Supplementary Information

A Brønsted Acid-Base Approach for the Net Monoselective C–F Substitution of (Trifluoromethyl)alkanes

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I. General Information

General Reagent information: All reactions were conducted under an ambient atmosphere unless otherwise noted. 2-Ethyl-1-hexanol (Sigma Aldrich, catalog #538051), 1,4,7,10,13,16-hexaoxacyclooctadecane-6 (18-crown-6, Chem-Impex catalog #03901), triethylamine trihydrofluoride ($NEt_3 \cdot 3HF$, Oakwood, catalog #003029), hydrogen fluoride-pyridine (HF-pyridine, Oakwood, catalog #002844), trifluoroacetic acid (TFA, Sigma Aldrich, catalog #T6508), and methanesulfonic acid (MsOH, TCI, catalog #M0093) were purchased from the indicated vendors and used as received. Potassium bis(trimethylsilyl)amide (MilliporeSigma, catalog #324671) was purchased as a 95% pure powder and potassium *tert*-butoxide (KO-*t*-Bu, Chem-Impex catalog #27317) was purchased as a 99.8% pure powder and were used as received. *N*,*N*-Dimethylformamide (DMF, anhydrous, Sigma Aldrich, catalog #227056) and toluene (Alfa Aesar, anhydrous, catalog #L10967-AU) were used as received. All solid bases, 18-crown-6, and DMF were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. $NEt_3 \cdot 3HF$, TFA, MsOH, and toluene were stored at room temperature. Potassium bis(trimethylsilyl)amide (1M in THF, Sigma Aldrich, catalog #702722) and sodium bis(trimethylsilyl)amide solution (2M in THF, Oakwood, catalog #S14980), and HF-pyridine were stored at -32 °C in a freezer. All other solvents and reagents were purchased from Millipore Sigma, Combi-Blocks, TCI, Acros Organics, Matrix Scientific, AlfaAesar, ChemScene and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm). Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma. Automated flash column chromatography was conducted on a Biotage® Selekt Enkel (Biotage, SEL-ESV).

General Analytical Information: All reported compounds were characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, FTIR spectroscopy, and high-resolution mass spectrometry. Melting point analysis was conducted if the compound was solid. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were obtained on a Bruker NEO400, Bruker US400, or Bruker Ascend 400 spectrometer. ^{1}H NMR spectroscopic data is reported as follows: chemical shift (δ ppm), multiplicity (if applicable, s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, qdd = quartet of doublet of doublets, ddt = doublet of doublet of triplets, tt = triplet of triplets, tdd = triplet of doublet of doublets, ttt = triplet of triplet of triplets, dtd, doublet of triplet of doublets, ddp = doublet of doublet of pentets , ttq = triplet of triplet of quartets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR spectrum signals are reported as chemical shifts (δ ppm) relative to residual $CDCl_3$ at 7.26 ppm, CD_3CN at 1.94 ppm, CD_2Cl_2, or tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectroscopic data is reported as follows: chemical shift (δ ppm), multiplicity (if applicable, d = doublet, t = triplet, q = quartet, quin = quintet, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), and coupling constant (Hz). ^{13}C NMR signals are reported as chemical shifts (δ ppm) relative to $CDCl_3$ at 77.16 ppm, CD_3CN at 1.32 ppm, CD_2Cl_2 at 53.5 ppm or tetramethylsilane at 0.00 ppm.[1] Chemical shifts (δ ppm) for ^{19}F NMR are reported in terms of chemical shift in reference to an internal standard (1,4-difluorobenzene set to δ -119.7 ppm or 1,2-difluorobenzene set to δ -138.9 ppm). ^{19}F NMR spectroscopic data is reported as follows: chemical shift (δ ppm), multiplicity (d = doublet, t = triplet, dt = doublet of triplet, br s = broad singlet, m = multiplet), and coupling constant (Hz). [2,3] High resolution mass spectra (HRMS) were recorded on an Agilent 6230 LC-MS B-TOF equipped with a dual ESI source or an Agilent 5890 GC coupled to Xevo G2 QTOF *via* APGC ionization source provided by the Colorado State University Analytical Resource Core – Molecular and Materials Analysis Center. IR spectra were recorded using a Thermo Scientific Nicolet iS-50 FTIR Spectrometer and reported as frequency of

absorption (cm^{-1}). Melting point analyses were conducted using a MelTemp capillary melting point apparatus. Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 µm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm) or $KMnO_4$ stain.

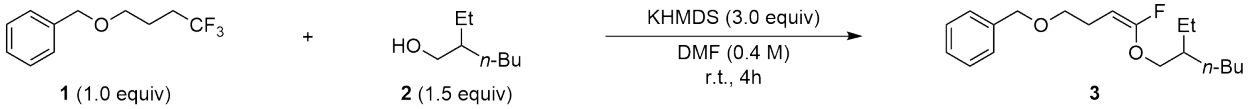
Nomenclature Note: The names provided for the structures in this document were obtained from ChemDraw Professional 23.1.2.

II. Optimization for (Trifluoromethyl)alkane Monodefluorofunctionalization

(a) Optimization of vinyl ether formation: Evaluation of changes in base identity and equivalents, alcohol equivalents, solvent, reaction time, and temperature.

Discussion. Preliminary experiments varying base and solvent indicated that multiple combinations of base and solvent promoted vinyl ether formation of (4,4,4-trifluorobutoxy)methyl)benzene (**1**) using 2-ethyl-1-hexanol (**2**) as a model alcohol. Table S1 lists a set of conditions where base, solvent, temperature, reagent equivalents, and reaction time were varied to achieve high yield of vinyl ether **3**. We found that KHMDS and NaHMDS were optimal bases to promote vinyl ether formation. Despite potassium KO-*t*-Bu affording a high yield of the vinyl ether, we found that KHMDS is more general for a variety of alcohols, affording full conversion of the (trifluoromethyl)alkane, which allows for easier purification of the α,α-difluoroether product. For model (trifluoromethyl)alkane **1**, KHMDS was selected over NaHMDS because each reaction (Table S1) resulted in complete consumption of (trifluoromethyl)alkane starting material, which was often difficult to separate from the α,α-difluoro ether product *via* silica chromatography.

General procedure for condition variation for vinyl ether synthesis (Step 1): (4,4,4-Trifluorobutoxy)methyl)benzene (21.8 mg, 0.1 mmol) was added to an oven-dried, 4 mL dram vial (KIMBLE®, #0333919A) charged with a magnetic stir bar. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13) and was brought into a N_2 filled glovebox. The vial was unsealed and anhydrous DMF (0.25 mL, 0.4M) was added *via* a micropipette. 2-Ethyl-1-hexanol (19.5 mg, 1.5 equiv, 0.15 mmol) was then added *via* pipette followed by KHMDS (59.9 mg, 3.0 equiv, 0.3 mmol). The vial was sealed with the screw cap, removed from the glovebox, and placed into an aluminum reaction block at room temperature. The reaction solution was stirred at room temperature for 4 h. At this time, the vial was unsealed, and methanol (0.1 mL, 2.47 mmol, 24.7 equiv) was added *via* syringe to quench the reaction solution. 1,4-Difluorobenzene standard was then measured into the reaction solution *via* pipette; for each experiment, the mass of 1,4-difluorobenzene weighed into the vial was recorded separately. A small aliquot was removed, charged into an NMR tube, and constituted in $CDCl_3$ (0.5 mL). ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was used to determine the yield of (*Z*)-(((4-((2-ethylhexyl)oxy)-4-fluorobut-3-en-1-yl)oxy)methyl)benzene (**3*Z***) and (*E*)-(((4-((2-ethylhexyl)oxy)-4-fluorobut-3-en-1-yl)oxy)methyl)benzene (**3*E***). We note that the ratio of **3*E*** to **3*Z*** is usually greater than 5:1. The aromatic fluorine signal of 1,4-difluorobenzene at -119.7 ppm (q, 2F) was integrated against the vinyl fluorine signal of (((4-((2-ethylhexyl)oxy)-4-fluorobut-3-en-1-yl)oxy)methyl)benzene at -89.50 ppm (d, J = 4.6 Hz, *Z*-isomer) and -89.51 ppm (d, J = 30.5 Hz, *E*-isomer) to determine the yield. The results are summarized in Table S1 below. Representative ^1H and ^{19}F NMR spectra for this reaction are provided below. **Note:** A 20 second relaxation delay was used to acquire quantitative ^{19}F NMR data.



Entry	Change from above conditions	Yield
1	None	84%
2	3.0 equiv NaHMDS	91%
3	2.0 equiv KHMDS	72%
4	4.0 equiv KHMDS	83%
5	3.0 equiv LiHMDS	0%
6	3.0 equiv KO-*t*-Bu	90%
7	3.0 equiv KOMe	0%
8	reaction run under ambient atmosphere instead of under N_2	91%
9	1.0 equiv alcohol instead of 1.5 equiv	75%
10	40°C	85%
11	60 °C instead of r.t.	75%
12	0 °C → r.t, instead of r.t.[a]	83%
13	0 °C → 40 °C, instead of r.t.[a]	84%
14	3.0 equiv NaHMDS 0 °C → 40 °C, instead of r.t.[a]	32%
15	5 min instead of 4 h	61%
16	30 min instead of 4 h	83%
17	20 h instead of 4 h	80%
18	0.5M instead of 0.4M	89%
19	0.1M instead of 0.4M	79%
20	MeCN instead of DMF	0%
21	DMSO instead of DMF	59%
22	THF instead of DMF	25%
23	DME used instead of DMF	56%
24	Toluene instead of DMF	0%
25	KHMDS solution (1M in THF, 3.0 equiv)	87%
26	NaHMDS solution (2M in THF, 3.0 equiv)	84%
27	NaHMDS solution (1M in THF, 3.0 equiv), 0°C→40 °C[a]	55%
28	KHMDS solution (1M in THF, 3.0 equiv), 0 °C → 40 °C[a]	77%
29	KHMDS solution (1M in THF, 3.0 equiv), 0 °C → 40 °C (1.0 mmol scale)[a]	83%

Table S1: Condition variation of vinyl ether formation from ((4,4,4-trifluorobutoxy)methyl)benzene (**1**). A > 5:1 ratio of ***3E*** to ***3Z*** is usually observed and the combined yield is reported. [a] reaction was run under ambient atmosphere.

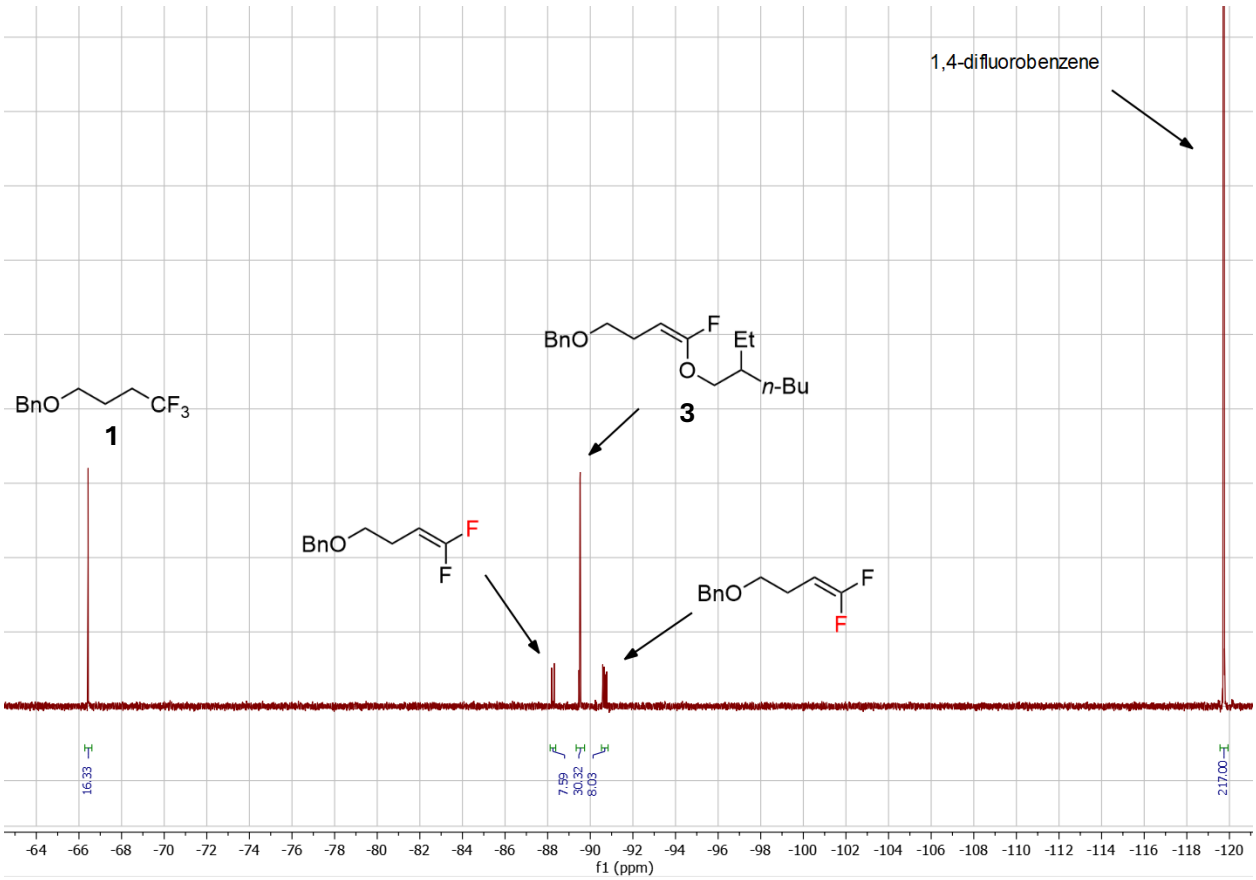


Figure S1: Representative ^{19}F NMR spectrum of a crude reaction solution from optimization studies. Reaction stopped after 5 min to show starting material (**1**) (Table S1, Entry 15), *gem*-difluoroalkene intermediate, and vinyl ether product (**3**). 1,4-Difluorobenzene (24.8 mg, 217 µmol, signal at -119.7 ppm) was used to determine the amount of ((4,4,4-trifluorobutoxy)methyl)benzene (**1**, 10.9 µmol, 11%), (((4,4-difluorobut-3-en-1-yl)oxy)methyl)benzene (15.6 µmol, 16% yield) and (*E/Z*)-(((4-((2-ethylhexyl)oxy)-4-fluorobut-3-en-1-yl)oxy)methyl)benzene (**3**, 60.6 µmol, 61% yield).

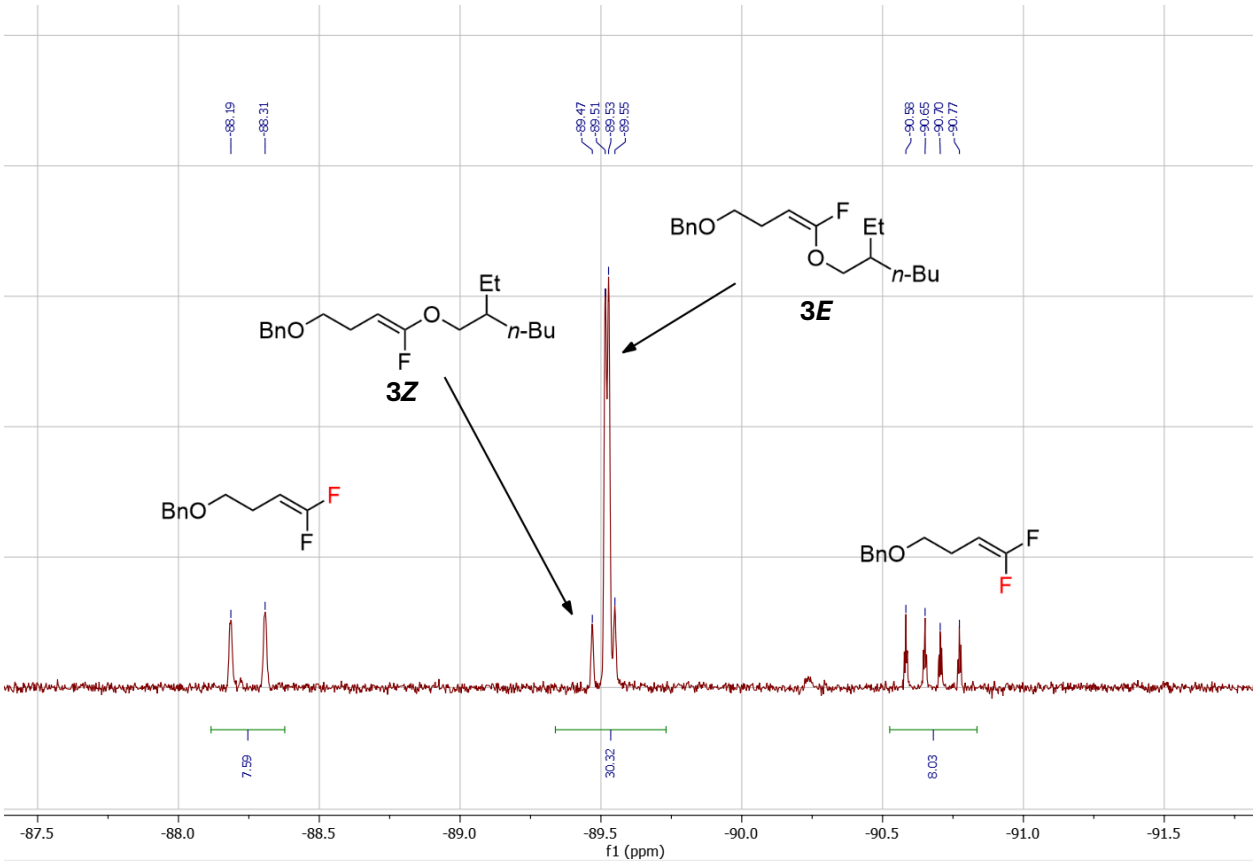


Figure S2: ^{19}F NMR spectral window of spectrum depicted in **Figure S1** depicting the ^{19}F NMR signals for the *gem*-difluoroalkene intermediate and both *E* and *Z* isomers (**3*E*** and **3*Z***, respectively) of the vinyl ether product.

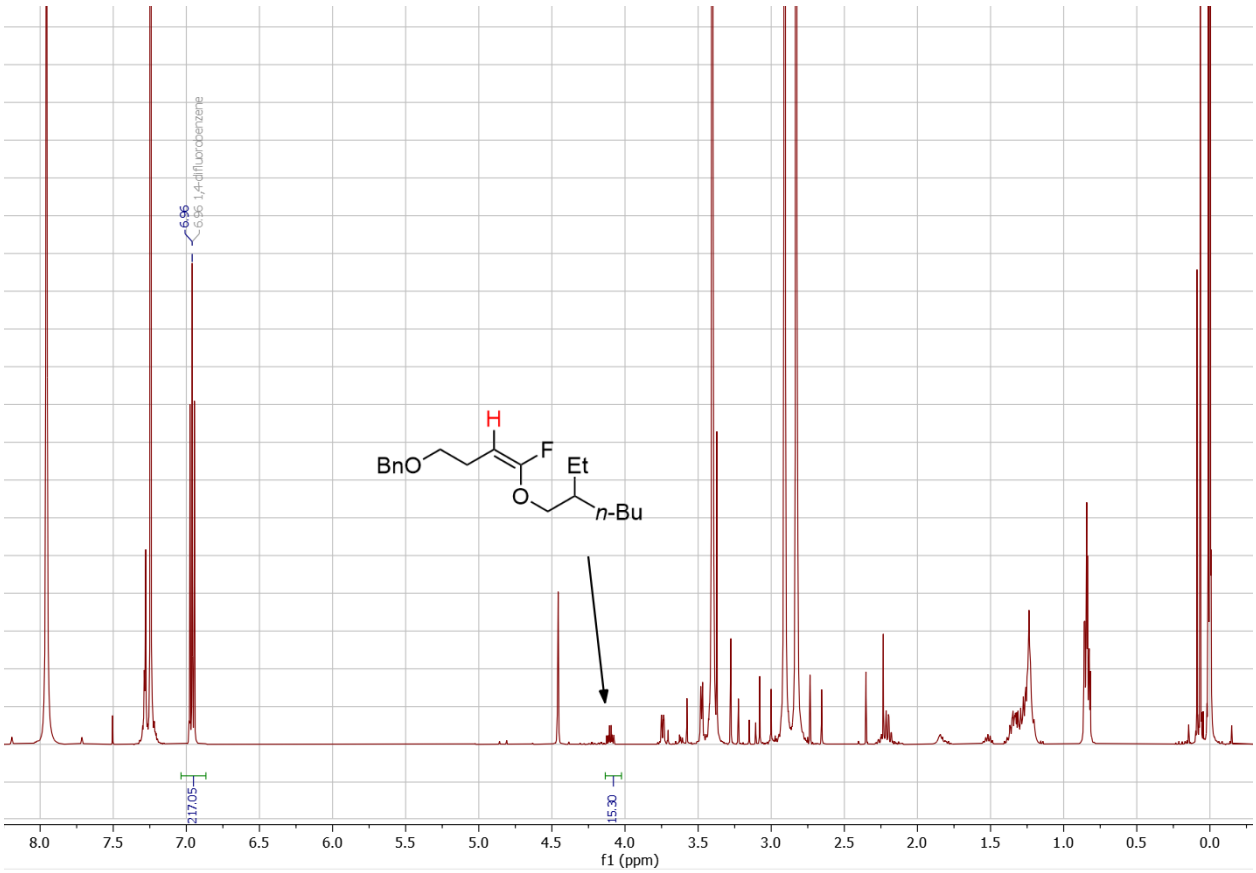


Figure S3: Representative ^{1}H NMR spectrum of the crude reaction solution from the optimization studies, quenching the reaction mixture with methanol (0.1 mL, 2.5 mmol) after 5 min (Table S1, Entry 15). 1,4-Difluorobenzene (24.8 mg, 217 µmol, signal at 6.96 ppm) was used to corroborate the yield of **3** (61.2 µmol, 61% yield) determined *via* ^{19}F NMR spectroscopy.

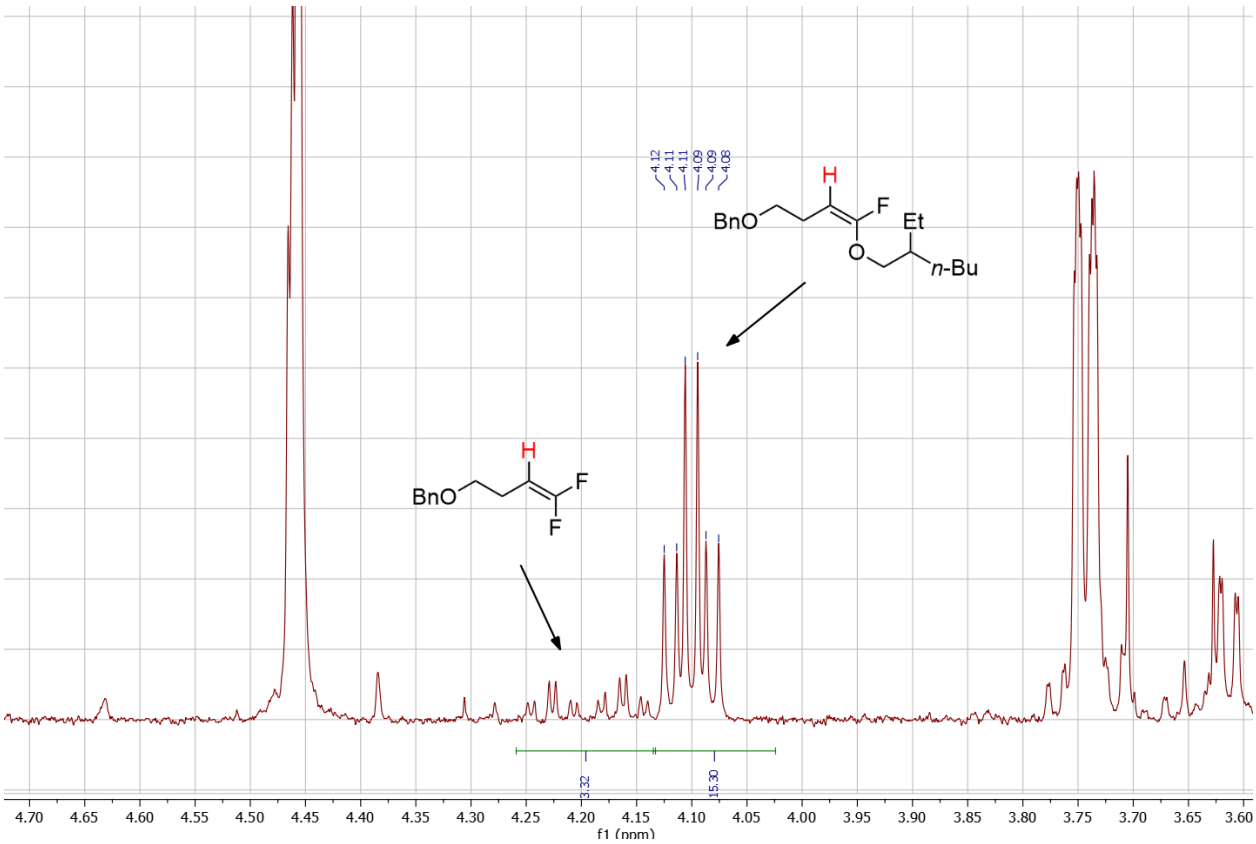


Figure S4: ^{1}H NMR spectral window of spectrum depicted in **Figure S3** depicting the ^{1}H NMR signals for the (((4,4-difluorobut-3-en-1-yl)oxy)methyl)benzene intermediate and vinyl ether product (*E*)-(((4-((2-ethylhexyl)oxy)-4-fluorobut-3-en-1-yl)oxy)methyl)benzene (***3E***). ***3Z*** is not observable here.

Preparation of crude vinyl ether solution for hydrofluorination optimization: For optimization of hydrofluorination, 1 mmol scale preparation of **3** was conducted using General Procedure 1 (**GP1** Step 1, page S11). The crude reaction mixture from this step was transferred to a 125 mL separatory funnel, saturated aqueous $NaHCO_3$ (50 mL) was added and extracted with dichloromethane (DCM, 3 x 25 mL). The resulting organic solution was then dried with Na_2SO_4, filtered, transferred to a 500 mL round bottom flask, and concentrated *in vacuo*. *n*-Heptane (100 mL) was added, and the solution was reconcentrated. To the mixture, 1,4-diflurobenzene (30 µL, 305 µmol) was added *via* microsyringe. $CDCl_3$ (~0.5 mL) was then added to give a homogenous solution. A small aliquot from this solution was removed, charged into an NMR tube, and constituted in $CDCl_3$ (0.5 mL). ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was used to determine the yield of (***3E***) and (***3Z***) with a 20 second relaxation delay. The NMR sample was recombined with the crude material, taken up with DCM and transferred to a 20 mL scintillation vial of a known mass. The solution was then reconcentrated *in vacuo*. The mass of the crude material was determined by weighing the vial containing the concentrated crude material. An aliquot with the mass 1/10th of the crude material mass was charged into a HDPE scintillation vial (Fisher, #03-341-72B) with a stir bar (i.e., if the total mass of the crude material weighed 250 mg, a 25 mg aliquot was taken).

(b) Optimization of hydrofluorination of 1-fluorovinyl ether 3: evaluation of hydrofluorination reagent, co-acid, and solvent.

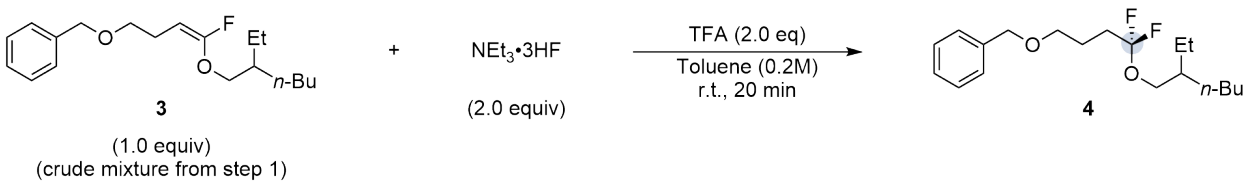
Discussion. Hydrofluorination optimization studies were conducted using the crude vinyl ether mixture acquired from the procedure above. Initial studies varying hydrofluoric acid source indicated that

pyridine·HF (70% hydrogen fluoride % w/w) and DMPU·HF (65% hydrogen fluoride % w/w) in toluene promote regioselective hydrofluorination of **3** to afford ((4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)methyl)benzene (**4)** in good to excellent yield (Table S2, Entry 9 and 12, respectively). We also found that use of NEt_3·3HF with TFA affords quantitative conversion of **3** to **4**. We reasoned one potential advantage of a co-acid system would be that the identity of the coacid could be modularly changed to promote hydrofluorination of more difficult-to-protonate vinyl ether compounds. This is illustrated in Figure 4 in which methanesulfonic acid was required to promote regioselective hydrofluorination of fluorovinyl arylether intermediates. In addition to the coacid system affording high hydrofluorination yield, use of NEt_3·3HF has practical advantages over pyridine·HF and DMPU·HF. Namely, NEt_3·3HF by itself does not etch glass, can be measured in a glass microsyringe and does not evolve hydrogen fluoride vapor.[4] Although we found that hydrofluorination of the model vinyl ether (**3**) works best using 2.0 equivalents of NEt_3·3HF and 2.0 equivalents of TFA after 20 min, all preparative scale hydrofluorination reactions of model substrate **1** vinyl ether adducts were conducted with 3.0 equivalents of each acid for 30 min. This was done because we found this generally allowed for full consumption of the vinyl ethers in Chart 1. The vinyl ether starting material and corresponding α,α-difluoroether product are inseparable *via* silica gel chromatography. For vinyl ether compounds bearing an amine group, higher equivalents of each acid are required to achieve high α,α-difluoroether yield and complete consumption of the vinyl ether.

General procedure for condition variation of hydrofluorination (Step 2): To the HDPE vial containing the crude vinyl ether mixture (**3**) obtained from Step 1, toluene (0.5 mL, 0.2 M) was added *via* syringe. NEt_3·3HF (32.6 µL, 0.2 mmol, 2.0 equiv) was added *via* syringe and the solution was stirred. Trifluoroacetic acid (15.3 µL, 0.2 mmol, 2.0 equiv) was added *via* syringe, the vial was sealed with a screwcap, and the reaction mixture was stirred at room temperature for 20 min. At this time, the vial was unsealed, 1,2-difluorobenzene (30 µL, 305 µmol) was added with a microsyringe and aqueous saturated sodium bicarbonate (1 mL + 1 mL per mmol of acid) was added *via* a syringe. K_2CO_3 (solid) was added until the aqueous phase of the biphasic mixture achieved a pH of 8. With a Pasteur pipette, a small aliquot was taken from the organic phase and loaded onto a sodium sulfate plug to remove residual water (the plug was prepared by tamping a small piece of Kimwipe into Pasteur pipette and filling the pipette ¾ full with sodium sulfate) and the crude solution was flushed with $CDCl_3$ (0.5 mL) into an NMR tube. ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was used to determine the yield of ((4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)methyl)benzene (**4**). The aromatic fluorine signal of 1,2-difluorobenzene at -138.9 ppm (q, 2F) was integrated against the fluorine signal of **4** at -74.88 ppm (t, J = 10.7 Hz, 2F) to determine the yield. The results are summarized in **Table S2** below. Yields shown are out of total possible yield benchmarked against the yield of fluorovinyl ether from Step 1. Representative ^{19}F NMR spectra for this reaction are provided below. **Note:** A 20 second relaxation delay was used to acquire quantitative ^{19}F NMR data.

Safety note: Organic hydrogen fluoride (HF) complexes (e.g., pyridine·HF, NEt_3·3HF) are highly toxic and corrosive compounds and must be handled with care. Read HF standard operating procedures before handing HF reagents.[5] When conducting experiments with HF reagents the following safety precautions were employed in addition to standard lab safety procedures recommended by Colorado State University Environmental Health Services: unexpired calcium gluconate gel (Calgonate, Fisher, #NC1209914) was on hand at all times, and a prepared beaker of saturated sodium bicarbonate solution was on hand. Needles and syringes that were used to measure and dispense HF reagents in the reactions described below were thoroughly neutralized with saturated $NaHCO_3$ before being cleaned or disposed of. When measuring HF reagents in syringes, 1 mL, Luer lock syringes (Fisher, #14-817-252) were used (with the exception of NEt_3·3HF). Pyridine·HF readily etches glass and produces hydrogen fluoride vapors at room temperature. Pyridine·HF was measured and dispensed using either a micropipette with a disposible plastic pipette tip or a plastic Luer lock syringe; do not measure pyridine·HF in a glass syringe. We note that NEt_3·3HF does not

readily etch glass and $NEt_3 \cdot 3HF$ was measured in a glass microsyringe many times without any observable damage to the syringe. **Note:** the co-acid system (mixture of either TFA or MsOH with $NEt_3 \cdot 3HF$) does etch glass and these reactions should be conducted in HF resistent vessels (e.g., HDPE, PTFE). After conducting any reaction with hydrofluoric acid, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution followed by excess solid K_2CO_3. Before analysis by NMR spectroscopy, the pH of the resulting aqueous layer was analyzed to ensure no HF remained. Never handle hydrofluoric acid outside of a fumehood and never evaporate a solution containing dissolved hydrogen fluoride.



Entry	Change from above conditions	Yield
1	none	99%
2	3.0 equiv NEt_3•3HF and 3.0 equiv TFA instead of 2.0 equiv of both acids	96%
3	0 equiv TFA instead of 2.0 equiv	5%
4	10 min instead of 20 min	98%
5	1 h instead of 20 min	91%
6	2.0 equiv acetic acid instead of TFA	9%
7	2.0 equiv oxalic acid instead of TFA	77%
8	2.0 equiv MsOH instead of TFA	83%
9	2.0 equiv Pyr•HF instead of 2.0 equiv NEt_3•3HF and 2.0 equiv TFA	75%
10	2.0 equiv KHF_2 instead of 2.0 equiv NEt_3•3HF and 2.0 equiv TFA	<1%
11	2.0 equiv HBF_4•Et_2O instead of 2.0 equiv NEt_3•3HF and 2.0 equiv TFA	0%
12	2.0 equiv DMPU•HF instead of 2.0 equiv NEt_3•3HF and 2.0 equiv TFA	95%
13	1.0 equiv TFA instead of 2.0 equiv	100%
14	3.0 equiv TFA instead of 2.0 equiv	100%
15	MTBE instead of toluene	56%
16	*i*-Pr-OAc instead of toluene	91%
17	Anisole instead of toluene	99%
18	DCM instead of toluene	94%

Table S2: Condition variation for α,α-difluoroether (**4**) formation from crude fluorovinyl ether (**3**).

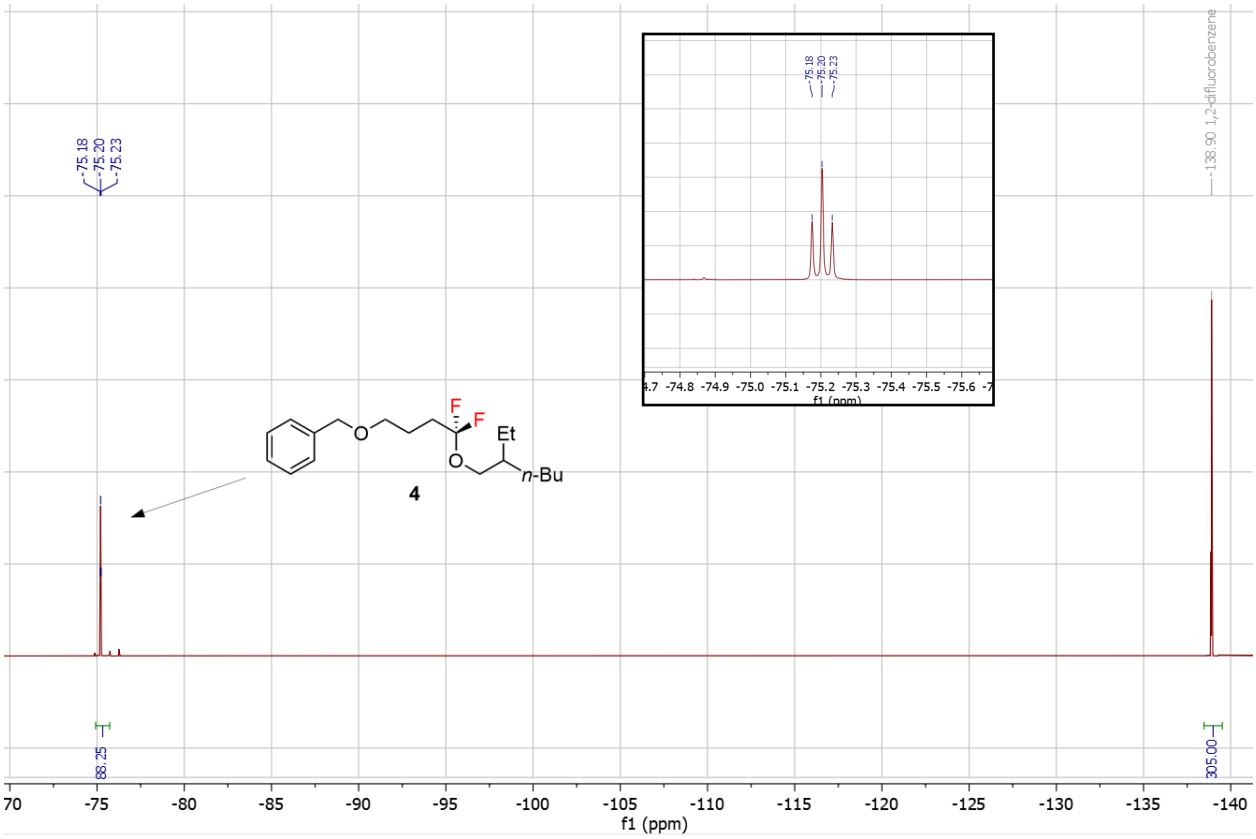
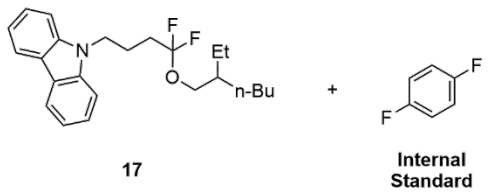


Figure S5: Representative ^{19}F NMR spectrum of the crude, quenched reaction solution for the hydrofluorination of vinyl ether **3**. 1,2-difluorobenzene (30 µL, 34.8 mg, 305 µmol, signal at -138.9 ppm) was used to determine the yield of ((4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)methyl)benzene (0.1 mmol scale) (**4**, 88 µmol out of possible 89 µmol, 99% yield; Table S2, Entry 1).

(c) Discussion of yields and reaction assessments determined by ^{19}F NMR spectroscopy method

Discussion: For yields reported based on ^{19}F NMR spectroscopy a 20 second D_1 delay was used based on the following experiment where the % error in quantification of analyte **17** is insignificant at D_1 = 15 seconds (1%). A 20 second delay was used to account for potential variation in substrate ^{19}F T_1 relaxation.

Procedure: 17 (20.0 mg, 0.052 mmol) was added to a 4 mL dram vial. $CDCl_3$ (0.5 mL) was then added. To the vial, 1,4-difluorobenzene (18.8 mg, 0.165 mmol) was added. The solution was loaded into an NMR tube and analyzed *via* ^{19}F NMR spectroscopy using various D_1 delay times.



17 + Internal Standard

^{19}F NMR Spectroscopy

D_1 Delay times

D_1 Delay time	calculated amount (mmol)	% Error
1 sec	0.162	213%
5 sec	0.076	46%
10 sec	0.058	12%
15 sec	0.053	1%
20 sec	0.051	3%
30 sec	0.049	5%

Figure S6: Percentage error in ^{19}F NMR integration versus D_1 delay time.

Analysis: The *gem*-difluoride signal at -73.9 ppm (t, J = 10.4 Hz, 2F) was integrated against the fluorine signal of 1,4-diflurobenene (p, J = 6.0 Hz, 2F) to calculate the amount of **17** in solution. The percentage error was calculated based on the known amount of **17** in solution (0.052 mmol). From the data, we conclude that a 15 second D_1 time is sufficient for quantifying **17**. To account for potential variation in substrate ^{19}F T_1 time, a 20 second delay was used to determine yields where ^{19}F NMR spectroscopy is used to report a yield.

Notes on discrepancy between yields determined *via* ^{19}F NMR spectroscopy and isolated yields

Discussion: In most cases, we report only the isolated product yields. In certain cases, yields based on ^{19}F NMR spectroscopy are included to inform readers of the initial yield of the reaction (Figure 4b and 5c). Several of these compounds have a discrepancy between the yield determined by ^{19}F NMR spectroscopy of the crude reaction mixture and the isolated yield. We note a few potential factors that can contribute to the yield loss. First, substituted *gem*-difluoride products are sensitive to hydrolysis, which may take place during the aqueous workup or during chromatography. We reason this is the largest contributing factor to the yield loss for the compounds in Figure 4b. For the complex compounds in Figure 5c, the resolution between the products, starting material and side products are poor on silica and necessitated careful purification *via* preparatory thin layer chromatography without full separation.

Assessment of *E/Z* fluorovinyl ether isomers

Discussion: Throughout this work, we report the vinyl fluoro(thio)ether intermediates as the *E* isomer. We note that the *E* isomer is the major product for all vinyl(thio)ether formation reactions that we have observed. Analysis of crude reaction mixtures *via* ^{19}F NMR spectroscopy shows two ^{19}F signals representing the *E* and *Z* isomers. The isomers were assigned based on the $^3J_{HF}$ coupling constant compared with each other, with the major (*E*) isomer having a smaller coupling constant. A representative ^{19}F NMR spectrum of a fluorovinyl ether mixture (the intermediate to product **5**) is shown below to illustrate a case where both isomers are visible. A mixture (*E*-isomer major) is also observed for the model substrate in Figure S2.

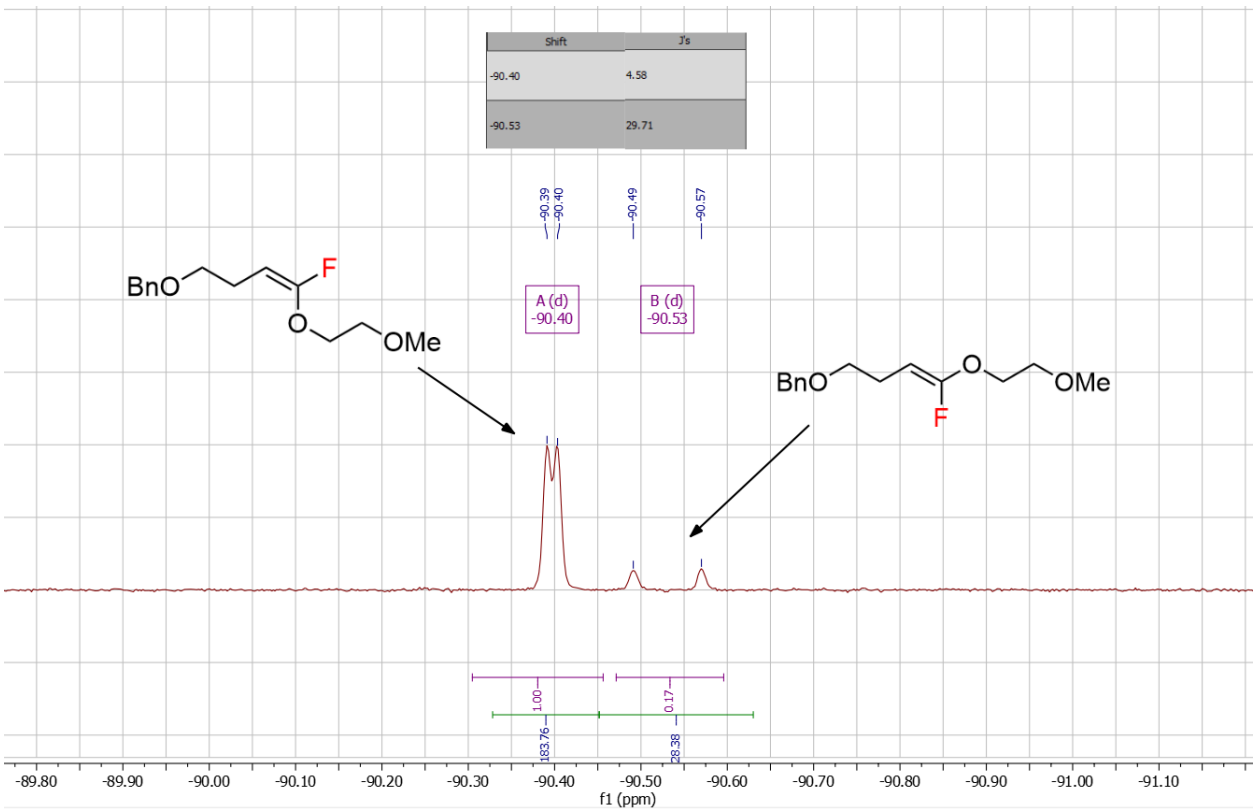


Figure S7: ^{19}F NMR spectral window of the formation of (*E/Z*)-(((4-fluoro-4-(2-methoxyethoxy)but-3-en-1-yl)oxy)methyl)benzene displaying both isomer ^{19}F signals with their respective coupling $^{3}J_{HF}$ constants. The signals at -90.4 ppm (d, J = 4.6 Hz, 1F) and -90.5 (d, J = 29.7 Hz, 1F) were integrated against 1,4-difluorobenzene (not shown, 48.3 mg, 423 µmol) to show 85% combined yield (368 µmol, 74% yield; 57 µmol, 11% yield).

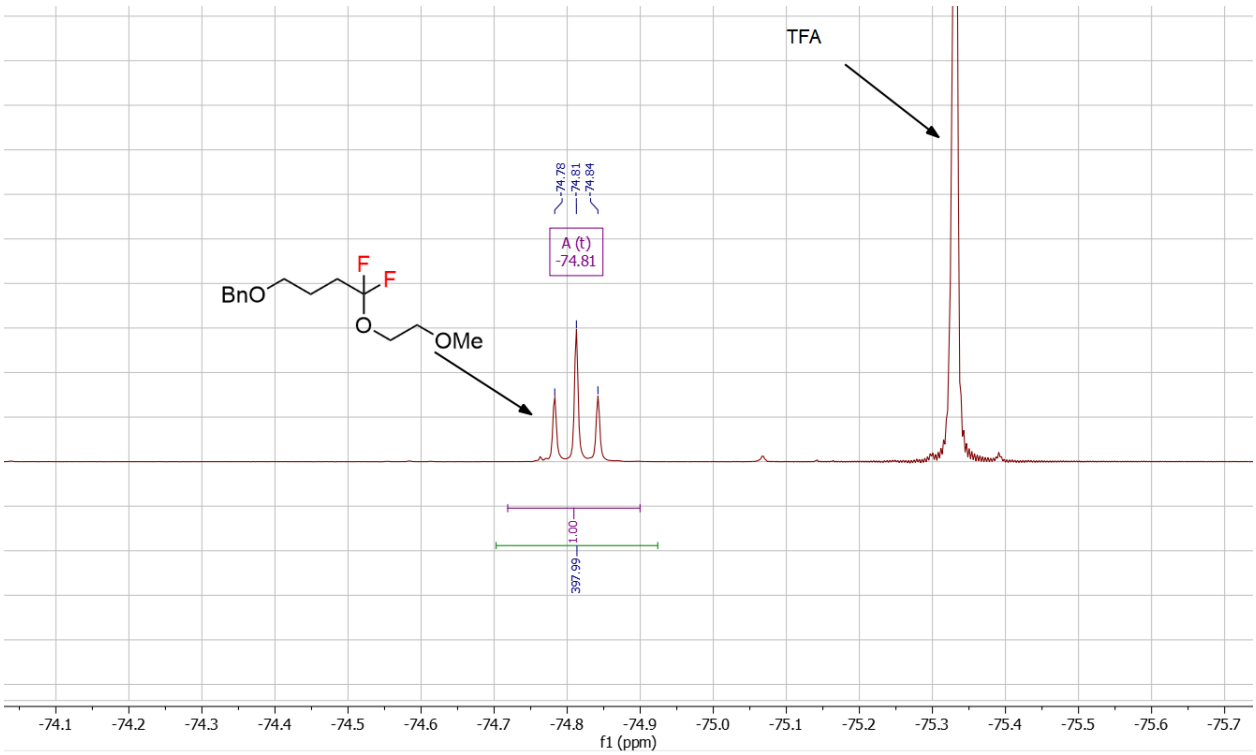


Figure S8: ^{19}F NMR spectral window of the formation of ((4,4-difluoro-4-(2-methoxyethoxy)butoxy)methyl)benzene (**5**). The ^{19}F signal of **5** (t, J = 11.1 Hz, 2F) (398 µmol, 80% yield) was integrated against 1,2-difluorobenzene (not shown, 30 µL, 306 µmol).

Analysis: The presence of two distinct ^{19}F signals in Figure S7 that exhibit different coupling constants is consistent with the formation of both *E* (74% yield) and *Z* (11% yield) isomers with the *E* isomer being the major intermediate. Furthermore, a yield of 80% for the hydrofluorination step is consistent with both isomers reacting to form **5**. We note that in all cases other than this representative example similar scenarios are observed (*E* isomer being major intermediate).

(d) Role of CuCl in hydrofluorination of fluorovinyl thioethers:

Discussion: During hydrofluorination studies of fluorovinyl thioether intermediates, we found poor yield and mass balance were observed under standard hydrofluorination conditions (Figure S9a). Lower acid loadings gave poor conversion while higher acid loadings resulted in complete consumption of starting material with little product formation. We investigated various additives that could bind to amine·HF sources and alter their reactivity. When CuCl was used with Olah's reagent, a substantial product yield increase was observed. We speculate that CuCl disrupts the H-bonding in Olah's reagent to achieve the requisite balance of acidity and nucleophilicity for fluorovinyl thioether hydrofluorination without decomposition. There are other mechanistic possibilities, including olefin binding[6], and the full role of this additive is not currently known.

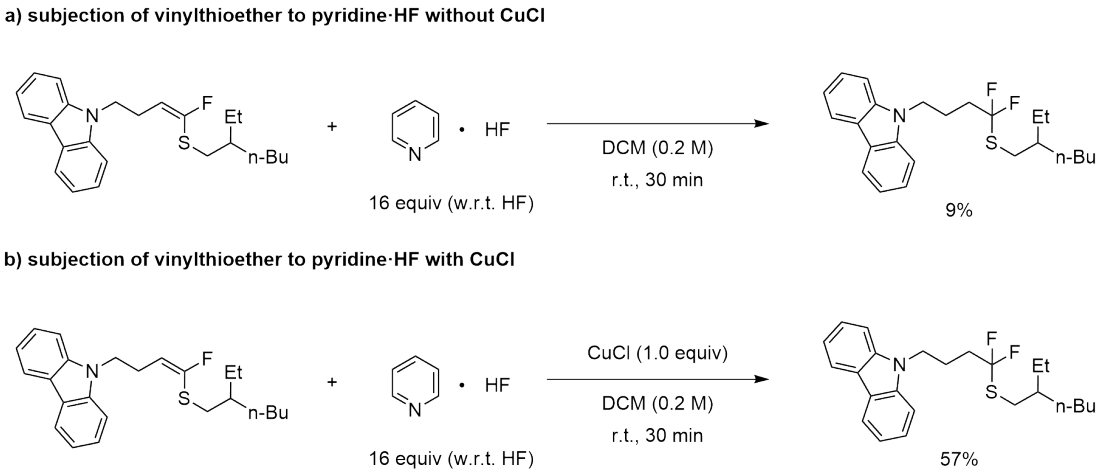


Figure S9: Fluorovinyl thioether hydrofluorination yield increase using CuCl additive.

III. Limitations of the Pronucleophile Coupling Partner:

Discussion: During these studies, we also explored *N*- and *P*-based pronucleophiles to try to achieve broader range of C–F substitution products. We found that these classes of pronucleophiles are sufficiently nucleophilic to form the respective fluorovinyl intermediates; however, neither class underwent productive hydrofluorination. We reason that this is likely due to a more challenging fluoride addition step or the potential instability of the resulting products which is well documented for *N*-substituted *gem*-difluorides.[7]

Amine pronucleophiles: we found that alkylamines (e.g., piperidine) do not add to give the fluorinated enamine intermediate and poor mass balance is observed alongside *gem*-difluoroalkene intermediate. This is likely due to the low acidity of alkylamines. Anilines, on the other hand, afford the corresponding fluoroenamine in good yield (e.g., **1** and *N*-methylaniline give 82% yield under standard conditions using NaHMDS in *N*,*N*-dimethylacetamide). Hydrofluorination of this enamine intermediate was unsuccessful under a variety of our optimized conditions for fluorovinyl ether hydrofluorination.

Phosphine pronucleophiles: we found that diphenylphosphine undergoes the addition/elimination sequence with **1** to afford the corresponding fluorovinyl phosphine interemediate in moderate yield (37% yield) under standard conditions. However, subjection of this fluorovinyl phosphine to standard hydrofluorination conditions results in a complex mixture of products with no desired phosphorus substituted *gem*-difluoride detected.

Tertiary alcohol pronucleophiles: tertiary alcohol pronucleophiles (e.g., *t*-BuOH) undergo the addition/elimination sequence to afford the corresponding vinyl ether in moderate yield under standard conditions (e.g., *t*-BuOH and 9-(4,4,4-trifluorobutyl)-9H-carbazole give 51% fluorovinyl ether yield under standard conditions); however, subjection of this material to standard hydrofluorination conditions results in poor yield and mass balance (4% yield by ^{19}F NMR spectroscopy).

Diol pronucleophiles: during the alcohol pronucleophile studies, we investigated diols and hypothesized that steric effects could influence site-selectivity. We found, however, that these substrates result in low yield and mass balance of the corresponding vinyl ether (e.g., 3-methylbutane-1,3-diol and **1** gave a mixture of characteristic fluorovinyl ether signals that integrate to 28% yield in the ^{19}F NMR spectrum under standard conditions), likely due to a lower nucleophilicity caused by additional H-bonding.

IV. General Procedures for (Trifluoromethyl)alkane Monodefluorofunctionalization:

General Procedure 1 (GP1) for primary-substituted (trifluoromethyl)alkane defluoroetherification: **(Step 1)** To an oven-dried, 7.5 mL dram vial (Fisher, #14-955-326) with a stir bar containing (trifluoromethyl)alkane (0.5 mmol 1.0 equiv), anhydrous DMF (1.25 mL) and alcohol (0.75 mmol, 1.5 equiv) were added *via* syringe. The vial was sealed with a screwcap, placed in a 0 °C ice bath and the solution was stirred for five min. The vial was then unsealed, and potassium bis(trimethylsilyl)amide solution (1M in THF, 1.5 mL, 1.5 mmol) or sodium bis(trimethylsilyl)amide solution (2M in THF, 0.75 mL, 1.5 mmol) was added *via* syringe. The vial was resealed with the screwcap, and the mixture was stirred at 0 °C for an additional one minute. The vial was then removed from the ice bath and placed in an aluminum reaction block (Chemglass, #CG-1991-05) preheated to 40 °C and the reaction mixture was stirred. The reaction mixture was monitored by thin layer chromatography (TLC) until complete consumption of the (trifluoromethyl)alkane was observed (typically 10 hours). At this time, the vial was unsealed, and methanol (0.5 mL, 12.4 mmol) was added *via* syringe to quench the reaction solution. 1,4-Difluorobenzene standard was then measured into the crude solution with a pipette and the mass of standard added was recorded. A small aliquot (~0.1 mL) was charged into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was used to determine the yield of the fluorovinyl ether product. The NMR sample and the crude reaction solution were combined in a 250 mL separatory funnel with DCM. Saturated aqueous $NaHCO_3$ solution (100 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). **Note:** Initial studies into the aqueous workup suggested that the vinyl ether is sensitive to hydrolysis under neutral aqueous conditions and found that using saturated sodium bicarbonate as the aqueous phase instead of water mitigated hydrolysis. The resulting organic solution was then dried with Na_2SO_4, filtered and concentrated *in vacuo*. To the concentrated solution containing residual DMF, *n*-heptane (50 mL) was added, and the resulting solution was reconcentrated *in vacuo*. This was done to remove residual DMF which forms a low-boiling azeotrope with *n*-heptane.[8] The concentrated mixture was taken up with DCM and transferred to a 25 mL PTFE round bottom flask (Fisher, #50-977-980) and reconcentrated *via* air blowdown evaporation. The flask was fitted with a rubber septum and placed under vacuum *via* a needle connected to a Schlenk line for 1 minute. **Note:** due to issues with bumping while concentrating solutions in the PTFE round bottom flask (the internal flask surface is not smooth) *via* rotary evaporation, we found concentration *via* air blowdown evaporation followed by drying under vacuum to be more efficient.

(Step 2) The PTFE round bottom flask containing the crude mixture from Step 1 was backfilled with nitrogen before being disconnected from the Schlenk line. The rubber septum was removed, and a stir bar was added. The flask was then fitted with a rubber septum and evacuated and backfilled with nitrogen gas three times and left under a positive pressure of nitrogen gas on a manifold Schlenk line. Toluene (2.5 mL) was then added *via* syringe. At this time, $NEt_3 \cdot 3HF$ (244 µL, 1.5 mmol, 3.0 equiv) was added *via* syringe and the solution was stirred. To this solution, trifluoroacetic acid (115 µL, 1.5 mmol, 3.0 equiv) was added *via* syringe and the reaction mixture was stirred at rt for 30 min (unless otherwise noted). At this time, 1,2-difluorobenzene (30 µL, 34.8 mg, 0.305 mmol) was added *via* syringe, the septum was pierced with a vent needle, and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (1 mL + (1 mL per 1 mmol of acid)) which was added slowly (~1 mL / 5 seconds) *via* syringe. The septum was removed and excess solid K_2CO_3 was added until gas evolution ceased (~50 mg). The pH of the aqueous phase was measured using pH paper to ensure all HF was consumed (pH ~ 9). From the organic layer of the biphasic mixture, a small aliquot (~ 0.2 mL) was removed and filtered through a sodium sulfate plug with $CDCl_3$ (0.5 mL) into an NMR tube (the plug was prepared by tamping a small piece of Kimwipe into Pasteur pipette and filling the pipette ¾ full with sodium sulfate). The solution was analyzed with NMR

spectroscopy (^{1}H and ^{19}F) to determine the crude yield of the α,α-difluoroether product. The biphasic mixture and the NMR sample were then combined in a 250 mL separatory funnel. Saturated aqueous $NaHCO_3$ solution (100 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The resulting organic solution was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was isolated *via* silica flash column chromatography according to the eluent conditions provided. Reported isolated yields represent total yield of both steps (i.e., out of 0.5 mmol).

General Procedure 2 (GP2) for secondary-substituted (trifluoromethyl)alkane defluoroetherificatiom: GP1 Step 1 was followed with the following modifications: After addition of the (trifluoromethyl)alkane, the vial was sealed with a screwcap lined with a PTFE septum, and the vial was evacuated and backfilled three times with anhydrous nitrogen gas and left under a positive pressure of nitrogen gas on a manifold Schlenk line. DMF (1.25 mL) was added *via* syringe followed by alcohol (0.5 mmol, 1.0 equiv) *via* syringe. The vial was placed in a 0 °C ice bath with stirring, and the solution was stirred at 0 °C for 5 min. At this time, the vial was unsealed and KO-*t*-Bu (140.3 mg, 1.25 mmol, 2.5 equiv) was added at once. The vial was resealed with a screwcap and new septum and the vial was flushed for 30 seconds with nitrogen using a positive pressure of nitrogen gas *via* an inlet needle connected to a Schlenk line and a vent needle. The vial was removed from the ice bath; the top of the vial was sealed with electrical tape and the vial cap was wrapped in parafilm. The vial was placed in an aluminum reaction block preheated to 80 °C and the reaction mixture was stirred for 15 hours. **Step 2** and the purification procedure are identical to **GP1**.

General Procedure 3 (GP3) for amine-bearing (trifluoromethyl)alkane defluoroetherification: This procedure was employed when either the pronucleophile or (trifluoromethyl)alkane contained a primary or secondary amine functional group. **GP2 Step 1** was followed with the following modifications: anhydrous *N,N*-dimethylacetamide (DMA, 0.5 mL, 0.4 M) was used instead of DMF, 1.5 equivalents of alcohol (0.75 mmol, 1.5 equiv) was used instead of 1.0 equivalent, 3.0 equivalents of solid KO-*t*-Bu (168.3 mg, 1.5 mmol, 3.0 equiv) was used instead of 2.5 equivalents, and the reaction mixture was stirred at 40 °C instead of 80 °C. **Step 2** and the purification procedure are identical to **GP1**.

General Procedure 4 (GP4) for (trifluoromethyl)alkane defluoroetherification with phenols: GP1 Step 1 was followed with the following modifications: After addition of DMF (1.25 mL, 0.4 M), 18-crown-6 (396.5 mg, 1.5 mmol, 3.0 equiv) was added directly to the solution of (trifluoromethyl)alkane in DMF. Solid KHMDS (299.3 mg, 1.5 mmol, 3.0 equiv) was used instead of the KHMDS solution in THF which was added directly to the solution. The reaction mixture was stirred at 50 °C instead of 40 °C. **Step 2** and the purification procedure are identical to **GP1**.

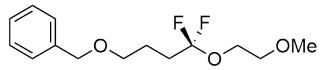
General Procedure 5 (GP5) for (trifluoromethyl)alkane defluorothioetherification: Step 1: To a 7.5 mL, oven-dried dram vial, (trifluoromethyl)alkane (0.5 mmol 1.0 equiv) was added *via* pipette. Anhydrous *N,N*-dimethylformamide (1.25 mL, 0.4 M) was added *via* syringe followed by 18-crown-6 (330.4 mg, 1.25 mmol, 2.5 equiv). The vial was sealed with a screwcap lined with a PTFE septum, placed in a 0 °C ice bath, and the mixture was stirred for five min. The vial was then unsealed, and solid KHMDS (249.4 mg, 1.25 mmol, 2.5 equiv) was added at once. The vial was resealed with the screwcap and allowed to stir at 0 °C for 5 seconds. At this time, the vial was removed from the ice bath and was stirred at room temperature for 30 seconds. The vial was then unsealed and thiol (1.5 mmol, 3.0 equiv) was added *via* syringe. The vial was then resealed with the screwcap and septum and was flushed with nitrogen gas for 30 seconds with nitrogen using a positive pressure of nitrogen gas *via* an inlet needle connected to a Schlenk line and a vent needle. Both needles were then removed, and the reaction mixture was stirred at room temperature for 1 hour. At this time, the vial was unsealed, and methanol (0.5 mL, 12.4 mmol) was added *via* syringe. **GP1** was followed for the aqueous workup and preparation of the crude vinyl thioether mixture for

hydrofluorination. **Step 2:** To the PTFE flask containing the crude vinyl thioether and a stir bar, DCM (2.5 mL, 0.2 M) was added *via* syringe followed by cuprous chloride (49.5 mg, 0.5 mmol, 1.0 equiv) and the solution was stirred. Pyridine·HF (70% hydrogen fluoride % w/w, 208 µL – 312 µL, 0.88 mmol - 1.2 mmol, 1.8 equiv – 2.6 equiv) was added *via* micropipette. The flask was sealed with a rubber septum and the reaction mixture was stirred for 30 min (unless otherwise noted) at room temperature. At this time, 1,2-difluorobenzene (30 µL, 34.8 mg, 0.305 mmol) was added *via* syringe, the septum was pierced with a vent needle, and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (1 mL + (1 mL per 1 mmol of acid)) which was added slowly (~1 mL / 5 seconds) *via* syringe. The septum was removed and excess solid K_2CO_3 was added until gas evolution ceased (~50 mg). The pH of the aqueous phase was measured using pH paper to ensure all HF was consumed (pH ~ 9). From the organic layer of the biphasic mixture, a small aliquot (~ 0.2 mL) was removed and filtered through a sodium sulfate and neutralized silica plug with $CDCl_3$ (0.5 mL) into an NMR tube (the plug was prepared by tamping a small piece of Kimwipe into Pasteur pipette and filling the pipette with 1 cm of neutralized silica and then ¾ full with sodium sulfate) (the silica was neutralized by preparing a slurry of silica in 2% triethylamine in hexanes and allowing that slurry to dry). This was done to dry the crude mixture and remove copper which severely broadens both ^{19}F and ^{1}H NMR spectra. The solution was analyzed with NMR spectroscopy (^{1}H and ^{19}F) to determine the crude yield of the α,α-difluorothioether product. The workup and isolation for α,α-difluorothioether products is described in **GP1** Step 2.

V. Characterization Data of C–F Substituted Products

Note: For (trifluoromethyl)alkane substrates that possess stereocenters, when racemic 2-ethyl-1-hexanol is used as an alcohol, a 1:1 diastereomeric ratio is assumed (no NMR signals were discernable to directly measure the dr). This is the case for products **19**, **22**, **26**, **27** and **50**.

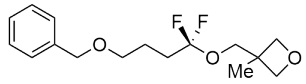
((4,4-difluoro-4-(2-methoxyethoxy)butoxy)methyl)benzene (5)



Note: This is a one-pot procedure to demonstrate that the entire procedure can be conducted without any intermediate forms of purification (i.e., aqueous workup). We found, however, that evaporation of the crude reaction mixture / *n*-Heptane mixture *via* rotary evaporation results in strong bumping as solid inorganic precipitate forms such that the air evaporation and vial switching described in GP1 is more practical for routine mmol-scale reactions. **Procedure:** To an oven-dried 25 mL PTFE round bottom flask with stir bar containing ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol) and anhydrous N,N-dimethylformamide (1.25 mL), 2-methoxyethanol (57.1 mg, 0.75 mmol, 1.5 equiv) was added. The flask was placed in a 0 °C ice bath and was stirred for five min. To the flask, potassium bis(trimethylsilyl)amide solution 1M in THF (1.5 mL, 1.5 mmol, 3.0 equiv) was added at once. The flask was fitted with a rubber septum and allowed to stir at 0°C for one minute. At this time, the flask was removed from the ice bath and placed in an oil bath preheated to 40°C for 4 hours. At this time, the reaction mixture was cooled to 0°C and methanol (0.5 mL, 12.4 mmol) was added *via* syringe. The stir bar was removed and rinsed with dichloromethane. The crude reaction mix was concentrated *in vacuo* until most of the low boiling point solvents (THF, DCM) were removed. At this time, *n*-heptane (10 mL) was added and the solution was reconcentrated. This was repeated four times. A fresh stir bar was added to the flask, the flask was fitted with a rubber septum and was evacuated and backfilled three times with anhydrous nitrogen gas and left under a positive pressure of nitrogen gas on a manifold Schlenk line. For the remaining procedure, **GP1** was followed using NEt_3·3HF (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid, (114.8 µL, 1.5 mmol, 3.0 equiv), and toluene (2.5 mL) (Step 2). The titled compound was purified *via* silica gel chromatography with the eluent conditions 2%

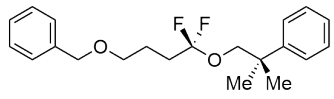
EtOAc, 2% Triethylamine/ hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (97.5mg, 0.36 mmol, 71% yield). **^{1}H NMR** (400 MHz, CD_3CN) δ 7.41 – 7.23 (m, 5H), 4.48 (s, 2H), 4.12 – 3.80 (m, 2H), 3.56 – 3.45 (m, 4H), 3.32 (s, 3H), 2.13 – 2.00 (m, 2H), 1.85 – 1.64 (m, 2H). **^{13}C NMR** (101 MHz, CD_3CN) δ 140.0, 129.3, 128.6, 128.4, 127.1 (t, *J* = 259.9 Hz), 73.3, 71.5, 69.7, 63.4 (t, *J* = 6.7 Hz), 59.0, 33.1 (t, *J* = 30.2 Hz), 24.1 (t, *J* = 3.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.10 (t, *J* = 11.1 Hz). **IR** (neat, cm^{-1}) 2935, 2859, 1453, 1262, 1099, 992. **HRMS** (ESI) $[M+NH4]^+$ calcd. for $[C_{14}H_{20}F_2O_3•NH_4]^+$ = 292.1719, 292.1758 found.

3-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-3-methyloxetane (6)



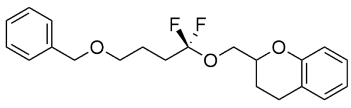
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), (3-methyloxetan-3-yl)methanol (76.6 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 4 h (Step 1); NEt_3·3HF (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 5% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 10% triethylamine / hexanes solution) to afford the product as a colorless oil (107.0 mg, 0.36 mmol, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 5H), 4.51 (t, *J* = 2.9 Hz, 5H), 4.36 (d, *J* = 5.9 Hz, 2H), 3.92 (s, 2H), 3.51 (t, *J* = 6.3 Hz, 2H), 2.25 – 1.99 (m, 2H), 1.85 (ddt, *J* = 10.6, 7.6, 6.2 Hz, 2H), 1.32 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.5, 128.5, 127.7, 125.9 (t, *J* = 261.8 Hz), 79.5, 73.0, 69.2, 67.4 (t, *J* = 6.2 Hz), 39.1, 32.7 (t, *J* = 30.0 Hz), 23.3 (t, *J* = 3.0 Hz), 21.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.60 (t, *J* = 11.0 Hz) **IR** (neat, cm^{-1}) 2960, 2869, 1452, 1259, 1098, 1064, 978, 835, 736, 697. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{16}H_{23}F_2O_3]^+$ = 301.1615, 301.1617 found.

(1-(4-(benzyloxy)-1,1-difluorobutoxy)-2-methylpropan-2-yl)benzene (7)



The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), 2-methyl-2-phenylpropan-1-ol (112.7 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 4 h (Step 1); NEt_3·3HF (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography using hexanes as an eluent on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution). Fractions containing product with impurities were further purified *via* silica gel chromatography with eluent conditions 2% EtOAc in hexanes on neutralized silica to afford the product as a yellow oil (98.5 mg, 0.29 mmol, 57% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.15 (m, 10H), 4.47 (s, 2H), 3.86 (s, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.10 – 1.93 (m, 2H), 1.77 (ddt, *J* = 10.3, 7.5, 6.3 Hz, 2H), 1.35 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.6, 138.6, 128.5, 128.3, 127.8, 127.71, 126.3, 126.1, 124.6 (t, *J* = 261.2 Hz), 73.0, 71.5 (t, *J* = 5.8 Hz), 69.3, 38.3, 32.7 (t, *J* = 30.4 Hz), 25.9, 23.3 (t, *J* = 3.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.41 (t, *J* = 10.8 Hz). **IR** (neat, cm^{-1}) 3036, 2967, 2858, 1497, 1403, 1328, 1262, 1100, 1063, 973. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{21}H_{26}F_2O_2•NH_4]^+$ = 366.2228, 366.2264 found.

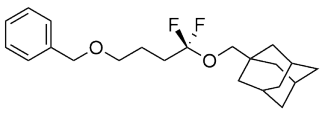
2-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)chromane (8)



The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), chroman-2-ylmethanol (123.2 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M

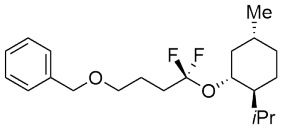
solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 4 h (Step 1); $NEt_3 \cdot 3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 100% hexanes to 2% ethyl acetate in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (117.7mg, 0.33 mmol, 65% yield). **^{1}H NMR** (400 MHz, CD_3CN) δ 7.44 – 7.20 (m, 5H), 7.07 (dddd, *J* = 8.4, 4.6, 1.9, 1.1 Hz, 2H), 6.83 (td, *J* = 7.4, 1.2 Hz, 1H), 6.74 (dd, *J* = 8.6, 1.2 Hz, 1H), 4.47 (s, 2H), 4.21 (dddd, *J* = 12.5, 6.2, 4.1, 2.4 Hz, 1H), 4.02 (dd, *J* = 4.8, 2.4 Hz, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.96 – 2.67 (m, 2H), 2.20 – 1.97 (m, 4H), 1.86 – 1.68 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.5, 138.5, 129.6, 128.5, 127.7, 127.7, 127.5, 125.9 (t, *J* = 262.2 Hz), 121.8, 120.5, 117.0, 73.8, 73.0, 69.2, 64.9 (t, *J* = 6.3 Hz), 32.6 (t, *J* = 29.8 Hz), 24.3, 24.2, 23.3 (t, *J* = 3.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.74 (t, *J* = 11.1 Hz). **IR** (neat, cm^{-1}) 3029, 2951, 2856, 1583, 1488, 1456, 1233, 1100, 1000. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{21}H_{24}F_2O_3 \bullet NH_4]^+$ = 380.2037, 380.2100 found.

1-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)adamantane (9)



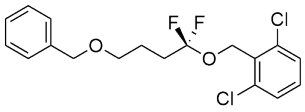
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), 1-adamantan-1-ylmethanol (124.7 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 4 h (Step 1); $NEt_3 \cdot 3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The title compound was purified *via* silica gel chromatography with the eluent conditions 2% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a colorless oil (143.0 mg, 0.39 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 4.50 (s, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 3.38 (s, 2H), 2.16 – 2.00 (m, 2H), 1.97 (s, 3H), 1.89 – 1.78 (m, 2H), 1.78 – 1.58 (m, 6H), 1.52 (d, *J* = 2.9 Hz, 6H). **^{13}C NMR** (101 MHz, CD_3CN) δ 139.5, 128.9, 128.2, 128.0, 126.7 (t, *J* = 5.7 Hz), 73.0, 72.9, 69.4, 39.4, 37.2, 33.3, 32.8 (t, *J* = 30.8 Hz), 28.7, 23.8 (t, *J* = 3.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.71 (t, *J* = 10.8 Hz). **IR** (neat, cm^{-1}) 2901, 2848, 1452, 1328, 1305, 1264, 1001, 1067, 985, 732, 696. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{22}H_{31}F_2O_2]^+$ = 365.2287, 365.2248 found.

((4,4-difluoro-4-(((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl)oxy)butoxy)methyl)benzene (10)



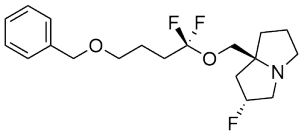
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), (1*S*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexan-1-ol (117.2 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 19 h (Step 1); $NEt_3 \cdot 3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 2% ethyl acetate in hexanes) to afford the product as a colorless oil (132.5 mg, 0.38 mmol, 75% yield). **^{1}H NMR** (400 MHz, CDCl3) δ 8.44 – 5.95 (m, 5H), 4.50 (s, 2H), 4.01 (td, *J* = 10.7, 4.5 Hz, 1H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.14 – 1.97 (m, 4H), 1.88 – 1.77 (m, 2H), 1.65 (dt, *J* = 11.7, 2.9 Hz, 2H), 1.41 (m, 1H), 1.21 (ddd, *J* = 13.2, 9.8, 3.5 Hz, 1H), 1.13 – 0.94 (m, 2H), 0.90 (dd, *J* = 6.8, 4.4 Hz, 7H), 0.76 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.5, 127.6, 127.6, 126.2 (t, *J* = 260.9 Hz), 74.6 (t, *J* = 4.0 Hz), 72.9, 69.3, 47.9, 43.1, 34.2, 33.2 (t, *J* = 31.0 Hz), 31.6, 25.4, 23.4 (t, *J* = 3.0 Hz), 23.0, 22.2, 21.2, 15.5 (d, *J* = 2.4 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.97 (dt, *J* = 143.3, 10.6 Hz), -70.53 (dt, *J* = 143.5, 10.7 Hz). **IR** (neat, cm^{-1}) 2954, 2936, 2867, 1454, 1329, 1268, 1247, 1215 1181, 1102, 966, 732, 696. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{33}F_2O_2]^+$ = 355.2443, 355.2647 found.

2-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-1,3-dichlorobenzene (11)



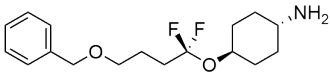
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), (2,6-dichlorophenyl)methanol (88.5 mg, 0. 5 mmol, 1.0 equiv), KHMDS (1 M solution in THF, 1.25 mL, 1.25 mmol, 2.5 equiv), and anhydrous DMF (1.25 mL) for 1 h (Step 1); $NEt_3 \cdot 3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 2%-5% ethyl acetate in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (98.5 mg, 0.26 mmol, 53% yield). **^{1}H NMR** (400 MHz, CD_3CN) δ 7.50 – 7.22 (m, 8H), 5.17 (s, 2H), 4.43 (s, 2H), 3.46 (t, J = 6.3 Hz, 2H), 2.17 – 2.00 (m, 2H), 1.82 – 1.65 (m, 2H). **^{13}C NMR** (101 MHz, CD_3CN) δ 139.9, 137.6, 132.3, 132.1, 129.7, 129.3, 128.6, 128.4, 128.4 (t, J = 261.9 Hz), 73.3, 69.6, 60.8 (t, J = 7.9 Hz), 33.0 (t, J = 29.7 Hz), 24.0 (t, J = 3.2 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.33 (t, J = 11.1 Hz). **IR** (neat, cm^{-1}) 3030, 2935, 2858, 1583, 1565, 1438, 1260, 1149, 1094, 980, 767. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{18}H_{18}Cl_2F_2O_2 \bullet NH_4]^+$ = 392.0996, 392.0989 found.

(2*R*,7a*S*)-7a-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-2-fluorohexahydro-1H-pyrrolizine (12)



The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol), ((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (119.4 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 14 h (Step 1); $NEt_3 \cdot 3HF$ (407.1 µL, 2.5 mmol, 5.0 equiv), trifluoroacetic acid (191.3 µL, 2.5 mmol, 5.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 10%-20% ethyl acetate, 2% triethylamine in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (116.7 mg, 0.33 mmol, 65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 5H), 5.18 (d, J = 54.2 Hz, 1H), 4.49 (s, 2H), 3.65 (d, J = 9.4 Hz, 1H), 3.60 – 3.40 (m, 3H), 3.29 – 2.83 (m, 4H), 2.31 – 1.58 (m, 10H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.4, 128.4, 127.6, 125.7 (t, J = 261.4 Hz), 98.7, 97.0, 72.9, 72.1, 69.2 (t, J = 5.4 Hz), 69.2, 60.5 (d, J = 19.3 Hz), 57.1, 42.4 (d, J = 20.4 Hz), 35.9, 32.6 (t, J = 30.3 Hz), 25.5, 23.2 (t, J = 3.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.15 (dt, J = 141.9, 10.8 Hz), -74.65 (dt, J = 141.8, 11.1 Hz), -172.57 – -173.34 (m). **IR** (neat, cm^{-1}) 2956, 2856, 1452, 1258, 1100, 1064, 1028, 952, 735, 697. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{27}F_3NO_2]^+$ = 358.1989, 358.2081 found.

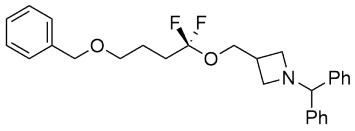
***Trans*-4-(4-(benzyloxy)-1,1-difluorobutoxy)cyclohexan-1-amine (13)**



The title product was prepared according to **GP3** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol), *trans*-4-aminocyclohexanol (86.4 mg, 0.75 mmol, 1.5 equiv), KO-*t*-Bu (168.3 mg, 1.5 mmol, 3.0 equiv), DMA (1.25 mL, 0.4 M) for 4 h (Step 1); $NEt_3 \cdot 3HF$ (488.5 µL, 3.0 mmol, 6.0 equiv), trifluoroacetic acid (229.6 µL, 3.0 mmol, 6.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 5% methanol, 2% triethylamine in dichloromethane on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / dichloromethane solution) to afford the product as a yellow oil (67.6 mg, 0.22 mmol, 43% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.09 (m, 5H), 4.49 (s, 2H), 4.15 (tt, J = 10.8, 4.4 Hz, 1H), 3.49 (t, J = 6.4 Hz, 2H), 2.82 – 2.52 (m, 1H), 2.14 – 1.65 (m, 7H), 1.60 – 0.92 (m, 7H). **^{13}C**

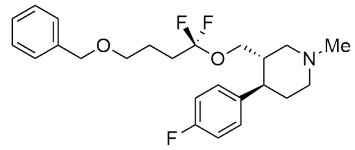
NMR (101 MHz, $CDCl_3$) δ 138.4, 128.4, 127.6, 127.6, 126.0 (t, *J* = 260.9 Hz), 72.9, 72.5 (t, *J* = 5.3 Hz), 69.2, 49.4, 34.2, 32.9 (t, *J* = 30.6 Hz), 31.8, 23.3 (t, *J* = 3.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.74 (t, *J* = 10.7 Hz). **IR** (neat, cm^{-1}) 2941, 2861, 1452, 1331, 1261, 1092, 1059, 1021, 950, 735, 697. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{17}H_{26}F_2NO_2]^+$ = 314.1927, 314.1997 found.

1-benzhydryl-3-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)azetidine (14)



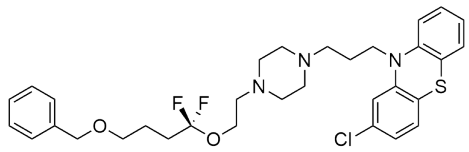
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), (1-benzhydrylazetidin-3-yl)methanol (190.0 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 4 h (Step 1); NEt_3·3HF (407.1 µL, 2.5 mmol, 5.0 equiv), trifluoroacetic acid (191.3 µL, 2.5 mmol, 5.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 5% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (132.5 mg, 0.30 mmol, 59% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 4H), 7.36 – 7.10 (m, 11H), 4.49 (s, 2H), 4.32 (s, 1H), 3.96 (d, *J* = 6.8 Hz, 2H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.26 (t, *J* = 7.6 Hz, 2H), 2.99 – 2.80 (m, 2H), 2.69 (p, *J* = 6.9 Hz, 1H), 2.20 – 1.93 (m, 2H), 1.91 – 1.59 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.3, 138.5, 128.5, 128.5, 127.7, 127.6, 127.2, 125.8 (t, *J* = 261.5 Hz), 78.1, 73.0, 69.2, 65.0 (t, *J* = 6.4 Hz), 56.1, 32.7 (t, *J* = 30.2 Hz), 29.3, 23.4 (t, *J* = 3.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.33 (t, *J* = 10.8 Hz). **IR** (neat, cm^{-1}) 3025, 2949, 2857, 2359, 1490, 1452, 1258, 1101, 742, 697. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{28}H_{32}F_2NO_2]^+$ = 452.2396, 452.2415 found.

