Ligand-Enabled *Meta*-C–H Alkylation and Arylation Using A Modified Norbornene

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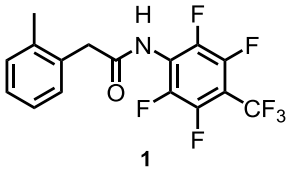
1. General Information

Carboxylic acids or carboxylic chlorides and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline were obtained from the commercial sources or synthesized following literature procedures, and used to prepare the corresponding amides. Alkyl iodides were obtained either from the commercial sources or synthesized following literature procedures. Solvents were obtained from Sigma-Aldrich, Alfa-Aesar and Acros and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. ^{1}H NMR was recorded on Bruker AMX-400 instrument (400 MHz) and Bruker DRX-500 instrument (500 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to the literature values of the solvent residual peaks. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker DRX-500 instrument (125 MHz) or Bruker DRX-600 instrument (150 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to either the center line of a triplet at 77.0 ppm of chloroform-*d* or the center line of a multiplet at 29.84 ppm of acetone-d^6. In the ^{13}C NMR analysis, peaks that correspond to those of the polyfluoroarylamide auxiliary appeared as nearly invisible, complex sets of multiplets; they were omitted in the following spectroscopic analysis. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points were recorded using a Thomas-Hoover melting point apparatus. IR spectrums were recorded on Thermo Scientific Nicolet 380 Fourier transform infrared spectrometer. Enantiomeric excesses (ee) were determined on a Hitachi LaChrom Elite HPLC system using commercially available chiral columns.

2. Substrate Structures

Phenylacetamides



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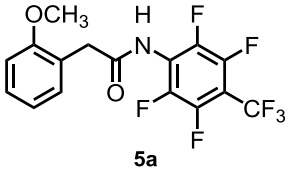

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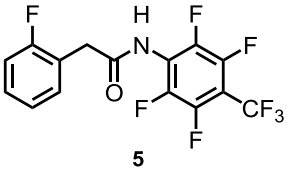

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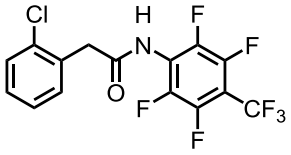

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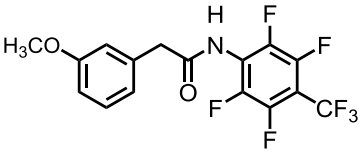

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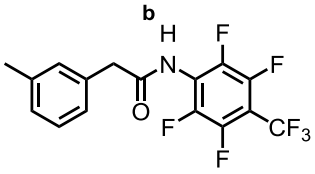

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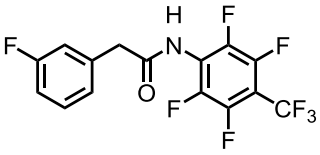

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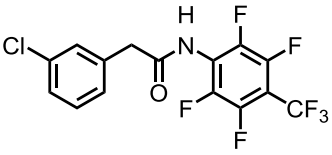

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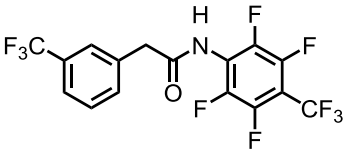

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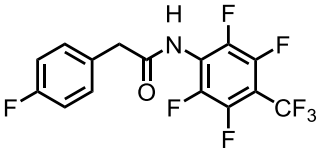

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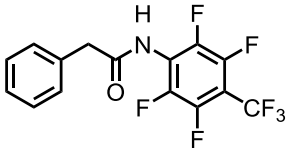

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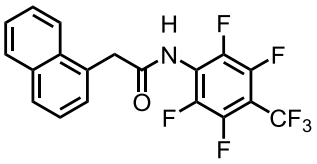

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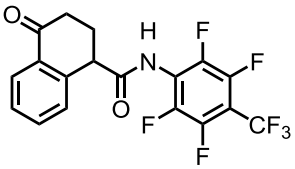

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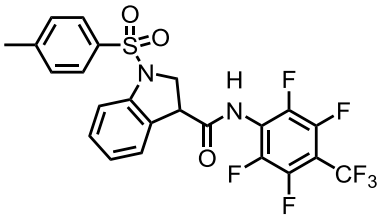

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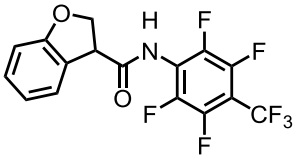

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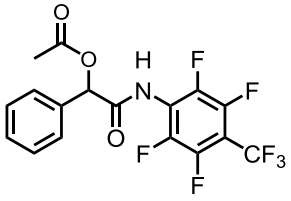

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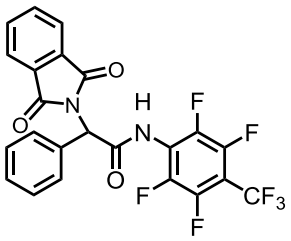
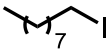


5p

Alkyl iodides

2a

2b



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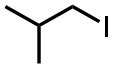

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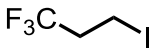

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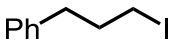

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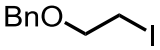

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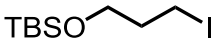

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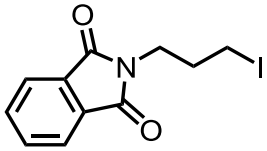

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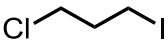

2j

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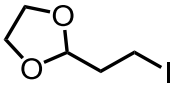

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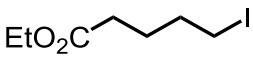
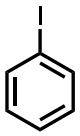
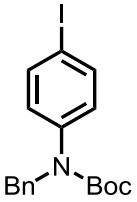


2m

Aryl iodides

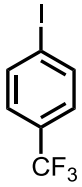


7a



7b

7c



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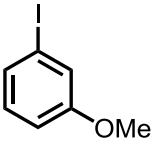

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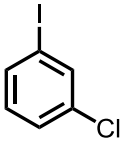

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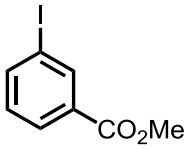

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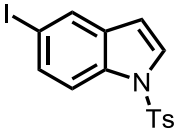
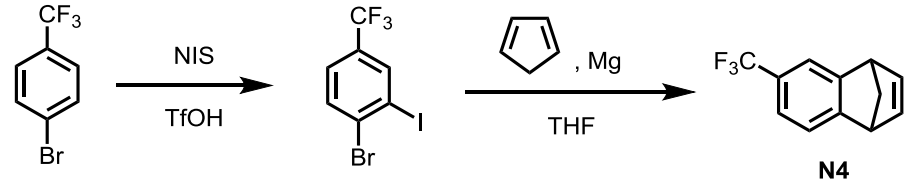


7h

3. Experimental Section

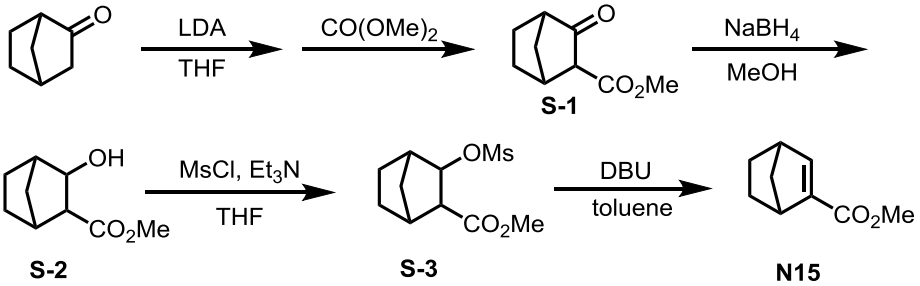
3.1 Preparation of Substituted Norbornenes

N2[1], **N3**[2], **N5**[3], **N6**[4], **N7**[5], **N8**[6], **N9**[7], **N10**[8], **N11**[9], **N12**[10], **N13**[11], **N14**[12], **N15**[13] were synthesized following the reported procedure.



N4

1-bromo-2-iodo-4-trifluorobenzene was prepared following the reported procedure.[14] A 150 ml three-neck flask connected with a reflux condenser was charged with Mg (33 mmol, 0.81 g). 1-bromo-2-iodo-4-trifluorobenzene (30 mmol, 10.5 g) and cyclopentadiene (30 mmol, 2.0 g) in 40 mL of THF was added dropwise to the flask under the flow of N_2. The mixture was heated to reflux during the addition. After that the mixture was refluxed for another 8 h, and then cooled to room temperature. After being quenched with saturated NH_4Cl, the aqueous layer was extracted with Et_2O. The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was then subjected to column chromatography with hexanes as the eluent to isolate the pure compound **N4** 0.7 g (10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.76-6.82 (m, 2H), 3.92-3.96 (m, 2H), 2.34-2.38 (m, 2H), 2.24-2.28 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.33, 153.03,143.22, 142.79, 126.78 (q, *J* = 31 Hz), 124.76 (q, *J* = 270 Hz), 122.12 (q, *J* = 4.2 Hz), 121.38, 118.25 (q, *J* = 3.3 Hz), 70.38, 50.46, 50.39. ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.91 (s, 3F).



S-1 **S-2** **S-3** **N15**

Synthesis of **S-1**: To a mixture of 1.5 g (13.6 mmol) of norcamphor and 53 ml of THF was added dropwise 14.2 mmol of lithium diisopropylamide at -78 ^{o}C under argon atmosphere, and the mixture was stirred at the same temperature for 30 minutes. A mixture of 2.45 g (27.2 mmol) of dimethyl carbonate and 20 ml of THF was added dropwise *via* a syringe, and the mixture was stirred at room temperature for 15 h. The reaction was quenched by addition of water, followed by extraction with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography with hexanes/ethyl acetate (4:1) as eluent.

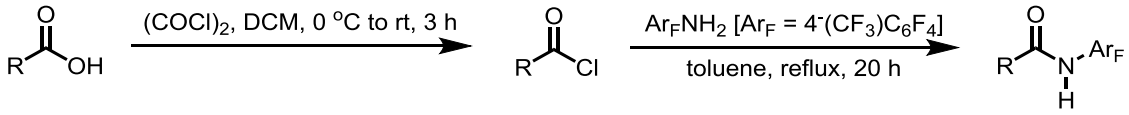
Synthesis of **S-2:** To a mixture of 0.59 g (3.51 mmol) of **S-1** and 10 ml of MeOH was added

0.13 g (3.51 mmol) of $NaBH_4$ at 0 °C, and the mixture was stirred at room temperature for 15 h. To the solution was added 5 ml of 5% aqueous HCl, and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was used without purification.

Synthesis of **S-3**: To a mixture of 0.37 g (2.17 mmol) of **S-2**, 0.31 g (3.04 mmol) of Et_3N and 10 mL of THF, was added 0.27 g (2.39 mmol) of methanesulfonyl chloride at 0 °C, and the mixture was stirred at room temperature for 14 h. Water was added to the reaction solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was used without purification.

Synthesis of **N15**: A mixture of 0.41 g (1.65 mol) of **S-3**, 0.50 g (3.30 mmol) of 1,8-diazabicyclo[5.4.0]undeca-7-ene and 10 mL of toluene was heated to reflux with stirring for 2 h. After being allowed to cool to room temperature, water and 5% aqueous HCl were added to the solution, followed by extraction with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography with pentane/ether (10/1) as eluent.

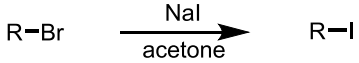
3.2 Preparation of Substrates.



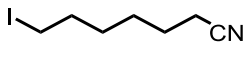
The previous reported procedure was followed.[15] 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline (6.0 mmol) and an acyl chloride (5.0 mmol), prepared from the corresponding carboxylic acid and oxalyl chloride, were dissolved in toluene (10.0 mL) in a 50 mL round-bottom flask. The mixture was refluxed under N_2 for 20 h. After being allowed to cool to room temperature, the crude product mixture was concentrated *in vacuo* and recrystallized from ethyl acetate/hexanes to give the pure amide substrate. All of phenylacetic amides had been synthesized and characterized before.[15]

3.3 Preparation of Alkyl Iodides

Alkyl iodide **2a**, **2b**, **2c**, **2d**, **2f**, **2j** were purchased from commercial source. **2f**[16], **2g**[16], **2k**, **2l**[17], **2m**[16] were prepared from corresponding alkyl bromide. **2h**[18], **2i**[19] were obtained from corresponding alcohol.



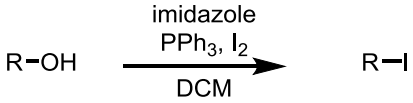
To a solution of corresponding alkyl bromide (5 mmol) in 15 mL of acetone, was added NaI (25 mmol, 4.15 g). The mixture was heated to reflux for 6 h. After being allowed to cool to room temperature, the solvent was evaporated, followed by addition of 15 mL DCM. Then the mixture was filtered, and the filtrate was washed with water, aqueous $Na_2S_2O_3$ and brine, and dried over Na_2SO_4. After evaporation of solvent, the alkyl iodide was obtained as a slightly yellowish liquid, and used without further purification.



2k

7-iodoheptanenitrile.

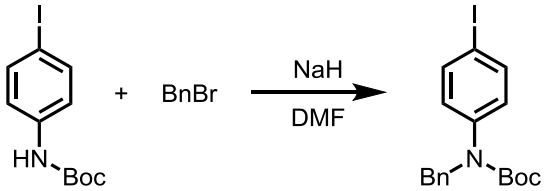
Alkyl iodide **2k** was prepared from 7-bromoheptanenitrile following standard procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20 (t, *J* = 6.8 Hz, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.81-1.87 (m, 2H), 1.65-1.72 (m, 2H), 1.41-1.52 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.69, 33.13, 29.76, 27.71, 25.32, 17.23, 6.64.



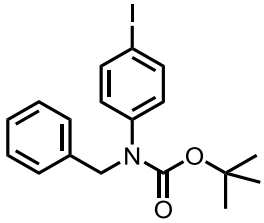
To a solution of imidazole (30 mmol, 2.0 g) and PPh_3 (11 mmol, 2.9 g) in 40 mL of DCM at 0 °C was added I_2 (11 mmol, 2.8 g). The solution was stirred for 10 min and then a solution of alcohol (10 mmol) in 20 mL of DCM was added to the mixture at 0 °C. After the addition, the mixture was allowed to warm to room temperature, and stirred for another 15 h in the dark. The reaction mixture was then diluted with 0.4 mL of saturated $Na_2S_2O_4$ solution and water. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was dried over Na_2SO_4, and concentrated under the reduced pressure. The pure product was isolated by column chromatography.

3.4 Preparation of Aryl Iodides

Aryl iodides **7a**, **7c**-**h** were purchased from commercial source.



To a solution of N-Boc-4-iodoaniline (0.32 g, 1.0 mmol) in 5 ml of DMF, was added NaH (2.5 mmol) portion-wise, and the mixture was stirred at room temperature for 10 min. BnBr (0.21g 1.2 mmol) was then added to the mixture. The reaction was stirred overnight and quenched with water. Ethyl acetate was added, and organic layer was separated and washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under the reduced pressure. The pure product was obtained by column chromatography.



7b

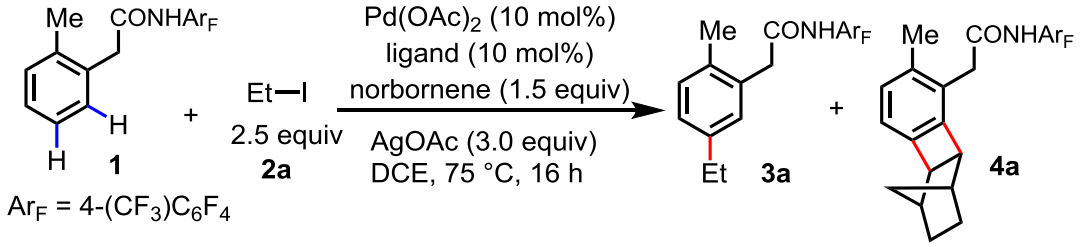
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.23-7.32 (m, 3H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 4.80 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.53, 142.68, 138.34, 137.81, 128.60, 128.48, 127.43, 127.34, 90.39, 81.07, 53.83, 28.38.

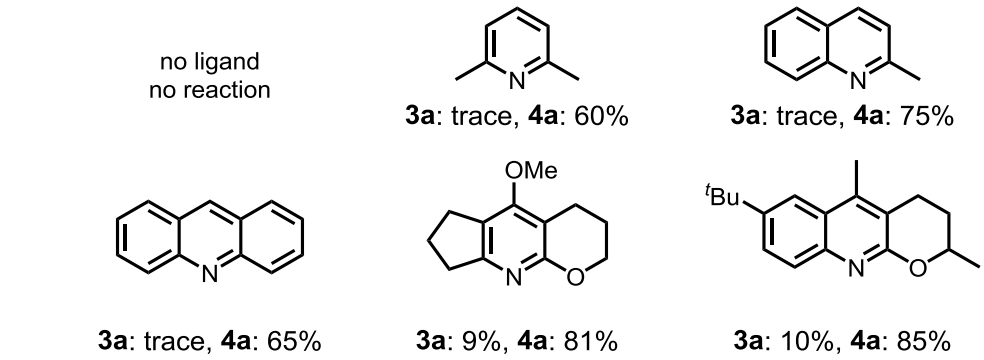
3.5 Preparation of Ligand

The ligand **L1** was prepared following previous reported procedure.[20]

3.6 Optimization of Conditions

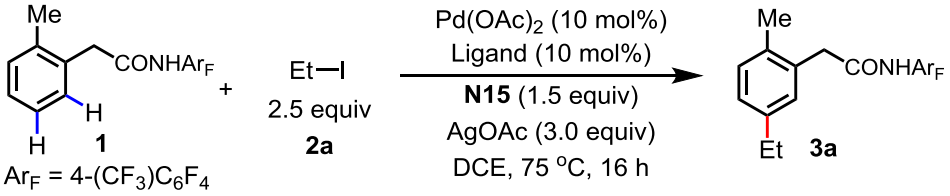
Preliminary screening ligands with norbornene[a,b]

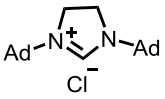
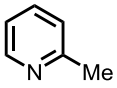
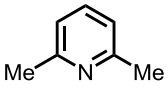
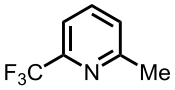
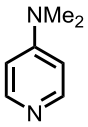
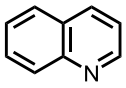
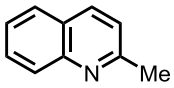
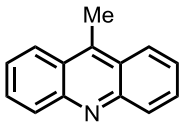
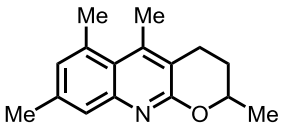
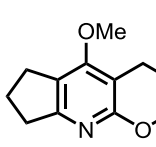
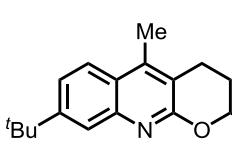
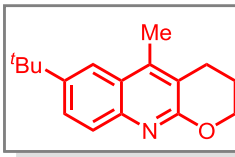




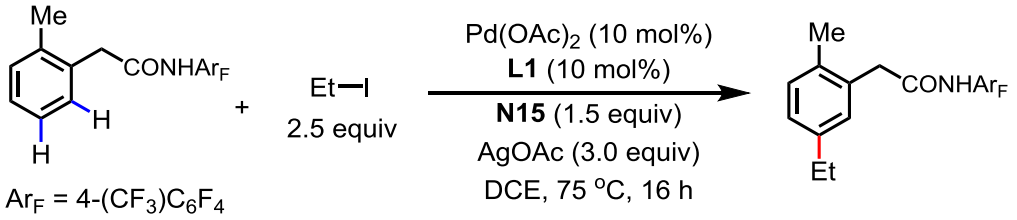
[a] Conditions: **1** (0.1 mmol), **2a** (2.5 equiv), Pd(OAc)$_2$ (10 mol%), ligand (10 mol%), norbornene (1.5 equiv), AgOAc (3.0 equiv), DCE (1.5 mL), 75 °C, air, 16 h. [b] ^{1}H NMR yields, using CH_2Br_2 as internal standard.

Screening of ligands with modified norbornene **N15**[a,b]



no ligand	Ac-Ala-OH	PPh_3	
	L2	**L3**	**L4**
trace	trace	10%	43%
			
L5	**L6**	**L7**	**L8**
40%	48%	16%	trace
			
L9	**L10**	**L11**	**L12**
30%	52%	55%	52%
			
L13	**L14**	**L15**	**L1**
53%	76%	13%	97%

[a] Conditions: **1** (0.1 mmol), **2a** (2.5 equiv), $Pd(OAc)_2$ (10 mol%), ligand (10 mol%), **N15** (1.5 equiv), AgOAc (3.0 equiv), DCE (1.5 mL), 75 °C, air, 16 h. [b] ^{1}H NMR yields, using CH_2Br_2 as internal standard.

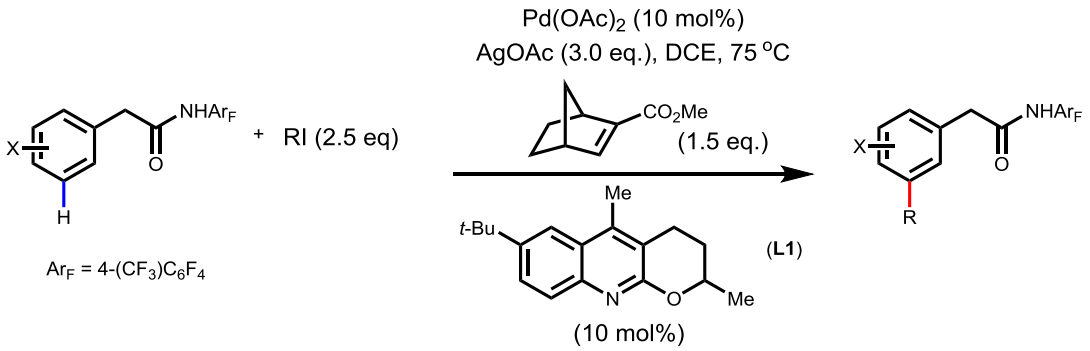


Entry	Reaction Condition[a,b]	^{1}H NMR Yield
1	no change	97%
2	Et-I (2.0 equiv)	90%
3	Et-I (3.0 equiv)	85%
4	95 °C	71%
5	**L1** (20 mol%)	88%
6	**N15** (0.5 equiv)	72%

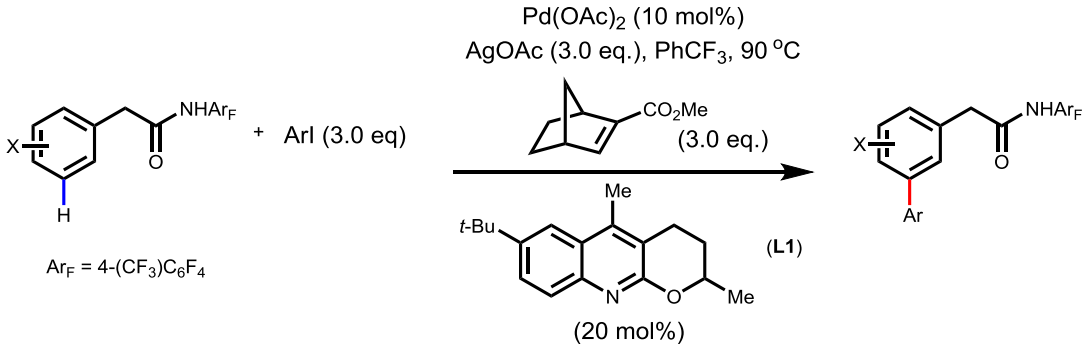
[a] Conditions: **1** (0.1 mmol), **2a** (2.5 equiv), Pd(OAc)$_2$ (10 mol%), **L1** (10 mol%), **N15** (1.5 equiv), AgOAc (3.0 equiv), DCE (1.5 mL), 75 °C, air, 16 h. [b] ^{1}H NMR yields, using CH_2Br_2 as internal standard.

General procedure for optimization: Standard conditions: A 2-dram vial equipped with a magnetic stir bar was charged with **1**(36.5 mg, 0.10 mmol), Pd(OAc)$_2$ (2.2 mg, 10 mol%), ligand (10 mol%), AgOAc (50 mg, 0.30 mmol) and norbronene derivative (0.15 mmol). Ethyl iodide (0.25 mmol) was then added *via* a microsyringe. Subsequently, DCE (1.5 mL) was injected, and the vial was capped and closed tightly. The reaction mixture was then stirred at 75 °C for 16 h. After being allowed to cool to room temperature, the mixture was passed through a pad of Celite with ethyl acetate as the eluent to remove any insoluble precipitate. The resulting solution was concentrated. The ^{1}H NMR yield was measured using CH_2Br_2 as internal standard.

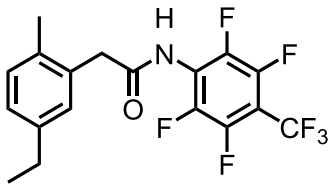
3.7 Meta-Alkylation and Arylation of Phenylacetamides



General procedure for meta-alkylation of phenylacetic amides: A 2-dram vial equipped with a magnetic stir bar was charged with the appropriate phenylacetic acid–derived amide substrate (0.10 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%), **L1** (2.7 mg, 10 mol%), AgOAc (50 mg, 0.30 mmol) and **N15** (22.8 mg, 0.15 mmol). Alkyl iodide (0.25 mmol) was then added. Subsequently, DCE (1.5 mL) was injected, and the vial was capped and closed tightly. The reaction mixture was then stirred at 75 °C for 16 h. After being allowed to cool to room temperature, the mixture was passed through a pad of Celite with ethyl acetate as the eluent to remove any insoluble precipitate. The resulting solution was concentrated, and the residual mixture was dissolved with a minimal amount of acetone and loaded onto a preparative TLC plate. The pure product was then isolated using preparative TLC with ethyl acetate and hexanes (1/4 to 1/2) as the eluent.



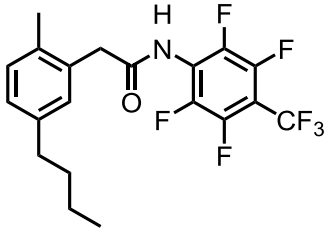
General procedure for meta-arylation of phenylacetic amides: A 2-dram vial equipped with a magnetic stir bar was charged with the appropriate phenylacetic acid–derived amide substrate (0.10 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%), **L1** (5.4 mg, 20 mol%), AgOAc (50 mg, 0.30 mmol) and **N15** (45.6 mg, 0.30 mmol). Aryl iodide (0.30 mmol) was then added. Subsequently, $PhCF_3$ (1.5 mL) was injected, and the vial was capped and closed tightly. The reaction mixture was then stirred at 90 °C for 24 h. After being allowed to cool to room temperature, the mixture was passed through a pad of Celite with ethyl acetate as the eluent to remove any insoluble precipitate. The resulting solution was concentrated, and the residual mixture was dissolved with a minimal amount of acetone and loaded onto a preparative TLC plate. The pure product was then isolated using preparative TLC with ethyl acetate/hexanes(1/4) or ethyl acetate/toluene(1/30) as the eluent.



3a

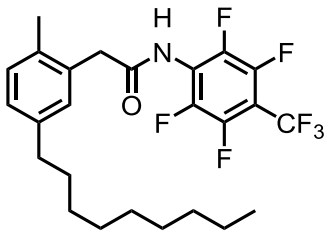
2-(5-ethyl-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (93% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.41 (br, 1H, N-H), 7.17 (s, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.03 (dd, *J* = 7.3, 1.3 Hz, 1H), 3.87 (s, 2H), 2.59 (q, *J* = 7.7 Hz, 2H), 2.31 (s, 3H), 1.19 (t, *J* = 7.5Hz, 3H); ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.62, 142.71, 135.06, 134.12, 131.08, 130.64, 127.58, 41.29, 28.95, 19.22, 16.07. ^{19}F NMR (376 MHz, acetone-d^{6}) δ -56.0 (t, *J* = 21 Hz, 3F), -143.3--143.7 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{18}H_{13}F_7NO^-$ [M-H]$^-$ 392.0891, found 392.0893. Melting point: 184 °C. IR (neat, cm^{-1}) 3217, 2962, 1698, 1656, 1536, 1511, 1477, 1348, 1238, 1181, 1141, 1013, 9587.

When using bromoethane instead of iodoethane, after heated 48 h, the product was obtained in 40% NMR yield.



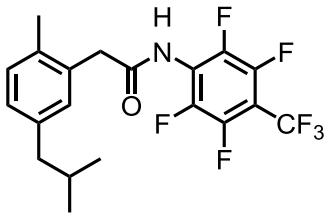
3b

2-(5-butyl-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (85% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.43 (br, 1H, N-H), 7.16(d, *J* = 2 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.02 (dd, *J* = 7.5, 2 Hz, 1H), 3.87 (s, 2H), 2.57 (t, *J* = 7.8, 2H), 2.31 (s, 3H), 1.54-1.61 (m, 2H), 1.31-1.39 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.64, 141.30, 135.03, 134.06, 131.17, 131.00, 128.15, 41.26, 35.75, 34.53, 22.98, 19.23, 14.20. ^{19}F NMR (376 MHz, acetone-d^{6}) δ -56.0 (t, *J* = 23 Hz, 3F), -143.3--143.7 (m, 4F).HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{17}F_7NO^-$ [M-H]$^-$ 420.1204, found 420.1204. Melting Point: 167 °C. IR (neat, cm^{-1}) 3212, 2931, 1694, 1656, 1534, 1511, 1476, 1349, 1243, 1182, 1140, 1011, 958



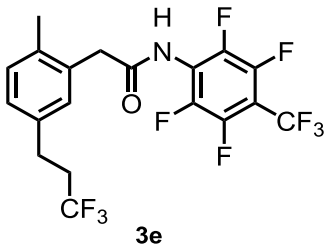
3c

2-(2-methyl-5-nonylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (84% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.42 (br, 1H, N-H), 7.16 (s, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.02 (dd, *J* = 7.8, 1.2 Hz, 1H), 3.86 (s, 2H), 2.57 (t, *J* = 7.8 Hz, 2H), 2.31 (s, 3H), 1.56-1.64 (m, 2H), 1.24-1.36 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.64, 141.35, 135.01, 134.04, 131.14, 131.00, 128.15, 41.25, 36.07, 32.64, 32.35, 30.32, 30.26, 30.08, 30.02, 23.33, 19.24, 14.34. HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{27}F_7NO^-$ [M-H]$^-$ 490.1986, found 490.1986. Melting Point: 129-132 °C. IR (neat, cm^{-1}) 3213, 2924, 2852, 1697, 1656, 1535, 1510, 1477, 1349, 1239, 1180, 1139, 1012, 958.



3d

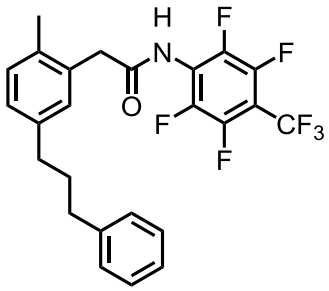
2-(5-isobutyl-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-acetamide. Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (84% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.42 (br, 1H, N-H), 7.13 (d, *J* = 1.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.7 Hz, 1H), 3.87 (s, 2H), 2.43 (d, *J* = 8 Hz, 2H), 2.32 (s, 3H), 1.80-1.89 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.63, 140.11, 135.12, 133.95, 131.83, 130.88, 128.85, 45.55, 41.23, 30.97, 22.62, 19.26. HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{17}F_7NO^-$ [M-H]$^-$ 420.1204, found 420.1204. Melting Point: 164-166 °C. IR (neat, cm^{-1}) 3228, 2953, 1699, 1658, 1536, 1510, 1476, 1348, 1238, 1182, 1143, 1012, 953.



3e

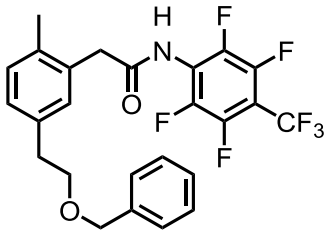
2-(2-methyl-5-(3,3,3-trifluoropropyl)phenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)-p

henyl)acetamide Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (77% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.48 (br, 1H, N-H), 7.25 (s, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 2H), 2.81-2.87 (m, 2H), 2.46-2.56 (m, 2H), 2.33(s, 3H); ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.52, 137.73, 136.18, 134.56, 131.30, 131.17, 128.12 (q, *J* = 274 Hz), 128.05, 41.12, 35.73 (q, *J* = 28 Hz), 28.19 (q, *J* = 3.0 Hz), 19.23. ^{19}F NMR (376 MHz, acetone-d^{6}) δ -56.0 (t, *J* = 21 Hz, 3F), -66.4 (s, 3F), -143.3--143.7 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{12}F_{10}NO^{-}$ [M-H]$^{-}$ 460.0765, found 460.0763. Melting Point: 178-179 °C. IR (neat, cm^{-1}) 3254, 3219, 1694, 1658, 1537, 1511, 1478, 1351, 1310, 1246, 1185, 1143, 1011, 959.



3f

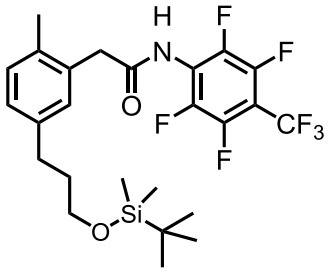
2-(2-methyl-5-(3-phenylpropyl)phenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)-phenyl)acetamide. Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (90% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.42 (br, 1H, N-H), 7.24-7.28 (m, 2H), 7.19-7.22 (m, 2H), 7.14-7.19 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.6 Hz, 1H), 3.88 (s, 2H), 2.59-2.67 (m, 4H), 2.32 (s, 3H), 1.89-1.97 (m, 2H); ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.61, 143.23, 140.89, 135.19, 134.15, 131.19, 131.08, 129.24, 129.12, 128.20, 126.53, 41.25, 36.06, 35.58, 34.08, 19.24. HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{19}F_{7}NO^{-}$ [M-H]$^{-}$ 482.1368, found 482.1368. Melting Point: 167-170 °C. IR (neat, cm^{-1}) 3218, 1693, 1656, 1530, 1509, 1476, 1347, 1239, 1187, 1146, 1012, 957.



3g

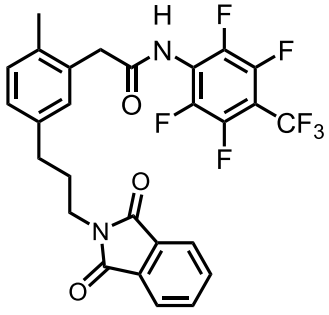
2-(5-(2-(benzyloxy)ethyl)-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)-phenyl)acetamide. Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (84% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.42 (br, 1H, N-H), 7.28-7.32 (m, 4H), 7.21-7.26 (m, 2H), 7.12 (d, *J*

= 7.5 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.51 (s, 2H), 3.87 (s, 2H), 3.68 (t, *J* = 7.0 Hz, 2H), 2.87 (t, *J* = 8 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, acetone-d^6) δ 169.56, 139.92, 137.99, 135.60, 134.10, 131.77, 131.02, 129.00, 128.75, 128.23, 128.05, 73.20, 71.96, 41.26, 36.51, 19.26. HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{21}F_7NO_2^+$ $[M+H]^+$ 500.1455, found 500.1455. Melting Point: 150-152 °C. IR (neat, cm^{-1}) 3216, 1697, 1657, 1533, 1509, 1473, 1347, 1237, 1182, 1140, 1101, 1011, 956.



3h

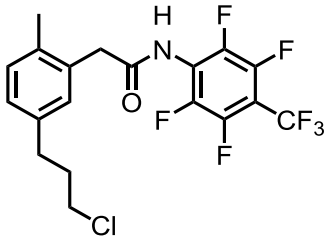
2-(5-(3-((tert-butyldimethylsilyl)oxy)propyl)-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (84% yield). ^{1}H NMR (500 MHz, acetone-d^6) δ 9.42 (br, 1H, N-H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.04 (dd, *J* = 7.5, 2 Hz, 1H), 3.87 (s, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 2.31 (s, 3H), 1.77-1.84 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, acetone-d^6) 169.60, 140.85, 135.14, 134.12, 131.22, 131.05, 128.23, 62.90, 41.26, 35.44, 32.25, 26.31, 19.24, 18.82, -5.15. HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{31}F_7NO_2Si^+$ $[M+H]^+$ 538.2007, found 538.2008. Melting Point: 135-137 °C. IR (neat, cm^{-1}) 3216, 2929, 2858, 1696,1656, 1533, 1509, 1473, 1348, 1242, 1181, 1142, 1102, 1011, 958, 835, 774, 719.



3i

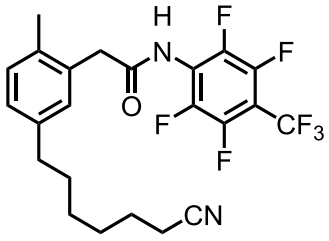
2-(5-(3-(1,3-dioxoisoindolin-2-yl)propyl)-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (86% yield). ^{1}H NMR (500 MHz, acetone-d^6) δ 9.36 (br, 1H, N-H), 7.80-7.85 (m, 4H), 7.19 (s, 1H), 7.04-7.10 (m, 2H), 3.84 (s, 2H), 3.70 (t, *J* = 7.2 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H), 2.28 (s, 3H), 1.97-2.04 (m, 2H). ^{13}C NMR (125 MHz, acetone-d^6) δ 169.51, 168.83, 140.06, 135.42, 134.90, 134.15, 133.17, 131.26, 131.13, 128.18, 123.62, 41.37, 38.29, 33.36, 30.68, 19.20. HRMS

(ESI-TOF) *m/z* Calcd for $C_{27}H_{20}F_7N_2O_3^+$ $[M+H]^+$ 553.1357, found 553.1356. Melting Point: 167-169 °C. IR (neat, cm^{-1}) 3249, 1705, 1655, 1531, 1509, 1397, 1346, 1236, 1186, 1148, 1013, 958, 719.



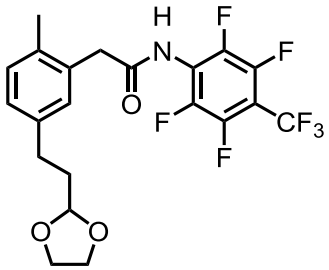
3j

2-(5-(3-chloropropyl)-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)-phenyl)acetamide Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (82% yield) . ^{1}H NMR (500 MHz, acetone-d^6) δ 9.44 (br, 1H, N-H), 7.20 (s, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.06 (dd, *J* = 7.3, 1.8 Hz, 1H), 3.89 (s, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 2.73 (t, *J* = 7.8 Hz, 2H), 2.32 (s, 3H), 2.04-2.09 (m, 2H); ^{13}C NMR (125 MHz, acetone-d^6) δ 169.57, 139.56, 135.61, 134.35, 131.32, 131.22, 128.29, 45.05, 41.21, 35.09, 32.96, 19.25. HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{14}ClF_7NO^-$ $[M-H]^-$ 440.0658, found 440.0663. Melting Point: 198-199 °C. IR (neat, cm^{-1}) 3215, 1696, 1657, 1535 1510, 1476, 1348, 1238, 1182, 1140, 1011, 958.



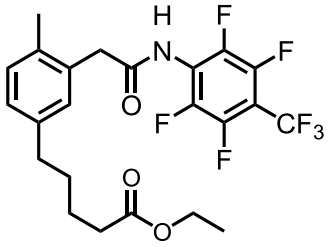
3k

2-(5-(6-cyanohexyl)-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-a cetamide Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 3/1). The product was obtained as a white solid (82% yield). ^{1}H NMR (500 MHz, acetone-d^6) δ 9.42 (br, 1H, N-H), 7.17 (s, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 3.87 (s, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 1.59-1.67 (m, 4H), 1.44-1.51 (m, 2H), 1.35-1.43 (m, 2H); ^{13}C NMR (125 MHz, acetone-d^6) δ 169.65, 141.12, 135.10, 134.08, 131.19, 131.03, 128.16, 120.64, 41.23, 35.87, 31.98, 29.19, 29.07, 26.14, 19.23, 17.09. HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{20}F_7N_2O^-$ $[M-H]^-$ 473.1469, found 473.1473. Melting Point: 115-116 °C. IR (neat, cm^{-1}) 3223, 2928,1697, 1657, 1531, 1509, 1473, 1348, 1238, 1179, 1144, 1011, 956.



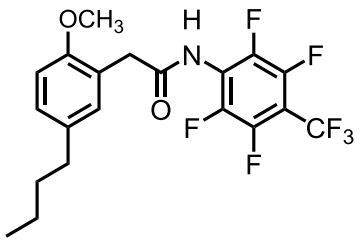
3l

2-(5-(2-(1,3-dioxolan-2-yl)ethyl)-2-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide Substrate **1** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 3/1). The product was obtained as a white solid (90% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.42 (br, 1H, N-H), 7.19 (d, *J* = 1.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.05 (dd, *J* = 7.8, 1.2 Hz, 1H), 4.83 (t, *J* = 4.8 Hz, 1H), 3.91-3.96 (m, 2H), 3.88 (s, 2H), 3.79-3.83 (m, 2H), 2.67 (t, *J* = 8.0 Hz, 2H), 2.32 (s, 3H), 1.85-1.90 (m, 2H). ^{13}C NMR (150 MHz, acetone-d^{6}) δ 169.57, 140.44, 135.31, 134.22, 131.16, 131.13, 128.10, 104.30, 65.47, 41.25, 36.59, 30.41, 19.22. HRMS (ESI-TOF) *m/z* Calcd for $C_{21}H_{19}F_7NO_3^+$ $[M+H]^+$ 466.1248, found 466.1246. Melting Point: 201-202 °C. IR (neat, cm^{-1}) 3216, 1694, 1655, 1529, 1509, 1475, 1350, 1238, 1187, 1146, 1012, 953.



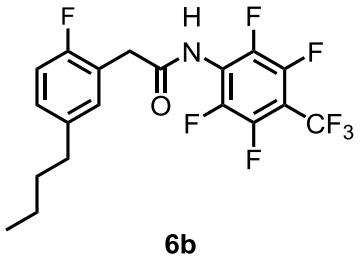
3m

Ethyl 5-(4-methyl-3-(2-oxo-2-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amino)ethyl)phenyl)pentanoate. Substrate **1** was alkylated following the general alkylation procedure except adding 3 equiv **N15** instead of 1.5 equiv (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (74% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.42 (br, 1H, N-H), 7.17 (d, *J* = 1.0 Hz, 1H), 7.11 (d, *J* = 8 Hz, 1H), 7.03 (dd, *J* = 7.5, 2 Hz, 1H), 4.06 (q, *J* = 7 Hz, 2H), 3.87 (s, 2H), 2.59 (t, 7 Hz, 2H), 2.27-2.33 (m, 5H), 1.59-1.67 (m, 4H), 1.19 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d^{6}) δ 173.56, 169.59, 140.89, 135.19, 134.12, 131.18, 131.06, 128.17, 60.44, 41.28, 35.66, 34.47, 31.63, 25.30, 19.23, 14.56. HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{23}F_7NO_3^+$ $[M+H]^+$ 494.1561, found 494.1561. Melting Point: 156-158 °C. IR (neat, cm^{-1}) 3220, 1732, 1696, 1656, 1528, 1508, 1475, 1350, 1238, 1182, 1147, 1011, 957.



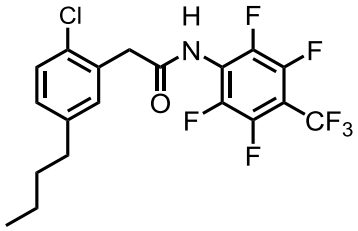
6a

2-(5-butyl-2-methoxyphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-acetamide. Substrate **5a** was alkylated following the general alkylation procedure except adding 3 equiv **N15** instead of 1.5 equiv (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (65% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.26 (br, 1H, N-H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.10 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.91 (d, *J* = 8 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 2H), 2.55 (t, *J* = 7.8 Hz, 2H), 1.53-1.60 (m, 2H), 1.31-1.39 (m, 2H), 0.91 (t, *J* = 7.5 H, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.70, 156.59, 135.62, 131.97, 129.18, 123.84, 111.42, 55.90, 38.54, 35.32, 34.72, 22.95, 14.20. ^{19}F NMR (376 MHz, acetone-d^{6}) δ -56.0 (t, *J* = 23 Hz, 3F), -143.7--143.3 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{19}F_7NO_2^+$ $[M+H]^+$ 438.1298, found 438.1297. Melting point: 148-149 °C. IR (neat, cm^{-1}) 3221, 2927, 1702, 1656, 1533, 1509, 1472, 1341, 1255, 1240, 1184, 1146, 1014, 951.



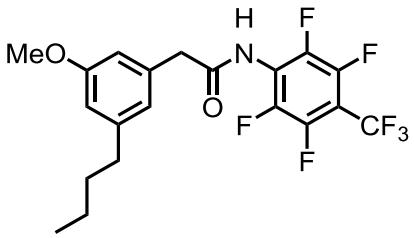
6b

2-(5-butyl-2-fluorophenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **5b** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (85% yield) . ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.61 (br, 1H, N-H), 7.26 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.13-7.18 (m, 1H), 7.03 (dd, *J* = 10, 8.5 Hz, 1H), 3.91 (s, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.55-1.62 (m, 2H), 1.31-1.39 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 168.70, 160.38 (d, *J* = 241 Hz), 139.62 (d, *J* = 3.8 Hz), 132.46 (d, *J* = 3.8 Hz), 129.75 (d, *J* = 7.5 Hz), 122.43 (d, *J* = 15 Hz), 115.62 (d, *J* = 21 Hz), 36.40 (d, *J* = 2.5 Hz), 35.35, 34.54, 22.89, 14.16. ^{19}F NMR (376 MHz, acetone-d^{6}) δ -56.0 (t, *J* = 23 Hz, 3F), -122.5 (s, 1F), -143.7--143.3 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{14}F_8NO^-$ $[M-H]^-$ 424.0953, found 424.0950. Melting Point: 150 °C. IR (neat, cm^{-1}) 3226, 2929, 1702, 1657, 1538, 1507, 1476, 1344, 1238, 1179, 1142, 953.



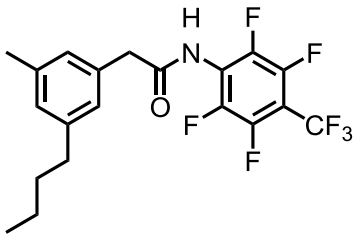
6c

2-(5-butyl-2-chlorophenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **5c** was alkylated following the general alkylation procedure except adding 3 equiv **N15** instead of 1.5 equiv (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (85% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.60 (br, 1H, N-H), 7.31-7.34 (m, 2H), 7.16 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.01 (s, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.56-1.63 (m, 2H), 1.32-1.40 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 168.58, 142.88, 133.52, 132.92, 132.27, 129.87, 129.79, 40.98, 35.47, 34.28, 22.91, 14.15. HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{16}ClF_7NO^+$ $[M+H]^+$ 442.0803, found 442.0801. Melting Point: 158-159 °C. IR (neat, cm^{-1}) 3204, 2933, 1699, 1657, 1547, 1513, 1484, 1344, 1241 1185, 1150, 1017.



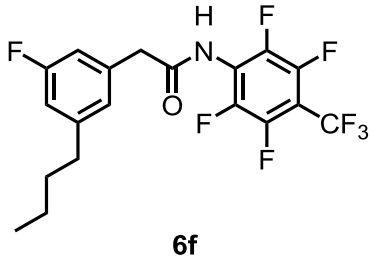
6d

2-(3-butyl-5-methoxyphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide Substrate **5d** was alkylated following the general alkylation procedure except adding 3 equiv **N15** instead of 1.5 equiv (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (73% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.50 (br, 1H, N-H), 6.81 (s, 1H), 6.79 (s, 1H), 6.70 (s, 1H), 3.81 (s, 2H), 3.78 (s, 3H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.55-1.63 (m, 2H), 1.32-1.40 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.57, 160.93, 145.40, 136.83, 122.47, 113.54, 112.96, 55.42, 43.37, 36.28, 34.37, 23.01, 14.20. HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{17}F_7NO_2^-$ $[M-H]^-$ 436.1153, found 436.1159. Melting Point: 124-126 °C. IR (neat, cm^{-1}) 3231, 2933, 1688, 1655, 1596, 1510, 1479, 1341, 1236, 1189, 1149, 1011.



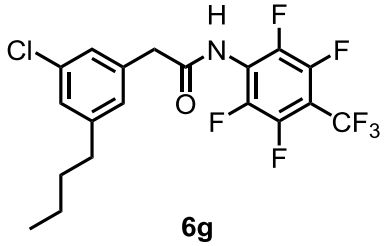
6e

2-(3-butyl-5-methylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **5e** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (73% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.51 (br, 1H, N-H), 7.02 (s, 1H), 7.01 (s, 1H), 6.94 (s, 1H), 3.79 (s, 2H), 2.56 (t, *J* = 7.8 Hz, 2H), 2.29 (s, 3H), 1.55-1.61 (m, 2H), 1.31-1.39 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.72, 143.86, 138.68, 135.51, 128.71, 128.14, 127.20, 43.24, 36.11, 34.51, 23.02, 21.34, 14.20. HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{19}F_7NO^+$ $[M+H]^+$ 422.1349, found 422.1348. Melting Point: 132-133 °C. IR (neat, cm^{-1}) 3222, 2954, 2929, 1702, 1658, 1536, 1508, 1475, 1345, 1241, 1181, 1143, 1011, 950.



