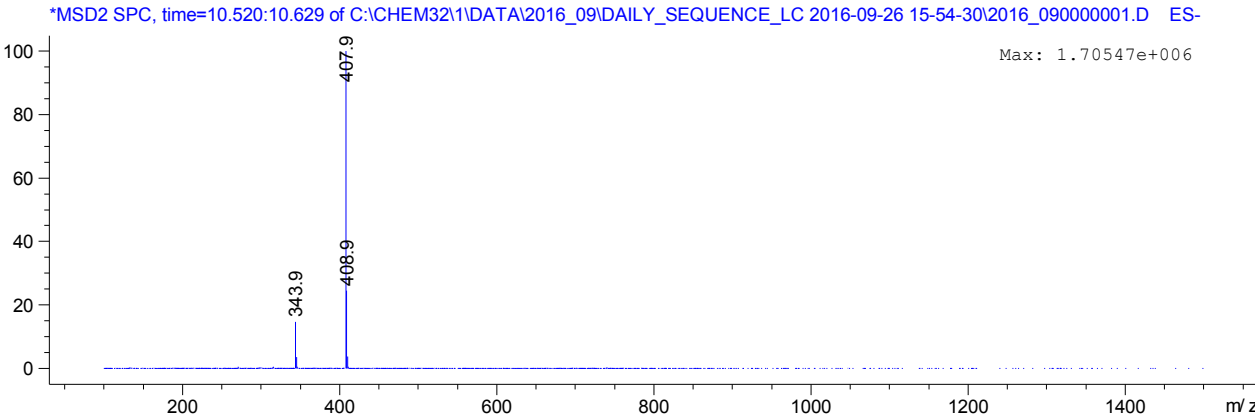
mAU
1400
1200
1000
800
600
400
200
0
10.512
2
4
6
8
10
12
14
16
18
min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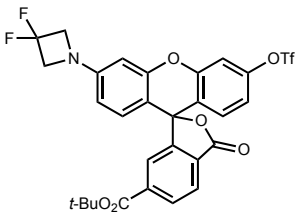
Max: 1.70547e+006
100
80
60
40
20
0
407.9
408.9
343.9
200
400
600
800
1000
1200
1400
m/z

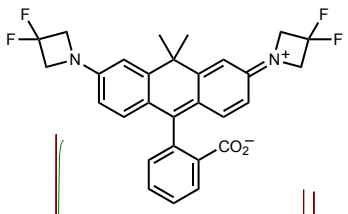
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.6
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2016-09-26T11:39:00
Modification Date	2016-09-26T11:39:15
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1545.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



39

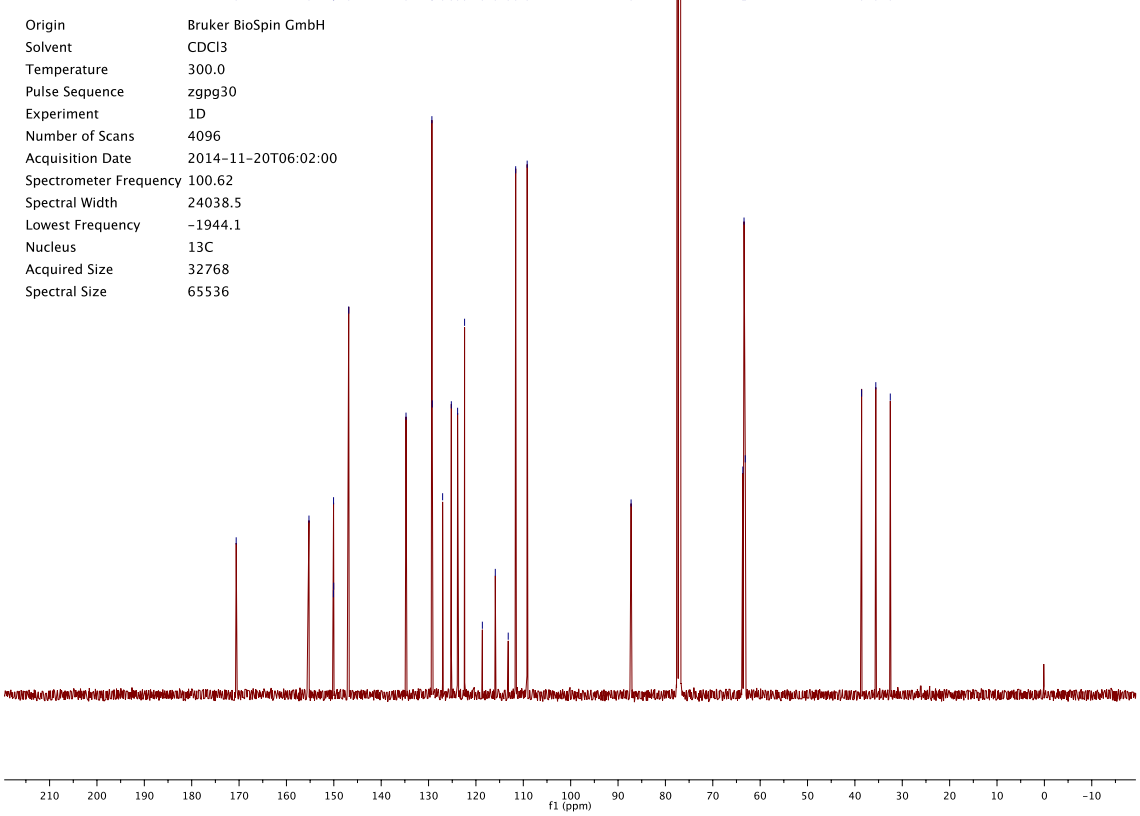
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	296.3
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	4096
Acquisition Date	2016-09-22T01:03:00
Modification Date	2016-09-22T01:03:01
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1945.1
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

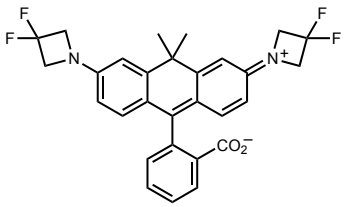
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-11-19T09:16:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1647.7
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



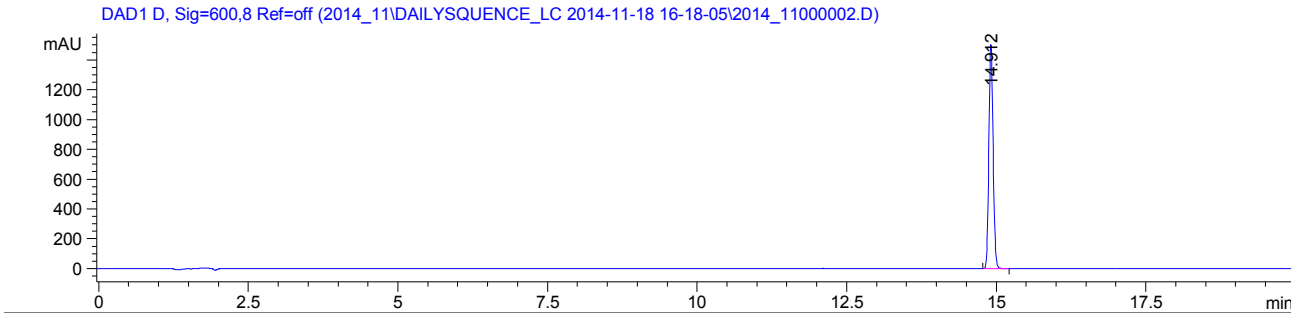
21

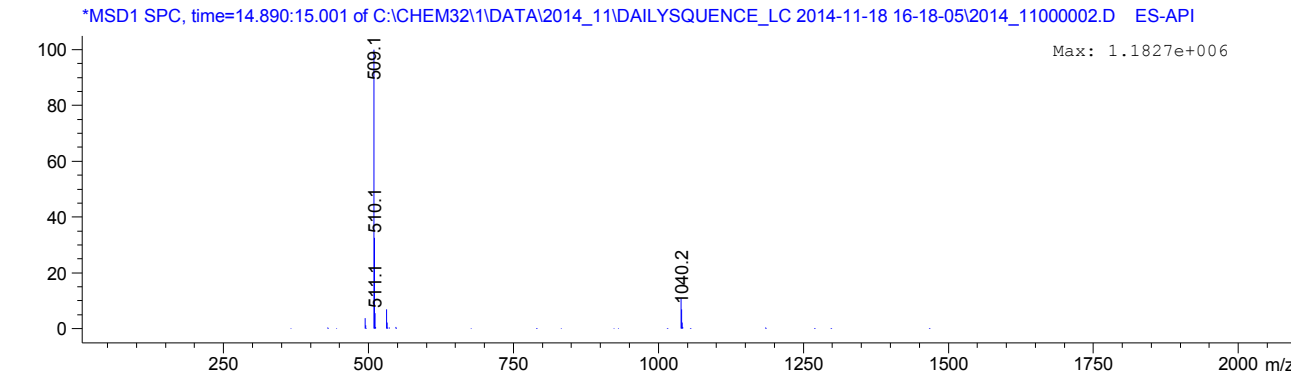
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	4096
Acquisition Date	2014-11-20T06:02:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1944.1
Nucleus	13C
Acquired Size	32768
Spectral Size	65536