(3*S*,4*R*)-3-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-4-(4-fluorophenyl)-1-methylpiperidine (15)



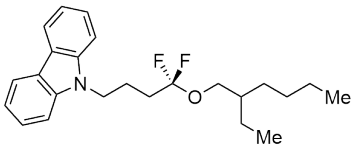
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), ((3*S*,4*R*)-4-(4-fluorophenyl)-1-methylpiperidin-3-yl)methanol (167.5 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 13 h (Step 1); NEt_3·3HF (407.1 µL, 2.5 mmol, 5.0 equiv), trifluoroacetic acid (191.3 µL, 2.5 mmol, 5.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The title compound was purified *via* silica gel chromatography with the eluent conditions 2% MeOH in dichloromethane on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / dichloromethane solution) to afford the product as a yellow oil (140.6 mg, 0.34 mmol, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 7.19 – 7.09 (m, 2H), 7.06 – 6.95 (m, 2H), 4.52 (s, 2H), 3.58 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.51 (t, *J* = 6.3 Hz, 2H), 3.43 (dd, *J* = 10.1, 7.2 Hz, 1H), 3.10 (ddd, *J* = 11.3, 3.8, 1.7 Hz, 1H), 2.96 (ddt, *J* = 11.3, 4.0, 2.5 Hz, 1H), 2.36 (s, 3H), 2.31 (td, *J* = 11.3, 4.9 Hz, 1H), 2.18 – 1.95 (m, 4H), 1.96 – 1.73 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9, 160.4, 139.5 (d, *J* = 3.2 Hz), 138.5, 128.9 (d, *J* = 7.8 Hz), 128.5, 125.7 (t, *J* = 261.6 Hz), 115.5 (d, *J* = 21.1 Hz), 73.0, 69.3, 63.5 (t, *J* = 6.5 Hz), 59.4, 56.3, 46.7, 43.6, 41.7, 34.7, 32.7 (t, *J* = 30.3 Hz), 23.3 (t, *J* = 2.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.87 (dt, *J* = 154.6, 11.05 Hz), -75.29 (dt, *J* = 141.98, 10.76 Hz), -116.63 (m). **IR** (neat, cm^{-1}) 2938, 2852, 2786, 1510, 1223, 1098, 1063, 997. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{24}H_{31}F_3NO_2]^+$ = 422.2302, 422.2345 found.

10-(3-(4-(2-(4-(benzyloxy)-1,1-difluorobutoxy)ethyl)piperazin-1-yl)propyl)-2-chloro-10H-phenothiazine (16)



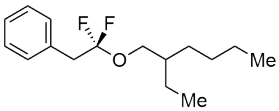
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol), 2-(4-(3-(2-chloro-10H-phenothiazin-10-yl)propyl)piperazin-1-yl)ethan-1-ol (303.0 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 27 h (Step 1); $NEt_3 \cdot 3HF$ (652.0 µL, 4.0 mmol, 8.0 equiv), trifluoroacetic acid (306.1 µL, 4.0 mmol, 8.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). **Note:** After Step 2 of the reaction, NaOH (1 M solution in H_2O, 50 mL) was used as the aqueous phase during the workup instead of aqueous $NaHCO_3$ (sat.). The compound was purified *via* silica gel chromatography with the eluent conditions 100% dichloromethane on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / DCM solution) to afford the product as a yellow oil (142.8 mg, 0.24 mmol, 47% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 7.19 – 7.06 (m, 2H), 7.01 (d, J = 8.1 Hz, 1H), 6.96 – 6.80 (m, 4H), 4.49 (s, 2H), 3.95 (t, J = 6.1 Hz, 2H), 3.89 (t, J = 6.9 Hz, 2H), 3.49 (t, J = 6.3 Hz, 2H), 2.60 (t, J = 6.1 Hz, 2H), 2.46 (m, 10H), 2.17 – 1.99 (m, 2H), 1.93 (p, J = 6.9 Hz, 2H), 1.87 – 1.75 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5, 144.6, 138.5, 133.3, 128.4, 127.9, 127.7, 127.6, 127.5, δ 125.7 (t, J = 261.6 Hz), 124.8, 123.5, 122.9, 122.3, 115.9 (d, J = 1.9 Hz), 72.9, 69.2, 60.7 (t, J = 6.5 Hz), 57.1, 55.6, 53.4, 53.3, 45.4, 32.6 (t, J = 30.1 Hz), 24.3, 23.3 (t, J = 2.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.02 (t, J = 11.2 Hz). **IR** (neat, cm^{-1}) 2939, 2873, 2808, 2360, 2341, 1566, 1456, 1243, 1097, 745. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{32}H_{39}ClF_2N_3O_2S]^+$ = 602.2415, 602.2419 found.

9-(4-((2-ethylhexyl)oxy)-4,4-difluorobutyl)-9H-carbazole (17)



The title product was prepared according to **GP1** using 9-(4,4,4-trifluorobutyl)-9H-carbazole (138.7 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 18 h (Step 1); $NEt_3 \cdot 3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 5% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (157.3 mg, 0.41 mmol, 81% yield). **^{1}H NMR** (400 MHz, CD_3CN) δ 8.12 (dt, J = 7.8, 1.0 Hz, 2H), 7.55 – 7.42 (m, 4H), 7.22 (ddd, J = 7.9, 6.8, 1.3 Hz, 2H), 4.41 (t, J = 6.7 Hz, 2H), 3.73 (d, J = 5.5 Hz, 2H), 2.01 (dddd, J = 10.6, 7.0, 3.8, 2.3 Hz, 3H), 1.63 – 1.40 (m, 1H), 1.38 – 1.14 (m, 9H), 0.85 (t, J = 7.4 Hz, 6H). **^{13}C NMR** (101 MHz, CD_3CN) δ 141.3, 126.8 (t, J = 259.6 Hz), 126.8, 121.3, 120.0, 118.3, 109.9, 66.0 (t, J = 6.1 Hz), 42.6, 39.9, 33.7 (t, J = 31.0 Hz), 30.9, 29.6, 24.3, 23.6, 23.2 (t, J = 2.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.86 (t, J = 10.1 Hz). **IR** (neat, cm^{-1}) 3053, 2958, 2930, 2860, 1598, 1484, 1452, 1324, 1239, 747, 722. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{24}H_{32}F_2NO]^+$ = 388.2447, 388.2478 found.

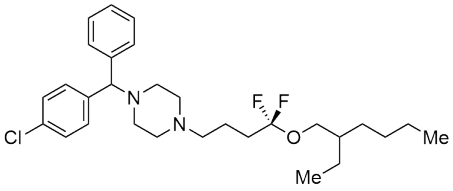
(2-((2-ethylhexyl)oxy)-2,2-difluoroethyl)benzene (18)



The title product was prepared according to **GP1** using (2,2,2-trifluoroethyl)benzene (80.1 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), NaHMDS (2 M solution in THF, 0.75 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 150 min (Step 1); $NEt_3 \cdot 3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 100% hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a colorless oil (107.7 mg, 0.4 mmol, 80% yield). **^{1}H NMR** (400 MHz,

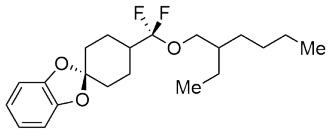
CD_3CN) δ 7.40 – 7.23 (m, 5H), 3.74 (d, *J* = 5.5 Hz, 2H), 3.27 (t, *J* = 10.7 Hz, 2H), 1.48 (p, *J* = 6.0 Hz, 1H), 1.40 – 1.13 (m, 9H), 1.06 – 0.70 (m, 7H). **^{13}C NMR** (101 MHz, CD_3CN) δ 134.0 (t, *J* = 3.3 Hz), 131.4, 129.1, 128.2, 125.8 (t, *J* = 260.7 Hz), 42.5 (t, *J* = 31.5 Hz), 39.9, 31.0, 29.6, 24.3, 23.7, 14.4, 11.3. **^{19}F NMR** (376 MHz, CD_3CN) δ -72.44 (td, *J* = 10.6, 5.4 Hz). **IR** (neat, cm^{-1}) 2960, 2931, 2874, 2861, 1456, 1350, 1274, 1232, 1165, 1030, 698. **HRMS** (APGC) [M+H] calcd. for $[C_{16}H_{25}F_2O]^+$ = 271.1868, 271.1873 found.

1-((4-chlorophenyl)(phenyl)methyl)-4-(4-((2-ethylhexyl)oxy)-4,4-difluorobutyl)piperazine (19)



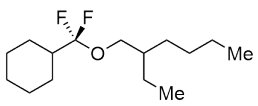
The title product was prepared according to **GP1** using 1-((4-chlorophenyl)(phenyl)methyl)-4-(4,4,4-trifluorobutyl)piperazine (198.5 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), and KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 16 h (Step 1); NEt_3·3HF (652.0 µL, 4.0 mmol, 8.0 equiv), trifluoroacetic acid (306.1 µL, 4.0 mmol, 8.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified via silica gel chromatography with the eluent conditions 10% ethyl acetate in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as yellow oil (110.2 mg, 0.22 mmol, 43% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 4H), 7.31 – 7.11 (m, 5H), 4.19 (s, 1H), 3.77 – 3.66 (m, 2H), 2.90 – 2.12 (m, 7H), 2.02 – 1.88 (m, 2H), 1.67 (p, *J* = 7.8 Hz, 2H), 1.48 (q, *J* = 5.9 Hz, 1H), 1.41 – 1.14 (m, 8H), 1.00 – 0.65 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.4, 141.6, 132.6, 129.3, 128.7, 128.7, 128.0, 127.26, 126.0 (t, *J* = 260.5 Hz), 75.6, 65.0 (t, *J* = 6.1 Hz), 57.7, 53.4, 52.0, 39.2, 33.9 (t, *J* = 30.5 Hz), 30.4, 29.0, 23.7, 23.1, 20.3, 14.2, 11.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.60 (t, *J* = 10.8 Hz). **IR** (neat, cm^{-1}) 2959, 2932, 2907, 2874, 2810, 1487, 1452, 1372, 1290, 1266, 1088, 907, 732. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{29}H_{42}ClF_2N_2O]^+$ = 507.2949, 507.3042 found.

4'-(((2-ethylhexyl)oxy)difluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane] (20)



The title product was prepared according to **GP2** using 4'-(trifluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane] (129.1 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), KO-*t*-Bu (224.4 mg, 2.0 mmol, 4.0 equiv), and anhydrous DMF (1.25 mL) at 50 °C instead of 80 °C (Step 1); NEt_3·3HF (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 2% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (87.4 mg, 0.24 mmol, 47% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 – 6.63 (m, 4H), 3.87 – 3.69 (m, 2H), 2.33 – 2.09 (m, 2H), 1.99 (dt, *J* = 10.6, 3.1 Hz, 3H), 1.89 – 1.67 (m, 4H), 1.54 (q, *J* = 5.7 Hz, 1H), 1.46 – 1.17 (m, 8H), 0.91 (td, *J* = 7.1, 2.8 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.4, 147.3, 126.2 (t, *J* = 263.2 Hz), 121.2, 121.2, 117.3, 108.8, 108.6, 65.0 (t, *J* = 6.2 Hz), 42.2 (t, *J* = 28.7 Hz), 39.2, 33.9, 30.4, 29.1, 23.8, 23.1, 22.8 (t, *J* = 2.5 Hz), 14.2, 11.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -81.33 (d, *J* = 7.5 Hz). **IR** (neat, cm^{-1}) 2958, 2931, 2907, 2874, 1485, 1359, 1235, 1063, 734. **HRMS** (APGC) $[M]^+$ calcd. for $[C_{21}H_{30}F_2O_3]$ = 368.2158, 368.2163 found.

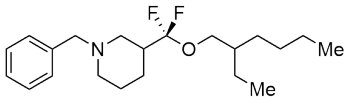
(((2-ethylhexyl)oxy)difluoromethyl)cyclohexane (21)



The title product was prepared according to **GP2** using (trifluoromethyl)cyclohexane (76.1 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (78.1 µL, 0.5 mmol, 1.0 equiv), KO-*t*-Bu (140.3 mg, 1.25 mmol, 2.5 equiv), and anhydrous DMF (1.25 mL) and was run for 4 h (Step 1) ; NEt_3·3HF (244.1.5 µL, 1.5 mmol, 3.0 equiv),

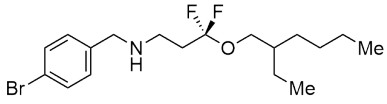
trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was filtered through neutralized silica with hexanes (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a colorless oil (86.9 mg, 0.33 mmol, 66% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.85 – 3.61 (m, 2H), 2.00 – 1.72 (m, 5H), 1.71 – 1.61 (m, 1H), 1.51 (dt, *J* = 11.8, 5.8 Hz, 1H), 1.45 – 1.02 (m, 12H), 1.01 – 0.76 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 126.7 (t, *J* = 263.0 Hz), 64.7 (t, *J* = 6.3 Hz), 44.0 (t, *J* = 27.8 Hz), 39.3, 30.5, 29.1, 26.1, 26.1, 26.1, 25.7, 23.8, 23.2, 14.2, 11.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -82.36 (d, *J* = 7.9 Hz). **IR** (neat, cm^{-1}) 2932, 2858, 1454, 1325, 1255, 1080, 1025, 981, 893. **HRMS** (APGC) $[M]^+$ calcd. for $[C_{15}H_{28}F_2O]$ = 262.2103, 262.2108 found.

1-benzyl-4-(((2-ethylhexyl)oxy)difluoromethyl)piperidine (22)



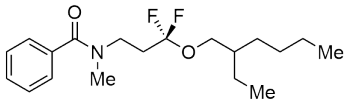
The title product was prepared according to **GP2** using 1-benzyl-3-(trifluoromethyl)piperidine (121.7 mg, 0.5 mmol), 2-ethyl-1-hexanol (78.1 µL, 0.5 mmol, 1.0 equiv), KO-*t*-Bu (140.3 mg, 1.25 mmol, 2.5 equiv), and anhydrous DMF (1.25 mL) for 16 h (Step 1); $NEt_3{\cdot}3HF$ (407.1 µL, 2.5 mmol, 5.0 equiv), trifluoroacetic acid (191.3 µL, 2.5 mmol, 5.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The title product was purified *via* by filtering the product through neutralized silica with 10% ethyl acetate in hexanes (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (145.4 mg, 0.41 mmol, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 5H), 3.71 (d, *J* = 5.6 Hz, 2H), 3.63 – 3.41 (m, 2H), 3.04 (ddt, *J* = 11.0, 3.6, 1.8 Hz, 1H), 2.90 – 2.76 (m, 1H), 2.21 (ttt, *J* = 11.8, 7.8, 3.6 Hz, 1H), 1.98 – 1.77 (m, 3H), 1.67 (dt, *J* = 13.4, 3.6 Hz, 1H), 1.61 – 1.42 (m, 2H), 1.40 – 1.14 (m, 9H), 0.88 (dt, *J* = 10.5, 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.3, 129.1, 128.2, 127.0, 125.6 (t, *J* = 263.2 Hz), 64.7 (t, *J* = 6.2 Hz), 63.4, 53.4, 42.7 (t, *J* = 27.8 Hz), 39.0, 30.3, 28.9 (d, *J* = 1.3 Hz), 24.6, 24.0, 23.0, 14.1, 11.1 (d, *J* = 1.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -80.28 – -81.32 (m). **IR** (neat, cm^{-1}) 2956, 2930, 2860, 2811, 2782, 2363, 1732, 1454, 1329, 1183, 1158, 1113, 1011, 733, 697. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{34}F_2NO]^+$ = 354.2603, 354.2733 found

***N*-(4-bromobenzyl)-3-((2-ethylhexyl)oxy)-3,3-difluoropropan-1-amine (23)**



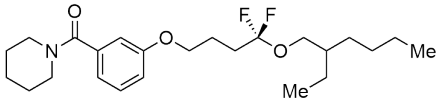
The title product was prepared according to **GP3** using *N*-(4-bromobenzyl)-3,3,3-trifluoropropan-1-amine (141.1 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), KO-*t*-Bu (1.5 mmol, 3.0 equiv), and anhydrous DMA (1.25 mL) for 4 h (Step 1); $NEt_3{\cdot}3HF$ (407.5 µL, 2.5 mmol, 5.0 equiv), trifluoroacetic acid (191.3 µL, 2.5 mmol, 5.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 2% triethylamine in DCM on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / DCM solution). Fractions containing product with impurities were further purified *via* silica gel chromatography with eluent conditions 2% MeOH in DCM on neutralized silica to afford the product as a yellow oil (131.9 mg, 0.34 mmol, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 3.74 (d, *J* = 5.0 Hz, 4H), 2.81 (t, *J* = 6.8 Hz, 2H), 2.18 (tt, *J* = 10.6, 6.8 Hz, 2H), 1.55 (s, 1H), 1.48 (q, *J* = 5.9 Hz, 1H), 1.38 – 1.11 (m, 8H), 0.88 (q, *J* = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.3, 131.6, 129.9, 125.5 (t, *J* = 261.4 Hz), 120.9, 65.2 (t, *J* = 6.2 Hz), 53.2, 43.3 (t, *J* = 3.4 Hz), 39.2, 36.0 (t, *J* = 29.3 Hz), 30.4, 29.0, 23.8, 23.1, 14.2, 11.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -72.90 (t, *J* = 10.5 Hz). **IR** (neat, cm^{-1}) 2959, 2930, 2906, 2860, 1487, 1461, 1265, 1243, 1132, 1011, 942, 800. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{18}H_{29}BrF_2NO]^+$ = 392.1396, 392.1449 found.

***N*-(3-((2-ethylhexyl)oxy)-3,3-difluoropropyl)-*N*-methylbenzamide (24)**



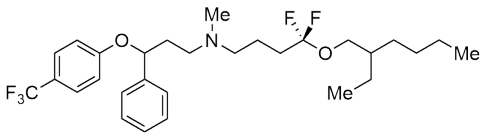
The title product was prepared according to **GP1** using *N*-methyl-*N*-(3,3,3-trifluoropropyl)benzamide (115.6 mg, 0.5 mmol), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), NaHMDS (2 M solution in THF, 0.75 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 22 h (Step 1); (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 10% EtOAc in hexanes to 15% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution). Fractions containing product with impurities were further purified via silica gel chromatography with eluent conditions 10% EtOAc in hexanes on neutralized silica to afford the product as a yellow oil (86.9 mg, 0.26 mmol, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 4.05 – 3.30 (m, 4H), 3.02 (d, *J* = 40.5 Hz, 2H), 2.29 (d, *J* = 69.4 Hz, 2H), 1.61 – 0.99 (m, 10H), 0.88 (t, *J* = 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.0, 158.9, 137.9, 129.5, 125.7 (t, *J* = 260.7 Hz), 118.9, 115.7, 112.8, 66.9, 65.0 (t, *J* = 6.1 Hz), 48.7, 43.1, 39.1, 32.5 (t, *J* = 30.8 Hz), 30.3, 28.9, 26.6, 25.7, 24.6, 23.6, 23.0, 22.9, 22.9, 14.1, 10.9. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.51, 129.67, 128.54, 127.07, 126.58, 65.27 (t, *J* = 6.1 Hz), 45.80, 42.81, 39.14, 38.35, 33.46, 30.30, 29.00, 23.65, 23.08, 14.18, 11.03. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.40, -73.79. **IR** (neat, cm^{-1}) 2958, 2930, 2860, 1635, 1400, 1277, 1242, 1068, 699. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{30}F_2NO_2]^+$ = 342.2240, 342.2270 found. **Note:** this compound exhibits severe broadening in the ^{1}H, ^{13}C, and ^{19}F NMR spectra.

(3-(4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)phenyl)(piperidin-1-yl)methanone (25)



The title product was prepared according to **GP1** using piperidin-1-yl(3-(4,4,4-trifluorobutoxy)phenyl)methanone (157.7 mg, 0.5 mmol), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), NaHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 4 h (Step 1); $NEt_3{\cdot}3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 100% DCM to 10 % ethyl acetate in DCM on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / DCM solution) to afford the product yellow oil (130.3 mg, 0.31 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.19 (m, 1H), 7.01 – 6.83 (m, 3H), 4.00 (t, *J* = 6.2 Hz, 2H), 3.76 (dd, *J* = 5.6, 2.8 Hz, 2H), 3.70 (br s, 2H), 3.34 (br s, 2H), 2.15 (tdd, *J* = 10.4, 8.1, 5.5 Hz, 2H), 2.06 – 1.93 (m, 2H), 1.76 – 1.44 (m, 7H), 1.43 – 1.16 (m, 8H), 1.01 – 0.82 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.0, 158.9, 137.9, 129.5, 125.7 (t, *J* = 260.7 Hz), 118.9, 115.7, 112.8, 66.9, 65.00 (t, *J* = 6.1 Hz), 48.7, 43.1, 39.1, 32.5 (t, *J* = 30.8 Hz), 30.3, 28.9, 26.6, 25.7, 24.6, 23.6, 23.0, 22.9, 22.9, 14.1, 10.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.52 (t, *J* = 10.5 Hz). **IR** (neat, cm^{-1}) 2932, 2858, 1633, 1442, 1272, 1052, 997, 790, 747. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{24}H_{38}F_2NO_3]^+$ = 426.2815, 426.2840 found.

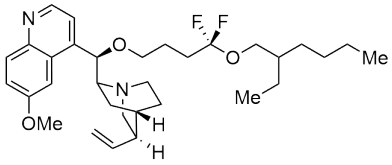
4-((2-ethylhexyl)oxy)-4,4-difluoro-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butan-1-amine (26)



The title product was prepared according to **GP1** using 4,4,4-trifluoro-*N*-methyl-N-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butan-1-amine (209.7 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 21 h (Step 1); $NEt_3{\cdot}3HF$ (407.1 µL, 2.5 mmol, 5.0 equiv), trifluoroacetic acid (229.6 µL, 3.0 mmol, 6.0

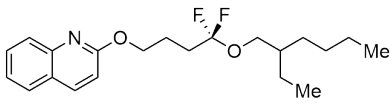
equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 5% triethylamine in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (120.8 mg, 0.23 mmol, 46% yield). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.45 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.22 (m, 5H), 6.95 (d, *J* = 8.6 Hz, 2H), 5.35 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.73 (dd, *J* = 5.6, 2.0 Hz, 2H), 2.54 (dt, *J* = 12.5, 7.2 Hz, 1H), 2.38 (dddd, *J* = 23.7, 12.5, 8.3, 5.5 Hz, 3H), 2.27 – 2.04 (m, 4H), 2.04 – 1.82 (m, 3H), 1.75 – 1.56 (m, 2H), 1.51 (p, *J* = 5.9 Hz, 1H), 1.44 – 1.19 (m, 9H), 1.01 – 0.80 (m, 6H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 160.9, 141.4, 128.6, 127.7, 126.6 (q, *J* = 3.8 Hz), 126.0, 126.5 (t, *J* = 260.5 Hz), 125.0 (q, *J* = 271.0 Hz), 122.3 (q, *J* = 32.4 Hz), 115.8, 78.3, 64.8, 56.7, 41.5, 39.1, 36.5, 33.4 (t, *J* = 30.4 Hz), 30.2, 28.9, 23.6, 23.0, 20.7 (t, *J* = 2.8 Hz), 13.8, 10.7. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -61.59, -74.57 (t, *J* = 10.8 Hz). **IR** (neat, cm^{-1}) 2959, 2931, 2860, 2798, 2373 1615, 1517, 1454, 1378, 1326, 1249, 1161, 1109, 1068, 1009, 909, 834, 700. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{29}H_{41}F_5NO_2]^+$ = 530.3052, 530.3188 found.

(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-(4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (27)



The title product was prepared according to **GP1** using (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(6-methoxyquinolin-4-yl)(4,4,4-trifluorobutoxy)methyl)-5-vinylquinuclidine (217.3 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), NaHMDS (2 M solution in THF, 0.75 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 5 h (Step 1); NEt_3·3HF (407.1 µL, 2.5 mmol, 5.0 equiv), trifluoroacetic acid (191.3 µL, 2.5 mmol, 5.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 100% ethyl acetate on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / ethyl acetate solution) to afford the product as a yellow oil (102.5 mg, 0.19 mmol, 38% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.4 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.47 – 7.27 (m, 3H), 5.73 (ddd, *J* = 17.6, 10.3, 7.7 Hz, 1H), 5.15 – 4.79 (m, 3H), 3.93 (s, 3H), 3.73 (dd, *J* = 5.7, 2.2 Hz, 2H), 3.39 (t, *J* = 6.2 Hz, 3H), 3.09 (dd, *J* = 13.5, 9.8 Hz, 2H), 2.71 (ddd, *J* = 14.3, 10.8, 4.7 Hz, 1H), 2.65 – 2.53 (m, 1H), 2.26 (s, 1H), 2.08 (dddd, *J* = 14.7, 12.4, 6.2, 3.4 Hz, 2H), 1.93 – 1.66 (m, 5H), 1.66 – 1.41 (m, 4H), 1.40 – 1.17 (m, 9H), 0.87 (q, *J* = 6.7 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9, 147.7, 145.1, 144.9, 142.2, 132.0, 127.5, 125.9 (t, *J* = 260.7 Hz), 121.8, 119.0, 114.3, 101.4, 82.0, 68.5, 65.1 (t, *J* = 6.0 Hz), 60.3, 57.4, 55.8, 43.4, 40.2, 39.2, 33.0 (t, *J* = 30.8 Hz), 30.3, 29.0, 28.1, 28.0, 23.8, 23.8, 23.7, 23.1, 14.2, 11.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.08 (t, *J* = 10.8 Hz). **IR** (neat, cm^{-1}) 2924, 2861, 2360, 1620, 1507, 1452, 1240,1107, 1058, 1030, 999, 910, 731. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{32}H_{47}F_2N_2O_3]^+$ = 545.3550, 545.3662 found.

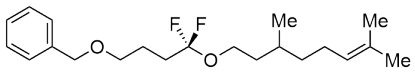
2-(4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)quinoline (28)



The title product was prepared according to **GP1** using 2-(4,4,4-trifluorobutoxy)quinoline (127.6 mg, 0.5 mmol, 1.0 equiv), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), NaHMDS (1 M solution in THF, 0.75 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 14 h (Step 1); NEt_3·3HF (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 5% ethyl acetate in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (113.9 mg, 0.31 mmol, 62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.62 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.37 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.90 (d, *J* = 8.8 Hz,

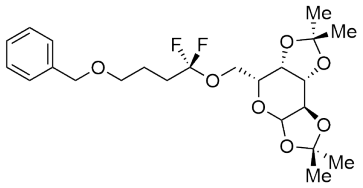
1H), 4.52 (t, *J* = 6.3 Hz, 2H), 3.87 – 3.69 (m, 2H), 2.29 – 1.98 (m, 4H), 1.52 (h, *J* = 4.3 Hz, 1H), 1.47 – 1.15 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.2, 146.7, 138.8, 129.6, 127.5, 127.4, 125.9 (t, *J* = 260.7 Hz), 125.2, 124.1, 113.3, 65.1 (t, *J* = 6.1 Hz), 64.9, 39.2, 32.9 (t, *J* = 30.8 Hz), 30.4, 29.1, 23.7, 23.1, 22.8 (t, *J* = 3.1 Hz), 14.2, 11.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.62 (t, *J* = 10.4 Hz). **IR** (neat, cm^{-1}) 2958, 2930, 2860, 1619, 1606, 1428, 1313, 1238, 965, 821, 755. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{30}F_2NO_2]^+$ = 366.2240, 366.2259 found.

((4-((3,7-dimethyloct-6-en-1-yl)oxy)-4,4-difluorobutoxy)methyl)benzene (29)



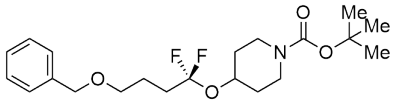
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), 3,7-dimethyloct-6-en-1-ol (117.2 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 4 h (Step 1); NEt_3·3HF (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The title compound was purified *via* silica gel chromatography with the eluent conditions 2% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (131.6 mg, 0.37 mmol, 74% yield). **^{1}H NMR** (400 MHz, CD_3CN) 7.41-7.24 (m, 5H), 5.51, (ddp, *J* = 1.4 Hz, 1.4 Hz, 5.8 Hz, 8.6 Hz, 1H), 4.47 (s, 2H), 3.38 (m, 2H), 3.38 (m, 2H), 3.49 (t, *J* = 6.3 Hz, 2H), 2.10-1.92 (m, 4H), 1.81-1.71 (m, 2H), 1.69-1.50 (m, 8H), 1.45-1.25 (m, 2H). **^{13}C NMR** (101MHz, CD_3CN) δ 139.9, 132.1, 129.3, 128.6, 128.4, 127.1 (t, *J* = 259.4 Hz), 125.6, 73.3, 69.8, 62.2 (t, *J* = 6.7 Hz), 37.6, 36.8, 33.3 (t, *J* = 30.6 Hz), 30.0, 26.1, 25.9, 24.1 (t, *J* = 3.08 Hz), 19.6, 17.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.29 (t, *J* = 10.6 Hz). **IR** (neat, cm^{-1}) 2962, 2914, 2856, 1453, 1263, 1101, 1069, 999. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{33}F_2O_2]^+$ = 355.2444, 355.2665 found.

(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-5-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (30)



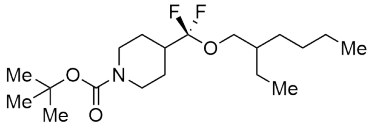
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol, 1.0 equiv), ((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methanol (195.2 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 16 h (Step 1); NEt_3·3HF (244.2 µL 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL ,1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions hexanes to 10% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a colorless oil (116.5 mg, 0.26 mmol, 51% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.17 (m, 5H), 5.54 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.5 Hz, 1H), 4.50 (s, 2H), 4.32 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.23 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.08 – 3.94 (m, 3H), 3.51 (t, *J* = 6.3 Hz, 2H), 2.17 – 2.03 (m, 2H), 1.89 – 1.77 (m, 2H), 1.52 (s, 3H), 1.45 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H). **^{13}C NMR (**101 MHz, $CDCl_3$) δ 138.6, 128.5, 127.7, 127.7, 126.0 (t, *J* = 262.3 Hz), 109.6, 108.9, 96.4, 73.0, 71.0, 70.8, 70.6, 69.3, 66.7, 62.1 (t, *J* = 6.4 Hz), 32.6 (t, *J* = 29.9 Hz), 26.1, 26.1, 25.1, 24.6, 23.3 (t, *J* = 2.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -74.34 (dt, *J* = 142.0, 10.8 Hz), -75.09 (dt, *J* = 142.0, 11.4 Hz). **IR** (neat, cm^{-1}) 2987, 2935, 2860, 1735, 1454, 1371, 1254, 1211, 1066. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{23}H_{32}F_2O_7{\bullet}NH_4]^+$ = 476.2454, 476.2690 found.

***tert*-butyl 4-(4-(benzyloxy)-1,1-difluorobutoxy)piperidine-1-carboxylate (31)**



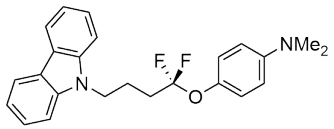
The title product was prepared according to **GP1** using ((4,4,4-trifluorobutoxy)methyl)benzene (**1**) (109.1 mg, 0.5 mmol), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (151.0 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 14 h (Step 1); $NEt_3 \cdot 3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 10% ethyl acetate in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (99.5 mg, 0.25 mmol, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.12 (m, 5H), 4.50 (s, 2H), 4.42 (tt, *J* = 7.9, 3.8 Hz, 1H), 3.80 – 3.57 (m, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 3.20 (ddd, *J* = 12.9, 8.5, 3.6 Hz, 2H), 2.15 – 1.97 (m, 2H), 1.91 – 1.74 (m, 4H), 1.60 (dtd, *J* = 12.6, 8.2, 3.9 Hz, 2H), 1.46 (d, *J* = 0.9 Hz, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.8, 138.4, 128.4, 127.6 (d, *J* = 1.4 Hz), 126.1 (t, *J* = 261.6 Hz), 79.6, 72.9, 69.5 (t, *J* = 5.4 Hz), 69.1, 32.9 (t, *J* = 30.3 Hz), 32.1, 28.4, 23.3 (t, *J* = 3.0 Hz), 22.7, 14.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -72.00 (br s). **IR** (neat, cm^{-1}) 2972, 2863, 2368, 1692, 1421, 1275, 1167, 1025, 965. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{32}F_2NO_4]^+$ = 400.2294, 400.2299 found

***tert*-butyl 4-(((2-ethylhexyl)oxy)difluoromethyl)piperidine-1-carboxylate (32)**



The title product was prepared according to **GP2** using *tert*-butyl 4-(trifluoromethyl)piperidine-1-carboxylate (126.7 mg, 0.5 mmol), 2-ethyl hexanol (65.1 mg, 0.5 mmol, 1.0 equiv), KO-*t*-Bu (140.3 mg, 1.25 mmol, 2.5 equiv), and DMF (1.25 mL, 0.4 mL) for 15 h (Step 1); $NEt_3 \cdot 3HF$ (244.2 µL, 1.5 mmol, 3.0 equiv), trifluoroacetic acid, (114.8 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2 M) (Step 2). The titled product was filtered through neutralized silica with 10% ethyl acetate in hexanes (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (160.7 mg, 0.44 mmol, 88% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.15 (s, 2H), 3.73 (dd, *J* = 5.5, 2.5 Hz, 2H), 2.64 (t, *J* = 13.0 Hz, 2H), 1.99 (ttt, *J* = 11.5, 7.5, 3.6 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.55 – 1.19 (m, 19H), 0.88 (td, *J* = 6.9, 4.8 Hz, 7H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.9, 125.9 (t, *J* = 262.8 Hz), 79.6, 64.9 (t, *J* = 6.1 Hz), 43.3, 42.4 (t, *J* = 29.1 Hz), 39.2, 30.4, 29.0, 28.6, 25.4, 23.8, 23.1, 14.2, 11.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -82.05 (d, *J* = 7.8 Hz). **IR** (neat, cm^{-1}) 2959, 2931, 2861, 1422, 1325, 1233, 1160, 1037, 979. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{36}F_2NO_3]^+$ = 364.2658, 364.2661 found.

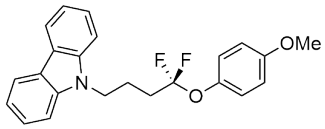
4-(4-(9H-carbazol-9-yl)-1,1-difluorobutoxy)-*N*,*N*-dimethylaniline (33)



The title product was prepared according to **GP4** using 9-(4,4,4-trifluorobutyl)-9H-carbazole (138.7 mg, 0.5 mmol), 18-crown-6 (396.5 mg, 1.5 mmol, 3.0 equiv), 4-(dimethylamino)phenol (102.9 mg, 0.75 mmol, 1.5 equiv), KHMDS (299.3 mg, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL, 0.4 M) (Step 1); $NEt_3 \cdot 3HF$ (815.0 µL, 5.0 mmol, 10.0 equiv), methanesulfonic acid (456.0 µL, 7.0 mmol, 14.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) for 2 h (Step 2). The title product was purified *via* silica gel chromatography with the eluent conditions 100% hexanes to 10% EtOAC in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a colorless oil (105.2 mg, 0.27 mmol, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.20 (m, 2H), 7.07 – 6.94 (m, 2H), 6.62 (d, *J* = 9.1 Hz, 2H), 4.39 (t, *J* = 6.8 Hz, 2H), 2.88 (s, 6H), 2.28 – 2.11 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.7, 140.7, 140.3, 125.8, 124.8 (t, *J* = 263.8 Hz), 122.9, 122.8, 120.4, 119.0,

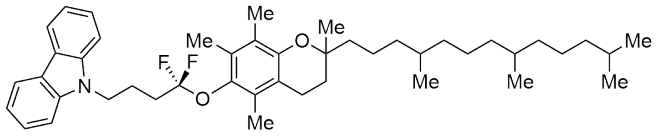
112.9, 108.5, 42.0, 40.9, 33.3 (t, J = 29.9 Hz), 22.4 (t, J = 2.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -70.05 (t, J = 10.2 Hz). **IR** (neat, cm^{-1}) 3049, 2940, 2883, 2802, 1597 1513, 1452, 1324, 1241, 1120, 1000, 748, 722. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{24}H_{25}F_2N_2O]^+$ = 395.1930, 395.1972 found.

9-(4,4-difluoro-4-(4-methoxyphenoxy)butyl)-9H-carbazole (34)



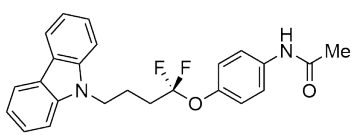
The title product was prepared according to **GP4** using 9-(4,4,4-trifluorobutyl)-9H-carbazole (138.7 mg, 0.5 mmol), 18-crown-6 (396.5 mg, 1.5 mmol, 3.0 equiv), 4-methoxyphenol (93.1 mg, 0.75 mmol, 1.5 equiv), KHMDS (299.3 mg, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL, 0.4 M) (Step 1); NEt_3·3HF (651.3 µL, 4.0 mmol, 8.0 equiv), methanesulfonic acid (259.8 µL, 4.0 mmol, 8.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) for 2 h (Step 2). The compound was purified *via* silica gel chromatography with the eluent conditions 5% ethyl acetate in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow solid (112.9 mg, 0.30 mmol, 59% yield). **MP:** 73-75 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.23 (t, J = 7.4 Hz, 2H), 7.03 (d, J = 9.1 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 4.36 (t, J = 6.6 Hz, 2H), 3.72 (s, 3H), 2.26 – 2.09 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 143.5 (t, J = 2.4 Hz), 140.2, 125.8, 124.7 (t, J = 264.8 Hz), 123.1, 122.9, 120.4, 119.0, 114.3, 108.5, 55.5, 42.0, 33.3 (t, J = 29.6 Hz), 22.3 (t, J = 2.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -70.26 (t, J = 10.2 Hz). **IR** (neat, cm^{-1}) 3051, 2935, 1595, 1505, 1462, 1240, 1137, 1030, 748, 723. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{23}H_{22}F_2NO_2]^+$ = 382.1614, 382.1614 found.

9-(4,4-difluoro-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy)butyl)-9H-carbazole (35)



The title product was prepared according to **GP4** using 9-(4,4,4-trifluorobutyl)-9H-carbazole (138.7 mg, 0.5 mmol), 18-crown-6 (396.5 mg, 1.5 mmol, 3.0 equiv), DL-α-tocopherol (323.0 mg, 0.75 mmol, 1.5 equiv), KHMDS (299.3 mg, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL, 0.4 M) (Step 1); NEt_3·3HF (651.3 µL, 4.0 mmol, 8.0 equiv), methanesulfonic acid (259.8 µL, 4.0 mmol, 8.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The compound was purified *via* flash column chromatography with eluent conditions 2% ethyl acetate in hexanes followed by automated flash column silica gel chromatography with the eluent conditions 100% hexanes to 1% ethyl acetate in hexanes to afford the product as a yellow oil (150.0 mg, 0.22 mmol, 44% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.7 Hz, 2H), 7.55 – 7.34 (m, 4H), 7.23 (ddd, J = 8.0, 6.7, 1.4 Hz, 2H), 4.42 (t, J = 6.7 Hz, 2H), 2.54 (t, J = 6.8 Hz, 2H), 2.37 – 2.16 (m, 4H), 2.19 – 1.99 (m, 9H), 1.91 – 1.64 (m, 2H), 1.64 – 0.94 (m, 24H), 0.85 (dd, J = 8.5, 6.5 Hz, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.3, 140.3, 139.3, 129.4, 127.7, 125.8, 123.0, 123.0, 108.5, 75.0, 42.2, 40.1 (d, J = 4.2 Hz), 39.4, 38.0 – 36.5 (m), 33.6 (t, J = 30.3 Hz), 32.8 (d, J = 2.0 Hz), 32.7 (d, J = 2.4 Hz), 31.1 (d, J = 4.8 Hz), 28.0, 24.8 (d, J = 1.7 Hz), 24.4, 23.9, 22.7, 22.6, 22.6, 21.0, 20.6, 19.8, 19.7, 19.7, 19.6, 19.6, 14.4 (t, J = 3.1 Hz), 13.5 (t, J = 3.1 Hz), 11.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.26 (t, J = 10.0 Hz). **IR** (neat, cm^{-1}) 2924, 2866, 2356, 2329, 1452, 1241, 1120, 1079, 1001, 747, 723. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{45}H_{64}F_2NO_2]^+$ = 688.4900, 688.4896 found.

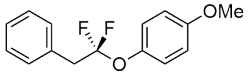
***N*-(4-(4-(9H-carbazol-9-yl)-1,1-difluorobutoxy)phenyl)acetamide (36)**



The title product was prepared according to **GP4** using 9-(4,4,4-trifluorobutyl)-9H-carbazole (138.7 mg, 0.5 mmol), 18-crown-6 (396.5 mg, 1.5 mmol, 3.0 equiv), *N*-(4-hydroxyphenyl)acetamide (113.4 mg, 0.75 mmol, 1.5 equiv), KHMDS (299.3 mg, 1.5 mmol, 3.0 equiv), and

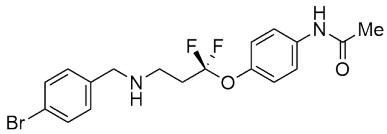
anhydrous DMF (1.25 mL, 0.4 M) for 4 h (Step 1); $NEt_3 \cdot 3HF$ (746.5 µL, 4.6 mmol, 9.2 equiv), methanesulfonic acid (389.0 µL, 6.0 mmol, 12.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) for 45 min (Step 2). The compound was purified *via* automated flash column silica gel chromatography with the eluent conditions 100% DCM. The resulting residue was recrystallized in methanol using H_2O as an anti-solvent to afford the product as a white powder (112.7 mg, 0.28 mmol, 55% yield). **MP:** 143-144 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.7 Hz, 2H), 7.57 – 7.27 (m, 6H), 7.24 (t, *J* = 7.4 Hz, 2H), 7.06 (d, *J* = 9.0 Hz, 2H), 4.69 – 4.14 (m, 2H), 2.43 – 2.15 (m, 4H), 2.12 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.3, 146.3, 140.2, 135.4, 125.8, 124.7 (t, *J* = 265.6 Hz), 123.9, 122.4, 120.8, 120.5, 119.1, 108.5, 42.0, 33.4 (t, *J* = 29.4 Hz), 24.4, 22.3 (t, *J* = 2.8 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -70.18 (t, *J* = 10.3 Hz). **IR** (neat, cm^{-1}) 3319, 3054, 2941, 1663, 1529, 1510, 1484, 1451, 1308, 1253, 1096, 1005, 836, 747, 721. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{24}H_{23}F_2N_2O_2]^+$ = 409.1723, 409.1730 found.

1-(1,1-difluoro-2-phenylethoxy)-4-methoxybenzene (37)



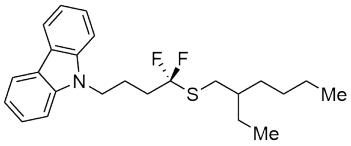
The title product was prepared according to **GP4** using (2,2,2-trifluoroethyl)benzene (80.1 mg, 0.5 mmol, 1.0 equiv), 18-crown-6 (396.5 mg, 1.5 mmol, 3.0 equiv), 4-methoxyphenol (93.1 mg, 0.75 mmol, 1.5 equiv), KHMDS (299.3 mg, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL, 0.4 M) for 30 min at room temperature (Step 1). For Step 2 the hydrofluorination was conducted according to **GP5** Step 2 using cuprous chloride (74.3 mg, 0.75 mmol, 1.5 equiv), pyridine·HF (70% hydrogen fluoride % w/w, 310 µL, 1.3 mmol, 2.6 equiv). The title product was purified *via* silica gel chromatography with the eluent conditions 10% to 20% ethyl acetate in hexanes to afford the product as a yellow oil (60.2 mg, 0.23 mmol, 46% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.28 (m, 5H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.86 – 6.72 (m, 2H), 3.76 (s, 3H), 3.42 (t, *J* = 11.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 143.8 (t, *J* = 2.3 Hz), 132.2 (t, *J* = 3.0 Hz), 130.4, 128.4, 127.5, 123.7 (t, *J* = 265.4 Hz), 123.1, 114.2, 55.6, 42.2 (t, *J* = 30.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.84 (t, *J* = 10.9 Hz). **IR** (neat, cm^{-1}) 2944, 1505, 1241, 1192, 1094, 1031, 843, 745, 697. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{15}H_{14}F_2O_2 \bullet NH_4]^+$ = 282.1300, 282.1914 found.

N-(4-(3-((4-bromobenzyl)amino)-1,1-difluoropropoxy)phenyl)acetamide (38)



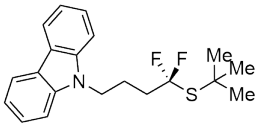
The title product was prepared according to **GP4** using *N*-(4-bromobenzyl)-3,3,3-trifluoropropan-1-amine (142.6 mg, 0.5 mmol), 18-crown-6 (396.5 mg, 1.5 mmol, 3.0 equiv), *N*-(4-hydroxyphenyl)acetamide (113.4 mg, 0.75 mmol, 1.5 equiv), KHMDS (399.0 mg, 2.0 mmol, 4.0 equiv), and anhydrous DMF (1.25 mL, 0.4 M). (Step 1); $NEt_3 \cdot 3HF$ (815.0 µL, 5.0 mmol, 10.0 equiv), methanesulfonic acid (454.5 µL, 7.0 mmol, 14.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). The product was purified via preparatory thin layer chromatography with the eluent conditions: 2% methanol in DCM on neutralized silica (the preparatory TLC plate was neutralized by covering the plate in a 2% triethylamine / hexanes solution and allowing the plate to dry prior to sample loading) to afford the product as a brown solid (80.8 mg, 0.20 mmol, 39% yield). **MP:** 104-109 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.35 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 2H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.36 (tt, *J* = 11.1, 7.0 Hz, 2H), 2.17 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.4, 146.3, 139.1, 135.4, 131.5, 129.8, 124.6 (t, *J* = 267.1 Hz), 122.4, 120.9, 120.8, 53.1, 42.8 (t, *J* = 3.3 Hz), 36.1 (t, *J* = 28.0 Hz), 24.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.13 (t, *J* = 11.1 Hz). (neat, cm^{-1}) 3258, 1660, 1607, 1546, 1506, 1487, 1406, 1318, 1245, 1102, 942, 870. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{18}H_{20}BrF_2N_2O_2]^+$ = 413.0671, 413.0689 found.

9-(4-((2-ethylhexyl)thio)-4,4-difluorobutyl)-9H-carbazole (39)



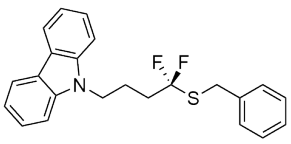
The title product was prepared according to **GP5** using 9-(4,4,4-trifluorobutyl)-9H-carbazole (138.7 mg, 0.5 mmol), 18-crown-6 (330.4 mg, 1.25 mmol, 2.5 equiv), 2-ethyl-1-hexanethiol (174.3 mg, 1.2 mmol, 2.4 equiv), KHMDS (249.4 mg, 1.25 mmol, 2.5 equiv), and anhydrous DMF (1.25 mL, 0.4 M) (Step 1); cuprous chloride (49.5 mg, 0.5 mmol, 1.0 equiv), pyridine·HF (70% hydrogen fluoride % w/w, 208 µL, 0.87 mmol, 1.7 equiv), and DCM (2.5 equiv, 0.2 M) (Step 2). ^{19}F NMR spectroscopy of the crude reaction mixture was used to initially evaluate the yield of **39** (346 µmol, 69% yield). The compound was purified *via* silica gel chromatography with the eluent conditions 1% ethyl acetate in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (73.5 mg, 0.18 mmol, 36% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 2H), 7.49 – 7.27 (m, 4H), 7.27 – 7.16 (m, 2H), 4.34 (m, 2H), 2.78 (d, *J* = 5.9 Hz, 2H), 2.24 – 2.08 (m, 3H), 1.51 (h, *J* = 6.2 Hz, 1H), 1.43 – 1.12 (m, 9H), 1.01 – 0.70 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.2, 131.0 (t, *J* = 275.9 Hz), 125.8, 123.0 (d, *J* = 2.2 Hz), 120.4, 119.0 (d, *J* = 2.1 Hz), 108.5, 42.1, 39.1, 36.8 (t, *J* = 24.3 Hz), 32.3, 31.6 (t, *J* = 2.8 Hz), 28.7, 25.5, 22.9 (t, *J* = 3.0 Hz), 22.9, 14.1, 10.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -72.83 (t, *J* = 13.9 Hz). **IR** (neat, cm^{-1}) 2958, 2928, 2871, 2858, 2598, 1484, 1453, 1347, 1325, 1240, 1153, 967, 748, 722. **HRMS** (APGC) [M] calcd. for $[C_{24}H_{31}F_2NS]$ = 403.2145, 403.2145 found.

9-(4-(tert-butylthio)-4,4-difluorobutyl)-9H-carbazole (40)



The title product was prepared according to **GP5** using 9-(4,4,4-trifluorobutyl)-9H-carbazole (138.7 mg, 0.5 mmol), 18-crown-6 (330.4 mg, 1.25 mmol, 2.5 equiv), 2-methylpropane-2-thiol (135.2 mg, 1.5 mmol, 3.0 equiv), KHMDS (249.4 mg, 1.25 mmol, 2.5 equiv), and anhydrous DMF (1.25 mL, 0.4 M) (Step 1); cuprous chloride (74.3 mg, 0.75 mmol, 1.5 equiv), pyridine·HF (70% hydrogen fluoride % w/w, 312 µL, 1.3 mmol, 2.6 equiv), and DCM (2.5 equiv, 0.2 M) (Step 2). ^{19}F NMR spectroscopy of the crude reaction mixture was used to initially evaluate the yield of **40** (323 µmol, 65% yield). The compound was purified *via* silica gel chromatography with the eluent conditions 2% EtOAc in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a yellow oil (88.4 mg, 0.26 mmol, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 2H), 7.61 – 7.35 (m, 4H), 7.34 – 7.17 (m, 2H), 4.45 – 4.33 (m, 2H), 2.32 – 2.05 (m, 4H), 1.50 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.2, 132.5 (t, *J* = 277.6 Hz), 125.8, 122.9, 120.4, 119.0, 108.5, 48.2, 42.2, 37.9 (t, *J* = 24.4 Hz), 32.3 (t, *J* = 1.8 Hz), 22.8 (t, *J* = 3.1 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -70.08 (t, *J* = 14.4 Hz). **IR** (neat, cm^{-1}) 2965, 2901, 2360, 2341, 1484, 1453, 1326, 1326, 1153, 1026, 749, 723. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{20}H_{23}F_2NS•NH_4]^+$ = 365.1858, 365.2041 found.

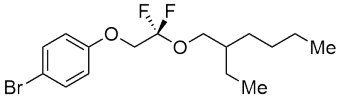
9-(4-(benzylthio)-4,4-difluorobutyl)-9H-carbazole (41)



The title product was prepared according to **GP5** using 9-(4,4,4-trifluorobutyl)-9H-carbazole (138.7 mg, 0.5 mmol), 18-crown-6 (330.4 mg, 1.25 mmol, 2.5 equiv), phenylmethanethiol (186.3 mg, 1.5 mmol, 3.0 equiv), KHMDS (249.4 mg, 1.25 mmol, 2.5 equiv), and anhydrous DMF (1.25 mL, 0.4 M) (Step 1); cuprous chloride (49.5 mg, 0.5 mmol, 1.0 equiv), pyridine·HF (70% hydrogen fluoride % w/w, 312 µL, 1.3 mmol, 2.6 equiv), and DCM (2.5 equiv, 0.2 M) (Step 2). ^{19}F NMR spectroscopy of the crude reaction mixture was initially used to evaluate the yield of **41** (187 µmol, 37% yield). The compound was purified *via* silica gel chromatography with the eluent conditions 1% ethyl acetate in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to

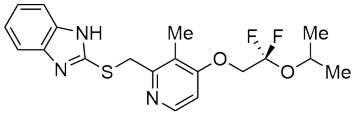
afford the product as a yellow oil (38.7 mg, 0.10 mmol, 20% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.8 Hz, 2H), 7.52 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.23 (m, 7H), 4.39 (t, *J* = 6.6 Hz, 2H), 4.08 (s, 2H), 2.32 – 2.08 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 136.7, 130.8 (t, *J* = 277.0 Hz), 129.1, 128.8, 127.6, 125.9, 120.6, 119.2, 108.6, 42.1, 36.7 (t, *J* = 24.0 Hz), 32.5 (t, *J* = 3.9 Hz), 23.0 (t, *J* = 3.07 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -72.59 (t, *J* = 14.2 Hz). **IR** (neat, cm^{-1}) 3052, 2936, 2881, 1596, 1439, 1452, 1325, 1153, 749, 722. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{23}H_{22}F_2NS]^+$ = 382.1436, 382.1433 found.

1-bromo-4-(2-((2-ethylhexyl)oxy)-2,2-difluoroethoxy)benzene (44)



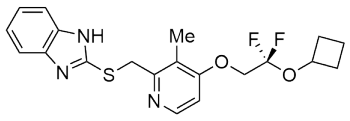
The title product was prepared according to **GP1** using 1-bromo-4-(2,2,2-trifluoroethoxy)benzene (127.5 mg, 0.5 mmol, 1.0 equiv), 2-ethylhexanol (97.7 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 3 h (Step 1); NEt_3·3HF (244.2 µL, 1.5 mmol, 3.0 equiv), methanesulfonic acid (97.4 µL, 1.5 mmol, 3.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) (Step 2). ^{19}F NMR spectroscopy of the crude reaction mixture was used to assess the yield of the intermediate, compound **43** (386 µmol, 77% yield). ^{19}F NMR spectroscopy of the crude reaction mixture was used to assess the yield of **44** against the yield from Step 1 (279 µmol, 72% yield). The compound was purified *via* silica gel chromatography with the eluent conditions 0.5% triethylamine in hexanes on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford the product as a colorless oil (87.4 mg, 0.24 mmol, 48% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 2H), 6.92 – 6.75 (m, 2H), 4.20 (t, *J* = 8.3 Hz, 2H), 3.84 (dd, *J* = 5.7, 1.5 Hz, 2H), 1.63 – 1.47 (m, 1H), 1.46 – 1.17 (m, 8H), 0.89 (td, *J* = 7.0, 3.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 132.5, 122.2 (t, *J* = 263.2 Hz), 117.1, 114.3, 68.1 (t, *J* = 36.6 Hz), 65.9 (t, *J* = 5.6 Hz), 39.1, 30.3, 29.0, 23.6, 23.1, 14.2, 11.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -81.05 (t, *J* = 8.3 Hz). **IR** (neat, cm^{-1}) 2959, 2931, 2860, 1488, 1233, 1173, 1057, 920, 820. **HRMS** (APGC) $[M]^+$ calcd. for $[C_{16}H_{23}BrF_2O_2]$ = 364.0844, 364.0850 found.

2-(((4-(2,2-difluoro-2-isopropoxyethoxy)-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (46)



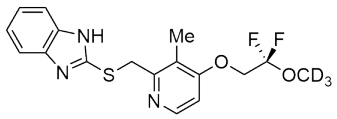
The title product was prepared according to **GP1** using 2-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (176.7 mg, 0.5 mmol), isopropyl alcohol (45.1 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 18 h (Step 1); For Step 2, **GP1** was followed except after 1 h the reaction mixture was cooled in a 0 °C ice bath and was quenched with NaOH (1 M in methanol, 12 mL, 12.0 mmol) instead of saturated $NaHCO_3$. For Step 2, NEt_3·3HF (488.5 µL, 3.0 mmol, 6.0 equiv), methanesulfonic acid (194.8 µL, 3.0 mmol, 6.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) were used and the reaction was conducted for 1 hour. **Note:** the addition of NaOH to the reaction is very exothermic. The compound was purified *via* silica gel chromatography with the eluent conditions 1% methanol in dichloromethane on neutralized silica (the silica gel was neutralized by preparing a silica slurry with 2% triethylamine / DCM solution) to afford the product as a yellow solid (137.5 mg, 0.35 mmol, 70% yield). **MP:** 94-99 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.93 (s, 1H), 8.36 (d, *J* = 5.8 Hz, 1H), 7.55 (d, *J* = 59.4 Hz, 2H), 7.20 (dt, *J* = 6.0, 3.6 Hz, 2H), 6.72 (d, *J* = 5.8 Hz, 1H), 4.74 – 4.60 (m, 1H), 4.43 (s, 2H), 4.25 (t, *J* = 8.0 Hz, 2H), 2.31 (s, 3H), 1.31 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, CD_3CN) δ 163.8, 157.5, 152.0, 148.6, 140.6, 123.3 (t, *J* = 261.4 Hz), 122.7, 121.9, 115.1, 107.8, 70.0 (t, *J* = 5.3 Hz), 68.6 (t, *J* = 37.1 Hz), 36.4, 23.6, 10.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.52 (t, *J* = 8.0 Hz). **IR** (neat, cm^{-1}) 2981, 2875, 1581, 1438, 1296, 1261, 1167, 1107, 1089, 1054, 1004, 911, 860, 816, 745. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{22}F_2N_3O_2S]^+$ = 394.1396, 394.1489 found.

2-(((4-(2-cyclobutoxy-2,2-difluoroethoxy)-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (47)



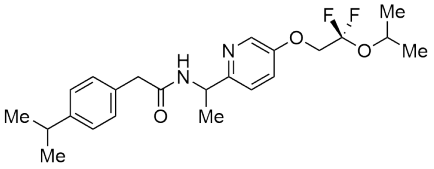
The title product was prepared according to **GP1** using 2-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (176.7 mg, 0.5 mmol), cyclobutanol (54.1 mg, 0.75 mmol, 1.5 equiv), KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv), and anhydrous DMF (1.25 mL) for 2 h (Step 1). For Step 2, **GP1** was followed except after 1 h the reaction mixture was cooled in a 0 °C ice bath and was quenched with NaOH (1 M in methanol, 12 mL, 12.0 mmol) instead of saturated $NaHCO_3$. For Step 2, $NEt_3 \cdot 3HF$ (569.9 µL, 3.5 mmol, 7.0 equiv), methanesulfonic acid (227.3 µL, 3.5 mmol, 7.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) were used and the reaction was run for 1 hour. ^{19}F NMR spectroscopy of the crude reaction mixture was used to initially evaluate the yield of **47** (299 µmol, 60% yield). The product was purified via preparatory thin layer chromatography with the eluent conditions: 1% triethylamine, 1% methanol in DCM on neutralized silica (the preparatory TLC plate was neutralized by covering the plate in a 2% triethylamine / hexanes solution and allowing the plate to dry prior to sample loading) to afford the product as a white powder (70.8 mg, 0.18 mmol, 35%). **MP:** 122-127 °C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.75 (s, 1H), 8.38 (d, J = 5.7 Hz, 1H), 7.54 (s, 2H), 7.22 – 7.13 (m, 2H), 6.75 (d, J = 5.8 Hz, 1H), 4.81 – 4.67 (m, 1H), 4.40 (s, 2H), 4.25 (t, J = 8.2 Hz, 2H), 2.37 – 2.24 (m, 5H), 2.15 (qdd, J = 10.0, 7.9, 2.9 Hz, 2H), 1.84 – 1.70 (m, 1H), 1.58 (qt, J = 10.8, 7.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4, 157.3, 151.6, 147.3, 122.0, 121.8, 121.6 (t, J = 263.6 Hz), 114.4, 106.5, 68.5 (t, J = 6.1 Hz), 67.7 (t, J = 36.7 Hz), 35.0, 31.3, 13.3, 10.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -79.13 (t, J = 8.1 Hz). **IR** (neat, cm^{-1}) 2949, 2859, 1581, 1439,1296, 1265, 1169, 1094, 1062, 987, 815, 746. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{22}F_2N_3O_2S]^+$ = 406.1396, 406.1454 found.

2-(((4-(2,2-difluoro-2-(methoxy-d3)ethoxy)-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (48)



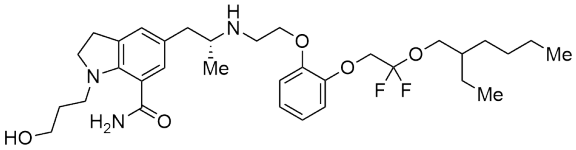
The title product was prepared according to **GP1** except 18-crown-6 was added after solvent addition, before addition of methanol-d_3 using (2-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (176.7 mg, 0.5 mmol), 18-crown-6 (132.2 mg, 0.5 mmol, 1.0 equiv), and methanol-d_3 (30.4 µL, 0.75 mmol, 1.5 equiv), and KHMDS (1 M solution in THF, 1.5 mL, 1.5 mmol, 3.0 equiv) for 1 h (Step 1); $NEt_3 \cdot 3HF$ (569.9 µL, 3.5 mmol, 7.0 equiv), methanesulfonic acid (227.3 µL, 3.5 mmol, 7.0 equiv), and anhydrous toluene (1.25 mL, 0.2M) (Step 2). ^{19}F NMR spectroscopy of the crude reaction mixture was used to initially evaluate the yield of **48** (216 µmol, 43% yield). The titled product was purified *via* preparatory thin layer chromatography with the eluent conditions: 50% diethyl ether in DCM on neutralized silica (the preparatory TLC plate was neutralized by covering the plate in a 2% triethylamine / hexanes solution and allowing the plate to dry prior to sample loading) to afford the product as an off-white solid (46.1 mg, 0.13 mmol, 25% yield). **MP:** 132-134 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.80 (s, 1H), 8.36 (d, J = 5.7 Hz, 1H), 7.53 (s, 2H), 7.18 (q, J = 3.6 Hz, 2H), 6.72 (d, J = 5.8 Hz, 1H), 4.40 (s, 2H), 4.27 (t, J = 8.1 Hz, 2H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.3, 157.4, 155.4, 151.6, 148.1, 147.4, 122.0, 121.8 (t, J = 264.1 Hz), 106.42, 67.48, 34.98, 10.84. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -83.74 (t, J = 8.0 Hz). **IR** (neat, cm^{-1}) 3137, 3086, 2927, 2894, 2812, 1581, 1439, 1412, 1331, 1296, 1263, 1179, 1113, 1080, 1020, 911, 841, 806. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{17}H_{15}D_3F_2N_3O_2S]^+$ = 369.1271, 369.1312 found.

***N*-(1-(5-(2,2-difluoro-2-isopropoxyethoxy)pyridin-2-yl)ethyl)-2-(4-isopropylphenyl)acetamide (49)**



The title product was prepared according to **GP1** using 2-(4-isopropylphenyl)-*N*-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide (190.2 mg, 0.5 mmol), isopropyl alcohol (57.3 µL, 0.75 mmol, 1.5 equiv), KHMDS (349.1 mg, 1.75 mmol, 3.5 equiv), and anhydrous DMF (1.25 mL) for 2 h (Step 1). For Step 2, **GP1** was followed except after 30 min the reaction mixture was cooled in a 0 °C ice bath and was quenched with NaOH (1 M in methanol, 12 mL, 12.0 mmol) instead of saturated $NaHCO_3$. For Step 2, $NEt_3{\cdot}3HF$ (407.5 µL, 2.5 mmol, 5.0 equiv), methanesulfonic acid (162.3 µL, 2.5 mmol, 5.0 equiv), and anhydrous toluene (2.5 mL, 0.2M) were used. ^{19}F NMR spectroscopy of the crude reaction mixture was used to initially evaluate the yield of **49** (346 µmol, 69% yield). The product was purified *via* silica preparatory thin layer chromatography plate (the silica was neutralized by subjecting the preparatory TLC plate to a solution of 2% triethylamine in hexanes and allowing the plate to dry) and developed with 1% methanol in DCM to afford the product as a yellow solid (87.8 mg, 0.21 mmol, 42% yield). **MP:** 64-66 °C. **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.21 (d, *J* = 3.0 Hz, 1H), 7.55 – 6.88 (m, 6H), 6.72 (d, *J* = 7.4 Hz, 1H), 5.05 (p, *J* = 6.9 Hz, 1H), 4.64 (hept, *J* = 6.2 Hz, 1H), 4.22 (t, *J* = 8.4 Hz, 2H), 3.50 (s, 2H), 2.90 (hept, *J* = 6.9 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 6H), 1.24 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 170.3, 155.0, 153.8, 148.1, 137.7, 133.2, 129.6, 127.1, 123.2, 122.6 (t, *J* = 262.7 Hz), 122.0, 69.5 (t, *J* = 5.2 Hz), 68.9 (t, *J* = 36.6 Hz), 49.6, 43.7, 34.2, 24.2, 23.5, 22.6. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -78.65 (t, *J* = 8.3 Hz). **IR** (neat, cm^{-1}) 3287, 2961, 2932, 2872, 2360, 2341, 1644, 1537, 1482, 1239, 1211, 1096, 1053, 916, 849, 787. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{23}H_{31}F_2N_2O_3]^+$ = 421.2298, 421.2399 found.

5-((2*R*)-2-((2-(2-(2-((2-ethylhexyl)oxy)-2,2-difluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (50)



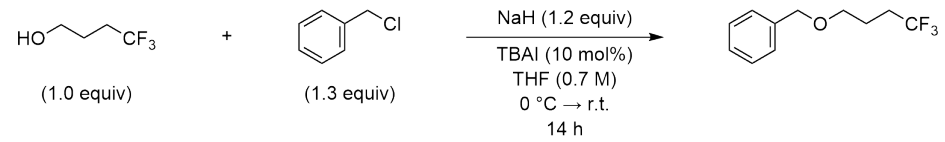
The title product was prepared according to **GP1** using (*R*)-1-(3-hydroxypropyl)-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carboxamide (247.8 mg, 0.5 mmol), 2-ethyl-1-hexanol (97.7 mg, 0.75 mmol, 1.5 equiv), KHMDS (349.1 mg, 1.75 mmol, 3.5 equiv), and anhydrous DMF (1.25 mL, 0.4 M) for 2 h (Step 1); $NEt_3{\cdot}3HF$ (597 µL, 3.7 mmol, 7.3 equiv), methanesulfonic acid (311.2 µL, 4.8 mmol, 9.6 equiv), and anhydrous toluene (1.25 mL, 0.2M) for 1 hour. (Step 2). For this substrate, Step 1 of the reaction was conducted under anhydrous nitrogen: the vial containing the (trifluoromethyl)alkane was evacuated and backfilled three times with anhydrous nitrogen gas and left under a positive pressure of nitrogen gas on a manifold Schlenk line. The vial was unsealed for addition of KHMDS and was resealed and flushed with a positive pressure of nitrogen using an inlet needle from the Schlenk line and a vent needle, the vial was then wrapped in parafilm before placing the vial in the reaction block. For Step 2 of the reaction, the reaction mixture was quenched by cooling the solution in a 0 °C ice bath and adding NaOH (1 M in methanol, 12 mL, 12.0 mmol) *via* syringe followed by excess K_2CO_3. ^{19}F NMR spectroscopy of the crude reaction mixture was used to initially evaluate the yield of **50** (196 µmol, 39% yield). The crude residue was loaded onto a neutralized silica preparatory thin layer chromatography plate (the silica was neutralized by subjecting the preparatory TLC plate to a solution of 2% triethylamine in hexanes and allowing the plate to dry) and developed with 5% methanol in DCM to afford the product as a yellow oil (70.5 mg, 0.12 mmol, 23% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.05 – 6.70 (m, 5H), 6.05 (s, 1H), 4.36 – 4.00 (m, 4H), 3.88 – 3.77 (m, 2H), 3.73 (t, *J* = 5.5 Hz, 2H), 3.38 (h, *J* = 9.5 Hz, 2H), 3.27 – 2.86 (m, 7H), 2.64 (ddd, *J* = 59.2, 13.6, 6.9 Hz, 2H), 1.78 (p, *J* = 6.4 Hz, 2H), 1.52 (p, *J* = 6.4 Hz, 1H), 1.44 – 1.16 (m, 9H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.87

(td, J = 7.1, 4.5 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.7, 150.0, 149.4, 148.4, 133.9, 129.8, 128.3, 128.2, 123.4, 122.5 (t, J = 263.8 Hz), 121.9, 118.1, 117.3, 115.5, 69.7 (t, J = 35.2 Hz), 68.9, 65.6 (t, J = 5.7 Hz), 59.6, 54.7, 53.7, 50.7, 46.0, 42.3, 39.1, 31.1, 30.2, 29.0, 28.3, 23.5, 23.1, 19.7, 14.2, 11.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -81.24 (t, J = 8.9 Hz). **IR** (neat, cm^{-1}) 3350, 2957, 2928, 2858, 2367, 1757, 1656, 1594, 1500, 1456, 1380, 1250, 1201, 1128, 1042, 918, 742, 668. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{33}H_{50}F_2N_3O_5]^+$ = 606.3714, 606.3770 found.

VI. Starting Material Syntheses and Characterization

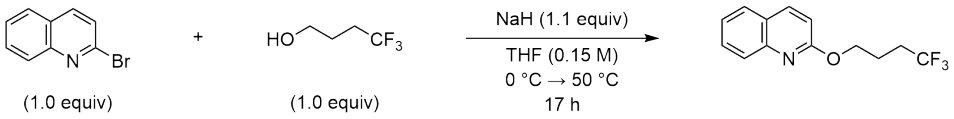
All substrates that are not described below were purchased from commercial suppliers and used as received. We note that all alcohols, thiols, and phenols used in the scope are commercially available.

((4,4,4-trifluorobutoxy)methyl)benzene (1)



Procedure: 4,4,4-Trifluorobutanol (2.562g, 20.0 mmol) was added *via* pipette to a 100 mL oven-dried round bottom flask containing a magnetic stir bar. To the flask, anhydrous THF (28.5 mL, 0.7 M) was added *via* syringe, and the solution was cooled to 0 °C in a 0 °C ice bath with stirring. NaH (60% dispersion in mineral oil, 960.0 mg, 24.0 mmol, 1.2 equiv) was added portion-wise and the reaction mixture was stirred for 20 min. At this time, tetrabutylammonium iodide (TBAI, 738.8 mg, 2.0 mmol, 10 mol%) was added followed by benzyl chloride (3.0 mL, 26.0 mmol, 1.3 equiv) which was added *via* syringe. The flask was fitted with a rubber septum (Chemglass, #CG302208) connected to a nitrogen balloon *via* a needle. The flask was removed from the ice bath and was stirred at room temperature for 14 hours. At this time, the reaction mixture was cooled to 0 °C in a 0 °C ice bath and the rubber septum was removed. To the flask, H_2O (50 mL) was slowly added, and the mixture was transferred to a 250 mL separatory funnel. The mixture was extracted with Et_2O (3 x 100 mL) and the organic layers were combined. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude mixture was purified *via* silica gel flash column chromatography (100% hexanes → 3% EtOAc in hexanes) to afford ((4,4,4-trifluorobutoxy)methyl)benzene as a colorless oil (2.7202g, 12.40 mmol, 62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 4.51 (s, 2H), 3.53 (t, J = 6.1 Hz, 2H), 2.30 – 2.14 (m, 2H), 1.92 – 1.81 (m, 2H). The spectroscopic data is consistent with a previous report.[9]

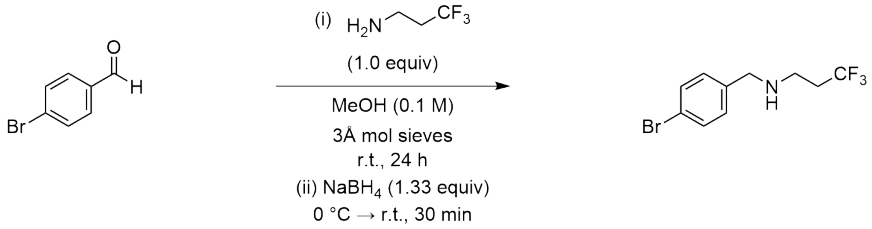
2-(4,4,4-trifluorobutoxy)quinoline



Procedure: To a 100 mL, oven-dried round bottom flask with a magnetic stir bar 4,4,4-trifluorobutan-1-ol (585.4 mg, 4.57 mmol, 1.0 equiv) was added *via* pipette. To the flask, anhydrous THF (33 mL) was added *via* syringe, the round bottom flask was placed in a 0 °C ice bath on stirring, and the solution was cooled to 0 °C. At this time, sodium hydride (60% dispersion in mineral oil, 200 mg, 5.0 mmol, 1.1 equiv) was added portion-wise. The flask was loosely covered with a plastic stopper and the reaction was stirred at 0 °C for 20 min. At this time, 2-bromoquinoline (950.0 mg, 4.57 mmol, 1.0 equiv) was added to the solution at once

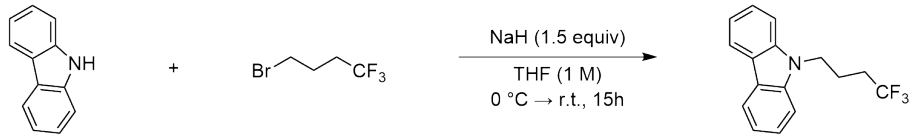
and the flask was removed from the ice bath. The flask was fitted with a reflux condenser and placed in an oil bath preheated to 50 °C. The reflux condenser was fitted with a rubber septum and connected to a manifold Schlenk line via a needle under a positive pressure of nitrogen. The reaction mixture was stirred at 50 °C for 17 hours. At this time, the flask was removed from the oil bath, and the reaction mixture was cooled to room temperature. The flask was then placed in a 0 °C ice bath and the reaction mix was cooled to 0 °C. H_2O (50 mL) was slowly added and the resulting mixture was transferred to a 250 mL separatory funnel and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified *via* silica gel flash column chromatography with eluent conditions 100% hexanes to 5% EtOAc to afford 2-(4,4,4-trifluorobutoxy)quinoline as a colorless oil (837.4 mg, 3.42 mmol, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.9 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.63 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.39 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.55 (t, *J* = 6.2 Hz, 2H), 2.42 – 2.25 (m, 2H), 2.17 – 2.03 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.9, 146.6, 139.0, 129.7, 127.6, 127.4, 127.4 (q, *J* = 276.1 Hz), 125.3, 124.3, 113.1, 64.2, 31.1 (q, *J* = 29.1 Hz), 22.1 (q, *J* = 3.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -66.41 (t, *J* = 10.9 Hz). 2957, 2359, 1619, 1574, 1429, 1312, 1240, 1151, 1016, 821, 781, 756, 622. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{13}F_3NO]^+$ = 256.0944, 256.0951 found.

***N*-(4-bromobenzyl)-3,3,3-trifluoropropan-1-amine**



Procedure: To a 100 mL, oven-dried round bottom flask with a magnetic stir bar, 4-bromobenzaldehyde (925.0 mg, 5.0 mmol) was added. To the flask, methanol (50 mL, 0.1M) was added *via* syringe followed by activated 3Å molecular sieves (Sigma-Aldrich, #208590; the molecular sieves were activated by drying in an oven at 120 °C overnight and allowing them to cool to room temperature in a desiccator). At this time, 3,3,3-trifluoropropan-1-amine (565.5 mg, 5.0 mmol, 1.0 equiv) was added *via* syringe. The round bottom flask was fitted with a plastic stopper and the reaction mixture was stirred at room temperature for 24 hours. At this time, the reaction mix was cooled to 0 °C in a 0 °C ice bath and sodium borohydride (251.4 mg, 6.65 mmol, 1.33 eq) was added portion-wise. The flask was then removed from the ice bath and stirred at room temperature for 30 min. At this time, the reaction mixture was cooled to 0 °C in a 0 °C ice bath and H_2O (25 mL) was added. The crude solution was decanted into a 500 mL round bottom flask and methanol was removed *via* rotary evaporation. The resulting aqueous mixture was transferred to a 250 mL separatory funnel with brine (20 mL) and extracted with DCM (3 x 50 mL) to afford *N*-(4-bromobenzyl)-3,3,3-trifluoropropan-1-amine (1.25 g, 4.40 mmol, 89% yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 3.76 (s, 2H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.31 (qt, *J* = 10.9, 7.1 Hz, 2H), 1.44 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.9, 131.7, 129.87, 126.8 (q, *J* = 276.6 Hz), 121.1, 53.2, 42.1 (q, *J* = 3.3 Hz), 34.51 (q, *J* = 27.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -65.02 (t, *J* = 11.0 Hz). **IR** (neat, cm^{-1}) 2842, 2361, 1487, 1400, 1251, 1138, 1069, 1011, 835, 803, 657, 561. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{10}H_{12}BrF_3N]^+$ = 282.0100, 282.0180 found.

9-(4,4,4-trifluorobutyl)-9H-carbazole

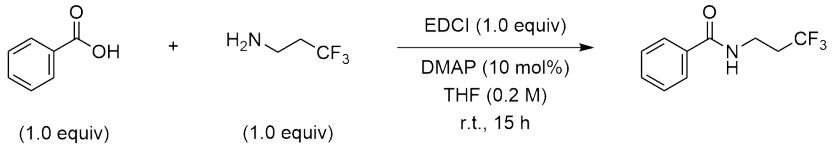


Procedure: To a 25 mL, oven-dried round bottom flask with a stir bar, 9H-carbazole (836.0 mg, 5.0 mmol) was added. Anhydrous THF (5 mL, 1M) was added, and the solution was cooled to 0 °C in a 0 °C ice bath. Sodium hydride (60% dispersion in mineral oil, 180.0 mg, 7.5 mmol, 1.5 equiv) was added portion-wise, and the reaction mixture was stirred at 0 °C for 30 min. At this time, 4-bromo-1,1,1-trifluorobutane (1.146g, 1.2 equiv, 6.0 mmol) was added *via* syringe. The flask was removed from the ice bath and the reaction mixture was stirred at room temperature for 15 hours. At this time, the reaction solution was cooled to 0 °C and H_2O (10 mL) was added slowly. The crude mixture was transferred to a 250 mL separatory funnel with brine (20 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, and the crude solution was concentrated *in vacuo*. The resulting residue was purified *via* silica gel flash column chromatography (100% hexanes to 10% EtOAc in hexanes) to afford 9-(4,4,4-trifluorobutyl)-9H-carbazole as a white solid (748.5 mg, 2.70 mmol, 54%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.69 – 7.50 (m, 2H), 7.46 – 7.41 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 4.38 (t, *J* = 6.5 Hz, 2H), 2.35 – 2.02 (m, 4H). The spectroscopic data is consistent with a previous report.[10]

1-benzyl-3-(trifluoromethyl)piperidine

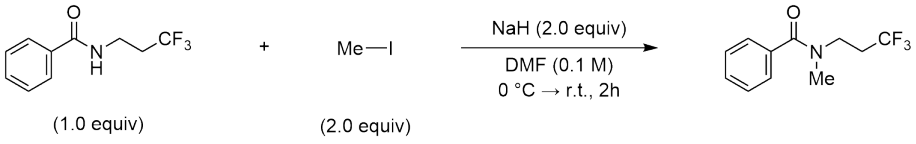
Procedure: to a 250 mL, oven-dried round bottom flask with a magnetic stir bar, 3-(trifluoromethyl)piperidine hydrochloride (948.0 mg, 5.0 mmol) was added. The flask was fitted with a rubber septum and the flask was evacuated and backfilled three times with anhydrous nitrogen gas and left under a positive pressure of nitrogen gas on a manifold Schlenk line. Acetonitrile (42 mL, 0.12 M) was added through the rubber septum *via* syringe. Diisopropylethylamine (DIPEA, 1.75 mL, 10 mmol, 2.0 equiv) was added *via* syringe and the solution was stirred. Benzyl bromide (855 mg, 5.0 mmol, 1.0 equiv) was then added dropwise through the rubber septum *via* syringe. The reaction mixture was stirred at room temperature for 3 hours. At this time H_2O (50 mL) was added and the mixture was transferred to a 250 mL separatory funnel and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and the crude solution was concentrated *in vacuo*. The product was filtered through silica with 10% EtOAc in hexanes to afford 1-benzyl-3-(trifluoromethyl)piperidine as a yellow oil (751.8 mg, 3.10 mmol, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.15 (m, 5H), 3.90 – 3.24 (m, 2H), 3.04 (ddt, *J* = 10.9, 3.6, 1.7 Hz, 1H), 2.85 (dtd, *J* = 11.2, 2.8, 1.4 Hz, 1H), 2.48 – 2.24 (m, 1H), 2.10 – 1.80 (m, 2H), 1.73 (dt, *J* = 13.9, 3.7 Hz, 1H), 1.58 (qt, *J* = 12.8, 4.0 Hz, 1H), 1.28 (qd, *J* = 12.7, 4.4 Hz, 1H). The spectroscopic data is consistent with a previous report.[11]

***N*-(3,3,3-trifluoropropyl)benzamide**



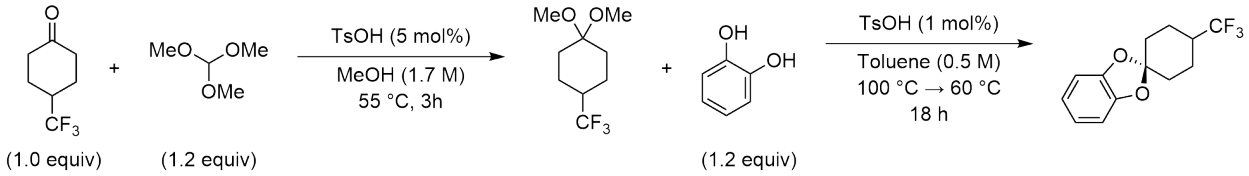
Procedure: To a 50 mL, oven-dried round bottom flask with a magnetic stir bar, benzoic acid (610.5 mg, 5.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 958.5 mg, 1.0 equiv), and 4-dimethylaminopyridine (DMAP, 61.1 mg, 10 mol%) were added. Anhydrous THF (25 mL, 0.2M) was added to the flask *via* syringe and the solution was stirred. 3,3,3-Trifluoropropan-1-amine (565.5 mg, 1.0 equiv) was added *via* syringe. The flask was sealed with a plastic stopper and the reaction mixture was stirred at room temperature for 15 hours. At this time, H_2O (20 mL) was added, and the mixture was transferred to a 250 mL separatory funnel and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with aqueous HCl (1M, 2 x 50 mL), the resulting organic solution was dried over Na_2SO_4 and concentrated *in vacuo* to afford crude white crystals. The crude residue was recrystallized in Et_2O to afford *N*-(3,3,3-trifluoropropyl)benzamide as a white solid (383.6 mg, 1.75 mmol, 35%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.70 (m, 2H), 7.56 – 7.49 (m, 1H), 7.48 – 7.40 (m, 2H), 6.37 (br s, 1H), 3.73 (q, J = 6.2 Hz, 2H), 2.48 (qt, J = 10.8, 6.4 Hz, 2H). The spectroscopic data is consistent with a previous report.[12]

***N*-methyl-N-(3,3,3-trifluoropropyl)benzamide**



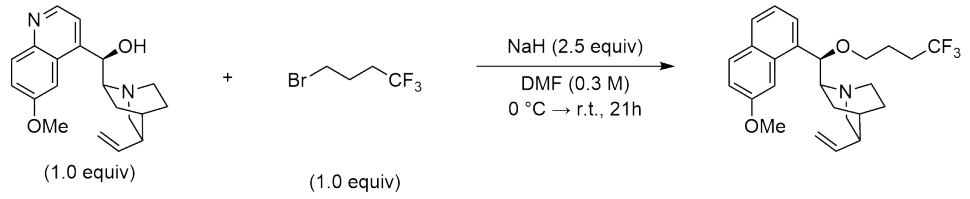
Procedure: To a 50 mL, flame-dried round bottom flask with a stir bar, *N*-(3,3,3-trifluoropropyl)benzamide (343.3 mg, 1.58 mmol) was added. DMF (15 mL, 0.1 M) was added *via* syringe and the flask was placed in a 0 °C ice bath for 5 min. NaH (60% wt. dispersion in mineral oil, 126.4 mg, 2.0 equiv, 3.16 mmol) was added portion-wise. The flask was loosely sealed with a plastic stopper and the reaction mixture was stirred at 0 °C for 15 min. At this time, iodomethane (448.4 mg, 2.0 equiv, 3.16 mmol) was added *via* syringe. The flask was removed from the ice bath stirred at room temperature for 14 hours. At this time, H_2O (20 mL) was added. The mixture was transferred to a 250 mL separatory funnel and was extracted with DCM (3 x 50 mL), and the combined organic layers were washed with H_2O (3 x 50 mL). The resulting organic solution was dried over Na_2SO_4, filtered, transferred to a 250 mL round bottom flask and concentrated *in vacuo*. To the flask, *n*-heptane (50 mL) was added, and the solution was reconcentrated. To the flask, acetonitrile (100 mL) was added, the solution was transferred to a 250 mL separatory funnel and extracted with hexanes (2 x 100 mL). The acetonitrile layer was collected and concentrated *in vacuo*. DMF remained, and thus *n*-heptane (50 mL) was added to the flask and the solution was reconcentrated *in vacuo* to afford *N*-methyl-*N*-(3,3,3-trifluoropropyl)benzamide as a yellow oil (287.8 mg, 1.24 mmol, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.31 (m, 5H), 3.90 – 3.44 (m, 2H), 3.16 – 2.84 (m, 3H), 2.70 – 2.23 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.6, 135.9, 129.8, 128.4, 126.9, 41.9, 38.3, 32.1 – 28.7 (m). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -65.10 (t, J = 10.7 Hz), -65.52. **Note:** the titled product exhibits severe broadening in the ^{1}H, ^{19}F, and ^{13}C NMR spectra, that could not be improved in different solvents. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{11}H_{13}F_3NO]^+$ = 232.0944, 232.1093 found.

