Electronic Supplementary Information

Catalyst-Free Defluorinative Alkylation of Trifluoromethyls

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1. General information

Unless otherwise noted, all the Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra were recorded on a Bruker AVANCE III 500MHz spectrometer. Chemical shifts were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; DMSO-d_6: 2.50 ppm ^{1}H NMR, 39.52 ppm ^{13}C NMR). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). All high-resolution mass spectra (HRMS) were obtained on an AB Sciex TripleTOF 4600 spectrometer. Cyclic voltammetry experiments were performed on a CH Instruments Electrochemical Analyzer. Blue LED (40 W, λ_{max} = 440 nm) purchased from Kessil was used for blue light irradiation. High pressure photoreactor purchased from WATTCAS was used for the reaction of ethylene. Reactions were monitored using thin layer chromatography (TLC) on aluminium backed plates and visualised by UV radiation at a wavelength of 254 nm.

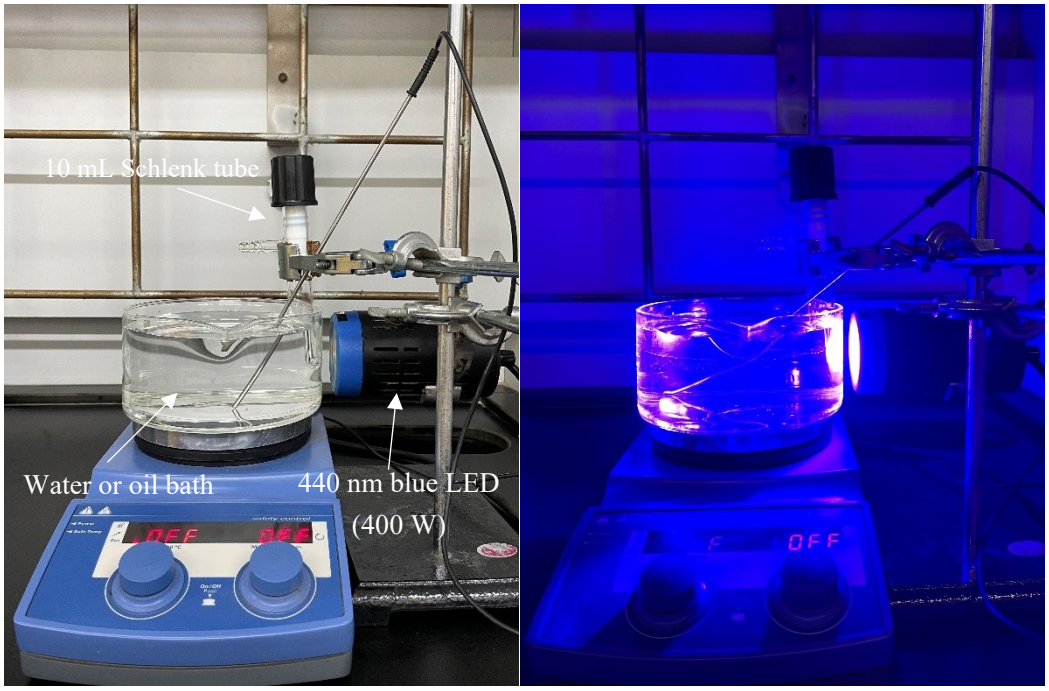
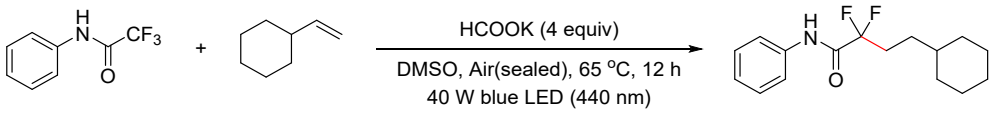


Figure S1. Standard setup for reactions.

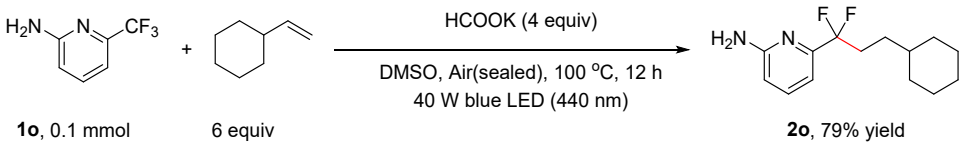
2. General procedures



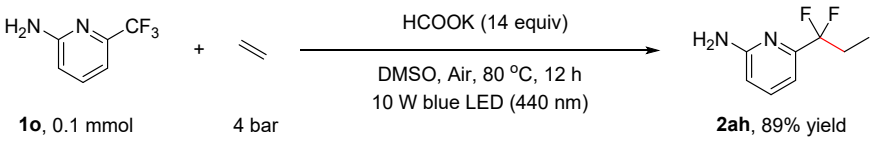
1a, 0.1 mmol 6 equiv **2a**, 72% yield

General procedure A: An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the substrate (0.1 mmol), HCOOK (Potassium formate, 0.4 mmol), vinylcyclohexane (0.6 mmol) and anhydrous DMSO (3 mL). Then the reaction was placed under a blue LED (wavelength 440 nm, 40 W) and irradiated for 12 hrs at 65 °C. The mixture was quenched with H_2O. Then extracted with EtOAc three times, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography isolation on silica gel

(eluent: PE/EA = 6/1 v/v) to give the pure desired product as white solid (**2a**, 72% yield, 20.3 mg).



General procedure B: An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the substrate (0.1 mmol), HCOOK (0.4 mmol), vinylcyclohexane (0.6 mmol) and anhydrous DMSO (3 mL). Then the reaction was placed under a blue LED (wavelength 440 nm, 40 W) and irradiated for 12 hrs at 100 °C. The mixture was quenched with H_2O. Then extracted with EtOAc three times, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography isolation on silica gel (eluent: PE/EA = 6/1 v/v) to give the pure desired product as white solid (**2o**, 79% yield, 20.1 mg).



General procedure C: A 25 mL vial tube equipped with a magnetic stir was charged with substrate (0.1 mmol), HCOOK (1.4 mmol), and anhydrous DMSO (3 mL). After filled with 4 bar of ethylene, the reaction mixture was then irradiated with a 10 W blue LED lamp with heating from circulating liquid (ethylene glycol: H_2O = 1:1) for 12 hrs at 80 °C. The mixture was quenched with H_2O. Then extracted with EtOAc three times, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography isolation on silica gel (eluent: PE/toluene = 1/2 v/v) to give the pure desired product as colorless oil (**2ah**, 89% yield, 15.2 mg).

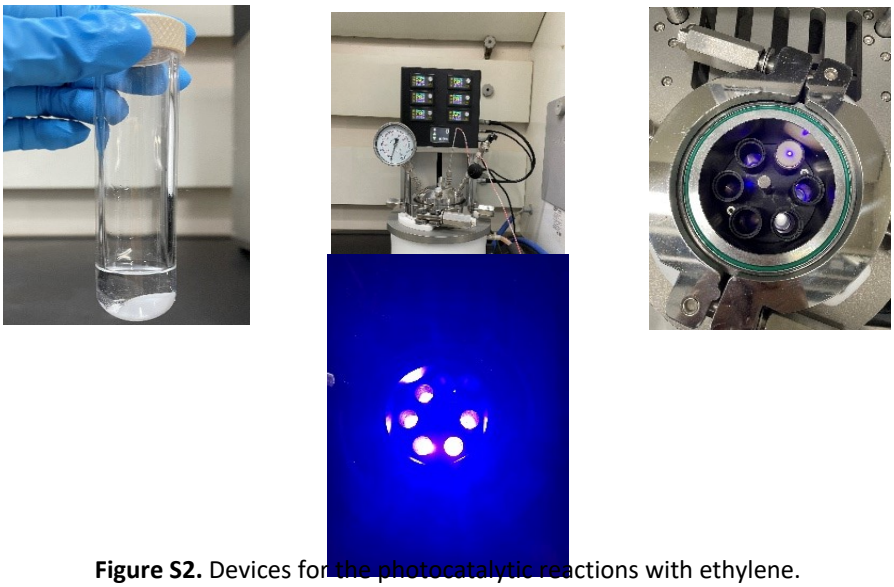
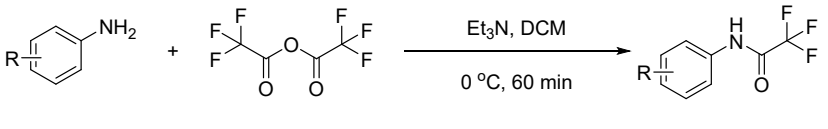
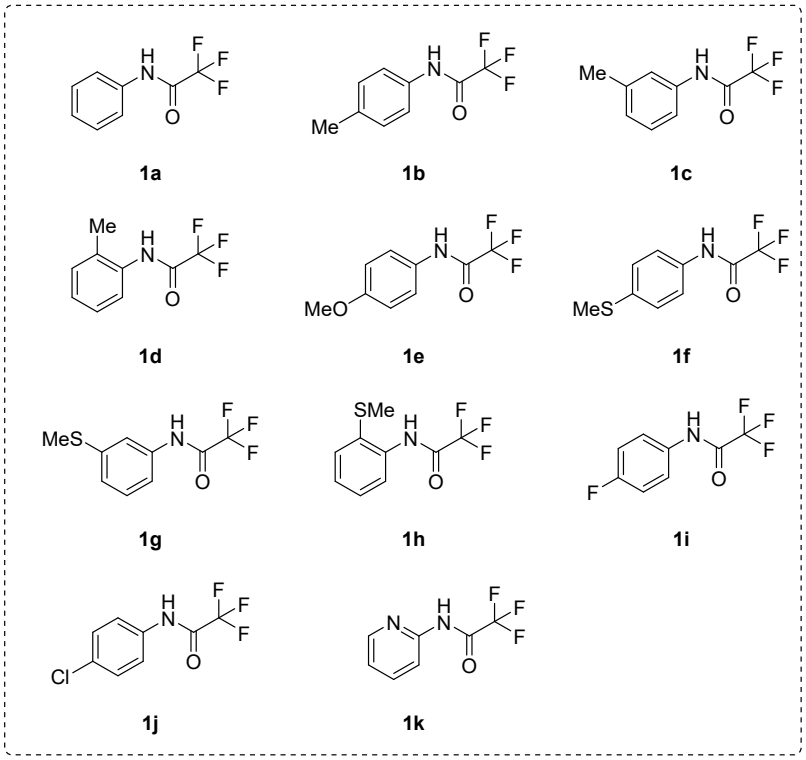


Figure S2. Devices for the photocatalytic reactions with ethylene.

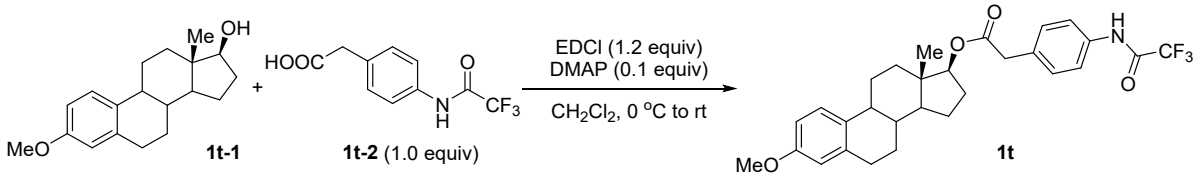
General procedure for the synthesis of trifluoro acetanilide derivatives [1] (**1a** – **1k**):





General procedure C: Substituted aniline (4.0 mmol) and triethylamine (6.0 mmol) were dissolved in anhydrous dichloromethane (12 mL), the mixture was cooled to 0 °C and added trifluoroacetic anhydride (4.2 mmol in 2 mL of dichloromethane). The reaction mixture was stirred at the same temperature for 60 min. After completion of the reaction monitored by TLC, dichloromethane (10 mL) was added, and the mixture was washed with saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel (eluent: PE/EA = 95/0.5 to 50/50 v/v) to give the corresponding trifluoro acetanilide derivative in 87-93% yield.

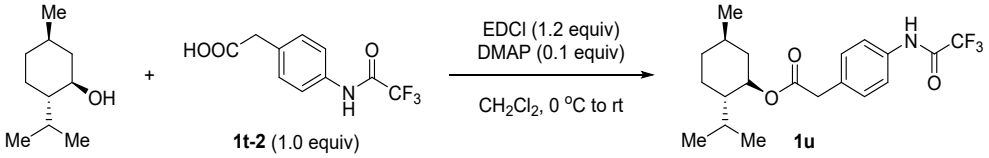
General procedure for the synthesis of ***(13S,17S)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl 2-(4-(2,2,2-trifluoroacetamido)phenyl)acetate (1t)*** [2]



To a solution of **1t-1** (0.54 g, 1.87 mmol), and 2-(4-(2,2,2-trifluoroacetamido)phenyl)acetic acid (**1t-2**) (0.46 g, 1.86 mmol) in CH_2Cl_2 (15 mL) was added 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.46 g, 2.39 mmol) and DMAP (35.8 mg, 0.29 mmol) at 0 °C. After addition, the mixture was stirred at room temperature until TLC indicating **1t-1** disappeared. The reaction was quenched with water and extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. The resulting crude material was purified by flash column

chromatography on silica gel (eluent: PE/EA = 10/1 v/v) to give desired product **1t**.

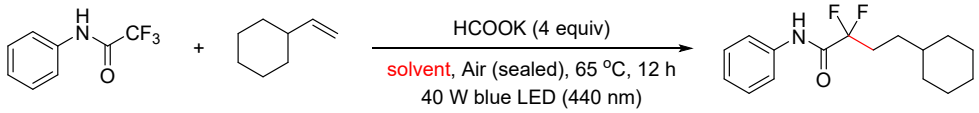
General procedure for the synthesis of ***2,2,2-trifluoro-N-(4-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)phenyl)acetamide (1u)*** [2]



To a solution of L-Menthol (1.78 g, 11.40 mmol), and 2-(4-(2,2,2-trifluoroacetamido)phenyl)acetic acid (**1t-2**) (2.83 g, 11.45 mmol) in CH_2Cl_2 (30 mL) was added 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.72 g, 14.16 mmol) and DMAP (141.5 mg, 1.16 mmol) at 0 °C. After addition, the mixture was stirred at room temperature until TLC indicating L-Menthol disappeared. The reaction was quenched with water and extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. The resulting crude material was purified by flash column chromatography on silica gel (eluent: PE/EA = 15/1 v/v) to give desired product (**1u**).

3. Investigation of the key reaction parameters

Table S1. Screening of solvents[a] (General procedure A)

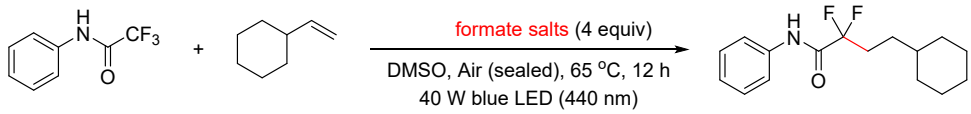


1a, 0.1 mmol 6 equiv **2a**

Entry	Conditions	**2a** [%][b]
1	none	**76**
2	DMF instead of DMSO	N.D.
3	NMP instead of DMSO	N.D.
5	2 mL DMSO instead of 3 mL	43
6	4 mL DMSO instead of 3 mL	76
7	3 mL DMSO (distilled)[c]	71
8	DMF (with 1 equiv MeSH) instead of DMSO	N.D.
9	NMP (with 1 equiv MeSH) instead of DMSO	N.D.

[a] **1a** (0.1 mmol), HCOOK (0.4 mmol), cyclohexylethene (0.6 mmol),solvent (3 mL), air (sealed), 65 °C, 40 W blue LED (440 nm), 12 h. [b] Yields were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [c] reduced pressure distillation at 65 °C

Table S2. Screening of formate salts[a] (General procedure A)



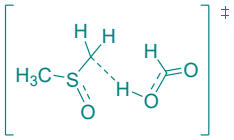
1a, 0.1 mmol 6 equiv **2a**

Entry	Conditions	**2a** [%][b]
1	none	**76**
2	3 equiv HCOOK instead of 4 equiv	44
3	HCOOCs instead of HCOOK	42
4	HCOONa instead of HCOOK	N.D.
5	$HCOONH_4$ instead of HCOOK	N.D.
6	Without HCOOK	N.D.

[a] **1a** (0.1 mmol), formate salts (0.4 mmol), cyclohexylethene (0.6 mmol),DMSO (3 mL), air (sealed), 65 °C, 40 W blue LED (440 nm), 12 h.[b] Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as internal standard.

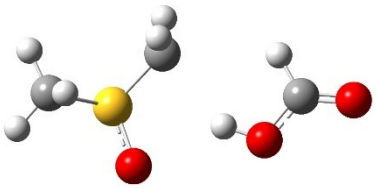
4. Computational studies

Table S3. Detail computational information of intermediate structure (at (u)m062x/6-311g+(d,p)/SMD(DMSO) level)



Ts-0

G = -742.331454 a.u.



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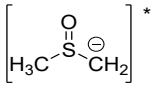
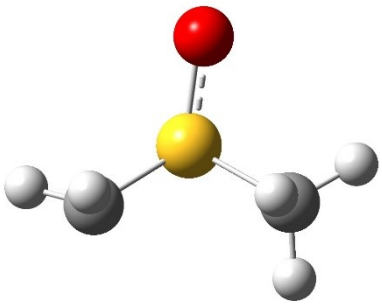
O -1.16181792 -1.31296028 -0.02204606
C -3.09152169 0.34732093 0.49663994
H -3.53075953 1.31349669 0.24565860
H -3.81159005 -0.46122756 0.36243702
H -2.72048080 0.34394264 1.52384491
C -0.50712816 1.24904815 -0.14814256
H -0.47270805 2.04309116 -0.89110724
H -0.59269419 1.59973863 0.88298797
H 0.88787915 -0.41107122 0.16172203
C 2.64929660 0.27683212 0.16269948
H 2.14713682 1.20604053 -0.14692890
O 1.81348365 -0.72010969 0.34496701
O 3.84399454 0.18799307 0.31802487



ii

G = -552.441241 a.u.



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O 0.13725700 1.49524900 0.34742700
C 1.31881000 -0.81842800 0.13070300
H 1.21940400 -0.98479700 1.20544600
H 1.34454100 -1.76743700 -0.40057100
H 2.21627600 -0.23737300 -0.07654700
C -1.37514000 -0.83068300 0.19725200
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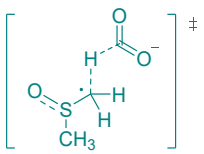
H -1.34372200 -0.93004400 1.28637900



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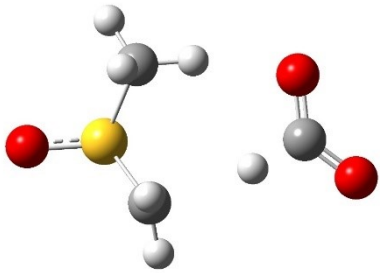

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O 3.35305061 -0.65445478 -0.16425192
S -1.50216365 -0.13121958 -0.41360834
O -2.97525774 -0.32434637 -0.06321953
C -0.94447337 1.27947813 0.56358099
H -1.21000043 1.08152124 1.60371870
H 0.13753673 1.41438568 0.42689901
H -1.50234493 2.14154418 0.19810539
C -0.58291939 -1.36181822 0.43898287
H -0.59934215 -1.35330281 1.52244035
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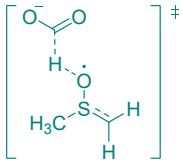

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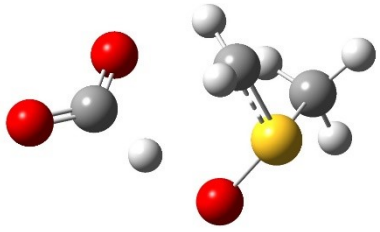

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H -0.95409491 -0.35092934 -0.65261051
O -1.65114776 1.23501644 0.40958625
O -2.86750816 -0.62605928 -0.05743457
S 1.57030723 -0.35444219 -0.10133003
O 0.59552398 -0.77501180 -1.25089391
C 1.44999036 1.44921263 -0.15091464
H 0.40883152 1.70665931 0.06236010
H 2.13551144 1.86332521 0.58654036
H 1.72510758 1.75513082 -1.15916953
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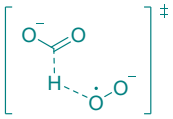
H 1.17619627 -1.69383424 1.79266495



Ts-3

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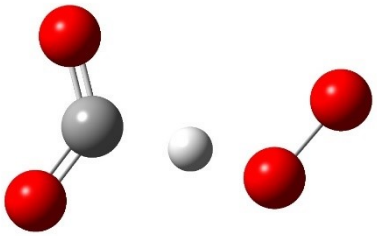

-2 2
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O -2.46993286 0.32786818 0.00002928
C 1.06175489 0.06718179 0.00002093
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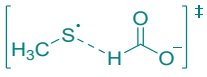
O 1.42044093 1.26006294 -0.00005007
O 1.75070200 -0.97437421 0.00002519



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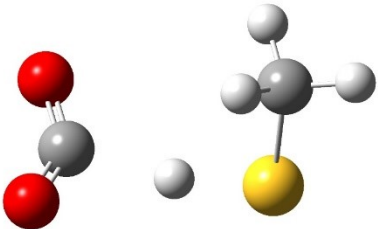

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H 2.51348711 0.97308384 1.21626664
H 0.89244455 1.50251523 0.72077572
H 2.28597002 1.81053210 -0.33547629

S 1.52152941 -0.50206620 -0.45143889
C -1.42577481 -0.08002262 0.12963285
H -0.17964326 -0.25831040 -0.11631546
O -2.11583605 -0.99339603 -0.29130946
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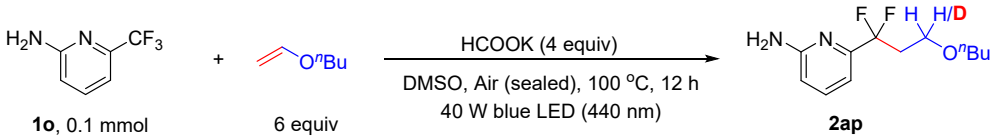
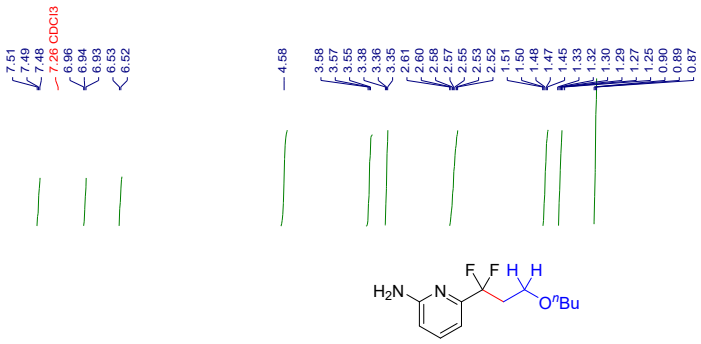
5. Mechanistic studies

5.1 Deuterium labeling experiments

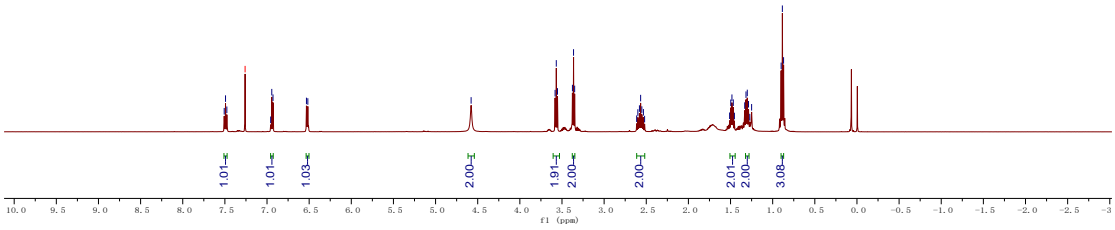


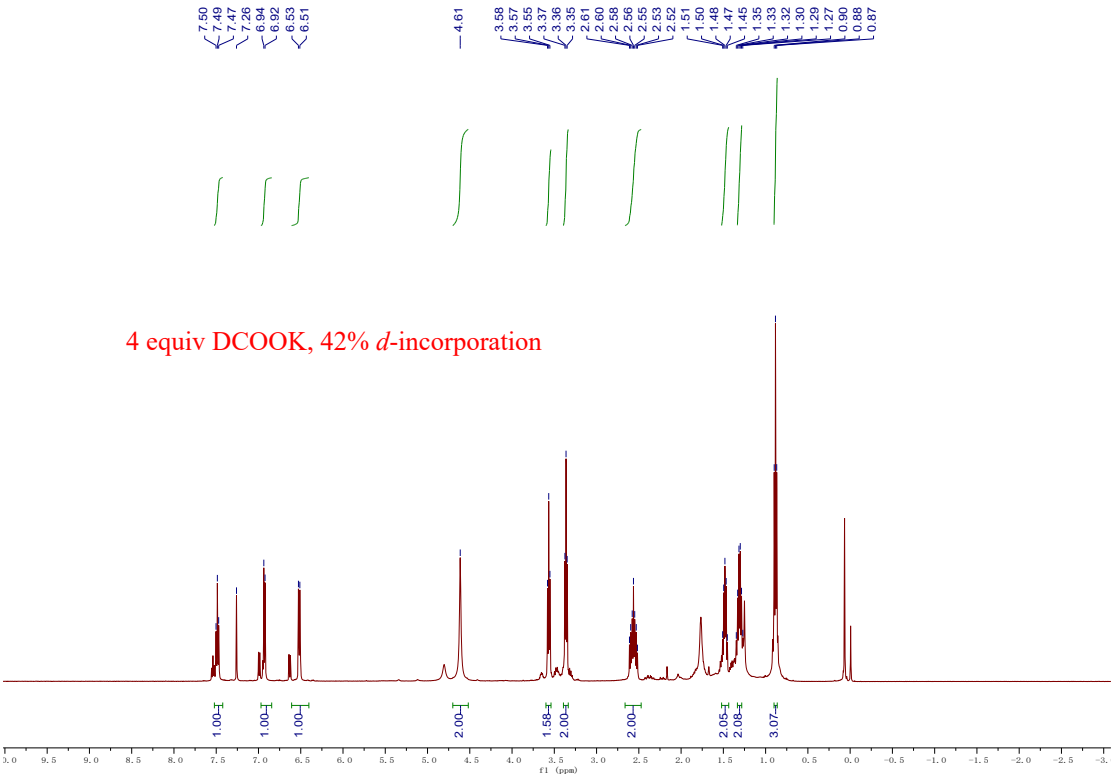
1o, 0.1 mmol 6 equiv **2ap**

1. 4 equiv DCOOK — 61% yield, 42% *d*-incorporation
2. 10 equiv D_2O — 49% yield, 70% *d*-incorporation
3. DMSO–d_6 — 74% yield, 22% *d*-incorporation
4. 4 equiv DCOOK + 10 equiv D_2O — 36% yield, 92% *d*-incorporation
5. 4 equiv DCOOK + 10 equiv D_2O + DMSO–d_6 — 37% yield, 95% *d*-incorporation



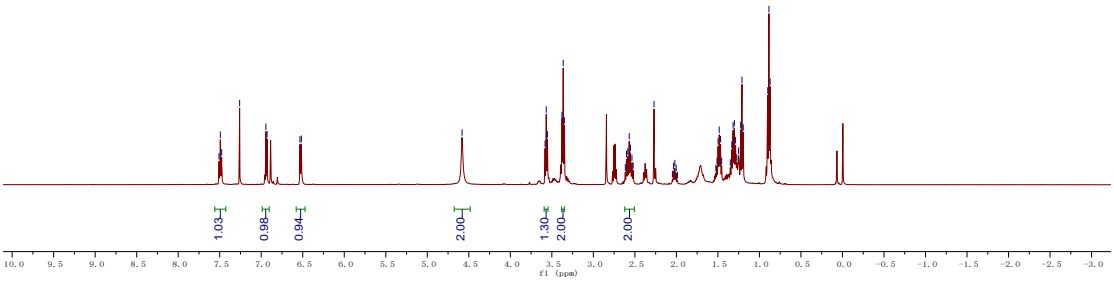
^{1}H NMR (500 MHz, $CDCl_3$): 7.5 (t, *J* = 7.9 Hz, 1H), 6.9 (t, *J* = 6.9 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 3.6 (t, *J* = 7.1 Hz, 2H), 3.4 (t, *J* = 6.6 Hz, 2H), 2.6 - 2.5 (m, 2H), 1.5 - 1.4 (m, 2H), 1.3 - 1.2 (m, 2H), 0.9 (t, *J* = 7.2 Hz, 3H).

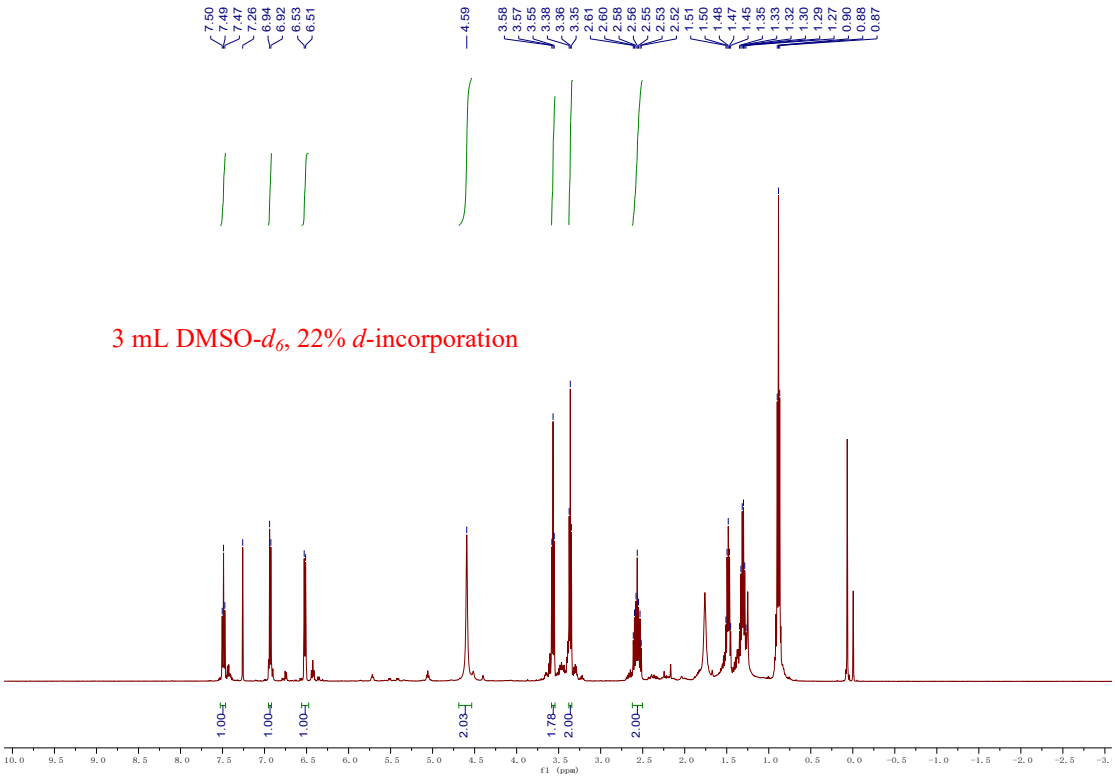




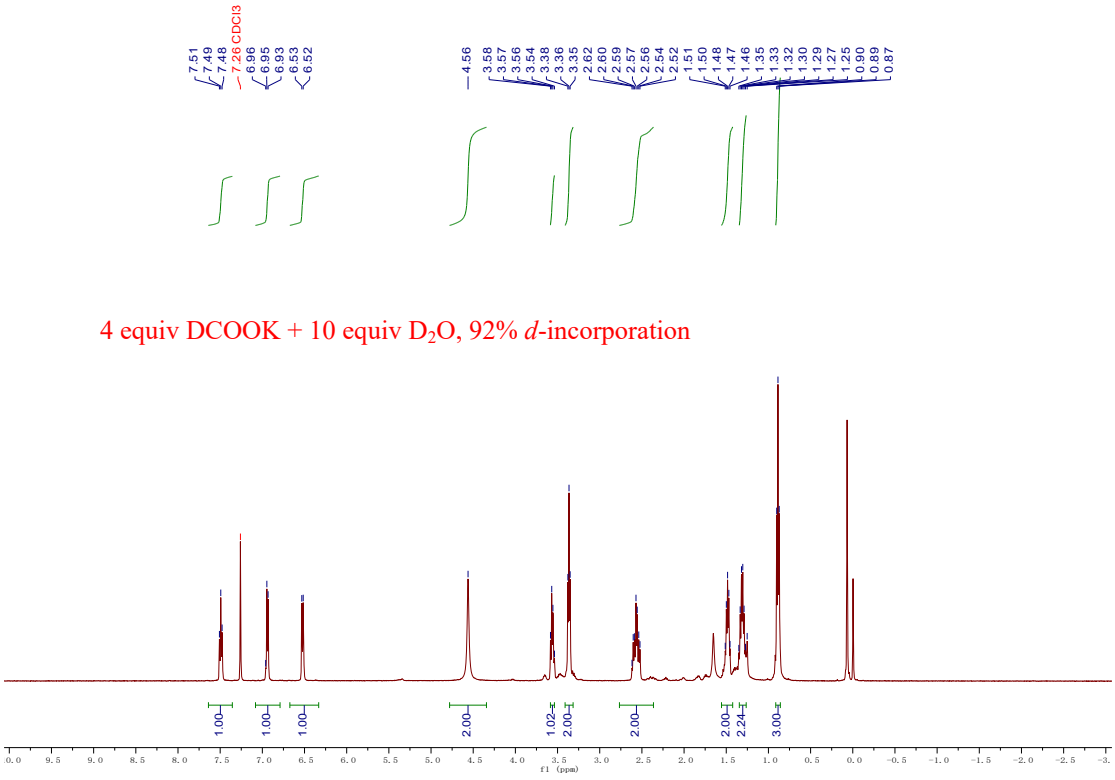
4 equiv DCOOK, 42% *d*-incorporation

10 equiv D_2O, 70% *d*-incorporation





3 mL DMSO-d_6, 22% *d*-incorporation



4 equiv DCOOK + 10 equiv D_2O, 92% *d*-incorporation

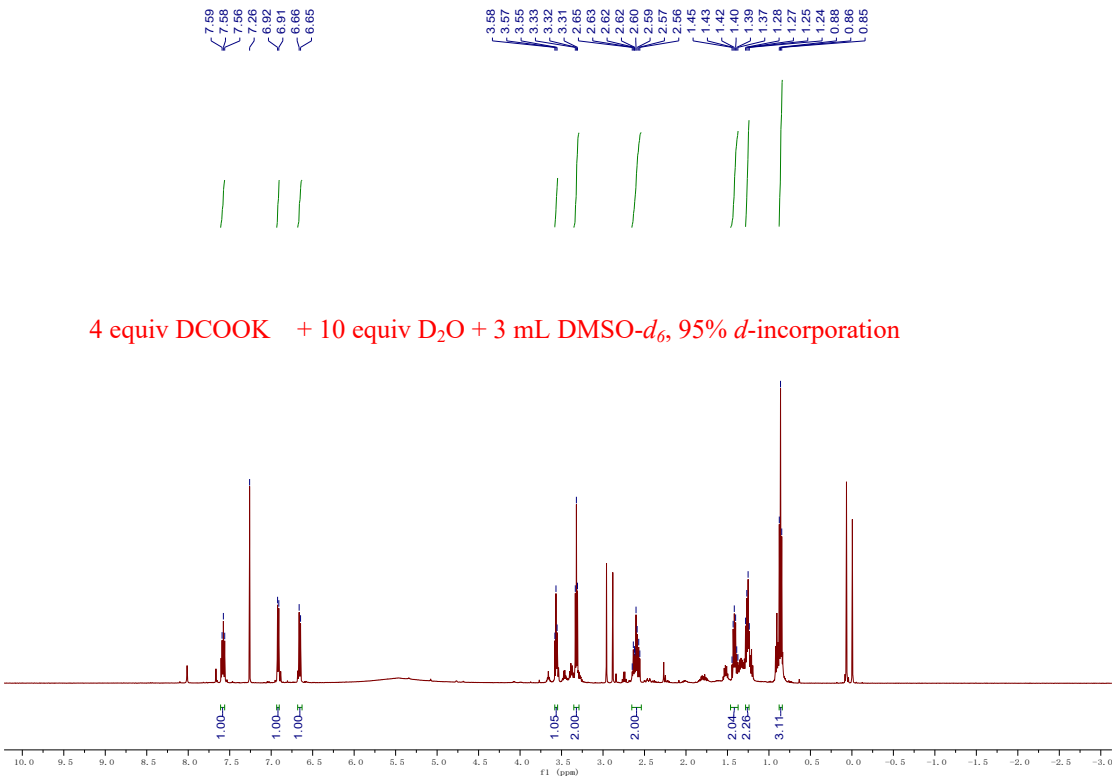
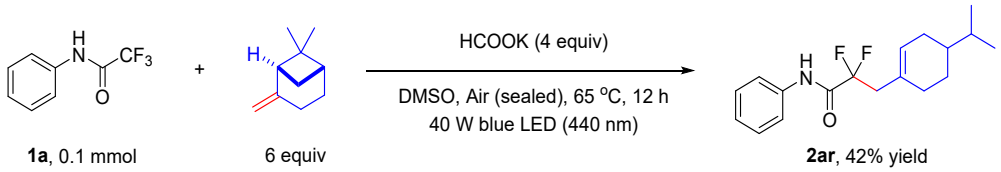


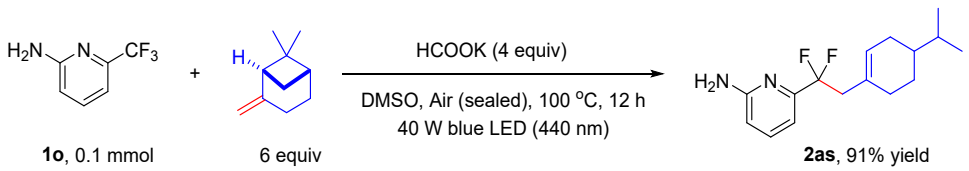
Figure S3. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of *d*-incorporation product **2ap**.

5.2 Radical clock experiment [2]



1a, 0.1 mmol 6 equiv **2ar**, 42% yield

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 2,2,2-trifluoro-*N*-phenylacetamide (0.1 mmol), HCOOK (0.4 mmol), beta-pinene (0.6 mmol) and anhydrous DMSO (3 mL). Then the reaction was placed under a blue LED (wavelength 440 nm, 40 W) and irradiated for 12 hrs at 65 °C. The mixture was quenched with H_2O. Then extracted with EtOAc three times, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography isolation on silica gel (eluent: PE/EA = 6/1 v/v) to give the pure desired ring-open product as white solid (**2ar**, 42% yield, 12.9 mg).

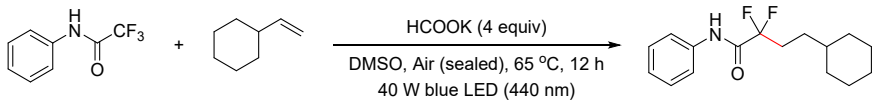


1o, 0.1 mmol 6 equiv **2as**, 91% yield

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 2-amino-6-(trifluoromethyl)pyridine (0.1 mmol), HCOOK (0.4 mmol), beta-pinene (0.6 mmol) and anhydrous DMSO (3 mL). Then the reaction was placed under a blue LED (wavelength 440 nm, 40 W) and irradiated for 12 hrs at 100 °C. The mixture was quenched with H_2O. Then extracted with EtOAc three times, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography isolation on silica gel (eluent: PE/EA = 6/1

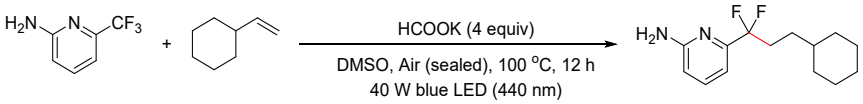
v/v) to give the pure desired ring-open product as white solid (**2as**, 91% yield, 25.6 mg).

5.3 Radical-trapping experiment with TEMPO



1a, 0.1 mmol 6 equiv **2a**, N.D.

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 2,2,2-trifluoro-*N*-phenylacetamide (0.1 mmol), HCOOK (0.4 mmol), TEMPO (0.3 mmol), vinylcyclohexane (0.6 mmol, 6 equiv) and anhydrous DMSO (3 mL). Then the reaction was placed under a blue LED (wavelength 440 nm, 40 W) and irradiated for 12 hrs at 65 °C. The mixture was quenched with H_2O. Then extracted with EtOAc three times, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The corresponding product **2a** was not detected by ^1H NMR spectroscopy.



1o, 0.1 mmol 6 equiv **2o**, N.D.

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 2-amino-6-(trifluoromethyl)pyridine (0.1 mmol), HCOOK (0.4 mmol), TEMPO (0.3 mmol), vinylcyclohexane (0.6 mmol) and anhydrous DMSO (3 mL). Then the reaction was placed under a blue LED (wavelength 440 nm, 40 W) and irradiated for 12 hrs at 100 °C. The mixture was quenched with H_2O. Then extracted with EtOAc three times, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The corresponding product **2o** was not detected by ^1H NMR spectroscopy.

5.4 UV-vis spectrum

Sample 01: HCOOK in DMSO, Ar (sealed)

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 0.4 mmol HCOOK and 3 mL anhydrous DMSO. The Schlenk tube was sealed and degassed via vacuum evacuation and subsequent backfilled with argon for three times. Then the reaction was placed in the dark for 3 hrs at 65 °C.

Sample 02: HCOOK in DMSO, Air (sealed)

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 0.4 mmol HCOOK and 3 mL anhydrous DMSO. The Schlenk tube was sealed and the reaction was placed in the dark for 3 hrs at 65 °C.

Sample 03: HCOOK in DMSO, Air (sealed)

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 0.4 mmol HCOOK and 3 mL anhydrous DMSO. The Schlenk tube was sealed and the reaction was irradiated with a blue LED (wavelength 440 nm, 40 W) for 3 hrs at 65 °C.

Sample 04: HCOOK in DMSO, Air (sealed)

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 0.4 mmol HCOOK and 3 mL anhydrous DMSO. The Schlenk tube was sealed and the reaction was irradiated with a LED (wavelength 427 nm, 40 W) for 3 hrs at 65 °C.

Sample 05: HCOOK in DMSO, Air (sealed)

An oven-dried Schlenk tube (10 mL) with a magnetic stir bar was added the 0.4 mmol HCOOK and 3 mL anhydrous DMSO. The Schlenk tube was sealed and the reaction was placed in the dark for 3 hrs at 65

°C. After reaction, the mixture was irradiated with a blue LED (wavelength 440 nm, 40 W) for 30 minutes at 65 °C.

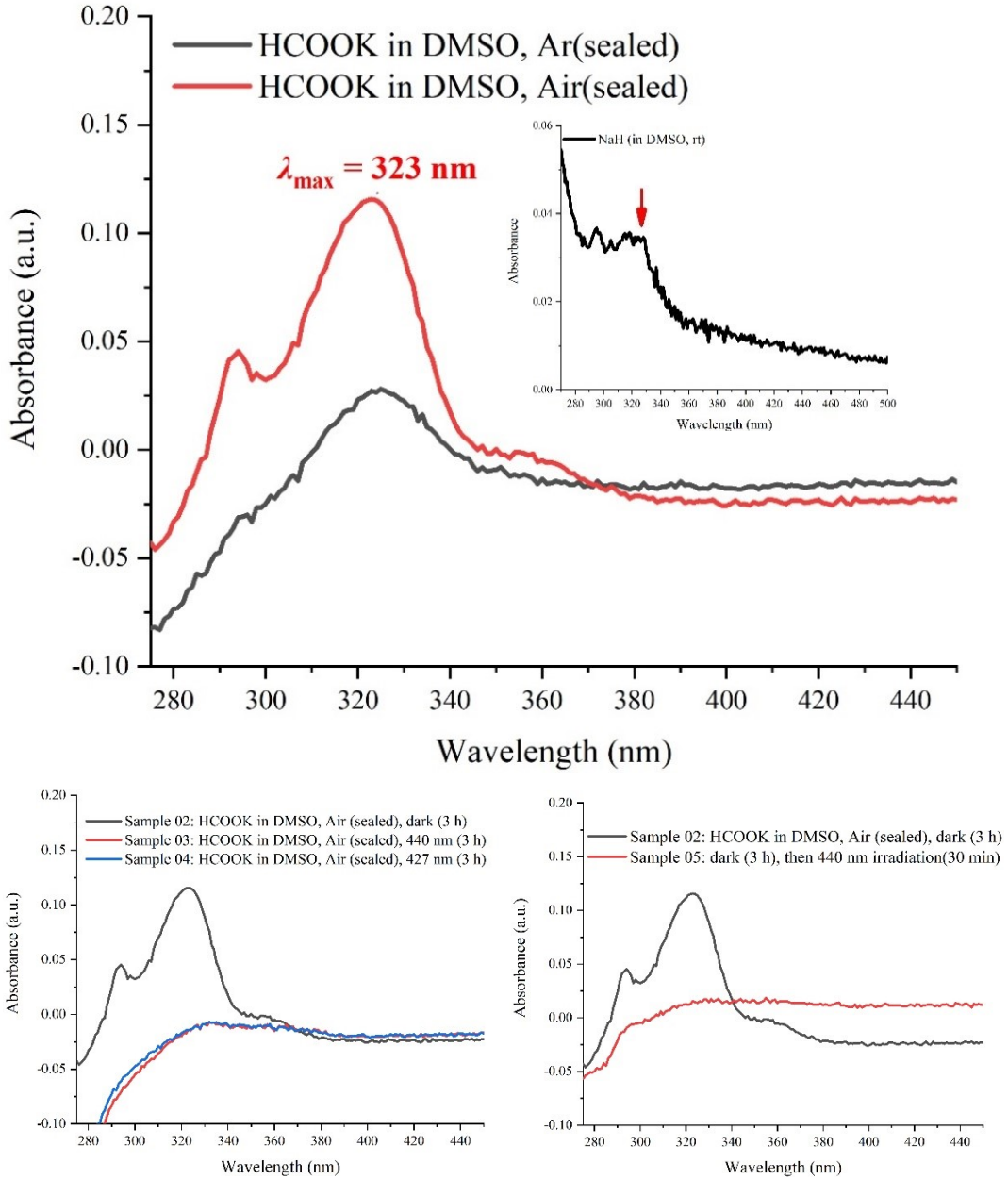


Figure S4. UV-vis spectrum of HCOOK in DMSO

5.5 Cyclic voltammetry studies

Sample 5 mM and tetrabutylammonium tetrafluoroborate 0.1 M in DMSO were used for tests. Measurements were run using glassy carbon working electrode, platinum wire counter electrode, and Hg-Hg_2Cl_2 reference electrode in a scan rate of 0.1 V/s.

