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Supplementary Information

Bioinspired Photocatalyzed C-H Fluoroalkylation of Arenes in Water Promoted by Native Vitamin B12 and Rose Bengal

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1. General information

All reactions were carried out under argon atmosphere unless otherwise indicated. Water was purified with a Millipore system. Chromatography and extraction solvents such as ethyl acetate, acetonitrile (MeCN), dichloromethane (DCM) and n-hexane were of chromatographic quality and used without further purification. 1-Bromotridecafluorohexane (perfluorohexyl bromide), 1-Iodotridecafluorohexane (perfluorohexyl iodide), 1-Bromoheptadecafluorooctane (perfluorooctyl bromide), 1-Iodoheptadecafluorooctane (perfluorooctyl iodide) and 1,2-Dibromotetrafluoroethane were commercial reagents and used without further purification. *N,N,N′,N′*-Tetramethyl ethylenediamine (TMEDA) was 99% pure and used as received from the supplier.

Dye Rose Bengal (4,5,6,7-tetrachloro-3′,6′-dihydroxy- 2′,4′,5′,7′-tetraiodo-3H-spiroisobenzofuran-1,9′-xanthen]-3-one) was 99.9% pure and used as-received from the supplier. Commercial cyanocobalamin (B12) employed met USP testing specifications. Organic substrates 2,6-dimethylaniline, 4-methylaniline, 2,6-difluoroaniline, 4-Aminobenzonitrile, 4-nitroaniline, 2-nitroaniline, 3,5-dimethoxyaniline, 4-methoxyaniline, 1,2-dimethoxybenzene, 1,2-diethoxybenzene, 1,3,5-trimethoxybenzene, 3,4,5-Trimethoxybenzaldehyde, 2,6-Dimethylanisole, 4-Tert-butylanisole and dibenzo-24-crown-8 were commercial and used as received. 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO) was an ultra-pure-grade reagent. $CoCl_2$ was of reagent grade.

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates (0.25 mm, Merck). TLC plates were visualized with ultraviolet light or by treatment with ceric ammonium molybdate (CAM) solution followed by heating. Purification of the reaction products was carried out by column chromatography using ultra-pure silica gel (230–400 mesh), standard silica-gel for column chromatography (60 mesh) or silica-gel for thin layer preparative chromatography with fluorescent indicator (rhodamine).

The light sources were commercially available high power LEDs (3 watts): green light, LED of λ_{max} = 525nm ± 2nm, ET=10mW.

2. Photocatalytic fluoroalkylation reactions of arenes in water. General procedure

In a 4 mL glass reaction vial provided with screw-cap septum and micro stir bar, substrate (0.2 mmol), *N,N,N´,N´*-tetramethylethylenediamine (TMEDA, 3 equiv), photocatalyst (5 mol %), co-catalyst (5 mol %) and 3 mL of solvent were introduced. The mixture was purged with a stream of Ar for 10 min. After deoxygenation, *n*-$C_6F_{13}Br$ (3 equiv) was introduced with a microliter syringe followed by a slight stream of Ar being passed through for 1 additional minute, then the vial was sealed. The closed reaction vessel containing a dark red solution is placed on a stir plate above the heat dissipator, according to Figure S1, and stirred vigorously for 20 hrs. (at 22 °C) under constant irradiation with high power LEDs (3 Watts).

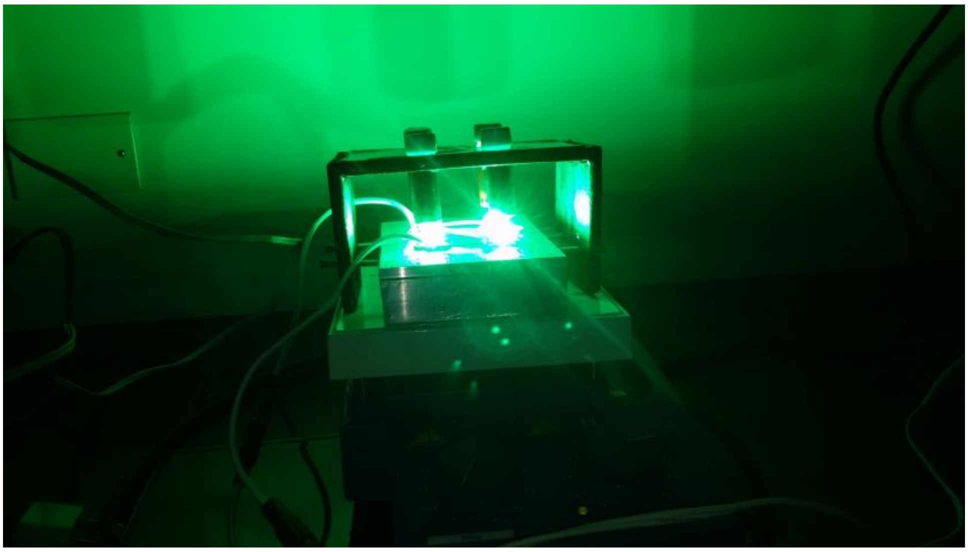
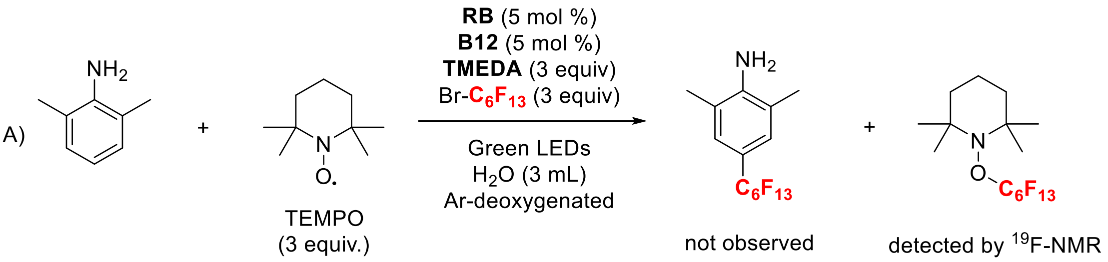


Figure S1 - Green (525 nm) LEDs set up for the Photocatalytic fluroalkylation reactions of arenes.

3. Mechanistic probe experiment for the perfluoroalkylation of 2,6-xylidine



Scheme S1 - Mechanistic Probe experiments for the perfluoroalkylation of 2,6-dimethylaniline. Reaction performed in presence of 3 equiv of TEMPO.

4. Quenching of fluorescence and Stern Volmer plot

Fluorescence measurements were performed with Perkin Elmer LS-55 spectrofluorometer. The aqueous Rose Bengal solution (0.05 mM) was excited at 525 nm and the fluorescence emission was recorded in the range of 535-750 nm. The fluorescence quenching data obtained were analyzed by Stern-Volmer formalism: $F_0/F = 1 + K_{SV}[Q]$, which relates the decrease in fluorescence intensity (F_0/F) to quencher concentration [Q]; K_{SV} is the Stern-Volmer quenching constant. The fluorescence of Rose Bengal is quenched by the addition of incremental quantities of an aqueous solution of cyanocobalamin (B12). The Stern Volmer constant obtained is 1.77×10^4 M^{-1} as shown in Figure S2.

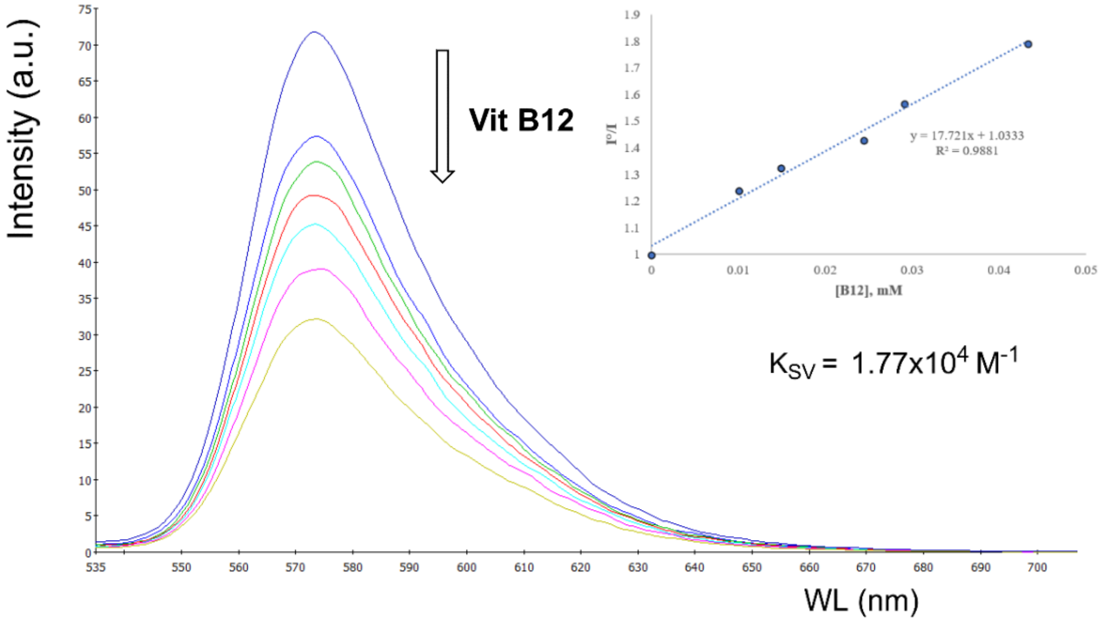


Figure S2 - Quenching of fluorescence of Rose Bengal with Vitamine B12 (H_2O solution) and Stern Volmer plots. $K_{SV} = 1.77\text{x}10^4$ M^{-1}.

5. UV-visible spectroscopy

The UV-visible spectra were performed as follow. An aqueous solution containing cyanocabalamin (B12, 6.0 x 10^{-5} M), Rose Bengal (6.0 x 10^{-5} M) and TMEDA (3.6 x 10^{-3} M) was introduced in a 4 mL UV quartz cuvette provided with an anaerobic septum screw cap and a micro stir bar. The solution is Ar purged and placed on a stir plate above the heat dissipator and stirred vigorously for 1 minute under irradiation with high power green LEDs (3 Watts, 525 nm). Absorption spectra of the solution before and after irradiation were recorded with a Perkin Elmer Lambda 45 spectrophotometer.

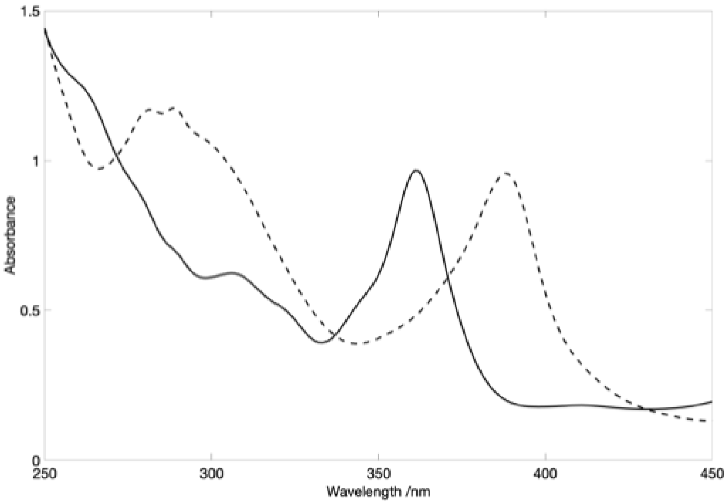


Figure S3 - UV-vis spectra (range 250 – 450 nm) of aqueous solution containing cyanocabalamin (6.0 x 10^{-5} M), Rose Bengal 2 (6.0 x 10^{-5} M) and TMEDA (3.6 x 10^{-3} M) before (—) and after (----) irradiation with green LEDs (l = 525 nm, 3 Watts).

6. Isolation of reaction products

After the reaction time was completed, the mixture was extracted thrice with CH_2Cl_2 / water /brine. The organic layers were gathered and dried over anhydrous Na_2SO_4, filtered and evaporated under vacuo. The crude reaction mixture was purified by silica-gel (60 mesh) column chromatography, with the eluants indicated in the TLC conditions (*vide infra*, spectral data). The polarity of the dye did not introduce any difficulty in the separation and purification protocol, the CH_2Cl_2 extractions eliminated the PC.

7. Calculation of environmental factor

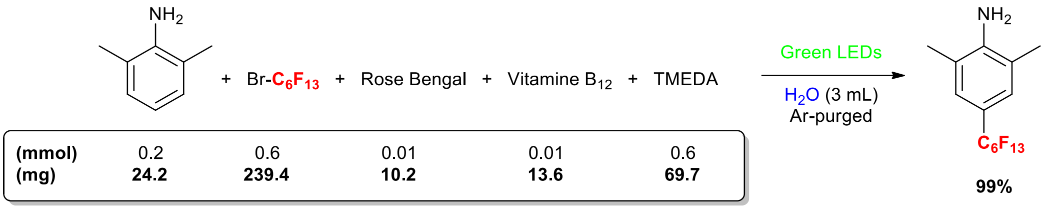
For calculation of the E-factor (EF) a 90% recovery of organic solvents was assumed, and water was excluded (see Eq.1).[1] The complete E-factor (cEF) was also calculated and all solvents used as well as water are considered as waste, according to equation 2.[2]

$$EF = \frac{\sum m(raw\ materials) + \sum m(reagents) + 0.1 \sum m(solvents) - \sum m(product)}{\sum m(product)} \qquad \text{Eq. 1}$$

$$cEF = \frac{\sum m(raw\ materials) + \sum m(reagents) + \sum m(solvents) + \sum m(water) - \sum m(product)}{\sum m(product)} \qquad \text{Eq. 2}$$

In all E-factor calculations the solid drying agents, sílica gel or other solids employed in purification techniques were not included in the formula. The amounts of solvents considered include those used in reaction and during the workup.

7.1 Calculation of environmental factors for the photocatalyzed fluoroalkylation of 2,6-xylidine in water with Vitamin B12 and Rose Bengal



(mmol)	0.2	0.6	0.01	0.01	0.6
(mg)	**24.2**	**239.4**	**10.2**	**13.6**	**69.7**

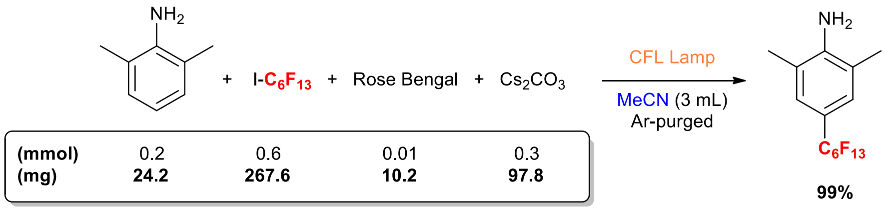
In a 4 mL glass reaction vial provided with screw-cap septum and micro stir bar, 2,6-xylidine (0.2 mmol, 24.2 mg), TMEDA (0.6 mmol, 69.7 mg), Rose Bengal (0.01 mmol, 10.2 mg), Vitamin B12 (0.01 mmol, 13.6 mg) and 3 mL of water were introduced. The mixture was purged with a stream of Ar for 10 min. After deoxygenation, *n*-$C_6F_{13}Br$ (0.6 mmol, 239.4 mg) was introduced with a microliter syringe followed by a slight stream of Ar being passed through for 1 additional minute, then the vial was sealed. The closed reaction vessel is placed on a stir plate above the heat dissipator and stirred vigorously for 20 hrs. (at 22 °C) under constant irradiation with high power LEDs (3 Watts). After the reaction time was completed, the mixture was extracted thrice with 1 mL CH_2Cl_2. The organic layers were gathered and dried over anhydrous Na_2SO_4, filtered and evaporated under vacuo.

***Note**: Density of each liquid at 25°C; 2,6-xylidine = 0.984 g/mL; perfluorohexyl bromide = 1.871 g/mL; TMEDA = 0.775 g/mL; CH_2Cl_2 = 1.327 g/mL

$$\mathrm{EF} = \frac{0.3571\,g + 0.1(3{,}981\,g) - 0.0869\,g}{0.0869\,g} = \boxed{7{,}7}$$

$$\mathrm{cEF} = \frac{0.3571\,g + 6{,}981\,g - 0.0869\,g}{0.0869\,g} = \boxed{83{,}4}$$

7.2 Calculation of environmental factors for the photocatalyzed fluoroalkylation of 2,6-xylidine in MeCN with Rose Bengal[3]



(mmol)	0.2	0.6	0.01	0.3
(mg)	**24.2**	**267.6**	**10.2**	**97.8**

In a 4 mL glass reaction vial provided with screw-cap septum and micro stir bar, 2,6-xylidine (0.2 mmol, 24.2 mg), cesium carbonate (0.3 mmol, 97.8 mg), Rose Bengal (0.01 mmol, 10.2 mg) and 3 mL of MeCN were introduced. The mixture was purged with a stream of Ar for 10 min. After deoxygenation, *n*-$C_6F_{13}I$ (0.6

mmol, 267.6 mg) was introduced with a microliter syringe followed by a slight stream of Ar being passed through for 1 additional minute, then the vial was sealed. The closed reaction vessel is placed front of a 60-Watt household fluorescent light bulb and illuminated under vigorous stirring for 20 hrs. at 22 °C. After the reaction time was completed, the mixture was extracted thrice with 3 mL CH_2Cl_2 from 10 mL of water. The organic layers were gathered and dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuo.

***Note**: Density of each liquid at 25°C; 2,6-xylidine = 0.984 g/mL; perfluorohexyl iodide = 2.063 g/mL; MeCN = 0.786 g/mL; CH_2Cl_2 = 1.327 g/mL

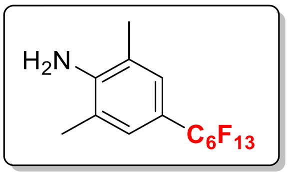
$$\mathrm{EF} = \frac{0.3995\ g + 0.1(14.301\ g) - 0.0869\ g}{0.0869\ g} = \boxed{\mathbf{20{,}1}}$$

$$\mathrm{cEF} = \frac{0.3995\ g + 24.301\ g - 0.0869\ g}{0.0869\ g} = \boxed{\mathbf{290{,}0}}$$

8. Characterization of reaction products

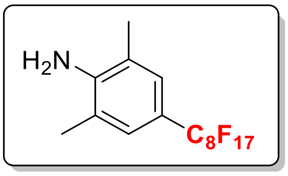
All compounds are unknown chemicals, unless otherwise noted, and are reported as % yields obtained by NMR integration (from ^{1}H and ^{19}F NMR integration) of the crude reaction mixtures. Characterizations employ ^{1}H, ^{13}C, ^{19}F 1D-NMR techniques, and 2D NMR spectroscopic techniques (HSQC, HMBC) and HRMS measurements.

^{1}H-NMR spectra were recorded on an Agilent DD2 500 and 400 (500 MHz and 400 MHz), or a Bruker Avance 600 (600 MHz) spectrometers, and are reported in ppm using the solvent residual peak resonance as the internal standard ($CDCl_3$ at 7.26 ppm). ^{1}H NMR data are reported as follows: chemical shift; multiplicity; coupling constants (Hz); number of hydrogen. Multiplicity is abbreviated as follows: s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet, br = broad. Proton-decoupled ^{13}C-NMR spectra were recorded on an Agilent DD2 500 and 400 (at 125.758 MHz and 100 MHz), or on a Bruker Avance 600 (at 150.903 MHz) spectrometers and are reported in ppm using the C resonance signal from the solvent as the internal standard ($CDCl_3$ at 77.00 ppm). ^{19}F NMR spectra were recorded on a Agilent DD2 500 (at 470.592 MHz), or a Bruker Avance 600 (at 564.686 MHz) spectrometers and are reported in ppm using the internal standard signal from the spectrometer. High-resolution mass spectra (HRMS) were obtained using JEOL-DX 700 mass spectrometer for compounds 2,3,9,10,13,14 and 17; Xevo G2-XS QTof for compounds 20 and 22; FTIR BOMEM DA8 modified for high resolution mass for compounds 4,6,7,8 and 12.



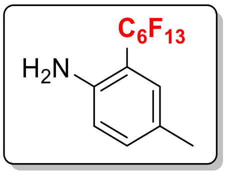
2,6-dimethyl-4-(perfluorohexyl)aniline[4] **(2)** obtained as white solid (99 %). TLC: *iso*octane:CH_2Cl_2 (1:1)

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 2.21 (6H, s), 3.88 (2H, br s), 7.14 (2H, s); **^{13}C NMR (150.903 MHz, $CDCl_3$):** δ (ppm): 17.7, 117.4 (m), 121.2, 126.9, 146.2; **^{19}F NMR (564.603 MHz, $CDCl_3$):** δ (ppm): -126.17 (2F, br s), -122.86 (2F, br s), -121.77 (2F, br s), -121.53 (2F, br s), -109.18 (2F, t), -80.84 (3F, t);
HRMS (ESI [M+H]$^+$): Mass calc. for $C_{14}H_{11}F_{13}N$: 440.0684, found for $C_{14}H_{11}F_{13}N$: 440.0682.



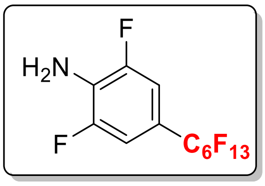
2,6-dimethyl-4-(perfluorooctyl)aniline[4,5] **(3)** obtained as white solid (99 %). TLC: *iso*octane:CH_2Cl_2 (1:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 2.21 (6H, s), 3.93 (2H, br s), 7.14 (2H, s); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 17.7, 117.5 (t, J = 24.6 Hz), 121.3, 126.7 (t, J = 6.6 Hz), 146.1; **^{19}F NMR (470.585 MHz, $CDCl_3$):** δ (ppm): -126.15 (2F, m), -122.75 (2F, m), -121.93 (4F, m), -121.74 (2F, m), -121.33 (2F, m), -109.20 (2F, t), -80.84 (3F, t);
HRMS (ESI [M+H]$^+$): Mass calc. for $C_{16}H_{11}F_{17}N$: 540.0620, found for $C_{16}H_{11}F_{17}N$: 540.0616



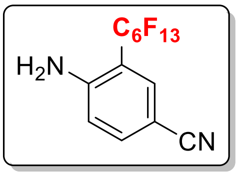
4-methyl-2-(perfluorohexyl)aniline[6] **(4)** obtained as yellow oil (90 %). TLC: *iso*octane:CH_2Cl_2 (1:1)

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 2.26 (3H, s), 4.08 (2H, br s), 6.63 (1H, d, J = 9.2 Hz), 7.10 (2H, overlapped d & s);
^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 20.4, 111.3 (t), 118.2, 127.3, 128.9 (t), 134.0, 143.6;
^{19}F NMR (564.603 MHz, $CDCl_3$): δ (ppm): -126.11 (2F, m), -122.7 (2F, m), -121.8 (4F, m), -108.40 (2F, t), -80.75 (3F, t);
HRMS (ESI [M+H]$^+$): Mass calc. for $C_{13}H_9F_{13}N$: 426.0527, found for $C_{13}H_9F_{13}N$: 426.0528.



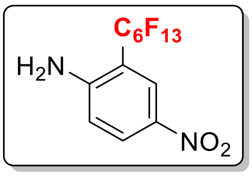
***2,6-difluoro-4-(perfluorohexyl)aniline* (5)** obtained as yellow oil (70 %). TLC: Hexane:CH_2Cl_2 (4:1)

^1H NMR (500 MHz, $CDCl_3$): δ (ppm): 4.09 (2H, br s), 7.07 (2H, dd, J = 6.6 Hz, J = 1.8 Hz);
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 110.4 (m), 127.9 (t, J = 15.8 Hz), 118.5 (t, J = 33 Hz),151.2 (dd, J = 242 Hz, J = 8.4 Hz);
^{19}F NMR (470.585 MHz, $CDCl_3$): δ (ppm): -131.25 (2F, m), -126.15 (2F, m), -122.84 (2F, m), -121.91 (2F, m), -121.51 (2F, m), 109,46 (2F, m), -80.82 (3F, t);
HRMS (ESI $[M-H]^-$): Mass calc. for $C_{12}H_3F_{15}N$: 446.0026, found for $C_{12}H_3F_{15}N$: 446.0039.



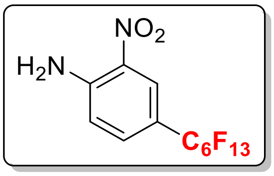
***4-amino-3-(perfluorohexyl)benzonitrile*[6] (6)** obtained as yellow solid (61 %). TLC: CH_2Cl_2:Hexane (4:1)

^1H NMR (500 MHz, $CDCl_3$): δ (ppm): 4,78 (2H, br s), 6.74 (1H, d, J = 8.6 Hz), 7.52 (1H, dd, J = 8.6 Hz, J = 1.9 Hz), 7.61 (1H, d, J = 1.8 Hz);
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 100.7, 111.2 (t, J = 23.6 Hz), 118.0, 118.7, 134.3 (t, J = 8.8 Hz), 136.2, 149.3 (t, J = 2.1 Hz);
^{19}F NMR (470.585 MHz, $CDCl_3$): δ (ppm): -126.12 (2F, m), -122.73 (2F, m), -121.88 (2F, m), -121.64 (2F, m), -109.37 (2F, m), -80.78 (3F, t).



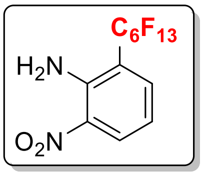
***4-nitro-2-(perfluorohexyl)aniline* (7)** obtained as yellow solid (55 %). TLC: CH_2Cl_2:Hexane (7:3)

^1H NMR (500 MHz, $CDCl_3$): 4.98 (2H, br s), 6.75 (1H, d, J = 9.1 Hz), 8.17 (1H, dd, J = 9.1 Hz, J = 2.5 Hz), 8.30 (1H, d, J = 2.5 Hz);
^{13}C NMR (125 MHz, $CDCl_3$): 110.1 (t, J = 23.8 Hz), 117.3, 126.8 (t, J = 9.1 Hz), 128.8, 138.7, 151.0;
^{19}F NMR (470.585 MHz, $CDCl_3$): -126.11 (2F, m), -122.70 (2F, m), -121.74 (2F, m), -121.62 (2F, m), -109.31 (2F, m), -80.78 (3F, t);
HRMS (ESI $[M-H]^-$): Mass calc. for $C_{12}H_4F_{13}N_2O_2$: 455.0065, found for $C_{12}H_4F_{13}N_2O_2$: 455.0071.



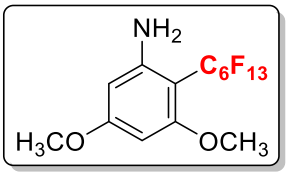
***2-nitro-4-(perfluorohexyl)aniline* (8)** obtained as yellow solid (43 %). TLC Hexane:CH_2Cl_2 (1:1)

^{1}H NMR (500 MHz, $CDCl_3$): 6.39 (2H, br s), 6.93 (1H, d, J = 8.8 Hz), 7.52 (1H, dd, J = 8.8 Hz, J = 1.7 Hz), 8.40 (1H, d, J = 1.8 Hz);
^{13}C NMR (125 MHz, $CDCl_3$): 117.4 (t, J = 26.2 Hz), 119.4, 126.3 (t, J = 7.4 Hz), 131.7, 133.0 (t, J = 5.9 Hz), 146.7;
^{19}F NMR (470.585 MHz, $CDCl_3$): -126.11 (2F, m), -122.79 (2F, m), -121.80 (2F, m), -121.43 (2F, m), -110.13 (2F, m), -80.78 (3F, m);
HRMS (ESI [M+H]$^{+}$): Mass calc. for $C_{12}H_6F_{13}N_2O_2$: 457.0222, found for $C_{12}H_4F_{13}N_2O_2$: 457.0197.



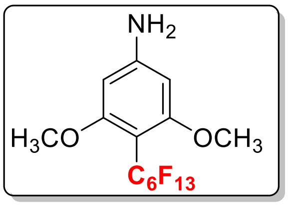
***2-nitro-6-(perfluorohexyl)aniline* (9)** obtained as yellow solid (21 %). TLC Hexane:CH_2Cl_2 (1:1)

^{1}H NMR (500 MHz, $CDCl_3$): 6.82 (3H, overlapped br s and triplet, J = 8.2 Hz), 7.64 (1H, dd, J = 7.7 Hz, J = 1.3 Hz), 8.39 (1H, dd, J = 8.5 Hz, J = 1.2 Hz);
^{13}C NMR (125 MHz, $CDCl_3$): 114.8 (t, J = 22.2 Hz), 115.5, 131.4, 134.3, 136.7 (t, J = 8.9 Hz), 143.8 (t, J = 1.5 Hz);
^{19}F NMR (470.585 MHz, $CDCl_3$): -126.11 (2F, m), -122.68 (2F, m), -121.54 (4F, m), -107.76 (2F, m), -80.75 (3F, t);
HRMS (ESI [M-H]$^{-}$): Mass calc. for $C_{12}H_4F_{13}N_2O_2$: 455.0065, found for $C_{12}H_4F_{13}N_2O_2$: 455.0074.



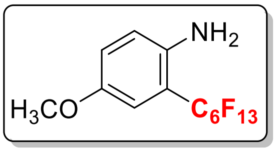
***3,5-dimethoxy-2-(perfluorohexyl)aniline* (10)** obtained as white solid (64 %). TLC Hexane:CH_2Cl_2 (3:2)

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 3.75 (3H, s), 3.77 (3H, s), 5.84 (s, 1H), 5.93 (s, 1H);
^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 55.7, 56.4, 90.5, 94.3, 97.1, 102.7, 162.1, 163.6;
^{19}F NMR (564.603 MHz, $CDCl_3$): δ (ppm): -126.12 (m, 2F), -122.66 (2F, m), -122.10 (4F, m), -103.10 (2F, m), -80.78 (3F, t, J = 9 Hz);
HRMS (ESI [M+H]$^{+}$): Mass calc. for $C_{14}H_{11}F_{13}NO_2$: 472.0582, found for $C_{14}H_{11}F_{13}NO_2$: 472.0581.



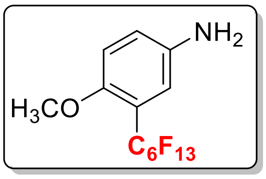
3,5-dimethoxy-4-(perfluorohexyl)aniline **(11)** obtained as colorless oil (32 %). TLC Hexane:CH_2Cl_2 (3:2)

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 3.83 (6H, s), 5.14 (2H, br s), 5.91 (2H, s)
^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 56.1, 86.7, 94.5, 150.2, 164.7;
^{19}F NMR (564.603 MHz, $CDCl_3$): δ (ppm): -126.12 (2F, m), -122.81 (2F, m), -121.67 (4F, m), -102.04, (2F, m), -80.77 (3F, m);
HRMS (ESI $[M+H]^+$): Mass calc. for $C_{14}H_{11}F_{13}NO_2$: 472.0582, found for $C_{14}H_{11}F_{13}NO_2$: 472.0578.



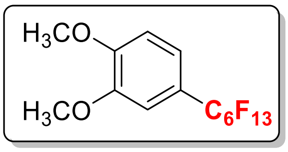
4-methoxy-2-(perfluorohexyl)aniline[7,8] **(12)** obtained as yellow solid (72 %). TLC: CH_2Cl_2:Hexane (7:3)

^{1}H NMR (500 MHz, $CDCl_3$): 3.76 (5H, overlapped br s and singlet), 6.70 (1H, d, J = 8.7 Hz), 6.84 (1H, d, J = 2.8 Hz), 6.94 (1H, dd, J = 8.8 Hz, J = 2.8 Hz);
^{13}C NMR (125 MHz, $CDCl_3$): 56.0, 112.1 (t, J = 22.5 Hz), 113.1 (t, J = 8.9 Hz), 119.8, 120.5, 139.7, 152.1;
^{19}F NMR (470.585 MHz, $CDCl_3$): -126.15 (2F, m), -122.76 (2F, m), -121.75 (4F, m), -108.64 (2F, m), -80.83 (3F, m).



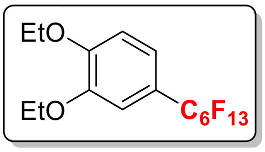
4-methoxy-3-(perfluorohexyl)aniline **(13)** obtained as yellow solid (8 %). TLC: CH_2Cl_2:Hexane (7:3)

^{1}H NMR (500 MHz, $CDCl_3$): 3.79 (5H, overlapped br s and singlet), 6.85 (3H, overlapped d & s);
^{13}C NMR (125 MHz, $CDCl_3$): 57.0, 114.8, 115.8 (t, J = 8.8 Hz), 117.9 (t, J = 22.6 Hz), 120.2, 139.9, 151.7 (t, J = 2.7 Hz);
^{19}F NMR (470.585 MHz, $CDCl_3$): -126.14 (2F, m), -122.72 (2F, m), -121.91 (2F, m), -121.19 (2F, m), -107.75 (2F, m), -80.80 (3F, t);
HRMS (ESI $[M+H]^+$): Mass calc. for $C_{13}H_9F_{13}NO$: 442.0477, found for $C_{13}H_9F_{13}NO$: 442.0465.



