

In the format provided by the authors and unedited.

A general method to optimize and functionalize red-shifted rhodamine dyes

Jonathan B. Grimm , Ariana N. Tkachuk, Liangqi Xie, Heejun Choi, Boaz Mohar, Natalie Falco, Kathy Schaefer , Ronak Patel, Qinsi Zheng, Zhe Liu , Jennifer Lippincott-Schwartz , Timothy A. Brown and Luke D. Lavis  

Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, VA, USA. ✉e-mail: lavisl@janelia.hhmi.org

SUPPLEMENTARY NOTE

A general method to optimize and functionalize red-shifted rhodamine dyes

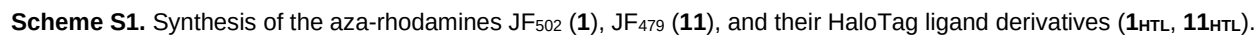
Jonathan B. Grimm, Ariana N. Tkachuk, Lianqi Xie, Heejun Choi, Boaz Mohar,
Natalie Falco, Kathy Schaefer, Ronak Patel, Qinsi Zheng, Zhe Liu,
Jennifer Lippincott-Schwartz, Timothy A. Brown, and Luke D. Lavis*

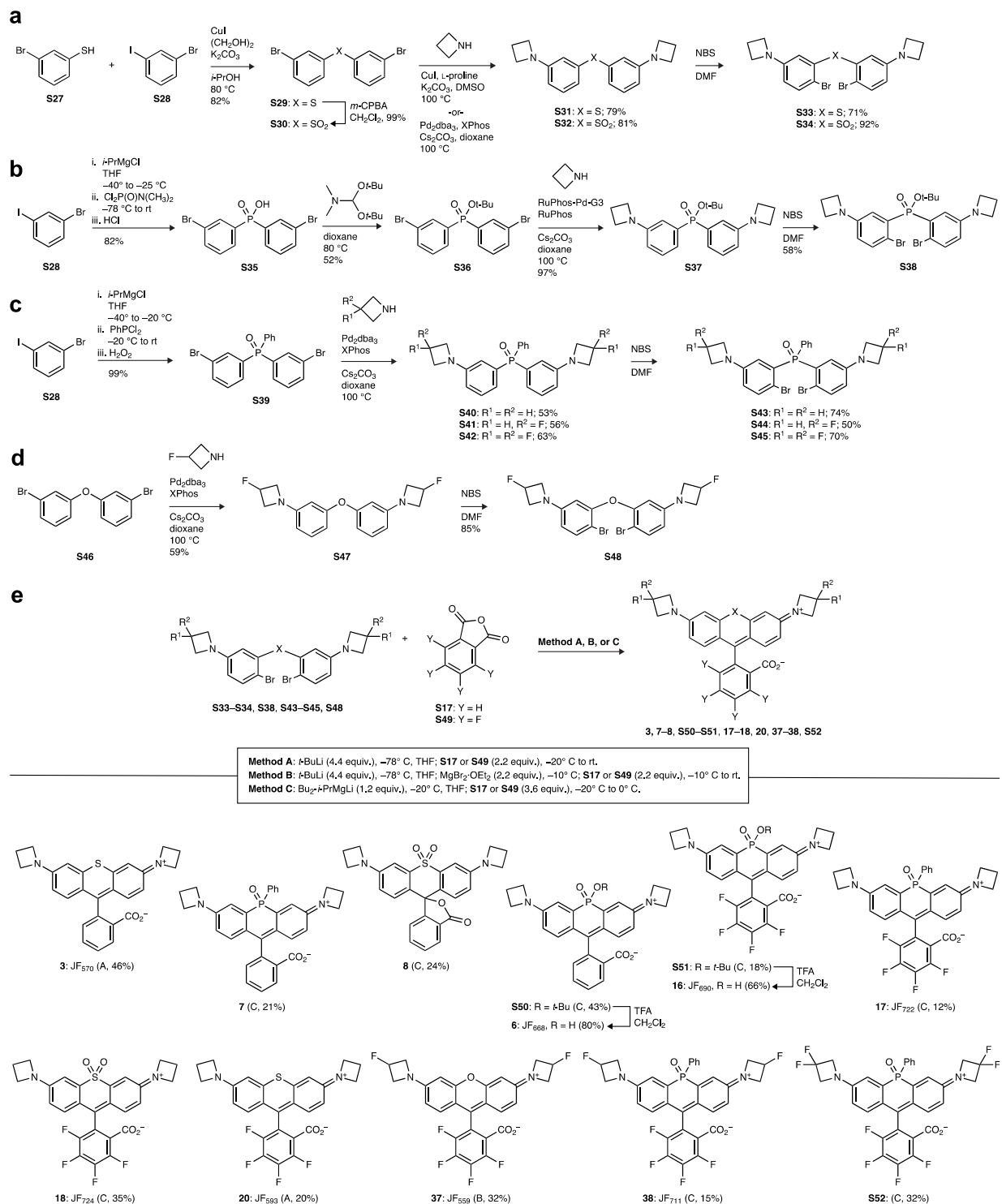
*Janelia Research Campus, Howard Hughes Medical Institute,
Ashburn, VA 20147, USA*

Email: lavisl@janelia.hhmi.org

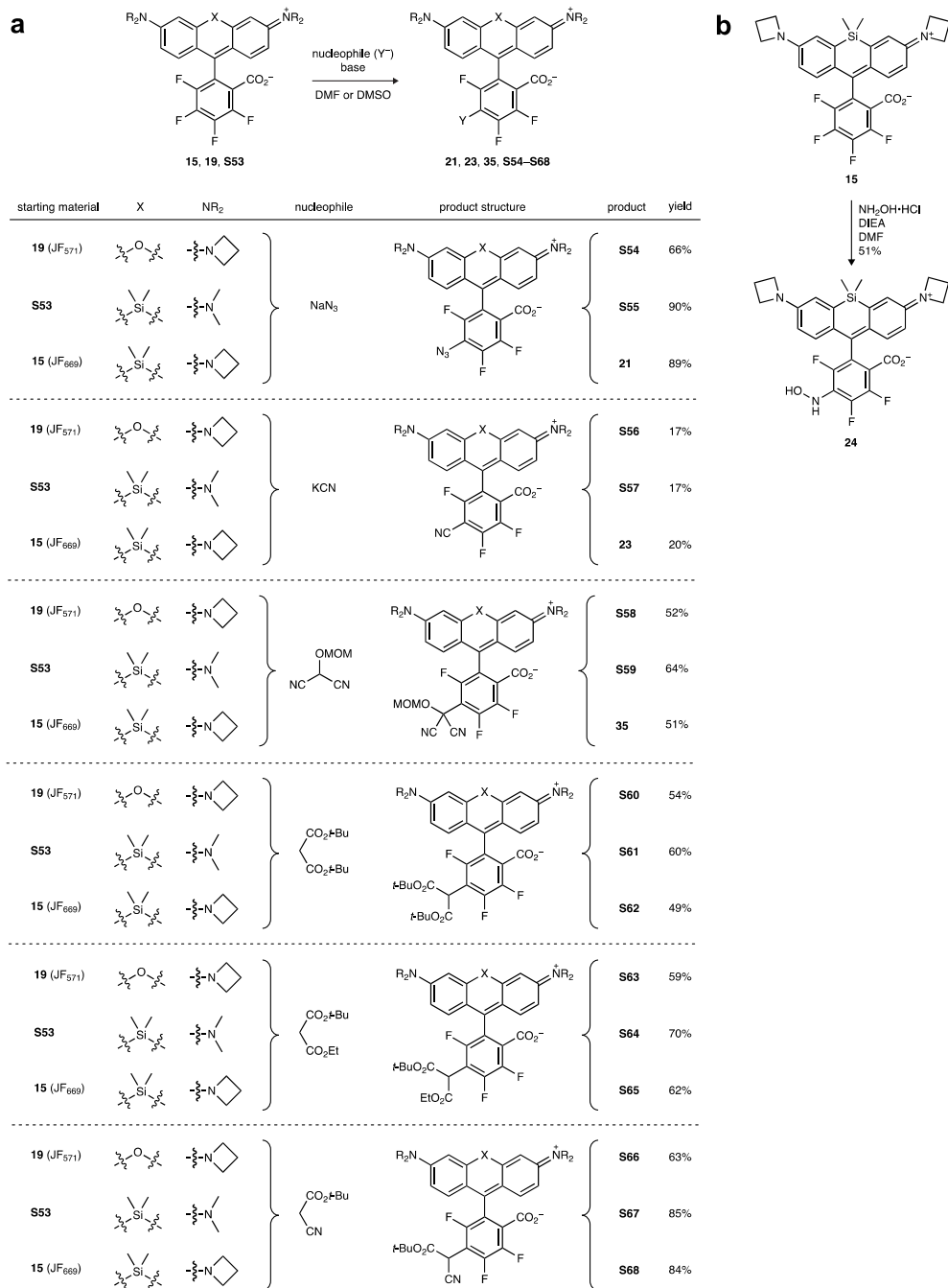
EXPERIMENTAL INFORMATION

Page	Contents
S2	Schemes S1–S5
S6	General Experimental Information for Synthesis
S7–S65	Experimentals and Characterization Data for All Compounds
S7	Preparation of Dibromide Intermediates
S22	Rhodamine Synthesis via Metal–Bromide Exchange of Dibromides
S33	Aza-Rhodamine HaloTag Ligands and Rhodamine SNAP-tag Ligands
S36	MAC Substitution of 4,5,6,7-Tetrafluororhodamines
S42	Conversion of MAC Substitution Products to Amides and Esters
S54	Substitution of 4,5,6,7-Tetrafluororhodamines with Other Nucleophiles
S65	Cycloadditions of 6-Azido-JF ₆₆₉
S66	X-Ray Crystallography
S69	NMR and HPLC/MS

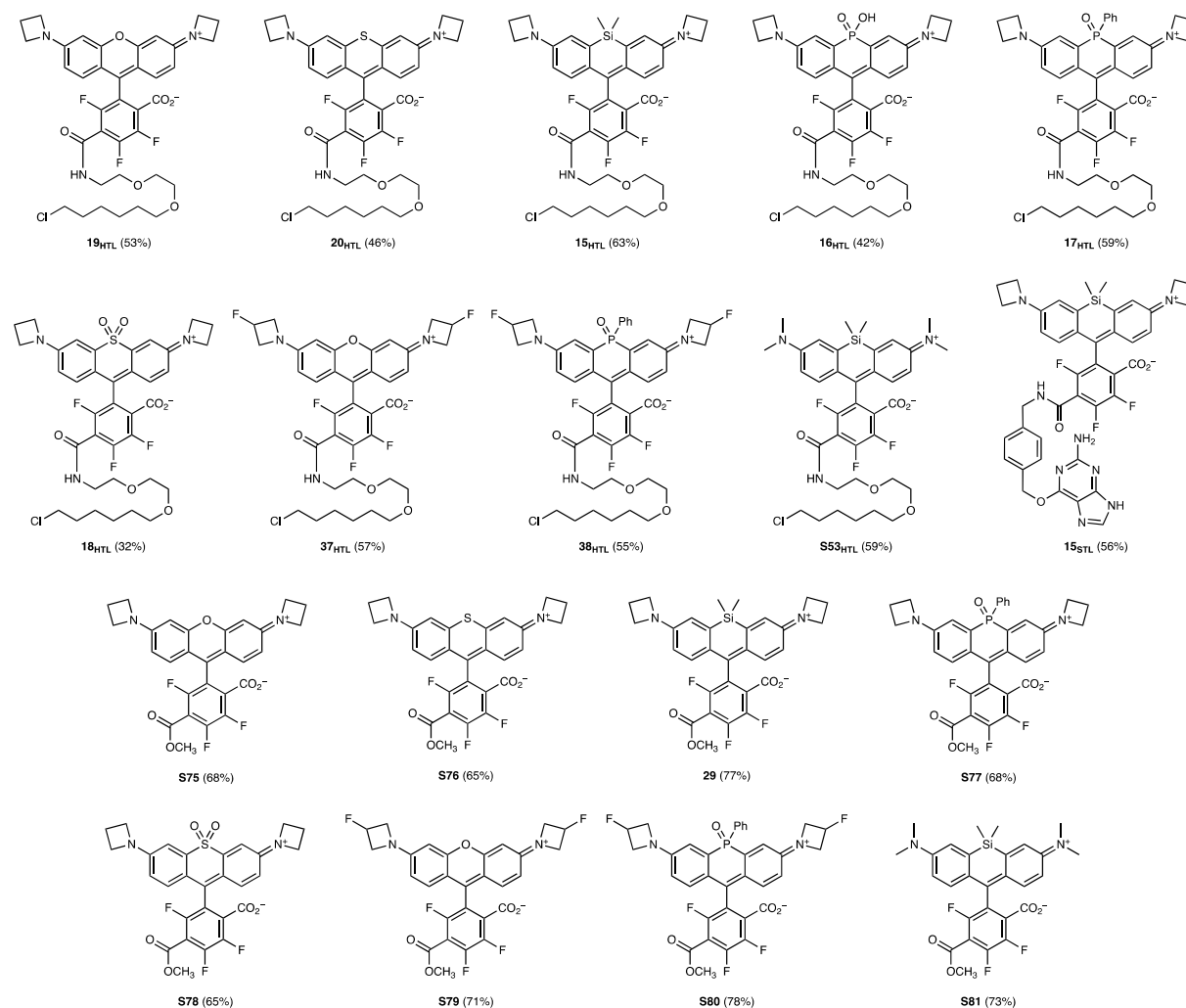
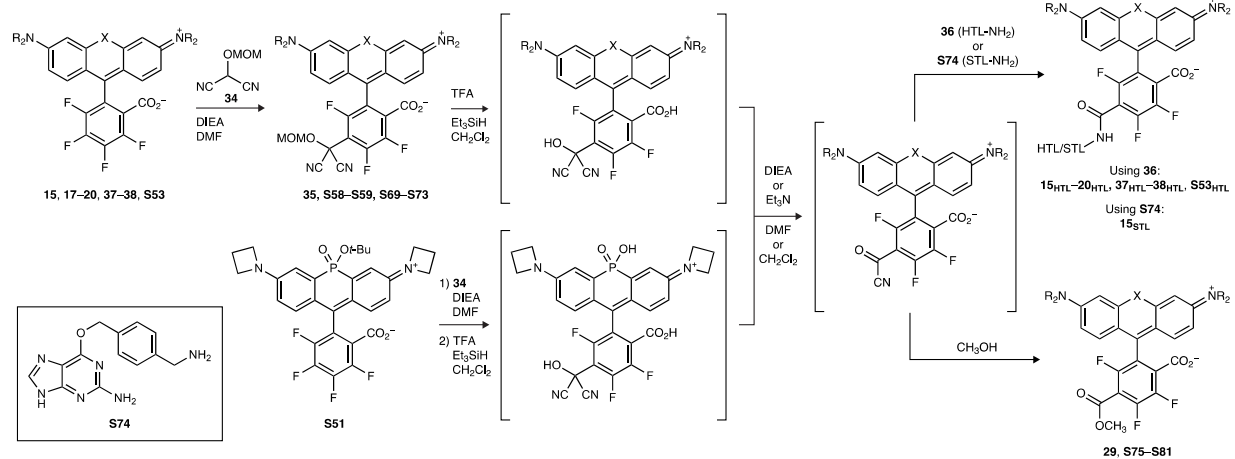




Scheme S3. (a) Synthesis of sulfide and sulfone dibromides **S33** and **S34**. (b) Synthesis of phosphinate dibromide **S38**. (c) Synthesis of phosphine oxide dibromides **S43–S45**. (d) Synthesis of ether dibromide **S48**. (e) Synthesis of heteroatom-containing rhodamines **3**, **7–8**, **S50–S51**, **17–18**, **20**, **37–38**, and **S52** via metal–bromide exchange of the dibromides described in (a–d) and addition to anhydrides **S17** or **S49**; TFA-mediated *tert*-butyl phosphinate deprotection of **S50** and **S51** yielded phosphinic acids **6** and **16**.



Scheme S4. (a) Nucleophilic substitution (S_NAr) reactions of 4,5,6,7-tetrafluororhodamines (**15**, **19**, and **S53**) with various nucleophiles. (b) Synthesis of hydroxylamine **24** from JF₆₆₉ (**15**).



Scheme S5. Substitution of 4,5,6,7-tetrafluororhodamines with masked acyl cyanide (MAC) reagent **34** and subsequent derivatization to access HaloTag and SNAP-tag ligand labels and methyl ester analogs.

GENERAL EXPERIMENTAL INFORMATION FOR SYNTHESIS

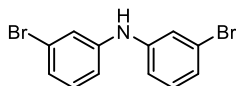
Commercial reagents were obtained from reputable suppliers and used as received. All solvents were purchased in septum-sealed bottles stored under an inert atmosphere. All reactions were sealed with septa through which a nitrogen atmosphere was introduced unless otherwise noted. Reactions were conducted 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 F₂₅₄, 250 μ m thickness) or by LC/MS (Phenomenex Kinetex 2.1 mm $\times$ 30 mm 2.6 μ m C18 column; 5 μ L injection; 5–98% MeCN/H₂O, linear gradient, with constant 0.1% v/v HCO₂H 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 KMnO₄ 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 $\times$ 150 mm 5 μ m C18 column). Analytical HPLC analysis was performed with an Agilent Eclipse XDB 4.6 $\times$ 150 mm 5 μ m C18 column under the indicated conditions. High-resolution mass spectrometry was performed by the High Resolution Mass Spectrometry Facility at the University of Iowa.

NMR spectra were recorded on a 400 MHz spectrometer. ¹H and ¹³C chemical shifts were referenced to TMS or residual solvent peaks, and ¹⁹F chemical shifts were referenced to CFCl₃. Data for ¹H 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 ¹³C NMR spectra are reported by chemical shift (δ ppm) with hydrogen multiplicity (C, CH, CH₂, CH₃) information obtained from DEPT spectra. The ¹³C NMR spectra are not reported for compounds containing trifluoro- or tetrafluoro-substituted aryl rings, as the numerous distinct fluorine couplings confounded interpretation of the spectra.

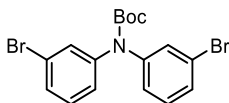
PREPARATION OF DIBROMIDE INTERMEDIATES

We previously described a new strategy for the efficient synthesis of Si-fluoresceins and Si-rhodamines through metal–bromide exchange of bis(2-bromophenyl)silanes and double addition of the resulting bis(arylmethyl) species to anhydrides.^[1] Given the success of this approach, we sought to apply the same methodology to the synthesis of the rhodamines with heteroatom substitution at the 10-position described in this report (**Fig. 1c**). **Scheme S1** and **Scheme S3** depict the routes used to access the necessary dibromides. In each case, a bis(3-bromophenyl) species (**S3**, **Scheme S1**; **S29**, **S35**, **S39**, **S46**, **Scheme S3**) was prepared through either a Chan–Lam coupling (nitrogen, **S3**; oxygen, **S46**),^[1] an Ullmann-type coupling (sulfur, **S29**), or the addition of 3-bromophenyl Grignard to a phosphoryl dichloride (phosphinate, **S35**) or dichlorophosphine (phosphine oxide, **S39**). The azetidine substituents were then installed through Pd- or Cu-catalyzed C–N cross-coupling of these bis(3-bromophenyl) intermediates. Dibromination of the bis(3-azetidin-1-yl) cross-coupling products **S5–S7**, **S31–S32**, **S37**, **S40–S42**, and **S47** was achieved with good to excellent regioselectivity using NBS in DMF. For the sulfur, phosphorus, and oxygen analogs (**Scheme S3a–d**), this directly provided the desired dibromides (**S33–S34**, **S38**, **S43–S45**, and **S48**) for metal–bromide exchange. In the case of the nitrogen analogs (**Scheme S1**), acceptable regioselectivity in the NBS bromination was only achieved when the central nitrogen was acylated (*i.e.*, Boc-protected). Following bromination, the Boc group was removed and the nitrogen alkylated to afford the necessary *N*-methyl dibromides **S14–S16**.

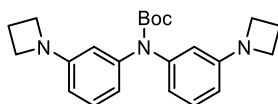


Bis(3-bromophenyl)amine (S3): An oven-dried round-bottom flask was charged with 3-bromophenylboronic acid (**S2**; 4.67 g, 23.3 mmol, 2 eq), Cu(OAc)₂ (2.11 g, 11.6 mmol, 1 eq), and 4 Å molecular sieves (10.00 g). After adding CH₂Cl₂ (50 mL), 3-bromoaniline (**S1**; 2.00 g, 11.6 mmol), and Et₃N (3.24 mL, 23.3 mmol, 2 eq), the reaction was stirred at room temperature under ambient atmosphere for 48 h. The reaction mixture was filtered through Celite with CH₂Cl₂ and concentrated to dryness. The resultant residue was partitioned between saturated NH₄Cl and Et₂O, and the aqueous layer was washed a second time with Et₂O. The combined organics were dried over anhydrous MgSO₄, filtered, and evaporated. Flash chromatography on silica gel (0–15% EtOAc/hexanes, linear gradient) provided dibromide **S3** as a yellow oil (3.64 g, 96%). ¹H NMR (CDCl₃, 400 MHz) δ 7.20 (t, *J* = 2.0 Hz, 2H), 7.13 (t, *J* = 7.9 Hz, 2H), 7.10 – 7.05 (m, 2H), 7.00 – 6.95 (m, 2H), 5.69 (s, 1H); ¹³C NMR (CDCl₃, 101 MHz) δ 143.9 (C), 130.9 (CH), 124.7 (CH), 123.3 (C), 121.0 (CH), 116.8 (CH); HRMS (ESI) calcd for C₁₂H₁₀Br₂N [M+H]⁺ 325.9175, found 325.9188.

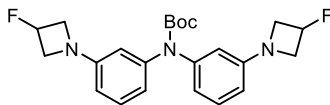
^[1] Grimm, J. B.; Brown, T. A.; Tkachuk, A. N.; Lavis, L. D. *ACS Cent. Sci.* **2017**, 3, 975–985.



tert-Butyl bis(3-bromophenyl)carbamate (S4): Aniline **S3** (3.35 g, 10.2 mmol) was taken up in CH₂Cl₂ (50 mL); Et₃N (2.86 mL, 20.5 mmol, 2 eq), Boc₂O (3.35 g, 15.4 mmol, 1.5 eq), and DMAP (125 mg, 1.02 mmol, 0.1 eq) were added, and the reaction was stirred at room temperature for 18 h. It was subsequently diluted with water and extracted with CH₂Cl₂ (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Silica gel chromatography (0–5% Et₂O/hexanes, linear gradient) provided 3.78 g (86%) of carbamate **S4** as a pale yellow gum. ¹H NMR (CDCl₃, 400 MHz) δ 7.37 (t, *J* = 1.9 Hz, 2H), 7.34 (ddd, *J* = 7.9, 1.9, 1.1 Hz, 2H), 7.20 (t, *J* = 7.9 Hz, 2H), 7.12 (ddd, *J* = 8.1, 2.1, 1.1 Hz, 2H), 1.45 (s, 9H); ¹³C NMR (CDCl₃, 101 MHz) δ 153.2 (C), 143.8 (C), 130.18 (CH), 130.16 (CH), 129.2 (CH), 125.8 (CH), 122.3 (C), 82.3 (C), 28.3 (CH₃); HRMS (ESI) calcd for C₁₇H₁₇Br₂NO₂Na [M+Na]⁺ 447.9518, found 447.9533.

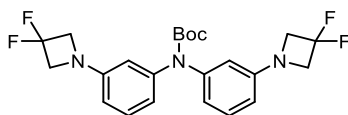


tert-Butyl bis(3-(azetidin-1-yl)phenyl)carbamate (S5): An oven-dried round-bottom flask was charged with CuI (259 mg, 1.36 mmol, 0.2 eq), L-proline (313 mg, 2.72 mmol, 0.4 eq), and K₂CO₃ (3.75 g, 27.2 mmol, 4 eq). The flask was sealed and evacuated/backfilled with nitrogen (3×). A solution of dibromide **S4** (2.90 g, 6.79 mmol) in DMSO (27 mL) was added, and the reaction was flushed again with nitrogen (3×). Following the addition of azetidine (2.75 mL, 40.7 mmol, 6 eq), the reaction was stirred at 100 °C for 18 h. It was then cooled to room temperature, diluted with saturated NH₄Cl, and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (0–50% EtOAc/hexanes, linear gradient) afforded **S5** (2.21 g, 86%) as a yellow gum. ¹H NMR (CDCl₃, 400 MHz) δ 7.09 (t, *J* = 8.0 Hz, 2H), 6.55 (ddd, *J* = 7.9, 2.0, 0.9 Hz, 2H), 6.31 (t, *J* = 2.2 Hz, 2H), 6.24 (ddd, *J* = 8.1, 2.3, 0.9 Hz, 2H), 3.82 (t, *J* = 7.2 Hz, 8H), 2.32 (p, *J* = 7.2 Hz, 4H), 1.45 (s, 9H); ¹³C NMR (CDCl₃, 101 MHz) δ 154.1 (C), 152.7 (C), 143.9 (C), 128.9 (CH), 116.2 (CH), 110.2 (CH), 108.8 (CH), 80.8 (C), 52.5 (CH₂), 28.5 (CH₃), 17.0 (CH₂); HRMS (ESI) calcd for C₂₃H₃₀N₃O₂ [M+H]⁺ 380.2333, found 380.2333.

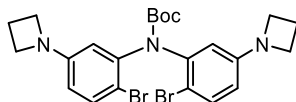


tert-Butyl bis(3-(3-fluoroazetidin-1-yl)phenyl)carbamate (S6): An oven-dried round-bottom flask was charged with 3-fluoroazetidine hydrochloride (4.23 g, 37.9 mmol, 2.4 eq), Pd₂dba₃ (1.45 g, 1.58 mmol, 0.1 eq), XPhos (2.26 g, 4.74 mmol, 0.3 eq), and Cs₂CO₃ (24.72 g, 75.9 mmol, 4.8 eq). The flask was sealed and evacuated/backfilled with nitrogen (3×). A solution of dibromide **S4** (6.75 g, 15.8 mmol) in dioxane (80 mL) was added, and after flushing the reaction again with nitrogen (3×), it was stirred at 100 °C for 18 h. It was then cooled to room temperature, filtered through Celite with CH₂Cl₂, and concentrated to dryness. Purification by flash chromatography (0–50%

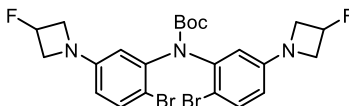
EtOAc/hexanes, linear gradient) provided **S6** as a yellow gum (5.50 g, 84%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.13 (t, J = 8.0 Hz, 2H), 6.60 (ddd, J = 7.9, 1.9, 0.8 Hz, 2H), 6.34 (t, J = 2.1 Hz, 2H), 6.28 (ddd, J = 8.1, 2.3, 0.7 Hz, 2H), 5.38 (dtt, $^2J_{\text{HF}}$ = 57.0 Hz, J = 5.9, 3.7 Hz, 2H), 4.20 – 4.07 (m, 4H), 3.98 – 3.84 (m, 4H), 1.45 (s, 9H); ^{19}F NMR (CDCl_3 , 376 MHz) δ –180.65 (dtt, J_{FH} = 57.1, 24.3, 18.1 Hz); ^{13}C NMR (CDCl_3 , 101 MHz) δ 153.9 (C), 151.6 (d, $^4J_{\text{CF}}$ = 1.2 Hz, C), 144.0 (C), 129.2 (CH), 117.1 (CH), 110.7 (CH), 109.4 (CH), 82.9 (d, $^1J_{\text{CF}}$ = 204.7 Hz, CHF), 81.1 (C), 59.7 (d, $^2J_{\text{CF}}$ = 23.5 Hz, CH_2), 28.5 (CH_3); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{27}\text{F}_2\text{N}_3\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 438.1964, found 438.1968.



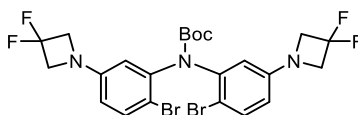
tert-Butyl bis(3-(3,3-difluoroazetidin-1-yl)phenyl)carbamate (S7): An oven-dried round-bottom flask was charged with 3,3-difluoroazetidine hydrochloride (4.88 g, 37.7 mmol, 2.4 eq), Pd_2dba_3 (1.44 g, 1.57 mmol, 0.1 eq), XPhos (2.24 g, 4.71 mmol, 0.3 eq), and Cs_2CO_3 (24.53 g, 75.3 mmol, 4.8 eq). The flask was sealed and evacuated/backfilled with nitrogen (3 $\times$). A solution of dibromide **S4** (6.70 g, 15.7 mmol) in dioxane (80 mL) was added, and after flushing the reaction again with nitrogen (3 $\times$), it was stirred at 100 $^\circ\text{C}$ for 18 h. It was then cooled to room temperature, filtered through Celite with CH_2Cl_2 , and concentrated to dryness. Purification by flash chromatography (0–50% Et_2O /hexanes, linear gradient) provided **S7** as a yellow solid (5.41 g, 76%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.17 (t, J = 8.0 Hz, 2H), 6.66 (ddd, J = 8.0, 1.9, 0.7 Hz, 2H), 6.37 (t, J = 2.2 Hz, 2H), 6.32 (ddd, J = 8.1, 2.3, 0.7 Hz, 2H), 4.18 (t, $^3J_{\text{HF}}$ = 11.8 Hz, 8H), 1.45 (s, 9H); ^{19}F NMR (CDCl_3 , 376 MHz) δ –99.96 (p, $^3J_{\text{FH}}$ = 11.7 Hz); ^{13}C NMR (CDCl_3 , 101 MHz) δ 153.8 (C), 150.21 (t, $^4J_{\text{CF}}$ = 2.7 Hz, C), 144.0 (C), 129.4 (CH), 117.9 (CH), 116.0 (t, $^1J_{\text{CF}}$ = 274.6 Hz, CF_2), 111.1 (CH), 109.9 (CH), 81.3 (C), 63.5 (t, $^2J_{\text{CF}}$ = 25.7 Hz, CH_2), 28.5 (CH_3); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{25}\text{F}_4\text{N}_3\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 474.1775, found 474.1785.



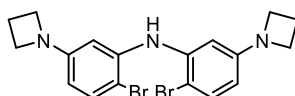
tert-Butyl bis(5-(azetidin-1-yl)-2-bromophenyl)carbamate (S8): Carbamate **S5** (425 mg, 1.12 mmol) was taken up in DMF (10 mL). *N*-Bromosuccinimide (399 mg, 2.24 mmol, 2 eq) was added portion-wise over 1–2 min, and the reaction was then stirred at room temperature for 2 h. The reaction mixture was subsequently diluted with water and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo*. Silica gel chromatography (0–50% Et_2O /hexanes, linear gradient) afforded 269 mg (45%) of dibromide **S8** as a white solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz, 350 K) δ 7.41 (d, J = 8.7 Hz, 2H), 6.44 (d, J = 2.8 Hz, 2H), 6.27 (dd, J = 8.7, 2.8 Hz, 2H), 3.75 (t, J = 7.2 Hz, 8H), 2.28 (p, J = 7.2 Hz, 4H), 1.40 (s, 9H); ^{13}C NMR ($\text{DMSO}-d_6$, 101 MHz, 350 K) δ 151.4 (C), 150.8 (C), 141.7 (C), 132.6 (CH), 111.3 (CH), 110.6 (CH), 108.1 (C), 79.9 (C), 51.4 (CH_2), 27.5 (CH_3), 15.8 (CH_2); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{28}\text{Br}_2\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 536.0543, found 536.0556.



tert-Butyl bis(2-bromo-5-(3-fluoroazetidin-1-yl)phenyl)carbamate (S9): Carbamate **S6** (5.35 g, 12.9 mmol) was taken up in DMF (130 mL) and cooled to 0 °C. *N*-Bromosuccinimide (4.58 g, 25.8 mmol, 2 eq) was added portion-wise over 10 min. The reaction was stirred at 0 °C for 30 min, then warmed to room temperature and stirred 1 h. The DMF was evaporated; the resulting residue was diluted with water and extracted with EtOAc (2×). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude was purified twice by silica gel chromatography (5–75% Et₂O/hexanes, linear gradient; then, 0–50% EtOAc/hexanes, linear gradient) to afford 3.51 g (48%) of dibromide **S9** as an off-white solid. ¹H NMR (DMSO-*d*₆, 400 MHz, 350 K) δ 7.46 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 2.8 Hz, 2H), 6.36 (dd, *J* = 8.7, 2.8 Hz, 2H), 5.43 (dtt, ²*J*_{HF} = 57.4 Hz, *J* = 6.0, 3.2 Hz, 2H), 4.16–4.02 (m, 4H), 3.89–3.76 (m, 4H), 1.40 (s, 9H); ¹⁹F NMR (DMSO-*d*₆, 376 MHz, 350 K) δ –179.66 (dtt, *J*_{FF} = 57.5, 23.8, 20.4 Hz); ¹³C NMR (DMSO-*d*₆, 101 MHz, 350 K) δ 150.8 (C), 150.4 (d, ⁴*J*_{CF} = 1.3 Hz, C), 141.7 (C), 132.8 (CH), 112.1 (CH), 111.3 (CH), 109.2 (C), 82.7 (d, ¹*J*_{CF} = 201.1 Hz, CHF), 80.1 (C), 58.7 (d, ²*J*_{CF} = 23.7 Hz, CH₂), 27.5 (CH₃); HRMS (ESI) calcd for C₂₃H₂₅Br₂F₂N₃O₂Na [M+Na]⁺ 594.0174, found 594.0193.

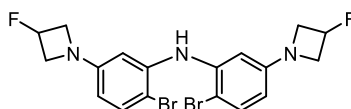


tert-Butyl bis(2-bromo-5-(3,3-difluoroazetidin-1-yl)phenyl)carbamate (S10): Carbamate **S7** (5.50 g, 12.2 mmol) was taken up in DMF (120 mL) and cooled to 0 °C. *N*-Bromosuccinimide (4.34 g, 24.4 mmol, 2 eq) was added portion-wise over 10 min. The reaction was stirred at 0 °C for 30 min, then warmed to room temperature and stirred 1 h. The DMF was evaporated; the resulting residue was diluted with water and extracted with EtOAc (2×). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (0–40% EtOAc/hexanes, linear gradient) afforded 3.41 g (46%) of dibromide **S10** as a yellow foam. ¹H NMR (DMSO-*d*₆, 400 MHz, 350 K) δ 7.52 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 2.9 Hz, 2H), 6.47 (dd, *J* = 8.7, 2.8 Hz, 2H), 4.21 (t, ³*J*_{HF} = 12.1 Hz, 8H), 1.41 (s, 9H); ¹⁹F NMR (DMSO-*d*₆, 376 MHz, 350 K) δ –99.12 (p, ³*J*_{FF} = 12.3 Hz); ¹³C NMR (DMSO-*d*₆, 101 MHz, 350 K) δ 150.8 (C), 149.2 (t, ⁴*J*_{CF} = 3.1 Hz, C), 141.6 (C), 133.0 (CH), 115.8 (t, ¹*J*_{CF} = 273.5 Hz, CF₂), 113.0 (CH), 112.2 (CH), 110.5 (C), 80.3 (C), 62.4 (t, ²*J*_{CF} = 25.7 Hz, CH₂), 27.5 (CH₃); HRMS (ESI) calcd for C₂₃H₂₃Br₂F₄N₃O₂Na [M+Na]⁺ 629.9985, found 629.9999.

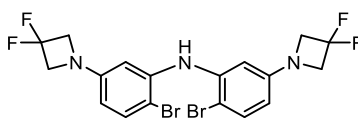


Bis(5-(azetidin-1-yl)-2-bromophenyl)amine (S11): Carbamate **S8** (2.10 g, 3.91 mmol) was taken up in CH₂Cl₂ (40 mL), and trifluoroacetic acid (8 mL) was added. The reaction was stirred at room temperature for 18 h. Toluene (40 mL) was added, and the reaction mixture was concentrated to dryness. The resulting residue was partitioned between

saturated NaHCO₃ and CH₂Cl₂, and the aqueous layer was extracted a second time with CH₂Cl₂. The combined organic extracts were dried over anhydrous MgSO₄, filtered, deposited onto Celite, and concentrated *in vacuo*. The crude material was purified twice by flash chromatography on silica gel (0–50% EtOAc/hexanes, linear gradient; then, 0–40% EtOAc/hexanes, linear gradient, with 20% constant v/v CH₂Cl₂ additive; dry loaded in both instances with Celite) to provide 1.14 g (67%) of **S11** as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.44 (d, *J* = 2.6 Hz, 2H), 6.36 (s, 1H), 5.95 (dd, *J* = 8.6, 2.7 Hz, 2H), 3.81 (t, *J* = 7.2 Hz, 8H), 2.34 (p, *J* = 7.2 Hz, 4H); ¹³C NMR (CDCl₃, 101 MHz) δ 152.2 (C), 140.2 (C), 133.2 (CH), 106.1 (CH), 101.6 (C), 100.9 (CH), 52.6 (CH₂), 16.9 (CH₂); HRMS (ESI) calcd for C₁₈H₂₀Br₂N₃ [M+H]⁺ 436.0018, found 436.0033.

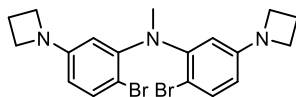


Bis(2-bromo-5-(3-fluoroazetidin-1-yl)phenyl)amine (S12): Carbamate **S9** (3.35 g, 5.84 mmol) was taken up in CH₂Cl₂ (50 mL), and trifluoroacetic acid (10 mL) was added. The reaction was stirred at room temperature for 18 h. Toluene (50 mL) was added, and the reaction mixture was concentrated to dryness. The resulting residue was partitioned between saturated NaHCO₃ and CH₂Cl₂, and the aqueous layer was extracted a second time with CH₂Cl₂. The combined organic extracts were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (0–40% EtOAc/hexanes, linear gradient, with 20% constant v/v CH₂Cl₂ additive) to provide 995 mg (36%) of **S12** as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.38 (d, *J* = 8.6 Hz, 2H), 6.43 (d, *J* = 2.7 Hz, 2H), 6.35 (s, 1H), 6.00 (dd, *J* = 8.6, 2.7 Hz, 2H), 5.39 (dt, ²*J*_{HF} = 56.8 Hz, *J* = 5.8, 3.7 Hz, 2H), 4.19 – 4.05 (m, 4H), 3.96 – 3.82 (m, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –180.51 (dt, *J*_{FH} = 56.6, 23.8, 17.8 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 151.1 (d, ⁴*J*_{CF} = 1.4 Hz, C), 140.3 (C), 133.4 (CH), 106.7 (CH), 102.7 (C), 101.4 (CH), 82.5 (d, ¹*J*_{CF} = 205.0 Hz, CHF), 59.7 (d, ²*J*_{CF} = 23.7 Hz, CH₂); HRMS (ESI) calcd for C₁₈H₁₈Br₂F₂N₃ [M+H]⁺ 471.9830, found 471.9850.

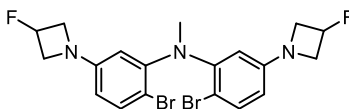


Bis(2-bromo-5-(3,3-difluoroazetidin-1-yl)phenyl)amine (S13): Carbamate **S10** (1.65 g, 2.71 mmol) was taken up in CH₂Cl₂ (25 mL), and trifluoroacetic acid (5 mL) was added. The reaction was stirred at room temperature for 6 h. Toluene (25 mL) was added, and the reaction mixture was concentrated to dryness. The resulting residue was partitioned between saturated NaHCO₃ and CH₂Cl₂, and the aqueous layer was extracted a second time with CH₂Cl₂. The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification of the crude material by flash chromatography on silica gel (0–20% EtOAc/hexanes, linear gradient, with 20% constant v/v CH₂Cl₂ additive) yielded 1.00 g (73%) of **S13** as a colorless, viscous oil. ¹H NMR (CDCl₃, 400 MHz) δ 7.41 (d, *J* = 8.6 Hz, 2H), 6.39 (d, *J* = 2.7 Hz, 2H), 6.34 (s, 1H), 6.03 (dd, *J* = 8.6, 2.7 Hz, 2H), 4.15 (t, ³*J*_{HF} = 11.7 Hz, 8H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –99.94 (p, ³*J*_{FH} = 11.7 Hz); ¹³C NMR (CDCl₃, 101 MHz)

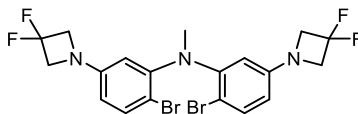
δ 149.8 (t, $^4J_{\text{CF}} = 2.8$ Hz, C), 140.5 (C), 133.7 (CH), 115.7 (t, $^1J_{\text{CF}} = 274.7$ Hz, CF_2), 107.3 (CH), 103.8 (C), 102.1 (CH), 63.5 (t, $^2J_{\text{CF}} = 25.9$ Hz, CH_2); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{16}\text{Br}_2\text{F}_4\text{N}_3$ $[\text{M}+\text{H}]^+$ 507.9642, found 507.9654.



5-(Azetidin-1-yl)-N-(5-(azetidin-1-yl)-2-bromophenyl)-2-bromo-N-methylaniline (S14): Sodium hydride (60% dispersion in mineral oil, 210 mg, 5.26 mmol, 2 eq) was suspended in DMF (25 mL). A solution of aniline **S11** (1.15 g, 2.63 mmol) in CH_2Cl_2 (25 mL) was added dropwise, and the reaction was stirred at room temperature for 1 h. Iodomethane (491 μL , 7.89 mmol, 3 eq) was then added, and the reaction was stirred at room temperature for an additional 45 min. It was subsequently quenched with saturated NH_4Cl , diluted with water, and extracted with CH_2Cl_2 (2 $\times$). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and evaporated. Flash chromatography on silica gel (0–25% EtOAc/hexanes, linear gradient, with 20% constant v/v CH_2Cl_2 additive) provided **S14** as a white solid (645 mg, 54%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.32 – 7.28 (m, 2H), 6.06 – 6.01 (m, 4H), 3.80 (t, $J = 7.2$ Hz, 8H), 3.16 (s, 3H), 2.32 (p, $J = 7.2$ Hz, 4H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 152.3 (C), 149.1 (C), 134.2 (CH), 108.0 (CH), 107.5 (C), 106.9 (CH), 52.6 (CH_2), 41.4 (CH_3), 16.9 (CH_2); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{Br}_2\text{N}_3$ $[\text{M}+\text{H}]^+$ 450.0175, found 450.0177.

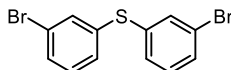


2-Bromo-N-(2-bromo-5-(3-fluoroazetidin-1-yl)phenyl)-5-(3-fluoroazetidin-1-yl)-N-methylaniline (S15): Sodium hydride (60% dispersion in mineral oil, 152 mg, 3.80 mmol, 2 eq) was suspended in DMF (15 mL). A solution of aniline **S12** (900 mg, 1.90 mmol) in CH_2Cl_2 (15 mL) was added dropwise, and the reaction was stirred at room temperature for 1 h. Iodomethane (355 μL , 5.71 mmol, 3 eq) was then added, and the reaction was stirred at room temperature for an additional 30 min. It was subsequently quenched with saturated NH_4Cl , diluted with water, and extracted with CH_2Cl_2 (2 $\times$). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and evaporated. Flash chromatography on silica gel (0–20% EtOAc/hexanes, linear gradient, with 20% constant v/v CH_2Cl_2 additive) provided **S15** as a white solid (644 mg, 69%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.34 (d, $J = 8.2$ Hz, 2H), 6.11 – 6.04 (m, 4H), 5.38 (dtt, $^2J_{\text{HF}} = 57.0$ Hz, $J = 6.1, 3.7$ Hz, 2H), 4.18 – 4.06 (m, 4H), 3.96 – 3.83 (m, 4H), 3.17 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz) δ –180.68 (dtt, $J_{\text{FH}} = 57.1, 23.9, 18.1$ Hz); ^{13}C NMR (CDCl_3 , 101 MHz) δ 151.2 (C), 149.1 (C), 134.5 (CH), 108.54 (CH), 108.46 (C), 107.3 (CH), 82.6 (d, $^1J_{\text{CF}} = 204.7$ Hz, CHF), 59.7 (d, $^2J_{\text{CF}} = 23.7$ Hz, CH_2), 41.4 (CH_3); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{Br}_2\text{F}_2\text{N}_3$ $[\text{M}+\text{H}]^+$ 485.9987, found 485.9999.

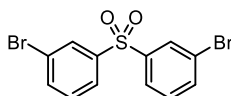


2-Bromo-N-(2-bromo-5-(3,3-difluoroazetidin-1-yl)phenyl)-5-(3,3-difluoroazetidin-1-yl)-N-methylaniline (S16):

Sodium hydride (60% dispersion in mineral oil, 220 mg, 5.50 mmol, 2 eq) was suspended in DMF (25 mL). A solution of aniline **S13** (1.40 g, 2.75 mmol) in CH₂Cl₂ (25 mL) was added dropwise, and the reaction was stirred at room temperature for 1 h. Iodomethane (514 μ L, 8.25 mmol, 3 eq) was then added, and the reaction was stirred at room temperature for an additional 1 h. It was subsequently quenched with saturated NH₄Cl, diluted with water, and extracted with CH₂Cl₂ (2 $\times$). The combined organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated. Silica gel chromatography (0–20% EtOAc/hexanes, linear gradient) provided **S16** as a white solid (1.09 g, 76%). ¹H NMR (CDCl₃, 400 MHz) δ 7.37 (d, J = 8.4 Hz, 2H), 6.10 (dd, J = 8.4, 2.8 Hz, 2H), 6.07 (d, J = 2.7 Hz, 2H), 4.15 (t, $^3J_{\text{HF}}$ = 11.7 Hz, 8H), 3.18 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –100.02 (p, $^3J_{\text{FH}}$ = 11.7 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 149.9 (t, $^4J_{\text{CF}}$ = 2.8 Hz, C), 149.1 (C), 134.7 (CH), 115.8 (t, $^1J_{\text{CF}}$ = 274.5 Hz, CF₂), 109.3 (C), 109.0 (CH), 107.8 (CH), 63.5 (t, $^2J_{\text{CF}}$ = 25.9 Hz, CH₂), 41.4 (CH₃); HRMS (ESI) calcd for C₁₉H₁₈Br₂F₄N₃ [M+H]⁺ 521.9798, found 521.9809.

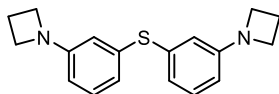


Bis(3-bromophenyl)sulfane (S29): An oven-dried round-bottom flask was charged with CuI (604 mg, 3.17 mmol, 0.1 eq) and K₂CO₃ (8.77 g, 63.5 mmol, 2 eq). The flask was sealed and evacuated/backfilled with nitrogen (3 $\times$). Isopropanol (125 mL) was added, followed by ethylene glycol (3.54 mL, 63.5 mmol, 2 eq), 3-bromothiophenol (**S27**; 3.28 mL, 31.7 mmol), and 3-bromoiodobenzene (**S28**; 4.45 mL, 34.9 mmol, 1.1 eq). The reaction mixture was stirred at 80 °C for 18 h. It was then diluted with saturated NH₄Cl (200 mL) and EtOAc (200 mL), vigorously stirred for 30 min, and filtered through Celite. The filtrate was separated, and the aqueous layer was extracted again with EtOAc. The combined organics were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated. Flash chromatography (100% hexanes, linear gradient) afforded 8.93 g (82%) of dibromide **S29** as a colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ 7.48 (t, J = 1.8 Hz, 2H), 7.40 (ddd, J = 7.8, 1.9, 1.2 Hz, 2H), 7.28 – 7.23 (m, 2H), 7.18 (t, J = 7.8 Hz, 2H); ¹³C NMR (CDCl₃, 101 MHz) δ 137.3 (C), 133.8 (CH), 130.79 (CH), 130.75 (CH), 129.8 (CH), 123.3 (C); HRMS (EI) calcd for C₁₂H₈Br₂S [M]⁺ 341.8708, found 341.8732.

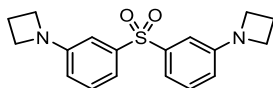


3,3'-Sulfonylbis(bromobenzene) (S30): To a solution of sulfide **S29** (6.45 g, 18.7 mmol) in CH₂Cl₂ (100 mL) was added *m*-CPBA (9.71 g, 56.2 mmol, 3 eq). After stirring the reaction at room temperature for 4 h, it was diluted with 10% Na₂S₂O₃ and extracted with CH₂Cl₂ (2 $\times$). The combined organic extracts were washed with 10% Na₂S₂O₃, saturated NaHCO₃, and brine, dried over anhydrous MgSO₄, filtered, and evaporated to provide sulfone **S30** as a white solid (7.01 g, 99%). Analytical HPLC and NMR indicated that the material was >95% pure and did not require further

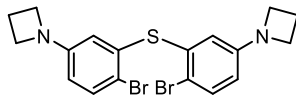
purification prior to cross-coupling with azetidine. ^1H NMR (CDCl_3 , 400 MHz) δ 8.08 (t, J = 1.9 Hz, 2H), 7.87 (ddd, J = 7.9, 1.8, 1.0 Hz, 2H), 7.72 (ddd, J = 8.0, 1.9, 1.0 Hz, 2H), 7.41 (t, J = 7.9 Hz, 2H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 142.9 (C), 136.8 (CH), 131.1 (CH), 130.8 (CH), 126.5 (CH), 123.6 (C); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_8\text{Br}_2\text{O}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$ 396.8504, found 396.8514.



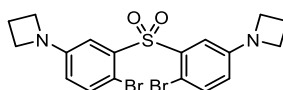
Bis(3-(azetidin-1-yl)phenyl)sulfane (S31): An oven-dried round-bottom flask was charged with CuI (985 mg, 5.17 mmol, 0.2 eq), L-proline (1.19 g, 10.4 mmol, 0.4 eq), and K_2CO_3 (14.30 g, 103.5 mmol, 4 eq). The flask was sealed and evacuated/backfilled with nitrogen ($3\times$). A solution of dibromide **S29** (8.90 g, 25.9 mmol) in DMSO (100 mL) was added, and the reaction was flushed again with nitrogen ($3\times$). Following the addition of azetidine (10.46 mL, 155.2 mmol, 6 eq), the reaction was stirred at 100 $^\circ\text{C}$ for 18 h. It was then cooled to room temperature, diluted with saturated NH_4Cl , and extracted with EtOAc ($2\times$). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (0–30% EtOAc/hexanes, linear gradient) afforded **S31** (6.08 g, 79%) as a white solid. ^1H NMR (CDCl_3 , 400 MHz) δ 7.11 (t, J = 7.9 Hz, 2H), 6.68 (ddd, J = 7.7, 1.7, 1.0 Hz, 2H), 6.45 (t, J = 2.0 Hz, 2H), 6.30 (ddd, J = 8.1, 2.3, 0.9 Hz, 2H), 3.83 (t, J = 7.2 Hz, 8H), 2.33 (p, J = 7.3 Hz, 4H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 152.8 (C), 136.3 (C), 129.5 (CH), 119.9 (CH), 113.6 (CH), 110.1 (CH), 52.5 (CH_2), 17.1 (CH_2); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{S}$ $[\text{M}+\text{H}]^+$ 297.1420, found 297.1428.



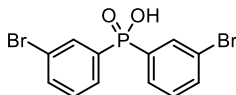
1,1'-(Sulfonylbis(3,1-phenylene))bis(azetidine) (S32): An oven-dried round-bottom flask was charged with sulfone **S30** (2.80 g, 7.45 mmol), Pd_2dba_3 (682 mg, 0.745 mmol, 0.1 eq), XPhos (1.06 g, 2.23 mmol, 0.3 eq), and Cs_2CO_3 (6.79 g, 20.9 mmol, 2.8 eq). The flask was sealed and evacuated/backfilled with nitrogen ($3\times$). Dioxane (35 mL) was added, and the reaction was flushed again with nitrogen ($3\times$). Following the addition of azetidine (1.51 mL, 22.3 mmol, 3 eq), the reaction was stirred at 100 $^\circ\text{C}$ for 4 h. It was then cooled to room temperature, filtered through Celite with CH_2Cl_2 , and concentrated to dryness. The resulting residue was purified by flash chromatography (0–40% EtOAc/hexanes, linear gradient, with constant 40% v/v CH_2Cl_2 additive) to provide a brown-orange solid. The solid was triturated with Et_2O , sonicated, and filtered; the filter cake was washed with additional Et_2O and dried to yield 1.97 g (81%) of **S32** as an off-white solid. ^1H NMR (CDCl_3 , 400 MHz) δ 7.26 (t, J = 7.9 Hz, 2H), 7.22 – 7.16 (m, 2H), 6.94 (t, J = 2.1 Hz, 2H), 6.52 (ddd, J = 8.0, 2.3, 1.0 Hz, 2H), 3.90 (t, J = 7.3 Hz, 8H), 2.38 (p, J = 7.2 Hz, 4H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 152.2 (C), 142.4 (C), 129.7 (CH), 115.9 (CH), 115.3 (CH), 109.4 (CH), 52.4 (CH_2), 16.9 (CH_2); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$ 351.1138, found 351.1137.



Bis(5-(azetidin-1-yl)-2-bromophenyl)sulfane (S33): Sulfide **S31** (6.00 g, 20.2 mmol) was taken up in DMF (100 mL). *N*-Bromosuccinimide (7.20 g, 40.5 mmol, 2 eq) was added portion-wise over 5 min, and the reaction was then stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*; the resulting residue was diluted with water and extracted with EtOAc (2×). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude product was triturated with Et₂O, sonicated, and filtered. The filter cake was washed with Et₂O and dried to provide the title compound as a white solid. The filtrate was concentrated, chromatographed on silica gel (0–50% Et₂O/hexanes, linear gradient), and triturated as before to yield additional dibromide product. The two crops of white powder were combined, affording 6.51 g (71%) of dibromide **S33**. ¹H NMR (CDCl₃, 400 MHz) δ 7.40 – 7.34 (m, 2H), 6.23 – 6.18 (m, 4H), 3.76 (t, *J* = 7.3 Hz, 8H), 2.31 (p, *J* = 7.2 Hz, 4H); ¹³C NMR (CDCl₃, 101 MHz) δ 151.9 (C), 135.6 (C), 133.3 (CH), 115.0 (CH), 112.3 (C), 112.1 (CH), 52.4 (CH₂), 16.9 (CH₂); HRMS (ESI) calcd for C₁₈H₁₉Br₂N₂S [M+H]⁺ 452.9630, found 452.9632.

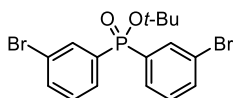


1,1'-(Sulfonylbis(4-bromo-3,1-phenylene))bis(azetidine) (S34): Sulfone **S32** (1.82 g, 5.54 mmol) was taken up in DMF (200 mL). *N*-Bromosuccinimide (1.97 g, 11.1 mmol, 2 eq) was added portion-wise over 10 min, and the reaction was then stirred at room temperature for 72 h. The reaction mixture was concentrated *in vacuo*; the resulting residue was diluted with saturated NaHCO₃ and extracted with CH₂Cl₂ (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated. Silica gel chromatography (0–10% EtOAc/toluene, linear gradient) afforded 2.47 g (92%) of dibromide **S34** as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.51 (d, *J* = 2.9 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 6.42 (dd, *J* = 8.6, 2.9 Hz, 2H), 3.95 (t, *J* = 7.3 Hz, 8H), 2.42 (p, *J* = 7.3 Hz, 4H); ¹³C NMR (CDCl₃, 101 MHz) δ 150.8 (C), 139.1 (C), 135.3 (CH), 116.8 (CH), 115.9 (CH), 105.8 (C), 52.6 (CH₂), 16.9 (CH₂); HRMS (ESI) calcd for C₁₈H₁₈Br₂N₂O₂SNa [M+Na]⁺ 506.9348, found 506.9362.

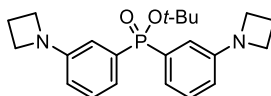


Bis(3-bromophenyl)phosphinic acid (S35): To a solution of 3-bromoiodobenzene (**S28**; 11.32 g, 40.0 mmol, 3 eq) in THF (100 mL) at –40 °C was added *i*-PrMgCl (2.0 M in THF, 20.00 mL, 40.0 mmol, 3 eq). The reaction was then gradually warmed to –25 °C while stirring for 2 h. After cooling the solution to –78 °C, *N,N*-dimethylphosphoramidic dichloride (1.59 mL, 13.3 mmol) was added dropwise. The reaction was allowed to warm to room temperature overnight (18 h). After adding 6 N HCl (10 mL), the resulting mixture was vigorously stirred at room temperature for 4 h. It was then diluted with water and extracted with EtOAc (2×). The organics were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude product was dissolved in CH₂Cl₂ (~100 mL), and hexanes (~100 mL) were slowly added. This solution was gently concentrated with rotary evaporation (~250 Torr)

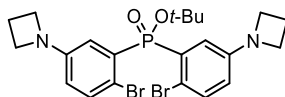
until a pale yellow solid precipitated. The solid was isolated by filtration, washed with 2:1 hexanes/ CH_2Cl_2 and Et_2O , and dried to afford 4.13 g (82%) of phosphinic acid **S35** as a yellow powder. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 7.86 (dt, $J = 12.1, 1.7$ Hz, 2H), 7.78 – 7.69 (m, 4H), 7.46 (td, $J = 7.8, 3.8$ Hz, 2H); ^{13}C NMR ($\text{DMSO}-d_6$, 101 MHz) δ 137.4 (d, $J_{\text{CP}} = 133.3$ Hz, C), 134.6 (d, $J_{\text{CP}} = 2.5$ Hz, CH), 133.2 (d, $J_{\text{CP}} = 10.7$ Hz, CH), 131.1 (d, $J_{\text{CP}} = 13.4$ Hz, CH), 130.1 (d, $J_{\text{CP}} = 9.8$ Hz, CH), 122.1 (d, $J_{\text{CP}} = 16.4$ Hz, C); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{10}\text{Br}_2\text{O}_2\text{P}$ $[\text{M}+\text{H}]^+$ 374.8780, found 374.8791.



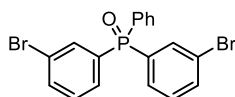
tert-Butyl bis(3-bromophenyl)phosphinate (S36): A suspension of phosphinic acid **S35** (3.00 g, 7.98 mmol) in dioxane (25 mL) was heated to 80 °C, and *N,N*-dimethylformamide di-*tert*-butyl acetal (9.57 mL, 39.9 mmol, 5 eq) was added dropwise over 5 min. The reaction was stirred at 80 °C for 1 h. After cooling the mixture to room temperature, it was diluted with saturated NaHCO_3 and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and evaporated. Flash chromatography (0–50% EtOAc /hexanes, linear gradient) provided phosphinate **S36** as a white solid (1.78 g, 52%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.92 (dt, $J = 12.4, 1.6$ Hz, 2H), 7.69 (ddt, $J = 12.0, 7.6, 1.2$ Hz, 2H), 7.62 (ddt, $J = 8.0, 1.9, 0.9$ Hz, 2H), 7.31 (td, $J = 7.8, 4.0$ Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 136.8 (d, $J_{\text{CP}} = 137.5$ Hz, C), 135.0 (d, $J_{\text{CP}} = 2.6$ Hz, CH), 134.1 (d, $J_{\text{CP}} = 10.7$ Hz, CH), 130.3 (d, $J_{\text{CP}} = 14.2$ Hz, CH), 129.9 (d, $J_{\text{CP}} = 9.9$ Hz, CH), 123.1 (d, $J_{\text{CP}} = 16.9$ Hz, C), 85.3 (d, $J_{\text{CP}} = 8.1$ Hz, C), 31.1 (d, $J_{\text{CP}} = 4.0$ Hz, CH_3); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{Br}_2\text{O}_2\text{PNa}$ $[\text{M}+\text{Na}]^+$ 452.9225, found 452.9243.



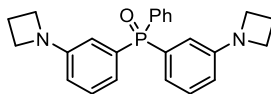
tert-Butyl bis(3-(azetidin-1-yl)phenyl)phosphinate (S37): A vial was charged with dibromide **S36** (1.25 g, 2.89 mmol), RuPhos-G3-palladacycle (484 mg, 0.579 mmol, 0.2 eq), RuPhos (270 mg, 0.579 mmol, 0.2 eq), and Cs_2CO_3 (2.83 mg, 8.68 mmol, 3 eq). The vial was sealed and evacuated/backfilled with nitrogen (3 $\times$). Dioxane (11 mL) was added, and the reaction was flushed again with nitrogen (3 $\times$). Following the addition of azetidine (585 μL , 8.68 mmol, 3 eq), the reaction was stirred at 100 °C for 18 h. It was then cooled to room temperature, filtered through Celite with CH_2Cl_2 , and concentrated to dryness. Purification by silica gel chromatography (0–40% acetone/ CH_2Cl_2 , linear gradient) afforded **S37** (1.08 g, 97%) as a pale yellow gum. ^1H NMR (CDCl_3 , 400 MHz) δ 7.20 (td, $J = 7.7, 4.2$ Hz, 2H), 7.07 (ddt, $J = 12.0, 7.5, 1.2$ Hz, 2H), 6.89 (ddd, $J = 13.7, 2.5, 1.3$ Hz, 2H), 6.49 (ddt, $J = 8.1, 2.4, 1.1$ Hz, 2H), 3.87 (t, $J = 7.2$ Hz, 8H), 2.34 (p, $J = 7.2$ Hz, 4H), 1.50 (s, 9H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 151.8 (d, $J_{\text{CP}} = 15.0$ Hz, C), 135.3 (d, $J_{\text{CP}} = 136.9$ Hz, C), 128.8 (d, $J_{\text{CP}} = 14.9$ Hz, CH), 120.1 (d, $J_{\text{CP}} = 9.9$ Hz, CH), 114.1 (d, $J_{\text{CP}} = 2.9$ Hz, CH), 113.9 (d, $J_{\text{CP}} = 11.6$ Hz, CH), 83.1 (d, $J_{\text{CP}} = 8.3$ Hz, C), 52.5 (CH_2), 31.0 (d, $J_{\text{CP}} = 4.0$ Hz, CH_3), 17.0 (CH_2); HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_2\text{PNa}$ $[\text{M}+\text{Na}]^+$ 407.1859, found 407.1864.



tert-Butyl bis(5-(azetidin-1-yl)-2-bromophenyl)phosphinate (S37): Phosphinate **S37** (1.00 g, 2.60 mmol) was taken up in DMF (13 mL) and cooled to 0 °C. *N*-Bromosuccinimide (926 mg, 5.20 mmol, 2 eq) was added portion-wise over 10 min. The reaction was stirred at 0 °C for 1 h, then warmed to room temperature and stirred 1 h. It was subsequently diluted with water and extracted with EtOAc (2×). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (0–40% MeCN/CH₂Cl₂, linear gradient) provided dibromide **S38** as an off-white solid (825 mg, 58%). ¹H NMR (CDCl₃, 400 MHz) δ 7.33 – 7.27 (m, 4H), 6.41 – 6.34 (m, 2H), 3.89 (t, *J* = 7.2 Hz, 8H), 2.38 (p, *J* = 7.2 Hz, 4H), 1.53 (s, 9H); ¹³C NMR (CDCl₃, 101 MHz) δ 150.7 (d, *J*_{CP} = 13.1 Hz, C), 134.3 (d, *J*_{CP} = 11.3 Hz, CH), 133.7 (d, *J*_{CP} = 144.4 Hz, C), 119.9 (d, *J*_{CP} = 8.5 Hz, CH), 115.9 (d, *J*_{CP} = 2.7 Hz, CH), 111.3 (d, *J*_{CP} = 6.7 Hz, C), 84.8 (d, *J*_{CP} = 8.3 Hz, C), 52.6 (CH₂), 30.8 (d, *J*_{CP} = 4.0 Hz, CH₃), 17.0 (CH₂); HRMS (ESI) calcd for C₂₂H₂₇Br₂N₂O₂PNa [M+Na]⁺ 563.0069, found 563.0080.

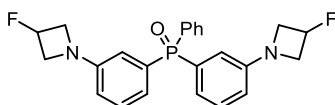


Bis(3-bromophenyl)(phenyl)phosphine oxide (S39): To a solution of 3-bromoiodobenzene (**S28**; 21.22 g, 75.0 mmol, 3 eq) in THF (200 mL) at –40 °C was added *i*-PrMgCl (2.0 M in THF, 37.50 mL, 75.0 mmol, 3 eq). The reaction was then gradually warmed to –20 °C over 2 h while stirring. Dichlorophenylphosphine (3.39 mL, 25.0 mmol) was added; the reaction was then warmed to room temperature and stirred for 2 h. It was subsequently quenched with saturated NH₄Cl and diluted with water (~100 mL). After adding H₂O₂ (30%, 100 mL), the mixture was vigorously stirred at room temperature for 30 min and then extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated. Flash chromatography on silica gel (10–100% EtOAc/toluene, linear gradient) afforded 10.81 g (99%) of phosphine oxide **S39** as a colorless gum. ¹H NMR (CDCl₃, 400 MHz) δ 7.82 (dt, *J* = 12.1, 1.6 Hz, 2H), 7.73 – 7.47 (m, 9H), 7.36 (td, *J* = 7.8, 3.4 Hz, 2H); ¹³C NMR (CDCl₃, 101 MHz) δ 135.5 (d, *J*_{CP} = 2.6 Hz, CH), 134.78 (d, *J*_{CP} = 101.6 Hz, C), 134.76 (d, *J*_{CP} = 10.6 Hz, CH), 132.7 (d, *J*_{CP} = 2.8 Hz, CH), 132.1 (d, *J*_{CP} = 10.1 Hz, CH), 131.2 (d, *J*_{CP} = 106.0 Hz, C), 130.6 (d, *J*_{CP} = 9.6 Hz, CH), 130.4 (d, *J*_{CP} = 13.0 Hz, CH), 129.0 (d, *J*_{CP} = 12.4 Hz, CH), 123.5 (d, *J*_{CP} = 15.4 Hz, C); HRMS (ESI) calcd for C₁₈H₁₄Br₂OP [M+H]⁺ 434.9144, found 434.9150.

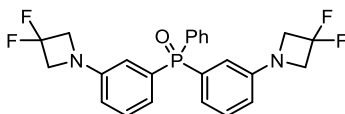


Bis(3-(azetidin-1-yl)phenyl)(phenyl)phosphine oxide (S40): A vial was charged with Pd₂dba₃ (210 mg, 0.229 mmol, 0.1 eq), XPhos (328 mg, 0.668 mmol, 0.3 eq), and Cs₂CO₃ (2.09 g, 6.42 mmol, 2.8 eq). The vial was sealed and evacuated/backfilled with nitrogen (3×). A solution of dibromide **S39** (1.00 g, 2.29 mmol) in dioxane (10 mL) was added, and the reaction was flushed again with nitrogen (3×). Following the addition of azetidine (371 μL, 5.50

mmol, 2.4 eq), the reaction was stirred at 100 °C for 18 h. It was then cooled to room temperature, filtered through Celite with CH₂Cl₂, and concentrated to dryness. The crude product was purified by flash chromatography (0–75% acetone/CH₂Cl₂, linear gradient) to yield 475 mg (53%) of **S40** as a pale yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.70 – 7.62 (m, 2H), 7.53 – 7.46 (m, 1H), 7.45 – 7.38 (m, 2H), 7.21 (td, *J* = 7.8, 3.7 Hz, 2H), 6.92 – 6.84 (m, 2H), 6.83 – 6.75 (m, 2H), 6.58 – 6.51 (m, 2H), 3.86 (t, *J* = 7.2 Hz, 8H), 2.34 (p, *J* = 7.3 Hz, 4H); ¹³C NMR (CDCl₃, 101 MHz) δ 152.0 (d, *J*_{CP} = 13.3 Hz, C), 133.4 (d, *J*_{CP} = 103.2 Hz, C), 133.1 (d, *J*_{CP} = 103.0 Hz, C), 132.2 (d, *J*_{CP} = 9.9 Hz, CH), 131.7 (d, *J*_{CP} = 2.7 Hz, CH), 128.8 (d, *J*_{CP} = 14.2 Hz, CH), 128.3 (d, *J*_{CP} = 12.0 Hz, CH), 120.8 (d, *J*_{CP} = 10.7 Hz, CH), 114.53 (d, *J*_{CP} = 8.8 Hz, CH), 114.47 (d, *J*_{CP} = 0.8 Hz, CH), 52.4 (CH₂), 17.0 (CH₂); HRMS (ESI) calcd for C₂₄H₂₆N₂OP [M+H]⁺ 389.1777, found 389.1779.

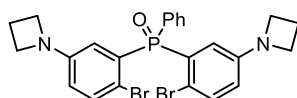


Bis(3-(3-fluoroazetidin-1-yl)phenyl)(phenyl)phosphine oxide (S41): An oven-dried round-bottom flask was charged with 3-fluoroazetidine hydrochloride (2.70 g, 24.2 mmol, 2.4 eq), Pd₂dba₃ (924 mg, 1.01 mmol, 0.1 eq), XPhos (1.44 g, 3.03 mmol, 0.3 eq), and Cs₂CO₃ (15.78 g, 48.4 mmol, 4.8 eq). The flask was sealed and evacuated/backfilled with nitrogen (3×). A solution of dibromide **S39** (4.40 g, 10.1 mmol) in dioxane (50 mL) was added, and after flushing the reaction again with nitrogen (3×), it was stirred at 100 °C for 18 h. It was then cooled to room temperature, filtered through Celite with CH₂Cl₂, and concentrated to dryness. The crude product was purified by flash chromatography (0–60% acetone/CH₂Cl₂, linear gradient) to yield 2.41 g (56%) of **S41** as a pale yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.69 – 7.61 (m, 2H), 7.56 – 7.49 (m, 1H), 7.48 – 7.40 (m, 2H), 7.25 (td, *J* = 8.0, 3.7 Hz, 2H), 6.93 (ddd, *J* = 13.2, 2.2, 1.4 Hz, 2H), 6.88 – 6.79 (m, 2H), 6.63 – 6.56 (m, 2H), 5.39 (dtt, ²*J*_{HF} = 57.0 Hz, *J* = 5.9, 3.7 Hz, 2H), 4.24 – 4.11 (m, 4H), 4.03 – 3.88 (m, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –180.52 (dtt, *J*_{FH} = 56.7, 23.8, 18.4 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 150.9 (dd, ³*J*_{CP} = 13.4 Hz, ⁴*J*_{CF} = 1.4 Hz, C), 133.3 (d, *J*_{CP} = 103.0 Hz, C), 132.9 (d, *J*_{CP} = 103.8 Hz, C), 132.2 (d, *J*_{CP} = 9.9 Hz, CH), 131.9 (d, *J*_{CP} = 2.9 Hz, CH), 129.0 (d, *J*_{CP} = 14.0 Hz, CH), 128.5 (d, *J*_{CP} = 12.1 Hz, CH), 121.6 (d, *J*_{CP} = 10.7 Hz, CH), 115.2 (d, *J*_{CP} = 2.8 Hz, CH), 115.0 (d, *J*_{CP} = 10.3 Hz, CH), 82.8 (d, ¹*J*_{CF} = 204.7 Hz, CFH), 59.6 (d, ²*J*_{CF} = 23.9 Hz, CH₂); HRMS (ESI) calcd for C₂₄H₂₄F₂N₂OP [M+H]⁺ 425.1589, found 425.1596.

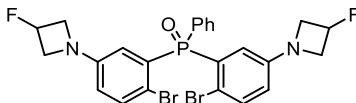


Bis(3-(3,3-difluoroazetidin-1-yl)phenyl)(phenyl)phosphine oxide (S42): An oven-dried round-bottom flask was charged with 3,3-difluoroazetidine hydrochloride (3.14 g, 24.2 mmol, 2.4 eq), Pd₂dba₃ (924 mg, 1.01 mmol, 0.1 eq), XPhos (1.44 g, 3.03 mmol, 0.3 eq), and Cs₂CO₃ (15.78 g, 48.4 mmol, 4.8 eq). The flask was sealed and evacuated/backfilled with nitrogen (3×). A solution of dibromide **S39** (4.40 g, 10.1 mmol) in dioxane (50 mL) was added, and after flushing the reaction again with nitrogen (3×), it was stirred at 100 °C for 18 h. It was then cooled to room temperature, filtered through Celite with CH₂Cl₂, and concentrated to dryness. The crude product was purified

by flash chromatography (0–40% acetone/CH₂Cl₂, linear gradient) to yield 2.91 g (63%) of **S42** as a yellow foam. ¹H NMR (CDCl₃, 400 MHz) δ 7.69 – 7.61 (m, 2H), 7.57 – 7.51 (m, 1H), 7.49 – 7.42 (m, 2H), 7.29 (td, *J* = 7.8, 3.7 Hz, 2H), 6.97 (ddd, *J* = 13.1, 2.3, 1.3 Hz, 2H), 6.93 – 6.85 (m, 2H), 6.66 – 6.61 (m, 2H), 4.22 (t, ³*J*_{HF} = 11.7 Hz, 8H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –99.92 (p, ³*J*_{FH} = 11.9 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 149.7 (dt, ³*J*_{CP} = 13.6 Hz, ⁴*J*_{CF} = 2.8 Hz, C), 133.5 (d, *J*_{CP} = 103.0 Hz, C), 132.6 (d, *J*_{CP} = 104.2 Hz, C), 132.13 (d, *J*_{CP} = 9.9 Hz, CH), 132.11 (d, *J*_{CP} = 2.7 Hz, CH), 129.2 (d, *J*_{CP} = 13.9 Hz, CH), 128.6 (d, *J*_{CP} = 12.2 Hz, CH), 122.4 (d, *J*_{CP} = 10.7 Hz, CH), 115.8 (t, ¹*J*_{CF} = 274.6 Hz, CF₂), 115.7 (d, *J*_{CP} = 2.8 Hz, CH), 115.5 (d, *J*_{CP} = 10.2 Hz, CH), 63.4 (t, ²*J*_{CF} = 26.0 Hz, CH₂); HRMS (ESI) calcd for C₂₄H₂₂F₄N₂OP [M+H]⁺ 461.1400, found 461.1403.

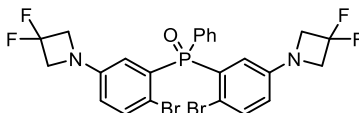


Bis(5-(azetidin-1-yl)-2-bromophenyl)(phenyl)phosphine oxide (S43): Phosphine oxide **S40** (3.00 g, 7.72 mmol) was taken up in DMF (250 mL). *N*-Bromosuccinimide (2.75 g, 15.5 mmol, 2 eq) was added portion-wise over 5 min, and the reaction was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*; the resulting residue was diluted with water and extracted with CH₂Cl₂ (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated to dryness. Silica gel chromatography (0–75% EtOAc/CH₂Cl₂, linear gradient) yielded 3.13 g (74%) of dibromide **S43** as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.86 – 7.79 (m, 2H), 7.56 – 7.50 (m, 1H), 7.48 – 7.43 (m, 2H), 7.41 (dd, *J* = 8.5, 4.7 Hz, 2H), 6.73 (dd, *J* = 14.7, 2.9 Hz, 2H), 6.40 (ddd, *J* = 8.6, 2.9, 0.7 Hz, 2H), 3.83 – 3.72 (m, 8H), 2.32 (p, *J* = 7.3 Hz, 4H); ¹³C NMR (CDCl₃, 101 MHz) δ 150.8 (d, *J*_{CP} = 12.8 Hz, C), 134.8 (d, *J*_{CP} = 9.1 Hz, CH), 132.9 (d, *J*_{CP} = 9.9 Hz, CH), 132.4 (d, *J*_{CP} = 108.2 Hz, C), 131.9 (d, *J*_{CP} = 2.9 Hz, CH), 131.5 (d, *J*_{CP} = 109.7 Hz, C), 128.3 (d, *J*_{CP} = 12.6 Hz, CH), 119.1 (d, *J*_{CP} = 11.2 Hz, CH), 115.8 (d, *J*_{CP} = 2.7 Hz, CH), 112.1 (d, *J*_{CP} = 4.6 Hz, C), 52.3 (CH₂), 16.8 (CH₂); HRMS (ESI) calcd for C₂₄H₂₄Br₂N₂OP [M+H]⁺ 544.9988, found 545.0004.

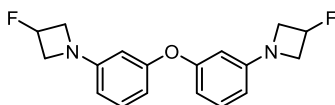


Bis(2-bromo-5-(3-fluoroazetidin-1-yl)phenyl)(phenyl)phosphine oxide (S44): Phosphine oxide **S41** (2.25 g, 5.30 mmol) was taken up in DMF (100 mL). *N*-Bromosuccinimide (1.89 g, 10.6 mmol, 2 eq) was added portion-wise over 5 min, and the reaction was then stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*; the resulting residue was diluted with water and extracted with CH₂Cl₂ (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated to dryness. Silica gel chromatography (0–60% EtOAc/CH₂Cl₂, linear gradient) afforded 1.53 g (50%) of dibromide **S44** as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.88 – 7.79 (m, 2H), 7.60 – 7.52 (m, 1H), 7.50 – 7.42 (m, 4H), 6.79 (dd, *J* = 14.5, 2.9 Hz, 2H), 6.46 (ddd, *J* = 8.6, 2.9, 0.8 Hz, 2H), 5.36 (dtt, ²*J*_{HF} = 56.9 Hz, *J* = 5.9, 3.6 Hz, 2H), 4.15 – 4.03 (m, 4H), 3.95 – 3.82 (m, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –180.60 (dtt, *J*_{FH} = 57.1, 23.8, 18.4 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 149.8 (dd, ³*J*_{CP} = 12.9 Hz, ⁴*J*_{CF} = 1.4 Hz, C), 135.0 (d, *J*_{CP} = 9.0 Hz, CH), 132.9 (d, *J*_{CP} = 9.9 Hz, CH), 132.8 (d, *J*_{CP} = 108.1 Hz, C),

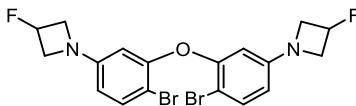
132.2 (d, J_{CP} = 2.9 Hz, CH), 131.1 (d, J_{CP} = 110.2 Hz, C), 128.4 (d, J_{CP} = 12.6 Hz, CH), 119.6 (d, J_{CP} = 11.2 Hz, CH), 116.5 (d, J_{CP} = 2.5 Hz, CH), 113.1 (d, J_{CP} = 4.7 Hz, C), 82.5 (d, $^1J_{CF}$ = 205.2 Hz, CFH), 59.5 (d, $^2J_{CF}$ = 24.0 Hz, CH₂); HRMS (ESI) calcd for C₂₄H₂₂Br₂F₂N₂OP [M+H]⁺ 580.9799, found 580.9811.



Bis(2-bromo-5-(3,3-difluoroazetidin-1-yl)phenyl)(phenyl)phosphine oxide (S45): Phosphine oxide **S42** (3.50 g, 7.60 mmol) was taken up in DMF (50 mL). *N*-Bromosuccinimide (2.71 g, 15.2 mmol, 2 eq) was added portion-wise over 5 min, and the reaction was then stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*; the resulting residue was diluted with water and extracted with CH₂Cl₂ (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated to dryness. Silica gel chromatography (10–100% EtOAc/toluene, linear gradient) afforded an off-white solid that was subsequently triturated with Et₂O (~100 mL), sonicated, and filtered. The filter cake was washed with additional Et₂O and dried to yield 3.31 g (70%) of dibromide **S45** as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.89 – 7.80 (m, 2H), 7.62 – 7.54 (m, 1H), 7.53 – 7.45 (m, 4H), 6.84 (dd, J = 14.4, 3.0 Hz, 2H), 6.50 (ddd, J = 8.6, 3.0, 0.8 Hz, 2H), 4.21 – 4.06 (m, 8H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –99.93 (p, $^3J_{HF}$ = 11.7 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 148.5 (dt, $^3J_{CP}$ = 12.9 Hz, $^4J_{CF}$ = 3.0 Hz, C), 135.2 (d, J_{CP} = 9.1 Hz, CH), 133.1 (d, J_{CP} = 107.9 Hz, C), 132.8 (d, J_{CP} = 10.0 Hz, CH), 132.4 (d, J_{CP} = 2.9 Hz, CH), 130.8 (d, J_{CP} = 110.4 Hz, C), 128.5 (d, J_{CP} = 12.7 Hz, CH), 120.0 (d, J_{CP} = 11.1 Hz, CH), 117.0 (d, J_{CP} = 2.6 Hz, CH), 115.6 (t, $^1J_{CF}$ = 274.7 Hz, CF₂), 114.1 (d, J_{CP} = 4.7 Hz, C), 63.4 (t, $^2J_{CF}$ = 26.3 Hz, CH₂); HRMS (ESI) calcd for C₂₄H₂₀Br₂F₄N₂OP [M+H]⁺ 616.9611, found 616.9615.



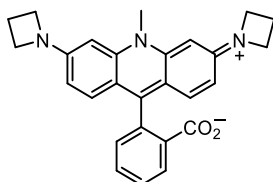
1,1'-(Oxybis(3,1-phenylene))bis(3-fluoroazetidine) (S47): An oven-dried round-bottom flask was charged with 3-fluoroazetidine hydrochloride (2.04 g, 18.3 mmol, 2.4 eq), Pd₂dba₃ (698 mg, 0.762 mmol, 0.1 eq), XPhos (1.09 g, 2.29 mmol, 0.3 eq), and Cs₂CO₃ (11.92 g, 36.6 mmol, 4.8 eq). The flask was sealed and evacuated/backfilled with nitrogen (3×). A solution of dibromide **S46**^[1] (2.50 g, 7.62 mmol) in dioxane (40 mL) was added, and after flushing the reaction again with nitrogen (3×), it was stirred at 100 °C for 18 h. It was then cooled to room temperature, filtered through Celite with CH₂Cl₂, and concentrated to dryness. Purification by flash chromatography (0–50% Et₂O/hexanes, linear gradient) yielded 1.43 g (59%) of ether **S47** as a yellow gum. ¹H NMR (CDCl₃, 400 MHz) δ 7.15 (t, J = 8.1 Hz, 2H), 6.41 (ddd, J = 8.1, 2.2, 0.7 Hz, 2H), 6.21 (ddd, J = 8.0, 2.2, 0.7 Hz, 2H), 6.15 (t, J = 2.3 Hz, 2H), 5.39 (dtt, $^2J_{HF}$ = 57.0 Hz, J = 5.9, 3.8 Hz, 2H), 4.21 – 4.09 (m, 4H), 3.99 – 3.87 (m, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –180.65 (dtt, J_{FH} = 57.2, 23.9, 18.0 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 158.2 (C), 152.6 (d, $^4J_{CF}$ = 1.1 Hz, C), 130.2 (CH), 108.7 (CH), 107.0 (CH), 102.8 (CH), 82.8 (d, $^1J_{CF}$ = 204.5 Hz, CFH), 59.7 (d, $^2J_{CF}$ = 23.7 Hz, CH₂); HRMS (ESI) calcd for C₁₈H₁₉F₂N₂O [M+H]⁺ 317.1460, found 317.1456.



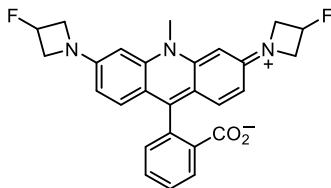
1,1'-(Oxybis(4-bromo-3,1-phenylene))bis(3-fluoroazetidine) (S48): Ether **S47** (1.50 g, 4.74 mmol) was taken up in DMF (30 mL). *N*-Bromosuccinimide (1.69 g, 9.48 mmol, 2 eq) was added portion-wise over 5 min, and the reaction was then stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*; the resulting residue was diluted with water and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated to dryness. Silica gel chromatography (0–10% EtOAc/toluene, linear gradient; mixed fractions repurified with 0–50% EtOAc/hexanes, linear gradient) provided 1.92 g (85%) of dibromide **S48** as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.41 (d, *J* = 8.6 Hz, 2H), 6.13 (dd, *J* = 8.6, 2.6 Hz, 2H), 5.93 (d, *J* = 2.7 Hz, 2H), 5.36 (dt, ²*J*_{HF} = 56.9 Hz, *J* = 5.9, 3.6 Hz, 2H), 4.15 – 4.04 (m, 4H), 3.96 – 3.82 (m, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –180.71 (dt, *J*_{FH} = 57.1, 23.8, 18.3 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 153.8 (C), 151.6 (d, ⁴*J*_{CF} = 1.3 Hz, C), 133.9 (CH), 108.9 (CH), 103.2 (CH), 101.9 (C), 82.5 (d, ¹*J*_{CF} = 205.0 Hz, CFH), 59.7 (d, ²*J*_{CF} = 23.9 Hz, CH₂); HRMS (ESI) calcd for C₁₈H₁₇Br₂F₂N₂O [M+H]⁺ 472.9670, found 472.9677.

RHODAMINE SYNTHESIS VIA METAL–BROMIDE EXCHANGE OF DIBROMIDES

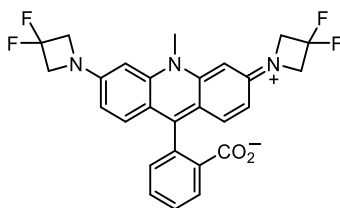
In applying the bis(arylmethyl)–anhydride approach^[1] to the synthesis of these new rhodamines (**Scheme S1**, **Scheme S3e**), we found that some variation of the reaction conditions was necessary depending on the dibromide substrate. For the nitrogen (**S14–S16**), sulfide (**S33**), and ether (**S48**) dibromides, the previously described conditions (*t*-BuLi alone or *t*-BuLi/MgBr·OEt₂) were typically adequate. Lithium–bromide exchange of **S14–S16** with *t*-BuLi and addition to phthalic anhydride yielded nitrogen rhodamines **1** (JF₅₀₂), **11** (JF₄₇₉), and **S18** (JF₄₉₀) in moderate yield. Alternatively, use of methyl ester **S19**^[1] as the electrophile ultimately provided the 6-carboxy analogs of JF₅₀₂ (**S22**) and JF₄₇₉ (**S23**) in excellent yield following ester hydrolysis (**Scheme S1**). Similar reaction of sulfide **S33** and ether **S48** with tetrafluorophthalic anhydride afforded the 4,5,6,7-tetrafluororhodamines **20** (JF₅₉₃) and **37** (JF₅₅₉) in moderate yield (**Scheme S3e**). For sulfone **S34**, phosphinate **S38**, and phosphine oxides **S43–S45**, however, we observed poor yields, complex mixtures of products, and/or decomposition when these transformations were attempted with *t*-BuLi or *t*-BuLi/MgBr·OEt₂. We instead found that the milder magnesate Bu₂-*i*-PrMgLi achieved reasonably clean magnesium–bromide exchange with these dibromides; subsequent addition to phthalic or tetrafluorophthalic anhydride allowed access to the sulfone (**8**, **18**), phosphine oxide (**7**, **17**, **38**, **S52**), and phosphinate (**S50**, **S51**) rhodamines, albeit in modest yields. Straightforward TFA deprotection of the *tert*-butyl phosphinates generated the phosphinic acids **6** (JF₆₆₈) and **16** (JF₆₉₀; **Scheme S3e**).



JF₅₀₂ (1): A solution of dibromide **S14** (150 mg, 0.332 mmol) in THF (10 mL) was cooled to –78 °C under nitrogen. *tert*-Butyllithium (1.7 M in pentane, 860 µL, 1.46 mmol, 4.4 eq) was added, and the reaction was stirred at –78 °C for 30 min. It was then warmed to –20 °C, and a solution of phthalic anhydride (**S17**; 108 mg, 0.731 mmol, 2.2 eq) in THF (10 mL) was added dropwise over 30 min via addition funnel. The reaction was allowed to warm to room temperature overnight (18 h). Following the addition of AcOH (100 µL), the mixture was diluted with MeOH, deposited onto Celite, and concentrated to dryness. Silica gel chromatography (0–10% MeOH (2 M NH₃)/CH₂Cl₂, linear gradient) followed by reverse phase HPLC (30–60% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive) afforded 77.6 mg (43%, TFA salt) of JF₅₀₂ (**1**) as a bright orange solid. ¹H NMR (CD₃OD, 400 MHz) δ 8.14 – 8.10 (m, 1H), 7.69 – 7.59 (m, 2H), 7.33 (d, *J* = 9.2 Hz, 2H), 7.21 – 7.16 (m, 1H), 6.66 (dd, *J* = 9.3, 2.0 Hz, 2H), 6.35 (d, *J* = 2.0 Hz, 2H), 4.27 – 4.13 (m, 8H), 3.94 (s, 3H), 2.51 (p, *J* = 7.6 Hz, 4H); ¹³C NMR (CD₃OD, 101 MHz) δ 158.8 (C), 156.3 (C), 144.7 (C), 135.8 (C), 133.2 (CH), 131.5 (CH), 131.13 (CH), 131.06 (CH), 131.04 (C), 130.3 (CH), 117.9 (C), 113.1 (CH), 91.8 (CH), 52.5 (CH₂), 36.3 (CH₃), 16.9 (CH₂); Analytical HPLC: *t*_R = 12.0 min, >99% purity (10–95% MeCN/H₂O, 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 C₂₇H₂₆N₃O₂ [M+H]⁺ 424.2020, found 424.2021.

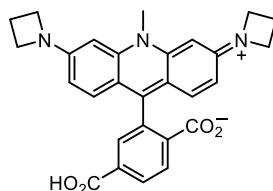


JF₄₉₀ (S18): A solution of dibromide **S15** (200 mg, 0.411 mmol) in THF (10 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ under nitrogen. *tert*-Butyllithium (1.7 M in pentane, 1.06 mL, 1.81 mmol, 4.4 eq) was added, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. It was then warmed to $-20\text{ }^{\circ}\text{C}$, and a solution of phthalic anhydride (**S17**; 134 mg, 0.903 mmol, 2.2 eq) in THF (10 mL) was added dropwise over 30 min via addition funnel. The reaction was allowed to warm to room temperature overnight (18 h). Following the addition of AcOH (100 μL), the mixture was diluted with MeOH, deposited onto Celite, and concentrated to dryness. Silica gel chromatography (0–20% MeOH (2 M NH_3)/ CH_2Cl_2 , linear gradient; dry load with Celite) followed by reverse phase HPLC (10–75% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive) afforded 105 mg (45%, TFA salt) of JF₄₉₀ (**S18**) as a bright orange solid. ^1H NMR (CD_3OD , 400 MHz) δ 8.39 – 8.34 (m, 1H), 7.84 (td, $J = 7.5, 1.7$ Hz, 1H), 7.79 (td, $J = 7.6, 1.6$ Hz, 1H), 7.36 – 7.31 (m, 1H), 7.27 (d, $J = 9.2$ Hz, 2H), 6.78 (dd, $J = 9.2, 2.0$ Hz, 2H), 6.61 (d, $J = 2.0$ Hz, 2H), 5.55 (dtt, $^2J_{\text{HF}} = 57.1$ Hz, $J = 6.0, 3.1$ Hz, 2H), 4.61 – 4.48 (m, 4H), 4.39 – 4.23 (m, 4H), 4.13 (s, 3H); ^{19}F NMR (CD_3OD , 376 MHz) δ –75.59 (s, 3F), –180.26 (dtt, $J_{\text{FH}} = 56.8, 23.7, 20.3$ Hz, 2F); ^{13}C NMR (CD_3OD , 101 MHz) δ 168.2 (C), 158.2 (C), 156.1 (d, $^4J_{\text{CF}} = 2.3$ Hz, C), 144.8 (C), 137.5 (C), 133.9 (CH), 132.62 (CH), 132.58 (CH), 132.21 (C), 132.17 (CH), 131.1 (CH), 118.3 (C), 114.3 (CH), 93.0 (CH), 83.7 (d, $^1J_{\text{CF}} = 203.4$ Hz, CHF), 60.2 (d, $^2J_{\text{CF}} = 26.0$ Hz, CH_2), 36.6 (CH_3); Analytical HPLC: $t_{\text{R}} = 10.9$ 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 500 nm); HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{24}\text{F}_2\text{N}_3\text{O}_2$ [$\text{M}+\text{H}$] $^{+}$ 460.1831, found 460.1835.



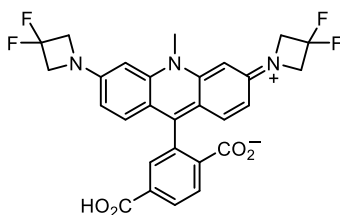
JF₄₇₉ (11): A solution of dibromide **S16** (200 mg, 0.382 mmol) in THF (10 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ under nitrogen. *tert*-Butyllithium (1.7 M in pentane, 989 μL , 1.68 mmol, 4.4 eq) was added, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. It was then warmed to $-20\text{ }^{\circ}\text{C}$, and a solution of phthalic anhydride (**S17**; 125 mg, 0.841 mmol, 2.2 eq) in THF (10 mL) was added dropwise over 30 min via addition funnel. The reaction was allowed to warm to room temperature overnight (18 h). Following the addition of AcOH (100 μL), the mixture was diluted with MeOH, deposited onto Celite, and concentrated to dryness. Silica gel chromatography (0–20% MeOH (2 M NH_3)/ CH_2Cl_2 , linear gradient; dry load with Celite) afforded 95 mg (50%) of JF₄₇₉ (**11**) as a bright orange solid. ^1H NMR (CD_3OD , 400 MHz) δ 8.19 – 8.13 (m, 1H), 7.69 (td, $J = 7.6, 1.5$ Hz, 1H), 7.64 (td, $J = 7.4, 1.6$ Hz, 1H), 7.49 (d, $J = 9.2$ Hz, 2H), 7.23 – 7.18 (m, 1H), 6.85 (dd, $J = 9.2, 2.0$ Hz, 2H), 6.73 (d, $J = 2.0$ Hz, 2H), 4.65 – 4.56 (m, 8H), 4.15 (s, 3H); ^{19}F NMR (CD_3OD , 376 MHz) δ –100.58 – –100.76 (m); Analytical HPLC: $t_{\text{R}} = 11.4$ min, >99% purity (10–75%

MeCN/H₂O, 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 C₂₇H₂₂F₄N₃O₂ [M+H]⁺ 496.1643, found 496.1651.



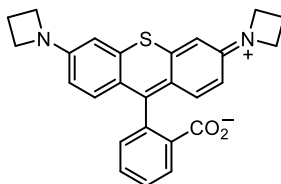
6-Carboxy-JF₅₀₂ (S22): A solution of dibromide **S14** (325 mg, 0.720 mmol, 1.5 eq) in THF (20 mL) was cooled to −78 °C under nitrogen. *tert*-Butyllithium (1.7 M in pentane, 1.69 mL, 2.88 mmol, 6 eq) was added, and the reaction was stirred at −78 °C for 30 min. It was then warmed to −20 °C, and a solution of ester **S19**^[1] (188 mg, 0.480 mmol) in THF (10 mL) was added dropwise over 30 min via addition funnel. The reaction was allowed to warm to room temperature overnight (18 h). It was subsequently diluted with saturated NH₄Cl and water and extracted with 15% *i*-PrOH/CHCl₃ (3×). The combined organic extracts were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The resulting residue was redissolved in MeOH (10 mL), and 1 M HCl (0.5 mL) was added. After stirring the solution at room temperature for 30 min, it was diluted with toluene (10 mL), deposited onto Celite, concentrated to dryness, and purified by flash chromatography (0–20% MeOH/CH₂Cl₂, linear gradient, with constant 1% v/v AcOH additive; dry load with Celite) to provide the bis(2,2-bis(hydroxymethyl)propyl) diester intermediate **S20** (213 mg, 61%, acetate salt).

Diester **S20** (213 mg, 0.291 mmol) was taken up in 2,2,2-trifluoroethanol (9 mL), and 25% w/w NaOH (3 mL) was added. The reaction was stirred at room temperature for 7 days. It was then acidified with AcOH (3 mL), diluted with water, and extracted with 15% *i*-PrOH/CHCl₃ (3×). The combined organic extracts were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (0–20% MeOH/CH₂Cl₂, linear gradient, with constant 1% v/v AcOH additive) afforded 6-carboxy-JF₅₀₂ (**S22**) as an orange solid (116 mg, 76%, acetate salt). ¹H NMR (CD₃OD, 400 MHz) δ 8.41 (d, *J* = 8.1 Hz, 1H), 8.37 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.18 (d, *J* = 9.2 Hz, 2H), 6.70 (dd, *J* = 9.2, 2.0 Hz, 2H), 6.45 (d, *J* = 2.0 Hz, 2H), 4.30 – 4.21 (m, 8H), 4.08 (s, 3H), 2.54 (p, *J* = 7.5 Hz, 4H); ¹³C NMR (CD₃OD, 101 MHz) δ 167.9 (C), 167.6 (C), 156.5 (C), 155.9 (C), 144.9 (C), 137.7 (C), 136.2 (C), 135.8 (C), 133.0 (CH), 132.7 (CH), 132.2 (CH), 131.8 (CH), 117.6 (C), 113.7 (CH), 91.9 (CH), 52.6 (CH₂), 36.4 (CH₃), 16.9 (CH₂); Analytical HPLC: *t*_R = 9.7 min, >99% purity (10–95% MeCN/H₂O, 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 C₂₈H₂₆N₃O₄ [M+H]⁺ 468.1918, found 468.1921.



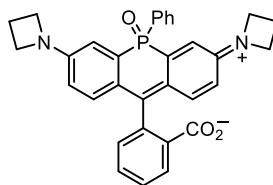
6-Carboxy-JF₄₇₉ (S23): A solution of dibromide **S16** (500 mg, 0.956 mmol, 1.5 eq) in THF (25 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ under nitrogen. *tert*-Butyllithium (1.7 M in pentane, 2.25 mL, 3.82 mmol, 6 eq) was added, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. It was then warmed to $-20\text{ }^{\circ}\text{C}$, and a solution of ester **S19** (250 mg, 0.637 mmol, 1 eq) in THF (15 mL) was added dropwise over 30 min via addition funnel. The reaction was allowed to warm to room temperature overnight (18 h). It was subsequently diluted with saturated NH_4Cl and water and extracted with EtOAc (1 $\times$) and 15% *i*-PrOH/ CHCl_3 (3 $\times$). The combined organic extracts were dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo*. The resulting residue was redissolved in MeOH (10 mL), and 1 M HCl (0.5 mL) was added. After stirring the solution at room temperature for 30 min, it was diluted with toluene (10 mL), concentrated to dryness, and purified by flash chromatography (0–20% MeOH/ CH_2Cl_2 , linear gradient, with constant 1% v/v AcOH additive) to provide the bis(2,2-bis(hydroxymethyl)propyl) diester intermediate **S21** (397 mg, 78%, acetate salt).

Diester **S21** (397 mg, 0.494 mmol) was taken up in 2,2,2-trifluoroethanol (15 mL), and 25% w/w NaOH (5 mL) was added. The reaction was stirred at room temperature for 6 days. It was then acidified with AcOH (5 mL), diluted with water, and extracted with 15% *i*-PrOH/ CHCl_3 (3 $\times$) and 10% MeOH/ CH_2Cl_2 (3 $\times$). The aqueous layer—which was still an orange suspension after extensive extraction—was filtered; the filter cake was washed with water and CH_2Cl_2 and dried to provide clean product as an orange powder. The combined organic extracts were dried over anhydrous MgSO_4 , filtered, and evaporated to dryness. The resultant residue was triturated with CH_2Cl_2 and filtered. The isolated solid was washed with CH_2Cl_2 and water and dried, affording additional clean product. The two crops of orange solid were combined, providing a total yield of 229 mg (86%) of 6-carboxy-JF₄₇₉ (**S23**). ^1H NMR (CD_3OD , 400 MHz) δ 8.45 (d, J = 8.2 Hz, 1H), 8.40 (dd, J = 8.2, 1.6 Hz, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 9.2 Hz, 2H), 6.89 (dd, J = 9.3, 2.0 Hz, 2H), 6.83 (d, J = 2.0 Hz, 2H), 4.66 (t, $^3J_{\text{HF}}$ = 11.8 Hz, 8H), 4.31 (s, 3H); ^{19}F NMR (CD_3OD , 376 MHz) δ -100.74 (p, $^3J_{\text{FH}}$ = 11.7 Hz); Analytical HPLC: t_{R} = 9.0 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 475 nm); HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{22}\text{F}_4\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$ 540.1541, found 540.1544.

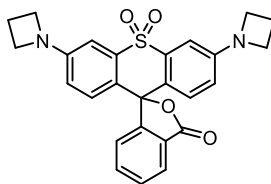


JF₅₇₀ (3): A solution of dibromide **S33** (200 mg, 0.440 mmol) in THF (10 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ under nitrogen. *tert*-Butyllithium (1.7 M in pentane, 1.14 mL, 1.94 mmol, 4.4 eq) was added, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. It was then warmed to $-20\text{ }^{\circ}\text{C}$, and a solution of phthalic anhydride (**S17**; 143 mg, 0.969 mmol, 2.2 eq) in THF (10 mL) was added dropwise over 30 min via addition funnel. The reaction was allowed to warm to room

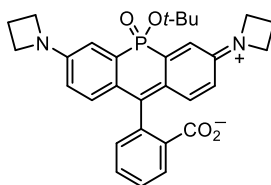
temperature overnight (18 h). Following the addition of AcOH (100 μ L), the mixture was diluted with MeOH, deposited onto Celite, and concentrated to dryness. Silica gel chromatography (0–10% MeOH (2 M NH_3)/ CH_2Cl_2 , linear gradient; dry load with Celite) afforded 87 mg (46%) of JF_{570} (**3**) as a dark purple solid. ^1H NMR (CD_3OD , 400 MHz) δ 8.14 – 8.08 (m, 1H), 7.68 – 7.59 (m, 2H), 7.25 (d, J = 9.3 Hz, 2H), 7.21 – 7.17 (m, 1H), 6.79 (d, J = 2.3 Hz, 2H), 6.55 (dd, J = 9.3, 2.3 Hz, 2H), 4.22 (t, J = 7.6 Hz, 8H), 2.51 (p, J = 7.6 Hz, 4H); ^{13}C NMR (CD_3OD , 101 MHz) δ 172.6 (C), 158.9 (C), 154.0 (C), 144.0 (C), 139.14 (C), 139.10 (C), 136.7 (CH), 131.3 (CH), 130.8 (CH), 130.4 (CH), 130.3 (CH), 120.7 (C), 113.9 (CH), 104.6 (CH), 52.6 (CH_2), 16.9 (CH_2); Analytical HPLC: t_{R} = 11.8 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 $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 427.1475, found 427.1489.



2-(3,7-Di(azetidino-1-yl)-5-oxido-5-phenyl-10H-acridophosphin-10-yl)benzoate (7): A solution of dibromide **S43** (250 mg, 0.458 mmol) in THF (40 mL) was cooled to -20 $^{\circ}\text{C}$ under nitrogen. Lithium dibutyl(isopropyl)magnesate (0.7 M in Et_2O /hexanes, 785 μL , 0.549 mmol, 1.2 eq) was added, and the reaction was stirred at -20 $^{\circ}\text{C}$ for 20 min. A solution of phthalic anhydride (**S17**; 244 mg, 1.65 mmol, 3.6 eq) in THF (5 mL) was added dropwise over 5 min, and the reaction was gradually warmed to 0 $^{\circ}\text{C}$ over 4 h. It was subsequently quenched with saturated NH_4Cl , diluted with water, and extracted with EtOAc ($2\times$). The combined organic extracts were washed with saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered, and evaporated. Flash chromatography on silica gel (0–75% acetone/ CH_2Cl_2 , linear gradient) yielded 50 mg (21%) of phosphine oxide rhodamine **7** as a white solid. ^1H NMR (CDCl_3 , 400 MHz) δ 7.94 (dt, J = 7.8, 1.0 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.54 – 7.36 (m, 4H), 7.22 (td, J = 7.7, 1.2 Hz, 1H), 7.13 (dd, J = 13.2, 2.6 Hz, 2H), 6.92 (dd, J = 8.8, 6.0 Hz, 2H), 6.49 (dd, J = 8.8, 2.6 Hz, 2H), 6.22 (d, J = 7.8 Hz, 1H), 4.01 – 3.88 (m, 8H), 2.38 (p, J = 7.3 Hz, 4H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 171.0 (C), 155.9 (d, J_{CP} = 0.8 Hz, C), 151.4 (d, J_{CP} = 11.9 Hz, C), 136.5 (d, J_{CP} = 108.0 Hz, C), 134.7 (CH), 131.6 (d, J_{CP} = 2.8 Hz, CH), 131.3 (d, J_{CP} = 10.0 Hz, CH), 129.0 (CH), 128.9 (d, J_{CP} = 2.9 Hz, CH), 128.7 (d, J_{CP} = 12.2 Hz, CH), 127.5 (d, J_{CP} = 100.2 Hz, C), 127.1 (d, J_{CP} = 7.6 Hz, C), 125.6 (CH), 124.8 (C), 122.4 (CH), 115.5 (d, J_{CP} = 2.4 Hz, CH), 112.1 (d, J_{CP} = 6.6 Hz, CH), 85.9 (d, J_{CP} = 7.5 Hz, C), 52.2 (CH_2), 16.8 (CH_2); 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 675 nm); HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{28}\text{N}_2\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$ 519.1832, found 519.1837.

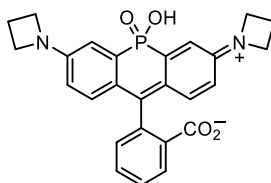


3',6'-Di(azetidin-1-yl)-3*H*-spiro[isobenzofuran-1,9'-thioxanthen]-3-one 10',10'-dioxide (8): A solution of dibromide **S34** (250 mg, 0.514 mmol) in THF (40 mL) was cooled to $-20\text{ }^{\circ}\text{C}$ under nitrogen. Lithium dibutyl(isopropyl)magnesate (0.7 M in Et₂O/hexanes, 881 μL , 0.617 mmol, 1.2 eq) was added, and the reaction was stirred at $-20\text{ }^{\circ}\text{C}$ for 20 min. A solution of phthalic anhydride (**S17**; 274 mg, 1.85 mmol, 3.6 eq) in THF (5 mL) was then added dropwise over 10 min. The reaction was gradually warmed to $0\text{ }^{\circ}\text{C}$ over 4 h while stirring. It was subsequently quenched with saturated NH₄Cl, diluted with water, and extracted with EtOAc (1 $\times$) and 15% *i*-PrOH/CHCl₃ (2 $\times$). The combined organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated. The crude residue was triturated with CH₂Cl₂, sonicated, and filtered; the filter cake was washed with additional CH₂Cl₂ and dried to yield 57 mg (24%) of SO₂-rhodamine **8** as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.95 – 7.91 (m, 1H), 7.82 – 7.79 (m, 1H), 7.52 (td, J = 7.5, 1.3 Hz, 1H), 7.46 (td, J = 7.4, 1.0 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 2.5 Hz, 2H), 6.47 (dd, J = 8.8, 2.6 Hz, 2H), 3.97 (t, J = 7.4 Hz, 8H), 2.42 (p, J = 7.3 Hz, 4H); ¹³C NMR (CDCl₃, 101 MHz) δ 170.9 (C), 154.6 (C), 152.0 (C), 136.6 (C), 135.5 (CH), 129.5 (CH), 127.5 (CH), 125.9 (CH), 123.8 (CH), 123.6 (C), 123.3 (C), 115.4 (CH), 104.7 (CH), 83.1 (C), 52.2 (CH₂), 16.8 (CH₂); Analytical HPLC: t_R = 15.5 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 280 nm); HRMS (ESI) calcd for C₂₆H₂₂N₂O₄SNa [M+Na]⁺ 481.1192, found 481.1201.

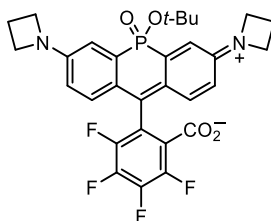


tert-Butyl-JF₆₆₈ (S50): A solution of dibromide **S38** (100 mg, 0.184 mmol) in THF (4 mL) was cooled to $-20\text{ }^{\circ}\text{C}$ under nitrogen. Lithium dibutyl(isopropyl)magnesate (0.7 M in Et₂O/hexanes, 316 μL , 0.221 mmol, 1.2 eq) was added, and the reaction was stirred at $-20\text{ }^{\circ}\text{C}$ for 20 min. A solution of phthalic anhydride (**S17**; 98 mg, 0.664 mmol, 3.6 eq) in THF (2 mL) was added dropwise over 10 min, and the reaction was allowed to warm to room temperature overnight (18 h). It was subsequently quenched with saturated NH₄Cl, diluted with water, and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered, and evaporated. Flash chromatography on silica gel (0–50% MeCN/CH₂Cl₂, linear gradient) afforded 41 mg (43%) of *tert*-butyl-JF₆₆₈ (**S50**) as a tan solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.93 – 7.88 (m, 1H), 7.72 – 7.66 (m, 1H), 7.44 – 7.37 (m, 2H), 7.13 (dd, J = 8.8, 6.9 Hz, 2H), 7.09 (dd, J = 14.4, 2.6 Hz, 2H), 6.47 (dd, J = 8.8, 2.6 Hz, 2H), 3.99 – 3.88 (m, 8H), 2.38 (p, J = 7.3 Hz, 4H), 1.66 (s, 9H); ¹³C NMR (CDCl₃, 101 MHz) δ 171.7 (C), 156.92 (d, J_{CP} = 1.2 Hz, C), 151.4 (d, J_{CP} = 13.1 Hz, C), 134.6 (CH), 129.4 (d, J_{CP} = 8.6 Hz, C), 129.0 (d, J_{CP} = 130.5 Hz, C), 128.8 (CH), 127.0 (d, J_{CP} = 11.7 Hz, CH), 125.9 (CH), 123.13 (CH), 123.12 (C), 115.2 (d, J_{CP} = 2.3 Hz, CH), 111.1 (d, J_{CP} = 6.4

Hz, CH), 85.8 (d, J_{CP} = 9.9 Hz, C), 84.8 (d, J_{CP} = 8.5 Hz, C), 52.4 (CH₂), 31.4 (d, J_{CP} = 3.9 Hz, CH₃), 17.0 (CH₂); Analytical HPLC: t_R = 14.8 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 700 nm); HRMS (ESI) calcd for C₃₀H₃₁N₂O₄PNa [M+Na]⁺ 537.1914, found 537.1930.

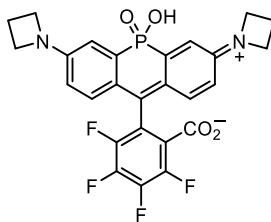


JF₆₆₈ (6): Phosphinate **S50** (28 mg, 54.4 μ mol) was taken up in CH₂Cl₂ (2 mL); triethylsilane (200 μ L) was added, followed by trifluoroacetic acid (200 μ L). The reaction was stirred at room temperature for 1 h. Toluene (2 mL) was added, and the reaction mixture was concentrated to dryness. The crude material was purified by reverse phase HPLC (10–50% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN and extracted with 15% *i*-PrOH/CHCl₃ (3 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 20 mg (80%) of JF₆₆₈ (**6**) as a blue solid. ¹H NMR (CD₃OD, 400 MHz) δ 8.07 (d, J = 7.7 Hz, 1H), 7.68 (td, J = 7.4, 1.2 Hz, 1H), 7.62 (td, J = 7.5, 1.0 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.14 (dd, J = 14.6, 2.6 Hz, 2H), 6.97 (dd, J = 9.0, 6.5 Hz, 2H), 6.58 (dd, J = 8.9, 2.3 Hz, 2H), 4.17 (t, J = 7.5 Hz, 8H), 2.49 (p, J = 7.5 Hz, 4H); Analytical HPLC: t_R = 9.5 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₂₆H₂₃N₂O₄PNa [M+Na]⁺ 481.1288, found 481.1292.

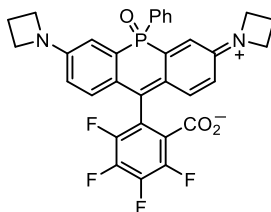


tert-Butyl-JF₆₉₀ (S51): A solution of dibromide **S38** (200 mg, 0.369 mmol) in THF (8 mL) was cooled to –20 °C under nitrogen. Lithium dibutyl(isopropyl)magnesate (0.7 M in Et₂O/hexanes, 632 μ L, 0.443 mmol, 1.2 eq) was added, and the reaction was stirred at –20 °C for 20 min. A solution of tetrafluorophthalic anhydride (**S49**; 292 mg, 1.33 mmol, 3.6 eq) in THF (4 mL) was added dropwise over 10 min, and the reaction was allowed to warm to room temperature over ~8 h. It was subsequently quenched with saturated NH₄Cl, diluted with water, and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered, and evaporated. Flash chromatography on silica gel (0–50% MeCN/CH₂Cl₂, linear gradient) afforded 38 mg (18%) of *tert*-butyl-JF₆₉₀ (**S51**) as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.02 (dd, J = 14.5, 2.6 Hz, 2H), 6.88 (dd, J = 8.8, 6.9 Hz, 2H), 6.48 (dd, J = 8.8, 2.6 Hz, 2H), 4.03 – 3.91 (m, 8H), 2.41 (p, J = 7.3 Hz, 4H), 1.59 (s, 9H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –138.63 (td, J = 19.9, 8.8 Hz, 1F), –139.62 – –139.78 (m, 1F), –142.54 – –142.73 (m, 1F), –151.67 – –151.86 (m, 1F); Analytical HPLC: t_R = 15.3 min, 97.1% purity (10–95% MeCN/H₂O,

linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 700 nm); HRMS (ESI) calcd for $C_{30}H_{27}F_4N_2O_4PNa$ $[M+Na]^+$ 609.1537, found 609.1546.

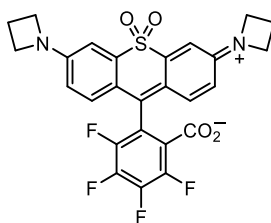


JF₆₉₀ (16): Phosphinate **S51** (27 mg, 46.0 μ mol) was taken up in CH_2Cl_2 (2 mL); triethylsilane (200 μ L) was added, followed by trifluoroacetic acid (200 μ L). The reaction was stirred at room temperature for 1 h. Toluene (2 mL) was added, and the reaction mixture was concentrated to dryness. The crude material was purified by reverse phase HPLC (10–50% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN and extracted with 15% *i*-PrOH/ $CHCl_3$ (3 $\times$). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to yield 16 mg (66%) of JF₆₉₀ (**16**) as a dark blue solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ 6.89 (dd, J = 8.9, 6.4 Hz, 2H), 6.87 (dd, J = 14.0, 2.6 Hz, 2H), 6.43 (dd, J = 8.7, 2.7 Hz, 2H), 3.92 (t, J = 7.3 Hz, 8H), 2.36 (p, J = 7.2 Hz, 4H); ^{19}F NMR ($DMSO-d_6$, 376 MHz) δ -73.16, -139.66 – -139.94 (m, 1F), -140.06 – -140.43 (m, 1F), -143.22 – -143.50 (m, 1F), -151.11 – -151.43 (m, 1F); 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 675 nm); HRMS (ESI) calcd for $C_{26}H_{19}F_4N_2O_4PNa$ $[M+Na]^+$ 553.0911, found 553.0921.