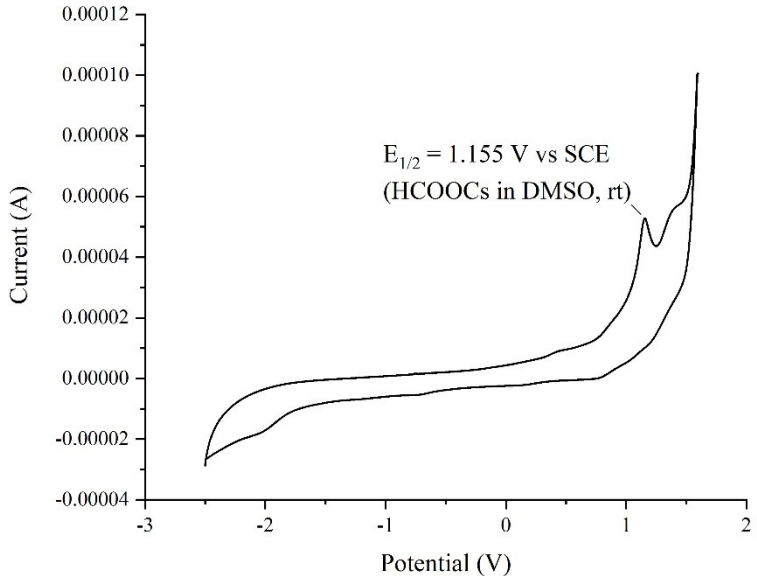
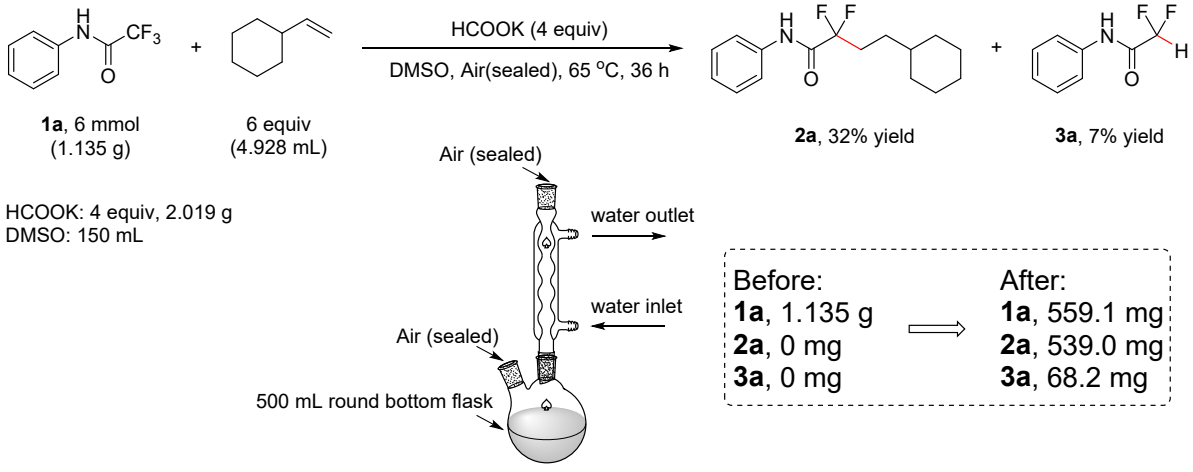


Figure S5. Cyclic voltammogram of HCOOCs in DMSO (room temperature). Scanned from -2.5 V to -2.5 V at 0.1 V/s.

6. The application of the reaction

Gram scale reaction: An oven-dried two-necked round bottom flask (500 mL) with a magnetic stir bar was added the **1a** (6 mmol, 1.135 g), HCOOK (2.4 mmol, 2.019 g), vinylcyclohexane (36 mmol, 4.928 mL) and anhydrous DMSO (150 mL). Then the reaction was placed under a water bath for 36 hrs at 65 ^{o}C. The mixture was quenched with H_2O. Then extracted with EtOAc three times, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography isolation on silica gel (eluent: PE/EA = 6/1 v/v) to give the pure desired product (**2a**, 539.0 mg, 32% yield, white solid; **3a**, 68.2 mg, 7% yield, light-yellow oil).



7. Other substrates

The limitations of this work were shown as follows:

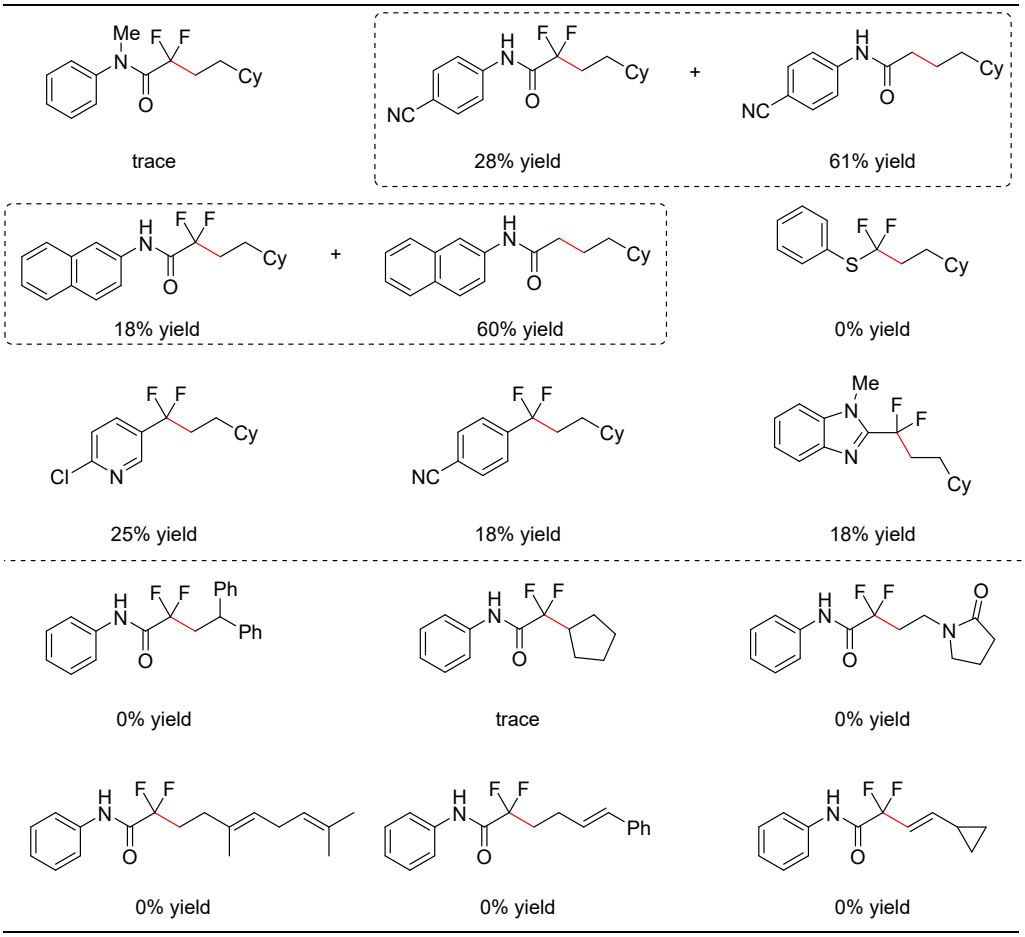
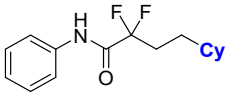


Figure S6. A summary of substrates that do not work in general condition.

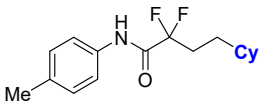
8. Characterization data



4-cyclohexyl-2,2-difluoro-*N*-phenylbutanamide (**2a**) [3]

20.3 mg, 72% yield, white solid, Rf (PE/ EA 6/1 v/v): 0.73

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 (d, *J* = 7.9 Hz, 2H), 7.4 (t, *J* = 7.7 Hz, 2H), 7.2 (t, *J* = 7.5 Hz, 1H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 (q, *J* = 7.3 Hz, 2H), 1.3 – 1.1 (m, 4H), 0.9 (q, *J* = 11.2, 10.4 Hz, 2H).



4-cyclohexyl-2,2-difluoro-*N*-(*p*-tolyl)butanamide (**2b**)

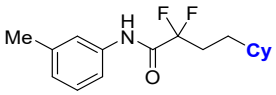
19.8 mg, 67% yield, white solid, 84.8 – 90.3 °C (m.p.), Rf (PE/ EA 6/1 v/v): 0.75

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (s, 1H), 7.5 (d, *J* = 8.0 Hz, 2H), 7.2 (d, *J* = 8.0 Hz, 2H), 2.3 (s, 3H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 (q, *J* = 7.0 Hz, 2H), 1.3 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 (t, *J* = 29.1 Hz), 135.4, 133.7, 129.8, 120.4, 118.9 (m), 37.4, 33.1, 31.6 (t, *J* = 23.0 Hz), 28.9 (t, *J* = 4.0 Hz), 26.6, 26.3, 21.0.

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.7 (t, *J* = 17.3 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{24}F_2NO]^+$: 296.1826, found: 296.1824.



4-cyclohexyl-2,2-difluoro-*N*-(*m*-tolyl)butanamide (**2c**)

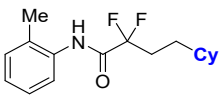
17.9 mg, 61% yield, light-yellow solid, 68.4 – 71.3 °C (m.p.), Rf (PE/ EA 6/1 v/v): 0.75

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.5 (s, 1H), 7.4 (d, *J* = 8.2 Hz, 1H), 7.3 – 7.2 (m, 1H), 7.0 (d, *J* = 7.6 Hz, 1H), 2.4 (s, 3H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 – 1.3 (m, 2H), 1.3 – 1.1 (m, 4H), 1.1 - 0.9 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 – 162.1 (m), 139.4, 136.1, 129.1, 126.4, 120.9, 120.7-116.8 (m), 117.4, 37.4, 33.1, 31.6 (t, *J* = 23.2 Hz), 28.9, 26.6, 26.3, 21.6.

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.5 - -105.6 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{24}F_2NO]^+$: 296.1826, found: 296.1824.



4-cyclohexyl-2,2-difluoro-*N*-(*o*-tolyl)butanamide (**2d**)

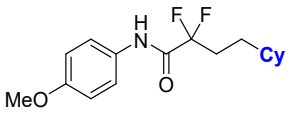
20.9 mg, 71% yield, light-yellow oil, Rf (PE/ EA 6/1 v/v): 0.73

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 – 7.8 (m, 2H), 7.3 – 7.2 (m, 2H), 7.1 (t, *J* = 7.9 Hz, 1H), 2.3 (s, 3H), 2.3 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 – 1.4 (m, 2H), 1.3 – 1.1 (m, 4H), 1.0 – 0.9 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4 (t, *J* = 28.7 Hz), 134.0, 130.8, 129.4, 127.1, 126.3, 123.0, 120.1 (t, *J* = 253.2 Hz), 37.4, 33.1, 31.6 (t, *J* = 23.1 Hz), 29.0 (t, *J* = 3.7 Hz), 26.6, 26.3, 17.6.

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.4 - -105.5 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{24}F_2NO]^+$: 296.1826, found: 296.1827.



4-cyclohexyl-2,2-difluoro-*N*-(4-methoxyphenyl)butanamide (**2e**)

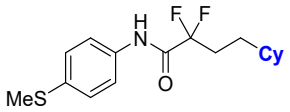
16.5 mg, 53% yield, light-yellow solid, 109.3 – 112.9 °C (m.p.), Rf (PE/ EA 6/1 v/v): 0.60

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (s, 1H), 7.5 (d, *J* = 8.9 Hz, 2H), 6.9 (d, *J* = 9.0 Hz, 2H), 3.8 (s, 3H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 – 1.3 (m, 2H), 1.2 – 1.1 (m, 4H), 0.9 – 0.8 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 (t, *J* = 28.4 Hz), 157.4, 129.2, 122.1, 119.9 (t, *J* = 253.3 Hz), 114.5, 55.6, 37.4, 33.1, 31.6 (t, *J* = 23.0 Hz), 28.9 (t, *J* = 3.6 Hz), 26.6, 26.3.

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.6 - -105.7 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{24}F_2NO_2]^+$: 312.1775, found: 312.1772.



4-cyclohexyl-2,2-difluoro-*N*-(4-(methylthio)phenyl)butanamide (**2f**)

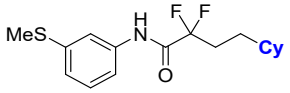
23.6 mg, 72% yield, white solid, 87.9 – 93.7 °C (m.p.), Rf (PE/ EA 6/1 v/v): 0.67

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (s, 1H), 7.5 (d, *J* = 8.7 Hz, 2H), 7.3 (d, *J* = 8.7 Hz, 2H), 2.5 (s, 3H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 – 1.3 (m, 2H), 1.2 – 1.1 (m, 4H), 0.9 – 0.8 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 – 162.0 (m), 135.6, 133.6, 127.8, 120.9, 120.9 – 116.8 (m), 37.4, 33.1, 31.6 (t, *J* = 23.0 Hz), 28.9 (t, *J* = 3.7 Hz), 26.6, 26.3, 16.5.

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.6 (t, *J* = 17.4 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{24}F_2NOS]^+$: 328.1547, found: 328.1548.



4-cyclohexyl-2,2-difluoro-*N*-(3-(methylthio)phenyl)butanamide (**2g**)

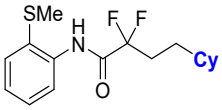
22.2 mg, 68% yield, white solid, 65.3 – 69.6 °C (m.p.), Rf (PE/ EA 6/1 v/v): 0.66

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (s, 1H), 7.6 (s, 1H), 7.3 – 7.2 (m, 2H), 7.1 – 7.0 (m, 1H), 2.5 (s, 3H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 – 1.3 (m, 2H), 1.3 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4 (t, *J* = 29.3 Hz), 140.3, 136.8, 129.6, 123.6, 119.8 (t, *J* = 253.5 Hz), 117.8, 116.7, 37.4, 33.1, 31.5 (t, *J* = 23.0 Hz), 28.9 (t, *J* = 3.6 Hz), 26.6, 26.3, 15.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.5 (t, *J* = 17.4 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{24}F_2NOS]^+$: 328.1547, found: 328.1543.



4-cyclohexyl-2,2-difluoro-*N*-(2-(methylthio)phenyl)butanamide (**2h**)

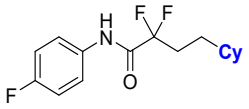
19.0 mg, 58% yield, white solid, Rf (PE/ EA 6/1 v/v): 0.72

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.2 (s, 1H), 8.3 – 8.2 (m, 1H), 7.5 – 7.4 (m, 1H), 7.4 – 7.3 (m, 1H), 7.2 – 7.1 (m, 1H), 2.4 (s, 3H), 2.3 – 2.1 (m, 2H), 1.8 – 1.6 (m, 5H), 1.4 – 1.4 (m, 2H), 1.3 – 1.1 (m, 4H), 0.9 – 0.9 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (t, *J* = 28.3 Hz), 137.6 – 136.4 (m), 133.4, 129.2, 126.6, 125.7, 120.8, 117.9 (t, *J* = 253.6 Hz), 37.4, 33.1, 31.7 (t, *J* = 23.1 Hz), 29.0 (t, *J* = 3.7 Hz), 26.6, 26.3, 19.1.

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.8 (t, *J* = 17.2 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{24}F_2NOS]^+$: 328.1547, found: 328.1547.



4-cyclohexyl-2,2-difluoro-*N*-(4-fluorophenyl)butanamide (**2i**)

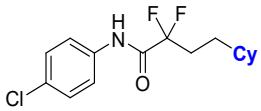
18.7 mg, 63% yield, white solid, 63.0 – 67.1 °C (m.p.), Rf (PE/ EA 6/1 v/v): 0.72

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 – 7.5 (m, 2H), 7.1 (t, *J* = 8.4 Hz, 2H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 – 1.3 (m, 2H), 1.3 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4 (t, *J* = 29.0 Hz), 160.2 (d, *J* = 245.3 Hz), 132.2, 128.7 (d, *J* = 171.2 Hz), 126.1, 122.2 (d, *J* = 7.9 Hz), 118.8 (t, *J* = 253.3 Hz), 116.1 (d, *J* = 22.7 Hz), 37.4, 33.1, 31.5 (t, *J* = 23.0 Hz), 28.9 (t, *J* = 3.8 Hz), 26.6, 26.3.

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.6 (t, *J* = 17.4 Hz), -116.0 – -116.1 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{16}H_{21}F_3NO]^+$: 300.1575, found: 300.1576.



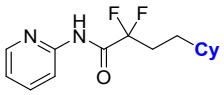
***N*-(4-chlorophenyl)-4-cyclohexyl-2,2-difluorobutanamide** (**2j**)

18.6 mg, 59% yield, white solid, 69.6 – 73.6 °C (m.p.), Rf (PE/ EA 6/1 v/v): 0.72

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.5 (d, *J* = 8.4 Hz, 2H), 7.3 (d, *J* = 8.4 Hz, 2H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 – 1.3 (m, 2H), 1.3 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.5 - -105.6 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{16}H_{21}ClF_2NO]^+$: 316.1280, found: 316.1276.



4-cyclohexyl-2,2-difluoro-*N*-(pyridin-2-yl)butanamide (**2k**)

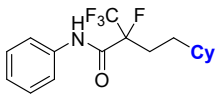
15.9 mg, 56% yield, white solid, Rf (PE/ EA 4/1 v/v): 0.44

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.7 (s, 1H), 8.4 – 8.3 (m, 1H), 8.2 (d, *J* = 8.4 Hz, 1H), 7.8 – 7.7 (m, 1H), 7.2 - 7.1 (m, 1H), 2.2 – 2.1 (m, 2H), 1.7 – 1.6 (m, 5H), 1.4 – 1.4 (m, 2H), 1.3 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1 – 162.6 (m), 150.0, 148.4, 138.8, 121.1, 120.5 – 116.5 (m), 114.4, 37.4, 33.1, 31.6 (t, *J* = 23.0 Hz), 28.9, 26.6, 26.3.

^{19}F NMR (470 MHz, $CDCl_3$) δ -106.0 (t, *J* = 17.0 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{15}H_{21}F_2N_2O]^+$: 283.1622, found: 283.1623.

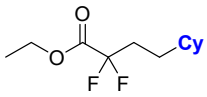


4-cyclohexyl-2-fluoro-*N*-phenyl-2-(trifluoromethyl)butanamide (**2l**) [4]

14.6 mg, 44% yield, white solid, Rf (PE/ EA 4/1 v/v): 0.63

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 (d, *J* = 7.9 Hz, 2H), 7.4 (t, *J* = 7.9 Hz, 2H), 7.2 (t, *J* = 7.7 Hz, 1H), 2.4 – 2.2 (m, 2H), 2.1 – 2.0 (m, 1H), 1.7 – 1.6 (m, 5H), 1.4 – 1.3 (m, 1H), 1.2 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -78.2 (d, *J* = 5.2 Hz), -176.7 (d, *J* = 38.5 Hz).



ethyl 4-cyclohexyl-2,2-difluorobutanoate (**2m**)

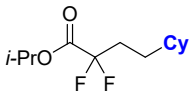
15.2 mg, 65% yield, Rf (PE/ EA 4/1 v/v): 0.72

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.3 (q, *J* = 7.2 Hz, 2H), 2.1 – 2.0 (m, 2H), 1.7 – 1.5 (m, 5H), 1.4 - 1.3 (m, 4H), 1.3 - 1.2 (m, 4H), 0.9 – 0.8 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 120.2 – 114.2 (m), 62.8, 37.3, 33.1, 32.2 (t, *J* = 23.1 Hz), 28.8 (t, *J* = 3.7 Hz), 26.6, 26.3, 14.1.

^{19}F NMR (470 MHz, DMSO) δ -106.7 (t, *J* = 16.7 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{12}H_{21}F_2O_2]^+$: 235.1510, found: 235.1504.



isopropyl 4-cyclohexyl-2,2-difluorobutanoate (**2n**)

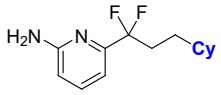
13.5 mg, 54% yield, Rf (PE/ EA 4/1 v/v): 0.75

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.2 - 5.1 (m, 1H), 2.1 – 2.0 (m, 2H), 1.7 - 1.6 (m, 5H), 1.3 (d, *J* = 6.3 Hz, 6H), 1.3 – 1.1 (m, 6H), 0.9 – 0.8 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5 – 163.7 (m), 116.8 (t, *J* = 249.5 Hz), 71.0, 37.3, 33.1, 32.2 (t, *J* = 23.2 Hz), 28.9 (t, *J* = 3.8 Hz), 26.6, 26.3, 21.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ -106.2 (t, *J* = 16.7 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{13}H_{23}F_2O_2]^+$: 249.1666, found: 249.1666.

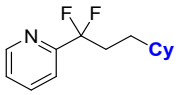


6-(3-cyclohexyl-1,1-difluoropropyl)pyridin-2-amine (**2o**) [3]

20.1 mg, 79% yield, white solid, Rf (PE/ EA 4/1 v/v): 0.33

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.8 Hz, 1H), 6.9 (d, *J* = 7.4 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 2.3 – 2.2 (m, 2H), 1.7 – 1.6 (m, 5H), 1.3 – 1.2 (m, 2H), 1.2 – 1.0 (m, 4H), 0.9 – 0.8 (m, 2H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -100.5 (t, *J* = 16.8 Hz).



2-(3-cyclohexyl-1,1-difluoropropyl)pyridine (**2p**)

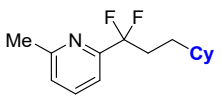
12.2 mg, 51% yield, brown oil, Rf (PE/ EA 4/1 v/v): 0.78

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.7 (d, *J* = 4.3 Hz, 1H), 7.8 (t, *J* = 7.7 Hz, 1H), 7.6 (d, *J* = 7.9 Hz, 1H), 7.4 – 7.3 (m, 1H), 2.4 – 2.2 (m, 2H), 1.7 – 1.6 (m, 5H), 1.3 – 1.3 (m, 2H), 1.2 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3 (t, *J* = 29.4 Hz), 149.5, 137.0, 124.6, 122.2 (t, *J* = 241.8 Hz), 120.0 (t, *J* = 4.6 Hz), 37.5, 34.1 (t, *J* = 25.2 Hz), 33.2, 29.5 (t, *J* = 3.8 Hz), 26.7, 26.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -99.4 (t, *J* = 16.9 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{14}H_{20}F_2N]^+$: 240.1564, found: 240.1565.



2-(3-cyclohexyl-1,1-difluoropropyl)-6-methylpyridine (**2q**)

13.8 mg, 55% yield, orange oil, Rf (PE/ EA 4/1 v/v): 0.80

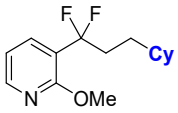
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.6 (t, *J* = 7.7 Hz, 1H), 7.4 (d, *J* = 7.8 Hz, 1H), 7.2 (d, *J* = 7.7 Hz, 1H), 2.6 (s,

3H), 2.4 – 2.2 (m, 2H), 1.7 – 1.6 (m, 5H), 1.3 – 1.2 (m, 2H), 1.2 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 154.9 – 154.4 (m), 137.1, 124.2, 122.3, 116.9 (t, *J* = 4.9 Hz), 37.5, 34.2 (t, *J* = 25.4 Hz), 33.2, 29.5 (t, *J* = 3.7 Hz), 26.7, 26.4, 24.6.

^{19}F NMR (470 MHz, $CDCl_3$) δ -99.7 (t, *J* = 16.9 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{15}H_{22}F_2N]^+$: 254.1720, found: 254.1719.



3-(3-cyclohexyl-1,1-difluoropropyl)-2-methoxypyridine (**2r**)

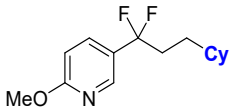
15.2 mg, 57% yield, light-yellow oil, Rf (PE/ EA 4/1 v/v): 0.83

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.2 (d, *J* = 4.5 Hz, 1H), 7.8 (d, *J* = 7.2 Hz, 1H), 7.0 - 6.9 (m, 1H), 4.0 (s, 3H), 2.4 – 2.2 (m, 2H), 1.7 – 1.6 (m, 5H), 1.2 – 1.1 (m, 5H), 0.9 – 0.8 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6 (t, *J* = 4.1 Hz), 148.3, 136.0 (t, *J* = 8.2 Hz), 121.4 (t, *J* = 242.3 Hz), 119.7 (t, *J* = 27.7 Hz), 116.5, 53.8, 37.4, 34.0 (t, *J* = 25.8 Hz), 33.2, 30.1 (t, *J* = 3.7 Hz), 26.7, 26.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -96.0 (t, *J* = 16.9 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{15}H_{22}F_2NO]^+$: 270.1669, found: 270.1669.



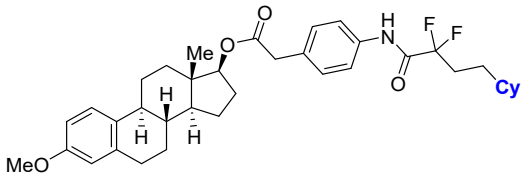
5-(3-cyclohexyl-1,1-difluoropropyl)-2-methoxypyridine (**2s**)

18.3 mg, 68% yield, yellow oil, Rf (PE/ EA 4/1 v/v): 0.85

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.3 (s, 1H), 7.7 - 7.6 (m, 1H), 6.8 (d, *J* = 8.7 Hz, 1H), 4.0 (s, 3H), 2.2 – 2.0 (m, 2H), 1.7 – 1.6 (m, 5H), 1.3 – 1.3 (m, 2H), 1.2 – 1.1 (m, 4H), 0.9 – 0.8 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 144.4 (t, *J* = 7.1 Hz), 135.9 (t, *J* = 5.6 Hz), 126.5 (t, *J* = 28.1 Hz), 123.0 (t, *J* = 241.4 Hz), 110.8, 53.8, 37.4, 36.6 (t, *J* = 27.3 Hz), 33.2, 29.9 (t, *J* = 3.8 Hz), 26.6, 26.3.

^{19}F NMR (470 MHz, $CDCl_3$) δ -93.9 (t, *J* = 16.0 Hz).



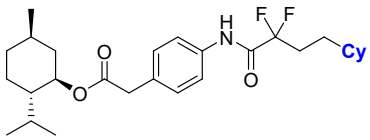
(8*R*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl 2-(4-(4-cyclohexyl-2,2-difluorobutanamido)phenyl)acetate (**2t**)

43.1 mg, 71% yield, white solid, Rf (PE/ EA 2/1 v/v): 0.65

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.5 (d, *J* = 8.5 Hz, 2H), 7.3 (d, *J* = 8.5 Hz, 2H), 7.2 (d, *J* = 8.6 Hz, 1H), 6.7 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.6 (d, *J* = 2.8 Hz, 1H), 4.7 (t, *J* = 8.4 Hz, 1H), 3.8 (s, 3H), 3.6 (s, 2H), 2.9 – 2.8 (m, 2H), 2.3 – 2.1 (m, 5H), 1.9 – 1.8 (m, 1H), 1.8 (dt, *J* = 12.5, 3.2 Hz, 1H), 1.7 – 1.7 (m, 4H), 1.6 (d, *J* = 14.0 Hz, 1H), 1.5 – 1.4 (m, 1H), 1.4 – 1.3 (m, 6H), 1.3 – 1.1 (m, 7H), 0.9 – 0.8 (m, 2H), 0.8 (s, 3H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.6 (t, *J* = 17.4 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{37}H_{48}F_2NO_4]^+$: 608.3551, found: 608.3547.



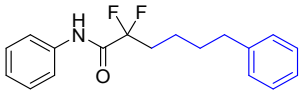
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(4-(4-cyclohexyl-2,2-difluorobutanamido)phenyl) acetate (**2u**)

36.2 mg, 76% yield, colorless solid, Rf (PE/ EA 6/1 v/v): 0.44

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (s, 1H), 7.5 (d, *J* = 8.5 Hz, 2H), 7.3 (d, *J* = 8.6 Hz, 2H), 4.7 (m, 1H), 3.6 (s, 2H), 2.2 – 2.1 (m, 2H), 1.9 – 1.8 (m, 1H), 1.8 – 1.6 (m, 8H), 1.5 (m, 1H), 1.4 – 1.3 (m, 3H), 1.3 – 1.1 (m, 6H), 1.1 – 1.0 (m, 1H), 1.0 – 0.9 (m, 2H), 0.9 (d, *J* = 6.5 Hz, 3H), 0.8 (d, *J* = 7.1 Hz, 3H), 0.7 (d, *J* = 7.0 Hz, 3H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.6 (t, *J* = 17.4 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{28}H_{42}F_2NO_3]^+$: 478.3133, found: 478.3127.

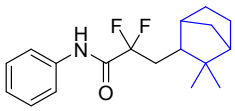


2,2-difluoro-*N*,6-diphenylhexanamide (**2v**) [3]

15.5 mg, 51% yield, white solid, Rf (PE/ EA 6/1 v/v): 0.57

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 (d, *J* = 7.9 Hz, 2H), 7.4 (t, *J* = 7.8 Hz, 2H), 7.3 (d, *J* = 6.9 Hz, 2H), 7.2 (t, *J* = 10.8 Hz, 4H), 2.7 (t, *J* = 7.8 Hz, 2H), 2.3 – 2.2 (m, 2H), 1.8 (p, *J* = 7.5 Hz, 2H), 1.7 - 1.6 (m, 2H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -105.5 (m).



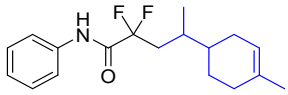
3-(3,3-dimethylbicyclo[2.2.1]heptan-2-yl)-2,2-difluoro-*N*-phenylpropanamide (**2w**)

14.5 mg, 47% yield, white solid, Rf (PE/ EA 6/1 v/v): 0.53

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 (d, *J* = 7.6 Hz, 2H), 7.4 (t, *J* = 8.0 Hz, 2H), 7.2 (t, *J* = 7.4 Hz, 1H), 2.2 – 2.1 (m, 3H), 1.8 (s, 1H), 1.7 – 1.6 (m, 2H), 1.4 – 1.3 (m, 5H), 1.2 – 1.1 (m, 1H), 1.0 (s, 3H), 0.8 (s, 3H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -103.3 – -105.3 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{18}H_{24}F_2NO]^+$: 308.1826, found: 308.1824.



2,2-difluoro-4-(4-methylcyclohex-3-en-1-yl)-*N*-phenylpentanamide (**2x**)

20.5 mg, 67% yield, light-yellow oil, Rf (PE/ EA 6/1 v/v): 0.48

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 (d, *J* = 7.5 Hz, 2H), 7.4 (t, *J* = 7.4 Hz, 2H), 7.2 (t, *J* = 7.1 Hz, 1H), 5.4 (s, 1H), 2.3 (q, *J* = 17.3 Hz, 1H), 2.0 – 1.9 (m, 4H), 1.8 – 1.7 (m, 2H), 1.7 – 1.6 (m, 1H), 1.6 (s, 3H), 1.3 – 1.2 (m, 1H), 1.0 (d, *J* = 6.5 Hz, 3H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -101.9 – -104.8 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{18}H_{24}F_2NO]^+$: 308.1826, found: 308.1821.

2,2-difluoro-3-methyl-*N*-phenylnonanamide (**2y**)

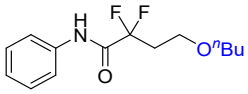
15.8 mg, 56% yield, colorless oil, Rf (PE/ EA 6/1 v/v): 0.56

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 (d, *J* = 8.0 Hz, 2H), 7.4 (t, *J* = 7.8 Hz, 2H), 7.2 (t, *J* = 7.7 Hz,

1H), 2.5 – 2.2 (m, 1H), 1.7 - 1.6 (m, 1H), 1.6 (s, 2H), 1.5 - 1.4 (m, 2H), 1.3 – 1.2 (m, 6H), 1.1 (d, *J* = 7.0 Hz, 1H), 1.0 (t, *J* = 7.5 Hz, 1H), 0.9 (t, *J* = 7.5 Hz, 3H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -109.8 - -112.9 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{16}H_{24}F_2NO]^+$: 284.1826, found: 284.1826.



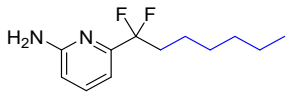
4-butoxy-2,2-difluoro-*N*-phenylbutanamide (**2z**) [2]

15.2 mg, 56% yield, yellow oil, Rf (PE/ toluene 1/2 v/v): 0.26

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 (d, *J* = 7.8 Hz, 2H), 7.4 (t, *J* = 8.0 Hz, 2H), 7.2 (t, *J* = 7.4 Hz, 1H), 3.6 (t, *J* = 6.3 Hz, 2H), 3.4 (t, *J* = 6.6 Hz, 2H), 2.6 – 2.4 (m, 2H), 1.5 - 1.4 (m, 2H), 1.3 – 1.2 (m, 2H), 0.8 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 – 161.0 (m), 136.4, 129.3, 125.5, 120.2, 119.5 - 115.5 (m), 71.2, 64.0 (t, *J* = 6.1 Hz), 34.4 (t, *J* = 23.3 Hz), 31.7, 19.4, 13.9.

^{19}F NMR (470 MHz, $CDCl_3$) δ -104.3 (m).



6-(1,1-difluoroheptyl)pyridin-2-amine (**2aa**)

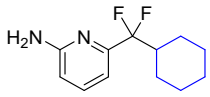
15.9 mg, 70% yield, yellow oil, Rf (PE/ EA 4/1 v/v): 0.52

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.8 Hz, 1H), 6.9 (d, *J* = 7.4 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 2.3 – 2.1 (m, 2H), 1.4 – 1.3 (m, 2H), 1.3 – 1.2 (m, 6H), 0.9 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 153.6 (t, *J* = 29.7 Hz), 138.5, 121.9 (t, *J* = 242.2 Hz), 109.9 (t, *J* = 5.2 Hz), 109.8, 36.7 (t, *J* = 25.5 Hz), 31.7, 29.1, 22.6, 22.2 (t, *J* = 4.0 Hz), 14.2.

^{19}F NMR (470 MHz, $CDCl_3$) δ -100.3 (t, *J* = 16.9 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{12}H_{19}F_2N_2]^+$: 229.1516, found: 229.1516.



6-(cyclohexyldifluoromethyl)pyridin-2-amine (**2ab**)

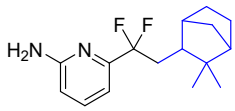
6.4 mg, 28% yield, white solid, Rf (PE/ EA 4/1 v/v): 0.31

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.8 Hz, 1H), 6.9 (d, *J* = 7.4 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 2.4 – 2.2 (m, 1H), 1.8 – 1.6 (m, 5H), 1.3 – 1.1 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 153.3, 138.2, 122.4, 110.7 (t, *J* = 5.6 Hz), 109.6, 43.5 (t, *J* = 24.2 Hz), 26.2, 25.8, 25.5 (t, *J* = 3.9 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ -109.2 (d, *J* = 14.9 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{12}H_{17}F_2N_2]^+$: 227.1360, found: 227.1353.



6-(2-(3,3-dimethylbicyclo[2.2.1]heptan-2-yl)-1,1-difluoroethyl)pyridin-2-amine (**2ac**)

14.1 mg, 51% yield, brown oil, Rf (PE/ EA 6/1 v/v): 0.40

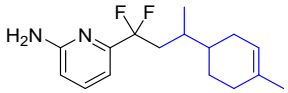
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.8 Hz, 1H), 6.9 (d, *J* = 7.4 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 2.3 - 2.2 (m, 2H), 2.1 (s, 1H), 1.7 (s, 1H), 1.6 (s, 1H), 1.6 – 1.5 (m, 2H), 1.4 – 1.3 (m, 1H), 1.3 – 1.2

(m, 2H), 1.1 (d, *J* = 9.6 Hz, 1H), 0.9 (s, 3H), 0.8 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 154.0 (t, *J* = 28.4 Hz), 138.5, 122.4 (t, *J* = 242.3 Hz), 109.8 (t, *J* = 5.3 Hz), 109.7, 48.8, 44.3, 42.3, 37.4, 37.2, 33.3 (t, *J* = 24.9 Hz), 31.9, 24.8, 22.3, 20.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -98.1 – -99.7 (m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{16}H_{23}F_2N_2]^+$: 281.1829, found: 281.1823.



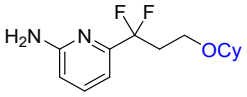
6-(1,1-difluoro-3-(4-methylcyclohex-3-en-1-yl)butyl)pyridin-2-amine (**2ad**)

12.5 mg, 45% yield, colorless oil, Rf (PE/ EA 4/1 v/v): 0.33

^{1}H NMR (500 MHz, $CDCl_3$) δ 1H NMR (500 MHz, CDCl3) δ 7.5 (t, J = 7.8 Hz, 1H), 6.9 (d, J = 7.4 Hz, 1H), 6.5 (d, J = 8.2 Hz, 1H), 5.3 (s, 1H), 4.6 (s, 2H), 2.4 – 2.3 (m, 1H), 2.0 – 1.8 (m, 4H), 1.7 – 1.6 (m, 3H), 1.6 (s, 3H), 1.5 - 1.4 (m, 1H), 1.3 – 1.2 (m, 1H), 0.9 (d, J = 6.8 Hz, 3H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -95.7 – -96.7 (m), -100.4 – -100.6(m).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{16}H_{23}F_2N_2]^+$: 281.1829, found: 281.1827.

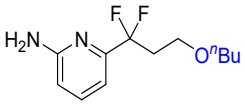


6-(3-(cyclohexyloxy)-1-fluoropropyl)pyridin-2-amine (2ae)

16.0 mg, 59% yield, light-yellow oil, Rf (PE/ EA 4/1 v/v): 0.15

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.8 Hz, 1H), 6.9 (d, *J* = 7.4 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 3.6 (t, *J* = 7.2 Hz, 2H), 3.2 – 3.1 (m, 1H), 2.6 – 2.5 (m, 2H), 1.8 – 1.7 (m, 2H), 1.7 – 1.6 (m, 3H), 1.5 – 1.4 (m, 1H), 1.2 – 1.1 (m, 4H).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{14}H_{21}F_2N_2O]^+$: 271.1622, found: 271.1623.

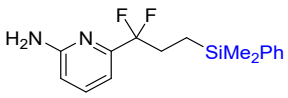


6-(3-butoxy-1,1-difluoropropyl)pyridin-2-amine (**2af**)[5]

15.3 mg, 63% yield, light-yellow oil, Rf (PE/ EA 4/1 v/v): 0.15

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.9 Hz, 1H), 6.9 (t, *J* = 6.9 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 3.6 (t, *J* = 7.1 Hz, 2H), 3.4 (t, *J* = 6.6 Hz, 3H), 2.6 – 2.5 (m, 2H), 1.5 – 1.4 (m, 2H), 1.3 – 1.2 (m, 2H), 0.9 (t, *J* = 7.2 Hz, 3H).

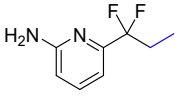
HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{12}H_{19}F_2N_2O]^+$: 245.1465, found: 245.1468.



6-(3-(dimethyl(phenyl)silyl)-1,1-difluoropropyl)pyridin-2-amine (**2ag**) [3]

27.7 mg, 91% yield, colorless oil, Rf (PE/ EA 6/1 v/v): 0.62

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 – 7.4 (m, 2H), 7.4 – 7.3 (m, 4H), 6.9 – 6.8 (m, 1H), 6.5 – 6.4 (m, 1H), 4.7 (s, 2H), 2.2 – 2.1 (m, 2H), 0.9 – 0.8 (m, 2H), 0.3 (s, 6H).



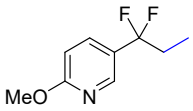
6-(1,1-difluoropropyl)pyridin-2-amine (2ah)[6]

15.2 mg, 89% yield, colorless oil, Rf (PE/ toluene 1/2 v/v): 0.28

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.8 Hz, 1H), 6.9 (d, *J* = 7.4 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 2.3 – 2.1 (m, 2H), 1.0 (t, *J* = 7.5 Hz, 3H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -102.3 (t, *J* = 16.6 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_8H_{11}F_2N_2]^+$: 173.0890, found: 173.0890.



5-(1,1-difluoropropyl)-2-methoxypyridine (2ai)

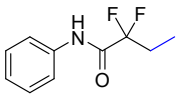
10.3 mg, 55% yield, colorless oil, Rf (PE/ toluene 1/2 v/v): 0.43

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.3 (s, 1H), 7.7 - 7.6 (m, 1H), 6.8 (d, *J* = 8.7 Hz, 1H), 4.0 (s, 3H), 2.2 – 2.1 (m, 2H), 1.0 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 144.4 (t, *J* = 7.0 Hz), 135.9 (t, *J* = 5.5 Hz), 126.2 (t, *J* = 27.6 Hz), 125.0 – 120.9 (m), 110.8, 53.8, 32.3 (t, *J* = 28.4 Hz), 6.9 (t, *J* = 5.0 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ -96.2 (t, *J* = 16.0 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_9H_{12}F_2NO]^+$: 188.0887, found: 188.0883.



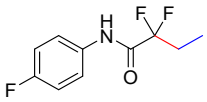
2,2-difluoro-*N*-phenylbutanamide (2aj)

9.4 mg, 47% yield, colorless oil, Rf (PE/ EA 4/1 v/v): 0.54

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.6 (d, *J* = 7.7 Hz, 2H), 7.4 (t, *J* = 8.0 Hz, 2H), 7.2 (t, *J* = 7.4 Hz, 1H), 2.3 – 2.1 (m, 2H), 1.1 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1 – 160.4 (m), 136.2, 129.4, 125.7, 120.3, 118.8, 27.4 (t, *J* = 24.0 Hz), 6.0 (t, *J* = 5.5 Hz).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{10}H_{12}F_2NO]^+$: 200.0887, found: 200.0885.



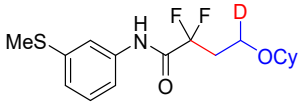
2,2-difluoro-*N*-(4-fluorophenyl)butanamide (2ak)

8.1 mg, 37% yield, light-yellow oil, Rf (PE/ toluene 1/2 v/v): 0.65

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.5 (dd, *J* = 9.0, 4.6 Hz, 2H), 7.1 (t, *J* = 8.6 Hz, 2H), 2.3 – 2.1 (m, 2H), 1.1 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7 – 161.7 (m), 160.2 (d, *J* = 245.5 Hz), 132.2, 122.3 (d, *J* = 8.1 Hz), 118.8 (t, *J* = 253.1 Hz), 116.1 (d, *J* = 22.7 Hz), 27.4 (t, *J* = 24.0 Hz), 6.0 (t, *J* = 5.3 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ -107.4 (t, *J* = 17.4 Hz), -116.0 – -116.1 (m).

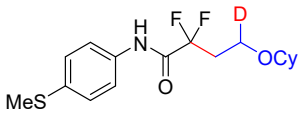


4-(cyclohexyloxy)-2,2-difluoro-*N*-(3-(methylthio)phenyl)butanamide (2al)

24.4 mg, 71% yield, white solid, Rf (PE/ EA 4/1 v/v): 0.43

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.1 (s, 1H), 7.6 (s, 1H), 7.3 (d, *J* = 5.2 Hz, 2H), 7.1 (d, *J* = 5.8 Hz, 1H), 3.7 – 3.6 (m, 1H), 3.3 – 3.2 (m, 1H), 2.6 – 2.4 (m, 5H), 1.9 - 1.8 (m, 2H), 1.7 – 1.6 (m, 2H), 1.5 – 1.4 (m, 1H), 1.3 – 1.1 (m, 5H).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{23}DF_2NO_2S]^+$: 345.1559, found: 345.1553.

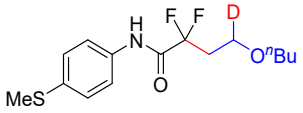


4-(cyclohexyloxy)-2,2-difluoro-*N*-(4-(methylthio)phenyl)butanamide (2am)

18.9 mg, 55% yield, white solid, Rf (PE/ EA 4/1 v/v): 0.48

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.5 (d, *J* = 8.7 Hz, 2H), 7.3 (d, *J* = 1.9 Hz, 2H), 3.7 – 3.6 (m, 1H), 3.3 – 3.2 (m, 1H), 2.6 – 2.4 (m, 5H), 1.9 - 1.8 (m, 2H), 1.7 – 1.6 (m, 2H), 1.5 – 1.4 (m, 1H), 1.2 – 1.1 (m, 5H).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{17}H_{23}DF_2NO_2S]^+$: 345.1559, found: 345.1551.