4'-(trifluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]



Procedure: To a 25 mL, oven-dried round bottom flask with a magnetic stir bar 4-(trifluoromethyl)cyclohexan-1-one (835 mg, 5.0 mmol) was added *via* pipette followed by methanol (2.9 mL, 1.7 M) *via* syringe. *p*-Toluenesulfonic acid monohydrate (47.6 mg, 0.25 mmol, 5 mol%) was added and the flask was fitted with a short path distilling head and receiving flask. **Note:** the addition of *p*-toluenesulfonic acid is exothermic. The flask was placed into a water bath preheated to 55 °C and the reaction mixture was stirred at 55 °C for 3 hours. At this time, the reaction flask was removed from heating and allowed to cool to room temperature. The distillation head and receiving flask were removed and the contents of the receiving flask were discarded. To the reaction flask saturated aqueous $NaHCO_3$ (20 mL) was added, the mixture was transferred to a 125 mL separatory funnel and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was taken up with Et_2O and transferred to a 50 mL, oven-dried round bottom flask and reconcentrated *in vacuo*. The flask was charged with a magnetic stir bar, toluene (10 mL, 0.5 M), and benzene-1,2-diol (661.2 mg, 1.2 equiv). The flask was fitted with a reflux condenser, and the reaction solution was brought to reflux in an oil bath preheated to 100 °C where it was refluxed for 20 min with stirring. At this time, the oil bath temperature was reduced to 60 °C, *p*-toluenesulfonic acid monohydrate (9.5 mg, 0.05 mmol, 1 mol %) was added, and the reaction mixture was stirred at 60 °C for 18 hours. At this time the flask was removed from the oil bath and the reaction mixture was cooled to room temperature. To the reaction flask saturated aqueous $NaHCO_3$ (5 mL) was added *via* syringe, the mixture was transferred to a 250 mL separatory funnel and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified *via* silica gel flash column chromatography on neutralized silica (1% EtOAc in hexanes) (the silica was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford 4'-(trifluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane] as a white powder (2 steps, 427.4 mg, 1.65 mmol, 33%). **MP:** 111-113 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.84 – 6.70 (m, 4H), 2.37 – 2.07 (m, 3H), 2.07 – 1.98 (m, 2H), 1.90 – 1.70 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.3, 147.1, 127.6 (q, J = 278.6 Hz), 121.4, 121.4, 116.5, 108.9, 108.8, 40.4 (q, J = 27.1 Hz), 33.5, 22.1 (q, J = 2.6 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.06 (d, J = 8.3 Hz). **IR** (neat, cm^{-1}) 2963, 2947, 2882, 2360, 2341, 1487, 1462, 1447, 1334, 1237, 1145,1089, 739. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{13}H_{13}F_3O_2•NH_4]^+$ = 276.1206, 276.1586 found.

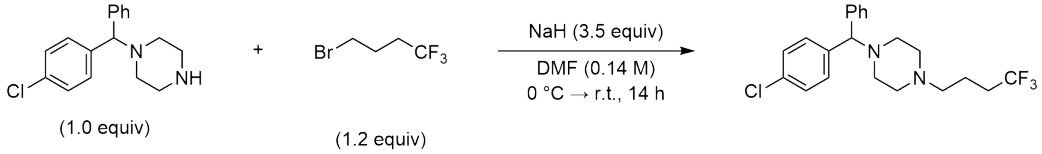
2(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(6-methoxyquinolin-4-yl)(4,4,4-trifluorobutoxy)methyl)-5-vinylquinuclidine



Procedure: To a 100 mL, oven-dried round bottom flask (*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol (1.621g, 5.0 mmol) was added. The flask was fitted with a rubber septum and was evacuated and backfilled three times with anhydrous nitrogen gas and left under a positive pressure

of nitrogen gas on a manifold Schlenk line. DMF (16.5 mL, 0.3M) was added through the septum *via* syringe and the solution was cooled 0 °C in a 0 °C ice bath. The septum was removed and NaH (60% dispersion in mineral oil, 500 mg, 2.5 equiv) was added portion-wise. At this time, the flask was resealed with a rubber septum, the septum was pierced with a vent and the flask was flushed with nitrogen gas from a manifold Schlenk line for two min. At this time, the vent needle was removed, and the reaction mixture was stirred at 0°C for 1 hour. At this time, 4-bromo-1,1,1-trifluorobutane (955.0 mg, 1.0 equiv) was added dropwise *via* syringe. After the addition, the flask was removed from the ice bath, and the reaction mixture was stirred at room temperature for 21 h. At this time, H_2O (50 mL) was added, the mixture was transferred to a 250 mL separatory funnel and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and the solution was concentrated *in vacuo*. The resulting crude residue was purified *via* silica gel flash column chromatography on neutralized silica (2% triethylamine, 2% methanol in DCM) (the silica was neutralized by preparing a silica slurry with 2% triethylamine / hexanes solution) to afford (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(6-methoxyquinolin-4-yl)(4,4,4-trifluorobutoxy)methyl)-5-vinylquinuclidine as a hard yellow wax (751.6 mg, 1.75 mmol, 35%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.4 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.48 – 7.28 (m, 3H), 5.73 (ddd, *J* = 17.6, 10.3, 7.6 Hz, 1H), 5.05 (br s, 1H), 5.00 – 4.85 (m, 2H), 3.93 (s, 3H), 3.41 (t, *J* = 6.1 Hz, 2H), 3.34 (s, 1H), 3.09 (dd, *J* = 13.7, 10.0 Hz, 2H), 2.80 – 2.67 (m, 1H), 2.61 (d, *J* = 13.8 Hz, 1H), 2.34 – 2.15 (m, 3H), 1.95 – 1.78 (m, 3H), 1.78 – 1.66 (m, 2H), 1.67 – 1.37 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9, 147.6, 144.8, 144.66, 141.9, 131.9, 127.3, 127.2 (q, *J* = 276.1 Hz), 121.7, 118.7, 114.32, 101.3, 81.9, 67.7, 60.14, 57.1, 55.7, 43.2, 40.0, 31.0 (q, *J* = 29.0 Hz), 27.90, 22.82 (q, *J* = 3.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -66.40 (t, *J* = 10.8 Hz). **IR** (neat, cm^{-1}) 3076, 2938, 2867, 2361, 2341, 1620, 1508, 1252, 1229, 1029, 909, 729. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{24}H_{30}F_3N_2O_2]^+$ = 435.2254, 435.2253 found.

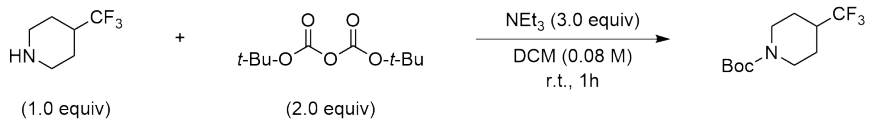
1-((4-chlorophenyl)(phenyl)methyl)-4-(4,4,4-trifluorobutyl)piperazine



Procedure: To a 250 mL, oven-dried round bottom flask 1-((4-chlorophenyl)(phenyl)methyl)piperazine (2.861g, 10.0 mmol) was added. The flask was fitted with a rubber septum and was evacuated and backfilled three times with anhydrous nitrogen gas and left under a positive pressure of nitrogen gas on a manifold Schlenk line. DMF (71 mL, 0.14 M) was added through the septum *via* syringe, and the solution was cooled 0 °C in a 0 °C ice bath. The septum was removed and NaH (60% dispersion in mineral oil, 1.400 g, 3.5 equiv, 35.0 mmol) was added portion-wise. At this time, the flask was resealed with a rubber septum, the septum was pierced with a vent needle, and the flask was flushed with nitrogen gas from a manifold Schlenk line for two min. At this time, the vent needle was removed, and the reaction solution was stirred at 0 °C for 30 min. At this time, 4-bromo-1,1,1-trifluorobutane (2.292 g, 1.2 equiv, 12.0 mmol) was added slowly *via* syringe. The flask was then removed from the ice bath and the reaction mixture was stirred for 14 h at room temperature. At this time, H_2O (50 mL) was added, the mixture was transferred to a 250 mL separatory funnel, and extracted with EtOAc (3 x 50 mL). The combined organic layers were transferred to a 1 L separatory funnel and washed with H_2O (2 x 200 mL). The organic phase was dried over Na_2SO_4, and the solution was transferred to a 250 mL round bottom flask and concentrated *in vacuo*. To remove residual DMF, *n*-heptane (100 mL) was added to the flask and the solution was concentrated *in vacuo*. This process was repeated once more. To further remove DMF, the solution was transferred to a 250 mL separatory funnel with DCM (50 mL) and the solution was washed with H_2O (3 x 100 mL). The organic phase was dried over Na_2SO_4, filtered, transferred to a round bottom flask and concentrated *in vacuo*. To the round

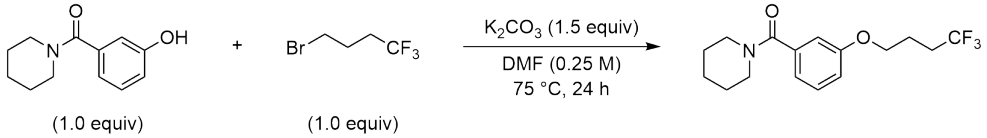
bottom, 50 mL *n*-heptane was added and the mixture was reconcentrated. The resulting crude residue was purified *via* silica gel plug with the eluent conditions 10% EtOAC in hexanes followed by a flush with 50% EtOAC in hexanes to afford 1-((4-chlorophenyl)(phenyl)methyl)-4-(4,4,4-trifluorobutyl)piperazine as a thick yellow wax (2.1511g, 5.40 mmol, 54% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 4H), 7.32 – 7.13 (m, 5H), 4.20 (s, 1H), 2.63 – 2.24 (m, 10H), 2.19 – 2.00 (m, 2H), 1.76 – 1.64 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.3, 141.5, 132.6, 129.3, 128.7, 128.7, 127.9, 127.5 (q, J = 276.12 Hz), 127.2, 75.6, 56.8, 53.3, 51.9, 31.7 (q, J = 28.8 Hz), 19.5 (q, J = 2.8 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -66.37 (t, J = 11.0 Hz). 2955, 2811, 1703, 1601, 1487, 1254, 1133, 1107, 1007, 757, 699. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{25}ClF_3N_2]^+$ = 397.1653, 397.1681 found.

***tert*-Butyl 4-(trifluoromethyl)piperidine-1-carboxylate**



Procedure: To a 250 mL, oven-dried round bottom flask with a magnetic stir bar, 4-(trifluoromethyl)piperidine (765.5 mg, 5.0 mmol) was added *via* pipette. DCM (62.5mL, 0.08 M) was added and the solution was stirred. To the solution triethylamine (2.1 mL, 3.0 equiv) was added *via* syringe followed by di-*tert*-butyl dicarbonate (2.181 g, 2.0 equiv). The flask was loosely sealed with a plastic stopper and the reaction mixture was stirred at room temperature for 1 hour. At this time, H_2O (50 mL) was added, the mixture was transferred to a 250 mL separatory funnel and extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and the solution was concentrated *in vacuo*. The resulting crude residue was purified via flash column chromatography (5% EtOAc in hexanes) to afford *tert*-butyl 4-(trifluoromethyl)piperidine-1-carboxylate as a white powder (575.9 mg, 2.25 mmol, 45%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.22 (br s, 2H), 2.71 (t, J = 13.1 Hz, 2H), 2.27 – 2.09 (m, 1H), 1.86 (d, J = 13.1 Hz, 2H), 1.58 – 1.49 (m, 2H), 1.48 (s, 9H). The spectroscopic data is consistent with a previous report. We note that this compound is commercially available.[13]

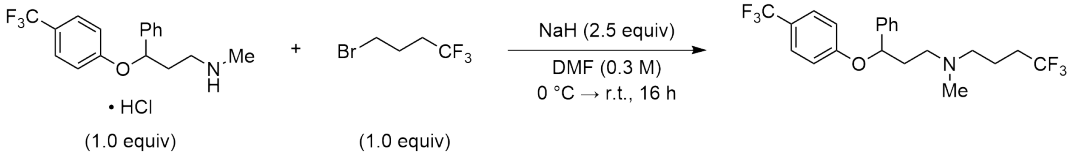
Piperidin-1-yl(3-(4,4,4-trifluorobutoxy)phenyl)methanone



Procedure: In a 25 mL, oven-dried round bottom flask (3-hydroxyphenyl)(piperidin-1-yl)methanone (650.7 mg, 3.17 mmol) and potassium carbonate (657.8 mg, 4.8 mmol, 1.5 equiv) were combined. DMF (12.7 mL, 0.25M) was added was added *via* syringe. 4-Bromo-1,1,1-trifluorobutane (605.4 mg, 3.17 mmol, 1.0 equiv) was added *via* syringe. The flask was fitted with a reflux condenser, placed in an oil bath preheated to 75 °C, and the reaction was stirred for 24h. At this time, the flask was removed from the oil bath and the reaction mixture was cooled to rt. The reaction mixture was then transferred to a 250 mL separatory funnel and H_2O (50 mL) was added. The mixture was extracted with EtOAc (3 x 50 mL), the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified *via* silica gel flash column chromatography (1:1 EtOAc:hexanes) to afford piperidin-1-yl(3-(4,4,4-trifluorobutoxy)phenyl)methanone as a white powder (436.3 mg, 1.39 mmol, 44%). **MP:** 36-39 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 1H), 7.04 – 6.86 (m, 3H), 4.05 (t, J = 6.0 Hz, 2H), 3.72 (br

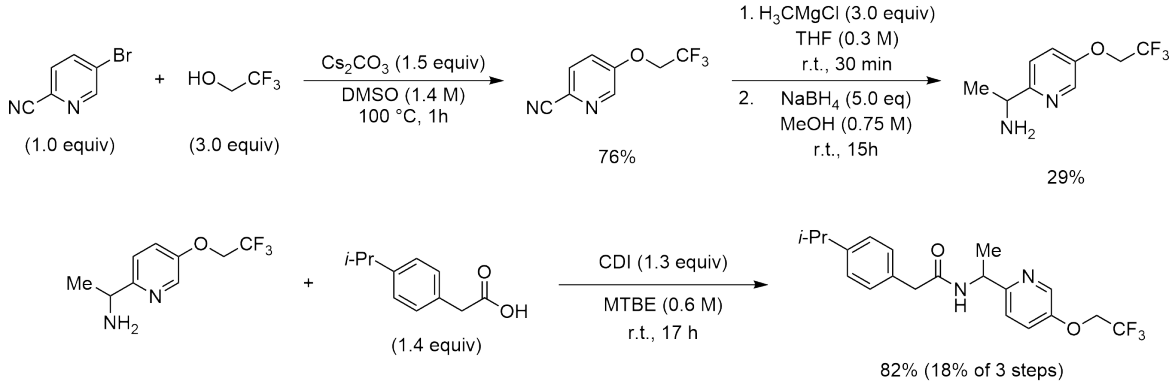
s, 2H), 3.36 (br s, 2H), 2.46 – 2.24 (m, 2H), 2.21 – 1.99 (m, 2H), 1.89 – 1.38 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.9, 158.7, 138.0, 129.6, 127.2 (q, J = 276.1 Hz), 119.2, 115.7, 112.8, 66.1, 48.7, 43.1, 30.7 (q, J = 29.2 Hz), 26.6, 25.6, 24.6, 22.2 (q, J = 3.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -66.35 (t, J = 10.8 Hz). **IR** (neat, cm^{-1}) 2947, 2864, 2360, 1625, 1584, 1439, 1243, 1133, 1025, 801. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{16}H_{21}F_3NO_2]^+$ = 316.1519, 316.1598 found.

4,4,4-trifluoro-*N*-methyl-N-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butan-1-amine



Procedure: To a 50 mL, flame-dried round bottom flask with a magnetic stir bar, (±)-*N*-Methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propylamine hydrochloride (691.6 mg, 2.0 mmol) was added. DMF (6.7 mL, 0.3 M) was added *via* syringe, the flask was placed in a 0 °C ice bath, and the solution was stirred at 0 °C for 5 min. NaH (60% dispersion in mineral oil, 200 g, 2.5 equiv, 5.0 mmol) was added portion-wise. The flask was loosely covered with a plastic stopper and the reaction mixture was stirred for 1 h at 0 °C. At this time the stopper was removed and 4-bromo-1,1,1-trifluorobutane (382.0 mg, 1.0 equiv, 2.0 mmol) was added *via* syringe. The flask was loosely covered with a plastic stopper and removed from the ice bath. The reaction was stirred at room temperature for 16 hours. At this time, H_2O (20 mL) was added, the mixture was transferred to a 250 mL separatory funnel and extracted with DCM (3 x 50 mL). The combined organic layers were transferred to a 250 mL separatory funnel and washed with H_2O (3 x 40 mL). The resulting organic solution was dried over Na_2SO_4, filtered, transferred to a 500 mL round bottom flask, and concentrated *in vacuo*. To the resulting concentrated mixture, *n*-heptane (50 mL) was added and the solution was reconcentrated *in vacuo*. To the crude concentrate, *n*-hexane (50 mL) was added to yield a cloudy solution. To the solution, HCl (4M in dioxane, 1 mL, 4.0 mmol) to yield a yellow sticky wax. The hexane solution was decanted and the solid was rinsed with *n*-hexane (50 mL) and decanted again. To the flask containing the crude solid, NaOH (2 M in H_2O, 50 mL) and DCM (100 mL) were added and the biphasic mixture was transferred to a 250 mL separatory funnel and extracted with DCM (1 x 100 mL, 2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude oil was taken up with DCM and filtered through silica *via* vacuum filtration with 10% MeOH in DCM (60 mL) to afford the title product as a bronze oil (426.5 mg, 1.02 mmol, 51% yield **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 5.0 Hz, 4H), 7.30 – 7.23 (m, 1H), 6.89 (d, J = 8.6 Hz, 2H), 5.28 (dd, J = 8.5, 4.6 Hz, 1H), 2.57 (dt, J = 12.4, 7.3 Hz, 1H), 2.41 (m, 3H), 2.20 (s, 3H), 2.20 – 1.89 (m, 4H), 1.75 – 1.49 (m, 2H). **^{13}C NMR** (101 MHz, CD_3CN) δ 162.1, 162.1 142.5, 129.7, 128.9 (q, J = 275.3 Hz), 127.7 (q, J = 3.8 Hz), 127.2, 125.7 (q, J = 270.4 Hz) 123.0 (q, J = 32.4 Hz), 117.1, 78.9, 56.9, 54.2, 42.0, 37.1, 31.8 (q, J = 28.3 Hz), 20.7 (q, J = 2.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.77 (d, J = 271.2 Hz), -66.49 (d, J = 276.0 Hz). **IR** (neat, cm^{-1}) 2956, 2801, 2360, 1615, 1517, 1325, 1248, 1159, 1108, 1067, 834, 700. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{24}F_6NO]^+$ = 420.1757, 420.1765 found.

2-(4-isopropylphenyl)-*N*-(1-(5-(2,2,2-trifluoroethoxy)pyridine-2-yl)ethyl)acetamide



Procedure:

Step 1: (5-(2,2,2-trifluoroethoxy)picolinonitrile): In a 100 mL flame-dried flask with a magnetic stir bar, 5-bromopicolinonitrile (3.66 g, 20.0 mmol), Cs_2CO_3 (9.774 g, 1.5 equiv, 30.0 mmol), and dimethyl sulfoxide (DMSO, 14.4 mL, 1.4 M) were combined. Trifluoroethanol (6.00 g, 60.0 mmol) was added *via* syringe, the round bottom flask was fitted with a reflux condenser and placed in an oil bath preheated to 100 °C. The reaction mixture was stirred for 1 h at 100 °C. At this time, the flask was removed from the oil bath, and the reaction mixture was cooled to room temperature. The mixture was transferred to a 250 mL separatory funnel with EtOAc and H_2O (50 mL) and was extracted with ethyl acetate (3 x 100 mL). The resulting organic phase was transferred to a round bottom flask and concentrated *in vacuo* to remove EtOAc. The resulting aqueous mixture was transferred to a 250 mL separatory funnel with toluene (50 mL) and was washed with H_2O (3 x 150 mL). The resulting organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the titled product as a white powder (3.057 g, 15.2 mmol, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (dd, J = 2.9, 0.7 Hz, 1H), 7.71 (dd, J = 8.7, 0.6 Hz, 1H), 7.33 (dd, J = 8.6, 3.0 Hz, 1H), 4.49 (q, J = 7.7 Hz, 2H). The spectroscopic data is consistent with a previous report.[14]

Step 2: (1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethan-1-amine):

A 100 mL round bottom flask fitted with a rubber septum was evacuated and backfilled with nitrogen gas three times and left under a positive pressure of nitrogen gas on a manifold Schlenk line. To the flask, tetrahydrofuran (THF, 20 mL) was added *via* syringe. Methylmagnesiumchloride (3M in THF, 15.1 mL, 45.4 mmol, 3.0 equiv) was then added *via* syringe. In a 20 mL oven-dried scintillation vial, 2,2,2-trifluoroethoxy)picolinonitrile (3.0566g, 15.2 mmol) was dissolved in THF (15 mL) and was taken up into a 20 mL syringe. The 2,2,2-trifluoroethoxy)picolinonitrile solution was added to the methylmagnesiumchloride solution using a syringe pump over the course of 30 min. After addition was complete, the reaction mixture was cooled to 0 °C in an ice bath, methanol (10 mL) was added dropwise, and the solution was then concentrated *in vacuo*. The resulting solid was taken up with dichloromethane and transferred to a 100 mL, oven-dried round bottom flask and concentrated *in vacuo*. To the flask, methanol (20 mL, 0.76 M) was added. The flask was placed in a 0 °C ice bath and the solution cooled to 0 °C. At this time, $NaBH_4$ (2.860 g, 75.6 mmol, 5.0 equiv) was added in 5 portions (**Note:** this addition is very exothermic). When the addition was complete, the reaction mixture was placed in a room temperature water bath, the flask was loosely covered with a plastic stopper and the reaction was stirred for 15 h at room temperature. At this time, the flask was placed in a 0 °C ice bath. H_2O (30 mL) was added, the resulting solution was transferred to a 250 mL separatory funnel, and the flask was rinsed with EtOAc (40 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4,

filtered, and concentrated *in vacuo*. The residue was purified *via* silica gel flash column chromatography with eluent conditions 100% methanol to 2% triethylamine in methanol to afford the titled product as a bronze oil (954.3 mg, 4.4 mmol, 29%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 2.9 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.26 (dd, *J* = 8.6, 2.9 Hz, 1H), 4.41 (q, *J* = 8.0 Hz, 2H), 4.17 (q, *J* = 6.7 Hz, 1H), 1.72 (s, 2H), 1.43 (d, *J* = 6.7 Hz, 3H). The spectroscopic data is consistent with a previous report.[14]

Step 3: (2-(4-isopropylphenyl)-*N*-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide): To a 100 mL, oven-dried round bottom flask, 2-(4-isopropylphenyl)acetic acid (1.079 g, 6.06 mmol, 1.4 equiv) was added. Methyl *tert*-butyl ether (MTBE, 5.7 mL) was added *via* syringe followed by carbonyldiimidazole portionwise (CDI, 908.3 mg, 5.6 mmol, 1.3 equiv), and the reaction mixture was stirred for 2 h at room temperature. At this time, 1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethan-1-amine (2.9 M in MTBE, 1.5 mL, 4.4 mmol) was added *via* syringe. The reaction mixture was stirred at room temperature for 17 hours. At this time, the crude reaction mixture was added to a 500 mL Erlenmeyer flask containing H_2O (100 mL) and a stir bar under vigorous stirring to afford a white precipitate. The crude titled product was recrystallized in *n*-hexane to afford the titled product as a white powder (1.361 g, 3.53 mmol, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 2.8, 0.8 Hz, 1H), 7.24 – 7.13 (m, 6H), 6.63 (d, *J* = 7.6 Hz, 1H), 5.10 (p, *J* = 6.9 Hz, 1H), 4.37 (q, *J* = 8.0 Hz, 2H), 3.55 (d, *J* = 1.2 Hz, 2H), 2.90 (hept, *J* = 6.9 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 6H).The spectroscopic data is consistent with a previous report.[14]

VII. References

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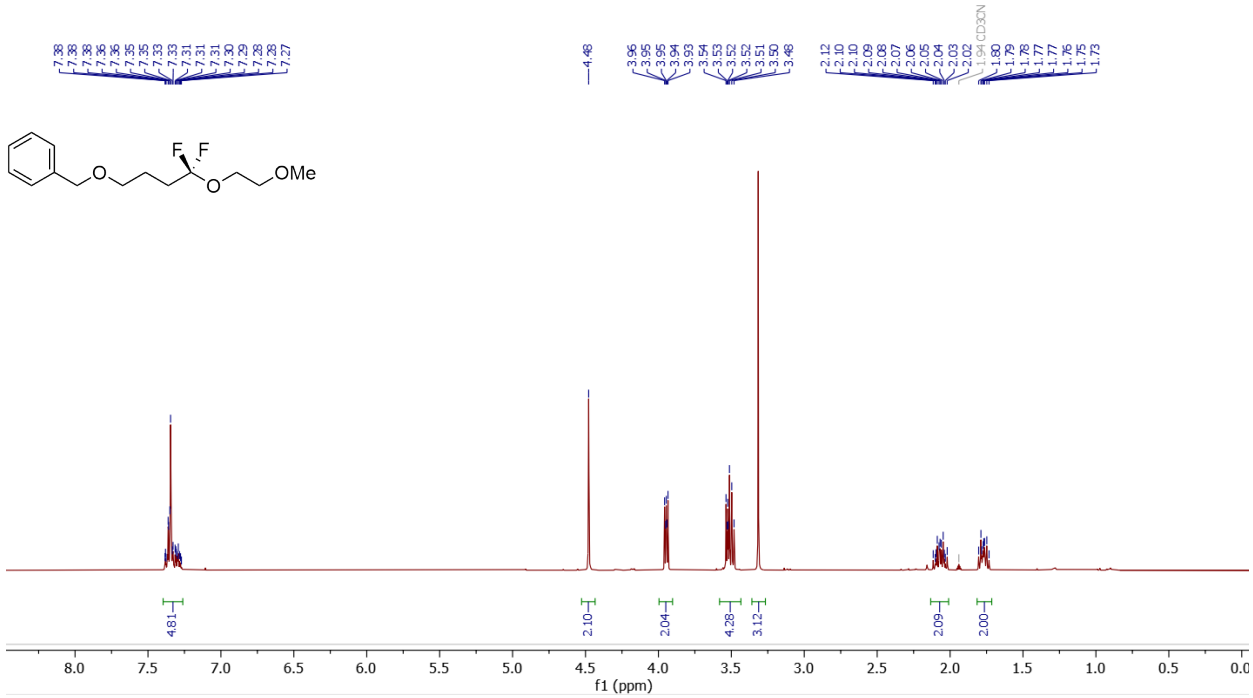
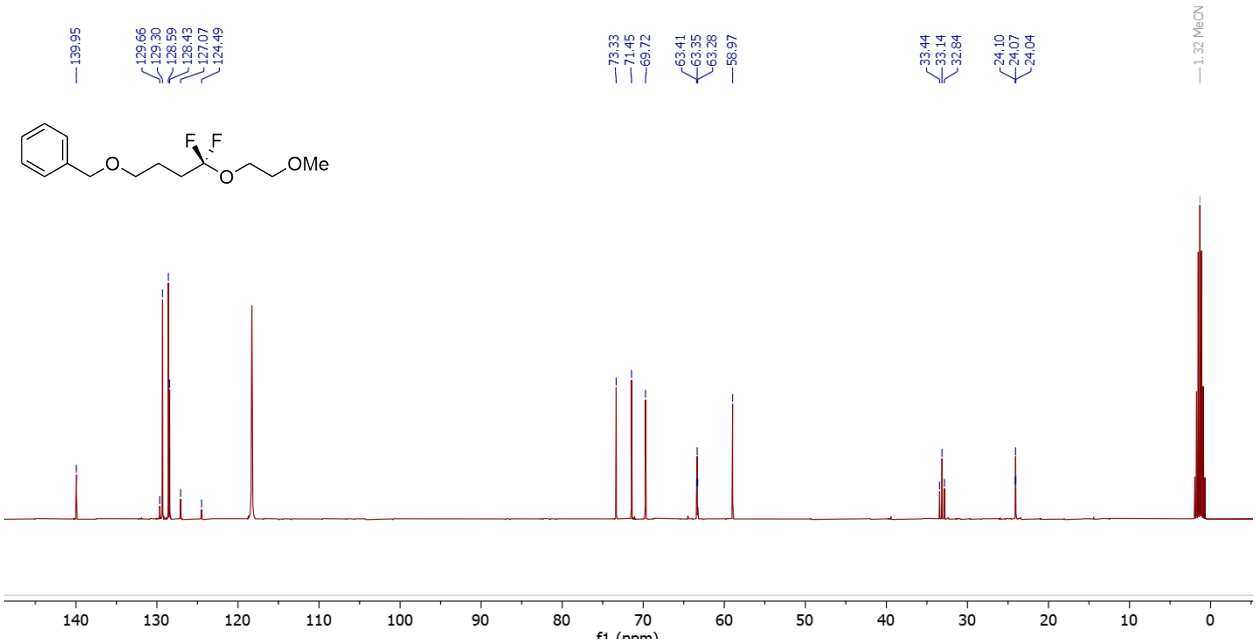
VIII. NMR Spectra

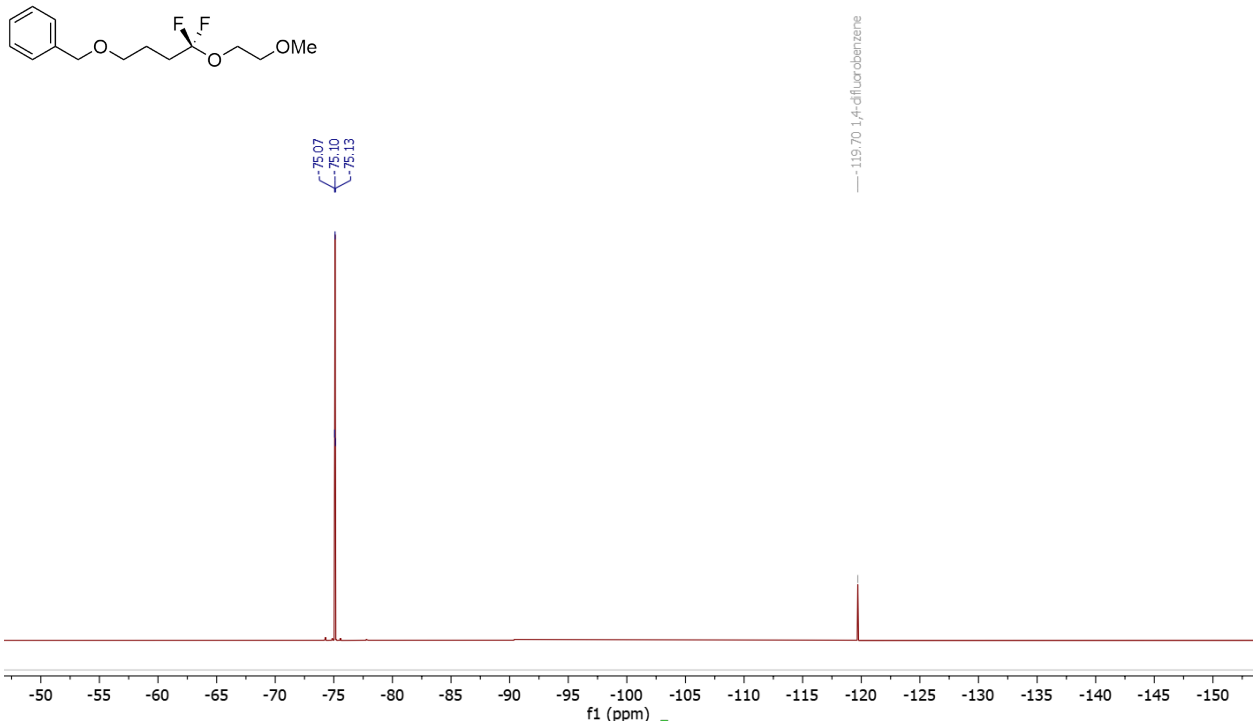
((4,4-difluoro-4-(2-methoxyethoxy)butoxy)methyl)benzene (5)



^{1}H NMR spectrum of **5** (400 MHz, CD_3CN)

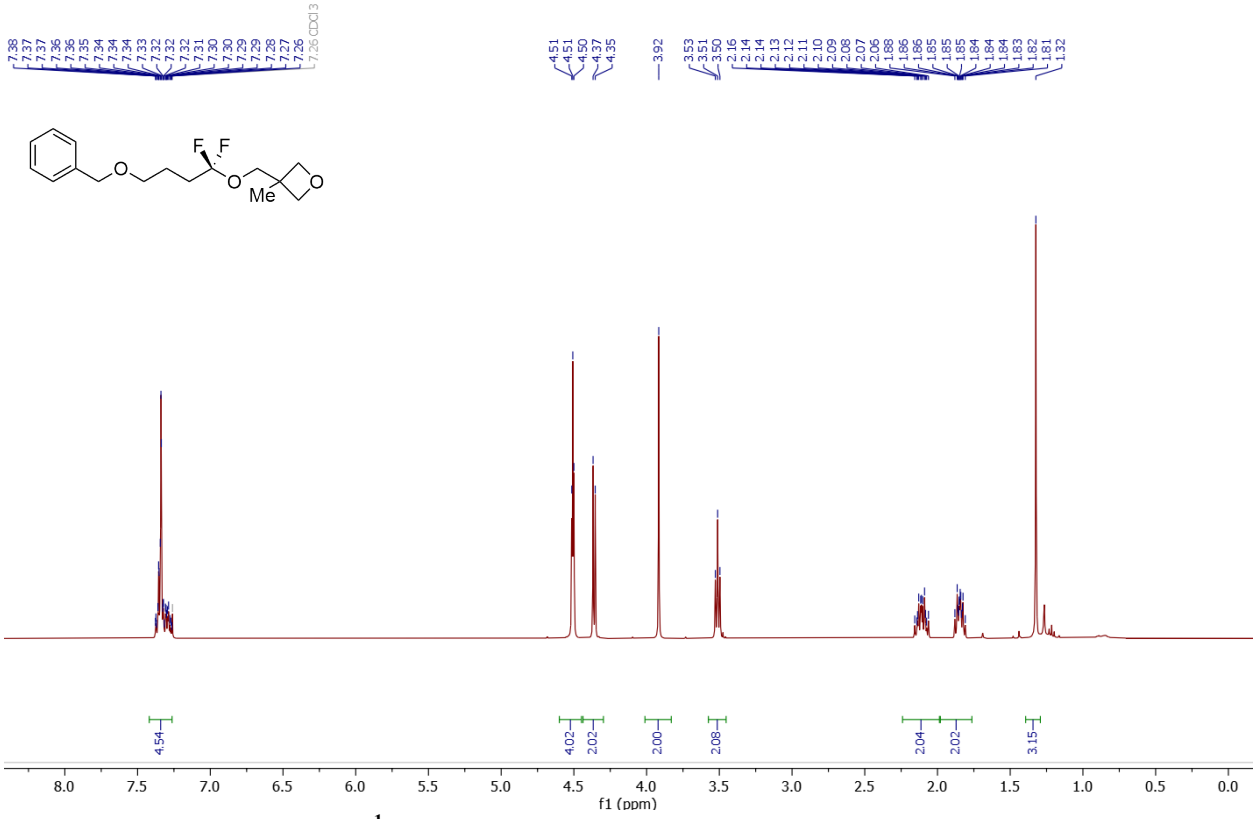


^{13}C NMR spectrum of **5** (101 MHz, CD_3CN)

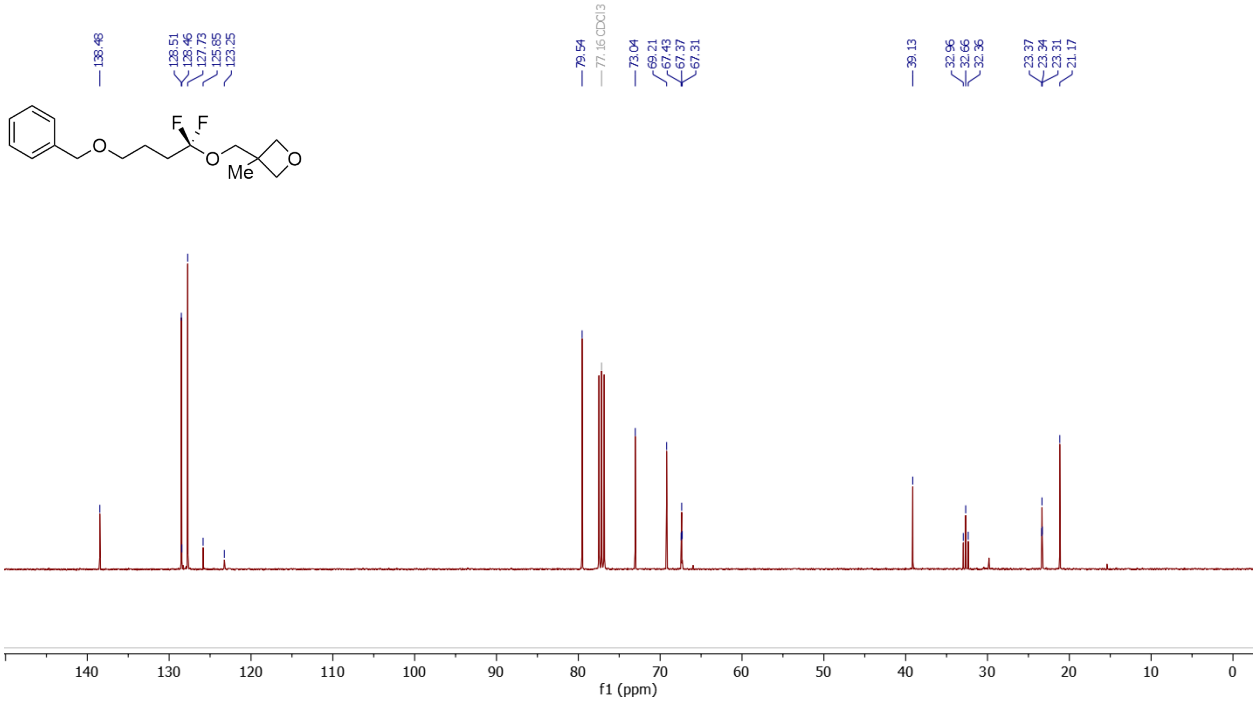


^{19}F NMR spectrum of **5** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

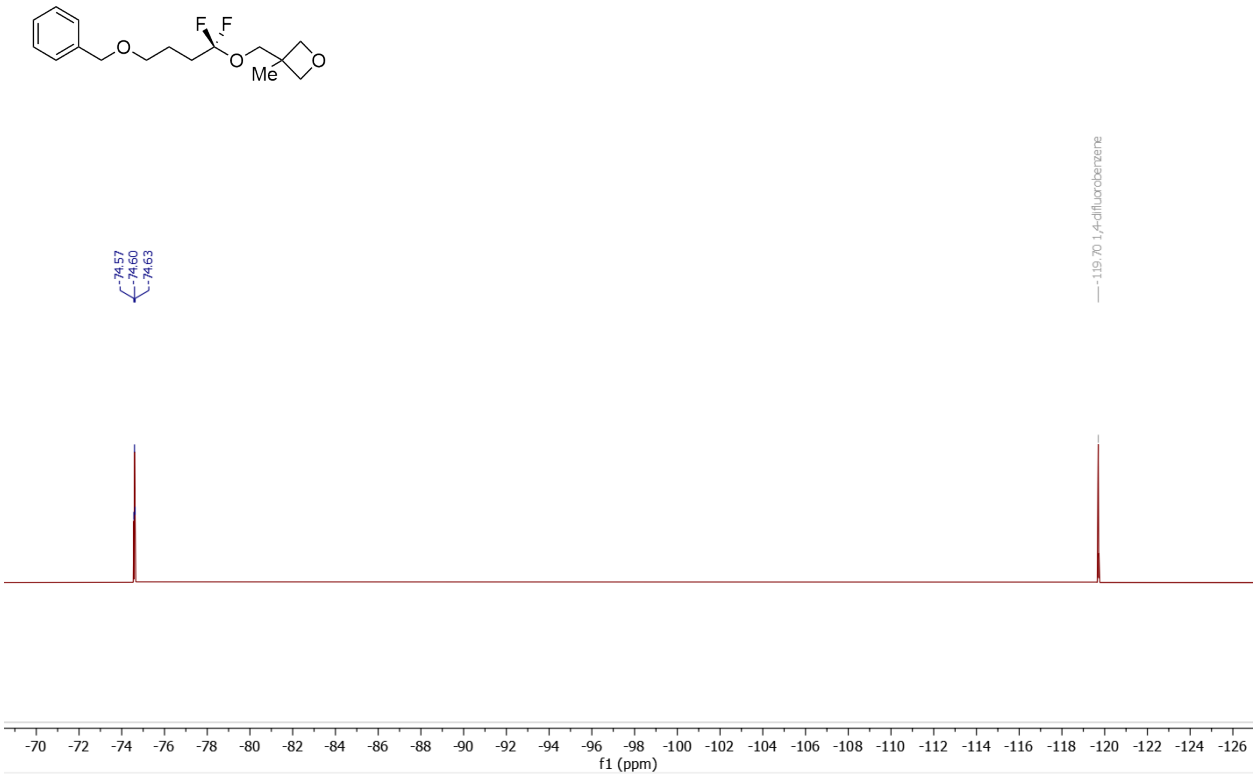
3-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-3-methyloxetane (6)



^{1}H NMR spectrum of **6** (400 MHz, $CDCl_3$)

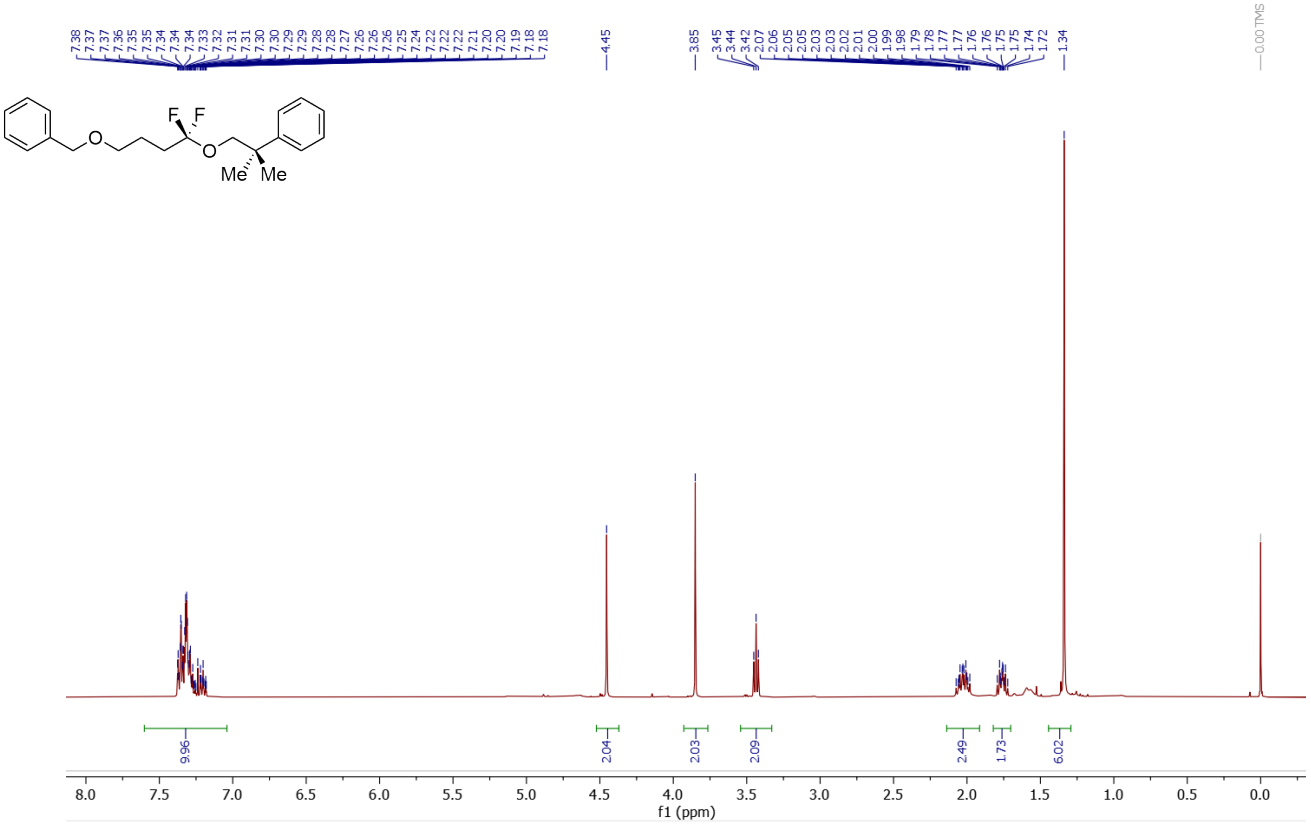


^{13}C NMR spectrum of **6** (101 MHz, $CDCl_3$)

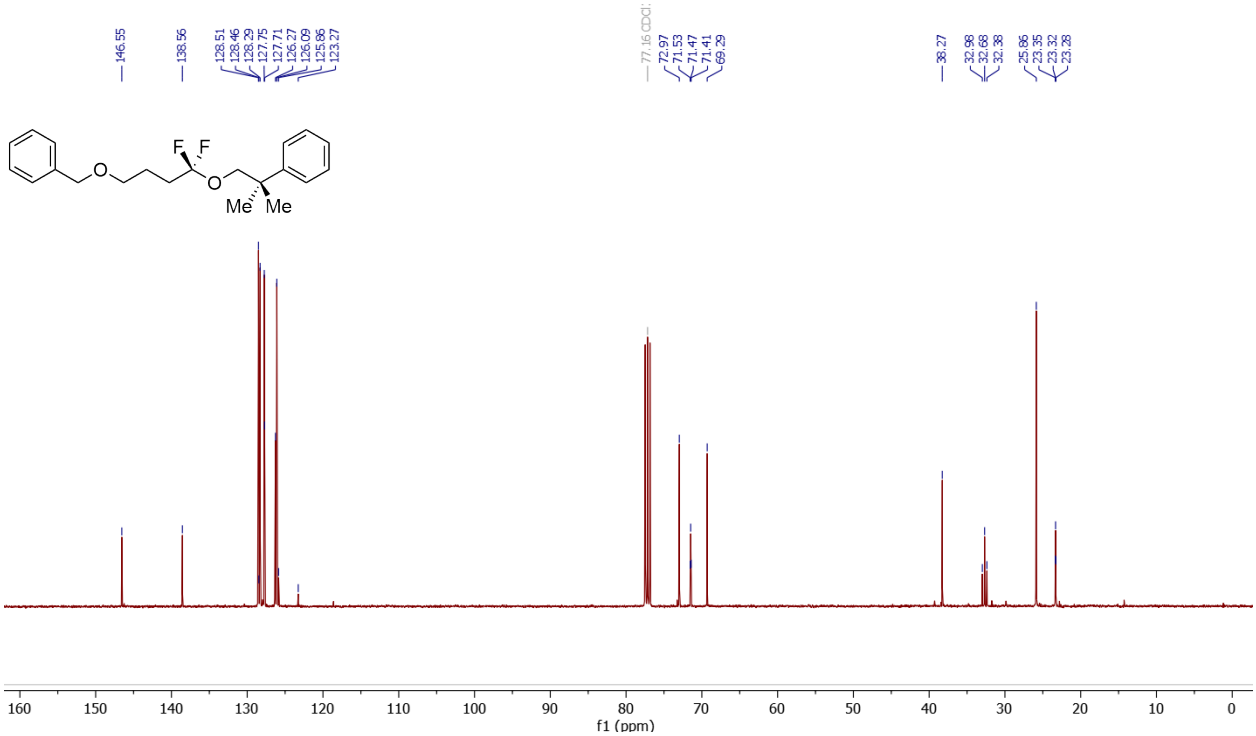


^{19}F NMR spectrum of **6** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

(1-(4-(benzyloxy)-1,1-difluorobutoxy)-2-methylpropan-2-yl)benzene (7)



^{1}H NMR spectrum of **7** (400 MHz, $CDCl_3$)



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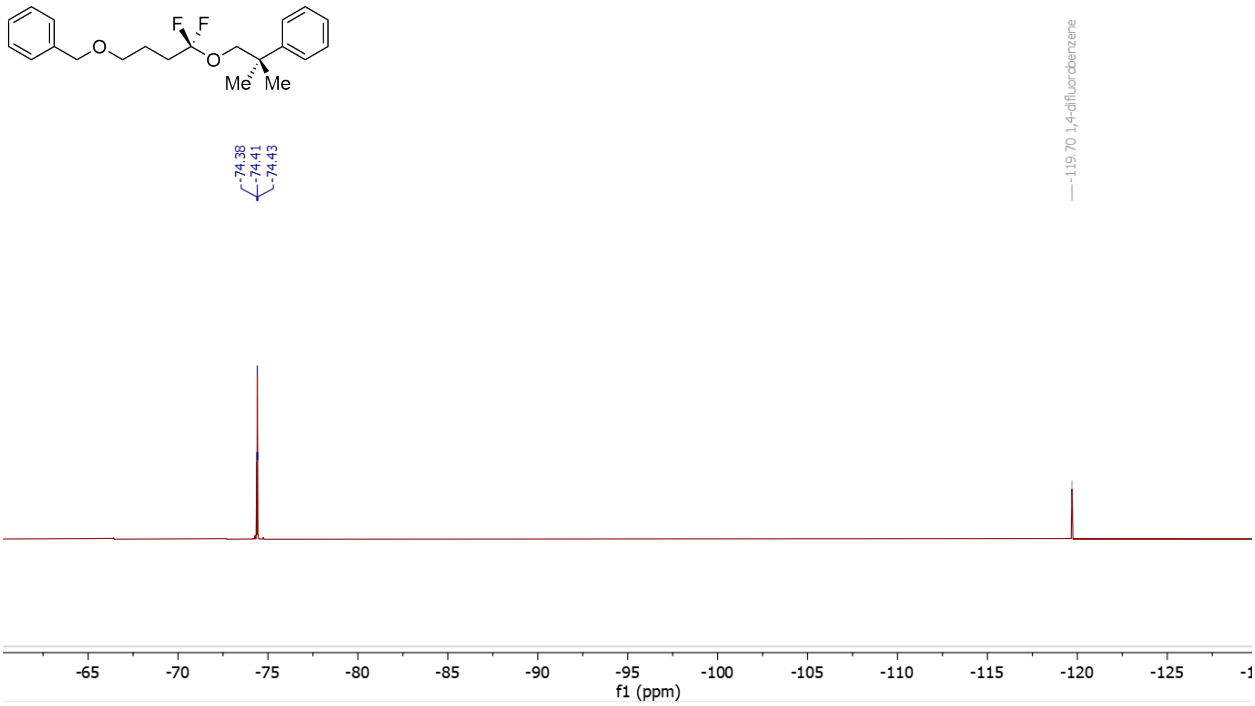
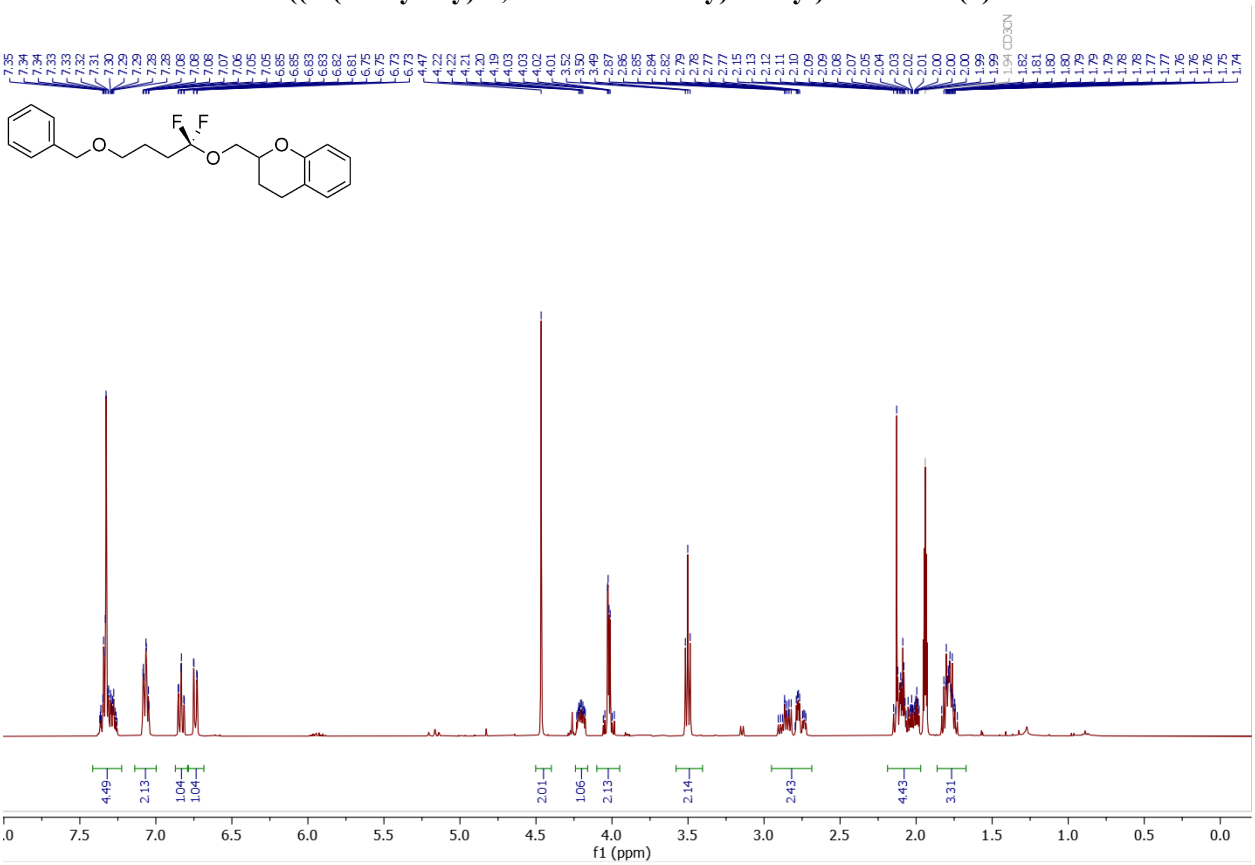
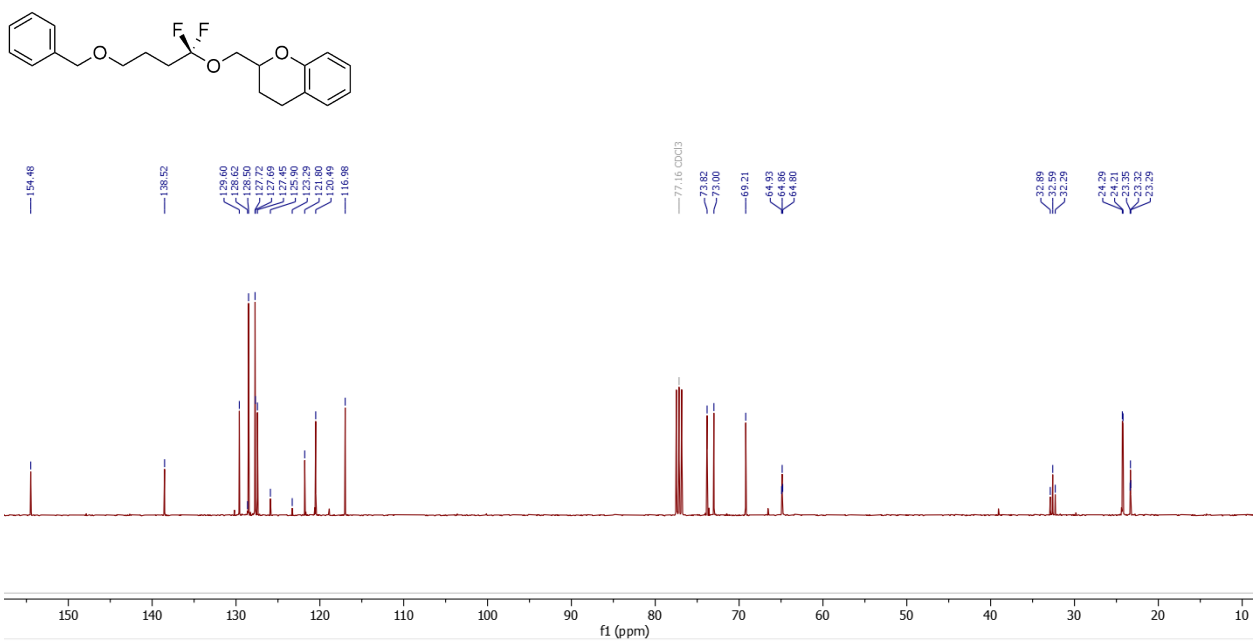


^{19}F NMR spectrum of **7** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

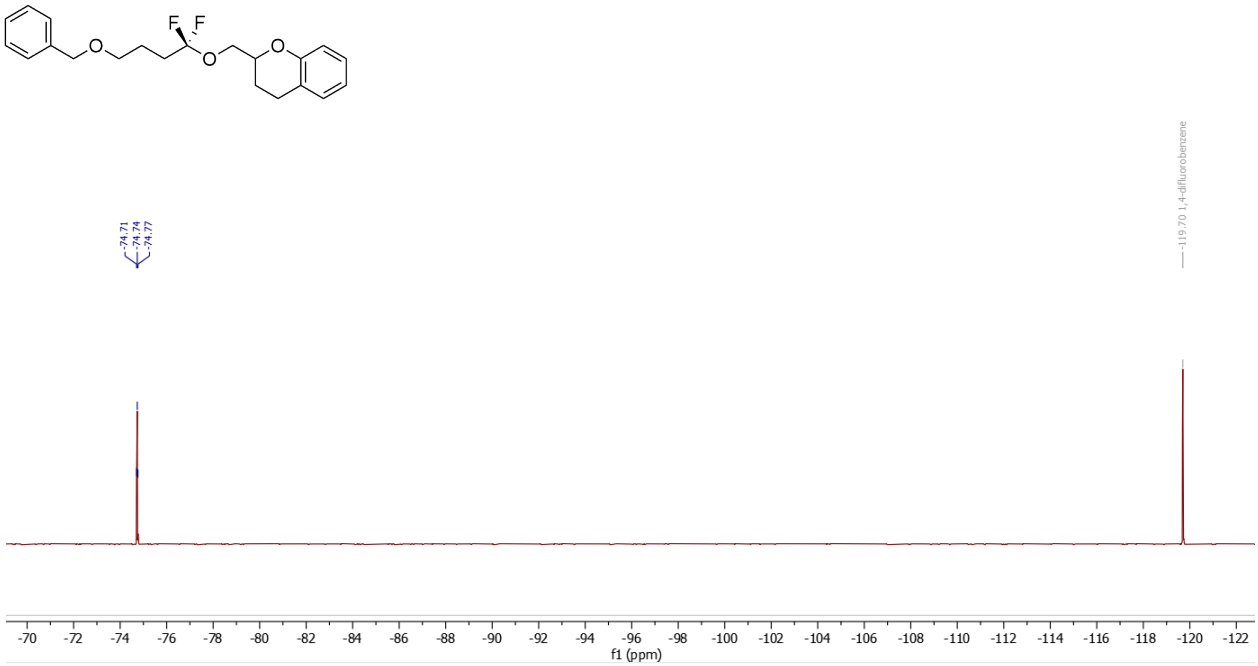
2-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)chromane (8)



^{1}H NMR spectrum of **8** (400 MHz, CD_3CN)

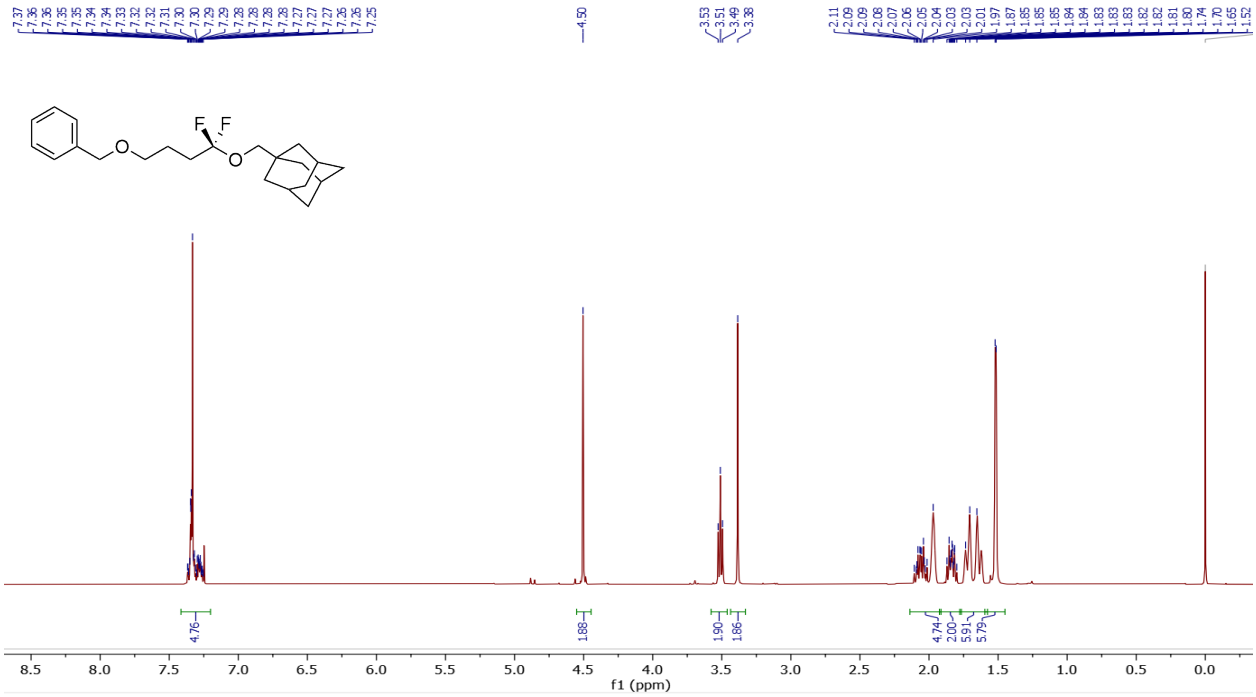


^{13}C NMR spectrum of **8** (101 MHz, $CDCl_3$)

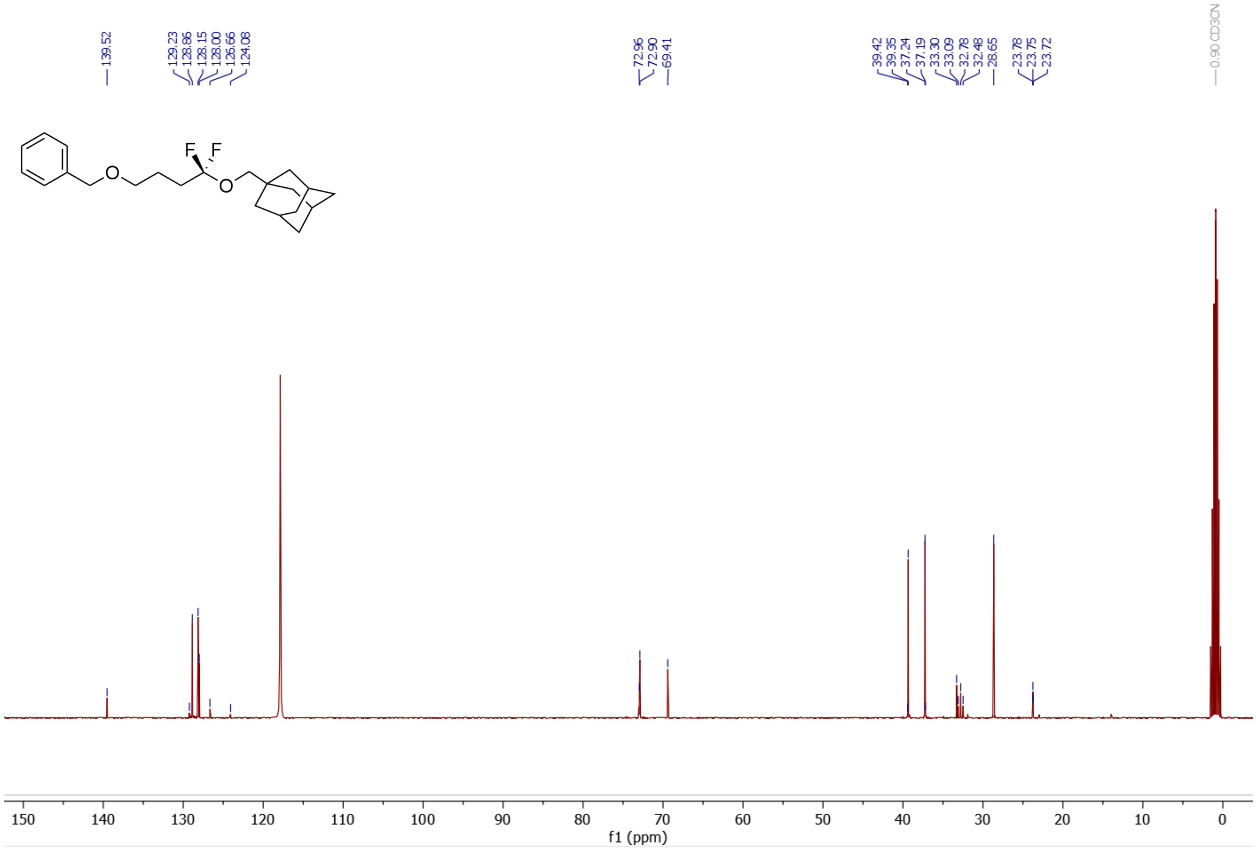


^{19}F NMR spectrum of **8** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

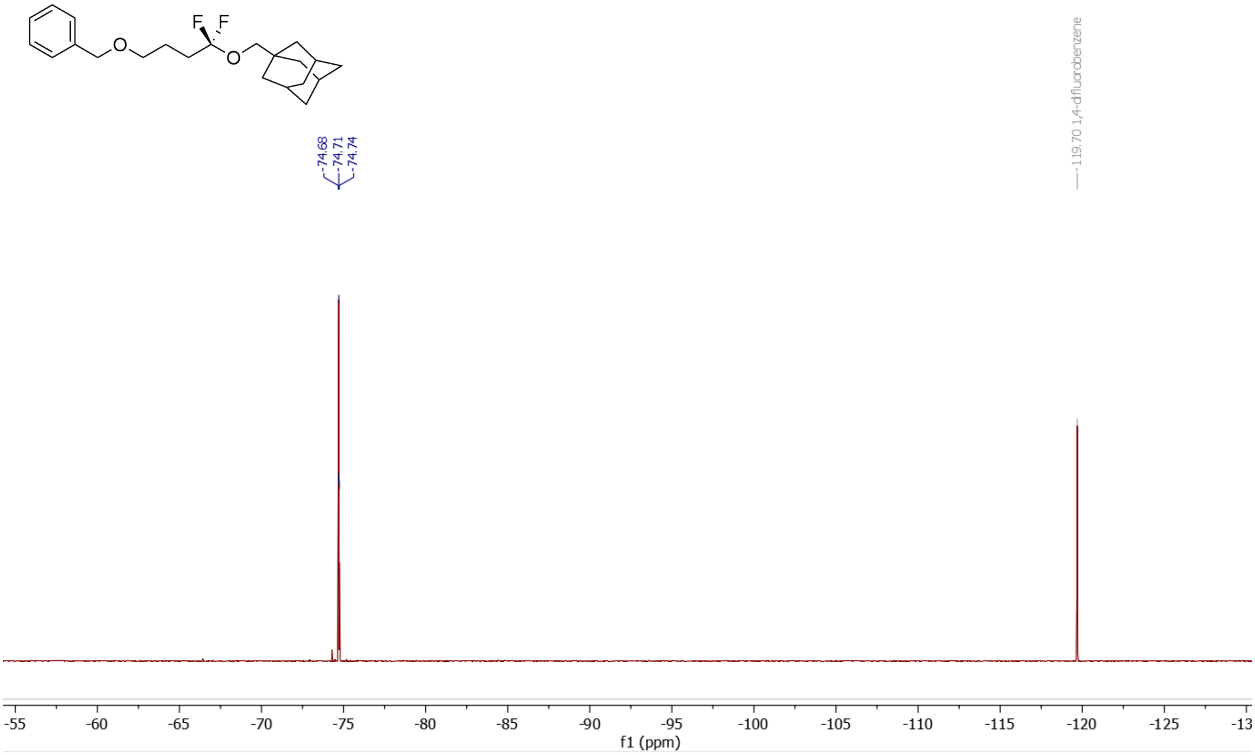
1-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)adamantane (9)



^{1}H NMR spectrum of **9** (400 MHz, $CDCl_3$)

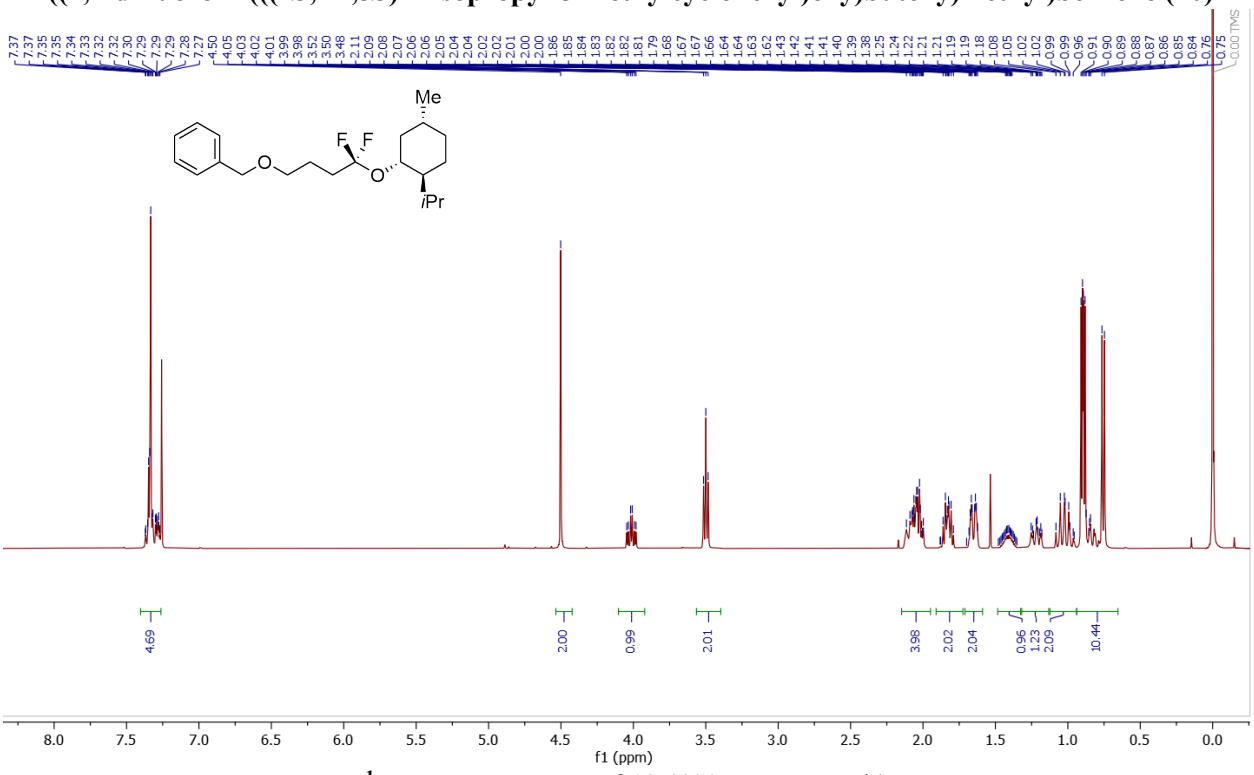


^{13}C NMR spectrum of **9** (101 MHz, CD_3CN)

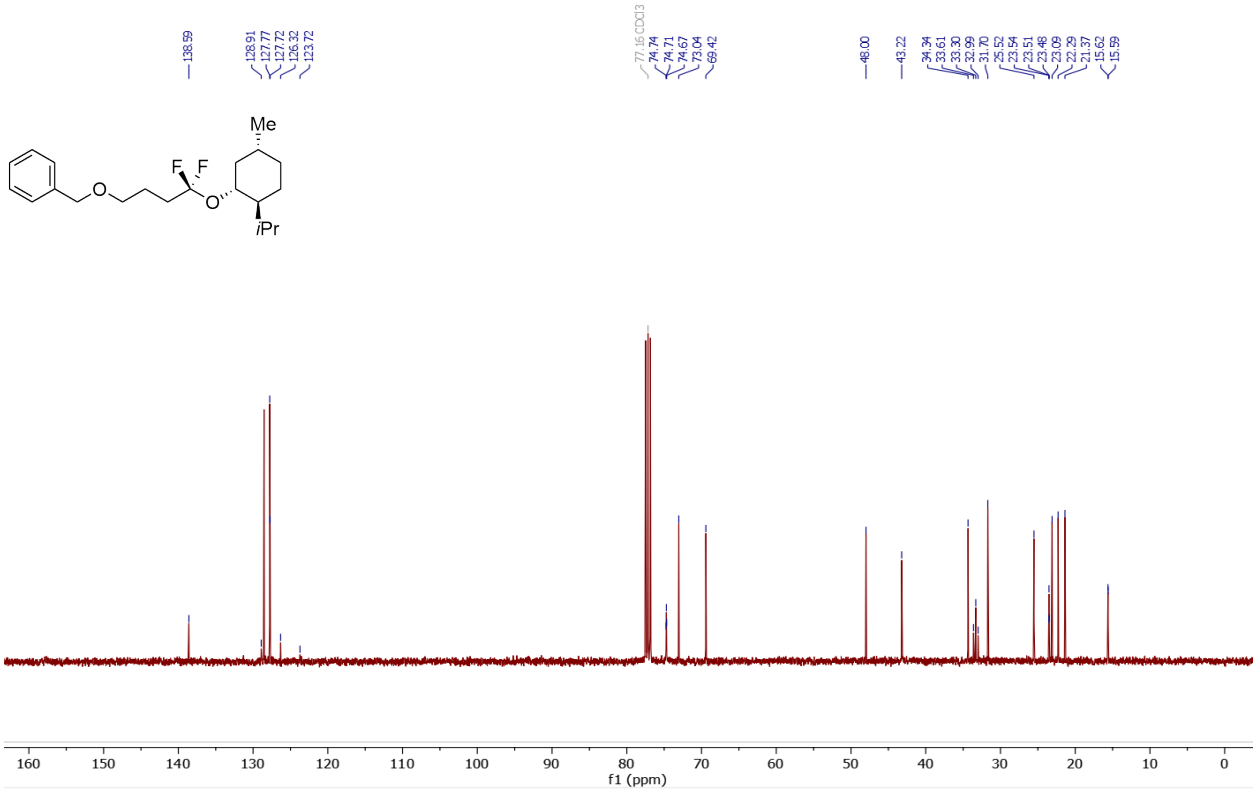


^{19}F NMR spectrum of **9** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

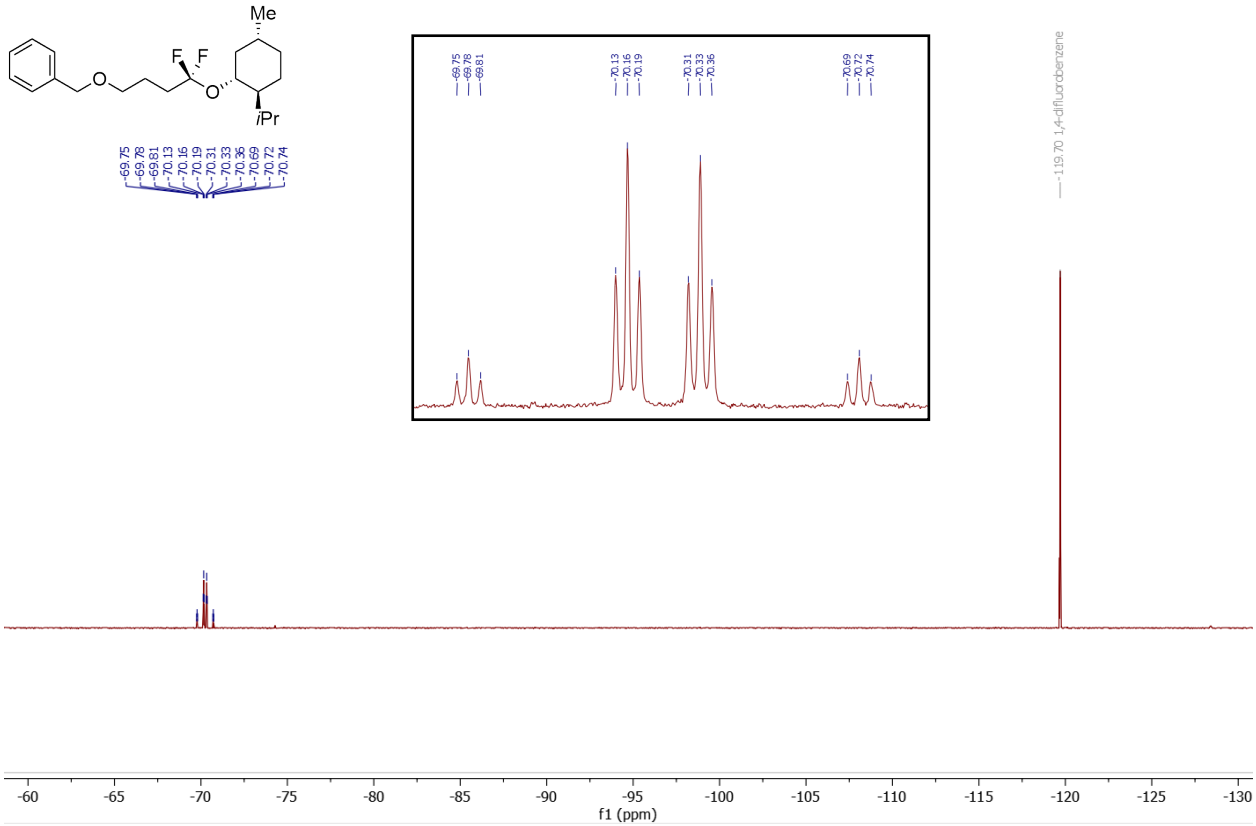
((4,4-difluoro-4-(((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl)oxy)butoxy)methyl)benzene (10)



^{1}H NMR spectrum of **10** (400 MHz, $CDCl_3$)