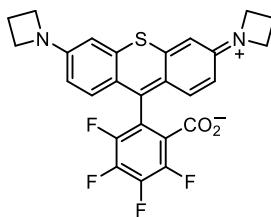


JF₇₂₂ (17): A solution of dibromide **S43** (500 mg, 0.915 mmol) in THF (100 mL) was cooled to -20 $^{\circ}C$ under nitrogen. Lithium dibutyl(isopropyl)magnesate (0.7 M in Et_2O /hexanes, 1.57 mL, 1.10 mmol, 1.2 eq) was added, and the reaction was stirred at -20 $^{\circ}C$ for 20 min. A solution of tetrafluorophthalic anhydride (**S49**; 725 mg, 3.30 mmol, 3.6 eq) in THF (5 mL) was added dropwise over 5 min, and the reaction was gradually warmed to 0 $^{\circ}C$ over 4 h. It was subsequently quenched with saturated NH_4Cl , diluted with water, and extracted with $EtOAc$ (2 $\times$). The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude material was purified by silica gel chromatography (0–75% acetone/ CH_2Cl_2 , linear gradient) followed by reverse phase HPLC (10–95% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (2 $\times$). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to yield 63 mg (12%) of JF₇₂₂ (**17**) as an off-white solid. 1H NMR ($CDCl_3$, 400 MHz) δ 7.75 – 7.67 (m, 2H), 7.53 – 7.46 (m,

1H), 7.46 – 7.39 (m, 2H), 6.78 (dd, $J = 13.8, 2.6$ Hz, 2H), 6.77 (d, $J = 8.8, 5.9$ Hz, 2H), 6.45 (dd, $J = 8.8, 2.5$ Hz, 2H), 3.98 – 3.82 (m, 8H), 2.36 (p, $J = 7.3$ Hz, 4H); ^{19}F NMR (CDCl_3 , 376 MHz) δ –138.39 (td, $J = 19.8, 9.0$ Hz, 1F), –141.27 (td, $J = 20.3, 3.9$ Hz, 1F), –142.40 (ddd, $J = 20.5, 18.4, 9.1$ Hz, 1F), –150.60 – –150.76 (m, 1F); 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 725 nm); HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{24}\text{F}_4\text{N}_2\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$ 591.1455, found 591.1464.

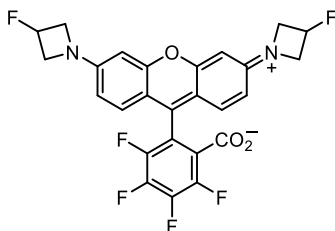


JF₇₂₄ (18): A solution of dibromide **S34** (800 mg, 1.65 mmol) in THF (125 mL) was cooled to –20 °C under nitrogen. Lithium dibutyl(isopropyl)magnesate (0.7 M in Et_2O /hexanes, 2.82 mL, 1.97 mmol, 1.2 eq) was added, and the reaction was stirred at –20 °C for 20 min. A solution of tetrafluorophthalic anhydride (**S49**; 1.30 g, 5.92 mmol, 3.6 eq) in THF (10 mL) was then added dropwise over 10 min. The reaction was gradually warmed to 0 °C over 4 h while stirring. It was subsequently quenched with saturated NH_4Cl , diluted with water, and extracted with EtOAc (2×). The combined organic extracts were washed with saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered, and evaporated. Flash chromatography on silica gel (0–40% EtOAc/hexanes, linear gradient, with constant 40% v/v CH_2Cl_2 additive) afforded 307 mg (35%) of JF₇₂₄ (**18**) as an off-white solid. ^1H NMR (CDCl_3 , 400 MHz) δ 7.09 (d, $J = 2.5$ Hz, 2H), 6.74 (d, $J = 8.7$ Hz, 2H), 6.40 (dd, $J = 8.7, 2.5$ Hz, 2H), 4.01 (t, $J = 7.4$ Hz, 8H), 2.44 (p, $J = 7.3$ Hz, 4H); ^{19}F NMR (CDCl_3 , 376 MHz) δ –137.58 (td, $J = 20.0, 9.3$ Hz, 1F), –138.15 (td, $J = 20.0, 4.7$ Hz, 1F), –141.77 (ddd, $J = 20.6, 18.4, 9.2$ Hz, 1F), –149.37 (ddd, $J = 20.4, 18.4, 4.7$ Hz, 1F); Analytical HPLC: $t_R = 15.7$ min, 98.4% 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 280 nm); HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{19}\text{F}_4\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 531.0996, found 531.1001.

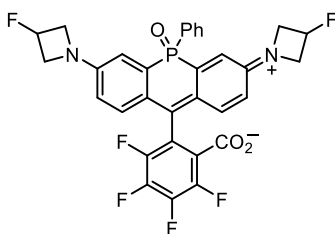


JF₅₉₃ (20): A solution of dibromide **S33** (2.00 g, 4.40 mmol) in THF (100 mL) was cooled to –78 °C under nitrogen. *tert*-Butyllithium (1.7 M in pentane, 11.40 mL, 19.4 mmol, 4.4 eq) was added, and the reaction was stirred at –78 °C for 30 min. It was then warmed to –20 °C, and a solution of tetrafluorophthalic anhydride (**S49**; 2.13 g, 9.69 mmol, 2.2 eq) in THF (25 mL) was added dropwise over 30 min via addition funnel. The reaction was allowed to warm to room temperature overnight (18 h). Following the addition of AcOH (1 mL), the mixture was diluted with MeOH, deposited onto Celite, and concentrated to dryness. Silica gel chromatography (0–10% MeOH/ CH_2Cl_2 , linear gradient,

with constant 1% v/v AcOH additive; dry load with Celite) afforded 484 mg (20%) of the acetate salt of JF₅₉₃ (**20**) as a dark purple solid. ¹H NMR (CD₃OD, 400 MHz) δ 7.40 (d, J = 9.3 Hz, 2H), 6.83 (d, J = 2.3 Hz, 2H), 6.68 (dd, J = 9.4, 2.3 Hz, 2H), 4.35 – 4.22 (m, 8H), 2.54 (p, J = 7.6 Hz, 4H), 1.99 (s, 3H); ¹⁹F NMR (CD₃OD, 376 MHz) δ –139.39 – –139.59 (m, 1F), –140.40 – –140.62 (m, 1F), –153.89 – –154.12 (m, 1F), –157.07 – –157.39 (m, 1F); Analytical HPLC: t_R = 12.3 min, >99% purity (10–95% MeCN/H₂O, 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 C₂₆H₁₉F₄N₂O₂S [M+H]⁺ 499.1098, found 499.1102.

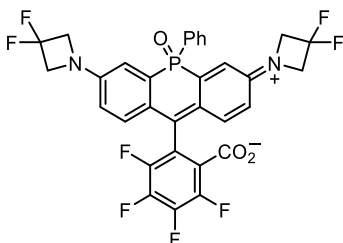


JF₅₅₉ (37): A solution of dibromide **S48** (500 mg, 1.05 mmol) in THF (20 mL) was cooled to –78 °C under nitrogen. *tert*-Butyllithium (1.7 M in pentane, 2.73 mL, 4.64 mmol, 4.4 eq) was added, and the reaction was stirred at –78 °C for 30 min. It was then warmed to –10 °C before adding a solution of MgBr₂·OEt₂ (599 mg, 2.32 mmol, 2.2 eq) in THF (10 mL). After an additional 30 min at –10 °C, a solution of tetrafluorophthalic anhydride (**S49**; 511 mg, 2.32 mmol, 2.2 eq) in THF (10 mL) was added dropwise over 30 min via addition funnel. The reaction was then allowed to warm to room temperature overnight (18 h). Following the addition of AcOH (100 μ L), the mixture was diluted with MeOH, deposited onto Celite, and concentrated to dryness. Silica gel chromatography (0–10% MeOH (2 M NH₃)/CH₂Cl₂, linear gradient; dry load with Celite) afforded 177 mg (32%) of JF₅₅₉ (**37**) as a dark red-purple solid. ¹H NMR (CD₃OD, 400 MHz) δ 7.37 (dd, J = 9.1, 0.5 Hz, 2H), 6.72 (dd, J = 9.2, 2.2 Hz, 2H), 6.58 (d, J = 2.2 Hz, 2H), 5.56 (dt, ² J_{HF} = 57.0 Hz, J = 6.0, 3.0 Hz, 2H), 4.66 – 4.53 (m, 4H), 4.44 – 4.30 (m, 4H); ¹⁹F NMR (CD₃OD, 376 MHz) δ –139.12 (ddd, J = 21.0, 12.7, 3.9 Hz, 1F), –140.70 (ddd, J = 22.1, 12.8, 4.0 Hz, 1F), –153.21 (ddd, J = 22.9, 19.1, 4.2 Hz, 1F), –157.02 – –157.18 (m, 1F), –180.54 (dt, J_{FH} = 57.1, 23.7, 20.4 Hz, 2F); Analytical HPLC: t_R = 11.1 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for C₂₆H₁₇F₆N₂O₃ [M+H]⁺ 519.1138, found 519.1138.



JF₇₁₁ (38): A solution of dibromide **S44** (1.35 g, 2.32 mmol) in THF (90 mL) was cooled to –20 °C under nitrogen. Lithium dibutyl(isopropyl)magnesate (0.7 M in Et₂O/hexanes, 3.97 mL, 2.78 mmol, 1.2 eq) was added, and the reaction was stirred at –20 °C for 20 min. A solution of tetrafluorophthalic anhydride (**S49**; 1.84 g, 8.35 mmol, 3.6

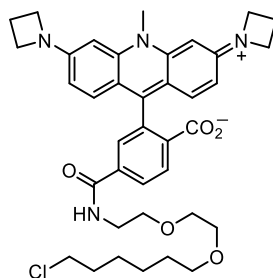
eq) in THF (10 mL) was added dropwise over 5 min, and the reaction was gradually warmed to 0 °C over 4 h. It was subsequently quenched with saturated NH₄Cl, diluted with water, and extracted with EtOAc (2×). The combined organic extracts were washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered, and evaporated. The crude was purified twice by silica gel chromatography (0–50% acetone/CH₂Cl₂, linear gradient; then, 25–100% EtOAc/hexanes, linear gradient) to afford 223 mg (15%) of JF₇₁₁ (**38**) as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.76 – 7.66 (m, 2H), 7.56 – 7.49 (m, 1H), 7.49 – 7.41 (m, 2H), 6.83 (dd, *J* = 13.6, 2.7 Hz, 2H), 6.82 (dd, *J* = 8.9, 5.8 Hz, 2H), 6.51 (dd, *J* = 8.9, 2.6 Hz, 2H), 5.38 (dtt, ²*J*_{HF} = 56.7 Hz, *J* = 6.1, 3.3 Hz, 2H), 4.29 – 4.11 (m, 4H), 4.09 – 3.89 (m, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –137.88 (td, *J* = 19.8, 9.2 Hz, 1F), –141.19 (td, *J* = 20.7, 4.1 Hz, 1F), –141.89 (ddd, *J* = 20.5, 18.5, 9.3 Hz, 1F), –150.00 – –150.17 (m, 1F), –180.55 (dtt, *J*_{FH} = 56.6, 23.4, 18.8 Hz, 2F); Analytical HPLC: *t*_R = 12.3 min, 97.6% purity (30–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 254 nm); HRMS (ESI) calcd for C₃₂H₂₂F₆N₂O₃P [M+H]⁺ 627.1267, found 627.1276.



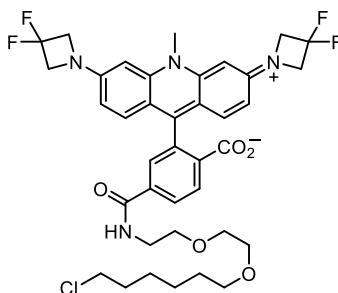
2-(3,7-Bis(3,3-difluoroazetidini-1-yl)-5-oxido-5-phenyl-10H-acridophosphin-10-ylum-10-yl)-3,4,5,6-

tetrafluorobenzoate (S52): A solution of dibromide **S45** (500 mg, 0.809 mmol) in THF (30 mL) was cooled to –20 °C under nitrogen. Lithium dibutyl(isopropyl)magnesate (0.7 M in Et₂O/hexanes, 1.39 mL, 0.971 mmol, 1.2 eq) was added, and the reaction was stirred at –20 °C for 20 min. A solution of tetrafluorophthalic anhydride (**S49**; 641 mg, 2.91 mmol, 3.6 eq) in THF (5 mL) was added dropwise over 5 min, and the reaction was gradually warmed to 0 °C over 4 h. It was subsequently quenched with saturated NH₄Cl, diluted with water, and extracted with EtOAc (2×). The combined organic extracts were washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered, and evaporated. Flash chromatography on silica gel (0–100% EtOAc/toluene, linear gradient) afforded 172 mg (32%) of **S52** as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.76 – 7.67 (m, 2H), 7.59 – 7.52 (m, 1H), 7.52 – 7.44 (m, 2H), 6.90 (dd, *J* = 14.0, 2.6 Hz, 2H), 6.88 (dd, *J* = 9.0, 5.6 Hz, 2H), 6.58 (dd, *J* = 8.8, 2.7 Hz, 2H), 4.34 – 4.16 (m, 8H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –100.01 (p, *J* = 11.6 Hz, 4F), –137.35 (td, *J* = 19.9, 9.7 Hz, 1F), –141.18 (td, *J* = 19.8, 4.1 Hz, 1F), –141.46 (ddd, *J* = 20.8, 18.4, 9.6 Hz, 1F), –149.46 – –149.62 (m, 1F); Analytical HPLC: *t*_R = 13.0 min, >99% purity (30–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 254 nm); HRMS (ESI) calcd for C₃₂H₂₀F₈N₂O₃P [M+H]⁺ 663.1078, found 663.1088.

AZA-RHODAMINE HALOTAG LIGANDS AND RHODAMINE SNAP-TAG LIGANDS

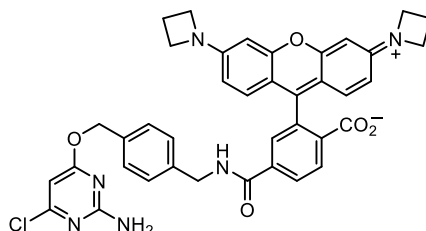


JF₅₀₂-HaloTag ligand (1_{HTL}): A suspension of acid **S22** (acetate salt; 25 mg, 47.4 μ mol) in DMF (10 mL) was heated to 50 °C. DIEA (41.3 μ L, 0.237 mmol, 5 eq) and HBTU (27.0 mg, 71.1 μ mol, 1.5 eq) were added, and the reaction was stirred for 10 min at 50 °C. A solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 24.0 mg, 71.1 μ mol, 1.5 eq) in DMF (500 μ L) was then added. After stirring the reaction for 1 h at 50 °C, it was cooled to room temperature and concentrated to remove DMF. Reverse phase HPLC of the crude material (30–60% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive) afforded JF₅₀₂-HaloTag ligand (**1_{HTL}**) as an orange solid (11.2 mg, 30%, TFA salt). ¹H NMR (CD₃OD, 400 MHz) δ 8.77 (t, J = 5.2 Hz, 1H), 8.39 (d, J = 8.3 Hz, 1H), 8.19 (dd, J = 8.2, 1.8 Hz, 1H), 7.75 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 9.2 Hz, 2H), 6.69 (dd, J = 9.3, 2.0 Hz, 2H), 6.47 (d, J = 2.0 Hz, 2H), 4.27 (t, J = 7.7 Hz, 8H), 4.12 (s, 3H), 3.69 – 3.54 (m, 8H), 3.52 (t, J = 6.6 Hz, 2H), 3.41 (t, J = 6.5 Hz, 2H), 2.55 (p, J = 7.5 Hz, 4H), 1.75 – 1.66 (m, 2H), 1.52 – 1.44 (m, 2H), 1.43 – 1.27 (m, 4H); Analytical HPLC: t_R = 12.5 min, >99% purity (10–95% MeCN/H₂O, 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 C₃₈H₄₆ClN₄O₅ [M+H]⁺ 673.3151, found 673.3158.

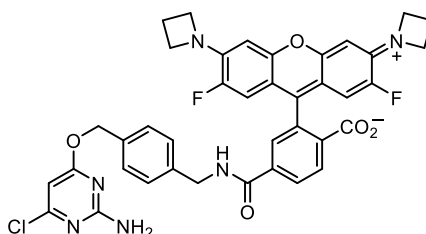


JF₄₇₉-HaloTag ligand (11_{HTL}): A suspension of acid **S23** (25 mg, 46.3 μ mol) in DMF (10 mL) was heated to 50 °C. DIEA (40.4 μ L, 0.232 mmol, 5 eq) and HBTU (21.1 mg, 55.6 μ mol, 1.2 eq) were added, and the reaction was stirred for 15 min at 50 °C. A solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 18.8 mg, 55.6 μ mol, 1.2 eq) in DMF (500 μ L) was then added. After stirring the reaction for 2 h at 50 °C, it was cooled to room temperature and concentrated to remove DMF. Reverse phase HPLC of the crude material (35–55% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive) afforded JF₄₇₉-HaloTag ligand (**11_{HTL}**) as a yellow-orange solid (11.4 mg, 29%, TFA salt). ¹H NMR (CD₃OD, 400 MHz) δ 8.76 (t, J = 5.3 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.22 (dd, J = 8.2, 1.8 Hz, 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 9.2 Hz, 2H), 6.89 (dd, J = 9.2, 2.1 Hz, 2H), 6.85 (d, J = 2.0 Hz, 2H), 4.67 (t, J_{HF} = 11.7 Hz, 8H), 4.34 (s, 3H), 3.69 – 3.54 (m, 8H), 3.52 (t, J = 6.6 Hz, 2H), 3.43 (t, J = 6.5 Hz, 2H), 1.76 – 1.67

(m, 2H), 1.55 – 1.46 (m, 2H), 1.45 – 1.28 (m, 4H); ^{19}F NMR (CD_3OD , 376 MHz) δ -75.26 (s, 3F), -100.72 (p, $^3J_{\text{FH}}$ = 12.0 Hz, 4F); 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 475 nm); HRMS (ESI) calcd for $\text{C}_{38}\text{H}_{42}\text{ClF}_4\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$ 745.2774, found 745.2787.



JF₅₄₉-cpSNAP-tag ligand (2_{STL}): JF₅₄₉-NHS^[2] (**S24**; TFA salt; 25 mg, 37.6 μmol) and 4-((4-(aminomethyl)benzyl)oxy)-6-chloropyrimidin-2-amine (**S25**; 29.8 mg, 0.113 mmol, 3 eq) were combined in DMF (2 mL), and Et₃N (31.4 μL , 0.225 mmol, 6 eq) was added. After stirring the reaction at room temperature for 18 h, it was directly purified by reverse phase HPLC (10–75% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive) to afford 15.0 mg (49%, TFA salt) of JF₅₄₉-cpSNAP-tag ligand (**2_{STL}**) as a red solid. ^1H NMR (CD_3OD , 400 MHz) δ 9.22 (t, J = 5.9 Hz, 1H), 8.39 (d, J = 8.2 Hz, 1H), 8.20 (dd, J = 8.2, 1.8 Hz, 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.37 (AB quartet, ν_{A} = 2953.2 Hz, ν_{B} = 2942.4 Hz, J_{AB} = 8.5 Hz, 4H), 7.04 (d, J = 9.2 Hz, 2H), 6.58 (dd, J = 9.2, 2.2 Hz, 2H), 6.53 (d, J = 2.2 Hz, 2H), 6.07 (s, 1H), 5.32 (s, 2H), 4.62 – 4.52 (m, 2H), 4.30 (t, J = 7.6 Hz, 8H), 2.56 (p, J = 7.7 Hz, 4H); 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 $\text{C}_{39}\text{H}_{34}\text{ClN}_6\text{O}_5$ $[\text{M}+\text{H}]^+$ 701.2, found 701.2.



JF₅₅₂-cpSNAP-tag ligand (13_{STL}): 6-Carboxy-JF₅₅₂^[3] (**S26**; TFA salt; 7.4 mg, 12.2 μmol) was combined with TSTU (8.8 mg, 29.4 μmol , 2.4 eq) in DMF (1 mL). After adding DIEA (49.0 μL , 0.282 mmol, 23 eq), the reaction was stirred at room temperature for 1 h. Following the addition of 4-((4-(aminomethyl)benzyl)oxy)-6-chloropyrimidin-2-amine (**S25**; 9.7 mg, 36.7 μmol , 3 eq), the reaction was stirred at room temperature for 18 h, 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) to provide 6.2 mg (59%, TFA salt) of JF₅₅₂-cpSNAP-tag ligand (**13_{STL}**) as a purple solid. ^1H NMR (CD_3OD , 400 MHz) δ 9.25 (t, J = 6.0 Hz, 1H), 8.41 (d, J = 8.2 Hz, 1H), 8.21 (dd, J = 8.2, 1.8 Hz, 1H), 7.78 (d, J =

^[2] Spahn, C. K.; Glaesmann, M.; Grimm, J. B.; Ayala, A. X.; Lavis, L. D.; Heilemann, M. *Sci. Rep.* **2018**, 8, 14768.

^[3] Zheng, Q.; Ayala, A. X.; Chung, I.; Weigel, A. V.; Ranjan, A.; Falco, N.; Grimm, J. B.; Tkachuk, A. N.; Wu, C.; Lippincott-Schwartz, J.; Singer, R. H.; Lavis, L. D. *ACS Cent. Sci.* **2019**, 5, 1602–1613.

1.7 Hz, 1H), 7.38 (AB quartet, $\nu_A = 2958.4$ Hz, $\nu_B = 2949.4$ Hz, $J_{AB} = 8.3$ Hz, 4H), 6.76 (d, $^3J_{HF} = 12.7$ Hz, 2H), 6.66 (d, $^4J_{HF} = 7.3$ Hz, 2H), 6.08 (s, 1H), 5.33 (s, 2H), 4.63 – 4.57 (m, 2H), 4.56 – 4.40 (m, 8H), 2.57 (p, $J = 7.7$ Hz, 4H); ^{19}F NMR (CD_3OD , 376 MHz) δ –77.77 (s, 3F), –132.96 (dd, $^3J_{FH} = 12.3$ Hz, $^4J_{FH} = 7.3$ Hz, 2F); 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); MS (ESI) calcd for $\text{C}_{39}\text{H}_{32}\text{ClF}_2\text{N}_6\text{O}_5$ $[\text{M}+\text{H}]^+$ 737.2, found 736.8.

MAC SUBSTITUTION OF 4,5,6,7-TETRAFLUORORHODAMINES

Given the generality of the pendant aryl ring fluorination as a strategy to tune the lactone–zwitterion equilibria and spectral properties of various rhodamine dyes, we then sought a convenient method to install the functionality necessary for labeling with and bioconjugation of 4,5,6,7-tetrafluororhodamines. It had been well-established that thiols undergo efficient substitution reactions with 4,5,6,7-tetrafluoroxanthene fluorophores—including fluoresceins and rhodamines—to form aryl sulfides at the 6-position.^[4,5] Nevertheless, the *general* nucleophile scope for the S_NAr of fluorinated xanthenes was less explored. We aimed to briefly investigate the reactivity of fluorinated rhodamines as substrates for nucleophilic aromatic substitution with a variety of common nucleophiles, including carbon-centered anions (*e.g.*, malonates) and heteroatom-based species (*e.g.*, azide, amine; see **Substitution of 4,5,6,7-Tetrafluororhodamines with Other Nucleophiles**).

Our overriding interest, however, was to develop an efficient approach to install a carboxyl group—or related functional surrogate—onto the fluorinated aryl ring. This would allow for the application of more traditional methods of bioconjugation, which typically involve the formation of an amide through a 5- or 6-carboxy substituent on the xanthene fluorophore. More specifically, it would enable the synthesis of self-labeling tag ligands (*e.g.*, HaloTag ligands) directly comparable to the existing des-fluorinated analogs, which already demonstrate ideal, optimized labeling kinetics. We required, therefore, a mild transformation that substituted one fluoride substituent with a carboxyl group; this suggested the use of an *umpolung*-type acyl anion equivalent. The elegant (albeit underused) masked acyl cyanide (MAC) chemistry developed by Nemoto and coworkers seemed most promising.^[6,7]

With this in mind, the known MOM-protected MAC reagent **34** (2-(methoxymethoxy)malononitrile)^[8,9] was reacted with a selection of 4,5,6,7-tetrafluororhodamines, including the yellow/orange oxygen- (**19**, **37**) and sulfide- (**20**) derivatives, the red silicon analogs (**15**, **S53**), and the NIR sulfone (**18**) and phosphine oxide (**17**, **38**) dyes (**Fig. 2f, Schemes S4–S5**).^[1] In the presence of an amine base (DIEA), each rhodamine underwent clean displacement of one fluoride substituent with **34** to provide a single regioisomeric substitution product in moderate to good yield. Although we expected—based on the thiol precedent and the probable S_NAr mechanism—that the substitution was most likely occurring at the position *para* to the lactone (*i.e.*, the 6-position), the regiochemistry of the reaction was definitively confirmed by single crystal X-ray diffraction (see **X-Ray Crystallography**). Compound **S59** was chosen for structural determination by SC-XRD simply out of convenience, as it entailed the shortest synthetic route and could be easily scaled up.

^[4] Panchuk-Voloshina, N.; Haugland, R.P.; Bishop-Stewart, J. et al. *J. Histochem. Cytochem.* **1999**, *47*, 1179–1188.

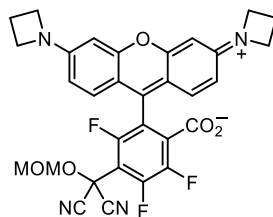
^[5] Gee, K.R.; Sun, W.-C.; Klaubert, D.H. et al. *Tetrahedron Lett.* **1996**, *37*, 7905–7908.

^[6] Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515–4516.

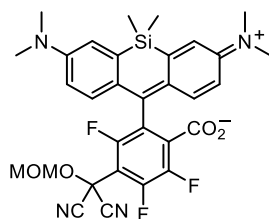
^[7] Nemoto, H.; Ibaragi, T.; Bando, M.; Kido, M.; Shibuya, M. *Tetrahedron Lett.* **1999**, *40*, 1319–1322.

^[8] Nemoto, H.; Li, X.; Ma, R.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2003**, *44*, 73–75.

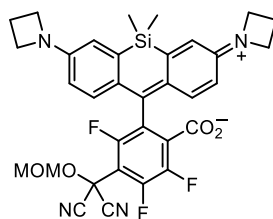
^[9] Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 16050–16053.



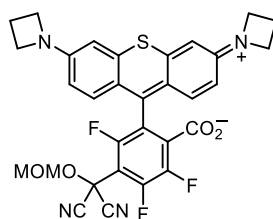
6-(MOM-MAC)-JF₅₇₁ (S58): JF₅₇₁^[1] (**19**; 155 mg, 0.321 mmol) and 2-(methoxymethoxy)malononitrile (**34**; 40.5 mg, 0.321 mmol, 1 eq) were combined in DMF (5 mL), and DIEA (112 μ L, 0.643 mmol, 2 eq) was added. After stirring the reaction at room temperature for 2 h, it was evaporated to dryness. Flash chromatography on silica gel (0–15% MeOH/CH₂Cl₂, linear gradient, with constant 1% v/v AcOH additive) afforded **S58** as a dark red-purple solid (108 mg, 52%, acetate salt). ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (d, J = 9.1 Hz, 2H), 6.46 (dd, J = 9.1, 2.2 Hz, 2H), 6.27 (d, J = 2.2 Hz, 2H), 5.15 (s, 2H), 4.22 (t, J = 7.6 Hz, 8H), 3.55 (s, 3H), 2.56 (p, J = 7.6 Hz, 4H), 2.05 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -114.38 (d, J = 16.5 Hz, 1F), -127.29 (d, J = 22.6 Hz, 1F), -138.86 (dd, J = 22.5, 16.6 Hz, 1F); Analytical HPLC: t_R = 10.4 min, 99.0% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for C₃₁H₂₄F₃N₄O₅ [M+H]⁺ 589.1693, found 589.1698.



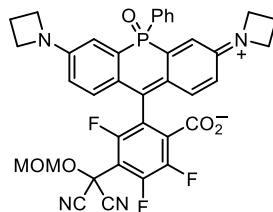
4,5,7-Trifluoro-6-(MOM-MAC)-SiTMR (S59): 4,5,6,7-Tetrafluoro-SiTMR^[1] (**S53**; 1.50 g, 3.00 mmol) and 2-(methoxymethoxy)malononitrile (**34**; 378 mg, 3.00 mmol, 1 eq) were combined in DMF (30 mL), and DIEA (1.04 mL, 5.99 mmol, 2 eq) was added. After stirring the reaction at room temperature for 1 h, it was evaporated to dryness. Flash chromatography on silica gel (10–100% EtOAc/hexanes, linear gradient) afforded **S59** as a blue-green solid (1.17 g, 64%). ¹H NMR (CDCl₃, 400 MHz) δ 6.94 (d, J = 2.9 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 6.62 (dd, J = 8.9, 2.9 Hz, 2H), 5.16 (s, 2H), 3.53 (s, 3H), 3.00 (s, 12H), 0.59 (s, 3H), 0.56 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -113.66 (d, J = 22.7 Hz, 1F), -127.80 (d, J = 20.4 Hz, 1F), -139.94 (dd, J = 22.6, 20.3 Hz, 1F); Analytical HPLC: t_R = 12.5 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₃₁H₃₀F₃N₄O₄Si [M+H]⁺ 607.1983, found 607.1990.



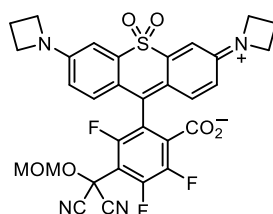
6-(MOM-MAC)-JF₆₆₉ (35): JF₆₆₉^[1] (**15**; 72 mg, 0.137 mmol) and DIEA (47.8 μ L, 0.275 mmol, 2 eq) were combined in DMF (3 mL), and a solution of 2-(methoxymethoxy)malononitrile (**34**; 17.3 mg, 0.137 mmol, 1 eq) in DMF (1 mL) was added dropwise. After stirring the reaction at room temperature for 4 h, it was concentrated to dryness. Flash chromatography on silica gel (10–100% EtOAc/hexanes, linear gradient) afforded 44.4 mg (51%) of **35** as a green foam. ¹H NMR (CDCl₃, 400 MHz) δ 6.70 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 2.6 Hz, 2H), 6.32 (dd, J = 8.7, 2.6 Hz, 2H), 5.16 (s, 2H), 3.93 (t, J = 7.2 Hz, 8H), 3.53 (s, 3H), 2.39 (p, J = 7.3 Hz, 4H), 0.55 (s, 3H), 0.53 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -113.41 (d, J = 22.6 Hz, 1F), -127.72 (d, J = 20.3 Hz, 1F), -139.78 (dd, J = 22.7, 20.2 Hz, 1F); Analytical HPLC: t_R = 13.0 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₃₃H₃₀F₃N₄O₄Si [M+H]⁺ 631.1983, found 631.1989.



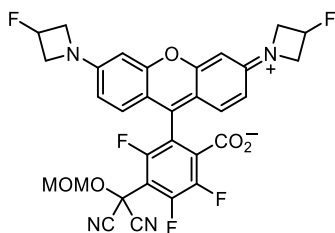
6-(MOM-MAC)-JF₅₉₃ (S69): JF₅₉₃ (**20**, acetate salt; 250 mg, 0.448 mmol) and 2-(methoxymethoxy)malononitrile (**34**; 56 mg, 0.448 mmol, 1 eq) were combined in DMF (10 mL), and DIEA (234 μ L, 1.34 mmol, 3 eq) was added. After stirring the reaction at room temperature for 3 h, it was concentrated *in vacuo*. The residue was redissolved in MeOH/CH₂Cl₂, deposited onto Celite, and evaporated to dryness. Flash chromatography on silica gel (0–15% MeOH/CH₂Cl₂, linear gradient, with constant 1% v/v AcOH additive; dry load with Celite) afforded **S69** as a dark purple solid (164 mg, 55%, acetate salt). ¹H NMR (CD₃OD, 400 MHz) δ 7.38 (d, J = 9.4 Hz, 2H), 6.87 (d, J = 2.2 Hz, 2H), 6.71 (dd, J = 9.4, 2.3 Hz, 2H), 5.21 (s, 2H), 4.31 (t, J = 7.7 Hz, 8H), 3.53 (s, 3H), 2.55 (p, J = 7.7 Hz, 4H); ¹⁹F NMR (CD₃OD, 376 MHz) δ -114.32 (d, J = 15.0 Hz, 1F), -130.76 (d, J = 21.5 Hz, 1F), -143.57 (dd, J = 21.8, 15.2 Hz, 1F); Analytical HPLC: t_R = 12.2 min, >99% purity (10–95% MeCN/H₂O, 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 C₃₁H₂₄F₃N₄O₄S [M+H]⁺ 605.1465, found 605.1464.



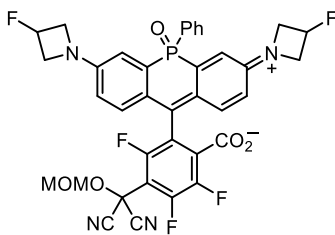
6-(MOM-MAC)-JF₇₂₂ (S70): JF₇₂₂ (**17**; 145 mg, 0.246 mmol) and 2-(methoxymethoxy)malononitrile (**34**; 31.0 mg, 0.246 mmol, 1 eq) were combined in DMF (8 mL), and DIEA (85.5 μ L, 0.491 mmol, 2 eq) was added. After stirring the reaction at room temperature for 2 h, it was evaporated to dryness. Flash chromatography on silica gel (0–75% acetone/CH₂Cl₂, linear gradient) afforded **S70** as a pale yellow solid (75.4 mg, 44%). ¹H NMR (CDCl₃, 400 MHz) δ 7.74 – 7.65 (m, 2H), 7.51 – 7.37 (m, 3H), 6.83 (dd, J = 13.7, 2.6 Hz, 2H), 6.76 (dd, J = 8.8, 5.9 Hz, 2H), 6.47 (dd, J = 8.8, 2.6 Hz, 2H), 5.10 (s, 2H), 4.01 – 3.83 (m, 8H), 3.48 (s, 3H), 2.37 (p, J = 7.3 Hz, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –116.06 (d, J = 22.6 Hz, 1F), –126.27 (d, J = 20.2 Hz, 1F), –138.85 (dd, J = 22.5, 20.3 Hz, 1F); Analytical HPLC: t_R = 13.8 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 725 nm); HRMS (ESI) calcd for C₃₇H₂₉F₃N₄O₅P [M+H]⁺ 697.1822, found 697.1825.



6-(MOM-MAC)-JF₇₂₄ (S71): To a solution of JF₇₂₄ (**18**; 150 mg, 0.283 mmol) in DMF (5 mL) were added DIEA (99 μ L, 0.566 mmol, 2 eq) and 2-(methoxymethoxy)malononitrile (**34**; 35.7 mg, 0.283 mmol, 1 eq). After stirring the reaction at room temperature for 2 h, it was evaporated to dryness. Flash chromatography on silica gel (0–50% EtOAc/hexanes, linear gradient, with constant 40% v/v CH₂Cl₂ additive) afforded **S71** as a yellow-green solid (76.4 mg, 42%). ¹H NMR (CDCl₃, 400 MHz) δ 7.10 (d, J = 2.5 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 6.40 (dd, J = 8.7, 2.5 Hz, 2H), 5.17 (s, 2H), 4.02 (t, J = 7.4 Hz, 8H), 3.54 (s, 3H), 2.45 (p, J = 7.4 Hz, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –112.54 (d, J = 22.8 Hz, 1F), –124.88 (d, J = 20.2 Hz, 1F), –138.16 (dd, J = 23.0, 20.3 Hz, 1F); Analytical HPLC: t_R = 13.0 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 725 nm); HRMS (ESI) calcd for C₃₁H₂₄F₃N₄O₆S [M+H]⁺ 637.1363, found 637.1365.



6-(MOM-MAC)-JF₅₅₉ (S72): JF₅₅₉ (**37**; 250 mg, 0.482 mmol) and 2-(methoxymethoxy)malononitrile (**34**; 60.8 mg, 0.482 mmol, 1 eq) were combined in DMF (10 mL), and DIEA (168 μ L, 0.964 mmol, 2 eq) was added. After stirring the reaction at room temperature for 3 h, it was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (0–15% MeOH/CH₂Cl₂, linear gradient, with constant 1% v/v AcOH additive) followed by reverse phase HPLC (10–75% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 153 mg (51%) of **S72** as a dark red-purple solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.75 (d, J = 8.6 Hz, 2H), 6.26 (d, J = 2.3 Hz, 2H), 6.22 (dd, J = 8.6, 2.3 Hz, 2H), 5.45 (dt, $^2J_{\text{HF}}$ = 56.7 Hz, J = 6.1, 3.5 Hz, 2H), 5.14 (s, 2H), 4.31 – 4.19 (m, 4H), 4.12 – 4.00 (m, 4H), 3.52 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –116.80 (d, J = 22.5 Hz, 1F), –126.23 (d, J = 20.3 Hz, 1F), –139.30 (dd, J = 22.5, 20.5 Hz, 1F), –180.63 (dt, J_{FH} = 56.6, 23.8, 18.6 Hz, 2F); Analytical HPLC: t_{R} = 11.9 min, 97.2% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for C₃₁H₂₂F₅N₄O₅ [M+H]⁺ 625.1505, found 625.1514.

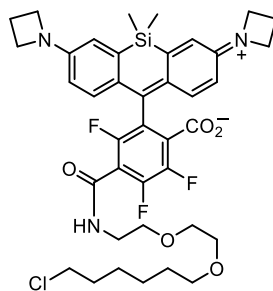


6-(MOM-MAC)-JF₇₁₁ (S73): JF₇₁₁ (**38**; 190 mg, 0.303 mmol) and 2-(methoxymethoxy)malononitrile (**34**; 38.3 mg, 0.303 mmol, 1 eq) were combined in DMF (6 mL), and DIEA (106 μ L, 0.607 mmol, 2 eq) was added. After stirring the reaction at room temperature for 2 h, it was concentrated *in vacuo*. The crude material was purified by silica gel chromatography (0–40% acetone/CH₂Cl₂, linear gradient) followed by reverse phase HPLC (20–80% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 88 mg (40%) of **S73** as a blue-green solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.74 – 7.65 (m, 2H), 7.54 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 6.88 (dd, J = 13.6, 2.6 Hz, 2H), 6.81 (dd, J = 8.8, 5.8 Hz, 2H), 6.54 (dd, J = 8.7, 2.6 Hz, 2H), 5.40 (dt, $^2J_{\text{HF}}$ = 56.8 Hz, J = 6.3, 3.5 Hz, 2H), 5.10 (s, 2H), 4.31 – 4.14 (m, 4H), 4.13 – 3.92 (m, 4H), 3.49 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –116.15 (d, J = 22.3 Hz, 1F), –125.67 (d, J = 20.1 Hz, 1F), –138.35 (dd, J = 22.6, 20.1 Hz, 1F), –180.54 (dt, J_{FH} = 56.5, 23.7, 18.9 Hz, 2F); Analytical HPLC: t_{R} = 14.5 min, 97.3% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20

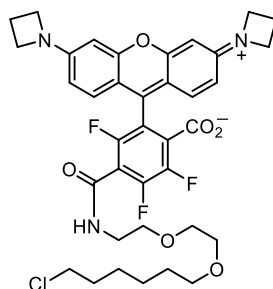
min run; 1 mL/min flow; ESI; positive ion mode; detection at 280 nm); HRMS (ESI) calcd for $C_{37}H_{27}F_5N_4O_5P$ $[M+H]^+$ 733.1634, found 733.1651.

CONVERSION OF MAC SUBSTITUTION PRODUCTS TO AMIDES AND ESTERS

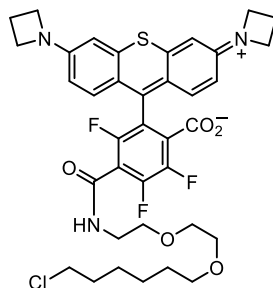
With the MAC-rhodamine products in hand, we then applied a variation of the protocols previously described by Nemoto^[6,7] and Rawal^[9] to convert these masked acyl groups into esters and amides such as HaloTag and SNAP-tag ligands (**Fig. 2f**, **Fig. 3a,f**, **Supplementary Fig. 6a,c**, **Supplementary Fig. 7e**, **Scheme S5**). Removal of the MOM protecting group on the MAC oxygen is achieved with TFA to yield a gem-dicyano alcohol. Following the removal of acid and solvent, this crude intermediate is reacted with an amine or alcohol in the presence of TEA or DIEA to directly afford an amide or ester. This conversion is presumed to proceed through an acyl cyanide (an activated ester equivalent) formed through a base-mediated cyanide elimination (**Supplementary Fig. 6a**, **Scheme S5**). This approach permitted direct access to the HaloTag ligands without formation and isolation of an intermediate 6-carboxyrhodamine. Although not detailed here, this transformation is quite general in scope and allows for the efficient amidation of fluorinated rhodamines with large and functionally diverse amines via this activated acyl cyanide intermediate. We also note that the structure of ester **S81** as determined by SC-XRD was consistent with the regiochemistry confirmed by X-ray diffraction of its precursor, MAC product **S59** (see **X-Ray Crystallography**).



JF₆₆₉–HaloTag ligand (15_{HTL}): Ether **35** (151 mg, 0.239 mmol) was taken up in CH₂Cl₂ (10 mL); triethylsilane (1 mL) was added, followed by trifluoroacetic acid (2 mL). The reaction was stirred at room temperature for 6 h. Toluene (10 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O₂)amine (HTL-NH₂, **36**; TFA salt; 162 mg, 0.479 mmol, 2 eq) and DIEA (417 μL, 2.39 mmol, 10 eq) in CH₂Cl₂ (10 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2×). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 114 mg (63%) of JF₆₆₉–HaloTag ligand (**15_{HTL}**) as a blue solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.78 (d, *J* = 8.6 Hz, 2H), 6.74 (bs, 1H), 6.63 (d, *J* = 2.7 Hz, 2H), 6.32 (dd, *J* = 8.7, 2.6 Hz, 2H), 3.92 (t, *J* = 7.3 Hz, 8H), 3.66 – 3.59 (m, 6H), 3.55 – 3.48 (m, 4H), 3.37 (t, *J* = 6.7 Hz, 2H), 2.38 (p, *J* = 7.3 Hz, 4H), 1.78 – 1.69 (m, 2H), 1.53 – 1.45 (m, 2H), 1.43 – 1.25 (m, 4H), 0.53 (s, 6H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –118.50 (d, *J* = 22.5 Hz, 1F), –133.47 (d, *J* = 21.6 Hz, 1F), –142.24 (t, *J* = 22.1 Hz, 1F); Analytical HPLC: *t_R* = 13.6 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₃₉H₄₆ClF₃N₃O₅Si [M+H]⁺ 756.2842, found 756.2856.

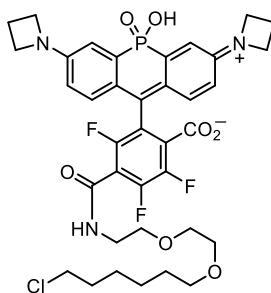


JF₅₇₁-HaloTag ligand (19_{HTL}): Ether **S58** (50 mg, 77.1 μ mol) was taken up in CH₂Cl₂ (5 mL); triethylsilane (500 μ L) was added, followed by trifluoroacetic acid (1 mL). The reaction was stirred at room temperature for 6 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 52.1 mg, 0.154 mmol, 2 eq) and DIEA (134 μ L, 0.771 mmol, 10 eq) in CH₂Cl₂ (4 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (30–60% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive) to yield 33.7 mg (53%, TFA salt) of JF₅₇₁-HaloTag ligand (**19_{HTL}**) as a dark red-purple solid. ¹H NMR (CD₃OD, 400 MHz) δ 9.08 (t, J = 5.3 Hz, 1H), 7.28 (d, J = 9.2 Hz, 2H), 6.67 (dd, J = 9.2, 2.2 Hz, 2H), 6.53 (d, J = 2.2 Hz, 2H), 4.34 (t, J = 7.6 Hz, 8H), 3.67 – 3.55 (m, 8H), 3.52 (t, J = 6.7 Hz, 2H), 3.43 (t, J = 6.5 Hz, 2H), 2.57 (p, J = 7.6 Hz, 4H), 1.76 – 1.67 (m, 2H), 1.54 – 1.46 (m, 2H), 1.44 – 1.29 (m, 4H); ¹⁹F NMR (CD₃OD, 376 MHz) δ -75.40 (s, 3F), -116.71 (d, J = 15.3 Hz, 1F), -132.53 (d, J = 22.4 Hz, 1F), -140.20 (dd, J = 22.6, 15.3 Hz, 1F); Analytical HPLC: t_R = 12.8 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for C₃₇H₄₀ClF₃N₃O₆ [M+H]⁺ 714.2552, found 714.2561.



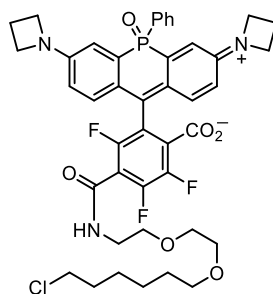
JF₅₉₃-HaloTag ligand (20_{HTL}): Ether **S69** (acetate salt; 50 mg, 75.2 μ mol) was taken up in CH₂Cl₂ (4 mL); triethylsilane (400 μ L) was added, followed by trifluoroacetic acid (800 μ L). The reaction was stirred at room temperature for 6 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 50.8 mg, 0.150 mmol, 2 eq) and DIEA (131 μ L, 0.752 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (30–60% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive) to afford JF₅₉₃-HaloTag ligand (**20_{HTL}**) as a dark purple solid (28.9 mg, 46%, TFA salt). ¹H NMR (CD₃OD, 400 MHz) δ 9.10 (t, J = 5.4 Hz, 1H), 7.39 (d, J = 9.3 Hz,

2H), 6.89 (d, $J = 2.3$ Hz, 2H), 6.70 (dd, $J = 9.4, 2.3$ Hz, 2H), 4.32 (t, $J = 7.7$ Hz, 8H), 3.67 – 3.54 (m, 8H), 3.52 (t, $J = 6.6$ Hz, 2H), 3.42 (t, $J = 6.5$ Hz, 2H), 2.56 (p, $J = 7.6$ Hz, 4H), 1.76 – 1.67 (m, 2H), 1.54 – 1.45 (m, 2H), 1.44 – 1.27 (m, 4H); ^{19}F NMR (CD_3OD , 376 MHz) δ –75.42 (s, 3F), –117.12 (d, $J = 15.4$ Hz, 1F), –133.08 (d, $J = 22.2$ Hz, 1F), –139.93 (dd, $J = 21.7, 15.8$ Hz, 1F); Analytical HPLC: $t_{\text{R}} = 12.5$ 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 600 nm); HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{40}\text{ClF}_3\text{N}_3\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$ 730.2324, found 730.2333.

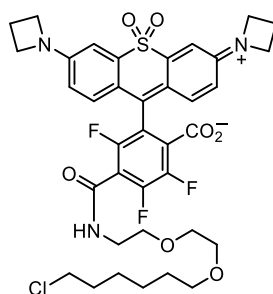


JF₆₉₀-HaloTag ligand (16_{HTL}): Phosphinate **S51** (110 mg, 0.188 mmol) and 2-(methoxymethoxy)malononitrile (**34**; 23.7 mg, 0.188 mmol, 1 eq) were combined in DMF (4 mL), and DIEA (65.3 μL , 0.375 mmol, 2 eq) was added. After stirring the reaction at room temperature for 2 h, it was evaporated to dryness. Flash chromatography on silica gel (0–40% acetone/ CH_2Cl_2 , linear gradient) afforded the MOM-MAC-substituted *tert*-butyl phosphinate adduct as a yellow solid (31 mg, 24%). Analytical HPLC: $t_{\text{R}} = 14.0$ min, 96.1% 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 725 nm); MS (ESI) calcd for $\text{C}_{35}\text{H}_{33}\text{F}_3\text{N}_4\text{O}_6\text{P}$ $[\text{M}+\text{H}]^+$ 693.2, found 692.8.

This ether (30 mg, 43.3 μmol) was taken up in CH_2Cl_2 (3 mL); triethylsilane (300 μL) was added, followed by trifluoroacetic acid (600 μL). The reaction was stirred at room temperature for 6 h. Toluene (3 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O2)amine (HTL- NH_2 , **36**; TFA salt; 29.3 mg, 86.6 μmol , 2 eq) and DIEA (75.4 μL , 0.433 mmol, 10 eq) in CH_2Cl_2 (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (10–75% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN and extracted with CH_2Cl_2 (2 $\times$). The organic extracts were dried over anhydrous MgSO_4 , filtered, and evaporated to yield 14.0 mg (42%) of JF₆₉₀-HaloTag ligand (**16_{HTL}**) as a dark blue-green solid. ^1H NMR (CD_3OD , 400 MHz) δ 7.08 (dd, $J = 14.5, 2.5$ Hz, 2H), 6.98 (dd, $J = 9.1, 6.0$ Hz, 2H), 6.47 (dd, $J = 9.1, 2.5$ Hz, 2H), 4.25 (t, $J = 7.6$ Hz, 8H), 3.67 – 3.55 (m, 8H), 3.53 (d, $J = 6.6$ Hz, 2H), 3.44 (t, $J = 6.5$ Hz, 2H), 2.52 (p, $J = 7.6$ Hz, 4H), 1.79 – 1.68 (m, 2H), 1.59 – 1.49 (m, 2H), 1.47 – 1.31 (m, 4H); ^{19}F NMR (CD_3OD , 376 MHz) δ –117.71 – –118.09 (m, 1F), –133.70 – –133.93 (m, 1F), –141.50 – –141.84 (m, 1F); Analytical HPLC: $t_{\text{R}} = 12.3$ 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 700 nm); HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{41}\text{ClF}_3\text{N}_3\text{O}_7\text{P}$ $[\text{M}+\text{H}]^+$ 762.2317, found 762.2334.

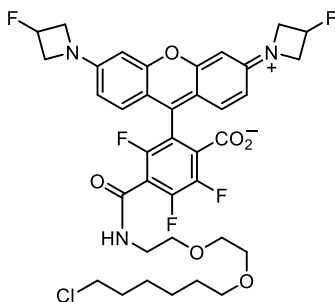


JF₇₂₂-HaloTag ligand (17_{HTL}): Ether **S70** (35 mg, 50.2 μ mol) was taken up in CH₂Cl₂ (3 mL); triethylsilane (300 μ L) was added, followed by trifluoroacetic acid (600 μ L). The reaction was stirred at room temperature for 6 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 33.9 mg, 0.100 mmol, 2 eq) and DIEA (87.5 μ L, 0.502 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 24.3 mg (59%) of JF₇₂₂-HaloTag ligand (17_{HTL}) as a blue-green solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.76 – 7.65 (m, 2H), 7.50 – 7.37 (m, 3H), 6.76 (dd, J = 8.8, 6.0 Hz, 2H), 6.74 (dd, J = 13.9, 2.6 Hz, 2H), 6.66 (s, 1H), 6.44 (dd, J = 8.8, 2.5 Hz, 2H), 3.96 – 3.81 (m, 8H), 3.64 – 3.56 (m, 6H), 3.53 – 3.47 (m, 4H), 3.36 (t, J = 6.7 Hz, 2H), 2.35 (p, J = 7.3 Hz, 4H), 1.78 – 1.69 (m, 2H), 1.54 – 1.37 (m, 4H), 1.35 – 1.27 (m, 2H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –120.45 (d, J = 22.7 Hz, 1F), –132.28 (d, J = 21.4 Hz, 1F), –141.55 (t, J = 22.2 Hz, 1F); Analytical HPLC: t_R = 14.8 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 725 nm); HRMS (ESI) calcd for C₄₃H₄₅ClF₃N₃O₆P [M+H]⁺ 822.2681, found 822.2688.



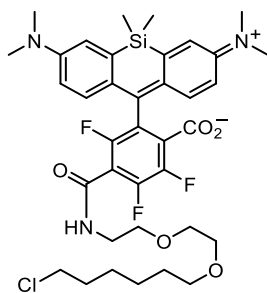
JF₇₂₄-HaloTag ligand (18_{HTL}): Ether **S71** (40 mg, 62.8 μ mol) was taken up in CH₂Cl₂ (4 mL); triethylsilane (400 μ L) was added, followed by trifluoroacetic acid (800 μ L). The reaction was stirred at room temperature for 18 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 42 mg, 0.126 mmol, 2 eq) and DIEA (109 μ L, 0.628 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 2 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (40–70% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated

to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2×). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 15.3 mg (32%) of JF₇₂₄-HaloTag ligand (**18_{HTL}**) as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.07 (d, *J* = 2.5 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.69 (bs, 1H), 6.42 (dd, *J* = 8.7, 2.5 Hz, 2H), 4.00 (t, *J* = 7.3 Hz, 8H), 3.66 – 3.57 (m, 6H), 3.56 – 3.48 (m, 4H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.44 (p, *J* = 7.3 Hz, 4H), 1.79 – 1.69 (m, 2H), 1.55 – 1.36 (m, 4H), 1.36 – 1.27 (m, 2H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –117.76 (d, *J* = 22.3 Hz, 1F), –130.89 (d, *J* = 22.2 Hz, 1F), –140.68 (t, *J* = 22.1 Hz, 1F); Analytical HPLC: *t*_R = 13.6 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 254 nm); HRMS (ESI) calcd for C₃₇H₄₀ClF₃N₃O₇S [M+H]⁺ 762.2222, found 762.2238.



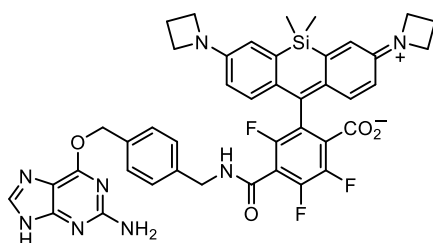
JF₅₅₉-HaloTag ligand (37_{HTL}**):** Ether **S72** (80 mg, 0.128 mmol) was taken up in CH₂Cl₂ (5 mL); triethylsilane (500 μL) was added, followed by trifluoroacetic acid (1 mL). The reaction was stirred at room temperature for 6 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 87 mg, 0.256 mmol, 2 eq) and DIEA (223 μL, 1.28 mmol, 10 eq) in DMF (4 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (10–75% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with 10% MeOH/CH₂Cl₂ (3×). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 54.3 mg (57%) of JF₅₅₉-HaloTag ligand (**37_{HTL}**) as a dark red-purple solid. ¹H NMR (CD₃OD, 400 MHz) δ 7.43 (d, *J* = 9.1 Hz, 2H), 6.76 (dd, *J* = 9.2, 2.2 Hz, 2H), 6.62 (d, *J* = 2.2 Hz, 2H), 5.59 (dt, ²*J*_{HF} = 57.0 Hz, *J* = 6.0, 3.0 Hz, 2H), 4.70 – 4.56 (m, 4H), 4.47 – 4.34 (m, 4H), 3.69 – 3.57 (m, 8H), 3.54 (t, *J* = 6.6 Hz, 2H), 3.45 (t, *J* = 6.5 Hz, 2H), 1.78 – 1.69 (m, 2H), 1.58 – 1.49 (m, 2H), 1.47 – 1.30 (m, 4H); ¹⁹F NMR (CD₃OD, 376 MHz) δ –117.57 (d, *J* = 15.7 Hz, 1F), –133.24 (d, *J* = 23.1 Hz, 1F), –143.33 (dd, *J* = 23.4, 15.7 Hz, 1F), –180.48 (dt, *J*_{FH} = 56.8, 23.3, 20.3 Hz, 2F); Analytical HPLC: *t*_R = 12.4 min, >99% purity (10–95% MeCN/H₂O, 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 C₃₇H₃₈ClF₅N₃O₆ [M+H]⁺ 750.2364, found 750.2378.

JF711–HaloTag ligand (38_{HTL}): Ether **S73** (50 mg, 68.3 μ mol) was taken up in CH₂Cl₂ (4 mL); triethylsilane (400 μ L) was added, followed by trifluoroacetic acid (800 μ L). The reaction was stirred at room temperature for 6 h. Toluene (4 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 46.1 mg, 0.137 mmol, 2 eq) and DIEA (119 μ L, 0.683 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (30–70% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 32 mg (55%) of JF711–HaloTag ligand (**38_{HTL}**) as a pale blue-green solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.76 – 7.67 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.40 (m, 2H), 6.82 (dd, J = 8.8, 5.7 Hz, 2H), 6.79 (dd, J = 13.7, 2.6 Hz, 2H), 6.68 (s, 1H), 6.51 (dd, J = 8.8, 2.6 Hz, 2H), 5.38 (dtt, ² J_{HF} = 56.7 Hz, J = 6.0, 3.4 Hz, 2H), 4.28 – 4.10 (m, 4H), 4.08 – 3.87 (m, 4H), 3.65 – 3.55 (m, 6H), 3.54 – 3.47 (m, 4H), 3.37 (t, J = 6.7 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.55 – 1.46 (m, 2H), 1.46 – 1.37 (m, 2H), 1.35 – 1.26 (m, 2H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –120.42 (d, J = 22.4 Hz, 1F), –131.74 (d, J = 21.8 Hz, 1F), –141.07 (t, J = 22.2 Hz, 1F), –180.54 (dtt, J_{FH} = 56.6, 23.7, 18.8 Hz, 2F); Analytical HPLC: t_{R} = 15.1 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 254 nm); HRMS (ESI) calcd for C₄₃H₄₃ClF₅N₃O₆P [M+H]⁺ 858.2493, found 858.2518.

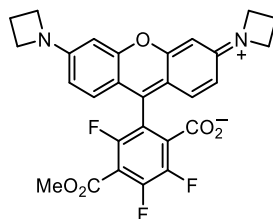


4,5,7-Trifluoro-SiTMR–HaloTag ligand (S53_{HTL}): Ether S59 (70 mg, 0.115 mmol) was taken up in CH₂Cl₂ (4 mL); triethylsilane (400 μL) was added, followed by trifluoroacetic acid (800 μL). The reaction was stirred at room temperature for 18 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of HaloTag(O2)amine (HTL-NH₂, **36**; TFA salt; 77.9 mg, 0.231 mmol, 2 eq) and DIEA (201 μL, 1.15 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 2 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (30–60%

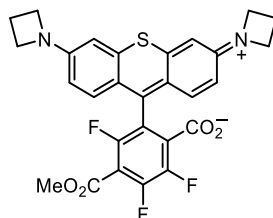
MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2×). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 49.5 mg (59%) of 4,5,7-trifluoro-SiTMR-HaloTag ligand (**S53_{HTL}**) as a blue-green solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.93 (d, *J* = 2.9 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.69 (s, 1H), 6.61 (dd, *J* = 8.9, 2.9 Hz, 2H), 3.66 – 3.58 (m, 6H), 3.54 – 3.47 (m, 4H), 3.37 (t, *J* = 6.7 Hz, 2H), 2.99 (s, 12H), 1.77 – 1.68 (m, 2H), 1.53 – 1.44 (m, 2H), 1.43 – 1.24 (m, 4H), 0.565 (s, 3H), 0.555 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -118.73 (d, *J* = 22.7 Hz, 1F), -133.63 (d, *J* = 21.3 Hz, 1F), -142.40 (t, *J* = 22.1 Hz, 1F); Analytical HPLC: *t_R* = 13.2 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₃₇H₄₆ClF₃N₃O₅Si [M+H]⁺ 732.2842, found 732.2848.



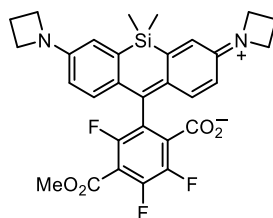
JF₆₆₉-SNAP-tag ligand (15_{STL}**):** Ether **35** (50 mg, 79.3 μmol) was taken up in CH₂Cl₂ (4 mL); triethylsilane (0.4 mL) was added, followed by trifluoroacetic acid (0.8 mL). The reaction was stirred at room temperature for 6 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed suspension of 6-((4-(aminomethyl)benzyl)oxy)-9H-purin-2-amine (**S74**; 42.9 mg, 0.159 mmol, 2 eq) and DIEA (138 μL, 0.793 mmol, 10 eq) in DMF (5 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (10–75% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, neutralized with saturated NaHCO₃, and extracted with CH₂Cl₂ (2×). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 35.8 mg (56%) of JF₆₆₉-SNAP-tag ligand (**15_{STL}**) as a blue solid. ¹H NMR (CD₃OD, 400 MHz) δ 7.82 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.92 (dd, *J* = 8.9, 0.8 Hz, 2H), 6.76 (d, *J* = 2.6 Hz, 2H), 6.36 (dd, *J* = 8.9, 2.6 Hz, 2H), 5.53 (s, 2H), 4.57 (s, 2H), 4.03 (t, *J* = 7.4 Hz, 8H), 2.42 (p, *J* = 7.3 Hz, 4H), 0.52 (s, 3H), 0.49 (s, 3H); ¹⁹F NMR (CD₃OD, 376 MHz) δ -118.98 (d, *J* = 20.2 Hz, 1F), -135.29 (d, *J* = 21.4 Hz, 1F), -143.71 (t, *J* = 21.0 Hz, 1F); Analytical HPLC: *t_R* = 10.2 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₄₂H₃₈F₃N₈O₄Si [M+H]⁺ 803.2732, found 803.2738.



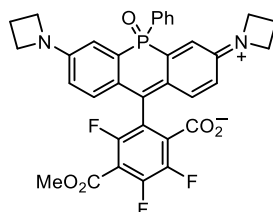
6-Methoxycarbonyl-JF₅₇₁ (S75): Ether **S58** (40 mg, 61.7 μ mol) was taken up in CH₂Cl₂ (4 mL); triethylsilane (400 μ L) was added, followed by trifluoroacetic acid (800 μ L). The reaction was stirred at room temperature for 6 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of MeOH (62.4 μ L, 1.54 mmol, 25 eq) and Et₃N (86.0 μ L, 0.617 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (20–50% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive) to afford 6-methoxycarbonyl-JF₅₇₁ (**S75**) as a dark purple solid (26.8 mg, 68%, TFA salt). ¹H NMR (CD₃OD, 400 MHz) δ 7.27 (d, J = 9.2 Hz, 2H), 6.67 (dd, J = 9.2, 2.2 Hz, 2H), 6.52 (d, J = 2.2 Hz, 2H), 4.34 (t, J = 7.7 Hz, 8H), 3.98 (s, 3H), 2.57 (p, J = 7.7 Hz, 4H); ¹⁹F NMR (CD₃OD, 376 MHz) δ -75.52 (s, 3F), -114.14 (d, J = 15.4 Hz, 1F), -129.35 (d, J = 21.2 Hz, 1F), -139.46 (dd, J = 21.5, 15.4 Hz, 1F); Analytical HPLC: t_R = 11.2 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for C₂₈H₂₂F₃N₂O₅ [M+H]⁺ 523.1475, found 523.1480.



6-Methoxycarbonyl-JF₅₉₃ (S76): Ether **S69** (acetate salt; 50 mg, 75.2 μ mol) was taken up in CH₂Cl₂ (4 mL); triethylsilane (400 μ L) was added, followed by trifluoroacetic acid (800 μ L). The reaction was stirred at room temperature for 6 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of MeOH (76.1 μ L, 1.88 mmol, 25 eq) and Et₃N (105 μ L, 0.752 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (30–50% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive) to afford 6-methoxycarbonyl-JF₅₉₃ (**S76**) as a dark purple solid (32.1 mg, 65%, TFA salt). ¹H NMR (CD₃OD, 400 MHz) δ 7.38 (d, J = 9.4 Hz, 2H), 6.88 (d, J = 2.3 Hz, 2H), 6.71 (dd, J = 9.4, 2.3 Hz, 2H), 4.31 (t, J = 7.7 Hz, 8H), 3.98 (s, 3H), 2.55 (p, J = 7.6 Hz, 4H); ¹⁹F NMR (CD₃OD, 376 MHz) δ -75.45 (s, 3F), -114.79 (d, J = 15.4 Hz, 1F), -130.14 (d, J = 21.7 Hz, 1F), -139.89 (dd, J = 21.3, 15.6 Hz, 1F); Analytical HPLC: t_R = 11.4 min, >99% purity (10–95% MeCN/H₂O, 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 C₂₈H₂₂F₃N₂O₄S [M+H]⁺ 539.1247, found 539.1254.

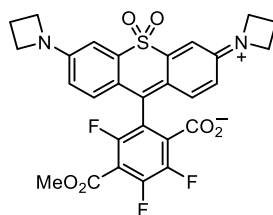


6-Methoxycarbonyl-JF₆₆₉ (29): Ether 35 (140 mg, 0.222 mmol) was taken up in CH₂Cl₂ (10 mL); triethylsilane (1 mL) was added, followed by trifluoroacetic acid (2 mL). The reaction was stirred at room temperature for 18 h. Toluene (10 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of MeOH (224 μ L, 5.55 mmol, 25 eq) and Et₃N (309 μ L, 2.22 mmol, 10 eq) in CH₂Cl₂ (6 mL), and the reaction was stirred at room temperature for 30 min. The solvent was removed by rotary evaporation, and the crude material was purified by silica gel chromatography (10–100% EtOAc/hexanes, linear gradient) to yield 97 mg (77%) of 6-methoxycarbonyl-JF₆₆₉ (**29**) as a blue-green solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.74 (d, J = 8.6 Hz, 2H), 6.64 (d, J = 2.7 Hz, 2H), 6.31 (dd, J = 8.7, 2.6 Hz, 2H), 3.95 (s, 3H), 3.92 (t, J = 7.2 Hz, 8H), 2.38 (p, J = 7.3 Hz, 4H), 0.545 (s, 3H), 0.538 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -116.04 (d, J = 22.6 Hz, 1F), -131.67 (d, J = 20.9 Hz, 1F), -142.29 (dd, J = 22.9, 20.9 Hz, 1F); Analytical HPLC: t_R = 12.6 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₃₀H₂₈F₃N₂O₄Si [M+H]⁺ 565.1765, found 565.1774.

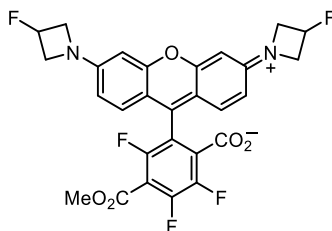


6-Methoxycarbonyl-JF₇₂₂ (S77): Ether **S70** (30 mg, 43.1 μ mol) was taken up in CH₂Cl₂ (3 mL); triethylsilane (300 μ L) was added, followed by trifluoroacetic acid (600 μ L). The reaction was stirred at room temperature for 6 h. Toluene (4 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of MeOH (43.6 μ L, 1.08 mmol, 25 eq) and Et₃N (60.0 μ L, 0.431 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (40–50% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 18.6 mg (68%) of 6-methoxycarbonyl-JF₇₂₂ (**S77**) as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.76 – 7.67 (m, 2H), 7.51 – 7.38 (m, 3H), 6.76 (dd, J = 8.8, 6.0 Hz, 2H), 6.75 (dd, J = 13.8, 2.6 Hz, 2H), 6.45 (dd, J = 8.8, 2.5 Hz, 2H), 3.96 – 3.81 (m, 8H), 3.91 (s, 3H), 2.35 (p, J = 7.3 Hz, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -118.57 (d, J = 22.6 Hz, 1F), -130.21 (d, J = 20.9 Hz, 1F), -141.33 – -141.52 (m, 1F); Analytical HPLC: t_R = 13.5 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min

flow; ESI; positive ion mode; detection at 725 nm); HRMS (ESI) calcd for $C_{34}H_{27}F_3N_2O_5P$ $[M+H]^+$ 631.1604, found 631.1608.

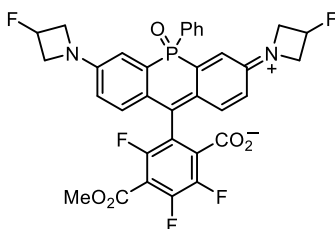


6-Methoxycarbonyl-JF₇₂₄ (S78): Ether **S71** (20 mg, 31.4 μ mol) was taken up in CH_2Cl_2 (2 mL); triethylsilane (200 μ L) was added, followed by trifluoroacetic acid (400 μ L). The reaction was stirred at room temperature for 6 h. Toluene (3 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of MeOH (31.8 μ L, 0.785 mmol, 25 eq) and Et_3N (43.8 μ L, 0.314 mmol, 10 eq) in CH_2Cl_2 (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (30–70% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive). The pooled product fractions were partially concentrated to remove MeCN, diluted with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (2 $\times$). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to yield 11.6 mg (65%) of 6-methoxycarbonyl-JF₇₂₄ (**S78**) as a pale yellow solid. 1H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, J = 2.5 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.41 (dd, J = 8.7, 2.6 Hz, 2H), 4.00 (t, J = 7.4 Hz, 8H), 3.93 (s, 3H), 2.44 (p, J = 7.3 Hz, 4H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -115.63 (d, J = 22.7 Hz, 1F), -129.24 (d, J = 20.7 Hz, 1F), -140.60 (t, J = 21.8 Hz, 1F); Analytical HPLC: t_R = 15.2 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 254 nm); HRMS (ESI) calcd for $C_{28}H_{22}F_3N_2O_6S$ $[M+H]^+$ 571.1145, found 571.1156.

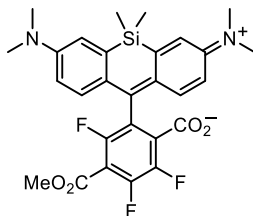


6-Methoxycarbonyl-JF₅₅₉ (S79): Ether **S72** (40 mg, 64.0 μ mol) was taken up in CH_2Cl_2 (2.5 mL); triethylsilane (250 μ L) was added, followed by trifluoroacetic acid (500 μ L). The reaction was stirred at room temperature for 6 h. Toluene (3 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of MeOH (64.9 μ L, 1.60 mmol, 25 eq) and Et_3N (89.3 μ L, 0.640 mmol, 10 eq) in CH_2Cl_2 (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (20–60% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive) to yield 30.7 mg (71%, TFA salt) of 6-methoxycarbonyl-JF₅₅₉ (**S79**) as a dark red-purple solid. 1H NMR (CD_3OD , 400 MHz) δ 7.37 (d, J = 9.1 Hz, 2H), 6.77 (dd, J = 9.2, 2.2 Hz, 2H), 6.67 (d, J = 2.2 Hz, 2H), 5.57 (dtt, $^2J_{HF}$ = 56.9 Hz, J = 5.9, 2.9 Hz, 2H), 4.70 – 4.57 (m, 4H), 4.49 – 4.35 (m, 4H), 3.98 (s, 3H); ^{19}F NMR (CD_3OD , 376 MHz)

δ -75.50 (s, 3F), -114.05 (d, J = 15.4 Hz, 1F), -129.03 (d, J = 21.5 Hz, 1F), -139.23 (dd, J = 21.5, 15.4 Hz, 1F), -180.58 (dt, J_{FH} = 56.7, 23.2, 20.1 Hz, 2F); Analytical HPLC: t_{R} = 11.0 min, >99% purity (10–95% MeCN/H₂O, 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 C₂₈H₂₀F₅N₂O₅ [M+H]⁺ 559.1287, found 559.1296.



6-Methoxycarbonyl-JF₇₁₁ (S80): Ether **S73** (25 mg, 34.1 μ mol) was taken up in CH₂Cl₂ (2 mL); triethylsilane (200 μ L) was added, followed by trifluoroacetic acid (400 μ L). The reaction was stirred at room temperature for 6 h. Toluene (3 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of MeOH (34.6 μ L, 0.853 mmol, 25 eq) and Et₃N (47.6 μ L, 0.341 mmol, 10 eq) in CH₂Cl₂ (3 mL), and the reaction was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude material was purified by reverse phase HPLC (20–70% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 17.7 mg (78%) of 6-methoxycarbonyl-JF₇₁₁ (**S80**) as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.72 (dd, J = 12.7, 7.4 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.48 – 7.41 (m, 2H), 6.81 (dd, J = 8.7, 5.9 Hz, 2H), 6.80 (dd, J = 13.5, 2.7 Hz, 2H), 6.52 (dd, J = 8.8, 2.6 Hz, 2H), 5.38 (dt, ² J_{HF} = 56.8 Hz, J = 6.1, 3.4 Hz, 2H), 4.29 – 4.10 (m, 4H), 4.09 – 3.92 (m, 4H), 3.92 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -118.65 (d, J = 22.5 Hz, 1F), -129.59 (d, J = 20.7 Hz, 1F), -140.88 (t, J = 21.8 Hz, 1F), -180.52 (dt, J_{FH} = 57.0, 23.8, 18.8 Hz, 2H); Analytical HPLC: t_{R} = 14.1 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 280 nm); HRMS (ESI) calcd for C₃₄H₂₅F₅N₂O₅P [M+H]⁺ 667.1416, found 667.1423.



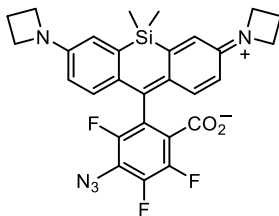
4,5,7-Trifluoro-6-methoxycarbonyl-SiTMR (S81): Ether **S59** (600 mg, 0.989 mmol) was taken up in CH₂Cl₂ (30 mL); triethylsilane (3 mL) was added, followed by trifluoroacetic acid (6 mL). The reaction was stirred at room temperature for 18 h. Toluene (15 mL) was added, and the reaction mixture was concentrated to dryness. The residue was combined with a premixed solution of MeOH (1.00 mL, 24.7 mmol, 25 eq) and Et₃N (1.38 mL, 9.89 mmol, 10 eq) in CH₂Cl₂ (20 mL), and the reaction was stirred at room temperature for 30 min. The solvent was removed by

rotary evaporation, and the crude material was purified by silica gel chromatography (10–100% EtOAc/hexanes, linear gradient) to yield 392 mg (73%) of **S81** as a yellow-green solid. ^1H NMR (CDCl_3 , 400 MHz) δ 6.94 (d, J = 2.9 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 6.61 (dd, J = 8.9, 2.9 Hz, 2H), 3.94 (s, 3H), 2.99 (s, 12H), 0.58 (s, 3H), 0.56 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz) δ -116.26 (d, J = 22.8 Hz, 1F), -131.82 (d, J = 20.9 Hz, 1F), -142.43 (dd, J = 22.7, 21.0 Hz, 1F); Analytical HPLC: t_{R} = 10.3 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 675 nm); HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ 541.1765, found 541.1769.

SUBSTITUTION OF 4,5,6,7-TETRAFLUORORHODAMINES WITH OTHER NUCLEOPHILES

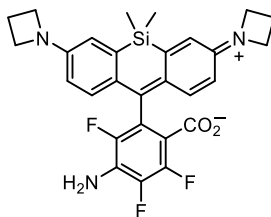
During our efforts to develop a method for the installation of amides and esters on the bottom aryl ring of fluorinated rhodamines, we also explored the scope of fluoride substitution with nucleophiles beyond MAC reagents. As shown in **Figure 2f**, **Supplementary Figure 5**, and **Scheme S4**, the range of tolerated nucleophiles was quite broad, encompassing azide (NaN_3), cyanide (KCN), malonates, cyanoacetates, amines (including ammonia and secondary amines), hydroxylamine, and the previously described MAC reagent; thiols are also excellent reagents for this process, but their utility was well-known prior to this work.^{4,5} In each case, the rhodamine was simply combined with the nucleophile in DMF or DMSO; a mild base (DIEA or K_2CO_3) was added for nucleophiles other than azide and cyanide; heating was only required for larger secondary amines (**30–31**, **Supplementary Fig. 5c**) and *tert*-butyl malonates. Si-rhodamines (JF_{669} , **15**; F_4SiTMR , **S53**) and traditional oxygen rhodamines (*e.g.*, JF_{571} , **19**) showed similar reactivity for the different nucleophile types tested (**Scheme S4**).

We hypothesized these $\text{S}_{\text{N}}\text{Ar}$ substitutions would proceed with the same regioselectivity as observed for the MAC reagent nucleophiles. Indeed, we observed one predominant product in every case with many reactions showing clean conversion to a single rhodamine derivative. In order to more definitively confirm the regiochemical preferences of these reactions, we converted several different substituted JF_{669} products to a common derivative (**22**, **Supplementary Fig. 5b**). The crystal structures of **S59** and **S81** demonstrated that the MAC chemistry provided the 6-isomer (see **X-Ray Crystallography**); hence, the structures of MAC- JF_{669} **35** and JF_{669} methyl ester **29** were as shown. Hydrolysis and Curtius rearrangement of methyl ester **29** afforded 6-amino- JF_{669} (**22**). Because reduction of the azide substitution product (**21**) and direct substitution of JF_{669} with ammonia provided material analytically identical ($^1\text{H}/^{19}\text{F}$ NMR, HPLC, HRMS) to the Curtius product **22**, the azide and amine substitution products were similarly assigned to be the 6-isomers.



6-Azido- JF_{669} (21**):** To a solution of JF_{669} (**15**; 200 mg, 0.381 mmol) in DMSO (4 mL) was added NaN_3 (24.8 mg, 0.381 mmol, 1 eq). After stirring the reaction at room temperature for 2 h, it was diluted with water and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and evaporated. Silica gel chromatography (0–50% EtOAc/hexanes, linear gradient) afforded azide **21** as a blue-green solid (186 mg, 89%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.77 (dd, J = 8.7, 0.8 Hz, 2H), 6.63 (d, J = 2.6 Hz, 2H), 6.32 (dd, J = 8.7, 2.7 Hz, 2H), 3.92 (t, J = 7.3 Hz, 8H), 2.38 (p, J = 7.2 Hz, 4H), 0.54 (s, 3H), 0.52 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz) δ -129.29 (dd, J = 19.8, 4.7 Hz, 1F), -141.30 (t, J = 19.8 Hz, 1F), -142.83 (dd, J = 19.6, 4.8 Hz, 1F); Analytical HPLC: t_{R} = 13.8 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 675 nm); HRMS (ESI) calcd for $C_{28}H_{25}F_3N_5O_2Si$ $[M+H]^+$ 548.1724, found 548.1722.



6-Amino-JF₆₆₉ (22): The title compound was prepared from three different substrates via three different approaches: (a) S_NAr of JF₆₆₉ (**15**) with ammonia; (b) Staudinger reduction of 6-azido-JF₆₆₉ (**21**); and (c) hydrolysis and Curtius rearrangement of 6-methoxycarbonyl-JF₆₆₉ (**29**). The NMR spectra and LC/MS analyses of the three products were identical. Because the crystal structures of **S59** and **S81** had confirmed the regioselectivity of the MAC substitution (*vide infra*), this result also corroborated the regiochemical outcomes of the azide and amine substitutions.

Via S_NAr : To a solution of JF₆₆₉ (**15**; 100 mg, 0.191 mmol) in DMF (2.5 mL) was added NH_3 in dioxane (0.5 M, 2.29 mL, 1.14 mmol, 6 eq). After stirring the sealed reaction at room temperature for 72 h, it was concentrated *in vacuo* and purified by flash chromatography on silica gel (0–75% EtOAc/hexanes, linear gradient) to provide 78 mg (78%) of **22** as a pale blue solid.

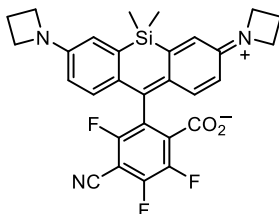
Via Staudinger reduction: To a solution of 6-azido-JF₆₆₉ (**21**; 25 mg, 45.7 μ mol) in THF (2 mL) was added PPh_3 (23.9 mg, 91.3 μ mol, 2 eq). The reaction was stirred at room temperature for 30 min, at which point LC/MS analysis indicated complete conversion to the iminophosphorane. Following the addition of 1 M H_2SO_4 (500 μ L), the mixture was vigorously stirred at room temperature for 3 h. It was subsequently diluted with saturated $NaHCO_3$ and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (0–75% EtOAc/hexanes, linear gradient) yielded 21.9 mg (92%) of **22** as a pale blue solid.

Via Curtius rearrangement: To a solution of 6-methoxycarbonyl-JF₆₆₉ (**29**; 525 mg, 0.930 mmol) in THF (19 mL) was added 1 M LiOH (4.65 mL, 4.65 mmol, 5 eq). After stirring the reaction at room temperature for 18 h, it was acidified with 1 M HCl (5 mL), diluted with water, and extracted with EtOAc (2 $\times$). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to provide 6-carboxy-JF₆₆₉ as a dark blue solid (382 mg, 75%). An analytically pure sample of 6-carboxy-JF₆₆₉ for spectral characterization was obtained by reverse phase HPLC (20–60% MeCN/ H_2O , linear gradient, with constant 0.1% TFA). 1H NMR (CD_3OD , 400 MHz) δ 7.04 (d, J = 9.2 Hz, 2H), 6.87 (d, J = 2.6 Hz, 2H), 6.41 (dd, J = 9.2, 2.6 Hz, 2H), 4.26 (t, J = 7.6 Hz, 8H), 2.51 (p, J = 7.6 Hz, 4H), 0.56 (s, 3H), 0.49 (s, 3H); ^{19}F NMR (CD_3OD , 376 MHz) δ -116.97 – -117.17 (m, 1F), -133.81 – -134.08 (m, 1F), -141.65 – -141.92 (m, 1F); Analytical HPLC: t_R = 10.9 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 675 nm); HRMS (ESI) calcd for $C_{29}H_{26}F_3N_2O_4Si$ $[M+H]^+$ 551.1608, found 551.1616.

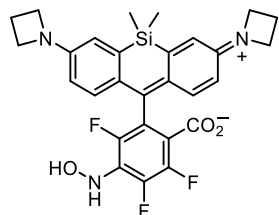
A vial was charged with 6-carboxy-JF₆₆₉ (20 mg, 36.3 μ mol), sealed, and evacuated/backfilled with nitrogen (3 $\times$). After suspending the starting material in dry *tert*-butanol (2 mL), DPPA (15.7 μ L, 72.6 μ mol, 2 eq) and Et_3N (15.2

μL , 109 μmol , 3 eq) were added. The sealed reaction was then stirred at 100 °C for 18 h. It was subsequently cooled to room temperature and concentrated *in vacuo*. The resulting residue was redissolved in CH_2Cl_2 (3 mL); triethylsilane (300 μL) was added, followed by trifluoroacetic acid (600 μL). The reaction was stirred at room temperature for 2 h. Toluene (5 mL) was added, and the reaction mixture was concentrated to dryness. The crude material was diluted with saturated NaHCO_3 and extracted with CH_2Cl_2 (2 $\times$). The combined organic extracts were dried over anhydrous MgSO_4 , filtered, and evaporated. Flash chromatography on silica gel (0–75% EtOAc/hexanes, linear gradient) afforded 8.4 mg (44%) of **22** as a pale blue solid.

^1H NMR (CDCl_3 , 400 MHz) δ 6.84 (dd, J = 8.6, 0.8 Hz, 2H), 6.64 (d, J = 2.6 Hz, 2H), 6.31 (dd, J = 8.6, 2.6 Hz, 2H), 4.36 (s, 2H), 3.91 (t, J = 7.2 Hz, 8H), 2.37 (p, J = 7.3 Hz, 4H), 0.54 (s, 3H), 0.53 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz) δ -140.63 (dd, J = 18.1, 11.5 Hz, 1F), -143.85 (dd, J = 20.3, 18.1 Hz, 1F), -154.70 (dd, J = 20.3, 11.6 Hz, 1F); Analytical HPLC: t_R = 12.3 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 675 nm); HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 522.1819, found 522.1828.

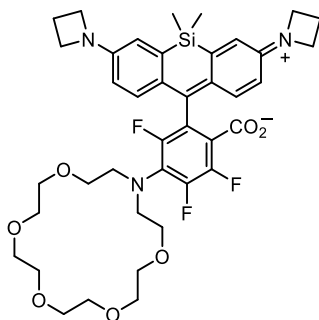


6-Cyano-JF₆₆₉ (23): To a solution of JF₆₆₉ (**15**; 200 mg, 0.381 mmol) in DMSO (4 mL) was added NaCN (28.0 mg, 0.572 mmol, 1.5 eq). After stirring the reaction at room temperature for 2 h, it was diluted with water and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , filtered, and evaporated. Silica gel chromatography (25–100% EtOAc/hexanes, linear gradient) afforded nitrile **23** as a dark green solid (40.2 mg, 20%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.69 (dd, J = 8.7, 0.8 Hz, 2H), 6.63 (d, J = 2.7 Hz, 2H), 6.31 (dd, J = 8.7, 2.6 Hz, 2H), 3.93 (t, J = 7.3 Hz, 8H), 2.39 (p, J = 7.2 Hz, 4H), 0.56 (s, 3H), 0.53 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz, ^1H decoupled) δ -109.23 (dd, J = 22.6, 2.2 Hz, 1F), -124.52 (dd, J = 20.0, 2.1 Hz, 1F), -140.61 (dd, J = 22.7, 20.1 Hz, 1F); Analytical HPLC: t_R = 12.5 min, 98.9% 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 675 nm); HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{25}\text{F}_3\text{N}_3\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 532.1663, found 532.1667.

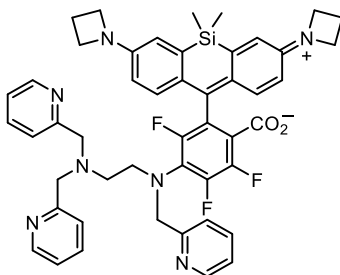


6-Hydroxylamino-JF₆₆₉ (24): JF₆₆₉ (**15**; 100 mg, 0.191 mmol) was dissolved in DMF (2 mL); DIEA (99.6 μL , 0.572 mmol, 3 eq) and hydroxylamine hydrochloride (14.6 mg, 0.210 mmol, 1.1 eq) were added, and the reaction was stirred

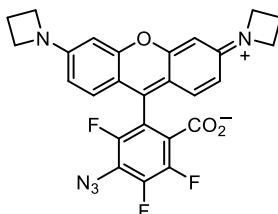
at room temperature for 4 h. It was then concentrated to dryness and purified by flash chromatography on silica gel (0–50% EtOAc/toluene, linear gradient) to provide 52 mg (51%) of **24** as a blue solid. ^1H NMR (CDCl_3 , 400 MHz) δ 6.98 (s, 1H), 6.79 (dd, J = 8.6, 1.0 Hz, 2H), 6.64 (d, J = 2.7 Hz, 2H), 6.31 (dd, J = 8.6, 2.6 Hz, 2H), 5.87 (s, 1H), 3.91 (t, J = 7.2 Hz, 8H), 2.37 (p, J = 7.2 Hz, 4H), 0.55 (s, 3H), 0.54 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz, ^1H decoupled) δ –132.16 (dd, J = 19.5, 6.9 Hz, 1F), –142.58 (t, J = 20.1 Hz, 1F), –145.42 (dd, J = 20.5, 6.9 Hz, 1F); Analytical HPLC: t_{R} = 10.0 min, 96.8% 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 675 nm); HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 538.1768, found 538.1779.



JF₆₆₉-18-crown-6 (32): JF₆₆₉ (**15**; 100 mg, 0.191 mmol) and 1-aza-18-crown-6 (**30**; 100 mg, 0.381 mmol, 2 eq) were combined in DMF (2 mL). After adding DIEA (99.6 μL , 0.572 mmol, 3 eq), the reaction was stirred at 50 °C for 72 h. The crude reaction mixture was directly purified by reverse phase HPLC (30–50% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive). The pooled product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO_3 , and extracted with CH_2Cl_2 (2 $\times$). The organic extracts were dried over anhydrous MgSO_4 , filtered, and evaporated to provide 54.0 mg of **32** (37%) as a light blue solid. ^1H NMR (CDCl_3 , 400 MHz) δ 6.79 (dd, J = 8.6, 0.9 Hz, 2H), 6.64 (d, J = 2.6 Hz, 2H), 6.28 (dd, J = 8.6, 2.6 Hz, 2H), 3.91 (t, J = 7.3 Hz, 8H), 3.70 (t, J = 5.5 Hz, 4H), 3.68 – 3.52 (m, 20H), 2.37 (p, J = 7.2 Hz, 4H), 0.54 (s, 3H), 0.54 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz) δ –126.05 (dd, J = 18.0, 8.1 Hz, 1F), –141.75 (dd, J = 20.1, 8.1 Hz, 1F), –142.95 (dd, J = 19.9, 18.2 Hz, 1F); Analytical HPLC: t_{R} = 12.9 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 675 nm); HRMS (ESI) calcd for $\text{C}_{40}\text{H}_{49}\text{F}_3\text{N}_3\text{O}_7\text{Si}$ $[\text{M}+\text{H}]^+$ 768.3286, found 768.3298.



JF₆₆₉-TPMED (33): JF₆₆₉ (**15**; 75 mg, 0.143 mmol) and *N*¹,*N*¹,*N*²-tris(pyridin-2-ylmethyl)ethane-1,2-diamine^[10,11] (**31**; 95.3 mg, 0.286 mmol, 2 eq) were combined in DMF (2 mL). After adding DIEA (74.7 μ L, 0.429 mmol, 3 eq), the reaction was stirred at 50 °C for 96 h. The reaction mixture was concentrated to dryness and purified by reverse phase HPLC (10–75% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to provide 55.6 mg of **33** (46%) as a purple solid. ¹H NMR (CD₃OD, 400 MHz) δ 8.41 – 8.36 (m, 3H), 7.72 – 7.64 (m, 3H), 7.45 (dt, *J* = 7.9, 1.1 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.23 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 2H), 6.70 (d, *J* = 2.6 Hz, 2H), 6.54 (dd, *J* = 8.7, 1.0 Hz, 2H), 6.23 (dd, *J* = 8.7, 2.7 Hz, 2H), 4.49 (s, 2H), 3.89 (t, *J* = 7.3 Hz, 8H), 3.75 (s, 4H), 3.46 (t, *J* = 6.3 Hz, 2H), 2.76 (t, *J* = 6.2 Hz, 2H), 2.38 (p, *J* = 7.2 Hz, 4H), 0.53 (s, 3H), 0.46 (s, 3H); ¹⁹F NMR (CD₃OD, 376 MHz) δ –123.75 (dd, *J* = 17.9, 7.1 Hz, 1F), –139.44 (dd, *J* = 19.5, 7.3 Hz, 1F), –143.27 (t, *J* = 18.8 Hz, 1F); Analytical HPLC: *t*_R = 9.4 min, 97.7% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₄₈H₄₇F₃N₇O₂Si [M+H]⁺ 838.3507, found 838.3526.

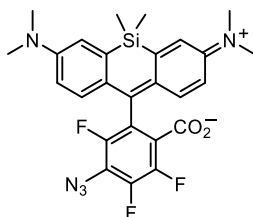


6-Azido-JF₅₇₁ (S54): To a solution of JF₅₇₁ (**19**; 20 mg, 41.5 μ mol) in DMSO (1 mL) was added NaN₃ (3.0 mg, 45.6 μ mol, 1.1 eq). After stirring the reaction at room temperature for 2 h, it was directly purified by reverse phase HPLC (30–60% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive) to provide 17.0 mg (66%, TFA salt) of azide **S54** as a dark red-purple solid. ¹H NMR (CD₃OD, 400 MHz) δ 7.29 (d, *J* = 9.2 Hz, 2H), 6.67 (dd, *J* = 9.2, 2.2 Hz, 2H), 6.54 (d, *J* = 2.2 Hz, 2H), 4.34 (t, *J* = 7.6 Hz, 8H), 2.57 (p, *J* = 7.7 Hz, 4H); ¹⁹F NMR (CD₃OD, 376 MHz) δ –75.41 (s, 3F), –126.37 (dd, *J* = 12.6, 6.2 Hz, 1F), –137.79 (dd, *J* = 19.6, 12.6 Hz, 1F), –142.08 (dd, *J* = 20.0, 6.3 Hz, 1F); Analytical HPLC: *t*_R = 11.7 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA

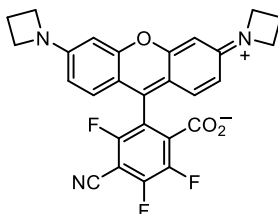
^[10] Que, E. L.; Bleher, R.; Duncan, F. E.; Kong, B. Y.; Gleber, S. C.; Vogt, S.; Chen, S.; Garwin, S. A.; Bayer, A. R.; Dravid, V. P.; Woodruff, T. K.; O'Halloran, T. V. *Nat. Chem.* **2015**, *7*, 130–139.

^[11] Hureau, C.; Groni, S.; Guillot, R.; Blondin, G.; Duboc, C.; Anxolabéhère-Mallart, E. *Inorg. Chem.* **2008**, *47*, 9238–9247.

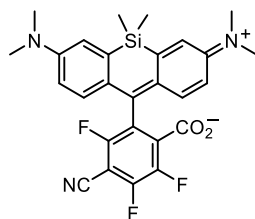
additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for $C_{26}H_{19}F_3N_5O_3$ $[M+H]^+$ 506.1435, found 506.1439.



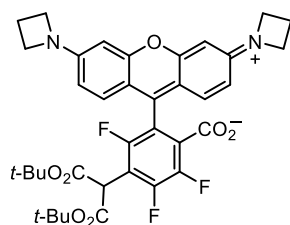
6-Azido-4,5,7-trifluoro-SiTMR (S55): To a solution of 4,5,6,7-tetrafluoro-SiTMR (**S53**; 100 mg, 0.200 mmol) in DMSO (2 mL) was added NaN_3 (14.3 mg, 0.220 mmol, 1.1 eq). After stirring the reaction at room temperature for 1 h, it was diluted with water and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Silica gel chromatography (0–50% EtOAc/hexanes, linear gradient) afforded azide **S55** as a blue-green solid (94 mg, 90%). 1H NMR ($CDCl_3$, 400 MHz) δ 6.93 (d, J = 2.9 Hz, 2H), 6.82 (dd, J = 8.9, 0.8 Hz, 2H), 6.62 (dd, J = 8.9, 2.9 Hz, 2H), 2.99 (s, 12H), 0.58 (s, 3H), 0.55 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -129.60 (dd, J = 20.3, 4.7 Hz, 1F), -141.41 (t, J = 19.8 Hz, 1F), -142.94 (dd, J = 19.7, 4.7 Hz, 1F); Analytical HPLC: t_R = 13.2 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 675 nm); HRMS (ESI) calcd for $C_{26}H_{25}F_3N_5O_2Si$ $[M+H]^+$ 524.1724, found 524.1731.



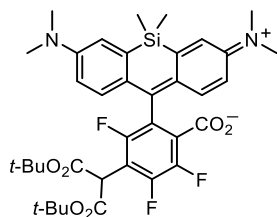
6-Cyano-JF₅₇₁ (S56): To a solution of JF₅₇₁ (**19**; 75 mg, 0.155 mmol) in DMSO (1.5 mL) was added NaCN (11.4 mg, 0.233 mmol, 1.5 eq). After stirring the reaction at room temperature for 18 h, it was directly purified by reverse phase HPLC (30–50% MeCN/ H_2O , linear gradient, with constant 0.1% v/v TFA additive) to provide 16.1 mg (17%, TFA salt) of nitrile **S56** as a dark red solid. 1H NMR (CD_3OD , 400 MHz) δ 7.29 (d, J = 9.2 Hz, 2H), 6.67 (dd, J = 9.2, 2.2 Hz, 2H), 6.52 (d, J = 2.2 Hz, 2H), 4.34 (t, J = 7.6 Hz, 8H), 2.57 (p, J = 7.7 Hz, 4H); ^{19}F NMR (CD_3OD , 376 MHz) δ -75.50 (s, 3F), -109.22 (d, J = 14.9 Hz, 1F), -123.89 (d, J = 21.3 Hz, 1F), -139.51 (dd, J = 21.2, 15.0 Hz, 1F); Analytical HPLC: t_R = 11.6 min, 99.0% 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 575 nm); HRMS (ESI) calcd for $C_{27}H_{19}F_3N_3O_3$ $[M+H]^+$ 490.1373, found 490.1376.



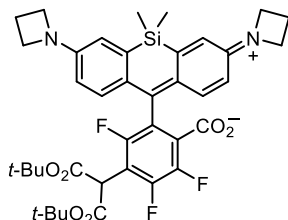
6-Cyano-4,5,7-trifluoro-SiTMR (S57): To a solution of 4,5,6,7-tetrafluoro-SiTMR (**S53**; 100 mg, 0.200 mmol) in DMSO (2 mL) was added NaCN (14.7 mg, 0.300 mmol, 1.5 eq). After stirring the reaction at room temperature for 4 h, it was diluted with water and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated. Silica gel chromatography (25–100% EtOAc/hexanes, linear gradient) afforded nitrile **S57** as a dark green solid (17.0 mg, 17%). ¹H NMR (CDCl₃, 400 MHz) δ 6.94 (d, *J* = 2.8 Hz, 2H), 6.74 (dd, *J* = 8.9, 0.8 Hz, 2H), 6.61 (dd, *J* = 8.9, 2.9 Hz, 2H), 3.00 (s, 12H), 0.59 (s, 3H), 0.55 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz, ¹H decoupled) δ -109.43 (d, *J* = 22.8, 2.2 Hz, 1F), -124.68 (dd, *J* = 20.1, 2.2 Hz, 1F), -140.75 (dd, *J* = 22.7, 20.1 Hz, 1F); Analytical HPLC: *t*_R = 12.0 min, 98.7% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₂₇H₂₅F₃N₃O₂Si [M+H]⁺ 508.1663, found 508.1667.



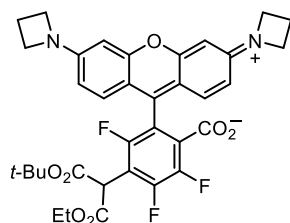
6-(Di-tert-butyl malonate)-JF₅₇₁ (S60): JF₅₇₁ (**19**; 75 mg, 0.155 mmol) and di-tert-butyl malonate (41.8 μL, 0.187 mmol, 1.2 eq) were combined in DMF (2 mL), and K₂CO₃ (51.6 mg, 0.373 mmol, 2.4 eq) was added. After stirring the reaction at 50 °C for 18 h, it was directly purified by reverse phase HPLC (30–60% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2×). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 57 mg (54%) of malonate **S60** as a dark red-purple solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.82 (d, *J* = 8.6 Hz, 2H), 6.20 (d, *J* = 2.2 Hz, 2H), 6.17 (dd, *J* = 8.6, 2.3 Hz, 2H), 4.75 (s, 1H), 3.96 (t, *J* = 7.4 Hz, 8H), 2.41 (p, *J* = 7.3 Hz, 4H), 1.38 (s, 18H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -119.24 – -119.66 (m, 1F), -131.54 (d, *J* = 21.0 Hz, 1F), -142.90 – -143.40 (m, 1F); Analytical HPLC: *t*_R = 10.9 min, >99% purity (30–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for C₃₇H₃₈F₃N₂O₇ [M+H]⁺ 679.2626, found 679.2623.



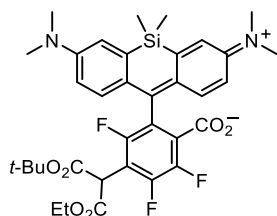
6-(Di-*tert*-butyl malonate)-4,5,7-trifluoro-SiTMR (S61): 4,5,6,7-Tetrafluoro-SiTMR (S53; 100 mg, 0.200 mmol) and di-*tert*-butyl malonate (49.2 μ L, 0.220 mmol, 1.1 eq) were combined in DMF (2 mL), and K_2CO_3 (55.2 mg, 0.400 mmol, 2 eq) was added. After stirring the reaction at room temperature for 18 h, additional di-*tert*-butyl malonate (49.2 μ L, 0.220 mmol, 1.1 eq) and K_2CO_3 (55.2 mg, 0.400 mmol, 2 eq) were added. The mixture was stirred at 50 $^{\circ}C$ for 24 h. It was then cooled to room temperature, diluted with water, and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification of the crude by silica gel chromatography (0–50% EtOAc/hexanes, linear gradient) yielded 83 mg (60%) of malonate **S61** as a blue-green solid. 1H NMR ($CDCl_3$, 400 MHz) δ 6.96 (d, J = 2.9 Hz, 2H), 6.79 (dd, J = 8.8, 1.4 Hz, 2H), 6.55 (dd, J = 8.9, 2.9 Hz, 2H), 4.83 (s, 1H), 2.97 (s, 12H), 1.41 (s, 18H), 0.583 (s, 3H), 0.581 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz, 1H decoupled) δ -115.39 (d, J = 21.5 Hz, 1F), -132.72 (d, J = 20.7 Hz, 1F), -143.43 (t, J = 21.3 Hz, 1F); Analytical HPLC: t_R = 12.8 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 675 nm); HRMS (ESI) calcd for $C_{37}H_{44}F_3N_2O_6Si$ $[M+H]^+$ 697.2915, found 697.2920.



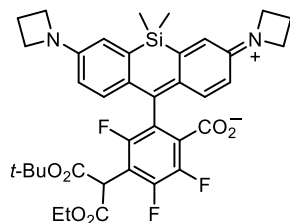
6-(Di-*tert*-butyl malonate)-JF₆₆₉ (S62): JF₆₆₉ (**15**; 150 mg, 0.286 mmol) and di-*tert*-butyl malonate (76.8 μ L, 0.343 mmol, 1.2 eq) were combined in DMF (3 mL), and K_2CO_3 (94.8 mg, 0.686 mmol, 2.4 eq) was added. After stirring the reaction at 50 $^{\circ}C$ for 48 h, it was cooled to room temperature, diluted with water, and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification of the crude by silica gel chromatography (0–50% EtOAc/hexanes, linear gradient) yielded 101 mg (49%) of malonate **S62** as a blue-green solid. 1H NMR ($CDCl_3$, 400 MHz) δ 6.75 (dd, J = 8.6, 1.7 Hz, 2H), 6.66 (d, J = 2.6 Hz, 2H), 6.25 (dd, J = 8.6, 2.6 Hz, 2H), 4.84 (s, 1H), 3.90 (t, J = 7.2 Hz, 8H), 2.37 (p, J = 7.2 Hz, 4H), 1.42 (s, 18H), 0.56 (s, 3H), 0.55 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz, 1H decoupled) δ -114.87 (d, J = 21.3 Hz, 1F), -132.66 (d, J = 20.8 Hz, 1F), -143.30 (t, J = 21.2 Hz, 1F); Analytical HPLC: t_R = 13.4 min, 98.0% 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 675 nm); HRMS (ESI) calcd for $C_{39}H_{44}F_3N_2O_6Si$ $[M+H]^+$ 721.2915, found 721.2924.



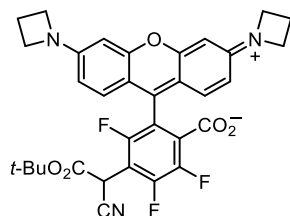
6-(*tert*-Butyl ethyl malonate)-JF₅₇₁ (S63): JF₅₇₁ (**19**; 75 mg, 0.155 mmol) and *tert*-butyl ethyl malonate (35.3 μ L, 0.187 mmol, 1.2 eq) were combined in DMF (2 mL), and K₂CO₃ (51.6 mg, 0.373 mmol, 2.4 eq) was added. After stirring the reaction at 50 °C for 18 h, it was directly purified by reverse phase HPLC (30–60% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 60 mg (59%) of malonate **S63** as a dark red-purple solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.90 – 6.82 (m, 2H), 6.22 – 6.17 (m, 4H), 4.83 (s, 1H), 4.24 – 4.12 (m, 2H), 3.98 (t, J = 7.3 Hz, 8H), 2.42 (p, J = 7.2 Hz, 4H), 1.38 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –119.43 – –119.90 (m, 1F), –131.51 (d, J = 21.1 Hz, 1F), –142.52 – –143.06 (m, 1F); Analytical HPLC: t_R = 9.9 min, >99% purity (30–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for C₃₅H₃₄F₃N₂O₇ [M+H]⁺ 651.2313, found 651.2315.



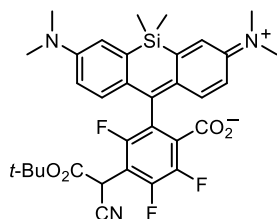
6-(*tert*-Butyl ethyl malonate)-4,5,7-trifluoro-SiTMR (S64): 4,5,6,7-Tetrafluoro-SiTMR (**S53**; 90 mg, 0.180 mmol) and *tert*-butyl ethyl malonate (40.9 μ L, 0.216 mmol, 1.2 eq) were combined in DMF (2 mL), and K₂CO₃ (59.6 mg, 0.432 mmol, 2.4 eq) was added. After stirring the reaction at 50 °C for 18 h, it was cooled to room temperature, diluted with water, and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated. Purification of the crude by silica gel chromatography (0–50% EtOAc/hexanes, linear gradient) yielded 84 mg (70%) of malonate **S64** as a blue-green solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.96 (d, J = 2.9 Hz, 2H), 6.81 – 6.74 (m, 2H), 6.58 – 6.52 (m, 2H), 4.93 (s, 1H), 4.28 – 4.19 (m, 2H), 2.98 (s, 12H), 1.42 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), 0.59 (s, 3H), 0.58 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –115.61 (d, J = 21.9 Hz, 1F), –132.63 (d, J = 20.6 Hz, 1F), –143.27 (t, J = 21.3 Hz, 1F); Analytical HPLC: t_R = 11.6 min, >99% purity (30–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₃₅H₄₀F₃N₂O₆Si [M+H]⁺ 669.2602, found 669.2610.



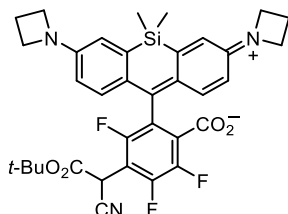
6-(*tert*-Butyl ethyl malonate)-JF₆₆₉ (S65): JF₆₆₉ (**15**; 150 mg, 0.286 mmol) and *tert*-butyl ethyl malonate (65.0 μ L, 0.343 mmol, 1.2 eq) were combined in DMF (3 mL), and K₂CO₃ (94.8 mg, 0.686 mmol, 2.4 eq) was added. After stirring the reaction at 50 °C for 18 h, it was cooled to room temperature, diluted with water, and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated. Purification of the crude by silica gel chromatography (0–50% EtOAc/hexanes, linear gradient) yielded 122 mg (62%) of malonate **S65** as a blue-green solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.77 – 6.71 (m, 2H), 6.66 (d, J = 2.6 Hz, 2H), 6.29 – 6.23 (m, 2H), 4.93 (s, 1H), 4.28 – 4.19 (m, 2H), 3.90 (t, J = 7.2 Hz, 8H), 2.37 (p, J = 7.2 Hz, 4H), 1.43 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), 0.57 (s, 3H), 0.55 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –115.07 (d, J = 21.7 Hz, 1F), –132.59 (d, J = 20.7 Hz, 1F), –143.13 (t, J = 21.2 Hz, 1F); Analytical HPLC: t_R = 12.1 min, >99% purity (30–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₃₇H₄₀F₃N₂O₆Si [M+H]⁺ 693.2602, found 693.2608.



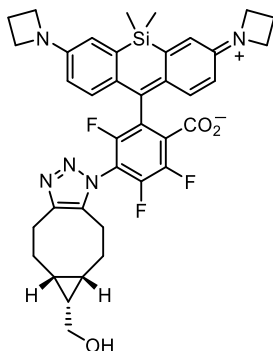
6-(*tert*-Butyl cyanoacetate)-JF₅₇₁ (S66): JF₅₇₁ (**19**; 75 mg, 0.155 mmol) and *tert*-butyl cyanoacetate (26.7 μ L, 0.187 mmol, 1.2 eq) were combined in DMF (2 mL), and K₂CO₃ (51.6 mg, 0.373 mmol, 2.4 eq) was added. After stirring the reaction at room temperature for 18 h, it was directly purified by reverse phase HPLC (30–60% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive). The pooled HPLC product fractions were partially concentrated to remove MeCN, diluted with saturated NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$). The organic extracts were dried over anhydrous MgSO₄, filtered, and evaporated to yield 59 mg (63%) of **S66** as a dark red-purple solid. ¹H NMR (CDCl₃, 400 MHz) δ 6.96 (d, J = 8.7 Hz, 2H), 6.26 (dd, J = 8.8, 2.3 Hz, 2H), 6.22 (d, J = 2.2 Hz, 2H), 4.97 (s, 1H), 4.04 (t, J = 7.4 Hz, 8H), 2.46 (p, J = 7.4 Hz, 4H), 1.44 (s, 9H); ¹⁹F NMR (CDCl₃, 376 MHz) δ –120.49 (d, J = 20.0 Hz, 1F), –131.85 (d, J = 21.6 Hz, 1F), –141.12 (t, J = 20.8 Hz, 1F); Analytical HPLC: t_R = 12.2 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 575 nm); HRMS (ESI) calcd for C₃₃H₂₉F₃N₃O₅ [M+H]⁺ 604.2054, found 604.2050.



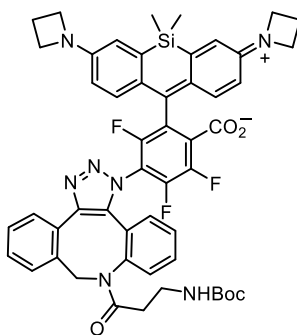
6-(*tert*-Butyl cyanoacetate)-4,5,7-trifluoro-SiTMR (S67): 4,5,6,7-Tetrafluoro-SiTMR (**S53**; 90 mg, 0.180 mmol) and *tert*-butyl cyanoacetate (30.8 μ L, 0.216 mmol, 1.2 eq) were combined in DMF (2 mL), and K_2CO_3 (59.6 mg, 0.432 mmol, 2.4 eq) was added. After stirring the reaction at room temperature for 18 h, it was diluted with water and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification of the crude by silica gel chromatography (10–75% EtOAc/hexanes, linear gradient) yielded 95 mg (85%) of **S67** as a blue-green foam. 1H NMR ($CDCl_3$, 400 MHz) δ 6.97 – 6.93 (m, 2H), 6.77 – 6.71 (m, 2H), 6.61 – 6.55 (m, 2H), 5.03 (s, 1H), 2.99 (s, 6H), 2.99 (s, 6H), 1.46 (s, 9H), 0.59 (s, 3H), 0.57 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ –117.92 (d, J = 22.3 Hz, 1F), –132.35 (d, J = 20.4 Hz, 1F), –141.60 (dd, J = 22.4, 20.4 Hz, 1F); Analytical HPLC: t_R = 10.4 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 675 nm); HRMS (ESI) calcd for $C_{33}H_{35}F_3N_3O_4Si$ $[M+H]^+$ 622.2343, found 622.2345.



6-(*tert*-Butyl cyanoacetate)-JF₆₆₉ (S68): JF₆₆₉ (**15**; 150 mg, 0.286 mmol) and *tert*-butyl cyanoacetate (49.0 μ L, 0.343 mmol, 1.2 eq) were combined in DMF (3 mL), and K_2CO_3 (94.8 mg, 0.686 mmol, 2.4 eq) was added. After stirring the reaction at room temperature for 48 h, it was diluted with water and extracted with EtOAc (2 $\times$). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification of the crude by silica gel chromatography (10–75% EtOAc/hexanes, linear gradient) yielded 155 mg (84%) of **S68** as a blue-green solid. 1H NMR ($CDCl_3$, 400 MHz) δ 6.73 – 6.67 (m, 2H), 6.67 – 6.63 (m, 2H), 6.29 (dd, J = 8.7, 2.7 Hz, 2H), 5.03 (s, 1H), 3.92 (t, J = 7.3 Hz, 8H), 2.44 – 2.33 (m, 4H), 1.46 (s, 9H), 0.56 (s, 3H), 0.55 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ –117.51 (d, J = 22.4 Hz, 1F), –132.27 (d, J = 20.5 Hz, 1F), –141.37 – –141.55 (m, 1F); Analytical HPLC: t_R = 10.9 min, 99.0% 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 675 nm); HRMS (ESI) calcd for $C_{35}H_{35}F_3N_3O_4Si$ $[M+H]^+$ 646.2343, found 646.2350.

CYCLOADDITIONS OF 6-AZIDO-JF₆₆₉

JF₆₆₉-BCN triazole (27): 6-Azido-JF₆₆₉ (**21**; 40 mg, 73.0 μ mol) and (1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (**25**; 14.3 mg, 95.0 μ mol, 1.3 eq) were combined in DMF (1.5 mL) and stirred at room temperature for 1 h. The reaction was concentrated to dryness and purified by flash chromatography on silica gel (25–100% EtOAc/CH₂Cl₂, linear gradient) to afford **27** as a dark blue-green solid (48.2 mg, 95%). ¹H NMR (DMSO-*d*₆, 400 MHz, 350 K) δ 6.87 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 2.6 Hz, 2H), 6.38 – 6.32 (m, 2H), 4.04 – 3.99 (m, 1H), 3.89 (t, *J* = 7.3 Hz, 8H), 3.56 – 3.43 (m, 2H), 3.14 – 3.07 (m, 1H), 2.93 – 2.77 (m, 2H), 2.69 – 2.55 (m, 1H), 2.34 (p, *J* = 7.2 Hz, 4H), 2.19 – 2.09 (m, 1H), 2.07 – 1.98 (m, 1H), 1.64 – 1.49 (m, 2H), 1.07 – 0.96 (m, 1H), 0.94 – 0.75 (m, 2H), 0.54 (s, 3H), 0.48 (s, 3H); ¹⁹F NMR (DMSO-*d*₆, 376 MHz, 350 K) δ –124.27 (d, *J* = 20.8 Hz, 1F), –137.21 (d, *J* = 22.1 Hz, 1F), –140.63 (t, *J* = 21.3 Hz, 1F); Analytical HPLC: *t*_R = 11.7 min, >99% purity (10–95% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₃₈H₃₉F₃N₅O₃Si [M+H]⁺ 698.2769, found 698.2779.

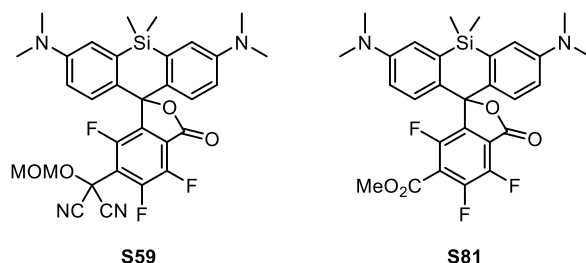


JF₆₆₉-DBCO triazole (28): 6-Azido-JF₆₆₉ (**21**; 30 mg, 54.8 μ mol) and DBCO-NH-Boc (**26**; 24.8 mg, 65.7 μ mol, 1.2 eq) were combined in DMF (1 mL) and stirred at room temperature for 1 h. The reaction was concentrated to dryness and purified by flash chromatography on silica gel (25–100% EtOAc/hexanes, linear gradient) to provide the desired product **28** as a mixture of regioisomers (pale green solid, 50.1 mg, 99%). Although the NMR spectra were not interpretable, HPLC and HRMS analyses were consistent with the expected product mixture. Analytical HPLC: *t*_R (major isomer) = 11.5 min, 60.3% by peak integration; *t*_R (minor isomer) = 11.9 min, 39.7% by peak integration (45–55% MeCN/H₂O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; detection at 675 nm); HRMS (ESI) calcd for C₅₁H₄₉F₃N₇O₅Si [M+H]⁺ 924.3511, found 924.3531.

X-RAY CRYSTALLOGRAPHY

Confirmation of the regioselectivity of masked acyl cyanide (MAC) substitution

Single crystal X-ray diffraction (SC-XRD) of **S59** and **S81**



MAC substitution product S59: Crystallization and SC-XRD of **S59** were performed by Ardena in Amsterdam, The Netherlands. Crystals of adequate quality for SC-XRD were obtained by vapor diffusion crystallization from 1,4-dioxane (solvent) and water (anti-solvent). The single crystal measurements were performed on a Nonius Kappa-CCD. The data were collected at 296 K. The full sphere data were collected up to $\theta = 32.7^\circ$ (20840 reflections). Data reduction was performed using HKL Scalepack and cell parameters were obtained using Denzo and Scalepak from 11297 reflections within θ range 1 to 32.7° .^[12] The structure was solved using direct methods by SHELXT-2014/7.^[13] The structure was refined by least square full matrix refinement using SHELXL-2014/7.^[14] All H-atoms were included from the geometry and kept with fixed thermal parameters. The obtained crystal structure (**Figure S1**) confirmed that substitution by the MAC reagent occurred exclusively at the position *para* to the carbonyl.

