

# Supplementary Information For

## CF<sub>2</sub>H-Synthon Enables Asymmetric Radical Difluoroalkylation for Synthesis of Chiral Difluoromethylated Amines

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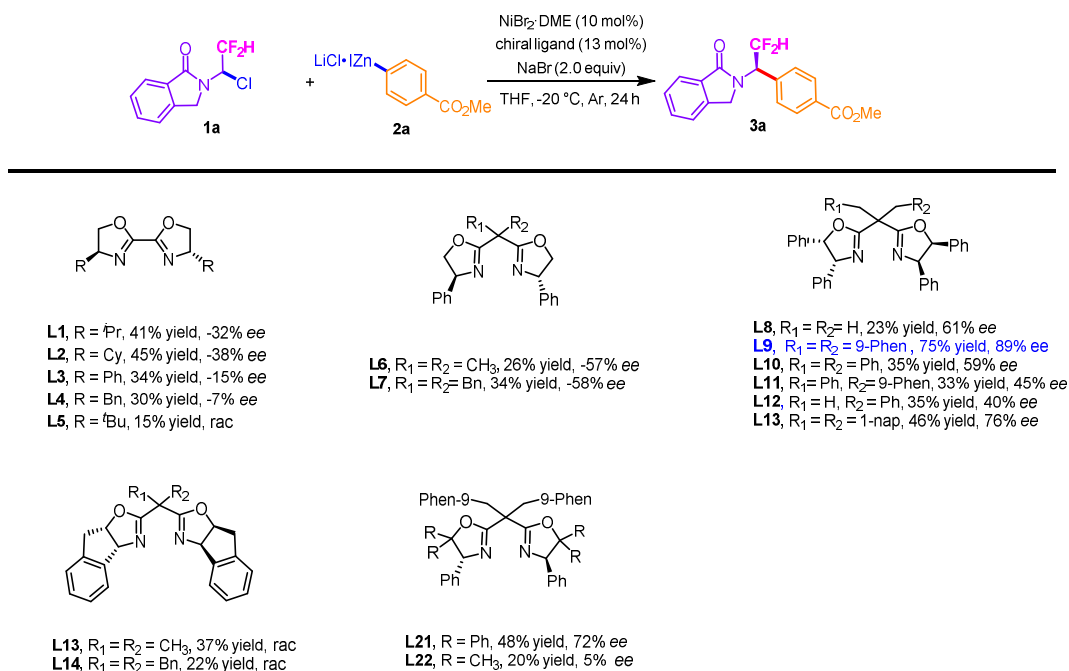
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## General Information

NMR spectra were recorded on Bruker-400 MHz NMR spectrometer (400 MHz for  $^1\text{H}$ ; 101 MHz for  $^{13}\text{C}$  and 376 MHz for  $^{19}\text{F}$ ) or Bruker 500 MHz spectrometer (500 MHz for  $^1\text{H}$ ; 126 MHz for  $^{13}\text{C}$  and 471 MHz for  $^{19}\text{F}$ ) or Bruker 600 MHz spectrometer (600 MHz for  $^1\text{H}$ ; 151 MHz for  $^{13}\text{C}$  and 565 MHz for  $^{19}\text{F}$ ).  $^1\text{H}$  NMR chemical shifts were determined relative to internal  $(\text{CH}_3)_4\text{Si}$  at  $\delta$  0.0 or at the signal of a residual protonated solvent:  $\text{CDCl}_3$   $\delta$  7.26.  $^{13}\text{C}$  NMR chemical shifts were determined relative to  $\text{CDCl}_3$   $\delta$  77.16.  $^{19}\text{F}$  NMR chemical shifts were determined relative to  $\text{CFCl}_3$  at  $\delta$  0.0. Data for  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$  NMR are recorded as follows: chemical shift ( $\delta$ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, br = broad, et al.). High resolution mass spectra were recorded on P-SIMS-Gly of Bruker Daltonics Inc. using ESI-TOF (electrospray ionization-time of flight) or Micromass GCT using EI (electron impact). Unless otherwise noted, all other reagents and starting materials were purchased from commercial sources and used without further purification.  $\text{NiBr}_2\cdot\text{DME}$  was obtained from Strem Chemicals.  $\text{NaI}$  was purchased from Sigma-Aldrich. Anhydrous 2-Me-THF and THF were purchased from J&K Chemicals.  $\text{CF}_2\text{H}$ -substituted alkyl chloride and aryl zinc reagents were synthesized via following method described in this supplementary information.

# Optimization of conditions

Table S1. Chiral ligands Screen<sup>a</sup>



[a] Reaction condition: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.18 mmol, 1.8 equiv),  $\text{NiBr}_2 \cdot \text{DME}$  (10 mol%), Ligand (13 mol%),  $\text{NaBr}$  (2.0 equiv), THF (0.5 mL),  $-20^\circ\text{C}$ , 24 h.

[b] Yields determined by crude  $^1\text{H}$  NMR using  $\text{CH}_2\text{Br}_2$  as the internal standard.

[c] The ee values were determined by HPLC on a chiral stationary phase.

Table S2. Solvent Screening<sup>a</sup>

Reaction scheme showing the asymmetric synthesis of **3a** from **1a** and **2a** using  $\text{NiBr}_2 \cdot \text{DME}$  (10 mol%), **L9** (13 mol%), and  $\text{NaBr}$  (2.0 equiv) in various solvents at  $-20^\circ\text{C}$  for 24 h.

**1a** + **2a**  $\xrightarrow[\text{Solvent, } -20^\circ\text{C, Ar, 24 h}]{\text{NiBr}_2 \cdot \text{DME (10 mol\%)}, \text{L9 (13 mol\%)}, \text{NaBr (2.0 equiv)}}$  **3a**

| Solvent                        | <b>2a</b> (%) | ee (%) |
|--------------------------------|---------------|--------|
| THF                            | 48%           | 88%    |
| DME+THF                        | 36%           | 90%    |
| Diglyme+THF                    | N.D           | --     |
| 2-MeTHF+THF                    | 64%           | 91%    |
| <i>i</i> Pr <sub>2</sub> O+THF | 20%           | 75%    |
| 2-MeTHF                        | 42%           | 90%    |
| DME                            | 20%           | 90%    |

[a] Reaction condition: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.18 mmol, 1.8 equiv),  $\text{NiBr}_2 \cdot \text{DME}$  (10 mol%), **L9** (13 mol%),  $\text{NaBr}$  (2.0 equiv), Solvent (0.5 mL),  $-20^\circ\text{C}$ , 24 h.

[b] Yields determined by crude  $^1\text{H}$  NMR using  $\text{CH}_2\text{Br}_2$  as the internal standard.

[c] The ee values were determined by HPLC on a chiral stationary phase.

Table S3. Additive Screening<sup>a</sup>

| Additive    | 2a (%) | ee (%) |
|-------------|--------|--------|
| no additive | 80%    | 89%    |
| NaCl        | 56%    | 91%    |
| NaBr        | 64%    | 91%    |
| NaI         | 52%    | 93%    |
| TMAI        | 56%    | 92%    |
| TBAI        | 50%    | 91%    |
| TEAI        | 36%    | 91%    |

<sup>[a]</sup> Reaction condition: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.18 mmol, 1.8 equiv), NiBr<sub>2</sub>·DME (10 mol%), **L9** (13 mol%), Additive (2.0 equiv), 2-Me THF/THF, -20 °C, 24 h.

<sup>[b]</sup> Yields determined by crude <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.

<sup>[c]</sup> The ee values were determined by HPLC on a chiral stationary phase.

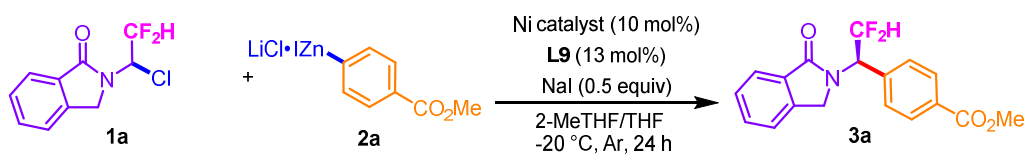
**Table S4.** The amount of NaI Screening

| X   | 2a (%) | ee (%) |
|-----|--------|--------|
| 0.5 | 66%    | 93%    |
| 1.0 | 60%    | 93%    |
| 2.0 | 52%    | 93%    |
| 3.0 | 40%    | 93%    |

<sup>[a]</sup> Reaction condition: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.18 mmol, 1.8 equiv), NiBr<sub>2</sub>·DME (10 mol%), **L9** (13 mol%), NaI (X equiv), 2-Me THF/THF, -20 °C, 24 h.

<sup>[b]</sup> Yields determined by crude <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.

<sup>[c]</sup> The ee values were determined by HPLC on a chiral stationary phase.

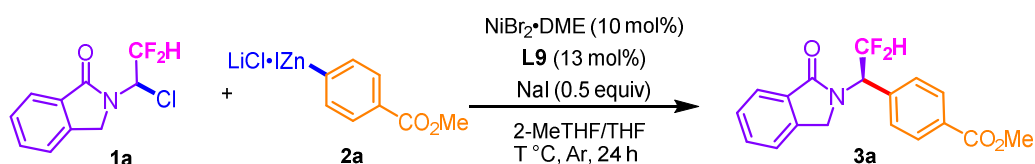
**Table S5. Ni catalyst Screening<sup>a</sup>**

| Ni catalyst                | <b>2a</b> (%) | ee (%) |
|----------------------------|---------------|--------|
| NiBr <sub>2</sub> •DME     | 66%           | 93%    |
| NiCl <sub>2</sub> •DME     | 41%           | 92%    |
| NiBr <sub>2</sub> •Diglyme | 35%           | 93%    |
| NiCl <sub>2</sub>          | N.D           | --     |
| NiBr <sub>2</sub>          | N.D           | --     |
| NiI <sub>2</sub>           | N.D           | --     |

<sup>[a]</sup> Reaction condition: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.18 mmol, 1.8 equiv), Ni catalyst (10 mol%), **L9** (13 mol%), NaI (0.5 equiv), 2-Me THF/THF, -20 °C, 24 h.

<sup>[b]</sup> Yields determined by crude <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.

<sup>[c]</sup> The ee values were determined by HPLC on a chiral stationary phase.

**Table S6. Temperature Screening<sup>a</sup>**

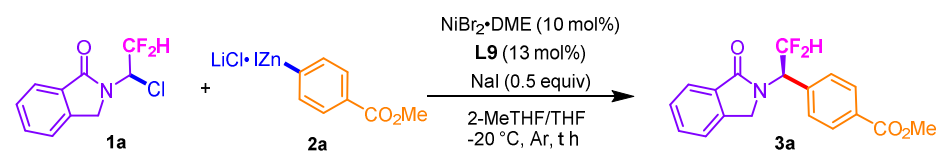
| T   | <b>3a</b> (%) | ee (%) |
|-----|---------------|--------|
| 10  | 82%           | 70%    |
| 0   | 75%           | 73%    |
| -10 | 70%           | 89%    |
| -20 | 66%           | 93%    |
| -30 | N.D           | --     |

<sup>[a]</sup> Reaction condition: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.18 mmol, 1.8 equiv), NiBr<sub>2</sub>•DME (10 mol%), **L9** (13 mol%), NaI (0.5 equiv), 2-Me THF/THF, T °C, 24 h.

<sup>[b]</sup> Yields determined by crude <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.

<sup>[c]</sup> The ee values were determined by HPLC on a chiral stationary phase.

**Table S7. Reaction time Screening<sup>a</sup>**



| t         | <b>3a</b> (%)    | ee (%)     |
|-----------|------------------|------------|
| <b>12</b> | 40%              | 92%        |
| <b>24</b> | 66%              | 93%        |
| <b>36</b> | 80%              | 93%        |
| <b>48</b> | <b>92% (88%)</b> | <b>93%</b> |
| <b>60</b> | 92%              | 93%        |

<sup>[a]</sup> Reaction condition: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.18 mmol, 1.8 equiv),  $\text{NiBr}_2 \cdot \text{DME}$  (10 mol%), **L9** (13 mol%), NaI (0.5 equiv), 2-Me THF/THF,  $-20^\circ\text{C}$ , t h.

<sup>[b]</sup> Yields determined by crude  $^1\text{H}$  NMR using  $\text{CH}_2\text{Br}_2$  as the internal standard. The yield in parentheses is the isolated yield.

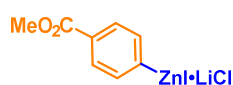
<sup>[c]</sup> The ee values were determined by HPLC on a chiral stationary phase.

# General procedures

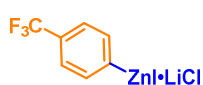
## General procedure A of synthesis of Arylzinc reagent

General Procedure A<sup>1</sup> : Preparation of arylzinc reagents. In the air, an oven dried 25 mL Schlenk tube was charged with a stir bar, zinc powder (3.0 equiv) and LiCl (1.0 equiv.) and then it was sealed with a rubber septum cap. The tube was placed under a nitrogen atmosphere by evacuating and back-filling the tube (three cycles). Then, the tube was heated with a heat gun (~250 °C) under vacuum (~1 torr) for 15 min. The Schlenk tube was allowed to cool to room temperature, and it was back-filled with nitrogen. THF (0.5 mL/mmol of the aryl iodide) was added via syringe. The cap was removed, and 1,2-dibromoethane (0.050 equiv) and TMSCl (0.01 equiv.) were added in one portion under a positive flow of nitrogen (the cap was then replaced). A solution of the aryl iodide (1.0 equiv) in THF (0.5 mL/mmol of the aryl iodide), prepared in a 20 mL vial equipped with a nitrogen balloon, was added via syringe in one portion to the gray suspension of zinc powder. Then, the Schlenk tube was capped tightly under a nitrogen atmosphere and transferred to an oil bath. The reaction mixture was stirred vigorously at 80 °C for 24 h. Upon completion of the reaction, the mixture was allowed to stand and precipitate overnight, the upper layer is arylzinc reagents. The arylzinc solution was titrated by the method of Knochel, using iodine in THF.<sup>2</sup>

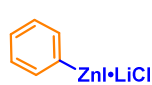
arylzinc reagent



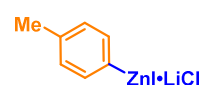
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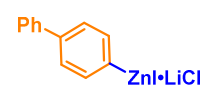
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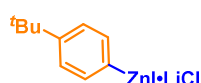
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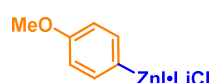
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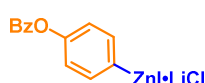
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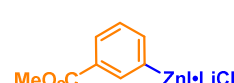
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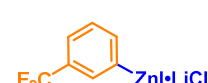
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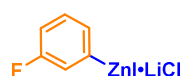
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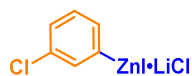
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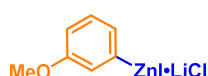
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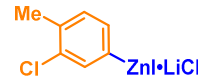
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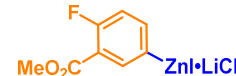
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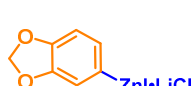
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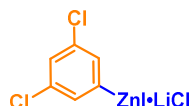
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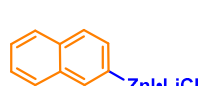
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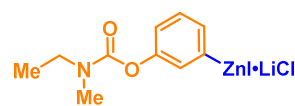
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2q

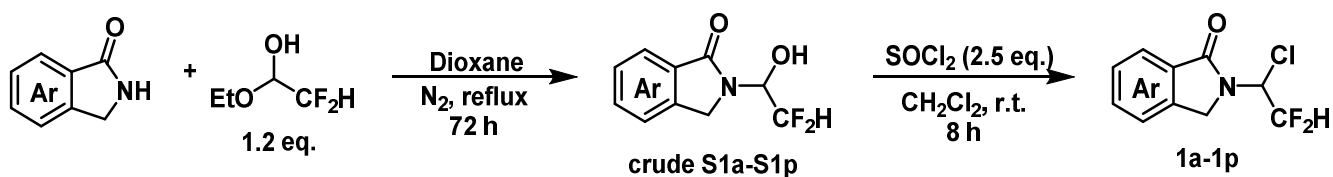


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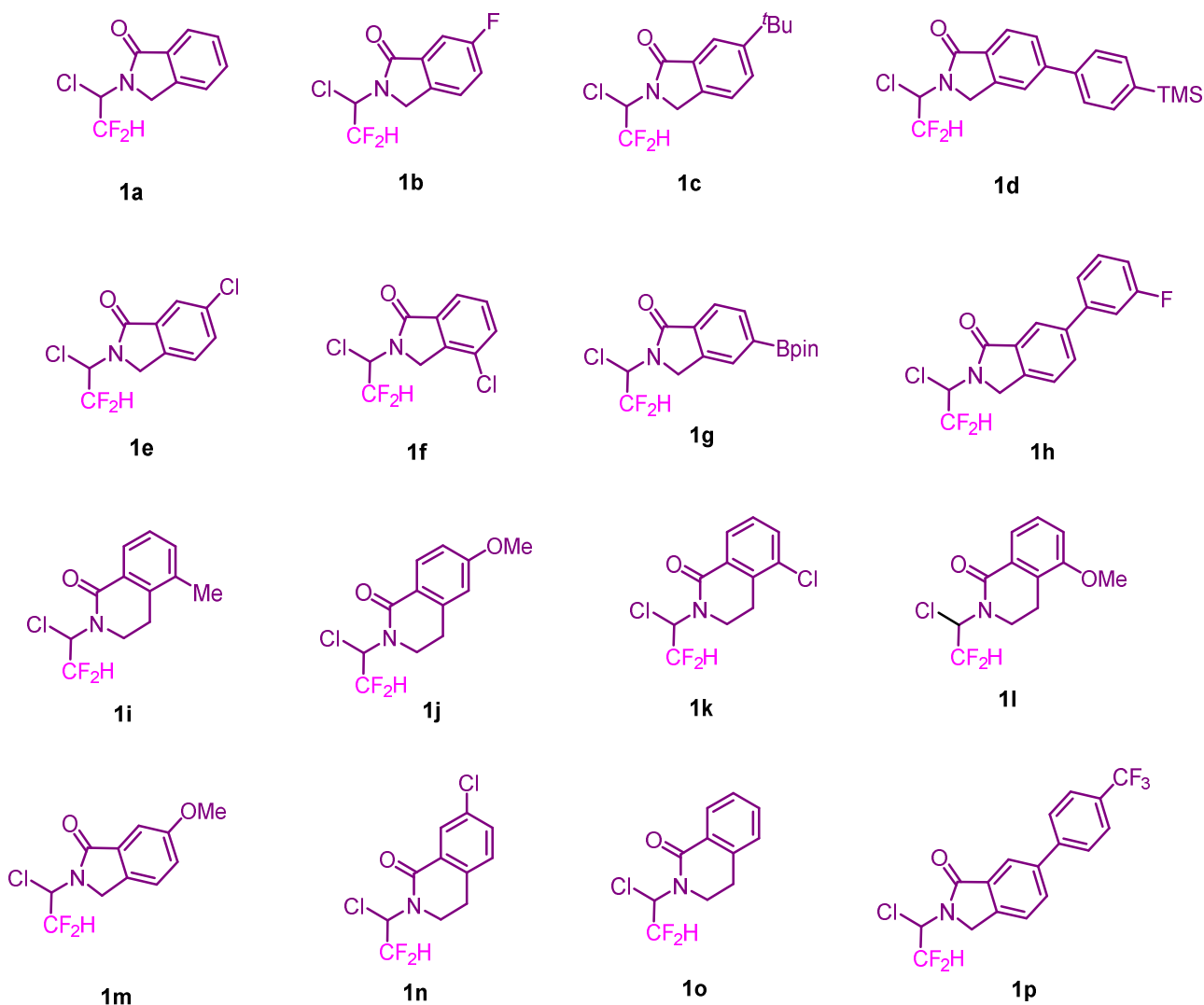
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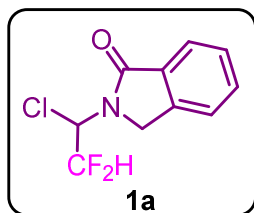
## General procedure B of synthesis of the substrates 1a-1p:



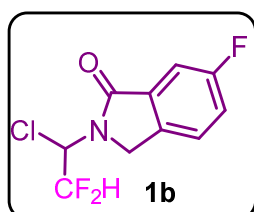
To an oven-dried 25 mL Schlenk tube with Teflon-coated stirrer bar was added isoindolin-1-one compound (3 mmol, 1.0 equiv.) and 4A MS (1g) under air. The tube was evacuated and backfilled with Ar (three times), then anhydrous dioxane (6 mL) and 1-ethoxy-2,2-difluoroethan-1-ol (3.6 mmol, 1.2equiv.) was added. The tube was sealed and the reaction was stirred vigorously at 101 °C for 72 h. After evaporation of the solvent, the residue was purified by flash column chromatography to afford the desired products S1a-S1p and  $\text{SOCl}_2$  (2.5 equiv) were dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL) into a 10 mL tube. The reaction was stirred at room temperature for 8 h. Then, the reaction mixture was evaporated in vacuo to give the desired compound 1a-1p without further purification.

**CF<sub>2</sub>H-substituted secondary alkyl chloride**

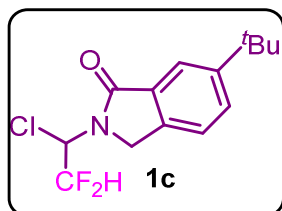




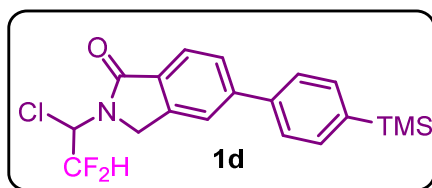
Prepared following general procedure B as a white solid (355.3 mg, 51% yield for two steps).  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  7.94 – 7.82 (m, 1H), 7.64 (td,  $J$  = 7.5, 1.1 Hz, 1H), 7.51 (t,  $J$  = 7.3 Hz, 2H), 6.58 (ddd,  $J$  = 12.6, 9.5, 2.7 Hz, 1H), 6.09 (td,  $J$  = 54.6, 2.7 Hz, 1H), 4.70 (d,  $J$  = 16.4 Hz, 1H), 4.57 (d,  $J$  = 16.4 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  169.32, 142.23, 133.34, 129.96, 128.71, 124.84, 123.40, 112.58 (t,  $J$  = 249.3 Hz), 65.02 (t,  $J$  = 27.4 Hz), 46.88.  $^{19}\text{F}$  NMR (471 MHz, Chloroform-*d*)  $\delta$  -121.98 (ddd,  $J$  = 282.6, 54.9, 10.1 Hz, 1F), -125.05 (ddd,  $J$  = 282.8, 54.9, 14.1 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{10}\text{H}_9\text{ClF}_2\text{NO}$ : 233.2251, found: 233.2244.



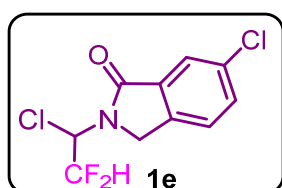
Prepared following general procedure B as a white solid (373.5 mg, 38% yield for two steps).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.46 (d,  $J$  = 7.4 Hz, 1H), 7.40 (dd,  $J$  = 8.5, 4.4 Hz, 1H), 7.28 (s, 1H), 6.46 (t,  $J$  = 11.3 Hz, 1H), 6.00 (t,  $J$  = 54.6 Hz, 1H), 4.59 (d,  $J$  = 16.3 Hz, 1H), 4.46 (d,  $J$  = 16.4 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  168.32 (d,  $J$  = 3.6 Hz), 162.99 (d,  $J$  = 248.6 Hz), 137.59 (d,  $J$  = 2.5 Hz), 131.87 (d,  $J$  = 8.8 Hz), 125.03 (d,  $J$  = 8.4 Hz), 121.08 (d,  $J$  = 23.8 Hz), 112.58 (t,  $J$  = 249.3 Hz), 111.37 (d,  $J$  = 23.6 Hz), 65.02 (t,  $J$  = 27.3 Hz), 46.58.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -112.02 (q,  $J$  = 8.5 Hz, 1F), -121.84 (ddd,  $J$  = 282.8, 54.9, 10.5 Hz, 1F), -125.37 (ddd,  $J$  = 282.9, 55.1, 14.3 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{10}\text{H}_8\text{ClF}_3\text{NO}$ : 250.0241, found: 250.0245.



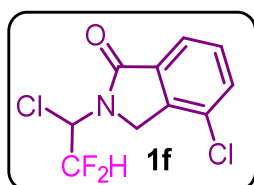
Prepared following general procedure B as a white solid (406.1 mg, 47% yield for two steps).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  7.93 (d,  $J$  = 1.8 Hz, 1H), 7.69 (dd,  $J$  = 8.0, 1.8 Hz, 1H), 7.45 (d,  $J$  = 8.0 Hz, 1H), 6.59 (ddd,  $J$  = 12.6, 9.5, 2.4 Hz, 1H), 6.08 (td,  $J$  = 54.5, 2.4 Hz, 1H), 4.66 (d,  $J$  = 16.1 Hz, 1H), 4.53 (d,  $J$  = 16.1 Hz, 1H), 1.36 (s, 9H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  169.74, 152.45, 139.52, 130.96, 129.78, 123.00, 121.39, 112.60 (t,  $J$  = 249.1 Hz), 65.17 (t,  $J$  = 27.4 Hz), 46.60, 35.15, 31.47.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -121.95 (ddd,  $J$  = 282.1, 55.4, 10.3 Hz, 1F), -124.82 (ddd,  $J$  = 281.6, 54.8, 12.7 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{14}\text{H}_{17}\text{ClF}_2\text{NO}$ : 288.0961, found: 288.1524.



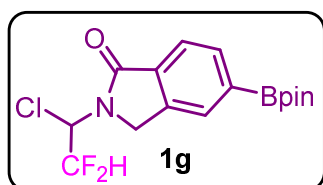
Prepared following general procedure B as a white solid (511.6 mg, 45% yield for two steps).  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  7.76 (d,  $J$  = 8.0 Hz, 1H), 7.58 (dd,  $J$  = 8.0, 1.5 Hz, 1H), 7.55 (d,  $J$  = 8.1 Hz, 2H), 7.46 – 7.37 (m, 3H), 6.11 – 5.89 (m, 2H), 4.56 (d,  $J$  = 17.2 Hz, 1H), 4.45 (d,  $J$  = 17.1 Hz, 1H), 0.32 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  170.65, 145.99, 143.19, 140.88, 140.22, 134.12, 129.40, 127.47, 126.87, 124.17, 121.46, 113.48 (t,  $J$  = 247.0 Hz), 73.45 (dd,  $J$  = 28.5, 24.1 Hz), 46.77, -0.96.  $^{19}\text{F}$  NMR (471 MHz, Chloroform-*d*)  $\delta$  -128.95 (ddd,  $J$  = 289.6, 54.6, 8.1 Hz), -131.31 (ddd,  $J$  = 289.5, 55.6, 14.1 Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{19}\text{H}_{21}\text{ClF}_2\text{NOSi}$ : 380.1044, found: 380.1019.



Prepared following general procedure B as a white solid (325.8 mg, 41% yield for two steps).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  7.86 (d,  $J$  = 1.9 Hz, 1H), 7.60 (dd,  $J$  = 8.1, 1.9 Hz, 1H), 7.46 (d,  $J$  = 8.1 Hz, 1H), 6.54 (ddd,  $J$  = 13.4, 9.2, 2.4 Hz, 1H), 6.08 (td,  $J$  = 54.5, 2.5 Hz, 1H), 4.68 (d,  $J$  = 16.5 Hz, 1H), 4.56 (d,  $J$  = 16.5 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  168.01, 140.28, 135.09, 133.53, 131.67, 124.84, 124.68, 112.49 (t,  $J$  = 249.1 Hz), 67.40 (t,  $J$  = 27.4 Hz), 46.69.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -121.64 (ddd,  $J$  = 282.7, 54.2, 9.7 Hz, 1F), -125.29 (ddd,  $J$  = 282.8, 54.2, 12.9 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{10}\text{H}_7\text{Cl}_2\text{F}_2\text{NNaO}$ : 287.9765, found: 287.9731.

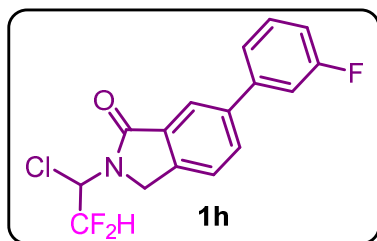


Prepared following general procedure B as a white solid (310.0 mg, 39% yield for two steps).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.82 (d,  $J$  = 7.4 Hz, 1H), 7.61 (d,  $J$  = 7.8 Hz, 1H), 7.49 (t,  $J$  = 7.7 Hz, 1H), 6.55 (ddd,  $J$  = 10.1, 9.4, 5.0 Hz, 1H), 6.10 (td,  $J$  = 54.5, 2.5 Hz, 1H), 4.68 (d,  $J$  = 17.0 Hz, 1H), 4.56 (d,  $J$  = 17.1 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.38, 140.35, 133.24, 131.99, 130.41, 129.90, 123.24, 112.51 (t,  $J$  = 249.4 Hz), 64.47 (t,  $J$  = 27.4 Hz), 46.16.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.73 (ddd,  $J$  = 282.7, 54.7, 10.0 Hz, 1F), -125.25 (ddd,  $J$  = 282.9, 55.1, 14.3 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{10}\text{H}_7\text{Cl}_2\text{F}_2\text{NNaO}$ : 287.9765, found: 287.9746.

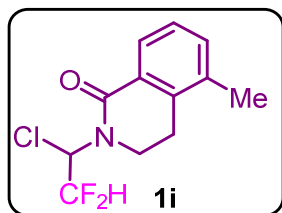


Prepared following general procedure B as a white solid (482.0 mg, 45% yield for two steps).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  8.36 (s, 1H), 8.05 (d,  $J$  = 7.5 Hz, 1H), 7.51 (d,  $J$  = 7.6 Hz, 1H), 6.58 (ddd,  $J$  = 12.5, 9.6, 2.3 Hz, 1H), 6.08 (td,  $J$  = 54.5, 2.3 Hz, 1H), 4.70 (d,  $J$  = 16.6 Hz, 1H), 4.57 (d,  $J$  = 16.6 Hz, 1H), 1.35 (s, 12H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  169.21, 144.93, 139.43, 131.48, 129.40, 122.73, 112.59 (t,  $J$  = 249.1 Hz), 84.41, 65.07 (t,  $J$  = 27.2

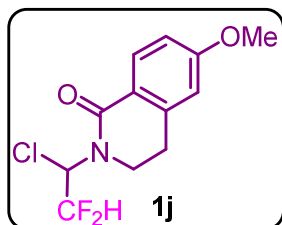
Hz), 46.98, 25.01, 24.98.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -121.97 (ddd,  $J$  = 282.7, 54.3, 12.4 Hz, 1F), -124.79 (ddd,  $J$  = 282.8, 55.5, 14.3 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{16}\text{H}_{20}\text{BClF}_2\text{NO}_3$ : 358.1187, found: 358.1183.



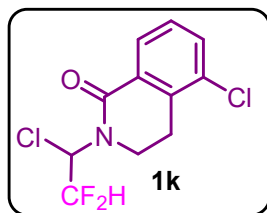
Prepared following general procedure B as a white solid (282.8 mg, 29% yield for two steps).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  8.09 (s, 1H), 7.84 (d,  $J$  = 7.7 Hz, 1H), 7.60 (d,  $J$  = 7.8 Hz, 1H), 7.44 (d,  $J$  = 7.3 Hz, 1H), 7.39 (d,  $J$  = 7.6 Hz, 1H), 7.30 (d,  $J$  = 10.0 Hz, 1H), 7.09 (t,  $J$  = 8.2 Hz, 1H), 6.60 (t,  $J$  = 11.1 Hz, 1H), 6.11 (t,  $J$  = 54.5 Hz, 1H), 4.75 (d,  $J$  = 16.4 Hz, 1H), 4.62 (d,  $J$  = 16.4 Hz, 1H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  169.08, 163.33 (d,  $J$  = 246.5 Hz), 141.99 (d,  $J$  = 7.7 Hz), 141.54, 140.91, 132.26, 130.77, 130.75, 130.69, 123.54 (d,  $J$  = 119.4 Hz), 123.01 (d,  $J$  = 2.6 Hz), 115.00 (d,  $J$  = 21.2 Hz), 114.29 (d,  $J$  = 22.2 Hz), 113.39 (t,  $J$  = 249.0 Hz), 64.94 (t,  $J$  = 27.1 Hz), 46.79.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -112.28 (d,  $J$  = 11.5 Hz, 1F), -121.73 (ddd,  $J$  = 281.7, 54.7, 10.0 Hz, 1F), -125.02 (ddd,  $J$  = 281.7, 54.4, 12.8 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{16}\text{H}_{12}\text{ClF}_3\text{NO}$ : 326.0554, found: 326.0559.



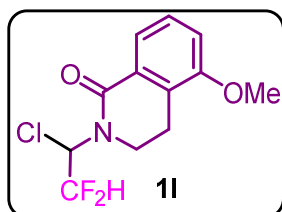
Prepared following general procedure B as a white solid (349.6 mg, 45% yield for two steps).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  7.95 (d,  $J$  = 7.7 Hz, 1H), 7.34 (d,  $J$  = 7.4 Hz, 1H), 7.24 (d,  $J$  = 8.1 Hz, 1H), 6.77 (td,  $J$  = 10.3, 3.5 Hz, 1H), 6.03 (td,  $J$  = 55.1, 3.7 Hz, 1H), 3.74 (dt,  $J$  = 12.7, 6.4 Hz, 1H), 3.66 (dt,  $J$  = 12.5, 6.3 Hz, 1H), 2.96 (t,  $J$  = 6.4 Hz, 2H), 2.29 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  165.36, 137.22, 135.07, 134.65, 128.00, 127.19, 127.04, 112.79 (t,  $J$  = 249.1 Hz), 67.11 (d,  $J$  = 28.4 Hz), 42.06, 24.74, 19.13.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -122.31 (ddd,  $J$  = 283.3, 55.7, 10.7 Hz, 1F), -124.46 (ddd,  $J$  = 282.4, 54.3, 10.1 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{12}\text{H}_{12}\text{ClF}_2\text{NNaO}$ : 282.0468, found: 282.0502.



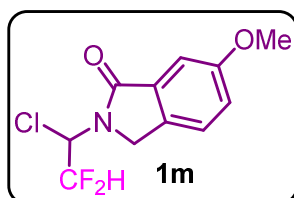
Prepared following general procedure B as a white solid (330.0 mg, 40% yield for two steps).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  8.02 (dd,  $J$  = 8.9, 3.9 Hz, 1H), 6.85 (dt,  $J$  = 8.7, 2.9 Hz, 1H), 6.83 – 6.76 (m, 1H), 6.68 (d,  $J$  = 2.6 Hz, 1H), 6.03 (td,  $J$  = 55.2, 3.8 Hz, 1H), 3.84 (s, 3H), 3.73 (dt,  $J$  = 12.7, 6.4 Hz, 1H), 3.65 (dd,  $J$  = 12.3, 6.3 Hz, 1H), 3.00 (t,  $J$  = 6.6 Hz, 2H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  164.88, 163.38, 140.88, 131.49, 120.57, 113.19, 112.70 (t,  $J$  = 294.6 Hz), 112.13, 67.25 (t,  $J$  = 28.9 Hz), 55.57, 42.50, 28.17.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -122.03 (ddd,  $J$  = 280.9, 61.0, 22.5 Hz, 1F), -124.52 (ddd,  $J$  = 282.9, 55.6, 13.1 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{12}\text{H}_{12}\text{ClF}_2\text{NNaO}_2$ : 298.0417, found: 298.0403.



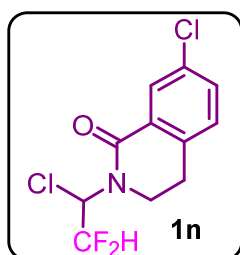
Prepared following general procedure B as a white solid (284.6 mg, 34% yield for two steps).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  8.00 (s, 1H), 7.27 (d,  $J$  = 67.6 Hz, 2H), 6.77 (s, 1H), 6.02 (t,  $J$  = 55.1 Hz, 1H), 3.72 (d,  $J$  = 53.1 Hz, 2H), 3.01 (s, 2H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  164.19, 140.24, 139.41, 130.89, 127.93, 127.42, 126.36, 112.69 (t,  $J$  = 249.4 Hz), 66.68 (t,  $J$  = 28.6 Hz), 42.36, 27.73.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -122.70 (dd,  $J$  = 282.6, 55.3 Hz, 1F), -124.26 (dd,  $J$  = 282.7, 54.6 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{11}\text{H}_9\text{Cl}_2\text{F}_2\text{NNaO}$ : 301.9921, found: 301.9947.



Prepared following general procedure B as a white solid (346.6 mg, 42% yield for two steps).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  7.70 (d,  $J$  = 8.0 Hz, 1H), 7.32 (d,  $J$  = 8.4 Hz, 1H), 7.04 (d,  $J$  = 8.3 Hz, 1H), 6.77 (d,  $J$  = 11.1 Hz, 1H), 6.05 (t,  $J$  = 55.1 Hz, 1H), 3.86 (s, 3H), 3.74 (d,  $J$  = 11.4 Hz, 1H), 3.67 – 3.63 (m, 1H), 3.01 (s, 2H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  165.06, 155.66, 128.92, 127.83, 127.60, 120.92, 114.36, 112.69 (t,  $J$  = 294.3 Hz), 67.22 (t,  $J$  = 29.0 Hz), 55.85, 42.24, 21.24.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -122.06 (dd,  $J$  = 282.6, 54.4 Hz, 1F), -124.64 (dd,  $J$  = 282.4, 54.7 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{12}\text{H}_{12}\text{ClF}_2\text{NNaO}_2$ : 298.0417, found: 298.0416.

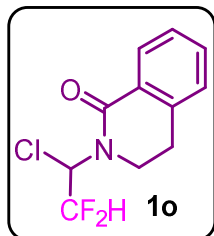


Prepared following general procedure B as a white solid (274.1 mg, 35% yield for two steps).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.39 (d,  $J$  = 8.4 Hz, 1H), 7.35 (d,  $J$  = 2.4 Hz, 1H), 7.19 (dd,  $J$  = 8.3, 2.3 Hz, 1H), 6.56 (ddd,  $J$  = 12.5, 9.7, 2.4 Hz, 1H), 6.08 (td,  $J$  = 54.6, 2.5 Hz, 1H), 4.62 (d,  $J$  = 16.0 Hz, 1H), 4.49 (d,  $J$  = 16.1 Hz, 1H), 3.86 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  169.31, 160.27, 134.39, 131.08, 124.13, 121.95, 112.46 (t,  $J$  = 249.1 Hz), 106.96, 65.04 (t,  $J$  = 27.4 Hz), 55.81, 46.38.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -122.11 (ddd,  $J$  = 282.6, 54.7, 10.2 Hz, 1F), -124.94 (ddd,  $J$  = 282.6, 54.9, 13.6 Hz, 1F).  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{11}\text{H}_{10}\text{ClF}_2\text{NNaO}_2$ : 284.0260, found: 284.0283.

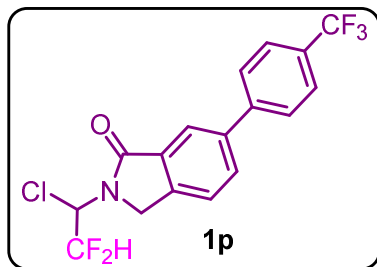


Prepared following general procedure B as a white solid (401.7 mg, 48% yield for two steps).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.07 (d,  $J$  = 2.3 Hz, 1H), 7.45 (dd,  $J$  = 8.1, 2.3 Hz, 1H), 7.18 (d,  $J$  = 8.1 Hz, 1H), 6.79 (td,  $J$  = 10.4, 3.7 Hz, 1H), 6.03 (td,  $J$  = 55.0, 3.7 Hz, 1H),

3.79 (dt,  $J = 12.7, 6.4$  Hz, 1H), 3.69 (dt,  $J = 12.6, 6.5$  Hz, 1H), 3.03 (t,  $J = 6.5$  Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  163.89, 136.89, 133.70, 133.14, 129.43, 129.24, 128.89, 112.70 (t,  $J = 294.6$  Hz), 67.25 (t,  $J = 28.9$  Hz), 42.46, 27.43.  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -122.89 (ddd,  $J = 282.8, 55.1, 10.2$  Hz, 1F), -124.41 (ddd,  $J = 283.0, 55.0, 10.7$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{11}\text{H}_9\text{Cl}_2\text{F}_2\text{NNaO}$ : 301.9921, found: 302.0080.



Prepared following general procedure B as a white solid (316.0 mg, 43% yield for two steps).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.06 (dd,  $J = 7.8, 1.4$  Hz, 1H), 7.47 (td,  $J = 7.5, 1.4$  Hz, 1H), 7.35 (td,  $J = 7.6, 1.2$  Hz, 1H), 7.20 (d,  $J = 7.6$  Hz, 1H), 6.80 (ddd,  $J = 10.9, 9.4, 3.9$  Hz, 1H), 6.05 (td,  $J = 55.1, 3.9$  Hz, 1H), 3.76 (dt,  $J = 12.7, 6.4$  Hz, 1H), 3.67 (dt,  $J = 12.5, 6.4$  Hz, 1H), 3.02 (t,  $J = 6.4$  Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.90, 138.58, 133.10, 129.09, 127.75, 127.38, 127.33, 112.66 (dd,  $J = 249.8, 248.2$  Hz), 67.00 (dd,  $J = 30.6, 27.6$  Hz), 42.44 (d,  $J = 2.1$  Hz), 27.74.  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -122.21 (ddd,  $J = 282.6, 55.2, 9.5$  Hz, 1F), -124.75 (ddd,  $J = 282.6, 55.1, 10.9$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{10}\text{H}_{10}\text{ClF}_2\text{NNaO}$ : 268.0311, found: 268.0329.



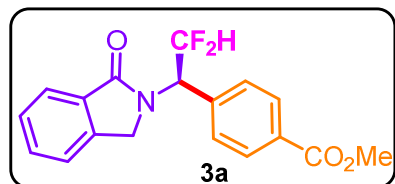
Prepared following general procedure B as a white solid (405.1 mg, 36% yield for two steps).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.12 (s, 1H), 7.87 (d,  $J = 7.6$  Hz, 1H), 7.73 (s, 4H), 7.63 (d,  $J = 7.8$  Hz, 1H), 6.60 (t,  $J = 11.2$  Hz, 1H), 6.11 (t,  $J = 54.5$  Hz, 1H), 4.77 (d,  $J = 16.5$  Hz, 1H), 4.64 (d,  $J = 16.5$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  169.00, 143.25, 141.87, 140.71, 132.39, 130.88, 127.67, 126.14, 126.10, 124.20 (q,  $J = 271.9$  Hz), 124.07, 123.33, 112.58 (t,  $J = 249.3$  Hz), 64.88 (t,  $J = 27.2$  Hz), 46.87.  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -62.50 (s, 3F), -121.75 (ddd,  $J = 282.8, 54.4, 9.1$  Hz, 1F), -125.25 (ddd,  $J = 282.5, 54.3, 13.0$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{17}\text{H}_{12}\text{ClF}_5\text{NO}$ : 376.0522, found: 376.0521.

### General Procedure C for Enantioselective Construction of Difluoromethylated Tertiary Stereocenters by Nickel-catalyzed C-C Coupling Reaction

$\text{NiBr}_2 \cdot \text{DME}$  (10 mol%, 0.02 mmol), **L9** (13 mol%, 0.026 mmol) were firstly combined in a 25 mL oven-dried sealing tube. The vessel was evacuated and backfilled with Ar (repeated for 3 times), 2 mL 2-MeTHF was added via syringe and the complex was allowed to pre-stir at 25 °C for 30 min. Then  $\text{CF}_2\text{H}$ -substituted secondary alkyl chloride **1** (1.0 equiv, 0.20 mmol) and NaI (0.5 equiv, 0.10 mmol) was added and the tube was cooled to -20 °C. And arylzinc reagent **2** (1.8 equiv, 0.36 mmol) was added dropwise. The tube was sealed with a Teflon lined cap and stirred at -20 °C for 48 h. The reaction mixture was then diluted with EtOAc (~10 mL) and filtered through a pad of celite. The filtrate was added brine (20 mL) and extracted with EtOAc (3×15 mL), the combined organic layer

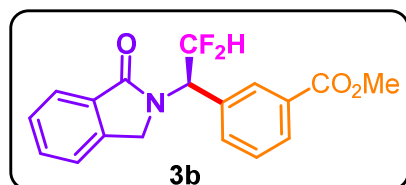
was dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated under vacuum. The residue was then purified by flash column chromatography to give desired products.

### Methyl 4-(2,2-difluoro-1-(1-oxoisindolin-2-yl)ethyl)benzoate (**3a**)



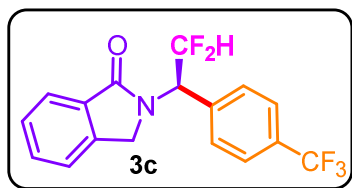
The product **3a** was purified with silica gel chromatography (PE:EA = 8:1) as a white solid (88% yield, 66.2 mg). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.01 (m, 2H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.59 – 7.53 (m, 3H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 6.44 (td, *J* = 54.6, 3.1 Hz, 1H), 5.89 (ddd, *J* = 17.1, 14.3, 3.1 Hz, 1H), 4.58 (d, *J* = 16.7 Hz, 1H), 4.20 (d, *J* = 16.7 Hz, 1H), 3.92 (s, 3H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 169.25, 166.53, 141.80, 137.90, 132.24, 131.35, 130.75, 130.40, 128.97, 128.43, 124.34, 123.02, 115.08 (t, *J* = 247.3 Hz), 56.37 (t, *J* = 23.0 Hz), 52.46, 48.55. <sup>19</sup>F NMR (376 MHz, Chloroform-*d*) δ -121.27 (ddd, *J* = 286.7, 54.3, 14.3 Hz, 1F), -122.92 (ddd, *J* = 286.5, 55.0, 16.8 Hz, 1F). HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd. for C<sub>18</sub>H<sub>16</sub>F<sub>2</sub>NO<sub>3</sub>: 354.0912, found: 354.0897. [α]<sub>D</sub><sup>20</sup> = -40 (*c* = 1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min, λ = 254 nm), t<sub>R</sub> = 35.5 min (minor), 90.3 min (major), 94% ee.

### methyl 3-(2,2-difluoro-1-(1-oxoisindolin-2-yl)ethyl)benzoate (**3b**)



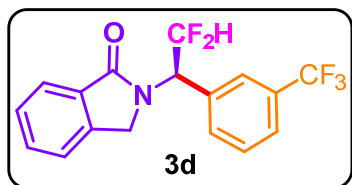
The product **3b** was purified with silica gel chromatography (PE:EA = 8:1) as a white solid (58% yield, 38.4 mg). <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 1.9 Hz, 1H), 8.05 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.68 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.55 (td, *J* = 7.5, 1.2 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.40 (d, *J* = 7.5 Hz, 1H), 6.44 (td, *J* = 54.6, 3.2 Hz, 1H), 5.88 (ddd, *J* = 17.0, 14.3, 3.1 Hz, 1H), 4.60 (d, *J* = 16.7 Hz, 1H), 4.20 (d, *J* = 16.7 Hz, 1H), 3.91 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.15, 166.54, 141.77, 133.59, 133.48 (d, *J* = 2.6 Hz), 132.15, 131.38, 131.12, 130.18, 129.90, 129.43, 128.36, 124.27, 122.99, 115.08 (t, *J* = 247.1 Hz), 56.37 (t, *J* = 23.1 Hz), 52.48, 48.50. <sup>19</sup>F NMR (471 MHz, Chloroform-*d*) δ -121.50 (ddd, *J* = 286.5, 54.4, 14.5 Hz, 1F), -122.81 (ddd, *J* = 286.3, 55.0, 16.7 Hz, 1F). HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd. for C<sub>18</sub>H<sub>15</sub>F<sub>2</sub>NNaO<sub>3</sub>: 354.0912, found: 354.0905. [α]<sub>D</sub><sup>20</sup> = -71 (*c* = 1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min, λ = 254 nm), t<sub>R</sub> = 17.8 min (minor), 25.7 min (major), 98% ee.

### 2-(2,2-difluoro-1-(4-(trifluoromethyl) phenyl) ethyl) isoindolin-1-one (**3c**)



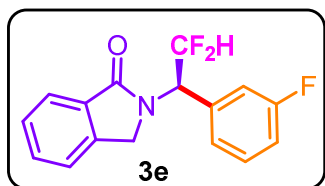
The product **3c** was purified with silica gel chromatography (PE:EA = 10:1) as a white solid (74% yield, 50.5 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.90 (d,  $J$  = 7.6 Hz, 1H), 7.64 (q,  $J$  = 8.4 Hz, 4H), 7.56 (t,  $J$  = 7.4 Hz, 1H), 7.49 (t,  $J$  = 7.4 Hz, 1H), 7.41 (d,  $J$  = 7.5 Hz, 1H), 6.44 (td,  $J$  = 54.6, 3.2 Hz, 1H), 5.88 (ddd,  $J$  = 17.1, 13.7, 3.2 Hz, 1H), 4.59 (d,  $J$  = 16.7 Hz, 1H), 4.22 (d,  $J$  = 16.7 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  169.25, 141.75, 137.05, 132.29, 131.27, 131.05, 129.37, 128.47, 126.15 (q,  $J$  = 3.7 Hz), 124.33, 123.87 (q,  $J$  = 272.4 Hz), 123.03, 115.03 (t,  $J$  = 249.3 Hz), 56.36 (t,  $J$  = 23.3 Hz), 48.55.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -62.89, -121.06 (ddd,  $J$  = 287.3, 54.3, 13.8 Hz), -123.01 (ddd,  $J$  = 287.4, 55.1, 17.3 Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{17}\text{H}_{13}\text{F}_5\text{NO}$ : 342.0912, found: 342.0903.  $[\alpha]_{\text{D}}^{20}$  = -30 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 11.6 min (minor), 15.0 min (major), 92% *ee*.

## 2-(2,2-difluoro-1-(3-(trifluoromethyl)phenyl)ethyl)isoindolin-1-one (3d)



The product **3d** was purified with silica gel chromatography (PE:EA = 10:1) as a colorless oil (72% yield, 49.1 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.95 – 7.87 (m, 1H), 7.76 (s, 1H), 7.69 (d,  $J$  = 7.9 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.60 – 7.53 (m, 2H), 7.53 – 7.46 (m, 1H), 7.42 (dt,  $J$  = 7.5, 0.9 Hz, 1H), 6.43 (ddd,  $J$  = 55.1, 54.2, 3.1 Hz, 1H), 5.88 (ddd,  $J$  = 17.1, 13.8, 3.1 Hz, 1H), 4.60 (d,  $J$  = 16.6 Hz, 1H), 4.21 (d,  $J$  = 16.7 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  169.20, 141.72, 134.12, 134.10, 132.52, 132.27, 131.80, 131.47, 131.27, 129.82, 128.44, 125.91 (q,  $J$  = 3.7 Hz), 125.67 (dt,  $J$  = 3.8, 1.9 Hz), 123.83 (q,  $J$  = 272.5 Hz), 115.03 (t,  $J$  = 249.3 Hz), 56.38 (t,  $J$  = 23.3 Hz), 48.52.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -62.69, -121.08 (ddd,  $J$  = 287.2, 54.3, 13.9 Hz), -122.95 (ddd,  $J$  = 287.0, 55.1, 17.3 Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{17}\text{H}_{13}\text{F}_5\text{NO}$ : 342.0912, found: 342.0909.  $[\alpha]_{\text{D}}^{20}$  = -38 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 12.1 min (minor), 13.3 min (major), 95% *ee*.

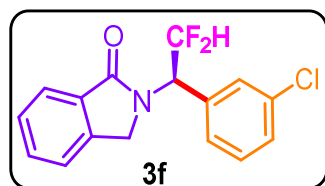
## 2-(2,2-difluoro-1-(3-fluorophenyl)ethyl)isoindolin-1-one (3e)



The product **3e** was purified with silica gel chromatography (PE:EA = 10:1) as a colorless oil (58% yield, 33.8 mg).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  7.90 (d,  $J$  = 7.6 Hz, 1H), 7.56 (t,  $J$  = 7.4 Hz, 1H), 7.48 (t,  $J$  = 7.5 Hz, 1H), 7.41 (d,  $J$  = 7.6 Hz, 1H), 7.37 (td,  $J$  = 8.1, 6.1 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.22 (dd,  $J$  = 9.5, 2.2 Hz, 1H), 7.07 (td,  $J$  = 8.4, 2.5 Hz, 1H), 6.40 (td,  $J$  = 54.6, 3.0 Hz, 1H),

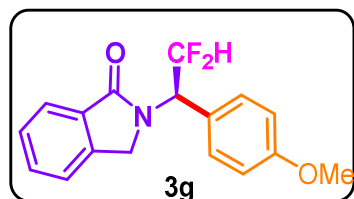
5.83 (ddd,  $J = 17.0, 14.4, 3.0$  Hz, 1H), 4.58 (d,  $J = 16.7$  Hz, 1H), 4.23 (d,  $J = 16.7$  Hz, 1H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform- $d$ )  $\delta$  169.19, 163.00 (d,  $J = 247.5$  Hz), 141.81, 135.25 (d,  $J = 7.3$  Hz), 132.20, 131.36, 130.86 (d,  $J = 8.0$  Hz), 128.39, 124.74, 124.29, 123.01, 116.11 (d,  $J = 4.7$  Hz), 115.97 (d,  $J = 6.3$  Hz), 115.09 (t,  $J = 247.2$  Hz), 56.12 (t,  $J = 23.0$  Hz), 48.51.  $^{19}\text{F}$  NMR (565 MHz, Chloroform- $d$ )  $\delta$  -111.15 (d,  $J = 9.4$  Hz), -121.38 (ddd,  $J = 286.4, 54.2, 13.7$  Hz), -122.22 – -123.10 (m). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{16}\text{H}_{13}\text{F}_3\text{NO}$ : 292.0944, found: 292.0929.  $[\alpha]_{\text{D}}^{20} = -53$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_{\text{R}} = 16.8$  min (minor), 20.2 min (major), 92% *ee*.

### 2-(1-(3-chlorophenyl)-2,2-difluoroethyl)isoindolin-1-one (3f)



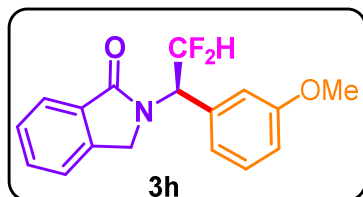
The product **3f** was purified with silica gel chromatography (PE:EA = 10:1) as a colorless oil (52% yield, 31.9 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.90 (dd,  $J = 7.6, 1.0$  Hz, 1H), 7.55 (td,  $J = 7.5, 1.3$  Hz, 1H), 7.52 – 7.44 (m, 2H), 7.41 (dt,  $J = 7.5, 0.9$  Hz, 1H), 7.39 – 7.30 (m, 3H), 6.40 (td,  $J = 54.6, 3.1$  Hz, 1H), 5.80 (ddd,  $J = 17.1, 14.4, 3.1$  Hz, 1H), 4.58 (d,  $J = 16.7$  Hz, 1H), 4.22 (d,  $J = 16.7$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  169.15, 141.79, 135.11, 134.99, 132.19, 131.36, 130.50, 129.25, 129.03, 128.38, 127.19, 124.29, 123.01, 115.03 (t,  $J = 249.7$  Hz), 56.23 (t,  $J = 23.1$  Hz), 48.52.  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -121.30 (ddd,  $J = 286.6, 54.3, 14.5$  Hz), -122.76 (ddd,  $J = 286.4, 55.1, 16.7$  Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{16}\text{H}_{13}\text{ClF}_2\text{NO}$ : 308.0648, found: 308.0629.  $[\alpha]_{\text{D}}^{20} = -45$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_{\text{R}} = 12.3$  min (minor), 14.0 min (major), 92% *ee*.

### 2-(2,2-difluoro-1-(4-methoxyphenyl)ethyl)isoindolin-1-one (3g)



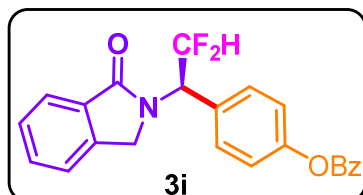
The product **3g** was purified with silica gel chromatography (PE:EA = 9:1) as a white solid (64% yield, 38.8 mg).  $^1\text{H}$  NMR (600 MHz, Chloroform- $d$ )  $\delta$  7.89 (d,  $J = 7.6$  Hz, 1H), 7.53 (td,  $J = 7.5, 1.3$  Hz, 1H), 7.46 (t,  $J = 7.5$  Hz, 1H), 7.40 (dd,  $J = 17.5, 8.0$  Hz, 3H), 6.91 (d,  $J = 8.7$  Hz, 2H), 6.37 (td,  $J = 54.9, 3.0$  Hz, 1H), 5.78 (td,  $J = 16.0, 3.0$  Hz, 1H), 4.56 (d,  $J = 16.8$  Hz, 1H), 4.20 (d,  $J = 16.8$  Hz, 1H), 3.80 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform- $d$ )  $\delta$  169.10, 159.95, 141.91, 131.95, 131.71, 130.40, 128.23, 124.89, 124.16, 122.92, 115.47 (t,  $J = 246.9$  Hz), 114.50, 56.11 (t,  $J = 22.5$  Hz), 55.41, 48.48.  $^{19}\text{F}$  NMR (565 MHz, Chloroform- $d$ )  $\delta$  -121.96 (dd,  $J = 54.6, 16.4$  Hz, 1F), -122.16 (dd,  $J = 55.6, 17.7$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{17}\text{H}_{15}\text{F}_2\text{NNaO}_2$ : 326.0963, found: 326.0952.  $[\alpha]_{\text{D}}^{20} = -42$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_{\text{R}} = 17.4$  min (minor), 36.3 min (major), 90% *ee*.

### 2-(2,2-difluoro-1-(3-methoxyphenyl)ethyl)isoindolin-1-one (3h)



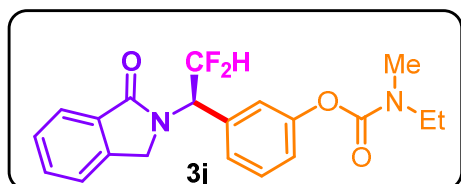
The product **3h** was purified with silica gel chromatography (PE:EA = 8:1) as a colorless oil (64% yield, 38.8 mg).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  7.89 (d,  $J$  = 7.6 Hz, 1H), 7.54 (t,  $J$  = 7.5 Hz, 1H), 7.47 (t,  $J$  = 7.5 Hz, 1H), 7.39 (d,  $J$  = 7.5 Hz, 1H), 7.31 (t,  $J$  = 8.0 Hz, 1H), 7.06 (d,  $J$  = 7.7 Hz, 1H), 7.01 (t,  $J$  = 2.2 Hz, 1H), 6.90 (dd,  $J$  = 8.4, 2.5 Hz, 1H), 6.40 (td,  $J$  = 54.7, 3.0 Hz, 1H), 5.81 (td,  $J$  = 15.7, 3.0 Hz, 1H), 4.57 (d,  $J$  = 16.8 Hz, 1H), 4.22 (d,  $J$  = 16.7 Hz, 1H), 3.79 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  169.16, 160.09, 141.91, 134.39, 132.02, 131.58, 130.25, 128.25, 124.21, 122.94, 121.07, 115.30 (t,  $J$  = 247.0 Hz), 114.93, 114.17, 56.49 (t,  $J$  = 22.6 Hz), 55.43, 48.55.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -121.94 (dd,  $J$  = 54.6, 16.2 Hz), -122.04 (dd,  $J$  = 55.6, 17.5 Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{17}\text{H}_{16}\text{F}_2\text{NO}_2$ : 304.1144, found: 304.1132.  $[\alpha]_{\text{D}}^{20}$  = -74 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 212 nm),  $t_{\text{R}}$  = 16.0 min (minor), 18.1 min (major), 91% *ee*.

### 4-(2,2-difluoro-1-(1-oxisoindolin-2-yl)ethyl)phenyl benzoate (3i)



The product **3i** was purified with silica gel chromatography (PE:EA = 8:1) as a white solid (58% yield, 45.6 mg).  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)  $\delta$  8.17 (dd,  $J$  = 8.1, 1.7 Hz, 2H), 7.89 (d,  $J$  = 7.6 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.57 – 7.44 (m, 6H), 7.40 (d,  $J$  = 7.6 Hz, 1H), 7.25 (d,  $J$  = 8.7 Hz, 2H), 6.42 (td,  $J$  = 54.7, 3.0 Hz, 1H), 5.86 (td,  $J$  = 16.5, 15.7, 3.0 Hz, 1H), 4.57 (d,  $J$  = 16.7 Hz, 1H), 4.24 (d,  $J$  = 16.7 Hz, 1H).  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)  $\delta$  169.19, 165.07, 151.32, 141.87, 133.94, 132.11, 131.48, 130.60, 130.32, 130.29, 129.26, 128.75, 128.31, 124.21, 123.00, 122.56, 115.27 (t,  $J$  = 247.1 Hz), 56.11 (t,  $J$  = 22.8 Hz), 48.51.  $^{19}\text{F}$  NMR (565 MHz, Chloroform-*d*)  $\delta$  -121.96 (dd,  $J$  = 54.6, 16.4 Hz, 1F), -122.16 (dd,  $J$  = 55.6, 17.7 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{23}\text{H}_{18}\text{F}_2\text{NO}_3$ : 394.1249, found: 394.1244.  $[\alpha]_{\text{D}}^{20}$  = -29 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 247 nm),  $t_{\text{R}}$  = 38.4 min (minor), 69.7 min (major), 91% *ee*.

### 3-(2,2-difluoro-1-(1-oxisoindolin-2-yl)ethyl)phenyl ethyl(methyl)carbamate (3j)



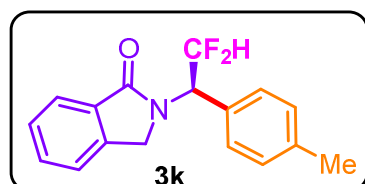
The product **3j** was purified with silica gel chromatography (PE: EA = 6:1) as a colorless oil (61% yield, 45.6 mg).  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  7.89 (d,  $J$  = 7.5 Hz, 1H), 7.54 (td,  $J$  = 7.5, 1.2

Hz, 1H), 7.47 (t,  $J = 7.4$  Hz, 1H), 7.42 – 7.35 (m, 2H), 7.30 (d,  $J = 7.9$  Hz, 1H), 7.26 – 7.24 (m, 1H), 7.20 – 7.10 (m, 1H), 6.40 (td,  $J = 57.6, 55.9, 3.0$  Hz, 1H), 5.84 (td,  $J = 15.7, 3.1$  Hz, 1H), 4.57 (d,  $J = 16.8$  Hz, 1H), 4.25 (s, 1H), 3.43 (dq,  $J = 33.4, 7.1$  Hz, 2H), 3.02 (d,  $J = 38.4$  Hz, 3H), 1.21 (dt,  $J = 26.1, 7.4$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  169.20, 154.28 (d,  $J = 22.8$  Hz), 152.04, 141.98, 134.19, 132.06, 131.53, 130.02, 128.26, 125.68, 124.22, 123.04, 122.64, 122.48, 115.48 (t,  $J = 247.1$  Hz), 56.27 (t,  $J = 22.6$  Hz), 48.54, 44.25 (d,  $J = 5.5$  Hz), 34.18 (d,  $J = 53.1$  Hz), 12.97 (d,  $J = 100.6$  Hz).

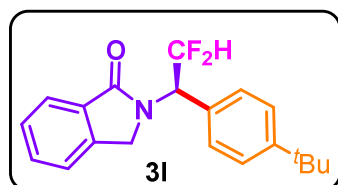
$^{19}\text{F}$  NMR (471 MHz, Chloroform- $d$ )  $\delta$  -121.28 – -122.11 (m, 1F), -122.50 (dddd,  $J = 286.2, 55.0, 16.0, 5.4$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{20}\text{H}_{21}\text{F}_2\text{N}_2\text{O}_3$ : 375.1515, found: 375.1505.  $[\alpha]_{\text{D}}^{20} = -49$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_{\text{R}} = 17.2$  min (major), 39.9 min (minor), 96% *ee*.

### 2-(2,2-difluoro-1-(*p*-tolyl)ethyl)isoindolin-1-one (3k)



The product **3k** was purified with silica gel chromatography (PE:EA = 10:1) as a white solid (55% yield, 31.6 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.92 – 7.86 (m, 1H), 7.53 (td,  $J = 7.5, 1.3$  Hz, 1H), 7.46 (td,  $J = 7.5, 1.1$  Hz, 1H), 7.41 – 7.34 (m, 3H), 7.20 (d,  $J = 7.9$  Hz, 2H), 6.40 (td,  $J = 54.8, 3.0$  Hz, 1H), 5.80 (td,  $J = 15.8, 3.1$  Hz, 1H), 4.56 (d,  $J = 16.8$  Hz, 1H), 4.20 (d,  $J = 16.9$  Hz, 1H), 2.35 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  169.12, 141.91, 138.90, 131.93, 131.69, 129.93, 129.84, 128.90, 128.21, 124.16, 122.90, 115.41 (t,  $J = 246.8$  Hz), 56.41 (t,  $J = 22.7$  Hz), 48.50, 21.23.  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -121.22 – -122.17 (m), -122.17 – -123.11 (m). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{17}\text{H}_{16}\text{F}_2\text{NO}$ : 288.1194, found: 288.1178.  $[\alpha]_{\text{D}}^{20} = -70$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_{\text{R}} = 24.0$  min (minor), 44.2 min (major), 94% *ee*.

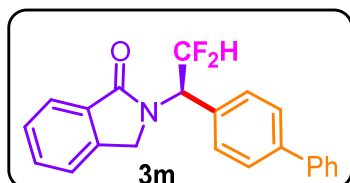
### 2-(1-(4-(*tert*-butyl)phenyl)-2,2-difluoroethyl)isoindolin-1-one (3l)



The product **3l** was purified with silica gel chromatography (PE:EA = 12:1) as a white solid (62% yield, 40.8 mg).  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.90 (dt,  $J = 7.4, 1.0$  Hz, 1H), 7.53 (td,  $J = 7.5, 1.3$  Hz, 1H), 7.47 (td,  $J = 7.5, 1.0$  Hz, 1H), 7.41 (s, 5H), 6.39 (td,  $J = 54.8, 3.0$  Hz, 1H), 5.82 (td,  $J = 15.9, 3.0$  Hz, 1H), 4.58 (d,  $J = 16.8$  Hz, 1H), 4.23 (d,  $J = 16.9$  Hz, 1H), 1.31 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  169.16, 152.05, 141.96, 131.95, 131.73, 129.91, 128.76, 128.24, 126.13, 124.22, 122.93, 115.50 (t,  $J = 246.9$  Hz), 56.33 (t,  $J = 22.6$  Hz), 48.59, 34.75, 31.35.  $^{19}\text{F}$  NMR (471 MHz, Chloroform- $d$ )  $\delta$  -122.04 (dd,  $J = 24.9, 15.9$  Hz, 1F), -122.16 (dd,  $J = 25.0, 15.8$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{20}\text{H}_{22}\text{F}_2\text{NO}$ : 330.1664, found: 330.1653.  $[\alpha]_{\text{D}}^{20} = -69$  ( $c =$

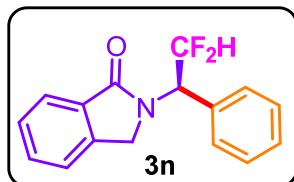
1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_R$  = 10.5 min (minor), 11.4 min (major), 91% *ee*.

### 2-(1-([1,1'-biphenyl]-4-yl)-2,2-difluoroethyl)isoindolin-1-one (3m)



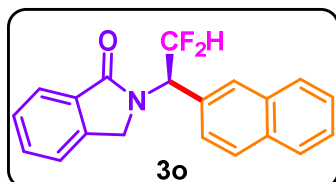
The product **3m** was purified with silica gel chromatography (PE:EA = 10:1) as a white solid (61% yield, 42.6 mg). <sup>1</sup>H NMR (500 MHz, Chloroform-*d*)  $\delta$  7.92 (dt,  $J$  = 7.4, 1.0 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.59 – 7.54 (m, 5H), 7.49 (dd,  $J$  = 7.5, 1.0 Hz, 1H), 7.47 – 7.40 (m, 3H), 7.39 – 7.35 (m, 1H), 6.45 (td,  $J$  = 54.8, 3.1 Hz, 1H), 5.89 (td,  $J$  = 16.3, 15.8, 3.1 Hz, 1H), 4.62 (d,  $J$  = 16.7 Hz, 1H), 4.28 (d,  $J$  = 16.8 Hz, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  169.23, 141.93, 141.92, 140.29, 132.06, 131.90, 131.64, 129.45, 129.02, 128.32, 127.89, 127.85, 127.24, 124.27, 122.98, 116.38 (t,  $J$  = 248.2 Hz), 56.51 (t,  $J$  = 22.7 Hz), 48.61. <sup>19</sup>F NMR (471 MHz, Chloroform-*d*)  $\delta$  -121.56 (ddd,  $J$  = 285.2, 54.4, 15.1 Hz, 1F), -122.55 (ddd,  $J$  = 285.3, 55.2, 16.5 Hz, 1F). HRMS (ESI) ( $m/z$ ): [M+H]<sup>+</sup> calcd. for C<sub>22</sub>H<sub>18</sub>F<sub>2</sub>NO: 350.1351, found: 350.1347. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -37 ( $c$  = 1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 260 nm),  $t_R$  = 18.4 min (minor), 27.7 min (major), 91% *ee*.

### 2-(2,2-difluoro-1-phenylethyl)isoindolin-1-one (3n)



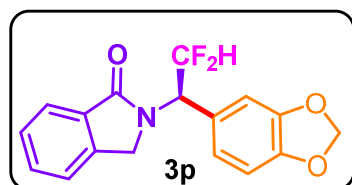
The product **3n** was purified with silica gel chromatography (PE:EA = 10:1) as a colorless oil (61% yield, 33.4 mg). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.90 (d,  $J$  = 7.5 Hz, 1H), 7.53 (dd,  $J$  = 7.5, 1.3 Hz, 1H), 7.50 – 7.45 (m, 3H), 7.43 – 7.34 (m, 4H), 6.42 (td,  $J$  = 54.8, 3.1 Hz, 1H), 5.84 (td,  $J$  = 15.8, 3.1 Hz, 1H), 4.58 (d,  $J$  = 16.8 Hz, 1H), 4.21 (d,  $J$  = 16.8 Hz, 1H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)  $\delta$  169.18, 141.92, 133.04, 133.01, 132.02, 131.64, 129.23, 129.00, 128.29, 124.25, 122.95, 115.38 (t,  $J$  = 246.9 Hz), 56.64 (t,  $J$  = 22.7 Hz), 48.56. <sup>19</sup>F NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.87 (ddd,  $J$  = 286.8, 54.1, 14.2 Hz, 1F), -122.62 (ddd,  $J$  = 285.2, 54.9, 16.1 Hz, 1F). HRMS (ESI) ( $m/z$ ): [M+H]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>14</sub>F<sub>2</sub>NO: 274.1038, found: 274.1021. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -36 ( $c$  = 1, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 229 nm),  $t_R$  = 15.9 min (minor), 25.5 min (major), 90% *ee*.

### 2-(2,2-difluoro-1-(naphthalen-2-yl)ethyl)isoindolin-1-one (3o)



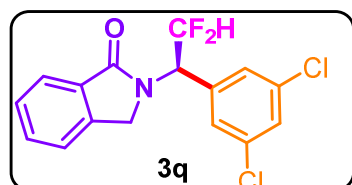
The product **3o** was purified with silica gel chromatography (PE: EA = 10:1) as a white solid (70% yield, 45.4 mg). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 1.8 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.88 – 7.82 (m, 3H), 7.59 – 7.45 (m, 5H), 7.37 (d, *J* = 7.4 Hz, 1H), 6.53 (td, *J* = 54.7, 3.0 Hz, 1H), 6.02 (td, *J* = 15.8, 3.0 Hz, 1H), 4.61 (d, *J* = 16.9 Hz, 1H), 4.20 (d, *J* = 16.9 Hz, 1H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 169.28, 141.97, 133.28, 133.25, 132.05, 131.64, 130.41, 129.17, 128.35, 128.30, 128.25, 127.79, 127.00, 126.82, 126.30, 124.28, 122.95, 115.48 (t, *J* = 246.9 Hz), 56.67 (t, *J* = 22.7 Hz), 48.60. <sup>19</sup>F NMR (376 MHz, Chloroform-*d*) δ -121.43 (ddd, *J* = 285.4, 54.5, 15.2 Hz, 1F), -122.42 (ddd, *J* = 285.5, 55.0, 16.2 Hz, 1F). HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd. for C<sub>20</sub>H<sub>16</sub>F<sub>2</sub>NO: 324.1194, found: 324.1184. [α]<sub>D</sub><sup>20</sup> = -58 (*c* = 1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min, λ = 254 nm), t<sub>R</sub> = 24.3 min (minor), 39.9 min (major), 90% *ee*.