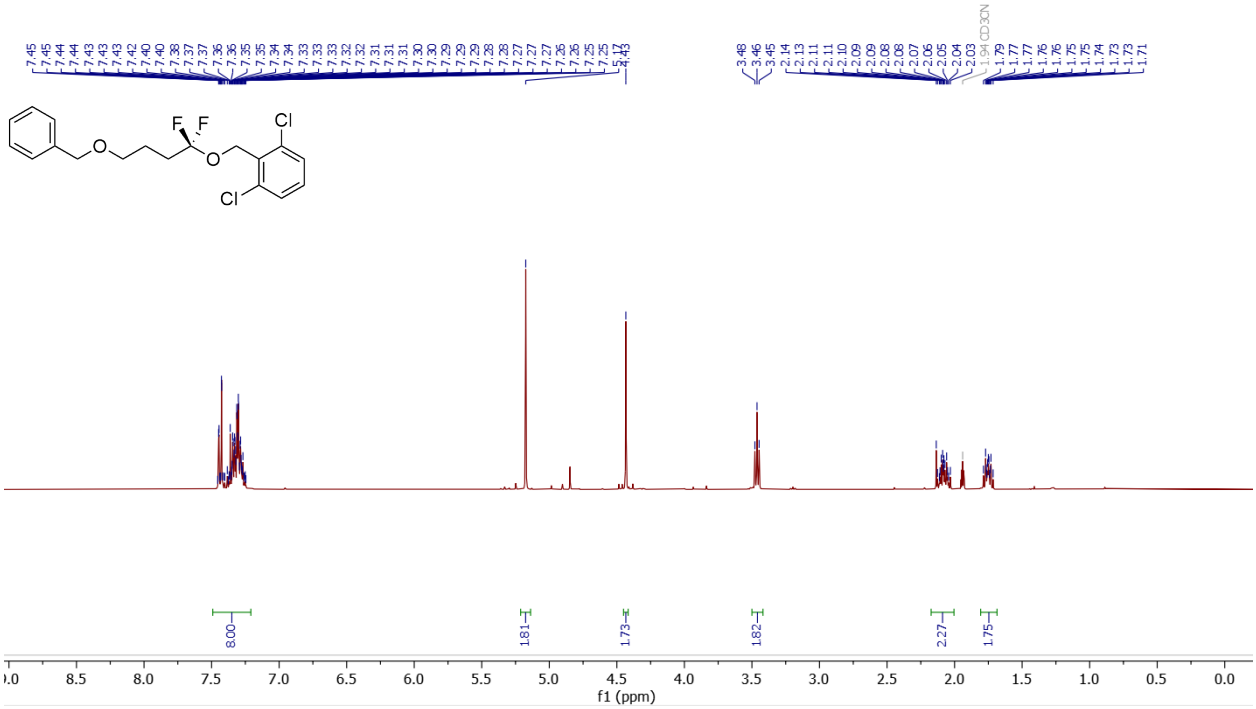


^{13}C NMR spectrum of **10** (101 MHz, $CDCl_3$)

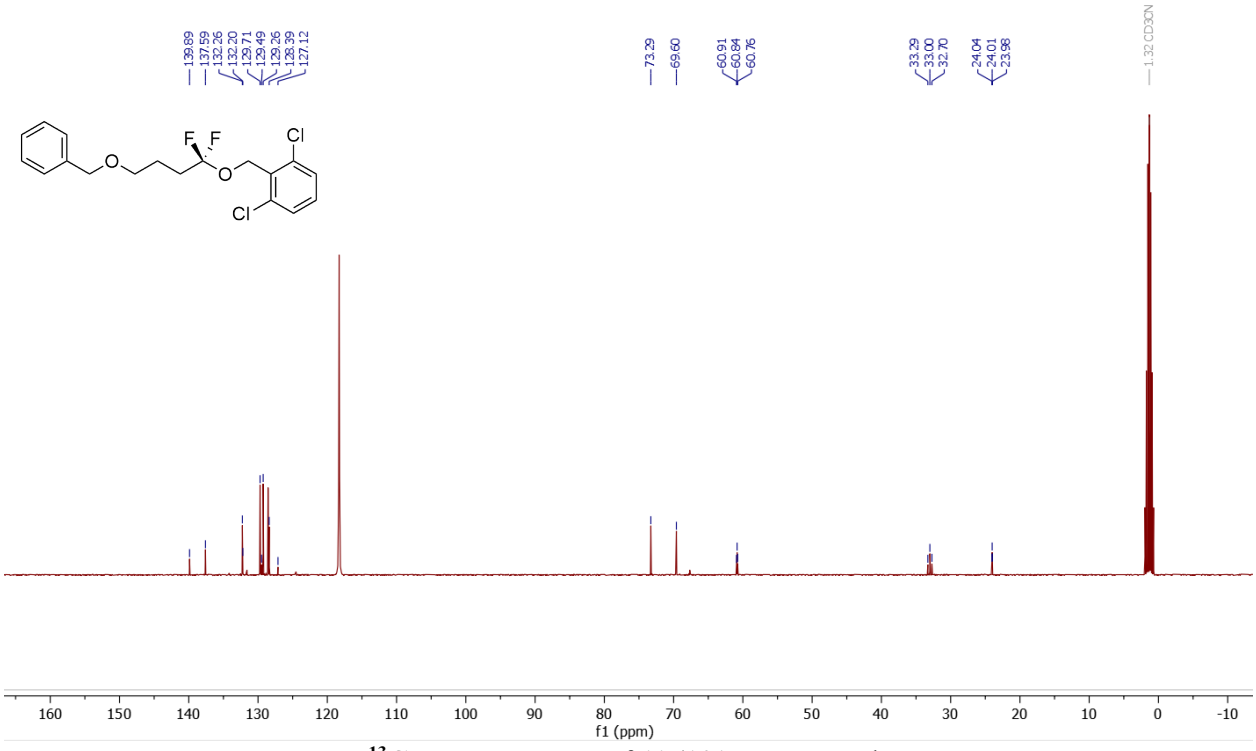


^{19}F NMR spectrum of **10** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

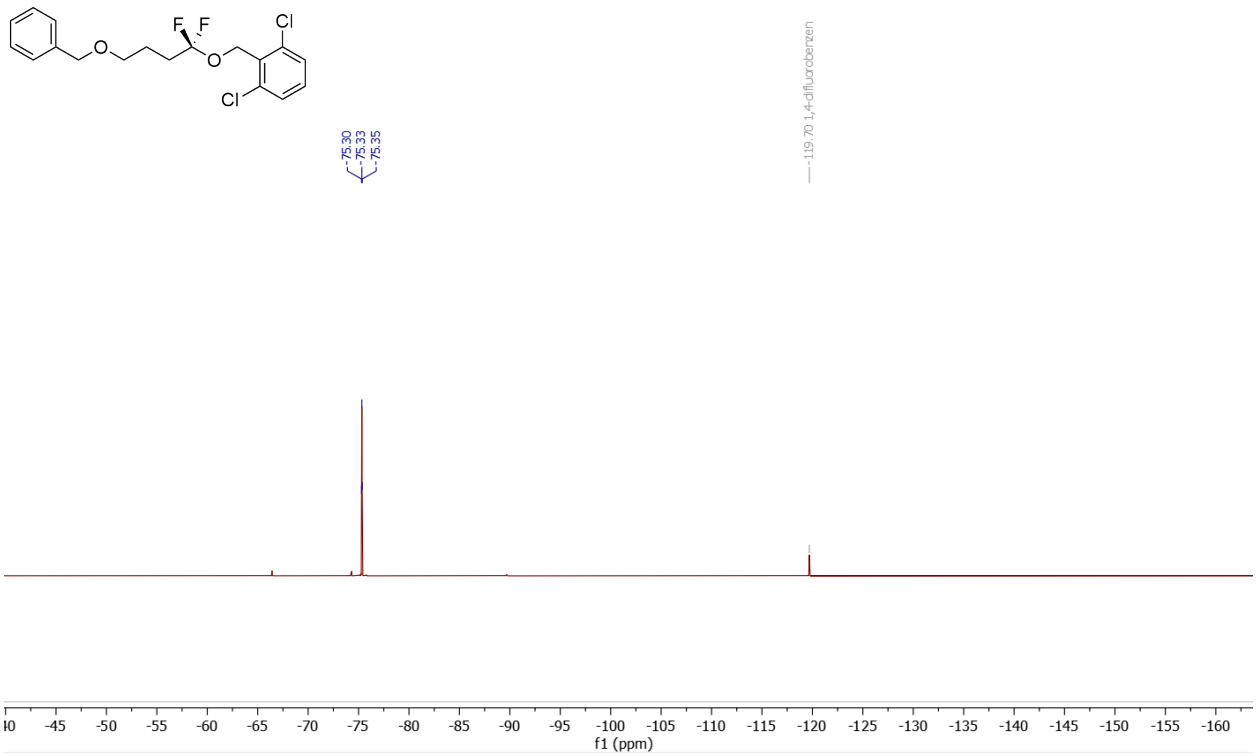
2-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-1,3-dichlorobenzene (11)



^{1}H NMR spectrum of **11** (400 MHz, CD_3CN)

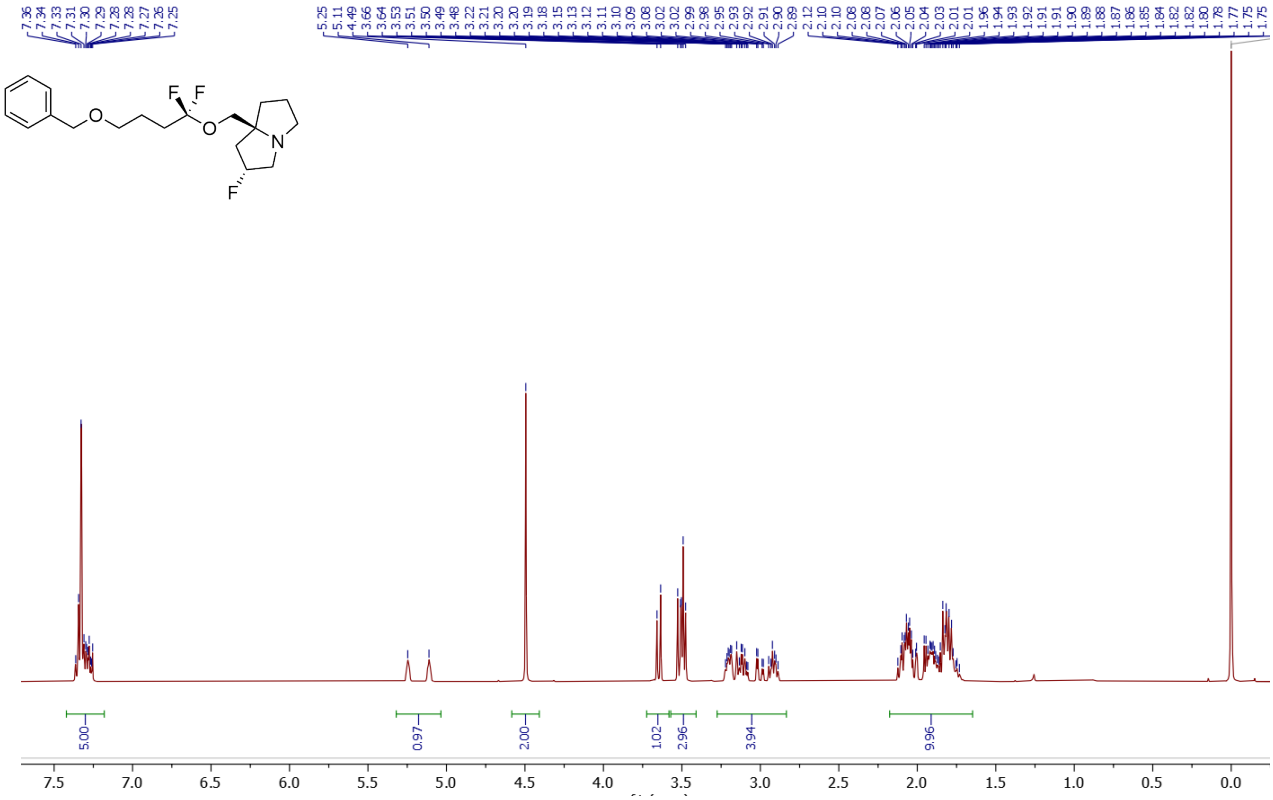


^{13}C NMR spectrum of **11** (101 MHz, $CDCl_3$)

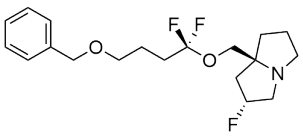


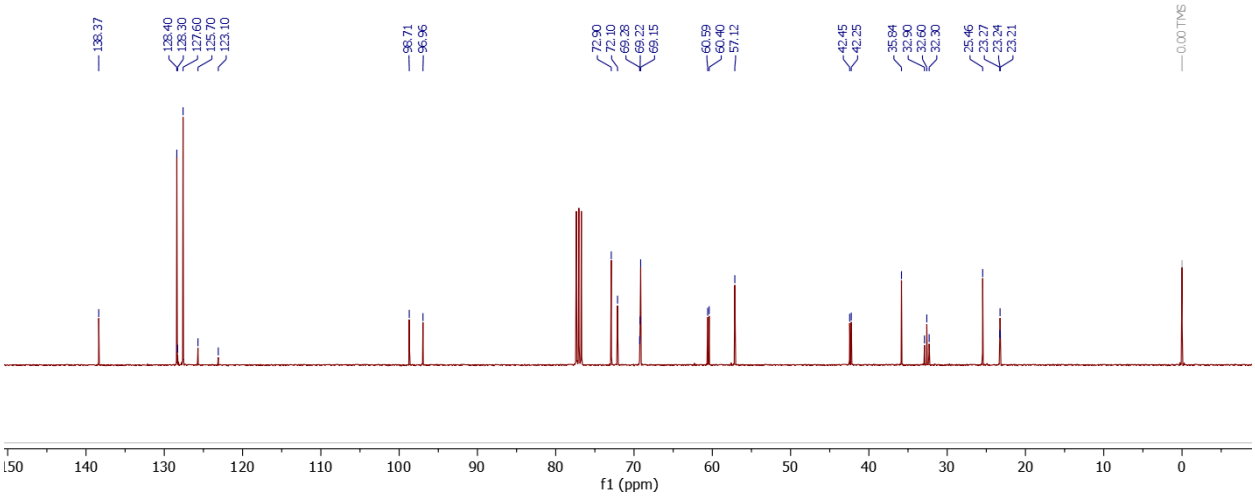
^{19}F NMR spectrum of **11** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

(2*R*,7a*S*)-7a-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-2-fluorohexahydro-1H-pyrrolizine (12)

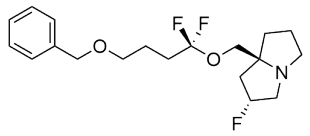


^{1}H NMR spectrum of **12** (400 MHz, $CDCl_3$)



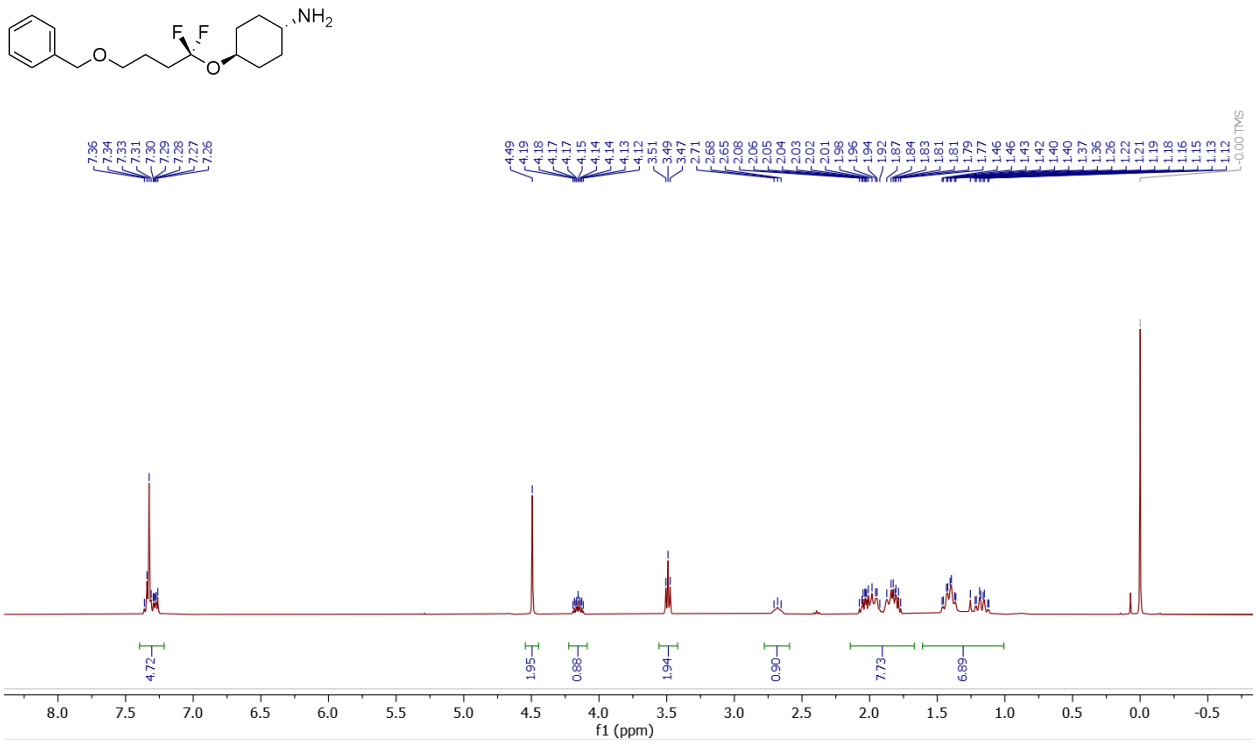


^{13}C NMR spectrum of **12** (101 MHz, $CDCl_3$)

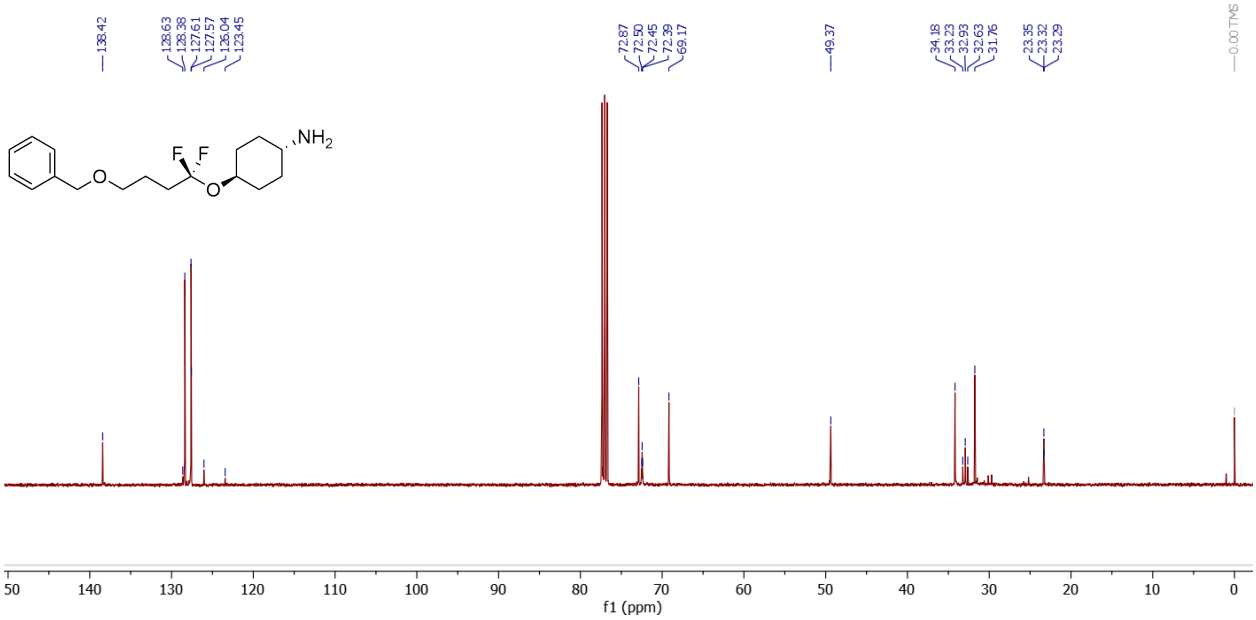


^{19}F NMR spectrum of **12** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

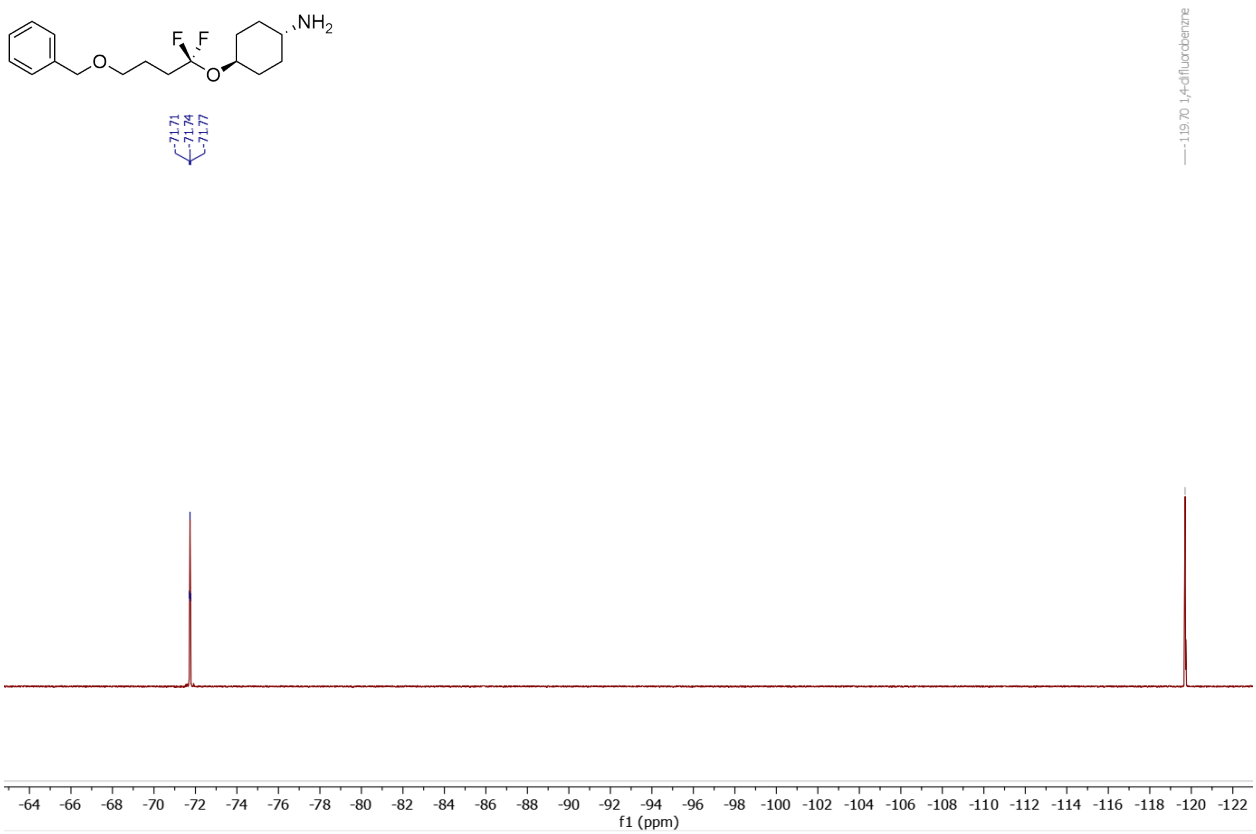
***trans*-4-(4-(benzyloxy)-1,1-difluorobutoxy)cyclohexan-1-amine (13)**



^{1}H NMR spectrum of **13** (400 MHz, $CDCl_3$)

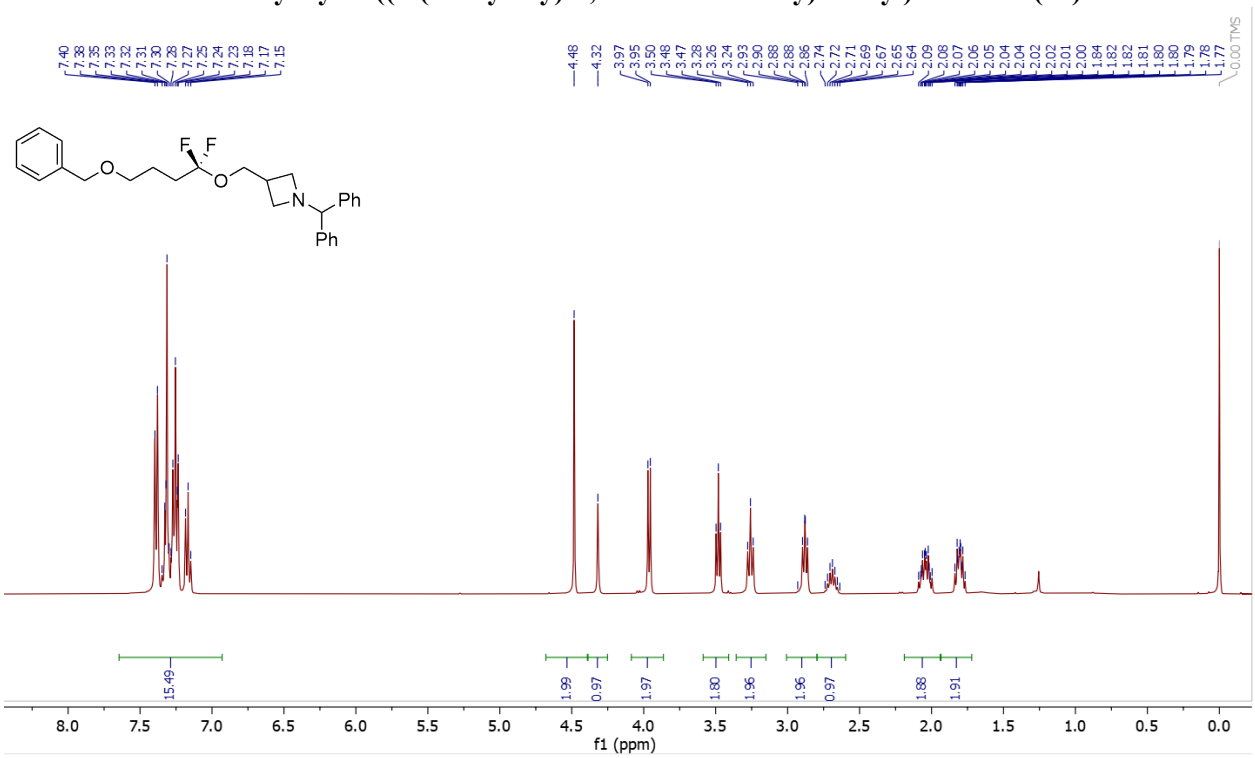


^{13}C NMR spectrum of **13** (101 MHz, $CDCl_3$)

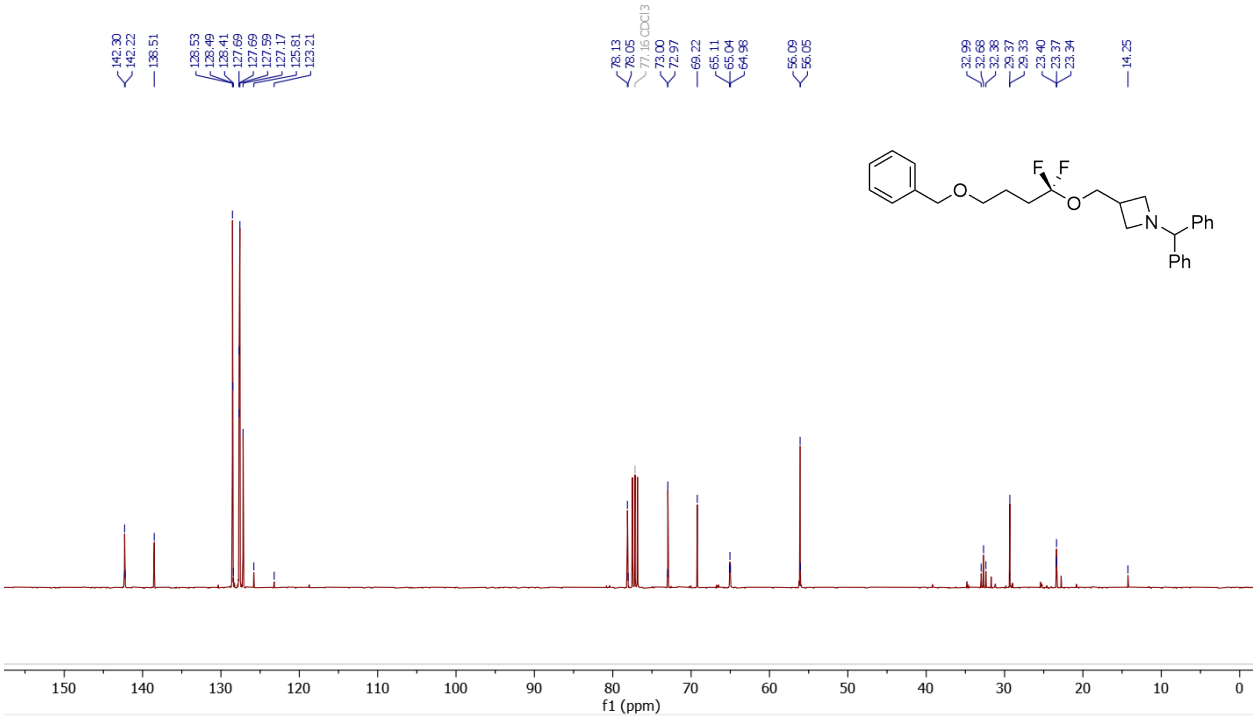


^{19}F NMR spectrum of **13** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

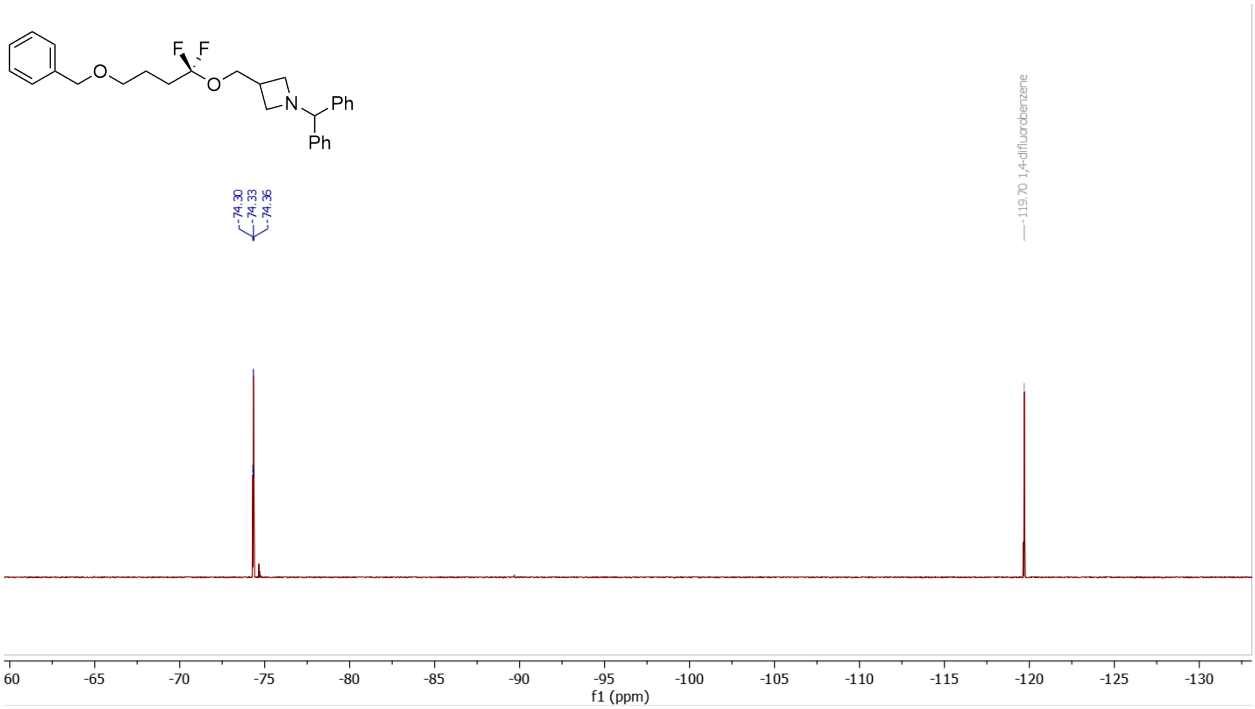
1-benzhydryl-3-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)azetidine (14)



^{1}H NMR spectrum of **14** (400 MHz, $CDCl_3$)

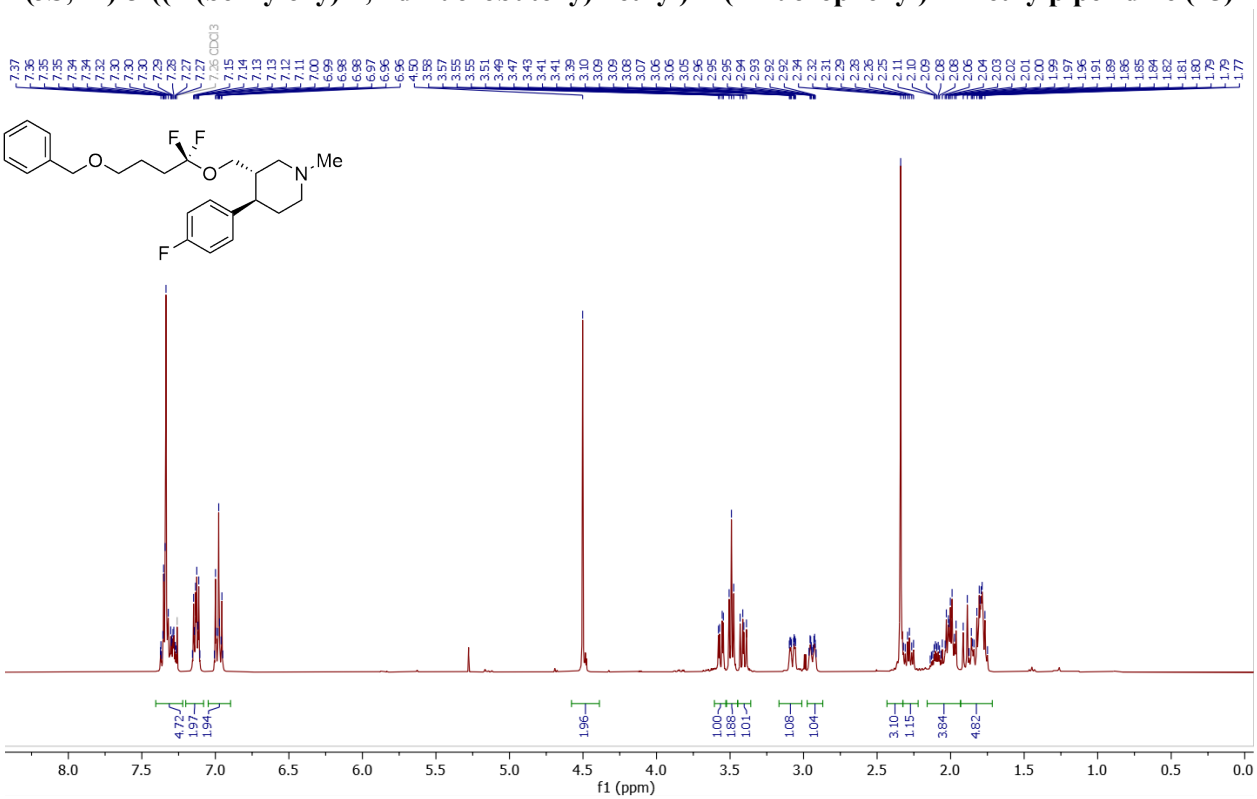


^{13}C NMR spectrum of **14** (101 MHz, $CDCl_3$

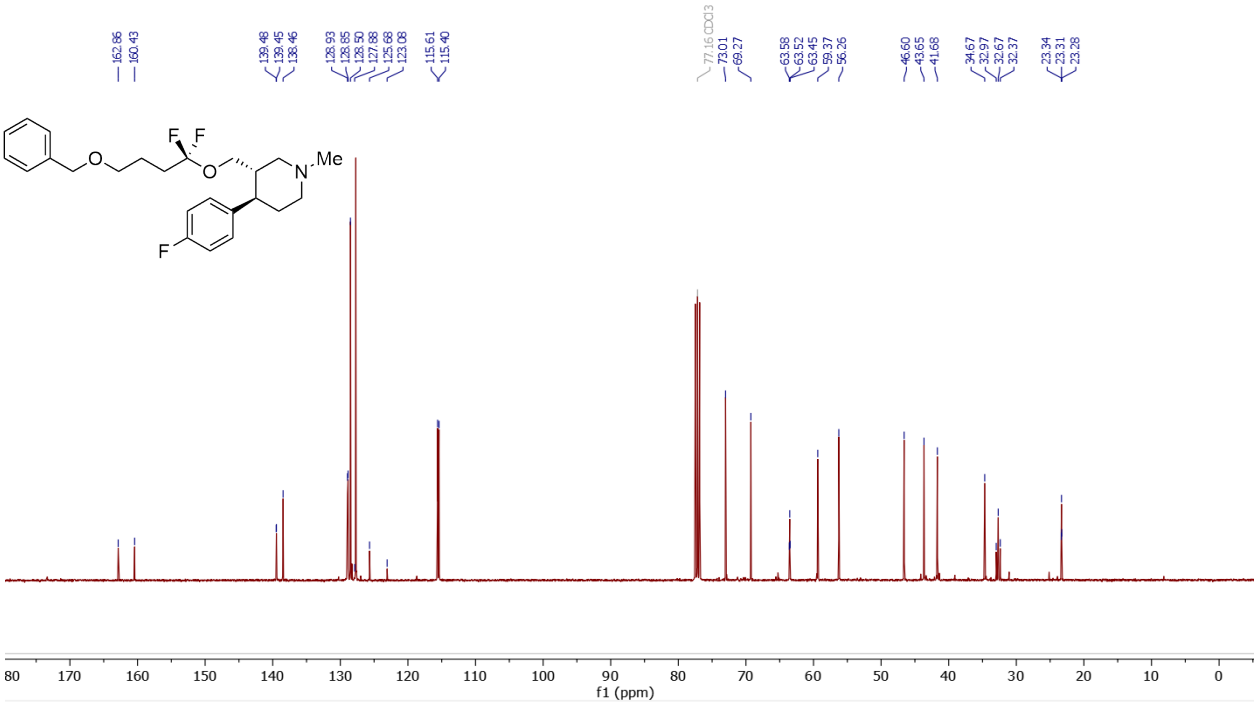


^{19}F NMR spectrum of **14** (376 MHz, $CDCl_3$), 1,4-difuorobenzene used as internal standard

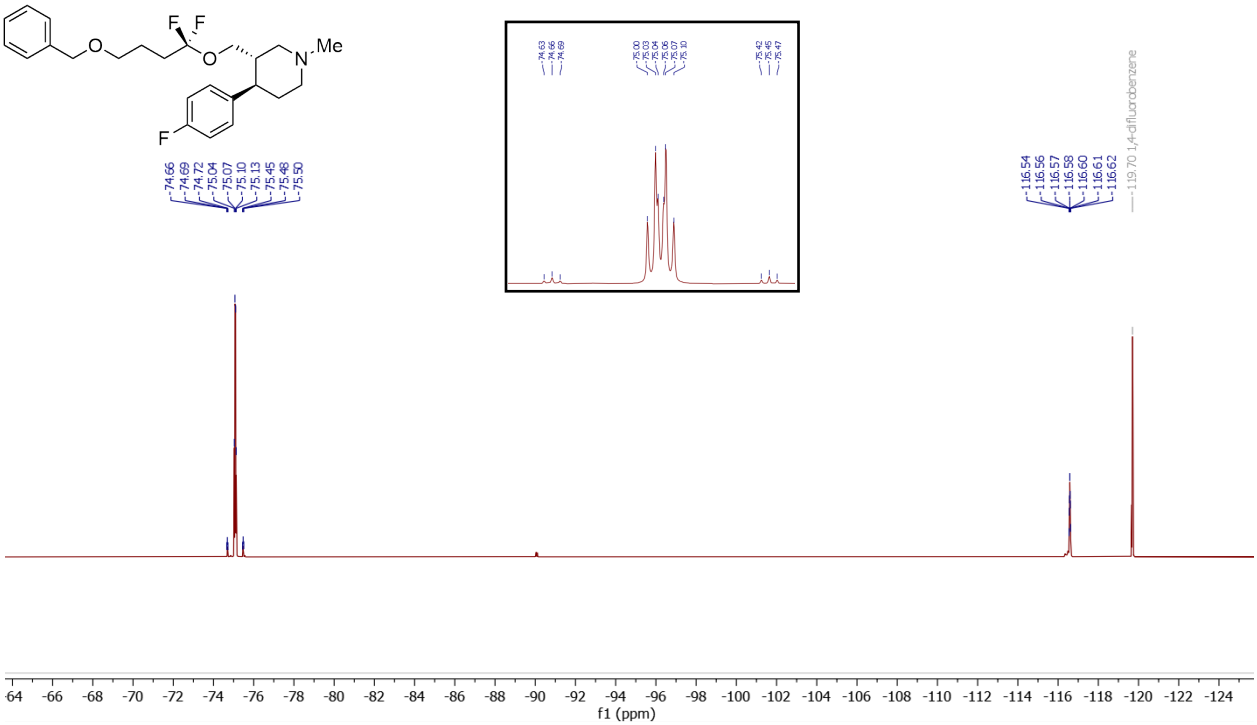
(*3S*,*4R*)-3-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-4-(4-fluorophenyl)-1-methylpiperidine (15)



^{1}H NMR spectrum of **15** (400 MHz, $CDCl_3$)

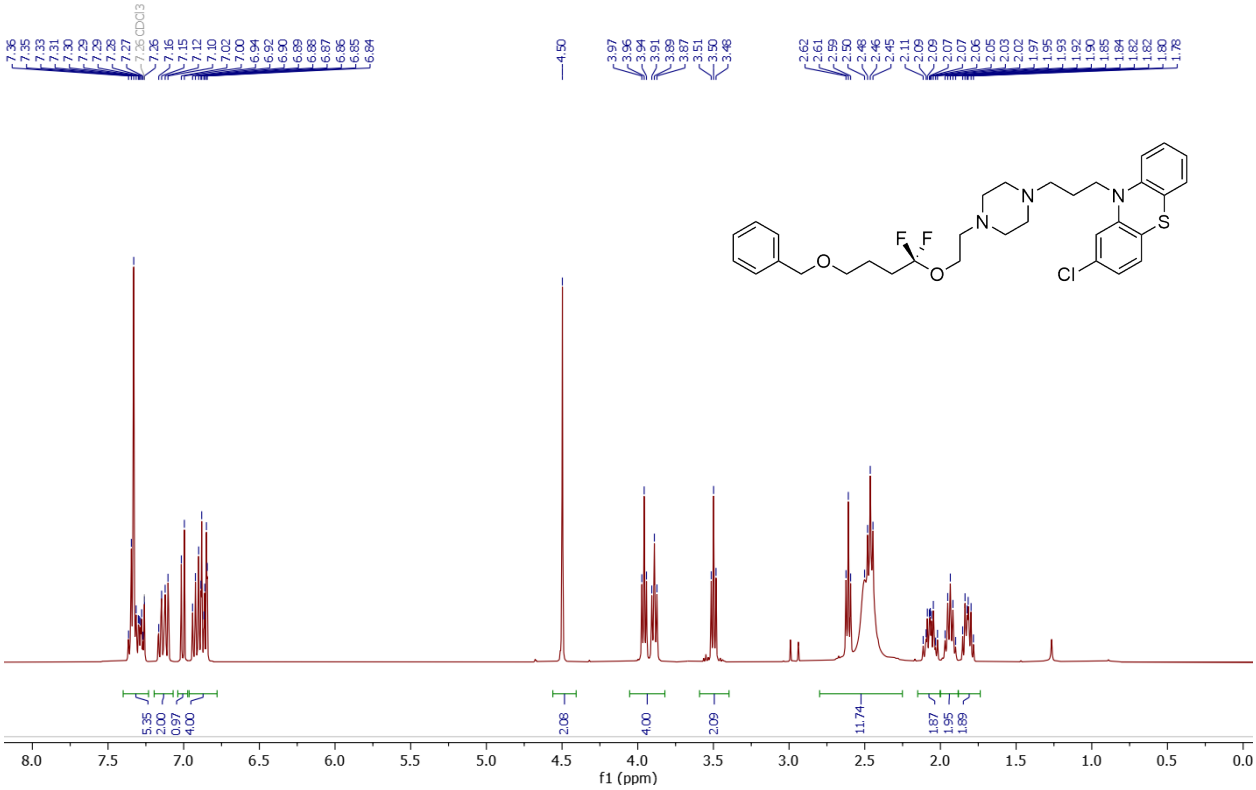


^{13}C NMR spectrum of **15** (101 MHz, $CDCl_3$)

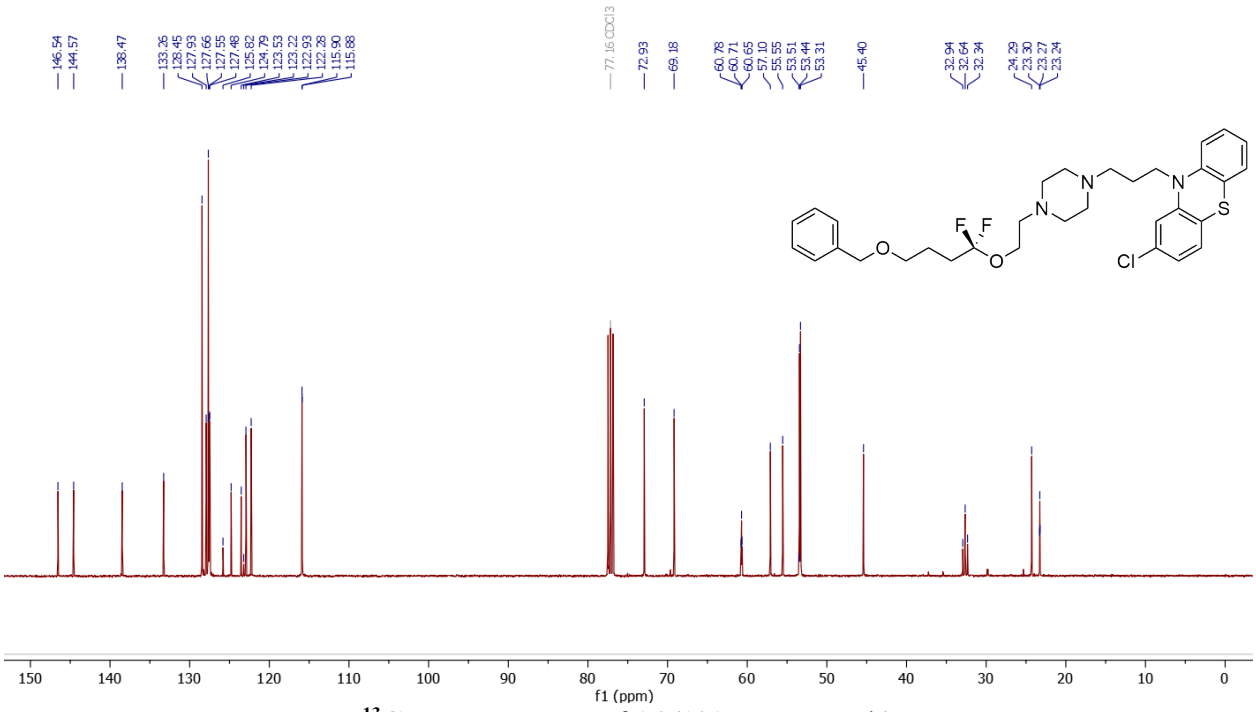


^{19}F NMR spectrum of **15** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

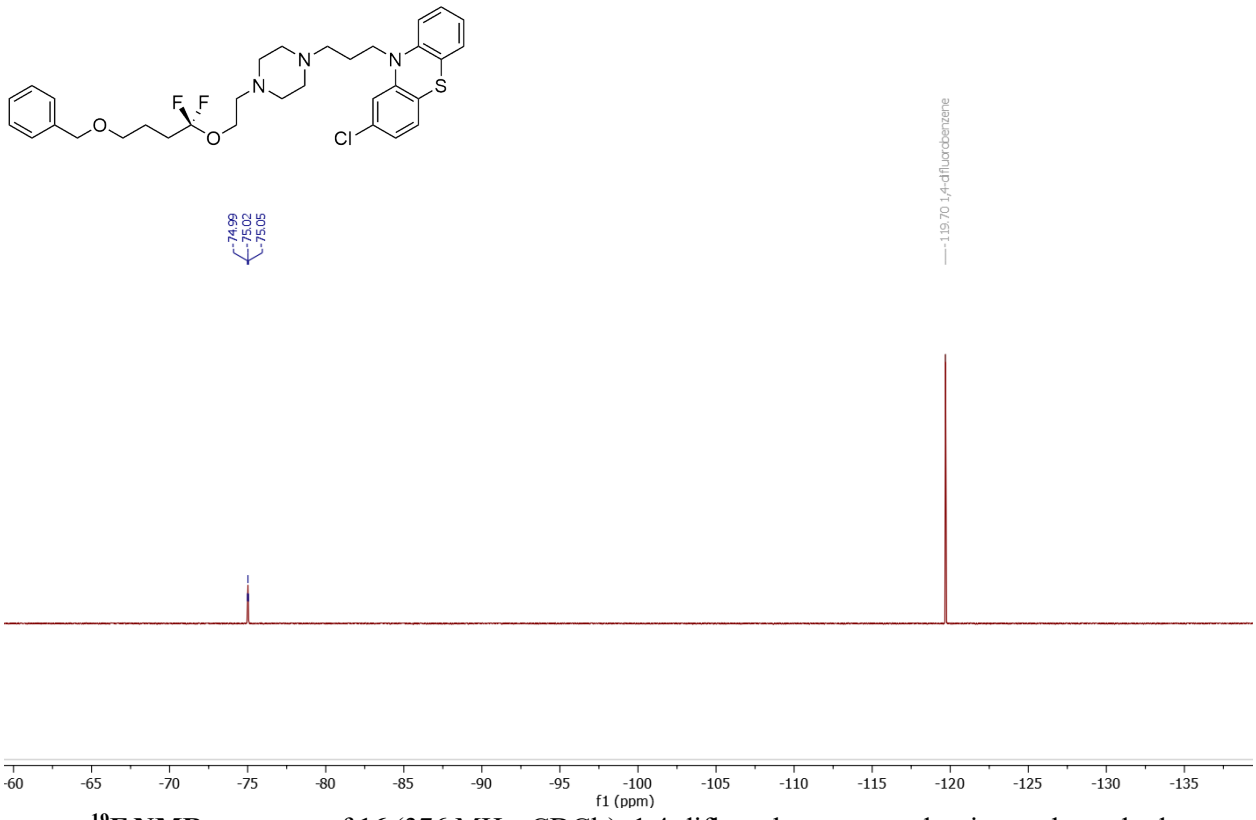
10-(3-(4-(2-(4-(benzyloxy)-1,1-difluorobutoxy)ethyl)piperazin-1-yl)propyl)-2-chloro-10H-phenothiazine (16)



^{1}H NMR spectrum of **16** (400 MHz, $CDCl_3$)

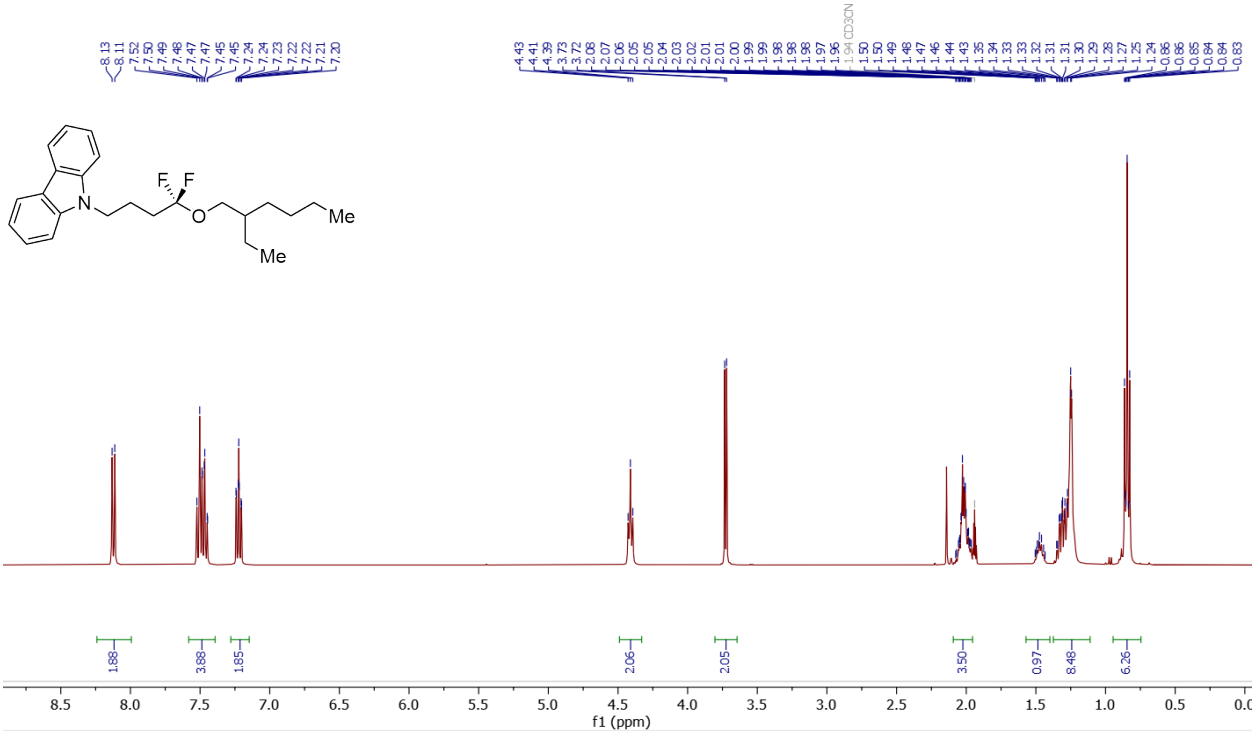


^{13}C NMR spectrum of **16** (101 MHz, $CDCl_3$)

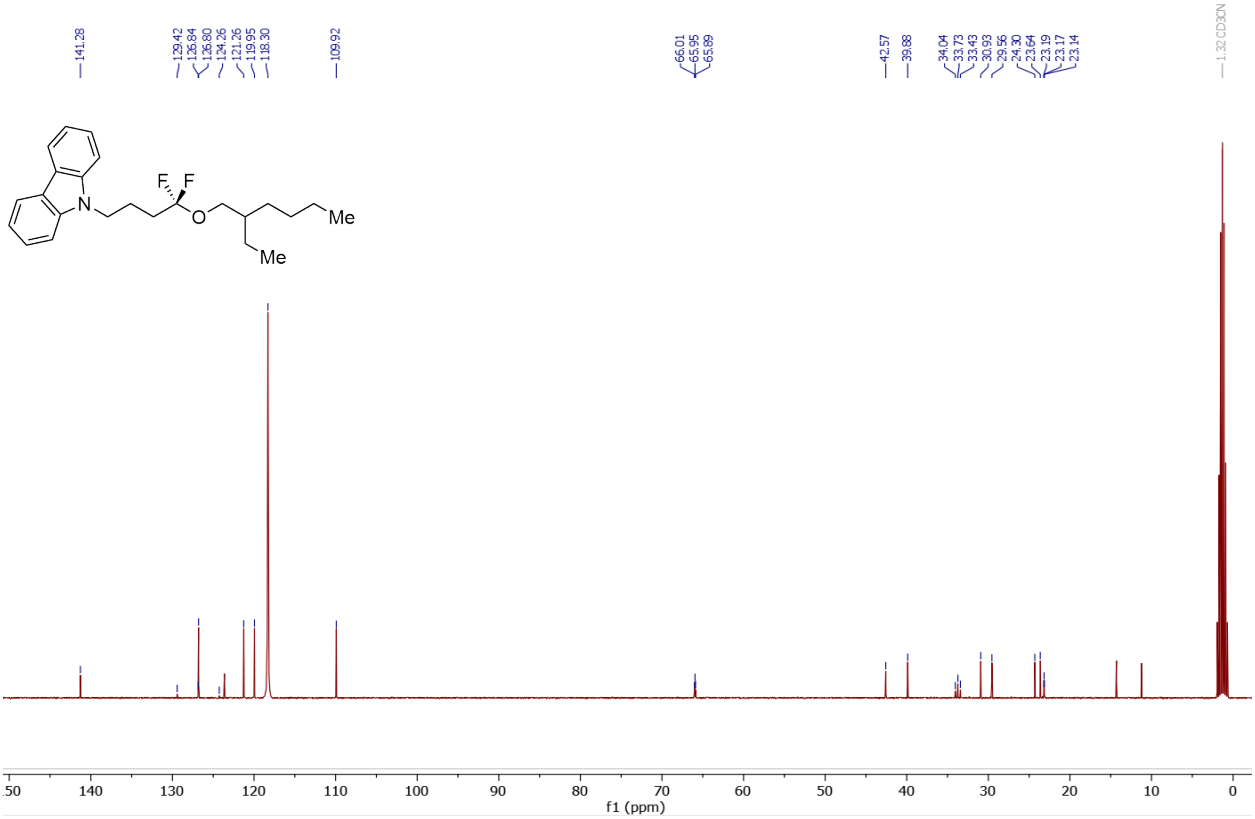


^{19}F NMR spectrum of **16** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

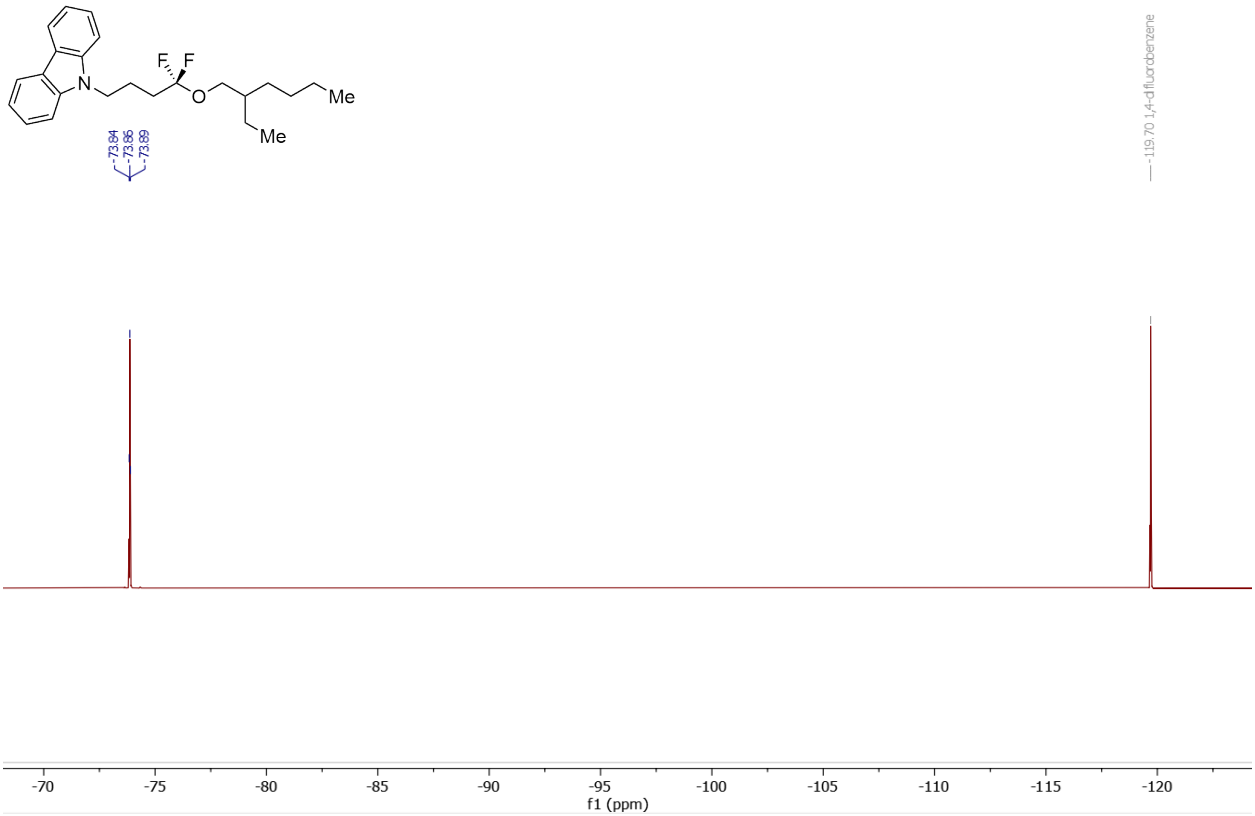
9-(4-((2-ethylhexyl)oxy)-4,4-difluorobutyl)-9H-carbazole (17)



^{1}H NMR spectrum of **17** (400 MHz, CD_3CN)

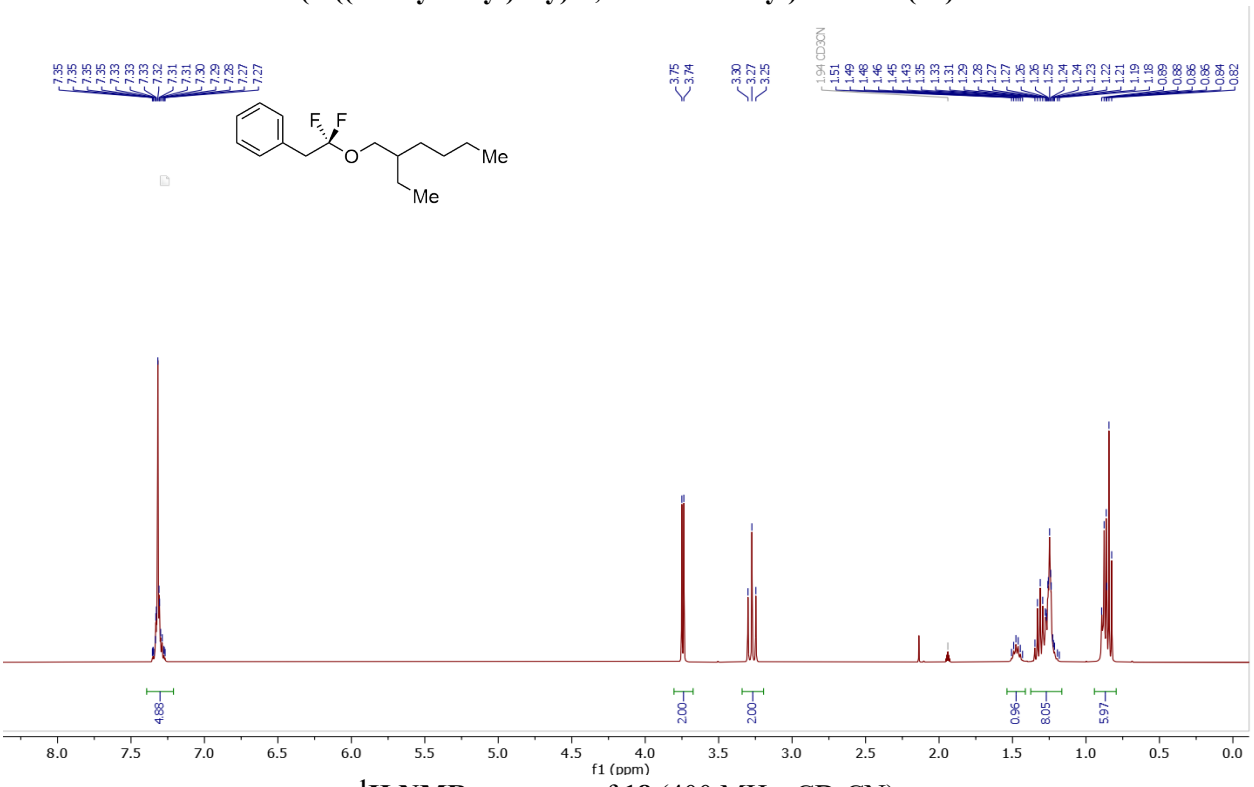


^{13}C NMR spectrum of **17** (101 MHz, CD_3CN)

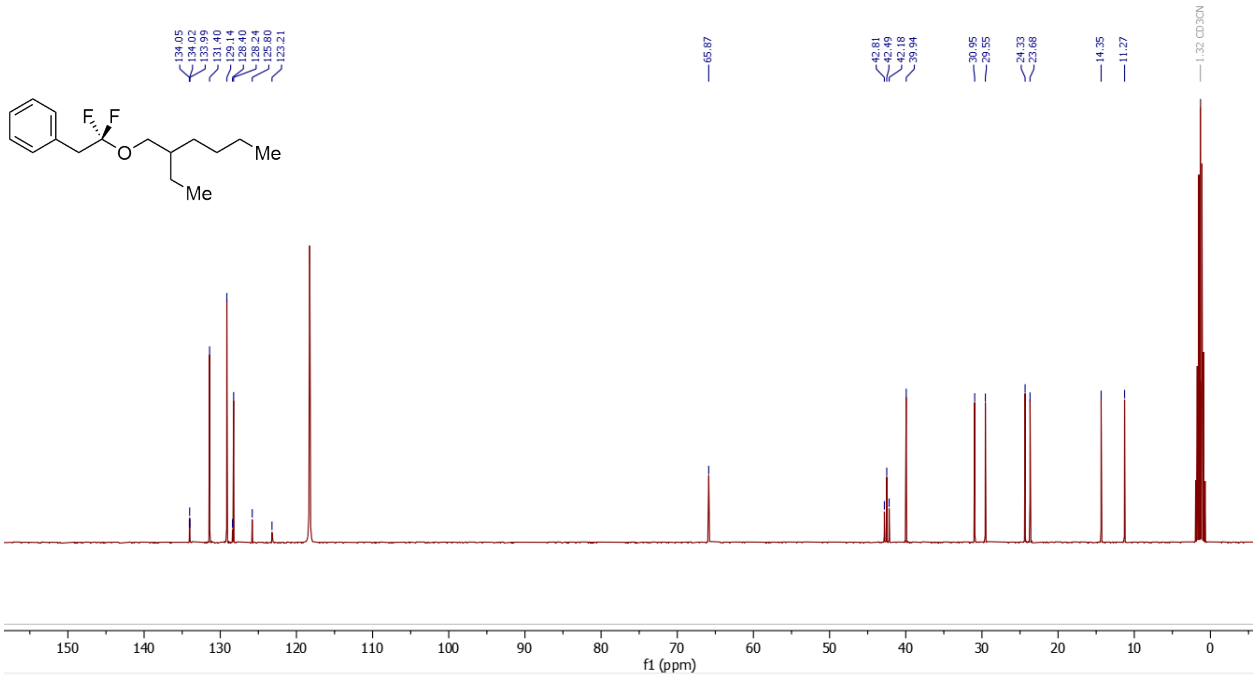


^{19}F NMR spectrum of **17** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

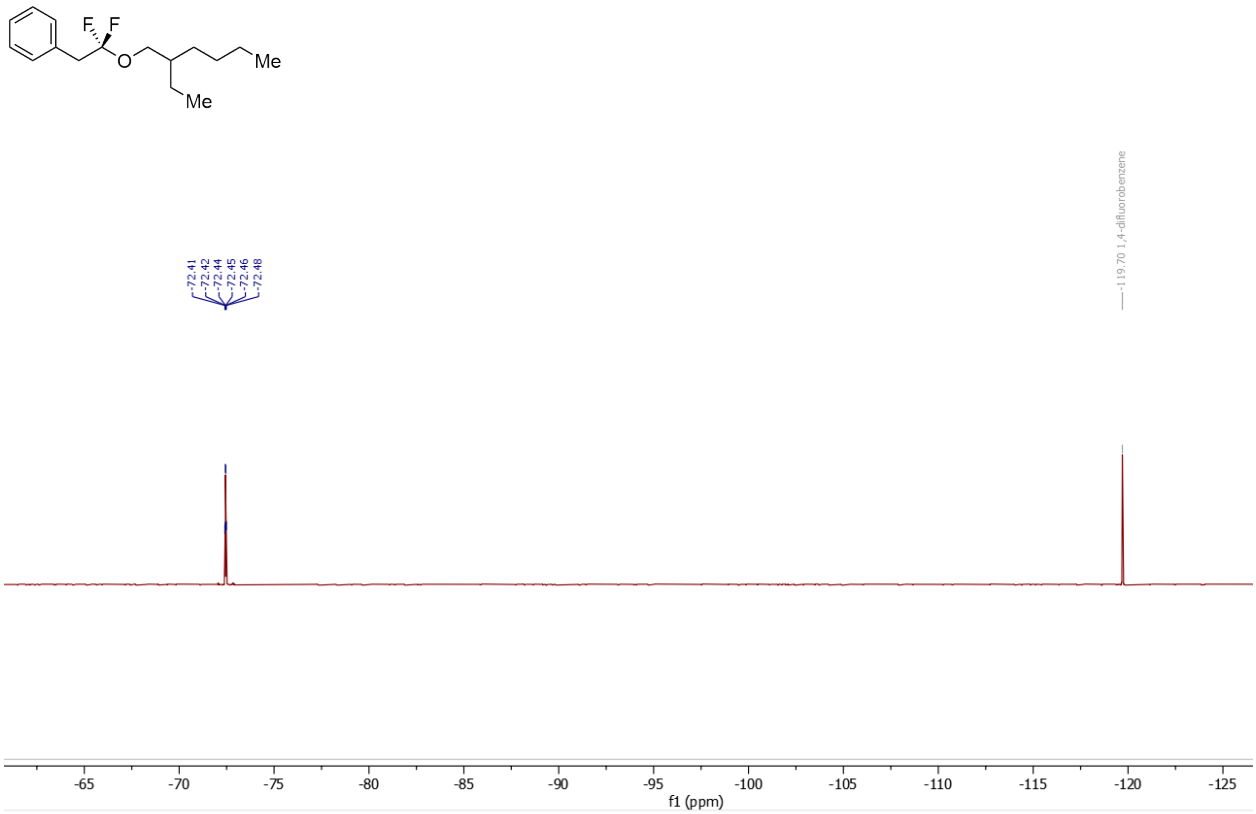
(2-((2-ethylhexyl)oxy)-2,2-difluoroethyl)benzene (18)



^{1}H NMR spectrum of **18** (400 MHz, CD_3CN)

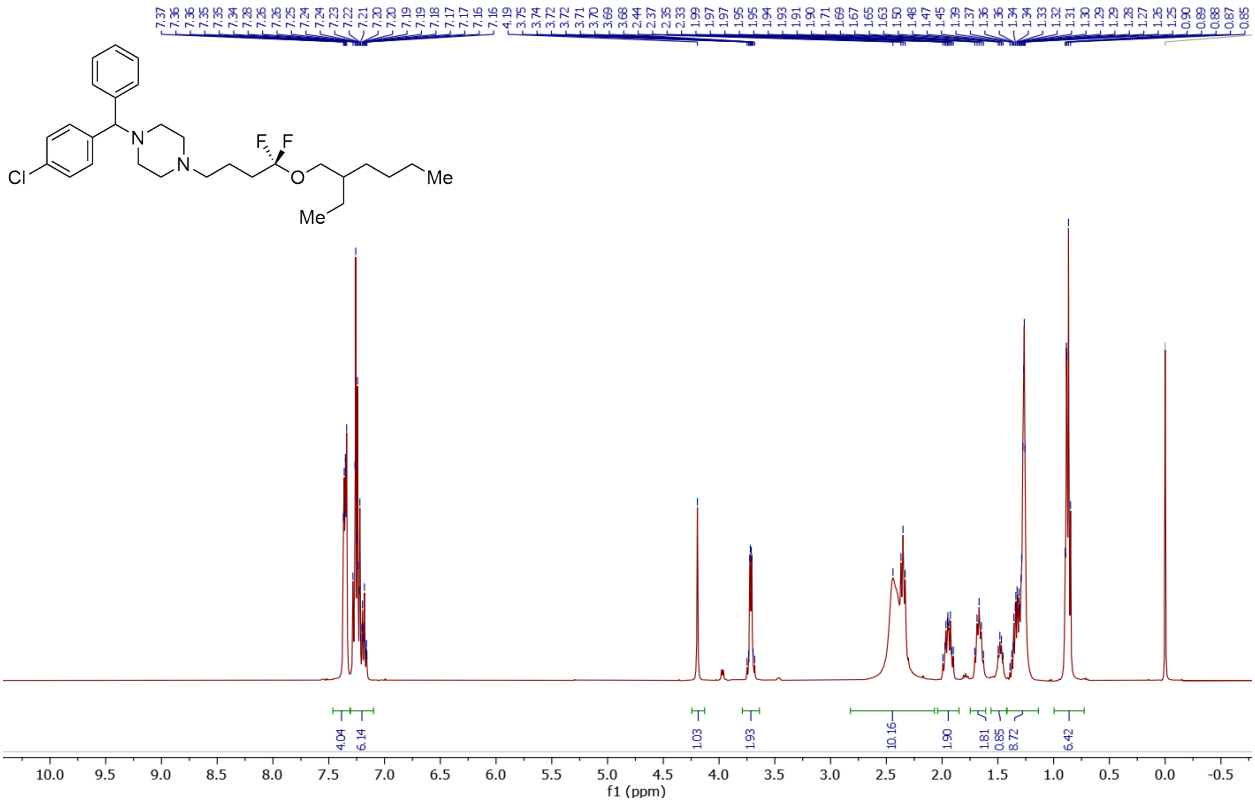


^{13}C NMR spectrum of **18** (101 MHz, CD_3CN)

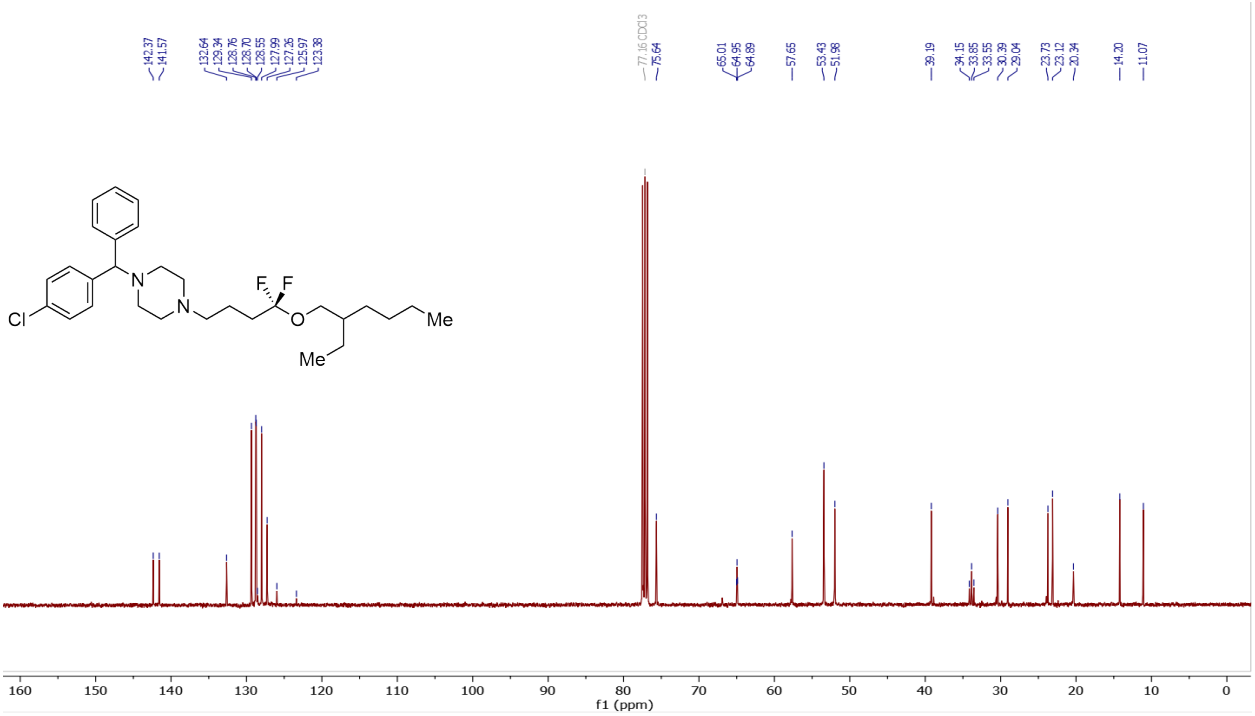


^{19}F NMR spectrum of **18** (376 MHz, CD_3CN), 1,4-difluorobenzene used as internal standard

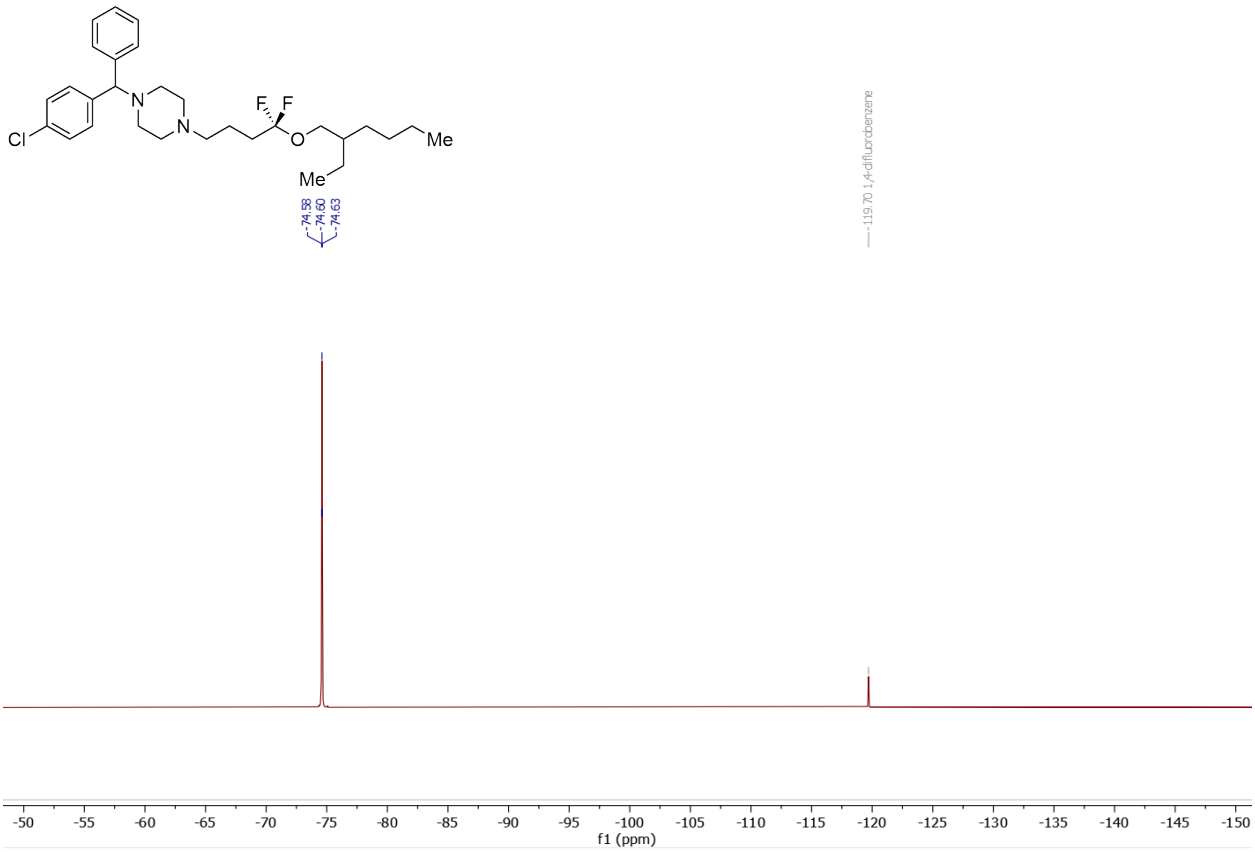
1-((4-chlorophenyl)(phenyl)methyl)-4-(4-((2-ethylhexyl)oxy)-4,4-difluorobutyl)piperazine (19)



^{1}H NMR spectrum of **19** (400 MHz, $CDCl_3$)