6f

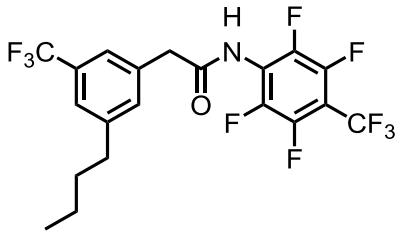
2-(3-butyl-5-fluorophenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **5f** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (75% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.61 (br, 1H, N-H), 7.07 (s, 1H), 6.98 (d, *J* = 10 Hz, 1H), 6.90 (d, *J* = 9.5 Hz, 1H), 3.89 (s, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.57-1.65 (m, 2H), 1.32-1.40 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.18, 163.76 (d, *J* = 241 Hz), 146.63 (d, *J* = 7.5 Hz), 138.01 (d, *J* = 8.8 Hz), 126.20 (d, *J* = 1.2 Hz), 114.44 (d, *J* = 21 Hz), 114.14 (d, *J* = 22 Hz), 42.78 (d, *J* = 1.2 Hz), 35.90 (d, *J* = 1.2 Hz), 34.13, 22.91, 14.14. ^{19}F NMR (376 MHz, acetone-d^{6}) δ -56.03 (t, *J* = 23 Hz, 3F), -115.11 (s, 1F), -143.62--143.22 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{14}F_8NO^-$ $[M-H]^-$ 424.0953, found 424.0961. Melting Point: 137 °C. IR (neat, cm^{-1}) 3259, 3222, 2961, 2934, 1701, 1658, 1537, 1511, 1477, 1344, 1239, 1182, 1144, 1010, 950.



6g

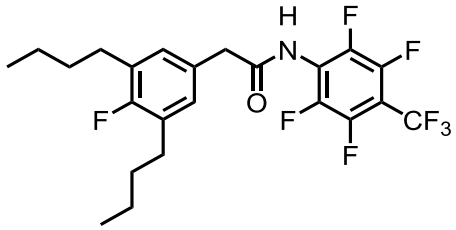
2-(3-butyl-5-chlorophenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **5g** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (85% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.62 (br, 1H, N-H), 7.25 (s, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 3.88 (s, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.57-1.64 (m, 2H), 1.32-1.40 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.15, 146.22, 137.82, 134.38, 128.87, 127.81, 127.45, 42.64, 35.78, 34.17, 22.90, 14.13. HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{16}ClF_7NO^+$ $[M+H]^+$

442.0803, found 442.0802. Melting Point: 147-149 °C. IR (neat, cm^{-1}) 3223, 2957, 2931, 1700, 1658, 1537, 1512, 1477, 1346, 1240, 1183, 1145, 1011, 951.



6h

2-(3-butyl-5-methoxyphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide Substrate **5h** was alkylated following the general alkylation procedure except adding 3 equiv **N15** instead of 1.5 equiv (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (66% yield). ^{1}H NMR (500 MHz, acetone-d^6) δ 9.69 (br, 1H, N-H), 7.55 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 4.00 (s, 2H), 2.73 (t, *J* = 7.8 Hz, 2H), 1.61-1.68 (m, 2H), 1.34-1.42 (m, 2H), 0.93 (t, *J* = 7.5 Hz). ^{13}C NMR (150 MHz, acetone-d^6) δ 169.13, 145.32, 137.06, 134.18, 131.11 (q, *J* = 31 Hz), 124.50 (q, *J* = 2.5 Hz), 124.27 (q, *J* = 2.5 Hz), 122.10 (q, *J* = 274 Hz), 42.60, 35.85, 34.25, 22.92, 14.13. ^{19}F NMR (376 MHz, acetone-d^6) δ -56.04 (t, *J* = 21 Hz, 3F), -62.16 (s, 3F), -143.66--143.25 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{16}F_{10}NO^+$ $[M+H]^+$ 476.1067, found 476.1065. Melting Point: 145-146 °C. IR (neat, cm^{-1}) 3266, 3234, 2936, 1703, 1660, 1540, 1514, 1479, 1346, 1243, 1179, 1148, 1127, 1011, 951.



6i-di

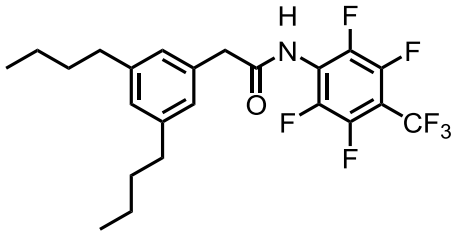
2-(3,5-dibutyl-4-fluorophenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-acetamide. Substrate **5i** was alkylated using 5.0 equiv ^{n}BuI, 20 mol% $Pd(OAc)_2$, 20 mol% **L1**, 3.0 equiv **N15**, 6.0 equiv AgOAc (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (77% yield). ^{1}H NMR (500 MHz, acetone-d^6) δ 9.52 (br, 1H, N-H), 7.10 (d, *J* = 12 Hz, 2H), 3.80 (s, 2H), 2.62 (t, *J* = 7.8 Hz, 4H), 1.54-1.62 (m, 4H), 1.33-1.42 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (125 MHz, acetone-d^6) δ 169.72, 159.36 (d, *J* = 241 Hz), 131.04 (d, *J* = 3.8 Hz), 129.95 (d, *J* = 18 Hz), 129.89 (d, *J* = 5 Hz), 42.50, 33.22, 29.36, 23.06, 14.15. ^{19}F NMR (376 MHz, acetone-d^6) δ -56.01 (t, *J* = 21 Hz, 3F), -128.72 (s, 1F), -143.64--142.27 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{24}F_8NO^+$ $[M+H]^+$ 482.1725, found 482.1723. Melting Point: 141-143 °C. IR (neat, cm^{-1}) 3248, 2958, 2930, 2863, 1693, 1659, 1512, 1476, 1354, 1337, 1242, 1178, 1150, 1007, 953.

Alkylation of **5j**

Method 1: Substrate **5j** was alkylated 5.0 equiv ^{n}BuI, 20 mol% $Pd(OAc)_2$, 20 mol% **L1**, 3.0 equiv **N15**, 6.0 equiv AgOAc. The disubstituted product **6j-di** was obtained as a white solid

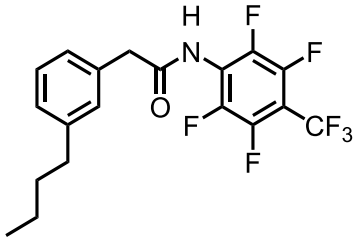
(65% yield) and the mono-substituted product **6j-mono** was obtained as a white solid (15% yield). (Eluent: hexanes/ethyl acetate = 4/1)

Method 2: Substrate **5j** was alkylated following general procedure using 2.0 equiv ^{n}BuI, 10 mol% $Pd(OAc)_2$, 20 mol% **L1**, 1.5 equiv **N15**, 3.0 equiv AgOAc and heating at 95℃. The disubstituted product **6j-di** was obtained as a white solid (8% yield) and the mono-substituted product **6j-mono** was obtained as a white solid (44% yield). (Eluent: hexanes/ethyl acetate = 4/1)



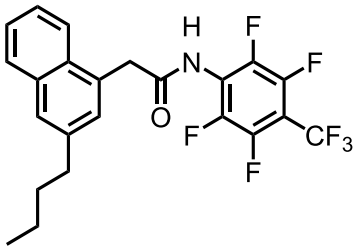
6j-di

2-(3,5-dibutylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide.
^{1}H NMR (500 MHz, acetone-d^6) δ 9.50 (br, 1H, N-H), 7.04 (s, 2H), 6.96 (s, 1H), 3.81 (s, 2H), 2.58 (t, *J* = 7.8 Hz, 4H), 1.55-1.63 (m, 4H), 1.32-1.40 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (125 MHz, acetone-d^6) δ 169.73, 143.82, 135.49, 128.11, 127.45, 43.32, 36.18, 34.54, 23.03, 14.21. ^{19}F NMR (376 MHz, acetone-d^6) δ -56.0 (t, *J* = 21 Hz, 3F) , -143.6--142.3 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{25}F_7NO^+$ $[M+H]^+$ 464.1819, found 464.1820. Melting point: 128-130 °C. IR (neat, cm^{-1}) 3259, 2955, 2926, 1703, 1658, 1529, 1509, 1473, 1350, 1239, 1145, 1011, 950



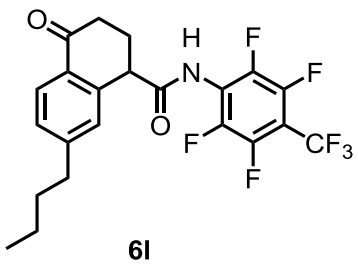
6j-mono

2-(3-butylphenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide.
^{1}H NMR (500 MHz, acetone-d^6) δ 9.62 (br, 1H, N-H), 7.30-7.34 (m, 2H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 3.92 (s, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 1.64-1.71 (m, 2H), 1.39-1.47 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d^6) δ 169.64, 143.90, 135.66, 130.12, 129.28, 127.90, 127.37, 43.23, 36.14, 34.49, 22.97, 14.19. HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{17}F_7NO^+$ $[M+H]^+$ 408.1193, found 408.1195. Melting point: 100 °C. IR (neat, cm^{-1}) 3255, 2958, 2928, 1700, 1659, 1535, 1512, 1478, 1346, 1239, 1183, 1143, 1013, 957.



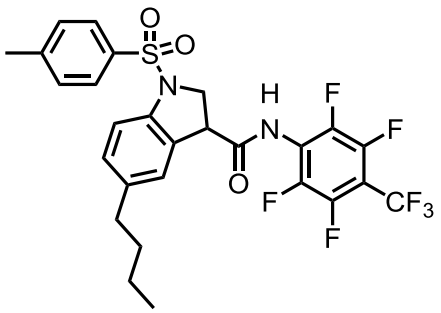
6k

2-(3-butylnaphthalen-1-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **5k** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (92% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.56 (br, 1H, N-H), 8.07-8.11 (m, 1H), 7.84-7.89 (m, 1H), 7.66 (s, 1H), 7.47-7.52 (m, 3H), 4.34 (s, 2H), 2.78 (t, *J* = 7.8 Hz, 2H), 1.67-1.75 (m, 2H), 1.37-1.46 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d^{6}) δ 169.72, 140.82, 135.19, 131.95, 131.75, 130.51, 129.02, 127.16, 126.69, 126.26, 124.66, 40.95, 36.23, 34.20, 23.06, 14.22. HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{19}F_7NO^+$ $[M+H]^+$ 458.1349, found 458.1350. Melting point: 201-203 °C. IR (neat, cm^{-1}) 3200, 2923, 1685, 1655, 1510, 1479, 1337, 1233, 1188, 1150, 1012, 948.



6l

7-butyl-4-oxo-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydronapht halene-1-carboxamide. Substrate **5i** was alkylated following the general alkylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (61% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.76 (br, 1H, N-H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.33 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 4.36 (t, *J* = 5.5 Hz, 1H), 2.84-2.91 (m, 1H), 2.68 (t, *J* = 7.8 Hz, 2H), 2.48-2.65 (m, 3H), 1.57-1.66 (m, 2H), 1.31-1.40 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 196.28, 172.02, 149.97, 141.94, 131.76, 129.28, 128.99, 127.97, 46.78, 36.27, 36.23, 33.96, 27.72, 22.94, 14.12. HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{19}F_7NO_2^+$ $[M+H]^+$ 462.1298, found 462.1298. Melting point: 191-193 °C. IR (neat, cm^{-1}) 3223, 2937, 1679, 1656, 1606, 1508, 1485, 1342, 1239, 1182, 1147, 998, 941.



6m

5-butyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1-tosylindoline-3-carboxamide

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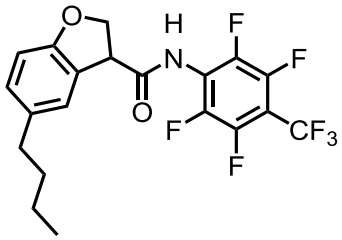
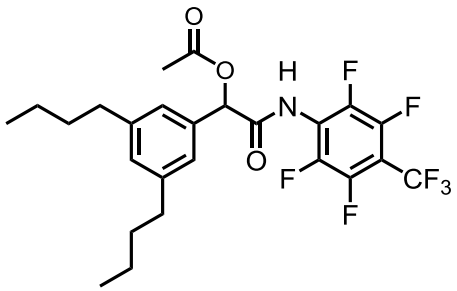
Substrate **5m** was alkylated following the general alkylation procedure except adding 3 equiv **N15** instead of 1.5 equiv (eluent: hexanes/ethyl acetate = 3/1). The product was obtained as a white solid (52% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.84 (br, 1H, N-H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.52, (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.28 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 4.48 (dd, *J* = 9.5, 7.5 Hz, 1H), 4.37 (dd, *J* = 10.5, 7 Hz, 1H), 4.27 (dd, *J* = 10.5, 10 Hz, 1H), 2.55 (t, *J* = 7.8 Hz, 2H), 2.37 (s, 3H), 1.50-1.57 (m, 2H), 1.26-1.35 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d^{6}) δ 169.75, 145.29, 140.79, 139.36, 134.88, 130.87, 130.61, 129.88, 128.38, 125.69, 115.20, 53.23, 47.06, 35.58, 34.47, 22.80, 21.40, 14.13. HRMS (ESI-TOF) *m/z* Calcd for $C_{27}H_{24}F_7N_2O_3S^+$ $[M+H]^+$ 589.1390., found 589.1390. Melting point: 192-193 °C. IR (neat, cm^{-1}) 3266, 2930, 1684, 1655, 1526, 1508, 1473, 1343, 1235, 1189, 1159, 996



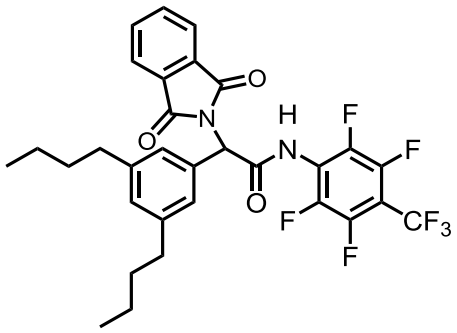
6n

5-butyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-2,3-dihydrobenzofuran-3-carb oxamide. Substrate **5n** was alkylated following the general alkylation procedure except adding 3 equiv **N15** instead of 1.5 equiv (eluent: hexanes/ethyl acetate = 3/1). The product was obtained as a white solid (52% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.86 (br, 1H, N-H), 7.32 (s, H), 7.03 (dd, *J* = 8.2, 1.8Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.93 (dd, *J* = 8.8, 6.2 Hz, 1H), 4.76 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.71 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.55 (t, *J* = 7.8 Hz, 2H), 1.52-1.59 (m, 2H), 1.29-1.37 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 170.37, 159.30, 135.77, 130.20, 126.45, 125.39, 110.05, 73.79, 49.39, 35.61, 34.92, 22.79, 14.18. HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{17}F_7NO_2^+$ $[M+H]^+$ 436.1142, found 436.1140. Melting point: 154-156 °C. IR (neat, cm^{-1}) 3219, 2959, 2927,1694, 1656, 1536, 1509, 1476, 1344, 1236, 1187, 1149, 1010, 989.



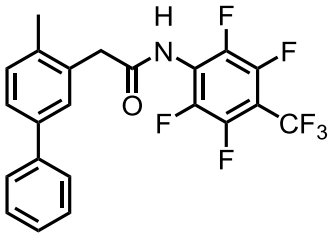
6o-di

1-(3,5-dibutylphenyl)-2-oxo-2-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amino)-ethyl acetate. Substrate **5o** was alkylated using 5.0 equiv ^{n}BuI, 20 mol% $Pd(OAc)_2$, 20 mol% **L1**, 3.0 equiv **N15**, 6.0 equiv AgOAc (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (80% yield). ^{1}H NMR (500 MHz, acetone-d^6) δ 9.85 (br, 1H, N-H), 7.25 (s, 2H), 7.11 (s, 1H), 6.15 (s, 1H), 2.62 (t, *J* = 7.8 Hz, 4H), 2.15 (s, 3H), 1.57-1.64 (m, 4H), 1.32-1.40 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, acetone-d^6) δ 170.39, 167.96, 144.17, 135.44, 130.33, 126.19, 76.54, 36.13, 34.46, 23.00, 20.69, 14.19. HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{27}F_7NO_3^+$ $[M+H]^+$ 522.1874, found 522.1871. Melting point: 133-134 °C. IR (neat, cm^{-1}) 3235, 2960, 2934, 1751, 1701, 1656, 1509, 1482, 1341, 1233, 1152, 1041, 1003



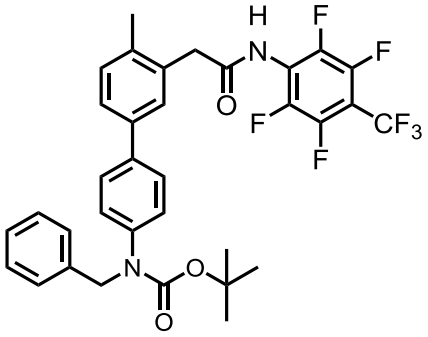
6p-di

2-(3,5-dibutylphenyl)-2-(1,3-dioxoisoindolin-2-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **5o** was alkylated using 5.0 equiv ^{n}BuI, 20 mol% $Pd(OAc)_2$, 20 mol% **L1**, 3.0 equiv **N15**, 6.0 equiv AgOAc (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (69% yield). ^{1}H NMR (500 MHz, acetone-d^6) δ 9.57 (br, 1H, N-H), 7.87-7.92 (m, 4H), 7.34 (s, 2H), 7.06 (s, 1H), 6.28 (s, 1H), 2.60 (t, *J* = 7.8 Hz, 4H), 1.55-1.62 (m, 4H), 1.32-1.40 (m, 4H), 0.90 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, acetone-d^6) δ 167.37, 166.22, 143.42, 135.01, 134.61, 132.28, 129.30, 127.85, 123.70, 57.76, 35.66, 33.92, 22.53, 13.68. HRMS (ESI-TOF) *m/z* Calcd for $C_{31}H_{28}F_7N_2O_3^+$ $[M+H]^+$ 609.1983, found 609.1981. Melting point: 125-127 °C. IR (neat, cm^{-1}) 3241, 2959, 2930, 1724, 1657, 1509, 1483, 1379, 1340, 1236, 1187, 1149, 986



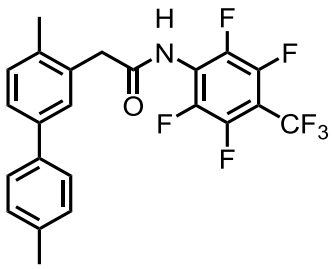
8a

2-(4-methyl-[1,1'-biphenyl]-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-aceta mide. Substrate **1** was arylated following the general arylation procedure. The product was obtained as a white solid (73% yield) (eluent: hexanes/ethyl acetate = 4/1 and toluene/ethyl acetate = 30/1). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.57 (br, 1H, N-H), 7.63-7.66 (m, 3H), 7.50 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.34 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 4.00 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.56, 141.52, 139.68, 137.29, 134.91, 131.68, 129.76, 129.68, 128.00, 127.50, 126.54, 41.40, 19.32. ^{19}F NMR (376 MHz, acetone-d^{6}) δ -56.0 (t, *J* = 21 Hz, 3F), -143.6--143.3 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{15}F_7NO^+$ $[M+H]^+$ 442.1036, found 442.1024. Melting point: 211-212 °C. IR (neat, cm^{-1}) 3243, 1700, 1655, 1532, 1510, 1475, 1348, 1241, 1183, 1146, 1011, 956.



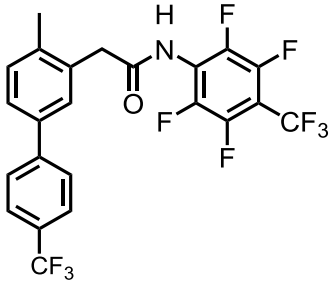
8b

***Tert*-butyl benzyl(4'-methyl-3'-(2-oxo-2-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl) amino)ethyl)-[1,1'-biphenyl]-4-yl)carbamate**. Substrate **1** was arylated following the general arylation procedure (eluent: hexanes/ethyl acetate = 3/1). The product was obtained as a white solid (86% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.53 (br, 1H, N-H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.56-7.59 (m, 2H), 7.47 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.27-7.33 (m, 7H), 7.22-7.25 (m, 1H), 4.93 (s, 2H), 3.97 (s, 2H), 2.39 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (150 MHz, acetone-d^{6}) δ 169.64, 155.20, 142.89, 139.76, 138.82, 138.56, 137.23, 134.90, 131.64, 129.56, 129.16, 128.17, 127.82, 127.65, 127.43, 126.31, 80.77, 54.01, 41.31, 28.42, 19.30. HRMS (ESI-TOF) *m/z* Calcd for $C_{34}H_{30}F_7N_2O_3^+$ $[M+H]^+$ 647.2139, found 647.2121. Melting point: 78-82 °C. IR (neat, cm^{-1}) 3224, 2973, 1697, 1667, 1509, 1479, 1390, 1366, 1340, 1236, 1147, 1010.



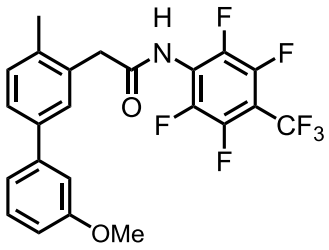
8c

2-(4,4'-dimethyl-[1,1'-biphenyl]-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-acetamide. Substrate **1** was arylated following the general arylation procedure. The product was obtained as a white solid (87% yield) (eluent: hexanes/ethyl acetate = 4/1 and toluene/ethyl acetate = 30/1). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.55 (br, 1H, N-H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.47 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 3.98 (s, 2H), 2.40 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.59, 139.62, 138.63, 137.62, 136.92, 134.82, 131.63, 130.32, 129.51, 127.34, 126.31, 41.42, 21.04, 19.30. HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{17}F_7NO^+$ $[M+H]^+$ 456.1193, found 456.1184. Melting point: 229-230 °C. IR (neat, cm^{-1}) 3247, 3212, 1698, 1657, 1534, 1510, 1474, 1347, 1240, 1180, 1141, 1010, 955.



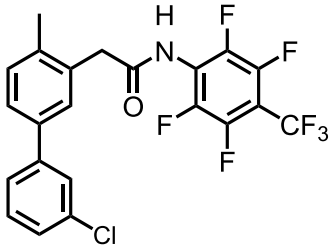
8d

2-(4-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide. Substrate **1** was arylated following the general arylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (84% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.59 (br, 1H, N-H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.58 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 4.03 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.43, 145.42, 138.60, 137.98, 135.28, 131.89, 130.05, 129.43 (q, *J* = 32 Hz), 128.13, 126.83, 126.58 (q, *J* = 4.0 Hz), 125.51 (q, *J* = 270 Hz), 41.28, 19.38. ^{19}F NMR (376 MHz, acetone-d^{6}) δ -56.02 (t, *J* = 21 Hz, 3F), -62.11 (s, 3F), -143.61--143.25 (m, 4F). HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{14}F_{10}NO^+$ $[M+H]^+$ 510.0910, found 510.0896. Melting point: 234-236 °C. IR (neat, cm^{-1}) 3221, 1699, 1657, 1534, 1510, 1472, 1349, 1322, 1241, 1177, 1137, 1070, 1009, 951, 821.



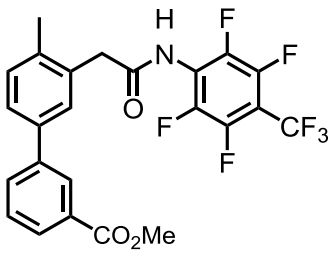
8e

2-(3'-methoxy-4-methyl-[1,1'-biphenyl]-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)-phenyl)acetamide. Substrate **1** was arylated following the general arylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (87% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.56 (br, 1H, N-H), 7.65 (d, *J* = 1.5 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.22 (ddd, *J* = 7.4, 1.4, 0.9 Hz, 1H), 7.19 (t, *J* = 2.0 Hz, 1H), 6.91 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 4.00 (s, 2H), 3.86 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.54, 161.19, 143.00, 139.60, 137.43, 134.87, 131.63, 130.68, 129.78, 126.62, 119.85, 113.48, 113.16, 55.56, 41.42, 19.33. HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{17}F_7NO_2^+$ $[M+H]^+$ 472.1142, found 472.1134. Melting point: 182-186 °C. IR (neat, cm^{-1}) 3215, 1697, 1656, 1532, 1510, 1474, 1348, 1240, 1180, 1143, 1011, 957.



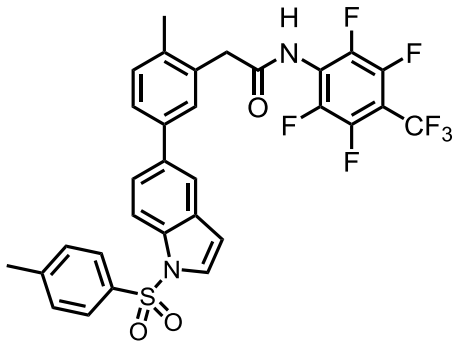
8f

2-(3'-chloro-4-methyl-[1,1'-biphenyl]-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)-phenyl)acetamide. Substrate **1** was arylated following the general arylation procedure (eluent: hexanes/ethyl acetate = 4/1 and toluene/ethyl acetate = 30:1). The product was obtained as a white solid (80% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.55 (br, 1H, N-H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.67 (t, *J* = 1.8 Hz, 1H), 7.61 (ddd, *J* = 7.9, 1.6, 0.9 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.37 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, acetone-d^{6}) δ 169.56, 143.63, 138.16, 137.99, 135.18, 135.13, 131.78, 131.36, 129.79, 127.85, 127.32, 126.57, 125.99, 41.22, 19.34. HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{14}ClF_7NO^+$ $[M+H]^+$ 476.0647, found 476.0632. Melting point: 229-231 °C. IR (neat, cm^{-1}) 3209, 1696, 1657, 1538, 1513, 1476, 1349, 1244, 1181, 1137, 1012, 958, 779.



8g

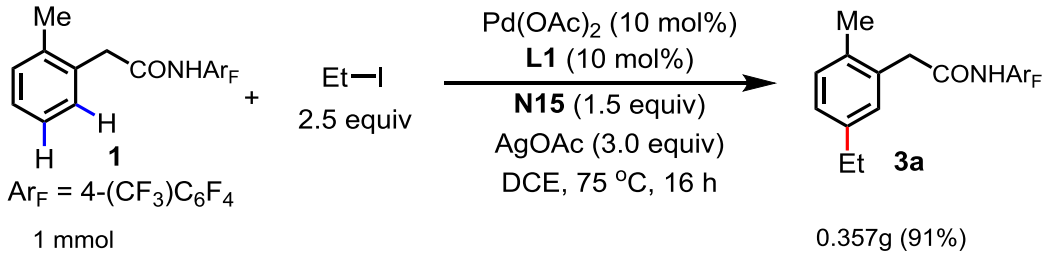
Methyl 4'-methyl-3'-(2-oxo-2-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amino) ethyl)-[1,1'-biphenyl]-3-carboxylate. Substrate **1** was arylated following the general arylation procedure (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (78% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.60 (br, 1H, N-H), 8.26 (t, *J* = 1.8 Hz, 1H), 7.98 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.90 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.59 (t, *J* =7.8 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 4.03 (s, 2H), 3.92 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.46, 167.16, 141.89, 138.51, 137.96, 135.17, 131.99, 131.82, 131.79, 130.00, 129.77, 128.81, 128.19, 126.58, 52.40, 41.30, 19.32. HRMS (ESI-TOF) *m/z* Calcd for $C_{24}H_{17}F_7NO_3^+$ $[M+H]^+$ 500.1091, found 500.1093. Melting point: 200-202 °C. IR (neat, cm^{-1}) 3220, 1723, 1697, 1656, 1533, 1511, 1476, 1349, 1242, 1182, 1144, 1012, 957, 754.



8h

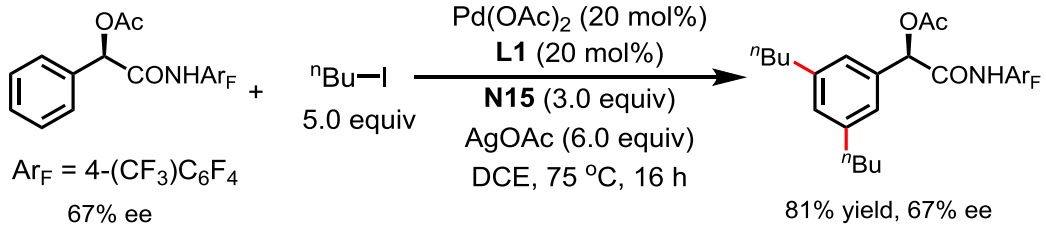
2-(2-methyl-5-(1-tosyl-1H-indol-5-yl)phenyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)-p henyl)acetamide. Substrate **1** was arylated following the general arylation procedure (eluent: hexanes/ethyl acetate = 3/1). The product was obtained as a white solid (57% yield). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 9.54 (br, 1H, N-H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 1.0 Hz, 1H), 7.73 (d, *J* = 3.5 Hz, 1H), 7.64 (d, *J* = 1.0 Hz, 1H), 7.63 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 4.0 Hz, 1H), 3.99 (s, 2H), 2.40 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 169.52, 146.44, 139.71, 137.26, 137.03, 136.05, 135.02, 134.88, 132.56, 131.68, 130.95, 130.04, 128.23, 127.76, 126.76, 124.58, 120.35, 114.59, 110.36, 41.42, 21.41, 19.29. HRMS (ESI-TOF) *m/z* Calcd for $C_{31}H_{22}F_7N2O_3S^+$ $[M+H]^+$ 635.1234, found 635.1237. Melting point: 202-205 °C. IR (neat, cm^{-1}) 3211, 1495, 1656, 1509, 1478, 1455, 1370, 1340, 1238, 1170, 1131, 1010, 957.

3.8 Reaction in 1.0 mmol Scale



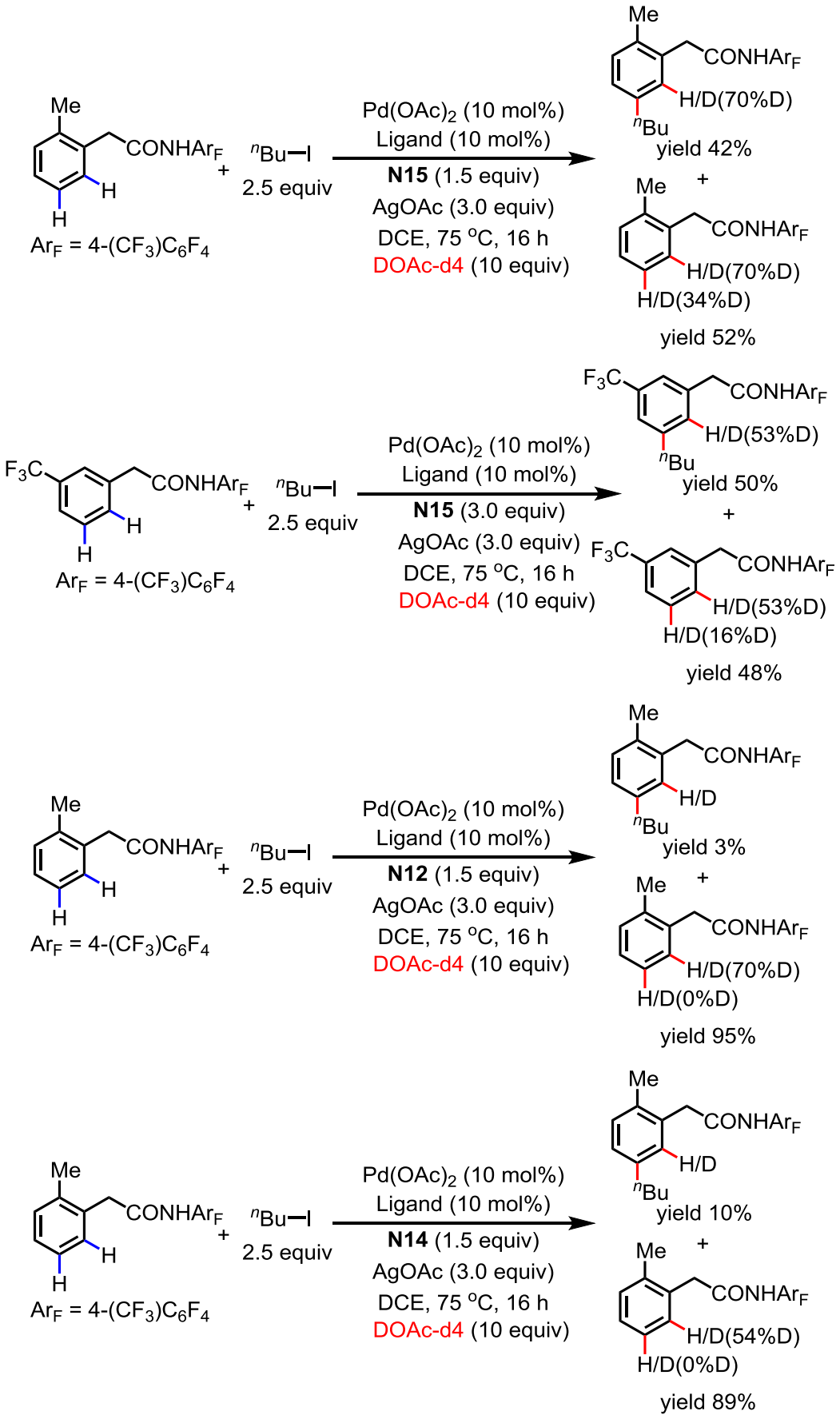
A 100 ml tube equipped with a magnetic stir bar was charged with **1** (0.365g, 1.0 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), **L1** (27 mg, 0.1 mmol), AgOAc (0.50 mg, 3.0 mmol) and **N15** (0.228 mg, 1.5 mmol). Iodoethane (0.390 g, 0.29 ml, 2.5 mmol) was then added *via* a microsyringe. Subsequently, DCE (15 mL) was injected, and the tube was capped and closed tightly. The reaction mixture was then stirred at 75 °C for 16 h. After being allowed to cool to room temperature, the mixture was passed through a pad of Celite with ethyl acetate as the eluent to remove any insoluble precipitate. The resulting solution was concentrated. The pure product was then isolated by column chromatography with hexanes and ethyl acetate (10:1) as the eluent.

3.9 Reaction with Chiral Substrate



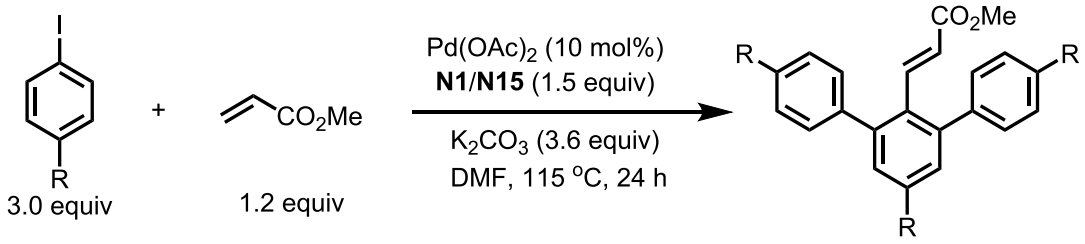
Substrate **5o** with 67% ee was alkylated using 5.0 equiv ^{n}BuI, 20 mol% $Pd(OAc)_2$, 20 mol% **L1**, 3.0 equiv **N15**, 6.0 equiv AgOAc (eluent: hexanes/ethyl acetate = 4/1). The product was obtained as a white solid (81% yield) with 67% ee. The enantiomeric purity of the substrate a was determined by HPLC analysis (CHIRALCEL ADH column, 10% isopropanol in hexanes, flow rate 0.8 mL/min, retention time 6.313 min (major) and 37.353 min (minor), 67% ee. The enantiomeric purity of the product a was determined by HPLC analysis (CHIRALCEL ADH column, 10% isopropanol in hexanes, flow rate 0.8 mL/min, retention time 4.447 min (major) and 22.380 min (minor), 67% ee.

3.10 Deuteration Experiment.

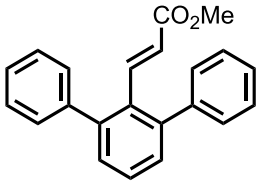


Procedure for deuterated experiment: A 2-dram vial equipped with a magnetic stir bar was charged with the appropriate phenylacetic acid–derived amide substrate (0.10 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%), **L1** (10 mol%), AgOAc (50 mg, 0.30 mmol) and norbronene derivitive (0.15 or 0.30 mmol). Butyl iodide (0.25 mmol) and DOAc-d4 (64 mg, 1.0 mmol) were then added *via* a microsyringe. Subsequently, DCE (1.5 mL) was injected, and the vial was capped and closed tightly. The reaction mixture was then stirred at 75 °C for 16 h. After being allowed to cool to room temperature, the mixture was passed through a pad of Celite with ethyl acetate as the eluent to remove any insoluble precipitate. The resulting solution was concentrated. The yield was measured by ^{1}H NMR using CH_2Br_2 as internal standard. The deuterium incorporation were measured by ^{1}H NMR after isolation through preparative TLC with ethyl acetate/hexanes(1/4) as eluent.

3.11 Catellani Reaction Using Modified Norbornene.



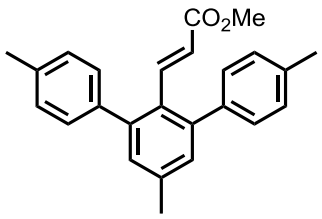
A 2-dram vial equipped with a magnetic stir bar was charged with aryl iodide (0.30 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%), K_2CO_3 (48.8 mg, 0.36 mmol) and **N1** or **N15** (0.15 mmol). Methyl acrylate (10.3 mg, 0.12 mmol) was then added *via* a microsyringe. Subsequently, DMF (1.5 mL) was injected, and the vial was capped and closed tightly. The reaction mixture was then stirred at 115 °C for 24 h. After being allowed to cool to room temperature, the mixture was passed through a pad of Celite with ethyl acetate as the eluent to remove any insoluble precipitate. The resulting solution was concentrated, and the residual mixture was dissolved with a minimal amount of acetone and loaded onto a preparative TLC plate. The pure product was then isolated using preparative TLC with ethyl acetate/hexanes (1/10) or ethyl acetate/toluene as the eluent.



9a

Methyl (E)-3-([1,1':3',1''-terphenyl]-2'-yl)acrylate.

The product was obtain as white solid (60% yield), when using **N15** (eluent: hexanes/ethyl acetate = 10/1). ^{1}H NMR (500 MHz, acetone-d^6) δ 7.49-7.57 (m, 2H), 7.42-7.46 (m, 4H), 7.34-7.40 (m, 8H), 5.34 (d, *J* = 16.5, 1H), 3.51 (s, 3H). ^{13}C NMR (125 MHz, acetone-d^6) δ 166.76, 143.80, 143.63, 142.23, 132.15, 130.82, 130.47, 129.54, 129.18, 128.20, 125.25, 51.49. HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{19}O_2^+$ $[M+H]^+$ 315.1379, found 315.1372. IR (neat, cm^{-1}) 2948, 1719, 1634, 1458, 1435, 1309, 1272, 1193, 1170, 758. 702.



9b

Methyl (E)-3-(4,4'',5'-trimethyl-[1,1':3',1''-terphenyl]-2'-yl)acrylate.

The product was obtain as white solid (84% yield), when using **N15** (eluent: toluene/ethyl acetate = 60/1). ^{1}H NMR (500 MHz, acetone-d^{6}) δ 7.55 (d, *J* = 16.0 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 4H), 7.21 (d, *J* = 8.0 Hz, 4H), 7.13 (s, 2H), 5.32 (d, *J* = 16.5 Hz, 1H), 3.51 (s, 3H), 2.41 (s, 3H), 2.38 (s, 6H). ^{13}C NMR (125 MHz, acetone-d^{6}) δ 166.53, 143.50, 143.24, 139.01, 138.99, 137.17, 131.01, 129.82, 129.27, 128.71, 123.59, 50.91, 20.67, 20.64. HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{25}O_2^+$ $[M+H]^+$ 357.1849, found 357.1849. Melting point: 126-130 °C. IR (neat, cm^{-1}) 2947, 2925, 1718, 1633, 1598, 1511, 1435, 1306, 1271, 1192, 1165, 821.

4. References

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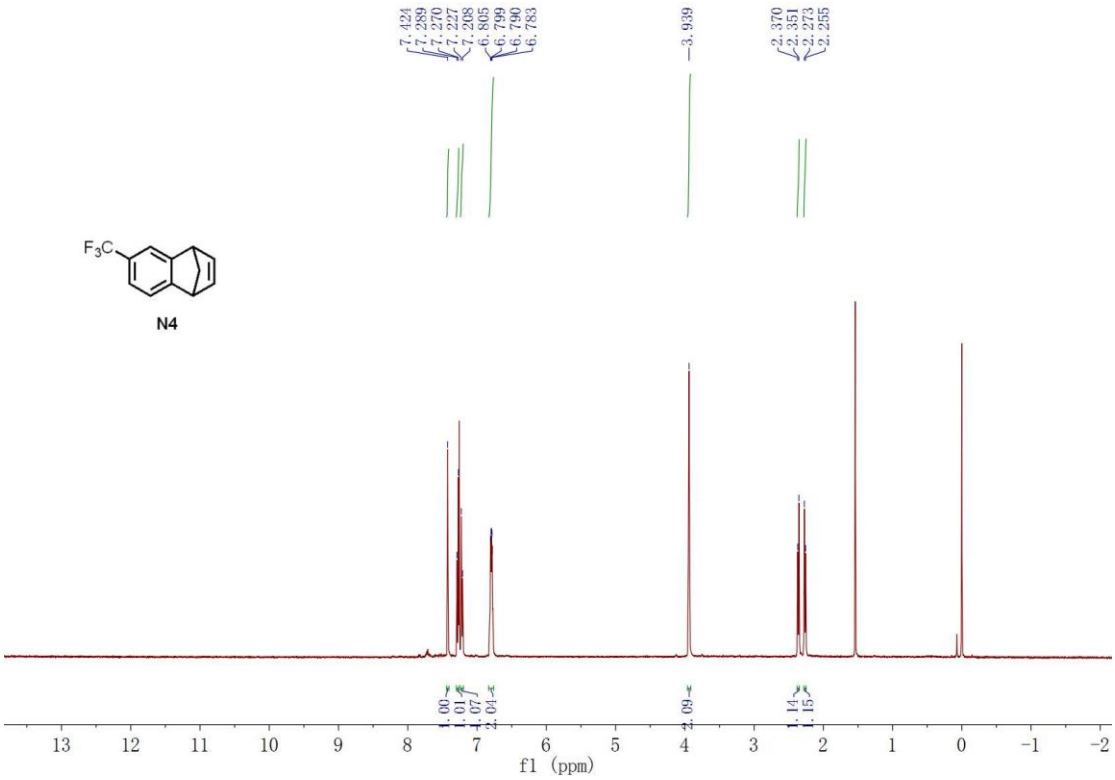
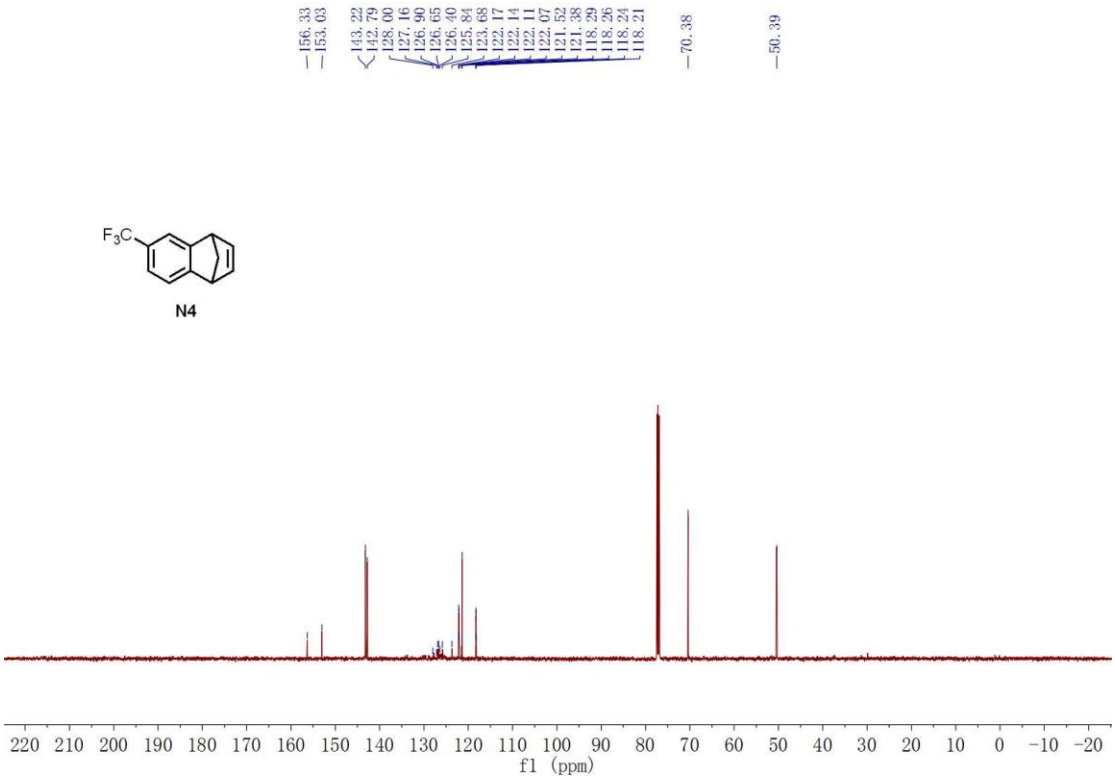
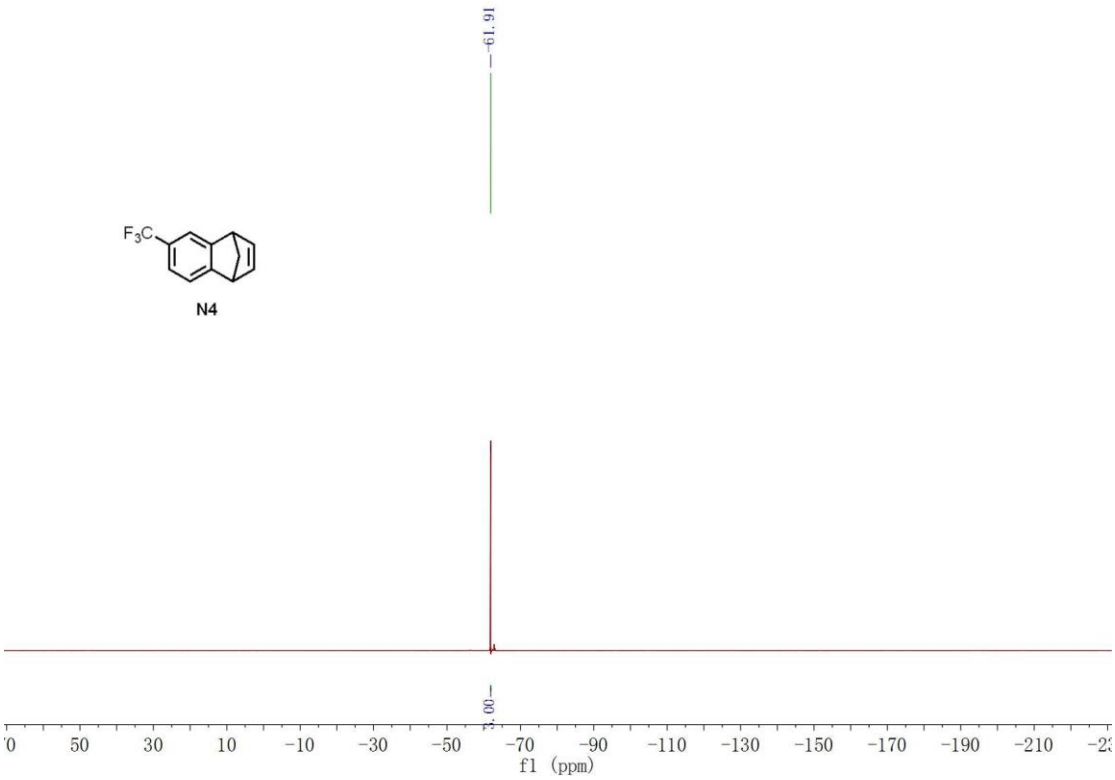
5. NMR Spectra