Methyl ester S81: Crystallization and SC-XRD of **S81** were performed by Ardena in Amsterdam, The Netherlands. Crystals of adequate quality for SC-XRD were obtained by vapor diffusion crystallization from EtOAc (solvent) and heptane (anti-solvent). The single crystal measurements were performed on a Nonius Kappa-CCD. The data were collected at 296 K. The full sphere data were collected up to $\theta = 32.6^\circ$ (18406 reflections). Data reduction was performed using HKL Scalepack and cell parameters were obtained using Denzo and Scalepak from 9087 reflections within θ range 1 to 32.6° .^[12] The structure was solved using direct methods by SHELXT-2014/7.^[13] The structure was refined by least square full matrix refinement using SHELXL-2014/7.^[14] All H-atoms were included from the geometry and kept with fixed thermal parameters. During the refinement the relatively high peak $\sim 2.4 \text{ e}/\text{\AA}^3$ was observed in the symmetry center associated with peaks of lower intensities. Attempts to model these peaks as solvent were unsuccessful (blue balls in the figure). During the final cycles it was found out that carbonyl O atom from the methyl ester group is disordered in two positions with following occupancy factors 0.65(5) and 0.35(5). Regardless, the obtained crystal structure (**Figure S1**) was consistent with the regiochemistry of the structure assigned to **S59**, from which **S81** was derived.

^[12] Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, 276, 307–326.

^[13] Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Adv.* **2015**, 71, 3–8.

^[14] Sheldrick, G. M. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, 71, 3–8.

Table S1. Crystal data and structure refinement for **S59** and **S81**.

	MAC product S59	Methyl ester S81
Empirical Formula	$C_{31}H_{29}F_3N_4O_4Si \cdot 1.5(C_4H_8O_2)$	$C_{28}H_{27}F_3N_2O_4Si \cdot 1/6(C_4H_8O_2)$
Formula Weight	738.83	540.62 + 14.66
Temperature	296(2) K	296(2) K
λ	0.71073 Å	0.71073 Å
Crystal System, Space Group	Triclinic, P-1	Trigonal, R-3
Unit Cell Dimensions	a = 9.4514(6) Å b = 12.9790(9) Å c = 15.4757(12) Å $\alpha = 88.026(1)^\circ$ $\beta = 81.890(1)^\circ$ $\gamma = 87.402(1)^\circ$	a = 30.3536(10) Å c = 15.4361(3) Å
Volume	1876.7(2) Å ³	12316.5(8) Å ³
Z	2	18
D _c	1.307 g/cm ³	1.357 g/cm ³
μ	0.130 mm ⁻¹	0.145 mm ⁻¹
F(000)	776	5244
Crystal Size	0.35 × 0.22 × 0.20 mm ³	0.45 × 0.30 × 0.22 mm ³
θ Range for Data Collection	2.7–32.7°	2.0–32.6°
Reflections Collected	20840	18406
Independent Reflections	13660 [$R_{\text{int}} = 0.0258$]	9910 [$R_{\text{int}} = 0.0267$]
Completeness to $\theta = 25.242^\circ$	99.7	99.3
Absorption Correction	Integration	Integration
Max. and Min. Transmission	0.990 and 0.958	0.978 and 0.953
Data / Restraint / Parameters	13660 / 0 / 476	9910 / 2 / 367
Goodness-of-Fit on F^2	1.023	1.021
Final R Indices [$I > 2\sigma(I)$]	R1 = 0.0673, wR2 = 0.1801	R1 = 0.0582, wR2 = 0.1478
R Indices (All Data)	R1 = 0.1248, wR2 = 0.2170	R1 = 1.077, wR2 = 0.1894
Largest Diff. Peak and Hole	0.490 and -0.324 e/Å ³	0.302 and -0.458 e/Å ³

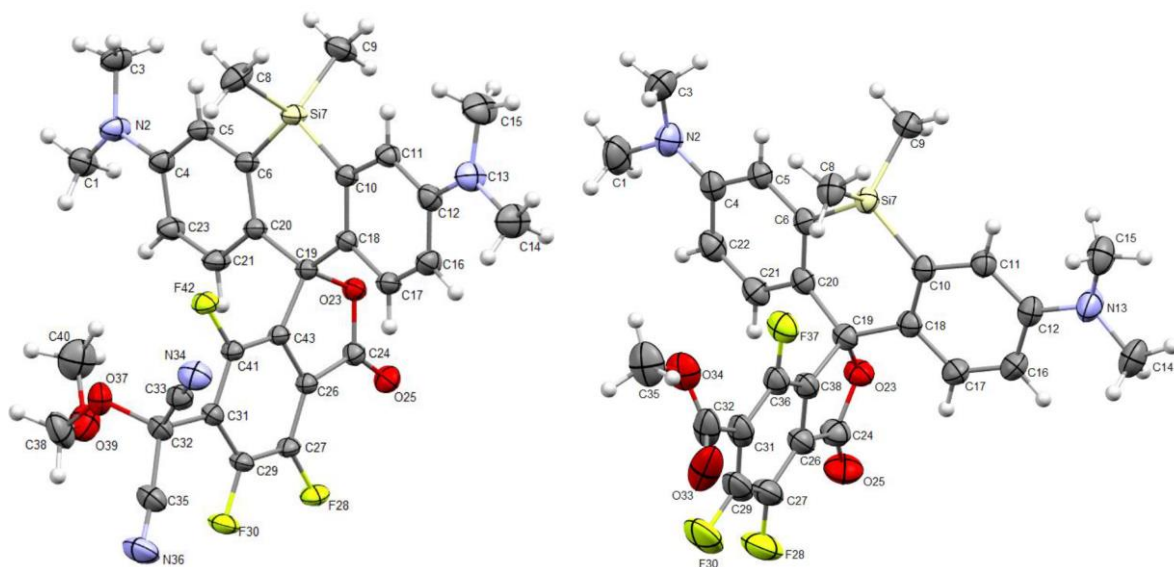


Figure S1. Molecular structure and atoms numbering scheme for **S59** (left) and **S81** (right); displacement ellipsoids at the 30% probability level.

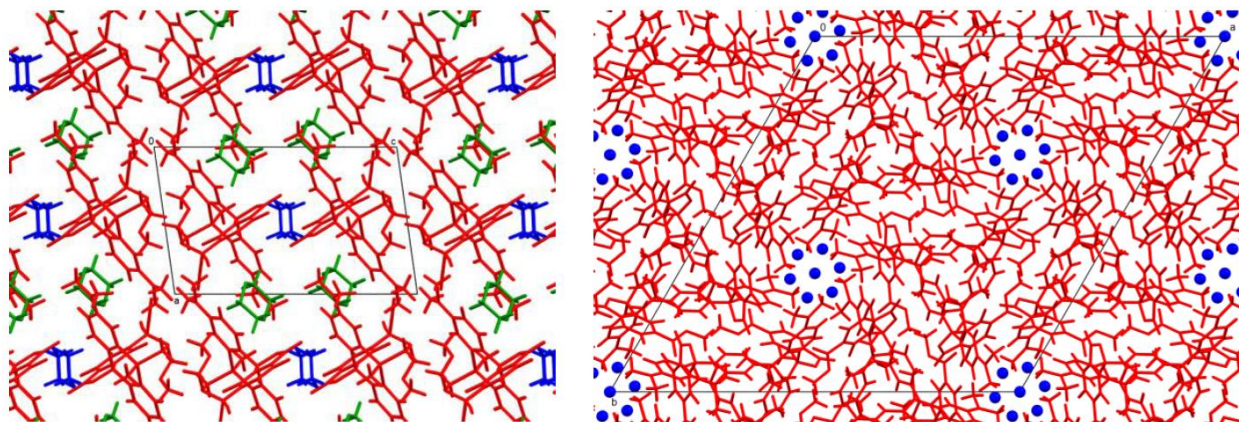
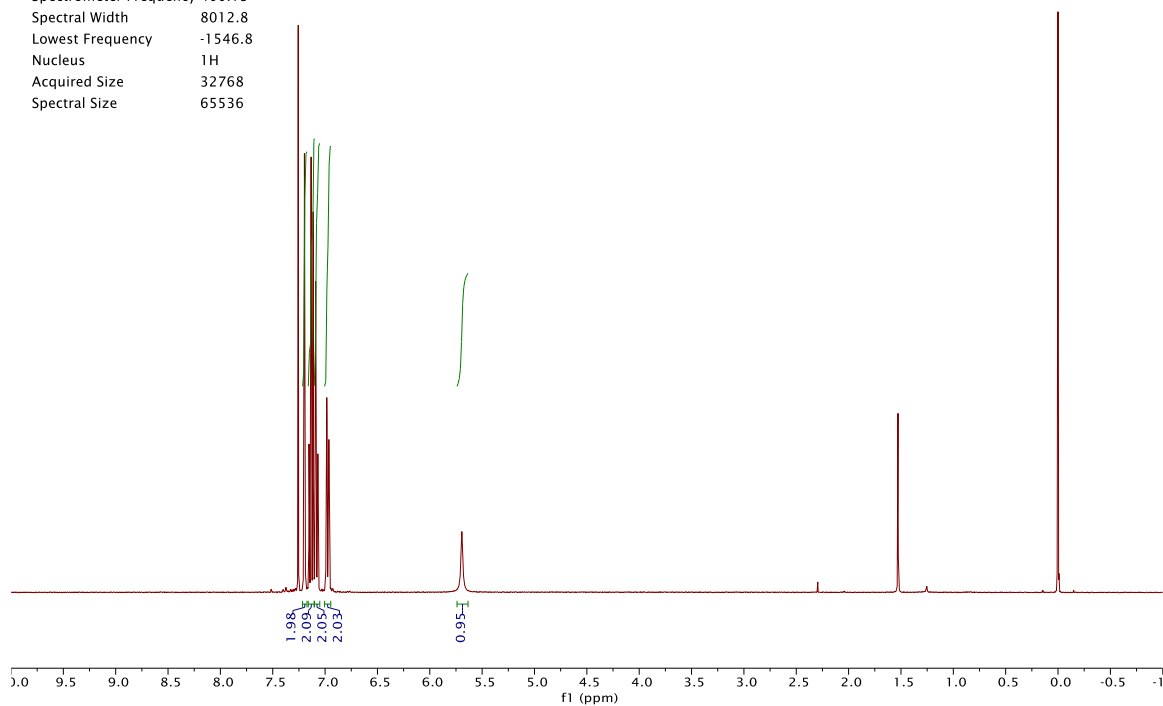
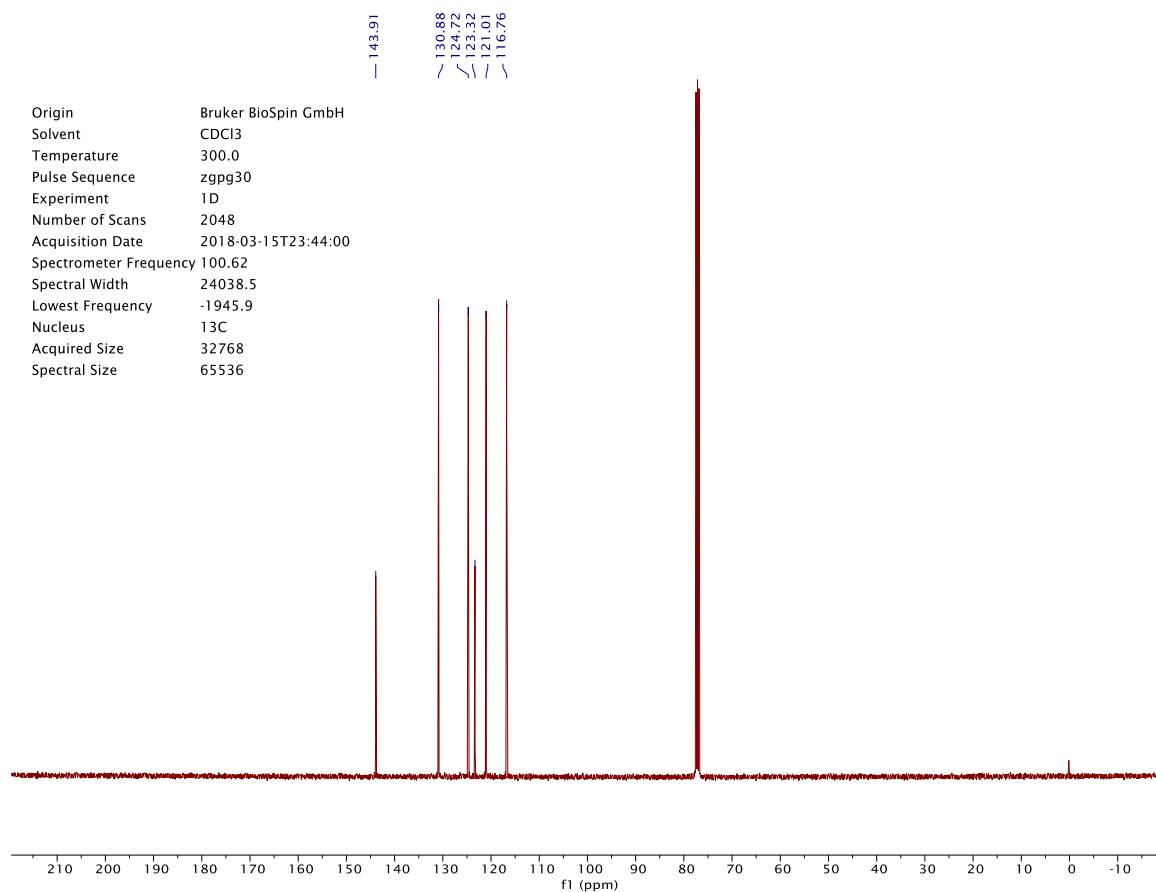


Figure S2. Packing along *b* axis in the crystal of **S59**-1,4-dioxane solvate (left) and along *c* axis in the crystal of **S81**-EtOAc solvate (right). In both images, **S59** and **S81** are shown in red while the solvent molecules are blue and green (left) and blue (right).

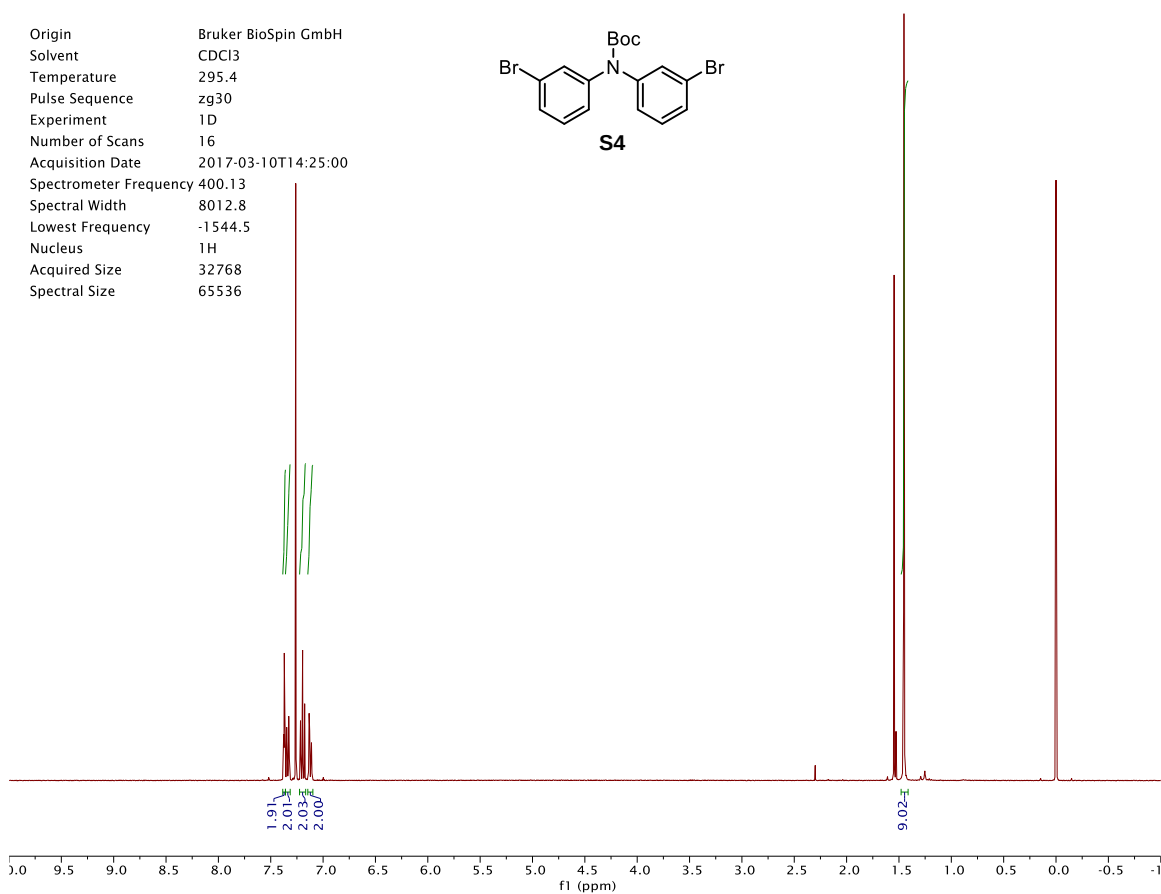
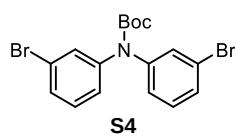
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-15T09:59:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1546.8
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



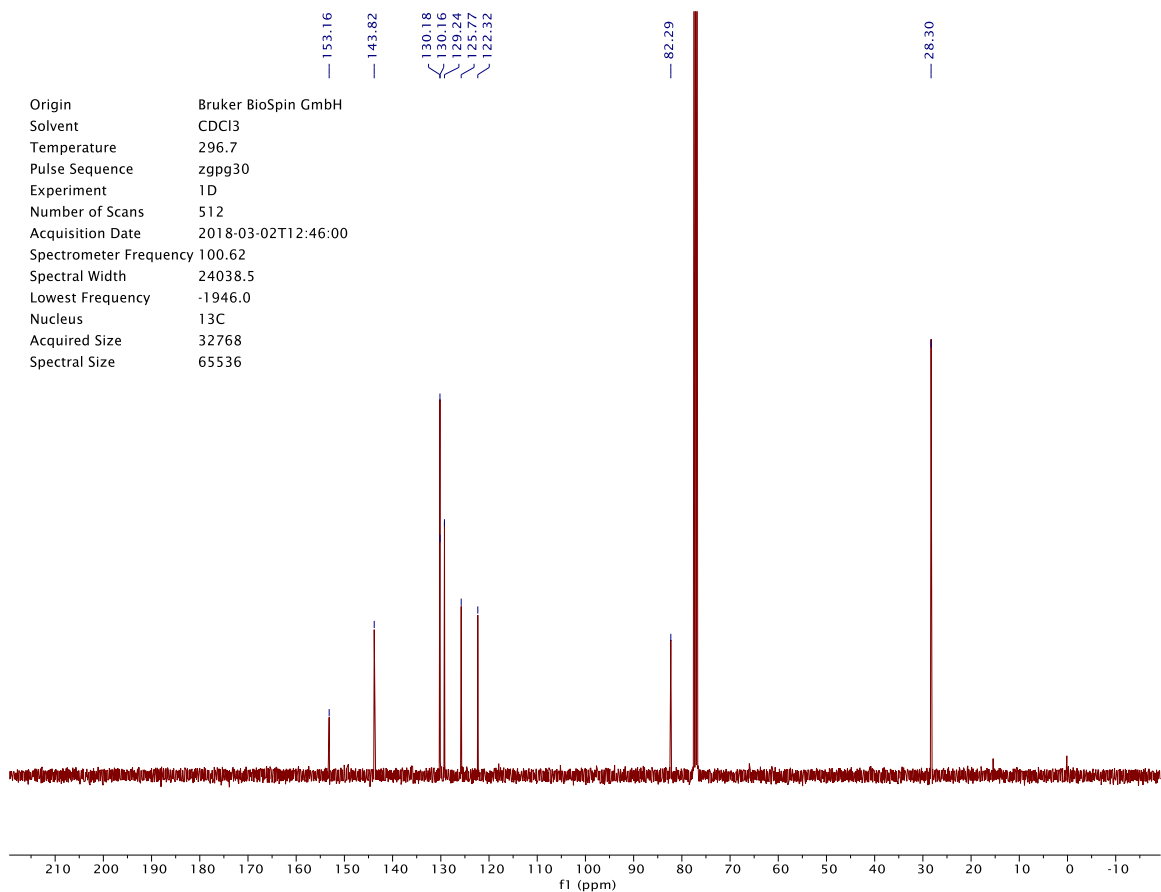
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-15T23:44:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1945.9
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



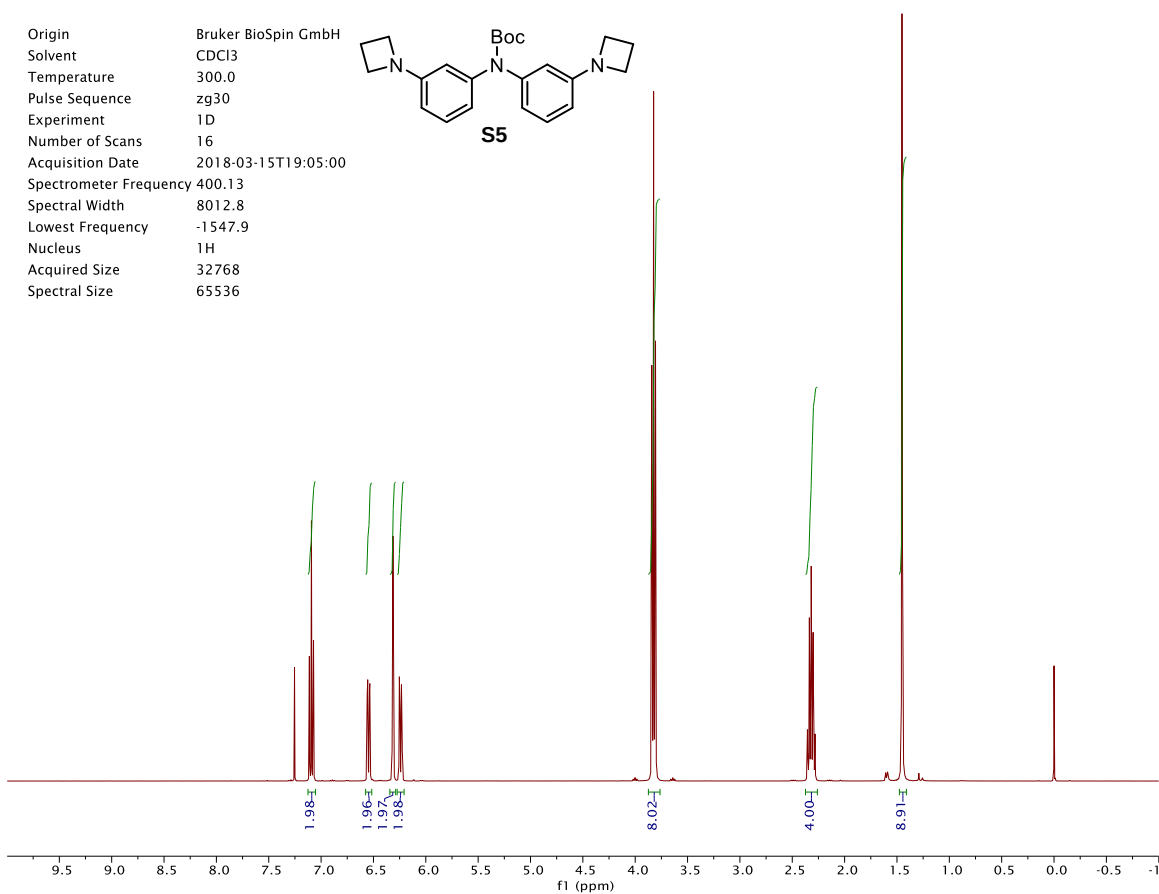
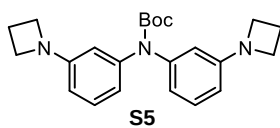
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 295.4
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-03-10T14:25:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1544.5
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



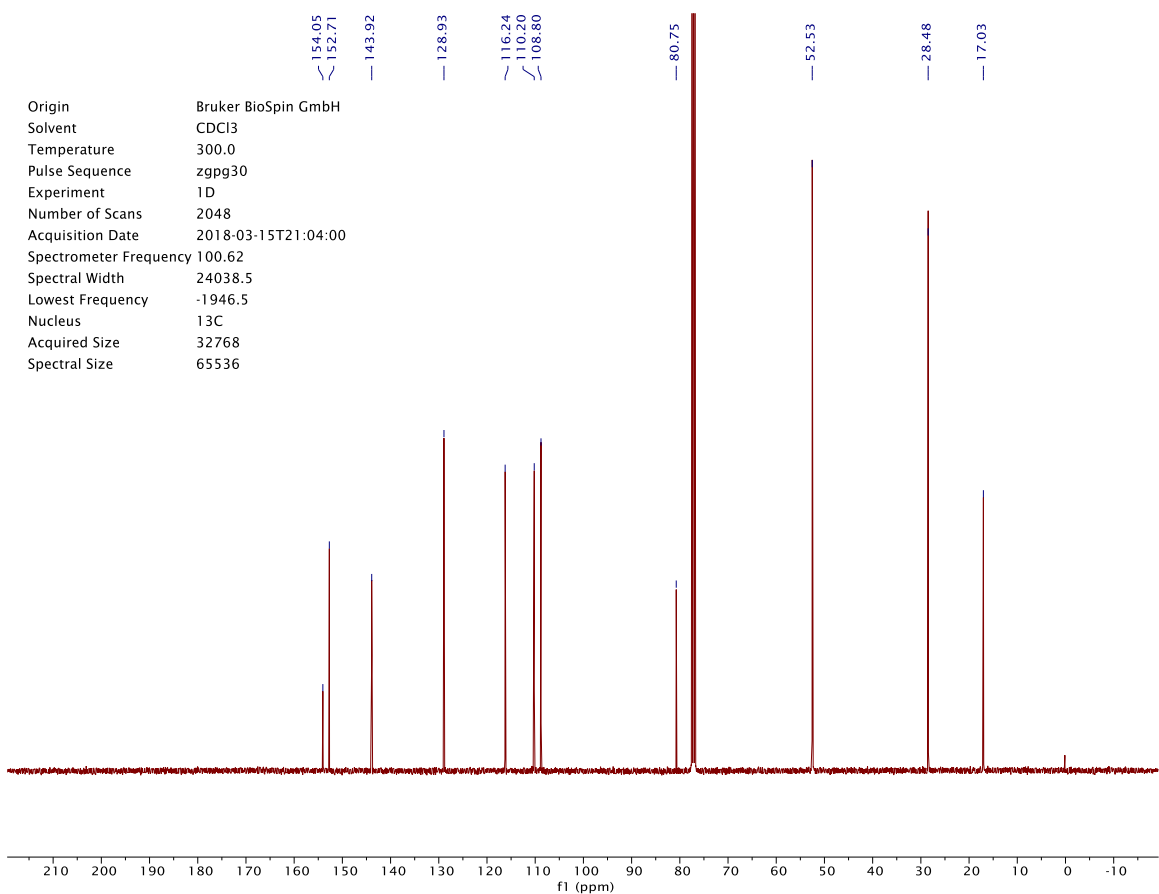
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 296.7
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 512
 Acquisition Date 2018-03-02T12:46:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1946.0
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



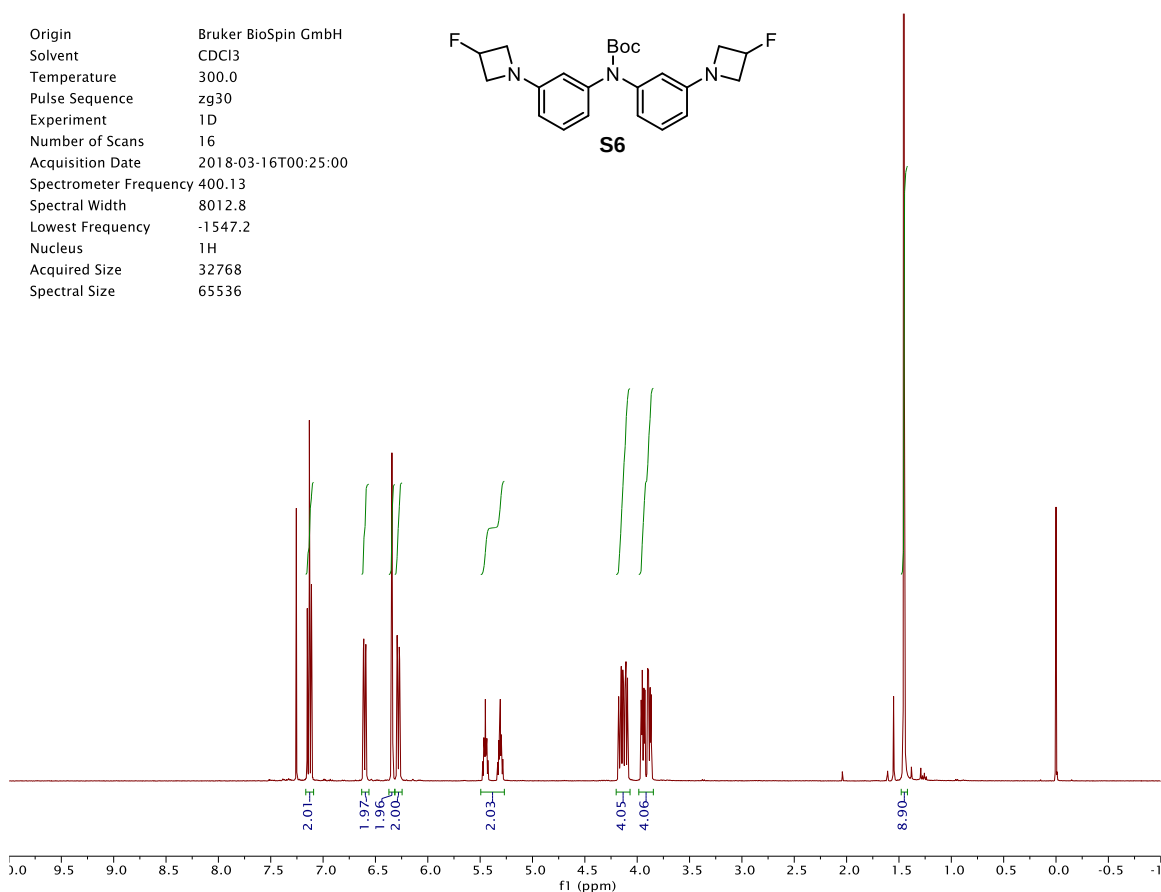
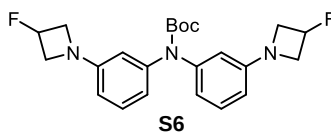
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-15T19:05:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1547.9
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



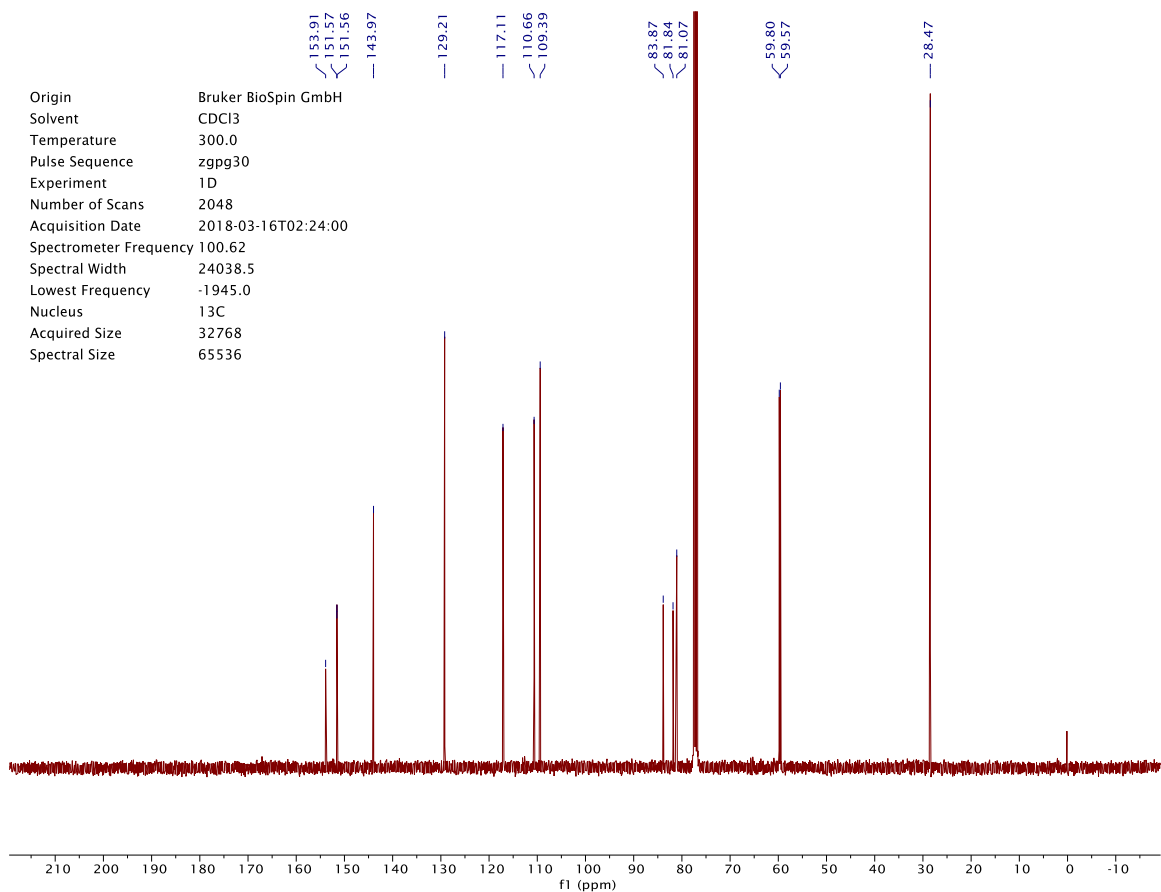
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-15T21:04:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1946.5
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



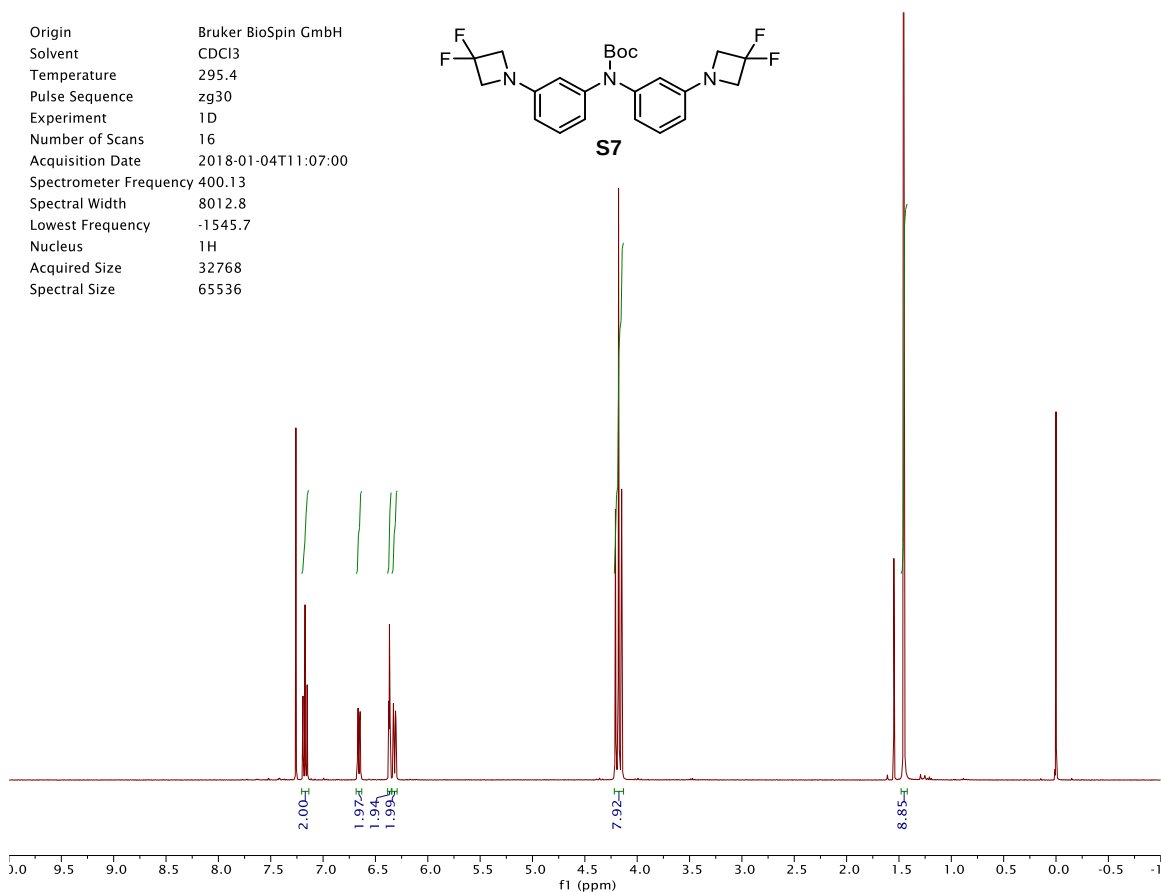
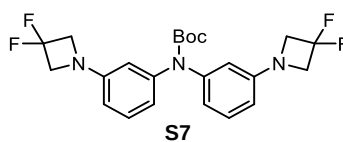
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-16T00:25:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1547.2
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



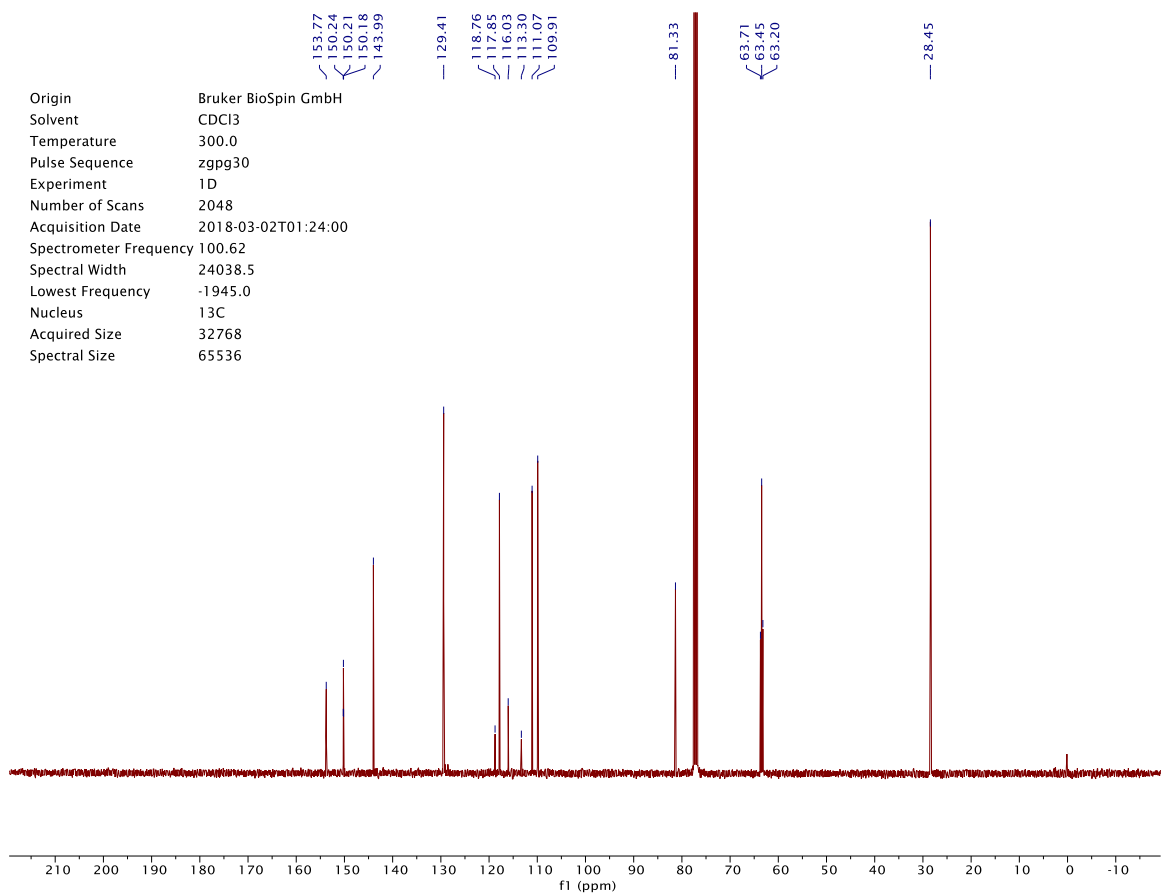
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-16T02:24:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1945.0
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



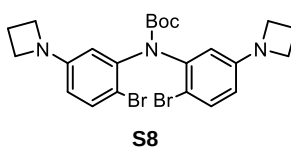
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 295.4
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-01-04T11:07:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.7
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



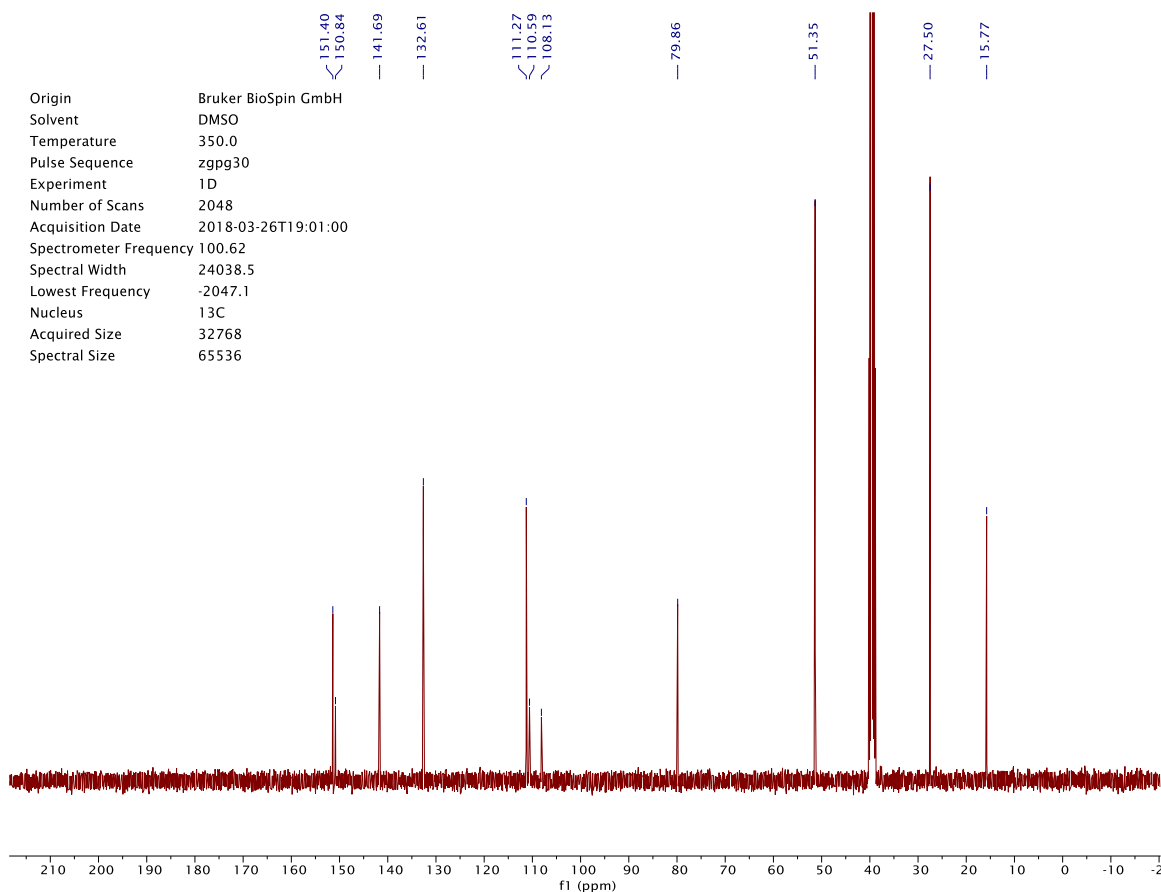
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-02T01:24:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1945.0
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



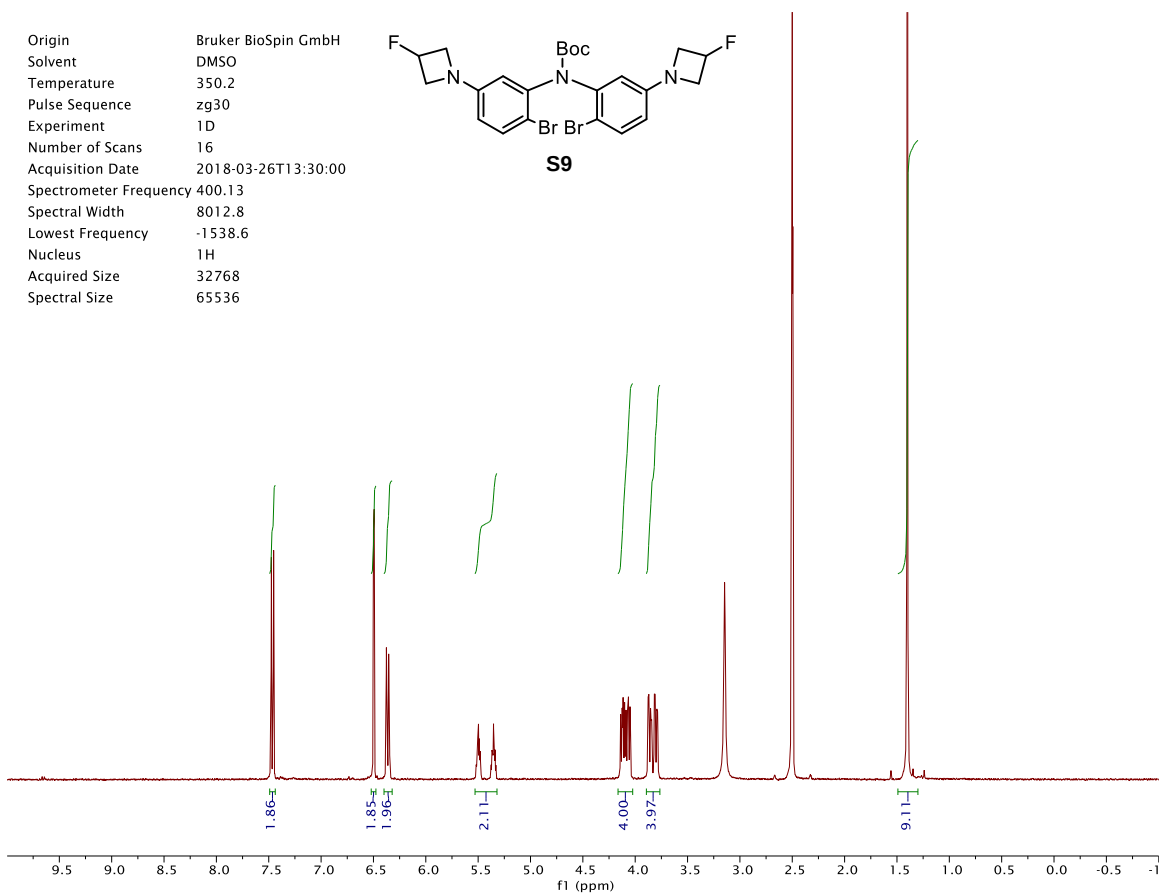
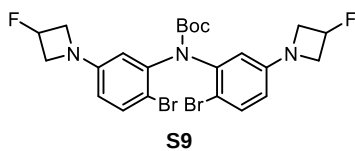
Origin Bruker BioSpin GmbH
 Solvent DMSO
 Temperature 350.2
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-26T17:02:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1538.4
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



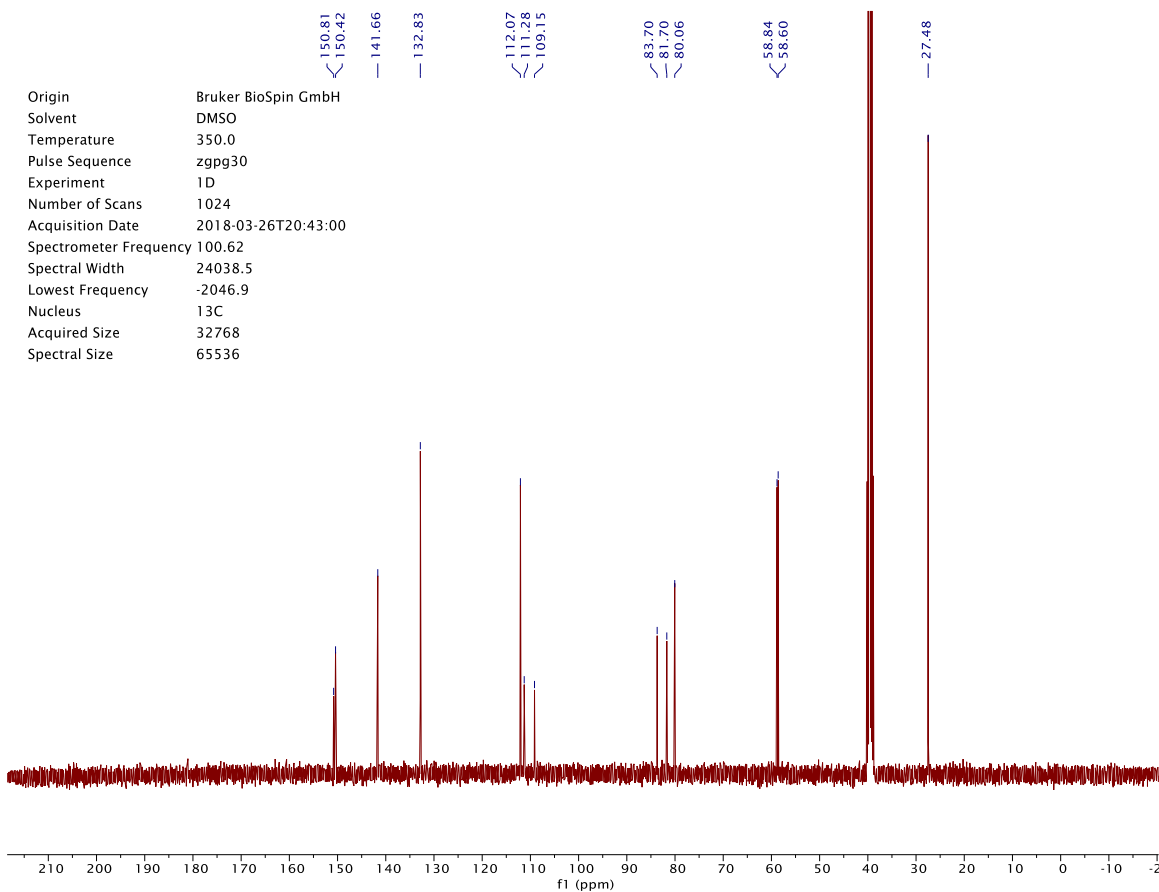
Origin Bruker BioSpin GmbH
 Solvent DMSO
 Temperature 350.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-26T19:01:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -2047.1
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



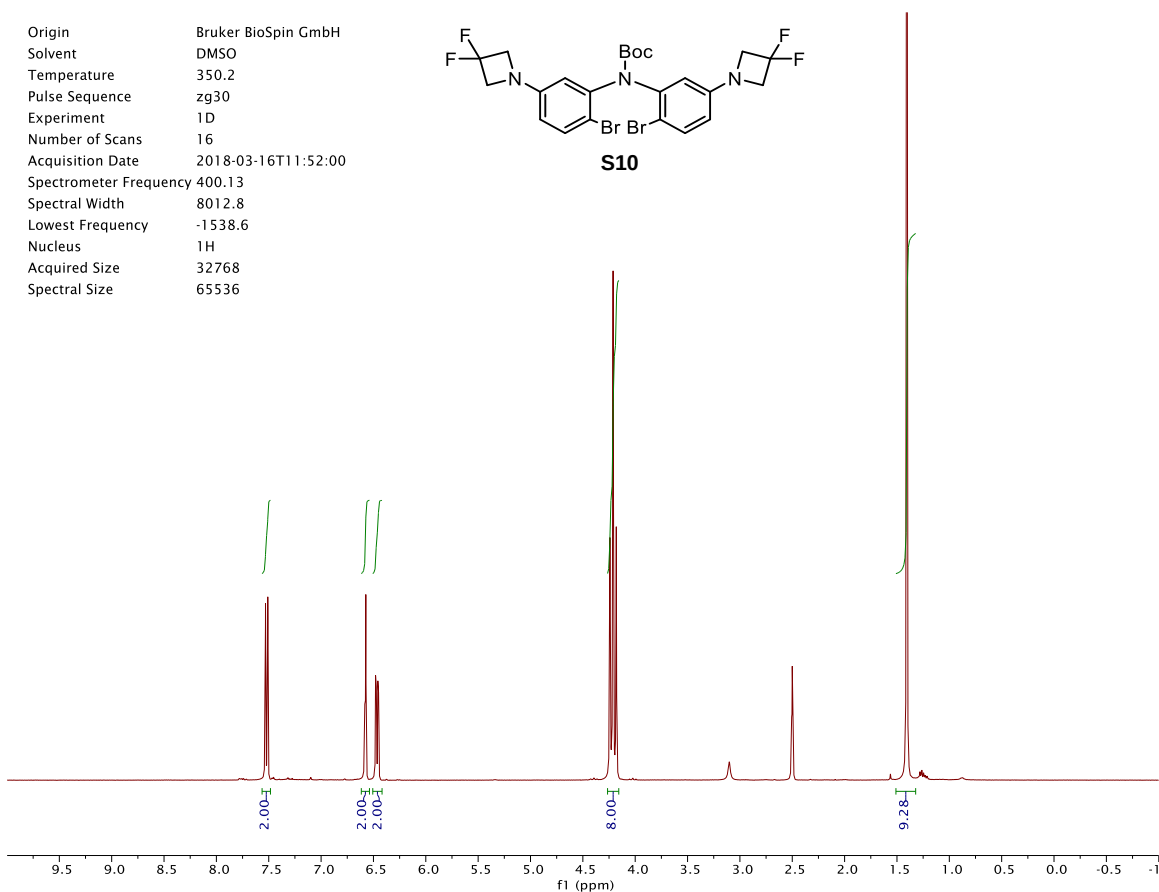
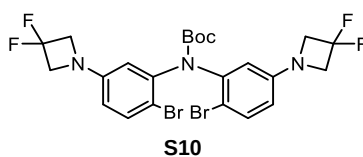
Origin: Bruker BioSpin GmbH
 Solvent: DMSO
 Temperature: 350.2
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-03-26T13:30:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1538.6
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



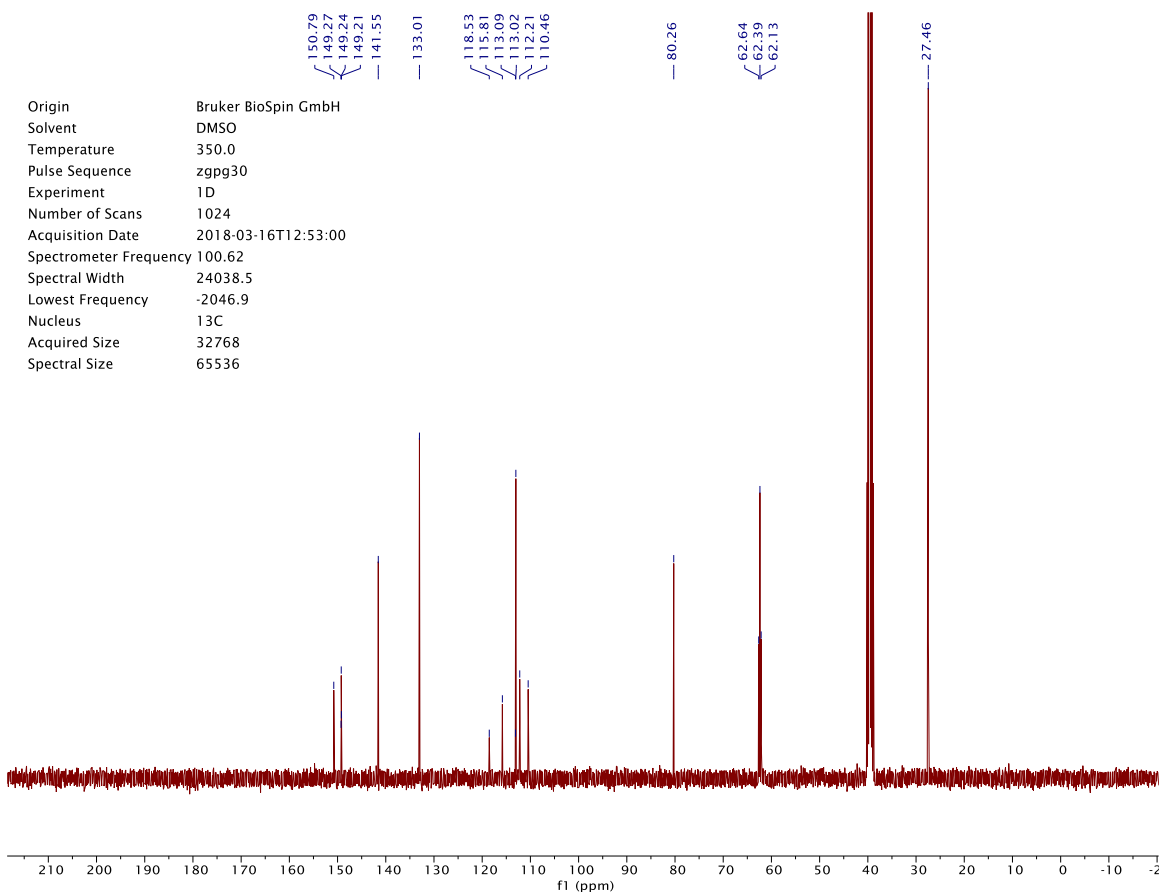
Origin: Bruker BioSpin GmbH
 Solvent: DMSO
 Temperature: 350.0
 Pulse Sequence: zgpg30
 Experiment: 1D
 Number of Scans: 1024
 Acquisition Date: 2018-03-26T20:43:00
 Spectrometer Frequency: 100.62
 Spectral Width: 24038.5
 Lowest Frequency: -2046.9
 Nucleus: ¹³C
 Acquired Size: 32768
 Spectral Size: 65536



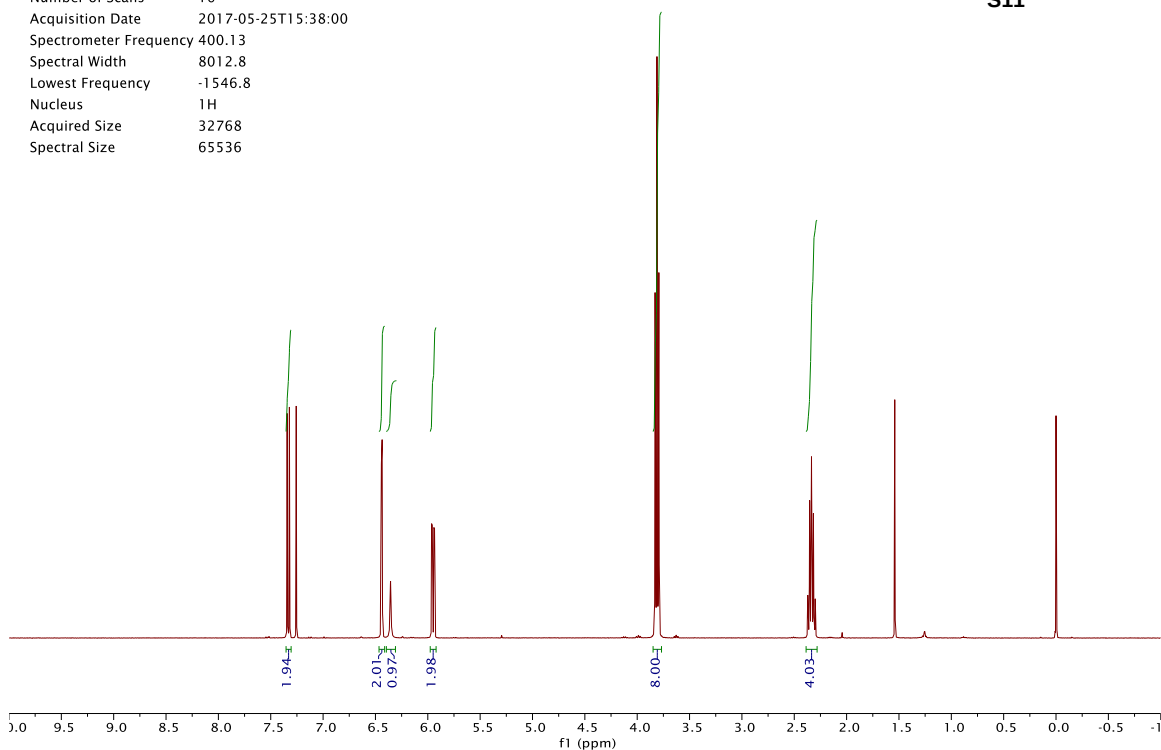
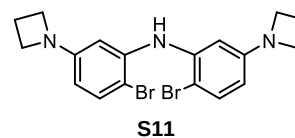
Origin Bruker BioSpin GmbH
 Solvent DMSO
 Temperature 350.2
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-16T11:52:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1538.6
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



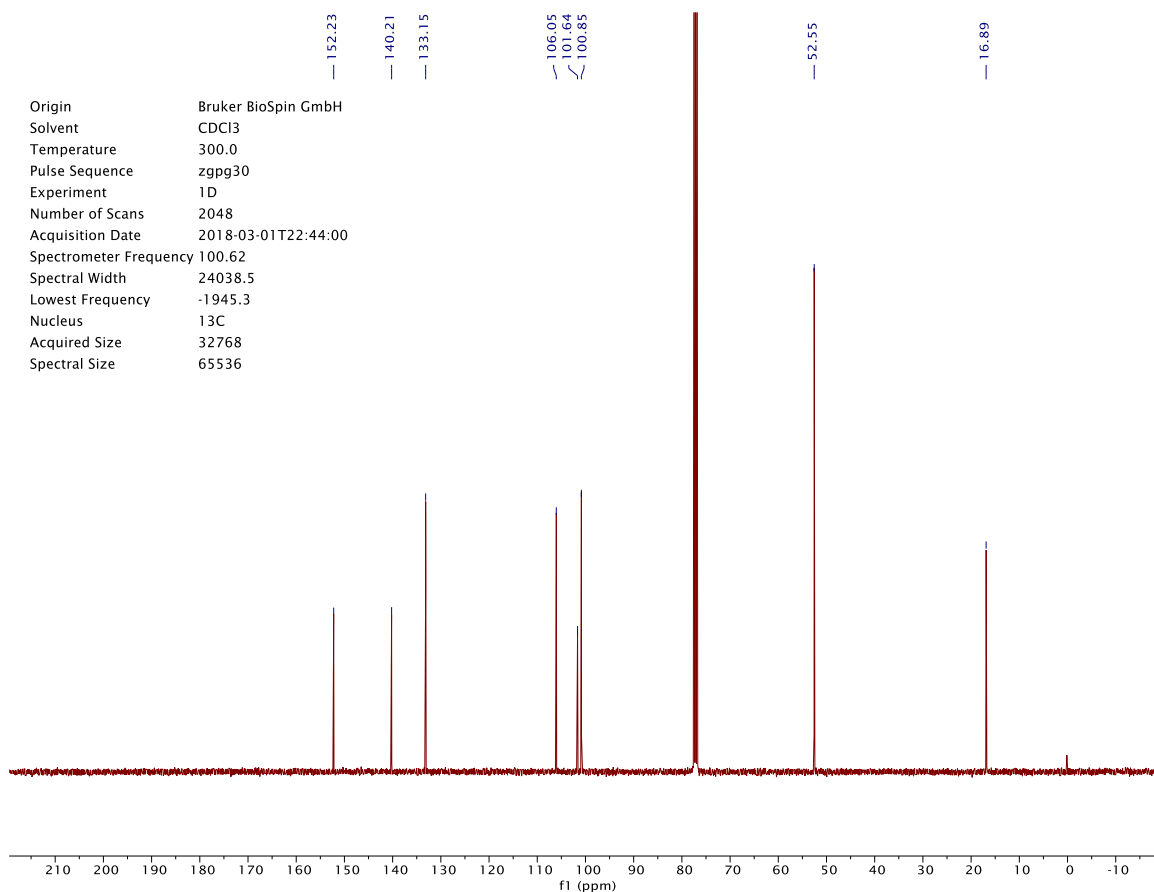
Origin Bruker BioSpin GmbH
 Solvent DMSO
 Temperature 350.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 1024
 Acquisition Date 2018-03-16T12:53:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -2046.9
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



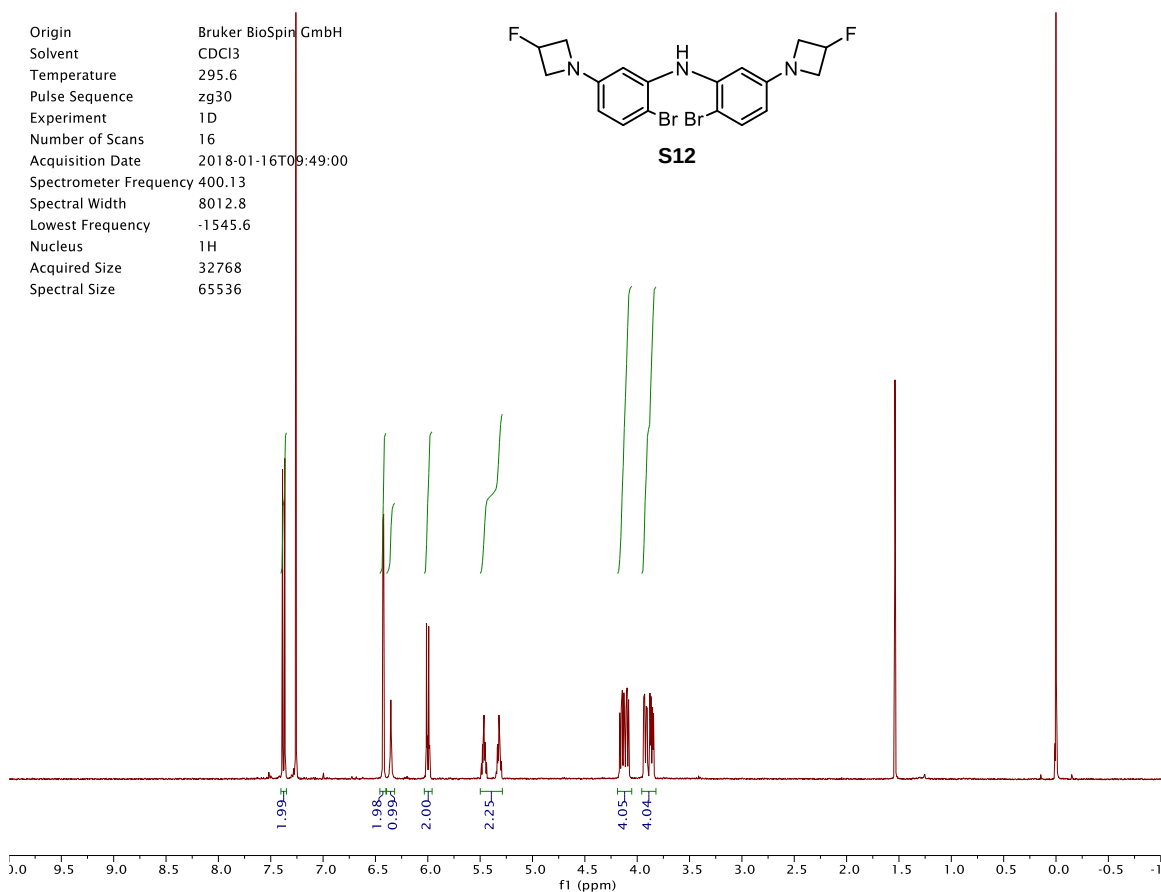
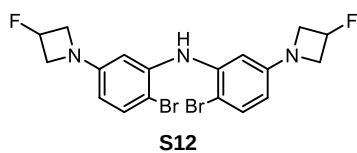
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-05-25T15:38:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1546.8
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



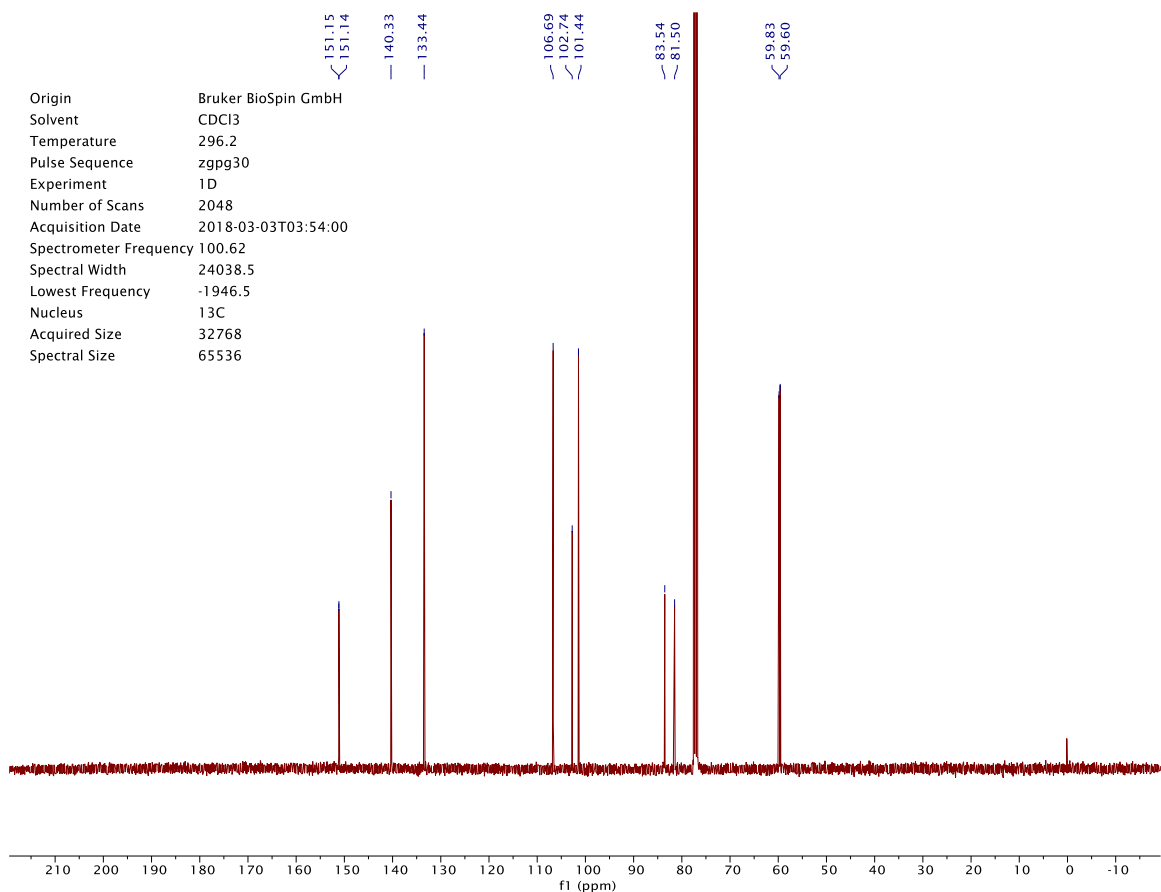
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-01T22:44:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1945.3
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



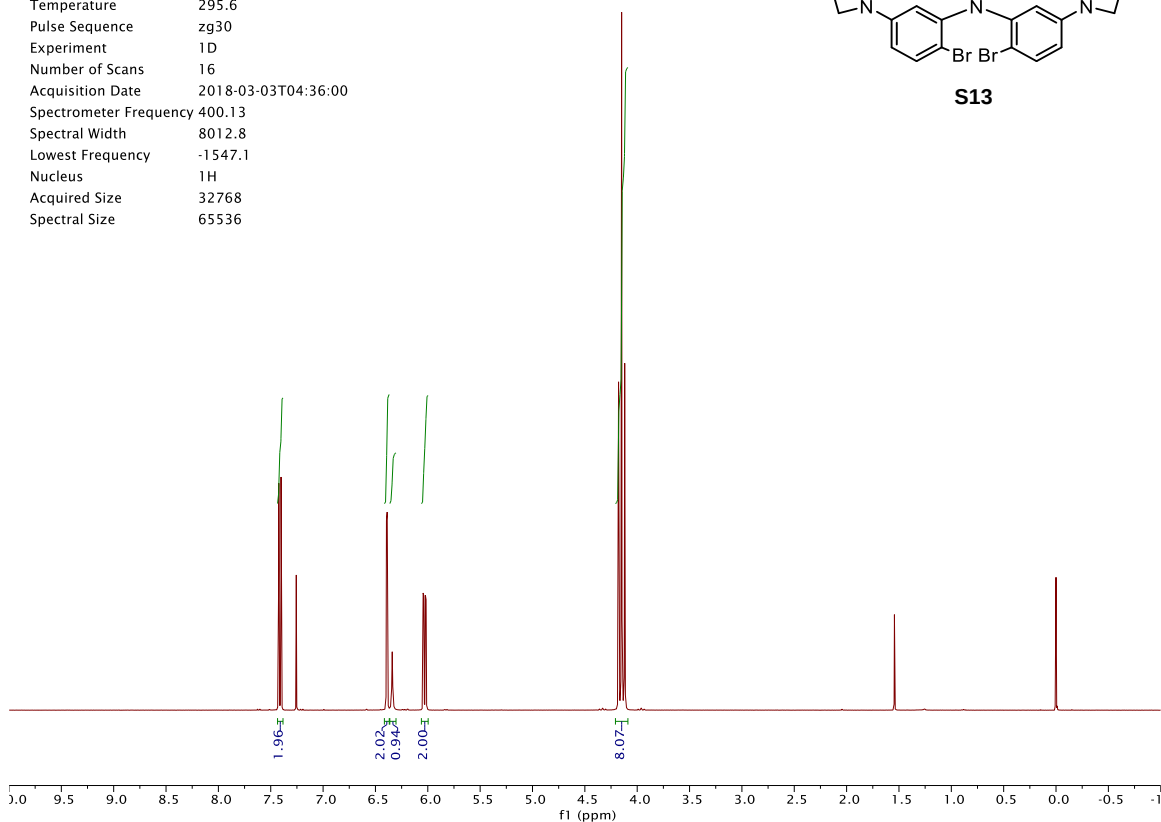
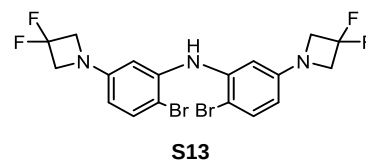
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 295.6
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-01-16T09:49:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.6
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



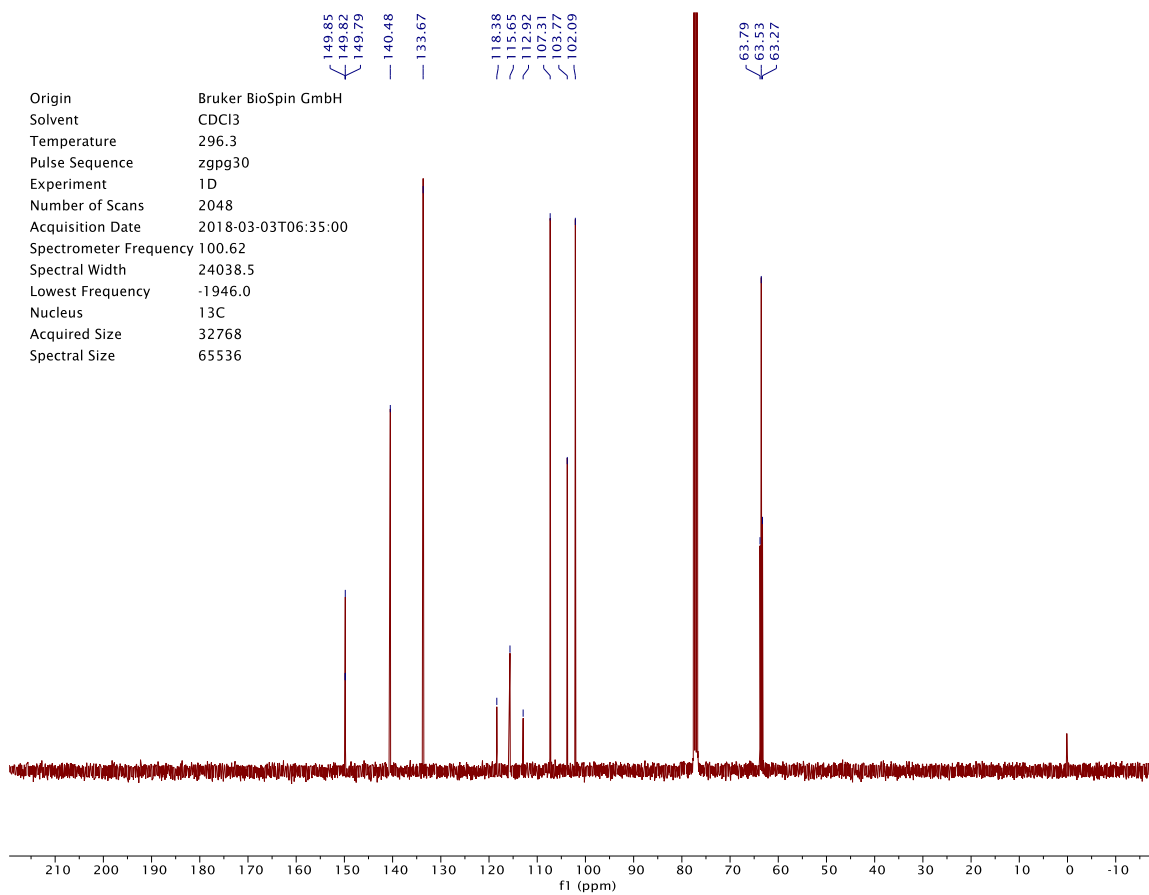
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 296.2
 Pulse Sequence: zgpg30
 Experiment: 1D
 Number of Scans: 2048
 Acquisition Date: 2018-03-03T03:54:00
 Spectrometer Frequency: 100.62
 Spectral Width: 24038.5
 Lowest Frequency: -1946.5
 Nucleus: ¹³C
 Acquired Size: 32768
 Spectral Size: 65536



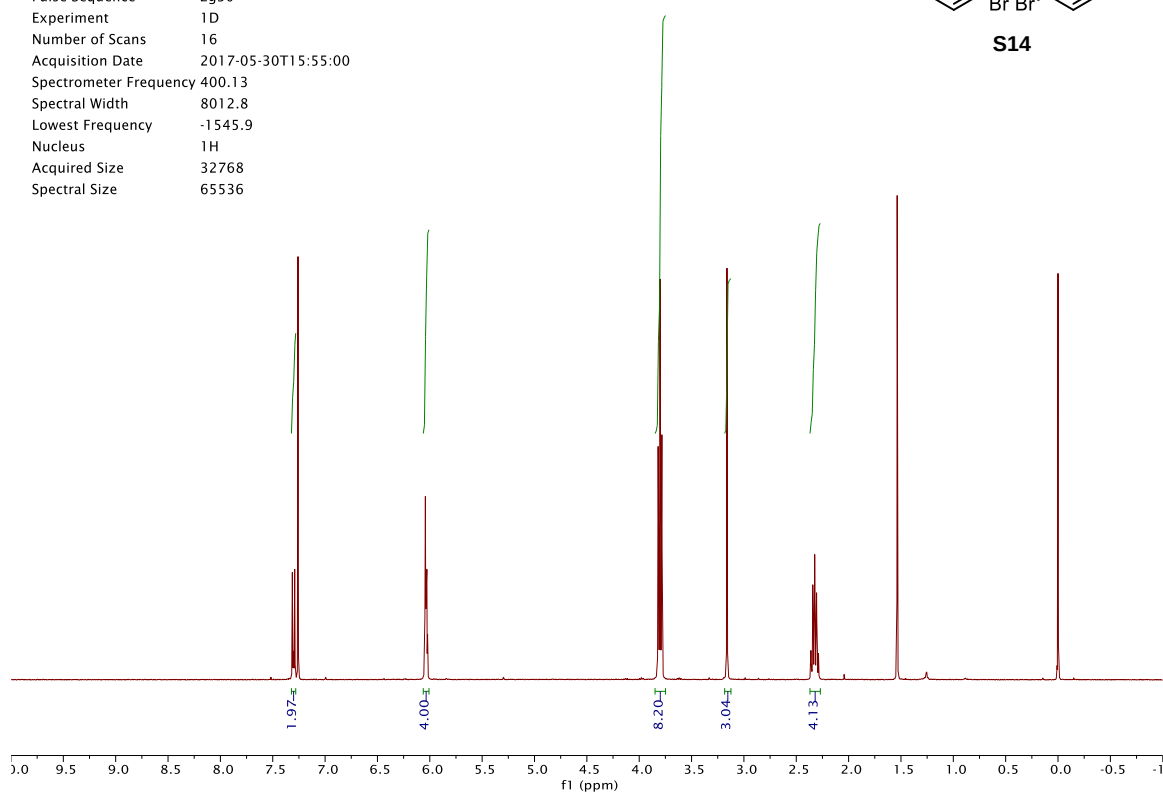
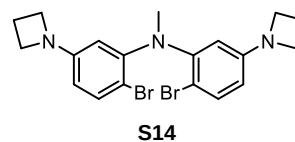
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 295.6
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-03T04:36:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1547.1
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



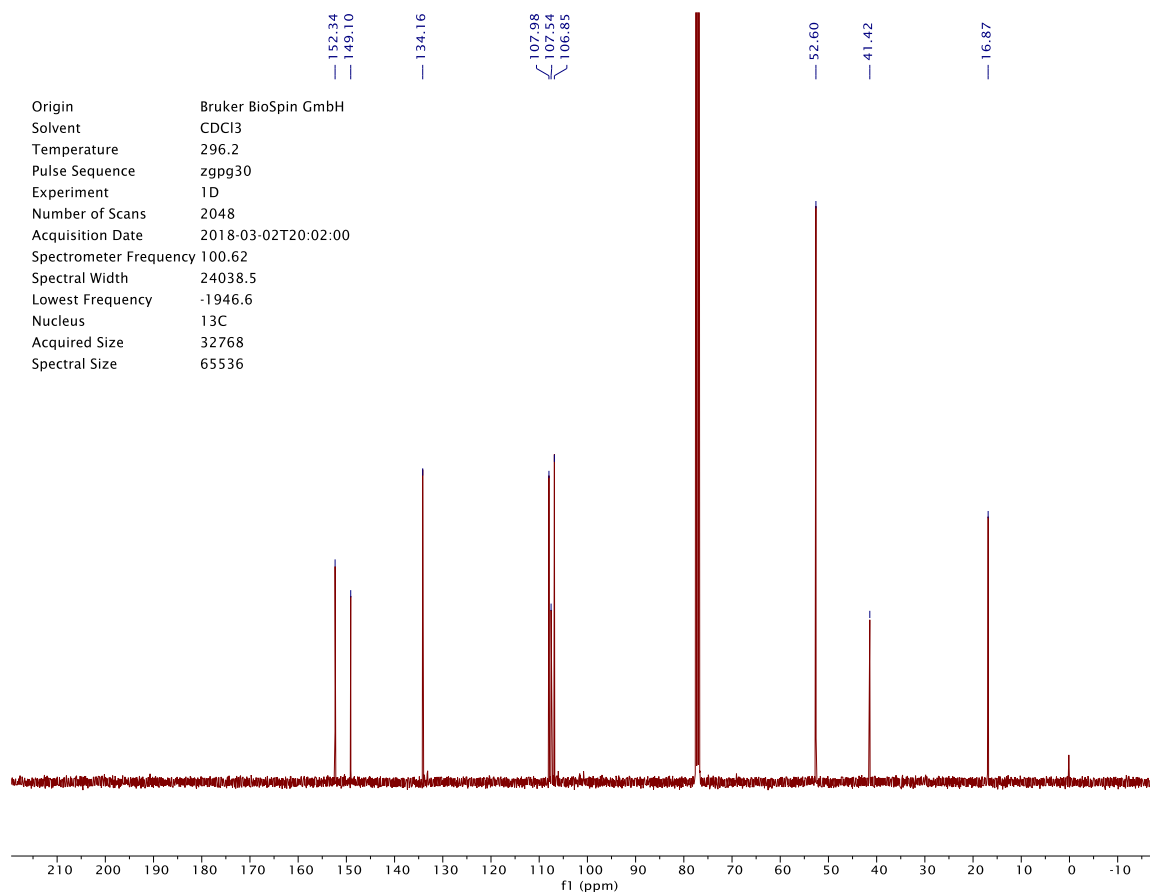
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 296.3
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-03T06:35:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1946.0
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



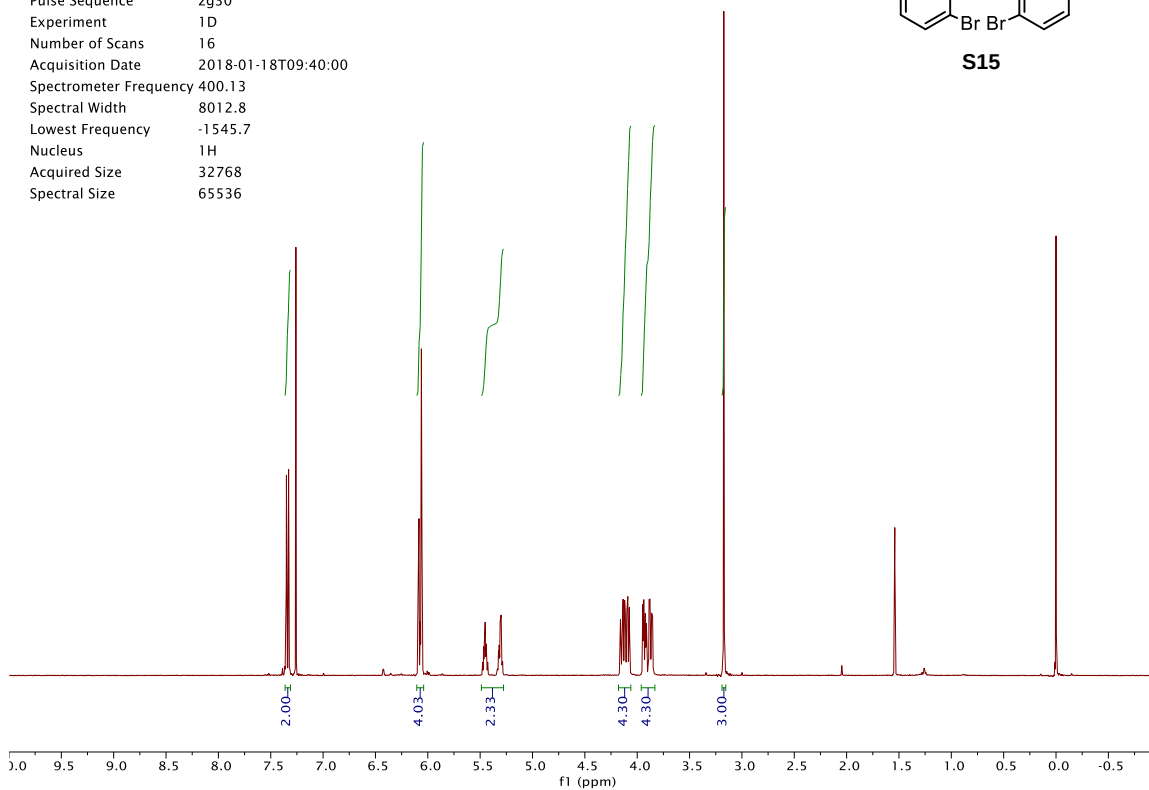
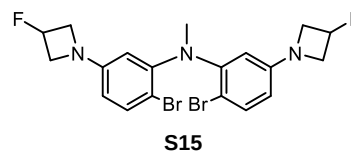
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2017-05-30T15:55:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.9
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



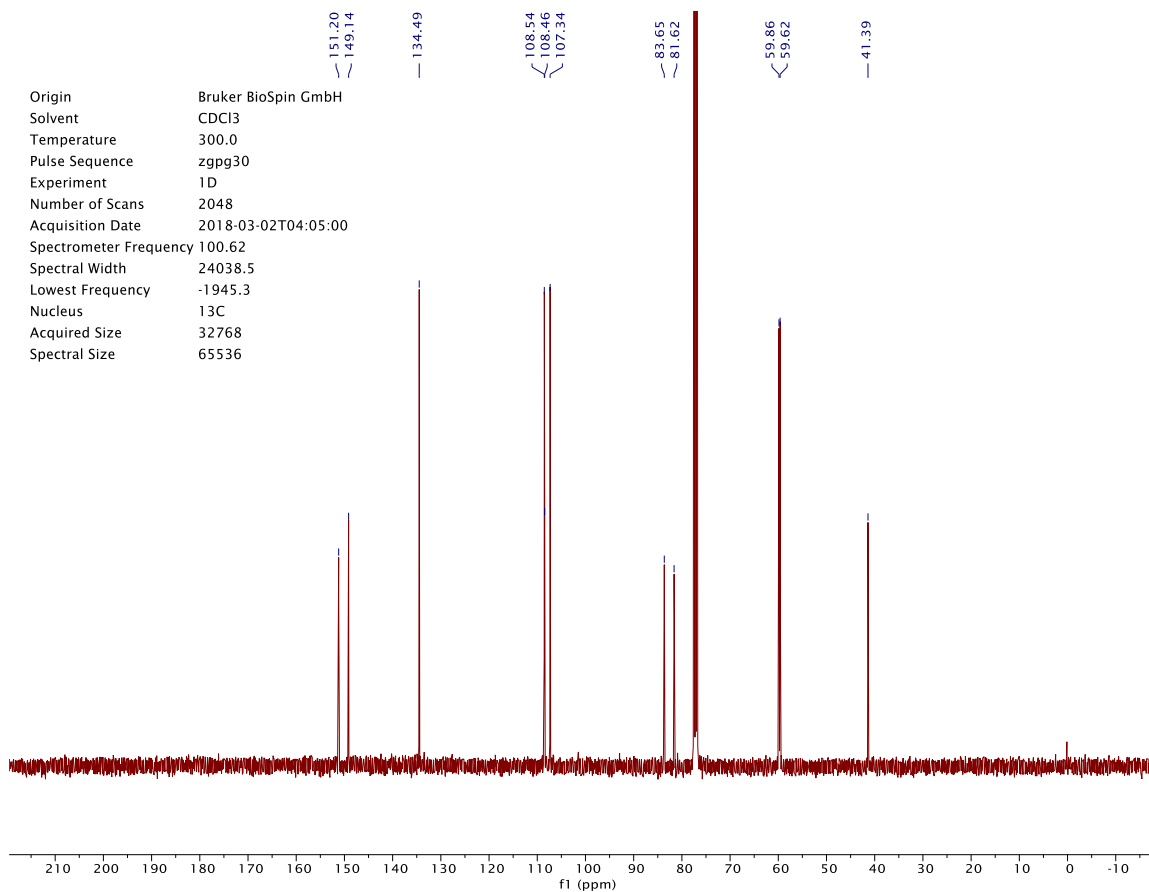
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 296.2
 Pulse Sequence: zgpg30
 Experiment: 1D
 Number of Scans: 2048
 Acquisition Date: 2018-03-02T20:02:00
 Spectrometer Frequency: 100.62
 Spectral Width: 24038.5
 Lowest Frequency: -1946.6
 Nucleus: ¹³C
 Acquired Size: 32768
 Spectral Size: 65536



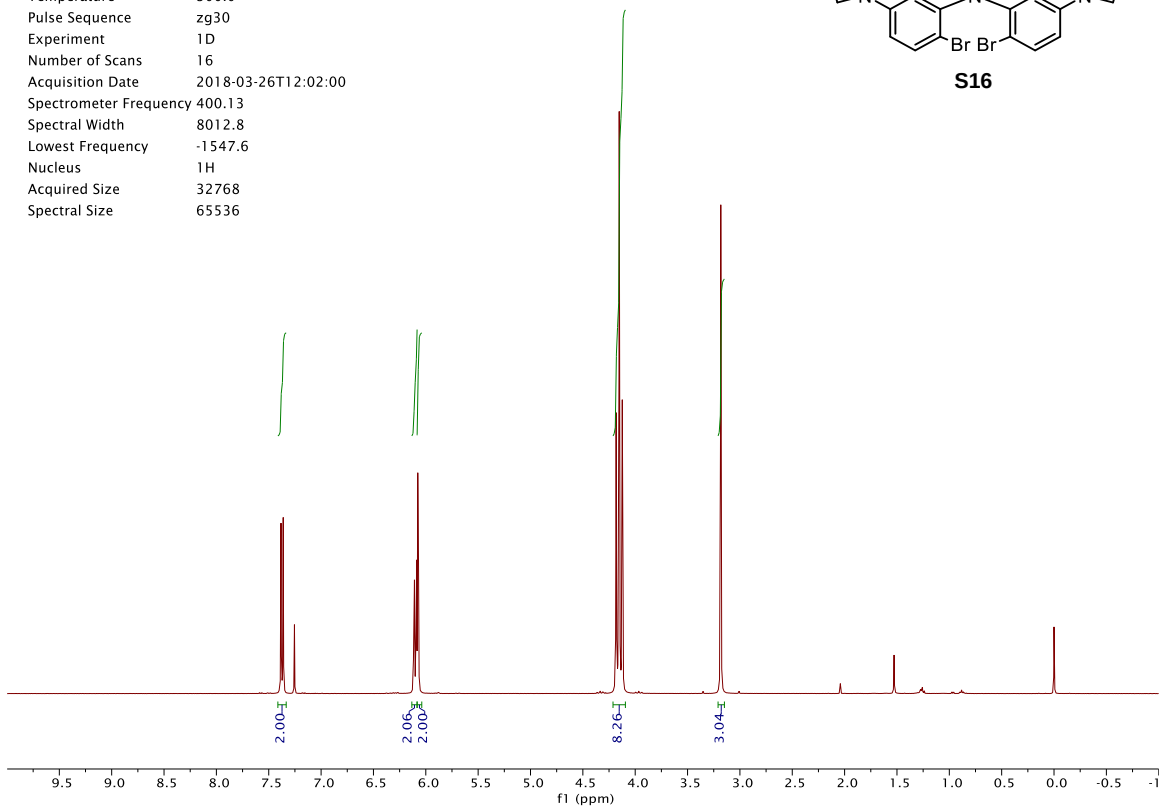
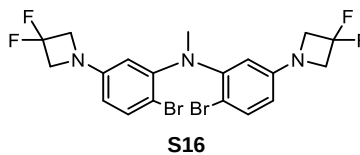
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 295.2
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-01-18T09:40:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.7
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



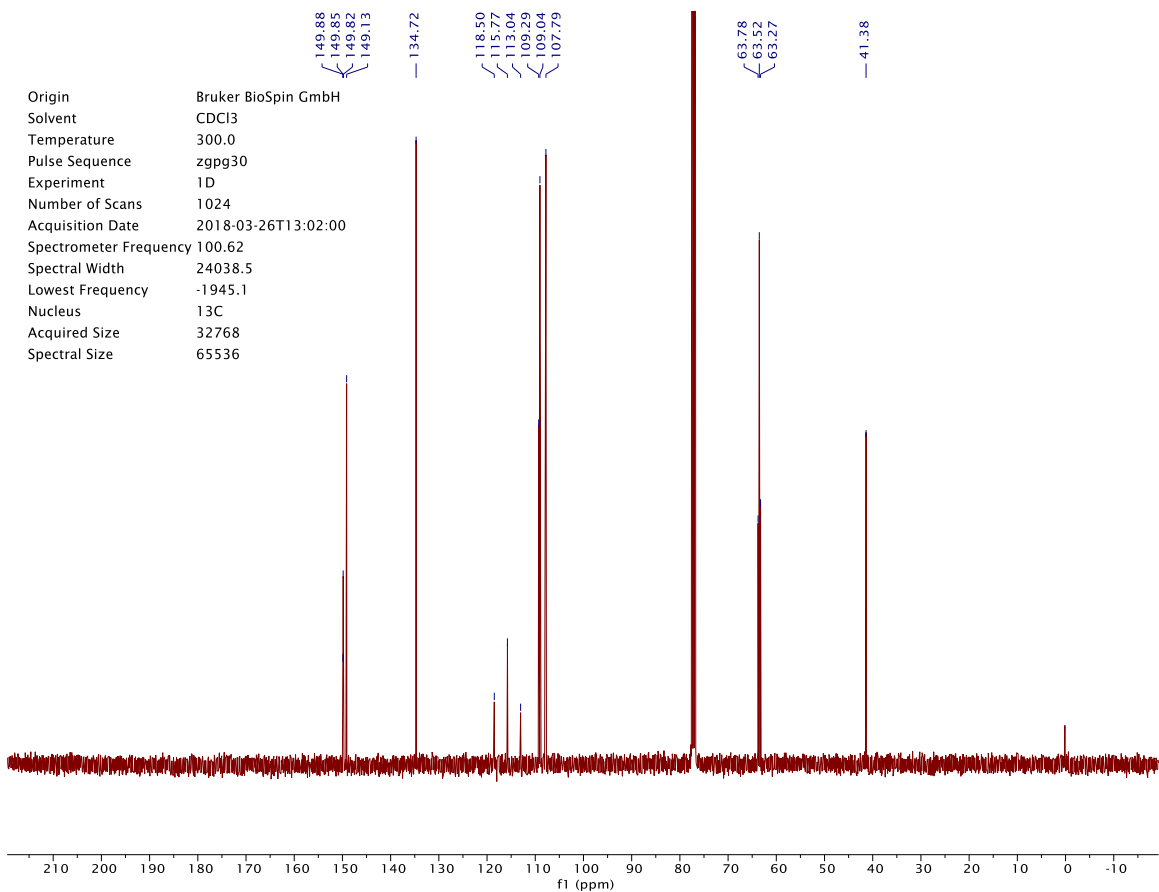
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zgpg30
 Experiment: 1D
 Number of Scans: 2048
 Acquisition Date: 2018-03-02T04:05:00
 Spectrometer Frequency: 100.62
 Spectral Width: 24038.5
 Lowest Frequency: -1945.3
 Nucleus: ¹³C
 Acquired Size: 32768
 Spectral Size: 65536



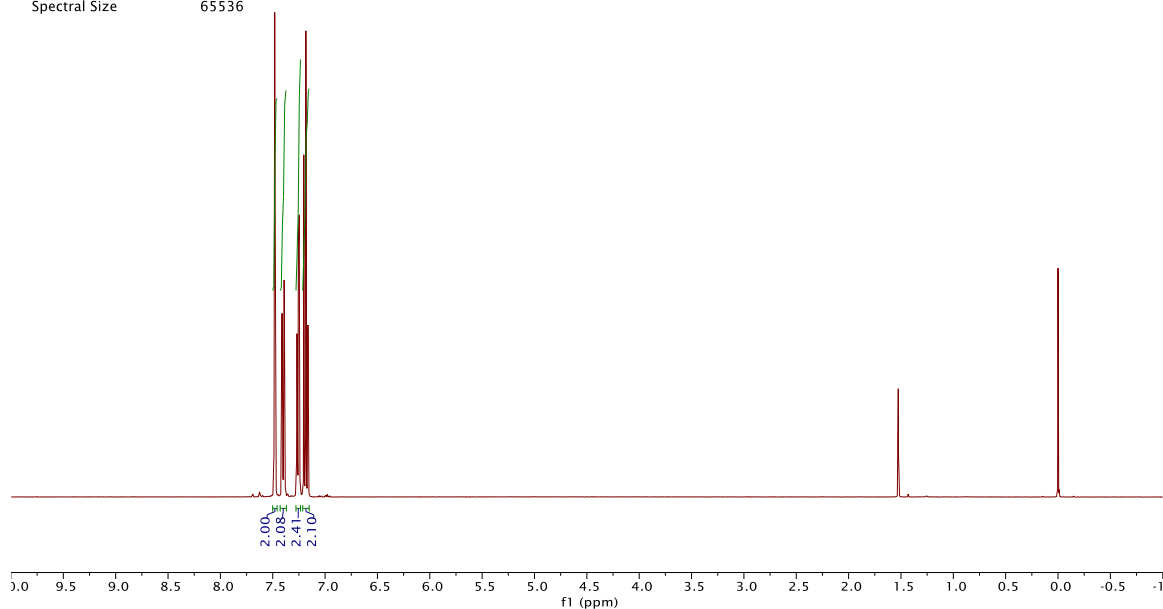
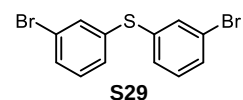
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-26T12:02:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1547.6
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



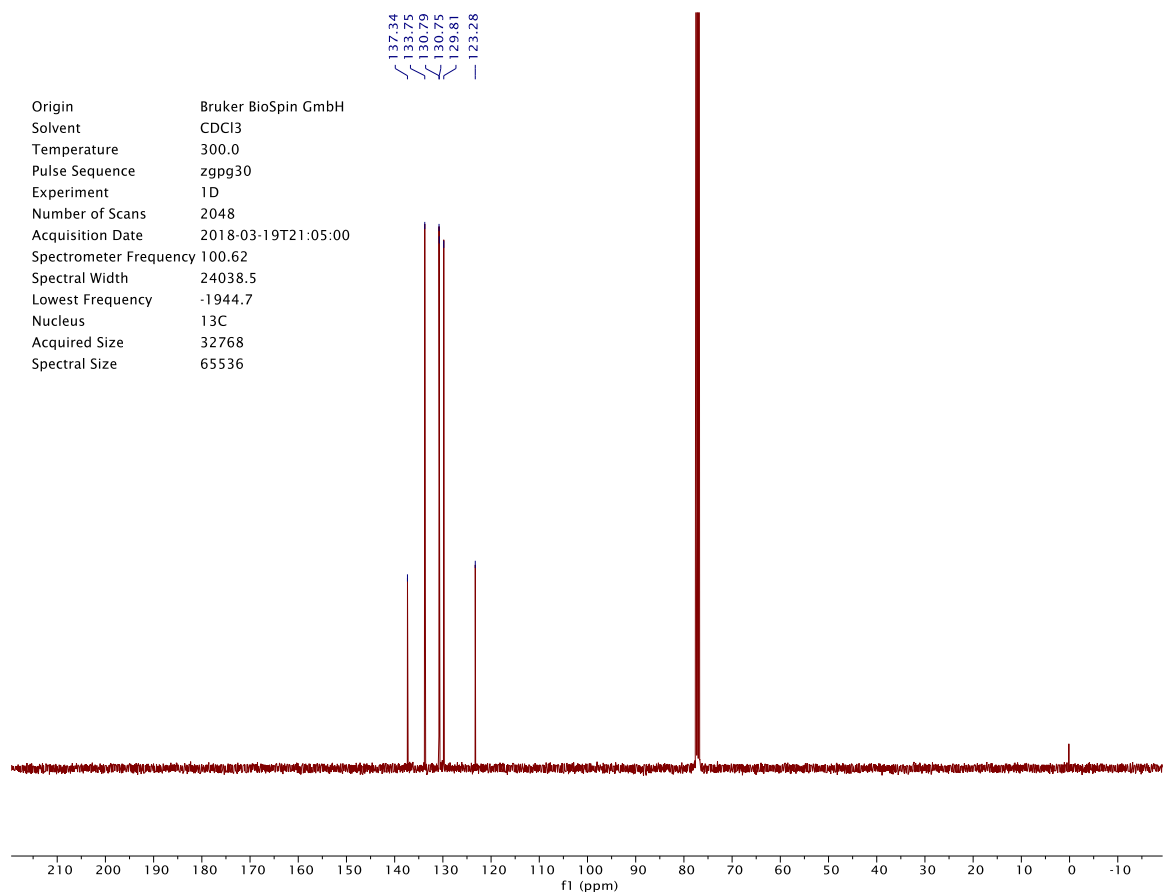
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 1024
 Acquisition Date 2018-03-26T13:02:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1945.1
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



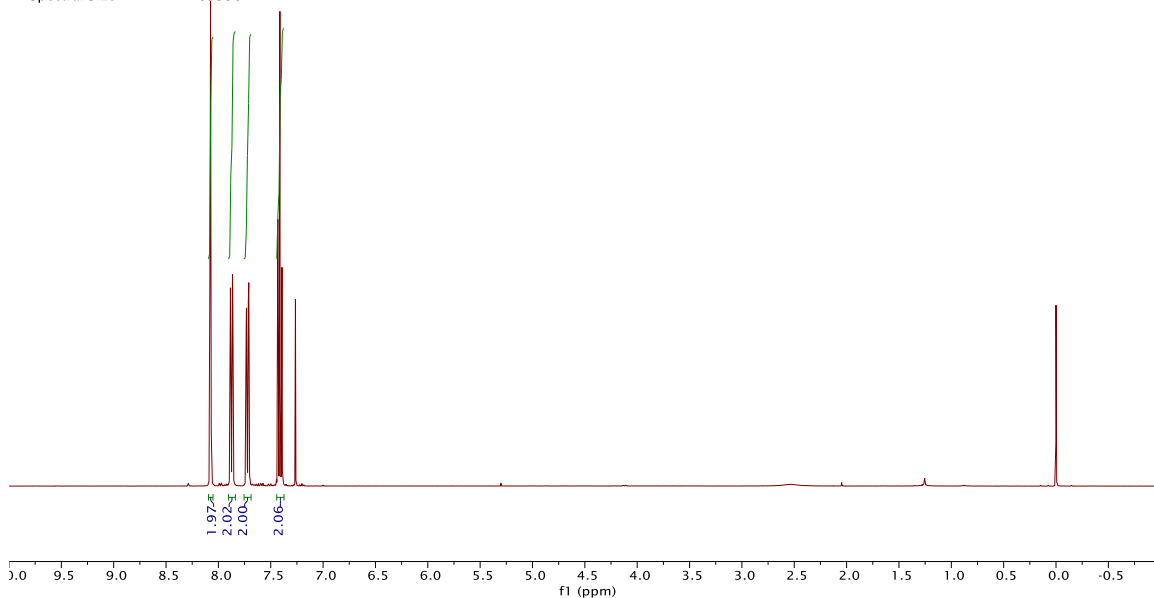
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-19T19:06:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1547.3
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



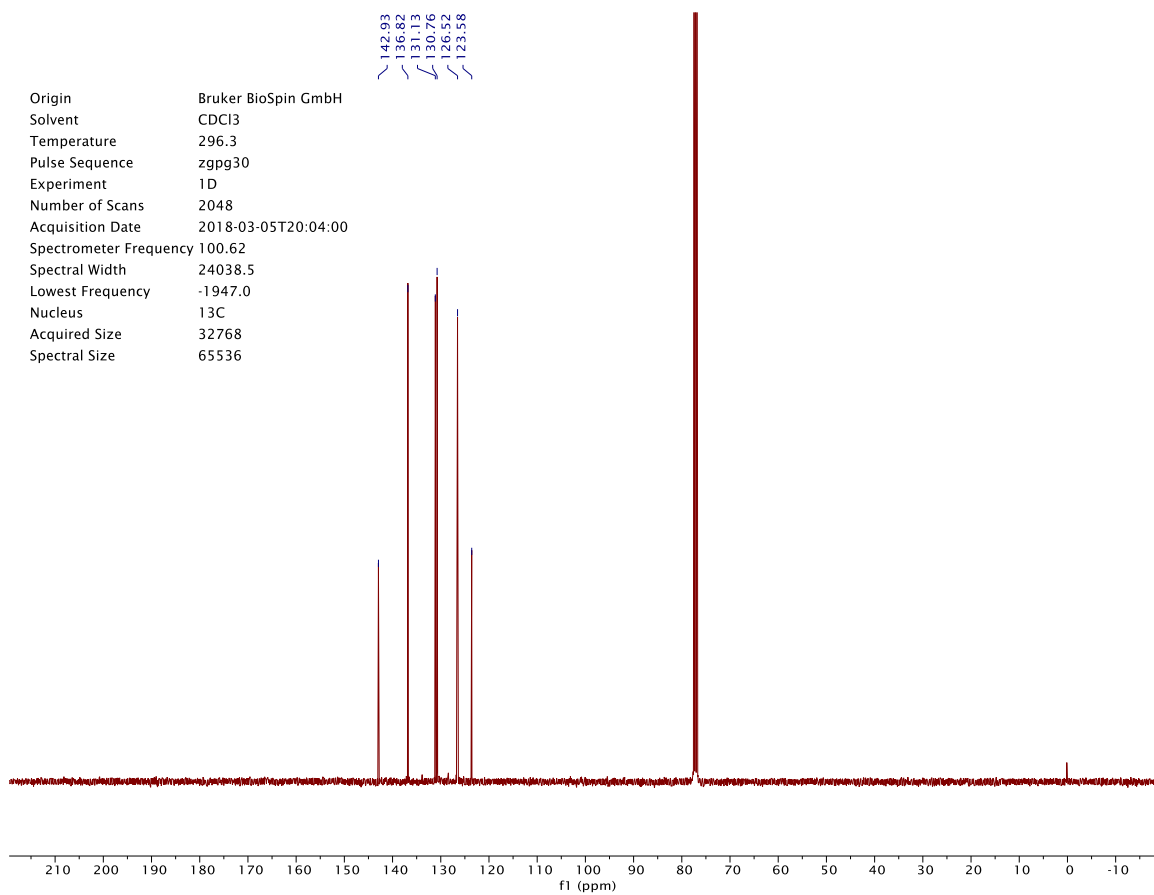
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-19T21:05:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1944.7
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



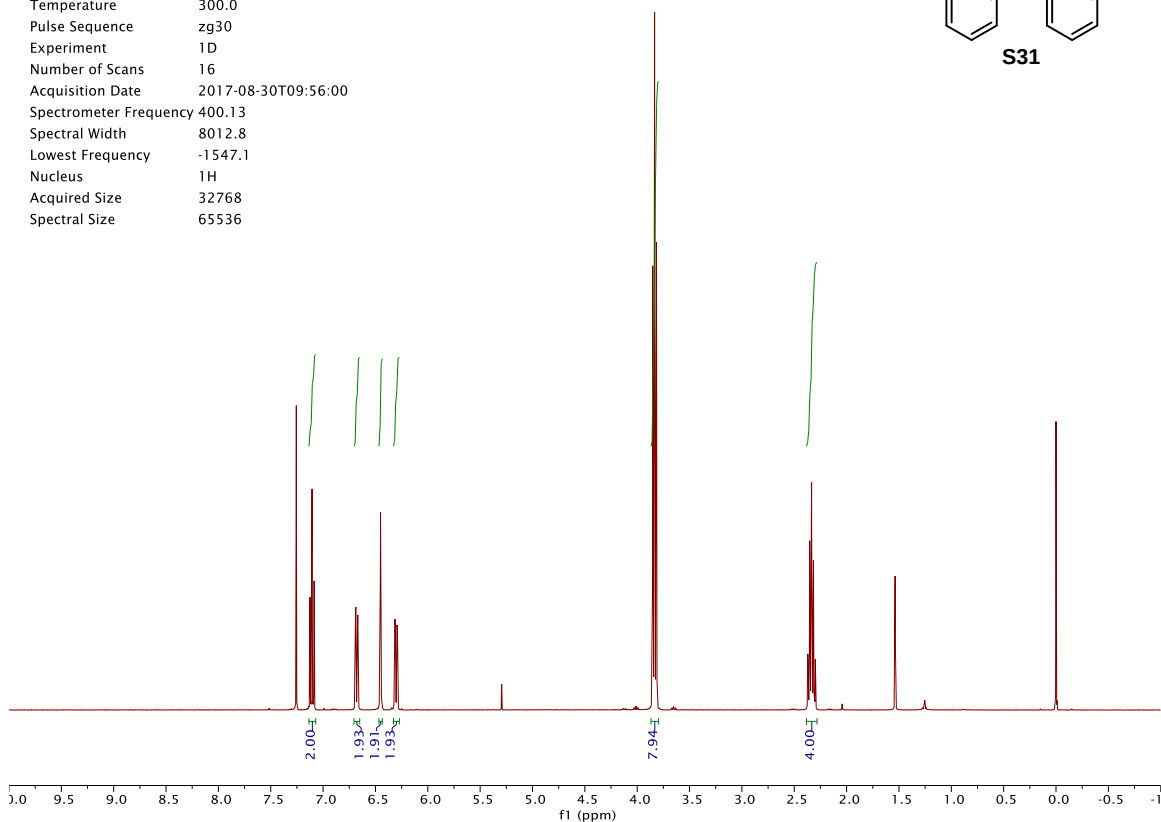
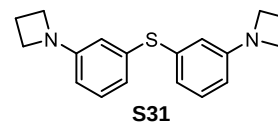
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 295.6
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-05T18:05:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.8
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



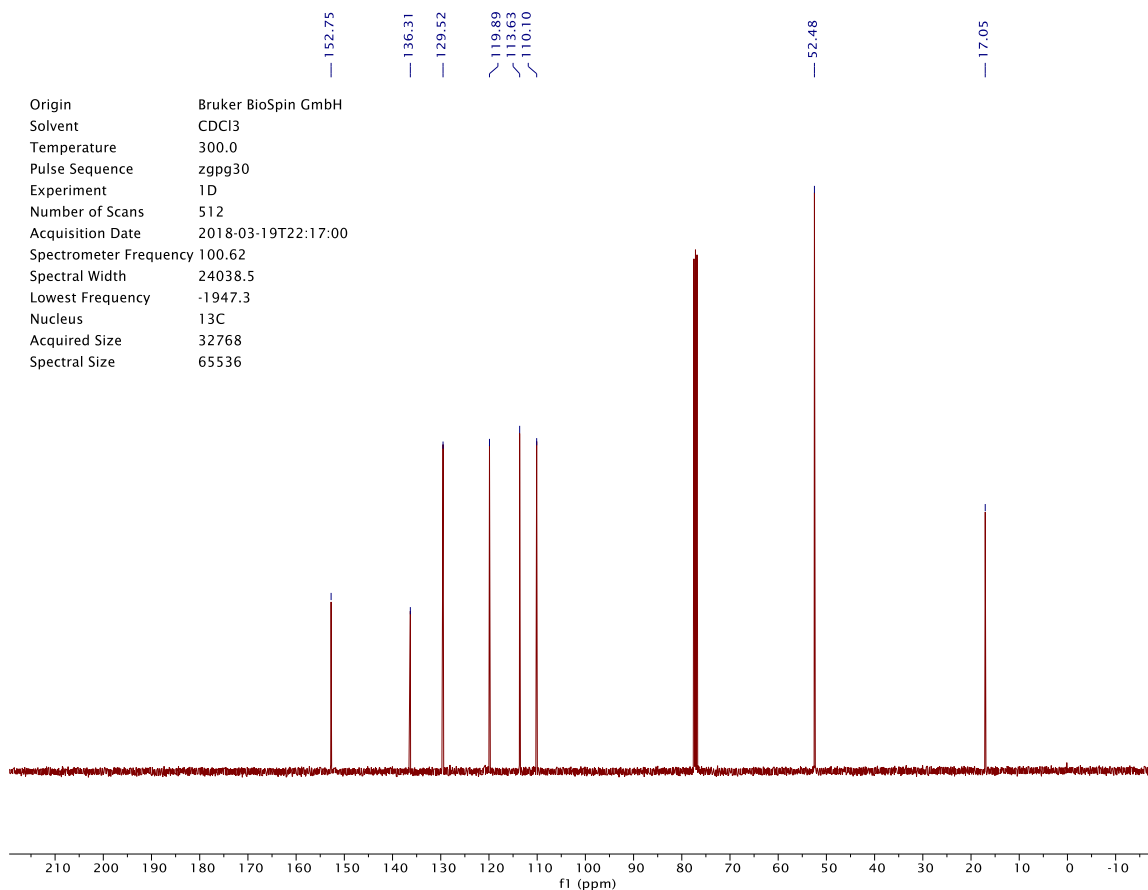
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 296.3
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-05T20:04:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1947.0
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



