Electronic Supplementary Information

for

Overcoming inaccessibility of fluorinated imines – synthesis of functionalized amines from readily available fluoroacetamides

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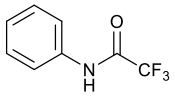
General Remarks

The reagents were purchased from Sigma Aldrich, Alfa Aesar or TCI Chemicals and used without further purification. All reactions involving air- and moisture-sensitive materials were carried out under argon atmosphere in oven-dried glassware with magnetic stirring. THF was distilled from Na and benzophenone. CH_2Cl_2 was distilled from CaH_2. Column chromatography was performed with Kieselgel (230-400 mesh). Analytical TLC was performed with Silica gel 60 F254 aluminum plates (Merck) with visualization by UV light and charring with Pancaldi reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O) or potassium permanganate solution ($KMnO_4$, K_2CO_3, NaOH, H_2O). NMR analyses were performed with Varian Mercury 400 MHz, Varian VNMRS 500 MHz and 600 MHz spectrometers. In case of ^{19}F spectroscopy, spectra from Varian Mercury 400 MHz were collected with ^{1}H decoupling in contrast to spectra from Varian VNMRS 500 MHz. Chemical shifts are calibrated using residual solvents signals ($CDCl_3$: δ (H)= 7.26, δ (C)= 77.0; C_6D_6: δ (H)= 7.16, δ (C)= 128.0; CD_3OD: δ (H)= 3.31, δ (C)= 49.0 toluene-d_8: δ (H)= 2.08, δ (C)= 20.4) and are reported in ppm. Infrared spectra (IR) were recorded on a JASCO FT/IR-6200 spectrophotometer and are reported in frequency of absorption (cm^{-1}). HRMS spectra were recorded on ESI-TOF Mariner spectrometer (Perspective Biosystem) and are given in m/z. Melting points were measured on Melting Point Meter MPMH2 apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-2000 polarimeter.

Synthesis of starting amides 1a-s

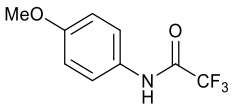
General synthetic procedure for trifluoromethyl derivatives

To a solution of amine in DCM (2 mL/mmol) cooled to 0 °C was added triethylamine (1.0 equiv.) and obtained mixture was stirred at this temperature for 15 minutes. After this time, TFAA (1.0 equiv.) was added dropwise and reaction mixture was allowed to warm up to room temperature and stirred until complete conversion of amine (TLC). The resulting mixture was washed with water (3 times), dried over Na_2SO_4 and evaporated. The obtained residue was crystallized from appropriate solvent to give a pure product.



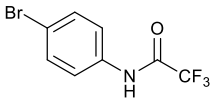
2,2,2-trifluoro-*N*-phenylacetamide (**1a**)

The compound was synthesized according to the general procedure starting with 1.8 mL (20.0 mmol) of aniline and crystallized from *n*-hexane. Product was collected as white crystal needles (3.27 g, 87%). mp 96-97 °C (from *n*-hexane, lit.[1] 91 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (br, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.44-7.37 (m, 1H). The spectroscopic data are in agreement with those reported.[2]



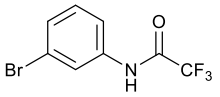
2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**1b**)

The compound was synthesized according to the general procedure starting with 1.85 mL (15.0 mmol) of *p*-anisidine and crystallized from *n*-heptane. Product was collected as off-white crystal needles (2.98 g, 91%). mp 123 °C (from *n*-heptane, lit.[3] 117-119 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (br, 1H), 7.50-7.43 (m, 2H), 6.95-6.87 (m, 2H), 3.81 (s, 3H). The spectroscopic data are in agreement with those reported.[2]



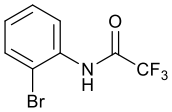
N-(4-bromophenyl)-2,2,2-trifluoroacetamide (**1c**)

The compound was synthesized according to the general procedure starting with 516.0 mg (3.0 mmol) of 4-bromoaniline and crystallized from diethyl ether/*n*-pentane solvent system. Product was collected as light grey crystalline powder (594.3 mg, 74%). mp 136 °C (from diethyl ether/*n*-pentane, lit.[4] 126 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (br, 1H), 7.55-7.49 (m, 2H), 7.49-7.44 (m, 2H). The spectroscopic data are in agreement with those reported.[2]



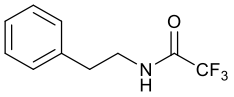
N-(3-bromophenyl)-2,2,2-trifluoroacetamide (**1d**)

The compound was synthesized according to the general procedure starting with 516.0 mg (3.0 mmol) of 3-bromoaniline and crystallized from *n*-heptane. Product was collected as opalescent white crystals (601.5 mg, 75%). mp 100-101 °C (from *n*-heptane, lit.[5] 92-93 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (br, 1H, NH), 7.84-7.77 (m, 1H), 7.45-7.38 (m, 1H), 7.42- 7.34 (m, 1H), 7.31 – 7.22 (m, 1H). The spectroscopic data are in agreement with those reported.[6]



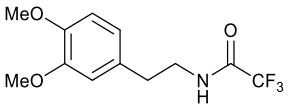
N-(2-bromophenyl)-2,2,2-trifluoroacetamide (**1e**)

The compound was synthesized according to the general procedure starting with 516.0 mg (3.0 mmol) of 4-bromoaniline and crystallized from DCM/*n*-heptane solvent system. Product was collected as white crystalline needles (530.1 mg, 66%). mp 76 °C (from DCM/*n*-heptane, lit.[7] 70-71 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (br, 1H, NH), 8.32 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.61 (dd, J = 8.1, 1.2 Hz, 1H), 7.40 (td, *J* = 8.0, 1.0 Hz, 1H), 7.12 (td, *J* = 8.0, 1.4 Hz, 1H). The spectroscopic data are in agreement with those reported.[8]



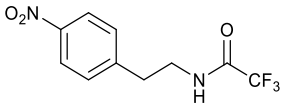
2,2,2-trifluoro-*N*-(2-phenylethyl)acetamide (**1f**)

The compound was synthesized according to the general procedure starting with 4.84 g (40.0 mmol) of 2-phenethylamine. Product was obtained as oil, which crystallized upon standing as white crystals (8.45 g, 97%). mp 65 °C (from DCM, lit.[9] 59 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 2H), 7.28-7.21 (m, 1H), 7.21-7.10 (m, 2H), 6.26 (br, 1H), 3.60 (q, *J* = 6.7 Hz, 2H), 2.87 (t, *J* = 7.0 Hz, 2H). The spectroscopic data are in agreement with those reported.[10]



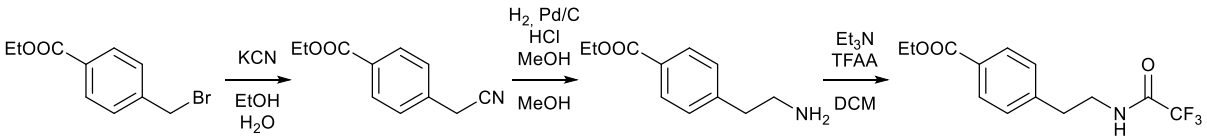
N-[2-(3,4-dimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (**1g**)

The compound was synthesized according to the general procedure starting with 906.0 mg (5.0 mmol) of 3,4-dimethoxyphenethylamine. Product was crystallized from DCM/*n*-pentane solvent system (1.15 g, 83%). mp 93-94 °C (from DCM/*n*-pentane, lit.[9] 87-88 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.1 Hz, 1H), 6.72 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.69 (d, *J* = 1.8 Hz, 1H), 6.31 (br, 1H, NH), 3.87 (s, 6H), 3.60 (q, *J* = 6.7 Hz, 2H), 2.83 (t, *J* = 6.9 Hz, 2H). The spectroscopic data are in agreement with those reported.[11]



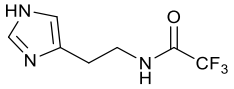
2,2,2-trifluoro-*N*-[2-(4-nitrophenyl)ethyl]acetamide (**1h**)

The compound was synthesized by directed nitration of 2,2,2-trifluoro-*N*-phenethylacetamide in according to the modified literature procedure.[12] To a solution of the amide (1.52 g, 7.0 mmol) in acetic anhydride (10 mL) cooled to 0 °C was added dropwise a solution of nitric acid (1.45 mL, 21.0 mmol, 3.0 equiv.) in acetic anhydride (10 mL). The reaction mixture was allowed to warm up to room temperature and stirred for 16h. The resulted mixture had been poured into ice water, but expected solid did not precipitated. The mixture was diluted with EtOAc. The organic phase was separated, washed with water (3 x 30mL), brine (1 x 50 mL), dried over $MgSO_4$ and evaporated. The residue was purified by FCC (30-60% MTBE/hexanes). Two products were isolated, a more polar was expected compound. An obtained yellowish solid was recrystallized from DCM/*n*-pentane solvent system and pure product was collected as white crystalline needles (717.2 mg, 39%). mp 107-108 °C (from DCM/*n*-pentane, lit.[13] 97-98 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26-8.18 (m, 2H), 7.45-7.36 (m, 2H), 6.35 (br, 1H), 3.67 (q, *J* = 6.7 Hz, 2H), 3.03 (t, *J* = 7.1 Hz, 2H). The spectroscopic data are in agreement with those reported.[14]



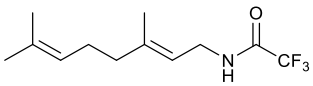
ethyl 4-{2-[(trifluoroacetyl)amino]ethyl}benzoate (**1i**)

The compound was synthesized by cyanation of ethyl 4-(bromomethyl)benzoate, reduction of obtained nitrile and subsequent trifluoroacetylation in according to the modified literature procedure.[15] To a solution of the benzoate (972.4 mg, 4.0 mmol) in ethanol (6 mL) was added water (1.35 mL) and a solution was stirred for 5 minutes at room temperature. Then potassium cyanide (312.6 mg, 4.8 mmol, 1.2 equiv.) was added and obtained solution was refluxed for 16 h. After this time, reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10mL), dried over Na_2SO_4 and evaporated. Obtained crude nitrile was used to reduction step without further purification. The compound (616 mg, 3.25 mmol) was dissolved in anhydrous methanol (50 mL), palladium on carbon (175.5 mg, 0.16 mmol; 5 mol%, 10 wt %) was added and HCl in dioxane (1.22 mL, 4.88 mmol, 1.5 equiv., 4M) was dropped into. The atmosphere of the flask was exchanged for hydrogen by evacuation by aspirator and refill (3 times). The reaction mixture was vigorously stirred for 16h at room temperature, filtered through short pad of celite, purging by methanol and evaporated. The residue was dried on oil pump and used to trifluoroacetylation step without further purification. The reaction was performed under standard procedure starting with 690.0 mg of crude amine. Product was crystallized from *n*-heptane (637.7 mg, 55% overall yield after 3 steps). mp 91-92 °C (from *n*-heptane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05-7.95 (m, 2H), 7.30-7.26 (m, 2H), 6.49 (br, 1H, NH), 4.37 (q, *J* = 7.1 Hz, 2H), 3.64 (q, *J* = 6.9 Hz, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.3, 157.2 (q, J_{CF} = 37.2 Hz), 142.8, 130.1, 129.3, 128.7, 115.7 (q, J_{CF} = 286.2 Hz), 61.0, 40.7, 35.0, 14.3. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -76.0 (s, 3F). **IR** (film) $\tilde{\nu}$: 3302, 3106, 2993, 2939, 1712, 1563, 1282, 1179, 1150, 1108, cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{13}H_{14}NO_3NaF_3$ $[M+Na]^+$ 312.0823 found: 312.0815.



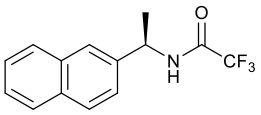
2,2,2-trifluoro-*N*-[2-(1*H*-imidazol-4-yl)ethyl]acetamide (**1j**)

The compound was exceptionally synthesized according to the procedure for difluoromethyl and perfluoro derivatives (see below), however under neat conditions, starting with 222 mg (2.0 mmol) of histamine and ethyl trifluoroacetate 238 µl (2.0 mmol). Product was collected as off-white crystals (398 mg, 96%). mp 91-92 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.63 (s, 1H), 6.87 (s, 1H), 3.52 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (100 MHz, CD_3OD) δ 159.0 (q, J_{CF} = 36.6 Hz), 136.2, 135.7, 117.5, 117.5 (q, J_{CF} = 284.9 Hz), 40.7, 27.2. **^{19}F NMR** (376 MHz, CD_3OD) δ -77.5 (s, 3F). **IR** (KBr) $\tilde{\nu}$: 3213, 3016, 2998, 1705, 1570, 1210, 1154 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_7H_9N_3OF_3[M+H]^+$ 208.0698, found: 208.0691.



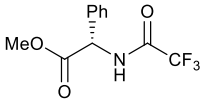
N-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]-2,2,2-trifluoroacetamide (**1k**)

The compound was exceptionally synthesized according to the procedure for difluoromethyl and perfluoro derivatives (see below) starting with 153 mg (1.0 mmol) of geranyl amine and ethyl trifluoroacetate 127 µl (1.0 mmol). Product was collected as orange oil (175 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.24 (br, 1H, NH), 5.23-5.17 (m, 1H), 5.10-5.02 (m, 1H), 3.95 (t, *J* = 6.3 Hz, 2H), 2.14-2.06 (m 2H), 2.06-1.99 (m, 2H), 1.69 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.9 (q, J_{CF} = 36.8 Hz), 142.2, 132.0, 123.5, 117.6, 115.8 (q, J_{CF} = 286.3 Hz), 39.4, 37.7, 26.2, 25.6, 17.6, 16.3. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -76.0 (s, 3F). **IR** (film) $\tilde{\nu}$: 3300, 3096, 2970, 2922, 2859, 1704, 1205, 1183, 1164 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{12}H_{17}NOF_3[M-H]^-$ 248.1262, found: 248.1264.



2,2,2-trifluoro-*N*-[(1*R*)-1-(naphthalen-2-yl)ethyl]acetamide (**1l**)

The compound was synthesized according to the general procedure starting with 342 mg (2.0 mmol) of (*R*)-(−)-1-(2-naphthyl)ethylamine. Product was crystallized from *n*-heptane (404 mg, 76%). mp 145-146 °C (from *n*-heptane). α = 191.7 (c = 1.18, DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91-7.81 (m, 3H), 7.77 (s, 1H), 7.56-7.47 (m, 2H), 7.42 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.61 (br, 1H, NH), 5.32 (p, *J* = 7.1 Hz, 1H), 1.68 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.4 (q, J_{CF} = 36.8 Hz), 138.2, 133.3, 133.0, 129.0, 127.9, 127.7, 126.6, 126.4, 125.0, 124.1, 115.8 (q, J_{CF} = 286.4 Hz), 49.9, 20.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.8 (s, 3F). **IR** (film) $\tilde{\nu}$: 3361, 3052, 2983, 2938, 2878, 1703, 1546, 1196, 1173, 1157 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{14}H_{12}NONaF_3$ $[M+Na]^+$ 290.0769, found: 290.0758.

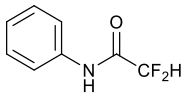


methyl (2*S*)-phenyl[(trifluoroacetyl)amino]ethanoate (**1m**)

The compound was synthesized according to the general procedure starting with 1.01 g (5.0 mmol) of (*S*)-phenylglycine methyl ester hydrochloride, however 2.0 equivalent of triethylamine was used instead of standard 1.0 equivalent. Product was crystallized from *n*-heptane (880 mg, 67%). mp 89-90 °C (from *n*-heptane). α = 208.9 (c =0.8, DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H + br, 1H, NH), 5.56 (d, *J* = 7.1 Hz, 1H), 3.78 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.0, 156.3 (q, J_{CF} = 37.7 Hz), 134.7, 129.3, 129.2, 127.2, 115.6 (q, J_{CF} = 286.0 Hz), 56.6, 53.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.8 (s, 3F). **IR** (film) $\tilde{\nu}$: 3317, 3071, 3037, 2957, 1743, 1704, 1549, 1440, 1308, 1269, 1211, 1185, 1164 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{11}H_{10}NO_3NaF_3$ $[M+Na]^+$ 284.0510, found: 284.0502.

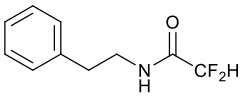
General synthetic procedure for difluoromethyl or perfluoro derivatives

To a solution of amine in DCM (2mL/mmol) was added fluoroester (1.0 equiv.) and obtained mixture was refluxed for 16 h. The reaction mixture was evaporated. The obtained residue was recrystallized from appropriate solvent to give a pure product.



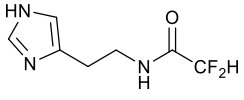
2,2-difluoro-*N*-phenylacetamide (**1n**)

The compound was synthesized according to the literature procedure.[16] The general procedure was failed, as well as protocol with addition of triethylamine. The reaction was performed under neat conditions with addition of catalytic amount of KOH. To the screw cap vial was charged 456 µl (5.0 mmol) of aniline, 526 µl (5.0 mmol) of ethyl difluoroacetate and catalytic amount of powdered KOH. The reaction mixture was heated to 120 °C for 36 h, then cooled to room temperature, diluted with DCM (2 mL) and washed with water (3 x 2 mL). The organic layer was dried over Na_2SO_4, evaporated and obtained residue was recrystallized from *n*-heptane. Product was collected as white crystal needles (238.2 mg, 28%). mp 65 °C (from *n*-heptane, lit.[17] 60 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (br, 1H, NH), 7.64-7.56 (m, 2H), 7.44-7.36 (m, 2H), 7.27-7.19 (m, 1H), 6.01 (t, J_{HF} = 54.4 Hz). The spectroscopic data are in agreement with those reported.[18]



2,2-difluoro-*N*-(2-phenylethyl)acetamide (**1o**)

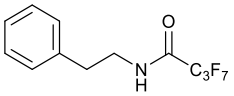
The compound was synthesized according to the general procedure starting with 881 µl (7.0 mmol) of 2-phenethylamine and ethyl difluoroacetate 868 µl (7.0 mmol). Product was collected as yellowish oil (1.37 g, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 2H), 7.29-7.23 (m, 1H), 7.22-7.17 (m, 2H), 6.31 (br, 1H, NH), 5.85 (t, J_{HF} = 54.3 Hz, 1H), 3.61 (q, J = 6.8 Hz, 2H), 2.88 (t, J = 7.0 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.5 (t, J_{CF} = 24.4 Hz), 137.9, 128.8, 128.7, 126.8, 108.4 (t, J_{CF} = 251.1 Hz), 40.4, 35.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -126.3 (s, 3F). **IR** (film) $\tilde{\nu}$: 3299, 3090, 3030, 2942, 1687, 1553, 1497, 1454, 1364, 1344, 1063 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{10}H_{10}NOF_2$ $[M-H]^-$ 198.0730, found: 198.0731.



2,2-difluoro-*N*-[2-(1*H*-imidazol-4-yl)ethyl]acetamide (**1p**)

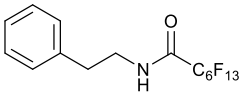
The compound was synthesized according to the general procedure starting with 450 mg (4.05 mmol) of histamine. Product crystallized from crude cold reaction mixture as a off-white crystals (753.5 mg, 98%). mp 122-123 °C (from DCM). **^{1}H NMR** (500 MHz, CD_3OD) δ 7.59 (s, 1H), 6.86 (s, 1H), 6.00 (t, J_{HF} = 54.1 Hz, 1H), 3.50 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H). **^{13}C NMR** (125 MHz, CD_3OD) δ

165.1 (t, J_{CF} = 25.2 Hz), 136.2, 135.9, 117.56, 110.0 (t, J_{CF} = 246.7 Hz), 40.3, 27.5. **^{19}F NMR** (470 MHz, CD_3OD) δ -128.3 (d, *J* = 54.0 Hz, 2F) **IR** (KBr) $\tilde{\nu}$: 3246, 3025, 2944,2857, 1679, 1573, 1491, 1453, 1359, 1319, 1300, 1287, 1259, 1227, 1191, 1118, 1088, 1061 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_7H_{10}N_3OF_2$ $[M+H]^+$ 190.0792, found: 190.0788.



2,2,3,3,4,4,4-heptafluoro-*N*-(2-phenylethyl)butanamide (**1r**)

The compound was synthesized according to the general procedure starting with 378 µl (3.0 mmol) of 2-phenetylamine and 520 µl (3.0 mmol) of ethyl heptafluorobutyrate. Product was crystallized from DCM/*n*-pentane solvent system (874.1 mg, 92%). mp 53 °C (from DCM/*n*-pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.32 (m, 2H), 7.32-7.25 (m, 1H), 7.24-7.16 (m, 2H), 6.39 (br, 1H, NH), 3.68 (q, J = 6.7 Hz, 2H), 2.91 (t, J = 6.9 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.5 (t, J_{CF} = 25.8 Hz), 137.5, 128.9, 128.6, 127.0, 41.3, 35.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -80.6 (t, *J* = 8.8 Hz, 3F), -120.7, (q, *J* = 8.8 Hz, 2F), -127.0, (s, 2F). **IR** (film) $\tilde{\nu}$: 3316, 3065, 3030, 2949, 2869, 1691, 1550, 1222, 1182, 1152, 1124 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{12}H_{10}NONaF_7$ $[M+Na]^+$ 340.0548, found: 340.0543.



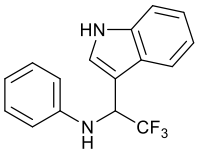
2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-*N*-(2-phenylethyl)heptanamide (**1s**)

The compound was synthesized according to the general procedure starting with 252 µl (2.0 mmol) of 2-phenethylamine and 756 mg (2.0 mmol) of ethyl perfluoroheptanoate. Product was crystallized from DCM/*n*-pentane solvent system (845.0 mg, 90%). mp 88 °C (from DCM/*n*-pentane) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.30 (m, 2H), 7.30-7.23 (m, 1H), 7.22-7.15 (m, 2H), 6.39 (br, 1H, NH), 3.66 (q, *J* = 6.7 Hz, 2H), 2.89 (t, *J* = 6.9 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.5 (t, J_{CF} = 2.5 Hz), 137.5, 128.9, 128.6, 127.0, 41.3, 35.0. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -80.8 (m, 3F), -119.8 (m, 2F), -121.8 (m, 2F), -122.6 (m, 2F), -122.8 (m, 2F), -126,1 (m, 2F). **IR** (film) $\tilde{\nu}$: 3352, 3318, 3064, 3028, 2945, 1689, 1549, 1455, 1230, 1208, 1146, 1080 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{15}H_{10}NONaF_{13}$ $[M+Na]^+$ 490.0453, found: 490.0435.

Synthesis of functionalized amines 2a-s (from Scheme 1 in main text)

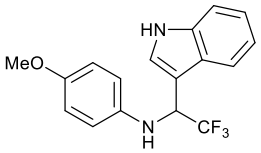
To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature (unless indicated otherwise) was added amide (0.15 mmol). The reaction mixture was stirred at RT until it cleared (from 15 to 45 minutes typically) and then was cooled to 0 °C. TFA (44.5 mg, 0.39 mmol, 2.6 equiv.) and indole (52.7 mg, 0.45 mmol, 3 equiv.) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted with ether (3x5 mL). The combined organic extracts were dried over Na_2SO_4 and

evaporated. The residue was purified by FCC in the appropriate solvent system to give a pure product.



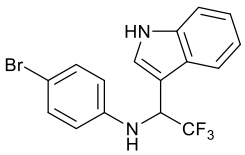
N-[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]aniline (**2a**)

The compound was synthesized according to the general procedure starting with 28.4 mg of **1a** and purified using 15-30% MTBE/hexanes solvent system. Product was isolated as yellowish solid (39.4 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (br, 1H, NH_{Het}), 7.64-7.56 (m, 1H), 7.44-7.36 (m, 1H), 7.33-7.13 (m, 5H), 6.86-6.79 (m, 1H), 6.78-6.71 (m, 2H), 5.29 (q, J = 7.1 Hz, 1H, $CHCF_3$), 4.15 (br, 1H, NH) . **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.3, 136.1, 129.36, 125.92, 125.9 (q, J_{CF} = 280.8 Hz), 123.1, 122.9, 120.5, 119.1, 119.0, 113.7, 111.5, 109.6 (d, J_{CF} = 1.1 Hz), 54.3 (q, J_{CF} = 31.6 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.9 (s, 3F). **IR** (KBr) $\tilde{\nu}$: 3409, 3051, 1600, 1507, 1308, 1266, 1245, 1166, 1108 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{16}H_{12}N_2F_3$ $[M-H]^-$ 289.0953, found: 289.0949.



4-methoxy-*N*-[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]aniline (**2b**)

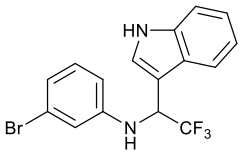
The compound was synthesized according to the general procedure starting with 32.9 mg of **1b** and purified using 15-30% MTBE/hexanes solvent system. Product was isolated as brown waxy oil (40.8 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (br, 1H, NH_{Het}), 7.60-7.38 (m, 2H), 7.30-7.22 (m, 2H), 7.17 (m, 1H), 6.80-6.72 (m, 4H), 5.16 (q, J_{HF} = 7.2 Hz, 1H), 3.76 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.2, 140.5, 136.2, 125.9, 126.0 (q, J_{CF} = 280.7 Hz), 123.1, 122.8, 120.4, 119.0, 115.5, 114.9, 111.5, 109.8, 55.7, 55.6 (q, J_{CF} = 31.2 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.8 (s, 3F). **IR** (film) $\tilde{\nu}$: 3410, 3059, 3000, 2934, 2836, 1513, 1459, 1270, 1237, 1166, 1118, 1034 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{17}H_{15}N_2ONaF_3$ $[M+Na]^+$ 343.1034, found: 343.1020.



4-bromo-*N*-[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]aniline (**2c**)

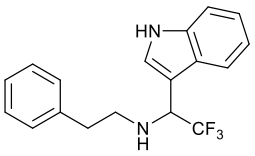
The compound was synthesized according to the general procedure starting with 40.2 mg of **1c** and purified using 15-30% MTBE/hexanes solvent system. Product was isolated as brown waxy oil (47.9 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (br, 1H, NH_{Het}), 7.57-7.41 (m, 2H), 7.34-7.25 (m, 4H), 7.18 (m, 1H), 6.68-6.58 (m, 2H), 5.23 (q, J_{HF} = 6.9 Hz, 1H), 4.16 (br, 1H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.3, 136.1, 132.1, 125.8, 125.7 (q, J_{CF} = 280.8 Hz), 123.1, 123.0, 120.6, 118.8, 115.3, 111.6, 110.9,

109.1, 54.4 (q, J_{CF} = 31.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.8 (s, 3F). **IR** (KBr) $\tilde{\nu}$: 3416, 3155, 3046, 2921, 2852, 1592, 1500, 1270, 1163, 1120 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{16}H_{11}N_2F_3Br$ $[M-H]^-$ 367.0058, found: 367.0058.



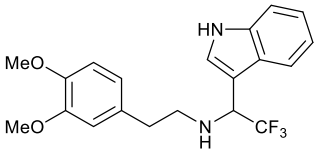
3-bromo-*N*-[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]aniline (**2d**)

The compound was synthesized according to the general procedure starting with 40.2 mg of **1d** and purified using 0-30% MTBE/hexanes solvent system. Product was isolated as brown oil (28.9 mg, 52%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (br, 1H, NH_{Het}), 7.59-7.52 (m, 1H), 7.46-7.39 (m, 1H), 7.35-7.30 (m, 1H), 7.29 – 7.23 (m, 1H), 7.20-7.14 (m, 1H), 7.08-7.00 (m, 1H), 6.95-6.88 (m, 2H), 6.69- 6.60 (m, 1H), 5.24 (q, J_{HF} = 7.0 Hz, 1H), 4.17 (br, 1H, NH). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 147.6, 136.1, 130.7, 125.7, 125.7 (q, J_{CF} = 281.0 Hz), 123.3, 123.1, 123.0, 122.0, 120.6, 118.9, 116.4, 112.2, 111.6, 109.1, 54.1 (q, J_{CF} = 32.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.8 (s, 3F). **IR** (film) $\tilde{\nu}$: 3417, 3059, 2925, 1596, 1501, 1480, 1265, 1168, 1119 cm^{-1}. **HRMS** (EI) m/z calcd for $C_{16}H_{12}N_2F_3Br$ $[M]^+$ 368.0136, found: 368.0142.



2,2,2-trifluoro-1-(1*H*-indol-3-yl)-*N*-(2-phenylethyl)ethanamine (**2f**)

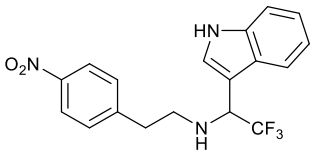
The compound was synthesized according to the general procedure starting with 32.6 mg of **1f** and purified using 30% MTBE/hexanes solvent system. Product was isolated as yellowish oil (43.4 mg; 91%). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.76-7.70 (m, 1H), 7.20-7.11 (m, 3H), 7.10-7.01 (m, 2H), 6.99-6.95 (m, 1H), 6.95-6.91 (m, 2H), 6.73 (br, 1H, NH_{Het}), 6.62 (d, J = 2.5 Hz, 1H), 4.36 (q, J_{HF} = 7.6 Hz, 1H), 2.76 (t, J = 7.1 Hz, 2H), 2.59-2.42 (m, 2H), 1.45 (br, 1H, NH). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.0, 136.4, 128.9, 128.6, 126.9 (q, J_{CF} = 280.2 Hz), 126.9, 126.4, 123.8, 122.7, 120.5, 119.9, 111.5, 109.8, 58.1 (q, J_{CF} = 29.5 Hz), 49.4, 36.7. **^{19}F NMR** (376 MHz, C_6D_6) δ -73.9 (s, 3F). **IR** (film) $\tilde{\nu}$: 3416, 3060, 3028, 2928, 2855, 1456, 1268, 1167, 1119 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{18}H_{17}N_2F_3Na$ $[M+Na]^+$ 341.1242, found: 341.1226.



N-[2-(3,4-dimethoxyphenyl)ethyl]-2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethanamine (**2g**)

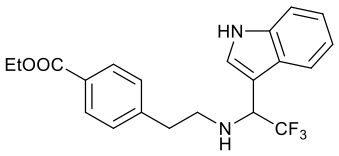
The compound was synthesized according to the general procedure starting with 41.6 mg of **1g** and purified using 50% MTBE/hexanes solvent system. Product was isolated as colorless oil (44.5 mg,

78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (br, 1H, NH_{Het}), 7.68-7.60 (m, 1H), 7.39-7.34 (m, 1H), 7.25-7.20 (m, 1H), 7.19-7.11 (m, 2H), 6.79-6.74 (m, 1H), 6.71-6.66 (m, 1H), 6.65-6.61 (m, 1H) 4.51 (q, J_{HF} = 7.6 Hz, 1H, $CHCF_3$), 3.85 (s, 3H), 3.74 (s, 3H), 3.06-2.88 (m, 2H), 2.84-2.66 (m, 2H), 1.77 (br, 1H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.9, 147.5, 136.1, 132.0, 126.3, 126.1 (q, J_{CF} = 279.7 Hz), 123.7, 122.5, 120.6, 120.1, 119.2, 111.9, 111.3, 109.6, 57.6 (q, J_{CF} = 29.8 Hz), 55.9, 55.7, 49.3, 35.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.1 (s, 3F). **IR** (film) $\tilde{\nu}$: 3354, 3059, 3002, 2936, 2837, 1516, 1463, 1262, 1235, 1157, 1141, 1119, 1027 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{21}N_2O_2F_3Na$ $[M+Na]^+$ 401.1453, found: 401.1438.



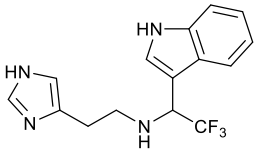
2,2,2-trifluoro-1-(1*H*-indol-3-yl)-*N*-[2-(4-nitrophenyl)ethyl]ethanamine (**2h**)

The compound was synthesized according to the general procedure starting with 39.3 mg of **1h** and purified using 30% MTBE/hexanes solvent system. Product was isolated as yellow oil (32.5 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (br, 1H, NH_{Het}), 8.12-8.04 (m, 2H), 7.66-7.59 (m, 1H), 7.42-7.36 (m, 1H), 7.31-7.18 (m, 4H), 7.17-7.10 (m, 1H), 4.50 (q, J_{HF} = 7.6 Hz, 1H, $CHCF_3$), 3.08-2.96 (m, 2H), 2.95-2.80 (m, 2H), 1.71 (br, 1H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.5, 146.6, 136.1, 129.5, 126.1, 125.9 (q, J_{CF} = 280.2 Hz), 123.7, 123.6, 122.7, 120.3, 119.2, 111.4, 109.4, 57.84 (q, J_{CF} = 29.8 Hz), 48.4, 36.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.9 (s, 3H). **IR** (film) $\tilde{\nu}$: 3410, 3056, 2928, 2852, 1601, 1517, 1458, 1345, 1265, 1165, 1118 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{18}H_{16}N_3O_2NaF_3$ $[M+Na]^+$ 386.1092, found: 386.1078.



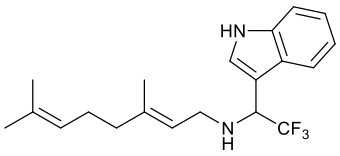
ethyl 4-(2-{[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]amino}ethyl)benzoate (**2i**)

The compound was synthesized according to the general procedure starting with 43.4 mg of **1i** and purified using 30-50% MTBE/hexanes solvent system. Product was isolated as colorless oil (29.3 mg, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (br, 1H, NH_{Het}), 7.96-7.88 (m, 2H), 7.67-7.60 (m, 1H), 7.42-7.34 (m, 1H) 7.28-7.23 (m, 1H), 7.22-7.16 (m, 3H),7.16-7.10 (m, 1H), 4.50 (q, J_{HF} = 7.5 Hz, 1H, $CHCF_3$), 4.36 (q, J = 7.1 Hz, 2H), 3.08-2.93 (m, 2H), 2.92-2.76 (m, 2H), 1.77 (br, 1H, NH), 1.39 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.6, 144.9, 136.1, 129.7, 128.7, 128.6, 126.3, 126.0 (q, J_{CF} = 280.1 Hz), 123.7, 122.6, 120.2, 119.2, 111.4, 109.6, 60.9, 57.7 (q, J_{CF} = 29.8 Hz), 48.8, 36.4, 14.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.1 (s, 3F). **IR** (film) $\tilde{\nu}$: 3406, 3354, 3059, 2982, 2932, 2857, 1708, 1281, 1166, 1115 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{21}N_2O_2NaF_3$ $[M+Na]^+$ 413.1453, found: 413.1438.



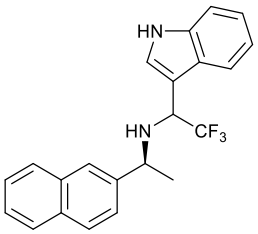
2,2,2-trifluoro-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-1-(1*H*-indol-3-yl)ethanamine (**2j**)

The compound was synthesized according to the general procedure starting with 31.1 mg of **1j** and purified using 5-10% MeOH/DCM solvent system. Product was isolated as waxy yellowish oil (34.1 mg, 74%). **^{1}H NMR** (500 MHz, CD_3OD) δ 7.61-7.56 (m, 1H), 7.54-7.51 (m, 1H), 7.40-7.35 (m, 1H), 7.32-7.28 (m, 1H), 7.15-7.09 (m, 1H), 7.05-7.00 (m, 1H), 6.75-6.71 (m, 1H), 4.58 (q, J_{HF} = 7.9 Hz, 1H), 2.92-2.84 (m, 2H), 2.80-2.69 (m, 2H). **^{13}C NMR** (125 MHz, CD_3OD) δ 138.0, 136.0, 127.7, 127.7 (q, J_{CF} = 278.5 Hz), 125.7, 125.5, 122.8, 120.4, 119.8, 112.5, 111.4, 109.3, 58.5 (q, J_{CF} = 29.7 Hz), 30.8, 27.8. **^{19}F NMR** (470 MHz, CD_3OD) δ -75.5 (d, J_{FH} = 7.9 Hz). **IR** (film) $\tilde{\nu}$: 3146, 2925, 2859, 1710, 1458, 1266, 1165, 1119 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{15}H_{15}N_4NaF_3$ $[M+Na]^+$ 331.1147, found: 331.1137.



(2*E*)-3,7-dimethyl-*N*-[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]octa-2,6-dien-1-amine (**2k**)

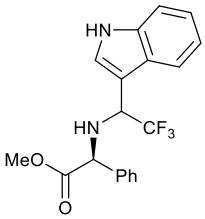
The compound was synthesized according to the general procedure starting with 37.4 mg of **1k** and purified using 30% MTBE/hexanes solvent system. Product was isolated as colourless oil (31.3 mg, 60%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.26 (br, 1H, NH_{Het}), 7.74 -7.70 (m, 1H), 7.42 -7.38 (m, 1H), 7.29 -7.22 (m, 3H), 5.27 – 5.22 (m, 1H), 5.12 – 5.06 (m, 1H), 4.53 (q, J_{HF} = 7.6 Hz, 1H), 3.37 – 3.26 (m, 2H), 2.12-2.05 (m, 2H), 2.05 – 1.98 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.51 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 139.2, 136.1, 131.7, 126.4, 126.2 (q, J_{CF} = 279.7 Hz), 124.0, 123.8, 122.6, 121.9, 120.2, 119.3, 111.3, 109.9, 56.5 (q, J_{CF} = 29.8 Hz), 45.2, 39.6, 26.4, 25.7, 17.7, 16.2. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.0 (s, 3F). **IR** (film) $\tilde{\nu}$: 3415, 3184, 3058, 2968, 2925, 2857, 1457, 1268, 1167, 1118 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{24}N_2F_3$ $[M-H]^-$ 349.1892, found: 349.1889.



2,2,2-trifluoro-1-(1*H*-indol-3-yl)-*N*-[(1*S*)-1-(naphthalen-2-yl)ethyl]ethanamine (**2l**)

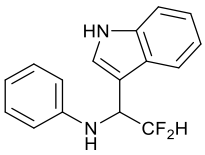
The compound was synthesized according to the general procedure starting with 40.1 mg of **1l** and purified using 15-30% MTBE/hexanes solvent system. Product was isolated as waxy colourless oil (as an inseparable mixture of diastereomers, dr 9:1 based on ^{1}H and ^{19}F NMR spectra) (38.9 mg, 70%). α = 166.1 (c = 1.03, DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereoisomer: δ 8.24 (br, 1H, NH_{Het}), 7.95-7.86 (m, 2H), 7.87 – 7.78 (m, 1H), 7.68 (s, 1H), 7.67-6.63 (m, 1H), 7.58 – 7.49 (m, 3H), 7.48-7.43 (m, 1H), 7.34 – 7.27 (m, 1H), 7.23 – 7.14 (m, 2H), 4.28 (q, J_{HF} = 8.1 Hz, 1H), 3.94 (q, J = 6.6 Hz, 1H),

2.08 (br, 1H, NH), 1.45 (d, *J* = 6.6 Hz, 3H); minor diastereoisomer (selected signals): 8.15 (br, 0.1H, NH_{Het}), 1.52 (d, *J* = 6.5 Hz, 0.3H). **^{13}C NMR** (100 MHz, $CDCl_3$) major isomer: δ 141.5, 136.3, 133.4, 133.0, 128.5, 127.8, 127.7, 126.5, 126.1, 125.9 (q, J_{CF} = 278.9 Hz), 125.8, 125.7, 124.8, 124.2, 122.6, 120.2, 119.6, 111.4, 109.8, 55.2 (q, J_{CF} = 30.1 Hz), 55.0, 24.7; minor isomer (selected signals): δ 141.9, 135.9, 132.9, 111.2, 23.9. **^{19}F NMR** (376 MHz, $CDCl_3$) diastereoisomer: δ -74.1 (s, 3F); minor diastereoisomer -73.1 (s, 0.3F). **IR** (film) $\tilde{\nu}$: 3419, 3056, 2965, 2927, 2866, 1457, 1350, 1264, 1184, 1168, 1120 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{18}N_2F_3$ $[M-H]^-$ 367.1422, found: 367.1414.



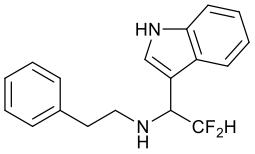
methyl (2*S*)-phenyl{[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]amino}ethanoate (**2m**)

The compound was synthesized according to the general procedure starting with 31.1 mg of **1m** and purified using 30-50% MTBE/pentane solvent system. Product was isolated (as an inseparable mixture of diastereomers, dr 2:1 based on ^{1}H NMR spectra) as yellowish oil (24.4 mg, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereoisomer: δ 8.26 (br, 1H, NH_{Het}), 7.66-7.58 (m, 1H), 7.43-7.32 (m, 4H), 7.31-7.22 (m, 4H), 7.17-7.09 (m, 1H), 4.43 (s, 1H) 4.31 (q, J_{HF} = 7.6 Hz, 1H), 3.61 (s, 3H); minor diastereoisomer (selected signals): δ 4.56 (q, J_{HF} = 7.5 Hz, 0.5H), 4.55 (s, 0.5H), 3.65 (s, 1.5H). **^{13}C NMR** (125 MHz, $CDCl_3$) major diastereosiomer: δ 172.6, 137.0, 136.2, 128.8, 128.4, 127.9, 126.4, 125.8 (q, J_{CF} = 279.0 Hz), 124.4, 122.7, 120.4, 119.6, 111.3, 108.6, 62.5, 55.0 (q, J_{CF} = 30.5 Hz), 52.4; minor diastereoisomer (selected signals): δ 172.9, 137.2, 136.1, 128.9, 127.6, 126.2, 122.7, 120.3, 119.7, 111.3, 108.7, 62.4, 52.3. **^{19}F NMR** (376 MHz, $CDCl_3$) major diastereoisomer: δ -74.12; minor diastereoisomer: δ -74.11. **IR** (film) $\tilde{\nu}$: 3411, 3061, 3033, 2954, 2927, 2855, 1736, 1457, 1269, 1173, 1120 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{17}N_2O_2NaF_3$ $[M+Na]^+$ 385.1140, found: 385.1128.



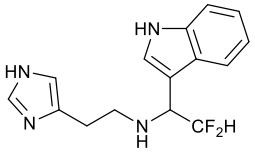
N-[2,2-difluoro-1-(1*H*-indol-3-yl)ethyl]aniline (**2n**)

The compound was synthesized according to the general procedure starting with 25.7 mg of **1n** and purified using 30% MTBE/hexanes solvent system. Product was isolated as yellowish oil (26.9 mg, 66%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (br, 1H, NH_{Het}), 7.71-7.62 (m, 1H), 7.43-7.35 (m, 1H), 7.30-7.22 (m, 2H), 7.22-7.12 (m, 3H), 6.81-6.75 (m, 1H), 6.75-6.69 (m, 2H), 6.17 (td, J_{HF} = 56.0, 2.8 Hz, 1H, CF_2HCH), 5.09 (td, *J* = 12.9, 2.2 Hz, 1H, $CHCF_2H$), 4.18 (br, 1H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.7, 136.3, 129.3, 126.10, 123.2, 122.7, 120.2, 119.0, 118.6, 115.7 (t, J_{CF} = 245.3 Hz), 113.8, 111.5, 110.6, 53.8 (t, J_{CF} = 23.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -124.2, -125.6 (ABq, *J* = 277.2 Hz, 2F). **IR** (film) $\tilde{\nu}$: 3411, 3054, 2972, 2924, 1602, 1504, 1063cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{16}H_{15}N_2F_2$ $[M+H]^+$ 273.1203, found: 273.1191.



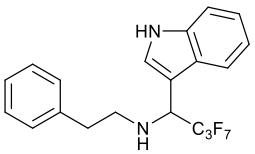
2,2-difluoro-1-(1*H*-indol-3-yl)-*N*-(2-phenylethyl)ethanamine (**2o**)

The compound was synthesized according to the general procedure starting with 29.9 mg of **1o** and purified using 25-30% EtOAc/hexanes solvent system. Product was isolated as pinkish oil (42.5 mg, 94%). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.82-7.74 (m, 1H), 7.23-7.18 (m, 1H), 7.13-7.06 (m, 3H), 7.06-6.98 (m, 2H), 6.98-6.93 (m, 2H), 6.72 (br, 1H, NH_{Het}), 6.62-6.55 (m, 1H), 5.80 (td, J_{HF} = 56.9, 5.0, 1H), 4.15 (td, J_{HF} = 11.2, 4.9, 1H), 2.81-2.66 (m, 2H), 2.57-2.47 (m, 2H), 1.32 (br, 1H, NH). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.3, 136.7, 129.0, 128.6, 127.0, 126.3, 123.6, 122.6, 120.2, 120.1, 117.5 (t, *J* = 243.5 Hz), 111.5, 111.3, 58.6 (t, *J* = 23.0 Hz), 49.0, 36.8. **^{19}F NMR** (376 MHz, C_6D_6) δ -122.2, -123.2 (ABq, *J* = 278.2 Hz, 2F). **IR** (film) $\tilde{\nu}$: 3417, 3171, 3060, 3028, 2926, 2854 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{18}H_{18}N_2NaF_2$ $[M+Na]^+$ 323.1336, found: 323.1331.



2,2-difluoro-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-1-(1*H*-indol-3-yl)ethanamine (**2p**)

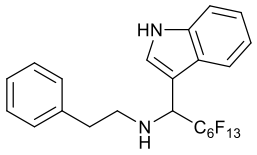
The compound was synthesized according to the general procedure starting with 28.4 mg of **1p** and purified using 10% MeOH/DCM solvent system. Product was isolated as waxy colourless oil (32.7 mg, 75%). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.63-7.56 (m, 1H), 7.53-7.50 (m, 1H), 7.39-7.33 (m, 1H), 7.25 (s, 1H), 7.15- 7.07 (m, 1H), 7.05- 6.97 (m, 1H), 6.74 (s, 1H), 6.01 (td, J_{HF} = 56.6, 4.4 Hz, 1H), 4.30 (td, *J* = 12.4, 4.4 Hz, 1H), 2.90-2.81 (m, 2H), 2.79-2.68 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD) δ 138.1, 136.1, 136.0, 128.0, 125.3, 122.7, 120.3, 119.7, 118.3 (t, J_{CF} = 242.3 Hz), 118.2, 112.5, 110.6, 58.7 (t, J_{CF} = 22.8 Hz), 48.0, 27.8. **^{19}F NMR** (376 MHz, CD_3OD) δ -125.1, -124.3, (ABq, *J* = 278.4 Hz, 2F). **IR** (film) $\tilde{\nu}$: 3406, 3136, 2976, 2923, 2854, 1456, 1104, 1048 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{15}H_{16}N_4NaF_2$ $[M+Na]^+$ 313.1241, found: 313.1233.



2,2,3,3,4,4,4-heptafluoro-1-(1*H*-indol-3-yl)-*N*-(2-phenylethyl)butan-1-amine (**2r**)

The compound was synthesized according to the general procedure starting with 47.6 mg of **1r** and purified using 10-30% MTBE /hexanes solvent system. Product was isolated as colorless waxy oil (49.5 mg, 79%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.16 (s, 1H, NH_{Het}), 7.62-7.58 (m, 1H), 7.37-7.33 (m, 1H), 7.26 – 7.19 (m, 3H), 7.19-7.15 (m, 1H), 7.15-7.11 (m, 1H), 7.10-7.05 (m,3H), 4.59 (dd, J_{HF} = 16.7, 11.9 Hz, 1H), 2.93 – 2.64 (m, 4H), 1.59 (s, 1H, NH). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 139.5, 136.1, 128.7, 128.4, 126.5, 126.2, 124.1, 122.5, 120.3, 119.2, 111.4, 109.2, 56.1 (dd, J_{CF} = 23.2, 23.2 Hz), 49.0, 36.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -80.8 (t, *J* = 10.7 Hz, 3F), -115.7, -120.5 (ABq, *J* = 277.1 Hz, 2F), -124.2, -125.2

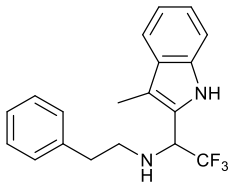
(ABq, J = 289.7 Hz, 2F). **IR** (film) $\tilde{\nu}$: 3418, 3061, 3030, 2929, 2855, 1457, 1345, 1223, 1188, 1110 cm^{-1}. **HRMS** (EI) m/z calcd for $C_{20}H_{17}N_2F_7$ $[M]^+$ 418.1280, found: 418.1283.



2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-1-(1*H*-indol-3-yl)-*N*-(2-phenylethyl)heptan-1-amine (**2s**)

The compound was synthesized according to the general procedure starting with 70.1 mg of **1s** and purified using 10-30% MTBE /hexanes solvent system. Product was isolated as colorless waxy oil (53.4 mg, 63%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.63-7.57 (m, 1H), 7.38-7.33 (m, 1H), 7.25-7.19 (m, 3H), 7.19-7.10 (m, 2H), 7.10-7.04 (m, 3H), 4.62 (dd, J_{HF} = 16.5, 12.0 Hz, 1H), 2.94-2.62 (m, 4H), 1.60 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ139.5, 136.1, 128.7, 128.4, 126.5, 126.2, 124.2, 122.6, 120.3, 119.2, 111.4, 109.3, 56.4 (dd, J_{CF} = 24.8, 21.5 Hz), 49.0, 36.3. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -80.8 (t, J = 10.0 Hz, 3F), -115.0, -119.7 (ABq, J = 277.2 Hz, 2F), -120.4 (m, 2F), -121.9 (m, 2F), -122.7 (m, 2F), -126,1 (m, 2F). **IR** (film) $\tilde{\nu}$: 3418, 3062, 3030, 2930, 2856, 1457, 1361, 1237, 1145 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{18}N_2F_{13}$ $[M+H]^+$ 569.1262, found: 569.1244.

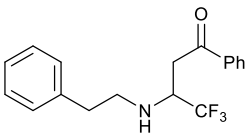
Synthesis of functionalized amines 5, 7, 9, 11, 14 and 16-18 (from Table 2 in main text)



2,2,2-trifluoro-1-(3-methyl-1*H*-indol-2-yl)-*N*-(2-phenylethyl)ethanamine (**5**)

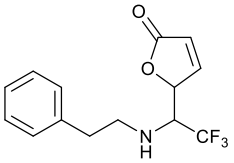
Reaction performed according to the general procedure synthesis of functionalized amines **2a-s**. To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (32.6 mg, 0.15 mmol). The reaction mixture was stirred at RT until it cleared (15 minutes) and then was cooled to 0 °C. TFA (44.5 mg, 0.39 mmol, 2.6 equiv.) and 3-methylindole (59.0 mg, 0.45 mmol, 3 equiv.) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted with ether (3x5 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by FCC (50-100% toluene/hexanes). Product was isolated as colourless waxy oil (37.2 mg, 75%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 (br, 1H, NH_{Het}), 7.58-7.54 (m, 1H), 7.33-7.24 (m, 4H), 7.24-7.18 (m, 1H), 7.18-7.09 (m, 3H), 4.56 (q, J_{HF} = 7.0 Hz, 1H), 2.92-2.85 (m, 1H), 2.83-2.69 (m, 3H), 2.30 (s, 3H), 1.69 (br, 1H, NH). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.2, 135.5, 128.7, 128.6, 128.5, 126.5, 125.5, 125.0 (q, J_{CF} = 280.2 Hz), 122.6, 119.2, 118.8, 112.4, 111.0, 56.6 (q, J_{CF} = 29.8 Hz), 48.3, 36.1, 8.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -

74.0 (s, 3F). **IR** (film) $\tilde{\nu}$: 3416, 3060, 3029, 2924, 2858, 1456, 1267, 1172, 1143, 1119 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{18}N_2F_3$ $[M-H]^-$ 331.1422, found: 331.1429.



4,4,4-trifluoro-1-phenyl-3-[(2-phenylethyl)amino]butan-1-one (**7**)

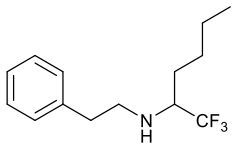
Reaction performed according to the literature procedure.[19] To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (32.6 mg, 0.15 mmol). The reaction mixture was stirred at RT until it cleared (45 minutes) and then was cooled to -65 °C. Acetophenone sillyl enol ether (33.8 µl, 31.7 mg, 0.165 mmol, 1.1 equiv.) and then boron trifluoride diethyl etherate (9.3 µl, 10.6 mg, 0.075 mmol, 0.5 equiv.) was added (the reaction mixture significantly heated up after addition of Lewis acid). The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted twice with ether (3x5 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by FCC (0-15% MTBE/hexanes). Product was isolated as yellowish oil (35.0 mg, 73%). The reaction was also prepared on 5.0 mmol scale of starting amide (scaled up 33 times), quantity of used reagents: $Cp_2Zr(H)Cl$ (1.68 g, 6.5 mmol, 1.3 equiv.); THF (33 mL); amide **1f** (1.09 g, 5.0 mmol); acetophenone sillyl enol ether (**5**) (1.13 mL, 5.5 mmol, 1.1 equiv.); boron trifluoride diethyl etherate (0.31 mL, 2.5 mmol, 0.5 equiv.). A reaction time and temperature were crucial factors in this case and the reaction mixture should be stirring for 16 h after a warm up to room temperature to give similar yield (1.02 g, 63%). **^{1}H NMR** (500 MHz, C_6D_6) δ 7.63-7.57 (m, 2H), 7.14 – 7.06 (m, 3H), 7.05 – 6.95 (m, 5H), 3.90-3.80 (m, 1H) 2.98-2.84 (m, 2H), 2.79 (dd, *J* = 17.2, 3.4 Hz, 1H), 2.69 (dd, *J* = 17.2, 9.1 Hz, 1H), 2.53 (t, *J* = 7.2 Hz, 2H), 0.93 (br, 1H, NH). **^{13}C NMR** (125 MHz, C_6D_6) δ 195.2, 139.9, 137.0, 133.2, 129.0, 128.7, 128.3, 128.0, 127.6 (q, J_{CF} = 282.0 Hz), 126.4, 56.3 (q, J_{CF} = 28.0 Hz), 49.8, 38.5, 37.0. **^{19}F NMR** (470 MHz, C_6D_6) δ -74.7 (d, J_{FH} = 7.7 Hz, 3F). **IR** (film) $\tilde{\nu}$: 3356, 3062, 3029, 2925, 2858, 1689, 1266, 1143, 1119 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{18}H_{19}NOF_3$ $[M+H]^+$ 322.1419, found: 322.1407.



5-{2,2,2-trifluoro-1-[(2-phenylethyl)amino]ethyl}furan-2(5*H*)-one (**9**)

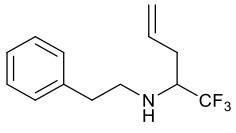
Reaction performed according to the literature procedure.[19] To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (32.6 mg, 0.15 mmol). The reaction mixture was stirred at rt until it cleared (45 minutes) and then was cooled to -65 °C. Trimethylsilyloxyfuran (28.0 µl, 26.0 mg, 0.165 mmol, 1.1 equiv.) and then boron trifluoride diethyl etherate (9.3 µl, 10.6 mg, 0.075 mmol, 0.5 equiv.) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted with ether

(3x5 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by FCC (30% MTBE/hexanes). Product was isolated as yellow oil mixture of unseparable diastereoisomers (dr 1.4:1 based on ^{1}H NMR) (25.2 mg, 59%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ signals of both diastereoisomers: 7.34-7.12 (m, 10.5H), 3.21-3.11 (m, 2H), 3.00-2.93 (m, 1.4H), 2.91-2.83(m, 1H), 2.78-2.67 (m, 2.4H); major diastereoisomer (selected signals): 6.18 (dd, J = 5.8, 1.9 Hz, 1H), 5.25-5.22 (m, 1H), 3.58 (qd, J_{HF} = 7.6 Hz, J = 4.4 Hz, 1H); minor diastereoisomer (selected signals): 6.13 (dd, J = 5.7, 2.1 Hz, 0.7H), 5.22-5.19 (m, 0.7H), 3.92-3.82 (m, 0.7H), 3.31(qd, J_{HF} = 7.4 Hz, J = 3.2 Hz, 0.7H). **^{13}C NMR** (125 MHz, $CDCl_3$) major diastereoisomer: δ 171.6, 151.5, 138.9, 128.6, 128.6, 126.4, 125.1 (q, J_{CF} = 281.6 Hz), 124.3, 80.2, 61.3 (q, J_{CF} = 27.6 Hz), 50.4, 36.7; minor diastereoisomer: δ 172.2, 152.5, 139.0, 128.7, 128.5, 126.4, 125.2 (q, J_{CF} = 278.9 Hz), 123.1, 79.8, 60.8 (q, J_{CF} = 27.9 Hz), 50.0, 36.8. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -72.4 (d, J_{FH} = 7.4 Hz, 2.1F), -72.6 (d, J_{FH} = 7.6 Hz, 3F). **IR** (film) $\tilde{\nu}$: 3352, 3087, 3063, 3029, 2926, 2856, 1764, 1667, 1455, 1362, 1262, 1156, 1129 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{14}H_{13}NO_2F_3$ $[M-H]^-$ 284.0898, found: 284.0895.