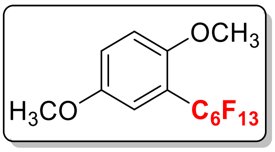
***1,2-dimethoxy-4-(perfluorohexyl)benzene* (14)** obtained as yellow oil (85 %). TLC: CH_2Cl_2:*iso*octane (7:3)

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 3.92 (3H, s), 3.94 (3H, s), 6.95 (1H, d, J = 8.5 Hz), 7.02 (1H, d, J = 1.6 Hz), 7.18 (1H, dd, J = 8.5 Hz, J = 1.6 Hz);
^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 56.1, 56.2, 109.6, 110.8, 120.4, 121.1, 149.1, 150.0;
^{19}F NMR (564.603 MHz, $CDCl_3$): δ (ppm): -126.14 (2F, br s), -122.83 (2F, br s), -121.86 (2F, m), -121.41 (2F, m), -109.64 (2F, t), -80.78 (3F, t);
HRMS (ESI $[M+Na]^+$): Mass calc. for $C_{14}H_9F_{13}NaO_2$: 479.0293, found for $C_{14}H_9F_{13}NaO_2$: 479.0285.



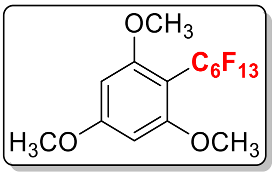
1,2-diethoxy-4-(perfluorohexyl)benzene (15) obtained as yellow oil (75 %). TLC: Hexane: CH_2Cl_2 (7:3)

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 1.46 (3H, t, J = 7 Hz), 1.48 (3H, t, J = 7 Hz), 4.13 (4H, hept, J = 7 Hz), 6.93 (1H, d, J = 8.45 Hz), 7.03 (1H, br s), 7.13 (1H, d, J = 8.45 Hz);
^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 14.7, 14.8, 64.7, 65.0, 111.7, 112.4, 120.3, 120.9, 148.6, 151.8;
^{19}F NMR (564.603 MHz, $CDCl_3$): δ (ppm): -126.13 (2F, m), -122.82 (2F, br s), -121.92 (2F, t), -121.52 (2F, br s), -109.66 (2F, t), -80.80 (3F, m);
HRMS (ESI $[M+Na]^+$): Mass calc. for $C_{16}H_{13}F_{13}NaO_2$: 507.0606, found for $C_{16}H_{13}F_{13}NaO_2$: 507.0603.



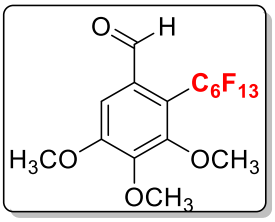
***1,4-dimethoxy-2-(perfluorohexyl)benzene*[9,10] (16)** obtained as colorless liquid (55 %). TLC: Hexane: AcOEt (9:1)

^{1}H NMR (500 MHz, $CDCl_3$): 3.80 (3H, s), 3.82 (3H, s), 6.96 (1H, d, J = 8.7 Hz), 7.05 (2H, overlapped d and m);
^{13}C NMR (125 MHz, $CDCl_3$): 56.0, 56.8, 114.4, 114.7 (t, J = 9.3 Hz), 117.9 (t, J = 22.1 Hz), 118.9, 152.8 (t, J = 2.7 Hz), 154.4;
^{19}F NMR (470.585 MHz, $CDCl_3$): -126.20 (2F, m), -122.77 (2F, m), -121.95 (2F, m), -121.21 (2F, m), -107.76 (2F, m), -80.89 (3F, m).



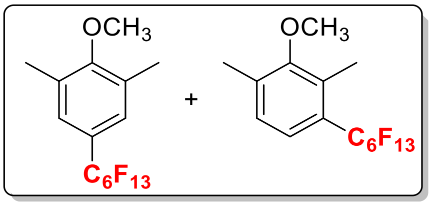
1,3,5-trimethoxy-2-(perfluorohexyl)benzene[11,12,13] **(17)** obtained as white solid (99 %). TLC: Hexane: CH_2Cl_2 (3:1)

^{1}H NMR (400 MHz, $CDCl_3$): 3.8 (6H, s), 3.84 (3H, s), 6.15 (2H, s);
^{13}C NMR (100 MHz, $CDCl_3$): 55.5, 56.5, 91.9, 98.64, 161.92 (t, J = 2.2 Hz), 164.0;
^{19}F NMR (470.585 MHz, $CDCl_3$): -126.18 (2F, m), -122.70 (2F, m), -122.26 (2F, m), -122.1 (2F, m), -102.7 (2F, m), -80.87 (3F, t).



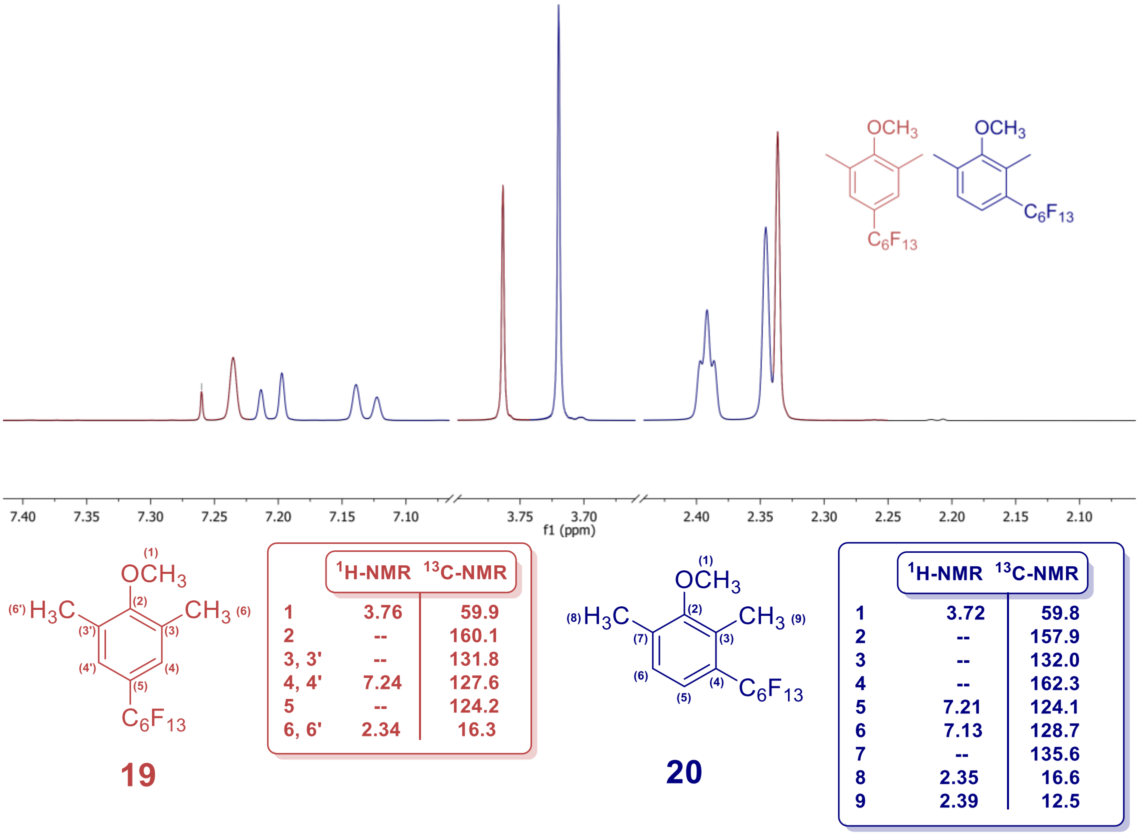
3,4,5-trimethoxy-2-(perfluorohexyl)benzaldehyde **(18)** obtained as yellow oil (40 %). TLC: CH_2Cl_2:Hexane (3:1)

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 3.93 (3H, s), 3.95 (3H, s), 3.97 (3H, s), 7.41 (s, 1H), 10.15 (1H, t, J = 6 Hz);
^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 56.4, 61.1, 62.2, 105.7, 108.0, 133.0, 147.4, 154.3, 156.3, 189.7;
^{19}F NMR (564.603 MHz, $CDCl_3$): δ (ppm): -126.09 (2F, m), -122.65 (2F, m), -121.78 (2F, m), -120.19 (2F, m), -96.10 (2F, m), -80.77 (3F, m);
HRMS (ESI [M+H]$^{+}$): Mass calc. for $C_{16}H_{12}F_{13}O_4$: 515.0528, found for: $C_{16}H_{12}F_{13}O_4$: 515.0523.



2-methoxy-1,3-dimethyl-5-(perfluorohexyl)benzene **(19);** ***2-methoxy-1,3-dimethyl-4-(perfluorohexyl)benzene*** **(20).** TLC: Hexane: CH_2Cl_2 (9:1)

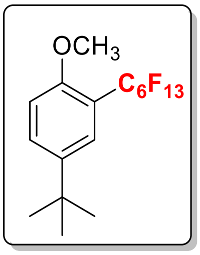
^{1}H NMR (500 MHz, $CDCl_3$): 2.34 (3H, s), 2.35 (3H, s), 2.39 (6H, t, J =), 3.72 (3H, s), 3.76 (3H, s), 7.13 (1H, d, J = 8.2 Hz), 7.21 (1H, d, J = 8.2 Hz), 7.24 (2H, s);
^{13}C NMR (125 MHz, $CDCl_3$): 12.5, 16.3, 16.6, 59.8, 59.9, 124.1 (t, J = 9.3 Hz), 124,2 (t, J = 24.1 Hz), 126.3 (t, J = 22.3 Hz), 127.6 (t, J = 6.5 Hz), 128.7, 131.8, 132.0 (t, J = 2.1 Hz), 135.6, 157.9, 160.1;
^{19}F NMR (470.585 MHz, $CDCl_3$): -126.20 (4F, m), -122.82 (4F, m), -121.73 (6F, m), -120.75 (2F, m), -110.08 (2F, m), -105.02 (2F, m), -80.91 (6F, m).



	^{1}H-NMR	^{13}C-NMR
1	3.76	59.9
2	--	160.1
3, 3'	--	131.8
4, 4'	7.24	127.6
5	--	124.2
6, 6'	2.34	16.3

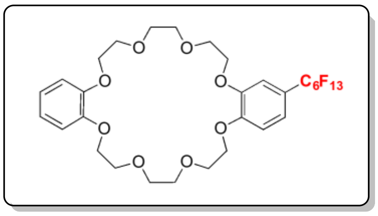
	^{1}H-NMR	^{13}C-NMR
1	3.72	59.8
2	--	157.9
3	--	132.0
4	--	162.3
5	7.21	124.1
6	7.13	128.7
7	--	135.6
8	2.35	16.6
9	2.39	12.5

Scheme S2 - ^{1}NMR and ^{13}NMR data interpretation of the mixture of compounds 19 and 20.



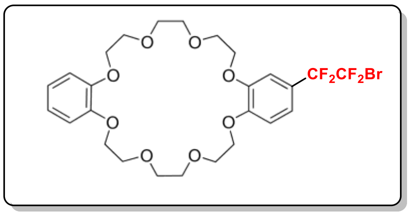
4-(tert-butyl)-1-methoxy-2-(perfluorohexyl)benzene **(21)** obtained as colorless liquid (97 %). TLC: Hexane: AcOEt (9:1)

^{1}H NMR (500 MHz, CDCl$_3$): 1.31 (9H, s), 3.84 (3H, s), 6.95 (1H, d, J = 8.7 Hz), 7.48 (1H, d, J = 2.5 Hz), 7.52 (1H, dd, J = 8.7 Hz, J = 2.5 Hz);
^{13}C NMR (125 MHz, CDCl$_3$): 31.5, 34.4, 56.2, 112.4, 116.4, 126.2 (t, J = 8.4 Hz), 130.4, 143.3, 156.4;
^{19}F NMR (470.585 MHz, CDCl$_3$): -126.15 (2F, m), -122.73 (2F, m), -121.90 (2F, m) -121.29 (2F, m), -107.59 (2F, m), -80.82 (3F, t);
HRMS (ESI [M+Na]$^+$): Mass calc. for $C_{17}H_{15}F_{13}ONa$: 505.0813, found for $C_{17}H_{15}F_{13}ONa$: 505.0813.



2-(perfluorohexyl)-6,7,9,10,12,13,20,21,23,24,26,27-dodecahydrodibenzo[b,n][1,4,7,10,13,16,19,22]octaoxacyclotetracosine (i.e.: perfluorohexyl dibenzo-24-crown-8) **(23)** obtained as an amorphous off-white solid (40 %). TLC: CH_2Cl_2: MeOH (2:0.1)

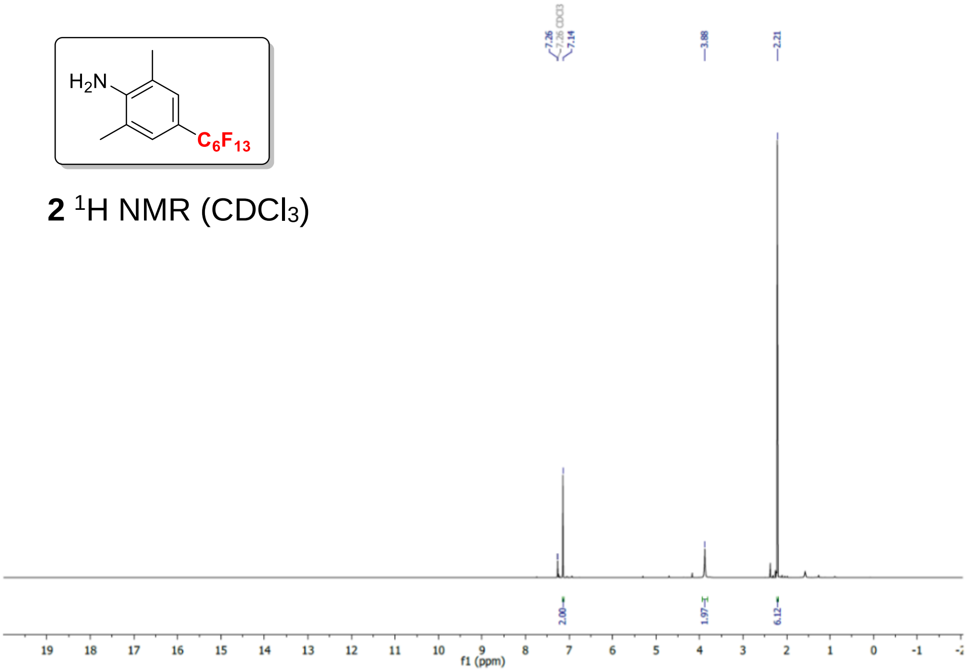
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 3.83 (8H, d), 3.93 (8H, m), 4.16 (8H, m), 6.88 (5H, m), 7.02 (1H, m), 7.14, (1H, d, J = 6.5 Hz);
^{13}C NMR (150.903 MHz, $CDCl_3$): δ (ppm): 69.5, 69.6, 69.7, 69.8, 70.1, 71.4, 71.5, 71.6, 112.2 (t), 112.7, 114.2, 120.7, 121.6, 148.8, 149.1, 152.0;
^{19}F NMR (564.603 MHz, $CDCl_3$): δ (ppm): -126.10 (2F, br s), -122.81 (2F, br s), -121.89 (2F, br s), -121.49 (2F, br s), -109.66 (2F, t), -80.78 (3F, t);
HRMS (ESI [M+Na]$^+$): Mass calc. for $C_{30}H_{31}F_{13}O_8Na$: 789.1709, found for: $C_{30}H_{31}F_{13}O_8Na$: 789.1709.



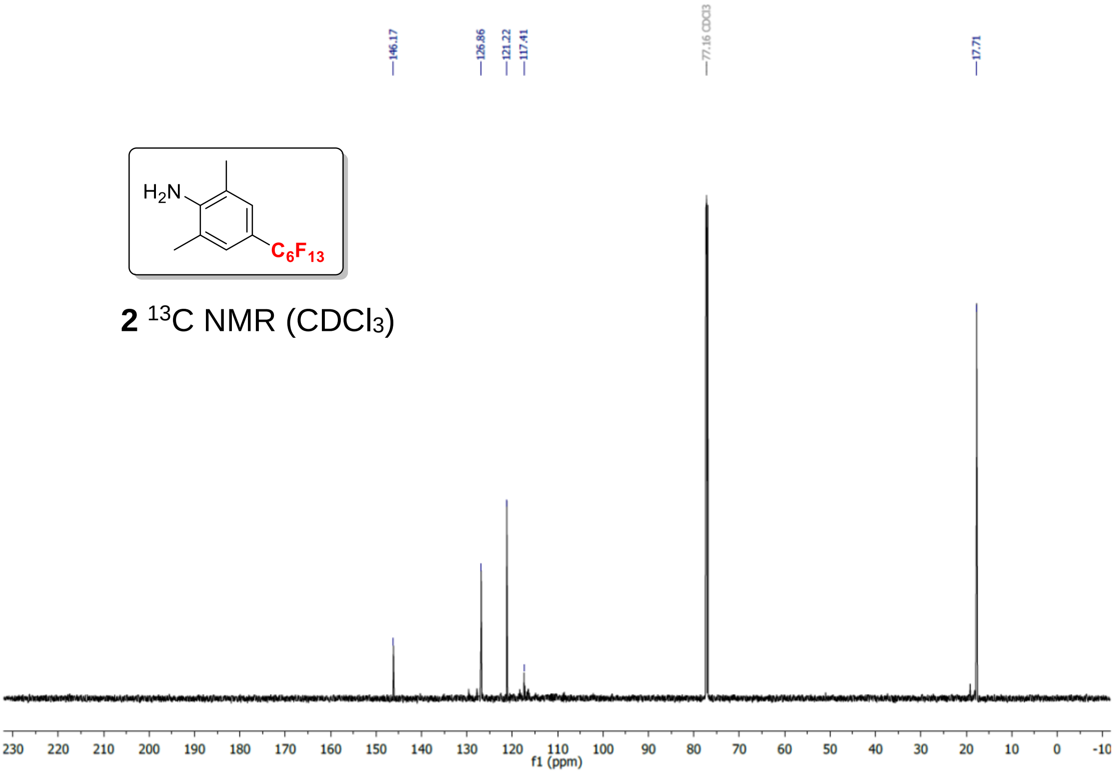
2-(2-bromo-1,1,2,2-tetrafluoroethyl)-6,7,9,10,12,13,20,21,23,24,26,27-dodecahydrodibenzo[b,n][1,4,7,10,13,16,19,22]octaoxacyclotetracosine **(24)** obtained as an amorphous off-white solid (50 %). TLC: CH_2Cl_2: MeOH (2:0.1)

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 3.83 (8H, d), 3.92 (8H, m), 4.16 (8H, m), 6.89 (5H, m), 7.03 (1H, d, J = 1.7 Hz), 7.14, (1H, dd, J = 8.3 Hz, J = 1.6 Hz);
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 69.5, 69.6, 69.7, 69.9, 70.1, 71.4, 71.5, 71.6, 112.5 (t, J = 5.2 Hz), 112.7, 114.2, 121.0, 121.6, 148.7, 149.1, 151.8;
^{19}F NMR (470.585 MHz, $CDCl_3$): δ (ppm): -107.18 (2F, t), -64.70 (2F, t).
HRMS (ESI [M+Na]$^+$): Mass calc. for $C_{26}H_{31}BrF_4NaO_8$: 649.1036, found for: $C_{26}H_{31}BrF_4NaO_8$: 649.1030.

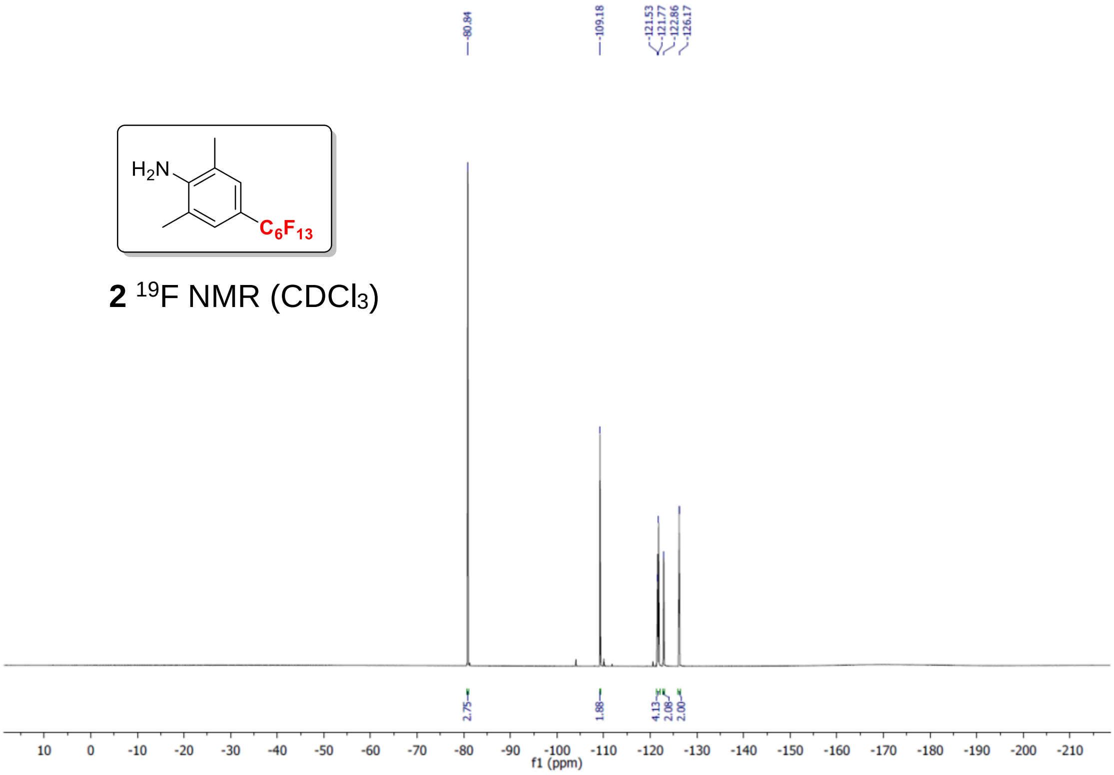
9. Copies of ^{1}H, ^{13}C, ^{19}F, HSQC, HMBC NMR and HRMS spectra



2 ^{1}H NMR ($CDCl_3$)



2 ^{13}C NMR ($CDCl_3$)



2 ^{19}F NMR (CDCl$_3$)

Acquisition Parameter

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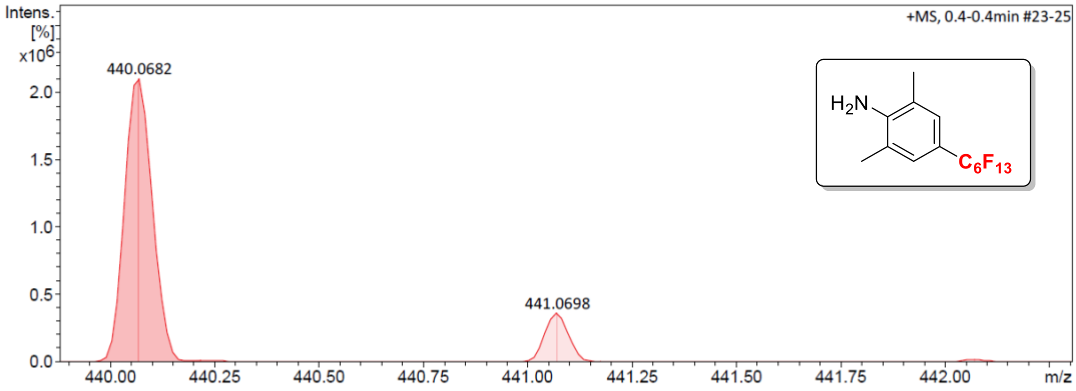
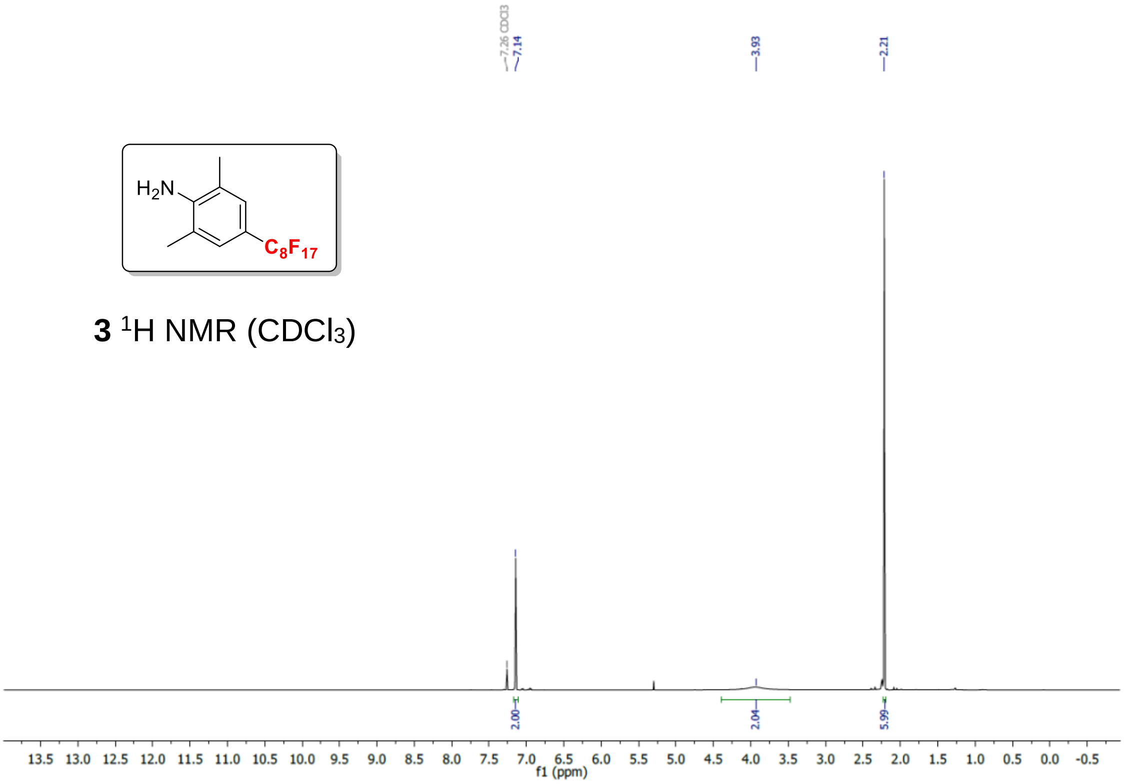
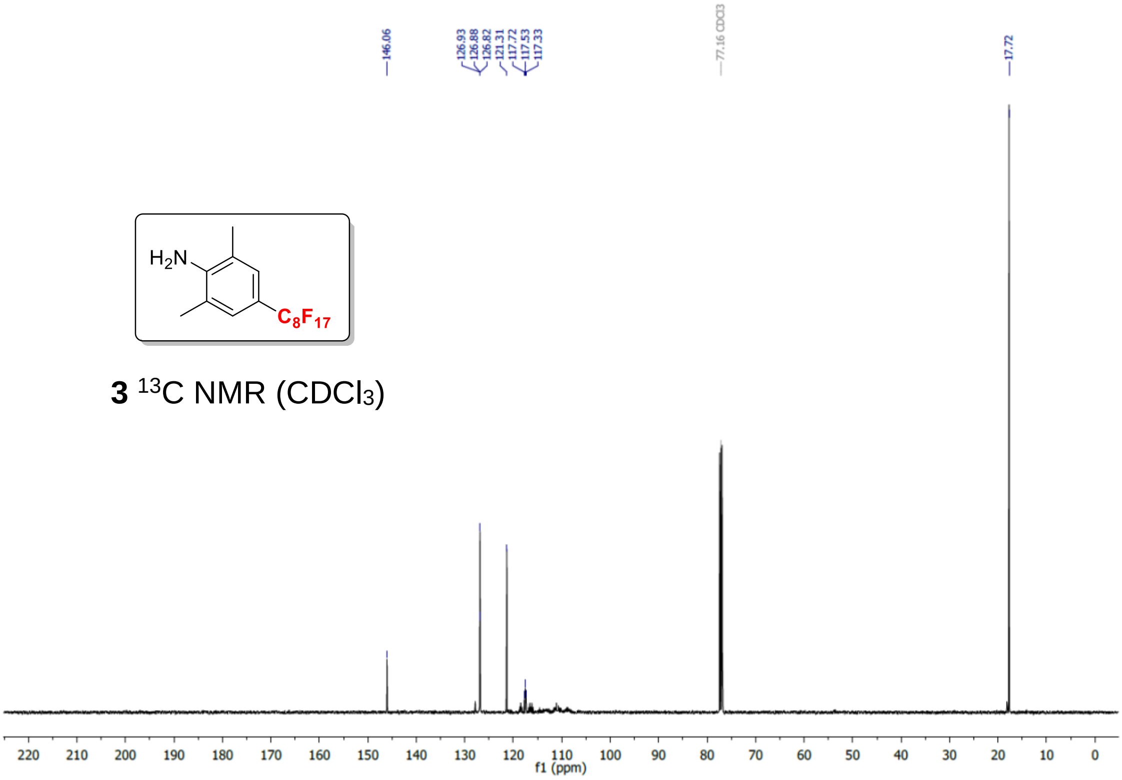
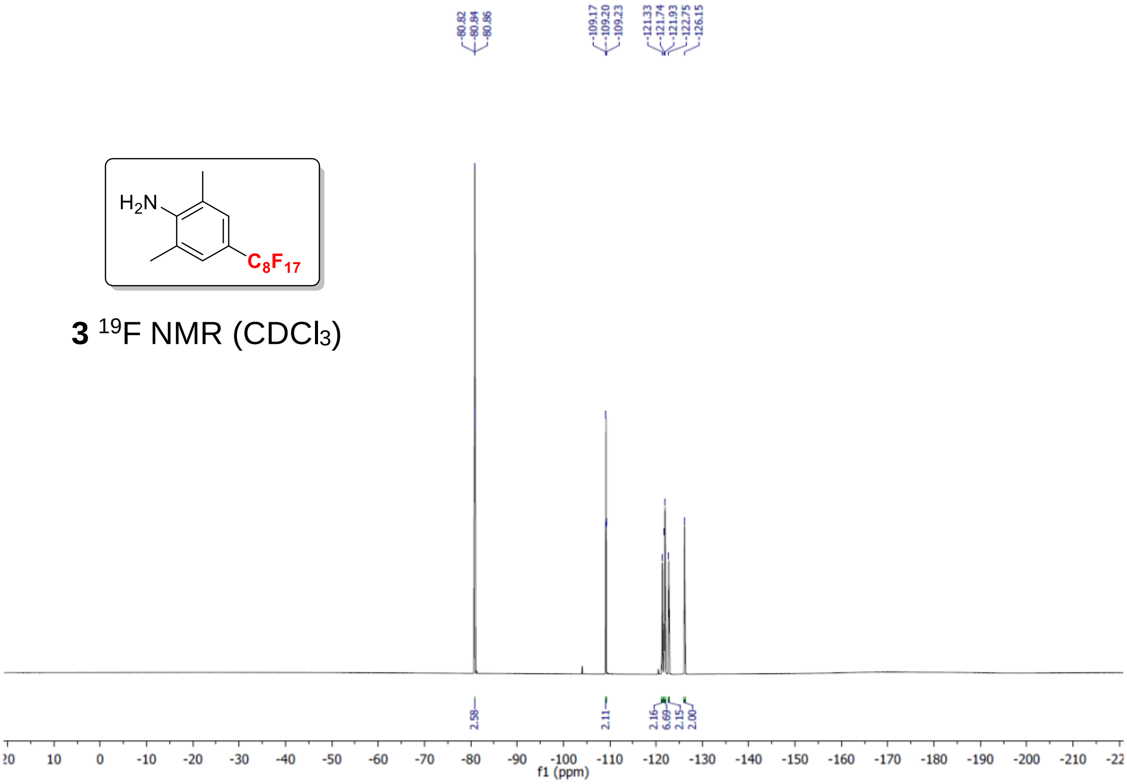




3 ^{1}H NMR ($CDCl_3$)



3 ^{13}C NMR ($CDCl_3$)


3 ^{19}F NMR (CDCl$_3$)