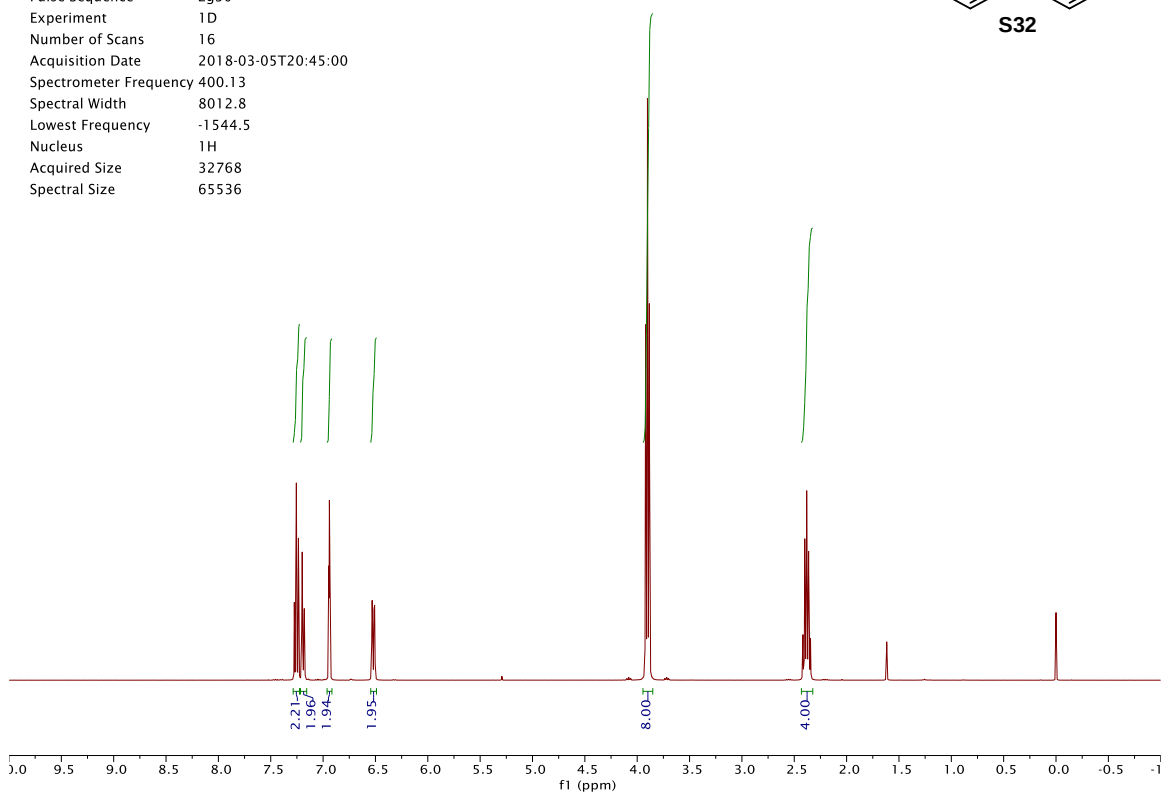
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-08-30T09:56:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1547.1
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



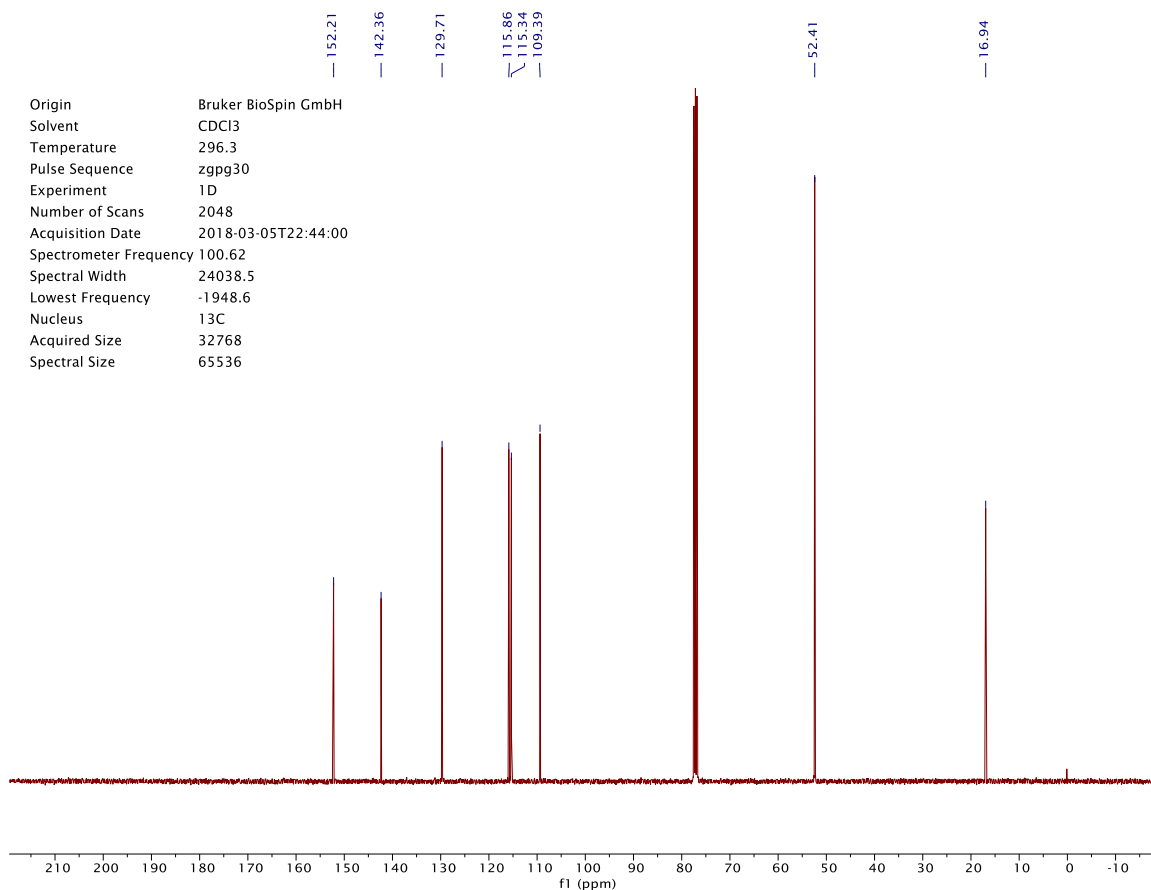
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 512
 Acquisition Date 2018-03-19T22:17:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1947.3
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



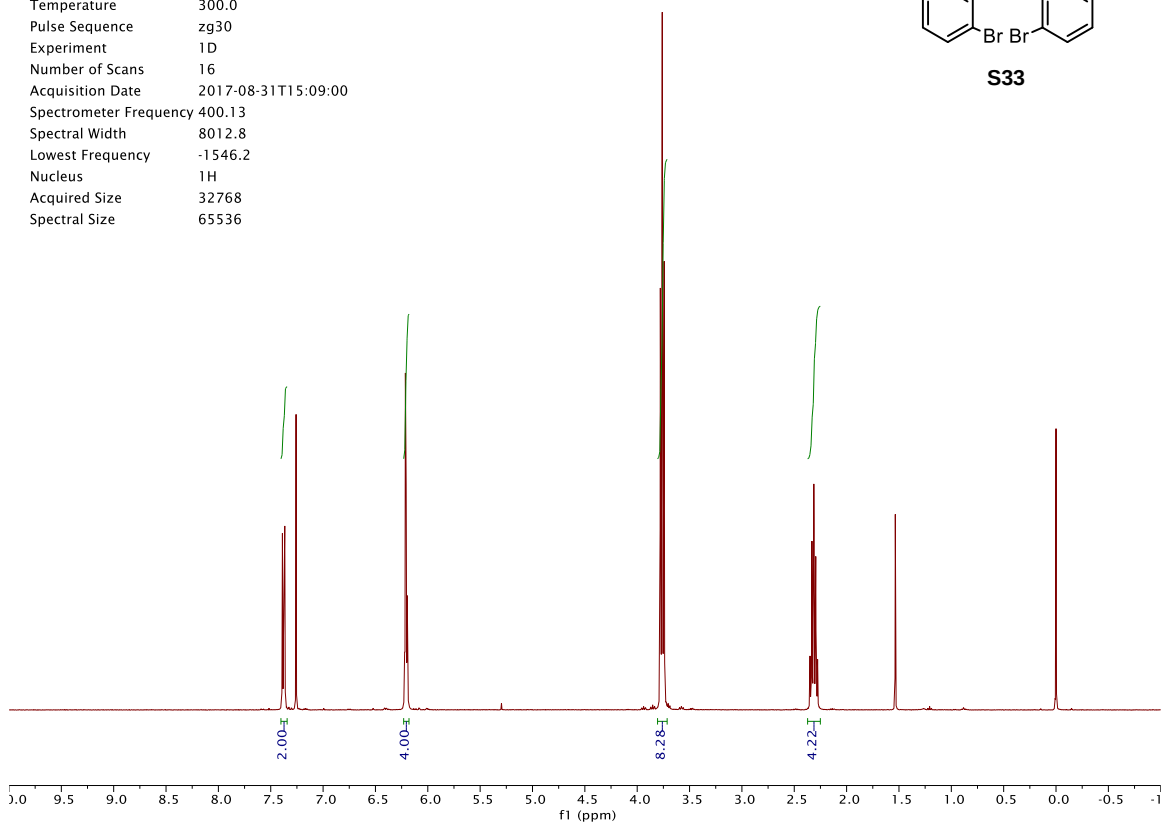
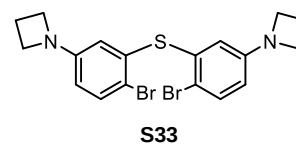
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 295.6
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-05T20:45:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1544.5
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



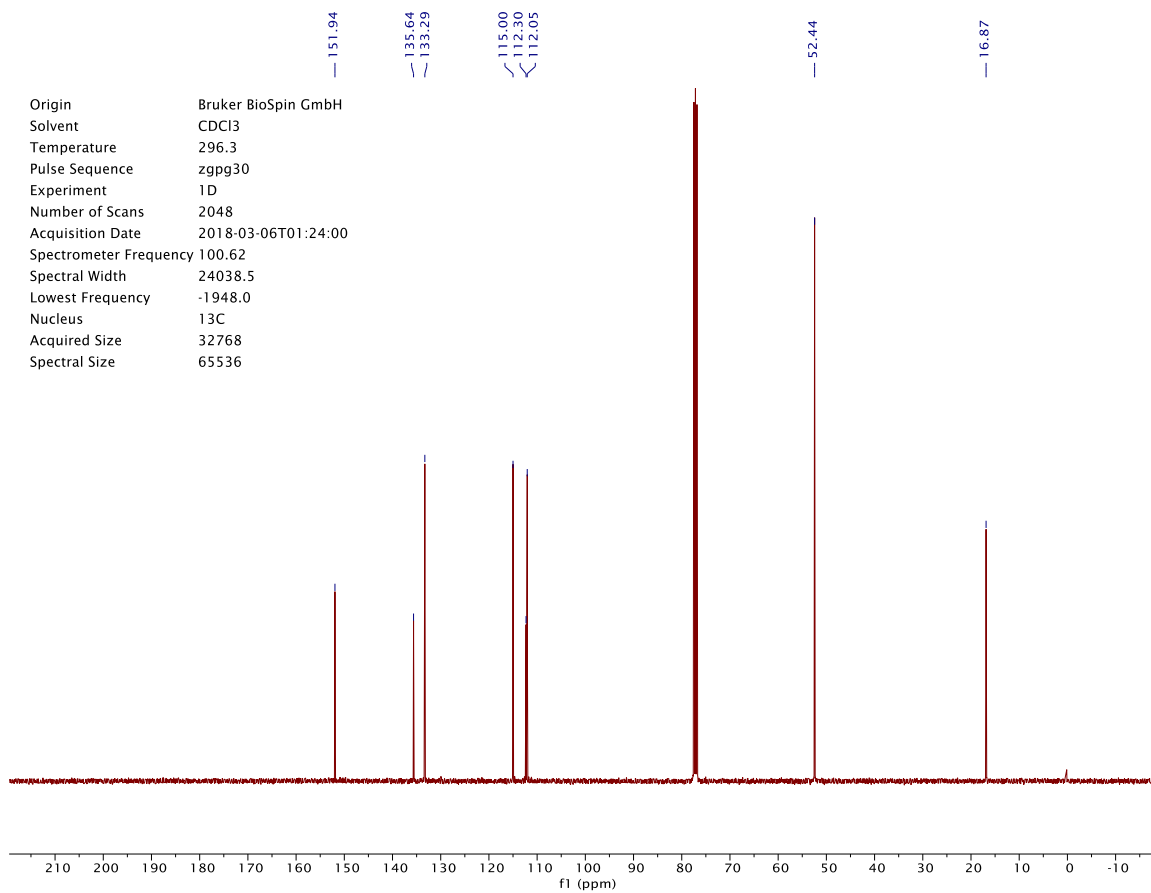
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 296.3
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-05T22:44:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1948.6
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



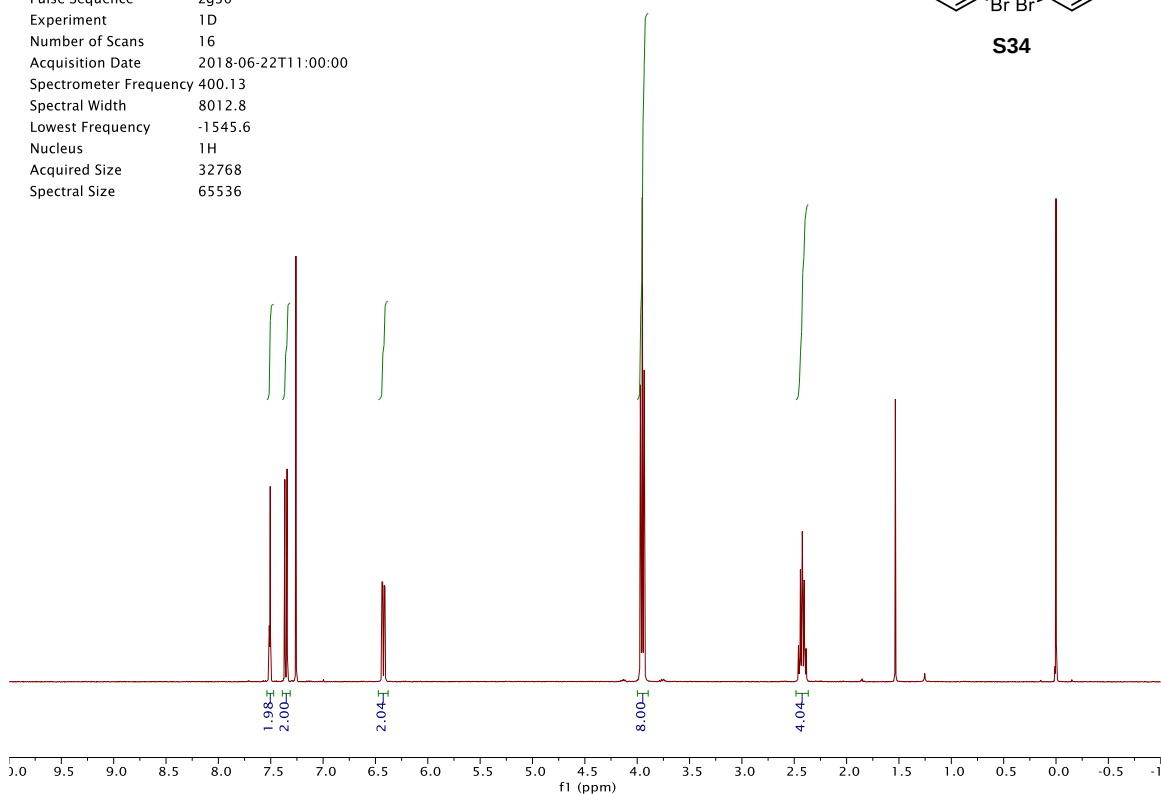
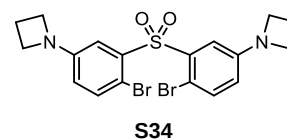
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-08-31T15:09:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1546.2
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



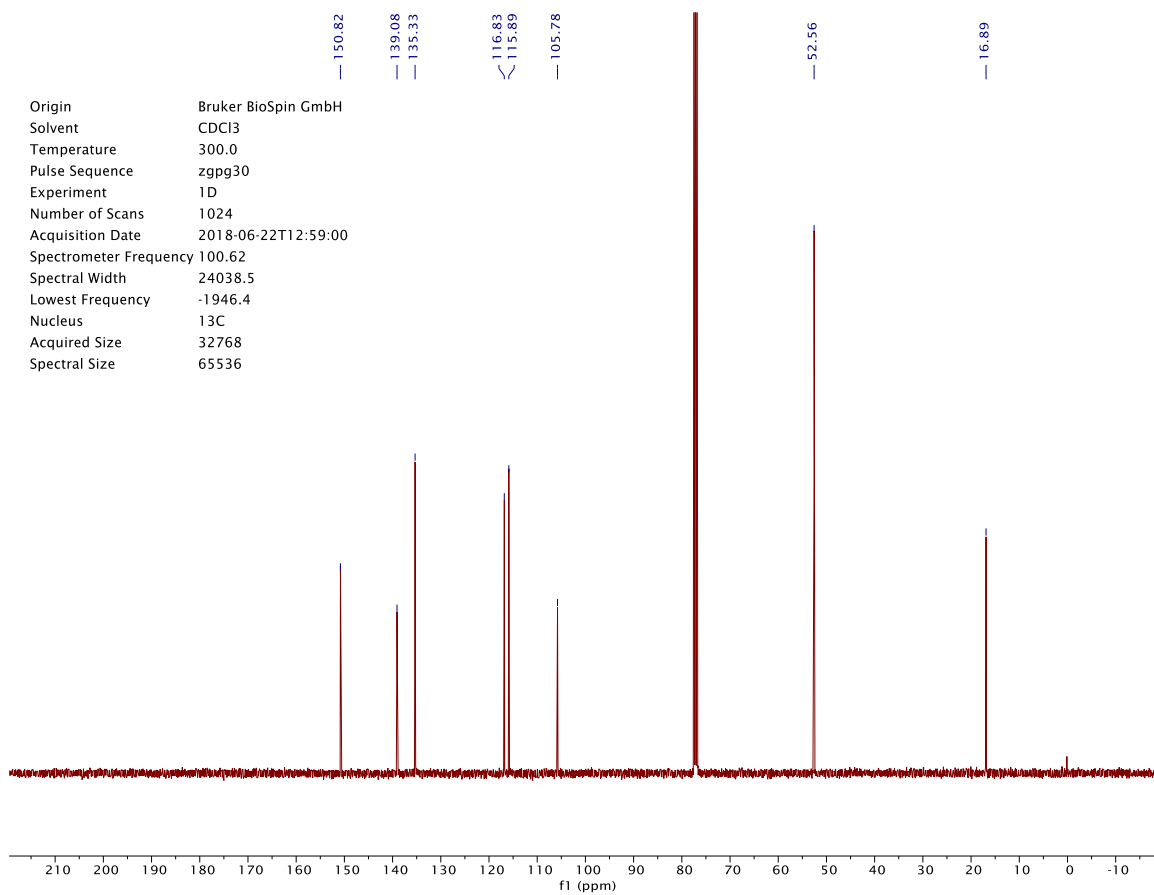
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 296.3
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-06T01:24:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1948.0
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



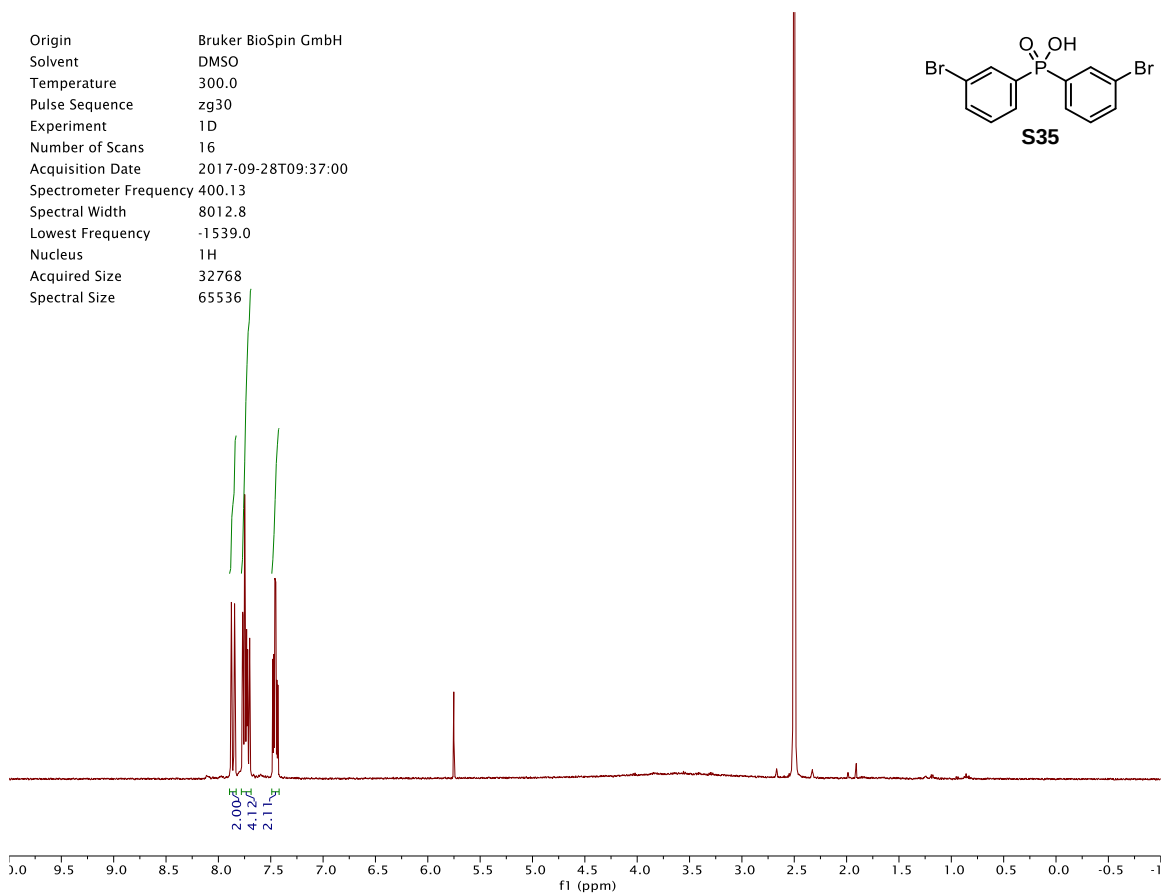
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-06-22T11:00:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.6
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



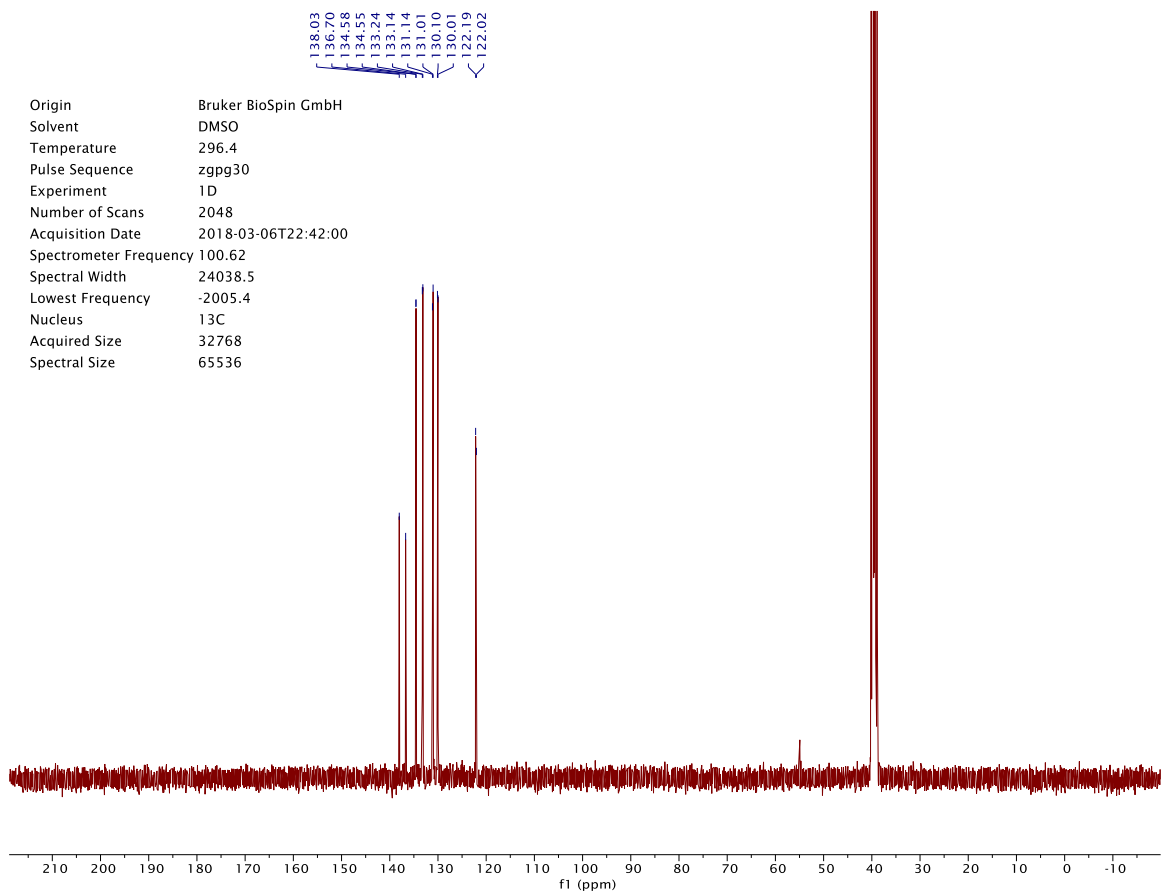
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 1024
 Acquisition Date 2018-06-22T12:59:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1946.4
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



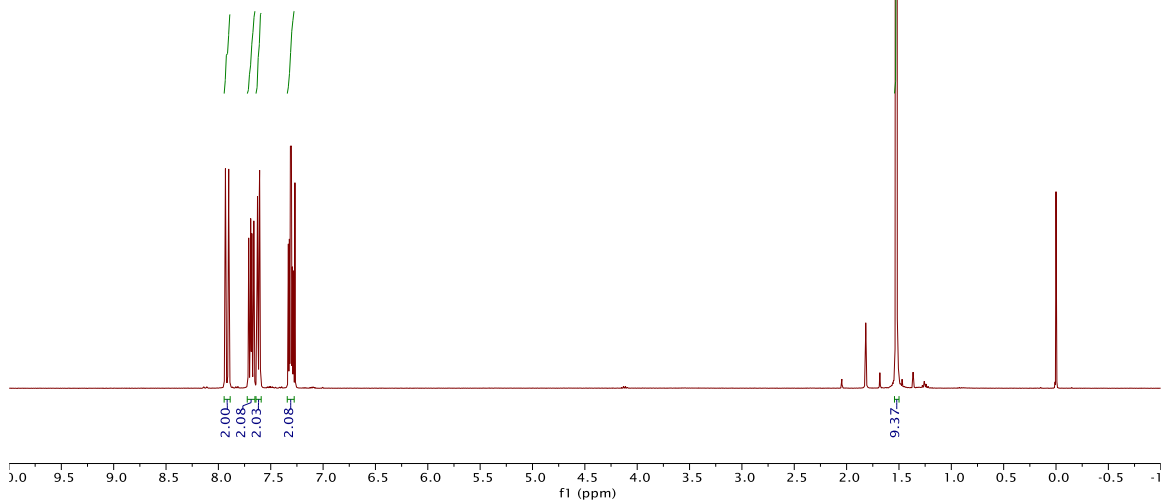
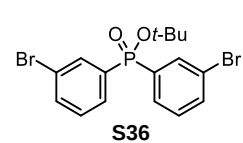
Origin Bruker BioSpin GmbH
 Solvent DMSO
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-09-28T09:37:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1539.0
 Nucleus ^1H
 Acquired Size 32768
 Spectral Size 65536



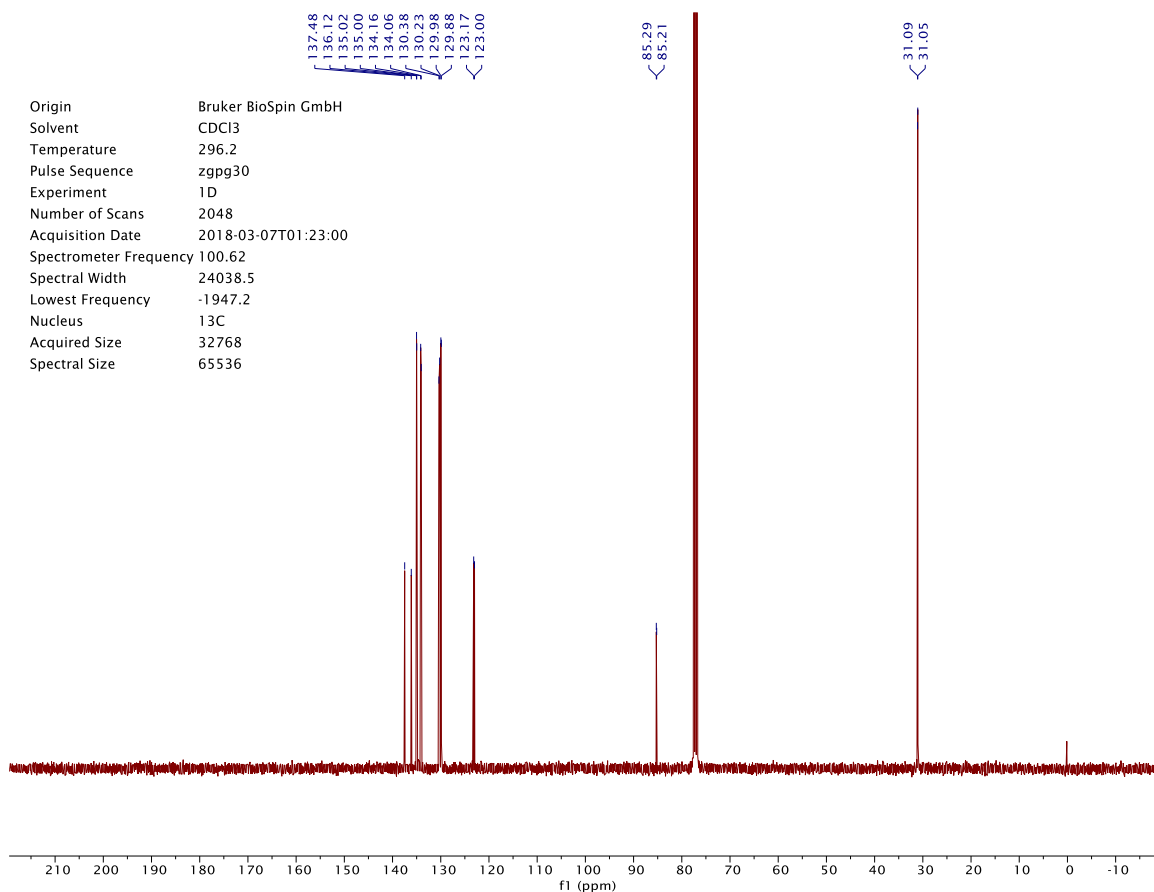
Origin Bruker BioSpin GmbH
 Solvent DMSO
 Temperature 296.4
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-06T22:42:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -2005.4
 Nucleus ^{13}C
 Acquired Size 32768
 Spectral Size 65536



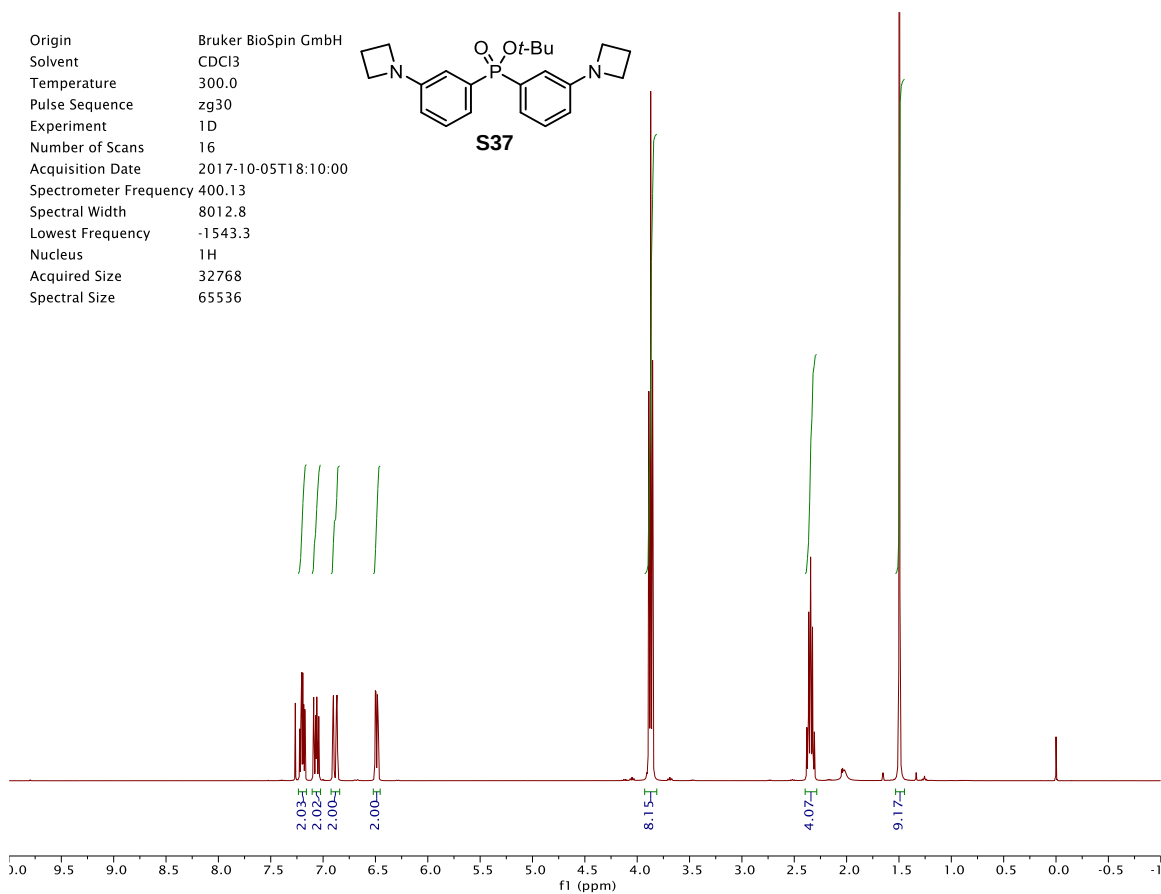
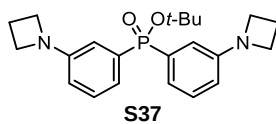
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 295.6
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-03-06T23:24:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1542.0
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



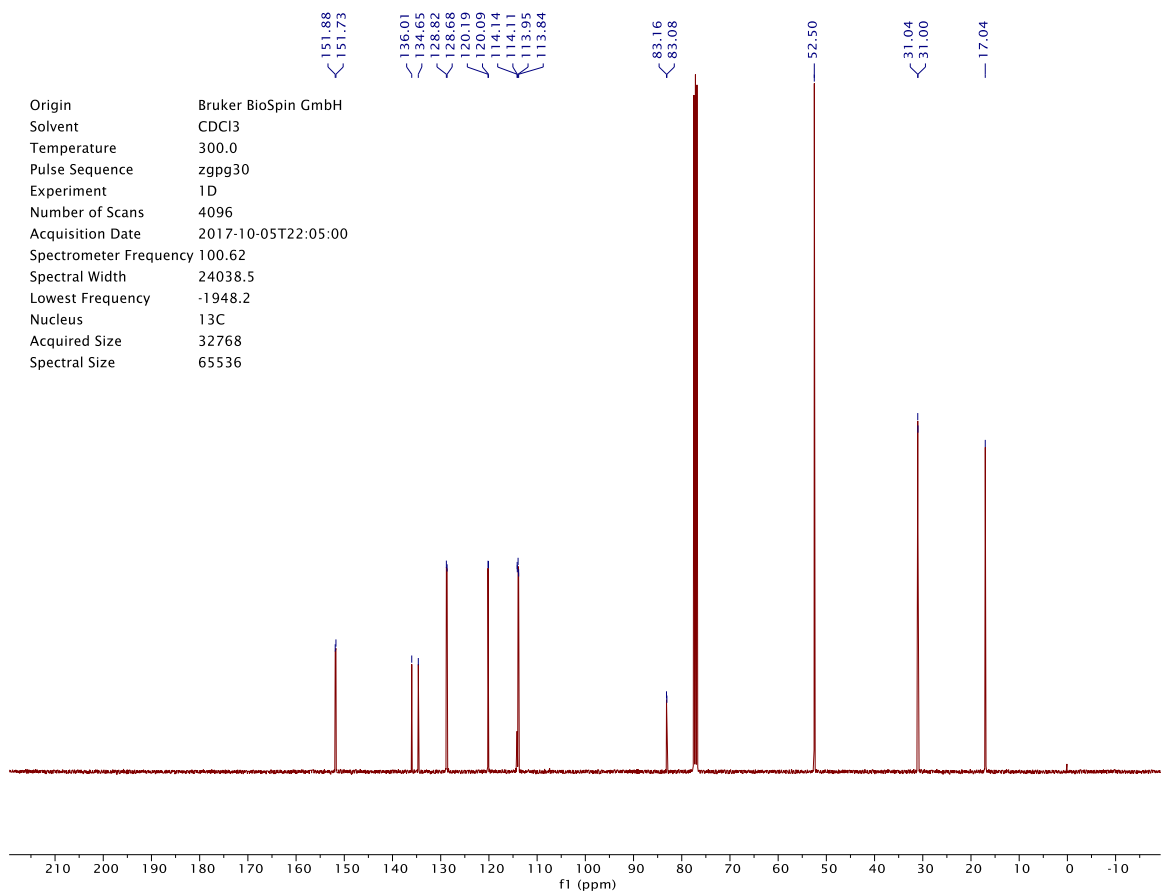
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 296.2
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-07T01:23:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1947.2
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



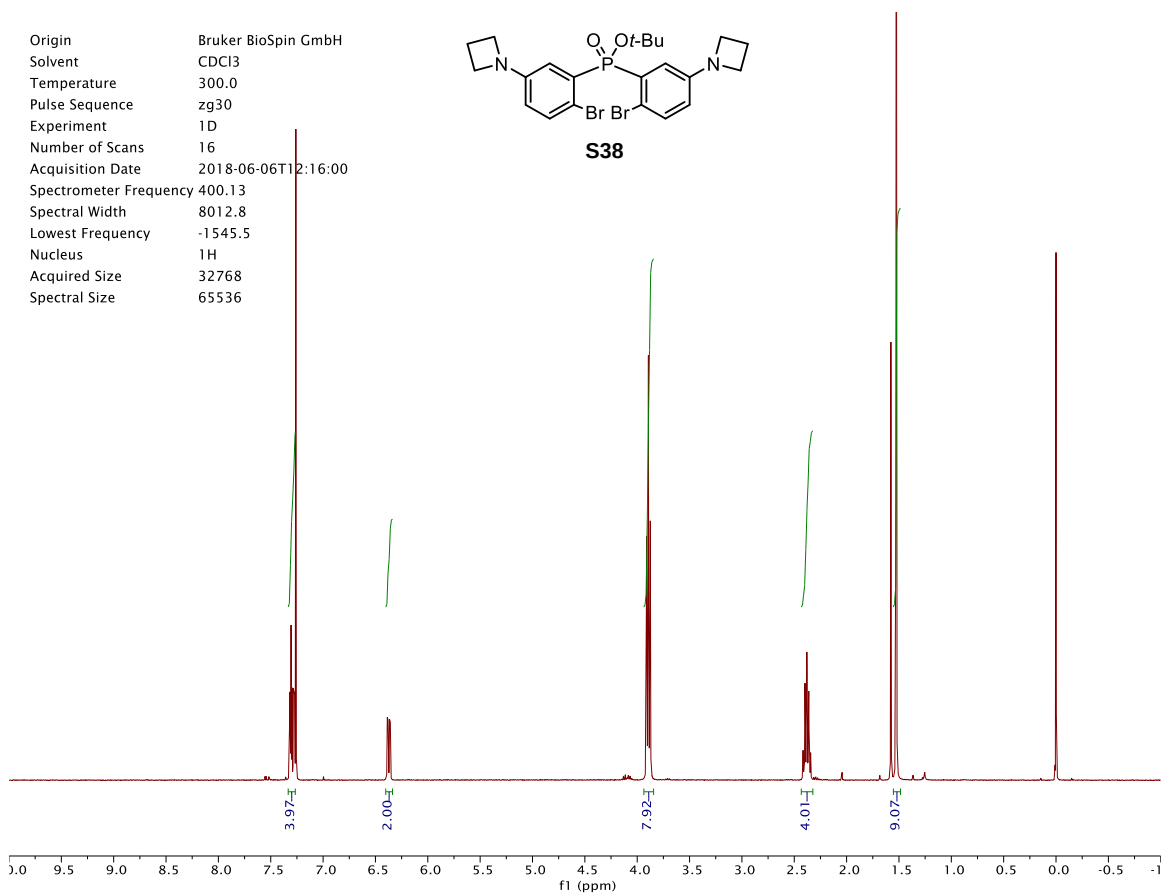
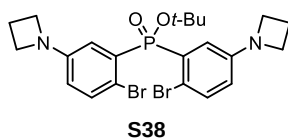
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-10-05T18:10:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.3
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



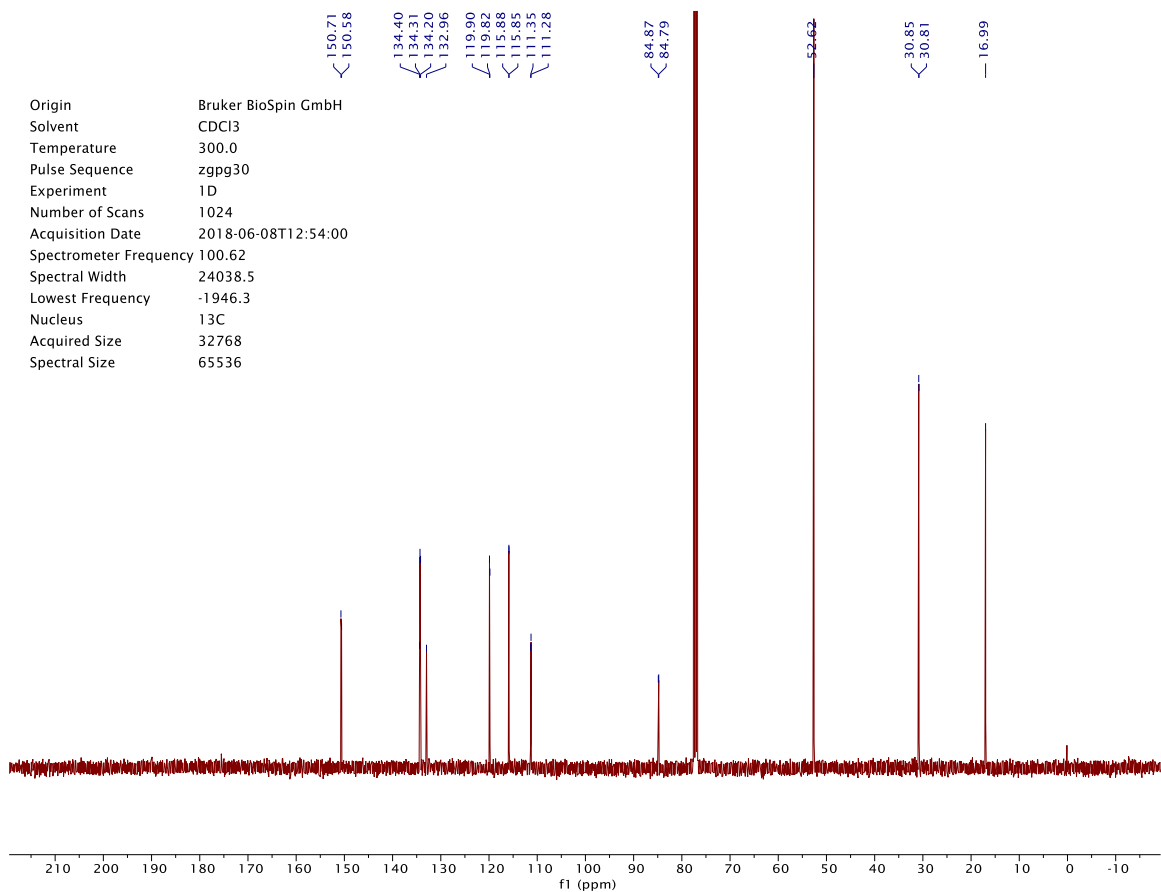
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 4096
 Acquisition Date 2017-10-05T22:05:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1948.2
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536

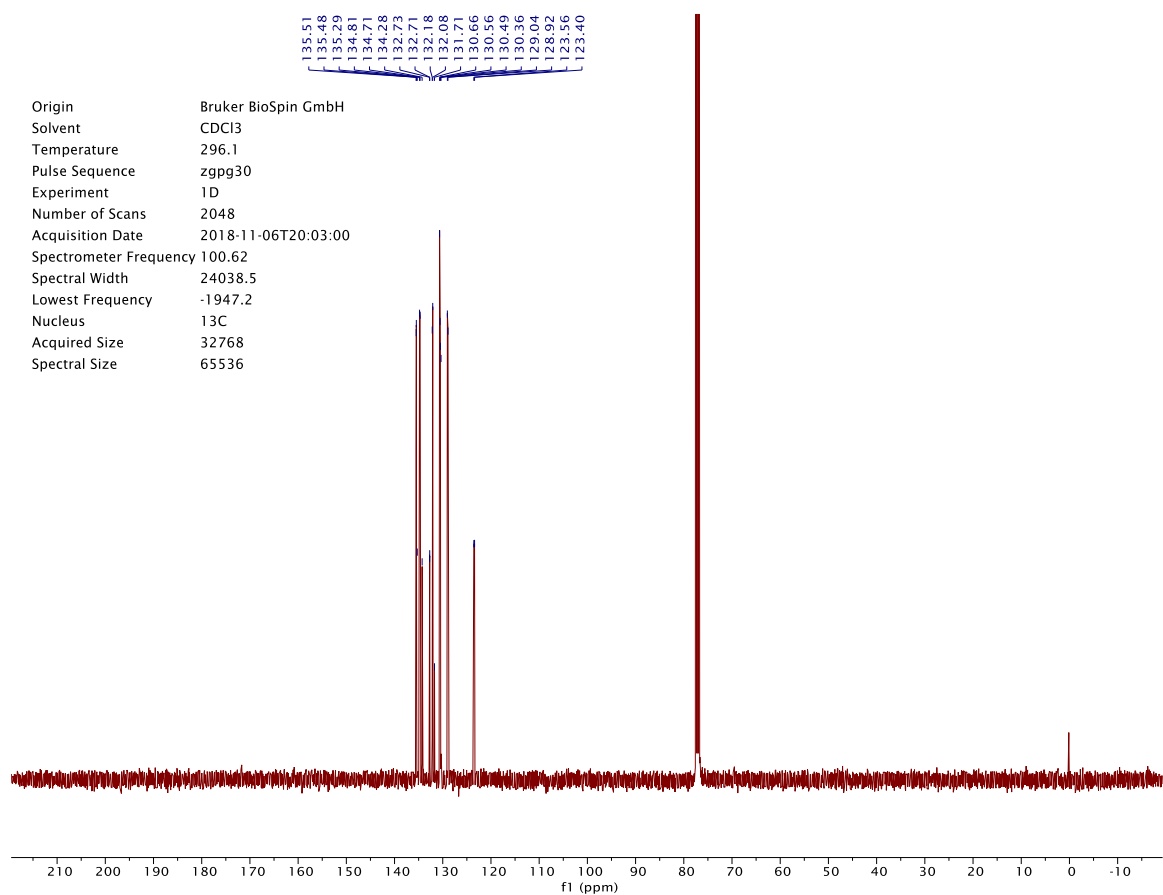
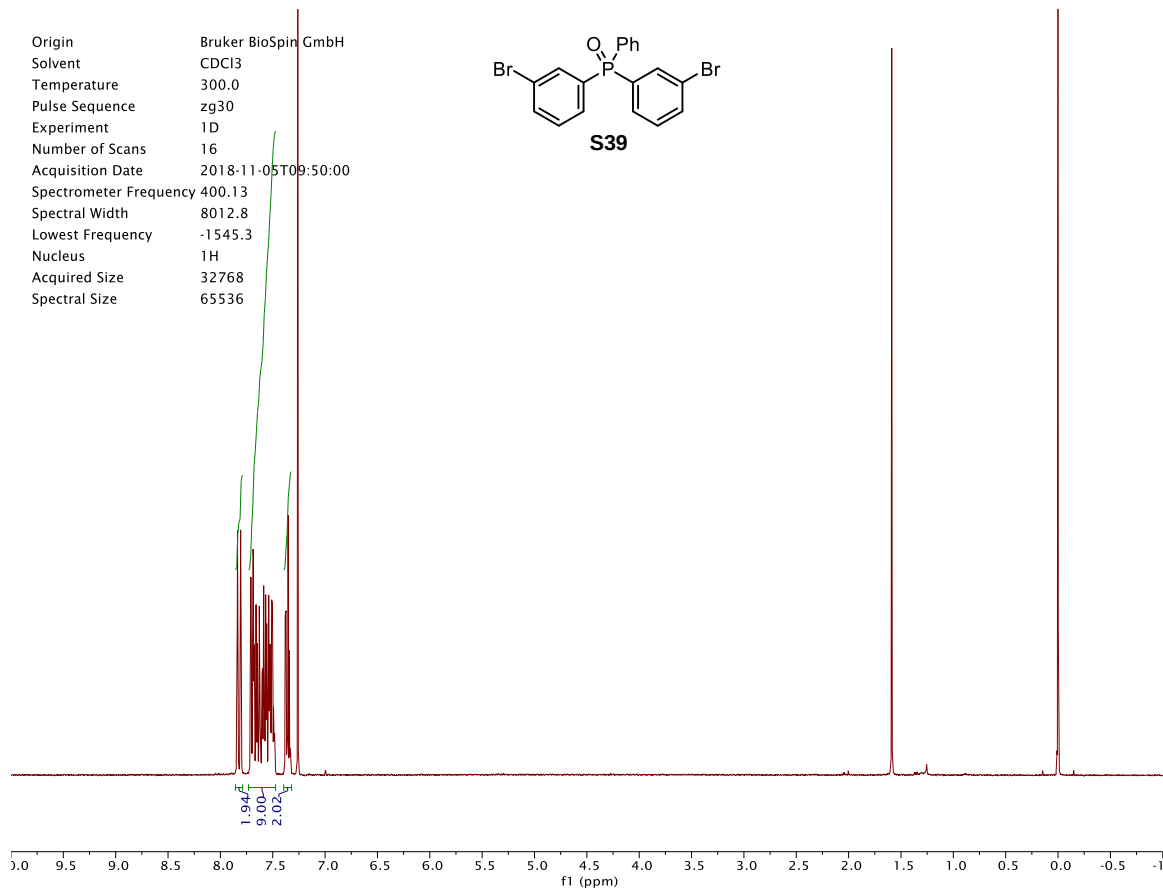


Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-06-06T12:16:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.5
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536

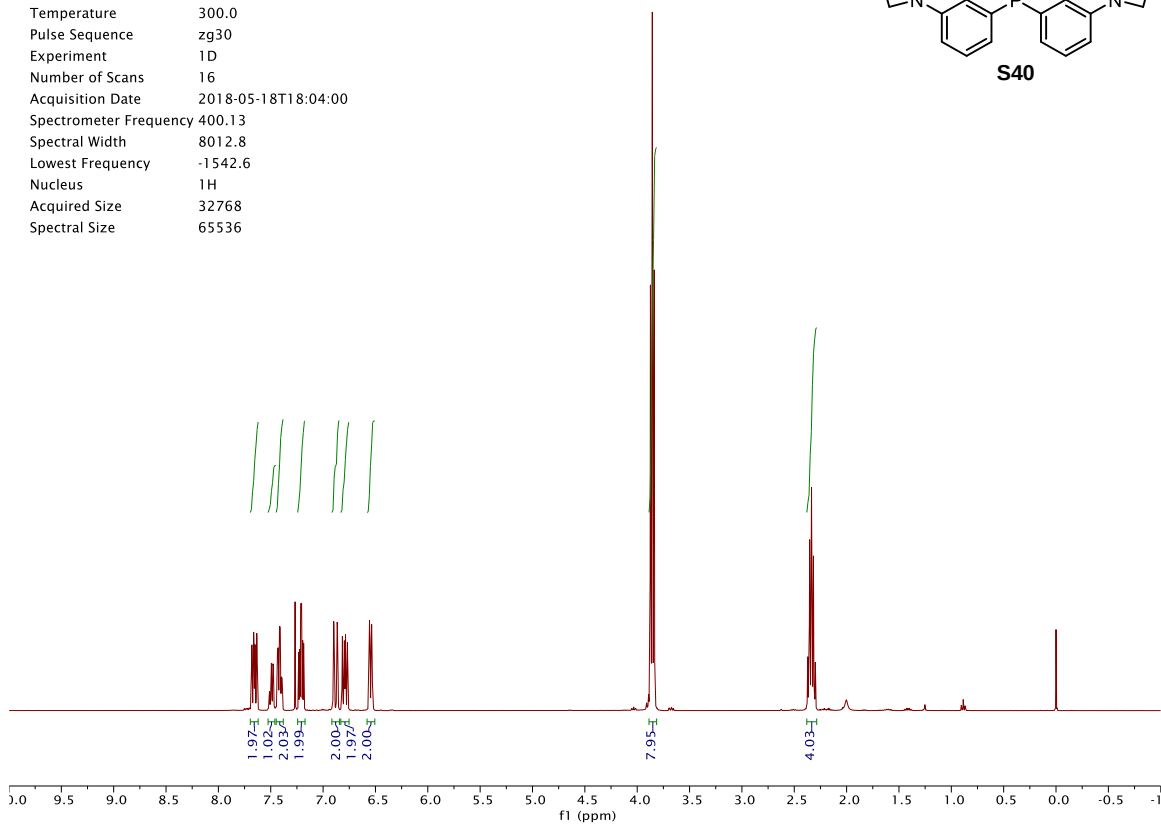
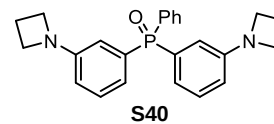


Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 1024
 Acquisition Date 2018-06-08T12:54:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1946.3
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536

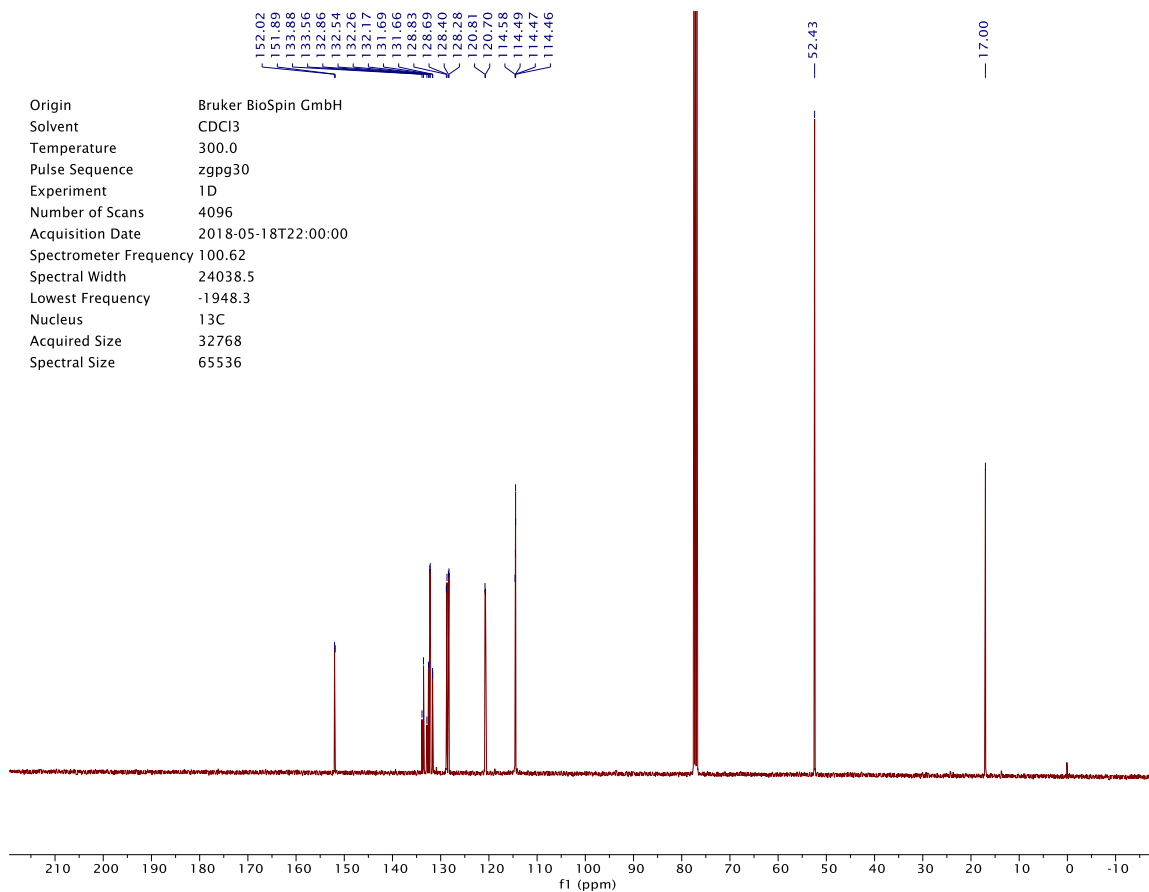




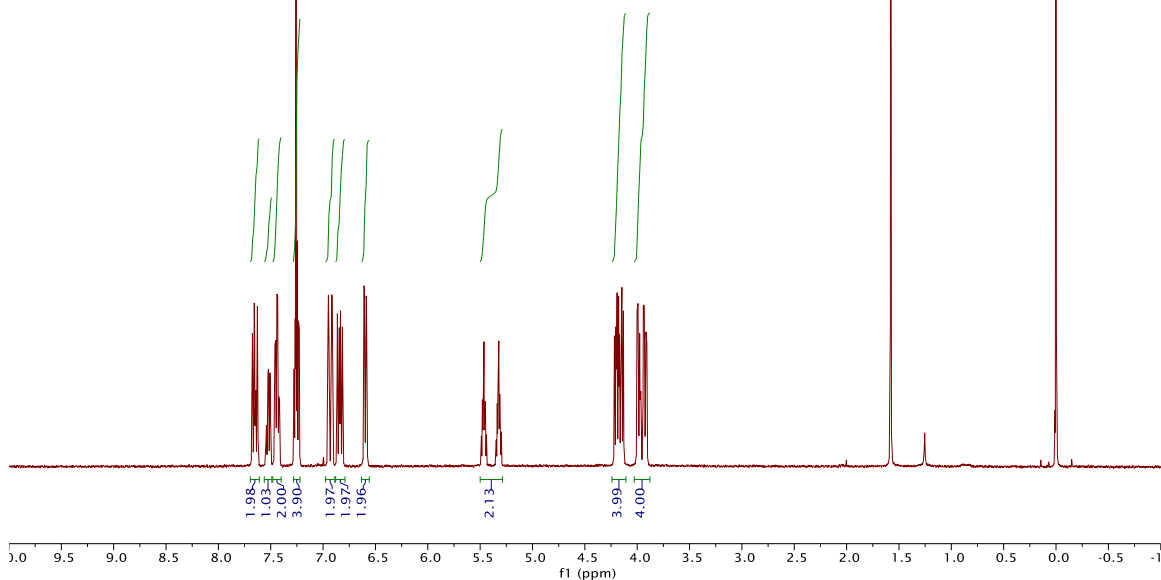
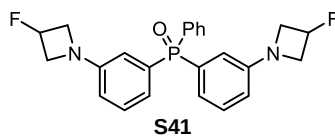
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-05-18T18:04:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1542.6
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



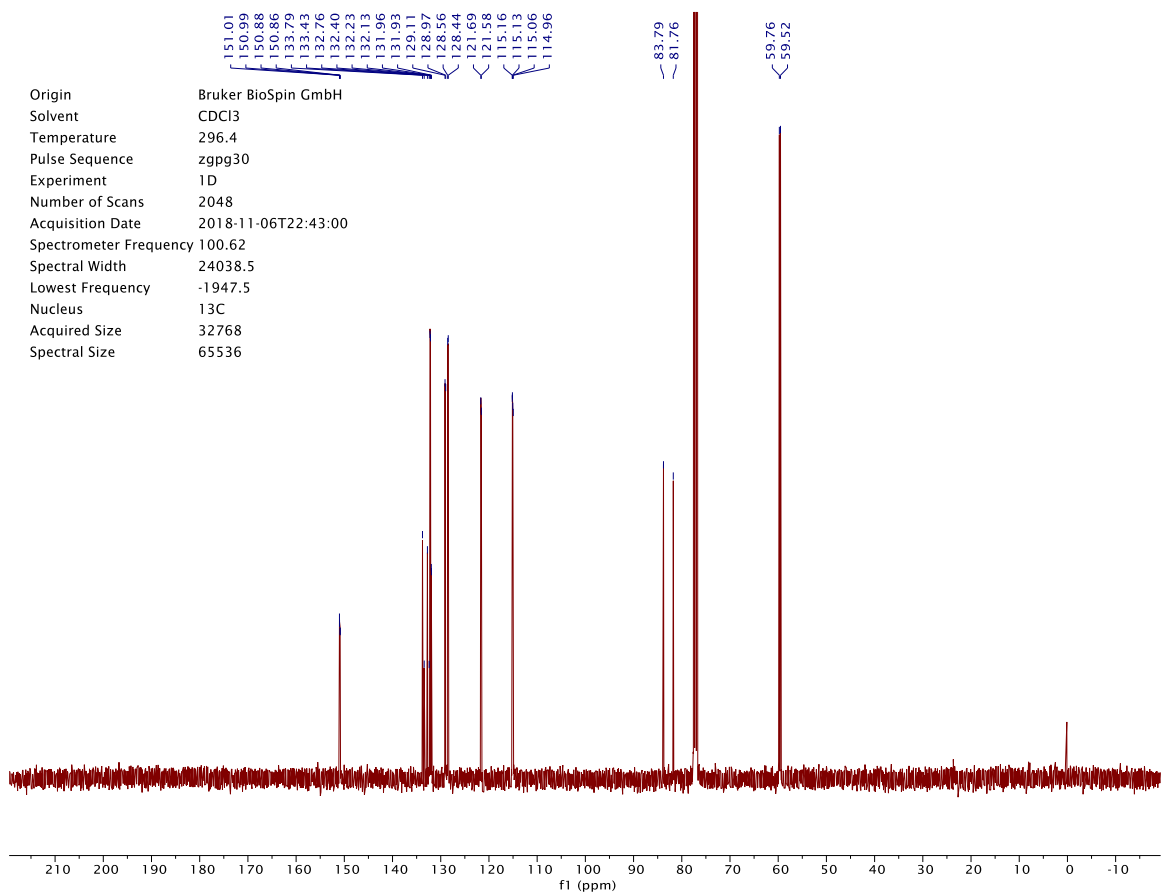
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 4096
 Acquisition Date 2018-05-18T22:00:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1948.3
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



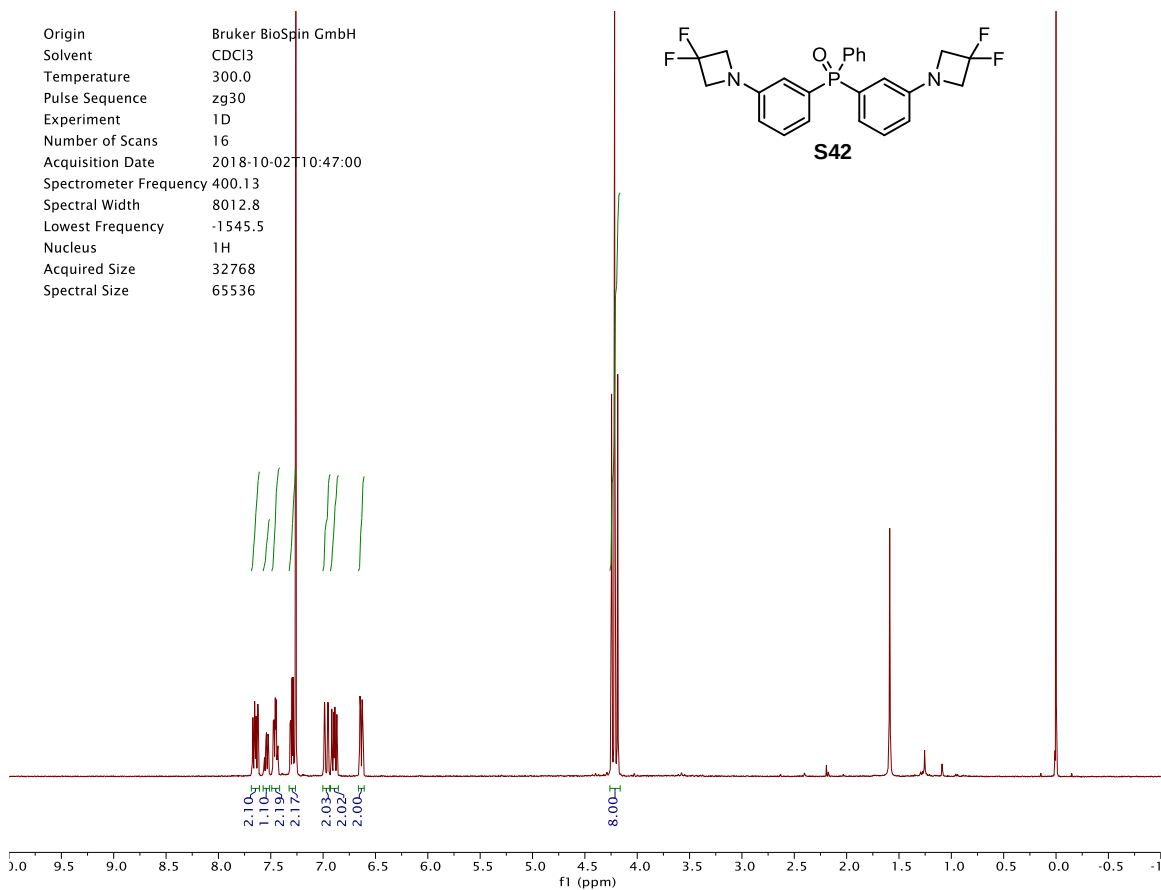
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-11-05T09:54:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.7
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 296.4
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-11-06T22:43:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1947.5
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536

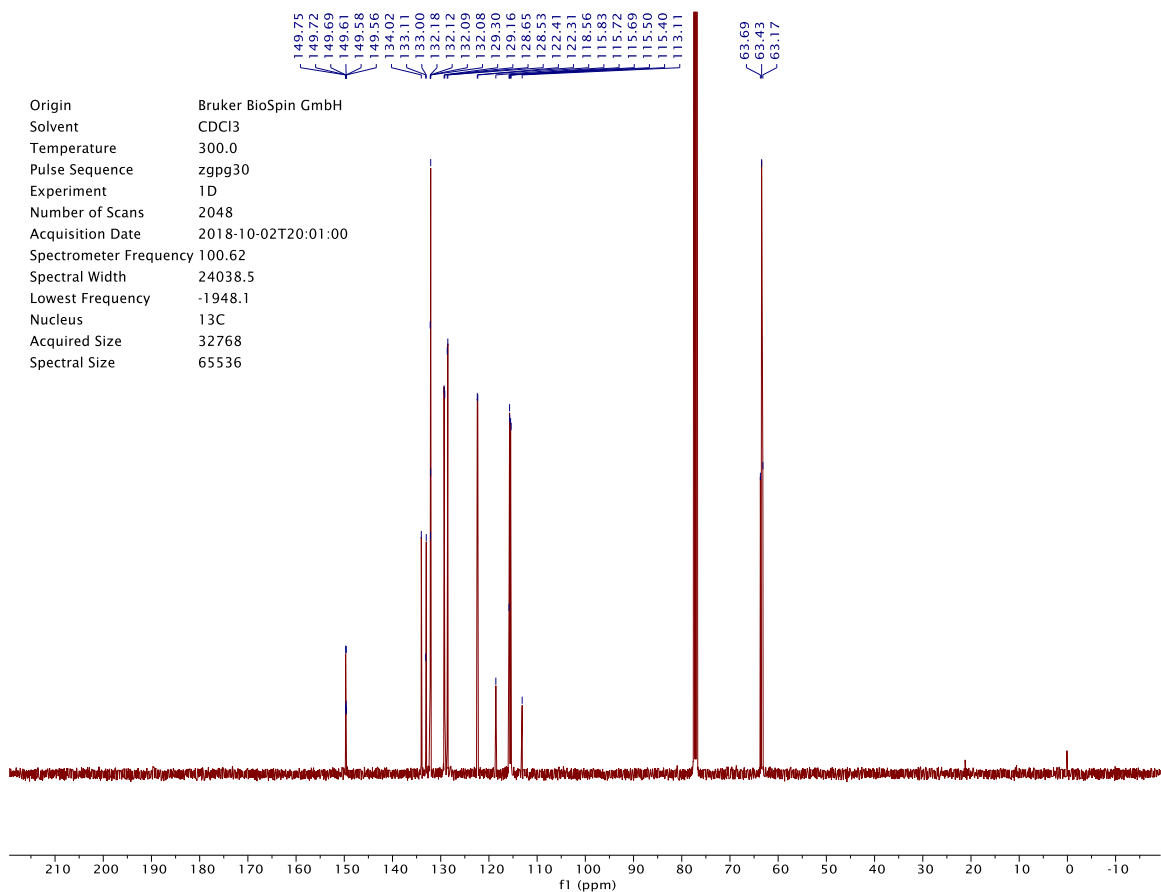


S42

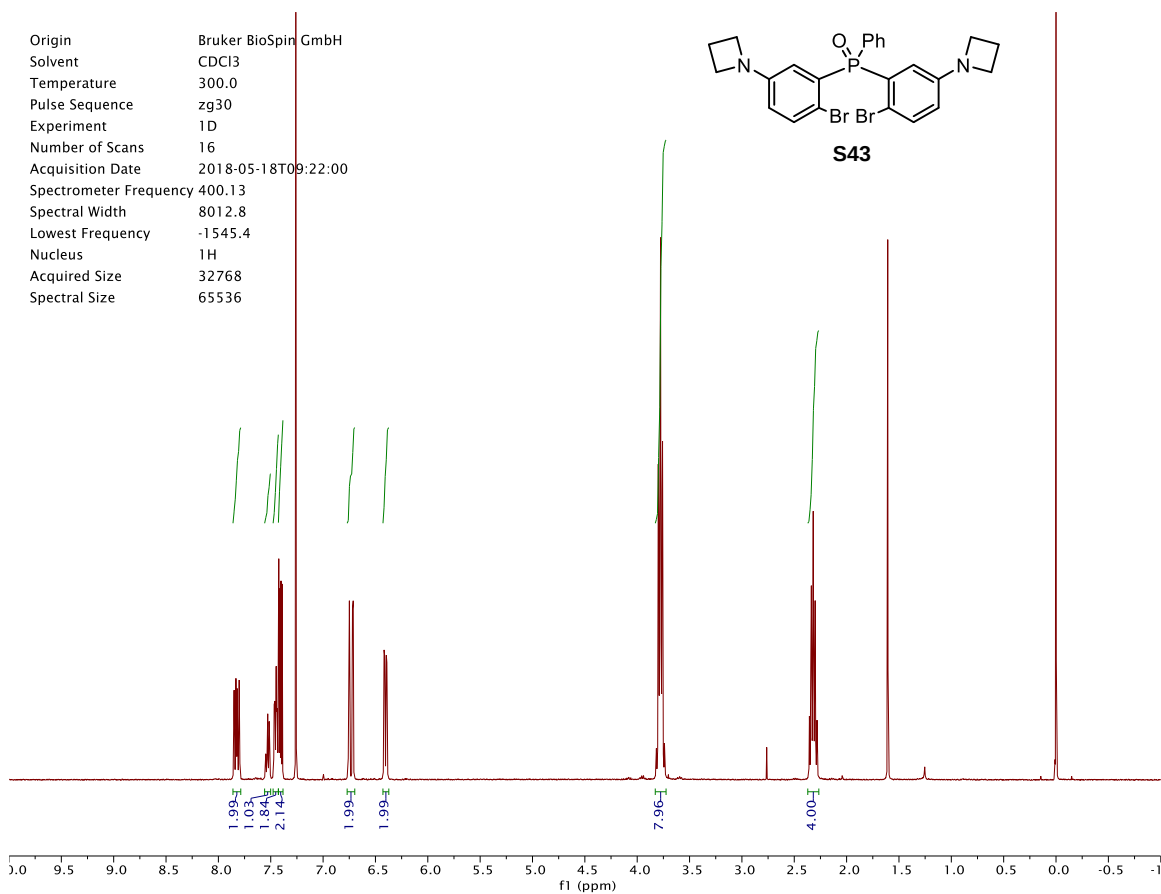
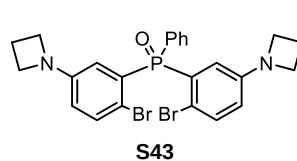


149.75
149.72
149.69
149.61
149.58
149.56
134.02
133.11
133.00
132.18
132.12
132.09
132.08
129.30
129.16
128.65
128.53
122.41
122.31
118.56
115.83
115.72
115.69
115.50
115.40
113.11

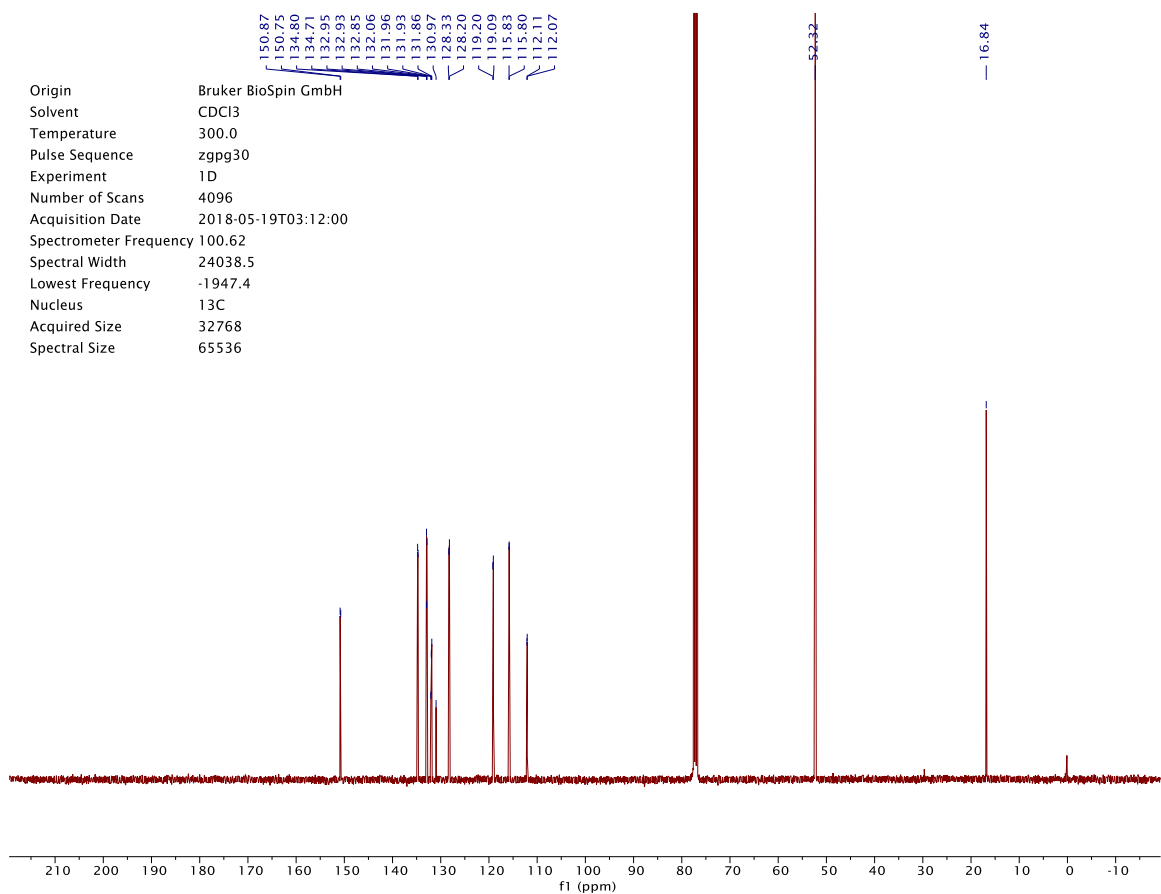
63.69
63.43
63.17



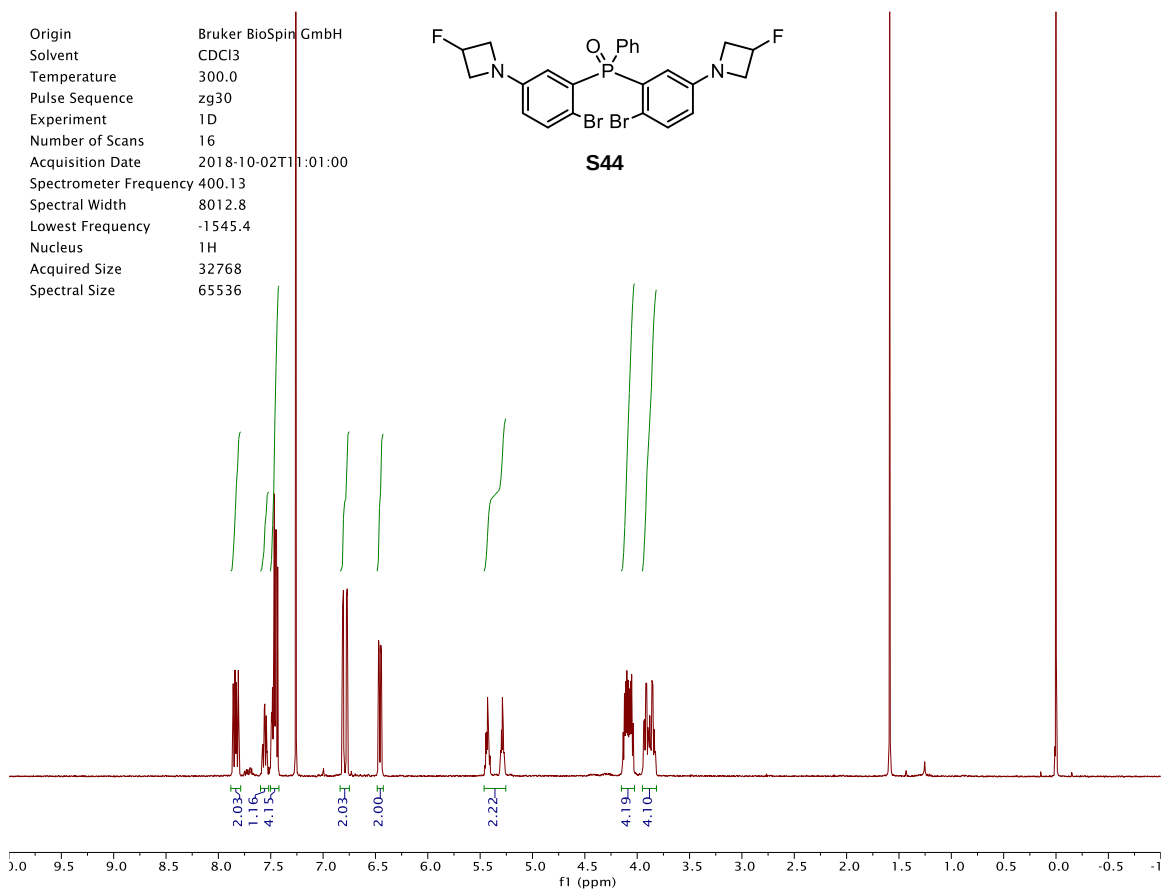
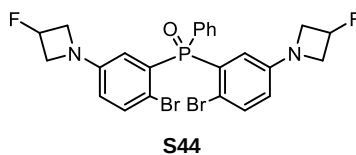
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-05-18T09:22:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.4
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



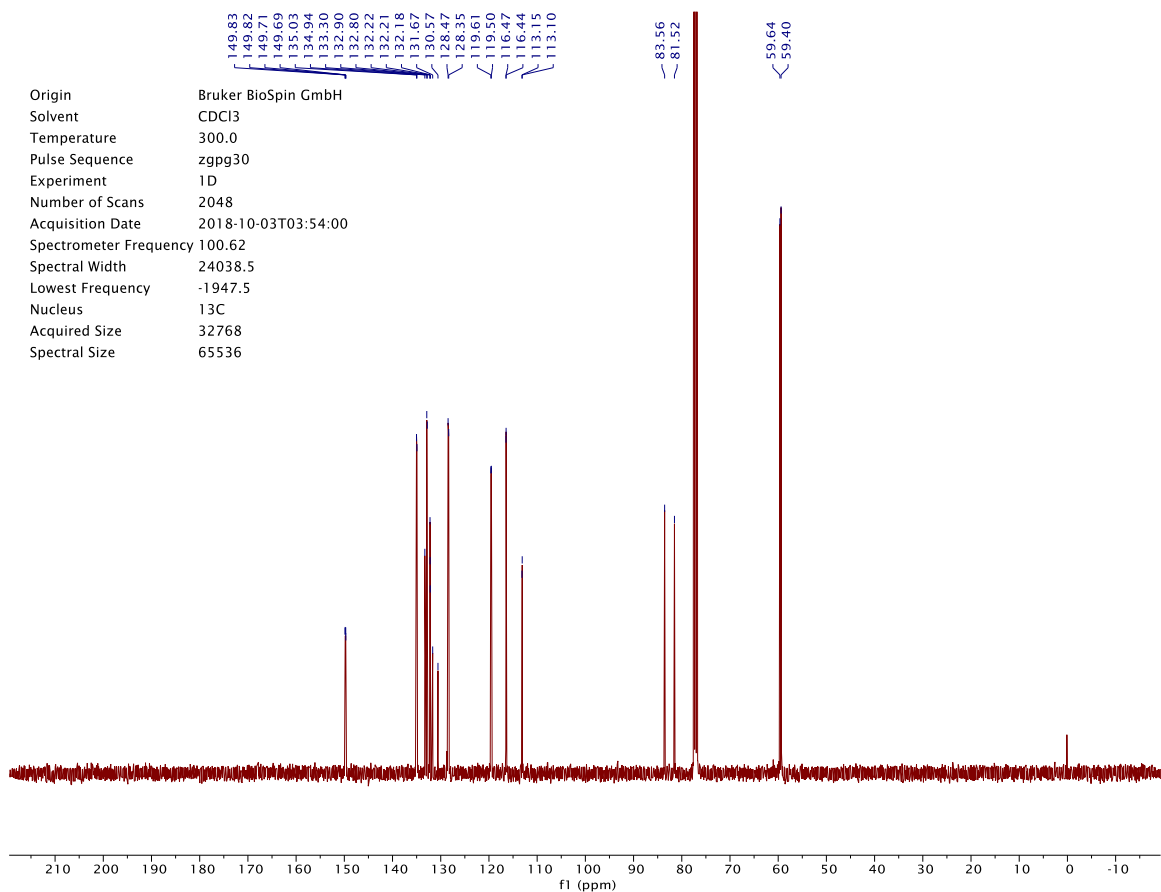
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zgpg30
 Experiment: 1D
 Number of Scans: 4096
 Acquisition Date: 2018-05-19T03:12:00
 Spectrometer Frequency: 100.62
 Spectral Width: 24038.5
 Lowest Frequency: -1947.4
 Nucleus: ¹³C
 Acquired Size: 32768
 Spectral Size: 65536



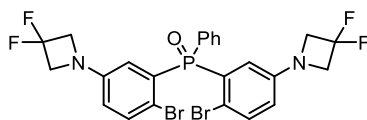
Origin Bruker BioSpin GmbH
 Solvent CDCl3
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-10-02T11:01:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.4
 Nucleus 1H
 Acquired Size 32768
 Spectral Size 65536



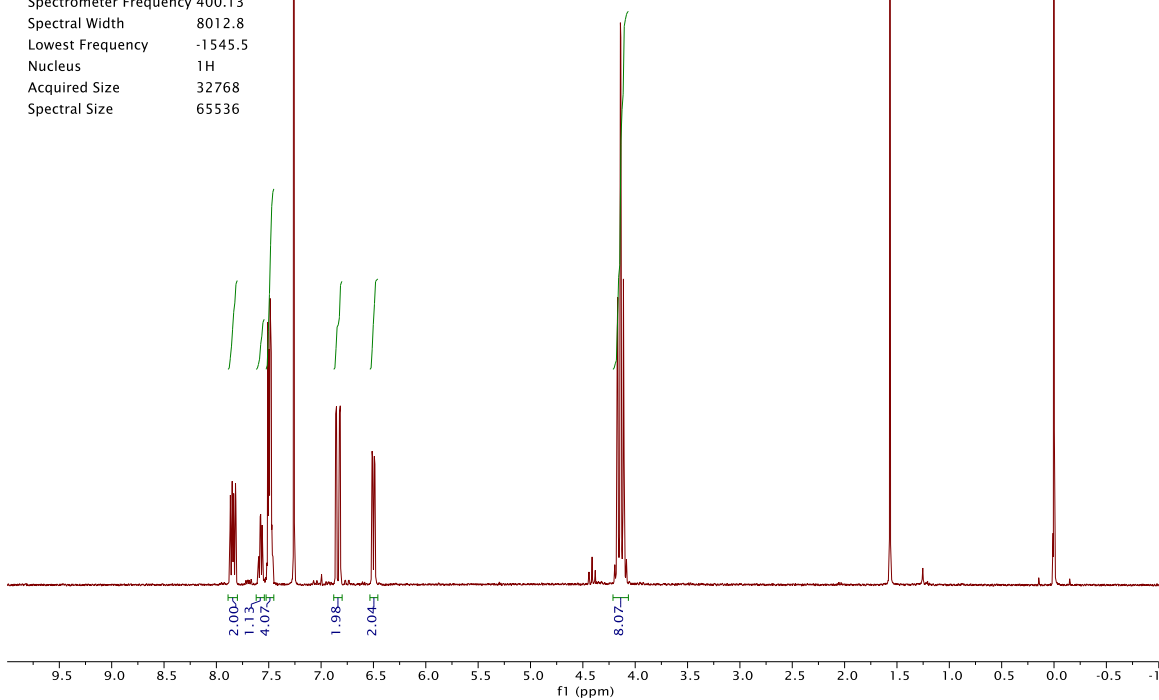
Origin Bruker BioSpin GmbH
 Solvent CDCl3
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-10-03T03:54:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1947.5
 Nucleus 13C
 Acquired Size 32768
 Spectral Size 65536



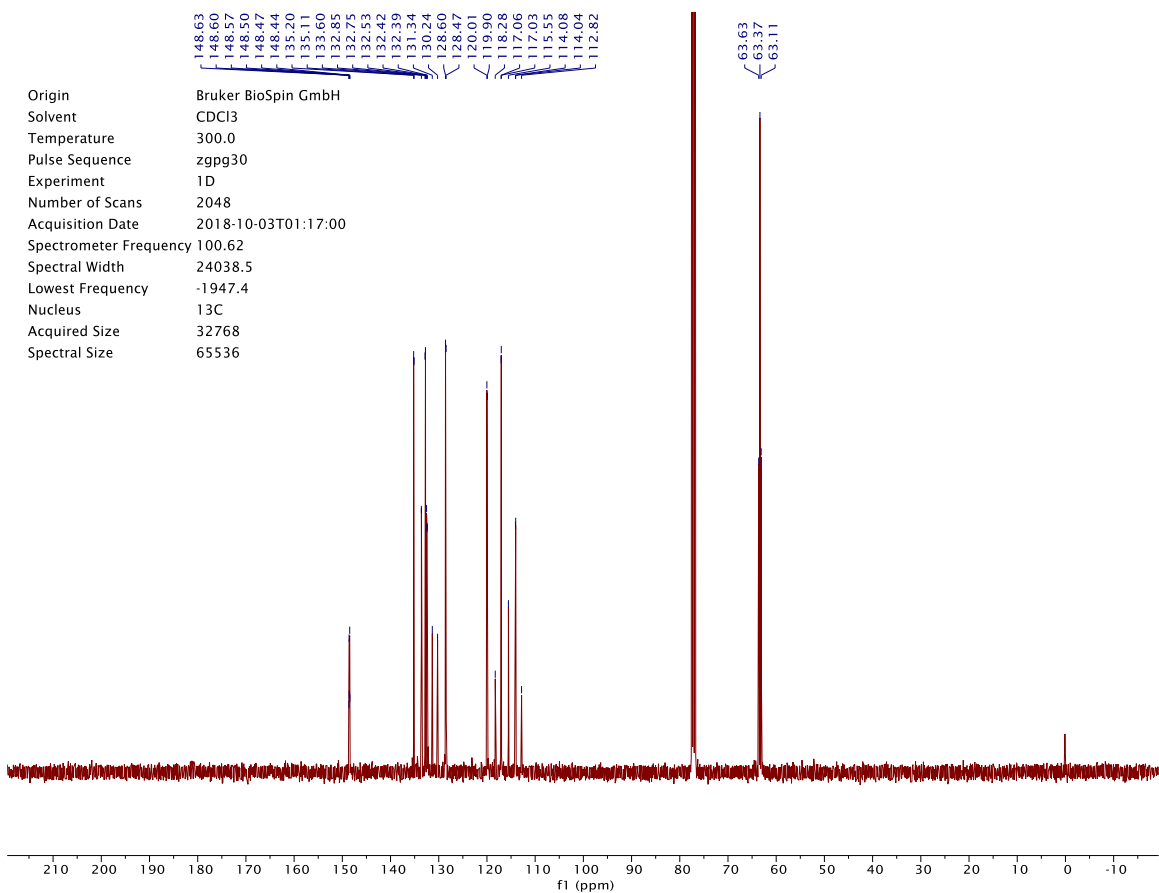
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-10-02T10:56:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.5
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



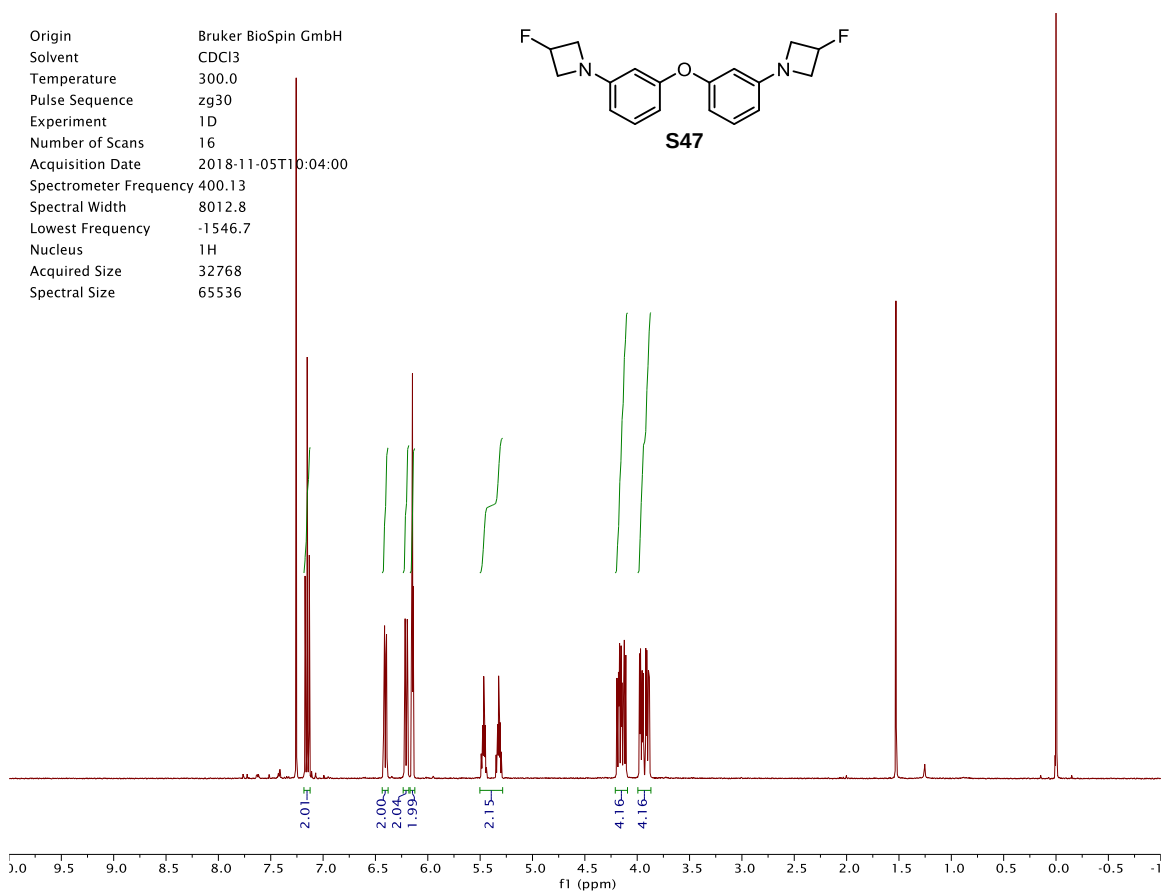
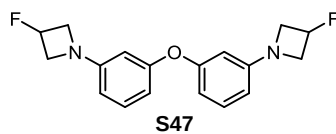
S45



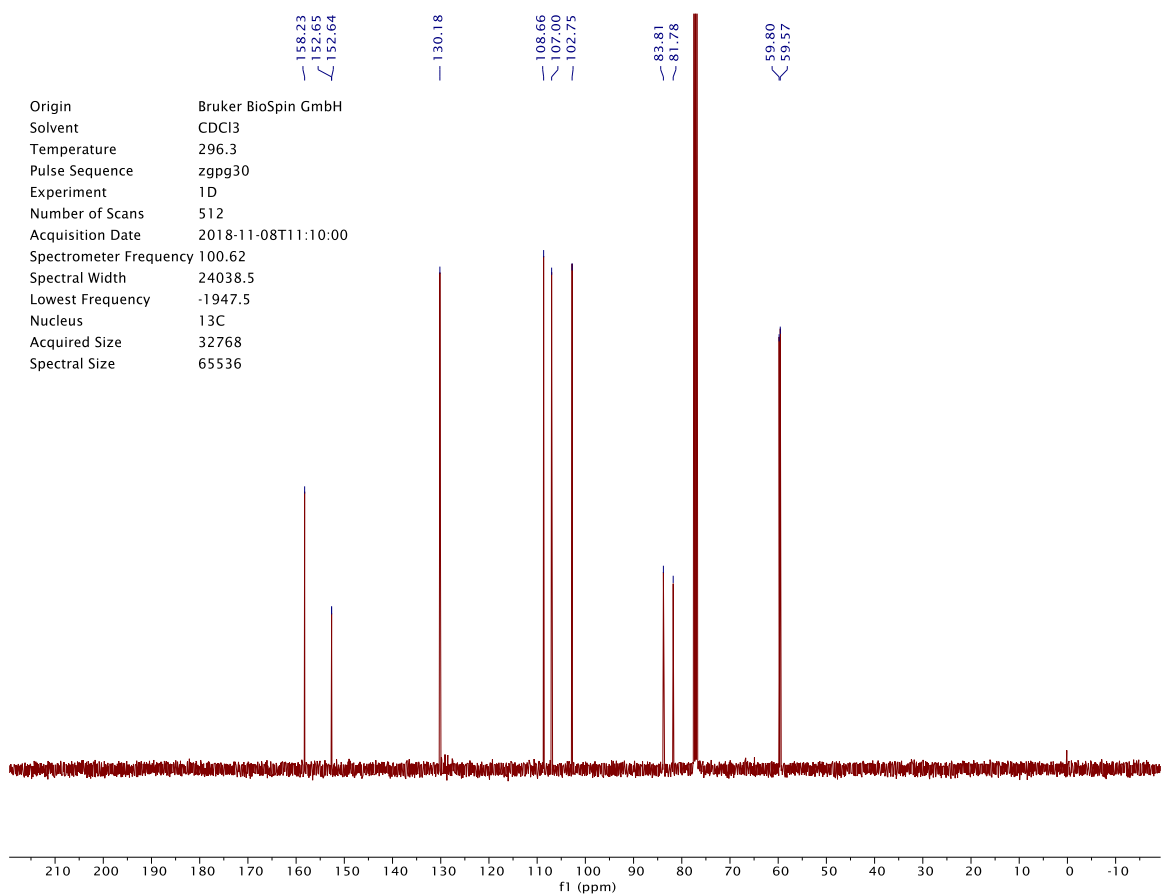
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zgpg30
 Experiment: 1D
 Number of Scans: 2048
 Acquisition Date: 2018-10-03T01:17:00
 Spectrometer Frequency: 100.62
 Spectral Width: 24038.5
 Lowest Frequency: -1947.4
 Nucleus: ¹³C
 Acquired Size: 32768
 Spectral Size: 65536



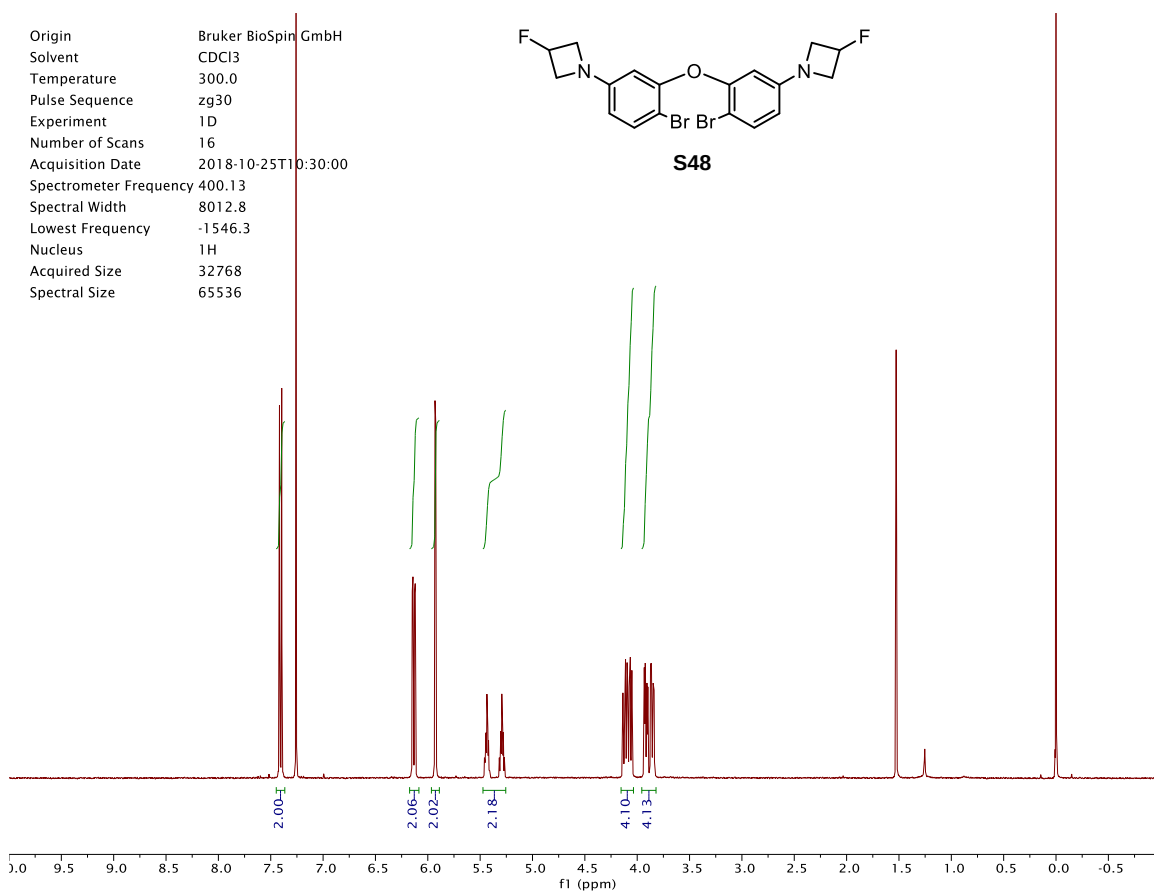
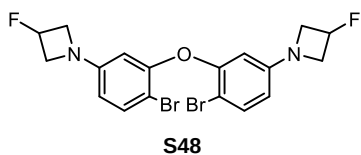
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-11-05T10:04:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1546.7
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



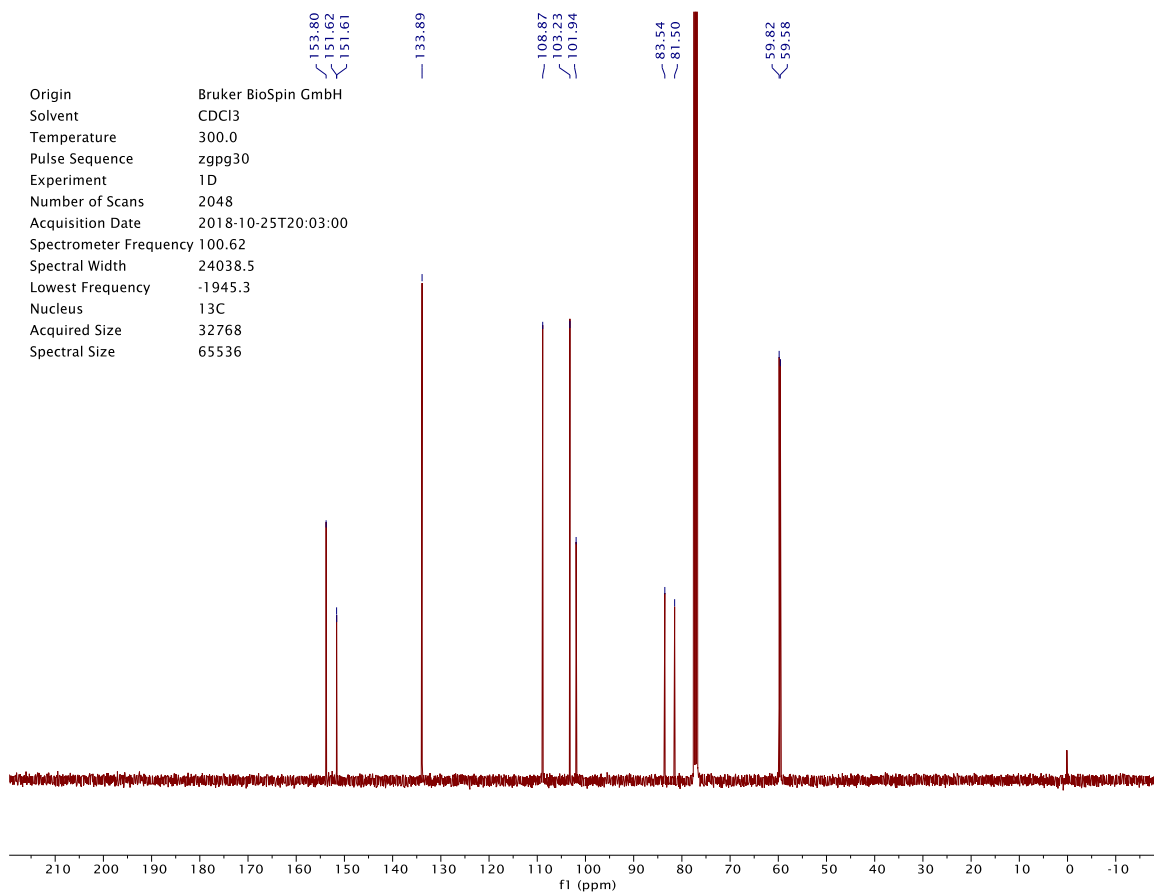
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 296.3
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 512
 Acquisition Date 2018-11-08T11:10:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1947.5
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536



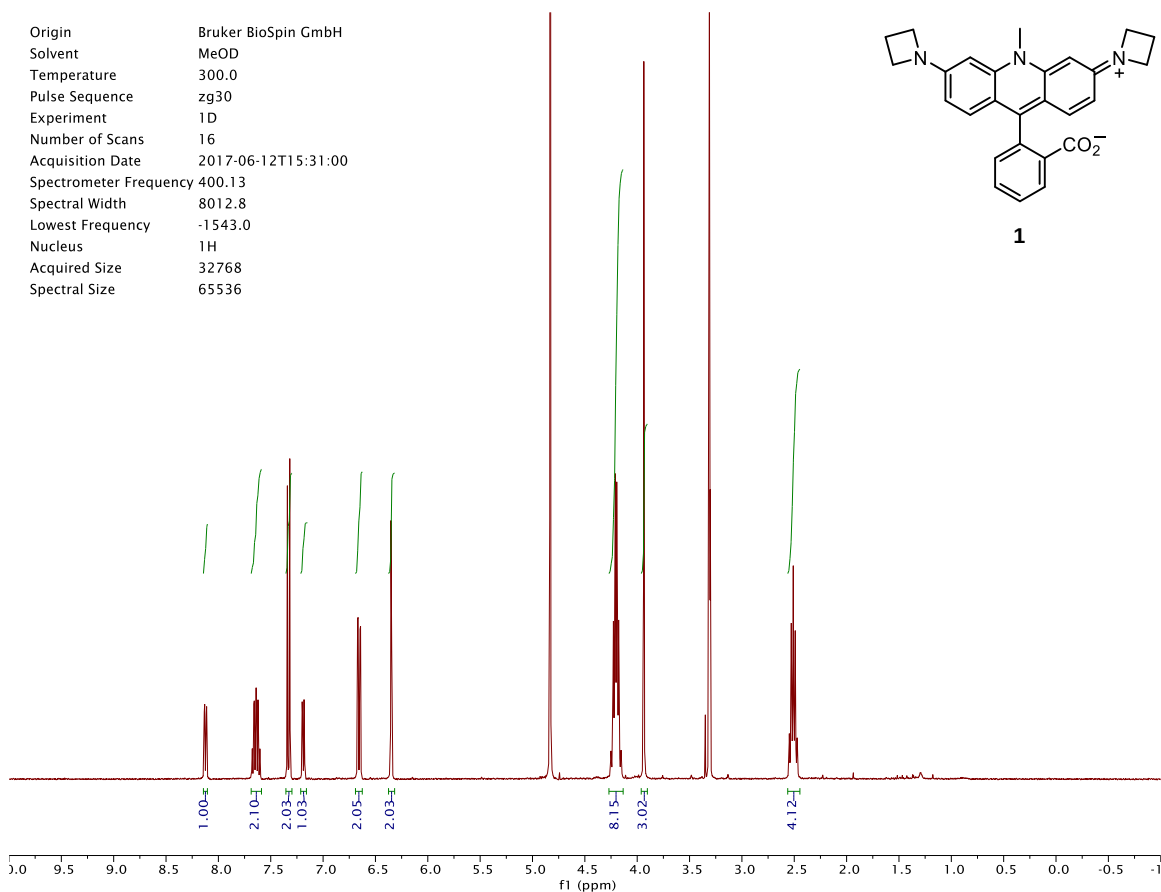
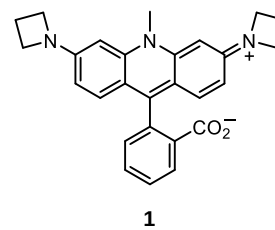
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-10-25T10:30:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1546.3
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



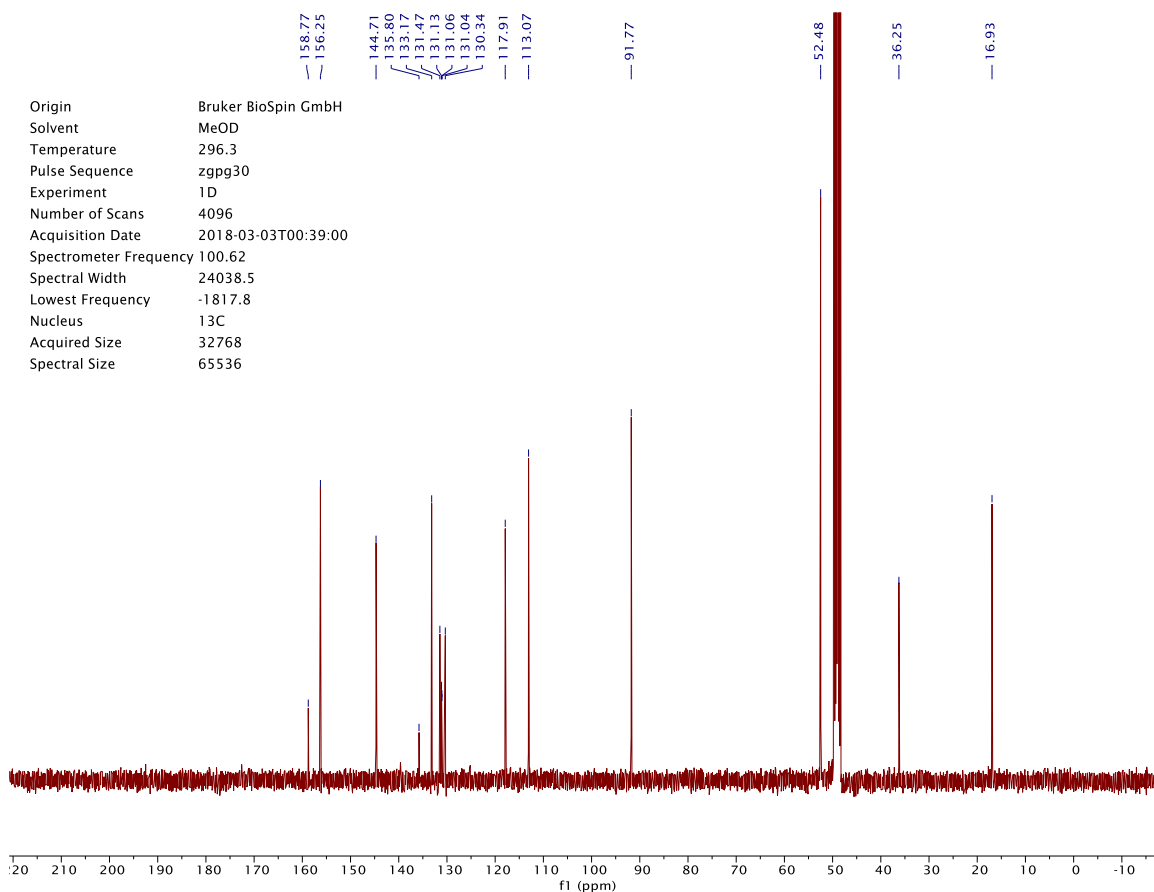
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zgpg30
 Experiment: 1D
 Number of Scans: 2048
 Acquisition Date: 2018-10-25T20:03:00
 Spectrometer Frequency: 100.62
 Spectral Width: 24038.5
 Lowest Frequency: -1945.3
 Nucleus: ¹³C
 Acquired Size: 32768
 Spectral Size: 65536

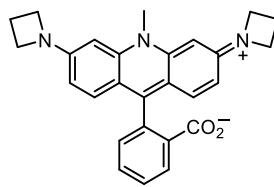


Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-06-12T15:31:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.0
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536

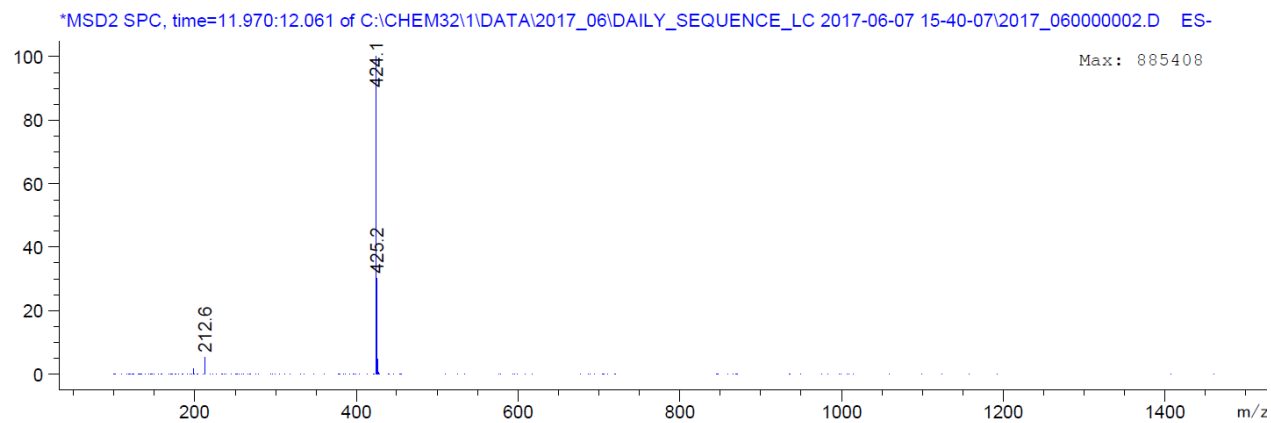
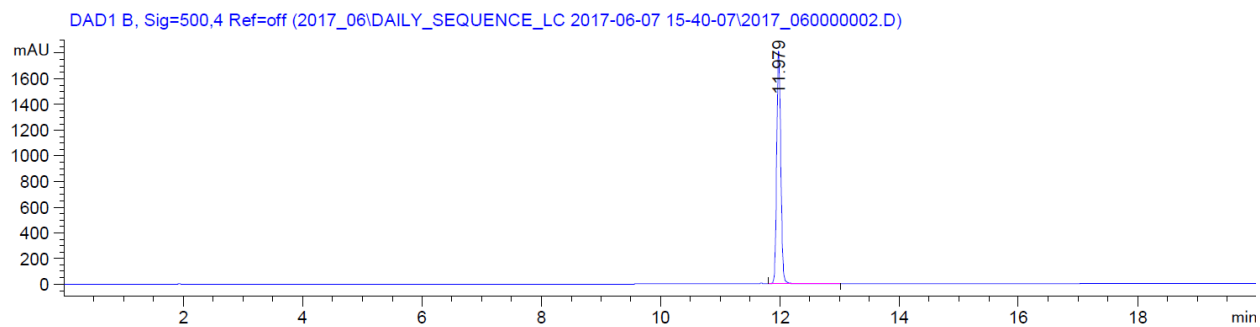


Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 296.3
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 4096
 Acquisition Date 2018-03-03T00:39:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1817.8
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536