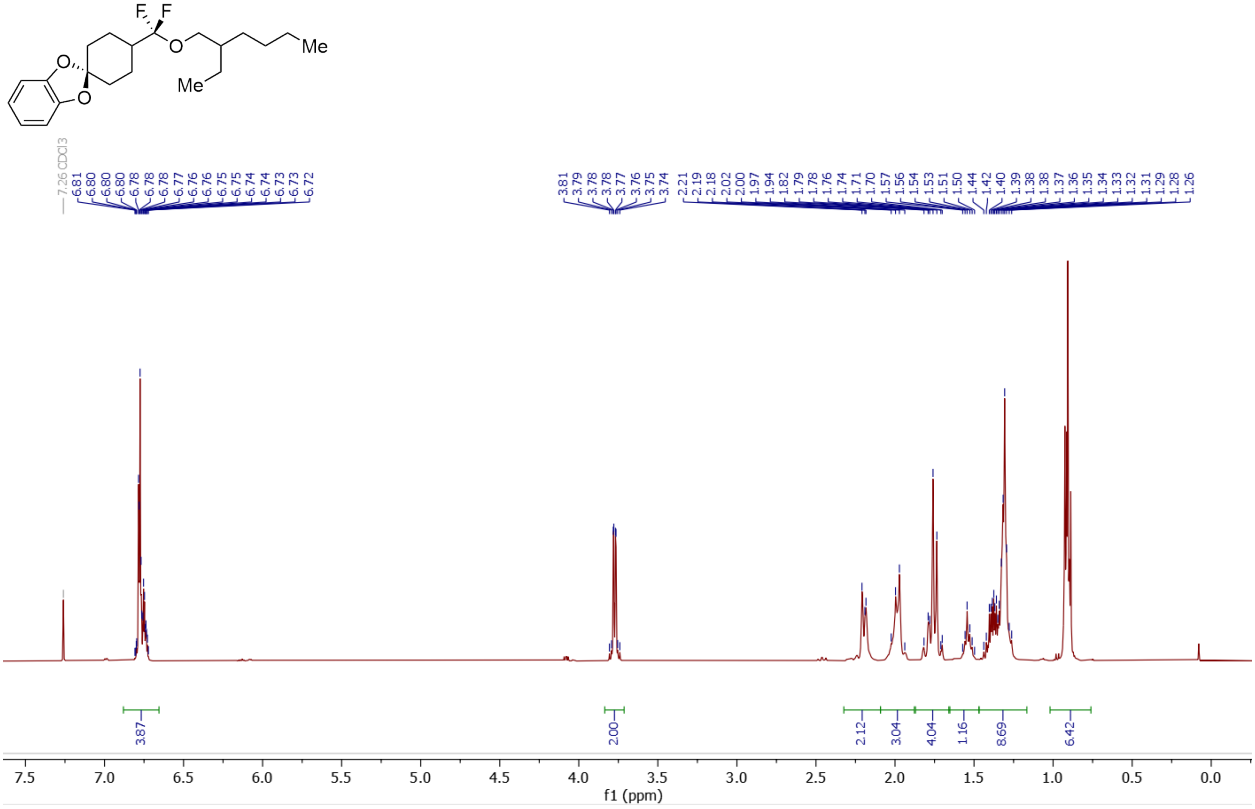


^{13}C NMR spectrum of **19** (101 MHz, $CDCl_3$

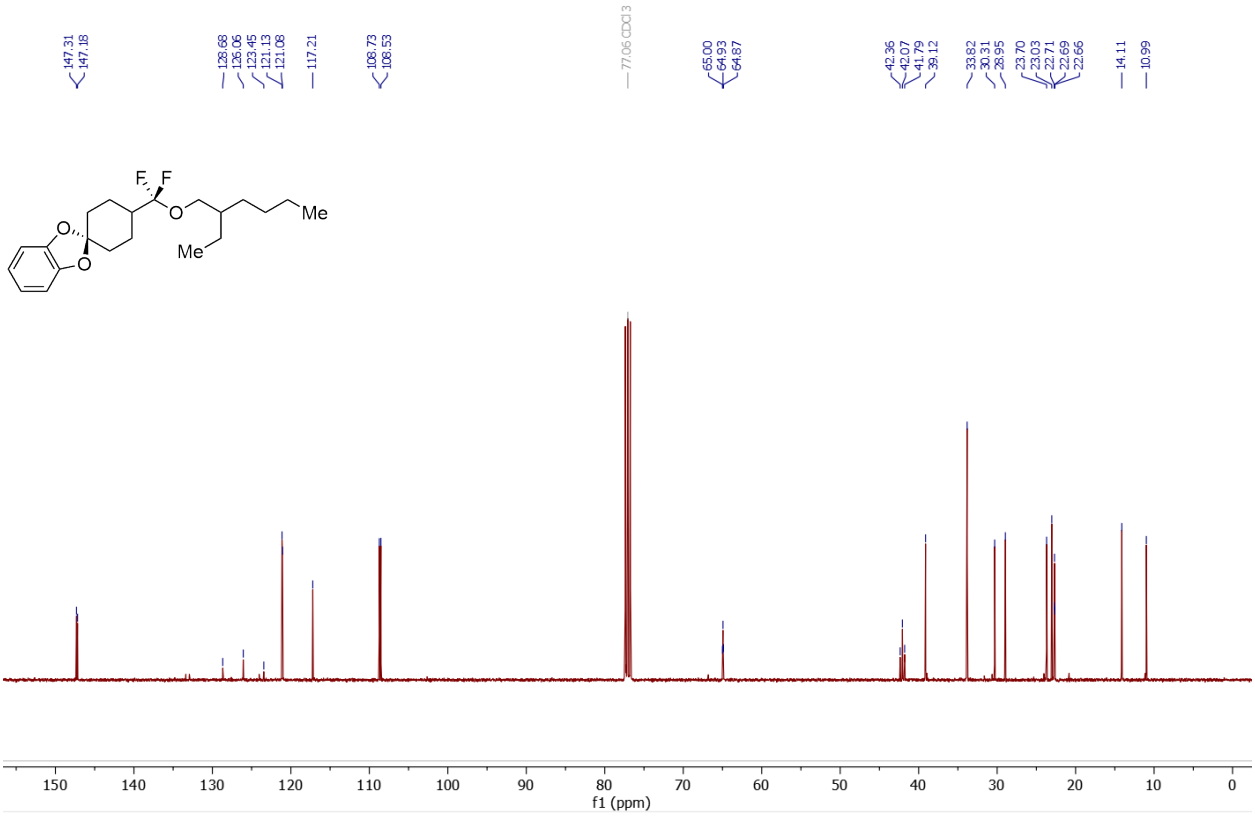


^{19}F NMR spectrum of **19** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

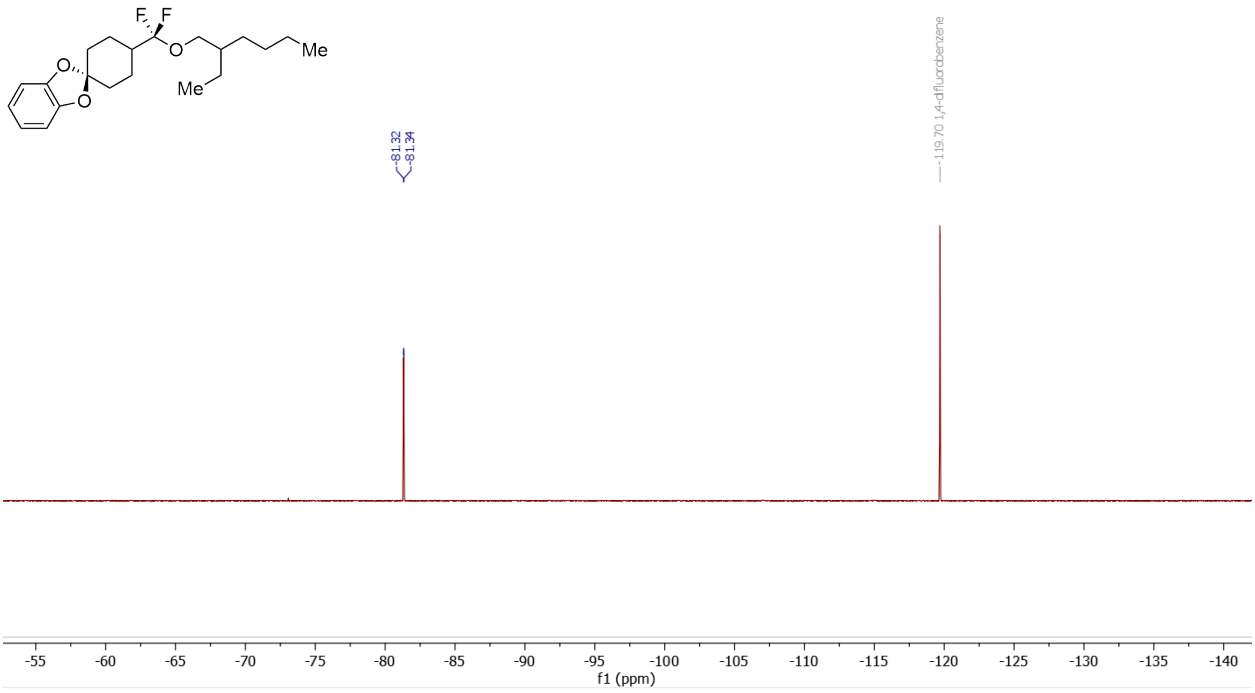
4'-(((2-ethylhexyl)oxy)difluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane (20)



^{1}H NMR spectrum of **20** (400 MHz, $CDCl_3$)

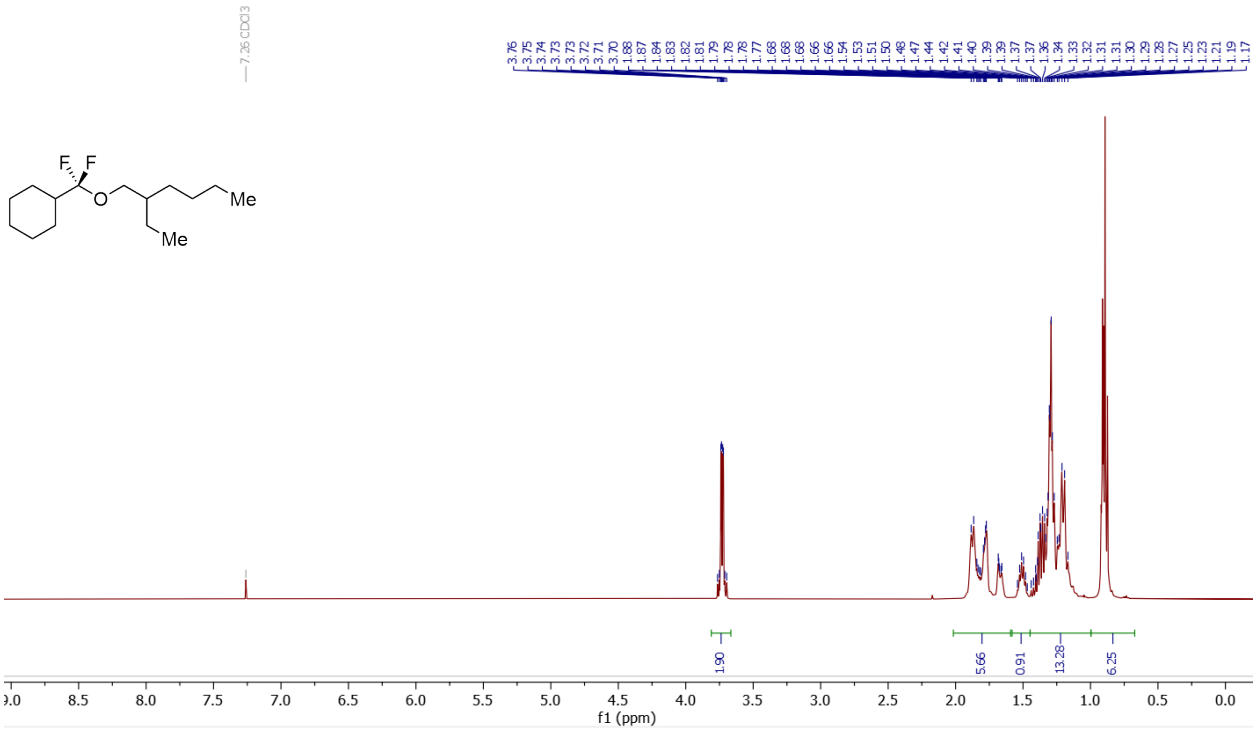


^{13}C NMR spectrum of **20** (101 MHz, $CDCl_3$)

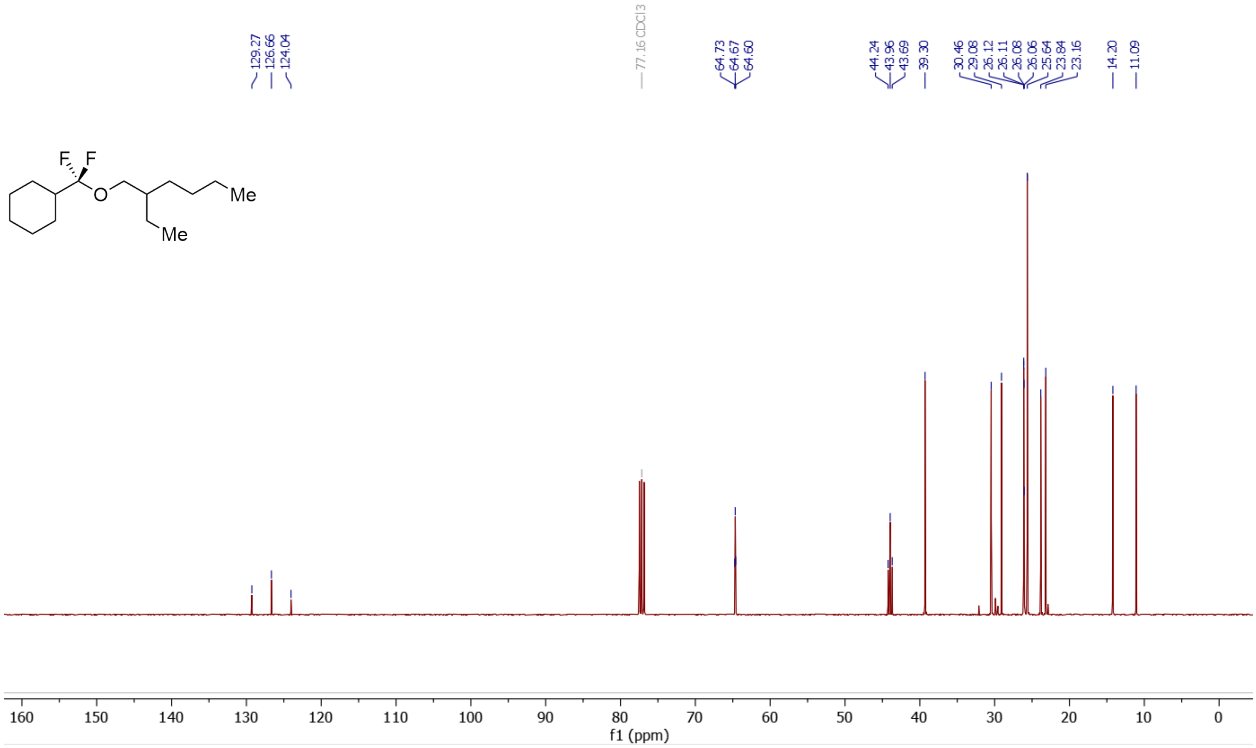


^{19}F NMR spectrum of **20** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

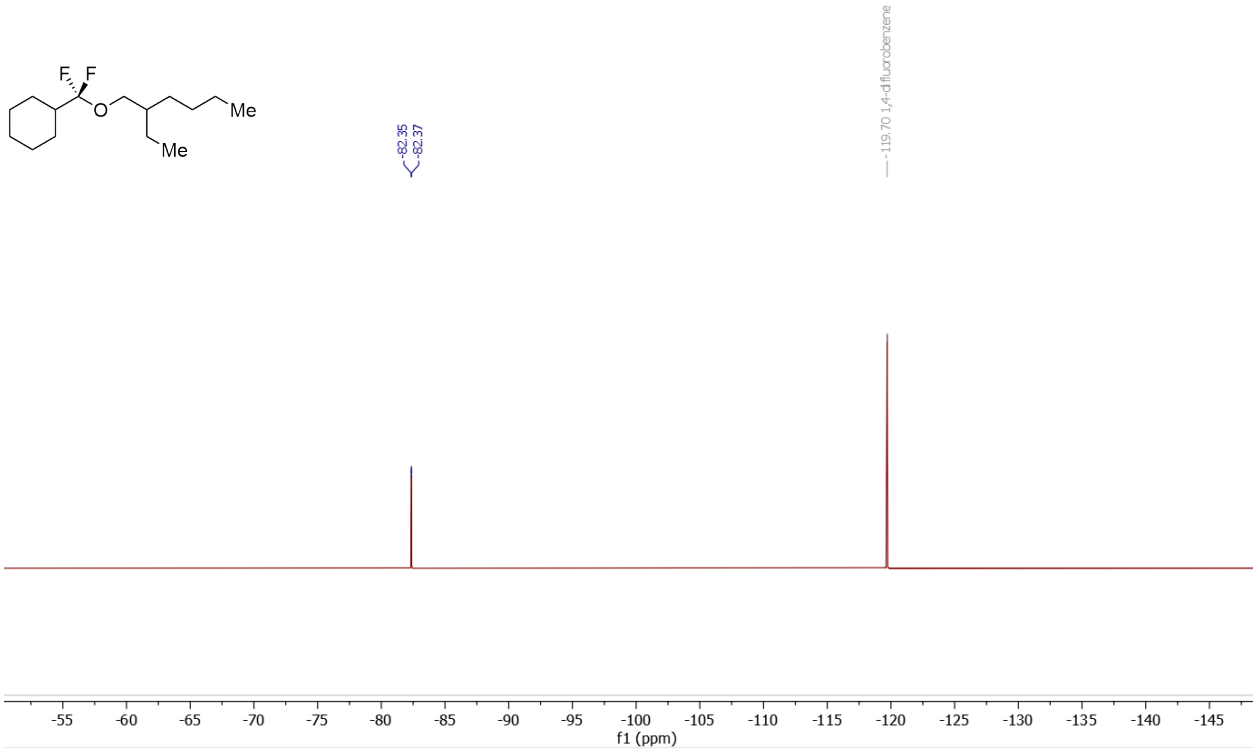
(((2-ethylhexyl)oxy)difluoromethyl)cyclohexane (21)



^{1}H NMR spectrum of **21** (400 MHz, $CDCl_3$)

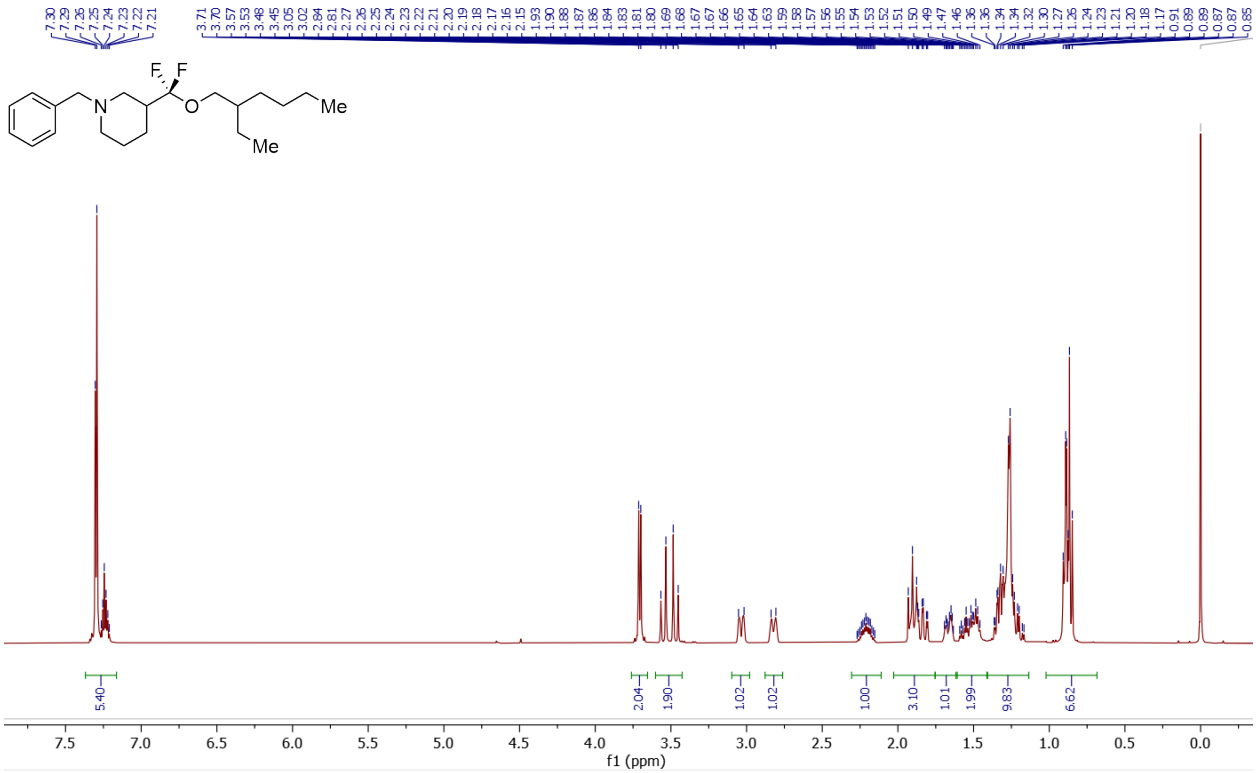


^{13}C NMR spectrum of **21** (101 MHz, $CDCl_3$)

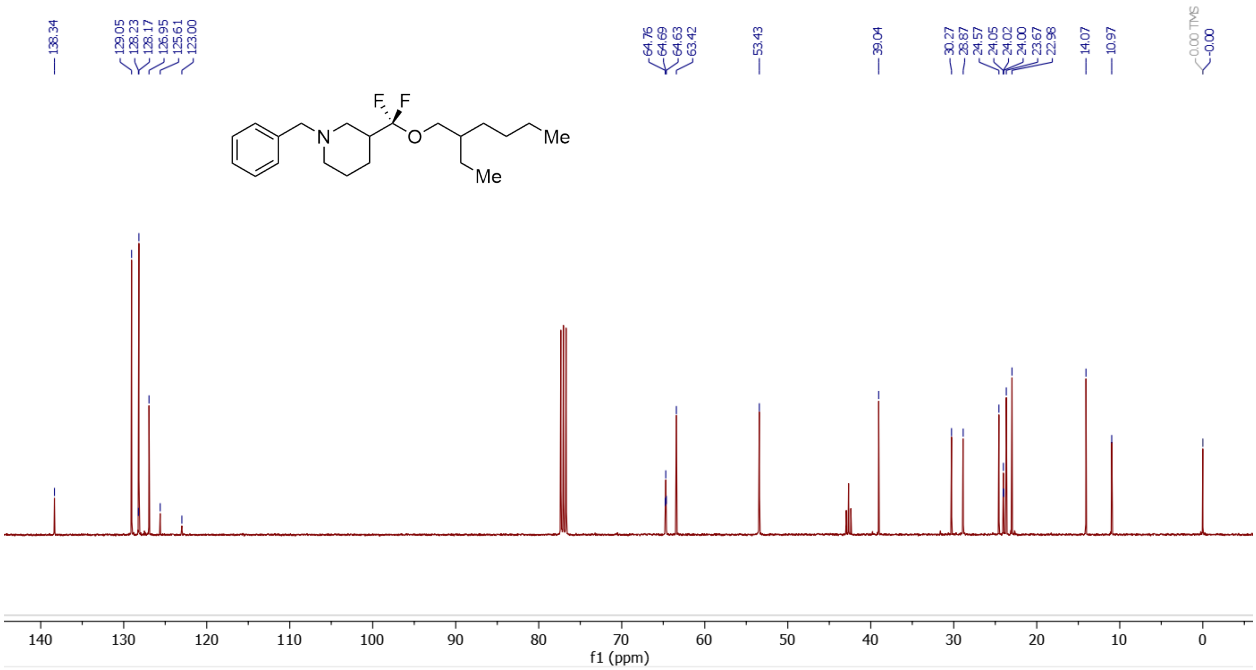


^{19}F NMR spectrum of **21** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

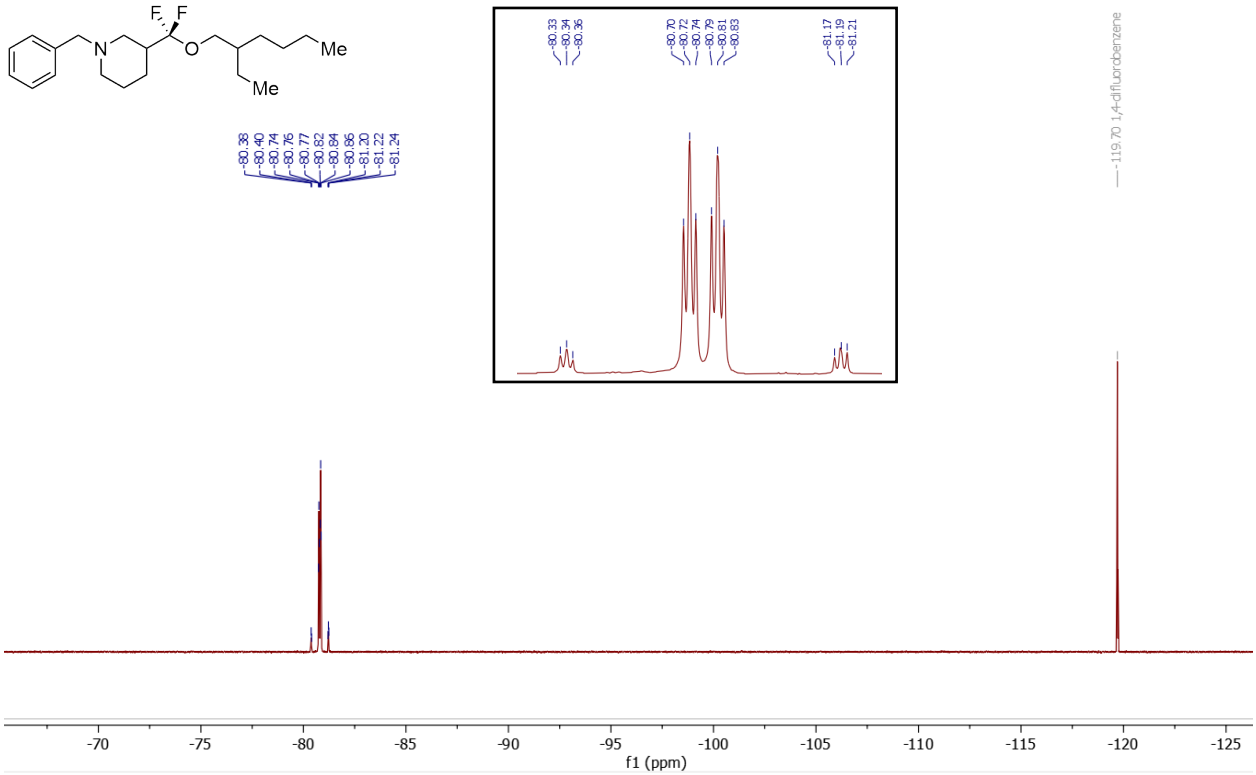
1-benzyl-4-(((2-ethylhexyl)oxy)difluoromethyl)piperidine (22)



^{1}H NMR spectrum of **22** (400 MHz, $CDCl_3$)

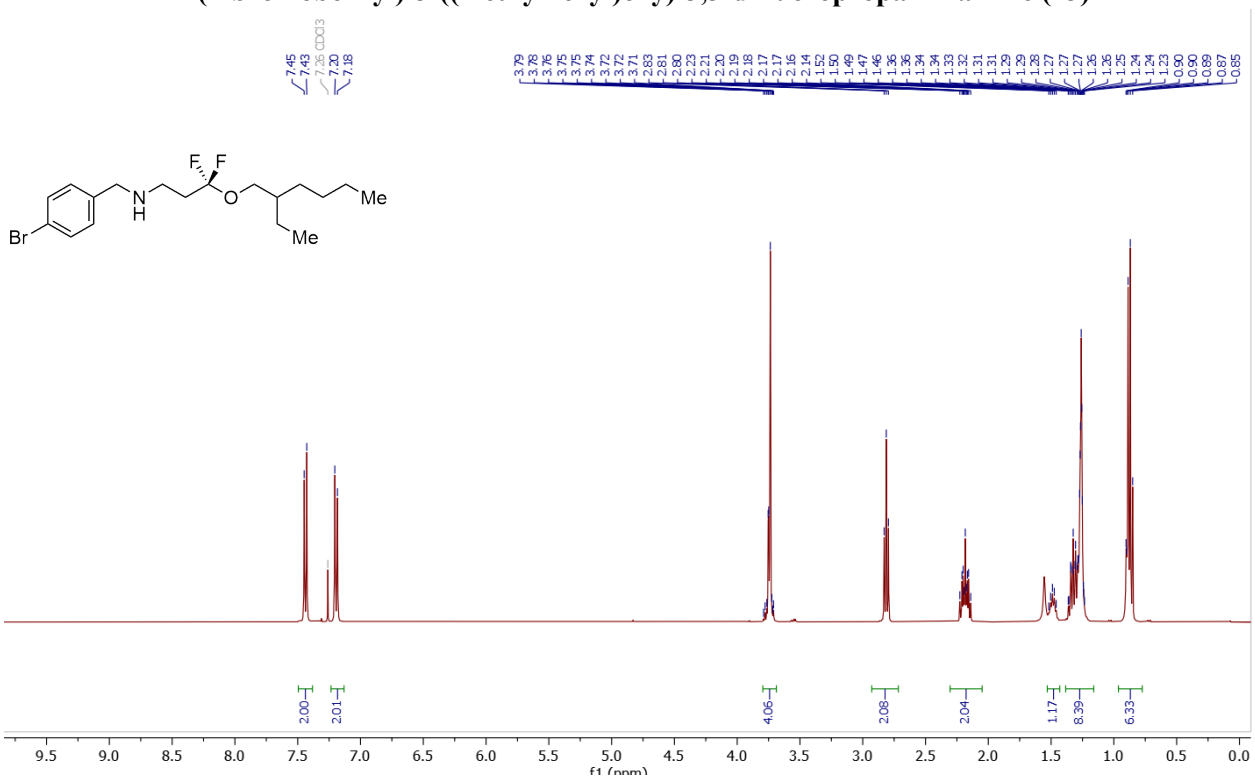


^{13}C NMR spectrum of **22** (101 MHz, $CDCl_3$)

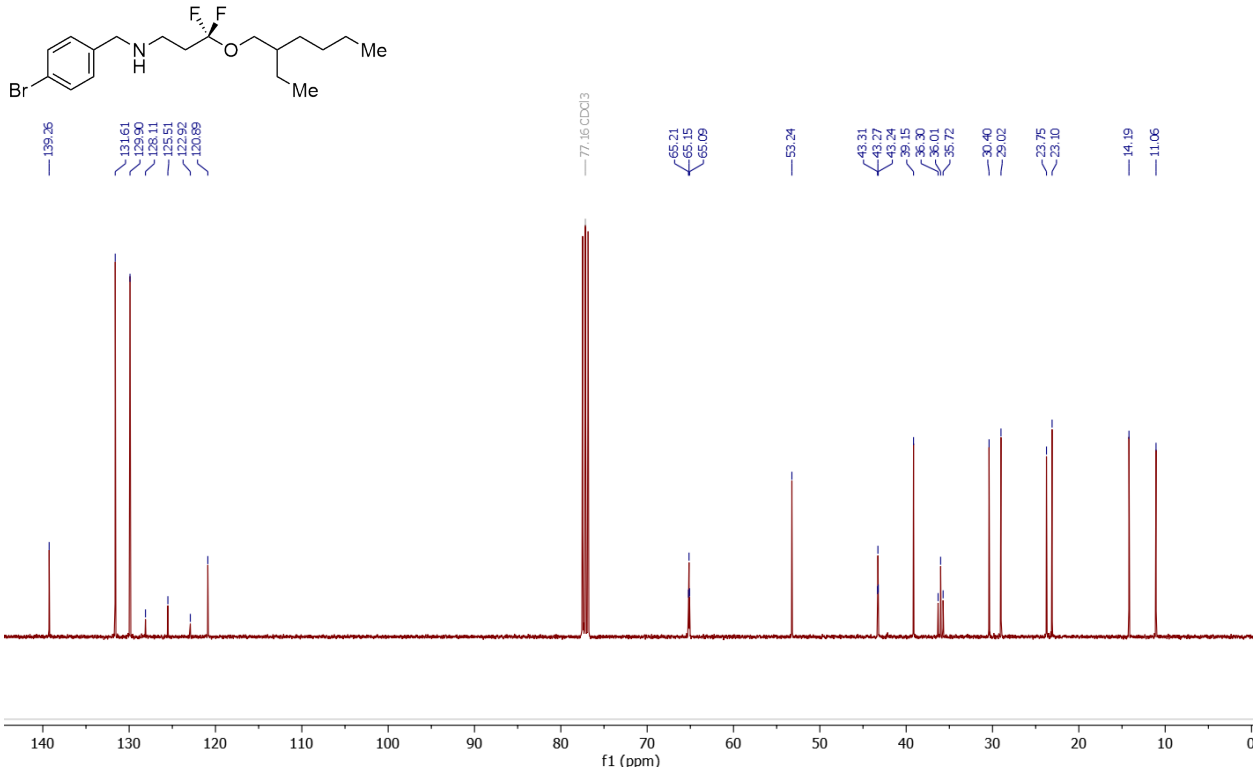


^{19}F NMR spectrum of **22** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

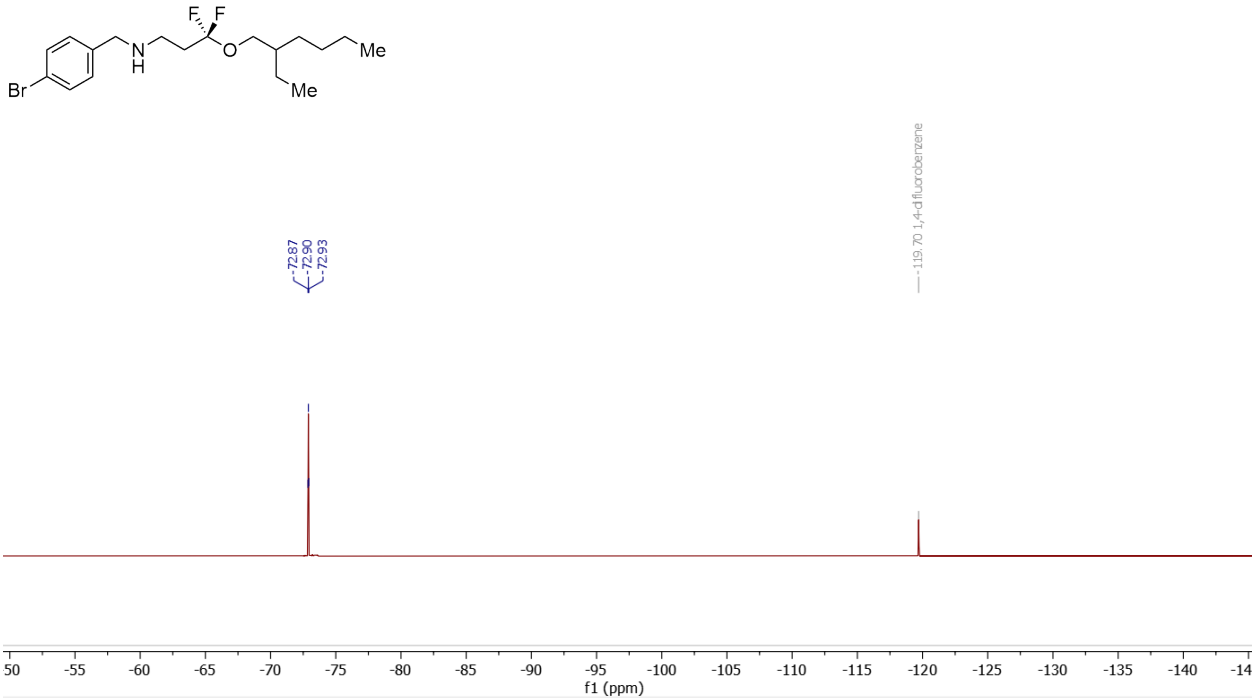
_N_-(4-bromobenzyl)-3-((2-ethylhexyl)oxy)-3,3-difluoropropan-1-amine (23)



^{1}H NMR spectrum of **23** (400 MHz, CD_3CN)

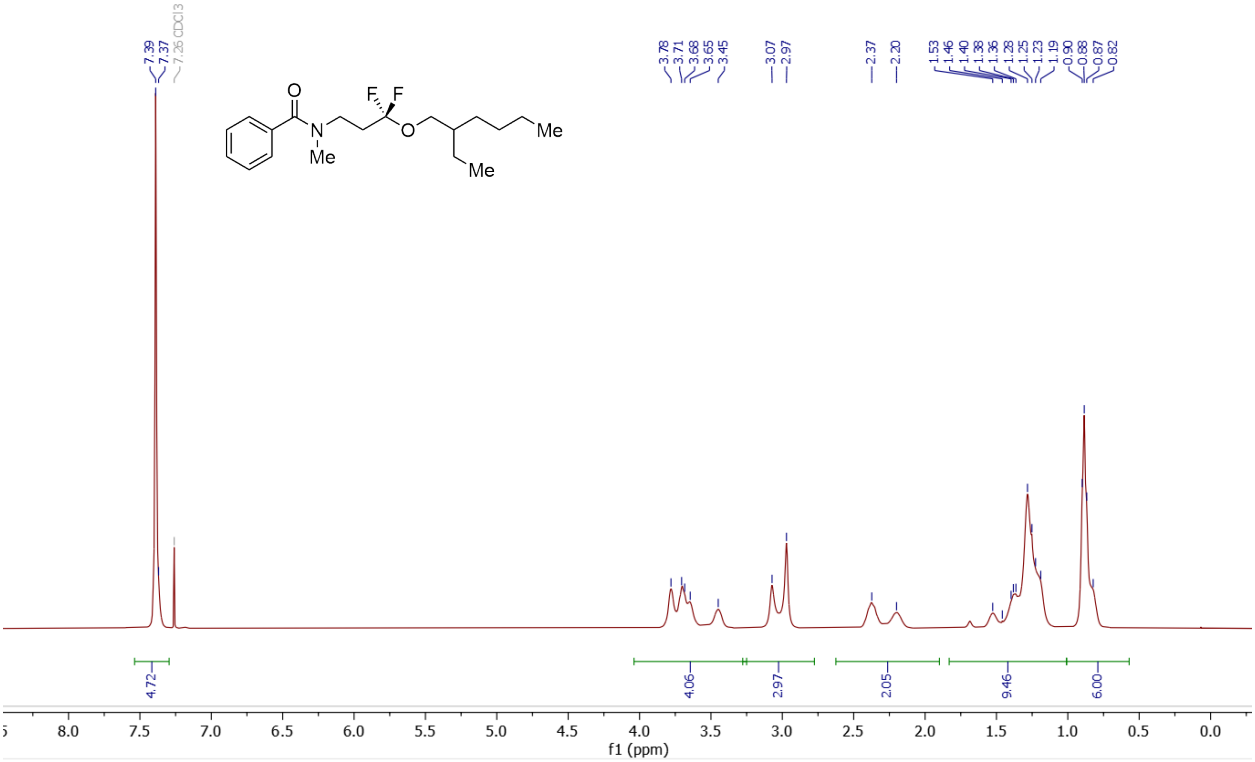


^{13}C NMR spectrum of **23** (101 MHz, $CDCl_3$)

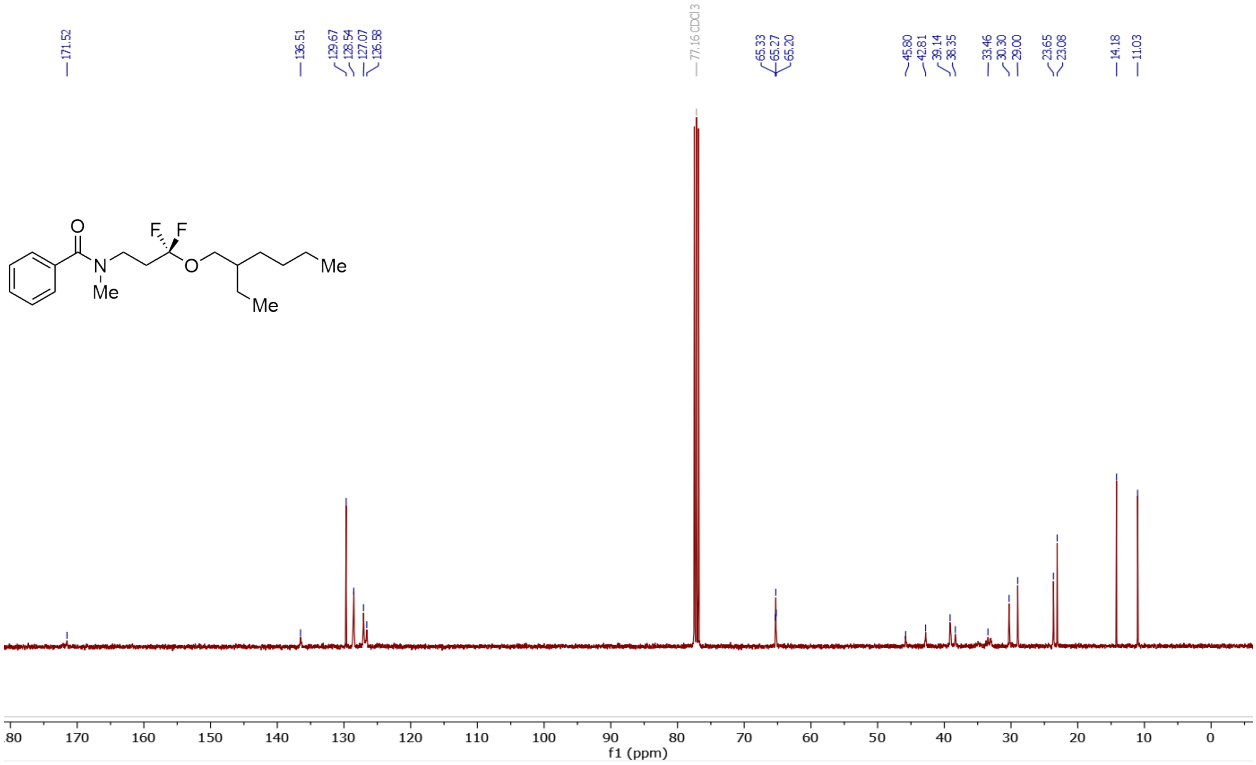


^{19}F NMR spectrum of **23** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

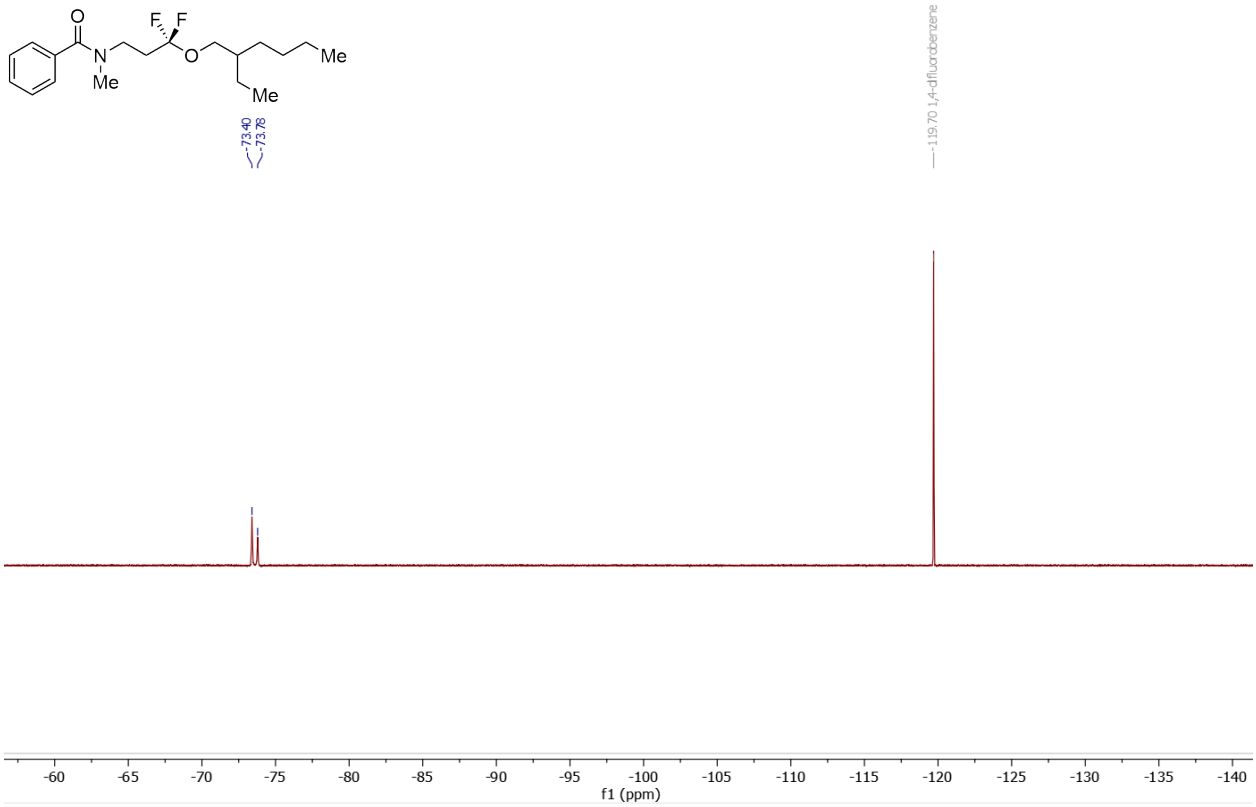
***N*-(3-((2-ethylhexyl)oxy)-3,3-difluoropropyl)-*N*-methylbenzamide (24)**



^{1}H NMR spectrum of **24** (400 MHz, $CDCl_3$)

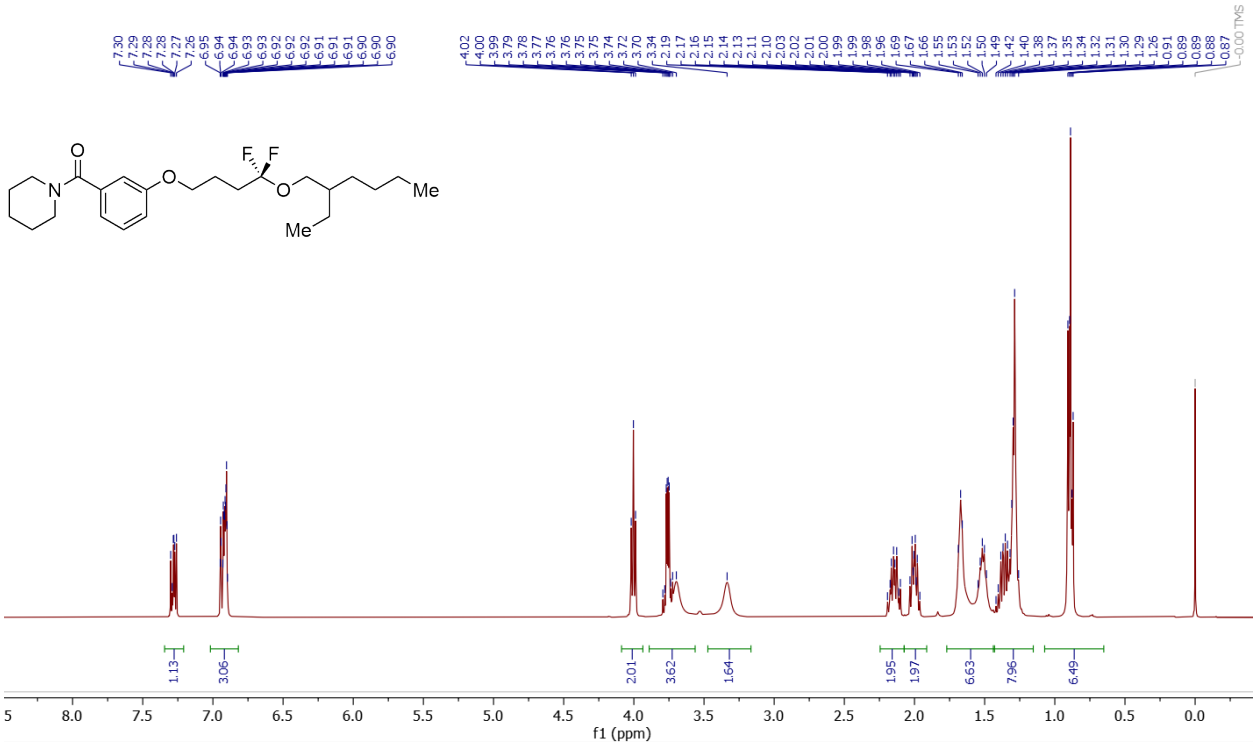


^{13}C NMR spectrum of **24** (101 MHz, $CDCl_3$)

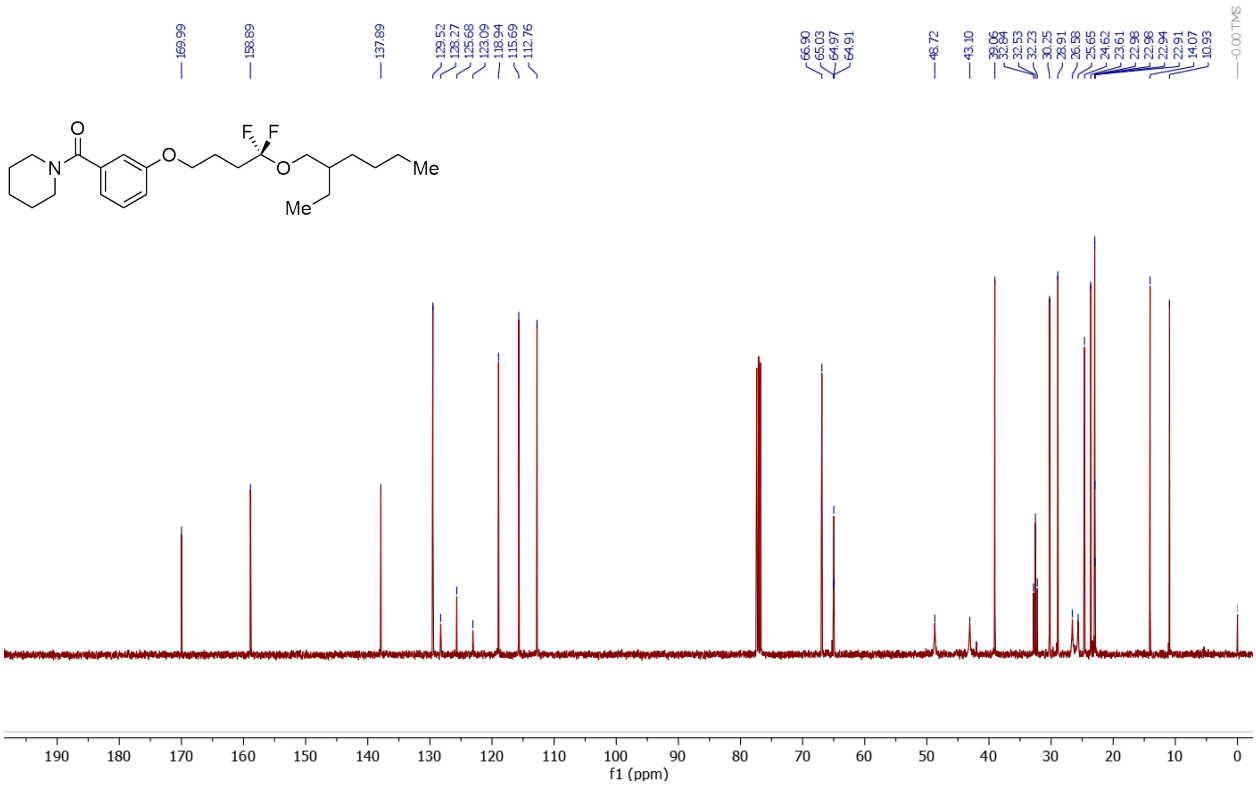


^{19}F NMR spectrum of **24** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

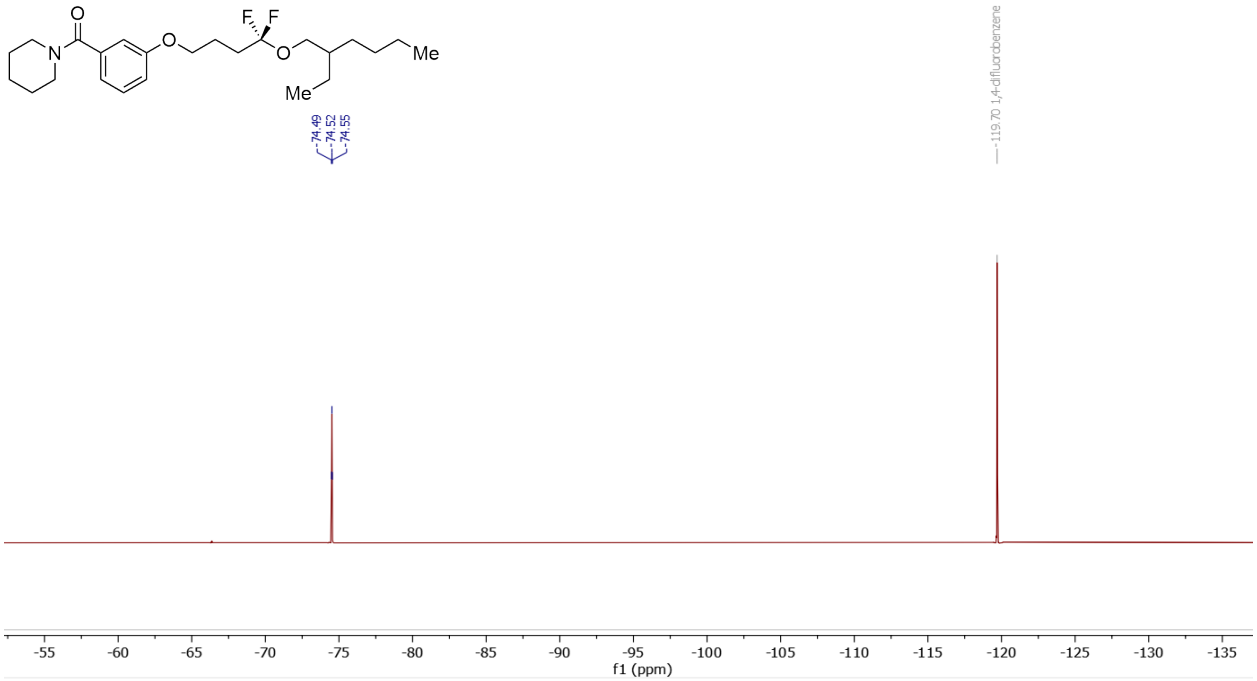
(3-(4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)phenyl)(piperidin-1-yl)methanone (25)



^{1}H NMR spectrum of **25** (400 MHz, $CDCl_3$)

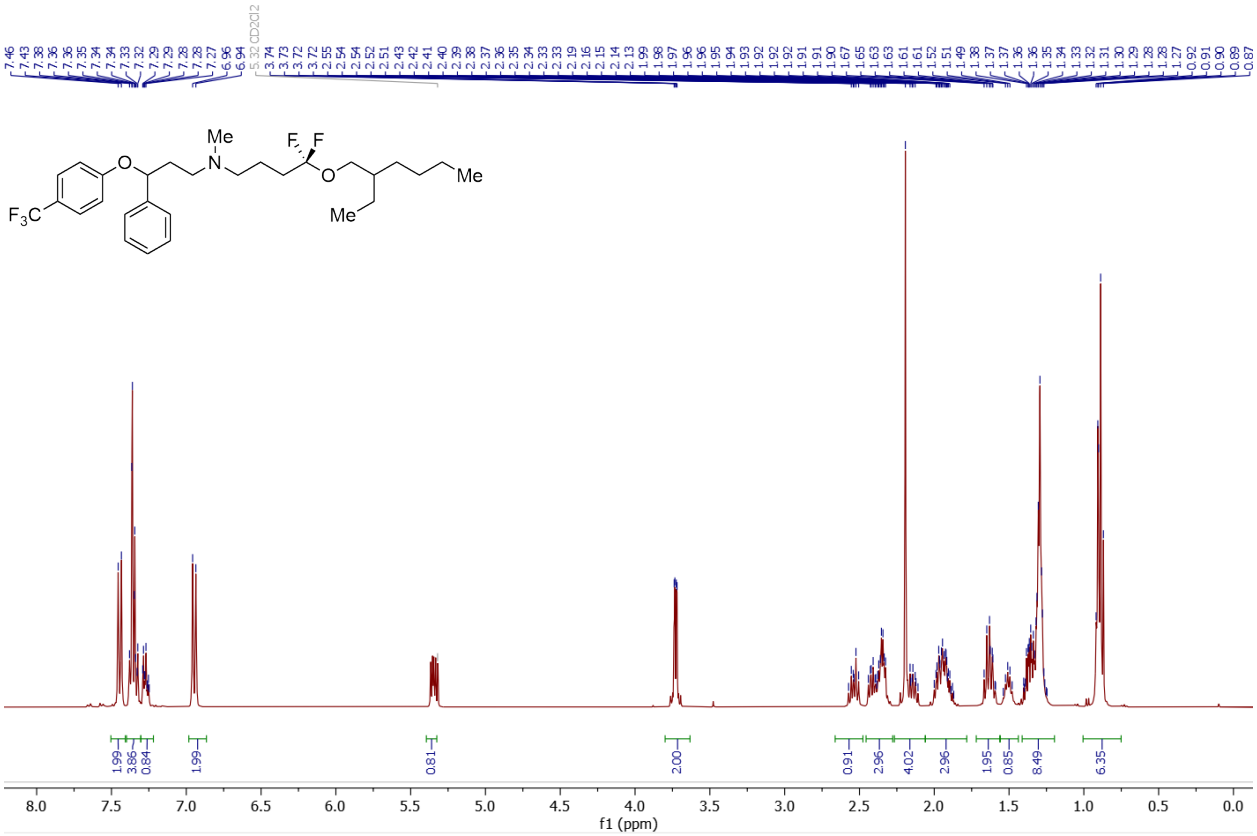


^{13}C NMR spectrum of **25** (101 MHz, $CDCl_3$)

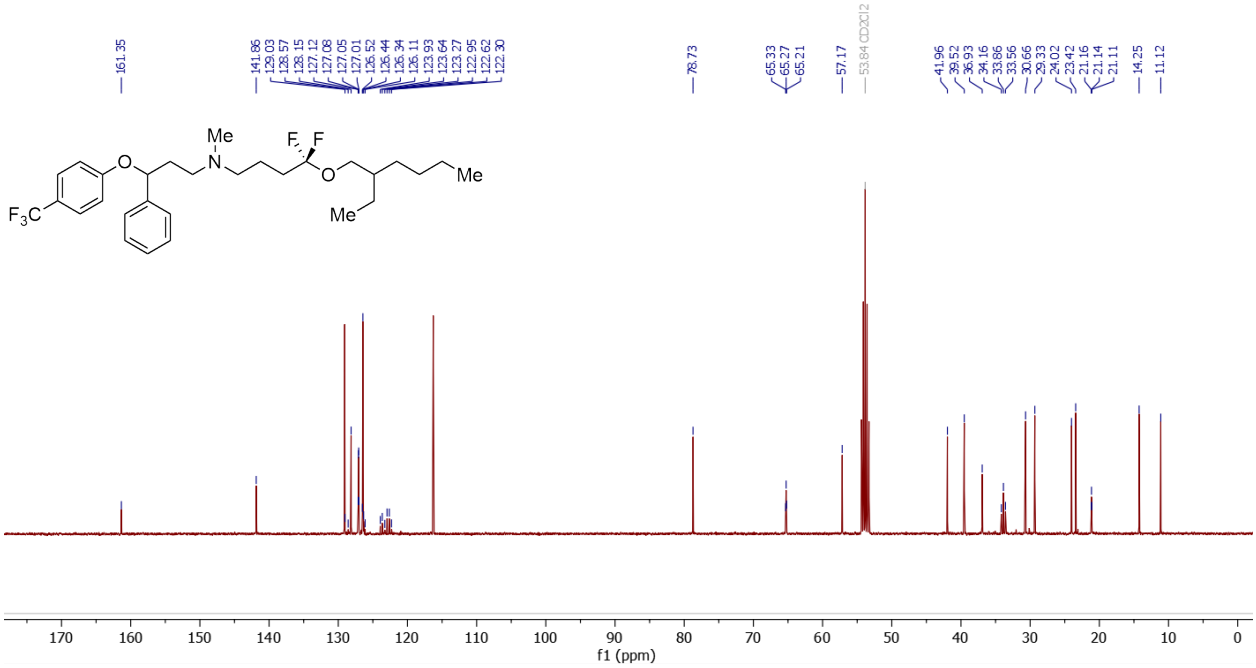


^{19}F NMR spectrum of **25** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

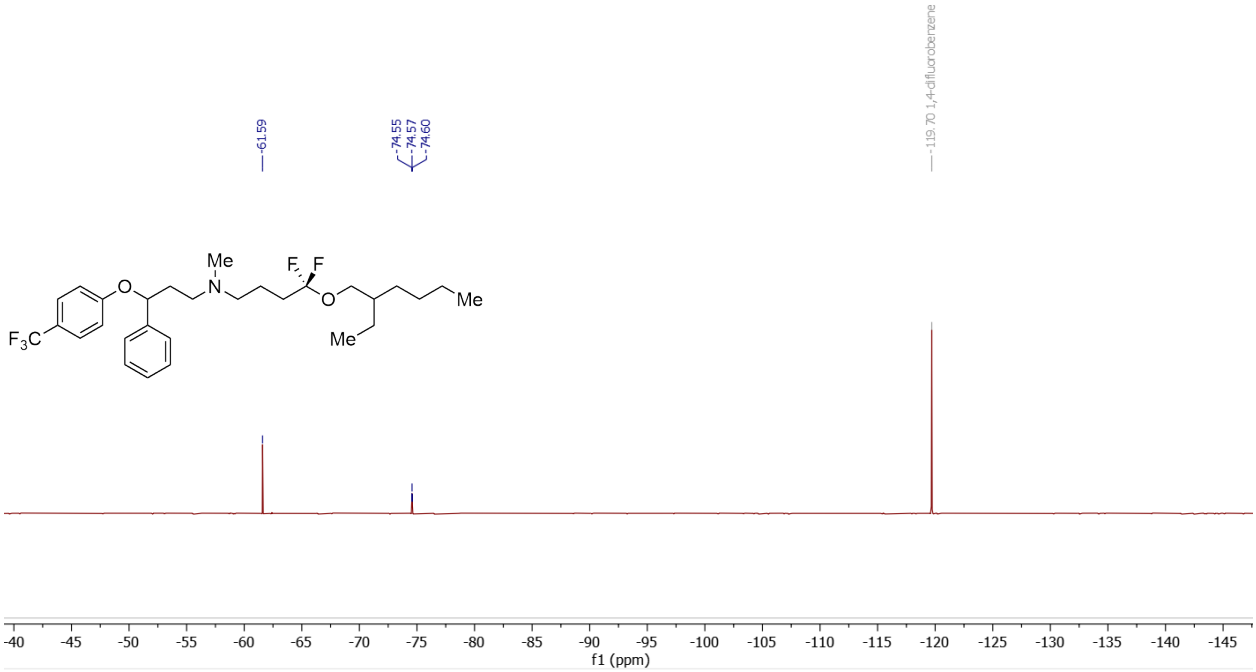
4-((2-ethylhexyl)oxy)-4,4-difluoro-*N*-methyl-N-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butan-1-amine (26)



^{1}H NMR spectrum of **26** (400 MHz, $CDCl_3$)

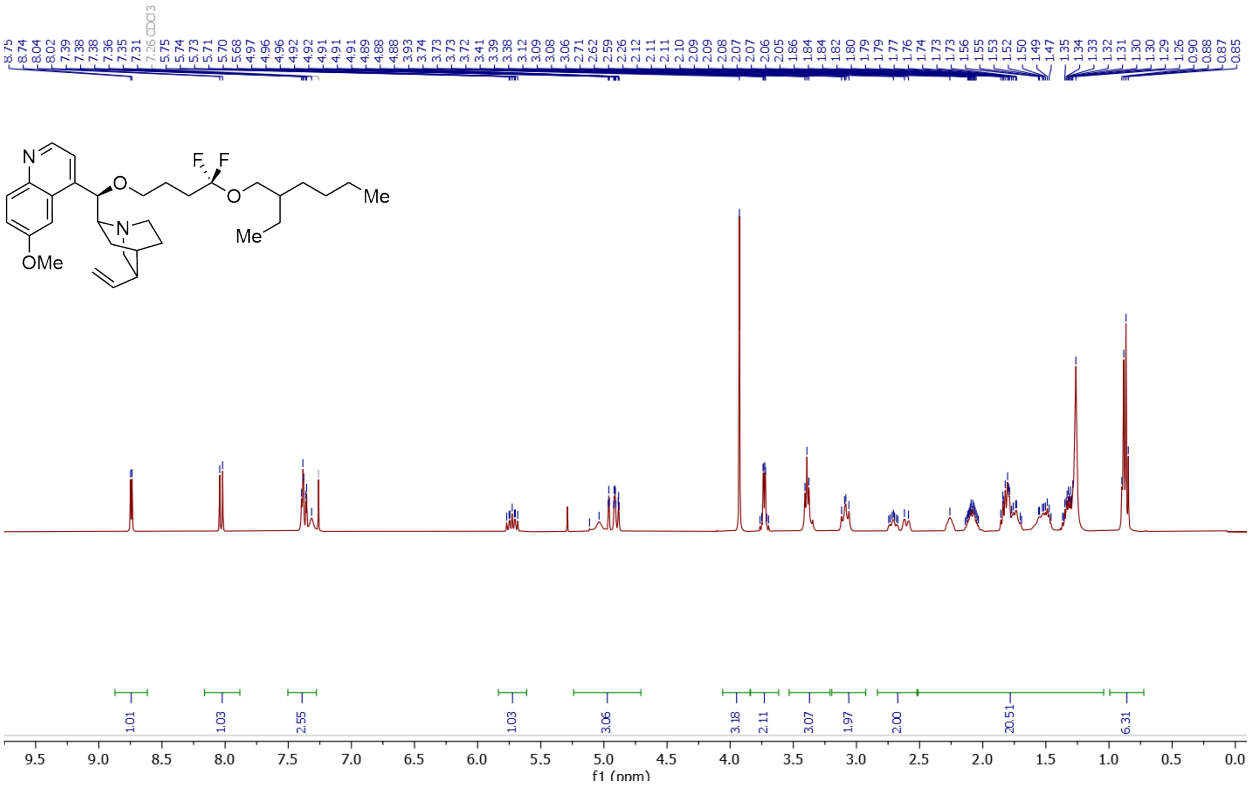


^{13}C NMR spectrum of **26** (101 MHz, $CDCl_3$

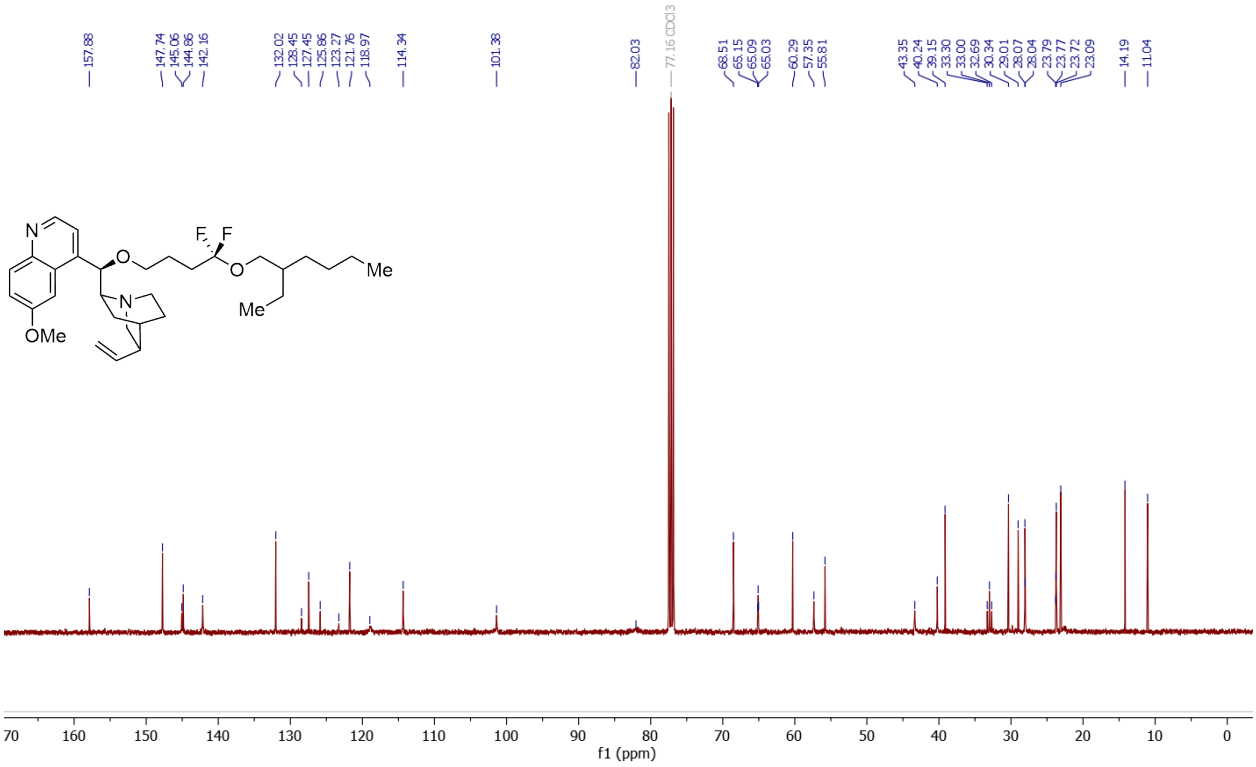


^{19}F NMR spectrum of **26** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

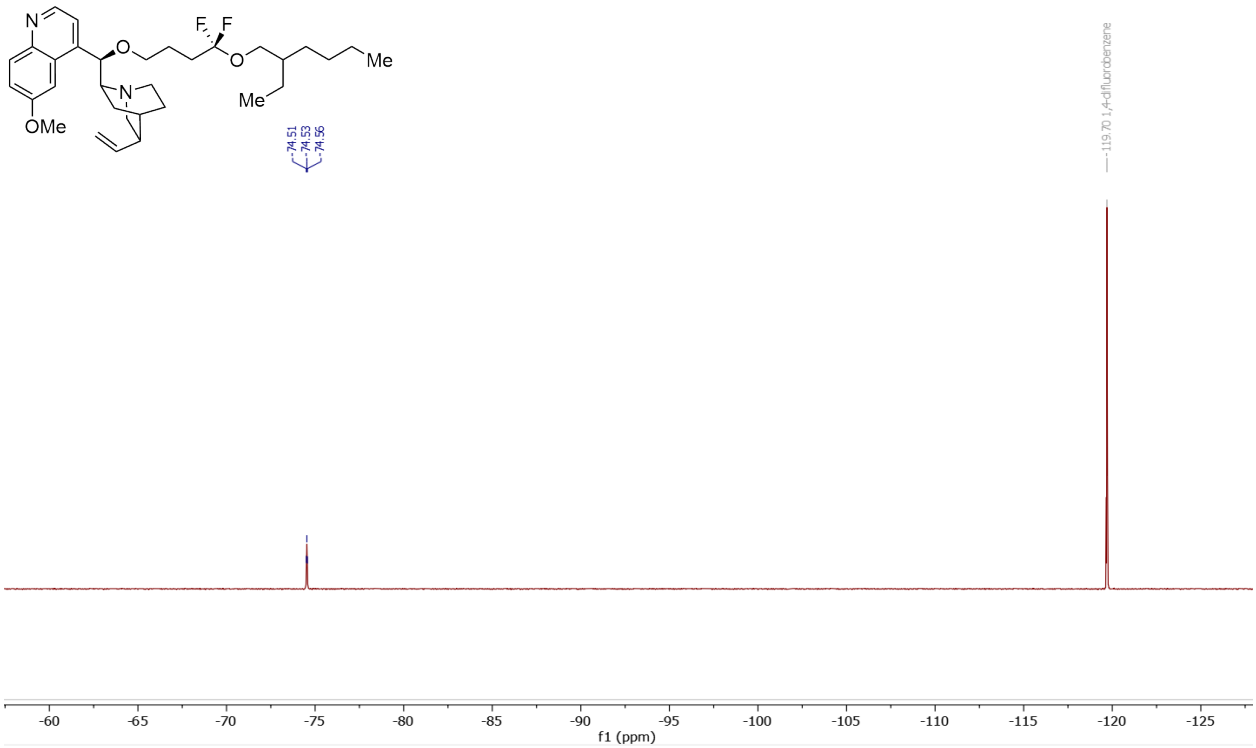
(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-(4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (27)



^{1}H NMR spectrum of **27** (400 MHz, $CDCl_3$)

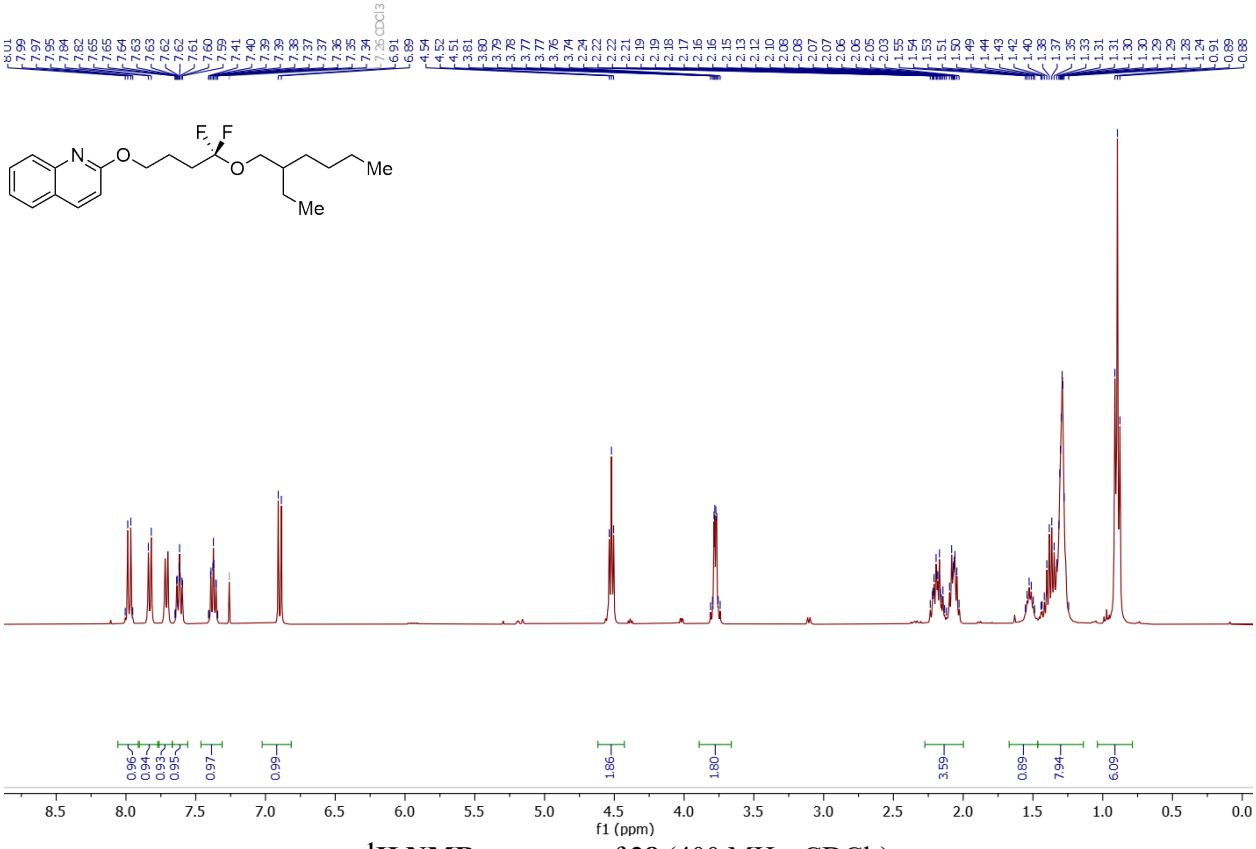


^{13}C NMR spectrum of **27** (101 MHz, $CDCl_3$)

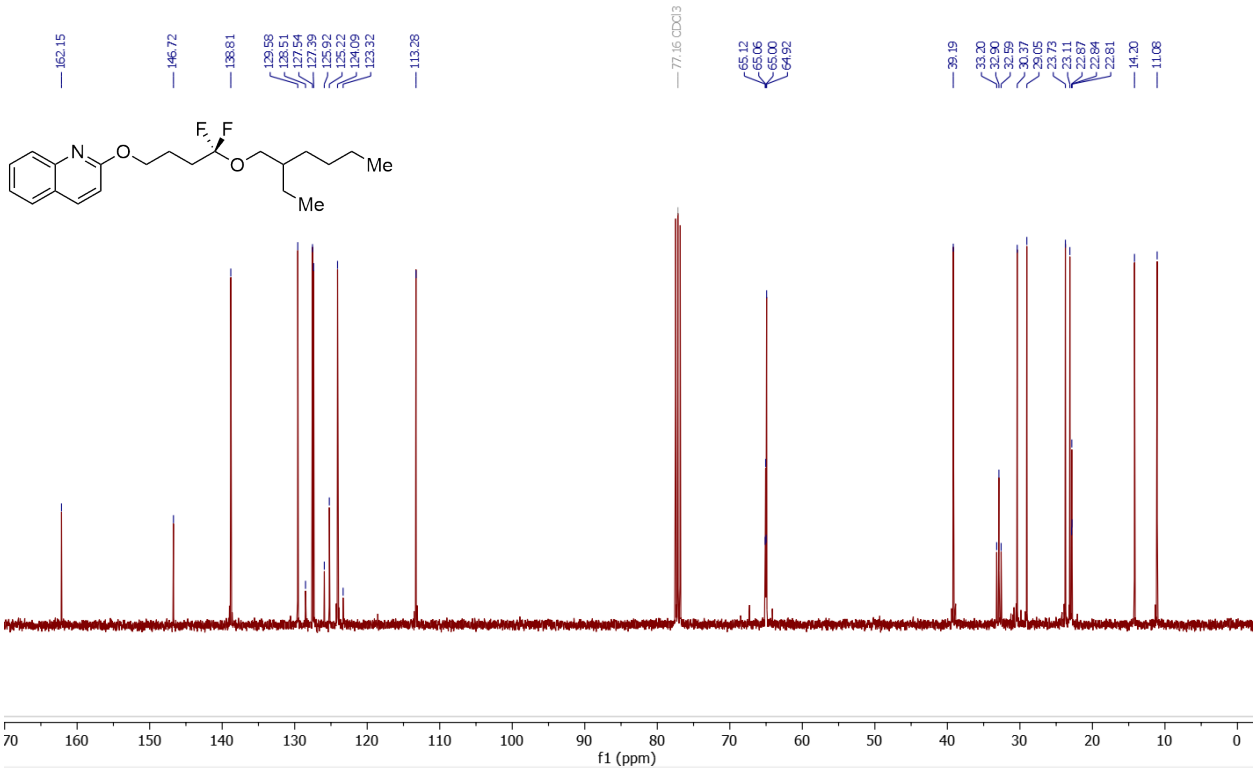


^{19}F NMR spectrum of **27** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

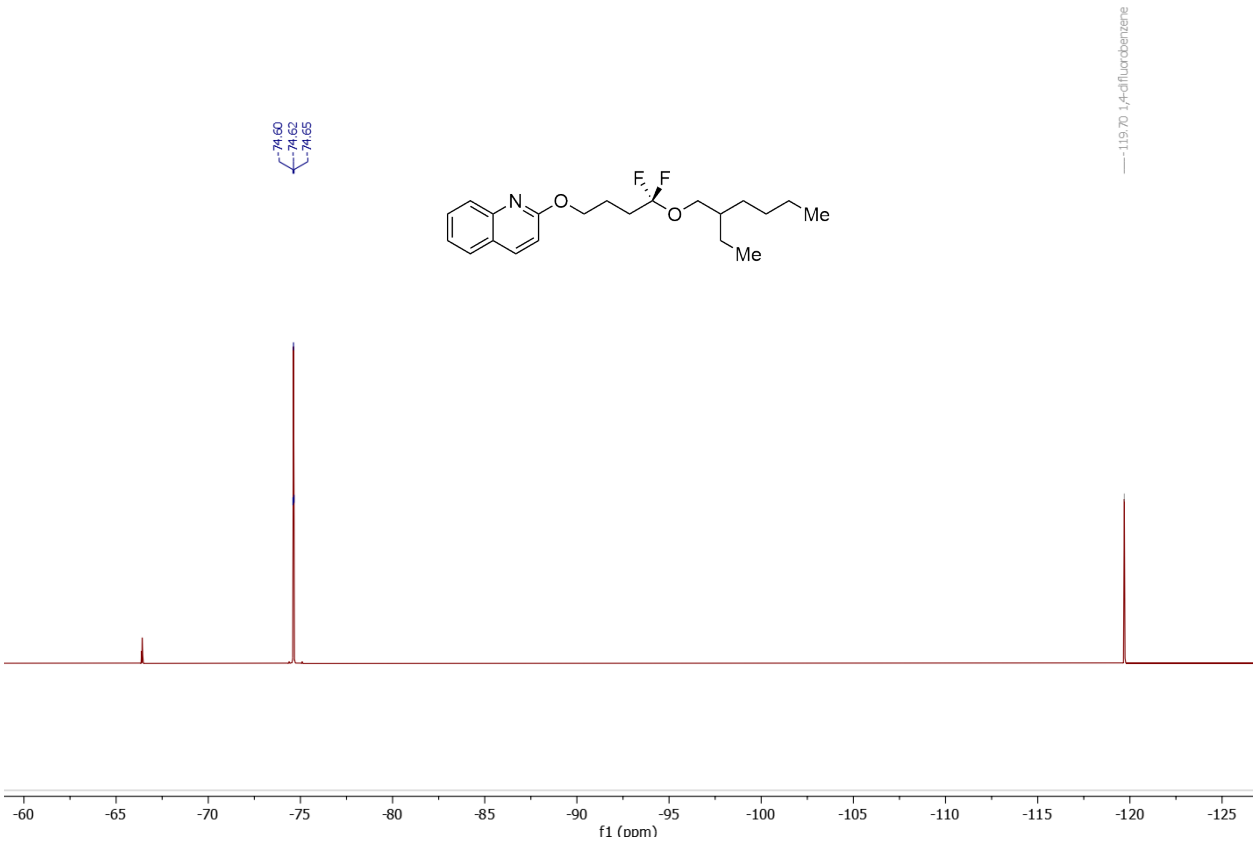
2-(4-((2-ethylhexyl)oxy)-4,4-difluorobutoxy)quinoline (28)



^{1}H NMR spectrum of **28** (400 MHz, $CDCl_3$)

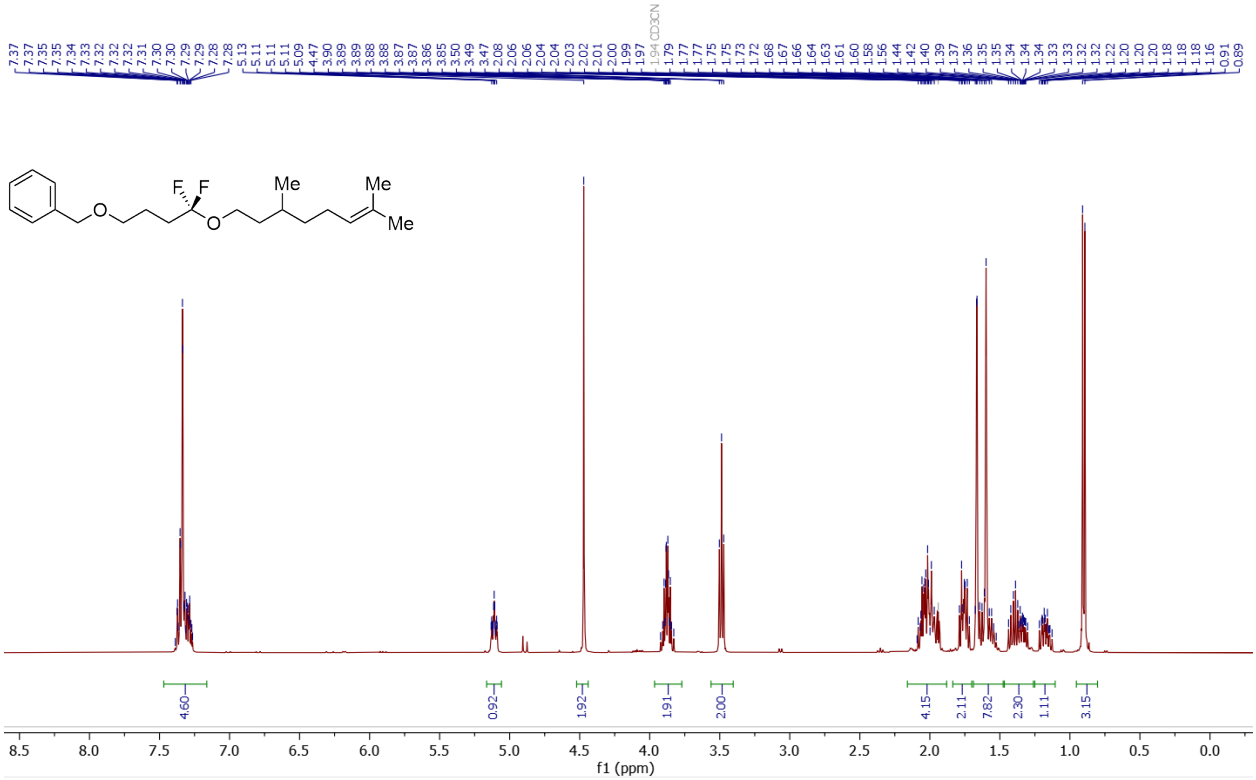


^{13}C NMR spectrum of **28** (101 MHz, $CDCl_3$)