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F3C
N4
1.00
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30
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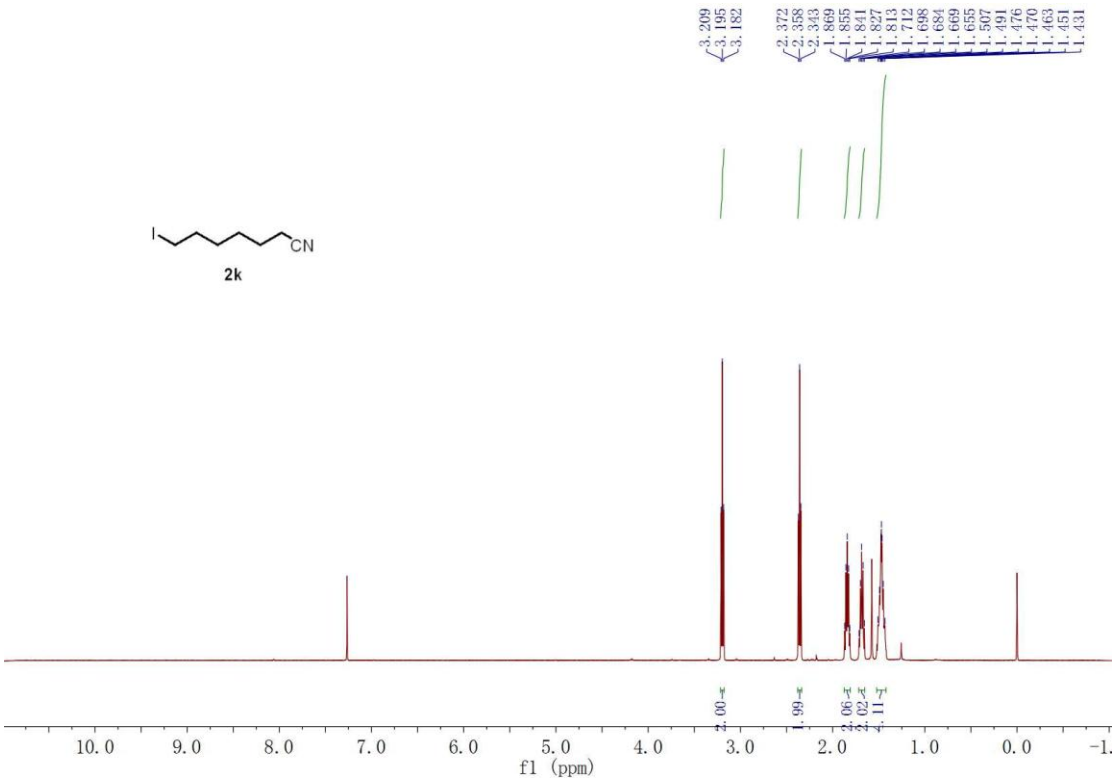
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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3.182
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2.343
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1.712
1.698
1.684
1.669
1.655
1.507
1.491
1.476
1.470
1.463
1.451
1.431
I
CN
2k
4.00
1.99
2.06
2.02
4.11
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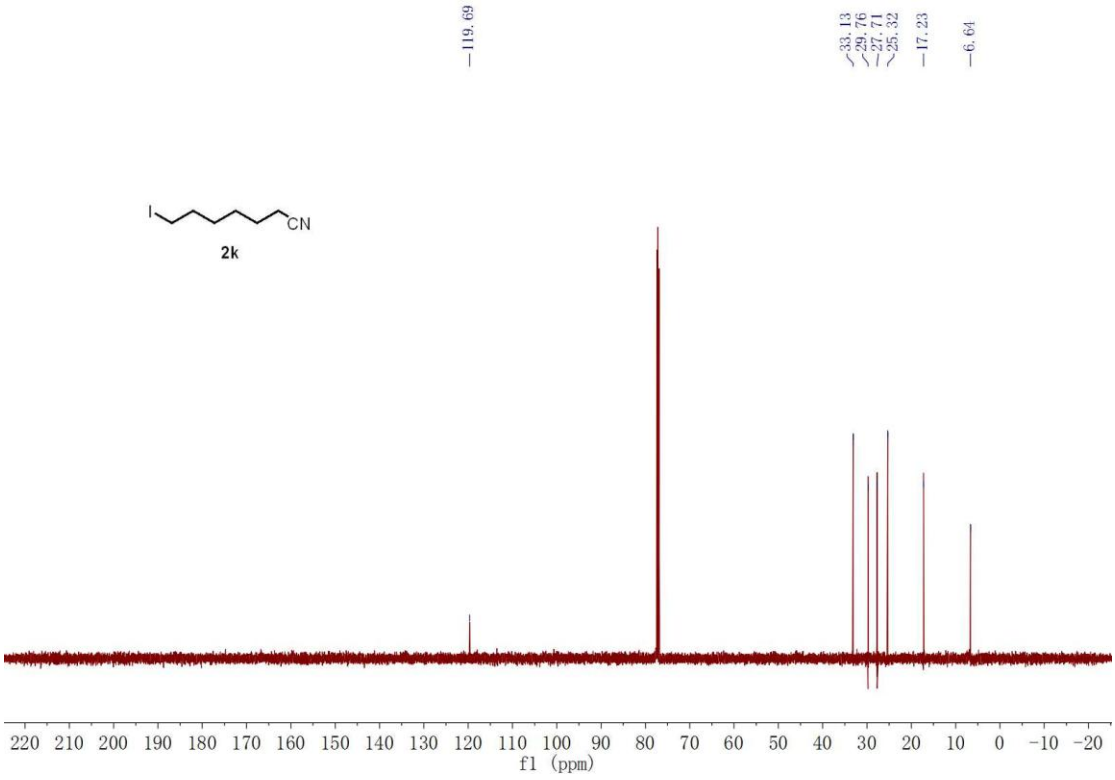
f1 (ppm)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29.76
27.71
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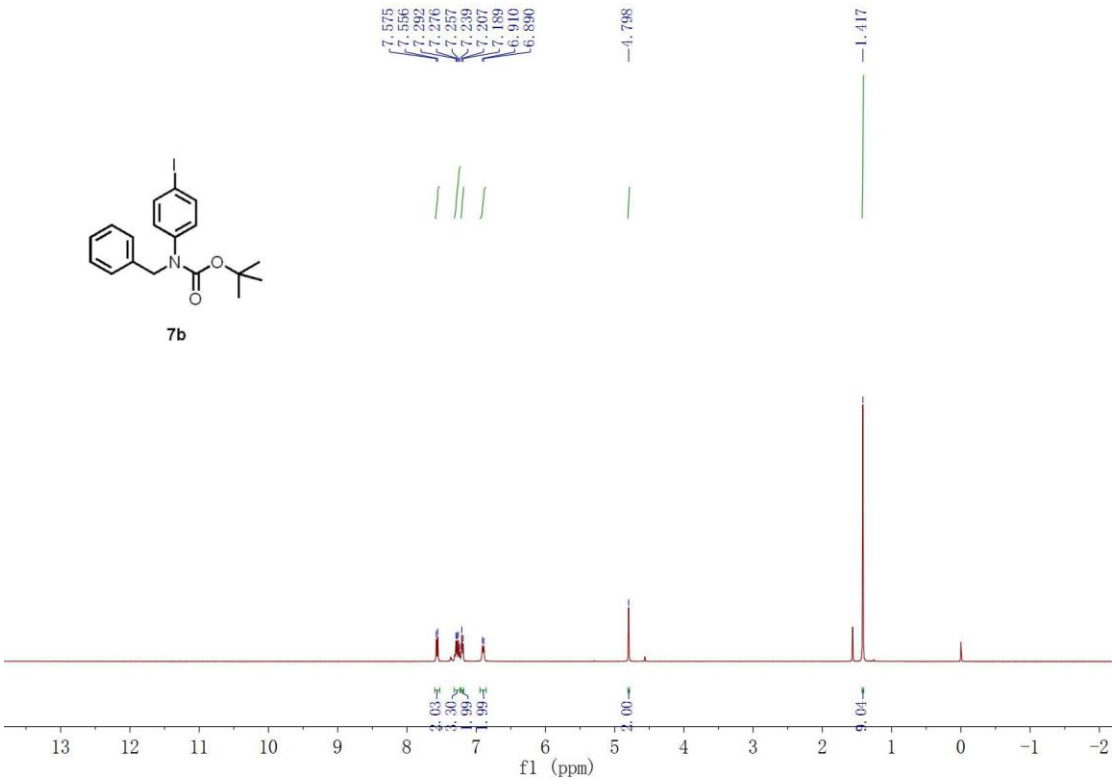
17.23
6.64
I
CN
2k
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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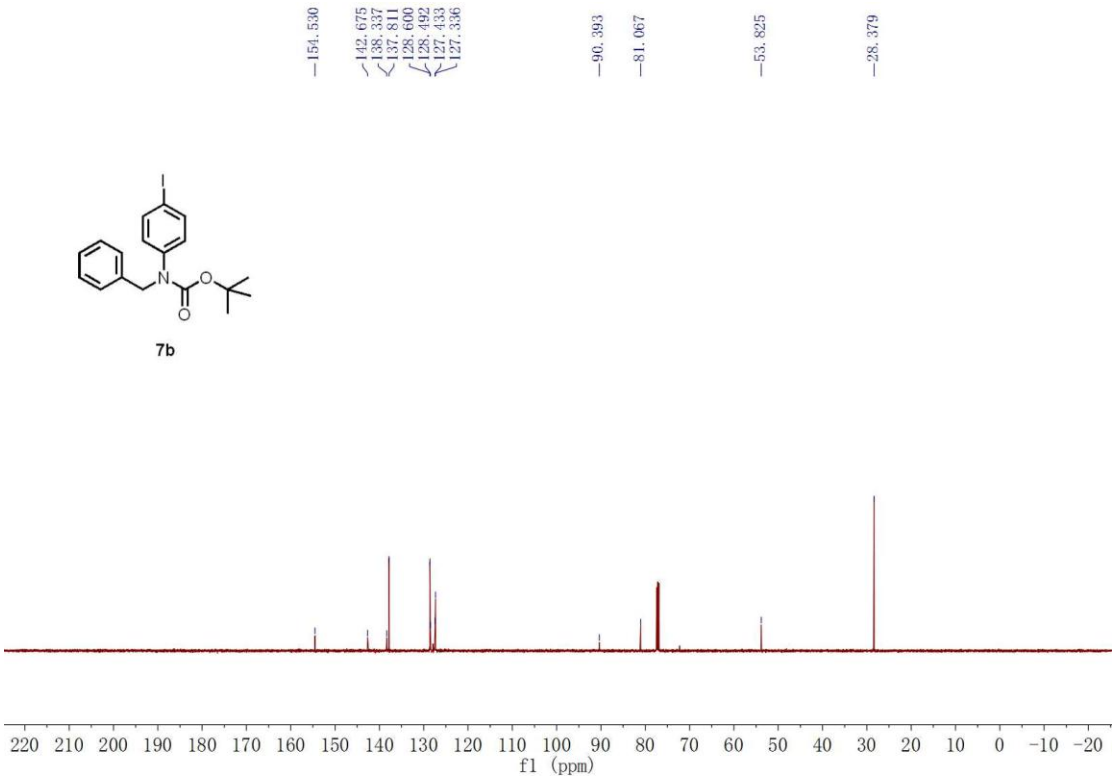
3.30
1.99
1.99
2.00
9.04
f1 (ppm)

7b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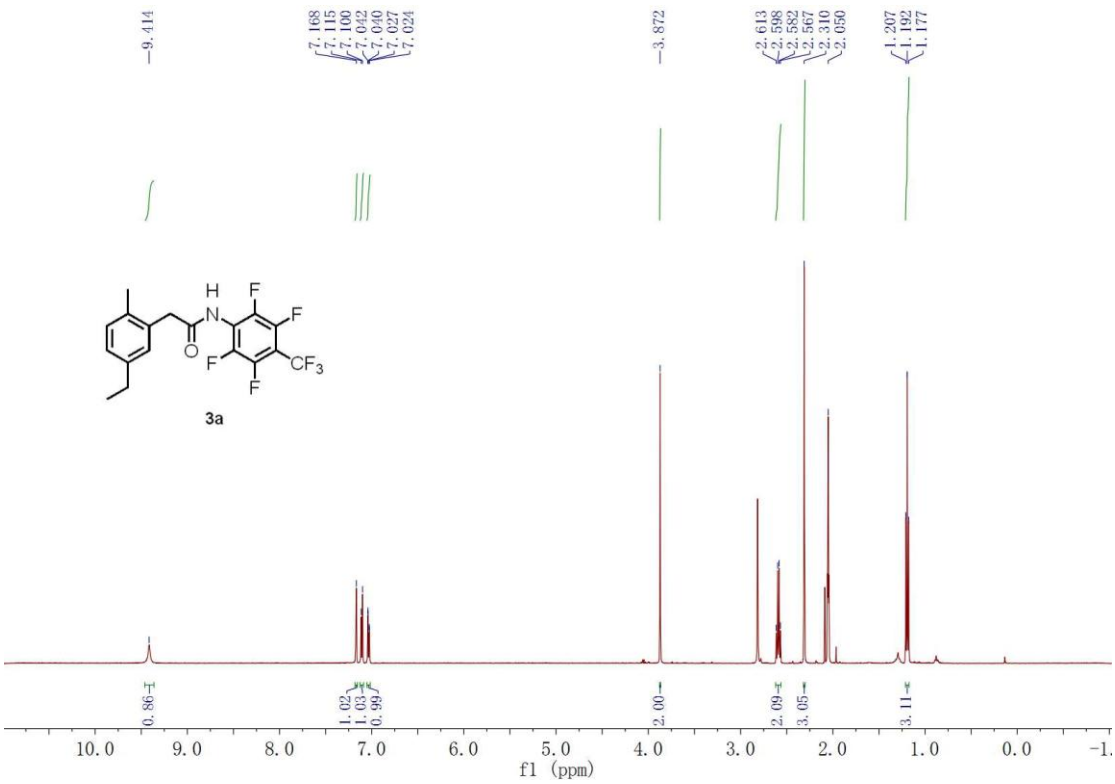
f1 (ppm)

7b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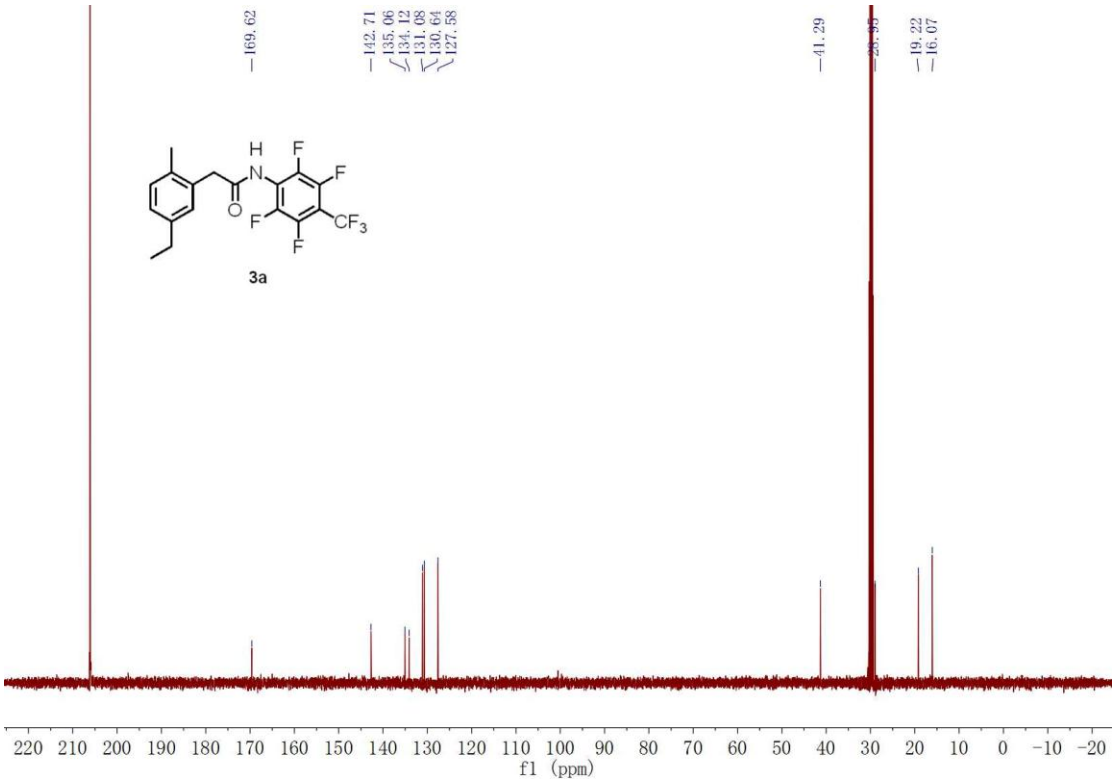
7.168
7.115
7.100
7.042
7.040
7.027
7.024
3.872
2.613
2.598
2.582
2.567
2.310
2.050
1.207
1.192
1.177
0.86
1.02
1.03
0.99
2.00
2.09
3.05
3.11
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
H
N
O
F
F
F
F
CF3
3a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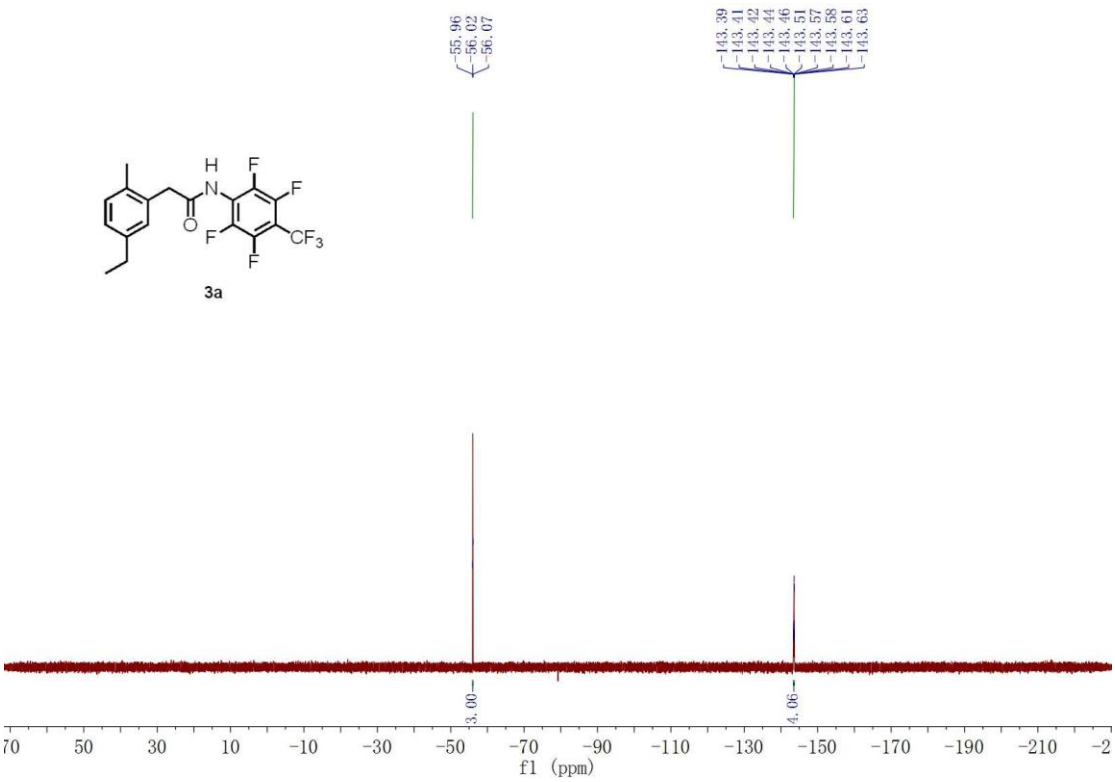
142.71
135.06
134.12
131.08
130.64
127.38
41.29
29.95
19.22
16.07
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)
H
N
O
F
F
F
F
CF3
3a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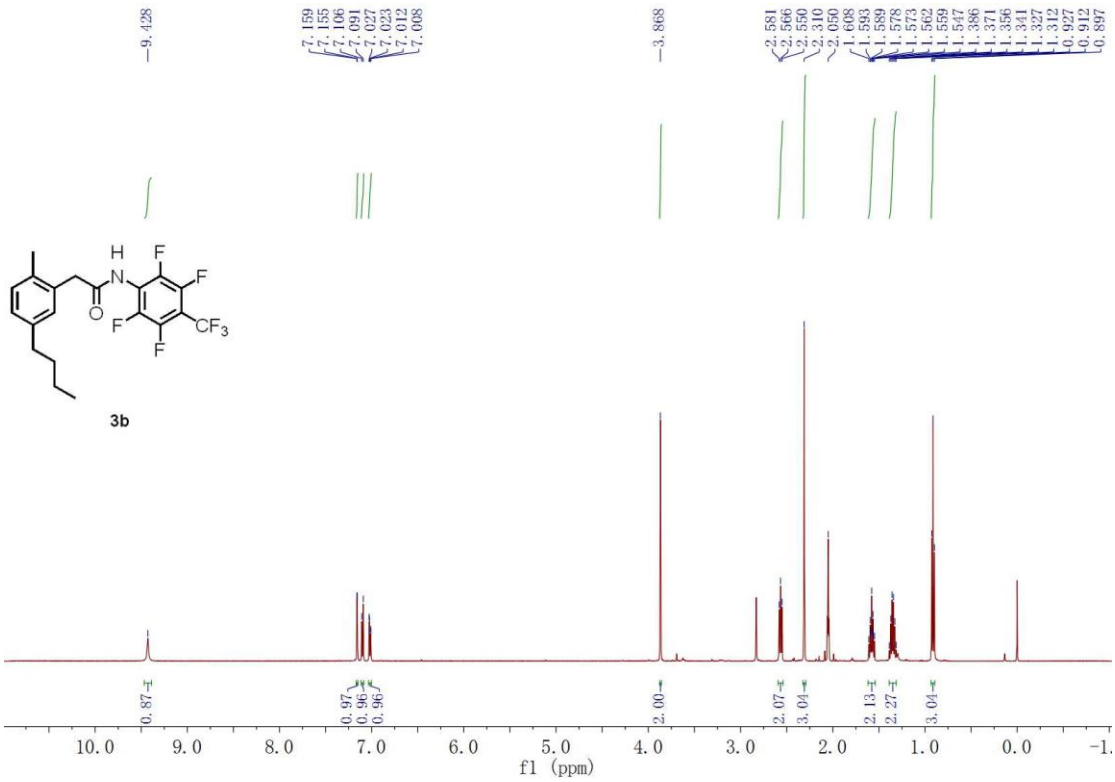
-56.02
-56.07
-143.39
-143.41
-143.42
-143.44
-143.46
-143.51
-143.57
-143.58
-143.61
-143.63
H
N
O
F
F
F
F
CF3
3a
3.00
4.06
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-2
f1 (ppm)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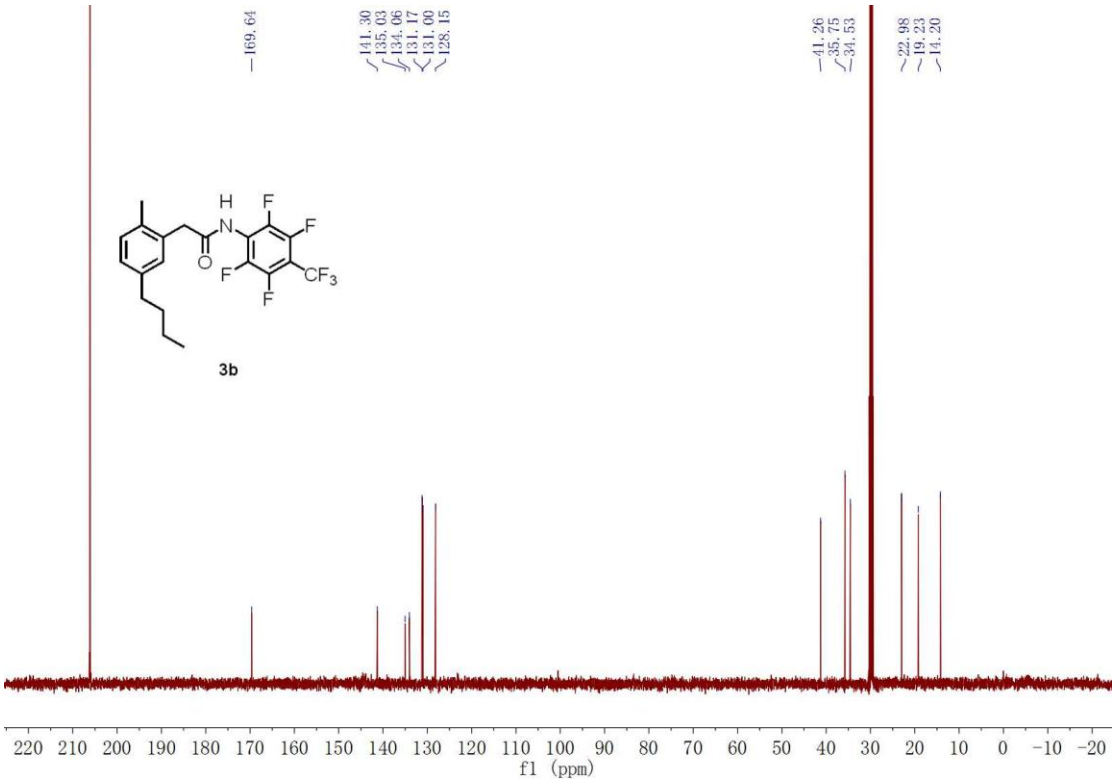
7.159
7.155
7.106
7.091
7.027
7.023
7.012
7.008
3.868
2.581
2.566
2.550
2.310
2.050
1.608
1.593
1.589
1.578
1.573
1.562
1.559
1.547
1.386
1.371
1.356
1.341
1.327
1.312
0.927
0.912
0.897
3b
0.87
0.97
0.96
0.96
2.00
2.07
3.04
2.13
2.27
3.04
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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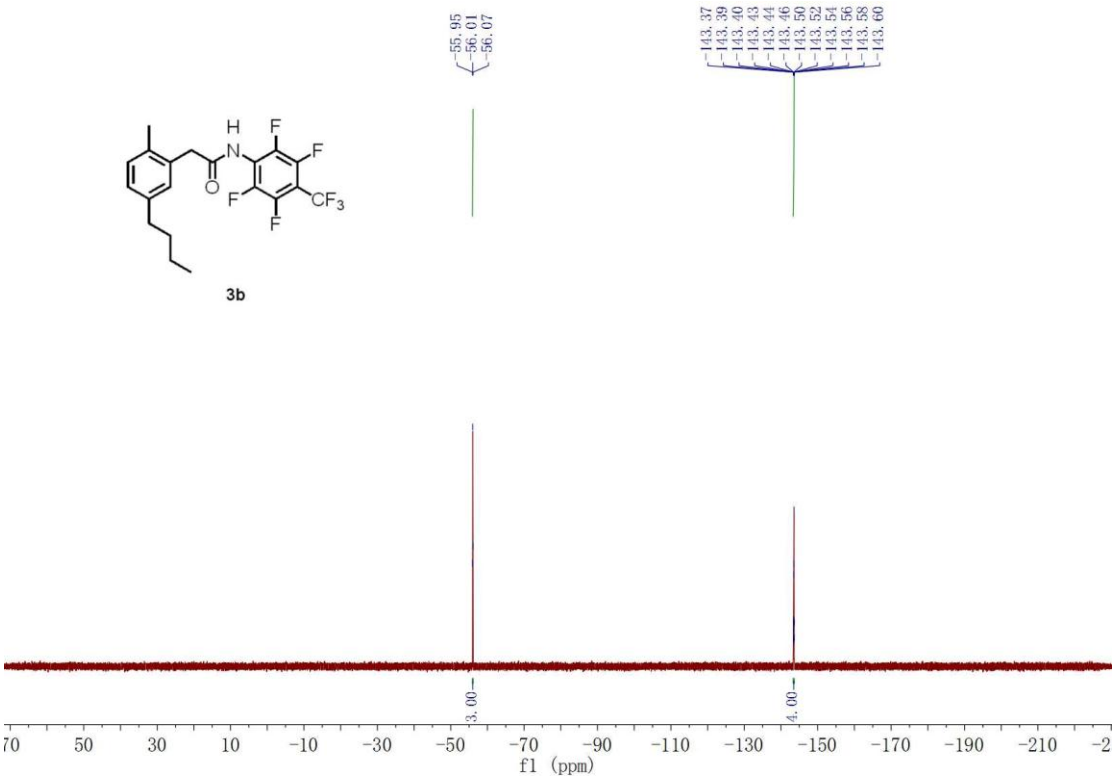
141.30
135.03
134.06
131.17
131.00
128.15
41.26
35.75
34.53
22.98
19.23
14.20
3b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)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-56.01
-56.07
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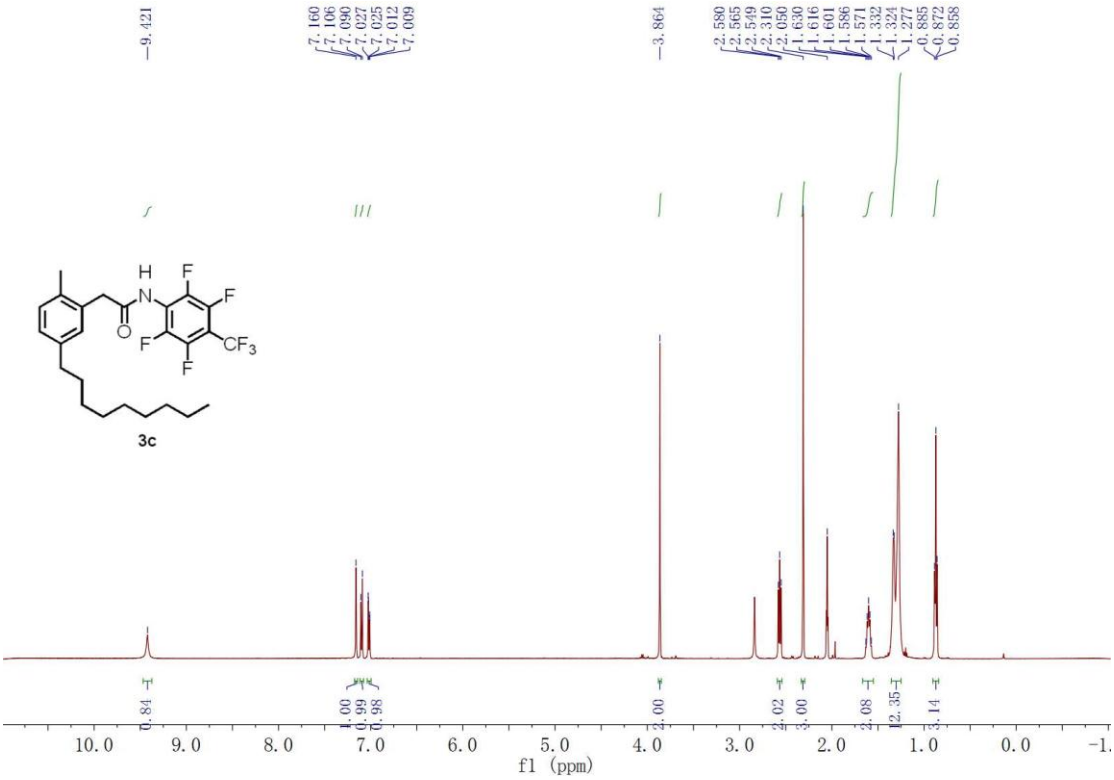
-143.39
-143.40
-143.43
-143.44
-143.46
-143.50
-143.52
-143.54
-143.56
-143.58
-143.60
H
N
O
F
F
F
F
F
CF3
3b
3.00
4.00
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-2
f1 (ppm)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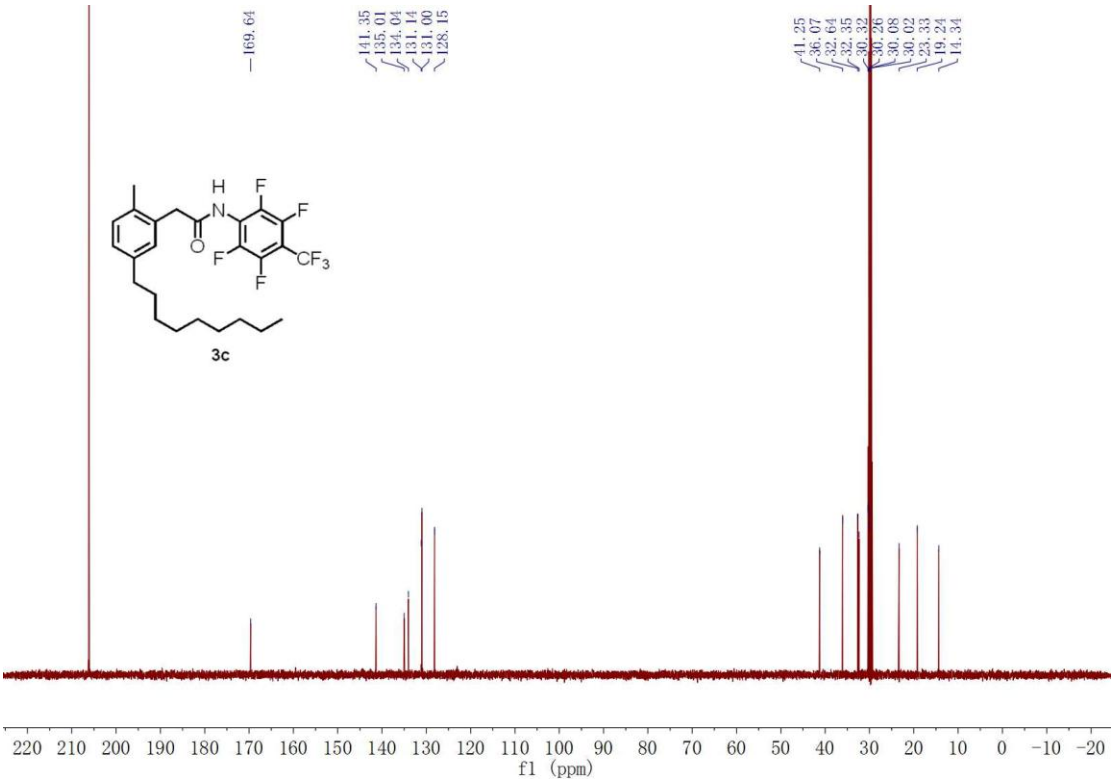
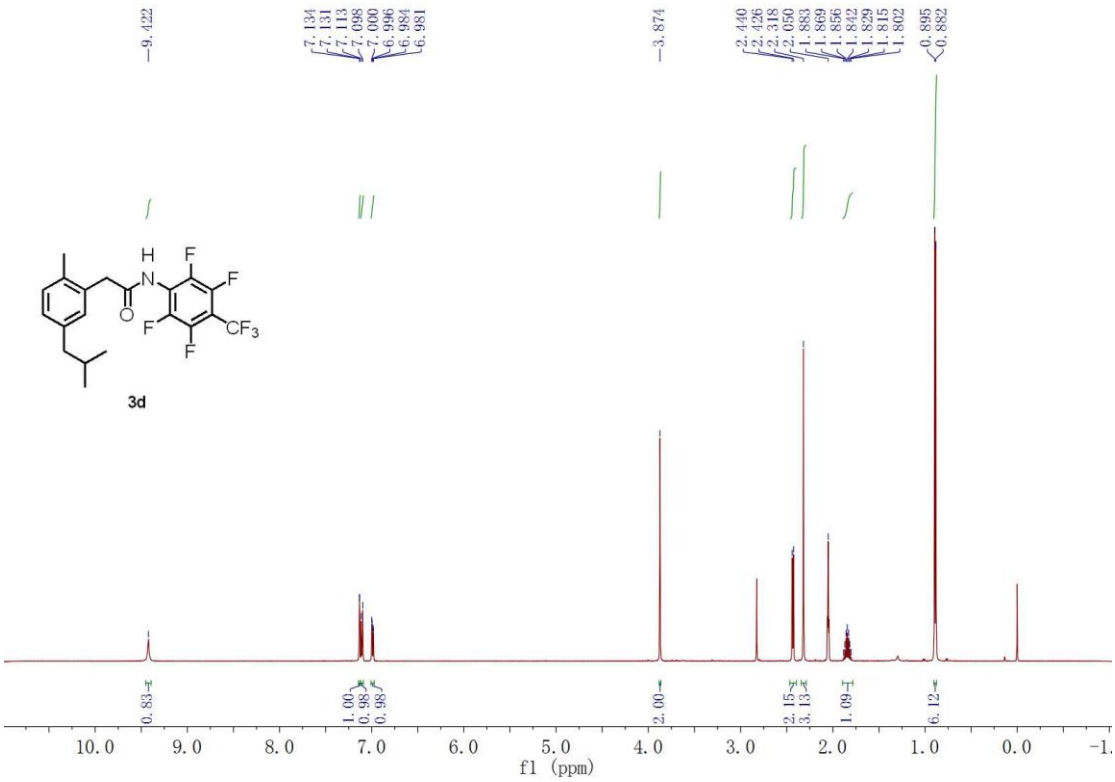
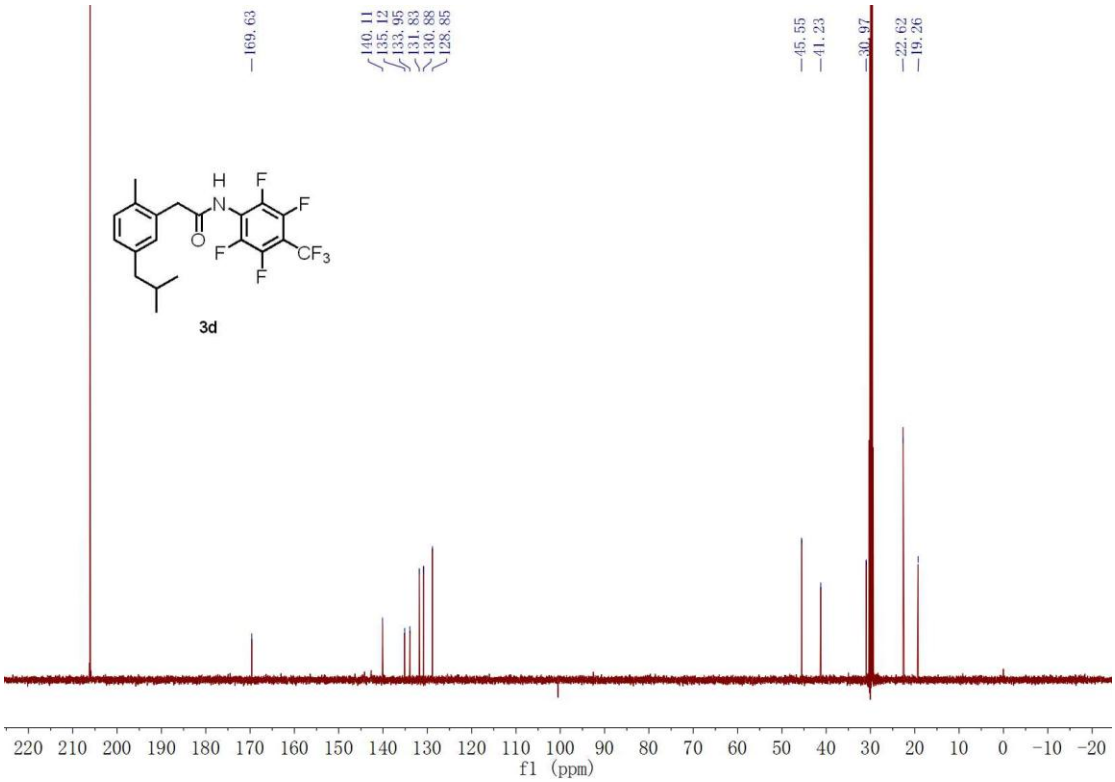
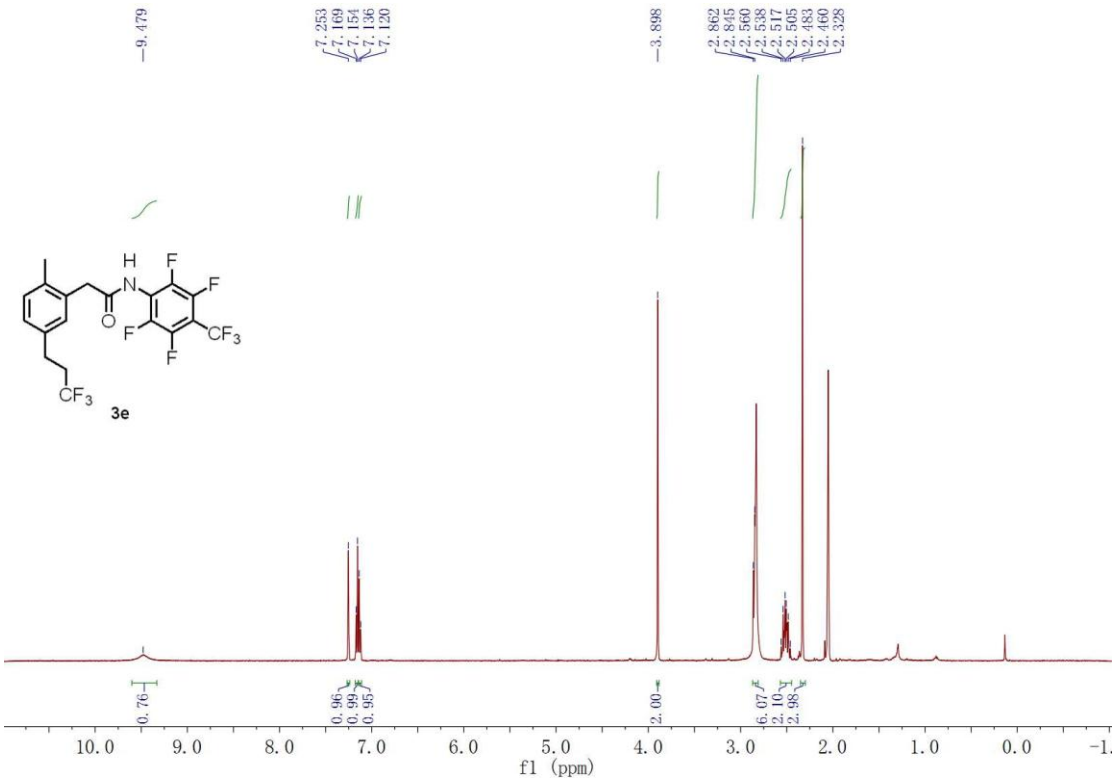
7.160
7.106
7.090
7.027
7.025
7.012
7.009
3.864
2.580
2.565
2.549
2.310
2.050
1.630
1.616
1.601
1.586
1.571
1.332
1.324
1.277
0.885
0.872
0.858
0.84
1.00
0.99
0.98
2.00
2.02
3.00
2.08
12.35
3.14
H
N
O
F
F
F
F
F
CF3
3c
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


169.64
141.35
135.01
134.04
131.14
131.00
128.15
41.25
36.07
32.64
32.35
30.32
30.26
30.08
30.02
23.33
19.24
14.34
H
N
O
F
F
F
F
F
CF3
3c
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)


9.422
7.134
7.131
7.113
7.098
7.000
6.996
6.984
6.981
3.874
2.440
2.426
2.318
2.050
1.883
1.869
1.856
1.842
1.829
1.815
1.802
0.895
0.882
3d
0.83
1.00
0.98
0.98
2.00
2.15
3.13
1.09
6.12
f1 (ppm)


169.63
140.11
135.12
133.95
131.83
130.88
128.85
45.55
41.23
30.97
22.62
19.26
3d
f1 (ppm)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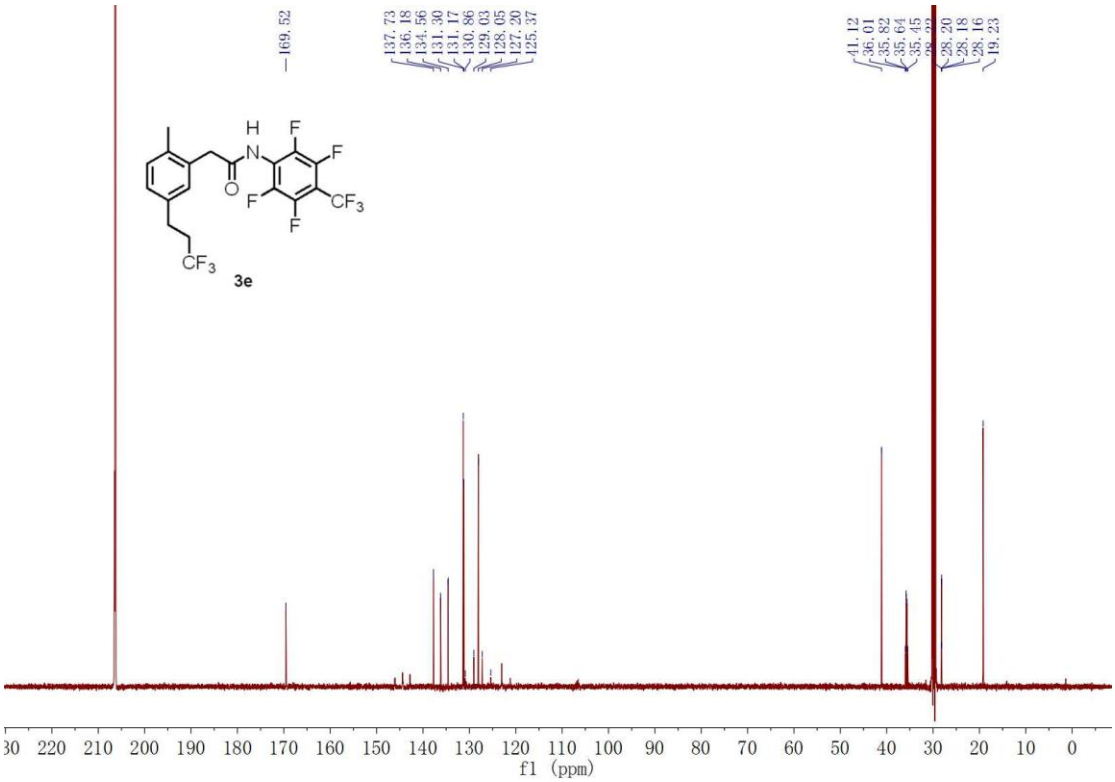
7.253
7.169
7.154
7.136
7.120
3.898
2.862
2.845
2.560
2.538
2.517
2.505
2.483
2.460
2.328
0.76
0.96
0.99
0.95
2.00
6.07
2.10
2.98
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
3e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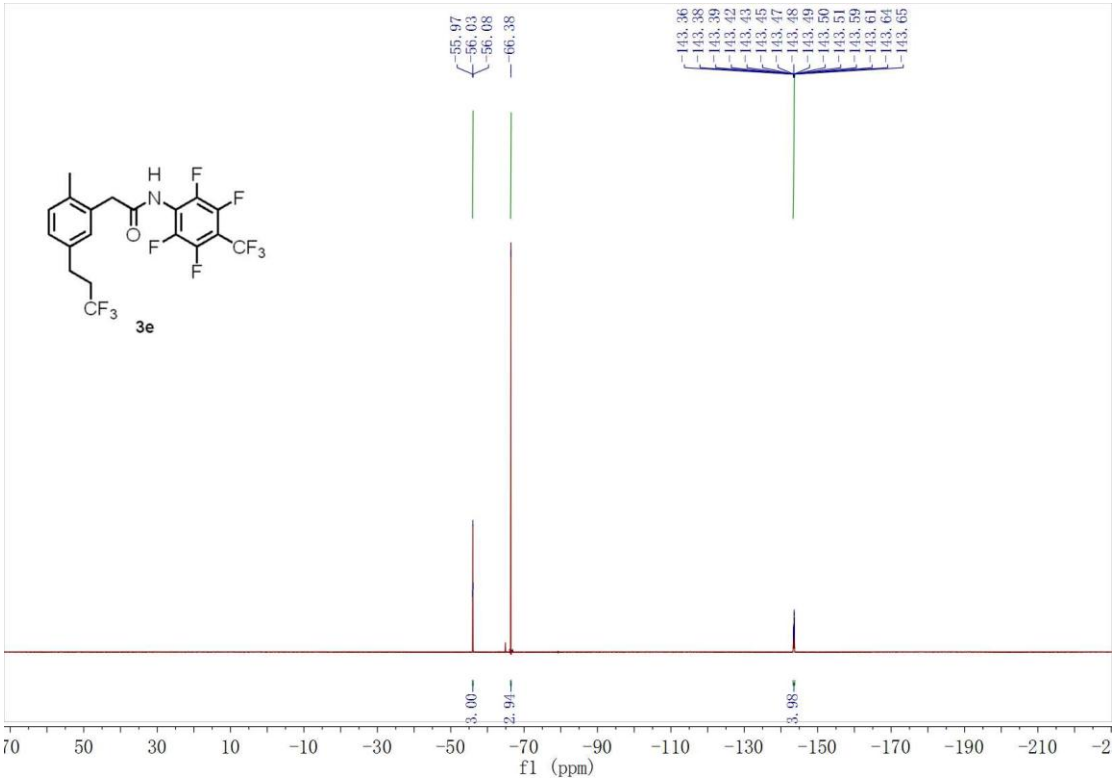
137.73
136.18
134.56
131.30
131.17
130.86
129.03
128.05
127.20
125.37
41.12
36.01
35.82
35.64
35.45
28.20
28.18
28.16
19.23
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
3e