Acquisition Parameter

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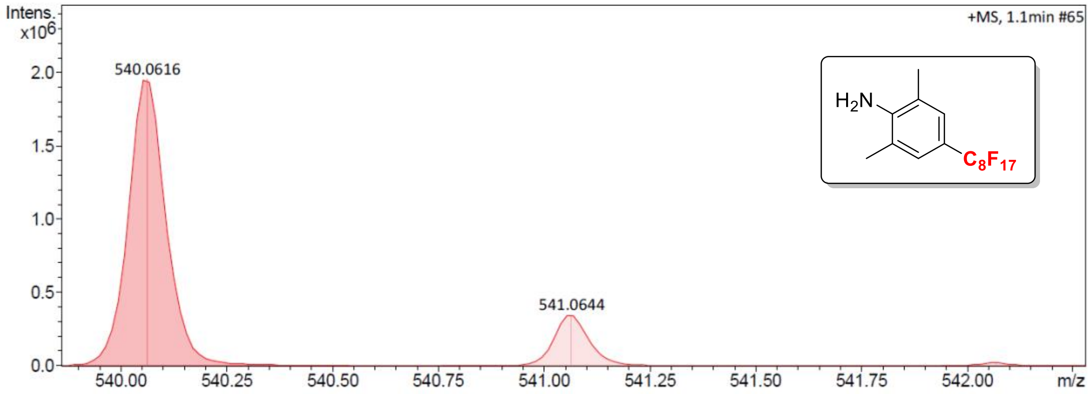
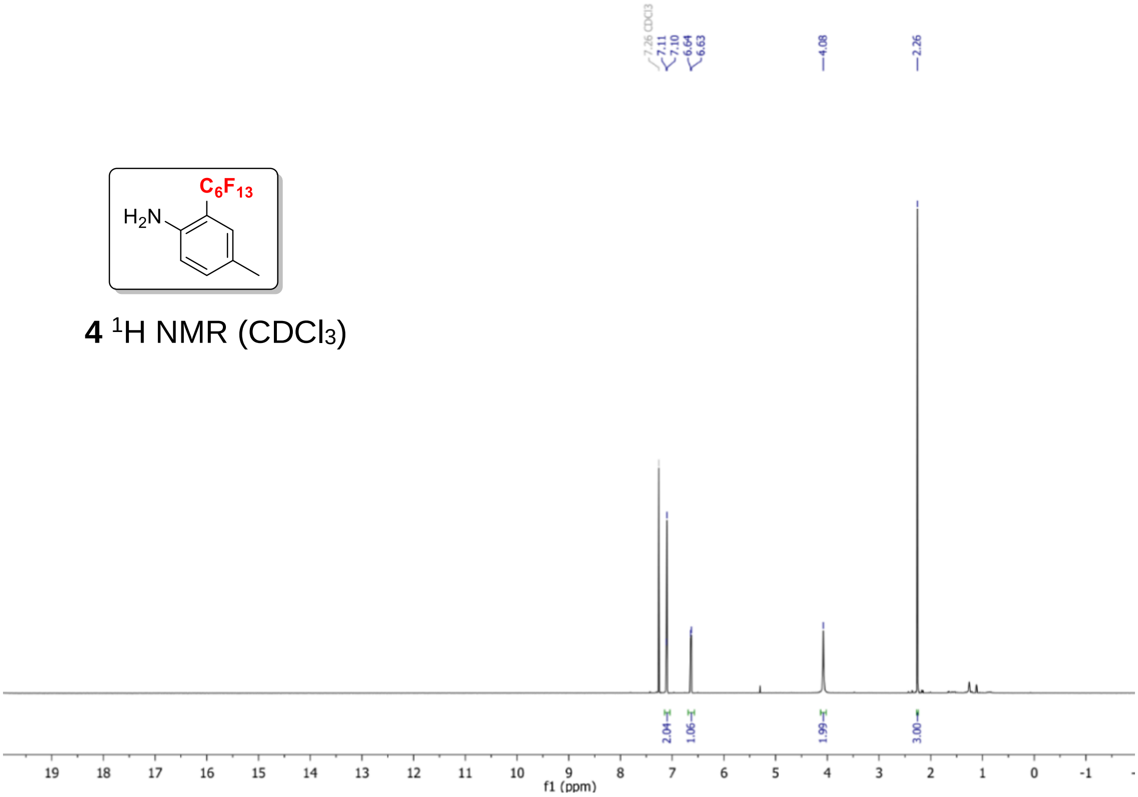
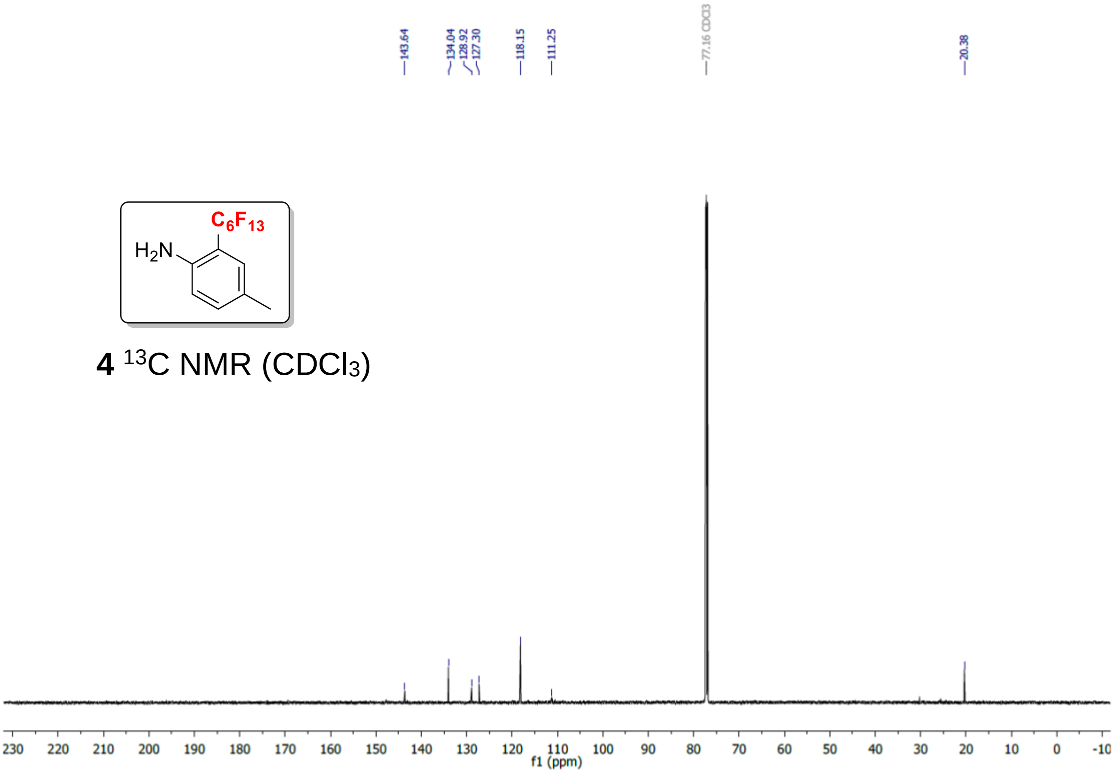
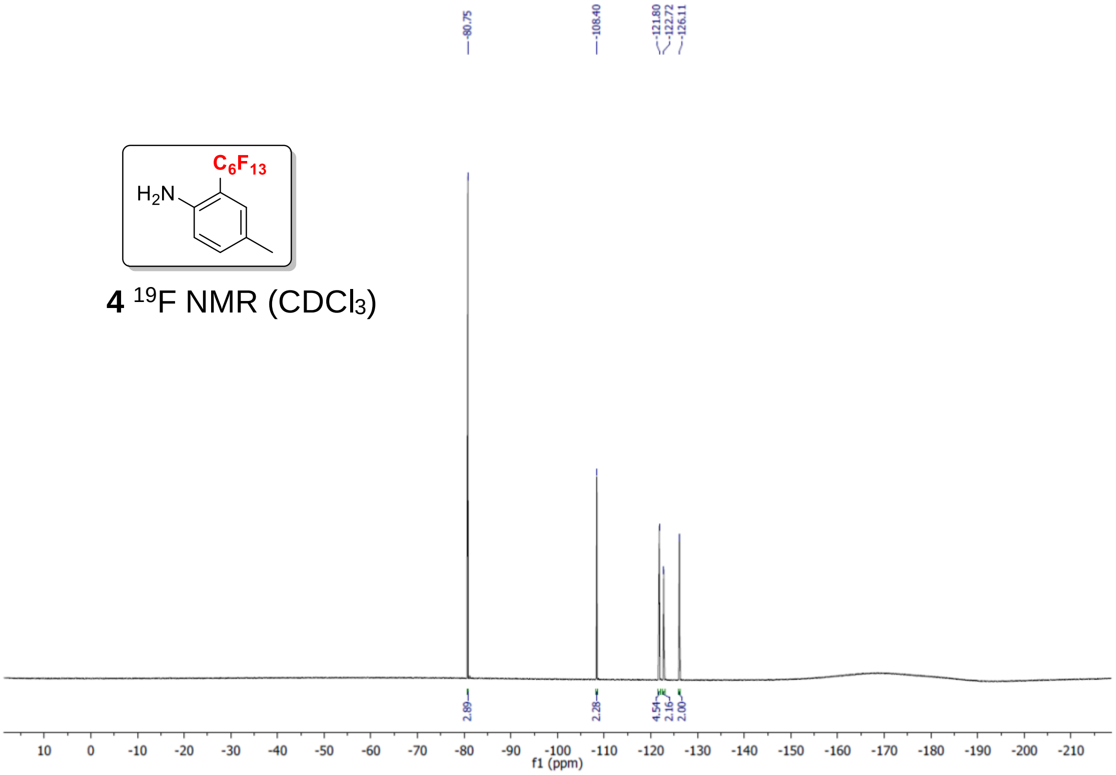




4 ^{1}H NMR ($CDCl_3$)



4 ^{13}C NMR ($CDCl_3$)



4 ^{19}F NMR ($CDCl_3$)

Acquisition Parameter

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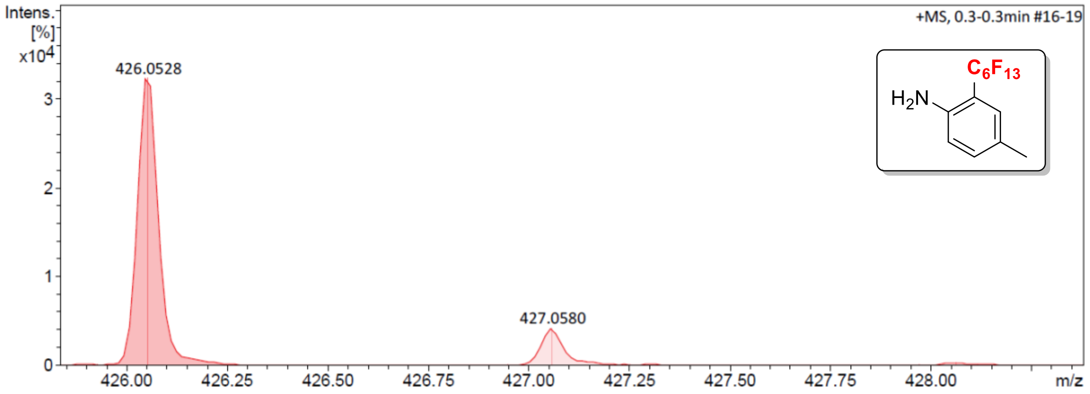
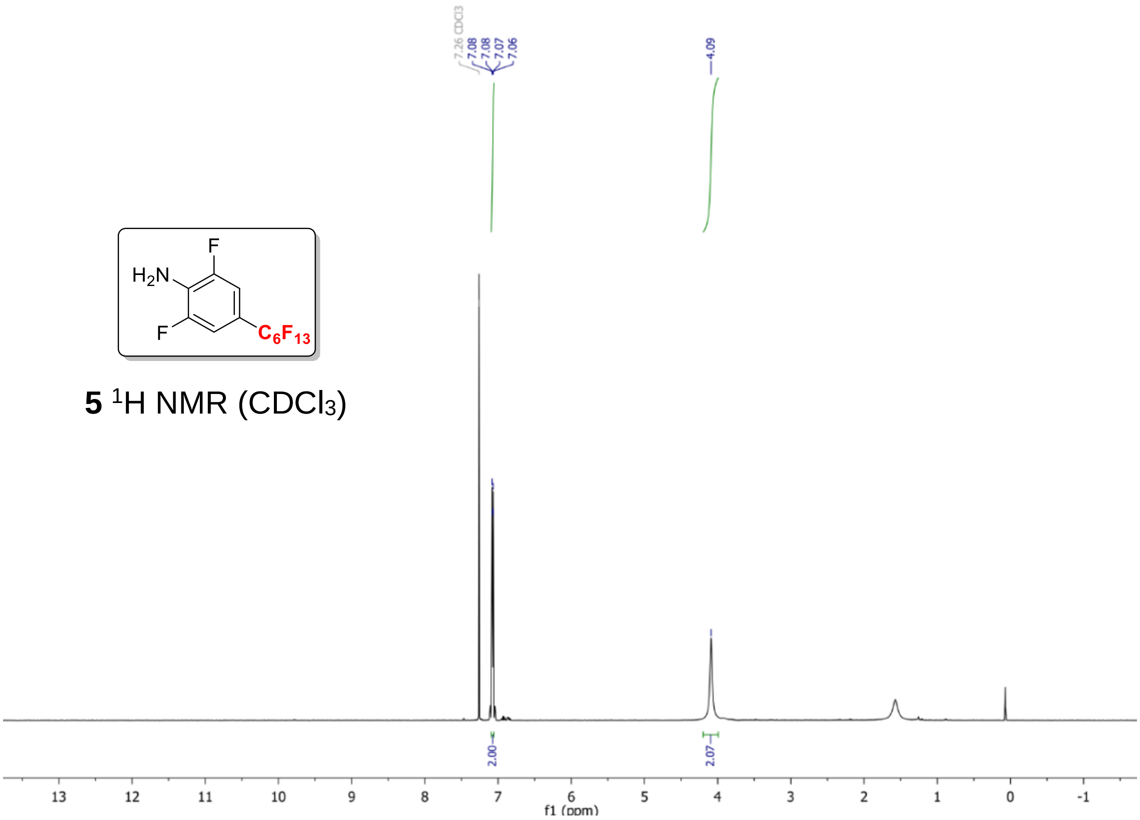
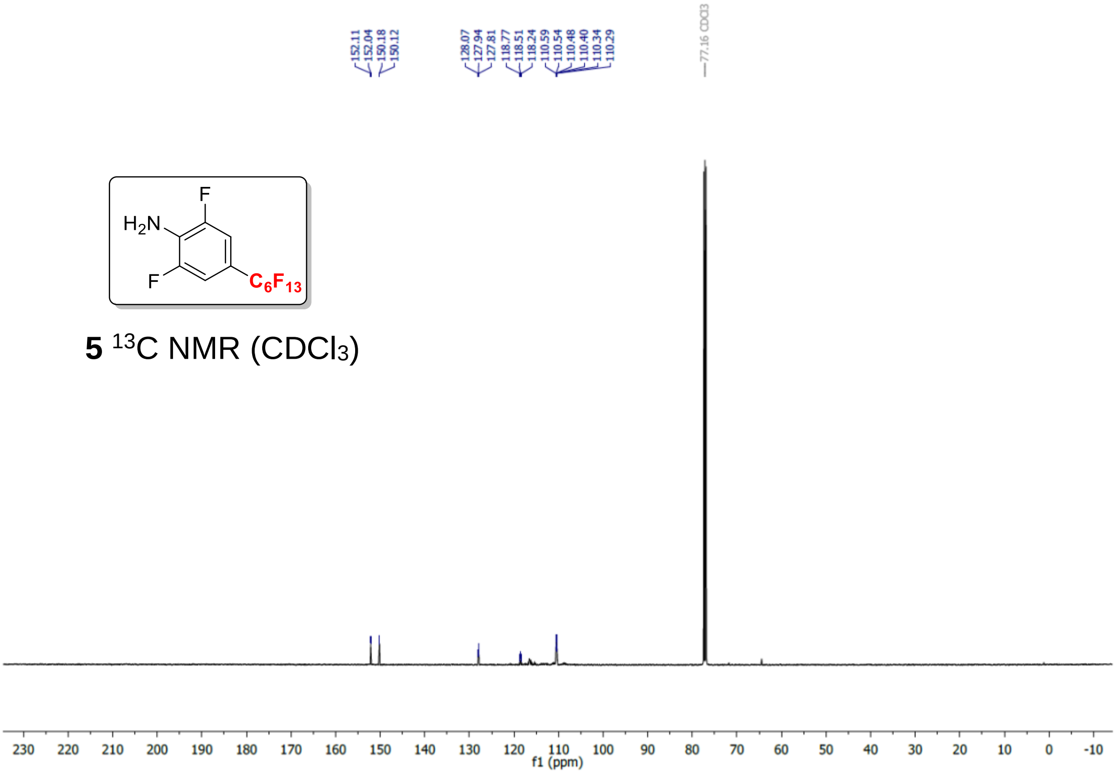
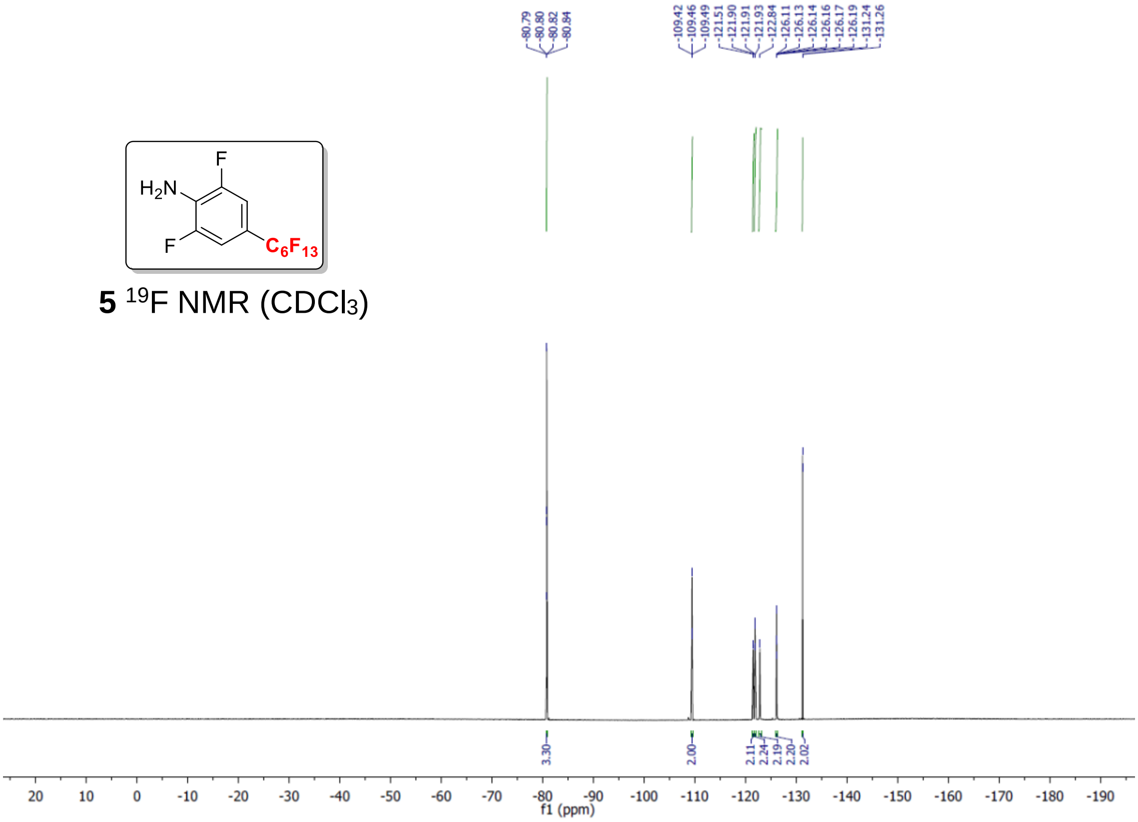




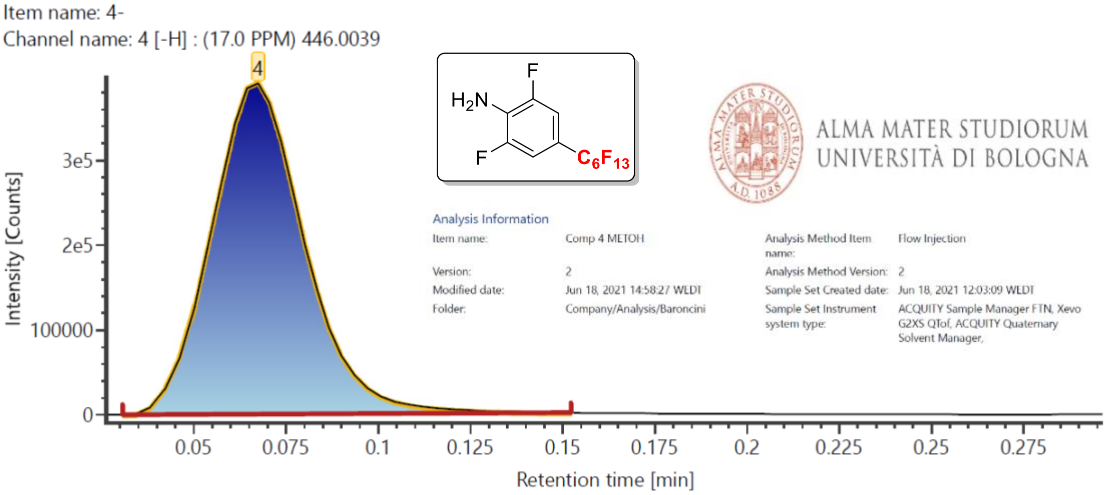
5 ^{1}H NMR (CDCl$_3$)



5 ^{13}C NMR (CDCl$_3$)



5 ^{19}F NMR (CDCl$_3$)



Item name: 4-
Channel name: 4 [-H] : (17.0 PPM) 446.0039

Analysis Information

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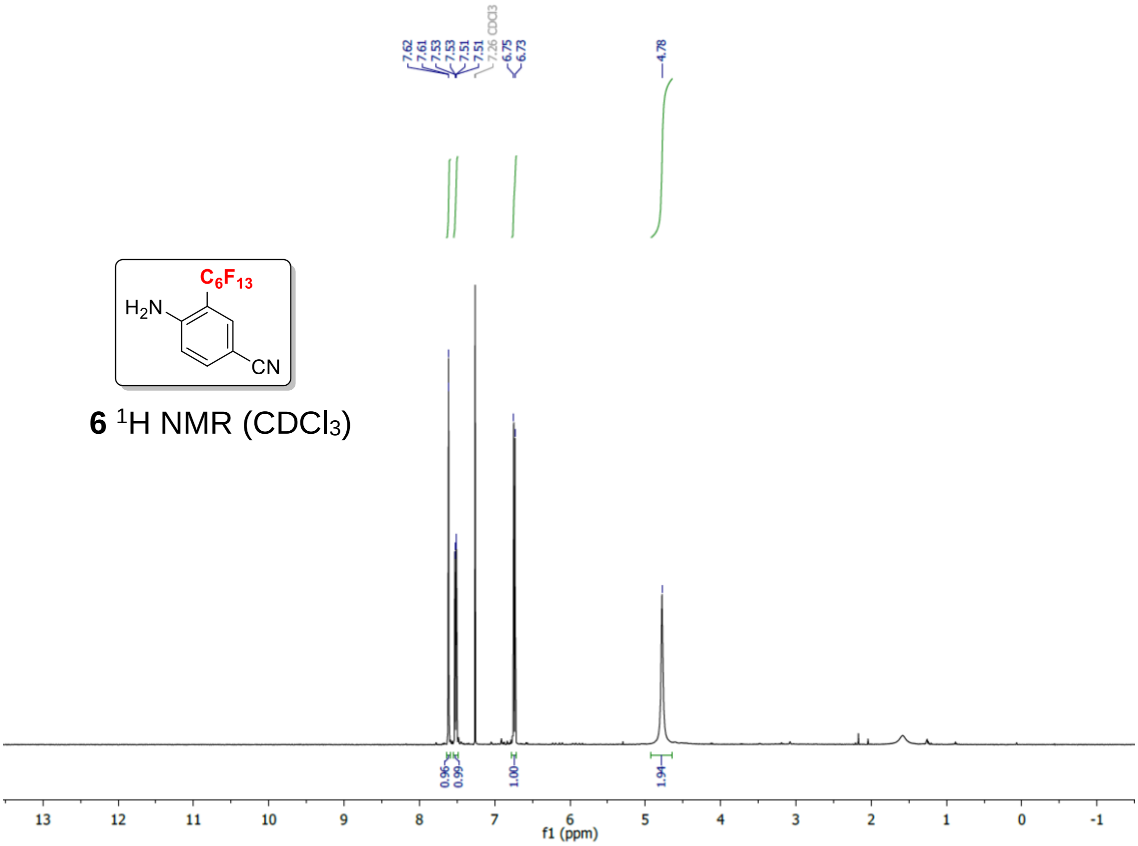
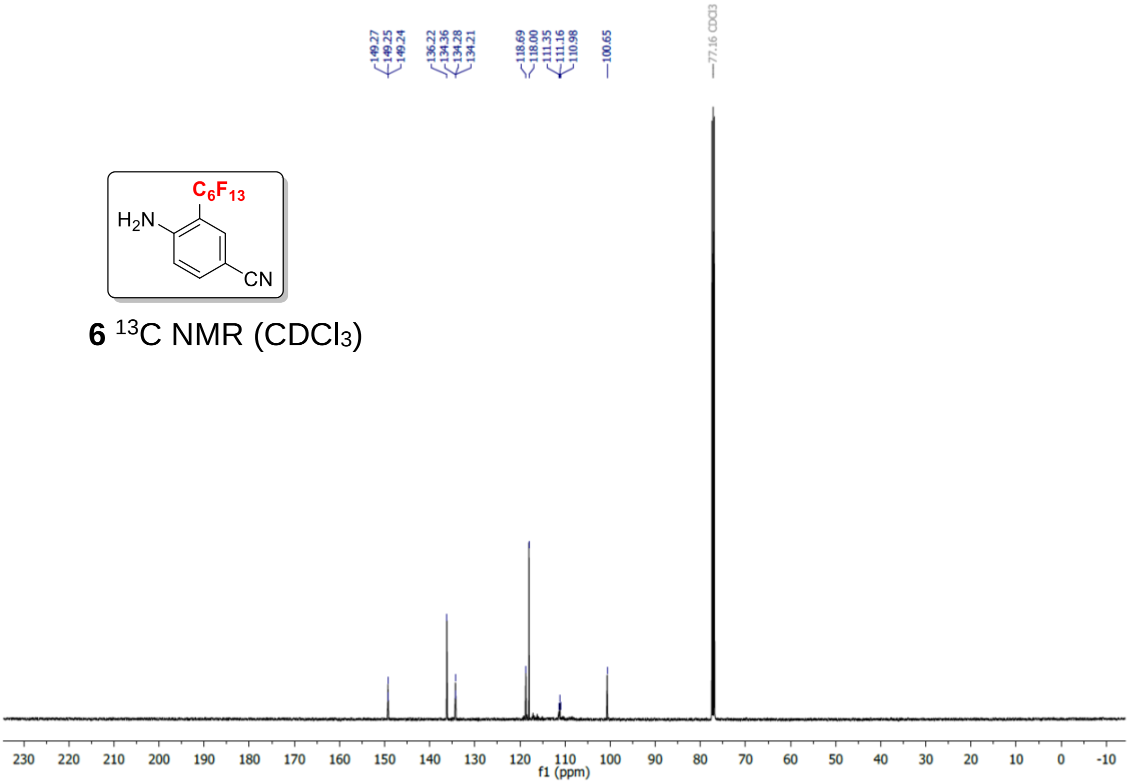
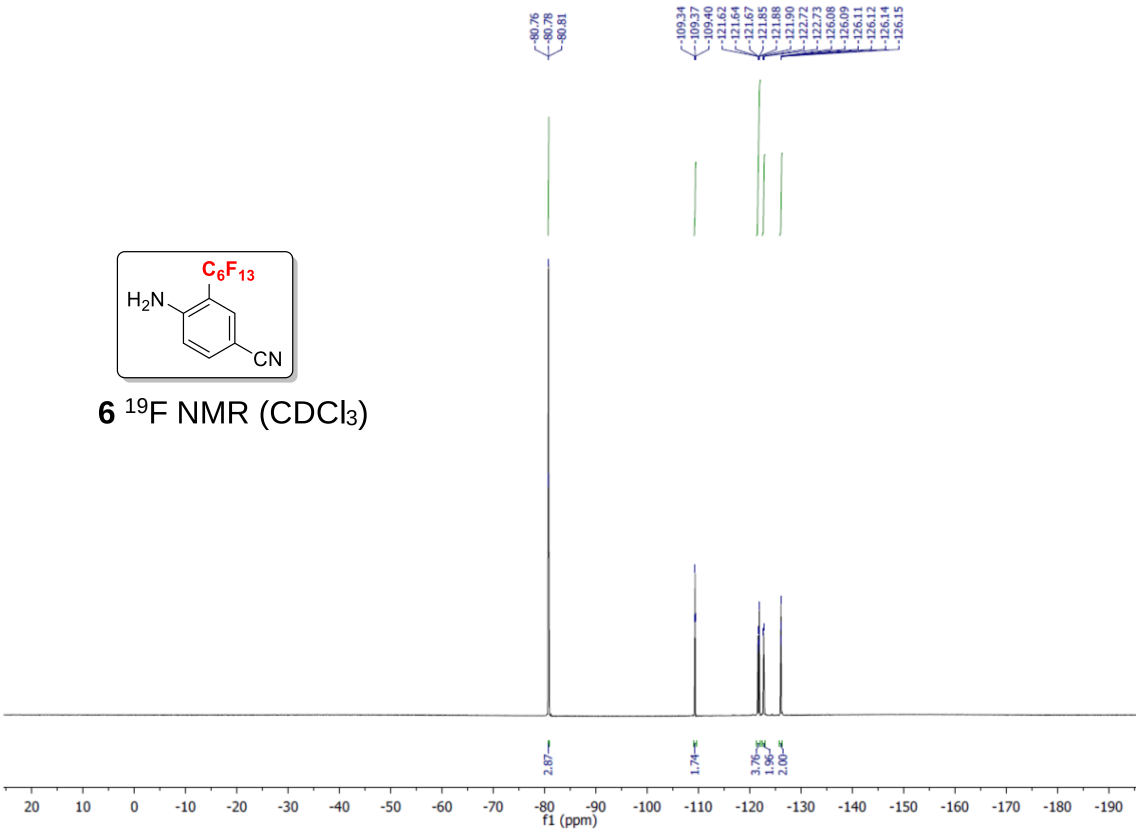


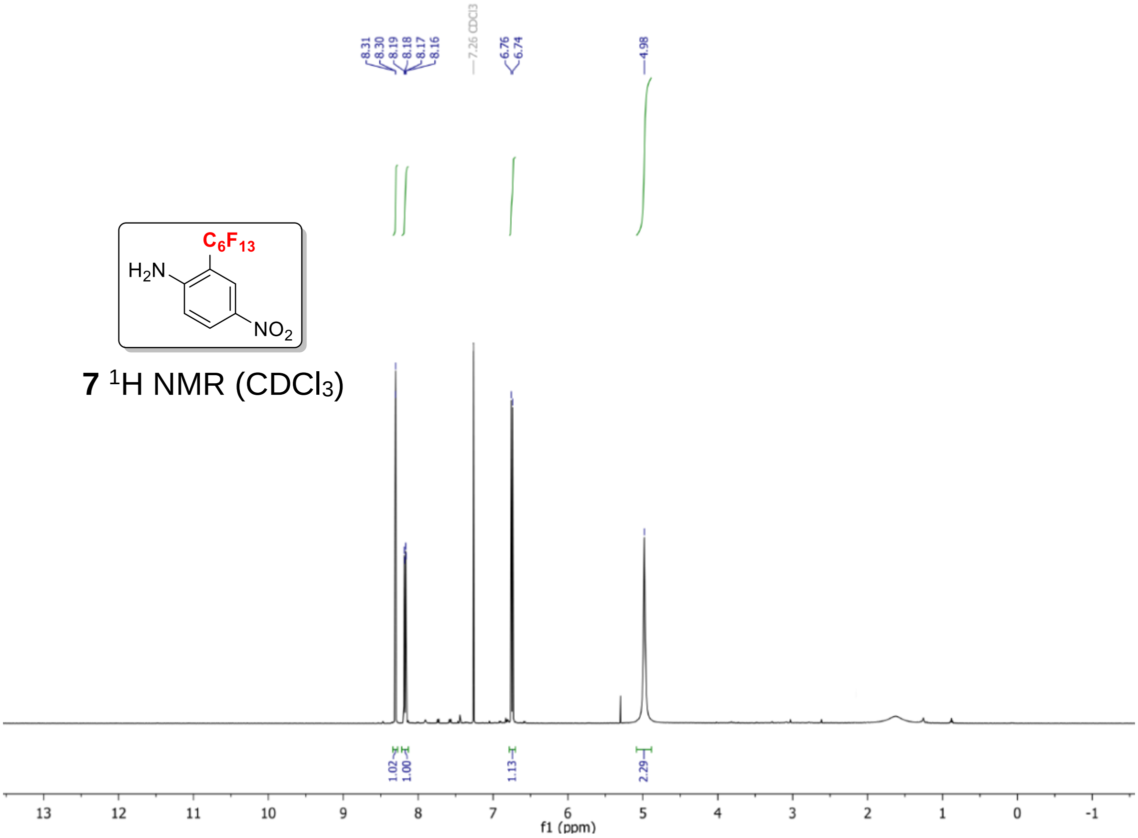
6 ^{1}H NMR (CDCl$_3$)