21


DAD1 D, Sig=600,8 Ref=off (2014_11\DAILYSQUENCE_LC 2014-11-18 16-18-05\2014_11000002.D)
mAU
1200
1000
800
600
400
200
0
14.912
0
2.5
5
7.5
10
12.5
15
17.5
min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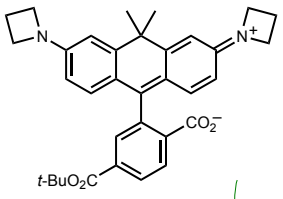
Max: 1.1827e+006
100
80
60
40
20
0
509.1
510.1
511.1
1040.2
250
500
750
1000
1250
1500
1750
2000 m/z

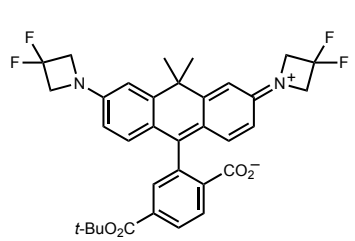
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2013-07-31T12:02:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1646.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



47

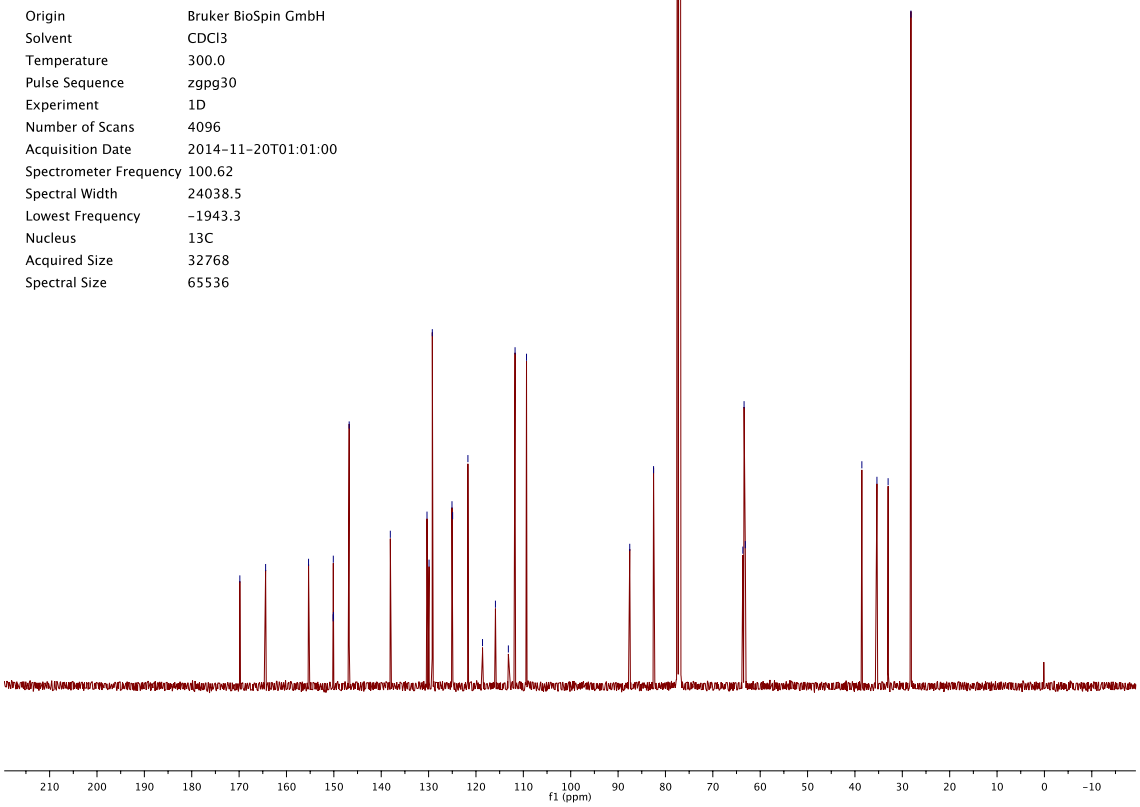
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	1024
Acquisition Date	2013-08-01T03:20:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1943.3
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-11-19T09:26:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1647.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

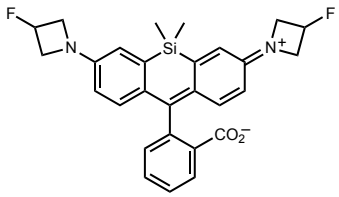


48

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	4096
Acquisition Date	2014-11-20T01:01:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1943.3
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

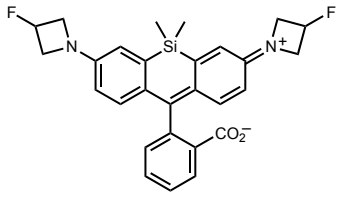


Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-10-20T09:21:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1647.3
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



25

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	4096
Acquisition Date	2014-10-21T00:58:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1944.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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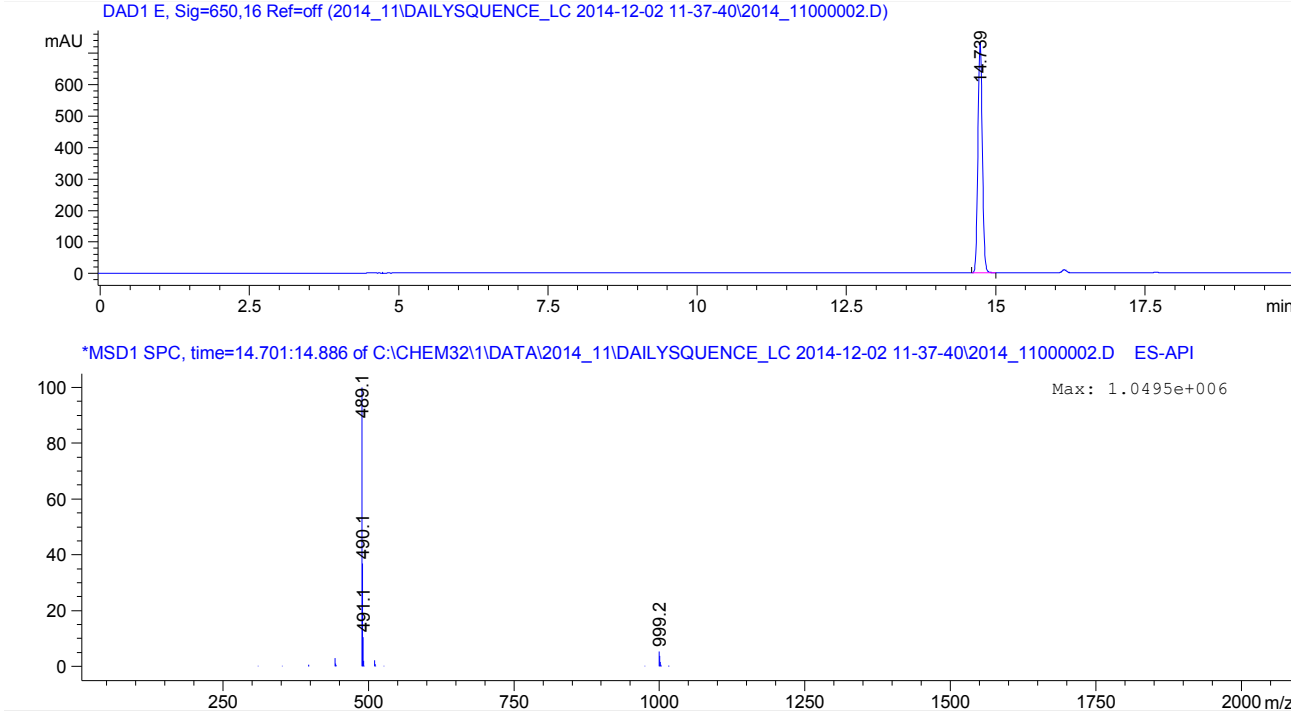
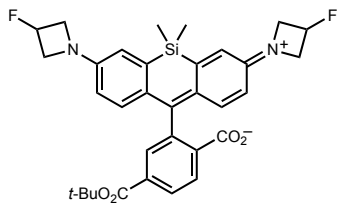
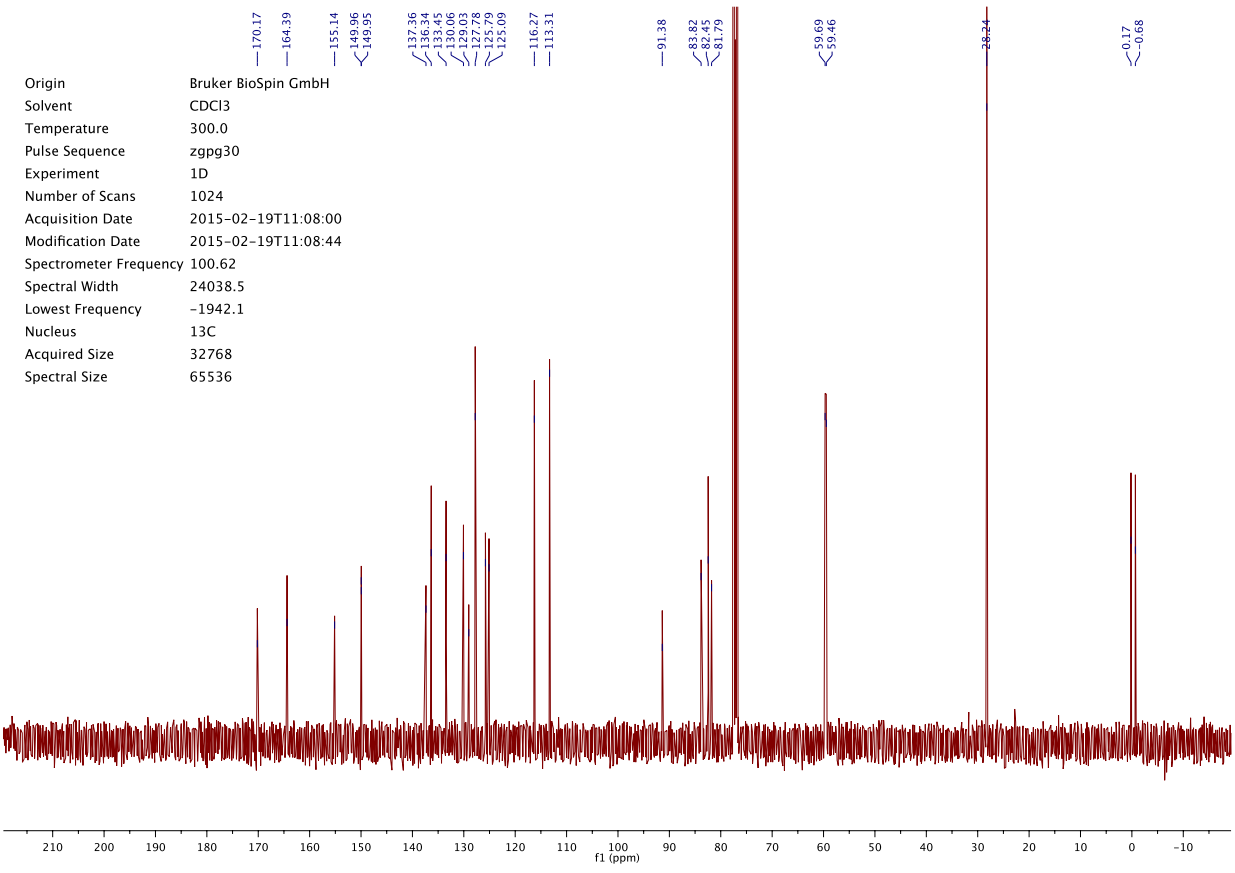