-55.97
-56.03
-56.08
-66.38
-143.36
-143.38
-143.39
-143.42
-143.43
-143.45
-143.47
-143.48
-143.49
-143.50
-143.51
-143.59
-143.61
-143.64
-143.65
H
N
O
F
F
F
F
CF3
CF3
3e
3.00
2.94
3.98
70
50
30
10
-10
-30
-50
-70
-90
-110
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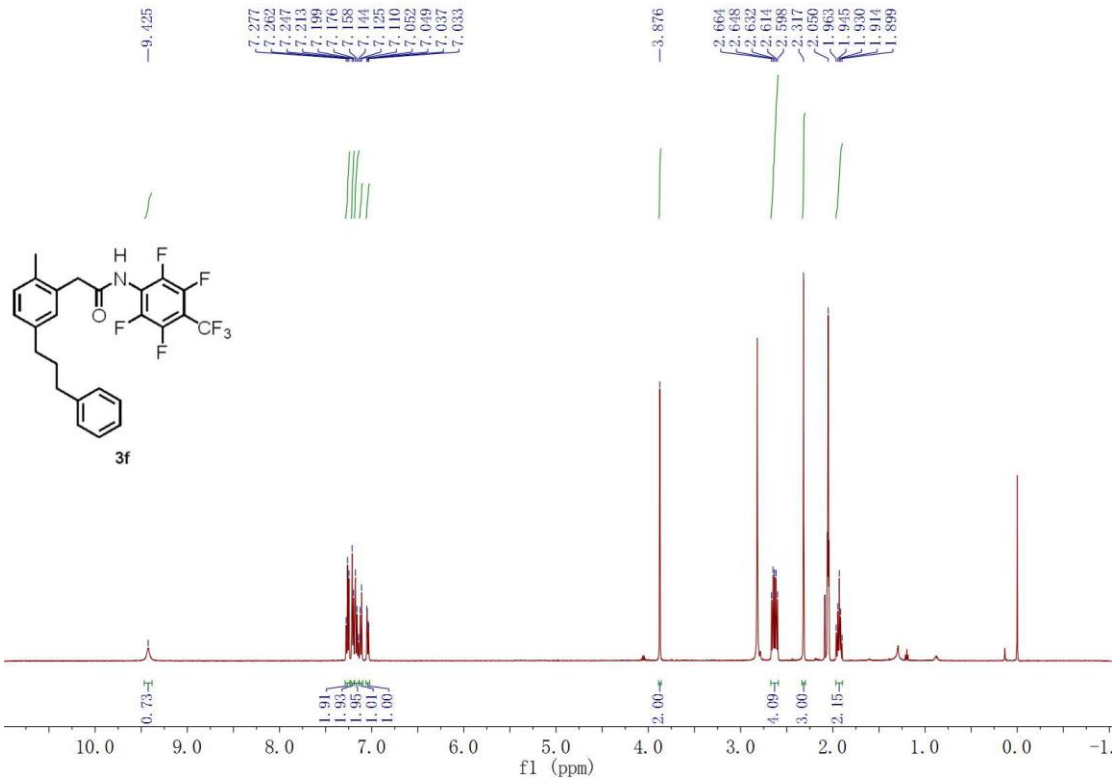
-150
-170
-190
-210
-2
f1 (ppm)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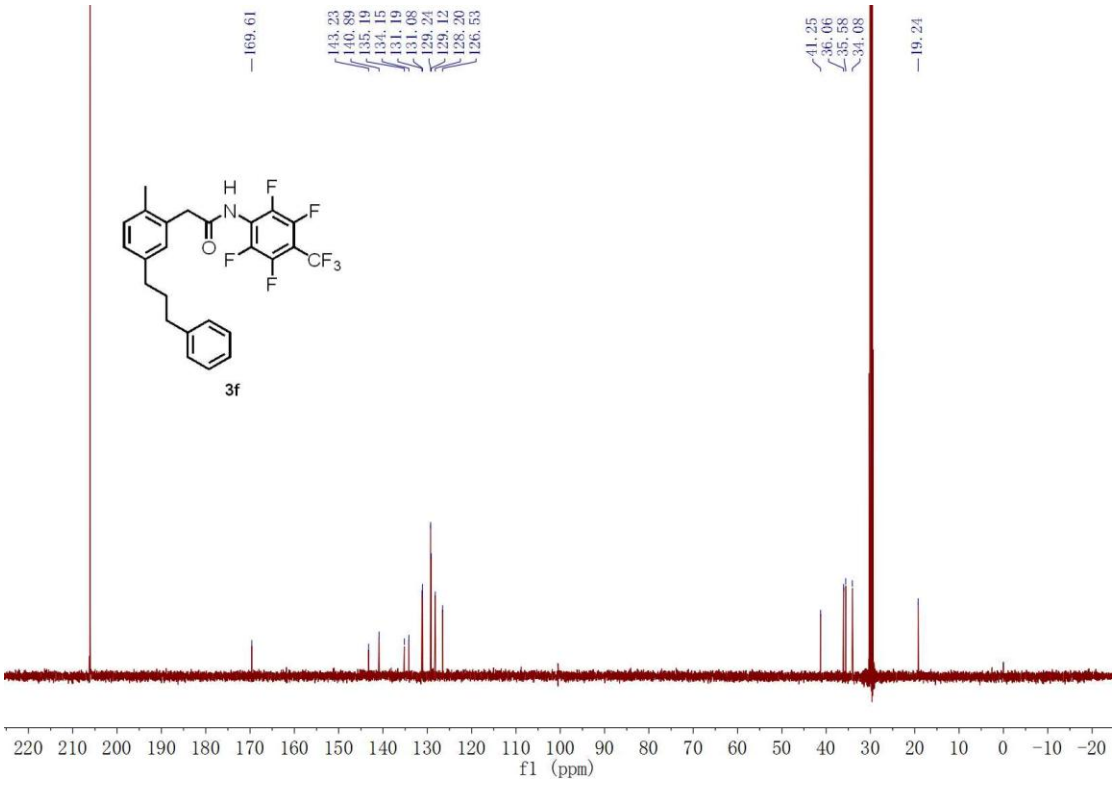
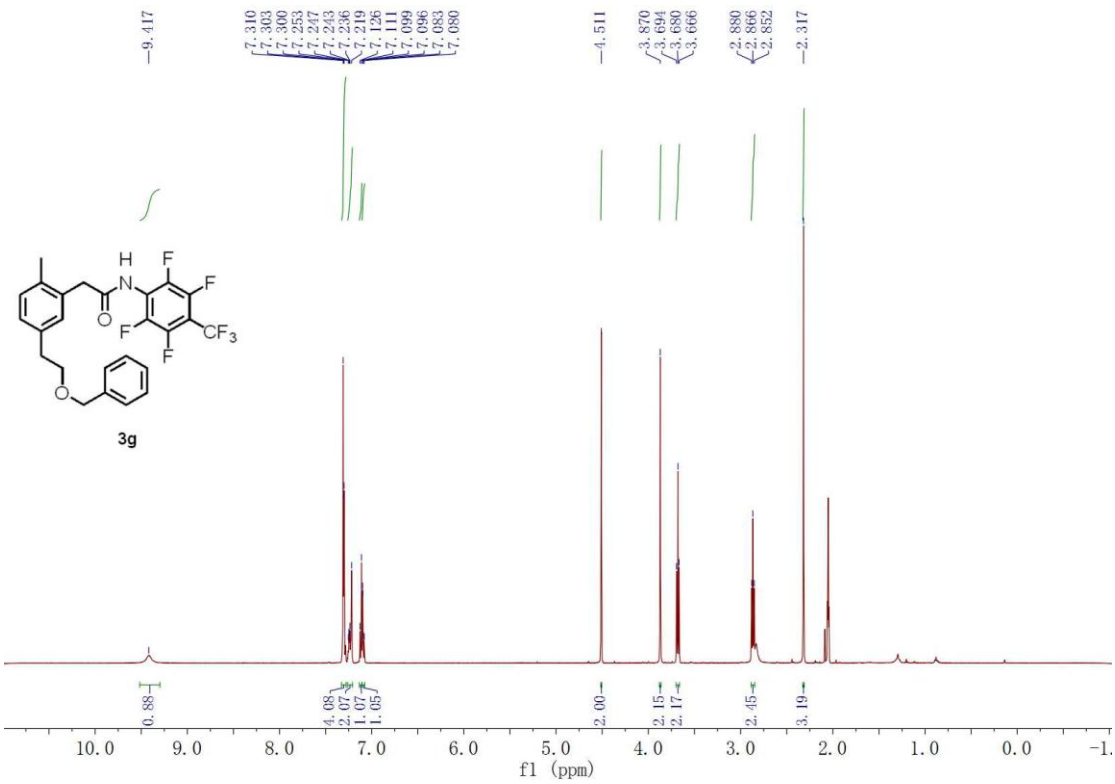
7.247
7.213
7.199
7.176
7.158
7.144
7.125
7.110
7.052
7.049
7.037
7.033
3.876
2.664
2.648
2.632
2.614
2.598
2.317
2.050
1.963
1.945
1.930
1.914
1.899
0.73
1.91
1.93
1.95
1.01
1.00
2.00
4.09
3.00
2.15
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)
3f


169.61
143.23
140.89
135.19
134.15
131.19
131.08
129.24
129.12
128.20
126.53
41.25
36.06
35.58
34.08
19.24
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)
3f


9.417
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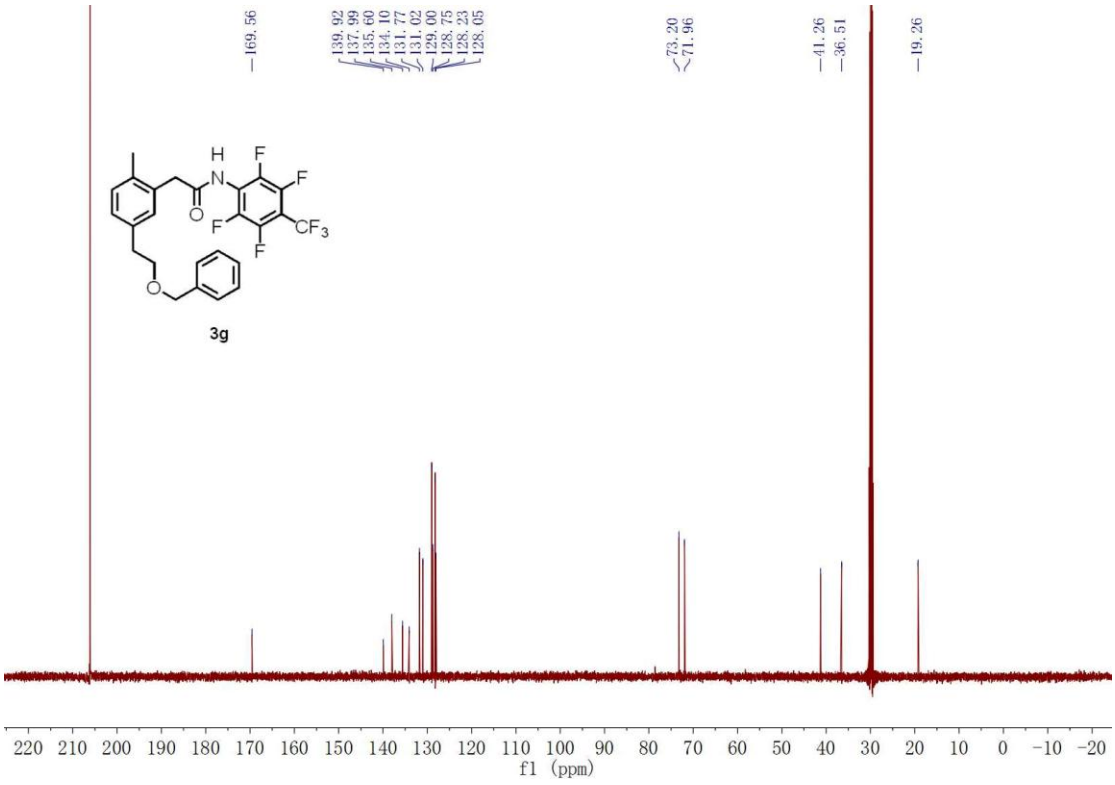
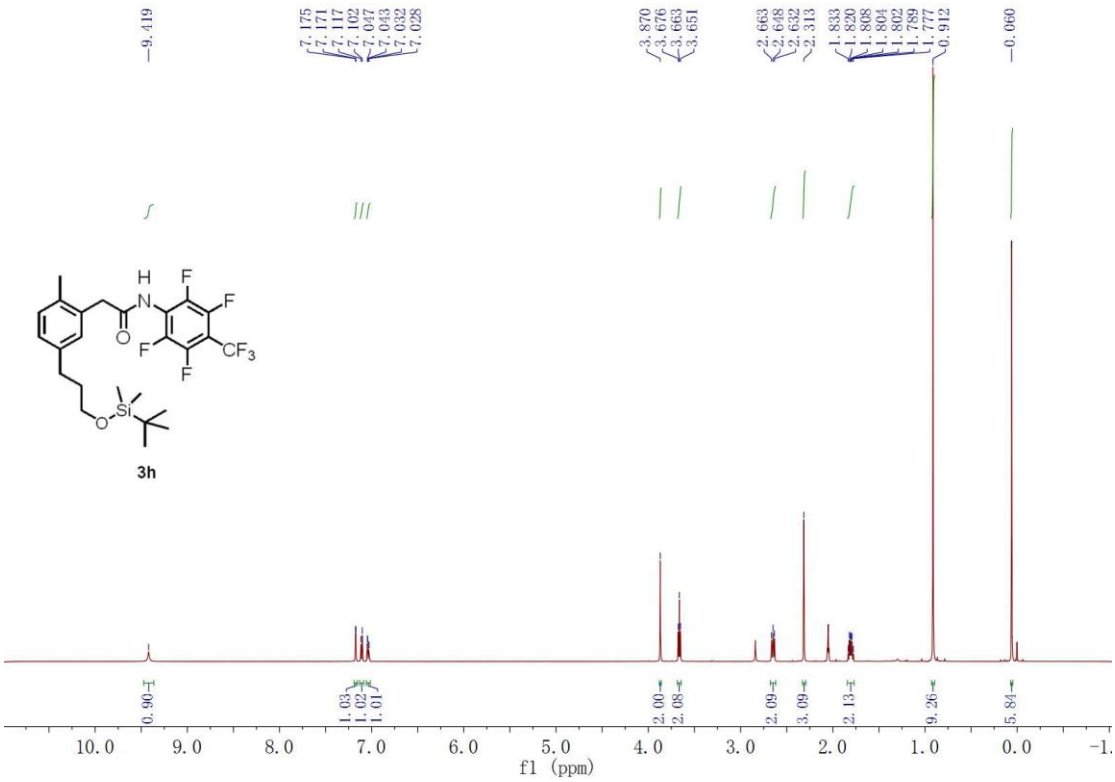
7.300
7.253
7.247
7.243
7.236
7.219
7.126
7.111
7.099
7.096
7.083
7.080
4.511
3.870
3.694
3.680
3.666
2.880
2.866
2.852
2.317
0.88
4.08
2.07
1.07
1.05
2.00
2.15
2.17
2.45
3.19
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
3g


169.56
139.92
137.99
135.60
134.10
131.77
131.02
129.00
128.75
128.23
128.05
73.20
71.96
41.26
36.51
19.26
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)
3g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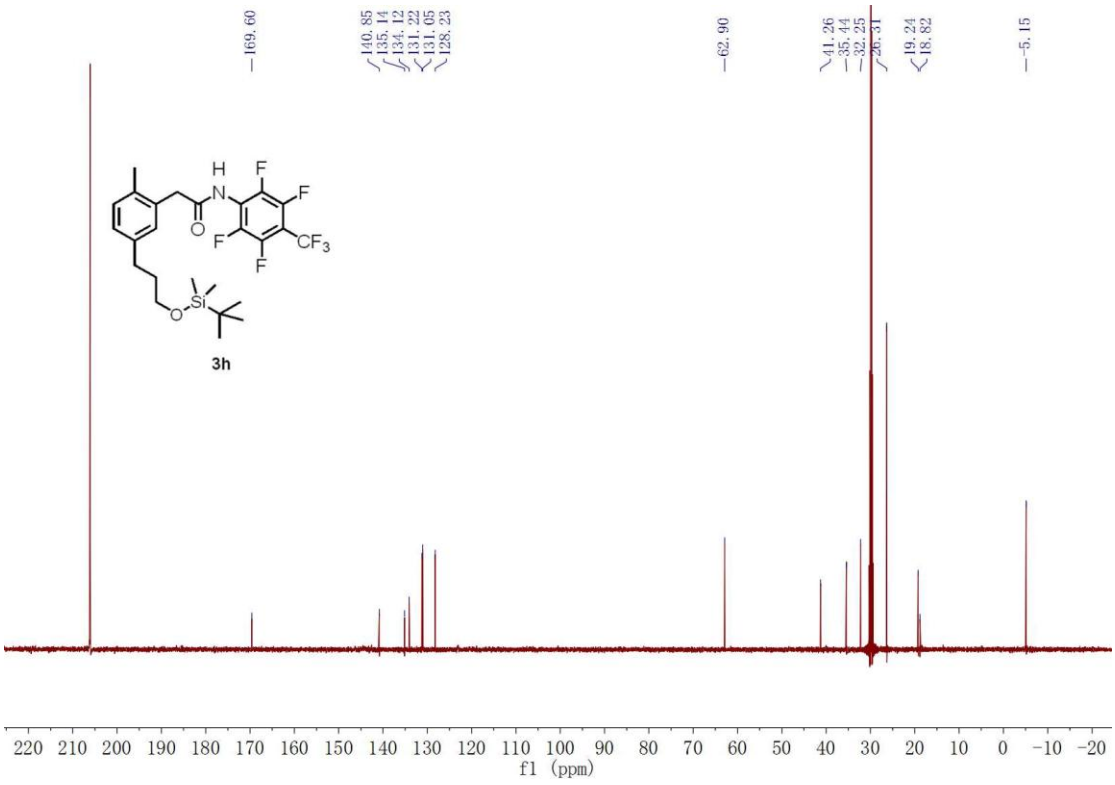
7.117
7.102
7.047
7.043
7.032
7.028
3.870
3.676
3.663
3.651
2.663
2.648
2.632
2.313
1.833
1.820
1.808
1.804
1.802
1.789
1.777
0.912
0.060
0.90
1.03
1.02
1.01
2.00
2.08
2.09
3.09
2.13
9.26
5.84
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
3h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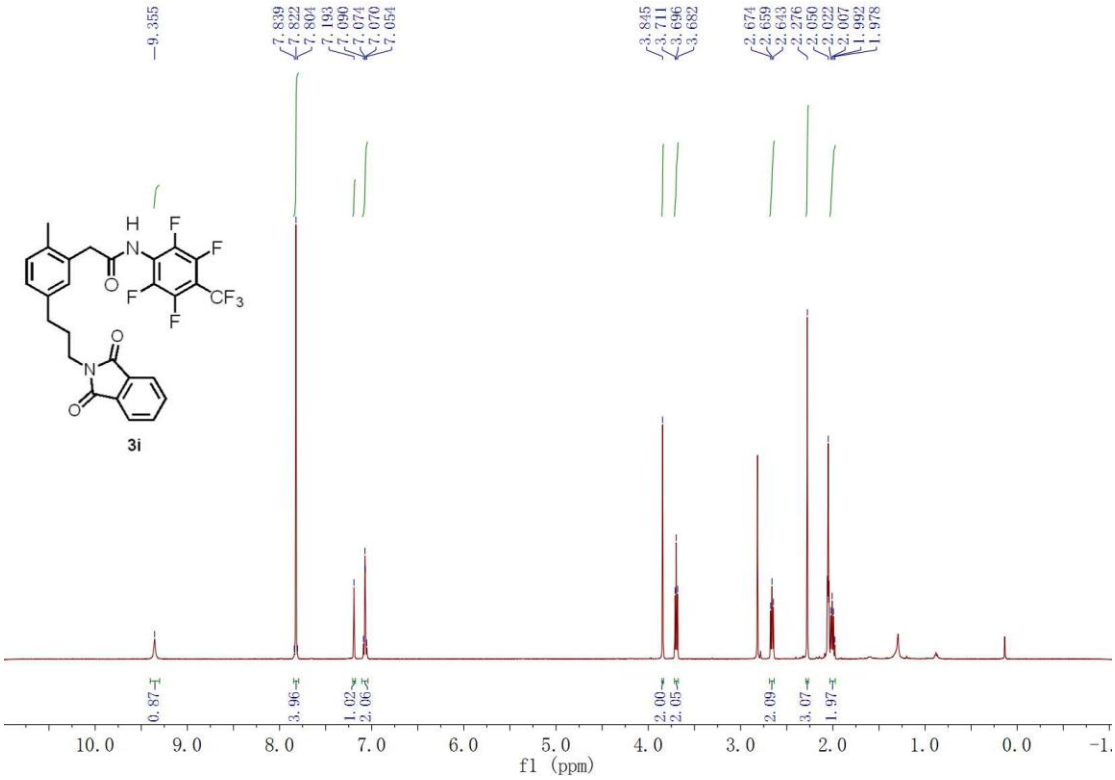
140.85
135.14
134.12
131.22
131.05
128.23
62.90
41.26
35.44
32.25
26.31
19.24
18.82
-5.15
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)
3h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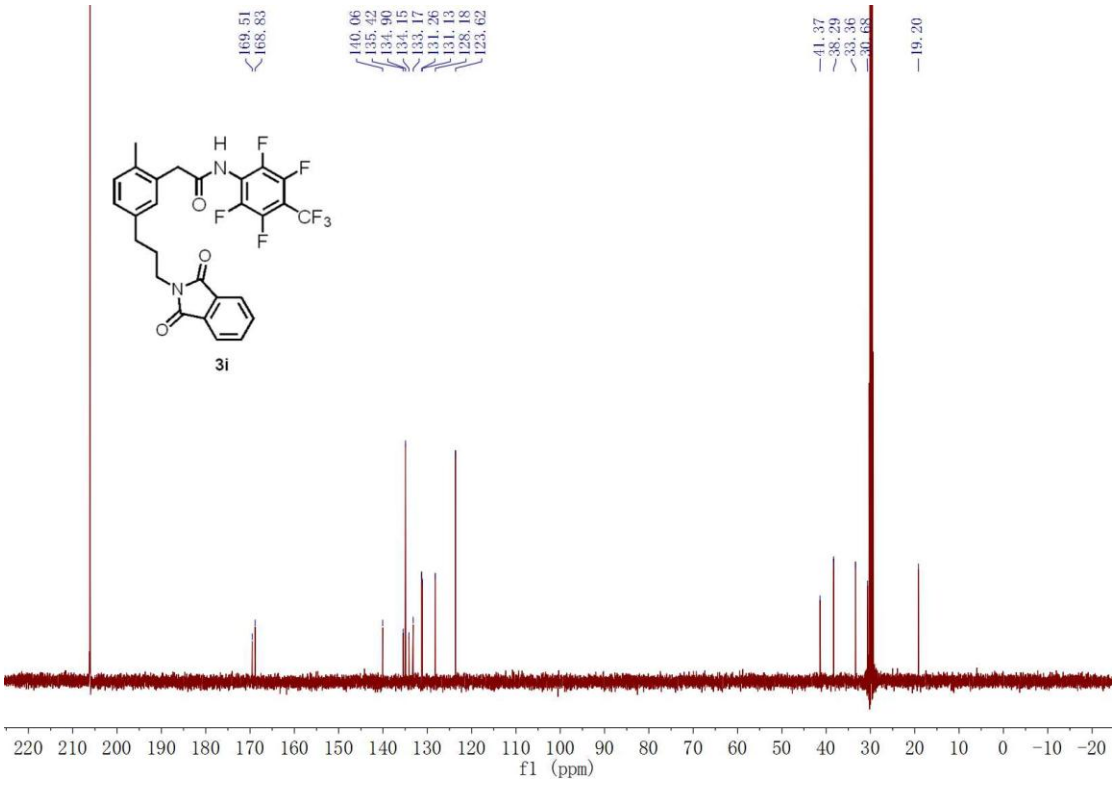
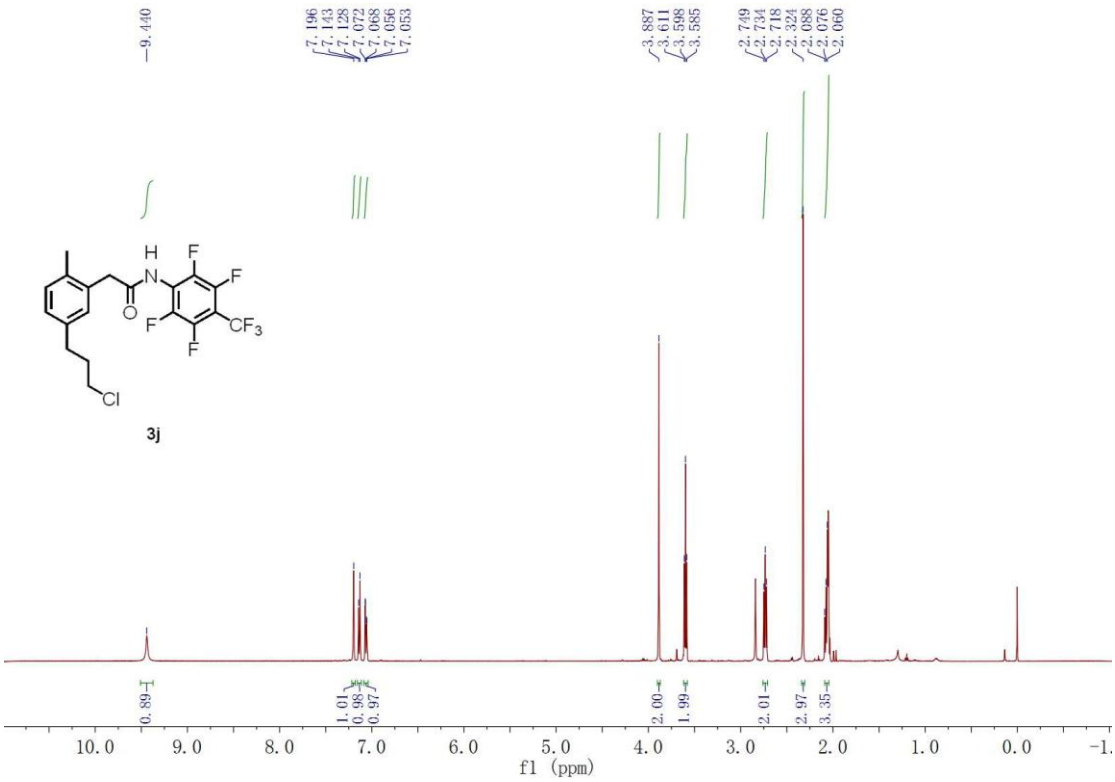
7.822
7.804
7.193
7.090
7.074
7.070
7.054
3.845
3.711
3.696
3.682
2.674
2.659
2.643
2.276
2.050
2.022
2.007
1.992
1.978
0.87
3.96
1.02
2.06
2.00
2.05
2.09
3.07
1.97
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
3i


169.51
168.83
140.06
135.42
134.90
134.15
133.17
131.26
131.13
128.18
123.62
41.37
38.29
33.36
30.68
19.20
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)
3i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7.128
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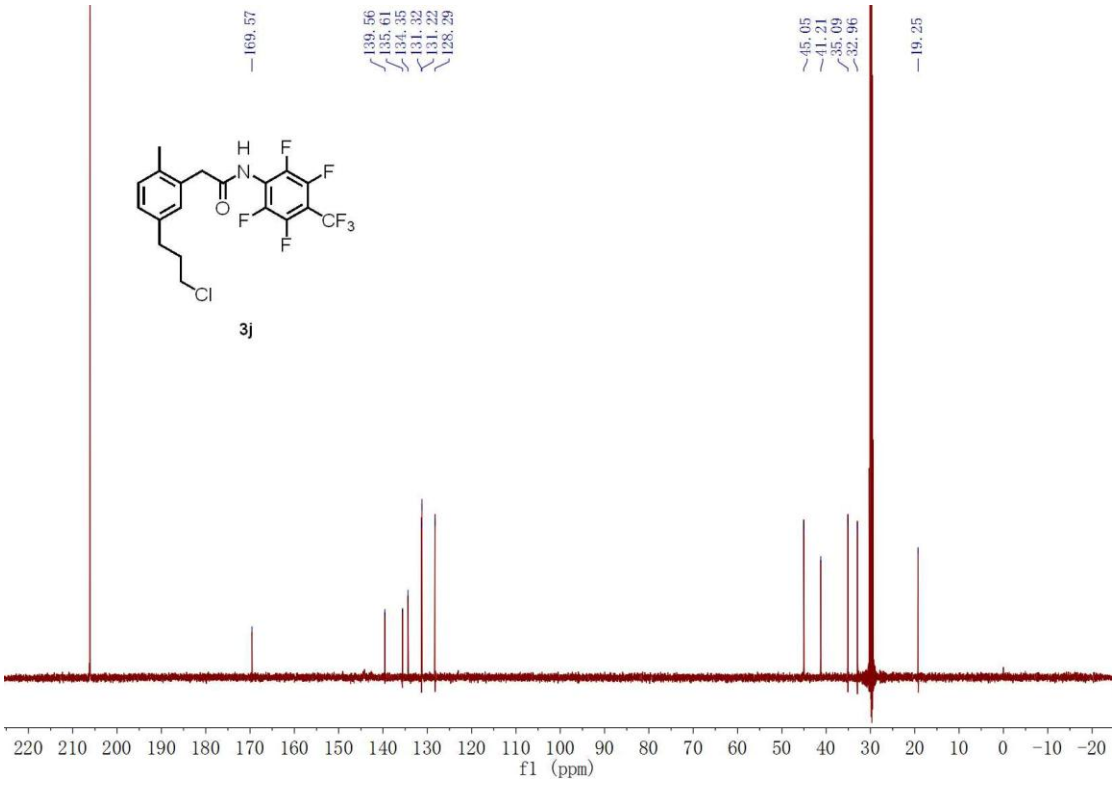
7.068
7.056
7.053
3.887
3.611
3.598
3.585
2.749
2.734
2.718
2.324
2.088
2.076
2.060
0.89
1.01
0.98
0.97
2.00
1.99
2.01
2.97
3.35
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
H
N
O
F
F
F
F
CF3
Cl
3j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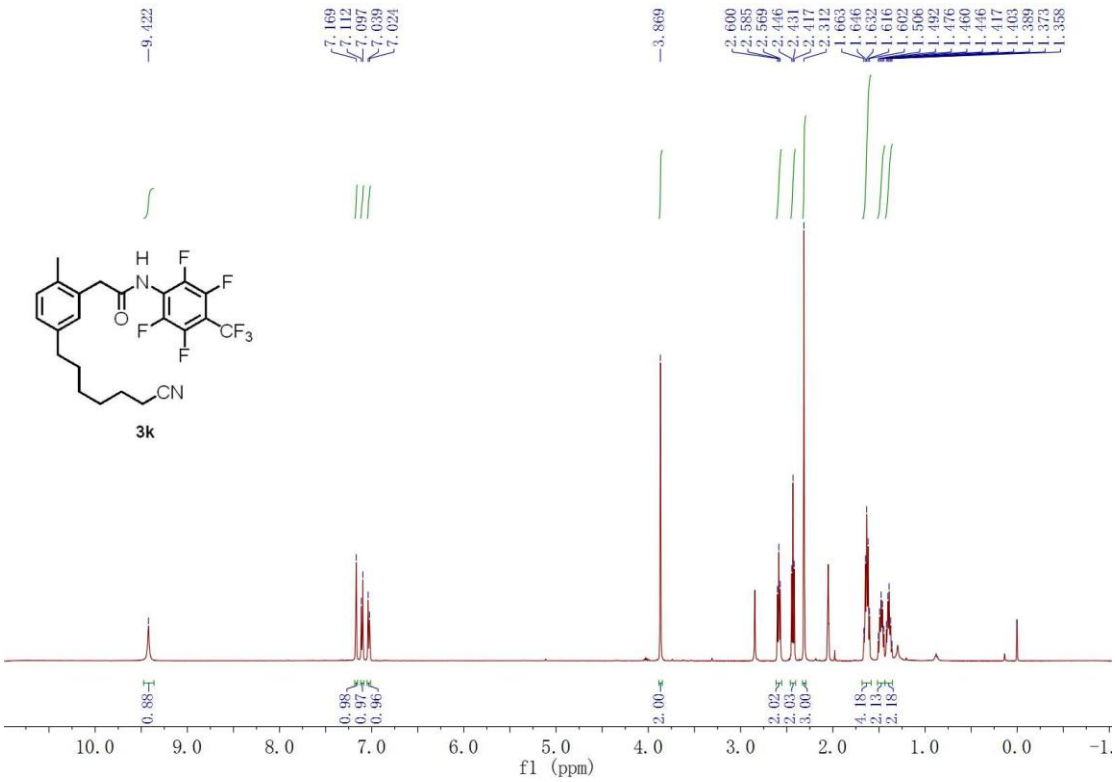
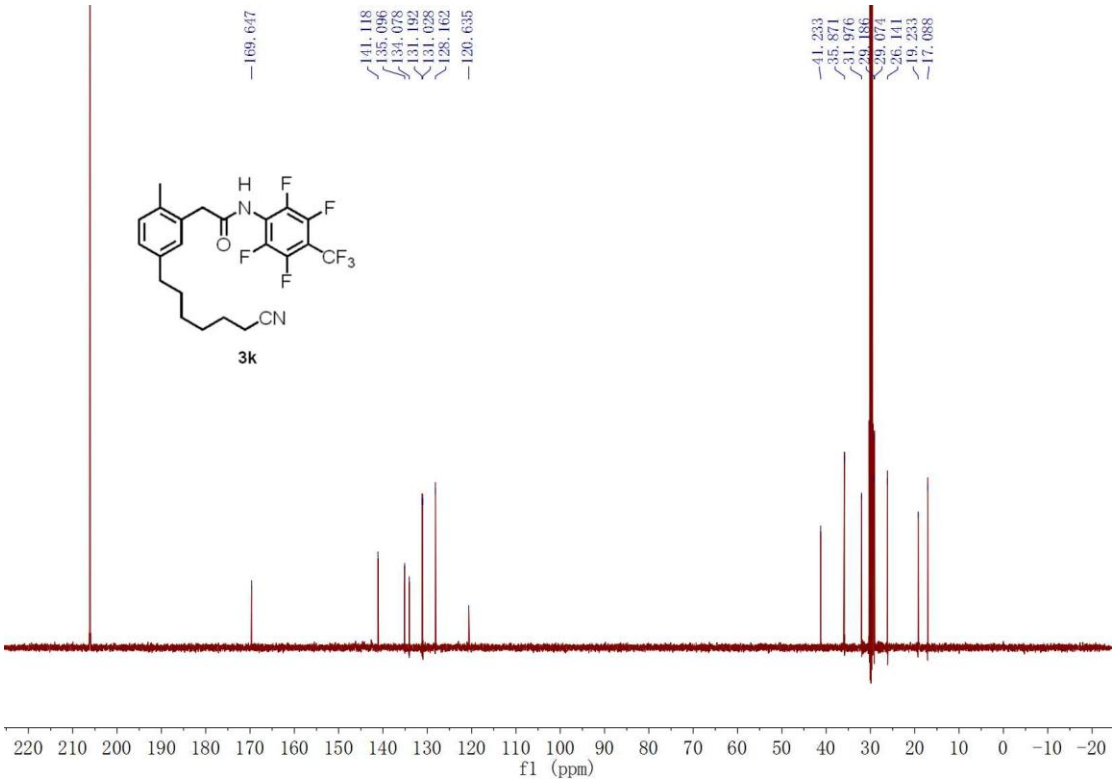
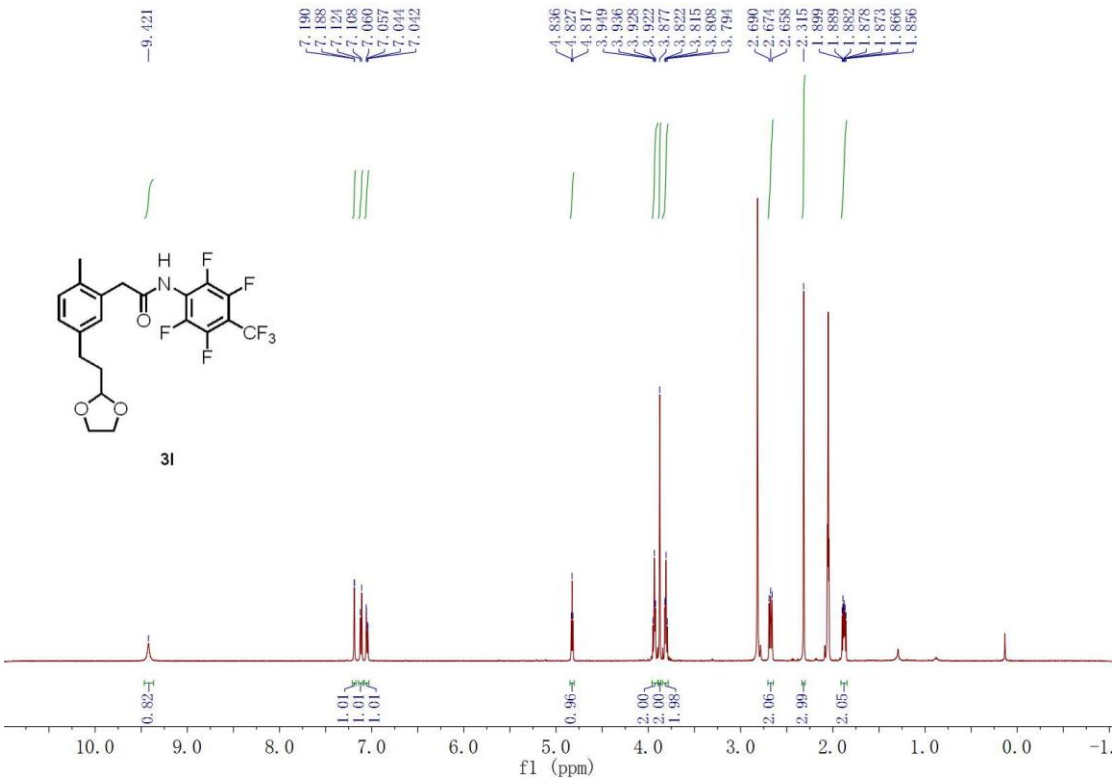
139.56
135.61
134.35
131.32
131.22
128.29
45.05
41.21
35.09
32.96
19.25
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20
f1 (ppm)
H
N
O
F
F
F
F
CF3
Cl
3j


9.422
7.169
7.112
7.097
7.039
7.024
3.869
2.600
2.585
2.569
2.446
2.431
2.417
2.312
1.663
1.646
1.632
1.616
1.602
1.506
1.492
1.476
1.460
1.446
1.417
1.403
1.389
1.373
1.358
0.88
0.98
0.97
0.96
2.00
2.02
2.03
3.00
4.18
2.13
2.18
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
3k


169.647
141.118
135.096
134.078
131.192
131.028
128.162
120.635
41.233
35.871
31.976
29.186
29.074
26.141
19.233
17.688
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)
3k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7.190
7.188
7.124
7.108
7.060
7.057
7.044
7.042
4.836
4.827
4.817
3.949
3.936
3.928
3.922
3.877
3.822
3.815
3.808
3.794
2.690
2.674
2.658
2.315
1.899
1.889
1.882
1.878
1.873
1.866
1.856
0.82
1.01
1.01
1.01
0.96
2.00
2.00
1.98
2.06
2.99
2.05
10.0
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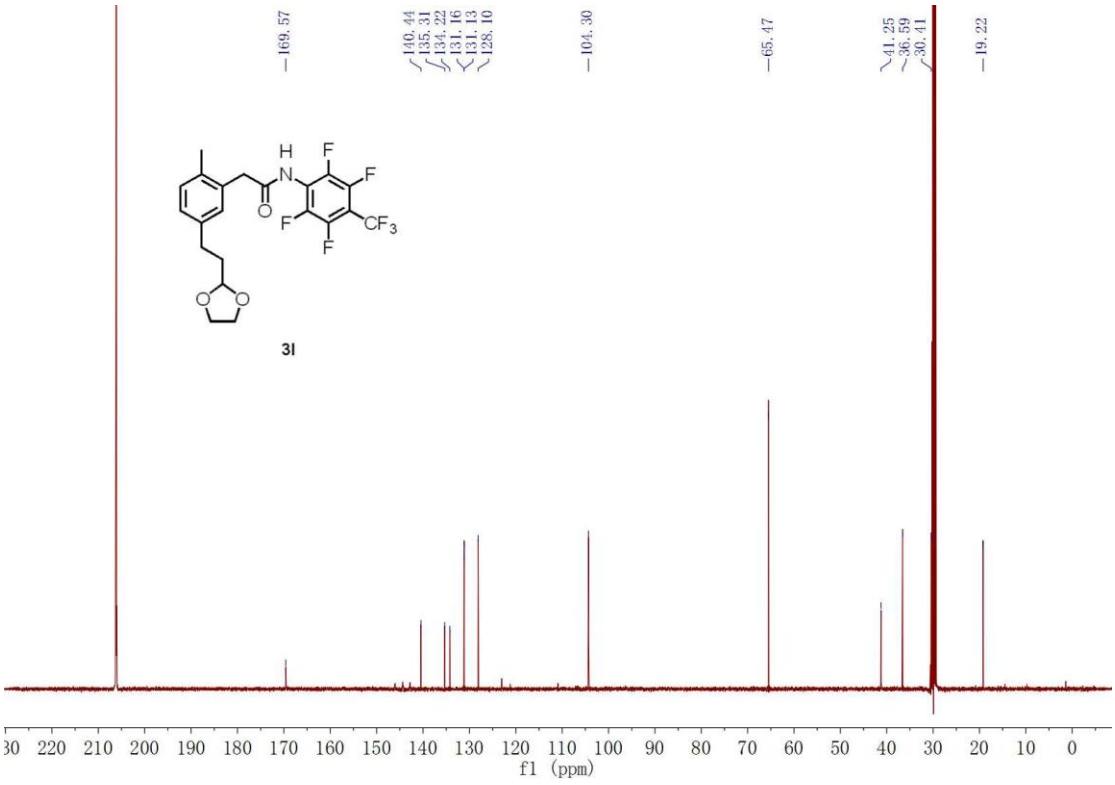
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
3l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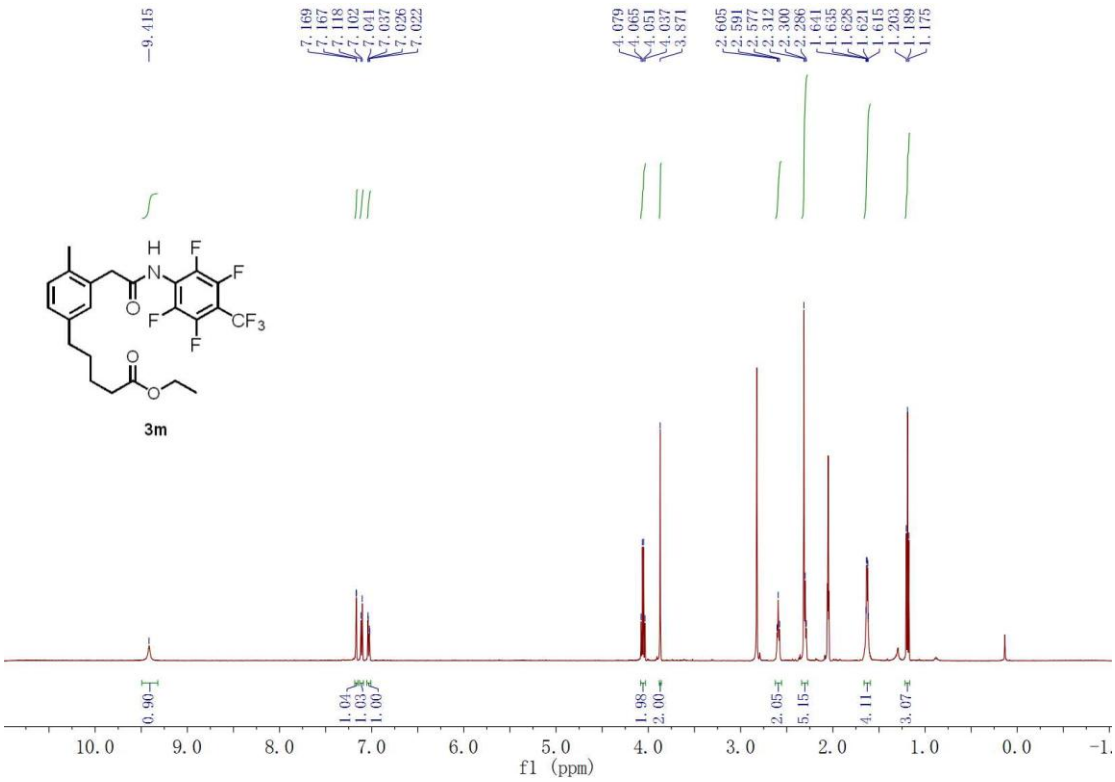
140.44
135.31
134.22
131.16
131.13
128.10
104.30
65.47
41.25
36.59
30.41
19.22
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
3l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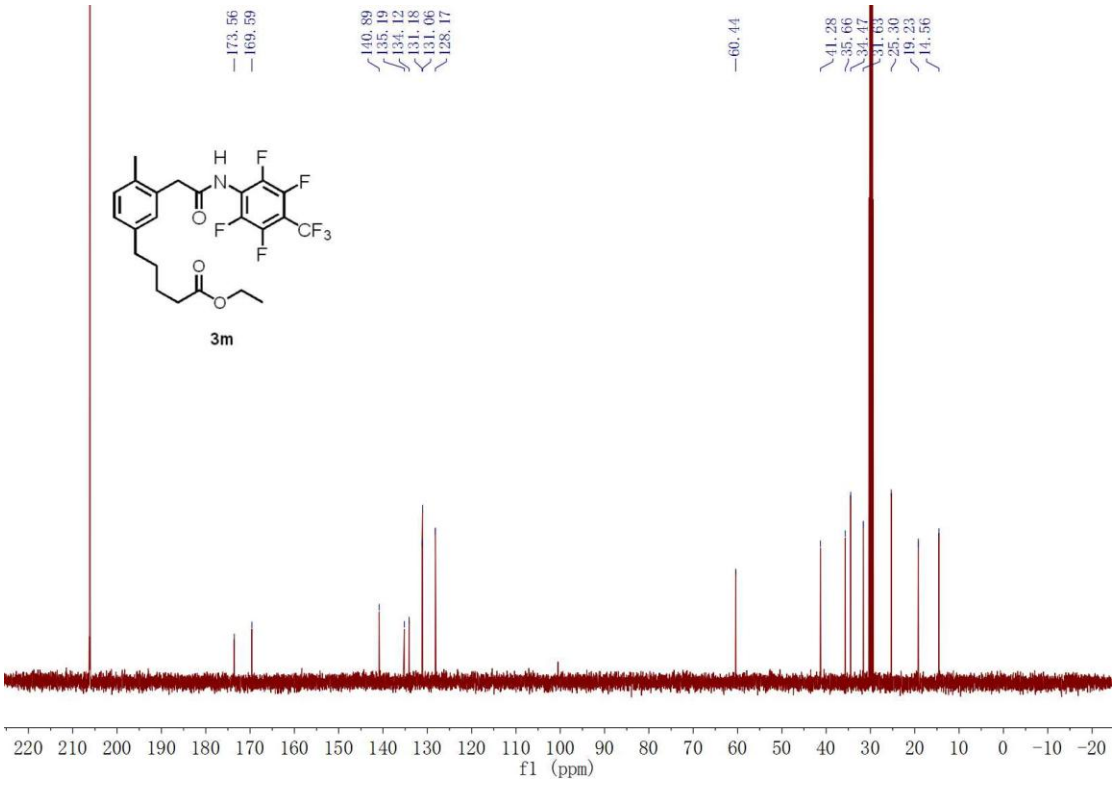
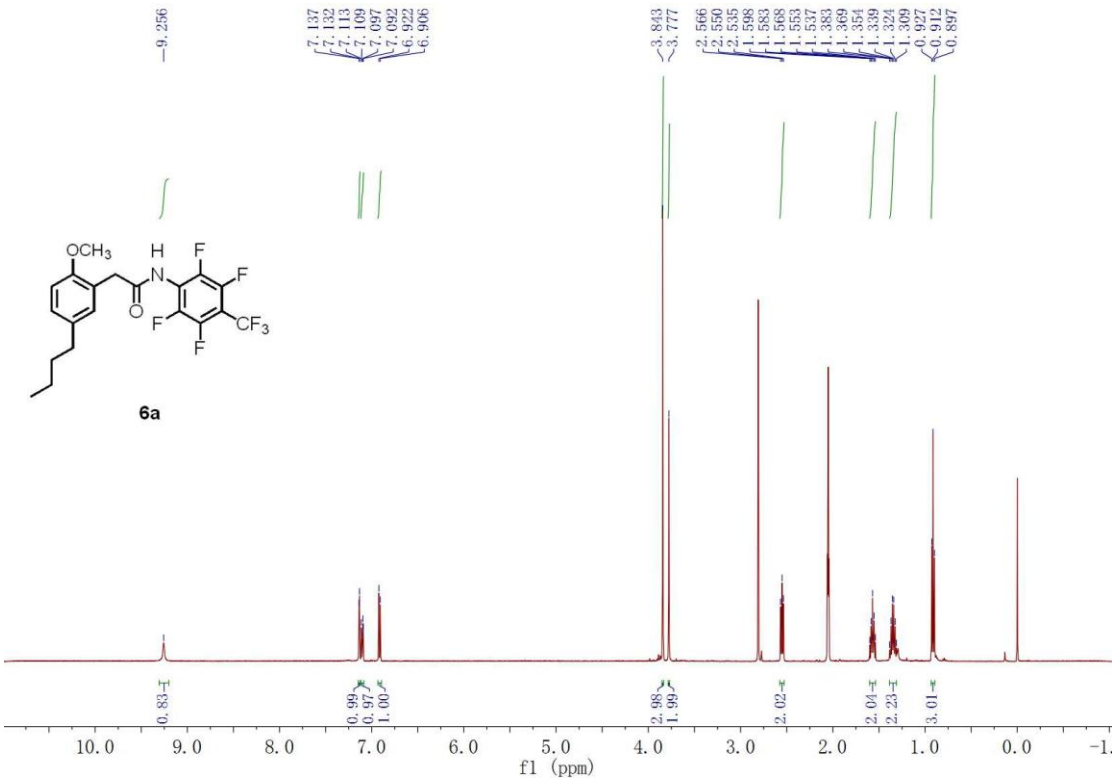
7.169
7.167
7.118
7.102
7.041
7.037
7.026
7.022
4.079
4.065
4.051
4.037
3.871
2.605
2.591
2.577
2.312
2.300
2.286
1.641
1.635
1.628
1.621
1.615
1.203
1.189
1.175
0.90
1.04
1.03
1.00
1.98
2.00
2.05
5.15
4.11
3.07
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
3m