1,1,1-trifluoro-*N*-(2-phenylethyl)hexan-2-amine (**11**)

To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (32.6 mg, 0.15 mmol). The reaction mixture was stirred at RT until it cleared (45 minutes) and then was cooled to -65 °C. *n*-BuLi (180 µl, 0.45 mmol, 3.0 equiv., 2.5M in hexanes) was dropped. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The brown sluggish reaction mixture was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted twice with ether (3x5 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by FCC (0-15% MTBE/hexanes). Product was isolated as pale yellow oil (17.8 mg, 46%). **^{1}H NMR** (600 MHz, C_6D_6) δ 7.15-7.11 (m, 2H), 7.08-7.00 (m, 3H), 2.97-2.90 (m, 1H), 2.71-2.58 (m, 2H), 2.50 (t, J = 7.0 Hz, 2H), 1.50 - 1.41 (m, 1H), 1.18-1.08 (m, 2H), 1.08 - 0.92 (m, 3H), 0.75 (t, J = 7.1 Hz, 3H), 0.66 (br, 1H, NH). **^{13}C NMR** (150 MHz, C_6D_6) δ 140.1, 129.0, 128.7, 127.9 (q, J_{CF} = 283.2 Hz), 126.5, 59.8 (q, J_{CF} = 26.7 Hz), 49.7, 37.3, 28.8, 27.9, 22.7, 14.0. **^{19}F NMR** (470 MHz, C_6D_6) δ -74.8 (d, J_{FH} = 7.5 Hz, 3F). **IR** (film) $\tilde{\nu}$: 3350, 3062, 3029, 2959, 2931, 2872, 2705, 2442, 1723, 1456, 1270, 1176, 1149, 1103 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{14}H_{21}NF_3$ $[M+H]^+$ 260.1626, found: 260.1614.



1,1,1-trifluoro-*N*-(2-phenylethyl)pent-4-en-2-amine (**14**)

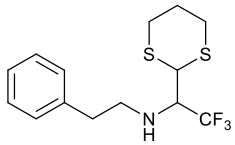
Product was obtained by addition of organozinc or organomagnesium nucleophiles as follows:

To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (32.6 mg, 0.15 mmol). The reaction mixture was stirred at RT until it cleared (45 minutes).

In the case of addition of organozinc nucleophile, the mixture was cooled to 0 °C. Then allyl bromide (39.0µl, 54.4 mg, 0.45 mmol, 3.0 equiv) was dropped and zinc dust (34.3 mg, 0.525 mmol, 3.5 equiv., <10 µm) was added. The reaction mixture was maintained in this temperature for 10 minutes and then allowed to warm up to room temperature and stirred for 16 h.

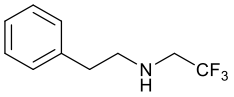
In the case of addition of organomagnesium nucleophile, the mixture was cooled to -65 °C. Then allylmagnesium bromide (600 µl, 0.6 mmol, 4.0 equiv., 1.0M in Et_2O) was dropped. The reaction mixture was maintained in this temperature for 10 minutes and then allowed to slowly warm up to room temperature and stirred for 16 h.

Both reaction mixtures was quenched and purified in the same way. The reaction mixture (organozinc - green and sluggish, organomagnesium - pale yellow and clear) was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted with ether (3x5 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by FCC (15% MTBE/hexanes). Product was isolated as yellow oil (organozinc - 24.5 mg, 67%, organomagnesium - 21.2 mg, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 7.25-7.16 (m, 3H), 5.74-5.59 (m, 1H), 5.09-5.05 (m, 1H), 5.05-5.01 (m, 1H), 3.15-3.07 (m, 1H), 3.07-2.98 (m, 1H), 2.96-2.87 (m, 1H), 2.86-2.70 (m, 2H), 2.52-2.38 (m, 1H), 2.25-2.12 (m, 1H), 1.29 (br, 1H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.4, 132.7, 128.7, 128.5, 126.6 (q, J_{CF} = 282.0 Hz), 126.3, 118.9, 59.2 (q, J_{CF} = 27.2 Hz), 49.8, 36.5, 33.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.9 (s, 3F). **IR** (film) $\tilde{\nu}$: 3348, 3084, 3066, 3029, 2927, 2856, 1495, 1480, 1452, 1442, 1381, 1273, 1145 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{13}H_{17}NF_3$ $[M+H]^+$ 244.1313, found: 244.1306.



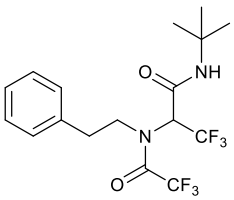
1-(1,3-dithian-2-yl)-2,2,2-trifluoro-*N*-(2-phenylethyl)ethanamine (**16**)

To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (32.6 mg, 0.15 mmol). The reaction mixture was stirred at RT until it cleared (45 minutes) and then was cooled to 0 °C. In another Schlenk tube, to cooled to -30 °C solution of 1,3-dithiane (39.7 mg, 0.33 mmol, 2.2 equiv.) in dry THF (3 mL), *n*-BuLi (120µl, 0.3 mmol, 2.0 equiv., 2.5M in hexanes) was dropped and stirred for 2 h. Next, the solution of crude imine was dropped, the reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted with ether (3x5 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by FCC (0-15% MTBE/hexanes). Product was isolated as a colorless oil (24.7 mg, 51%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.35 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 4.47 (d, J = 3.5 Hz, 1H), 3.39 (dq, *J* = 7.4, 3.6 Hz, 1H), 3.20 – 3.01 (m, 2H), 2.96 (ddd, *J* = 14.0, 11.4, 2.7 Hz, 1H), 2.91 – 2.79 (m, 5H), 2.22 (br, 1H, NH), 2.13 – 2.01 (m, 1H), 1.96-1.78 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.3, 128.7, 128.4, 126.2, 125.3 (q, J_{CF} = 283.7 Hz), 64.1 (q, J_{CF} = 28.0 Hz), 50.9, 47.7, 36.7, 30.9, 30.2, 25.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.0 (s, 3F). **IR** (film) $\tilde{\nu}$: 3337, 3061, 3027, 2934, 2903, 2857, 1476, 1422, 1362, 1256, 1153, 1131 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{14}H_{19}NS_2F_3$ $[M+H]^+$ 322.0911, found: 322.0902.



2,2,2-trifluoro-*N*-(2-phenylethyl)ethanamine (**17**)

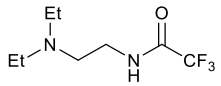
To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (32.6 mg, 0.15 mmol). The reaction mixture was stirred at RT until it cleared (45 minutes) and then was cooled to 0 °C. TFA (68 mg, 0.6 mmol, 4.0 equiv.) was dropped and then borane tetrahydrofuran complex (225 µl, 0.225 mmol, 1.5 equiv., 1M in THF) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted with ether (3x5 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by FCC (15% MTBE/hexanes). Product was isolated as colorless oil (18.5 mg, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 - 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 3.19 (q, *J* = 9.4 Hz, 2H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 1.42 (br, 1H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.3, 128.7. 128.6, 126.4, 125.5 (q, J_{CF} = 277.8 Hz), 50.6, 50.5 (q, J_{CF} = 31.1 Hz), 36.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.7 (s, 3F). **IR** (film) $\tilde{\nu}$: 3395, 2956, 2920, 2851, 1728, 1601, 1460, 1376, 1262, 1139, 1089, 1026 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{10}H_{13}NF_3$ $[M+H]^+$ 204.1000, found: 204.0997.



N-tert-butyl-3,3,3-trifluoro-N^2-(2-phenylethyl)-N^2-(trifluoroacetyl)alaninamide (**18**)

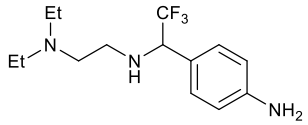
To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (32.6 mg, 0.15 mmol). The reaction mixture was stirred at RT until it cleared (45 minutes) and then was cooled to -70 °C. TFA (68 mg, 0.6 mmol, 4.0 equiv.) was dropped and then *tert*-butyl isocyanide (21.5 µl, 15.8 mg, 0.19 mmol, 1.25 equiv.) was added. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$ and diethyl ether (5 mL) was added. The aqueous layer was extracted twice with ether (3x5 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by FCC (0-15% MTBE/hexanes). Product was isolated as colorless waxy oil (34.1 mg, 57%). Major rotamer (selected signals): **^{1}H NMR** (500 MHz, toluene-d_8) δ 5.82 (br, 1H), 5.40 (q, *J* = 7.6 Hz, 1H), 4.00 – 3.88 (m, 1H), 3.79 -3.65 (m, 1H), 3.05 -2.95 (m, 1H), 2.88 – 2.75 (m, 1H), 1.12 (s, 9H); **^{13}C NMR** (125 MHz, toluene-d_8) δ 160.6, 159.3 (q, *J* = 36.9 Hz), 138.2, 127.2, 123.7 (q, *J* = 276.1 Hz), 117.0 (q, *J* = 287.1 Hz), 59.1 (q, *J* = 30.8 Hz), 52.4, 48.7, 36.4, 28.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -66.8, -68.6. Minor rotamer (selected signals): **^{1}H NMR** (500 MHz, toluene-d_8) δ 5.25-5.10 (m, 0.3H), 4.74-4.56 (m, 0.3H), 1.02 (s, 3H); **^{13}C NMR** (125 MHz, toluene-d_8) δ 61.1 (q, *J* = 30.8 Hz), 49.4, 33.5, 30.3; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -67.0, -67.4. **IR** (film) $\tilde{\nu}$: 3363, 2974, 1683, 1538, 1456, 1368, 1210, 1145, 1126 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{17}H_{20}N_2O_2F_6Na$ $[M+Na]^+$ 421.1327, found: 421.1312.

Synthesis of trifluoromethyl bioisostere of procainamide 22 (Scheme 2 in main text)



N-[2-(diethylamino)ethyl]-2,2,2-trifluoroacetamide (**20**)

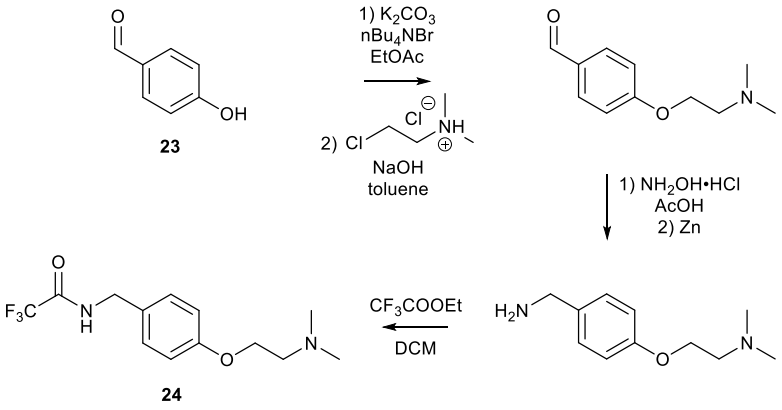
To neat *N*,*N*-diethylethylenediamine (1.12 mL, 8.0 mmol) was added ethyl trifluoroacetate (952 µl, 8.0 mmol, 1.0 equiv.) and a solution was stirred for 3 h at room temperature (full conversion of amine was checked by TLC). The reaction mixture was evaporated and dried on oil pump for 16 h to give pure product as orange oil (1.54 g, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (br, NH, 1H), 3.34 (t, *J* = 5.8 Hz, 2H), 2.59 (t, *J* = 5.9 Hz, 2H), 2.52 (q, *J* = 7.2 Hz, 4H), 0.99 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.9 (q, J_{CF} = 36.7 Hz), 115.9 (q, J_{CF} = 286.0 Hz), 50.4, 46.7, 37.0, 11.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -76.3. **IR** (film) $\tilde{\nu}$: 3319, 2974, 2819, 1712, 1557, 1163 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_8H_{16}N_2OF_3$ $[M+H]^+$ 213.1215, found: 213.1206.



N'-[1-(4-aminophenyl)-2,2,2-trifluoroethyl]-*N*,*N*-diethylethane-1,2-diamine (**22**)

To a suspension of Schwartz's reagent (50.3 mg, 0.195 mmol, 1.3 equiv.) in dry THF (1 mL) at room temperature was added amide (31.8 mg, 0.15 mmol). The reaction mixture was stirred at RT until it cleared (45 minutes) and then was cooled to -70 °C. In another Schlenk tube, to cooled to -70 °C solution of 4-bromo-*N,N*-bistrimethylsilylaniline (130 µl, 146mg, 0.45 mmol, 3.0 equiv.) in dry THF (1 mL), t-BuLi (529 µl, 0.9 mmol, 6.0 equiv., 1.7M in hexanes) was dropped and stirred at this temperature for 1 h. Next, the solution of crude imine was cooled to -70 °C, pale yellow solution of generated organolithium compound was dropped (the mixture changed colour from yellow to orange) and the reaction mixture was stirred at this temperature for 3 h. Next, to the reaction mixture was added TBAF (0.9 mL, 0.9 mmol, 6.0 equiv., 1M in THF) and solution was stirred for 15 minutes. After this time, a previously prepared solution of acetic acid (0.9 mL, 0.9 mmol, 6.0 equiv., 1M in THF) was added and the solution was stirred for additional 15 minutes. Next, a silica gel was added to the solution (ca. 500 mg) and the slurry mixture was evaporated. The residue was purified by FCC (1/5/94% aqueous ammonia/MeOH/DCM). Product was isolated as yellow oil (23.9 mg, 55%). **^{1}H NMR** (500 MHz, toluene-d_8) δ 7.15-7.10 (m, 2H), 6.22-6.18 (m, 2H), 3.91 (q, *J* = 7.6 Hz, 1H), 2.75 (br, 2H, NH_2), 2.51-2.38 (m, 2H), 2.38-2.31 (m, 1H), 2.30-2.18 (m, 5H), 0.85 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (125 MHz, toluene-d_8) δ 147.6, 129.8, 129.2, 126.6 (q, J_{CF} = 280.1 Hz) 114.8, 65.0 (q, J_{CF} = 28.1 Hz), 52.8, 47.2, 45.6, 12.3. The quartet with chemical shift 126.6 ppm was difficult to observation, therefore ^{19}F decoupled ^{13}C spectra was also done and 126.6 (d, J_{CH} = 6.7 Hz) was noticed. **^{19}F NMR** (470 MHz, toluene-d_8) δ -74.4 (d, J_{FH} = 7.6 Hz). **IR** (film) $\tilde{\nu}$: 3317, 3213 2970, 2936, 2874, 2817, 2653, 1626, 1520, 1470, 1261, 1168, 1118 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{14}H_{23}N_3F_3$ $[M+H]^+$ 290.1844, found: 290.1840.

Synthesis of trifluoromethyl bioisostere of itopride 26 (Scheme 2 in main text)



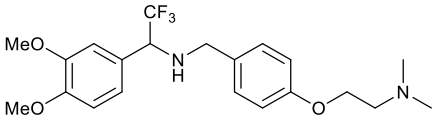
N-{4-[2-(dimethylamino)ethoxy]benzyl}-2,2,2-trifluoroacetamide (**24**)

The compound **24** was synthesized by alkylation of 4-hydroxybenzaldehyde, reductive amination of obtained derivative and subsequent trifluoroacetylation in according to the modified literature procedure.[15] To a solution of the 4-hydroxybenzaldehyde (**23**) (2.44 g, 20.0 mmol) in EtOAc (20 mL) was added potassium carbonate (3.06 g, 22.0 mmol, 1.1 equiv.), tetra-*N*-butylammonium bromide (66.0 mg, 0.2 mmol, 1 mol%) and the solution was refluxed for 5 minutes. In another flask, to a solution of 2-chloro-*N*,*N*-dimethylethylamine hydrochloride in toluene (6 mL) was added water (5 mL). The mixture was stirred vigorously and a solution of 25% aqueous NaOH (7 mL) was added into and stirred until organic phase cleared. Next, organic extract was dropped to the previously prepared boiling reaction mixture and refluxed for 16h. After this time, the reaction mixture was cooled to room temperature, water was added (12 mL) and vigorously stirred for 5 minutes. Next, the organic phase was separated and evaporated. Obtained yellow oily residue (2.7 g) was used to next step without further purification.

To the solution of hydroxylamine hydrochloride (458.6 mg, 6.6 mmol, 1.1 equiv.) in acetic acid (3 mL) cooled to 5 °C was added dropwise a solution of previously obtained alkylated aldehyde (1.16 g, 6.0 mmol) in acetic acid (2 mL). The yellow reaction mixture was stirred at this temperature for 2 h (full conversion of substrate, TLC). Next, a zinc powder (934.0 mg, 14.4 mmol, 2.4 equiv.) was added in portions and reaction mixture was allowed to warm up to room temperature. After 5 minutes, a mixture was turned colourless. After 1 h (full conversion of substrate, TLC) the reaction mixture was evaporated, to the residue was added water (30 mL) and aqueous ammonia (25%) was added dropwise until pH was 9-10 (heating up the mixture during alkalisation). After that, the solution was vigorously stirred for additional 15 minutes and extracted with DCM (8x30 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. Obtained yellow oily residue (1.05 g), was dried on oil pump and used to next step without further purification.

To the solution of crude benzylamine (1.05 g, 5.4 mmol) in DCM (anhydrous) was added ethyl trifluoroacetate (643 µl, 767 mg, 5.4 mmol; 1.0 equiv.) and reaction mixture was heating up to gently reflux (50 °C) for 16 h. After this time, mixture was cooled to room temperature and evaporated. Product was obtained as yellowish oil, which crystallized upon standing in refrigerator (1.25 g, 51%, overall yield after 4 steps). mp 59-60 °C (from DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21-7.16 (m, 2H), 6.93 (br, 1H, NH), 6.90-6.84 (m, 2H), 4.43 (d, *J* = 5.7 Hz, 2H), 4.05 (t, *J* = 5.6 Hz, 2H), 2.75 (t, *J* = 5.6 Hz, 2H), 2.35 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.7, 157.0 (q, J_{CF} = 37.1 Hz), 129.4, 128.2, 115.9 (q, J_{CF} = 37.1 Hz), 115.0, 65.8, 58.1, 45.7, 43.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.8. **IR** (film) $\tilde{\nu}$: 3199, 3040,

2948, 2881, 2828, 2783, 1712, 1513, 1217, 1179 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{13}H_{18}N_2O_2F_3$ $[M+H]^+$ 291.1320, found: 290.1311.

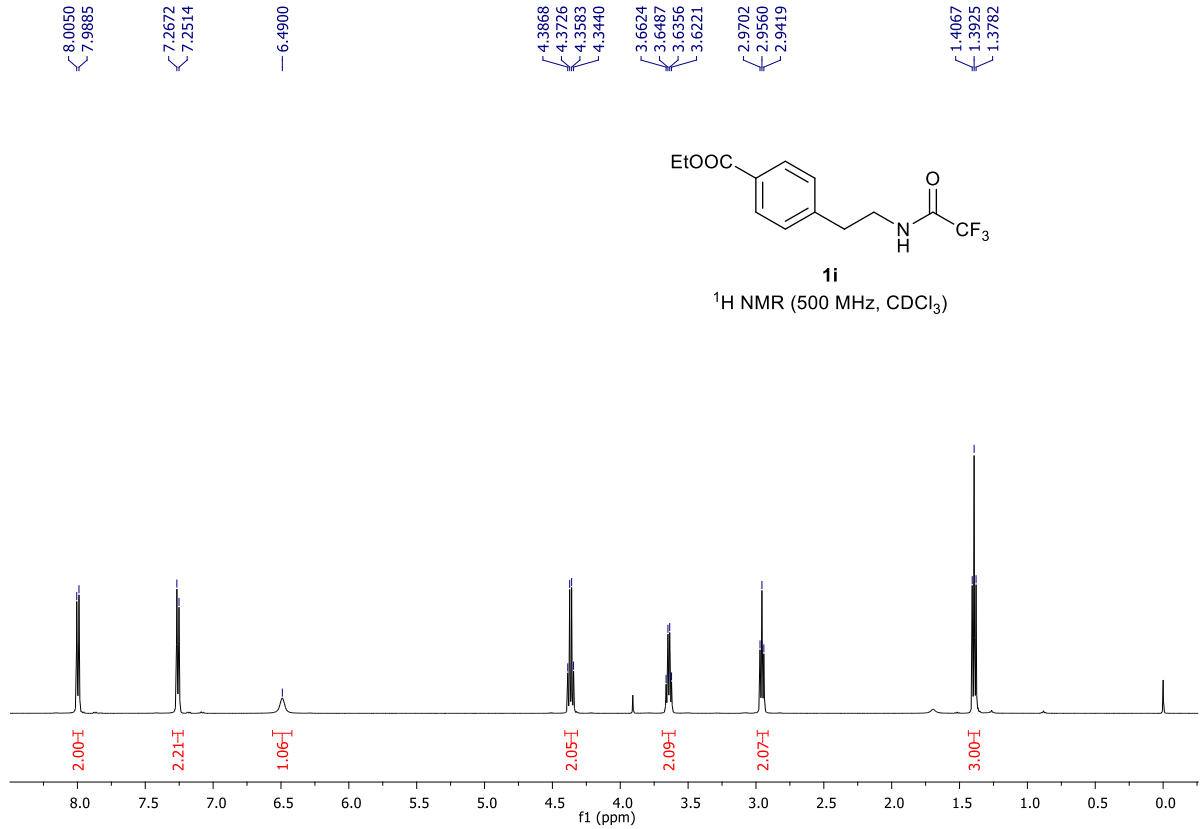


1-(3,4-dimethoxyphenyl)-*N*-{4-[2-(dimethylamino)ethoxy]benzyl}-2,2,2-trifluoroethanamine (**26**)

To a suspension of Schwartz's reagent (100.6 mg, 0.39 mmol, 1.3 equiv.) in dry THF (2 mL) at room temperature was added amide (87.1mg, 0.3 mmol). The reaction mixture was stirred at RT until it cleared (5 minutes) and then was cooled to -70 °C. In another Schlenk tube, to cooled to -70 °C solution of 4-bromo-1,2-dimethoxybenzene (129.5 µl, 195.3 mg, 0.9 mmol, 3.0 equiv.) in dry THF (2 mL), *t*-BuLi (1.06 mL, 1.8 mmol, 6.0 equiv., 1.7M in pentane) was dropped (reaction mixture has changed a colour from colourless to pale yellow) and stirred at this temperature for 1 h. Next, the solution of crude imine was cooled to -70 °C, pale orange solution of generated organolithium compound was dropped (the mixture has changed the colour from yellow to orange) and the reaction mixture was stirred at this temperature for 3 h. The reaction mixture was quenched with saturated $NaHCO_3$ and EtOAc (5 mL) was added. The aqueous layer was extracted with EtOAc (3x10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by FCC (0-5% MeOH/DCM). Product was isolated as a yellow oil (37.9 mg, 31%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18- 7.14 (m, 2H), 6.96- 6.90 (m, 2H), 6.90-6.82 (m, 3H), 4.10-4.02 (t, *J* = 5.7 Hz, 2H + q, *J* = 7.2 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.75, 3.58 (ABq, *J* = 13.3 Hz, 2H), 2.76 (t, *J* = 5.8 Hz, 2H), 2.36 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.0, 149.5, 149.2, 131.3, 129.7, 129.4, 125.5 (q, J_{CF} = 281.1 Hz), 121.4, 114.6, 111.2, 111.0, 65.7, 62.9 (q, J_{CF} = 28.6 Hz), 58.1, 56.0, 55.9, 50.3, 45.7. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.1 (d, J_{FH} = 7.4 Hz). **IR** (film) $\tilde{\nu}$: 2941, 2825, 2723, 1609, 1513, 1465, 1256, 1157, 1029 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{28}N_2O_3F_3$ $[M+H]^+$ 413.2052, found: 413.2050.

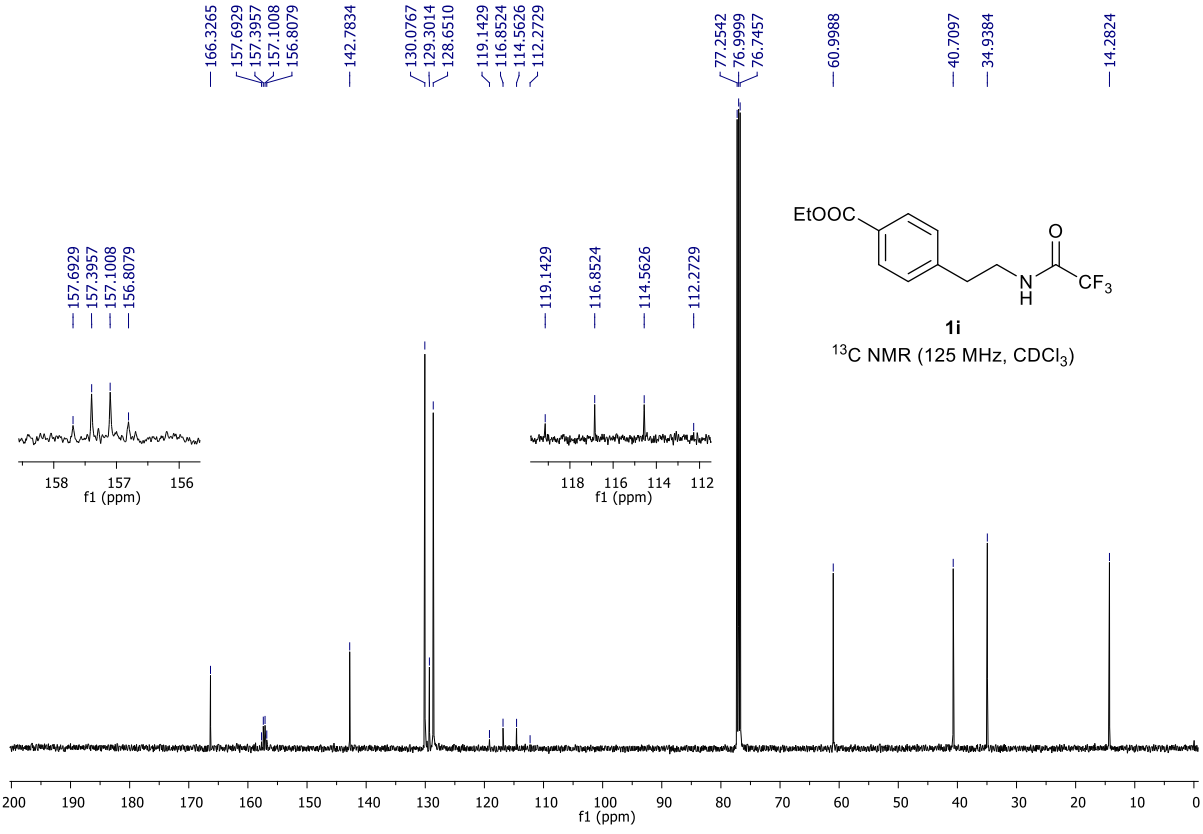
NMR spectra

NMR spectra of starting amides 1i-m and 1o-s



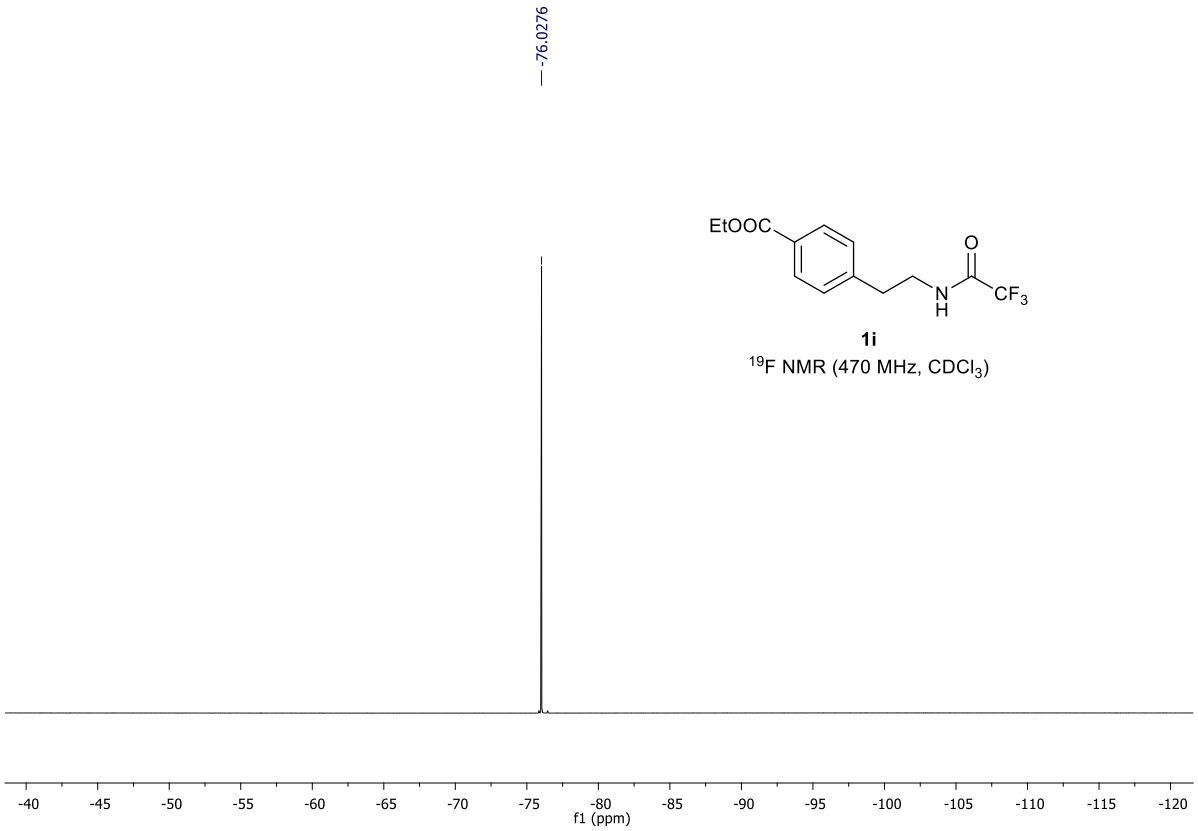
1i

^{1}H NMR (500 MHz, $CDCl_3$)



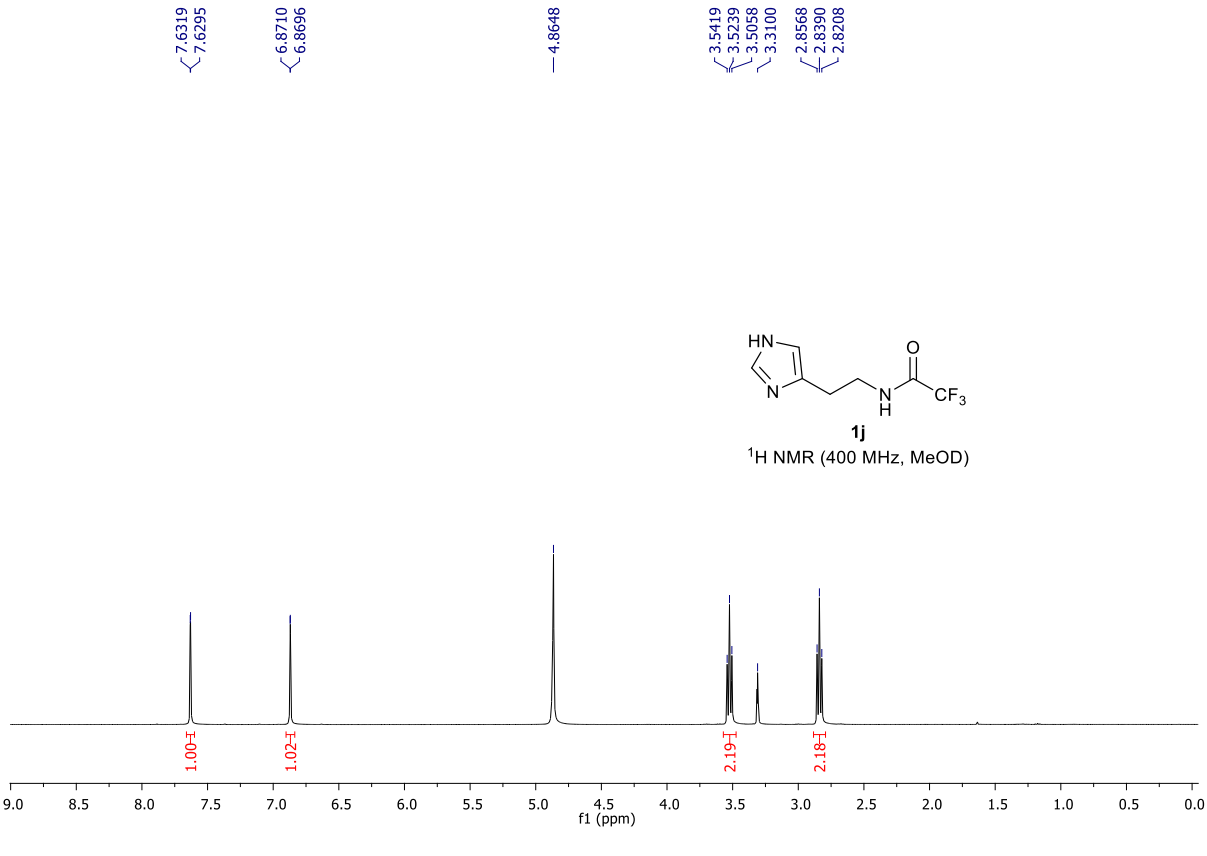
1i

^{13}C NMR (125 MHz, $CDCl_3$)



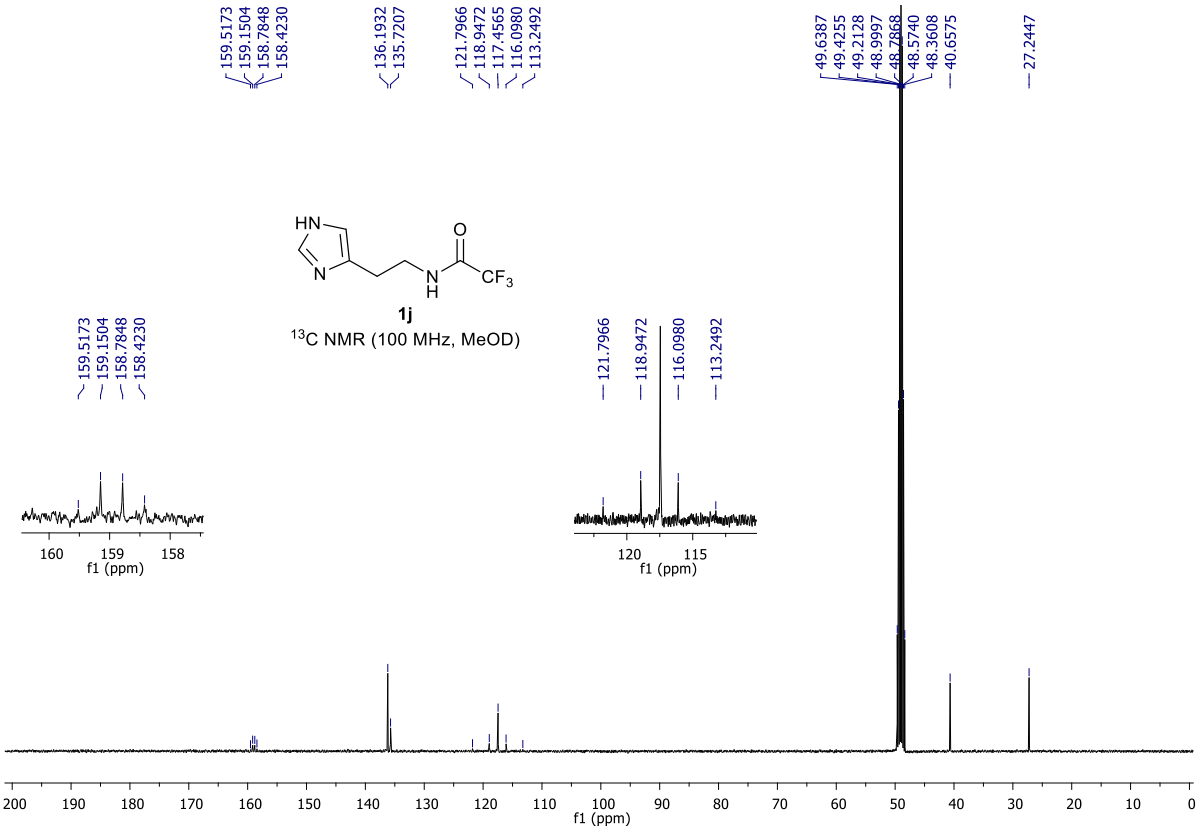
1i

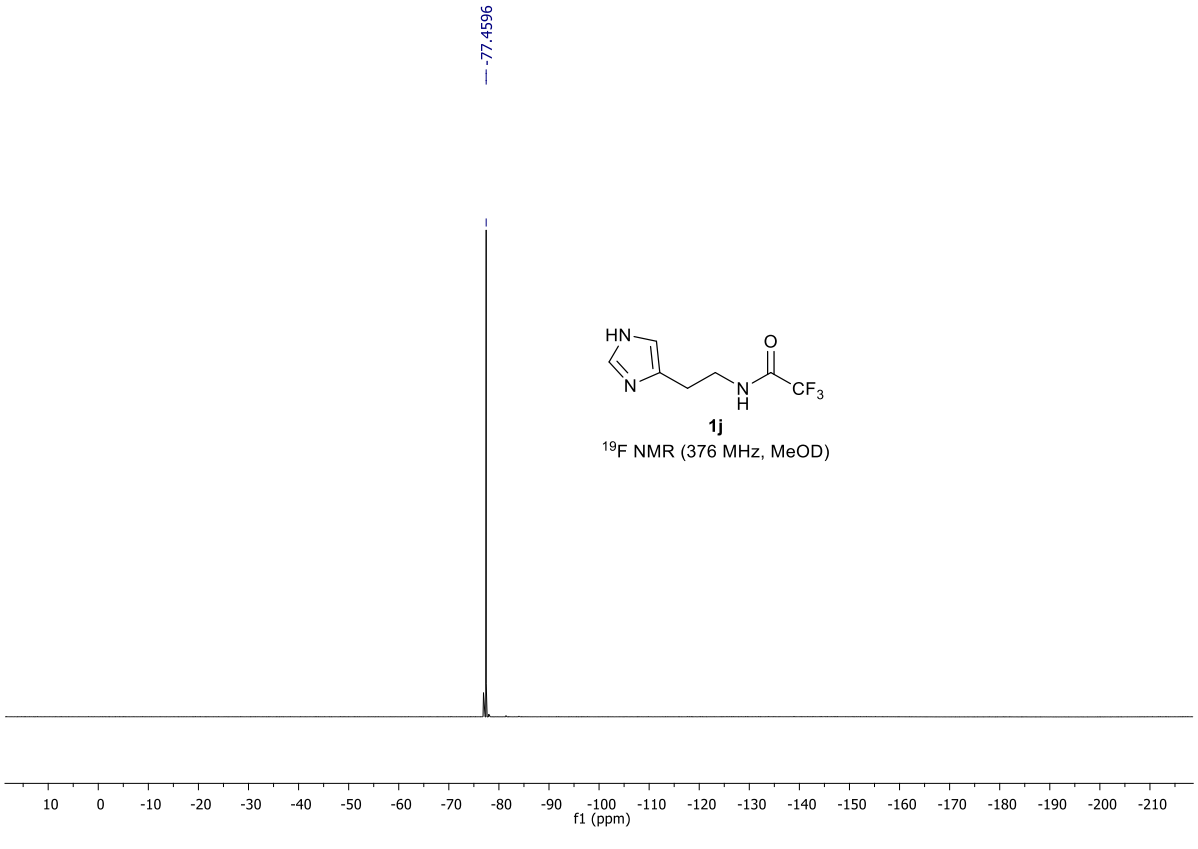
^{19}F NMR (470 MHz, $CDCl_3$)

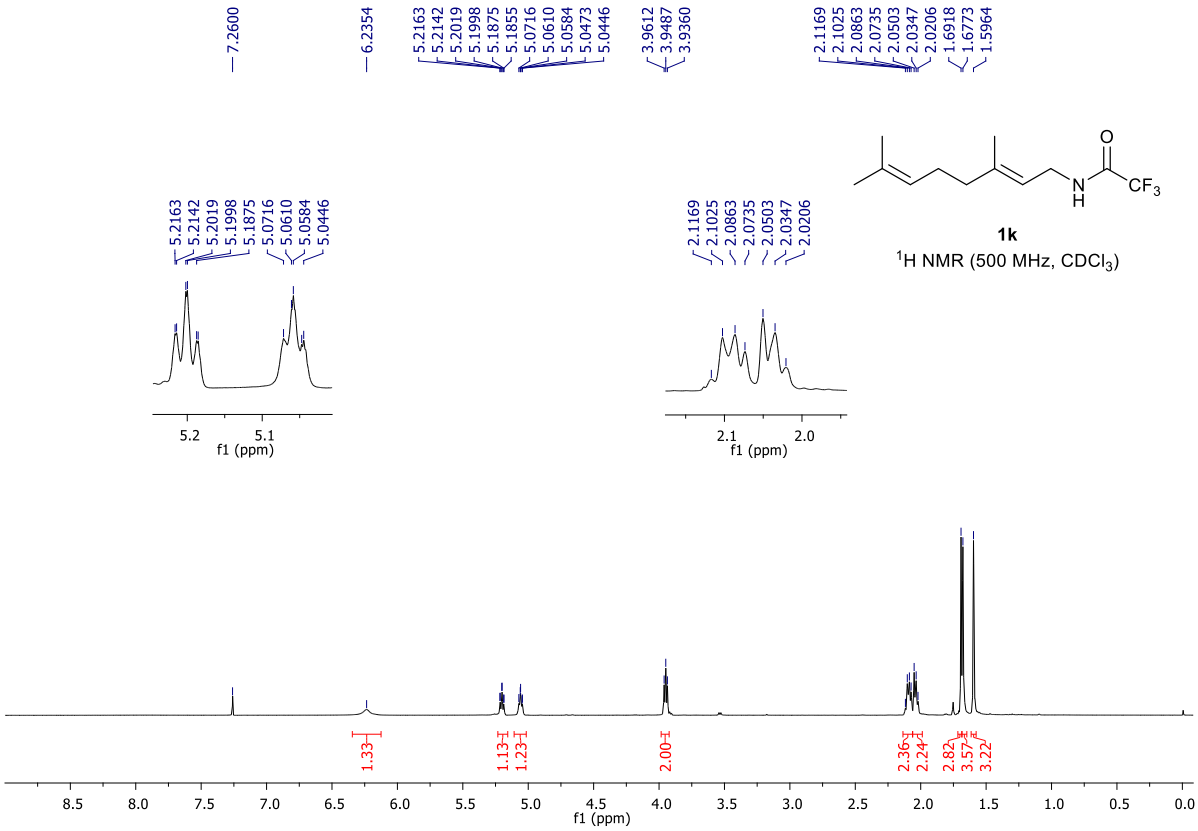


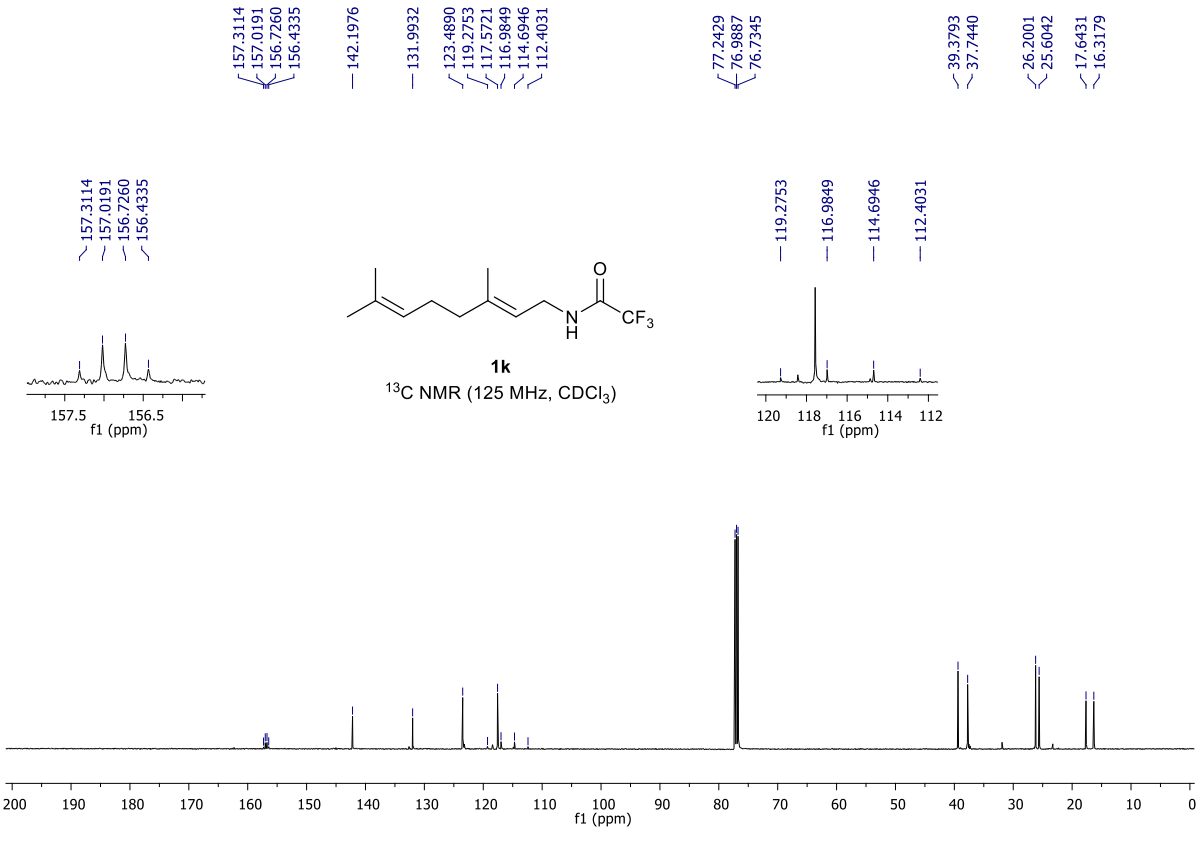
1j

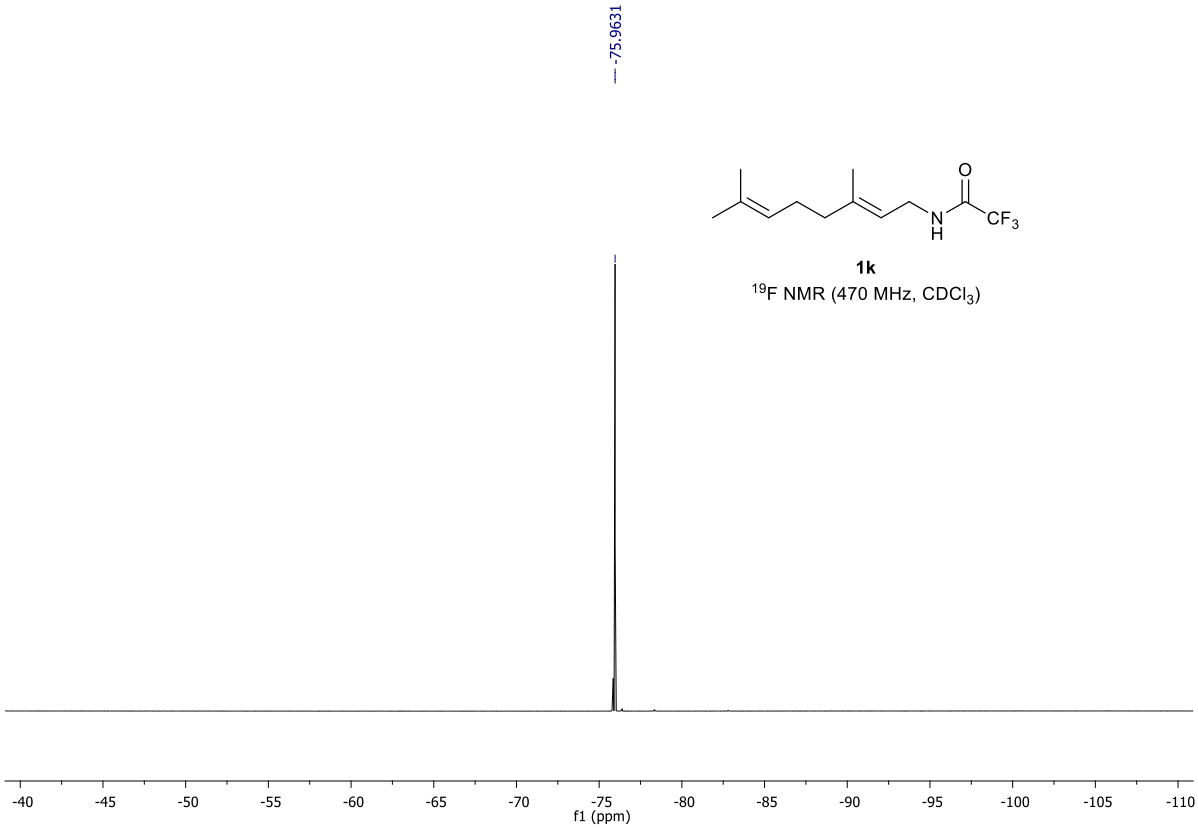
^{1}H NMR (400 MHz, MeOD)


159.5173
159.1504
158.7848
158.4230
136.1932
135.7207
121.7966
118.9472
117.4565
116.0980
113.2492
49.6387
49.4255
49.2128
48.9997
48.7868
48.5740
48.3608
40.6575
27.2447
HN
N
O
N
H
CF3
1j
13C NMR (100 MHz, MeOD)
f1 (ppm)


-77.4596
HN
N
O
N
H
CF3
1j
19F NMR (376 MHz, MeOD)
f1 (ppm)

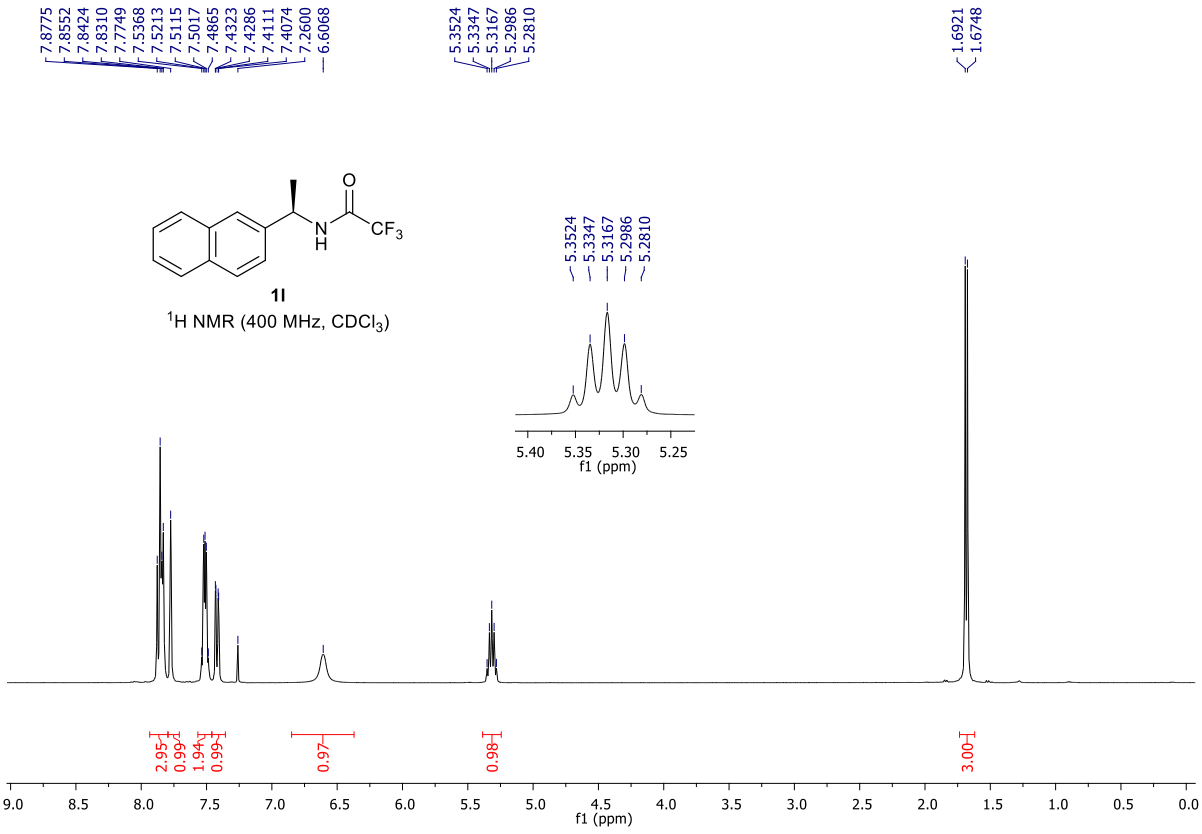

7.2600
6.2354
5.2163
5.2142
5.2019
5.1998
5.1875
5.1855
5.0716
5.0610
5.0584
5.0473
5.0446
3.9612
3.9487
3.9360
2.1169
2.1025
2.0863
2.0735
2.0503
2.0347
2.0206
1.6918
1.6773
1.5964
O
N
H
CF3
1k
1H NMR (500 MHz, CDCl3)
f1 (ppm)
1.33
1.13
1.23
2.00
2.36
2.24
2.82
3.57
3.22


157.3114
157.0191
156.7260
156.4335
142.1976
131.9932
123.4890
119.2753
117.5721
116.9849
114.6946
112.4031
77.2429
76.9887
76.7345
39.3793
37.7440
26.2001
25.6042
17.6431
16.3179
O
N
H
CF3
1k
13C NMR (125 MHz, CDCl3)
f1 (ppm)