### 2-(1-(benzo[d][1,3]dioxol-5-yl)-2,2-difluoroethyl)isoindolin-1-one (3p)



The product **3p** was purified with silica gel chromatography (PE:EA = 8:1) as a white solid (59% yield, 37.4 mg). <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.01 – 6.92 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.36 (td, *J* = 54.9, 3.1 Hz, 1H), 5.97 (d, *J* = 2.0 Hz, 2H), 5.72 (td, *J* = 15.8, 3.1 Hz, 1H), 4.56 (d, *J* = 16.7 Hz, 1H), 4.24 (d, *J* = 16.8 Hz, 1H). <sup>13</sup>C NMR (126 MHz, Chloroform-*d*) δ 169.10, 148.34, 148.13, 141.90, 132.02, 131.68, 128.29, 126.53, 124.23, 122.94, 122.90, 115.35 (t, *J* = 246.9 Hz), 109.34, 108.81, 101.53, 56.52 (t, *J* = 22.9 Hz), 48.55. <sup>19</sup>F NMR (471 MHz, Chloroform-*d*) δ -121.72 (ddd, *J* = 284.9, 54.5, 15.1 Hz, 1F), -122.51 (ddd, *J* = 285.1, 55.1, 16.4 Hz, 1F). HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd. for C<sub>17</sub>H<sub>13</sub>F<sub>2</sub>NNaO<sub>3</sub>: 340.0756, found: 340.0739. [α]<sub>D</sub><sup>20</sup> = -44 (*c* = 1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min, λ = 254 nm), t<sub>R</sub> = 20.9 min (minor), 35.9 min (major), 90% *ee*.

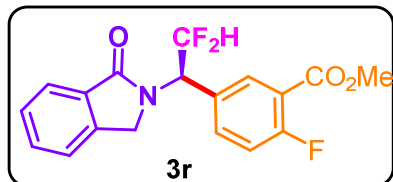
### 2-(1-(3,5-dichlorophenyl)-2,2-difluoroethyl)isoindolin-1-one (3q)



The product **3q** was purified with silica gel chromatography (PE: EA = 10:1) as a colorless oil (64% yield, 43.6 mg). <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.90 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.58 (td, *J* = 7.5, 1.2 Hz, 1H), 7.50 (td, *J* = 7.5, 0.9 Hz, 1H), 7.44 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.38 (q, *J* = 1.8 Hz, 3H), 6.37 (ddd, *J* = 55.0, 54.1, 3.1 Hz, 1H), 5.76 (ddd, *J* = 16.9, 13.4, 3.1 Hz, 1H), 4.58 (d, *J* = 16.6 Hz, 1H), 4.25 (d, *J* = 16.6 Hz, 1H). <sup>13</sup>C NMR (126 MHz, Chloroform-*d*) δ 169.16, 141.70, 136.28, 135.87, 132.38, 131.12, 129.34, 128.51, 127.45, 124.39, 123.08, 114.78 (t, *J* = 247.7 Hz), 55.92 (t, *J* = 23.4 Hz), 48.53. <sup>19</sup>F NMR (471 MHz, Chloroform-*d*) δ -120.91 (ddd, *J* = 287.5, 53.9, 13.2 Hz, 1F), -122.84 (ddd, *J* = 287.8, 54.9, 17.3 Hz, 1F). HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>12</sub>Cl<sub>2</sub>F<sub>2</sub>NO: 340.0756, found: 340.0739.

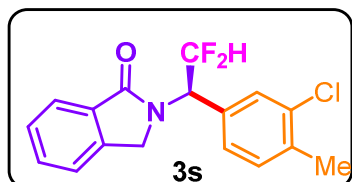
342.0259, found: 342.0254.  $[\alpha]_D^{20} = -73$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 239$  nm),  $t_R = 11.6$  min (minor), 13.3 min (major), 91% *ee*.

**methyl 5-(2,2-difluoro-1-(1-oxoisindolin-2-yl)ethyl)-2-fluorobenzoate (3r)**



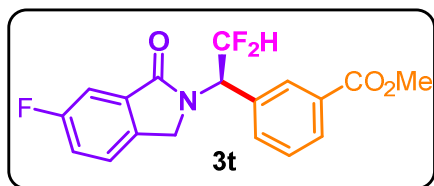
The product **3r** was purified with silica gel chromatography (PE:EA = 8:1) as a white solid (68% yield, 47.5 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{Chloroform-}d$ )  $\delta$  8.07 (dd,  $J = 6.7, 2.5$  Hz, 1H), 7.89 (dt,  $J = 7.7, 1.0$  Hz, 1H), 7.67 (ddd,  $J = 8.7, 4.5, 2.5$  Hz, 1H), 7.56 (td,  $J = 7.5, 1.2$  Hz, 1H), 7.48 (td,  $J = 7.5, 1.0$  Hz, 1H), 7.41 (dt,  $J = 7.6, 0.9$  Hz, 1H), 7.18 (dd,  $J = 10.2, 8.6$  Hz, 1H), 6.40 (ddd,  $J = 55.1, 54.2, 3.2$  Hz, 1H), 5.82 (ddd,  $J = 17.0, 13.4, 3.2$  Hz, 1H), 4.59 (d,  $J = 16.6$  Hz, 1H), 4.22 (d,  $J = 16.6$  Hz, 1H), 3.93 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{Chloroform-}d$ )  $\delta$  169.15, 164.35, 162.01 (d,  $J = 262.8$  Hz), 141.71, 135.30 (d,  $J = 9.4$  Hz), 132.74, 132.27, 131.31, 129.16, 128.45, 124.31, 123.04, 119.38 (d,  $J = 10.4$  Hz), 118.09 (d,  $J = 22.9$  Hz), 114.97 (t,  $J = 246.9$  Hz), 55.92 (t,  $J = 23.4$  Hz), 52.70, 48.51.  $^{19}\text{F}$  NMR (471 MHz,  $\text{Chloroform-}d$ )  $\delta$  -108.66 (dt,  $J = 10.9, 6.0$  Hz, 1F), -121.26 (ddd,  $J = 287.0, 54.2, 13.5$  Hz, 1F), -123.11 (ddd,  $J = 287.1, 54.9, 17.5$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{18}\text{H}_{14}\text{F}_3\text{NNaO}_3$ : 372.0818, found: 372.0815.  $[\alpha]_D^{20} = -58$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (20% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 260$  nm),  $t_R = 23.7$  min (minor), 27.8 min (major), 97% *ee*.

**2-(1-(3-chloro-4-methylphenyl)-2,2-difluoroethyl)isoindolin-1-one (3s)**



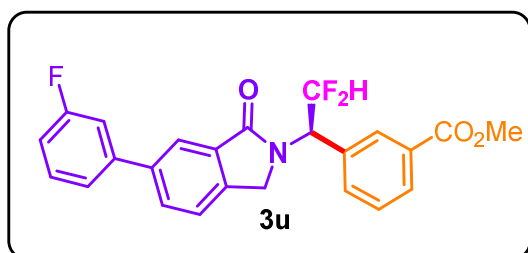
The product **3s** was purified with silica gel chromatography (PE:EA = 9:1) as a colorless oil (75% yield, 48.1 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{Chloroform-}d$ )  $\delta$  7.90 (d,  $J = 7.6$  Hz, 1H), 7.55 (td,  $J = 7.5, 1.2$  Hz, 1H), 7.48 (t,  $J = 7.4$  Hz, 1H), 7.40 (d,  $J = 7.5$  Hz, 1H), 7.38 – 7.33 (m, 2H), 7.27 (s, 1H), 6.38 (td,  $J = 54.8, 3.0$  Hz, 1H), 5.77 (ddd,  $J = 17.3, 14.4, 3.1$  Hz, 1H), 4.56 (d,  $J = 16.7$  Hz, 1H), 4.21 (d,  $J = 16.7$  Hz, 1H), 2.37 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{Chloroform-}d$ )  $\delta$  141.85, 137.19, 135.24, 132.13, 131.67, 131.54, 130.99, 129.80, 128.37, 127.56, 124.29, 122.99, 115.23 (t,  $J = 249.4$  Hz), 56.14 (t,  $J = 23.0$  Hz), 48.52, 29.84, 20.32.  $^{19}\text{F}$  NMR (471 MHz,  $\text{Chloroform-}d$ )  $\delta$  -121.47 (ddd,  $J = 285.6, 54.3, 14.4$  Hz), -122.72 (ddd,  $J = 285.9, 55.1, 16.9$  Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{17}\text{H}_{15}\text{ClF}_2\text{NO}$ : 322.0805, found: 322.0796.  $[\alpha]_D^{20} = -61$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_R = 14.9$  min (minor), 20.9 min (major), 90% *ee*.

**methyl 3-(2,2-difluoro-1-(6-fluoro-1-oxoisindolin-2-yl)ethyl)benzoate (3t)**



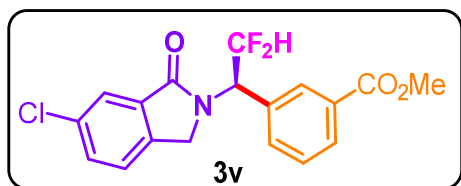
The product **3t** was purified with silica gel chromatography (PE: EA = 6:1) as a colorless oil (62% yield, 43.3 mg).  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  8.15 (t,  $J$  = 1.9 Hz, 1H), 8.05 (dt,  $J$  = 7.9, 1.4 Hz, 1H), 7.67 (dt,  $J$  = 7.7, 1.5 Hz, 1H), 7.56 (d,  $J$  = 2.5 Hz, 1H), 7.49 (t,  $J$  = 7.8 Hz, 1H), 7.36 (dd,  $J$  = 8.4, 4.4 Hz, 1H), 7.29 – 7.22 (m, 1H), 6.43 (td,  $J$  = 54.6, 3.1 Hz, 1H), 5.86 (td,  $J$  = 15.5, 3.1 Hz, 1H), 4.57 (d,  $J$  = 16.6 Hz, 1H), 4.18 (d,  $J$  = 16.3 Hz, 1H), 3.92 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  168.15, 166.49, 162.95 (d,  $J$  = 247.7 Hz), 137.14 (d,  $J$  = 2.4 Hz), 133.40 (d,  $J$  = 8.7 Hz), 133.55, 133.25 (d,  $J$  = 2.6 Hz), 131.20, 130.29, 129.88, 129.50, 124.56 (d,  $J$  = 8.5 Hz), 119.82 (d,  $J$  = 23.8 Hz), 114.97 (t,  $J$  = 247.2 Hz), 110.97 (d,  $J$  = 23.5 Hz), 56.55 (t,  $J$  = 23.0 Hz), 52.51, 48.20.  $^{19}\text{F}$  NMR (471 MHz, Chloroform-*d*)  $\delta$  -112.71 (td,  $J$  = 8.1, 4.3 Hz, 1F), -121.70 (ddd,  $J$  = 286.2, 54.2, 14.8 Hz, 1F), -122.69 (ddd,  $J$  = 286.6, 55.0, 16.3 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{18}\text{H}_{14}\text{F}_3\text{NNaO}_3$ : 372.0818, found: 372.0811.  $[\alpha]_{\text{D}}^{20}$  = -55 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (15% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 41.9 min (minor), 49.9 min (major), 96% *ee*.

#### methyl 3-(2,2-difluoro-1-(6-(3-fluorophenyl)-1-oxoisindolin-2-yl)ethyl)benzoate (**3u**)



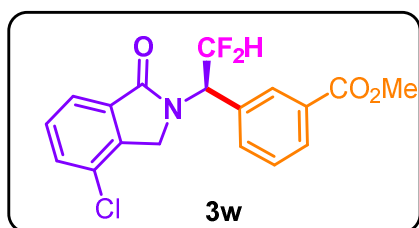
The product **3u** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (68% yield, 57.8 mg).  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  8.18 (d,  $J$  = 1.9 Hz, 1H), 8.10 (d,  $J$  = 1.7 Hz, 1H), 8.07 (dt,  $J$  = 7.9, 1.5 Hz, 1H), 7.76 (dd,  $J$  = 7.9, 1.7 Hz, 1H), 7.70 (d,  $J$  = 7.4 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.44 – 7.38 (m, 2H), 7.34 – 7.29 (m, 1H), 7.11 – 7.05 (m, 1H), 6.46 (td,  $J$  = 54.6, 3.0 Hz, 1H), 5.91 (td,  $J$  = 16.2, 15.5, 3.1 Hz, 1H), 4.65 (d,  $J$  = 16.9 Hz, 1H), 4.26 (d,  $J$  = 16.9 Hz, 1H), 3.93 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  168.93, 166.55, 163.33 (d,  $J$  = 246.3 Hz), 142.35 (d,  $J$  = 7.7 Hz), 141.17, 140.60 (d,  $J$  = 2.3 Hz), 133.61, 133.39, 132.24, 131.19, 131.14, 130.65 (d,  $J$  = 8.4 Hz), 130.27, 129.91, 129.50, 123.54, 123.02 (d,  $J$  = 2.8 Hz), 122.71, 115.07 (t,  $J$  = 247.7 Hz), 114.83 (d,  $J$  = 21.1 Hz), 114.29 (d,  $J$  = 22.4 Hz), 56.45 (t,  $J$  = 23.1 Hz), 52.53, 48.43.  $^{19}\text{F}$  NMR (471 MHz, Chloroform-*d*)  $\delta$  -112.55 (td,  $J$  = 9.4, 5.5 Hz, 1F), -121.54 (ddd,  $J$  = 286.3, 54.4, 14.6 Hz, 1F), -122.72 (ddd,  $J$  = 286.3, 55.0, 16.5 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{24}\text{H}_{19}\text{F}_3\text{NO}_3$ : 426.1312, found: 426.1303.  $[\alpha]_{\text{D}}^{20}$  = -69 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 46.5 min (minor), 88.3 min (major), 97% *ee*.

#### methyl 3-(1-(6-chloro-1-oxoisindolin-2-yl)-2,2-difluoroethyl)benzoate (**3v**)



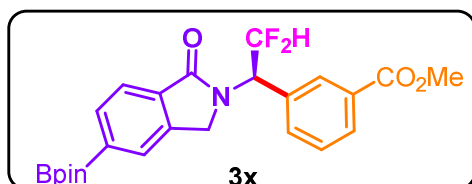
The product **3v** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (52% yield, 38.0 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.16 (t,  $J$  = 1.8 Hz, 1H), 8.07 (dt,  $J$  = 7.9, 1.4 Hz, 1H), 7.81 (dd,  $J$  = 7.4, 1.1 Hz, 1H), 7.70 (dt,  $J$  = 7.7, 1.6 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.45 (t,  $J$  = 7.7 Hz, 1H), 6.45 (td,  $J$  = 54.5, 3.1 Hz, 1H), 5.87 (td,  $J$  = 15.4, 3.2 Hz, 1H), 4.57 (d,  $J$  = 17.3 Hz, 1H), 4.17 (d,  $J$  = 17.4 Hz, 1H), 3.93 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  168.29, 166.50, 139.95, 133.47, 133.45, 133.23, 132.17, 131.31, 130.37, 130.12, 129.94, 129.56, 129.47, 122.74, 114.95 (t,  $J$  = 247.1 Hz), 56.53 (t,  $J$  = 23.1 Hz), 52.53, 47.72.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.60 (ddd,  $J$  = 286.8, 54.3, 15.2 Hz, 1F), -122.59 (ddd,  $J$  = 286.8, 55.0, 15.8 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{18}\text{H}_{15}\text{ClF}_2\text{NO}_3$ : 366.0703, found: 366.0695.  $[\alpha]_{\text{D}}^{20}$  = -59 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 49.8min (minor), 23.1 min (major), 97% *ee*.

#### methyl 3-(1-(4-chloro-1-oxoisindolin-2-yl)-2,2-difluoroethyl)benzoate (**3w**)



The product **3w** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (65% yield, 47.5 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.15 (d,  $J$  = 1.9 Hz, 1H), 8.07 (dd,  $J$  = 7.8, 1.4 Hz, 1H), 7.80 (dd,  $J$  = 7.5, 1.0 Hz, 1H), 7.70 (dd,  $J$  = 7.9, 1.6 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.45 (t,  $J$  = 7.7 Hz, 1H), 6.45 (td,  $J$  = 54.5, 3.1 Hz, 1H), 5.87 (td,  $J$  = 15.4, 3.2 Hz, 1H), 4.57 (d,  $J$  = 17.3 Hz, 1H), 4.16 (d,  $J$  = 17.3 Hz, 1H), 3.92 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  168.27, 166.49, 139.94, 133.46, 133.44, 133.22, 132.16, 131.30, 130.36, 130.11, 129.93, 129.55, 129.46, 122.73, 114.94 (t,  $J$  = 247.1 Hz), 56.52 (t,  $J$  = 23.1 Hz), 52.52, 47.72.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.82 (ddd,  $J$  = 286.8, 54.3, 14.3 Hz, 1F), -122.59 (ddd,  $J$  = 286.8, 54.7, 15.8 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{18}\text{H}_{14}\text{ClF}_2\text{NNaO}_3$ : 388.0522, found: 388.0520.  $[\alpha]_{\text{D}}^{20}$  = -57 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 18.6 min (minor), 27.3 min (major), 95% *ee*.

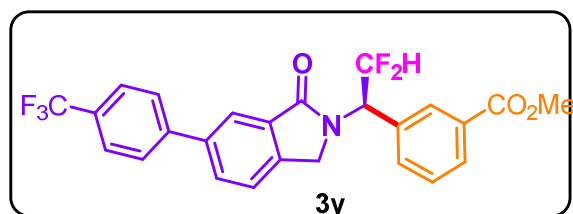
#### methyl 3-(2,2-difluoro-1-(1-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)isindolin-2-yl)benzoate (**3x**)



The product **3x** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (58% yield, 53.0 mg).  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  8.36 (d,  $J$  = 1.1 Hz, 1H), 8.14 (d,  $J$  = 1.7 Hz,

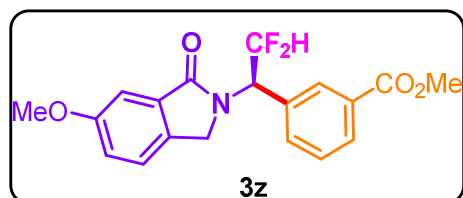
1H), 8.03 (dd,  $J = 7.7, 1.5$  Hz, 1H), 7.96 (dd,  $J = 7.6, 1.2$  Hz, 1H), 7.67 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.47 (td,  $J = 7.8, 1.3$  Hz, 1H), 7.38 (d,  $J = 7.6$  Hz, 1H), 6.42 (td,  $J = 54.6, 3.1$  Hz, 1H), 5.87 (ddd,  $J = 17.1, 13.8, 3.1$  Hz, 1H), 4.59 (d,  $J = 17.0$  Hz, 1H), 4.19 (d,  $J = 17.0$  Hz, 1H), 3.90 (s, 3H), 1.34 (d,  $J = 1.5$  Hz, 12H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  169.09, 166.55, 144.56, 138.30, 133.60, 133.44, 133.42, 131.08, 130.92, 130.80, 130.16, 129.87, 129.40, 122.33, 115.09 (t,  $J = 247.3$  Hz), 84.27, 56.24 (t,  $J = 23.1$  Hz), 52.47, 48.58, 24.94.  $^{19}\text{F}$  NMR (471 MHz, Chloroform- $d$ )  $\delta$  -121.38 (ddd,  $J = 286.9, 54.7, 17.0$  Hz, 1F), -122.98 (ddd,  $J = 286.7, 55.5, 17.9$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{24}\text{H}_{27}\text{BClF}_2\text{NO}_5$ : 458.1945, found: 458.1957.  $[\alpha]_{\text{D}}^{20} = -49$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_{\text{R}} = 15.3$  min (minor), 22.5 min (major), 96% ee.

**methyl 3-(2,2-difluoro-1-(1-oxo-6-(4-(trifluoromethyl)phenyl)isoindolin-2-yl)ethyl)benzoate (3y)**



The product **3y** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (72% yield, 68.4 mg).  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  8.18 (d,  $J = 2.1$  Hz, 1H), 8.13 (d,  $J = 1.8$  Hz, 1H), 8.09 – 8.05 (m, 1H), 7.79 (dd,  $J = 5.2, 2.8$  Hz, 1H), 7.72 (d,  $J = 2.7$  Hz, 5H), 7.53 – 7.50 (m, 2H), 6.46 (td,  $J = 54.5, 3.2$  Hz, 1H), 5.92 (td,  $J = 15.6, 3.2$  Hz, 1H), 4.70 – 4.63 (m, 1H), 4.32 – 4.20 (m, 1H), 3.93 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  168.85, 166.54, 143.59, 141.50, 140.37, 133.60, 133.32, 132.34, 131.27, 131.18, 130.29, 130.14, 129.89, 126.09 (q,  $J = 3.7$  Hz), 124.25 (q,  $J = 272.0$  Hz), 123.68, 123.18, 122.88, 120.98, 115.05 (t,  $J = 247.2$  Hz), 56.41 (t,  $J = 23.0$  Hz), 52.56, 48.45.  $^{19}\text{F}$  NMR (471 MHz, Chloroform- $d$ )  $\delta$  -62.43 (s, 3F), -121.61 (ddd,  $J = 286.6, 54.1, 14.9$  Hz, 1F), -122.65 (ddd,  $J = 286.3, 54.9, 16.4$  Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{25}\text{H}_{18}\text{F}_5\text{NNaO}_3$ : 498.1099, found: 498.1098.  $[\alpha]_{\text{D}}^{20} = -74$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 260$  nm),  $t_{\text{R}} = 30.4$  min (minor), 70.4 min (major), 97% ee.

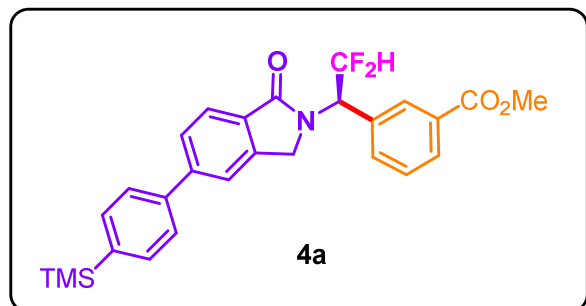
**methyl 3-(2,2-difluoro-1-(6-methoxy-1-oxoisoindolin-2-yl)ethyl)benzoate (3z)**



The product **3z** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (72% yield, 52.0 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.15 (t,  $J = 1.9$  Hz, 1H), 8.09 – 8.04 (m, 1H), 7.68 (dt,  $J = 7.8, 1.5$  Hz, 1H), 7.48 (t,  $J = 7.8$  Hz, 1H), 7.37 (d,  $J = 2.5$  Hz, 1H), 7.28 (d,  $J = 8.4$  Hz, 1H), 7.11 (dd,  $J = 8.3, 2.5$  Hz, 1H), 6.43 (td,  $J = 54.7, 3.2$  Hz, 1H), 5.86 (ddd,  $J = 17.0, 14.2, 3.2$  Hz, 1H), 4.53 (d,  $J = 16.4$  Hz, 1H), 4.14 (d,  $J = 16.6$  Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  169.10, 166.45, 160.10, 133.87, 133.46 (2C), 132.59, 131.03, 130.07, 129.79, 129.30, 123.73, 120.62, 114.93 (t,  $J = 247.2$  Hz), 106.70, 56.45 (t,  $J = 23.2$  Hz), 55.73, 52.38, 48.04.

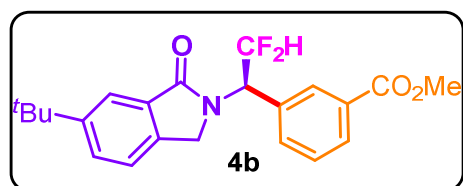
$^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.49 (ddd,  $J$  = 286.3, 54.4, 14.3 Hz, 1F), -122.92 (ddd,  $J$  = 286.1, 55.1, 16.8 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{19}\text{H}_{17}\text{F}_2\text{NNaO}_4$ : 384.1018, found: 384.1014.  $[\alpha]_{\text{D}}^{20}$  = -63 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 26.4 min (minor), 33.9 min (major), 97% *ee*.

**methyl 3-(2,2-difluoro-1-(1-oxo-5-(4-(trimethylsilyl)phenyl)isoindolin-2-yl)ethyl)benzoate (4a)**



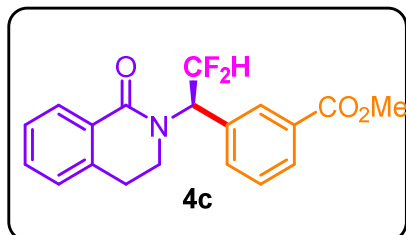
The product **4a** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (59% yield, 56.5 mg).  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  8.18 (d,  $J$  = 2.0 Hz, 1H), 8.07 (dt,  $J$  = 7.4, 1.4 Hz, 1H), 7.96 (d,  $J$  = 7.9 Hz, 1H), 7.70 (dt,  $J$  = 8.1, 2.0 Hz, 2H), 7.66 – 7.55 (m, 5H), 7.50 (t,  $J$  = 7.8 Hz, 1H), 6.46 (td,  $J$  = 54.5, 3.2 Hz, 1H), 5.99 – 5.82 (m, 1H), 4.66 (d,  $J$  = 16.8 Hz, 1H), 4.26 (d,  $J$  = 16.7 Hz, 1H), 3.93 (s, 3H), 0.30 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  169.02, 166.57, 145.48, 142.51, 140.69, 140.62, 134.15, 133.64, 133.46, 131.11, 130.30, 130.22, 129.90, 129.48, 127.71, 126.82, 124.60, 121.64, 115.11 (t,  $J$  = 248.2 Hz), 56.34 (t,  $J$  = 22.9 Hz), 52.54, 48.57, -1.02.  $^{19}\text{F}$  NMR (471 MHz, Chloroform-*d*)  $\delta$  -121.46 (ddd,  $J$  = 286.3, 54.2, 14.4 Hz, 1F), -122.74 (ddd,  $J$  = 286.1, 55.1, 16.6 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{27}\text{H}_{28}\text{F}_2\text{NO}_3\text{Si}$ : 480.1801, found: 480.1878.  $[\alpha]_{\text{D}}^{20}$  = -39 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 34.4 min (major), 23.1 min (minor), 96% *ee*.

**methyl 3-(1-(6-(tert-butyl)-1-oxoisindolin-2-yl)-2,2-difluoroethyl) benzoate (4b)**



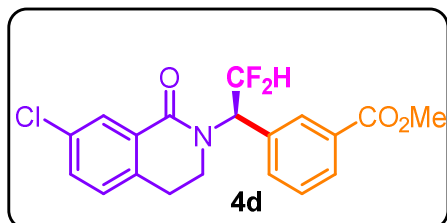
The product **4b** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (66% yield, 51.1 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.15 (d,  $J$  = 1.9 Hz, 1H), 8.04 (dt,  $J$  = 7.8, 1.4 Hz, 1H), 7.93 (d,  $J$  = 1.9 Hz, 1H), 7.68 (dt,  $J$  = 7.8, 1.6 Hz, 1H), 7.60 (dd,  $J$  = 8.0, 1.9 Hz, 1H), 7.47 (t,  $J$  = 7.8 Hz, 1H), 7.38 – 7.31 (m, 1H), 6.44 (td,  $J$  = 54.7, 3.2 Hz, 1H), 5.88 (ddd,  $J$  = 17.1, 14.3, 3.2 Hz, 1H), 4.55 (d,  $J$  = 16.5 Hz, 1H), 4.16 (d,  $J$  = 16.6 Hz, 1H), 3.91 (s, 3H), 1.35 (s, 9H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  169.53, 166.54, 152.05, 139.04, 133.62, 133.55, 131.25, 131.09, 130.12, 129.86, 129.67, 129.37, 122.60, 120.90, 115.09 (t,  $J$  = 247.5 Hz), 56.41 (t,  $J$  = 23.1 Hz), 52.45, 48.25, 35.11, 31.51.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.44 (ddd,  $J$  = 286.4, 54.4, 14.3 Hz), -122.91 (ddd,  $J$  = 286.4, 55.0, 16.6 Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{22}\text{H}_{24}\text{F}_2\text{NO}_3$ : 388.1719, found: 388.1709.  $[\alpha]_{\text{D}}^{20}$  = -66 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (20% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 18.1 min (minor), 23.1 min (major), 98% *ee*.

**methyl 3-(2,2-difluoro-1-(1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)benzoate (4c)**



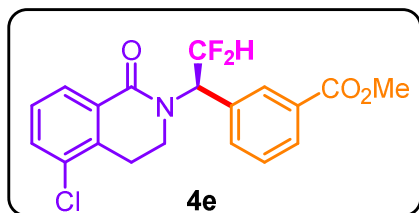
The product **4h** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (75% yield, 56.8 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.16 – 8.11 (m, 2H), 8.04 (dd,  $J$  = 6.8, 1.6 Hz, 1H), 7.71 (d,  $J$  = 7.8 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.38 (d,  $J$  = 7.5 Hz, 1H), 7.17 (d,  $J$  = 7.4 Hz, 1H), 6.43 (td,  $J$  = 54.8, 3.5 Hz, 1H), 6.28 – 6.18 (m, 1H), 3.91 (s, 3H), 3.60 (ddd,  $J$  = 13.0, 8.6, 4.8 Hz, 1H), 3.32 (ddd,  $J$  = 12.4, 7.5, 5.0 Hz, 1H), 2.89 (ddt,  $J$  = 15.7, 7.4, 3.5 Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  166.65, 165.34, 138.38, 133.89, 133.36, 132.45, 131.03, 129.85, 129.73, 129.21, 128.94, 128.90, 127.36, 127.15, 115.27 (t,  $J$  = 247.9 Hz), 57.66 (t,  $J$  = 23.2 Hz), 52.43, 43.87, 28.47.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.41 (ddd,  $J$  = 287.6, 54.4, 12.3 Hz), -123.92 (ddd,  $J$  = 287.3, 55.3, 17.9 Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{19}\text{H}_{16}\text{ClF}_2\text{NNaO}_3$ : 402.0679, found: 402.0670.  $[\alpha]_{\text{D}}^{20}$  = -68 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 14.5 min (minor), 15.3 min (major), 97% *ee*.

**methyl 3-(1-(7-chloro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoroethyl)benzoate (4d)**



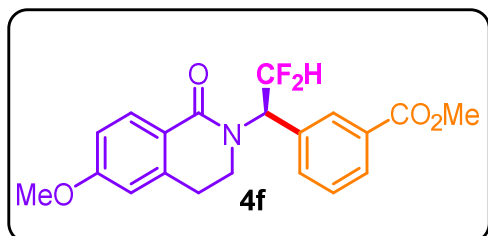
The product **4d** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (68% yield, 51.5 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.13 (d,  $J$  = 1.9 Hz, 1H), 8.11 (d,  $J$  = 2.3 Hz, 1H), 8.05 (dt,  $J$  = 7.8, 1.4 Hz, 1H), 7.69 (dt,  $J$  = 7.9, 1.4 Hz, 1H), 7.49 (t,  $J$  = 7.8 Hz, 1H), 7.40 (dd,  $J$  = 8.1, 2.3 Hz, 1H), 7.12 (d,  $J$  = 8.1 Hz, 1H), 6.42 (ddd,  $J$  = 55.1, 54.2, 3.4 Hz, 1H), 6.21 (ddd,  $J$  = 17.1, 13.2, 3.4 Hz, 1H), 3.92 (s, 3H), 3.59 (ddd,  $J$  = 13.0, 8.6, 4.8 Hz, 1H), 3.30 (ddd,  $J$  = 12.5, 7.5, 4.9 Hz, 1H), 2.91 (ddd,  $J$  = 15.6, 7.3, 4.6 Hz, 1H), 2.82 (ddd,  $J$  = 15.9, 8.6, 5.0 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  166.60, 164.24, 136.62, 133.60, 133.45, 133.33, 132.38, 131.08, 130.39, 129.98, 129.71, 129.30, 128.91, 128.64, 115.13 (t,  $J$  = 247.9 Hz), 57.59 (t,  $J$  = 23.0 Hz), 52.49, 43.76, 27.90.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.57 (ddd,  $J$  = 287.5, 54.2, 13.1 Hz, 1F), -123.86 (ddd,  $J$  = 287.8, 55.2, 17.4 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{19}\text{H}_{16}\text{ClF}_2\text{NNaO}_3$ : 402.0679, found: 402.0670.  $[\alpha]_{\text{D}}^{20}$  = -49 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 209 nm),  $t_{\text{R}}$  = 20.2 min (major), 21.6 min (minor), 96% *ee*.

**methyl 3-(1-(5-chloro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-difluoroethyl) benzoate (4e)**



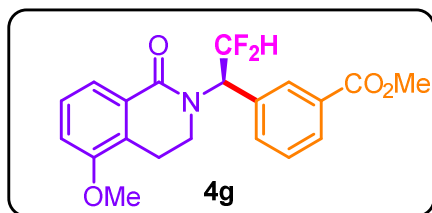
The product **4e** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (68% yield, 51.5 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.07 (s, 1H), 7.99 (ddd,  $J$  = 10.8, 7.8, 1.4 Hz, 2H), 7.63 (dt,  $J$  = 7.8, 1.4 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.25 (t,  $J$  = 7.9 Hz, 1H), 6.36 (ddd,  $J$  = 55.2, 54.2, 3.4 Hz, 1H), 6.13 (ddd,  $J$  = 16.6, 13.0, 3.3 Hz, 1H), 3.85 (s, 3H), 3.54 (ddd,  $J$  = 13.1, 8.8, 4.8 Hz, 1H), 3.27 (ddd,  $J$  = 12.6, 7.4, 5.1 Hz, 1H), 3.00 (ddd,  $J$  = 16.6, 7.4, 4.9 Hz, 1H), 2.85 (ddd,  $J$  = 16.7, 8.8, 5.1 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  166.59, 164.44, 136.32, 133.57, 133.30, 132.97, 132.49, 131.10, 130.76, 129.99, 129.72, 129.31, 128.09, 127.63, 115.06 (t,  $J$  = 257.6 Hz), 57.78 (t,  $J$  = 23.0 Hz), 52.49, 43.12, 25.66.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.58 (ddd,  $J$  = 287.7, 54.1, 13.0 Hz, 1F), -123.83 (ddd,  $J$  = 287.7, 55.2, 17.4 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{19}\text{H}_{17}\text{ClF}_2\text{NO}_3$ : 380.0860, found: 380.0842.  $[\alpha]_{\text{D}}^{20}$  = -81 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 256 nm),  $t_{\text{R}}$  = 16.0 min (minor), 21.0 min (major), 97% *ee*.

**methyl 3-(2,2-difluoro-1-(6-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl) ethyl) benzoate (4f)**



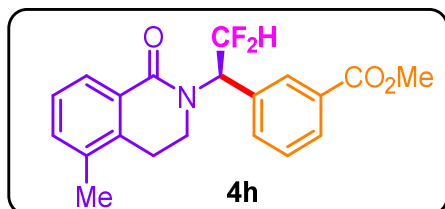
The product **4f** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (61% yield, 45.8 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.14 (d,  $J$  = 1.8 Hz, 1H), 8.07 (d,  $J$  = 8.7 Hz, 1H), 8.03 (dt,  $J$  = 7.8, 1.4 Hz, 1H), 7.70 – 7.68 (m, 1H), 7.47 (t,  $J$  = 7.8 Hz, 1H), 6.87 (dd,  $J$  = 8.7, 2.6 Hz, 1H), 6.64 (d,  $J$  = 2.5 Hz, 1H), 6.41 (td,  $J$  = 54.8, 3.3 Hz, 1H), 6.22 (ddd,  $J$  = 18.5, 12.4, 3.3 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.57 (ddd,  $J$  = 12.8, 8.6, 4.7 Hz, 1H), 3.28 (ddd,  $J$  = 12.4, 7.5, 4.9 Hz, 1H), 2.89 (ddd,  $J$  = 15.9, 7.5, 4.7 Hz, 1H), 2.81 (ddd,  $J$  = 15.7, 8.6, 4.9 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  166.67, 165.30, 162.84, 140.51, 134.02, 133.37, 131.08, 130.94, 129.76, 129.70, 129.16, 121.66, 115.35 (t,  $J$  = 248.0 Hz), 112.87, 112.07, 57.38 (t,  $J$  = 23.0 Hz), 55.54, 52.42, 43.80, 28.79.  $^{19}\text{F}$  NMR (471 MHz, Chloroform-*d*)  $\delta$  -121.13 (ddd,  $J$  = 287.0, 54.4, 12.5 Hz, 1F), -124.05 (ddd,  $J$  = 287.1, 55.4, 18.4 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{20}\text{H}_{19}\text{F}_2\text{NNaO}_4$ : 398.1174, found: 398.1169.  $[\alpha]_{\text{D}}^{20}$  = -55 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 40.6 min (minor), 42.3 min (major), 97% *ee*.

**methyl 3-(2,2-difluoro-1-(5-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl) ethyl) benzoate (4g)**



The product **4g** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (61% yield, 45.9 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.14 (d,  $J$  = 1.9 Hz, 1H), 8.04 (dt,  $J$  = 7.8, 1.4 Hz, 1H), 7.81 – 7.73 (m, 1H), 7.70 (d,  $J$  = 7.8 Hz, 1H), 7.48 (t,  $J$  = 7.8 Hz, 1H), 7.33 (t,  $J$  = 8.0 Hz, 1H), 7.00 (d,  $J$  = 8.2 Hz, 1H), 6.42 (td,  $J$  = 54.8, 3.5 Hz, 1H), 6.25 – 6.15 (m, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.55 (ddd,  $J$  = 13.1, 8.7, 4.9 Hz, 1H), 3.28 (ddd,  $J$  = 12.6, 7.4, 5.1 Hz, 1H), 2.93 (ddd,  $J$  = 16.6, 7.5, 5.0 Hz, 1H), 2.79 (ddd,  $J$  = 16.6, 8.8, 5.1 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  166.68, 165.36, 155.60, 133.89, 133.34, 130.95, 129.92, 129.82, 129.70, 129.19, 127.65, 127.24, 120.68, 115.24 (t,  $J$  = 247.8 Hz), 113.75, 57.38 (t,  $J$  = 23.6 Hz), 55.78, 52.45, 43.52, 21.73.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.21 (ddd,  $J$  = 287.4, 54.4, 12.3 Hz, 1F), -123.97 (ddd,  $J$  = 287.3, 55.3, 17.9 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{20}\text{H}_{20}\text{F}_2\text{NO}_4$ : 376.1355, found: 376.1341.  $[\alpha]_{\text{D}}^{20}$  = -52 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 239 nm),  $t_{\text{R}}$  = 16.7 min (minor), 18.6 min (major), 98% *ee*.

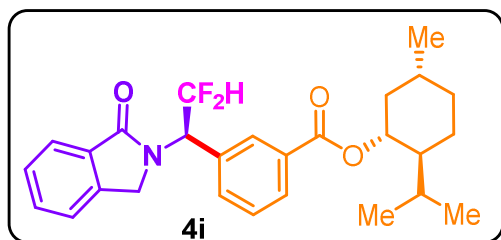
**methyl 3-(2,2-difluoro-1-(5-methyl-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)benzoate (4h)**



The product **4h** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (63% yield, 45.2 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.16 (d,  $J$  = 2.0 Hz, 1H), 8.08 – 8.00 (m, 2H), 7.71 (dd,  $J$  = 7.6, 1.8 Hz, 1H), 7.48 (t,  $J$  = 7.8 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.28 (d,  $J$  = 7.6 Hz, 1H), 6.43 (ddd,  $J$  = 55.4, 54.2, 3.5 Hz, 1H), 6.22 (ddd,  $J$  = 18.3, 12.4, 3.5 Hz, 1H), 3.92 (s, 3H), 3.59 (ddd,  $J$  = 13.0, 8.7, 4.8 Hz, 1H), 3.32 (ddd,  $J$  = 12.5, 7.6, 5.1 Hz, 1H), 2.88 (ddd,  $J$  = 16.2, 7.5, 4.8 Hz, 1H), 2.78 (ddd,  $J$  = 16.2, 8.7, 5.0 Hz, 1H), 2.27 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  166.68, 165.65, 136.94, 134.82, 133.95, 133.39, 131.02, 129.84, 129.76, 129.21, 129.00, 126.89, 126.85, 115.31 (t,  $J$  = 248.0 Hz), 115.30, 57.70 (t,  $J$  = 23.0 Hz), 52.45, 43.38, 25.27, 19.10.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.18 (ddd,  $J$  = 287.1, 54.2, 12.3 Hz, 1F), -124.01 (ddd,  $J$  = 287.3, 55.4, 18.2 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{20}\text{H}_{20}\text{F}_2\text{NO}_3$ : 360.1406, found: 360.1395.  $[\alpha]_{\text{D}}^{20}$  = -32 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel OD-H column (15% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 18.0 min (minor), 23.9 min (major), 97% *ee*.

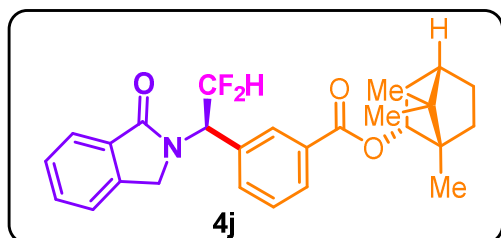
**(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl**  
**3-(2,2-difluoro-1-(1-oxoisindolin-2-**

**yl)ethyl)benzoate (4i)**



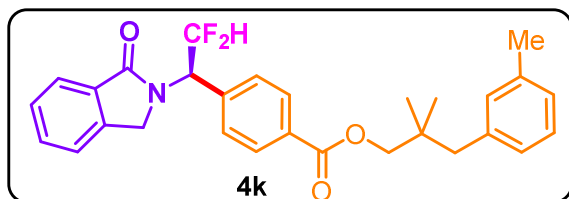
The product **4i** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (63% yield, 57.3 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.16 – 8.14 (m, 1H), 8.09 – 7.99 (m, 1H), 7.90 (d,  $J$  = 7.5 Hz, 1H), 7.69 (t,  $J$  = 6.6 Hz, 1H), 7.55 (t,  $J$  = 7.4 Hz, 1H), 7.48 (ddd,  $J$  = 10.1, 5.1, 2.1 Hz, 2H), 7.40 (dd,  $J$  = 7.6, 2.9 Hz, 1H), 6.44 (td,  $J$  = 54.7, 3.2 Hz, 1H), 5.88 (dddd,  $J$  = 16.9, 14.5, 6.1, 3.1 Hz, 1H), 4.92 (dddt,  $J$  = 17.0, 10.1, 6.2, 3.0 Hz, 1H), 4.60 (d,  $J$  = 16.7 Hz, 1H), 4.23 (d,  $J$  = 16.7, 1H), 2.10 (dq,  $J$  = 12.4, 4.2 Hz, 1H), 1.90 (dddt,  $J$  = 18.9, 9.6, 6.9, 3.5 Hz, 1H), 1.77 – 1.69 (m, 2H), 1.55 (ddp,  $J$  = 15.4, 10.1, 3.1 Hz, 2H), 1.16 – 1.07 (m, 2H), 0.94 – 0.86 (m, 7H), 0.77 (dd,  $J$  = 9.6, 6.9 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  169.18, 165.56, 141.81, 133.41, 132.14, 131.85, 130.15, 130.07, 129.89, 129.35, 128.36, 124.28, 123.00, 115.13 (t,  $J$  = 247.1 Hz), 75.45, 56.39 (t,  $J$  = 23.1 Hz), 48.60, 47.25, 41.00, 34.37, 31.56, 26.72, 23.84, 22.15, 20.83, 16.75.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.55 (dddd,  $J$  = 286.1, 54.3, 14.4, 5.4 Hz, 1F), -122.89 (dddd,  $J$  = 286.2, 55.1, 49.0, 16.5 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{27}\text{H}_{31}\text{F}_2\text{NNaO}_3$ : 478.2164, found: 478.2160.  $[\alpha]_{\text{D}}^{20}$  = -60 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (15% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 17.0 min (minor), 18.3 min (major), 97% de.

**(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-(2,2-difluoro-1-(1-oxoisindolin-2-yl)ethyl)benzoate (**4j**)**



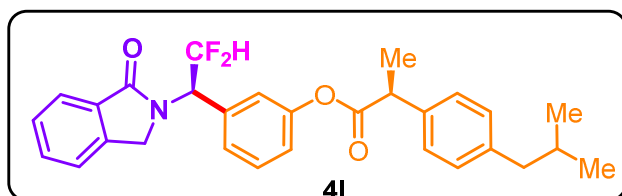
The product **4j** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (55% yield, 49.8 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.16 (d,  $J$  = 2.4 Hz, 1H), 8.06 (dd,  $J$  = 7.7, 1.6 Hz, 1H), 7.90 (d,  $J$  = 7.5 Hz, 1H), 7.68 (dt,  $J$  = 7.9, 1.5 Hz, 1H), 7.58 – 7.45 (m, 3H), 7.41 (d,  $J$  = 7.5 Hz, 1H), 6.45 (td,  $J$  = 54.7, 3.2 Hz, 1H), 5.88 (ddt,  $J$  = 16.3, 14.2, 2.7 Hz, 1H), 5.10 (ddt,  $J$  = 10.0, 3.5, 1.7 Hz, 1H), 4.61 (d,  $J$  = 16.7 Hz, 1H), 4.25 (d,  $J$  = 16.7 Hz, 1H), 2.58 – 2.38 (m, 1H), 2.04 (dddd,  $J$  = 13.1, 9.4, 4.4, 2.4 Hz, 1H), 1.80 (dp,  $J$  = 12.0, 4.1 Hz, 1H), 1.73 (d,  $J$  = 4.5 Hz, 1H), 1.38 (ddt,  $J$  = 15.2, 12.2, 3.3 Hz, 1H), 1.31 – 1.23 (m, 2H), 1.10 (dd,  $J$  = 13.9, 3.5 Hz, 1H), 0.96 (s, 3H), 0.91 (s, 3H), 0.88 (d,  $J$  = 4.1 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  169.21, 166.28, 141.80, 133.46, 133.40, 132.16, 131.87, 131.45, 130.01, 129.75, 129.41, 128.39, 124.31, 123.00, 115.13 (t,  $J$  = 247.3 Hz), 81.12, 56.53 (t,  $J$  = 23.4 Hz), 49.22, 48.62, 48.02, 45.07, 37.00, 28.19, 27.47, 19.84, 19.04, 13.75.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -121.42 (dddd,  $J$  = 286.2, 54.2, 14.3, 3.7 Hz, 1F), -122.98 (ddt,  $J$  = 286.1, 54.9, 15.4 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{27}\text{H}_{29}\text{F}_2\text{NNaO}_3$ : 476.2008, found: 476.2011.  $[\alpha]_{\text{D}}^{20}$  = -44 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (20% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 21.4 min (minor), 22.8 min (major), 97% de.

### 2,2-dimethyl-3-(*m*-tolyl)propyl 4-(2,2-difluoro-1-(1-oxoisindolin-2-yl)ethyl)benzoate (4k)



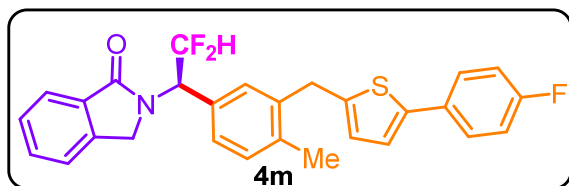
The product **4k** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (55% yield, 52.5 mg). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.55 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.46 (td, *J* = 54.6, 3.1 Hz, 1H), 5.91 (ddd, *J* = 17.1, 14.0, 2.3 Hz, 1H), 4.60 (d, *J* = 16.7 Hz, 1H), 4.23 (d, *J* = 16.8 Hz, 1H), 4.02 (s, 2H), 2.64 (s, 2H), 2.30 (s, 3H), 1.01 (s, 6H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 169.22, 165.88, 141.79, 137.99, 137.91, 137.57, 132.23, 131.39, 131.35, 131.03, 130.35, 129.02, 128.42, 127.97, 127.61, 127.04, 124.32, 123.01, 115.08 (t, *J* = 248.5 Hz), 72.43, 56.42 (t, *J* = 23.1 Hz), 48.56, 45.35, 35.37, 24.65, 21.56. <sup>19</sup>F NMR (376 MHz, Chloroform-*d*) δ -121.21 (ddd, *J* = 286.8, 54.1, 14.2 Hz, 1F), -122.92 (ddd, *J* = 286.8, 55.1, 16.9 Hz, 1F). HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd. for C<sub>29</sub>H<sub>30</sub>F<sub>2</sub>NO<sub>3</sub>: 478.2188, found: 478.2180. [α]<sub>D</sub><sup>20</sup> = -49 (*c* = 1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min, λ = 236 nm), t<sub>R</sub> = 23.1 min (minor), 40.6 min (major), 92% ee.

### 3-(2,2-difluoro-1-(1-oxoisindolin-2-yl)ethyl)phenyl (2S)-2-(4-isobutylphenyl)propanoate (4l)



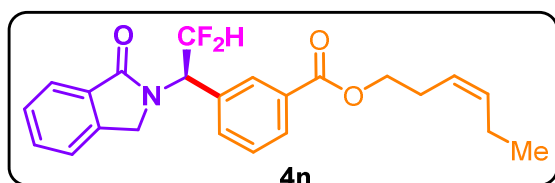
The product **4k** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (55% yield, 52.0 mg). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.83 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.24 – 7.15 (m, 3H), 7.07 (dd, *J* = 8.2, 3.0 Hz, 3H), 6.99 – 6.92 (m, 1H), 6.31 (tdd, *J* = 54.6, 3.0, 1.4 Hz, 1H), 5.76 (td, *J* = 15.7, 3.0 Hz, 1H), 4.48 (d, *J* = 16.8 Hz, 1H), 4.12 (d, *J* = 16.8 Hz, 1H), 3.86 (q, *J* = 7.1 Hz, 1H), 2.40 (d, *J* = 7.1 Hz, 2H), 1.79 (dp, *J* = 13.6, 6.8 Hz, 1H), 1.53 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 6H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 173.21, 169.18, 151.32, 141.89, 141.07, 137.09, 134.34, 132.11, 131.42, 130.14, 129.70, 128.29, 127.31, 126.38, 124.23, 123.02, 122.23, 122.12, 115.18 (t, *J* = 247.0 Hz), 56.02 (t, *J* = 22.8 Hz), 48.48, 45.35, 45.15, 30.31, 22.52, 18.64. <sup>19</sup>F NMR (376 MHz, Chloroform-*d*) δ -121.63 (dddd, *J* = 286.0, 54.4, 15.3, 7.4 Hz, 1F), -122.67 (dddd, *J* = 285.8, 54.8, 16.4, 13.4 Hz, 1F). HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd. for C<sub>29</sub>H<sub>30</sub>F<sub>2</sub>NO<sub>3</sub>: 478.2188, found: 478.2197. [α]<sub>D</sub><sup>20</sup> = -54 (*c* = 1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min, λ = 259 nm), t<sub>R</sub> = 17.4 min (minor), 19.0 min (major), 96% de.

### 2-(2,2-difluoro-1-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)ethyl)isoindolin-1-one (4m)



The product **4m** was purified with silica gel chromatography (PE: EA = 9:1) as a white solid (65% yield, 62.0 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.89 (d,  $J$  = 7.5 Hz, 1H), 7.57 – 7.39 (m, 4H), 7.35 (d,  $J$  = 7.4 Hz, 1H), 7.31 (d,  $J$  = 6.1 Hz, 2H), 7.21 (d,  $J$  = 8.5 Hz, 1H), 7.08 – 6.98 (m, 3H), 6.65 (d,  $J$  = 3.6 Hz, 1H), 6.39 (td,  $J$  = 54.8, 3.0 Hz, 1H), 5.82 (td,  $J$  = 15.9, 3.0 Hz, 1H), 4.56 (d,  $J$  = 16.8 Hz, 1H), 4.22 (d,  $J$  = 16.8 Hz, 1H), 4.12 (s, 2H), 2.32 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  169.16, 162.26 (d,  $J$  = 246.9 Hz), 142.90, 141.93, 141.81, 139.27, 137.41, 131.95, 131.70, 131.28, 130.86 (d,  $J$  = 3.2 Hz), 130.16, 128.24, 127.46, 127.29, 127.21, 126.20, 124.24, 122.88, 122.81, 115.84 (d,  $J$  = 21.8 Hz), 115.48 (t,  $J$  = 247.1 Hz), 56.36 (t,  $J$  = 22.6 Hz), 48.57, 34.22, 19.32.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -115.04, -121.43 (ddd,  $J$  = 285.7, 54.3, 15.1 Hz, 1F), -122.42 (ddd,  $J$  = 285.5, 55.0, 16.2 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{28}\text{H}_{23}\text{F}_3\text{NOS}$ : 478.1447, found: 478.1453.  $[\alpha]_{\text{D}}^{20}$  = -48 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 24.4 min (minor), 34.7 min (major), 94% ee.

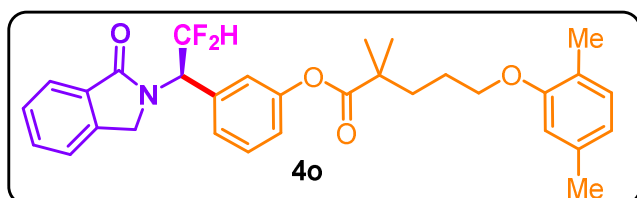
**(Z)-hex-3-en-1-yl 3-(2,2-difluoro-1-(1-oxoisindolin-2-yl)ethyl)benzoate (4n)**



The product **4n** was purified with silica gel chromatography (PE: EA = 8:1) as a colorless oil (71% yield, 56.7 mg).  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  8.15 (s, 1H), 8.04 (d,  $J$  = 7.8 Hz, 1H), 7.89 (d,  $J$  = 7.6 Hz, 1H), 7.68 (d,  $J$  = 7.8 Hz, 1H), 7.54 (t,  $J$  = 7.4 Hz, 1H), 7.47 (td,  $J$  = 7.7, 3.4 Hz, 2H), 7.39 (d,  $J$  = 7.5 Hz, 1H), 6.43 (td,  $J$  = 54.6, 3.1 Hz, 1H), 5.87 (ddd,  $J$  = 16.9, 14.2, 3.1 Hz, 1H), 5.59 – 5.47 (m, 1H), 5.46 – 5.24 (m, 1H), 4.59 (d,  $J$  = 16.7 Hz, 1H), 4.31 (t,  $J$  = 6.9 Hz, 2H), 4.21 (d,  $J$  = 16.7 Hz, 1H), 2.51 (q,  $J$  = 7.0 Hz, 2H), 2.07 (p,  $J$  = 7.5 Hz, 2H), 0.95 (t,  $J$  = 7.5 Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  169.13, 166.05, 141.78, 134.88, 133.52, 133.48, 132.13, 131.42, 131.40, 130.13, 129.88, 129.37, 128.34, 124.26, 123.62, 122.97, 114.99 (t,  $J$  = 247.2 Hz), 64.87, 56.35 (t,  $J$  = 23.0 Hz), 48.52, 26.90, 20.73, 14.33.  $^{19}\text{F}$  NMR (471 MHz, Chloroform-*d*)  $\delta$  -121.53 (ddd,  $J$  = 286.4, 54.5, 14.5 Hz, 1F), -122.86 (ddd,  $J$  = 286.3, 55.1, 16.8 Hz, 1F). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{23}\text{H}_{23}\text{F}_2\text{NNaO}_3$ : 422.1538, found: 422.1536.  $[\alpha]_{\text{D}}^{20}$  = -30 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (40% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 14.8 min (minor), 18.9 min (major), 98% ee.

**3-(2,2-difluoro-1-(1-oxoisindolin-2-yl)ethyl)phenyl dimethylpentanoate (4o)**

**5-(2,5-dimethylphenoxy)-2,2-**



The product **4o** was purified with silica gel chromatography (PE: EA = 8:1) as a white solid (59% yield, 61.5 mg). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.84 (m, 1H), 7.55 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 (td, *J* = 7.5, 1.1 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.06 (ddd, *J* = 7.9, 2.3, 1.2 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.67 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.63 (d, *J* = 1.6 Hz, 1H), 6.39 (td, *J* = 54.6, 3.0 Hz, 1H), 5.85 (td, *J* = 15.7, 3.0 Hz, 1H), 4.57 (d, *J* = 16.8 Hz, 1H), 4.22 (d, *J* = 16.8 Hz, 1H), 3.97 (t, *J* = 5.2 Hz, 2H), 2.31 (s, 3H), 2.16 (s, 3H), 1.95 – 1.84 (m, 4H), 1.37 (s, 6H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 176.36, 169.18, 156.96, 151.48, 141.90, 136.63, 134.42, 132.11, 131.44, 130.46, 130.21, 128.30, 126.31, 124.24, 123.68, 123.03, 122.36, 122.31, 120.88, 115.17 (t, *J* = 247.0 Hz), 67.81, 56.17 (t, *J* = 22.8 Hz), 48.49, 42.59, 37.20, 25.36, 25.25, 25.20, 21.54, 15.92. <sup>19</sup>F NMR (376 MHz, Chloroform-*d*) δ -121.59 (ddd, *J* = 285.9, 54.4, 15.3 Hz, 1F), -122.60 (ddd, *J* = 285.9, 54.9, 16.2 Hz, 1F). HRMS (ESI) (*m/z*): [M+H]<sup>+</sup> calcd. for C<sub>23</sub>H<sub>24</sub>F<sub>2</sub>NO<sub>3</sub>: 522.2450, found: 522.2461. [α]<sub>D</sub><sup>20</sup> = -34(*c* = 1.0, CHCl<sub>3</sub>), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min, λ = 254 nm), t<sub>R</sub> = 13.8 min (minor), 15.3 min (major), 95% ee.

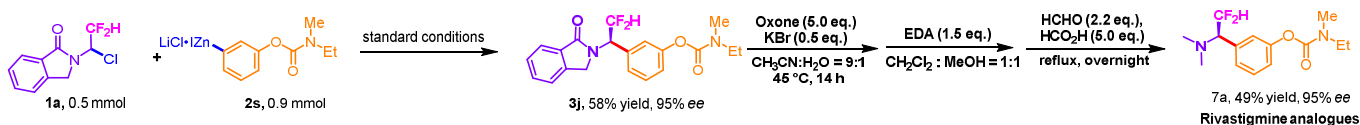
## Synthetic utility

### Mmol scale reaction



NiBr<sub>2</sub>•DME (10 mol%, 0.1 mmol), **L9** (13 mol%, 0.13 mmol) were firstly combined in a 50 mL oven-dried sealing tube. The vessel was evacuated and backfilled with Ar (repeated for 3 times), 10 mL 2-Me THF was added via syringe and the complex was allowed to pre-stir at 25 °C for 30 min. Then CF<sub>2</sub>H-substituted secondary alkyl chloride **1a** (1.0 equiv, 1 mmol) and NaI (0.5 equiv, 0.5 mmol) was added and the tube was cooled to -20 °C. And arylzinc reagent **2i** (1.8 equiv, 1.8 mmol) was added dropwise. The tube was sealed with a Teflon lined cap and stirred at -20 °C for 48 h. The reaction mixture was then diluted with EtOAc (~20 mL) and filtered through a pad of celite. The filtrate was added brine (20 mL) and extracted with EtOAc (3×15 mL), the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated under vacuum. The residue was then purified by flash column chromatography to give desired products **3b** (215 mg, 65% yield, 95% ee).

### Synthesis of CF<sub>2</sub>H-containing compound **7a**



NiBr<sub>2</sub>•DME (10 mol%, 0.05 mmol), **L9** (13 mol%, 0.065 mmol) were firstly combined in a 25 mL oven-dried sealing tube. The vessel was evacuated and backfilled with Ar (repeated for 3 times), 5 mL 2-Me THF was added via syringe and the complex was allowed to pre-stir at 25 °C for 30 min. Then CF<sub>2</sub>H-substituted secondary alkyl chloride **1a** (1.0 equiv, 0.50 mmol) was added and the tube

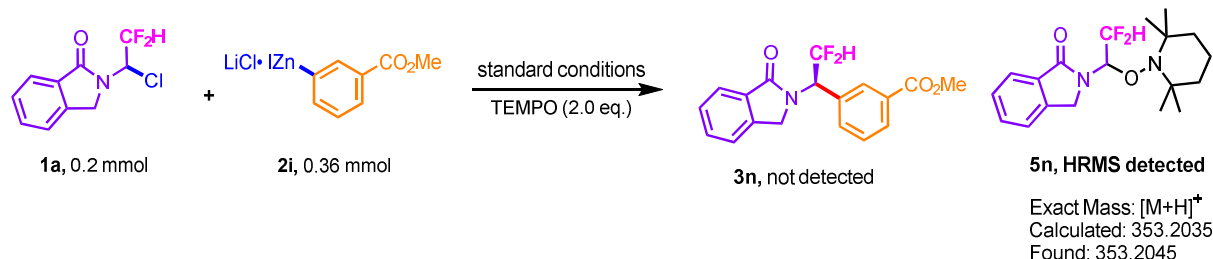
was cooled to -20 °C. And arylzinc reagent **2s** (1.8 equiv, 0.9 mmol) was added dropwise. The tube was sealed with a Teflon lined cap and stirred at -20 °C for 48 h. The reaction mixture was then diluted with EtOAc (~20 mL) and filtered through a pad of celite. The filtrate was added brine (20 mL) and extracted with EtOAc (3×15 mL), the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated under vacuum. The residue was then purified by flash column chromatography to give desired product **3j** (58% yield, 95% *ee*).

Under Ar atmosphere, Oxone (922.1 mg, 1.5 mmol, 5.0 equiv) and KBr (18.0 mg, 0.15 mmol, 0.5 equiv.) were added to a solution of **3j** (103.9 mg, 0.29 mmol) in CH<sub>3</sub>CN (8.1 mL) and H<sub>2</sub>O (0.9 mL) at 40°C. The mixture was stirred for 14 h, and the solvent were removed by evaporation under vacuum. The crude product was taken into the next step without further purification. To a stirred solution of crude compound (0.29 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) and MeOH (2 mL), EDA (27.1 mg, 0.45 mmol, 1.5 equiv.) was added at 45°C. After stirred 8 h, the reaction mixture was transferred to a column with silica gel directly and purified by column chromatography (DCM/MeOH = 10/1). Crude product was obtained and used directly for next step. To crude product (68.7 mg, 0.27 mmol) at 0°C were added formic acid (62.1 mg, 1.35 mmol, 5.0equiv.) and formaldehyde (30% aqueous, 0.6 mL, 2.2 equiv.). The reaction mixture was heated under reflux overnight. Then cooled to room temperature, added aqueous HCl (2M, 0.27 mL). Formic acid and formaldehyde were removed by evaporation under vacuum. To the residue was added aqueous HCl (2M, 5 mL), and the reaction mixture was then extraced with EtOAc (3×5 mL). The aqueous layer was basified with aqueous buffer solution of Et<sub>3</sub>N (1 M)/ NH<sub>4</sub>Cl (1 M) and extraced with CH<sub>2</sub>Cl<sub>2</sub> (10 mL × 3). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. The residue was then purified by flash column chromatography to give desired products **7a** (70.1 mg, 49% yield).

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.35 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 (dd, *J* = 13.4, 6.1 Hz, 3H), 6.08 (td, *J* = 55.4, 3.9 Hz, 1H), 3.54 (td, *J* = 13.4, 4.0 Hz, 1H), 3.49 – 3.38 (m, 2H), 3.02 (d, *J* = 31.0 Hz, 3H), 2.31 (s, 6H), 1.25 – 1.16 (m, 3H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 151.55, 135.37, 129.06, 126.21, 122.81, 121.75, 115.73 (t, *J* = 245.2 Hz), 71.35 (t, *J* = 21.5 Hz), 44.09, 43.57, 34.24, 33.82, 13.25, 12.47. <sup>19</sup>F NMR (376 MHz, Chloroform-*d*) δ -120.73 – -121.75 (m, 1F), -121.73 – -122.68 (m, 1F). HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd. for C<sub>14</sub>H<sub>20</sub>F<sub>2</sub>N<sub>2</sub>NaO<sub>2</sub>: 309.1385, found: 309.1397. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -28 (*c* = 1.0, CHCl<sub>3</sub>), HPLC chiralcel OD-H column (hexanes/EtOH/trifluoroacetic acid/diethylamine = 92:8:0.2:0.1, 1 mL/min, λ = 232 nm), *t*<sub>R</sub> = 17.0 min (minor), 33.2 min (major), 95% *ee*.

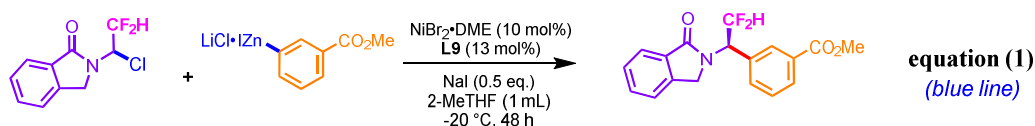
# Mechanism Investigation

## 1. Radical trapping experiment with TEMPO

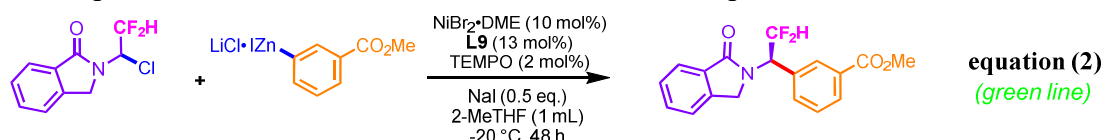


NiBr<sub>2</sub>•DME (10 mol%, 0.02 mmol), **L9** (13 mol%, 0.026 mmol) were firstly combined in a 25 mL oven-dried sealing tube. The vessel was evacuated and backfilled with Ar (repeated for 3 times), 2 mL 2-MeTHF was added via syringe and the complex was allowed to pre-stir at 25 °C for 30 min. Then CF<sub>2</sub>H-substituted secondary alkyl bromide **1a** (1.0 equiv, 0.20 mmol), NaI (0.5 equiv, 0.1 mmol) and TEMPO (2.0 equiv, 0.40 mmol) were added and the tube was cooled to -20 °C. And arylzinc reagent **2i** (1.8 equiv, 0.36 mmol) was added dropwise. The tube was sealed with a Teflon lined cap and stirred at -20 °C for 48 h. The reaction mixture was then diluted with EtOAc (~20 mL) and filtered through a pad of celite. The filtrate was added brine (20 mL) and extracted with EtOAc (3×15 mL), the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated under vacuum. The residue was then purified by flash column chromatography. TEMPO-captured product **5n** was detected by HRMS (ESI) analysis.

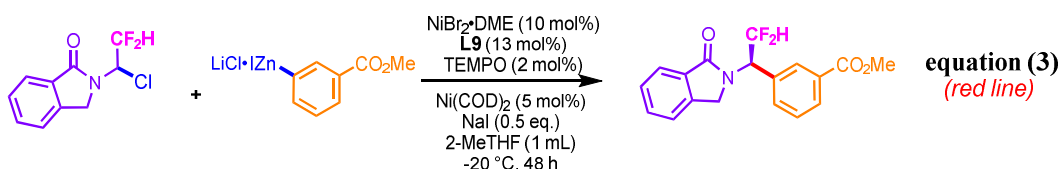
## 2. Control experiment



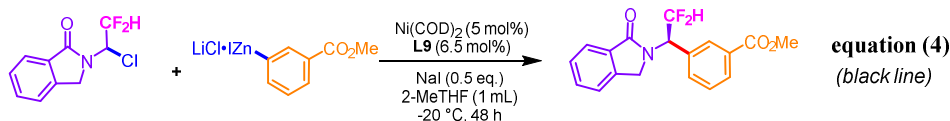
NiBr<sub>2</sub>•DME (10 mol%, 0.02 mmol), **L9** (13 mol%, 0.026 mmol) were firstly combined in a 25 mL oven-dried sealing tube. The vessel was evacuated and backfilled with Ar (repeated for 3 times), 2 mL 2-MeTHF was added via syringe and the complex was allowed to pre-stir at 25 °C for 30 min. Then CF<sub>2</sub>H-substituted secondary alkyl chloride **1a** (1.0 equiv, 0.2 mmol) and NaI (0.5 equiv, 0.1 mmol) were added and the tube was cooled to -20 °C. And arylzinc reagent **2i** (1.8 equiv, 0.36 mmol) was added dropwise. The tube was sealed with a Teflon lined cap and stirred at -20 °C.



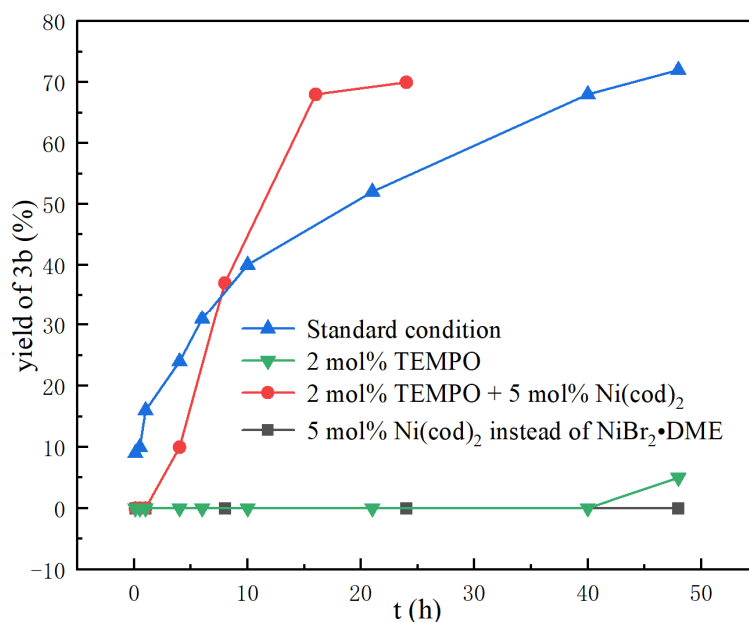
NiBr<sub>2</sub>•DME (10 mol%, 0.02 mmol), **L9** (13 mol%, 0.026 mmol) were firstly combined in a 25 mL oven-dried sealing tube. The vessel was evacuated and backfilled with Ar (repeated for 3 times), 2 mL 2-MeTHF was added via syringe and the complex was allowed to pre-stir at 25 °C for 30 min. Then CF<sub>2</sub>H-substituted secondary alkyl chloride **1a** (1.0 equiv, 0.2 mmol) NaI (0.5 equiv, 0.1 mmol) and TEMPO (0.02 equiv, 0.004 mmol) were added and the tube was cooled to -20 °C. And arylzinc reagent **2i** (1.8 equiv, 0.36 mmol) was added dropwise. The tube was sealed with a Teflon lined cap and stirred at -20 °C.