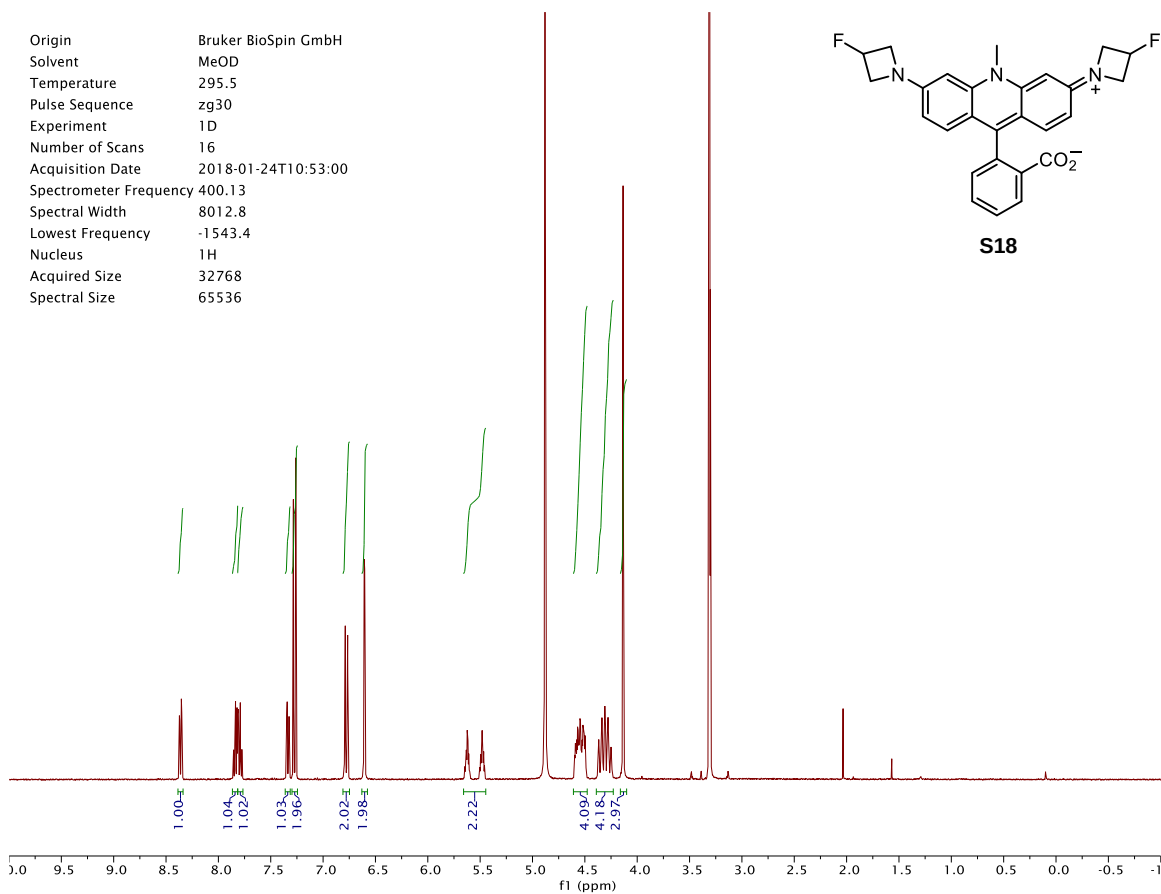
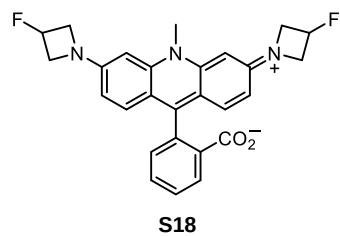




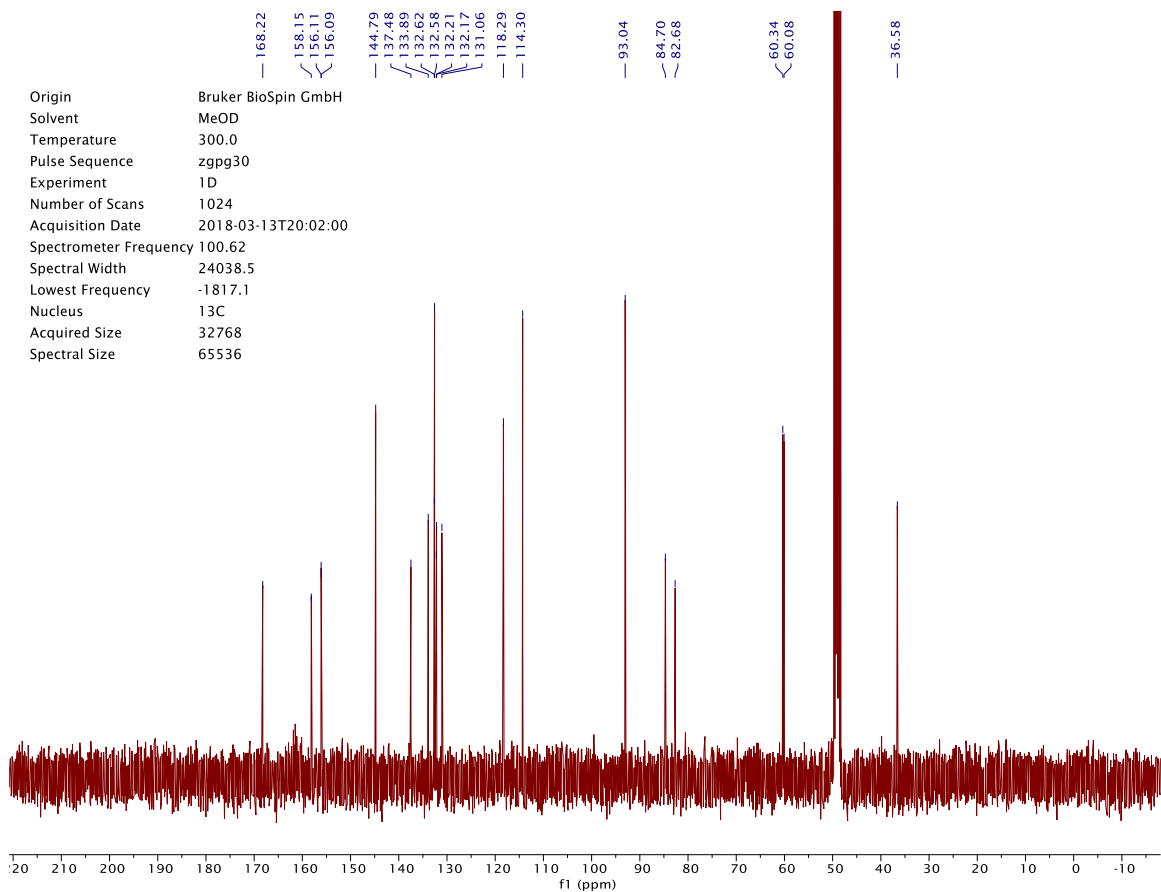
1

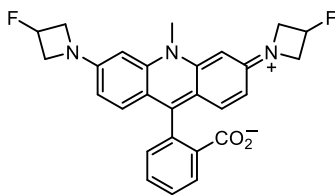


Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 295.5
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-01-24T10:53:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.4
 Nucleus ^1H
 Acquired Size 32768
 Spectral Size 65536

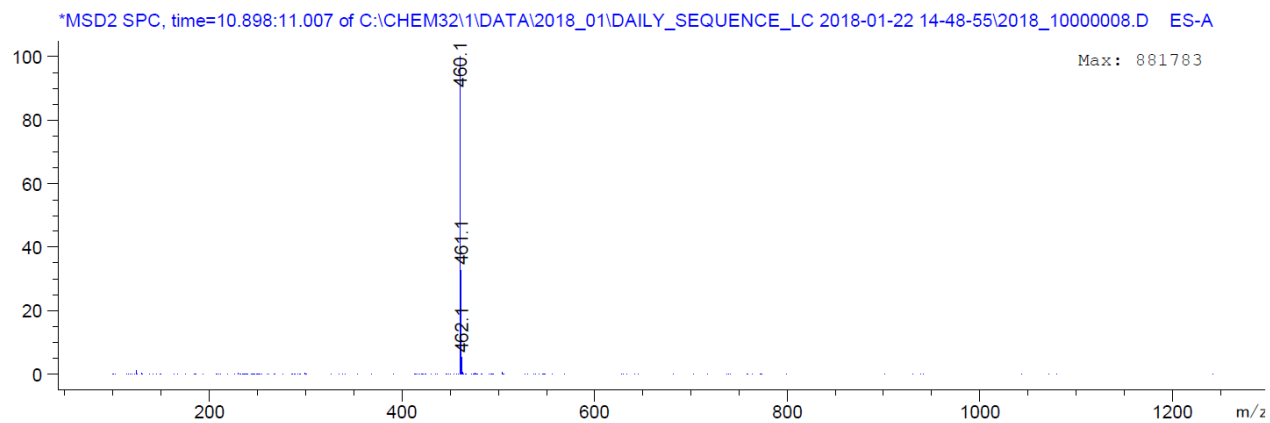
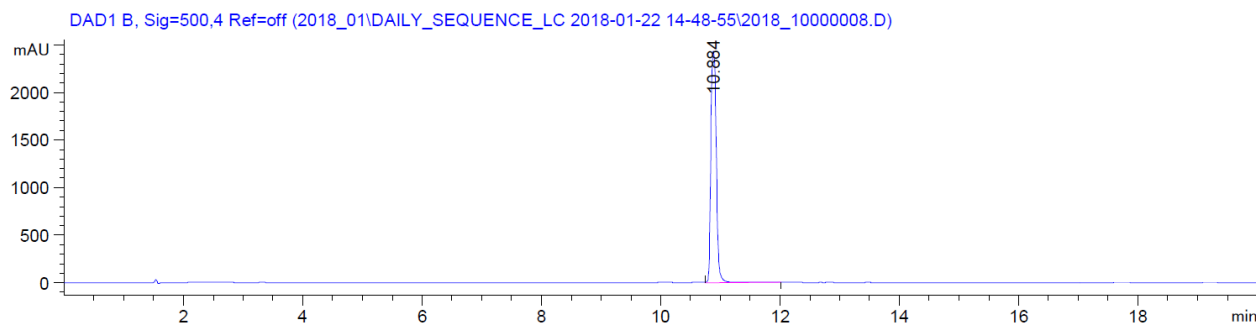


Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 1024
 Acquisition Date 2018-03-13T20:02:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1817.1
 Nucleus ^{13}C
 Acquired Size 32768
 Spectral Size 65536

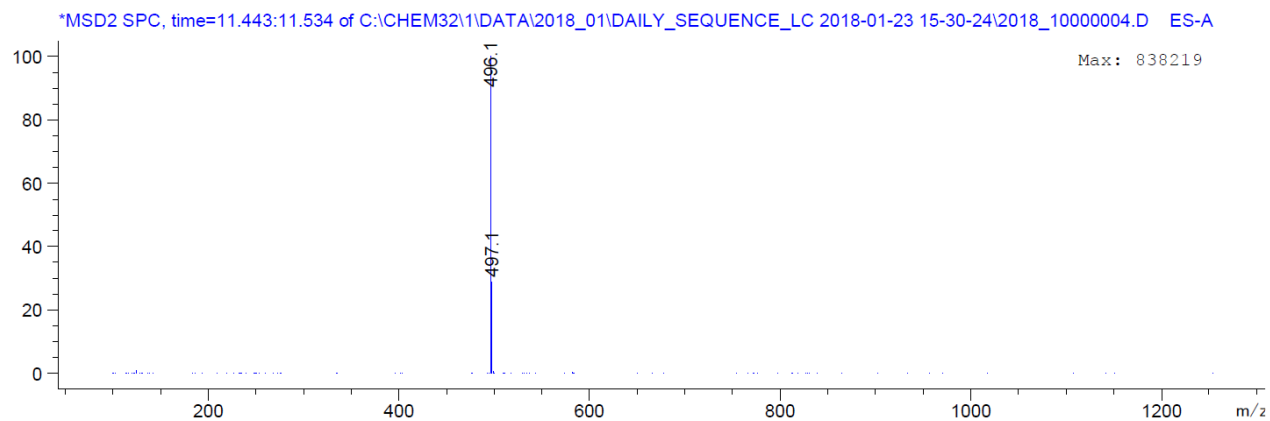
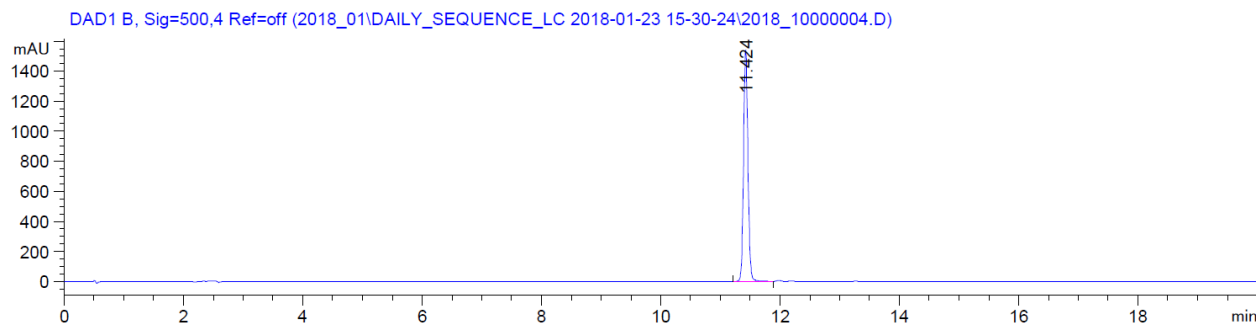
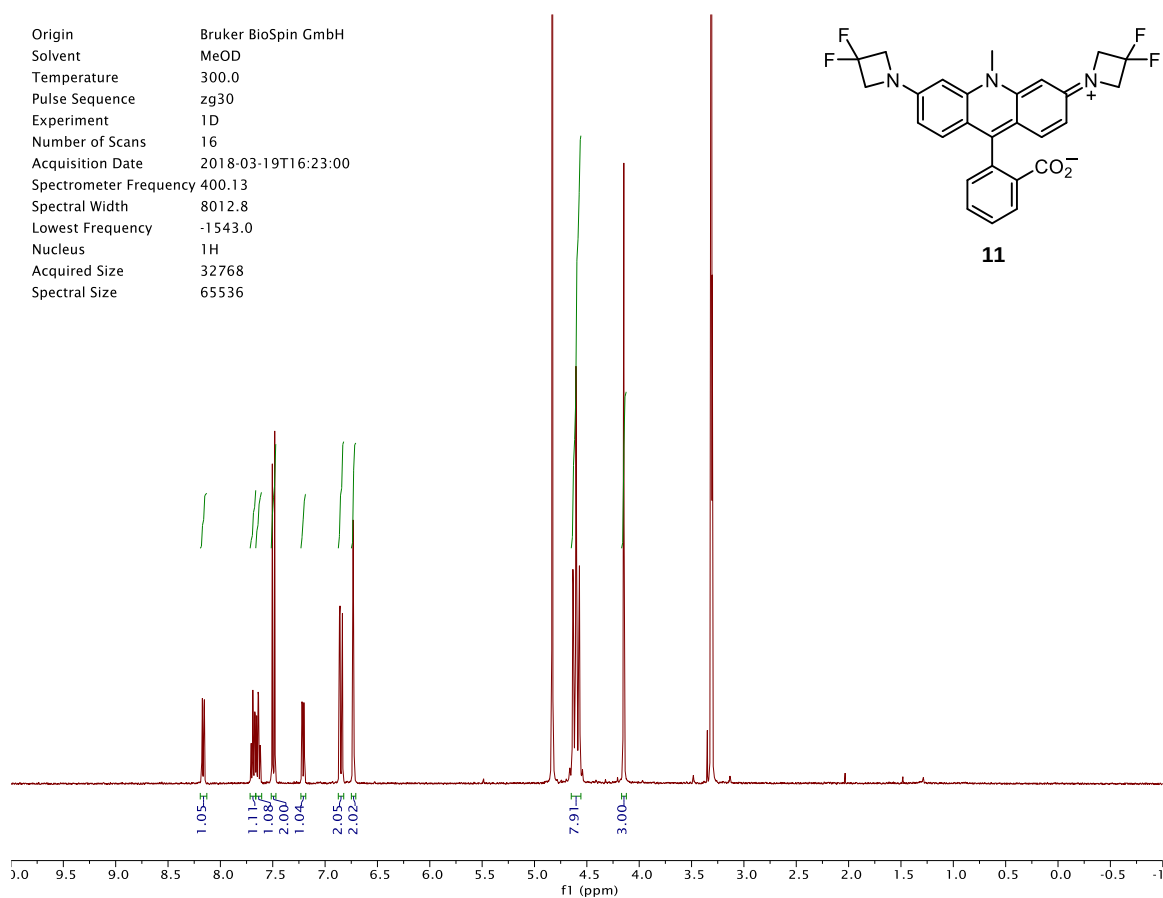
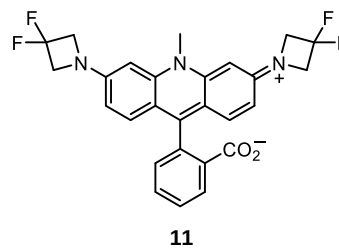




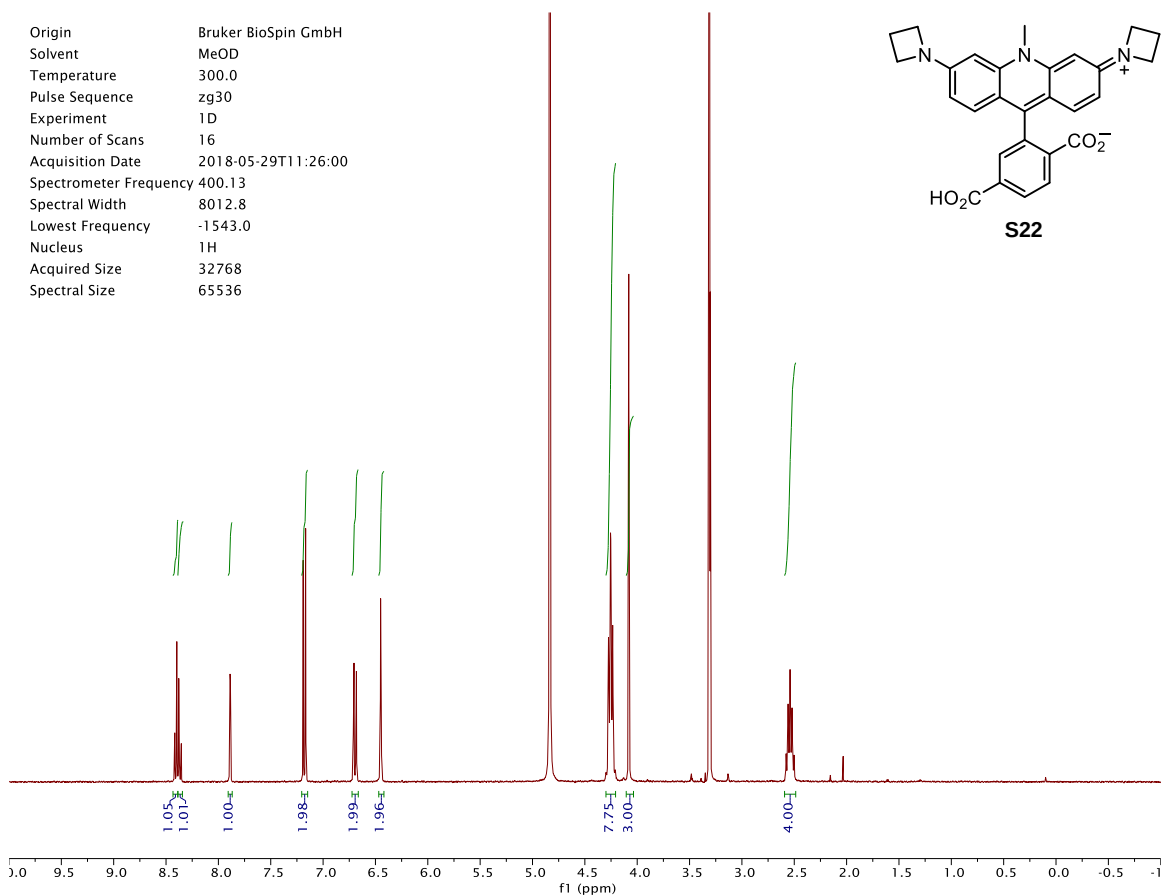
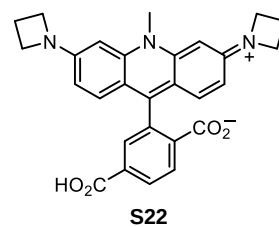
S18



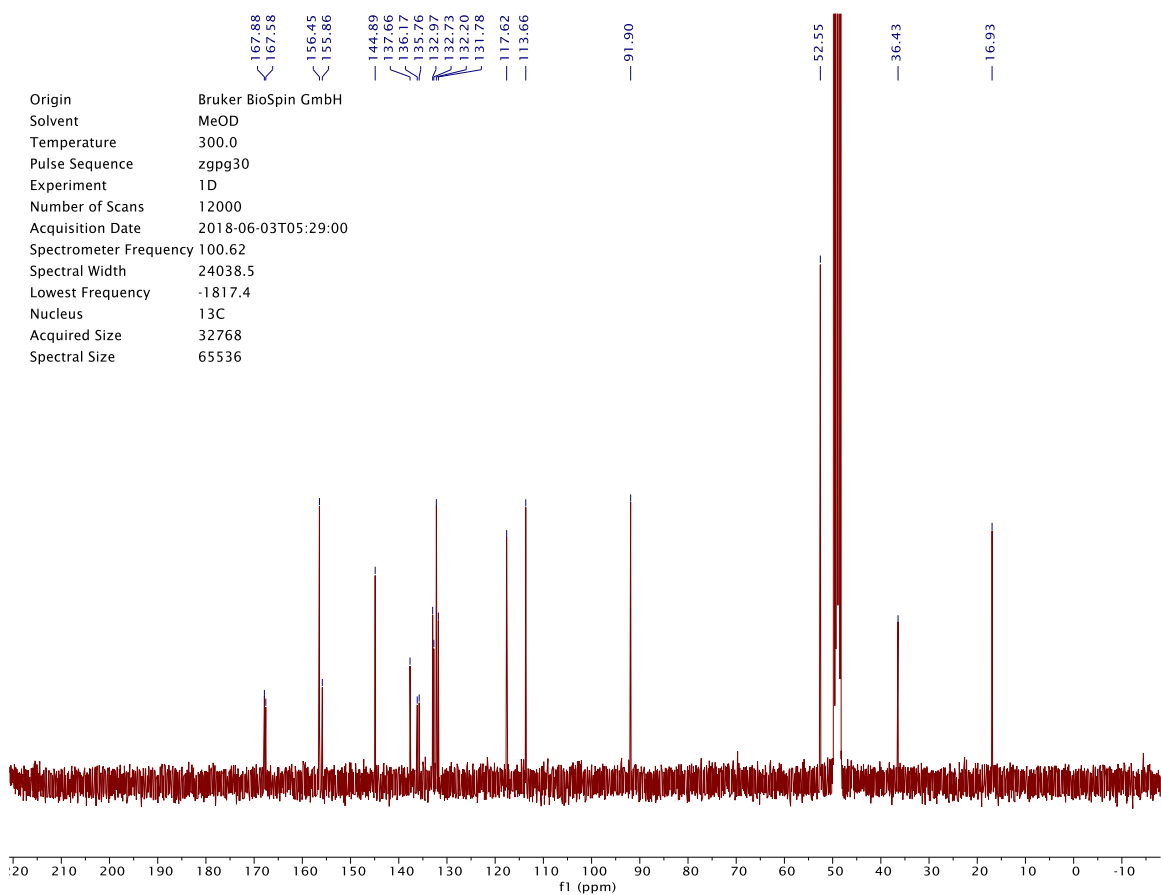
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-03-19T16:23:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.0
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536

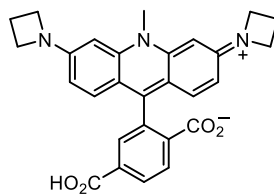


Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-05-29T11:26:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.0
 Nucleus ^1H
 Acquired Size 32768
 Spectral Size 65536

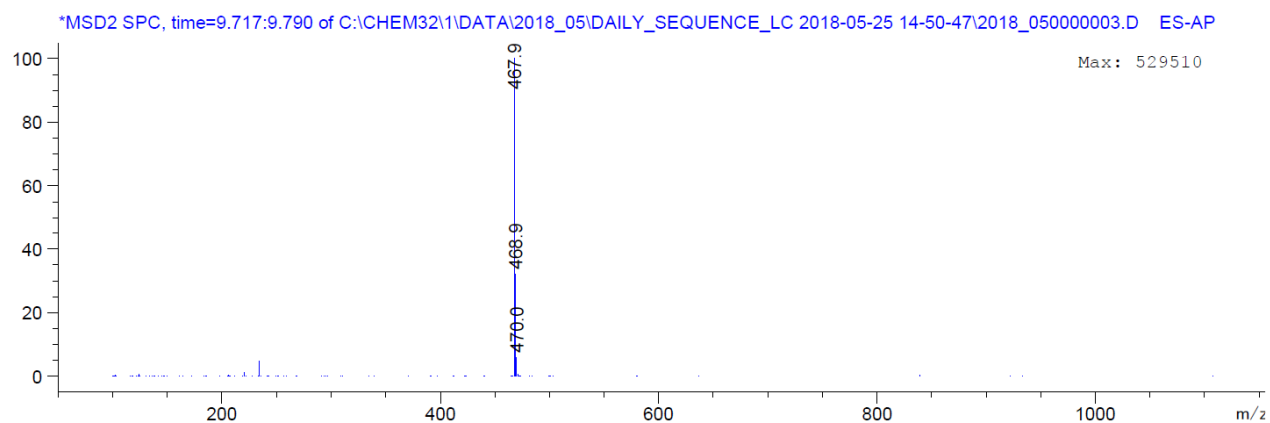
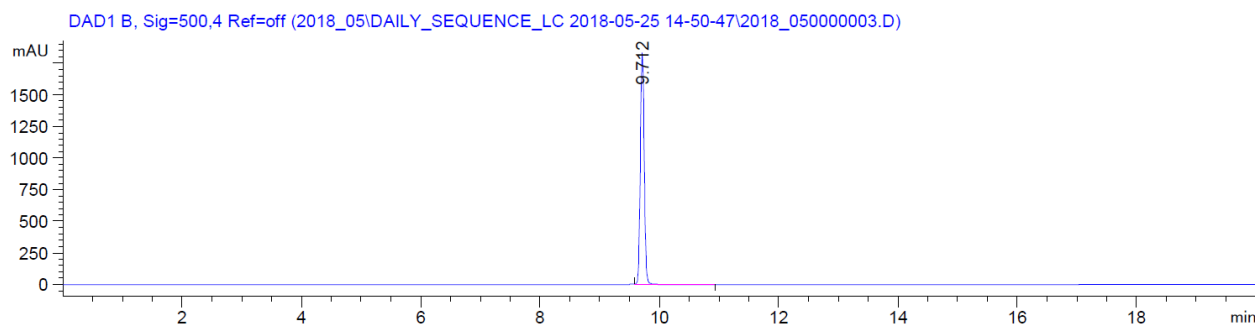


Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 12000
 Acquisition Date 2018-06-03T05:29:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1817.4
 Nucleus ^{13}C
 Acquired Size 32768
 Spectral Size 65536

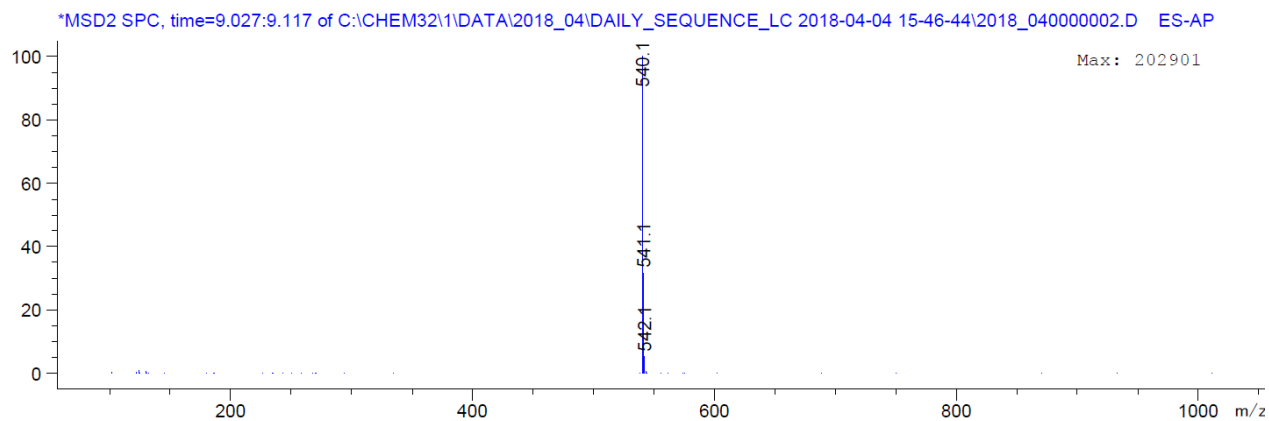
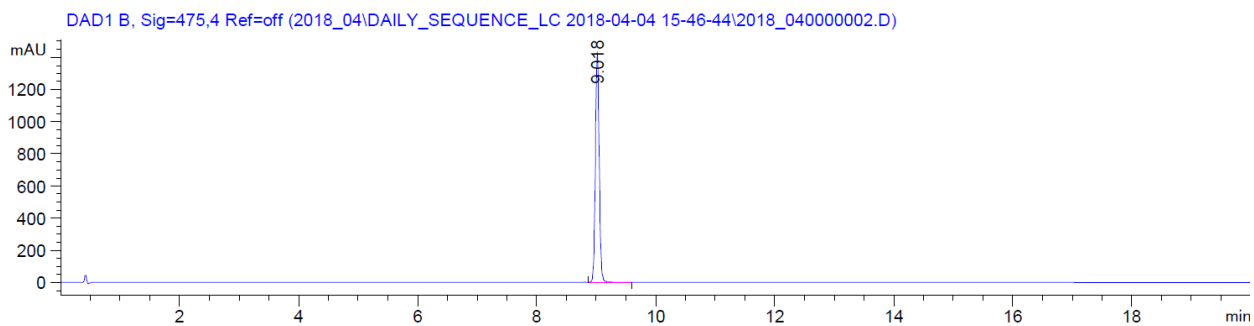
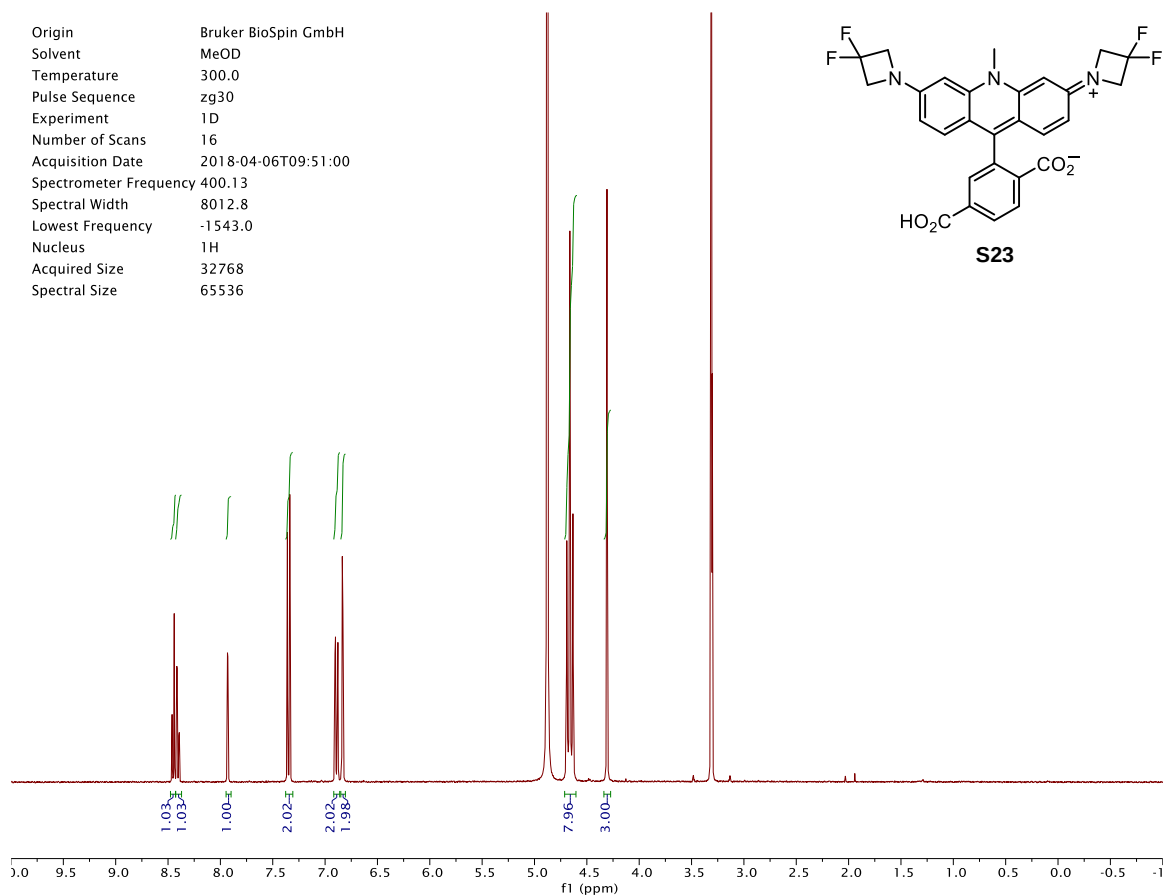
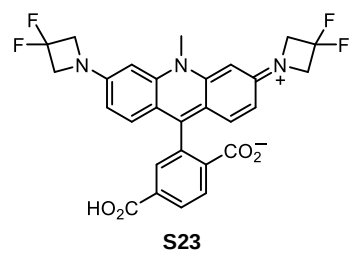




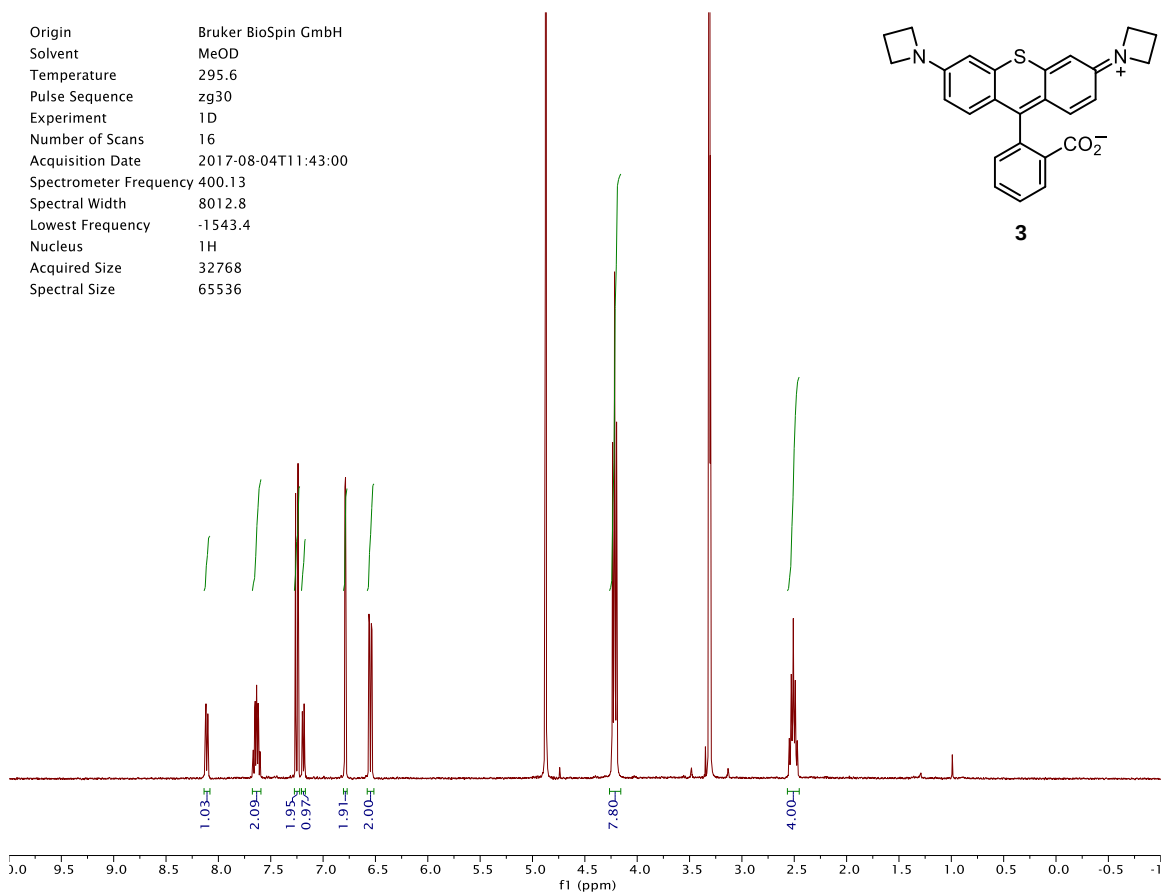
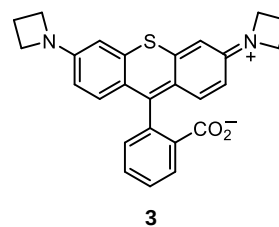
S22



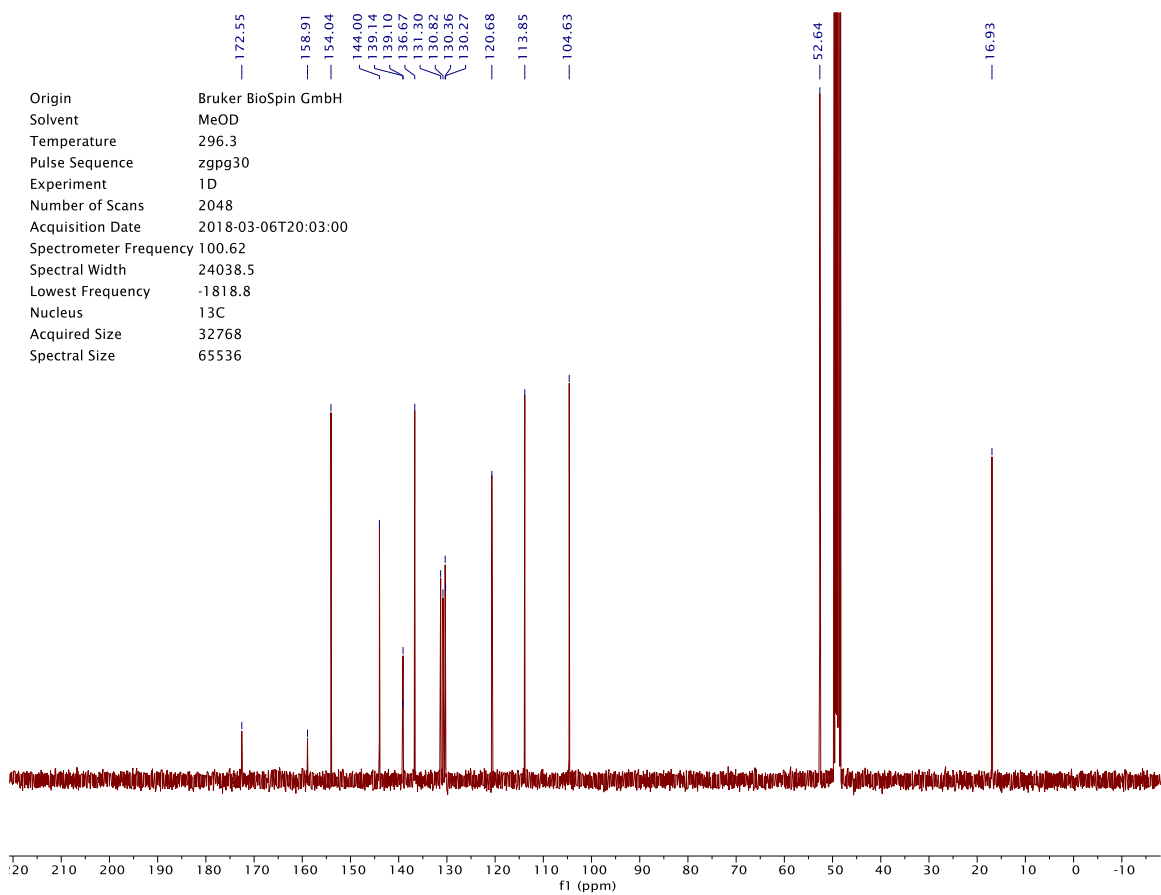
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-04-06T09:51:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.0
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536

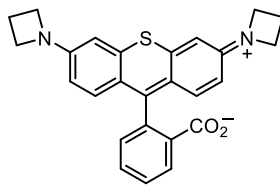


Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 295.6
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-08-04T11:43:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.4
 Nucleus ^1H
 Acquired Size 32768
 Spectral Size 65536

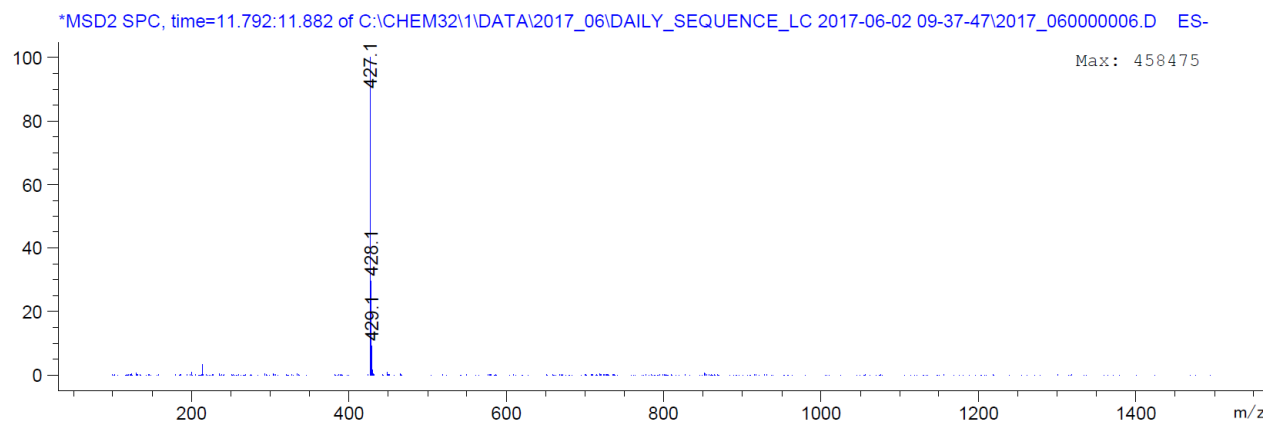
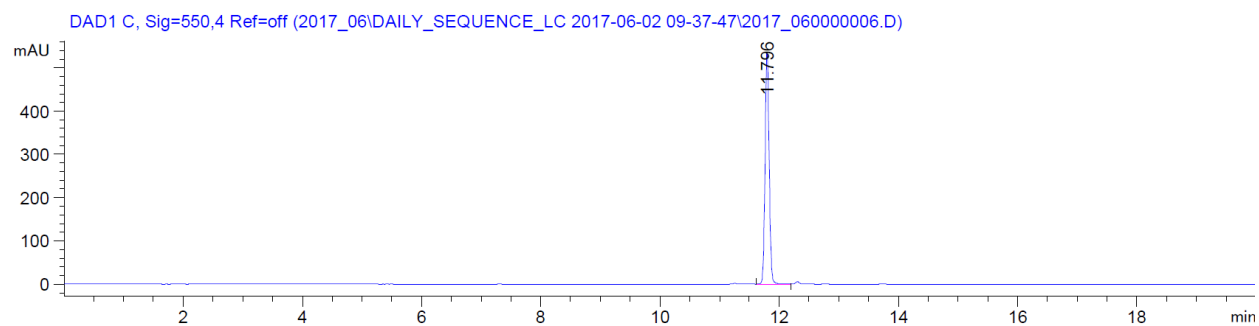


Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 296.3
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-03-06T20:03:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1818.8
 Nucleus ^{13}C
 Acquired Size 32768
 Spectral Size 65536

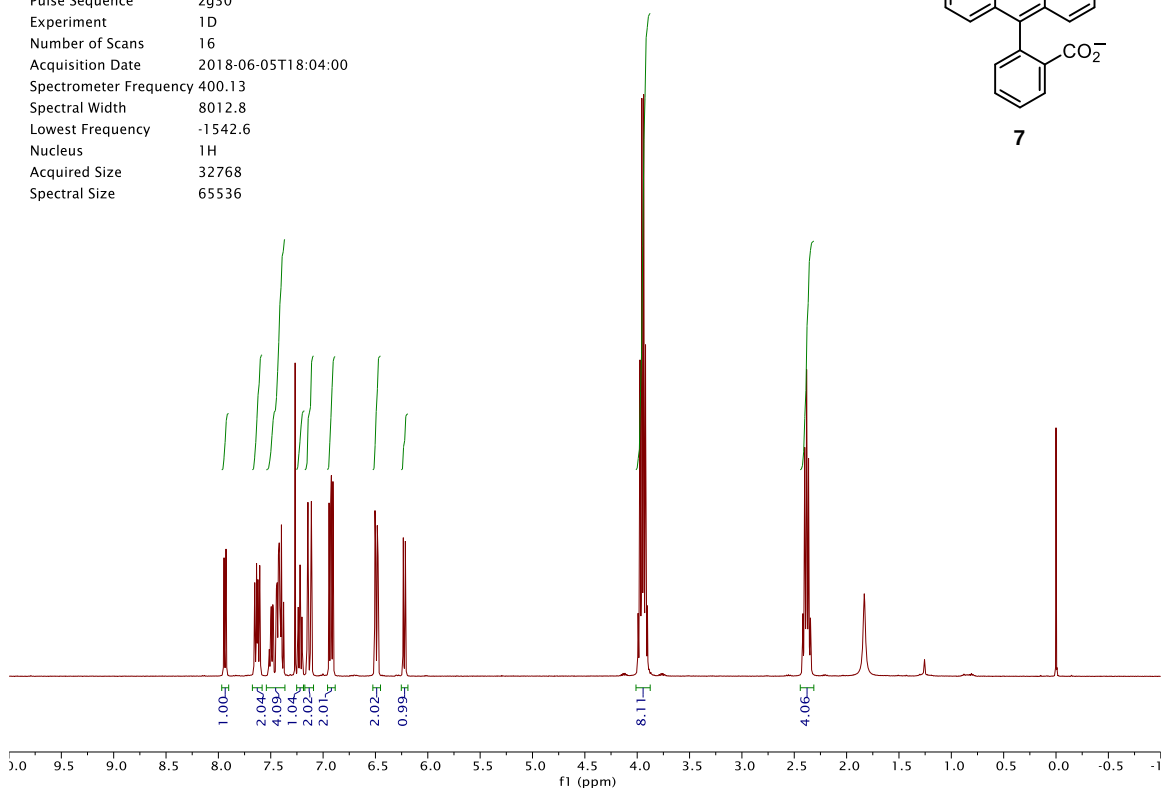
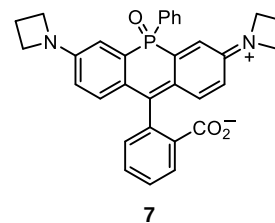




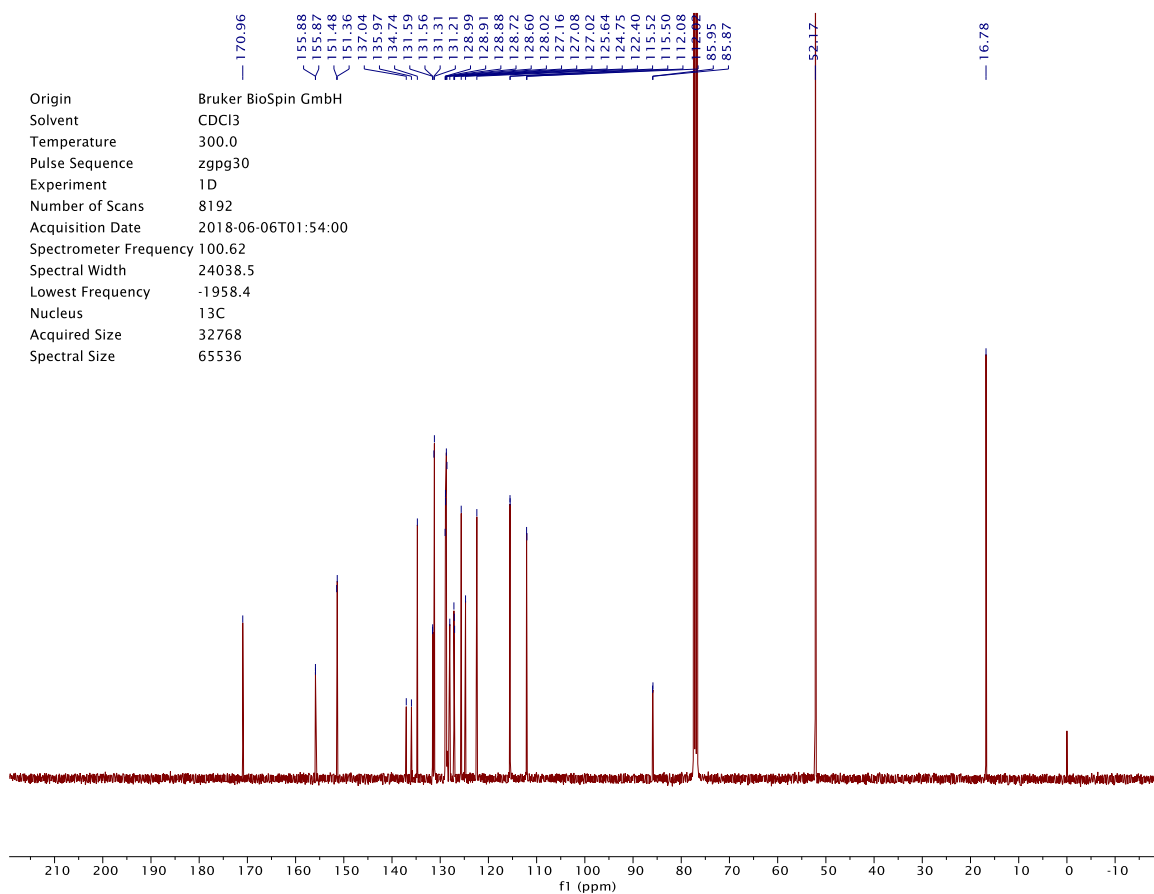
3

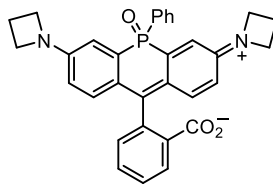


Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-06-05T18:04:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1542.6
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536

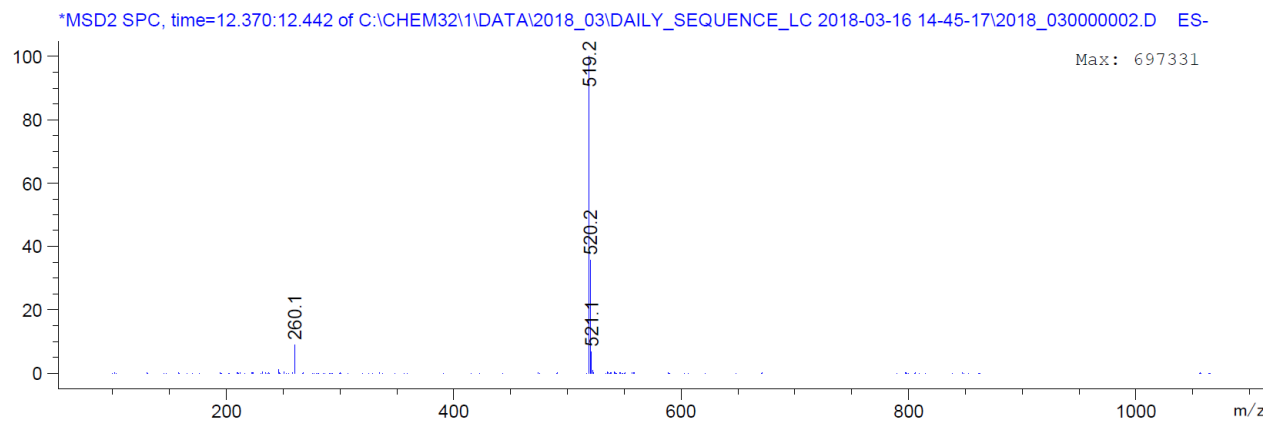
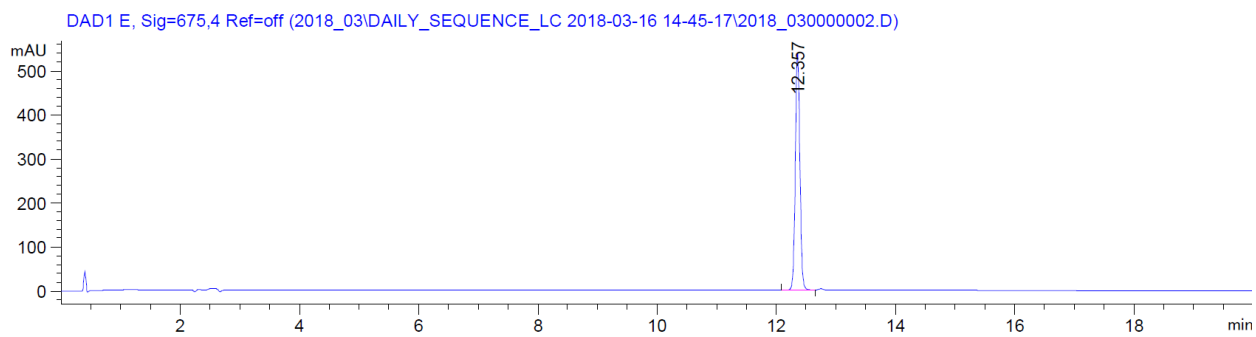


Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 8192
 Acquisition Date 2018-06-06T01:54:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1958.4
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536

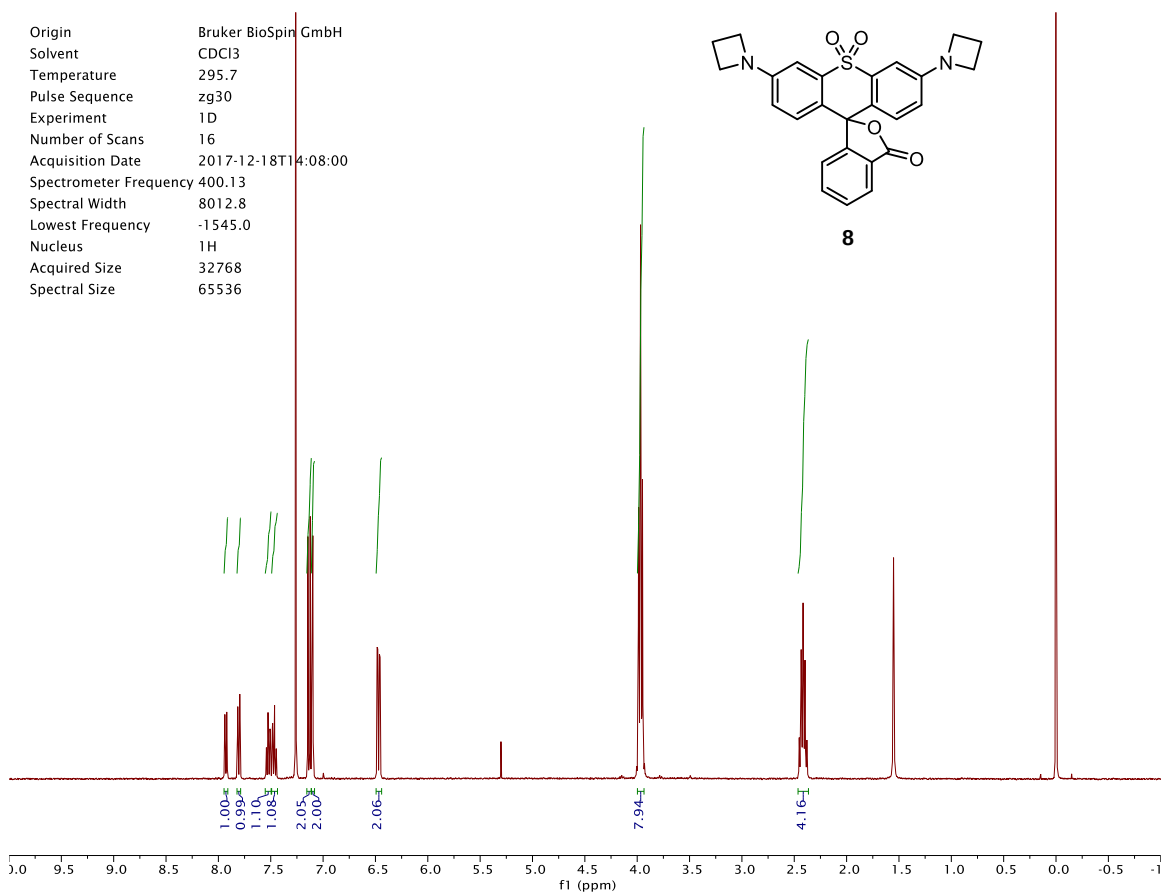
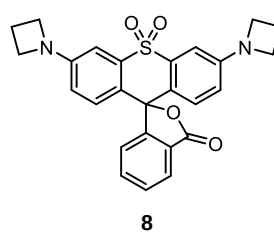




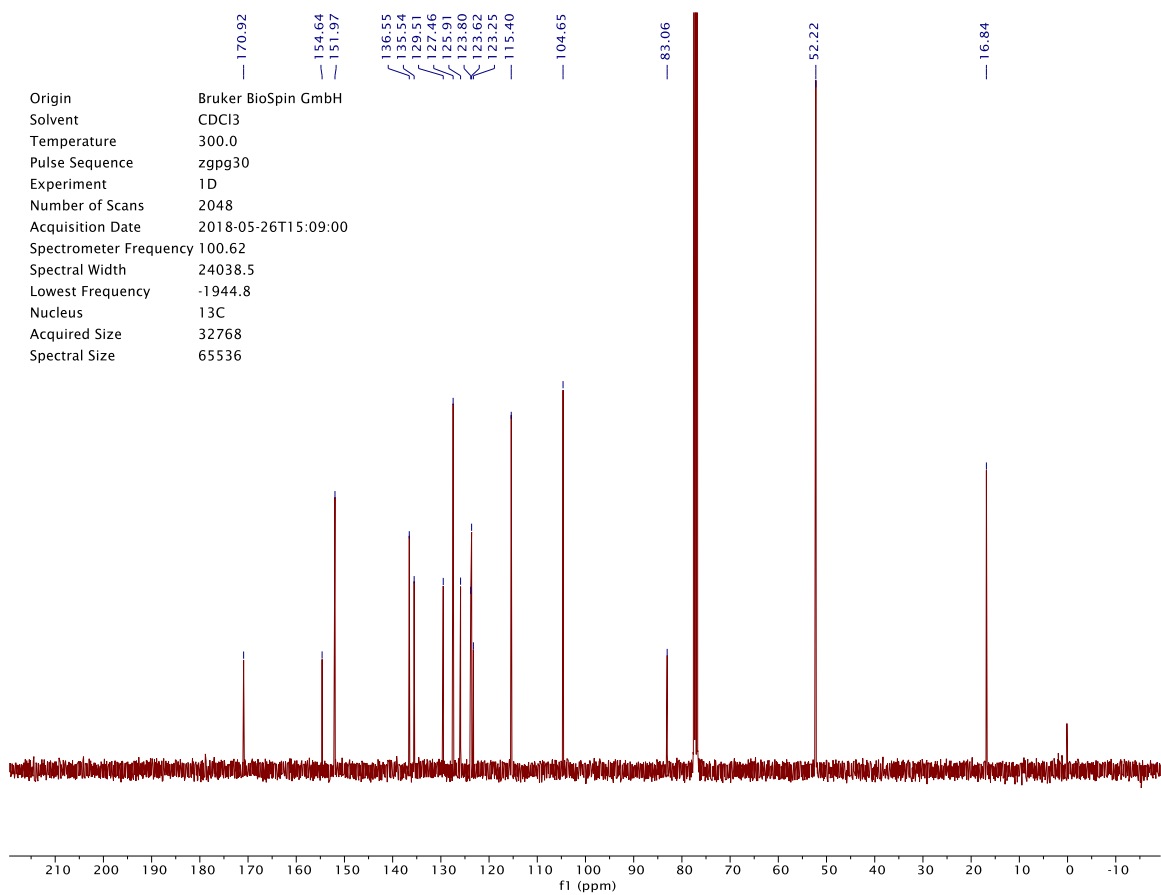
7

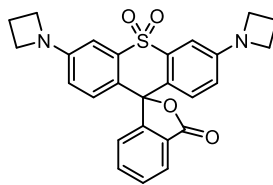


Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 295.7
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-12-18T14:08:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.0
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536

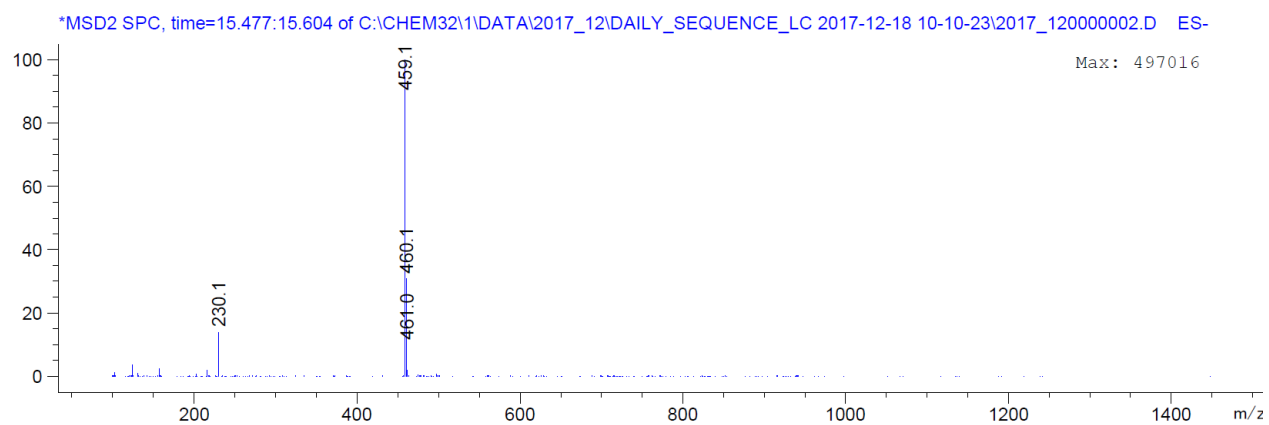
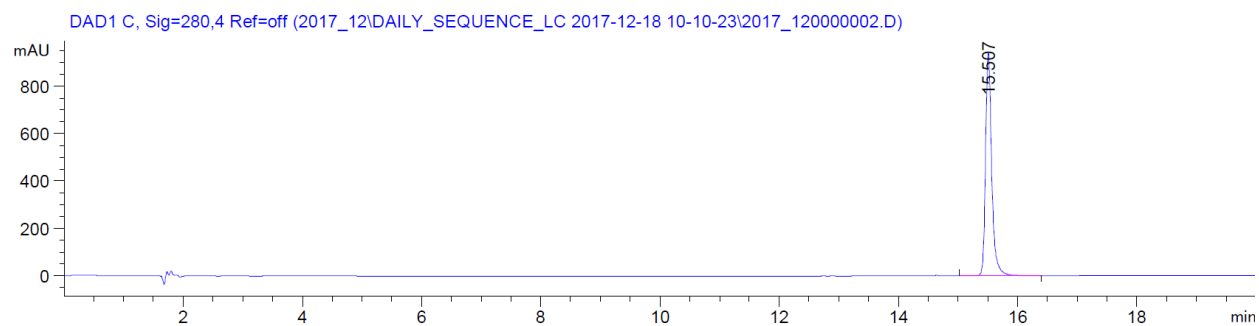


Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 300.0
 Pulse Sequence zgpg30
 Experiment 1D
 Number of Scans 2048
 Acquisition Date 2018-05-26T15:09:00
 Spectrometer Frequency 100.62
 Spectral Width 24038.5
 Lowest Frequency -1944.8
 Nucleus ¹³C
 Acquired Size 32768
 Spectral Size 65536

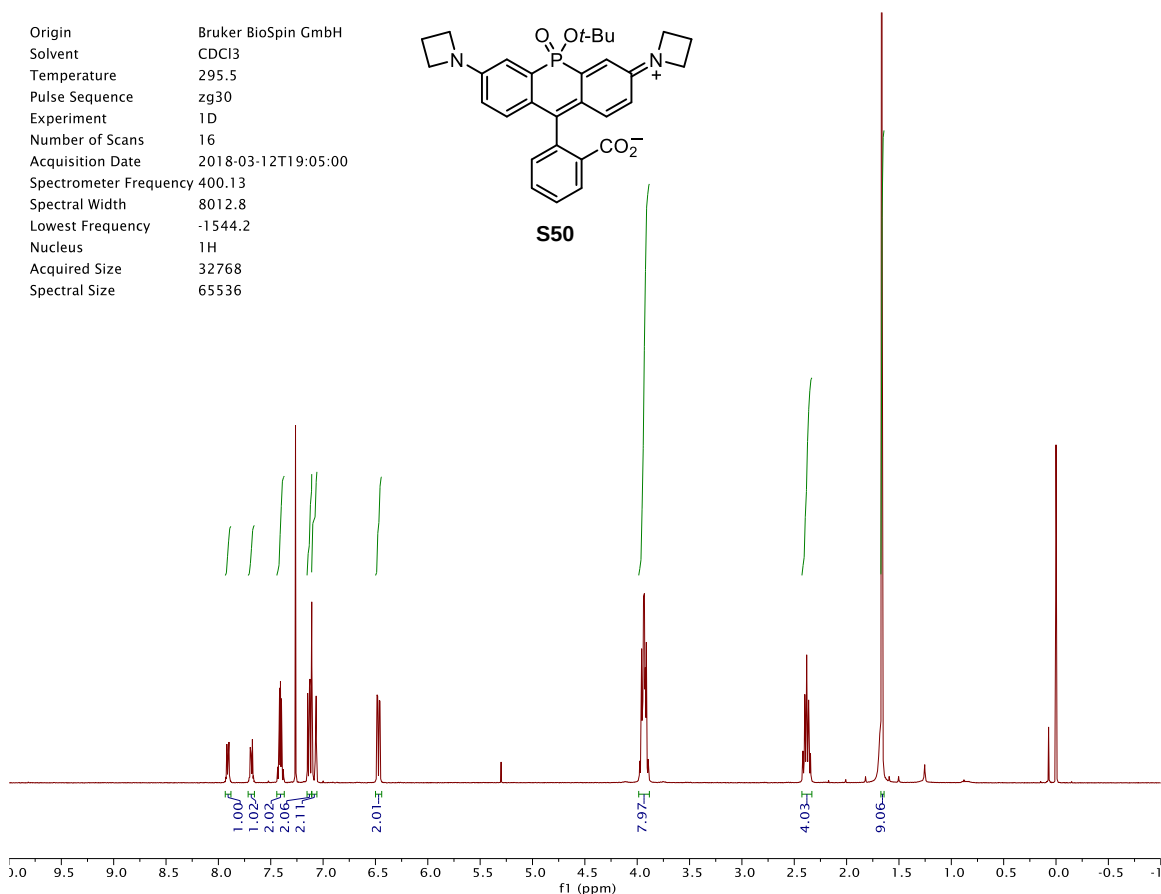
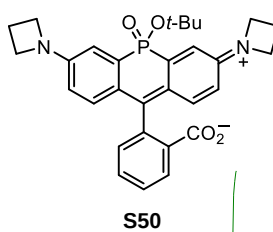




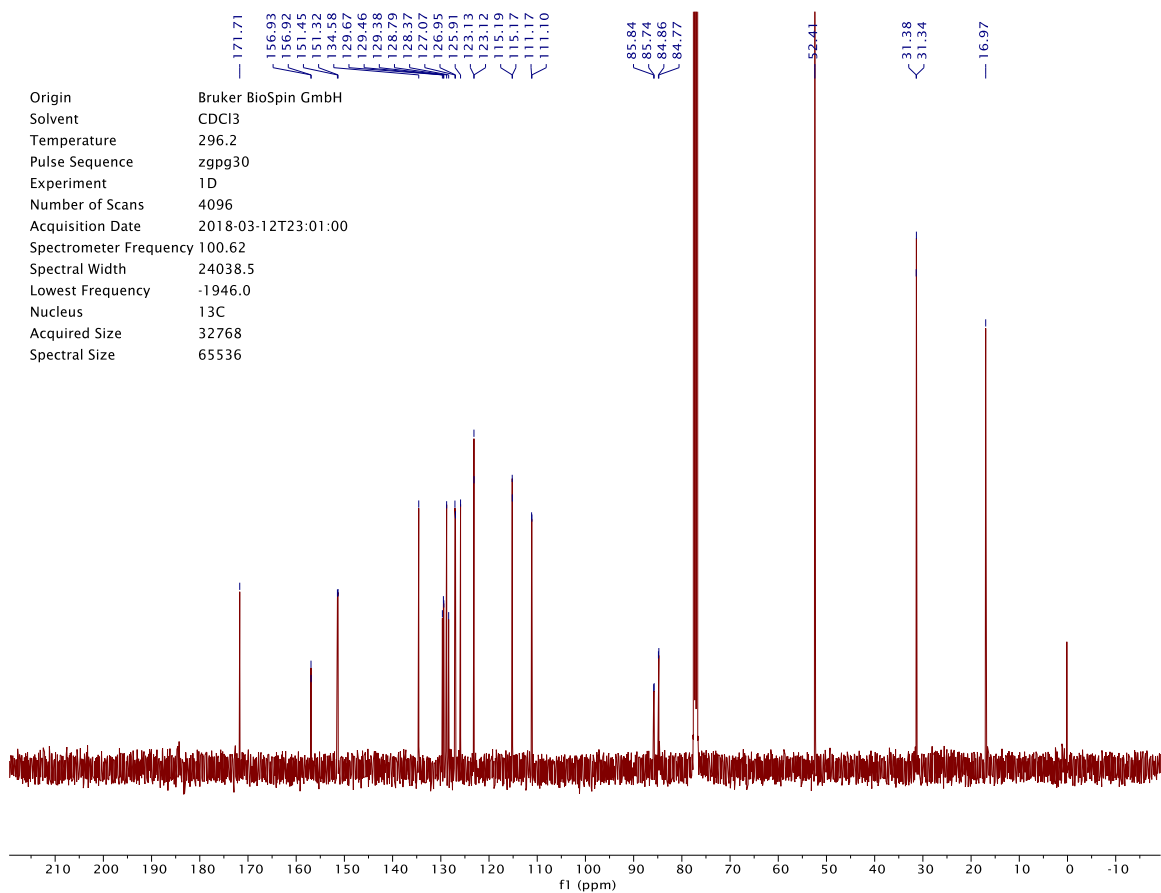
8

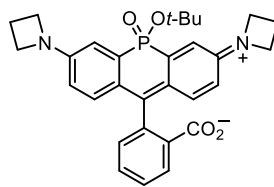


Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 295.5
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-03-12T19:05:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1544.2
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536

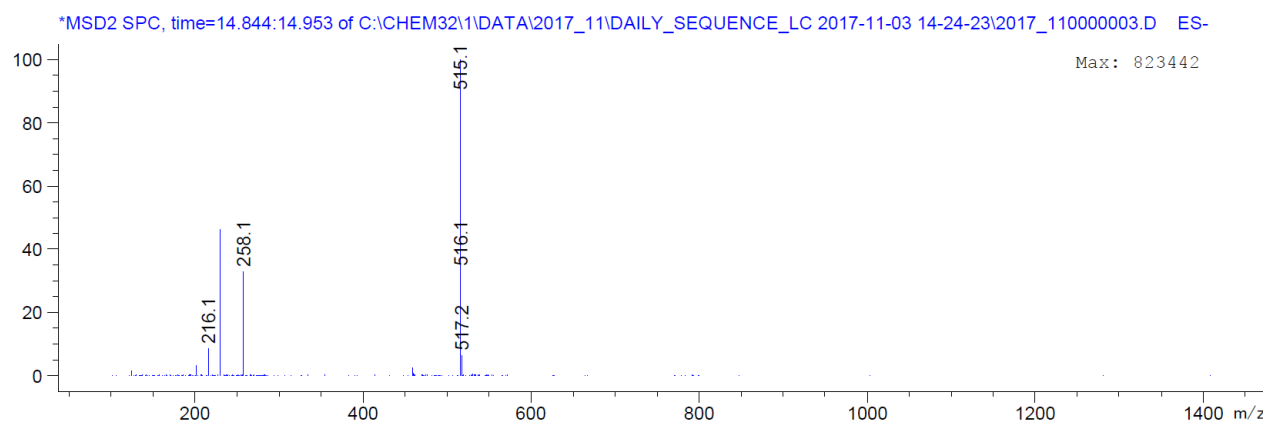
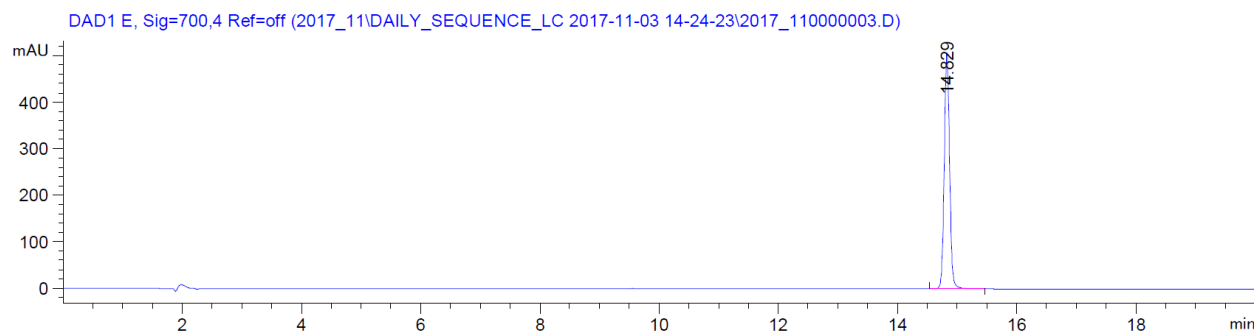


Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 296.2
 Pulse Sequence: zgpg30
 Experiment: 1D
 Number of Scans: 4096
 Acquisition Date: 2018-03-12T23:01:00
 Spectrometer Frequency: 100.62
 Spectral Width: 24038.5
 Lowest Frequency: -1946.0
 Nucleus: ¹³C
 Acquired Size: 32768
 Spectral Size: 65536

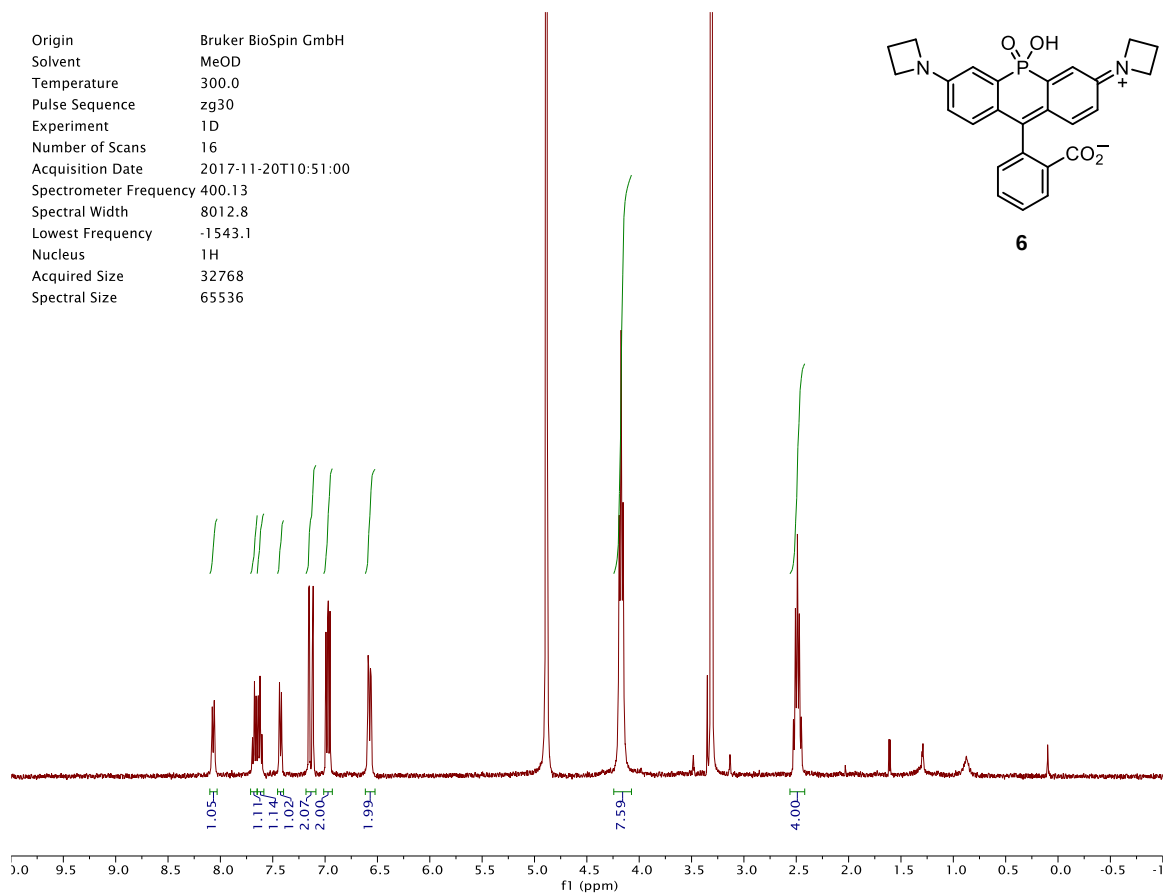
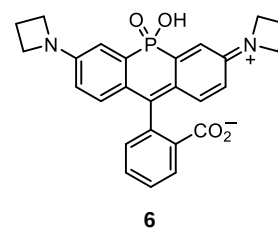




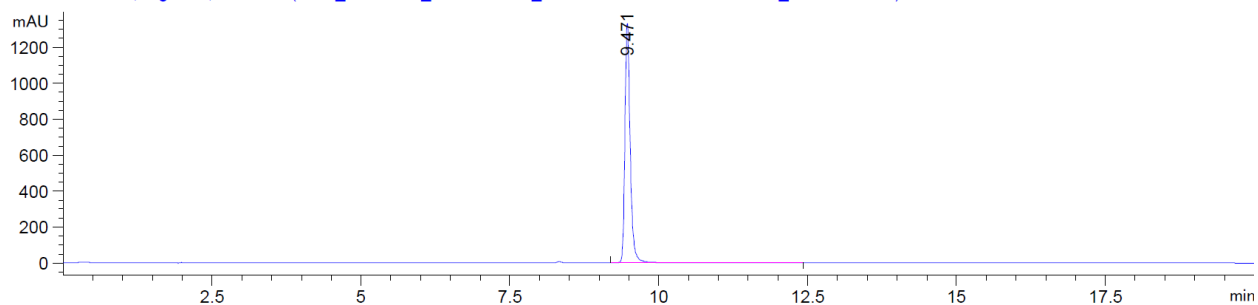
S50



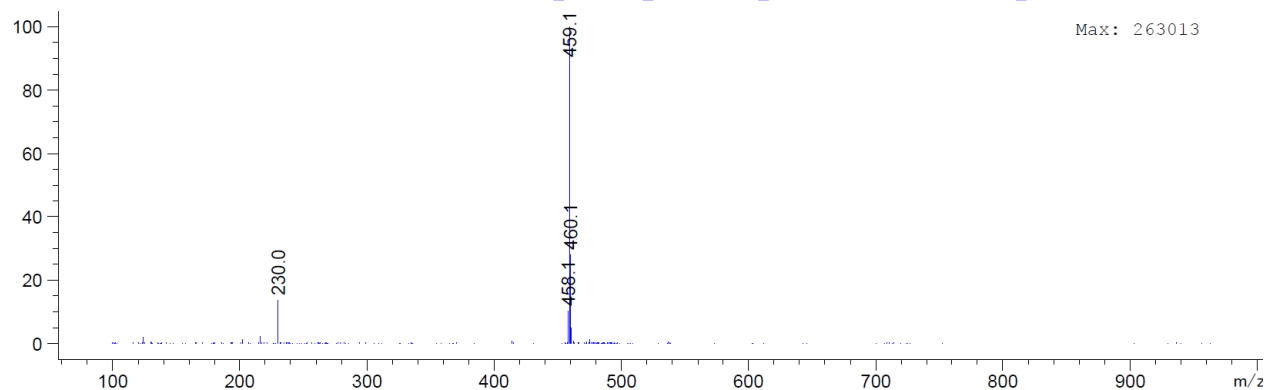
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2017-11-20T10:51:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.1
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



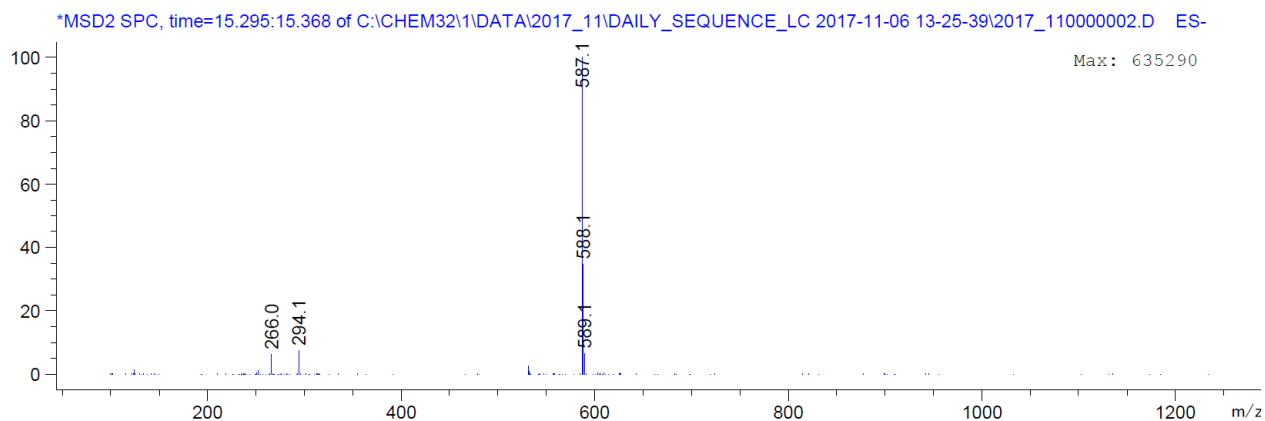
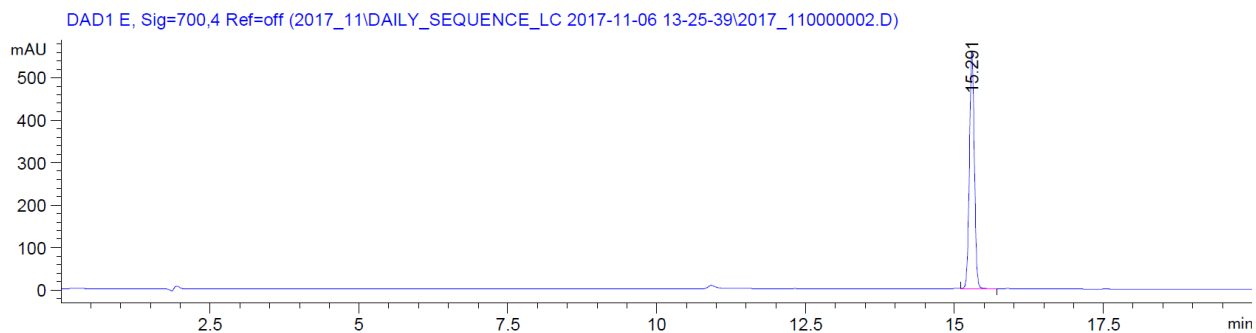
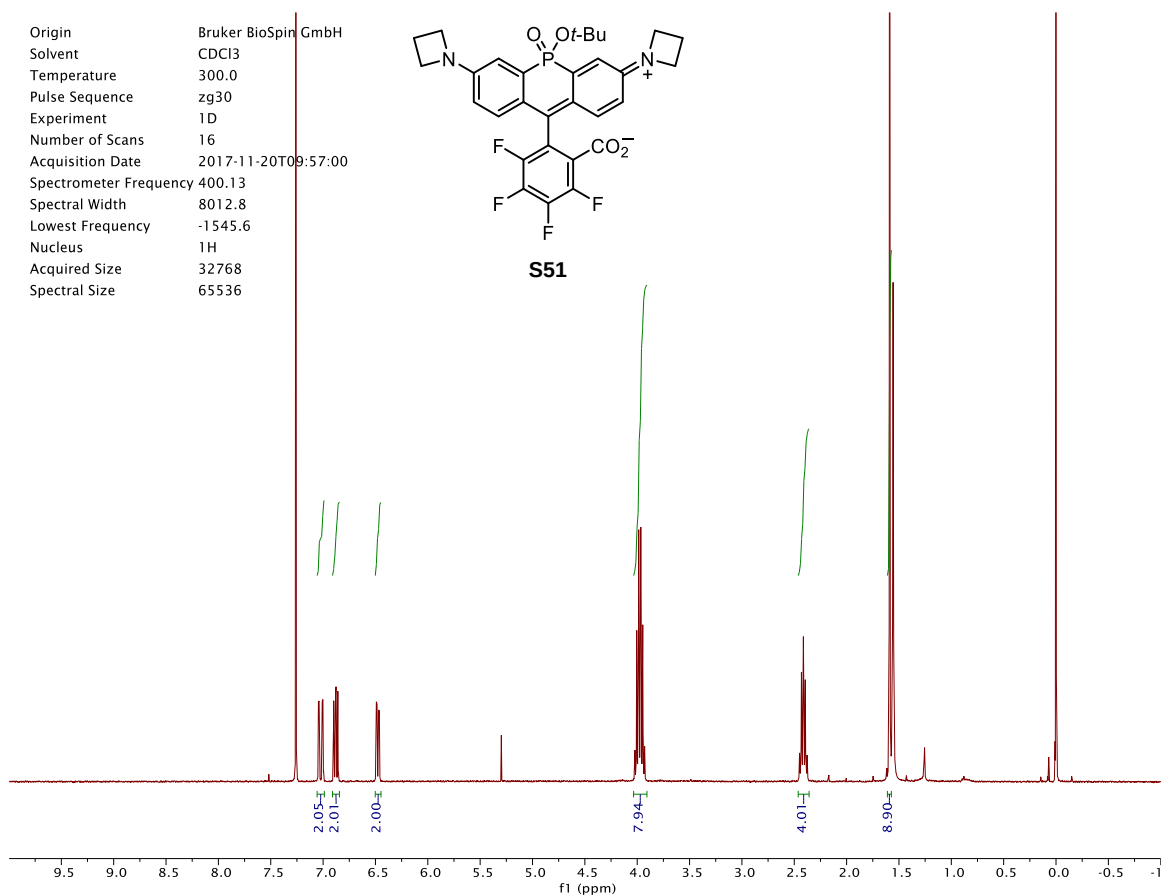
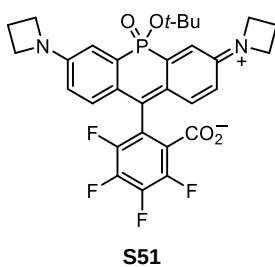
DAD1 E, Sig=675,4 Ref=off (2017_11\DAIY_SEQUENCE_LC 2017-11-16 13-39-31\2017_110000003.D)



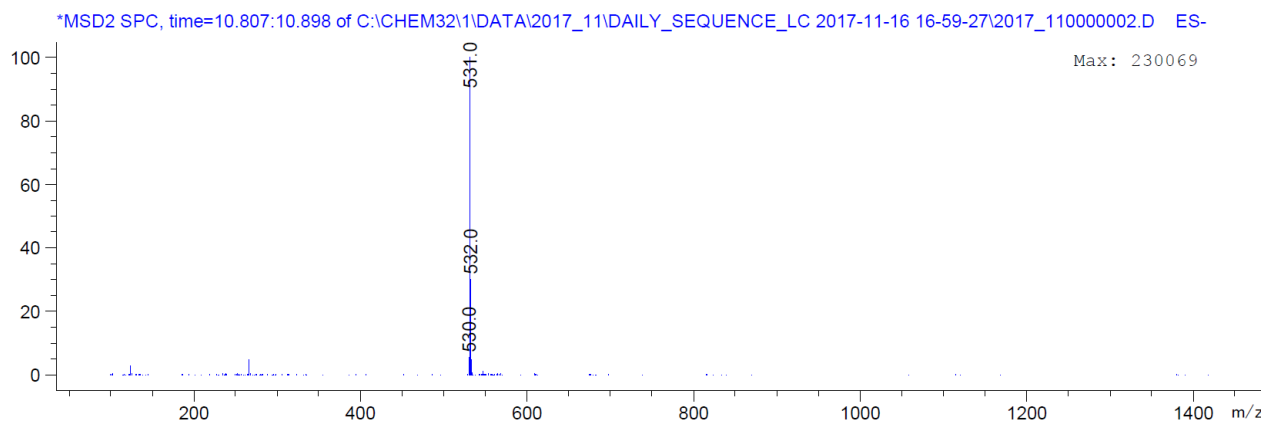
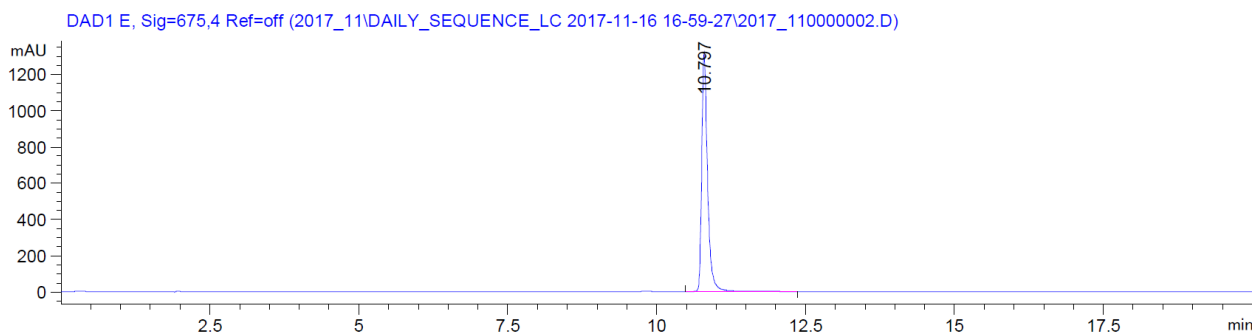
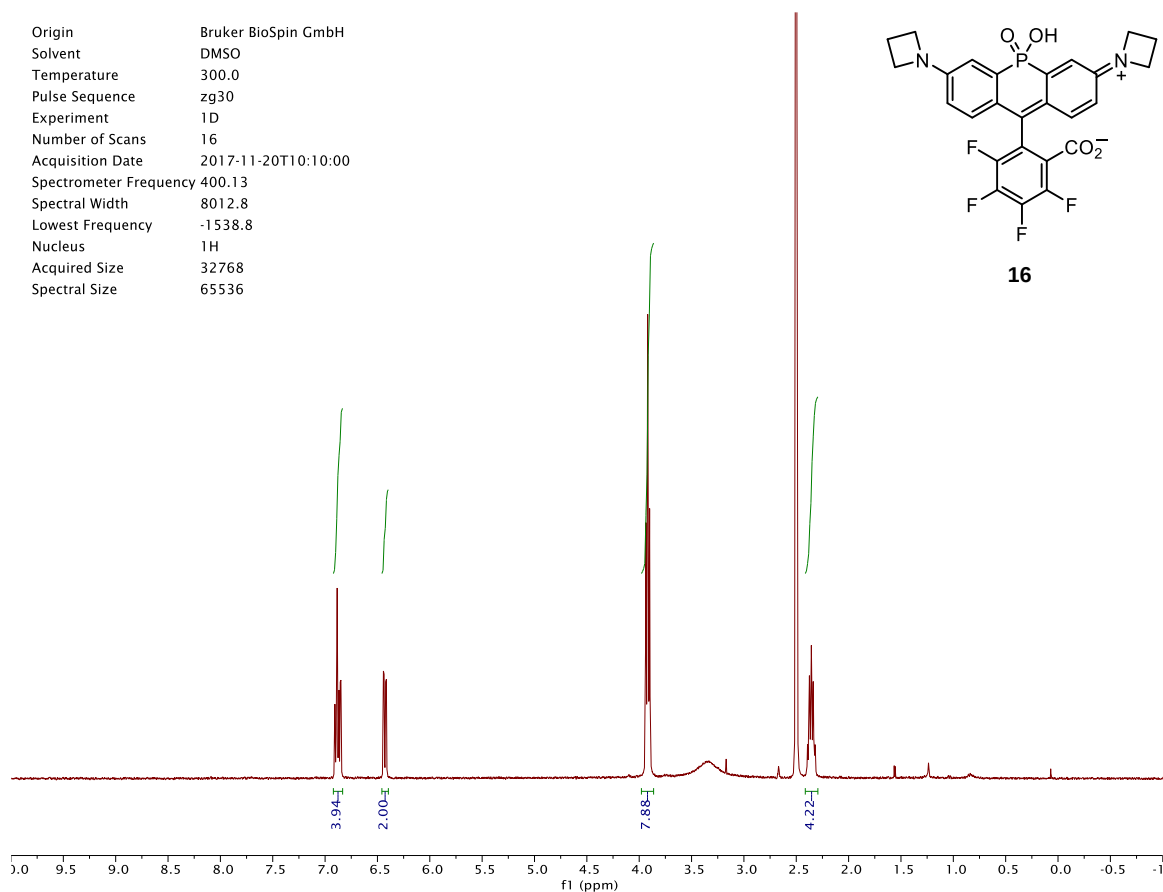
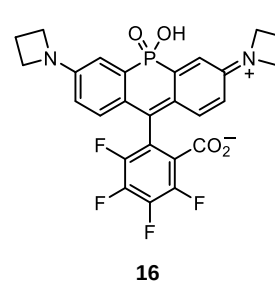
*MSD2 SPC, time=9.499:9.608 of C:\CHEM32\1\DATA\2017_11\DAIY_SEQUENCE_LC 2017-11-16 13-39-31\2017_110000003.D ES-AP



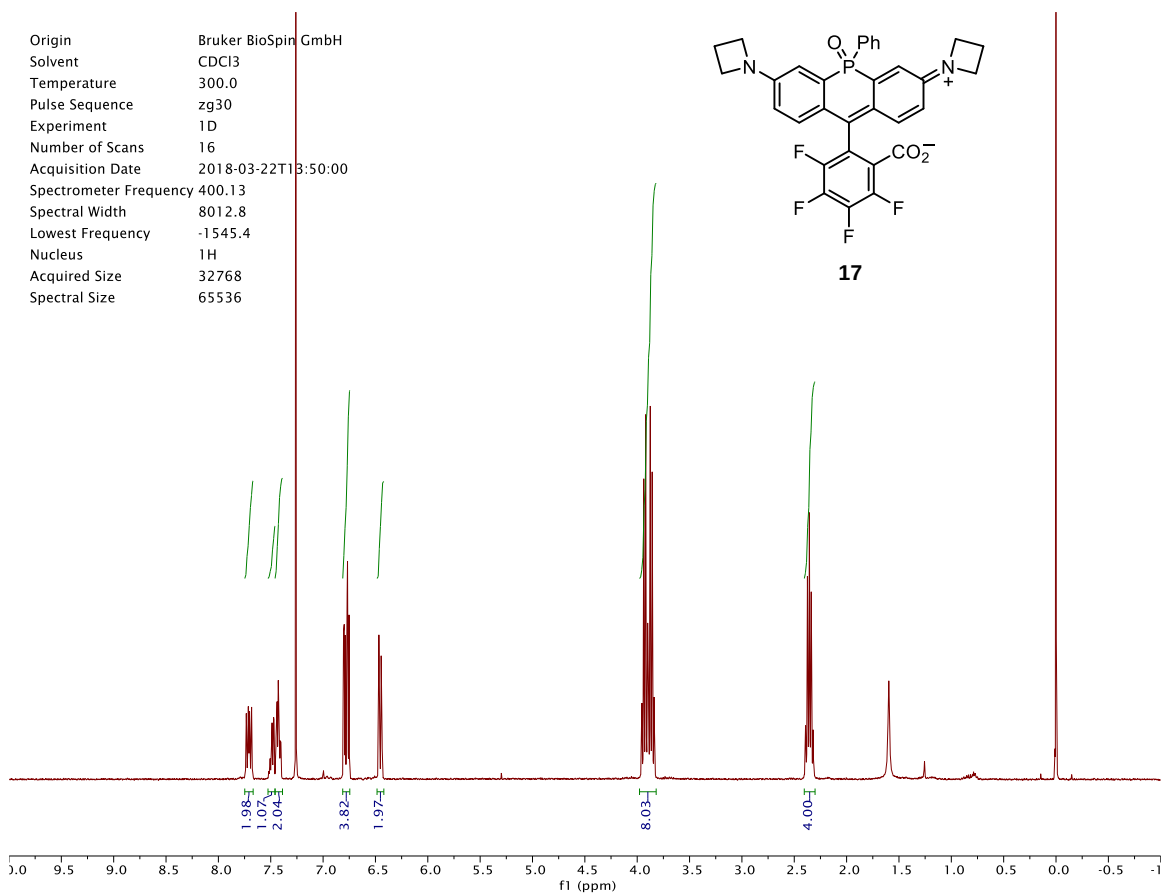
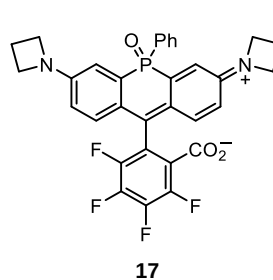
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2017-11-20T09:57:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.6
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



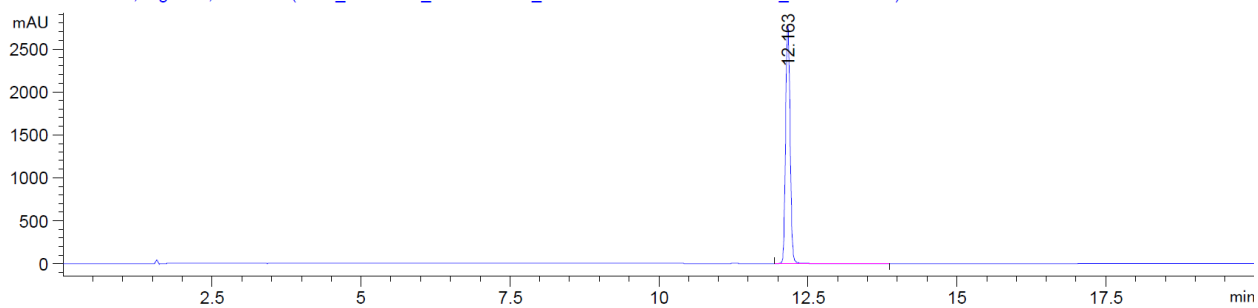
Origin: Bruker BioSpin GmbH
 Solvent: DMSO
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2017-11-20T10:10:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1538.8
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536



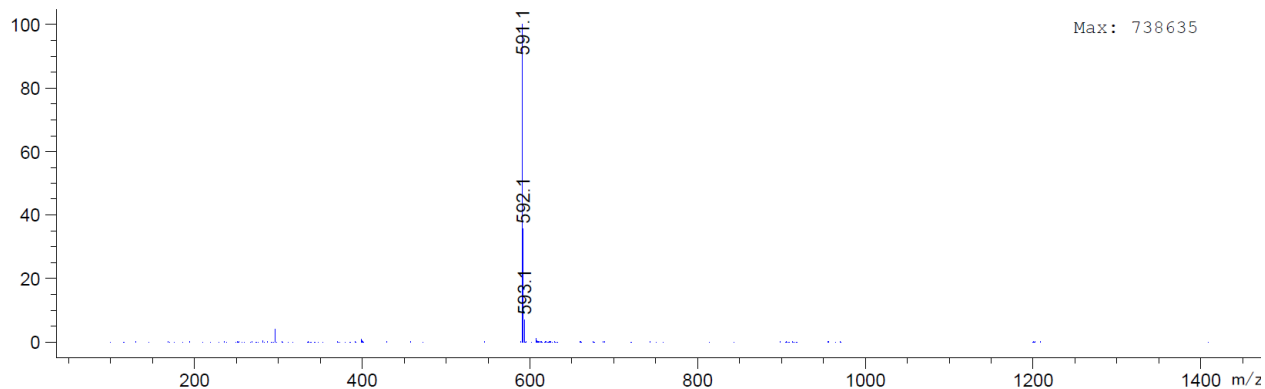
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-03-22T13:50:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.4
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



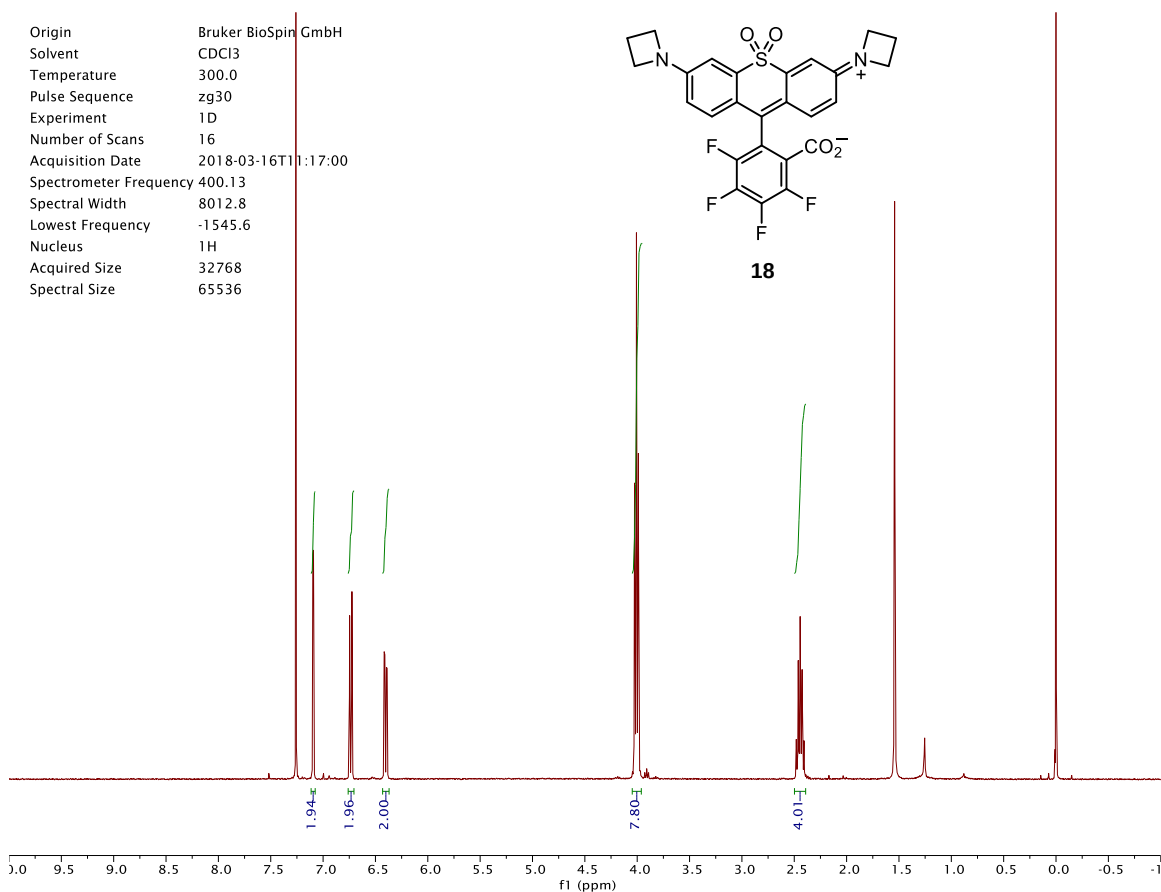
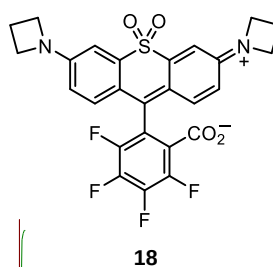
DAD1 E, Sig=725,4 Ref=off (2018_03\DAIY_SEQUENCE_LC 2018-03-20 12-54-56\2018_030000004.D)



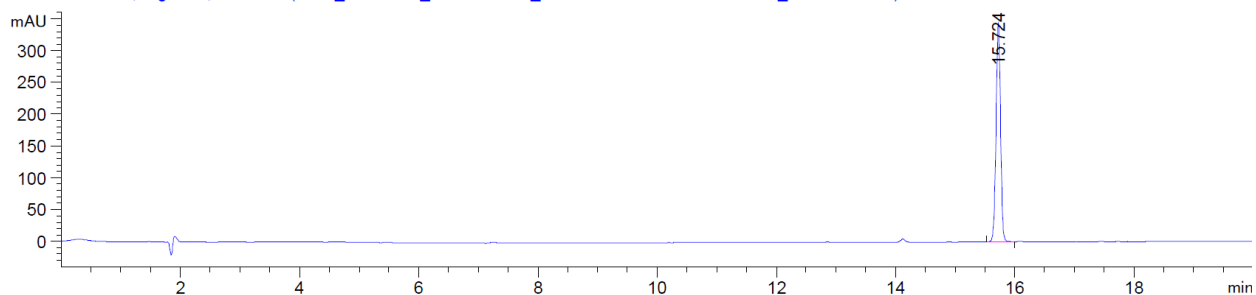
*MSD2 SPC, time=12.173:12.264 of C:\CHEM32\1\DATA\2018_03\DAIY_SEQUENCE_LC 2018-03-20 12-54-56\2018_030000004.D ES-



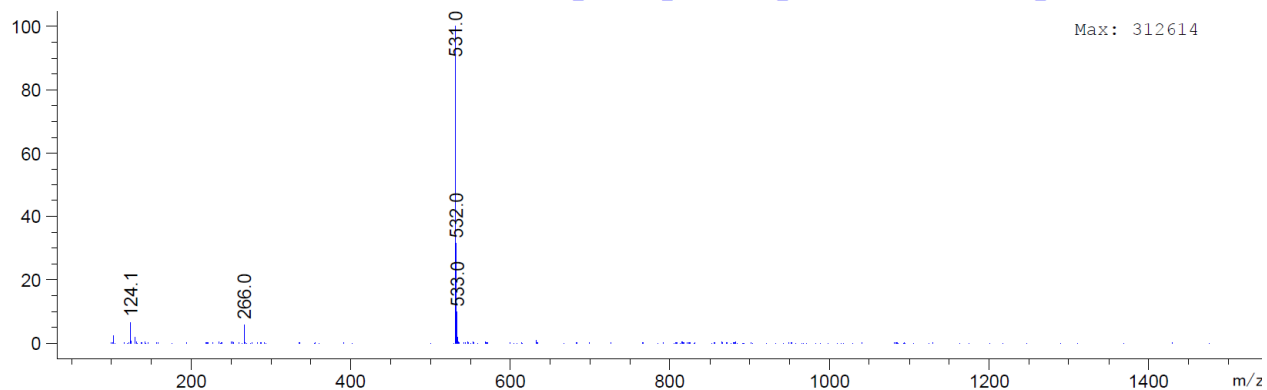
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-03-16T11:17:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.6
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



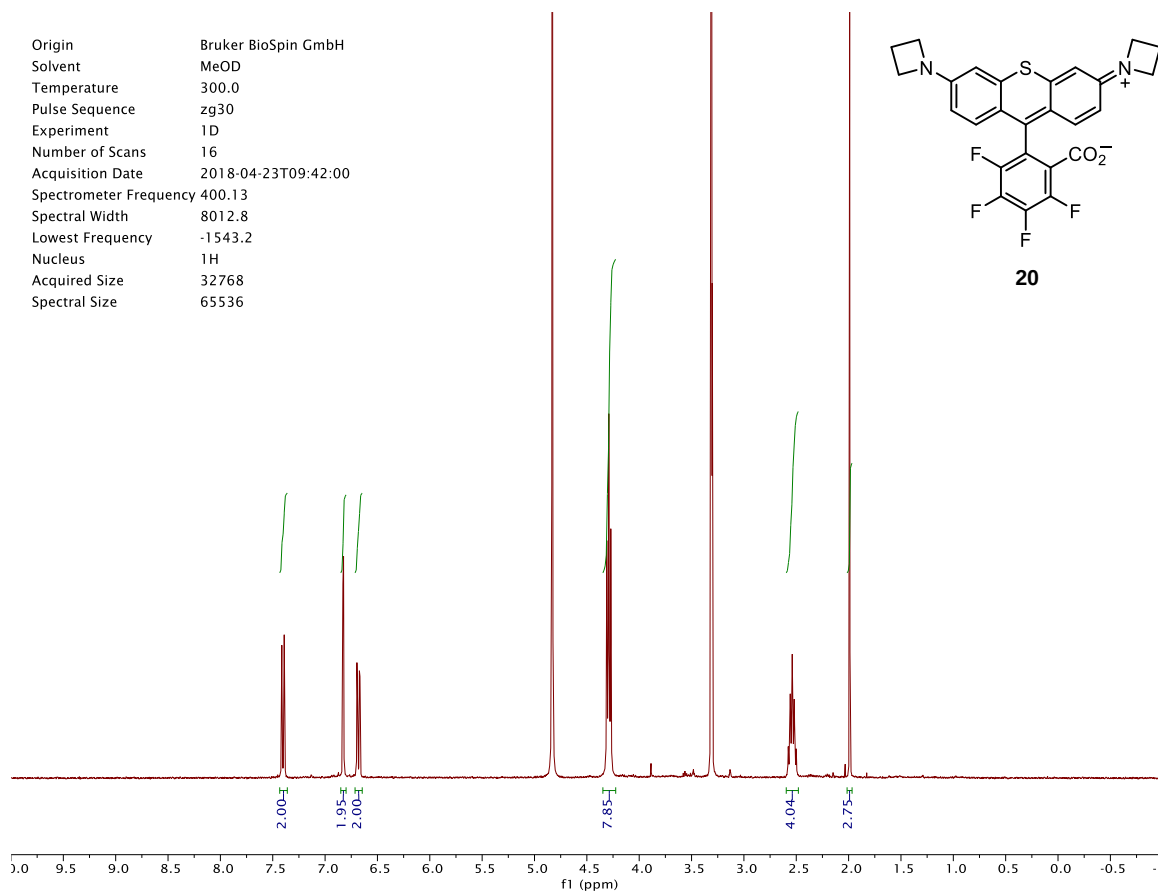
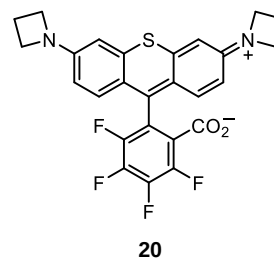
DAD1 C, Sig=280,4 Ref=off (2017_12\DAI\SEQUENCE_LC 2017-12-18 10-10-23\2017_120000004.D)



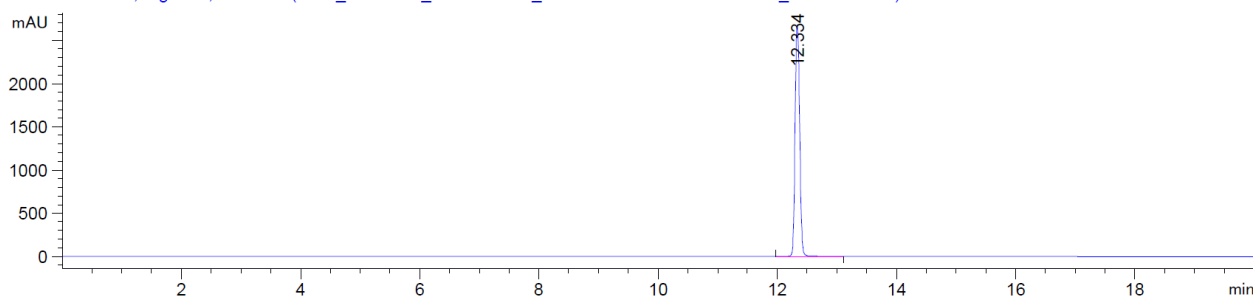
*MSD2 SPC, time=15.713:15.786 of C:\CHEM32\1\DATA\2017_12\DAI\SEQUENCE_LC 2017-12-18 10-10-23\2017_120000004.D ES-



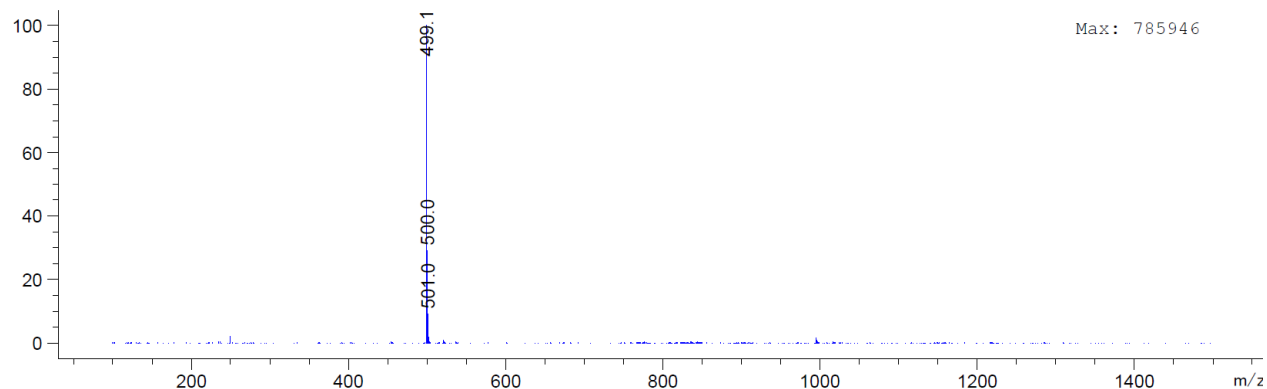
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-04-23T09:42:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.2
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536