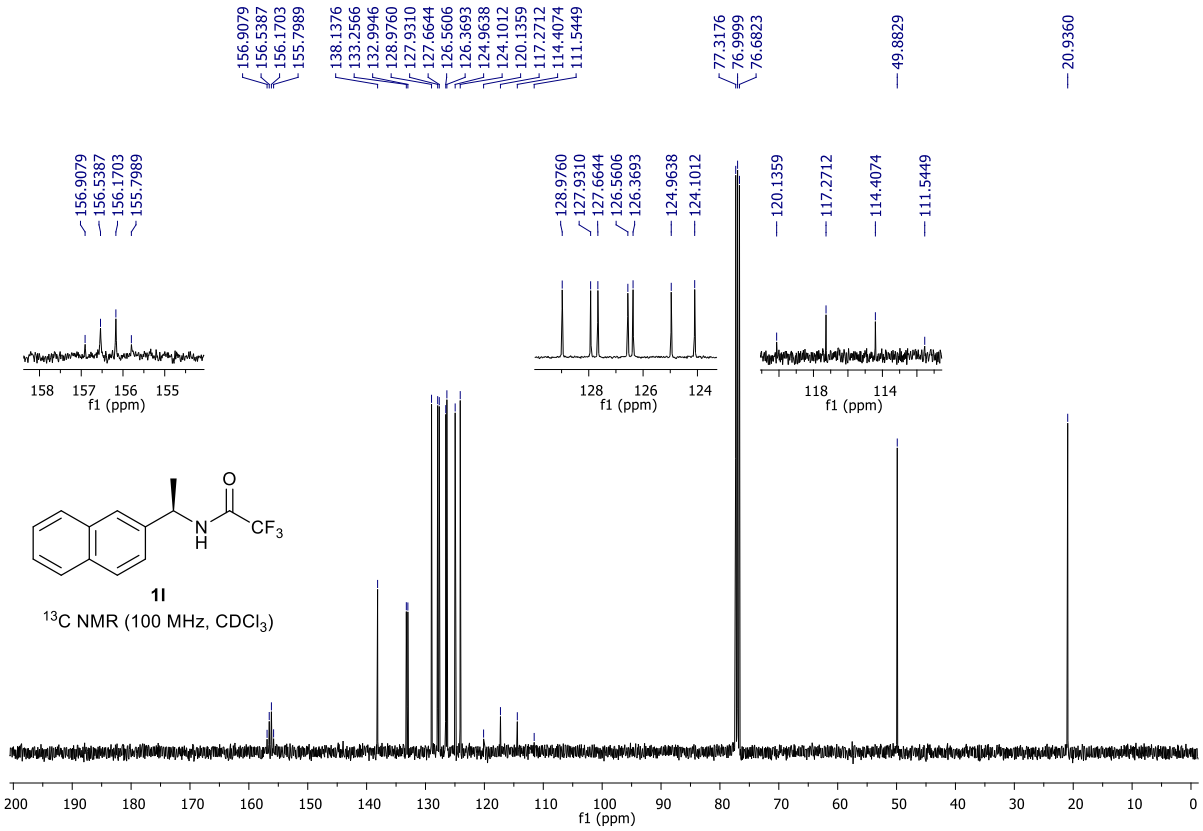
1k

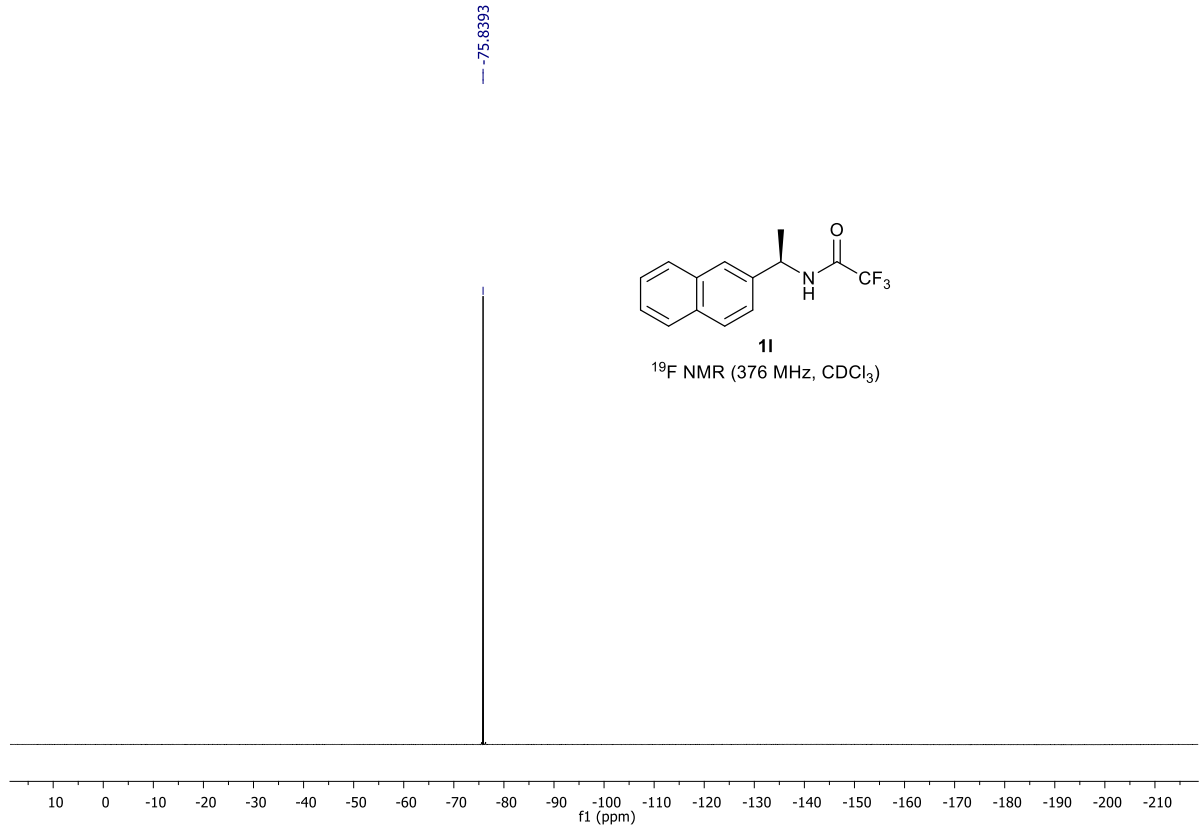
^{19}F NMR (470 MHz, $CDCl_3$)

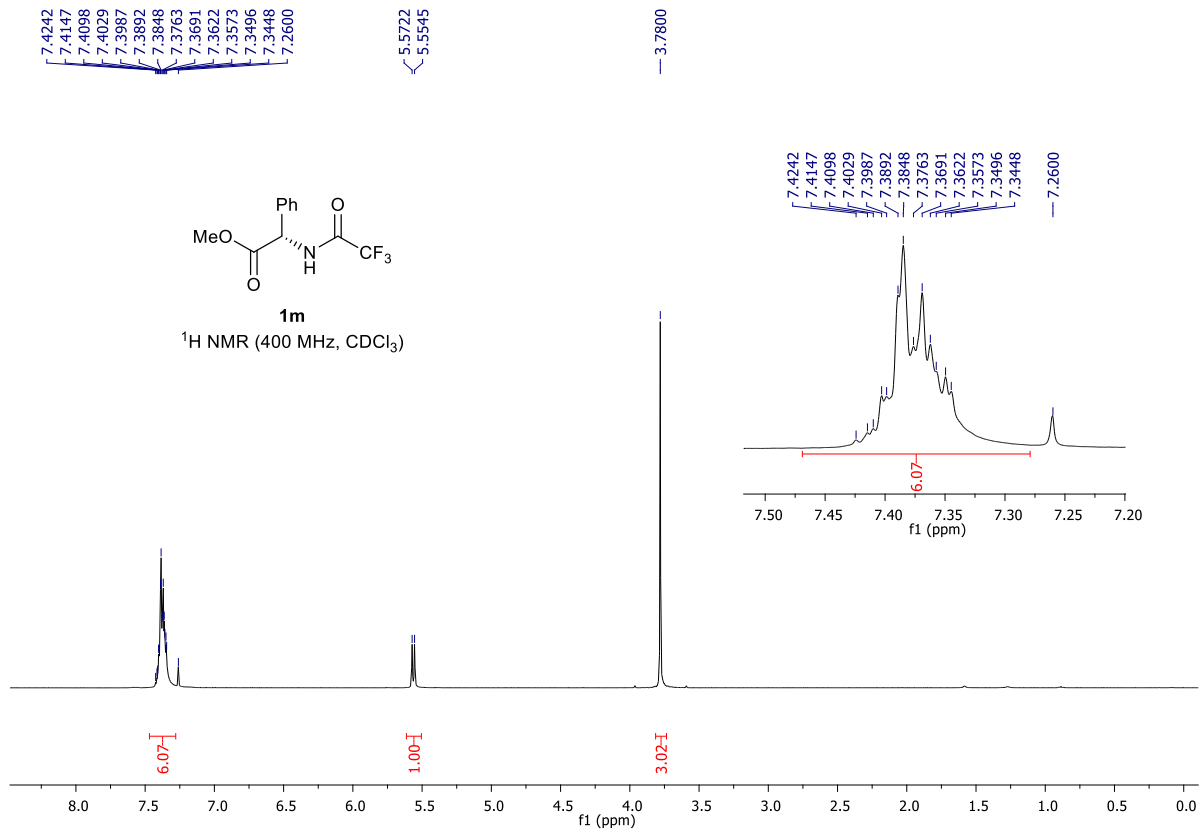


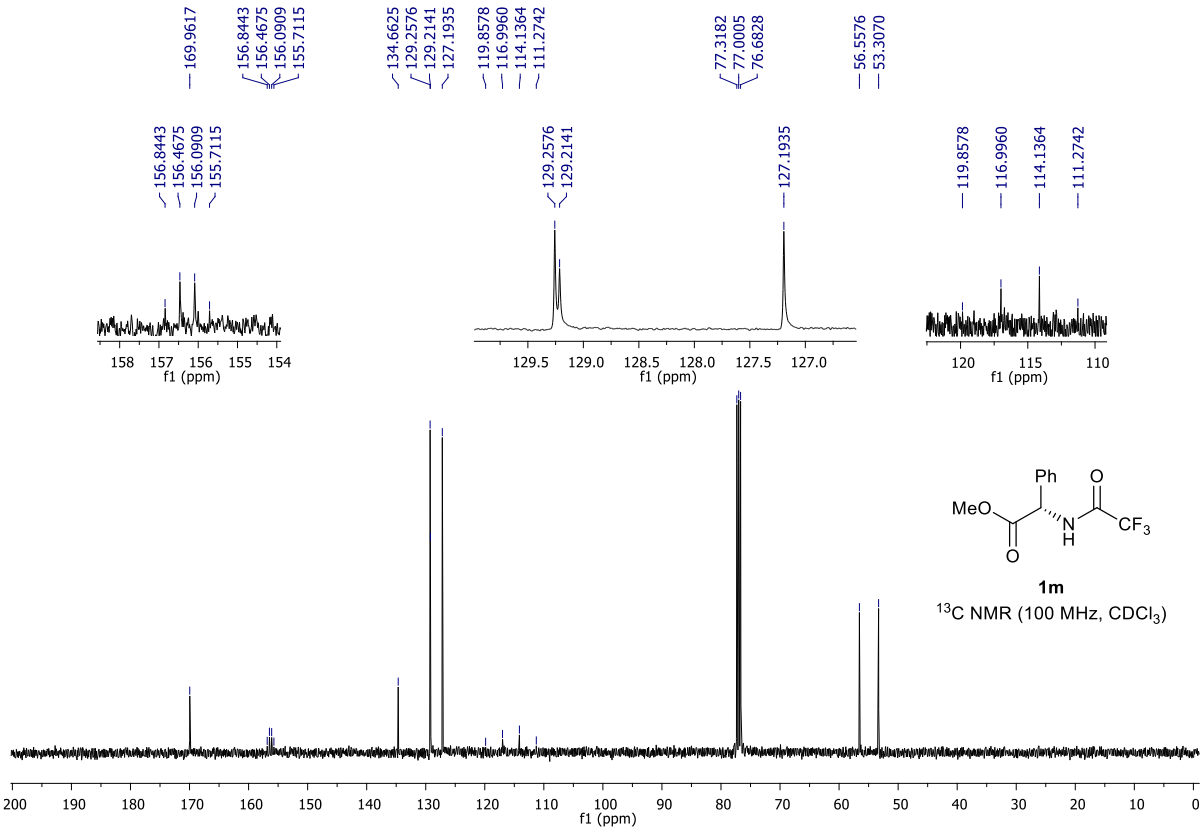
1l

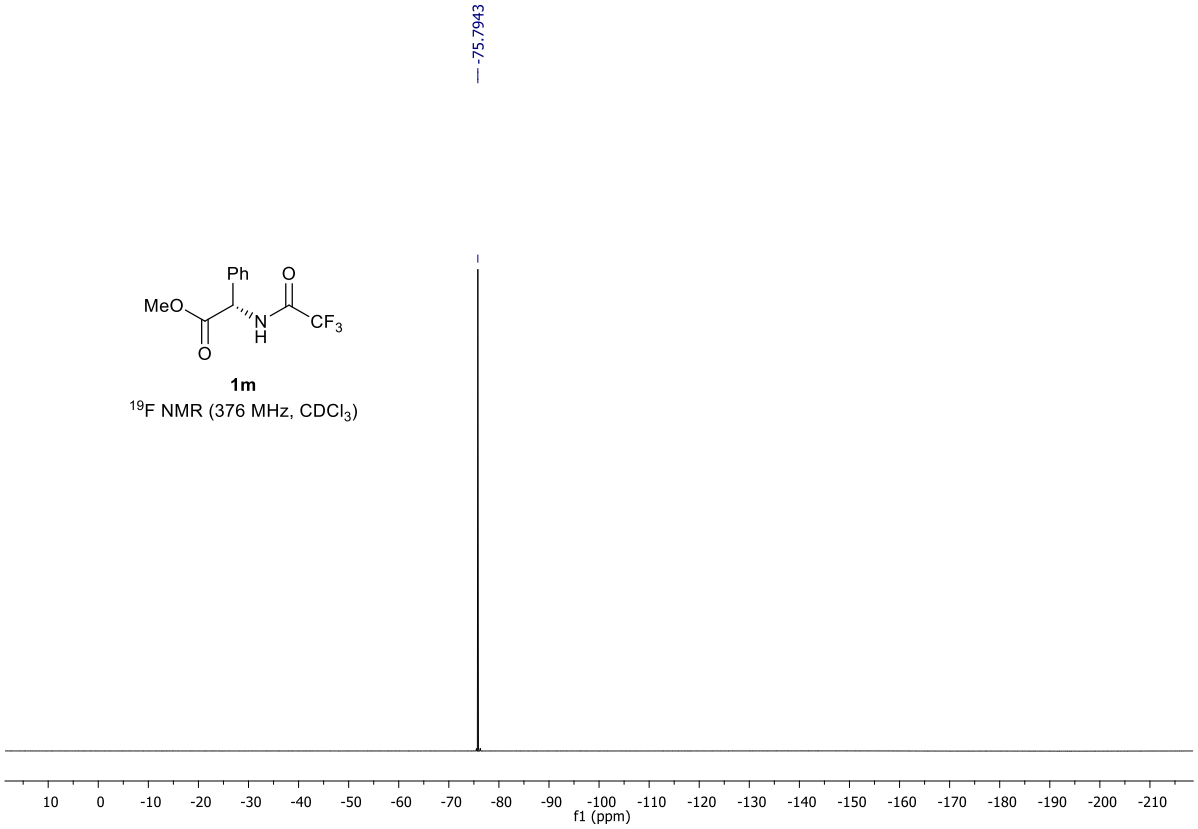
^{1}H NMR (400 MHz, $CDCl_3$)


156.9079
156.5387
156.1703
155.7989
138.1376
133.2566
132.9946
128.9760
127.9310
127.6644
126.5606
126.3693
124.9638
124.1012
120.1359
117.2712
114.4074
111.5449
77.3176
76.9999
76.6823
49.8829
20.9360
f1 (ppm)
O
N
H
CF3
1l
13C NMR (100 MHz, CDCl3)


-75.8393
f1 (ppm)
O
N
H
CF3
1l
19F NMR (376 MHz, CDCl3)

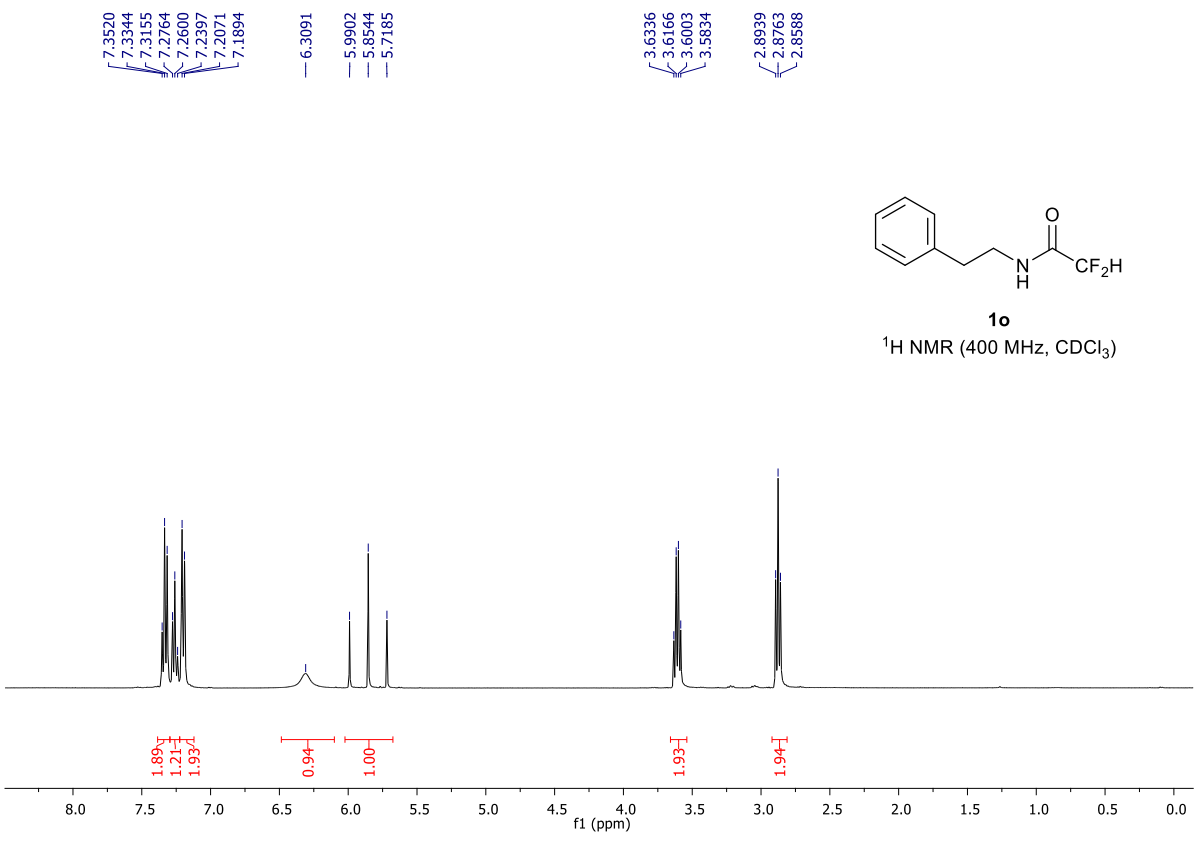

7.4242
7.4147
7.4098
7.4029
7.3987
7.3892
7.3848
7.3763
7.3691
7.3622
7.3573
7.3496
7.3448
7.2600
5.5722
5.5545
3.7800
Ph
O
MeO
N
H
CF3
O
1m
1H NMR (400 MHz, CDCl3)
6.07
1.00
3.02
f1 (ppm)


169.9617
156.8443
156.4675
156.0909
155.7115
134.6625
129.2576
129.2141
127.1935
119.8578
116.9960
114.1364
111.2742
77.3182
77.0005
76.6828
56.5576
53.3070
Ph
O
MeO
N
H
CF3
O
1m
13C NMR (100 MHz, CDCl3)
f1 (ppm)



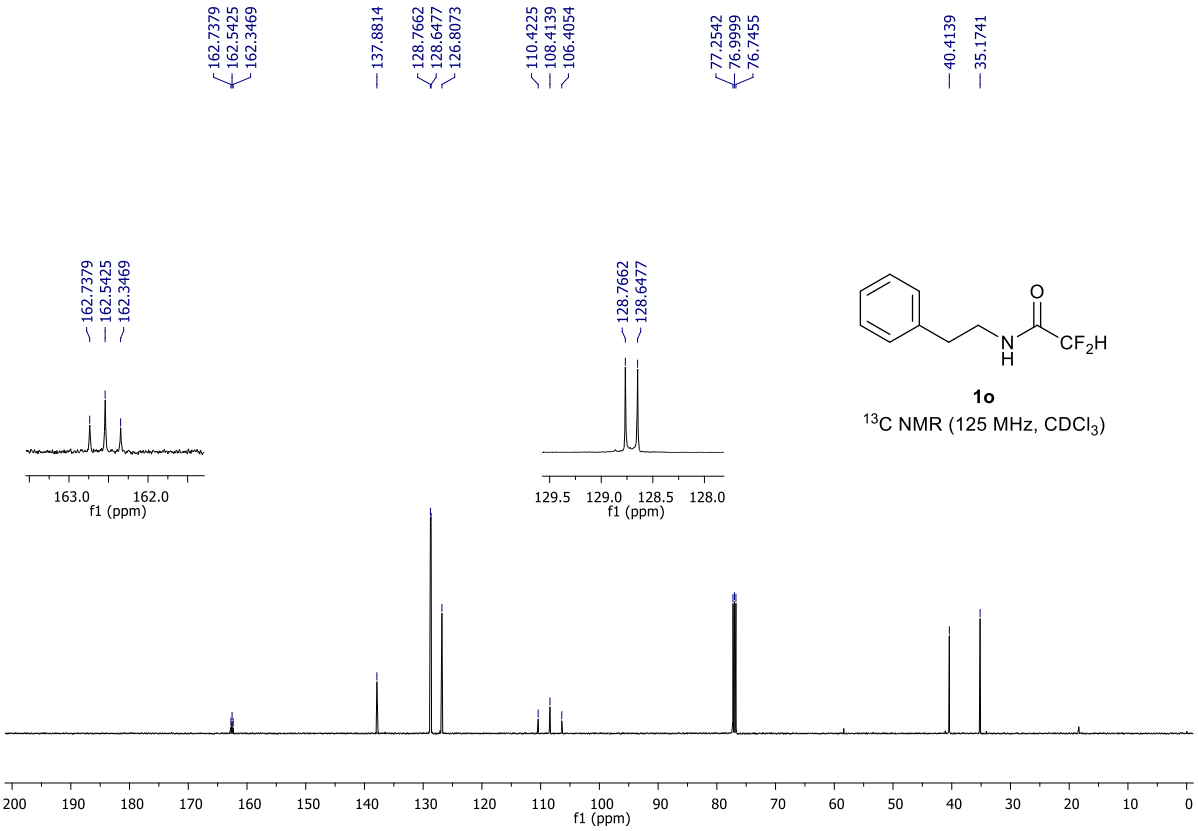
1m

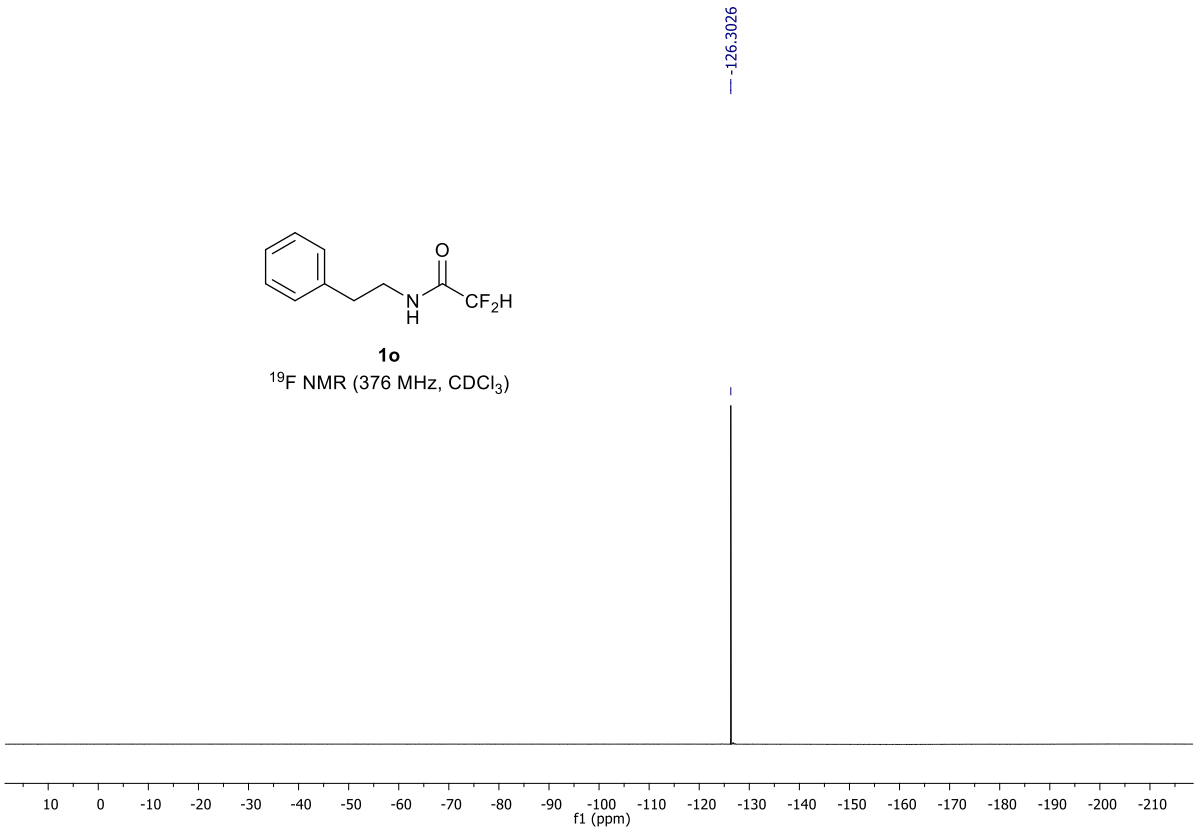
^{19}F NMR (376 MHz, $CDCl_3$)

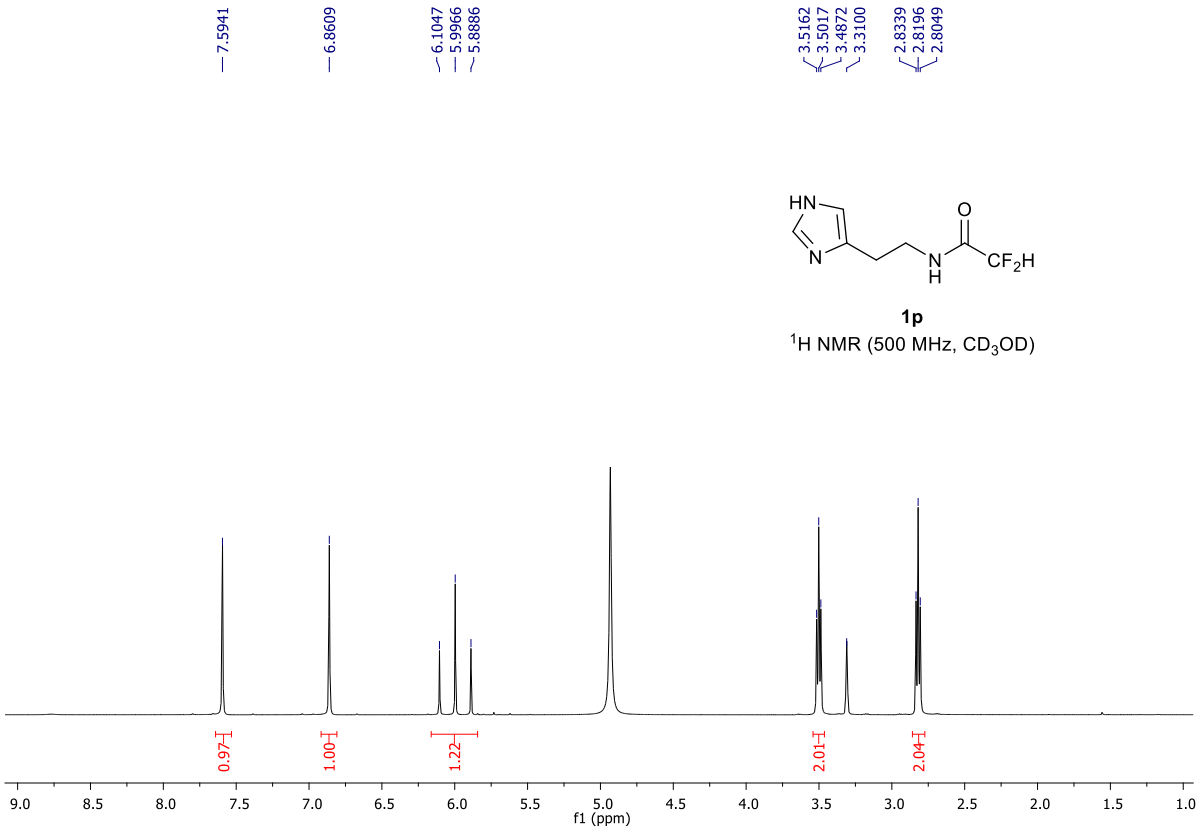


1o

^{1}H NMR (400 MHz, $CDCl_3$)

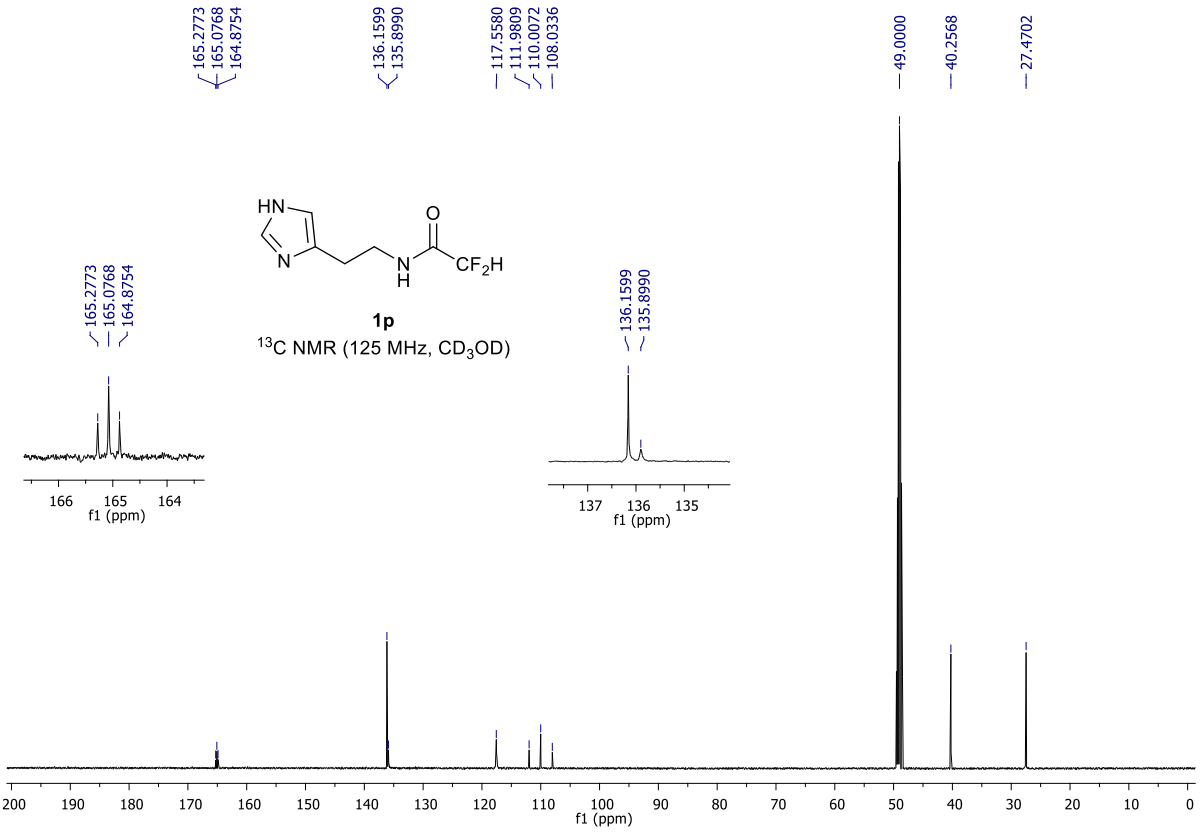

162.7379
162.5425
162.3469
137.8814
128.7662
128.6477
126.8073
110.4225
108.4139
106.4054
77.2542
76.9999
76.7455
40.4139
35.1741
163.0
162.0
f1 (ppm)
129.5
129.0
128.5
128.0
f1 (ppm)
O
N
H
CF2H
1o
13C NMR (125 MHz, CDCl3)
f1 (ppm)


-126.3026
O
N
H
CF2H
1o
19F NMR (376 MHz, CDCl3)
f1 (ppm)



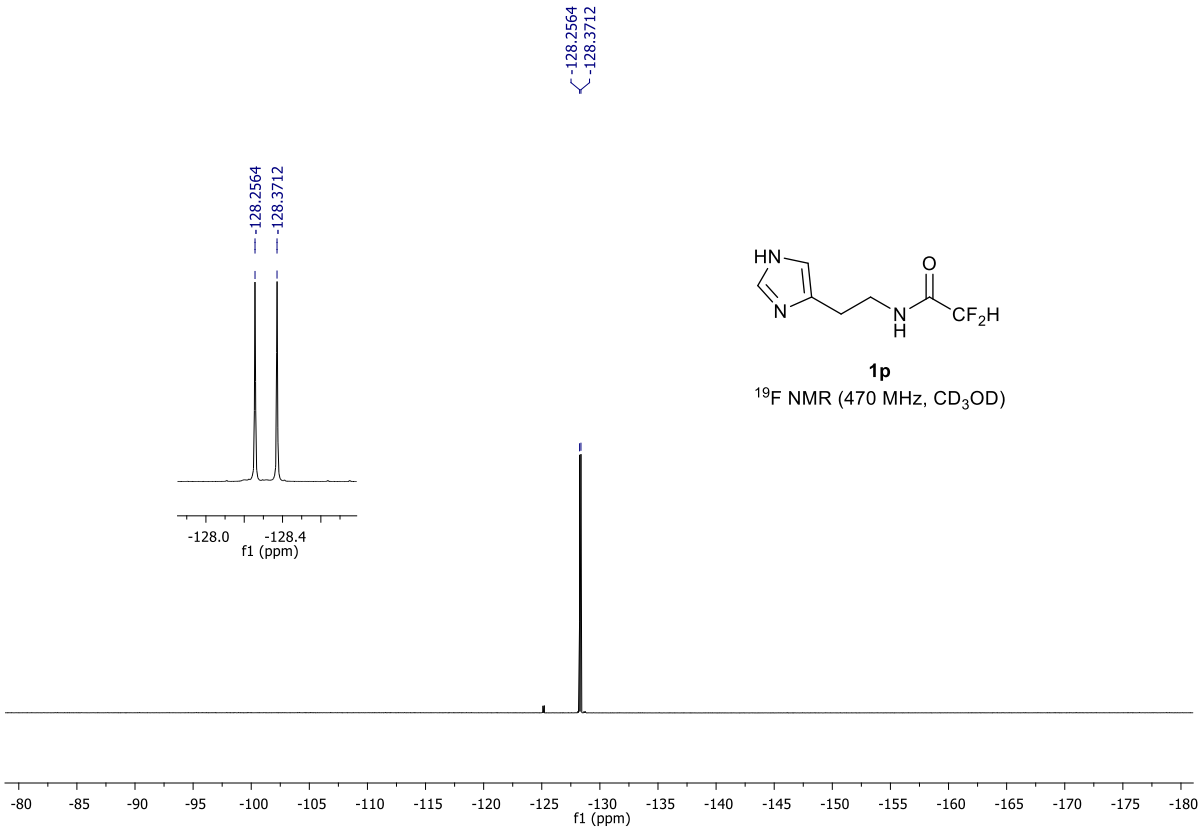
1p

^{1}H NMR (500 MHz, CD_3OD)



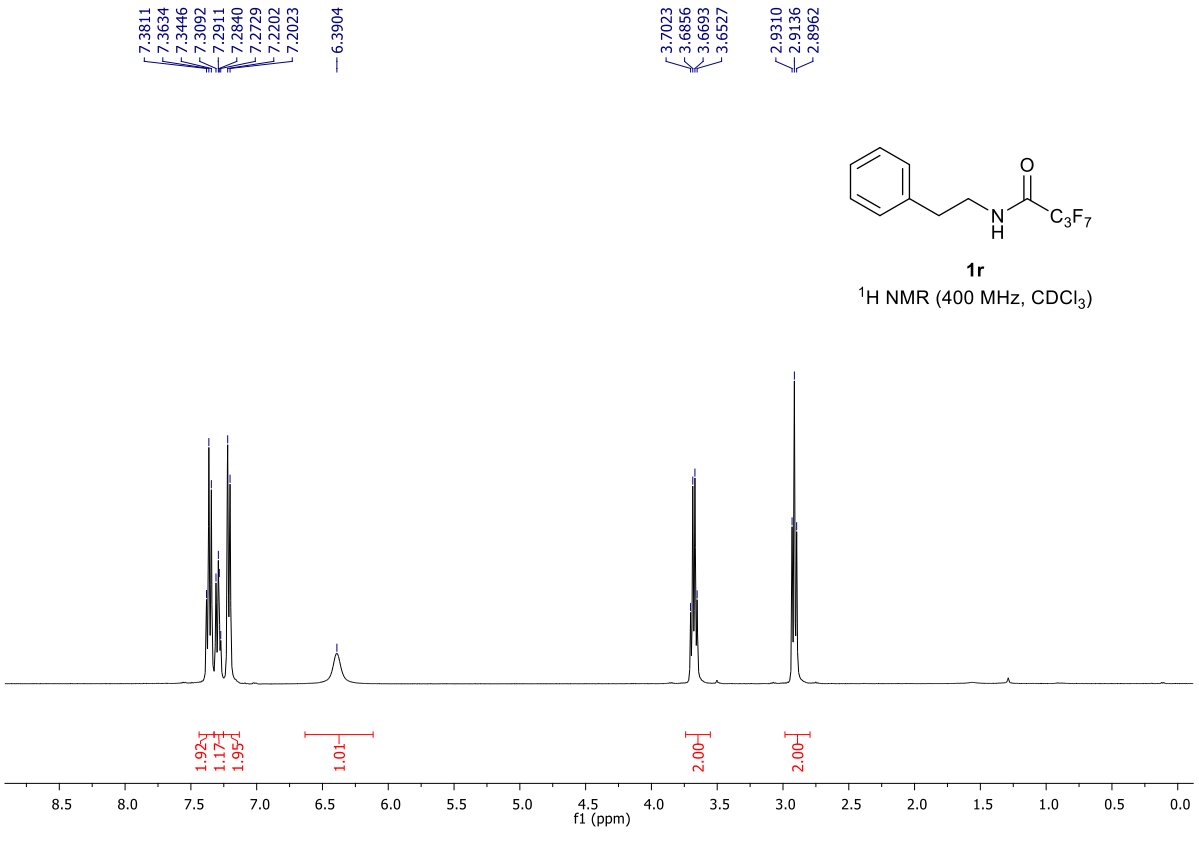
1p

^{13}C NMR (125 MHz, CD_3OD)



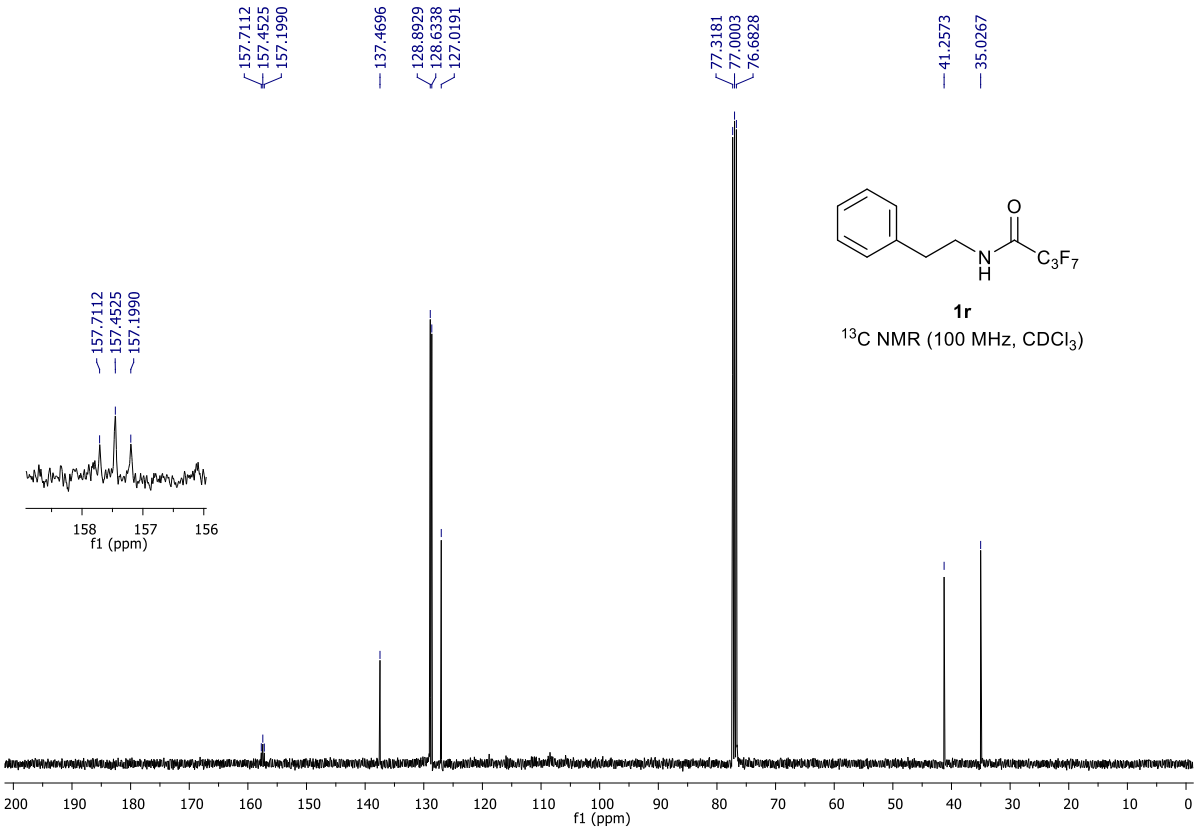
1p

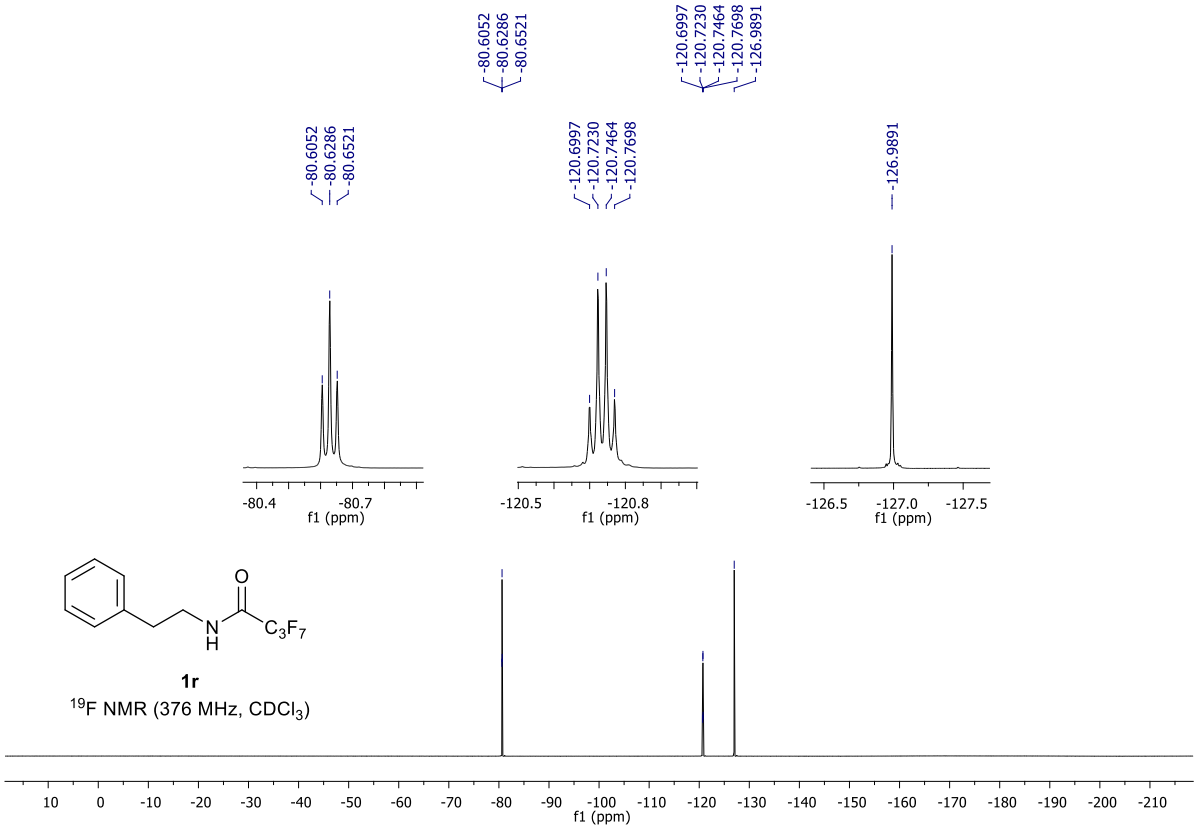
^{19}F NMR (470 MHz, CD_3OD)

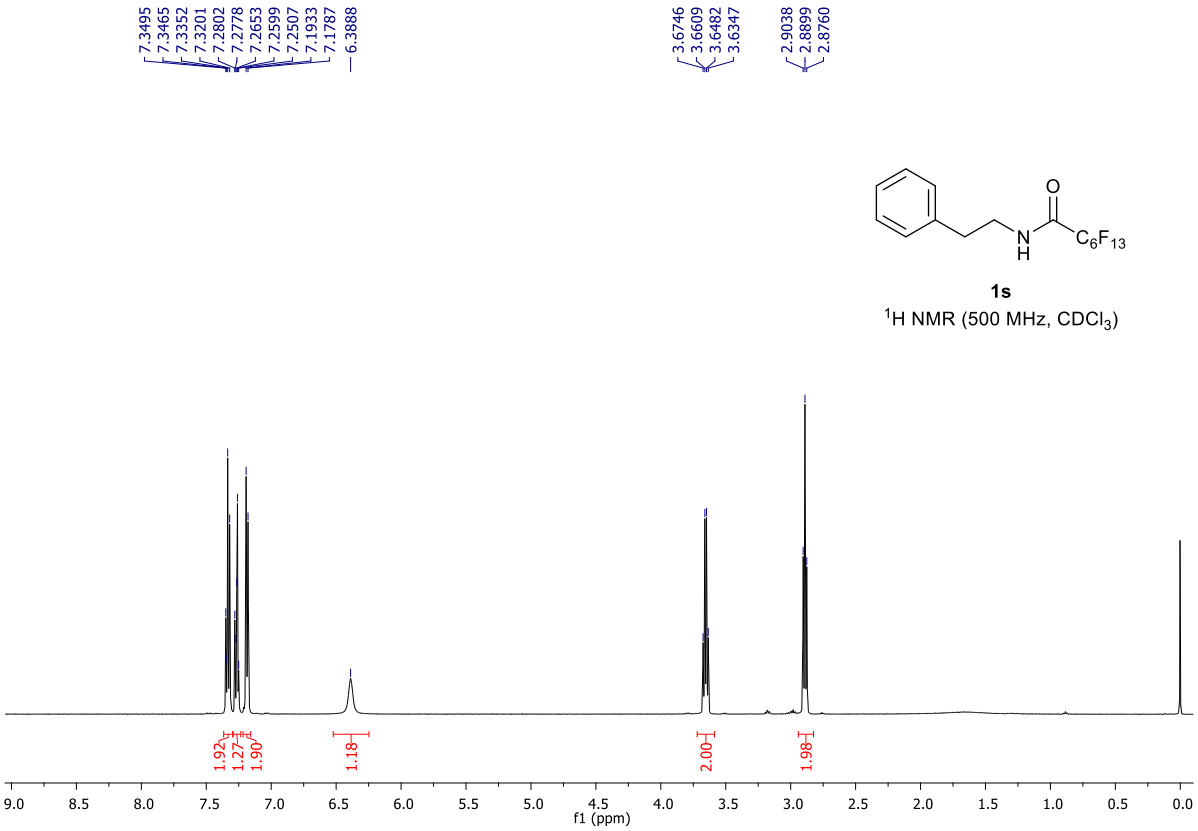


1r

^{1}H NMR (400 MHz, $CDCl_3$)

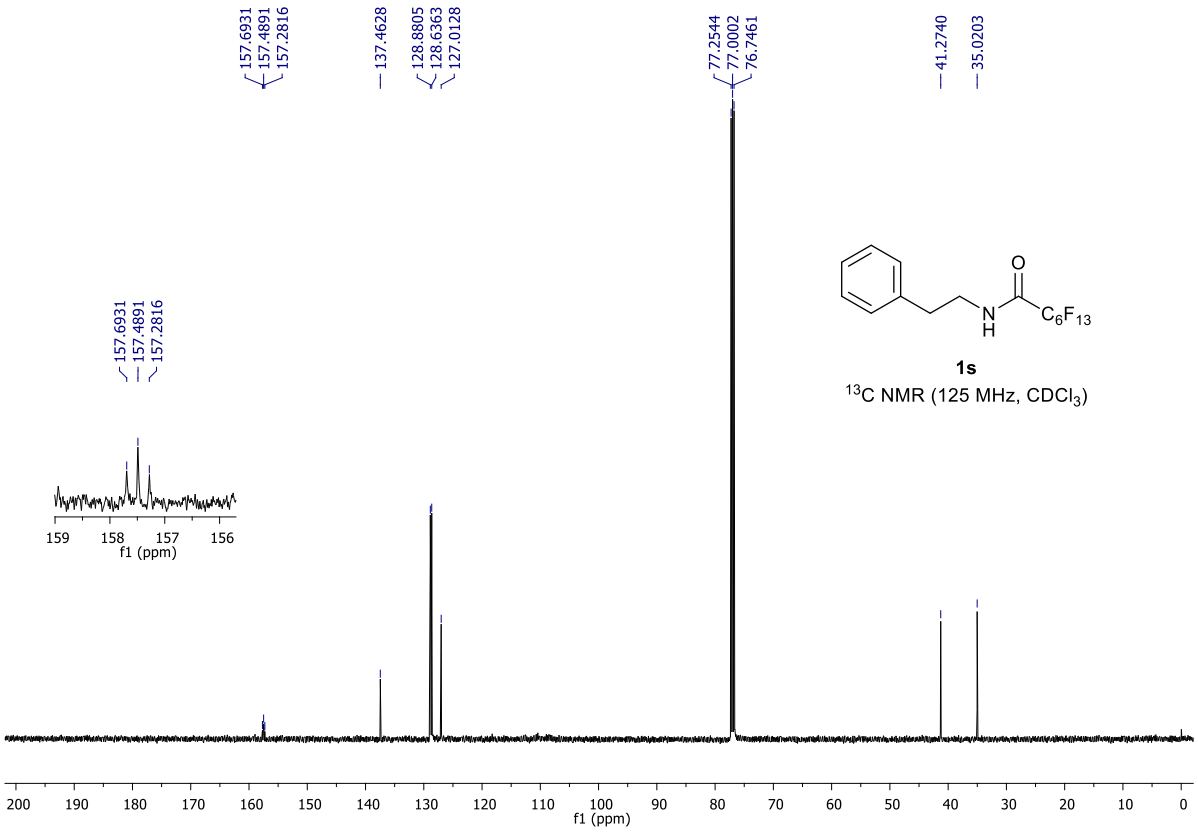

157.7112
157.4525
157.1990
137.4696
128.8929
128.6338
127.0191
77.3181
77.0003
76.6828
41.2573
35.0267
O
N
H
C_3F_7
1r
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)


-80.6052
-80.6286
-80.6521
-120.6997
-120.7230
-120.7464
-120.7698
-126.9891
f1 (ppm)
O
N
H
C_3F_7
1r
^{19}F NMR (376 MHz, $CDCl_3$)



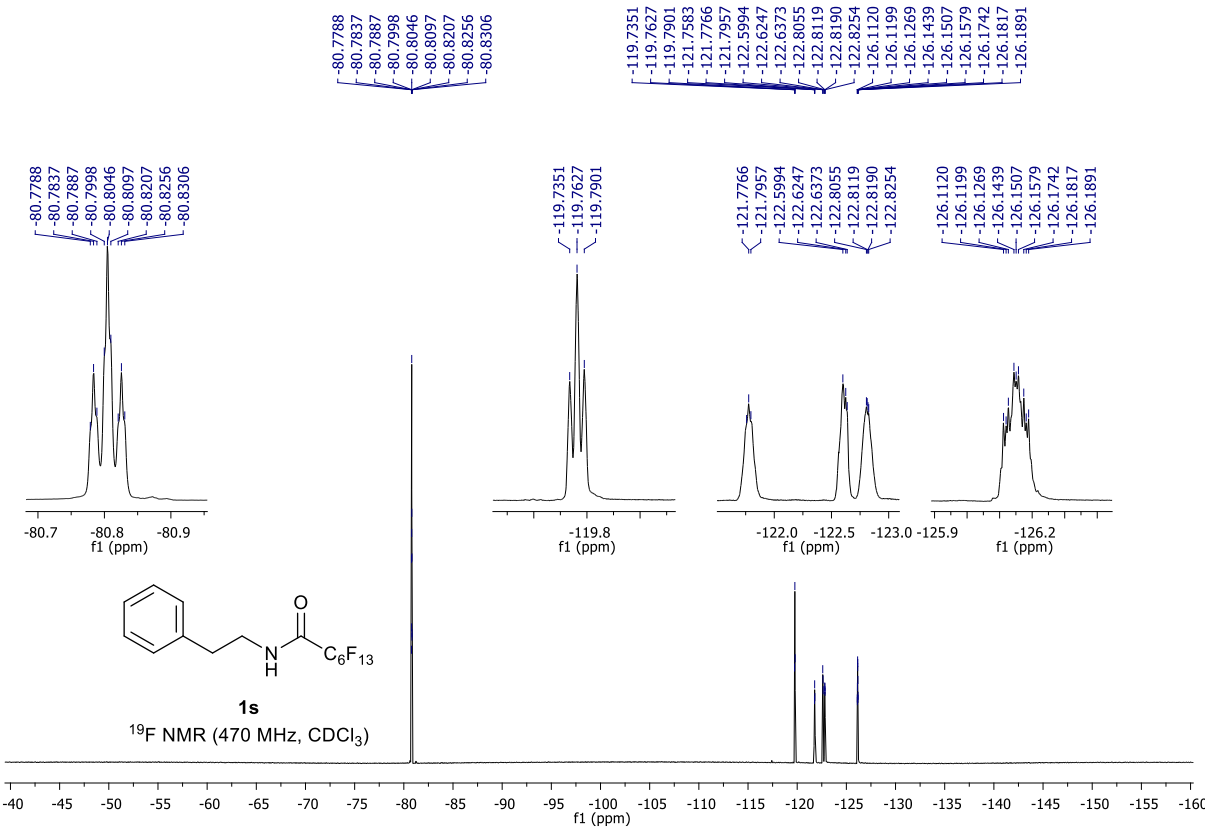
1s

^{1}H NMR (500 MHz, $CDCl_3$)