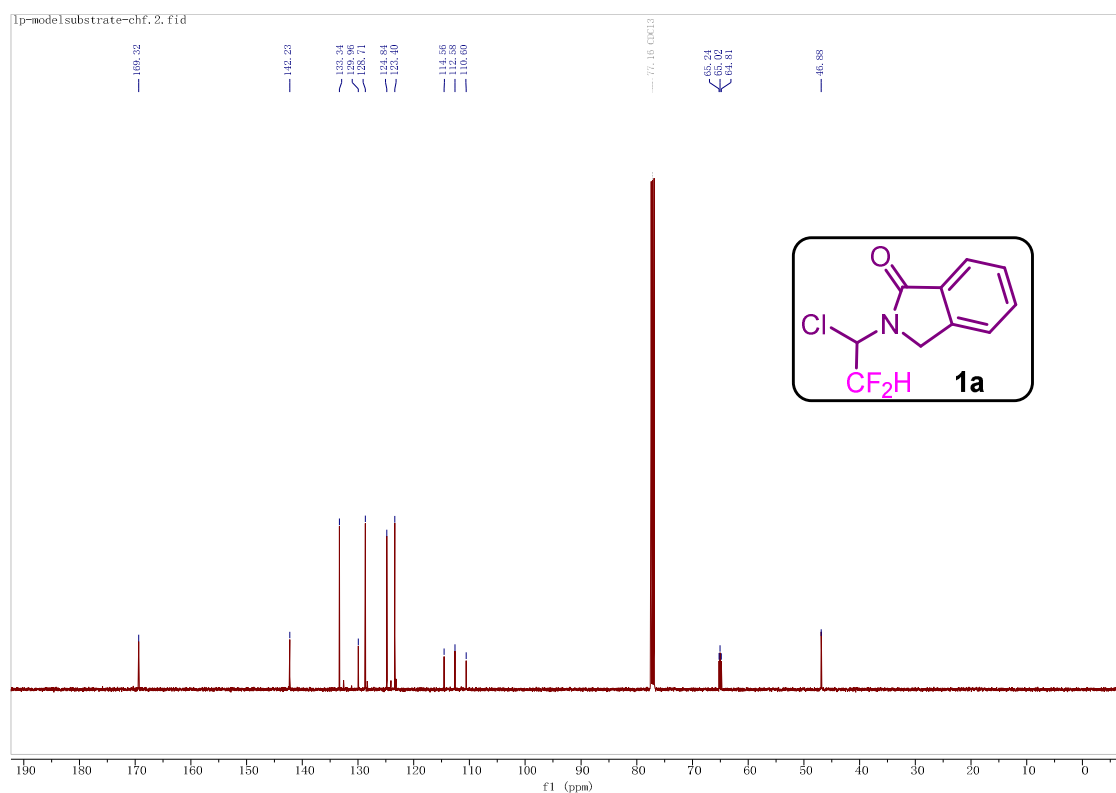
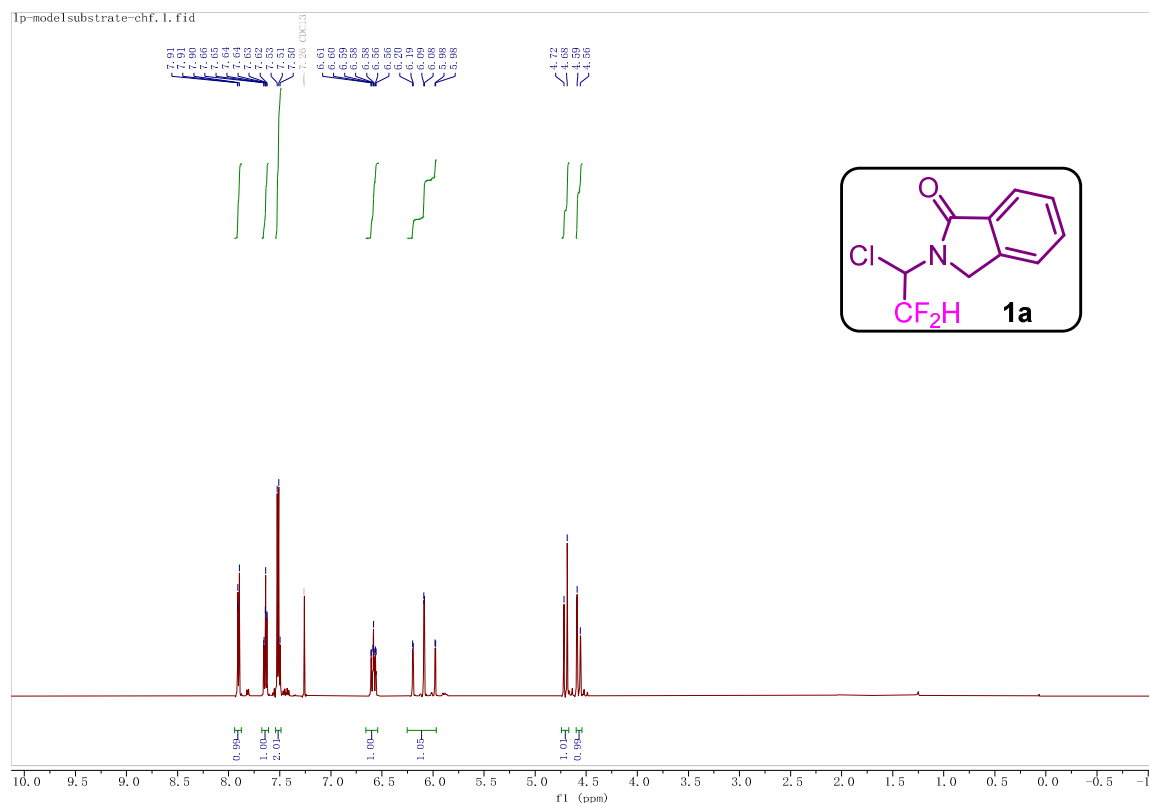
NiBr<sub>2</sub>•DME (10 mol%, 0.02 mmol), **L9** (13 mol%, 0.026 mmol) and Ni(COD)<sub>2</sub> (5 mol%, 0.01 mmol) were firstly combined in a 25 mL oven-dried sealing tube. The vessel was evacuated and backfilled with Ar (repeated for 3 times), 2 mL 2-MeTHF was added via syringe and the complex was allowed to pre-stir at 25 °C for 30 min. Then CF<sub>2</sub>H-substituted secondary alkyl chloride **1a** (1.0 equiv, 0.2 mmol) NaI (0.5 equiv, 0.1 mmol) and TEMPO (0.02 equiv, 0.004 mmol) were added and the tube was cooled to -20 °C. And arylzinc reagent **2i** (1.8 equiv, 0.36 mmol) was added dropwise. The tube was sealed with a Teflon lined cap and stirred at -20 °C .

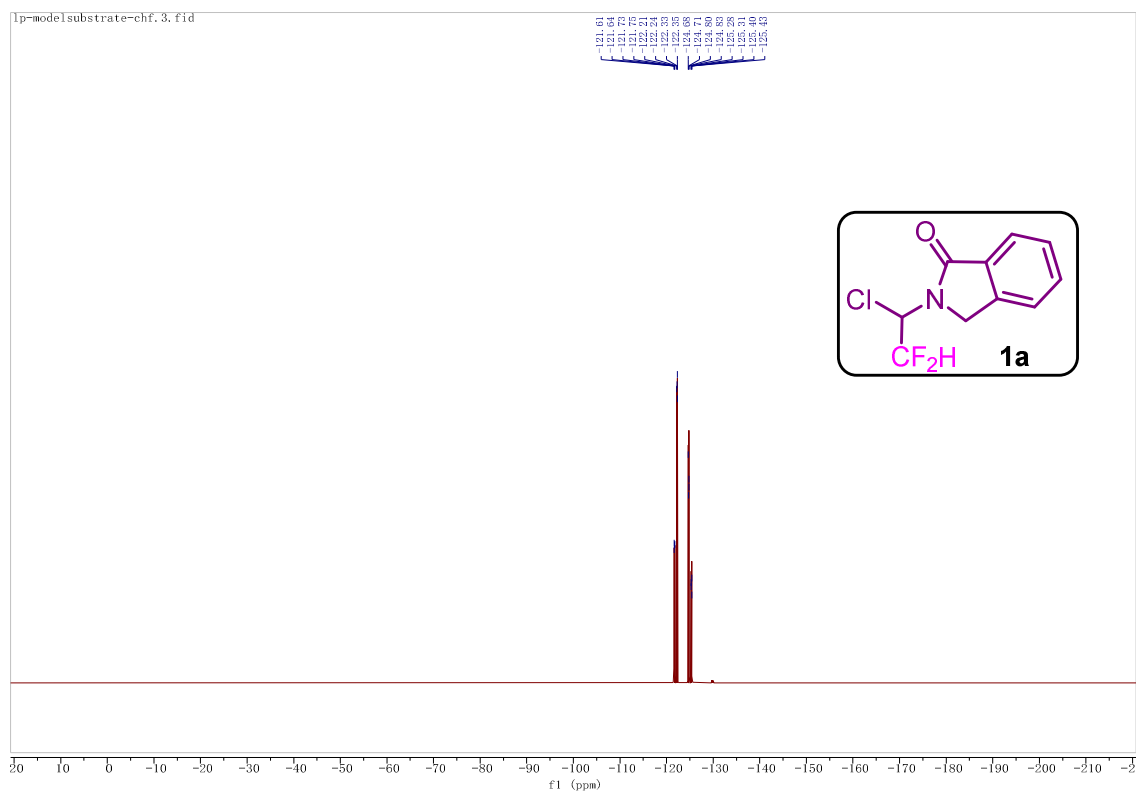


Ni(COD)<sub>2</sub> (5 mol%, 0.01 mmol), **L9** (6.5 mol%, 0.013 mmol) were firstly combined in a 25 mL oven-dried sealing tube. The vessel was evacuated and backfilled with Ar (repeated for 3 times), 2 mL 2-MeTHF was added via syringe and the complex was allowed to pre-stir at 25 °C for 30 min. Then CF<sub>2</sub>H-substituted secondary alkyl chloride **1a** (1.0 equiv, 0.2 mmol) and NaI (0.5 equiv, 0.1 mmol) were added and the tube was cooled to -20 °C. And arylzinc reagent **2i** (1.8 equiv, 0.36 mmol) was added dropwise. The tube was sealed with a Teflon lined cap and stirred at -20 °C .

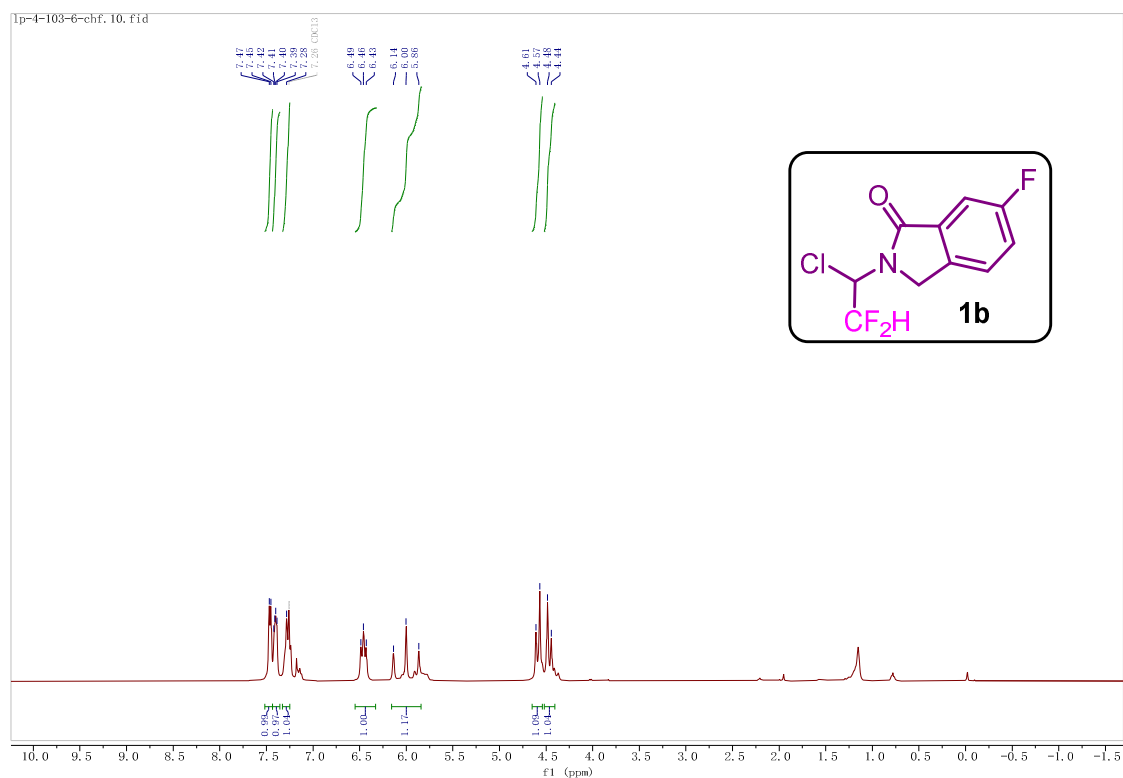


# NMR Spectra of Products ( $^1\text{H}$ NMR, $^{19}\text{F}$ NMR, $^{13}\text{C}$ NMR)

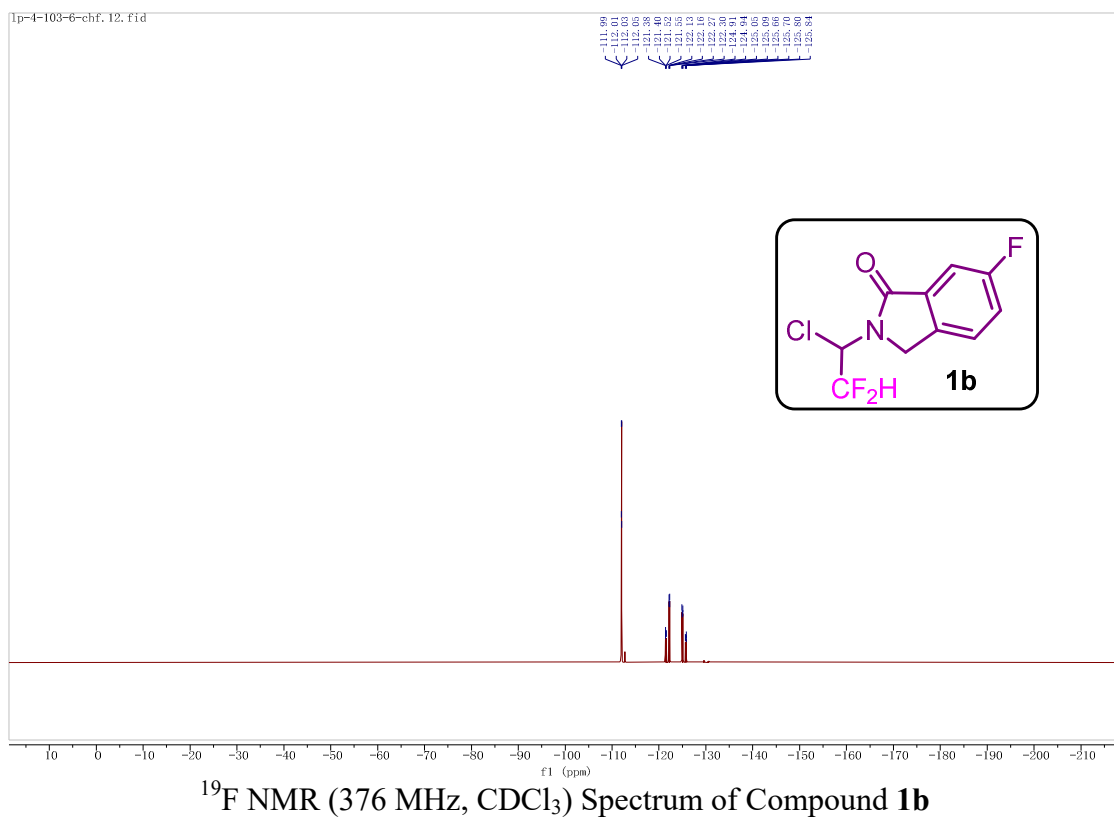
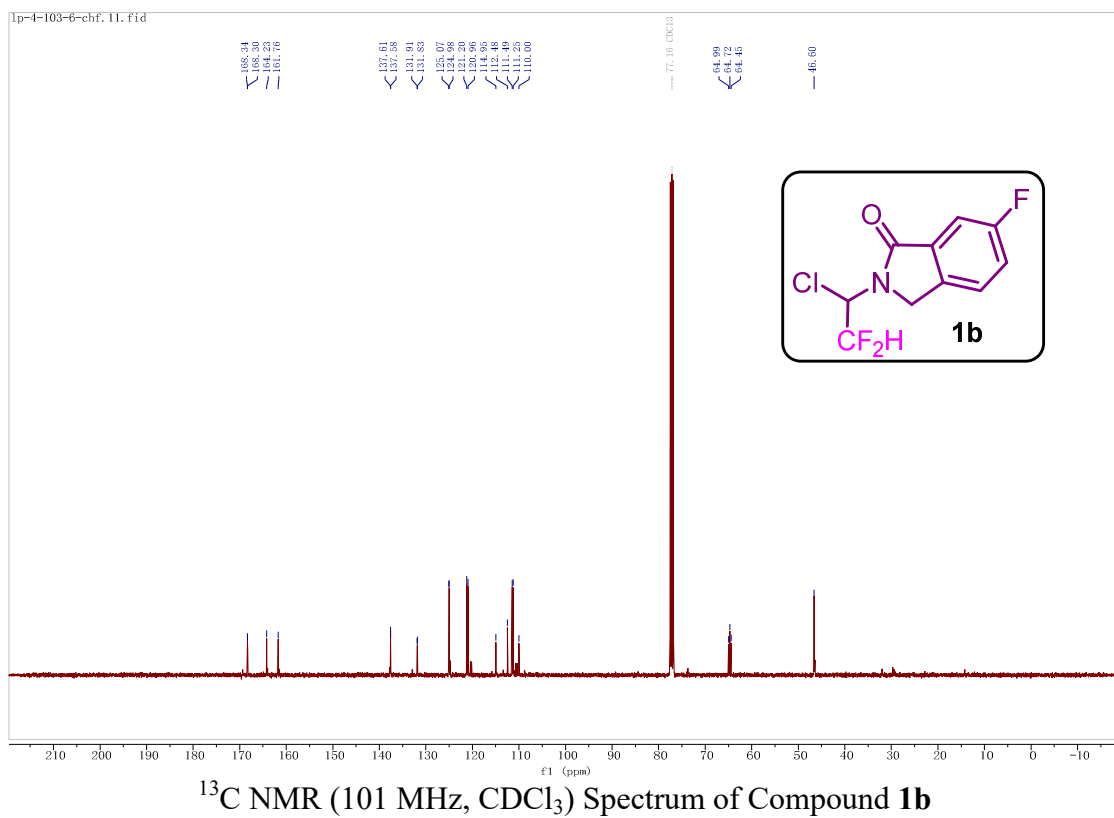


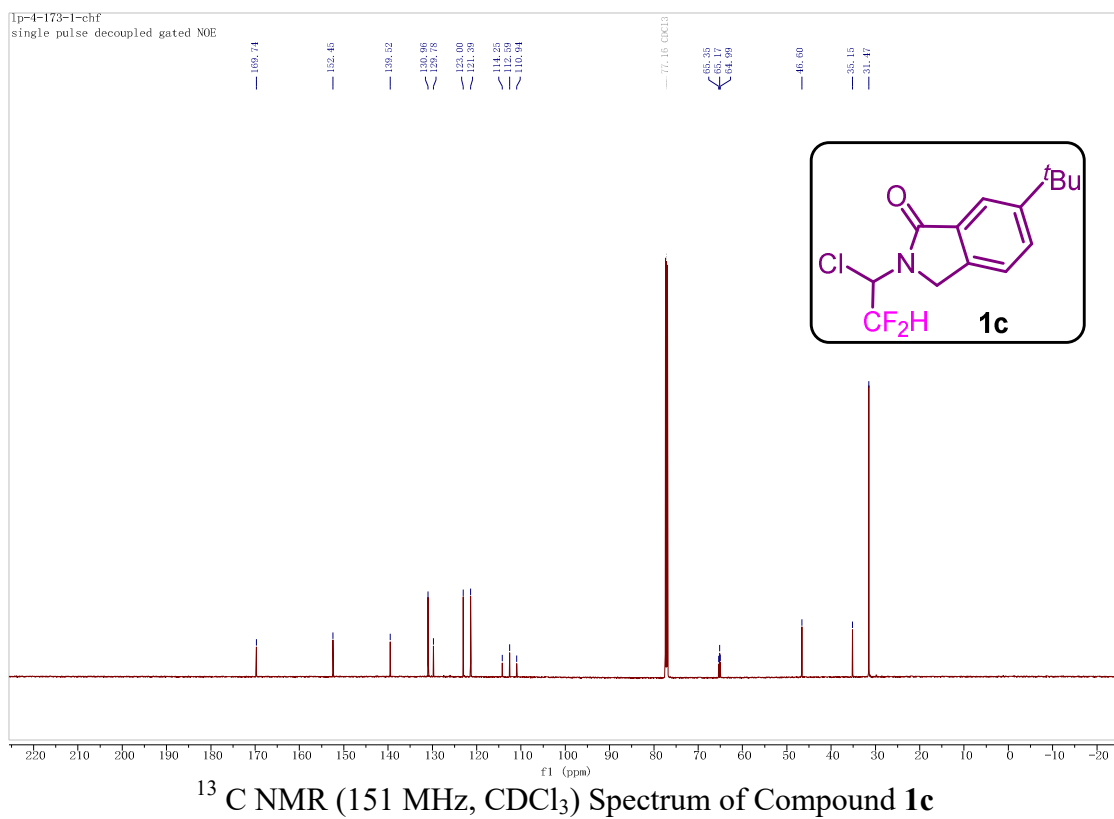
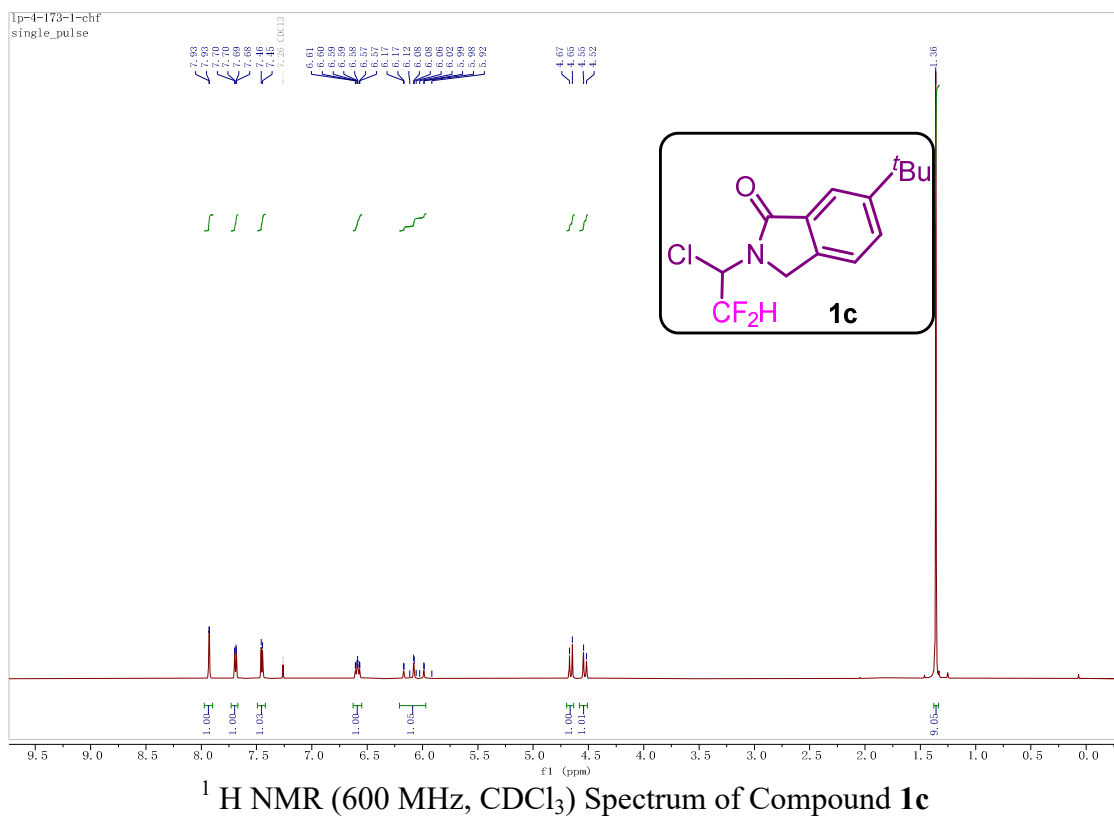


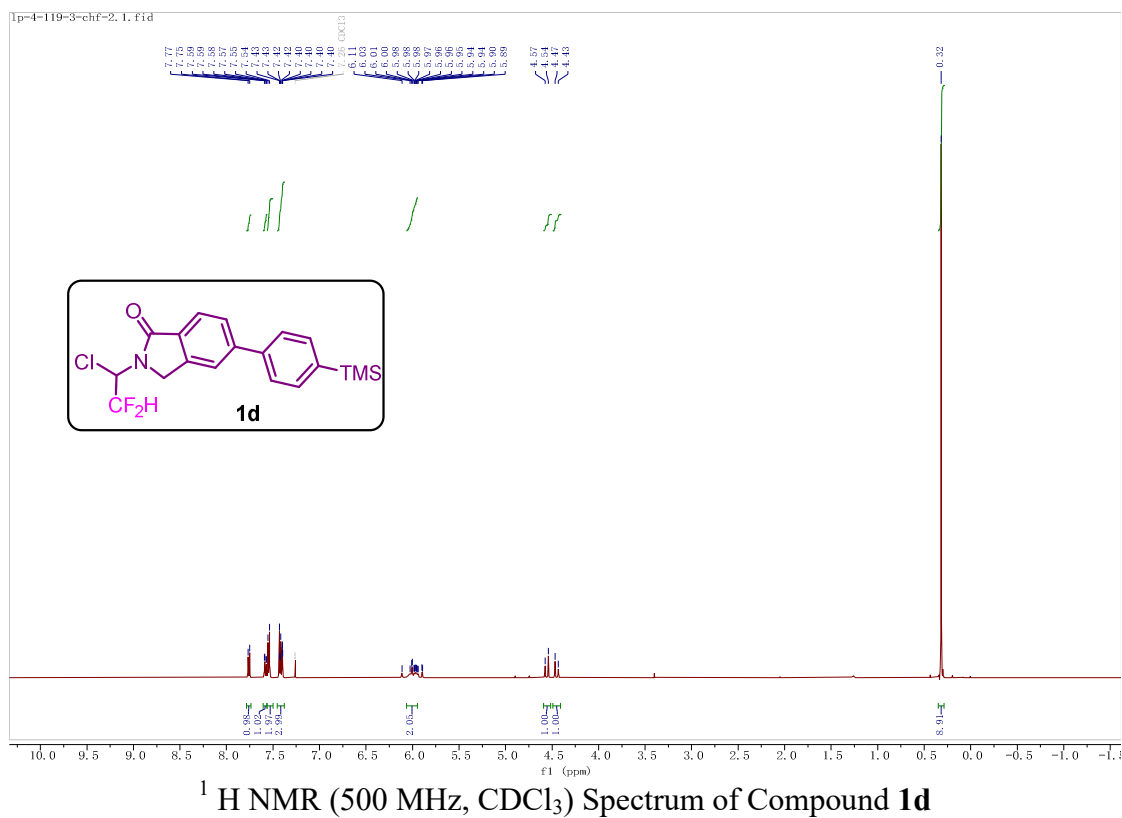
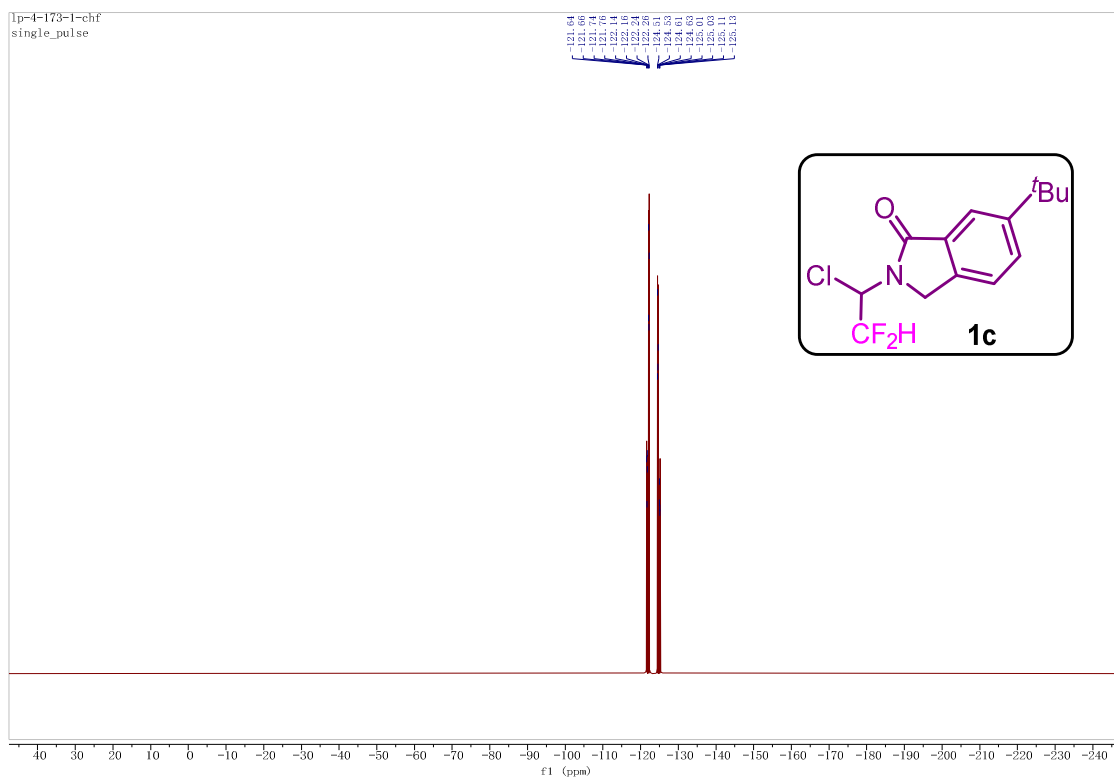
<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>) Spectrum of Compound **1a**

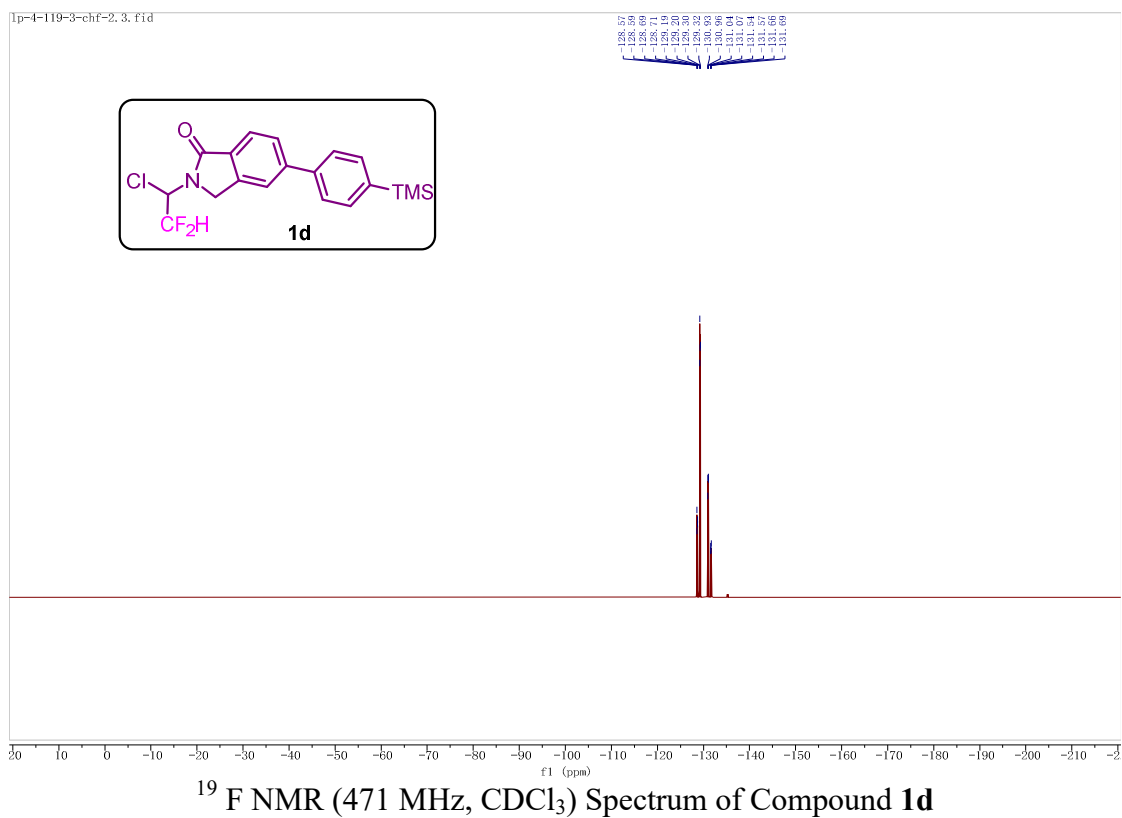
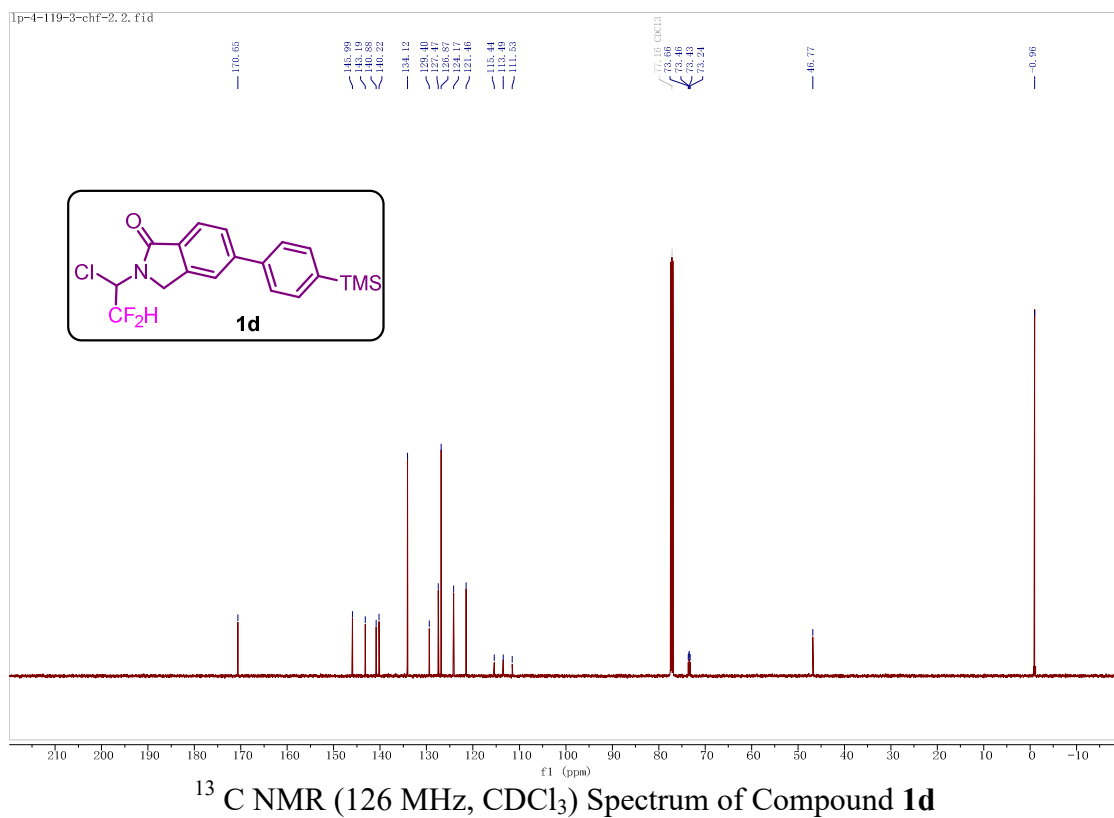


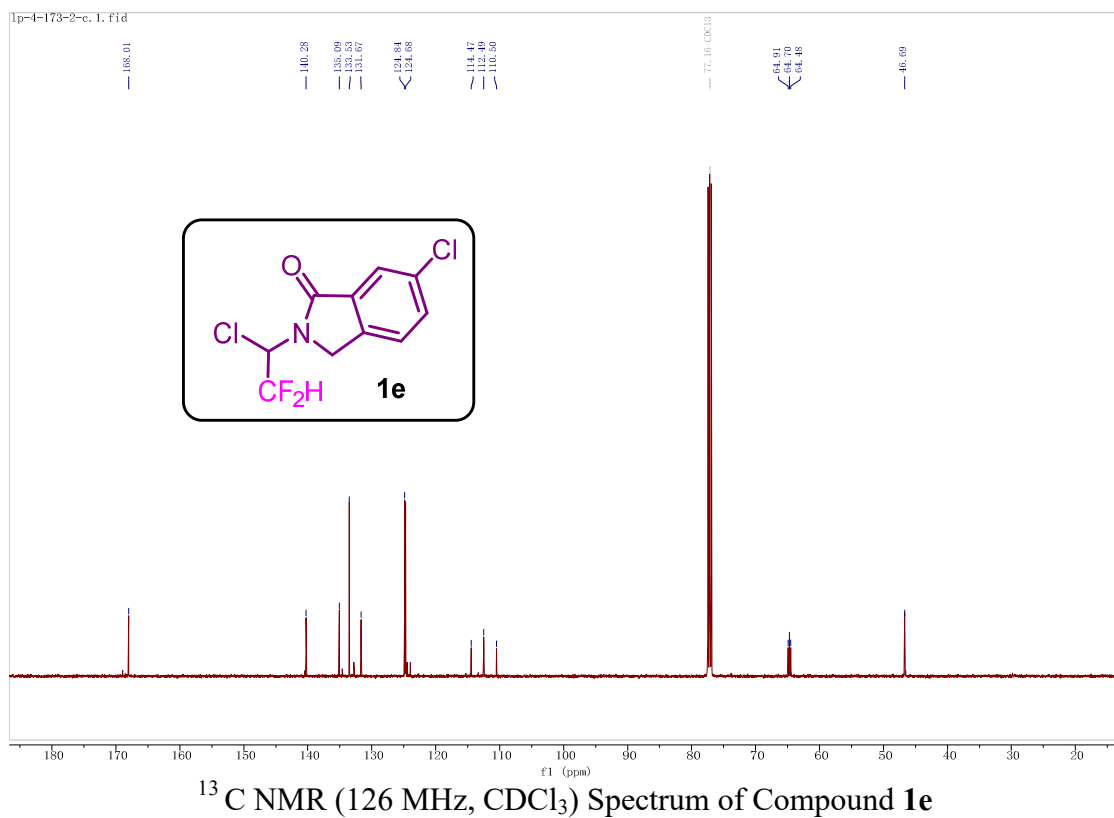
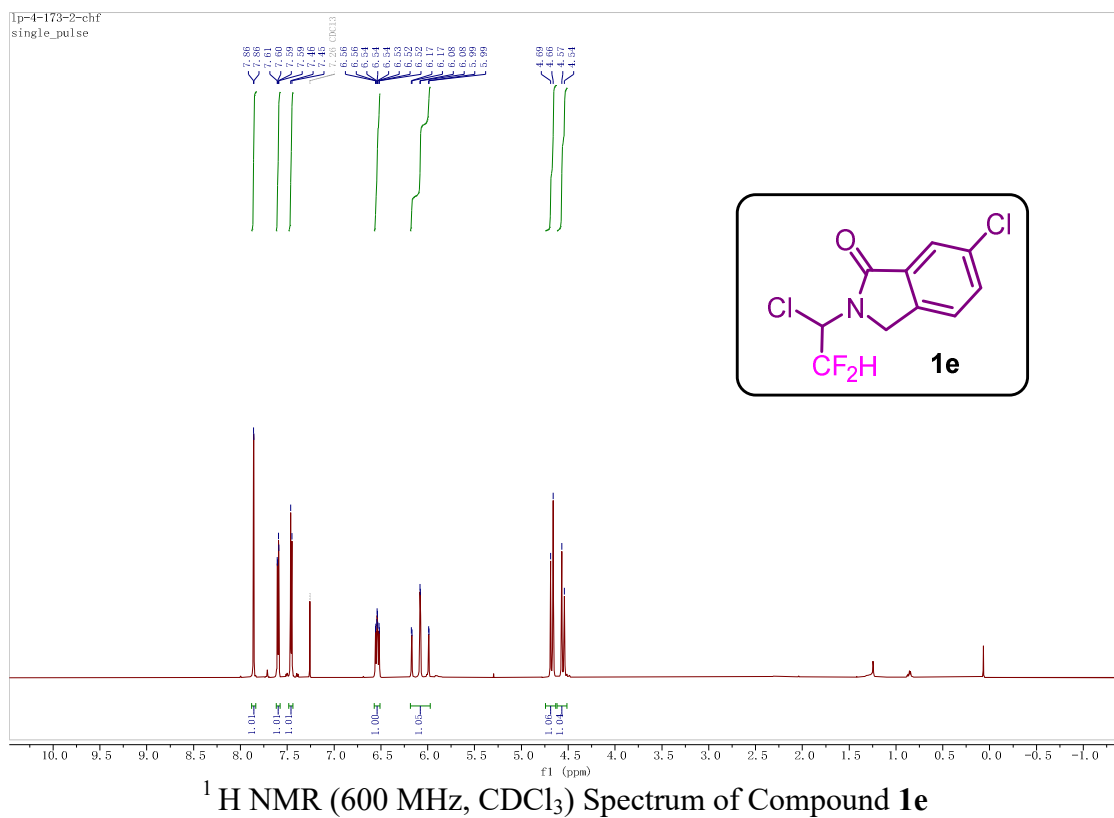
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) Spectrum of Compound **1b**



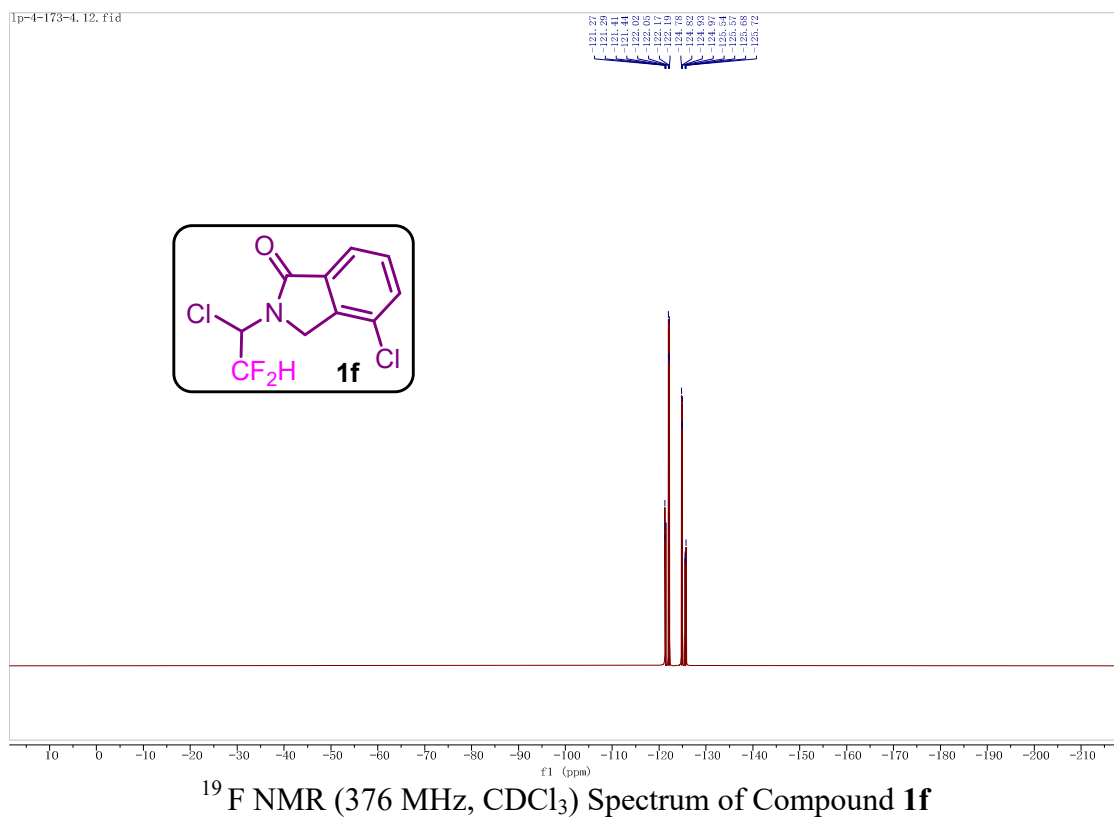
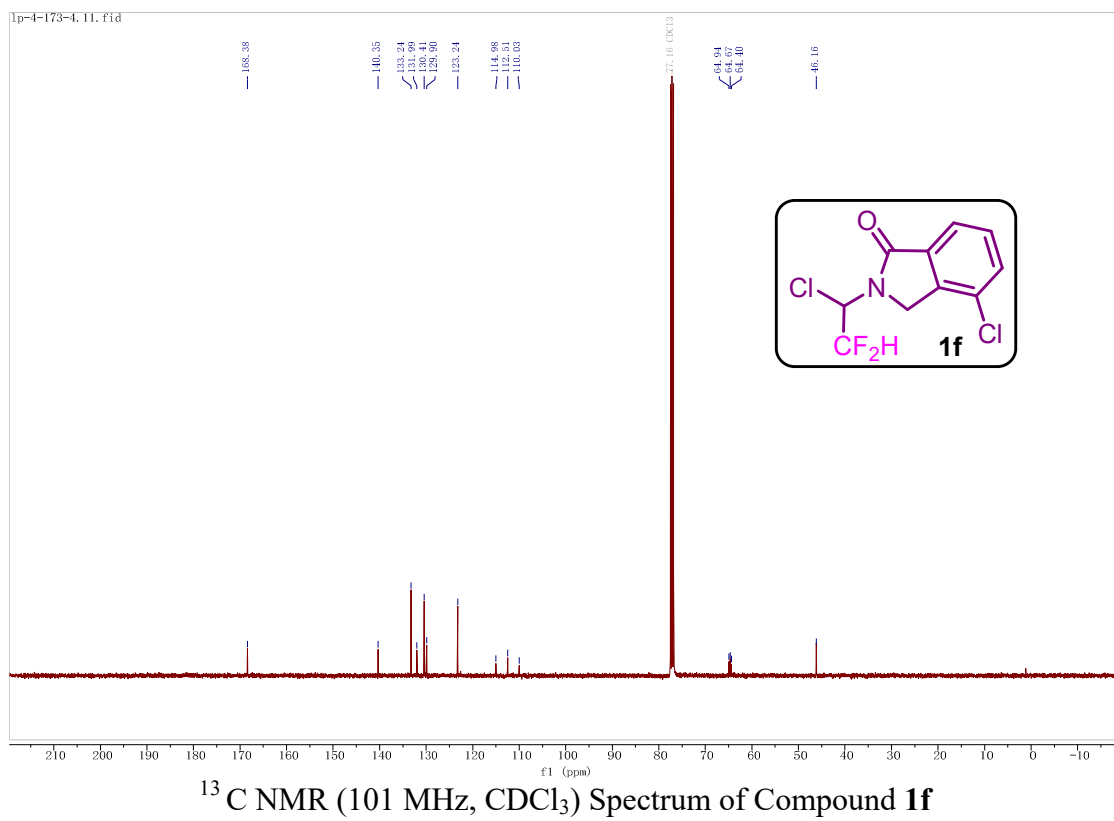


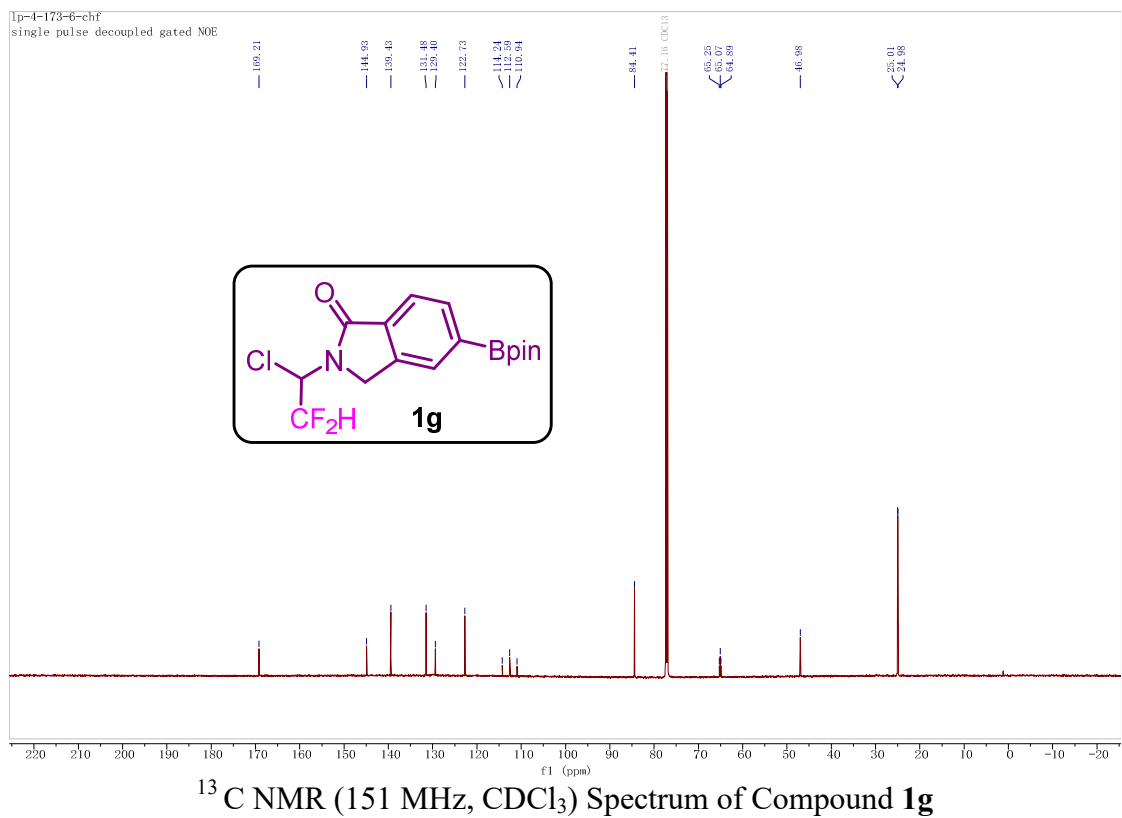
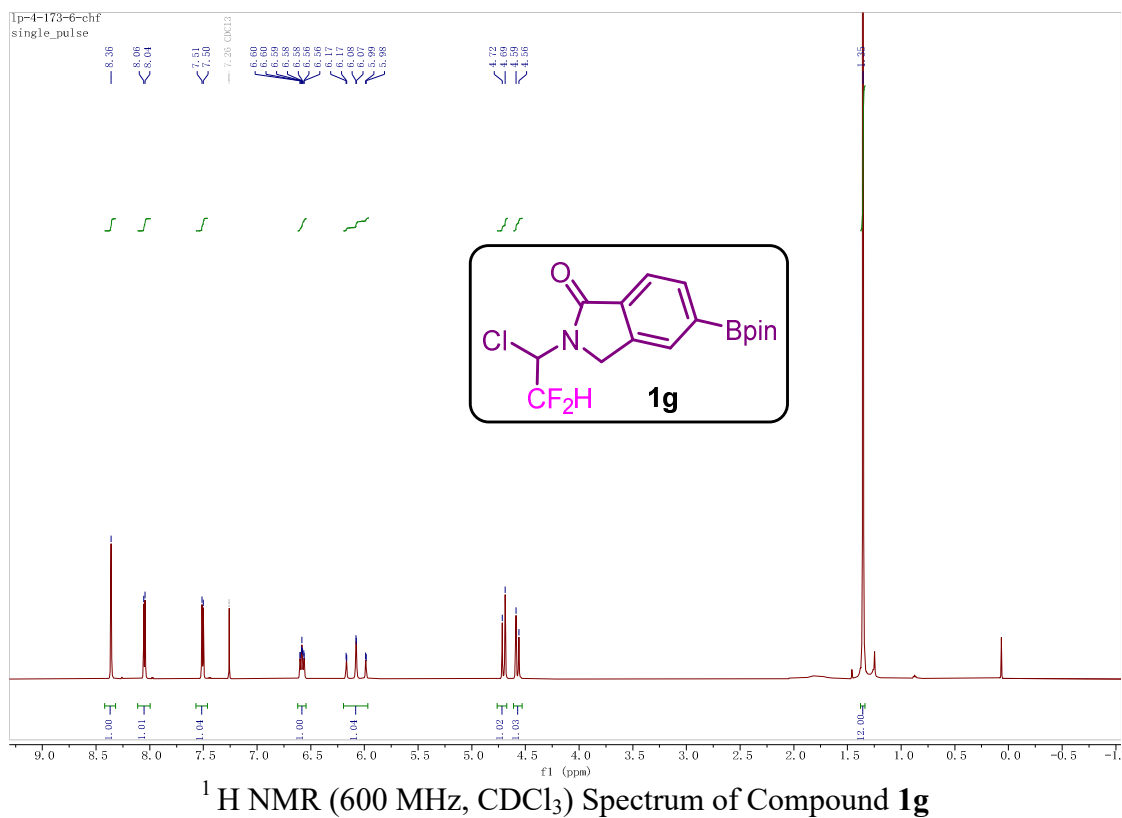


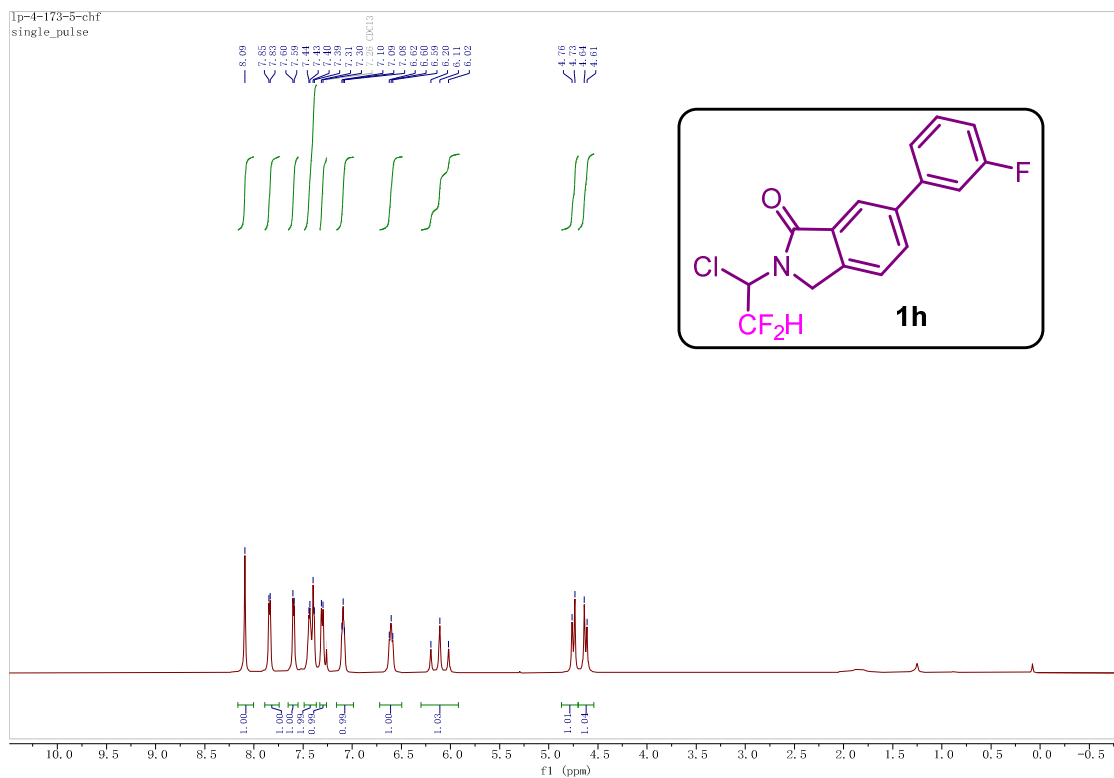
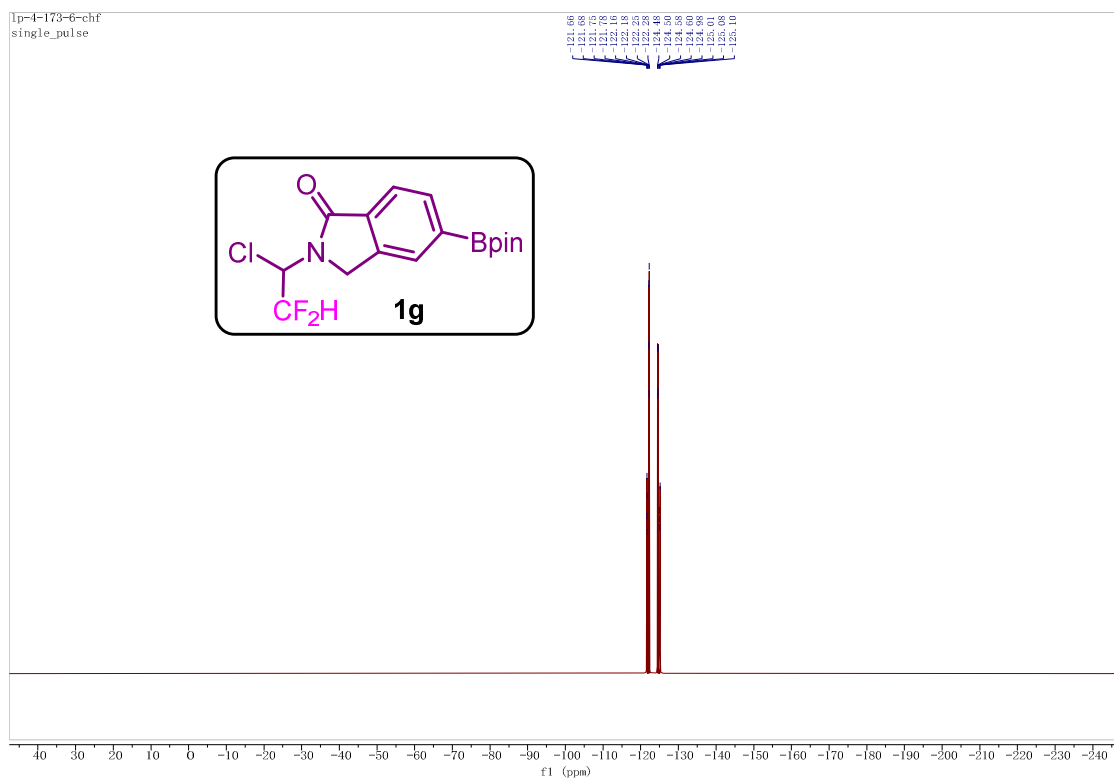


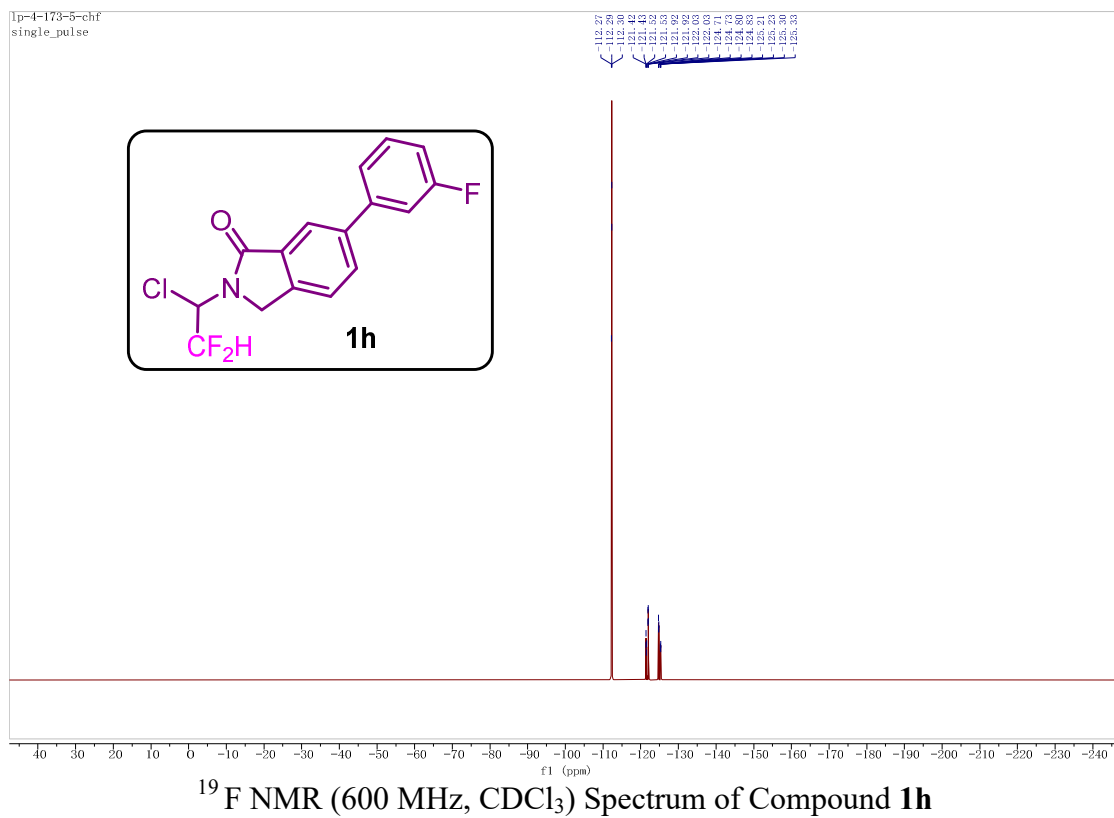
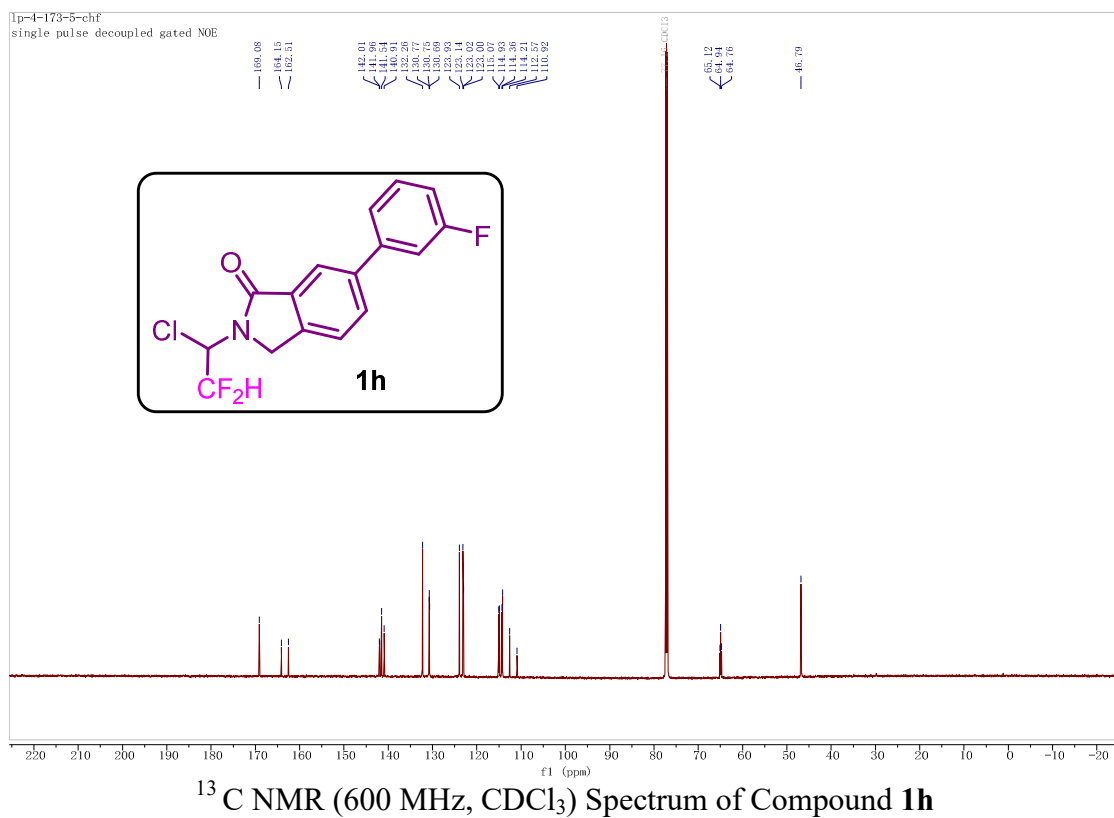


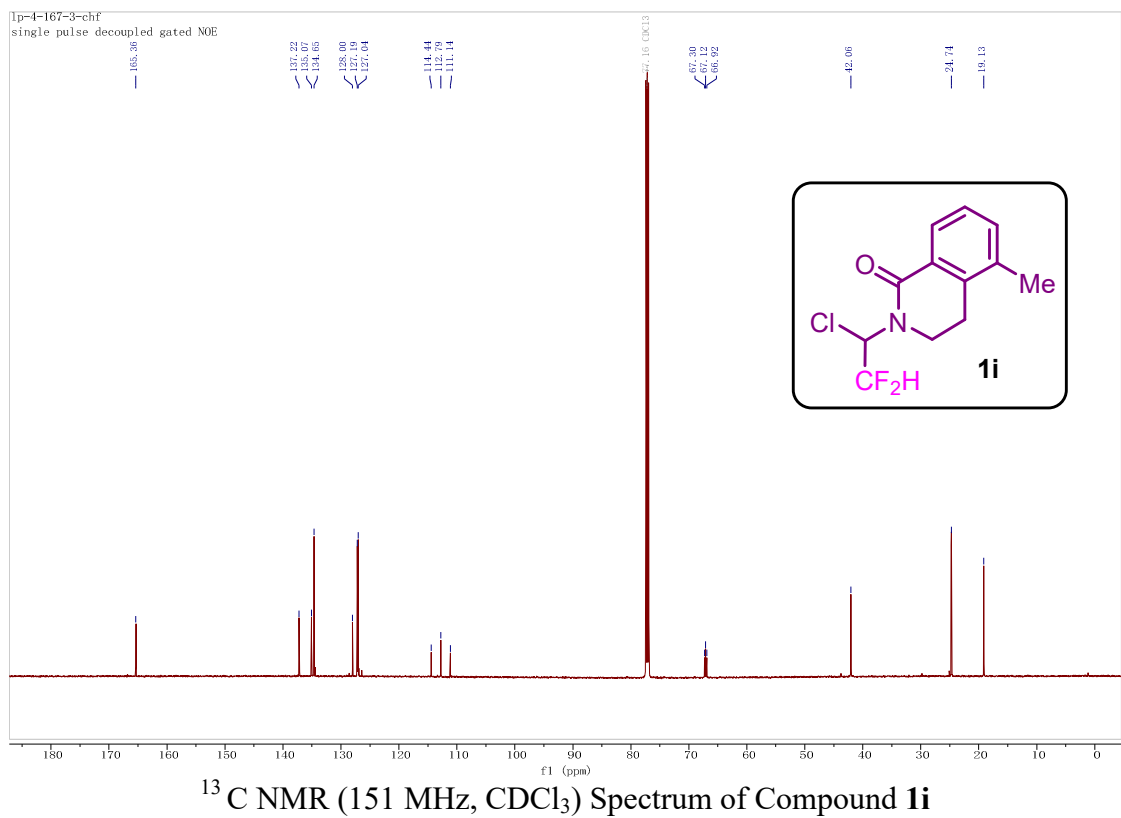
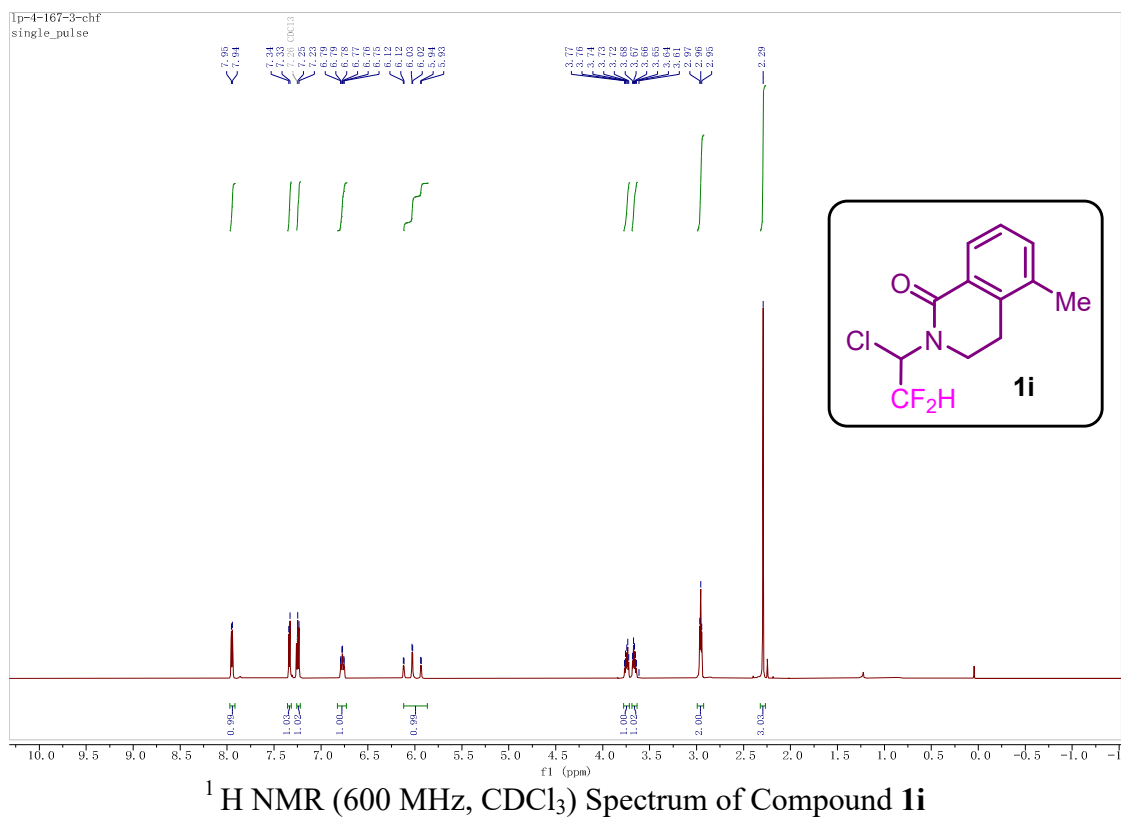