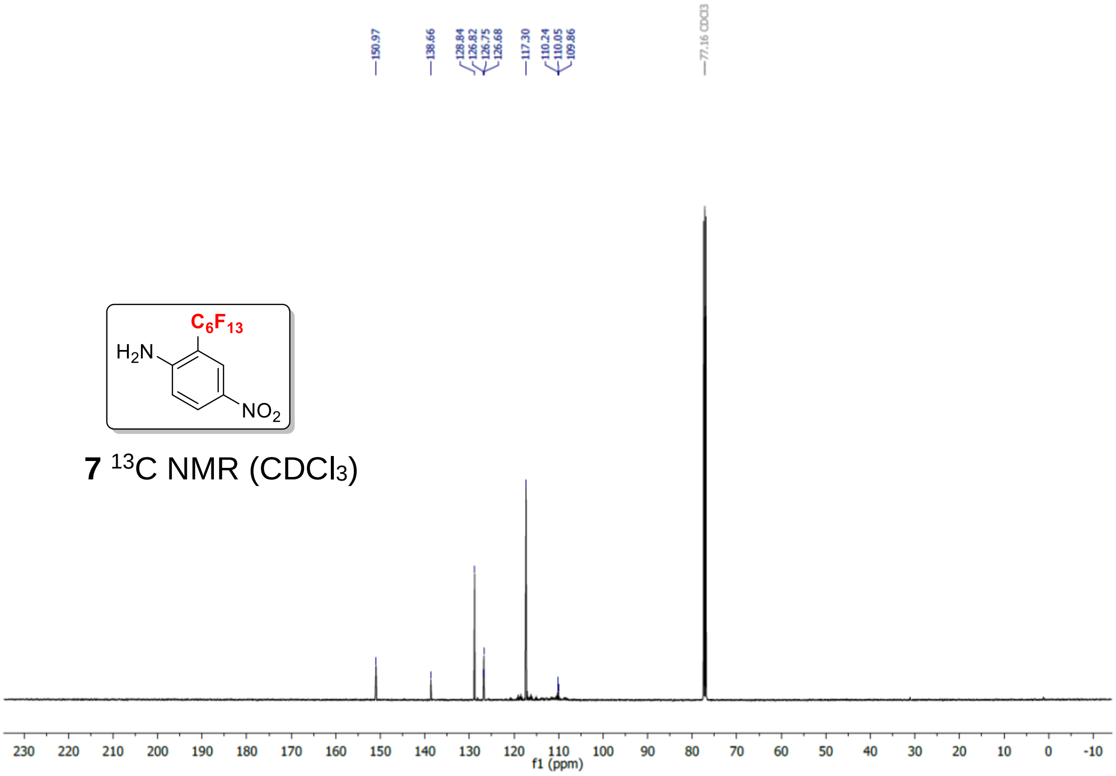
6 ^{13}C NMR (CDCl$_3$)



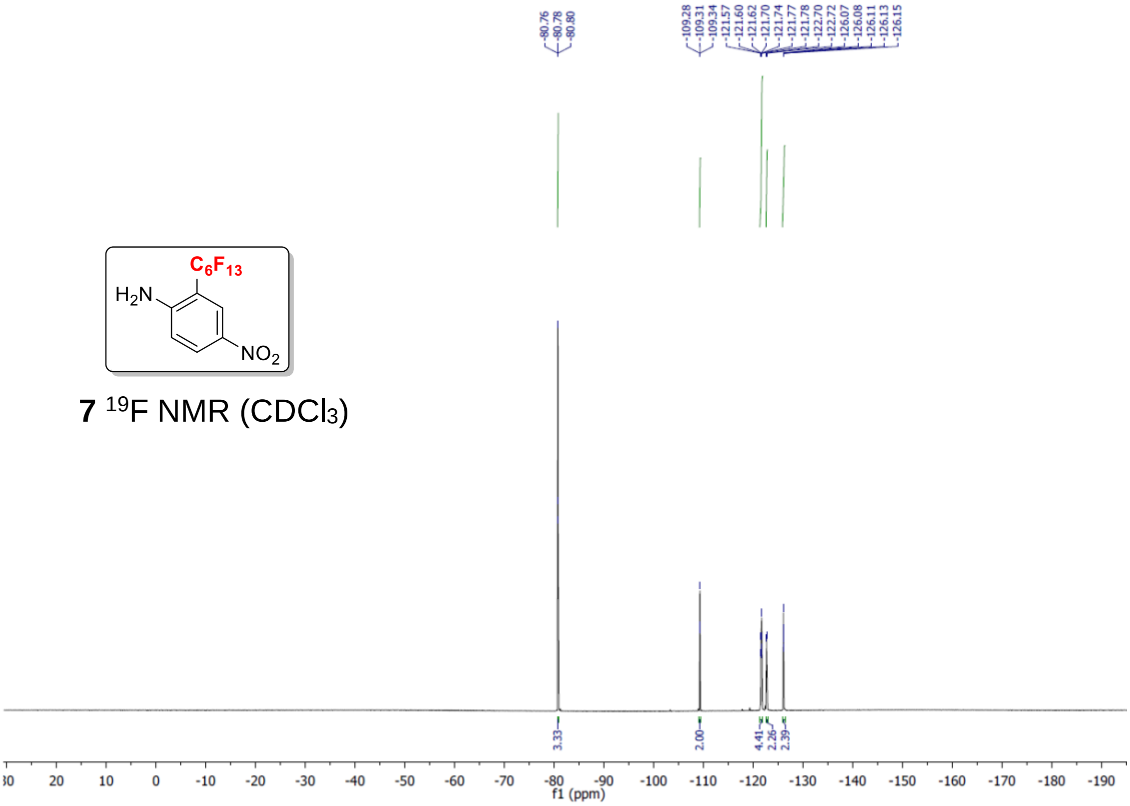
6 ^{19}F NMR ($CDCl_3$)

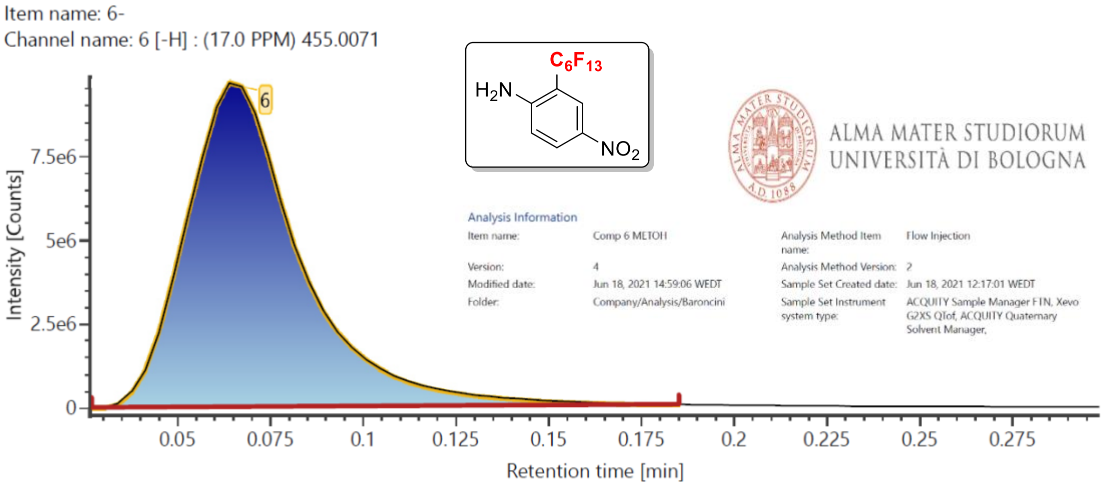


7 ^{1}H NMR (CDCl$_3$)



7 ^{13}C NMR (CDCl$_3$)

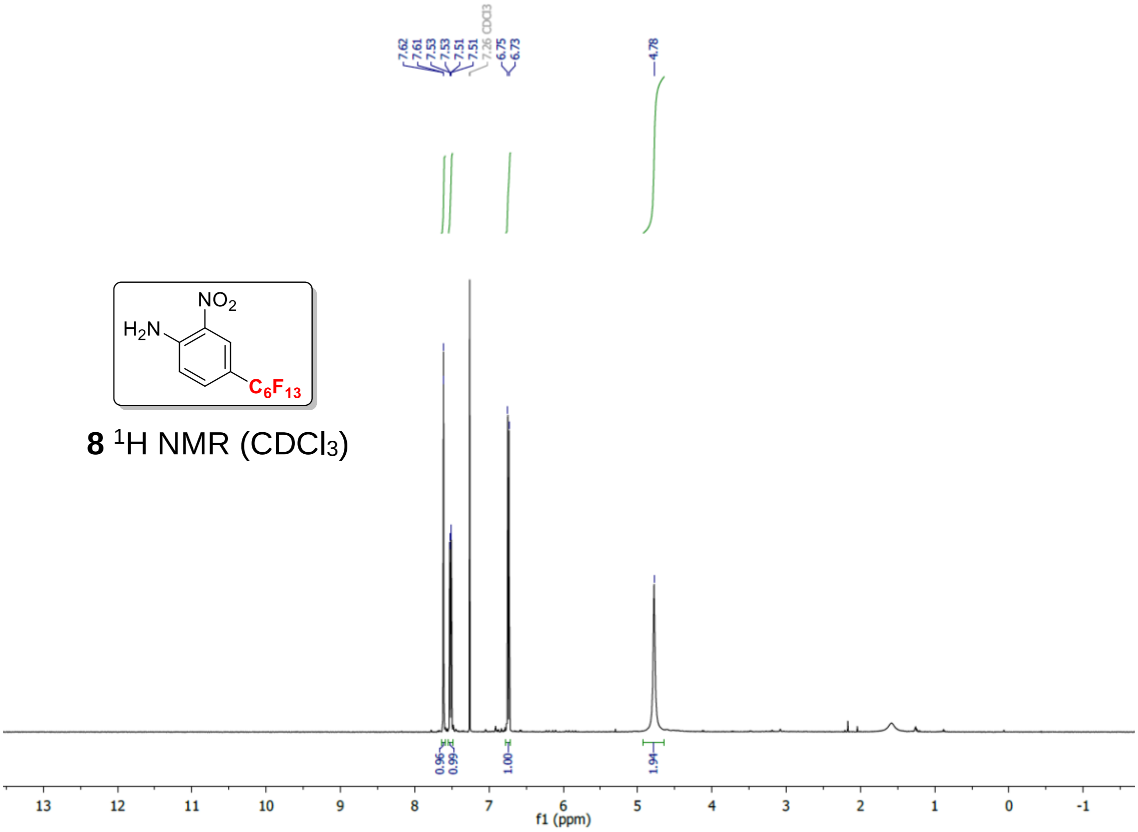

7 ^{19}F NMR (CDCl$_3$)


Item name: 6-

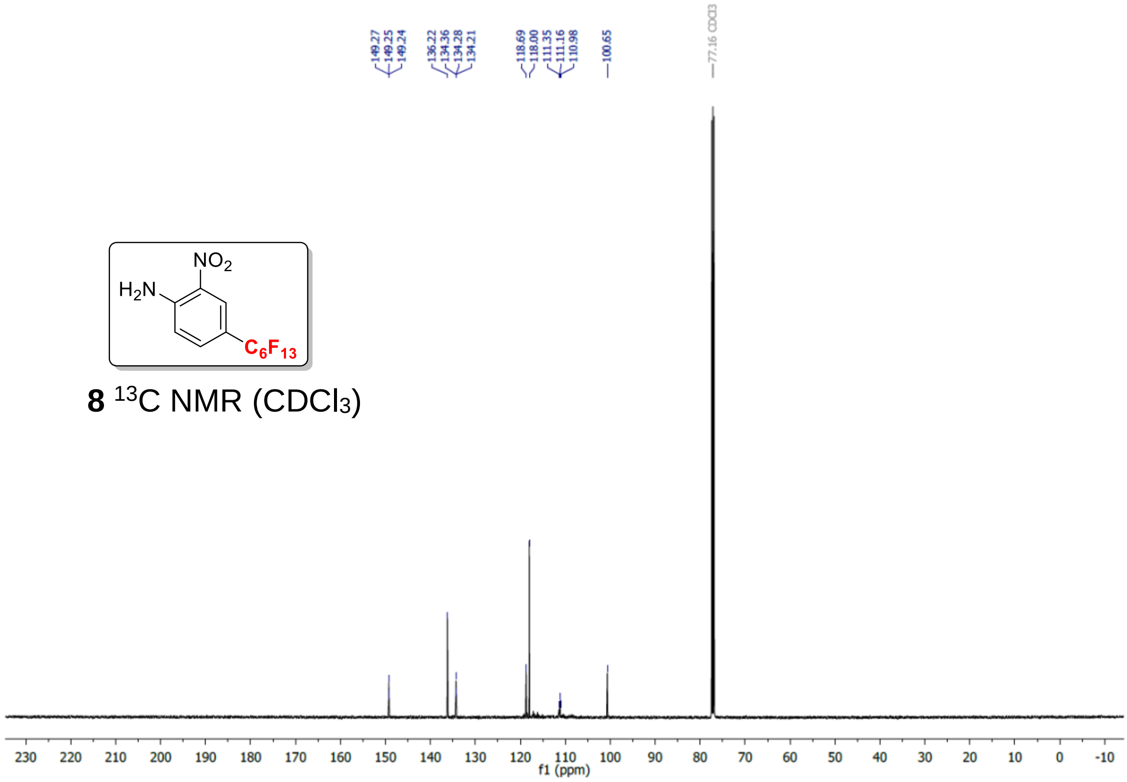
Channel name: 6 [-H] : (17.0 PPM) 455.0071

Analysis Information

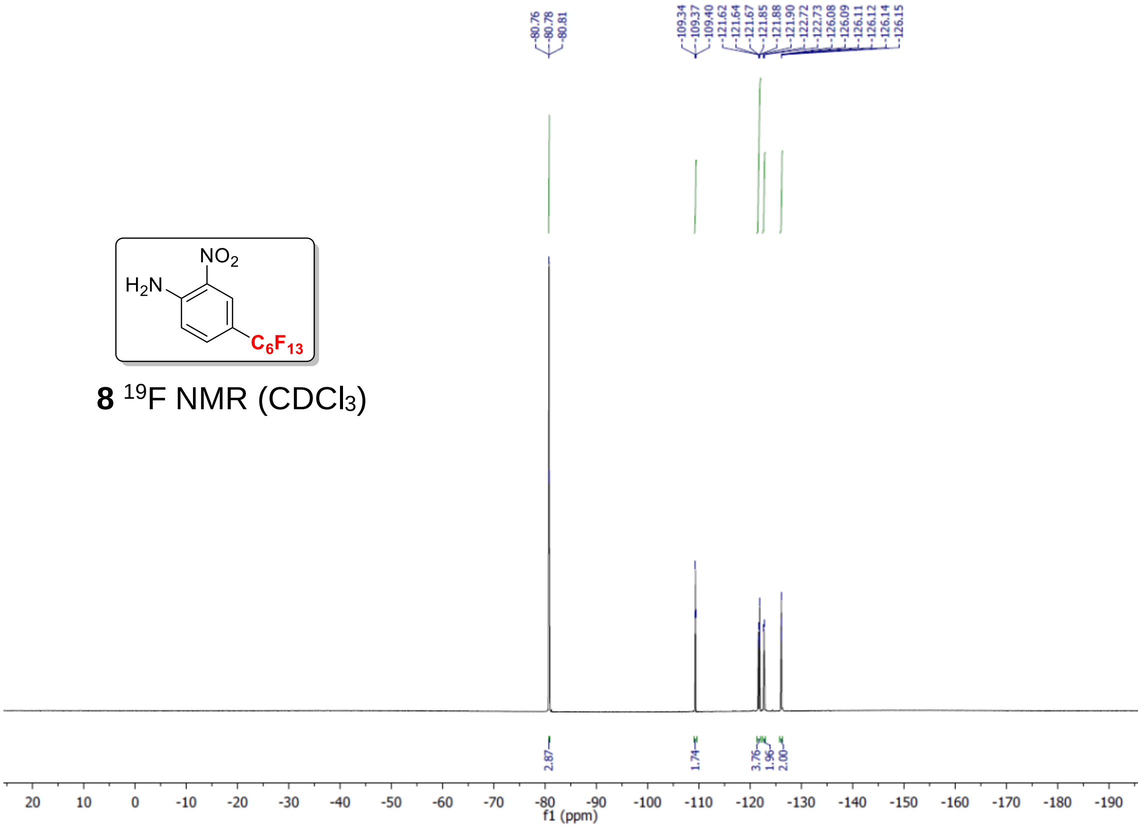
Item name: Comp 6 METOH
Version: 4
Modified date: Jun 18, 2021 14:59:06 WEDT
Folder: Company/Analysis/Baroncini
Analysis Method Item name: Flow Injection
Analysis Method Version: 2
Sample Set Created date: Jun 18, 2021 12:17:01 WEDT
Sample Set Instrument system type: ACQUITY Sample Manager FTN, Xevo G2XS QTof, ACQUITY Quaternary Solvent Manager,



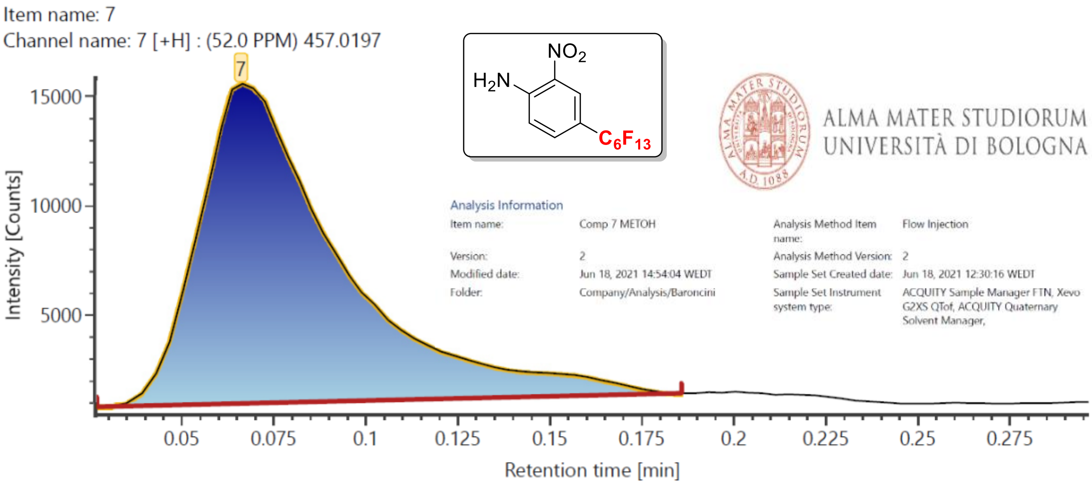
8 ^{1}H NMR (CDCl$_3$)



8 ^{13}C NMR ($CDCl_3$)



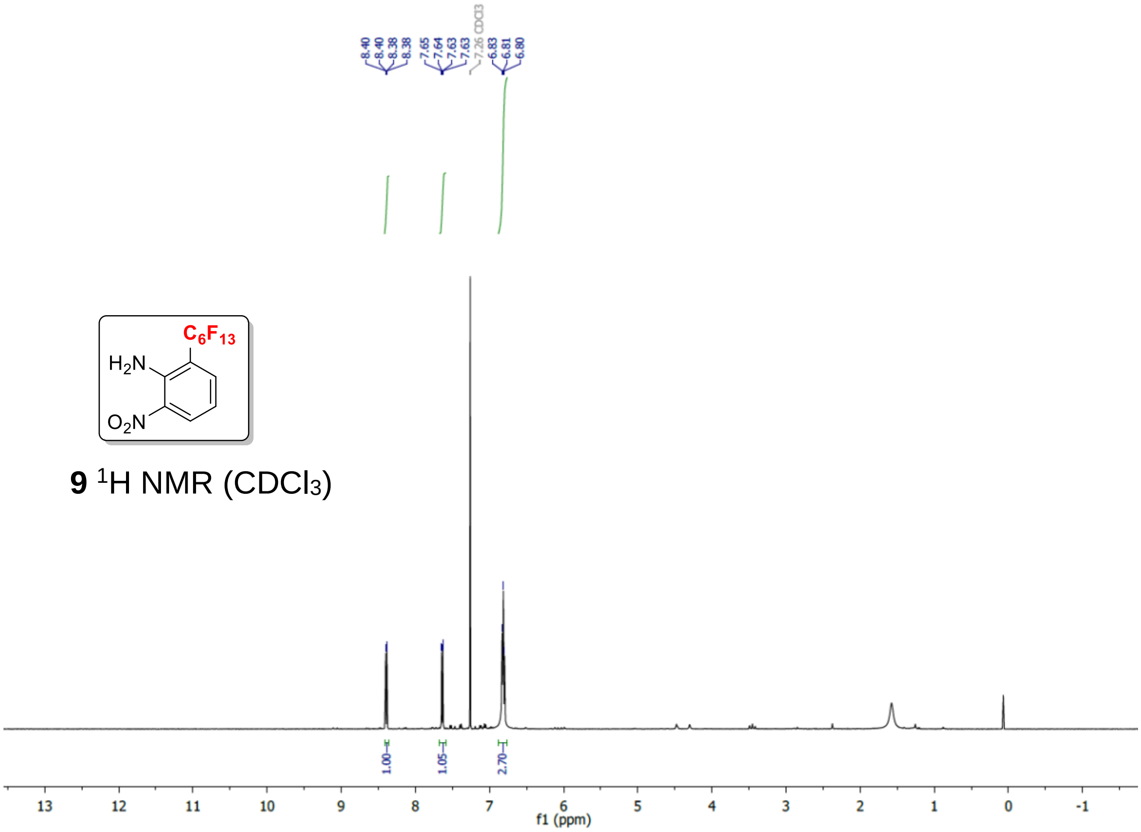
8 ^{19}F NMR ($CDCl_3$)



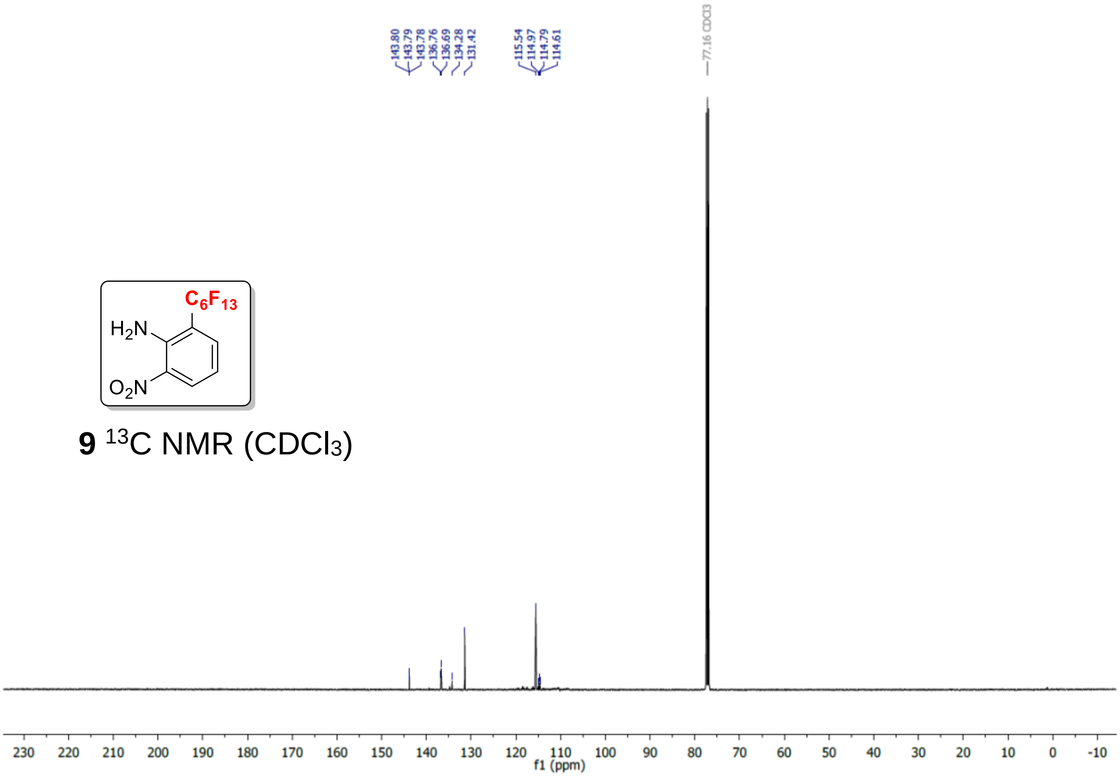
Item name: 7
Channel name: 7 [+H] : (52.0 PPM) 457.0197

Analysis Information

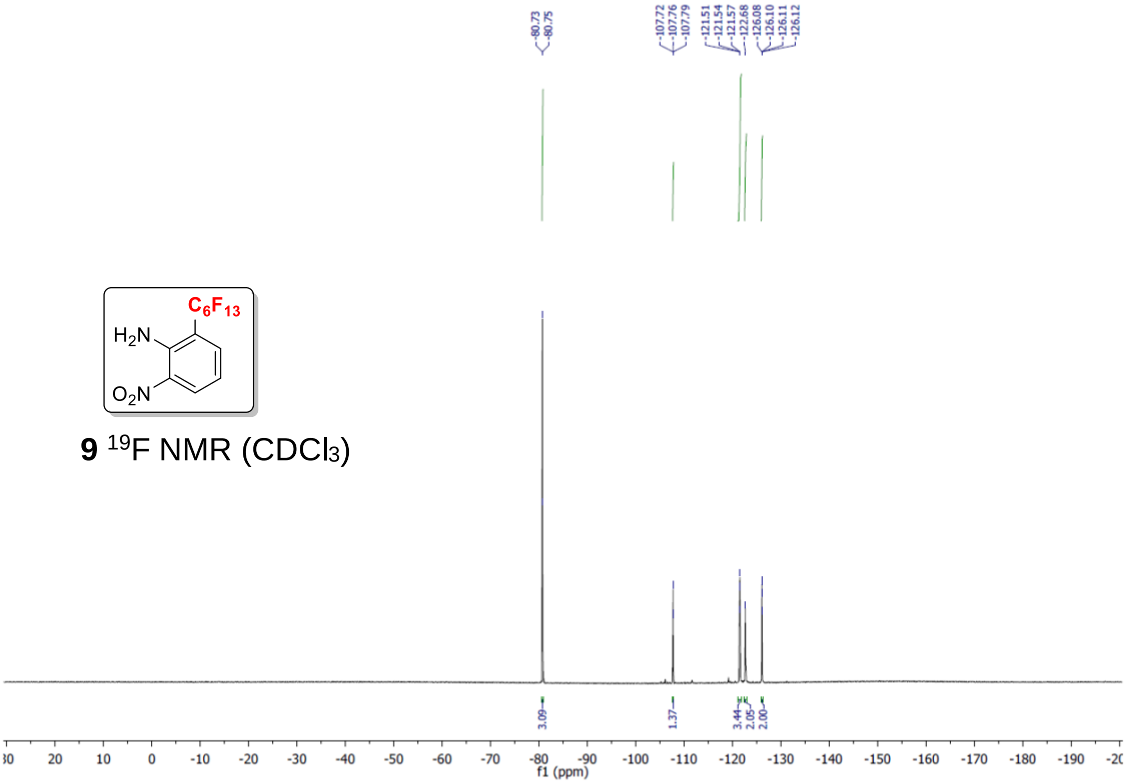
Item name:	Comp 7 METOH	Analysis Method Item name:	Flow Injection
Version:	2	Analysis Method Version:	2
Modified date:	Jun 18, 2021 14:54:04 WEDT	Sample Set Created date:	Jun 18, 2021 12:30:16 WEDT
Folder:	Company/Analysis/Baroncini	Sample Set Instrument system type:	ACQUITY Sample Manager FTN, Xevo G2XS QTof, ACQUITY Quaternary Solvent Manager,



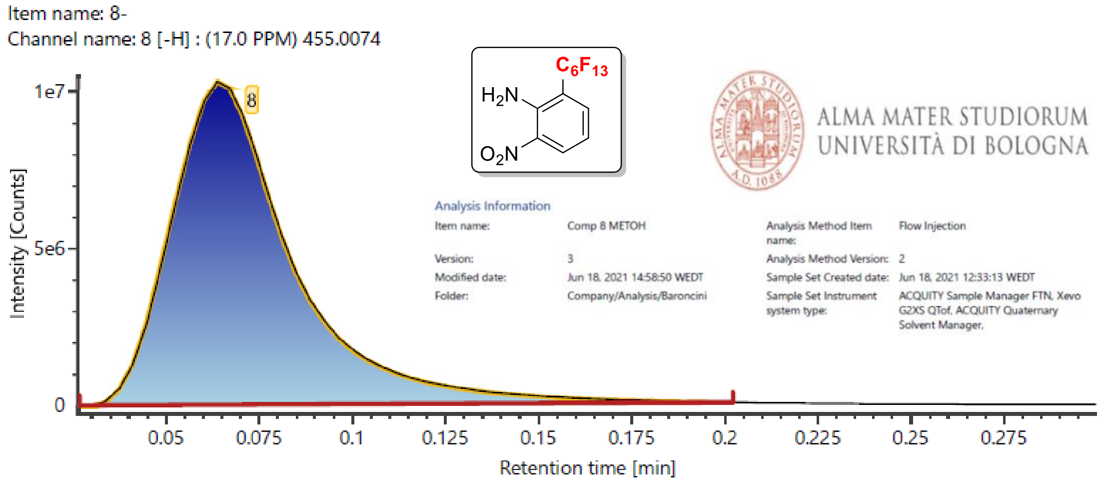
9 ^{1}H NMR ($CDCl_3$)



9 ^{13}C NMR ($CDCl_3$)



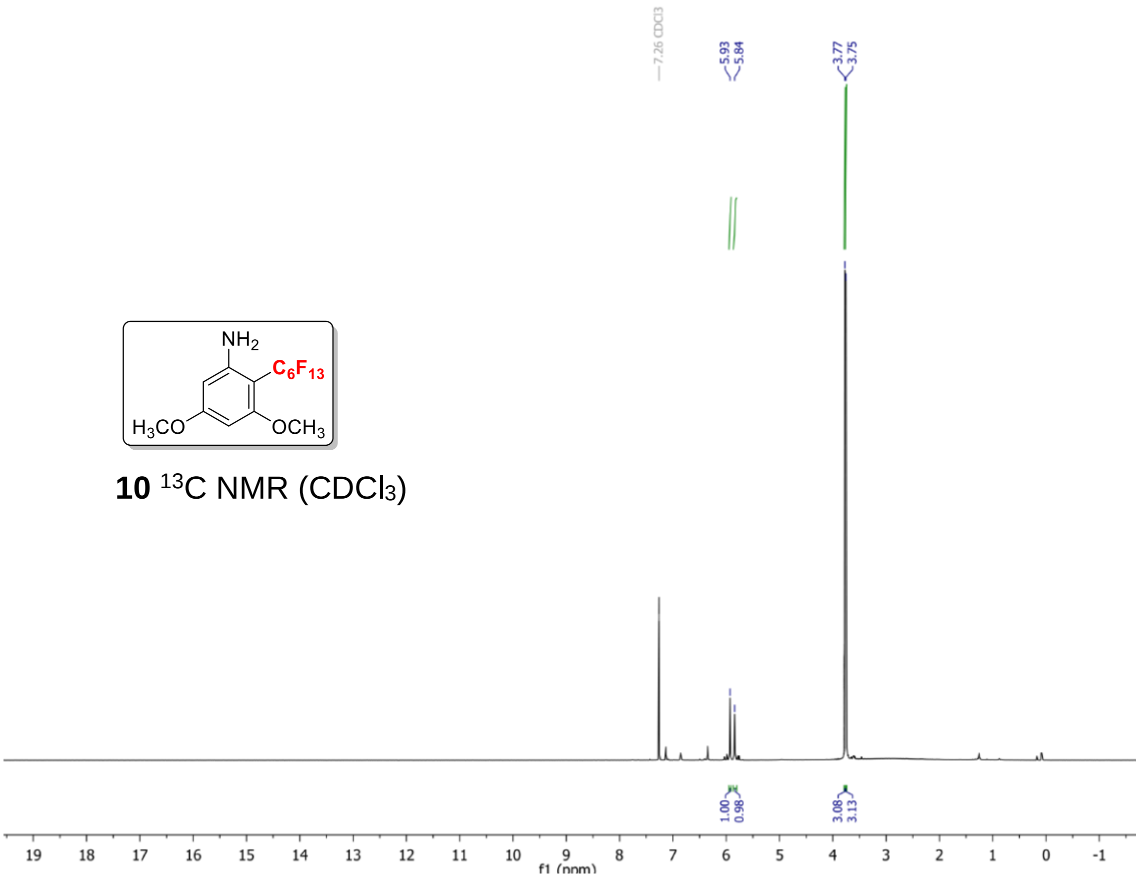
9 ^{19}F NMR (CDCl$_3$)



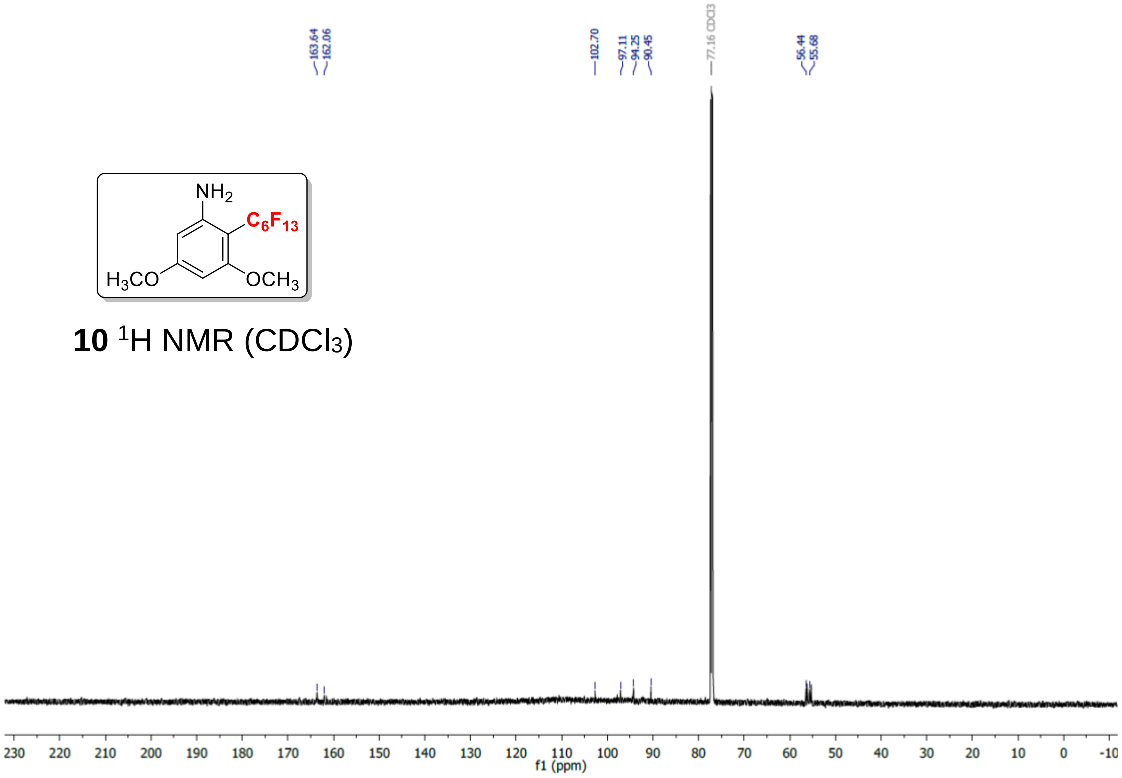
Item name: 8-
Channel name: 8 [-H] : (17.0 PPM) 455.0074