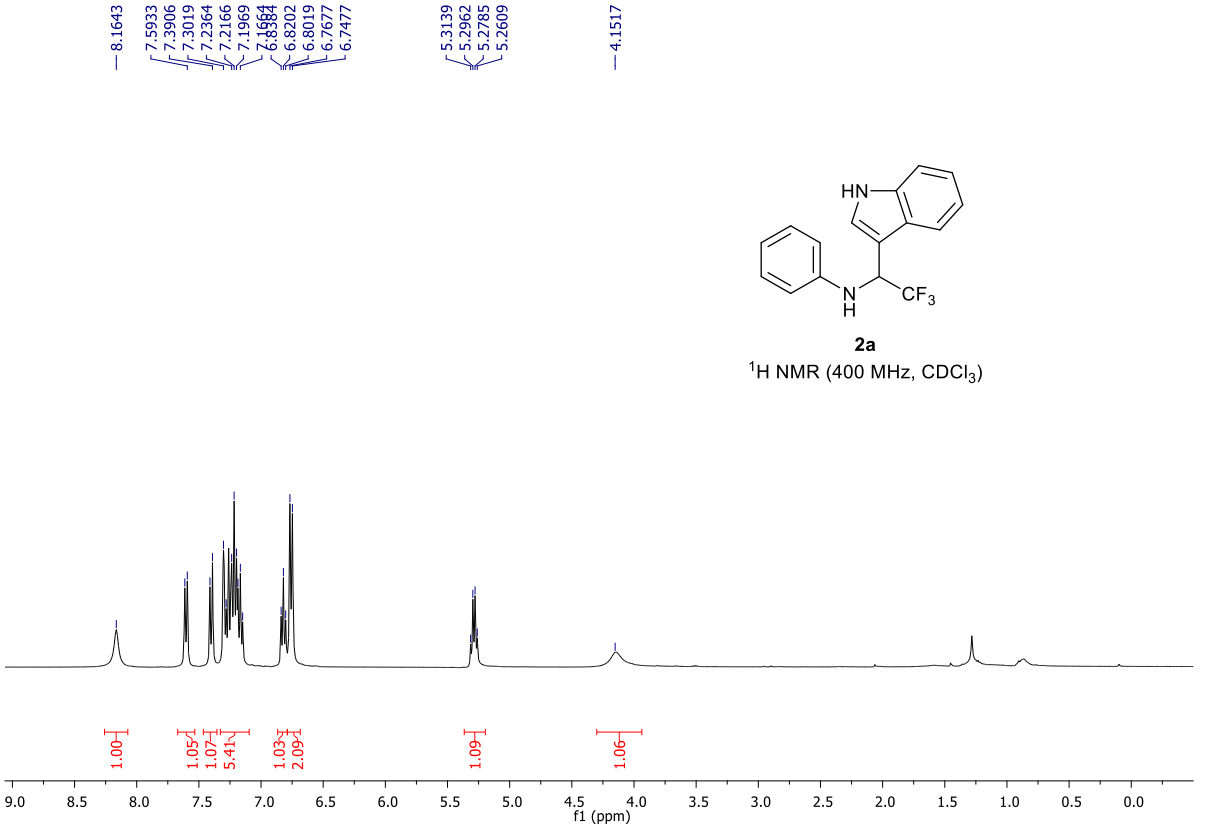


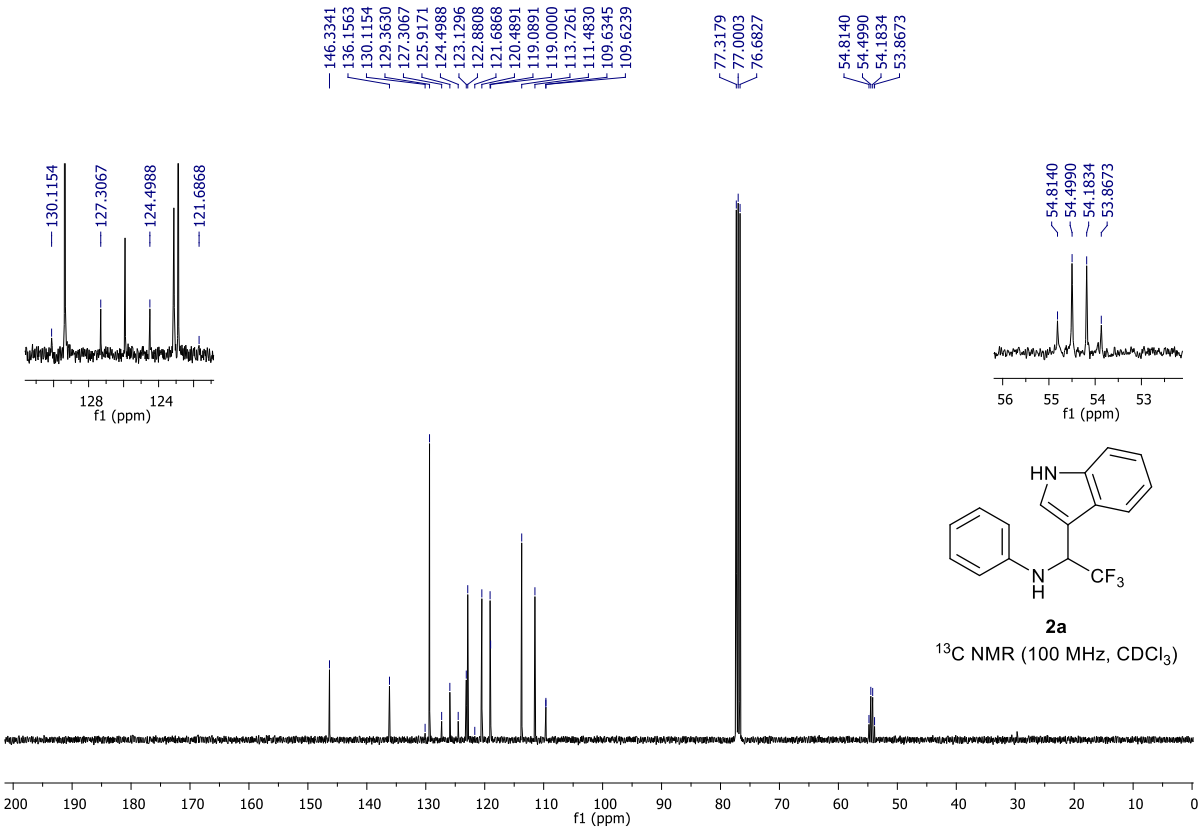
1s

^{13}C NMR (125 MHz, $CDCl_3$)



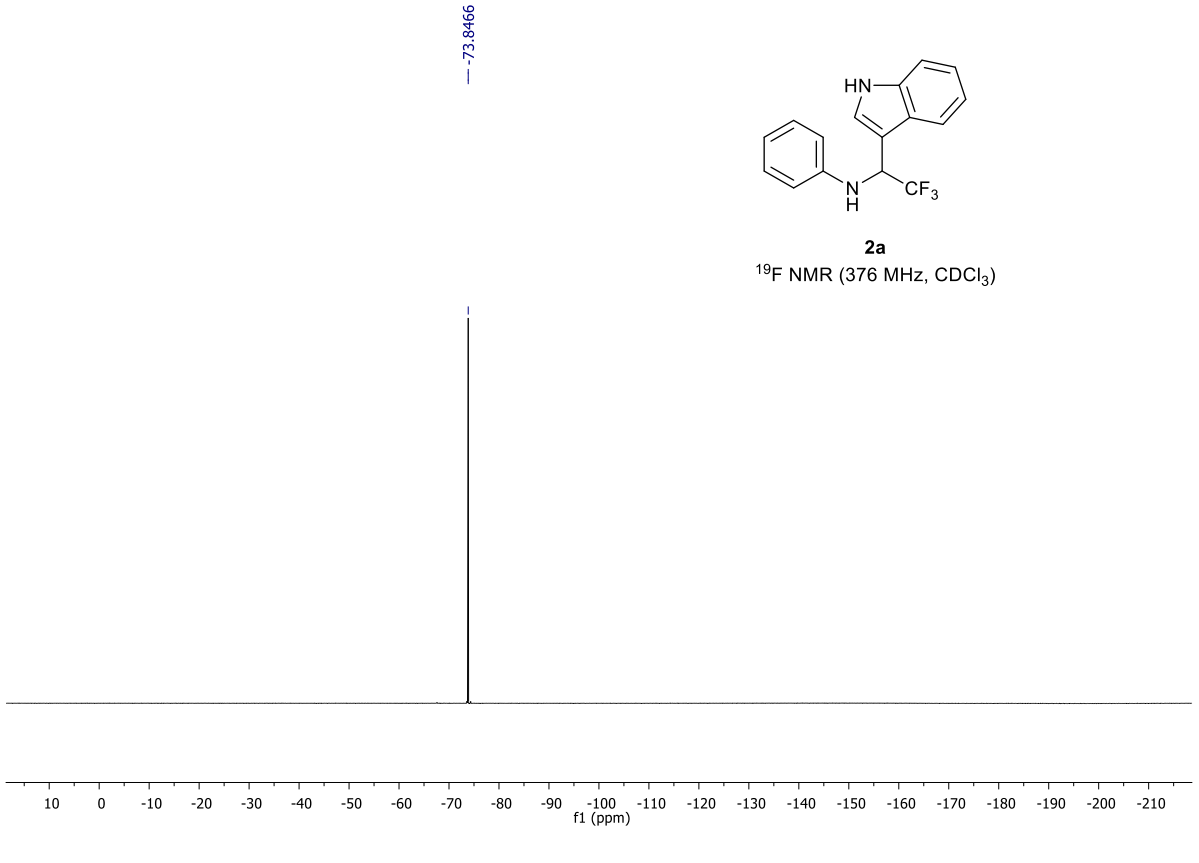
NMR spectra of amines 2a-s (from Scheme 1 in main text)





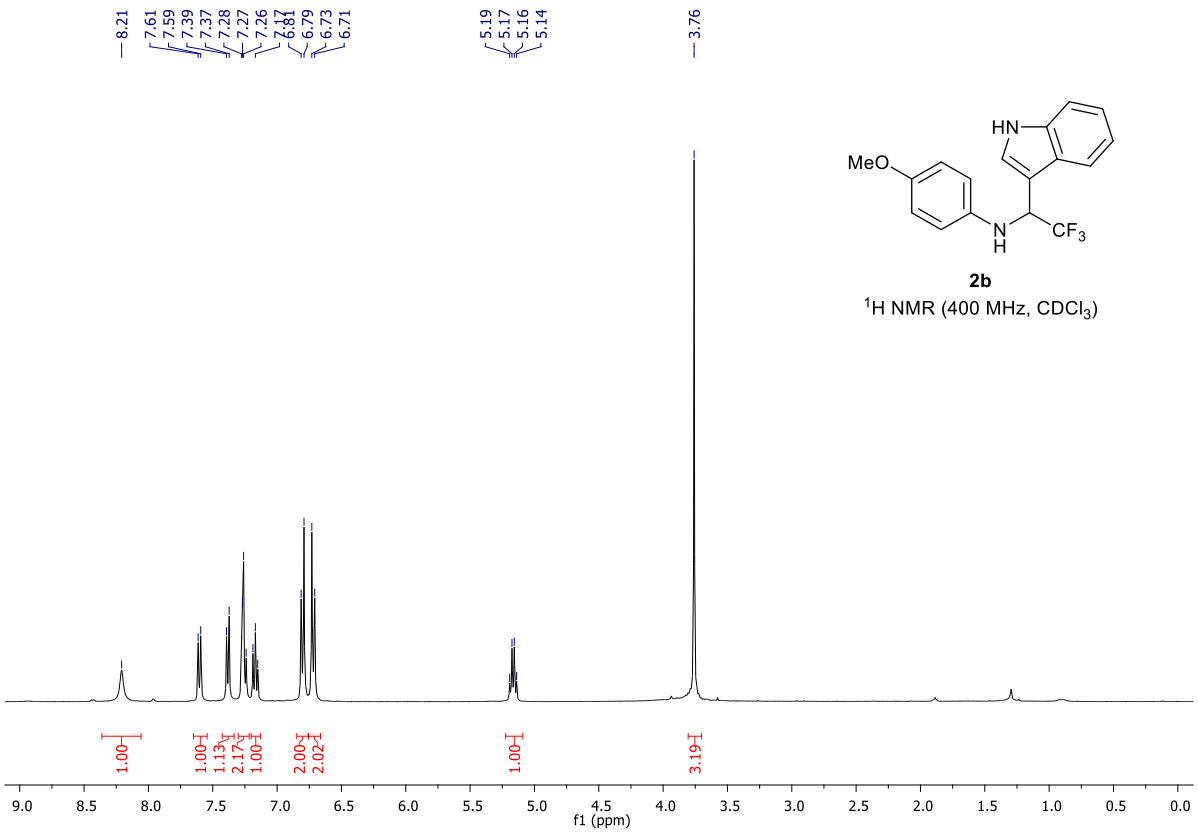
2a

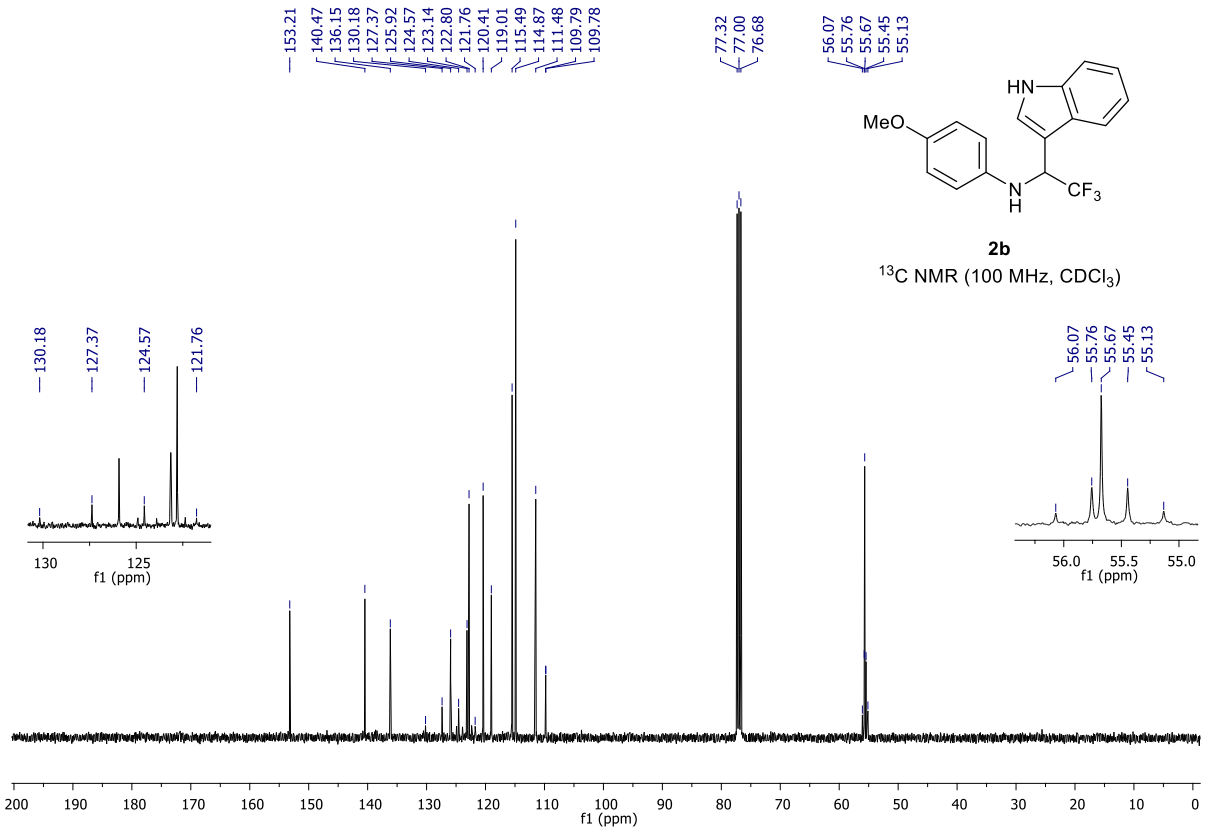
^{13}C NMR (100 MHz, $CDCl_3$)

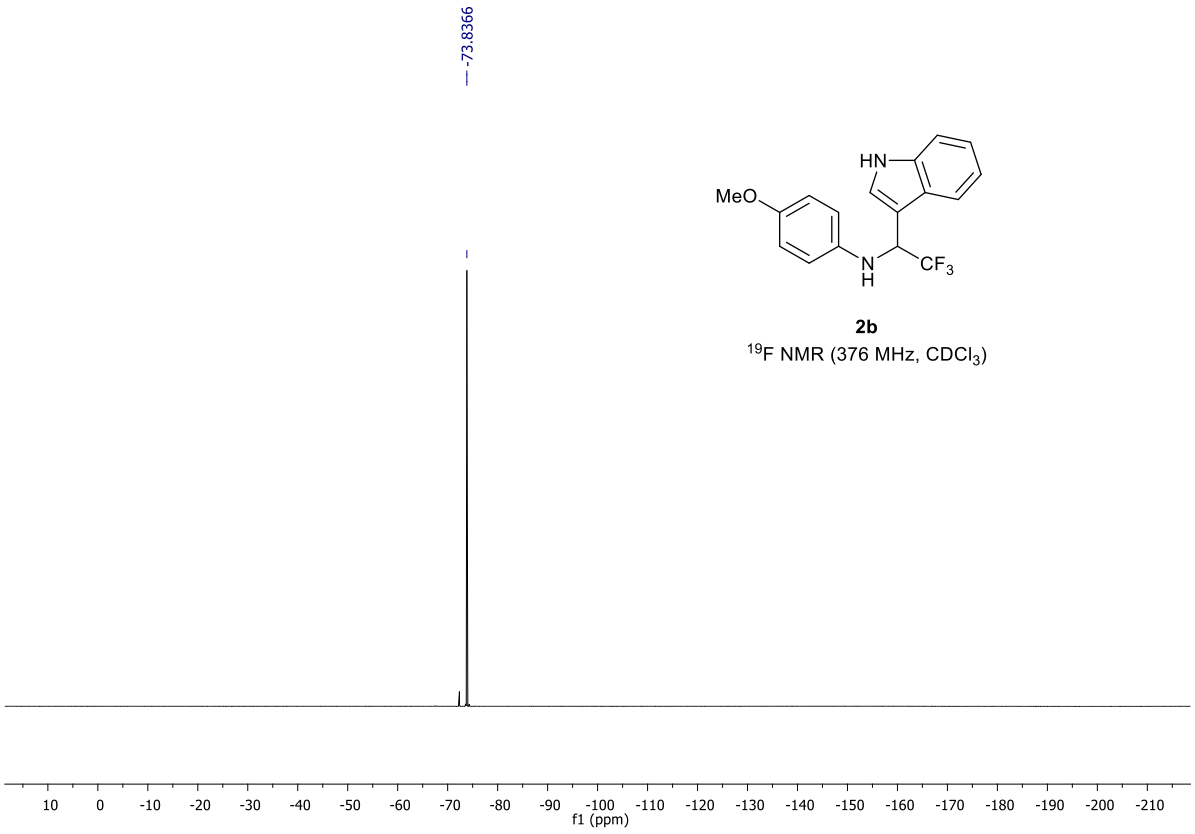


2a

^{19}F NMR (376 MHz, $CDCl_3$)

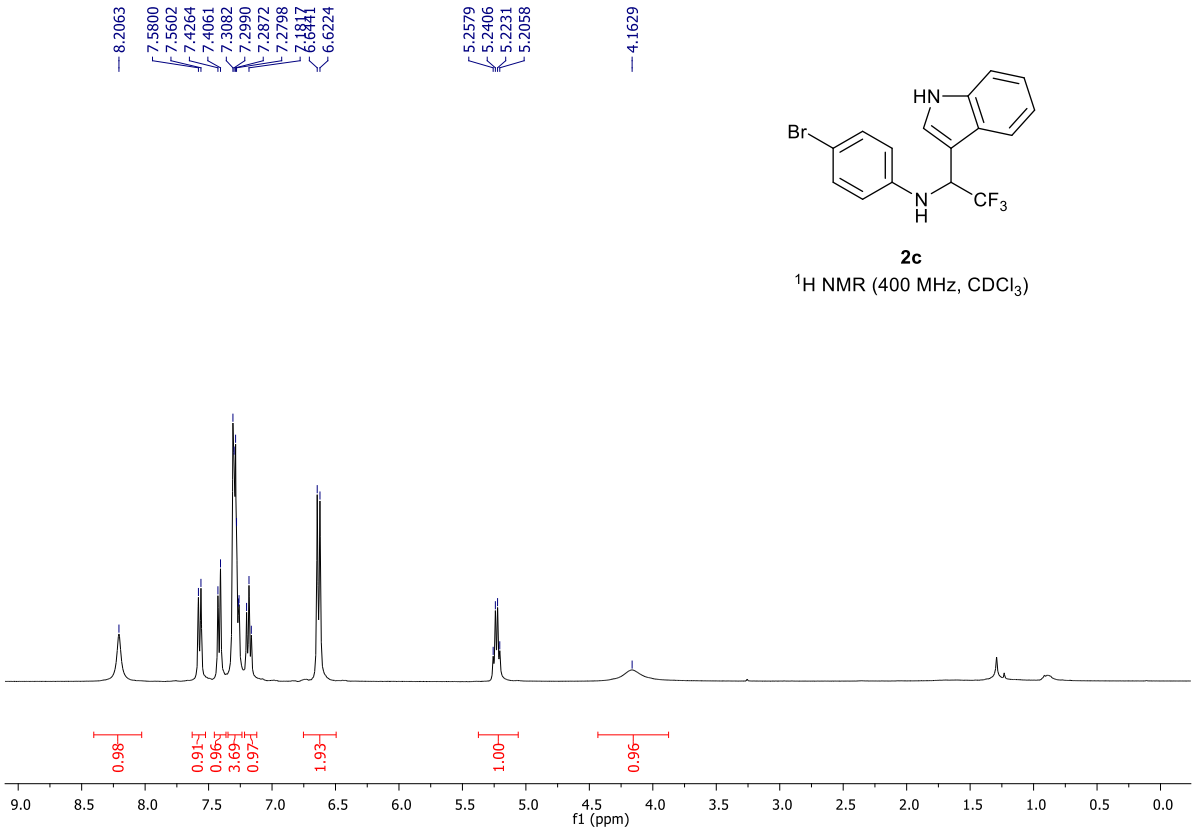

8.21
7.61
7.59
7.39
7.37
7.28
7.27
7.26
7.17
6.81
6.79
6.73
6.71
5.19
5.17
5.16
5.14
3.76
HN
MeO
N
H
CF3
2b
1H NMR (400 MHz, CDCl3)
1.00
1.00
1.13
2.17
1.00
2.00
2.02
1.00
3.19
f1 (ppm)


153.21
140.47
136.15
130.18
127.37
125.92
124.57
123.14
122.80
121.76
120.41
119.01
115.49
114.87
111.48
109.79
109.78
77.32
77.00
76.68
56.07
55.76
55.67
55.45
55.13
HN
MeO
N
H
CF3
2b
13C NMR (100 MHz, CDCl3)
130.18
127.37
124.57
121.76
f1 (ppm)
56.07
55.76
55.67
55.45
55.13
f1 (ppm)
f1 (ppm)



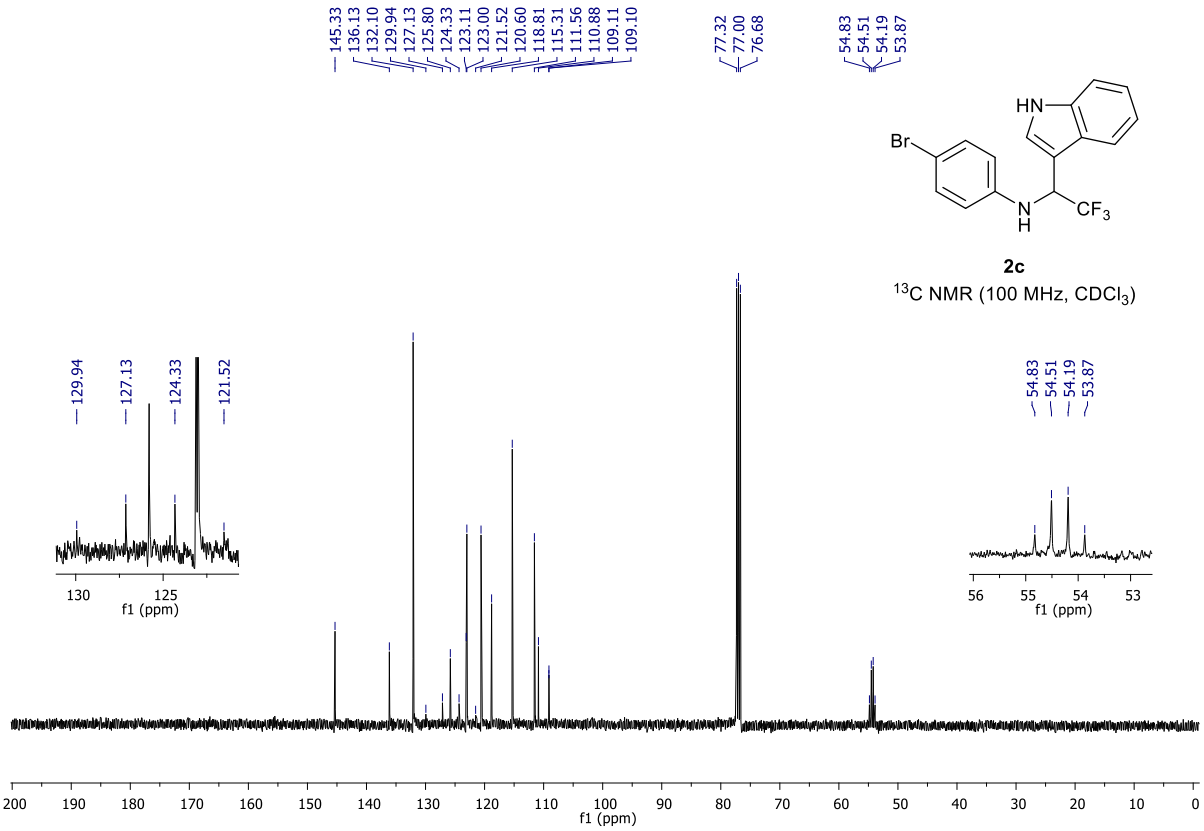
2b

^{19}F NMR (376 MHz, $CDCl_3$)



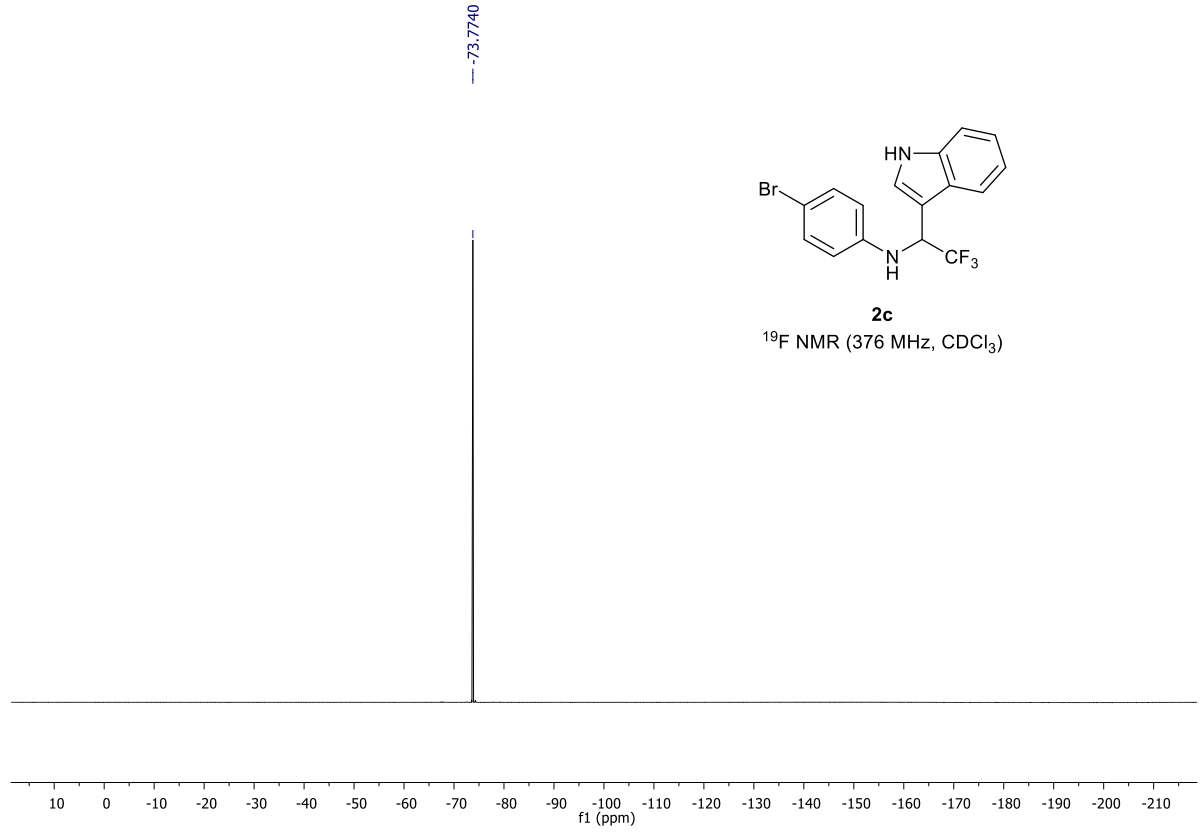
2c

^{1}H NMR (400 MHz, $CDCl_3$)



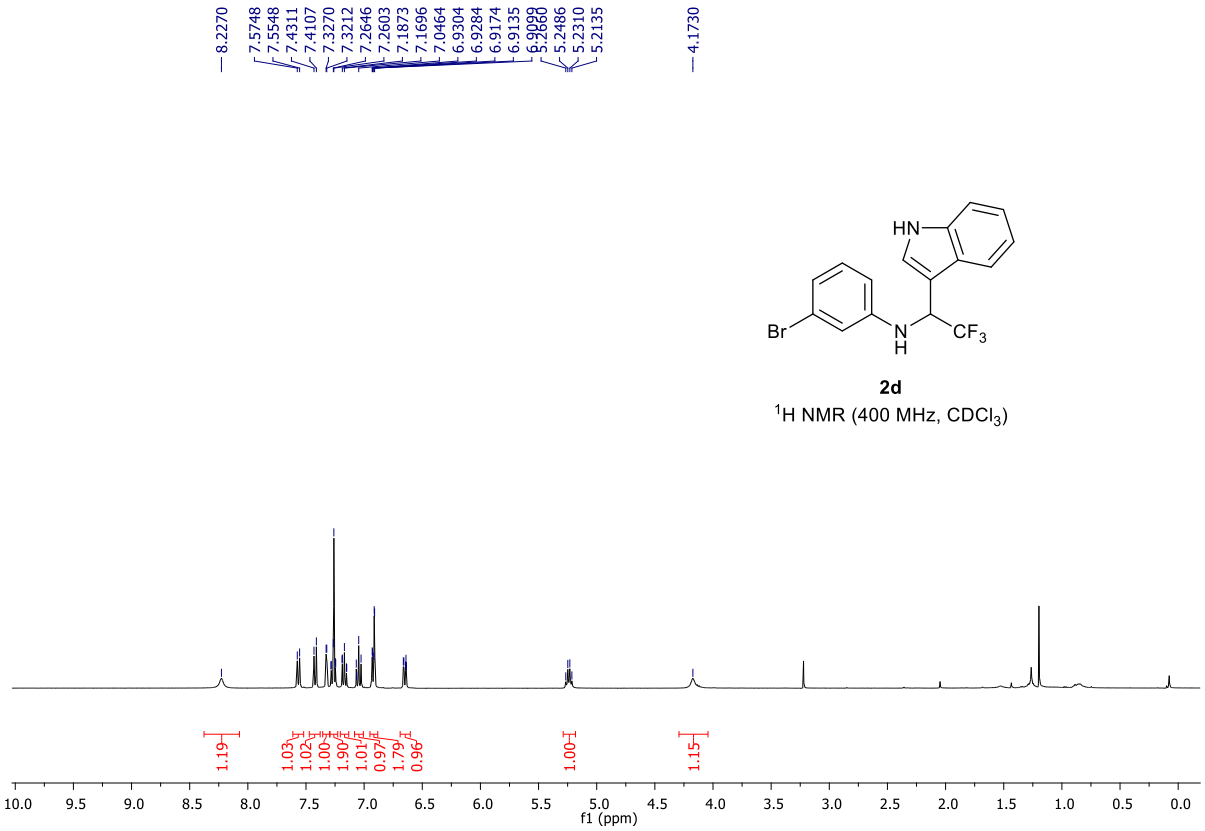
2c

^{13}C NMR (100 MHz, $CDCl_3$)



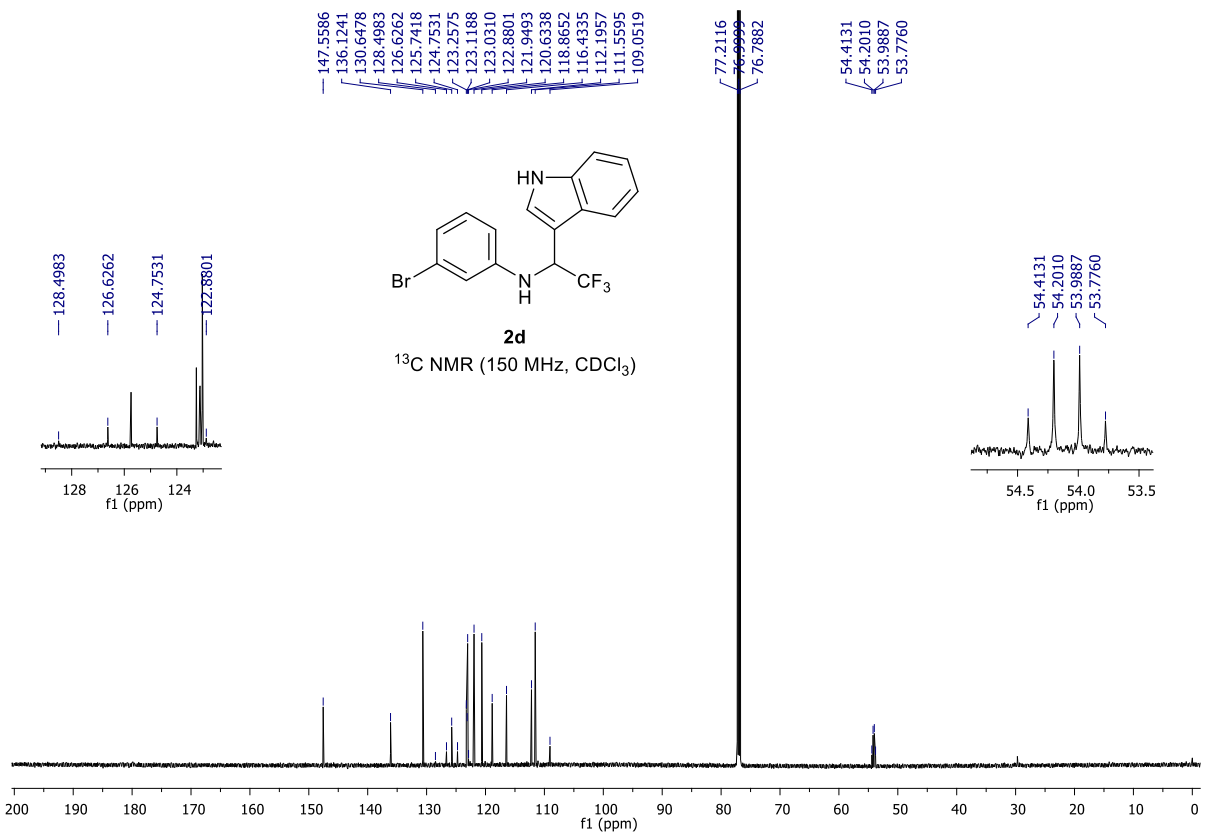
2c

^{19}F NMR (376 MHz, $CDCl_3$)



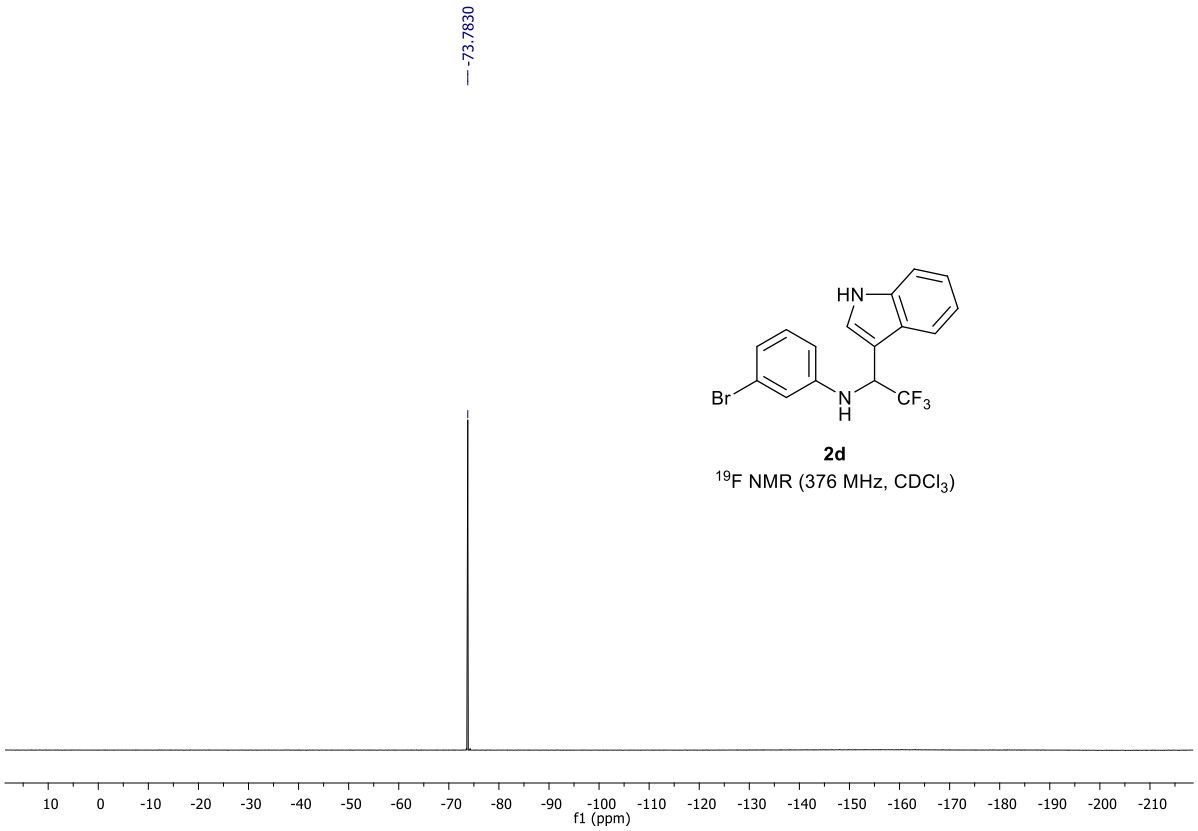
2d

^{1}H NMR (400 MHz, $CDCl_3$)



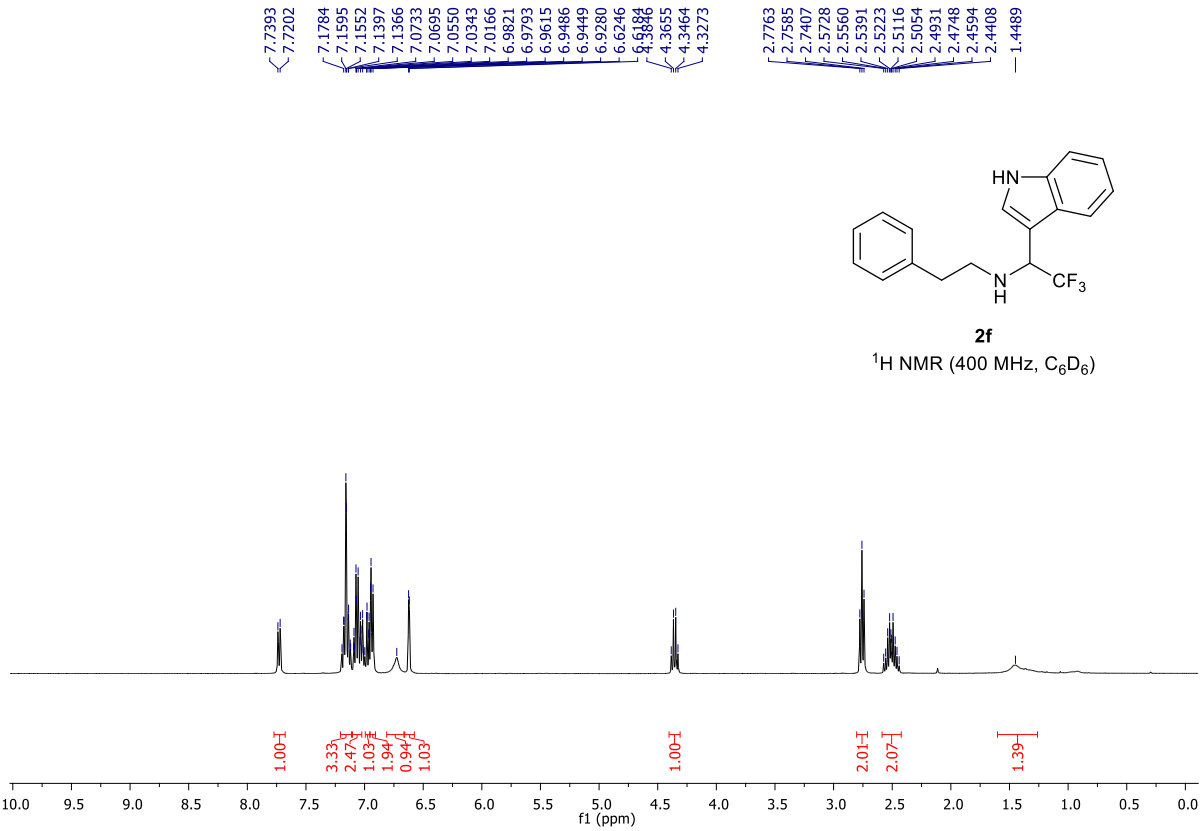
2d

^{13}C NMR (150 MHz, $CDCl_3$)



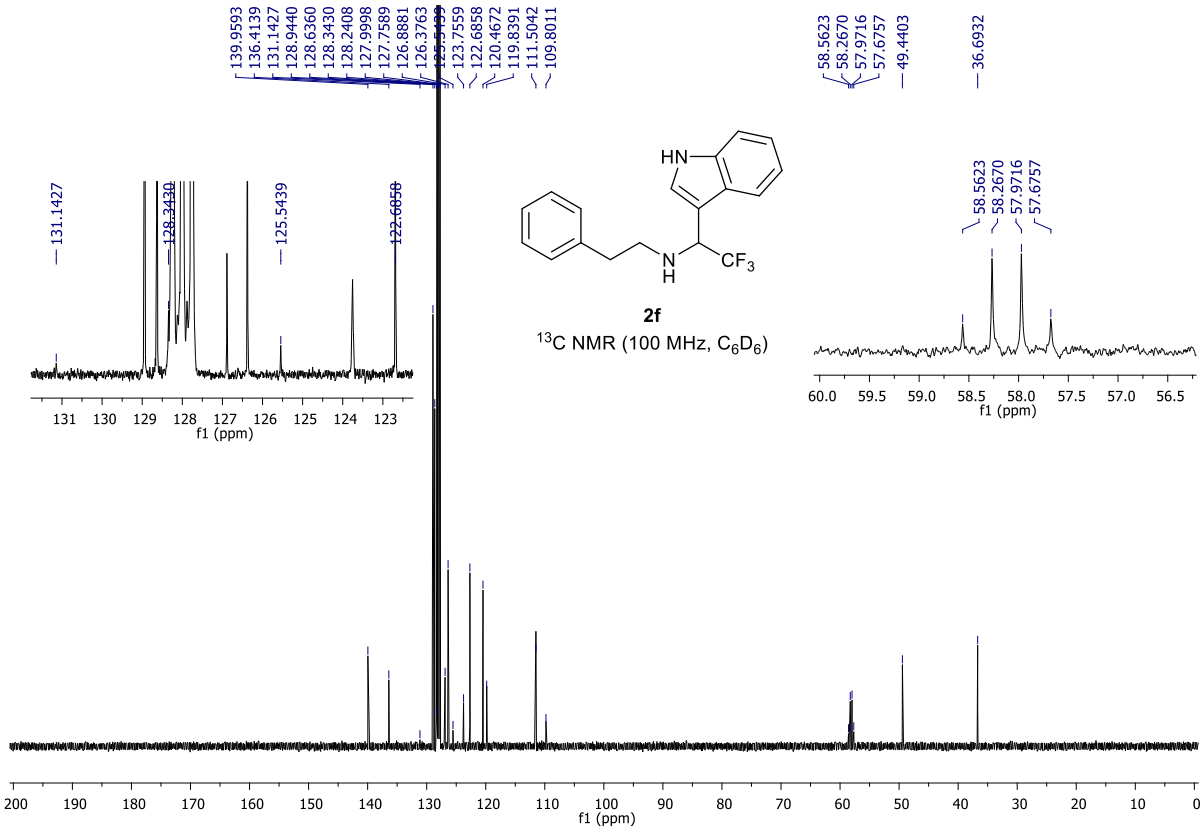
2d

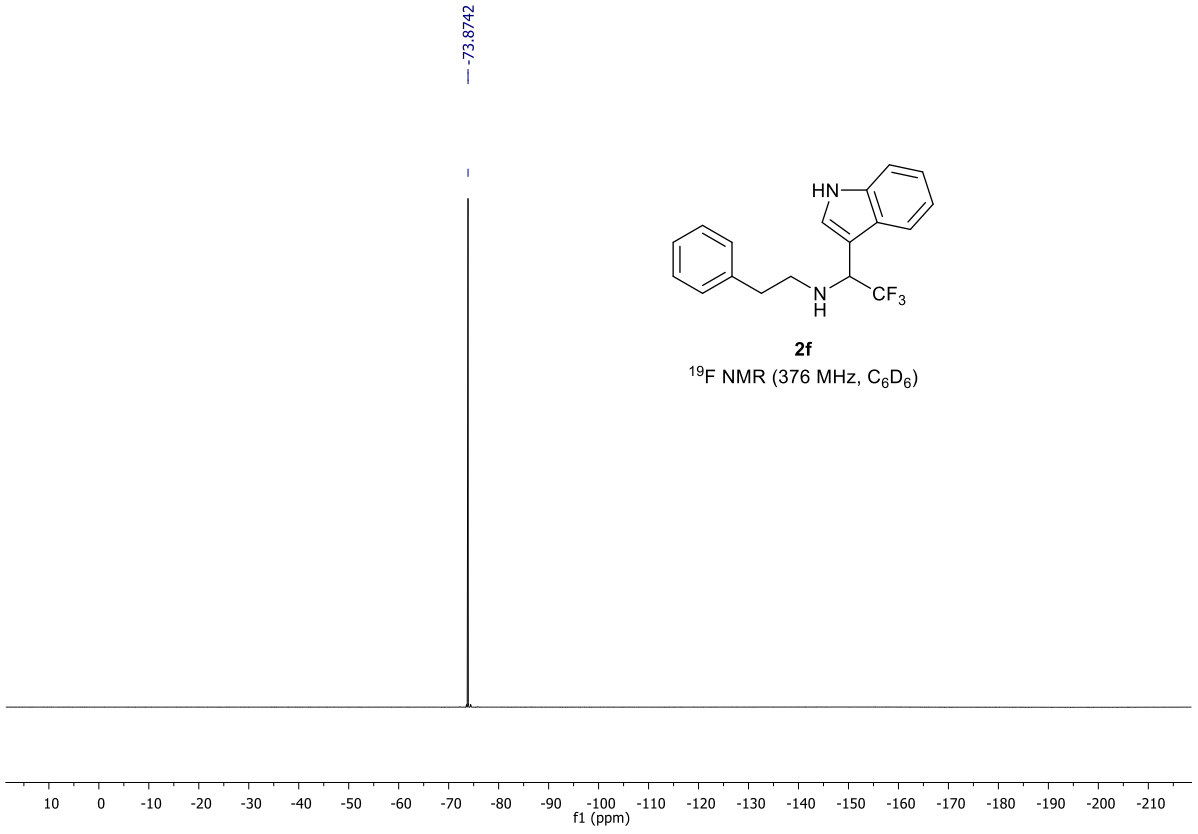
^{19}F NMR (376 MHz, $CDCl_3$)

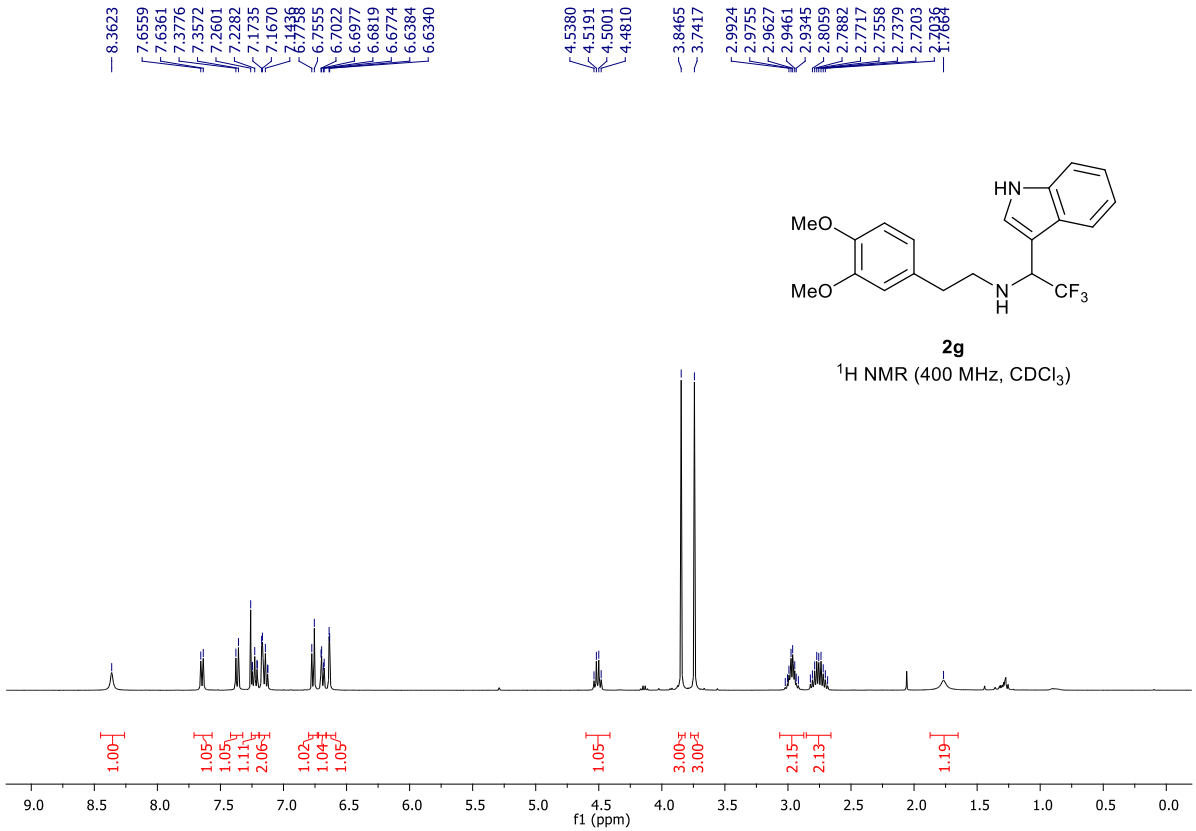


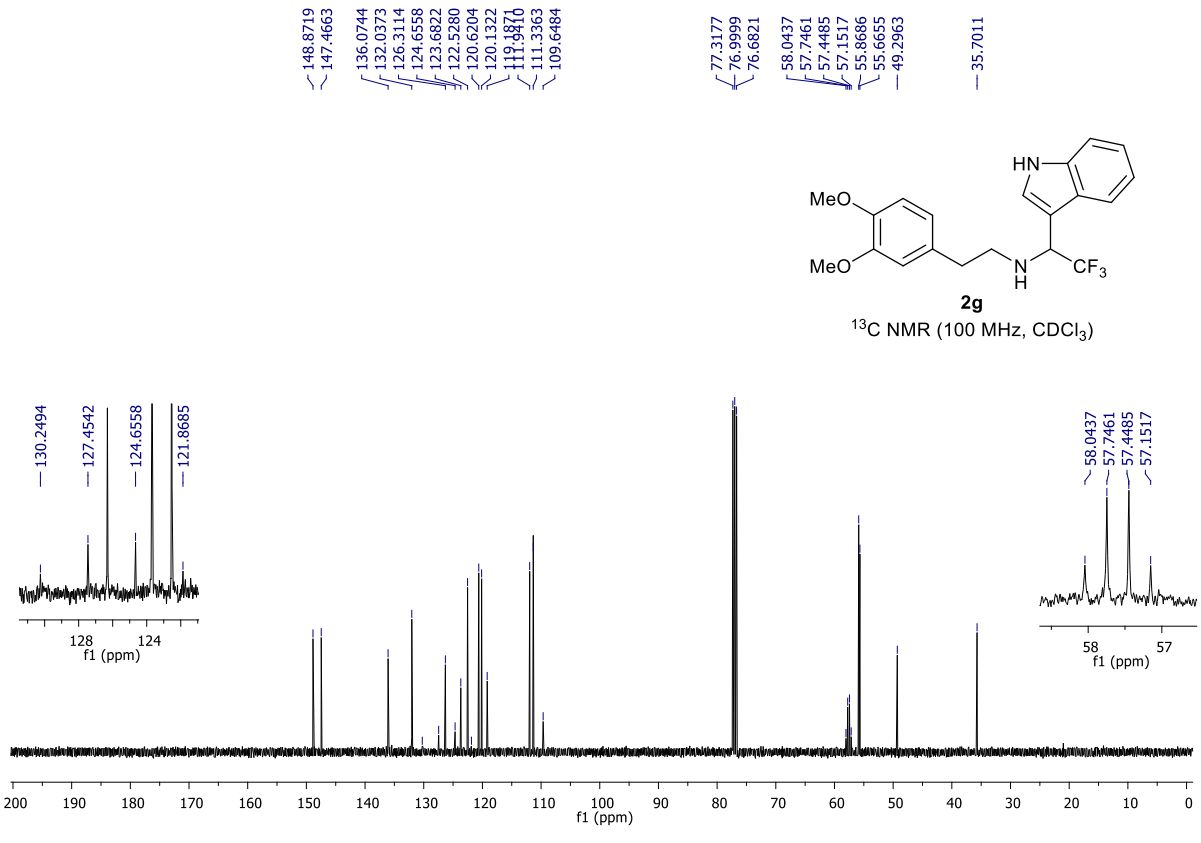
2f

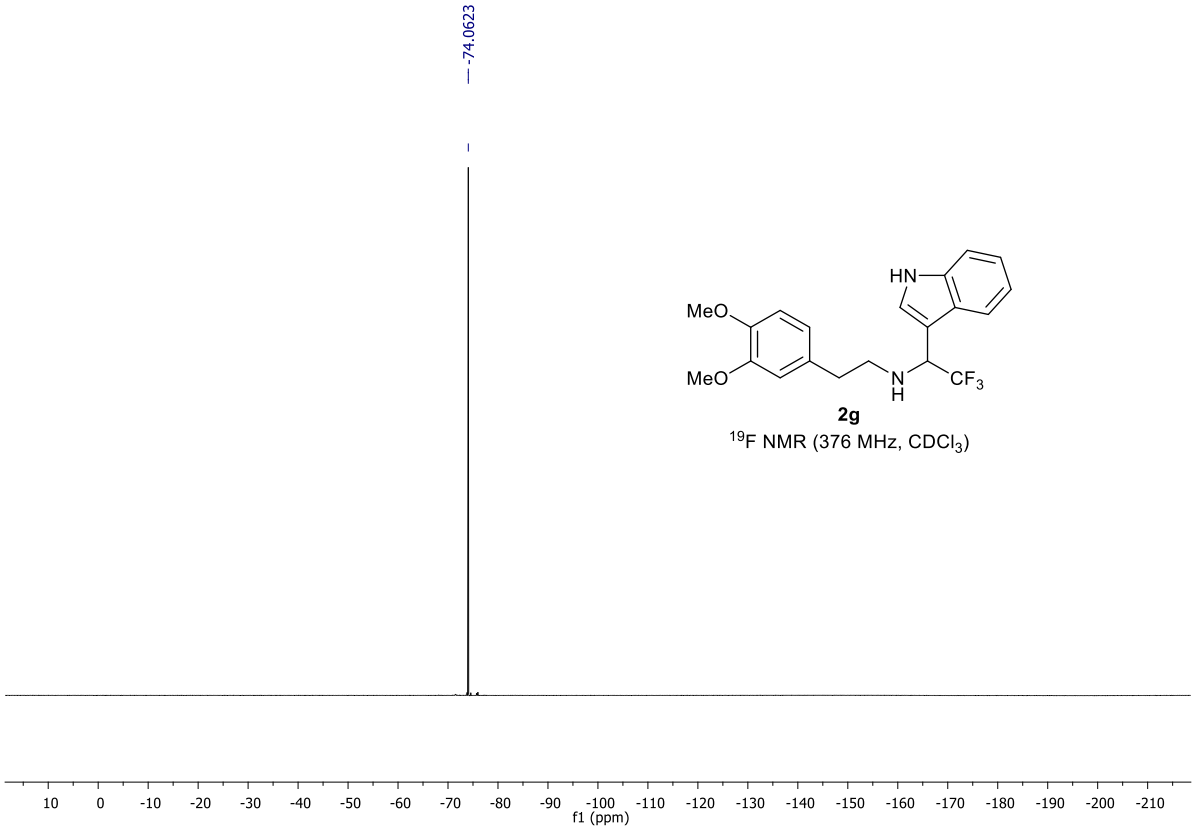
^{1}H NMR (400 MHz, C_6D_6)


139.9593
136.4139
131.1427
128.9440
128.6360
128.3430
128.2408
127.9998
127.7589
126.8881
126.3763
123.7559
122.6858
120.4672
119.8391
111.5042
109.8011
58.5623
58.2670
57.9716
57.6757
49.4403
36.6932
131.1427
128.3430
125.5439
122.6858
HN
N
H
CF3
2f
13C NMR (100 MHz, C6D6)
f1 (ppm)


-73.8742
HN
N
H
CF3
2f
19F NMR (376 MHz, C6D6)
f1 (ppm)