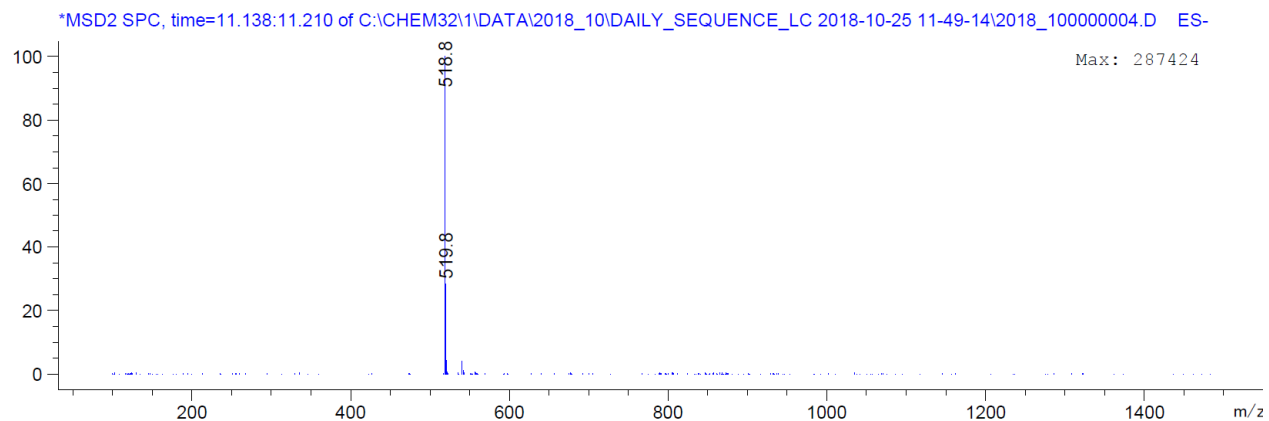
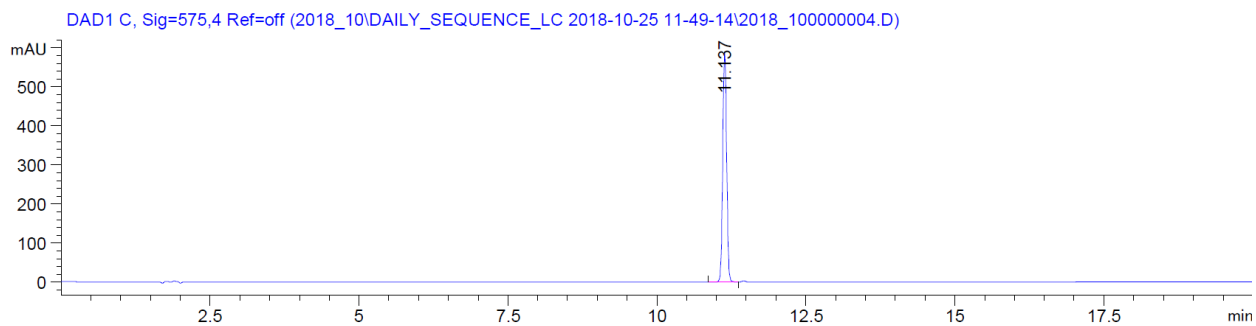
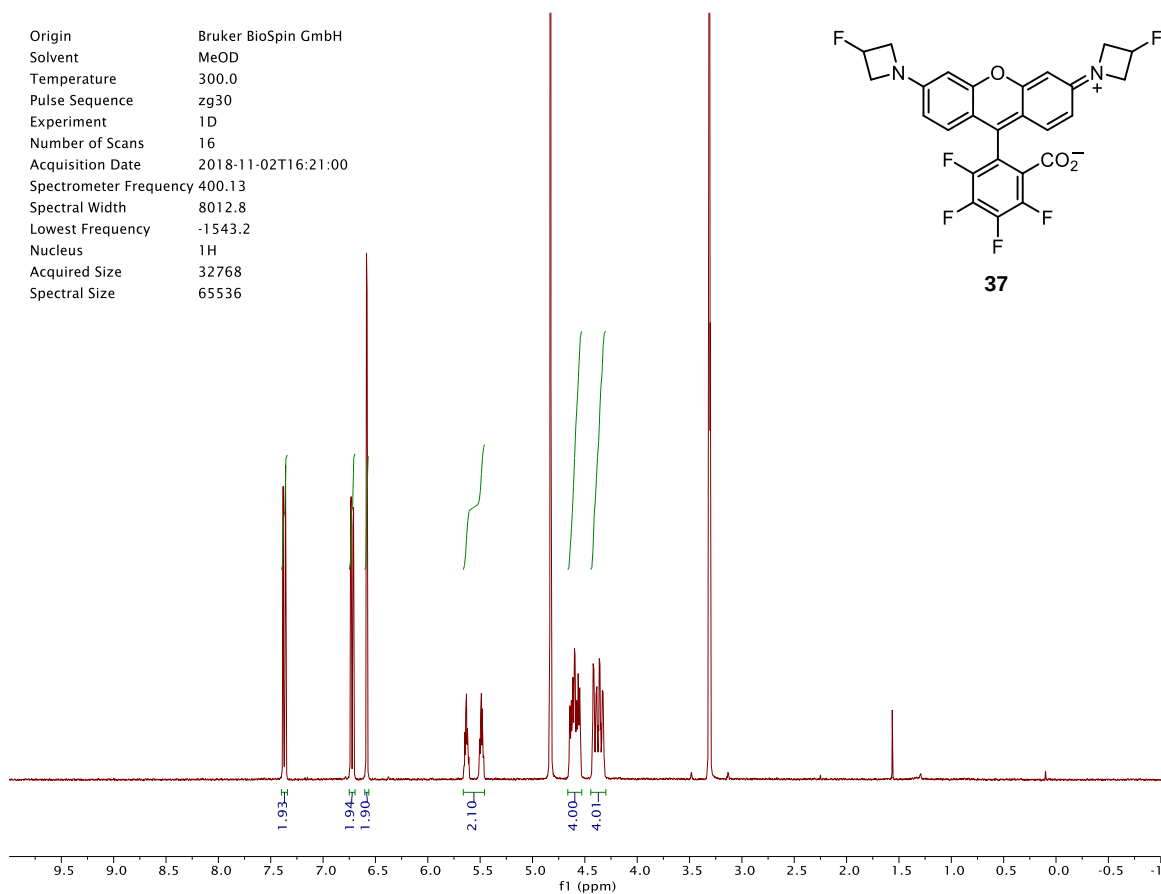
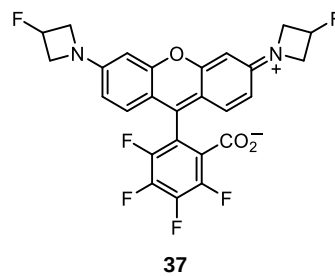
DAD1 D, Sig=600,4 Ref=off (2017_06\DAIY_SEQUENCE_LC 2017-06-07 13-59-58\2017_060000002.D)



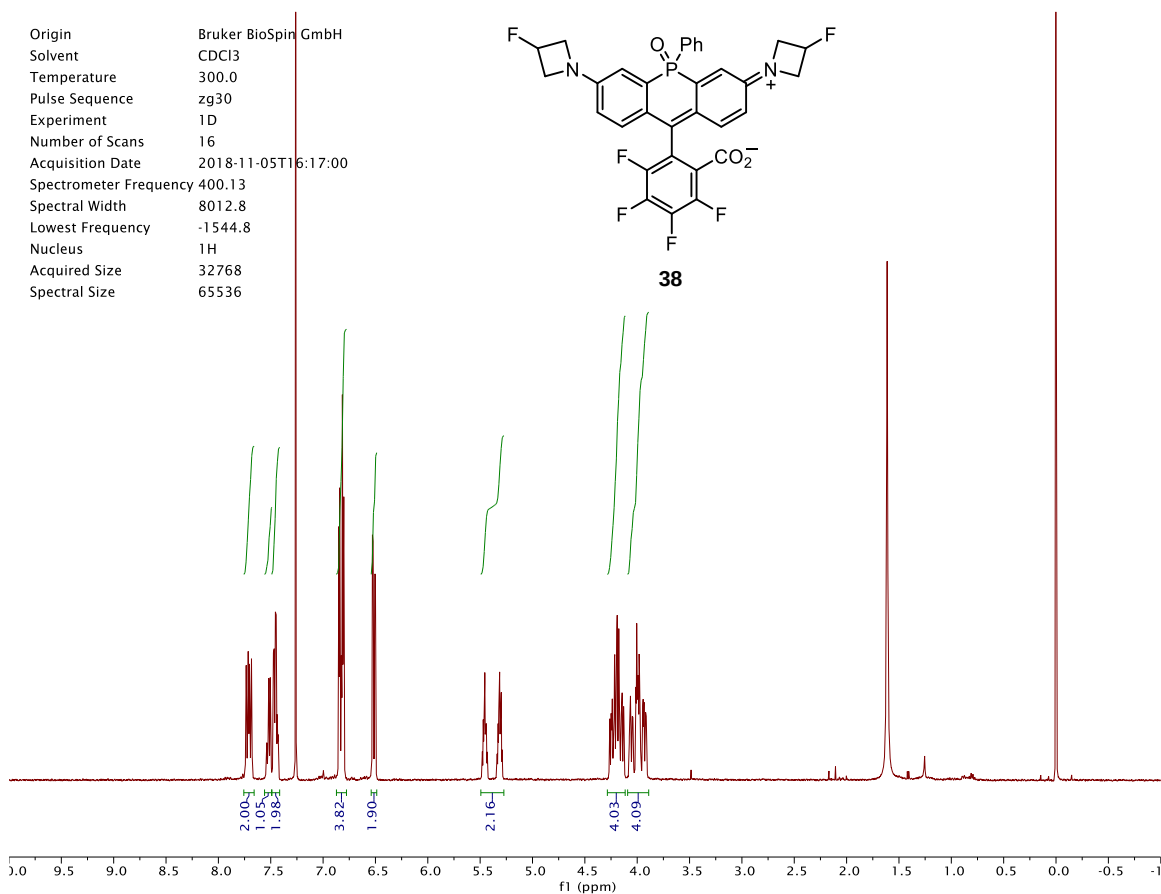
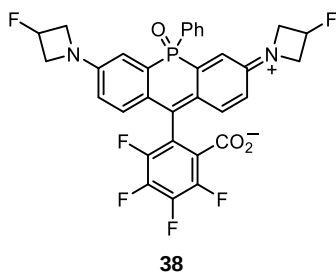
*MSD2 SPC, time=12.337:12.409 of C:\CHEM32\1\DATA\2017_06\DAIY_SEQUENCE_LC 2017-06-07 13-59-58\2017_060000002.D ES-



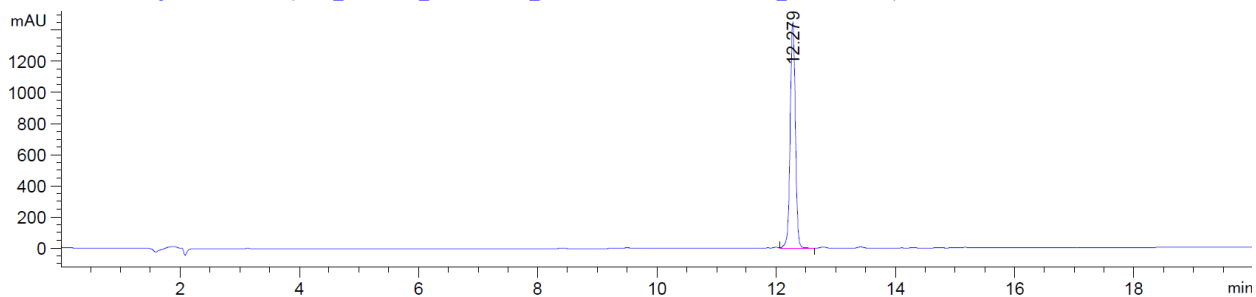
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-11-02T16:21:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.2
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536



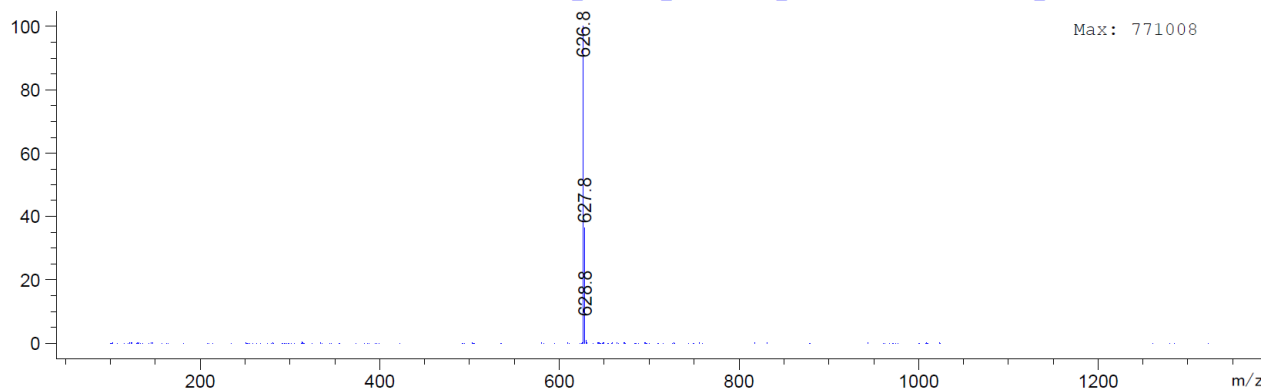
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-11-05T16:17:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1544.8
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



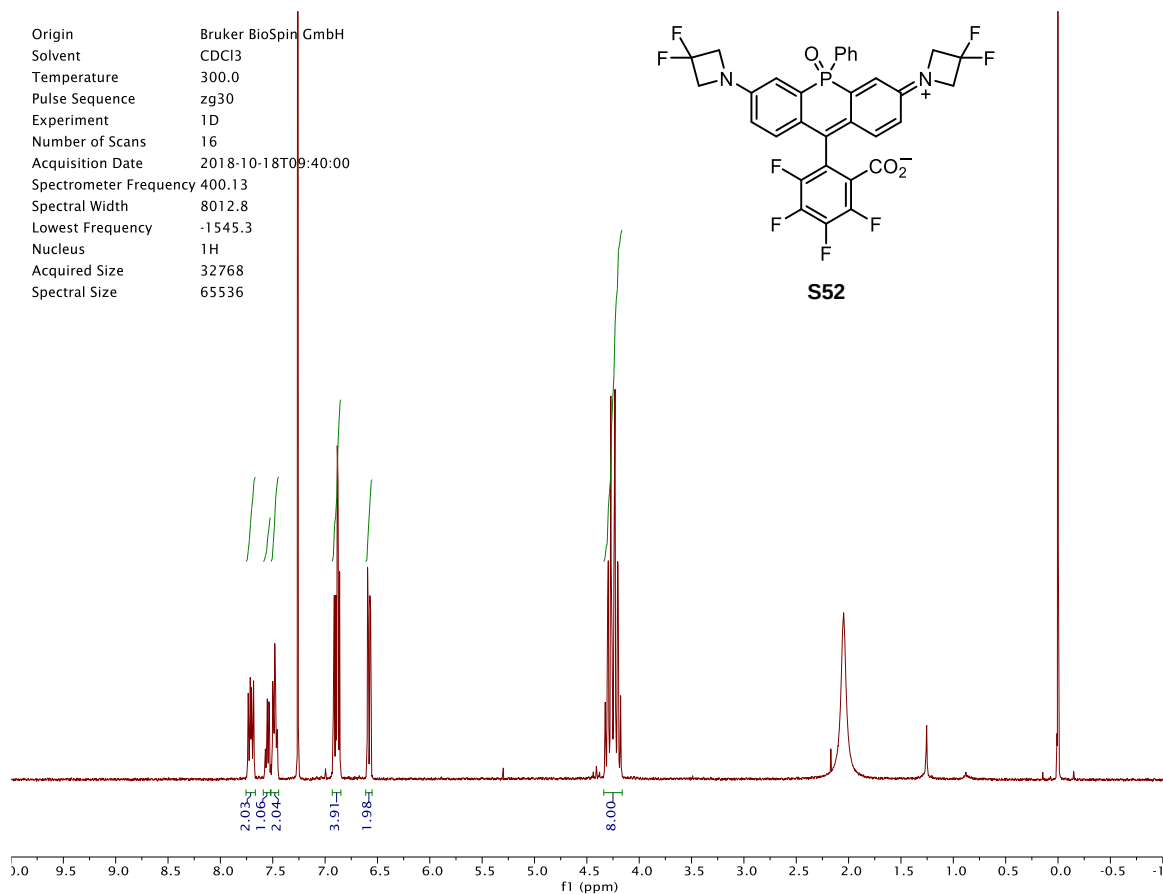
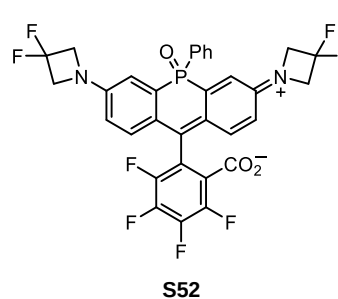
DAD1 A, Sig=254,4 Ref=off (2018_10\DAIY_SEQUENCE_LC 2018-10-16 12-45-58\2018_100000003.D)



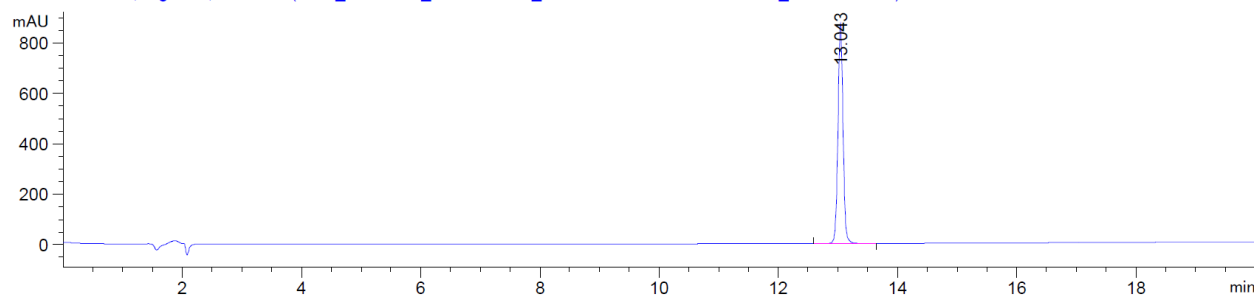
*MSD2 SPC, time=12.264:12.373 of C:\CHEM32\1\DATA\2018_10\DAIY_SEQUENCE_LC 2018-10-16 12-45-58\2018_100000003.D ES-



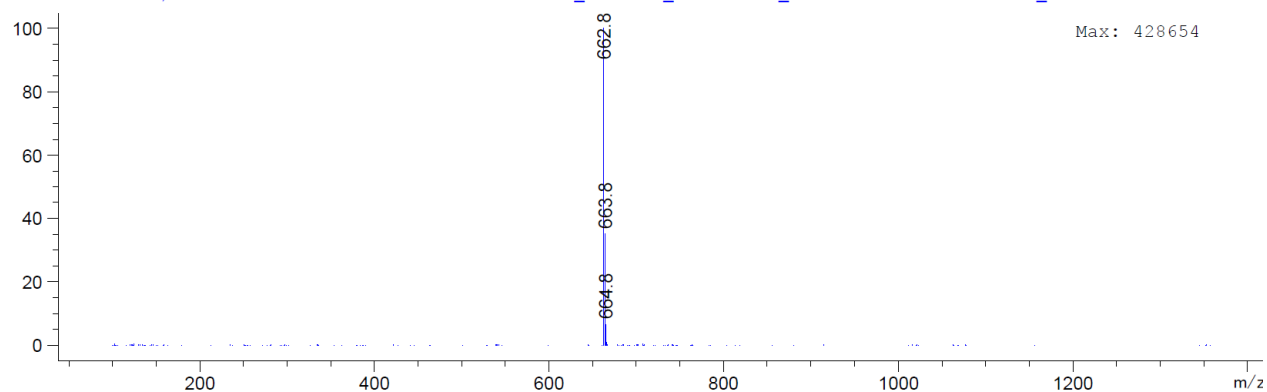
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-10-18T09:40:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.3
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



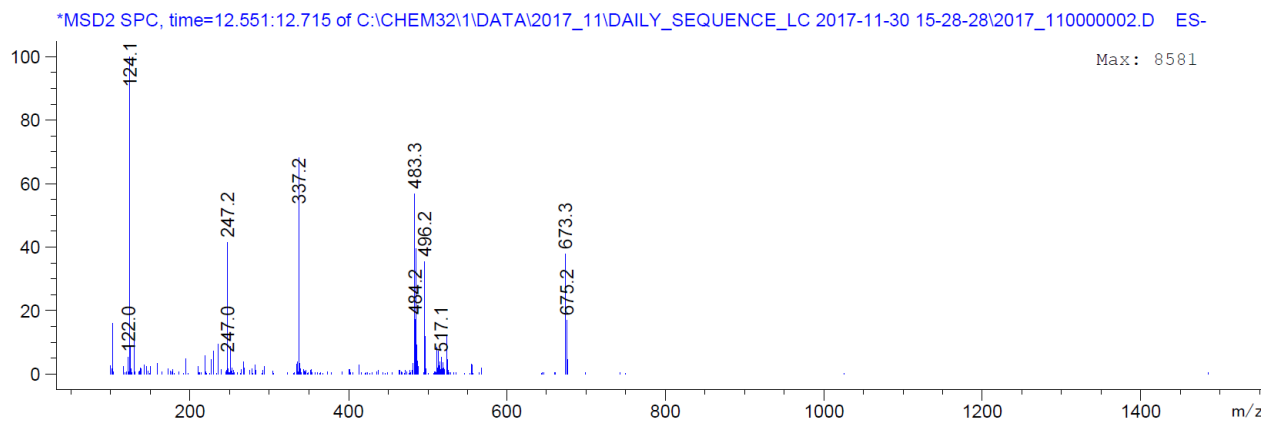
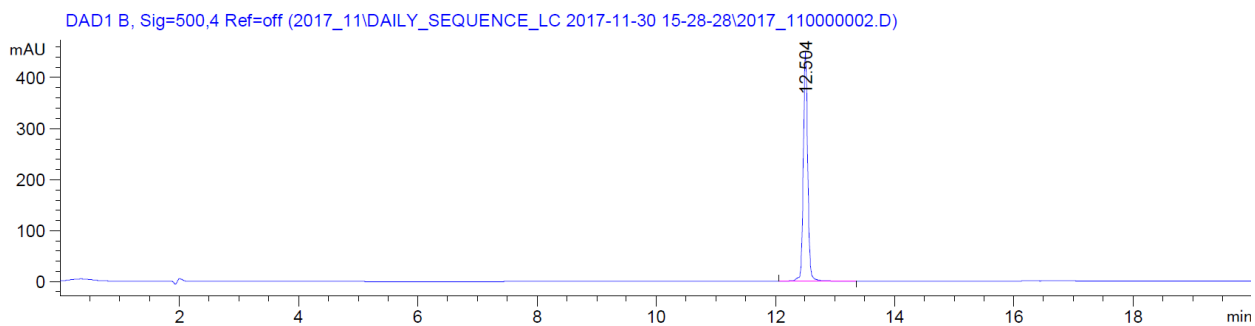
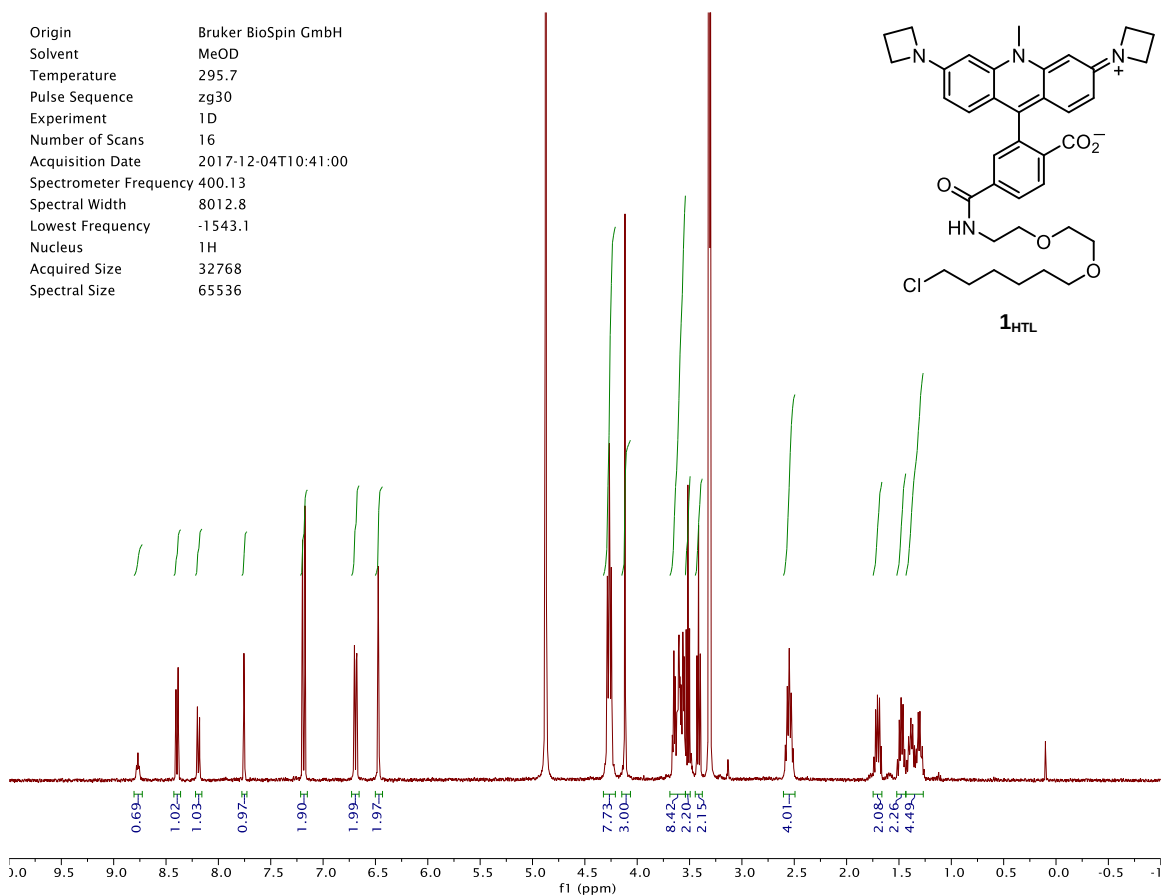
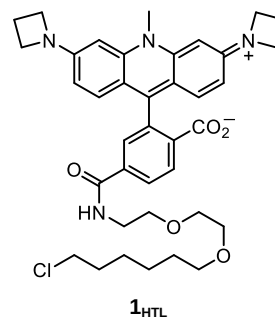
DAD1 A, Sig=254,4 Ref=off (2018_10\DAIY_SEQUENCE_LC 2018-10-17 10-37-24\2018_100000003.D)



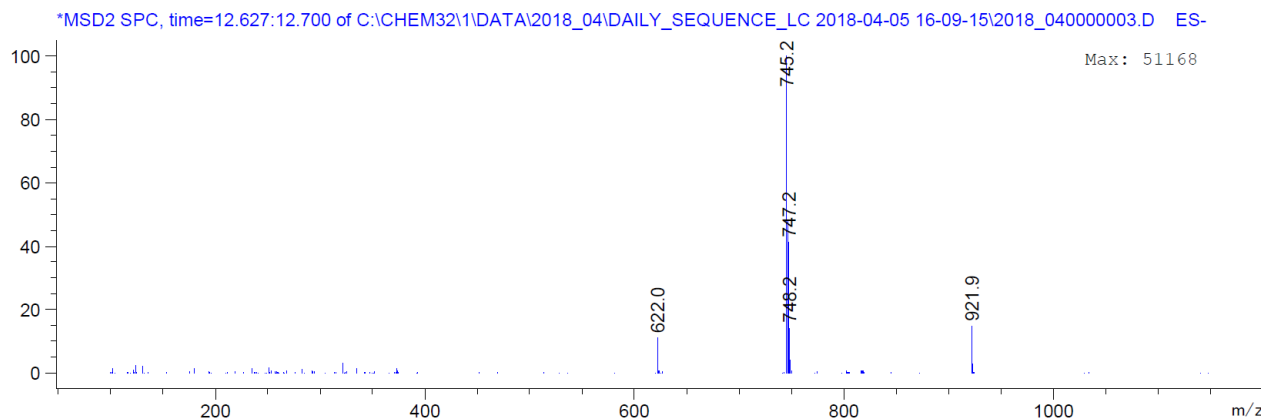
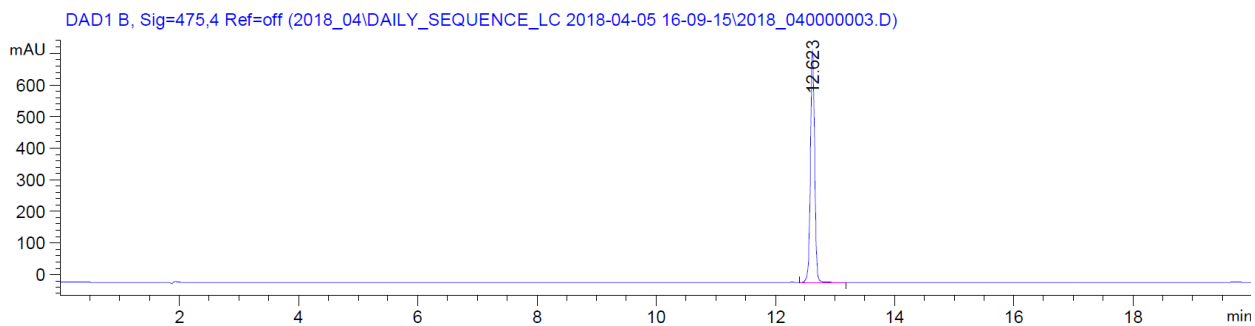
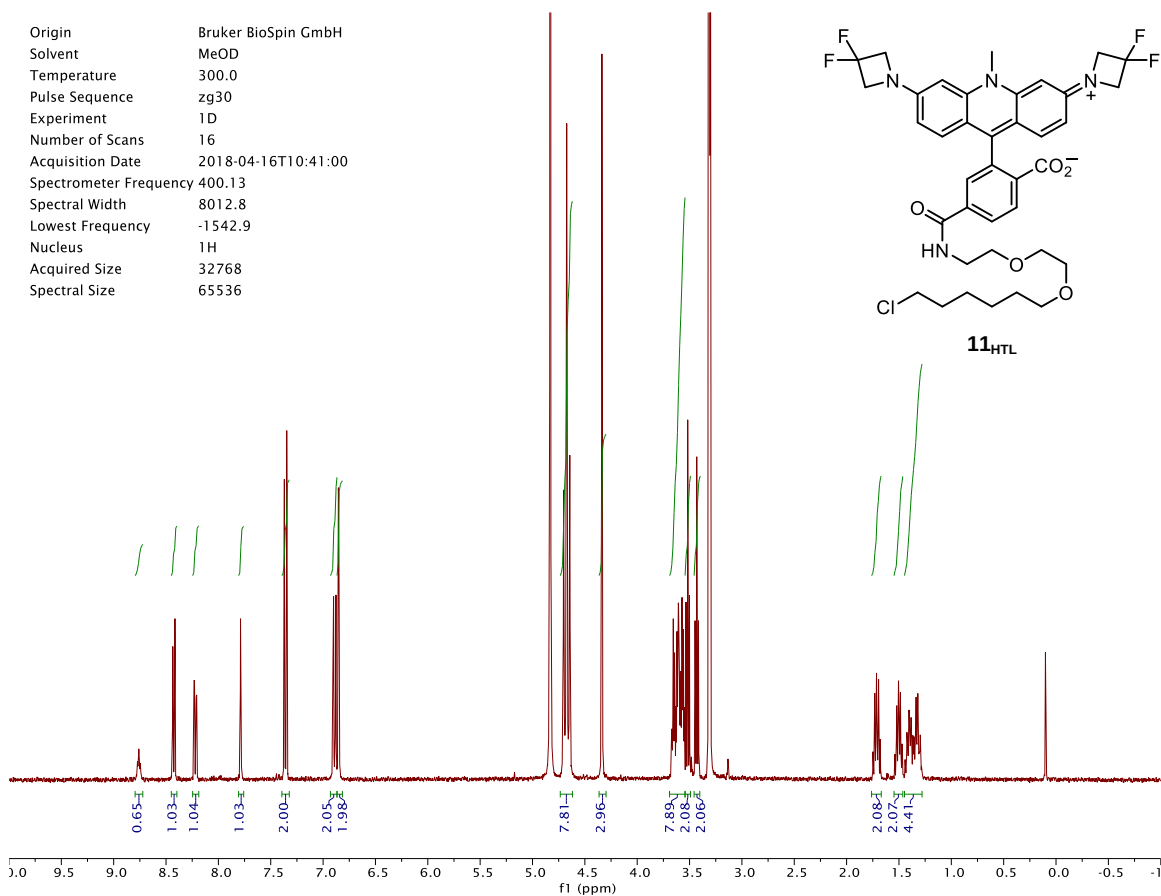
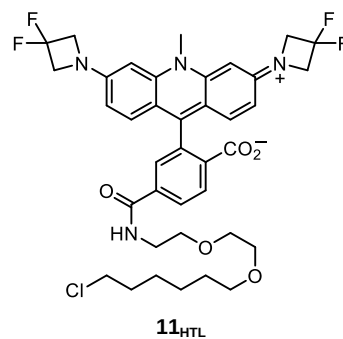
*MSD2 SPC, time=13.027:13.136 of C:\CHEM32\1\DATA\2018_10\DAIY_SEQUENCE_LC 2018-10-17 10-37-24\2018_100000003.D ES-



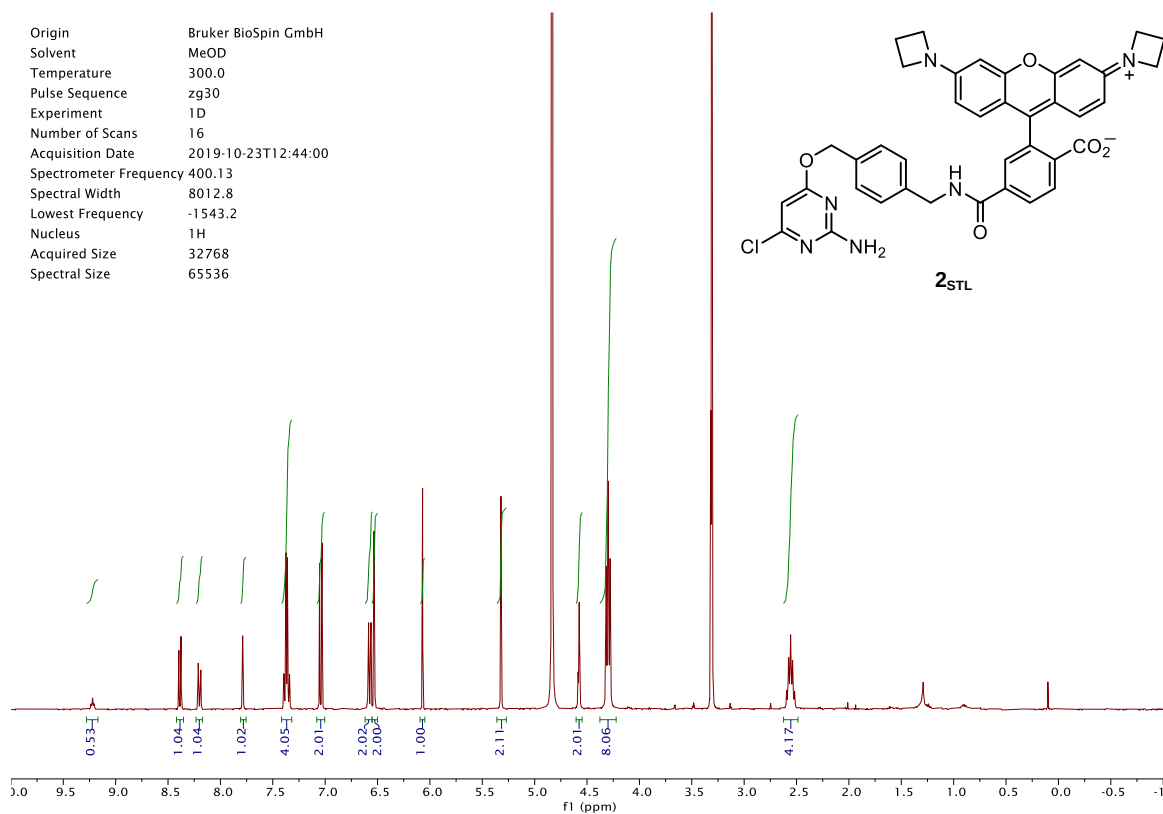
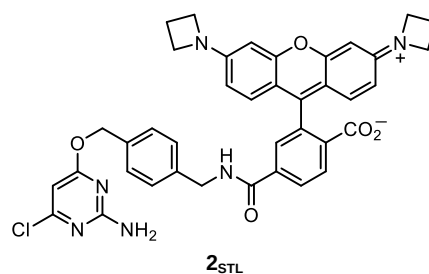
Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 295.7
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2017-12-04T10:41:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.1
 Nucleus ^1H
 Acquired Size 32768
 Spectral Size 65536



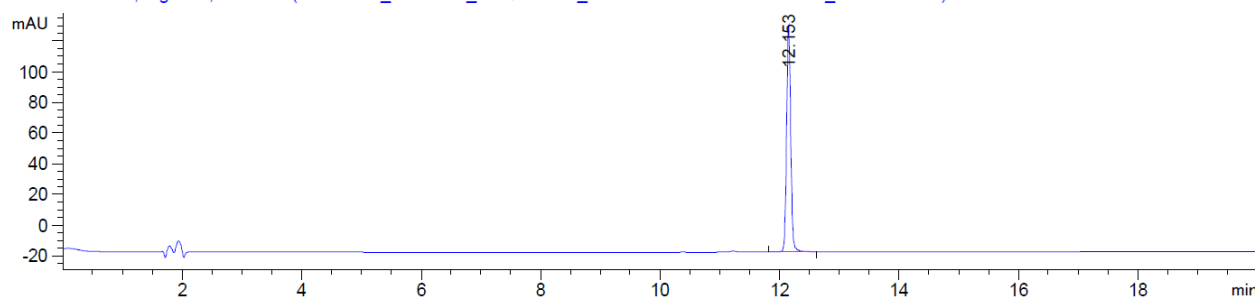
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-04-16T10:41:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1542.9
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



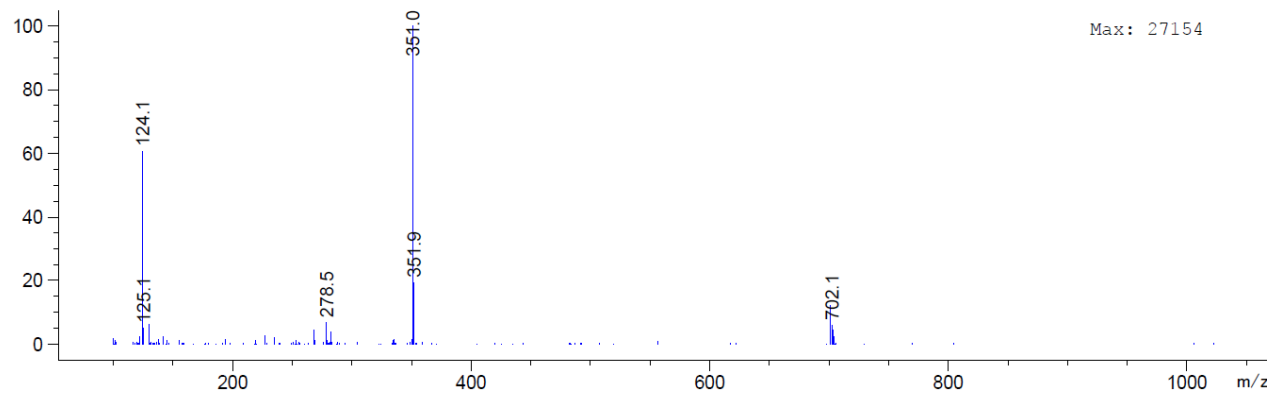
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2019-10-23T12:44:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.2
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



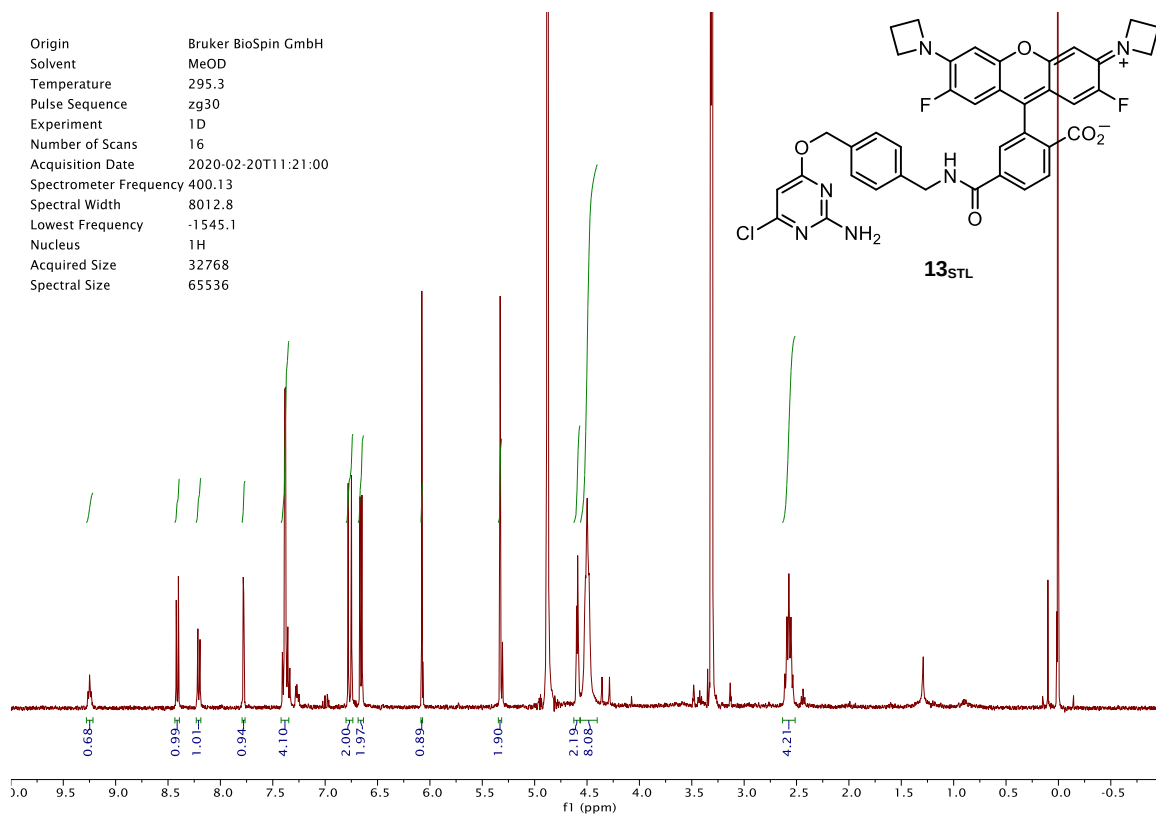
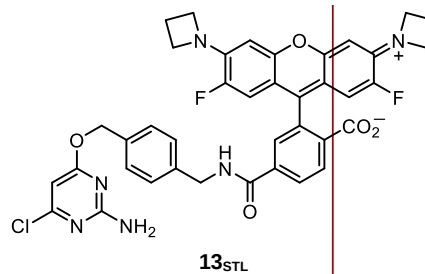
DAD1 C, Sig=550.4 Ref=off (2017\2017_11\DAILY_SEQUENCE_LC 2017-11-03 14-24-23\2017_110000004.D)



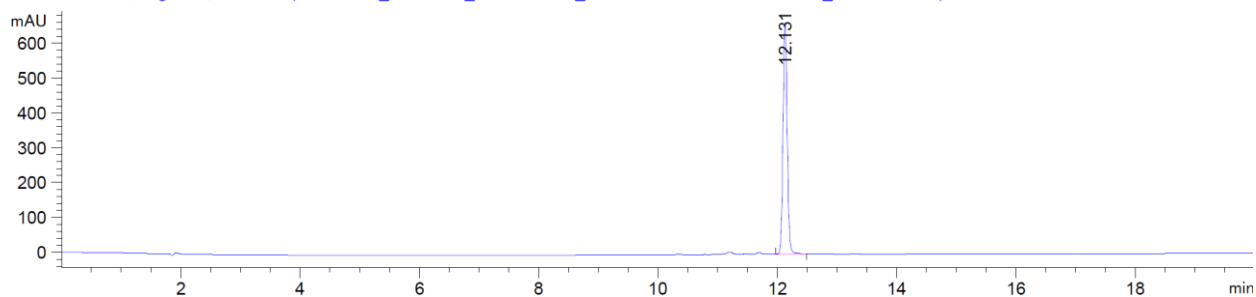
*MSD2 SPC, time=12.191:12.282 of C:\CHEM32\1\DATA\2017\2017_11\DAILY_SEQUENCE_LC 2017-11-03 14-24-23\2017_110000004.D



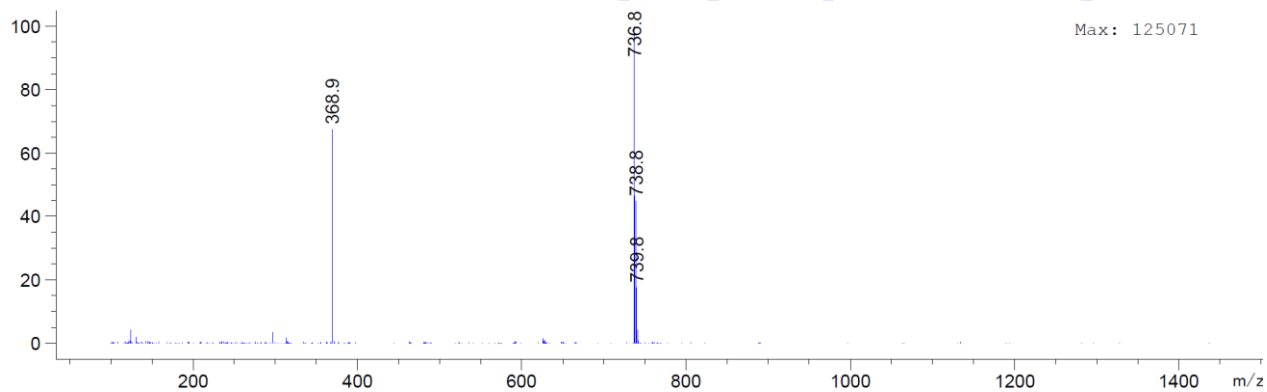
Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 295.3
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2020-02-20T11:21:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.1
 Nucleus ^1H
 Acquired Size 32768
 Spectral Size 65536



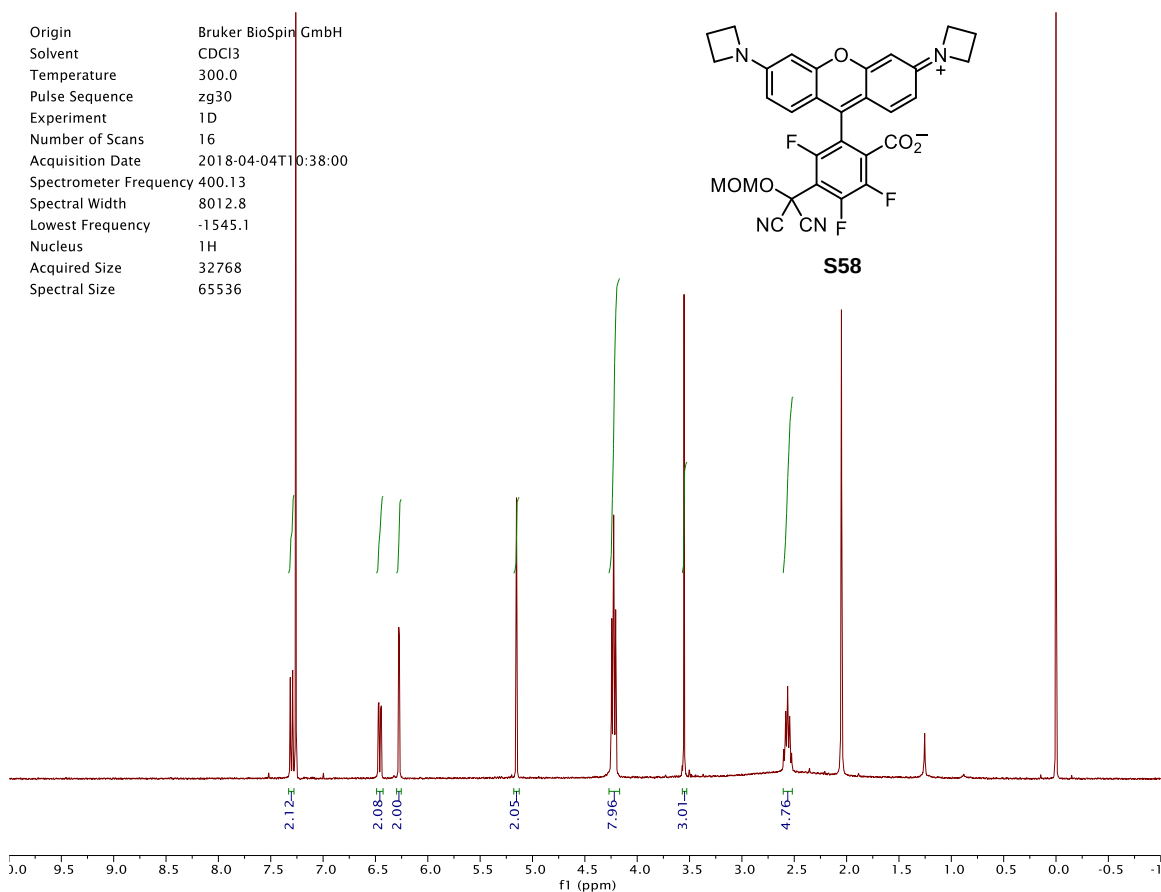
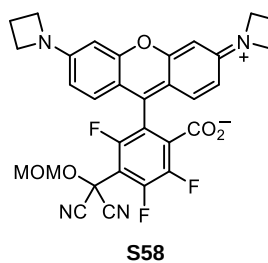
DAD1 C, Sig=550.4 Ref=off (2018\2018_12\DAIY_SEQUENCE_LC 2018-12-14 17-08-21\2018_120000001.D)



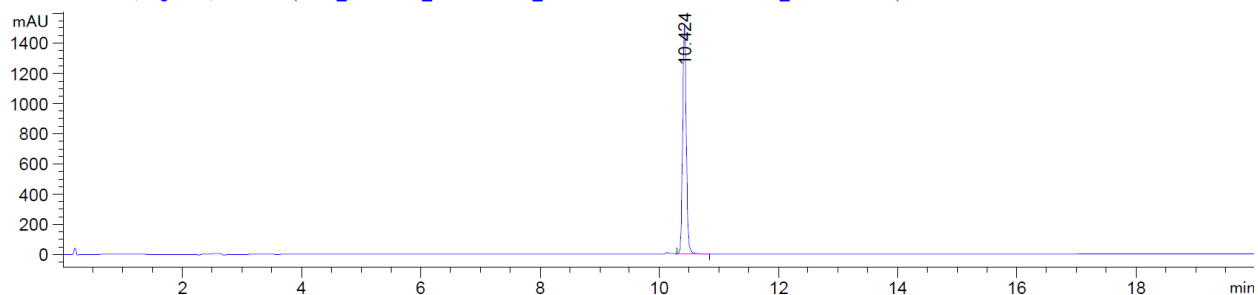
*MSD2 SPC, time=12.101:12.246 of C:\CHEM32\1\DATA\2018\2018_12\DAIY_SEQUENCE_LC 2018-12-14 17-08-21\2018_120000001.D



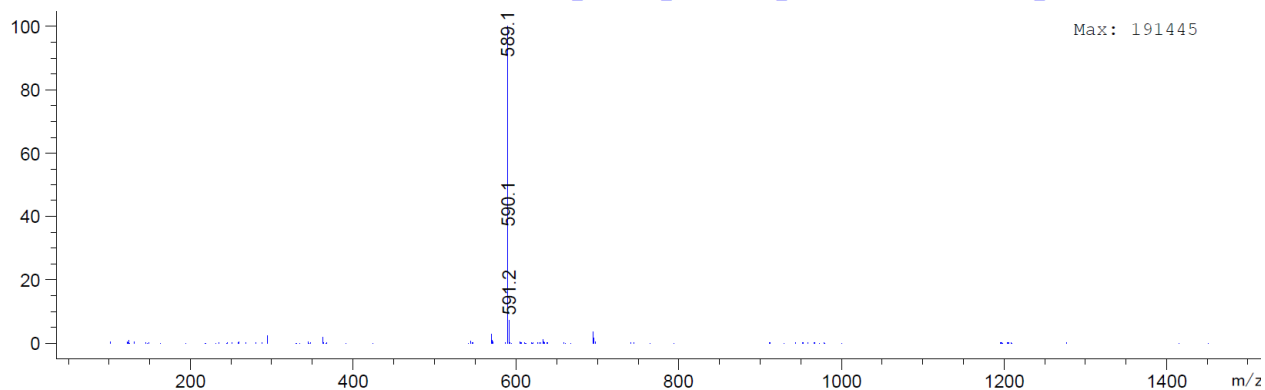
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-04-04T10:38:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.1
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



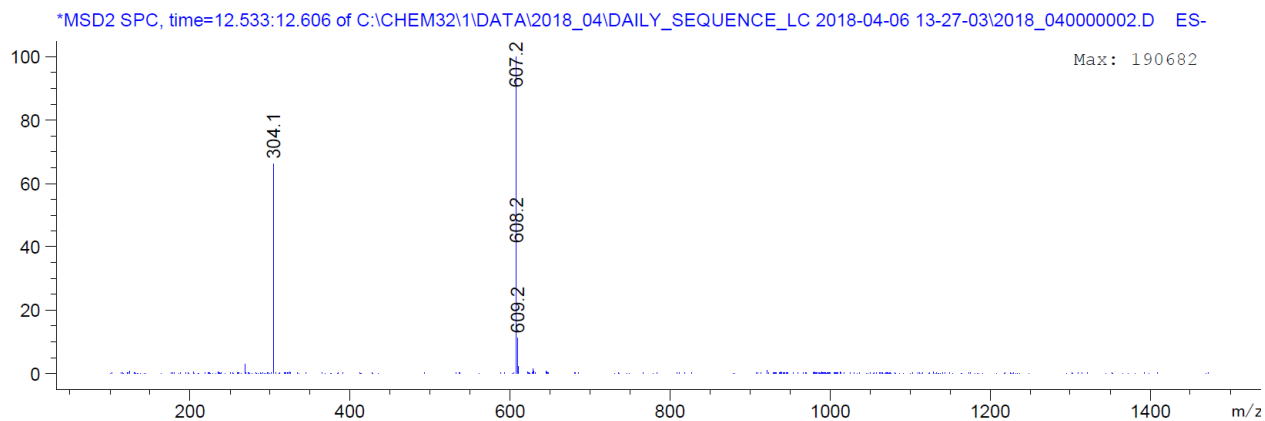
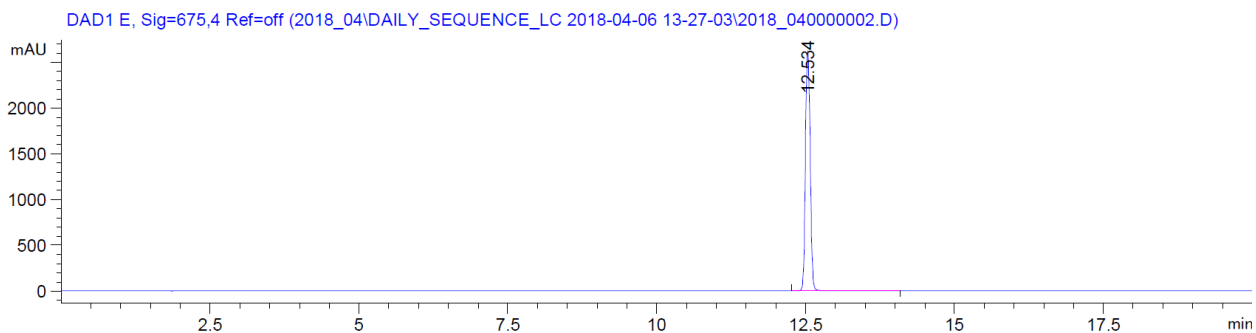
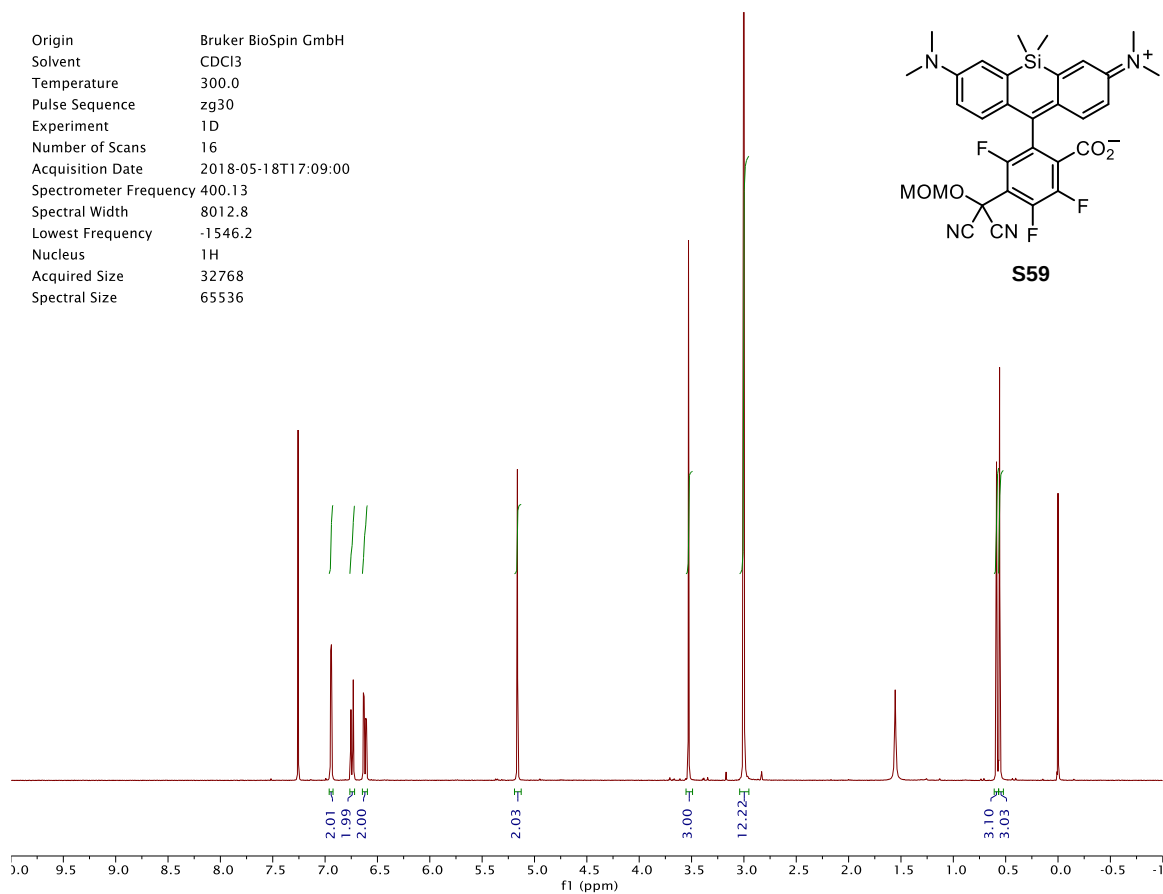
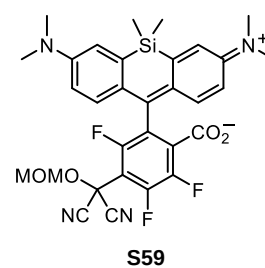
DAD1 C, Sig=575,4 Ref=off (2018_04\DAI\SEQUENCE_LC 2018-04-03 16-00-15\2018_040000002.D)



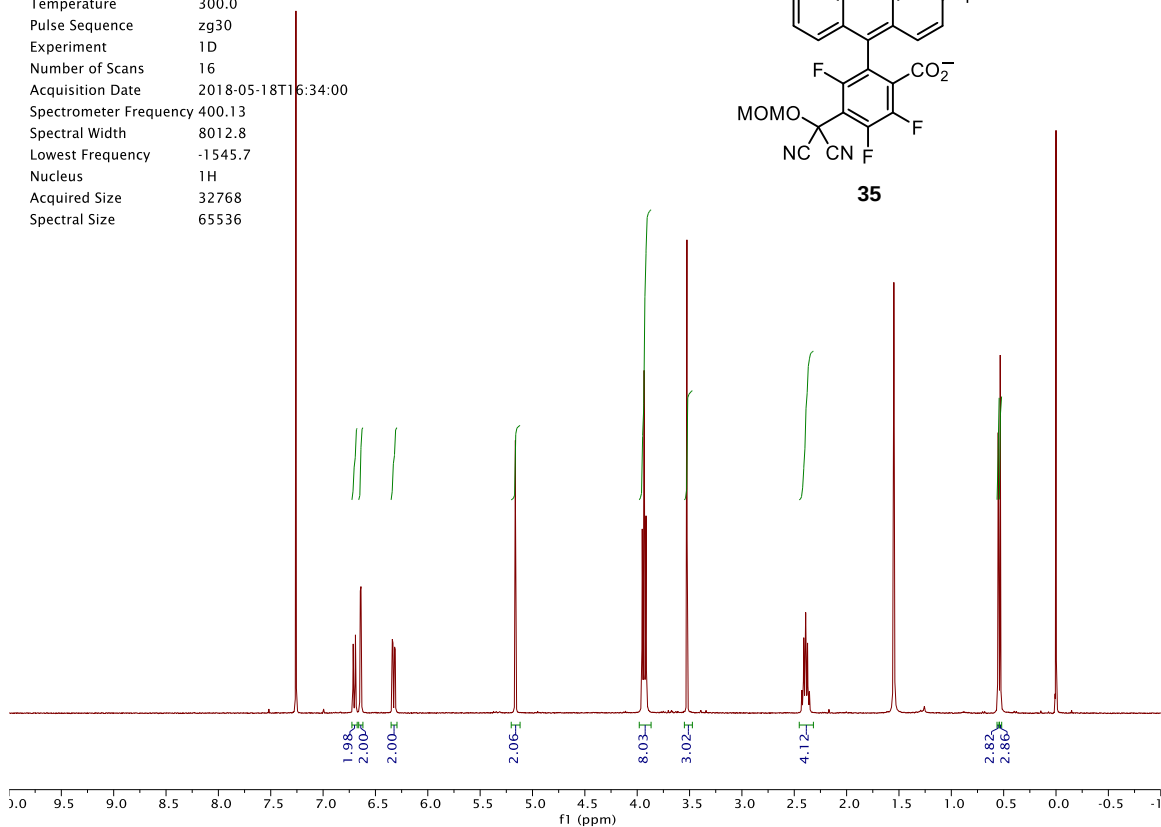
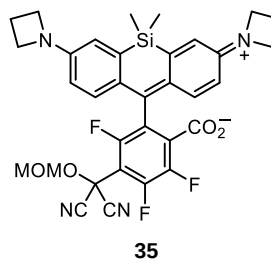
*MSD2 SPC, time=10.429:10.520 of C:\CHEM32\1\DATA\2018_04\DAI\SEQUENCE_LC 2018-04-03 16-00-15\2018_040000002.D ES-



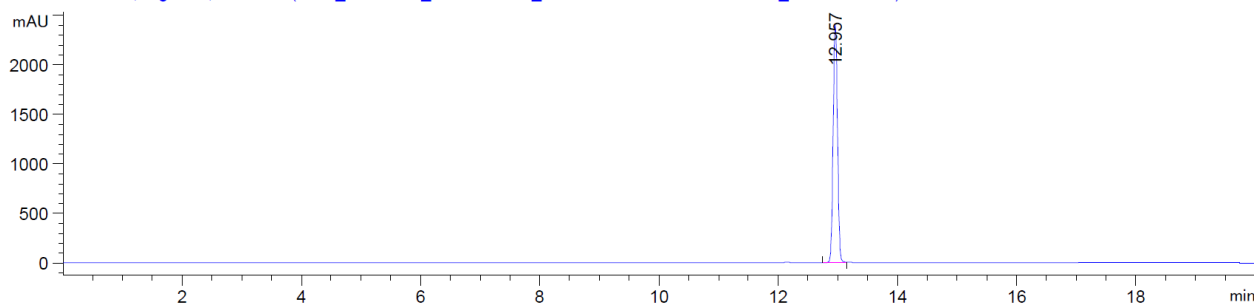
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-05-18T17:09:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1546.2
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



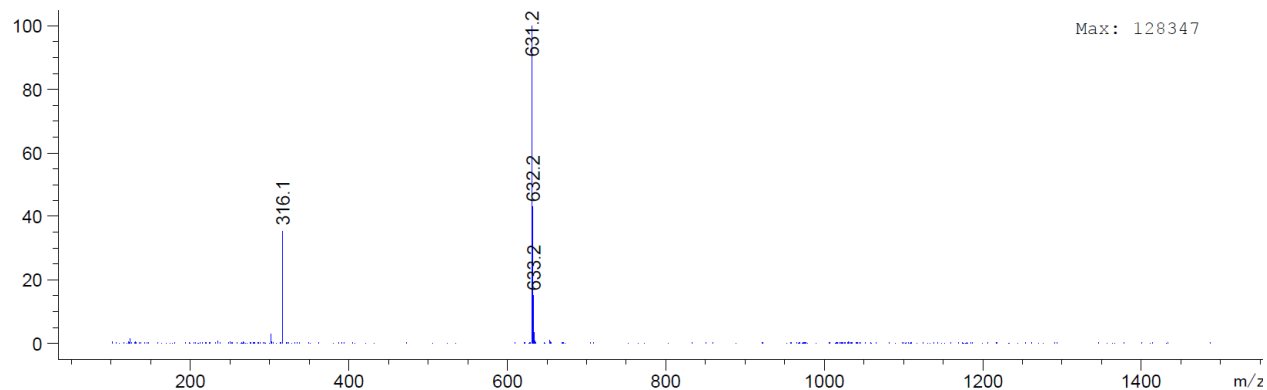
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-05-18T16:34:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.7
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



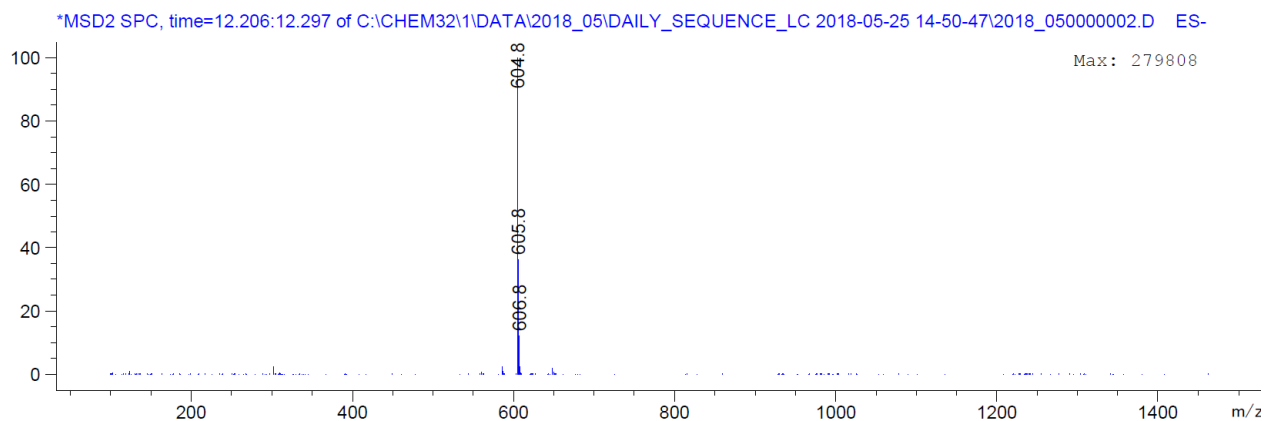
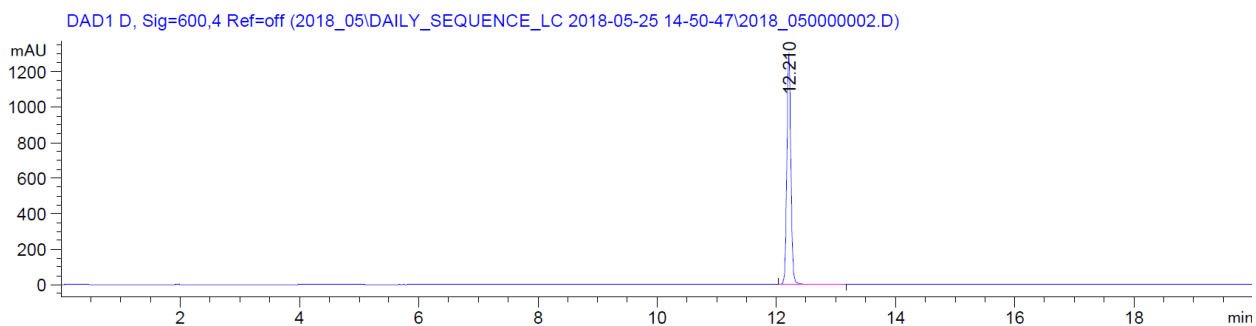
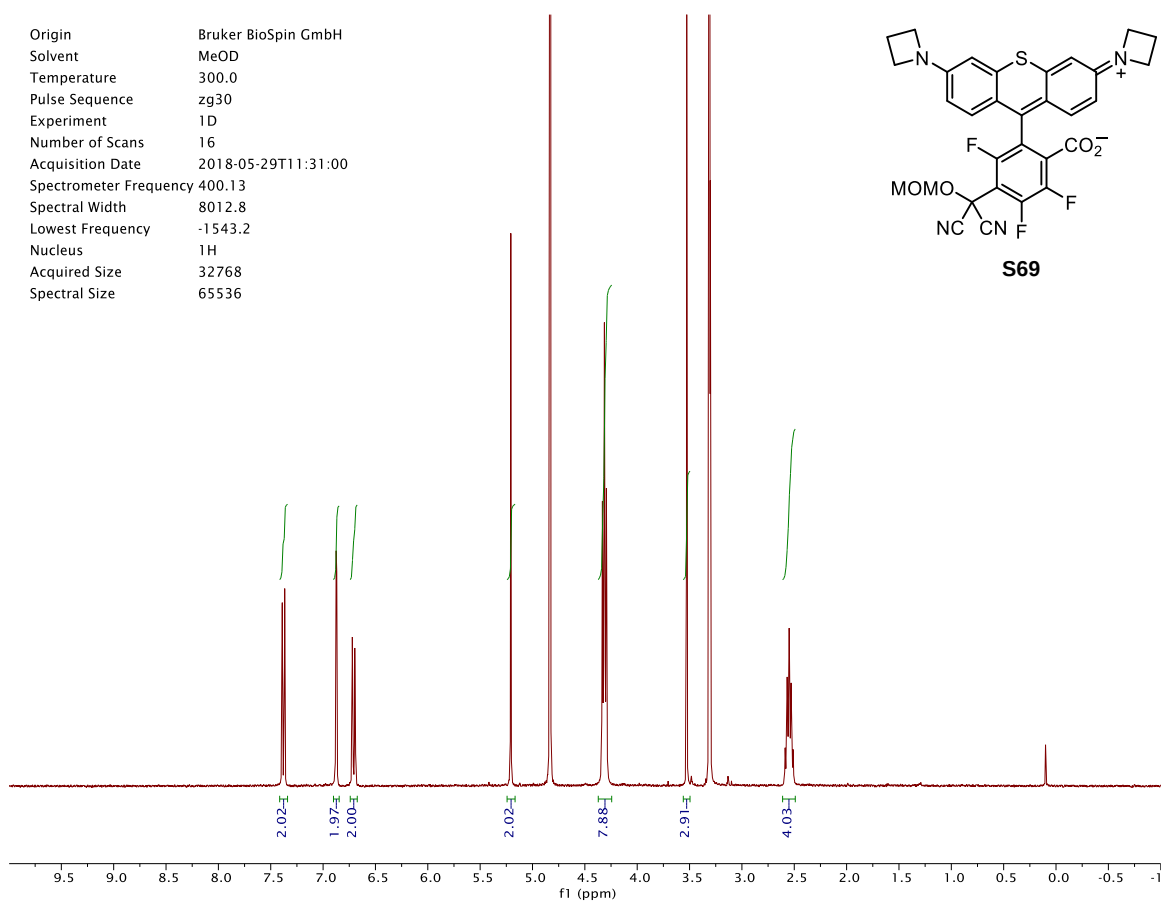
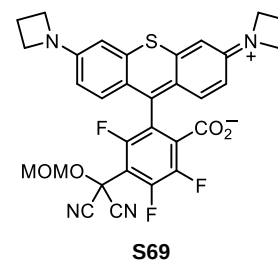
DAD1 E, Sig=675,4 Ref=off (2018_04\DAIY_SEQUENCE_LC 2018-04-06 13-27-03\2018_040000008.D)



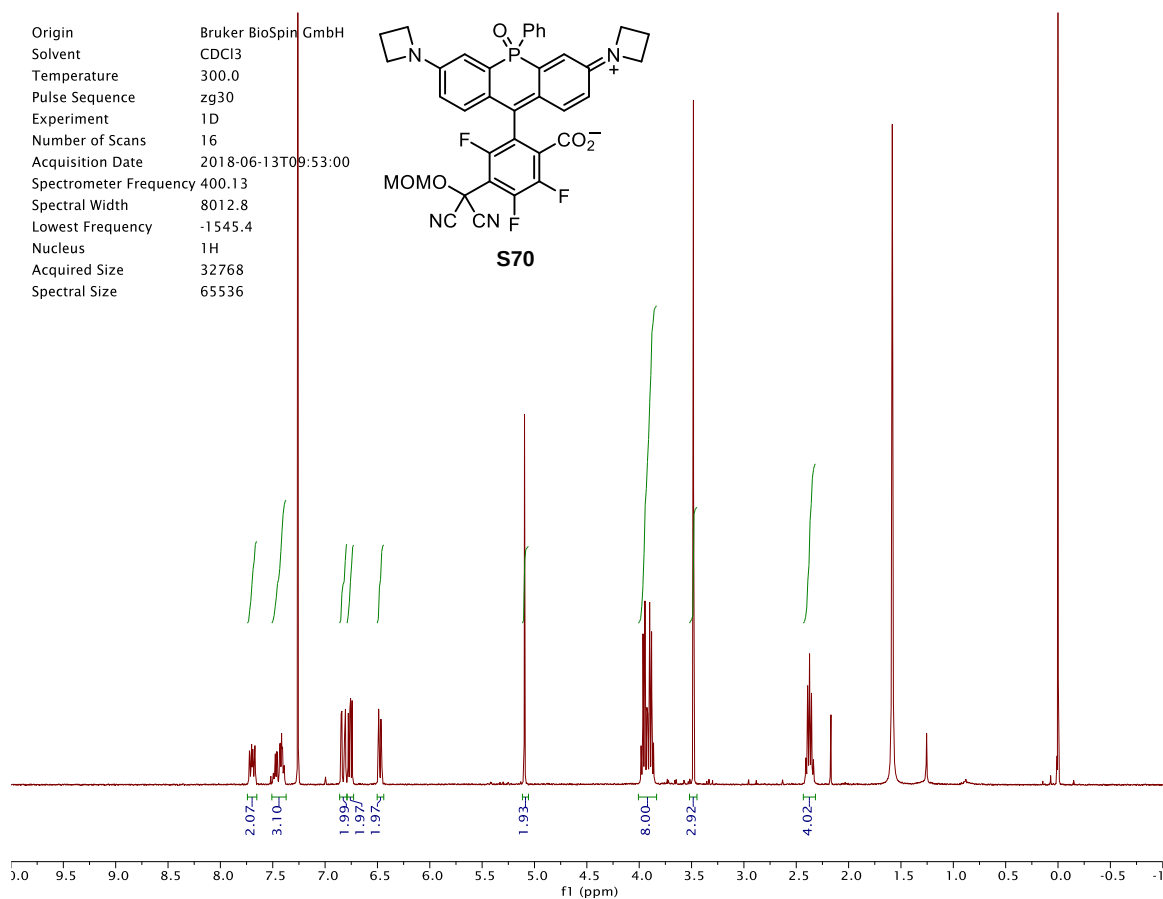
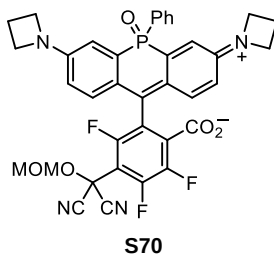
*MSD2 SPC, time=12.951:13.042 of C:\CHEM32\1\DATA\2018_04\DAIY_SEQUENCE_LC 2018-04-06 13-27-03\2018_040000008.D ES-



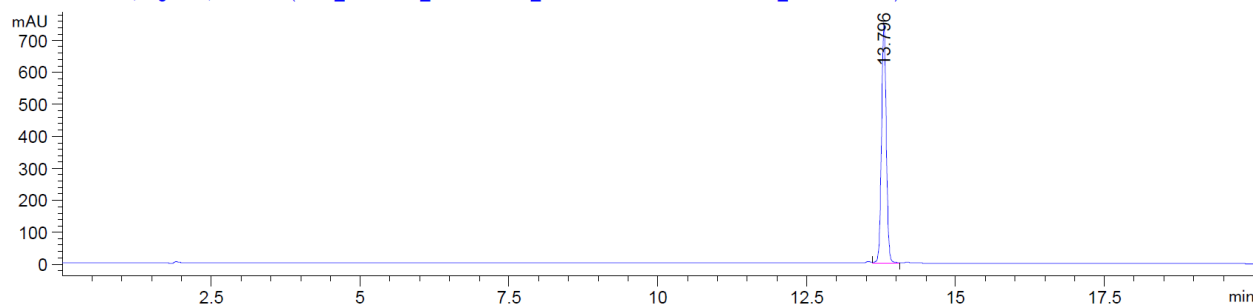
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-05-29T11:31:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.2
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536



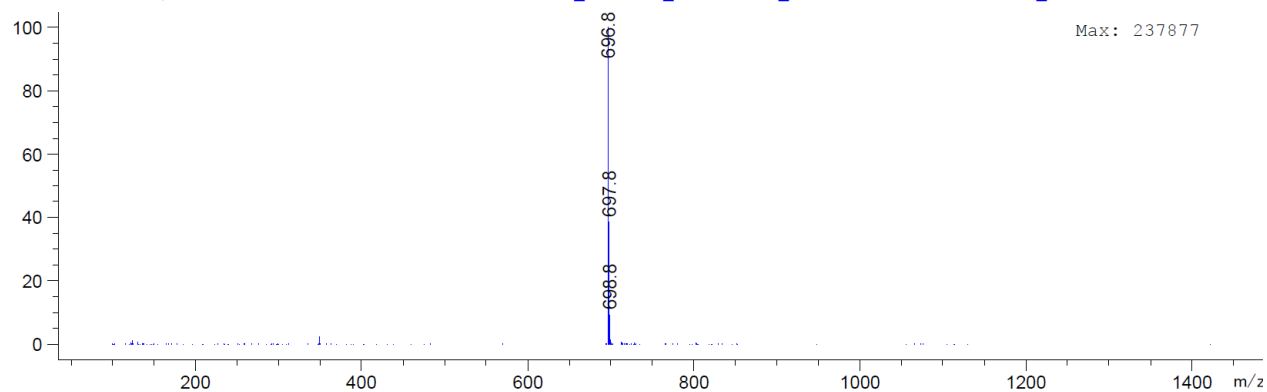
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-06-13T09:53:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.4
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



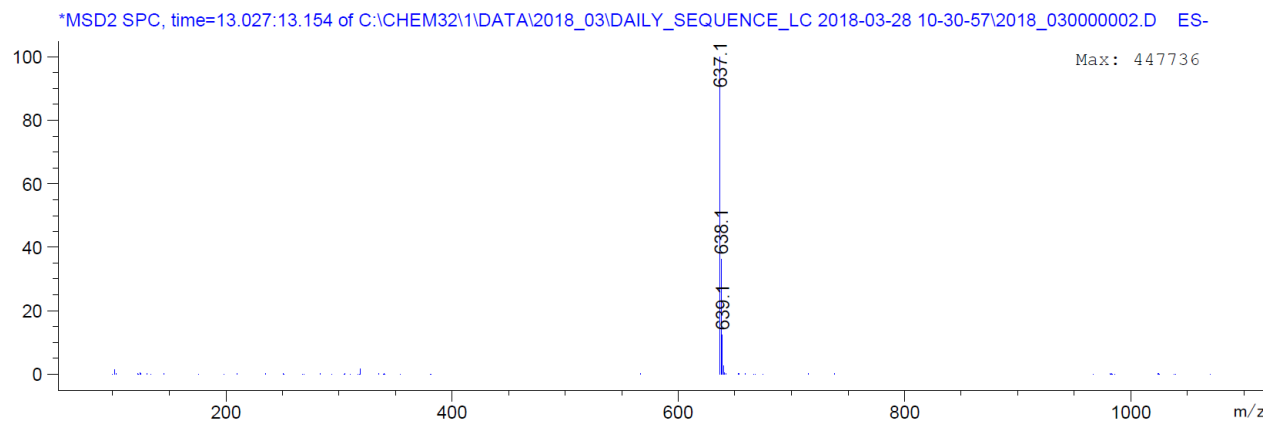
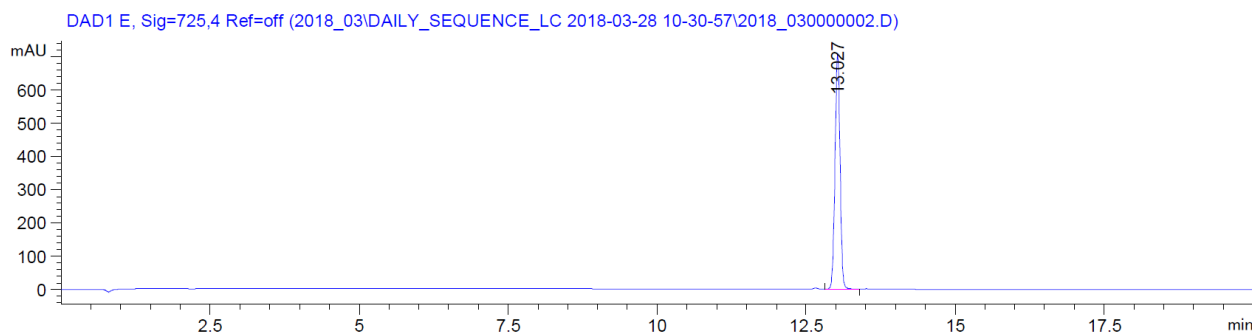
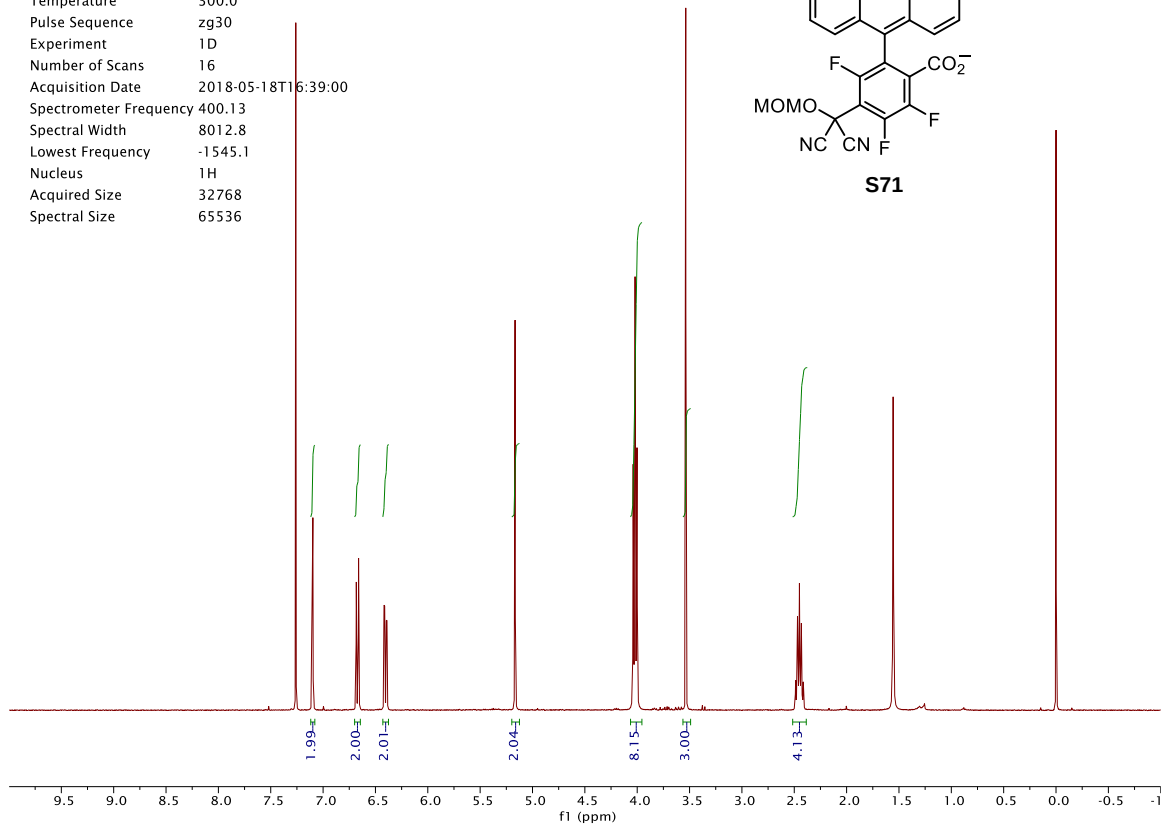
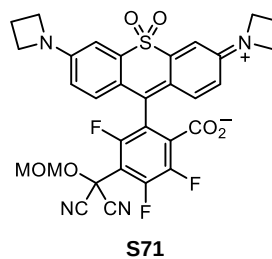
DAD1 E, Sig=725,4 Ref=off (2018_06\DAIY_SEQUENCE_LC 2018-06-12 15-51-37\2018_060000002.D)



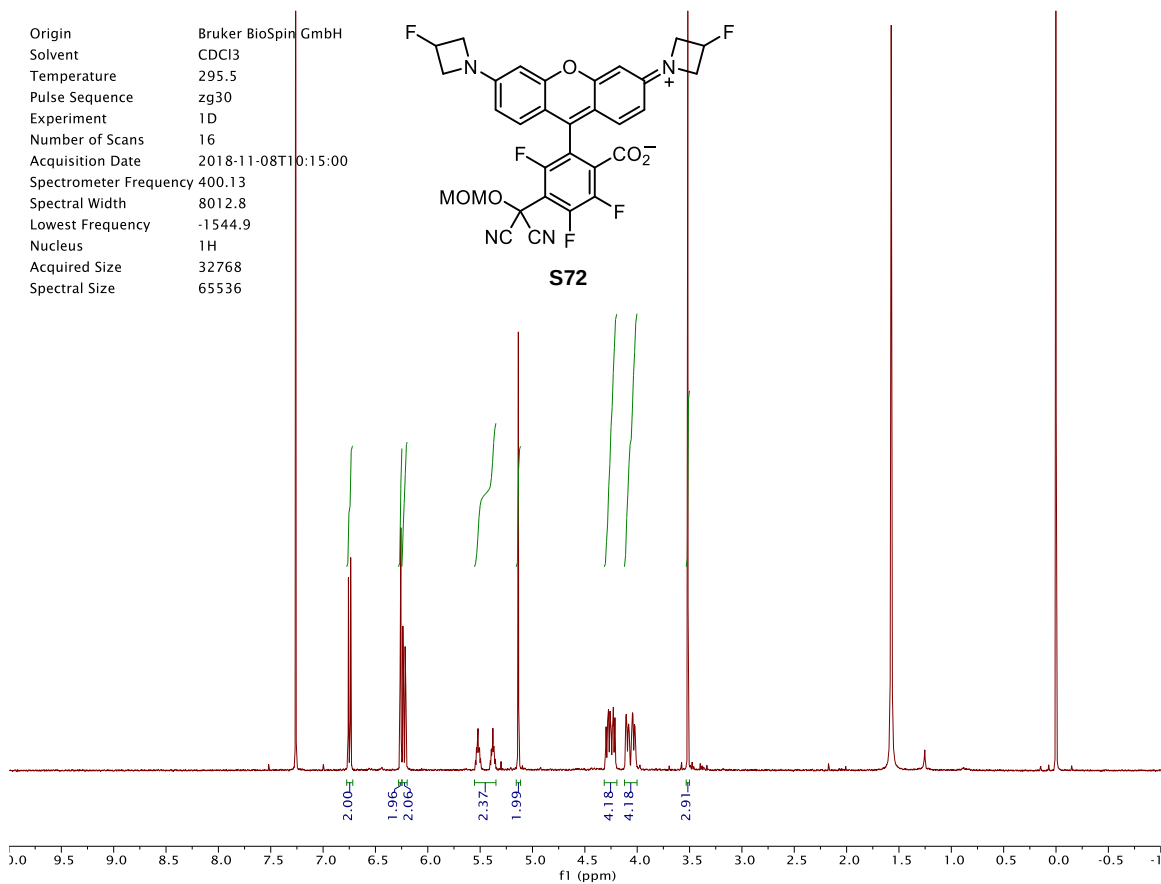
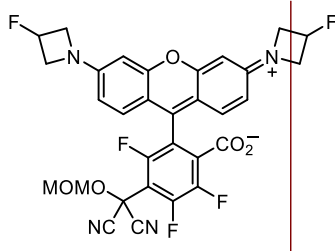
*MSD2 SPC, time=13.787:13.878 of C:\CHEM32\1\DATA\2018_06\DAIY_SEQUENCE_LC 2018-06-12 15-51-37\2018_060000002.D ES-



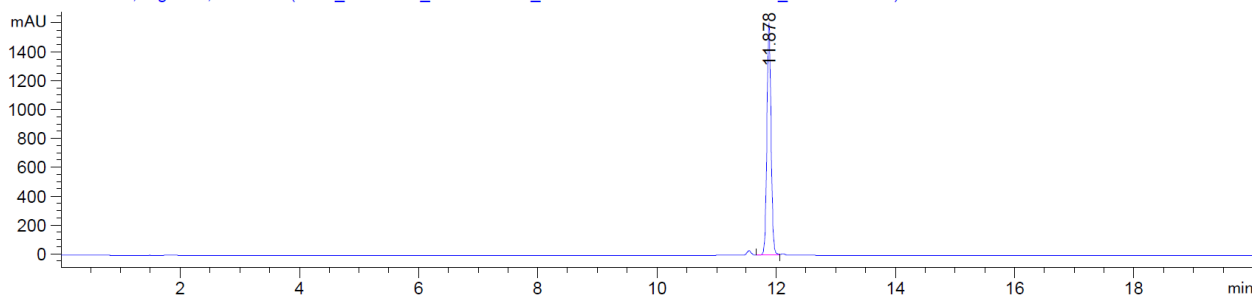
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-05-18T16:39:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.1
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



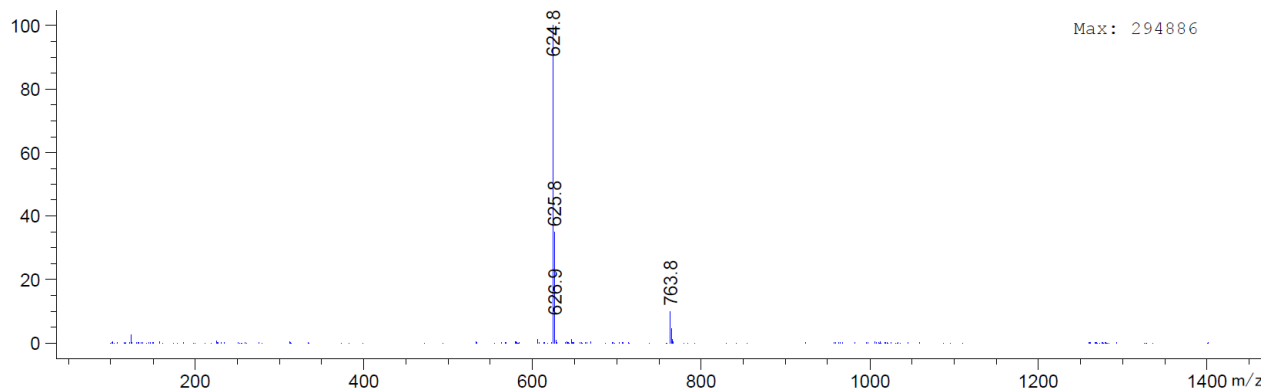
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 295.5
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-11-08T10:15:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1544.9
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



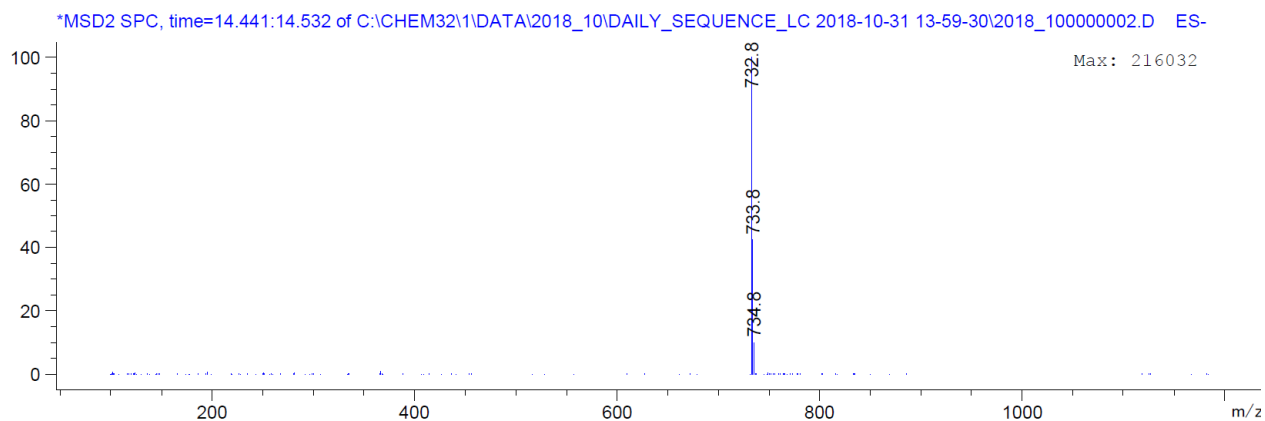
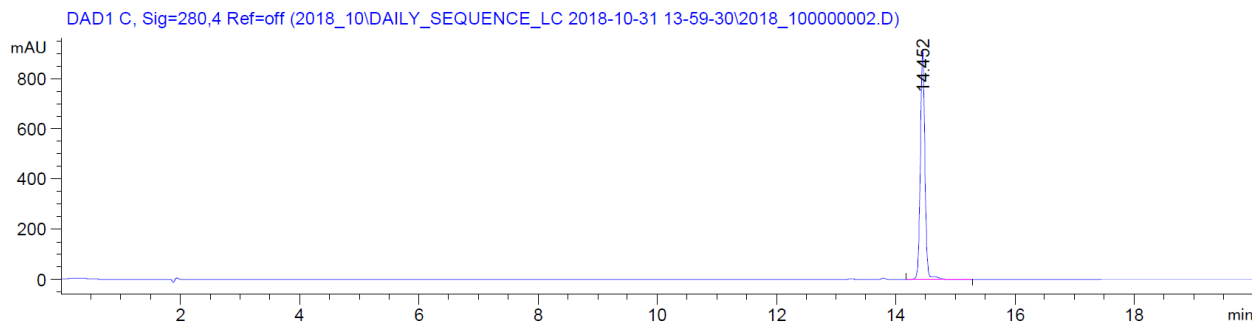
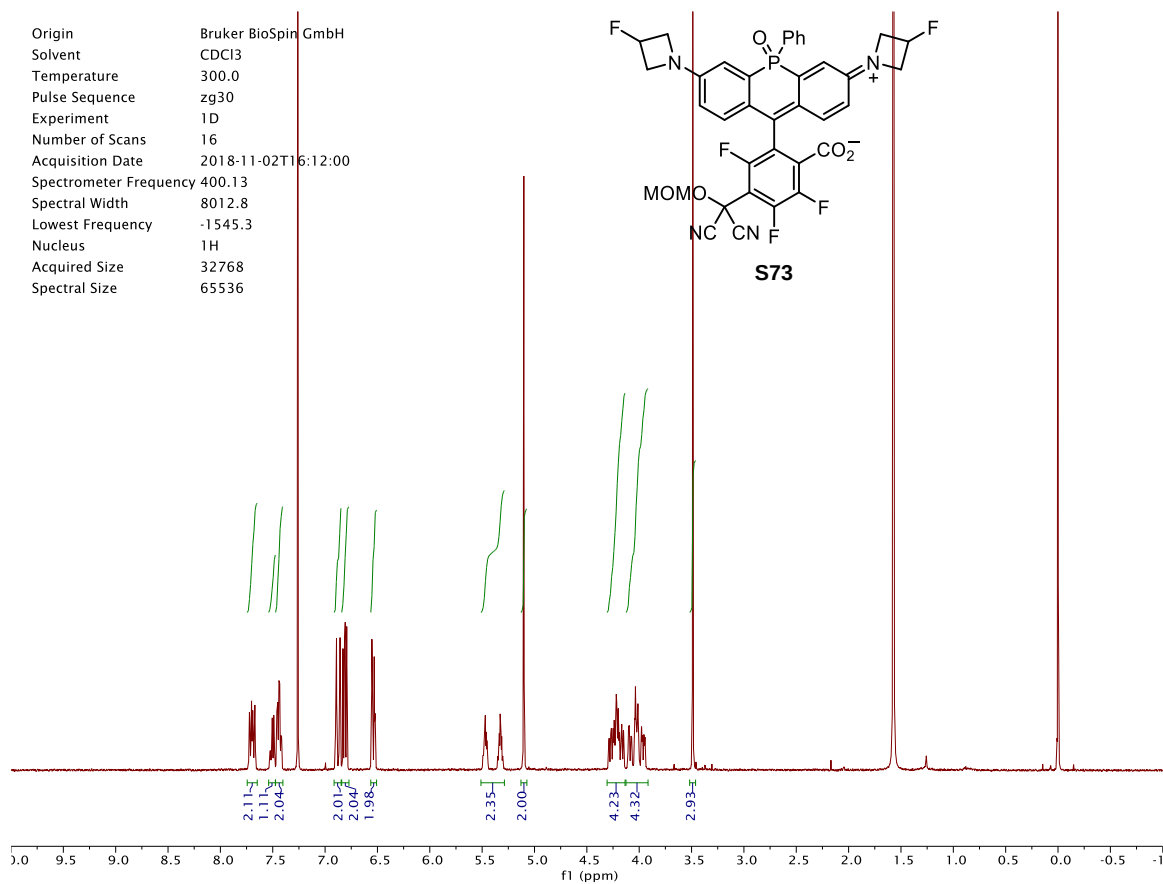
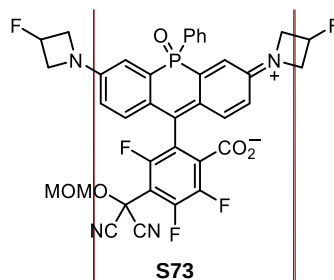
DAD1 C, Sig=575,4 Ref=off (2018_11\DAIY_SEQUENCE_LC 2018-11-07 09-55-12\2018_110000003.D)



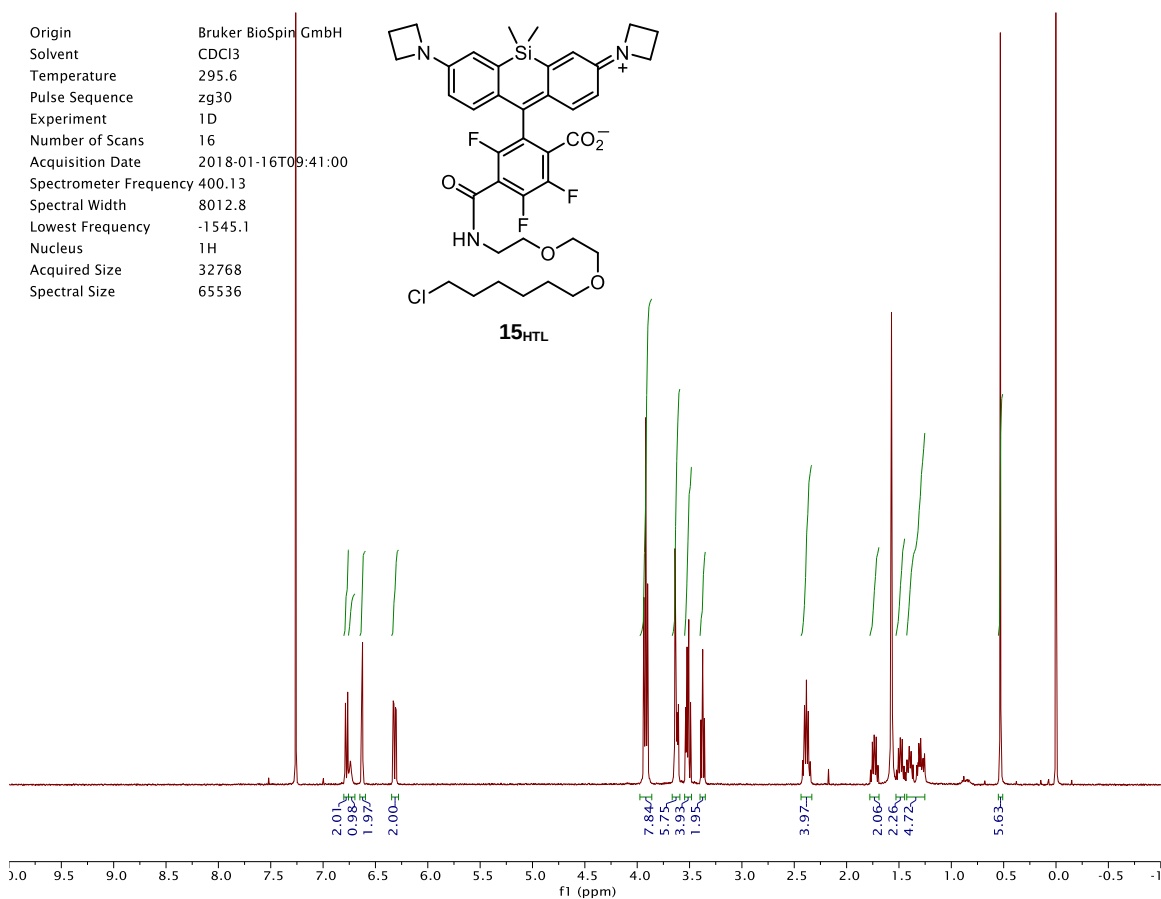
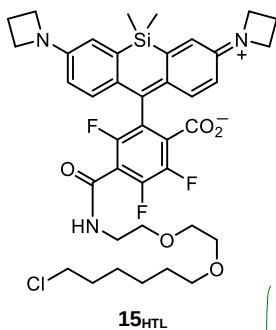
*MSD2 SPC, time=11.883:11.955 of C:\CHEM32\1\DATA\2018_11\DAIY_SEQUENCE_LC 2018-11-07 09-55-12\2018_110000003.D ES-



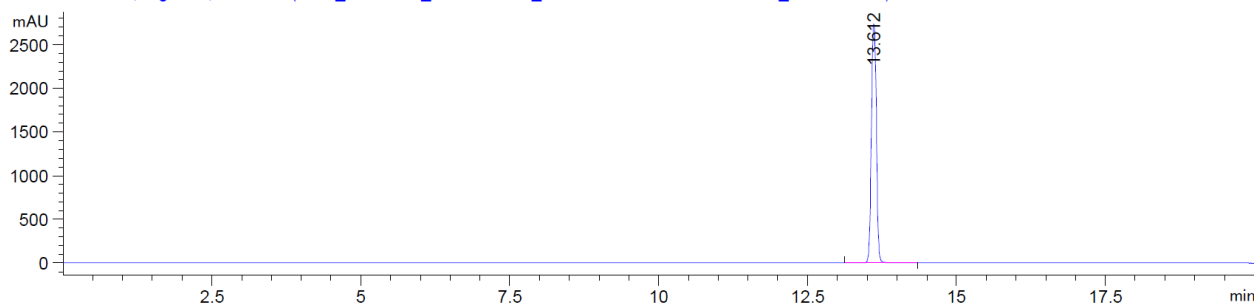
Origin Bruker BioSpin GmbH
 Solvent CDCl3
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-11-02T16:12:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.3
 Nucleus 1H
 Acquired Size 32768
 Spectral Size 65536



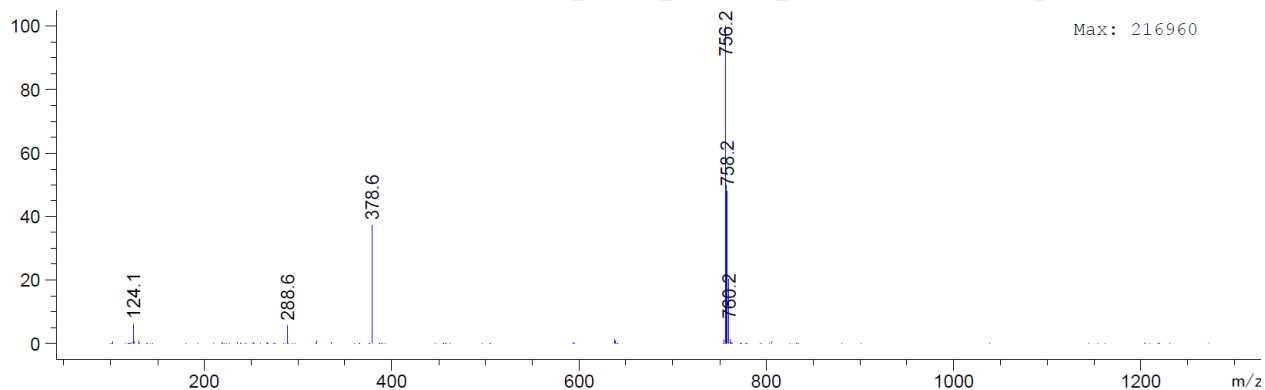
Origin Bruker BioSpin GmbH
 Solvent CDCl₃
 Temperature 295.6
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-01-16T09:41:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.1
 Nucleus ¹H
 Acquired Size 32768
 Spectral Size 65536



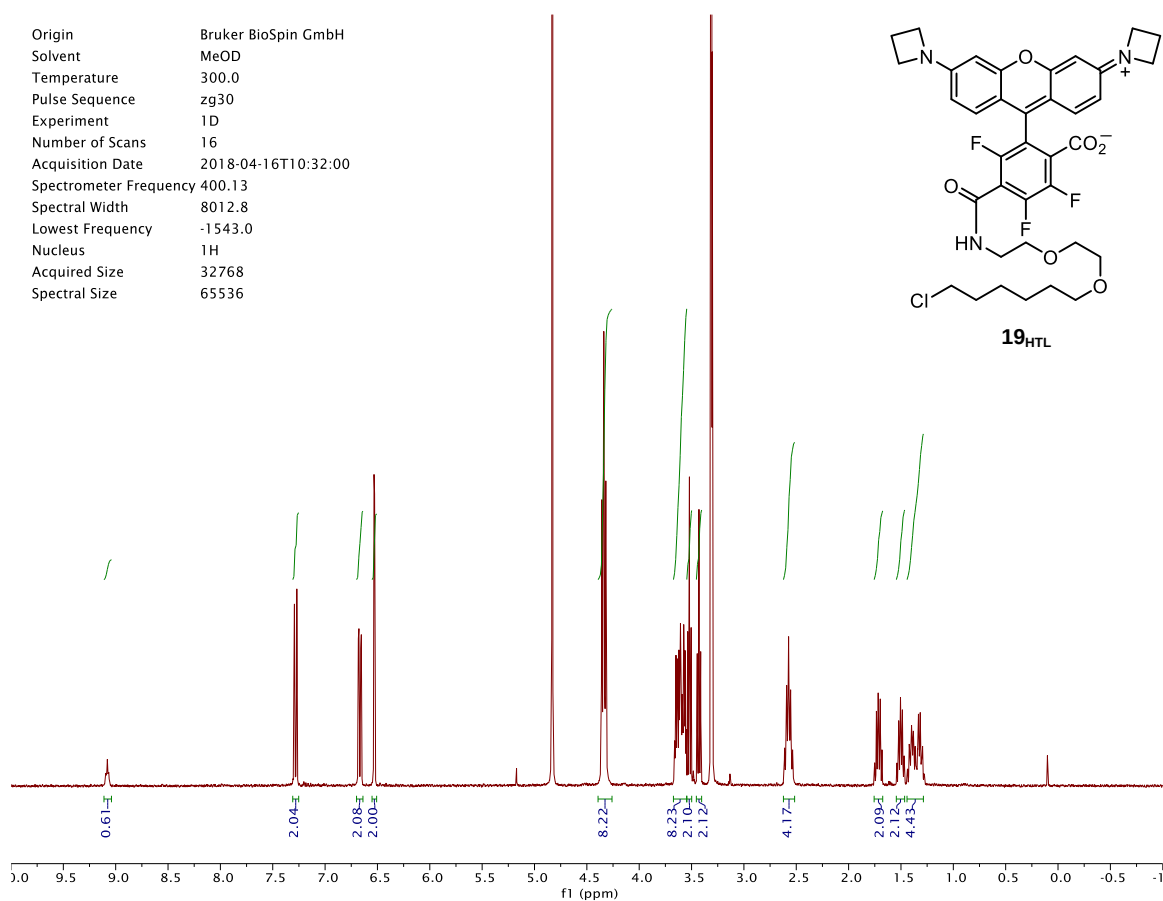
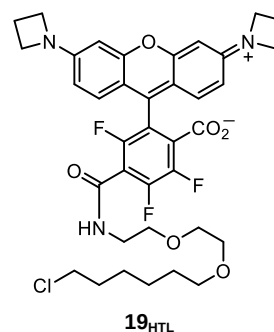
DAD1 E, Sig=675,4 Ref=off (2018_01\DAIY_SEQUENCE_LC 2018-01-12 11-56-53\2018_10000002.D)



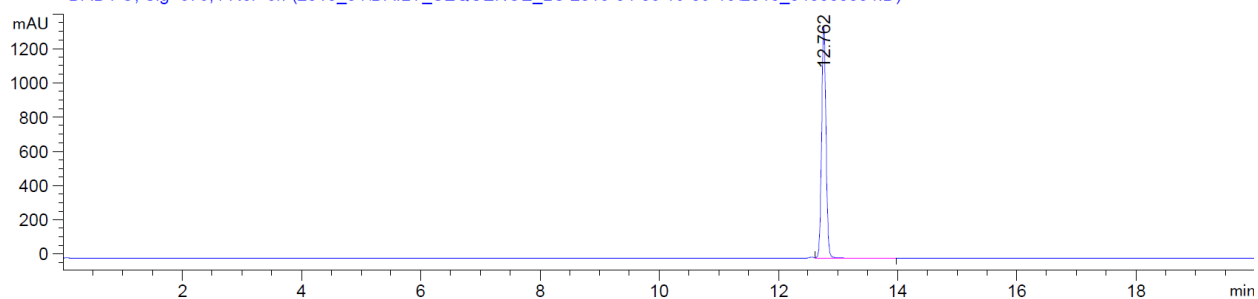
*MSD2 SPC, time=13.605:13.678 of C:\CHEM32\1\DATA\2018_01\DAIY_SEQUENCE_LC 2018-01-12 11-56-53\2018_10000002.D ES-A



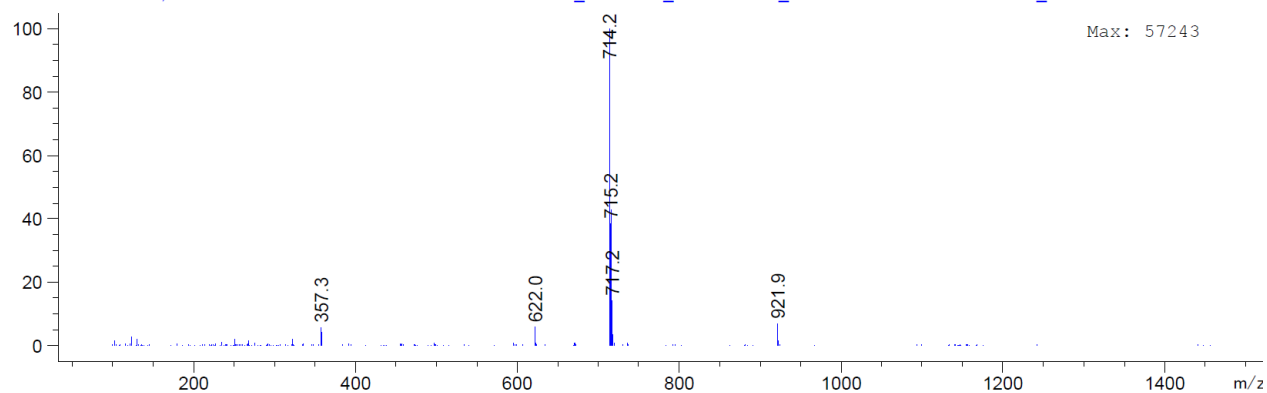
Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-04-16T10:32:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.0
 Nucleus ^1H
 Acquired Size 32768
 Spectral Size 65536



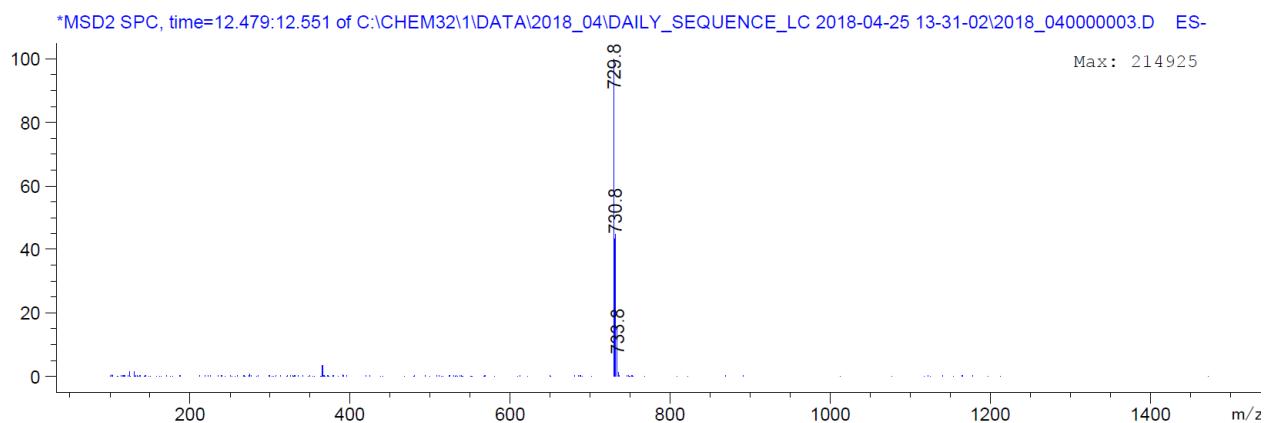
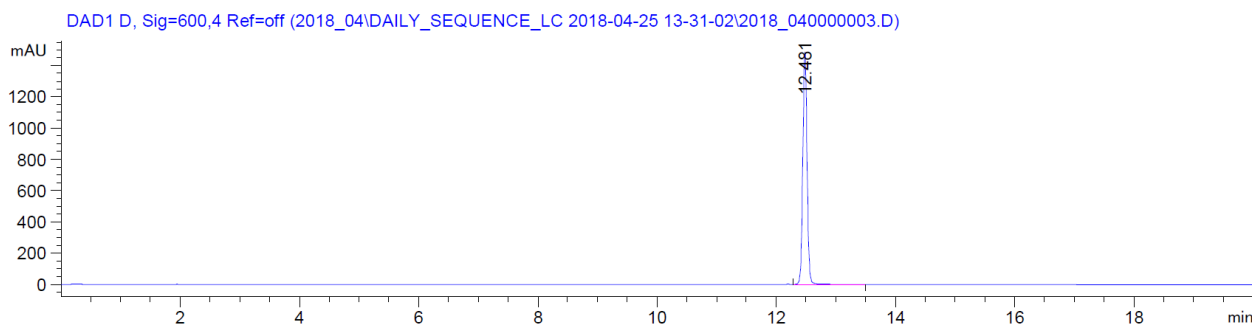
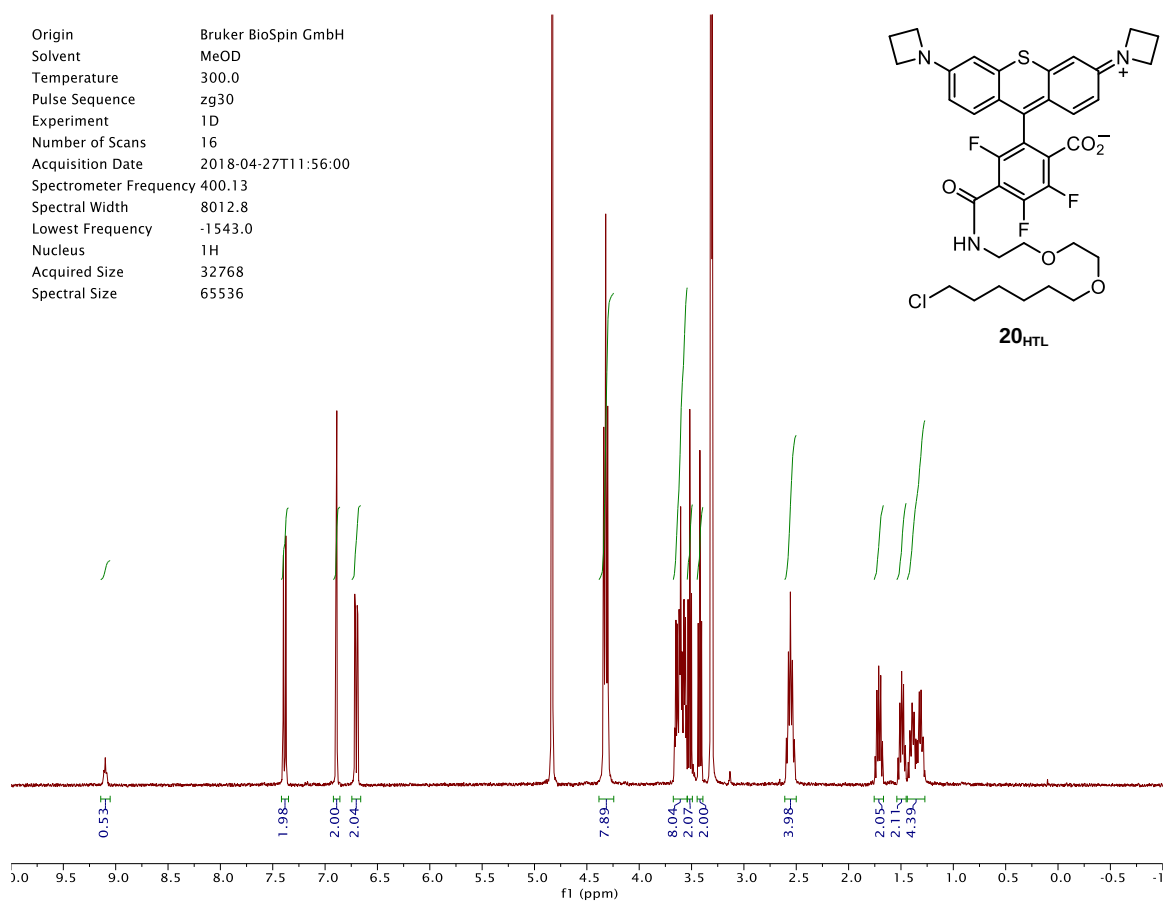
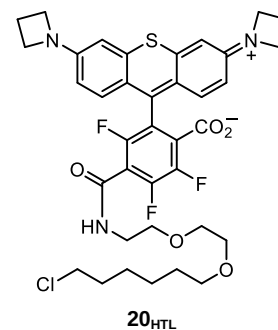
DAD1 C, Sig=575,4 Ref=off (2018_04\DAIY_SEQUENCE_LC 2018-04-05 16-09-15\2018_040000004.D)