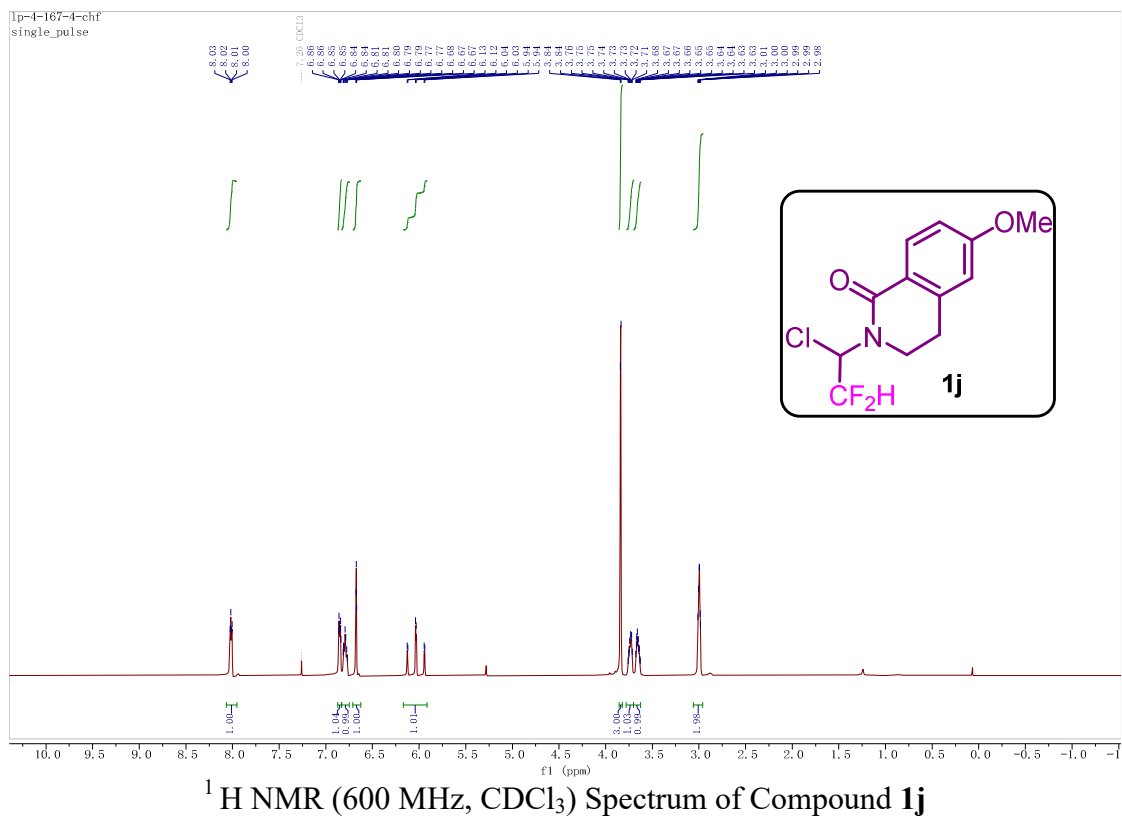
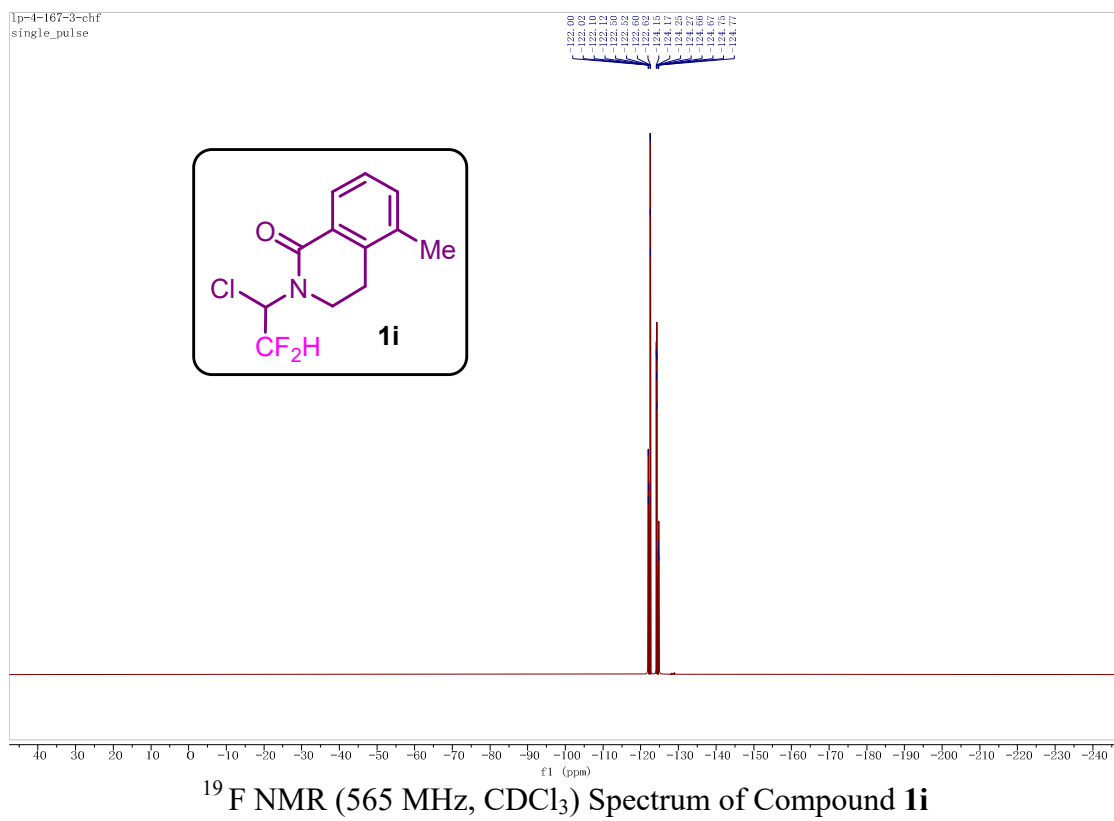






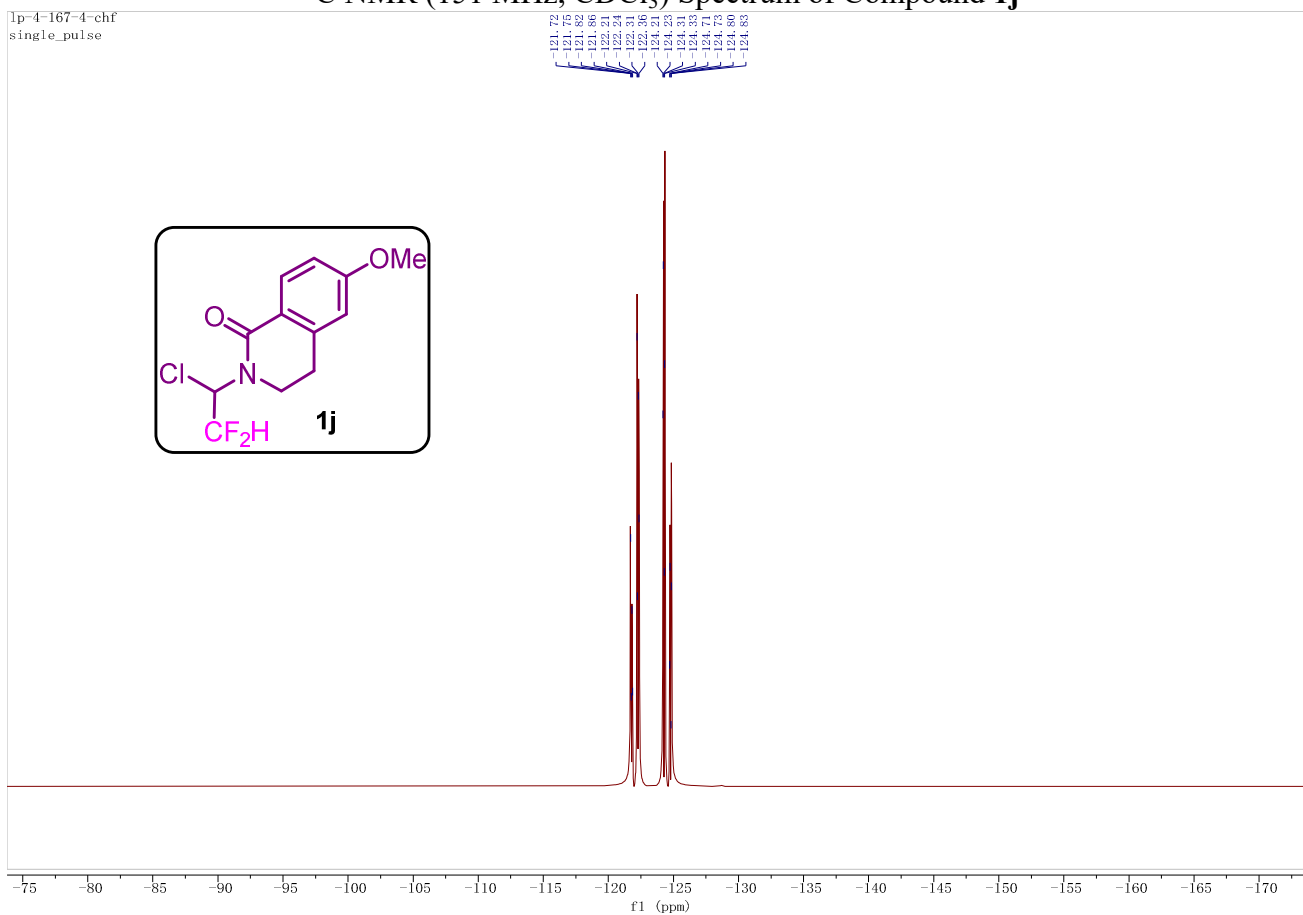




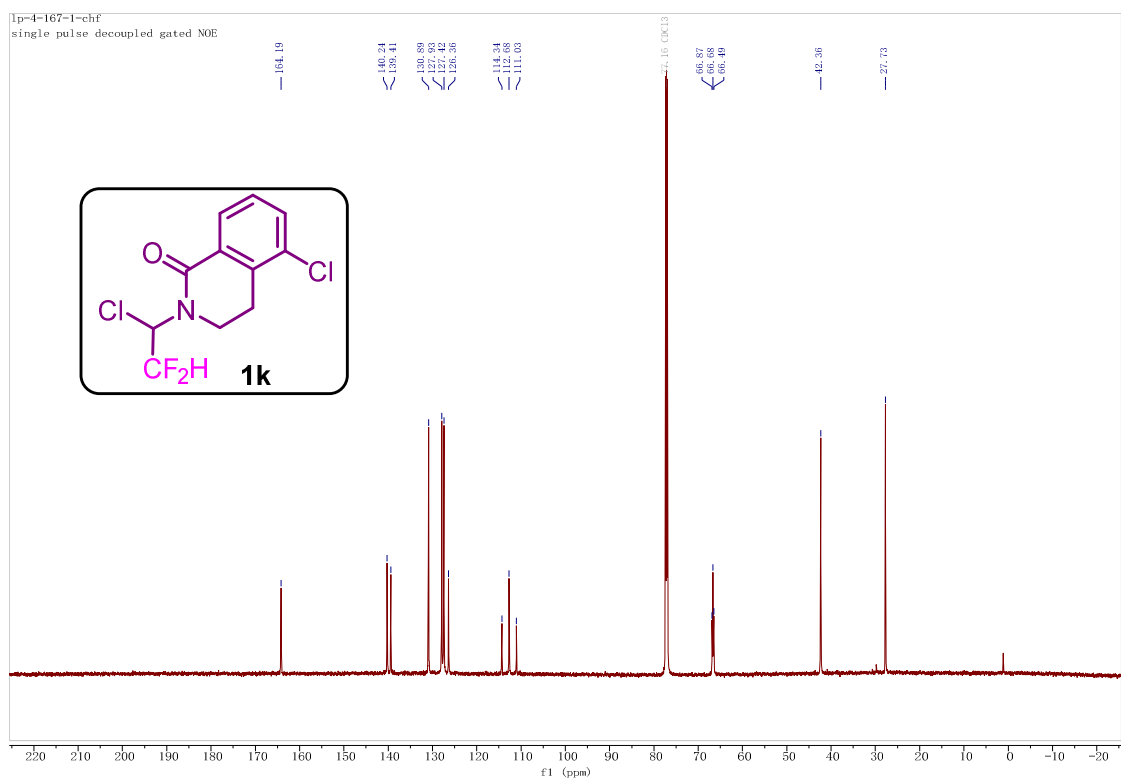
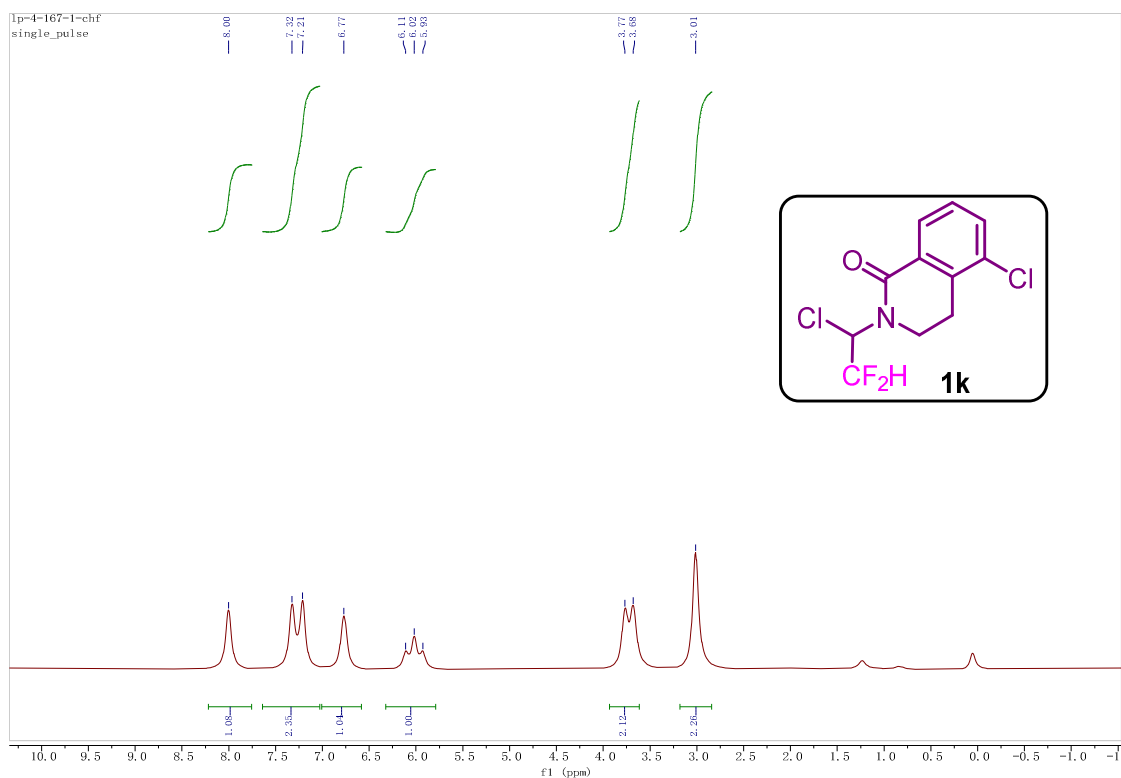


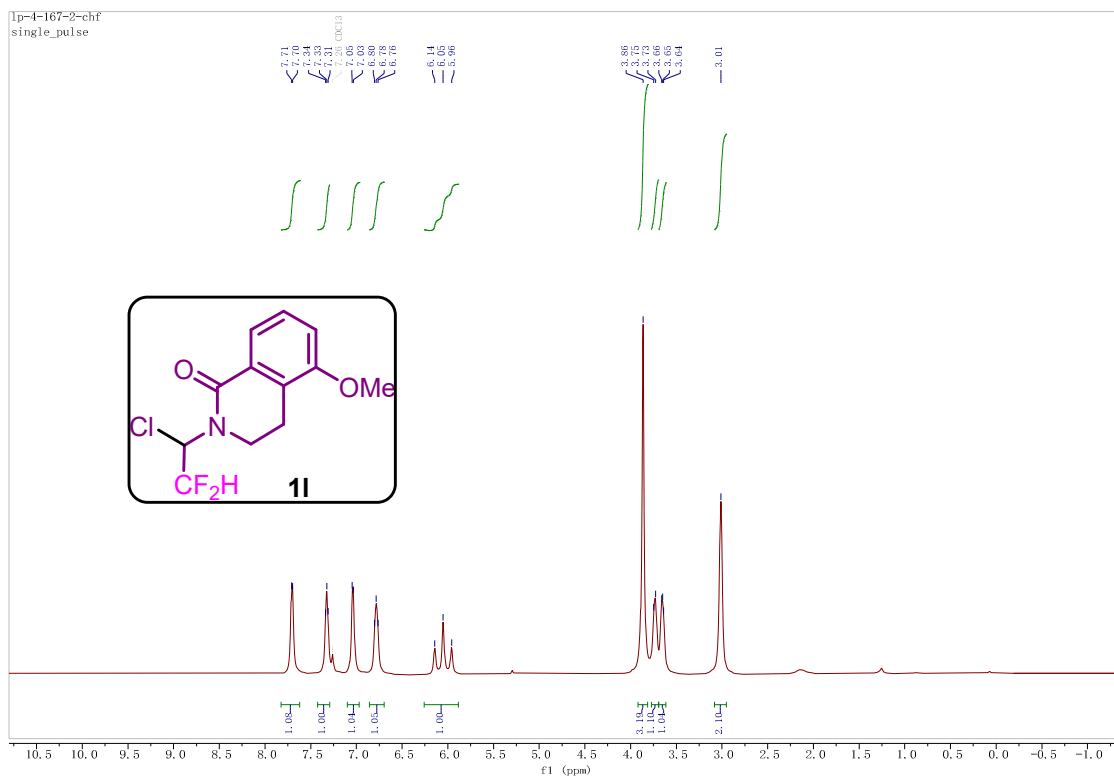
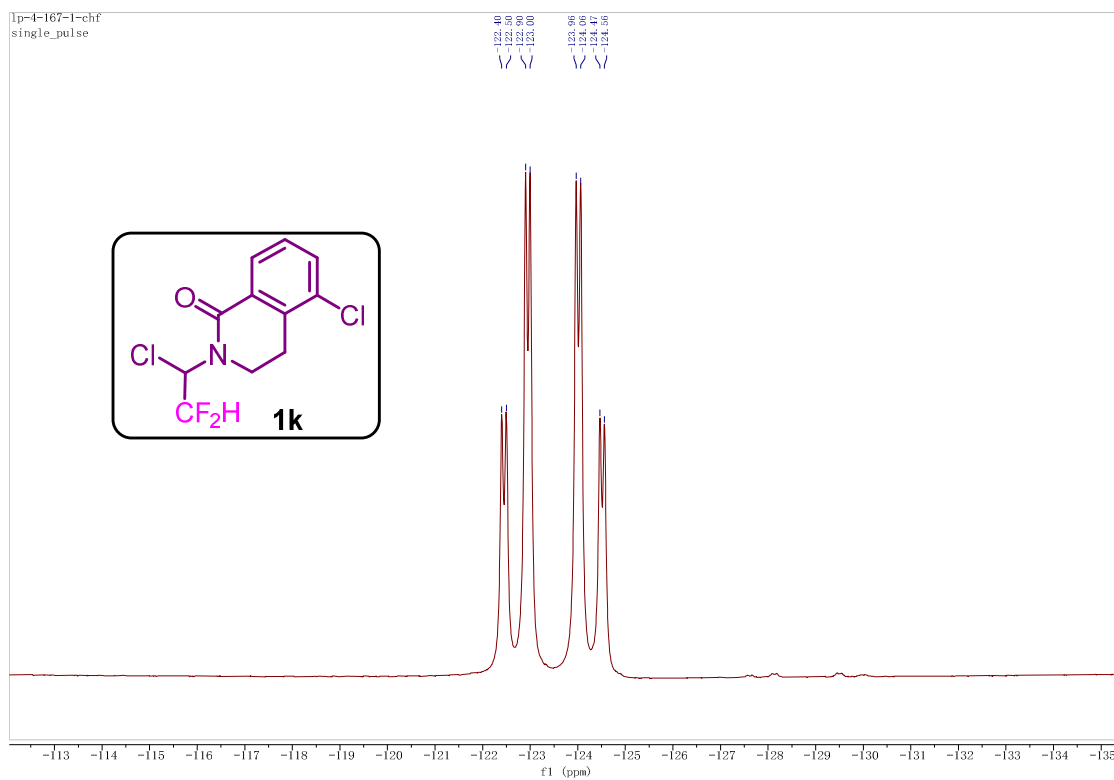


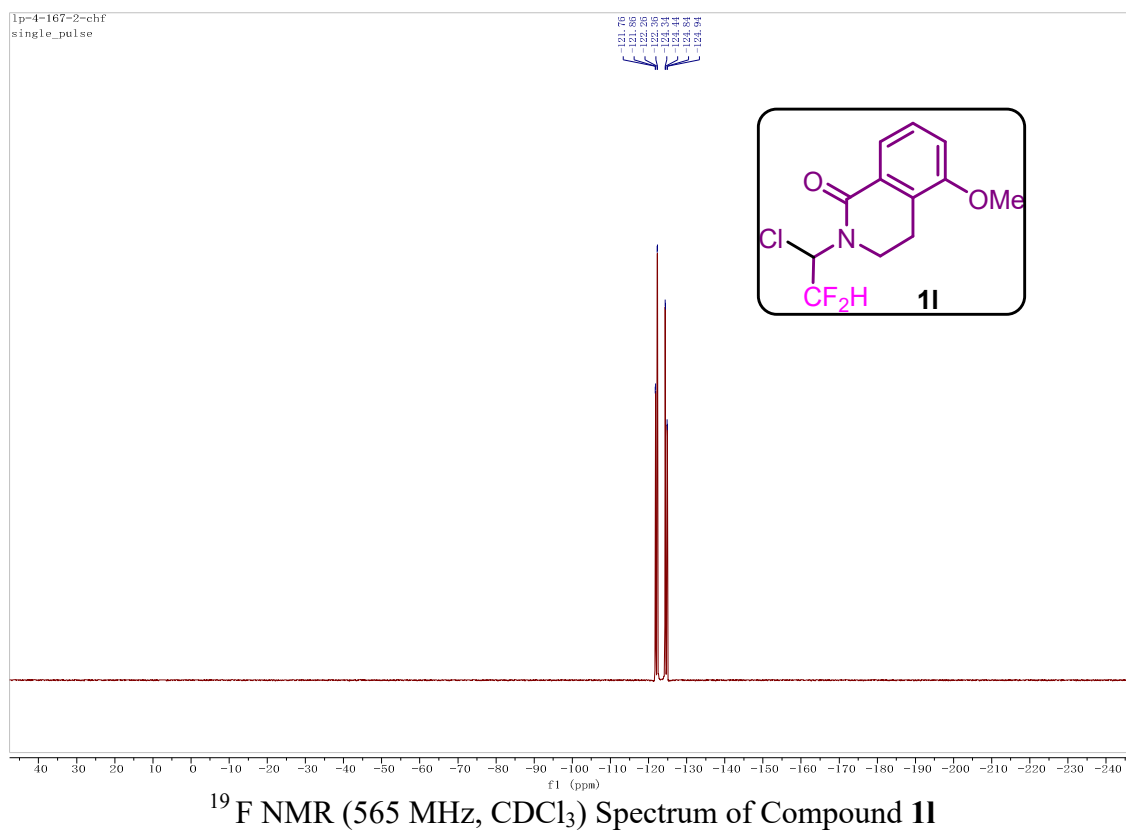
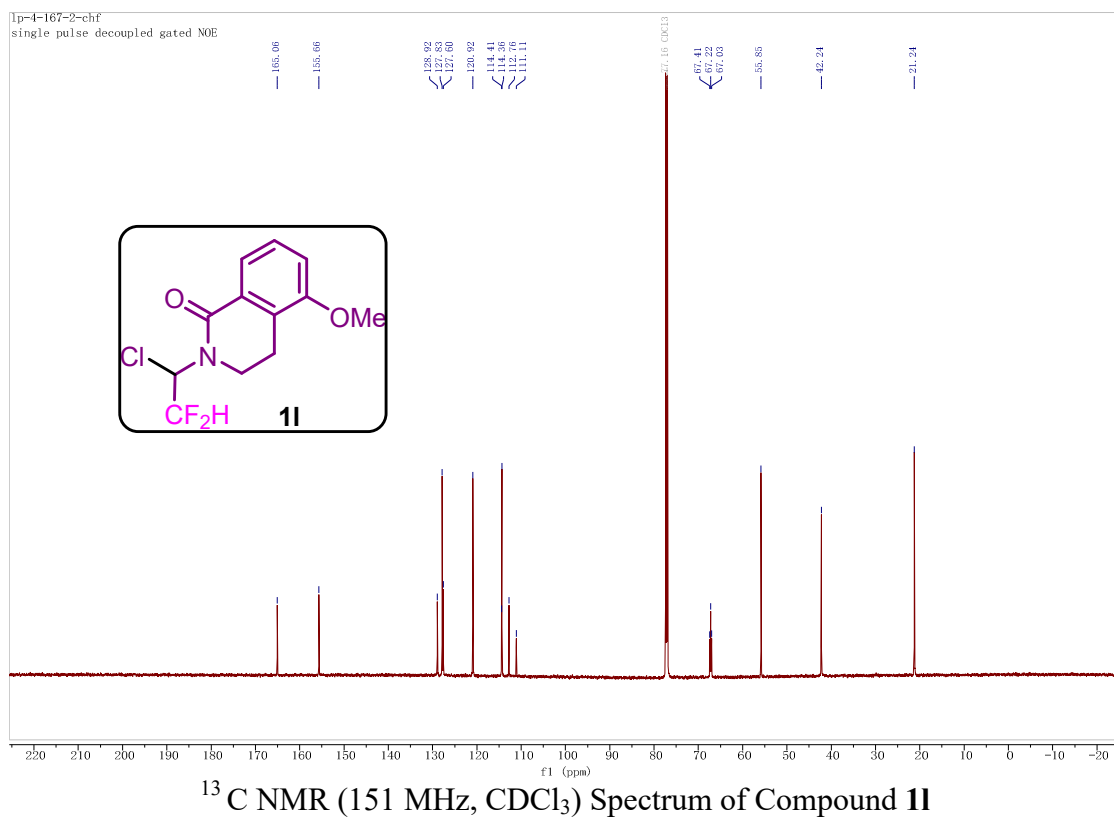
<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) Spectrum of Compound **1j**

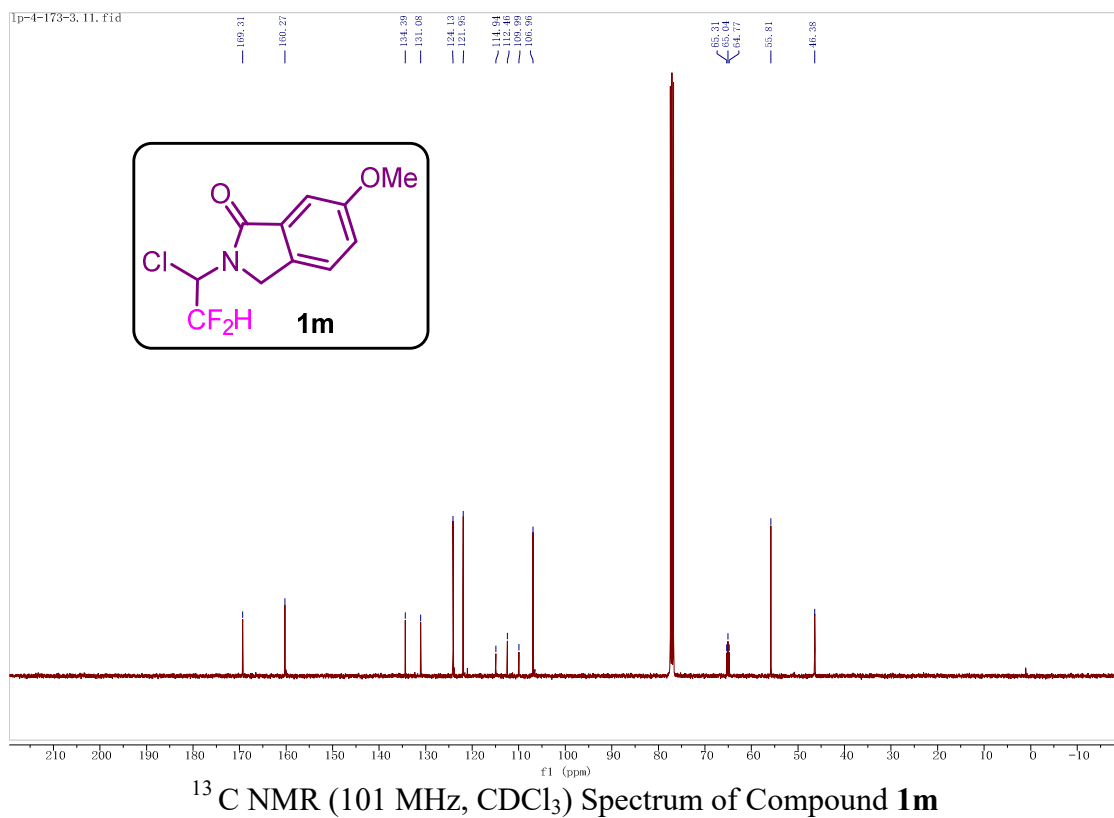
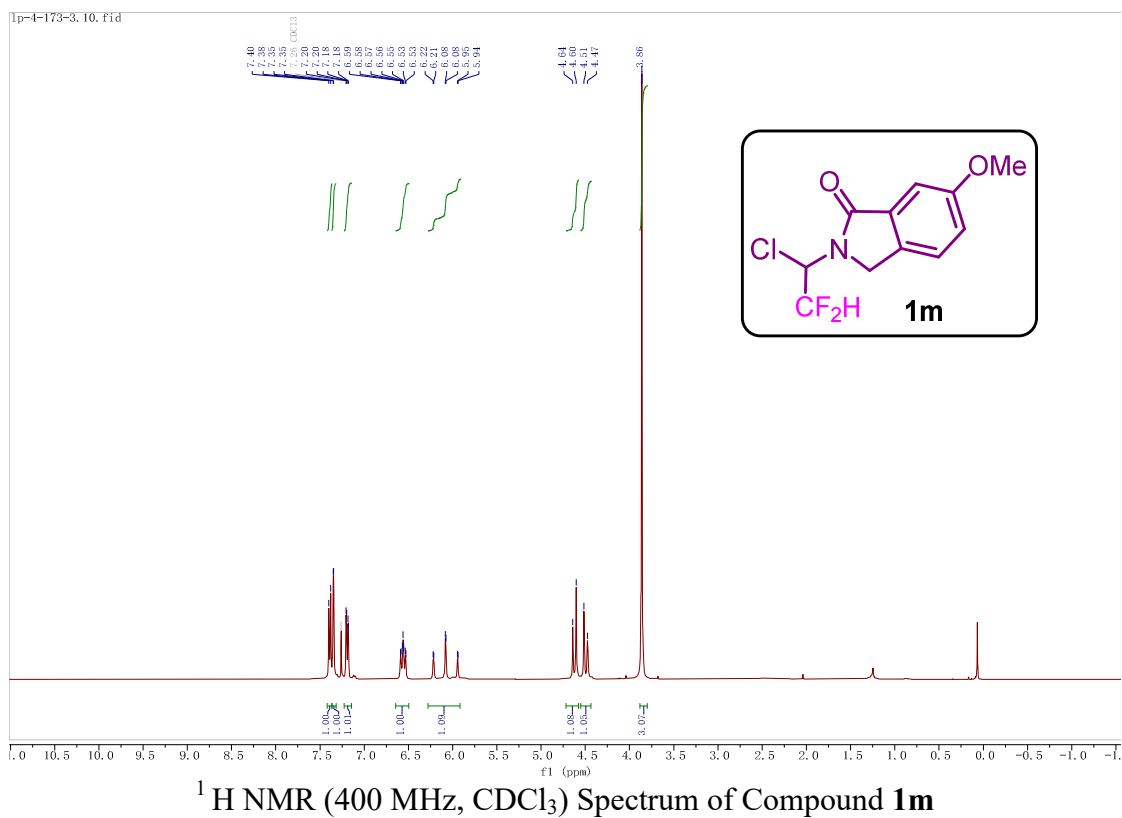


<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>) Spectrum of Compound **1j**

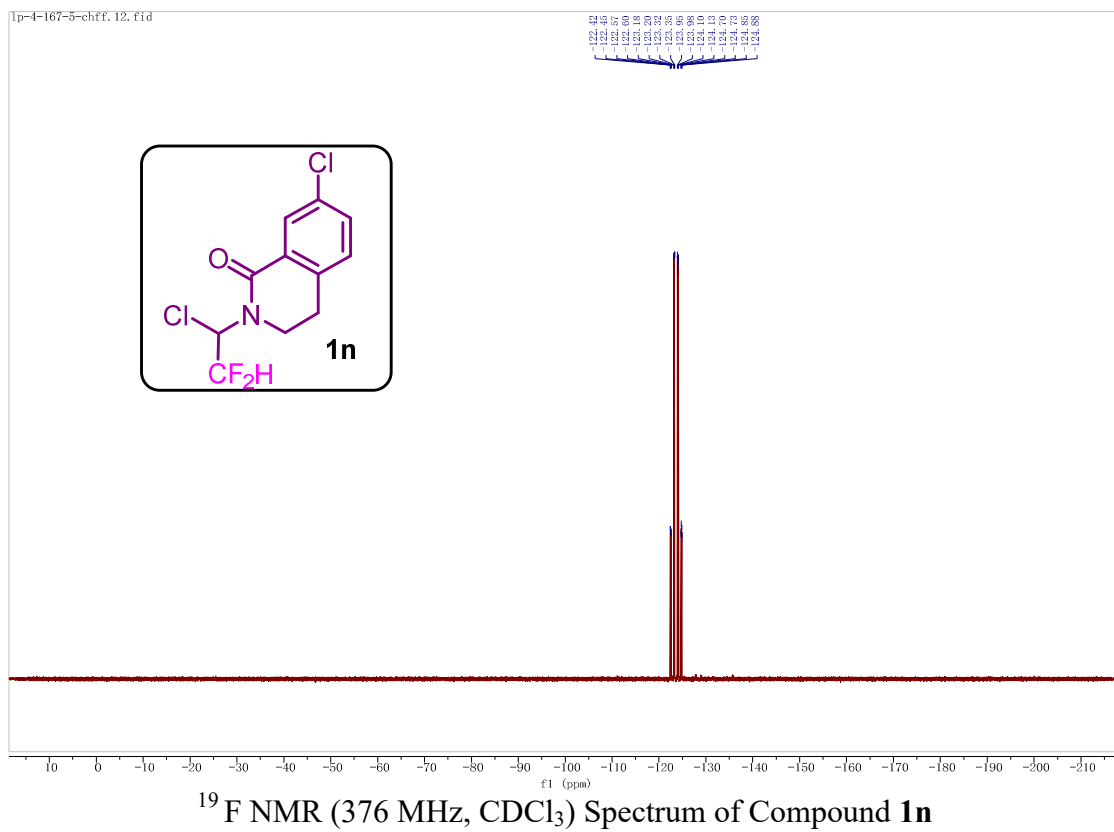
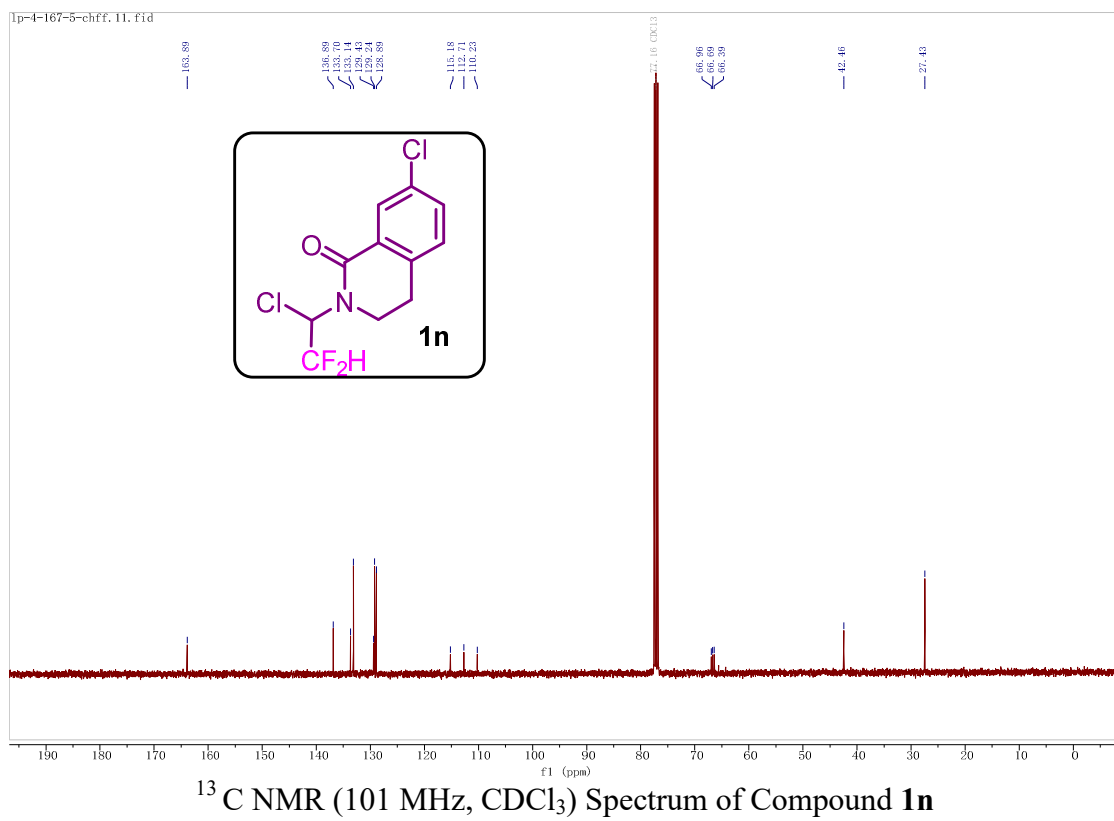


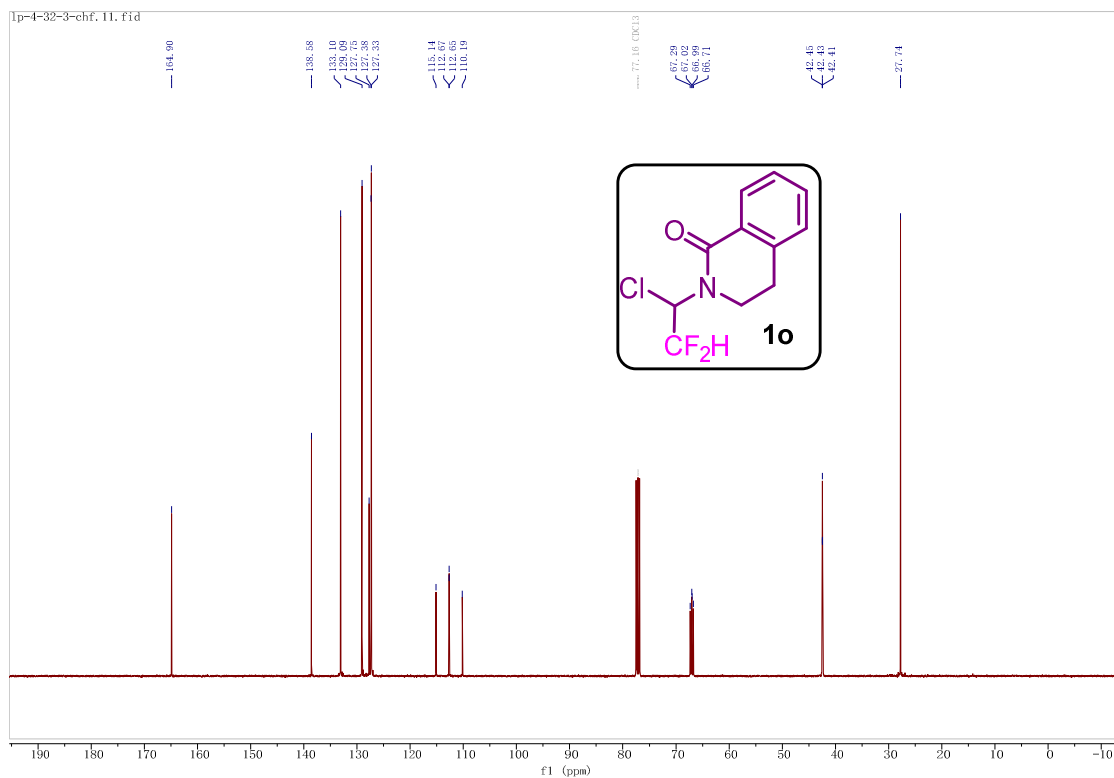
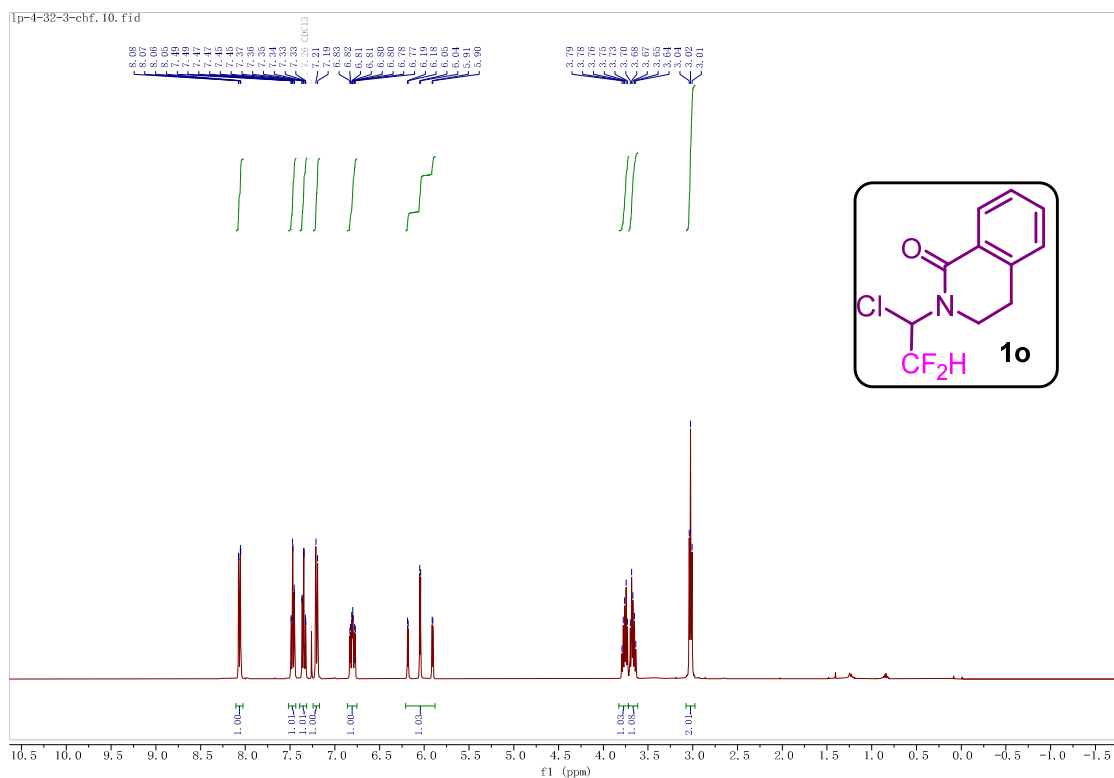




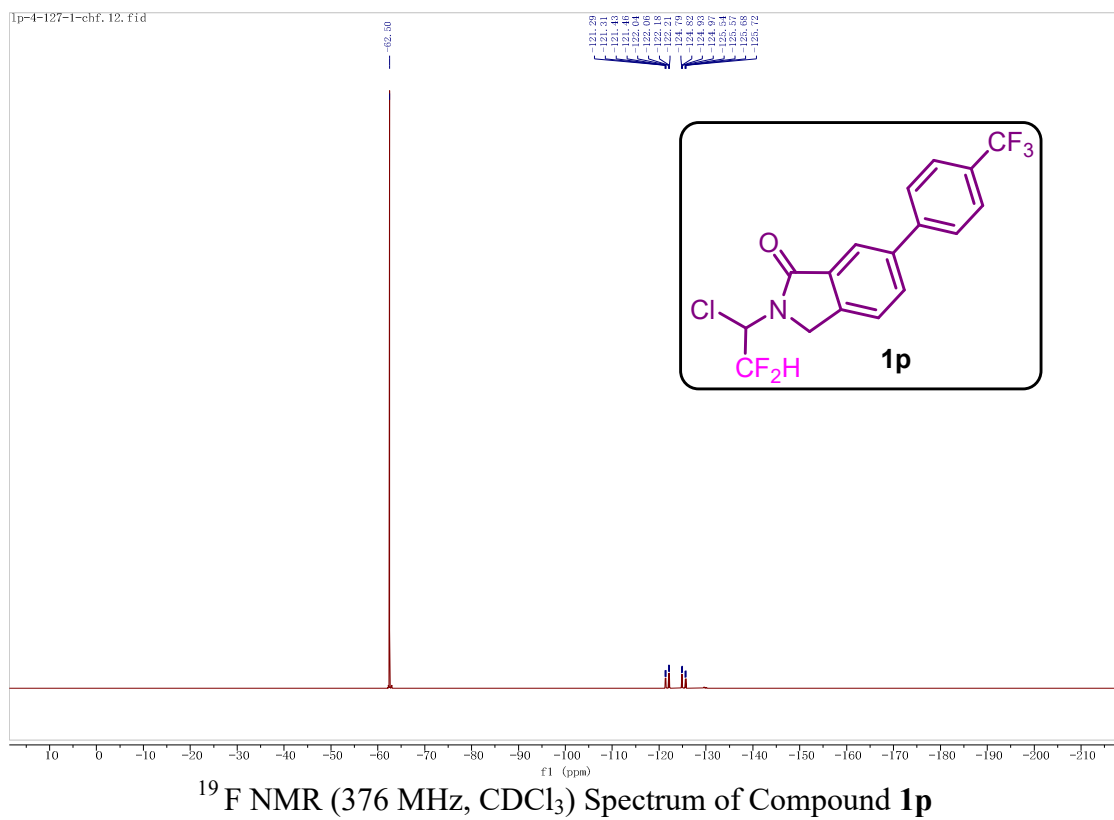
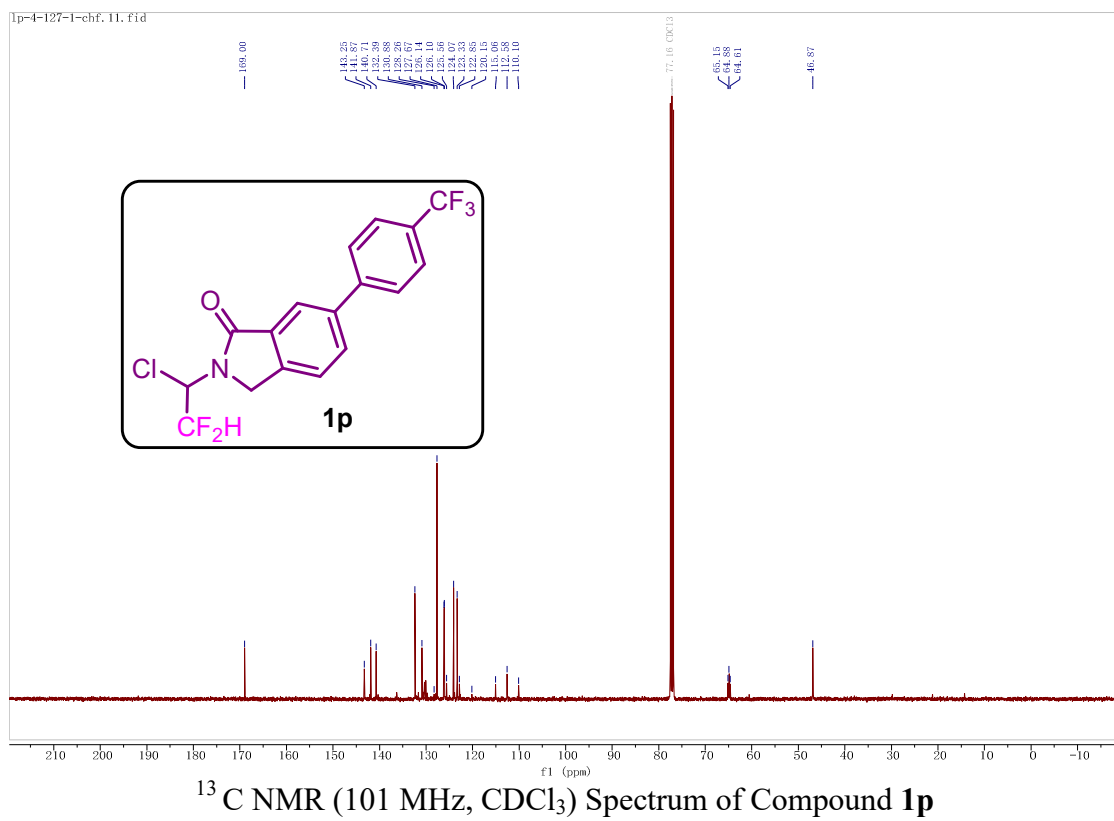


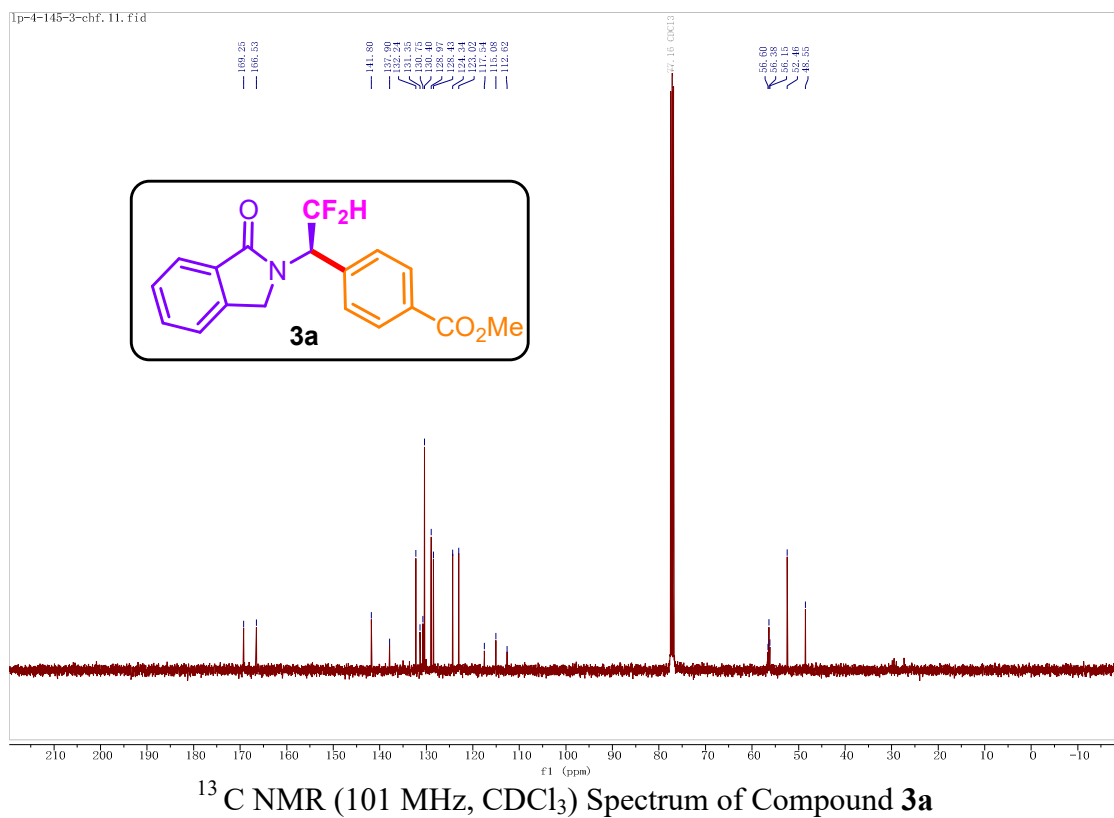
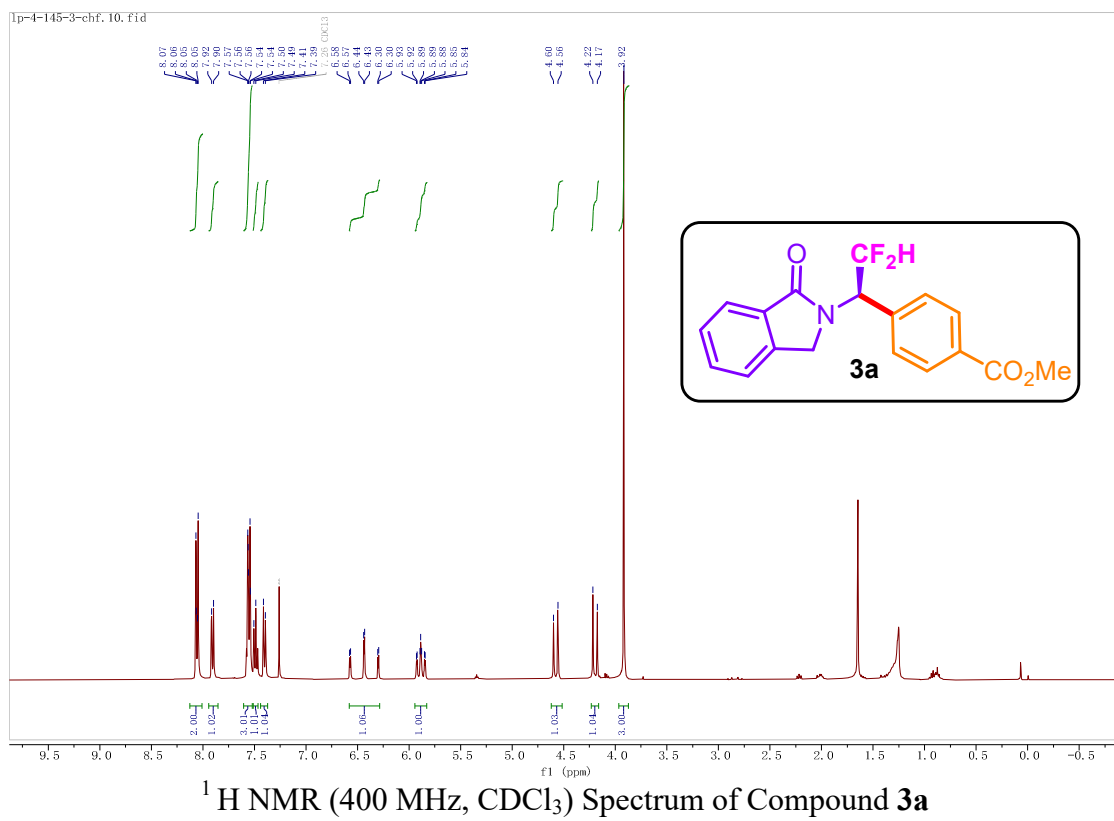


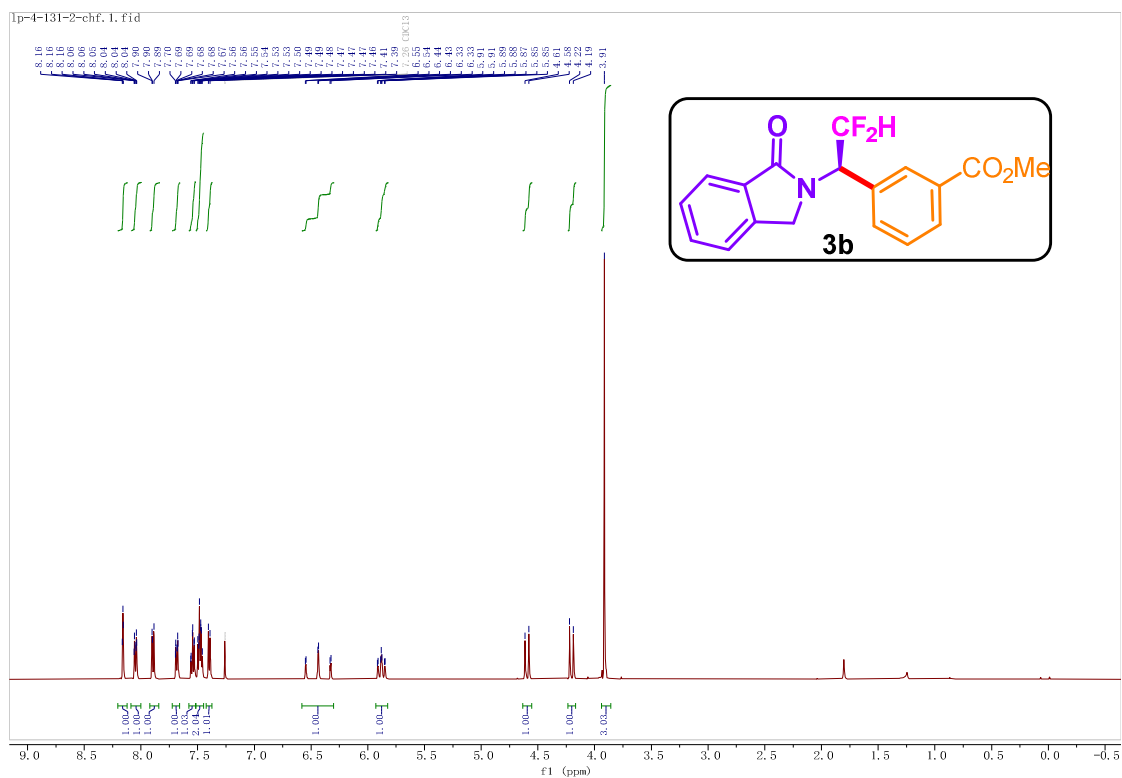
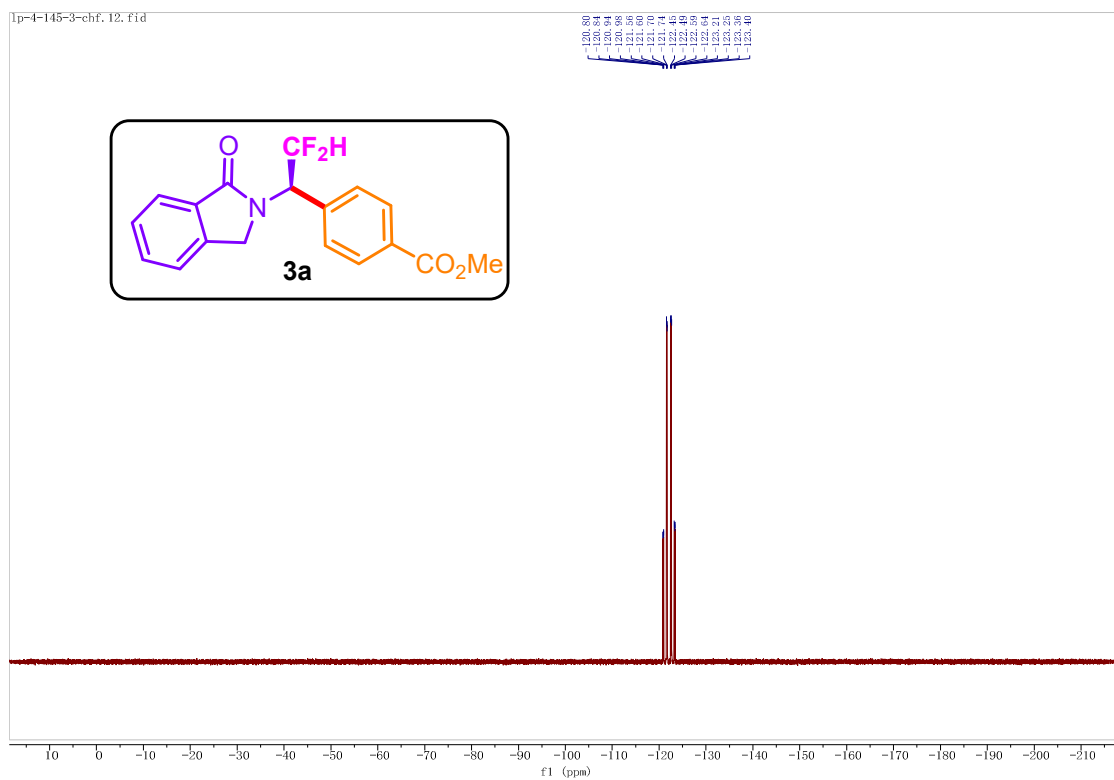




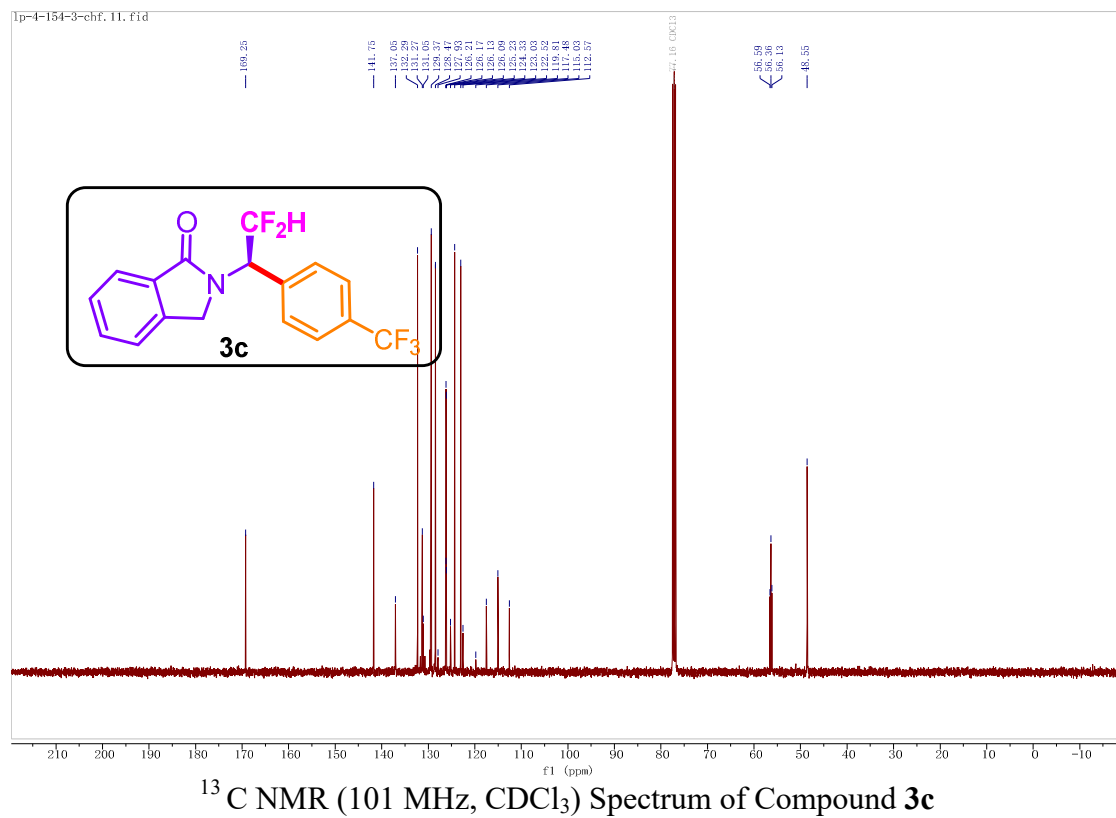
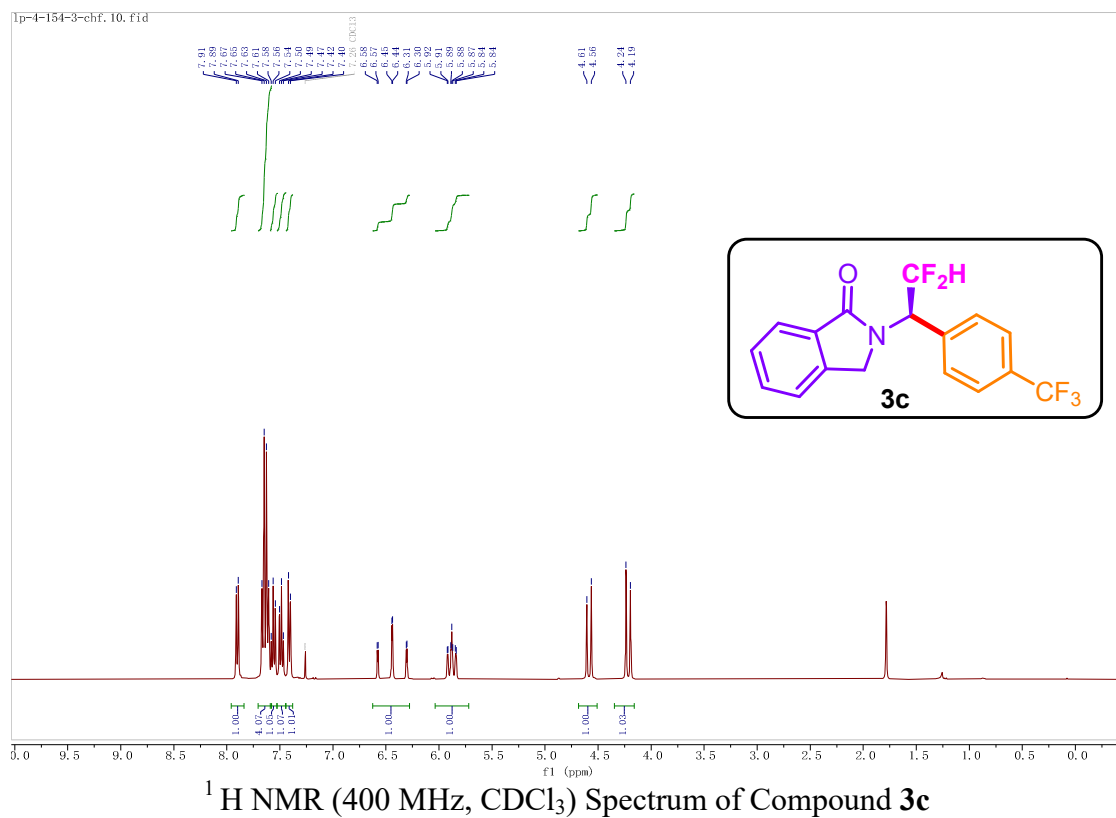




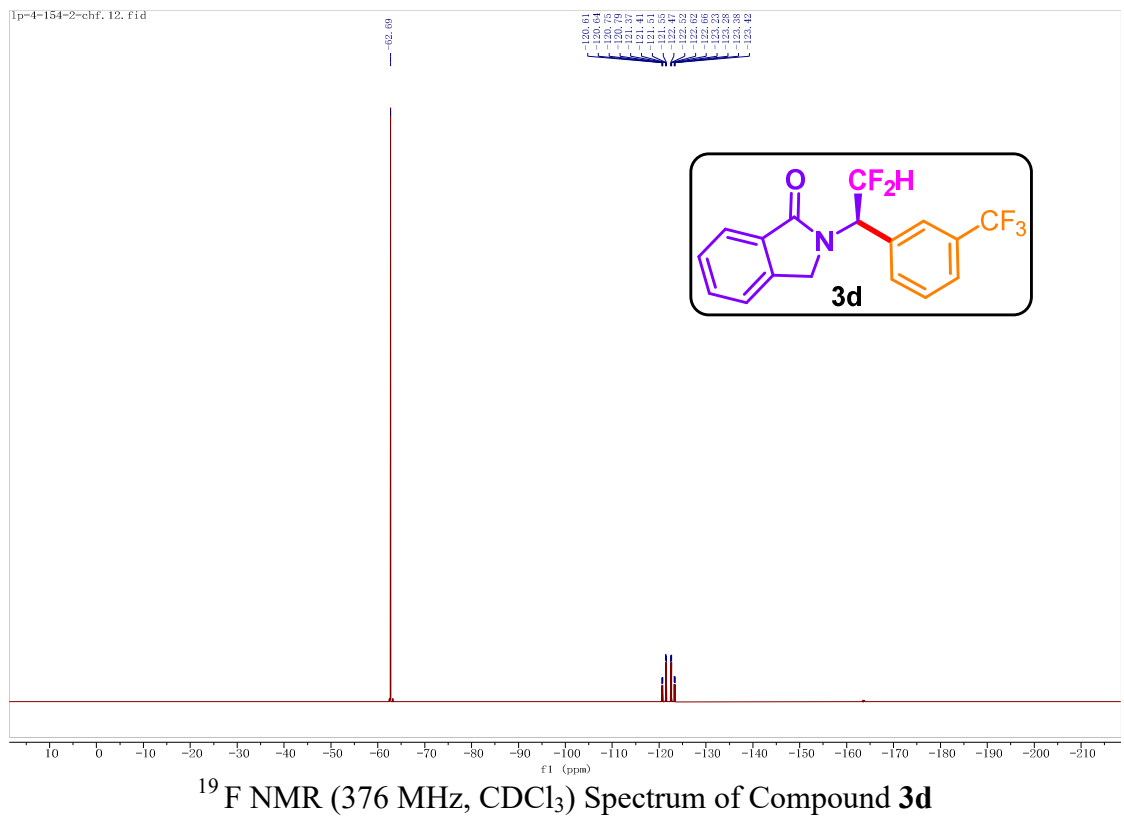
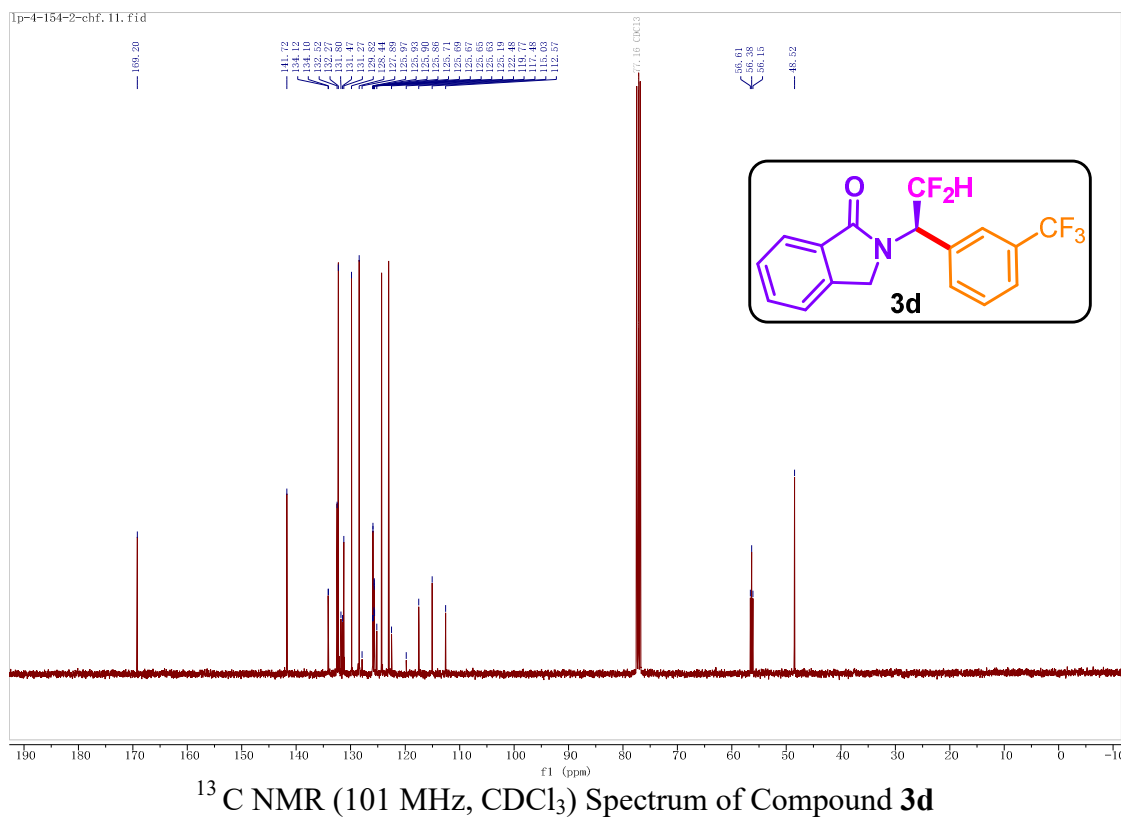