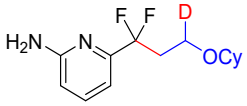


4-butoxy-2,2-difluoro-*N*-(4-(methylthio)phenyl)butanamide (2an)

18.7 mg, 59% yield, white solid, Rf (PE/ EA 4/1 v/v): 0.45

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.5 (d, *J* = 8.6 Hz, 2H), 7.3 (d, *J* = 3.5 Hz, 2H), 3.7 – 3.6 (m, 1H), 3.4 (t, *J* = 6.6 Hz, 2H), 2.6 – 2.4 (m, 5H), 1.5 – 1.4 (m, 2H), 1.3 – 1.2 (m, 2H), 0.8 (t, *J* = 7.4 Hz, 3H).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{15}H_{21}DF_2NO_2S]^+$: 319.1402, found: 319.1395.

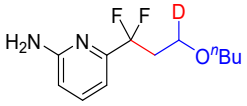


6-(3-(cyclohexyloxy)-1-fluoropropyl)pyridin-2-amine (2ao)

14.3 mg, 53% yield, light-yellow oil, Rf (PE/ EA 4/1 v/v): 0.15

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.9 Hz, 1H), 6.9 (d, *J* = 7.5 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 3.6 – 3.5 (m, 1H), 3.2 – 3.1 (m, 1H), 2.6 – 2.5 (m, 2H), 1.9 – 1.8 (m, 2H), 1.7 – 1.6 (m, 3H), 1.5 – 1.4 (m, 1H), 1.2 – 1.1 (m, 4H).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{14}H_{20}DF_2N_2O]^+$: 272.1685, found: 272.1678.

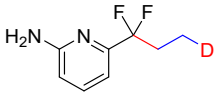


6-(3-butoxy-1,1-difluoropropyl)pyridin-2-amine (2ap)

8.8 mg, 36% yield, light-yellow oil, Rf (PE/ EA 4/1 v/v): 0.15

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.9 Hz, 1H), 6.9 (d, *J* = 7.3 Hz, 1H), 6.5 (d, *J* = 8.3 Hz, 1H), 4.6 (s, 2H), 3.6 – 3.5 (m, 1H), 3.4 (t, *J* = 6.7 Hz, 2H), 2.6 – 2.5 (m, 2H), 1.5 – 1.4 (m, 2H), 1.3 – 1.2 (m, 2H), 0.9 (t, *J* = 7.5 Hz, 3H).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_{12}H_{18}DF_2N_2O]^+$: 246.1528, found: 246.1522.

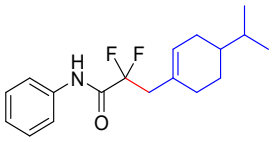


6-(1,1-difluoropropyl-3-*d*)pyridin-2-amine (2aq)

14.6 mg, 84% yield, light-yellow oil, Rf (PE/ toluene 1/2 v/v): 0.28

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.8 Hz, 1H), 6.9 (d, *J* = 7.3 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 4.6 (s, 2H), 2.3 – 2.1 (m, 2H), 1.0 (t, *J* = 7.5 Hz, 2H).

HRMS (ESI+TOF): calculated m/z $[M+H]^+$ for $[C_8H_{10}DF_2N_2]^+$: 174.0953, found: 174.0942.



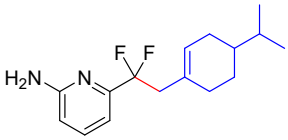
α,α-difluoro-4-(1-methylethyl)-*N*-phenyl-1-cyclohexene-1-propanamide (2ar) [2]

13.0 mg, 42% yield, colorless oil, Rf (PE/ EA 6/1 v/v): 0.37

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (s, 1H), 7.5 (d, *J* = 8.2 Hz, 2H), 7.4 (t, *J* = 7.7 Hz, 2H), 7.2 (t, *J* = 7.3 Hz, 1H), 5.7 (s, 1H), 2.8 (t, *J* = 17.5 Hz, 2H), 2.1 - 2.0 (m, 2H), 1.8 – 1.7 (m, 2H), 1.5 - 1.4 (m, 1H), 1.3 – 1.1 (m, 3H), 0.8 (t, *J* = 7.3 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (t, *J* = 169.5 Hz), 136.2, 129.4, 129.3, 128.2 (t, *J* = 4.0 Hz), 125.7, 120.4, 117.9, 41.8 (t, *J* = 23.2 Hz), 39.7, 32.2, 30.3, 29.3, 26.5, 20.0, 19.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ -104.0 (t, *J* = 17.5 Hz).



6-(1,1-difluoro-2-(4-isopropylcyclohex-1-en-1-yl)ethyl)pyridin-2-amine (2as) [2]

25.4 mg, 91% yield, light-yellow oil, Rf (PE/ EA 4/1 v/v): 0.32

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5 (t, *J* = 7.8 Hz, 1H), 6.9 (d, *J* = 7.4 Hz, 1H), 6.5 (d, *J* = 8.2 Hz, 1H), 5.5 (s, 1H), 4.7 (s, 2H), 2.8 (t, *J* = 17.2 Hz, 2H), 2.0 – 1.9 (m, 2H), 1.7 – 1.6 (m, 2H), 1.5 – 1.3 (m, 1H), 1.3 – 1.0 (m, 3H), 0.8 (t, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 153.7 (t, *J* = 28.9 Hz), 138.3, 129.9 (t, *J* = 3.1 Hz), 127.9, 121.1, 109.9 (t, *J* = 5.3 Hz), 109.7, 44.7 (t, *J* = 26.0 Hz), 39.7, 32.3, 30.3, 29.3, 26.6, 20.1, 19.8.

^{19}F NMR (470 MHz, $CDCl_3$) δ -98.9 (t, *J* = 17.3 Hz).

9. Reference

[1] D. R. Motati, D. Uredi, A. G. Burra, J. P. Bowen, F. R. Fronczek, C. R. Smitha, E. B. Watkins, *Org. Chem. Fron*t. 2020, **7**, 1095-1106.

[2] Y. J. Yu, F. L. Zhang, T. Y. Peng, C. L. Wang, J. Cheng, C. Chen, K. N. Houk, Y. F. Wang, *Science*, 2021, **371**, 1232-1240.

[3] C. Liu, K. Li, R. Shang, *ACS Catal.* 2022, **12(7)**, 4103-4109.

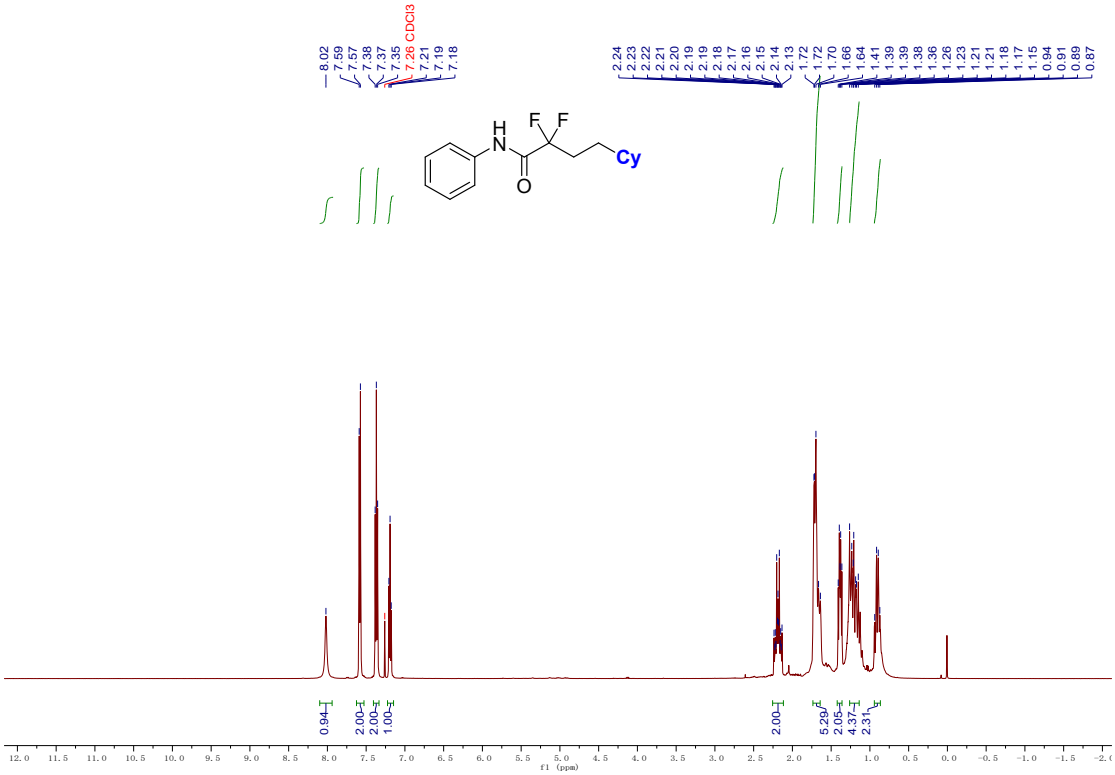
[4] J. H. Ye, P. Bellotti, C. Heusel, F. Glorius, *Angew. Chem.Int. Ed.* 2022, *61*, e2021154.

[5] P. Xu, X. Y. Wang, Z. J. Wang, J. J. Zhao, X. D. Cao, X. C. Xiong, Y. C. Yuan, S. L. Zhu, D. Guo, X. Zhu, *Org. Lett.* 2022, **24(22)**, 4075-4080.

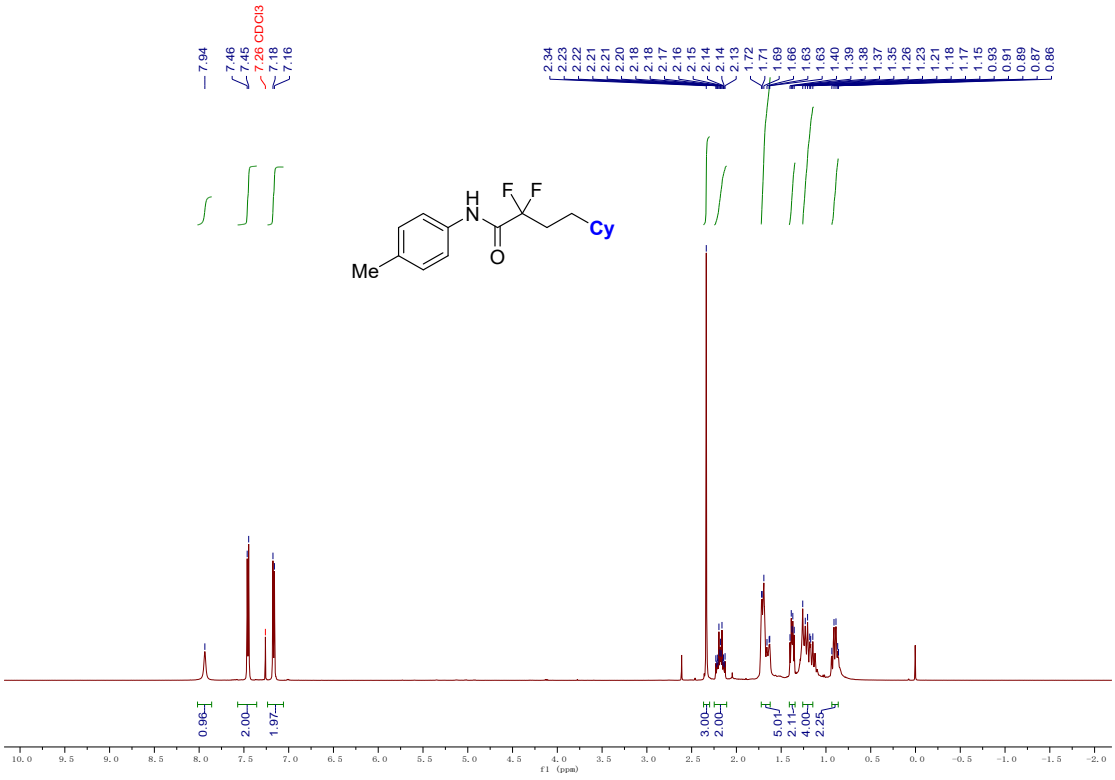
[6] N. Philippe, E. Omri, B. Simone, G. Andreas, US2022305010A1.

10 ^{1}H, ^{13}C and ^{19}F NMR spectra

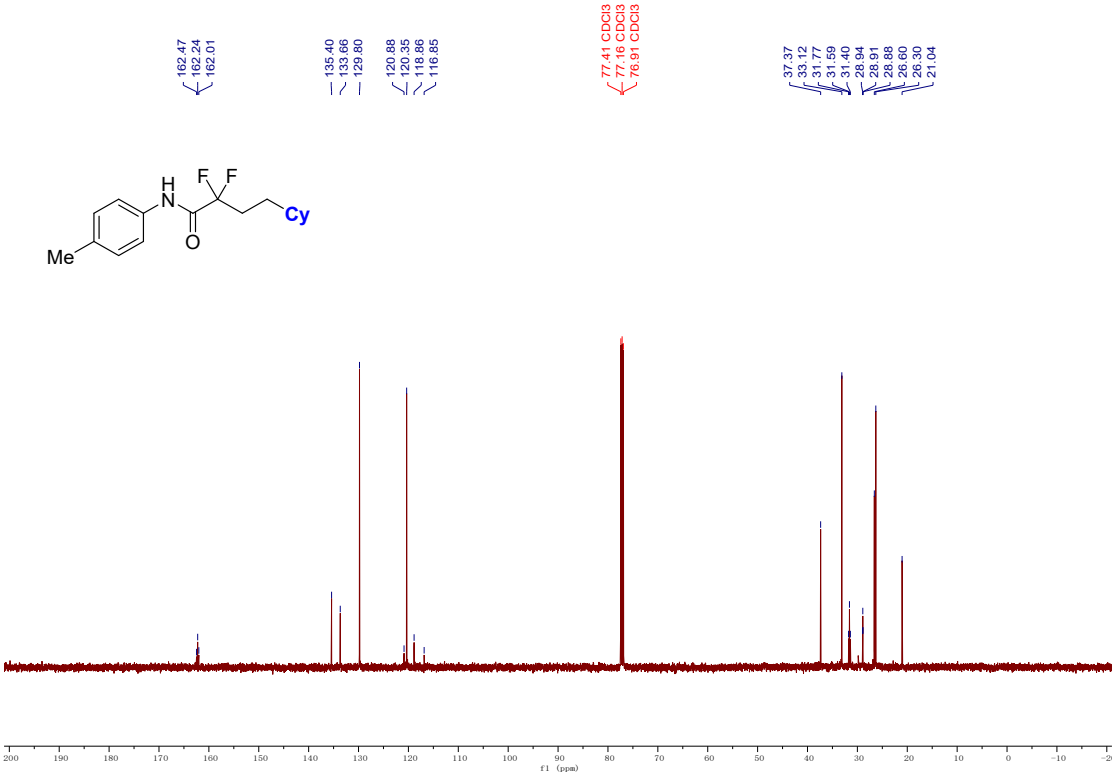
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-phenylbutanamide** (**2a**) (500 MHz, $CDCl_3$)



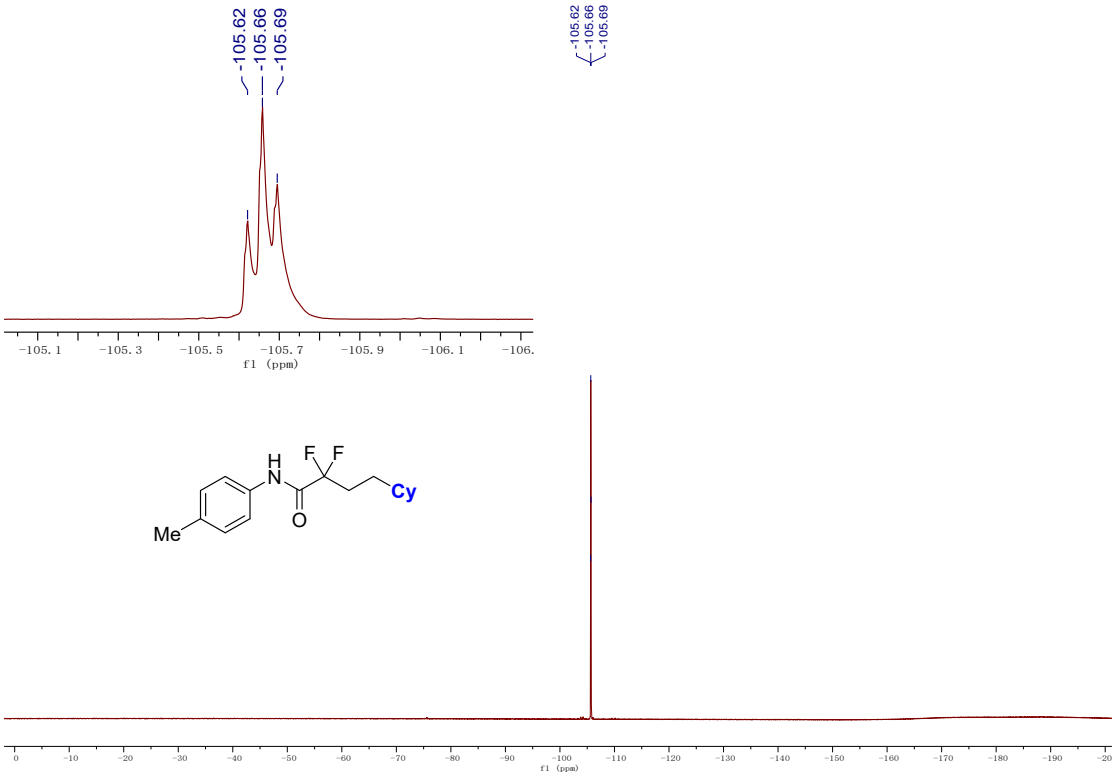
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*p*-tolyl)butanamide** (**2b**) (500 MHz, $CDCl_3$)



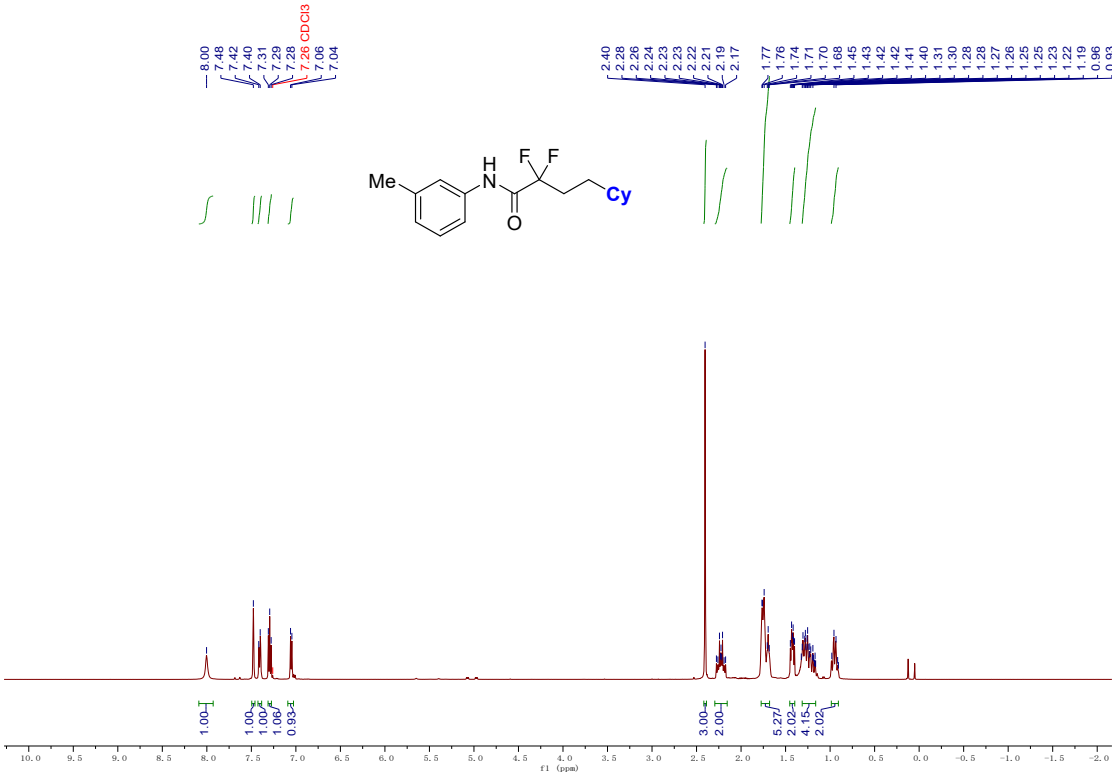
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*p*-tolyl)butanamide** (**2b**) (126 MHz, $CDCl_3$)



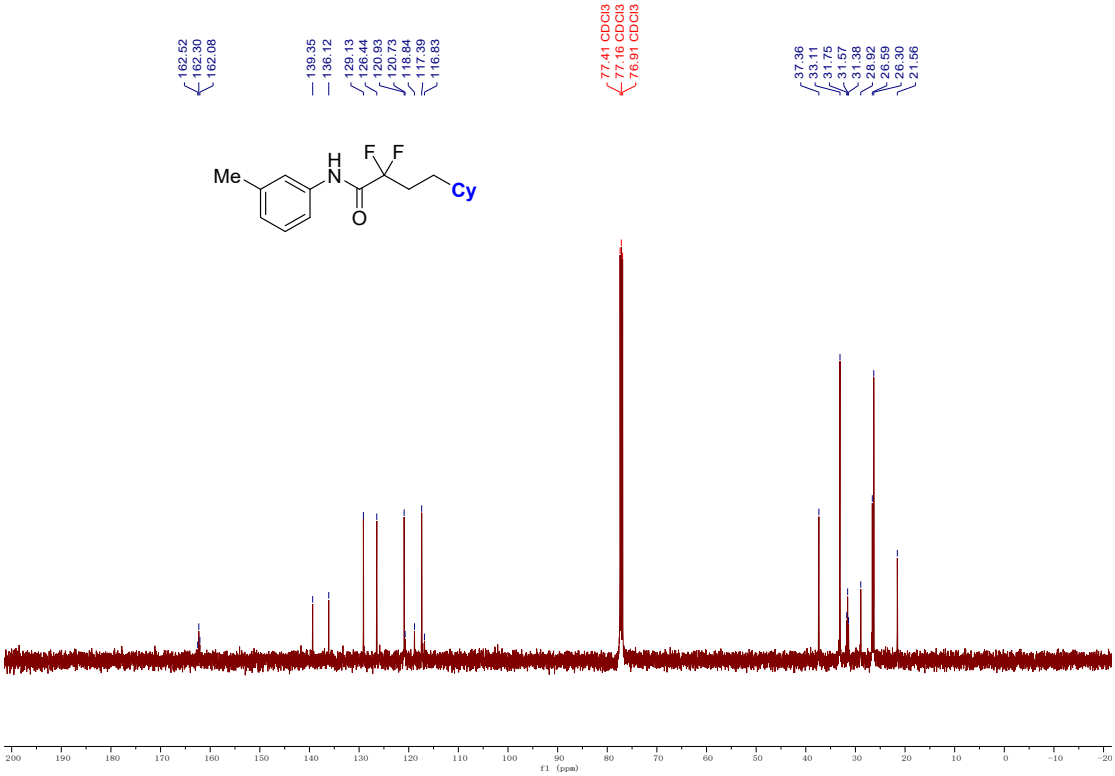
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*p*-tolyl)butanamide** (**2b**) (470 MHz, $CDCl_3$)



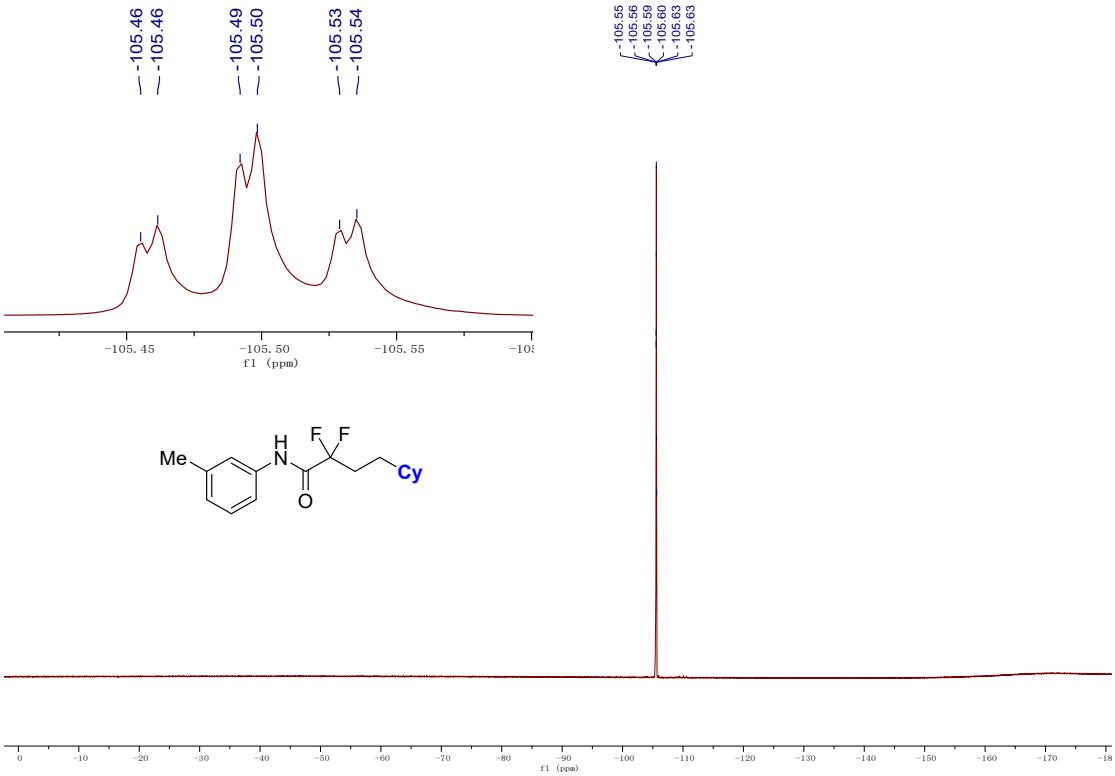
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*m*-tolyl)butanamide** (**2c**) (500 MHz, $CDCl_3$)



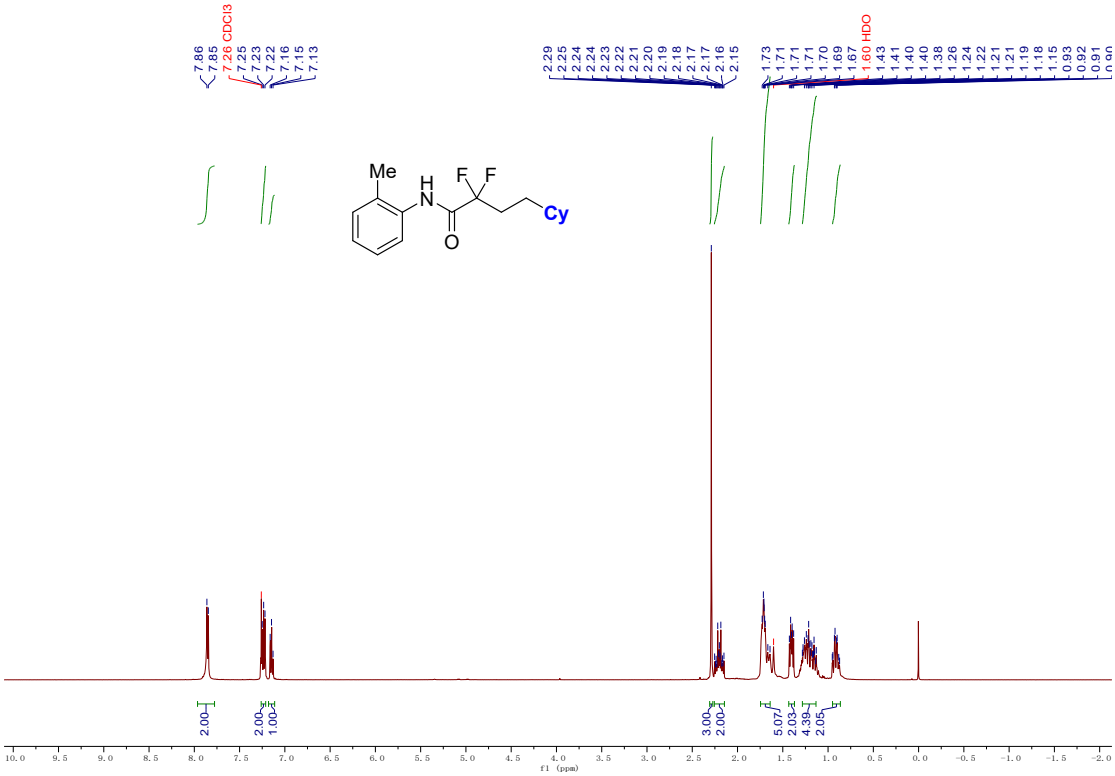
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*m*-tolyl)butanamide** (**2c**) (126 MHz, $CDCl_3$)



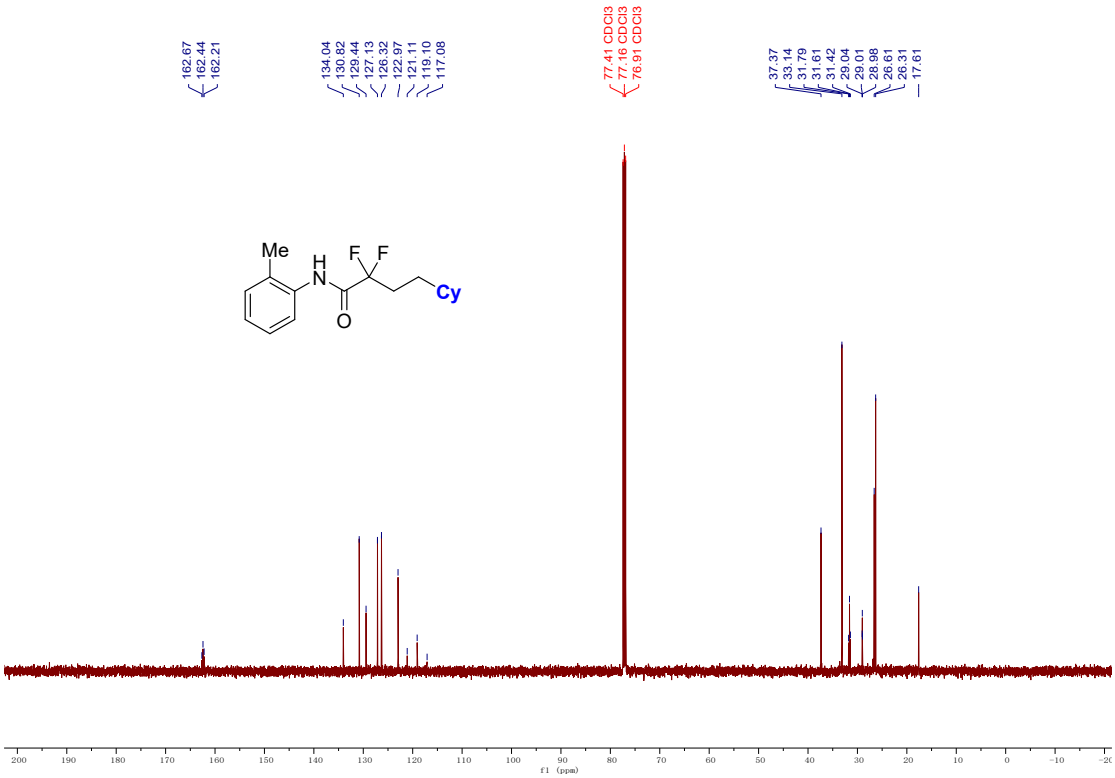
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*m*-tolyl)butanamide** (**2c**) (470 MHz, $CDCl_3$)



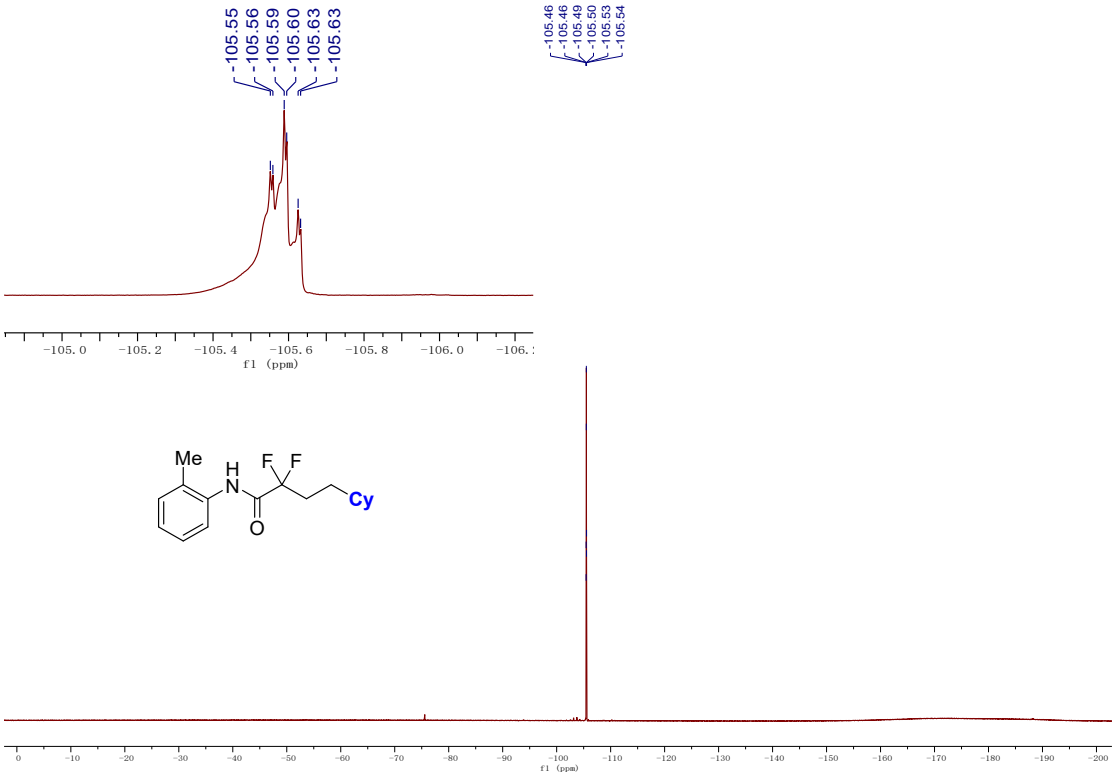
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*o*-tolyl)butanamide** (**2d**) (500 MHz, $CDCl_3$)



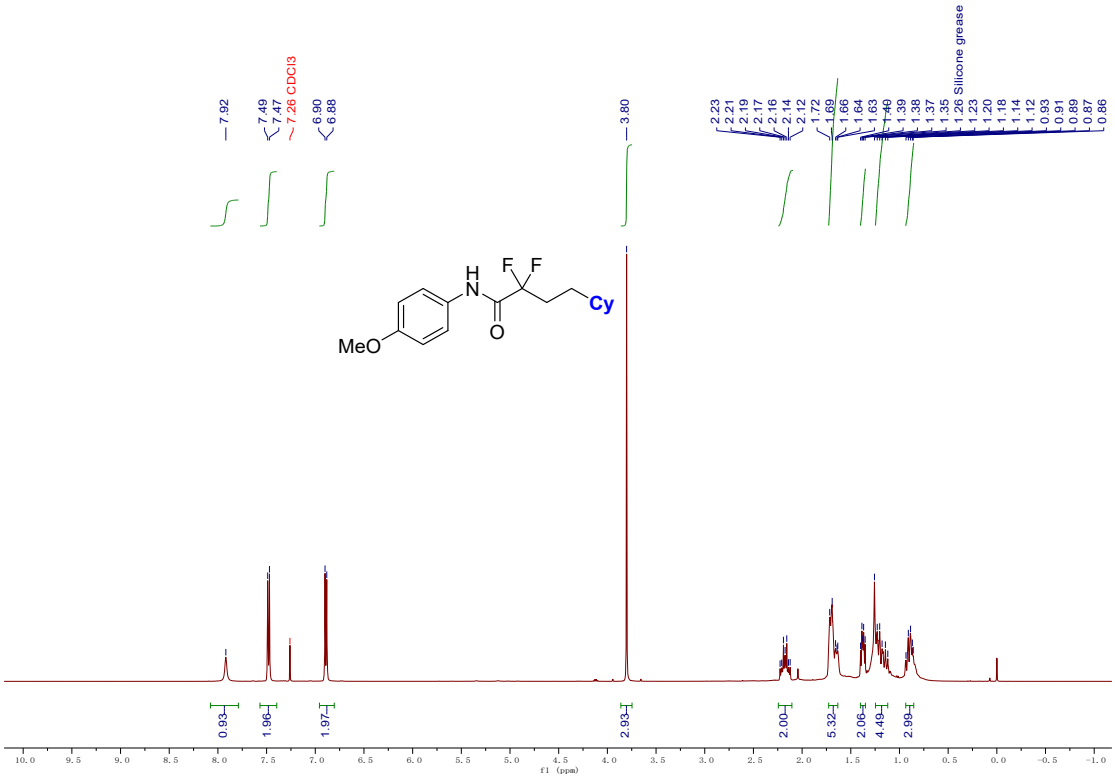
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*o*-tolyl)butanamide** (**2d**) (126 MHz, $CDCl_3$)



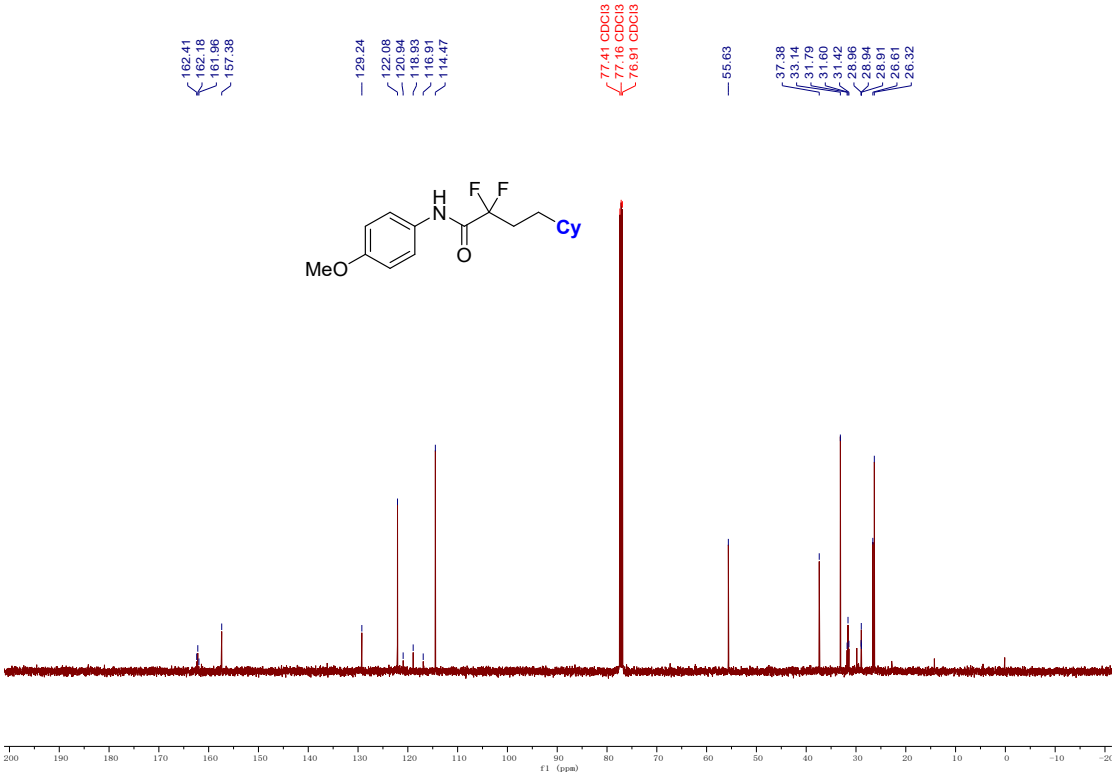
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(*o*-tolyl)butanamide** (**2d**) (470 MHz, $CDCl_3$)



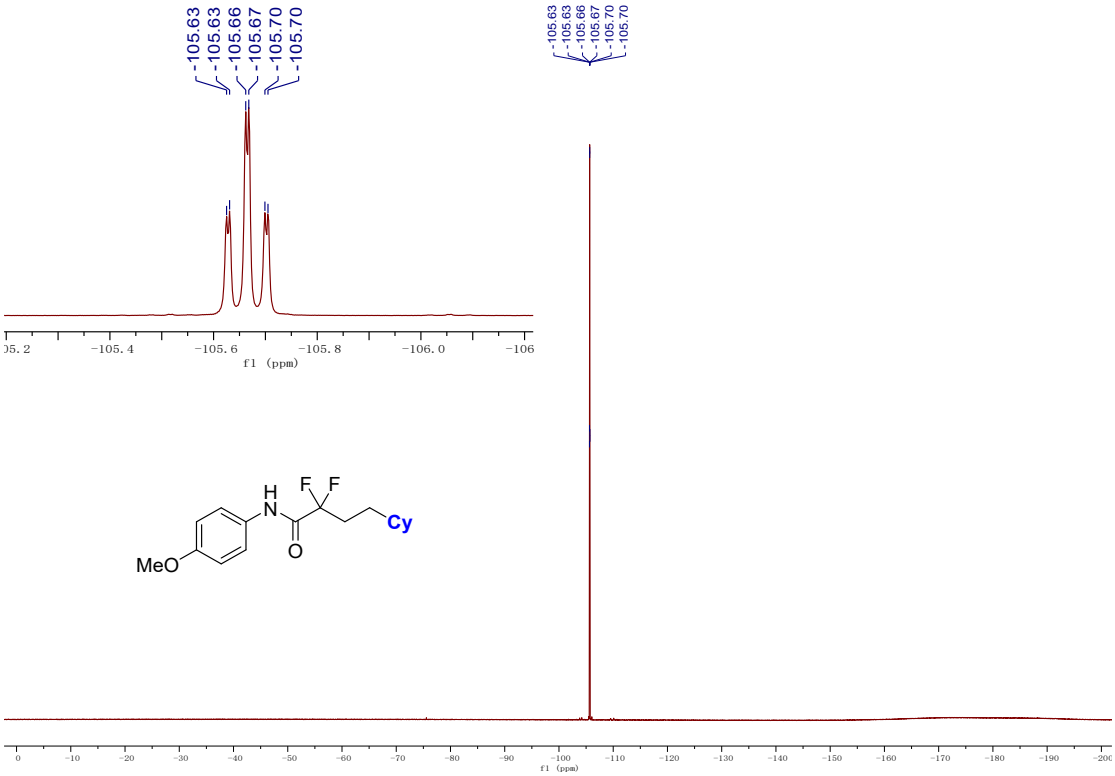
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-methoxyphenyl)butanamide** (**2e**) (500 MHz, $CDCl_3$)



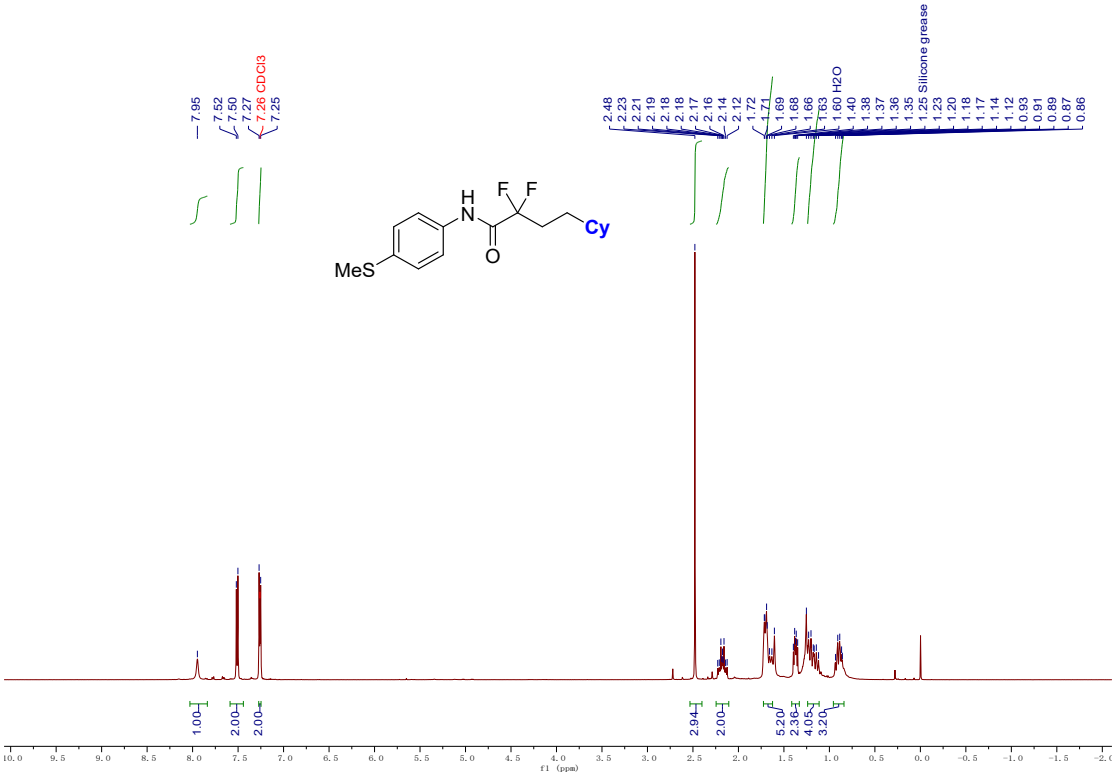
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-methoxyphenyl)butanamide** (**2e**) (126 MHz, $CDCl_3$)