DAD1 E, Sig=650,16 Ref=off (2014_11\DAILYSQUENCE_LC 2014-12-02 11-37-40\2014_11000002.D)
mAU
600
500
400
300
200
100
0
14.739
0
2.5
5
7.5
10
12.5
15
17.5
min
*MSD1 SPC, time=14.701:14.886 of C:\CHEM32\1\DATA\2014_11\DAILYSQUENCE_LC 2014-12-02 11-37-40\2014_11000002.D ES-API
Max: 1.0495e+006
100
80
60
40
20
0
489.1
490.1
491.1
999.2
250
500
750
1000
1250
1500
1750
2000 m/z

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2015-02-19T10:02:00
Modification Date	2015-02-19T10:02:58
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1646.2
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

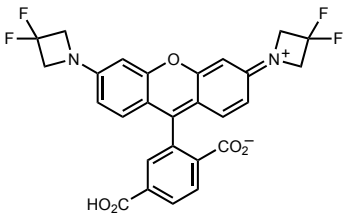


53



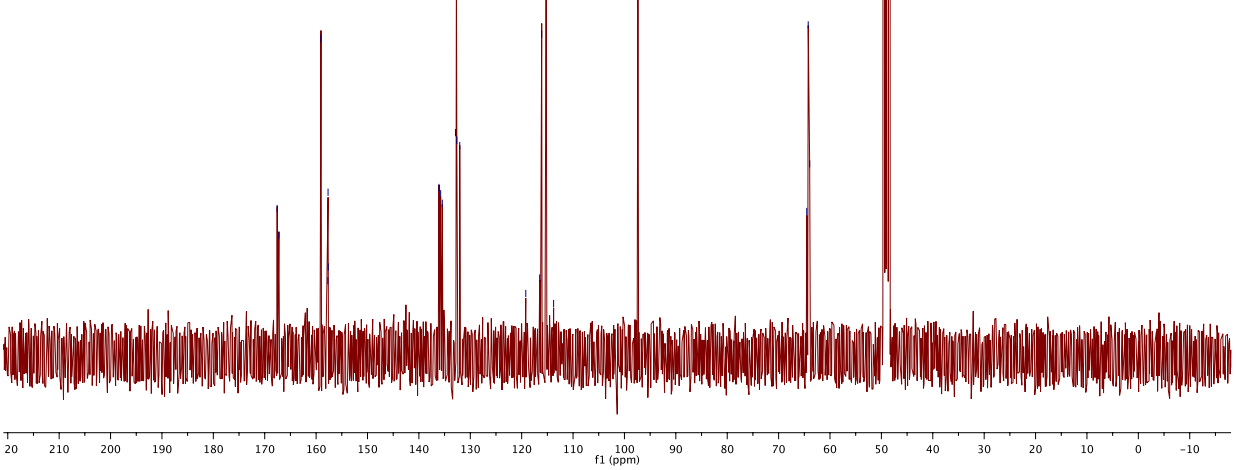
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	1024
Acquisition Date	2015-02-19T11:08:00
Modification Date	2015-02-19T11:08:44
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1942.1
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2016-09-28T15:41:00
Modification Date	2016-09-28T15:41:08
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1550.6
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

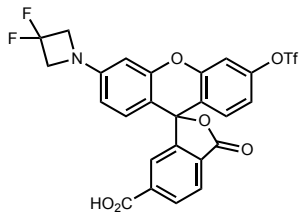


36

Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	1024
Acquisition Date	2015-03-16T16:09:00
Modification Date	2015-03-16T16:09:30
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1815.8
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



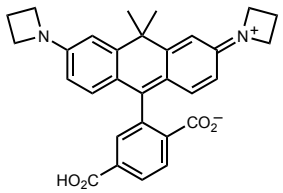
Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2016-09-27T09:46:00
Modification Date	2016-09-27T09:46:41
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1541.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



40

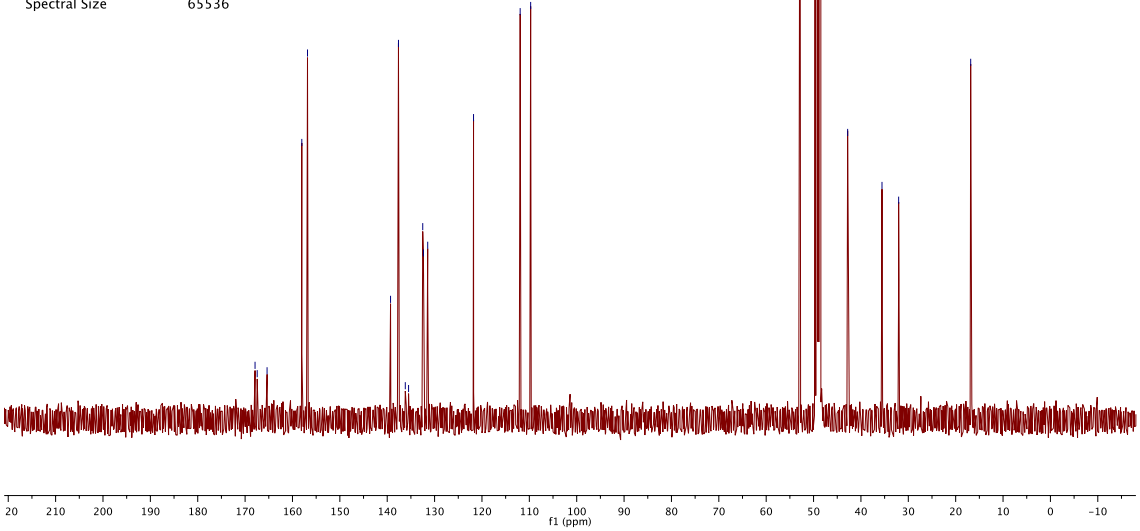
Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	8192
Acquisition Date	2016-09-29T04:52:00
Modification Date	2016-09-29T04:52:52
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-2007.7
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2013-08-13T16:58:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1644.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