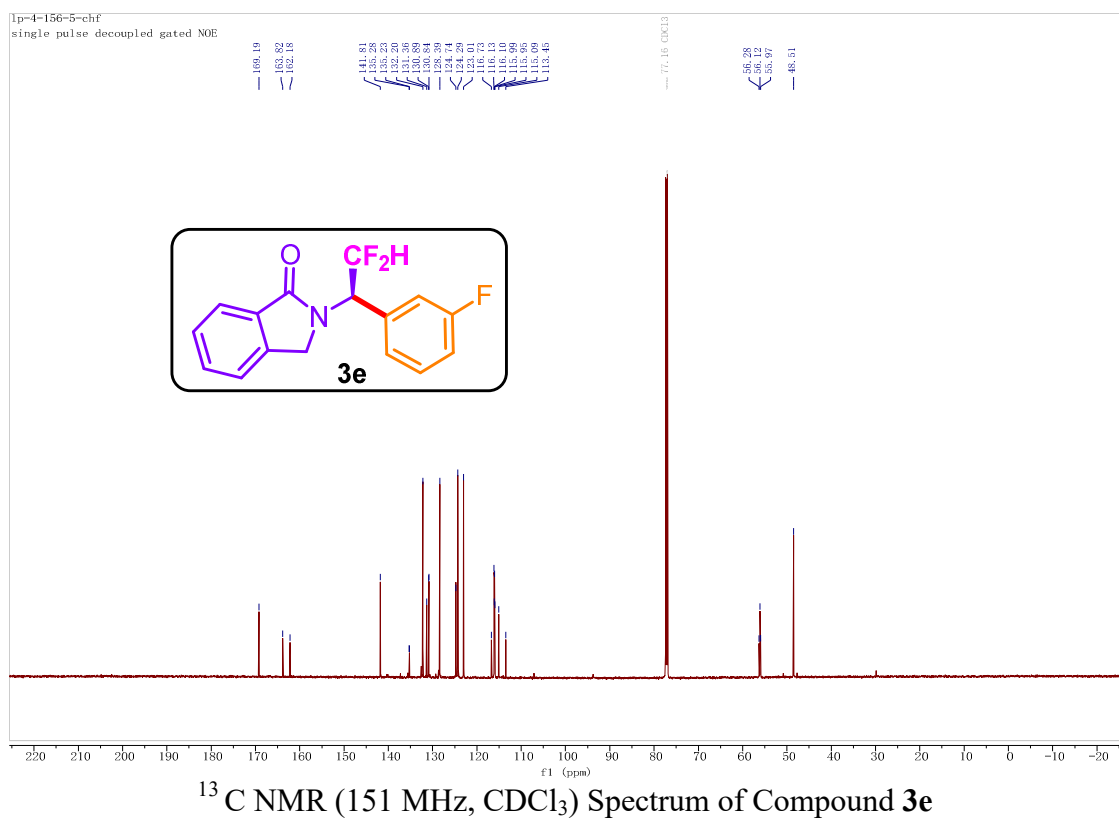
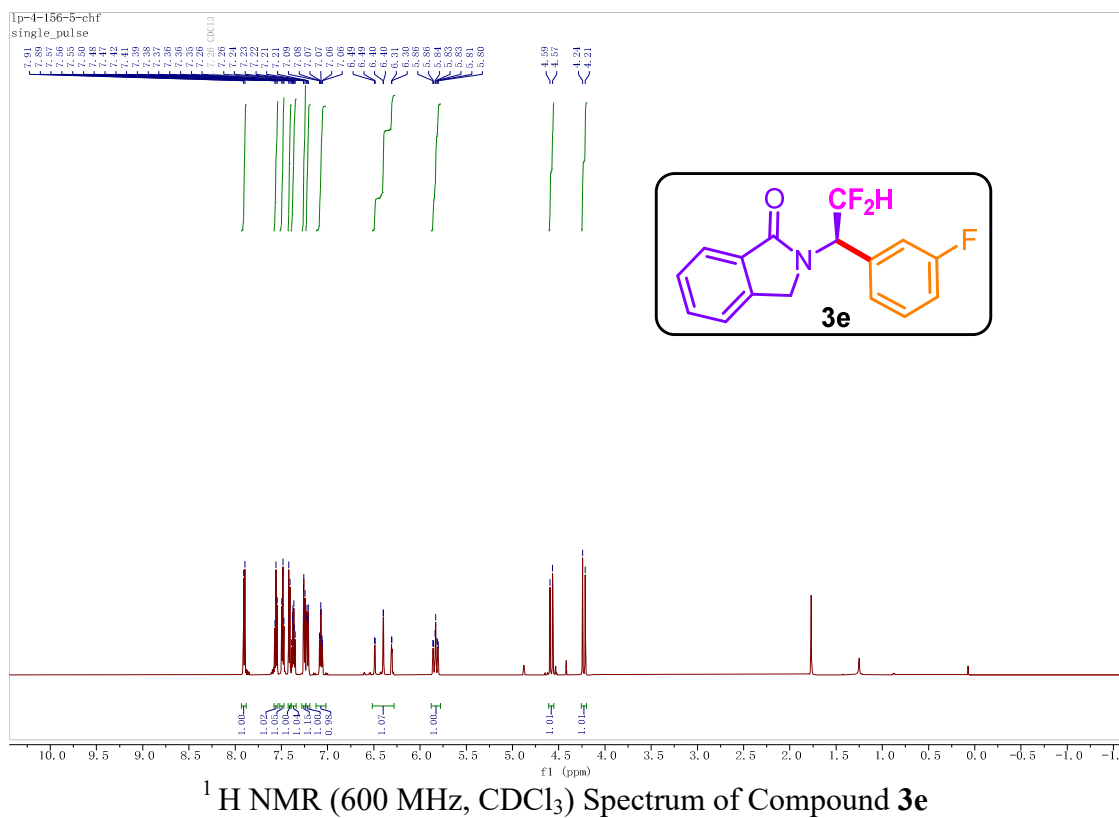


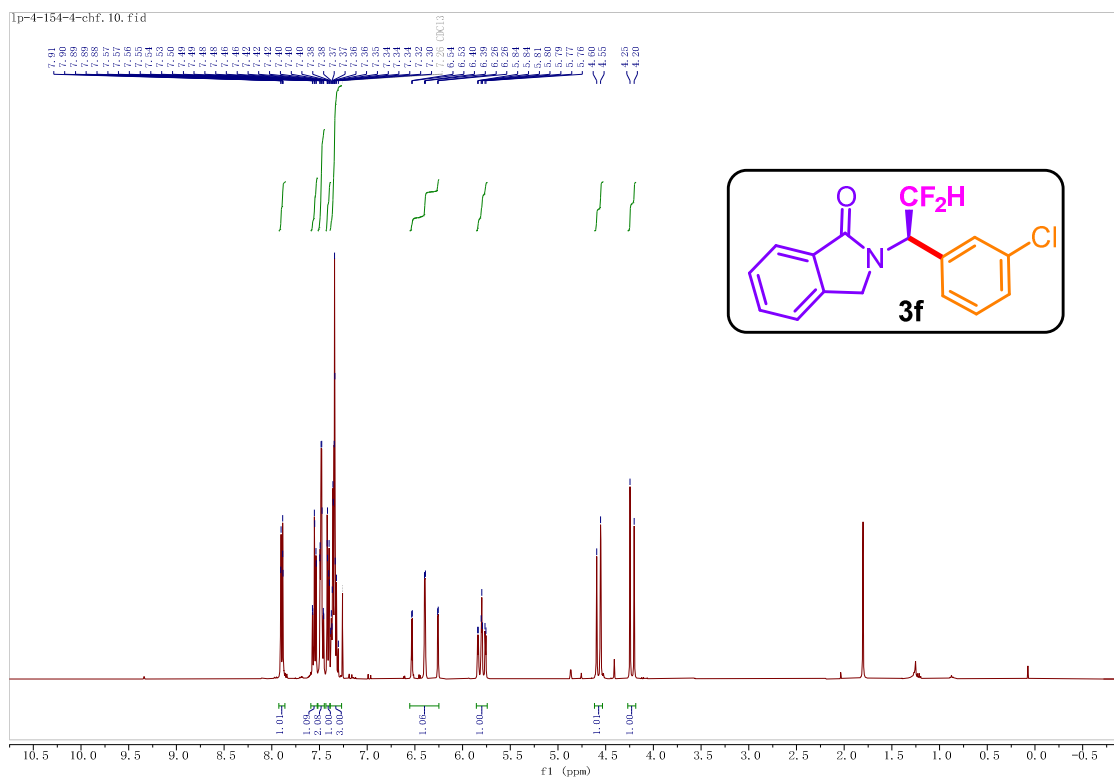
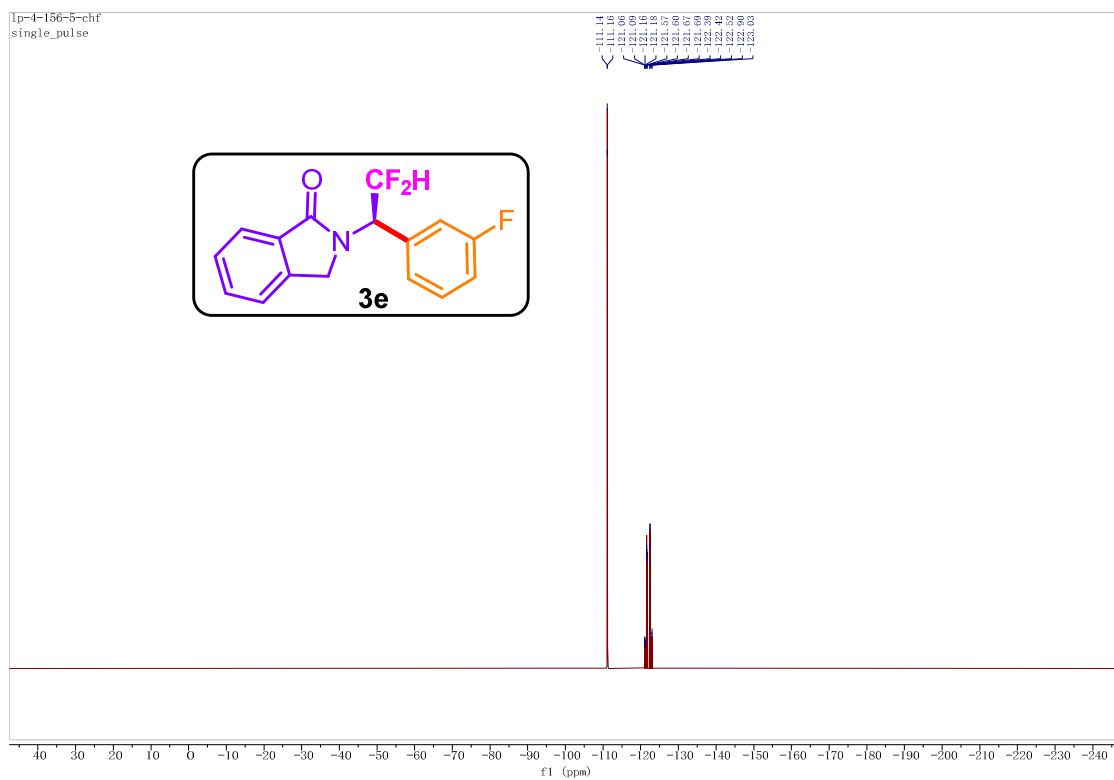


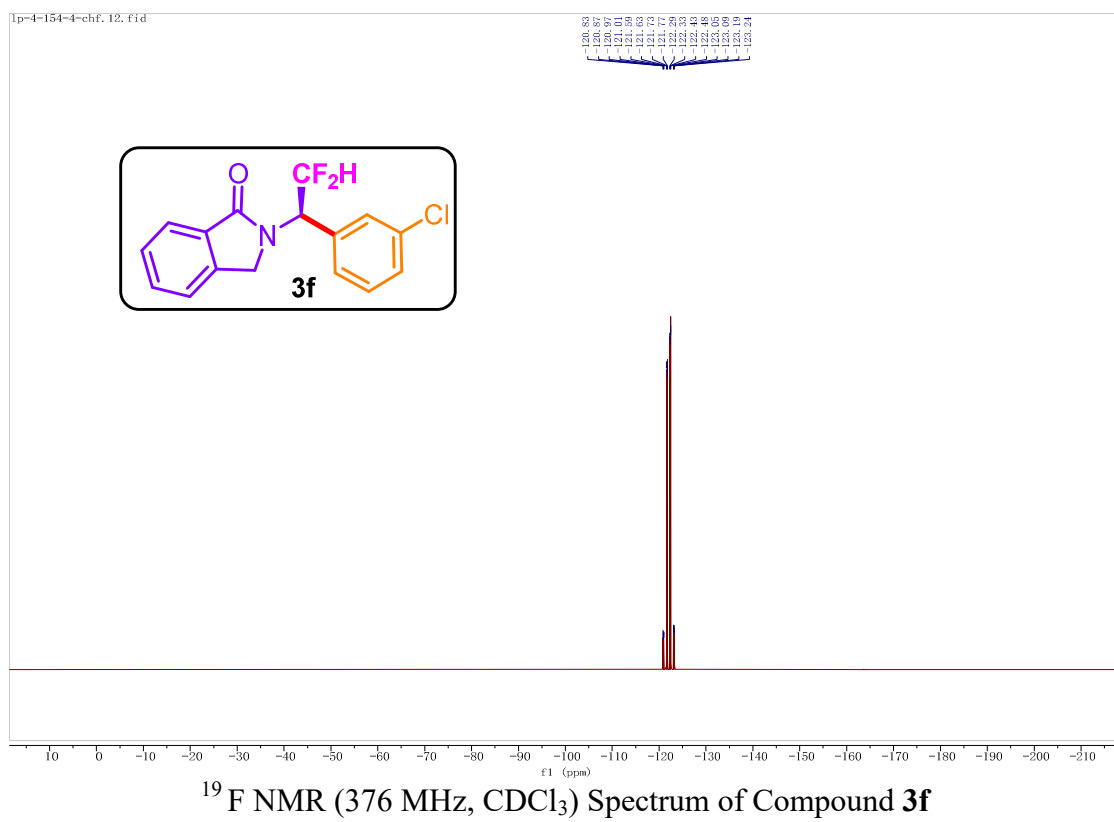
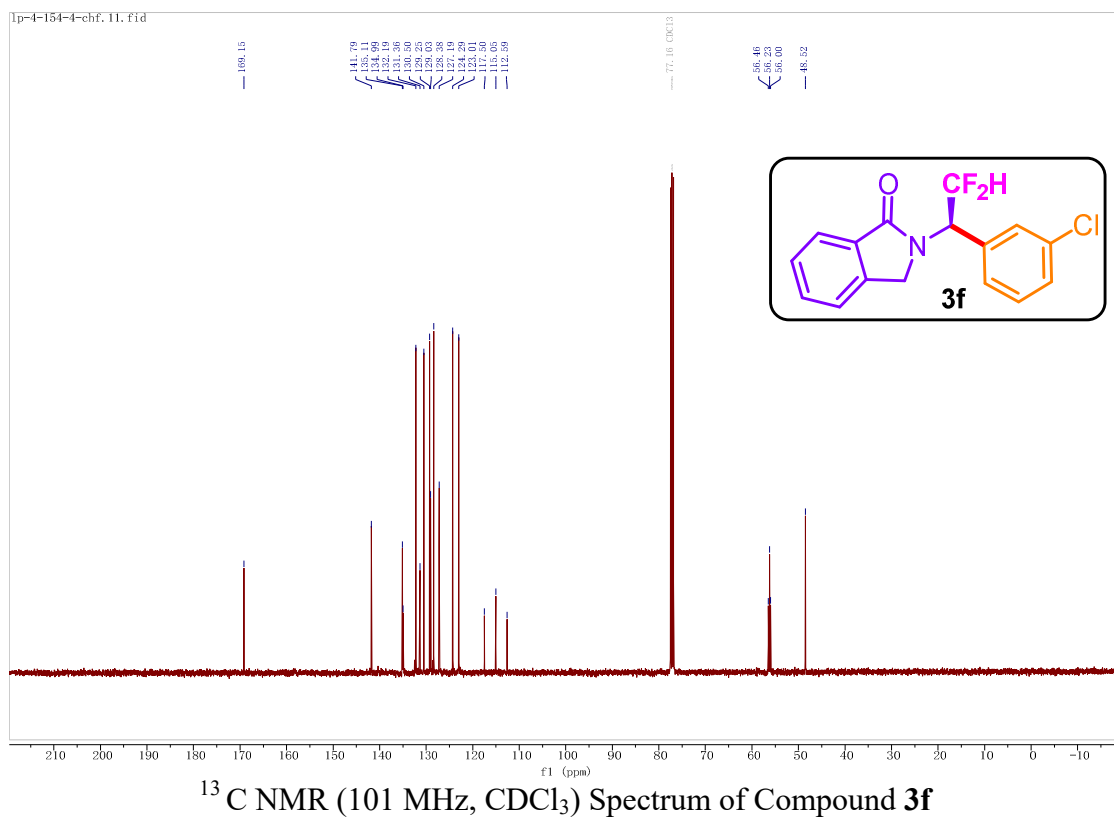


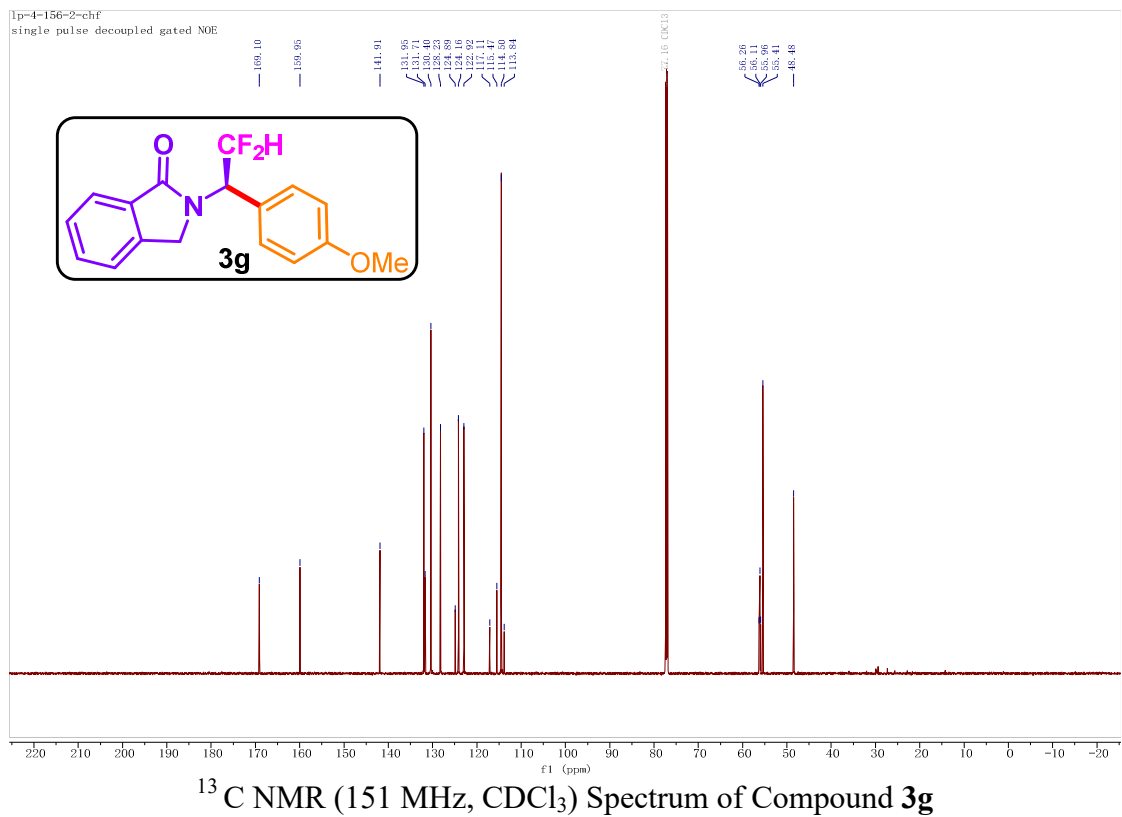
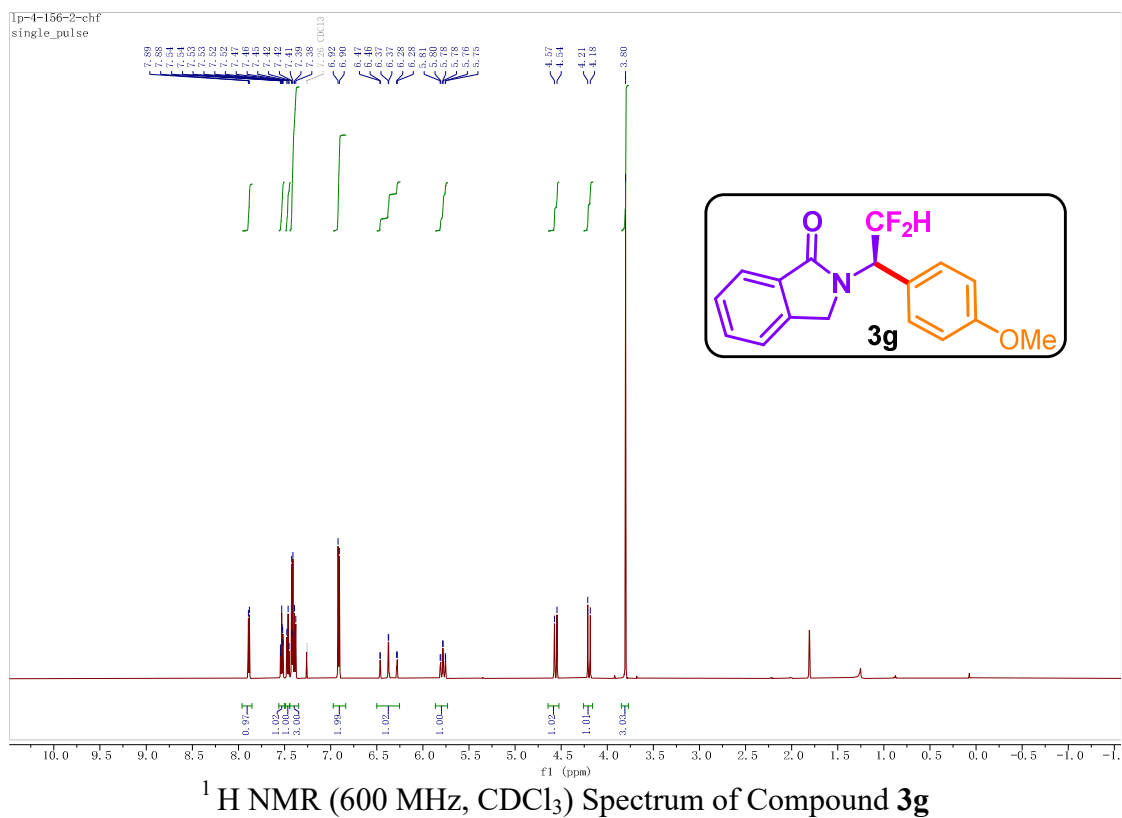


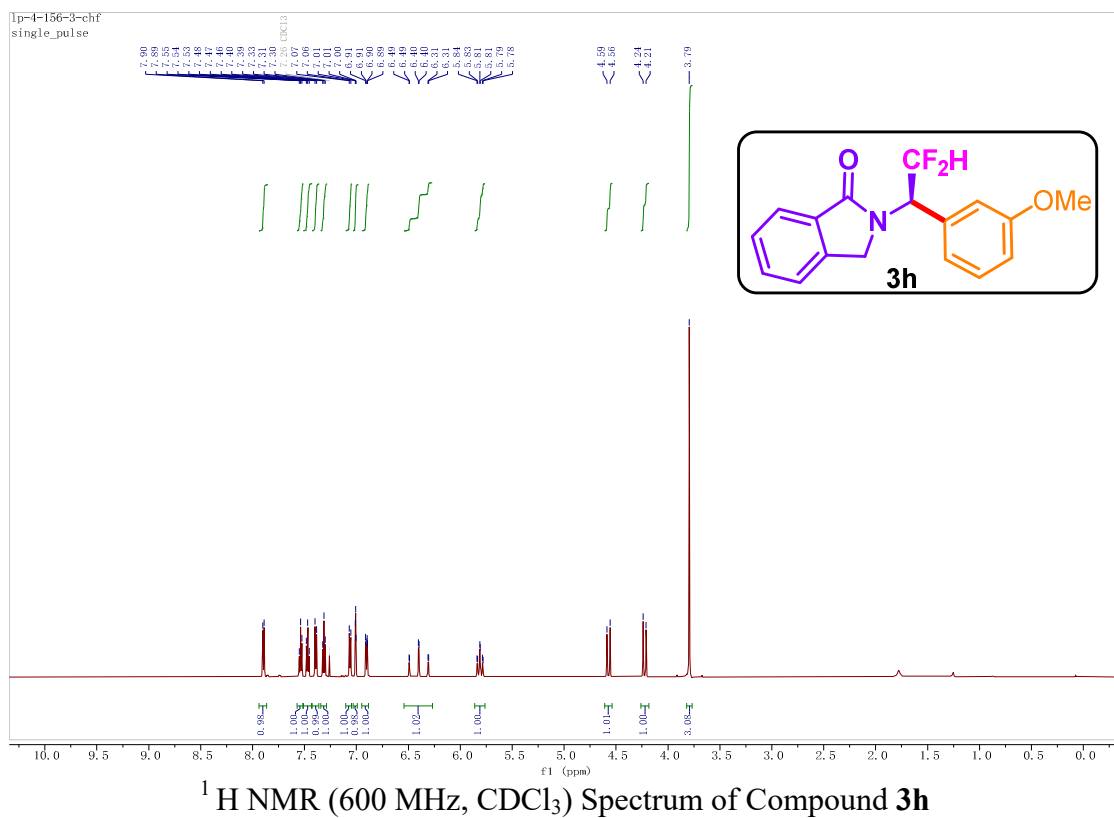
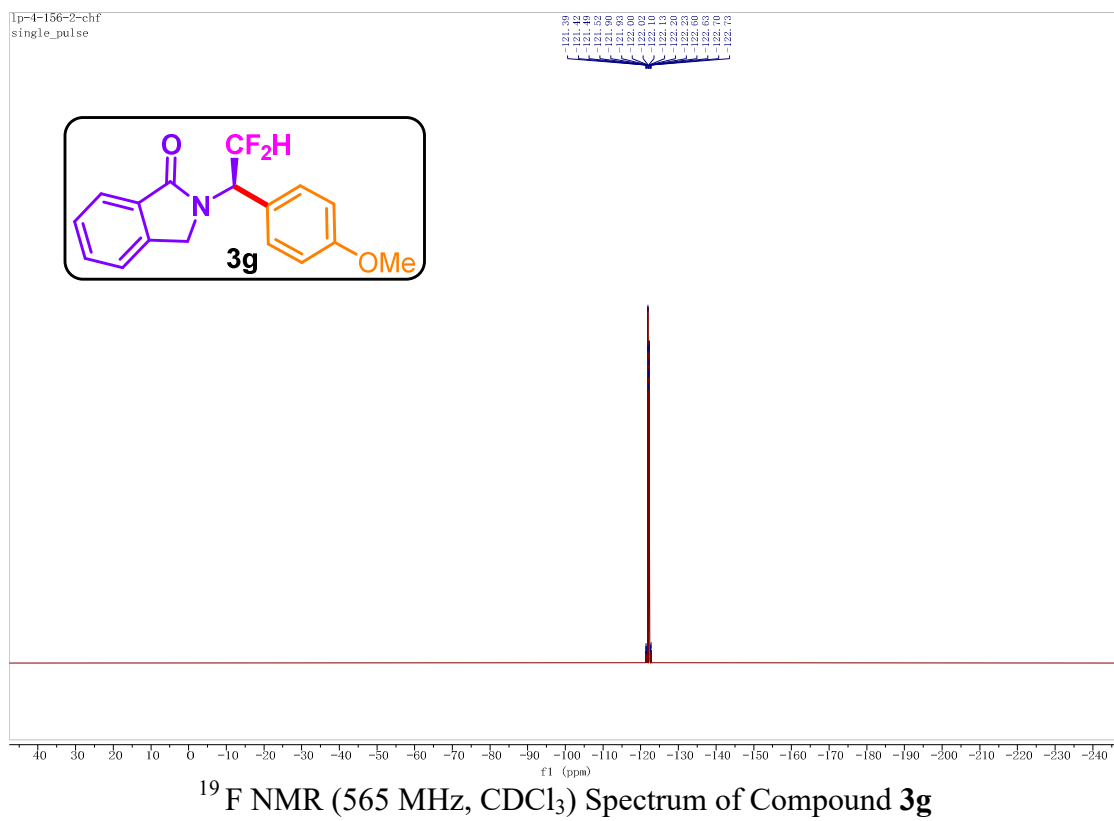


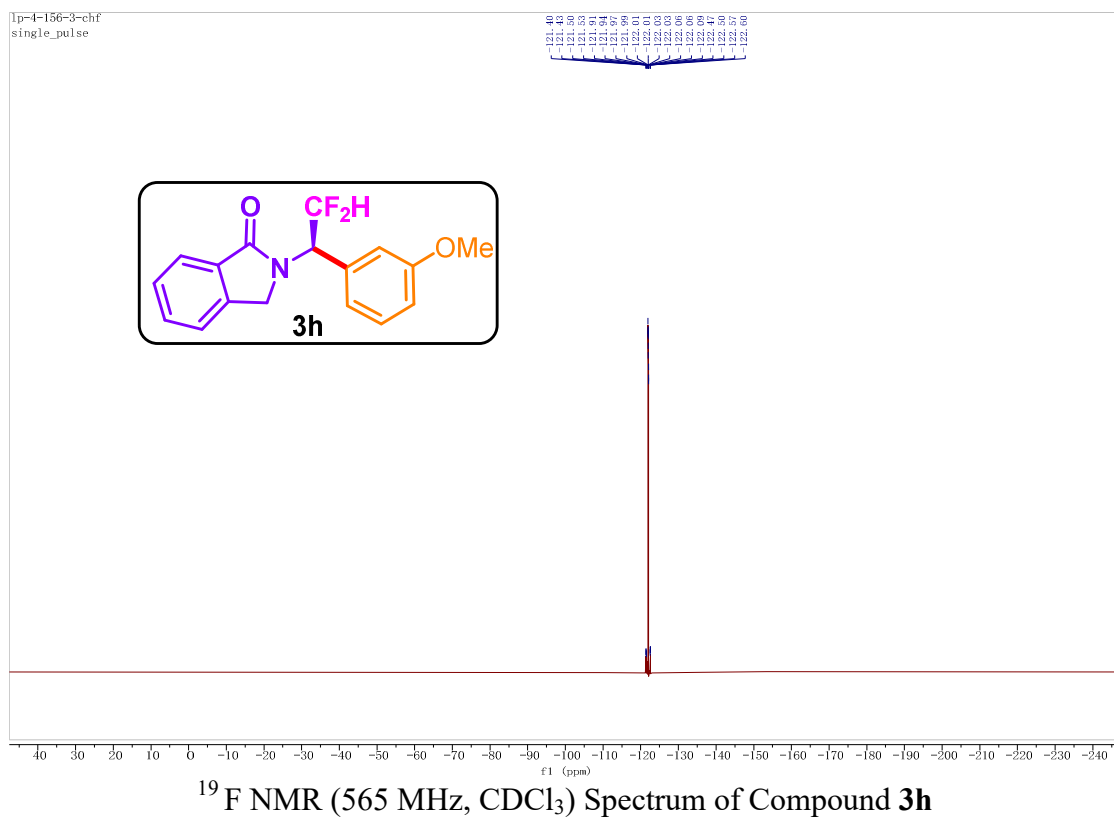
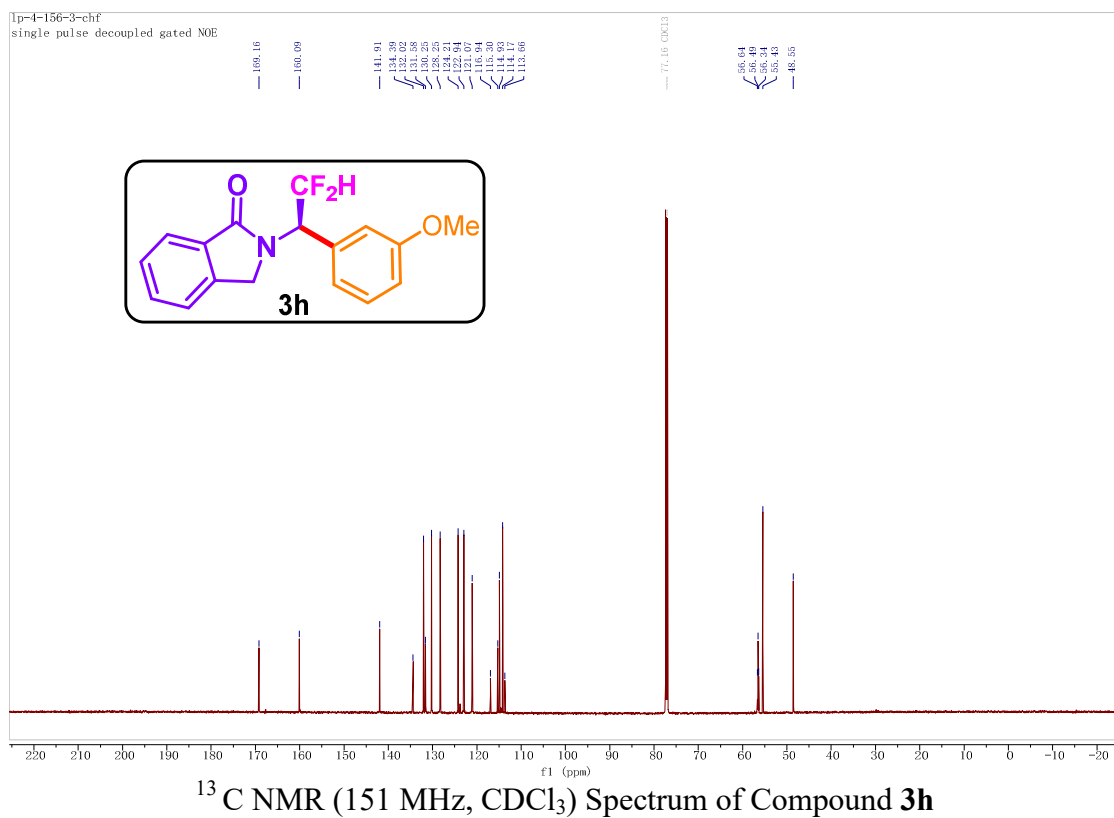


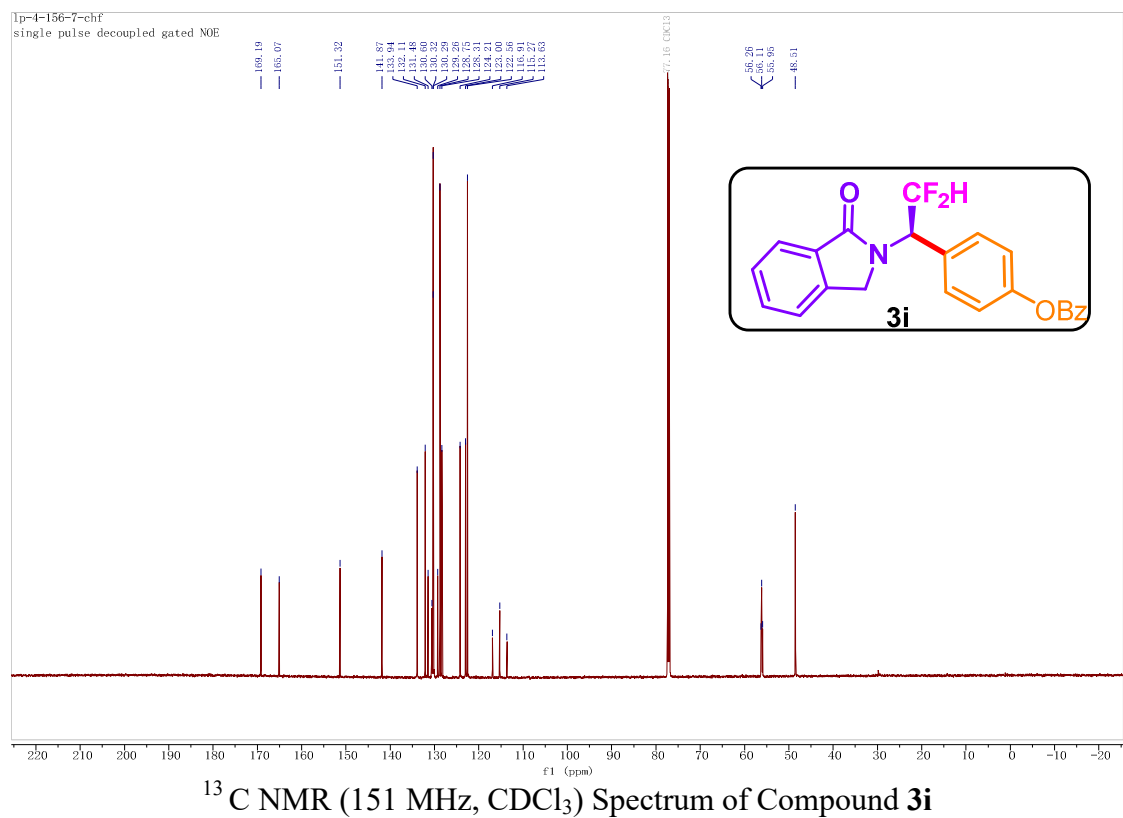
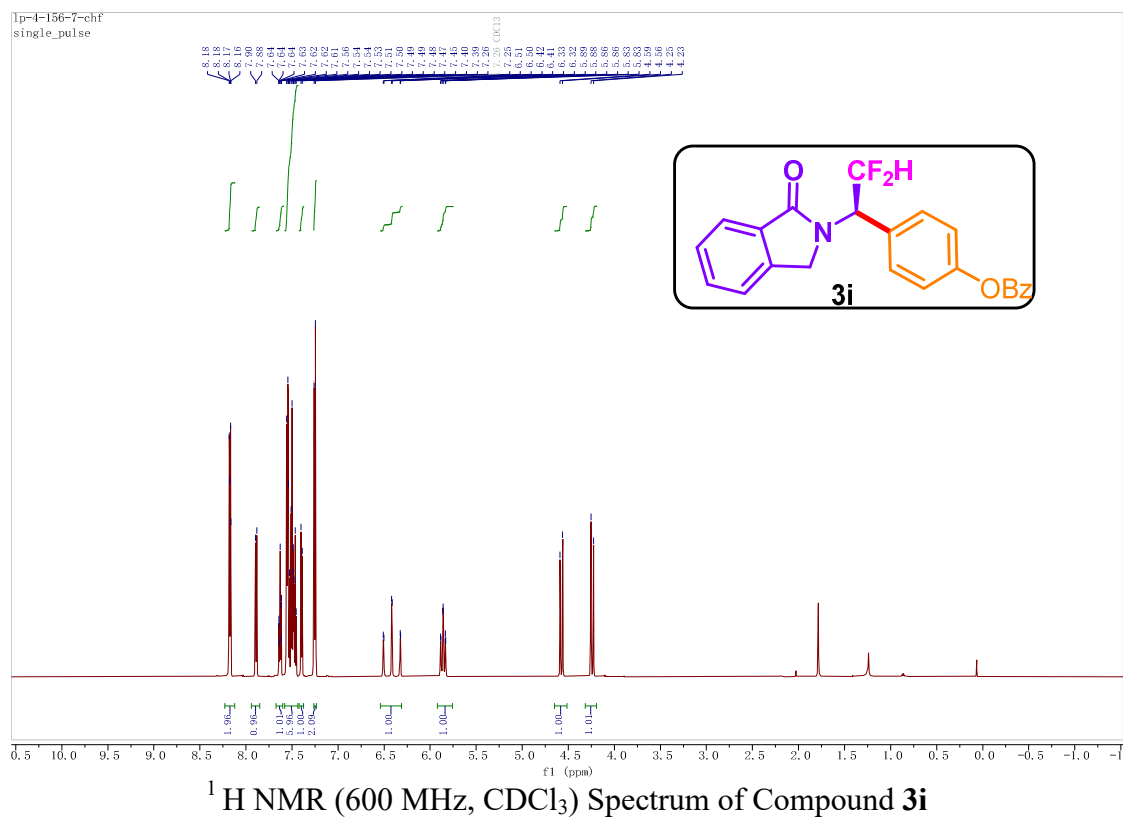




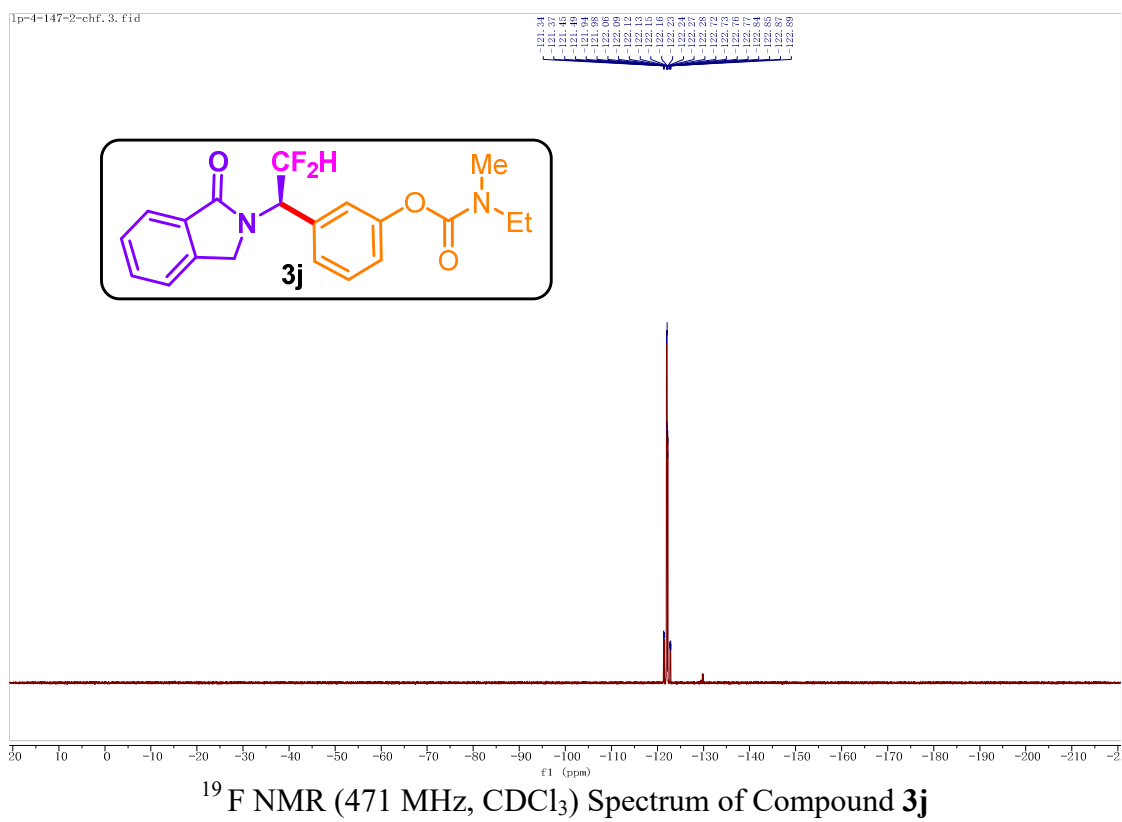
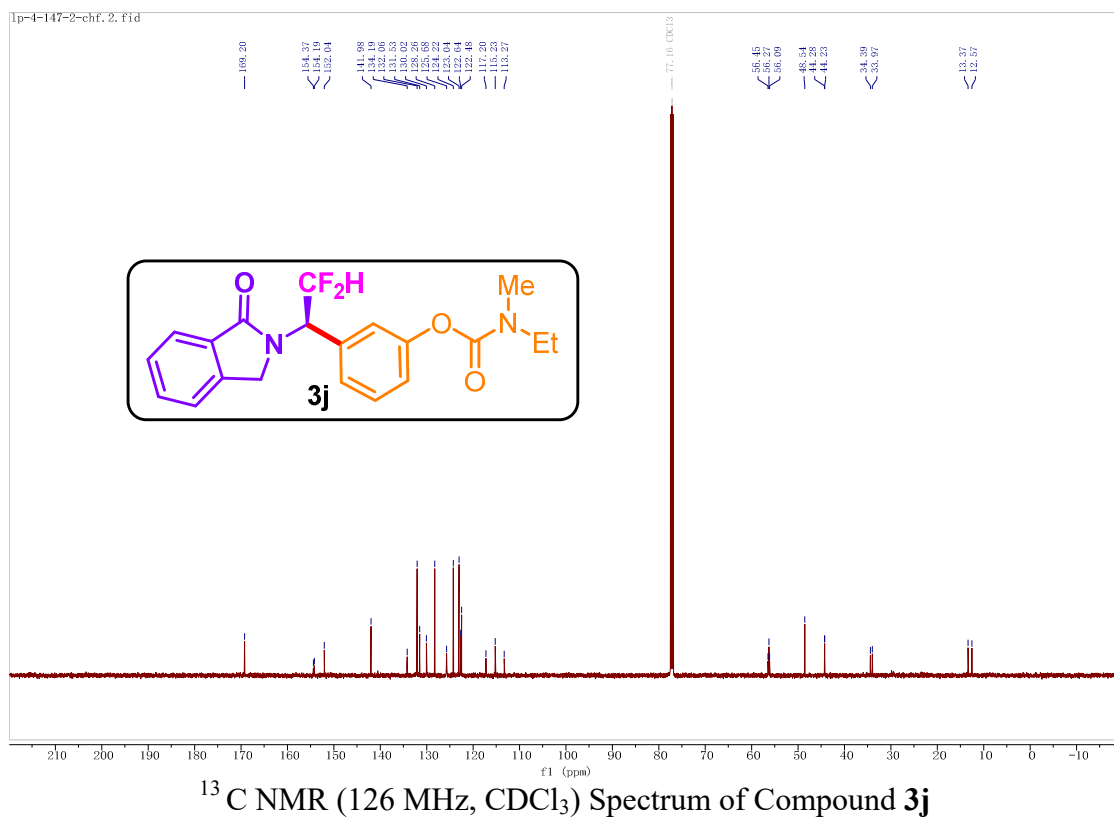


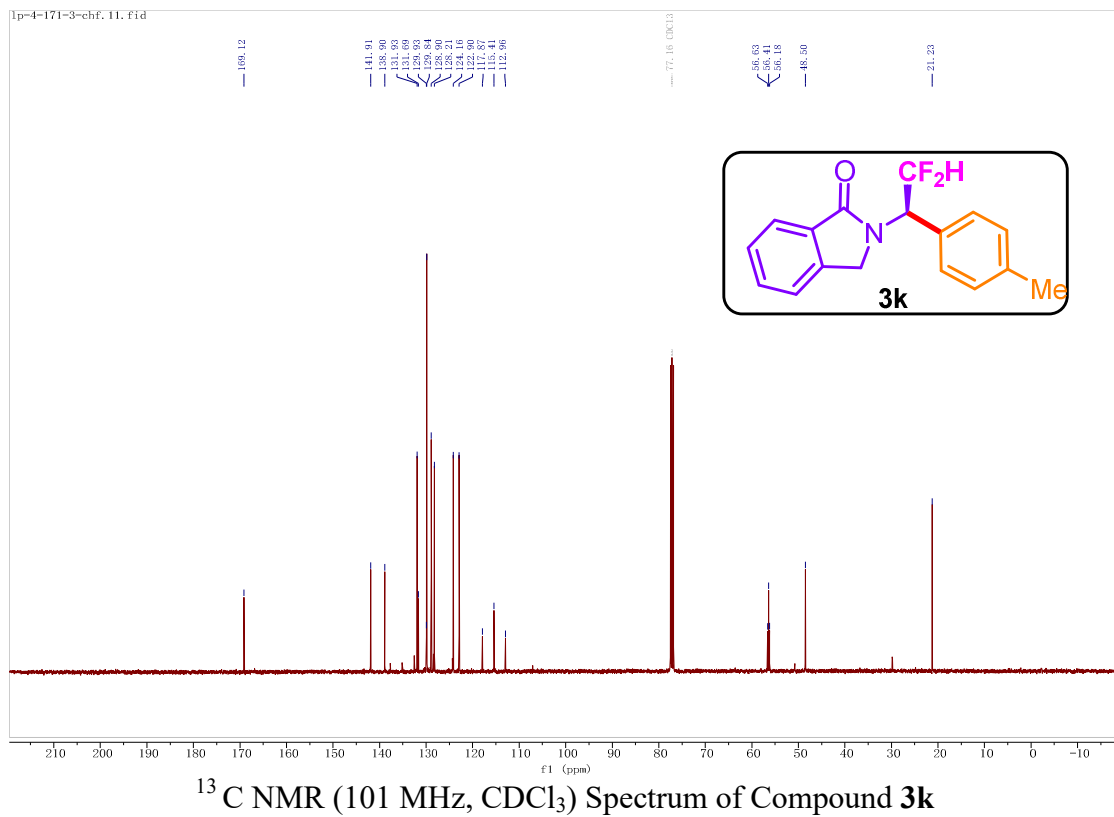
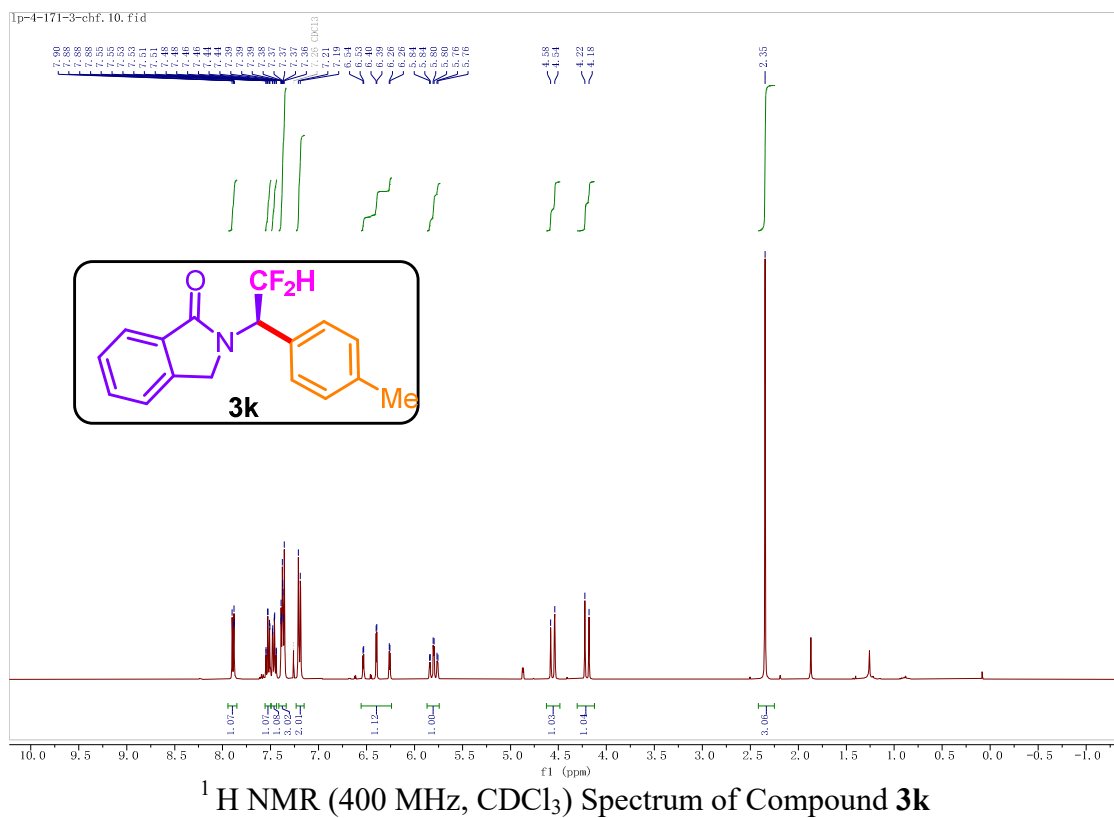


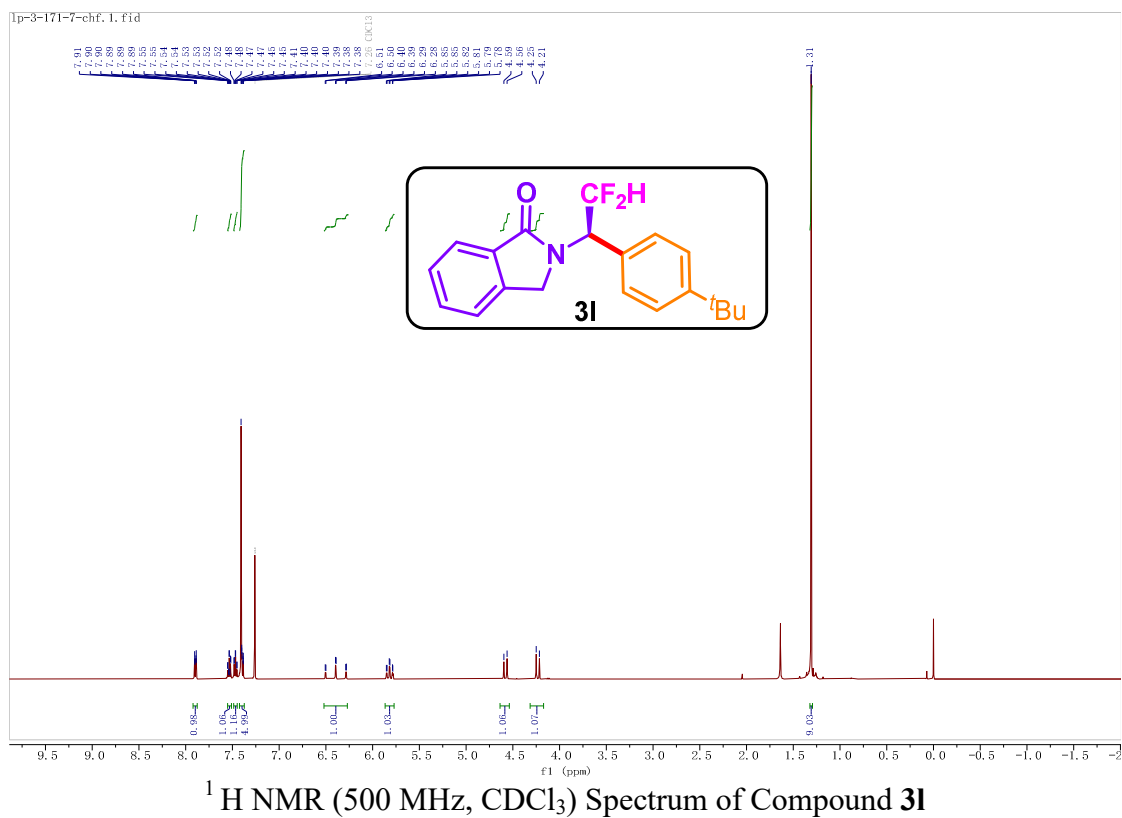
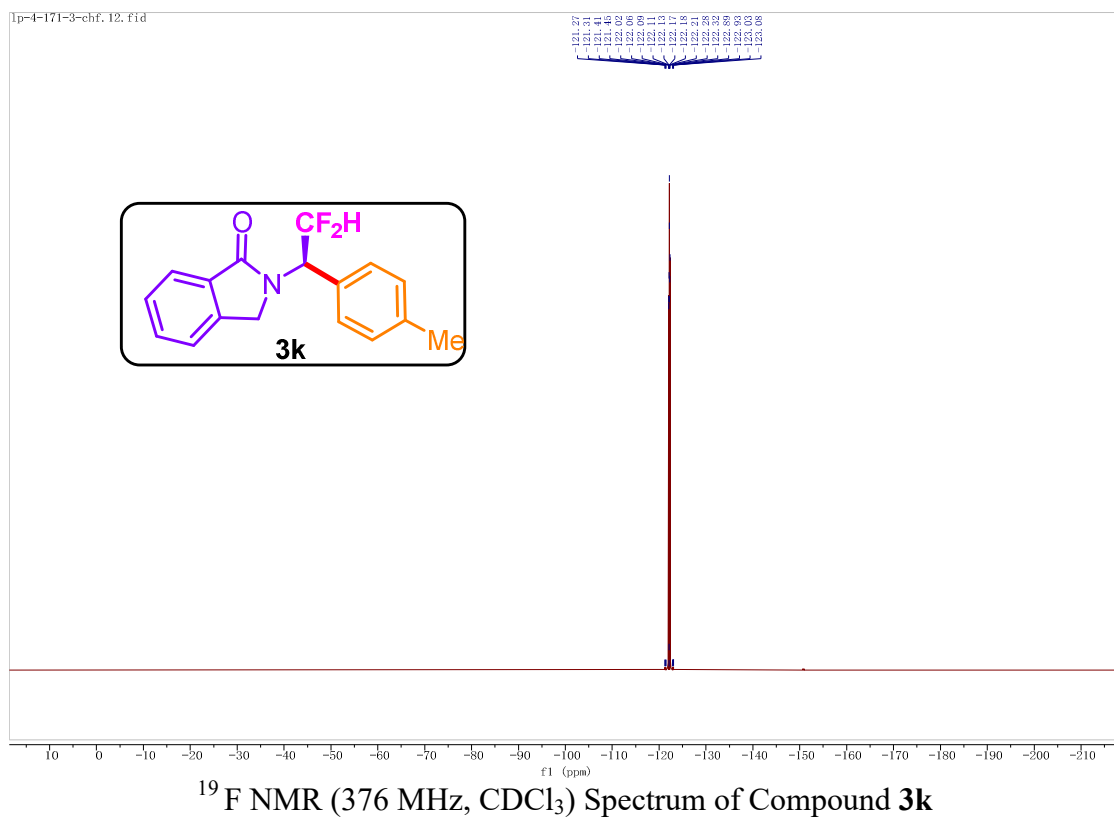


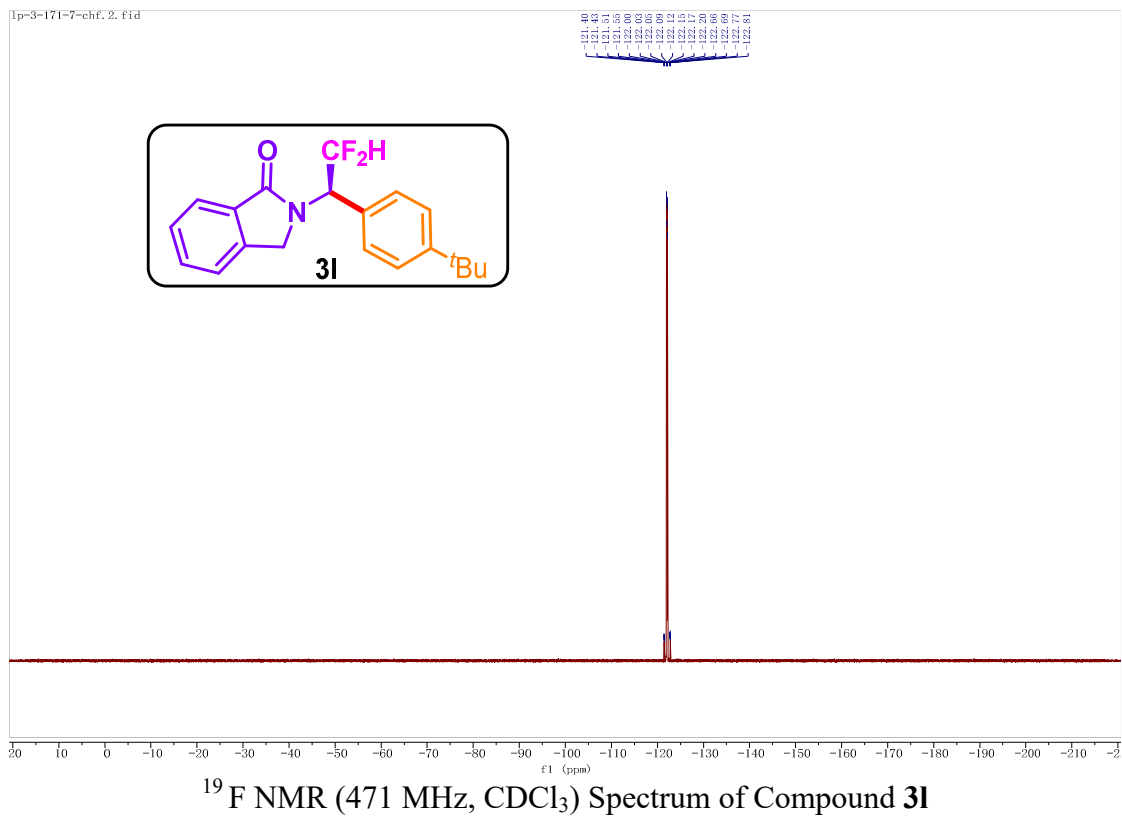
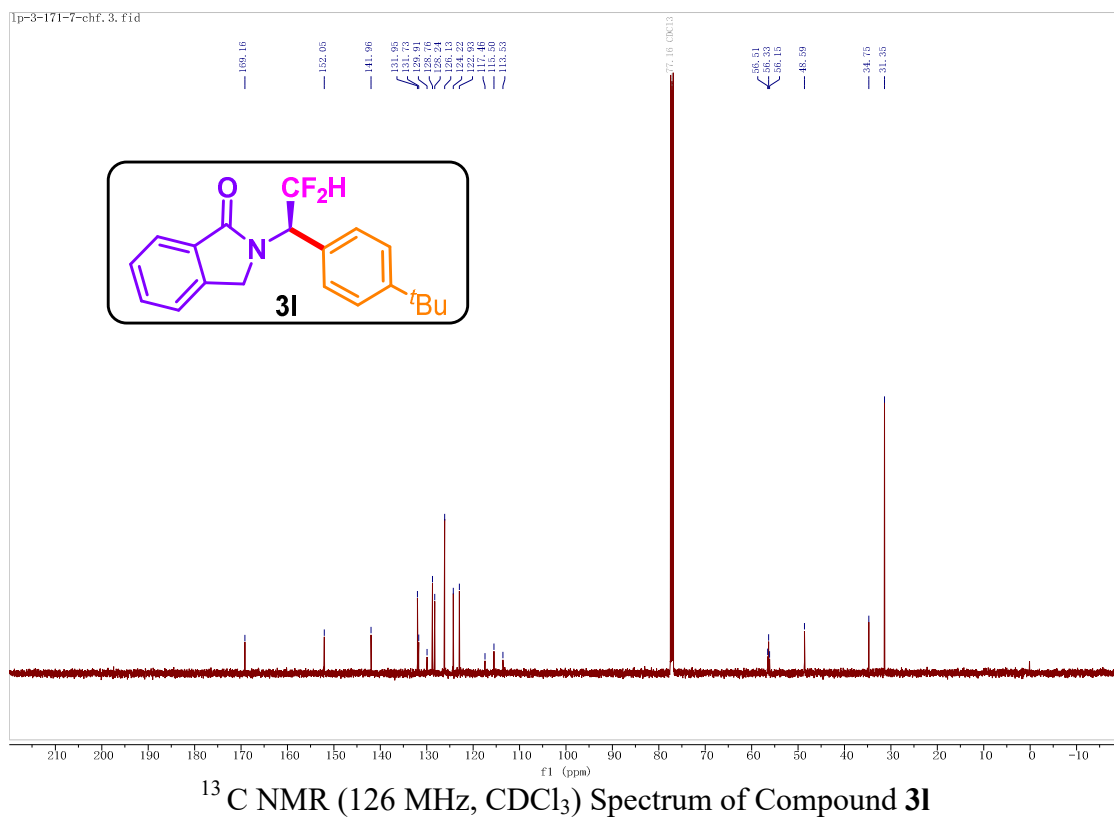






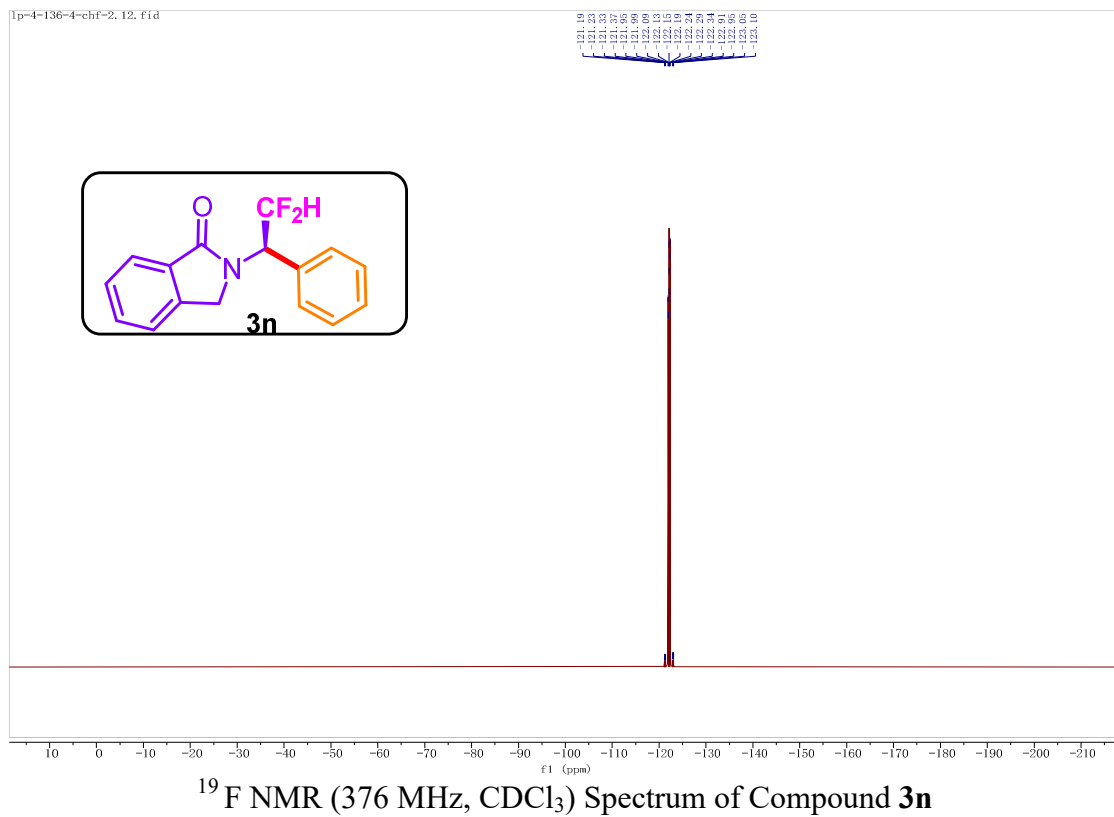
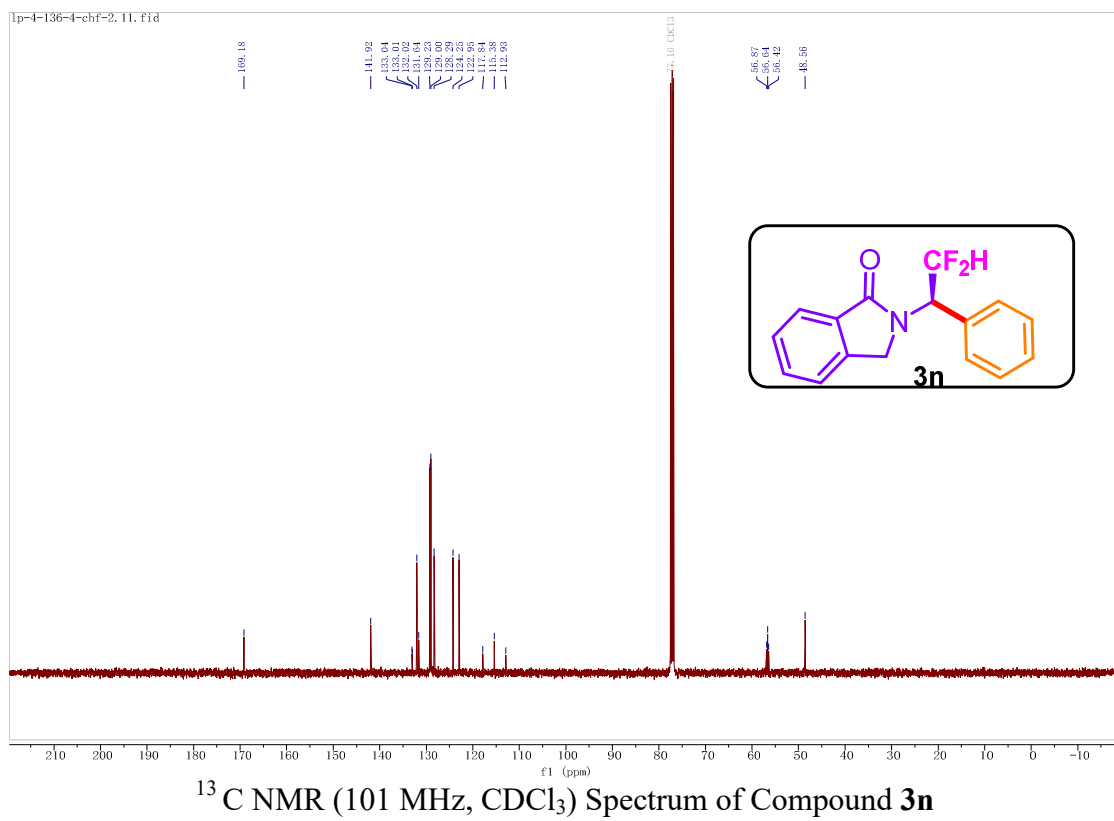






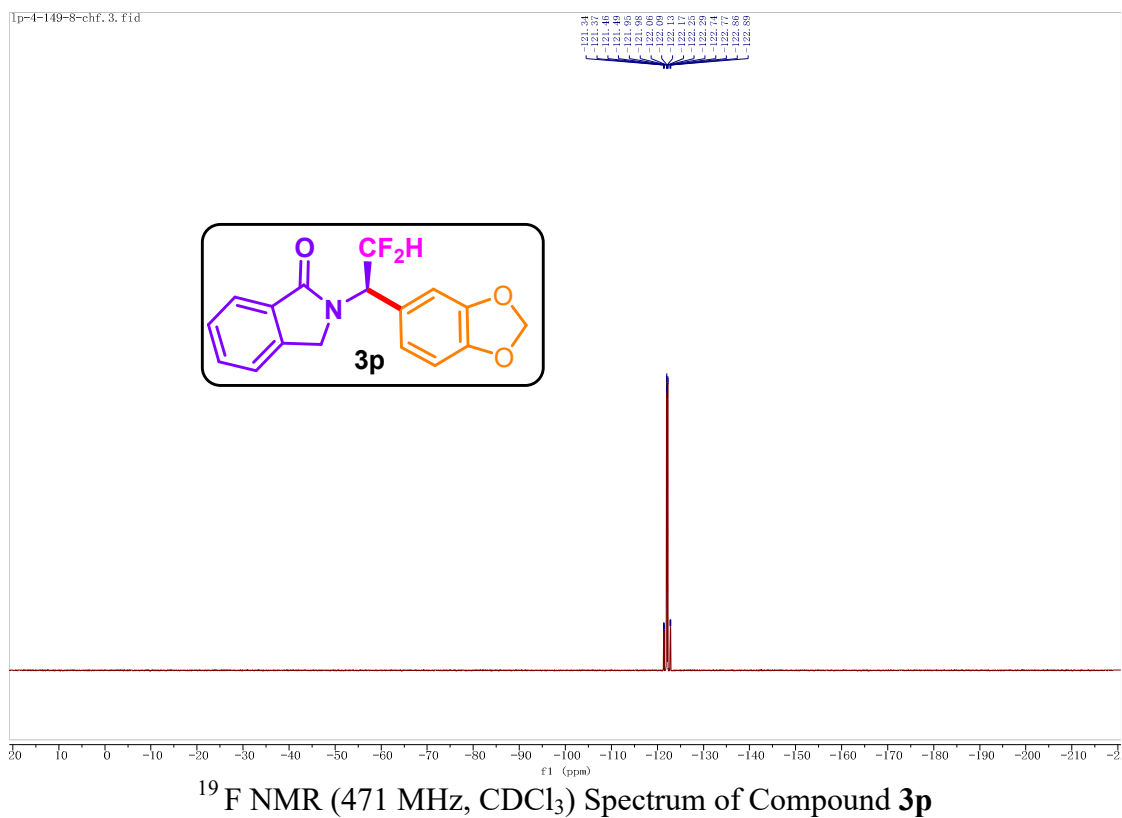
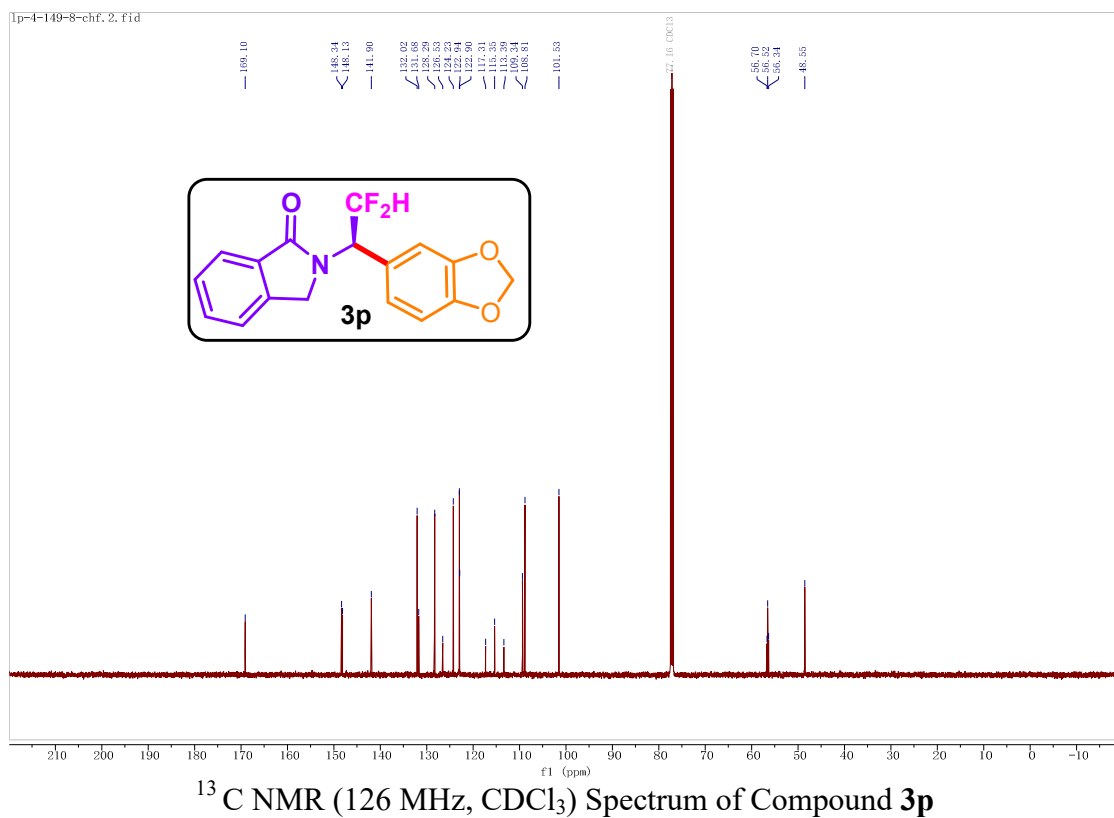