173.56
169.59
140.89
135.19
134.12
131.18
131.06
128.17
60.44
41.28
35.66
34.47
31.63
25.30
19.23
14.56
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20
f1 (ppm)
3m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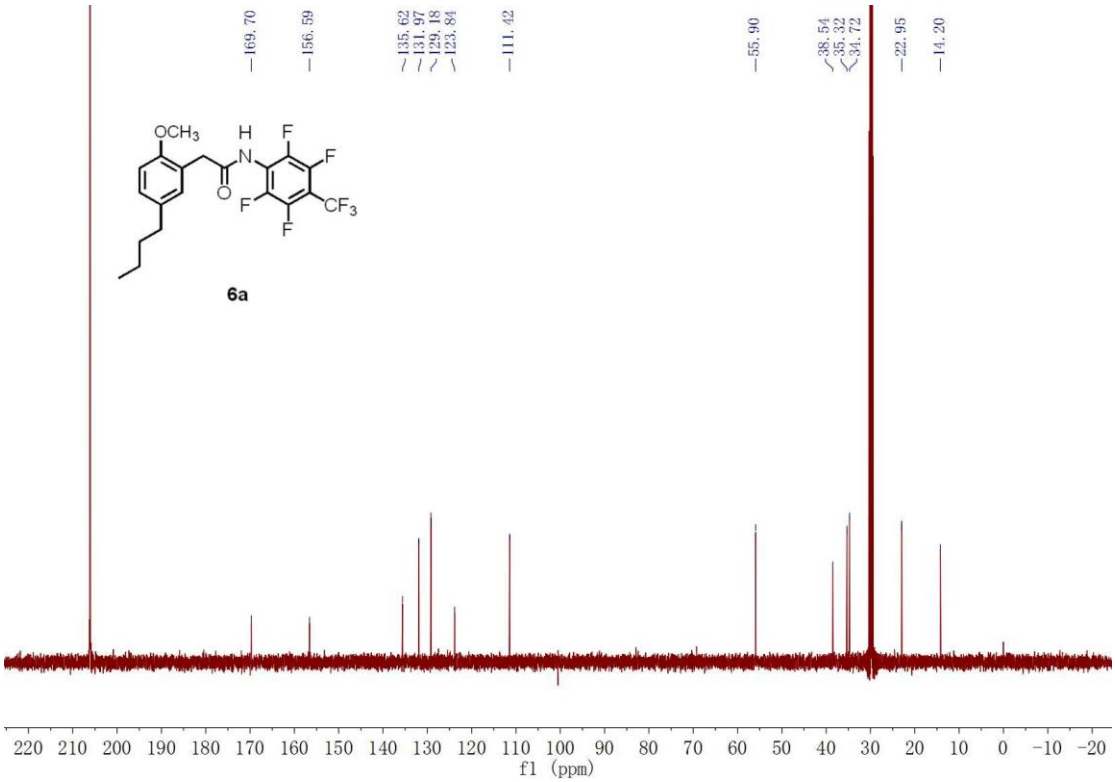
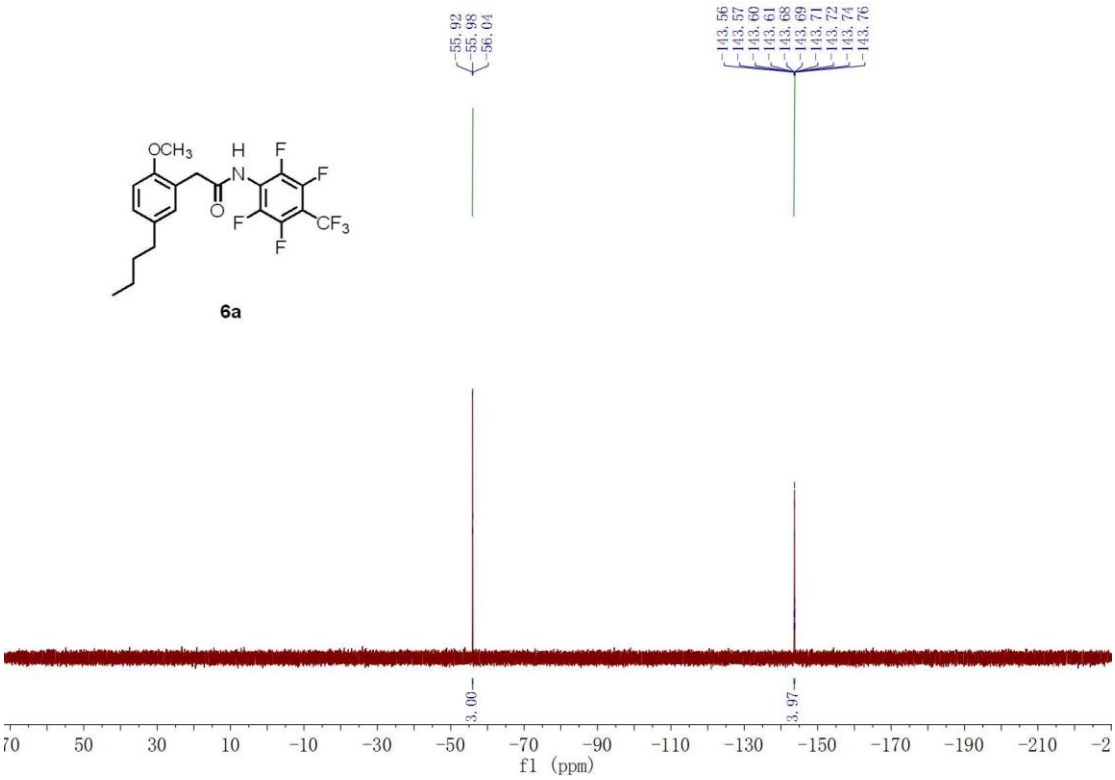
7.137
7.132
7.113
7.109
7.097
7.092
6.922
6.906
3.843
3.777
2.566
2.550
2.535
1.598
1.583
1.568
1.553
1.537
1.383
1.369
1.354
1.339
1.324
1.309
0.927
0.912
0.897
OCH3
H
N
O
F
F
F
F
CF3
6a
0.83
0.99
0.97
1.00
2.98
1.99
2.02
2.04
2.23
3.01
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


169.70
156.59
135.62
131.97
129.18
123.84
111.42
55.90
38.54
35.32
34.72
22.95
14.20
OCH3
H
N
O
F
F
F
F
CF3
6a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)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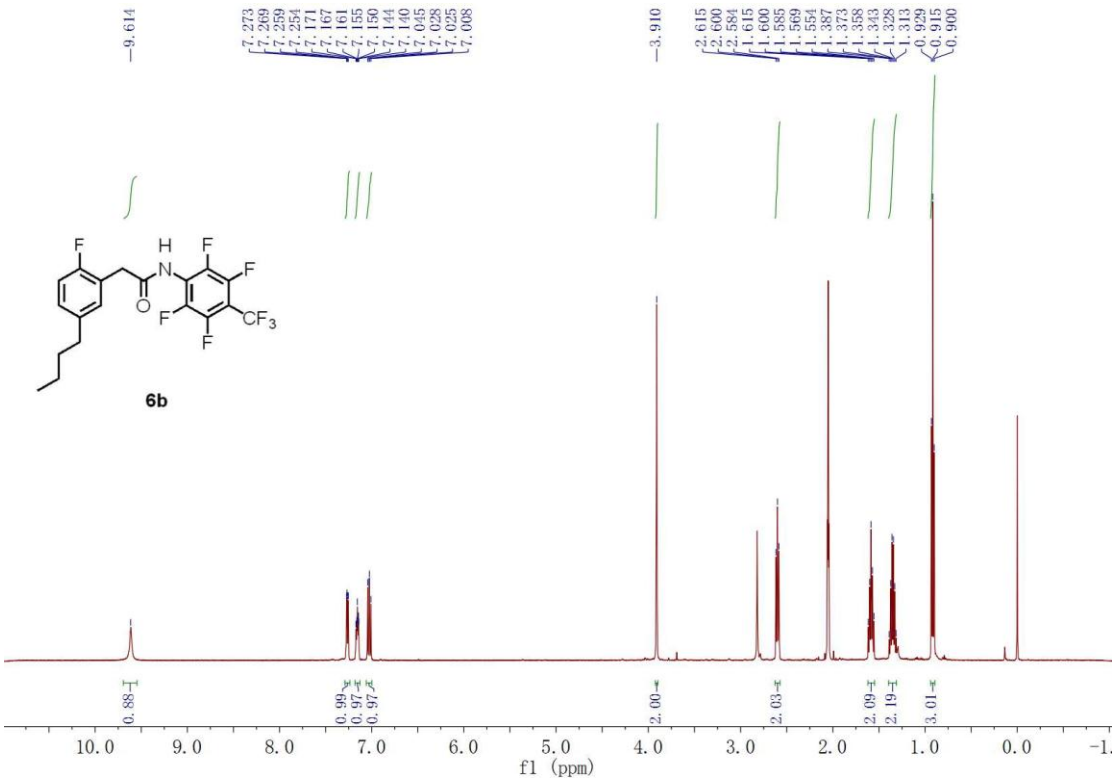
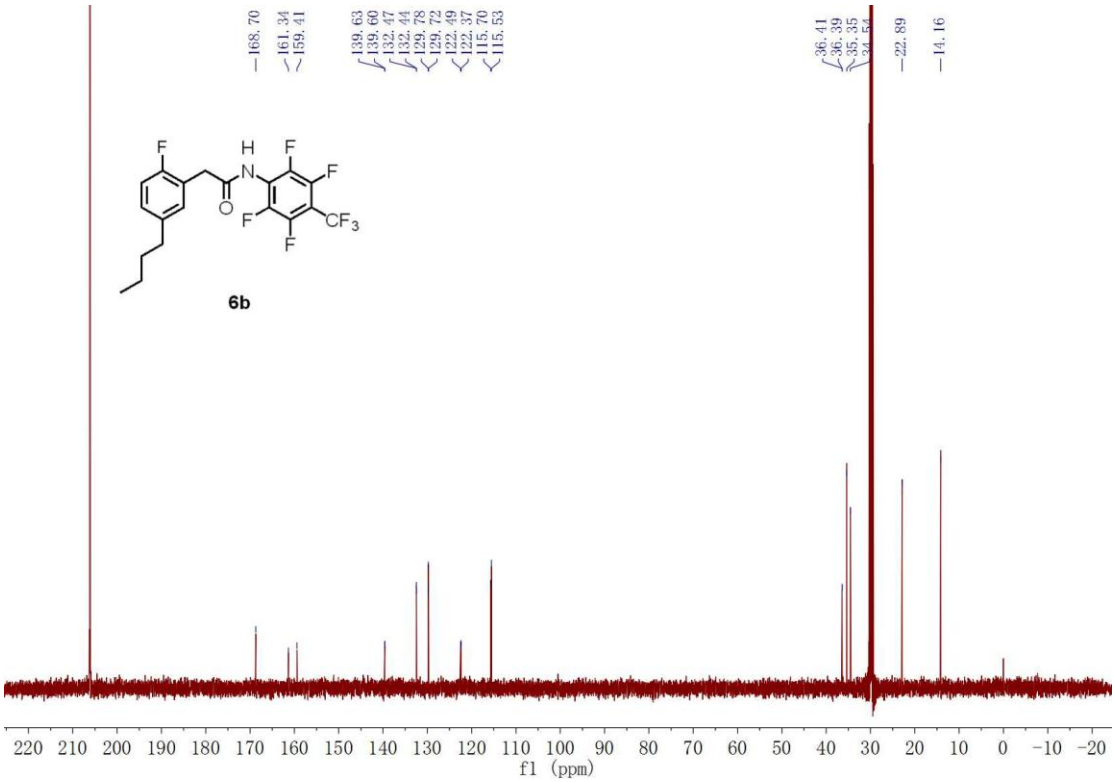
-55.98
-56.04
-143.56
-143.57
-143.60
-143.61
-143.68
-143.69
-143.71
-143.72
-143.74
-143.76
OCH3
H
N
O
F
F
F
F
CF3
6a
3.00
3.97
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-2
f1 (ppm)


9.614
7.273
7.269
7.259
7.254
7.171
7.167
7.161
7.155
7.150
7.144
7.140
7.045
7.028
7.025
7.008
3.910
2.615
2.600
2.584
1.615
1.600
1.585
1.569
1.554
1.387
1.373
1.358
1.343
1.328
1.313
0.929
0.915
0.900
F
H
F
N
F
F
O
F
CF3
F
6b
0.88
0.99
0.97
0.97
2.00
2.03
2.09
2.19
3.01
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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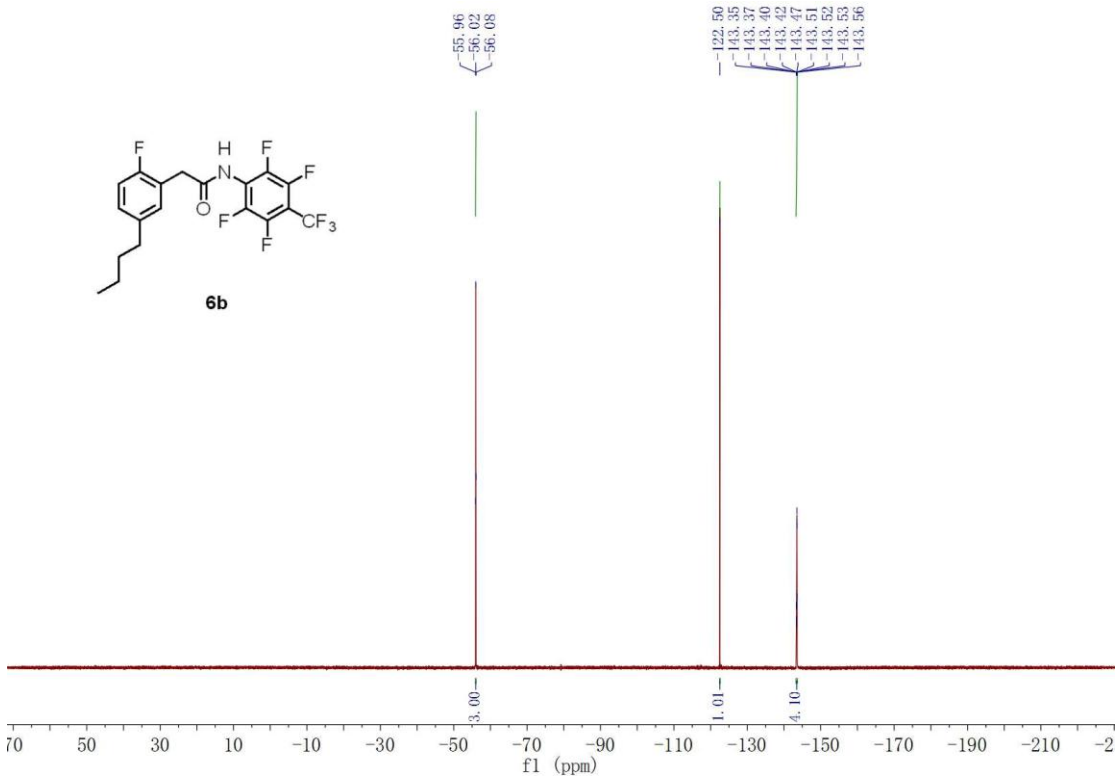
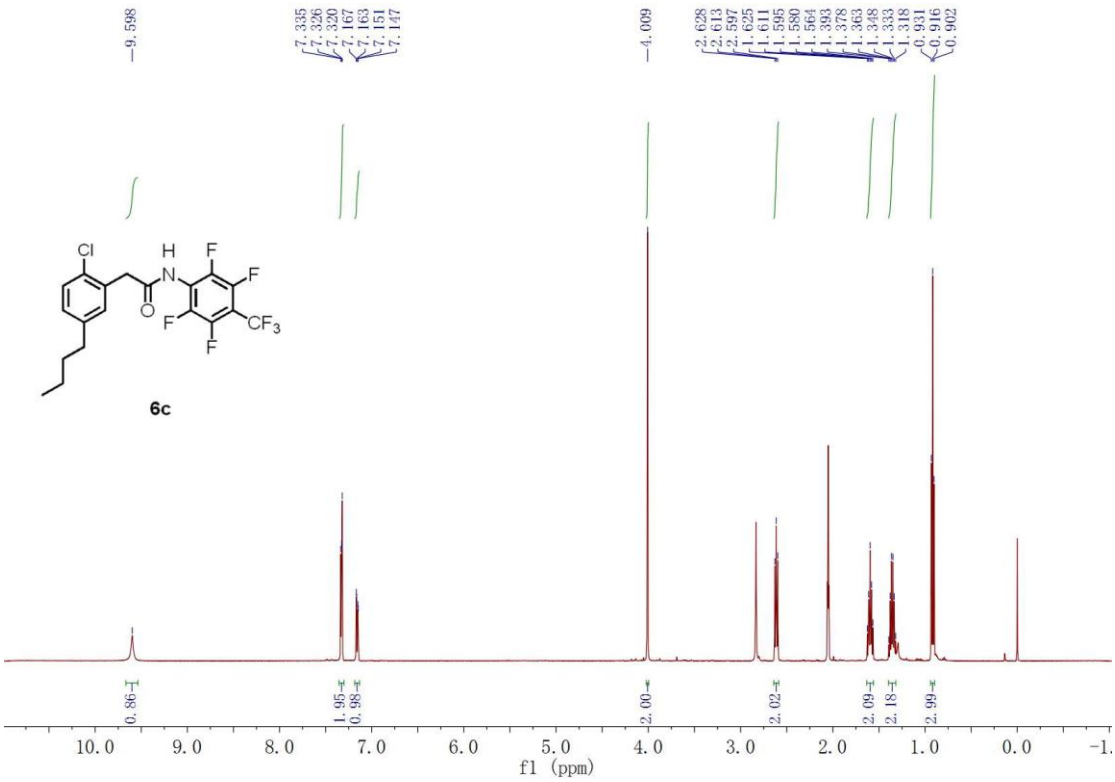
161.34
159.41
139.63
139.60
132.47
132.44
129.78
129.72
122.49
122.37
115.70
115.53
36.41
36.39
35.35
34.54
22.89
14.16
F
H
F
N
F
F
O
F
CF3
F
6b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)


F
H
N
O
F
F
F
F
CF3
6b
-55.96
-56.02
-56.08
-122.50
-143.35
-143.37
-143.40
-143.42
-143.47
-143.51
-143.52
-143.53
-143.56
3.00
1.01
4.10
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-2
f1 (ppm)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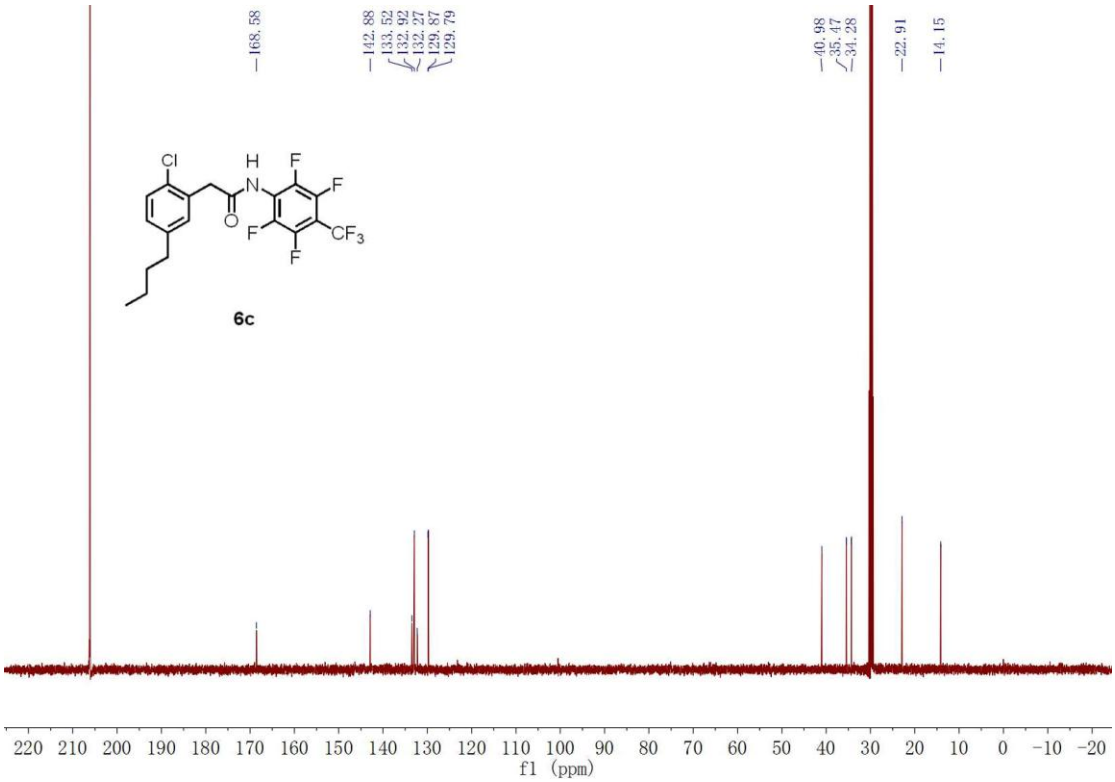
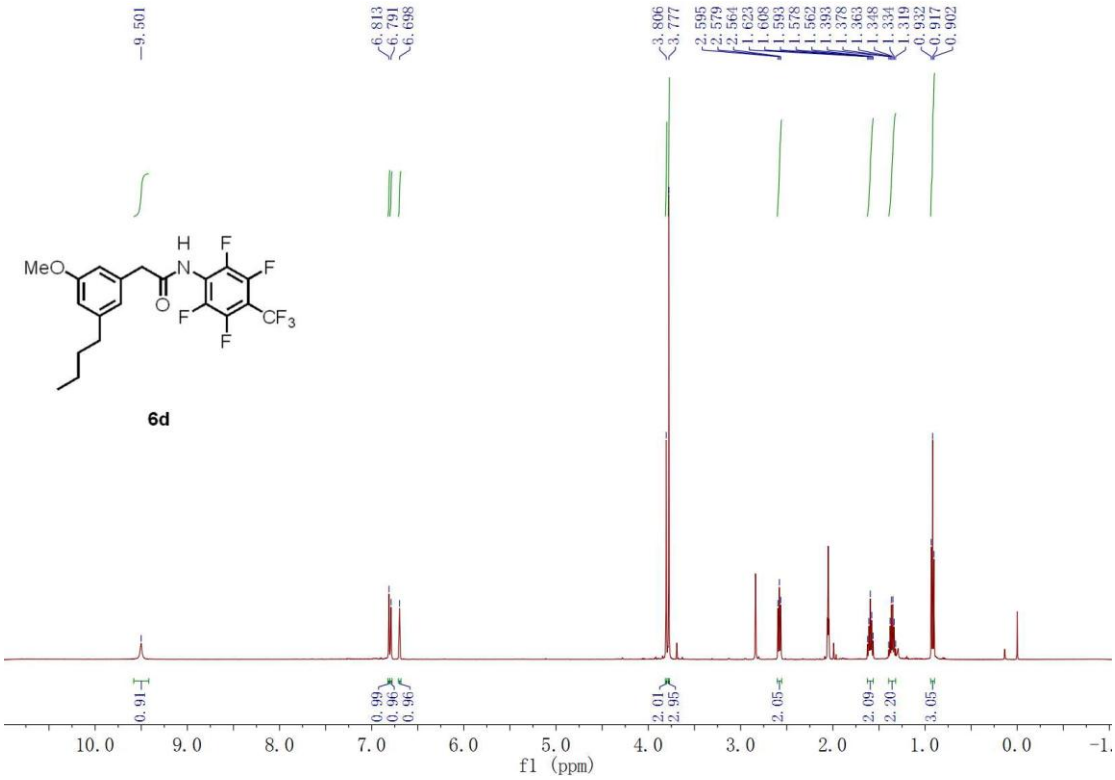
7.163
7.151
7.147
4.009
2.628
2.613
2.597
1.625
1.611
1.595
1.580
1.564
1.393
1.378
1.363
1.348
1.333
1.318
0.931
0.916
0.902
Cl
H
N
O
F
F
F
F
CF3
6c
0.86
1.95
0.98
2.00
2.02
2.09
2.18
2.99
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


168.58
142.88
133.52
132.92
132.27
129.87
129.79
40.98
35.47
34.28
22.91
14.15
Cl
H
N
O
F
F
F
F
CF3
6c
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)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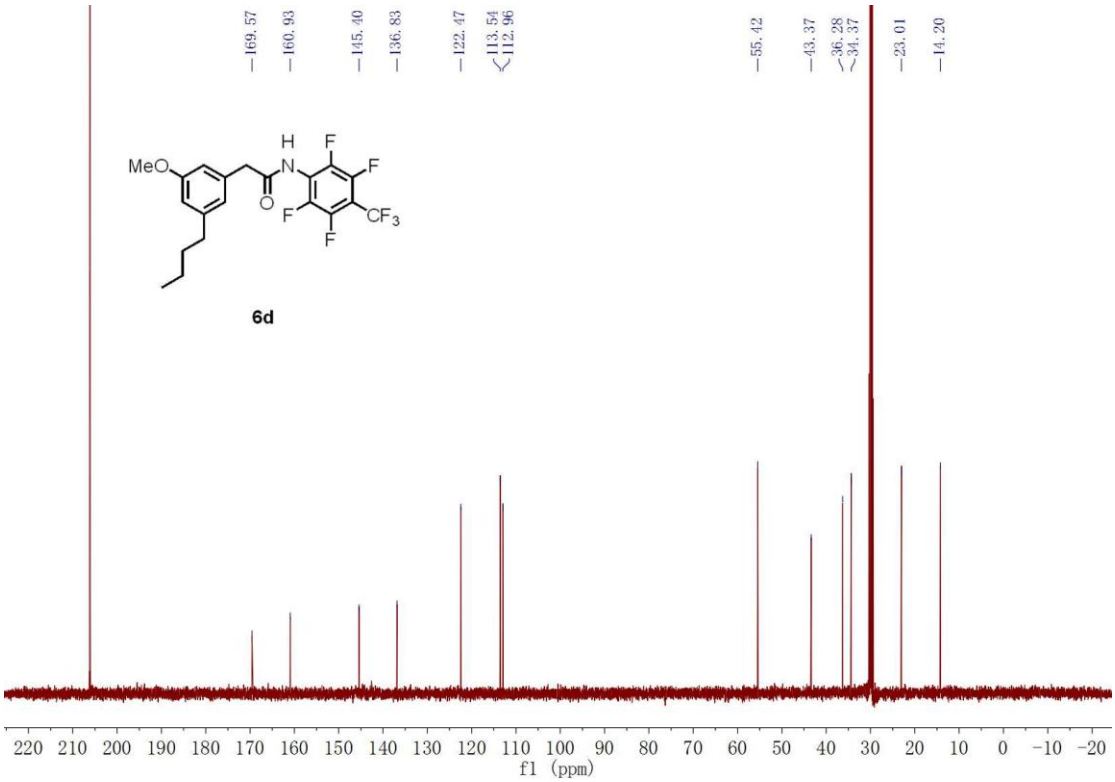
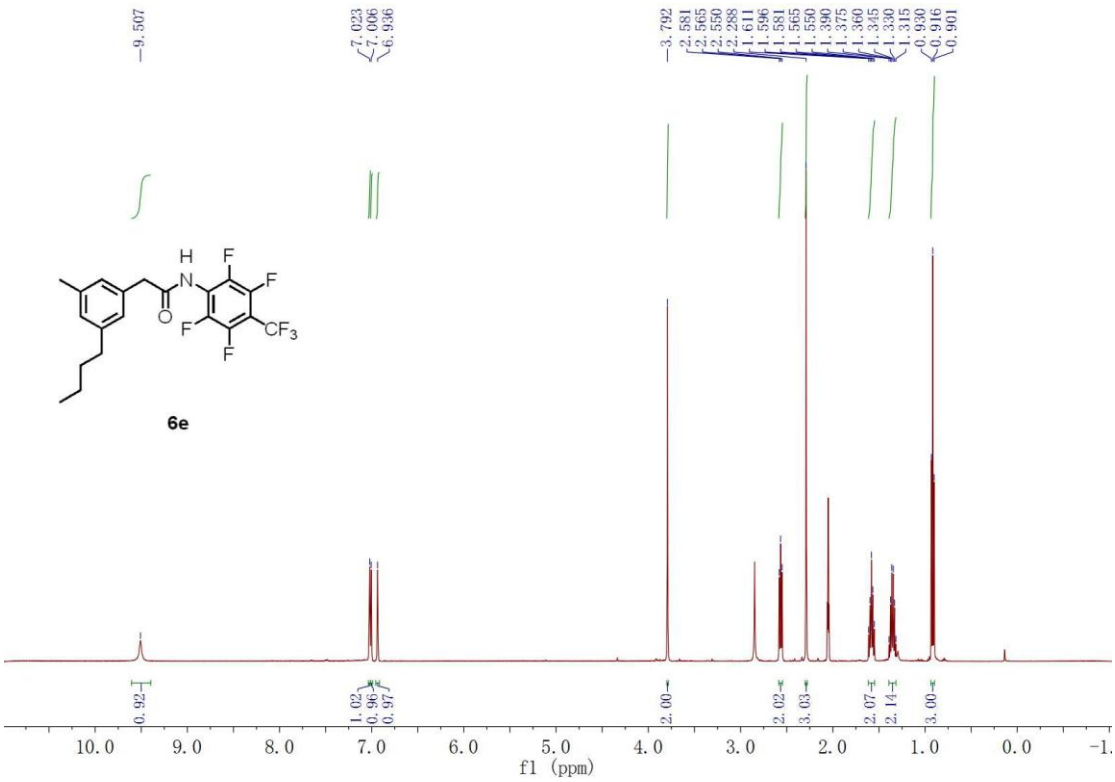
6.791
6.698
3.806
3.777
2.595
2.579
2.564
1.623
1.608
1.593
1.578
1.562
1.393
1.378
1.363
1.348
1.334
1.319
0.932
0.917
0.902
MeO
H
N
O
F
F
F
F
F
CF3
6d
0.91
0.99
0.96
0.96
2.01
2.95
2.05
2.09
2.20
3.05
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


169.57
160.93
145.40
136.83
122.47
113.54
112.96
55.42
43.37
36.28
34.37
23.01
14.20
MeO
H
N
O
F
F
F
F
F
CF3
6d
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)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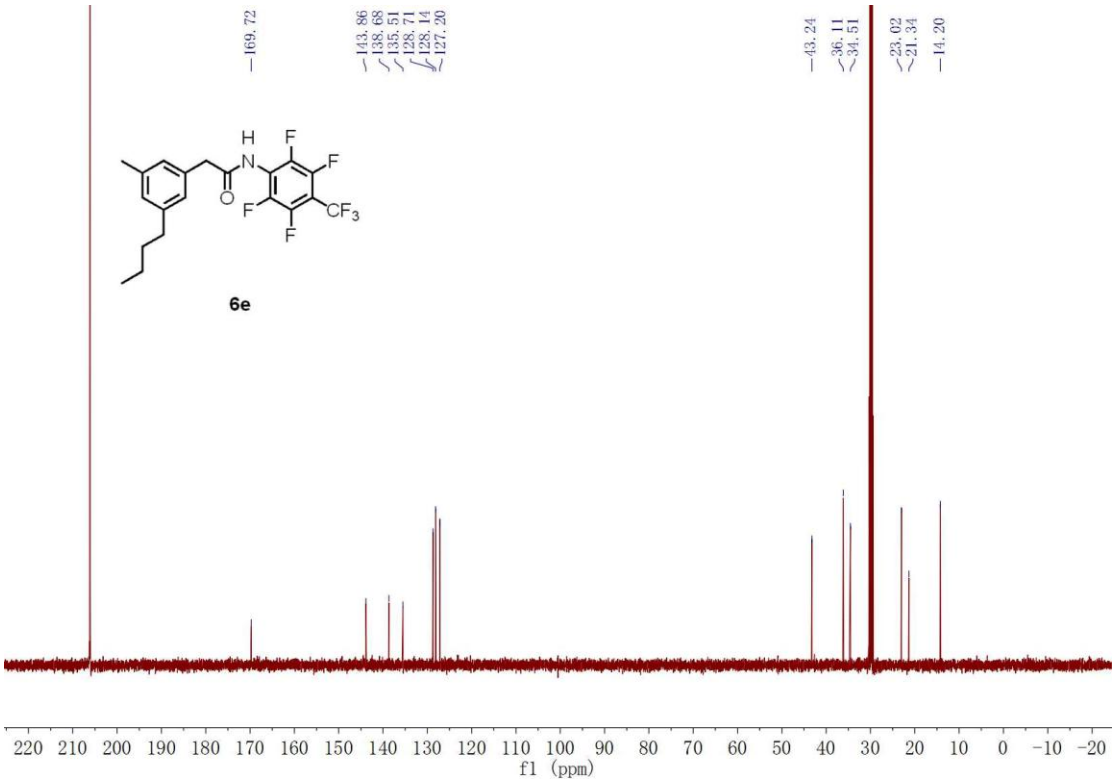
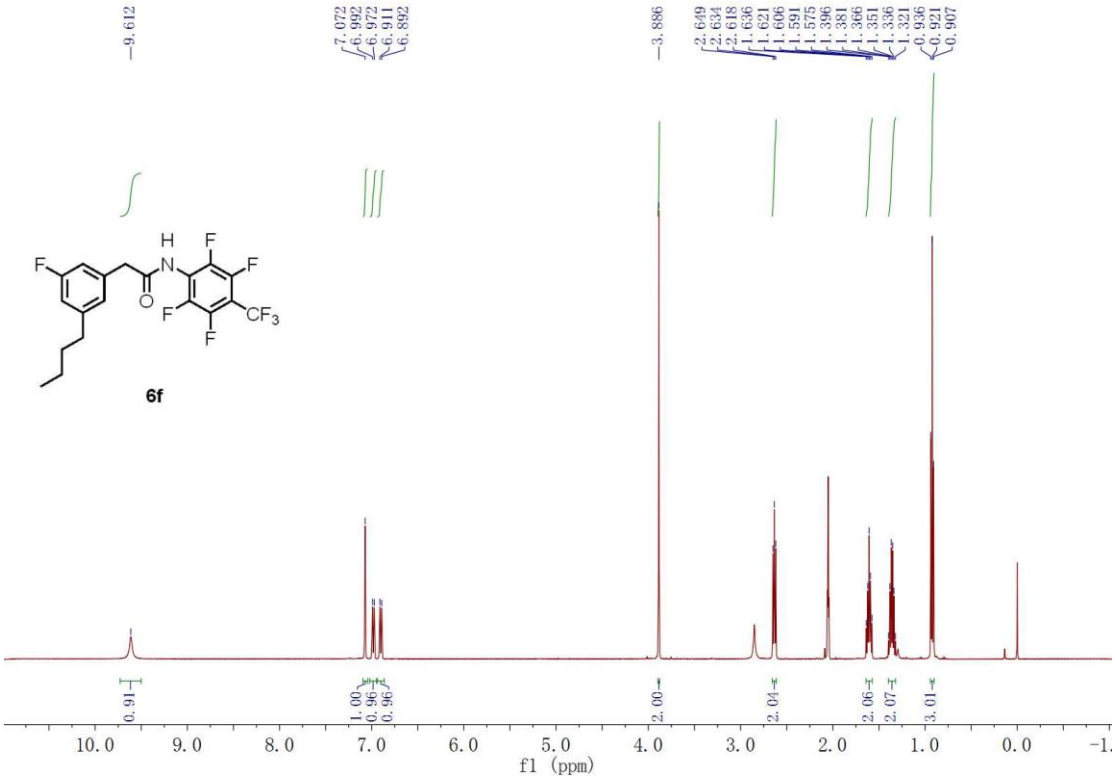
2.550
2.288
1.611
1.596
1.581
1.565
1.550
1.390
1.375
1.360
1.345
1.330
1.315
0.930
0.916
0.901
6e
0.92
1.02
0.96
0.97
2.00
2.02
3.03
2.07
2.14
3.00
f1 (ppm)