Analysis Information

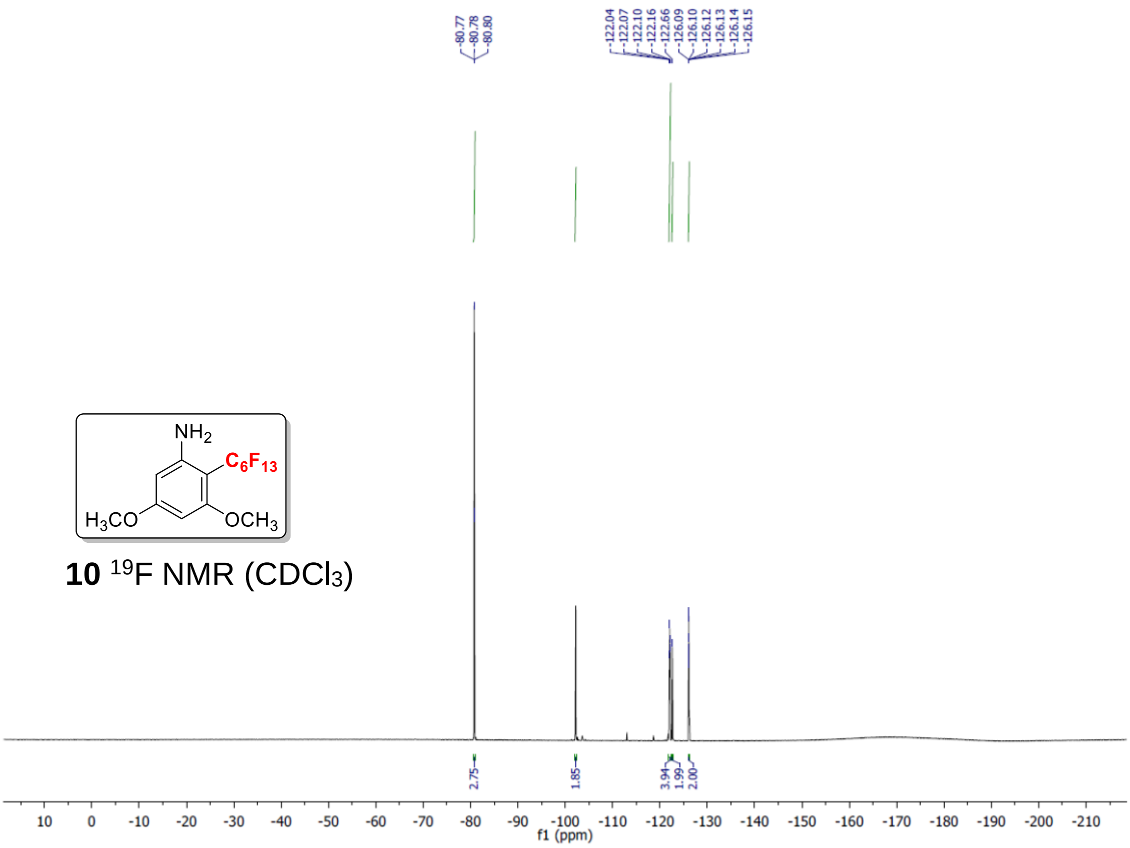
Item name: Comp 8 METOH
Version: 3
Modified date: Jun 18, 2021 14:58:50 WEDT
Folder: Company/Analysis/Baroncini
Analysis Method Item name: Flow Injection
Analysis Method Version: 2
Sample Set Created date: Jun 18, 2021 12:33:13 WEDT
Sample Set Instrument system type: ACQUITY Sample Manager FTN, Xevo G2XS QTof, ACQUITY Quaternary Solvent Manager,



10 ^{13}C NMR ($CDCl_3$)



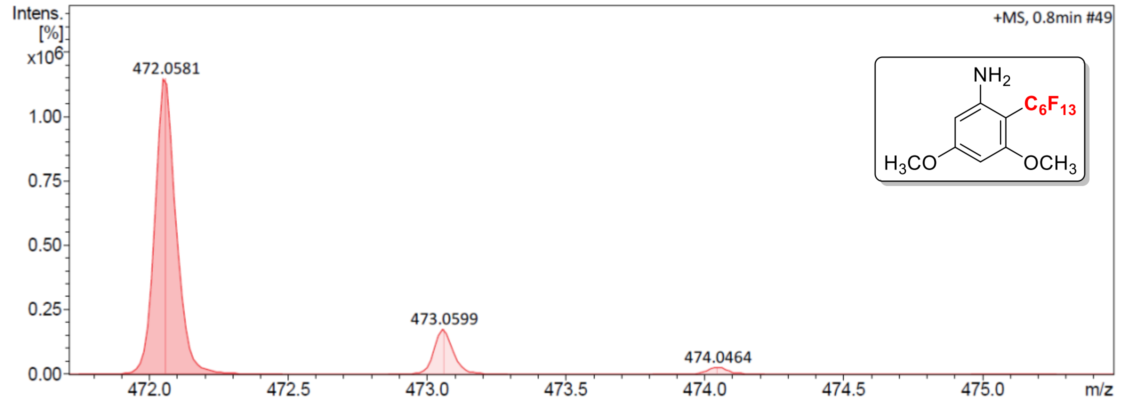
10 ^{1}H NMR ($CDCl_3$)

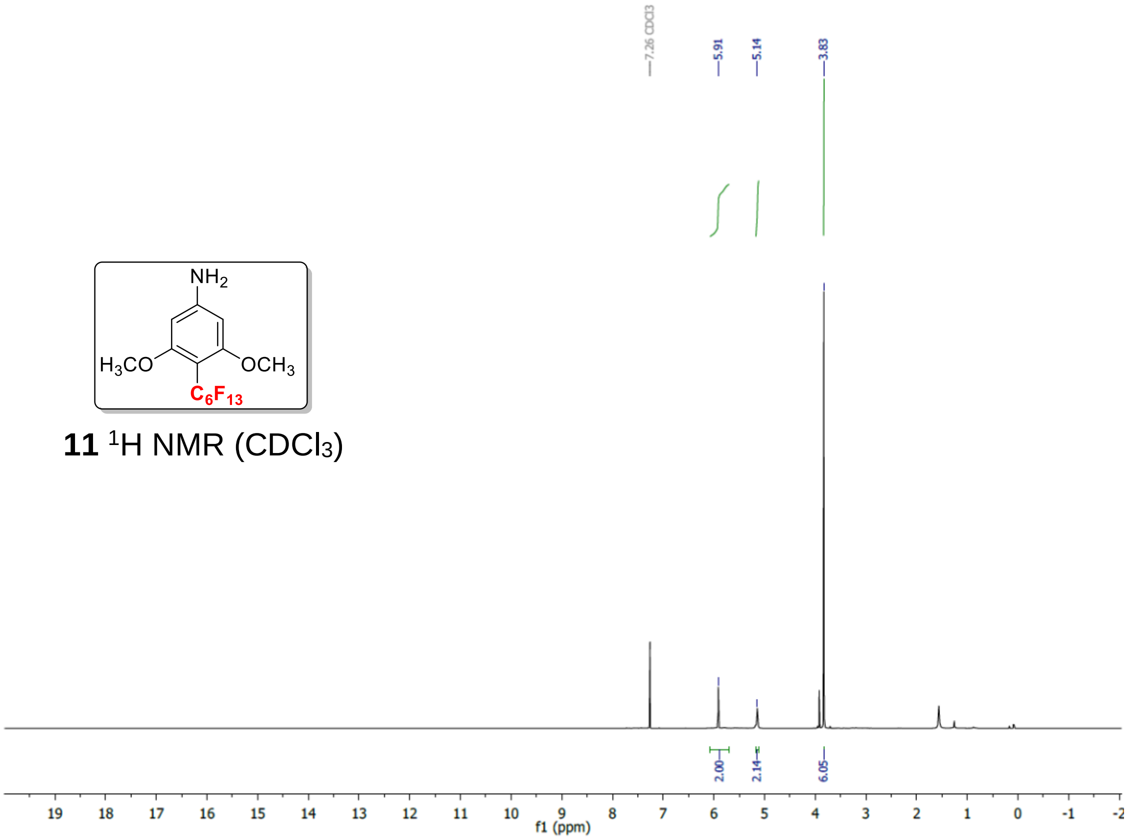


10 ^{19}F NMR (CDCl$_3$)

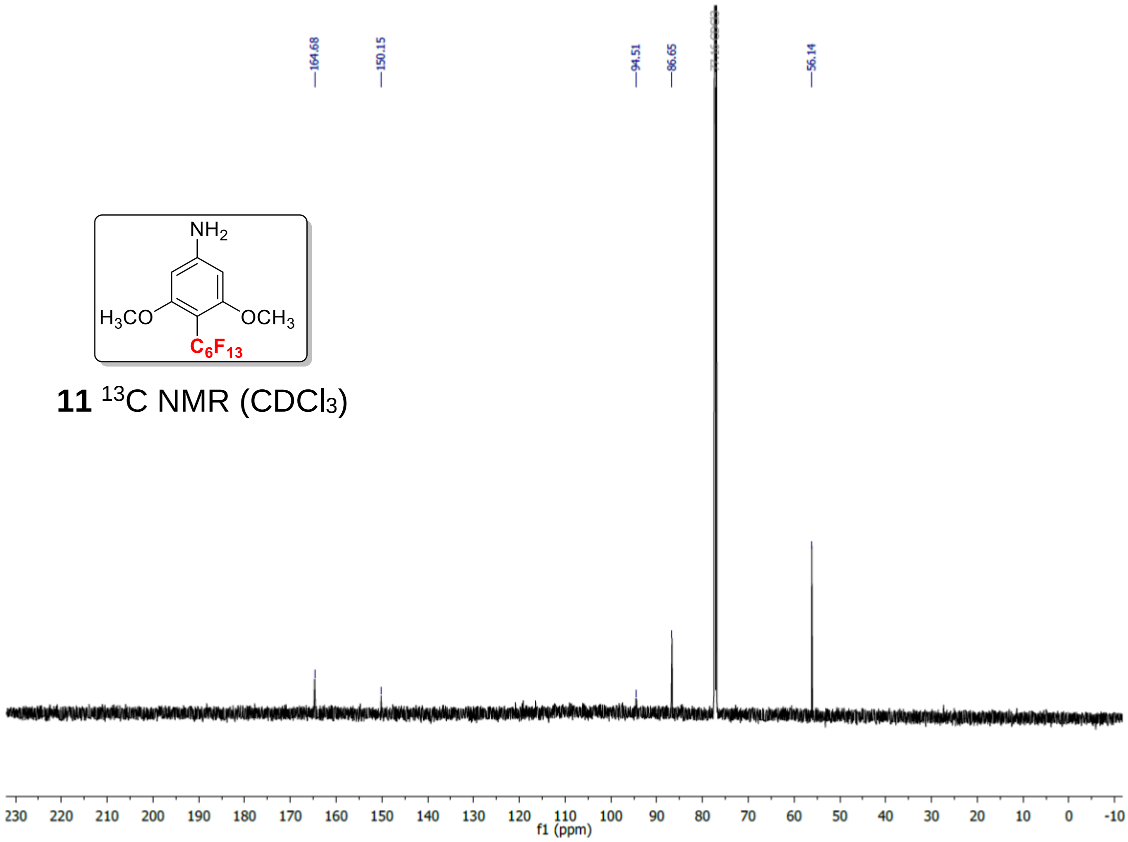
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	950 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Source

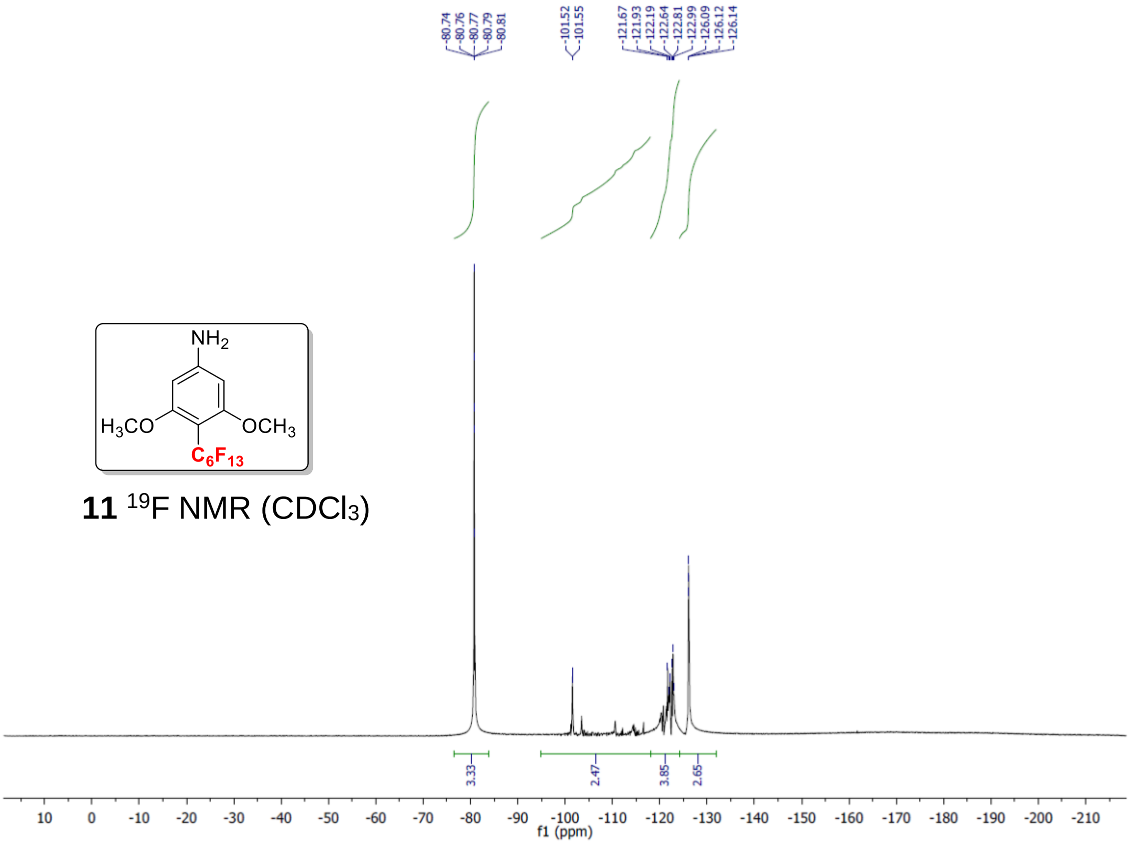




11 ^{1}H NMR (CDCl$_3$)



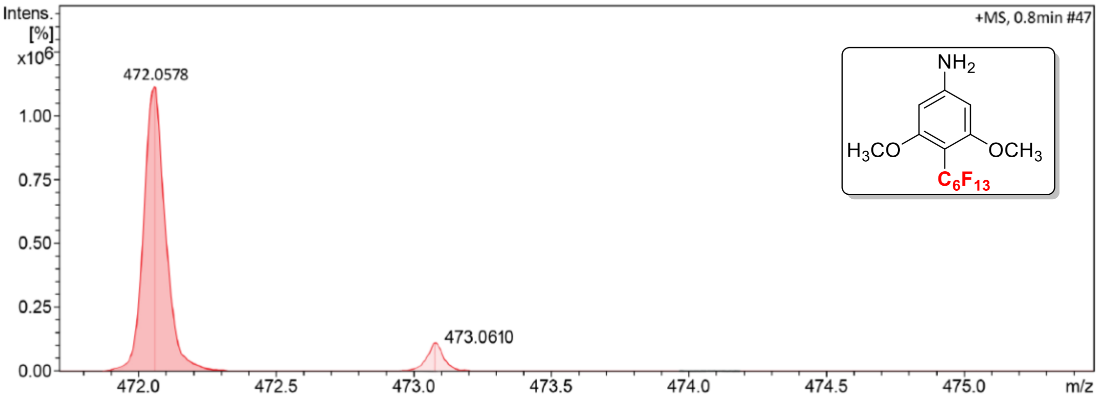
11 ^{13}C NMR (CDCl$_3$)

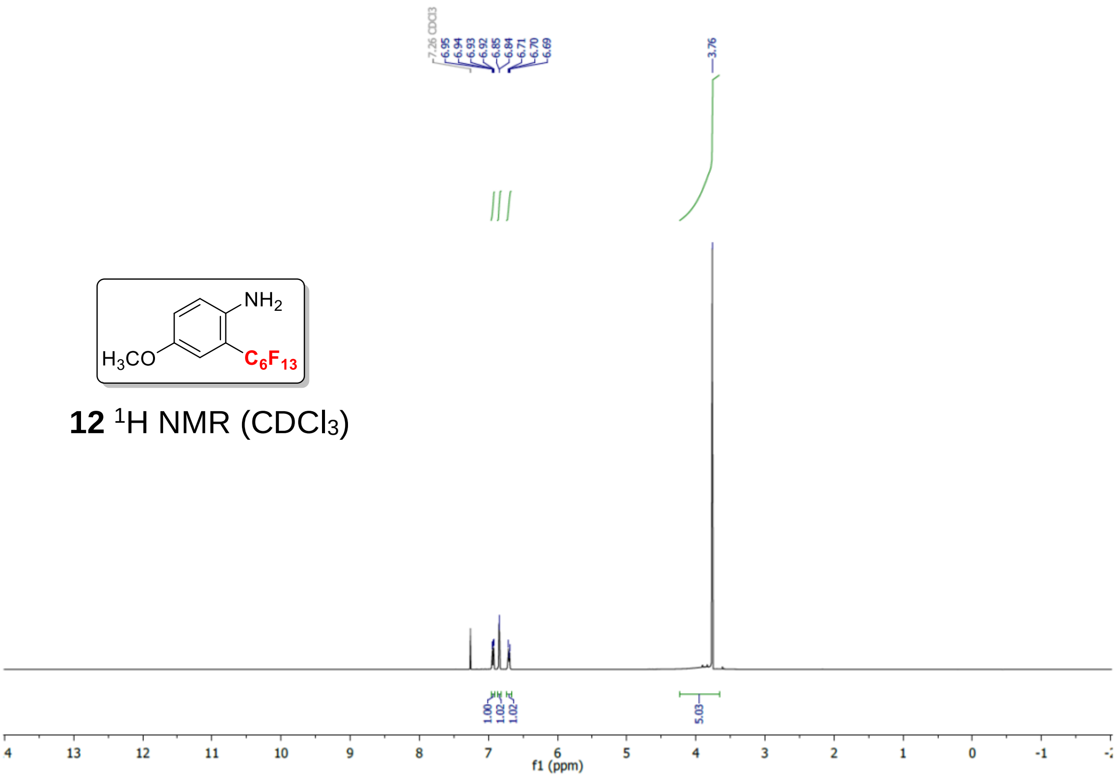


11 ^{19}F NMR (CDCl$_3$)

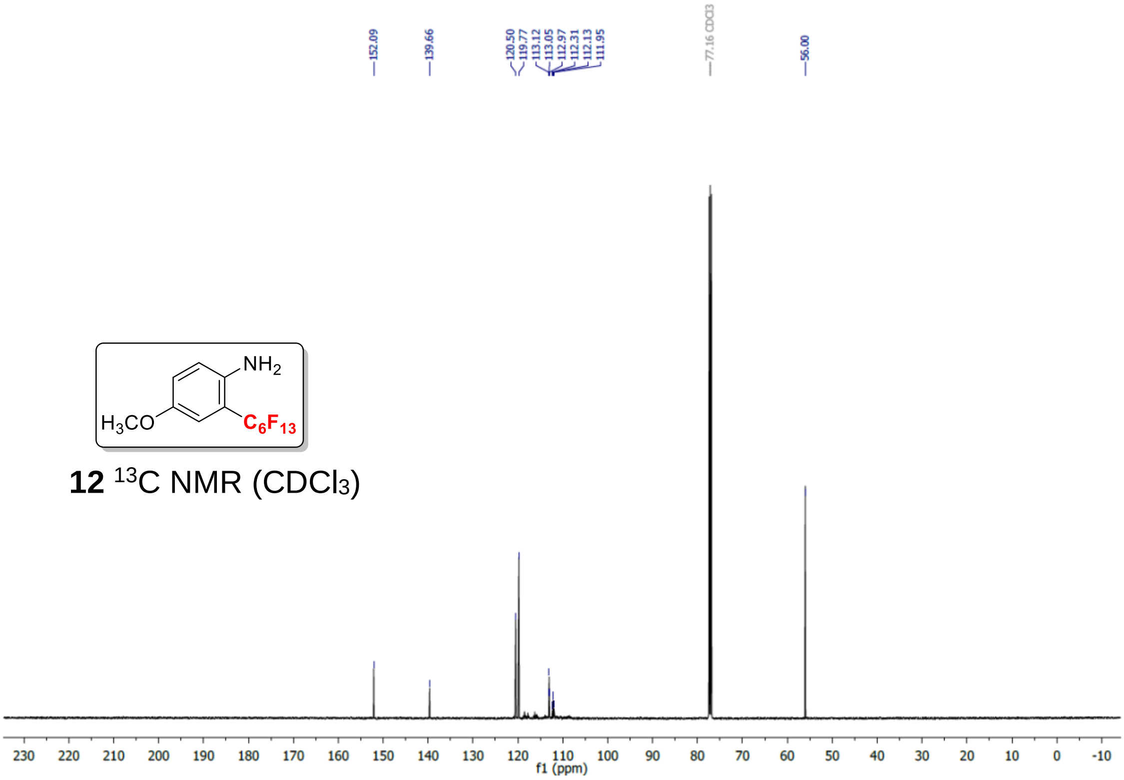
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	950 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Source

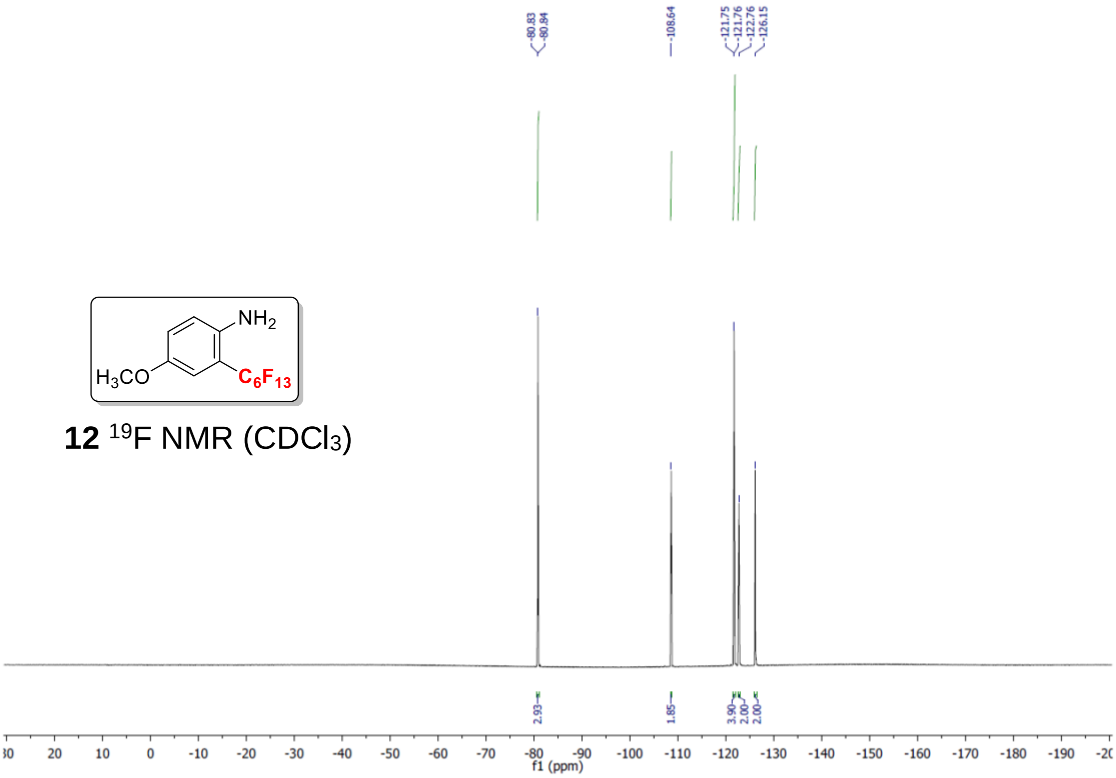




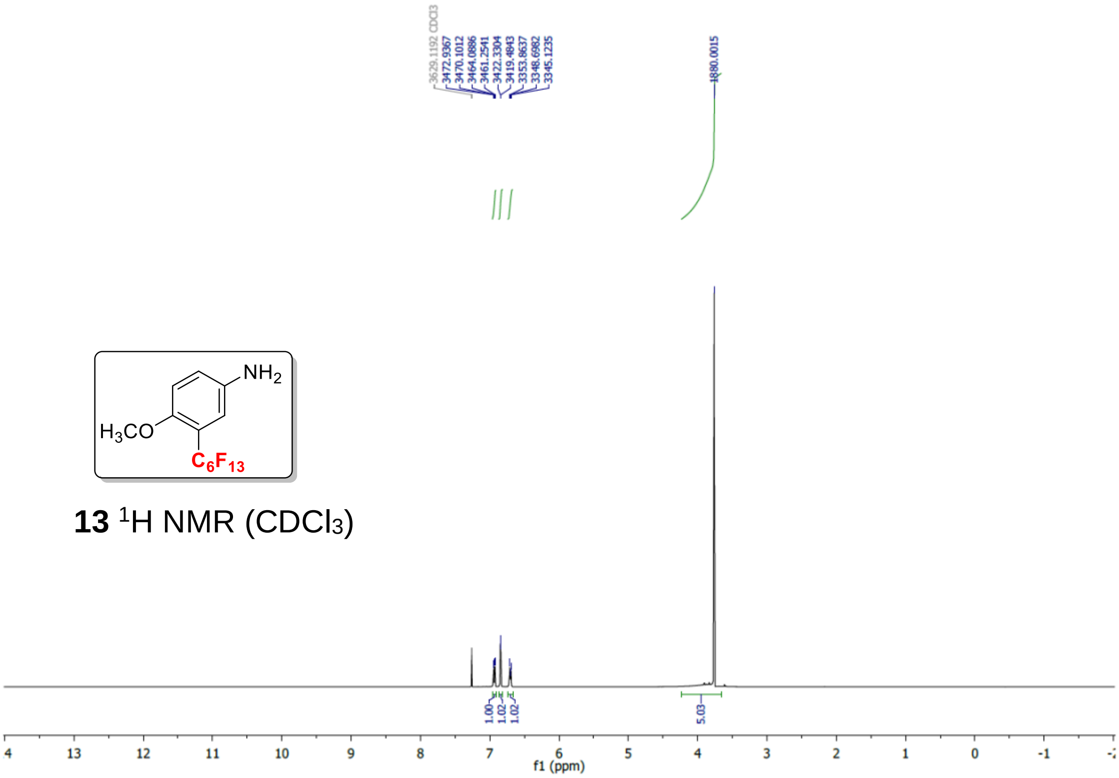
12 ^{1}H NMR (CDCl$_3$)



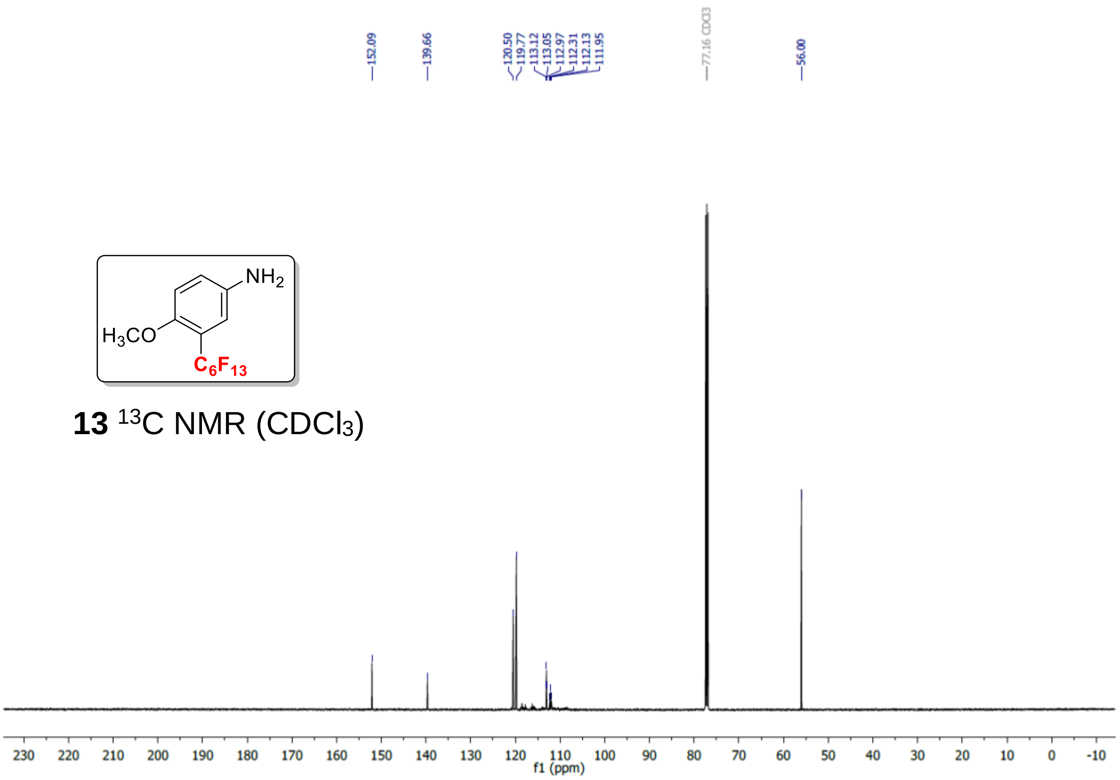
12 ^{13}C NMR (CDCl$_3$)



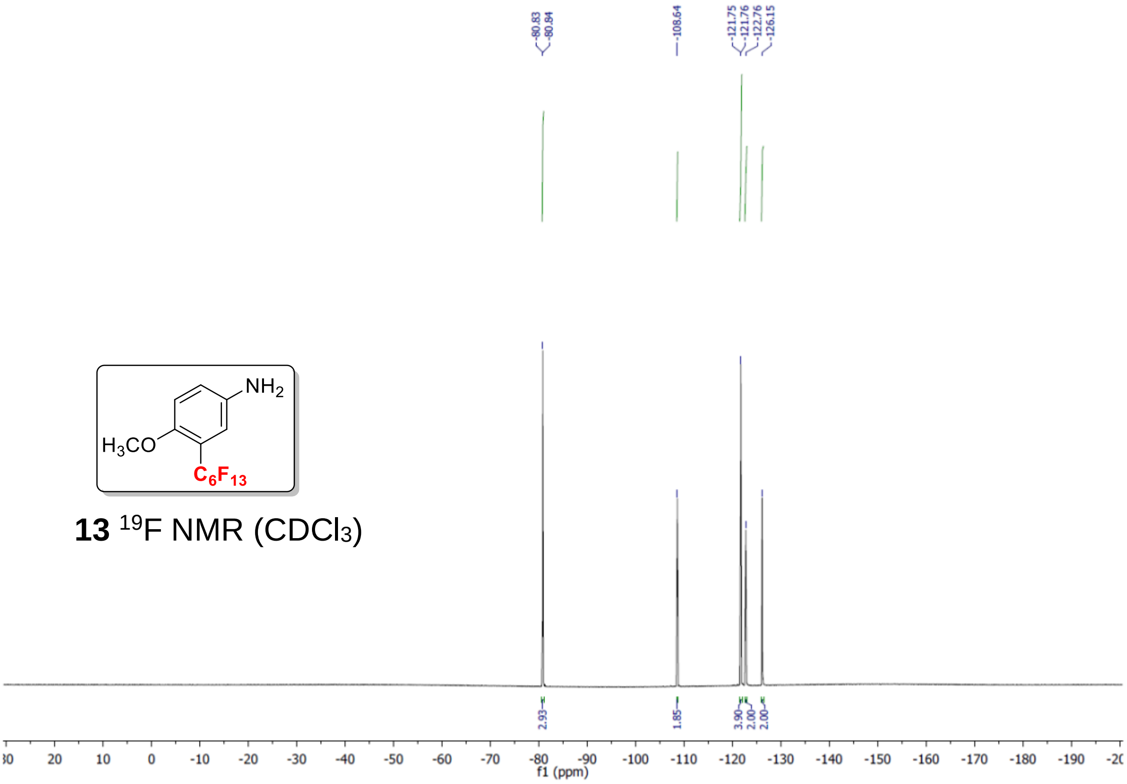
12 ^{19}F NMR ($CDCl_3$)