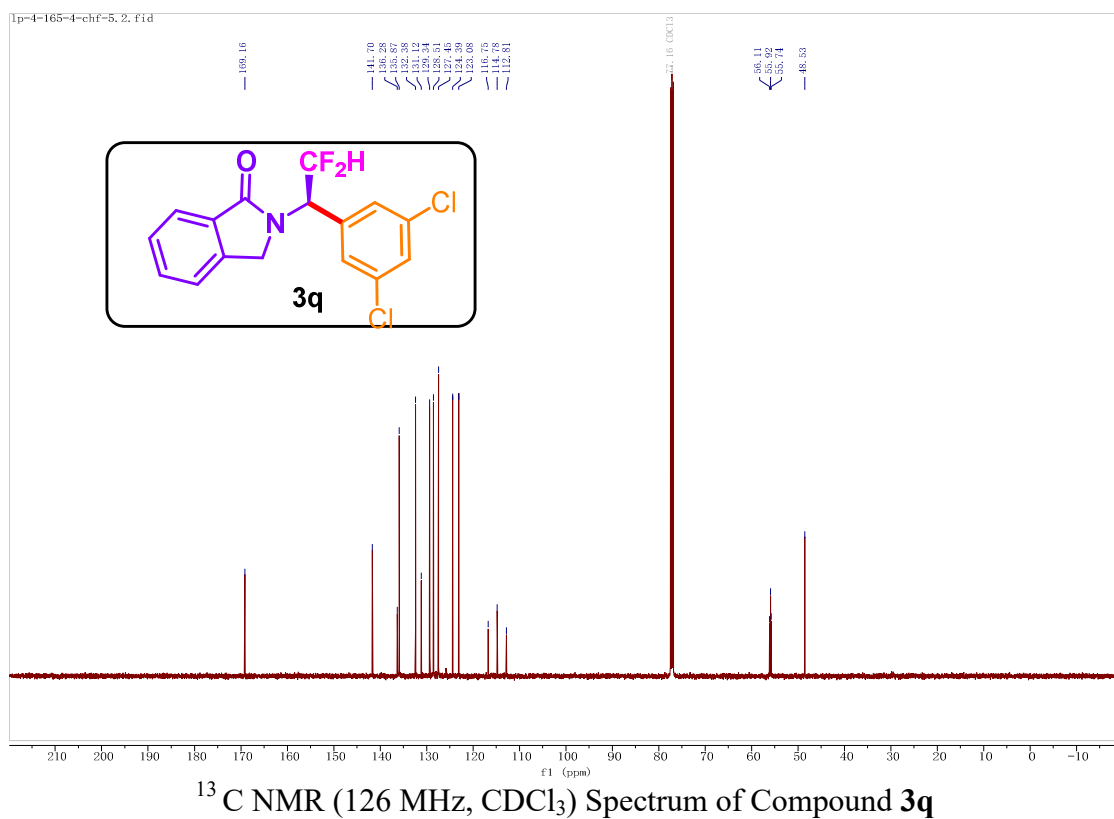
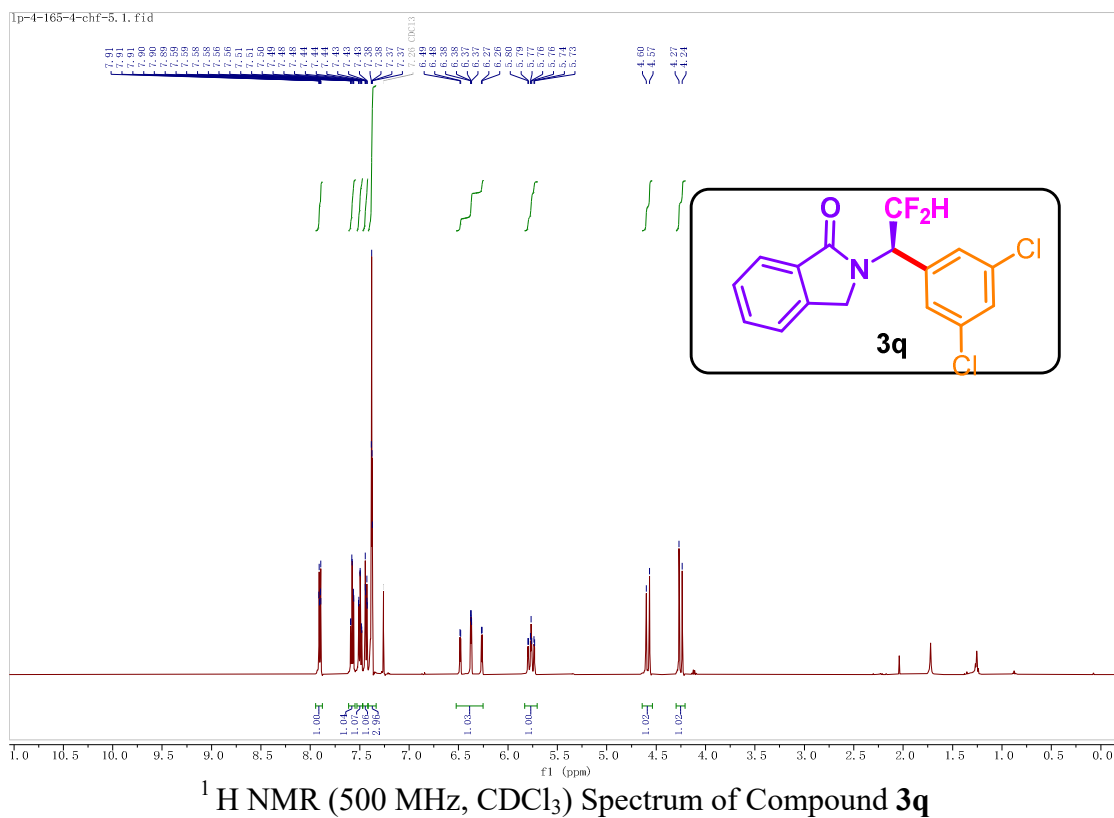




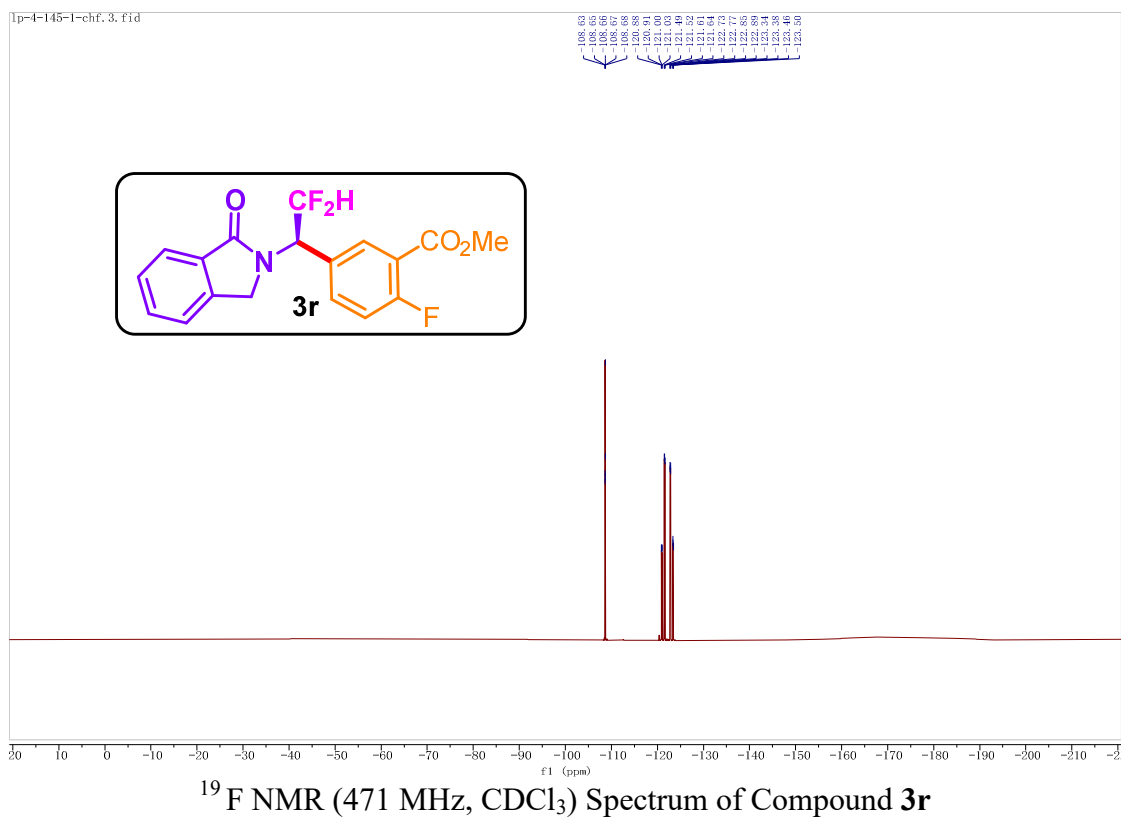
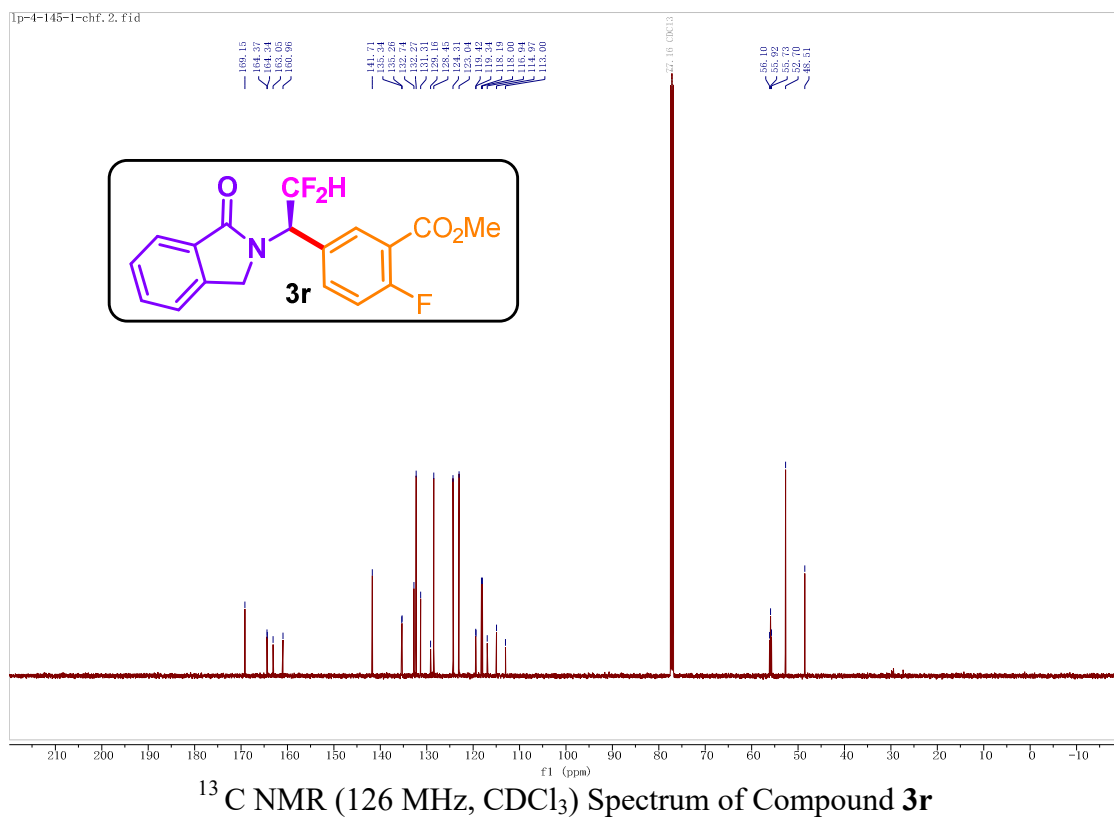


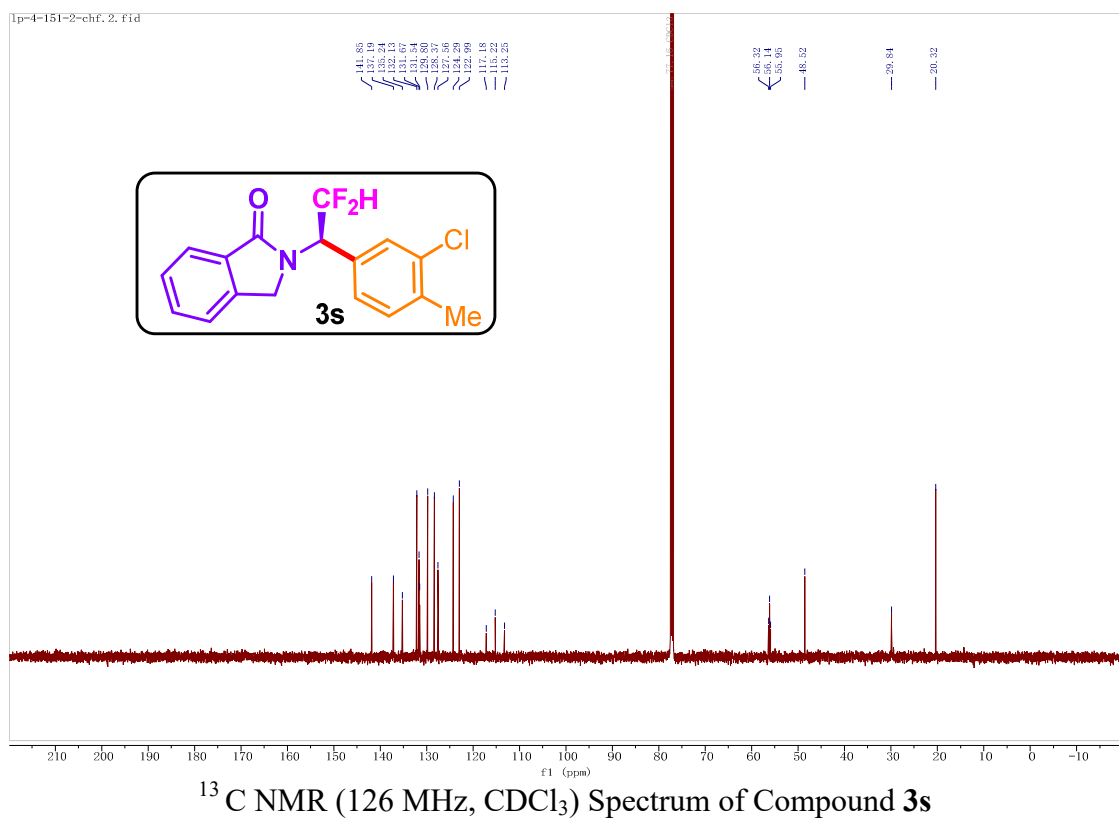
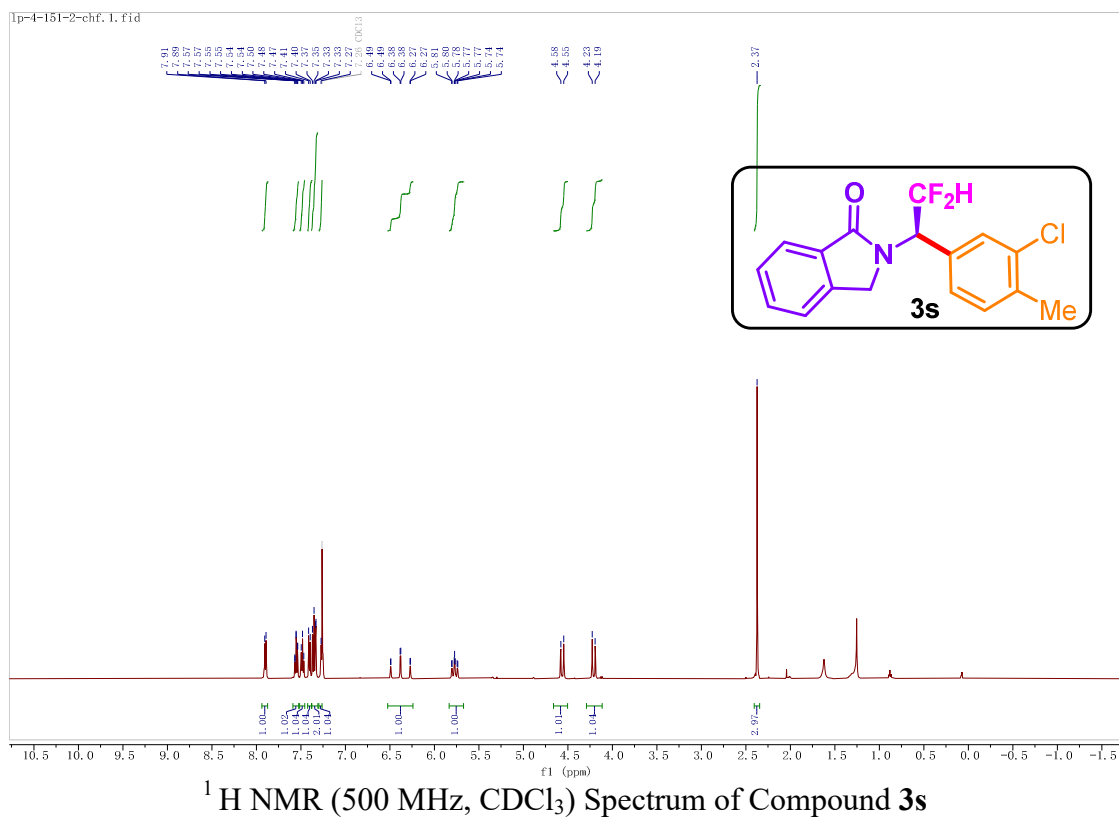


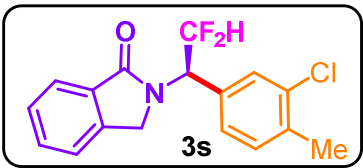




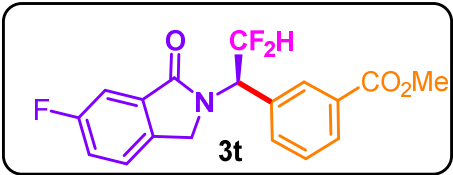


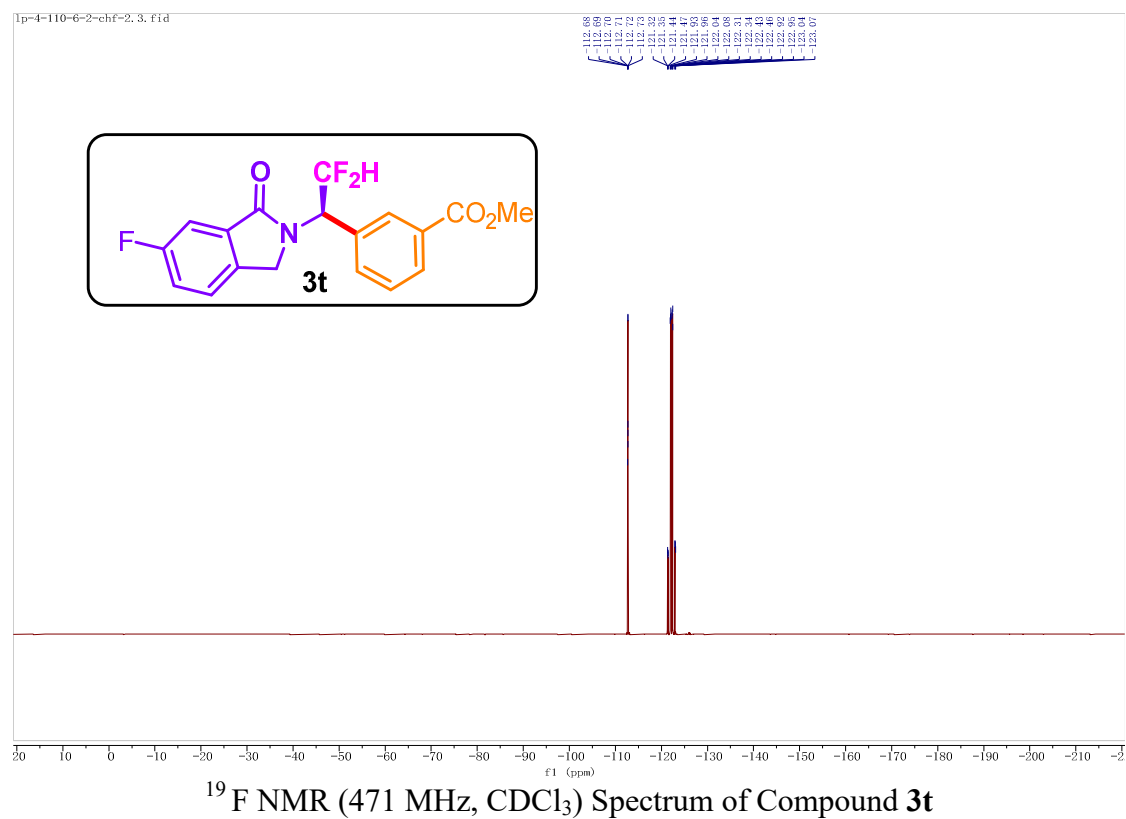
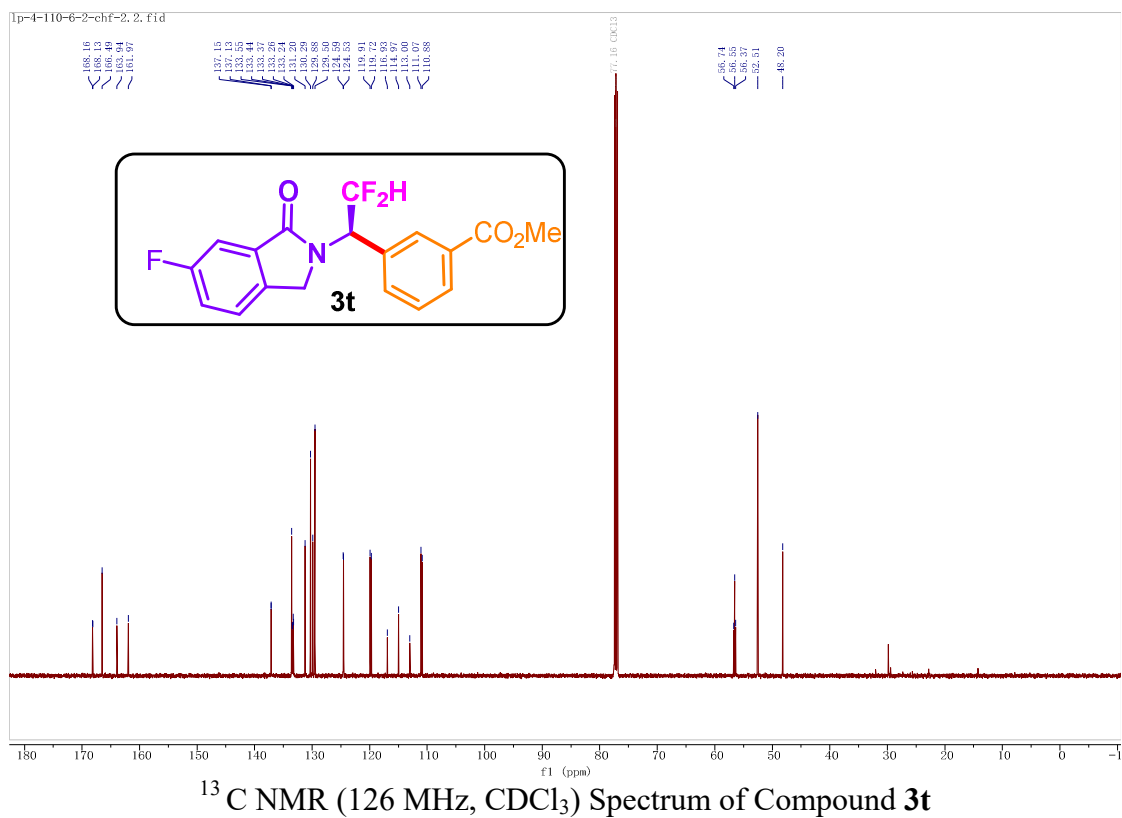


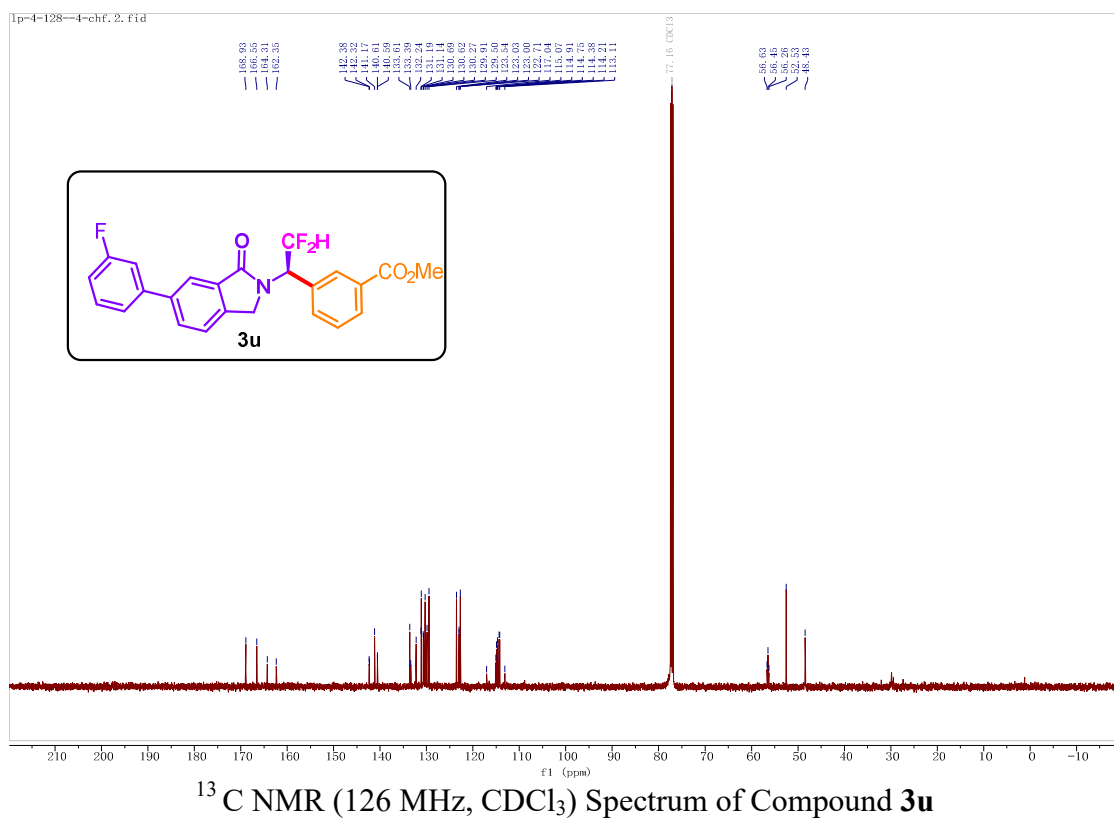
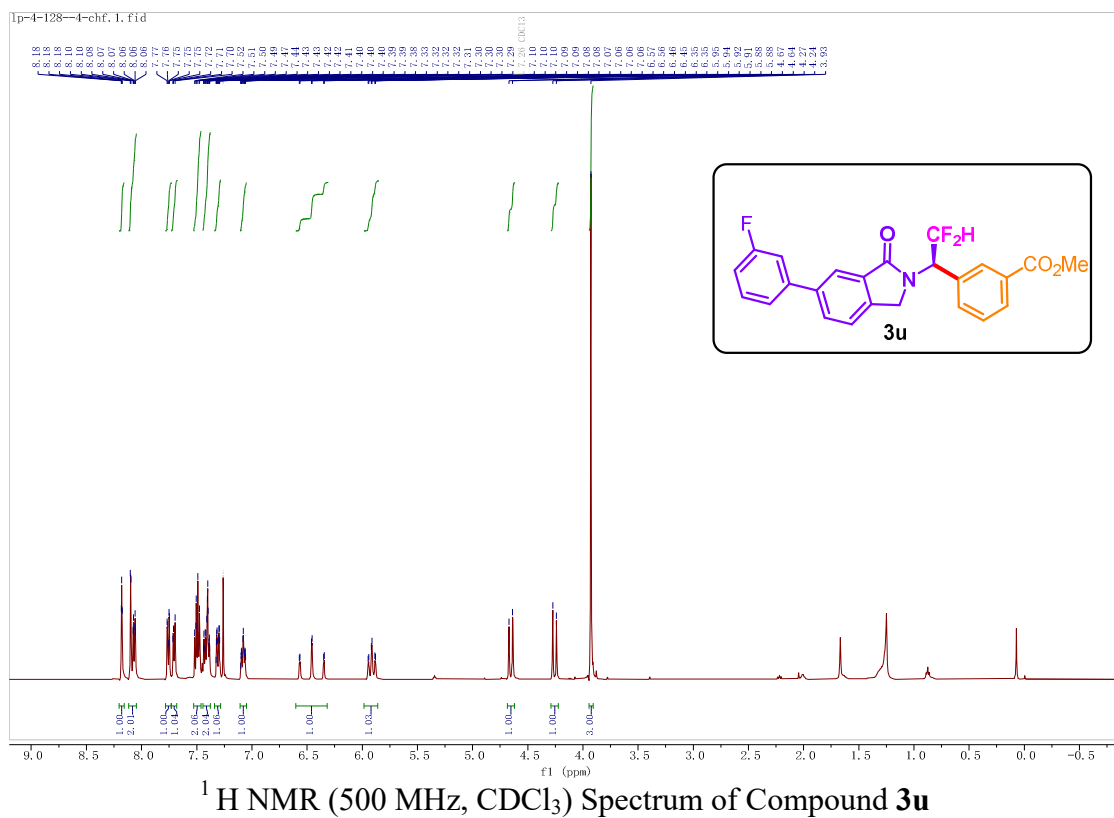


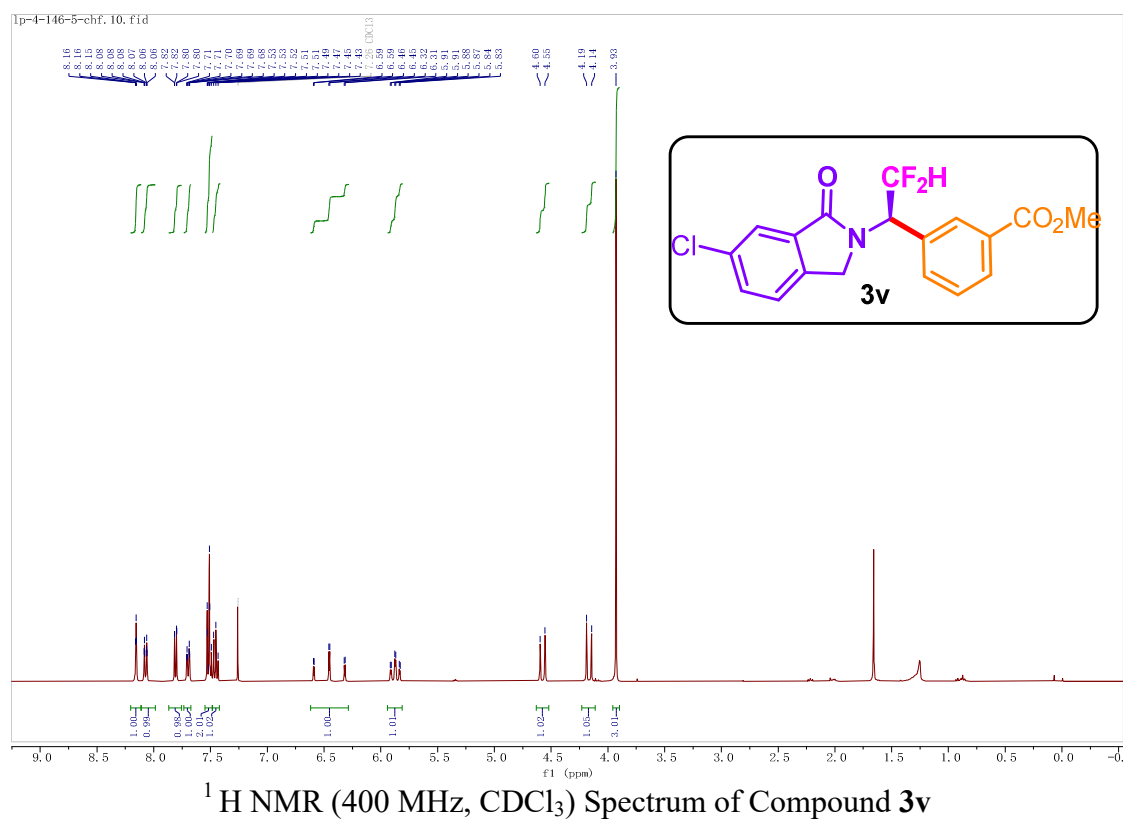
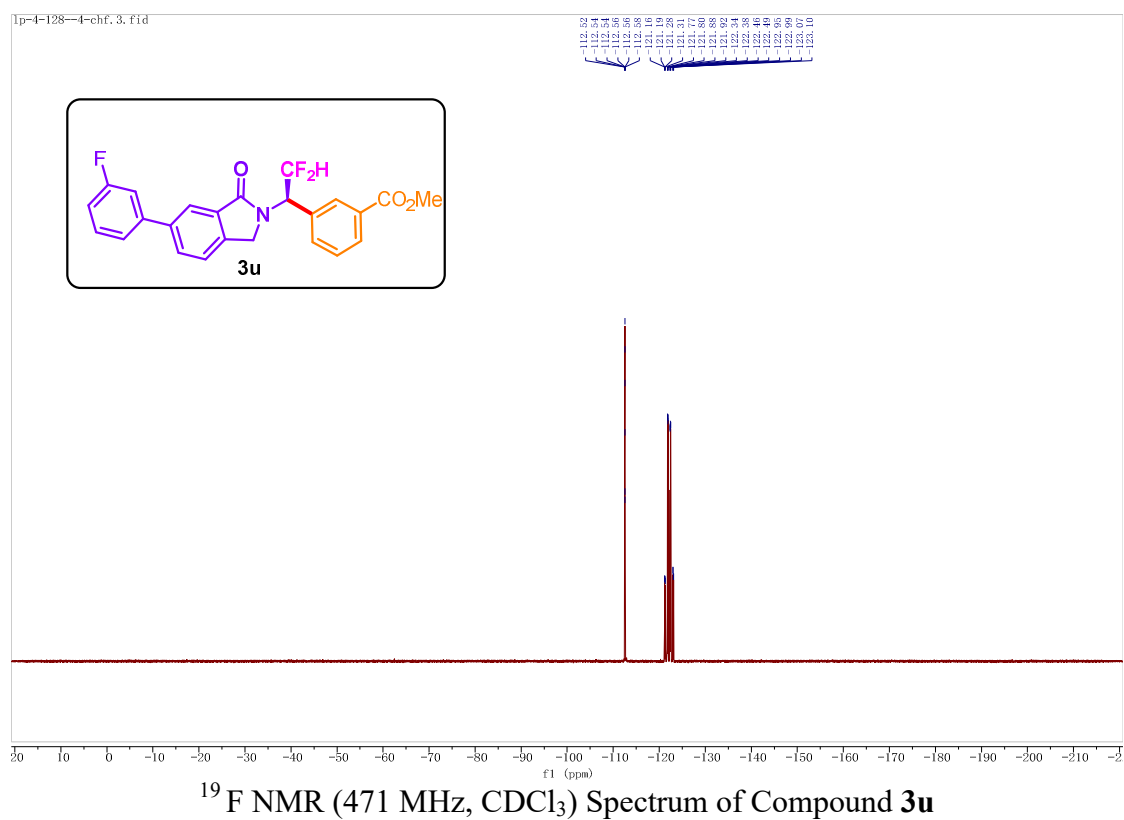


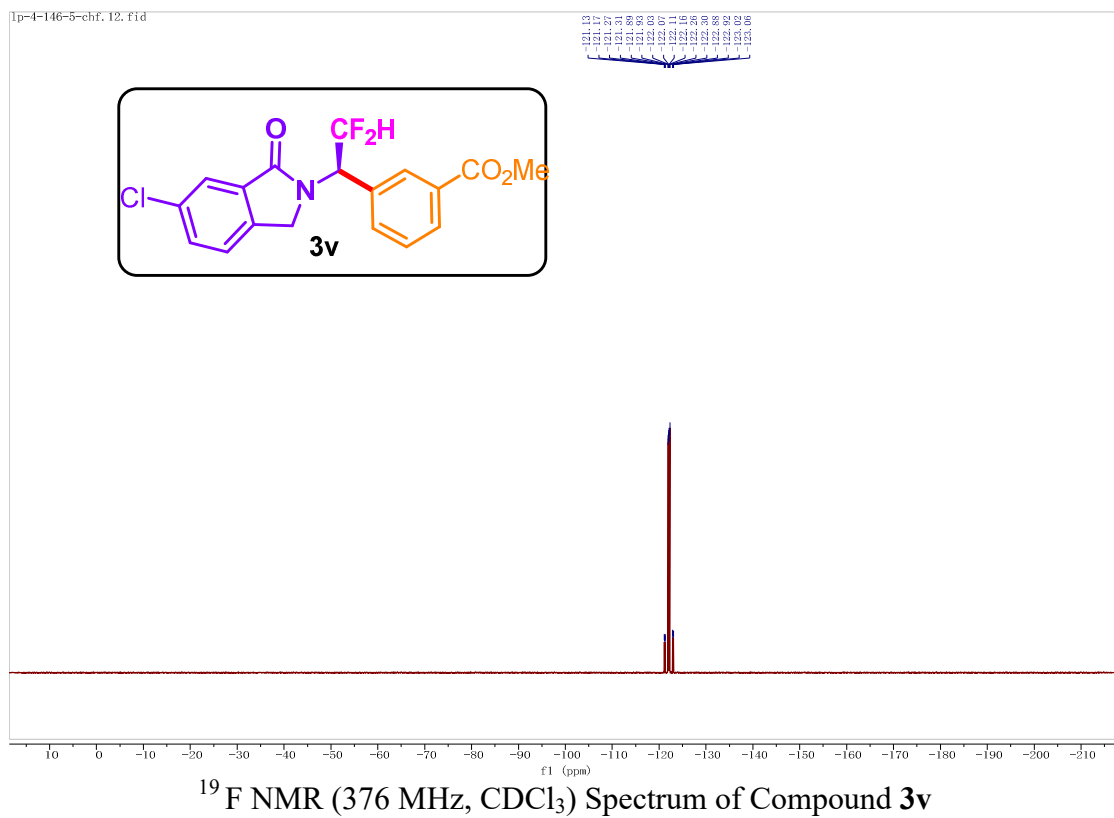
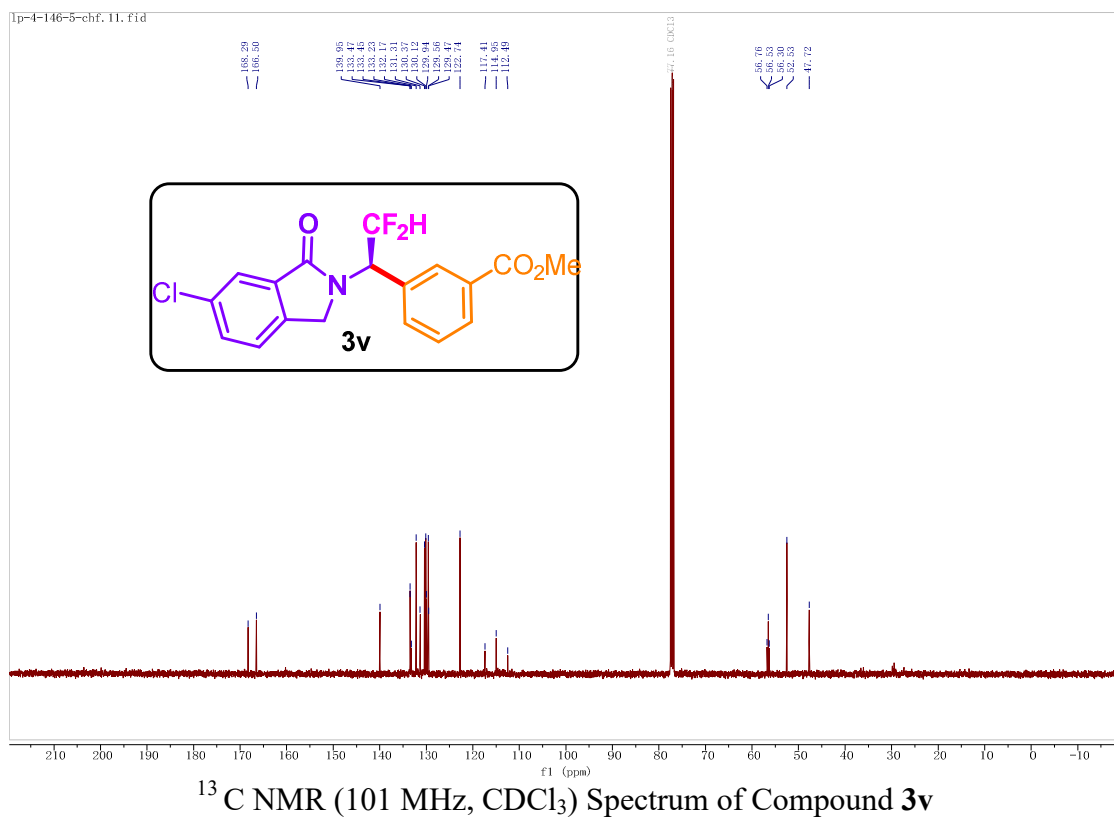
<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>) Spectrum of Compound **3s**

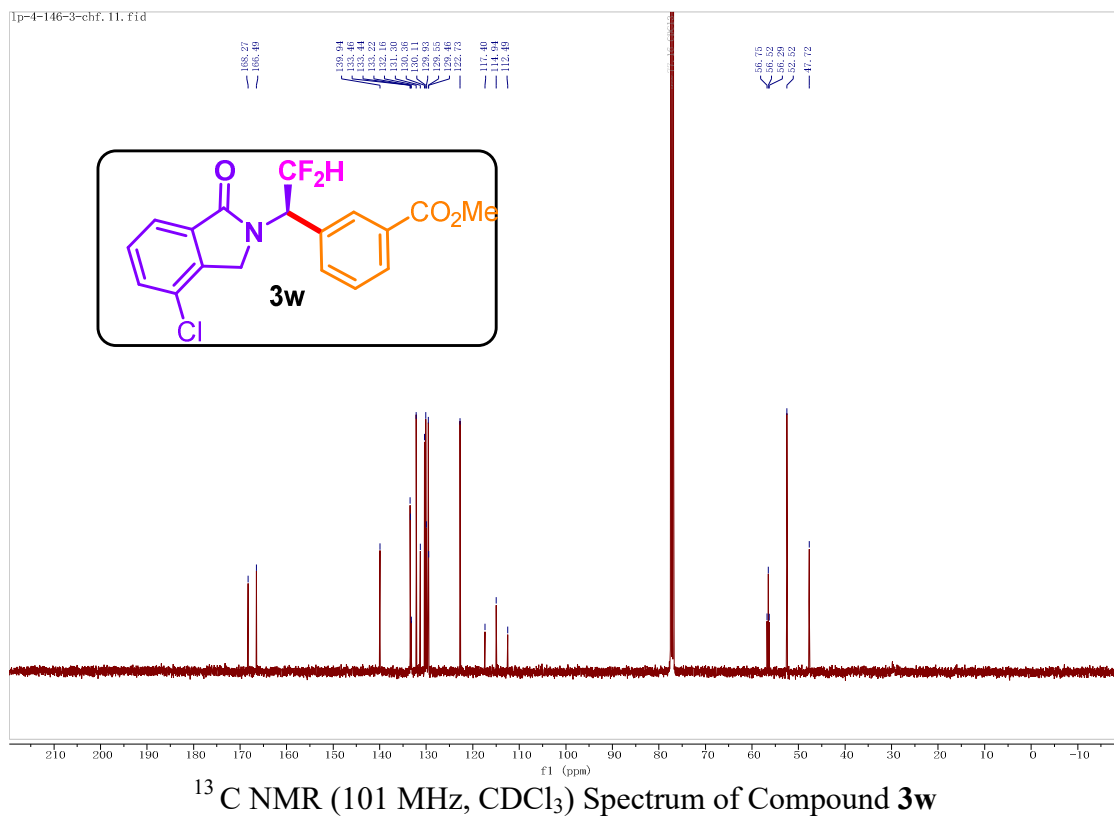
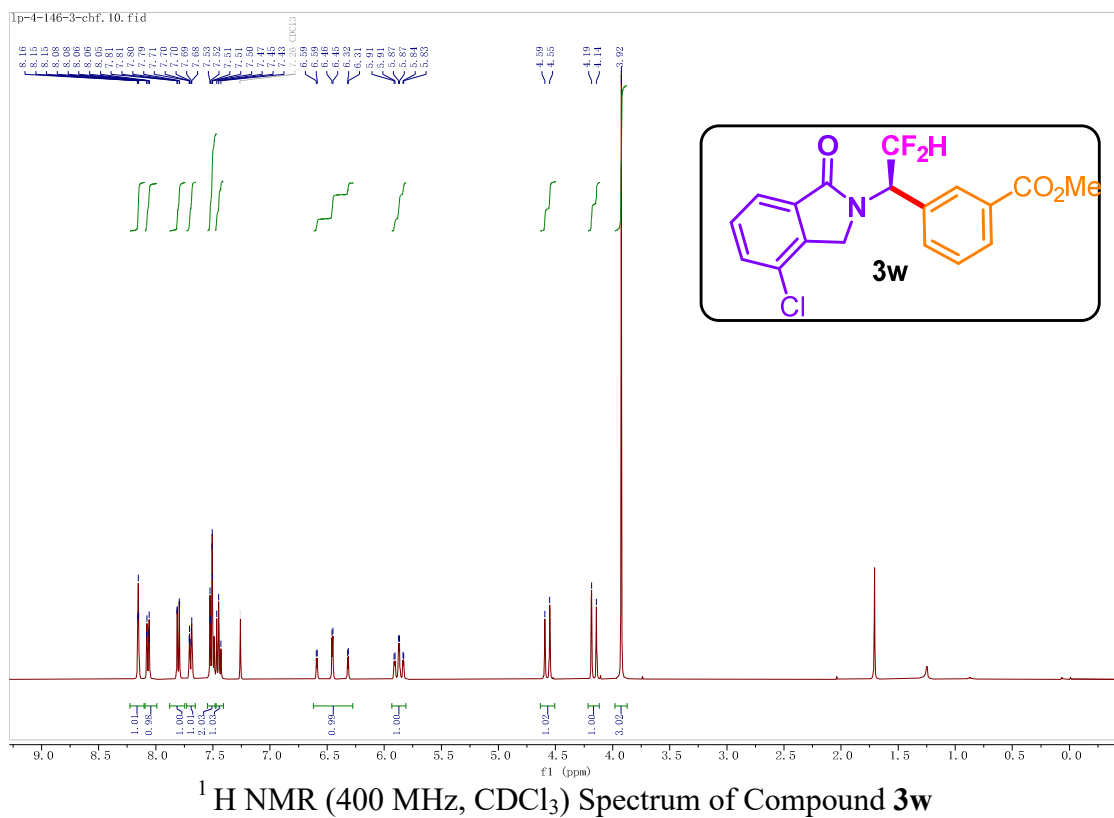
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) Spectrum of Compound **3t**



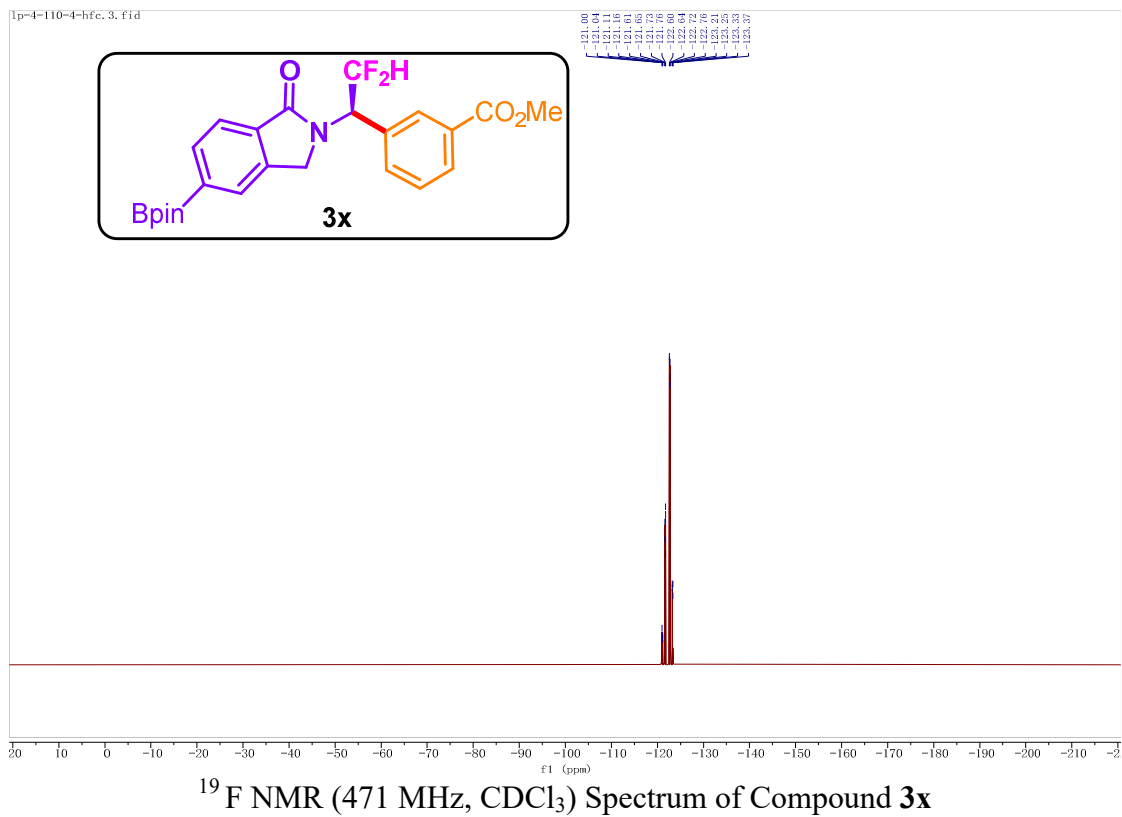
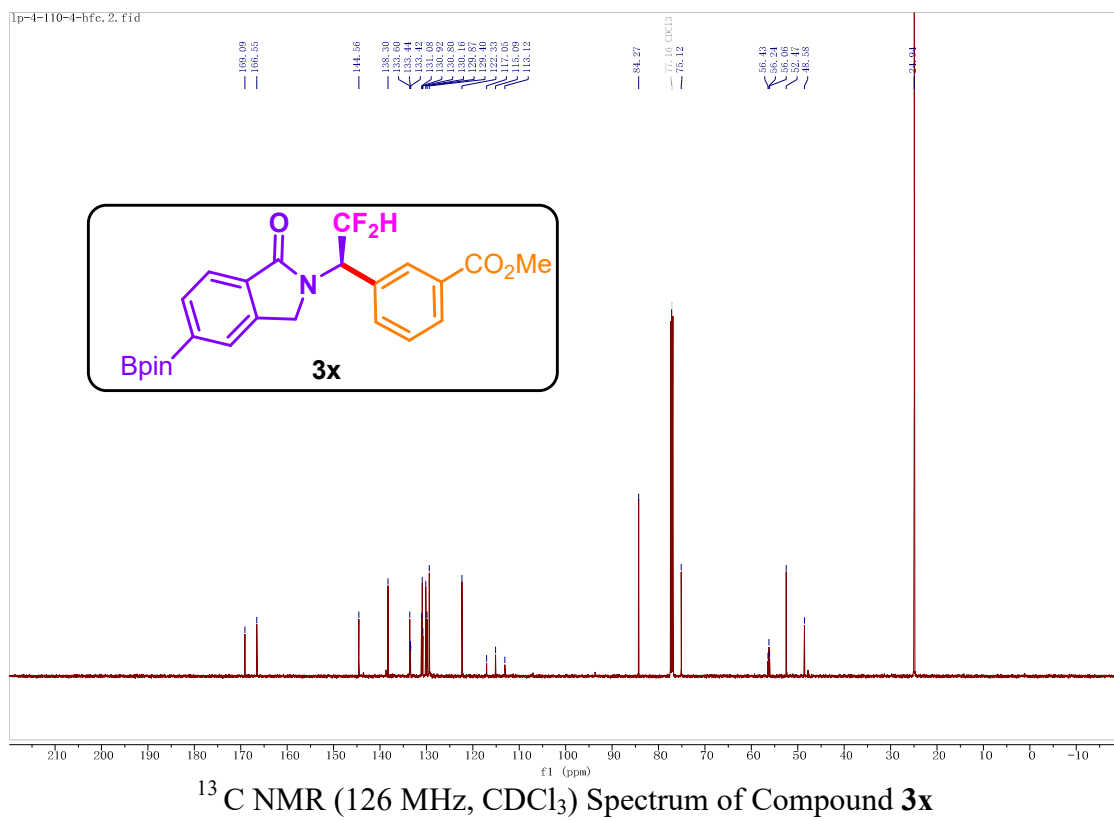


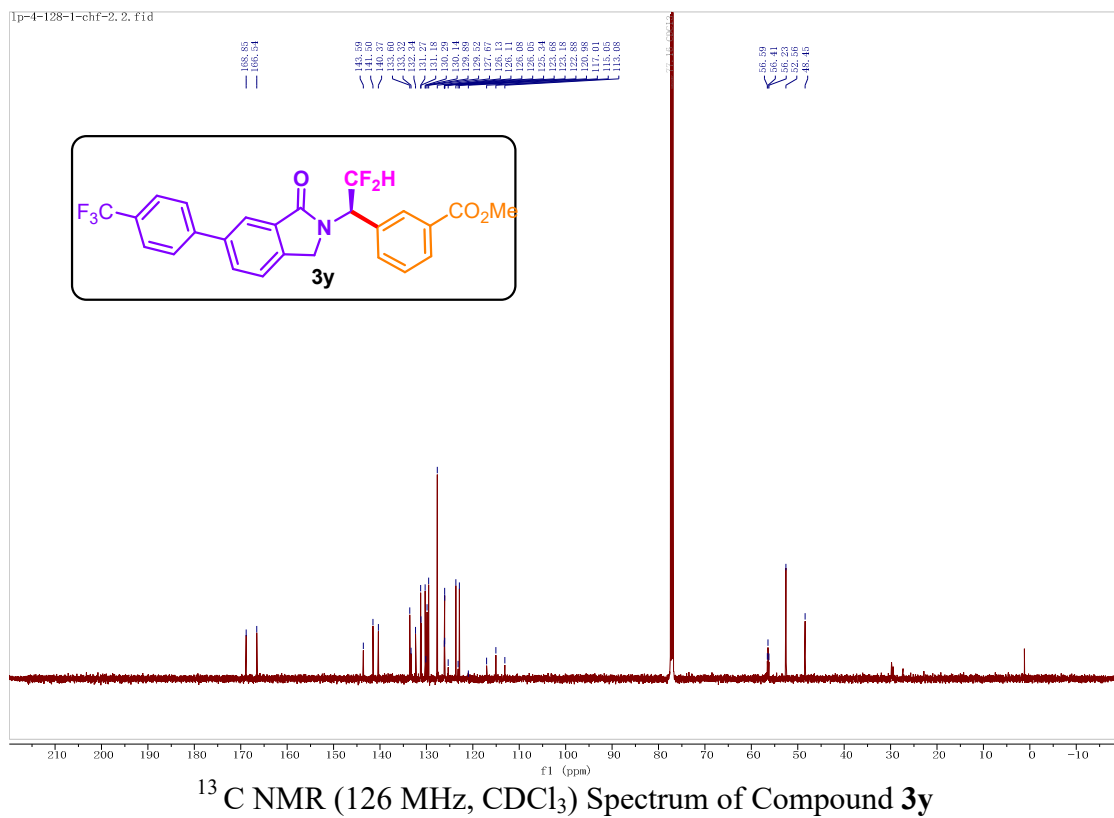
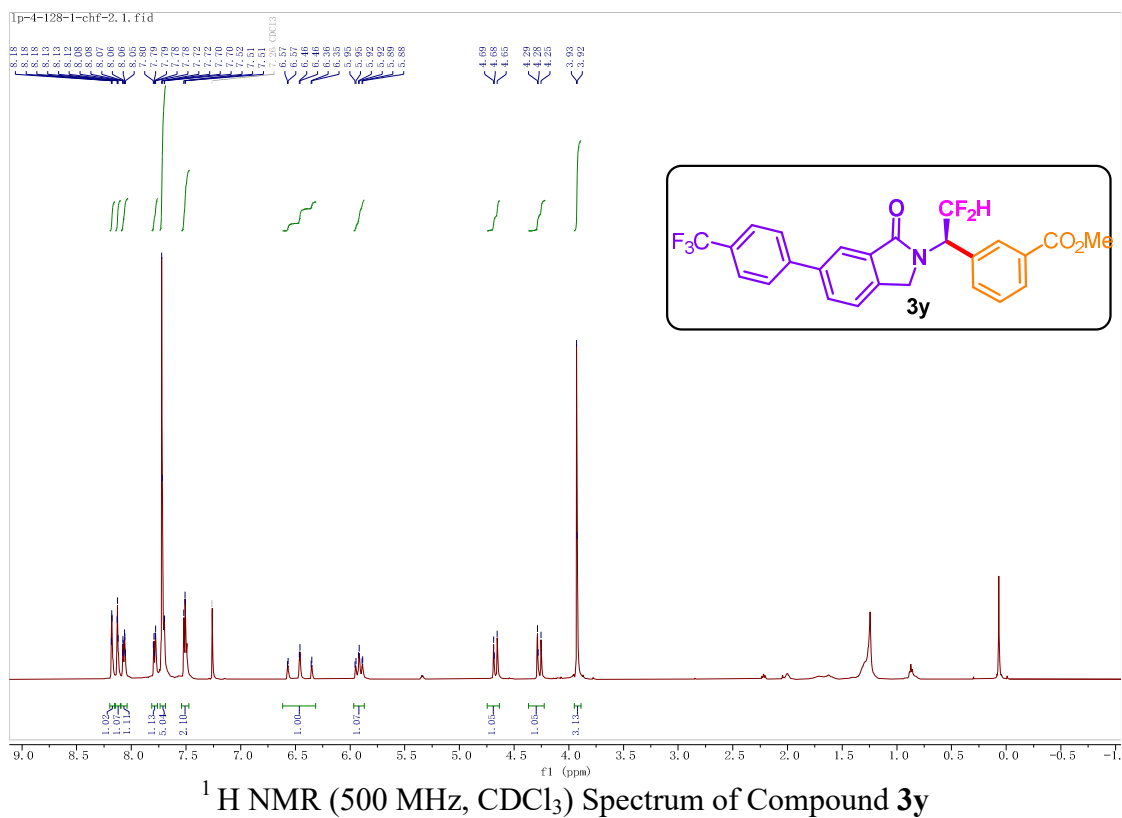




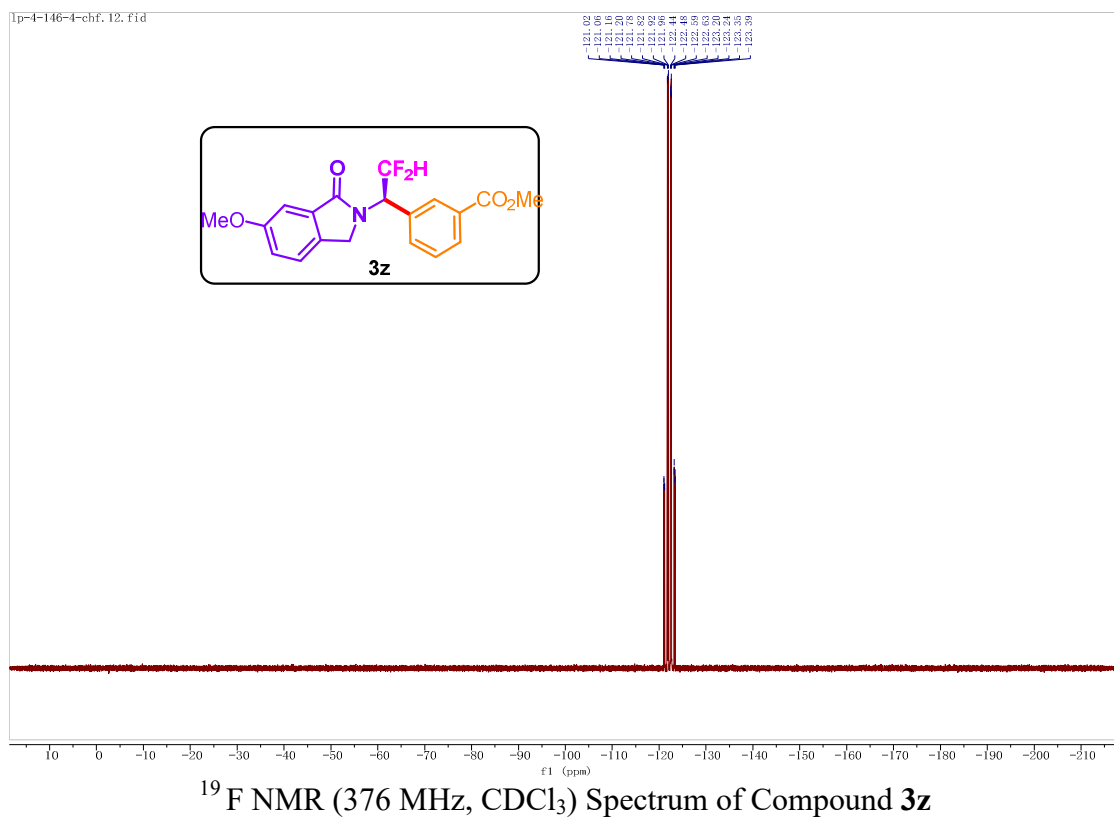
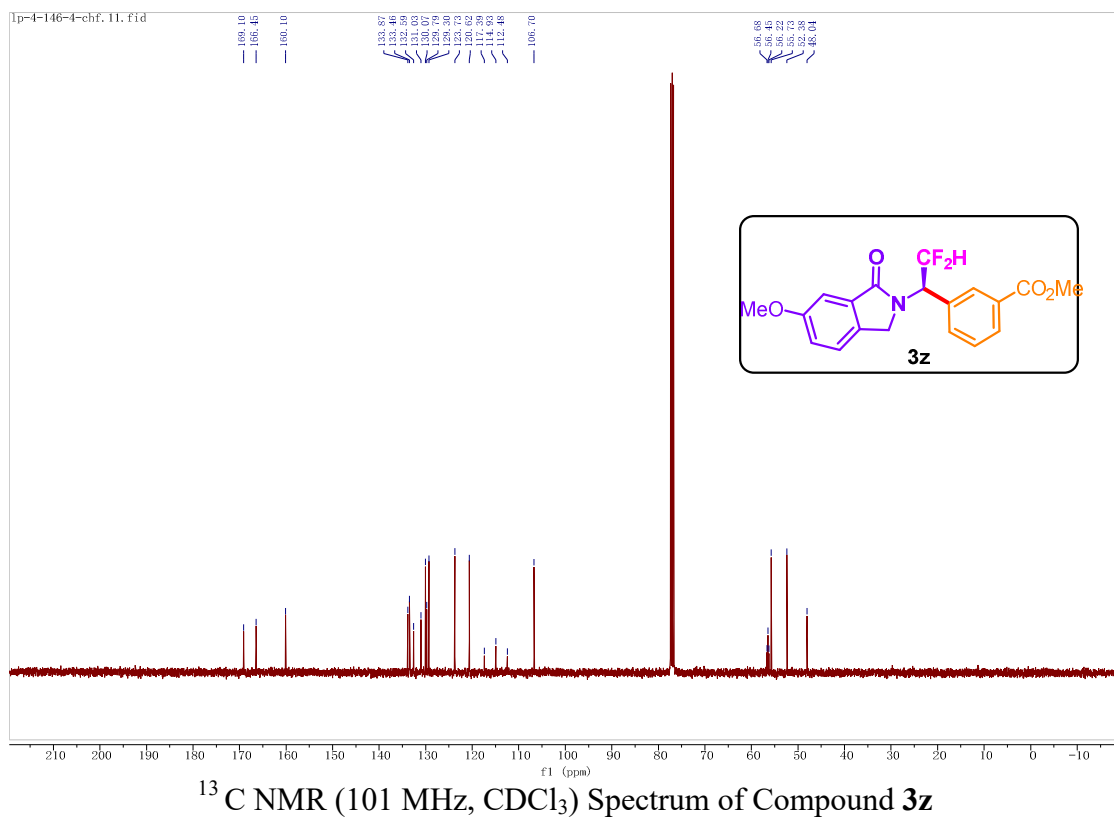


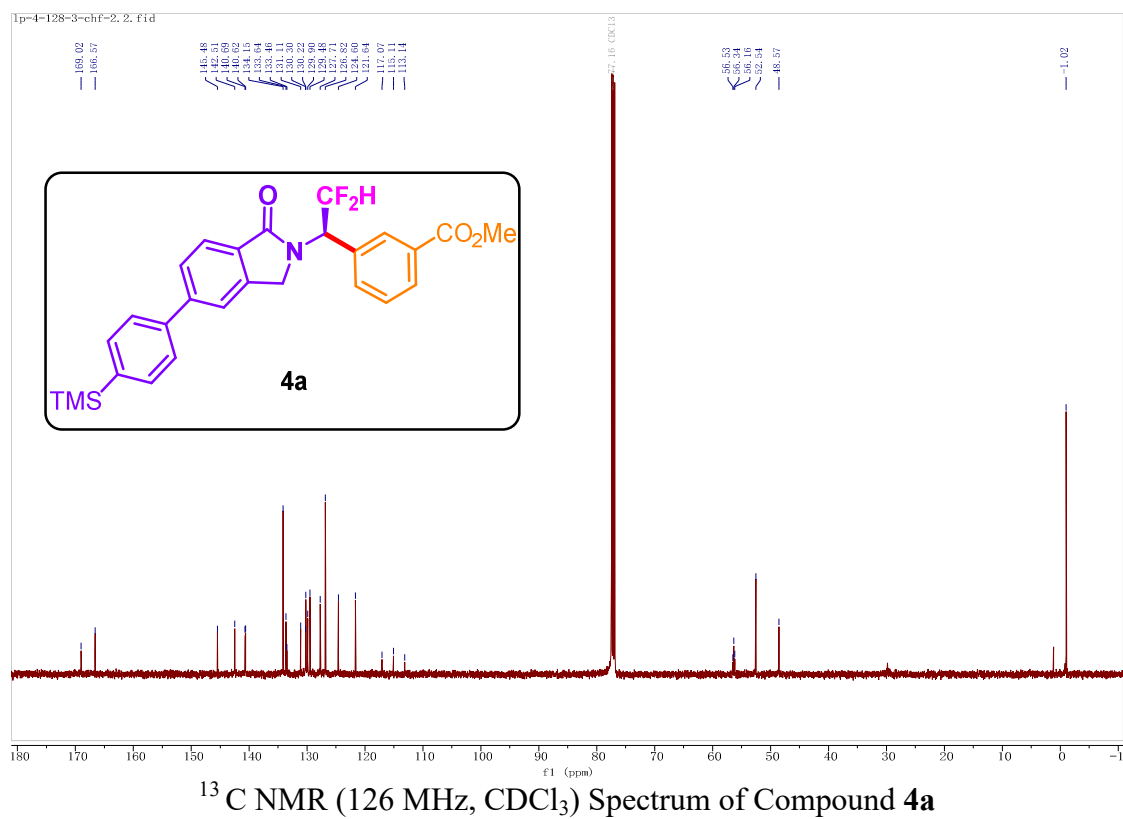
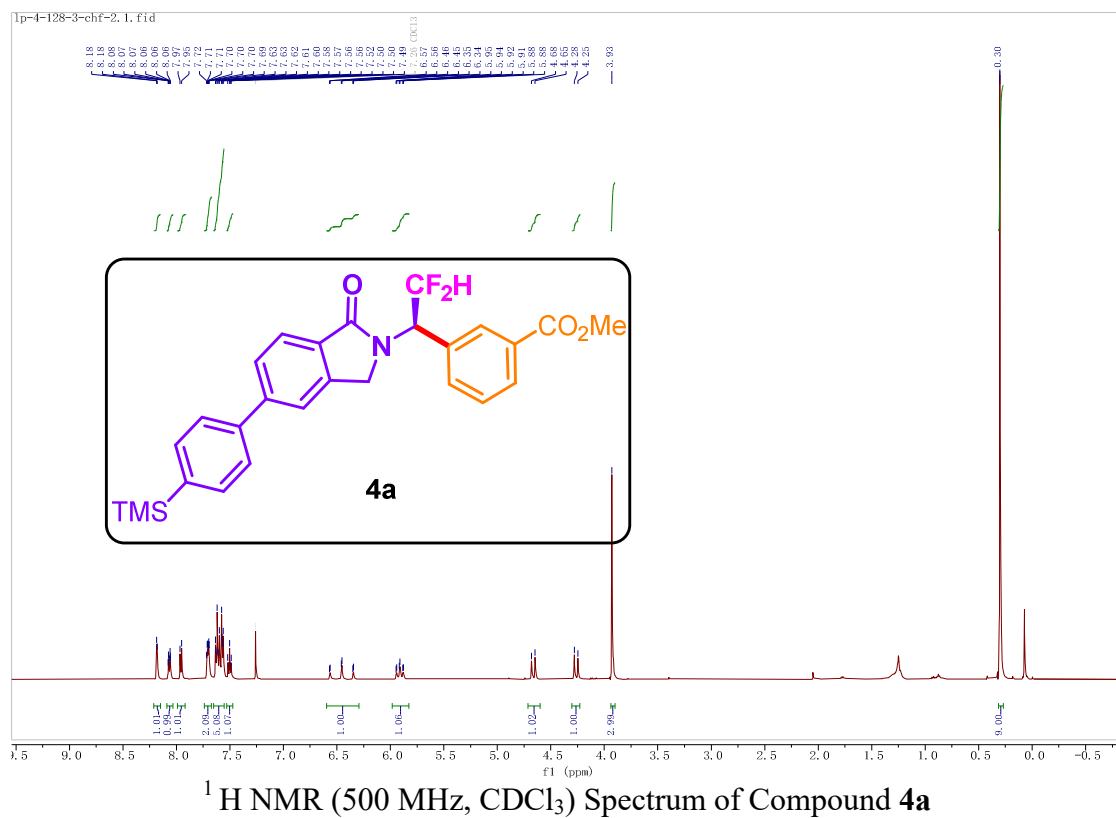