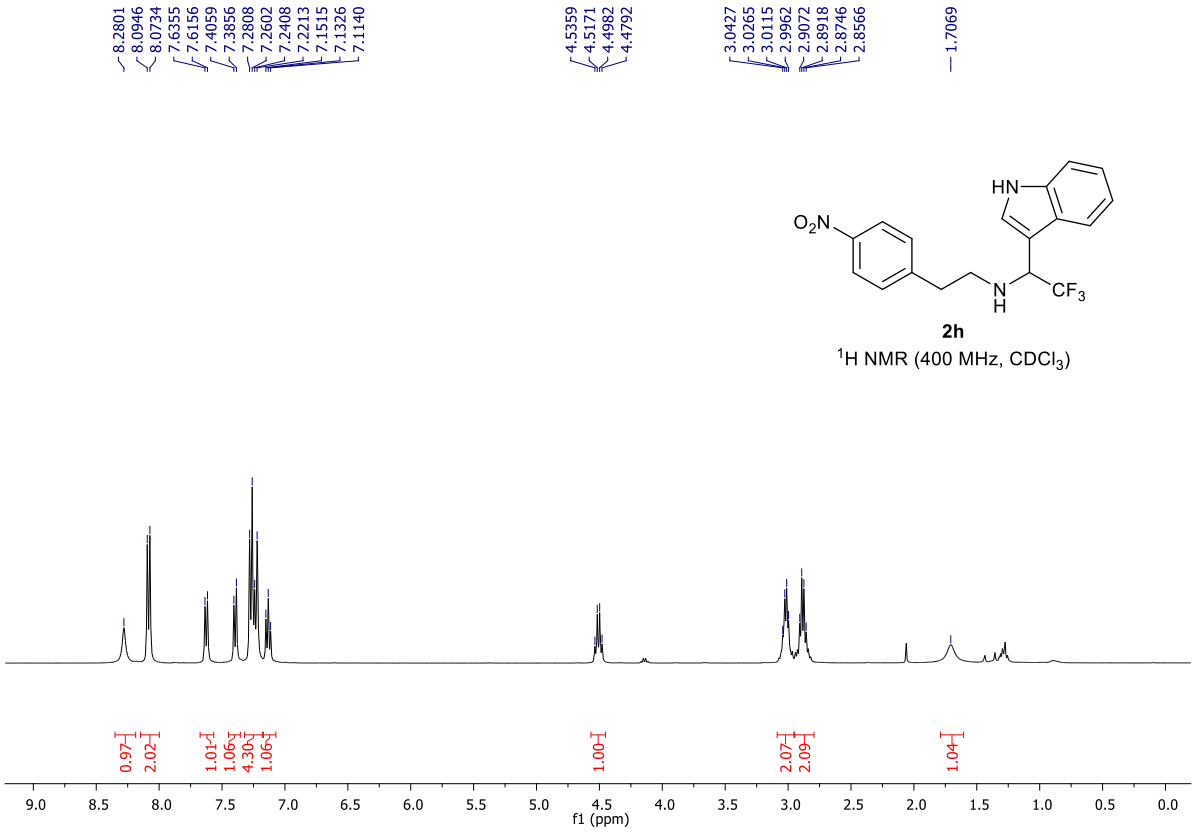

8.3623
7.6559
7.6361
7.3776
7.3572
7.2601
7.2282
7.1735
7.1670
7.1436
6.7758
6.7555
6.7022
6.6977
6.6819
6.6774
6.6384
6.6340
4.5380
4.5191
4.5001
4.4810
3.8465
3.7417
2.9924
2.9755
2.9627
2.9461
2.9345
2.8059
2.7882
2.7717
2.7558
2.7379
2.7203
2.7036
1.7864
HN
MeO
MeO
N
H
CF3
2g
1H NMR (400 MHz, CDCl3)
1.00
1.05
1.05
1.11
2.06
1.02
1.04
1.05
1.05
3.00
3.00
2.15
2.13
1.19
f1 (ppm)


148.8719
147.4663
136.0744
132.0373
126.3114
124.6558
123.6822
122.5280
120.6204
120.1322
111.3363
109.6484
77.3177
76.9999
76.6821
58.0437
57.7461
57.4485
57.1517
55.8686
55.6655
49.2963
35.7011
HN
MeO
MeO
N
H
CF3
2g
13C NMR (100 MHz, CDCl3)
130.2494
127.4542
124.6558
121.8685
128
124
f1 (ppm)
58.0437
57.7461
57.4485
57.1517
58
57
f1 (ppm)
f1 (ppm)



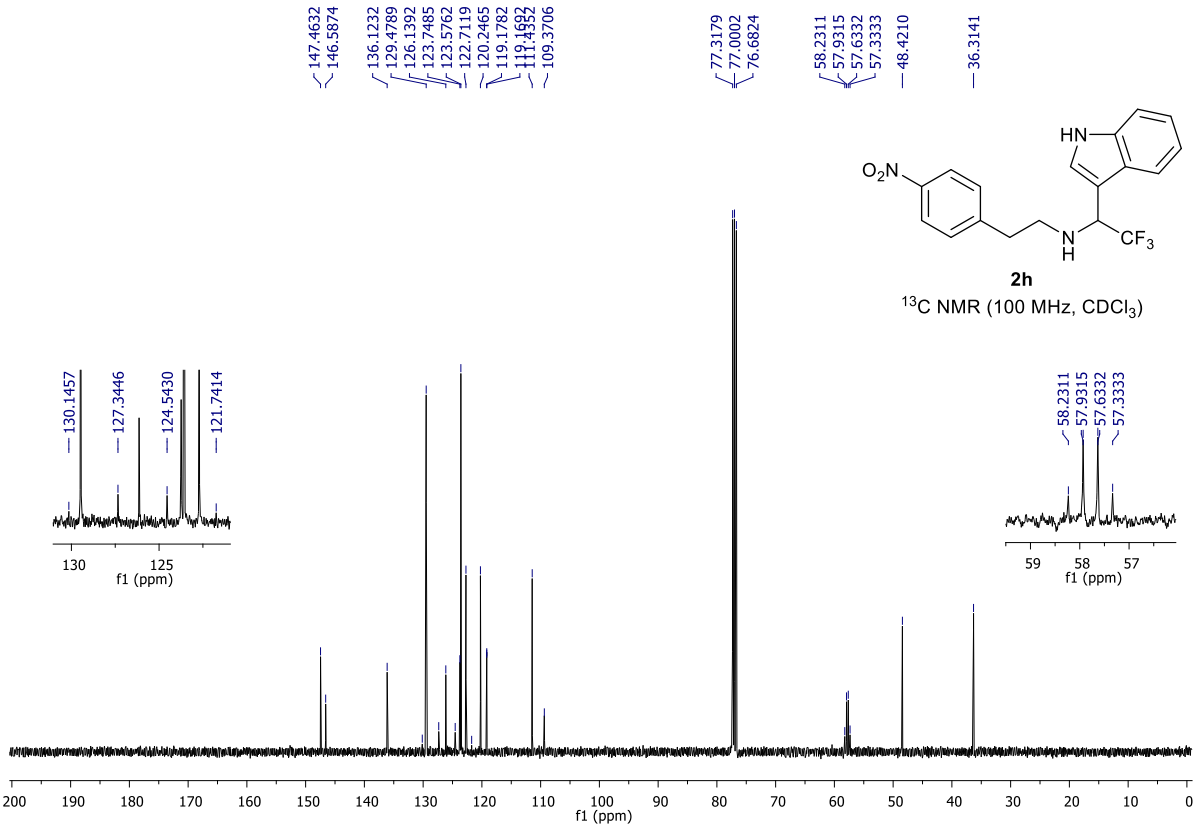
2g

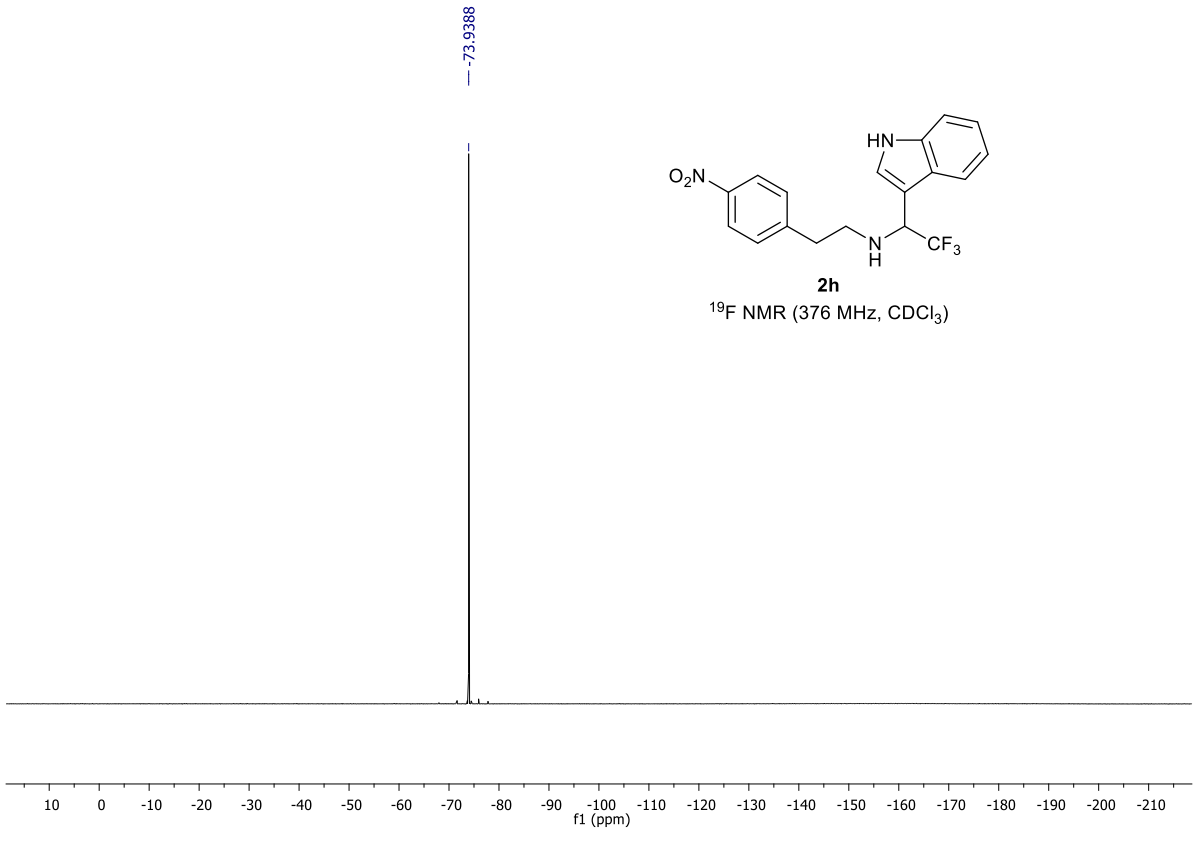
^{19}F NMR (376 MHz, $CDCl_3$)

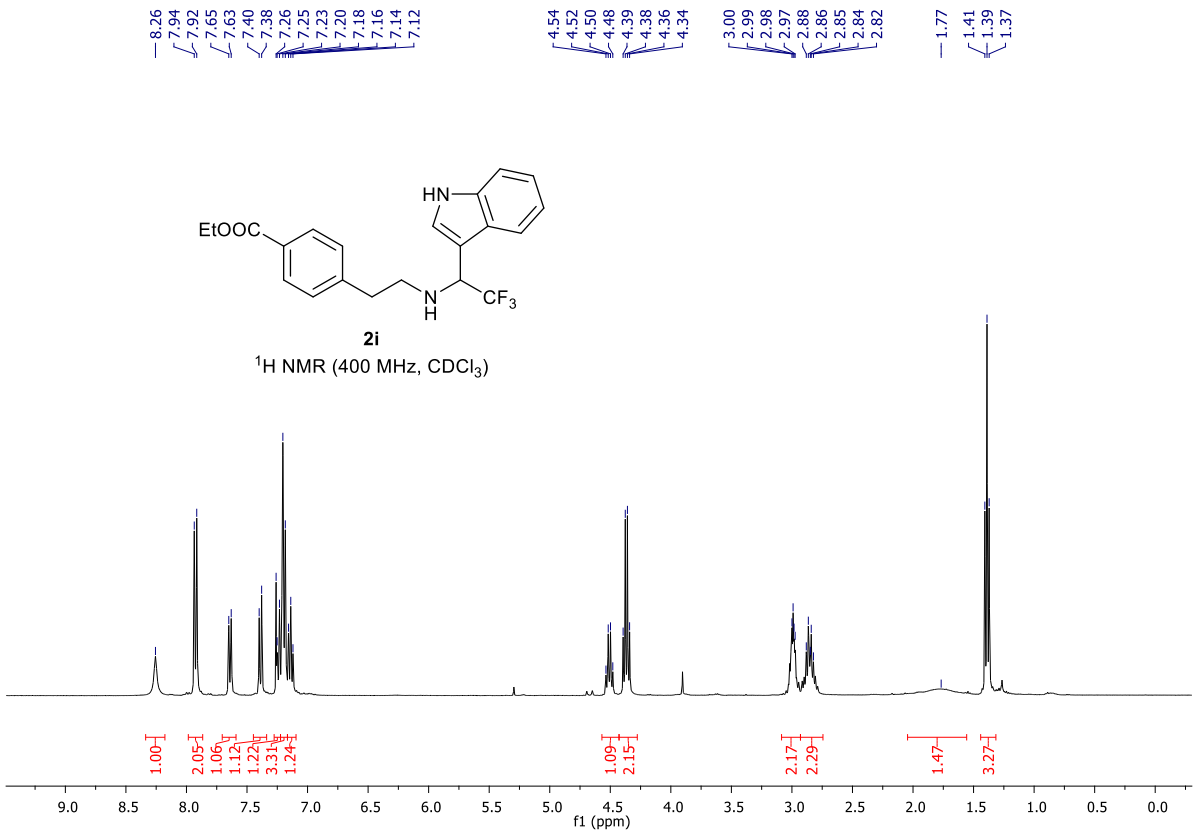


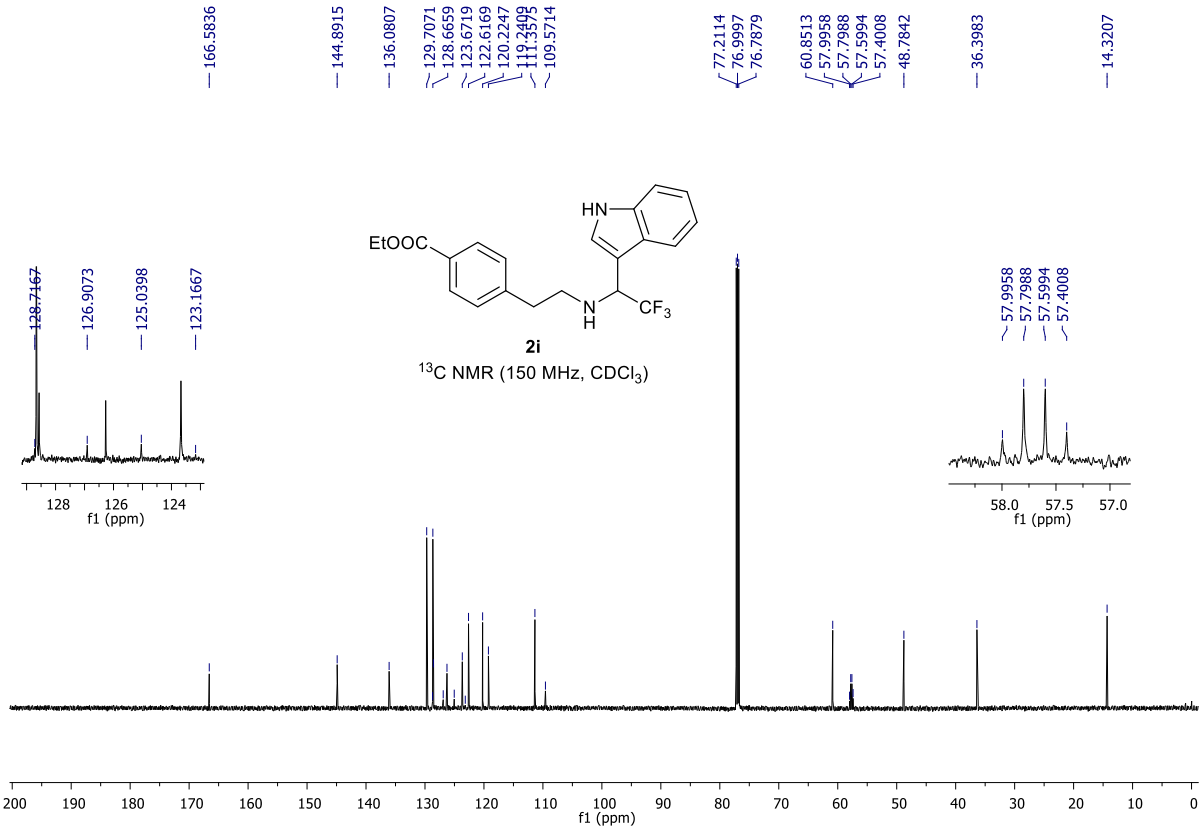
2h

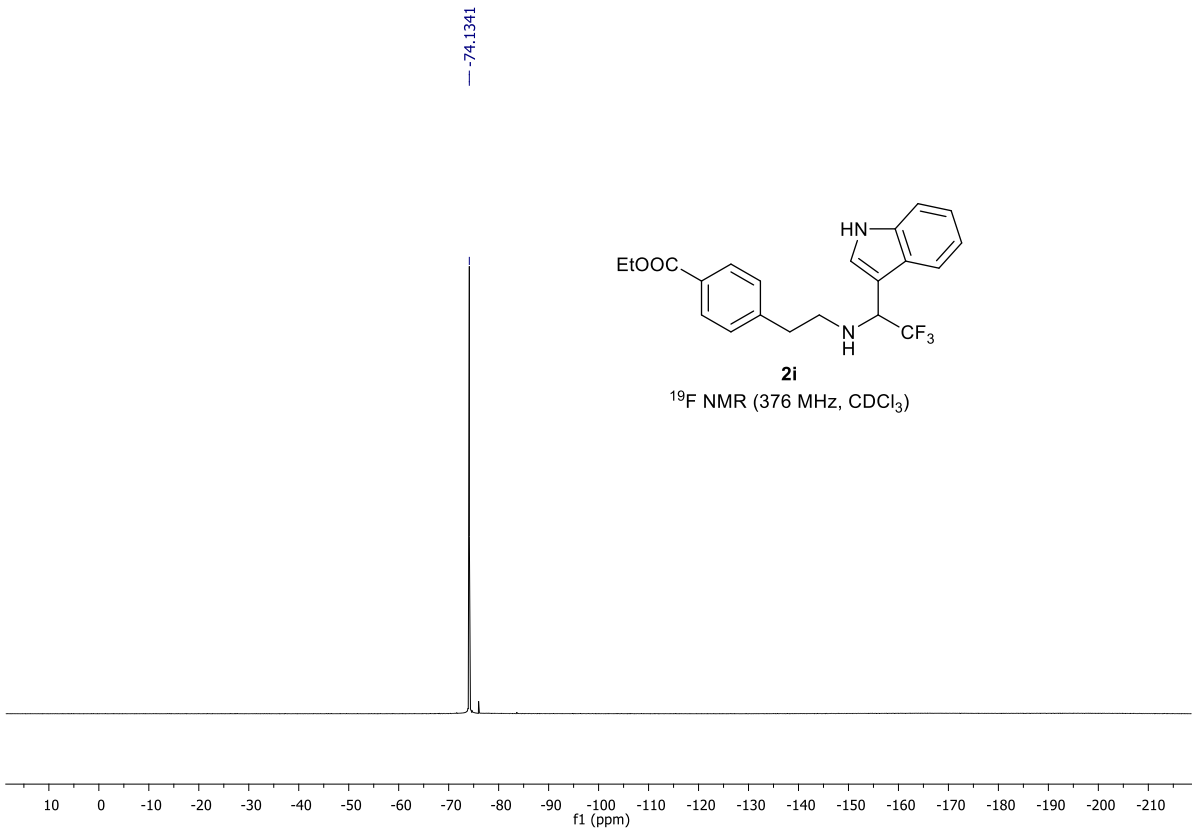
^{1}H NMR (400 MHz, $CDCl_3$)


147.4632
146.5874
136.1232
129.4789
126.1392
123.7485
123.5762
122.7119
120.2465
119.1782
109.3706
77.3179
77.0002
76.6824
58.2311
57.9315
57.6332
57.3333
48.4210
36.3141
130.1457
127.3446
124.5430
121.7414
f1 (ppm)
f1 (ppm)
HN
O2N
N
H
CF3
2h
13C NMR (100 MHz, CDCl3)


-73.9388
f1 (ppm)
HN
O2N
N
H
CF3
2h
19F NMR (376 MHz, CDCl3)

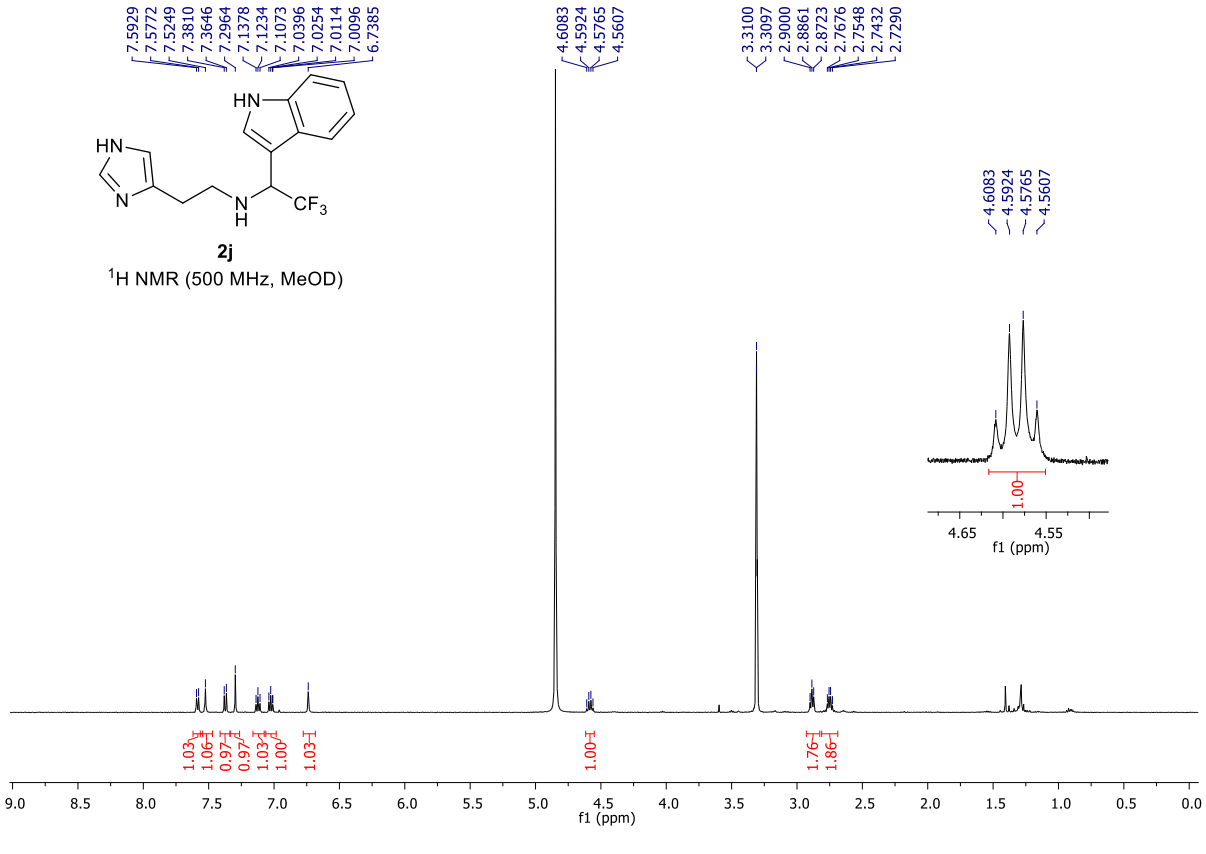

8.26
7.94
7.92
7.65
7.63
7.40
7.38
7.26
7.25
7.23
7.20
7.18
7.16
7.14
7.12
4.54
4.52
4.50
4.48
4.39
4.38
4.36
4.34
3.00
2.99
2.98
2.97
2.88
2.86
2.85
2.84
2.82
1.77
1.41
1.39
1.37
HN
EtOOC
N
H
CF3
2i
1H NMR (400 MHz, CDCl3)
1.00
2.05
1.06
1.12
1.22
3.31
1.24
1.09
2.15
2.17
2.29
1.47
3.27
f1 (ppm)


166.5836
144.8915
136.0807
129.7071
128.6659
123.6719
122.6169
120.2247
77.2114
76.9997
76.7879
60.8513
57.9958
57.7988
57.5994
57.4008
48.7842
36.3983
14.3207
HN
EtOOC
N
H
CF3
2i
13C NMR (150 MHz, CDCl3)
128.7167
126.9073
125.0398
123.1667
f1 (ppm)
57.9958
57.7988
57.5994
57.4008
f1 (ppm)



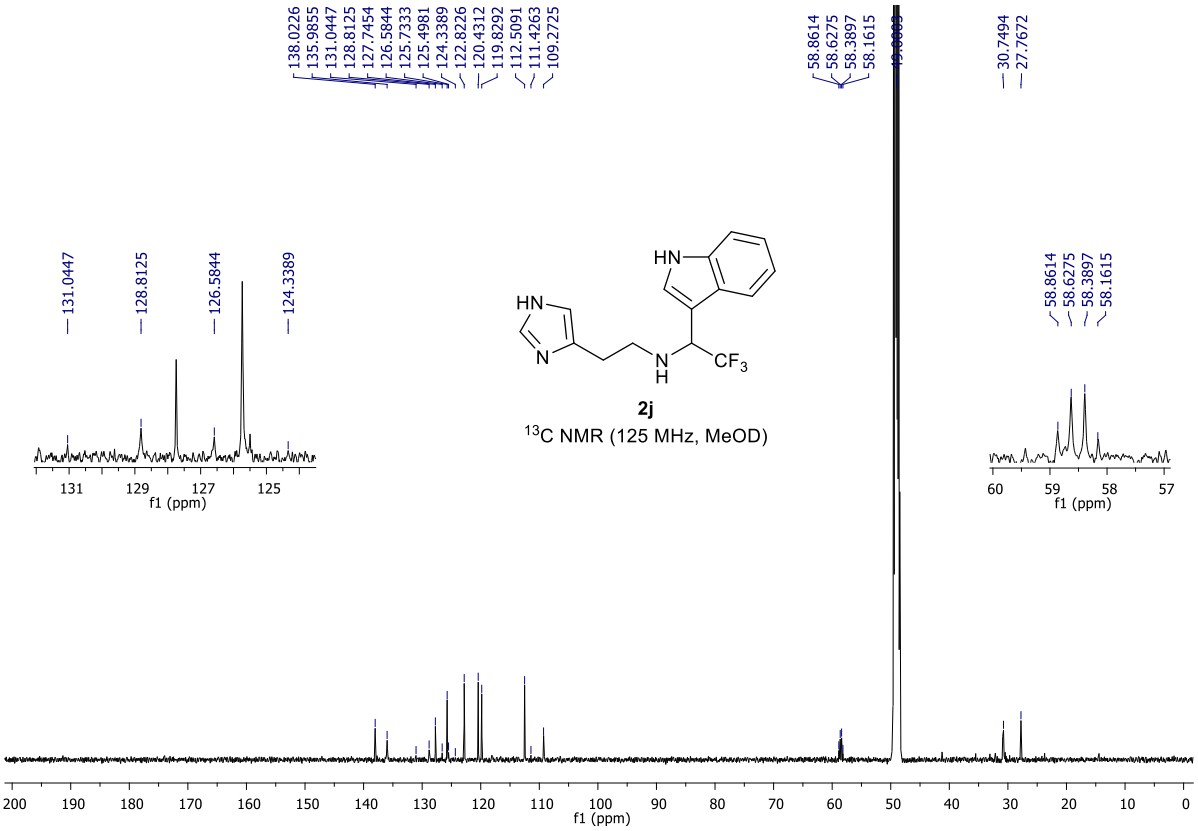
2i

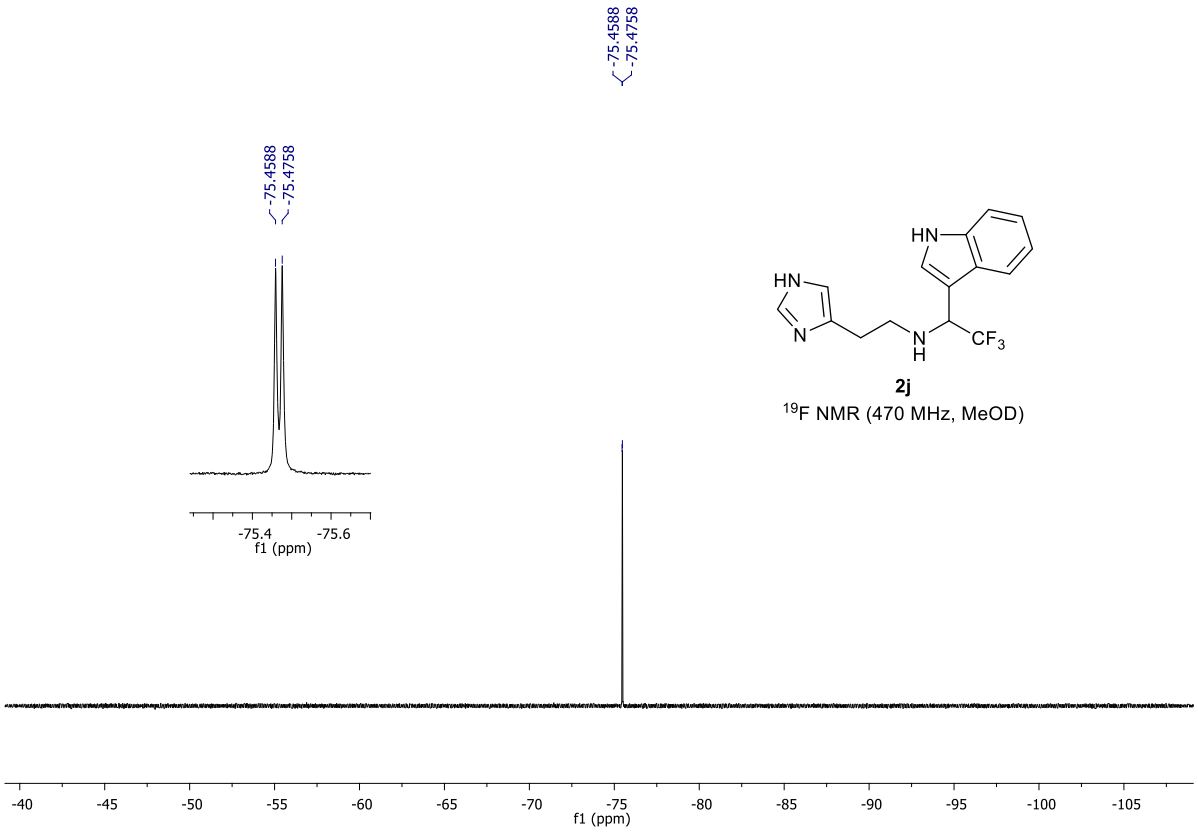
^{19}F NMR (376 MHz, $CDCl_3$)

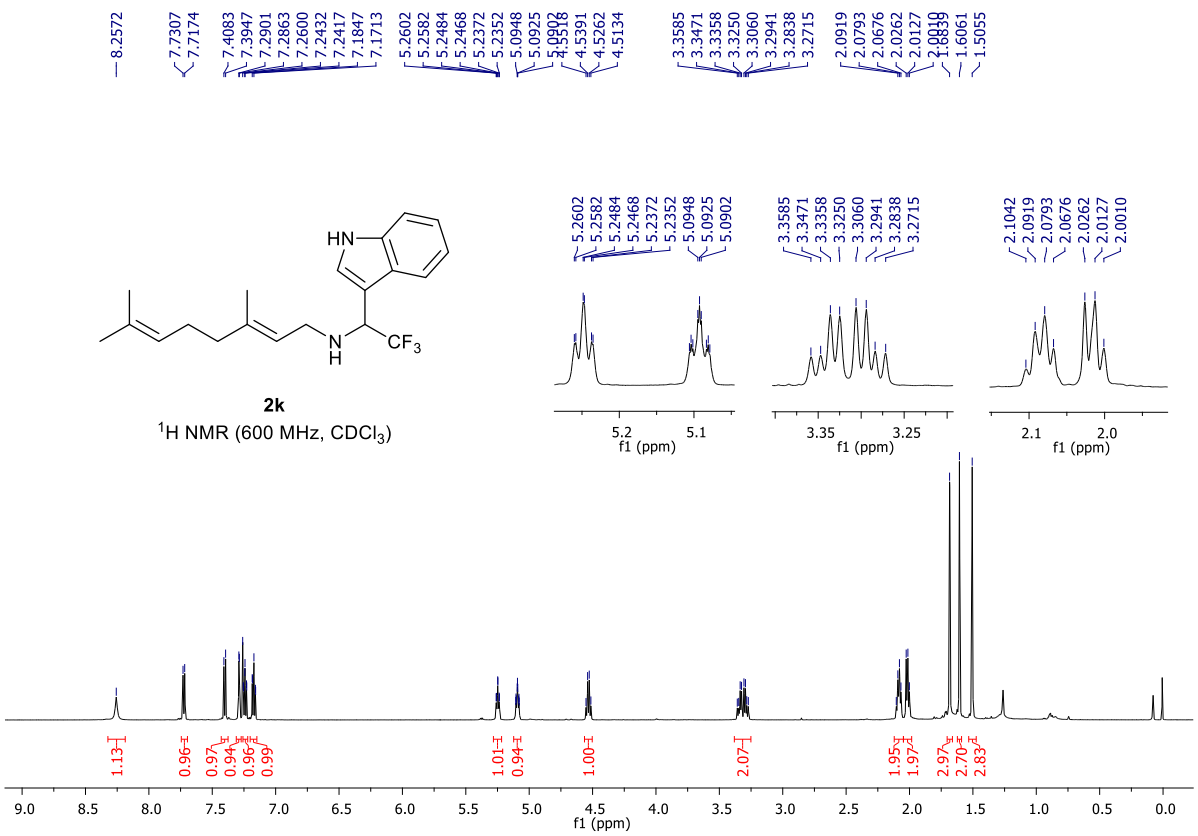


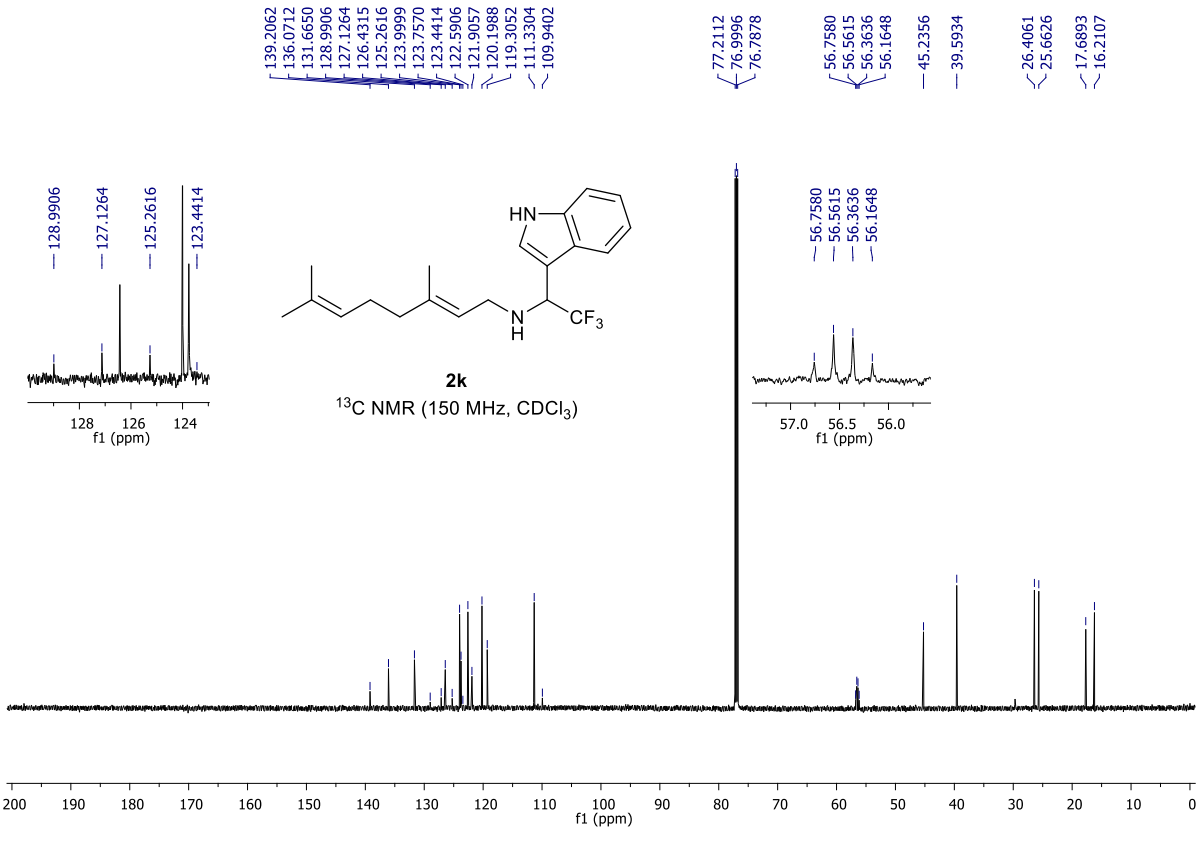
2j

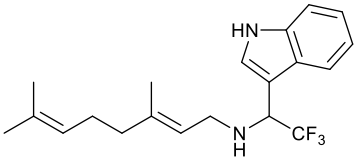
^{1}H NMR (500 MHz, MeOD)


138.0226
135.9855
131.0447
128.8125
127.7454
126.5844
125.7333
125.4981
124.3389
122.8226
120.4312
119.8292
112.5091
111.4263
109.2725
58.8614
58.6275
58.3897
58.1615
30.7494
27.7672
131.0447
128.8125
126.5844
124.3389
HN
HN
N
N
H
CF3
2j
13C NMR (125 MHz, MeOD)
f1 (ppm)


-75.4588
-75.4758
HN
HN
N
N
H
CF3
2j
19F NMR (470 MHz, MeOD)
f1 (ppm)

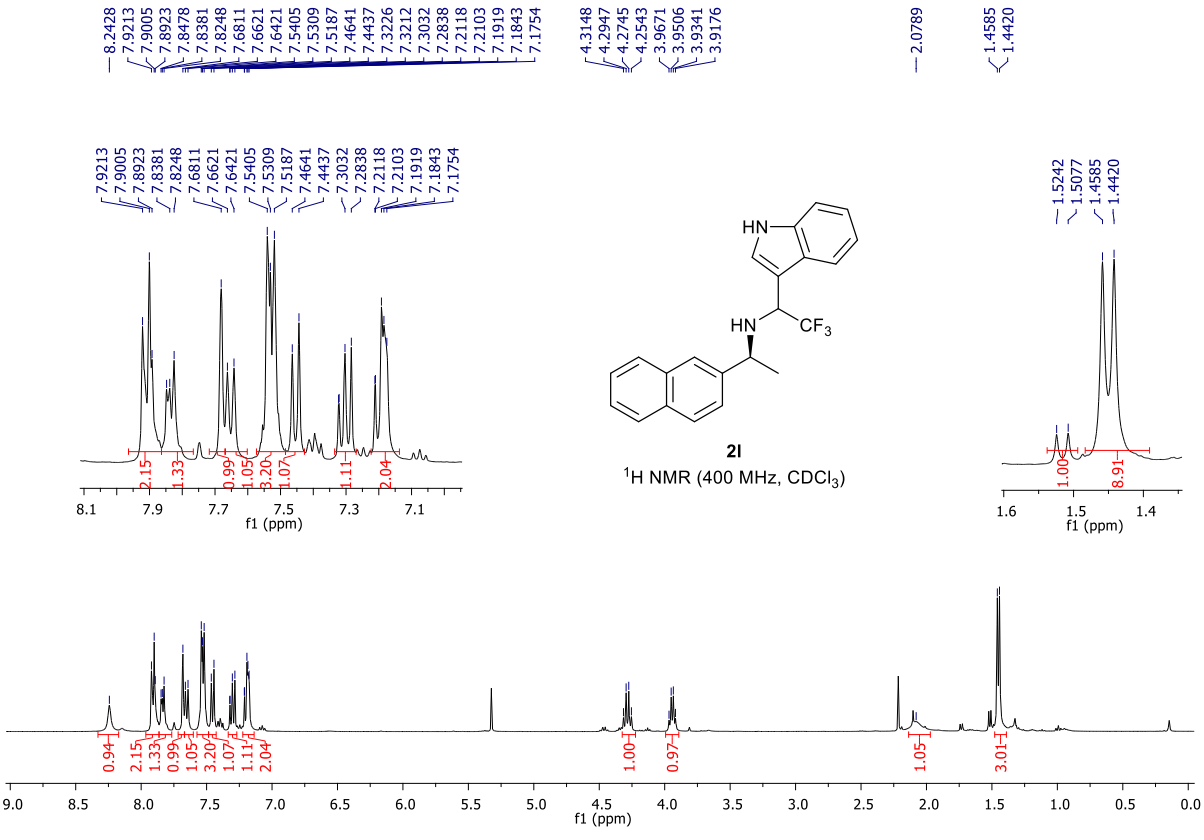

HN
N
H
CF3
2k
1H NMR (600 MHz, CDCl3)
f1 (ppm)


HN
N
H
CF3
2k
13C NMR (150 MHz, CDCl3)
f1 (ppm)



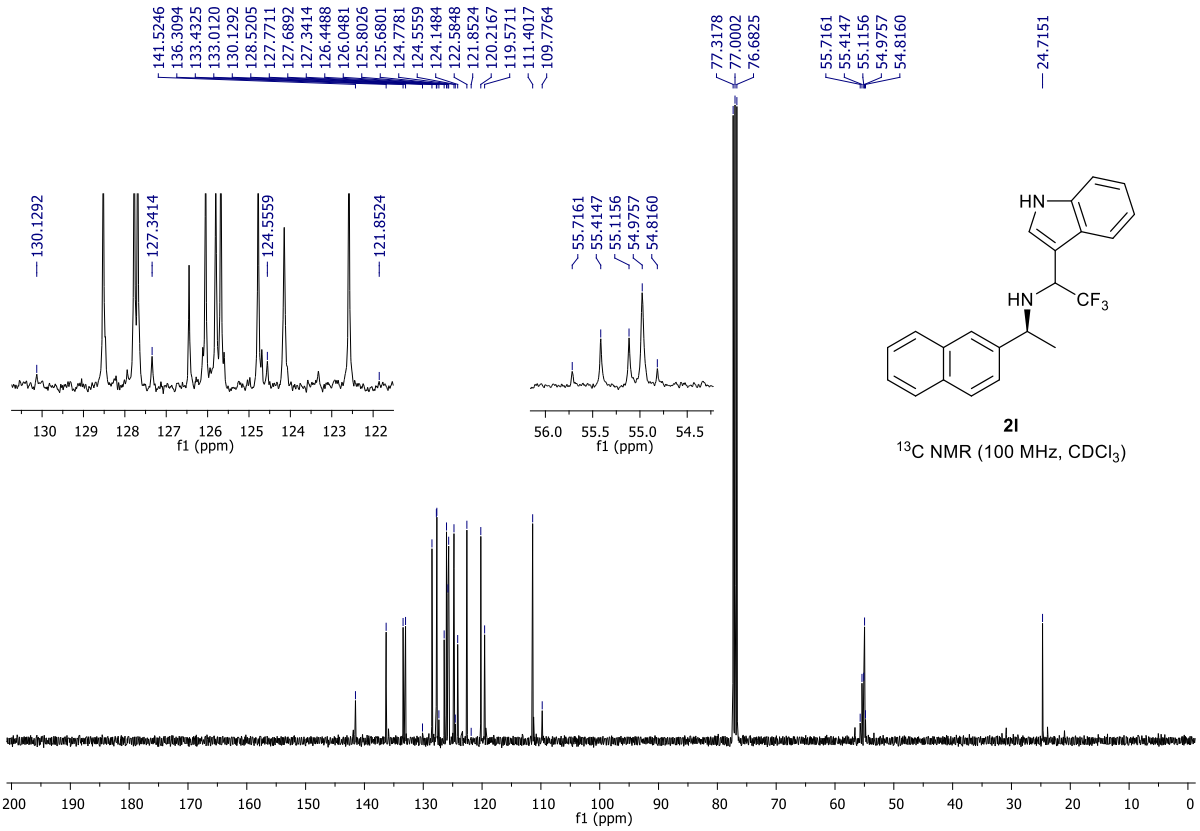
2k

^{19}F NMR (470 MHz, $CDCl_3$)



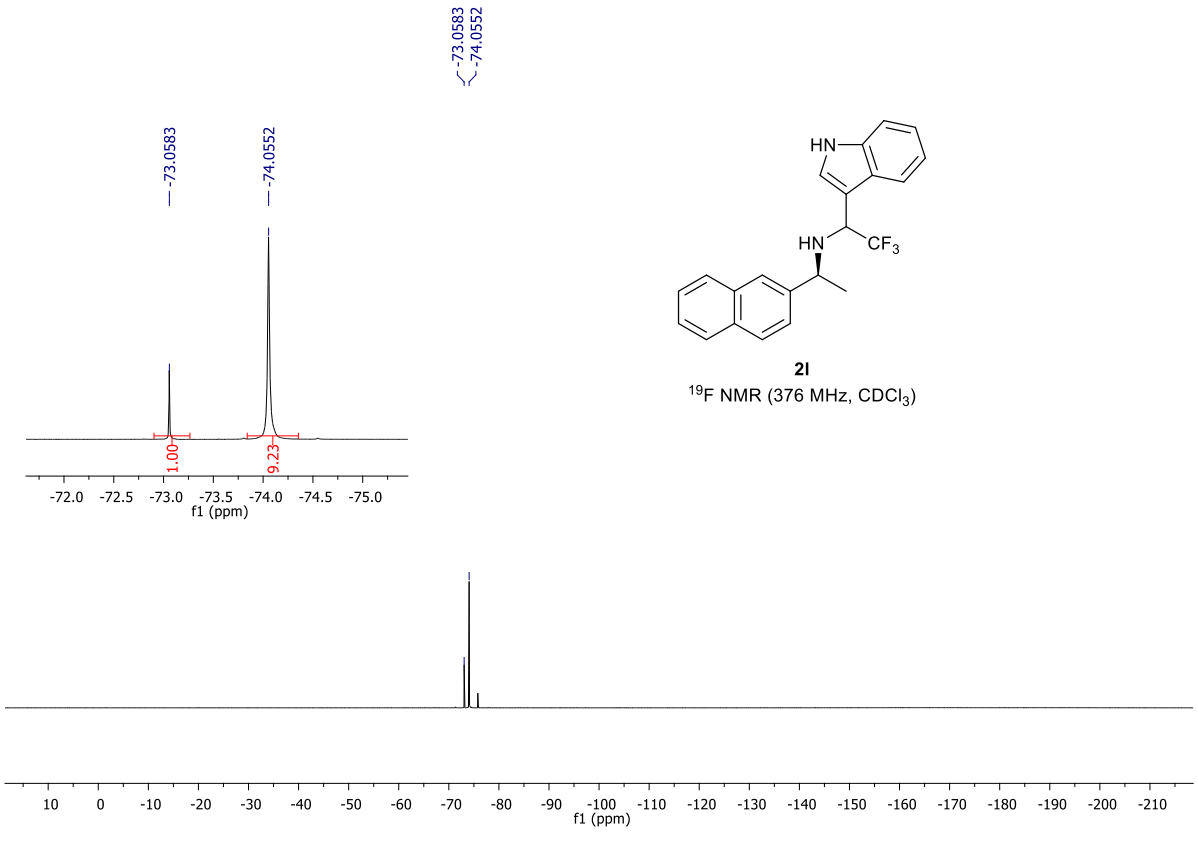
2l

^{1}H NMR (400 MHz, $CDCl_3$)



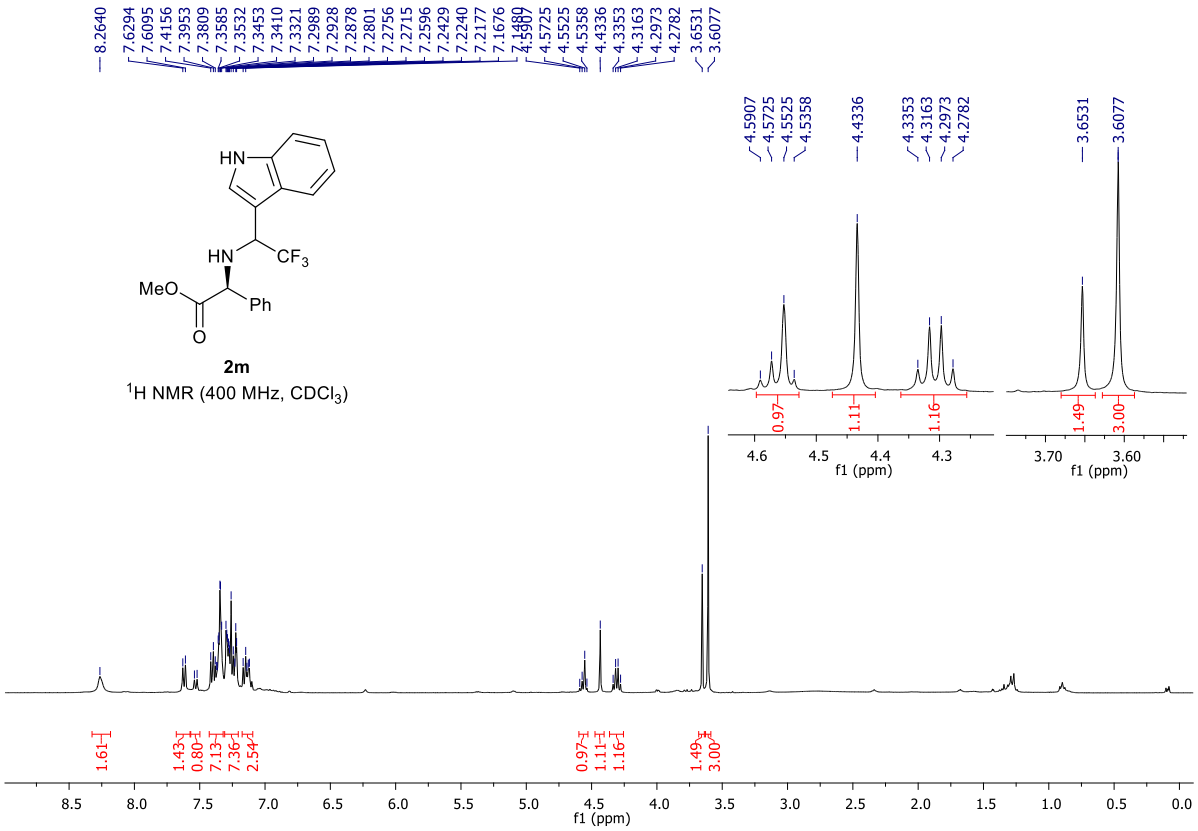
2l

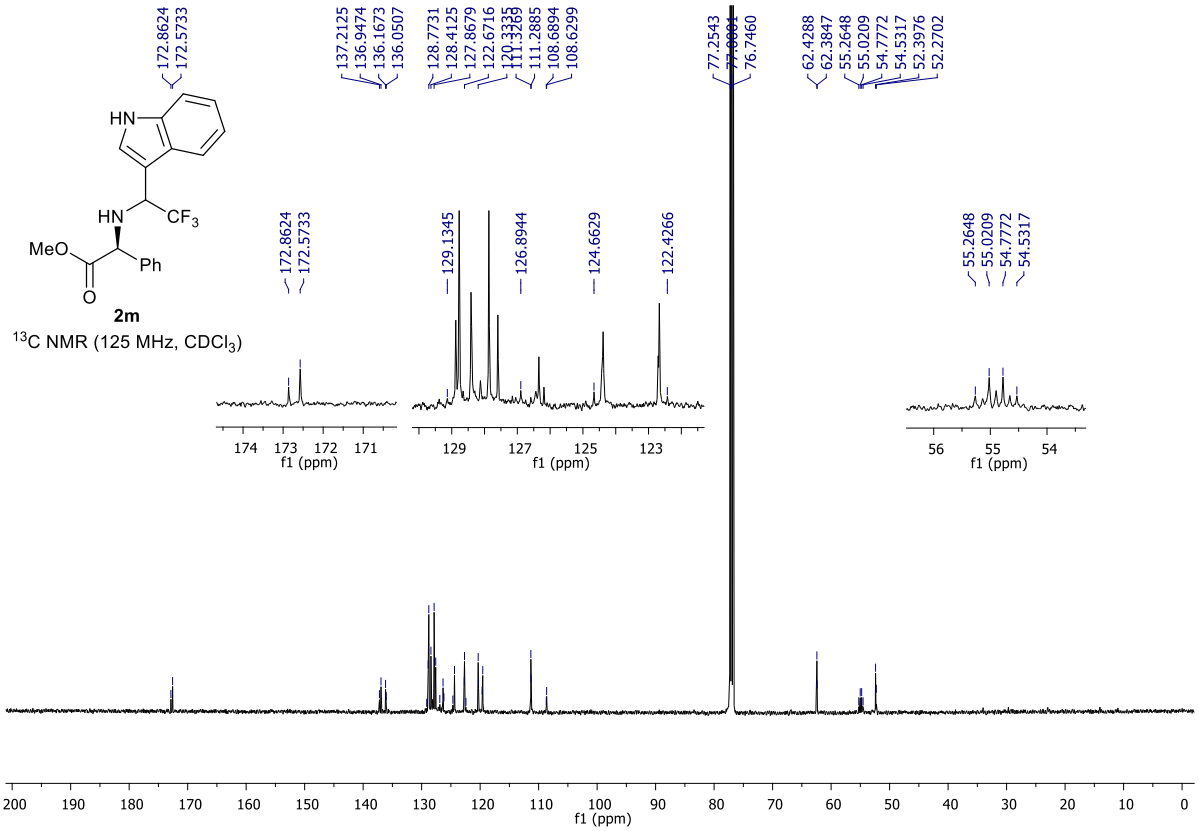
^{13}C NMR (100 MHz, $CDCl_3$)

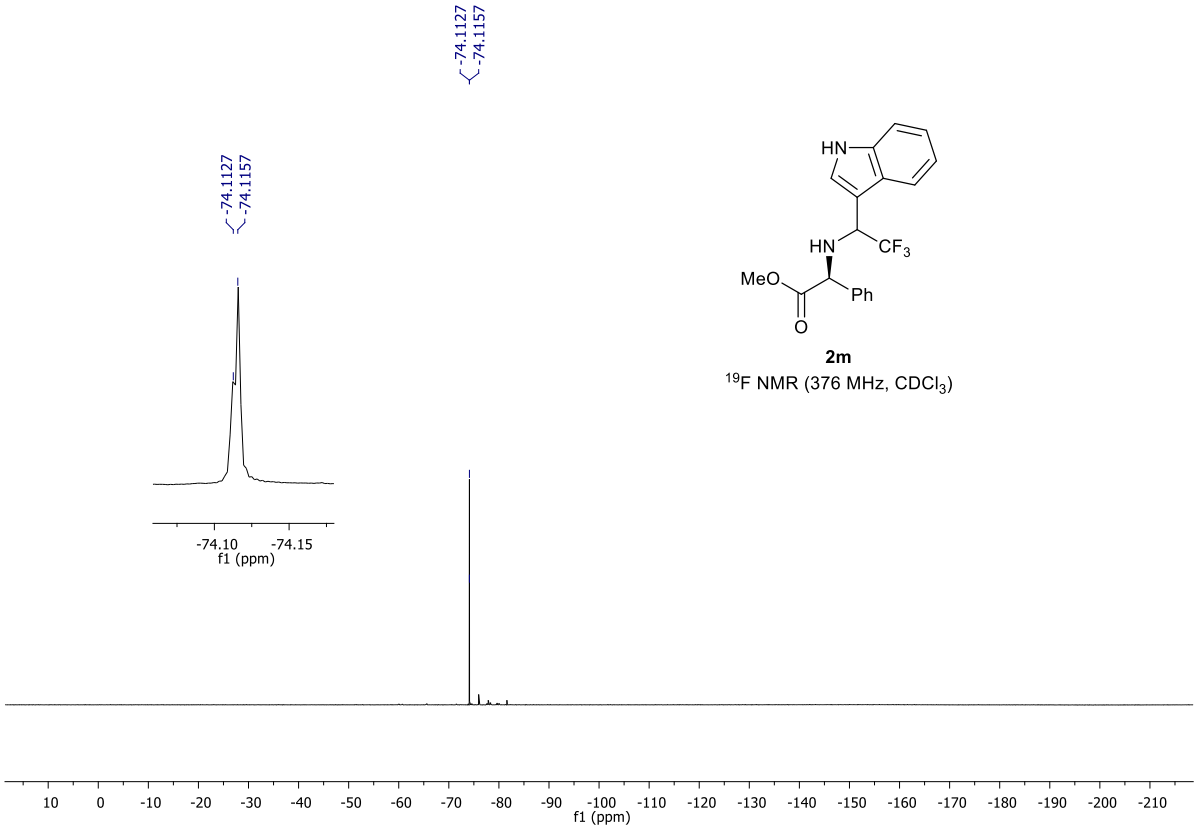


2l

^{19}F NMR (376 MHz, $CDCl_3$)