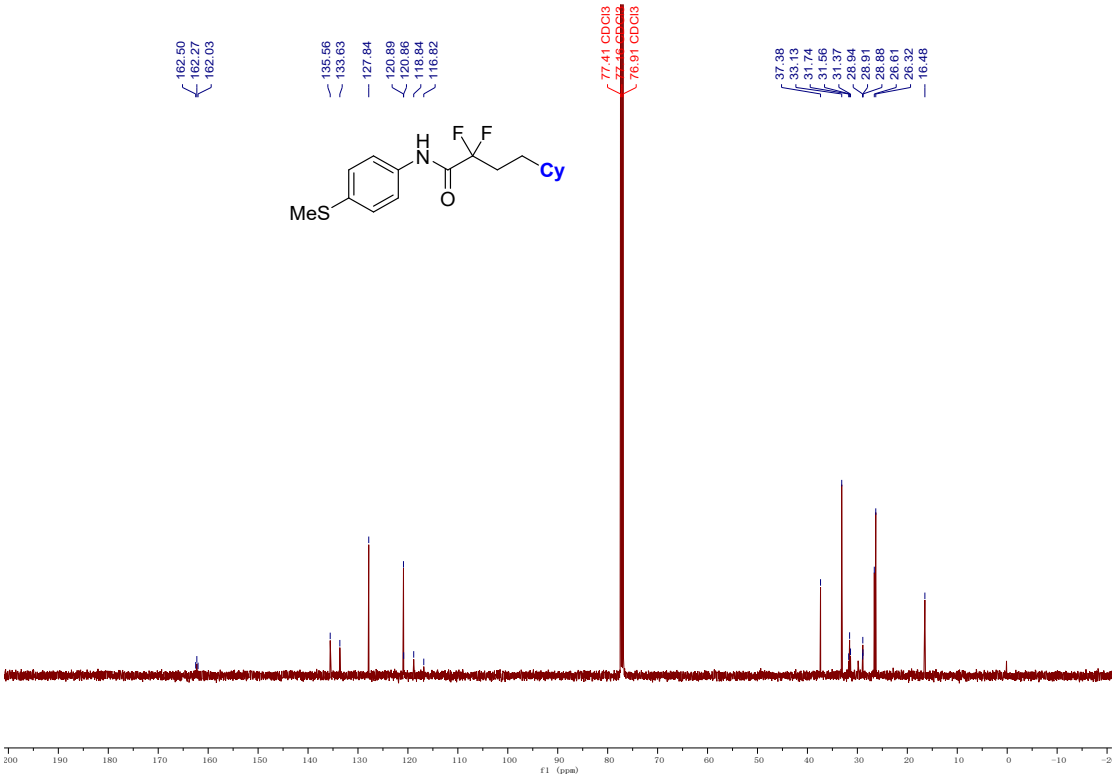
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-methoxyphenyl)butanamide** (**2e**) (470 MHz, $CDCl_3$)



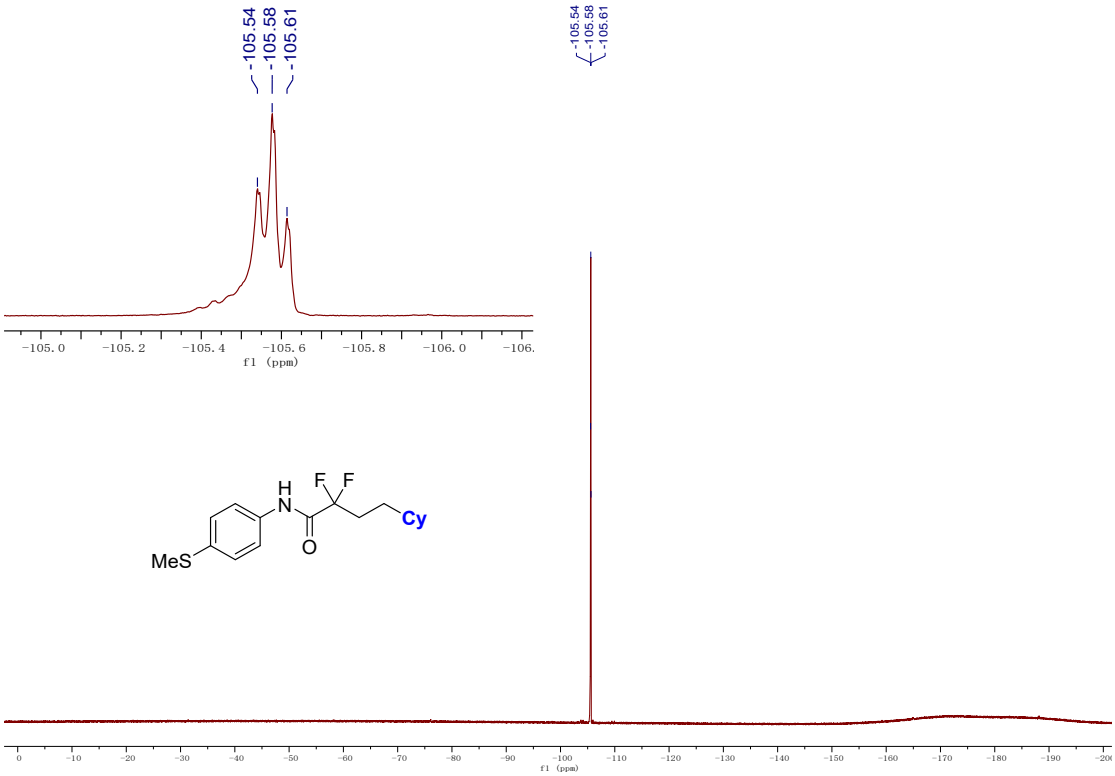
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-(methylthio)phenyl)butanamide** (**2f**) (500 MHz, $CDCl_3$)



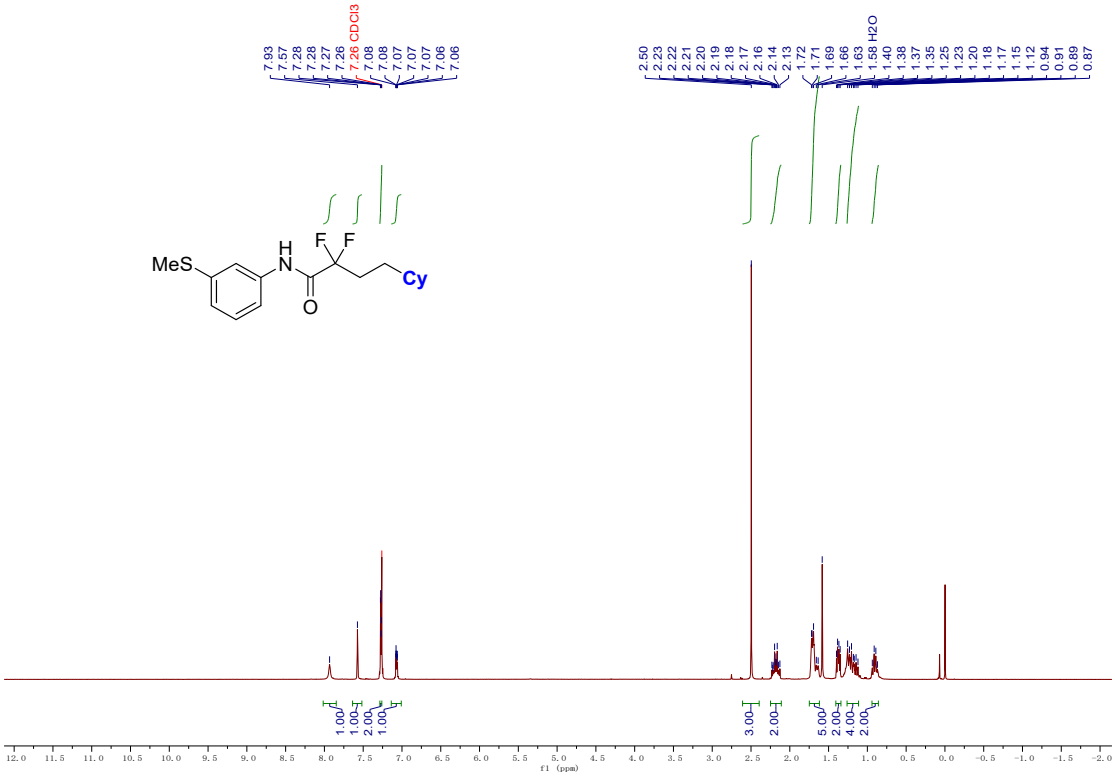
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-(methylthio)phenyl)butanamide** (**2f**) (126 MHz, $CDCl_3$)



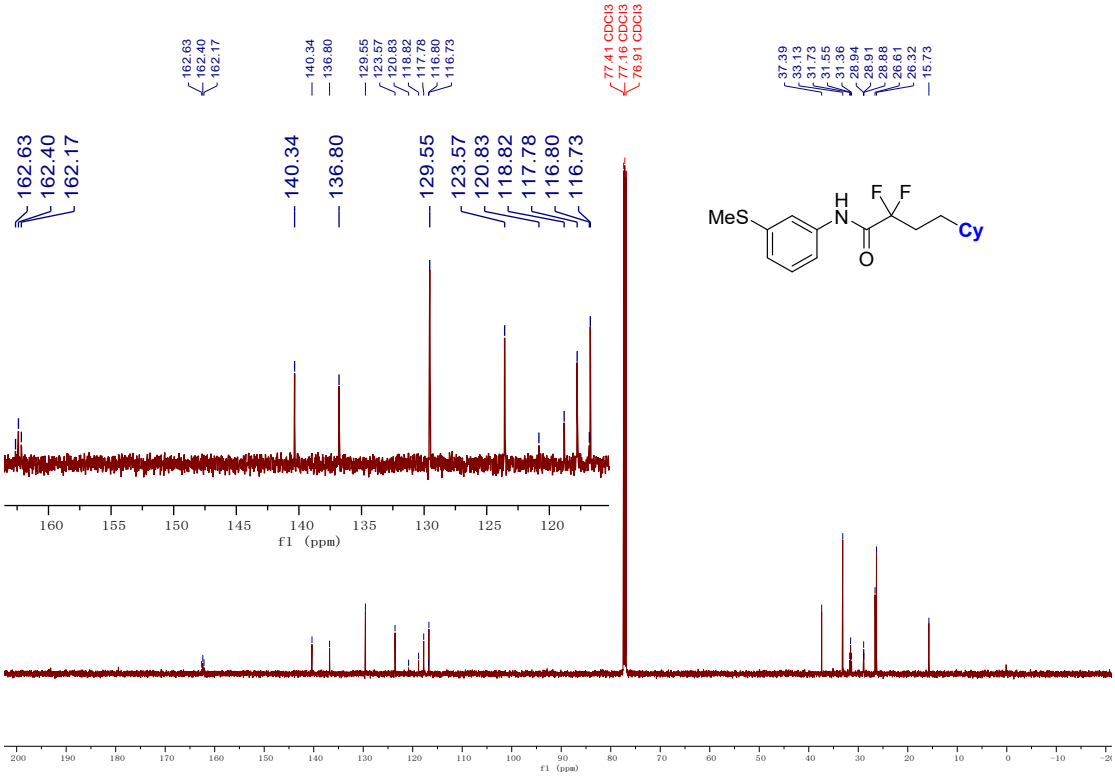
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-(methylthio)phenyl)butanamide** (**2f**) (470 MHz, $CDCl_3$)



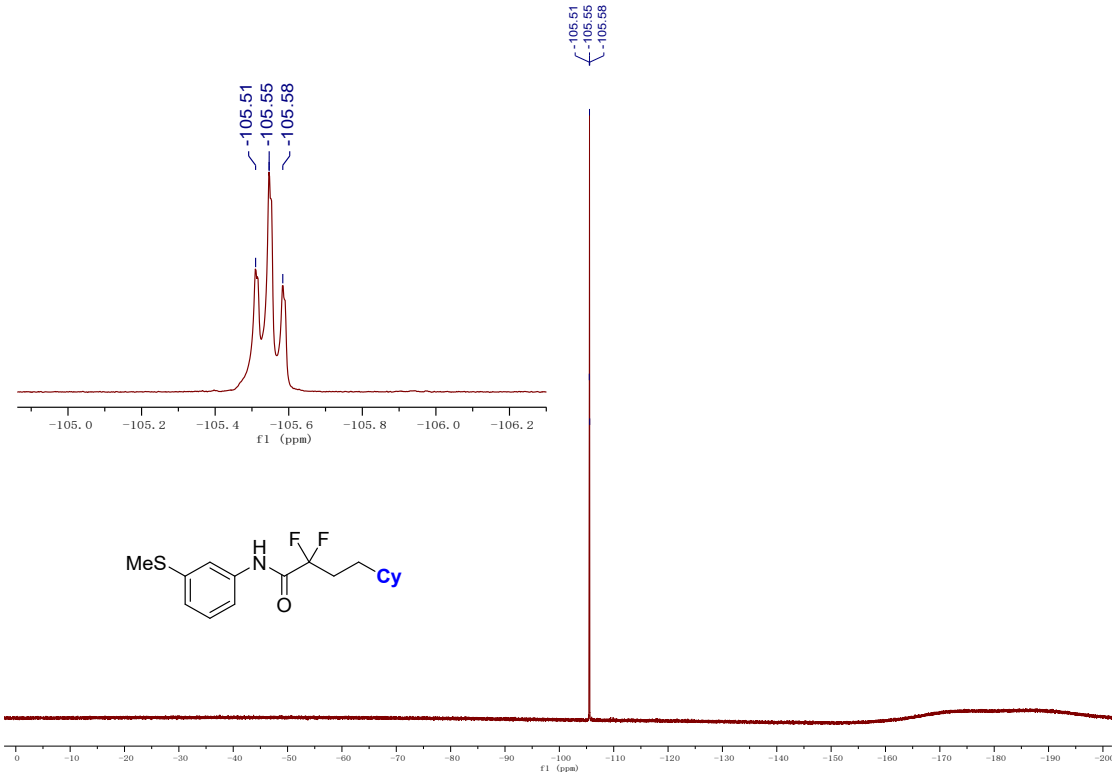
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(3-(methylthio)phenyl)butanamide** (**2g**) (500 MHz, $CDCl_3$)



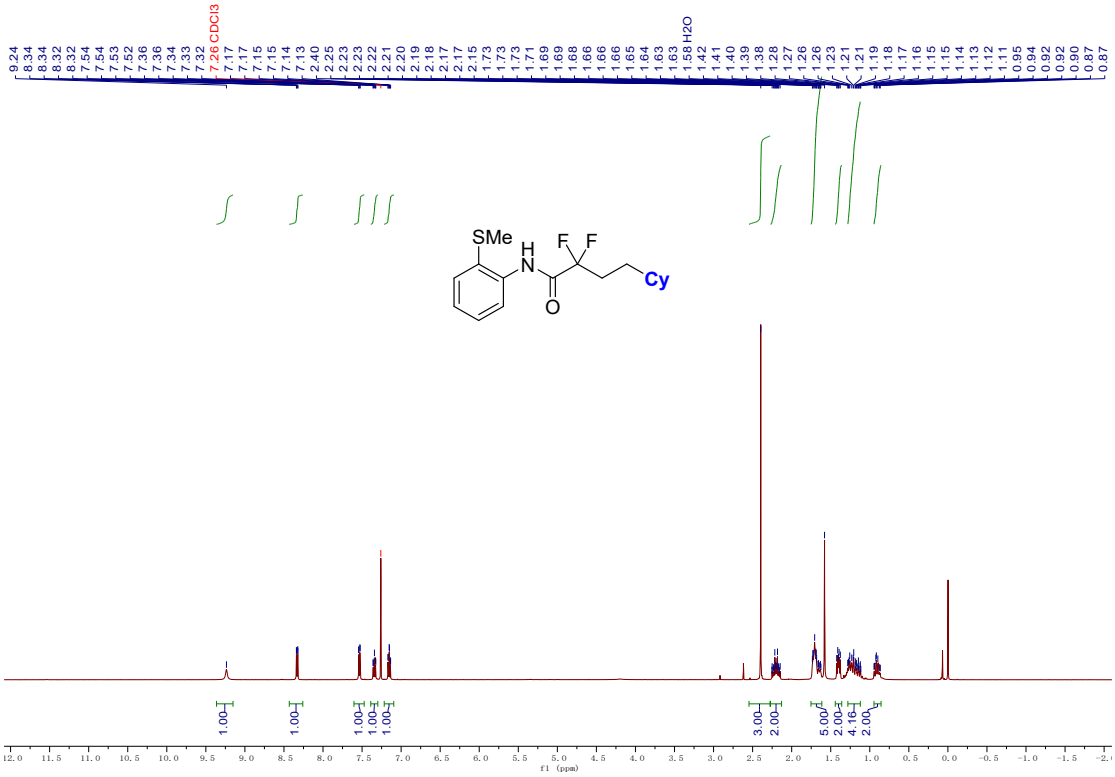
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(3-(methylthio)phenyl)butanamide** (**2g**) (126 MHz, $CDCl_3$)



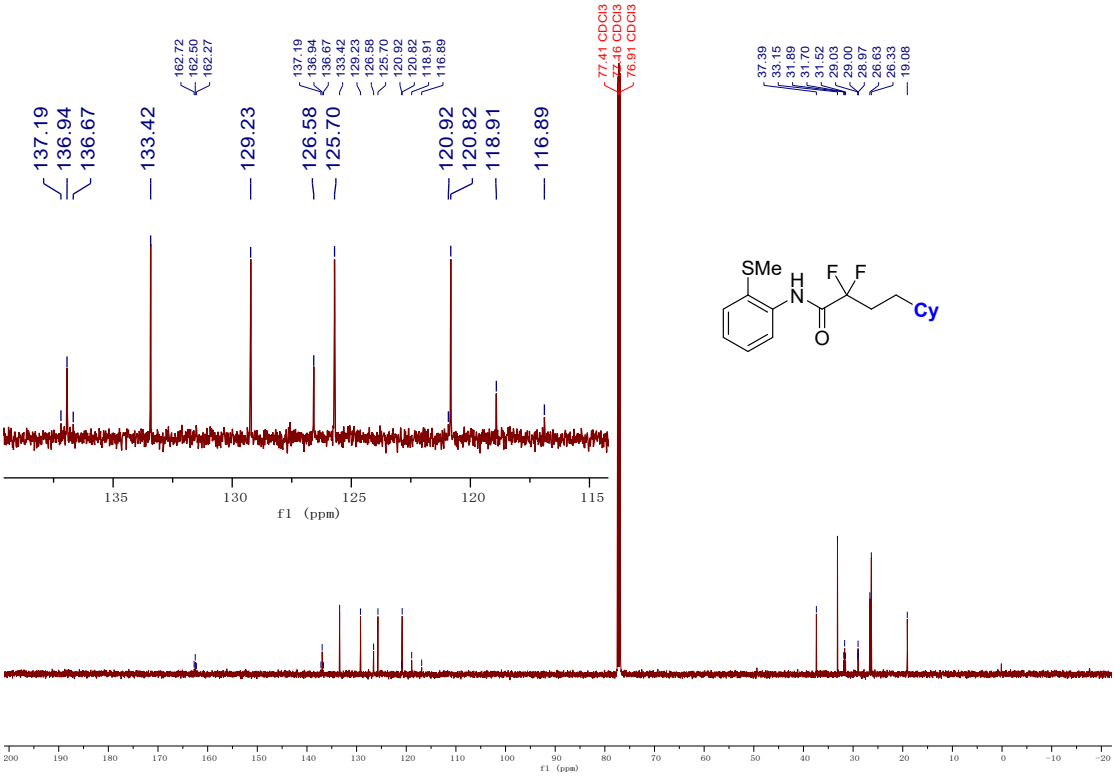
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(3-(methylthio)phenyl)butanamide** (**2g**) (470 MHz, $CDCl_3$)



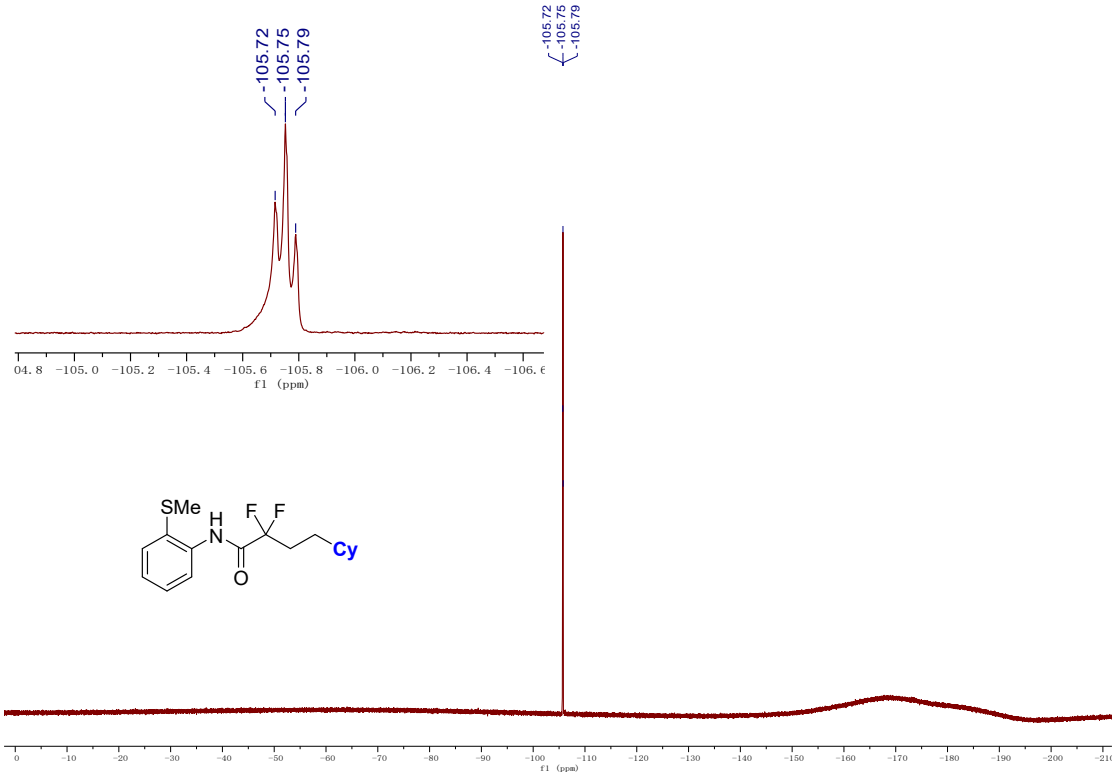
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(2-(methylthio)phenyl)butanamide** (**2h**) (500 MHz, $CDCl_3$)



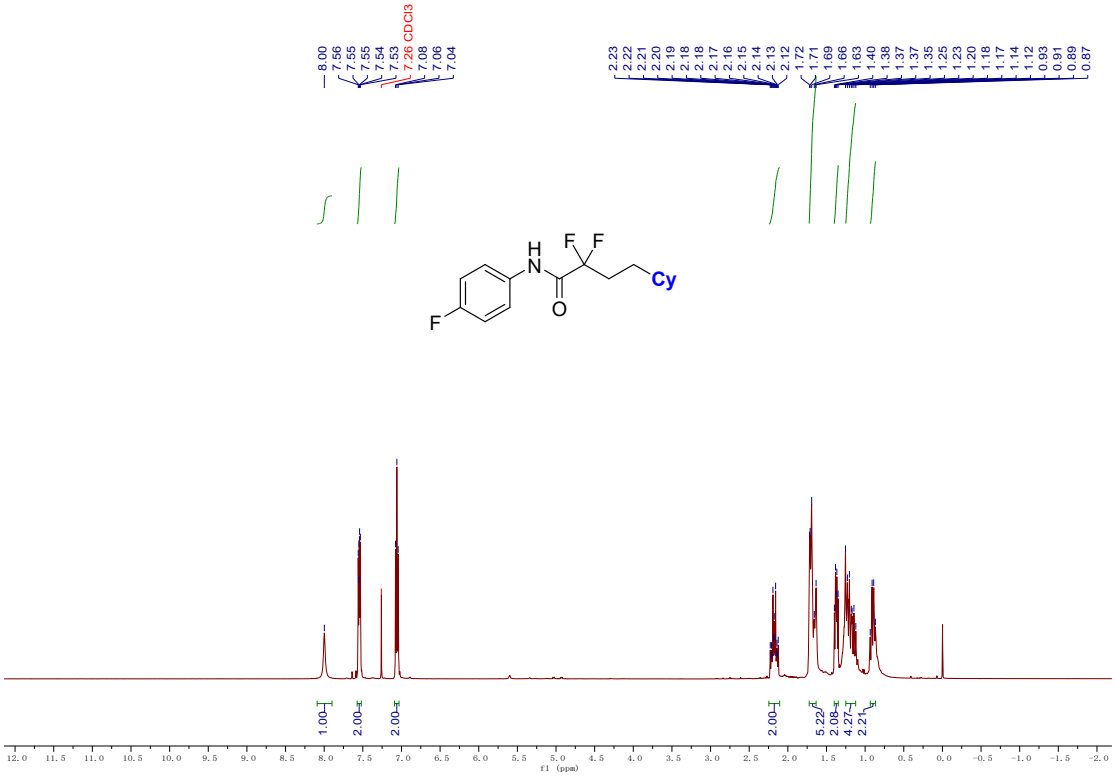
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(2-(methylthio)phenyl)butanamide** (**2h**) (126 MHz, $CDCl_3$)



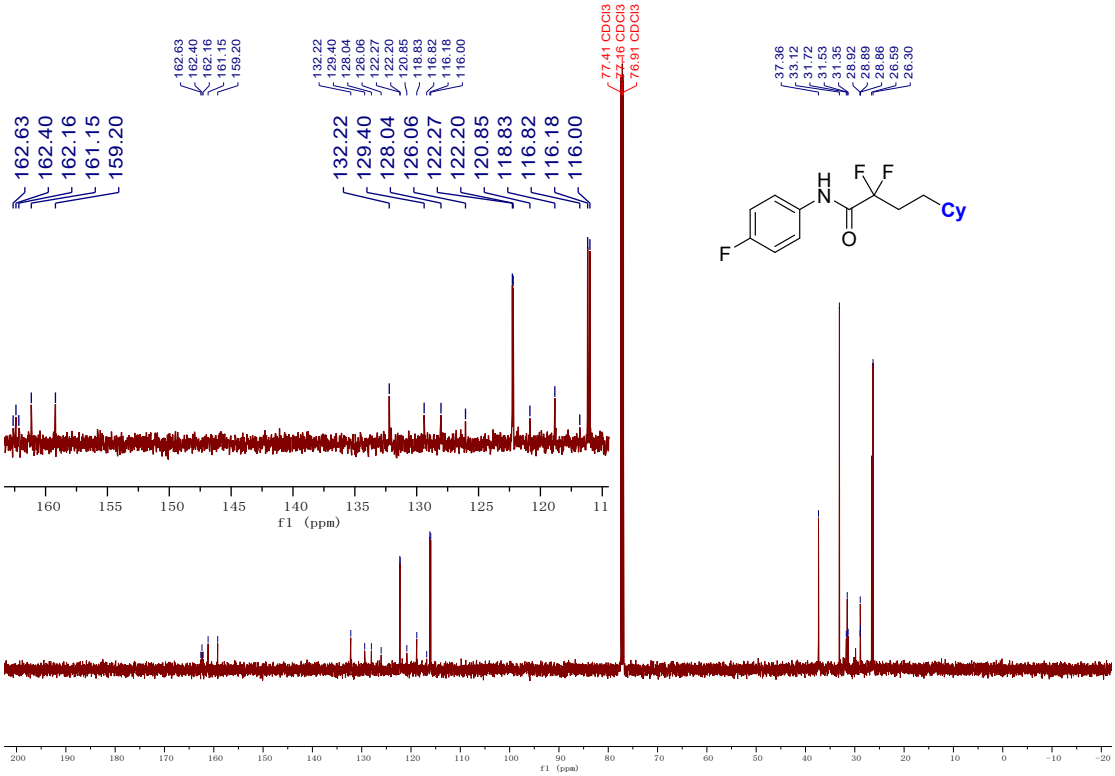
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(2-(methylthio)phenyl)butanamide** (**2h**) (470 MHz, $CDCl_3$)



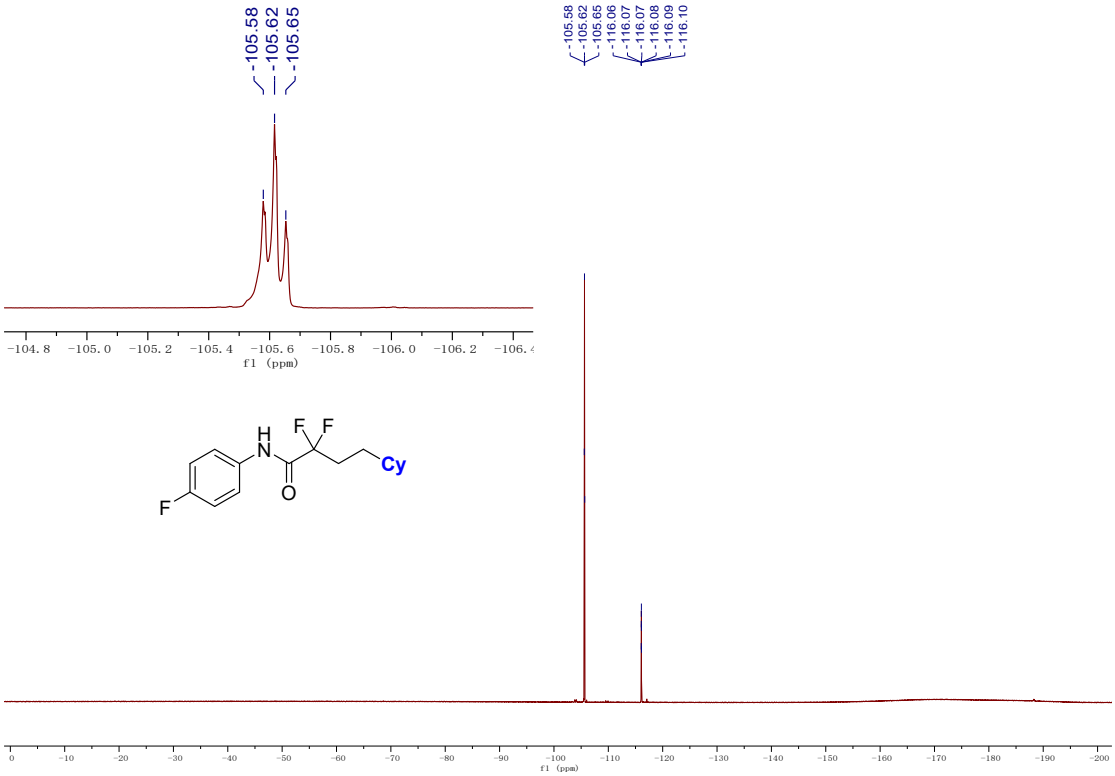
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-fluorophenyl)butanamide** (**2i**) (500 MHz, $CDCl_3$)



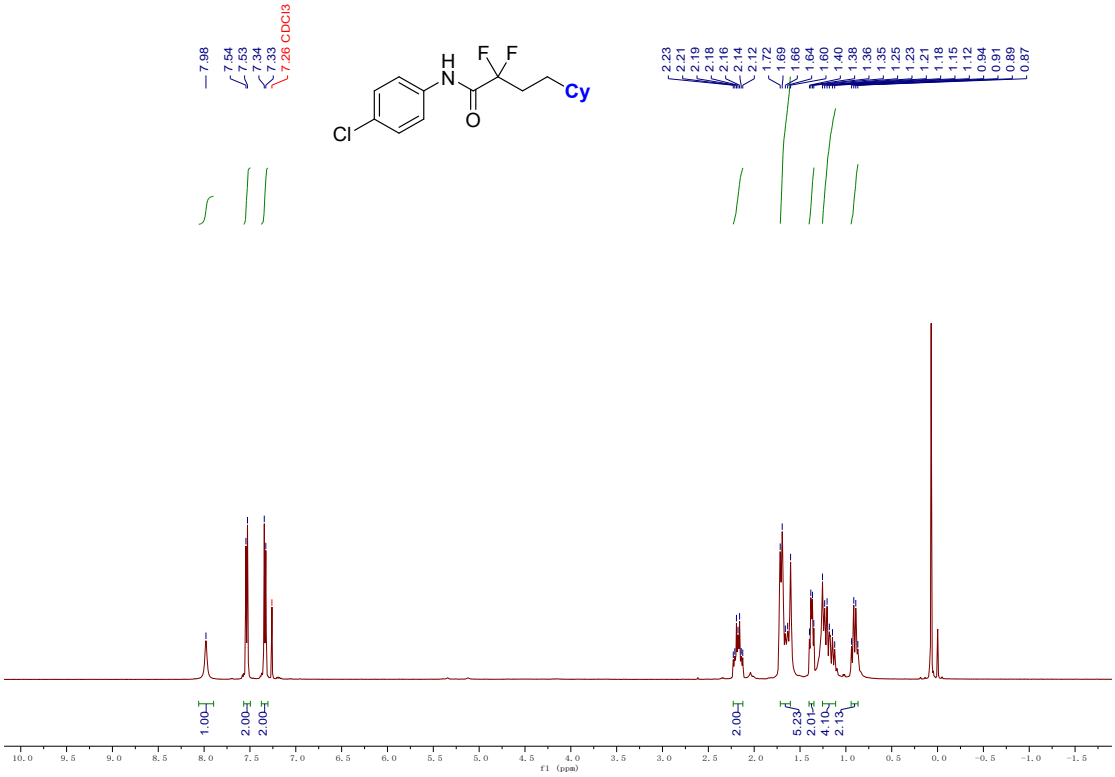
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-fluorophenyl)butanamide** (**2i**) (126 MHz, $CDCl_3$)



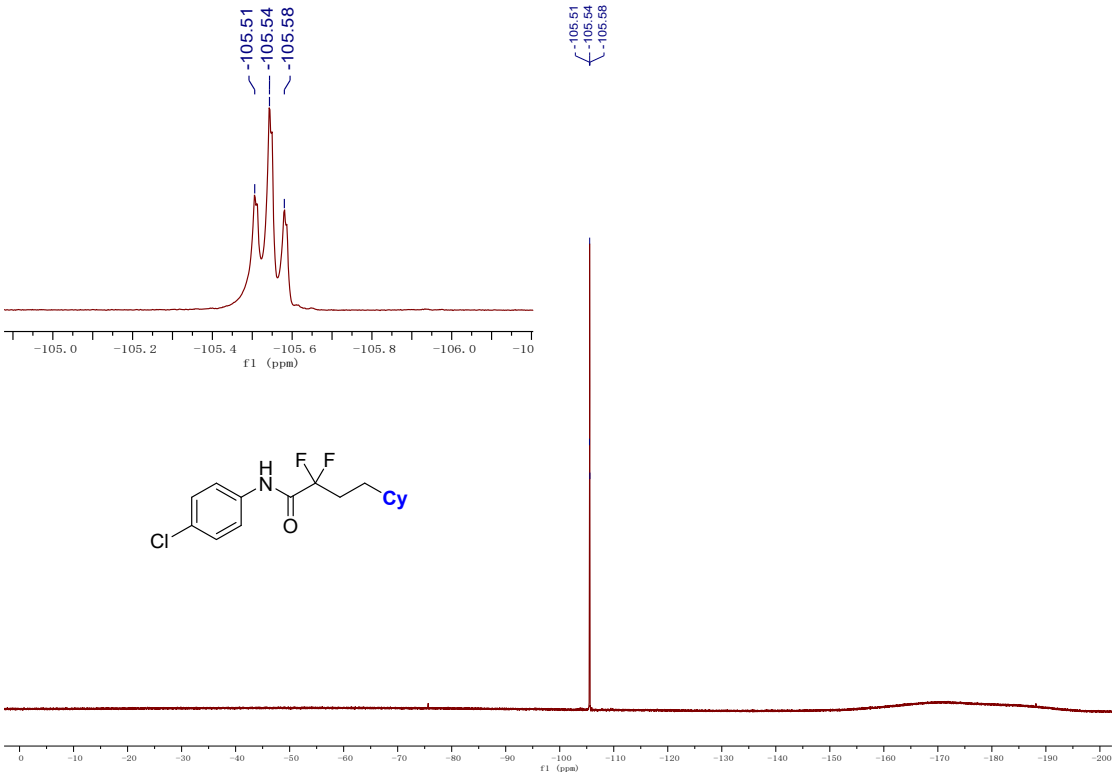
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(4-fluorophenyl)butanamide** (**2i**) (470 MHz, $CDCl_3$)



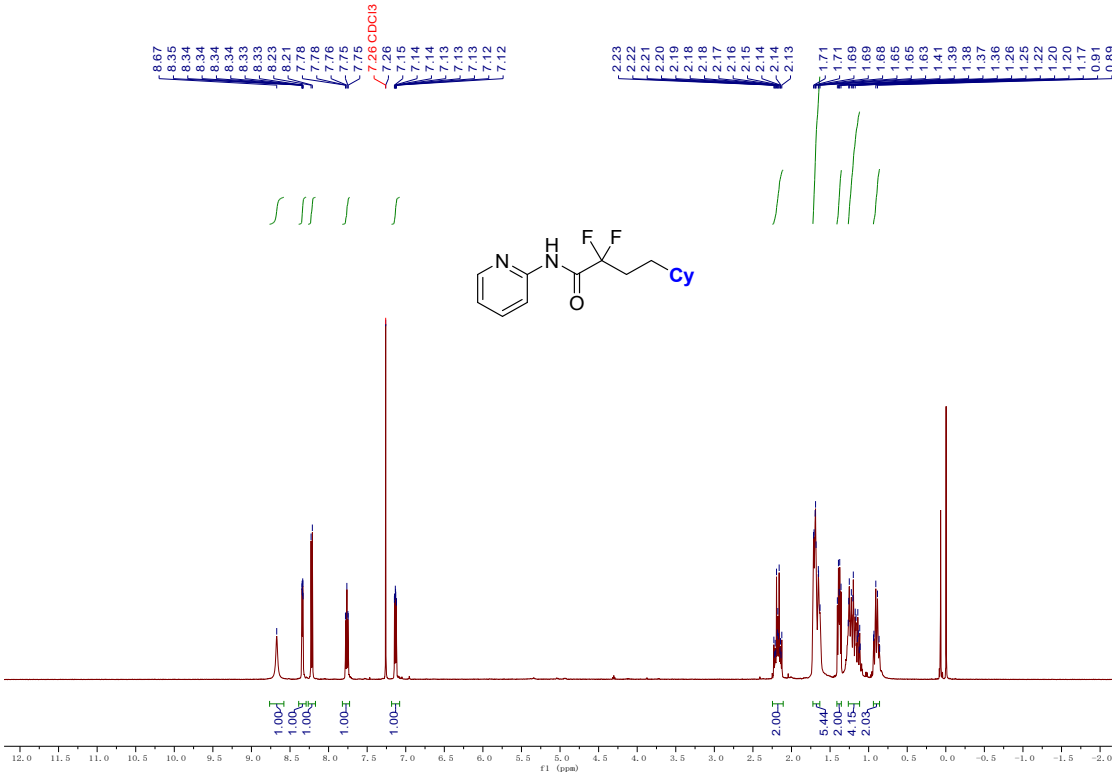
^{1}H NMR of ***N*-(4-chlorophenyl)-4-cyclohexyl-2,2-difluorobutanamide** (**2j**) (500 MHz, $CDCl_3$)



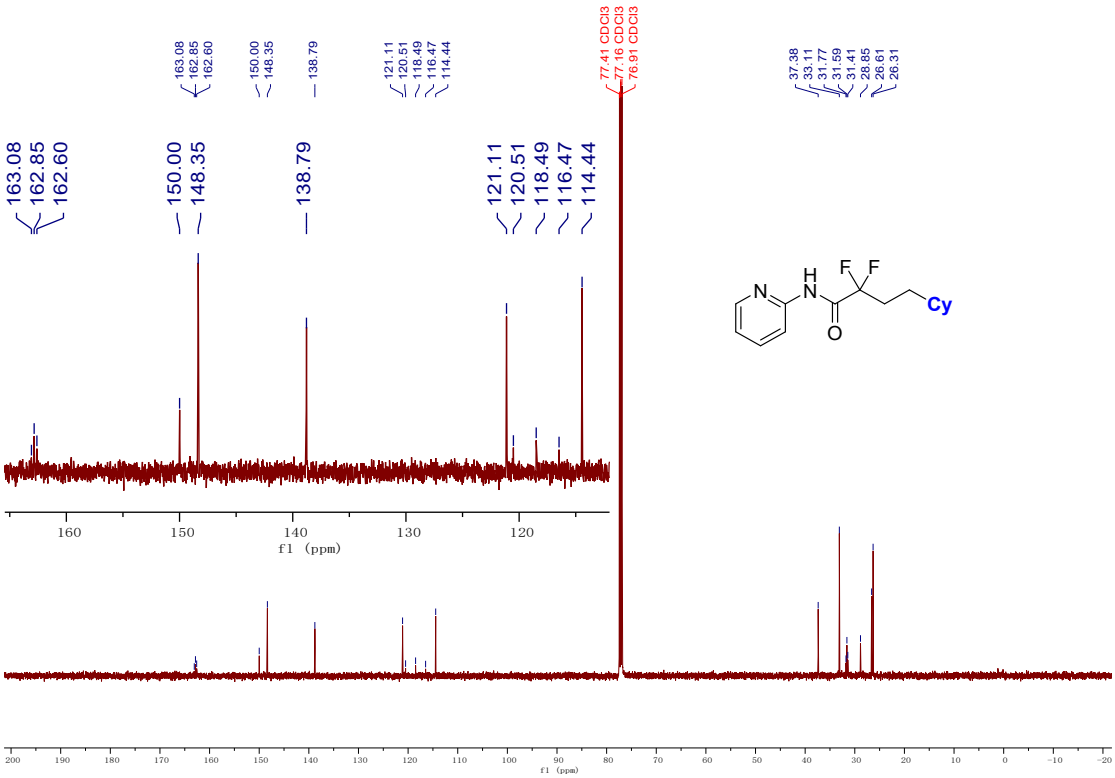
^{19}F NMR of ***N*-(4-chlorophenyl)-4-cyclohexyl-2,2-difluorobutanamide** (**2j**) (470 MHz, $CDCl_3$)



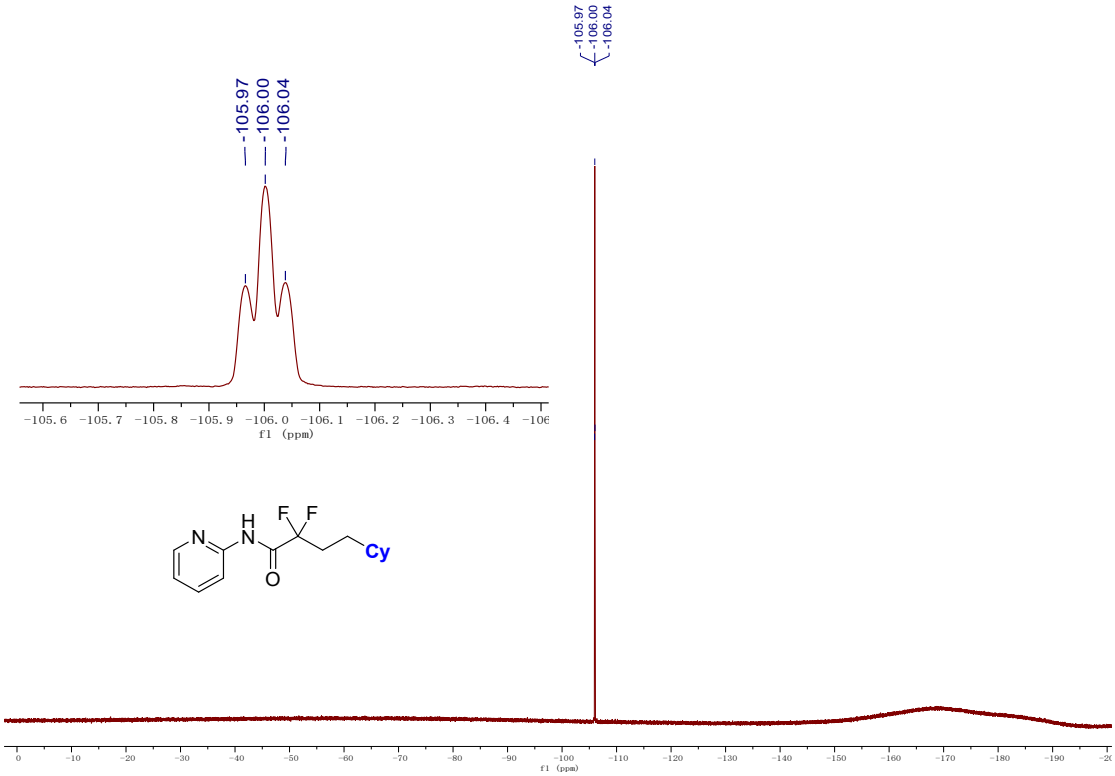
^{1}H NMR of **4-cyclohexyl-2,2-difluoro-*N*-(pyridin-2-yl)butanamide** (**2k**) (500 MHz, $CDCl_3$)