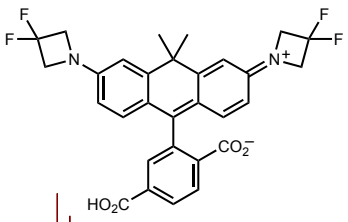


49

Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	8192
Acquisition Date	2013-08-16T04:51:00
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-1816.0
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-11-24T09:29:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1644.2
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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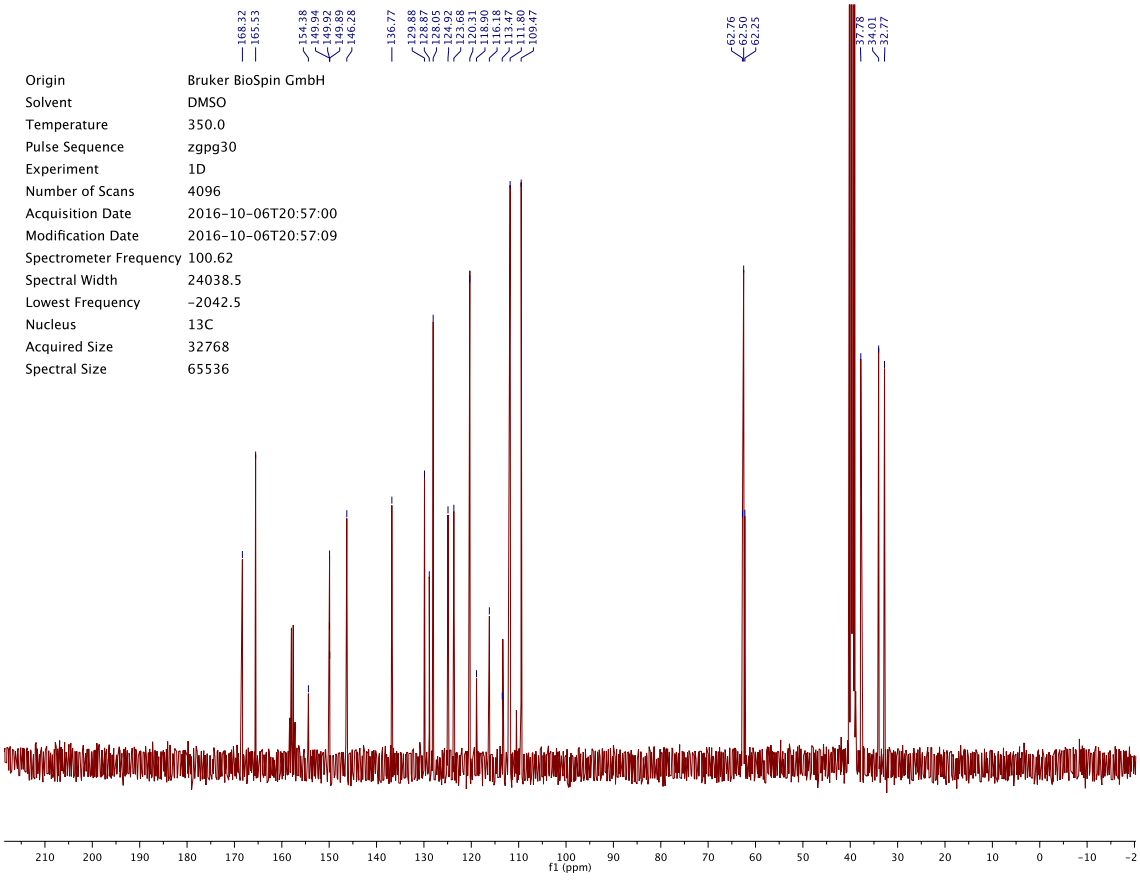
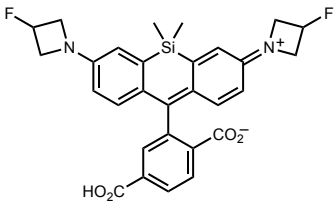
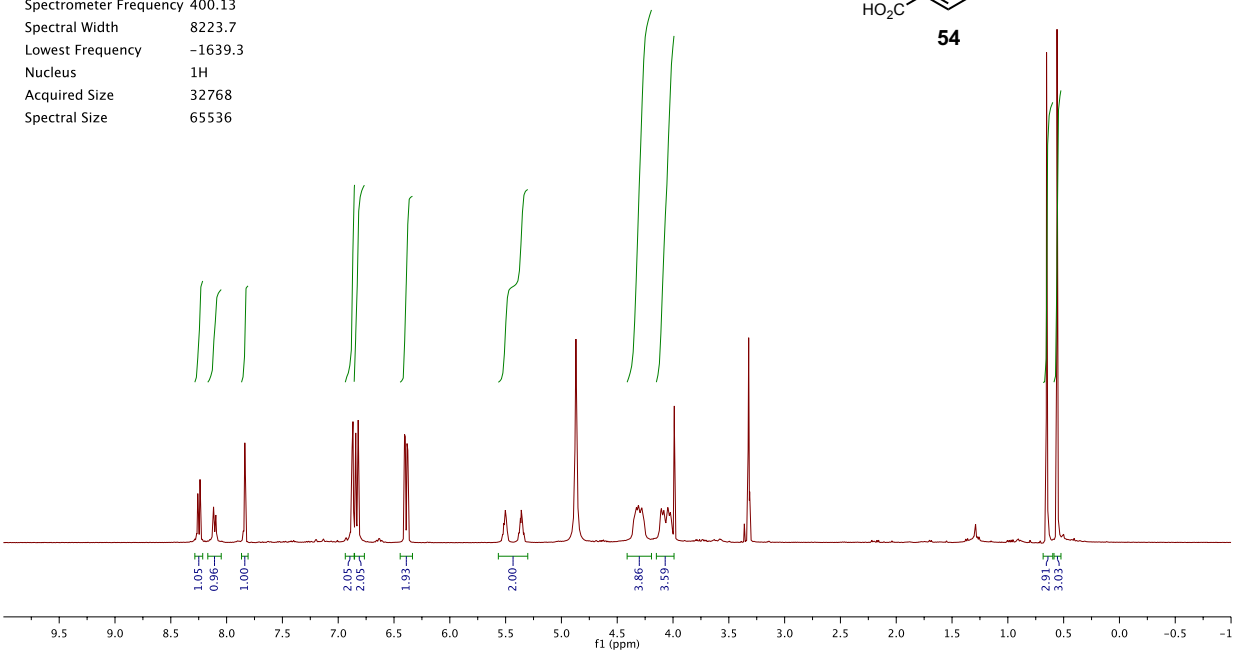


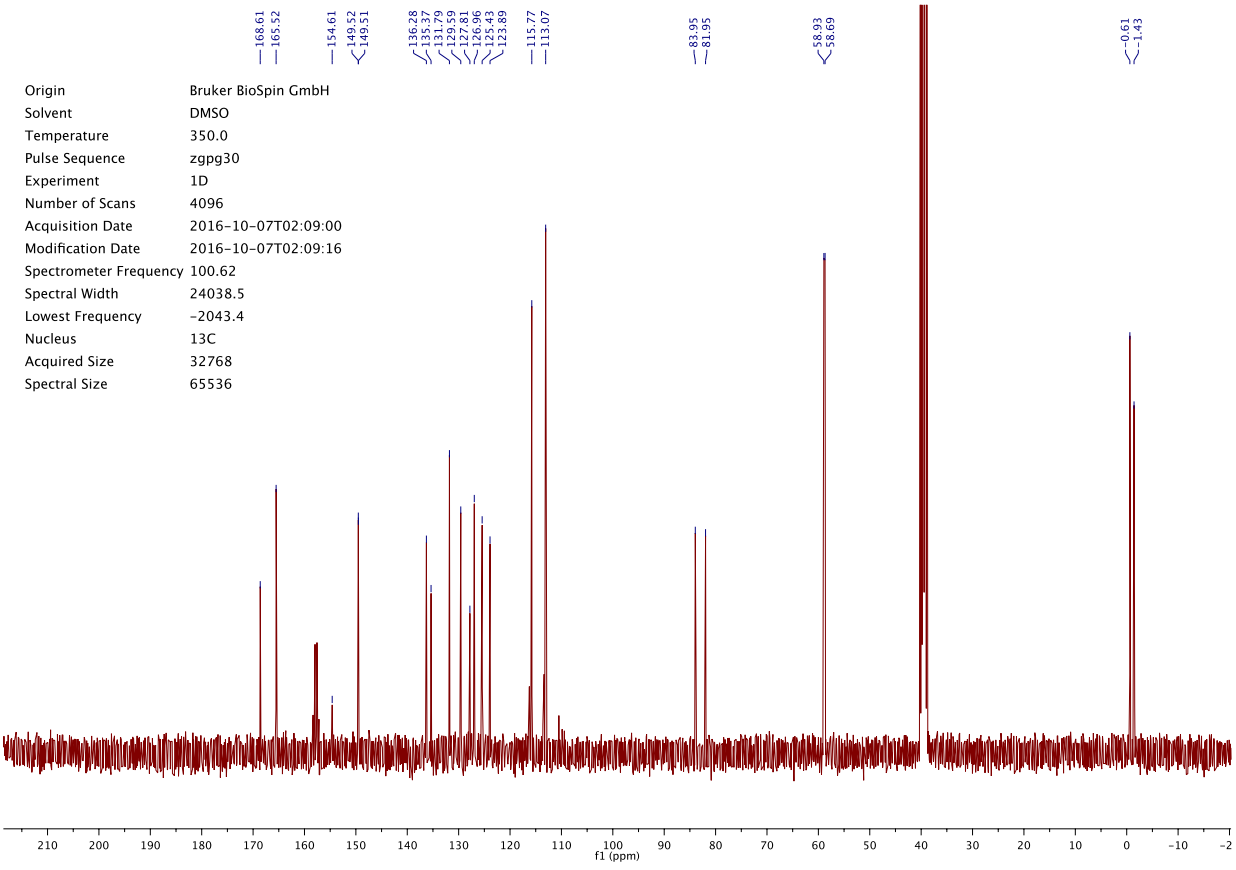
Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	350.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	4096
Acquisition Date	2016-10-06T20:57:00
Modification Date	2016-10-06T20:57:09
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-2042.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2015-02-24T17:52:00
Modification Date	2015-02-24T17:52:46
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1639.3
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