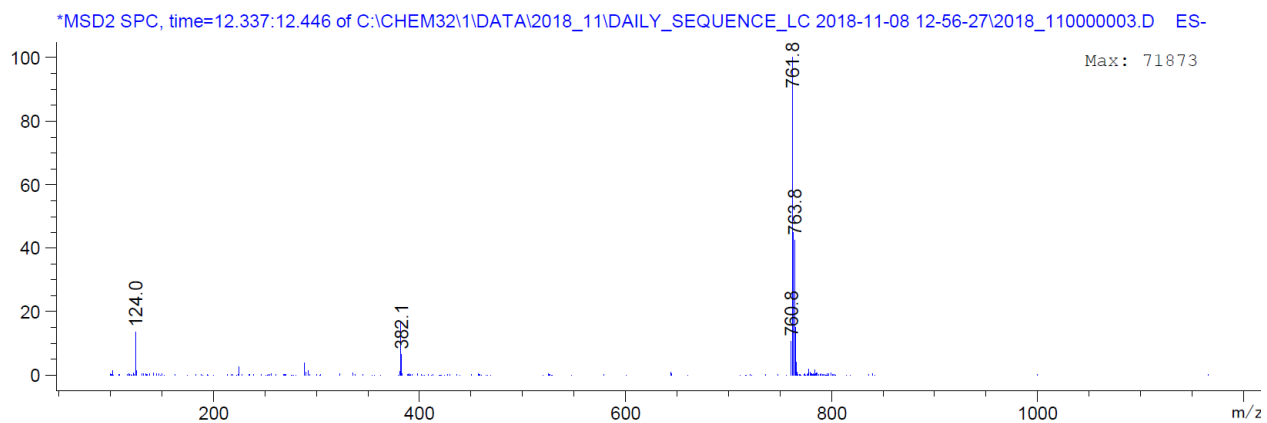
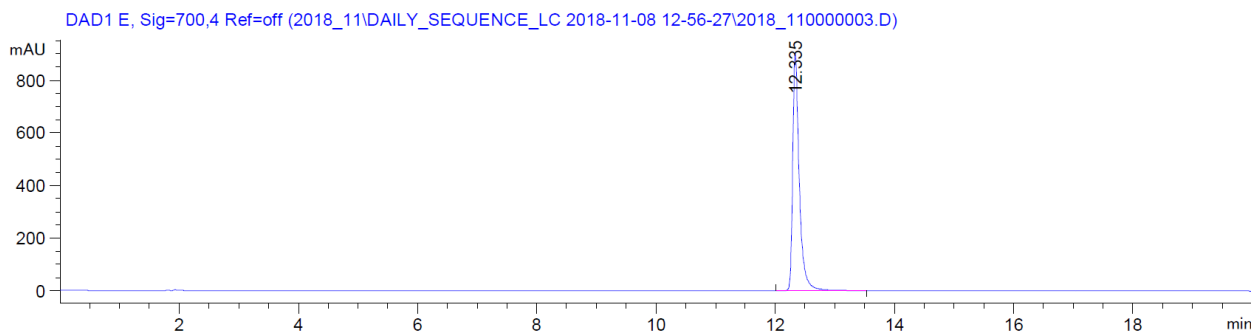
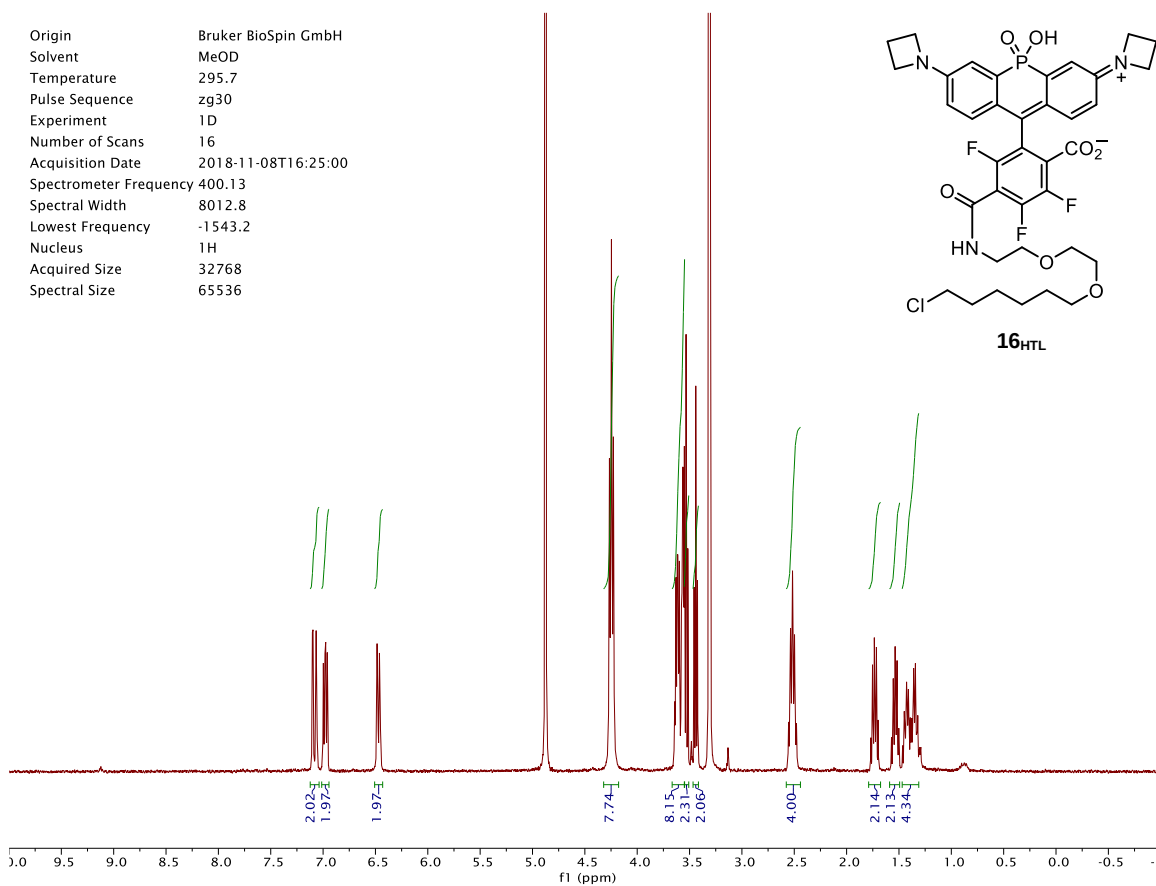
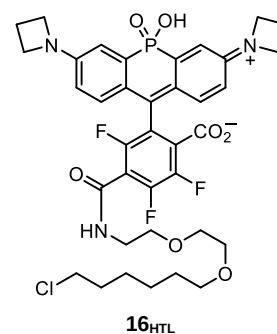
*MSD2 SPC, time=12.755:12.845 of C:\CHEM321\DATA\2018_04\DAIY_SEQUENCE_LC 2018-04-05 16-09-15\2018_040000004.D ES-



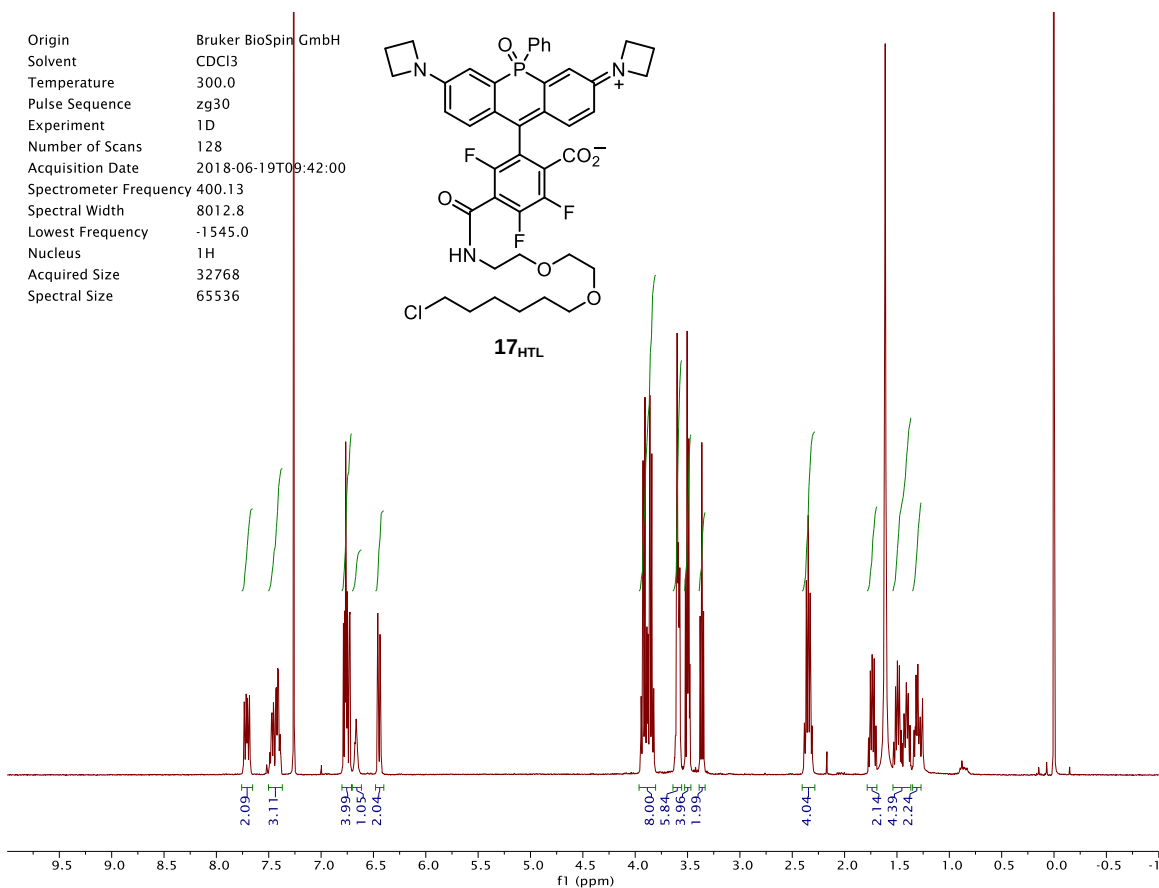
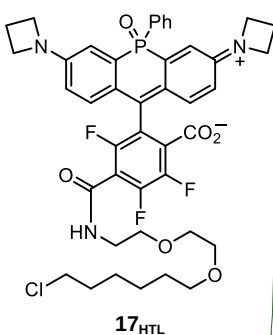
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-04-27T11:56:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.0
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



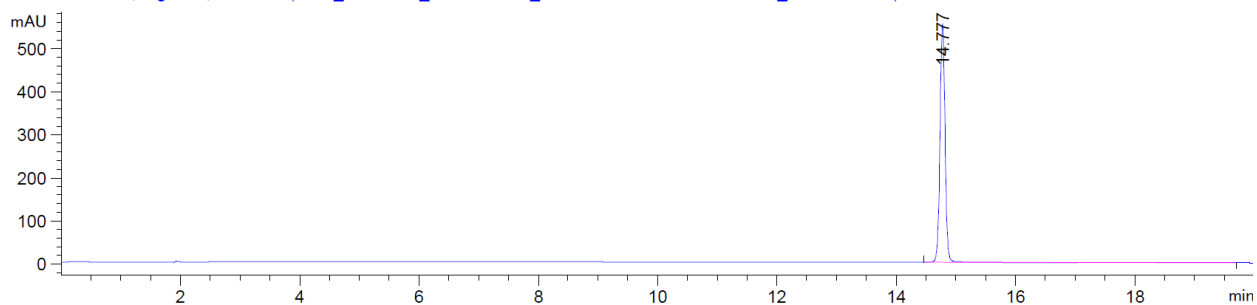
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 295.7
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-11-08T16:25:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.2
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536



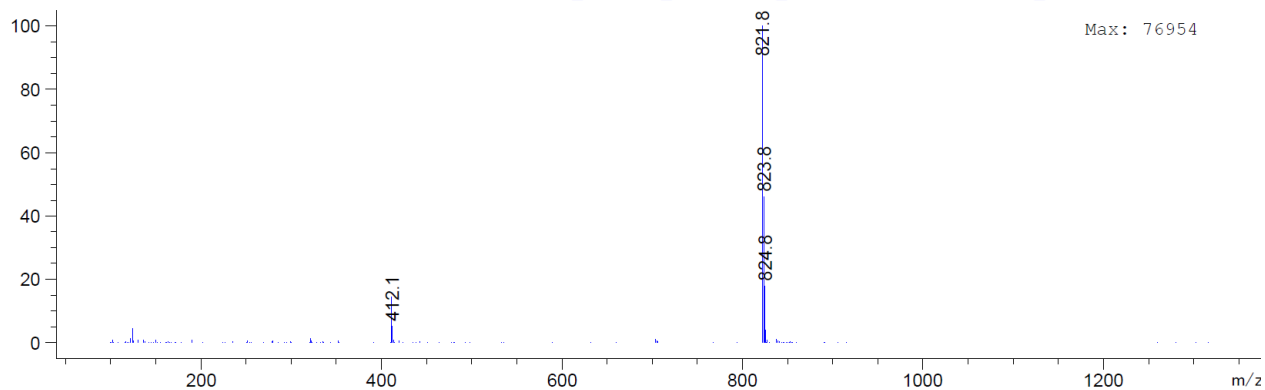
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 128
 Acquisition Date: 2018-06-19T09:42:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.0
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



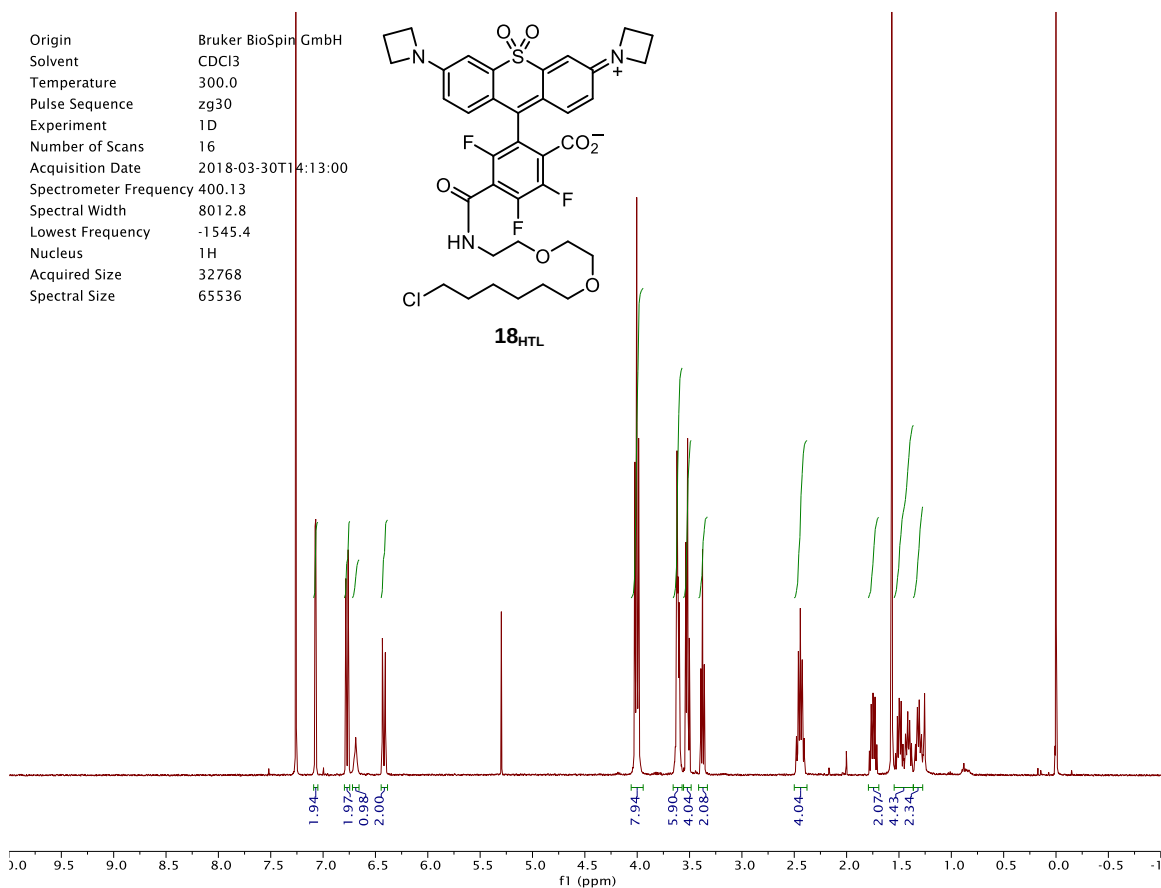
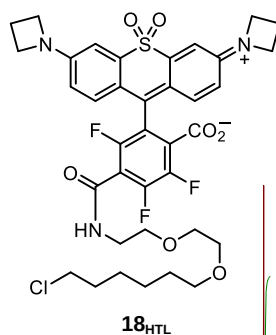
DAD1 E, Sig=725,4 Ref=off (2018_06\DAILY_SEQUENCE_LC 2018-06-14 11-21-15\2018_060000002.D)



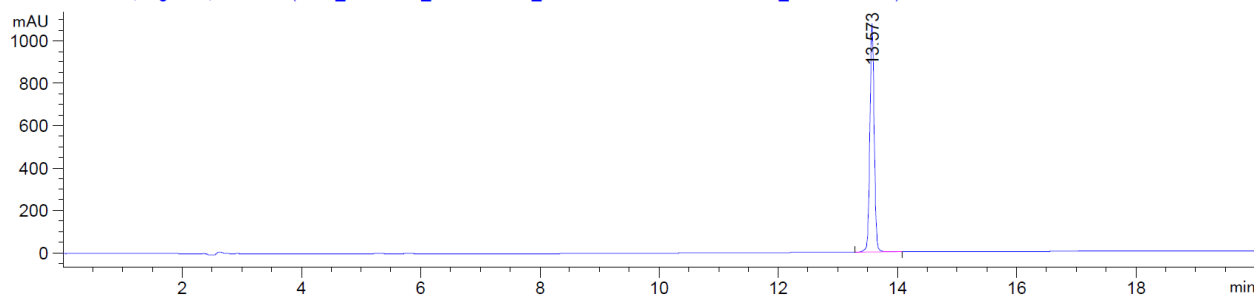
*MSD2 SPC, time=14.786:14.859 of C:\CHEM32\1\DATA\2018_06\DAILY_SEQUENCE_LC 2018-06-14 11-21-15\2018_060000002.D ES-



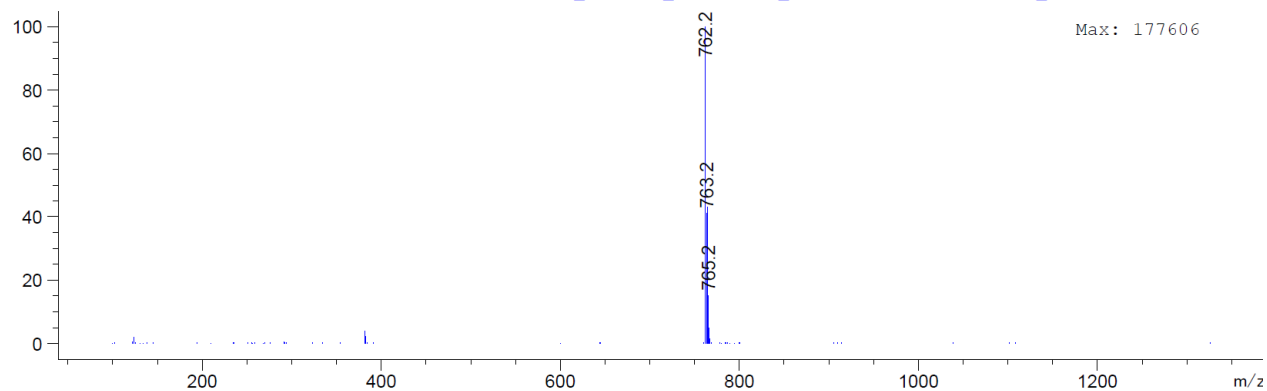
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-03-30T14:13:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.4
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



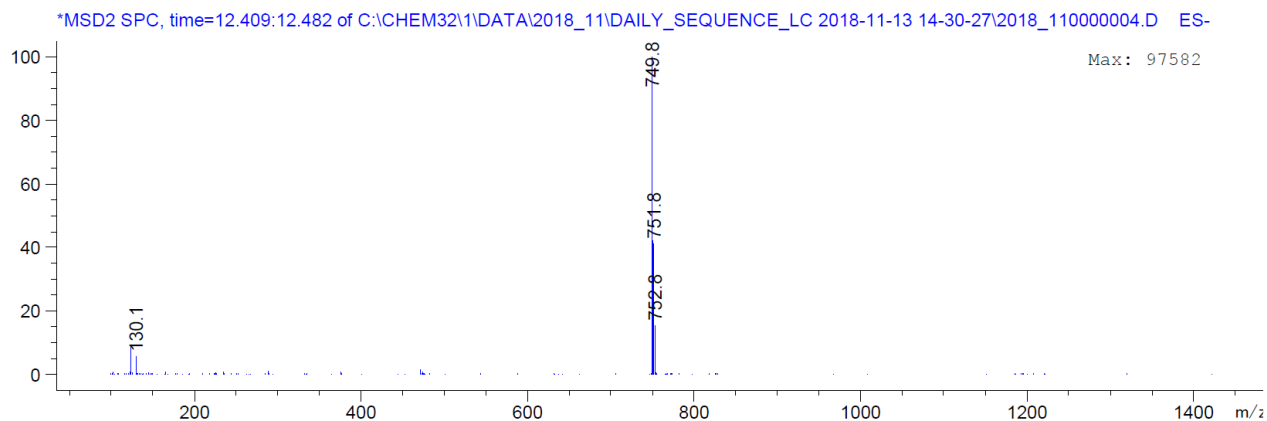
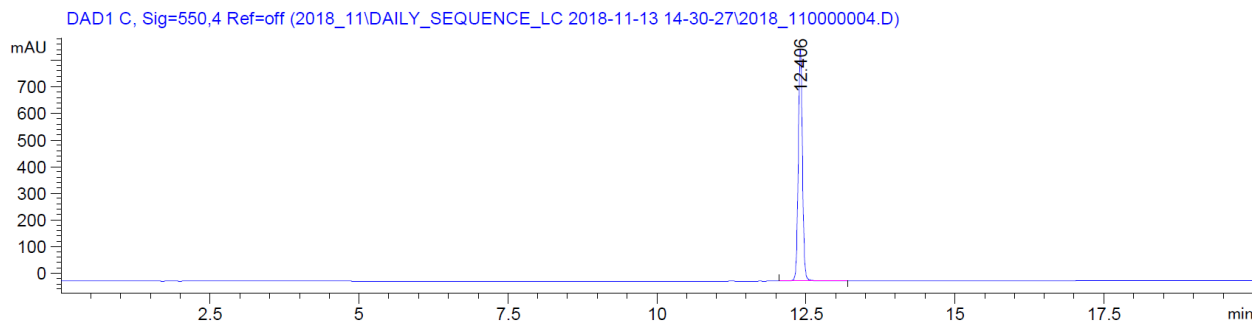
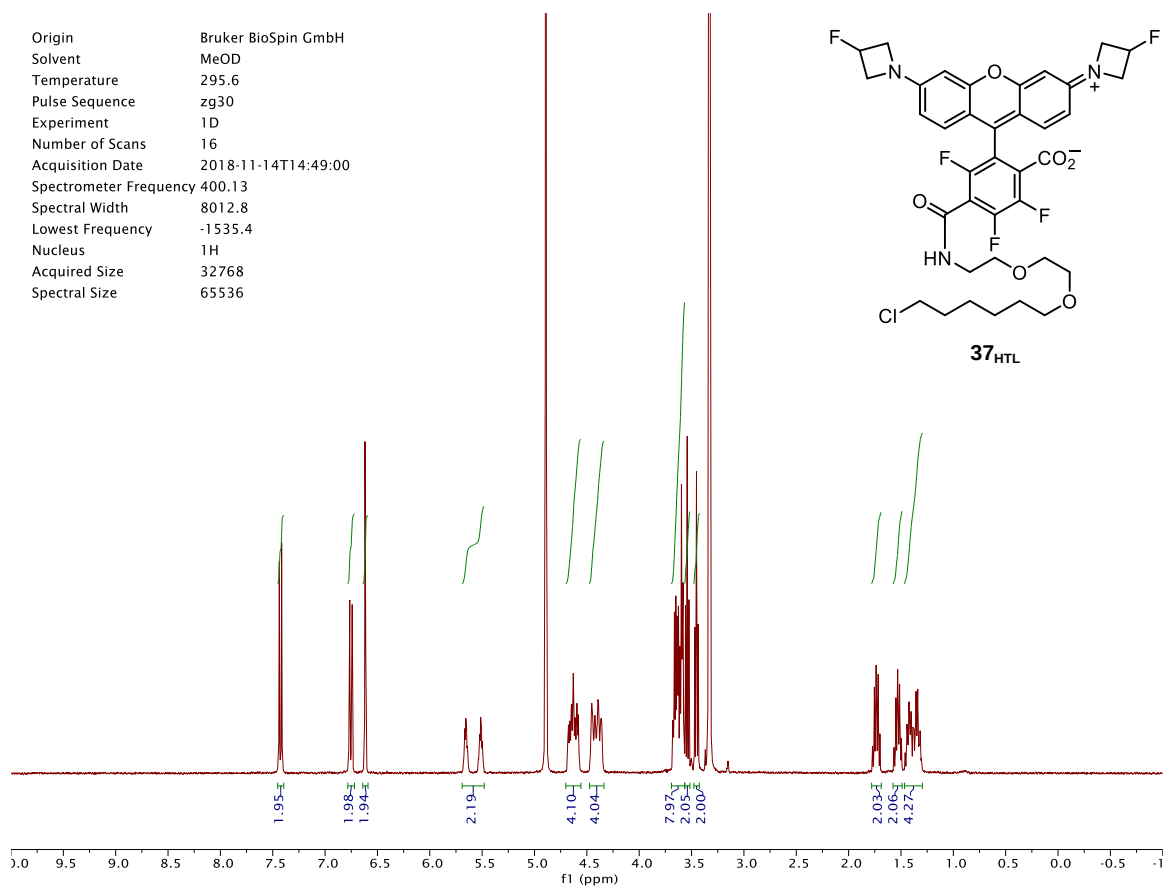
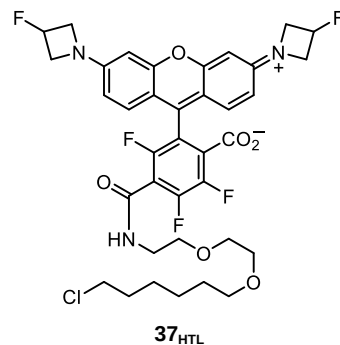
DAD1 A, Sig=254,4 Ref=off (2018_03\DAIY_SEQUENCE_LC 2018-03-29 14-38-11\2018_030000001.D)



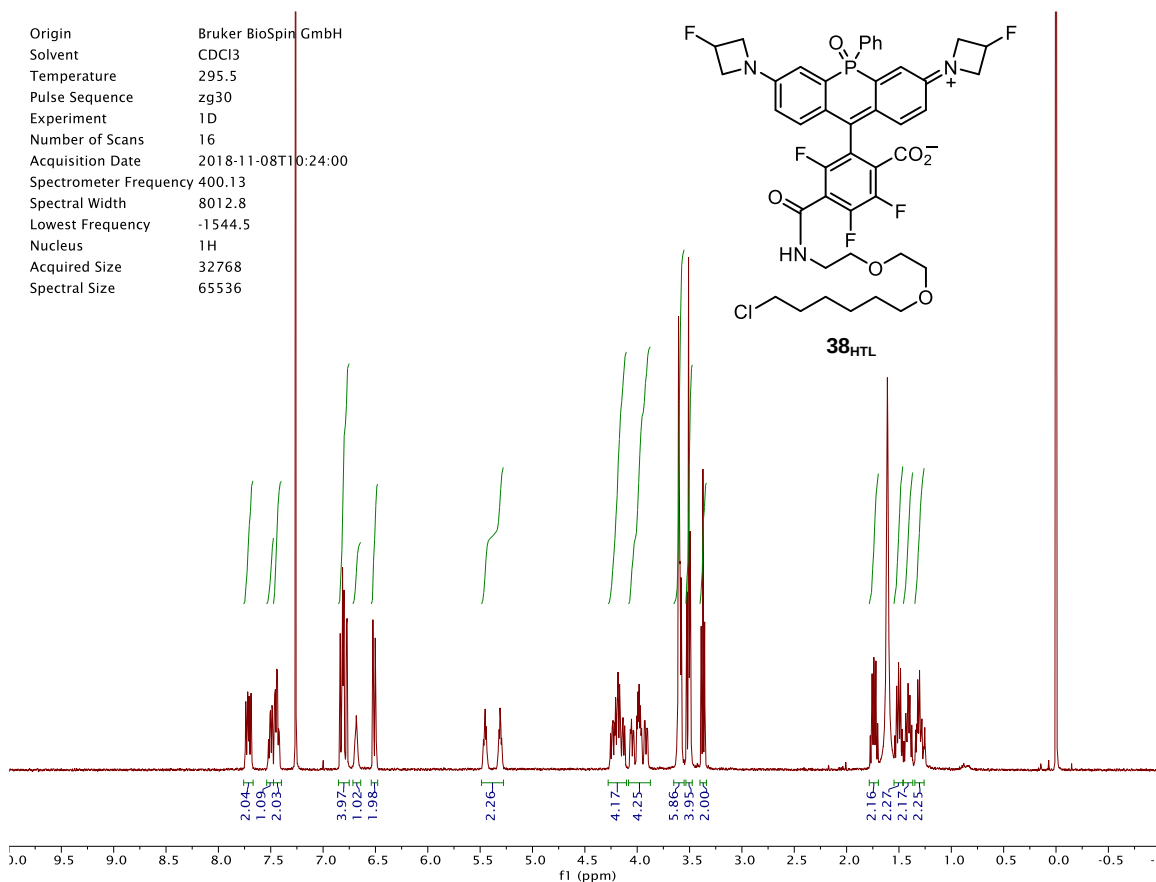
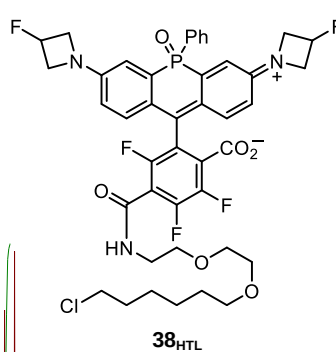
*MSD2 SPC, time=13.572:13.645 of C:\CHEM32\1\DATA\2018_03\DAIY_SEQUENCE_LC 2018-03-29 14-38-11\2018_030000001.D ES-



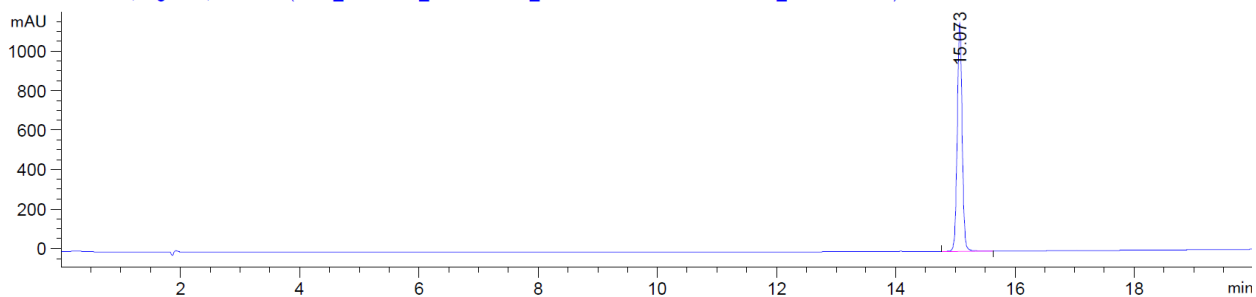
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 295.6
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-11-14T14:49:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1535.4
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



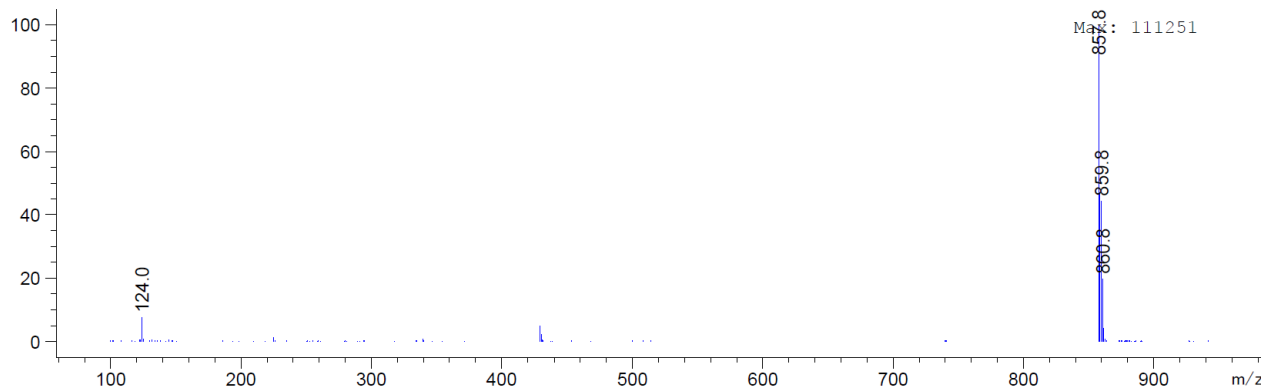
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 295.5
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-11-08T10:24:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1544.5
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



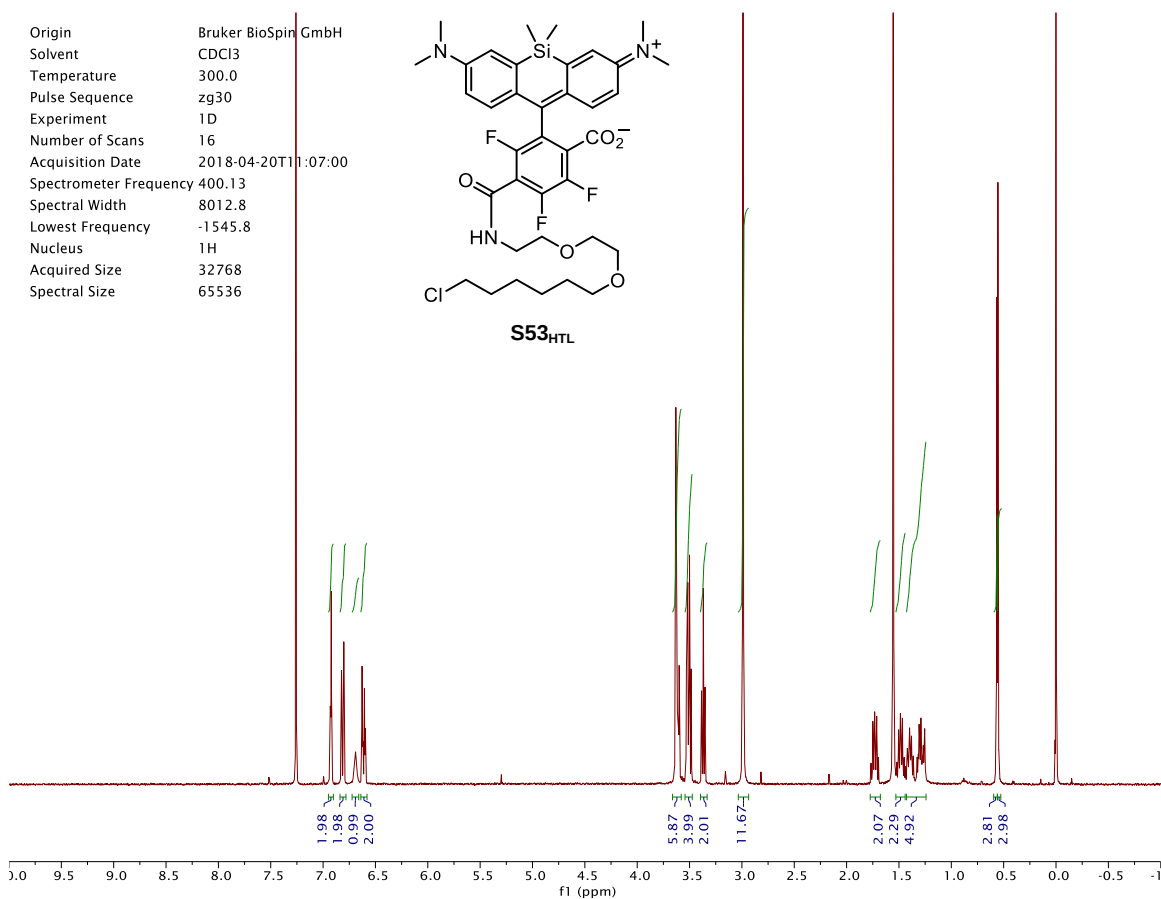
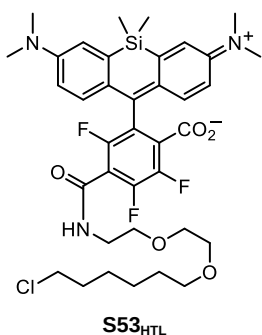
DAD1 A, Sig=254,4 Ref=off (2018_11\DAIY_SEQUENCE_LC 2018-11-07 09-55-12\2018_110000002.D)



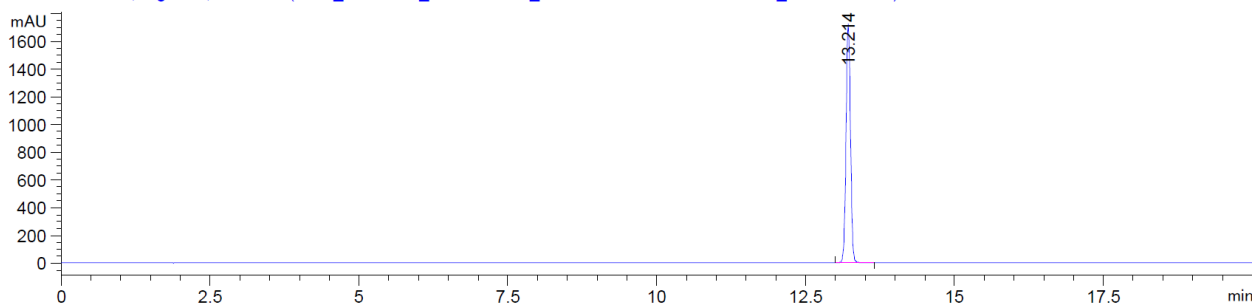
*MSD2 SPC, time=15.077:15.150 of C:\CHEM32\1\DATA\2018_11\DAIY_SEQUENCE_LC 2018-11-07 09-55-12\2018_110000002.D ES-



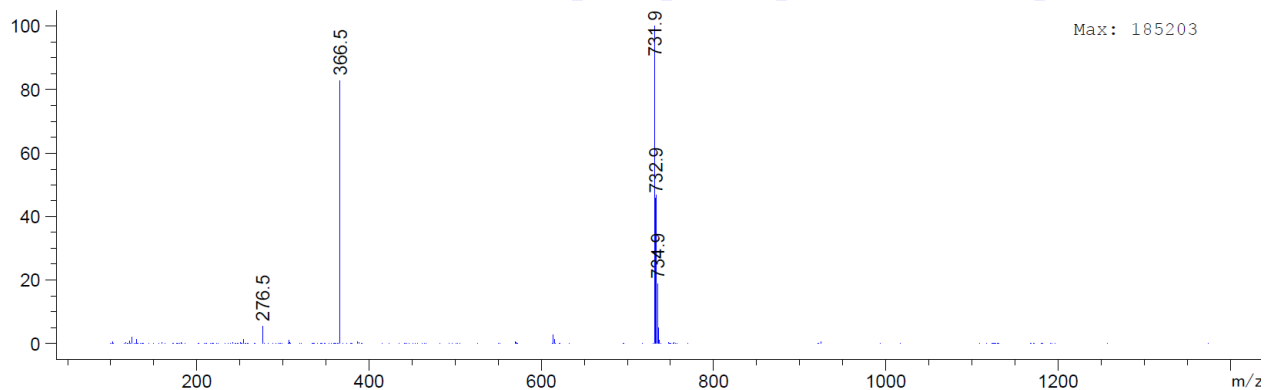
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-04-20T11:07:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.8
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



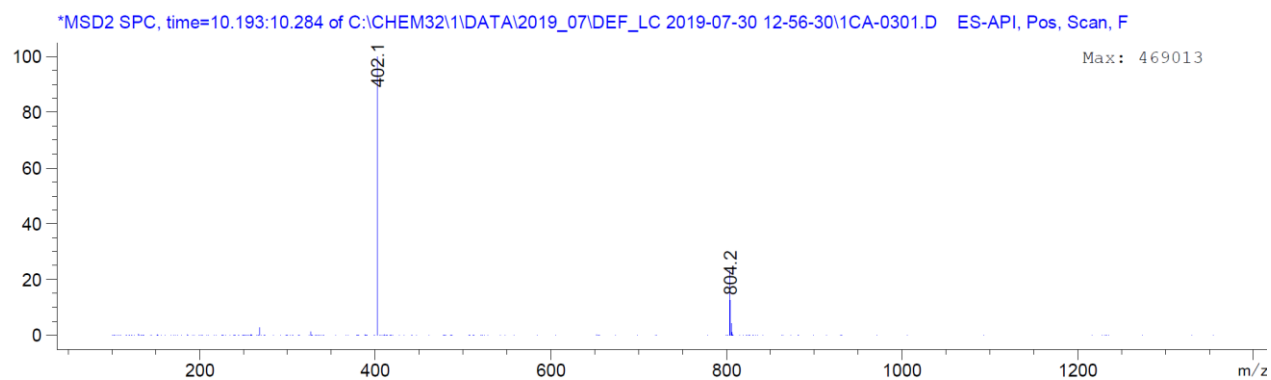
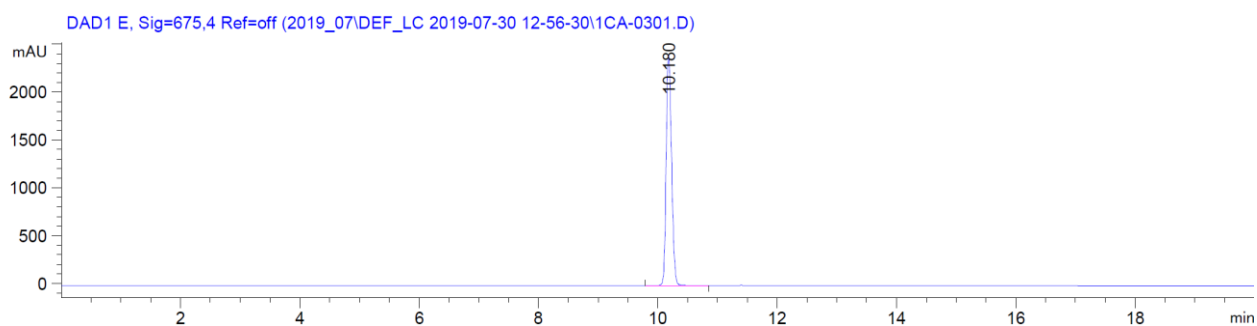
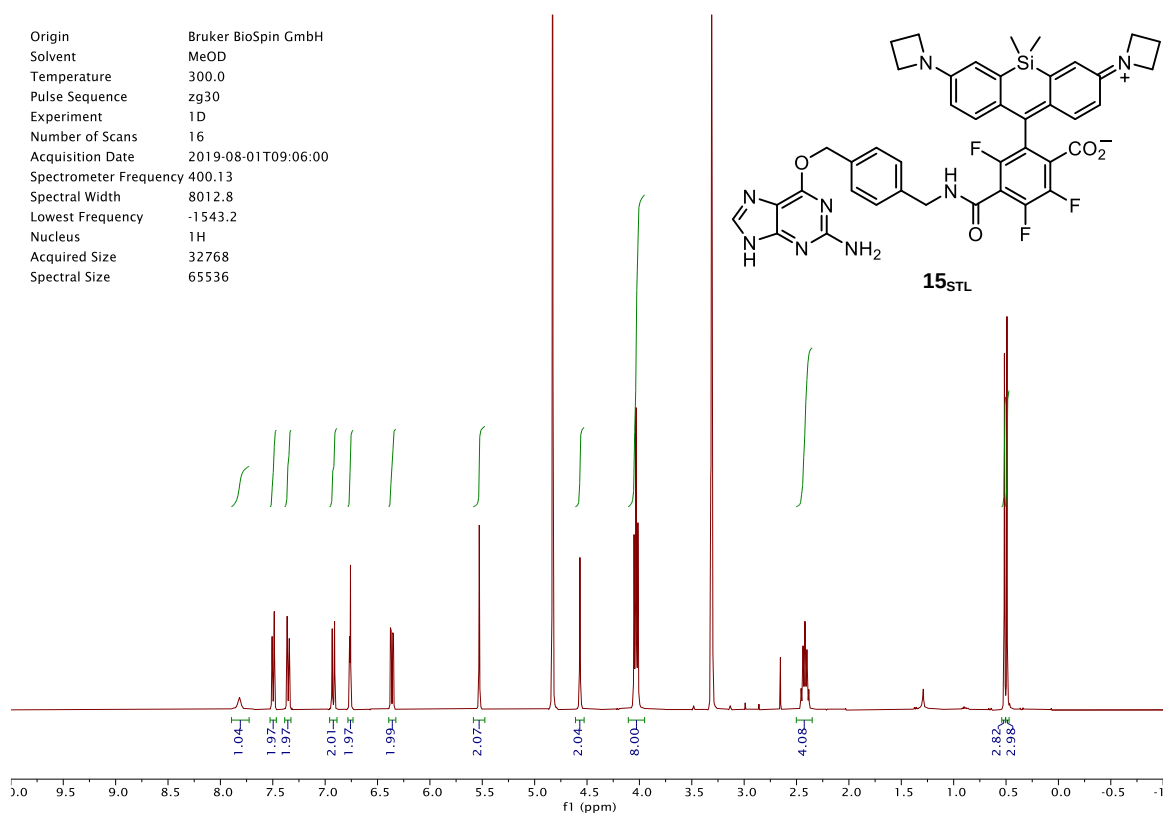
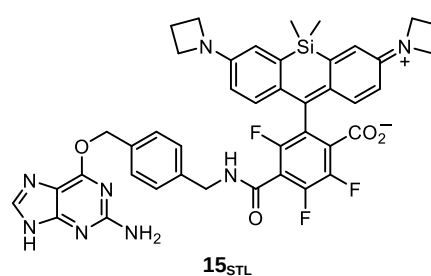
DAD1 E, Sig=675,4 Ref=off (2018_04\DAIY_SEQUENCE_LC 2018-04-19 11-55-50\2018_040000002.D)



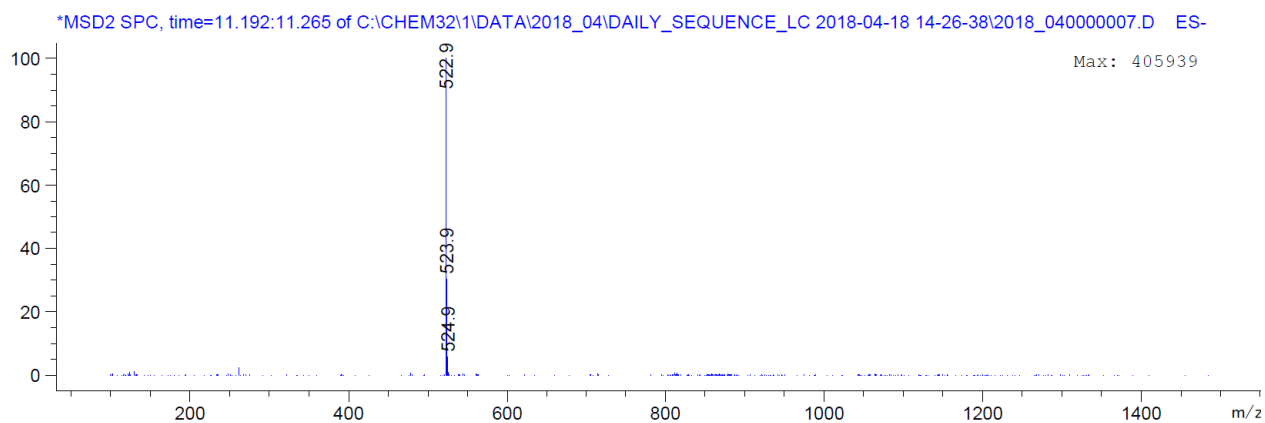
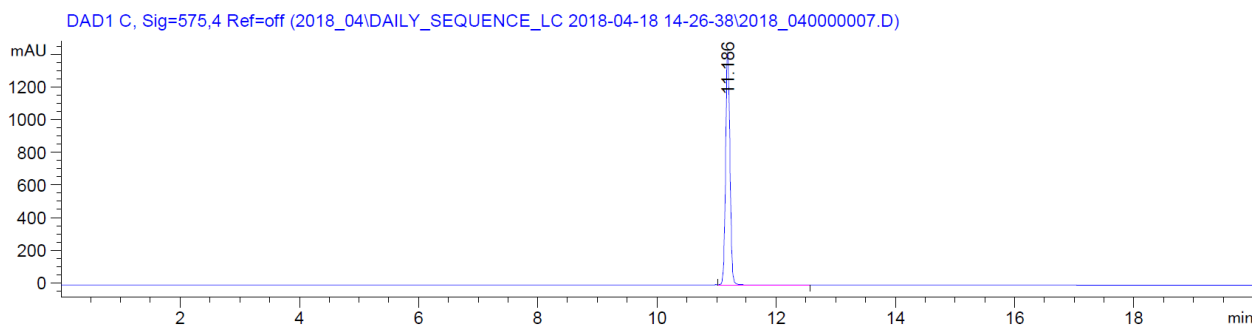
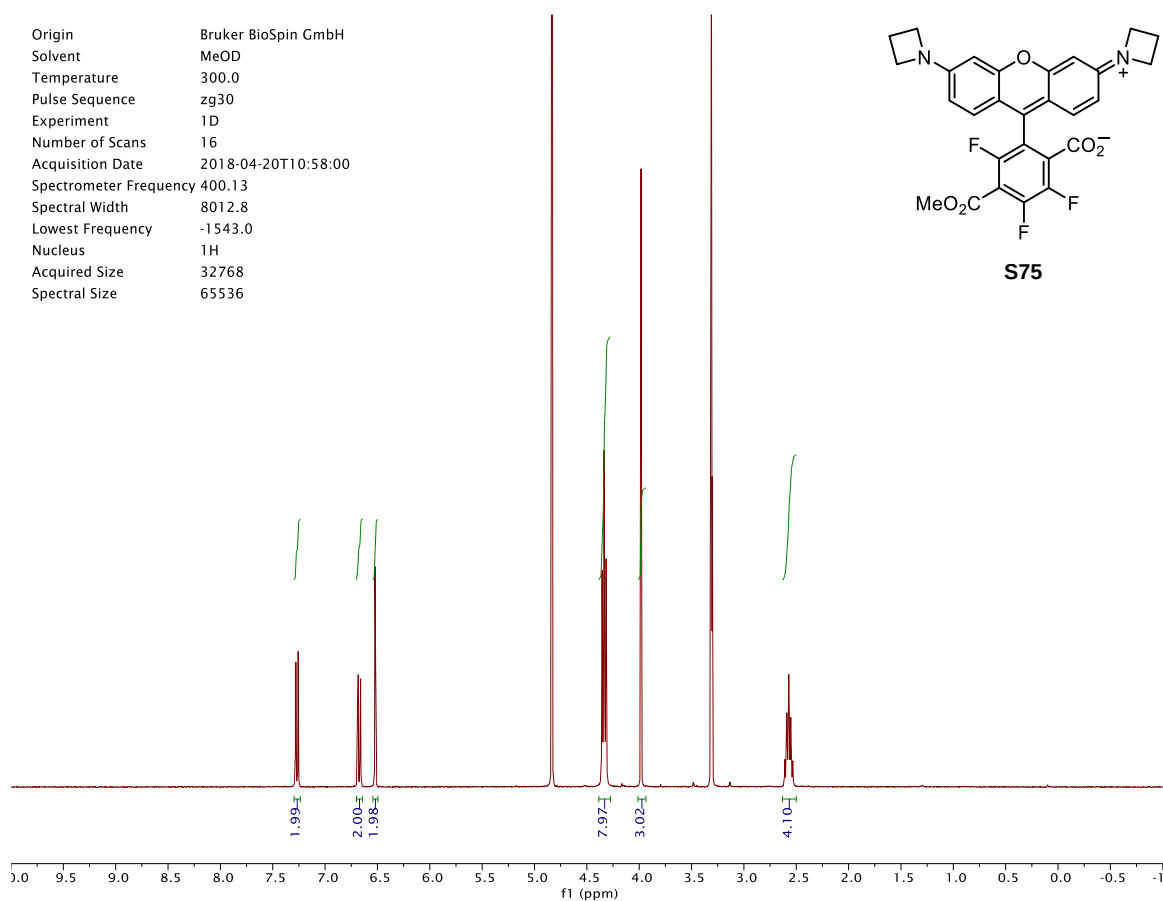
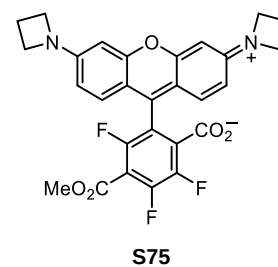
*MSD2 SPC, time=13.224:13.296 of C:\CHEM32\1\DATA\2018_04\DAIY_SEQUENCE_LC 2018-04-19 11-55-50\2018_040000002.D ES-



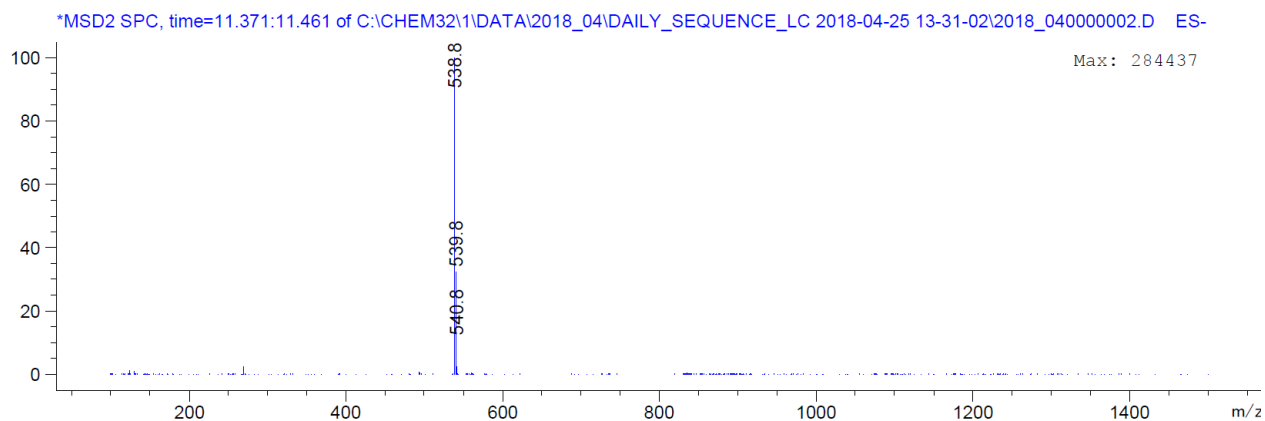
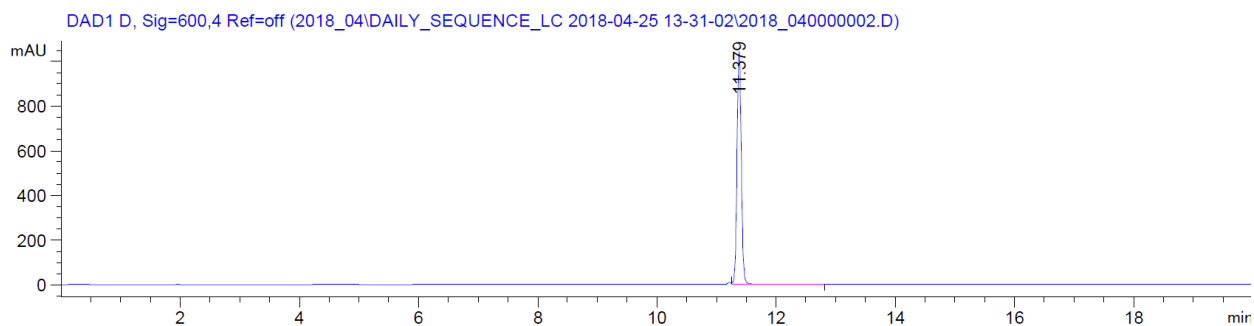
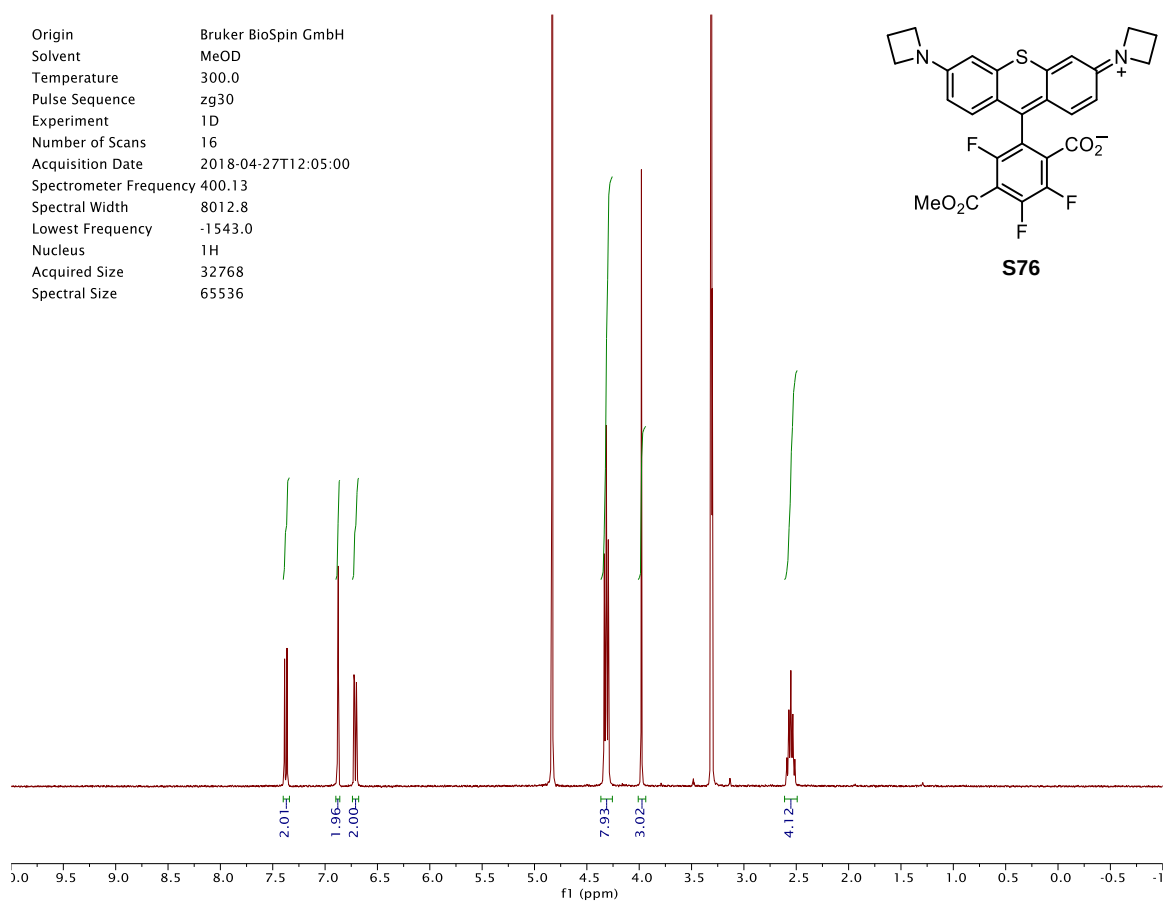
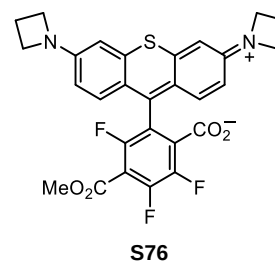
Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2019-08-01T09:06:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.2
 Nucleus 1H
 Acquired Size 32768
 Spectral Size 65536



Origin Bruker BioSpin GmbH
 Solvent MeOD
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-04-20T10:58:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1543.0
 Nucleus ^1H
 Acquired Size 32768
 Spectral Size 65536

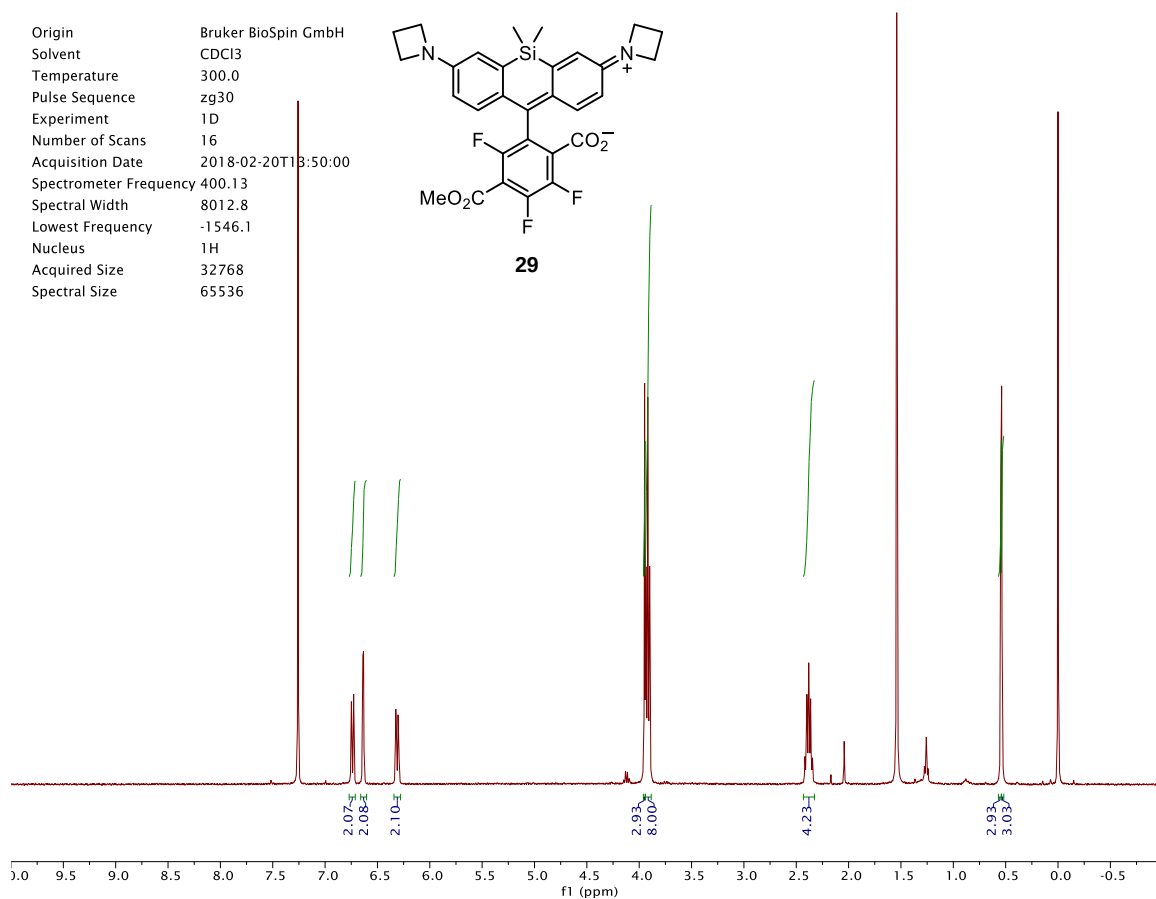
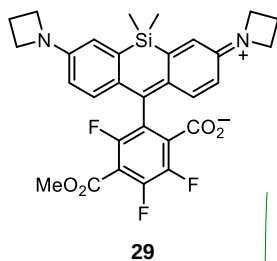


Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-04-27T12:05:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.0
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536

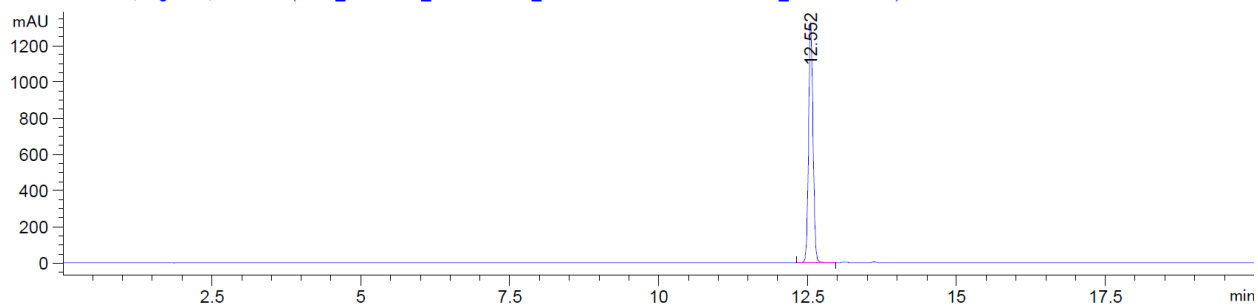


Origin
Solvent
Temperature
Pulse Sequence
Experiment
Number of Scans
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size

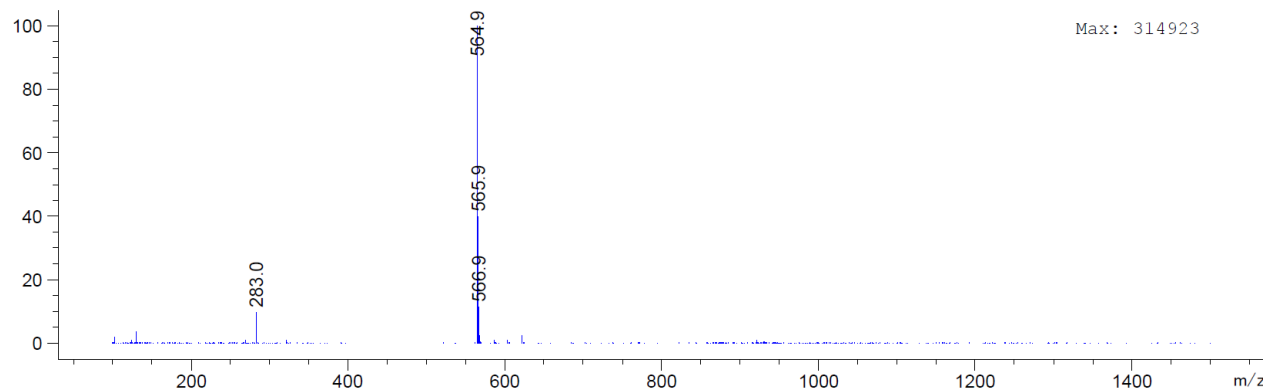
Bruker BioSpin GmbH
CDCl₃
300.0
zg30
1D
16
2018-02-20T18:50:00
400.13
8012.8
-1546.1
1H
32768
65536



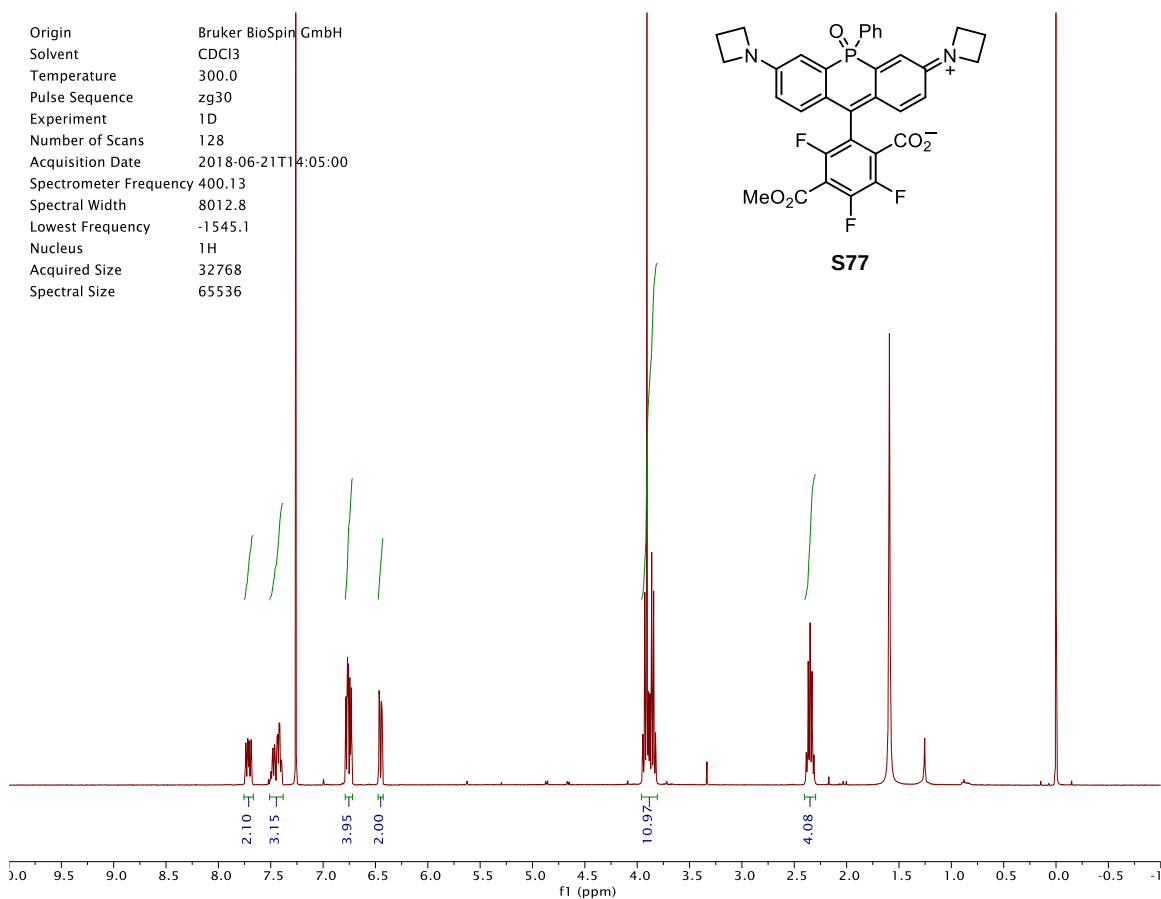
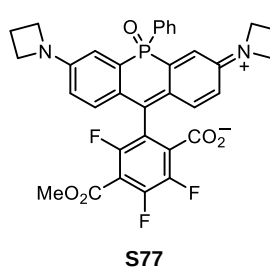
DAD1 E, Sig=675,4 Ref=off (2018_02\DAIY_SEQUENCE_LC 2018-04-16 11-42-42\2018_030000002.D)



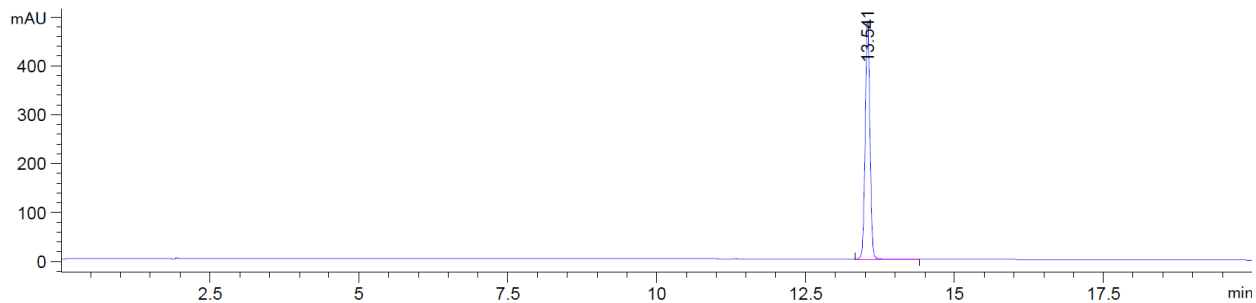
*MSD2 SPC, time=12.551:12.642 of C:\CHEM32\1\DATA\2018_02\DAIY_SEQUENCE_LC 2018-04-16 11-42-42\2018_030000002.D ES-



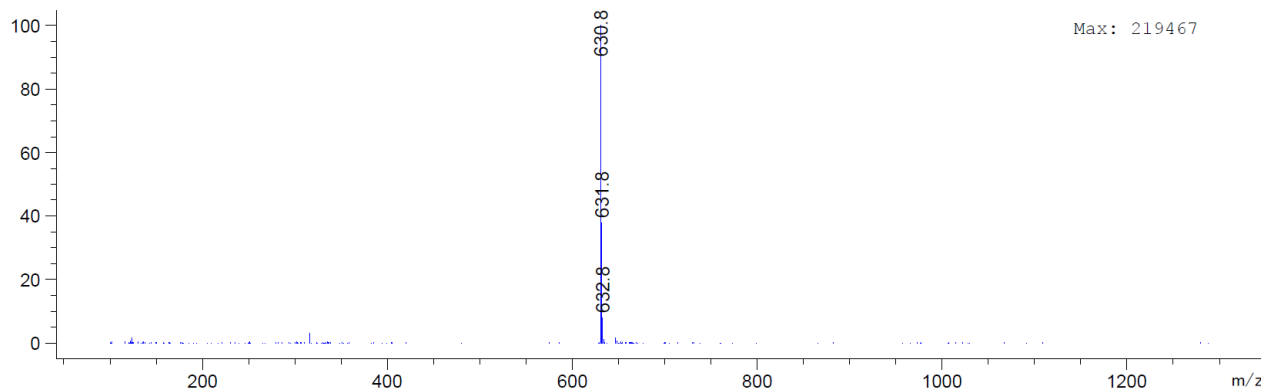
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 128
 Acquisition Date: 2018-06-21T14:05:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.1
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



DAD1 E, Sig=725,4 Ref=off (2018_06\DAIY_SEQUENCE_LC 2018-06-20 13-57-30\2018_060000002.D)

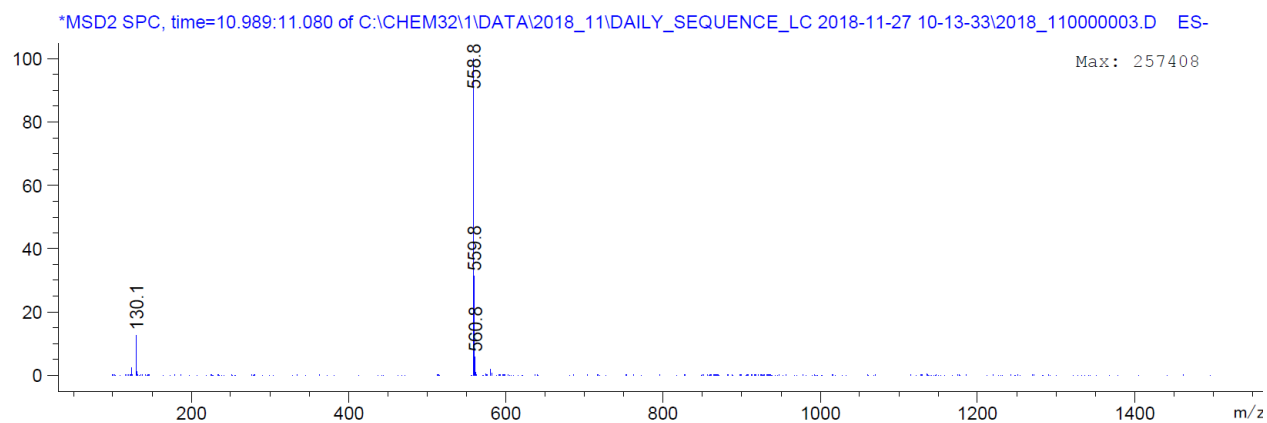
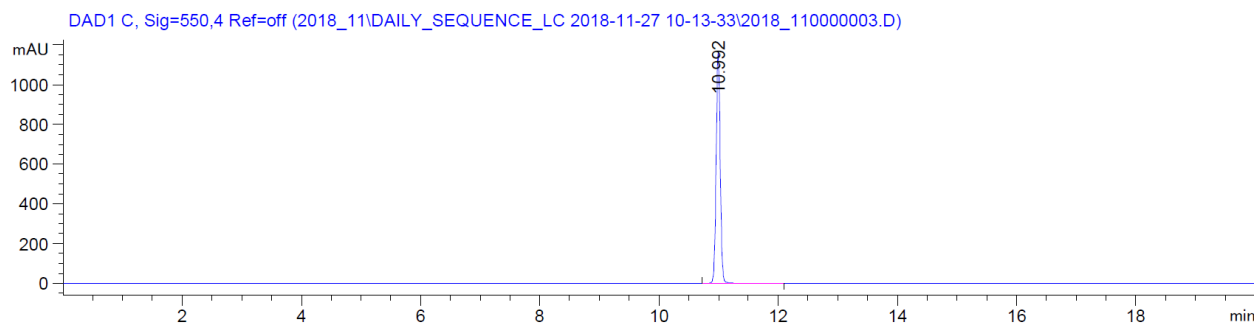
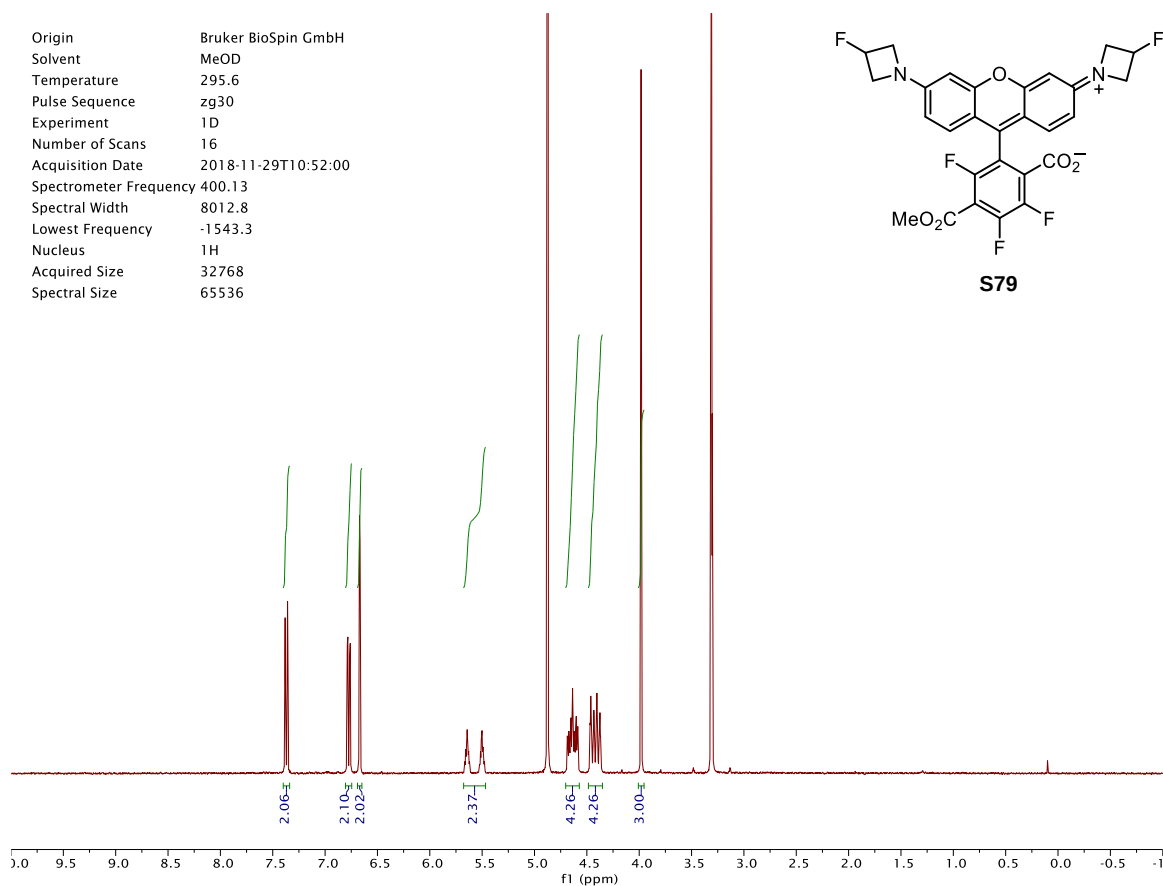
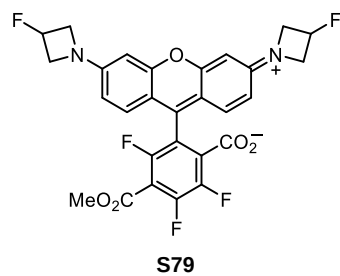


*MSD2 SPC, time=13.532:13.623 of C:\CHEM32\1\DATA\2018_06\DAIY_SEQUENCE_LC 2018-06-20 13-57-30\2018_060000002.D ES-



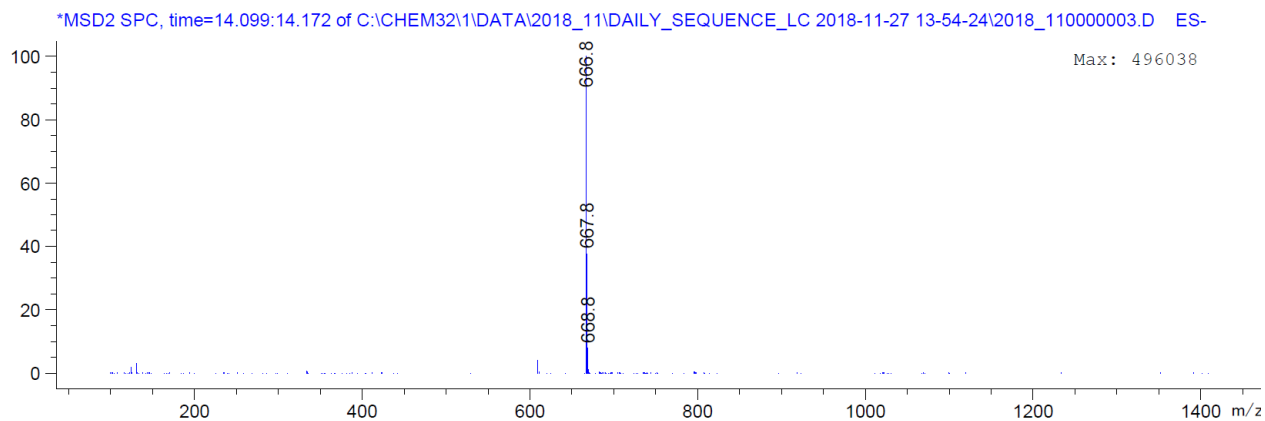
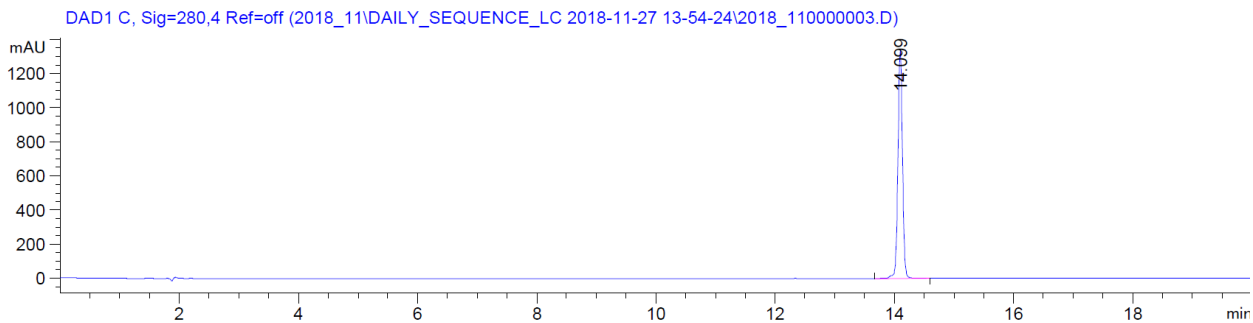
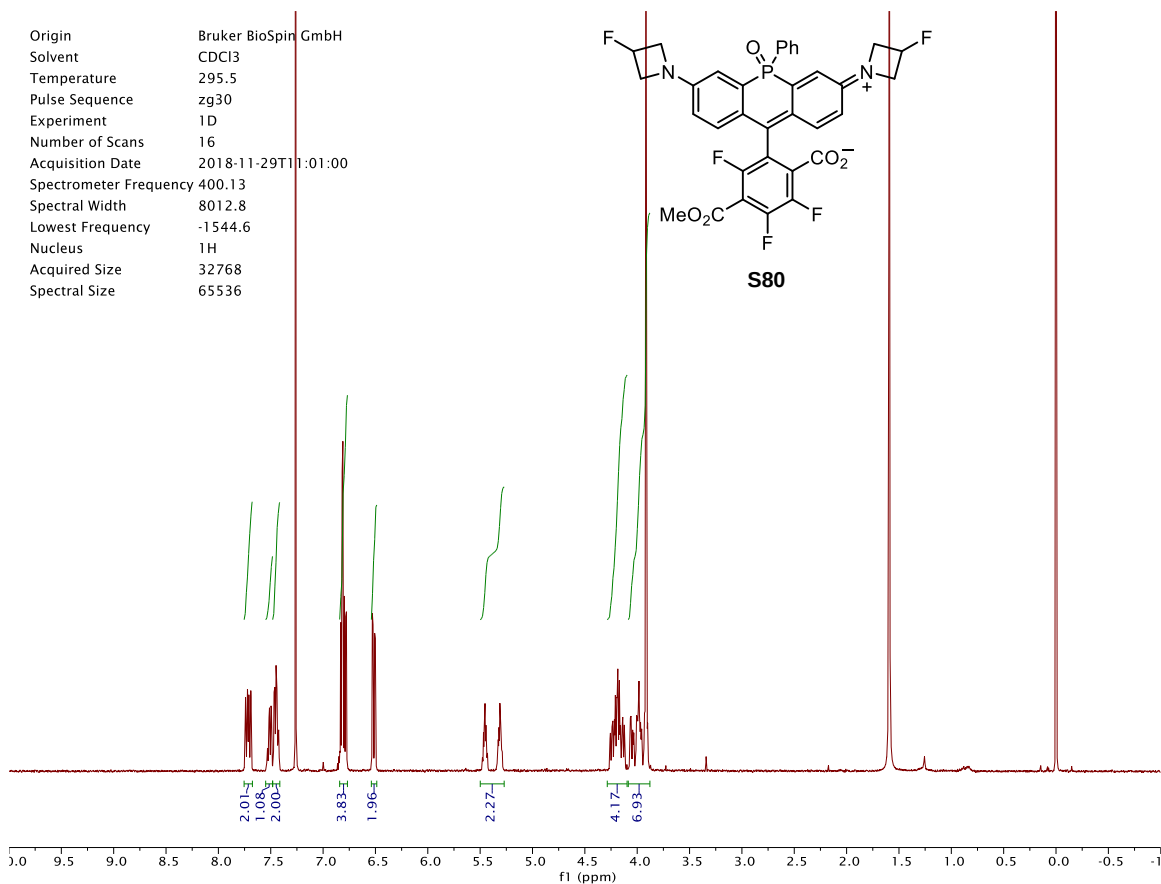
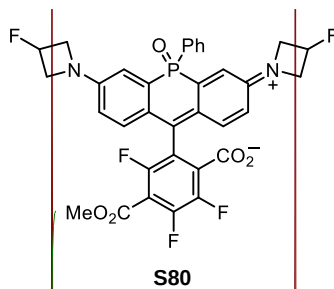


Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 295.6
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-11-29T10:52:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.3
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536

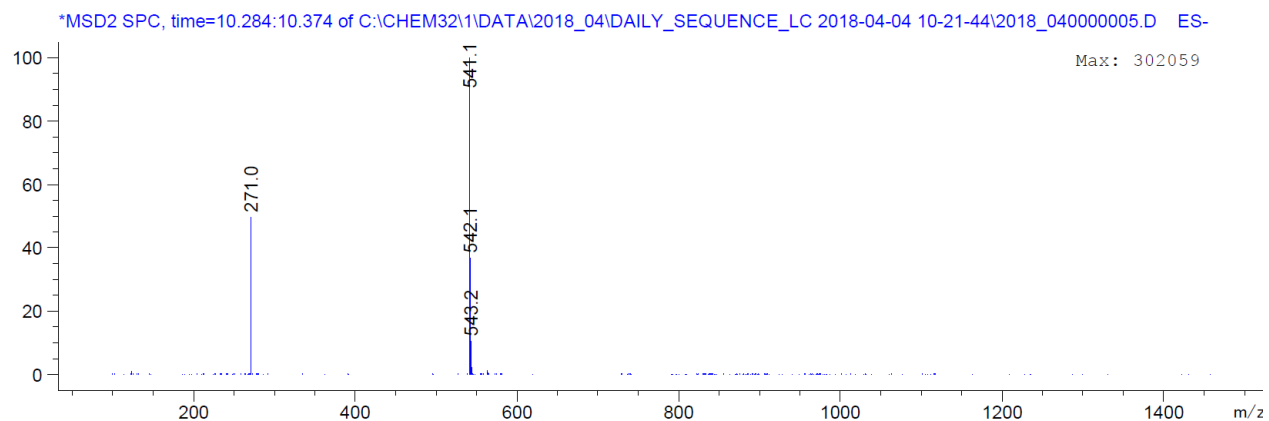
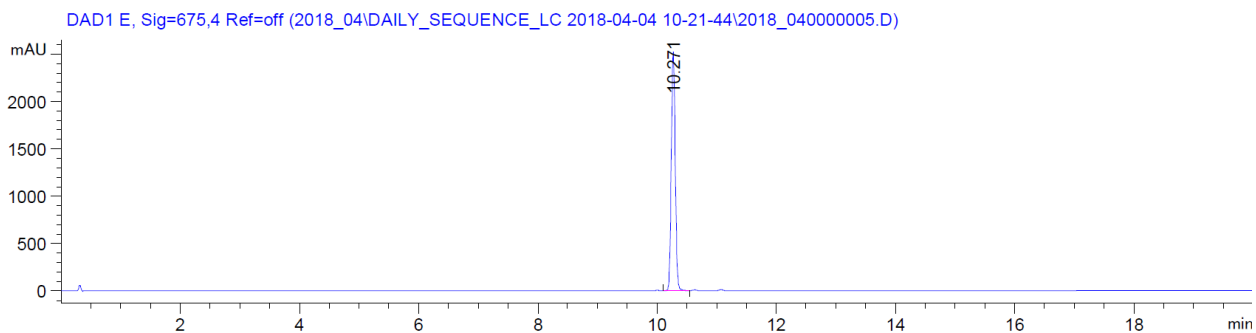
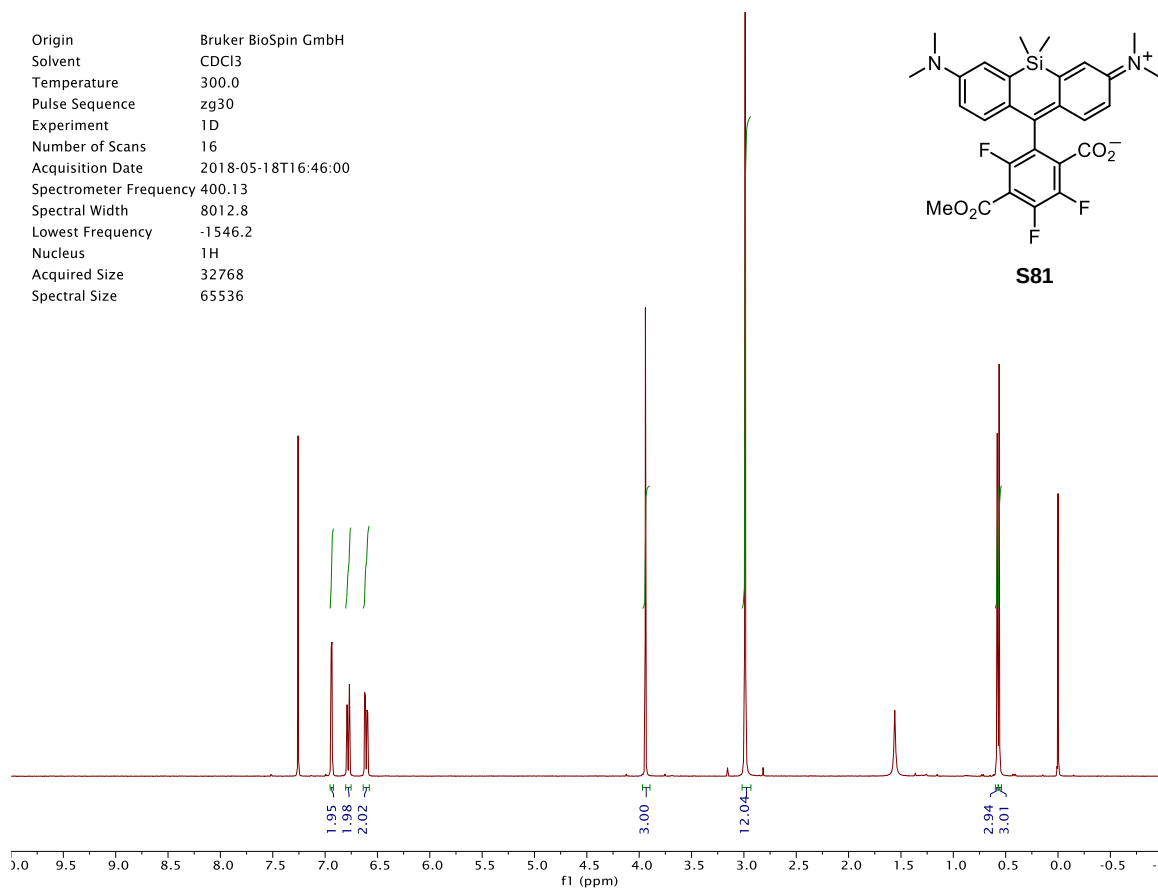
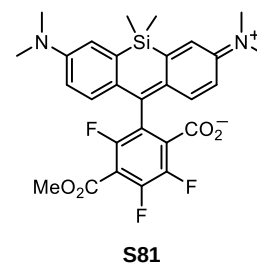


Origin
Solvent
Temperature
Pulse Sequence
Experiment
Number of Scans
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size

Bruker BioSpin GmbH
CDCl3
295.5
zg30
1D
16
2018-11-29T11:01:00
400.13
8012.8
-1544.6
1H
32768
65536

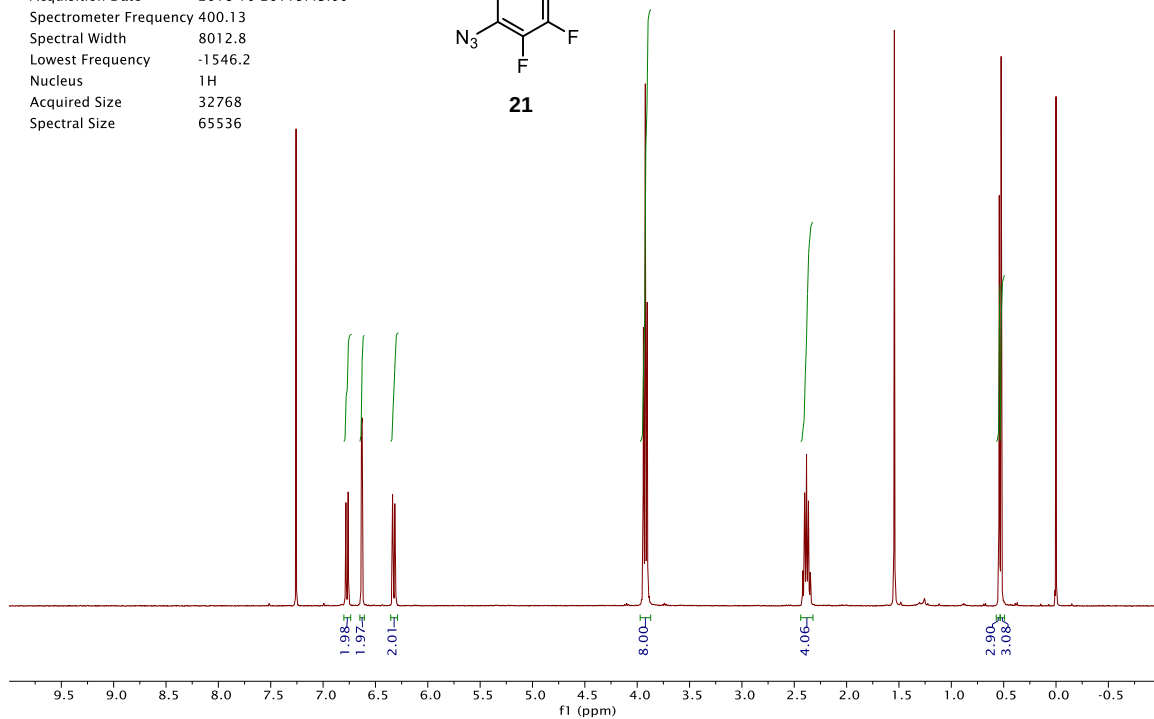
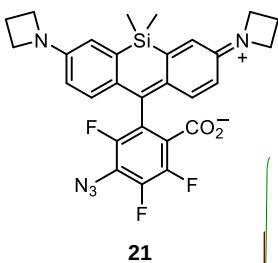


Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-05-18T16:46:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1546.2
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536

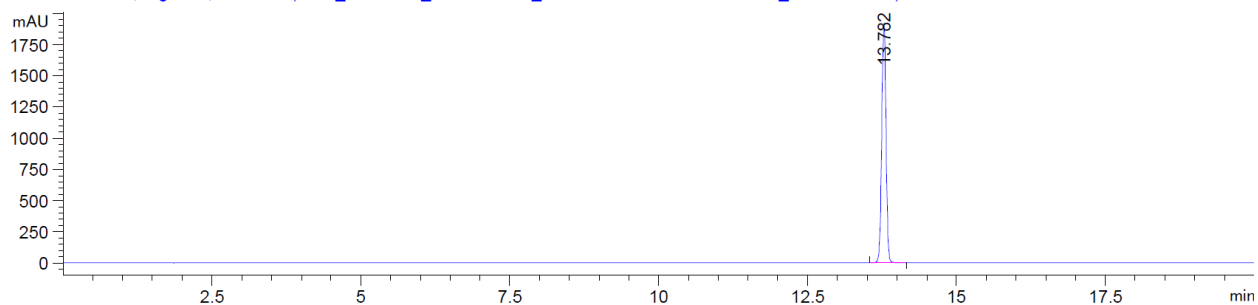


Origin
Solvent
Temperature
Pulse Sequence
Experiment
Number of Scans
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size

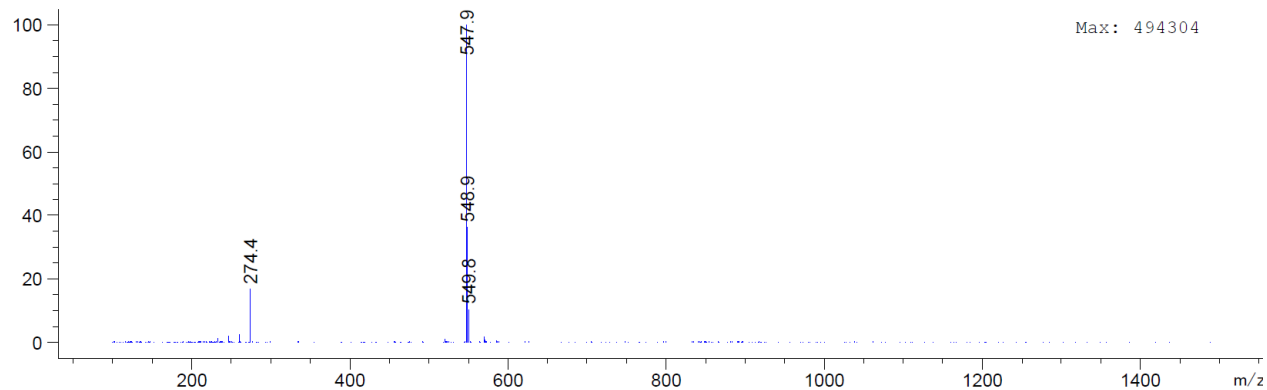
Bruker BioSpin GmbH
CDCl3
300.0
zg30
1D
16
2018-10-26T15:43:00
400.13
8012.8
-1546.2
1H
32768
65536



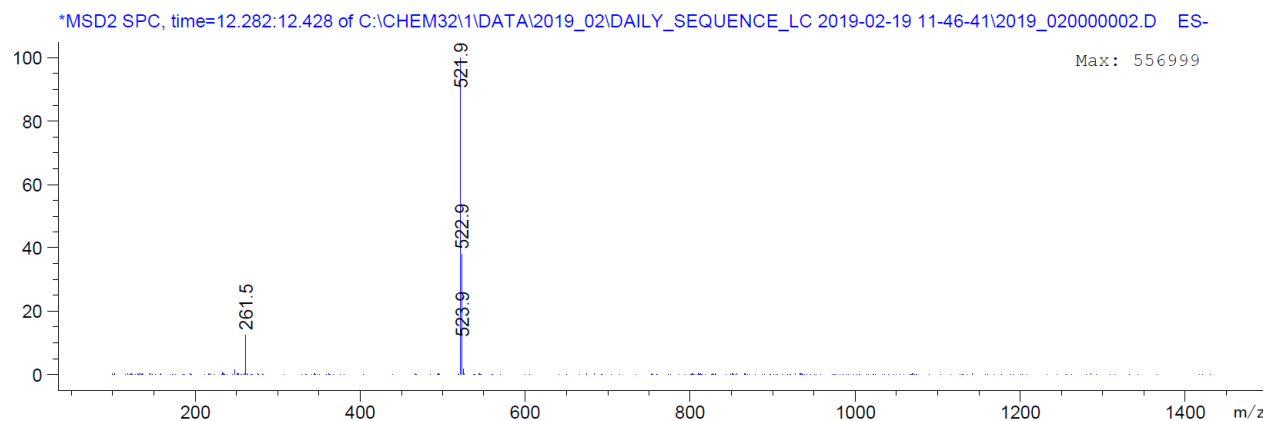
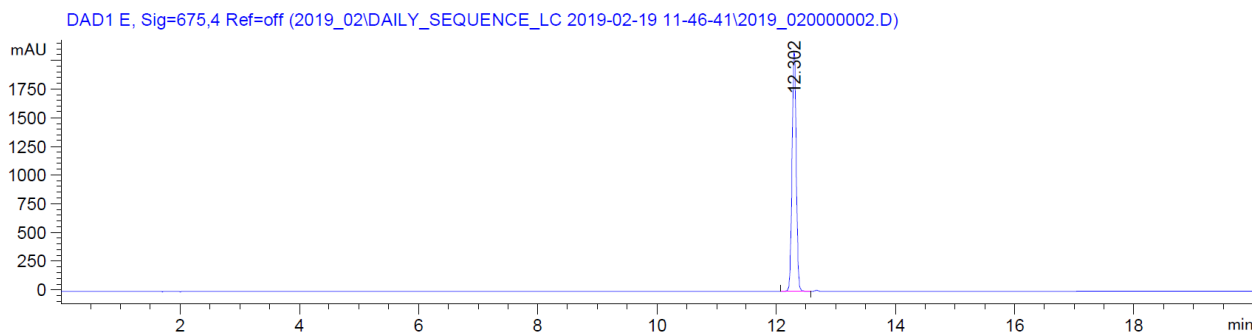
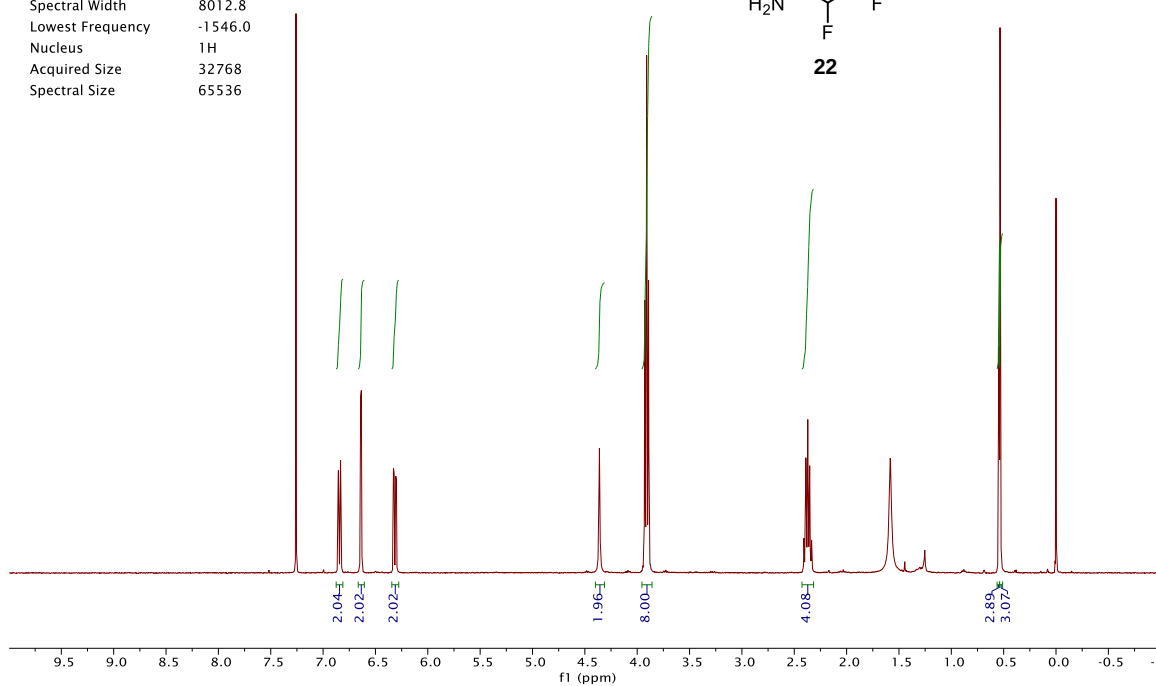
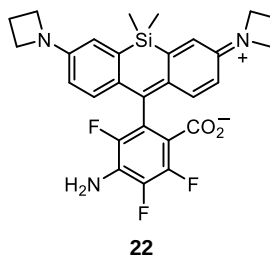
DAD1 E, Sig=675,4 Ref=off (2018_10\DAILY_SEQUENCE_LC 2018-10-18 14-12-26\2018_100000002.D)



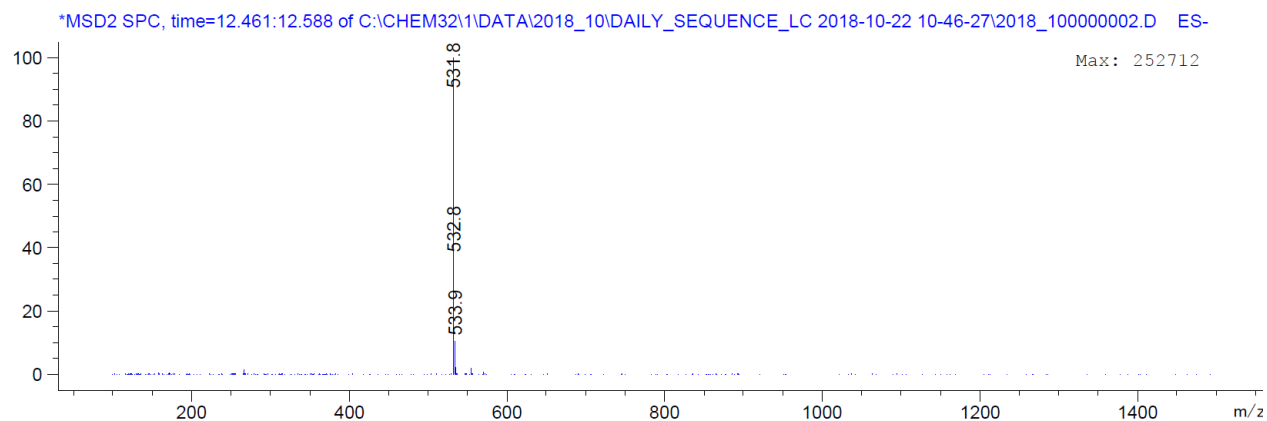
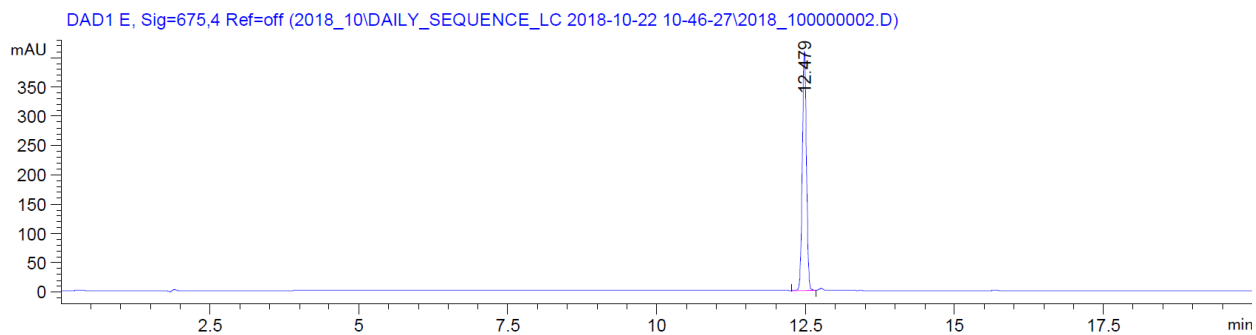
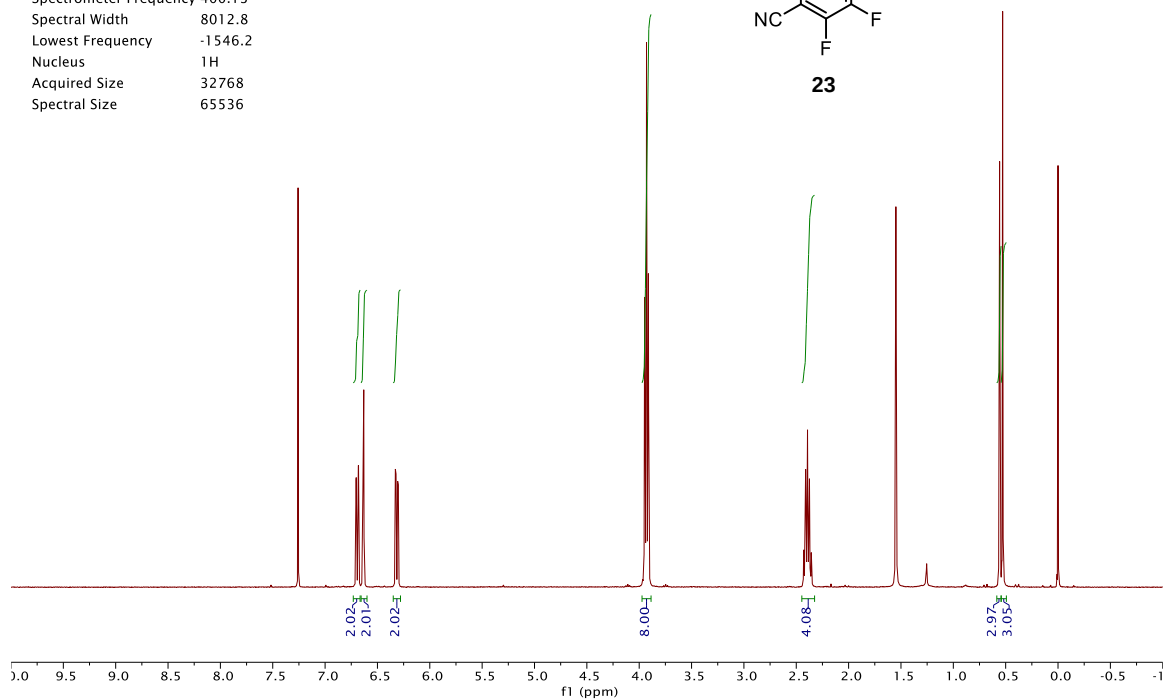
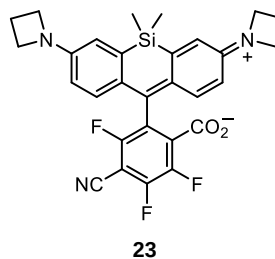
*MSD2 SPC, time=13.769:13.860 of C:\CHEM32\1\DATA\2018_10\DAILY_SEQUENCE_LC 2018-10-18 14-12-26\2018_100000002.D ES-