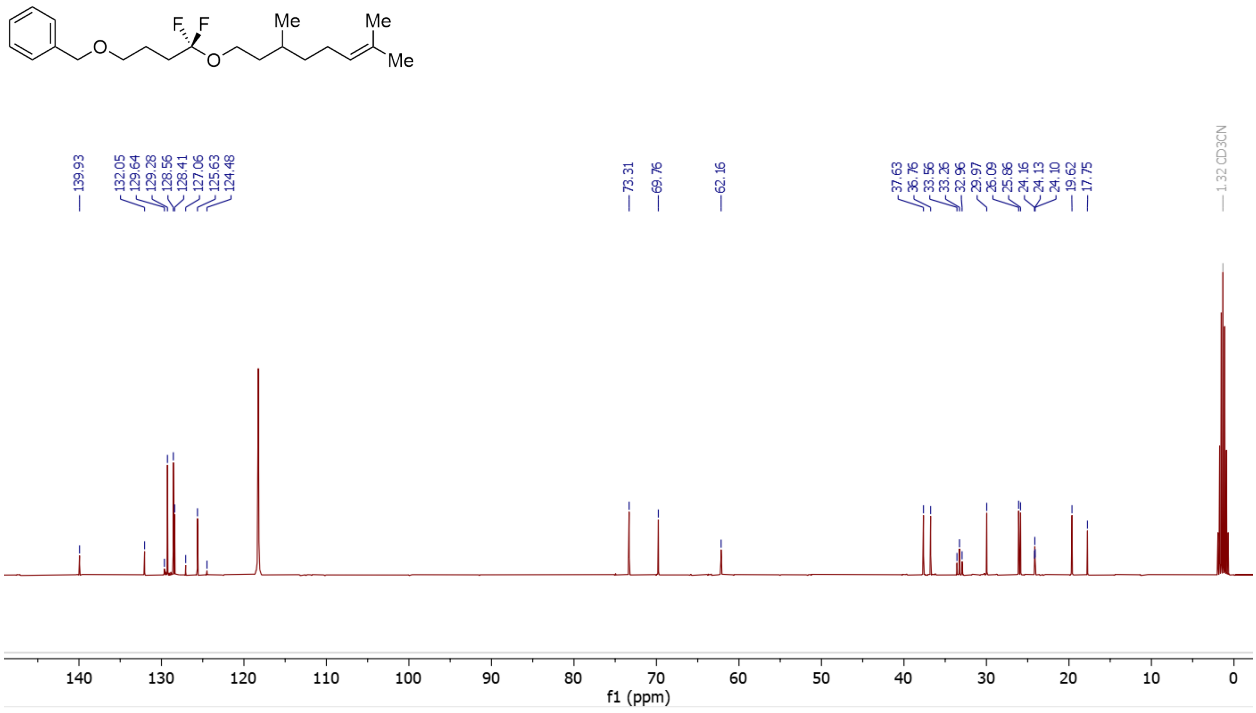


^{19}F NMR spectrum of **28** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

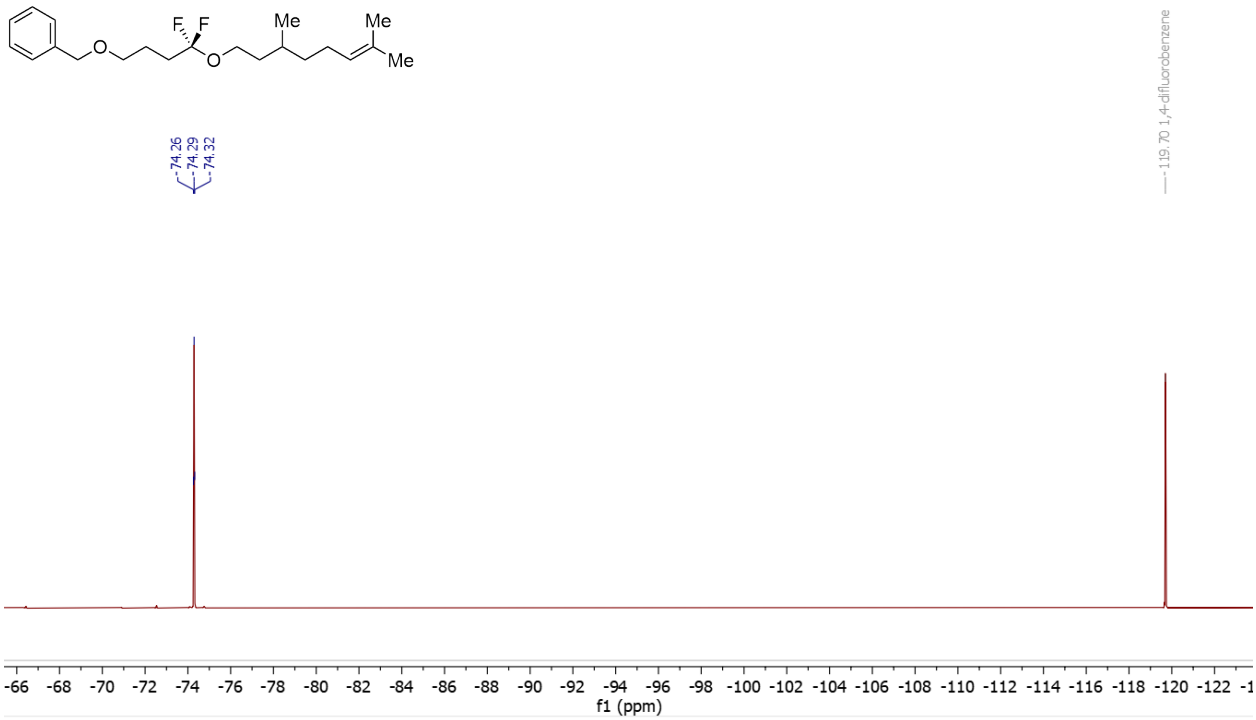
((4-((3,7-dimethyloct-6-en-1-yl)oxy)-4,4-difluorobutoxy)methyl)benzene (29)



^{1}H NMR spectrum of **29** (400 MHz, CD_3CN)

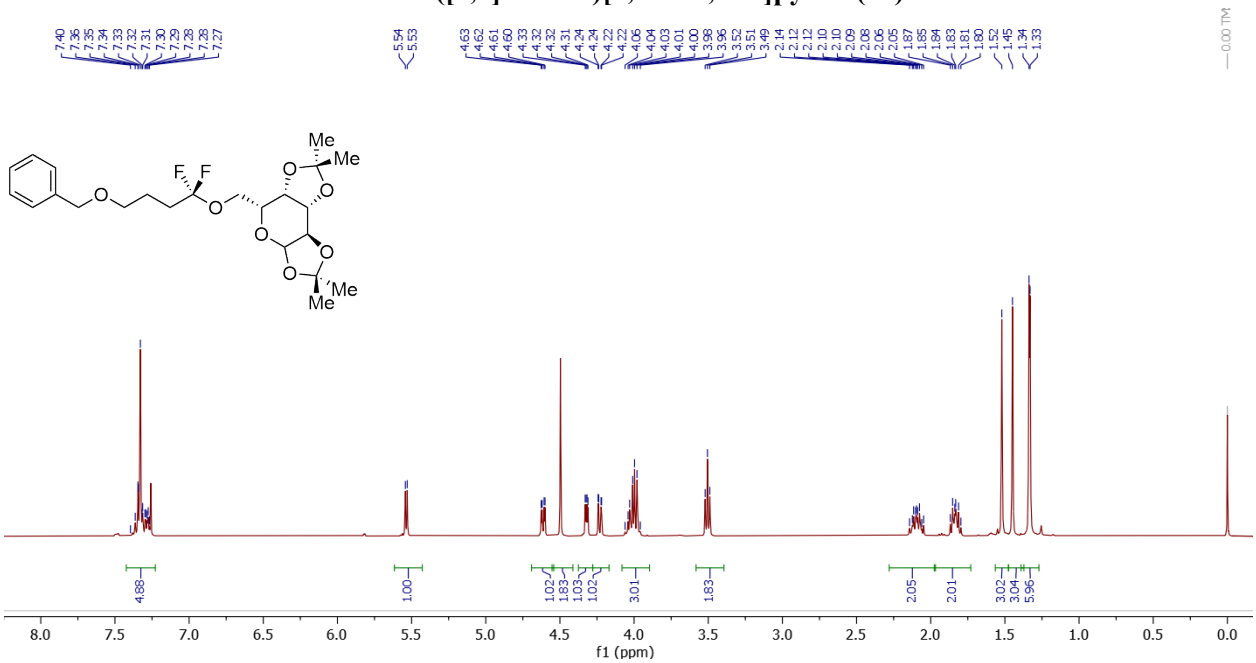


^{13}C NMR spectrum of **29** (101 MHz, CD_3CN)

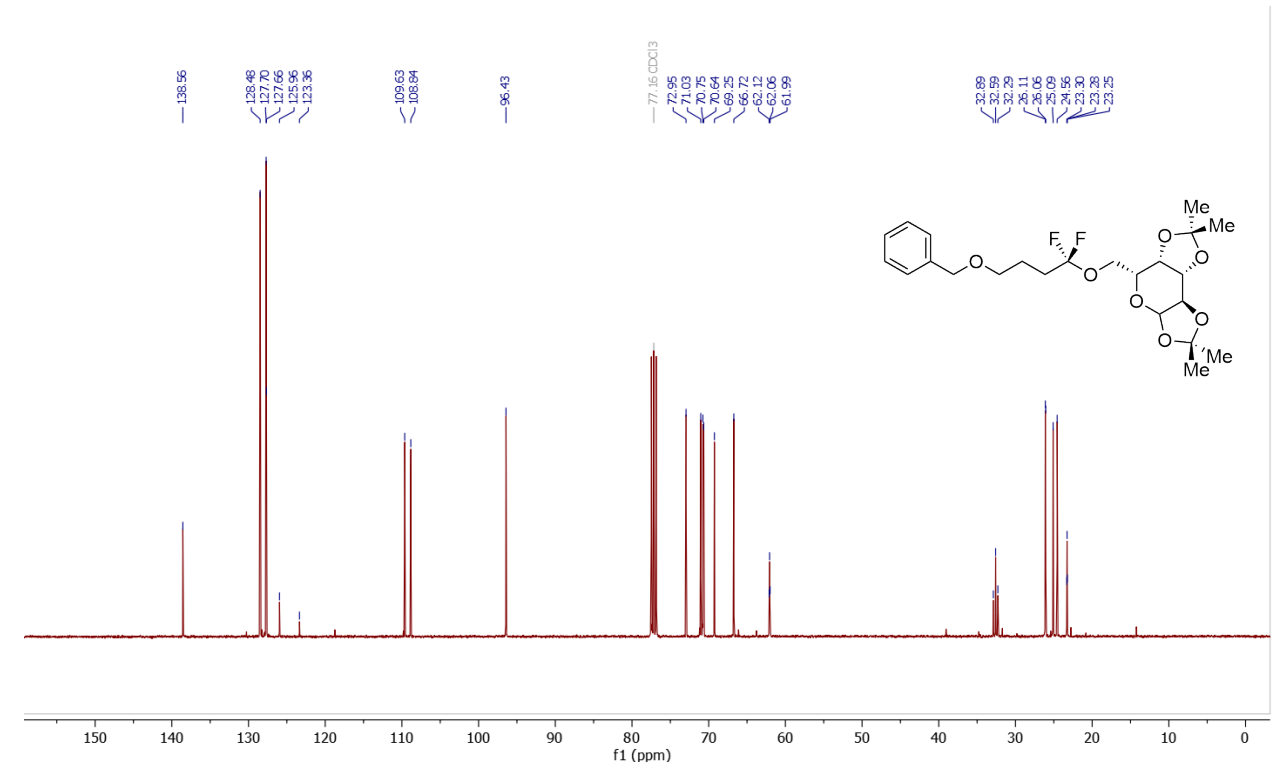


^{19}F NMR spectrum of **29** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

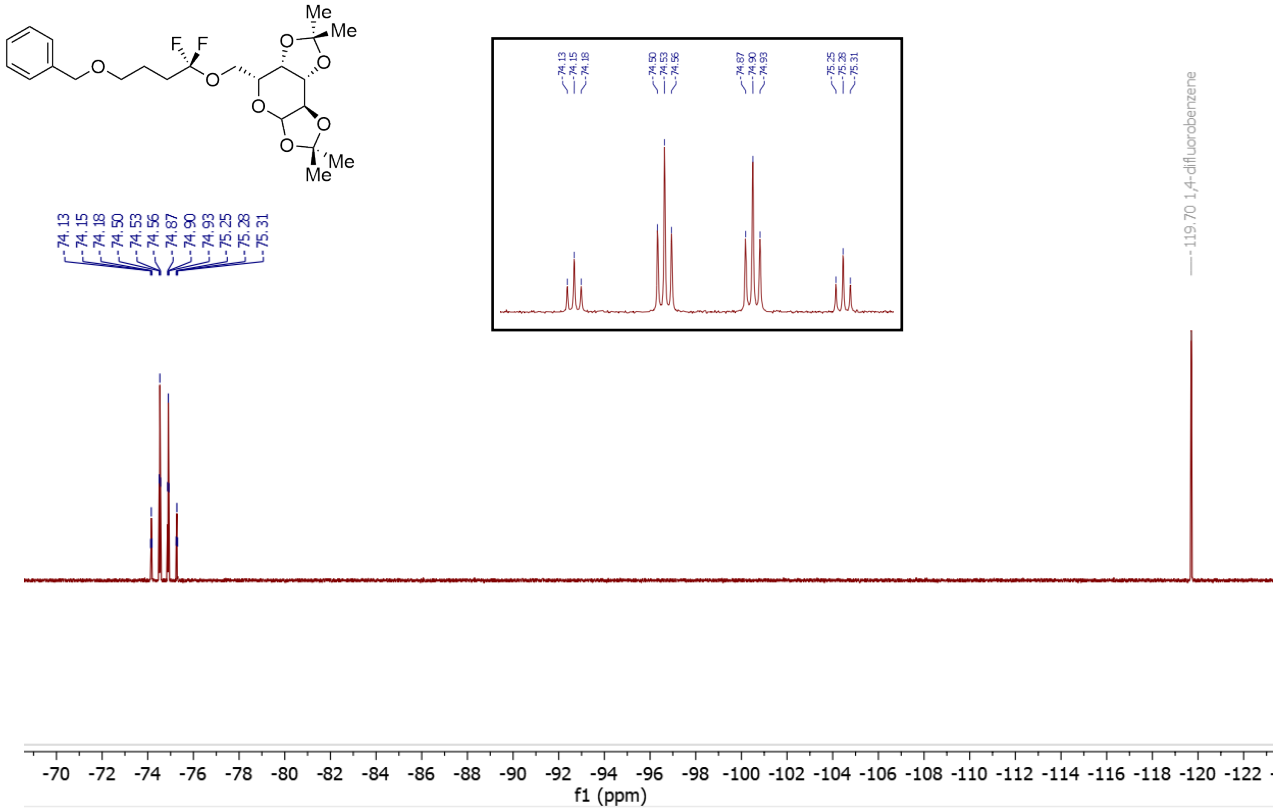
(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-5-((4-(benzyloxy)-1,1-difluorobutoxy)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (30)



^{1}H NMR spectrum of **30** (400 MHz, CD_3CN)

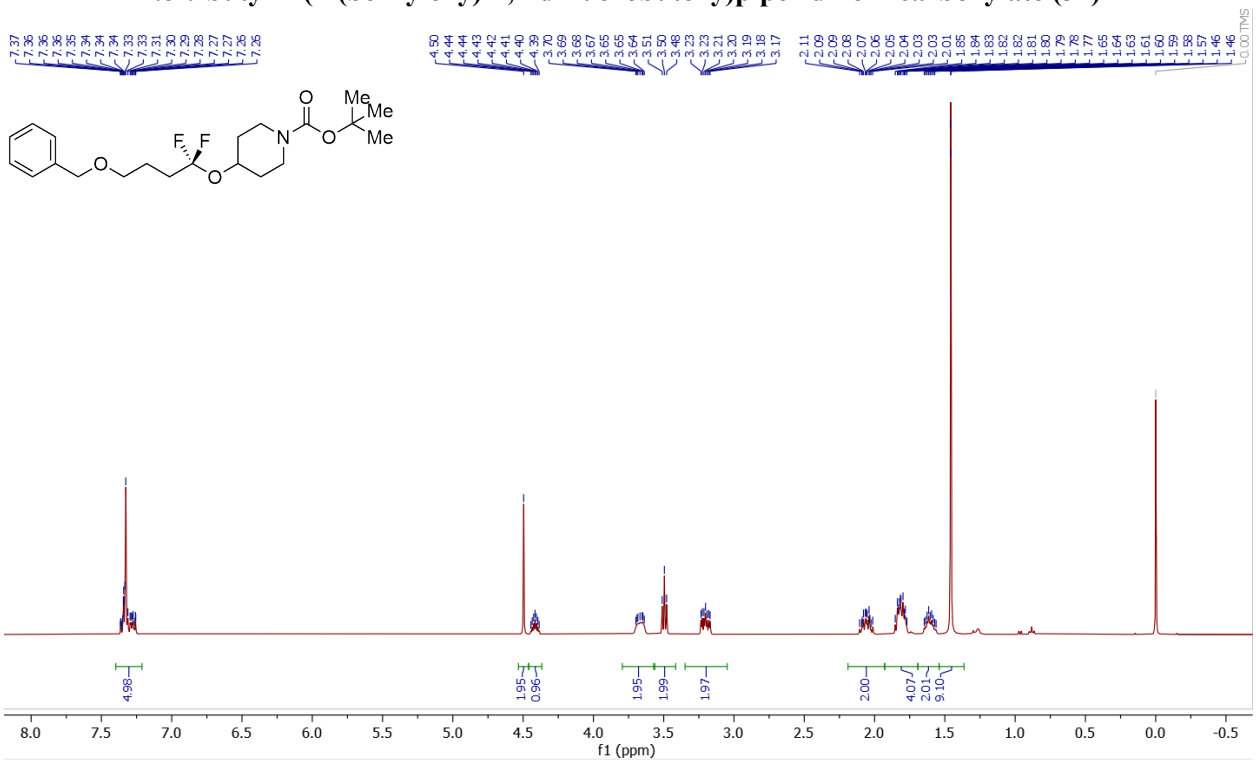


^{13}C NMR spectrum of **30** (101 MHz, $CDCl_3$)

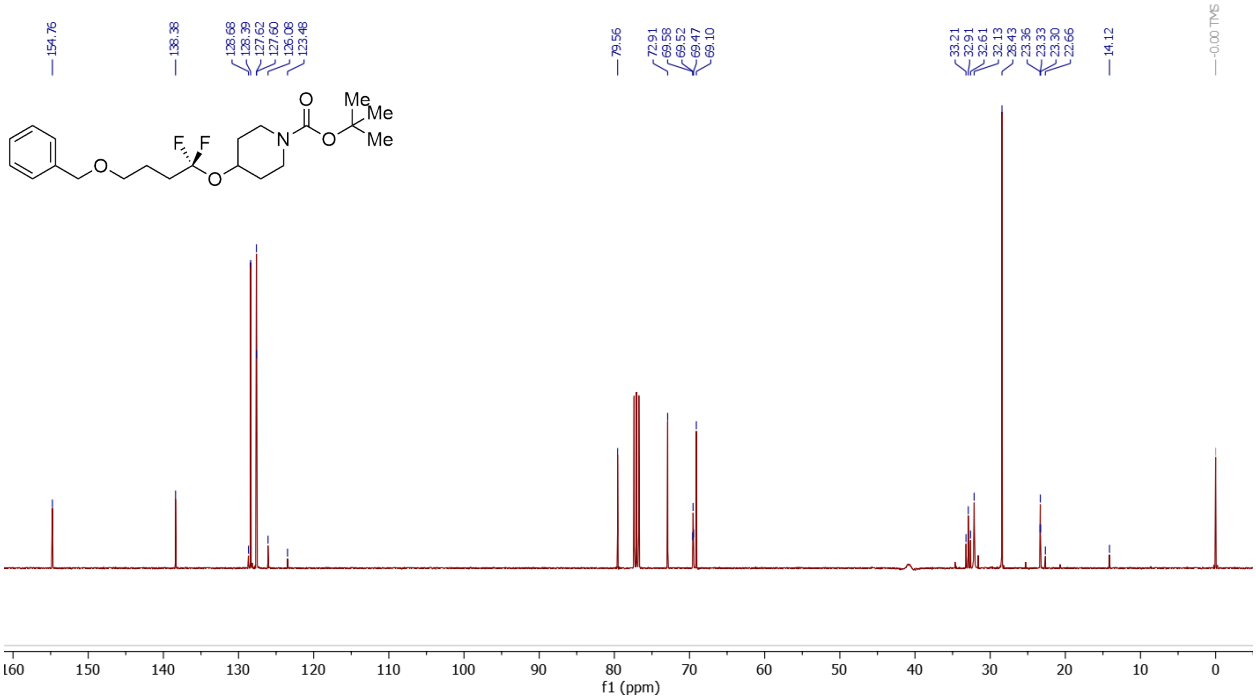


^{19}F NMR spectrum of **30** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

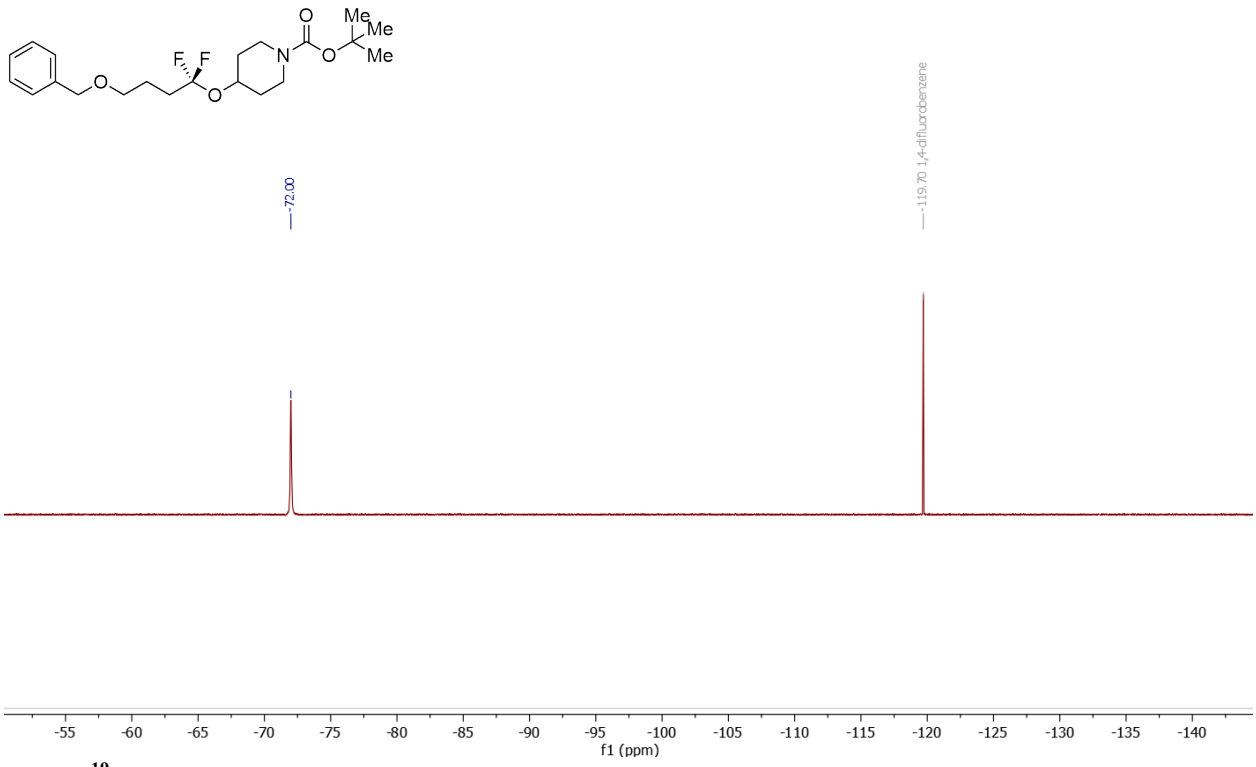
***tert*-butyl 4-(4-(benzyloxy)-1,1-difluorobutoxy)piperidine-1-carboxylate (31)**



^{1}H NMR spectrum of **31** (400 MHz, $CDCl_3$)

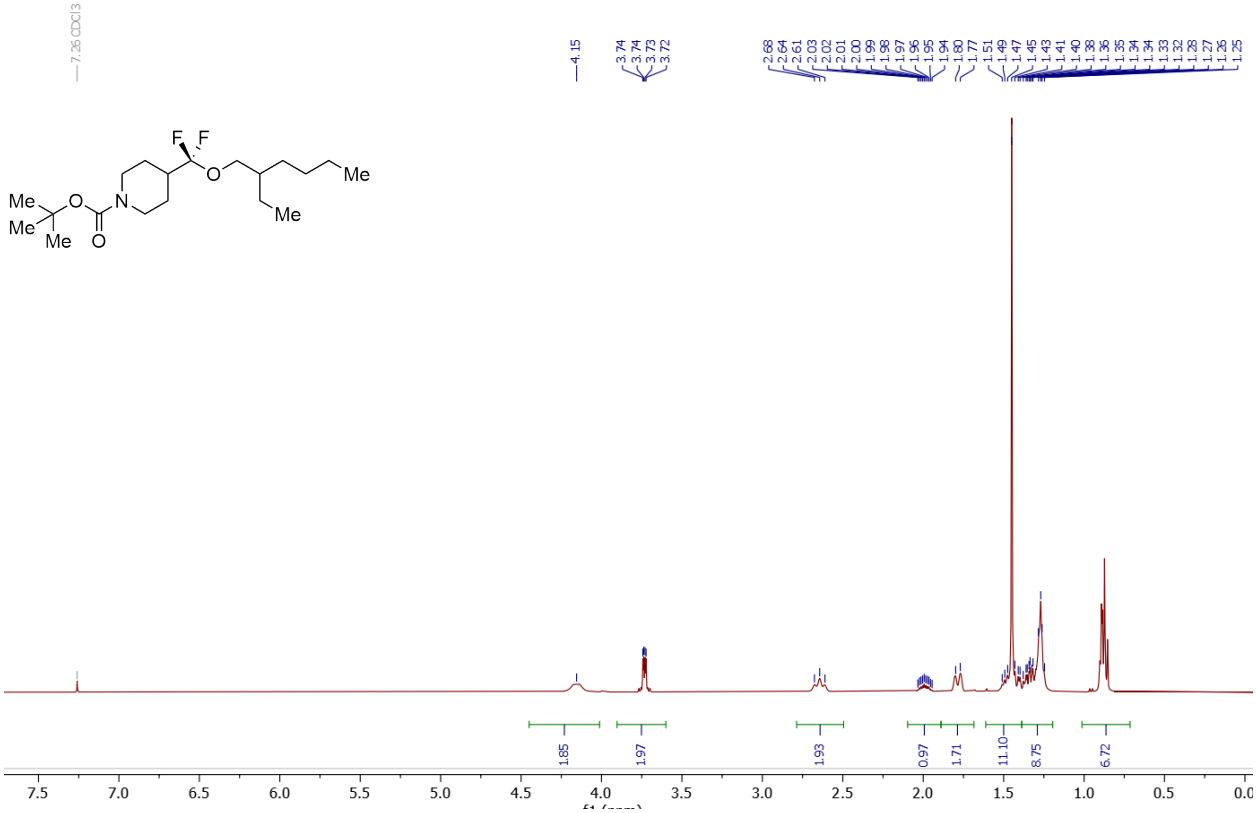


^{13}C NMR spectrum of **31** (101 MHz, $CDCl_3$

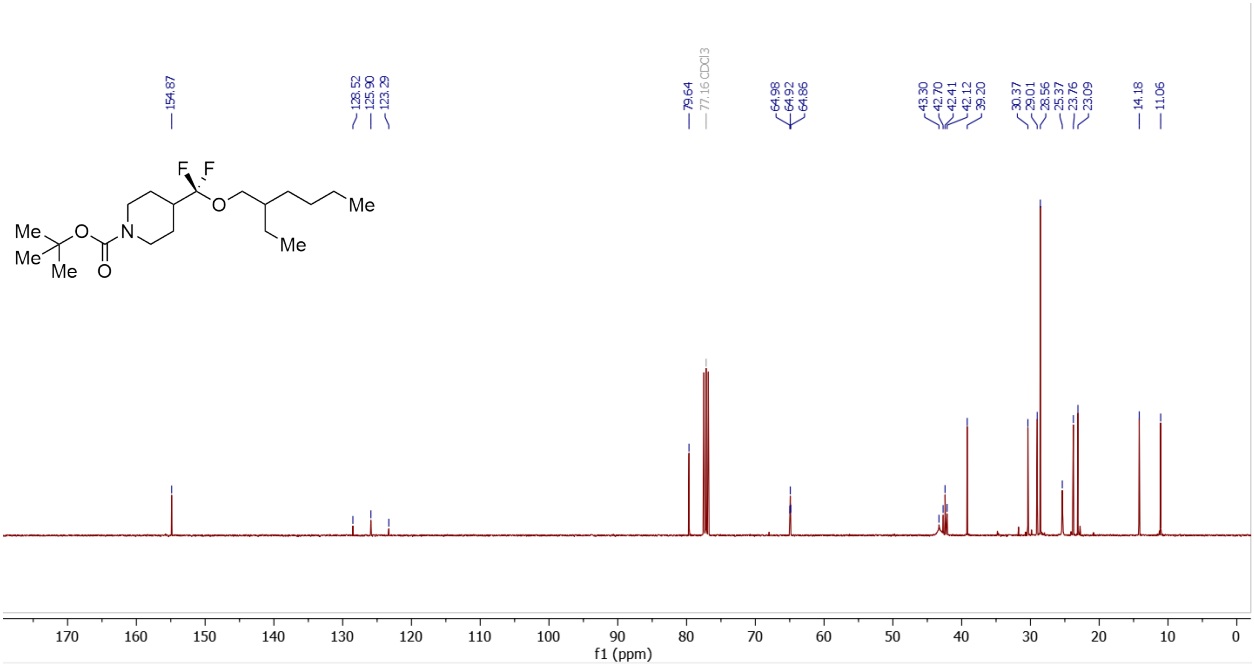


^{19}F NMR spectrum of **31** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

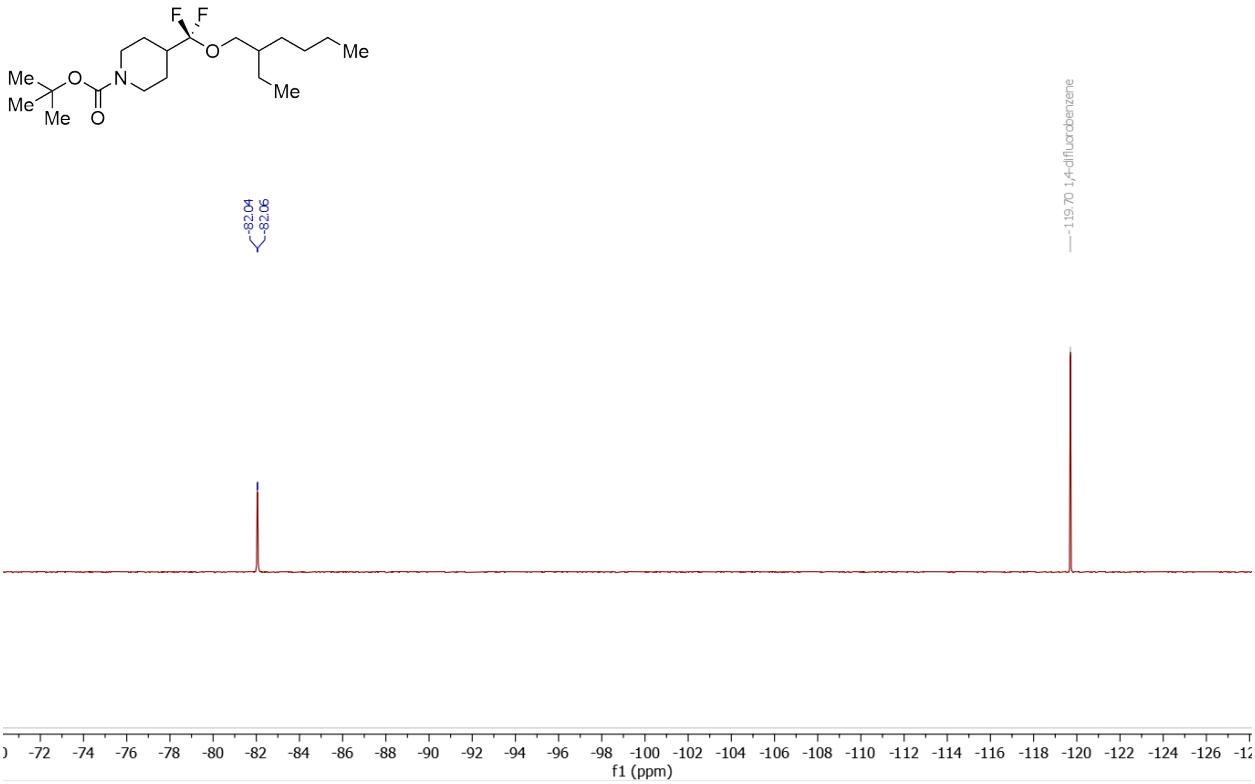
***tert*-butyl 4-(((2-ethylhexyl)oxy)difluoromethyl)piperidine-1-carboxylate (32)**



^{1}H NMR spectrum of **32** (400 MHz, $CDCl_3$)

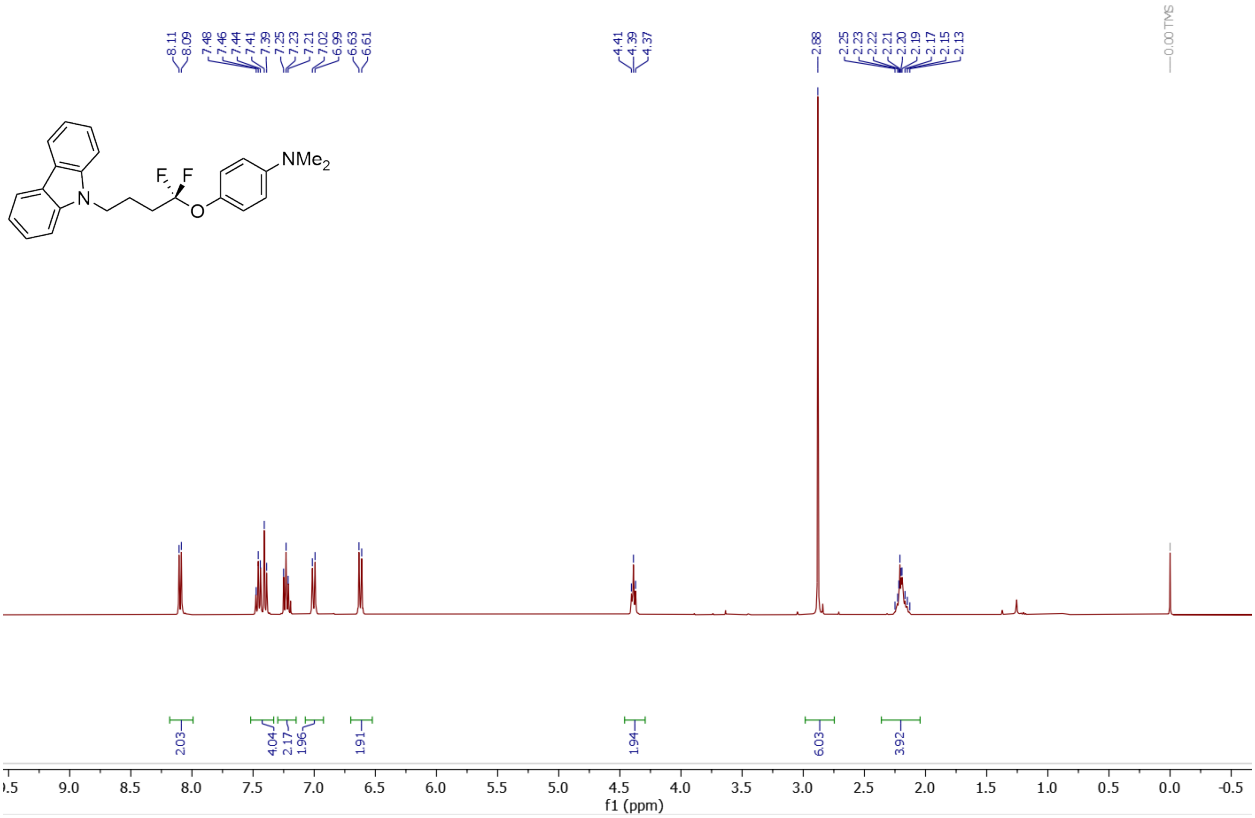


^{13}C NMR spectrum of **32** (400 MHz, $CDCl_3$)

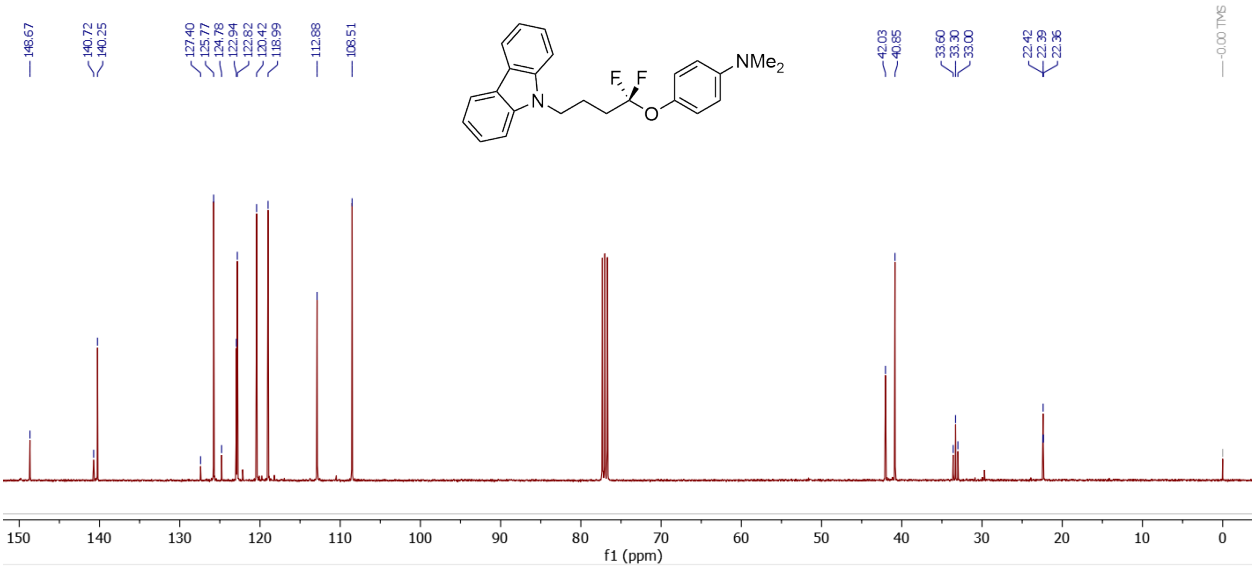


^{19}F NMR spectrum of **32** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

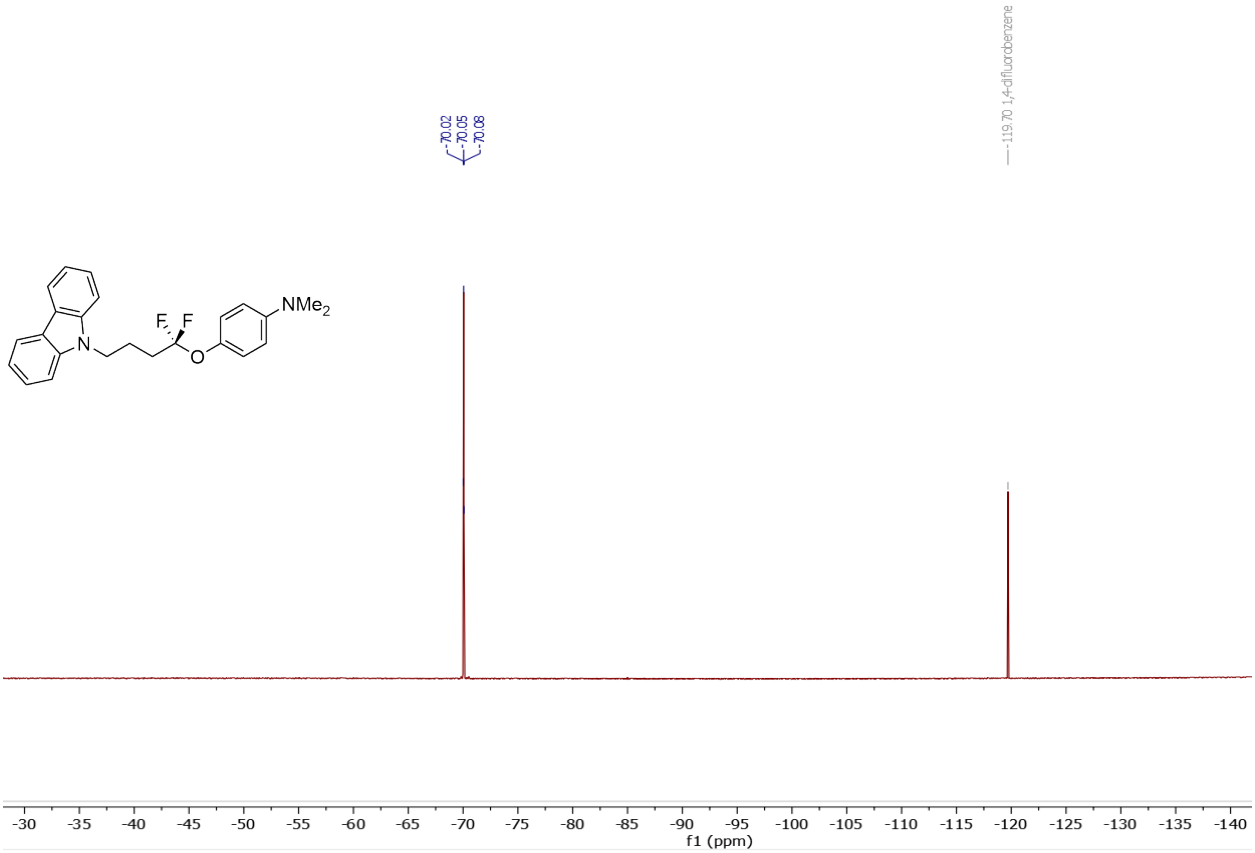
4-(4-(9H-carbazol-9-yl)-1,1-difluorobutoxy)-*N*,*N*-dimethylaniline (33)



^{1}H NMR spectrum of **33** (400 MHz, $CDCl_3$)

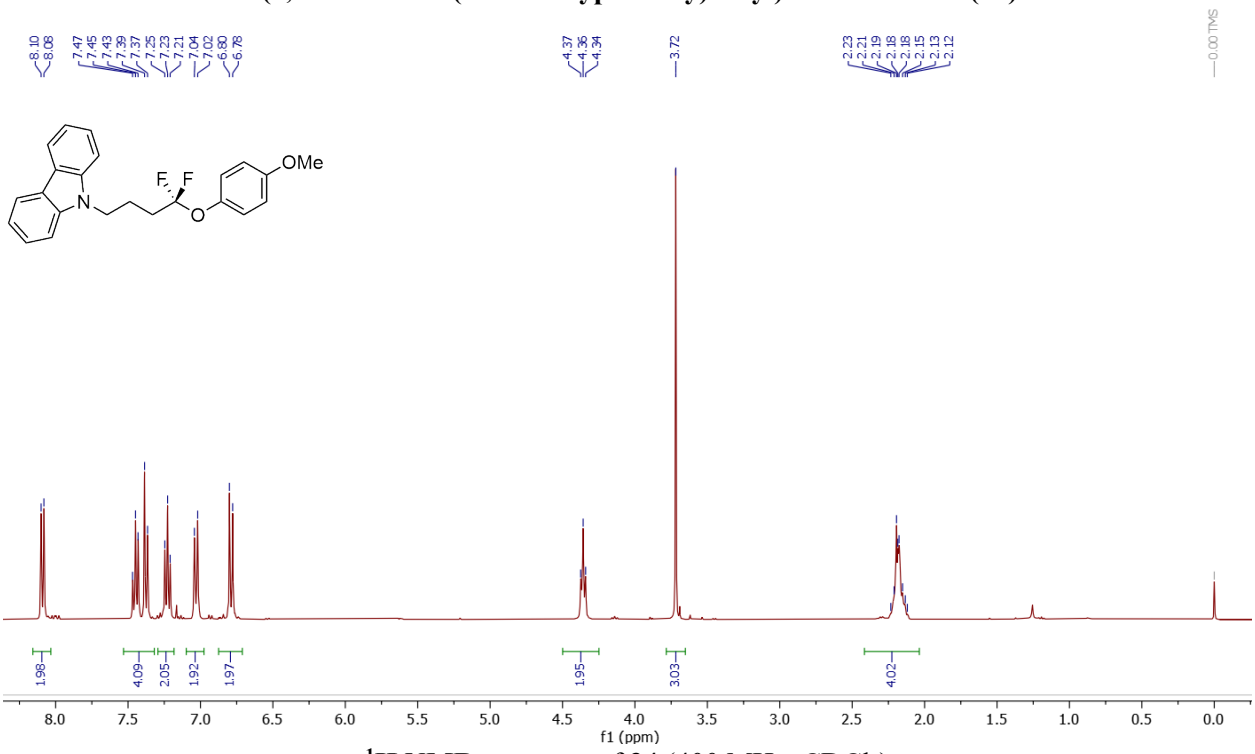


^{13}C NMR spectrum of **33** (101 MHz, $CDCl_3$)

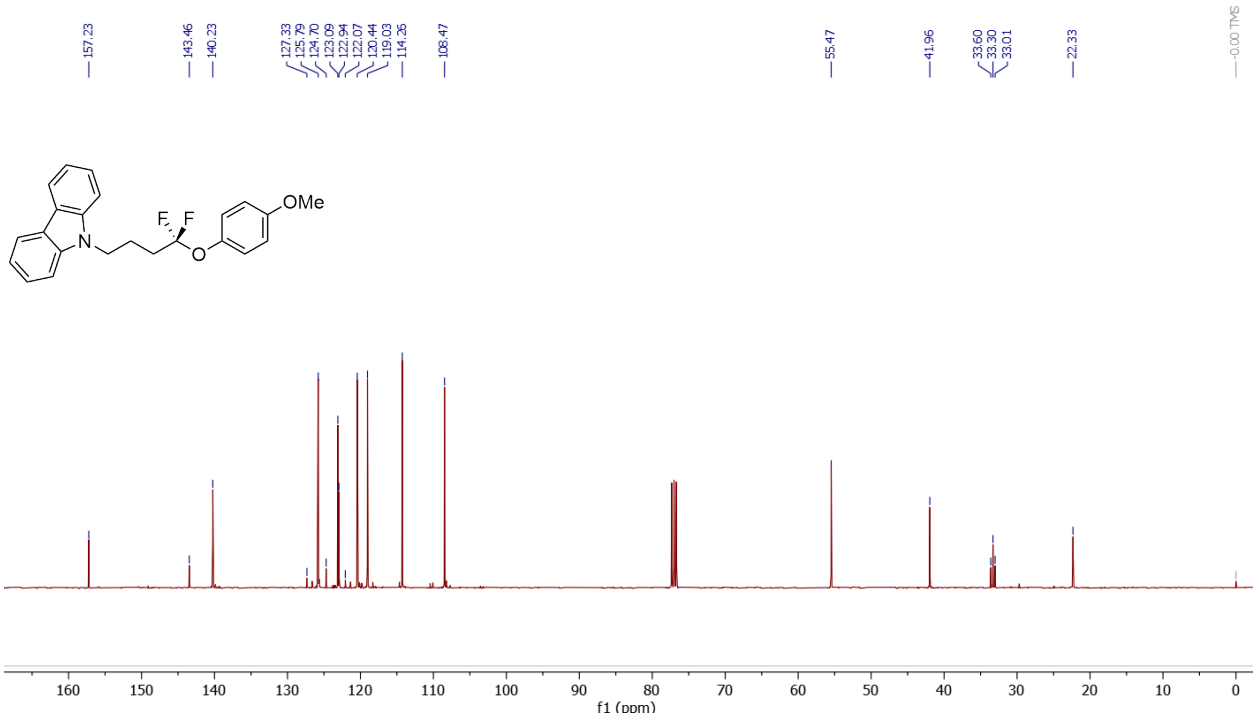


^{19}F NMR spectrum of **33** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

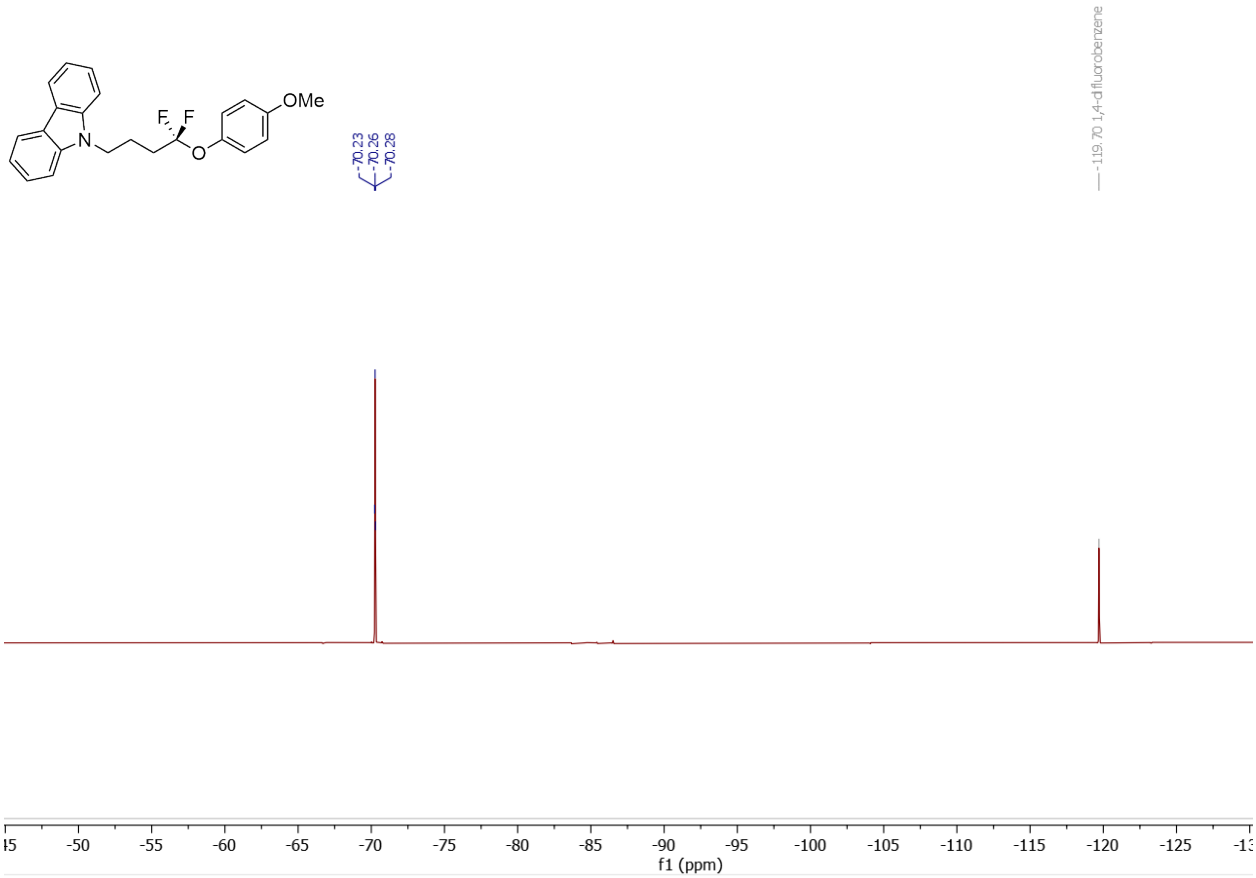
9-(4,4-difluoro-4-(4-methoxyphenoxy)butyl)-9H-carbazole (34)



^{1}H NMR spectrum of **34** (400 MHz, $CDCl_3$)

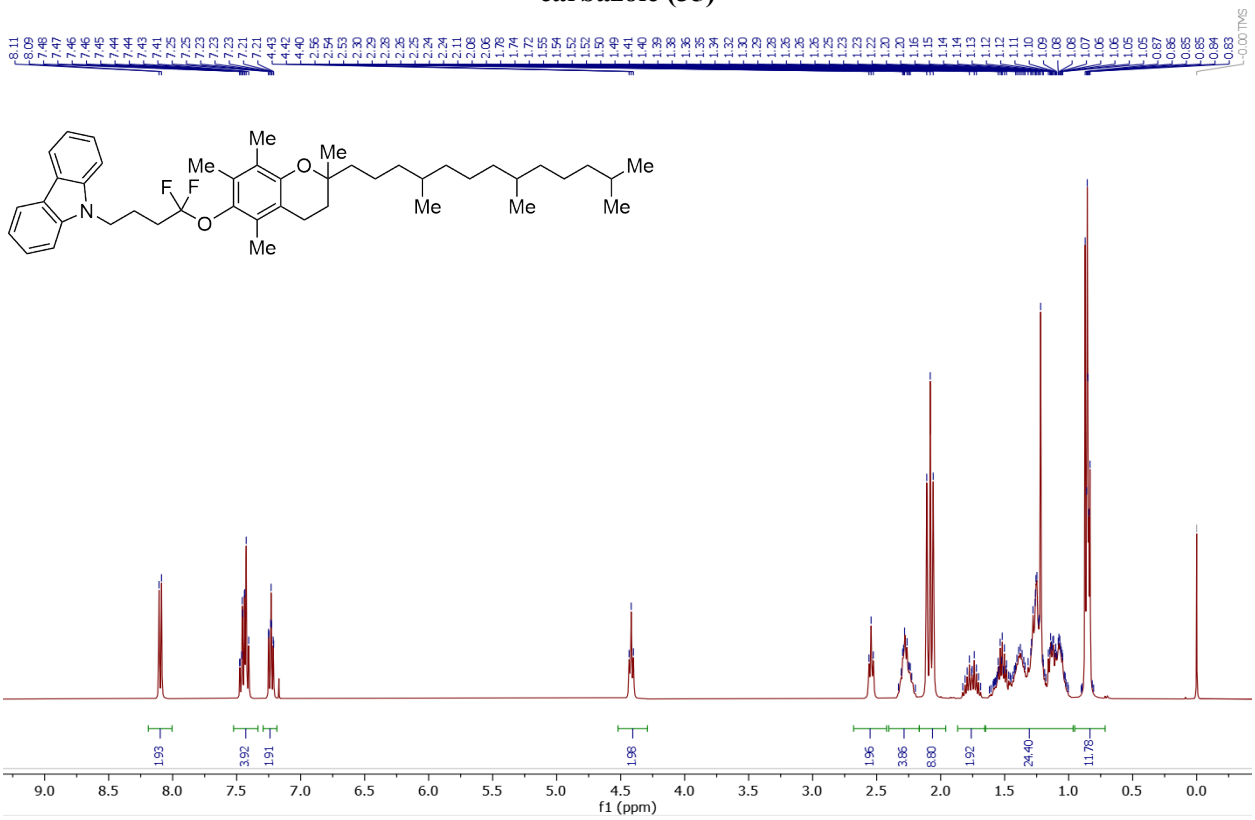


^{13}C NMR spectrum of **34** (101 MHz, $CDCl_3$)

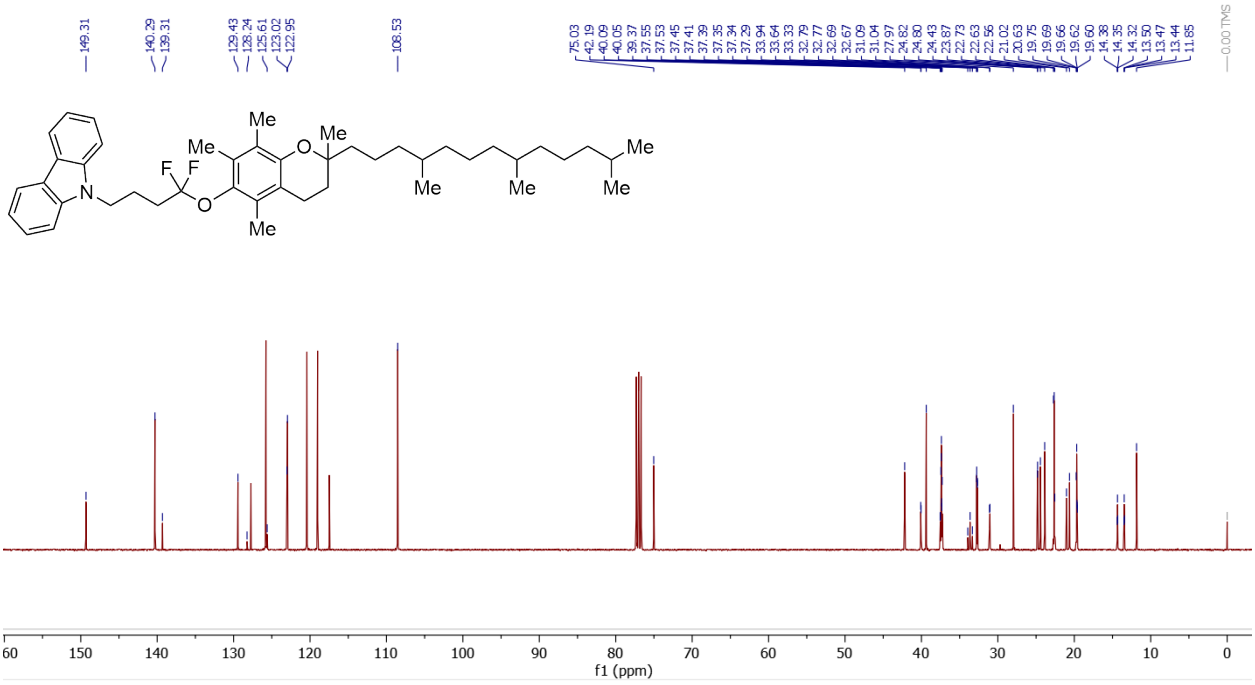


^{19}F NMR spectrum of **34** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

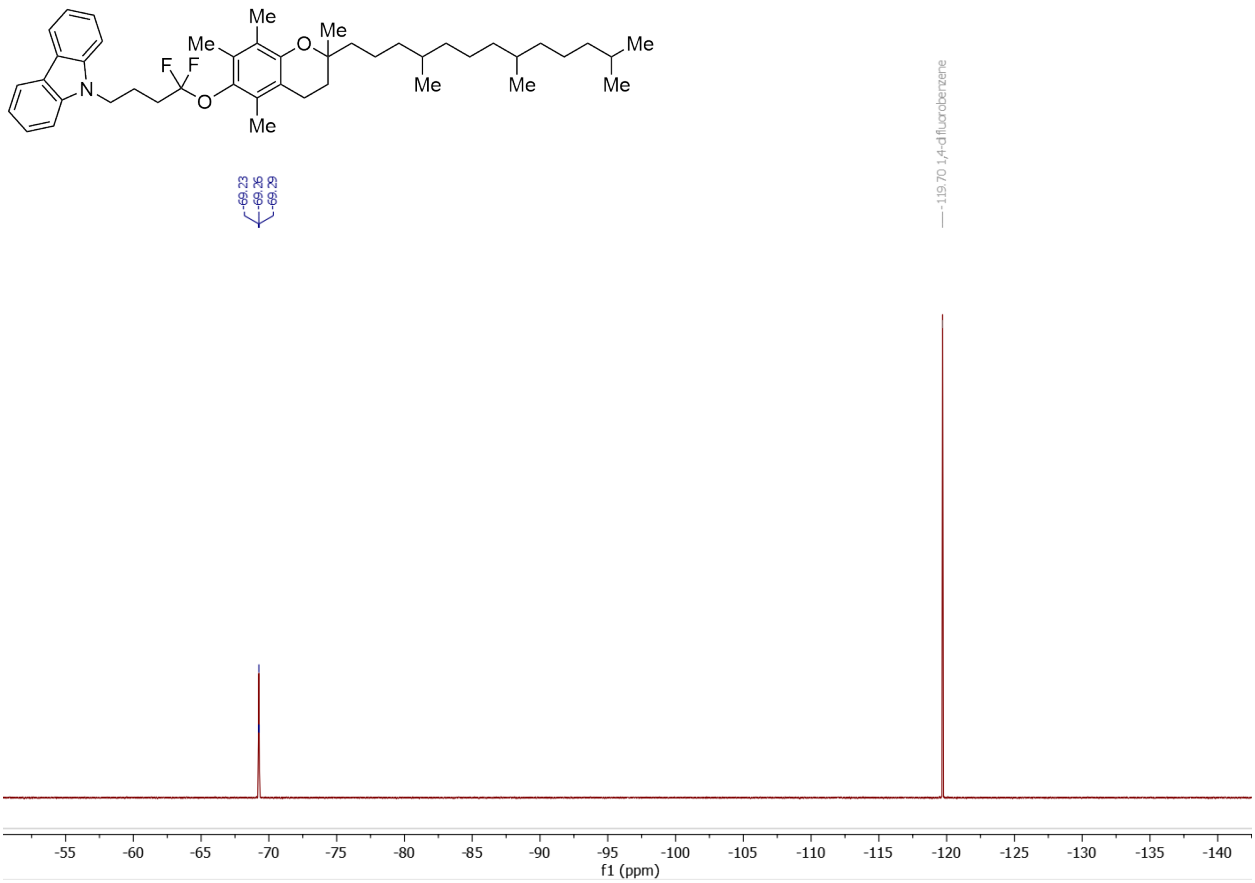
9-(4,4-difluoro-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy)butyl)-9H-carbazole (35)



^{1}H NMR spectrum of **35** (400 MHz, $CDCl_3$)

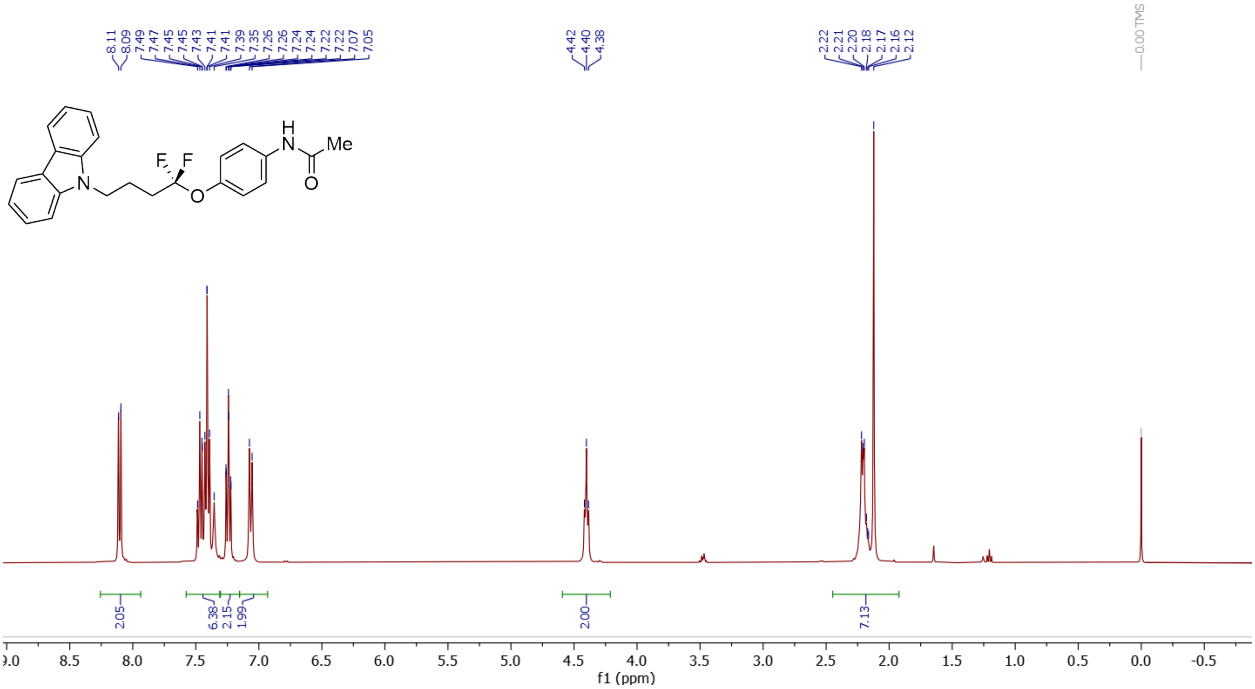


^{13}C NMR spectrum of **35** (101 MHz, $CDCl_3$)

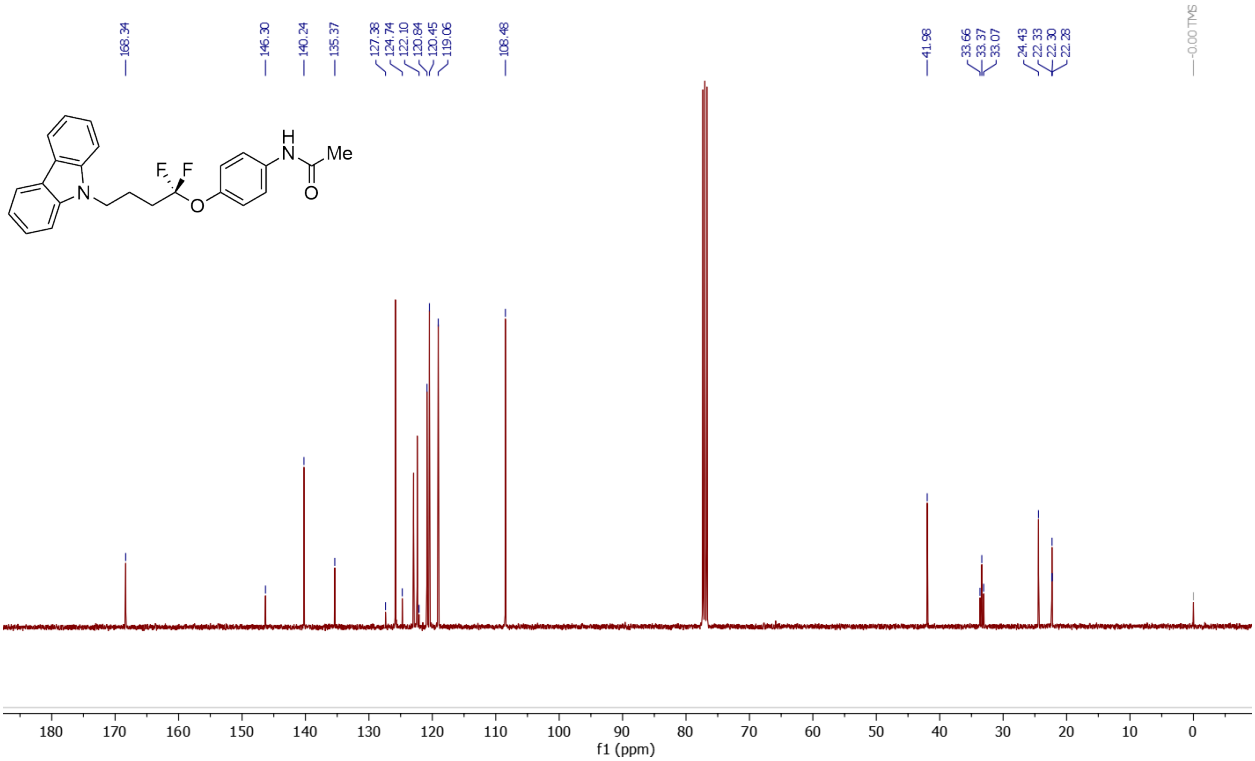


^{19}F NMR spectrum of **35** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

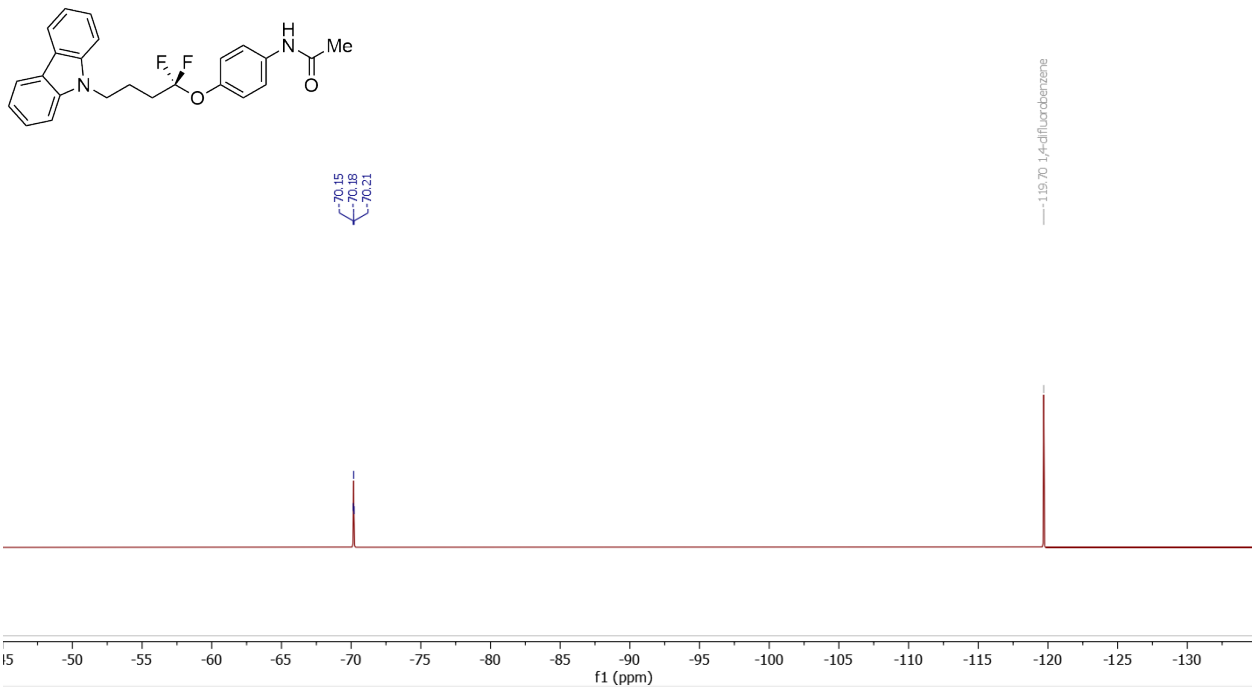
***N*-(4-(4-(9H-carbazol-9-yl)-1,1-difluorobutoxy)phenyl)acetamide (36)**



^{1}H NMR spectrum of **36** (400 MHz, $CDCl_3$)

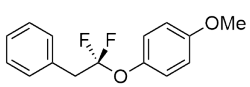


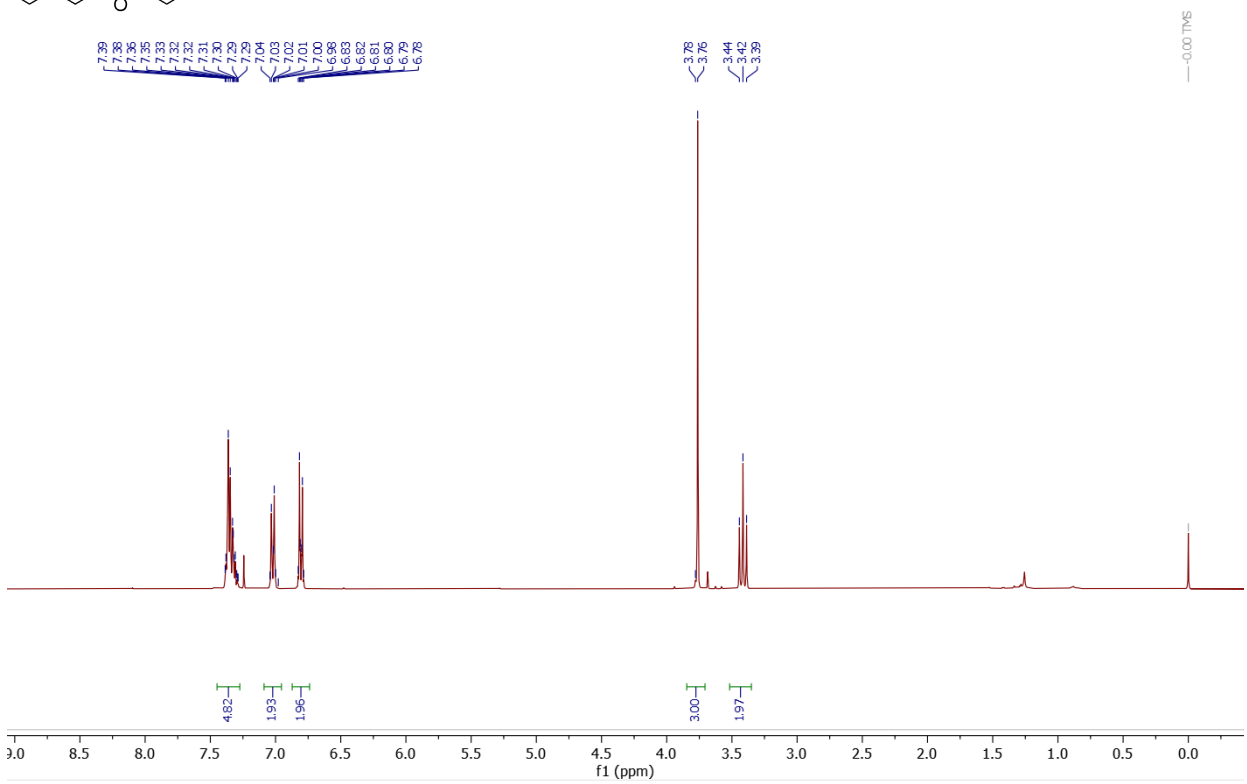
^{13}C NMR spectrum of **36** (101 MHz, $CDCl_3$)



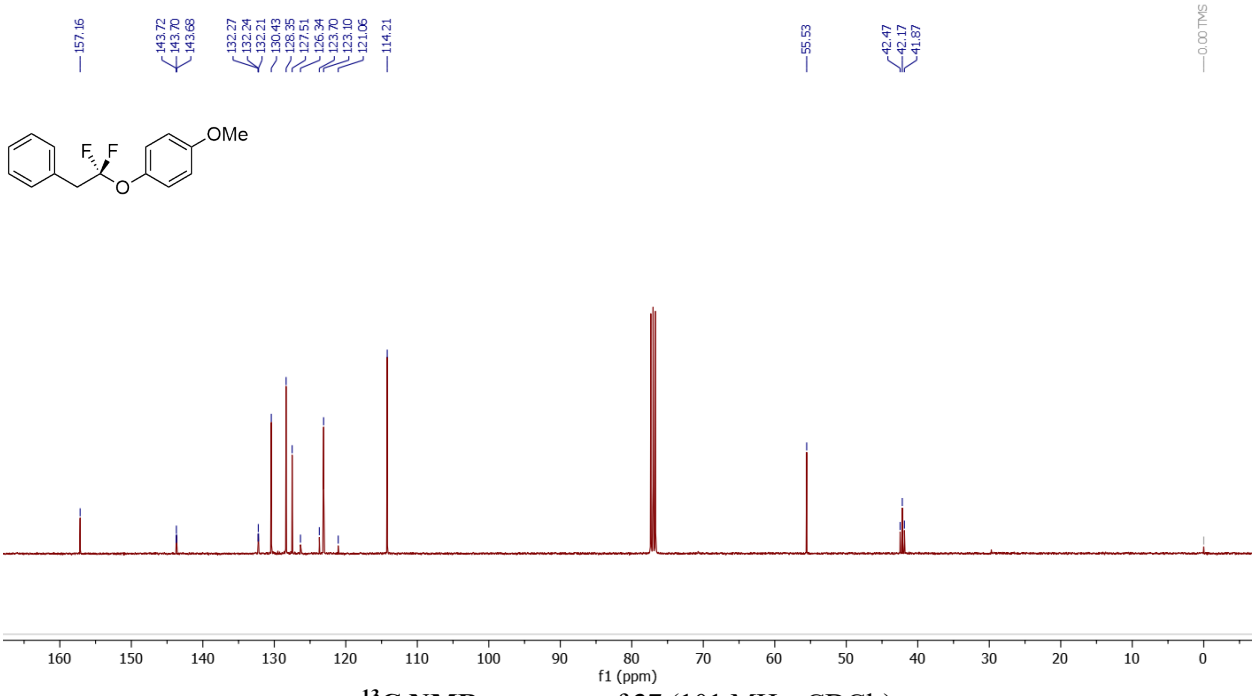
^{19}F NMR spectrum of **36** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

1-(1,1-difluoro-2-phenylethoxy)-4-methoxybenzene (37)

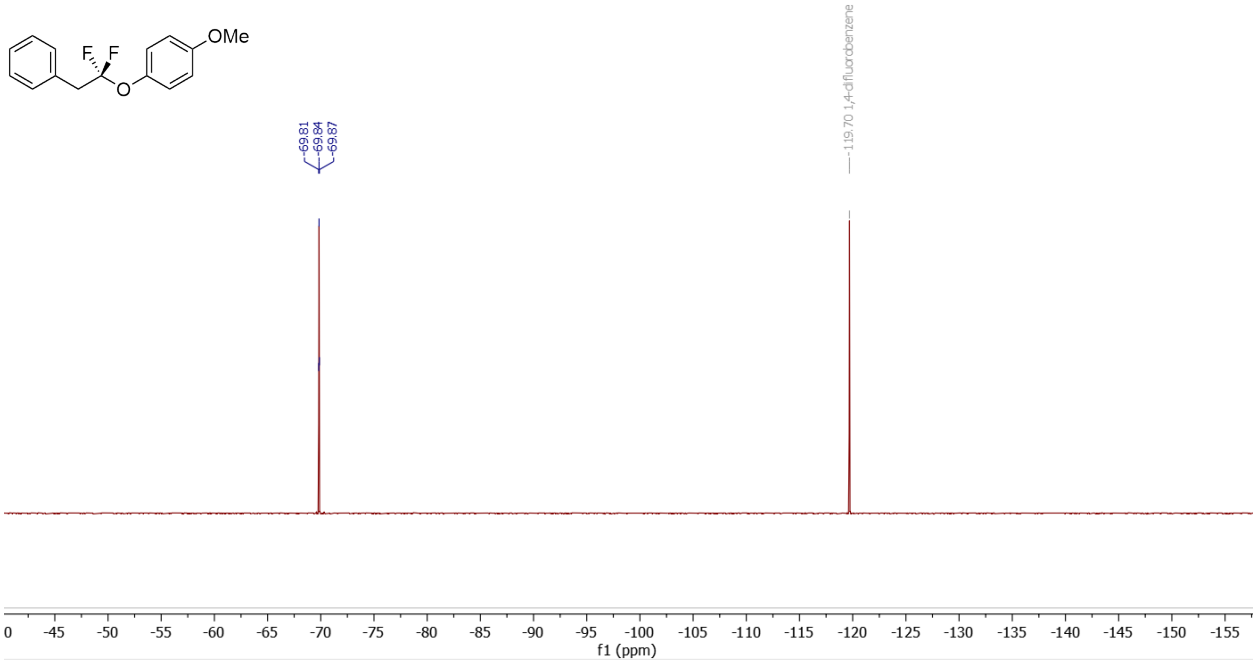




^{1}H NMR spectrum of **37** (400 MHz, $CDCl_3$)