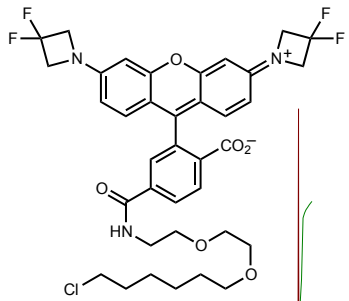
54





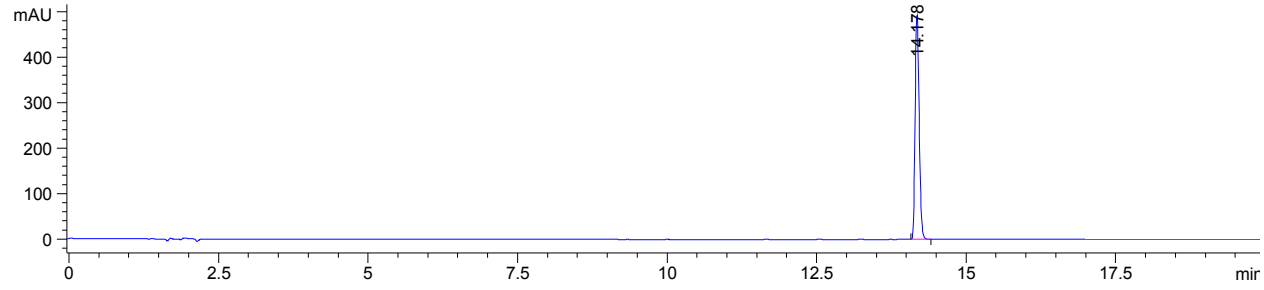
Origin	Bruker BioSpin GmbH
Solvent	DMSO
Temperature	350.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	4096
Acquisition Date	2016-10-07T02:09:00
Modification Date	2016-10-07T02:09:16
Spectrometer Frequency	100.62
Spectral Width	24038.5
Lowest Frequency	-2043.4
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2015-01-30T17:19:00
Modification Date	2015-01-30T17:19:30
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1646.2
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



13

DAD1 C, Sig=550,8 Ref=off (2015_01\DAILYSQUENCE_LC 2015-01-07 12-41-09\2015_01000007.D)



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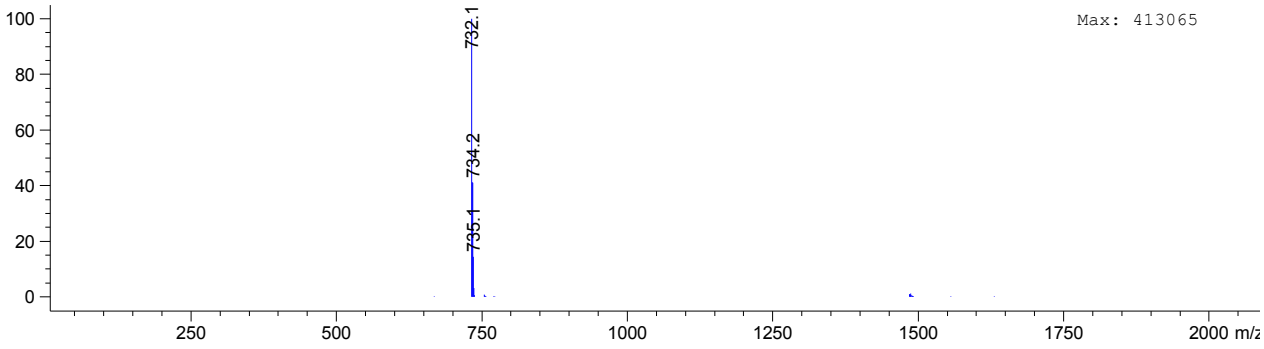
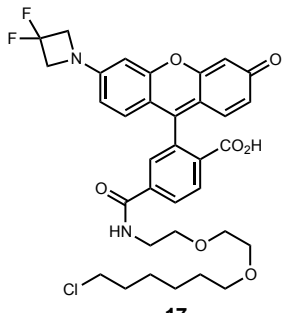
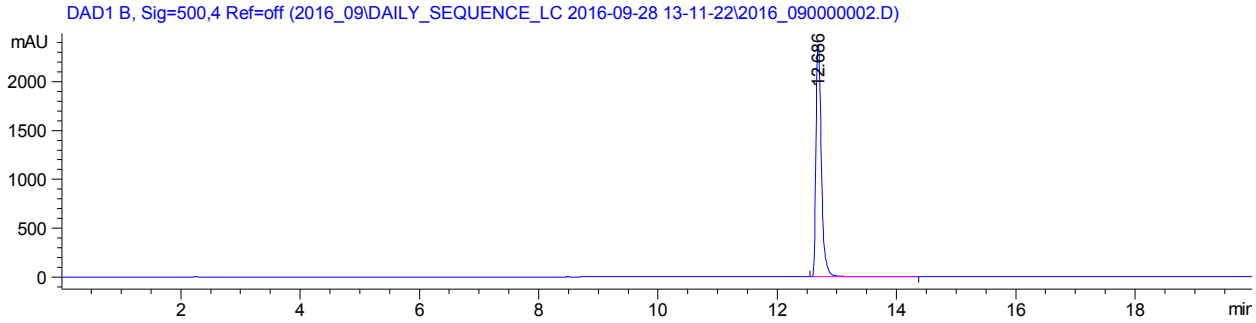
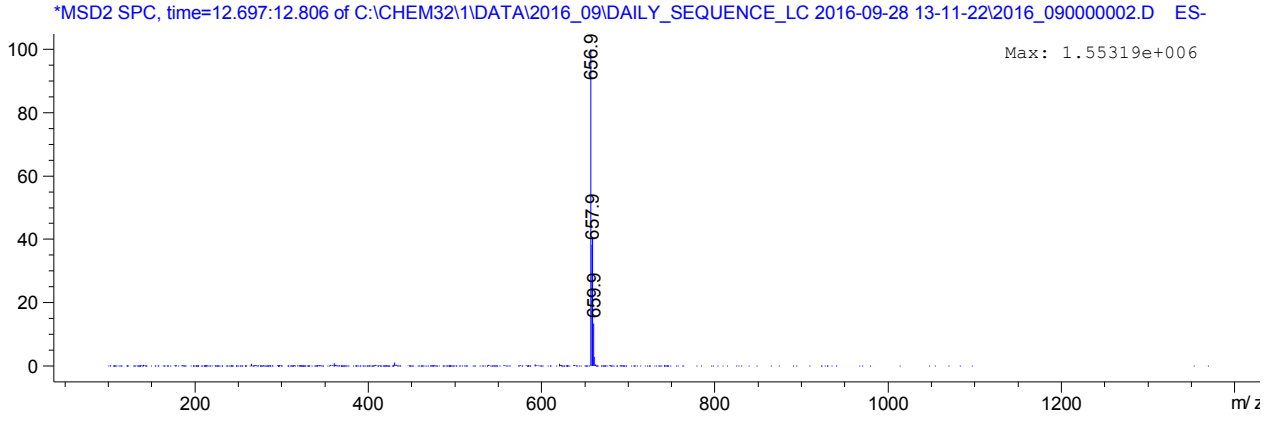


Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2016-10-03T10:13:00
Modification Date	2016-10-03T10:13:36
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1543.3
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