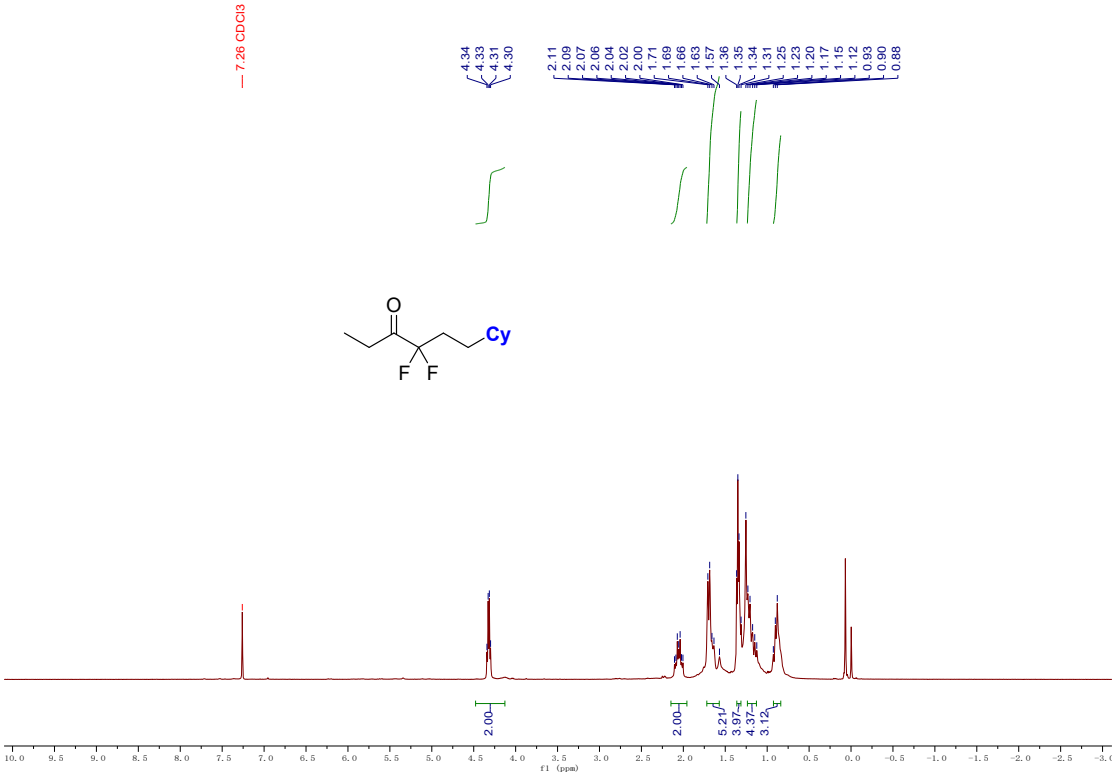
^{13}C NMR of **4-cyclohexyl-2,2-difluoro-*N*-(pyridin-2-yl)butanamide** (**2k**) (126 MHz, $CDCl_3$)



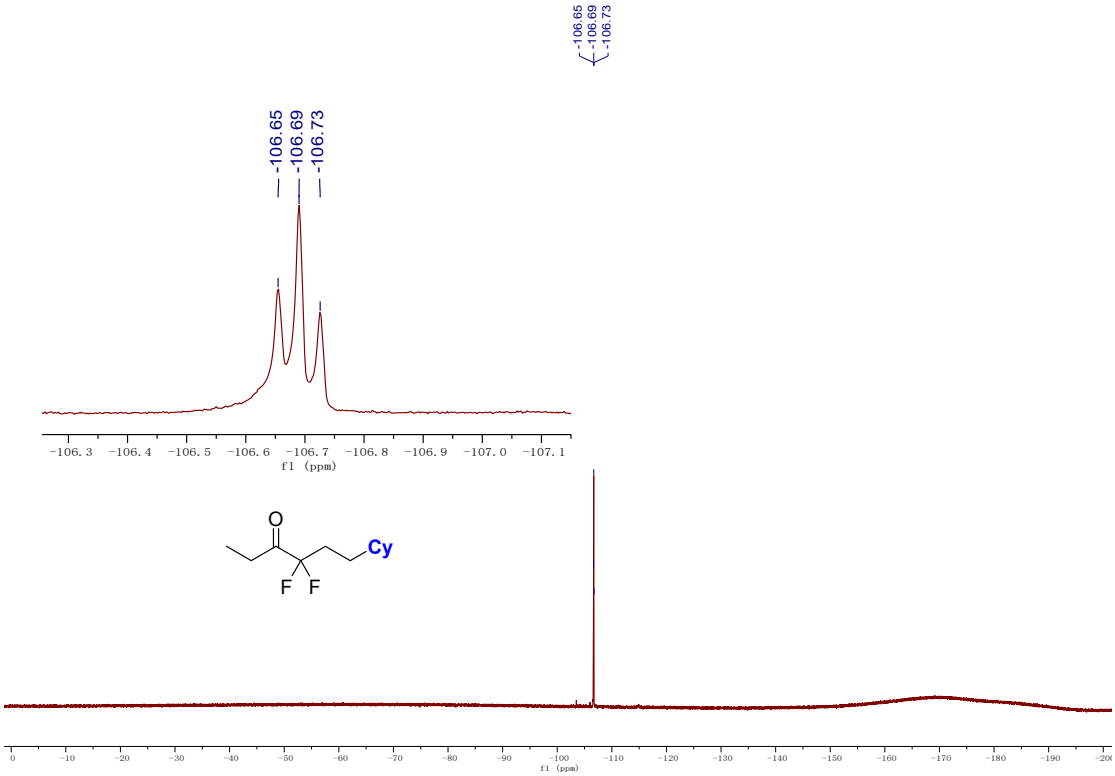
^{19}F NMR of **4-cyclohexyl-2,2-difluoro-*N*-(pyridin-2-yl)butanamide** (**2k**) (470 MHz, $CDCl_3$)



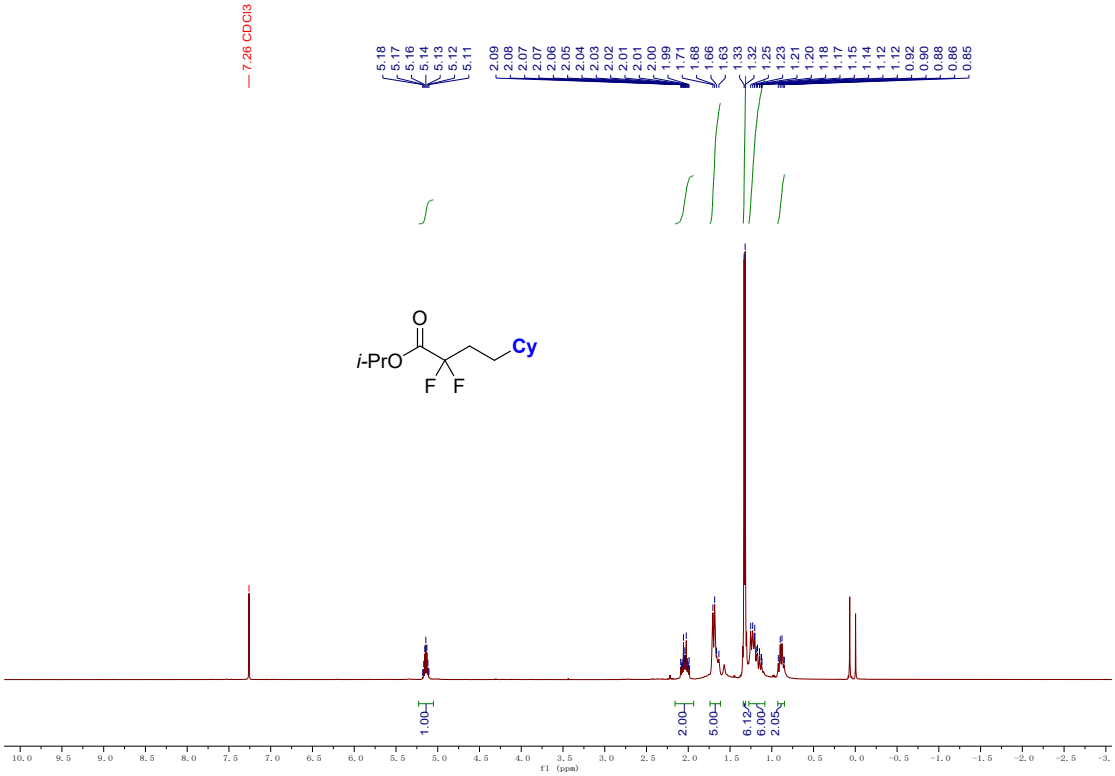
^{1}H NMR of **ethyl 4-cyclohexyl-2,2-difluorobutanoate** (**2m**) (500 MHz, $CDCl_3$)



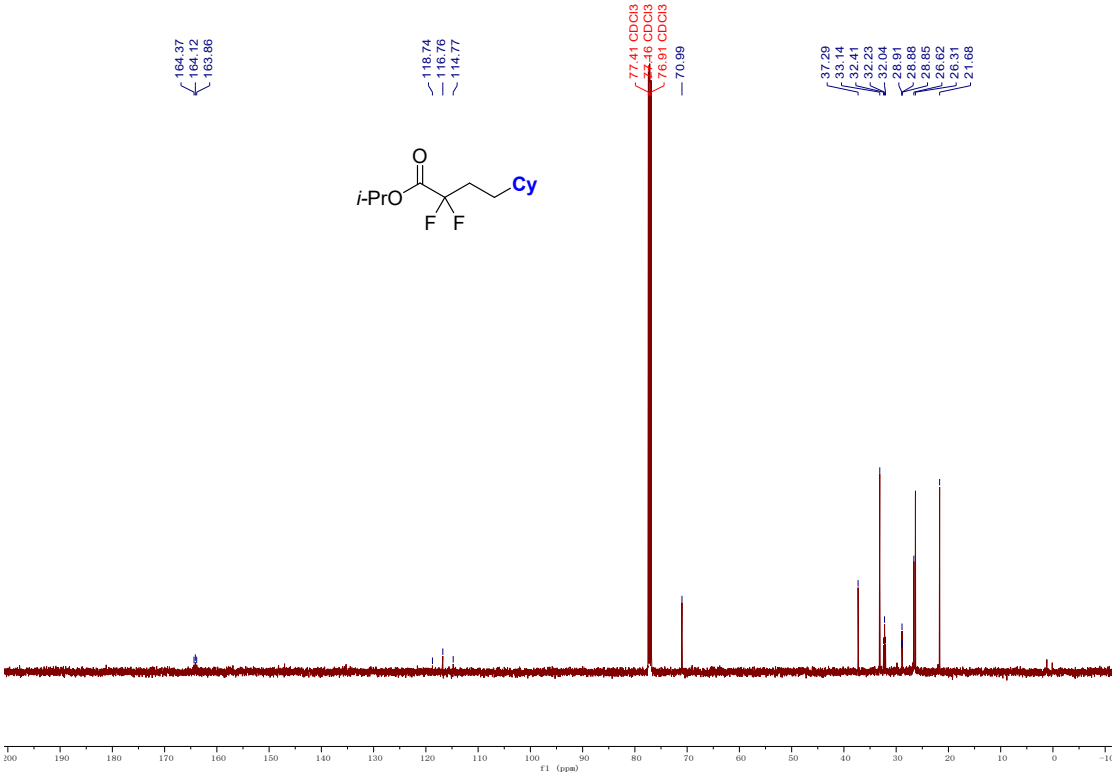
^{19}F NMR of **ethyl 4-cyclohexyl-2,2-difluorobutanoate** (**2m**) (470 MHz, $CDCl_3$)



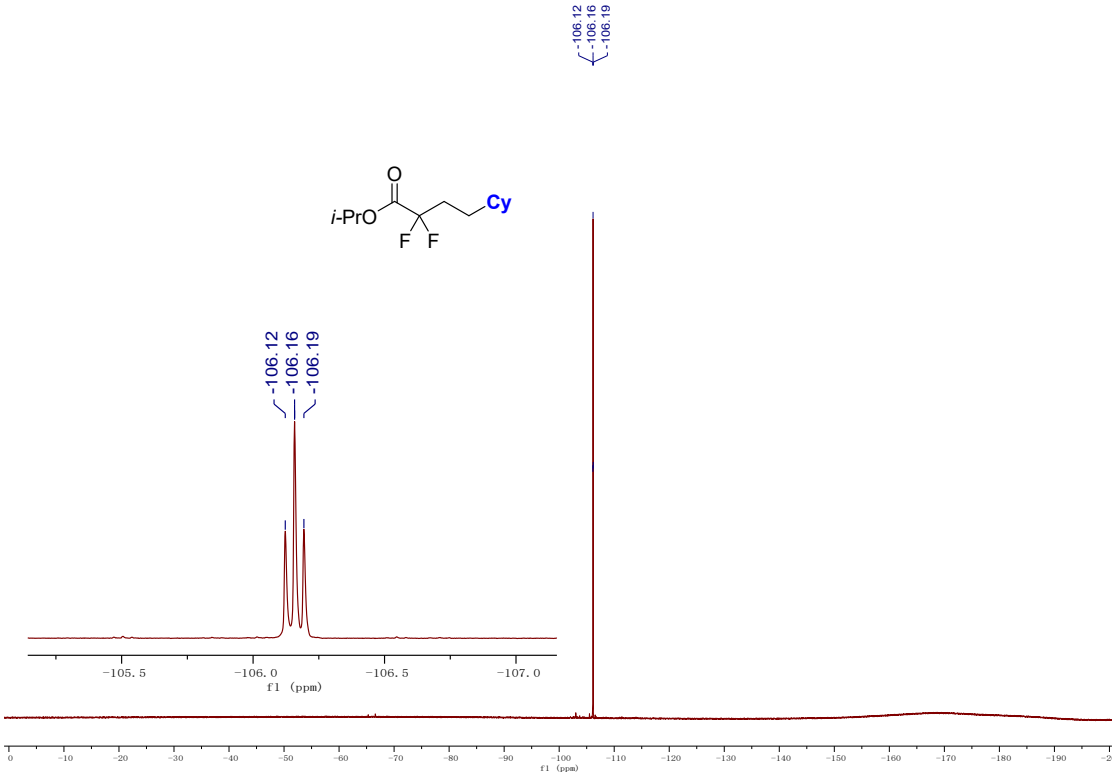
^{1}H NMR of **isopropyl 4-cyclohexyl-2,2-difluorobutanoate** (**2n**) (500 MHz, $CDCl_3$)



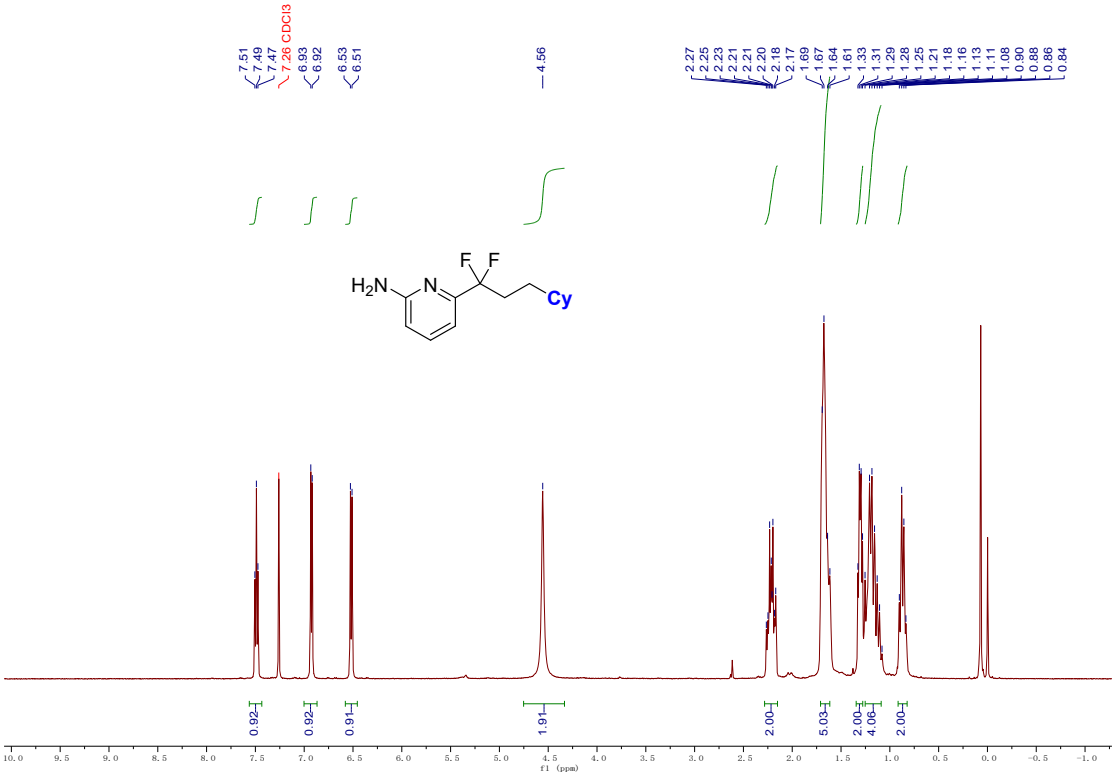
^{13}C NMR of **isopropyl 4-cyclohexyl-2,2-difluorobutanoate** (**2n**) (126 MHz, $CDCl_3$)



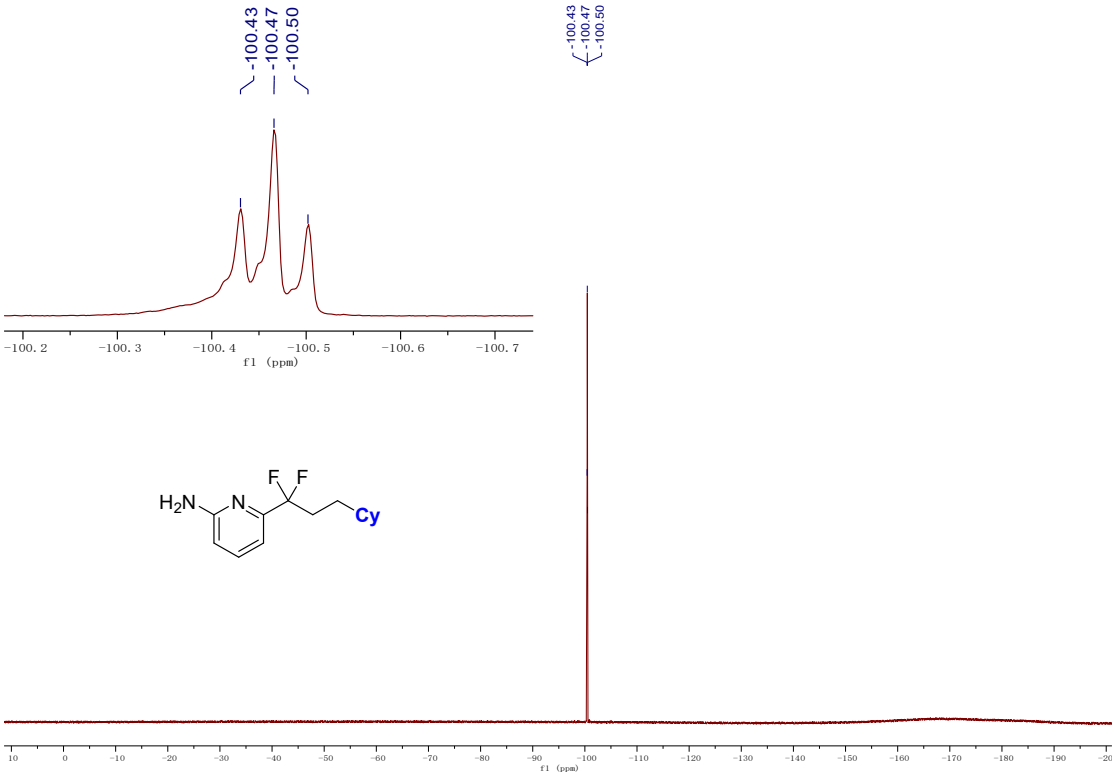
^{19}F NMR of **isopropyl 4-cyclohexyl-2,2-difluorobutanoate** (**2n**) (470 MHz, $CDCl_3$)



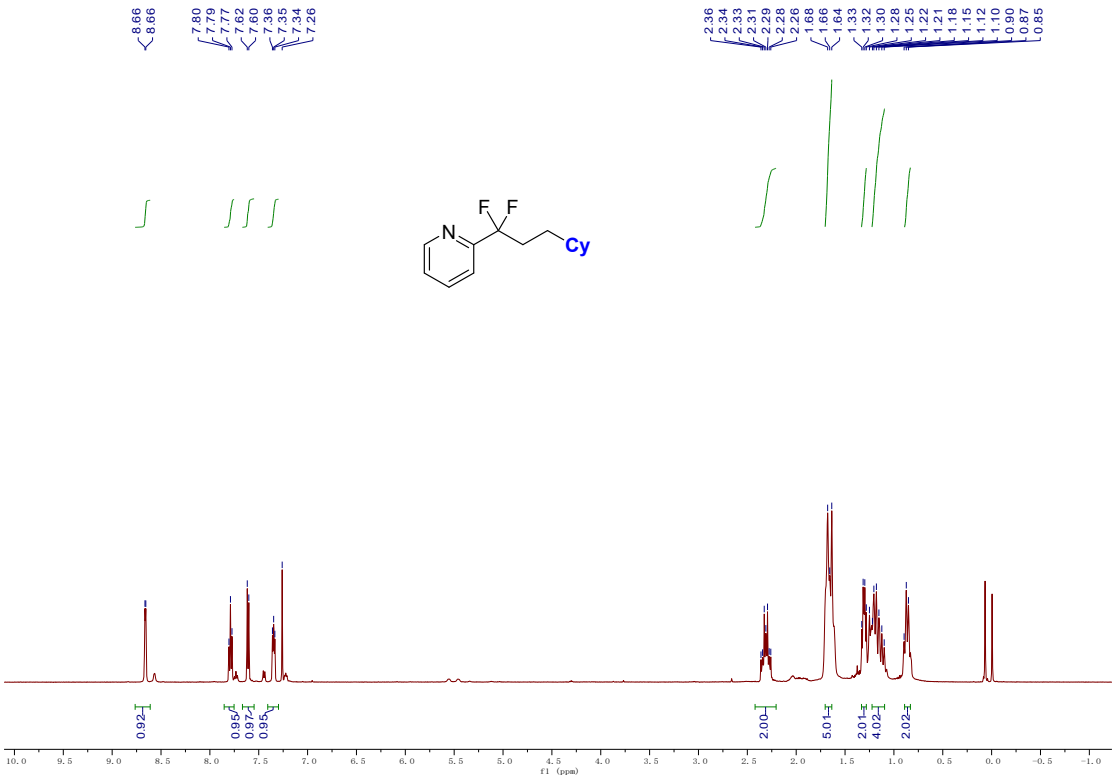
^{1}H NMR of **6-(3-cyclohexyl-1,1-difluoropropyl)pyridin-2-amine** (**2o**) (500 MHz, $CDCl_3$)



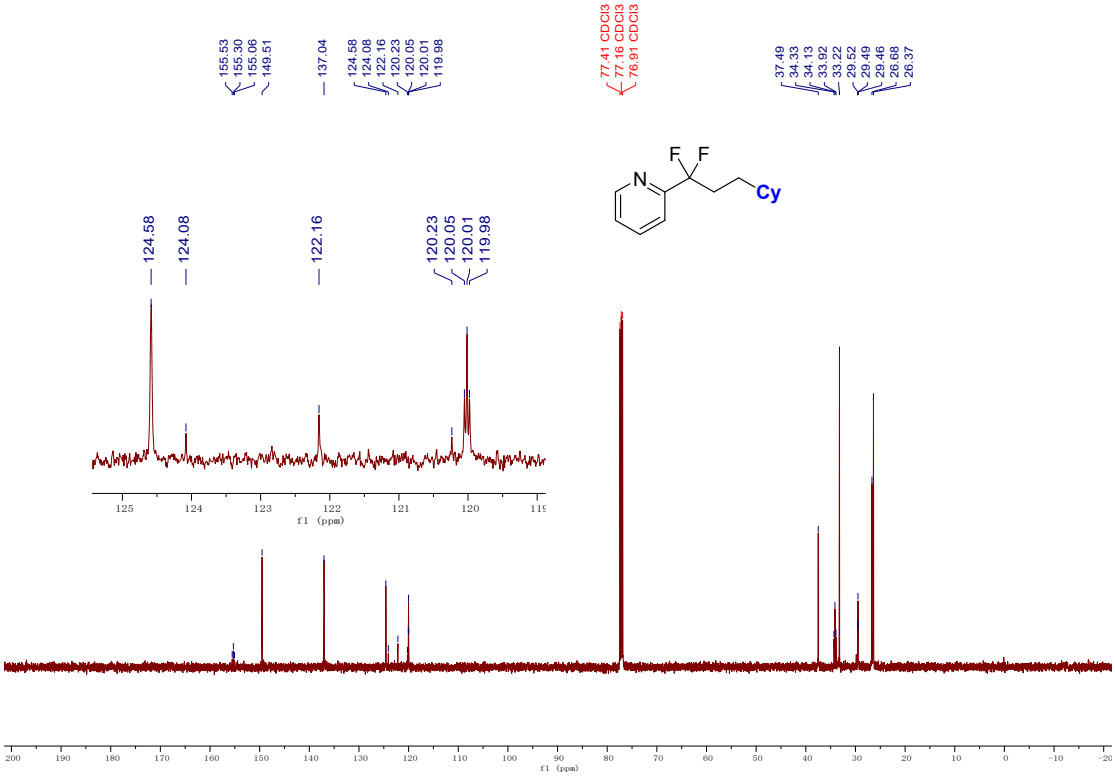
^{19}F NMR of **6-(3-cyclohexyl-1,1-difluoropropyl)pyridin-2-amine** (**2o**) (470 MHz, $CDCl_3$)



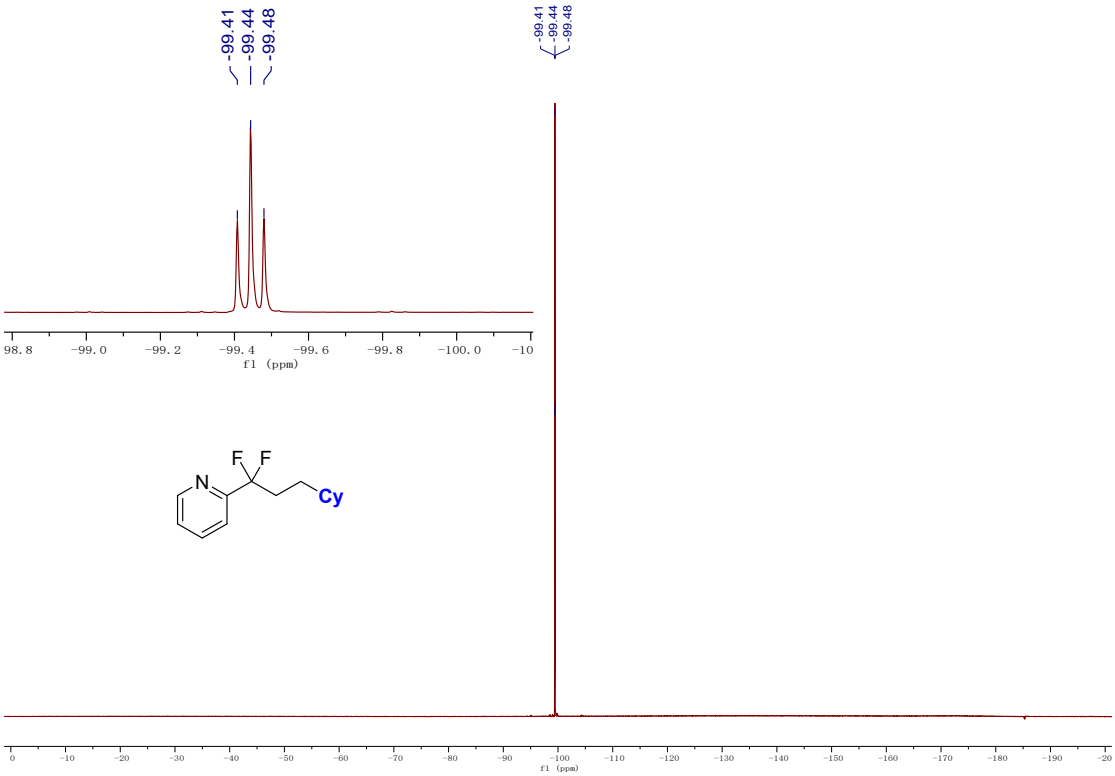
^{1}H NMR of **2-(3-cyclohexyl-1,1-difluoropropyl)pyridine** (**2p**) (500 MHz, $CDCl_3$)



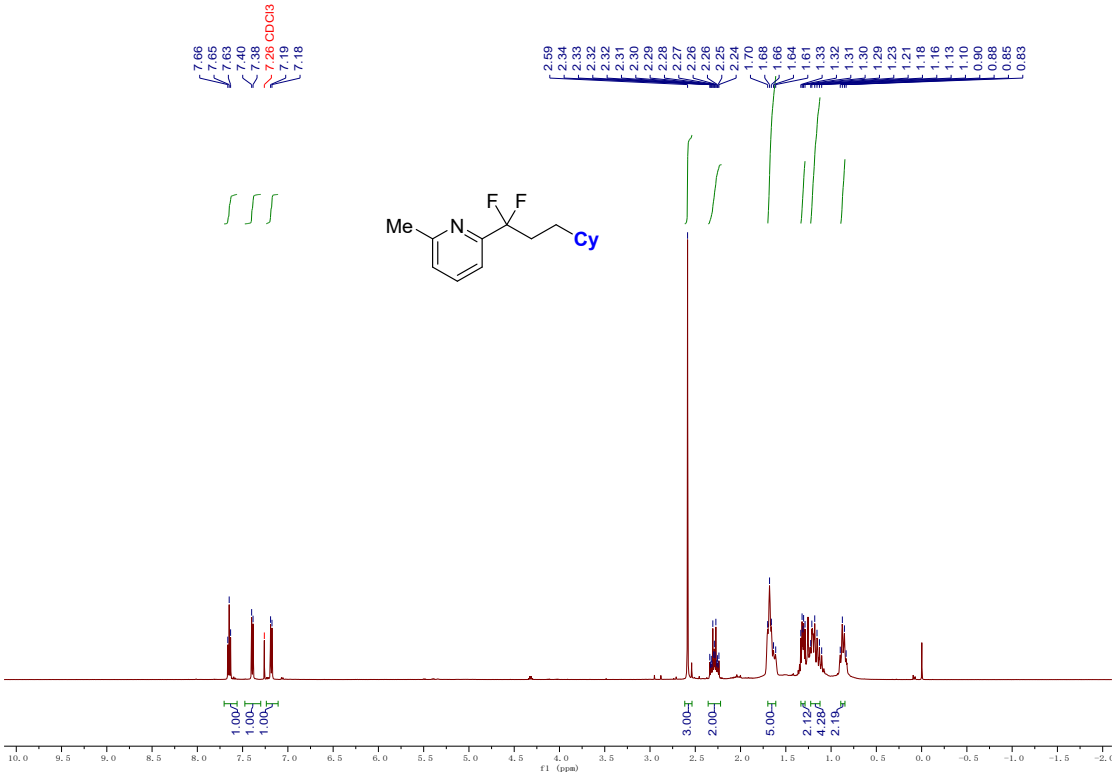
^{13}C NMR of **2-(3-cyclohexyl-1,1-difluoropropyl)pyridine** (**2p**) (126 MHz, $CDCl_3$)



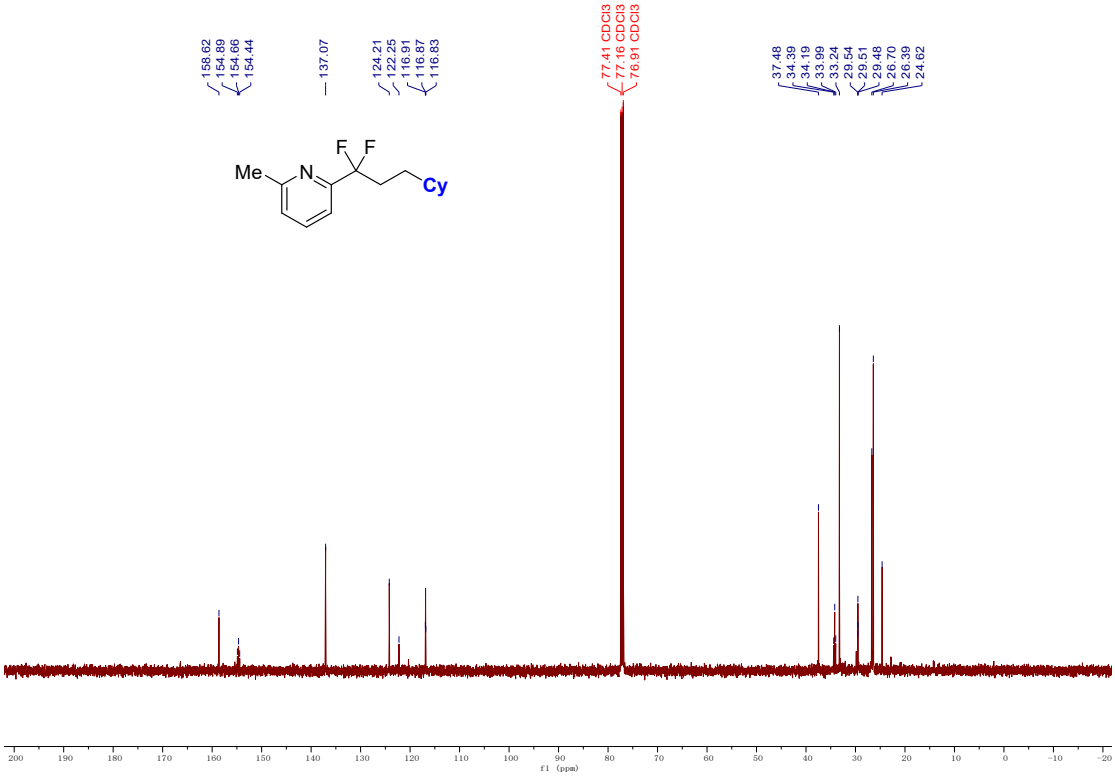
^{19}F NMR of **2-(3-cyclohexyl-1,1-difluoropropyl)pyridine** (**2p**) (470 MHz, $CDCl_3$)



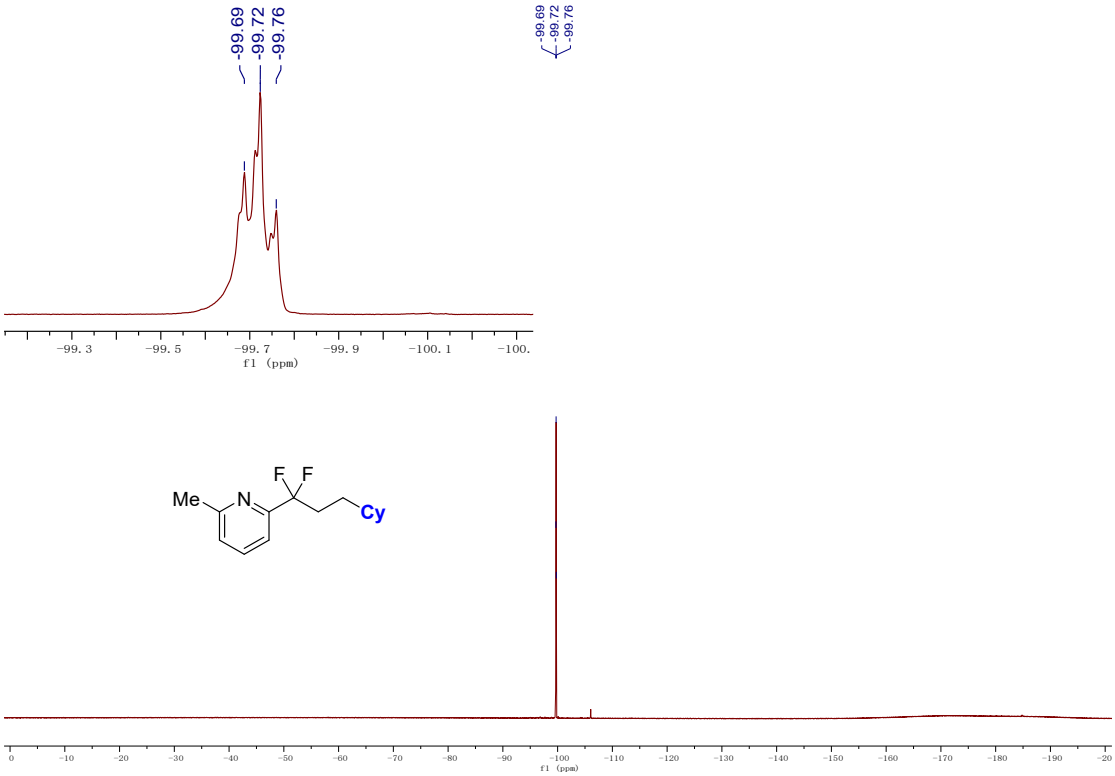
^{1}H NMR of **2-(3-cyclohexyl-1,1-difluoropropyl)-6-methylpyridine** (**2q**) (500 MHz, $CDCl_3$)



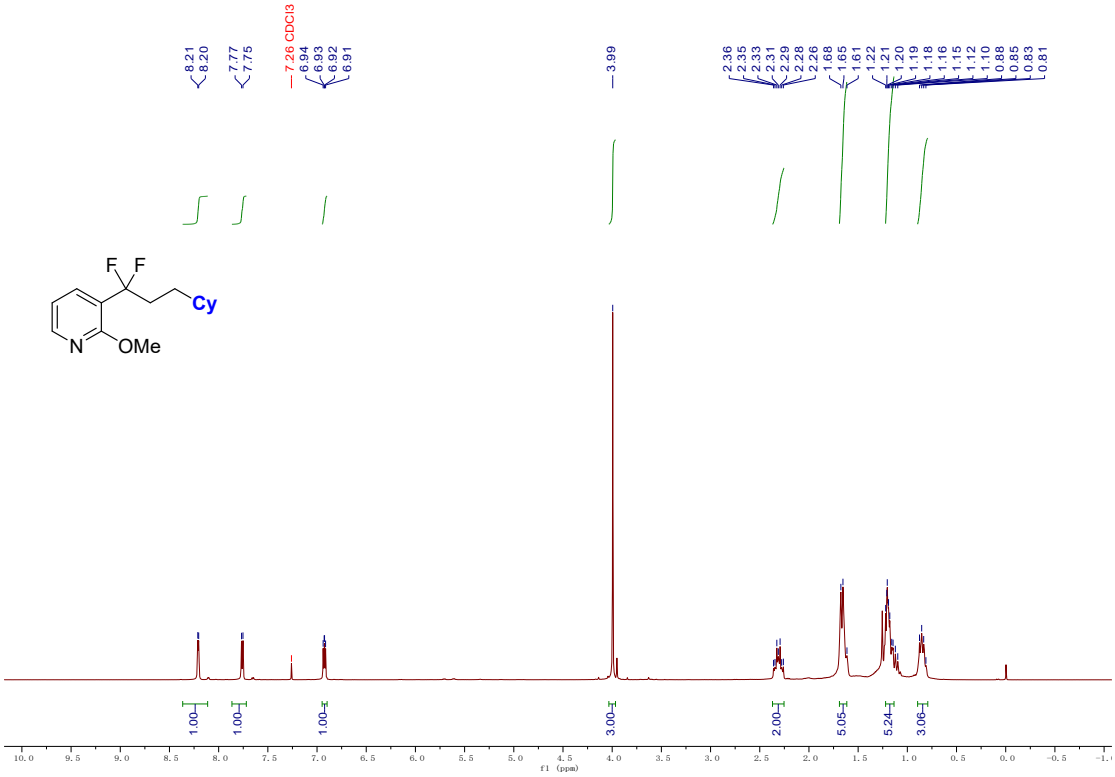
^{13}C NMR of **2-(3-cyclohexyl-1,1-difluoropropyl)-6-methylpyridine** (**2q**) (126 MHz, $CDCl_3$)



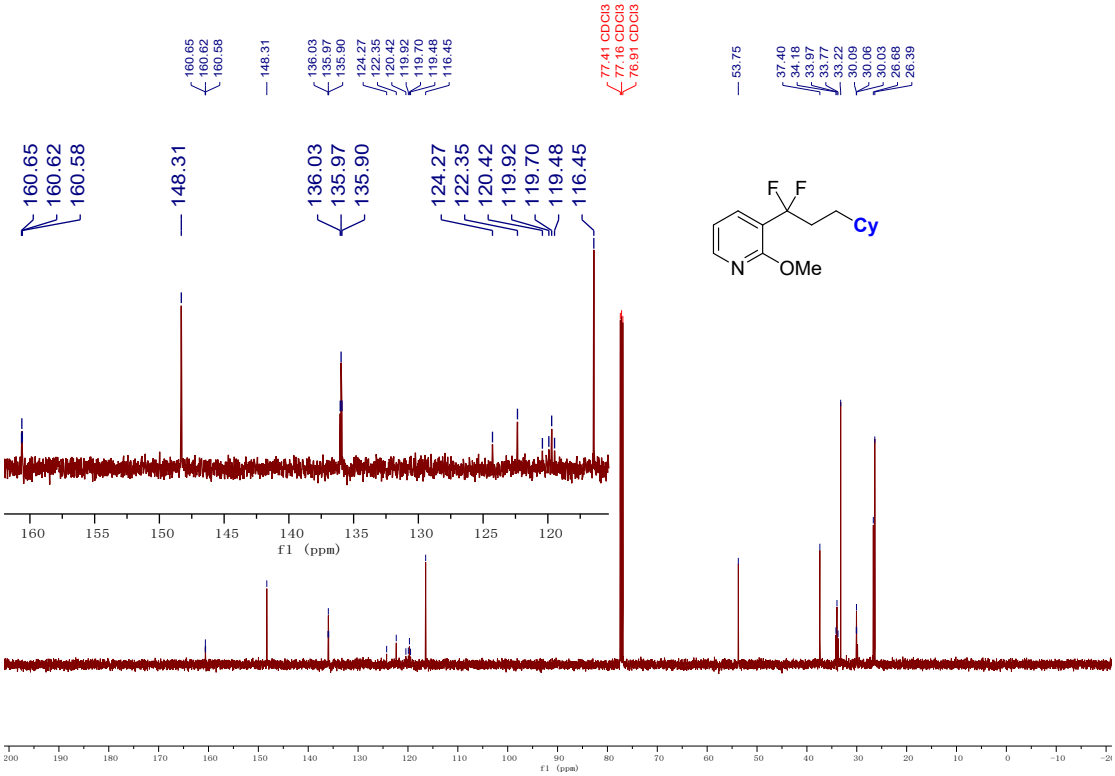
^{19}F NMR of **2-(3-cyclohexyl-1,1-difluoropropyl)-6-methylpyridine** (**2q**) (470 MHz, $CDCl_3$)



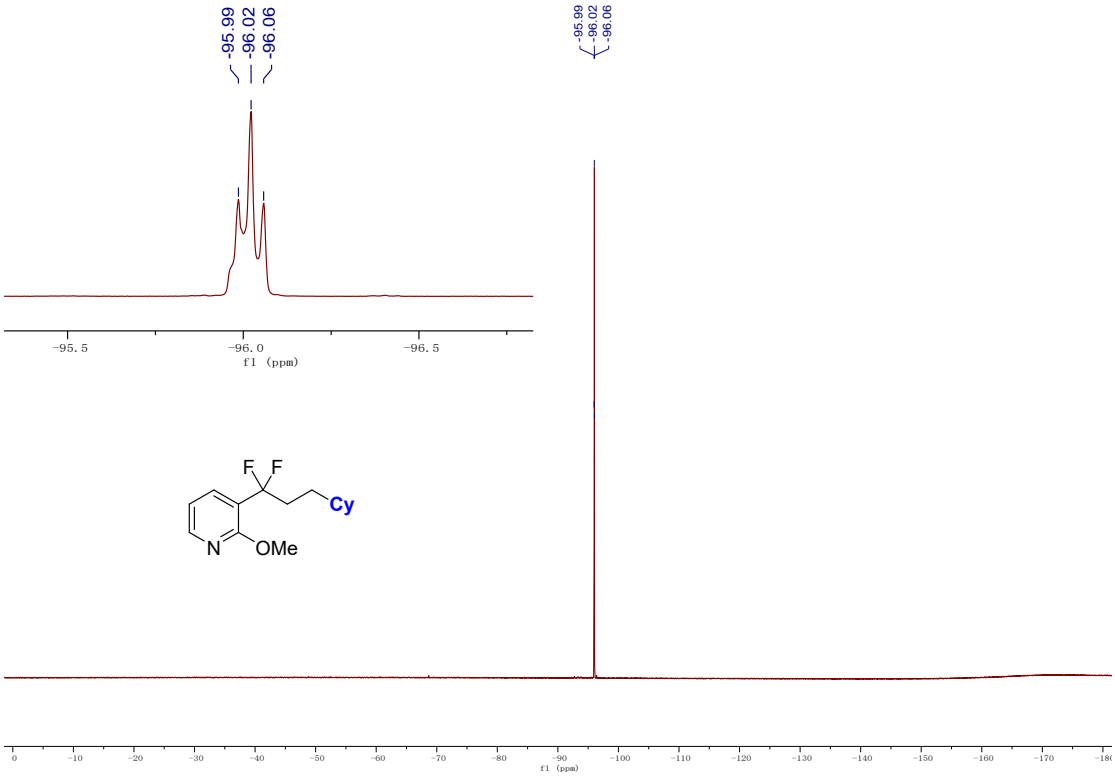
^{1}H NMR of **3-(3-cyclohexyl-1,1-difluoropropyl)-2-methoxypyridine** (**2r**) (500 MHz, $CDCl_3$)