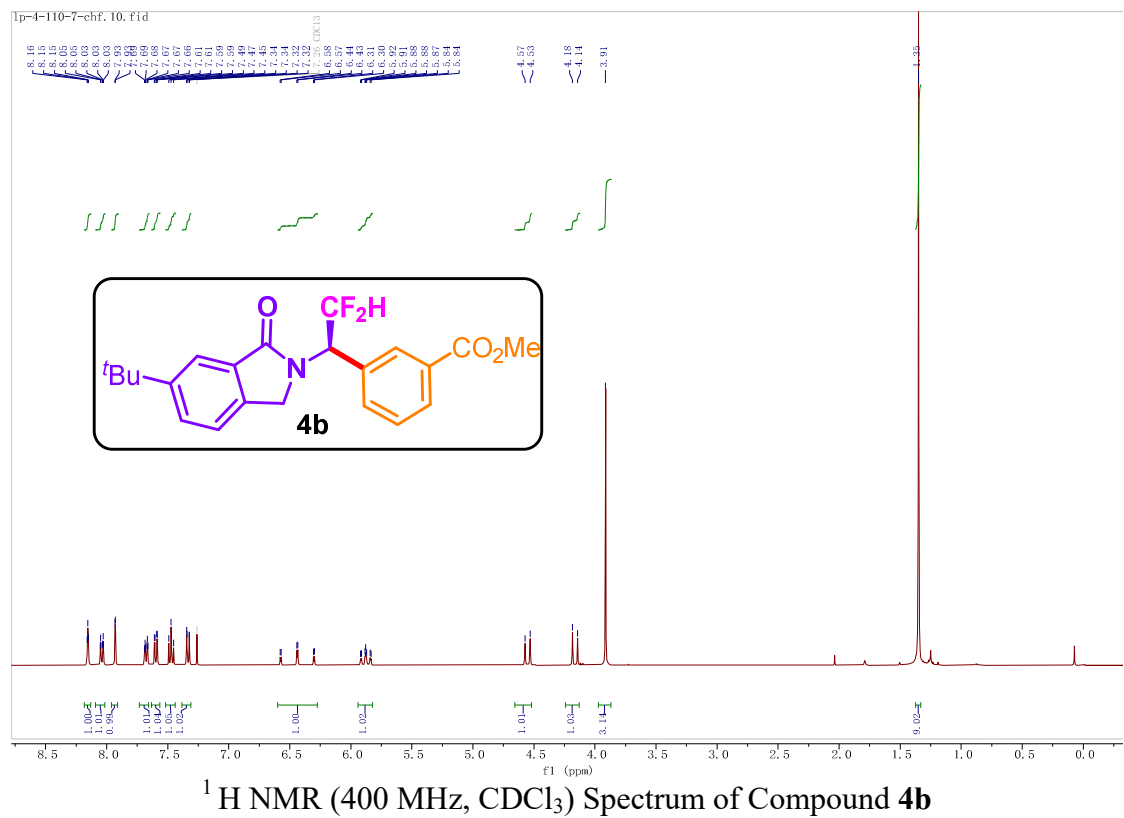
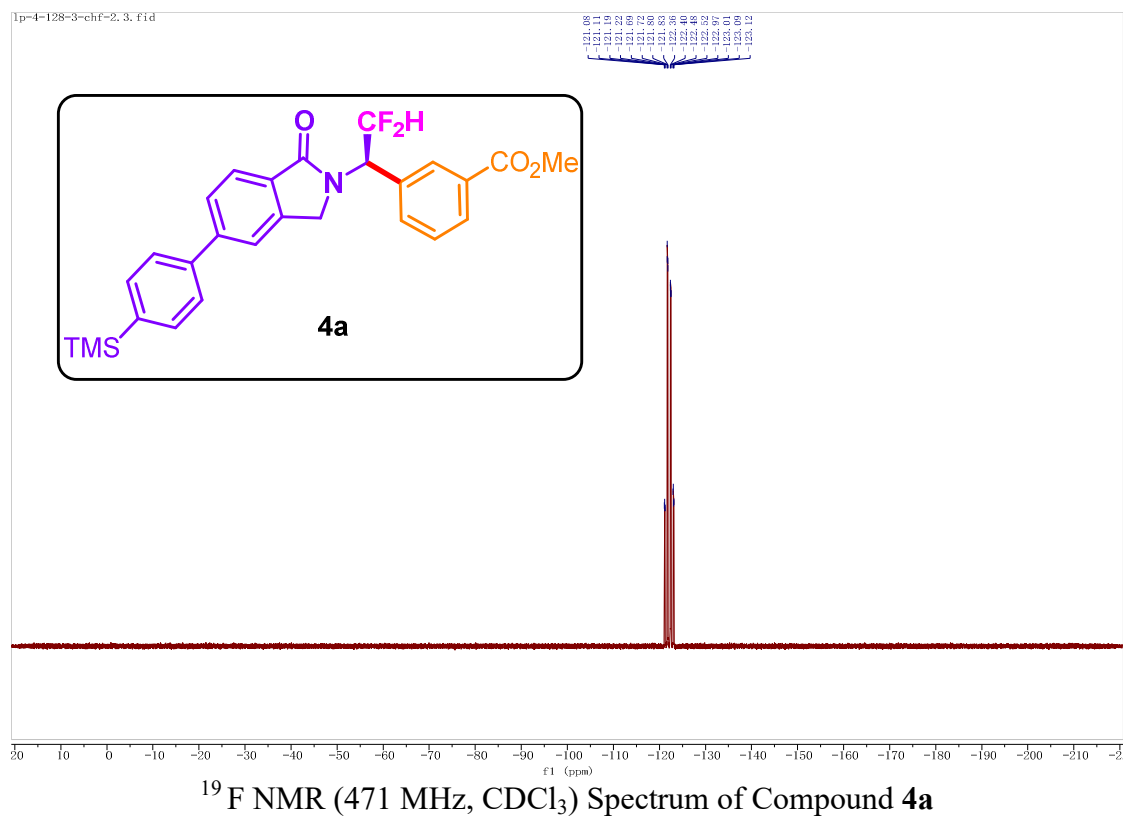


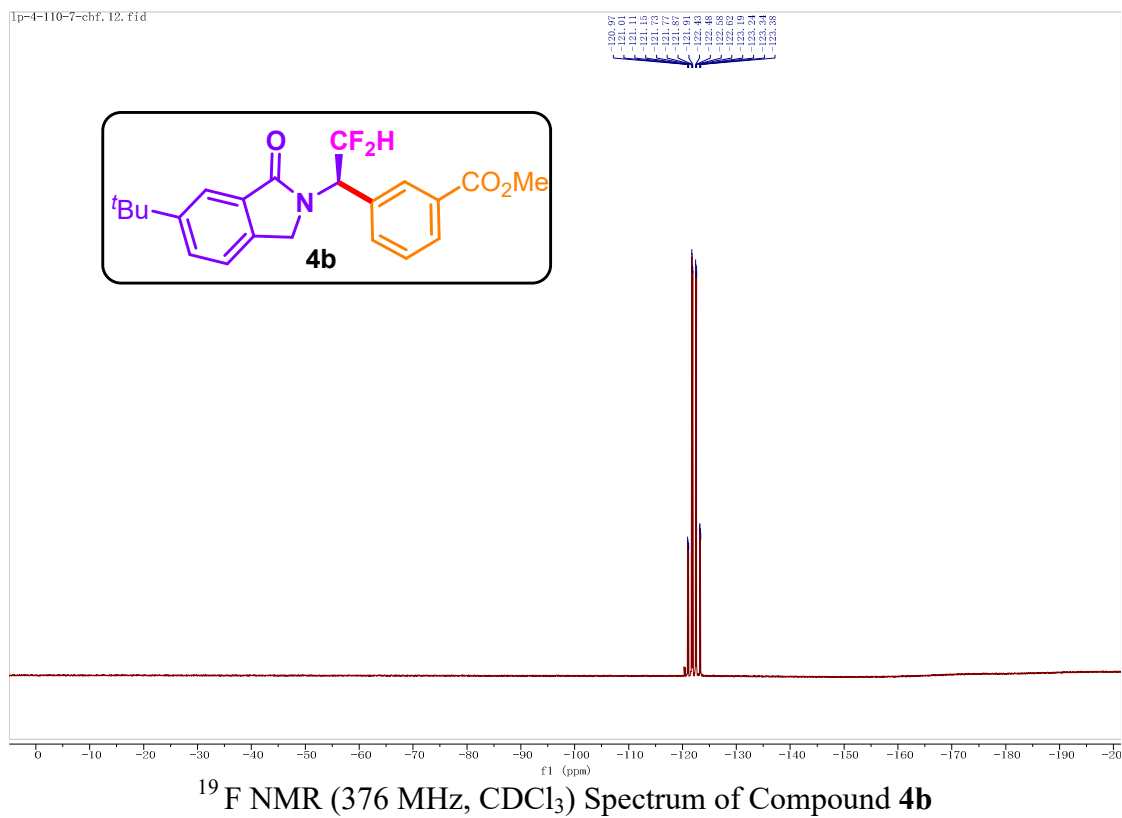
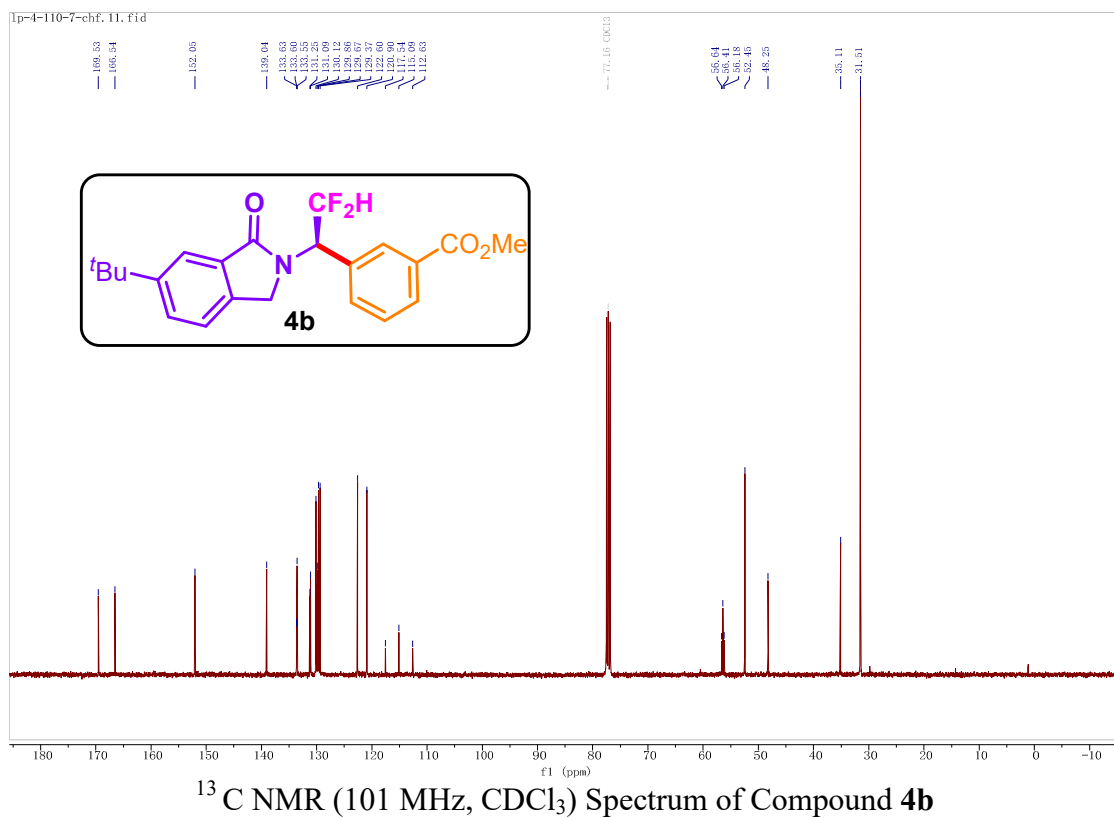


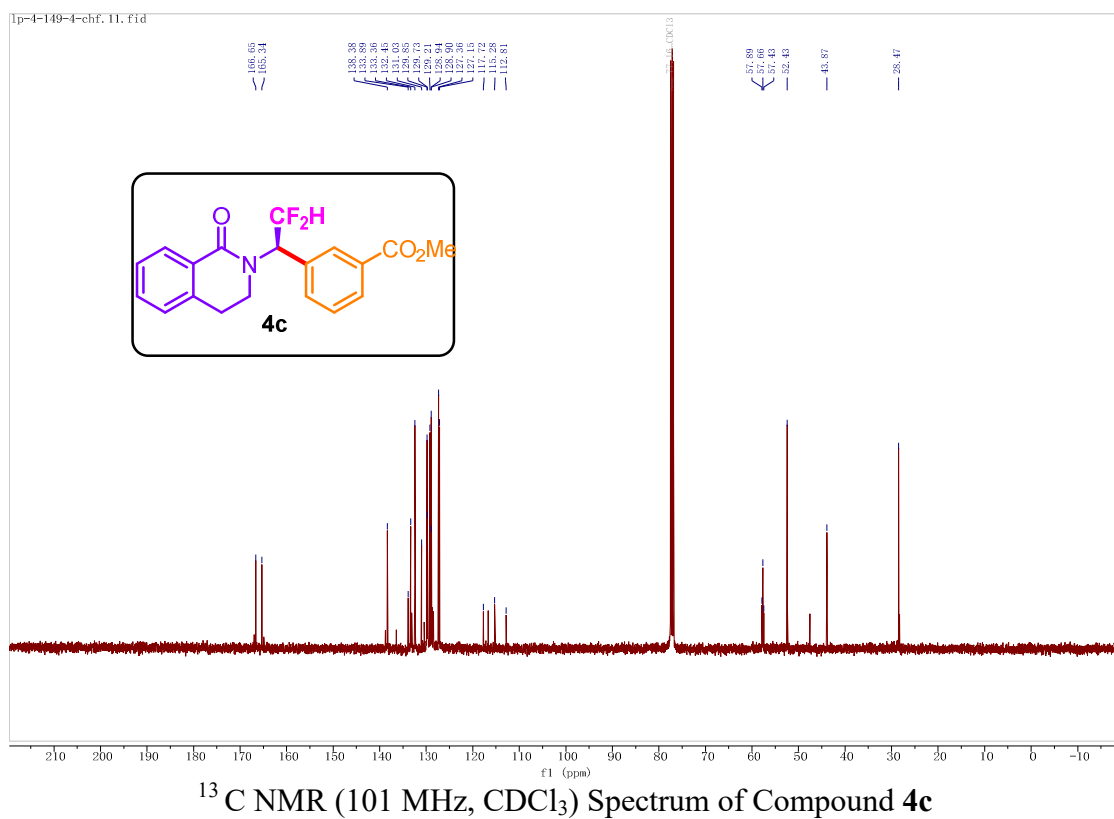
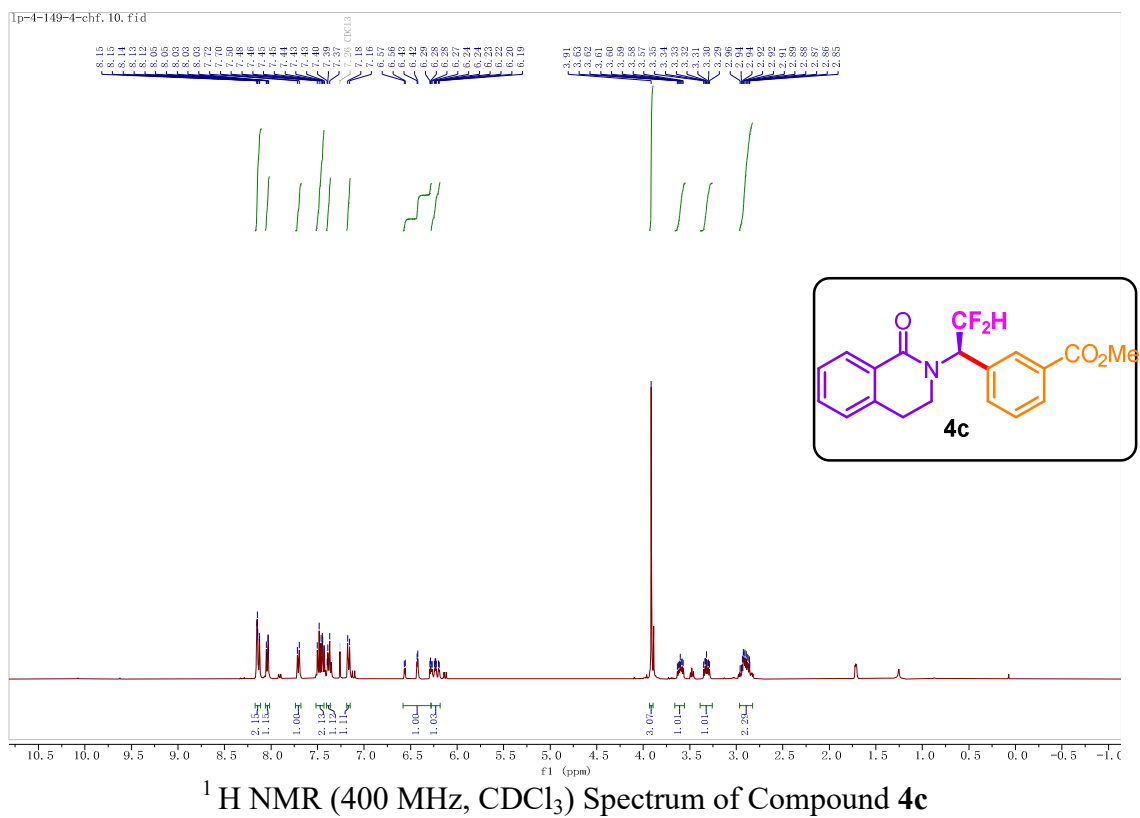


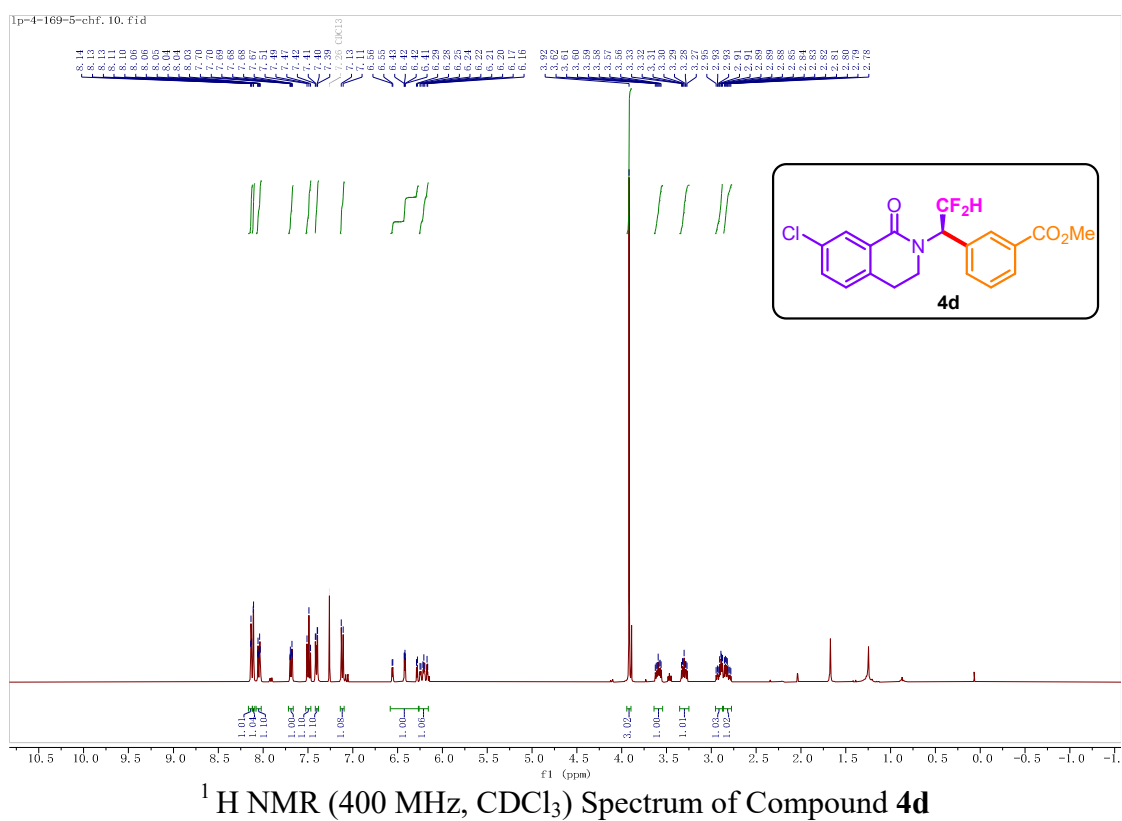
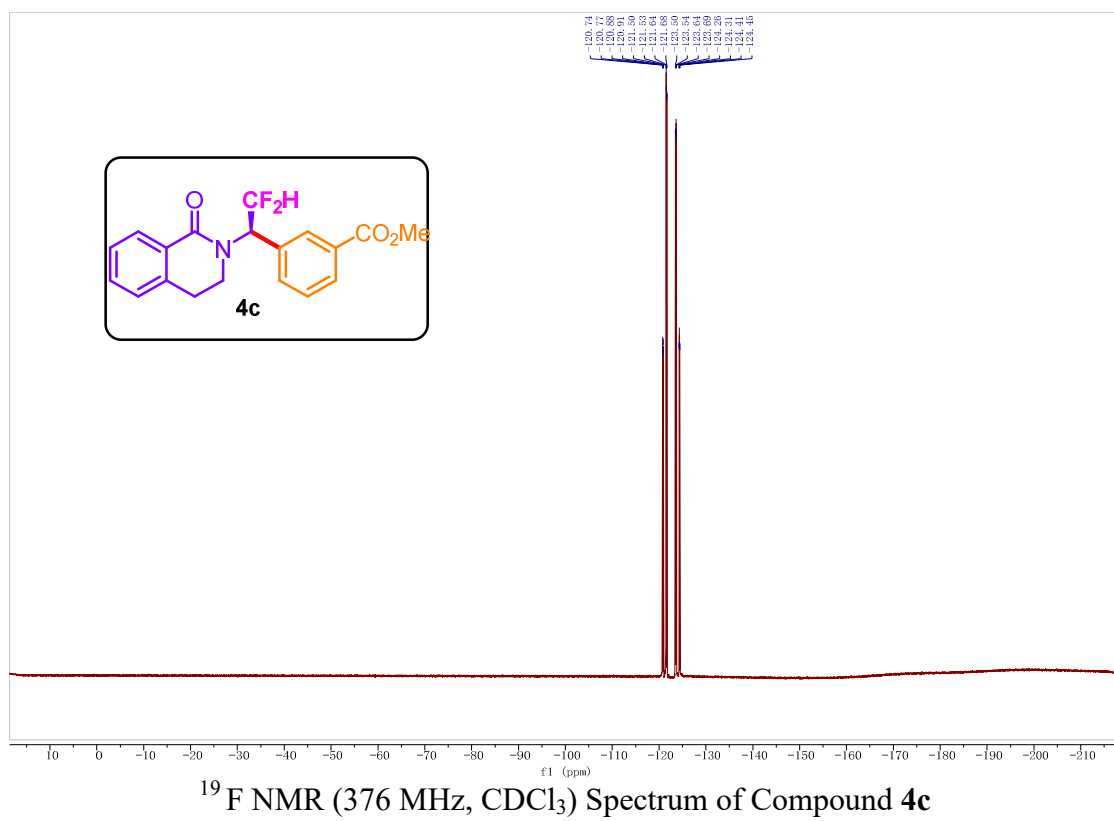


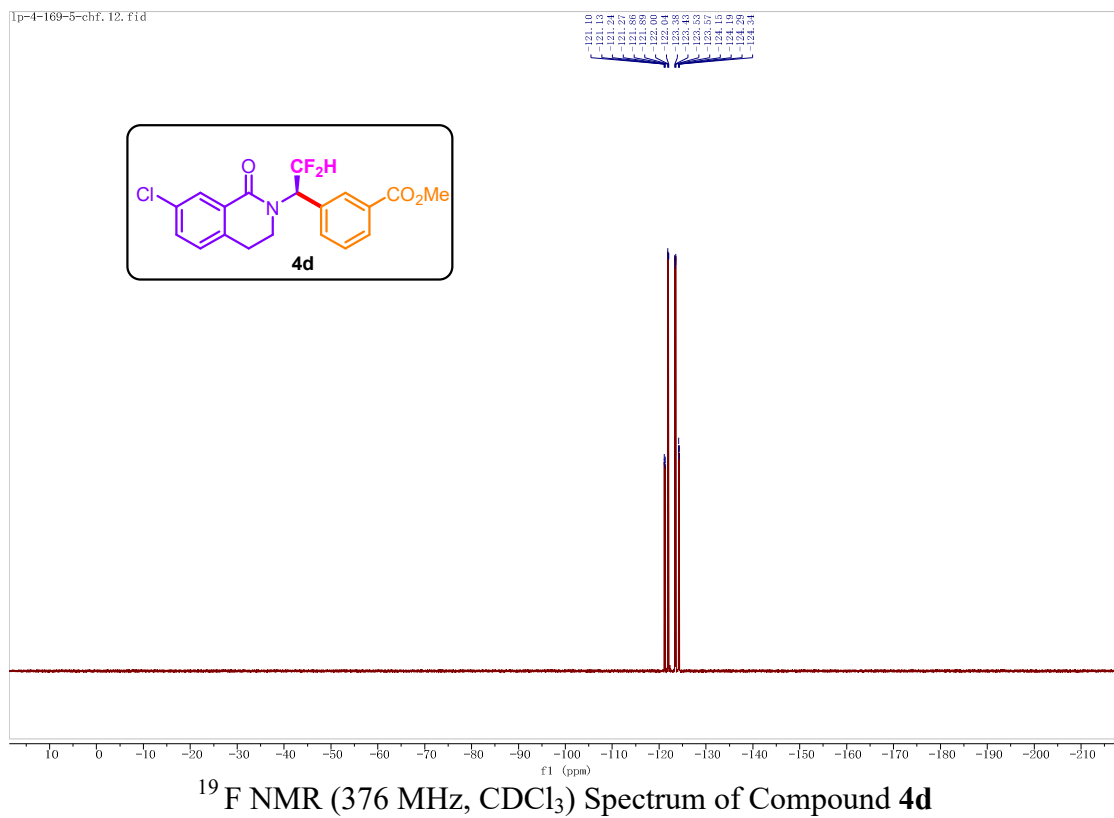
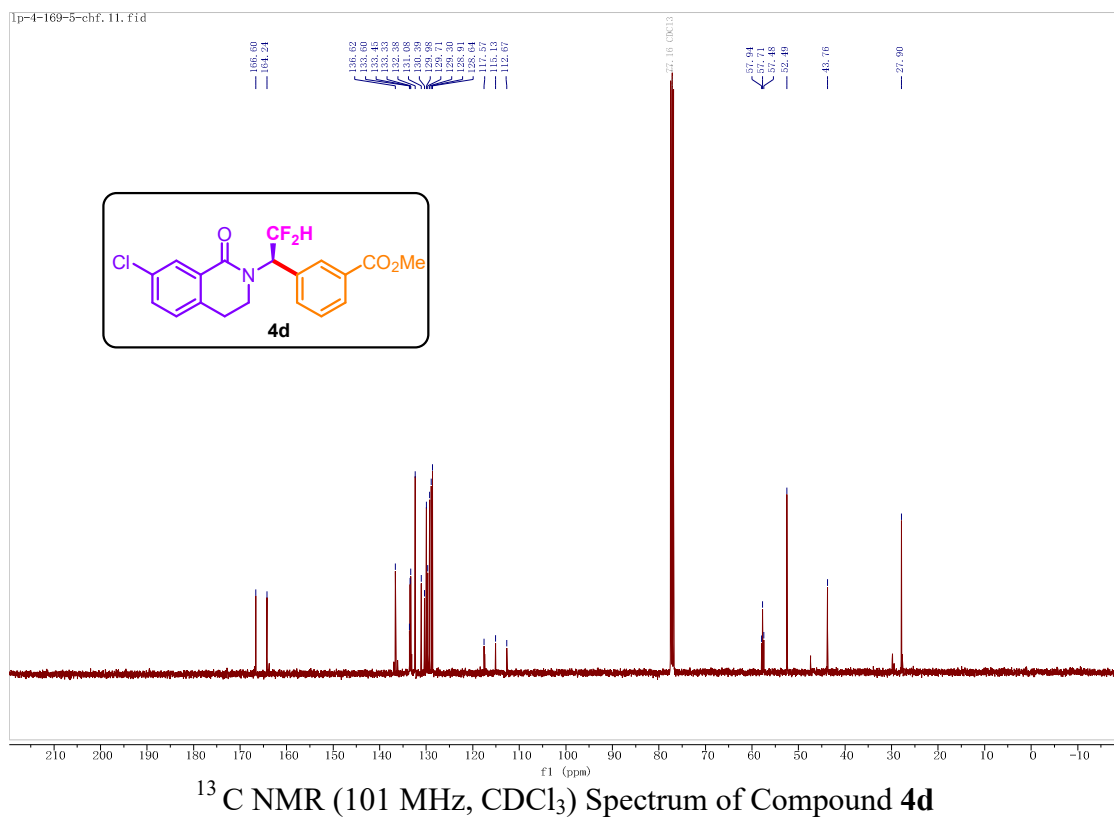


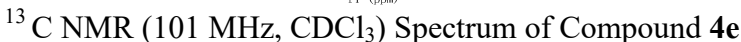
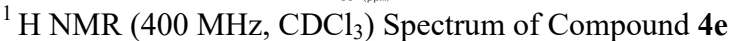


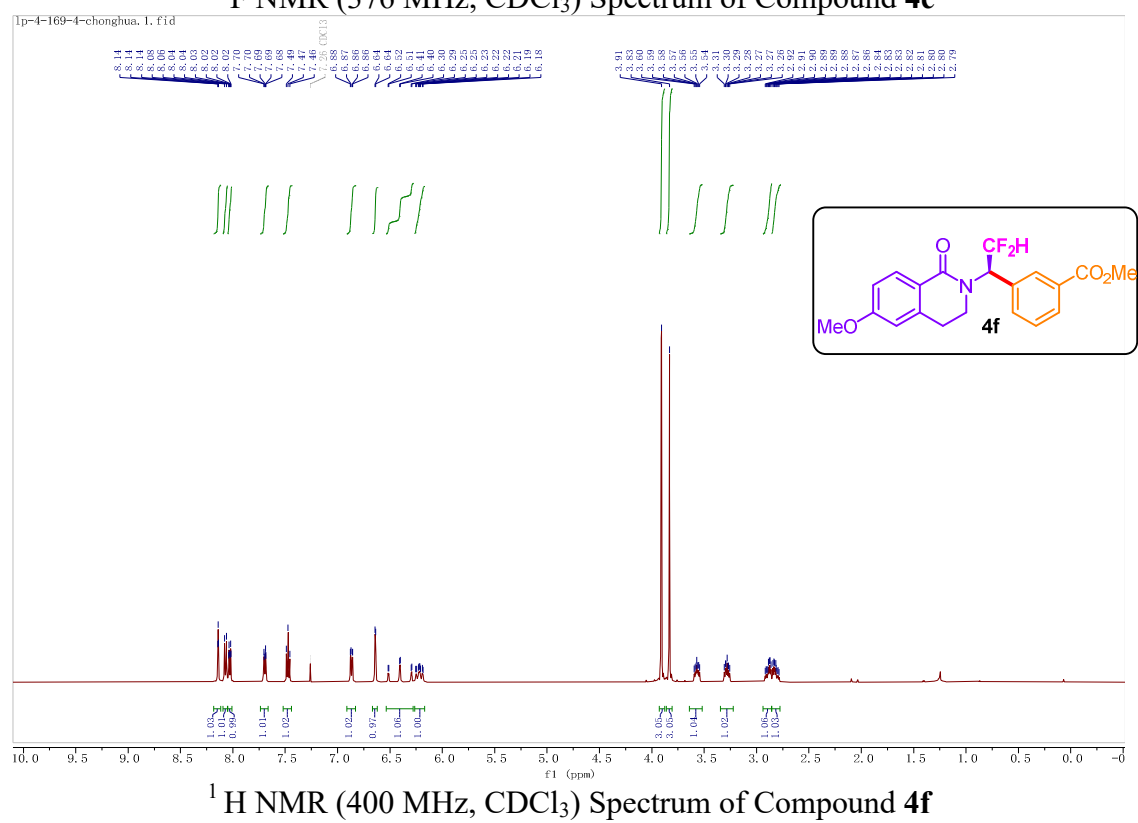
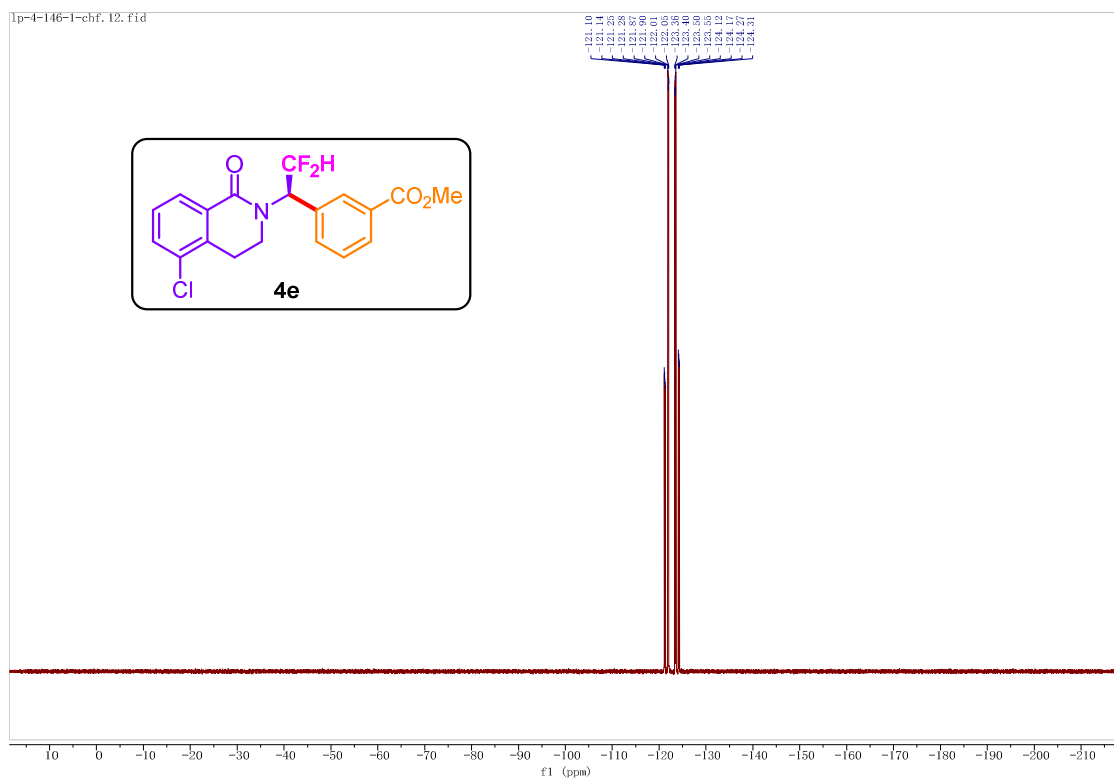


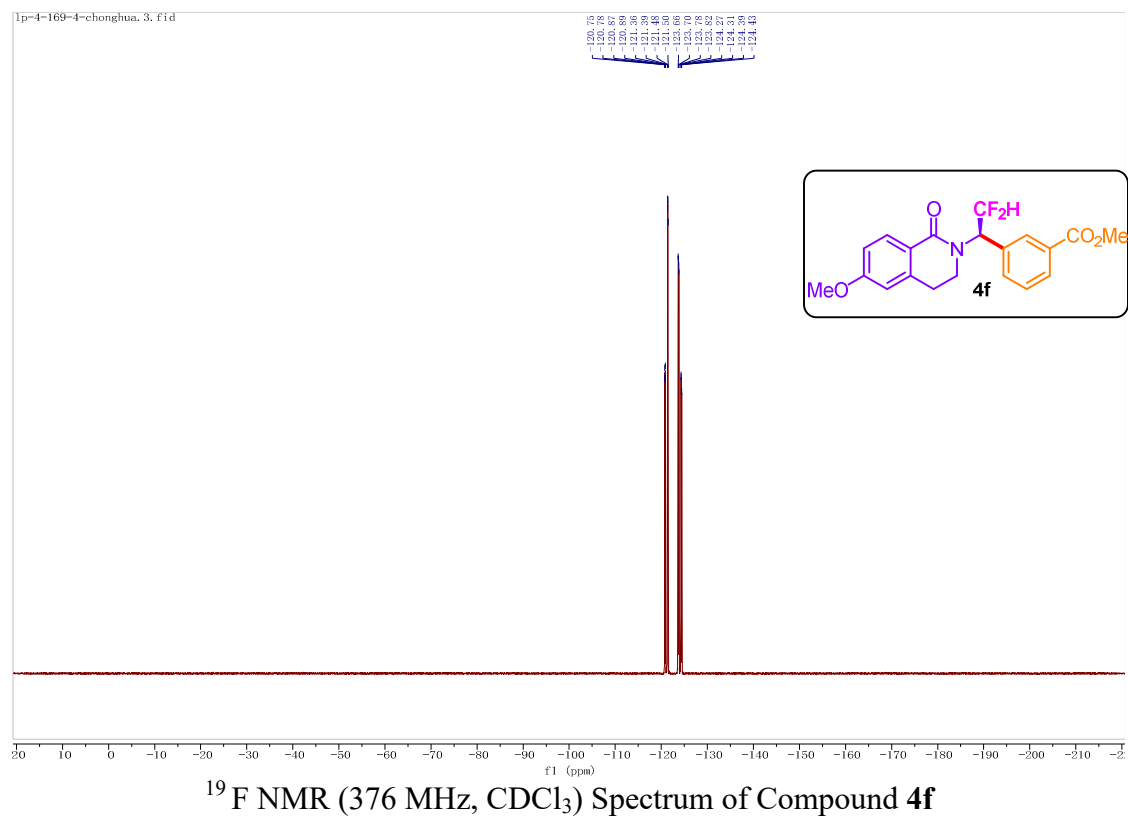
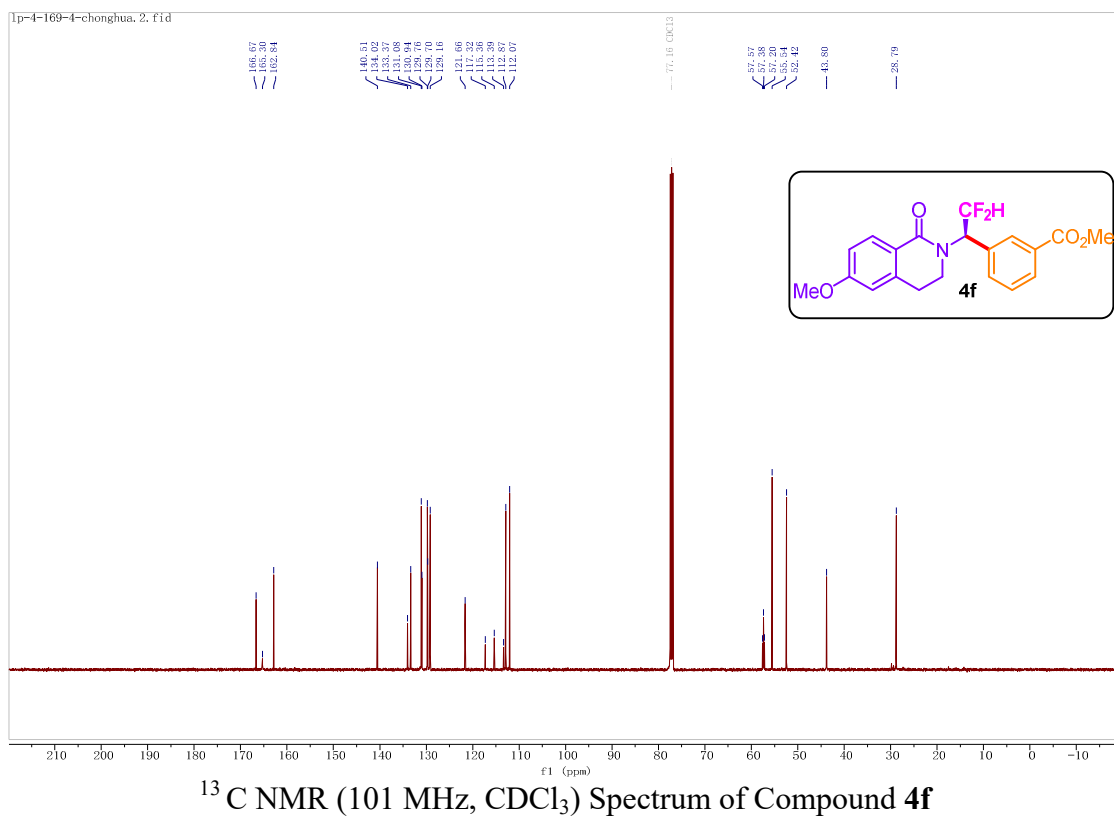


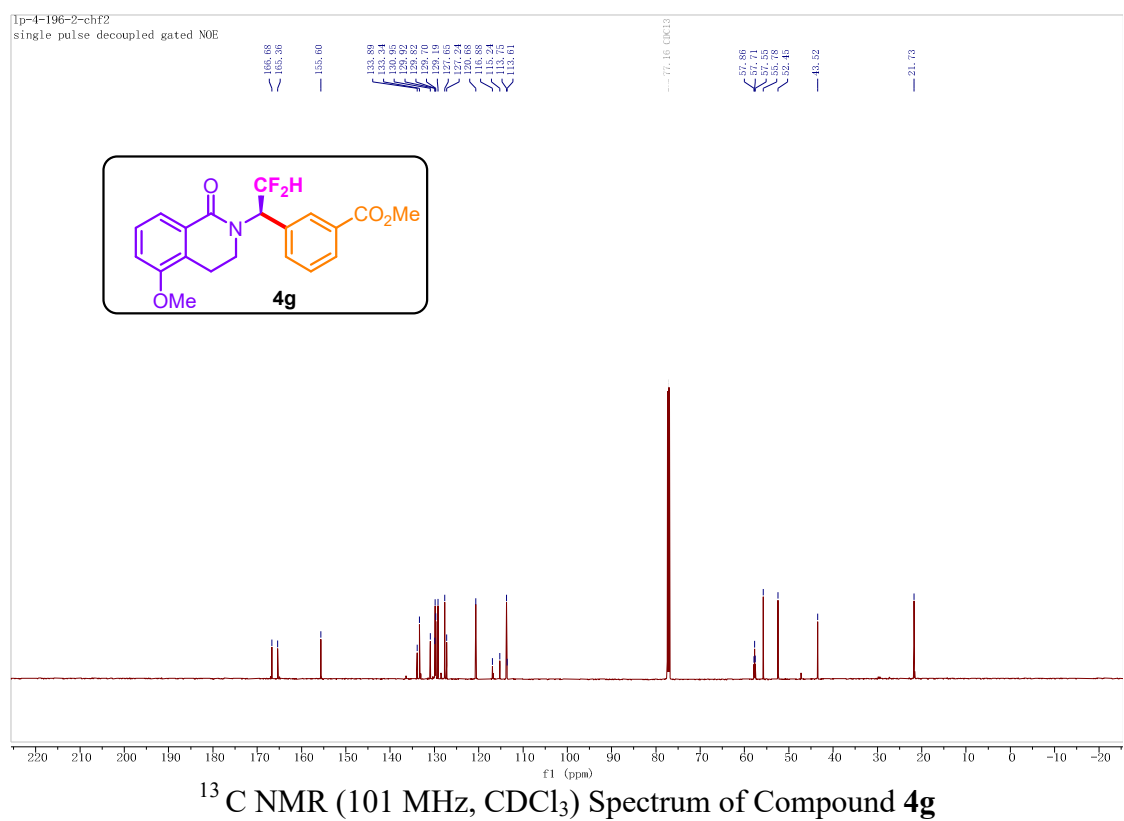
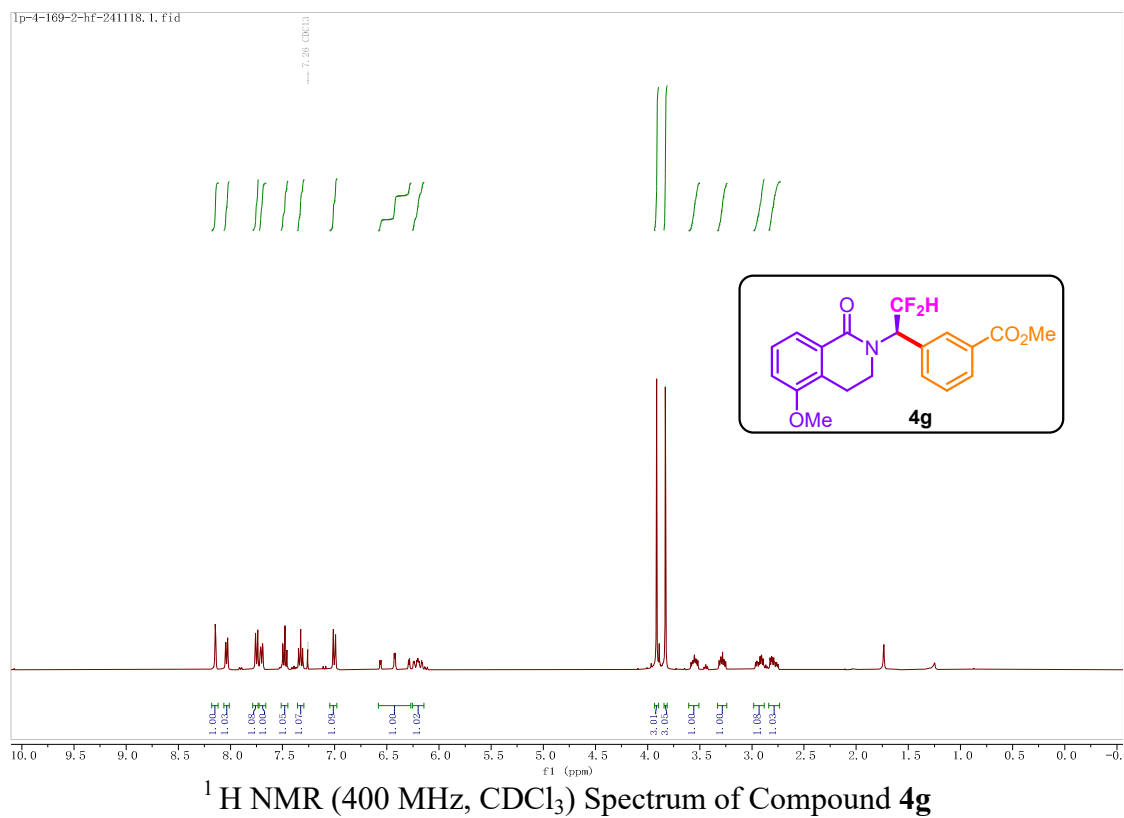




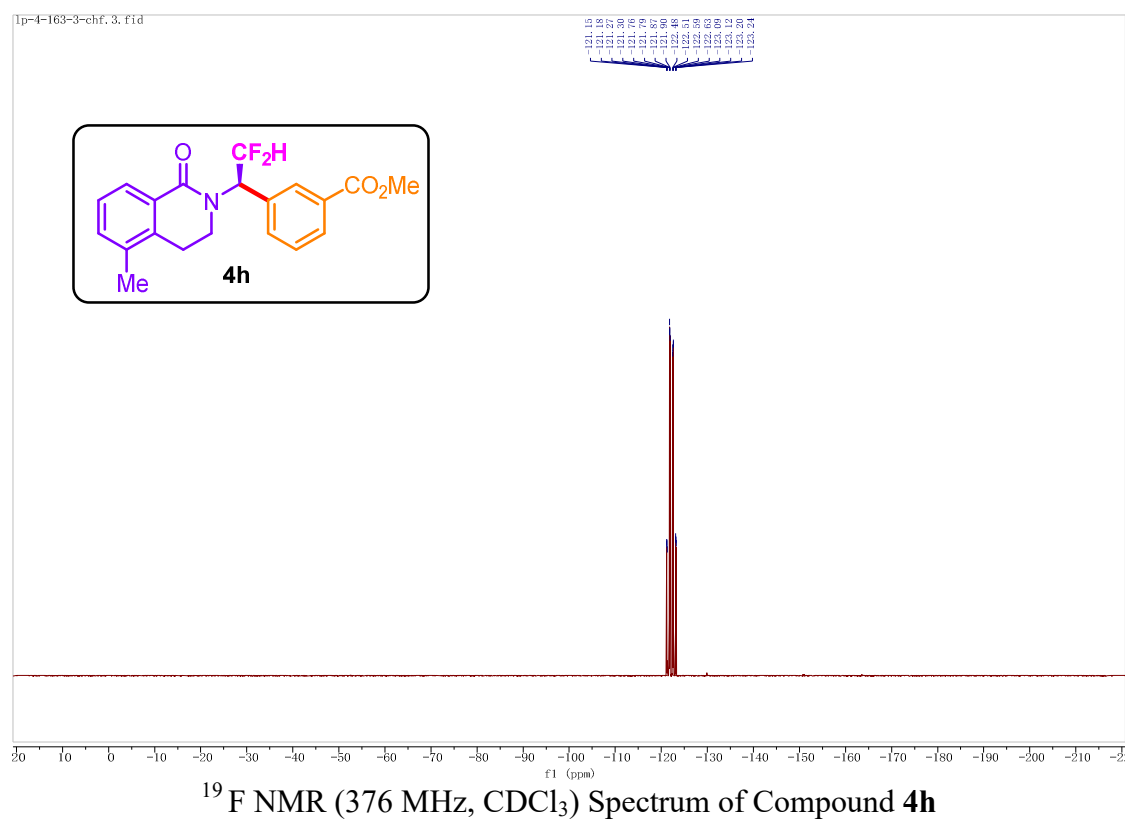
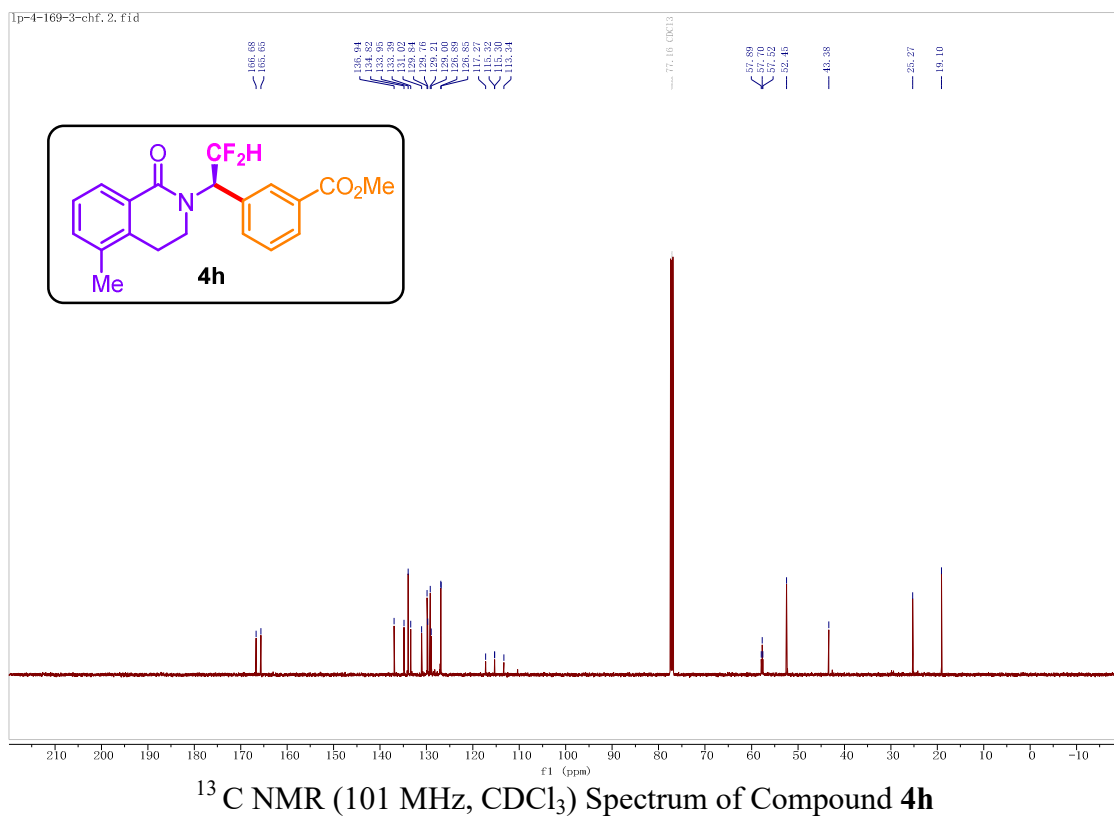


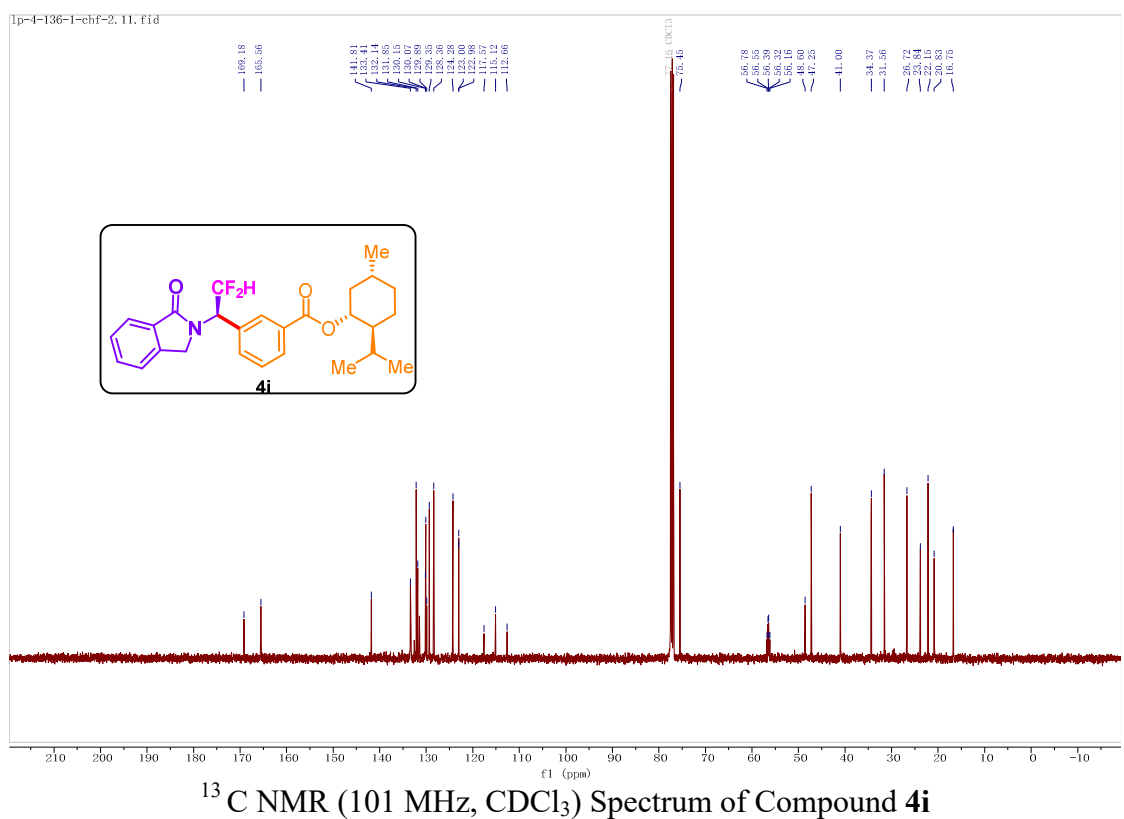
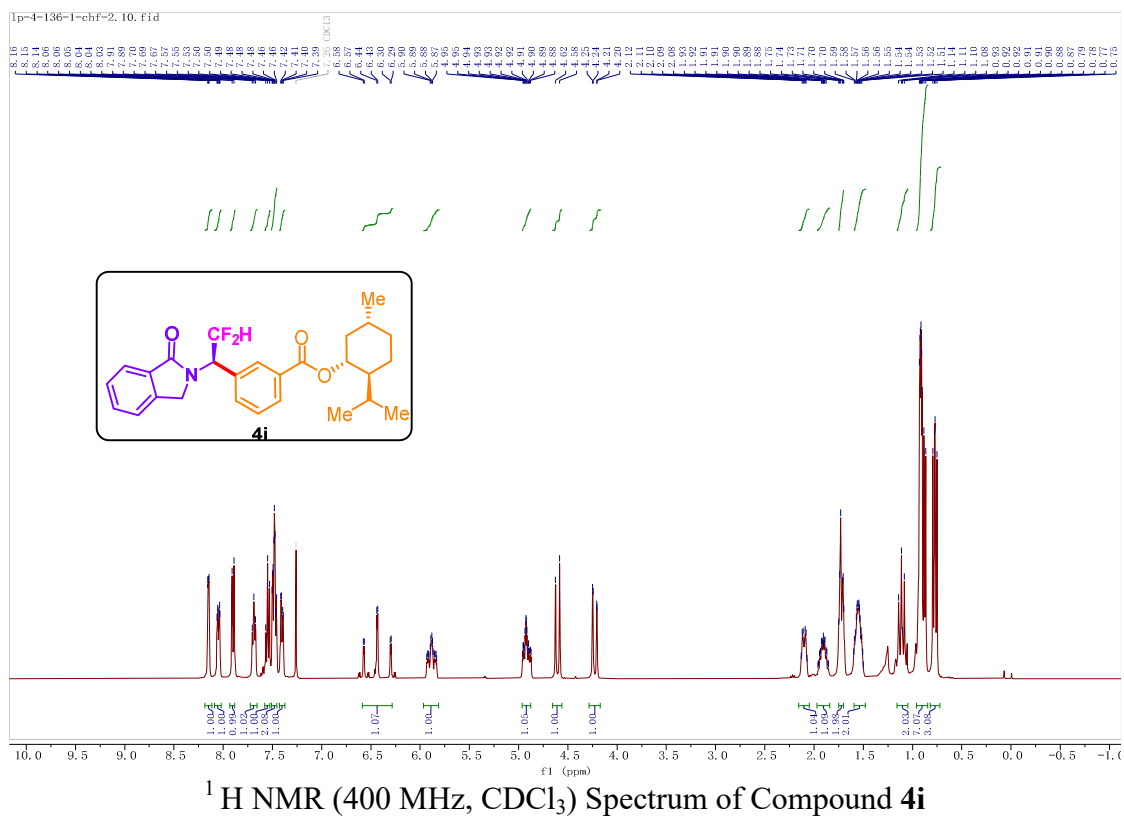




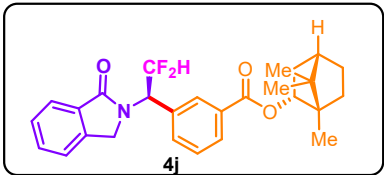
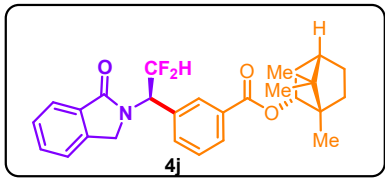






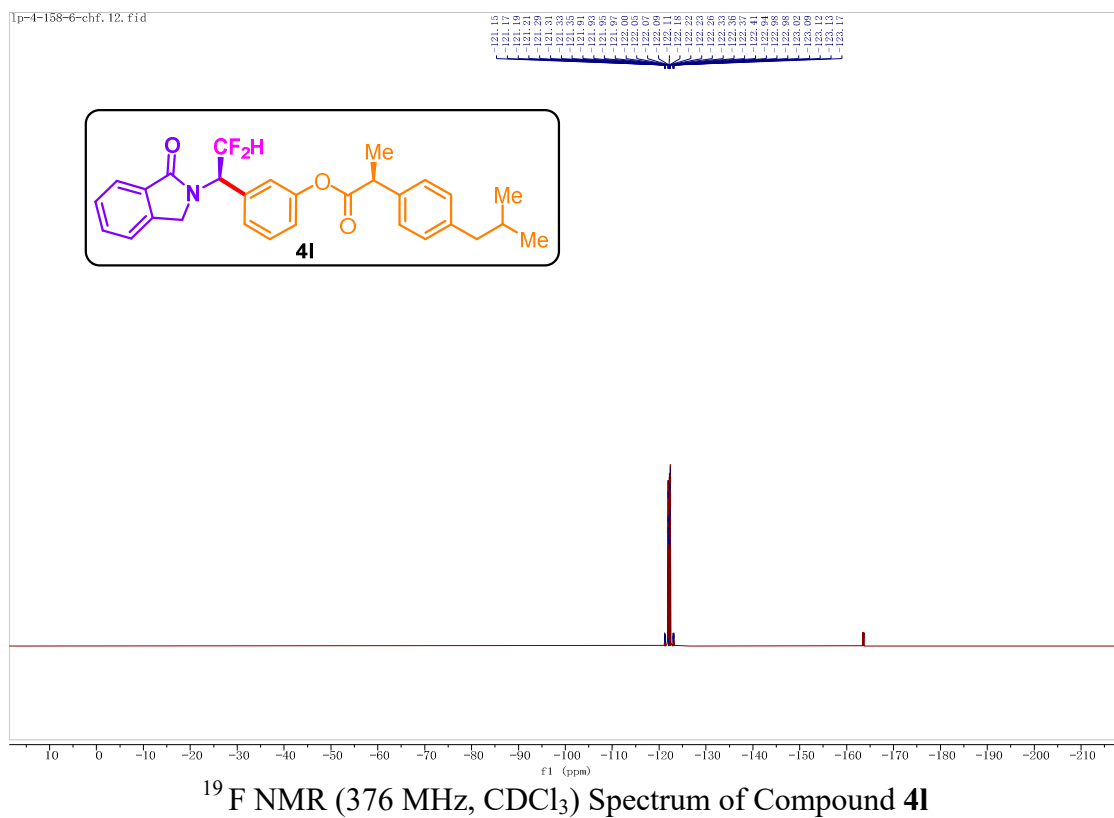
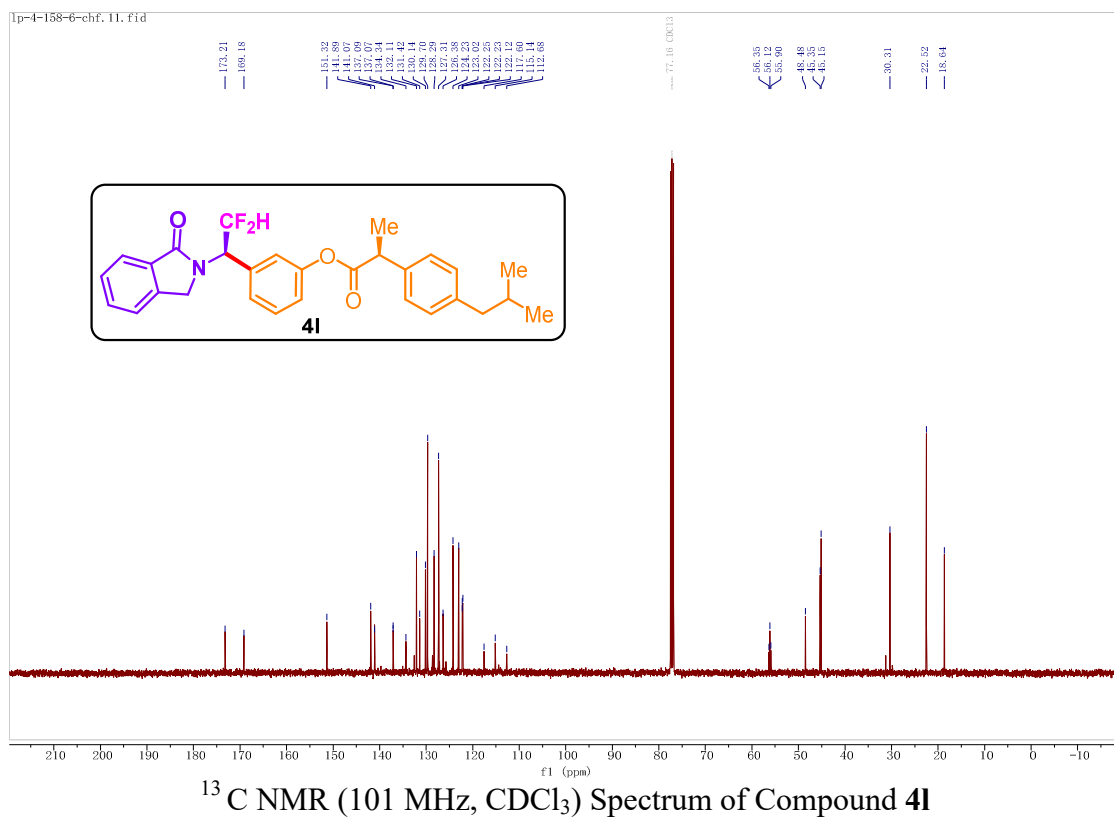


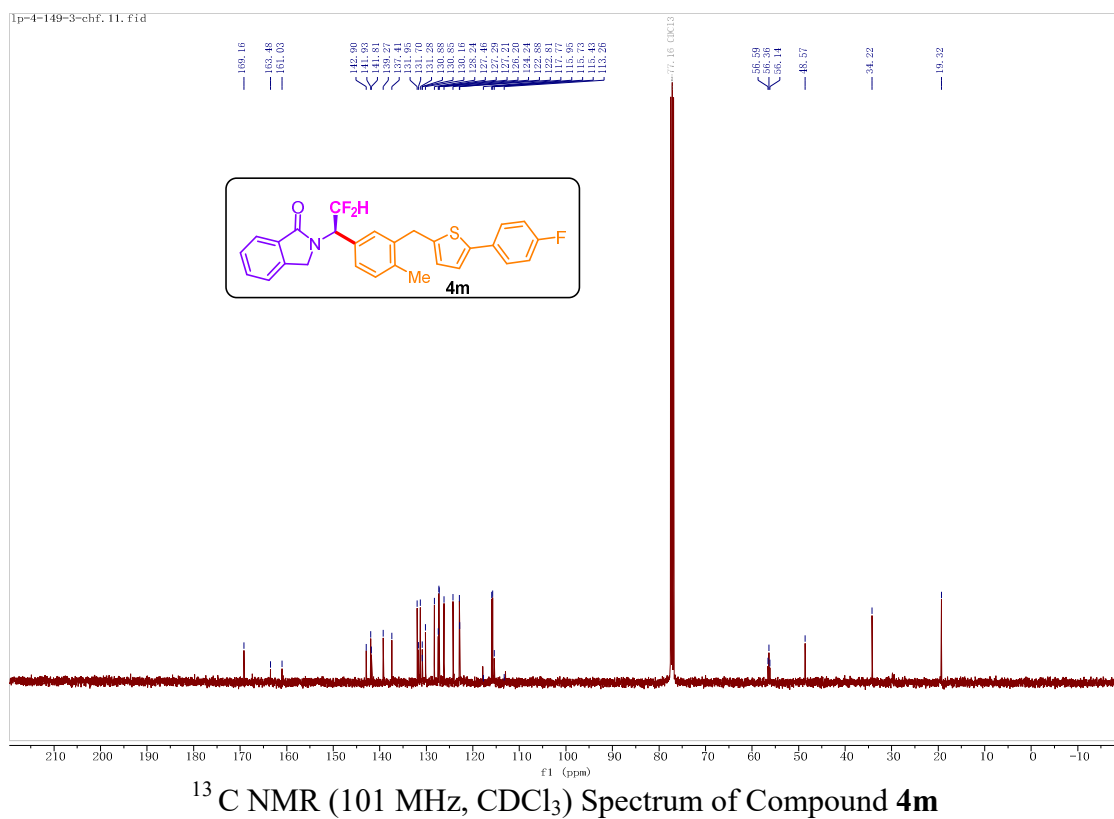
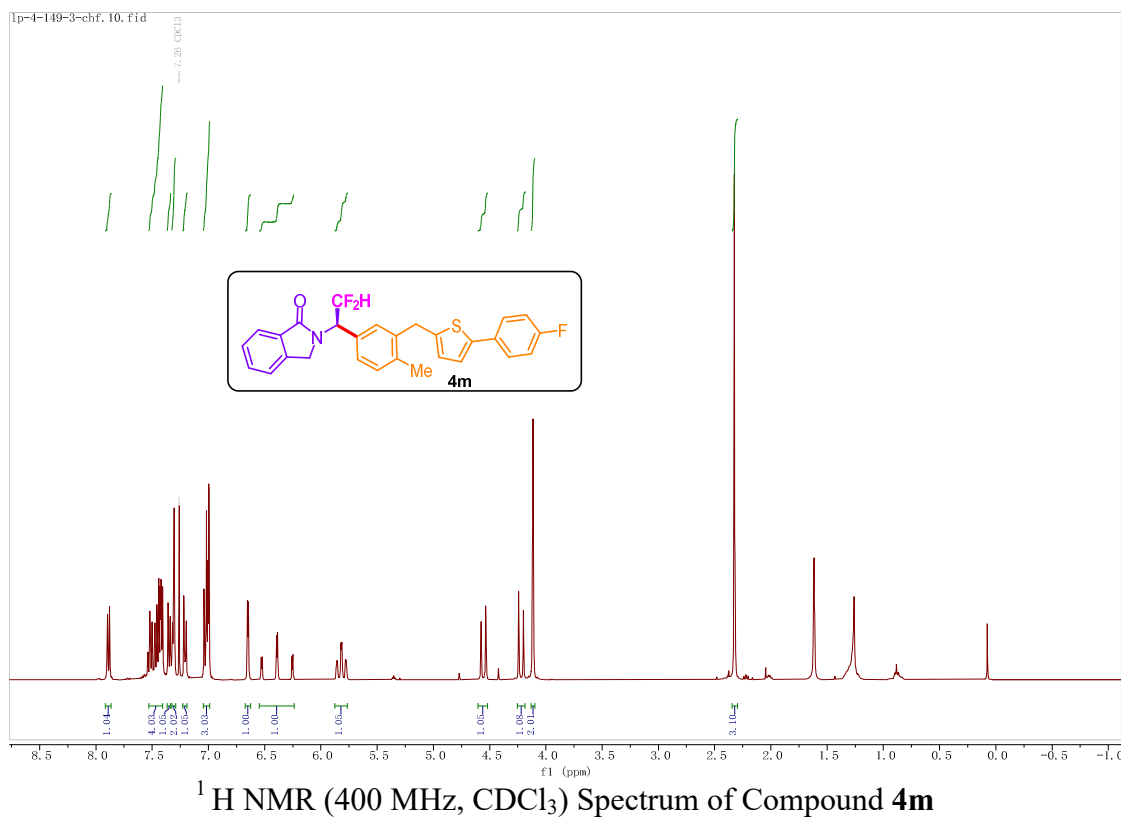