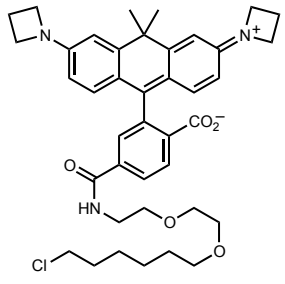


17

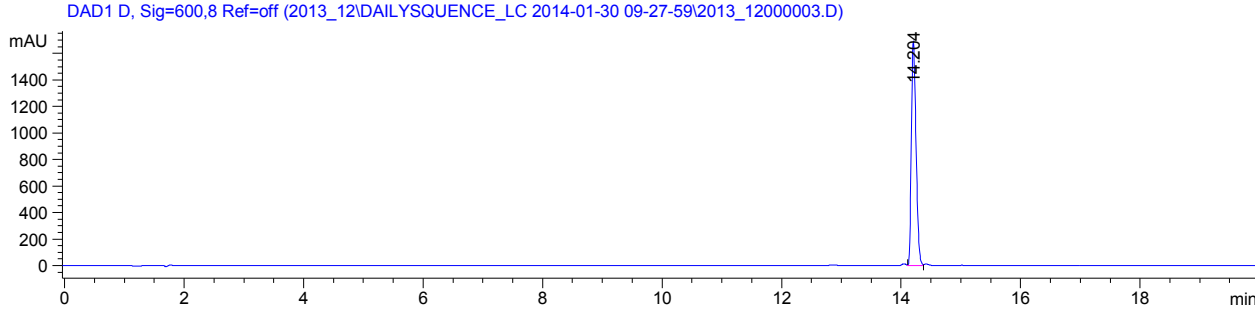


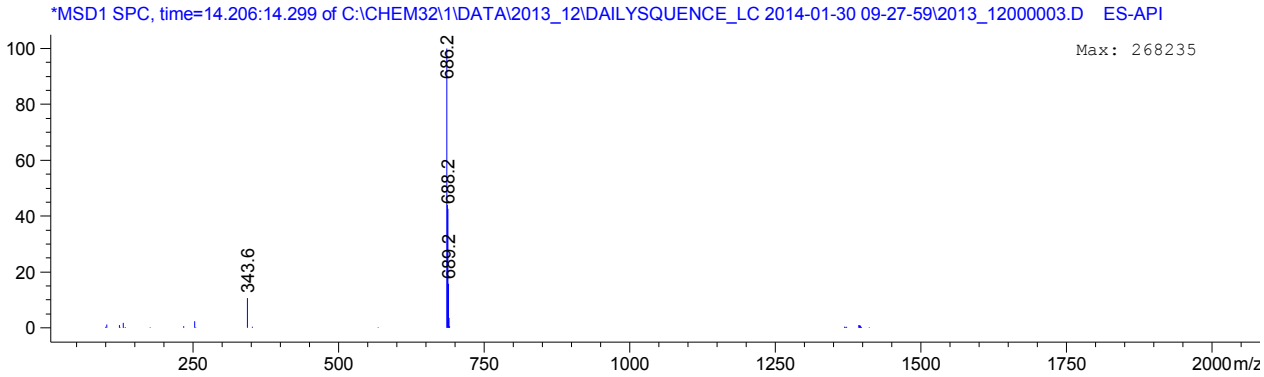


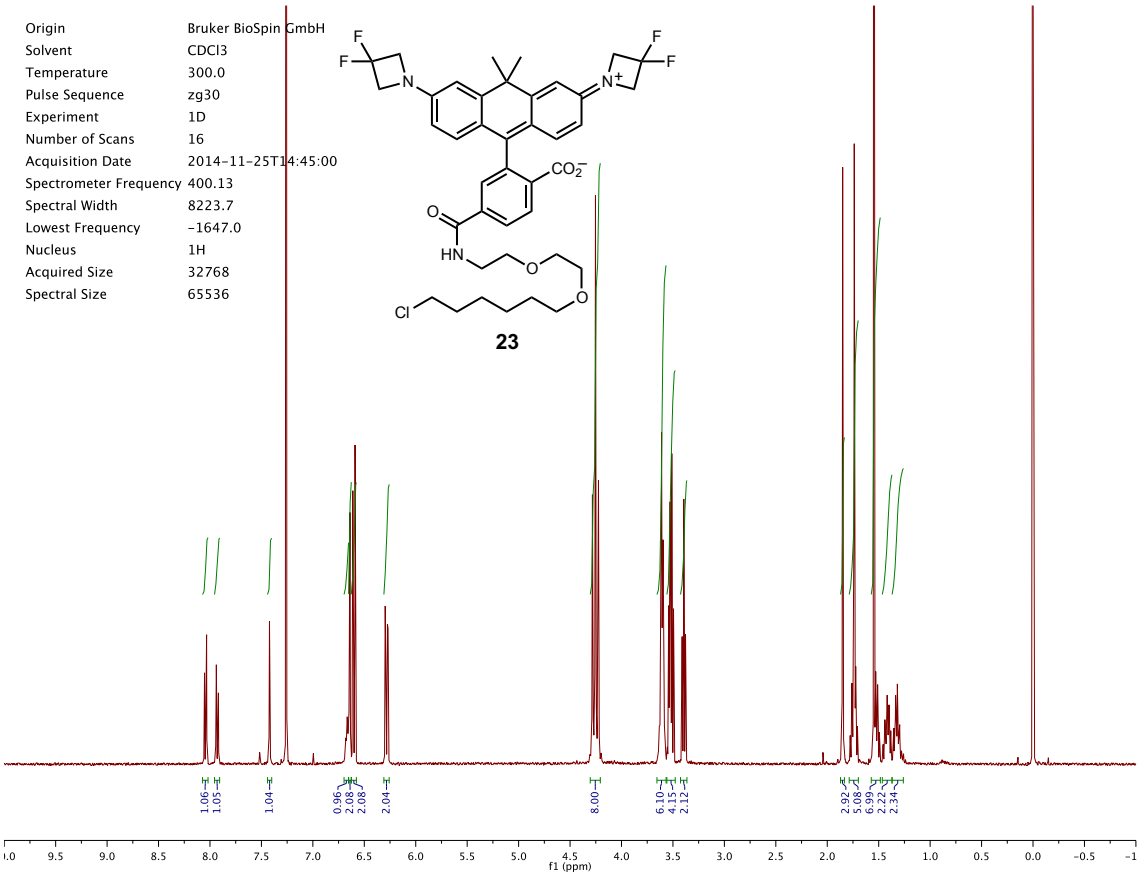
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2014-01-31T08:45:00
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1645.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

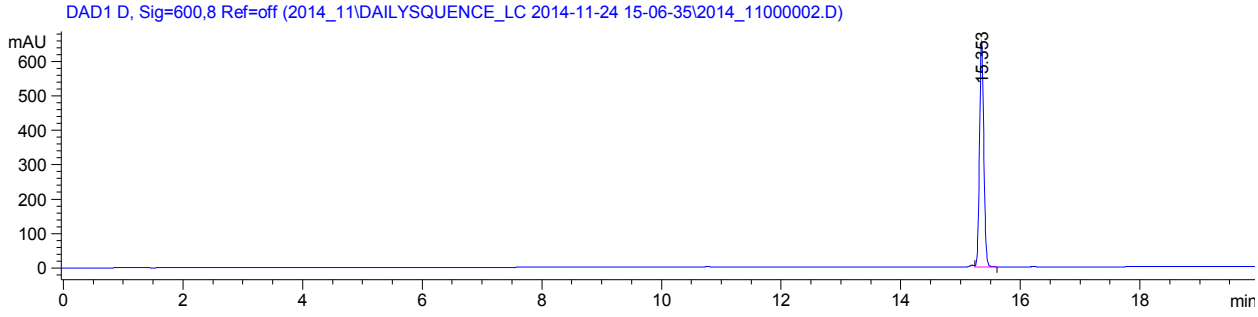


22






Origin Bruker BioSpin GmbH
Solvent CDCl3
Temperature 300.0
Pulse Sequence zg30
Experiment 1D
Number of Scans 16
Acquisition Date 2014-11-25T14:45:00
Spectrometer Frequency 400.13
Spectral Width 8223.7
Lowest Frequency -1647.0
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
23
f1 (ppm)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mAU
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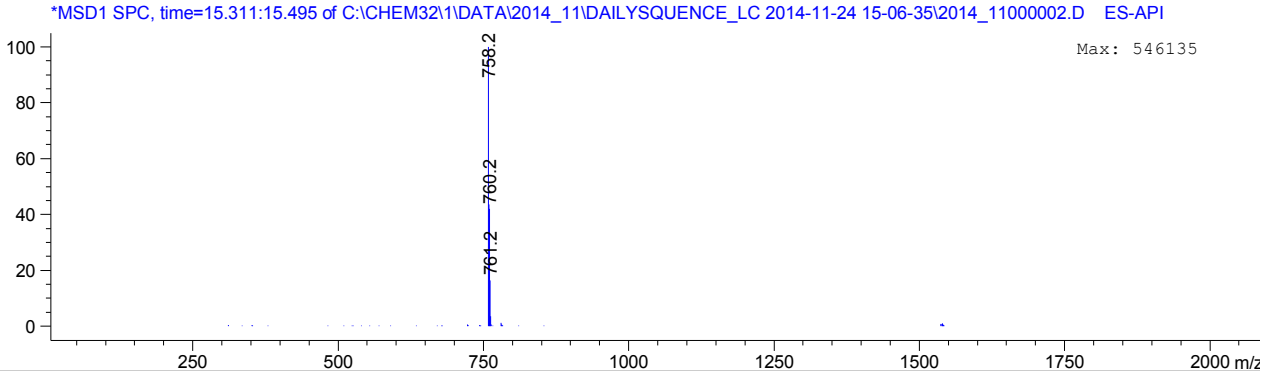
min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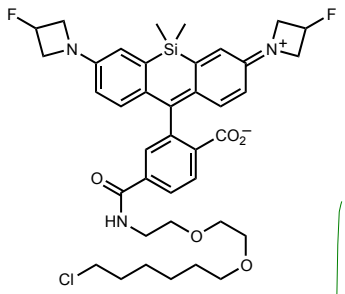
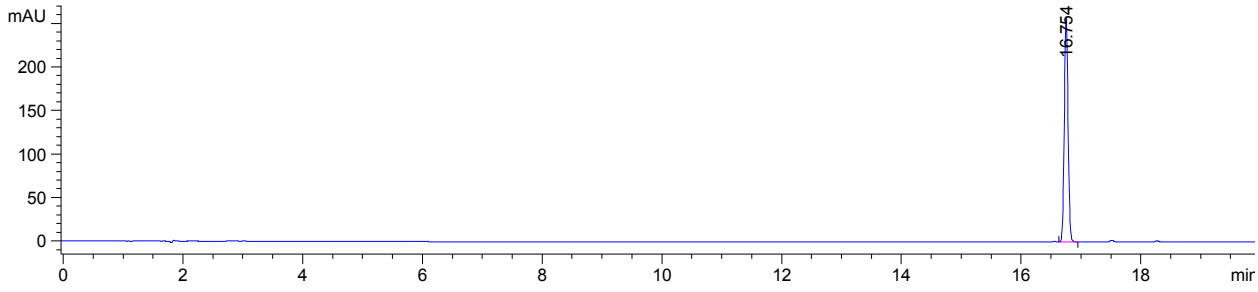
Max: 546135
758.2
760.2
761.2
m/z

Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2015-03-16T12:57:00
Modification Date	2015-03-16T12:57:06
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1646.2
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



27

DAD1 D, Sig=633,8 Ref=off (2015_03\DAILYSQUENCE_LC 2015-03-16 13-12-15\2015_03000010.D)



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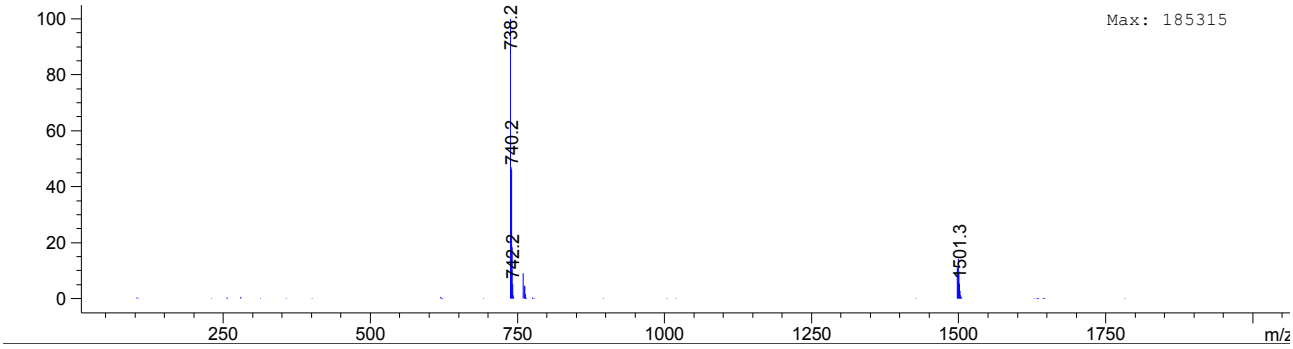
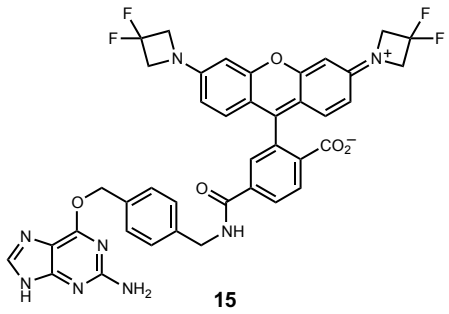
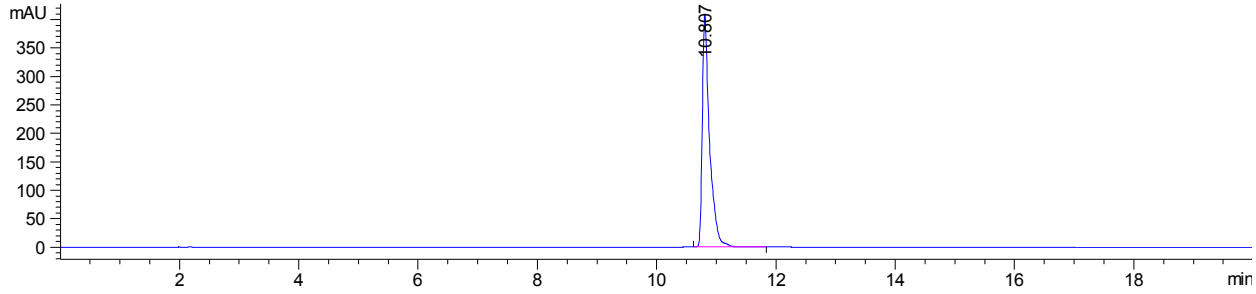


Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2015-05-18T15:44:00
Modification Date	2015-05-18T15:44:33
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1644.2
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



15

DAD1 C, Sig=550,4 Ref=off (2016_11\DAILY_SEQUENCE_LC 2016-11-28 09-43-52\2016_110000003.D)



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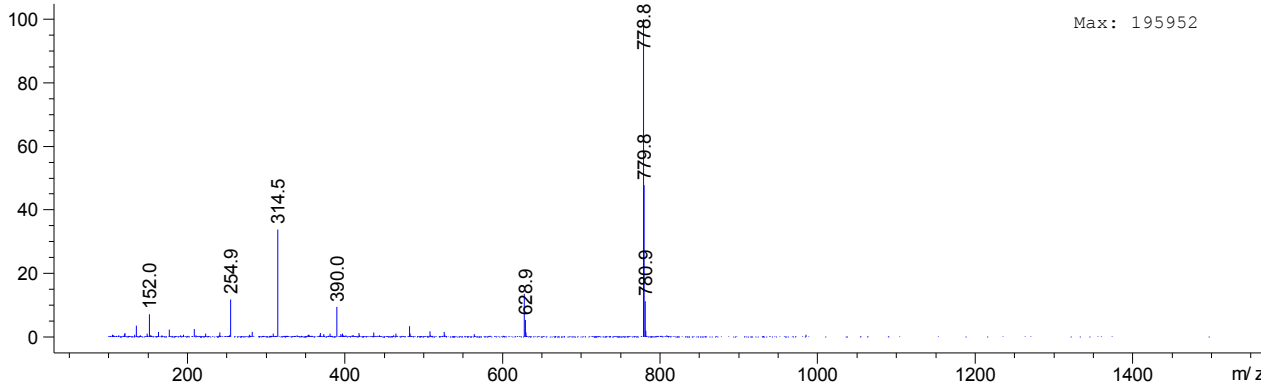
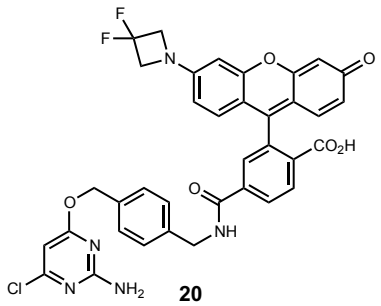


Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2016-11-28T12:25:00
Modification Date	2016-11-28T12:25:02
Spectrometer Frequency	400.13
Spectral Width	8012.8
Lowest Frequency	-1543.0
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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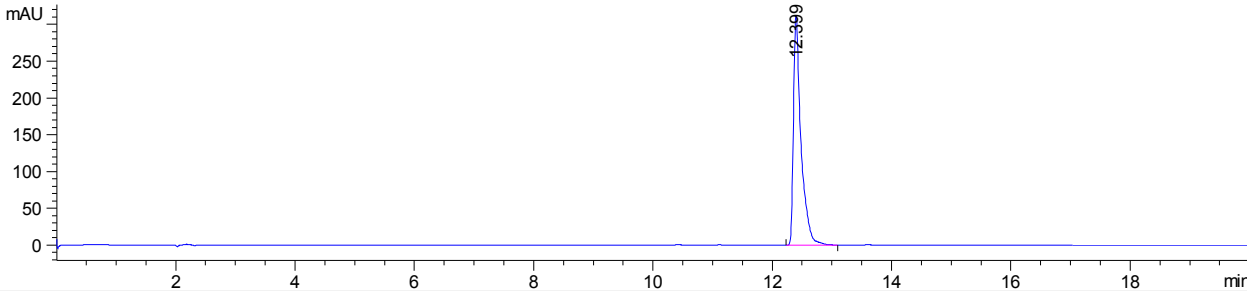
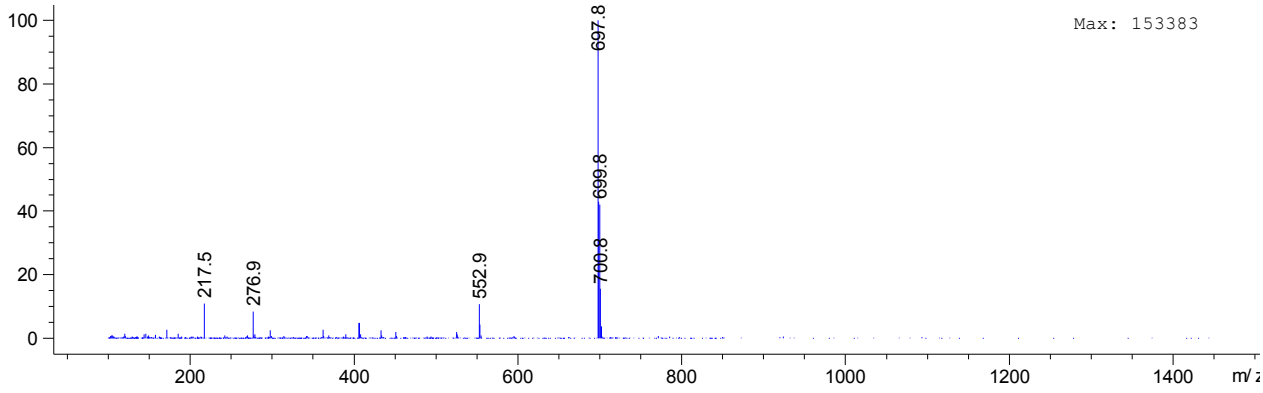
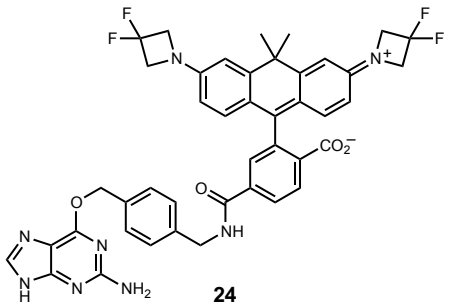
DAD1 B, Sig=500,4 Ref=off (2016_11\DAILY_SEQUENCE_LC 2016-11-28 09-43-52\2016_110000004.D)