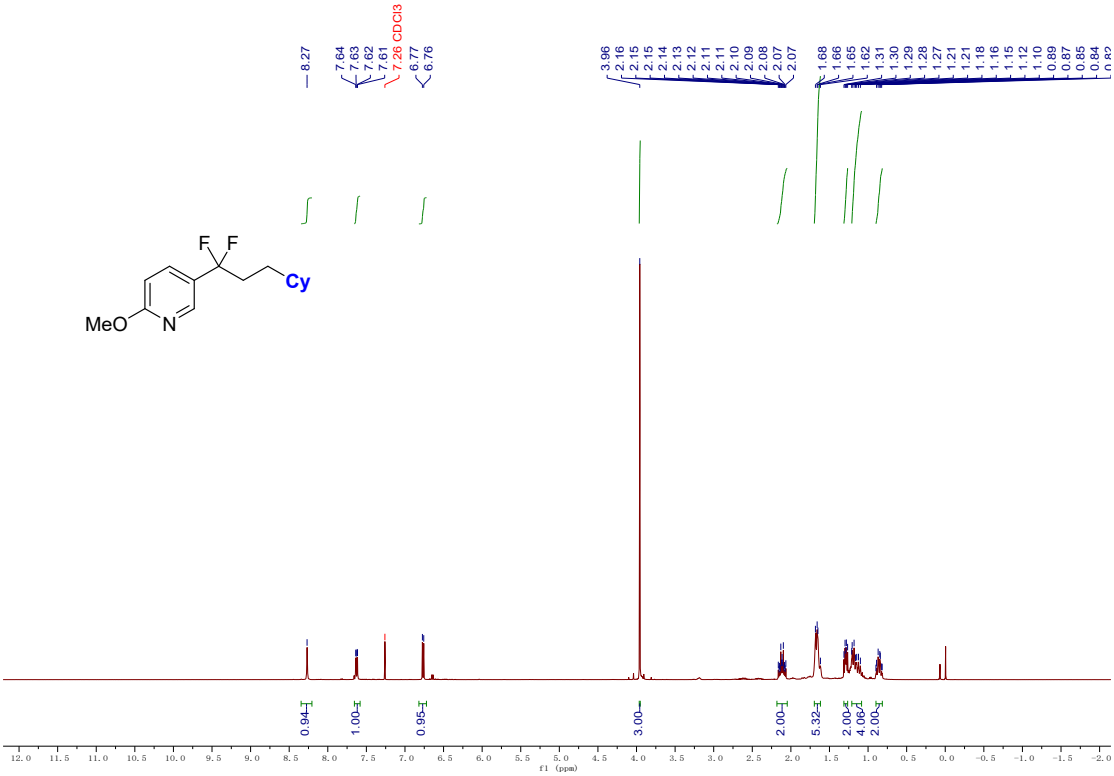
^{13}C NMR of **3-(3-cyclohexyl-1,1-difluoropropyl)-2-methoxypyridine** (**2r**) (126 MHz, $CDCl_3$)



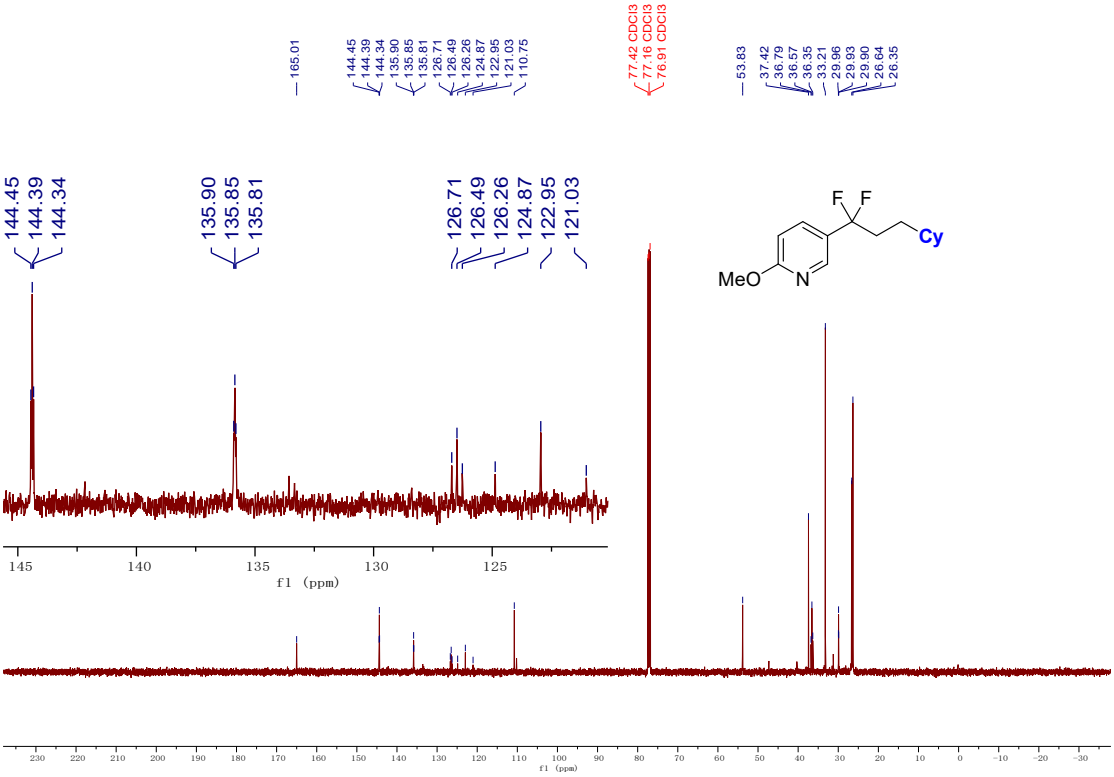
^{19}F NMR of **3-(3-cyclohexyl-1,1-difluoropropyl)-2-methoxypyridine** (**2r**) (470 MHz, $CDCl_3$)



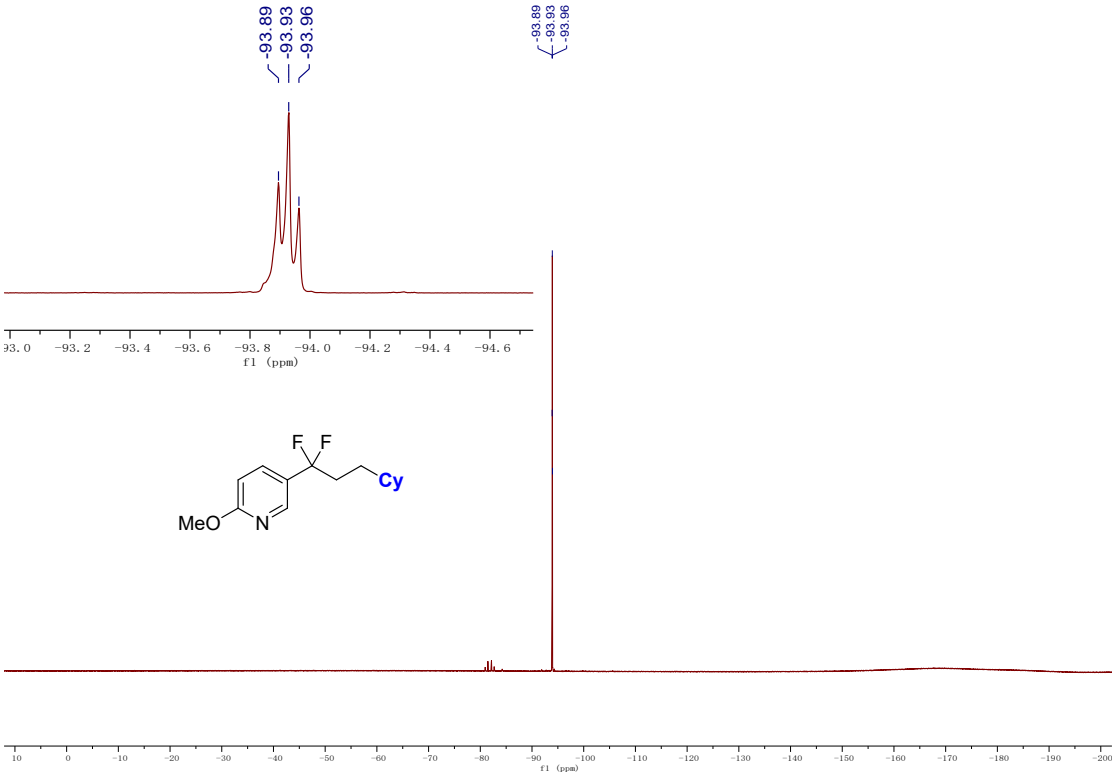
^{1}H NMR of **5-(3-cyclohexyl-1,1-difluoropropyl)-2-methoxypyridine** (**2s**) (500 MHz, $CDCl_3$)



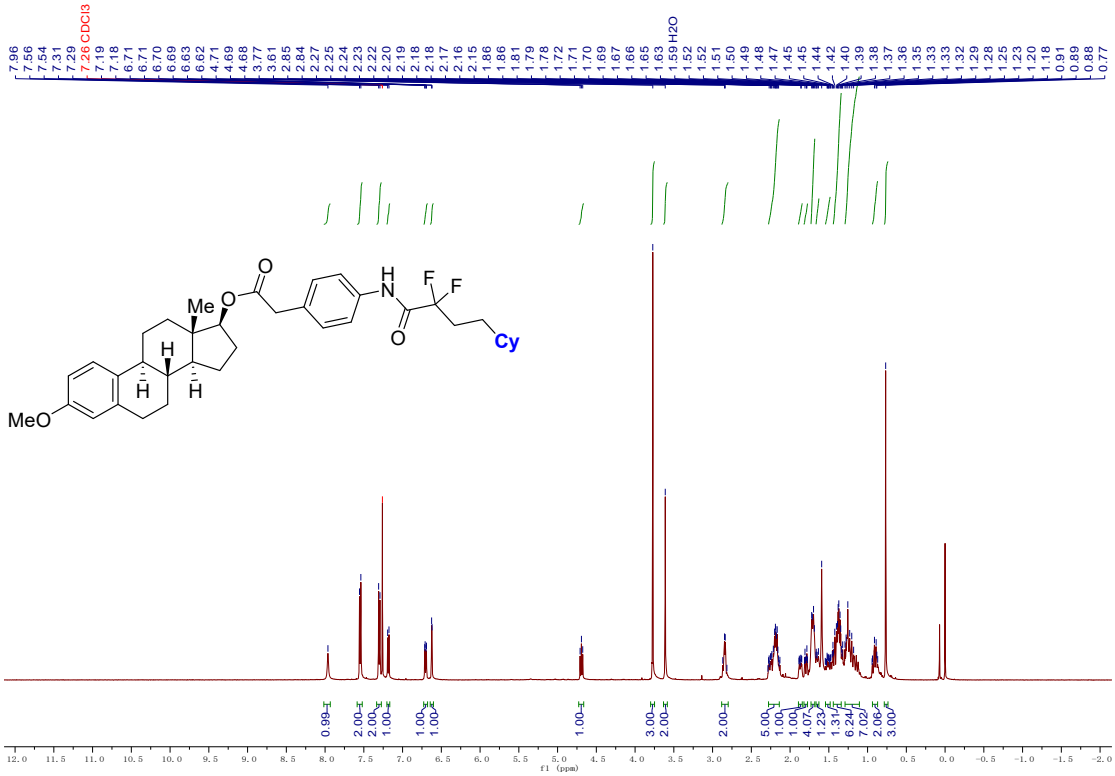
^{13}C NMR of **5-(3-cyclohexyl-1,1-difluoropropyl)-2-methoxypyridine** (**2s**) (126 MHz, $CDCl_3$)



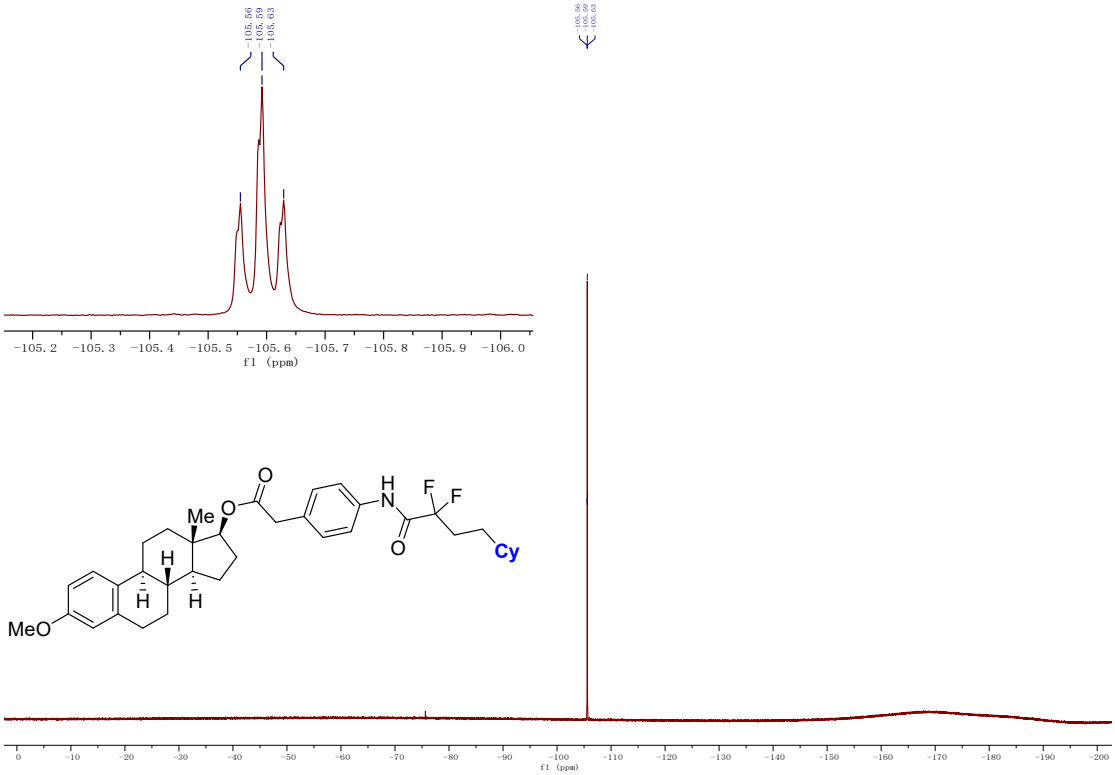
^{19}F NMR of **5-(3-cyclohexyl-1,1-difluoropropyl)-2-methoxypyridine** (**2s**) (470 MHz, $CDCl_3$)



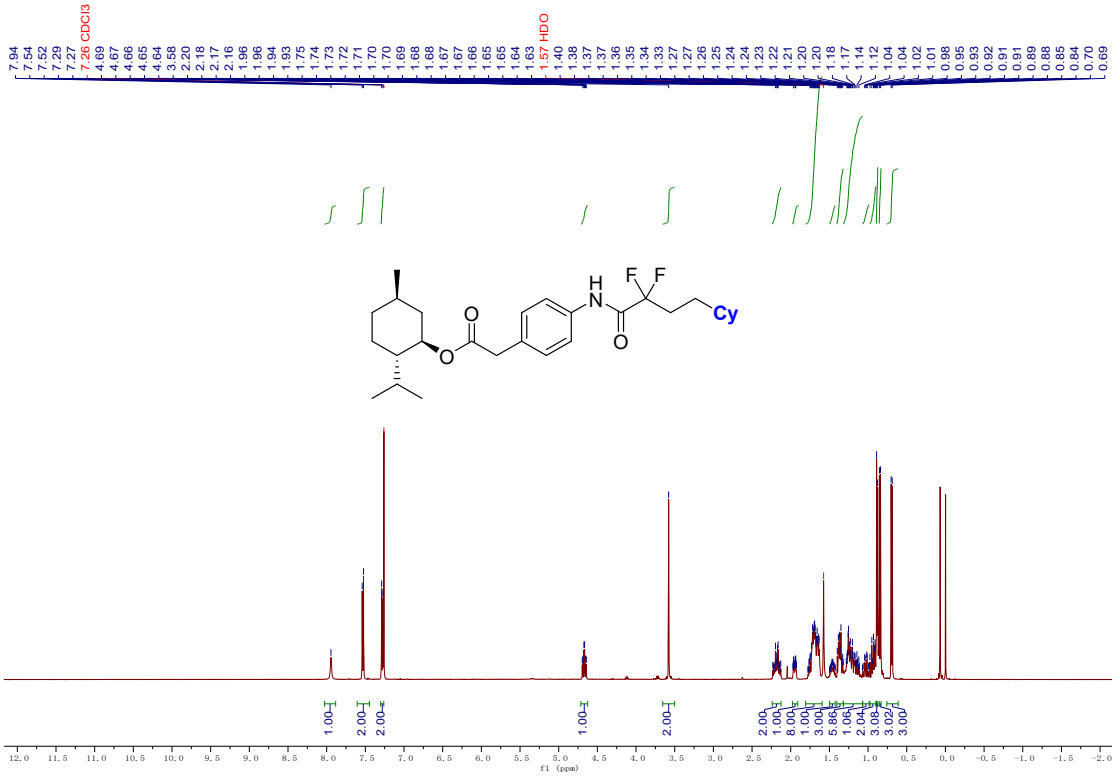
^{1}H NMR of **(8*R*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl 2-(4-(4-cyclohexyl-2,2-difluorobutanamido)phenyl)acetate** (**2t**) (500 MHz, $CDCl_3$)



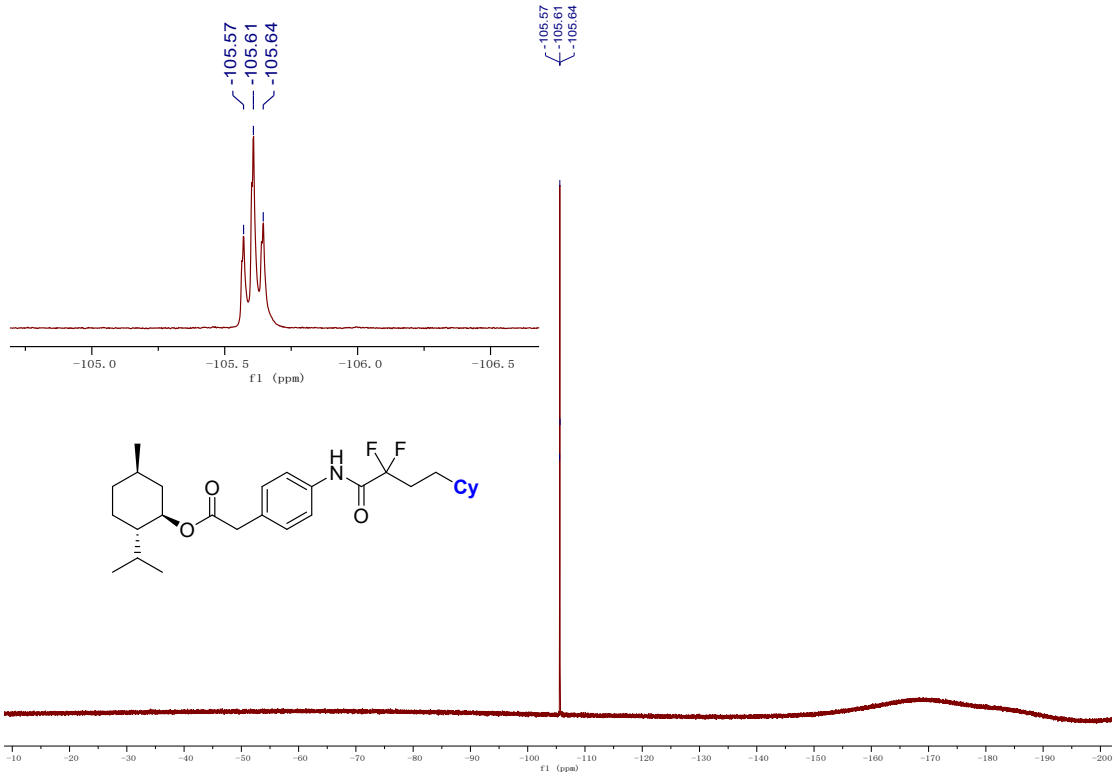
^{19}F NMR of **(8*R*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl 2-(4-(4-cyclohexyl-2,2-difluorobutanamido)phenyl)acetate** (**2t**) (470 MHz, $CDCl_3$)



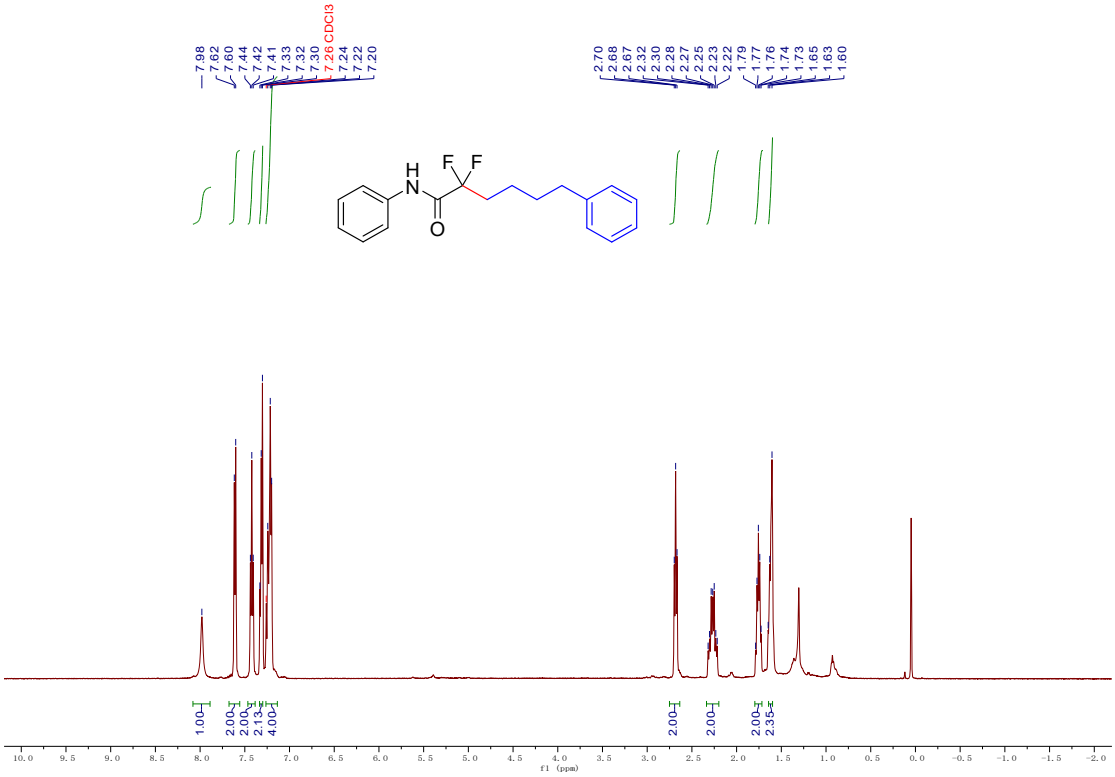
^{1}H NMR of **(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(4-(4-cyclohexyl-2,2-difluorobutanamido)phenyl) acetate** (**2u**) (500 MHz, $CDCl_3$)



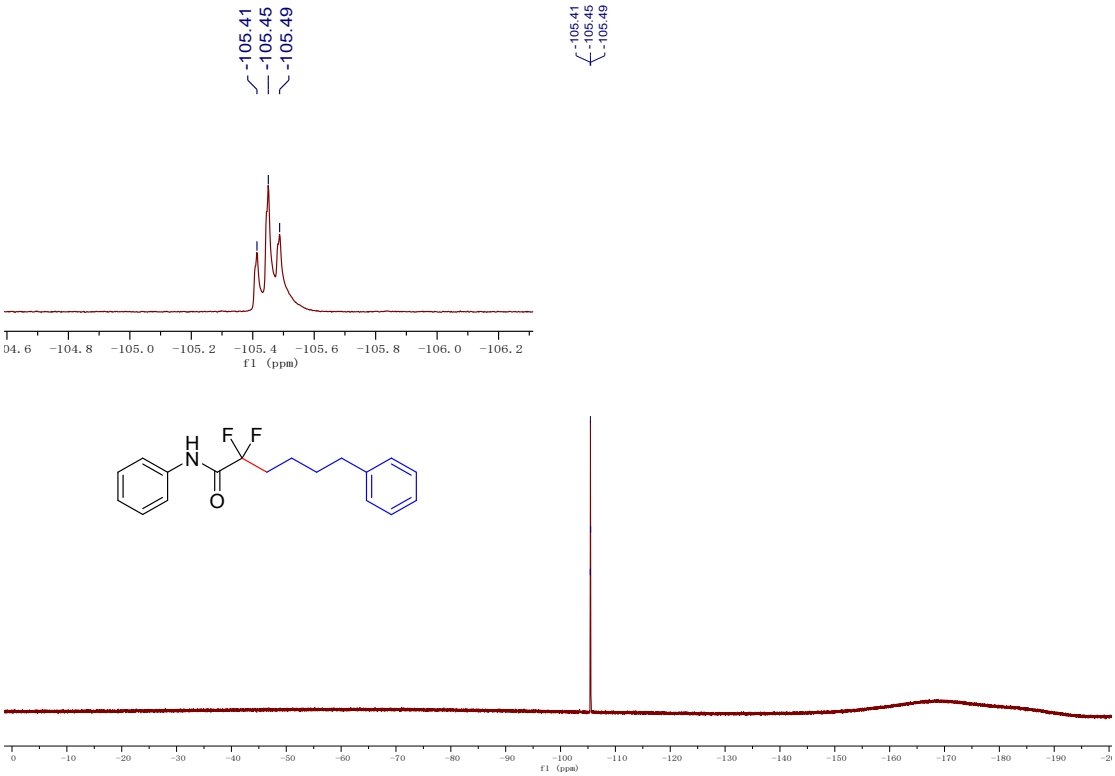
^{19}F NMR of **(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(4-(4-cyclohexyl-2,2-difluorobutanamido)phenyl) acetate** (**2u**) (470 MHz, $CDCl_3$)



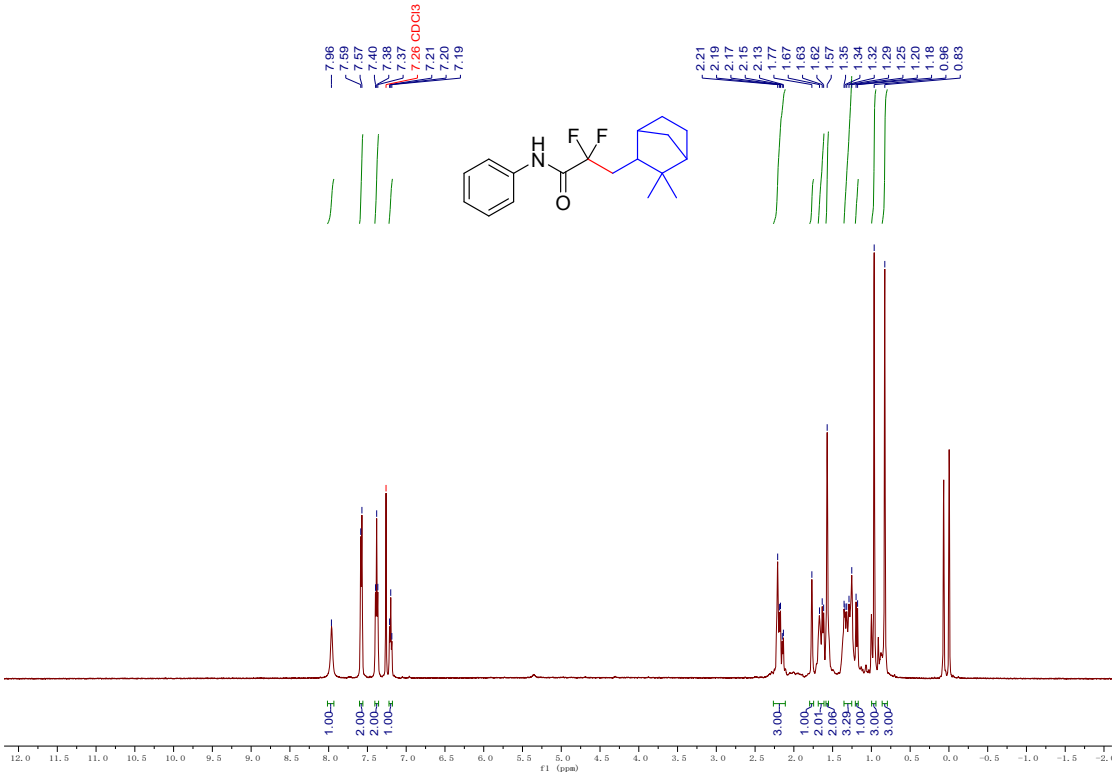
^{1}H NMR of **2,2-difluoro-*N*,6-diphenylhexanamide** (**2v**) (500 MHz, $CDCl_3$)



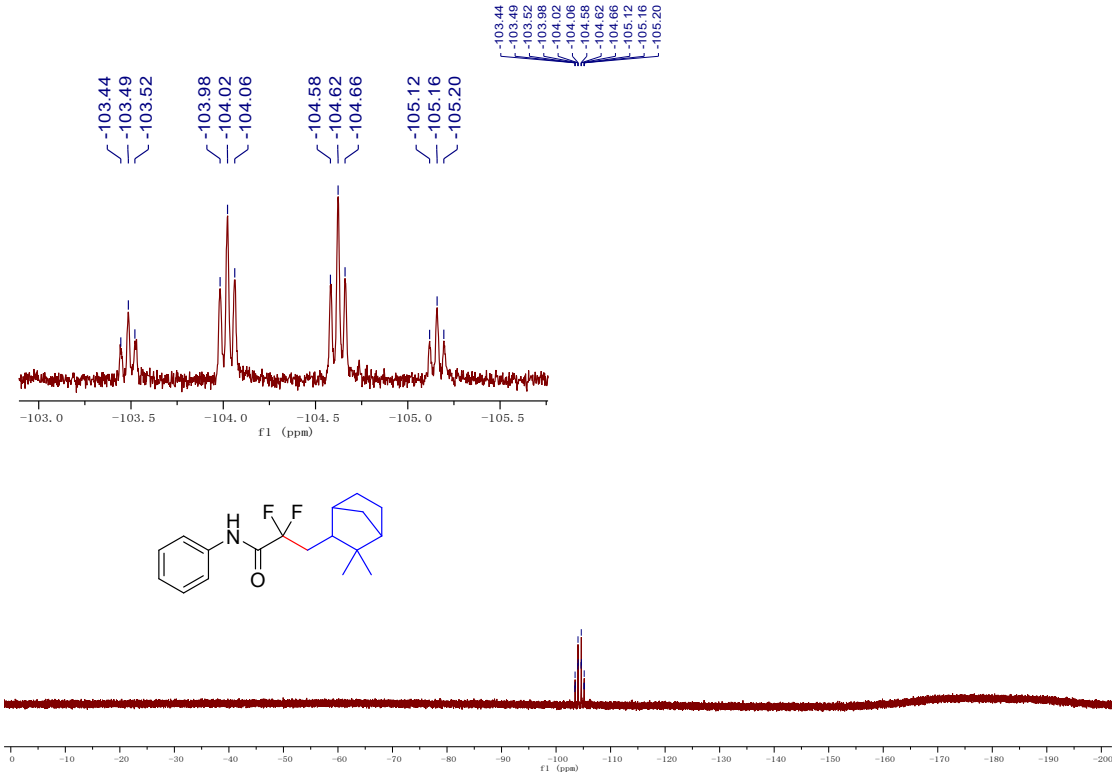
^{19}F NMR of **2,2-difluoro-*N*,6-diphenylhexanamide** (**2v**) (470 MHz, $CDCl_3$)



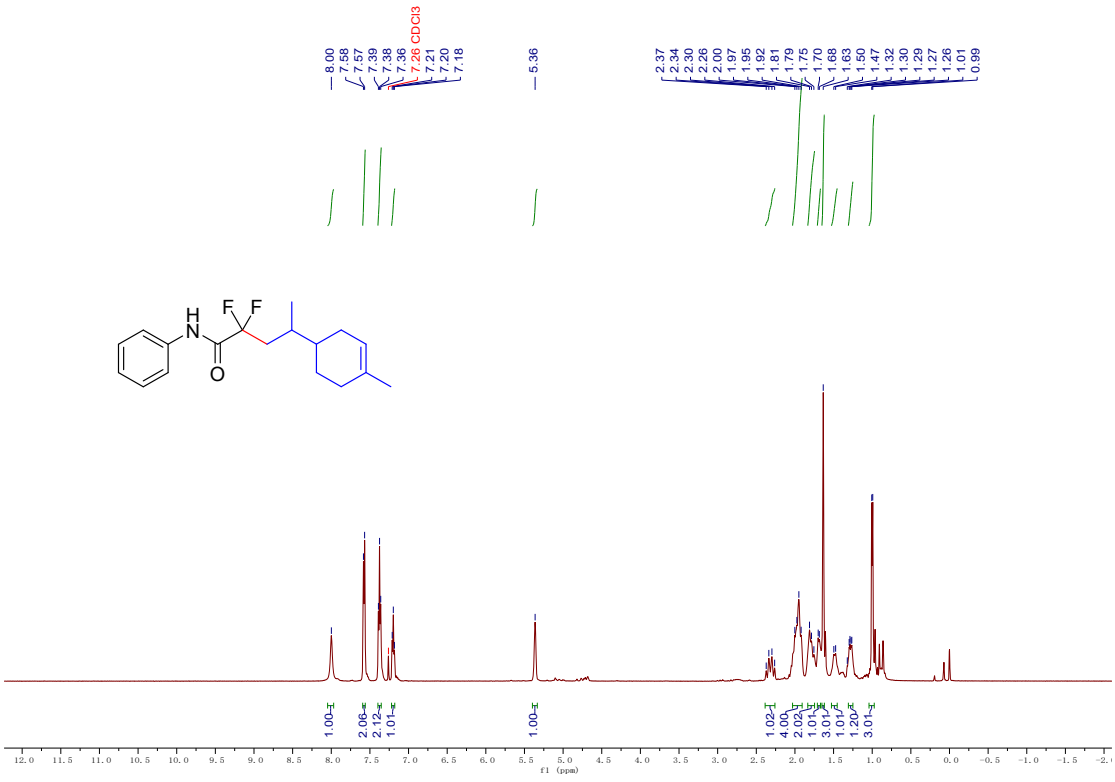
^{1}H NMR of **3-(3,3-dimethylbicyclo[2.2.1]heptan-2-yl)-2,2-difluoro-*N*-phenylpropanamide** (**2w**) (500 MHz, $CDCl_3$)



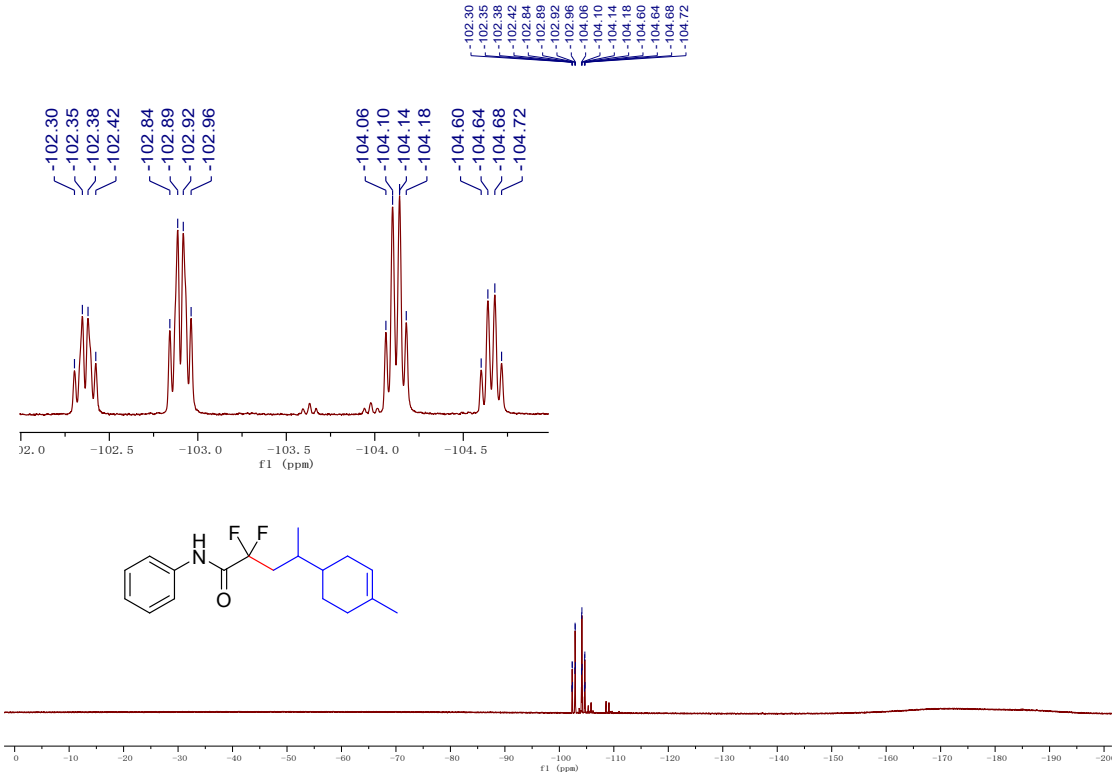
^{19}F NMR of **3-(3,3-dimethylbicyclo[2.2.1]heptan-2-yl)-2,2-difluoro-*N*-phenylpropanamide** (**2w**) (470 MHz, $CDCl_3$)



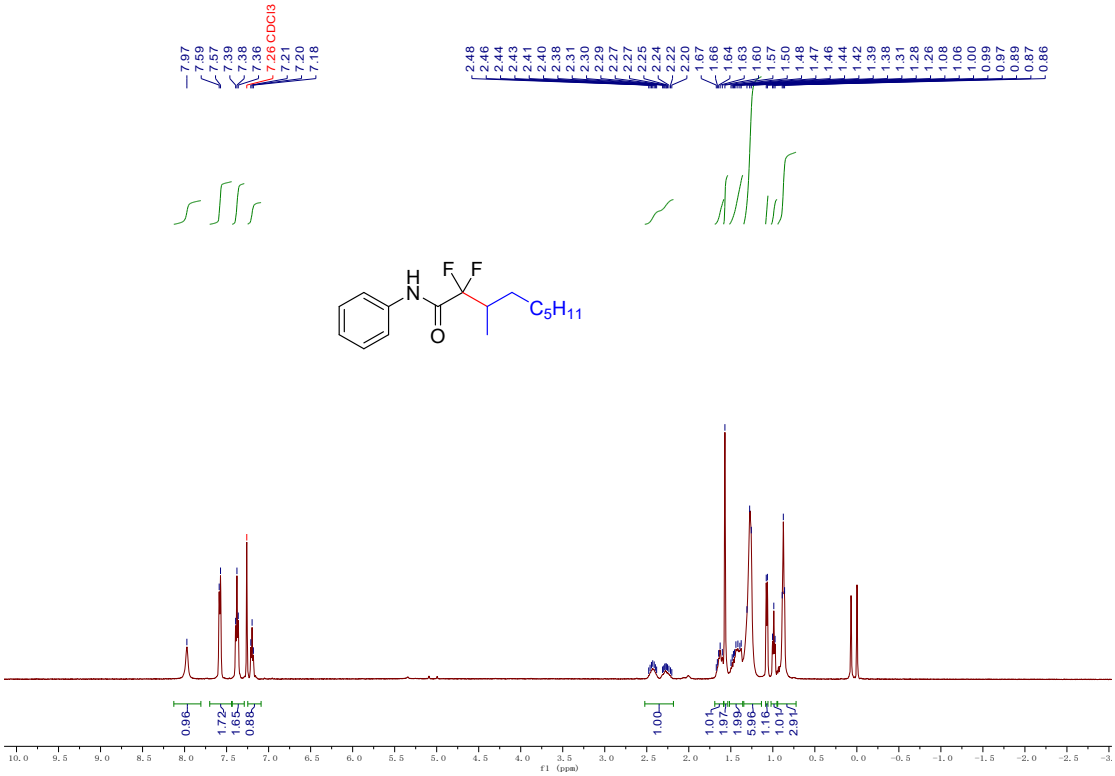
^{1}H NMR of **2,2-difluoro-4-(4-methylcyclohex-3-en-1-yl)-*N*-phenylpentanamide** (**2x**) (500 MHz, $CDCl_3$)



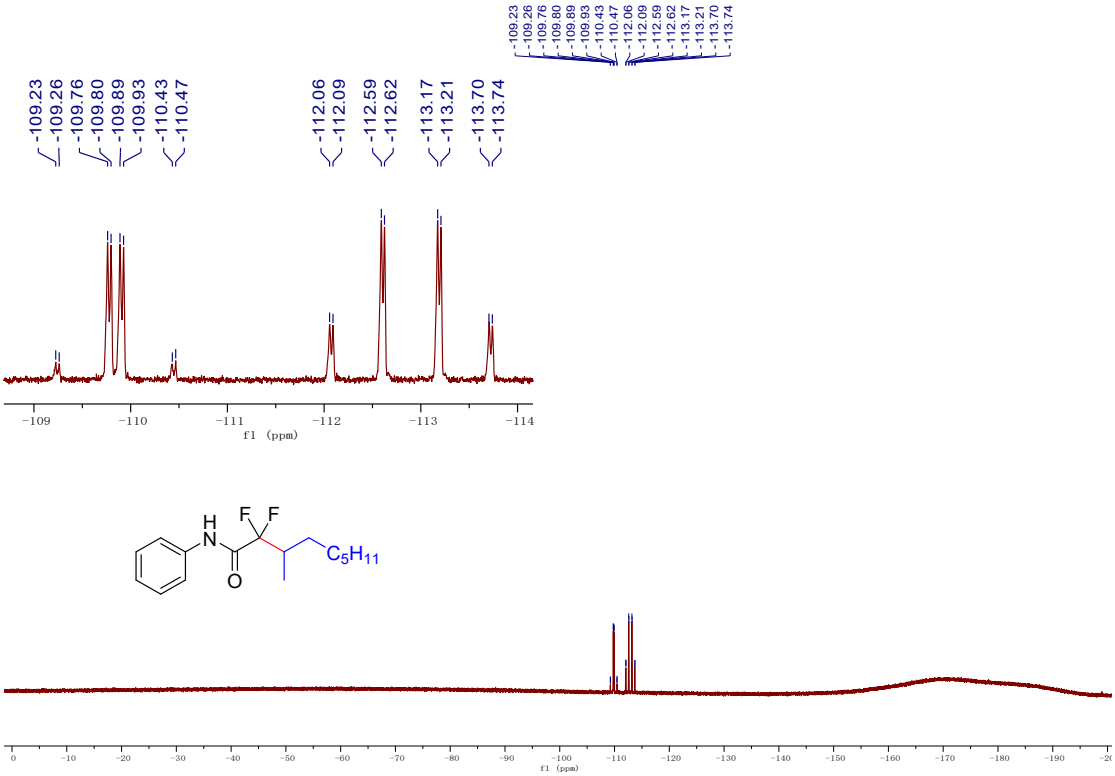
^{19}F NMR of **2,2-difluoro-4-(4-methylcyclohex-3-en-1-yl)-*N*-phenylpentanamide** (**2x**) (470 MHz, $CDCl_3$)



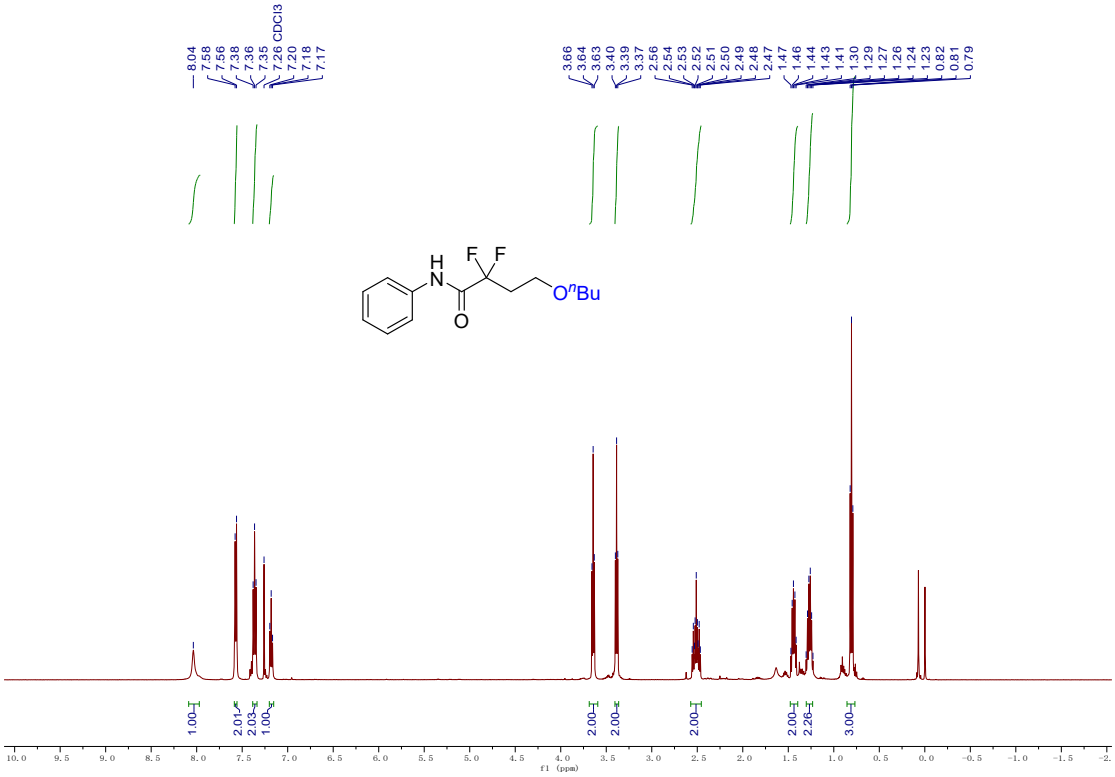
^{1}H NMR of **2,2-difluoro-3-methyl-*N*-phenylnonanamide** (**2y**) (500 MHz, $CDCl_3$)