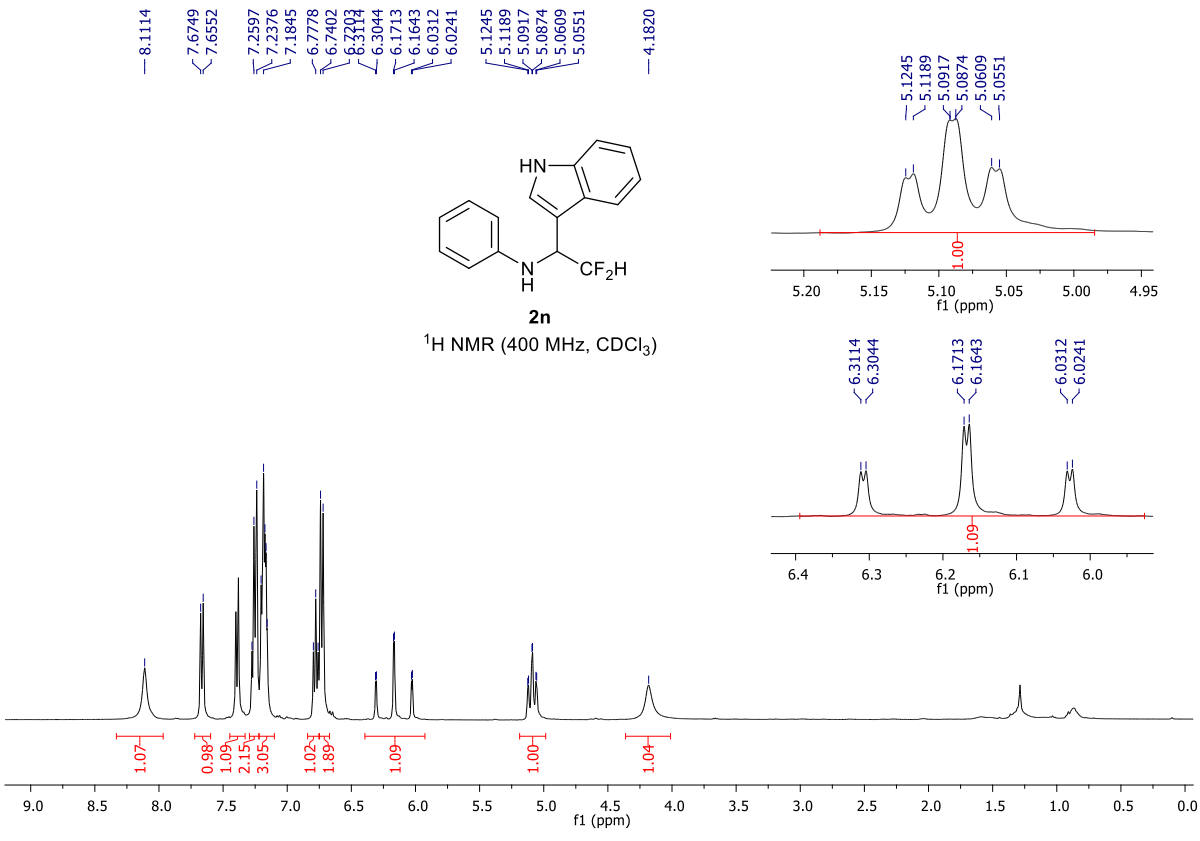

HN
HN
CF3
MeO
Ph
O
2m
1H NMR (400 MHz, CDCl3)
f1 (ppm)


HN
HN
CF3
MeO
Ph
O
2m
13C NMR (125 MHz, CDCl3)
f1 (ppm)



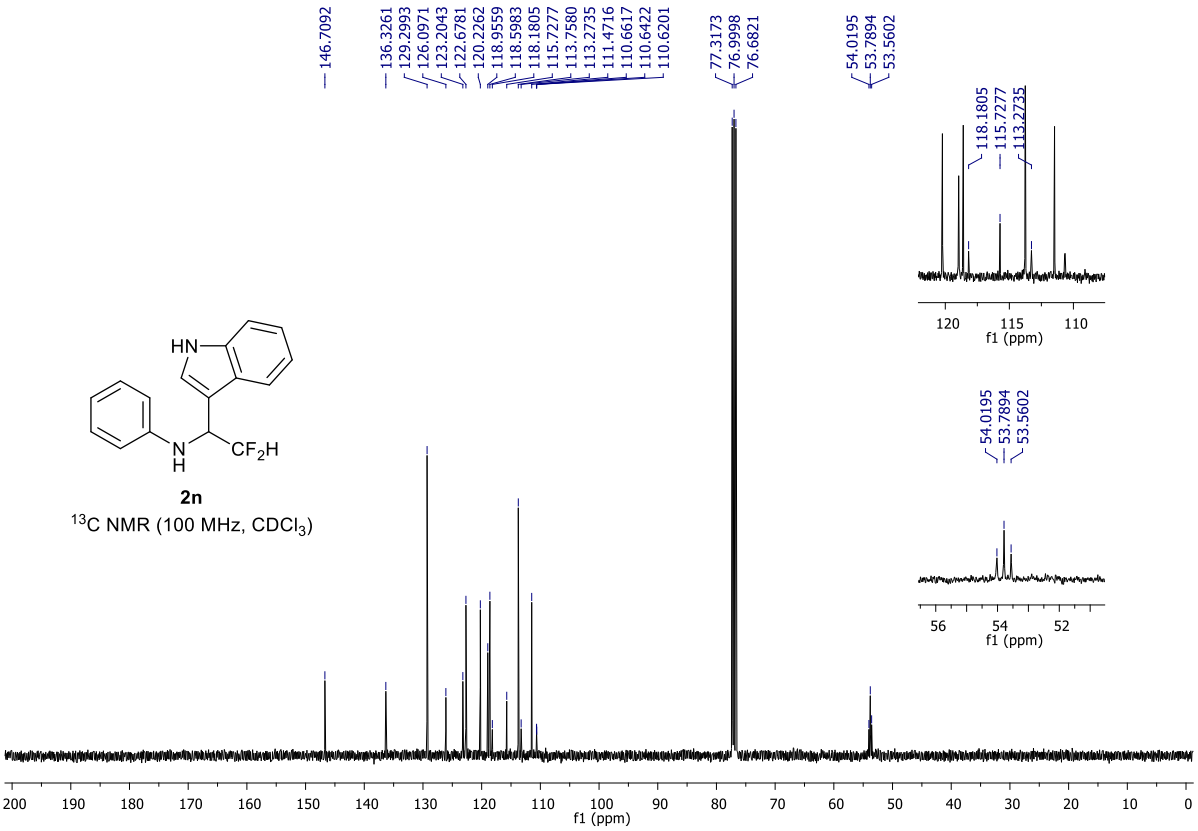
2m

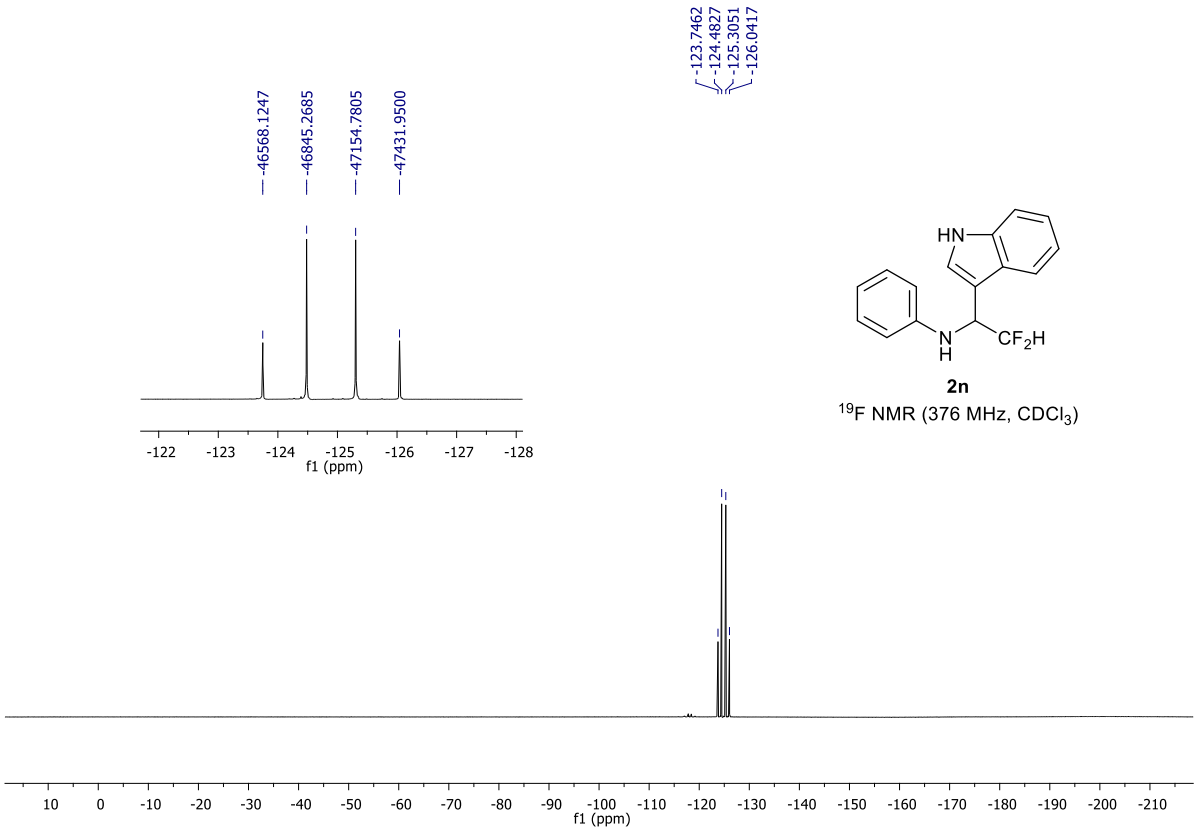
^{19}F NMR (376 MHz, $CDCl_3$)

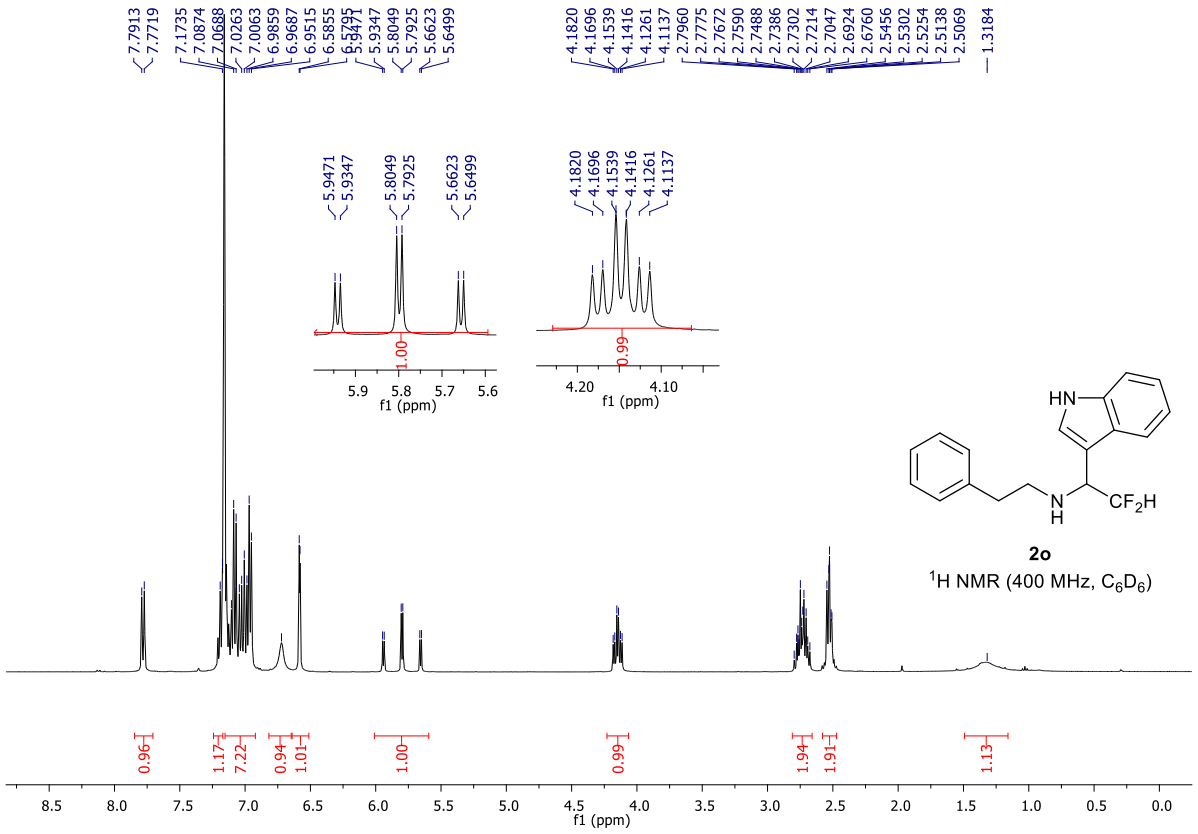


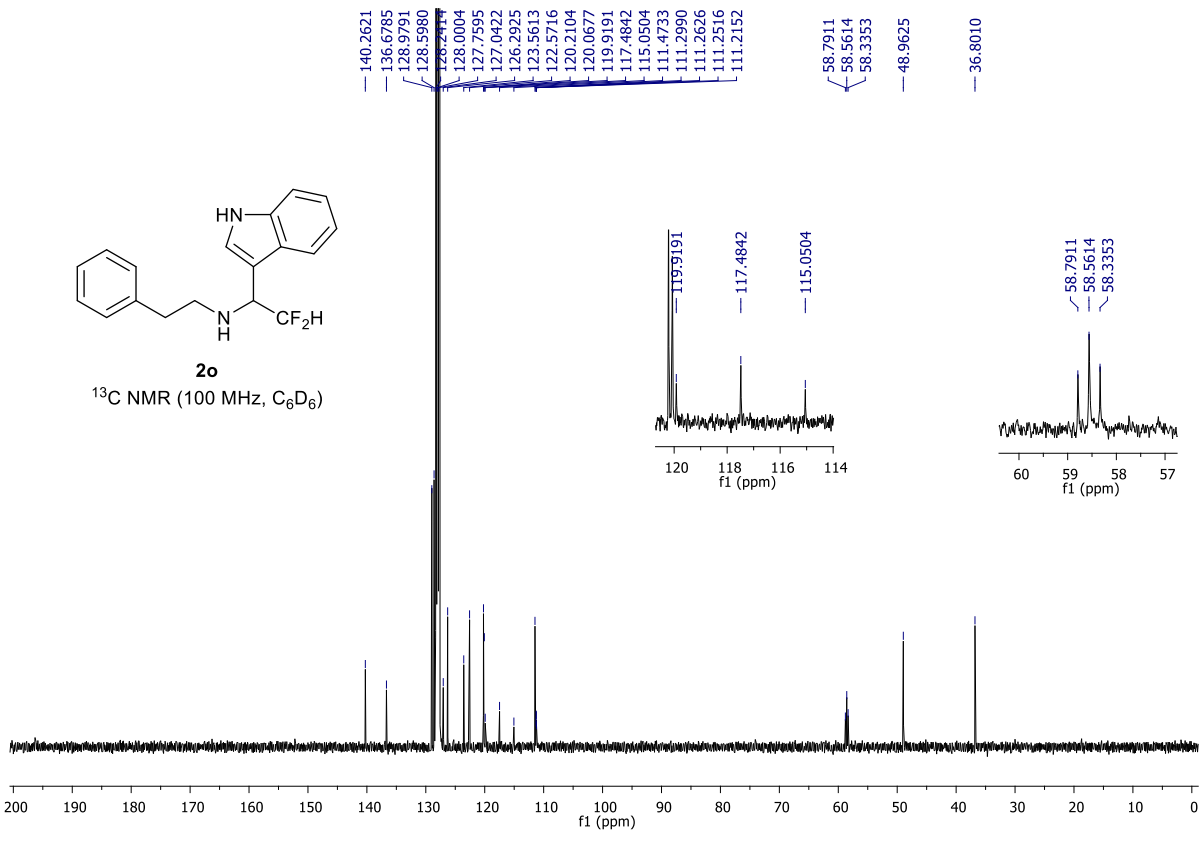
2n

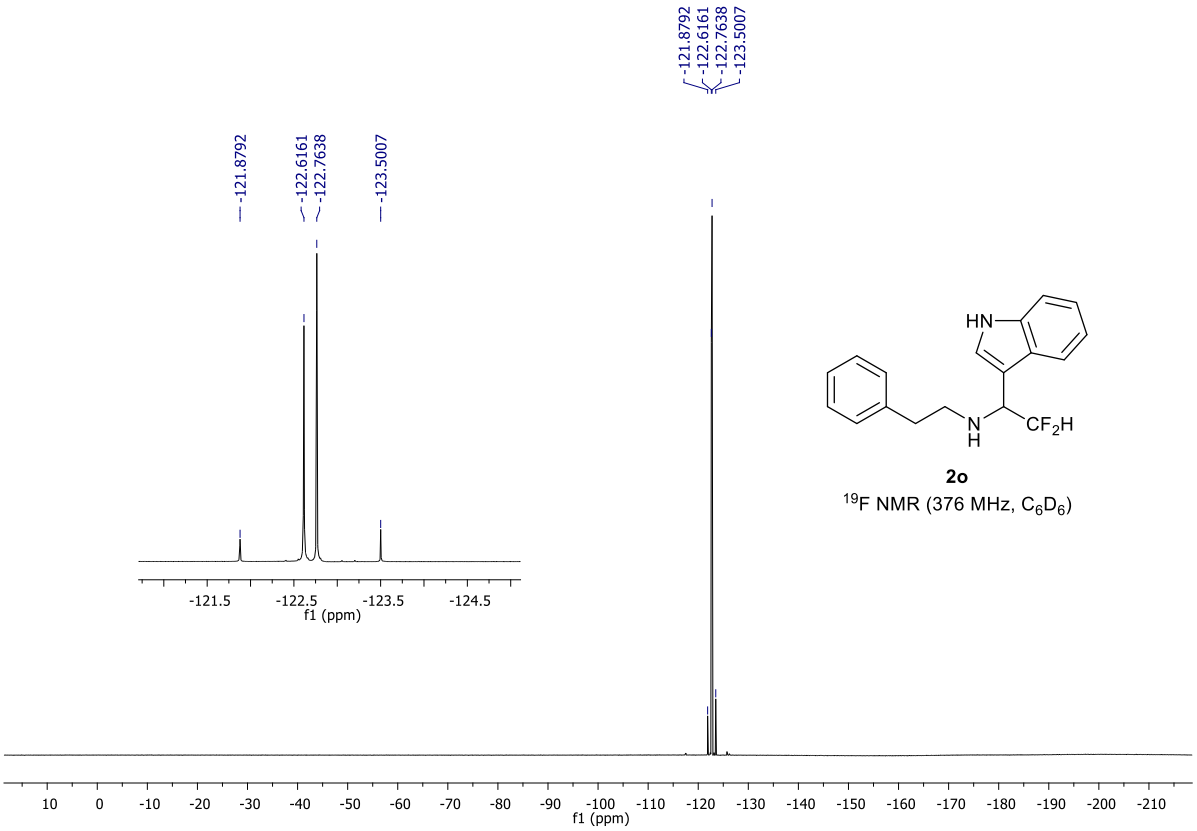
^{1}H NMR (400 MHz, $CDCl_3$)


146.7092
136.3261
129.2993
126.0971
123.2043
122.6781
120.2262
118.9559
118.5983
118.1805
115.7277
113.7580
113.2735
111.4716
110.6617
110.6422
110.6201
77.3173
76.9998
76.6821
54.0195
53.7894
53.5602
HN
N
H
CF2H
2n
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-123.7462
-124.4827
-125.3051
-126.0417
-46568.1247
-46845.2685
-47154.7805
-47431.9500
HN
N
H
CF2H
2n
19F NMR (376 MHz, CDCl3)
f1 (ppm)

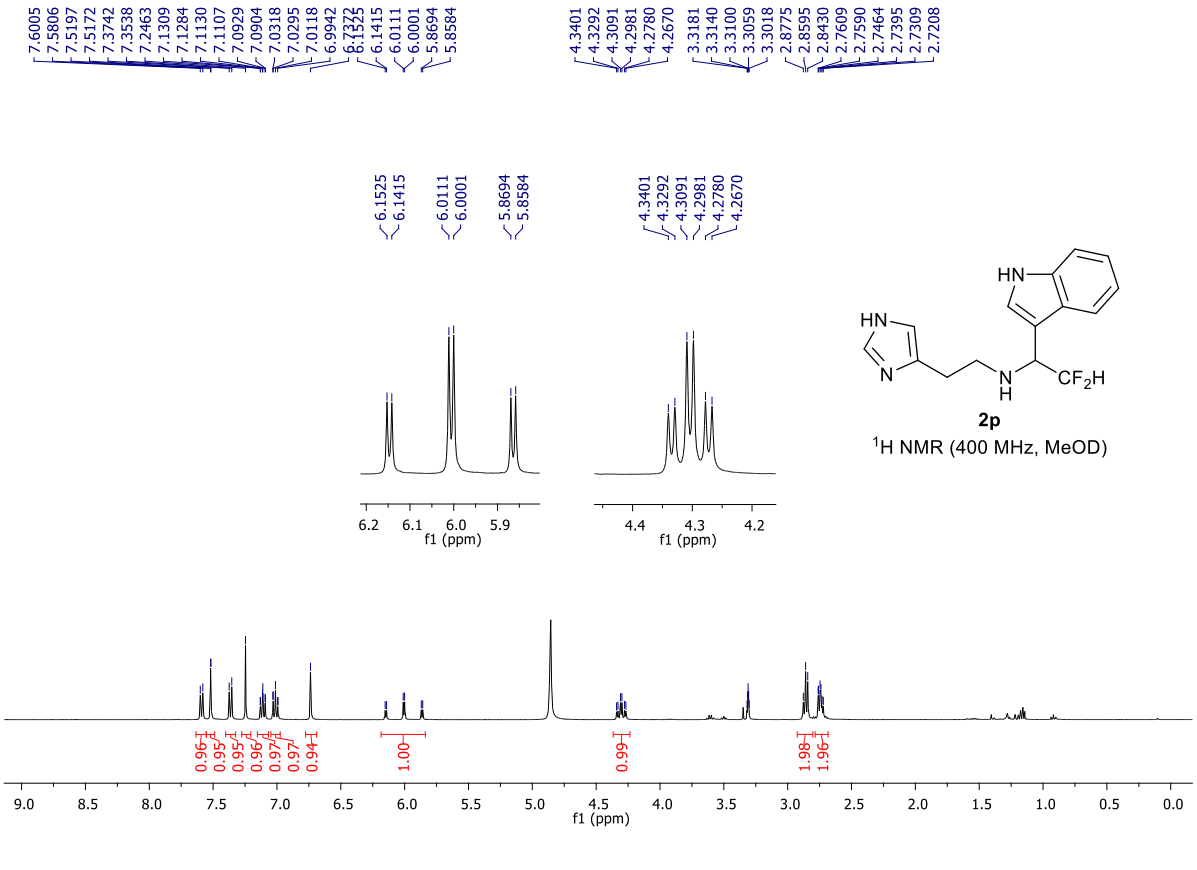

7.7913
7.7719
7.1735
7.0874
7.0688
7.0263
7.0063
6.9859
6.9687
6.9515
6.5855
6.5795
5.9471
5.9347
5.8049
5.7925
5.6623
5.6499
4.1820
4.1696
4.1539
4.1416
4.1261
4.1137
2.7960
2.7775
2.7672
2.7590
2.7488
2.7386
2.7302
2.7214
2.7047
2.6924
2.6760
2.5456
2.5302
2.5254
2.5138
2.5069
1.3184
1.00
0.99
f1 (ppm)
HN
N
H
CF2H
2o
1H NMR (400 MHz, C6D6)
0.96
1.17
7.22
0.94
1.01
1.00
0.99
1.94
1.91
1.13
f1 (ppm)


140.2621
136.6785
128.9791
128.5980
128.2414
128.0004
127.7595
127.0422
126.2925
123.5613
122.5716
120.2104
120.0677
119.9191
117.4842
115.0504
111.4733
111.2990
111.2626
111.2516
111.2152
58.7911
58.5614
58.3353
48.9625
36.8010
HN
N
H
CF2H
2o
13C NMR (100 MHz, C6D6)
f1 (ppm)



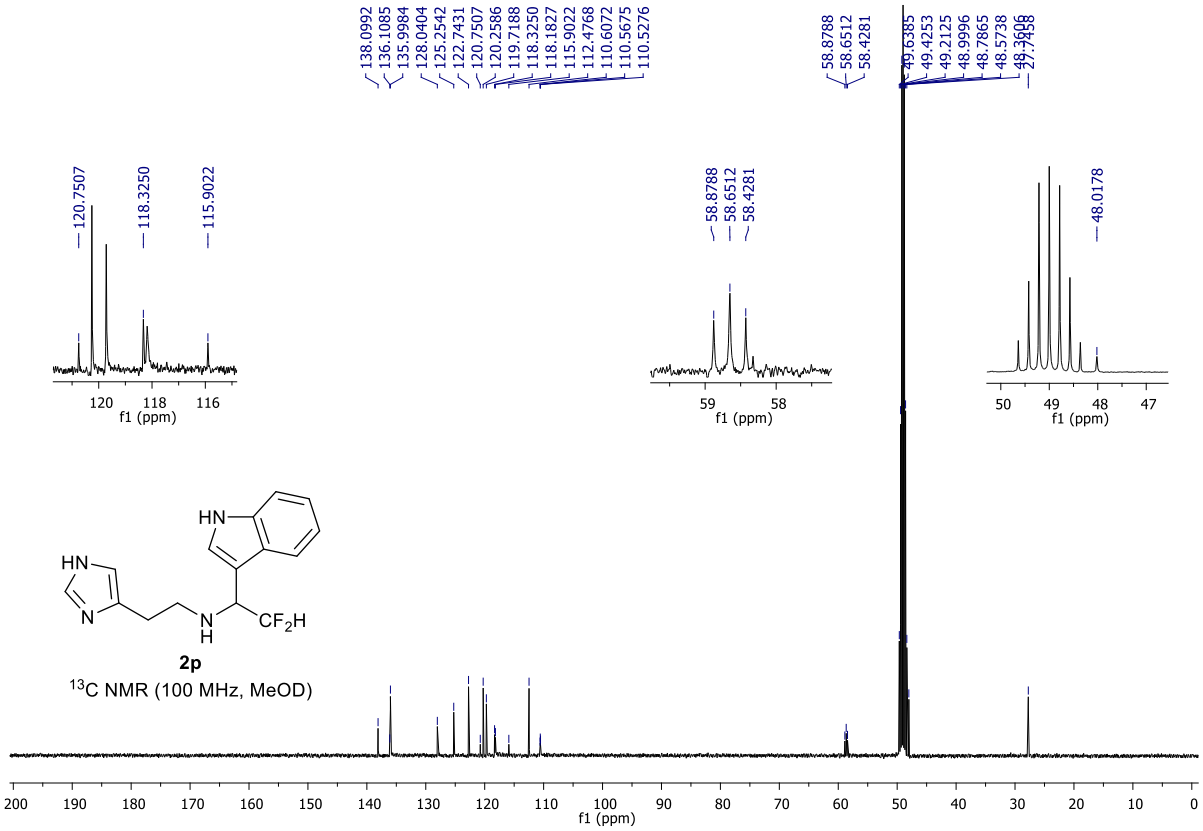
2o

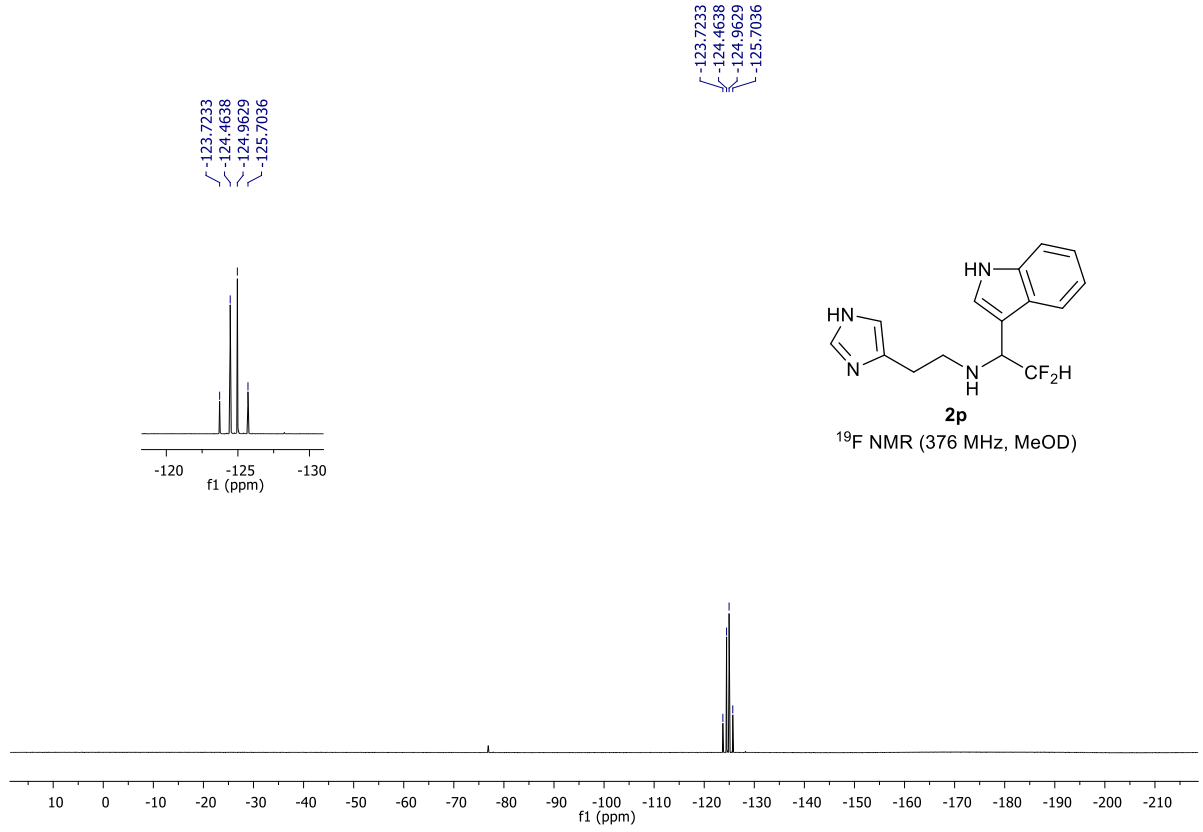
^{19}F NMR (376 MHz, C_6D_6)

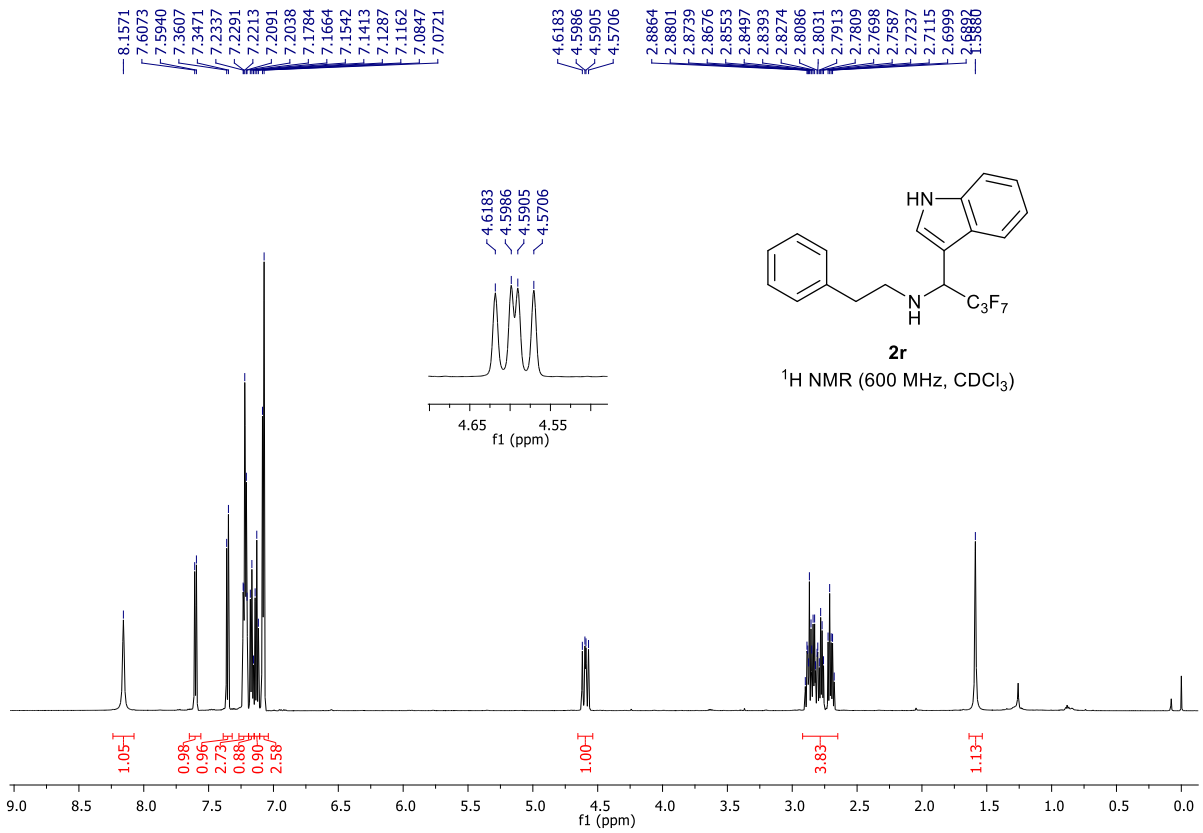


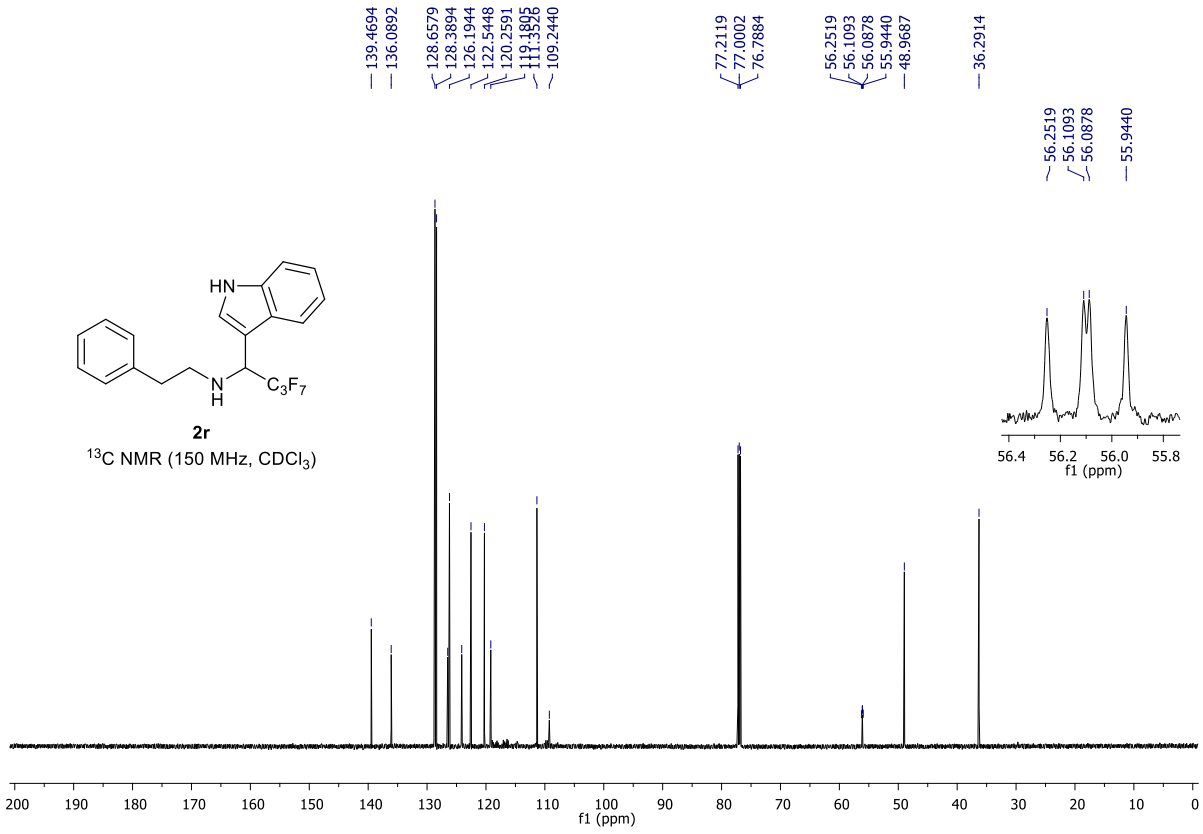
2p

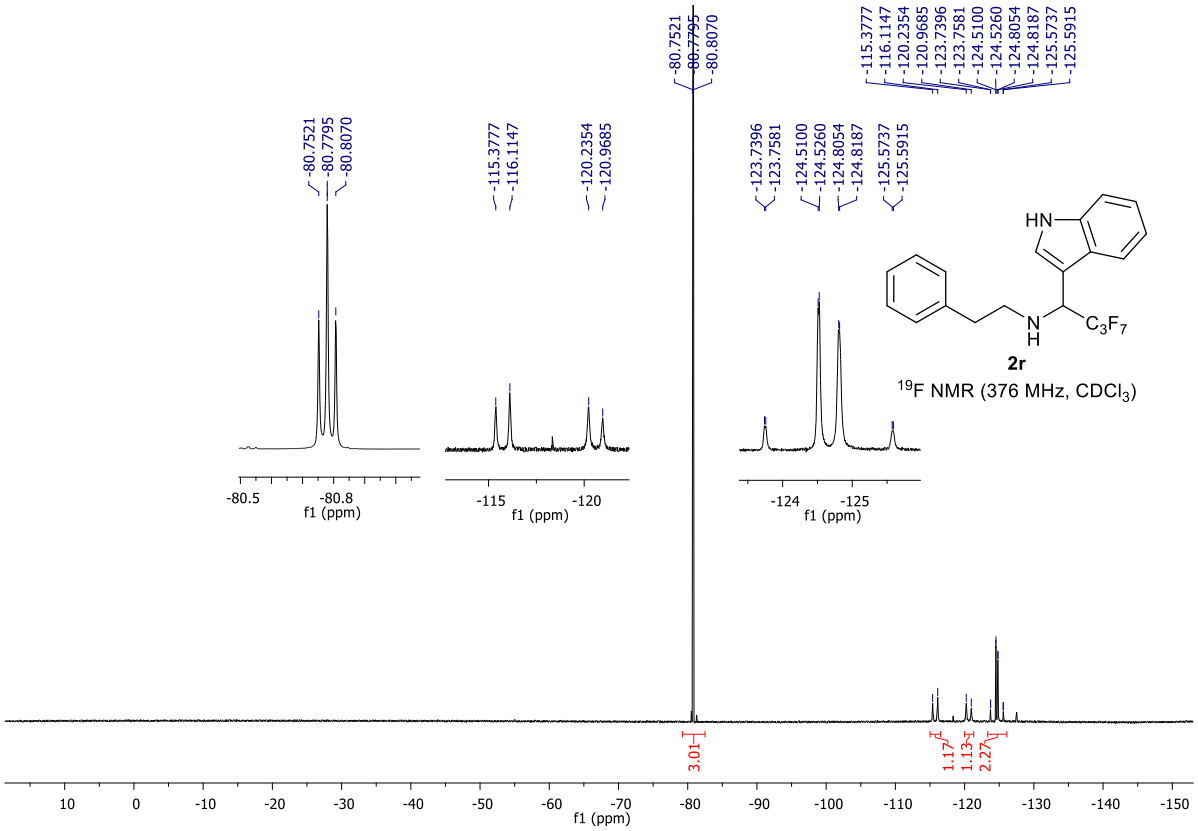
^{1}H NMR (400 MHz, MeOD)

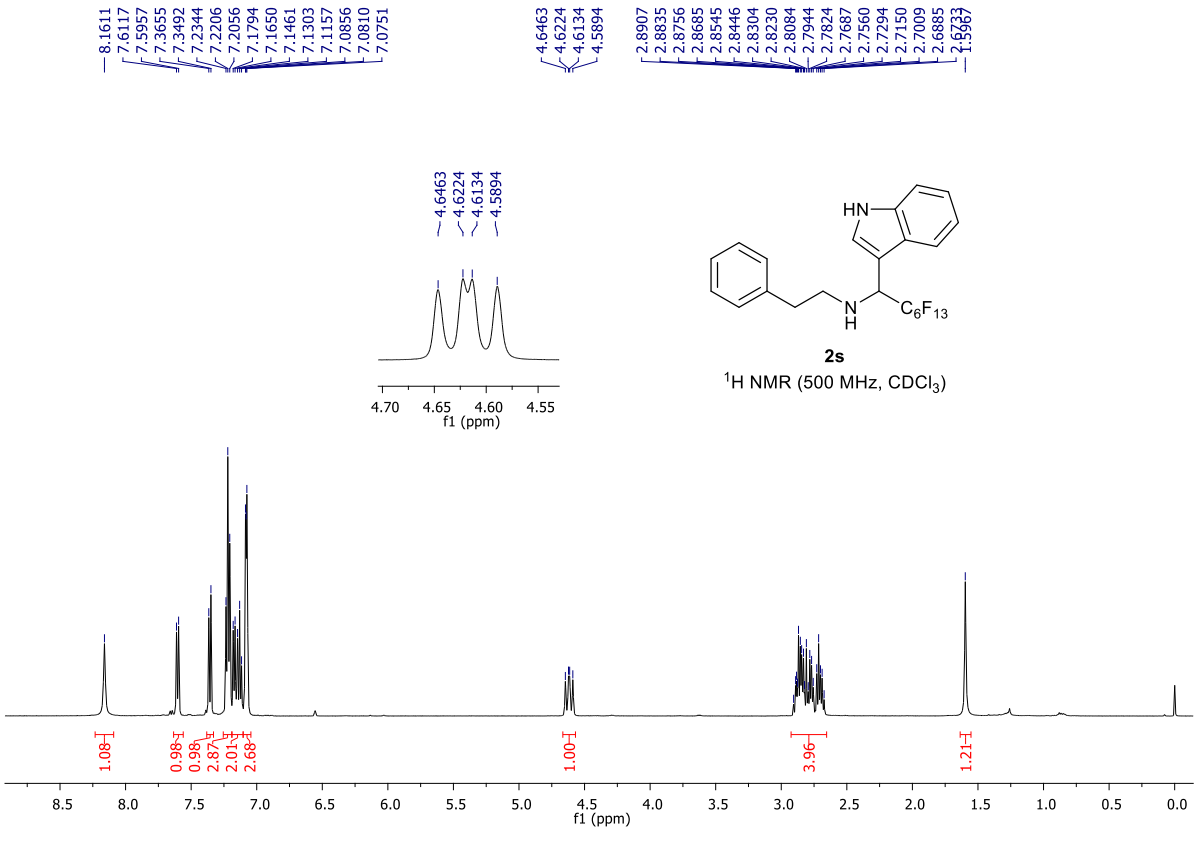

138.0992
136.1085
135.9984
128.0404
125.2542
122.7431
120.7507
120.2586
119.7188
118.3250
118.1827
115.9022
112.4768
110.6072
110.5675
110.5276
58.8788
58.6512
58.4281
49.6385
49.4253
49.2125
48.9996
48.7865
48.5738
48.3609
27.7458
120.7507
118.3250
115.9022
120 118 116
f1 (ppm)
58.8788
58.6512
58.4281
59 58
f1 (ppm)
48.0178
50 49 48 47
f1 (ppm)
HN
HN
N
N
H
CF2H
2p
13C NMR (100 MHz, MeOD)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

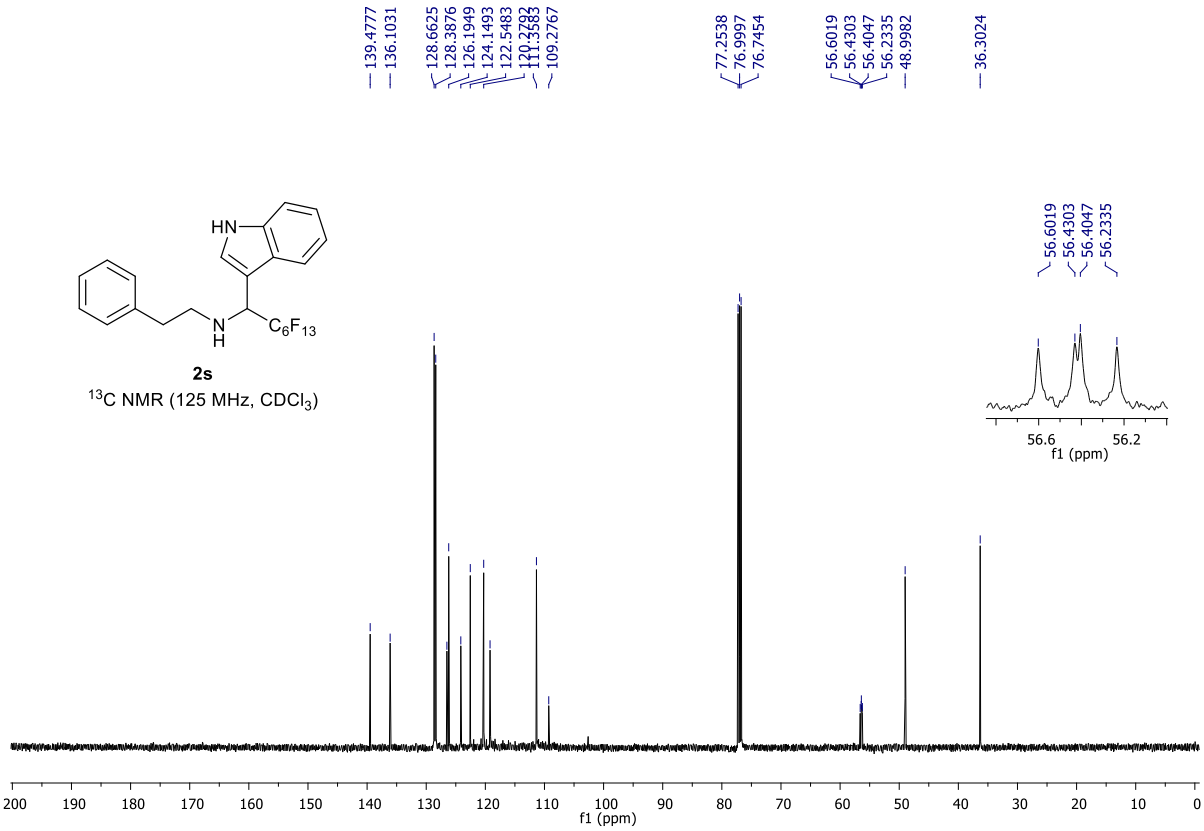

-123.7233
-124.4638
-124.9629
-125.7036
-123.7233
-124.4638
-124.9629
-125.7036
-120 -125 -130
f1 (ppm)
HN
HN
N
N
H
CF2H
2p
19F NMR (376 MHz, MeOD)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

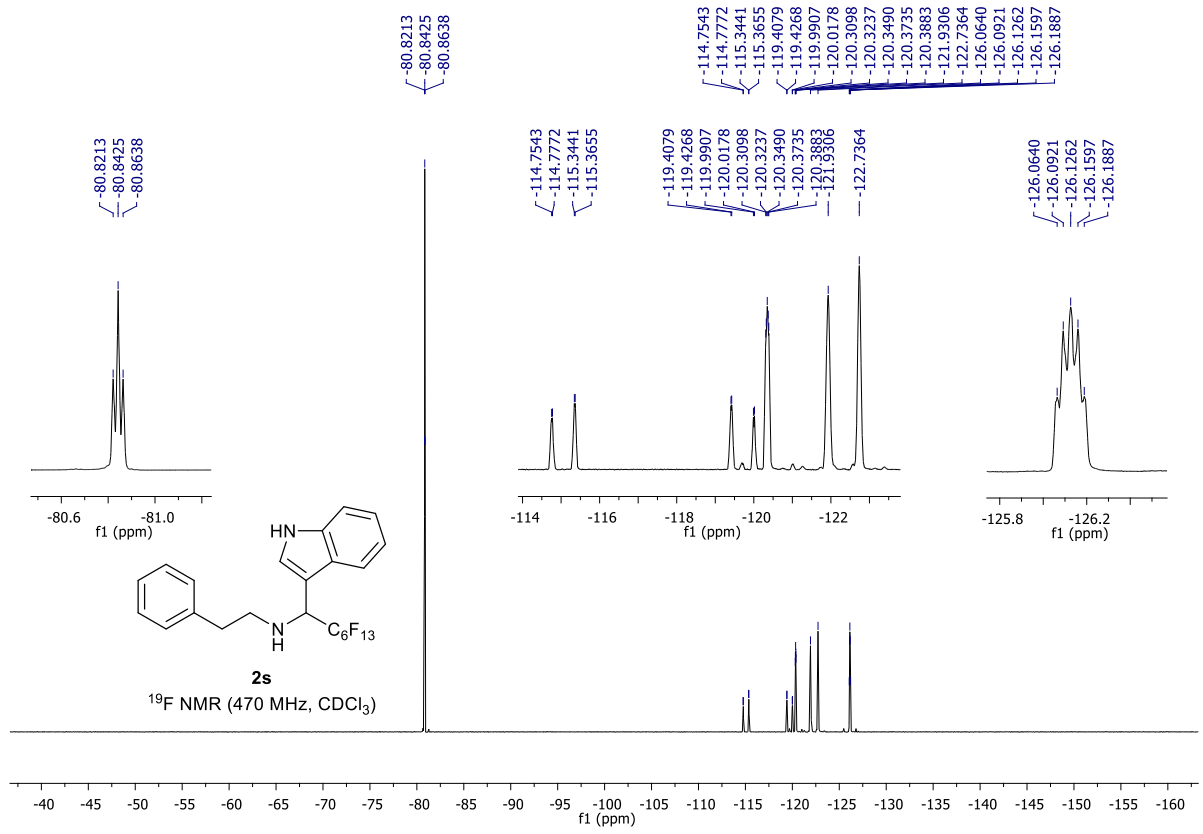

8.1571
7.6073
7.5940
7.3607
7.3471
7.2337
7.2291
7.2213
7.2091
7.2038
7.1784
7.1664
7.1542
7.1413
7.1287
7.1162
7.0847
7.0721
4.6183
4.5986
4.5905
4.5706
2.8864
2.8801
2.8739
2.8676
2.8553
2.8497
2.8393
2.8274
2.8086
2.8031
2.7913
2.7809
2.7698
2.7587
2.7237
2.7115
2.6999
2.6882
1.5880
HN
N
H
C_3F_7
2r
^{1}H NMR (600 MHz, $CDCl_3$)
4.65
4.55
f1 (ppm)
1.05
0.98
0.96
2.73
0.88
0.90
2.58
1.00
3.83
1.13
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


139.4694
136.0892
128.6579
128.3894
126.1944
122.5448
120.2591
111.3925
109.2440
77.2119
77.0002
76.7884
56.2519
56.1093
56.0878
55.9440
48.9687
36.2914
HN
N
H
C_3F_7
2r
^{13}C NMR (150 MHz, $CDCl_3$)
56.4
56.2
56.0
55.8
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

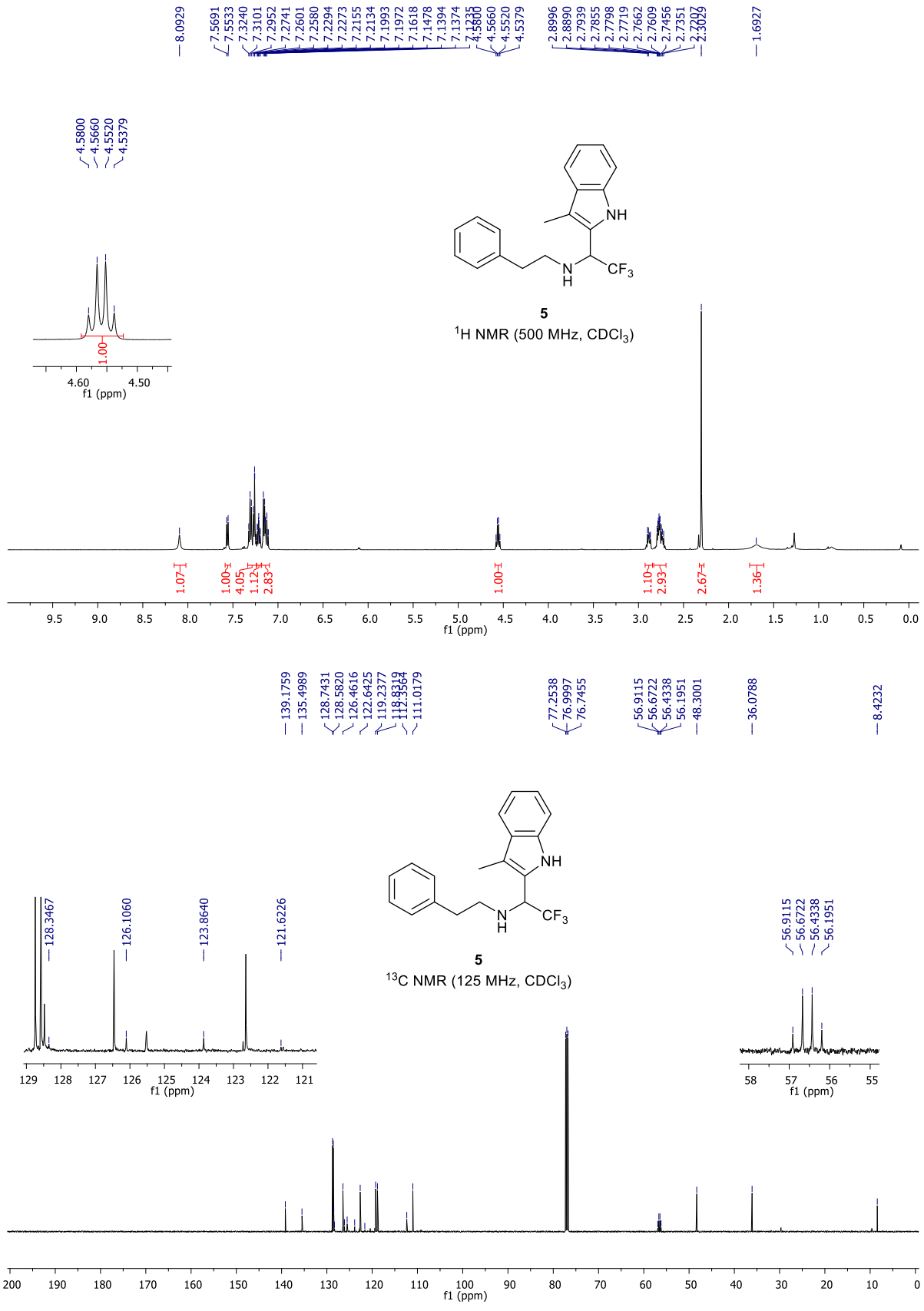

-80.7521
-80.7795
-80.8070
-115.3777
-116.1147
-120.2354
-120.9685
-123.7396
-123.7581
-124.5100
-124.5260
-124.8054
-124.8187
-125.5737
-125.5915
HN
N
H
C_3F_7
2r
^{19}F NMR (376 MHz, $CDCl_3$)
f1 (ppm)
3.01
1.17
1.13
2.27