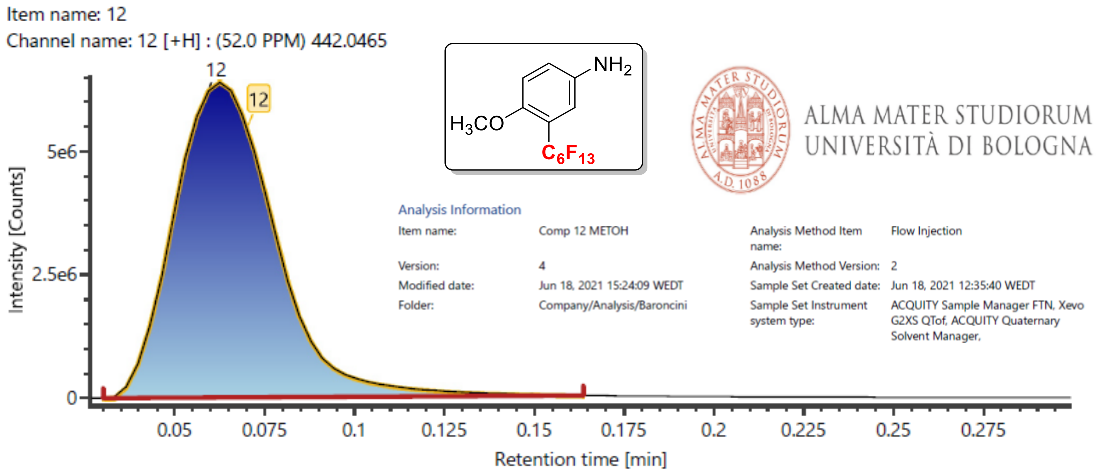
13 ^{1}H NMR ($CDCl_3$)



13 ^{13}C NMR ($CDCl_3$)



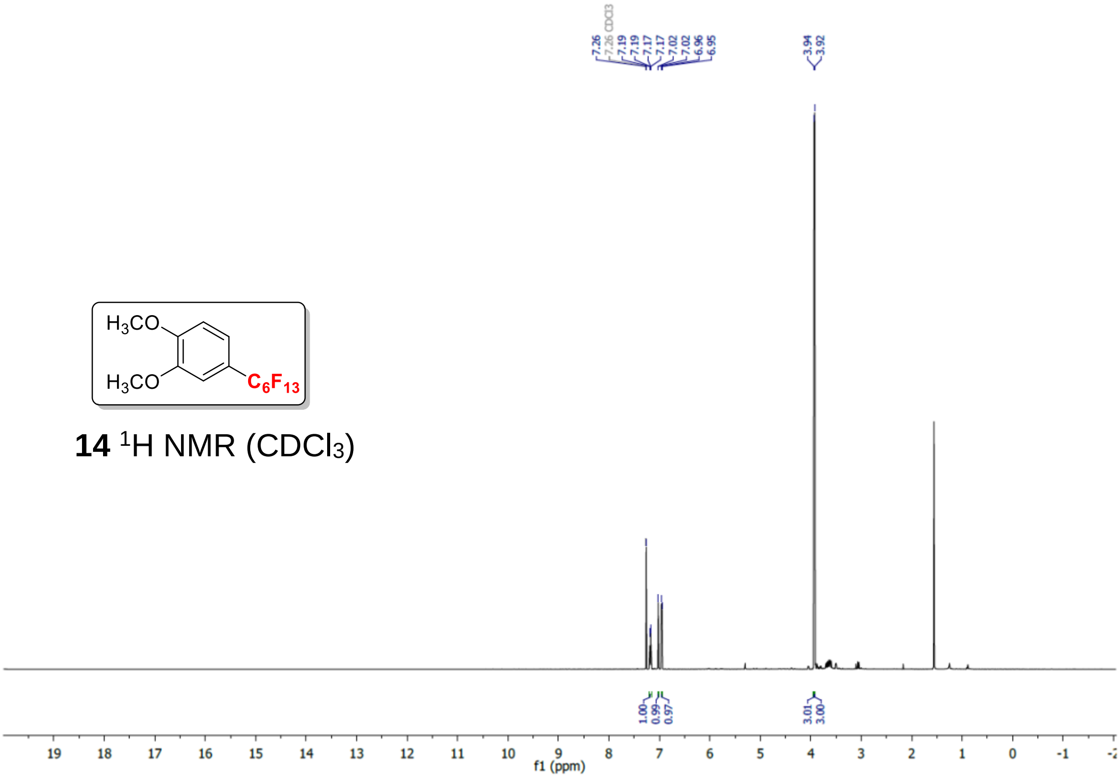
13 ^{19}F NMR ($CDCl_3$)


Item name: 12

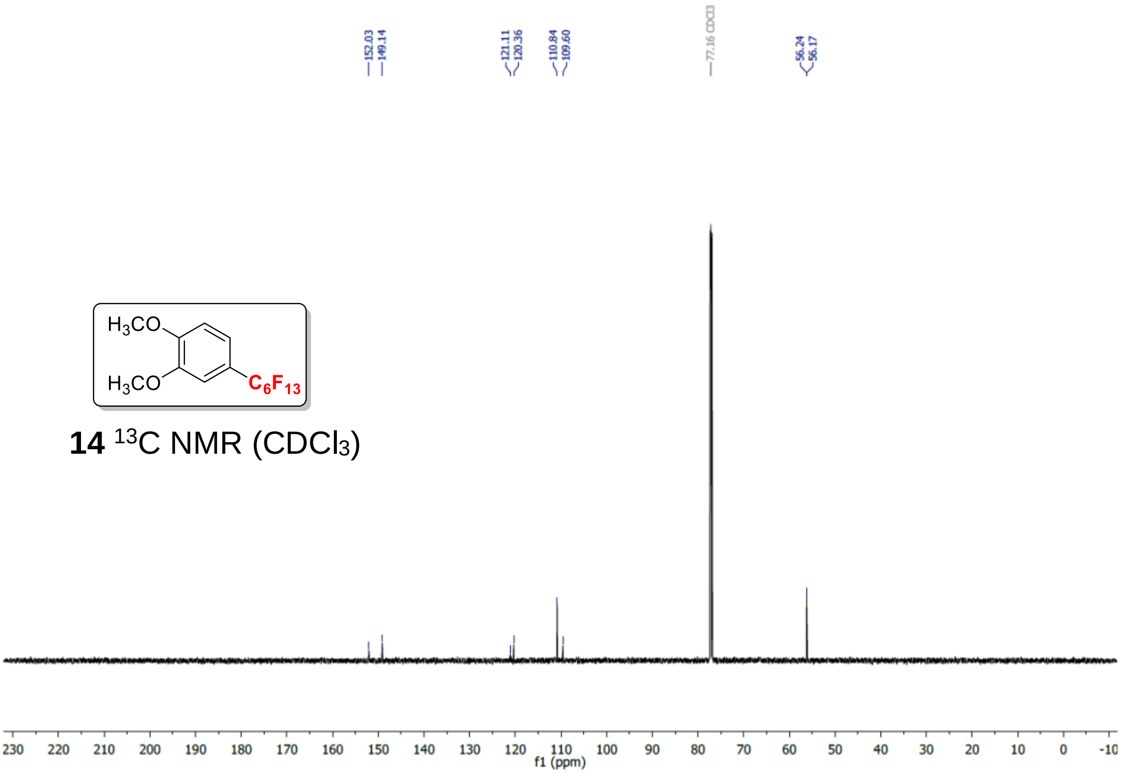
Channel name: 12 [+H] : (52.0 PPM) 442.0465

Analysis Information

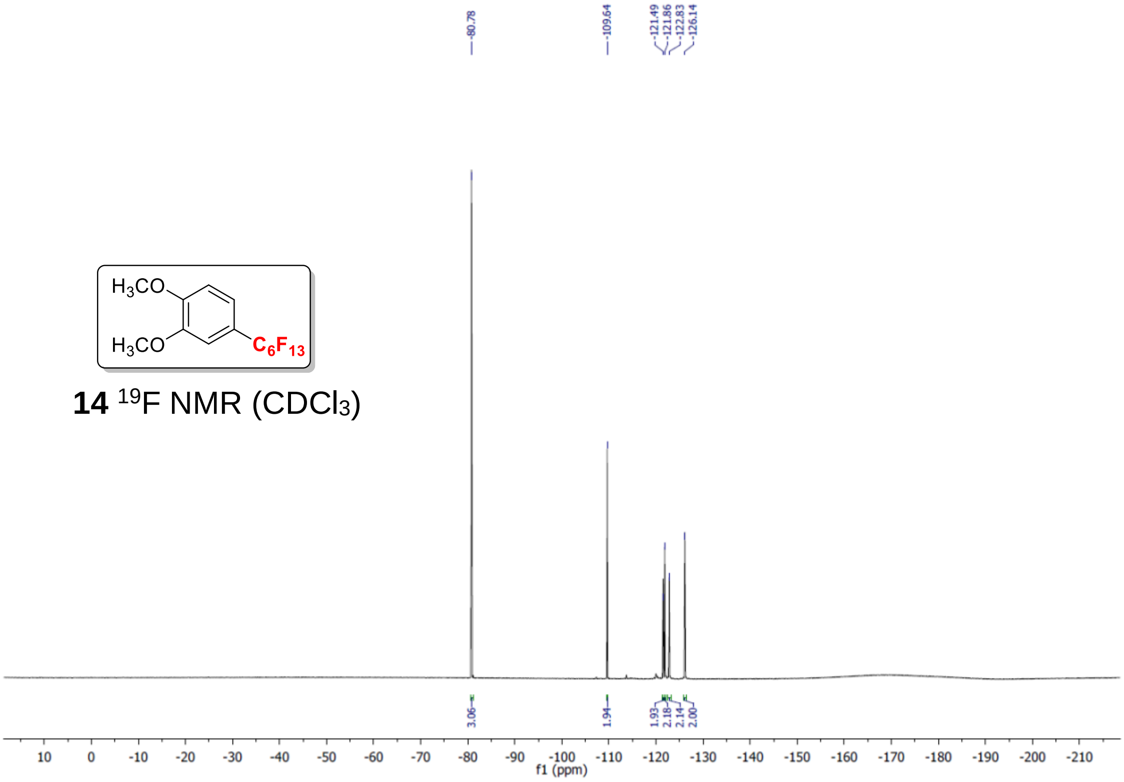
Item name:	Comp 12 METOH	Analysis Method Item name:	Flow Injection
Version:	4	Analysis Method Version:	2
Modified date:	Jun 18, 2021 15:24:09 WEDT	Sample Set Created date:	Jun 18, 2021 12:35:40 WEDT
Folder:	Company/Analysis/Baroncini	Sample Set Instrument system type:	ACQUITY Sample Manager FTN, Xevo G2XS QTof, ACQUITY Quaternary Solvent Manager,



14 ^{1}H NMR (CDCl$_3$)



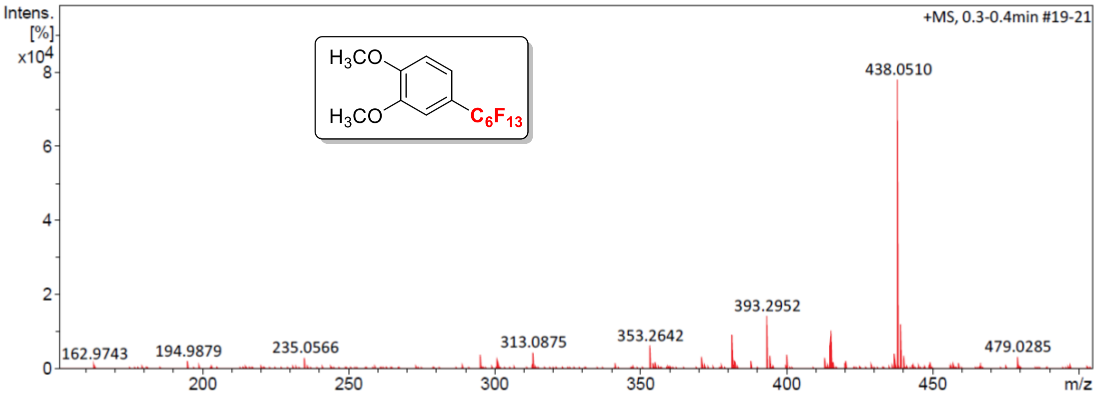
14 ^{13}C NMR (CDCl$_3$)



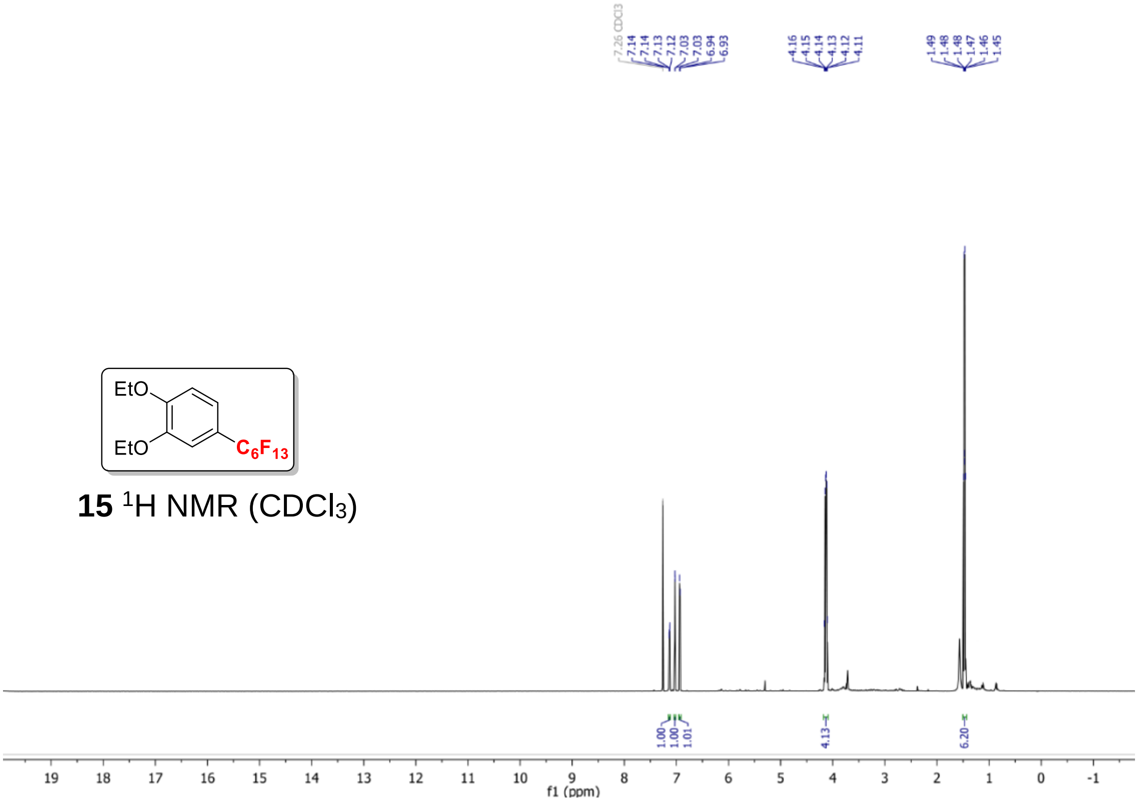
14 ^{19}F NMR (CDCl$_3$)

Acquisition Parameter

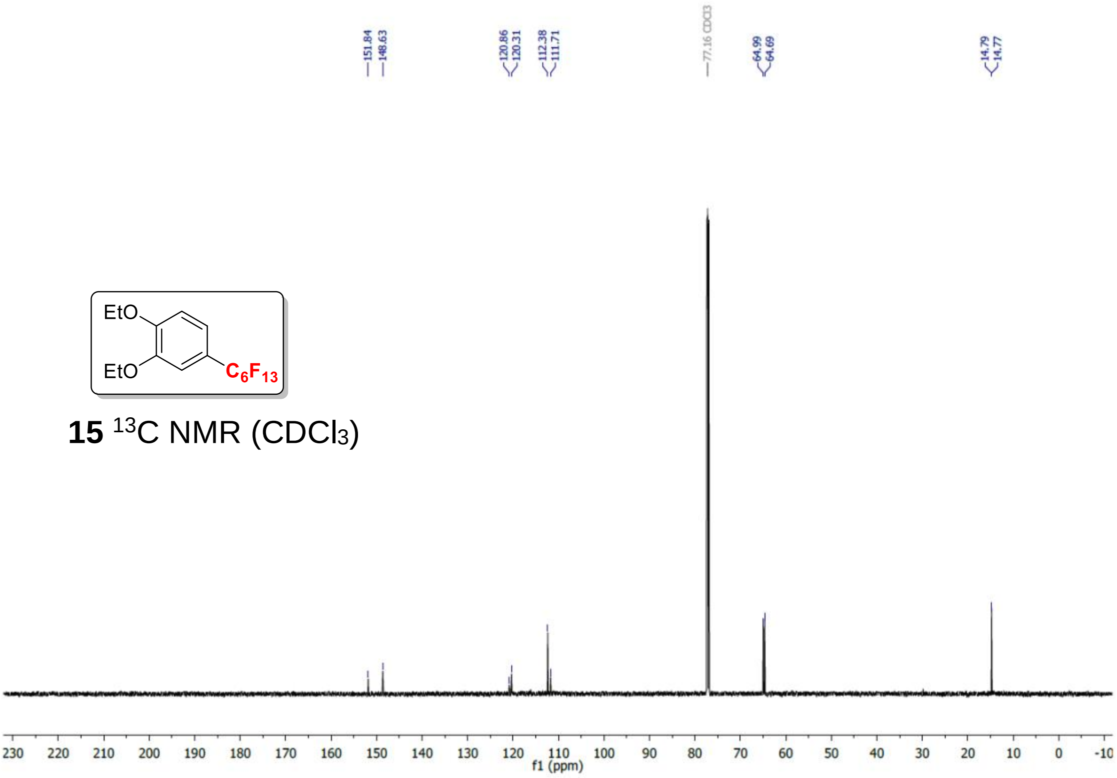
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1200 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source



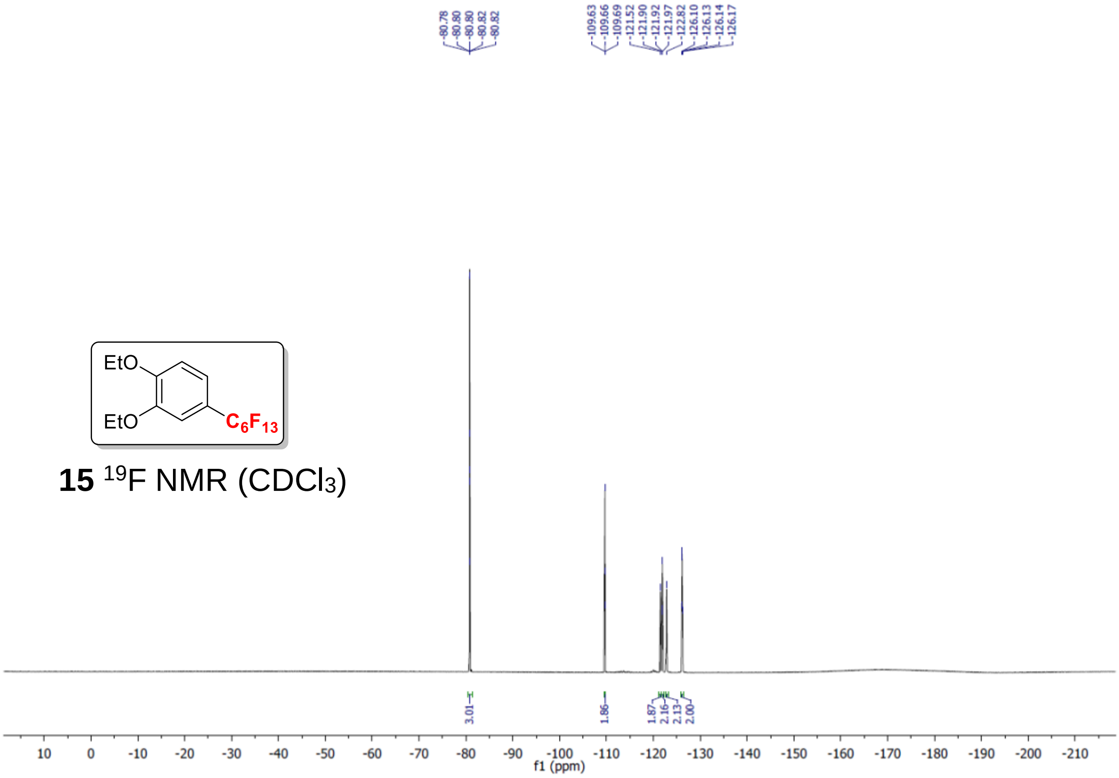
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
438.0510	1	C14H9F13N	438.0522	2.8	18.5	4	51.60	4.5	even	ok
	1	C14H11F10NNaO2	438.0522	2.9	16.1	2	95.35	4.5	even	ok
	2	C12H10F13NNa	438.0498	-2.7	23.1	3	85.32	1.5	even	ok
479.0285	1	C14H9F13NaO2	479.0287	0.4	9.9	1	100.00	3.5	even	ok



15 ^{1}H NMR (CDCl$_3$)



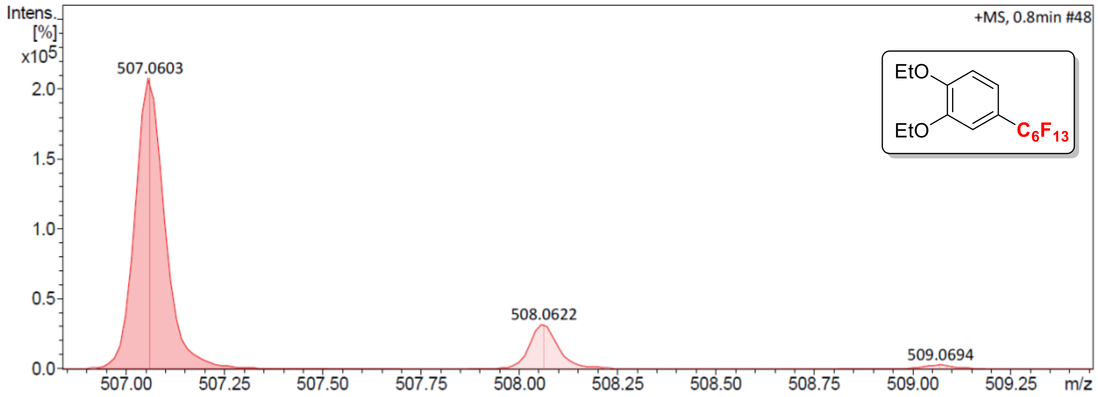
15 ^{13}C NMR ($CDCl_3$)

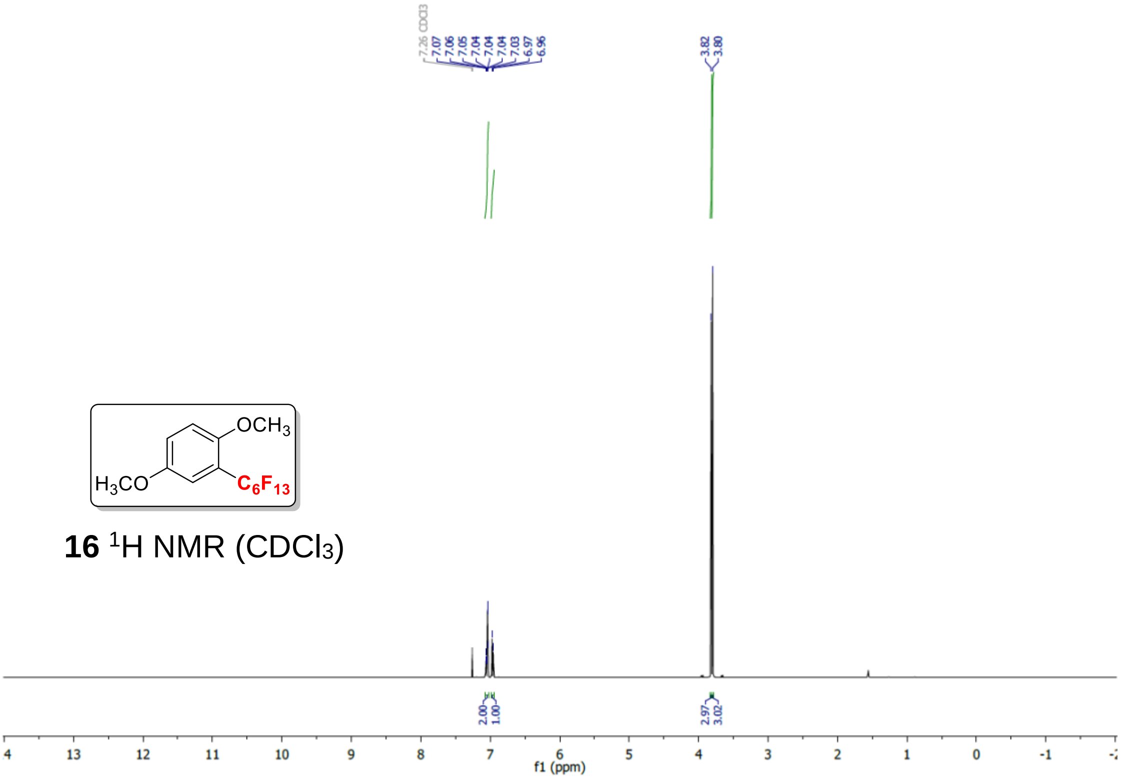


15 ^{19}F NMR ($CDCl_3$)

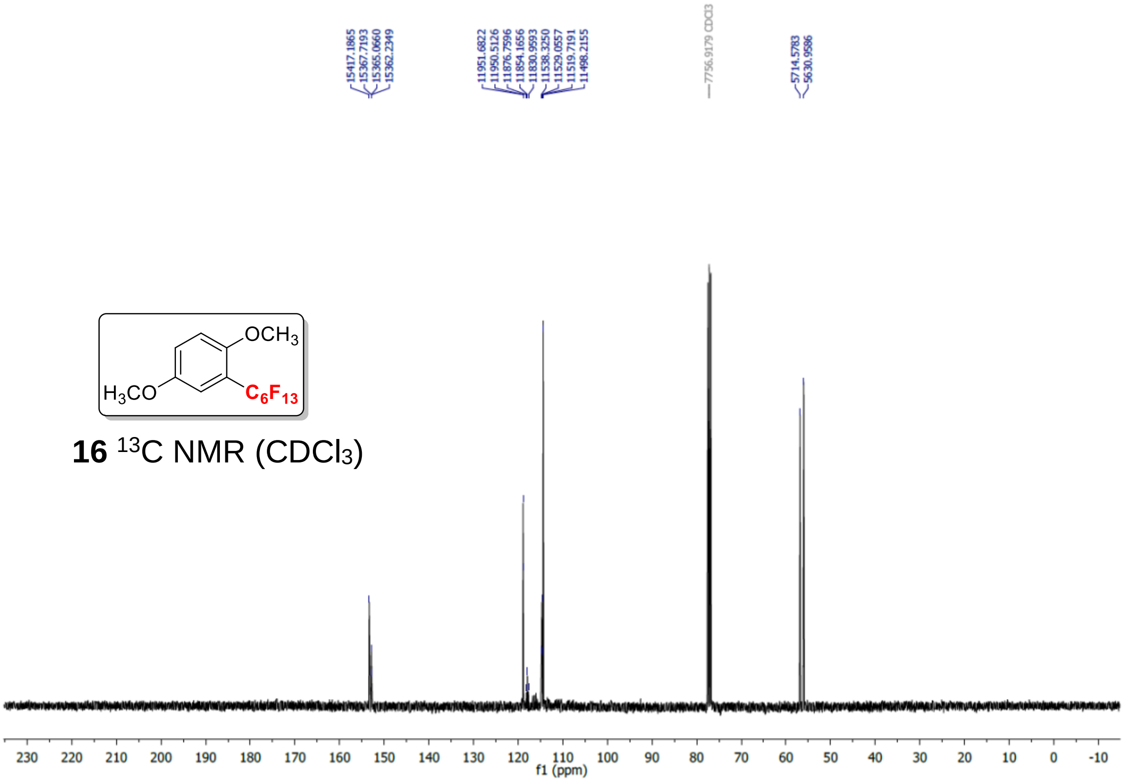
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	950 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Source

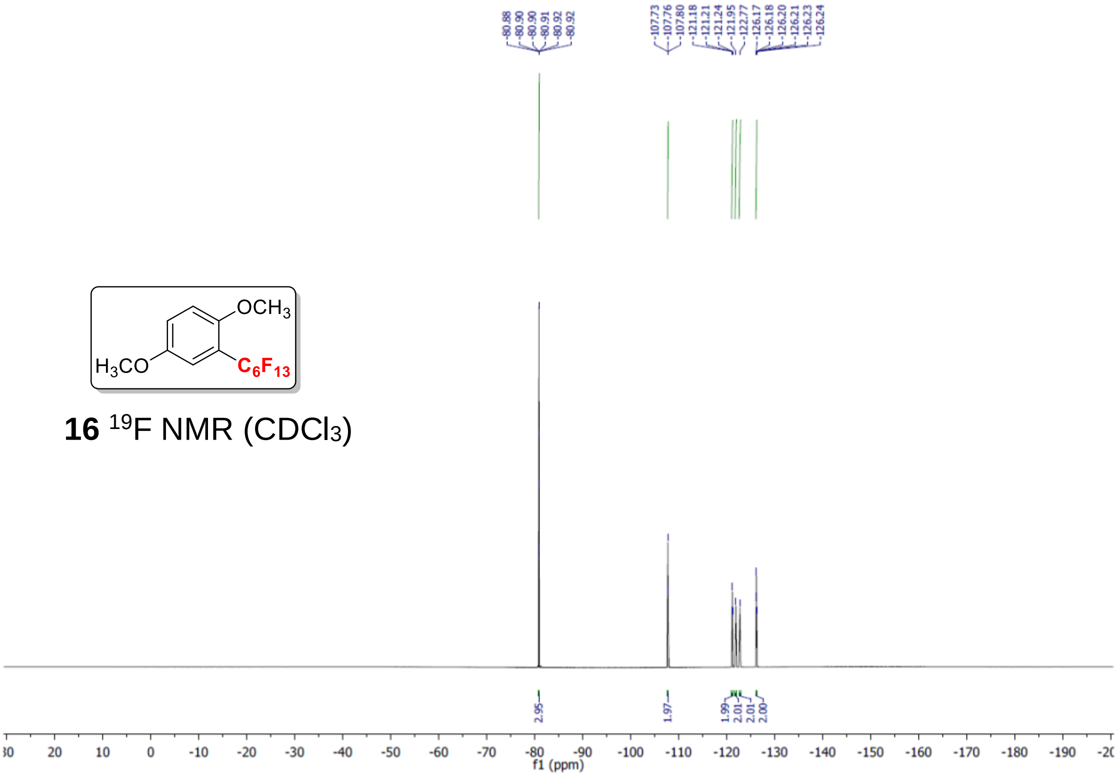




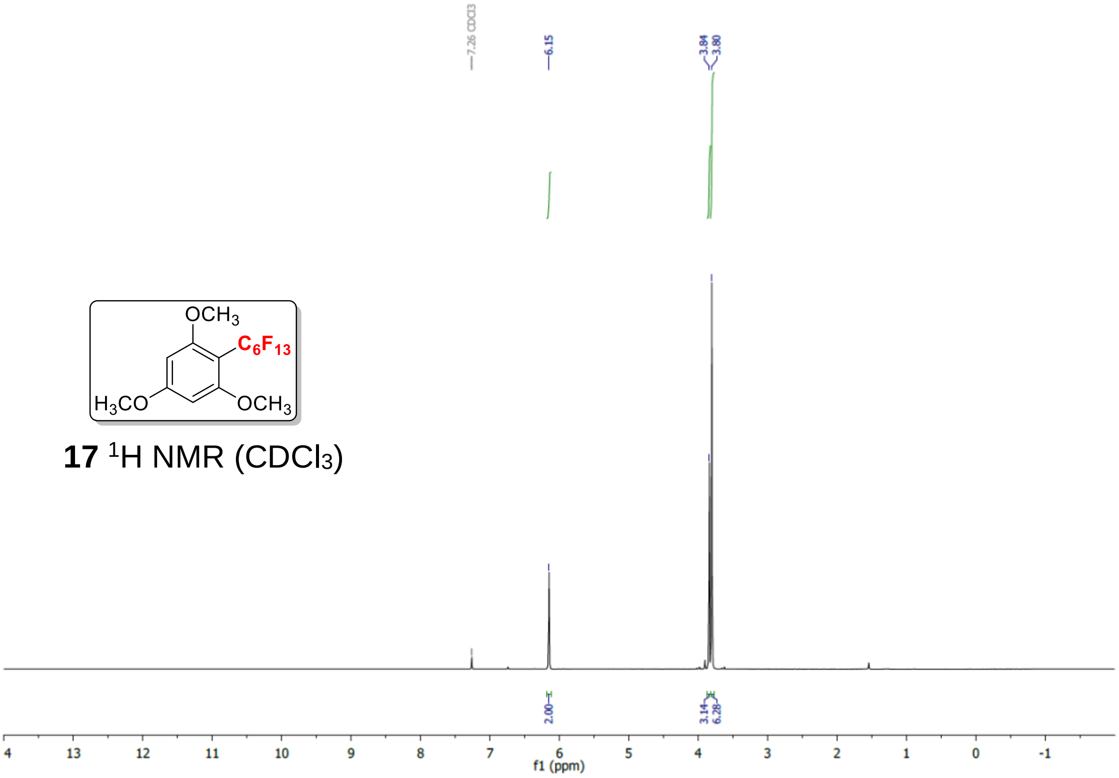
16 ^{1}H NMR (CDCl$_3$)