169.72
143.86
138.68
135.51
128.71
128.14
127.20
43.24
36.11
34.51
23.62
21.34
14.20
6e
f1 (ppm)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6.992
6.972
6.911
6.892
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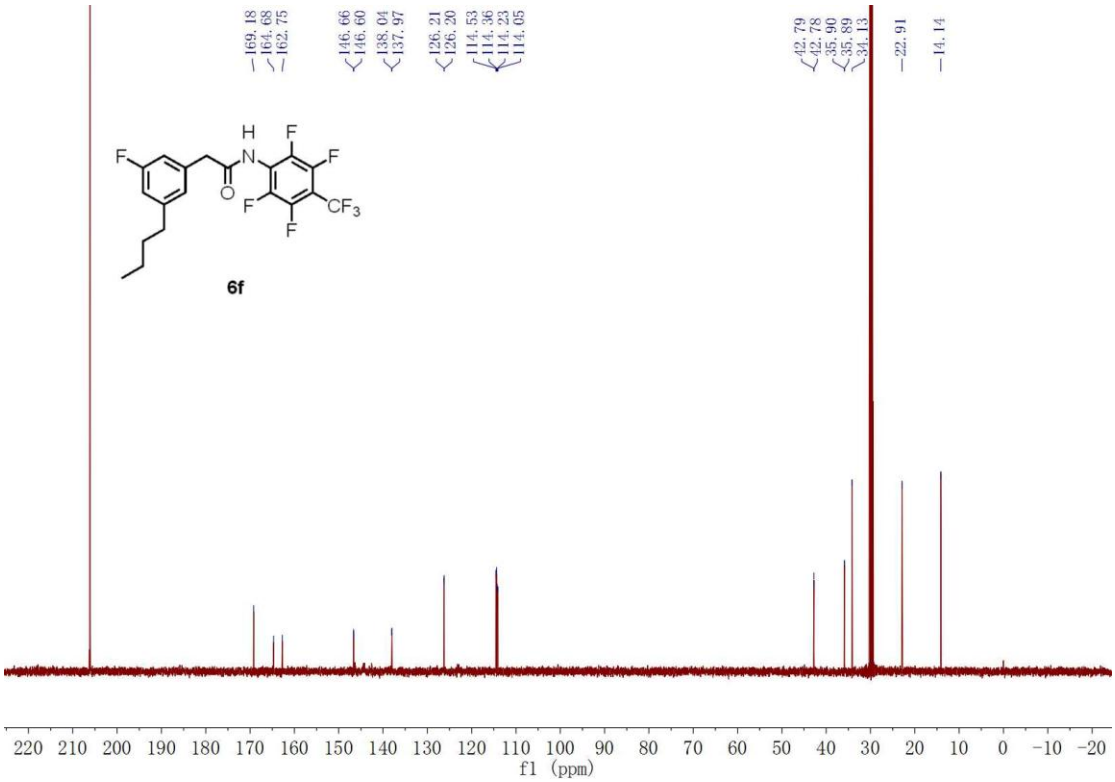
2.649
2.634
2.618
1.636
1.621
1.606
1.591
1.575
1.396
1.381
1.366
1.351
1.336
1.321
0.936
0.921
0.907
6f
0.91
1.00
0.96
0.96
2.00
2.04
2.06
2.07
3.01
f1 (ppm)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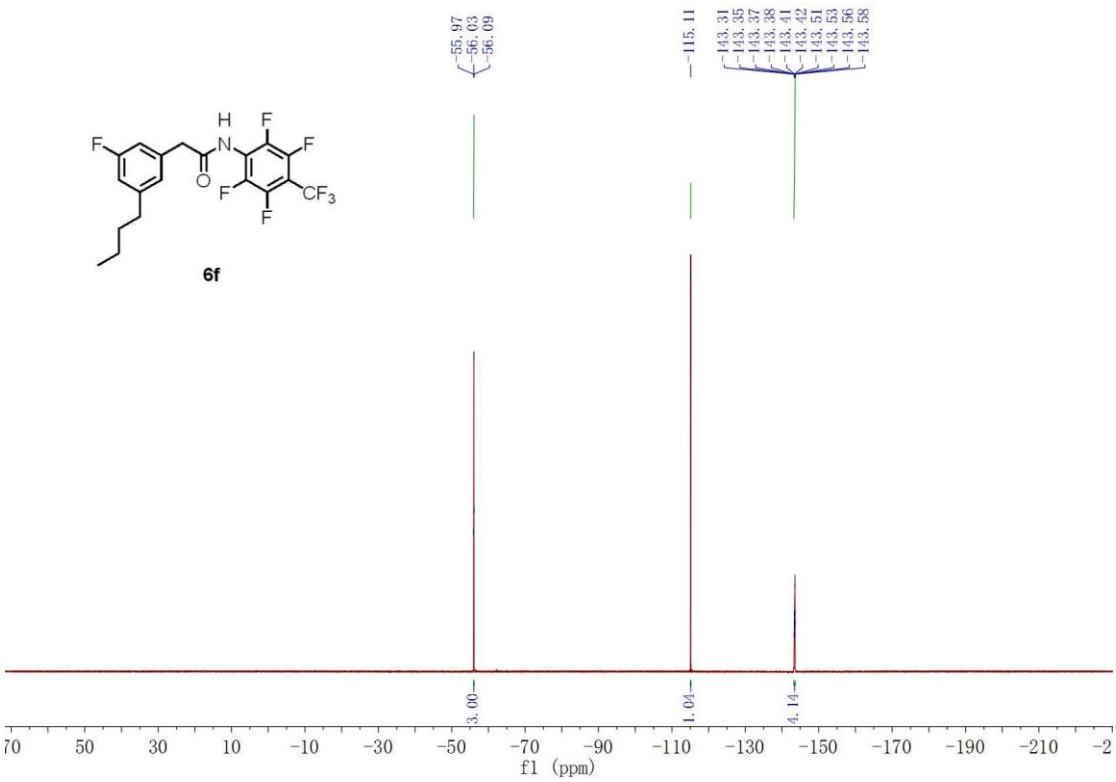
146.60
138.04
137.97
126.21
126.20
114.53
114.36
114.23
114.05
42.79
42.78
35.90
35.89
34.13
22.91
14.14
6f
f1 (ppm)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-56.09
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-143.31
-143.35
-143.37
-143.38
-143.41
-143.42
-143.51
-143.53
-143.56
-143.58
H
N
O
F
F
F
F
F
CF3
6f
3.00
1.04
4.14
70
50
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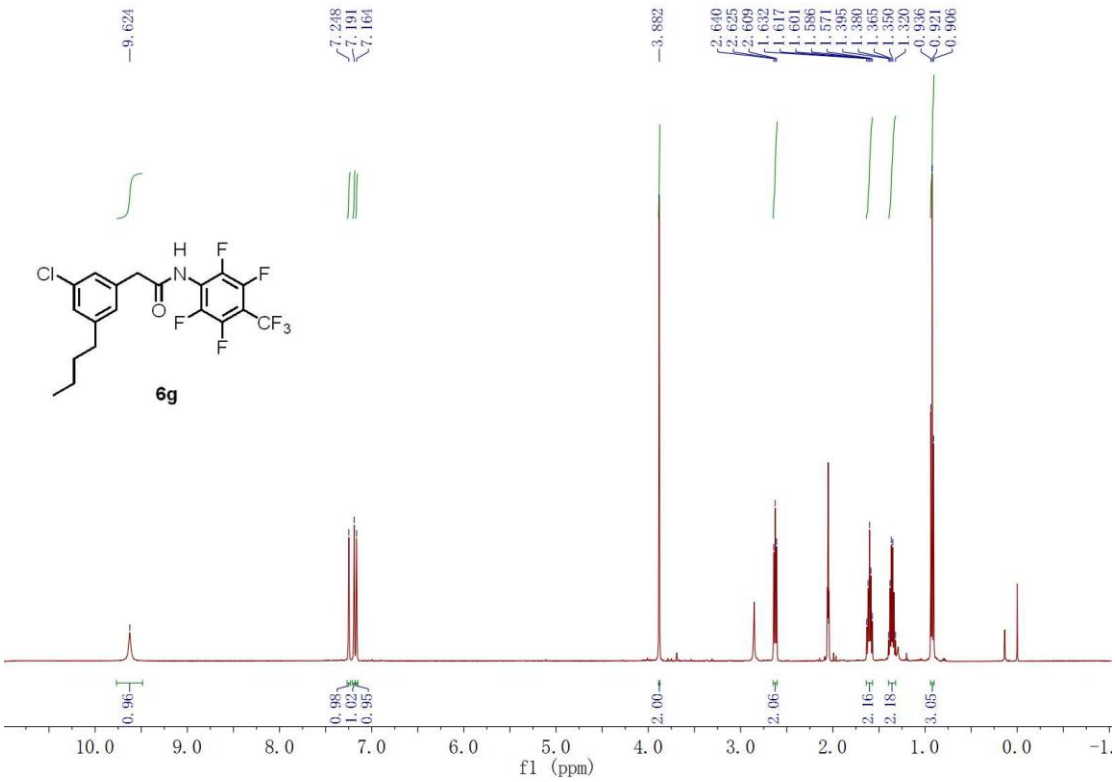
-150
-170
-190
-210
-2
f1 (ppm)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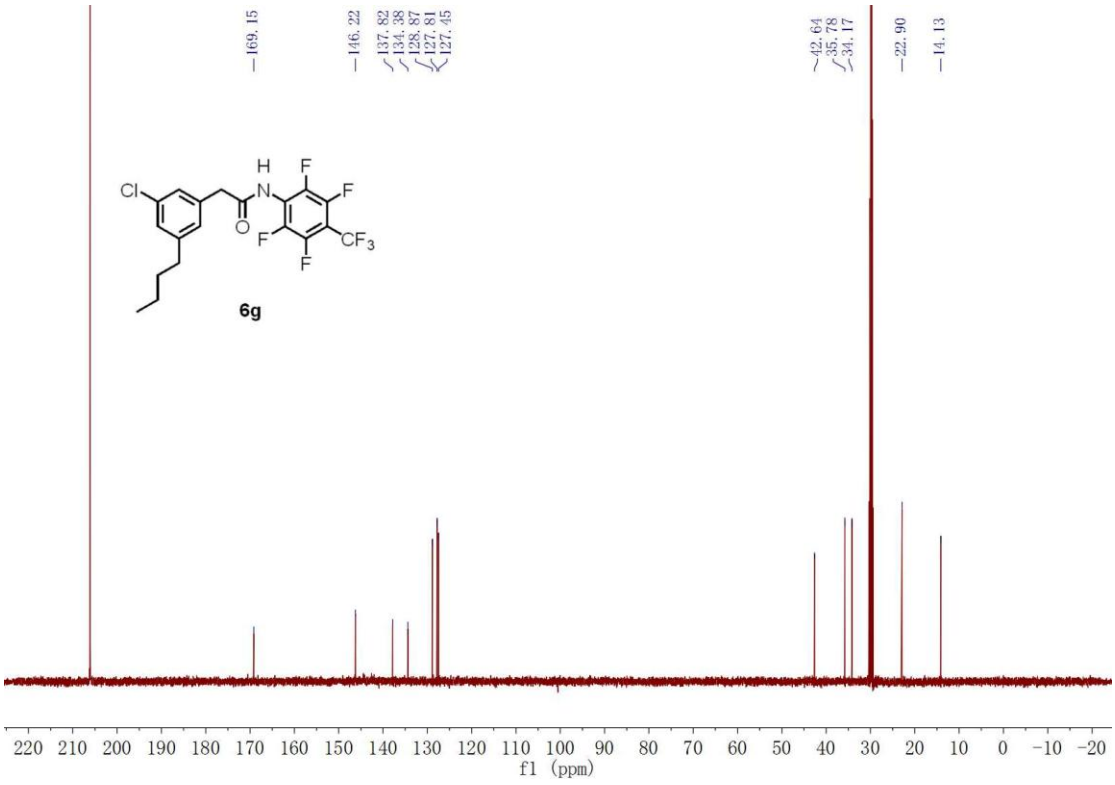
2.625
2.609
1.632
1.617
1.601
1.586
1.571
1.395
1.380
1.365
1.350
1.320
0.936
0.921
0.906
0.96
0.98
1.02
0.95
2.00
2.06
2.16
2.18
3.05
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
Cl
H
N
O
F
F
F
F
CF3
6g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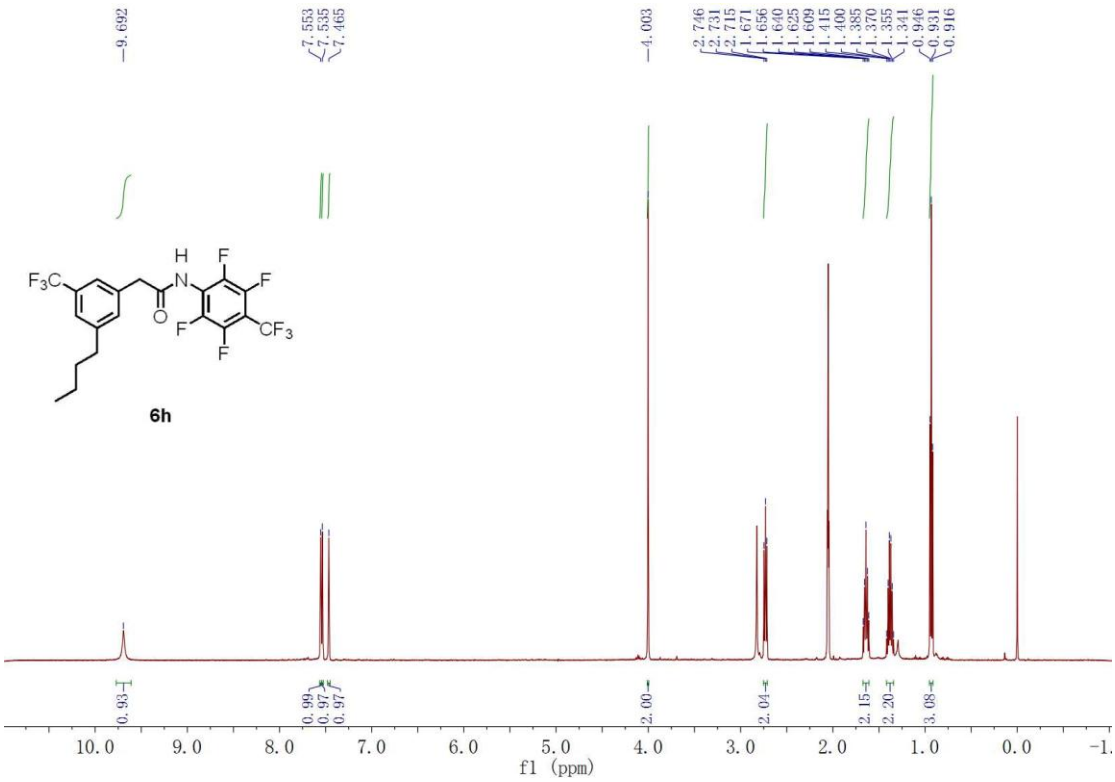
146.22
137.82
134.38
128.87
127.81
127.45
42.64
35.78
34.17
22.90
14.13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20
f1 (ppm)
Cl
H
N
O
F
F
F
F
CF3
6g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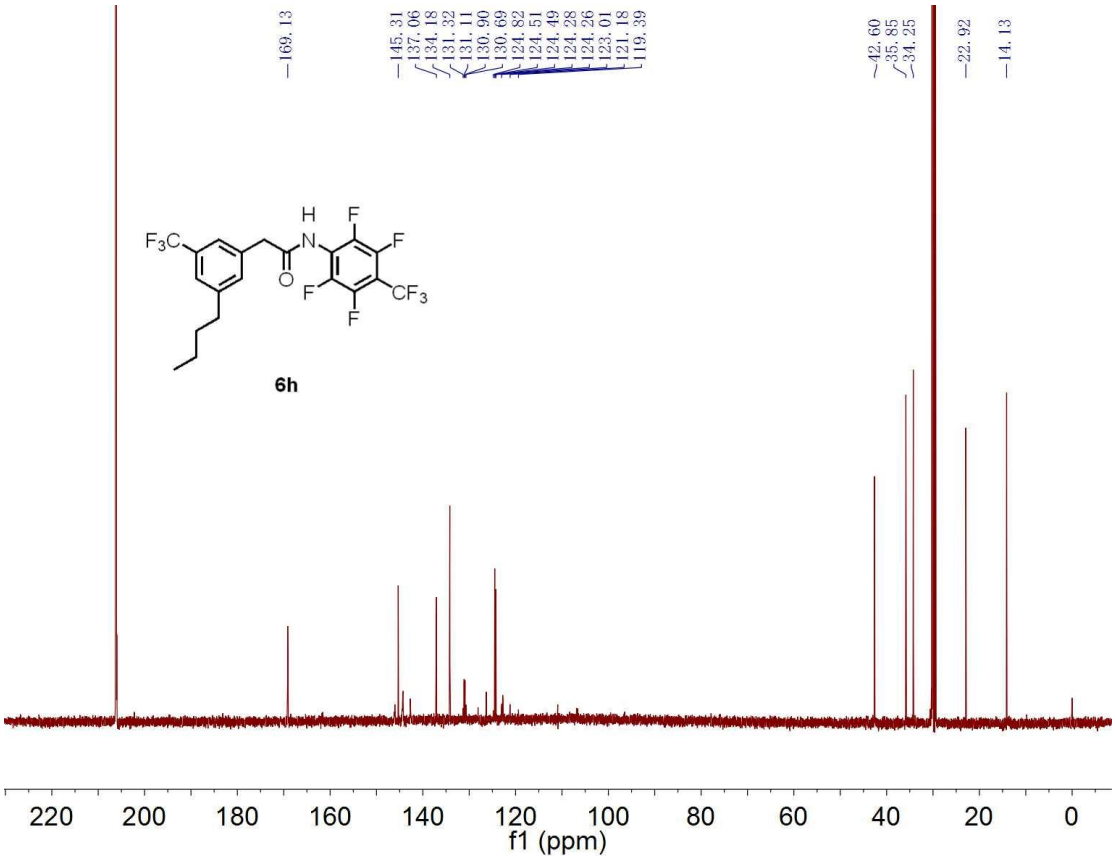
2.746
2.731
2.715
1.671
1.656
1.640
1.625
1.609
1.415
1.406
1.385
1.370
1.355
1.341
0.946
0.931
0.916
0.93
0.99
0.97
0.97
2.00
2.04
2.15
2.20
3.08
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
6h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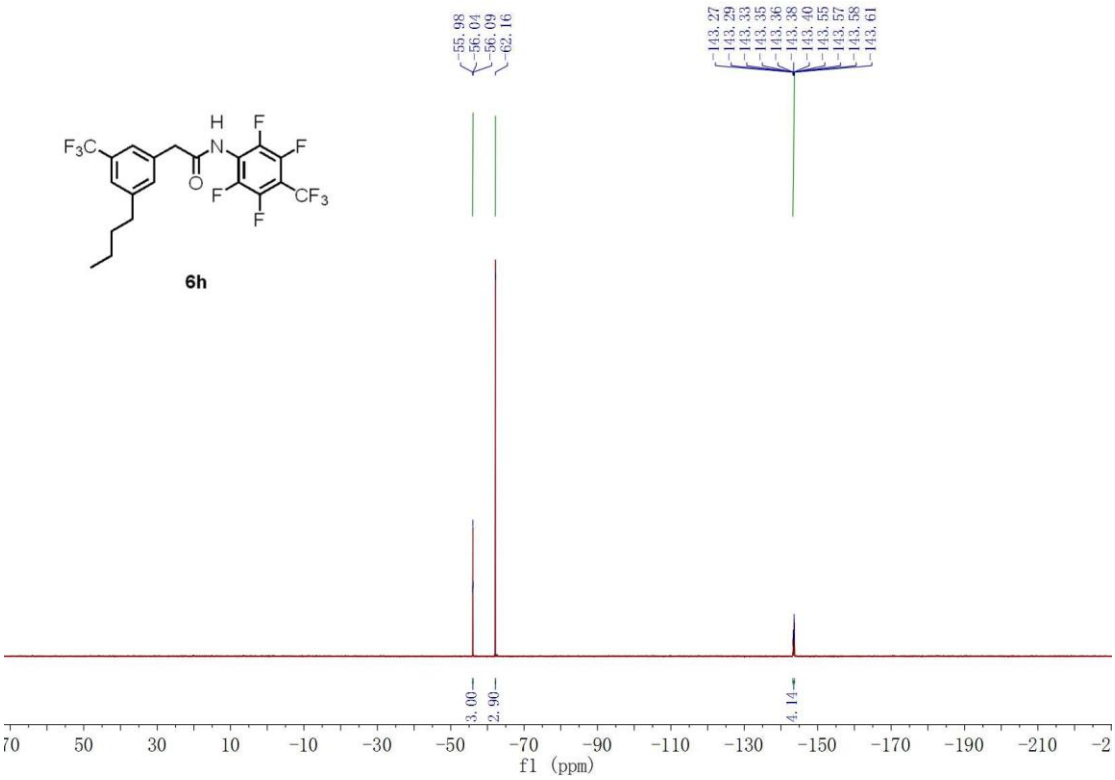
145.31
137.06
134.18
131.32
131.11
130.90
130.69
124.82
124.51
124.49
124.28
124.26
123.01
121.18
119.39
42.60
35.85
34.25
22.92
14.13
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)
6h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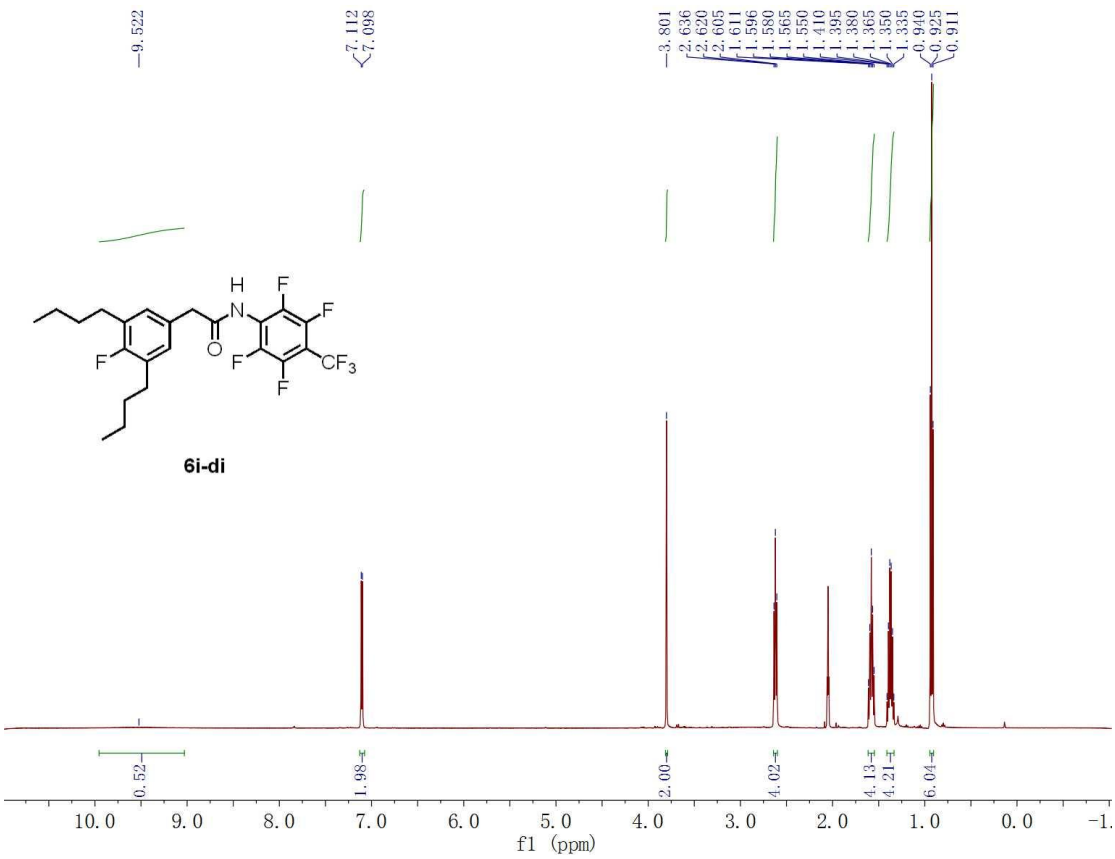
-56.04
-56.09
-62.16
-143.27
-143.29
-143.33
-143.35
-143.36
-143.38
-143.40
-143.55
-143.57
-143.58
-143.61
H
F
F3C
N
F
O
F
CF3
F
6h
3.00
2.90
4.14
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-2
f1 (ppm)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1.611
1.596
1.580
1.565
1.550
1.410
1.395
1.380
1.365
1.350
1.335
0.940
0.925
0.911
H
N
O
F
F
F
F
F
CF3
6i-di
0.52
1.98
2.00
4.02
4.13
4.21
6.04
10.0
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7.0
6.0
5.0
4.0
3.0
2.0
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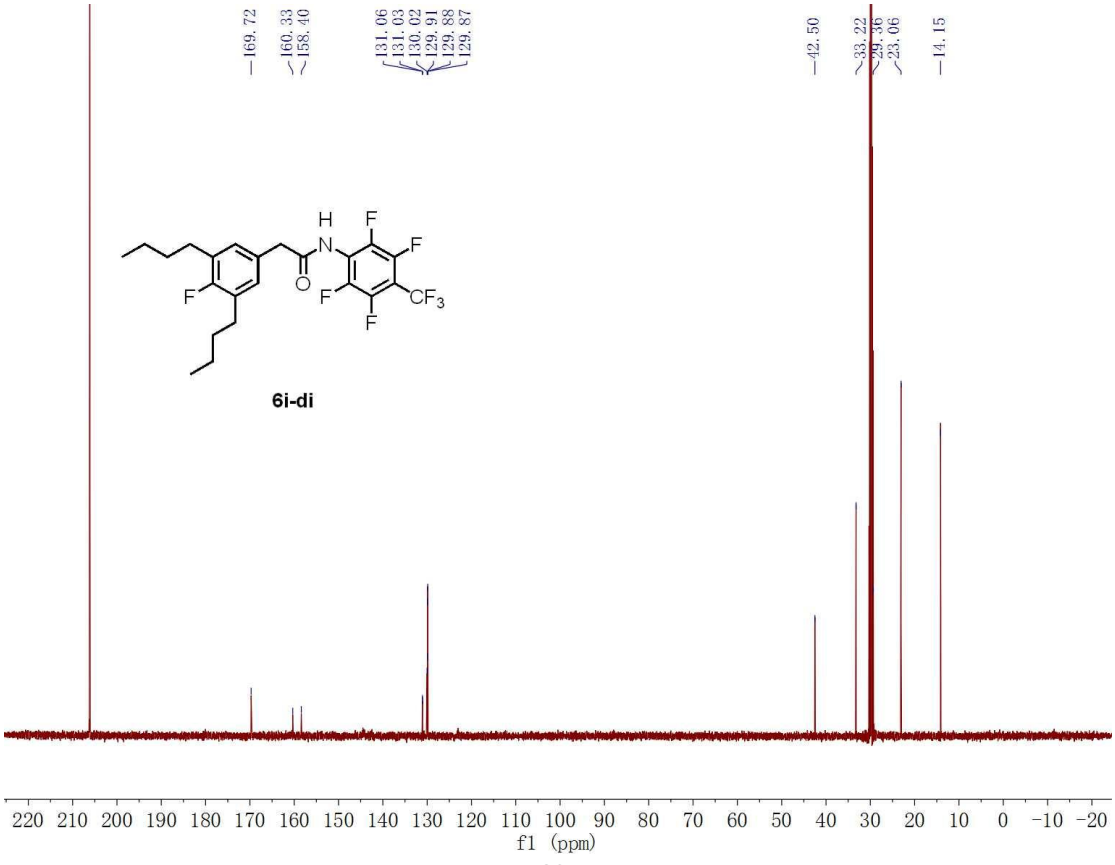
0.0
f1 (ppm)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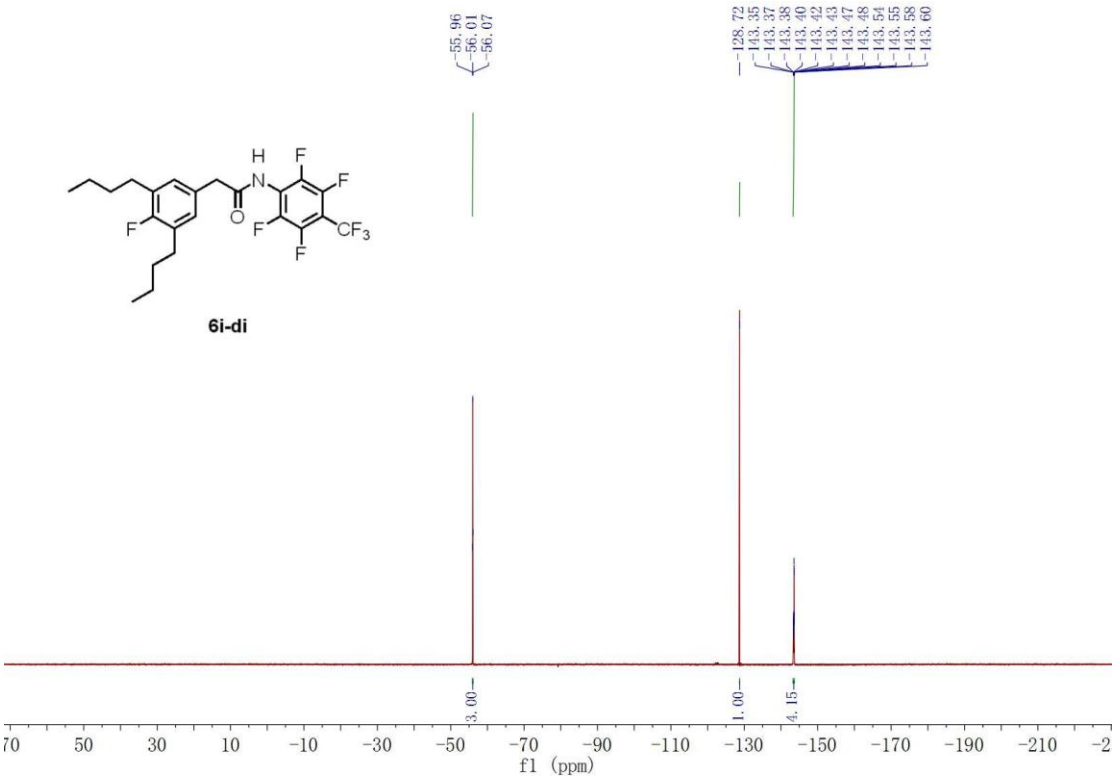
131.03
130.02
129.91
129.88
129.87
42.50
33.22
29.36
23.06
14.15
H
N
O
F
F
F
F
F
CF3
6i-di
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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-56.07
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-143.37
-143.38
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-143.48
-143.54
-143.55
-143.58
-143.60
H
N
O
F
F
F
F
F
CF3
3.00
1.00
4.15
70
50
30
10
-10
-30
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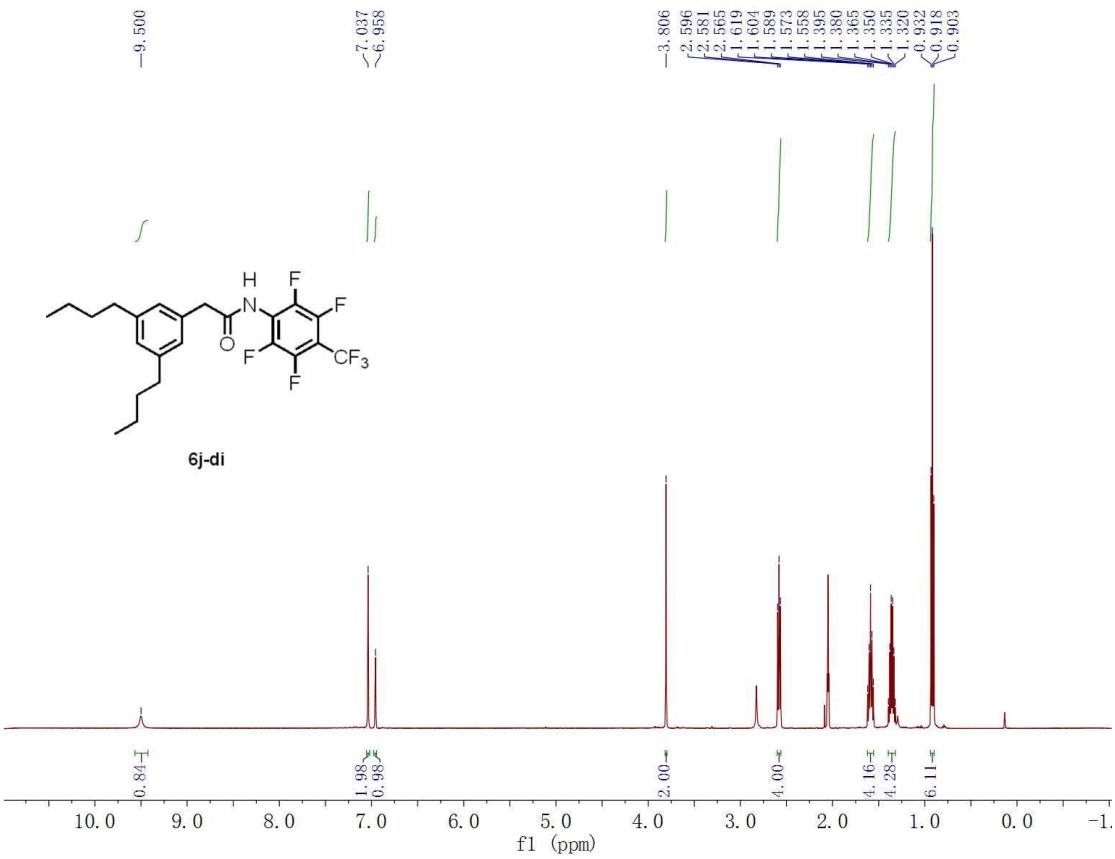
-70
-90
-110
-130
-150
-170
-190
-210
-2
f1 (ppm)

6i-di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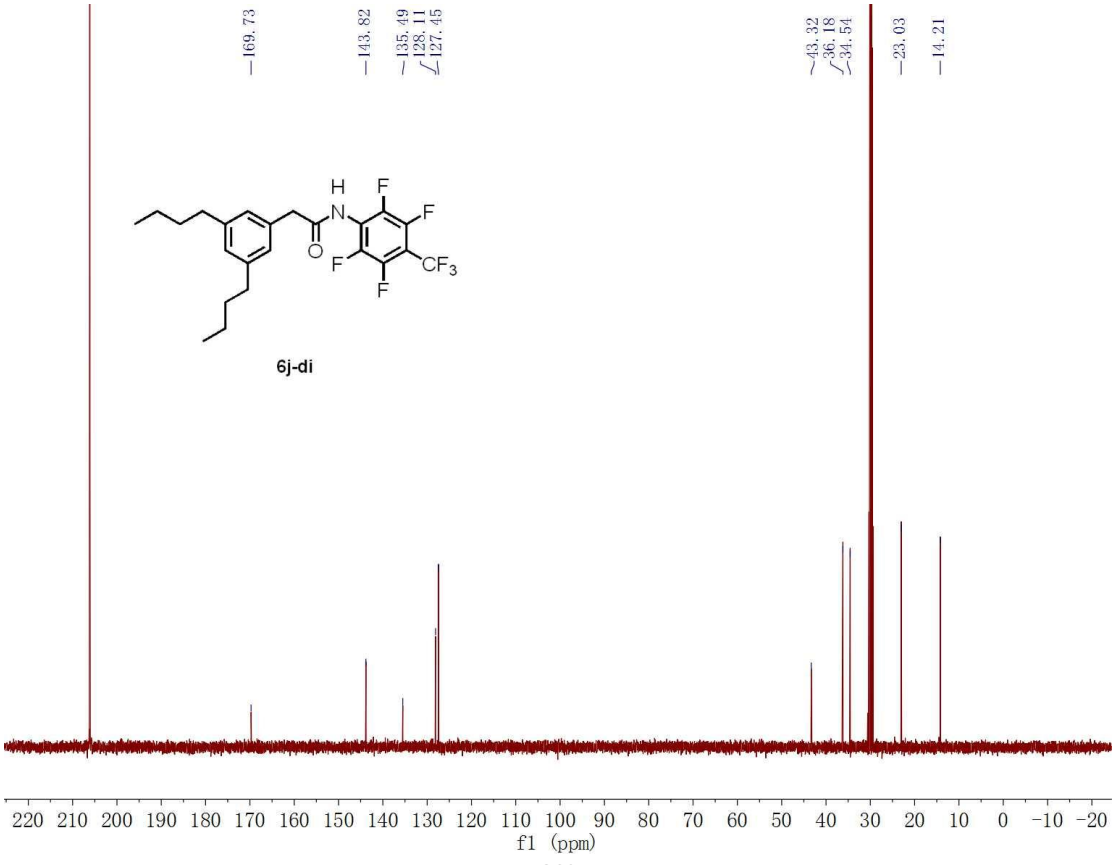
2.565
1.619
1.604
1.589
1.573
1.558
1.395
1.380
1.365
1.350
1.335
1.320
0.932
0.918
0.903
6j-di
0.84
1.98
0.98
2.00
4.00
4.16
4.28
6.11
f1 (ppm)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127.45
43.32
36.18
34.54
23.03
14.21
6j-di
f1 (ppm)

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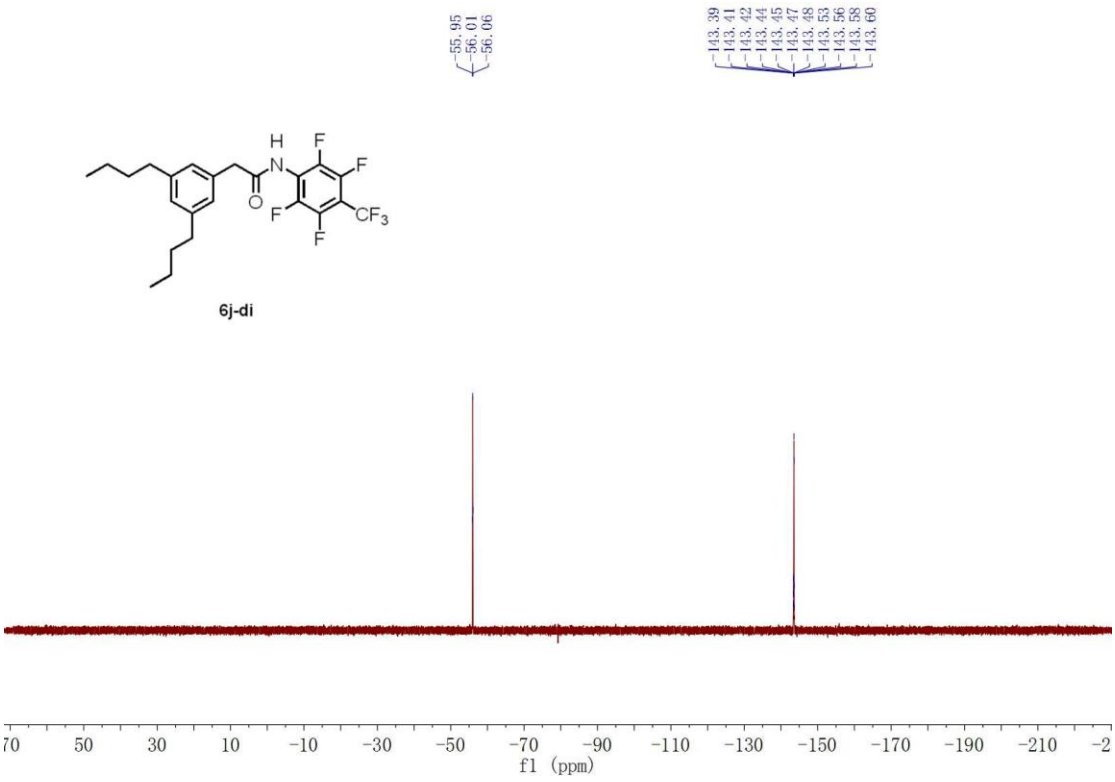
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-143.56
-143.58
-143.60
H
N
O
F
F
F
F
F
CF3
6j-di
70
50
30
10
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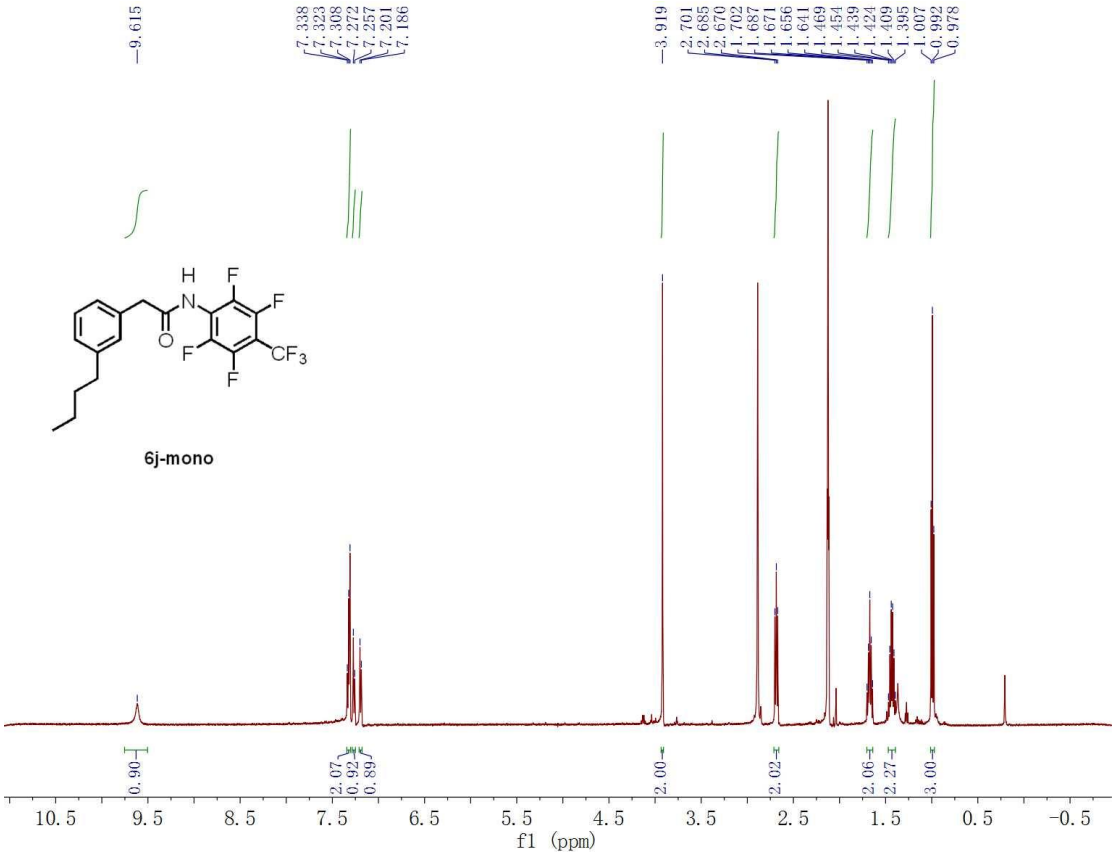
-150
-170
-190
-210
-2
f1 (ppm)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7.308
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7.257
7.201
7.186
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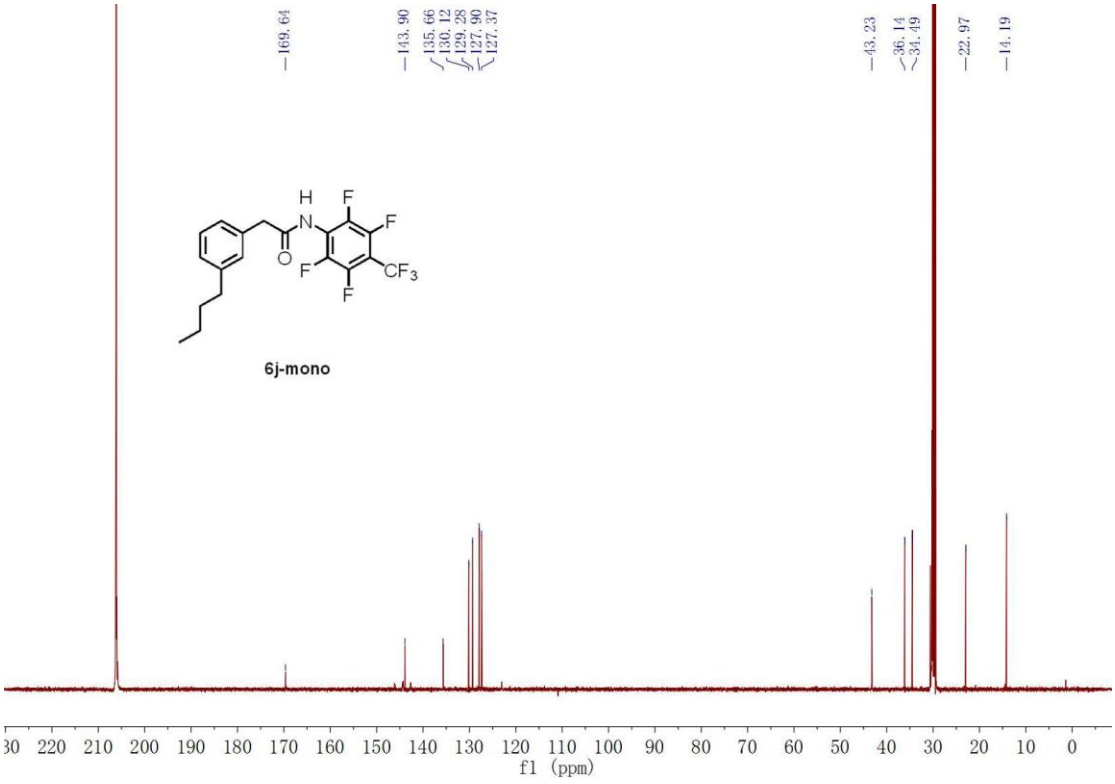
2.685
2.670
1.702
1.687
1.671
1.656
1.641
1.469
1.454
1.439
1.424
1.409
1.395
1.007
0.992
0.978
6j-mono
0.90
2.07
0.92
0.89
2.00
2.02
2.06
2.27
3.00
f1 (ppm)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143.90
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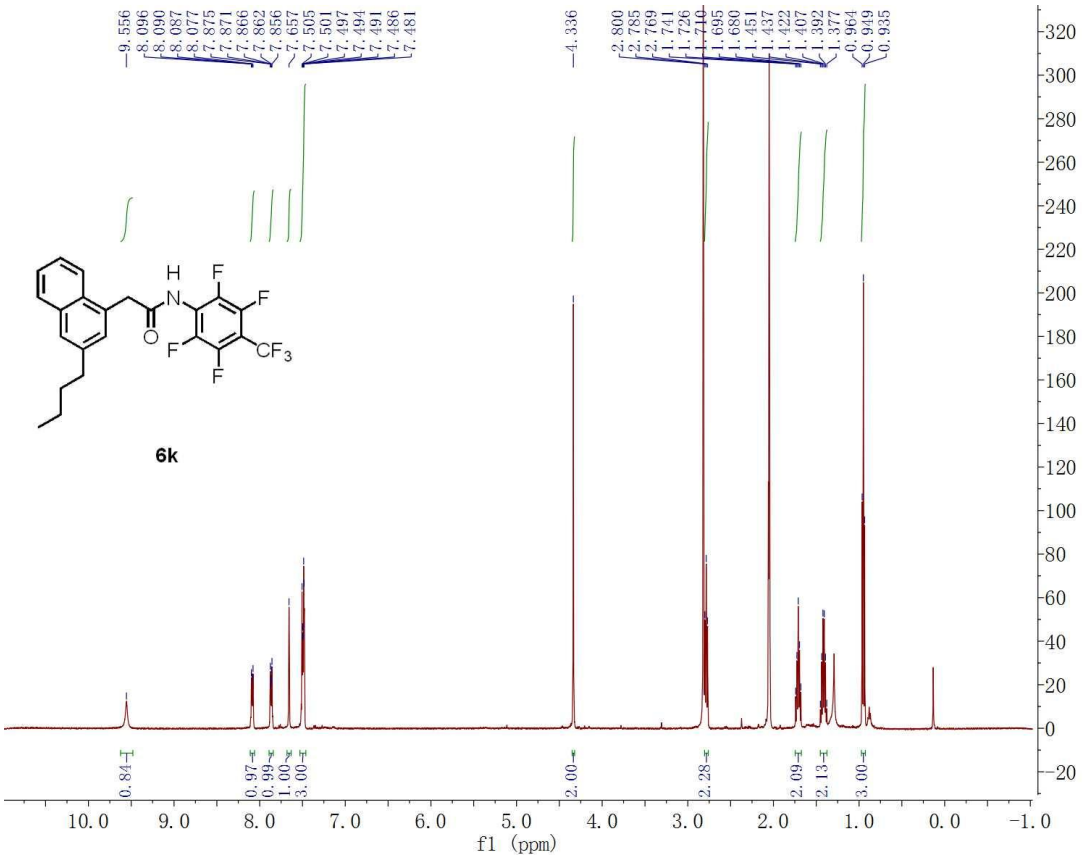
127.90
127.37
43.23
36.14
34.49
22.97
14.19
6j-mono
f1 (ppm)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8.087
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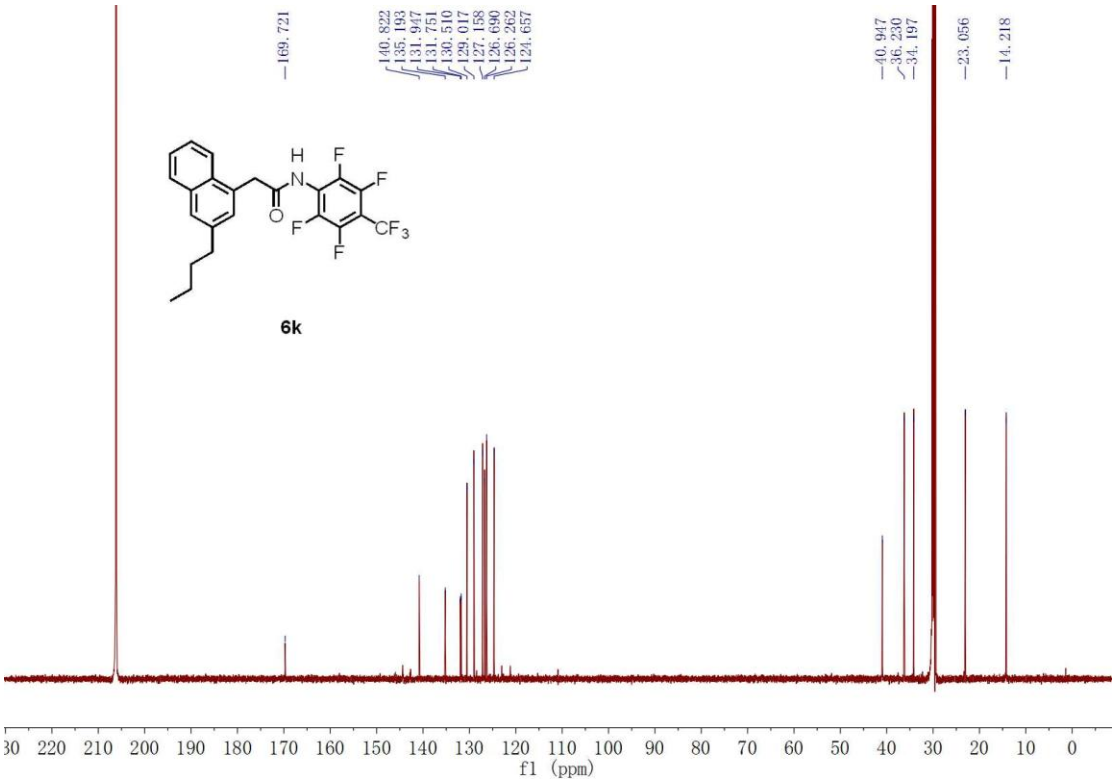
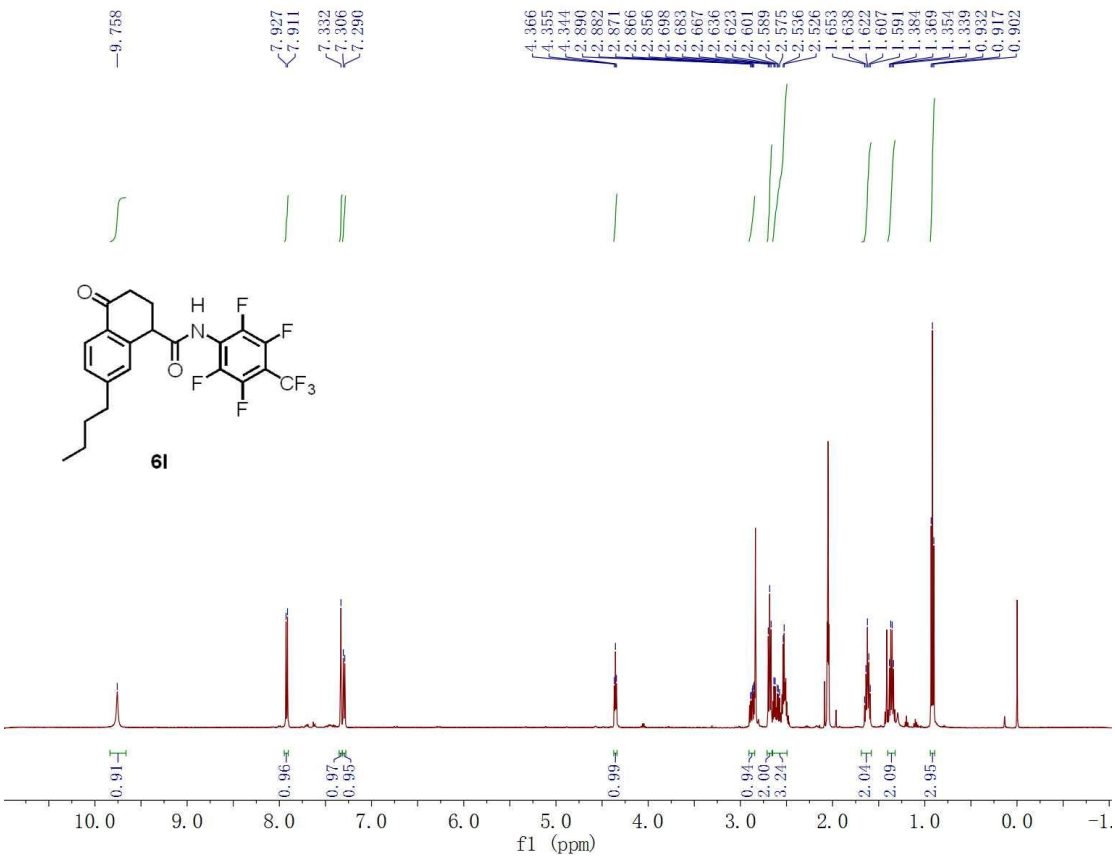
7.871
7.866
7.862
7.856
7.657
7.505
7.501
7.497
7.494
7.491
7.486
7.481
4.336
2.800
2.785
2.769
1.741
1.726
1.710
1.695
1.680
1.451
1.437
1.422
1.407
1.392
1.377
0.964
0.949
0.935
0.84
0.97
0.99
1.00
3.00
2.00
2.28
2.09
2.13
3.00
f1 (ppm)
6k


169.721
140.822
135.193
131.947
131.751
130.510
129.017
127.158
126.690
126.262
124.657
40.947
36.230
34.197
23.056
14.218
f1 (ppm)
6k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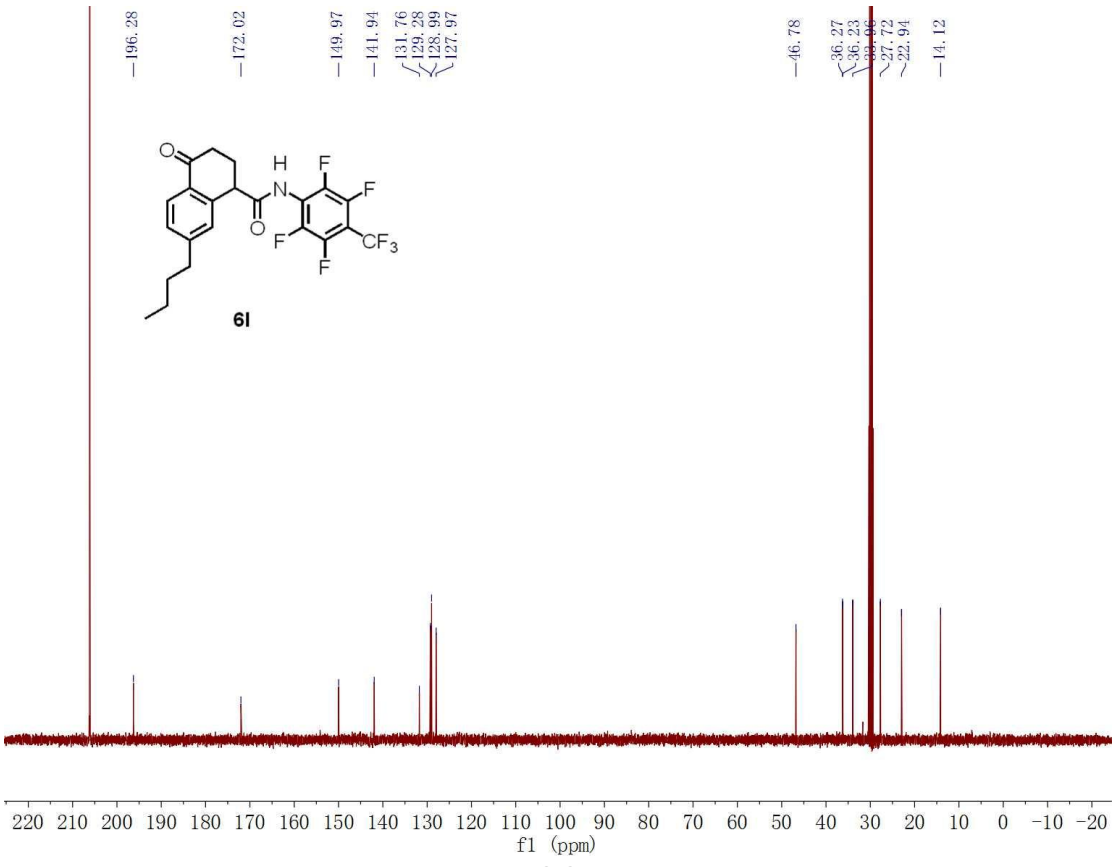
7.927
7.911
7.332
7.306
7.290
4.366
4.355
4.344
2.890
2.882
2.871
2.866
2.856
2.698
2.683
2.667
2.636
2.623
2.601
2.589
2.575
2.536
2.526
1.653
1.638
1.622
1.607
1.591
1.384
1.369
1.354
1.339
0.932
0.917
0.902
6l
0.91
0.96
0.97
0.95
0.99
0.94
2.00
3.24
2.04
2.09
2.95
f1 (ppm)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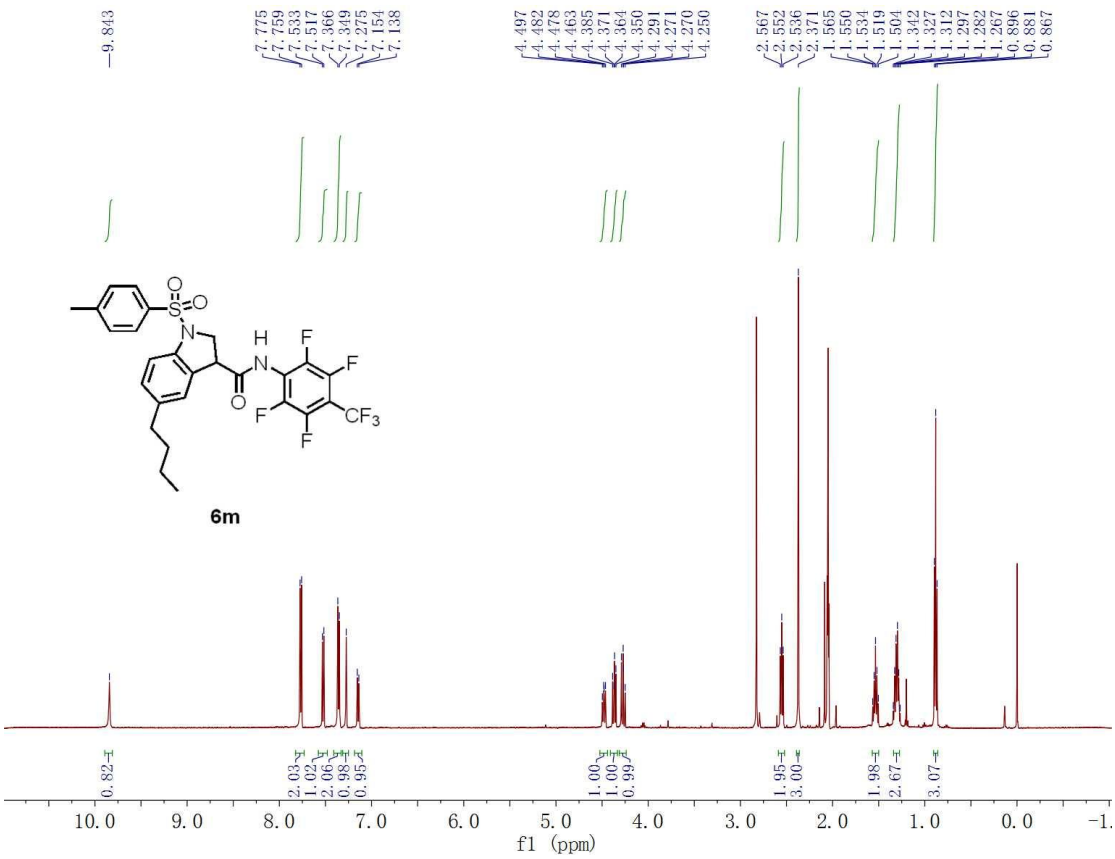
172.02
149.97
141.94
131.76
129.28
128.99
127.97
46.78
36.27
36.23
27.72
22.94
14.12
6l
f1 (ppm)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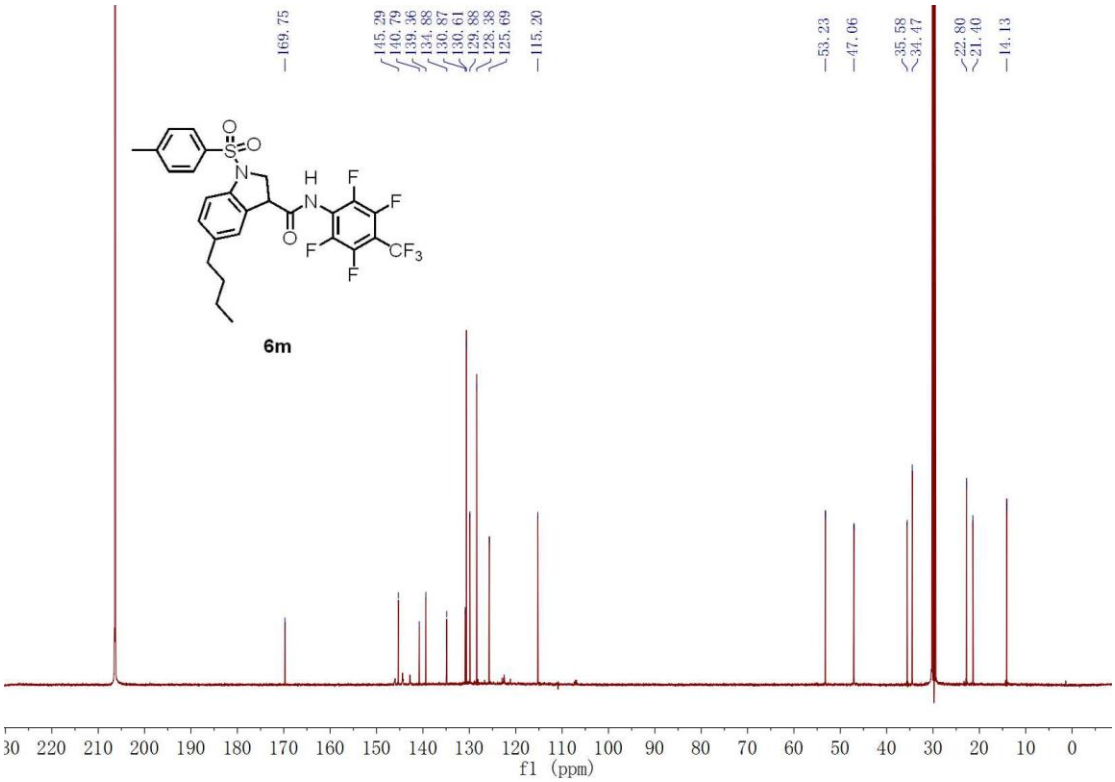
7.517
7.366
7.349
7.275
7.154
7.138
4.497
4.482
4.478
4.463
4.385
4.371
4.364
4.350
4.291
4.271
4.270
4.250
2.567
2.552
2.536
2.371
1.565
1.550
1.534
1.519
1.504
1.342
1.327
1.312
1.297
1.282
1.267
0.896
0.881
0.867
6m
0.82
2.03
1.02
2.06
0.98
0.95
1.00
1.00
0.99
1.95
3.00
1.98
2.67
3.07
f1 (ppm)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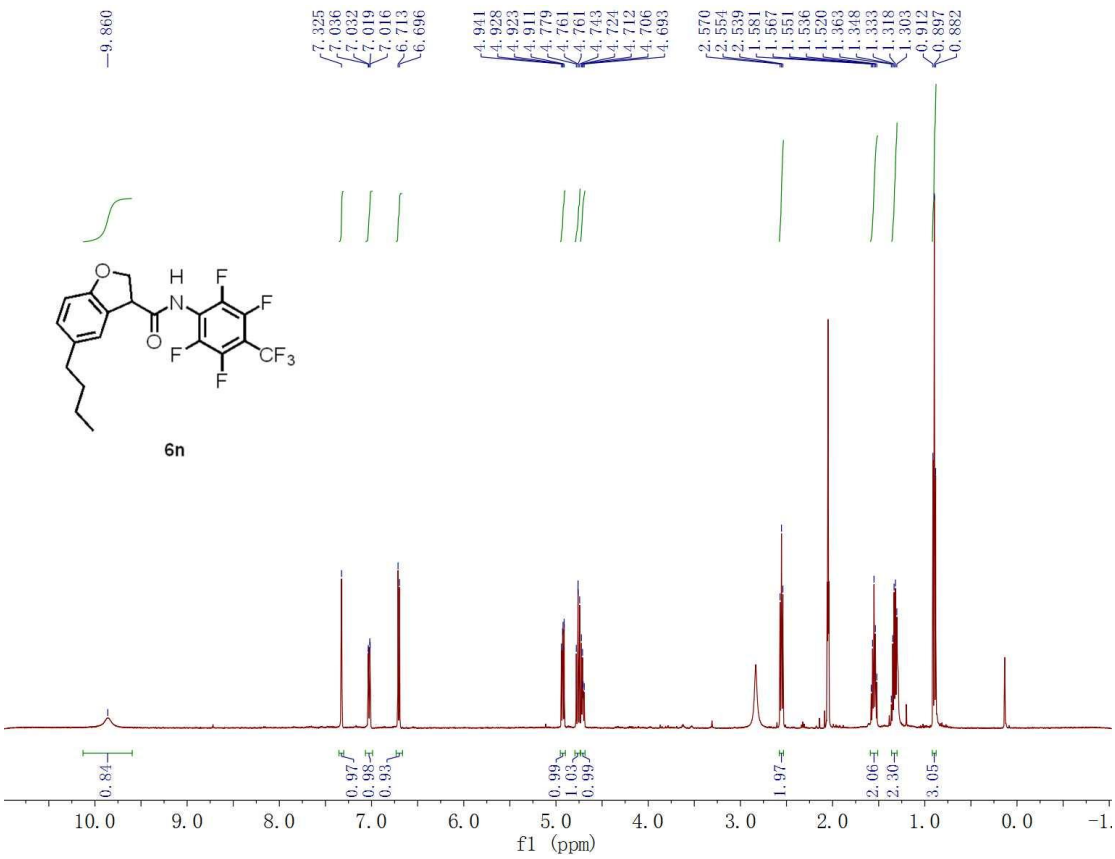
145.29
140.79
139.36
134.88
130.87
130.61
129.88
128.38
125.69
115.20
53.23
47.06
35.58
34.47
22.80
21.40
14.13
6m
f1 (ppm)