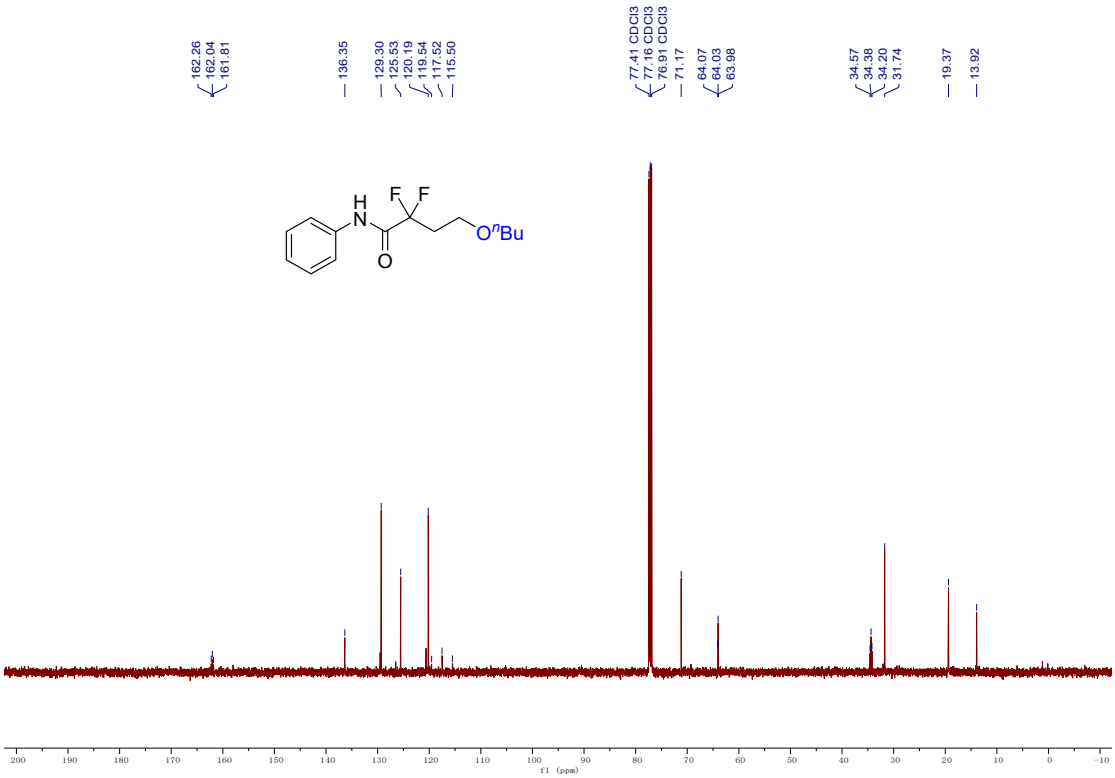
^{19}F NMR of **2,2-difluoro-3-methyl-*N*-phenylnonanamide** (**2y**) (470 MHz, $CDCl_3$)



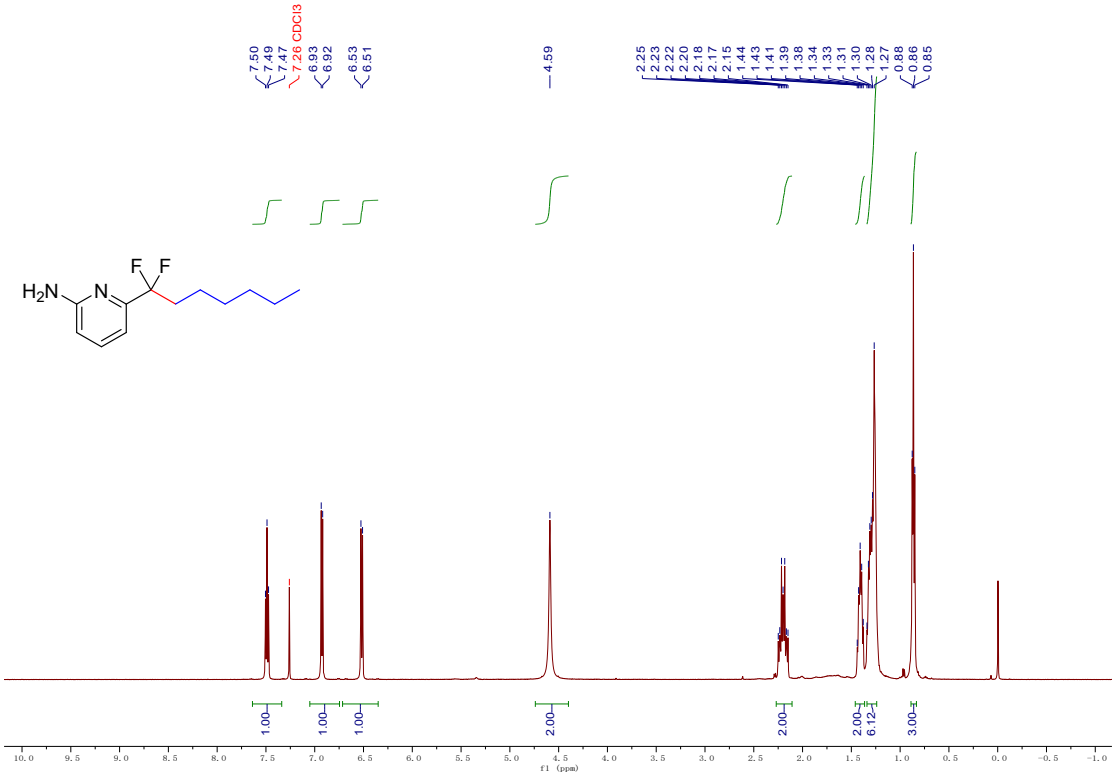
^{1}H NMR of **4-butoxy-2,2-difluoro-*N*-phenylbutanamide (2z)** (500 MHz, $CDCl_3$)



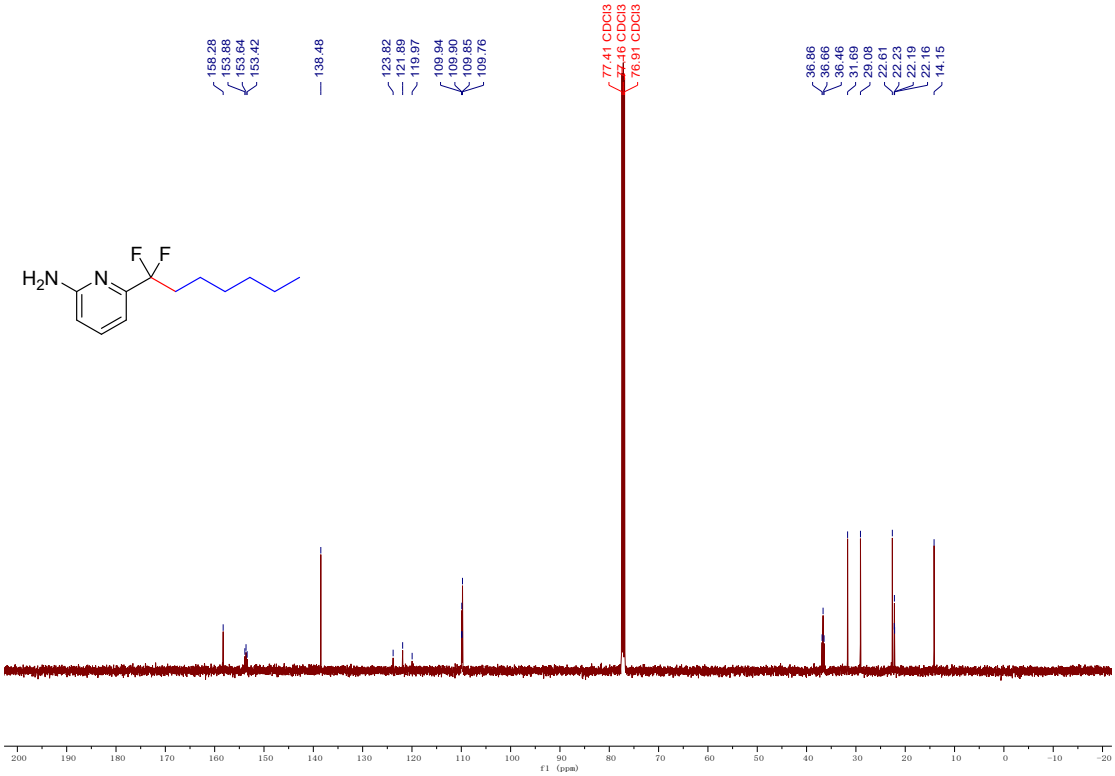
^{13}C NMR of **4-butoxy-2,2-difluoro-*N*-phenylbutanamide (2z)** (126 MHz, $CDCl_3$)



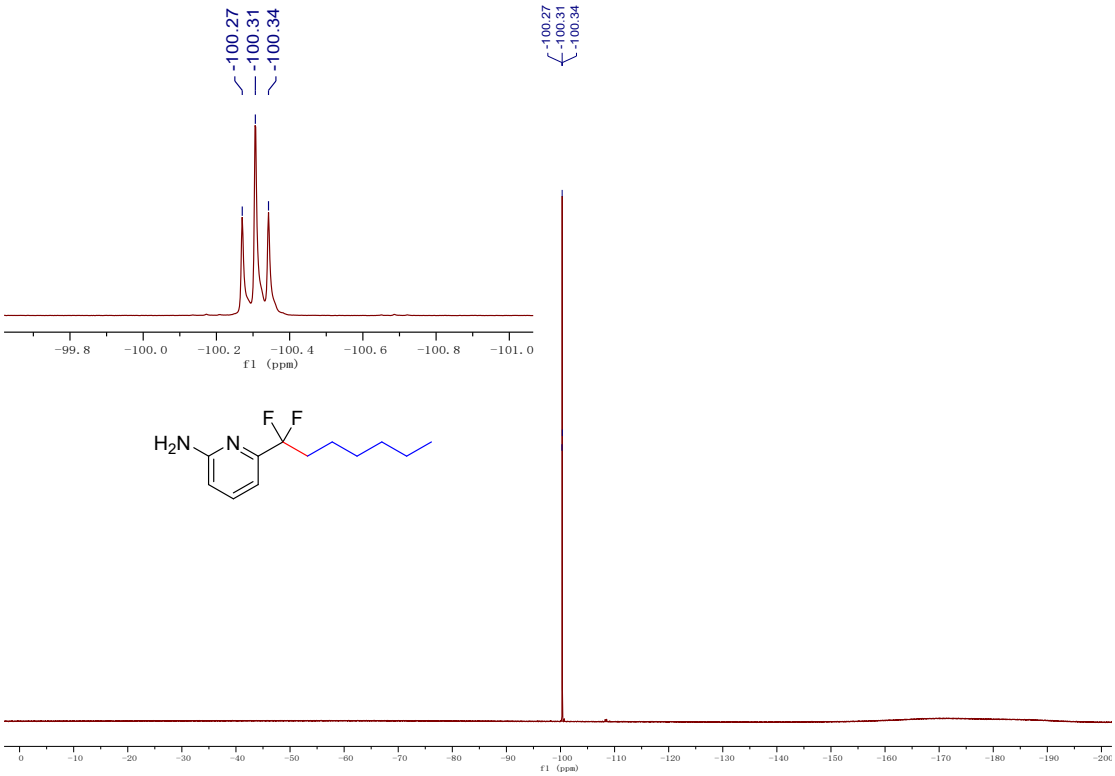
^{1}H NMR of **6-(1,1-difluoroheptyl)pyridin-2-amine** (**2aa**) (500 MHz, $CDCl_3$)



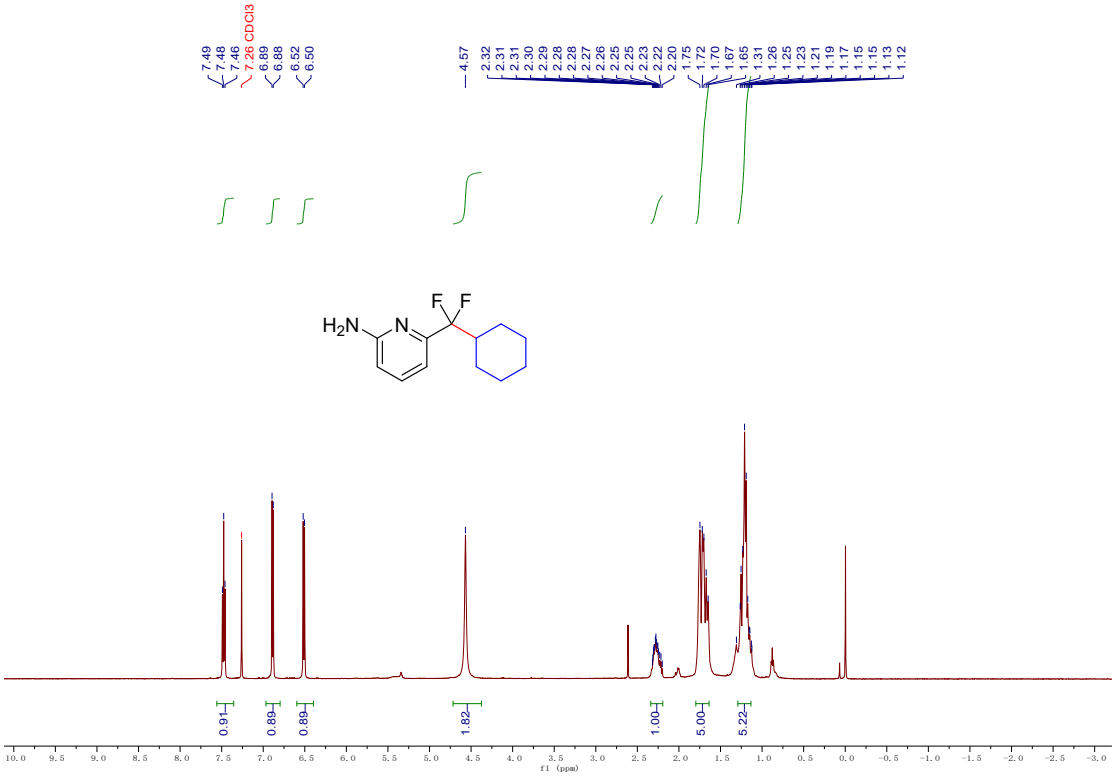
^{13}C NMR of **6-(1,1-difluoroheptyl)pyridin-2-amine** (**2aa**) (126 MHz, $CDCl_3$)



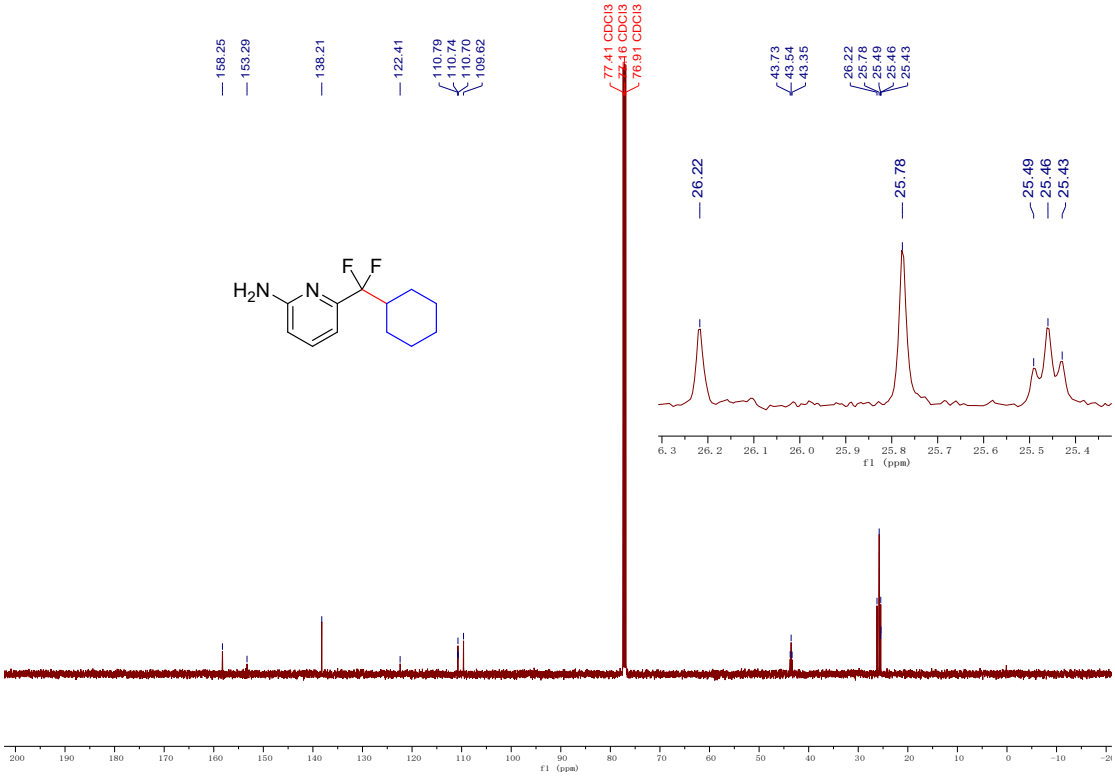
^{19}F NMR of **6-(1,1-difluoroheptyl)pyridin-2-amine** (**2aa**) (470 MHz, $CDCl_3$)



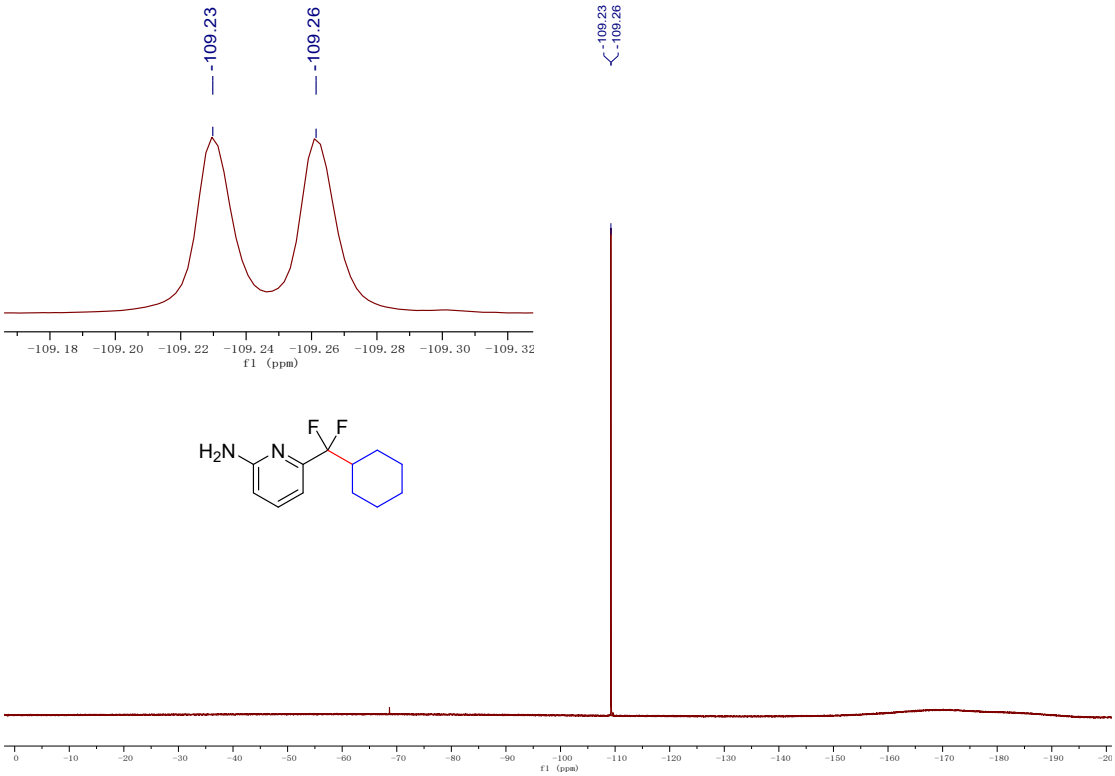
^{1}H NMR of **6-(cyclohexyldifluoromethyl)pyridin-2-amine** (**2ab**) (500 MHz, $CDCl_3$)



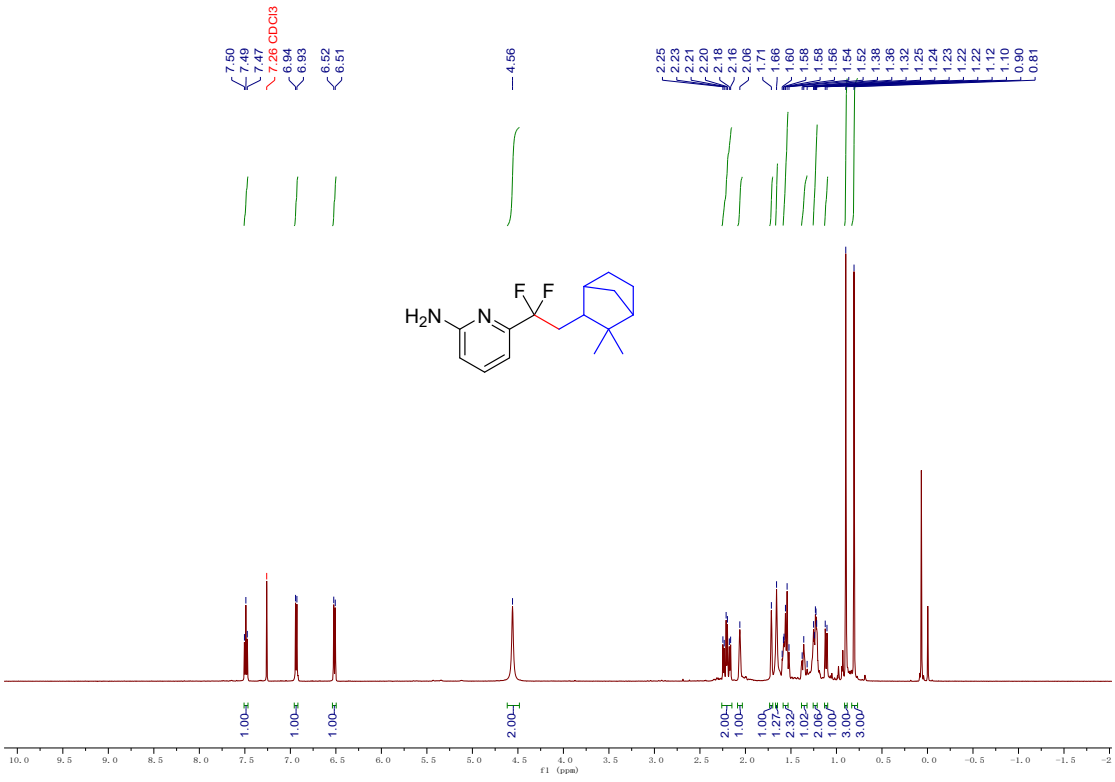
^{13}C NMR of **6-(cyclohexyldifluoromethyl)pyridin-2-amine** (**2ab**) (126 MHz, $CDCl_3$)



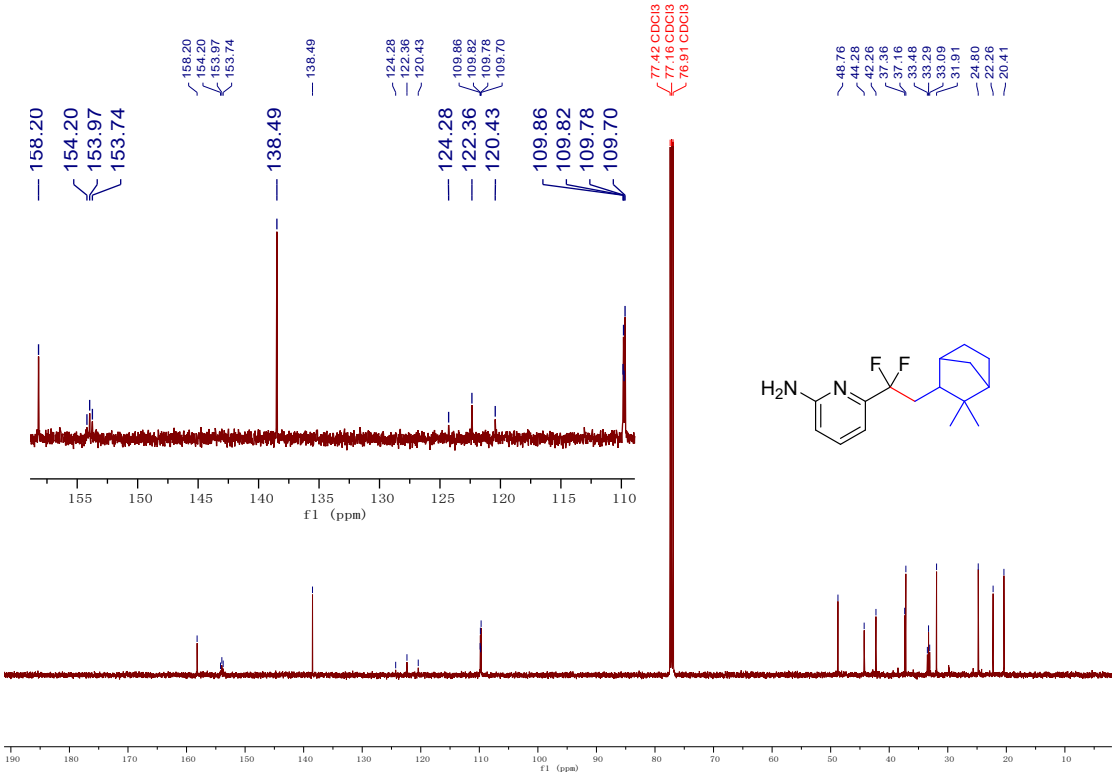
^{19}F NMR of **6-(cyclohexyldifluoromethyl)pyridin-2-amine** (**2ab**) (470 MHz, $CDCl_3$)



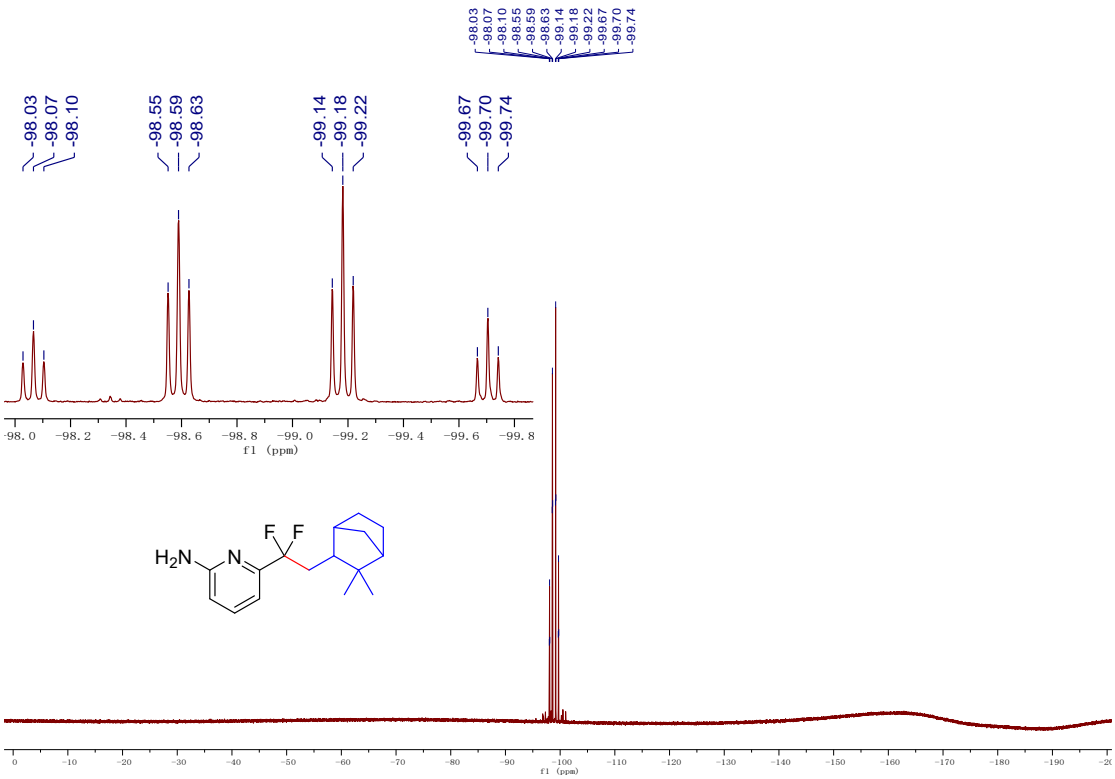
^{1}H NMR of **6-(2-(3,3-dimethylbicyclo[2.2.1]heptan-2-yl)-1,1-difluoroethyl)pyridin-2-amine** (**2ac**) (500 MHz, $CDCl_3$)



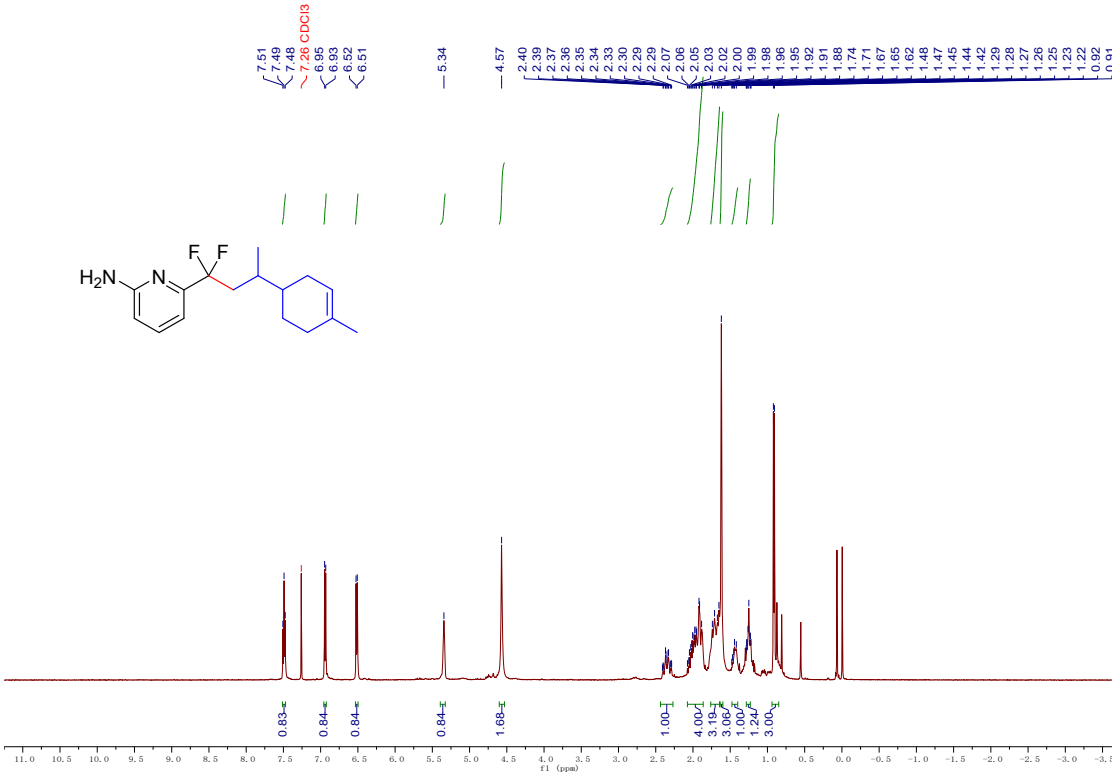
^{13}C NMR of **6-(2-(3,3-dimethylbicyclo[2.2.1]heptan-2-yl)-1,1-difluoroethyl)pyridin-2-amine** (**2ac**) (126 MHz, $CDCl_3$)



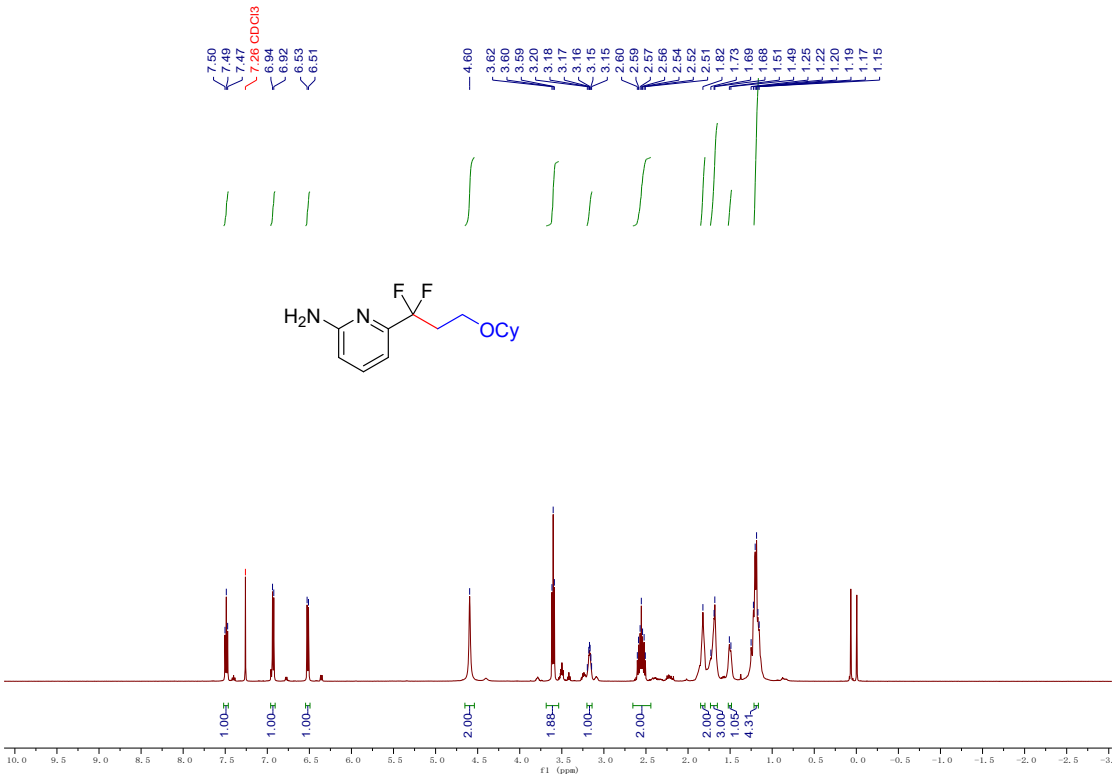
^{19}F NMR of **6-(2-(3,3-dimethylbicyclo[2.2.1]heptan-2-yl)-1,1-difluoroethyl)pyridin-2-amine** (**2ac**) (470 MHz, $CDCl_3$)



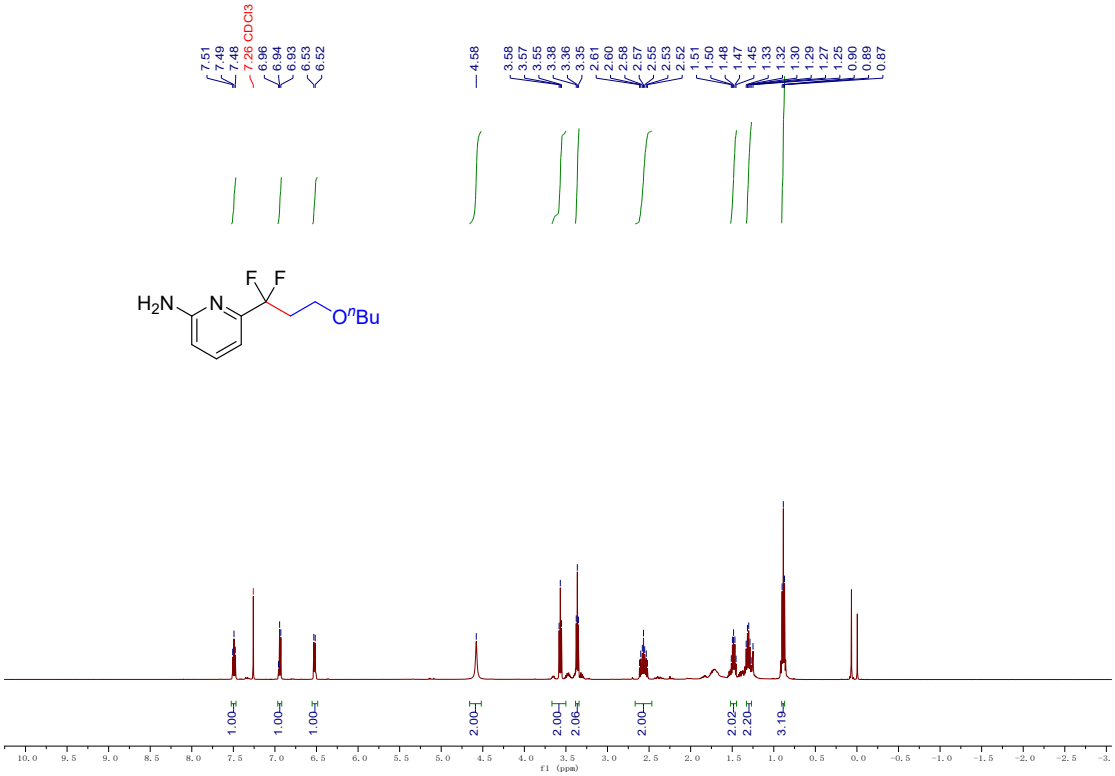
^{1}H NMR of **6-(1,1-difluoro-3-(4-methylcyclohex-3-en-1-yl)butyl)pyridin-2-amine** (**2ad**) (500 MHz, $CDCl_3$)



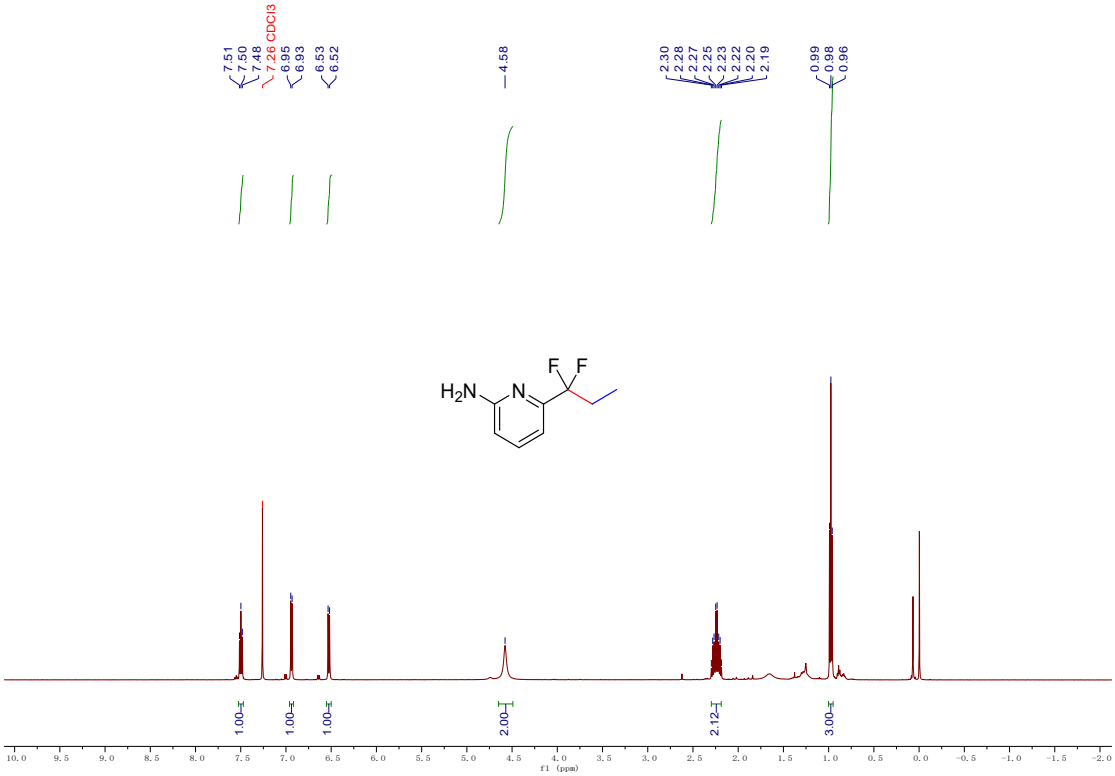
^{1}H NMR of **6-(3-(cyclohexyloxy)-1-fluoropropyl)pyridin-2-amine (2ae)** (500 MHz, $CDCl_3$)



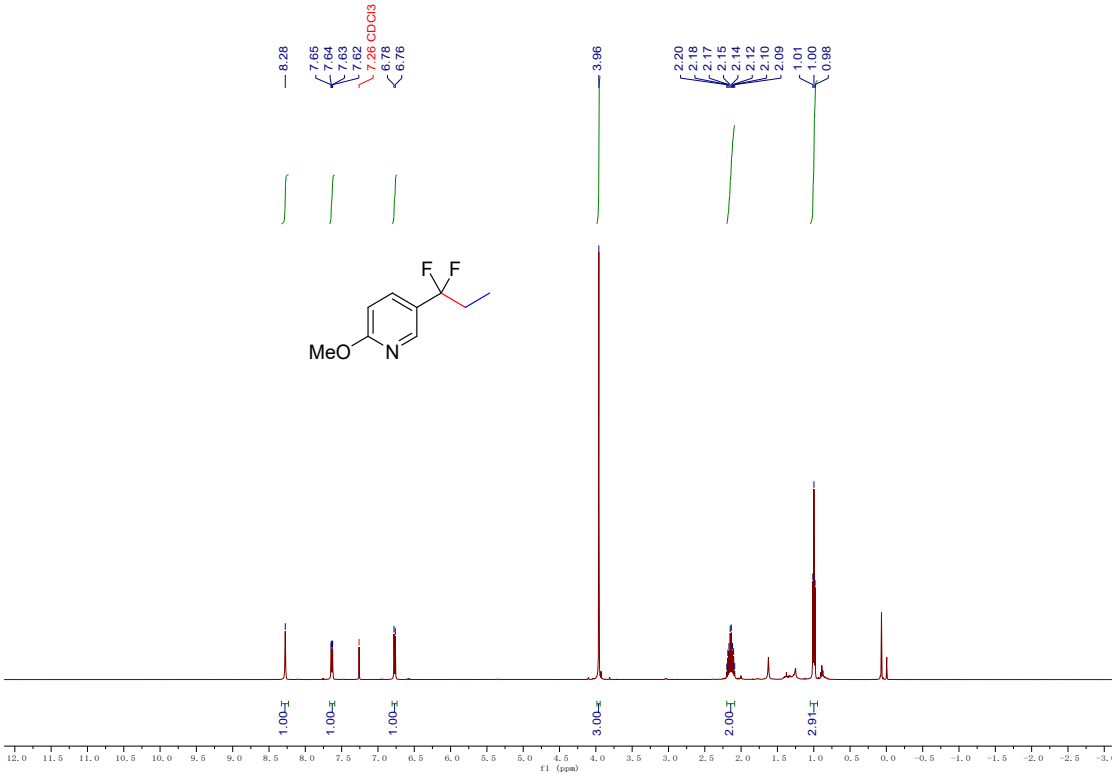
^{1}H NMR of **6-(3-butoxy-1,1-difluoropropyl)pyridin-2-amine** (**2af**) (500 MHz, $CDCl_3$)



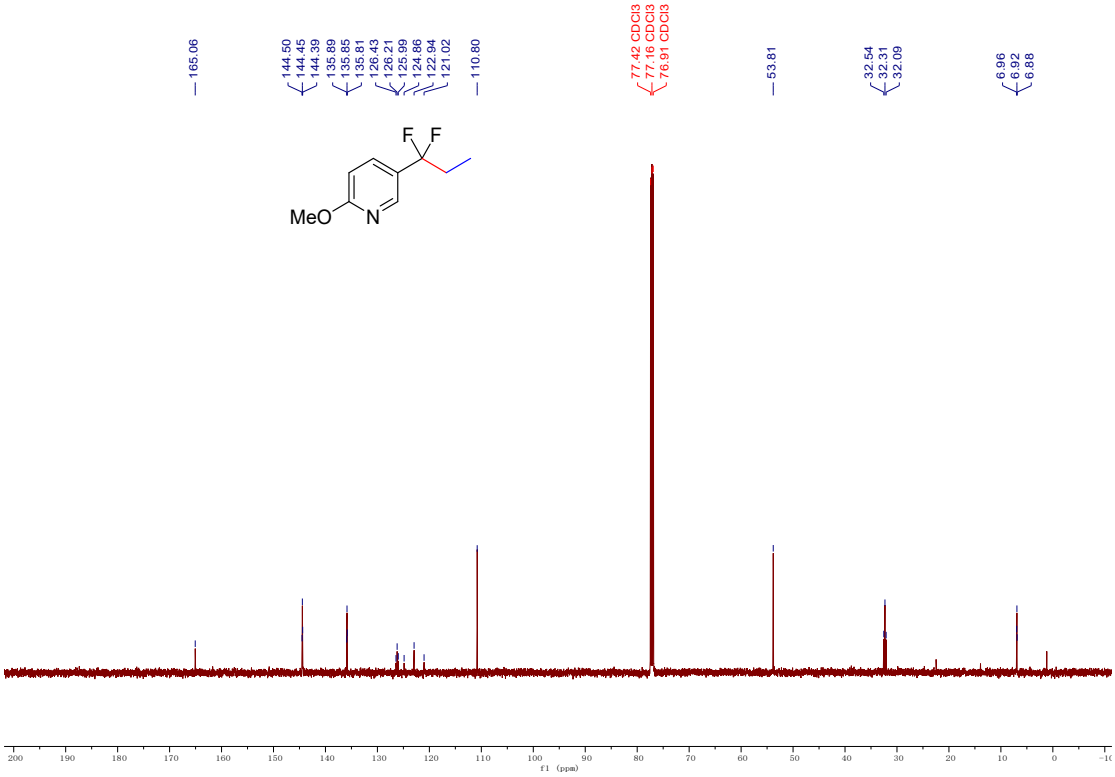
^{1}H NMR of **6-(1,1-difluoropropyl)pyridin-2-amine (2ah)** (500 MHz, $CDCl_3$)