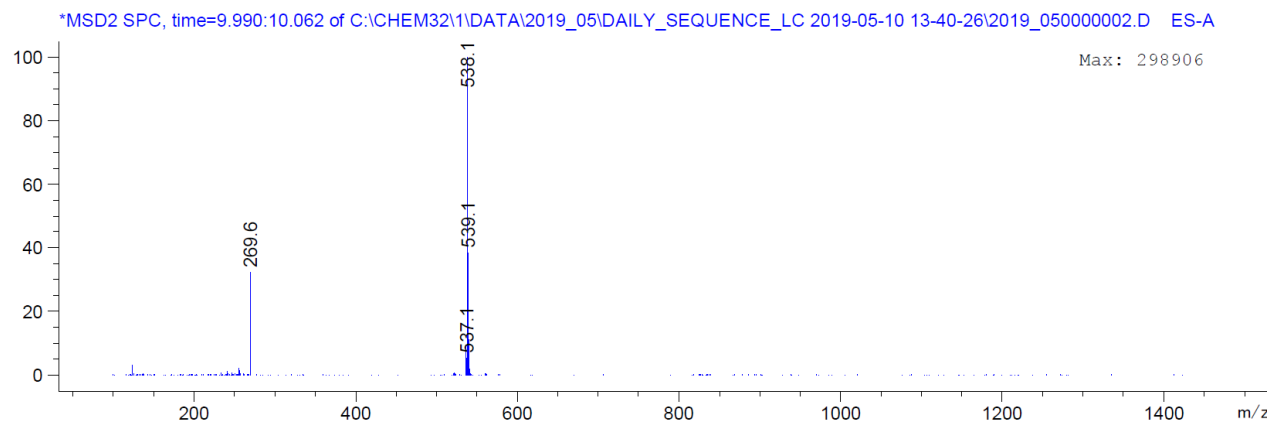
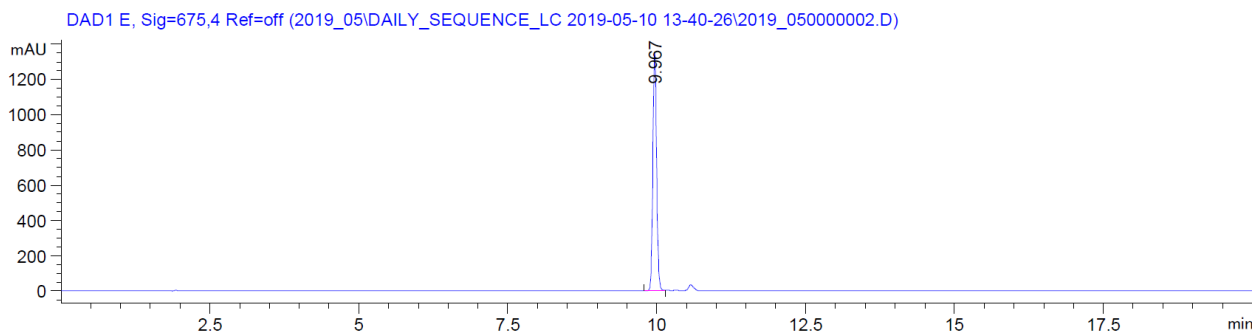
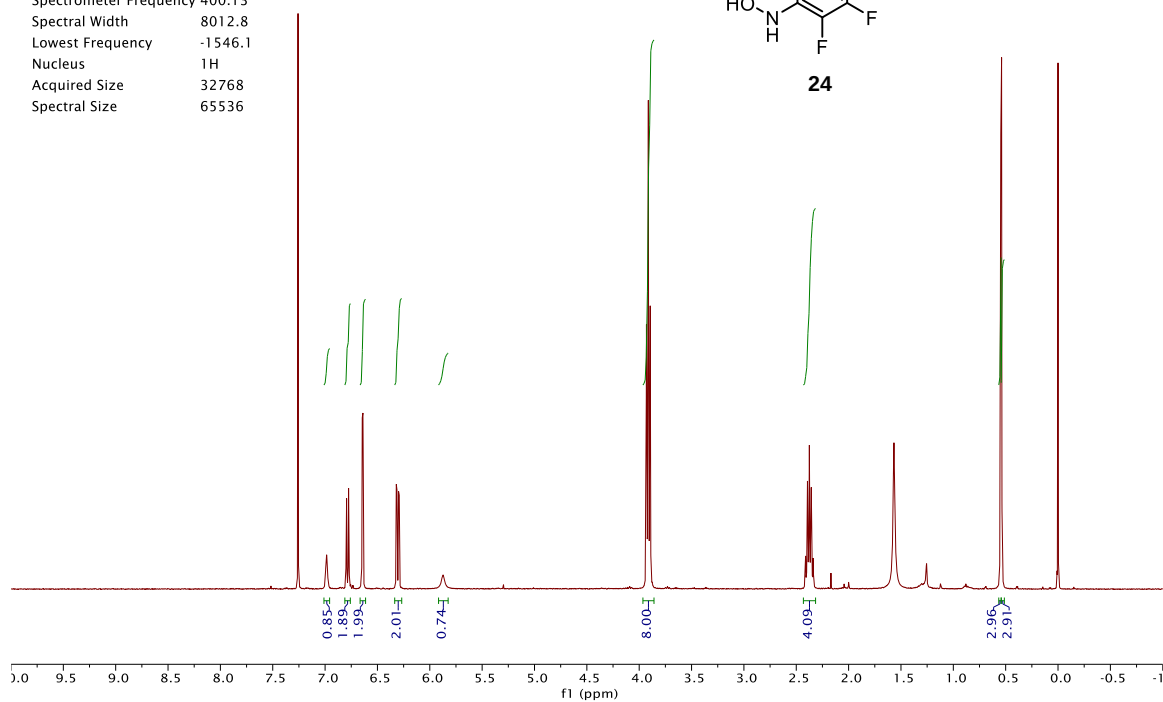
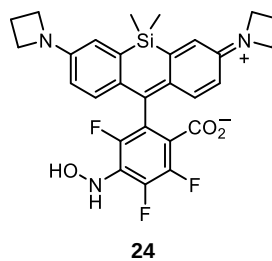
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2019-05-09T12:02:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1546.0
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



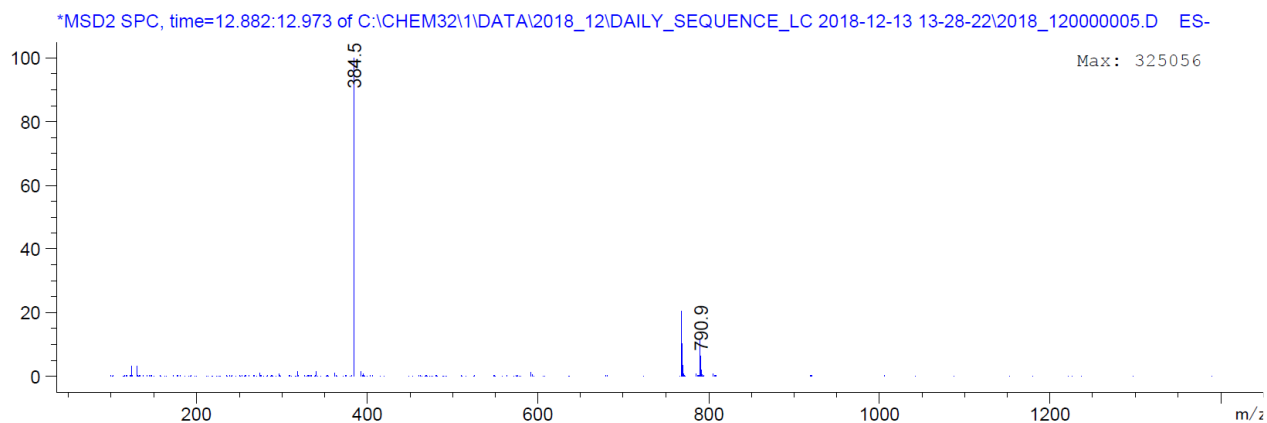
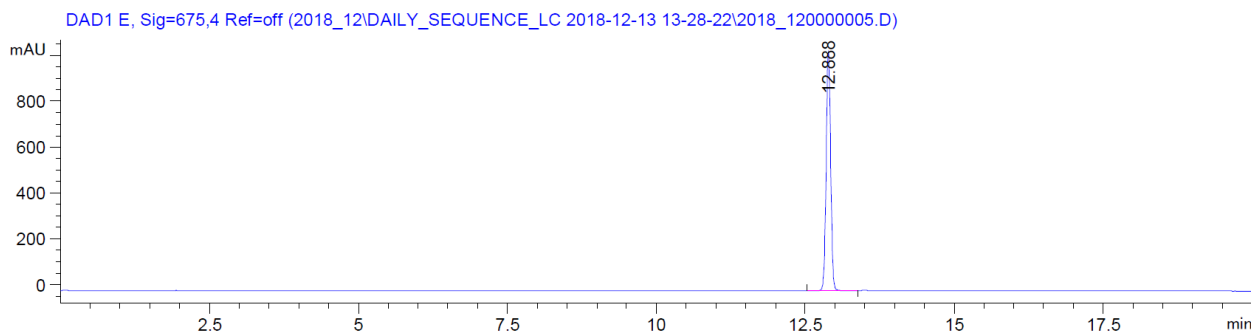
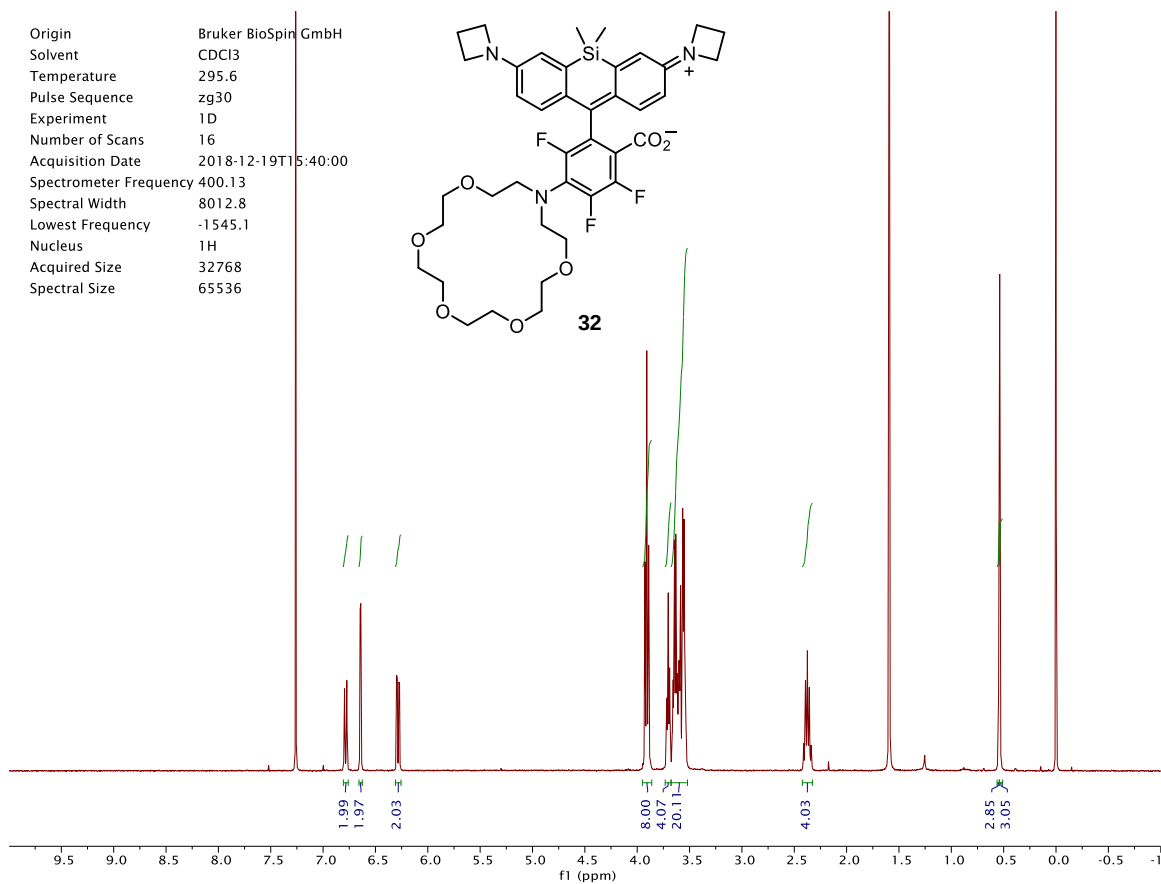
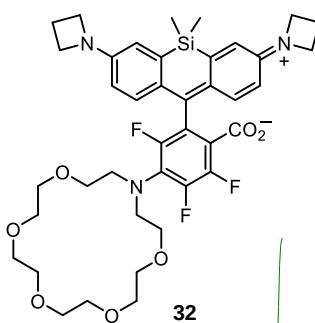
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-11-05T16:26:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1546.2
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



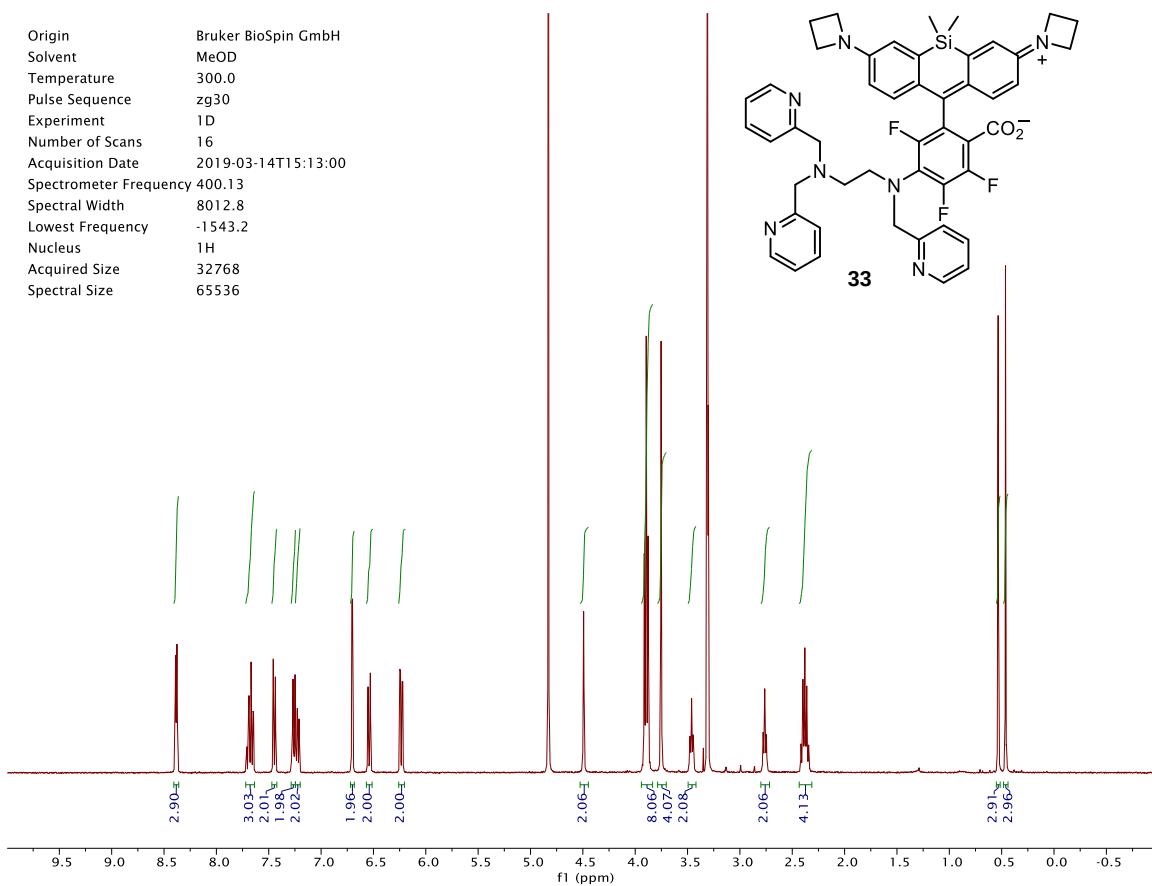
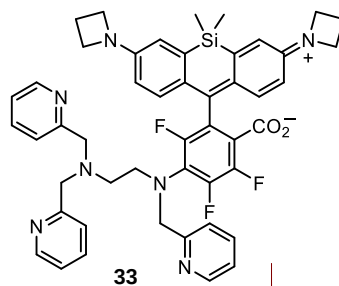
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2019-03-26T15:45:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1546.1
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



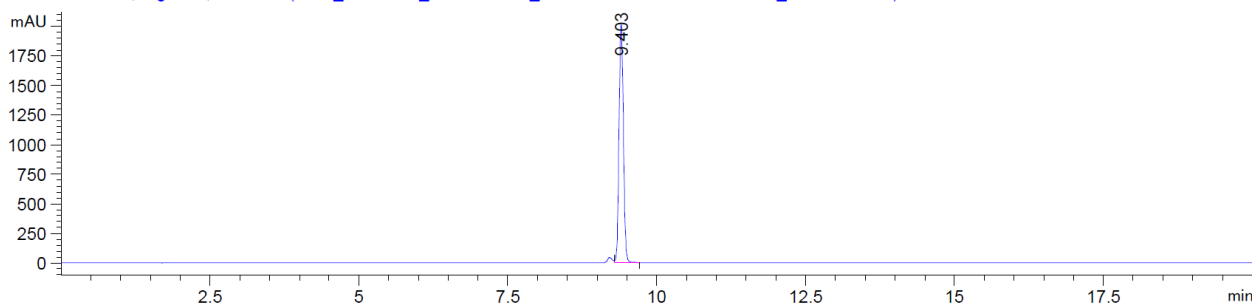
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 295.6
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-12-19T15:40:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.1
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



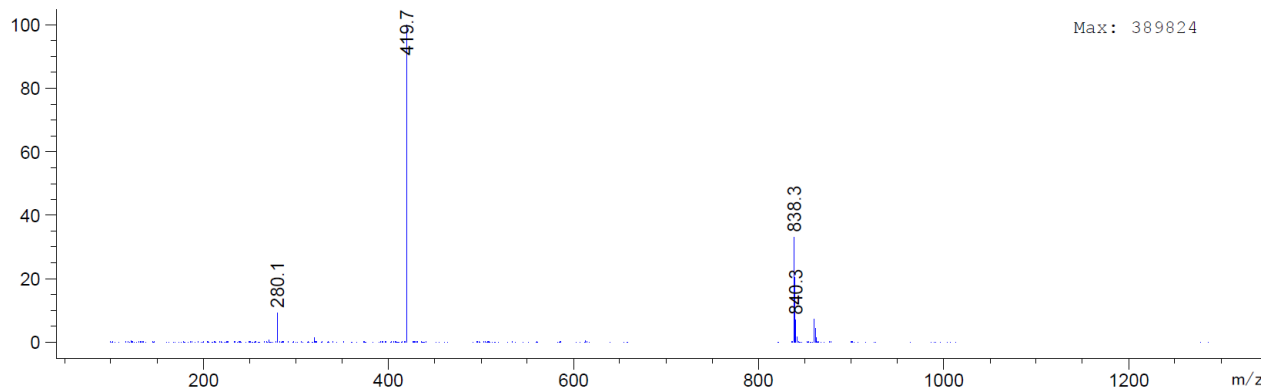
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2019-03-14T15:13:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.2
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



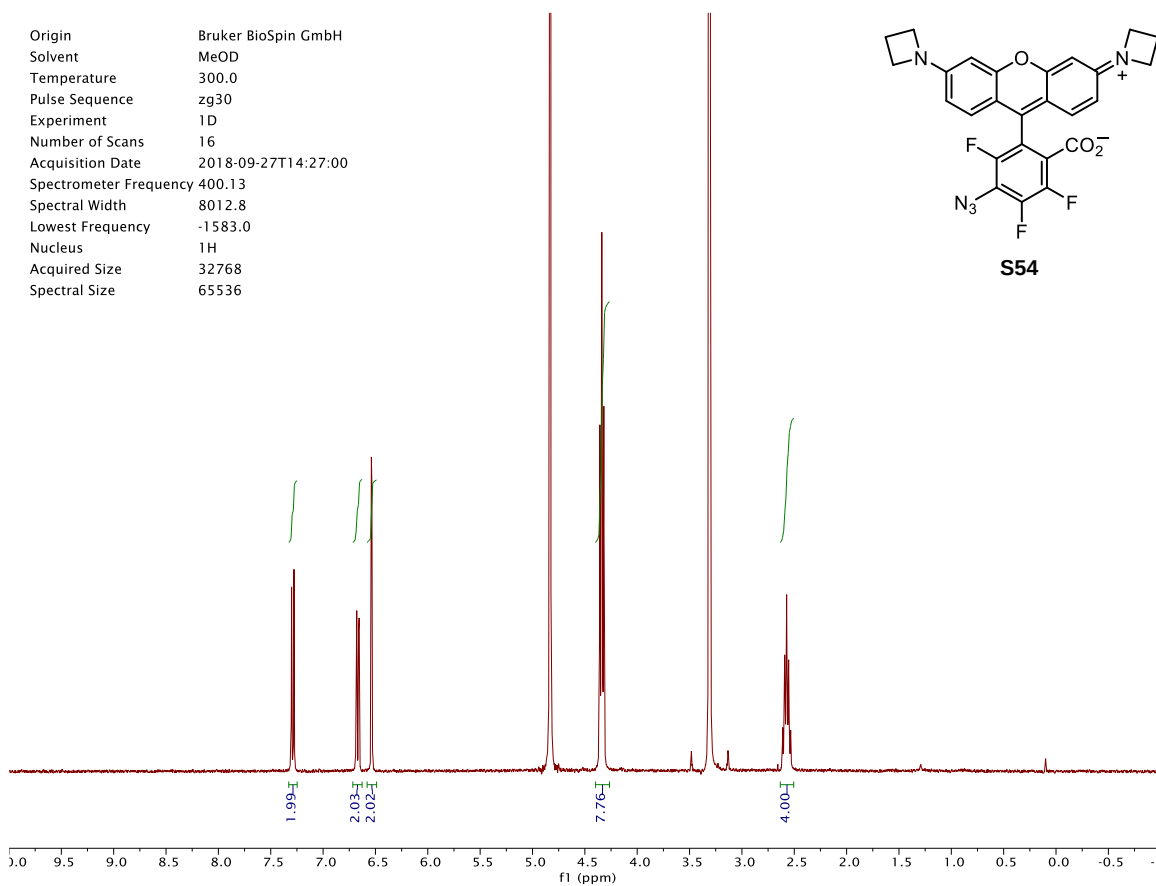
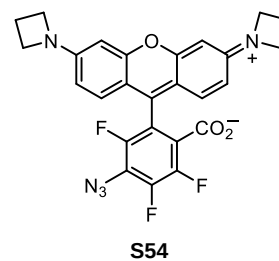
DAD1 E, Sig=675,4 Ref=off (2019_04\DAIY_SEQUENCE_LC 2019-04-08 14-40-21\2019_040000002.D)



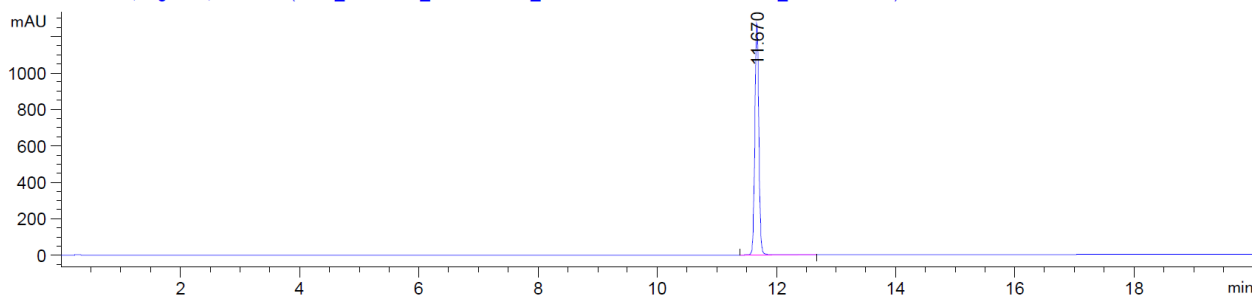
*MSD2 SPC, time=9.408:9.499 of C:\CHEM32\1\DATA\2019_04\DAIY_SEQUENCE_LC 2019-04-08 14-40-21\2019_040000002.D ES-AP



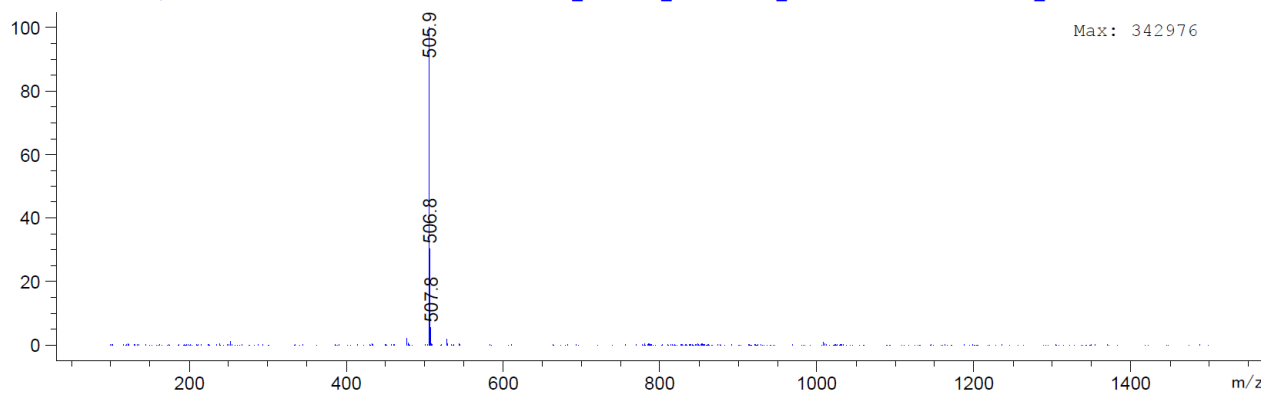
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-09-27T14:27:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1583.0
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536



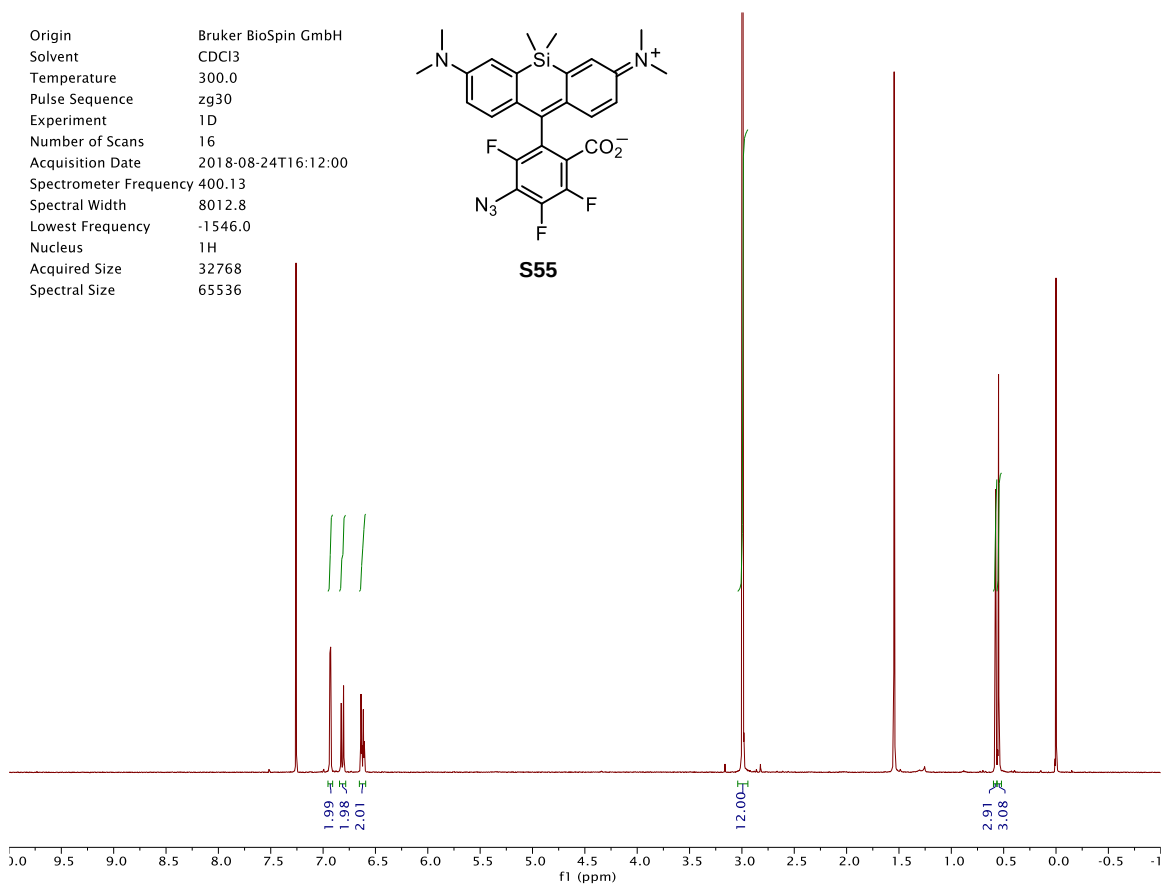
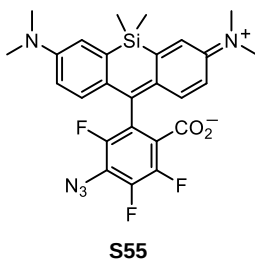
DAD1 C, Sig=575.4 Ref=off (2018_09\DAIY_SEQUENCE_LC 2018-09-24 11-32-46\2018_090000002.D)



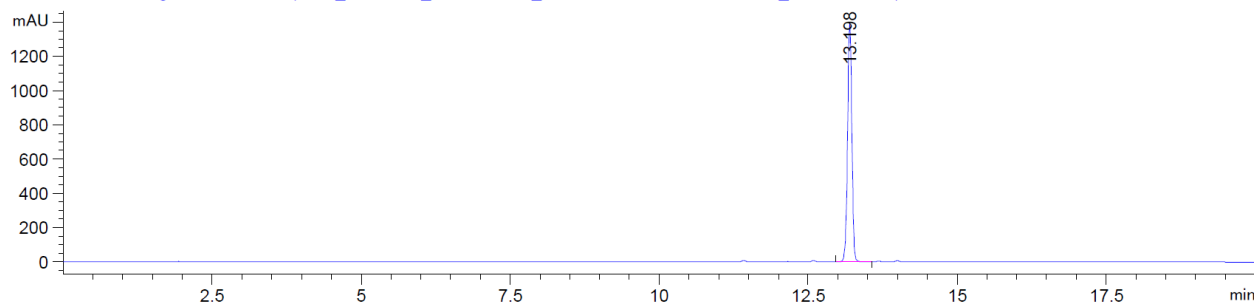
*MSD2 SPC, time=11.661:11.752 of C:\CHEM32\1\DATA\2018_09\DAIY_SEQUENCE_LC 2018-09-24 11-32-46\2018_090000002.D ES-



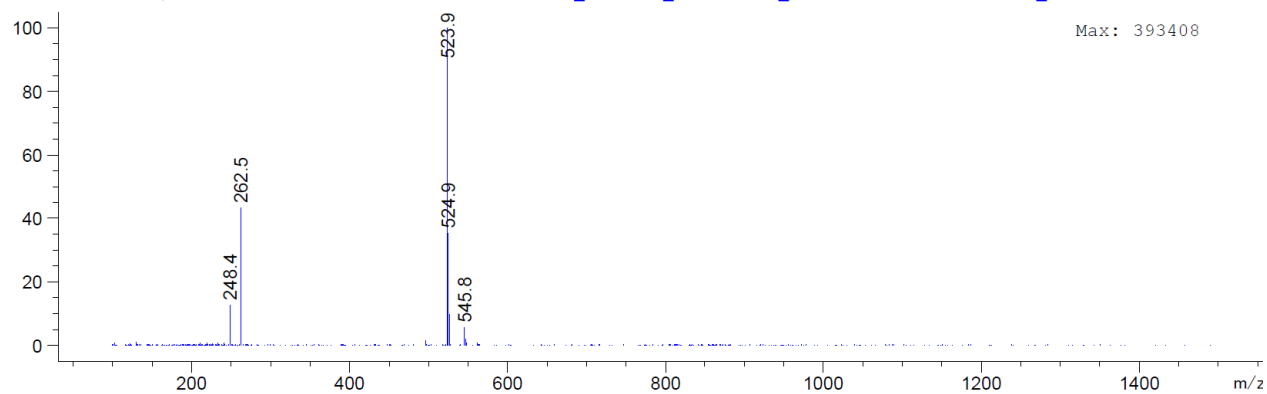
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-08-24T16:12:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1546.0
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



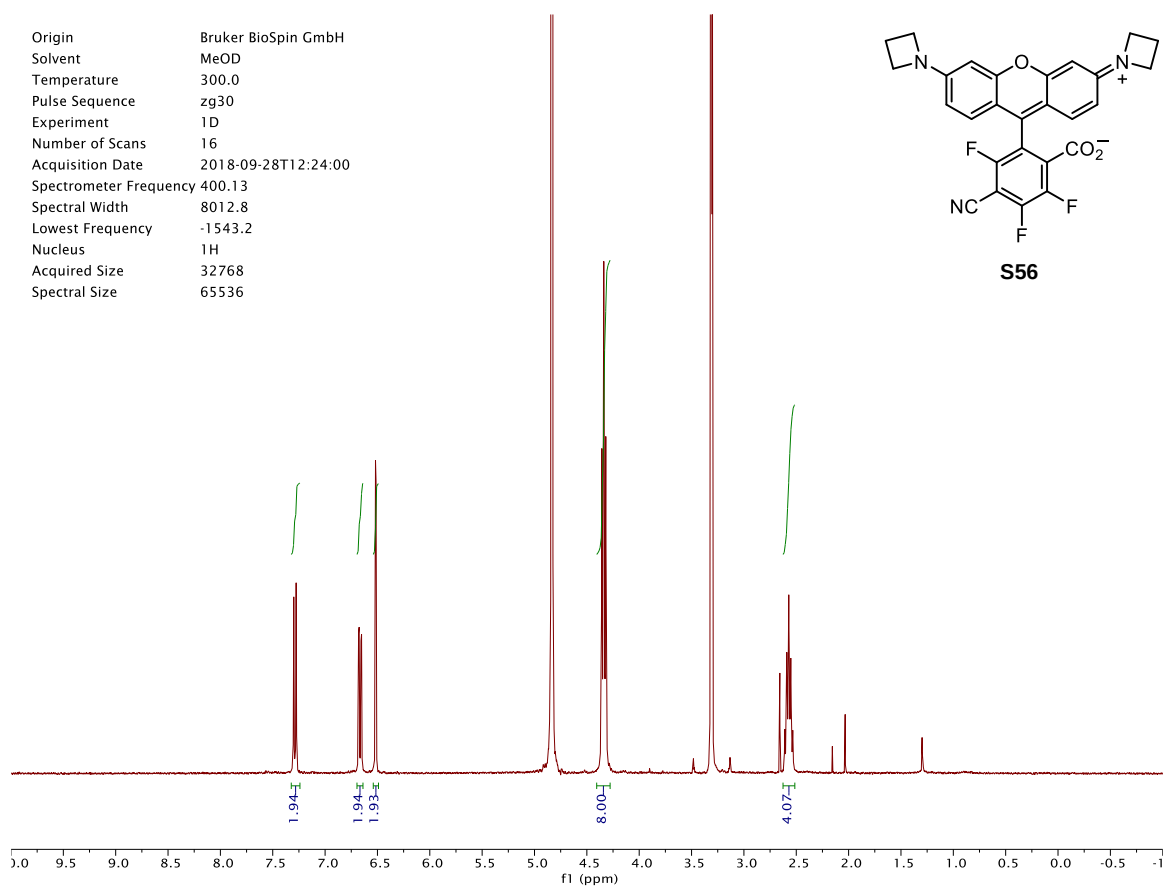
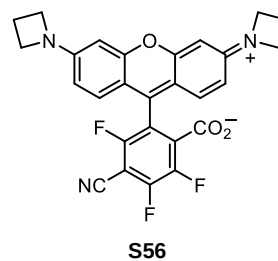
DAD1 E, Sig=675.4 Ref=off (2018_08\DAIY_SEQUENCE_LC 2018-08-24 15-41-36\2018_080000003.D)



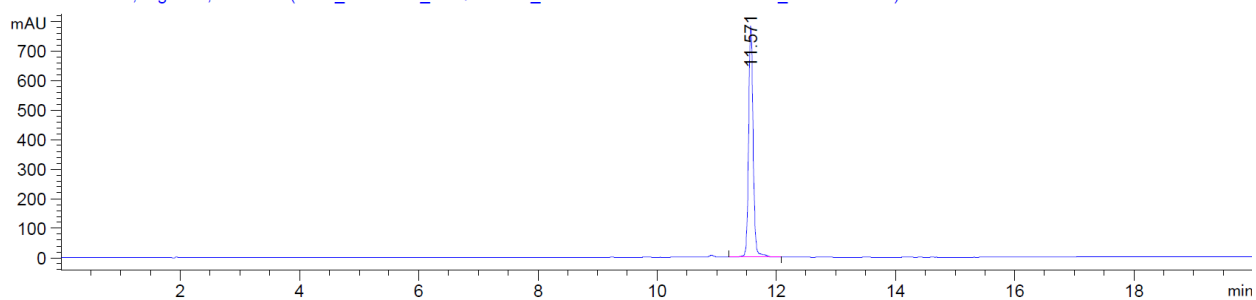
*MSD2 SPC, time=13.191:13.282 of C:\CHEM32\1\DATA\2018_08\DAIY_SEQUENCE_LC 2018-08-24 15-41-36\2018_080000003.D ES-



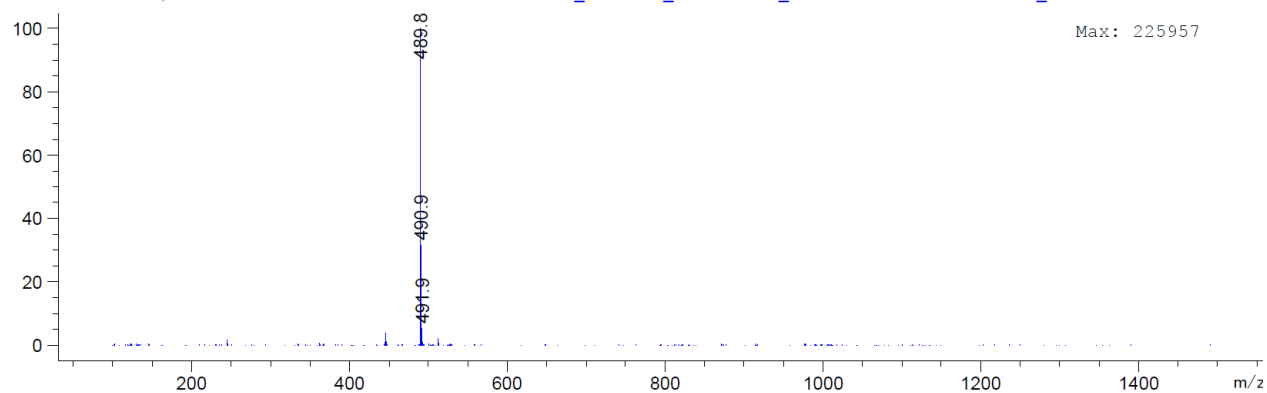
Origin: Bruker BioSpin GmbH
 Solvent: MeOD
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-09-28T12:24:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1543.2
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536



DAD1 C, Sig=575.4 Ref=off (2018_09\DAIY_SEQUENCE_LC 2018-09-25 14-52-24\2018_090000002.D)

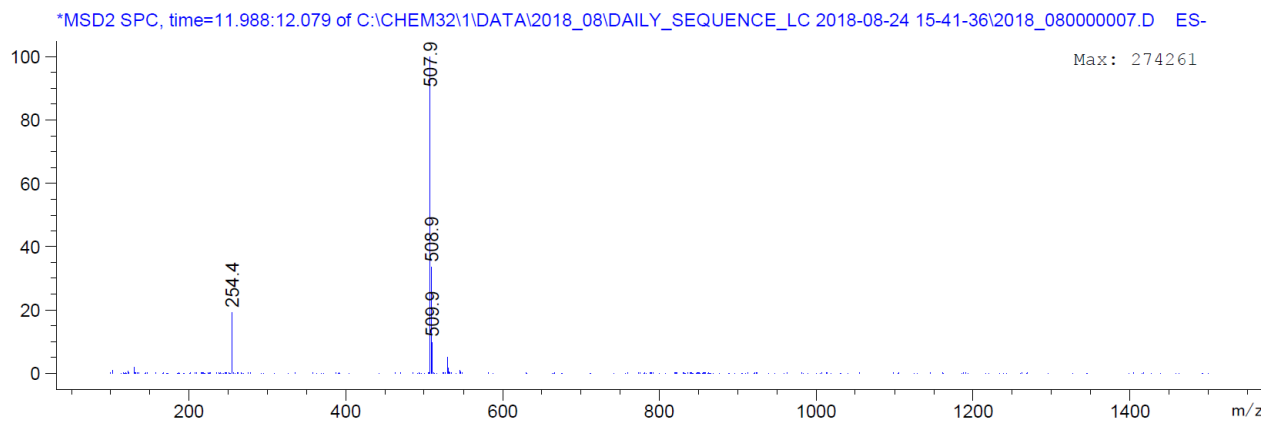
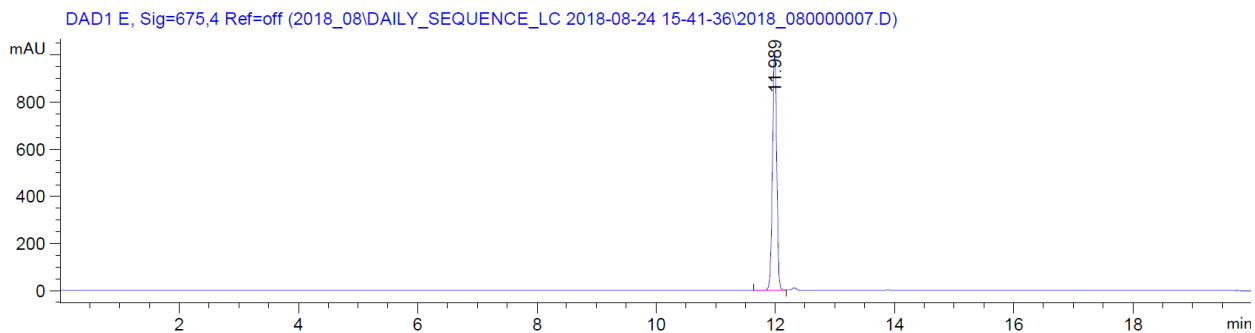
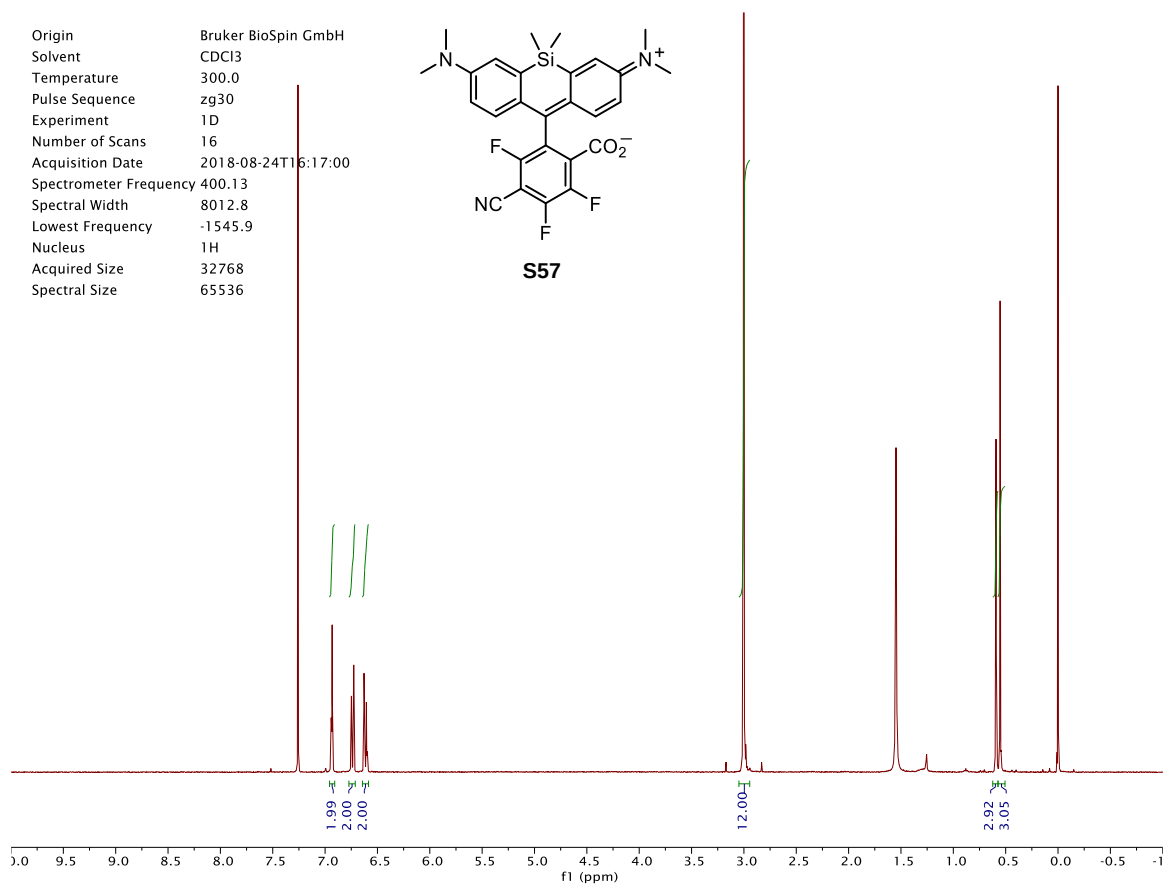
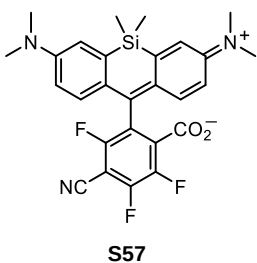


*MSD2 SPC, time=11.552:11.661 of C:\CHEM32\1\DATA\2018_09\DAIY_SEQUENCE_LC 2018-09-25 14-52-24\2018_090000002.D ES-



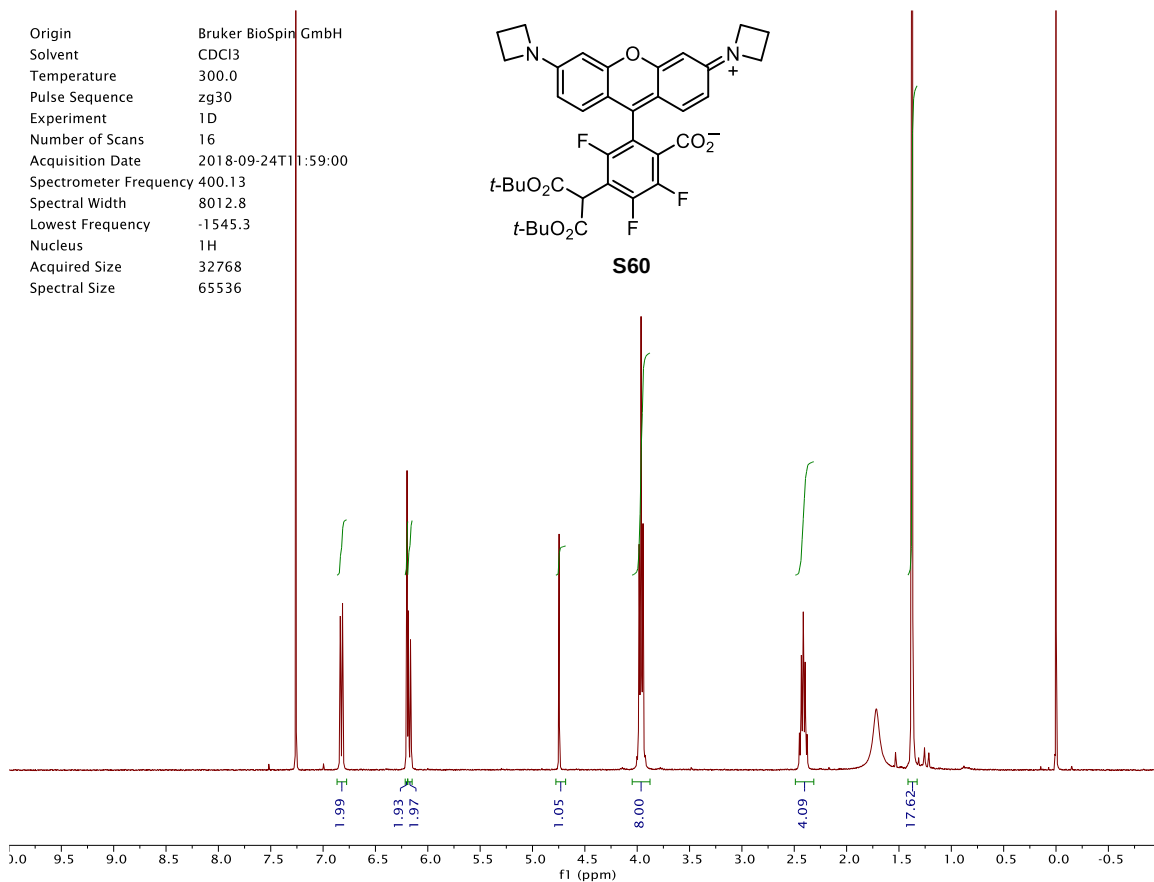
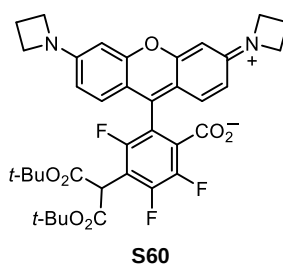
Origin
Solvent
Temperature
Pulse Sequence
Experiment
Number of Scans
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size

Bruker BioSpin GmbH
CDCl₃
300.0
zg30
1D
16
2018-08-24T16:17:00
400.13
8012.8
-1545.9
1H
32768
65536

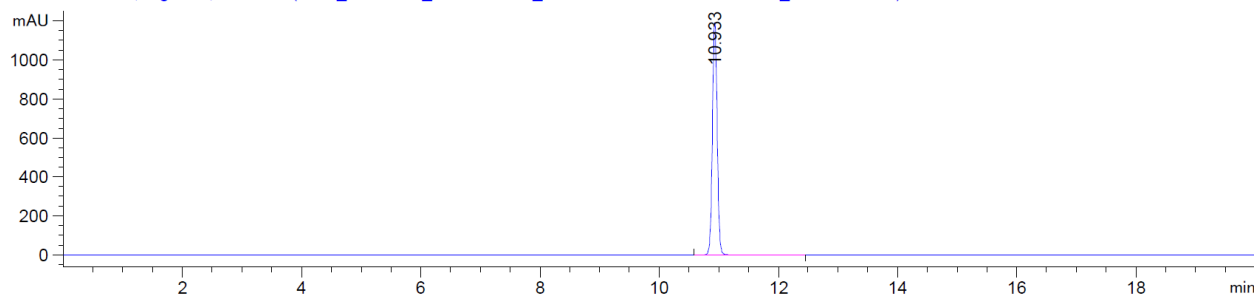


Origin
Solvent
Temperature
Pulse Sequence
Experiment
Number of Scans
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size

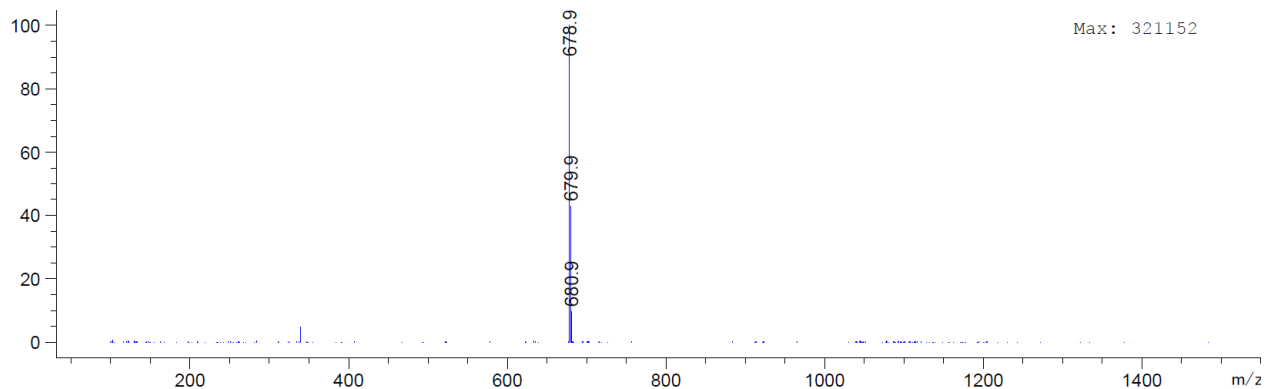
Bruker BioSpin GmbH
CDCl3
300.0
zg30
1D
16
2018-09-24T11:59:00
400.13
8012.8
-1545.3
1H
32768
65536



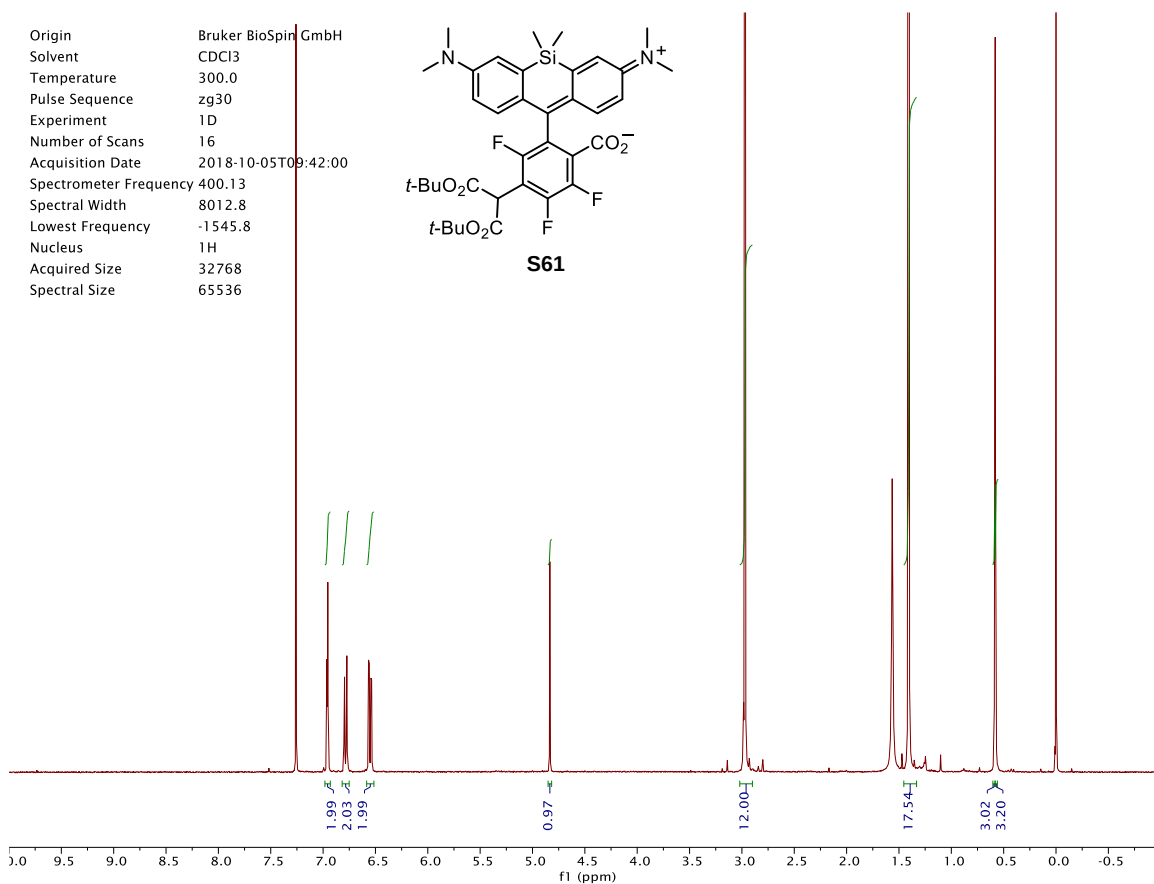
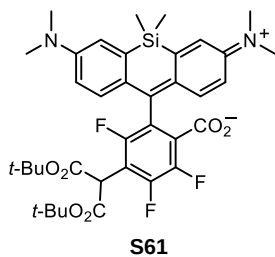
DAD1 C, Sig=575.4 Ref=off (2018_09\DAIY_SEQUENCE_LC 2018-09-20 10-37-17\2018_090000005.D)



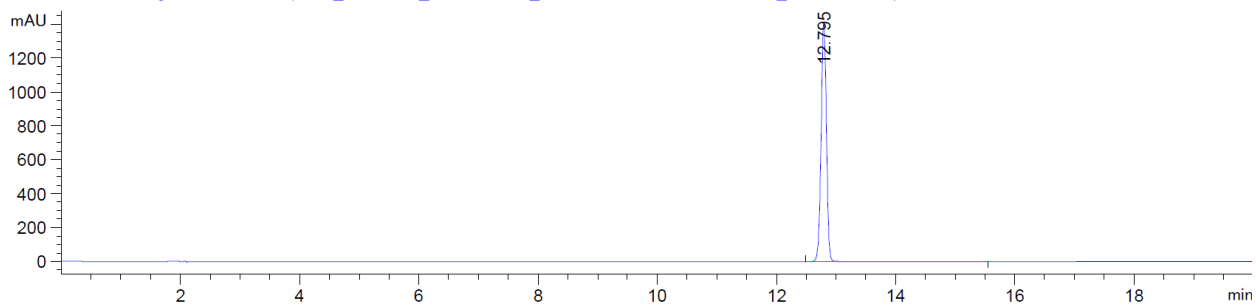
*MSD2 SPC, time=10.934:11.025 of C:\CHEM32\1\DATA\2018_09\DAIY_SEQUENCE_LC 2018-09-20 10-37-17\2018_090000005.D ES-



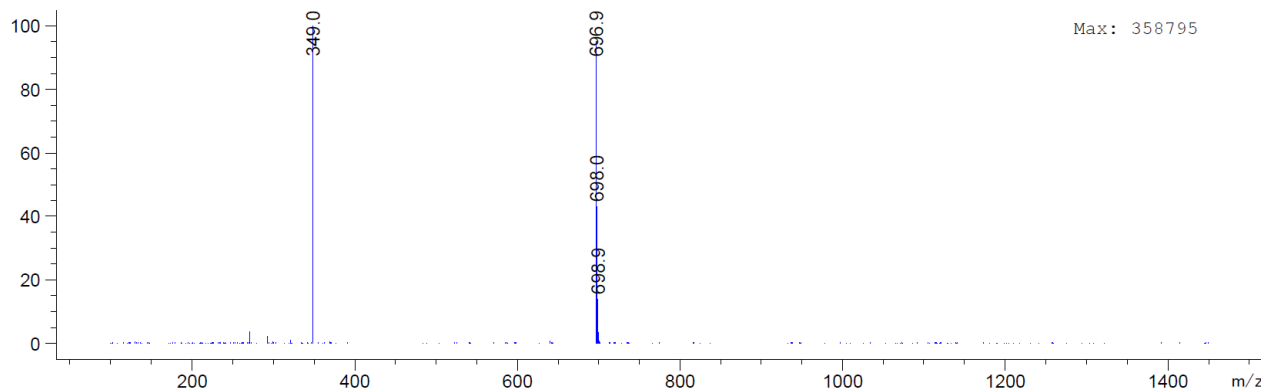
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-10-05T09:42:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.8
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



DAD1 E, Sig=675.4 Ref=off (2018_10\DAILY_SEQUENCE_LC 2018-10-05 15-15-33\2018_100000004.D)

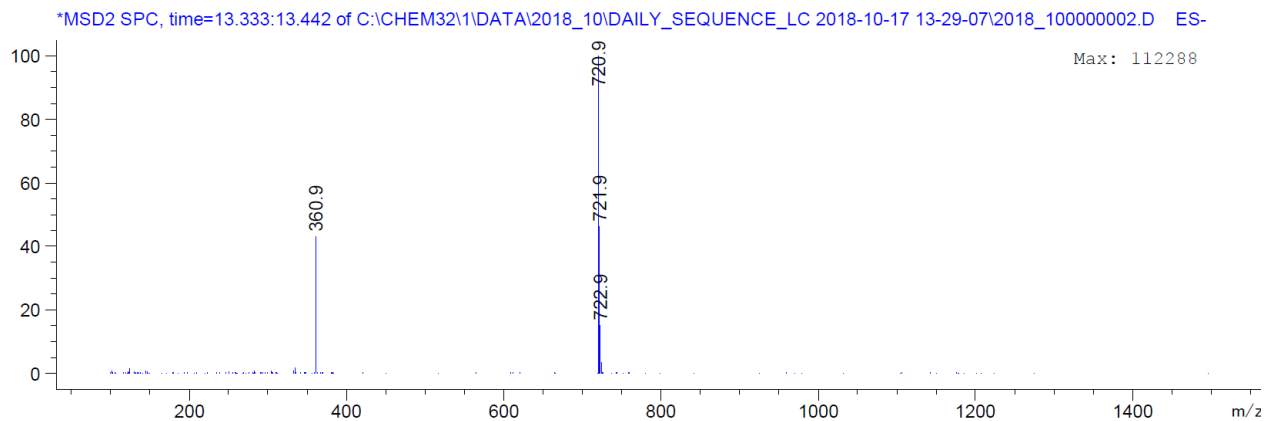
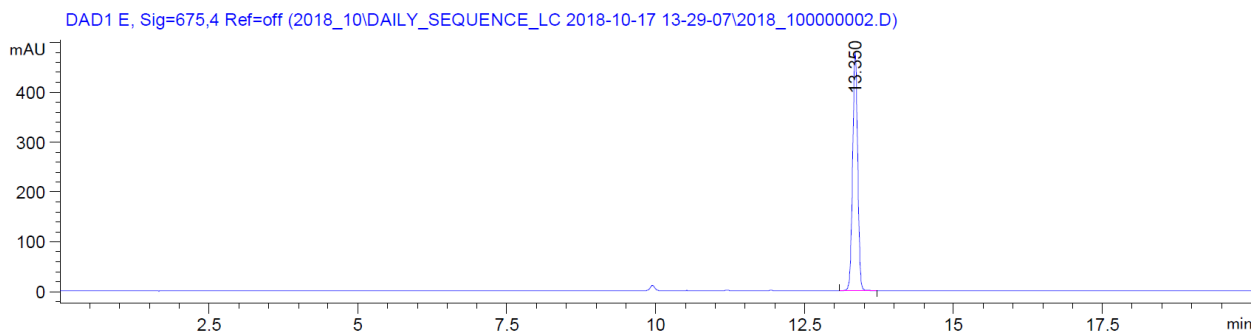
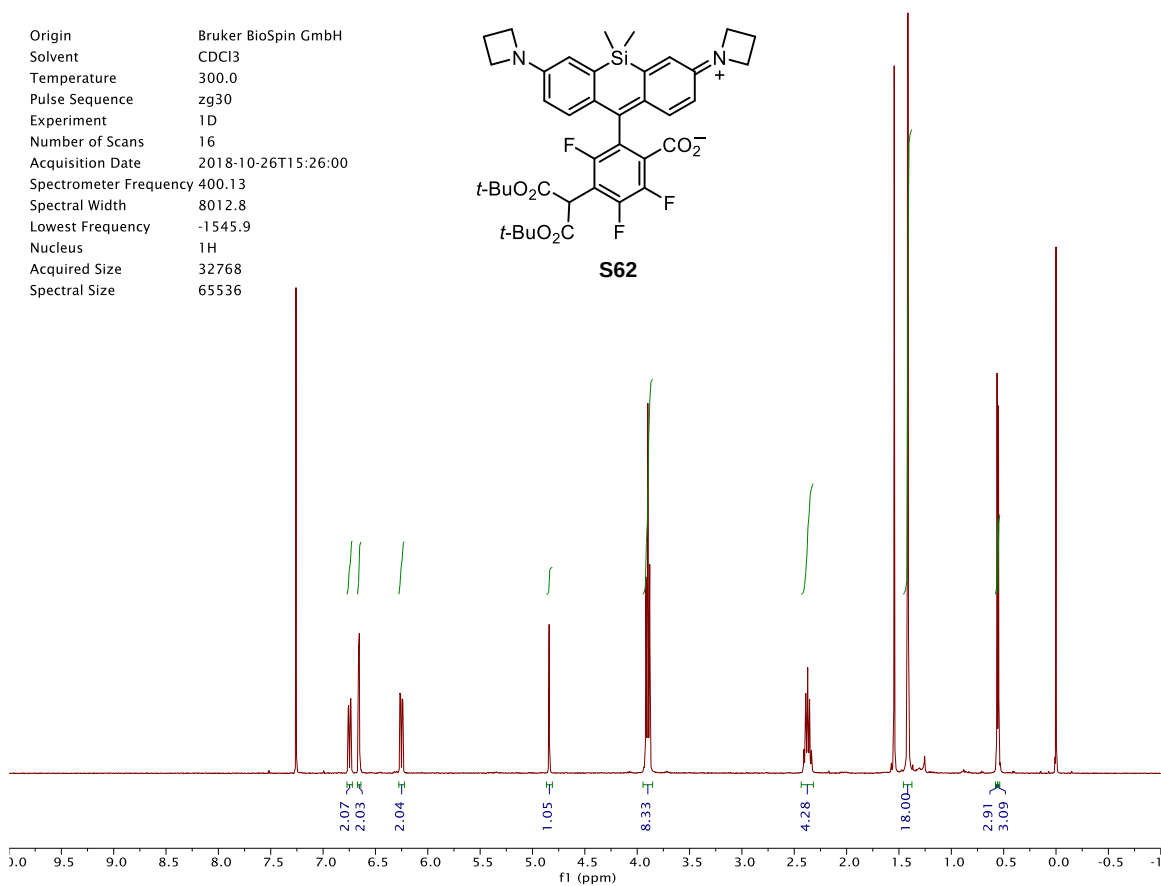
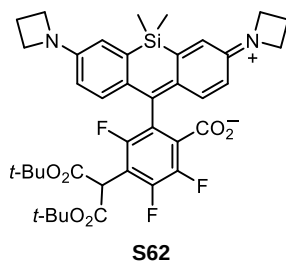


*MSD2 SPC, time=12.791:12.882 of C:\CHEM32\1\DATA\2018_10\DAILY_SEQUENCE_LC 2018-10-05 15-15-33\2018_100000004.D ES-

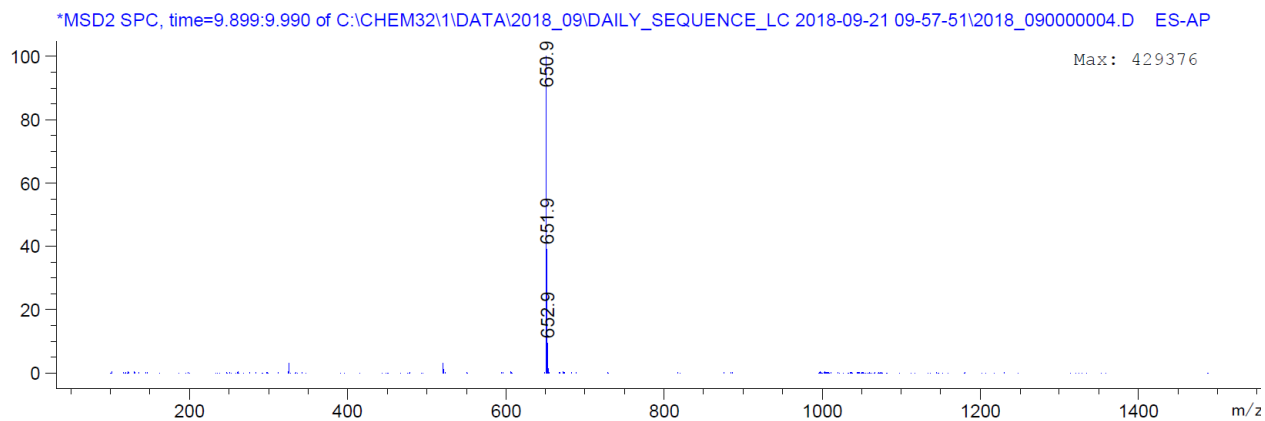
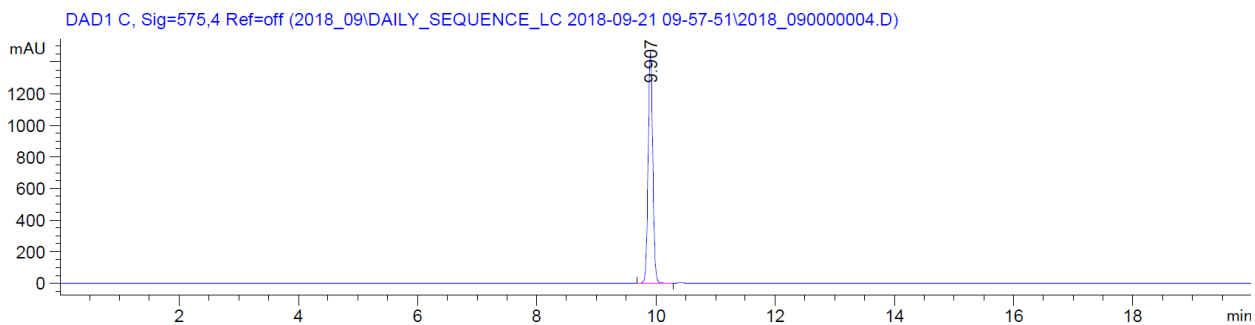
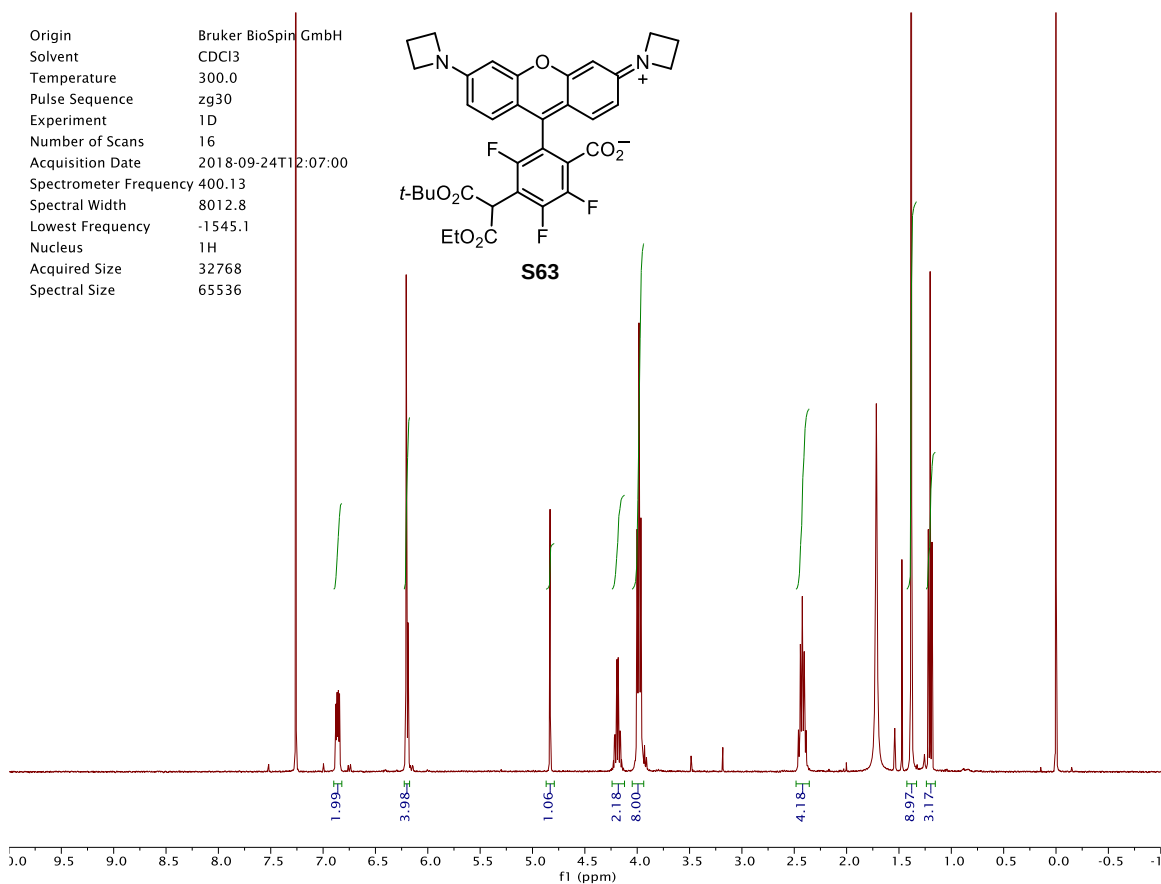
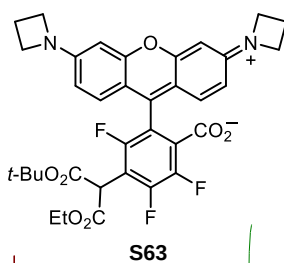


Origin
Solvent
Temperature
Pulse Sequence
Experiment
Number of Scans
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size

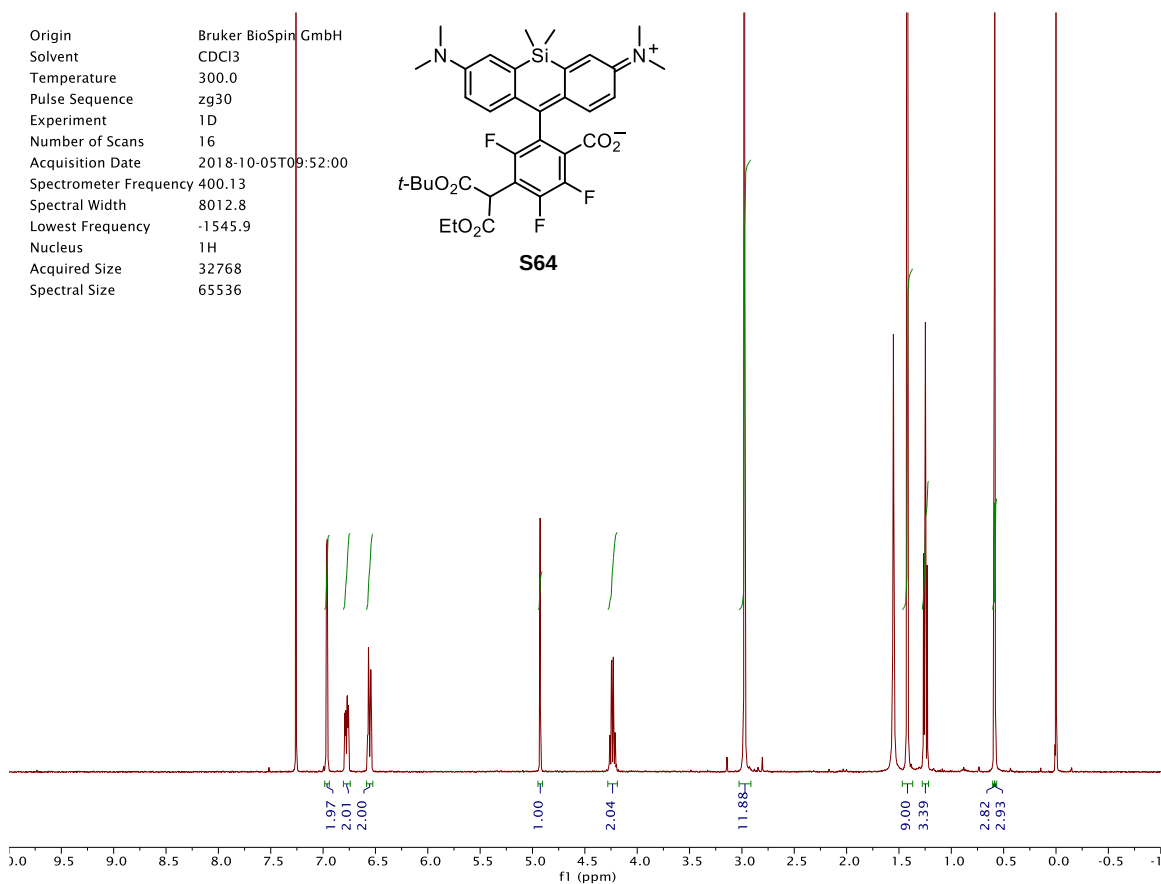
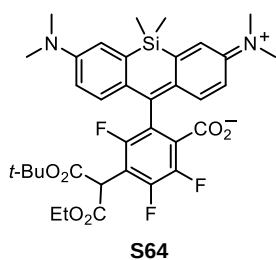
Bruker BioSpin GmbH
CDCl3
300.0
zg30
1D
16
2018-10-26T15:26:00
400.13
8012.8
-1545.9
1H
32768
65536



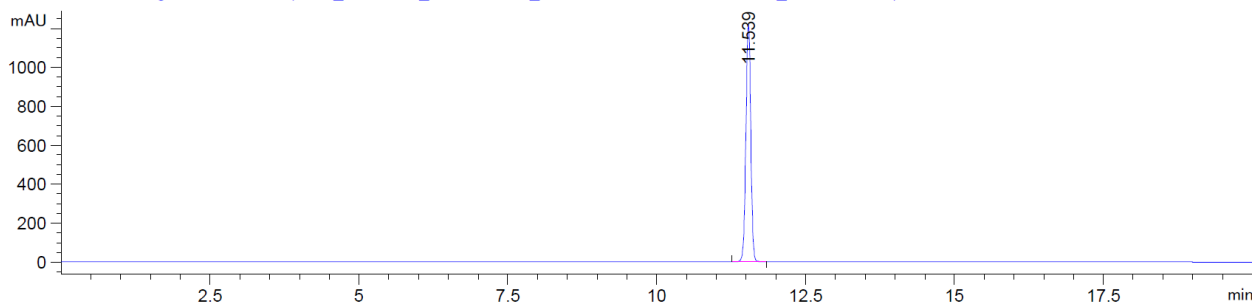
Origin Bruker BioSpin GmbH
 Solvent CDCl3
 Temperature 300.0
 Pulse Sequence zg30
 Experiment 1D
 Number of Scans 16
 Acquisition Date 2018-09-24T12:07:00
 Spectrometer Frequency 400.13
 Spectral Width 8012.8
 Lowest Frequency -1545.1
 Nucleus 1H
 Acquired Size 32768
 Spectral Size 65536



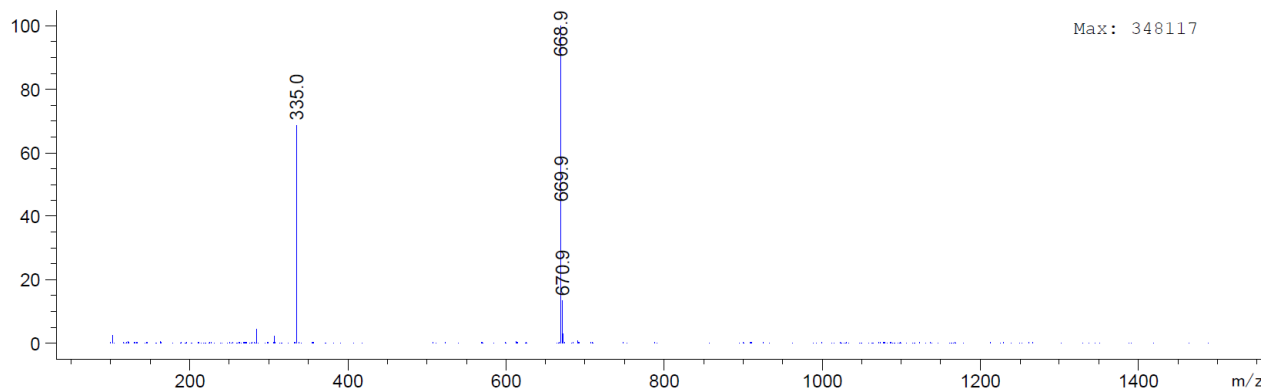
Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-10-05T09:52:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.9
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536



DAD1 E, Sig=675.4 Ref=off (2018_09\DAIY_SEQUENCE_LC 2018-09-07 15-47-51\2018_090000006.D)

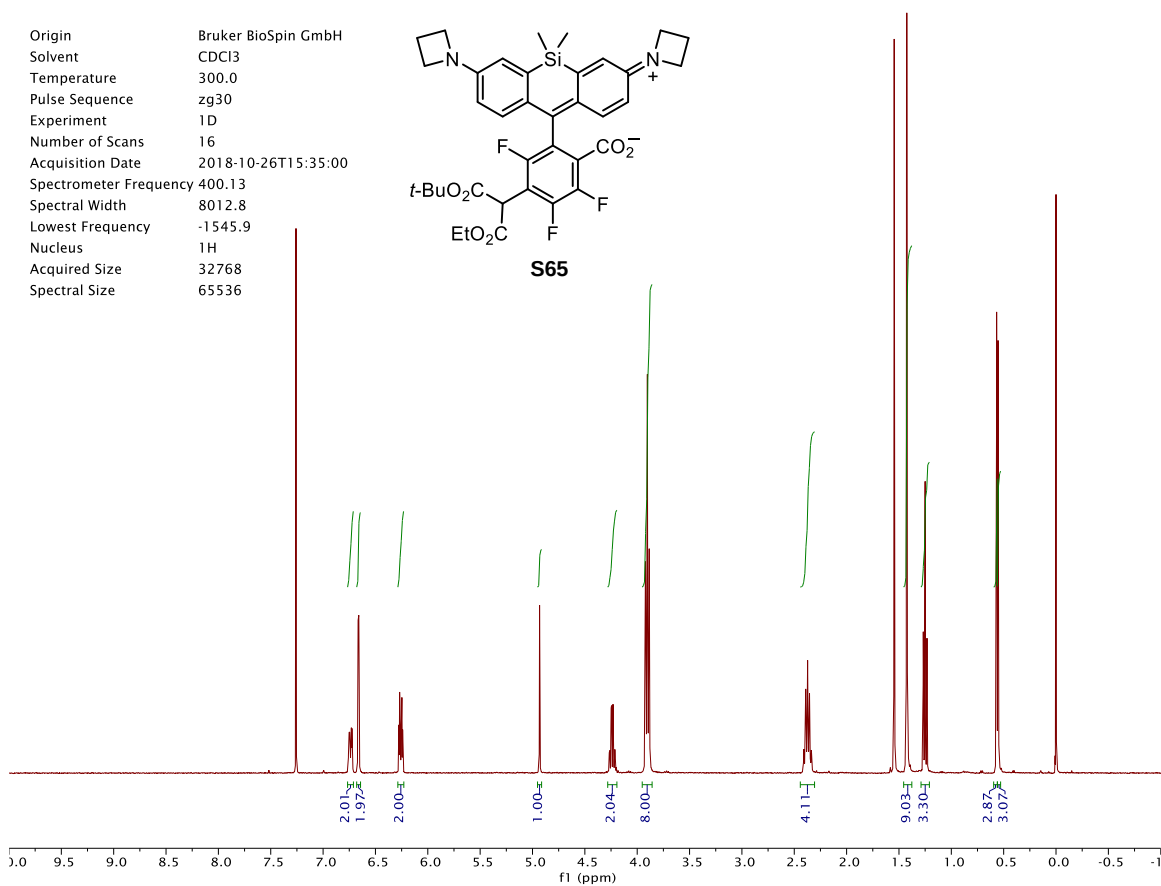
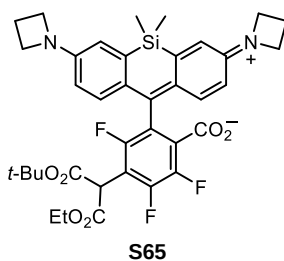


*MSD2 SPC, time=11.534:11.625 of C:\CHEM32\1\DATA\2018_09\DAIY_SEQUENCE_LC 2018-09-07 15-47-51\2018_090000006.D ES-

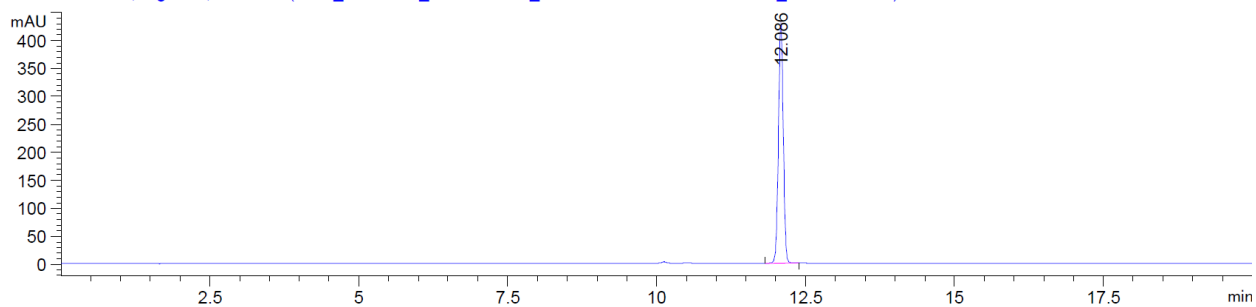


Origin
Solvent
Temperature
Pulse Sequence
Experiment
Number of Scans
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size

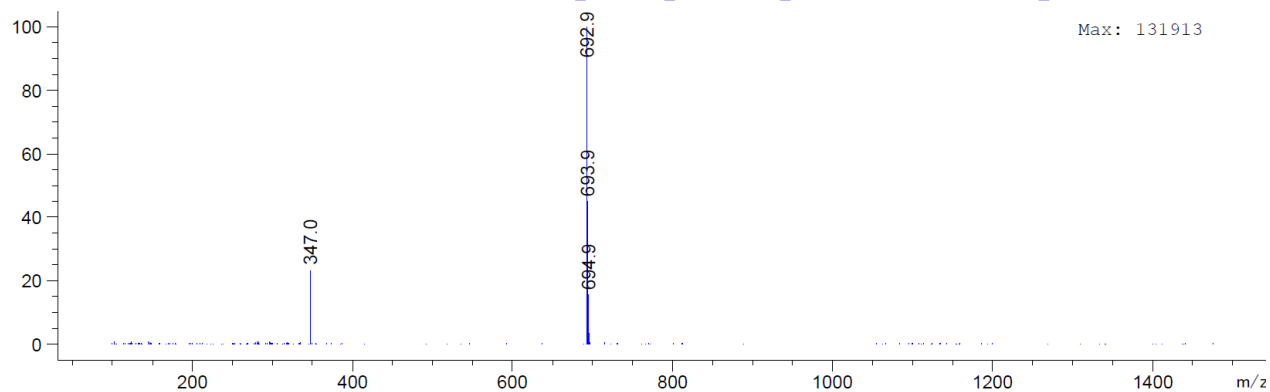
Bruker BioSpin GmbH
CDCl3
300.0
zg30
1D
16
2018-10-26T15:35:00
400.13
8012.8
-1545.9
1H
32768
65536



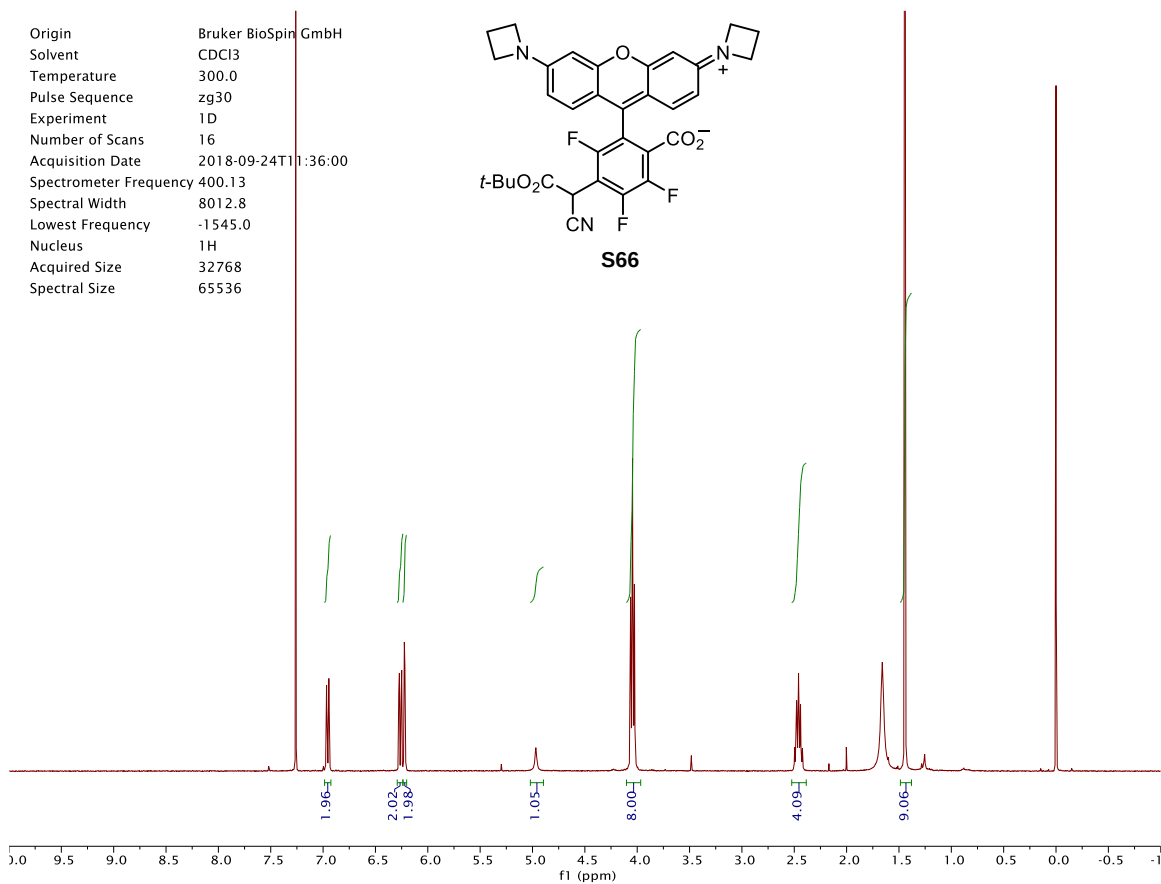
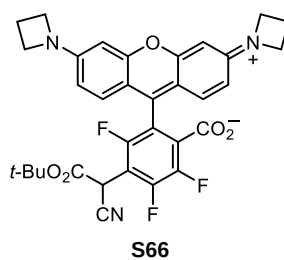
DAD1 E, Sig=675,4 Ref=off (2018_10\DAIY_SEQUENCE_LC 2018-10-16 15-48-57\2018_100000002.D)



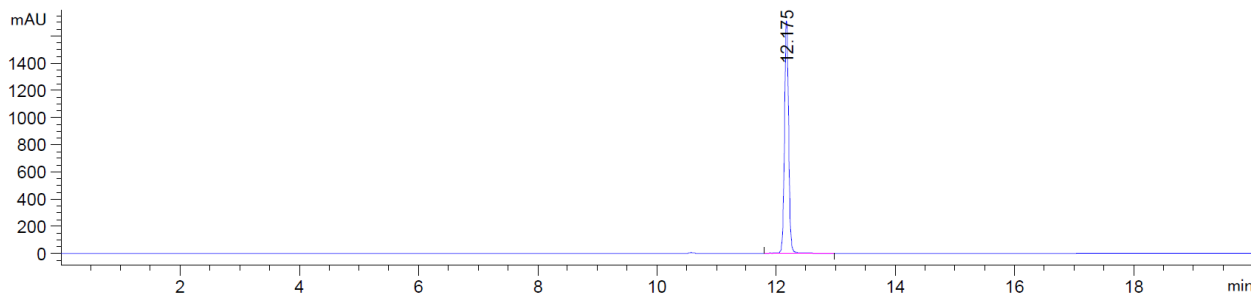
*MSD2 SPC, time=12.079:12.170 of C:\CHEM32\1\DATA\2018_10\DAIY_SEQUENCE_LC 2018-10-16 15-48-57\2018_100000002.D ES-



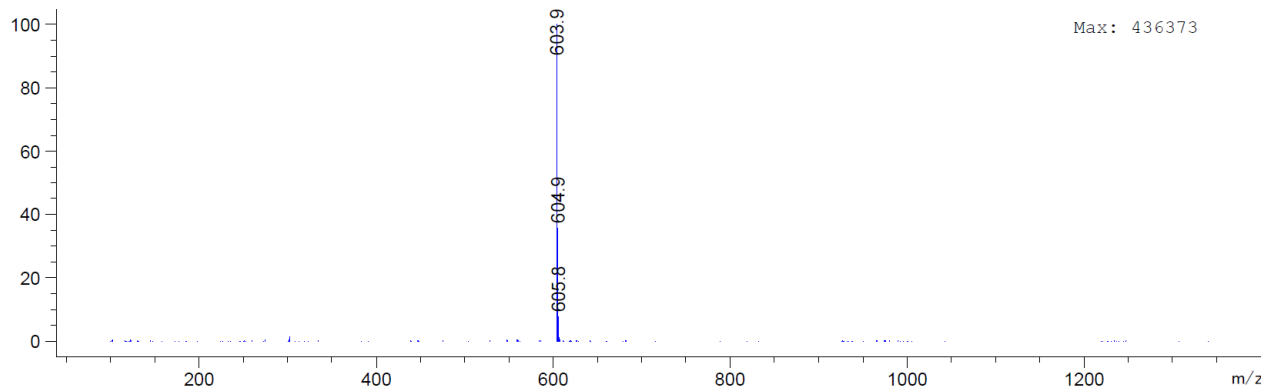
Origin: Bruker BioSpin GmbH
 Solvent: CDCl₃
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-09-24T11:36:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1545.0
 Nucleus: ¹H
 Acquired Size: 32768
 Spectral Size: 65536



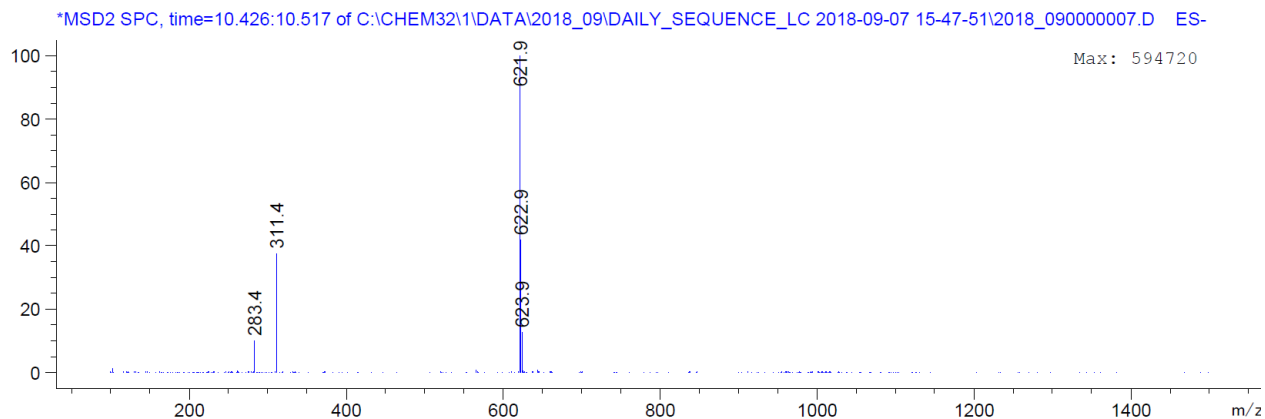
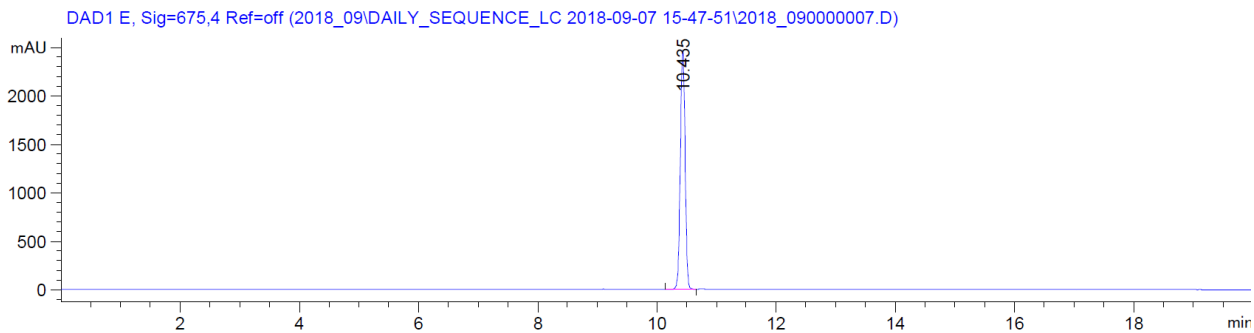
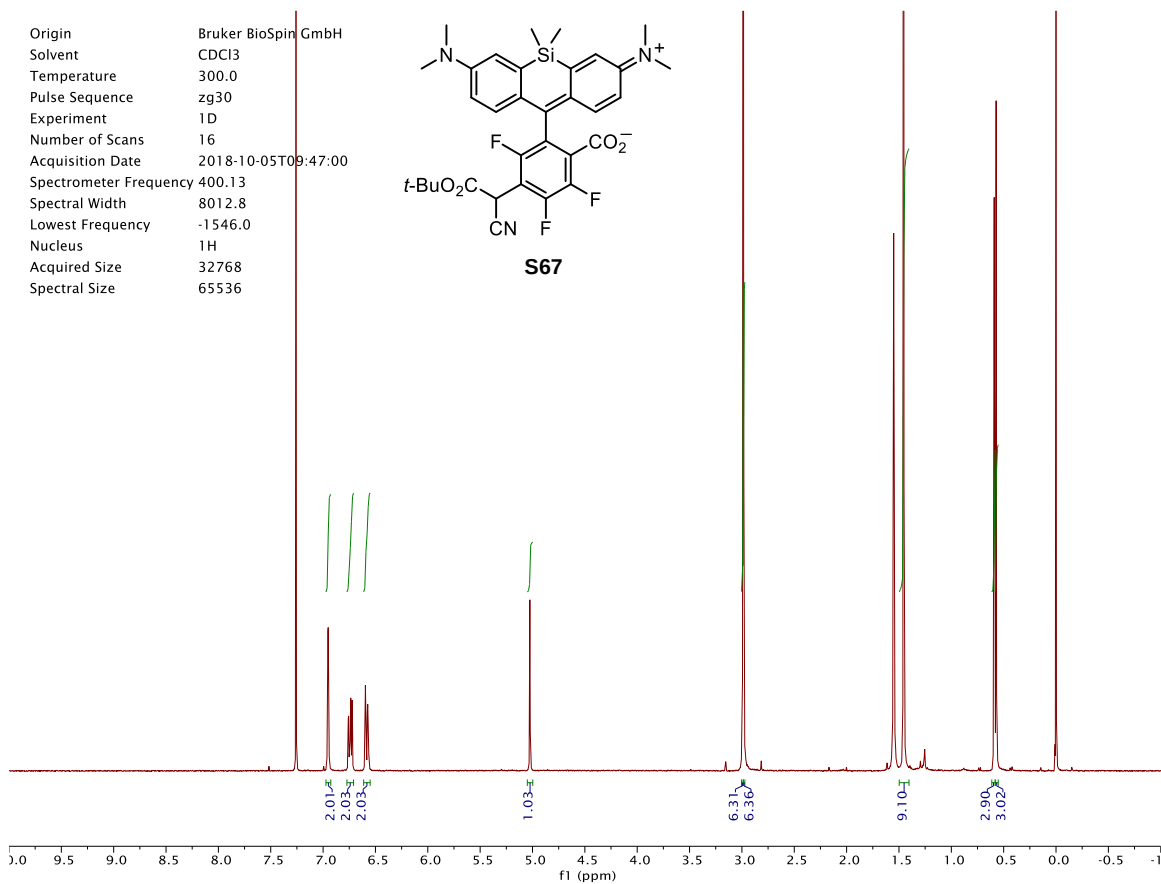
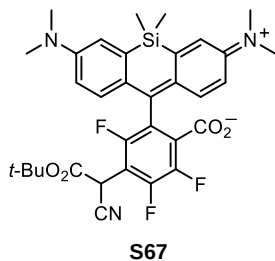
DAD1 C, Sig=575.4 Ref=off (2018_09\DAIY_SEQUENCE_LC 2018-09-21 13-49-40\2018_090000002.D)



*MSD2 SPC, time=12.170:12.261 of C:\CHEM32\1\DATA\2018_09\DAIY_SEQUENCE_LC 2018-09-21 13-49-40\2018_090000002.D ES-

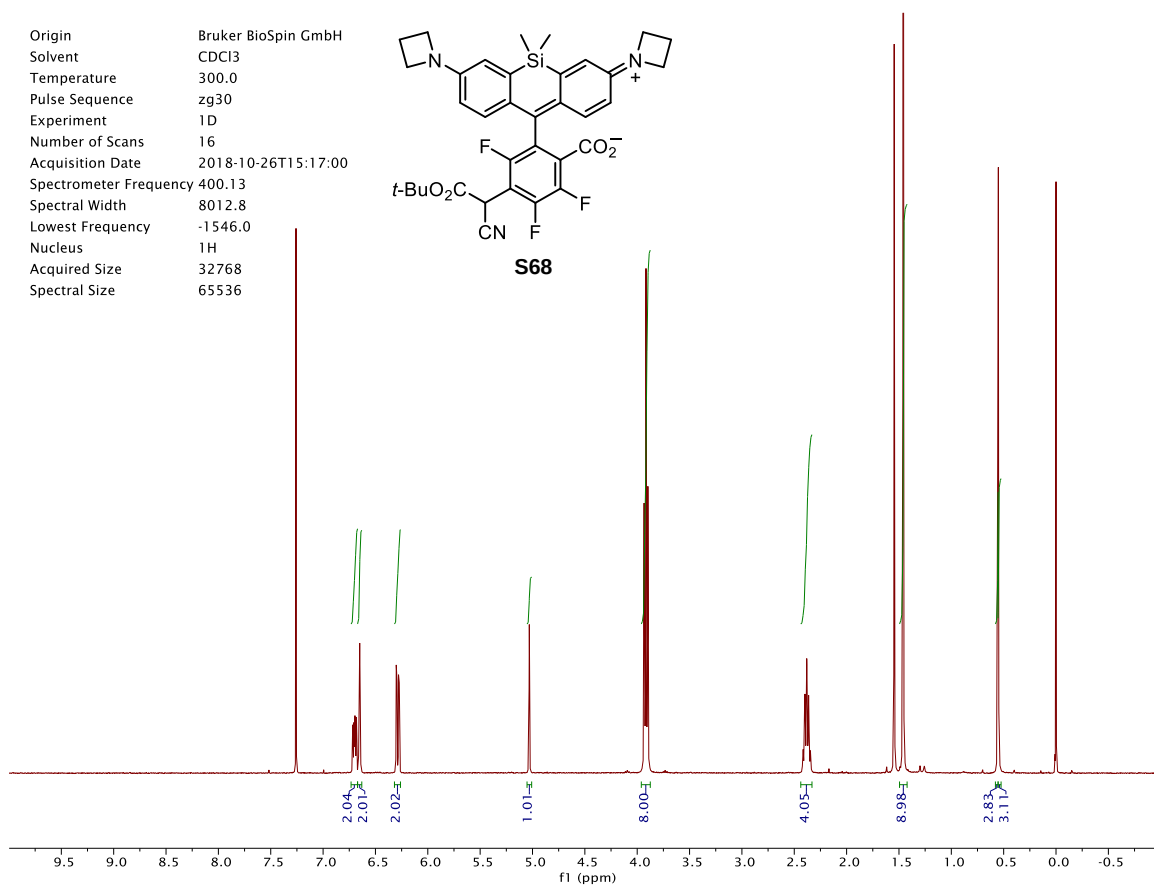
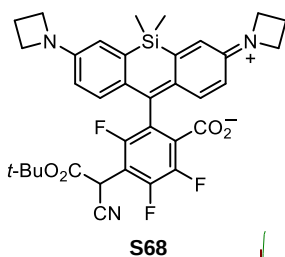


Origin: Bruker BioSpin GmbH
 Solvent: CDCl3
 Temperature: 300.0
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2018-10-05T09:47:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1546.0
 Nucleus: 1H
 Acquired Size: 32768
 Spectral Size: 65536

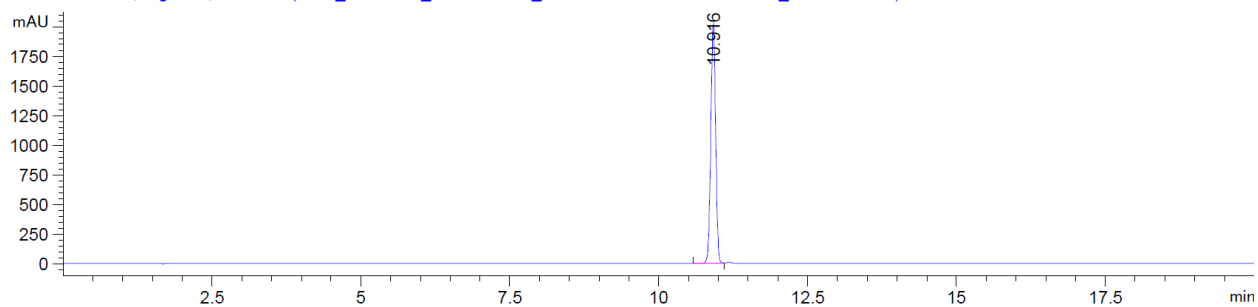


Origin
Solvent
Temperature
Pulse Sequence
Experiment
Number of Scans
Acquisition Date
Spectrometer Frequency
Spectral Width
Lowest Frequency
Nucleus
Acquired Size
Spectral Size

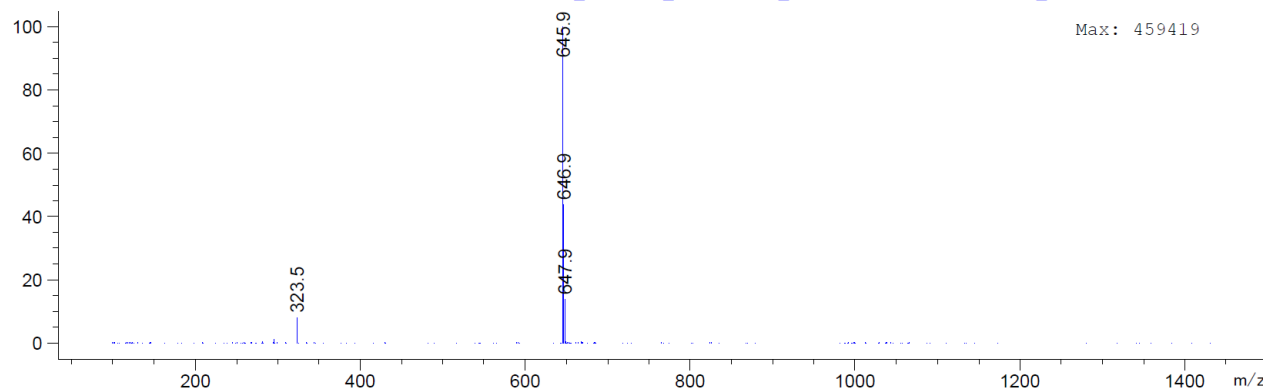
Bruker BioSpin GmbH
CDCl3
300.0
zg30
1D
16
2018-10-26T15:17:00
400.13
8012.8
-1546.0
1H
32768
65536



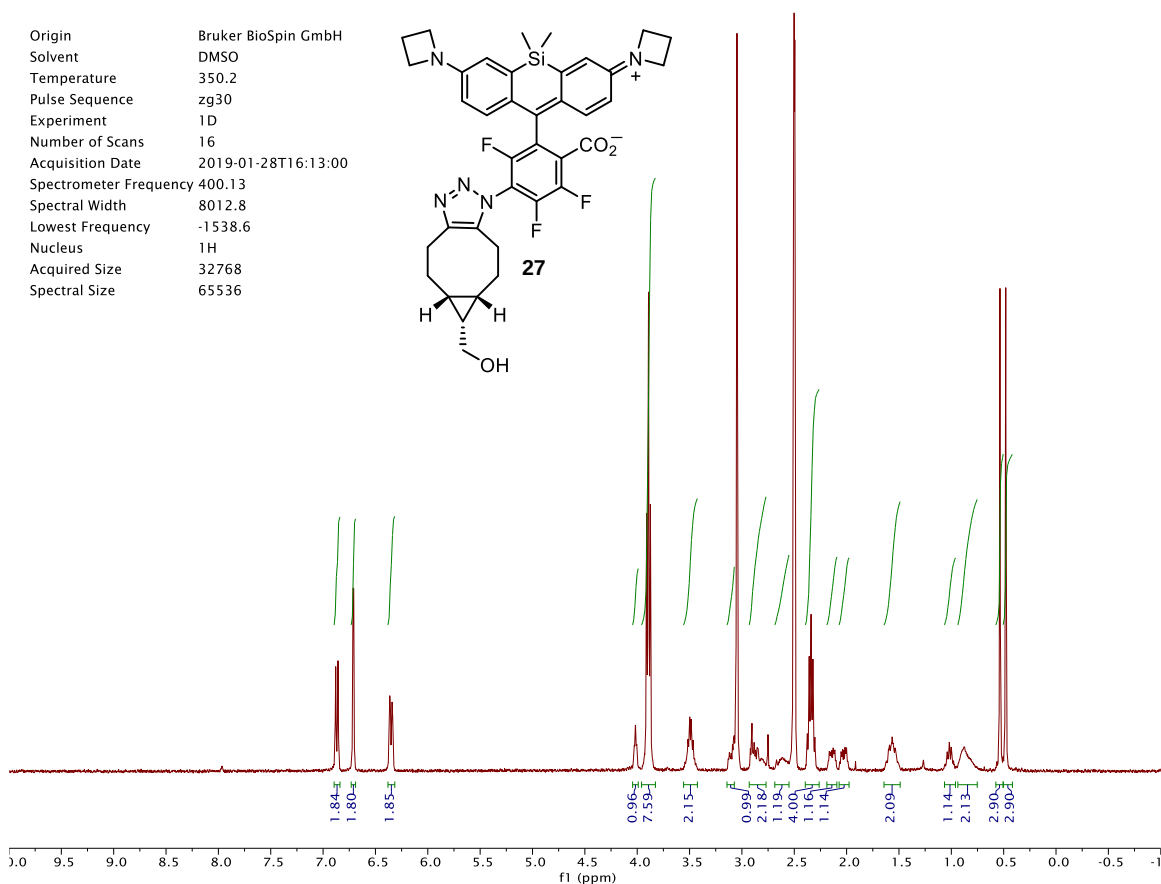
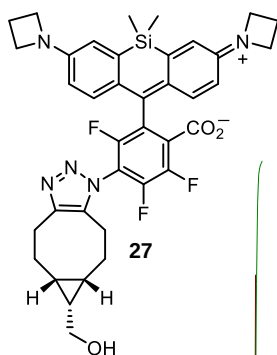
DAD1 E, Sig=675,4 Ref=off (2018_10\DAIY_SEQUENCE_LC 2018-10-26 09-30-22\2018_100000002.D)



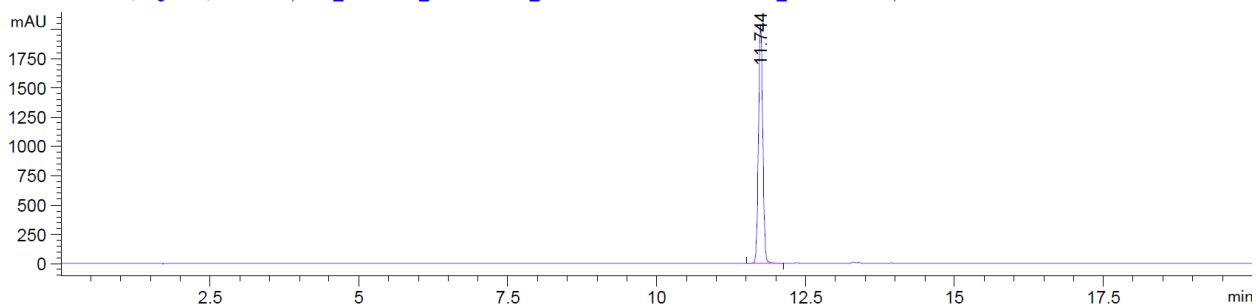
*MSD2 SPC, time=10.898:11.007 of C:\CHEM32\1\DATA\2018_10\DAIY_SEQUENCE_LC 2018-10-26 09-30-22\2018_100000002.D ES-



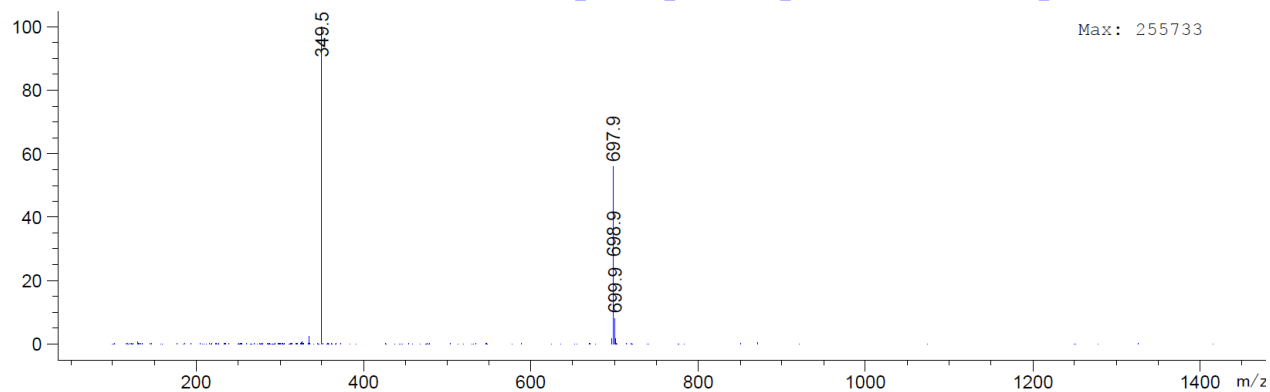
Origin: Bruker BioSpin GmbH
 Solvent: DMSO
 Temperature: 350.2
 Pulse Sequence: zg30
 Experiment: 1D
 Number of Scans: 16
 Acquisition Date: 2019-01-28T16:13:00
 Spectrometer Frequency: 400.13
 Spectral Width: 8012.8
 Lowest Frequency: -1538.6
 Nucleus: ^1H
 Acquired Size: 32768
 Spectral Size: 65536

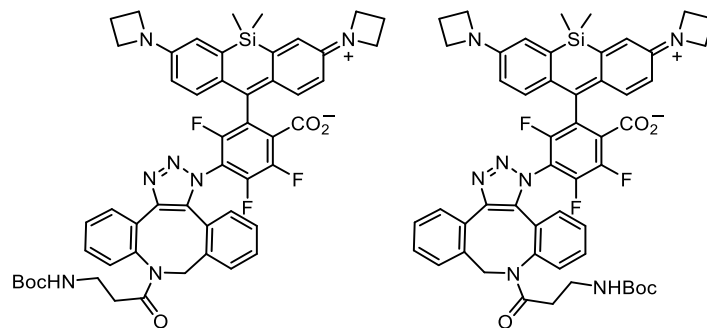


DAD1 E, Sig=675,4 Ref=off (2019_01\DAIY_SEQUENCE_LC 2019-01-24 10-00-16\2019_010000002.D)



*MSD2 SPC, time=11.734:11.825 of C:\CHEM32\1\DATA\2019_01\DAIY_SEQUENCE_LC 2019-01-24 10-00-16\2019_010000002.D ES-





28