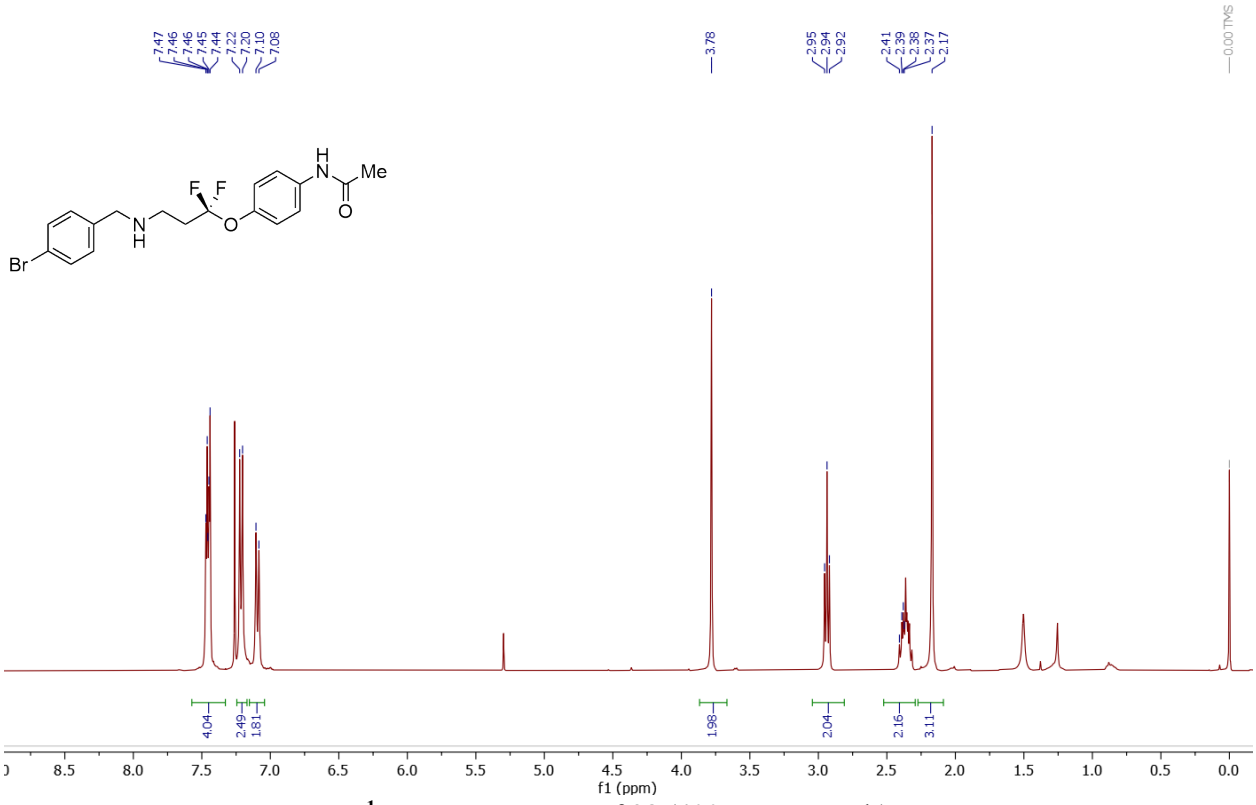


^{13}C NMR spectrum of **37** (101 MHz, $CDCl_3$)

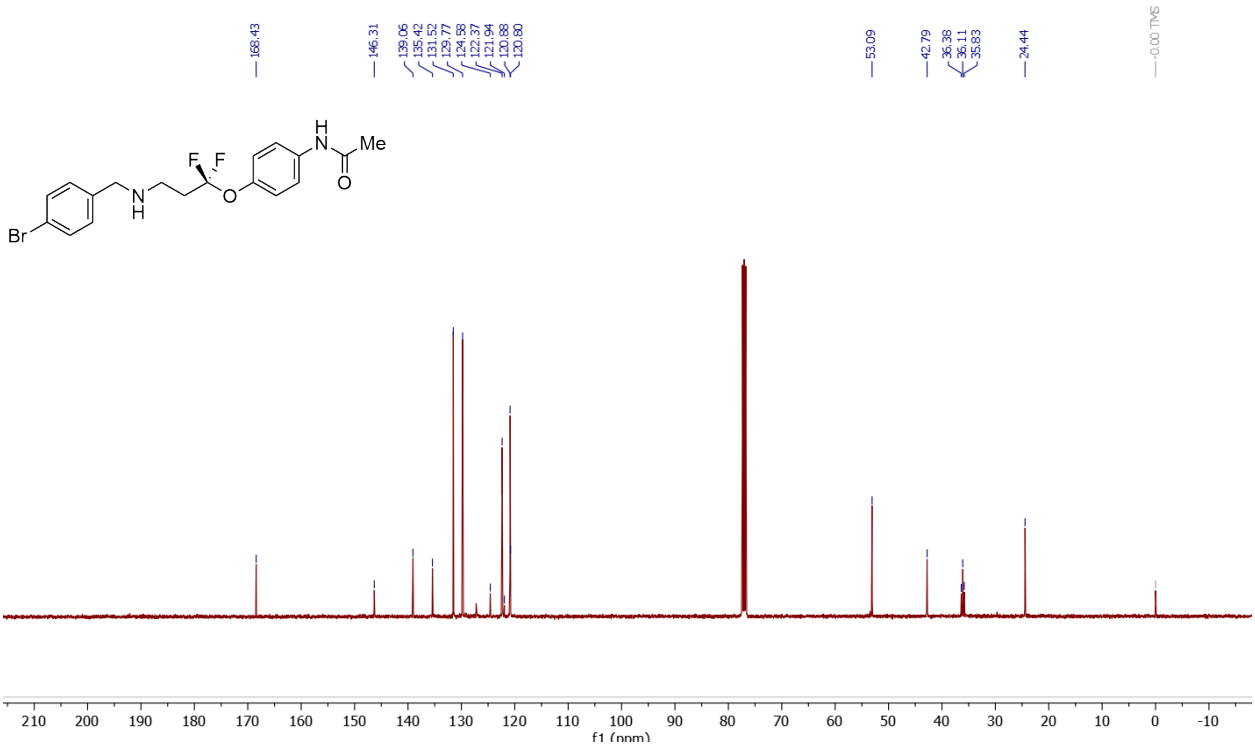


^{19}F NMR spectrum of **37** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

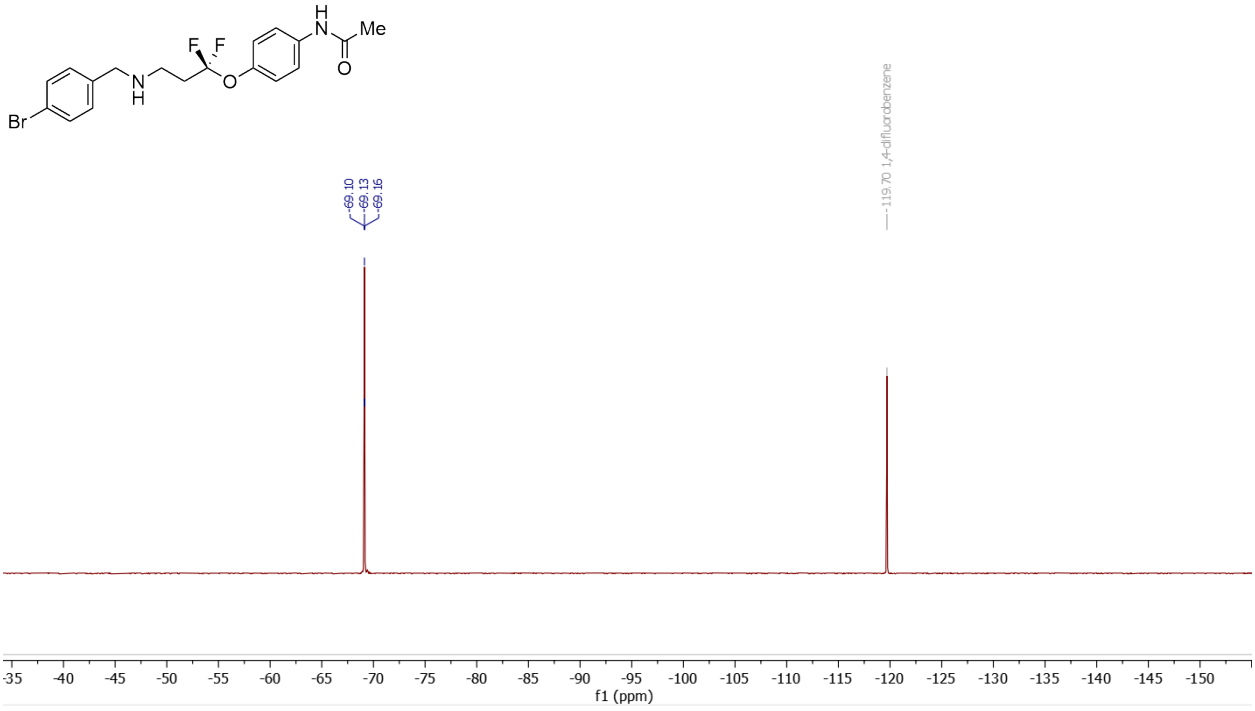
***N*-(4-(3-((4-bromobenzyl)amino)-1,1-difluoropropoxy)phenyl)acetamide (38)**



^{1}H NMR spectrum of **38** (400 MHz, $CDCl_3$)

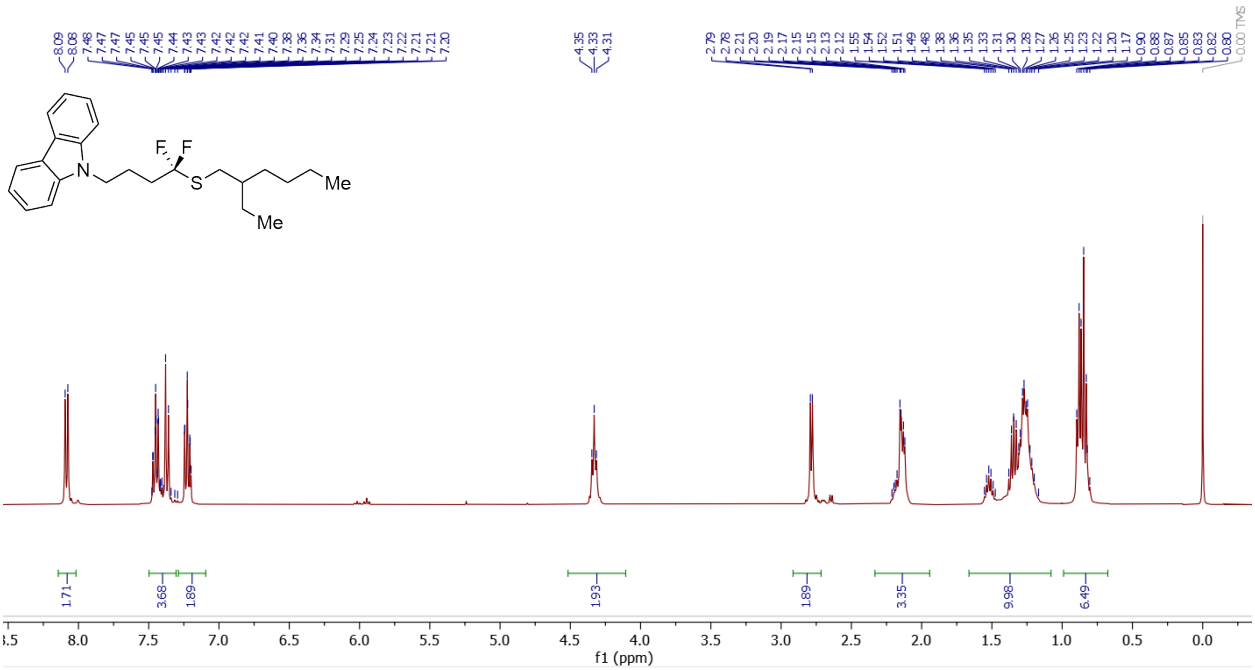


^{13}C NMR spectrum of **38** (101 MHz, $CDCl_3$)

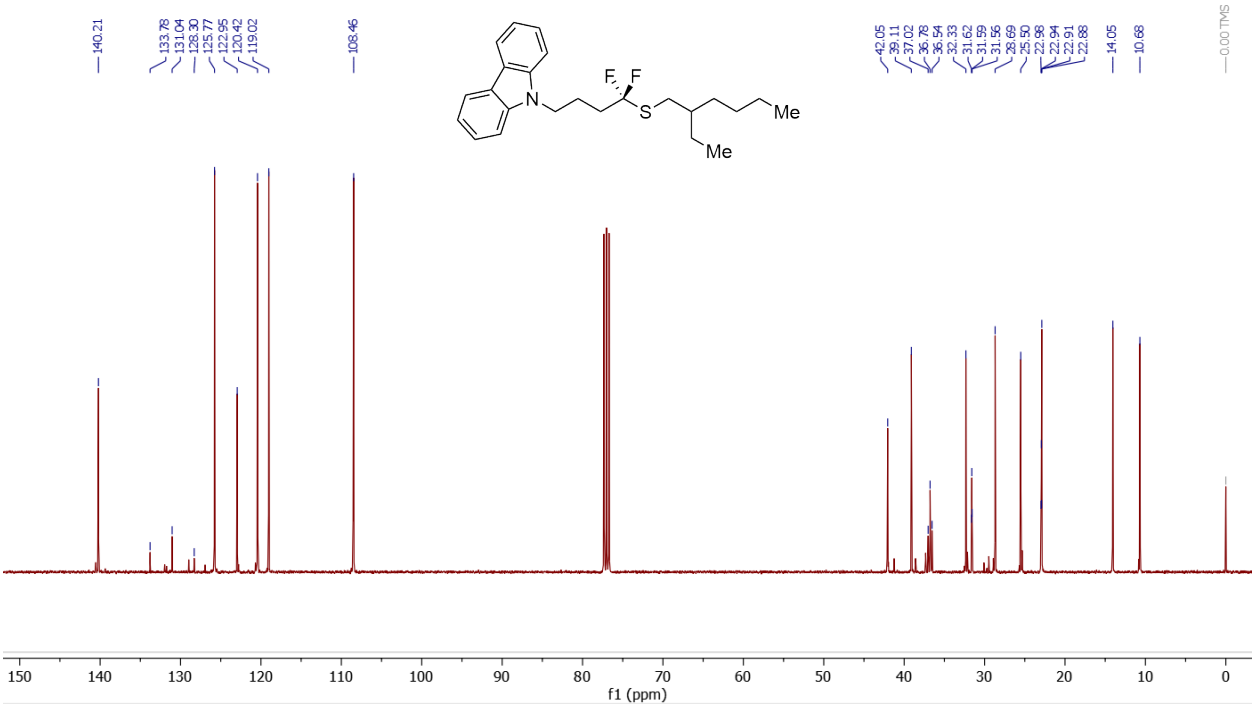


^{19}F NMR spectrum of **38** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

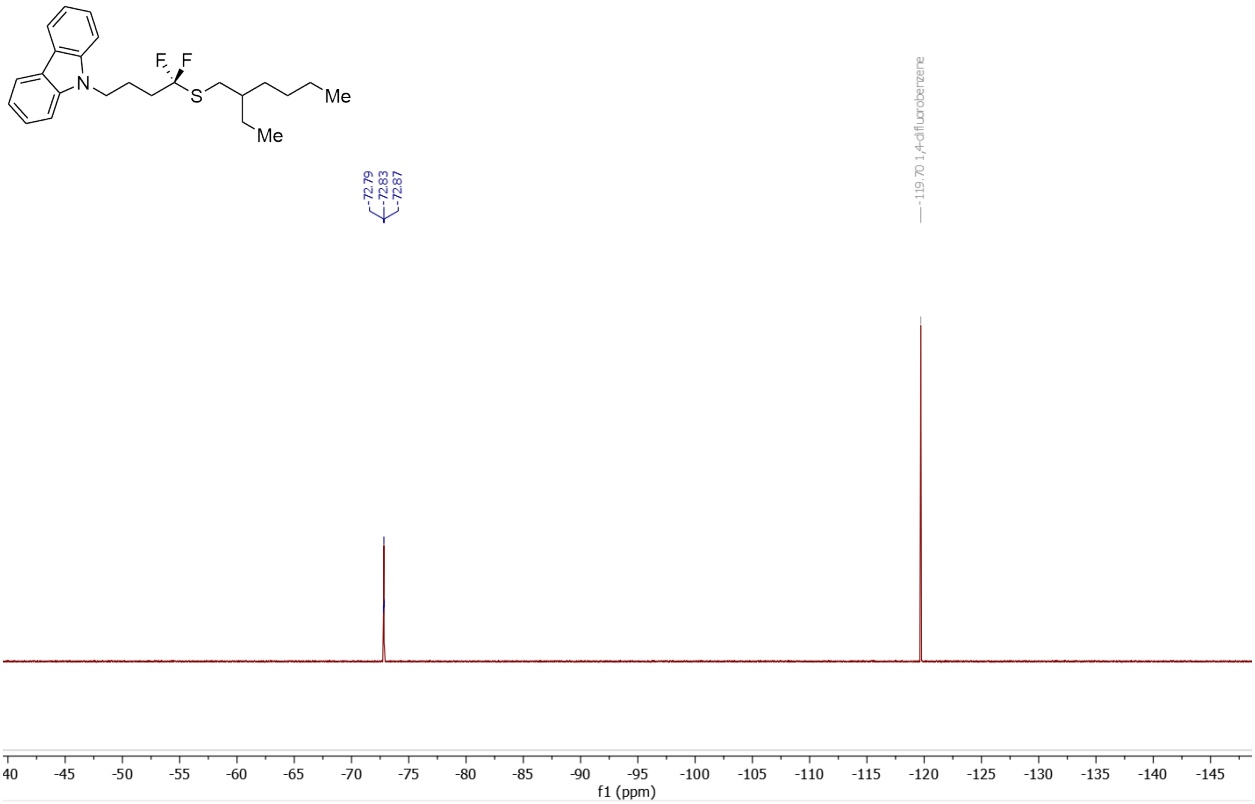
9-(4-((2-ethylhexyl)thio)-4,4-difluorobutyl)-9H-carbazole (39)



^{1}H NMR spectrum of **39** (400 MHz, $CDCl_3$)

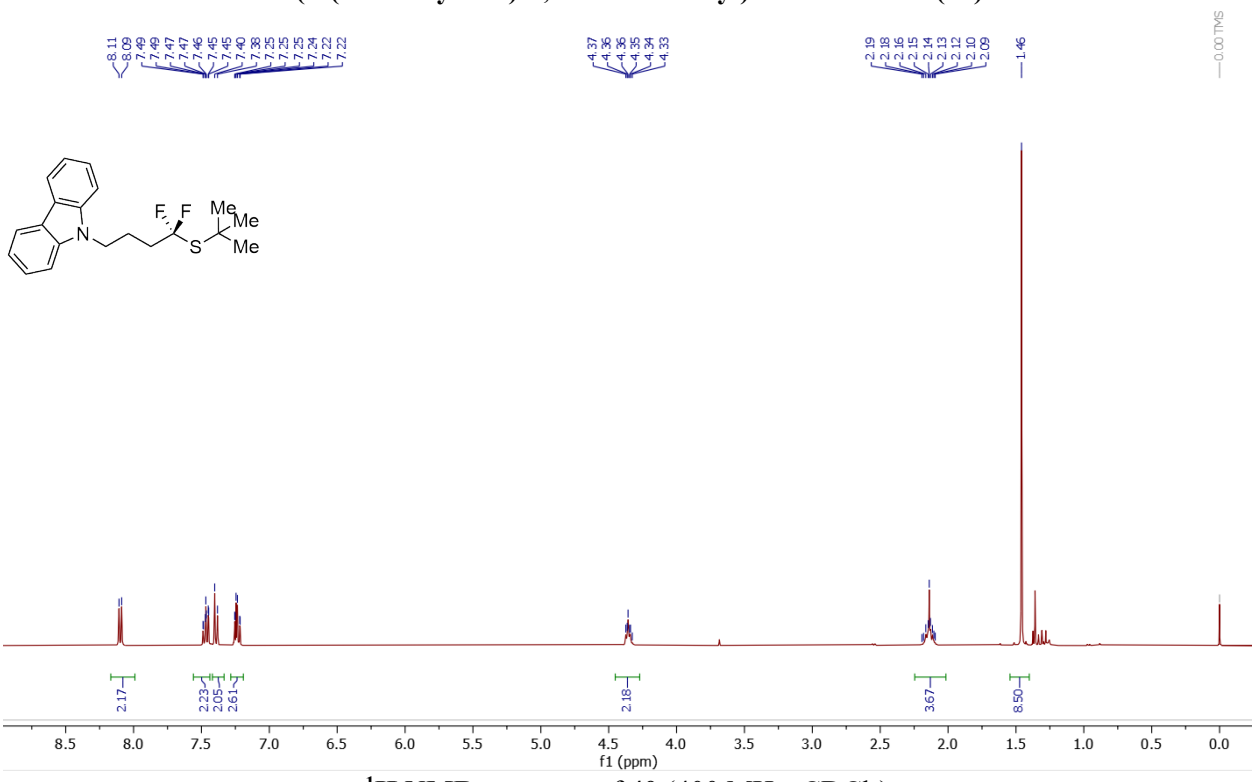


^{13}C NMR spectrum of **39** (101 MHz, $CDCl_3$)

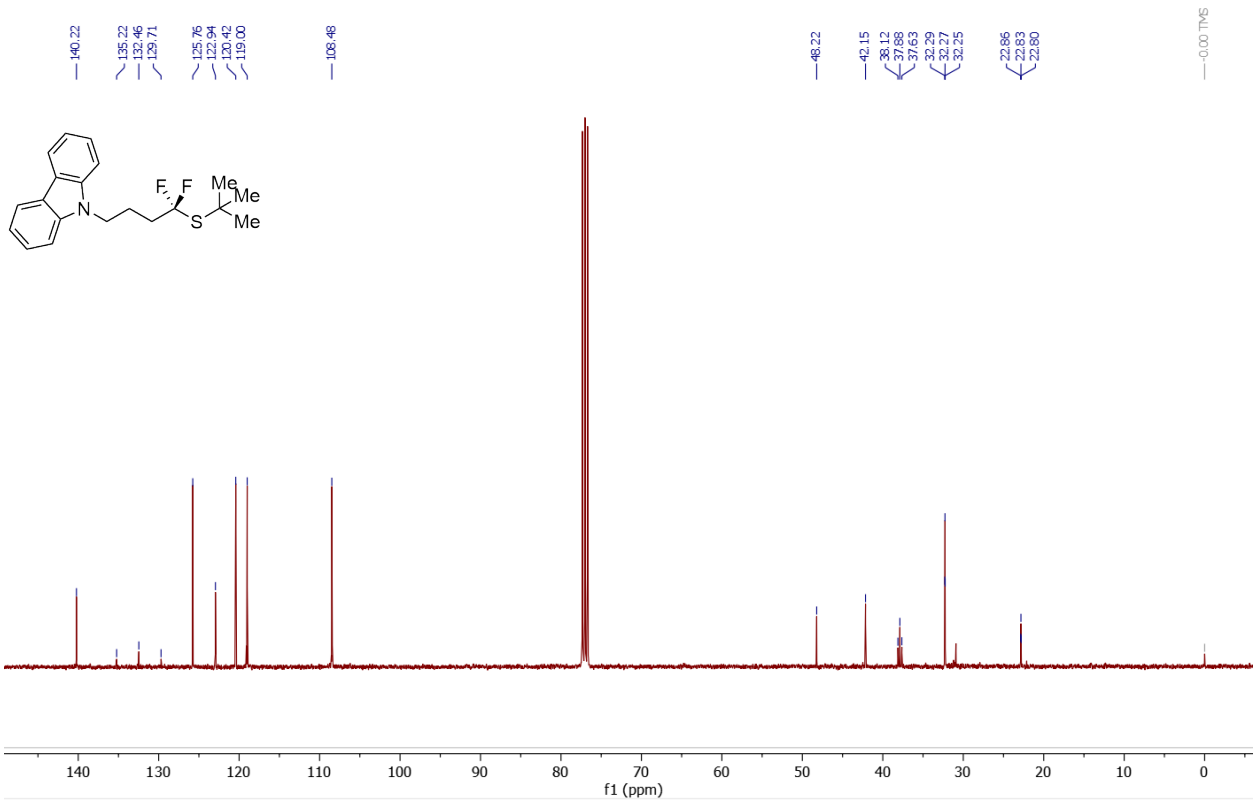


^{f19}F NMR spectrum of **39** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

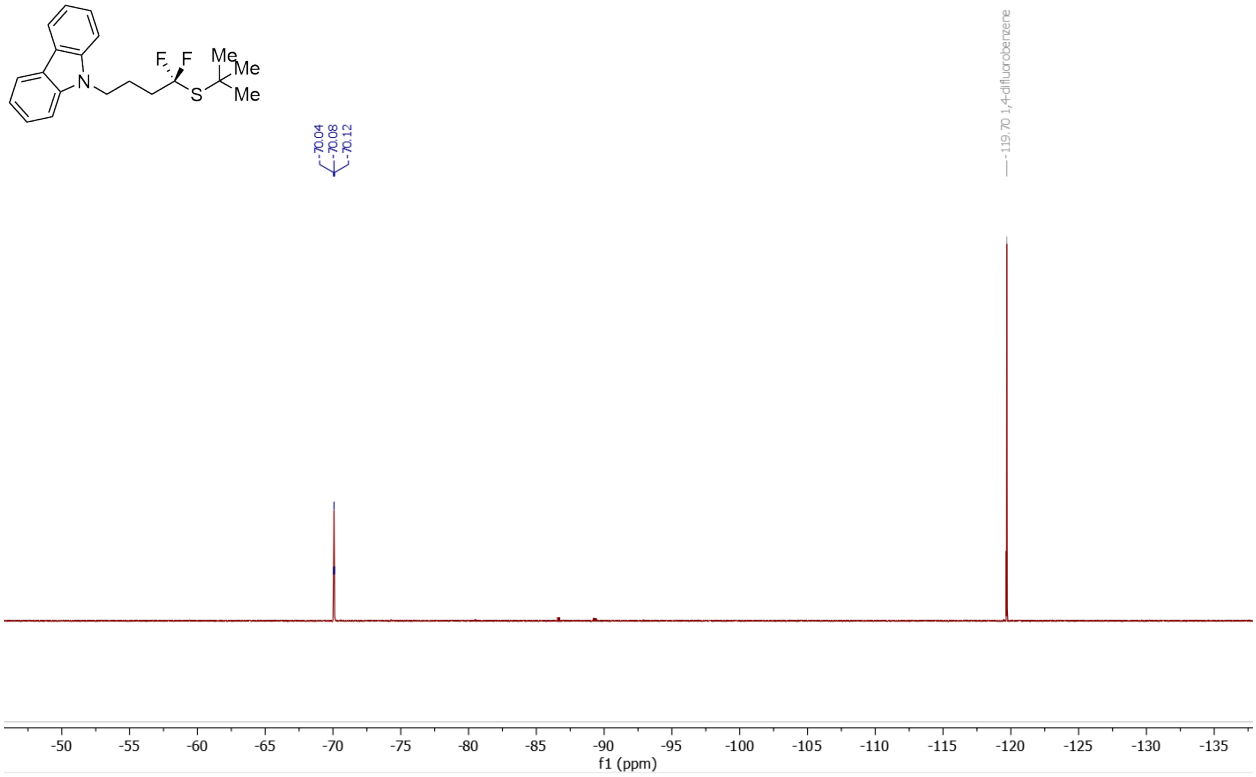
9-(4-(tert-butylthio)-4,4-difluorobutyl)-9H-carbazole (40)



^{1}H NMR spectrum of **40** (400 MHz, $CDCl_3$)

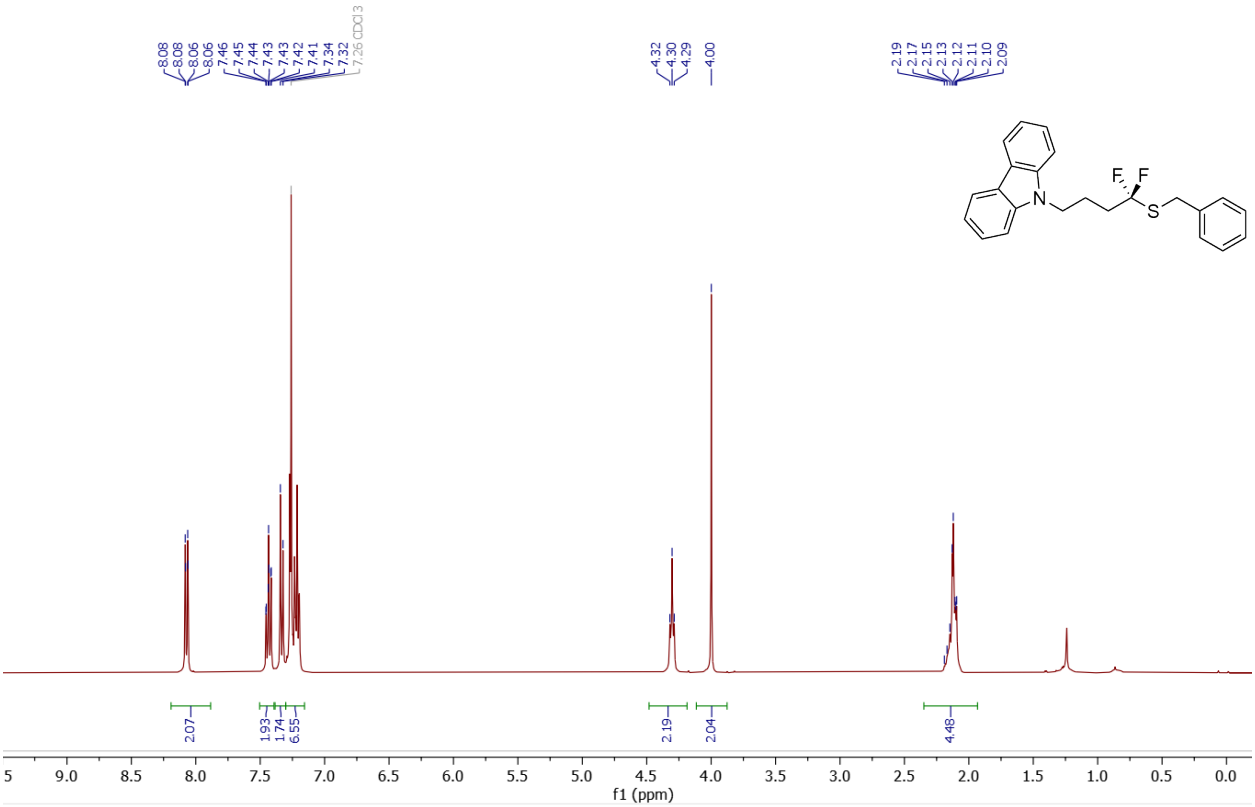


^{13}C NMR spectrum of **40** (101 MHz, $CDCl_3$)

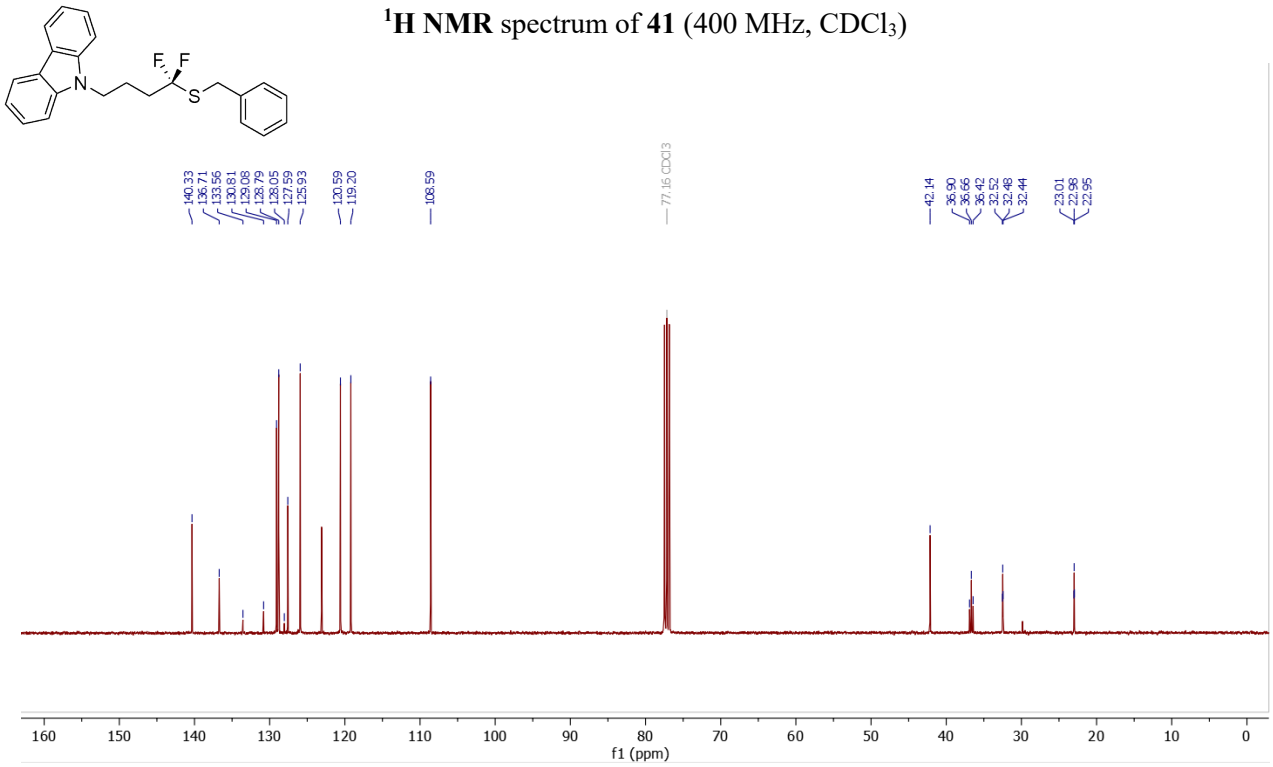


^{19}F NMR spectrum of **40** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

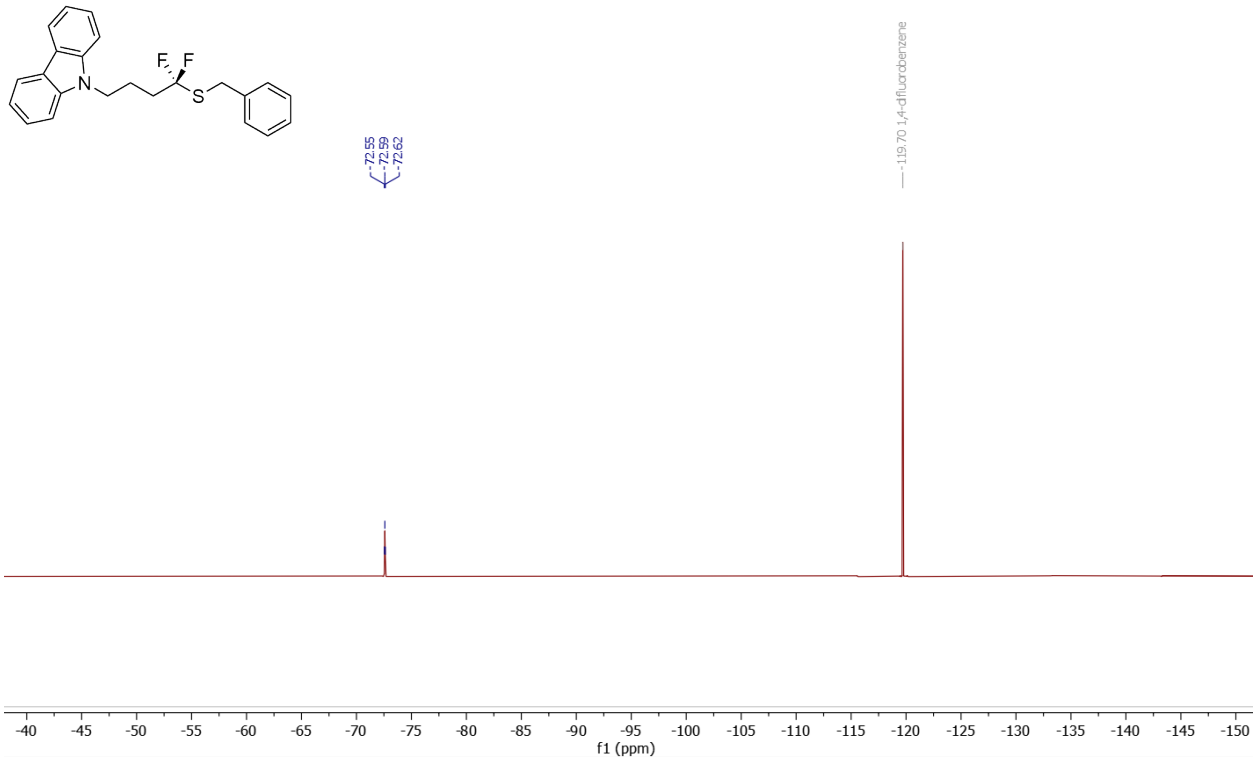
9-(4-(benzylthio)-4,4-difluorobutyl)-9H-carbazole (41)



^{1}H NMR spectrum of **41** (400 MHz, $CDCl_3$)

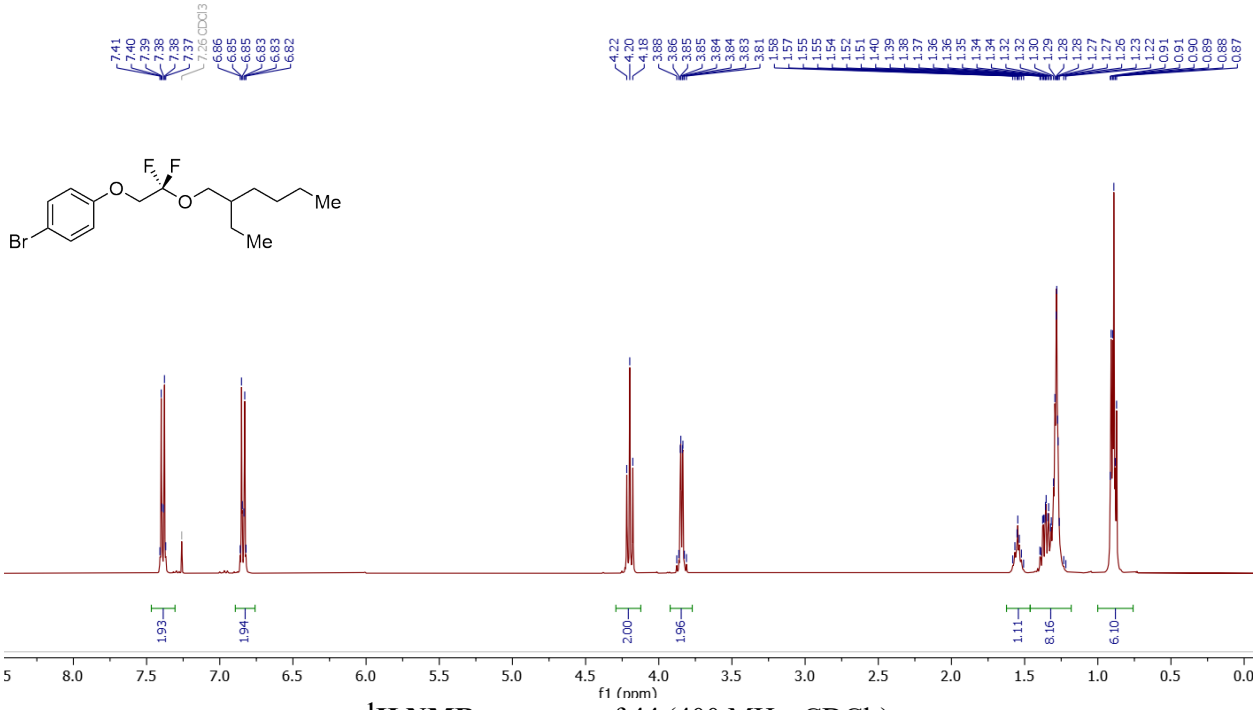


^{13}C NMR spectrum of **41** (101 MHz, $CDCl_3$)

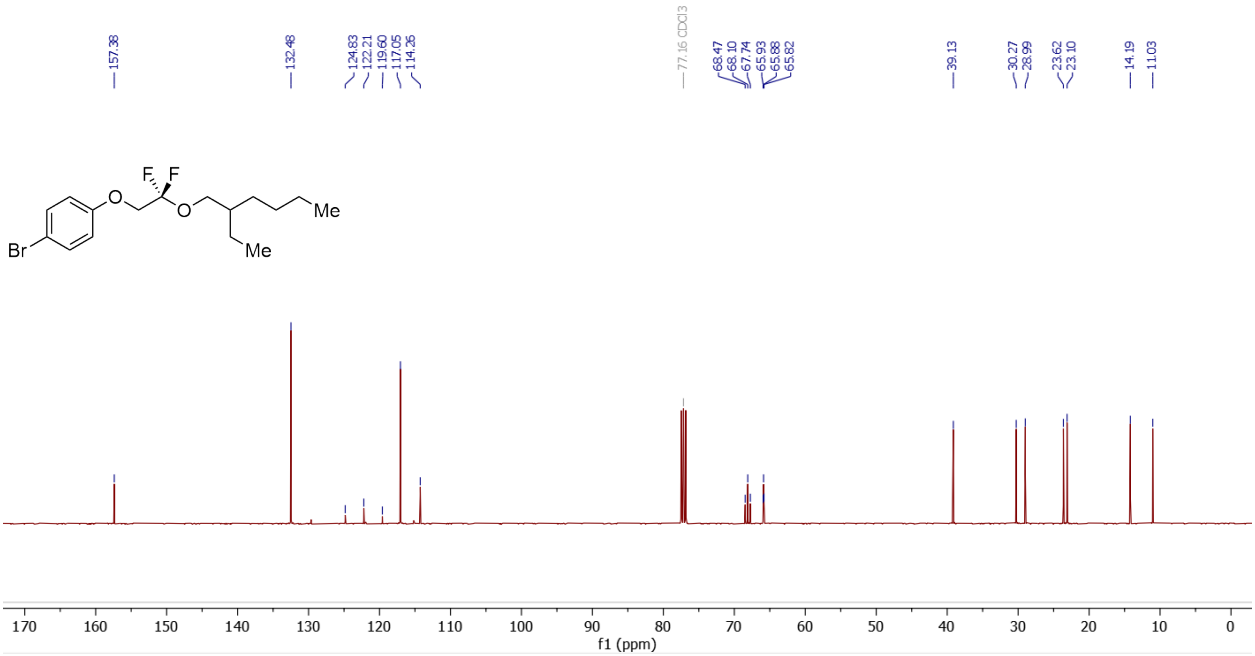


^{19}F NMR spectrum of **41** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

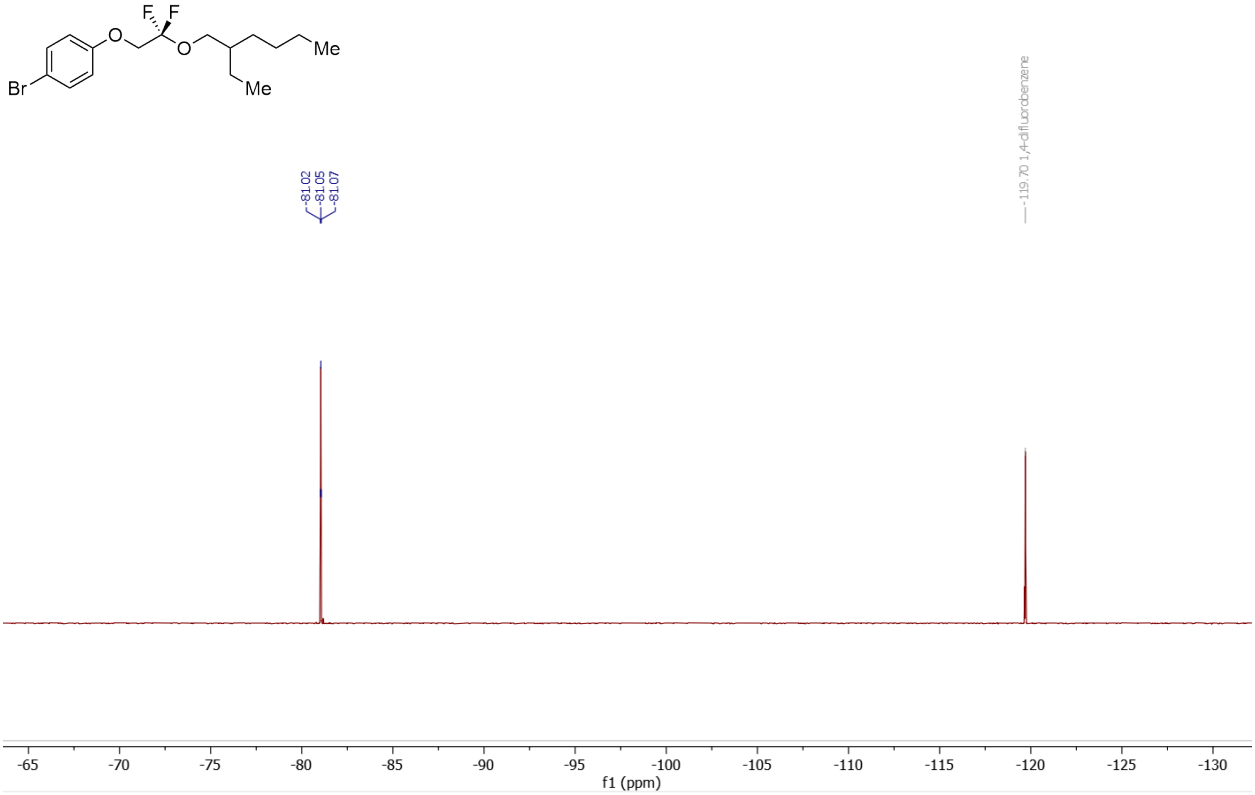
1-bromo-4-(2-((2-ethylhexyl)oxy)-2,2-difluoroethoxy)benzene (44)



^{1}H NMR spectrum of **44** (400 MHz, $CDCl_3$)

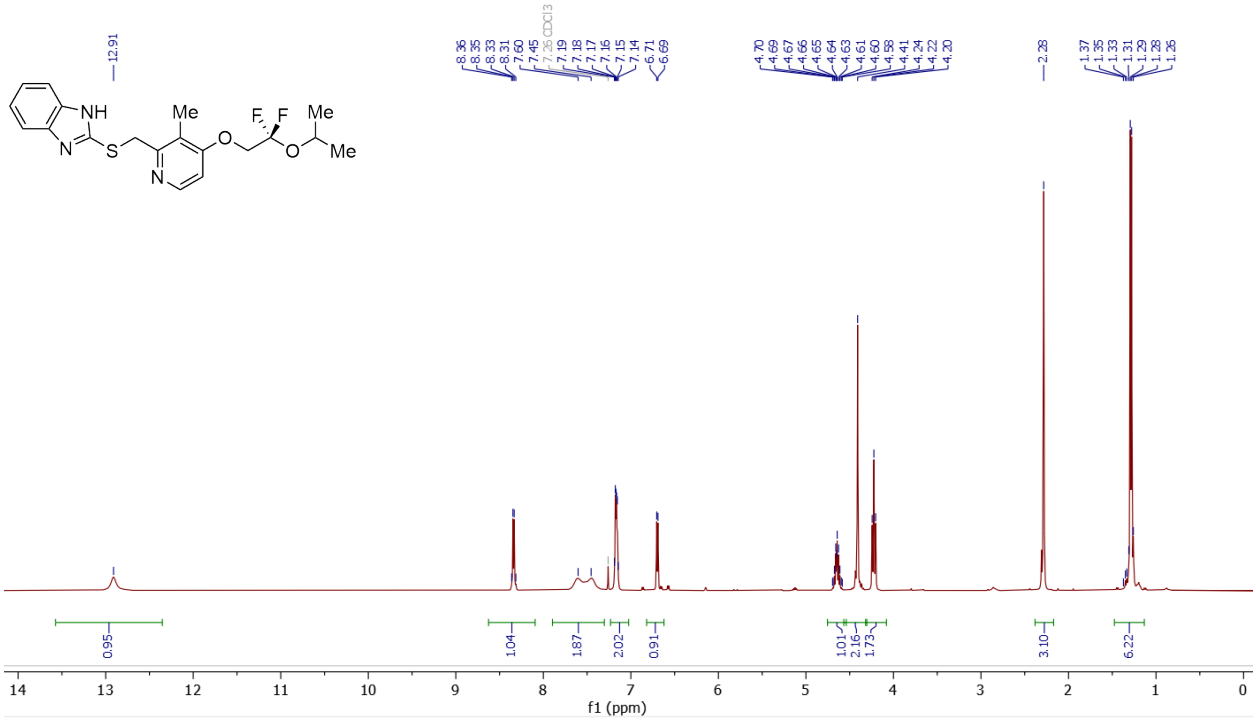


^{13}C NMR spectrum of **44** (101 MHz, $CDCl_3$)

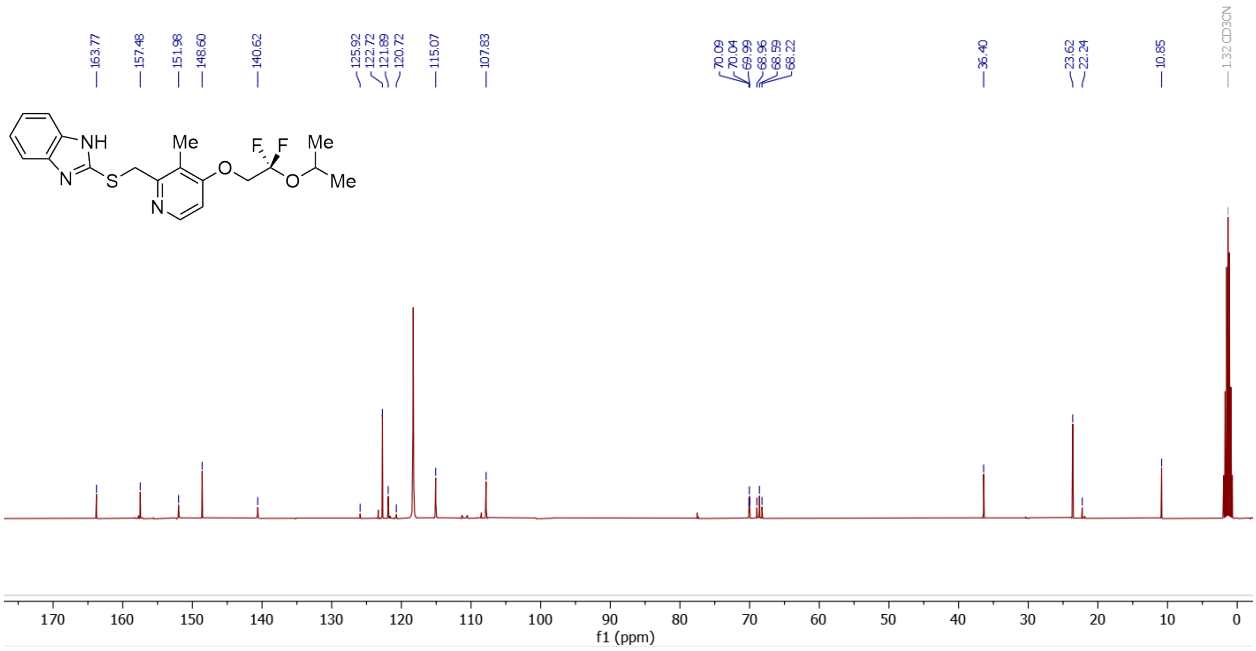


^{19}F NMR spectrum of **44** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

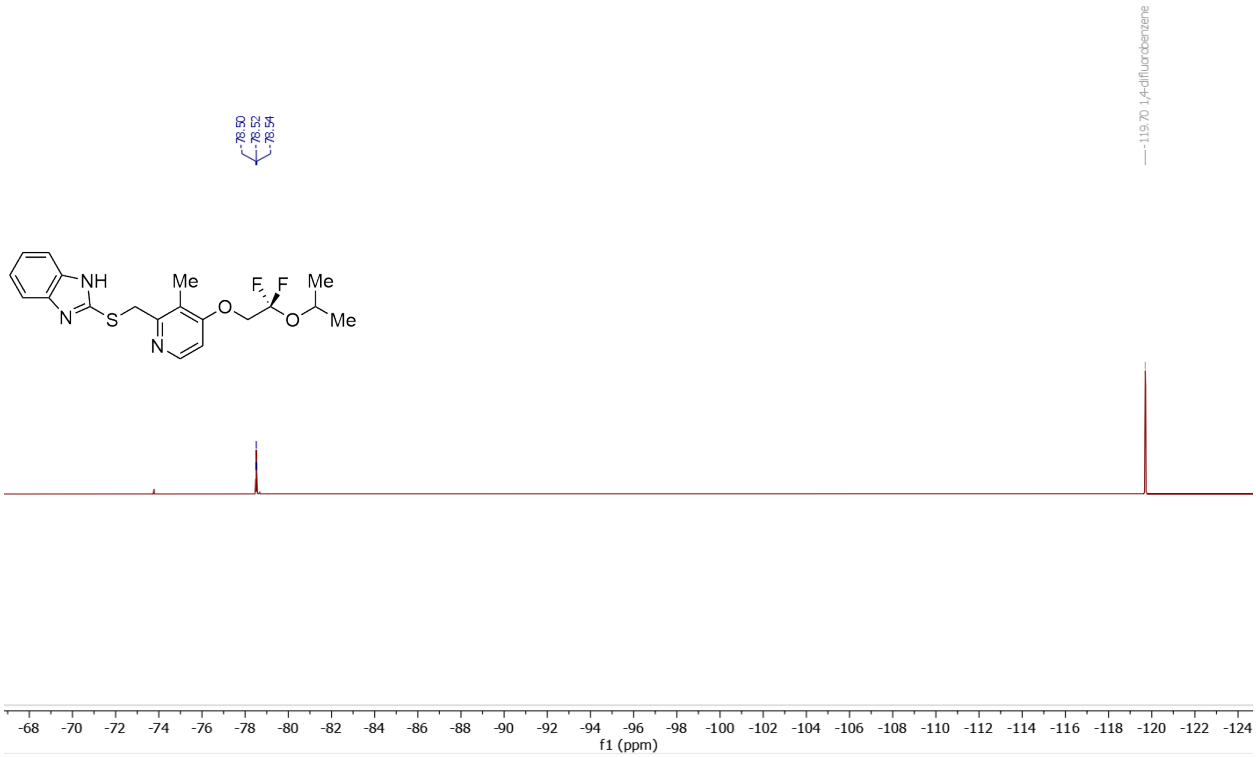
2-(((4-(2,2-difluoro-2-isopropoxyethoxy)-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (46)



^{1}H NMR spectrum of **46** (400 MHz, $CDCl_3$)

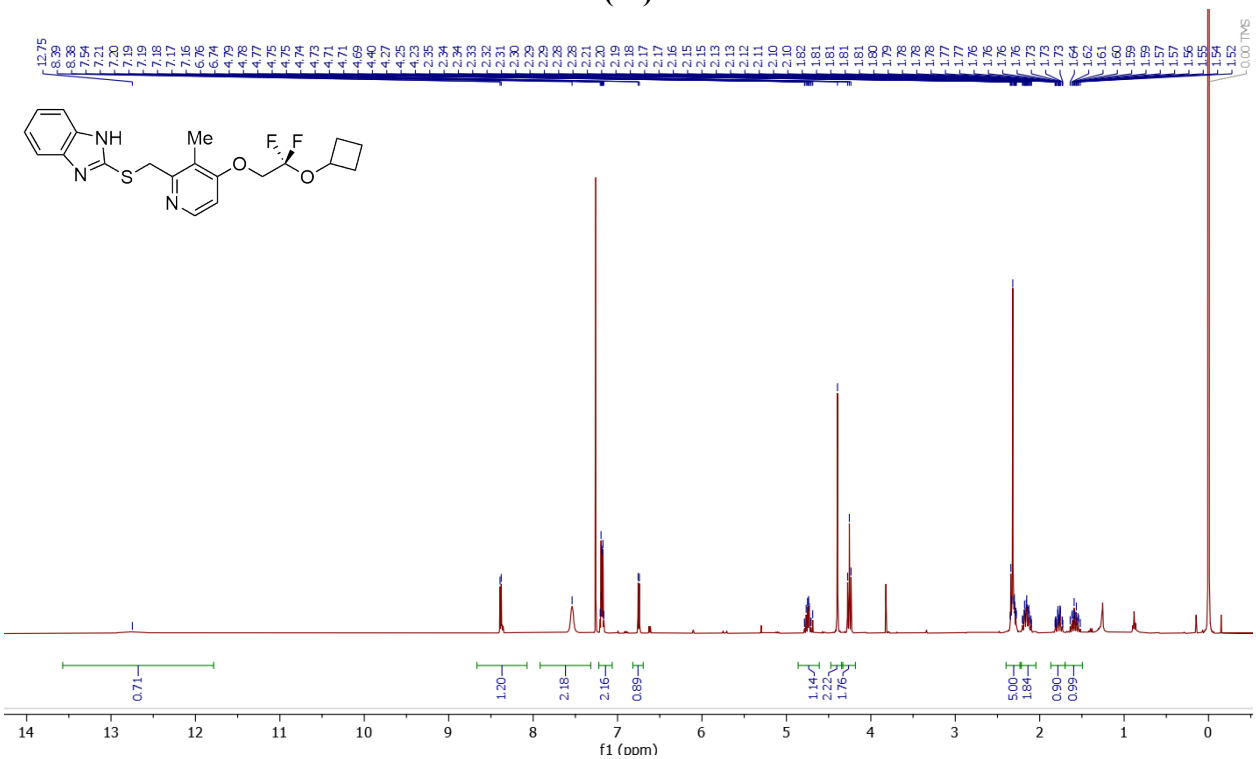


^{13}C NMR spectrum of **46** (101 MHz, CD_3CN)

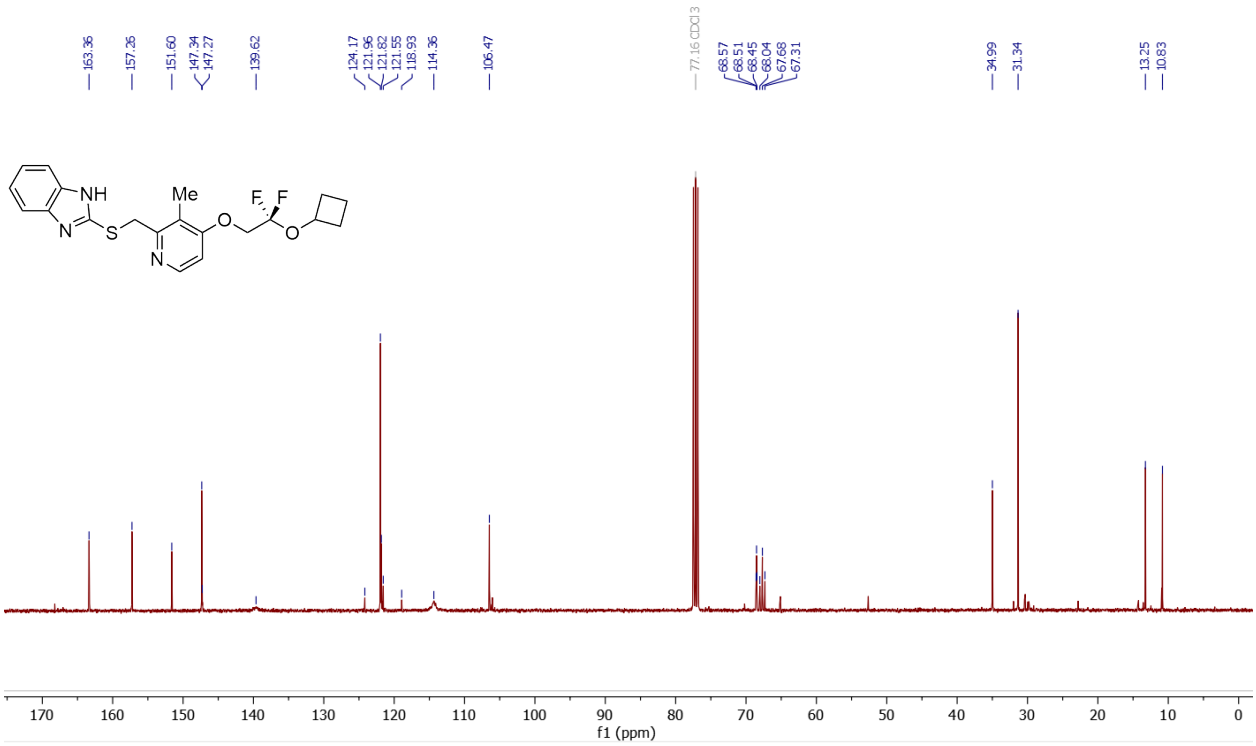


^{19}F NMR spectrum of **46** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

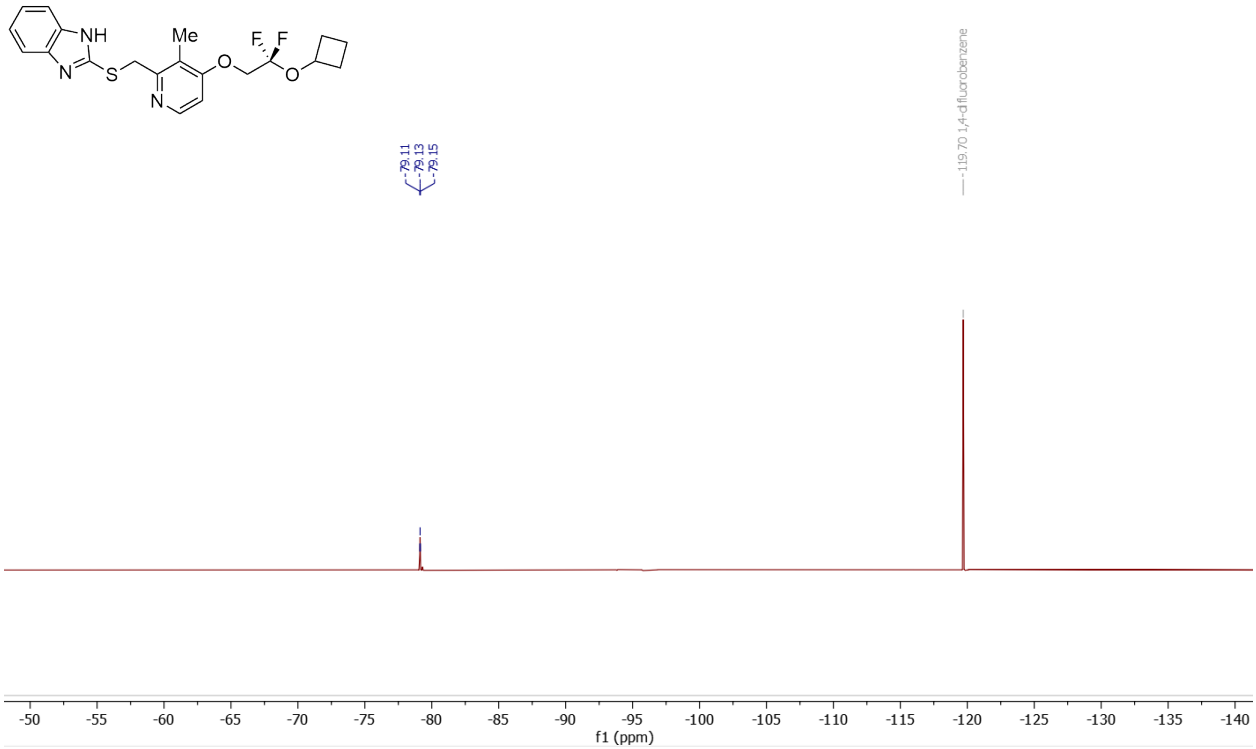
2-(((4-(2-cyclobutoxy-2,2-difluoroethoxy)-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (47)



^{1}H NMR spectrum of **47** (400 MHz, $CDCl_3$)

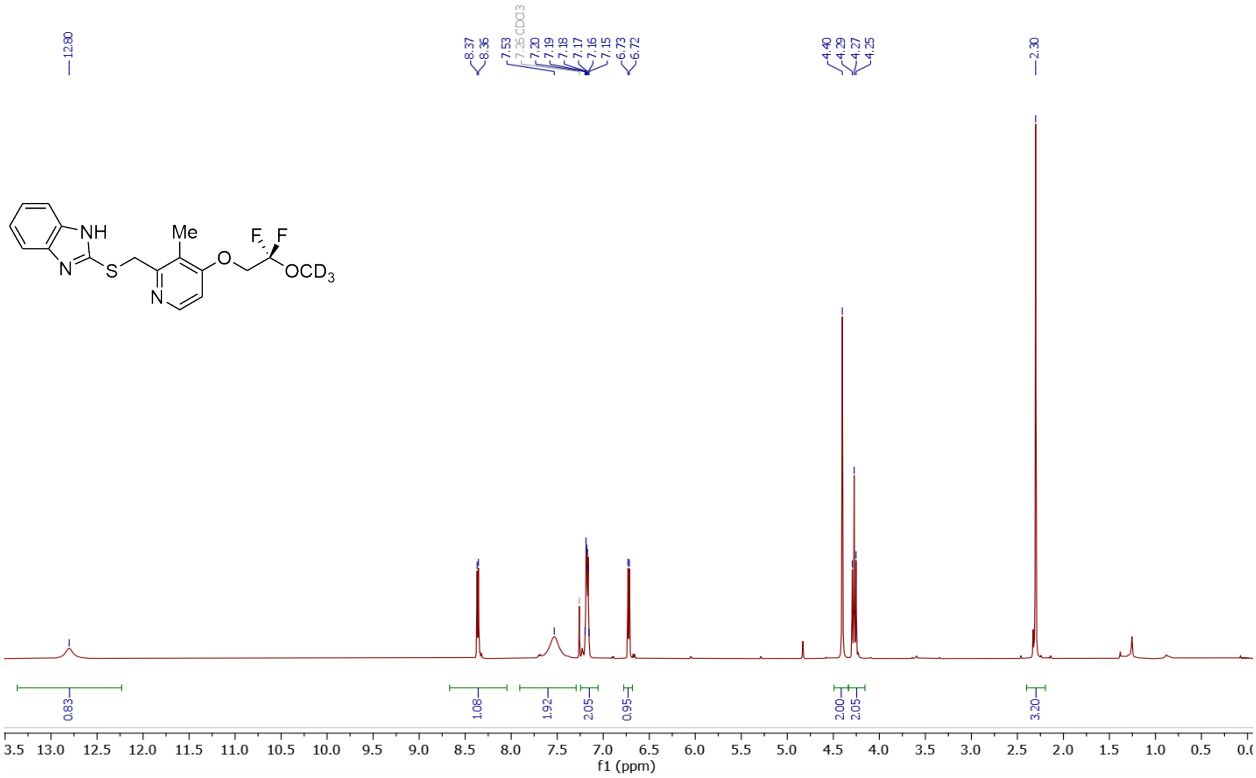


^{13}C NMR spectrum of **47** (101 MHz, $CDCl_3$)

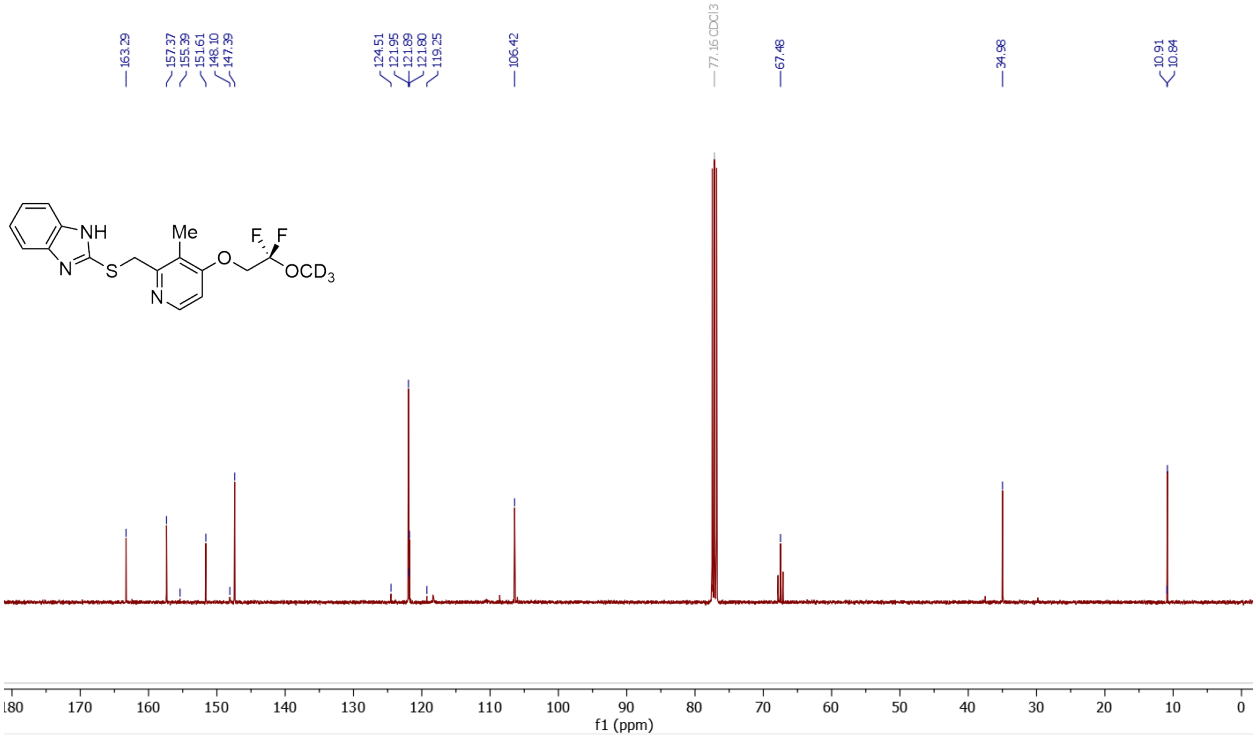


^{19}F NMR spectrum of **47** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

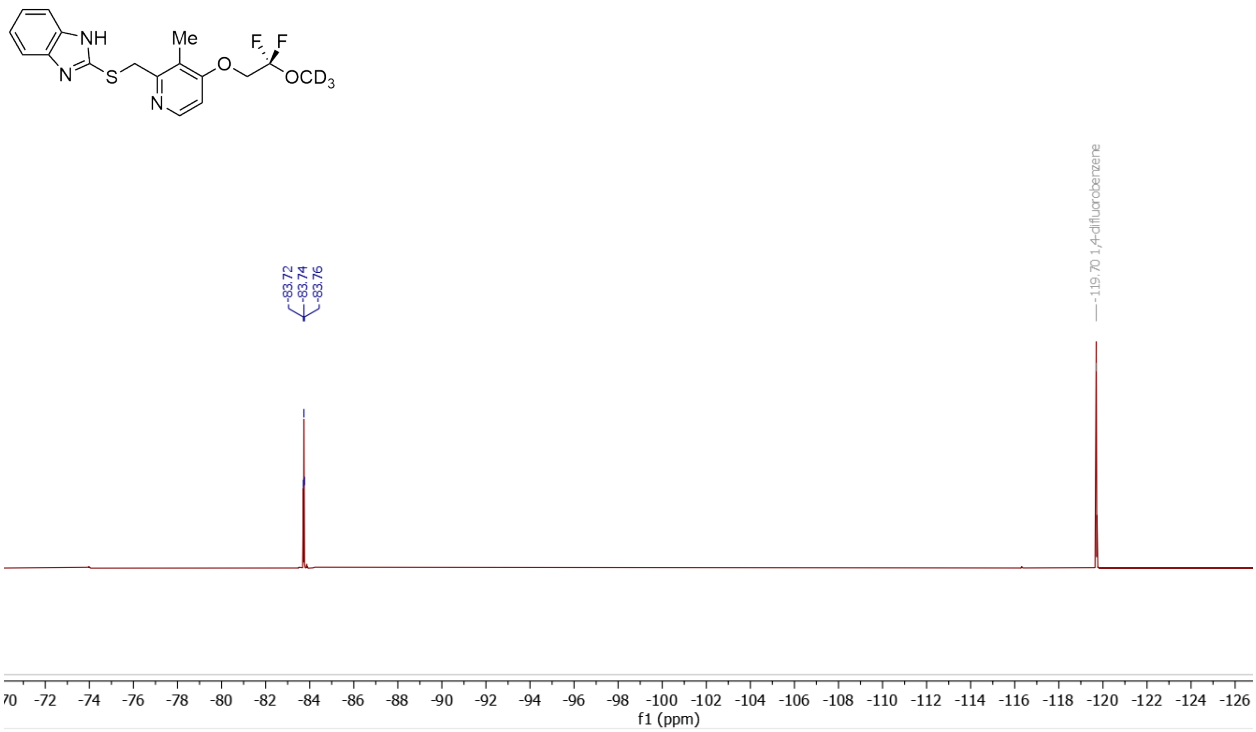
2-(((4-(2,2-difluoro-2-(methoxy-d3)ethoxy)-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (48)



^{1}H NMR spectrum of **48** (400 MHz, $CDCl_3$)

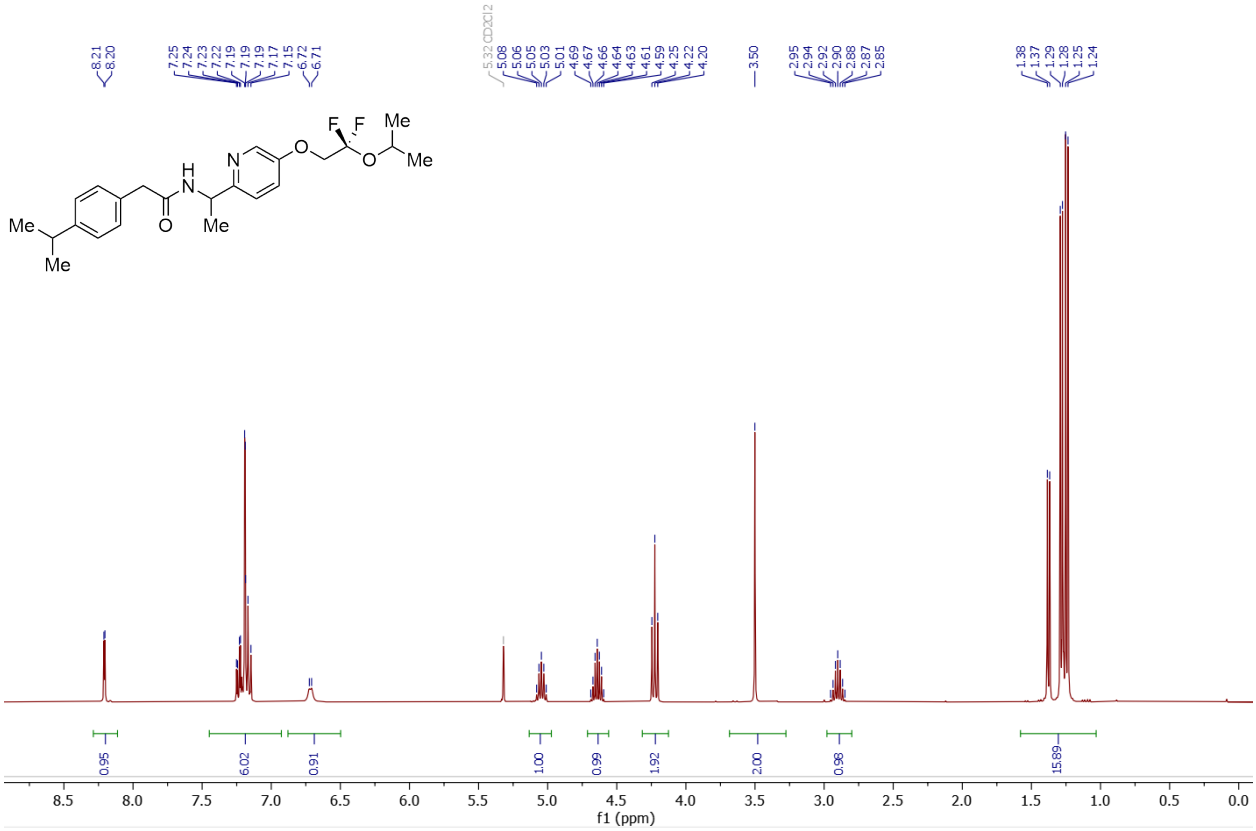


^{13}C NMR spectrum of **48** (101 MHz, $CDCl_3$)

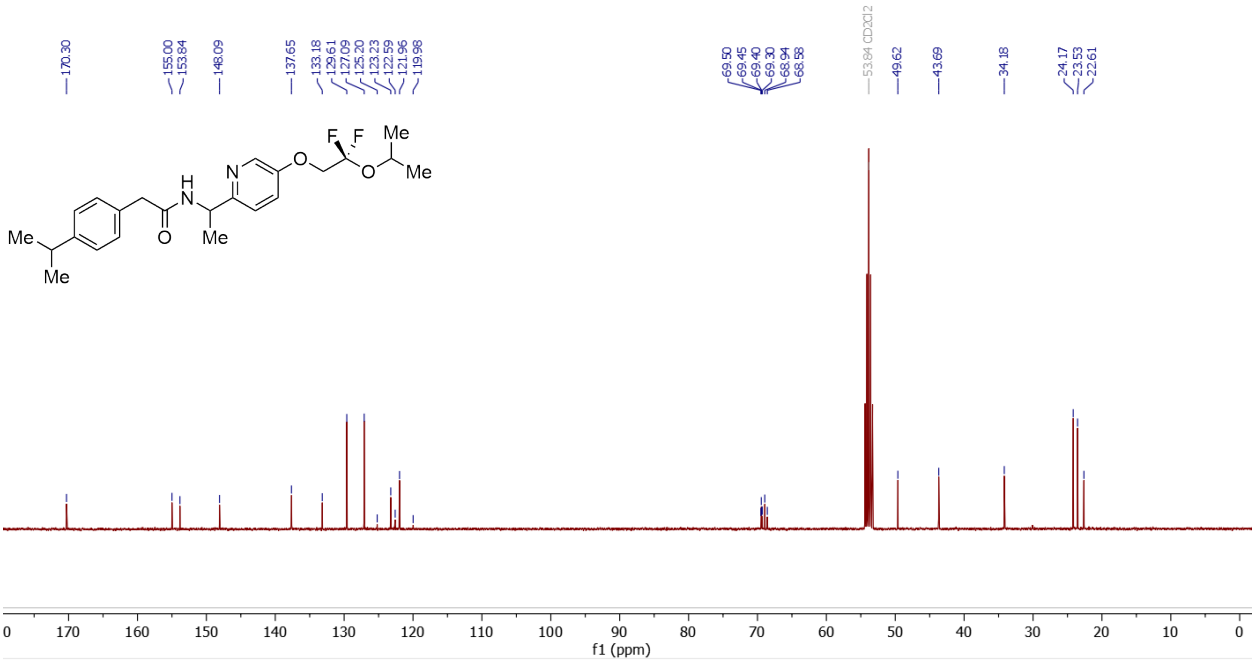


^{19}F NMR spectrum of **48** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

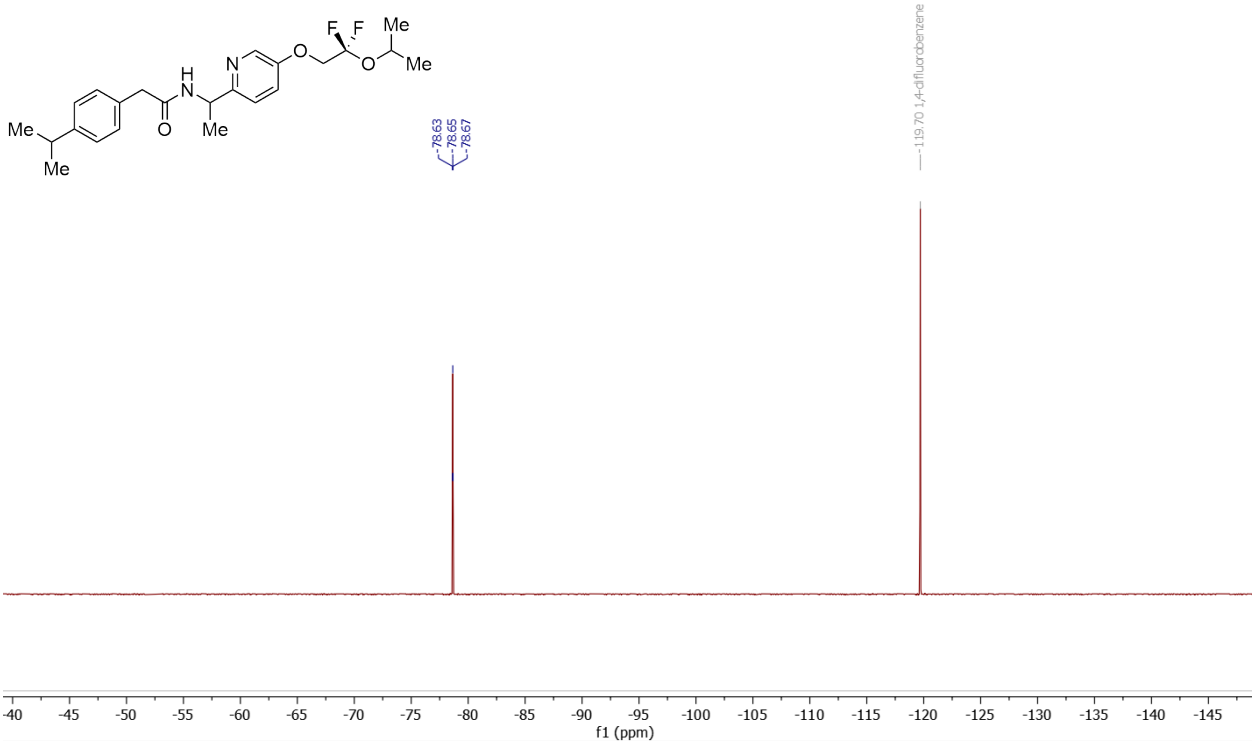
***N*-(1-(5-(2,2-difluoro-2-isopropoxyethoxy)pyridin-2-yl)ethyl)-2-(4-isopropylphenyl)acetamide (49)**



^{1}H NMR spectrum of **49** (400 MHz, CD_2Cl_2)