9.860
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7.019
7.016
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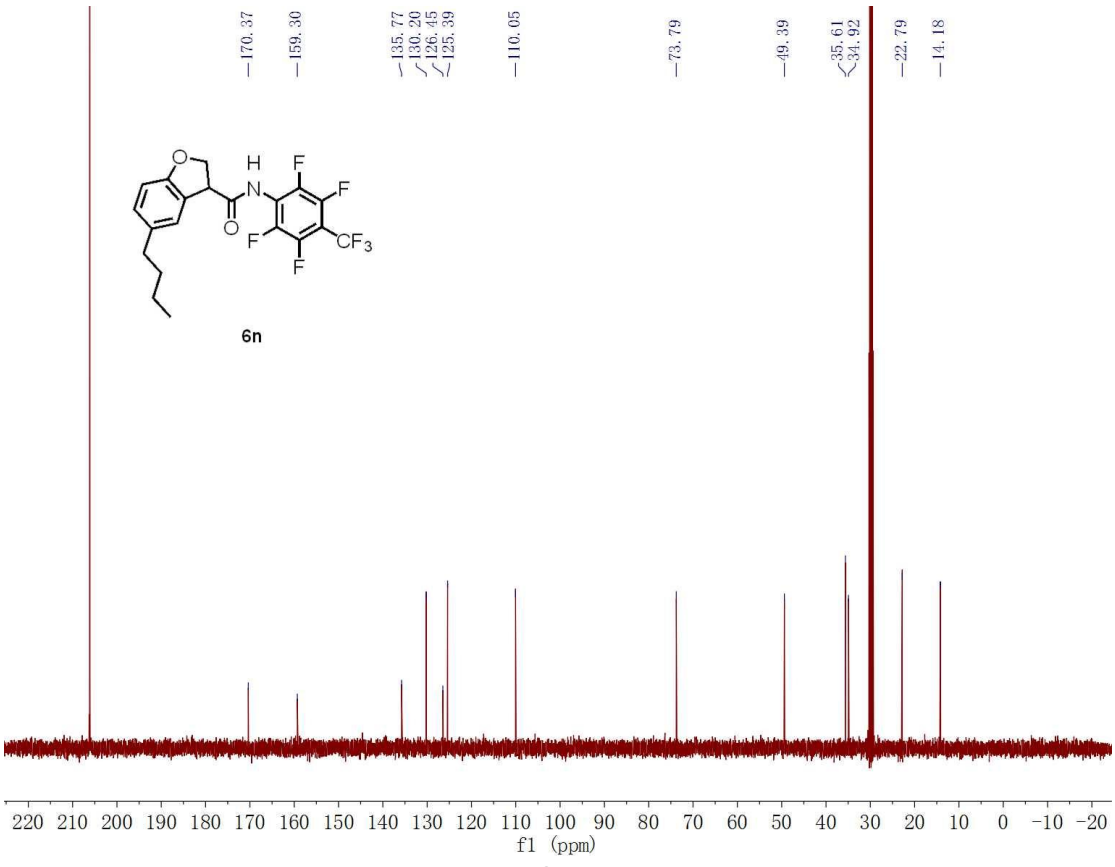
6.696
4.941
4.928
4.923
4.911
4.779
4.761
4.761
4.743
4.724
4.712
4.706
4.693
2.570
2.554
2.539
1.581
1.567
1.551
1.536
1.520
1.363
1.348
1.333
1.318
1.303
0.912
0.897
0.882
6n
0.84
0.97
0.98
0.93
0.99
1.03
0.99
1.97
2.06
2.30
3.05
f1 (ppm)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159.30
135.77
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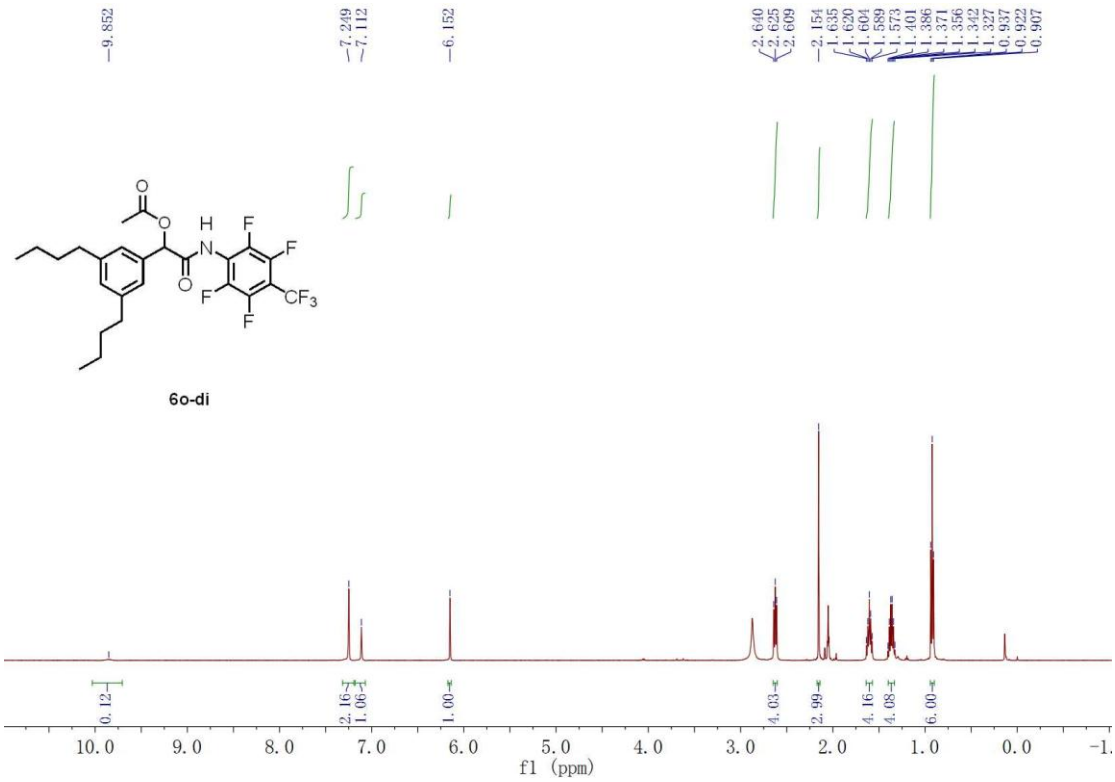
125.39
110.05
73.79
49.39
35.61
34.92
22.79
14.18
6n
f1 (ppm)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2.625
2.609
2.154
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1.620
1.604
1.589
1.573
1.401
1.386
1.371
1.356
1.342
1.327
0.937
0.922
0.907
6o-di
0.12
2.16
1.06
1.00
4.03
2.99
4.16
4.08
6.00
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4.0
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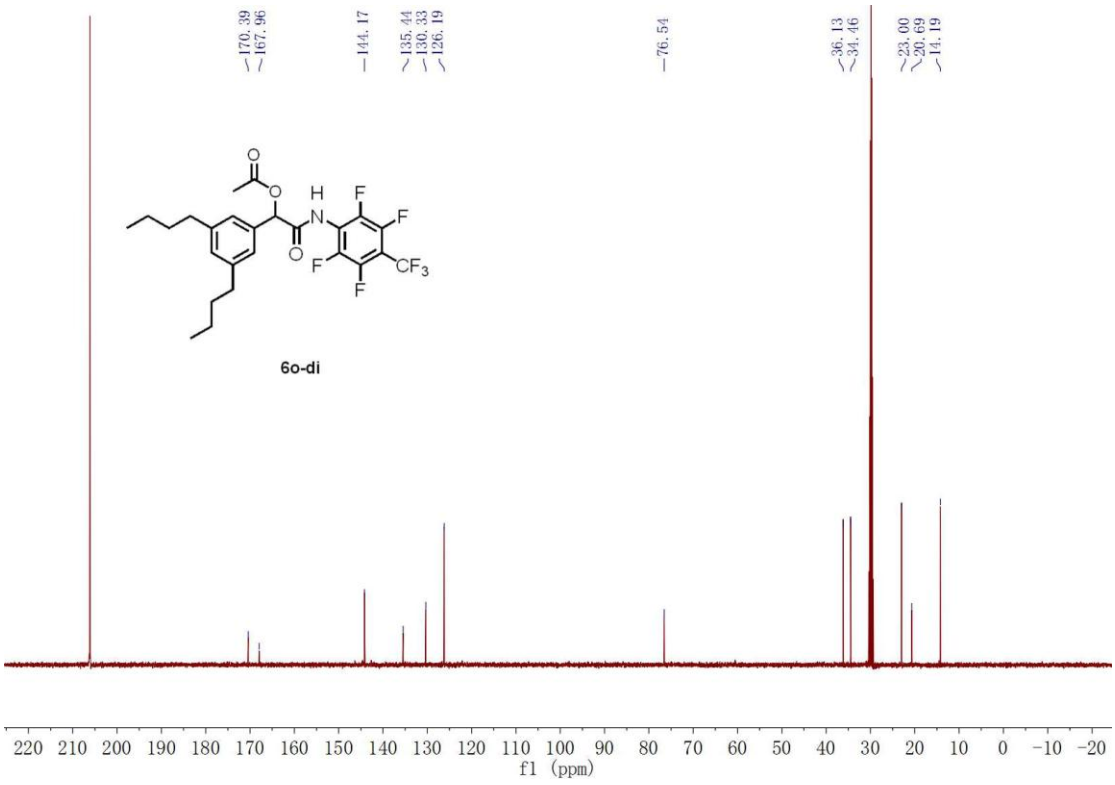
2.0
1.0
0.0
f1 (ppm)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167.96
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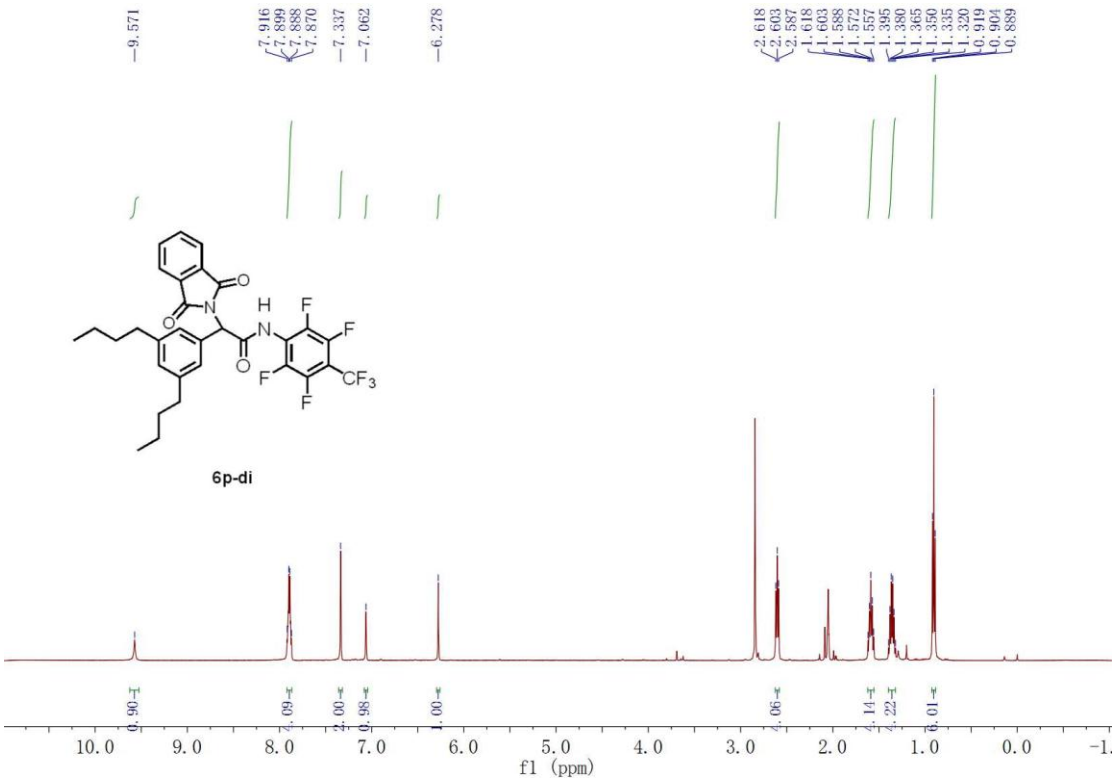
135.44
130.33
126.19
76.54
36.13
34.46
23.00
20.69
14.19
6o-di
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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6.278
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1.618
1.603
1.588
1.572
1.557
1.395
1.380
1.365
1.350
1.335
1.320
0.919
0.904
0.889
6p-di
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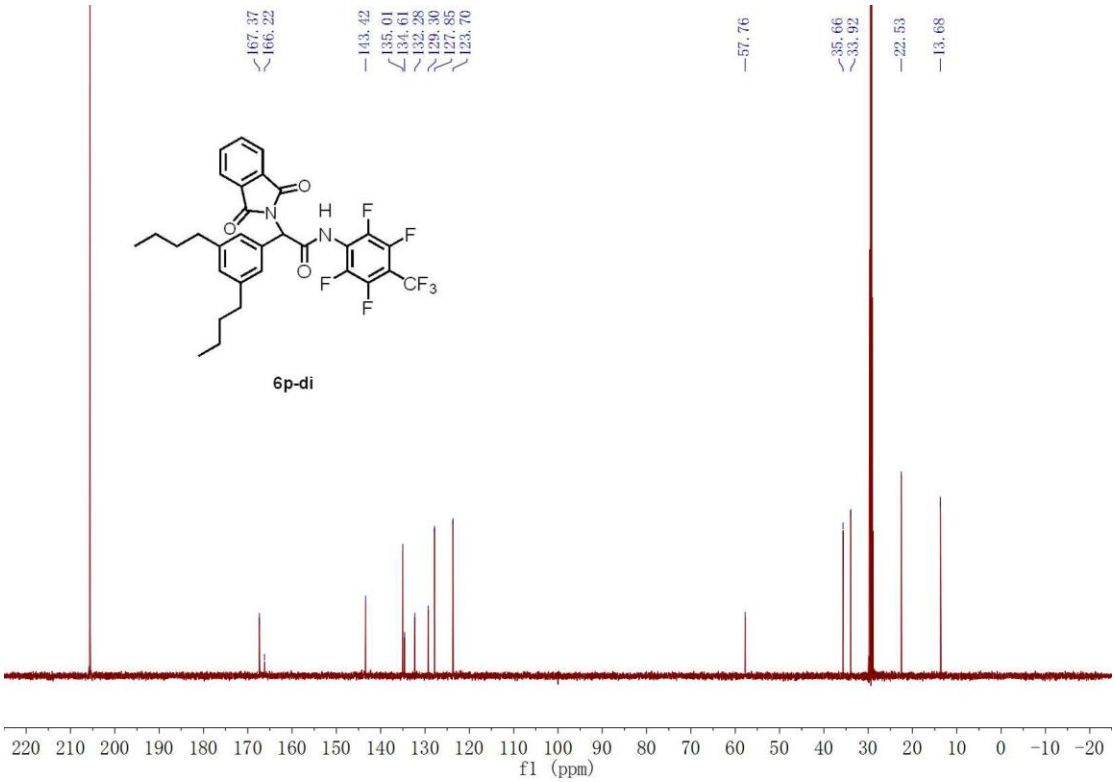
4.09
2.00
0.98
1.00
4.06
4.14
4.22
6.01
f1 (ppm)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127.85
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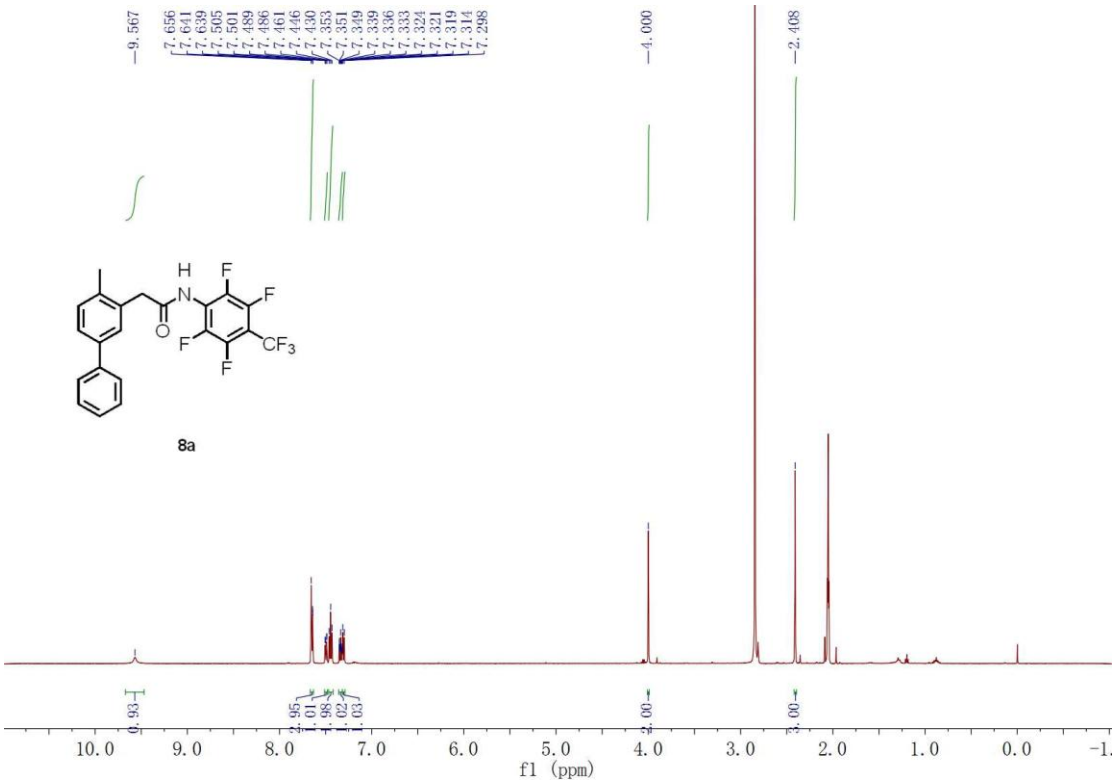
22.53
13.68
6p-di
f1 (ppm)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7.349
7.339
7.336
7.333
7.324
7.321
7.319
7.314
7.298
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0.93
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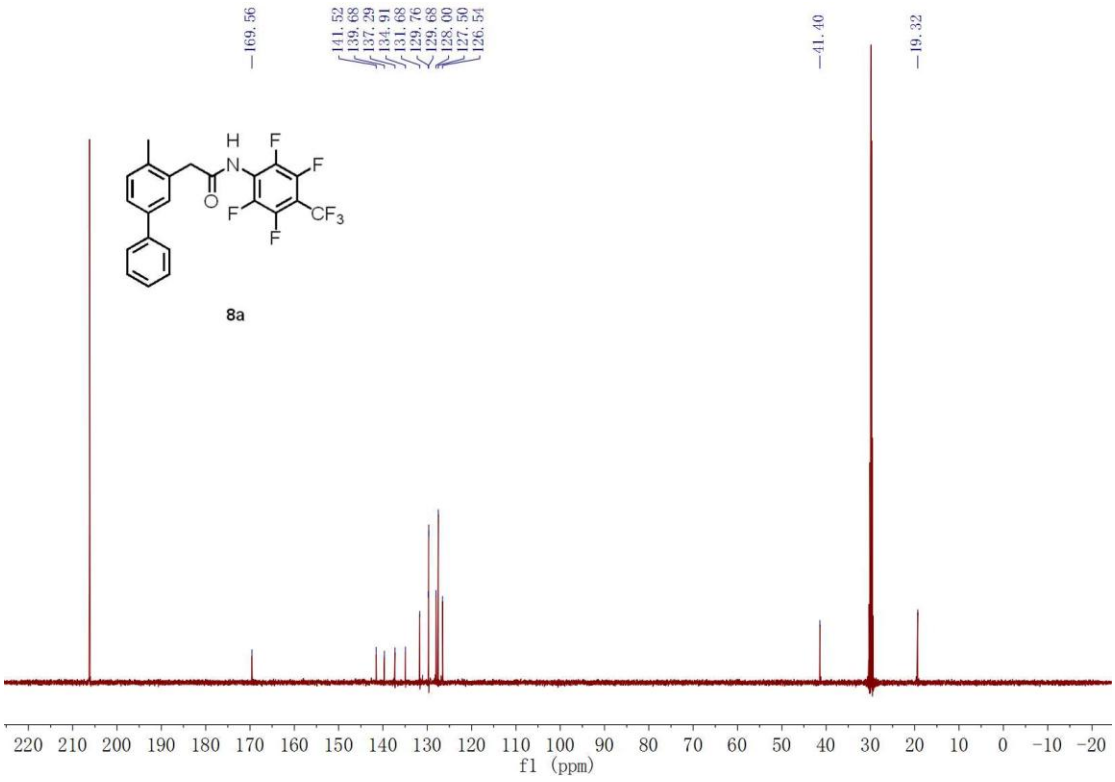
1.98
1.02
1.03
2.00
3.00
f1 (ppm)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126.54
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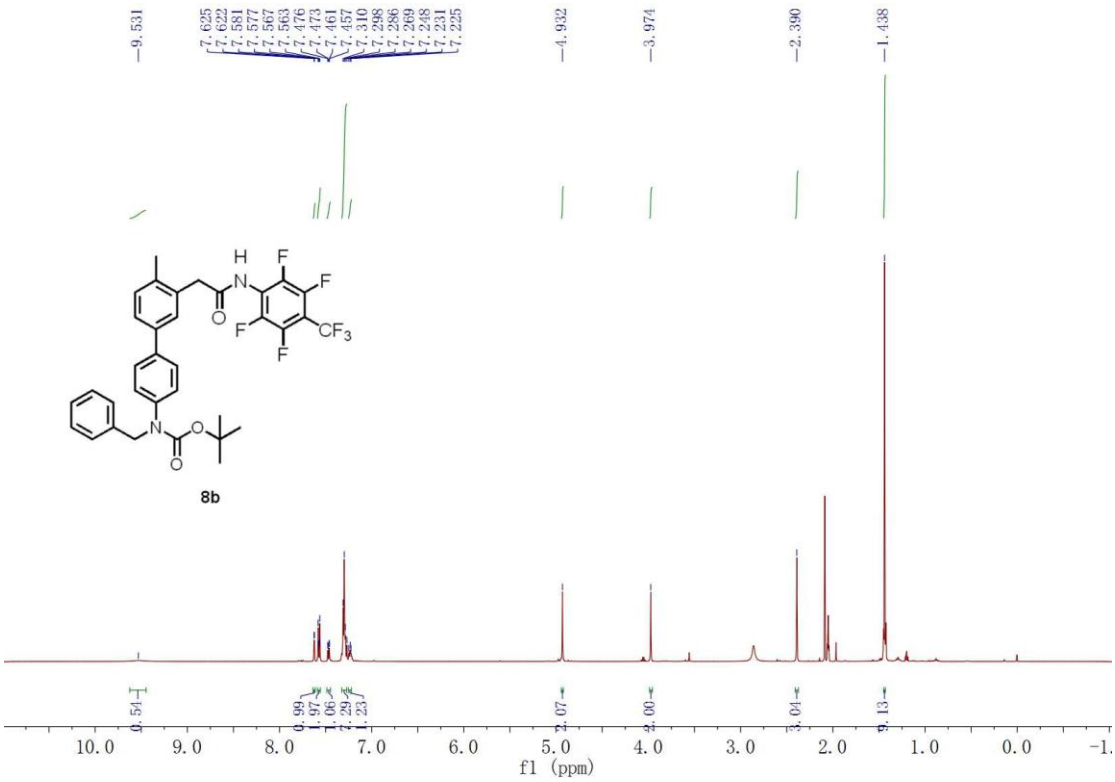
f1 (ppm)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7.298
7.286
7.269
7.248
7.231
7.225
4.932
3.974
2.390
1.438
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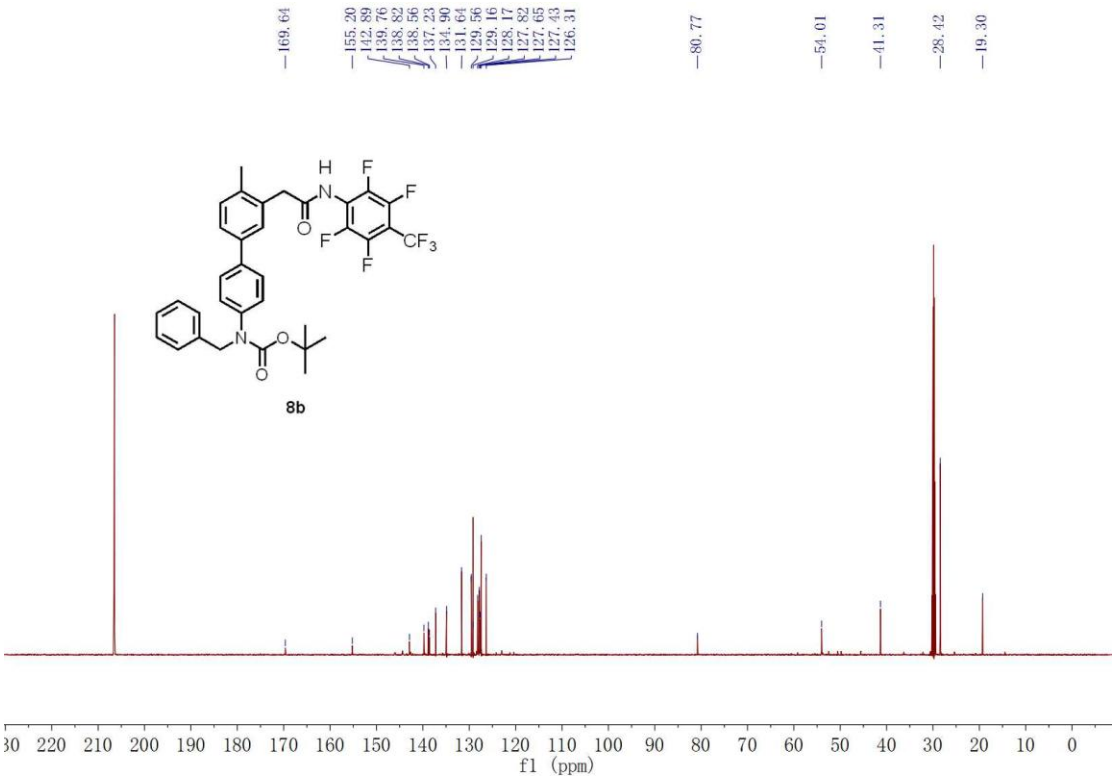
1.23
2.07
2.00
3.04
9.13
f1 (ppm)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137.23
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129.16
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80.77
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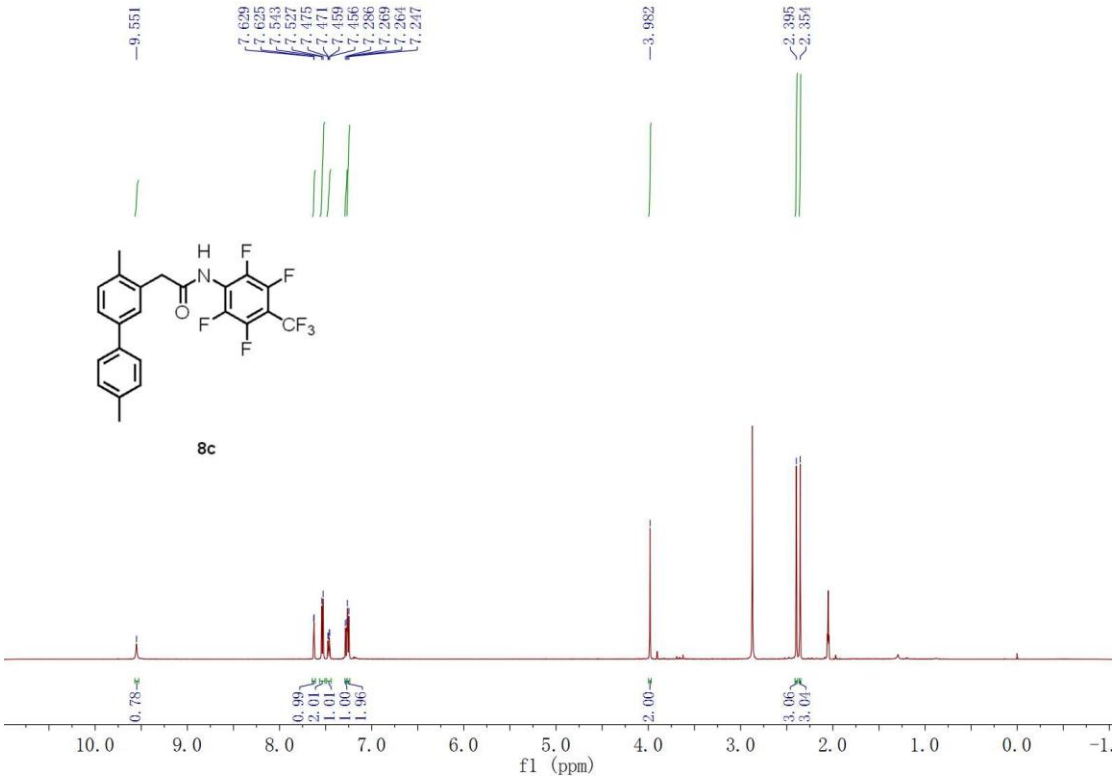
41.31
28.42
19.30
8b
f1 (ppm)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7.459
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7.286
7.269
7.264
7.247
3.982
2.395
2.354
8c
0.78
0.99
2.01
1.01
1.00
1.96
2.00
3.06
3.04
10.0
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8.0
7.0
6.0
5.0
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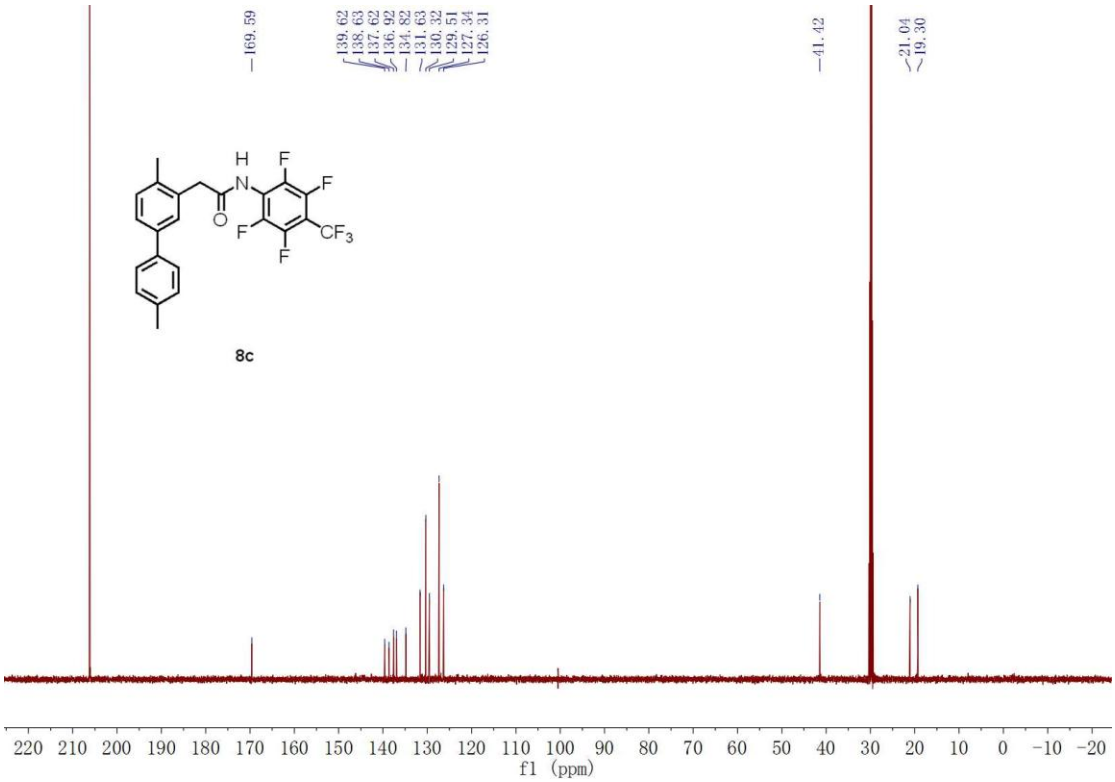
3.0
2.0
1.0
0.0
f1 (ppm)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137.62
136.92
134.82
131.63
130.32
129.51
127.34
126.31
41.42
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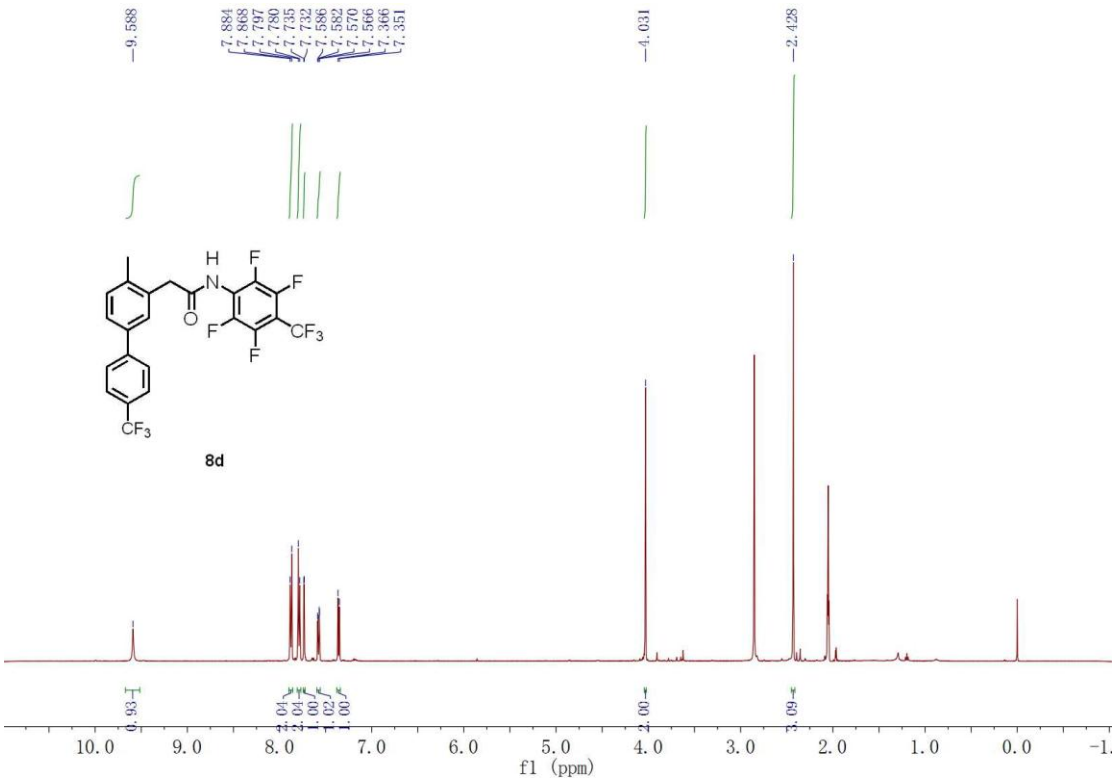
19.30
8c
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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7.735
7.732
7.586
7.582
7.570
7.566
7.366
7.351
4.031
2.428
8d
9.93
4.04
4.04
2.00
1.02
1.00
2.00
3.09
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9.0
8.0
7.0
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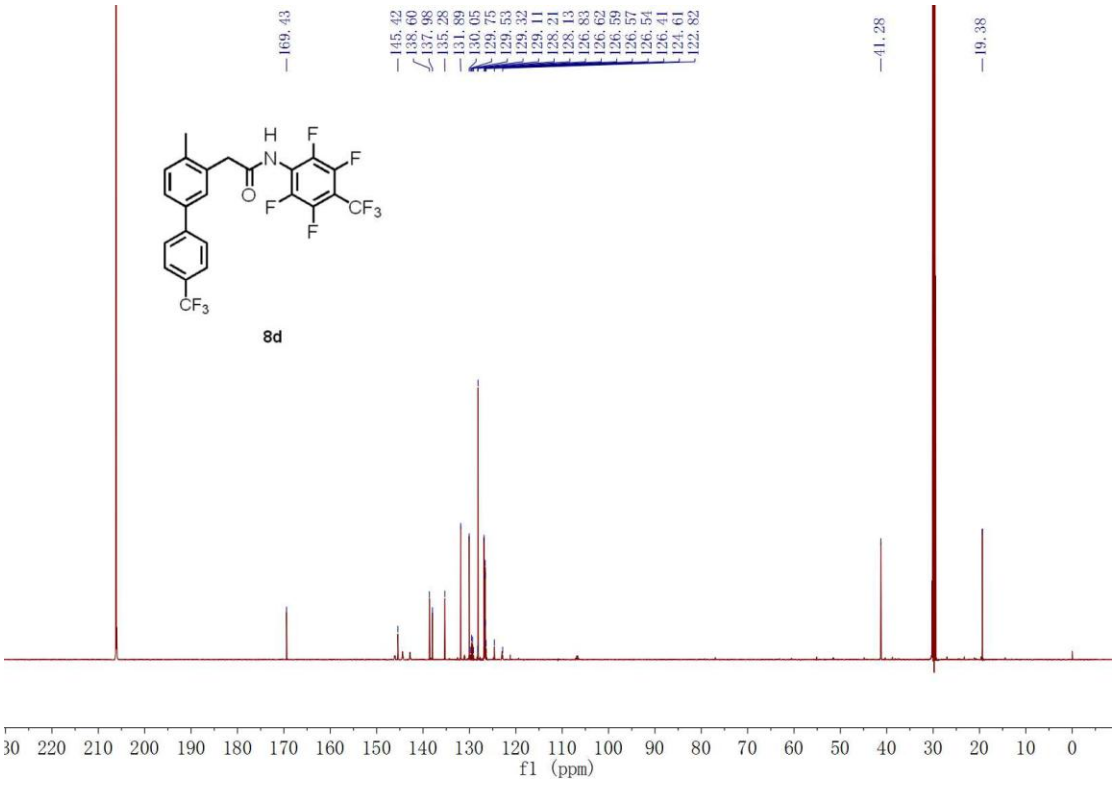
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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130.05
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129.32
129.11
128.21
128.13
126.83
126.62
126.59
126.57
126.54
126.41
124.61
122.82
41.28
19.38
8d
220
210
200
190
180
170
160
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120
110
100
90
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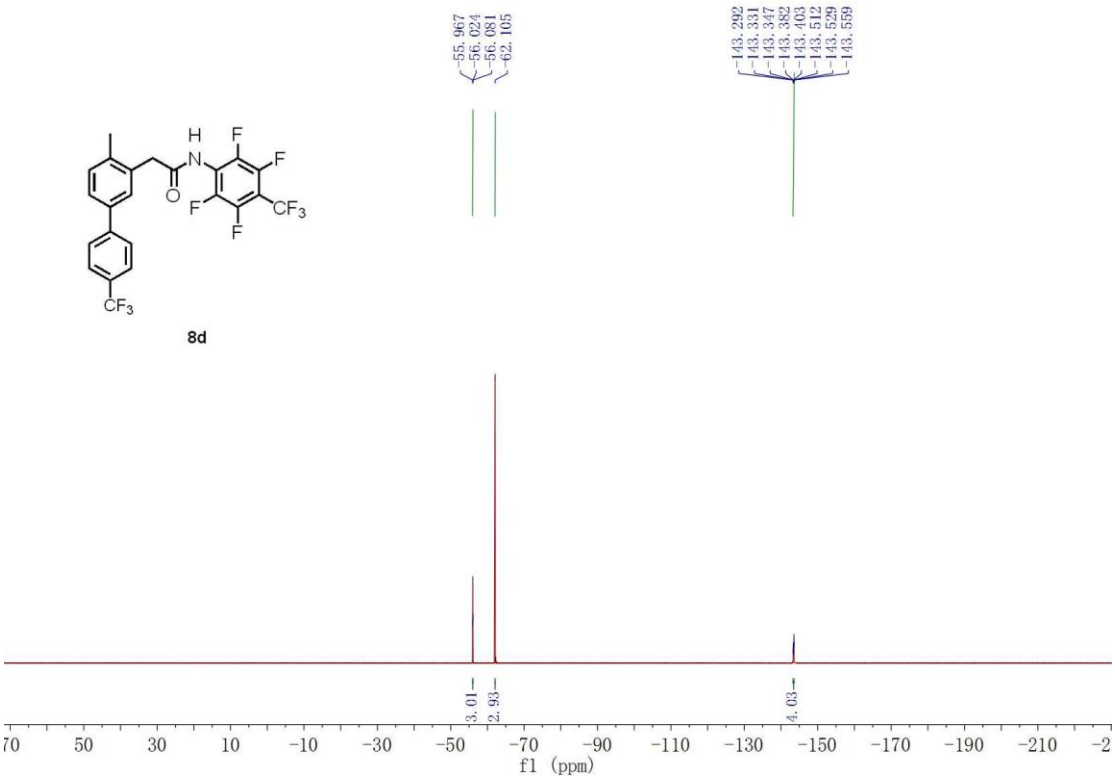
50
40
30
20
10
0
f1 (ppm)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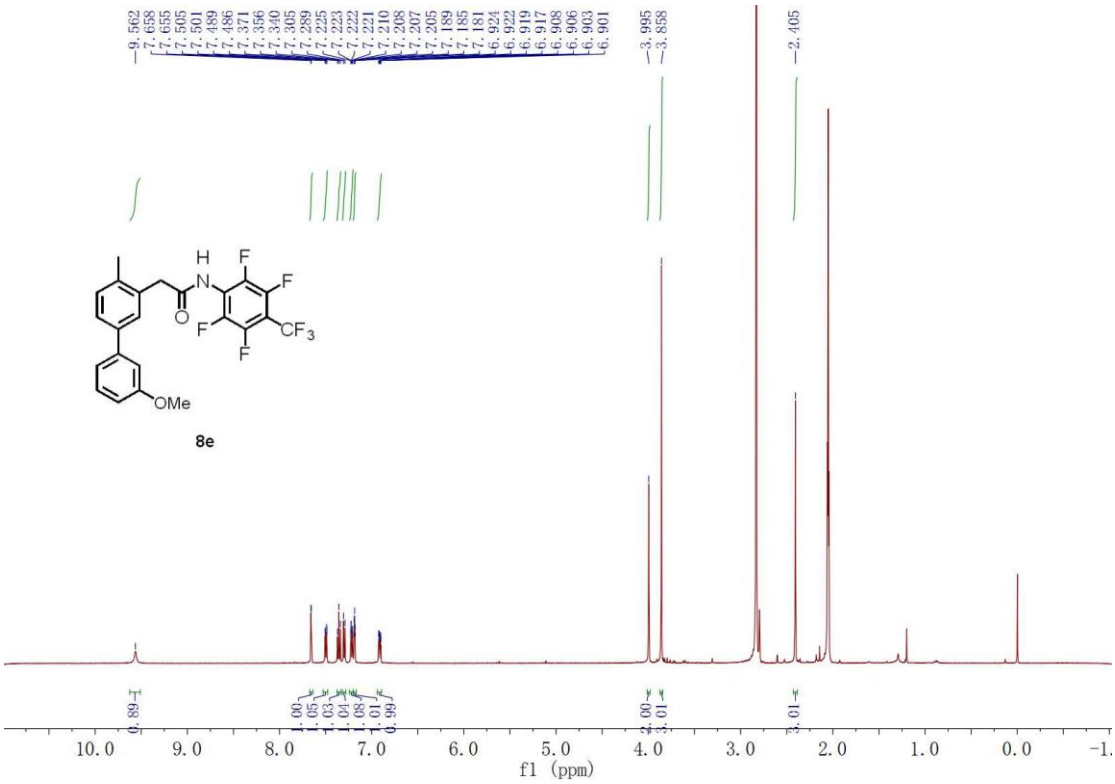
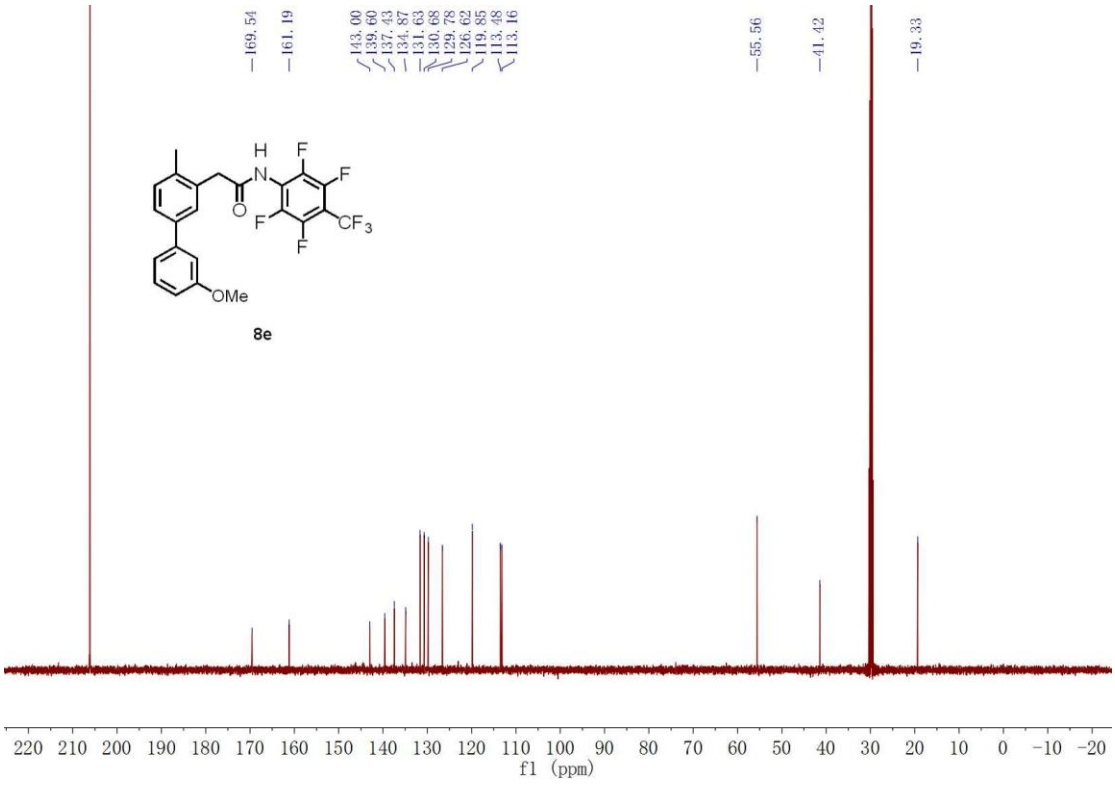
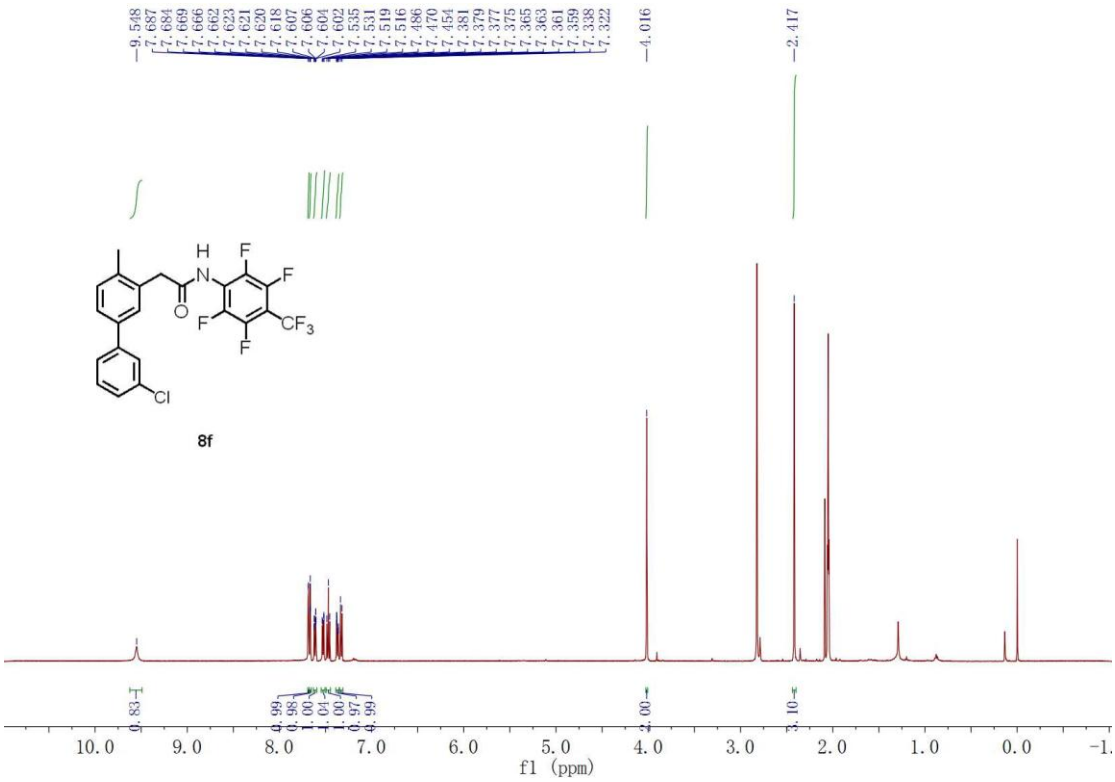
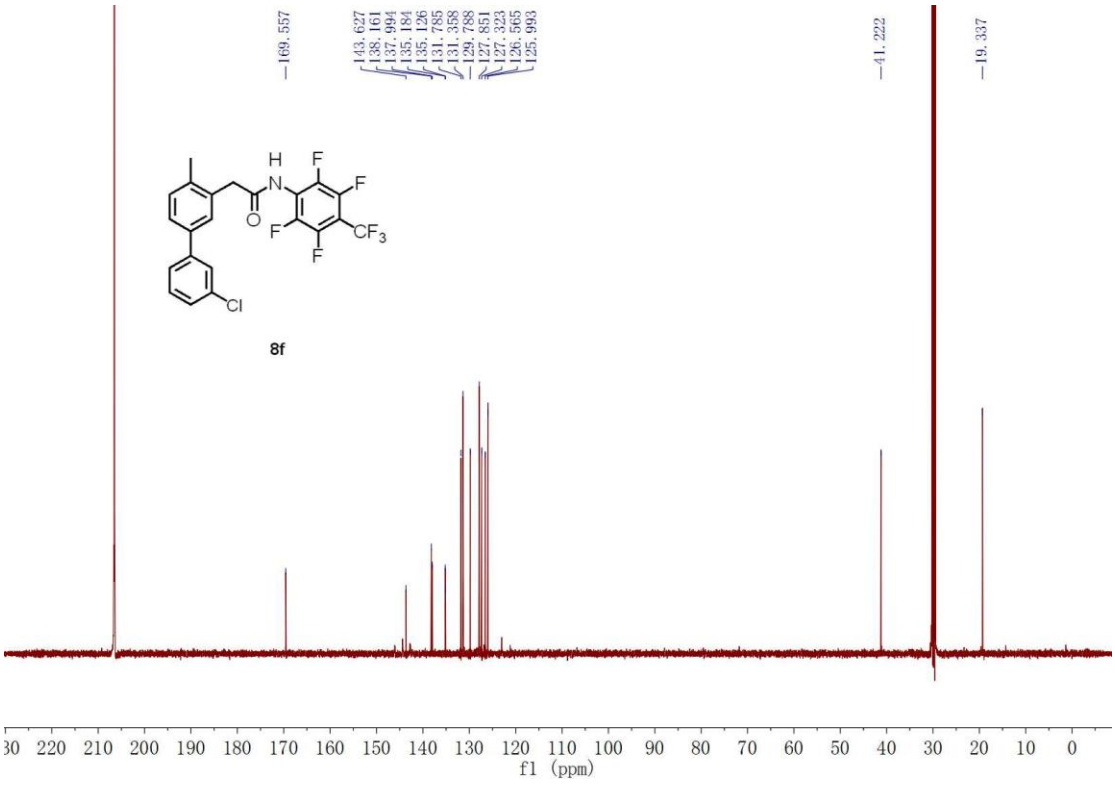
-56.081
-62.105
-143.292
-143.331
-143.347
-143.382
-143.403
-143.512
-143.529
-143.559
H
N
O
F
F
F
F
CF3
CF3
8d
3.01
2.93
4.03
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-2
f1 (ppm)