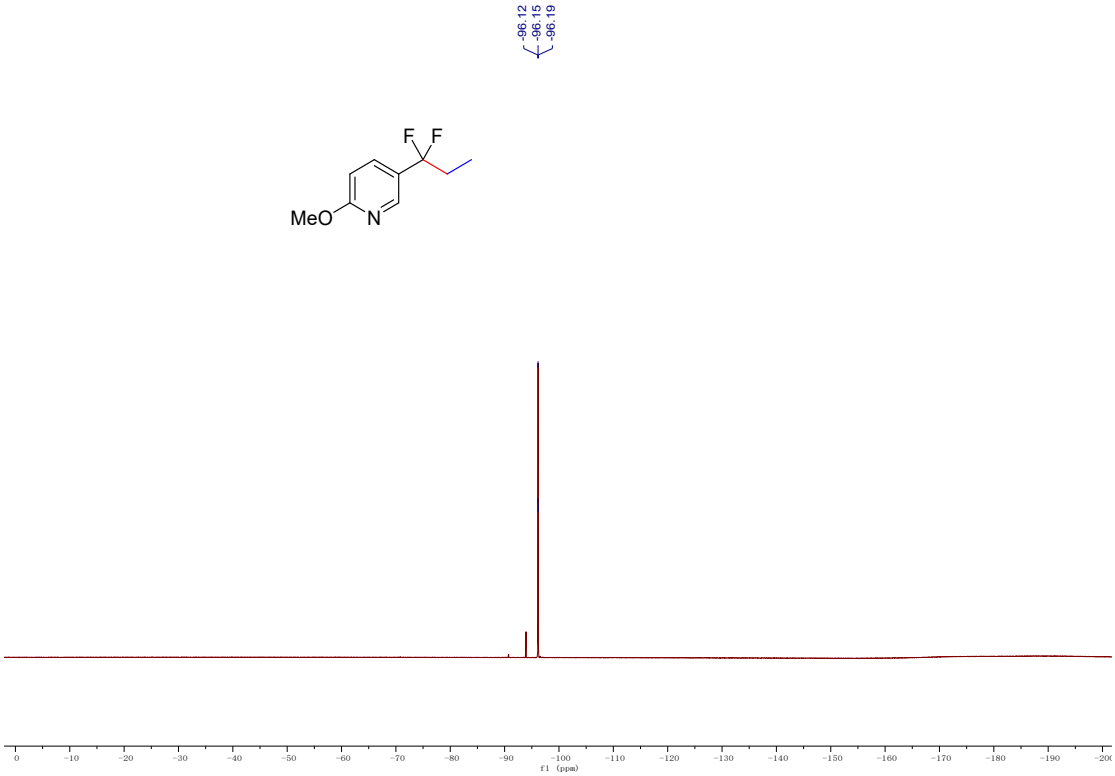
^{1}H NMR of **5-(1,1-difluoropropyl)-2-methoxypyridine (2ai)** (500 MHz, $CDCl_3$)



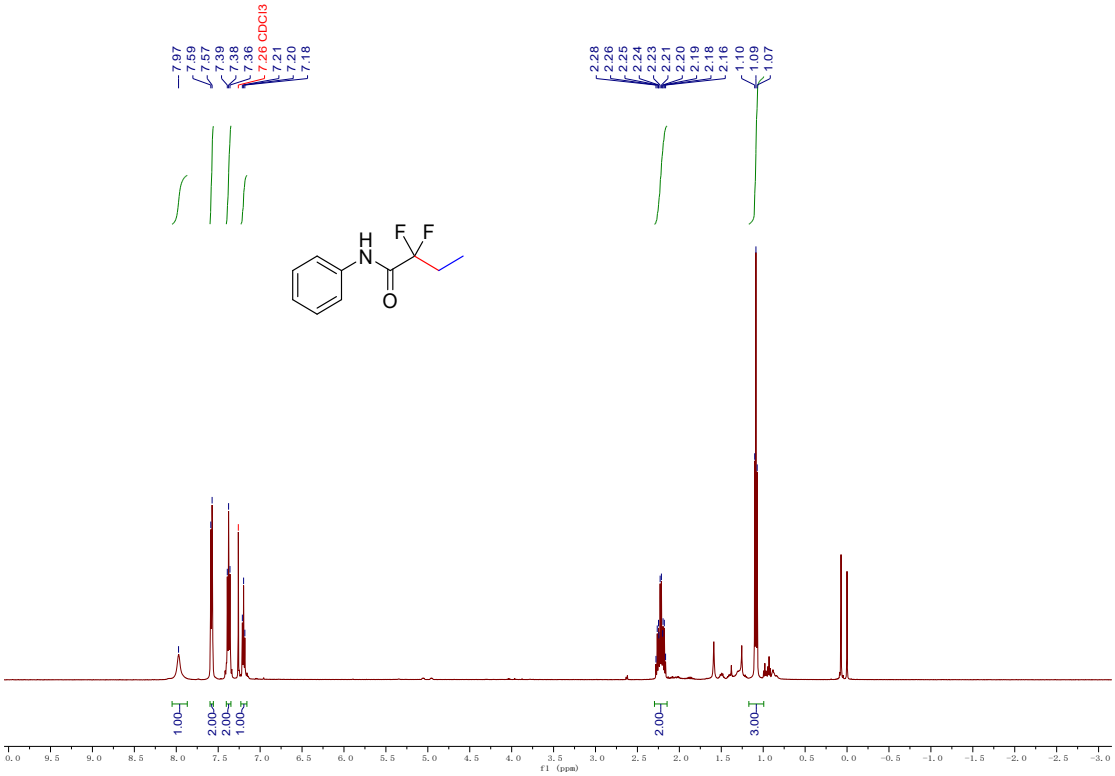
^{13}C NMR of **5-(1,1-difluoropropyl)-2-methoxypyridine (2ai)** (126 MHz, $CDCl_3$)



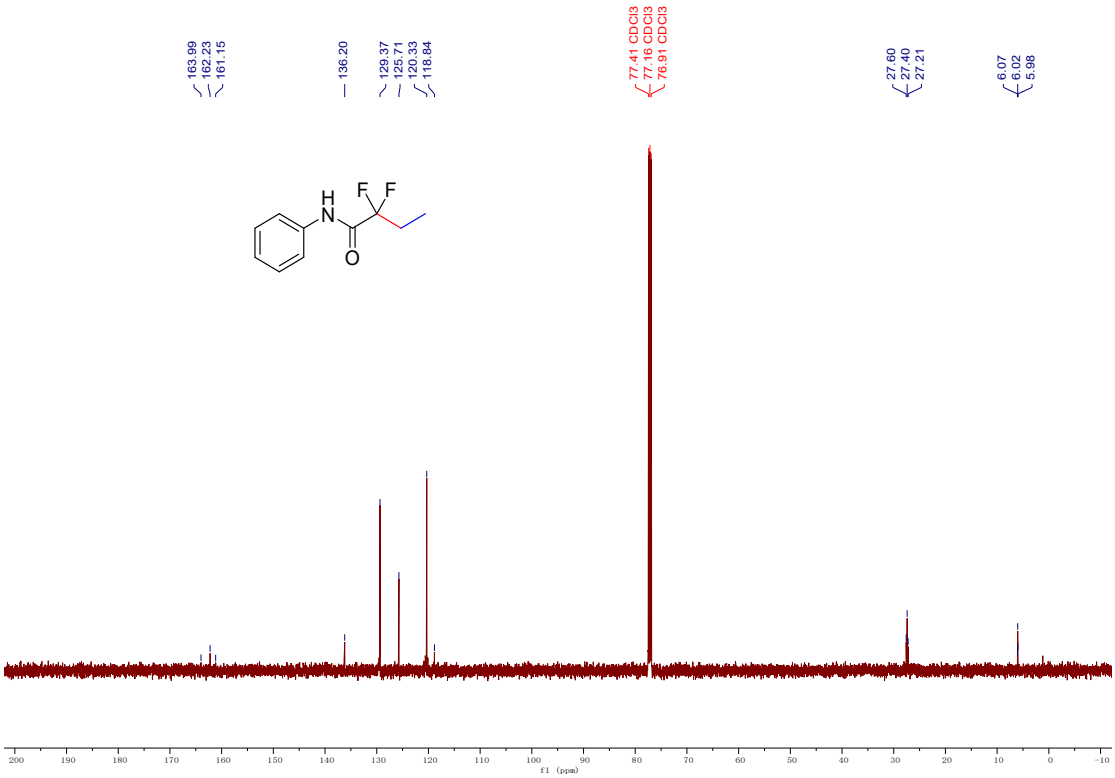
^{19}F NMR of **5-(1,1-difluoropropyl)-2-methoxypyridine (2ai)** (470 MHz, $CDCl_3$)



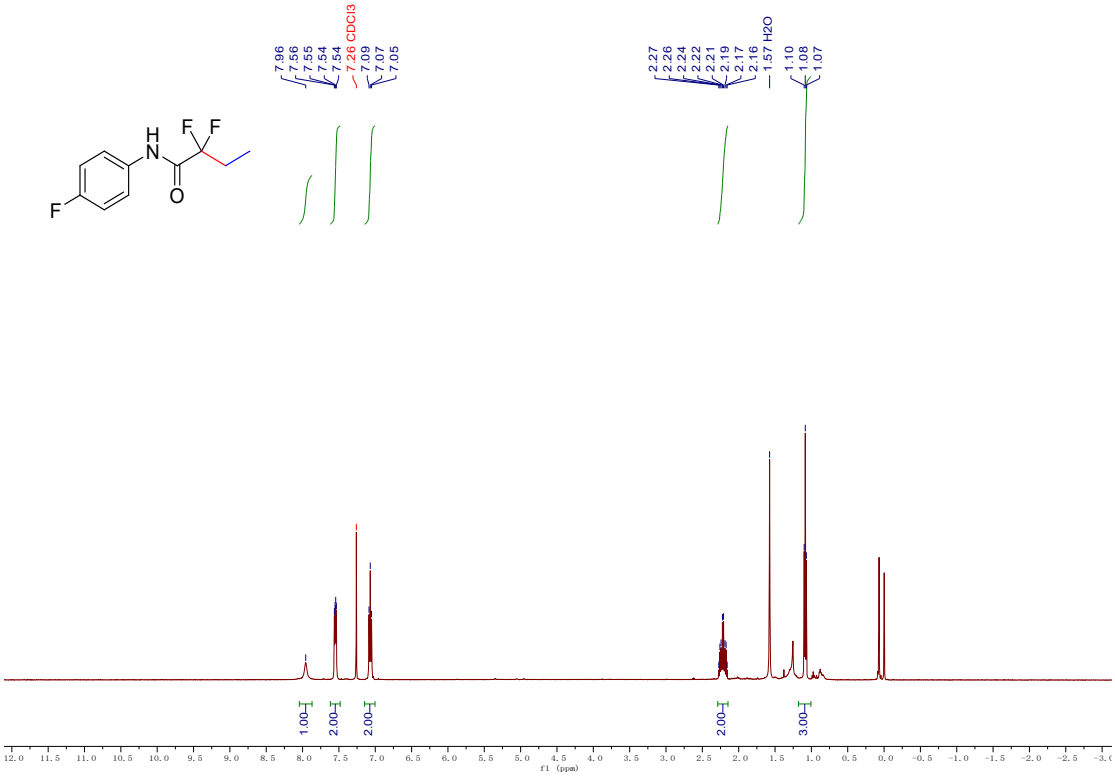
^{1}H NMR of **2,2-difluoro-*N*-phenylbutanamide (2aj)** (500 MHz, $CDCl_3$)



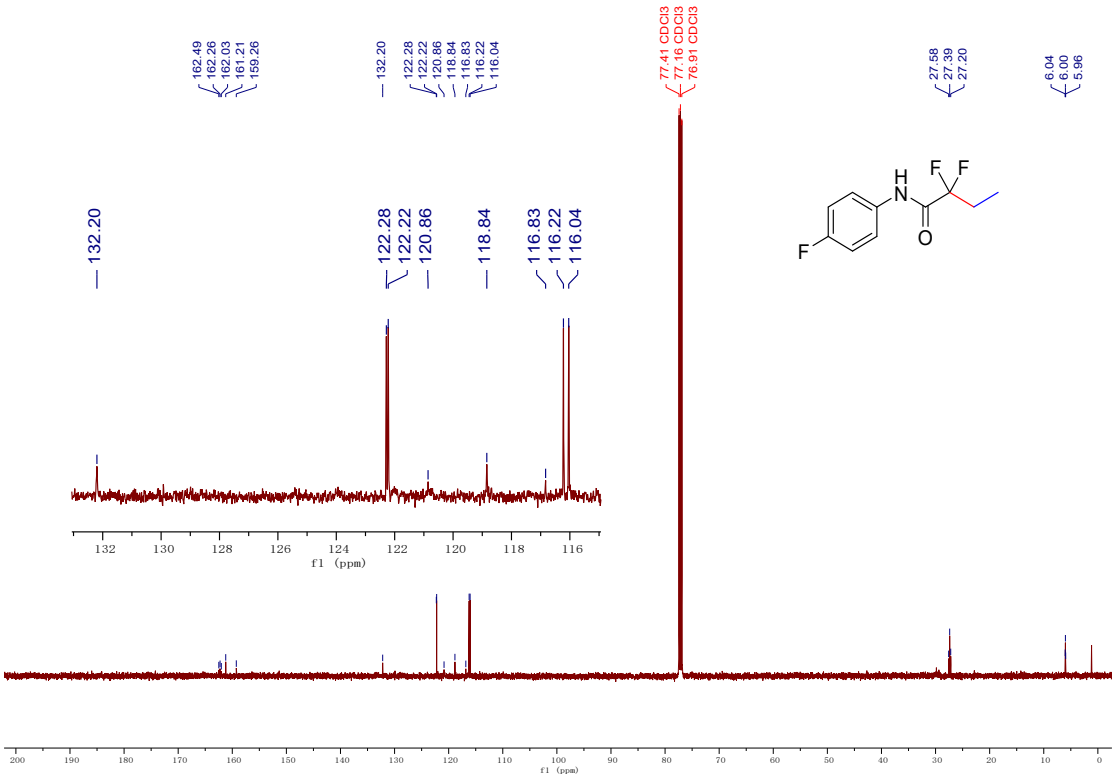
^{13}C NMR of **2,2-difluoro-*N*-phenylbutanamide (2aj)** (126 MHz, $CDCl_3$)



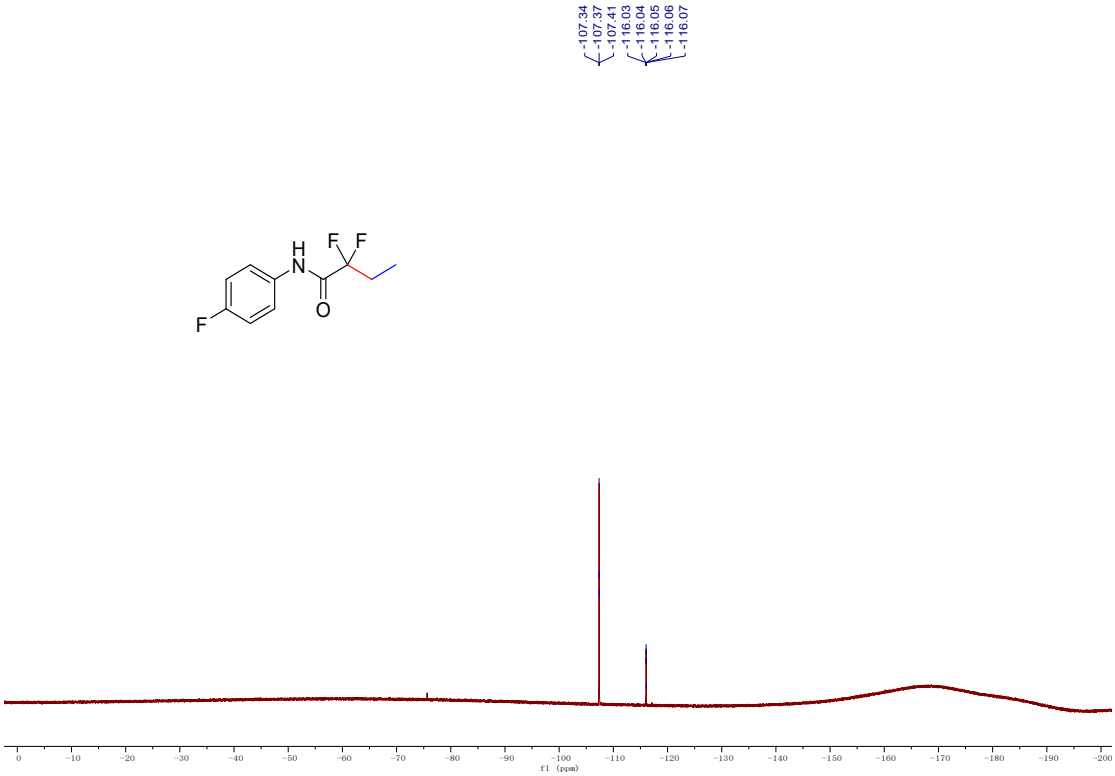
^{1}H NMR of **2,2-difluoro-*N*-(4-fluorophenyl)butanamide (2ak)** (500 MHz, $CDCl_3$)



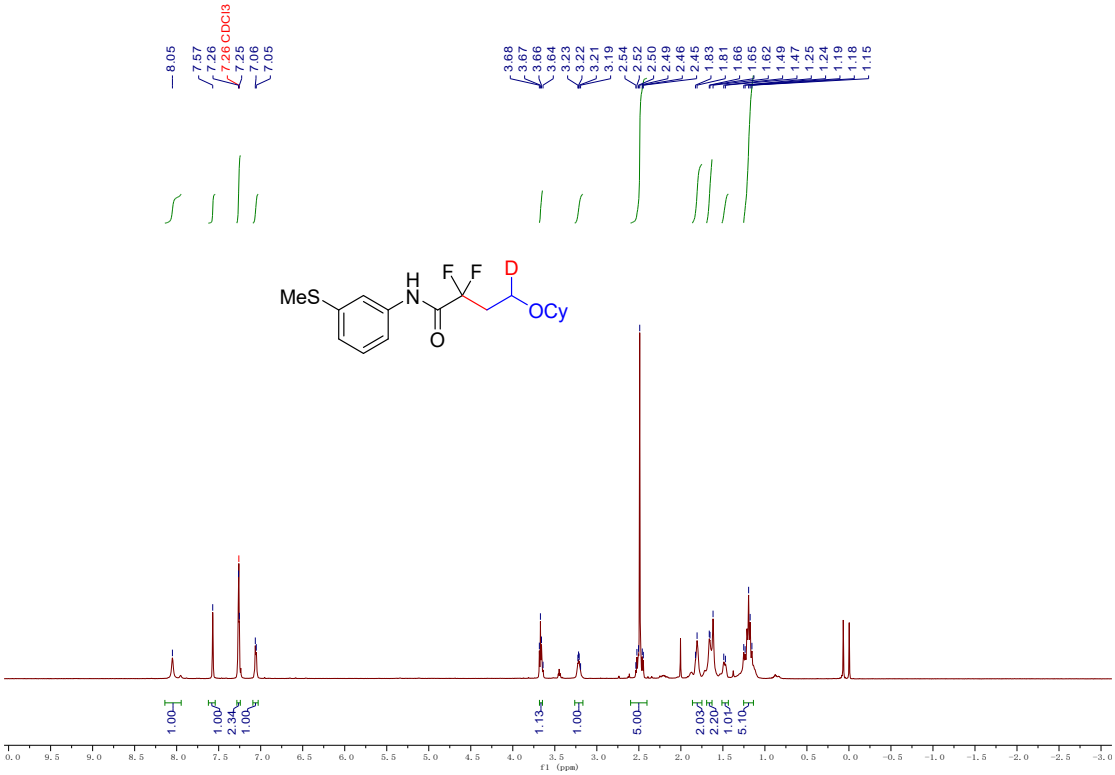
^{13}C NMR of **2,2-difluoro-*N*-(4-fluorophenyl)butanamide (2ak)** (126 MHz, $CDCl_3$)



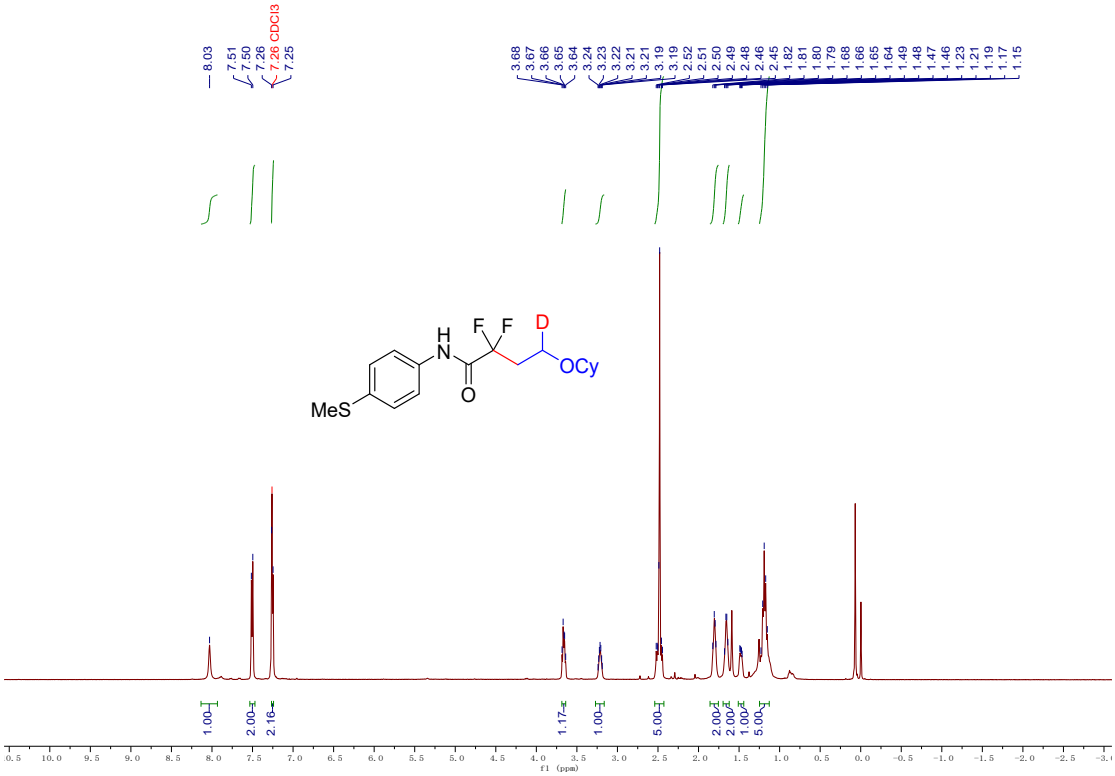
^{19}F NMR of **2,2-difluoro-*N*-(4-fluorophenyl)butanamide(2ak)** (470 MHz, $CDCl_3$)



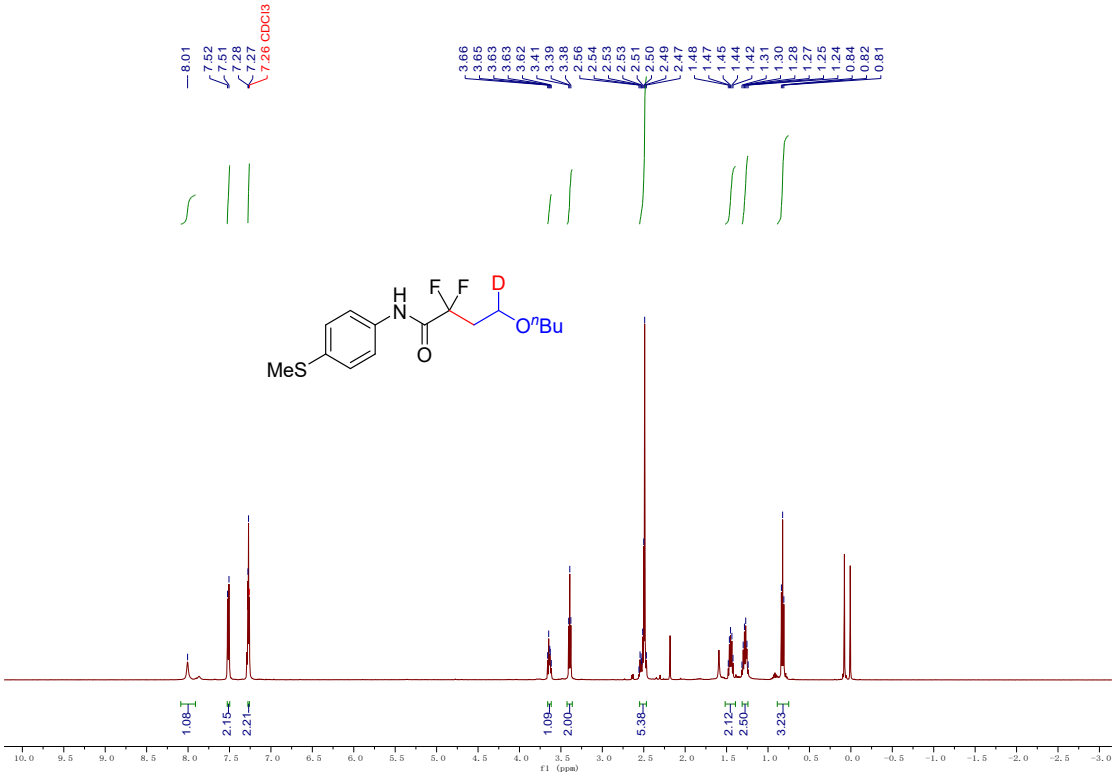
^{1}H NMR of **4-(cyclohexyloxy)-2,2-difluoro-*N*-(3-(methylthio)phenyl)butanamide (2al)** (500 MHz, $CDCl_3$)



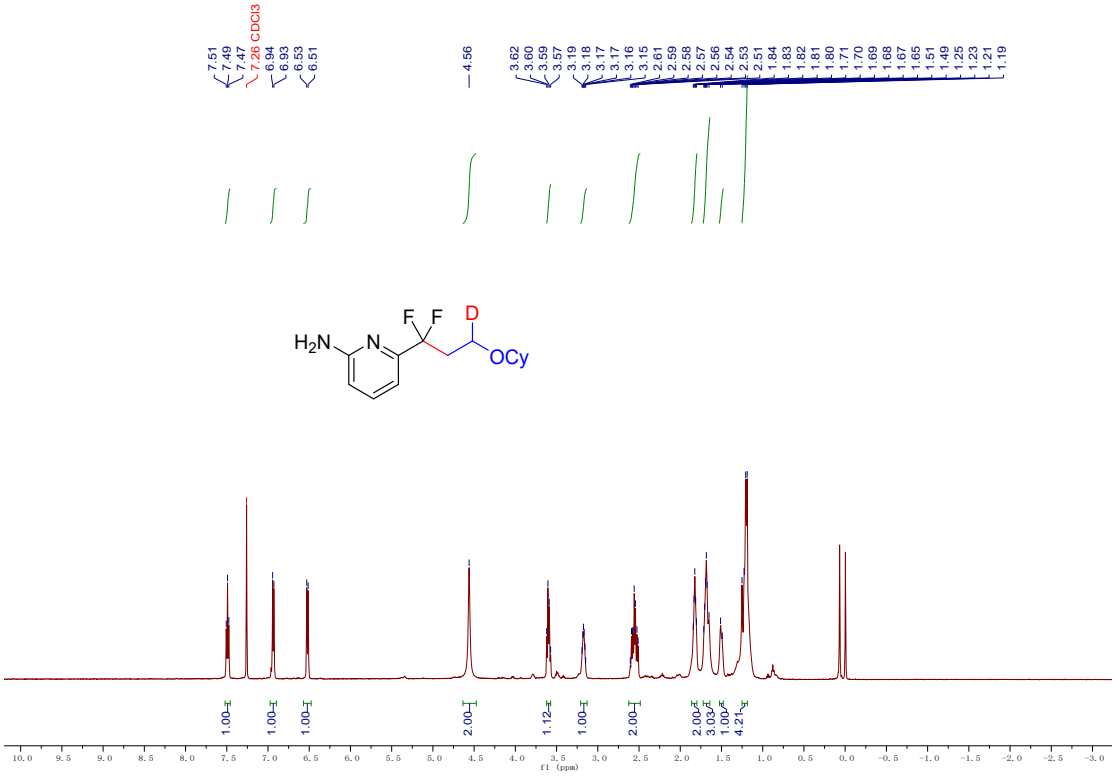
^{1}H NMR of **4-(cyclohexyloxy)-2,2-difluoro-*N*-(4-(methylthio)phenyl)butanamide (2am)** (500 MHz, $CDCl_3$)



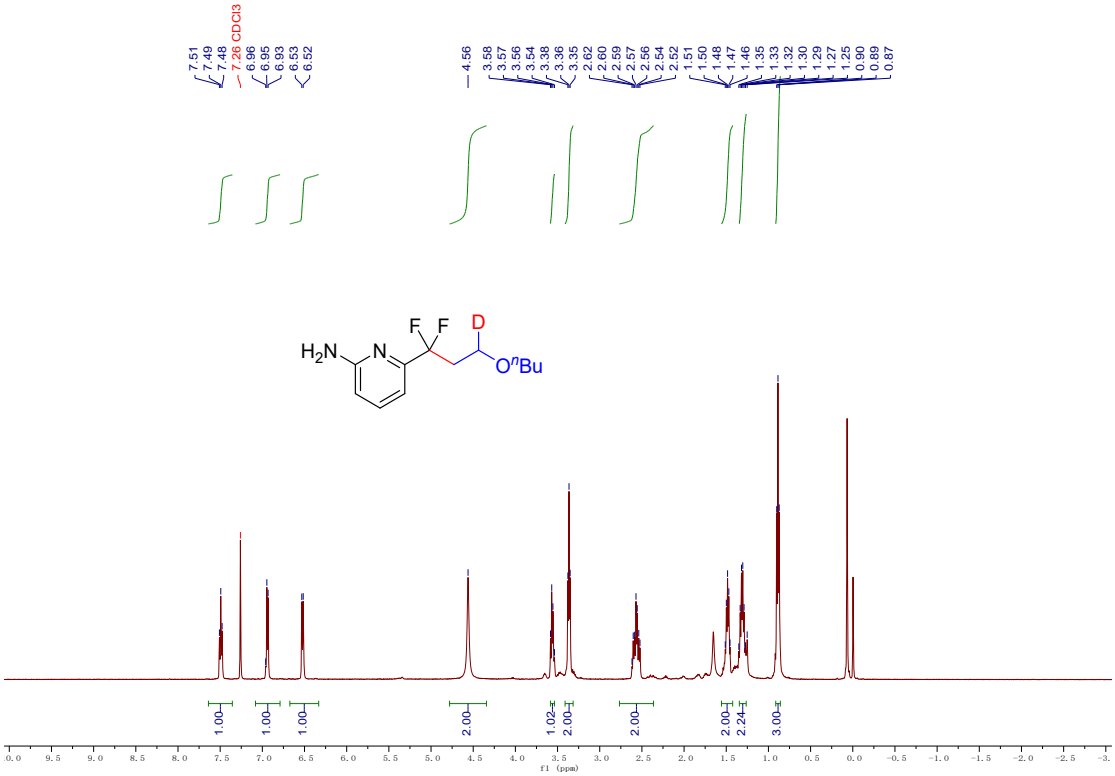
^{1}H NMR of **4-butoxy-2,2-difluoro-*N*-(4-(methylthio)phenyl)butanamide (2an)** (500 MHz, $CDCl_3$)



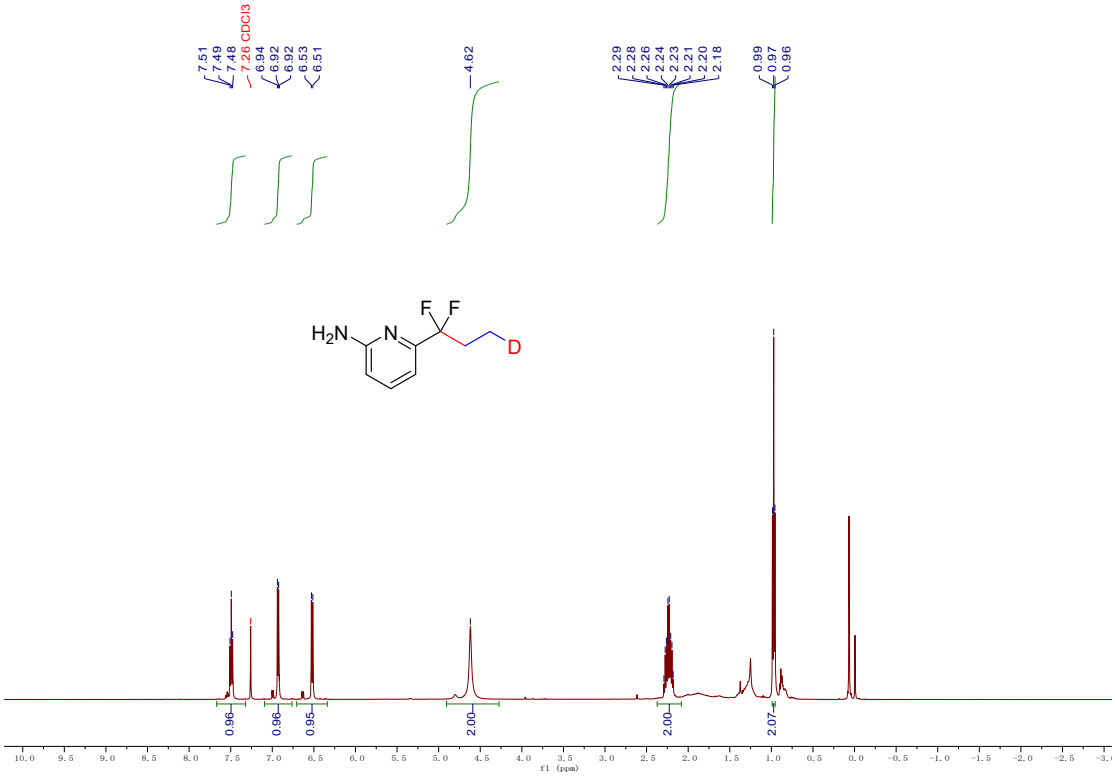
^{1}H NMR of **6-(3-(cyclohexyloxy)-1-fluoropropyl)pyridin-2-amine (2ao)** (500 MHz, $CDCl_3$)



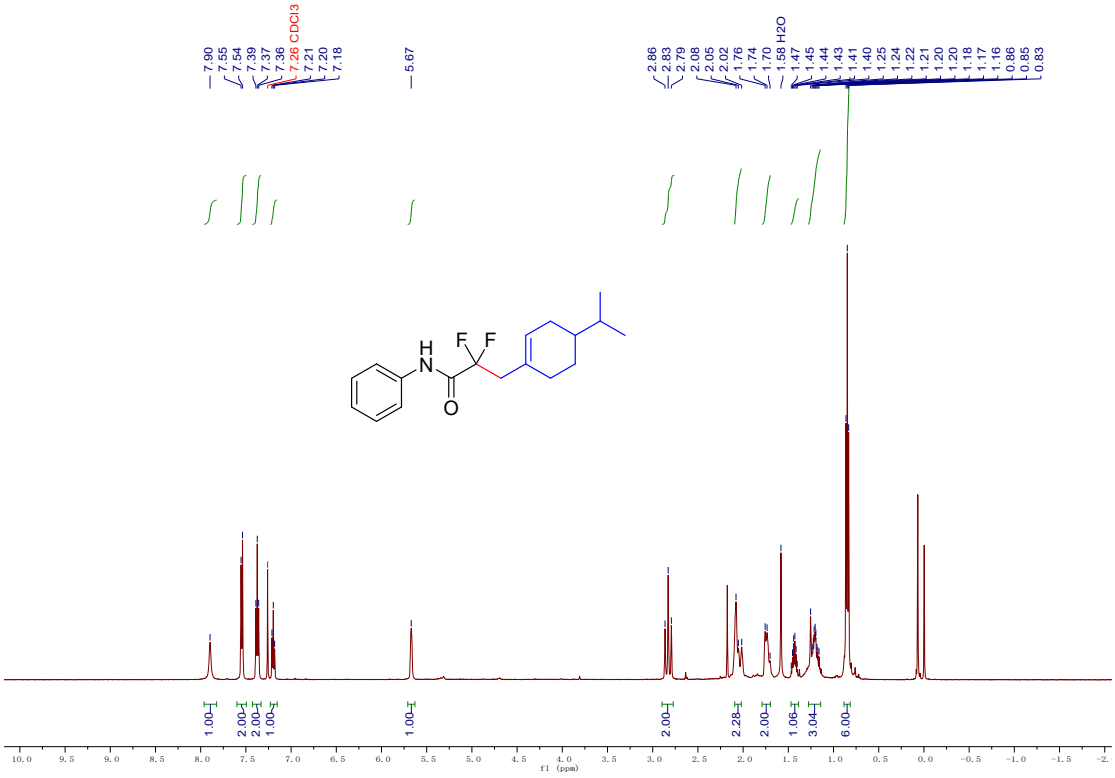
^{1}H NMR of **6-(3-butoxy-1,1-difluoropropyl)pyridin-2-amine (2ap)** (500 MHz, $CDCl_3$)



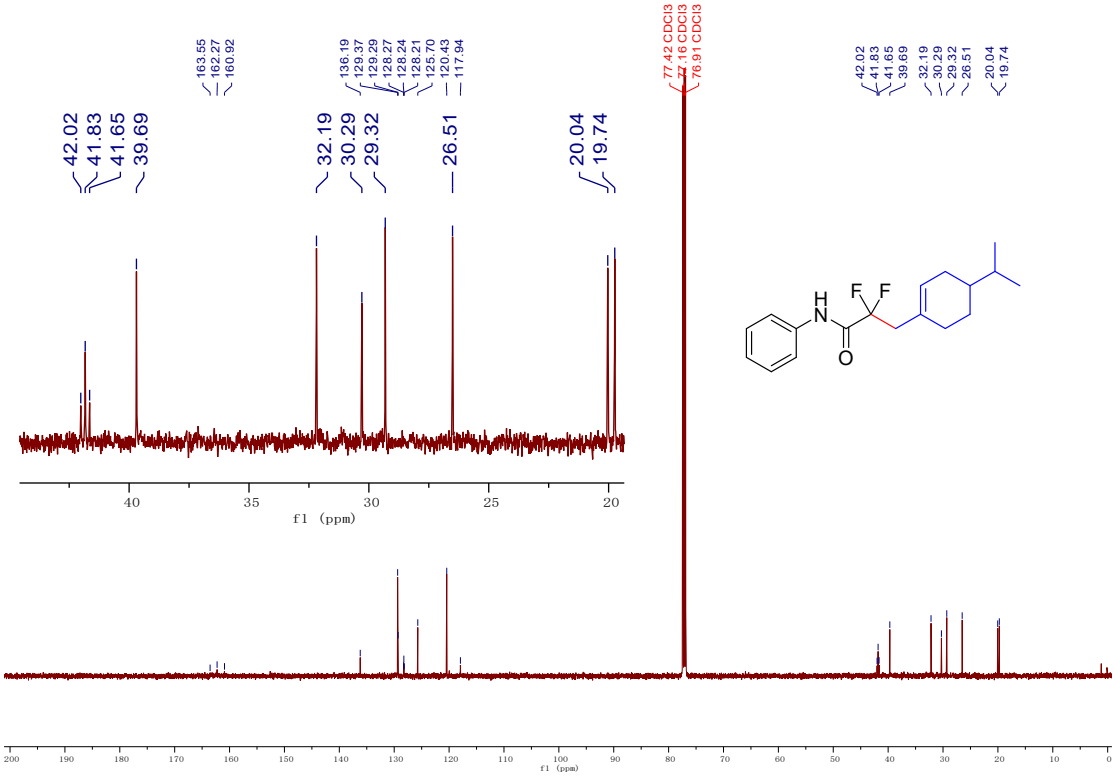
^{1}H NMR of **6-(1,1-difluoropropyl-3-*d*)pyridin-2-amine (2aq)** (500 MHz, $CDCl_3$)



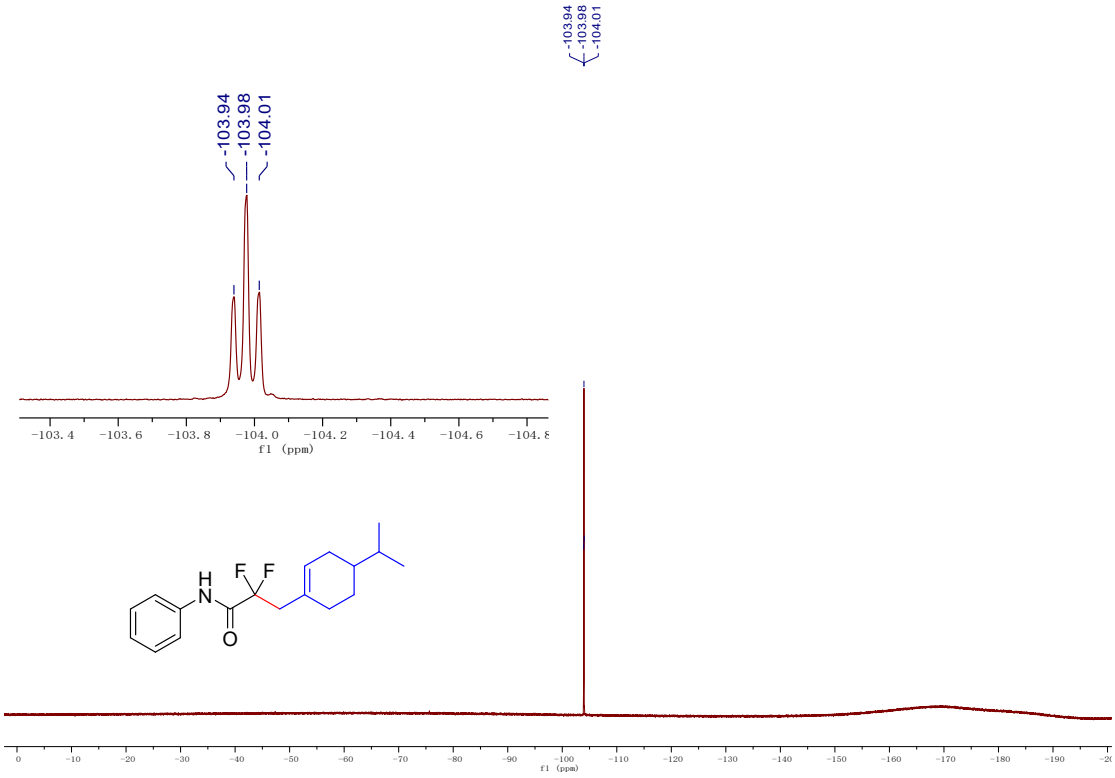
^{1}H NMR of ***α,α*-difluoro-4-(1-methylethyl)-*N*-phenyl-1-cyclohexene-1-propanamide (2ar)** (500 MHz, $CDCl_3$)



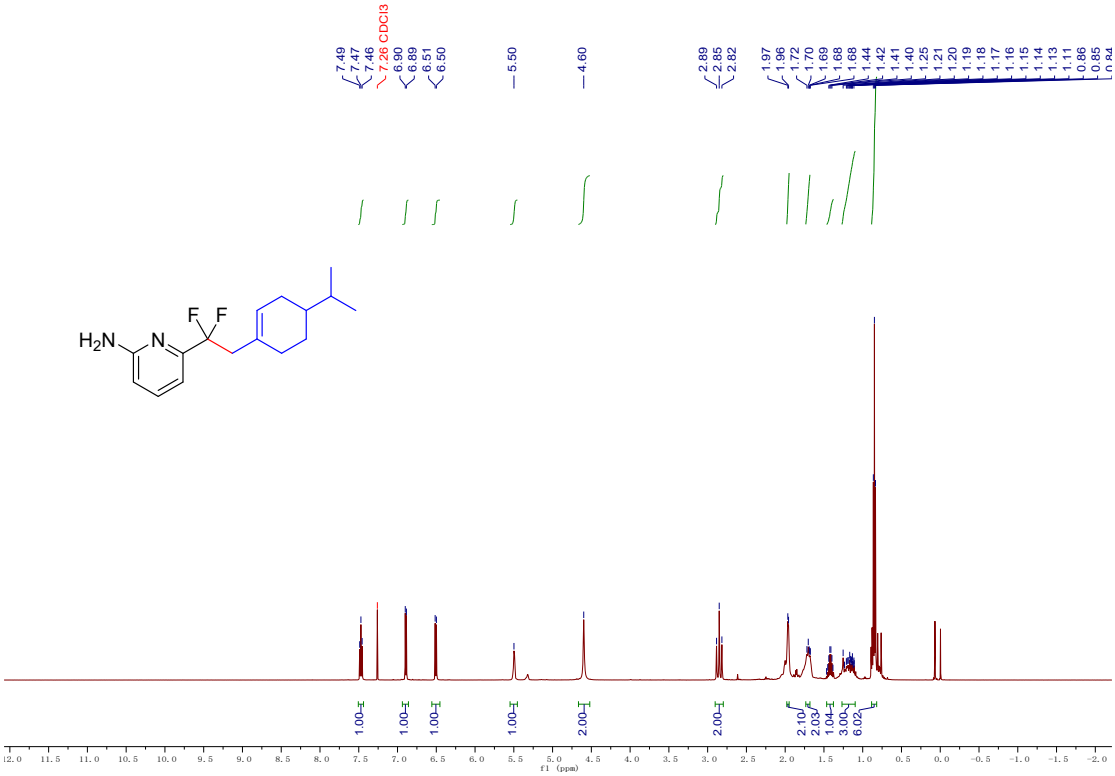
^{13}C NMR of ***α,α*-difluoro-4-(1-methylethyl)-*N*-phenyl-1-cyclohexene-1-propanamide (2ar)** (126 MHz, $CDCl_3$)



^{19}F NMR of ***α,α*-difluoro-4-(1-methylethyl)-*N*-phenyl-1-cyclohexene-1-propanamide (2ar)** (470 MHz, $CDCl_3$)



^{1}H NMR of **6-(1,1-difluoro-2-(4-isopropylcyclohex-1-en-1-yl)ethyl)pyridin-2-amine (2as)** (500 MHz, $CDCl_3$)



^{19}F NMR of **6-(1,1-difluoro-2-(4-isopropylcyclohex-1-en-1-yl)ethyl)pyridin-2-amine (2as)** (470 MHz, $CDCl_3$)