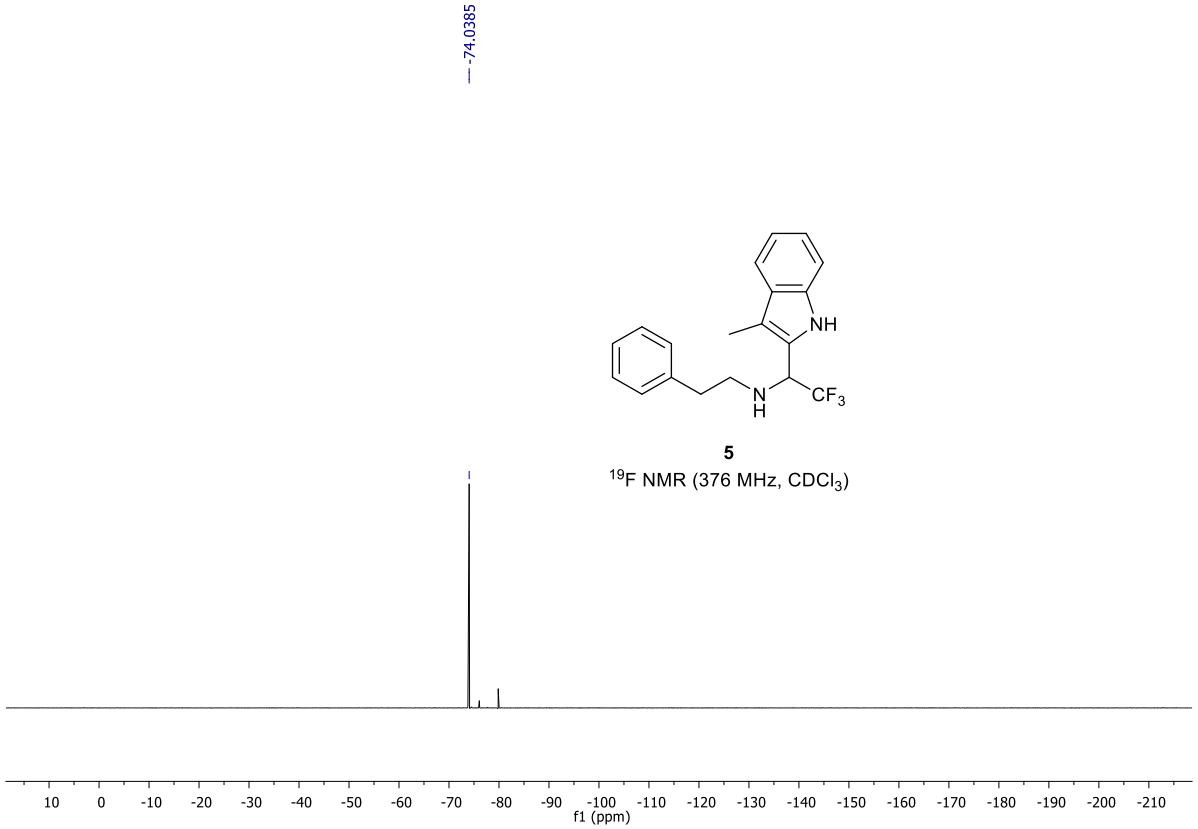

8.1611
7.6117
7.5957
7.3655
7.3492
7.2344
7.2206
7.2056
7.1794
7.1650
7.1461
7.1303
7.1157
7.0856
7.0810
7.0751
4.6463
4.6224
4.6134
4.5894
2.8907
2.8835
2.8756
2.8685
2.8545
2.8446
2.8304
2.8230
2.8084
2.7944
2.7824
2.7687
2.7560
2.7294
2.7150
2.7009
2.6885
HN
N
H
C_6F_{13}
2s
^{1}H NMR (500 MHz, $CDCl_3$)
f1 (ppm)
1.08
0.98
0.98
2.87
2.01
2.68
1.00
3.96
1.21

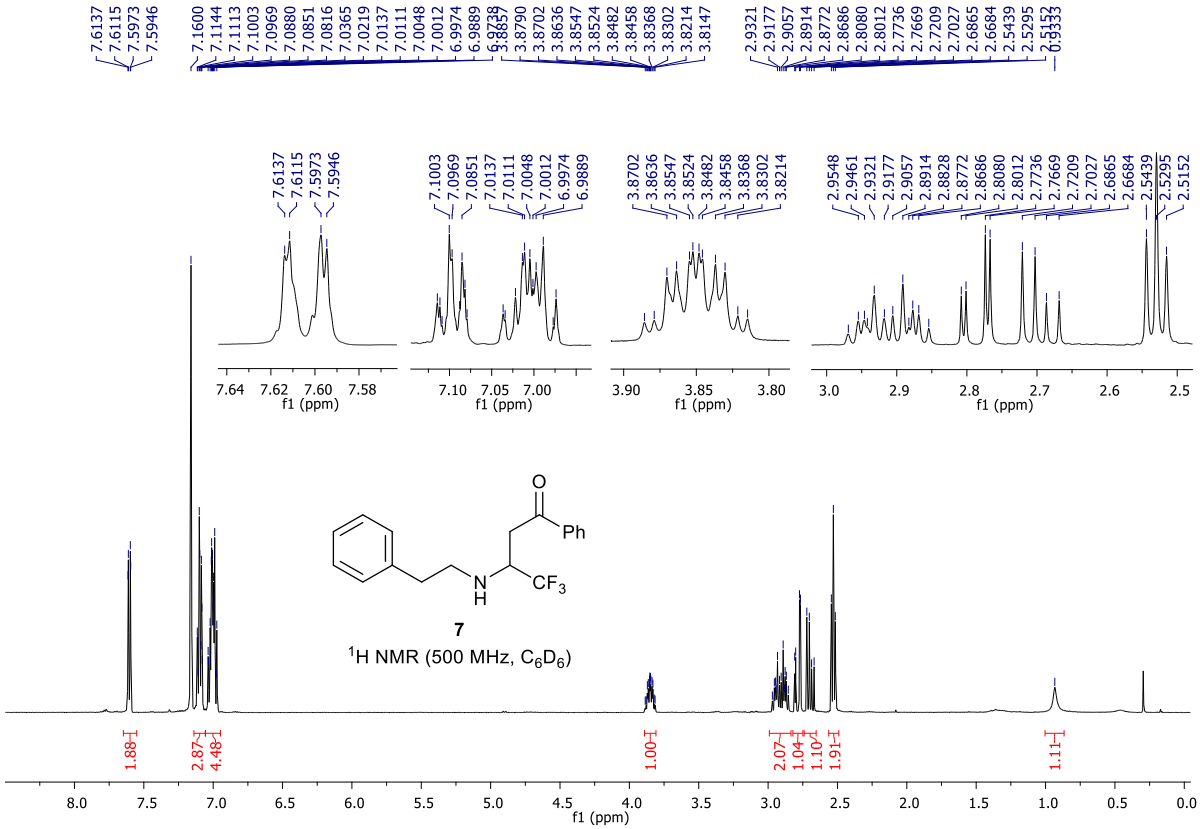

139.4777
136.1031
128.6625
128.3876
126.1949
124.1493
122.5483
120.2792
111.3583
109.2767
77.2538
76.9997
76.7454
56.6019
56.4303
56.4047
56.2335
48.9982
36.3024
HN
N
H
C6F13
2s
13C NMR (125 MHz, CDCl3)
f1 (ppm)


-80.8213
-80.8425
-80.8638
-114.7543
-114.7772
-115.3441
-115.3655
-119.4079
-119.4268
-119.9907
-120.0178
-120.3098
-120.3237
-120.3490
-120.3735
-120.3883
-121.9306
-122.7364
-126.0640
-126.0921
-126.1262
-126.1597
-126.1887
HN
N
H
C6F13
2s
19F NMR (470 MHz, CDCl3)
f1 (ppm)

NMR spectra of amines 5, 7, 9, 11, 14 and 16-18

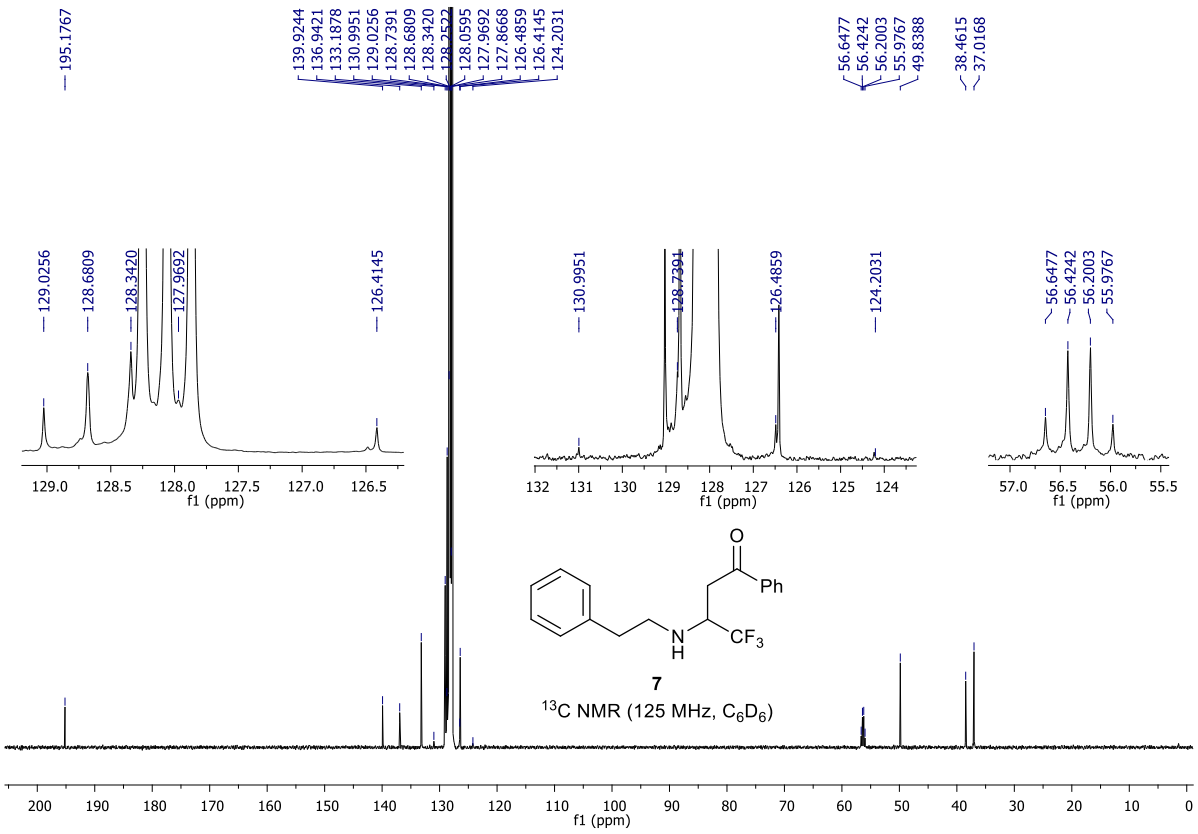


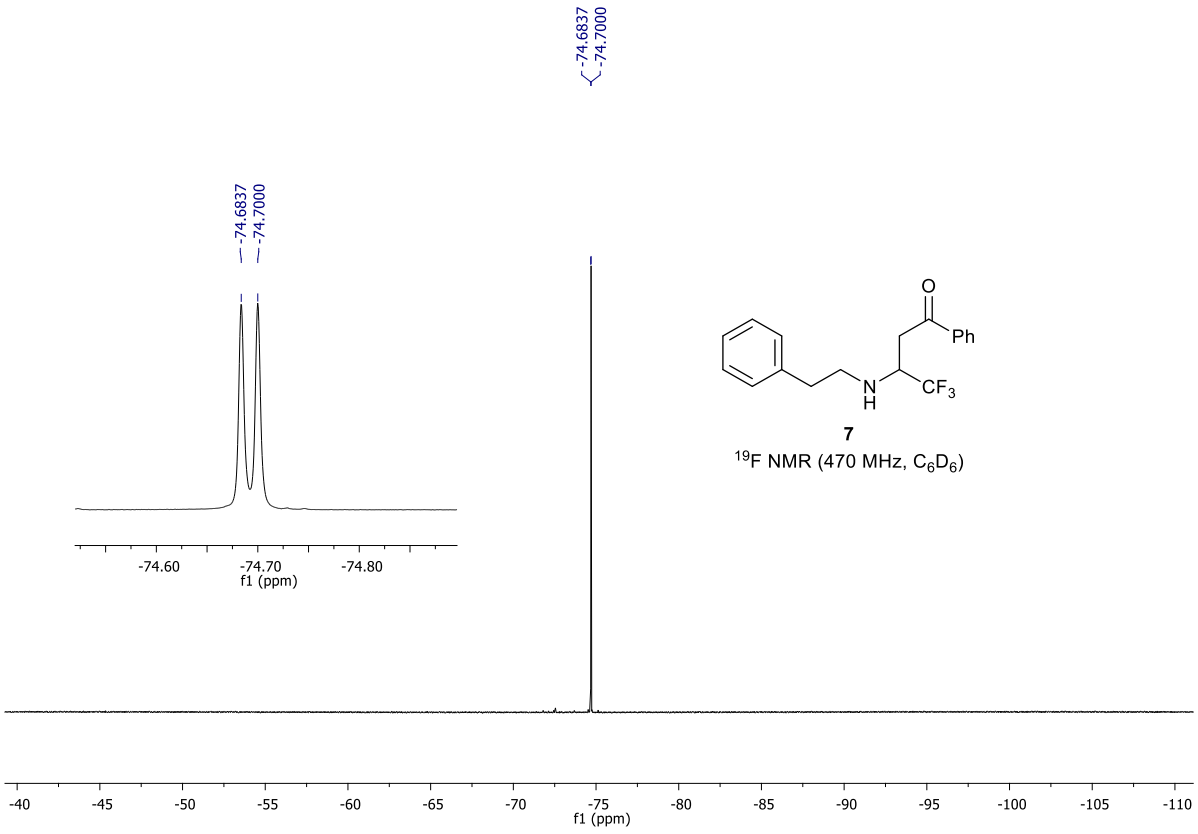

-74.0385
NH
N
H
CF3
5
19F NMR (376 MHz, CDCl3)
f1 (ppm)

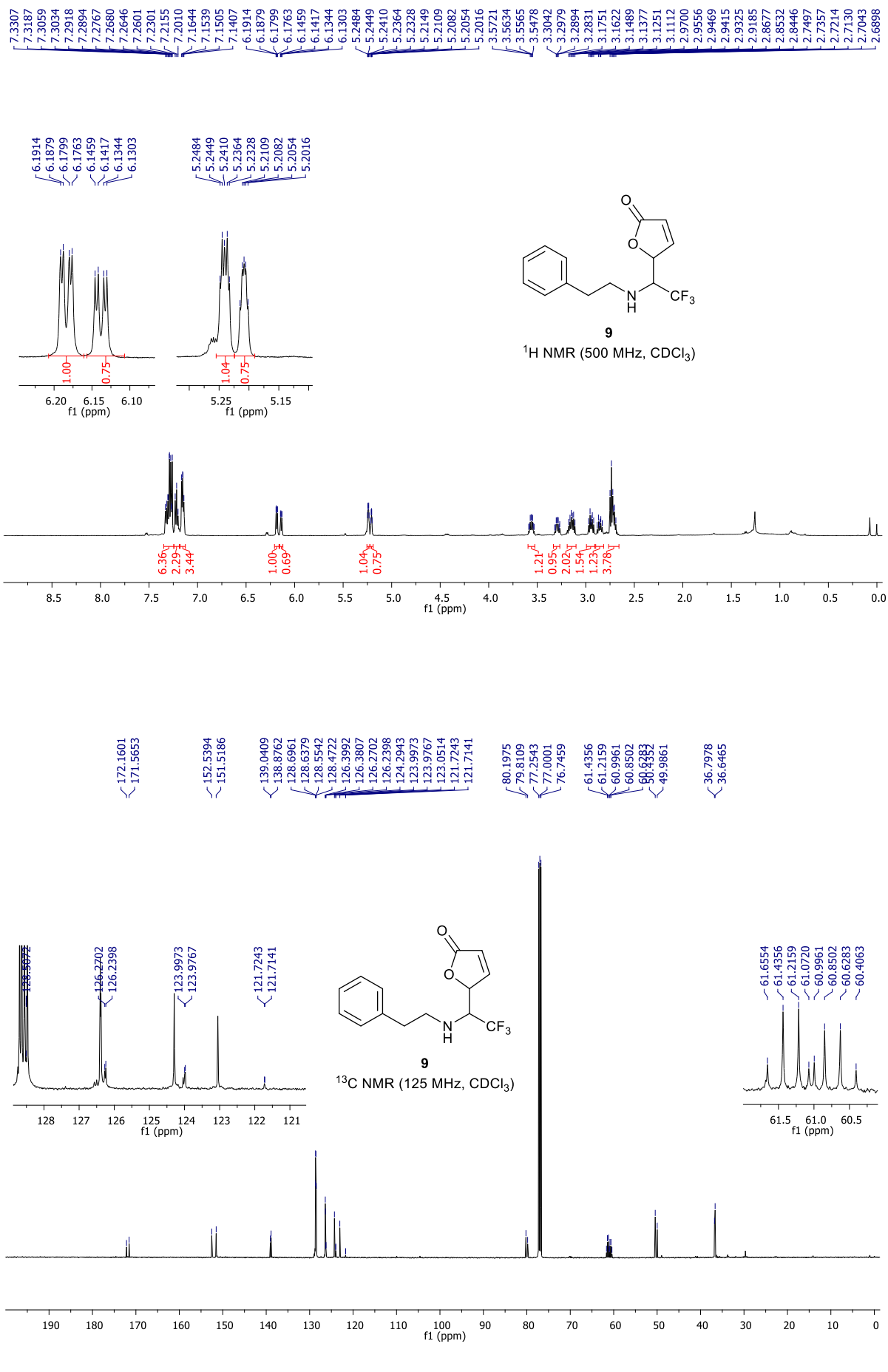

7.6137
7.6115
7.5973
7.5946
7.1600
7.1144
7.1113
7.1003
7.0969
7.0880
7.0851
7.0816
7.0365
7.0219
7.0137
7.0111
7.0048
7.0012
6.9974
6.9889
3.8790
3.8702
3.8636
3.8547
3.8524
3.8482
3.8458
3.8368
3.8302
3.8214
3.8147
2.9321
2.9177
2.9057
2.8914
2.8772
2.8686
2.8080
2.8012
2.7736
2.7669
2.7209
2.7027
2.6865
2.6684
2.5439
2.5295
2.5152
0.9333
f1 (ppm)

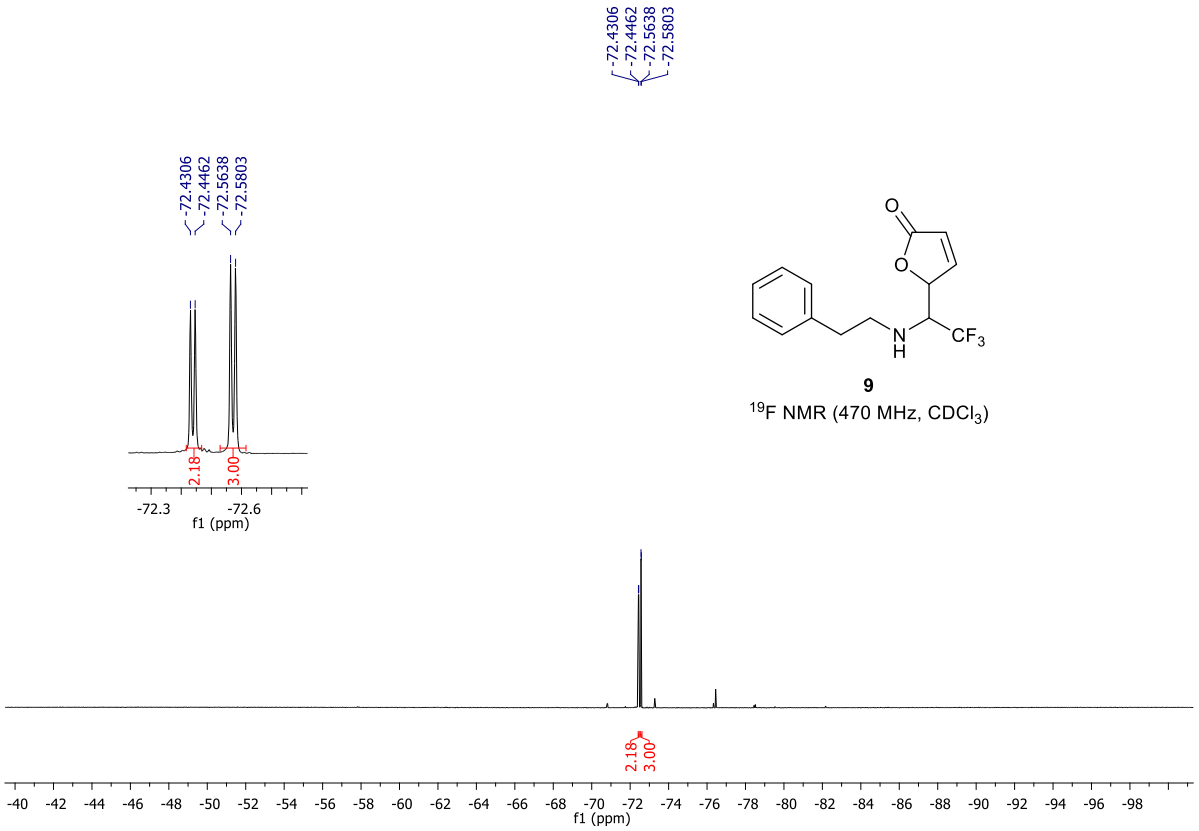
7.6137
7.6115
7.5973
7.5946
7.1003
7.0969
7.0851
7.0137
7.0111
7.0048
7.0012
6.9974
6.9889
3.8702
3.8636
3.8547
3.8524
3.8482
3.8458
3.8368
3.8302
3.8214
2.9548
2.9461
2.9321
2.9177
2.9057
2.8914
2.8828
2.8772
2.8686
2.8080
2.8012
2.7736
2.7669
2.7209
2.7027
2.6865
2.6684
2.5439
2.5295
2.5152
f1 (ppm)

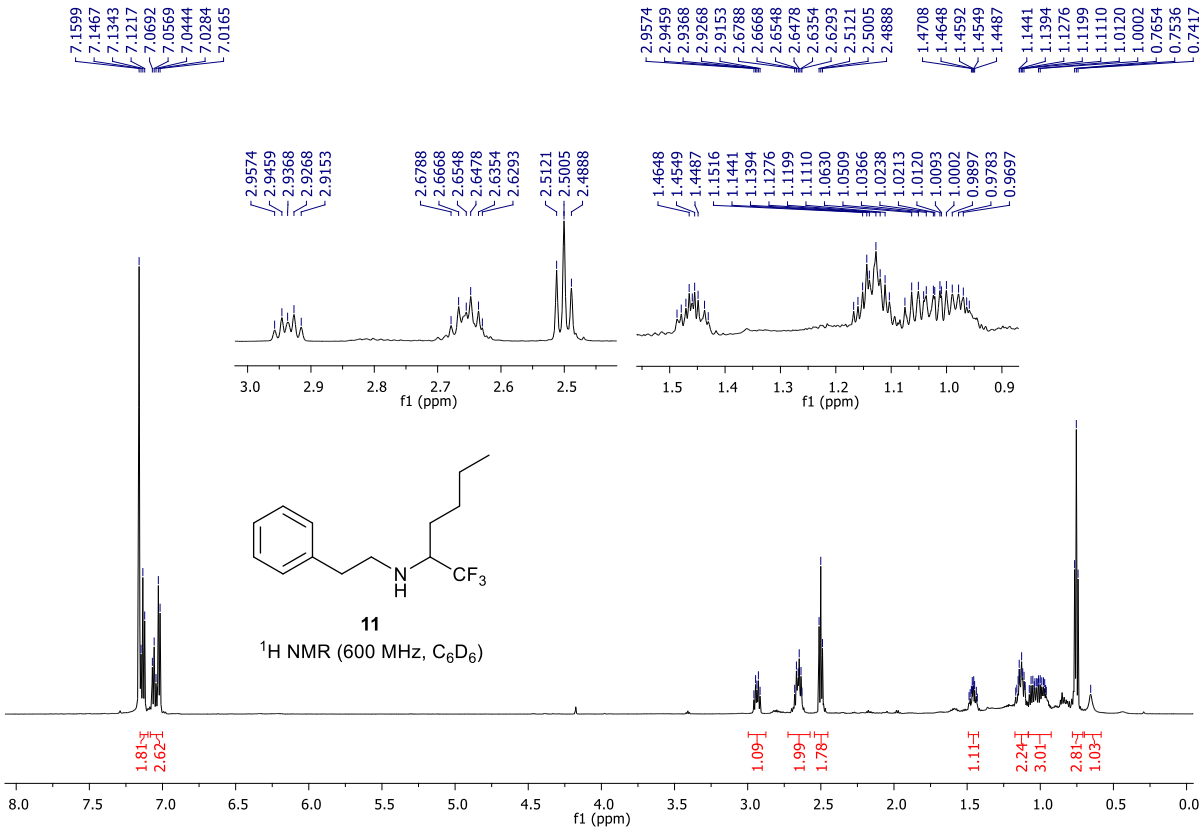
O
Ph
N
H
CF3
7
1H NMR (500 MHz, C6D6)
1.88
2.87
4.48
1.00
2.07
1.04
1.10
1.91
1.11
f1 (ppm)

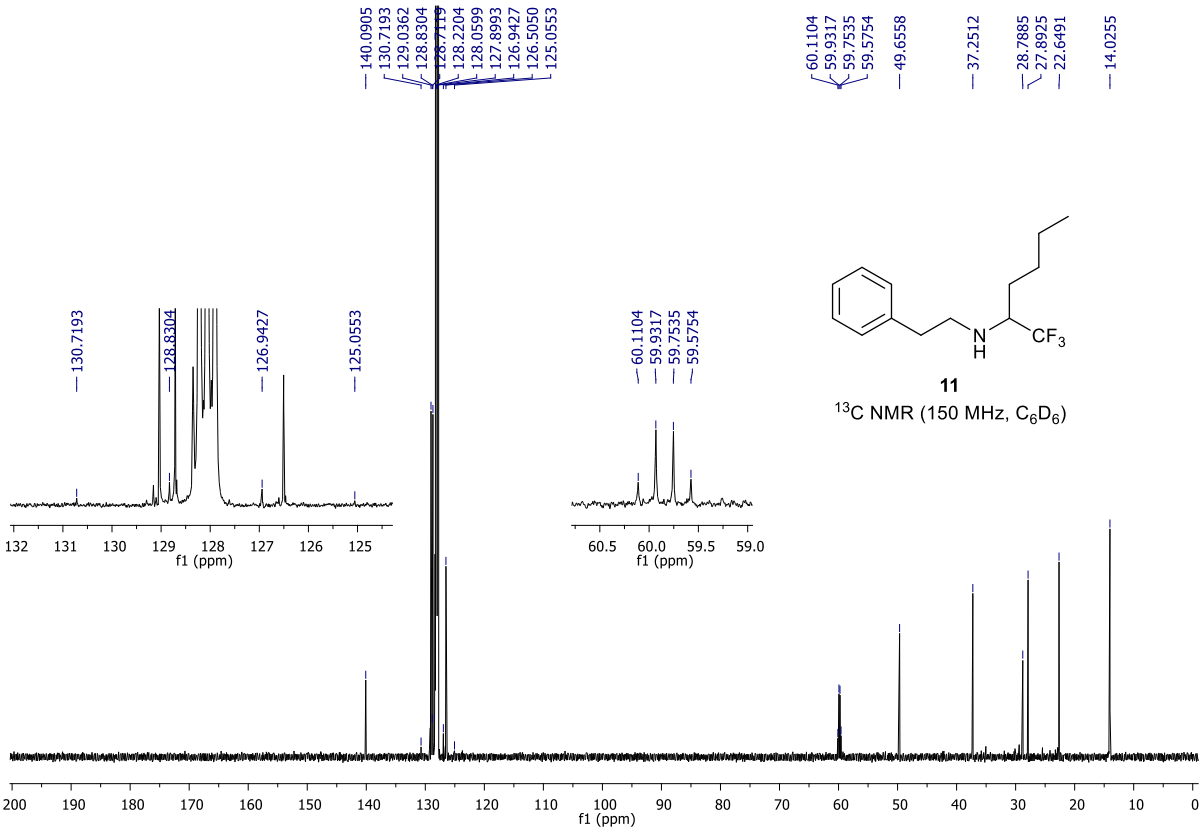

195.1767
139.9244
136.9421
133.1878
130.9951
129.0256
128.7391
128.6809
128.3420
128.0595
127.9692
127.8668
126.4859
126.4145
124.2031
56.6477
56.4242
56.2003
55.9767
49.8388
38.4615
37.0168
129.0256
128.6809
128.3420
127.9692
126.4145
130.9951
128.7391
126.4859
124.2031
56.6477
56.4242
56.2003
55.9767
f1 (ppm)
O
Ph
N
H
CF3
7
13C NMR (125 MHz, C6D6)

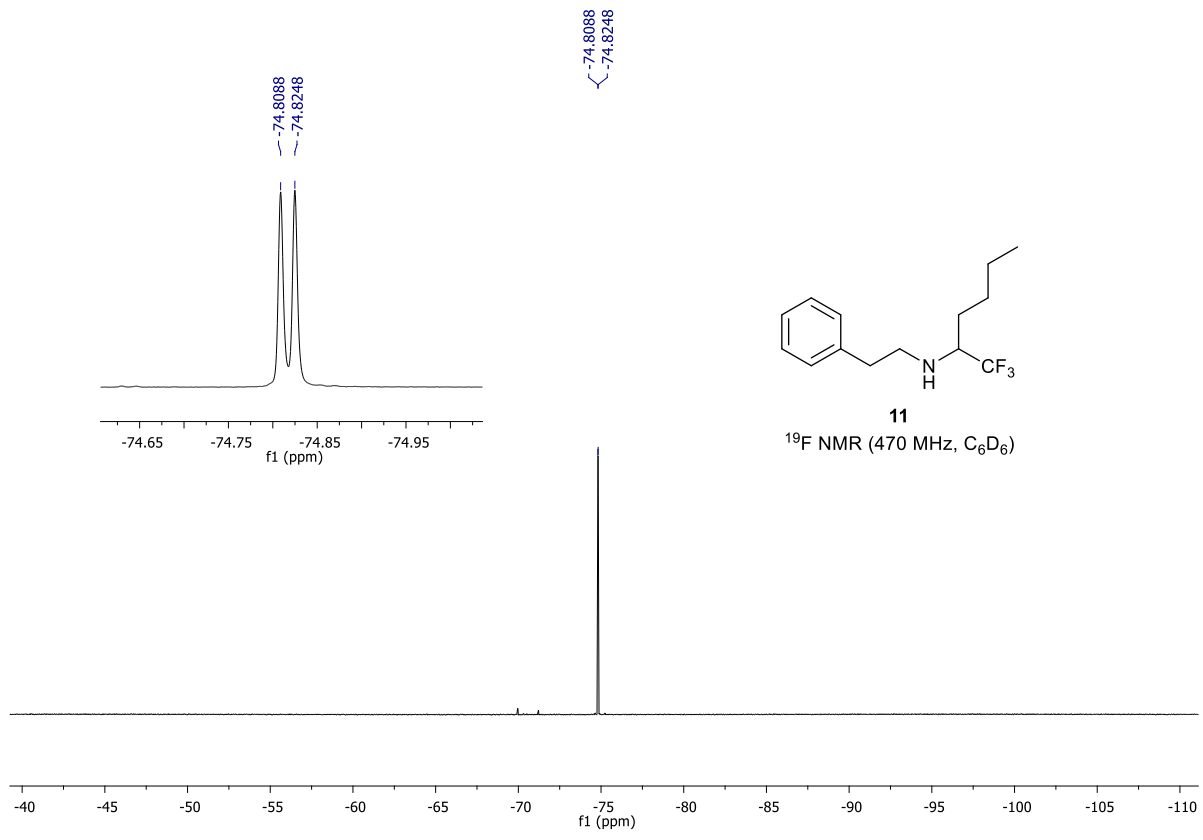

-74.6837
-74.7000
f1 (ppm)
O
Ph
N
H
CF3
7
19F NMR (470 MHz, C6D6)

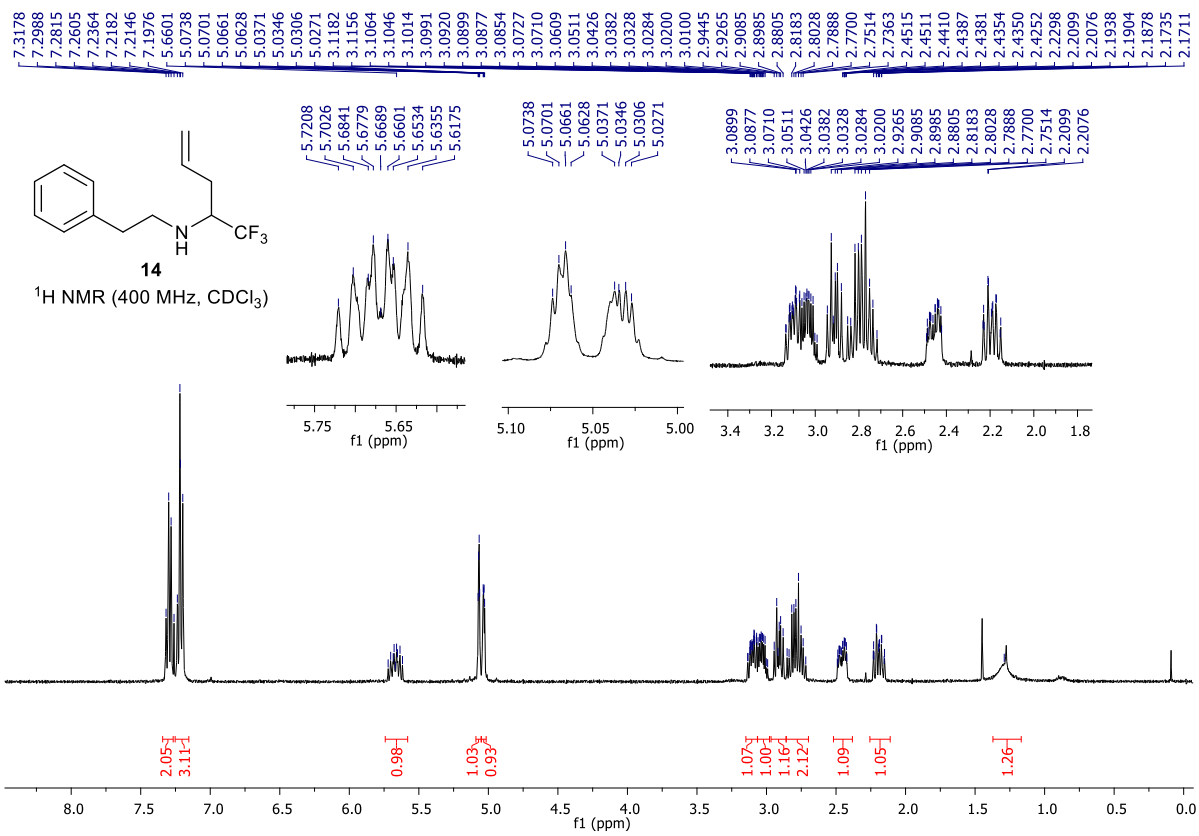

9
1H NMR (500 MHz, CDCl3)
9
13C NMR (125 MHz, CDCl3)
f1 (ppm)

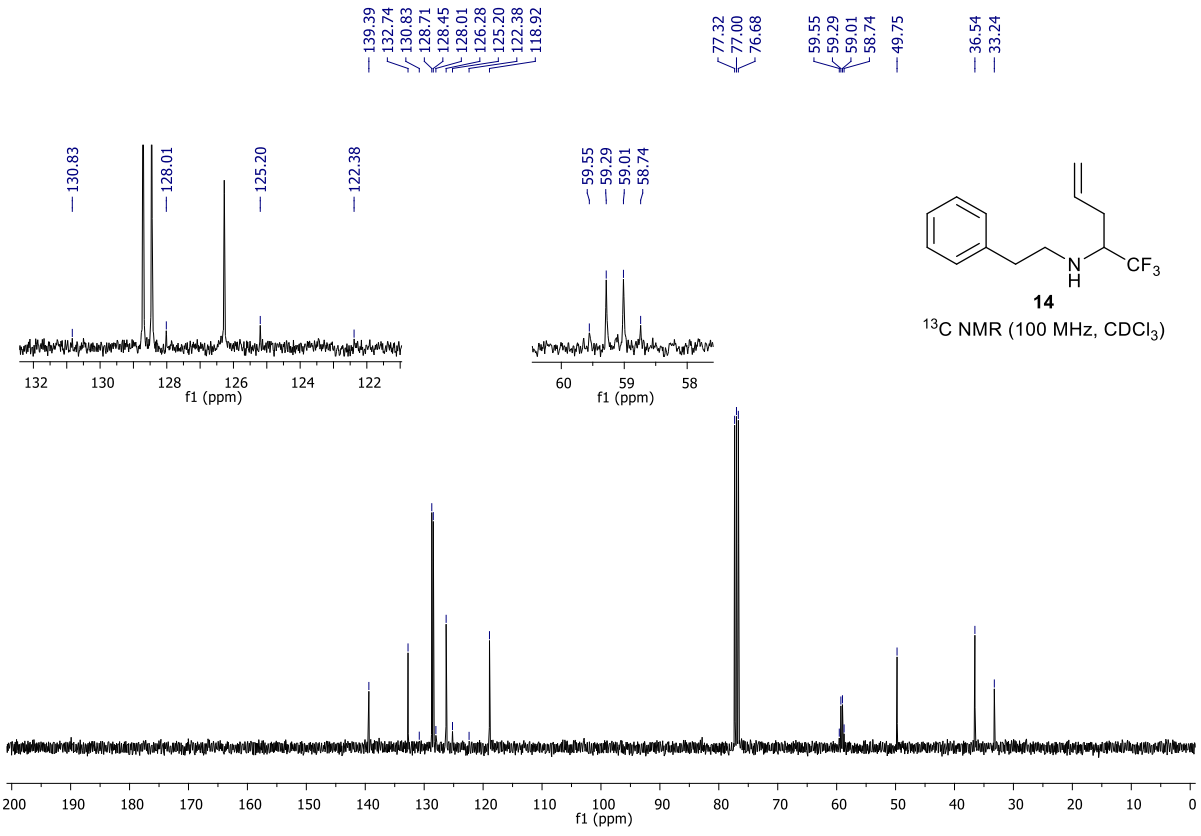

-72.4306
-72.4462
-72.5638
-72.5803
2.18
3.00
-72.3
-72.6
f1 (ppm)
O
O
N
H
CF3
9
19F NMR (470 MHz, CDCl3)
-40 -42 -44 -46 -48 -50 -52 -54 -56 -58 -60 -62 -64 -66 -68 -70 -72 -74 -76 -78 -80 -82 -84 -86 -88 -90 -92 -94 -96 -98
f1 (ppm)

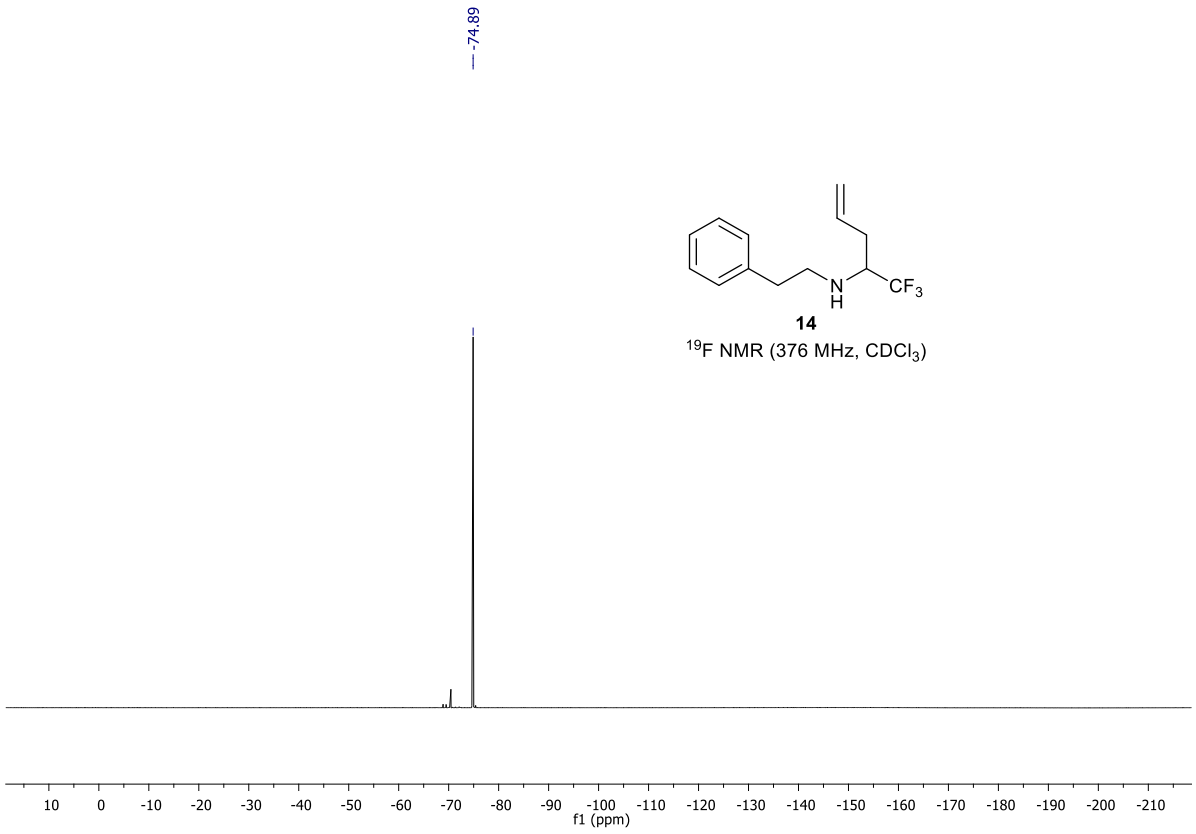

7.1599
7.1467
7.1343
7.1217
7.0692
7.0569
7.0444
7.0284
7.0165
2.9574
2.9459
2.9368
2.9268
2.9153
2.6788
2.6668
2.6548
2.6478
2.6354
2.6293
2.5121
2.5005
2.4888
1.4708
1.4648
1.4592
1.4549
1.4487
1.1441
1.1394
1.1276
1.1199
1.1110
1.0120
1.0002
0.7654
0.7536
0.7417
1.5161
1.1441
1.1394
1.1276
1.1199
1.1110
1.0630
1.0509
1.0366
1.0238
1.0213
1.0120
1.0093
1.0002
0.9897
0.9783
0.9697
3.0 2.9 2.8 2.7 2.6 2.5
f1 (ppm)
1.5 1.4 1.3 1.2 1.1 1.0 0.9
f1 (ppm)
N
H
CF3
11
1H NMR (600 MHz, C6D6)
1.81
2.62
1.09
1.99
1.78
1.11
2.24
3.01
2.81
1.03
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

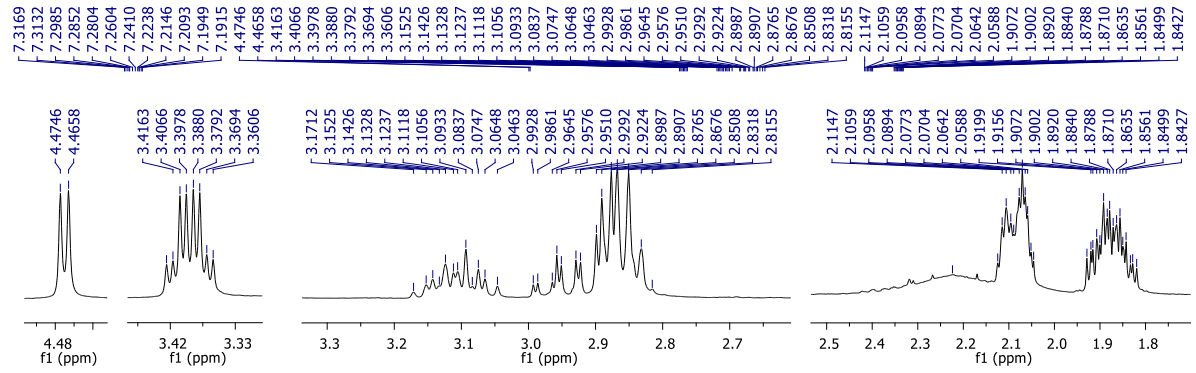

140.0905
130.7193
129.0362
128.8304
128.7119
128.2204
128.0599
127.8993
126.9427
126.5050
125.0553
60.1104
59.9317
59.7535
59.5754
49.6558
37.2512
28.7885
27.8925
22.6491
14.0255
f1 (ppm)
11
13C NMR (150 MHz, C6D6)

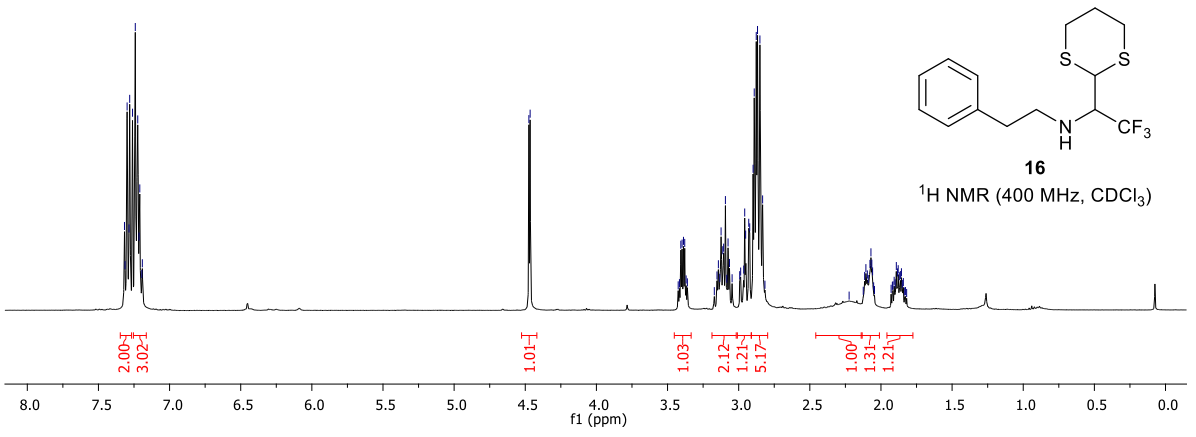

-74.8088
-74.8248
f1 (ppm)
11
19F NMR (470 MHz, C6D6)

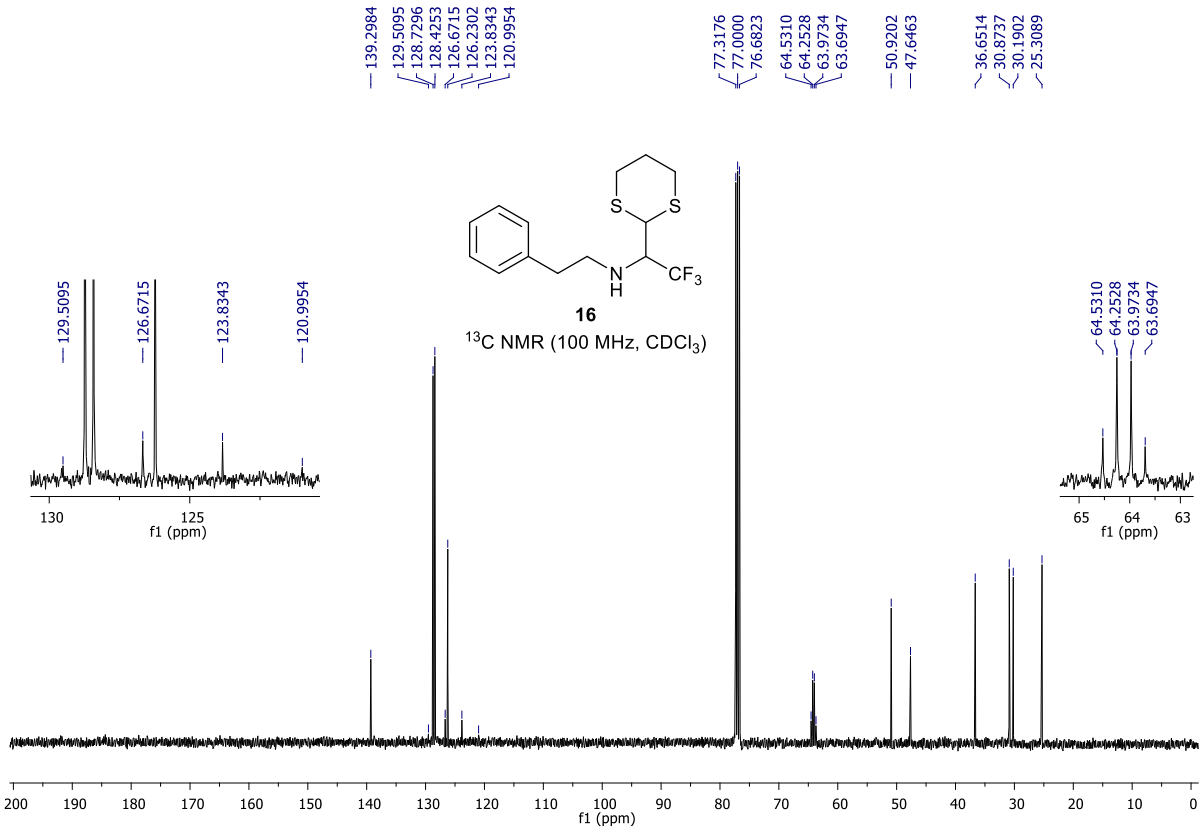

14
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)

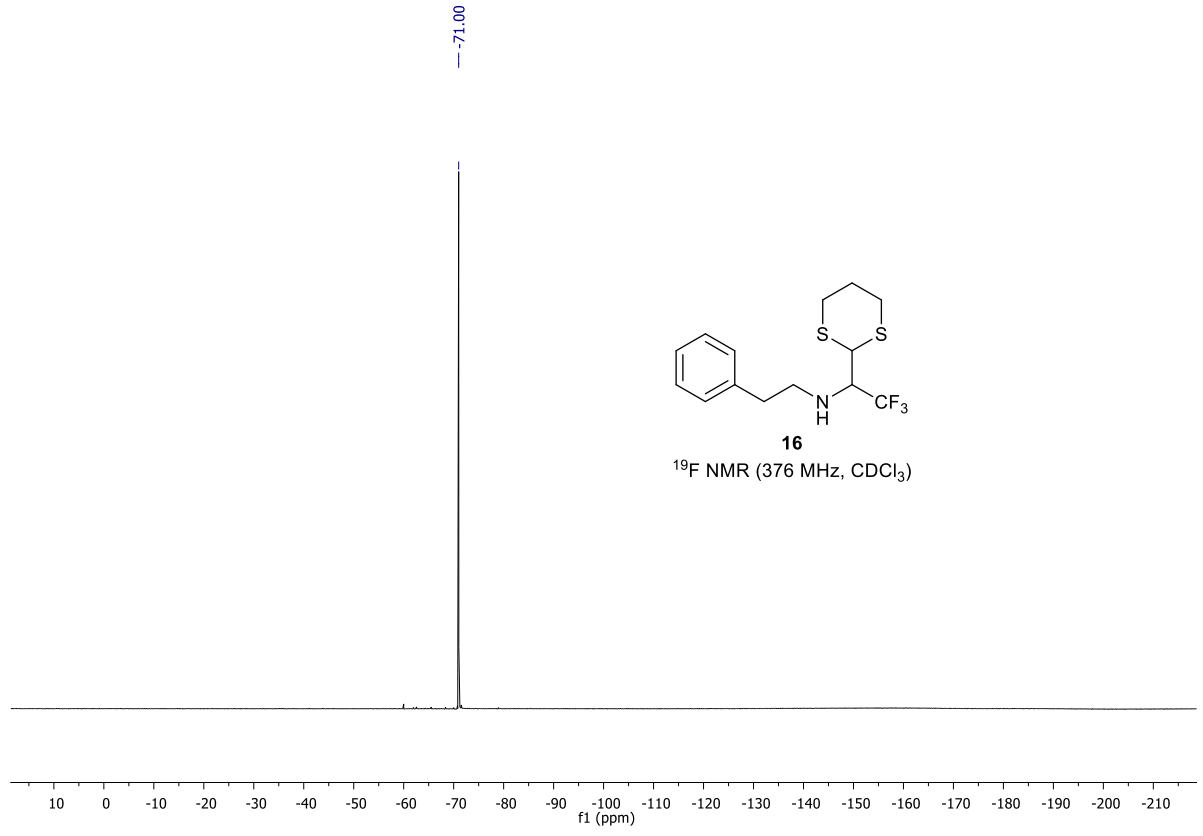

14
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

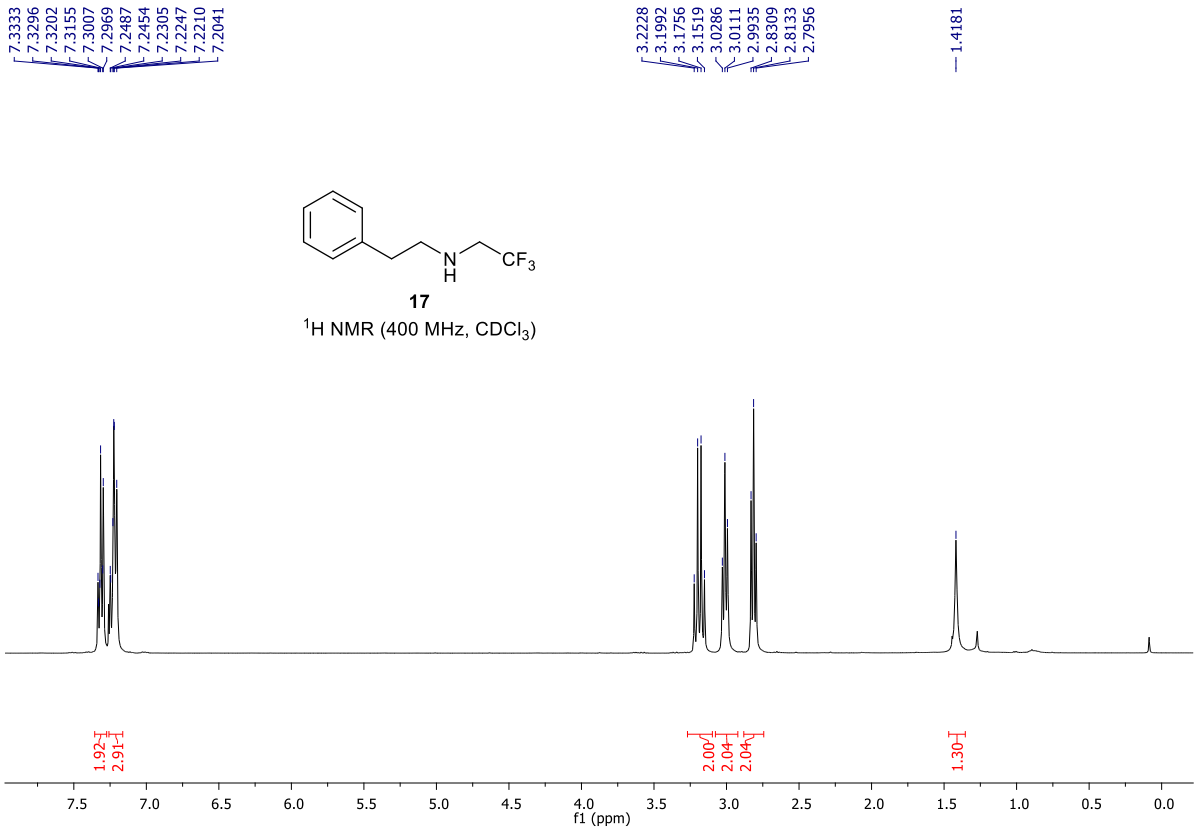

-74.89
N
H
CF3
14
19F NMR (376 MHz, CDCl3)
f1 (ppm)