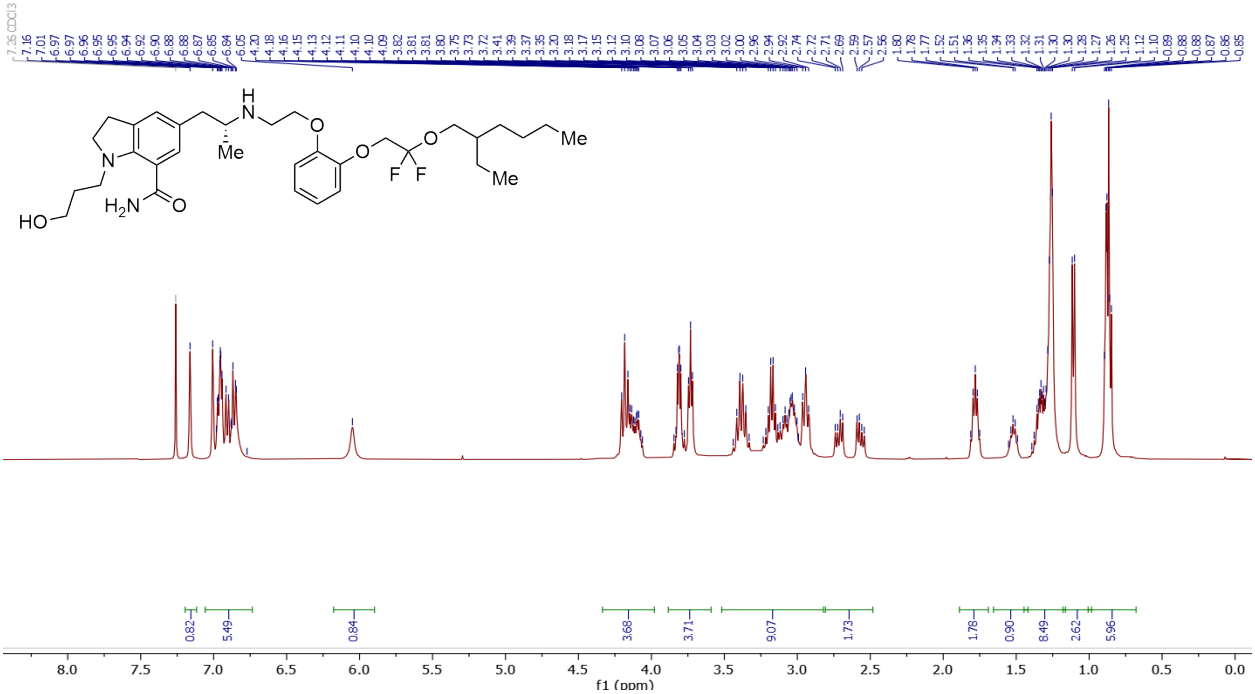


^{13}C NMR spectrum of **49** (400 MHz, CD_2Cl_2)

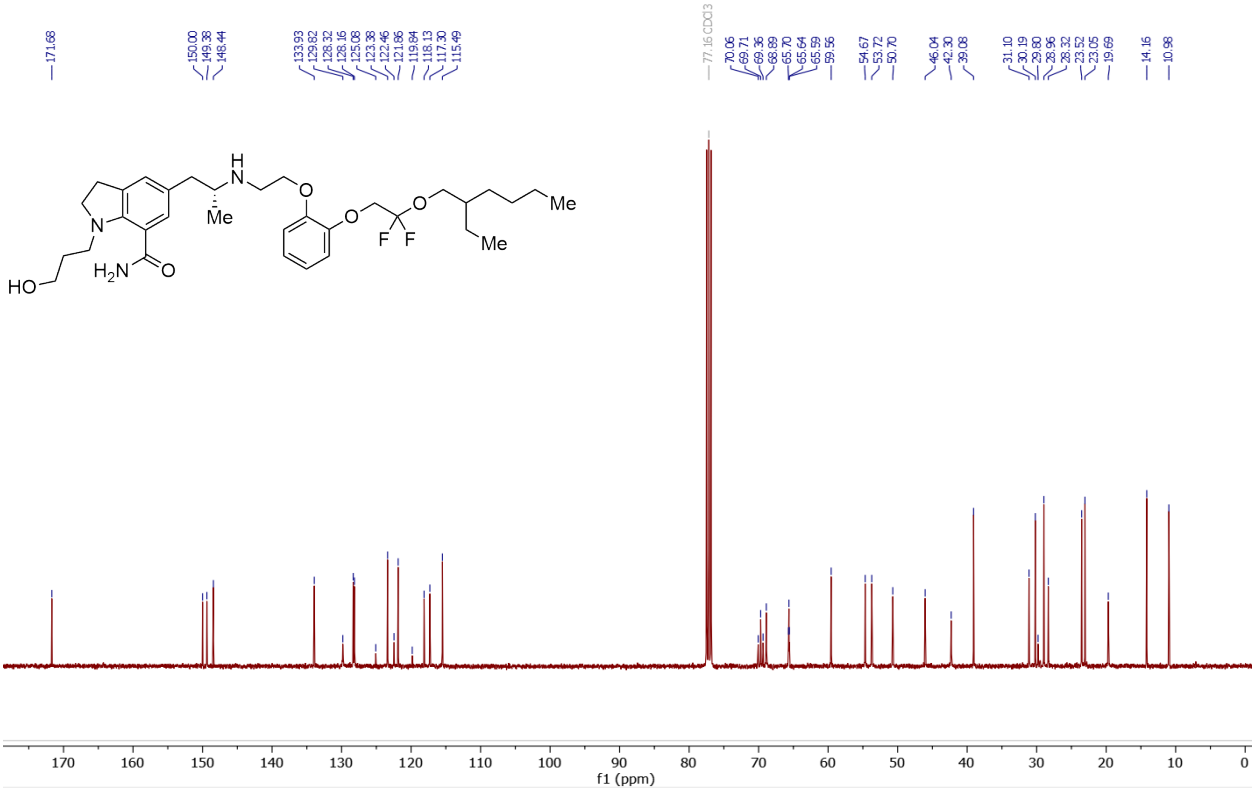


^{19}F NMR spectrum of **49** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

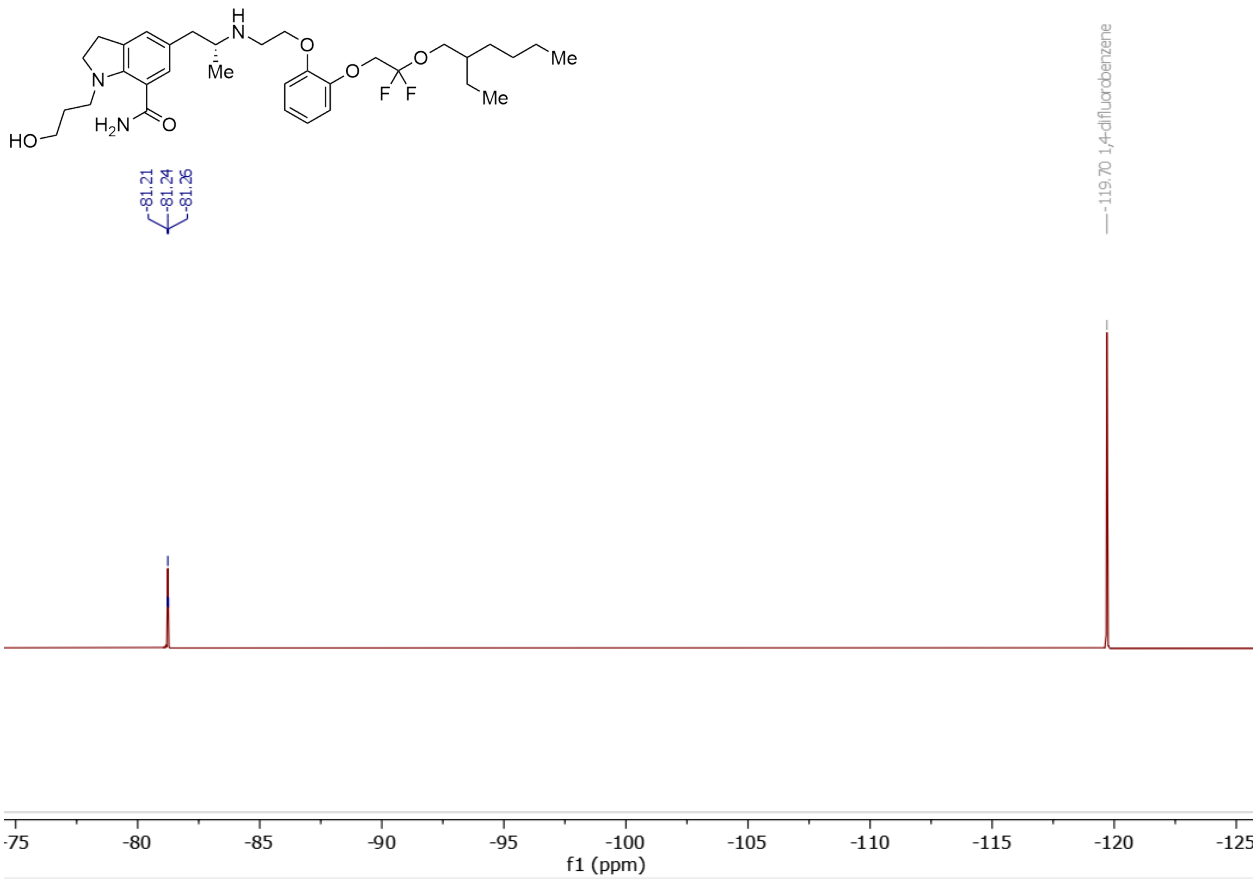
5-((2*R*)-2-((2-(2-(2-((2-ethylhexyl)oxy)-2,2-difluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide (50)



^{1}H NMR spectrum of **50** (400 MHz, $CDCl_3$)

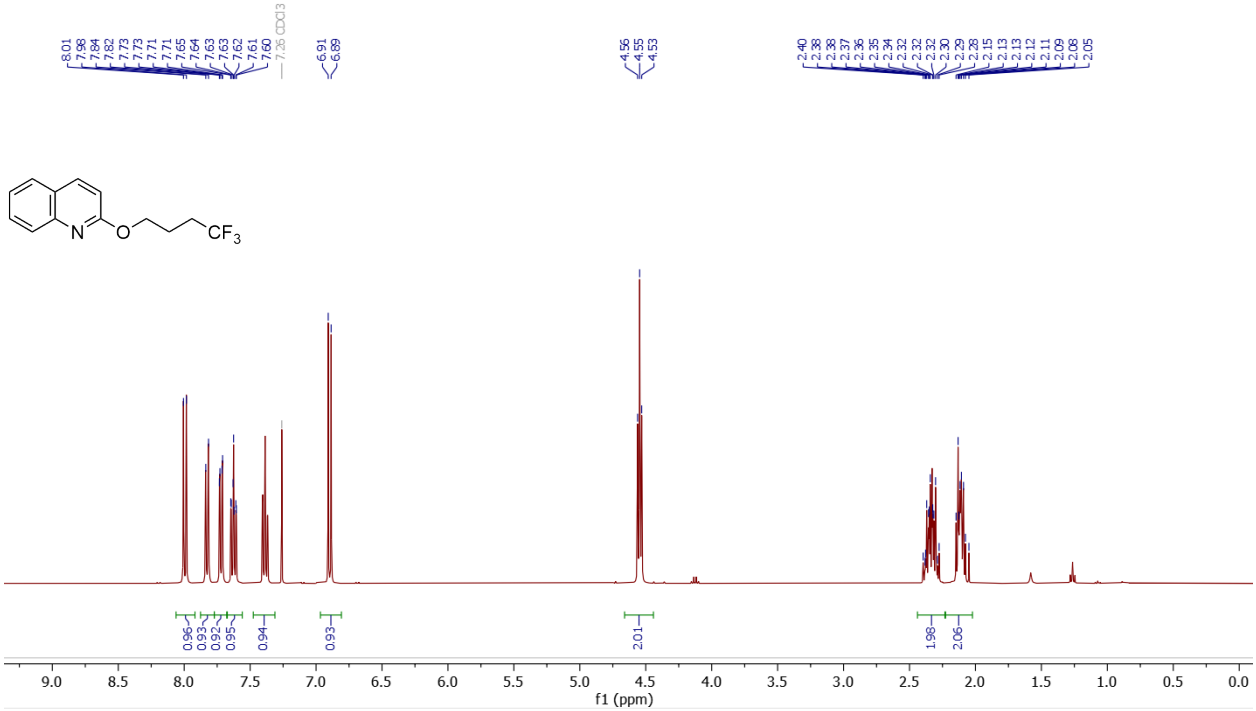


^{13}C NMR spectrum of **50** (101 MHz, $CDCl_3$)

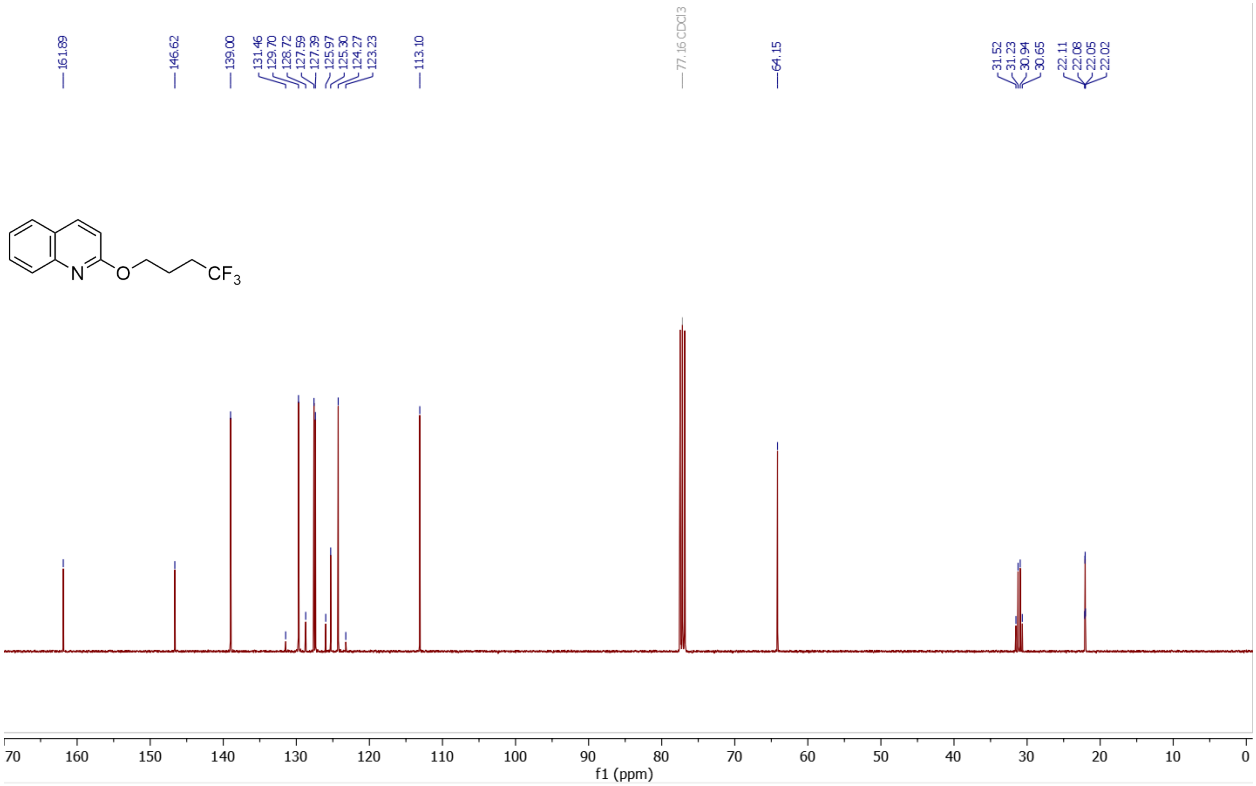


^{19}F NMR spectrum of **50** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

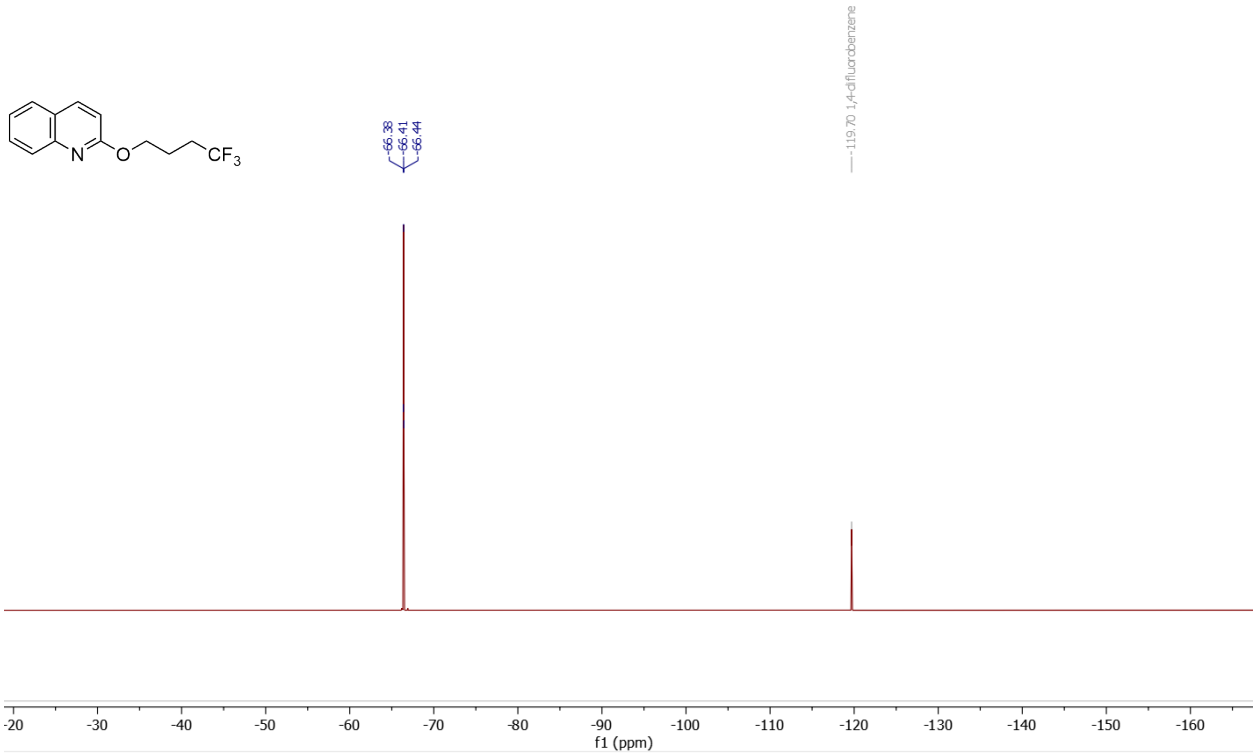
2-(4,4,4-trifluorobutoxy)quinoline



^{1}H NMR spectrum of **2-(4,4,4-trifluorobutoxy)quinoline** (400 MHz, $CDCl_3$)

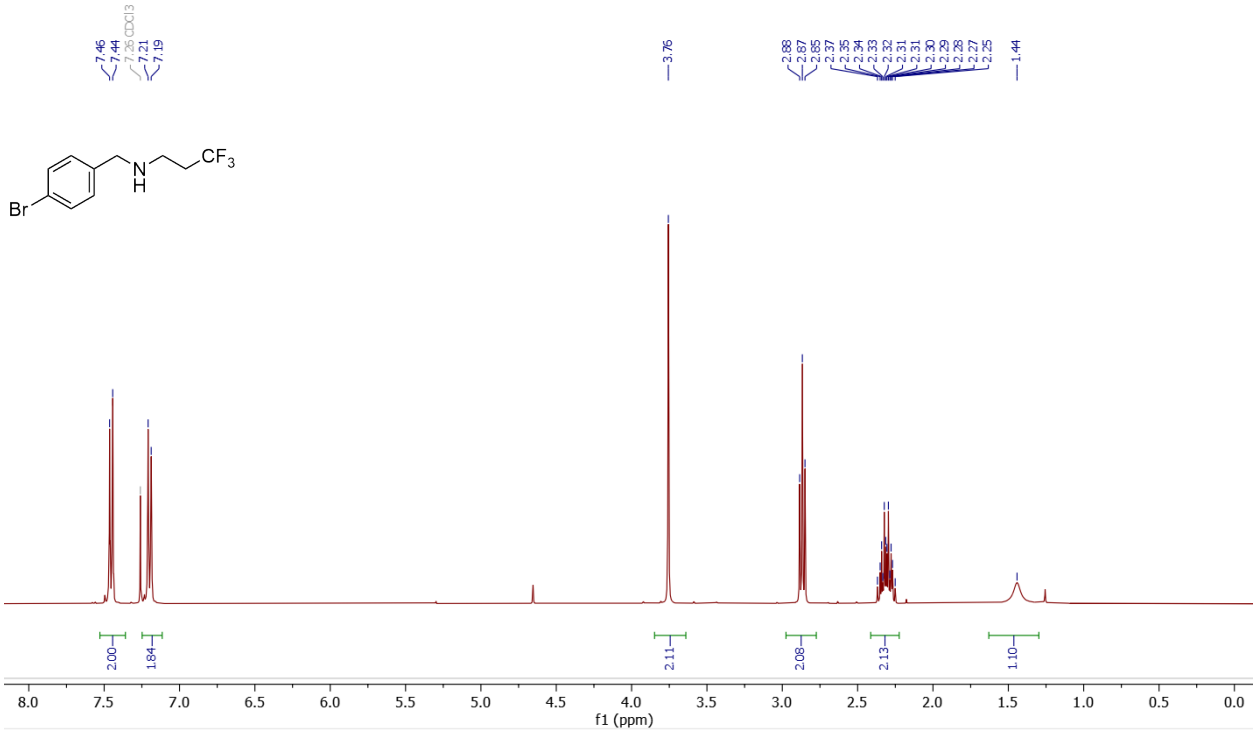


^{13}C NMR spectrum of **2-(4,4,4-trifluorobutoxy)quinoline** (101 MHz, $CDCl_3$)

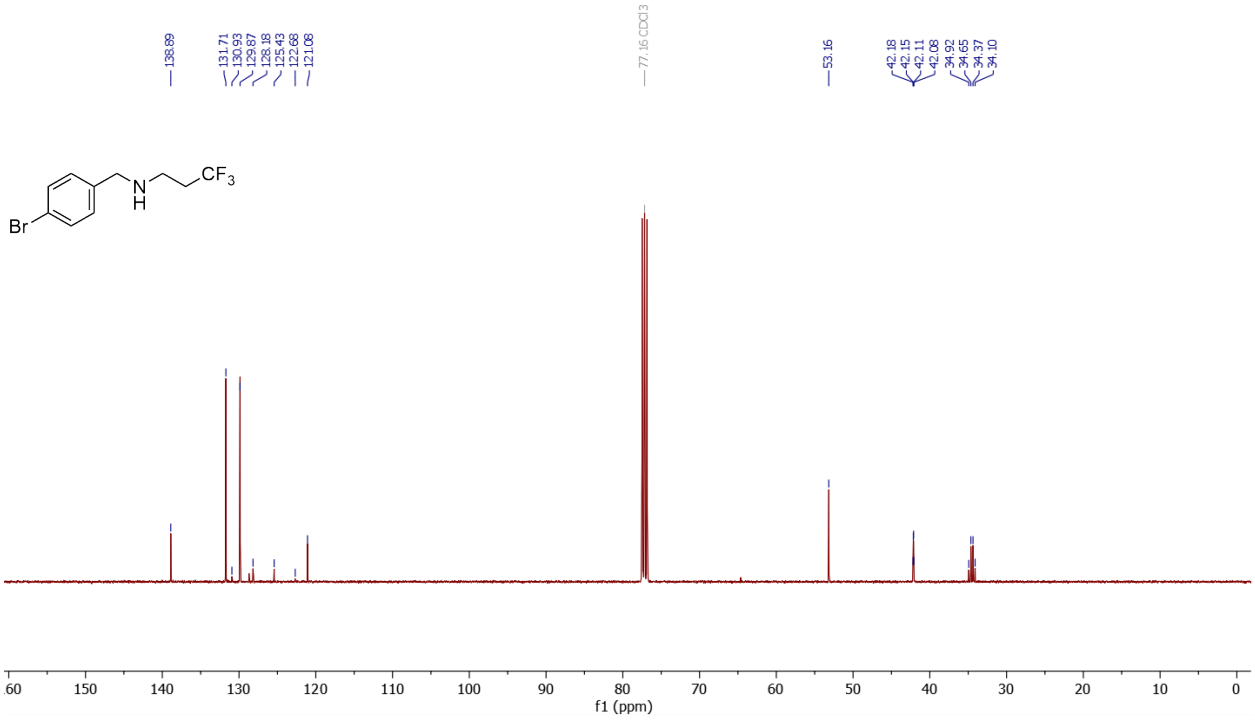


^{19}F NMR spectrum of **2-(4,4,4-trifluorobutoxy)quinoline** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

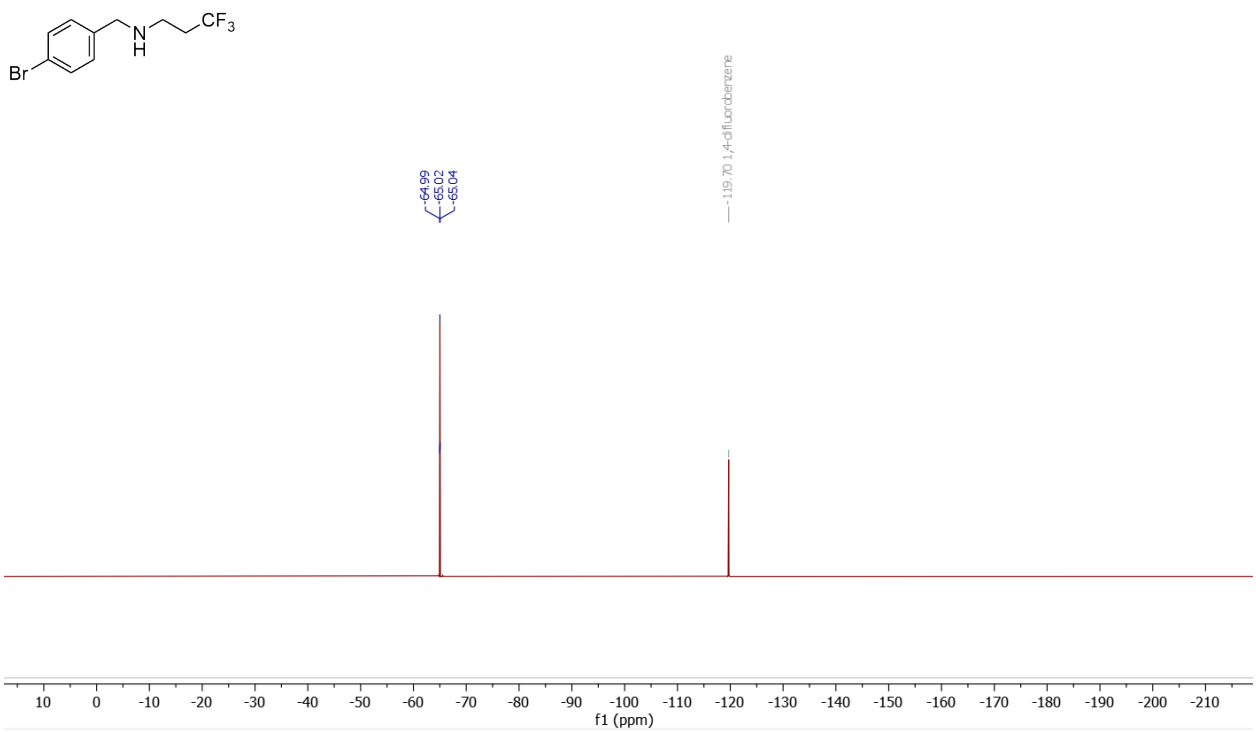
***N*-(4-bromobenzyl)-3,3,3-trifluoropropan-1-amine**



^{1}H NMR spectrum of ***N*-(4-bromobenzyl)-3,3,3-trifluoropropan-1-amine** (400 MHz, $CDCl_3$)

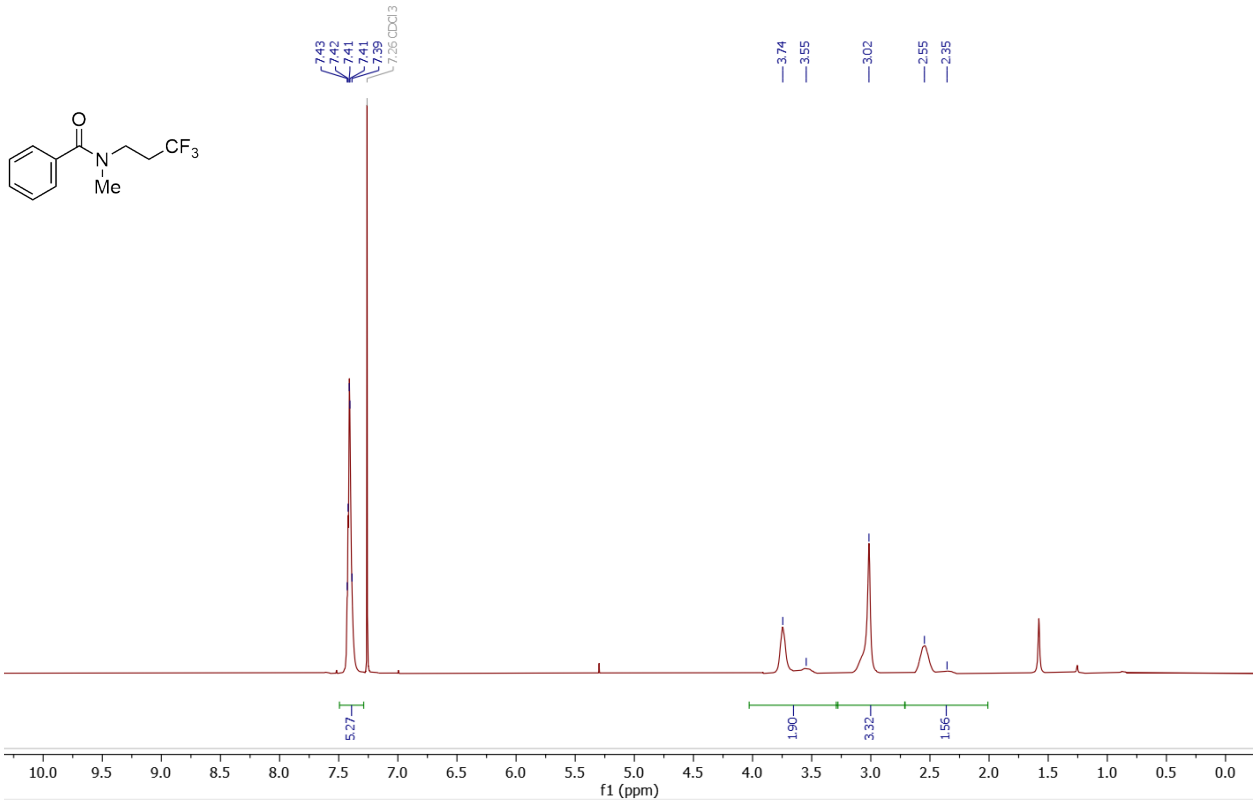


^{13}C NMR spectrum of ***N*-(4-bromobenzyl)-3,3,3-trifluoropropan-1-amine** (101 MHz, $CDCl_3$)

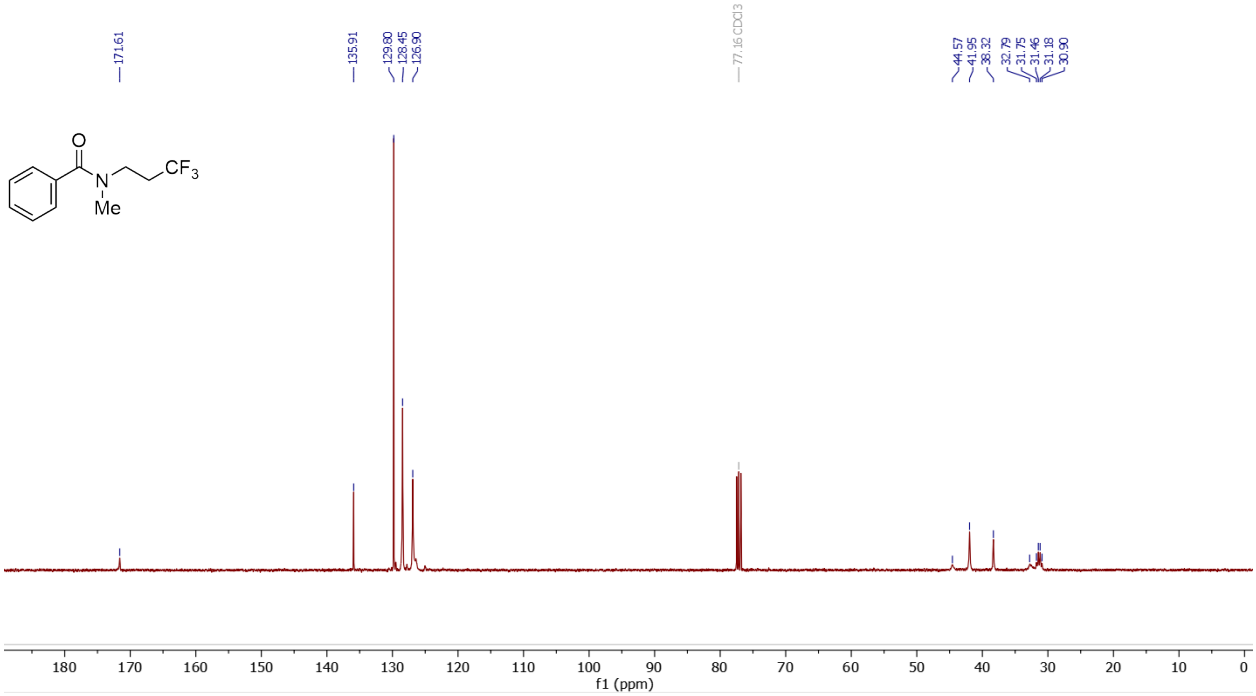


^{19}F NMR spectrum of ***N*-(4-bromobenzyl)-3,3,3-trifluoropropan-1-amine** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

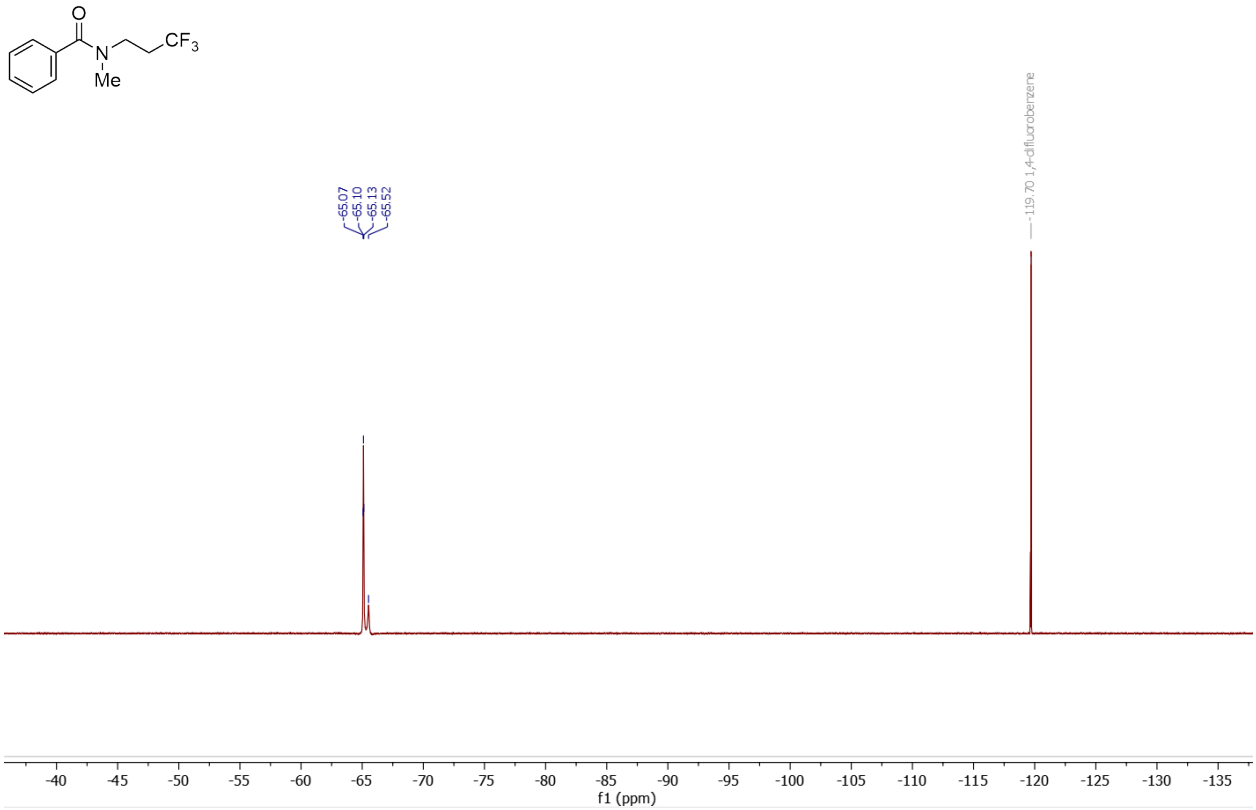
***N*-methyl-*N*-(3,3,3-trifluoropropyl)benzamide**



^{1}H NMR spectrum of ***N*-methyl-*N*-(3,3,3-trifluoropropyl)benzamide** (400 MHz, $CDCl_3$)

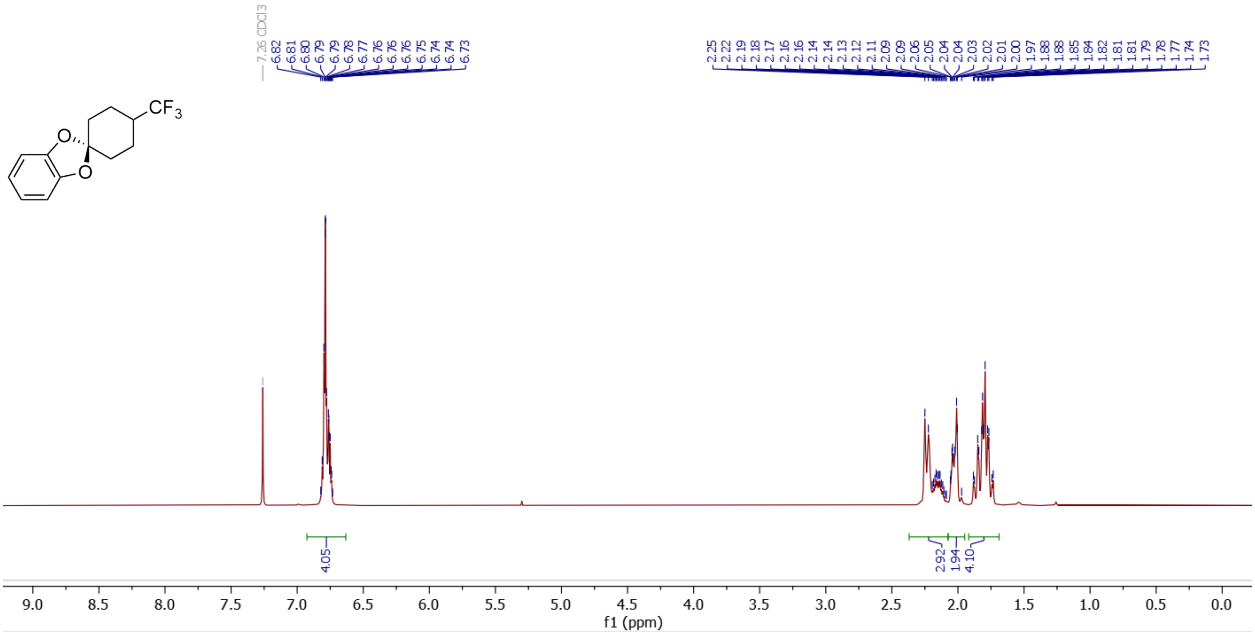


^{13}C NMR spectrum of ***N*-methyl-*N*-(3,3,3-trifluoropropyl)benzamide** (101 MHz, $CDCl_3$)

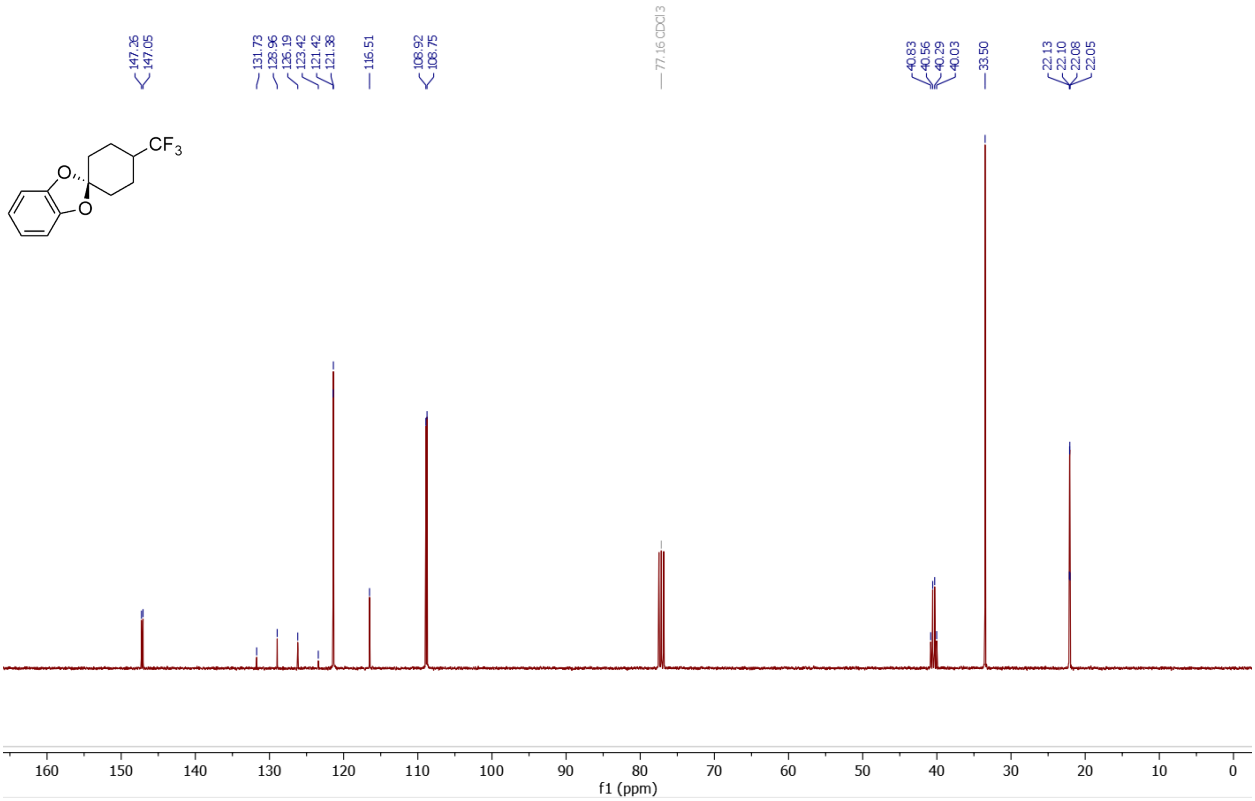


^{19}F NMR spectrum of ***N*-methyl-*N*-(3,3,3-trifluoropropyl)benzamide** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

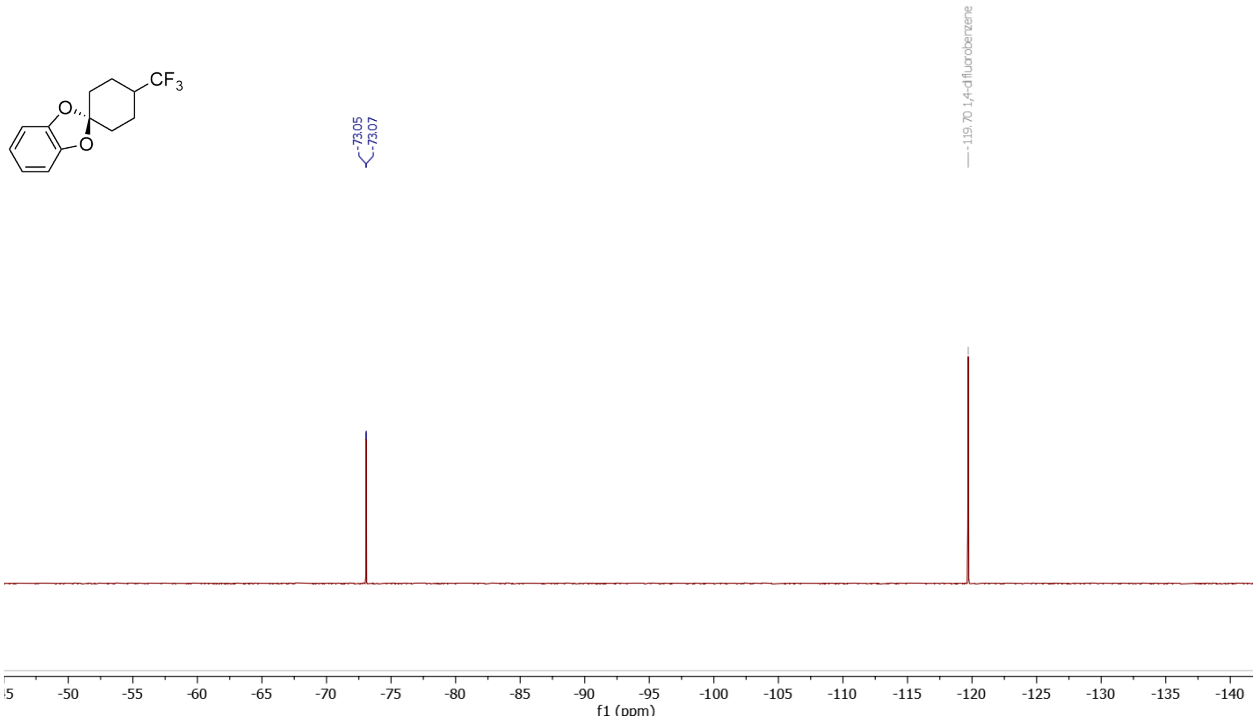
4'-(trifluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]



^{1}H NMR spectrum of **4'-(trifluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]** (400 MHz, $CDCl_3$)

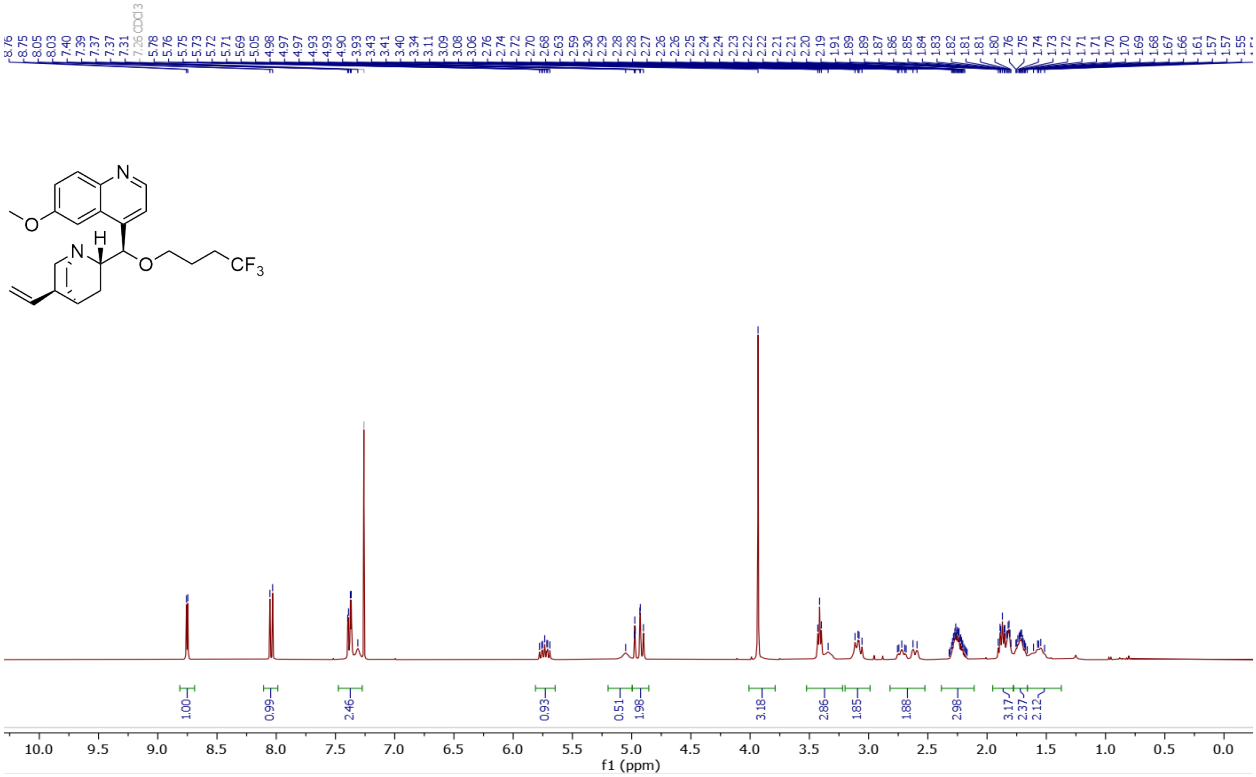


^{13}C NMR spectrum of **4'-(trifluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]** (101 MHz, $CDCl_3$)

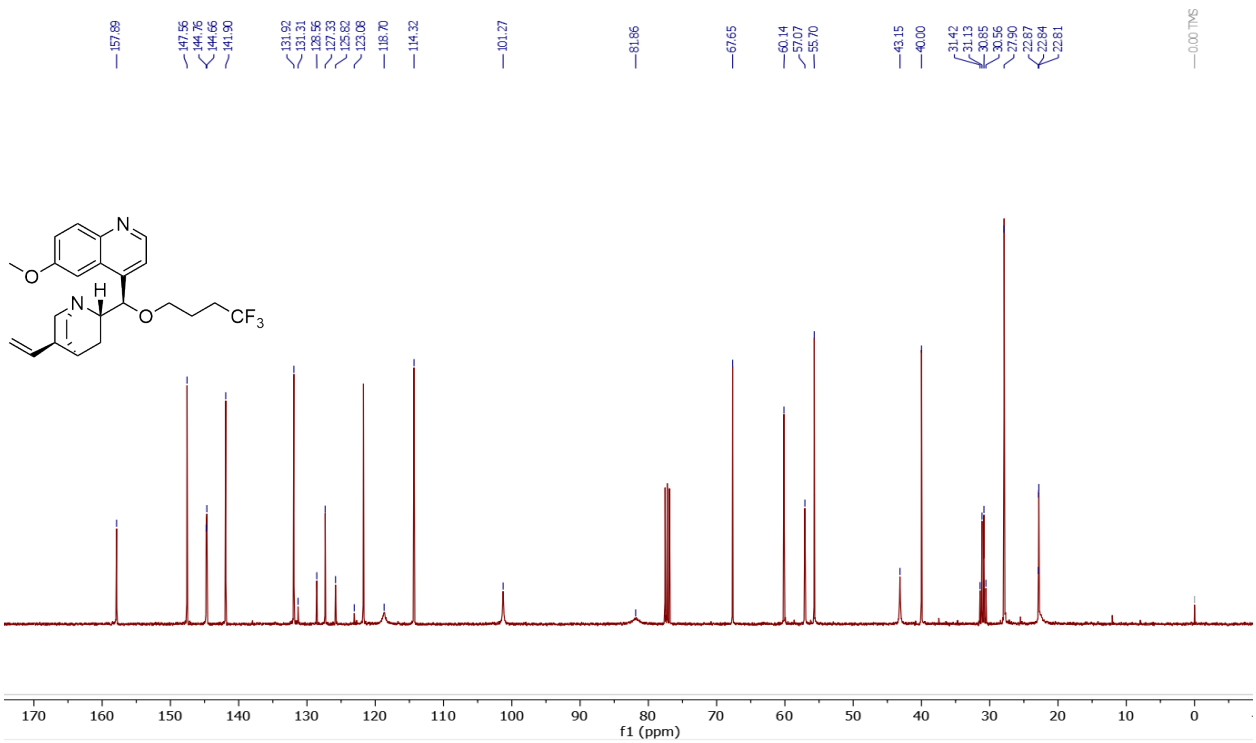


^{19}F NMR spectrum of **4'-(trifluoromethyl)spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

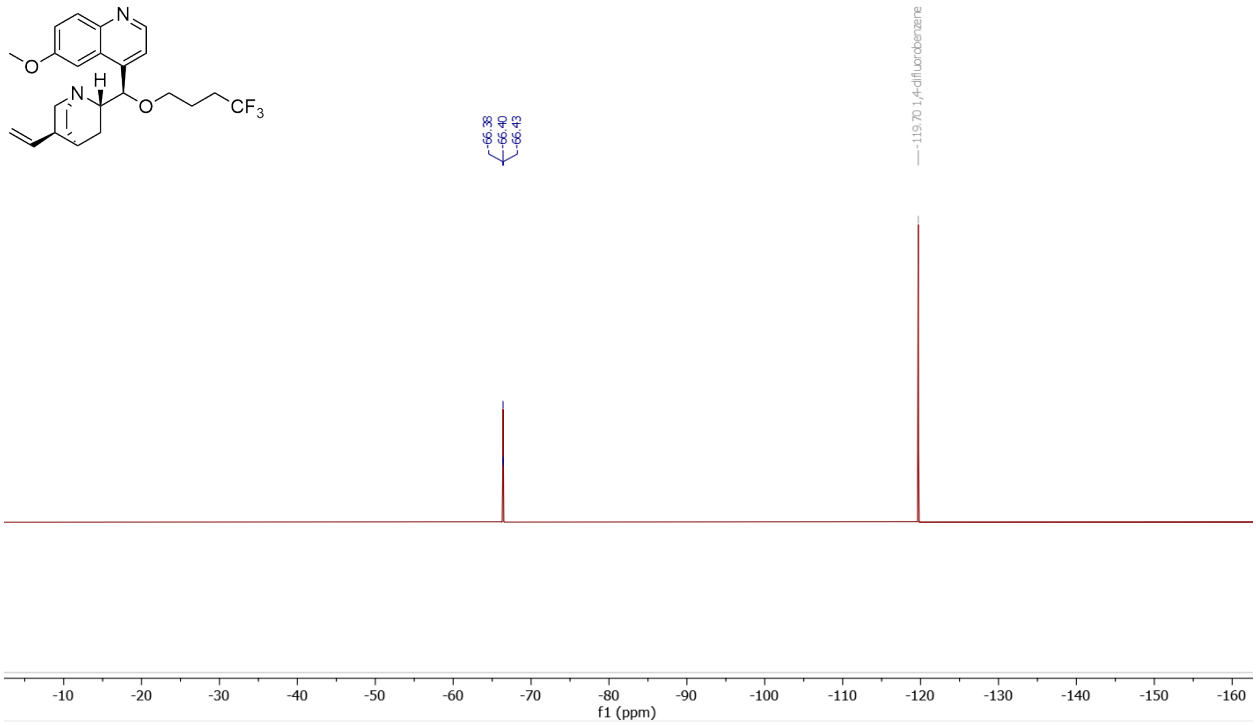
(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(6-methoxyquinolin-4-yl)(4,4,4-trifluorobutoxy)methyl)-5-vinylquinuclidine



^{1}H NMR spectrum of **(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(6-methoxyquinolin-4-yl)(4,4,4-trifluorobutoxy)methyl)-5-vinylquinuclidine** (400 MHz, $CDCl_3$)

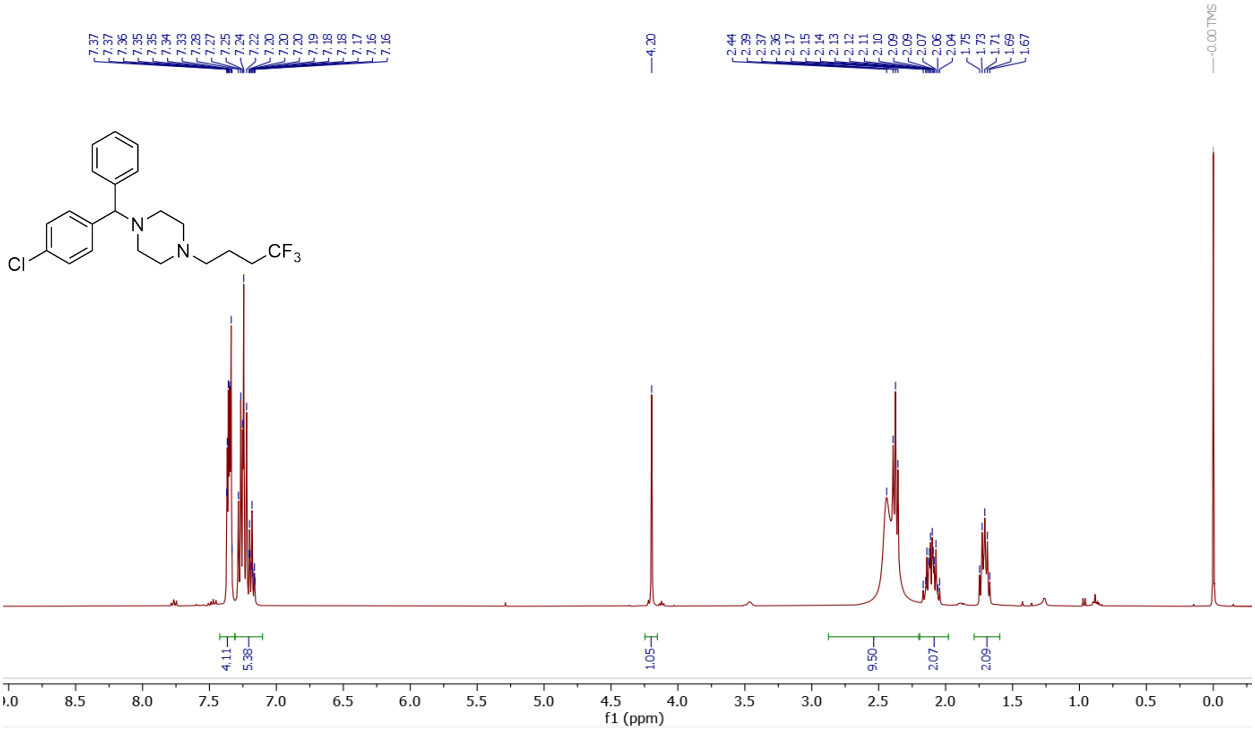


^{13}C NMR spectrum of **(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(6-methoxyquinolin-4-yl)(4,4,4-trifluorobutoxy)methyl)-5-vinylquinuclidine** (101 MHz, $CDCl_3$)

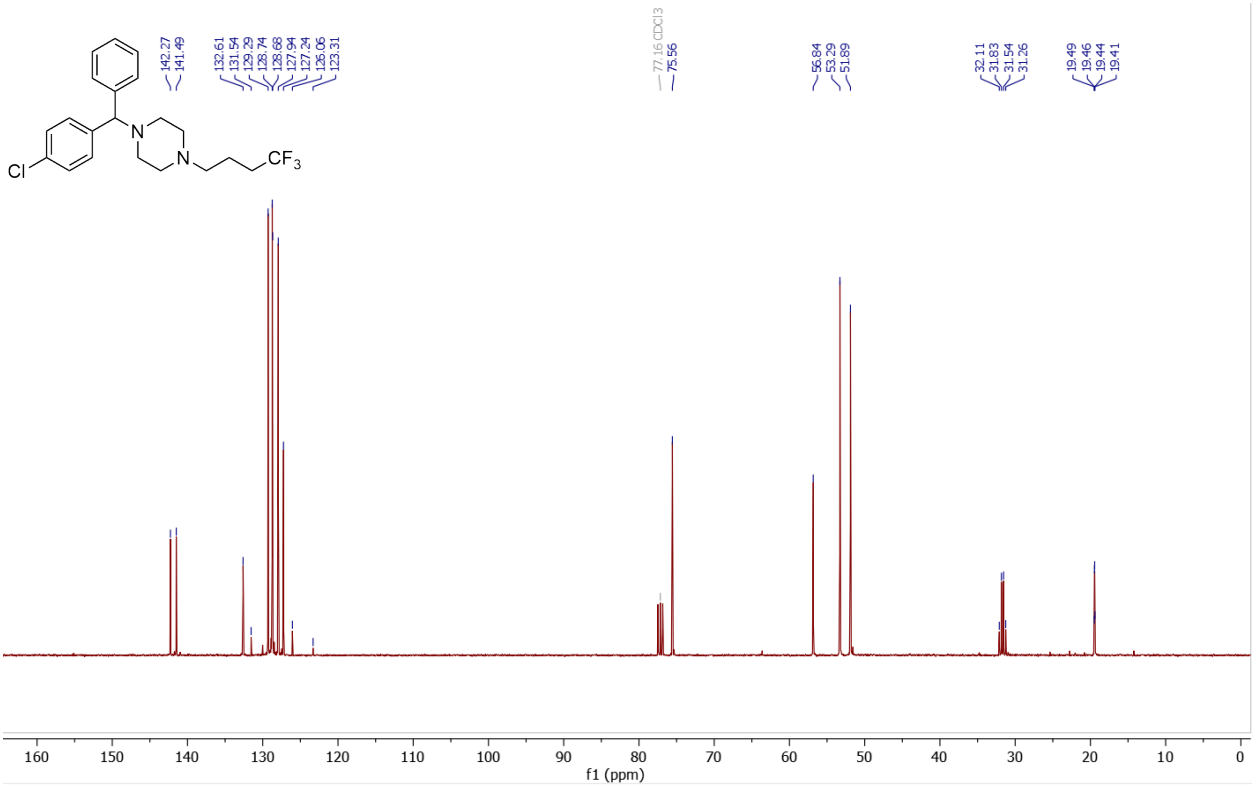


^{19}F NMR spectrum of **(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(6-methoxyquinolin-4-yl)(4,4,4-trifluorobutoxy)methyl)-5-vinylquinuclidine** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

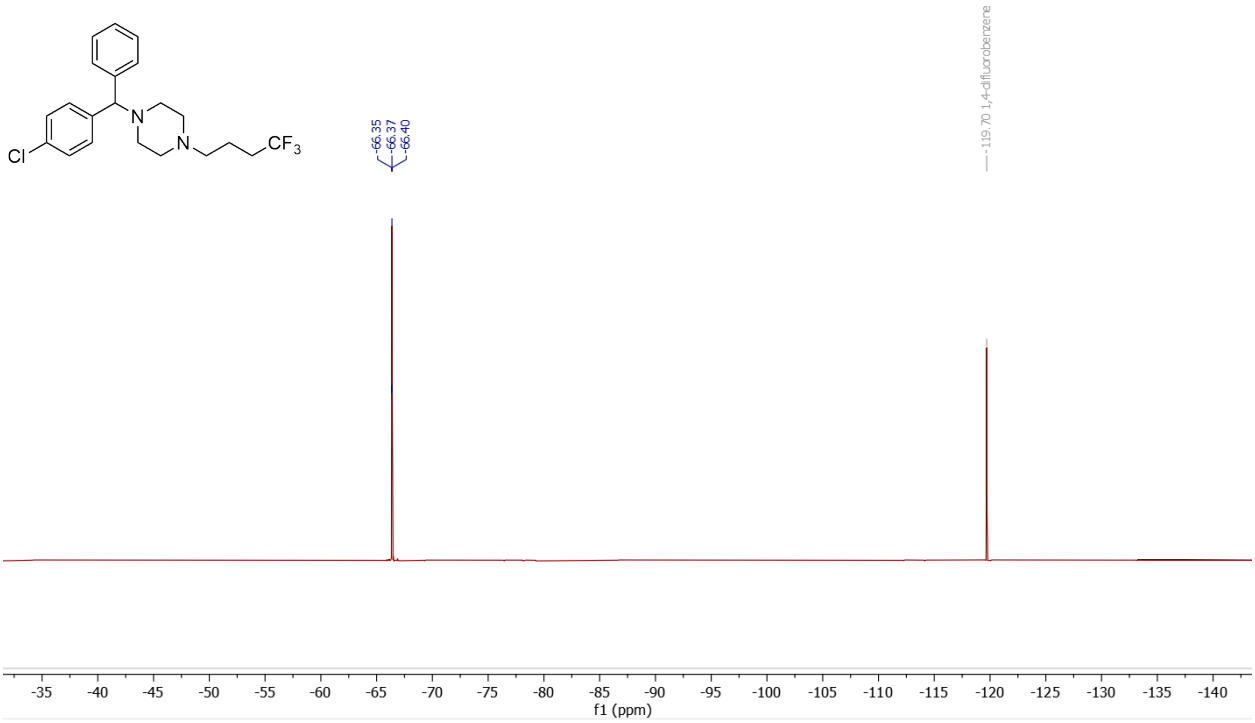
1-((4-chlorophenyl)(phenyl)methyl)-4-(4,4,4-trifluorobutyl)piperazine



^{1}H NMR spectrum of **1-((4-chlorophenyl)(phenyl)methyl)-4-(4,4,4-trifluorobutyl)piperazine** (400 MHz, $CDCl_3$)

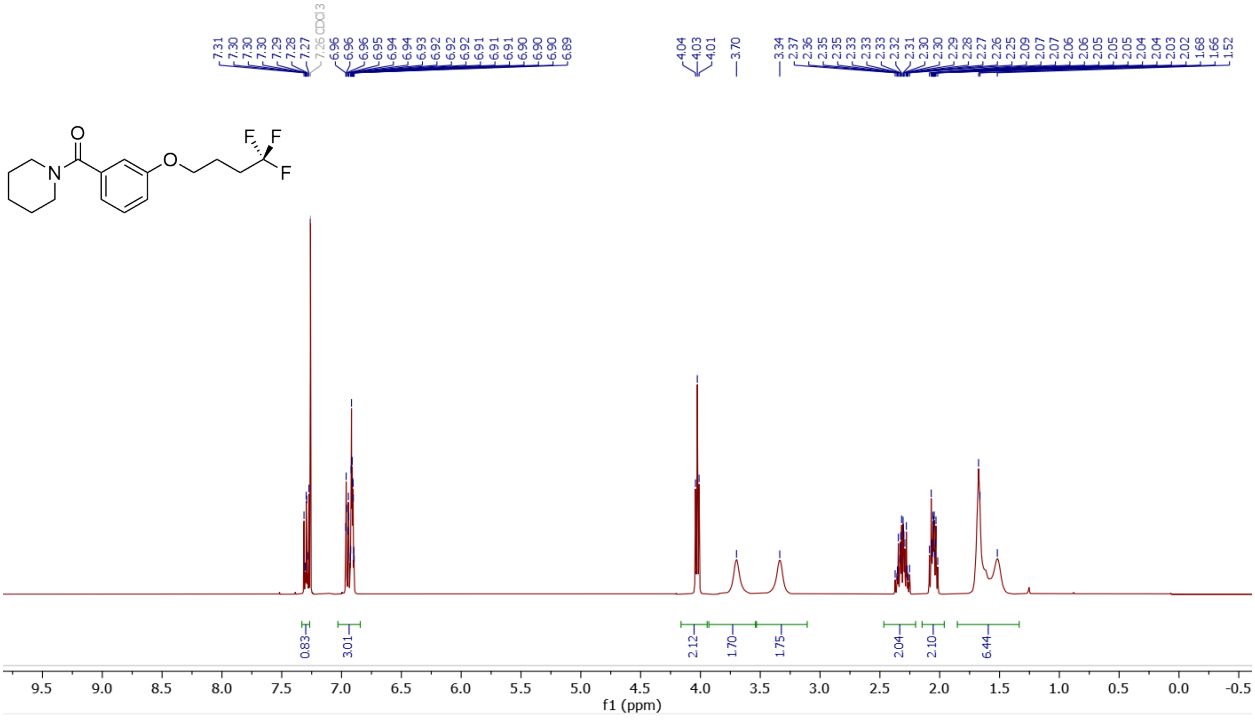


^{13}C NMR spectrum of **1-((4-chlorophenyl)(phenyl)methyl)-4-(4,4,4-trifluorobutyl)piperazine** (101 MHz, $CDCl_3$)

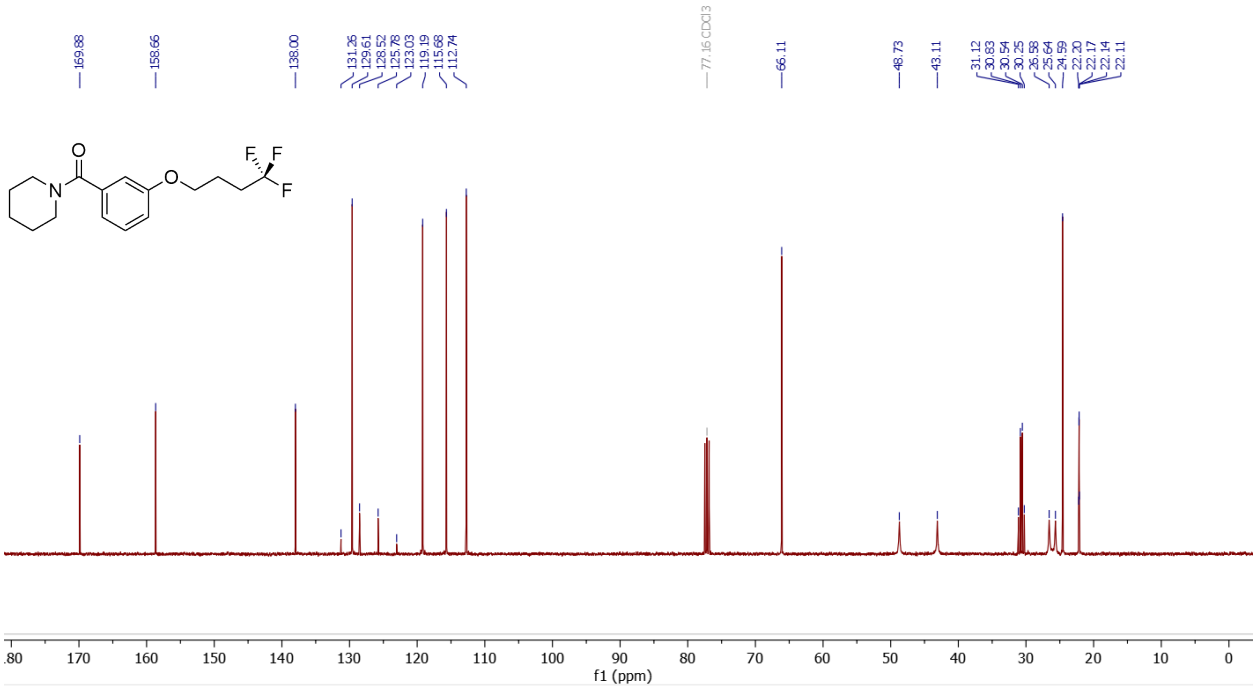


^{19}F NMR spectrum of **1-((4-chlorophenyl)(phenyl)methyl)-4-(4,4,4-trifluorobutyl)piperazine** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

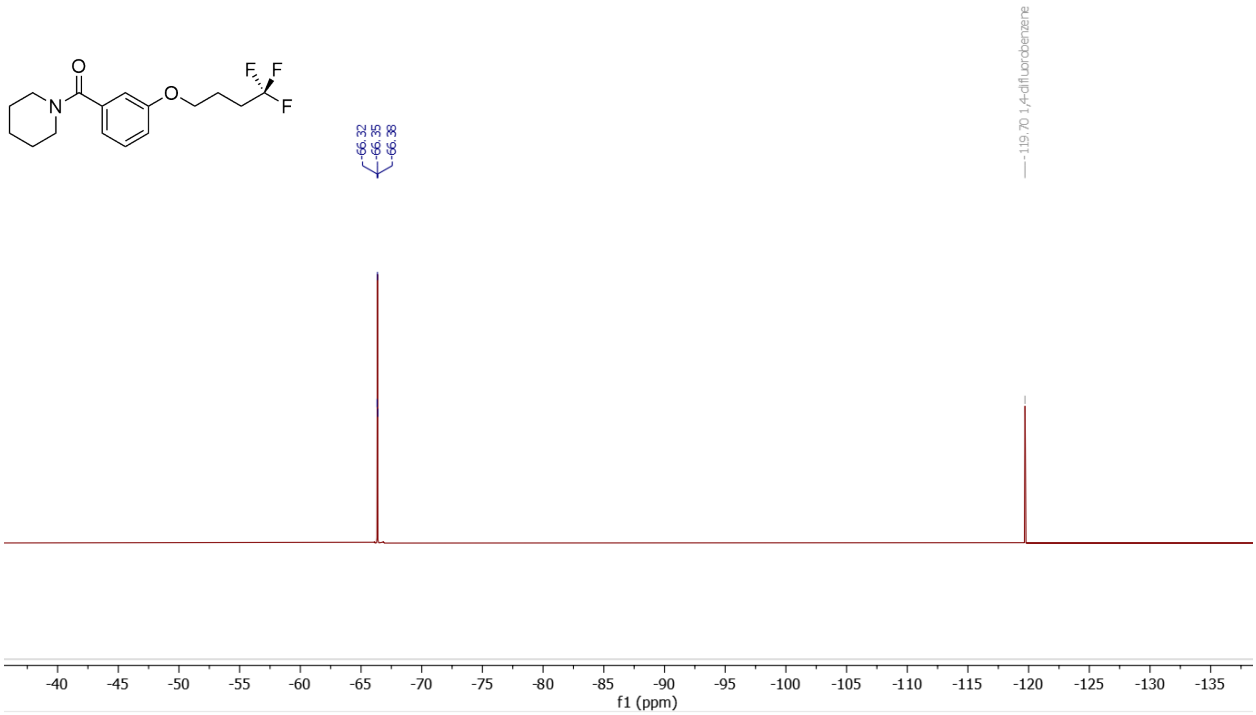
Piperidin-1-yl(3-(4,4,4-trifluorobutoxy)phenyl)methanone



^{1}H NMR spectrum of **Piperidin-1-yl(3-(4,4,4-trifluorobutoxy)phenyl)methanone** (400 MHz, $CDCl_3$)

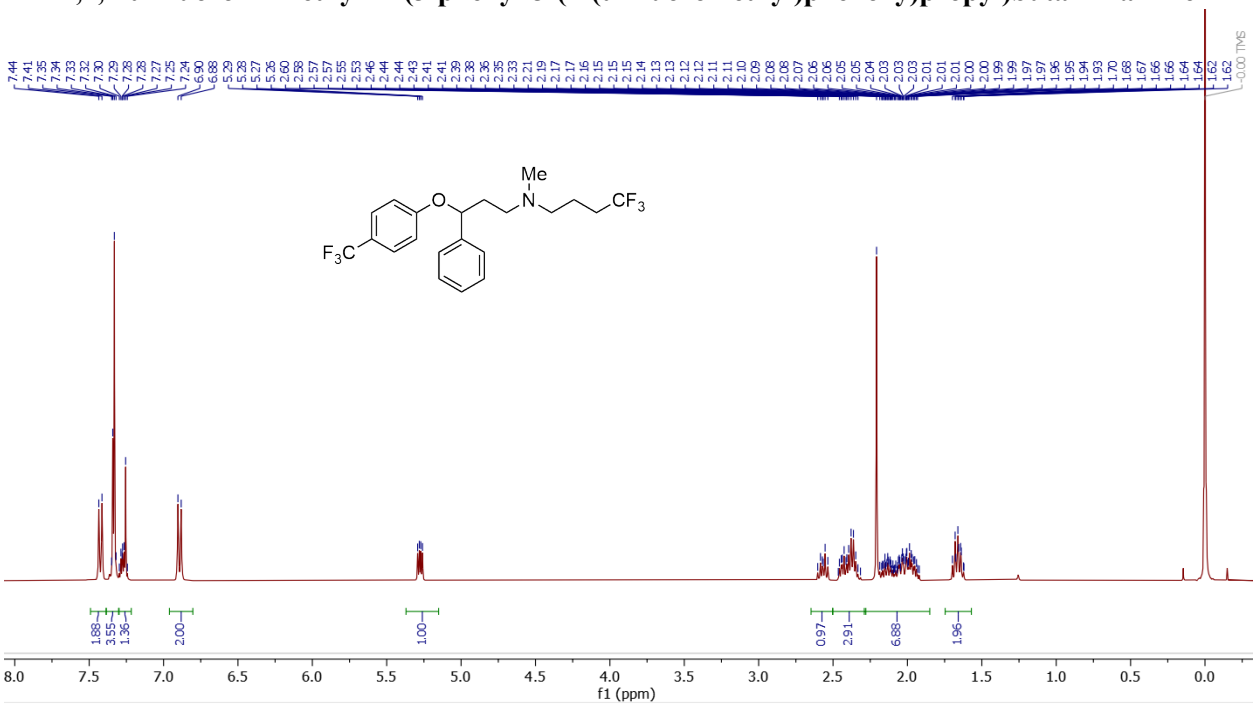


^{13}C NMR spectrum of **Piperidin-1-yl(3-(4,4,4-trifluorobutoxy)phenyl)methanone** (101 MHz, $CDCl_3$)

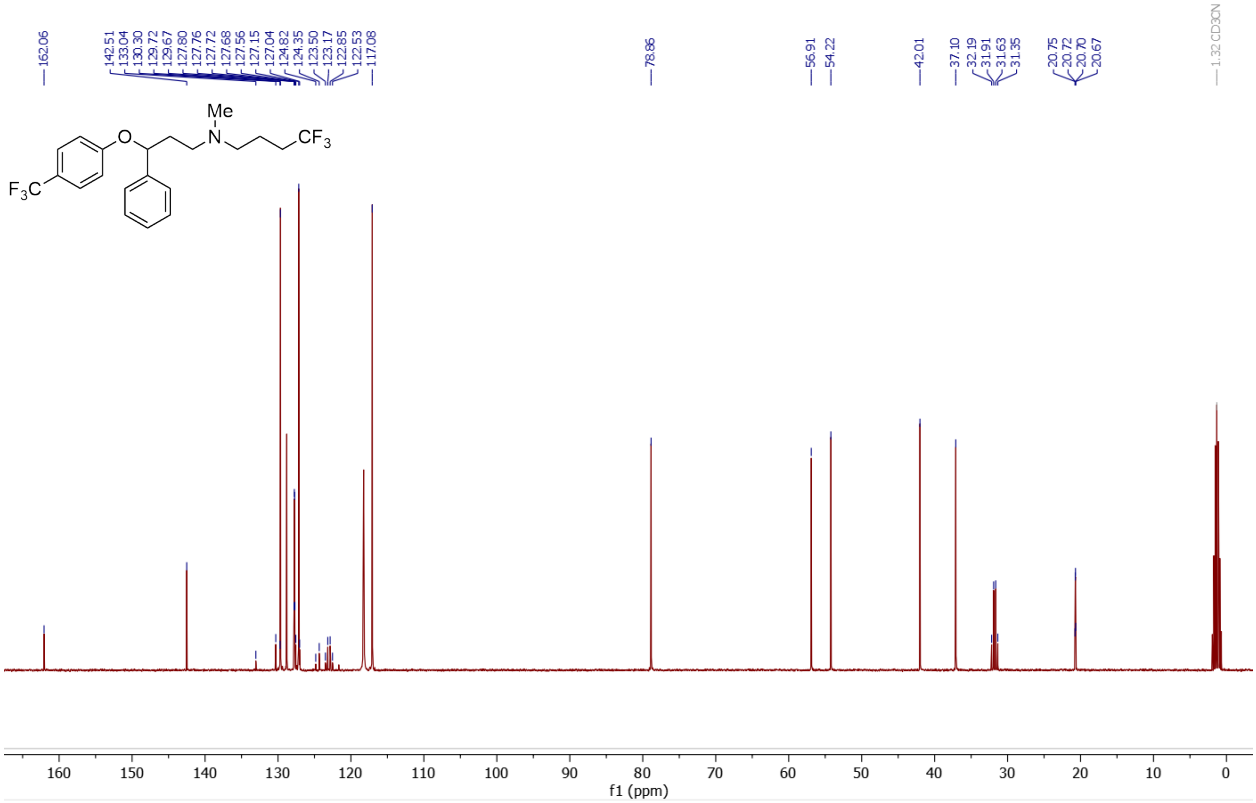


^{19}F NMR spectrum of **Piperidin-1-yl(3-(4,4,4-trifluorobutoxy)phenyl)methanone** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard

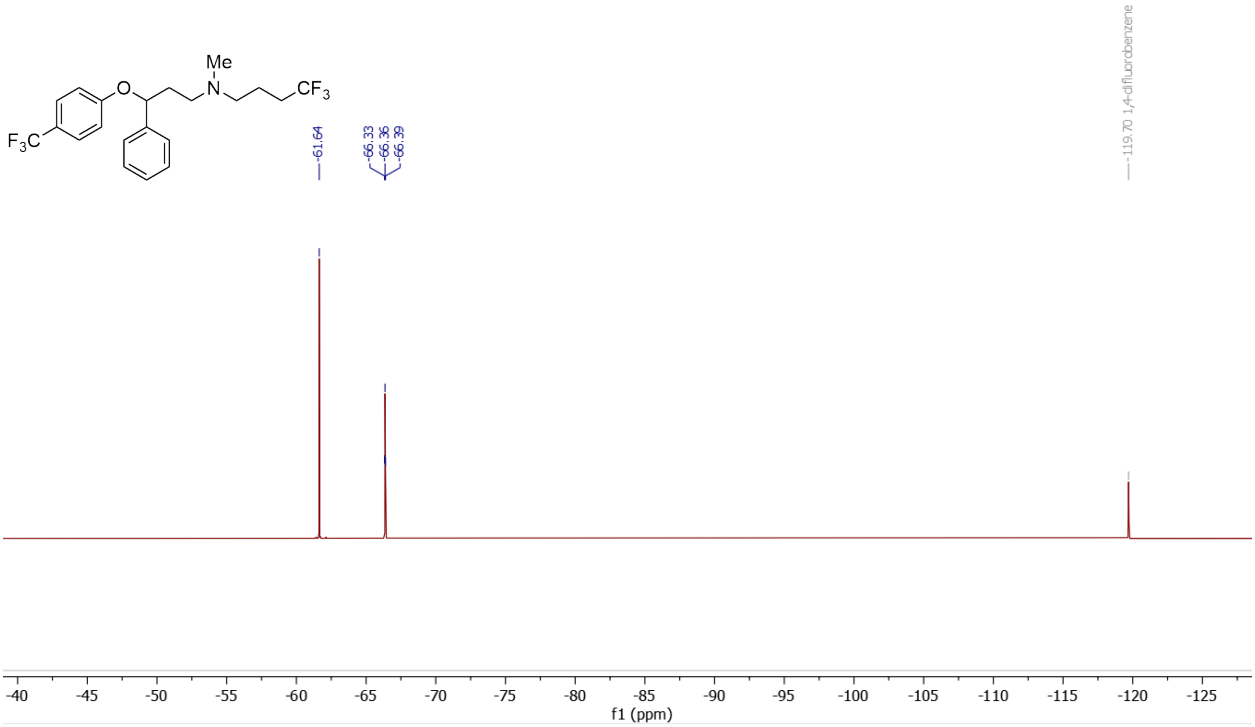
4,4,4-trifluoro-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butan-1-amine



^{1}H NMR spectrum of **4,4,4-trifluoro-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butan-1-amine** (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of **4,4,4-trifluoro-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butan-1-amine** (101 MHz, CD_3CN)



^{19}F NMR spectrum of **4,4,4-trifluoro-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)butan-1-amine** (376 MHz, $CDCl_3$), 1,4-difluorobenzene used as internal standard