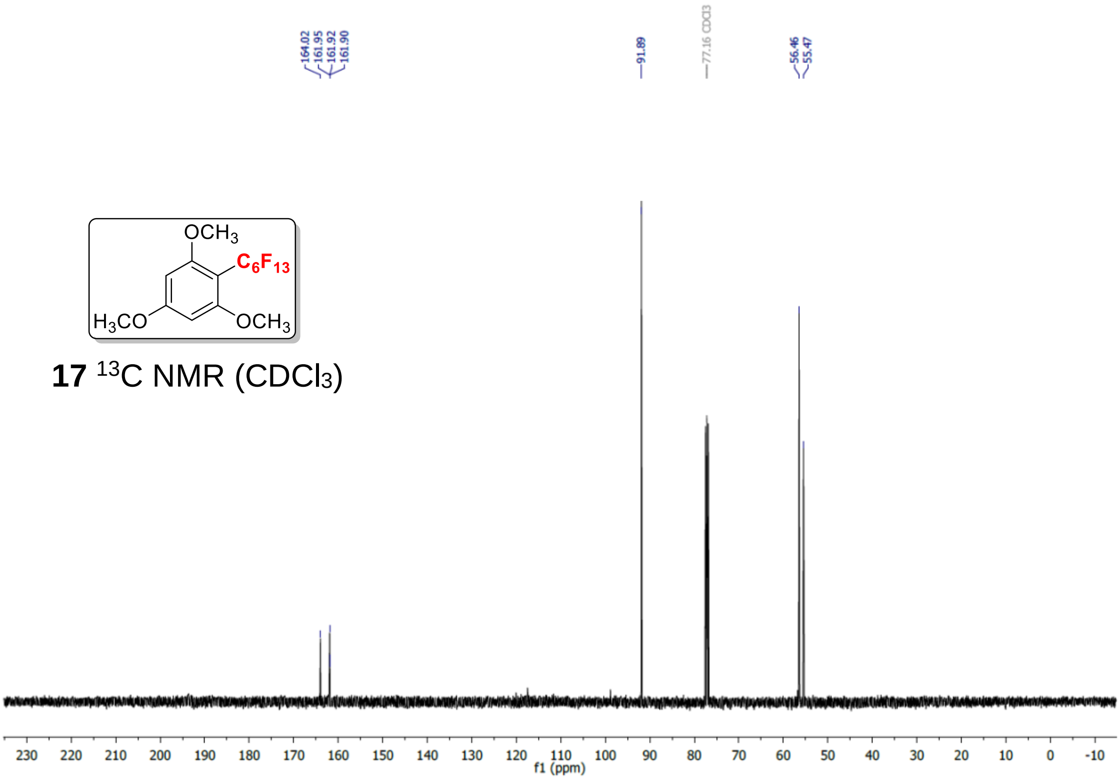
16 ^{13}C NMR ($CDCl_3$)



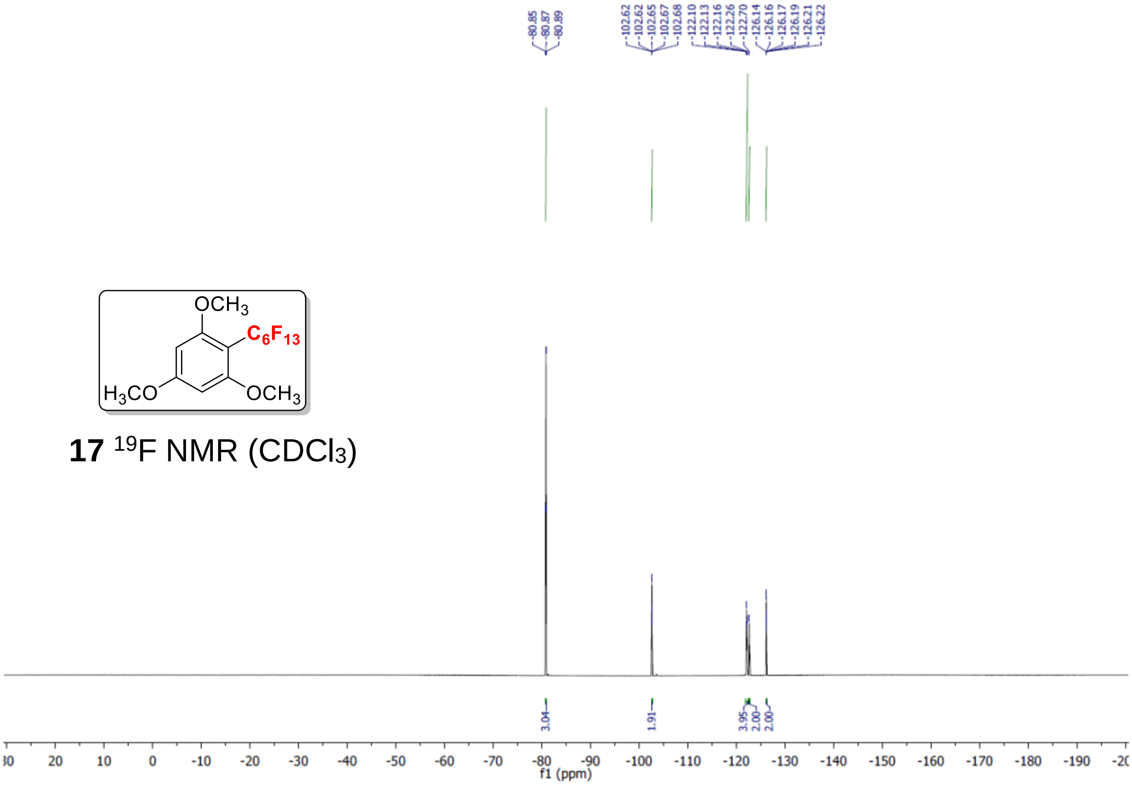
16 ^{19}F NMR ($CDCl_3$)



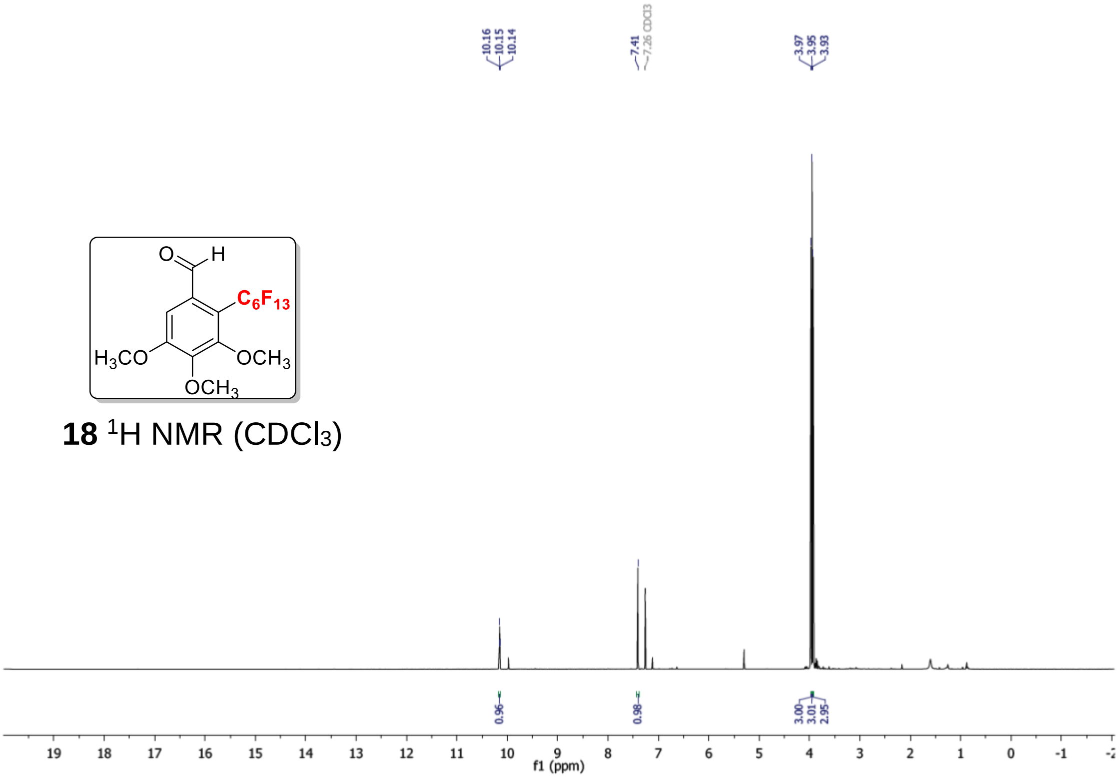
17 ^{1}H NMR (CDCl$_3$)



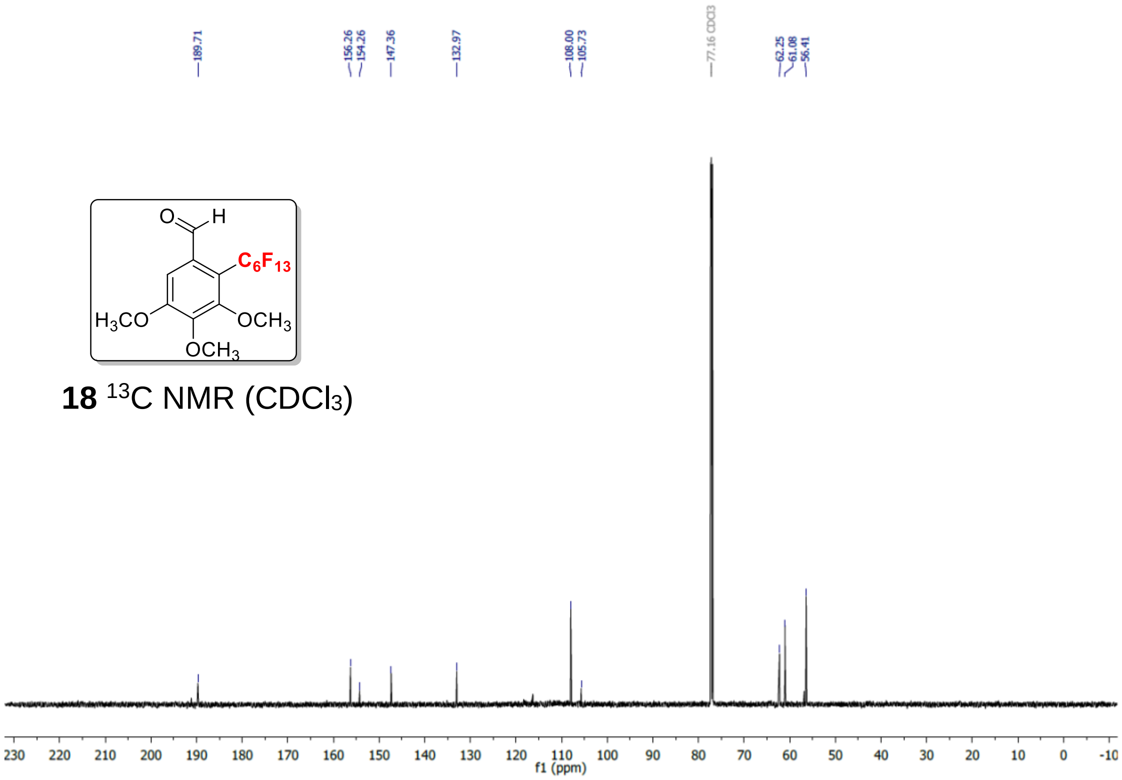
17 ^{13}C NMR (CDCl$_3$)



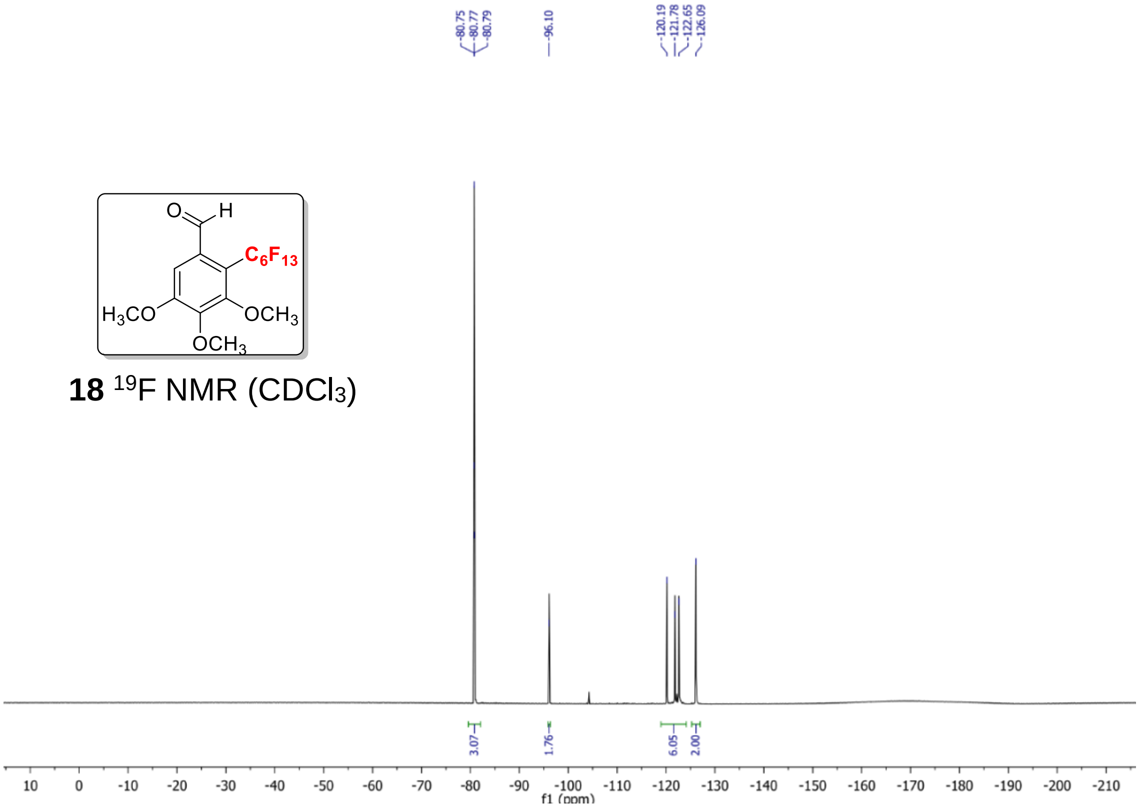
17 ^{19}F NMR (CDCl$_3$)



18 ^{1}H NMR (CDCl$_3$)



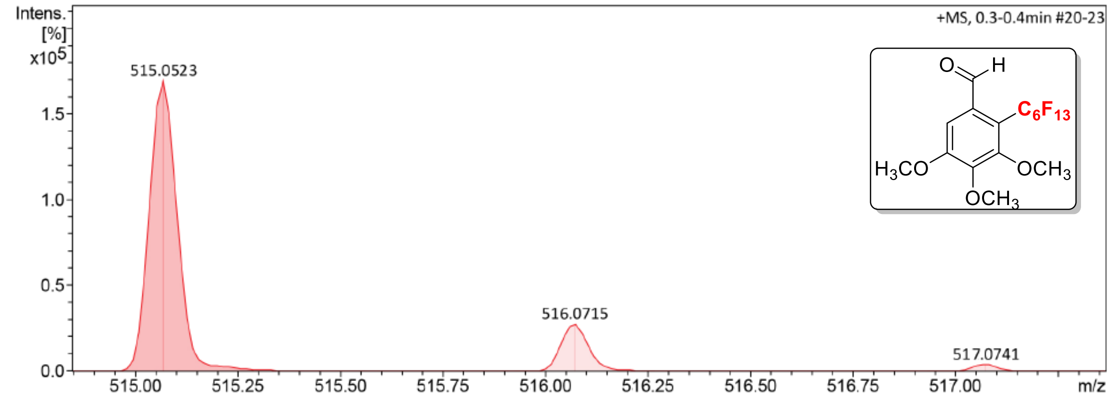
18 ^{13}C NMR (CDCl$_3$)

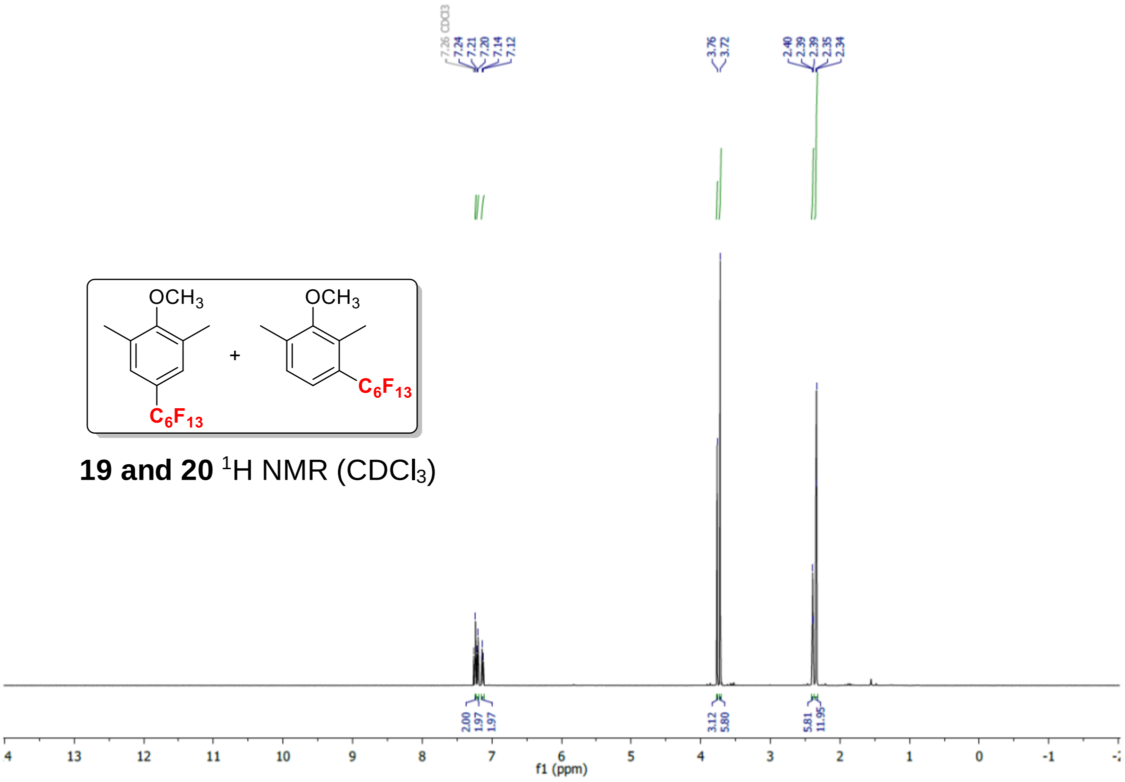


18 ^{19}F NMR (CDCl$_3$)

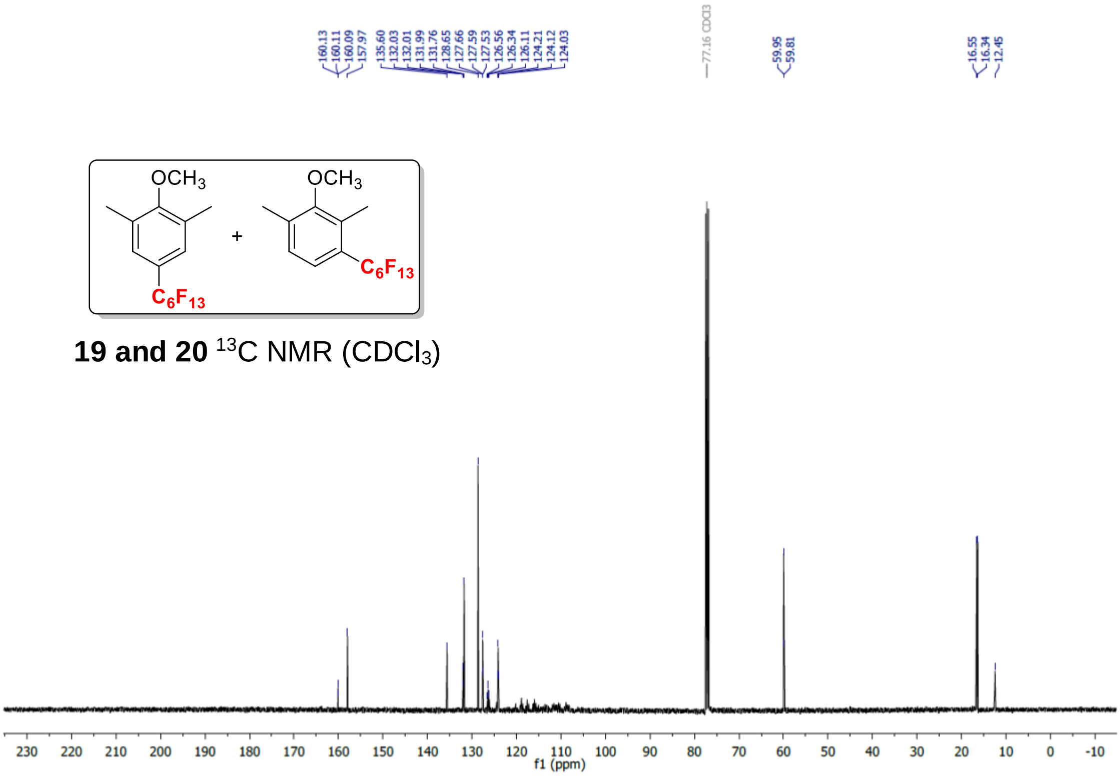
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	3.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	7.0 l/min
Scan End	1200 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Source

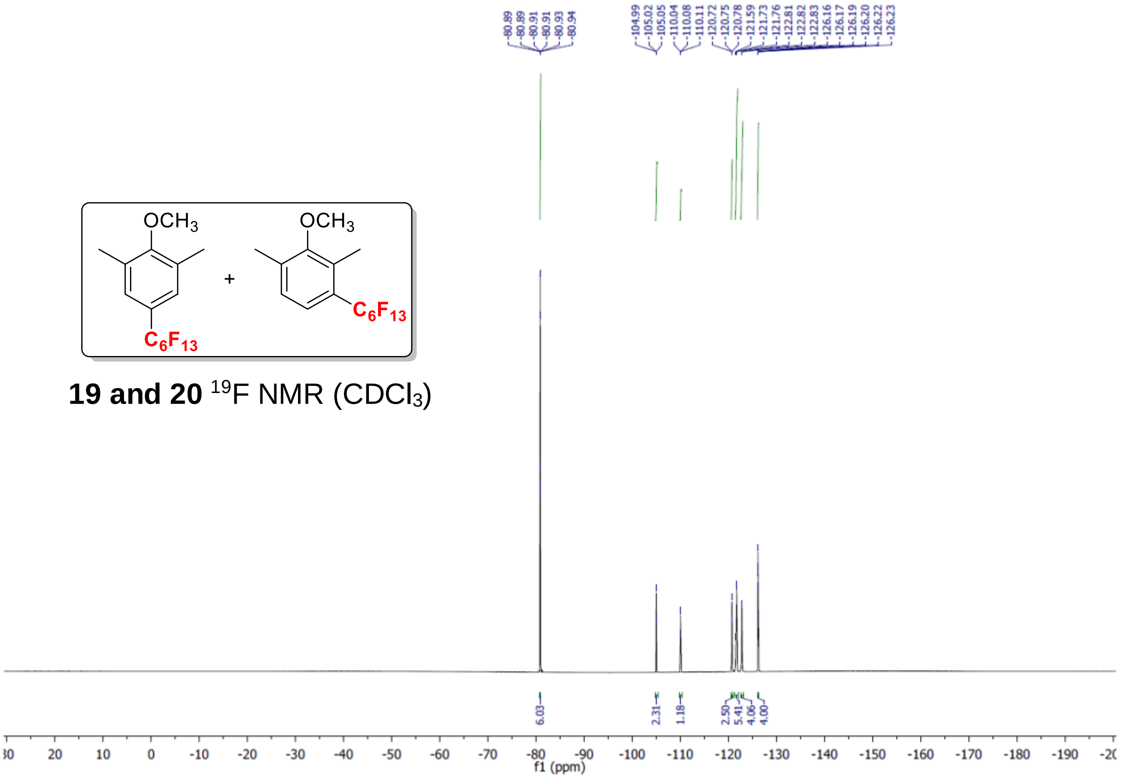




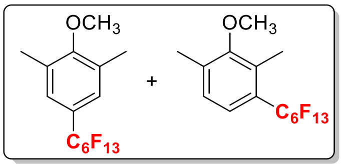
19 and 20 ^{1}H NMR ($CDCl_3$)



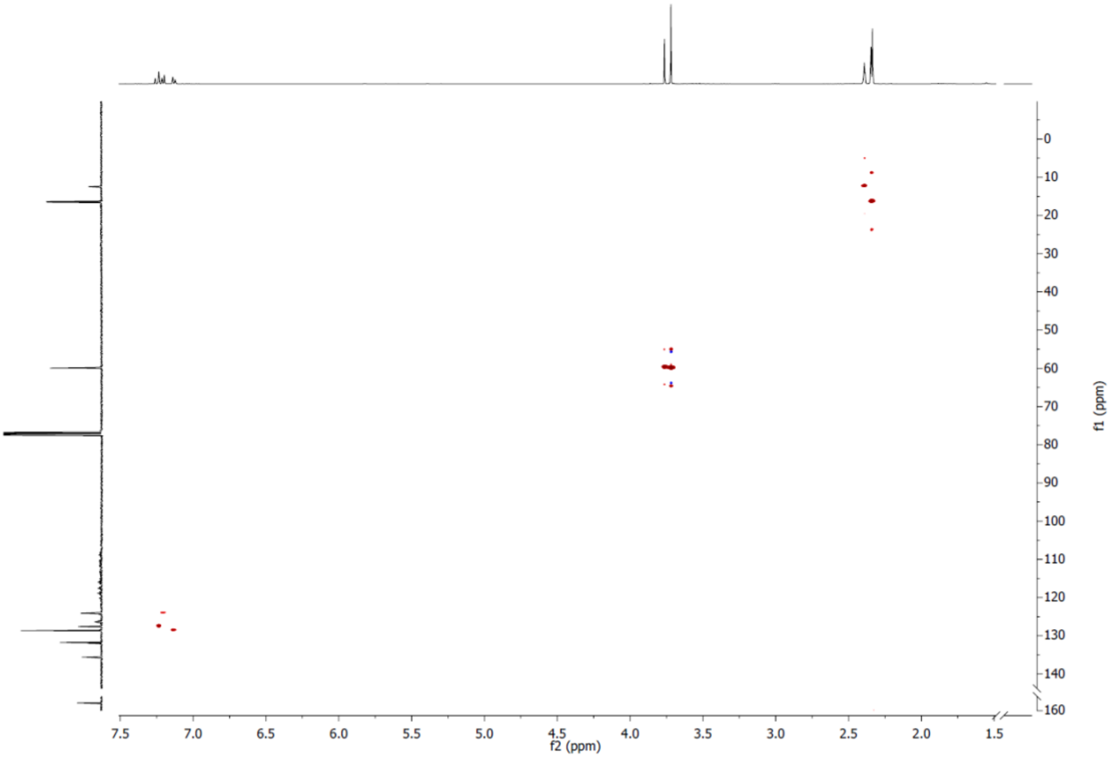
19 and 20 ^{13}C NMR ($CDCl_3$)

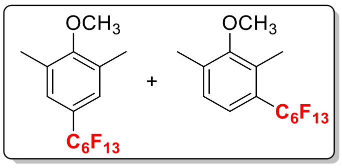


19 and 20 ^{19}F NMR ($CDCl_3$)

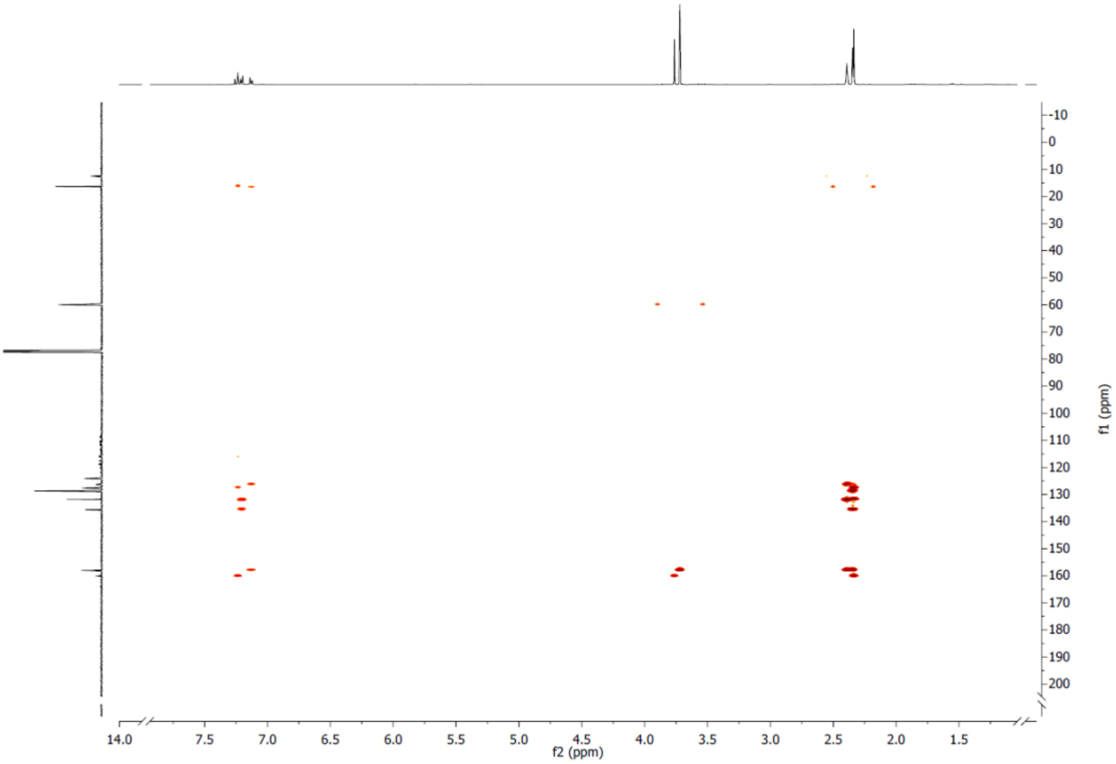


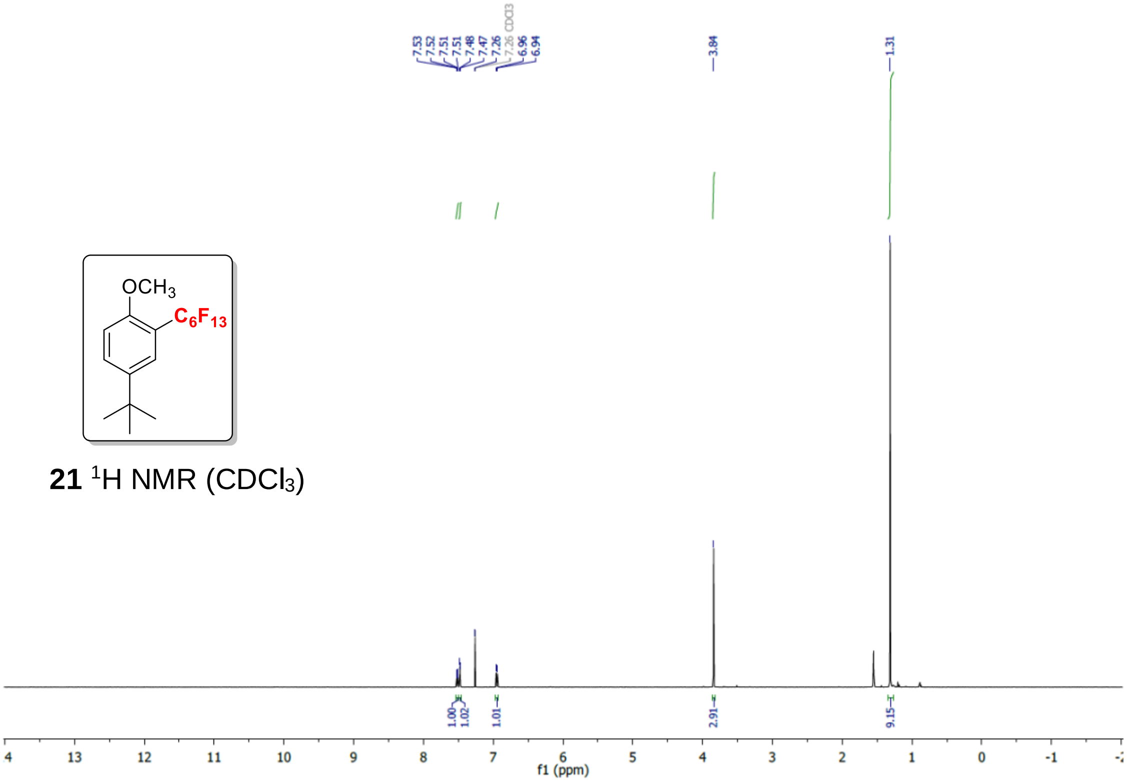
19 and 20 HSQC ($CDCl_3$)