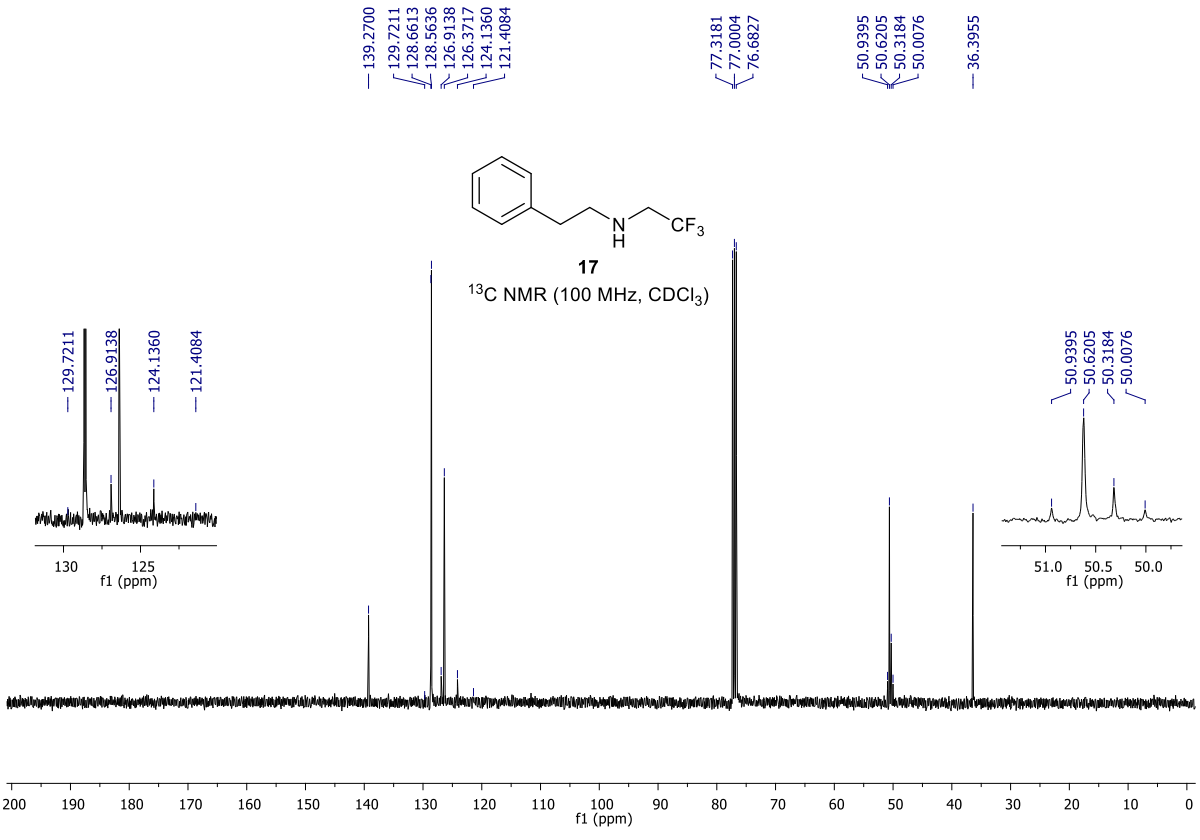

f1 (ppm)

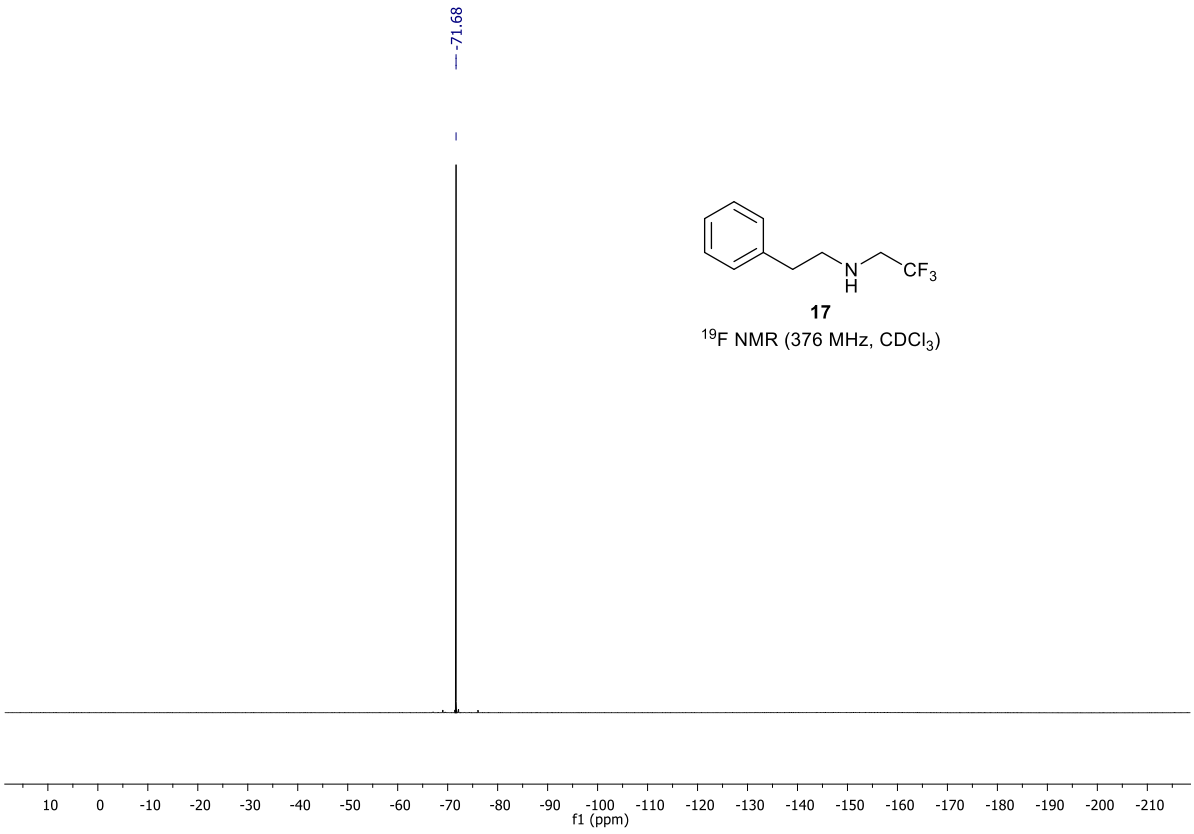

S
S
N
H
CF3
16
1H NMR (400 MHz, CDCl3)
f1 (ppm)


139.2984
129.5095
128.7296
128.4253
126.6715
126.2302
123.8343
120.9954
77.3176
77.0000
76.6823
64.5310
64.2528
63.9734
63.6947
50.9202
47.6463
36.6514
30.8737
30.1902
25.3089
S
S
N
H
CF3
16
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-71.00
S
S
N
H
CF3
16
19F NMR (376 MHz, CDCl3)
f1 (ppm)

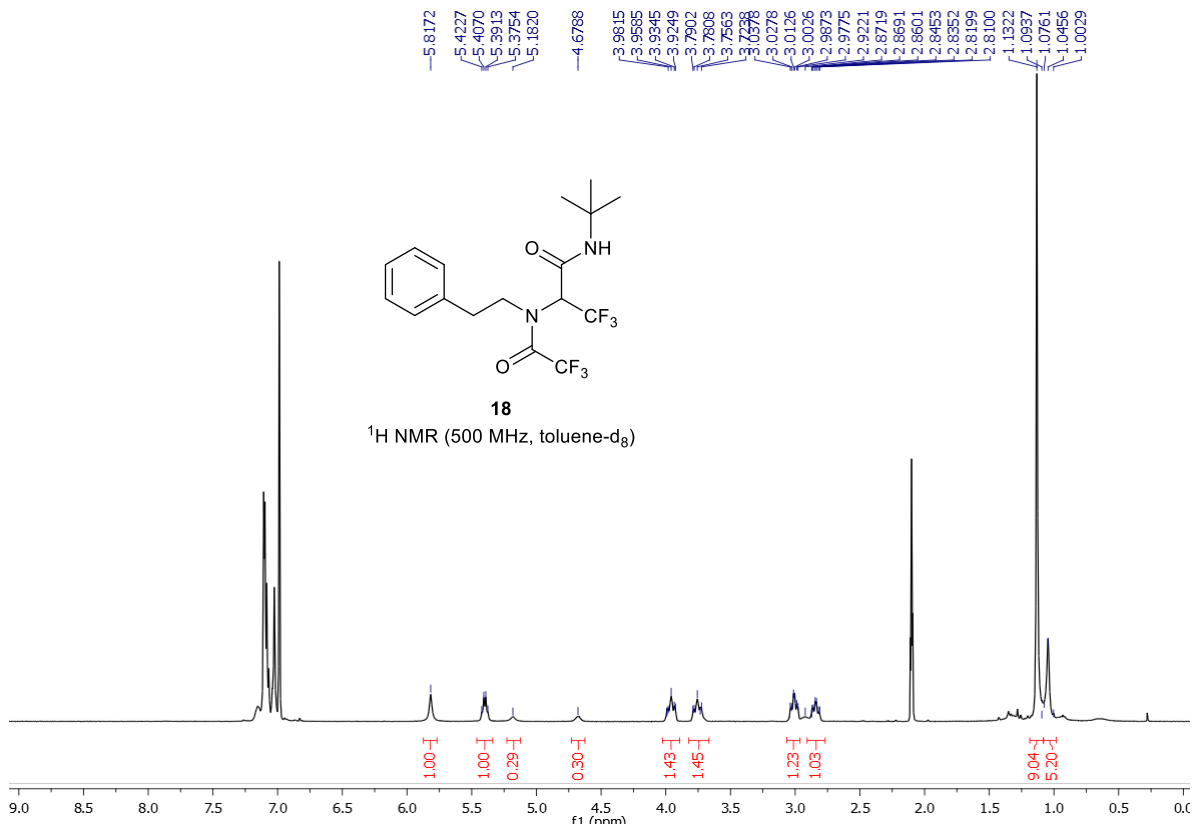

7.3333
7.3296
7.3202
7.3155
7.3007
7.2969
7.2487
7.2454
7.2305
7.2247
7.2210
7.2041
3.2228
3.1992
3.1756
3.1519
3.0286
3.0111
2.9935
2.8309
2.8133
2.7956
1.4181
N
H
CF3
17
1H NMR (400 MHz, CDCl3)
1.92
2.91
2.00
2.04
2.04
1.30
f1 (ppm)


139.2700
129.7211
128.8613
128.5636
126.9138
126.3717
124.1360
121.4084
77.3181
77.0004
76.6827
50.9395
50.6205
50.3184
50.0076
36.3955
N
H
CF3
17
13C NMR (100 MHz, CDCl3)
f1 (ppm)



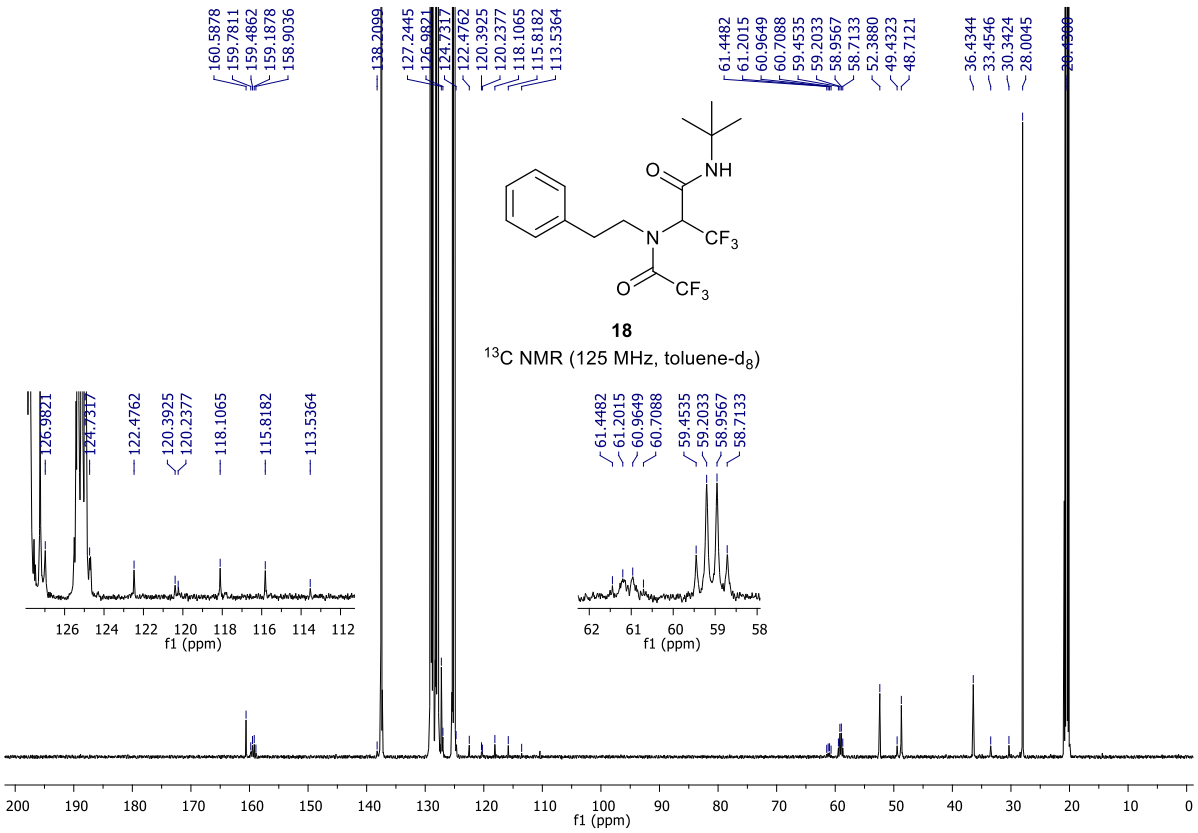
17

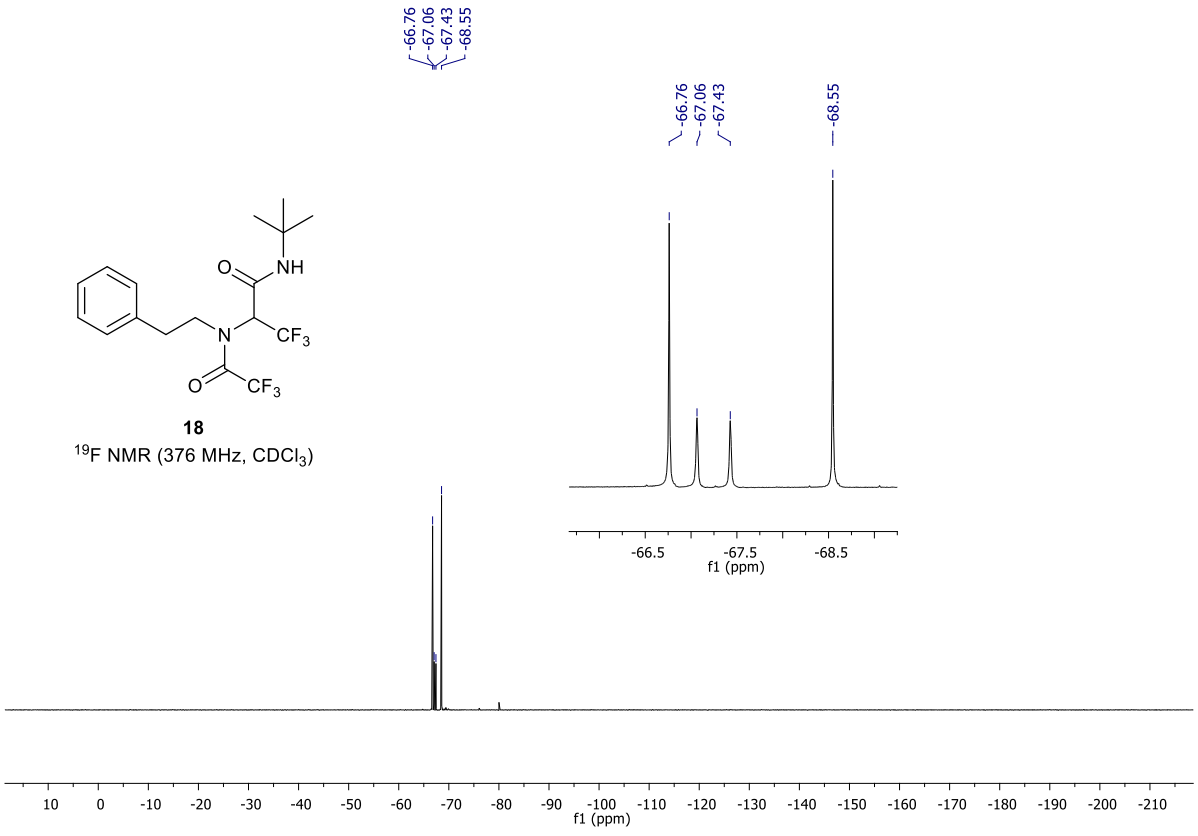
^{19}F NMR (376 MHz, $CDCl_3$)



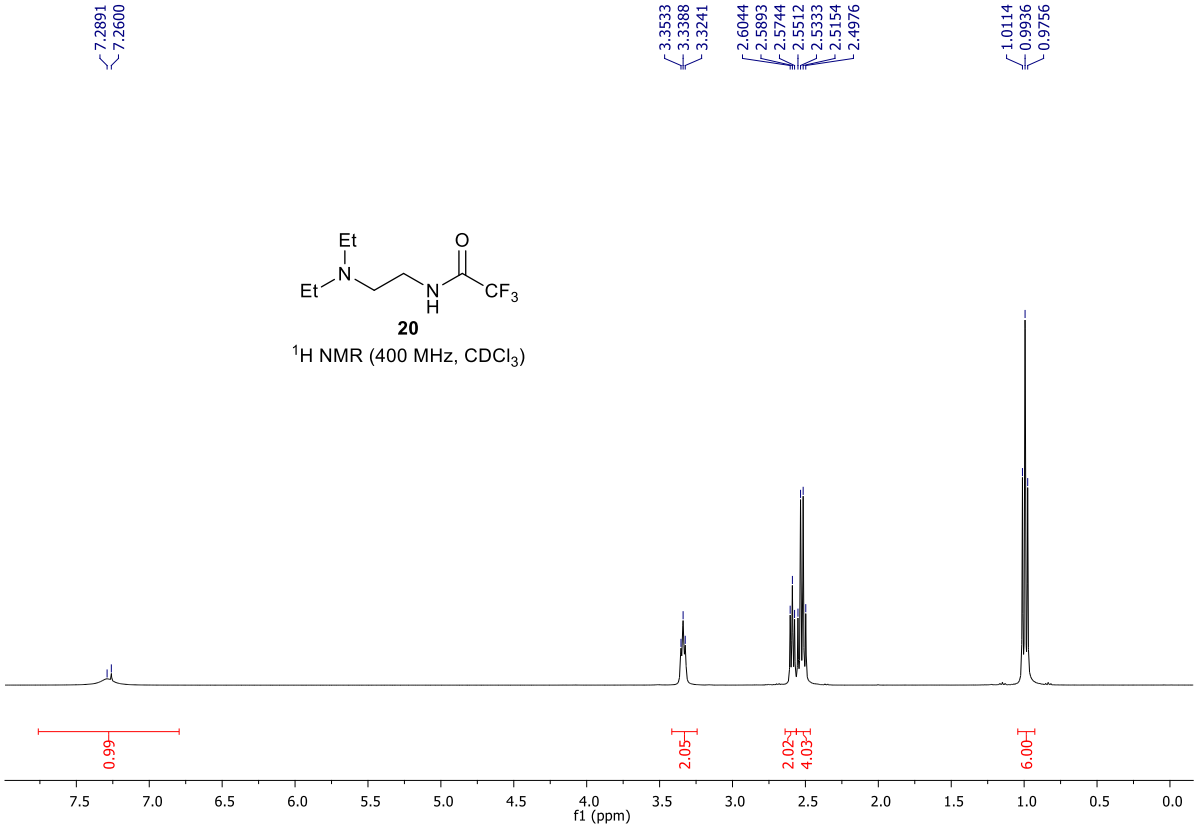
18

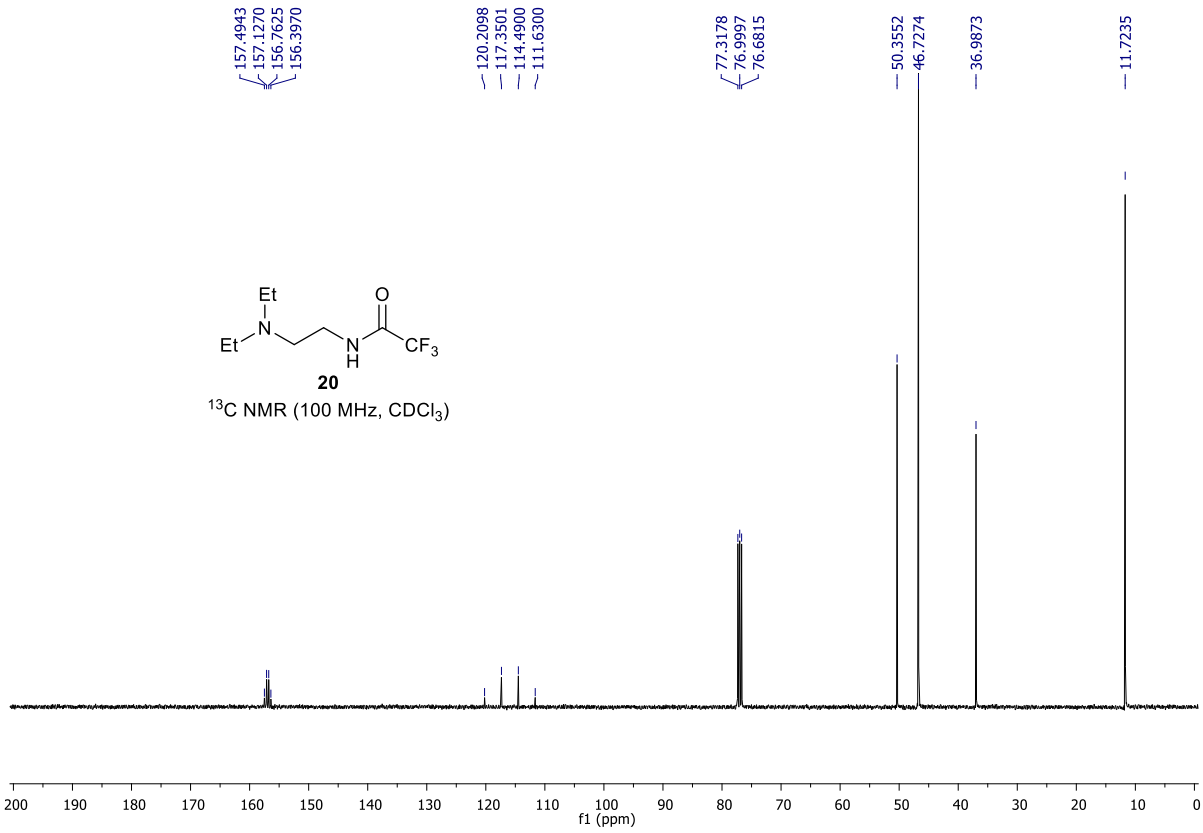
^{1}H NMR (500 MHz, toluene-d_8)

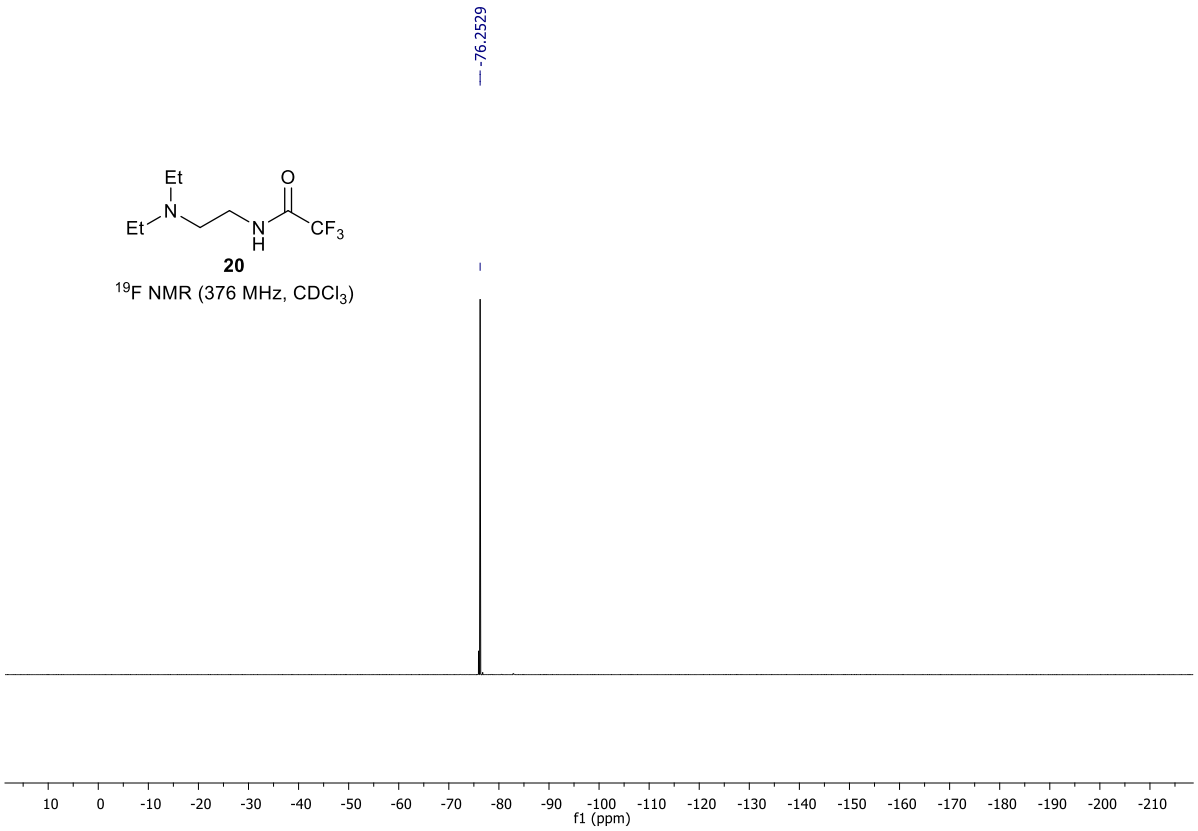

160.5878
159.7811
159.4862
159.1878
158.9036
138.2099
127.2445
126.9821
124.7317
122.4762
120.3925
120.2377
118.1065
115.8182
113.5364
61.4482
61.2015
60.9649
60.7088
59.4535
59.2033
58.9567
58.7133
52.3880
49.4323
48.7121
36.4344
33.4546
30.3424
28.0045
20.1300
O
NH
N
CF3
O
CF3
18
13C NMR (125 MHz, toluene-d8)
f1 (ppm)

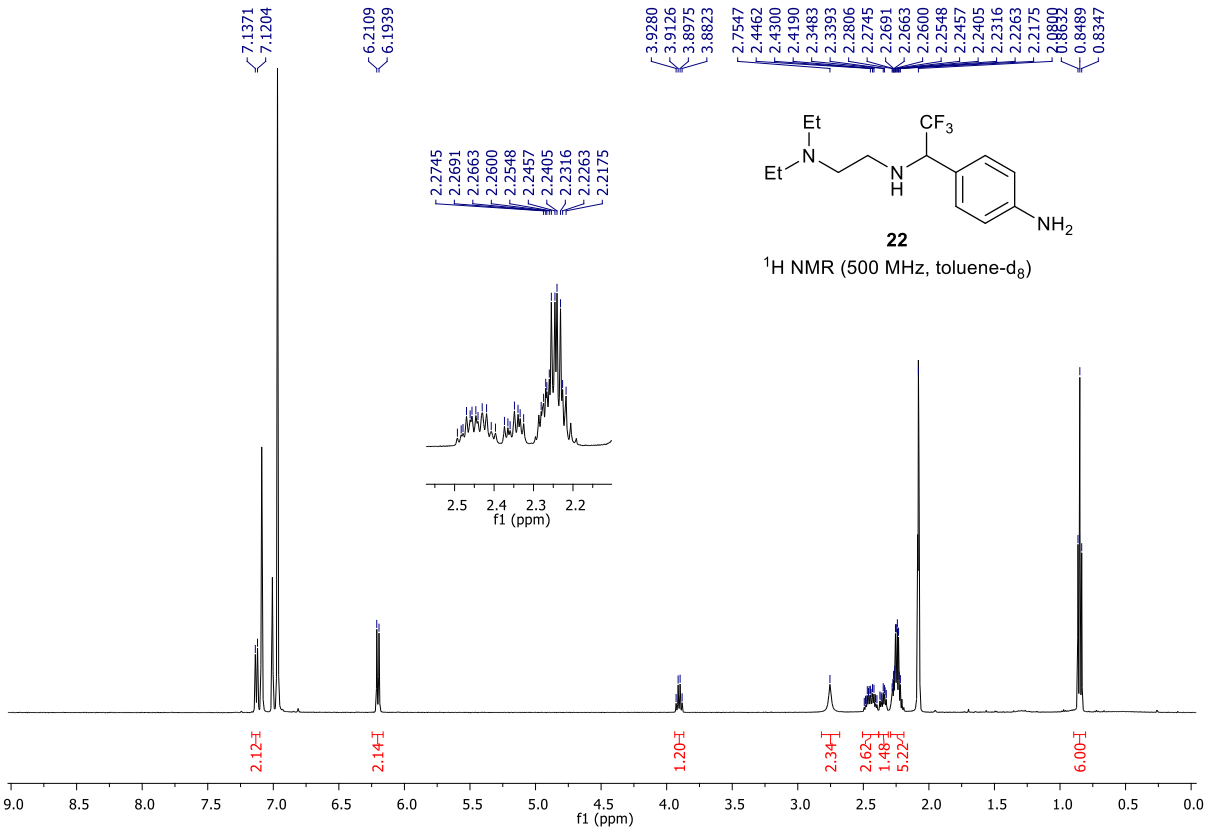

-66.76
-67.06
-67.43
-68.55
O
NH
N
CF3
O
CF3
18
19F NMR (376 MHz, CDCl3)
f1 (ppm)

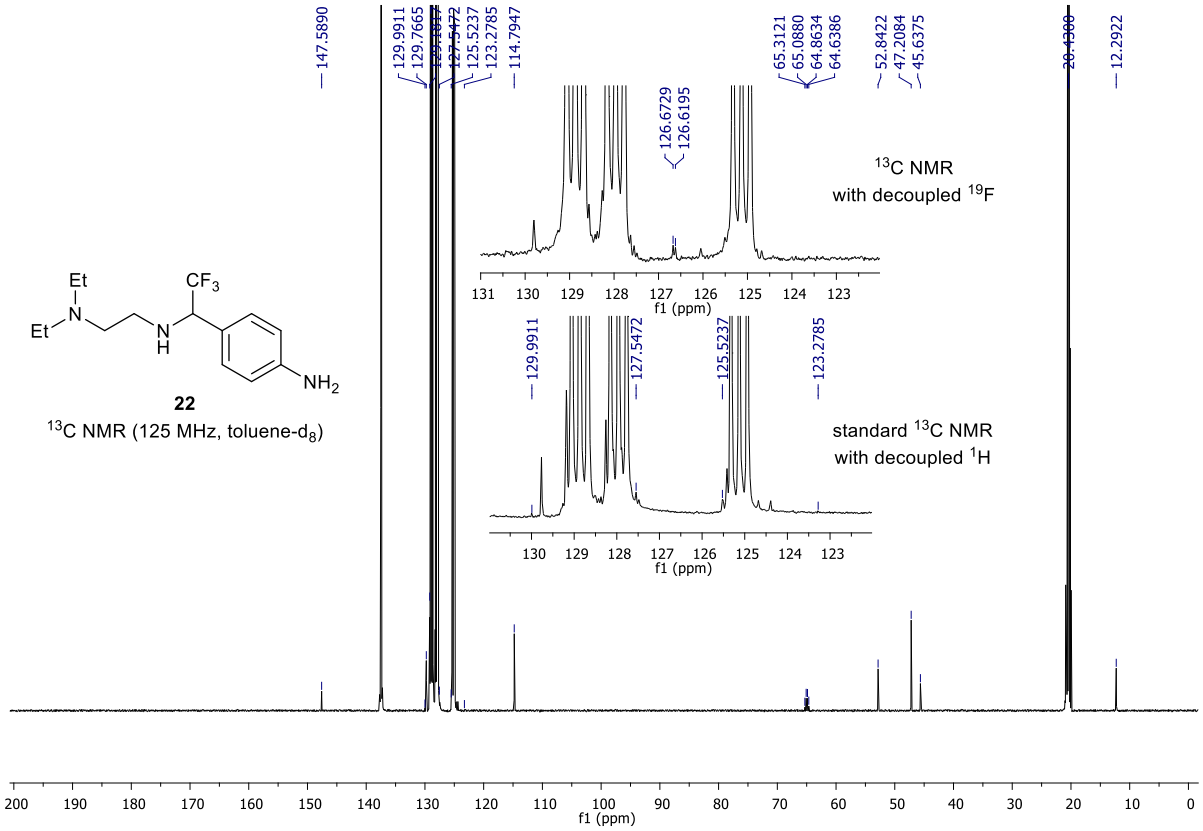
NMR spectra of products 20 and 22 from procainamide synthesis (from Scheme 2 in main text)

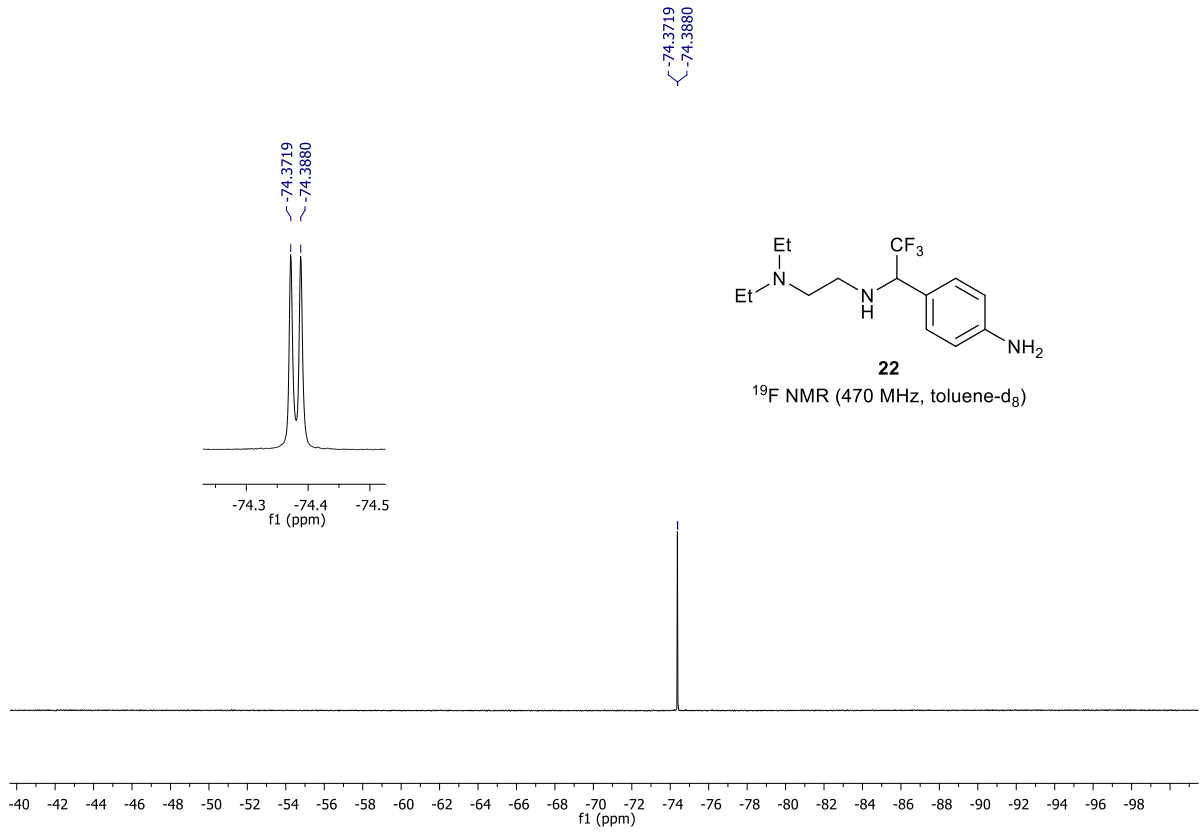




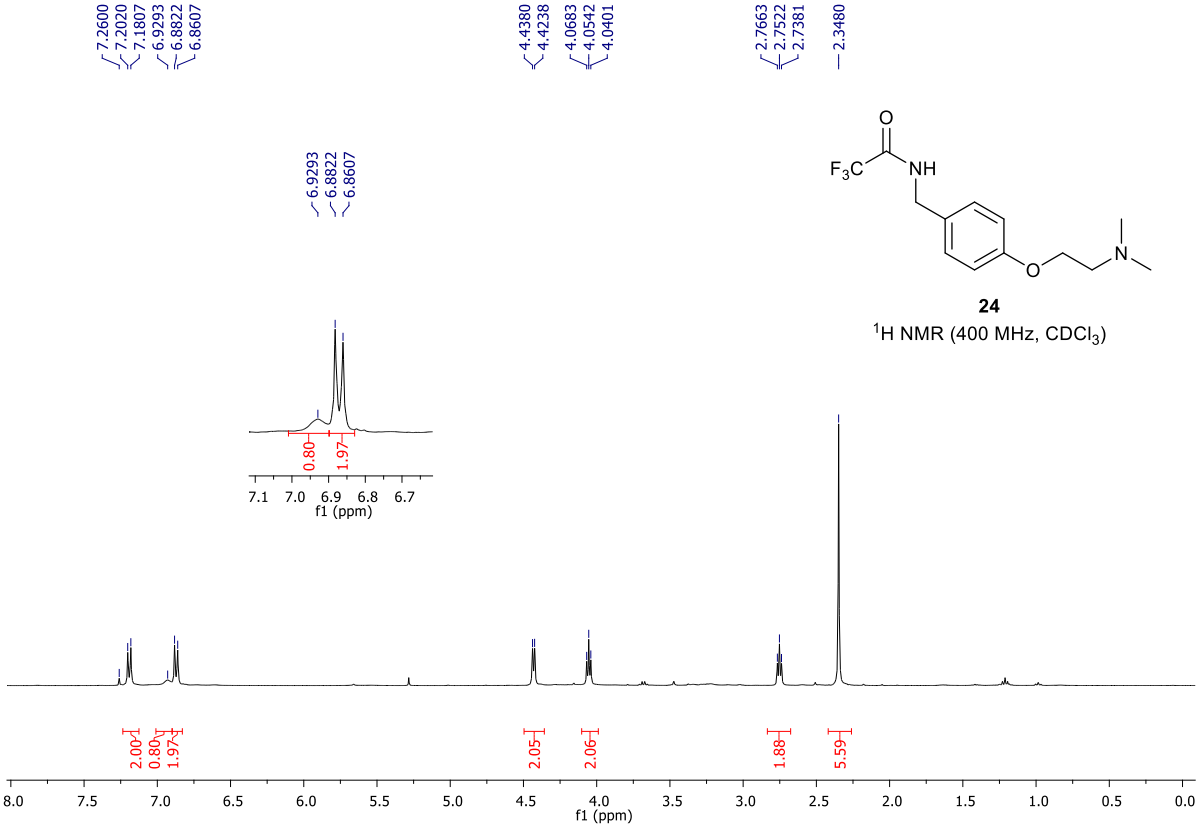

-76.2529
Et
N
Et
O
N
H
CF3
20
19F NMR (376 MHz, CDCl3)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

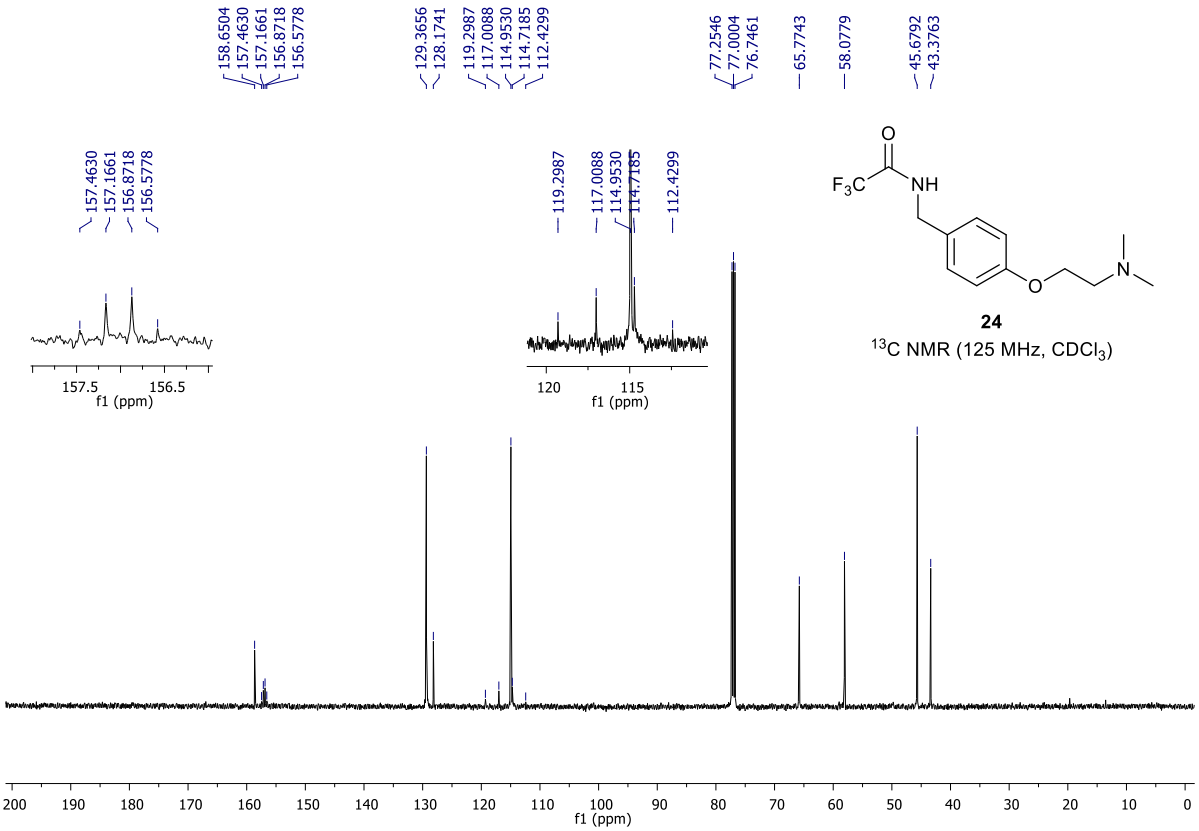

7.1371
7.1204
6.2109
6.1939
3.9280
3.9126
3.8975
3.8823
2.7547
2.4462
2.4300
2.4190
2.3483
2.3393
2.2806
2.2745
2.2691
2.2663
2.2600
2.2548
2.2457
2.2405
2.2316
2.2263
2.2175
0.8489
0.8347
Et
N
Et
CF3
N
H
NH2
22
1H NMR (500 MHz, toluene-d8)
2.5 2.4 2.3 2.2
f1 (ppm)
2.12
2.14
1.20
2.34
2.62
1.48
5.22
6.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

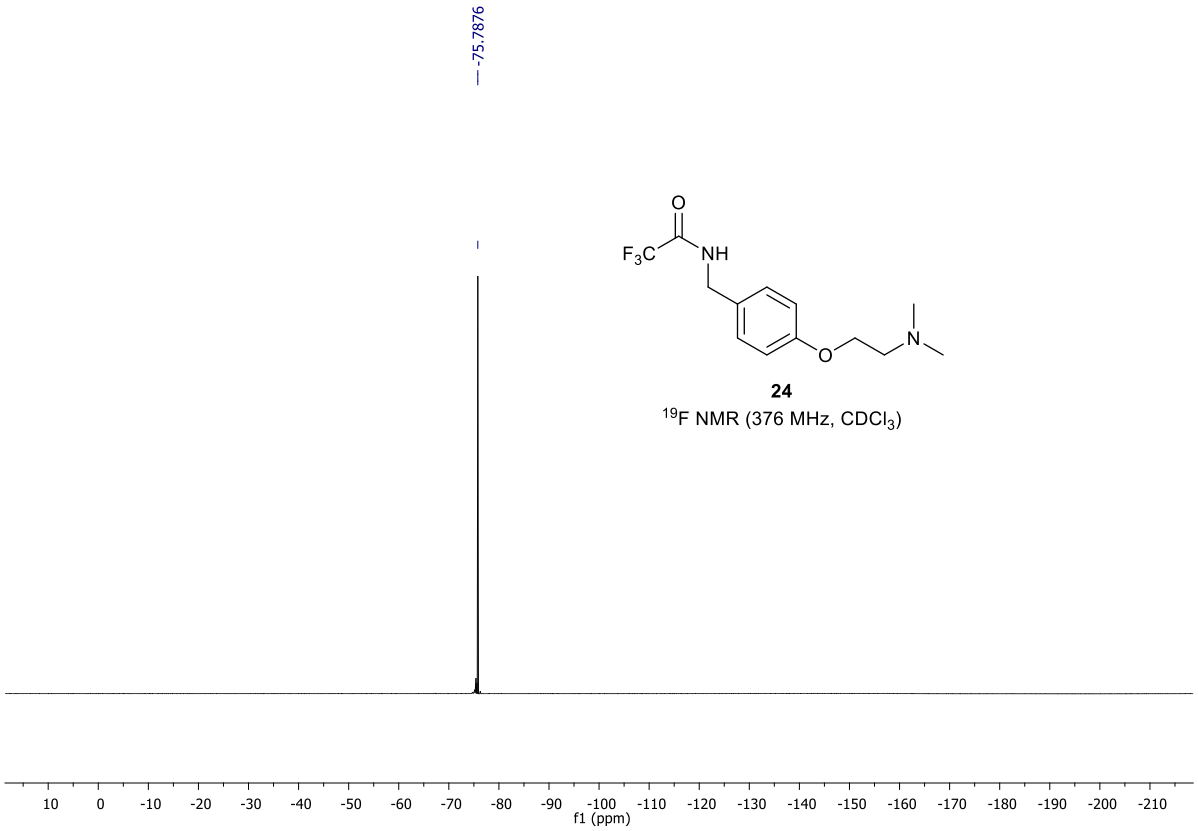

147.5890
129.9911
129.7665
127.5472
125.5237
123.2785
114.7947
65.3121
65.0880
64.8634
64.6386
52.8422
47.2084
45.6375
20.4300
12.2922
126.6729
126.6195
13C NMR
with decoupled 19F
131 130 129 128 127 126 125 124 123
f1 (ppm)
129.9911
127.5472
125.5237
123.2785
standard 13C NMR
with decoupled 1H
130 129 128 127 126 125 124 123
f1 (ppm)
Et
N
Et
CF3
N
H
NH2
22
13C NMR (125 MHz, toluene-d8)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-74.3719
-74.3880
-74.3719
-74.3880
-74.3 -74.4 -74.5
f1 (ppm)
Et
N
Et
CF3
N
H
NH2
22
19F NMR (470 MHz, toluene-d8)
-40 -42 -44 -46 -48 -50 -52 -54 -56 -58 -60 -62 -64 -66 -68 -70 -72 -74 -76 -78 -80 -82 -84 -86 -88 -90 -92 -94 -96 -98
f1 (ppm)

NMR spectra of products 24 and 26 from itopride synthesis (from Scheme 2 in main text)

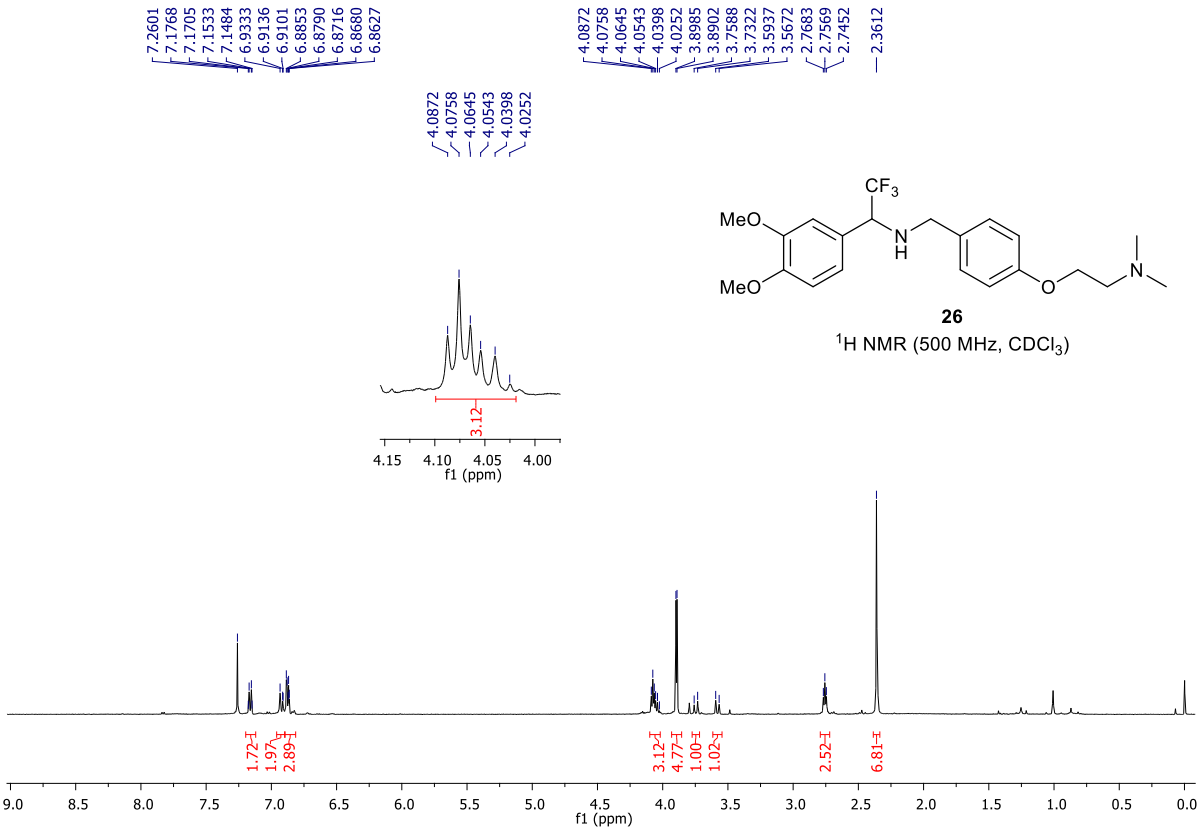






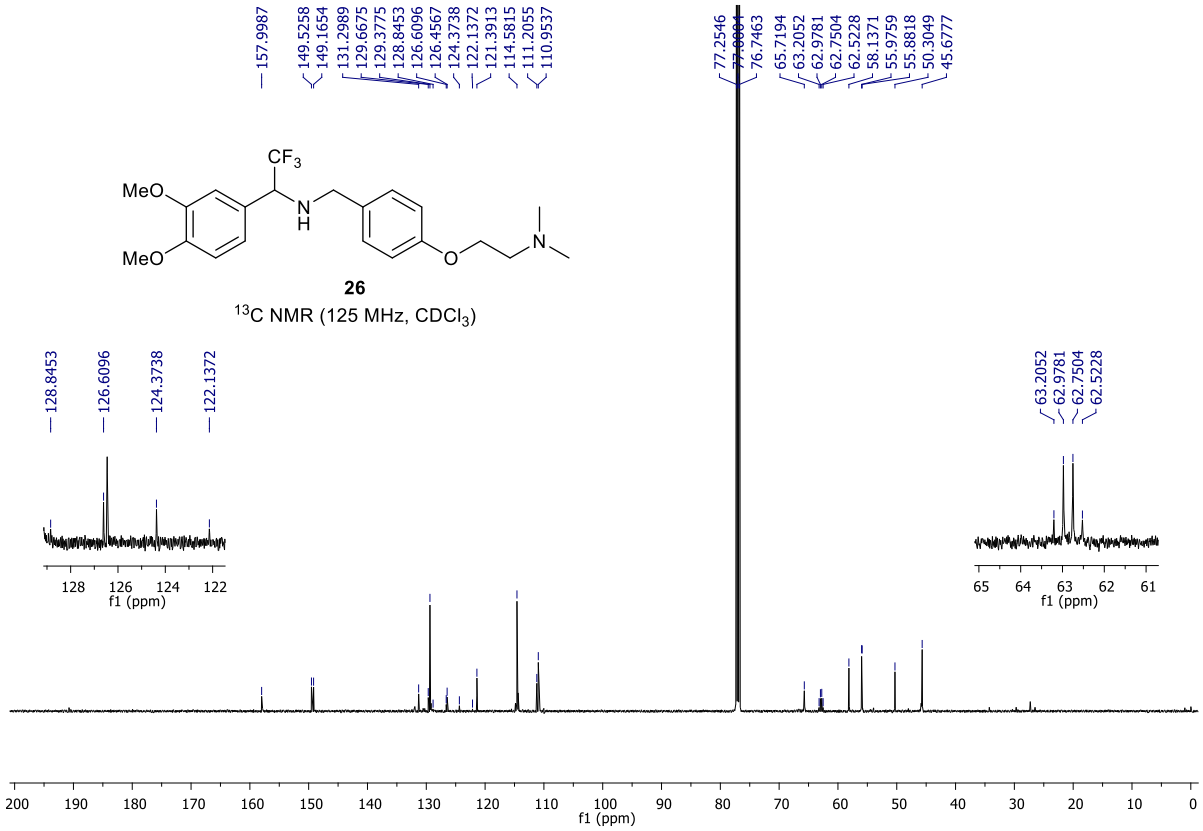
24

^{19}F NMR (376 MHz, $CDCl_3$)



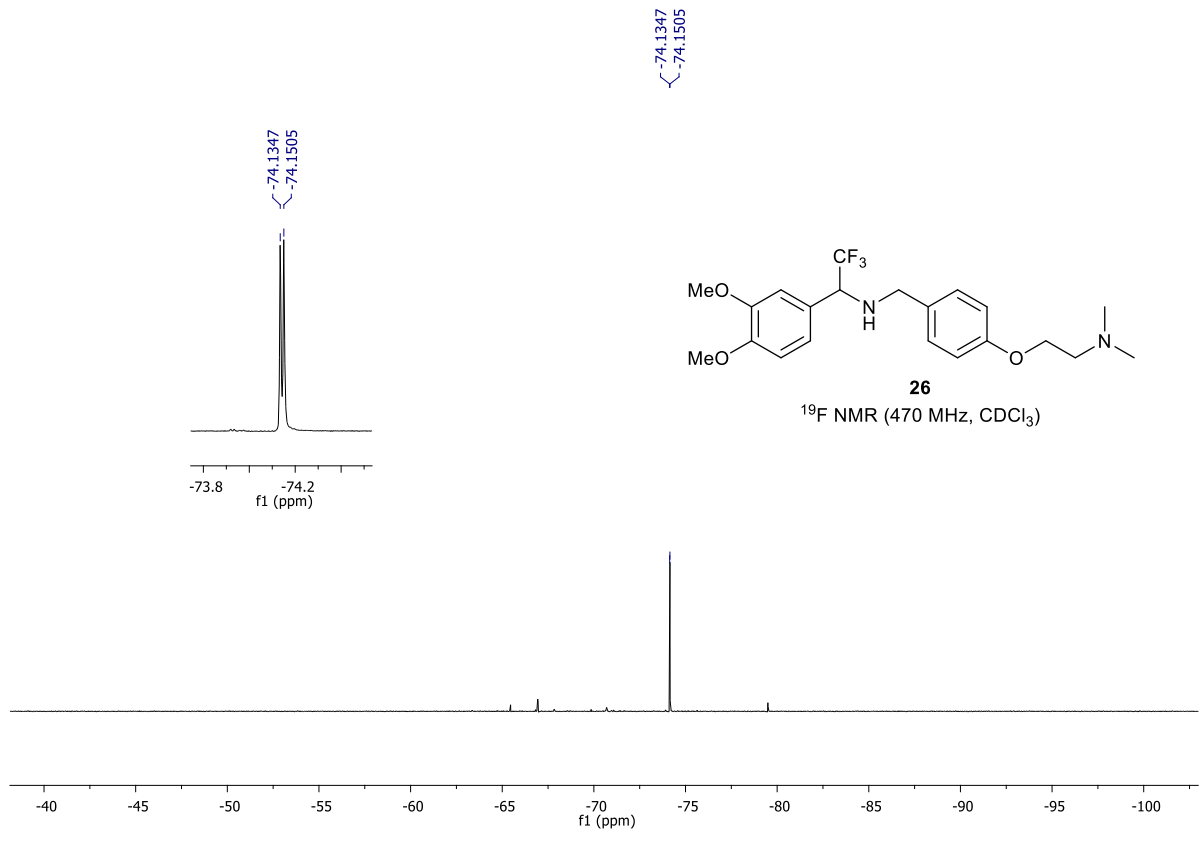
26

^{1}H NMR (500 MHz, $CDCl_3$)



26

^{13}C NMR (125 MHz, $CDCl_3$)



26

^{19}F NMR (470 MHz, $CDCl_3$)

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