*MSD2 SPC, time=12.406:12.588 of C:\CHEM32\1\DATA\2016_11\DAILY_SEQUENCE_LC 2016-11-28 09-43-52\2016_110000004.D ES-



Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Acquisition Date	2015-05-26T09:06:00
Modification Date	2015-05-26T09:06:27
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1644.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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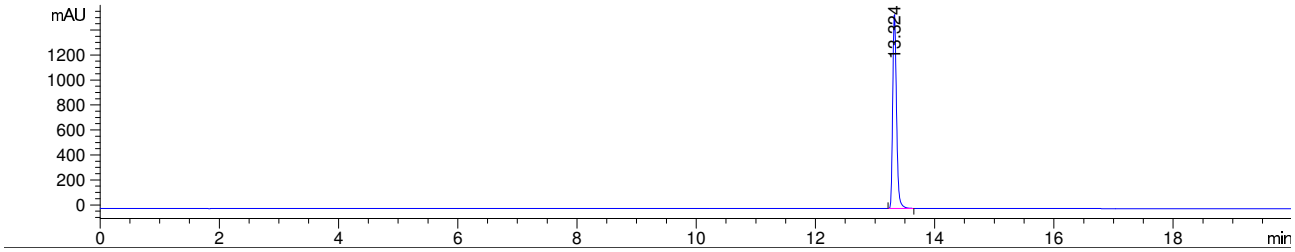
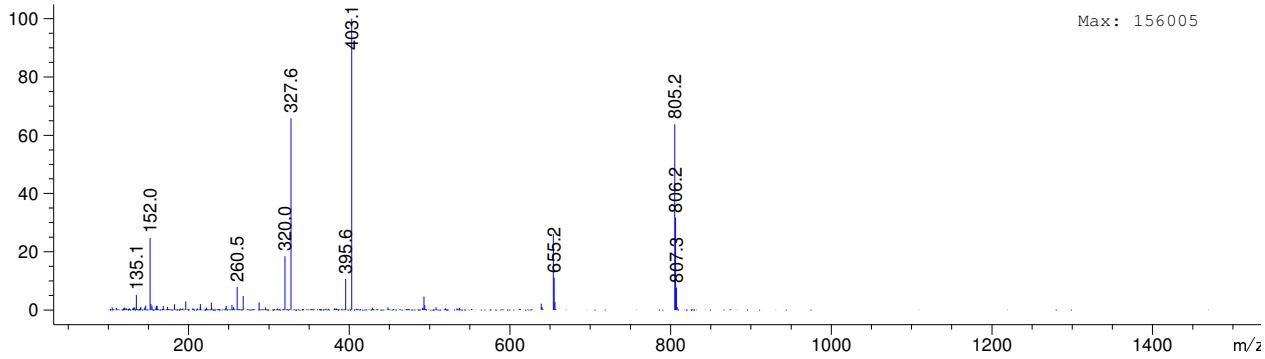
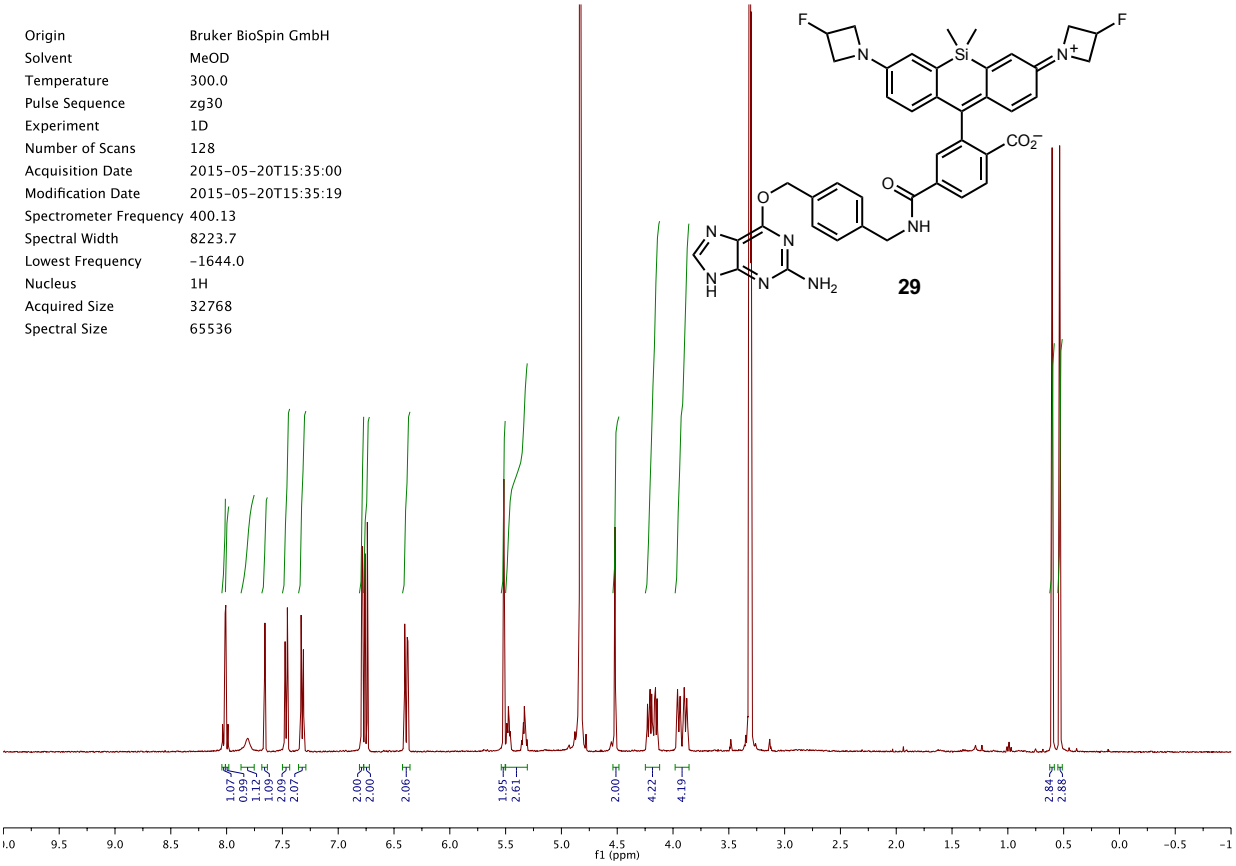
DAD1 D, Sig=600,4 Ref=off (2016_01\DAILY_SEQUENCE_LC 2016-01-11 15-33-37\2016_010000005.D)



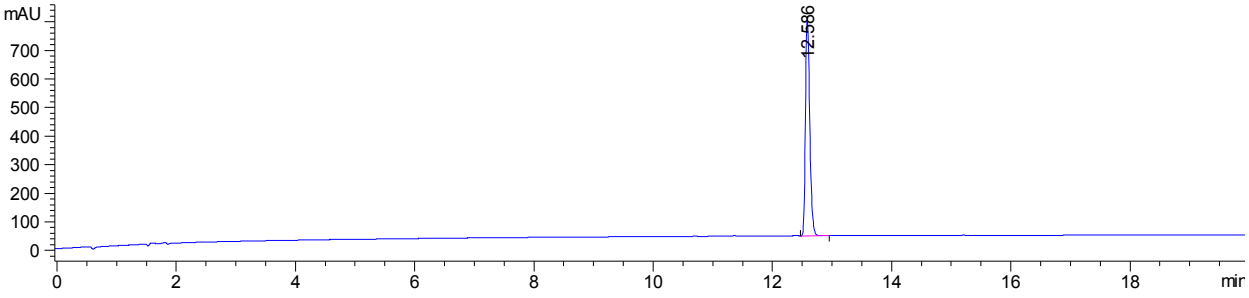
*MSD2 SPC, time=13.314:13.424 of C:\CHEM32\1\DATA\2016_01\DAILY_SEQUENCE_LC 2016-01-11 15-33-37\2016_010000005.D ES-



Origin	Bruker BioSpin GmbH
Solvent	MeOD
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	128
Acquisition Date	2015-05-20T15:35:00
Modification Date	2015-05-20T15:35:19
Spectrometer Frequency	400.13
Spectral Width	8223.7
Lowest Frequency	-1644.0
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



DAD1 D, Sig=633,8 Ref=off (E:\AGILENT...DATA\2015_05\DAILYSQUENCE_LC 2015-05-20 12-37-40\2015_05000001.D)



*MSD1 SPC, time=12.580:12.673 of E:\AGILENT_DATA_FILE\2015 DATA\2015_05\DAILYSQUENCE_LC 2015-05-20 12-37-40\2015_050000