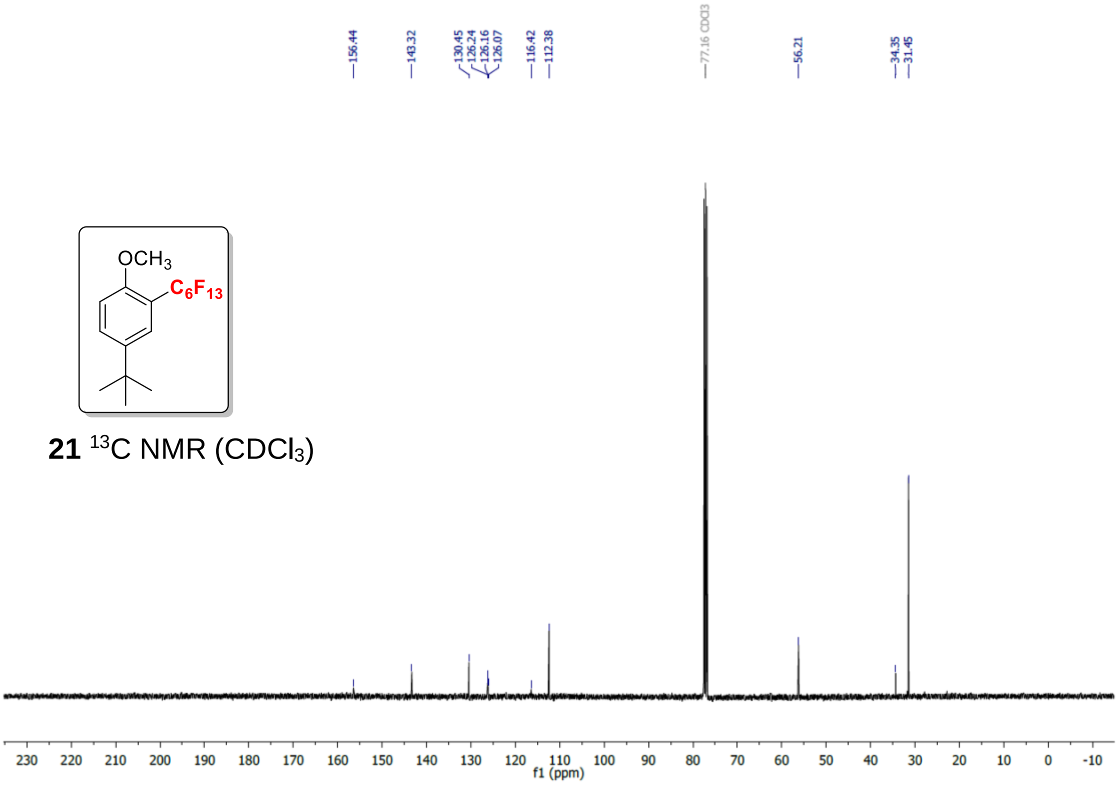


19 and 20 HMBC ($CDCl_3$)

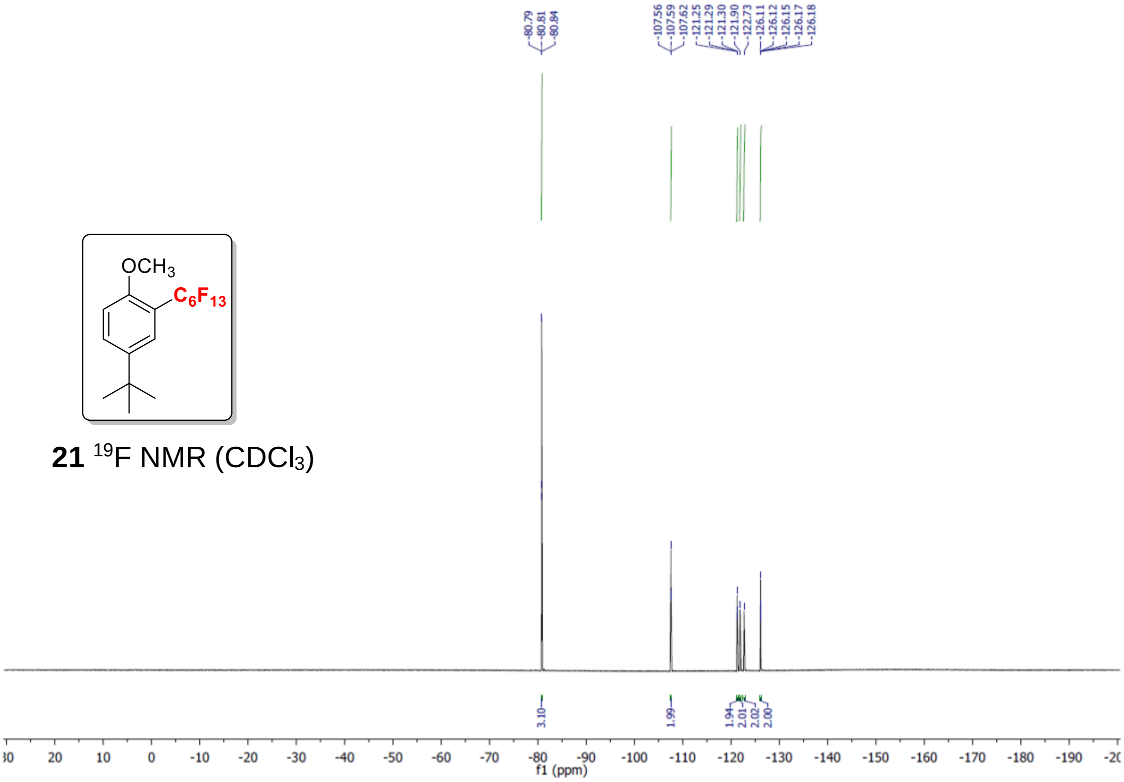




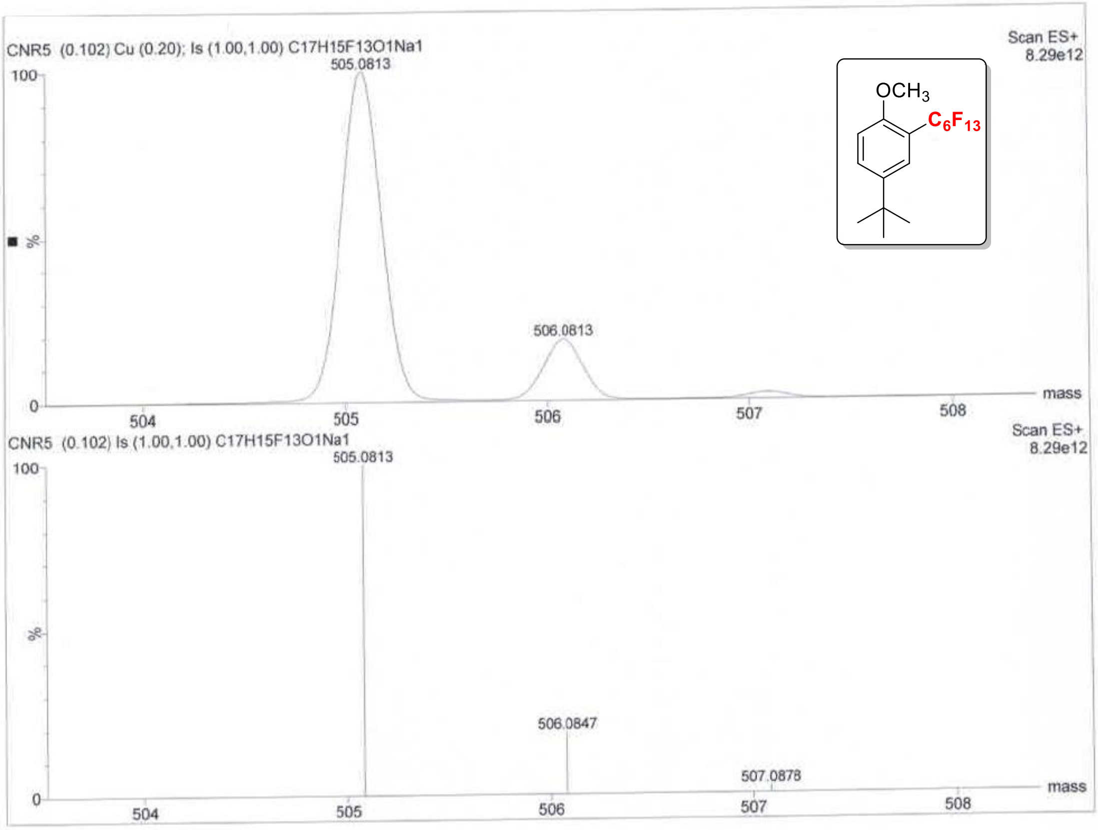
21 ^{1}H NMR ($CDCl_3$)

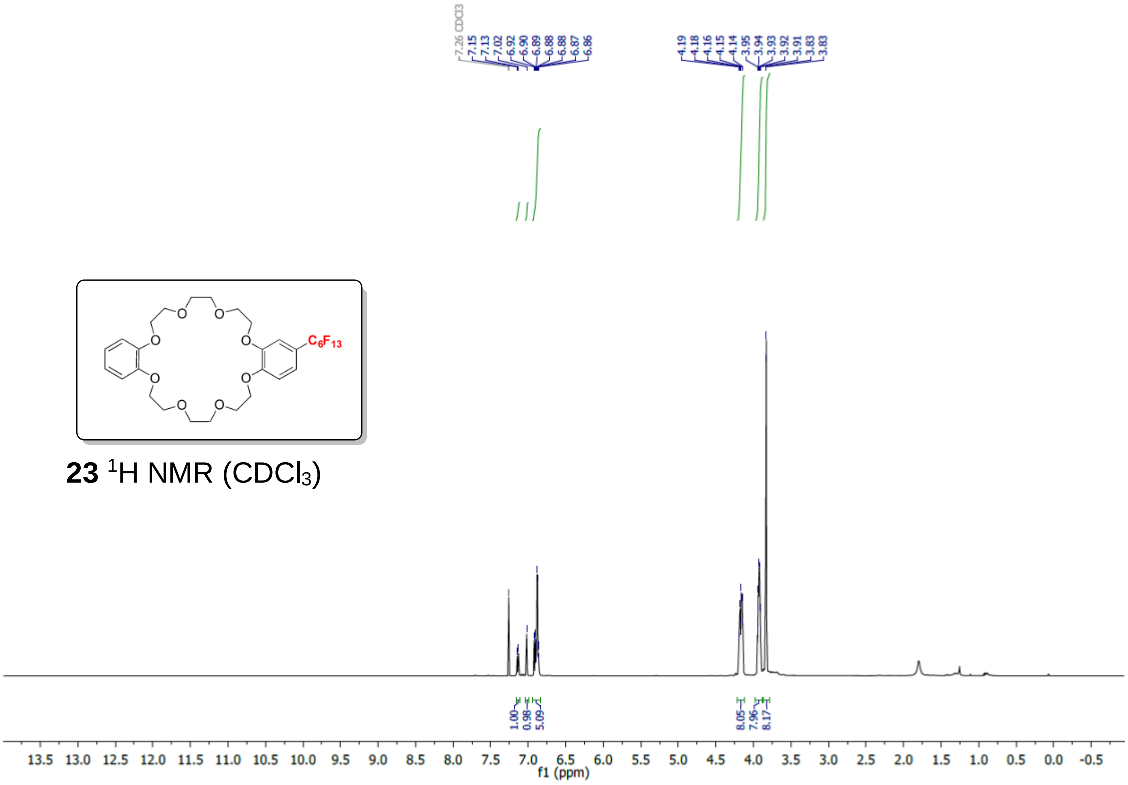


21 ^{13}C NMR (CDCl$_3$)

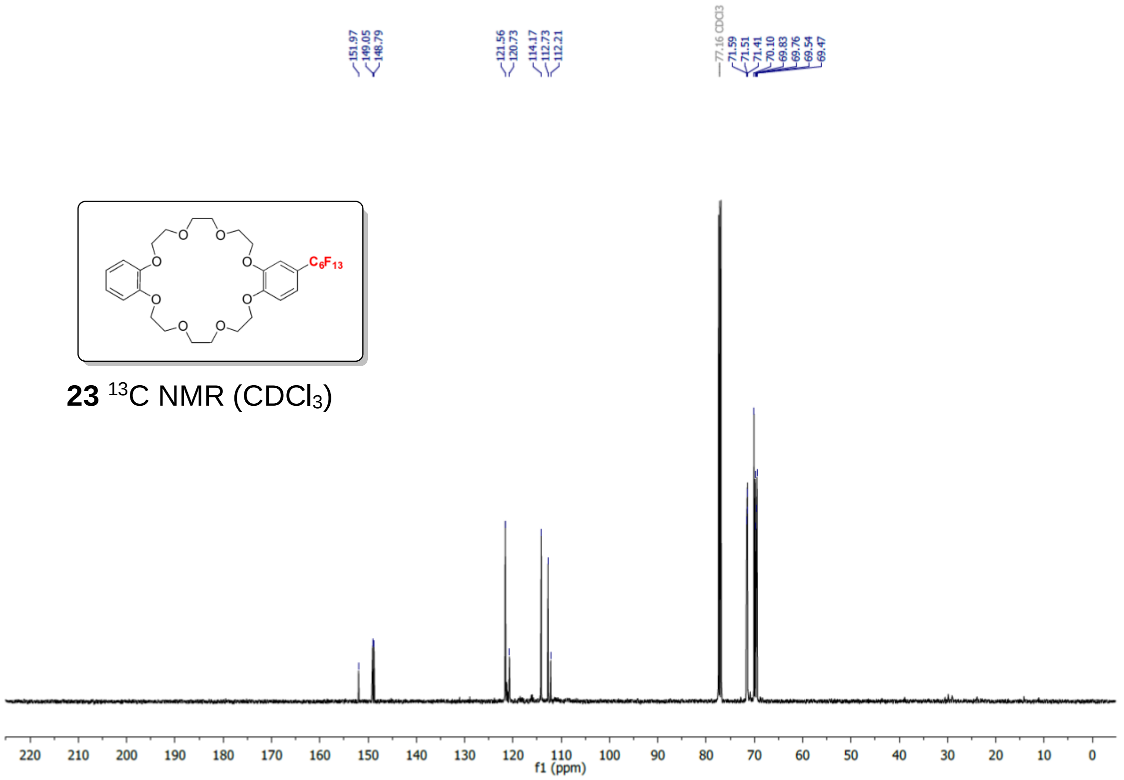


21 ^{19}F NMR (CDCl$_3$)

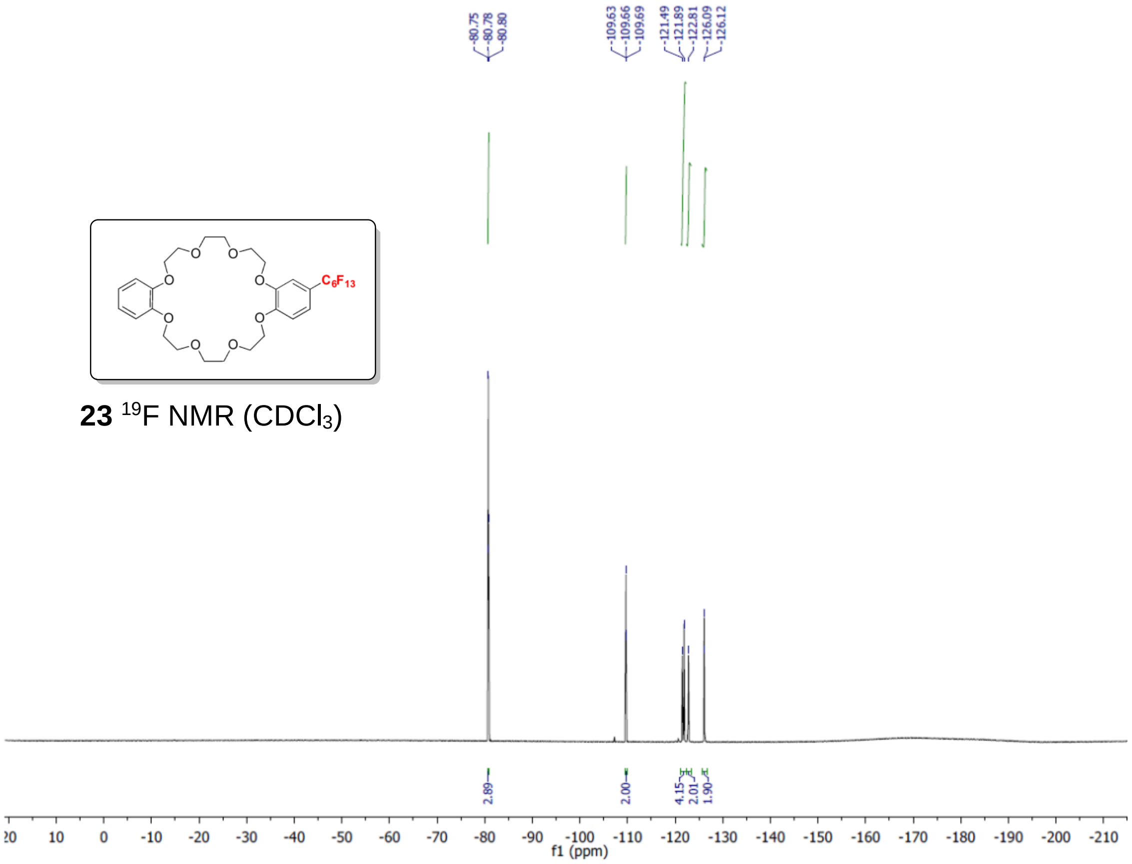




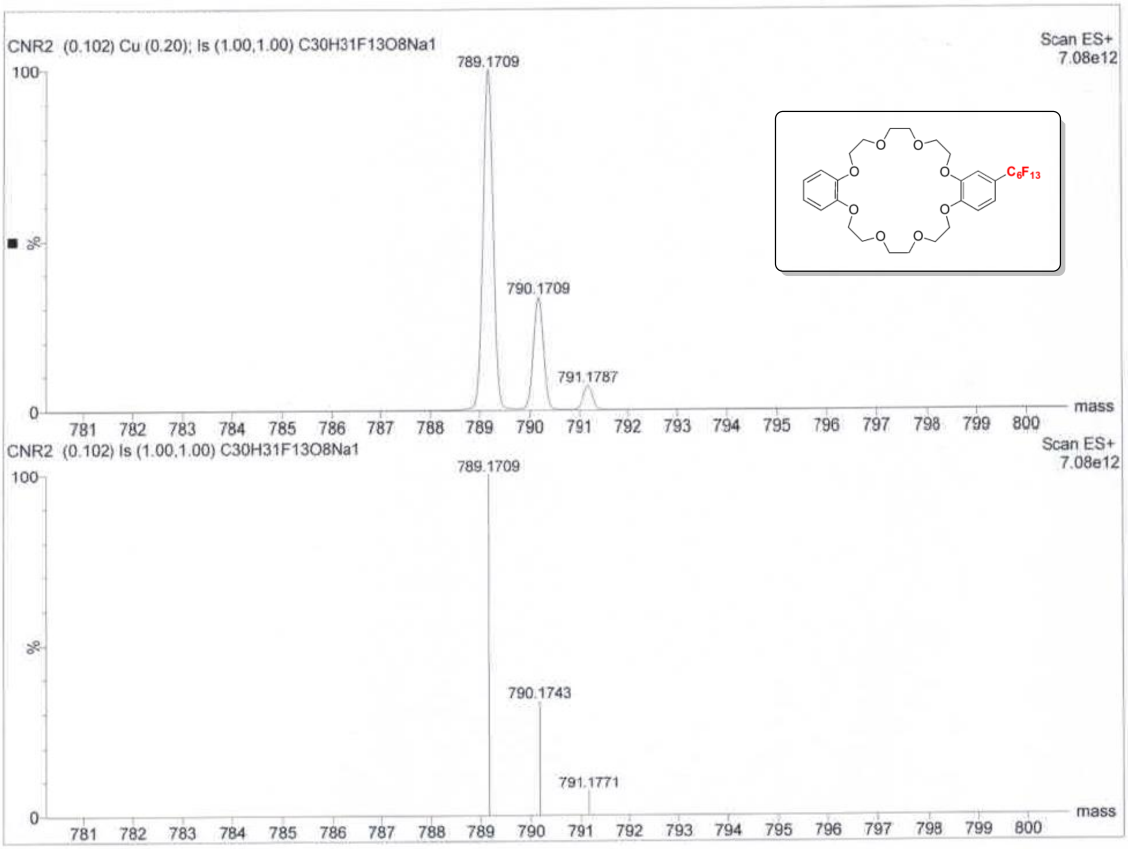
23 ^{1}H NMR (CDCl$_3$)

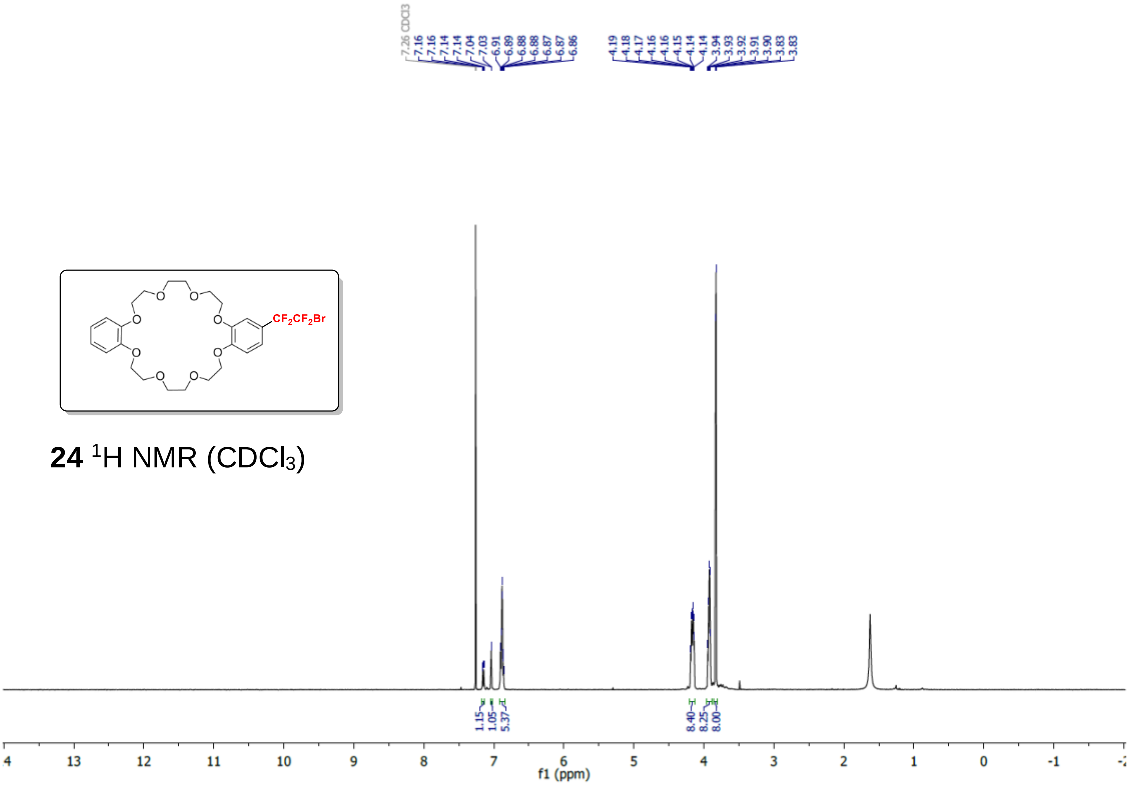


23 ^{13}C NMR ($CDCl_3$)

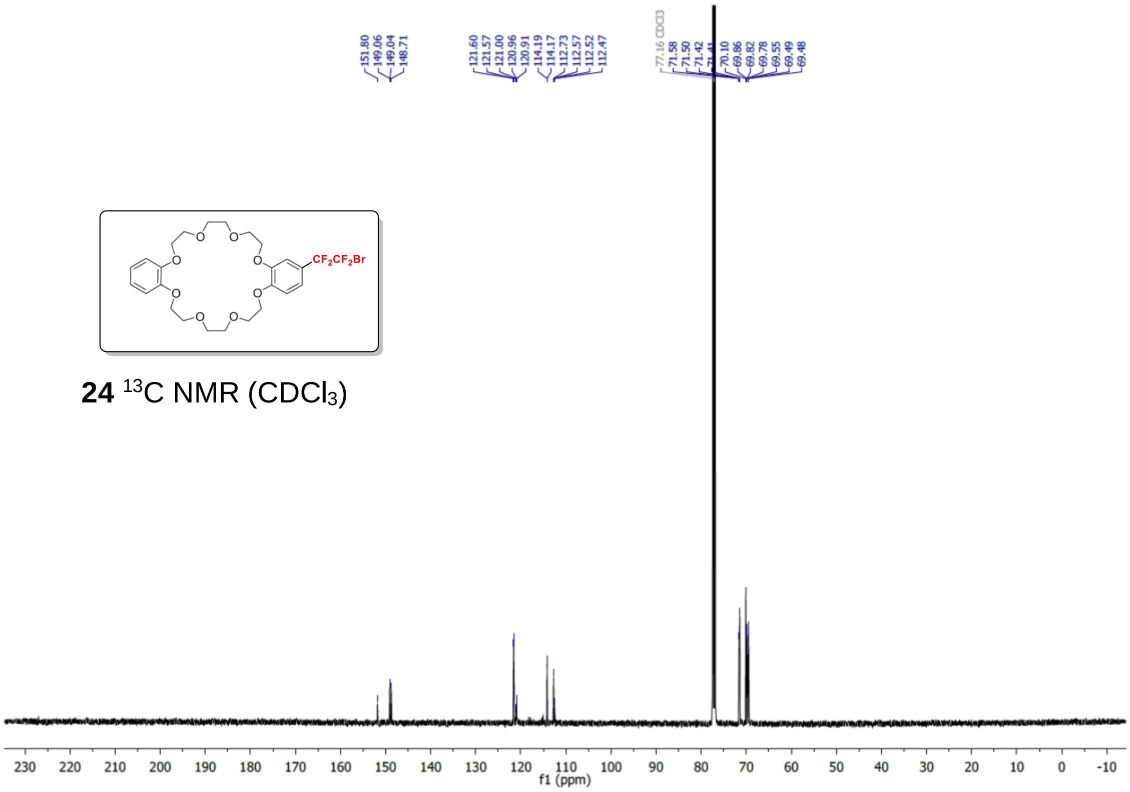


23 ^{19}F NMR ($CDCl_3$)

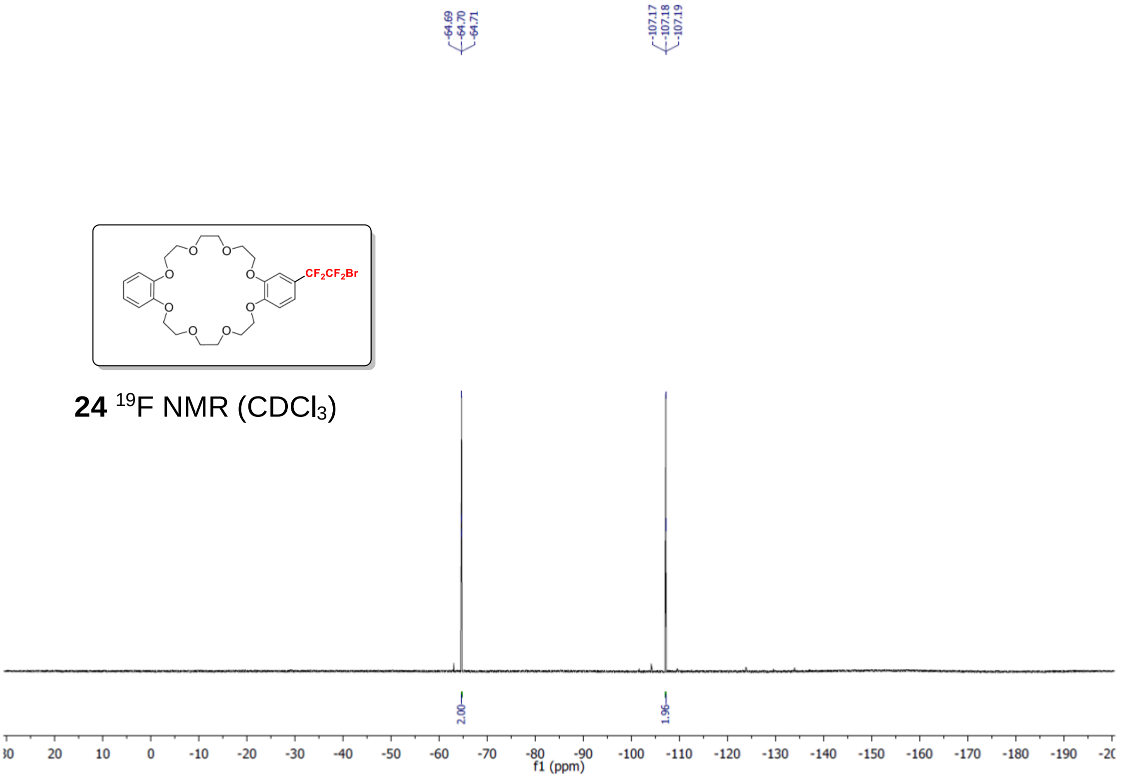




24 ^{1}H NMR ($CDCl_3$)



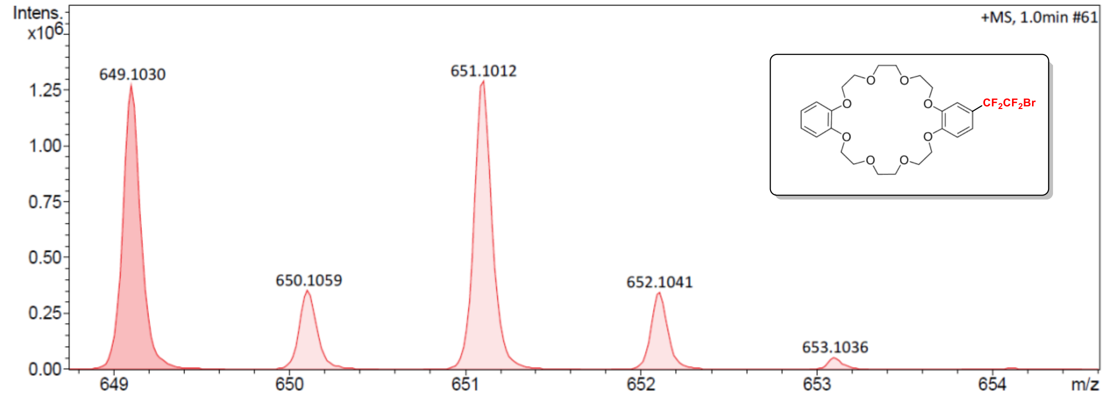
24 ^{13}C NMR (CDCl$_3$)



24 ^{19}F NMR (CDCl$_3$)

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	950 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Source



10. References

1. R. A. Sheldon, *Green Chem*, 2007, **9**, 1273-1283.
2. R. A. Sheldon, *Green Chem*, 2017,**19**, 18-43.
3. S. Barata-Vallejo, D. E. Yerien, A. Postigo, *Eur. J. Org. Chem*, **2015**, 7869-7875.
4. M. Onishi, A. Yoshiura, E. Kohno, K. Tsubata, US2002/198399, 2002, A1.
5. M. Moreno-Mañas, R. Pleixats, S. Villarroya, *Synlett*, 1999, **12**, 1996-1998.
6. C.-Y. He, J.-W. Gu, X. Zhang, *Tetrahedron Letters*; 2017, **58**, 3939-3941.
7. C. Huang, *Journal of Organic Chemistry*, 2001, **66**, 4651-4656.
8. Y. Li, H. Neumann, M. Beller, *Chemistry - A European Journal*, 2020, **26**, 6784-6788.
9. N. Kamigata, T. Fukushima, M. Yoshida, *Chemistry Letters*, 1990, **4**, 649-650.
10. N. Kamigata, T. Ohtsuka, T. Fukushima, M. Yoshida, T. Shimizu, *Journal of the Chemical Society. Perkin transactions I*, 1994, **10**, 1339-1346.
11. L. Cui, Y. Matusaki, N. Tada, T. Miura, B. Uno, A. Itoh, *Advanced Synthesis and Catalysis*, 2013, **355**, 2203-2207.
12. C. Rosso, G. Filippini, M. Prato, *Chemistry - A European Journal*, 2019, **25**, 16032-16036.
13. S. Bartling, M. Beller, S. Ellinger, C. R. Kreyenschulte, H. Lund, H. Neumann, C. Taeschler, F. Weniger, S. Zhang, *Catalysis science and technology*, 2020, **10**, 1731-1738.