9.562
7.658
7.655
7.505
7.501
7.489
7.486
7.371
7.356
7.340
7.305
7.289
7.225
7.223
7.222
7.221
7.210
7.208
7.207
7.205
7.189
7.185
7.181
6.924
6.922
6.919
6.917
6.908
6.906
6.903
6.901
3.995
3.858
2.405
0.89
1.00
1.05
1.03
1.04
1.08
1.01
0.99
2.00
3.01
3.01
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)
H
N
O
F
F
F
F
F
CF3
OMe
8e

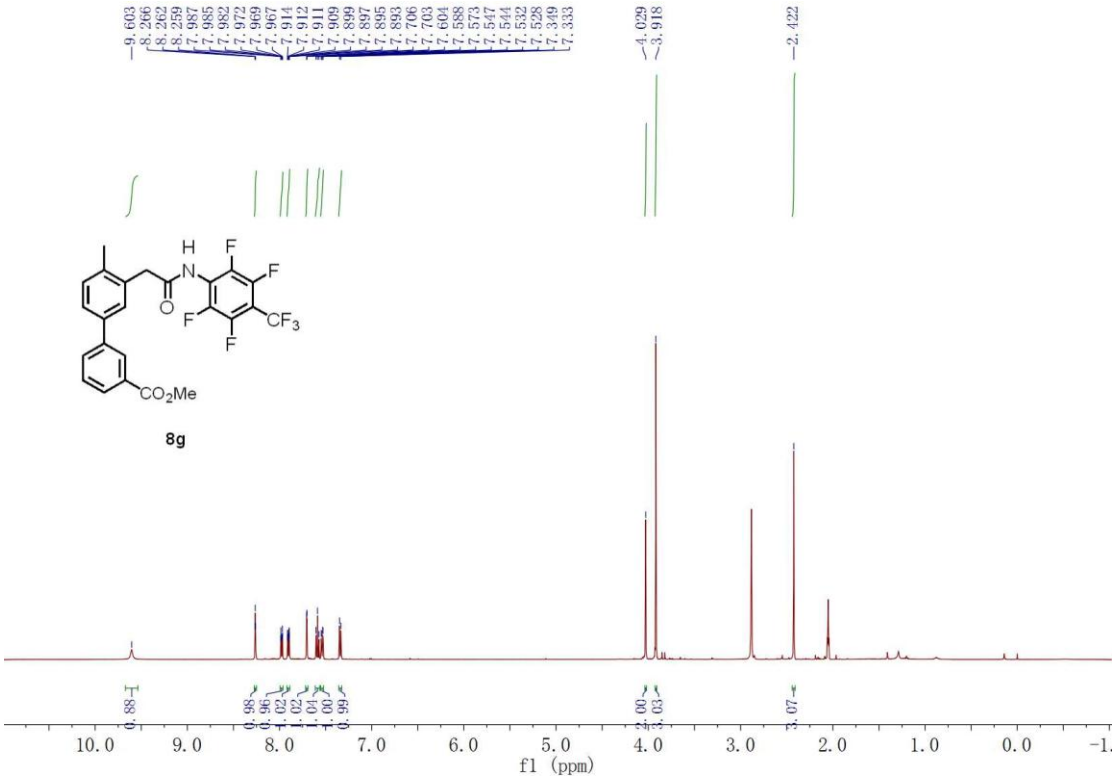

169.54
161.19
143.00
139.60
137.43
134.87
131.63
130.68
129.78
126.62
119.85
113.48
113.16
55.56
41.42
19.33
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)
H
N
O
F
F
F
F
F
CF3
OMe
8e

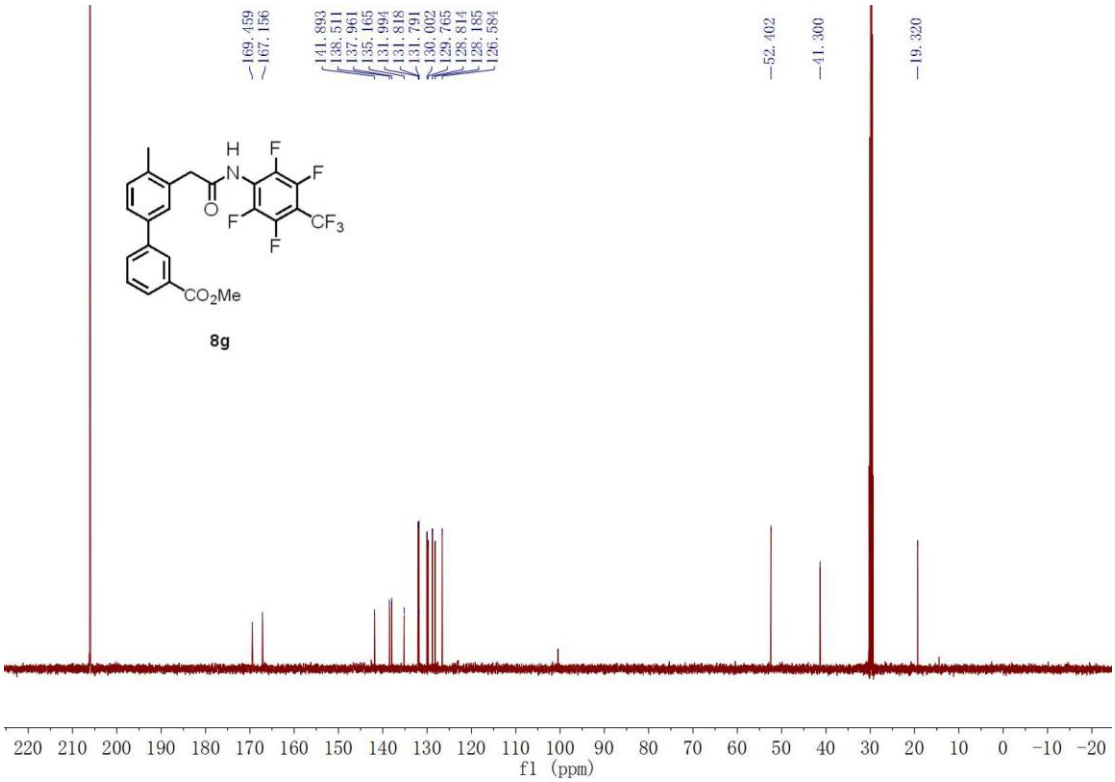

9.548
7.687
7.684
7.669
7.666
7.662
7.623
7.621
7.620
7.618
7.607
7.606
7.604
7.602
7.535
7.531
7.519
7.516
7.486
7.470
7.454
7.381
7.379
7.377
7.375
7.365
7.363
7.361
7.359
7.338
7.322
4.016
2.417
0.83
0.99
0.98
1.00
1.04
1.00
0.97
0.99
2.00
3.10
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

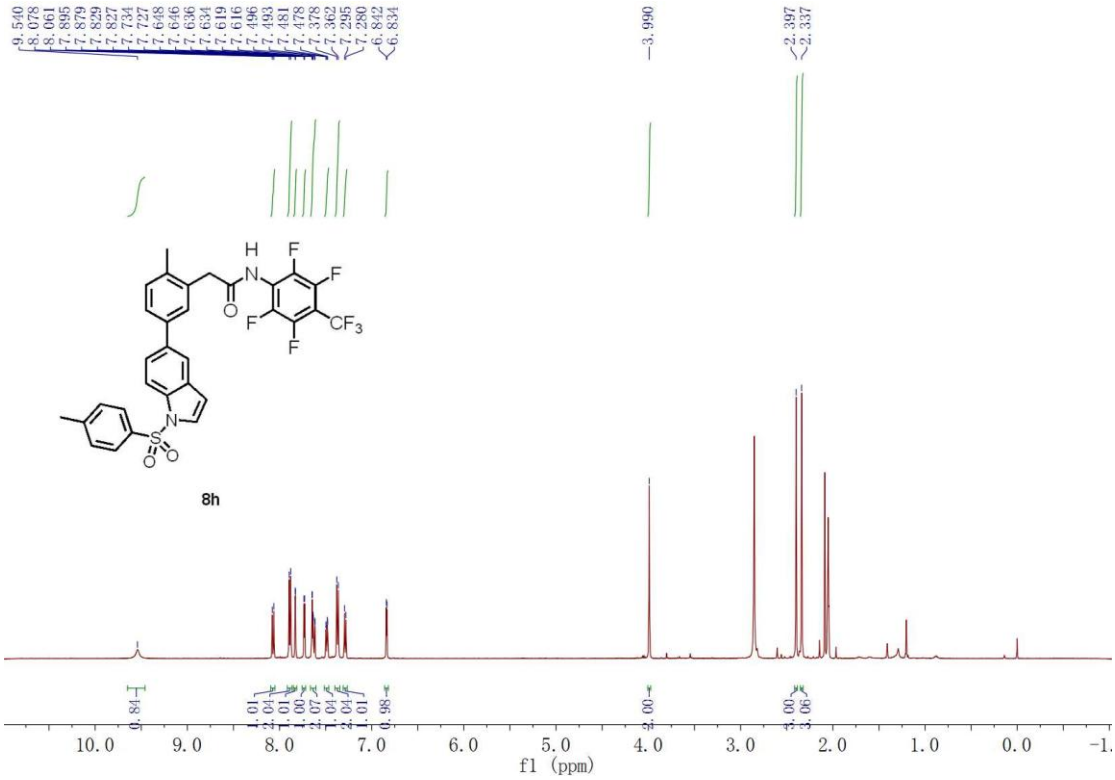
8f

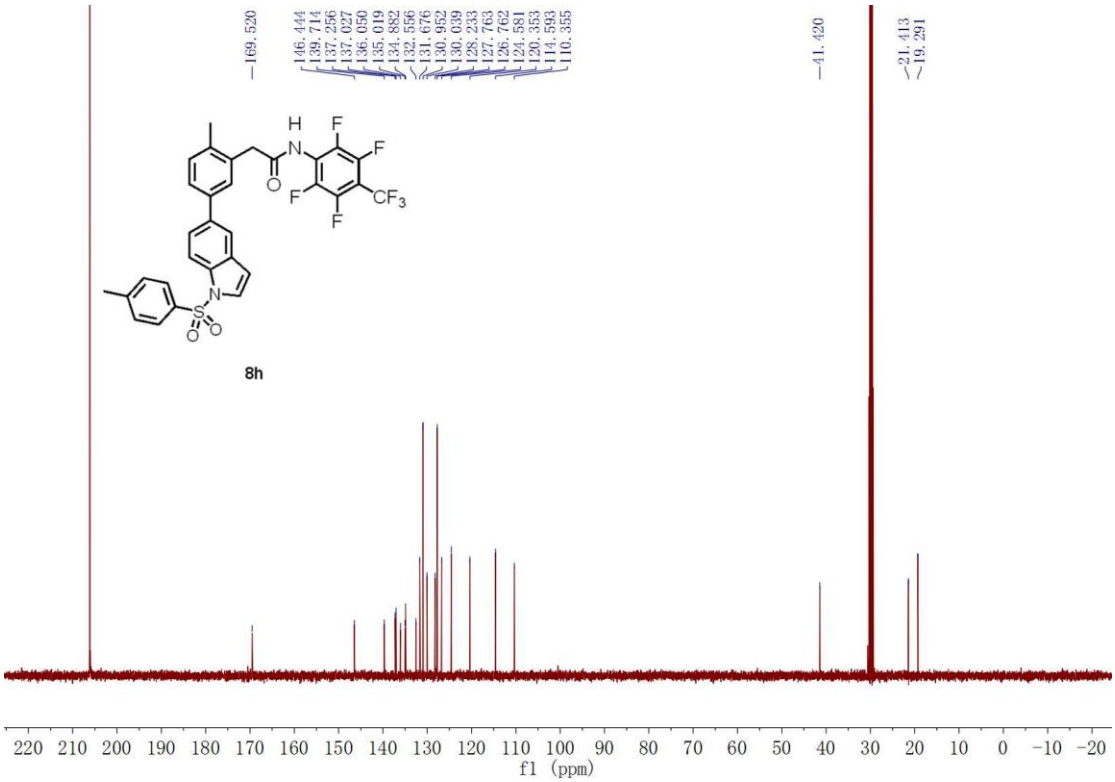

169.557
143.627
138.161
137.994
135.184
135.126
131.765
131.358
129.788
127.851
127.323
126.565
125.993
41.222
19.337
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

8f

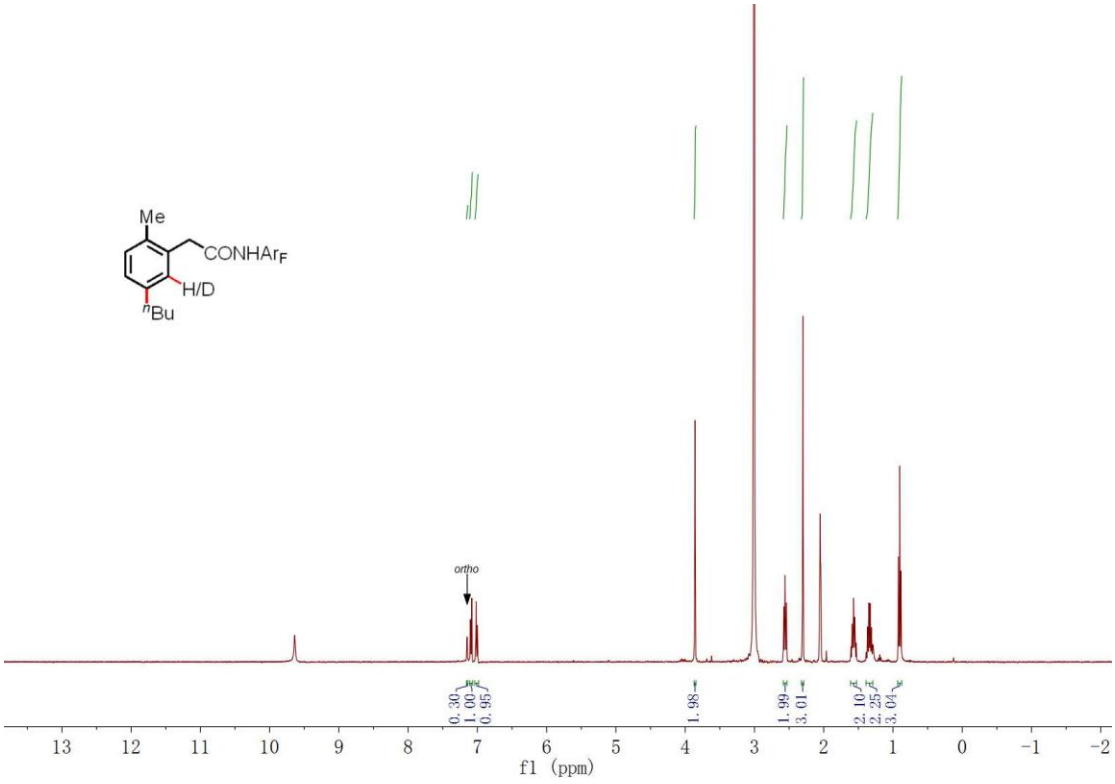

9.603
8.266
8.262
8.259
7.987
7.985
7.982
7.972
7.969
7.967
7.914
7.912
7.911
7.909
7.899
7.897
7.895
7.893
7.706
7.703
7.604
7.588
7.573
7.547
7.544
7.532
7.528
7.349
7.333
4.029
3.918
2.422
H
N
O
F
F
F
F
F
CF3
CO2Me
8g
0.88
0.98
0.96
1.02
1.02
1.01
1.00
0.99
2.00
3.03
3.07
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

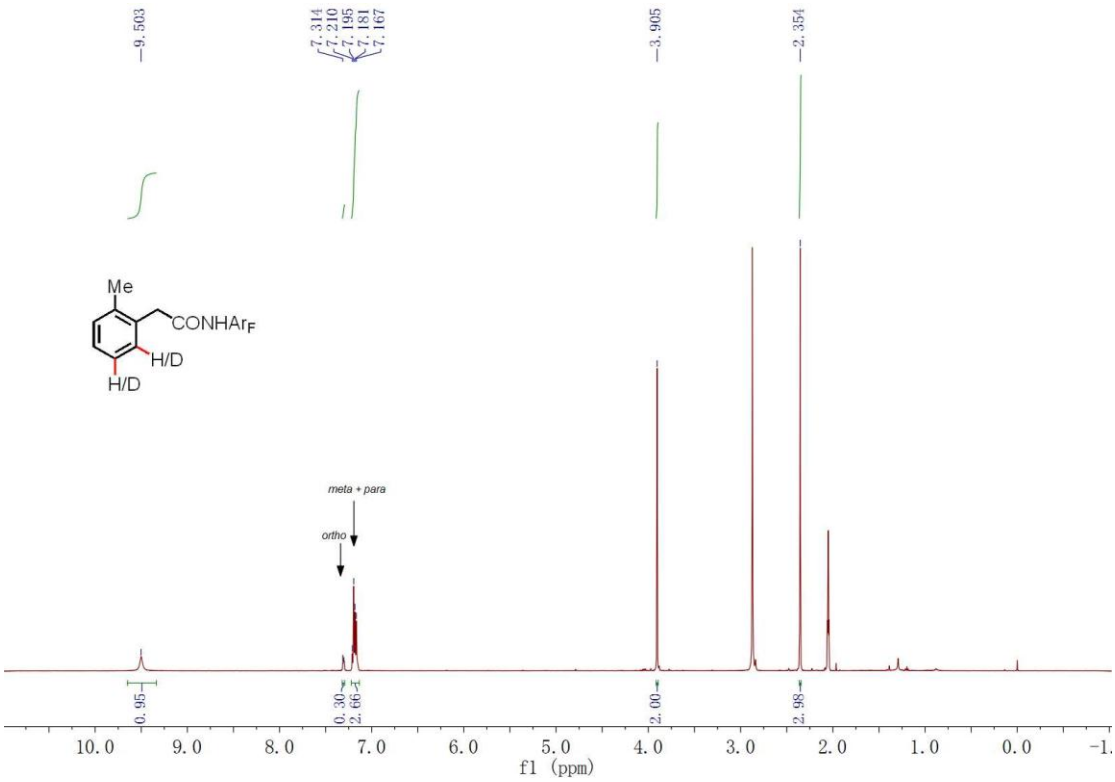

169.459
167.156
141.893
138.511
137.961
135.165
131.994
131.818
131.791
130.002
129.765
128.814
128.185
126.584
52.402
41.300
19.320
H
N
O
F
F
F
F
F
CF3
CO2Me
8g
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

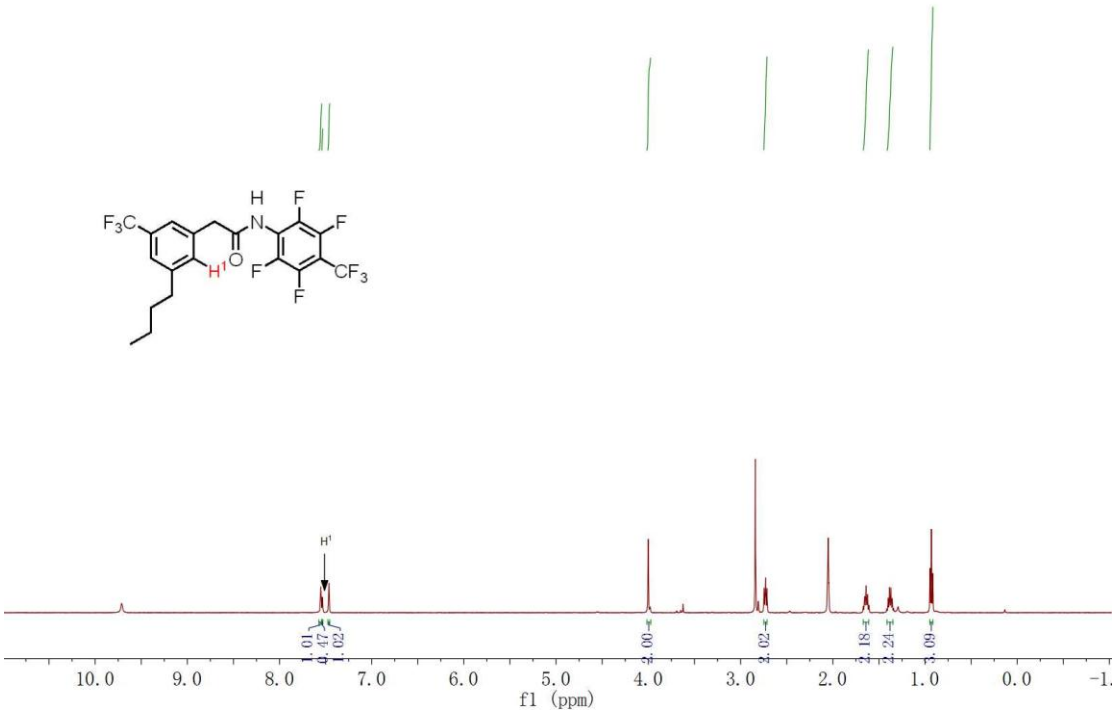

9.540
8.078
8.061
7.895
7.879
7.829
7.827
7.734
7.727
7.648
7.646
7.636
7.634
7.619
7.616
7.496
7.493
7.481
7.478
7.378
7.362
7.295
7.280
6.842
6.834
3.990
2.397
2.337
8h
0.84
1.01
2.04
1.01
1.00
2.07
1.04
2.04
1.01
0.98
2.00
3.00
3.06
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

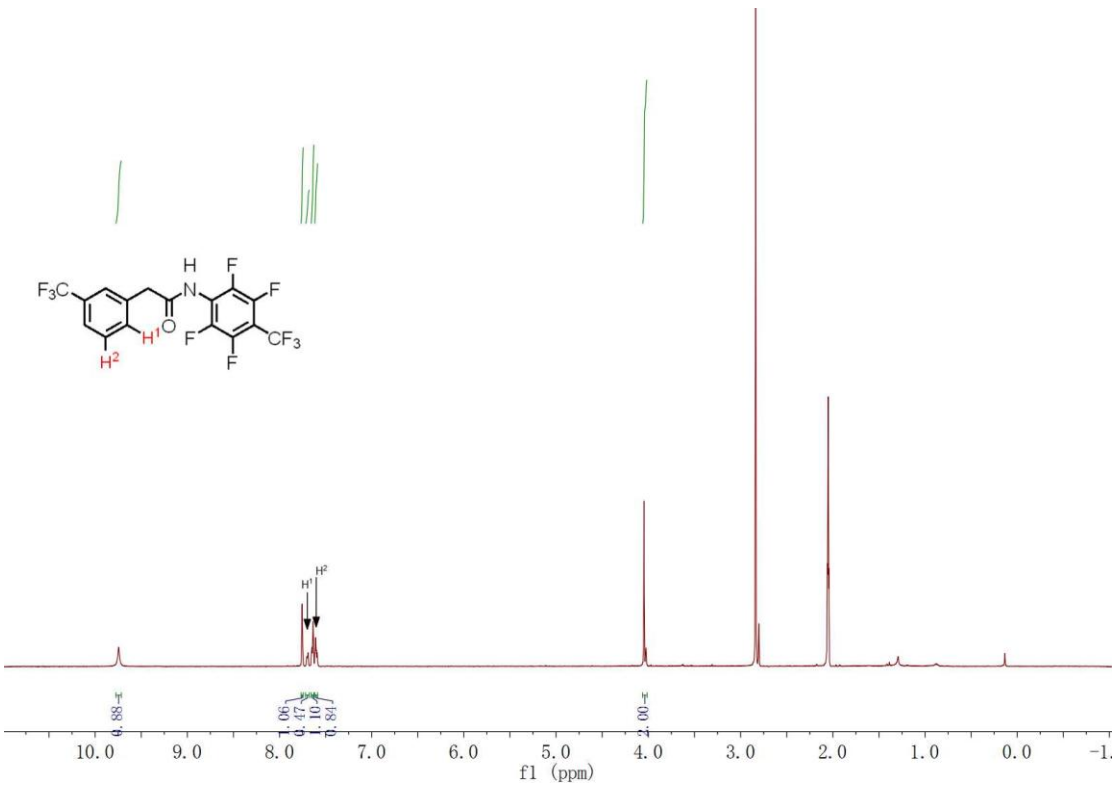

169.520
146.444
139.714
137.256
137.027
136.050
135.019
134.882
132.556
131.676
130.952
130.039
128.233
127.763
126.762
124.581
120.353
114.593
110.355
41.420
21.413
19.291
8h
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

Deuteration experiment with **N15**

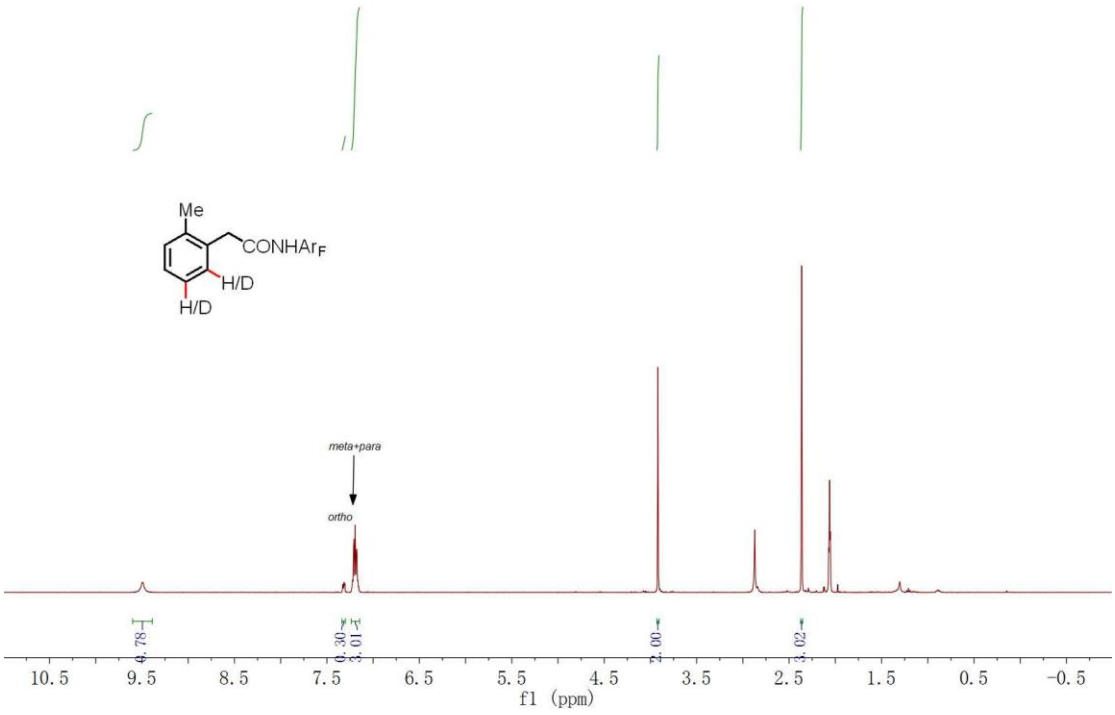




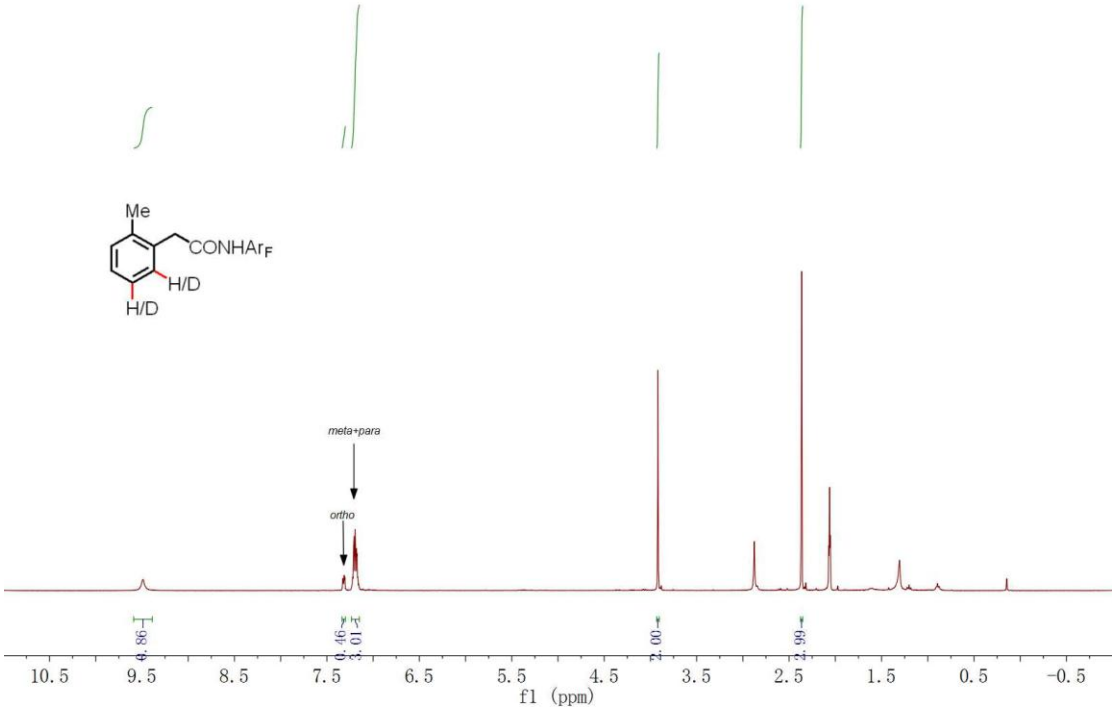

F3C
H
N
F
F
F
CF3
F
F
H1
O
H1
1.01
0.47
1.02
2.00
2.02
2.18
2.24
3.09
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

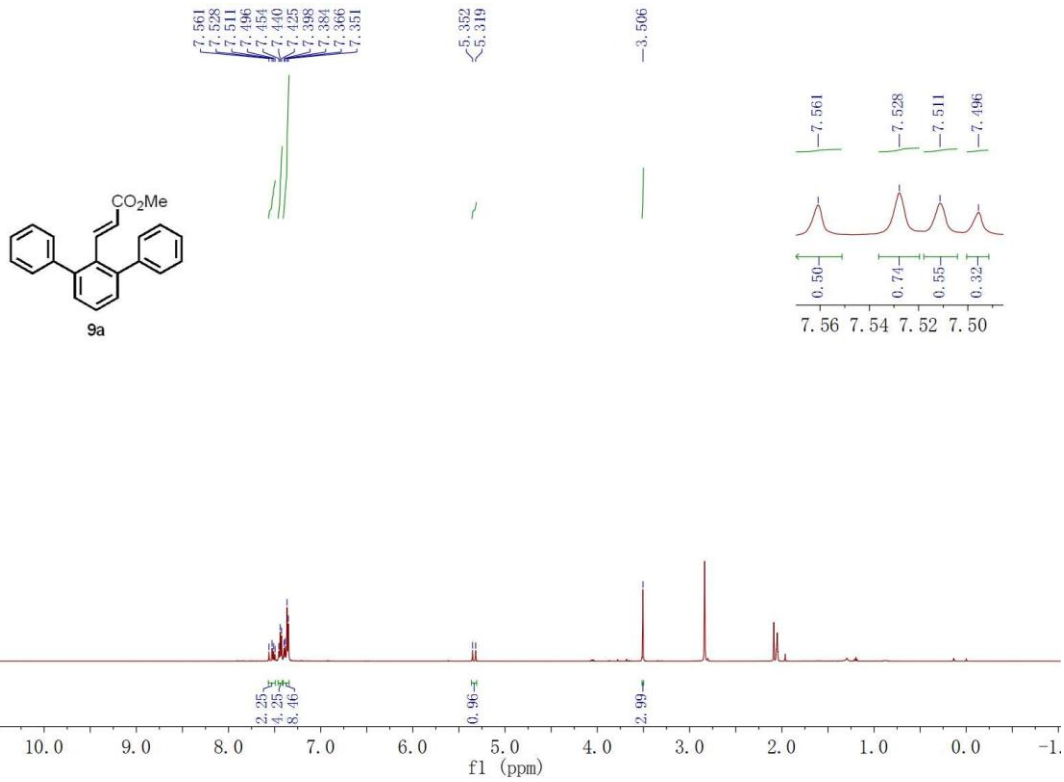

F3C
H
N
F
F
F
CF3
F
F
H1
O
H2
H1
H2
0.88
1.06
0.47
1.10
0.84
2.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

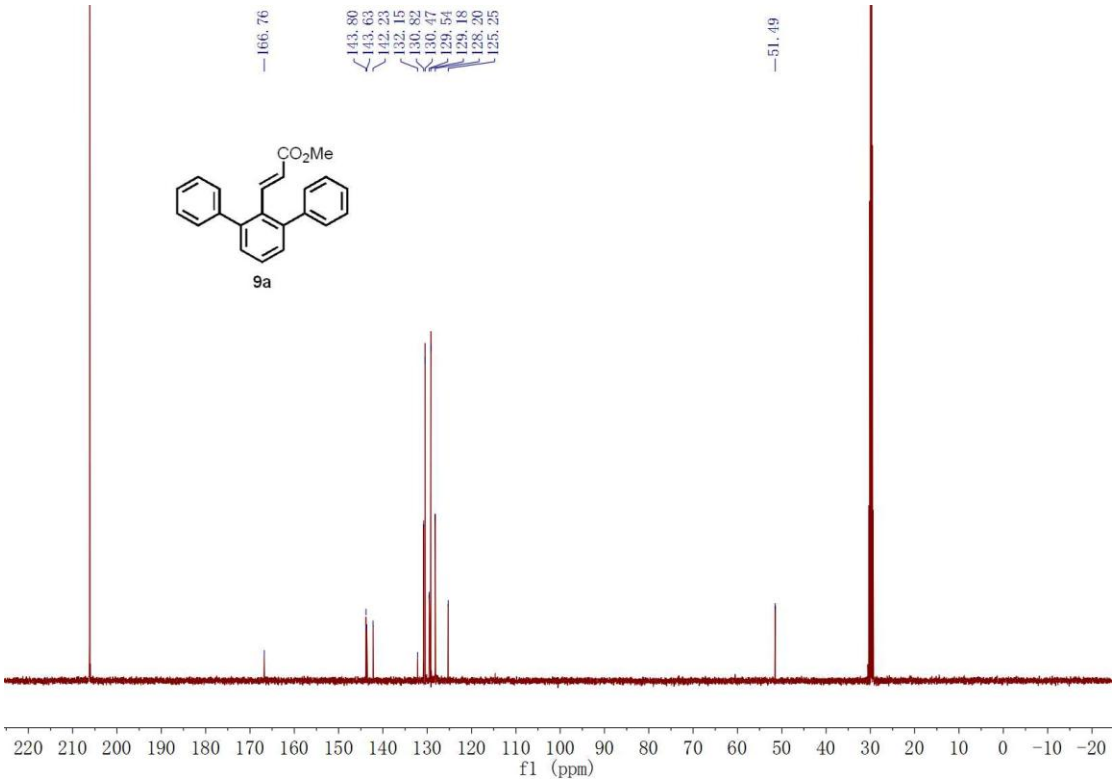
Deuteration experiment with **N12**

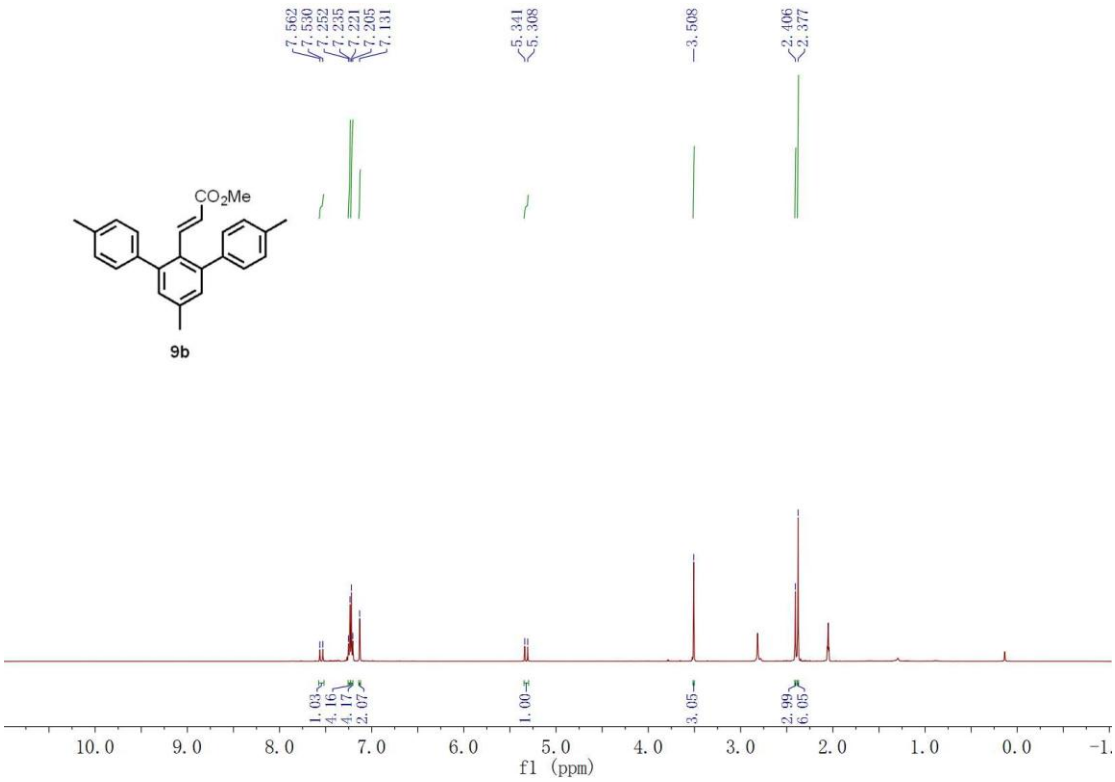


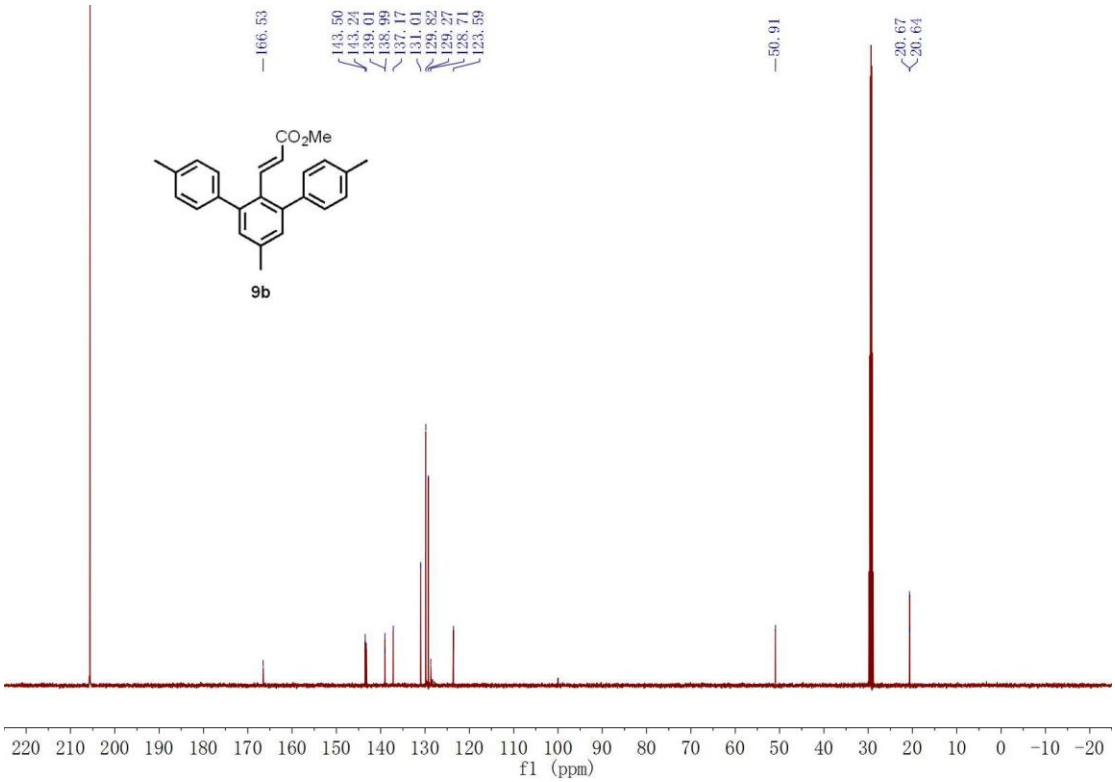
Deuteration experiment with **N14**



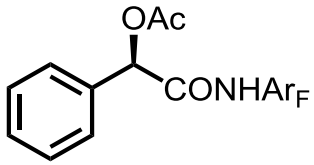

7.561
7.528
7.511
7.496
7.454
7.440
7.425
7.398
7.384
7.366
7.351
5.352
5.319
3.506
CO2Me
9a
0.50
0.74
0.55
0.32
7.56 7.54 7.52 7.50
2.25
4.25
8.46
0.96
2.99
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)


166.76
143.80
143.63
142.23
132.15
130.82
130.47
129.54
129.18
128.20
125.25
51.49
CO2Me
9a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

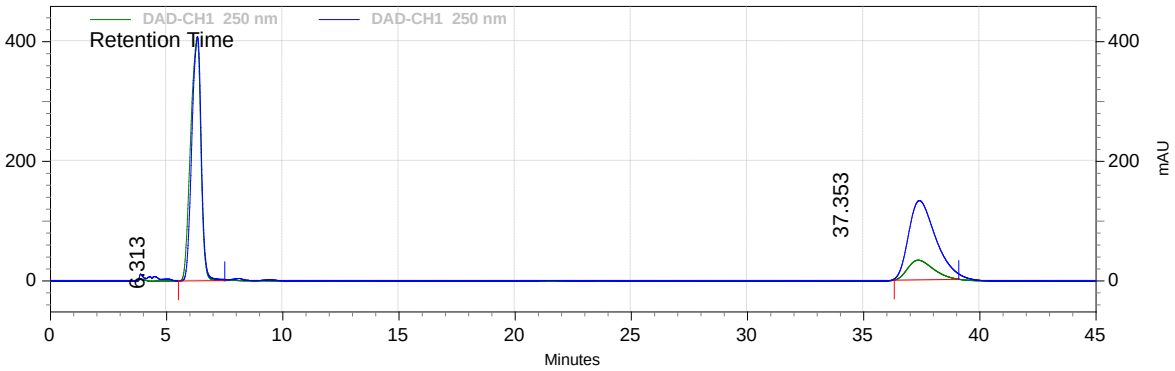

7.562
7.536
7.252
7.235
7.221
7.205
7.131
5.341
5.308
3.508
2.406
2.377
CO2Me
9b
1.03
4.16
4.17
2.07
1.00
3.05
2.99
6.05
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


166.53
143.50
143.24
139.01
138.99
137.17
131.01
129.82
129.27
128.71
123.59
50.91
20.67
20.64
CO2Me
9b
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

6. HPLC Spectra



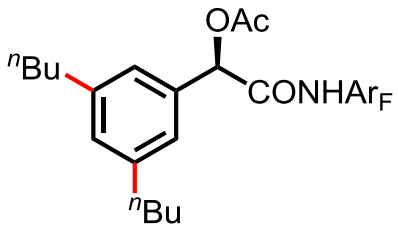
Area % Report



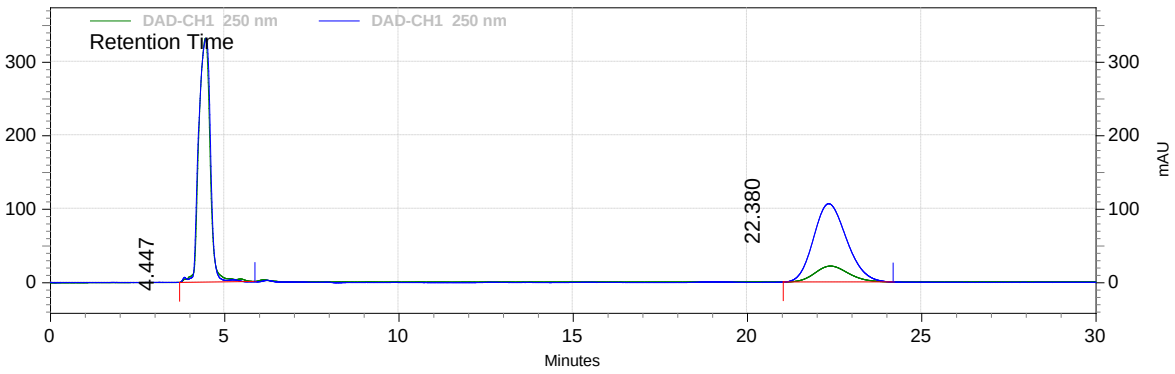
DAD-CH1 250 nm Results

Retention Time	Area	Area %	Height	Height %
6.313	49777942	83.23	1631228	92.55
37.353	10031132	16.77	131281	7.45

Totals	59809074	100.00	1762509	100.00



Area % Report



DAD-CH1 250 nm Results

Retention Time	Area	Area %	Height	Height %
4.447	29538298	83.62	1327139	93.90
22.380	5786258	16.38	86253	6.10

Totals	35324556	100.00	1413392	100.00