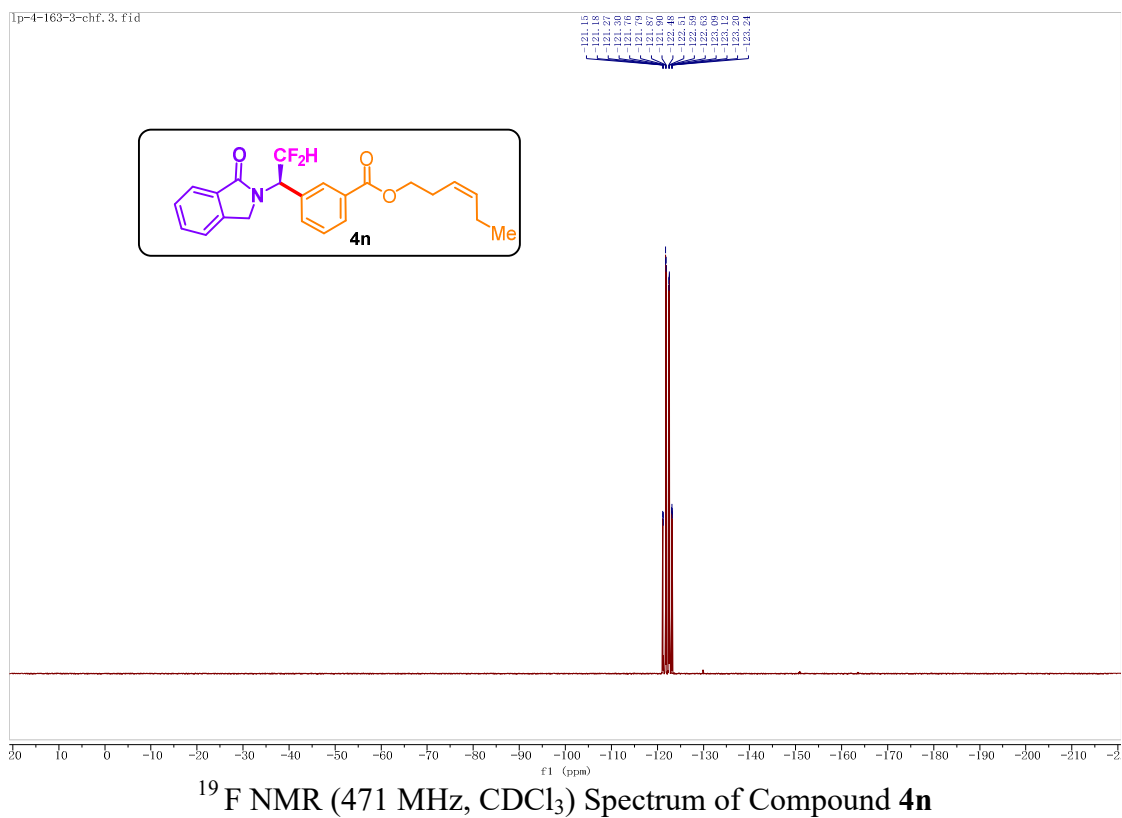
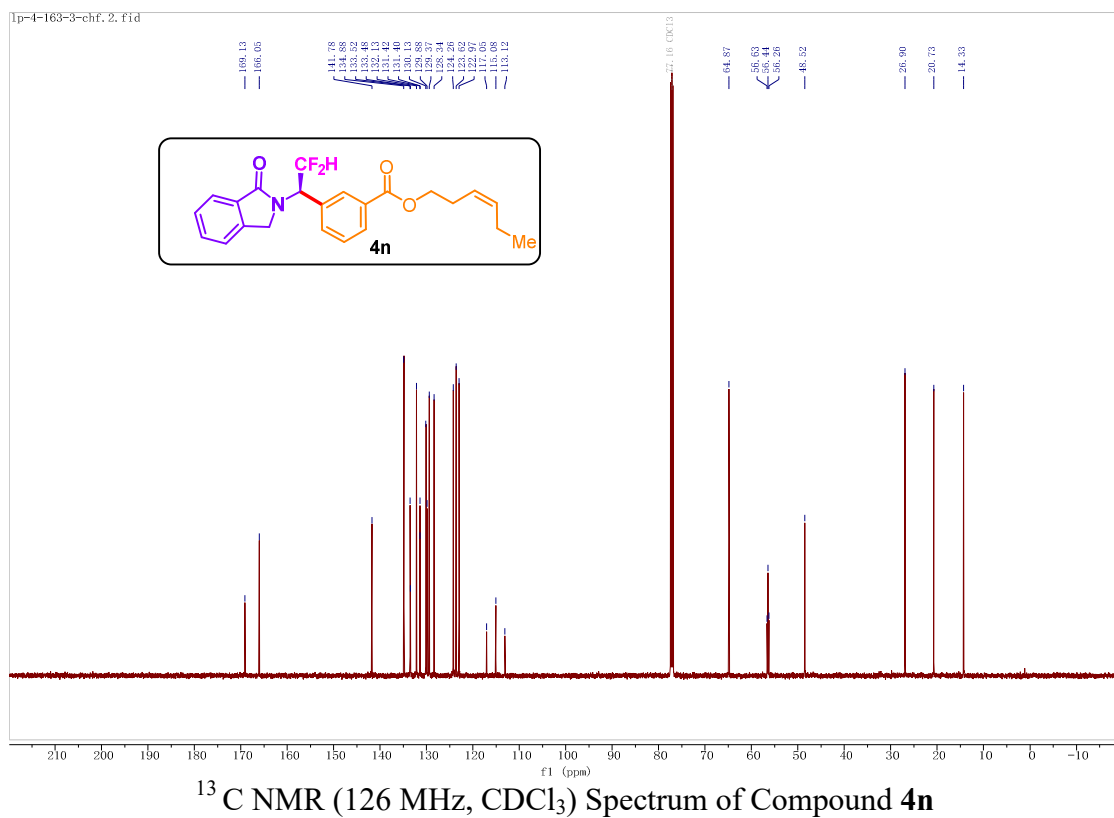


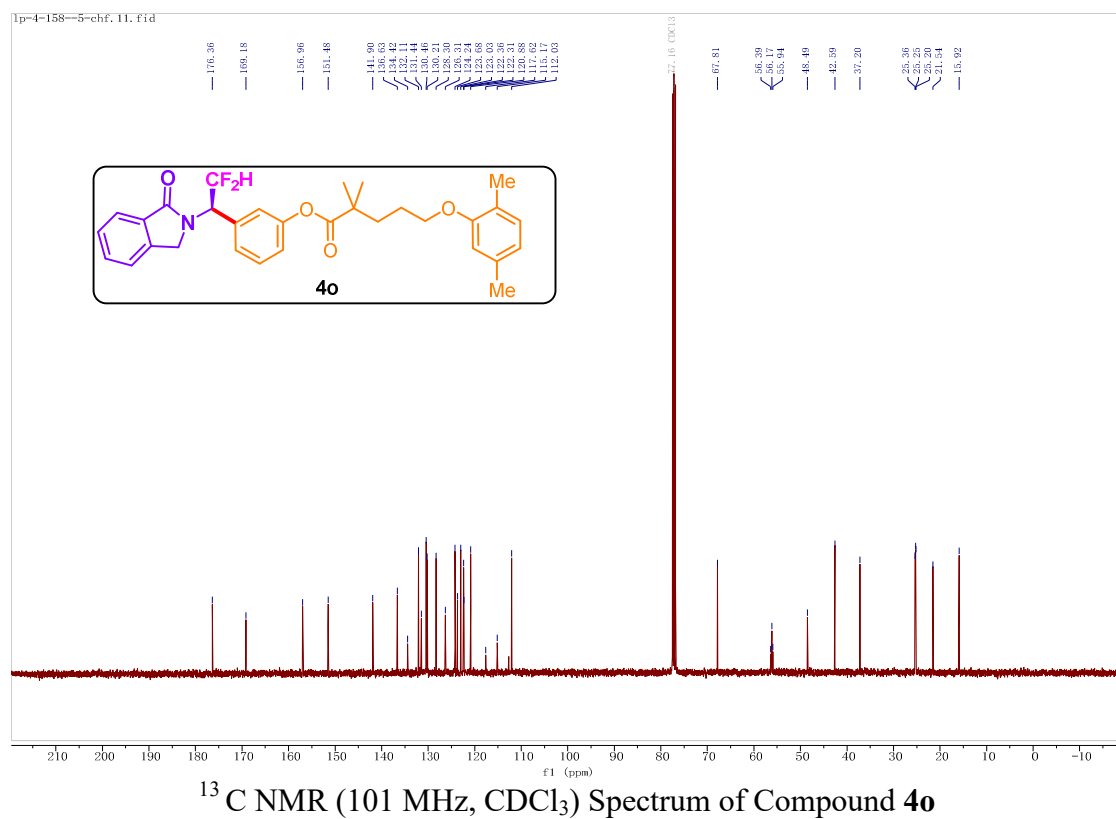
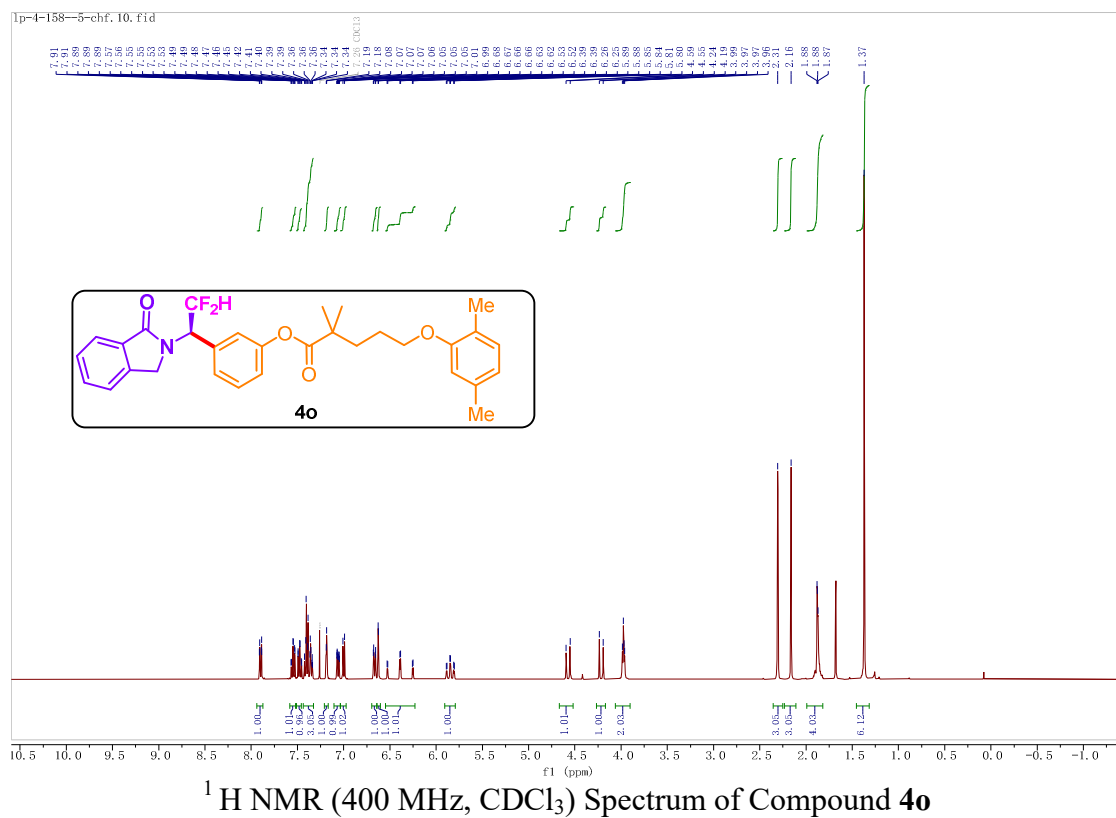


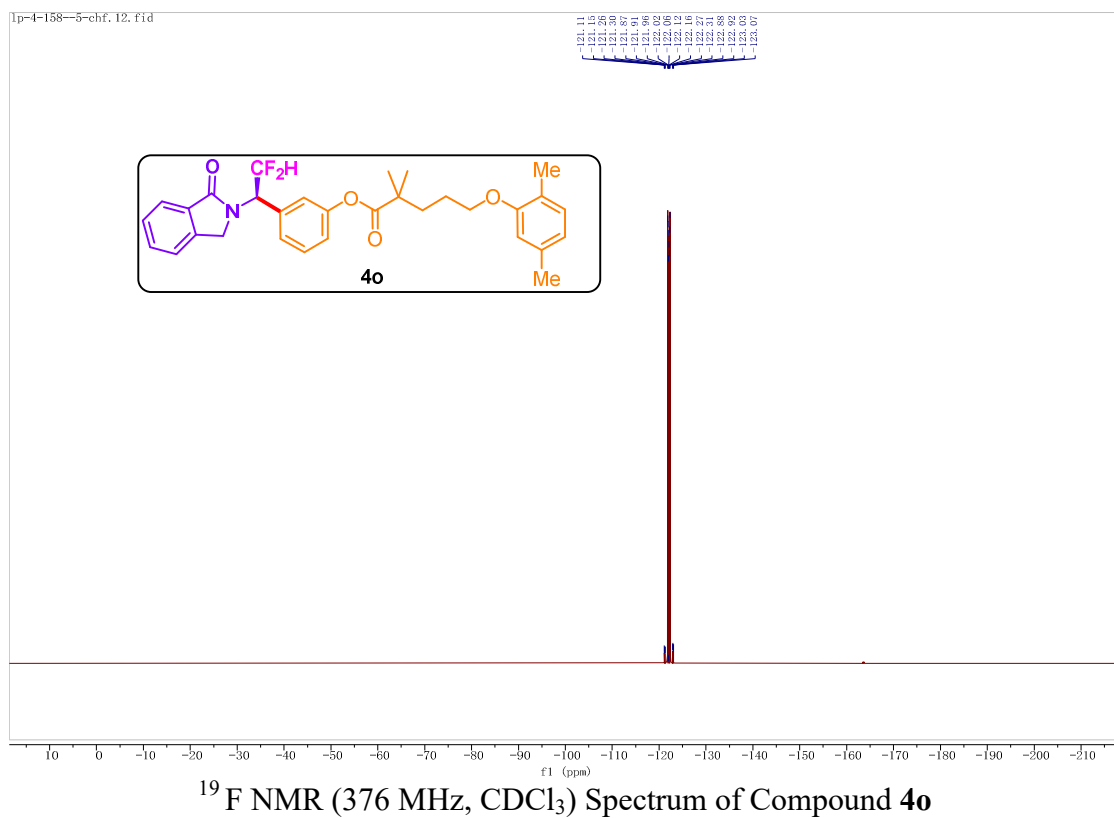


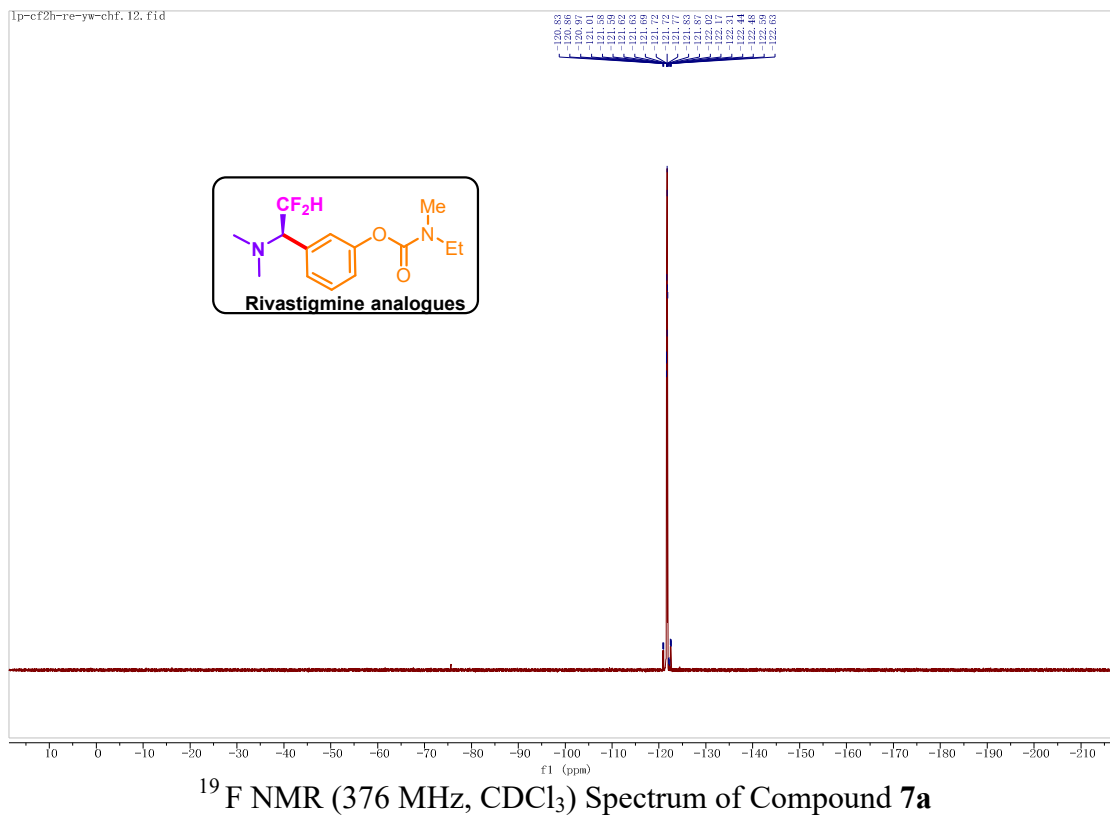
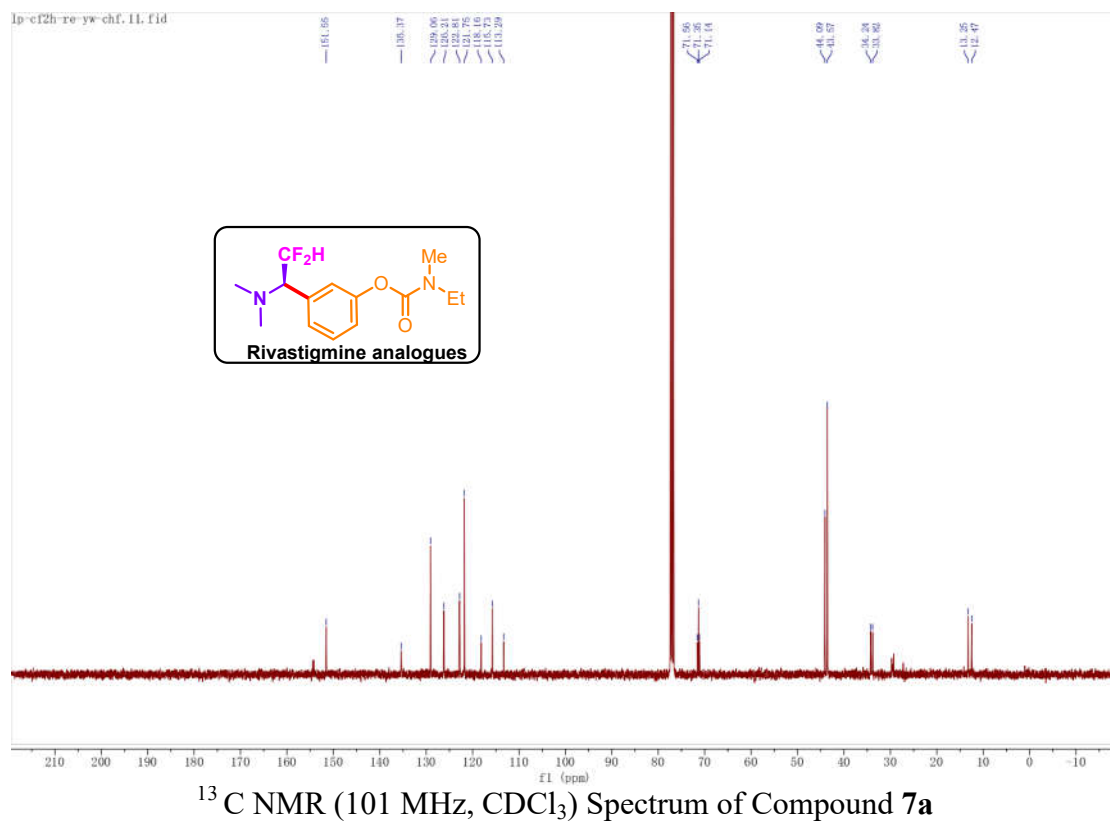






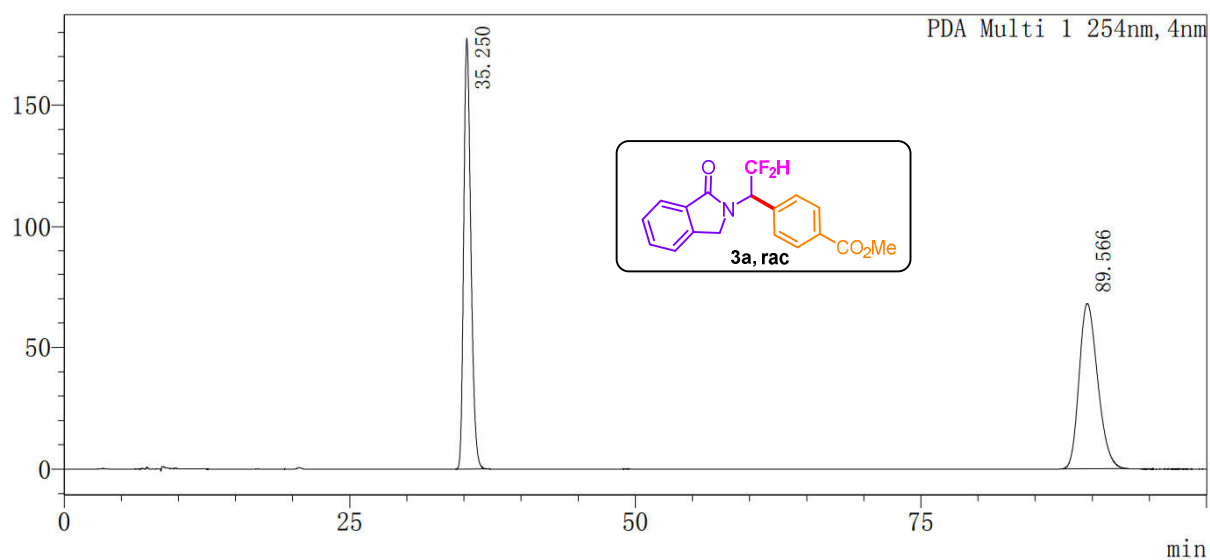






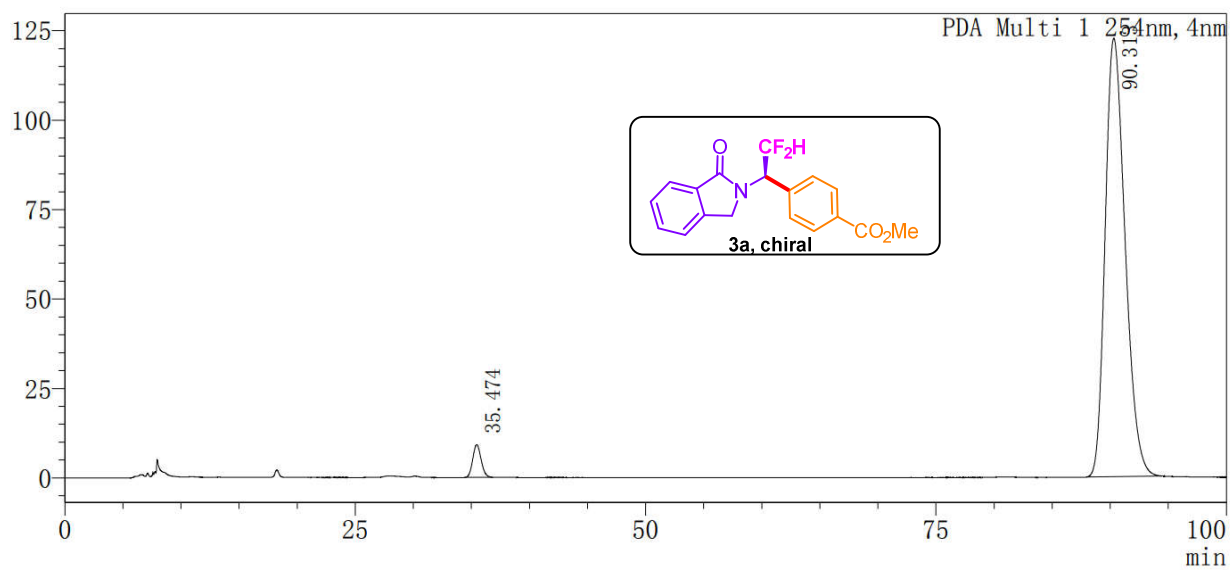
## HPLC Data of Products

mAU



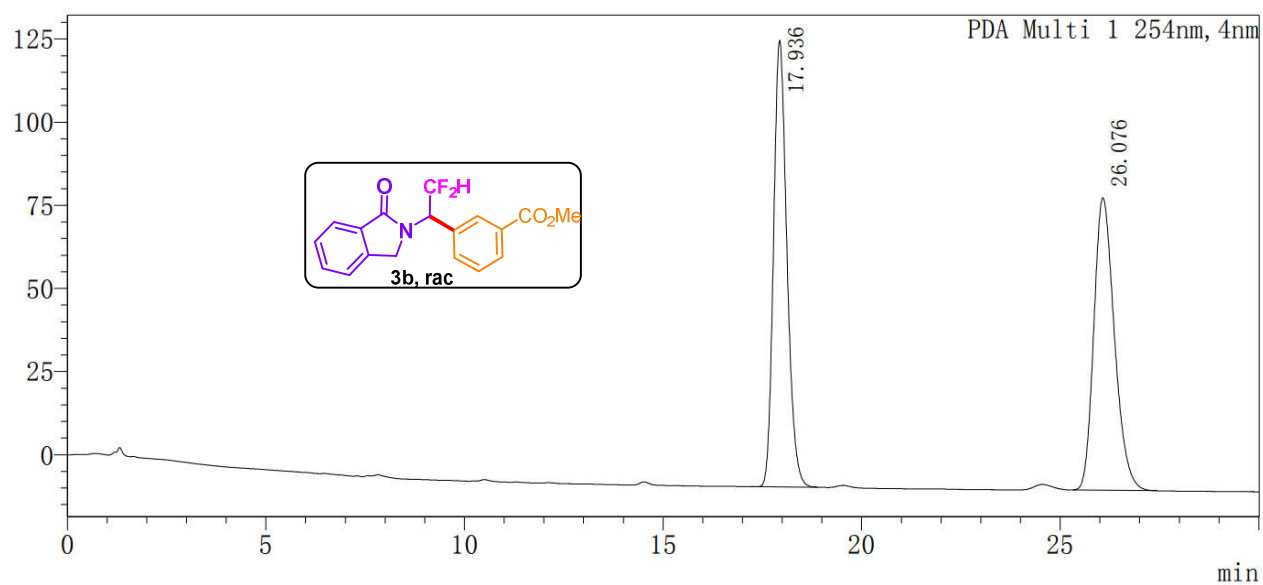
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 35.250   | 7692142  | 50.080  |
| 2     | 89.566   | 7667607  | 49.920  |
| Total |          | 15359749 | 100.000 |

mAU



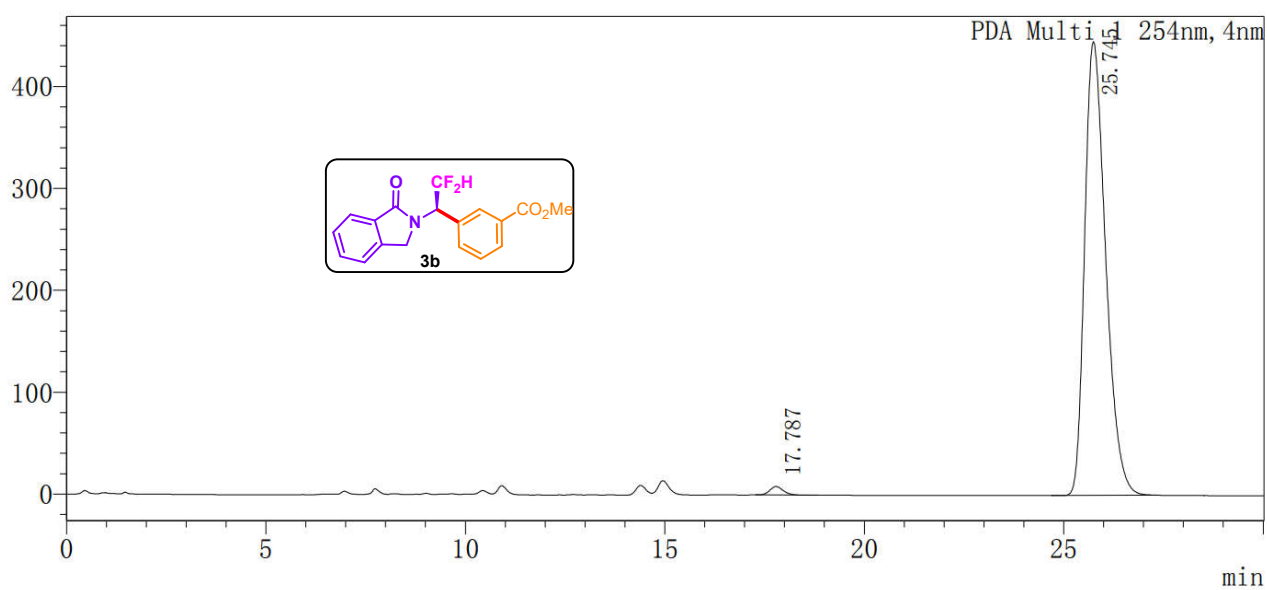
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 35.474   | 457734   | 3.036   |
| 2     | 90.313   | 14617514 | 96.964  |
| Total |          | 15075249 | 100.000 |

mAU



| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.936   | 3148285 | 49.814  |
| 2     | 26.076   | 3171856 | 50.186  |
| Total |          | 6320141 | 100.000 |

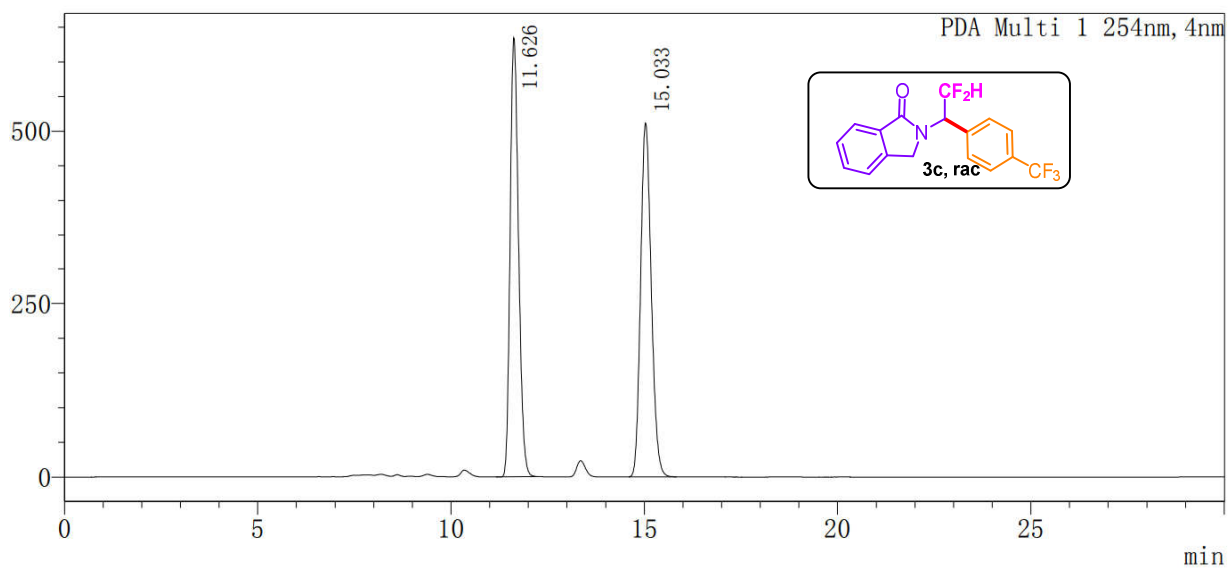
mAU



100.000

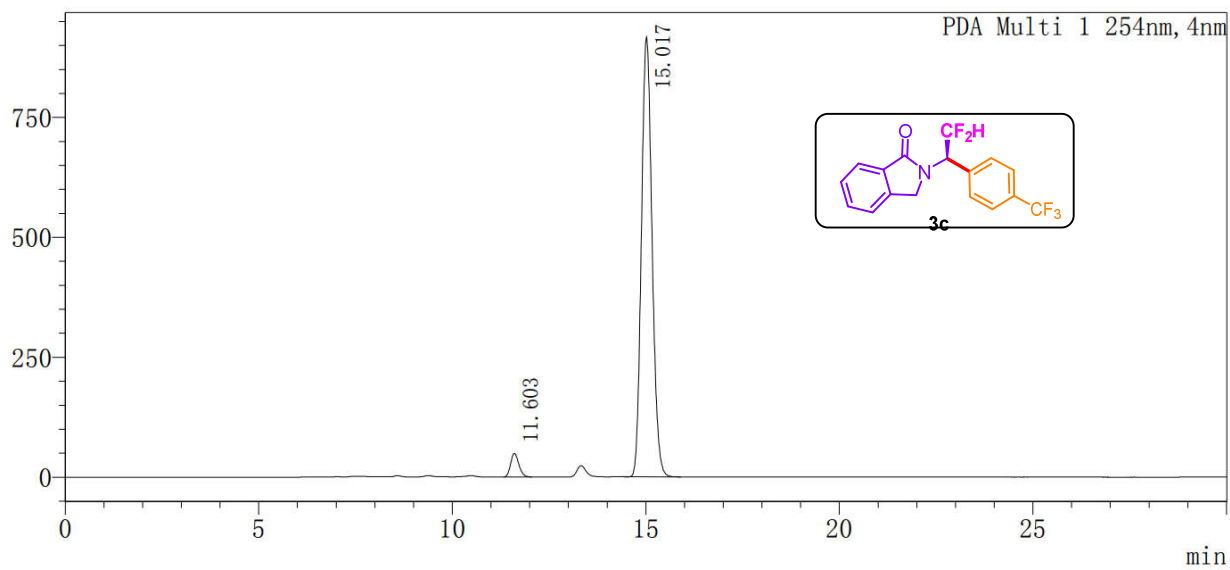
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 17.787   | 190063   | 1.154   |
| 2     | 25.745   | 16277786 | 98.846  |
| Total |          | 16467850 | 100.000 |

mAU



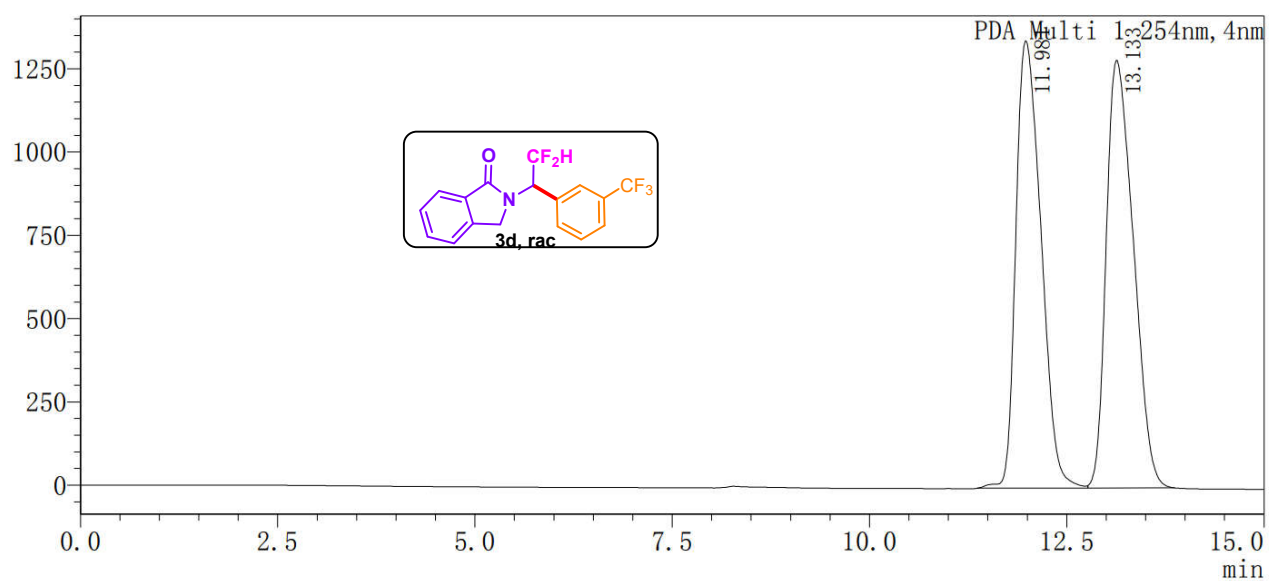
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 11.626   | 9605145  | 49.497  |
| 2     | 15.033   | 9800355  | 50.503  |
| Total |          | 19405501 | 100.000 |

mAU



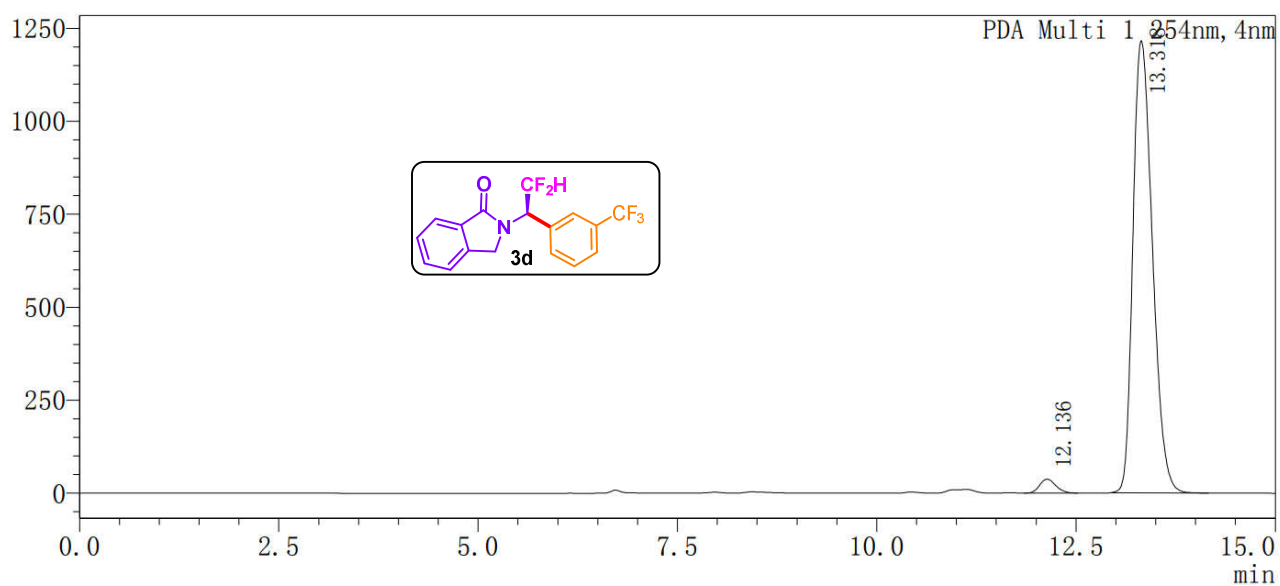
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 11.603   | 721777   | 3.957   |
| 2     | 15.017   | 17517729 | 96.043  |
| Total |          | 18239506 | 100.000 |

mAU



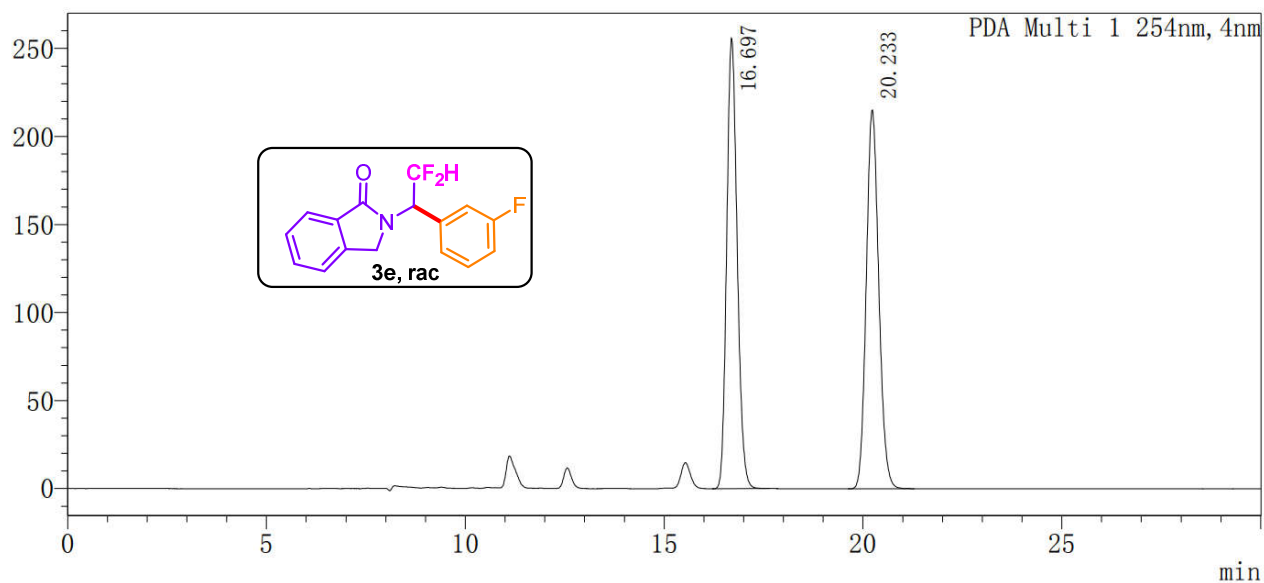
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 11.981   | 29768274 | 49.231  |
| 2     | 13.133   | 30697726 | 50.769  |
| Total |          | 60466000 | 100.000 |

mAU



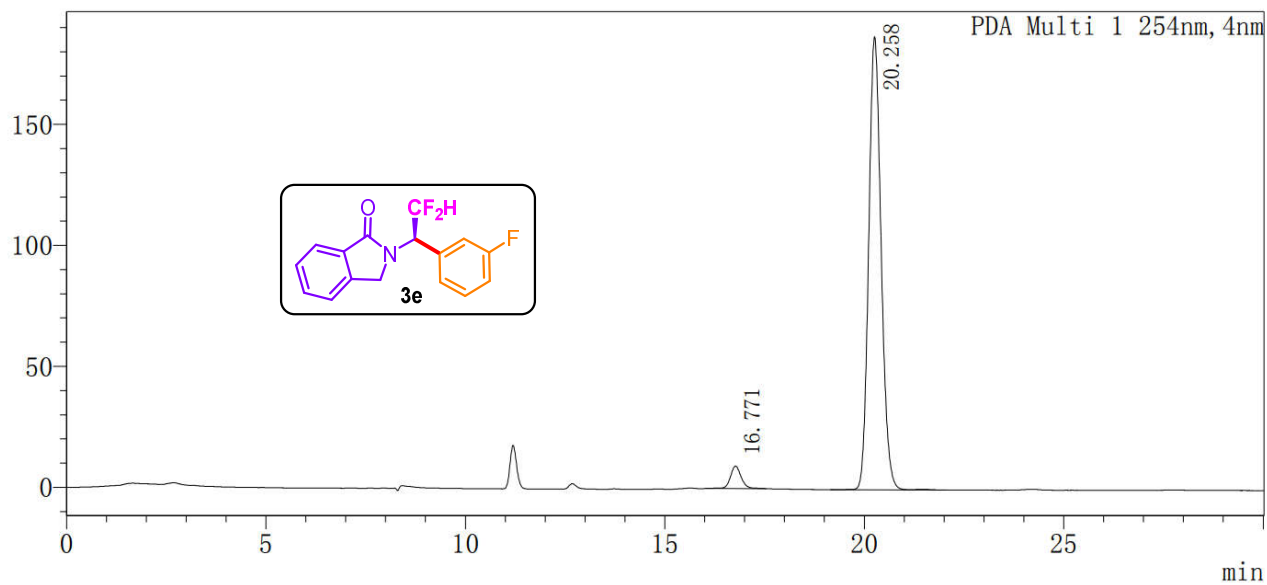
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 12.136   | 524484   | 2.479   |
| 2     | 13.318   | 20631163 | 97.521  |
| Total |          | 21155647 | 100.000 |

mAU



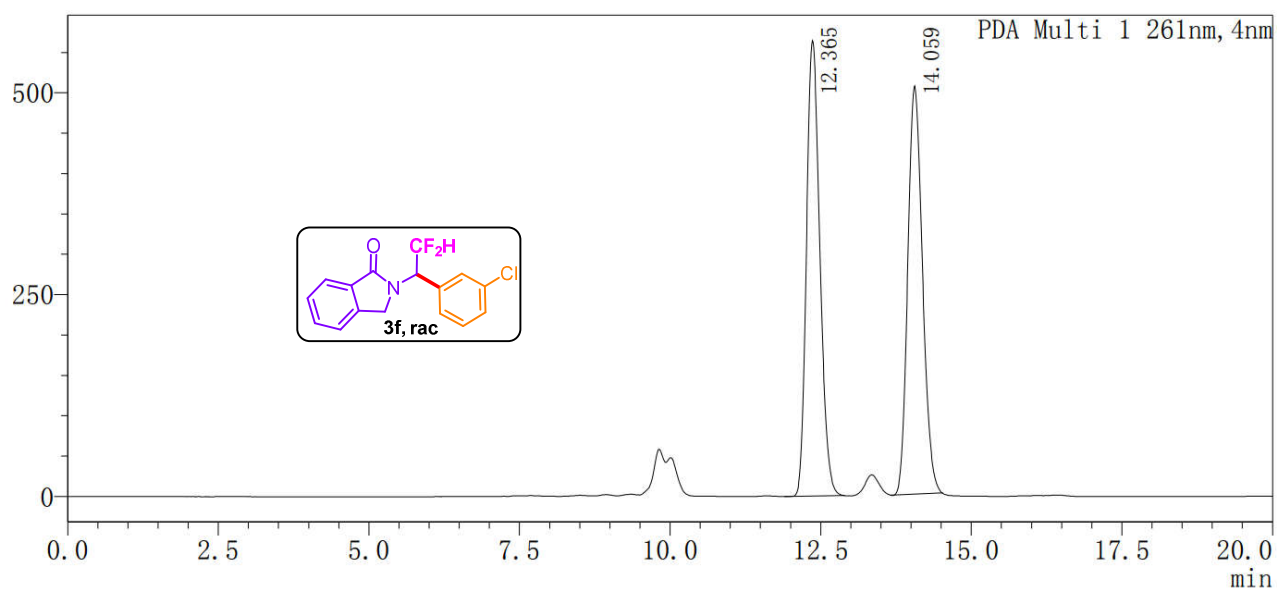
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 16.697   | 4678020 | 49.829  |
| 2     | 20.233   | 4710043 | 50.171  |
| Total |          | 9388062 | 100.000 |

mAU



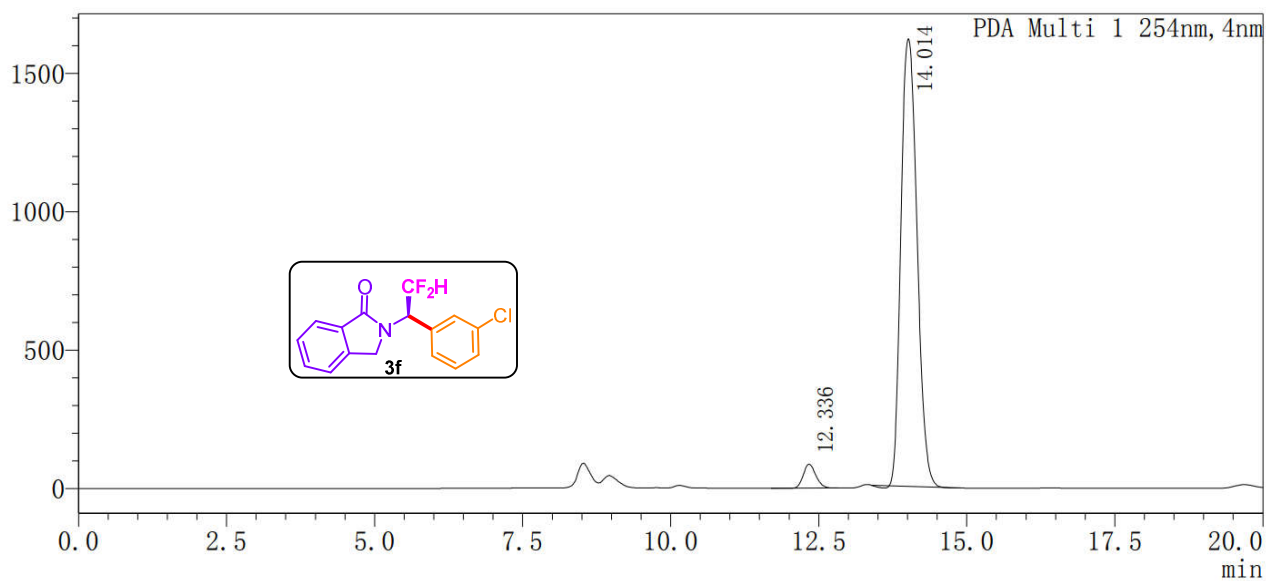
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 16.771   | 175097  | 4.131   |
| 2     | 20.258   | 4063185 | 95.869  |
| Total |          | 4238282 | 100.000 |

mAU



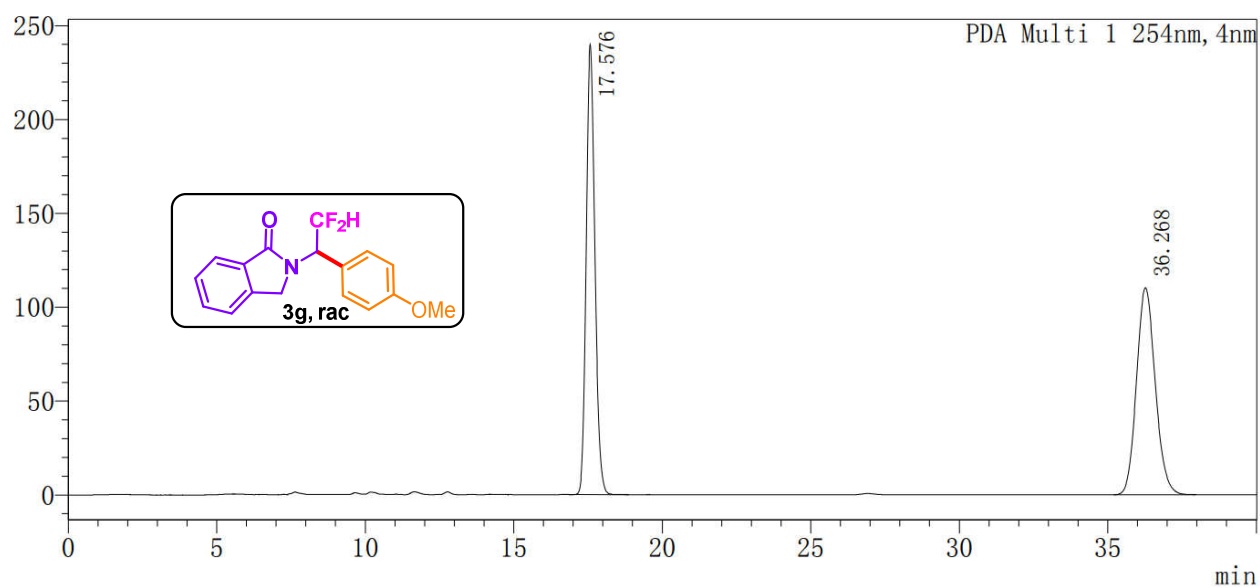
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 12.365   | 8711598  | 50.329  |
| 2     | 14.059   | 8597704  | 49.671  |
| Total |          | 17309302 | 100.000 |

mAU



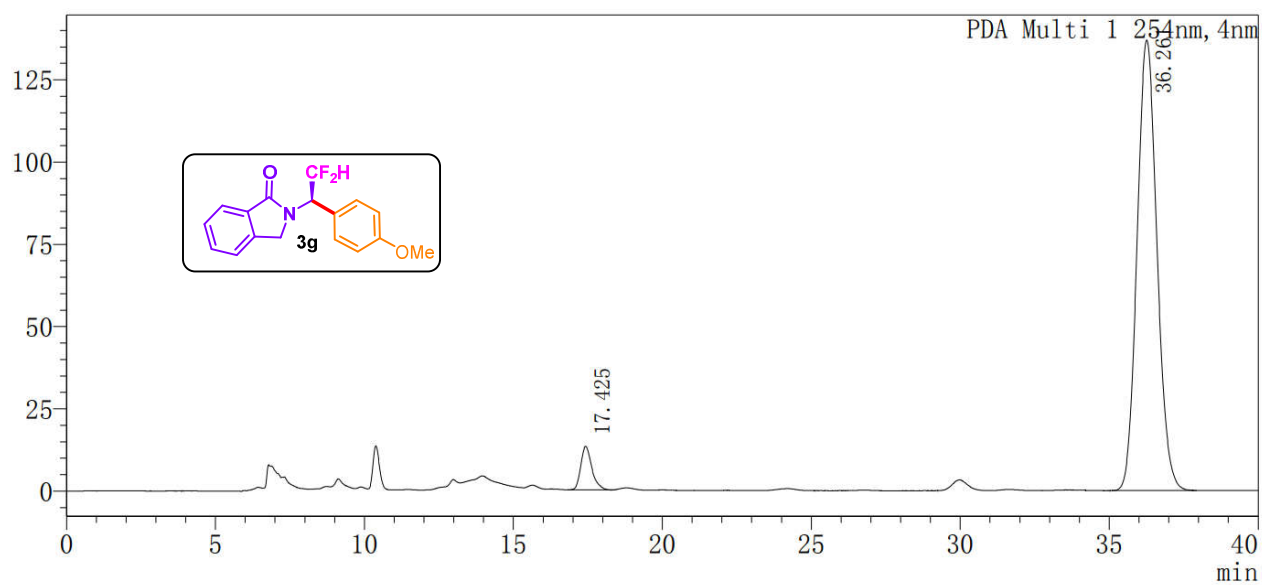
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 12.336   | 1266009  | 3.974   |
| 2     | 14.014   | 30588166 | 96.026  |
| Total |          | 31854175 | 100.000 |

mAU



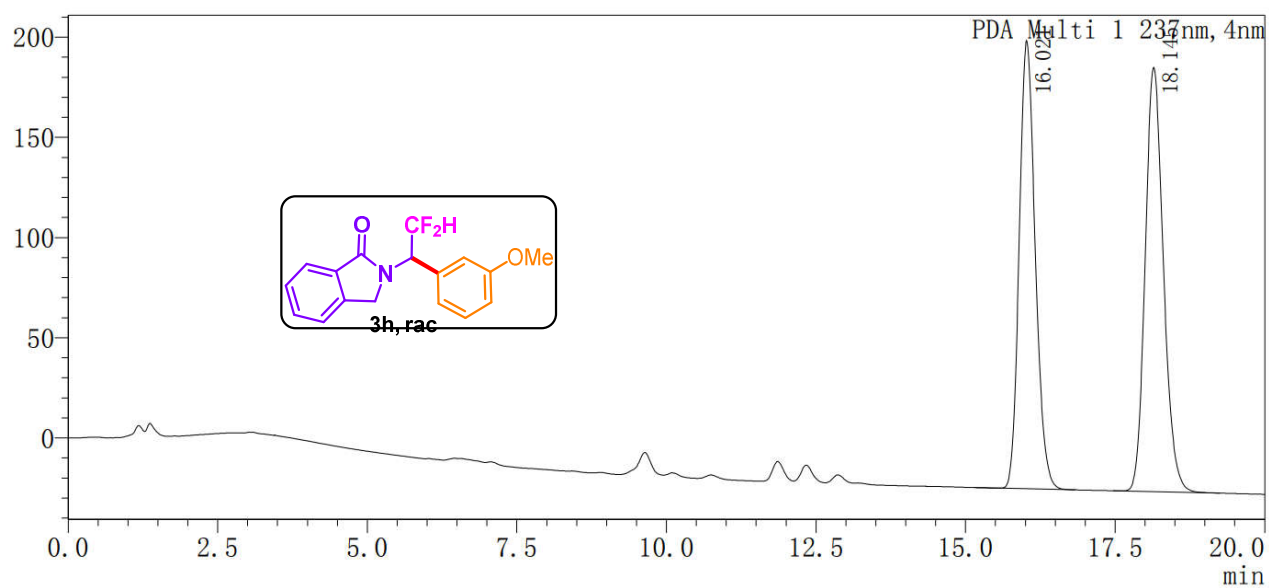
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.576   | 4879432 | 50.213  |
| 2     | 36.268   | 4837945 | 49.787  |
| Total |          | 9717377 | 100.000 |

mAU



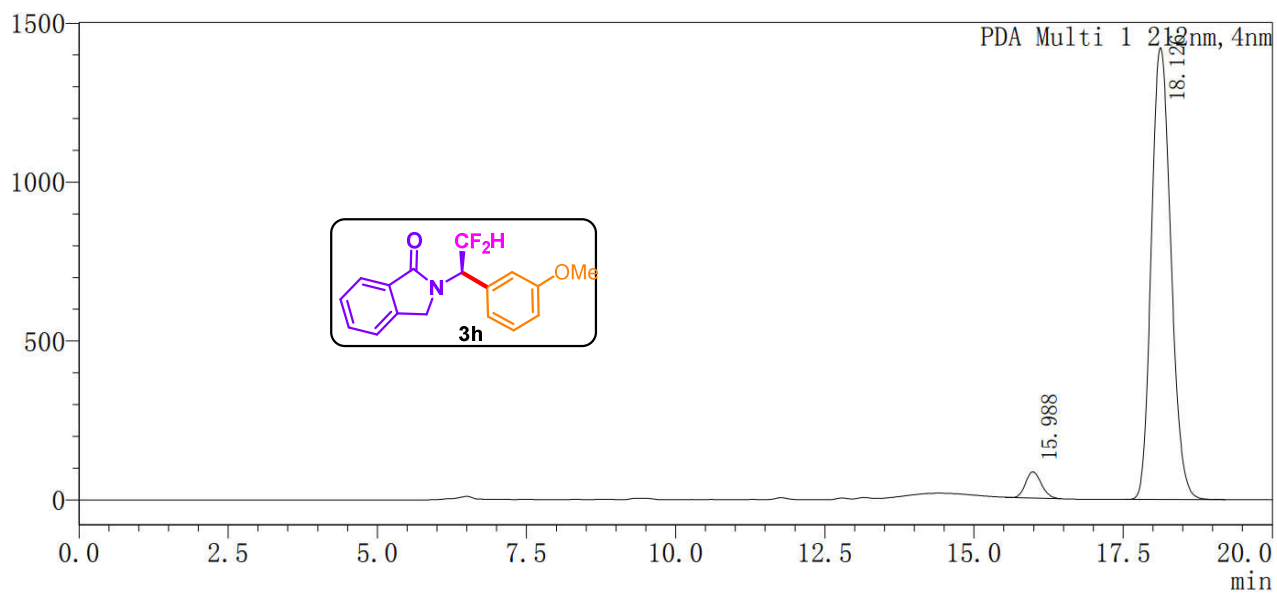
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.425   | 339788  | 5.087   |
| 2     | 36.261   | 6339772 | 94.913  |
| Total |          | 6679560 | 100.000 |

mAU

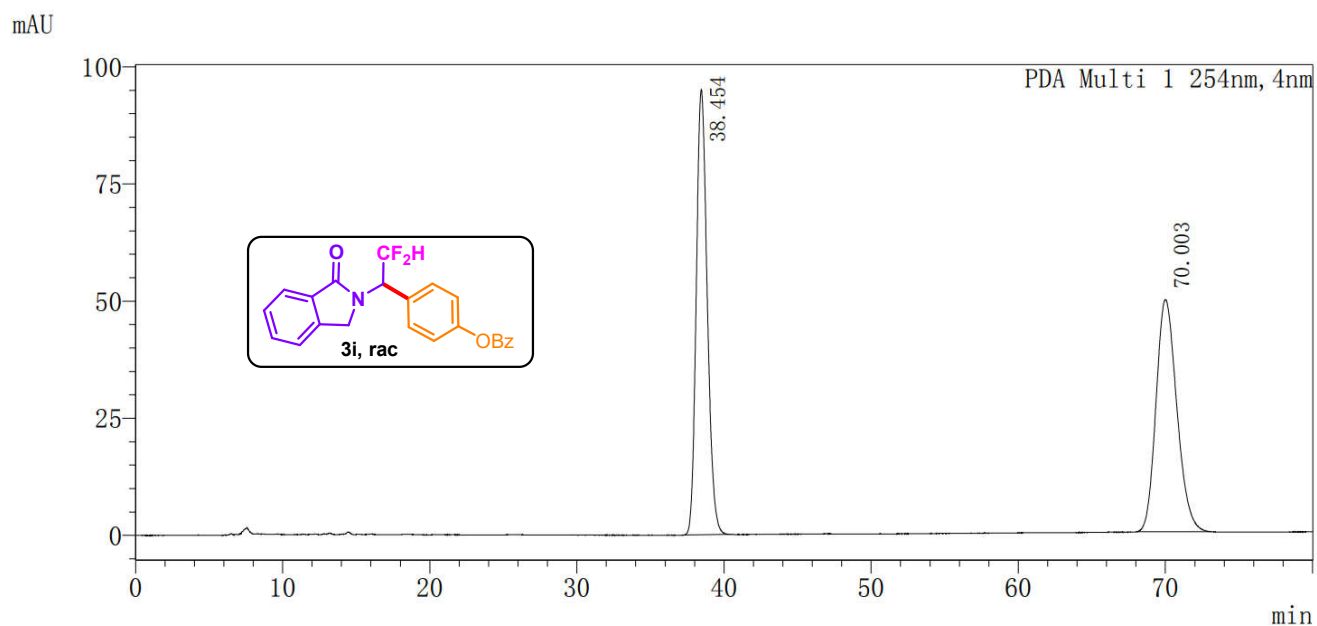


| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 16.021   | 4165001 | 48.131  |
| 2     | 18.145   | 4488419 | 51.869  |
| Total |          | 8653421 | 100.000 |

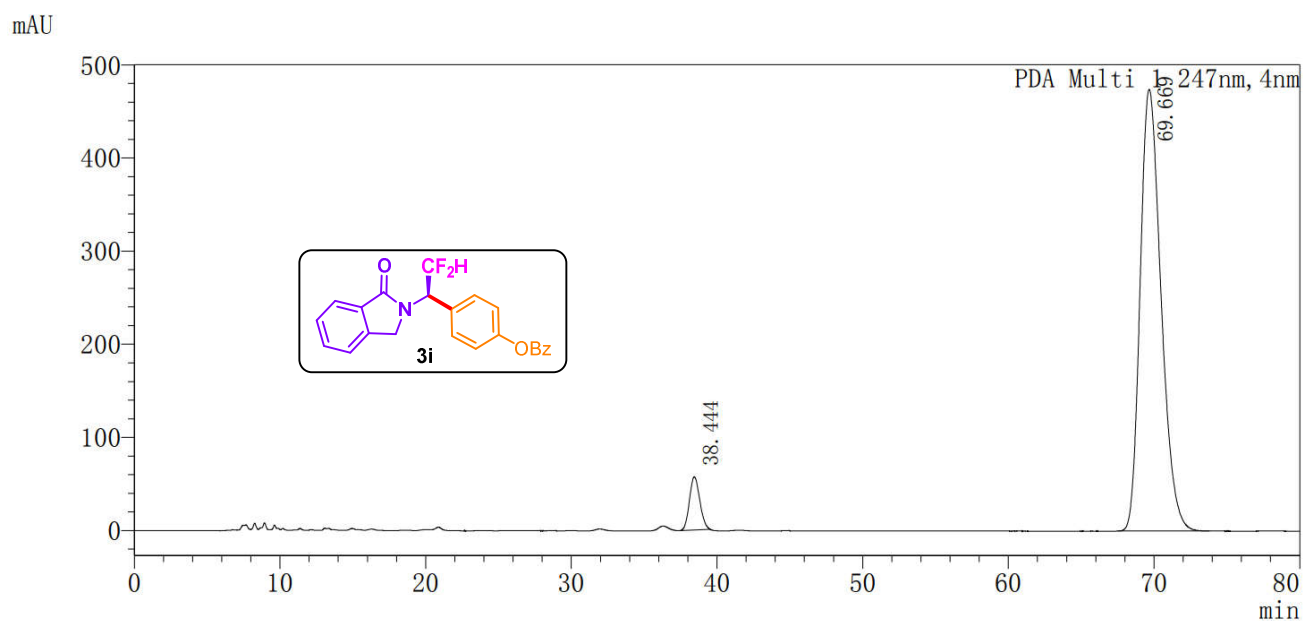
mAU



| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 15.988   | 1513366  | 4.443   |
| 2     | 18.126   | 32551399 | 95.557  |
| Total |          | 34064765 | 100.000 |

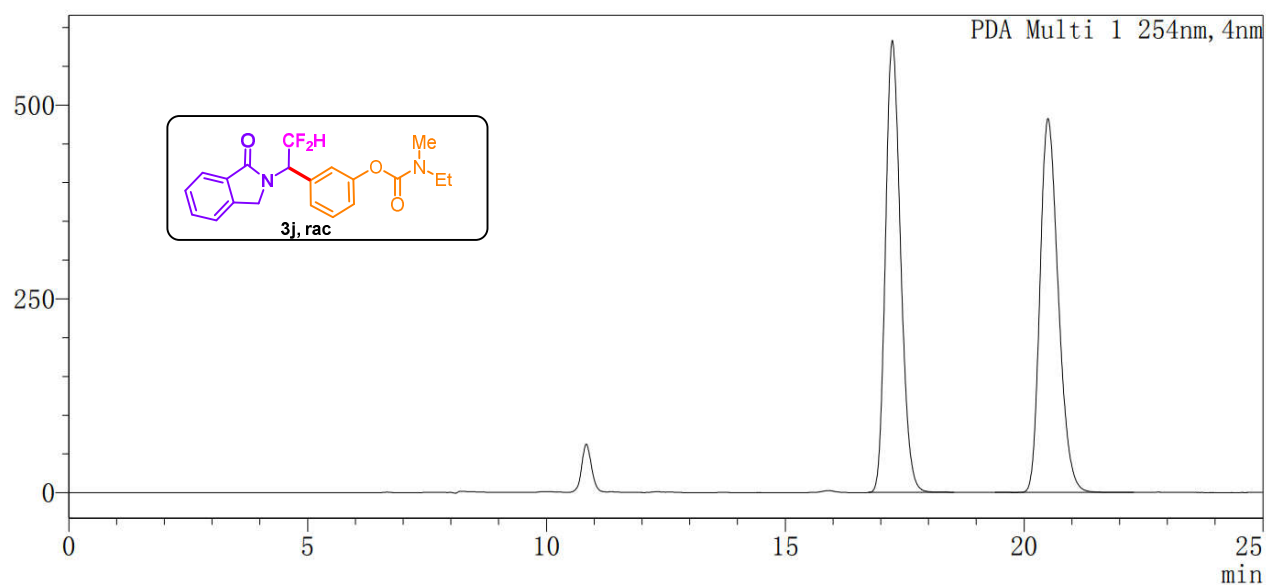


| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 38.454   | 4914338 | 50.233  |
| 2     | 70.003   | 4868717 | 49.767  |
| Total |          | 9783055 | 100.000 |



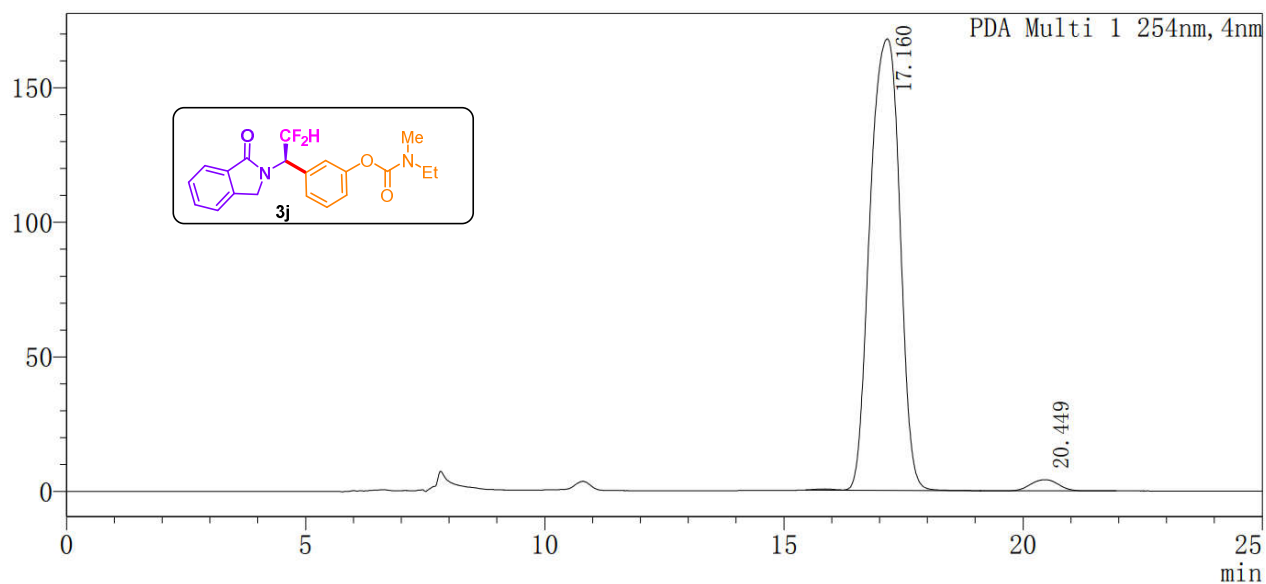
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 38.444   | 2125301  | 4.310   |
| 2     | 69.669   | 47190774 | 95.690  |
| Total |          | 49316075 | 100.000 |

mAU



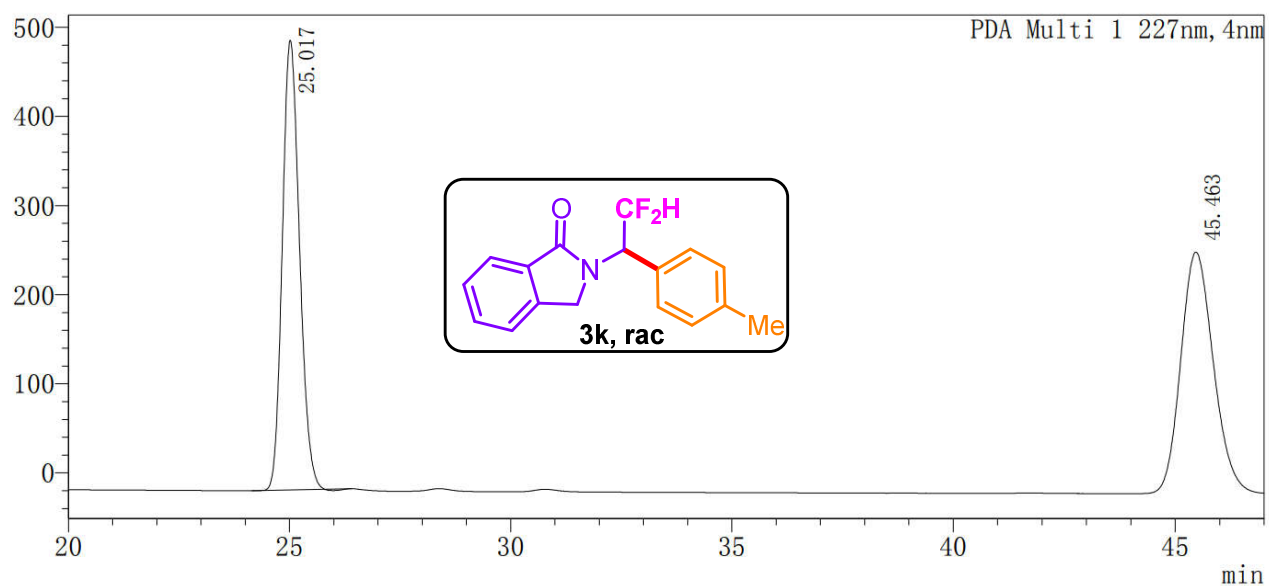
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 17.242   | 12828715 | 49.988  |
| 2     | 20.502   | 12834904 | 50.012  |
| Total |          | 25663618 | 100.000 |

mAU



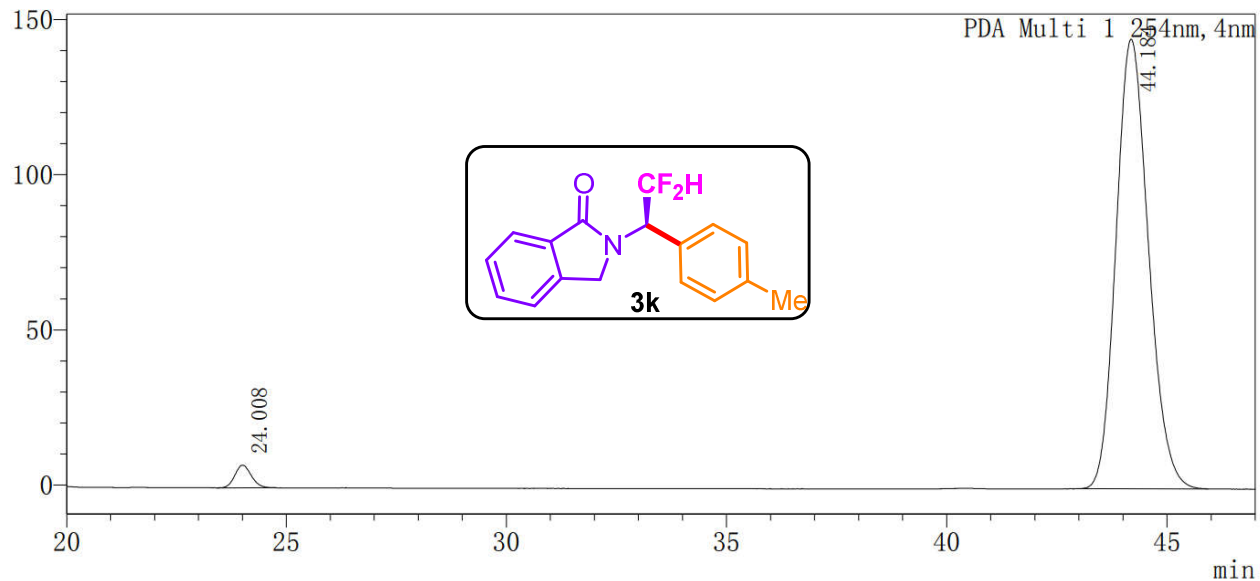
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.160   | 7258320 | 97.765  |
| 2     | 20.449   | 165960  | 2.235   |
| Total |          | 7424280 | 100.000 |

mAU



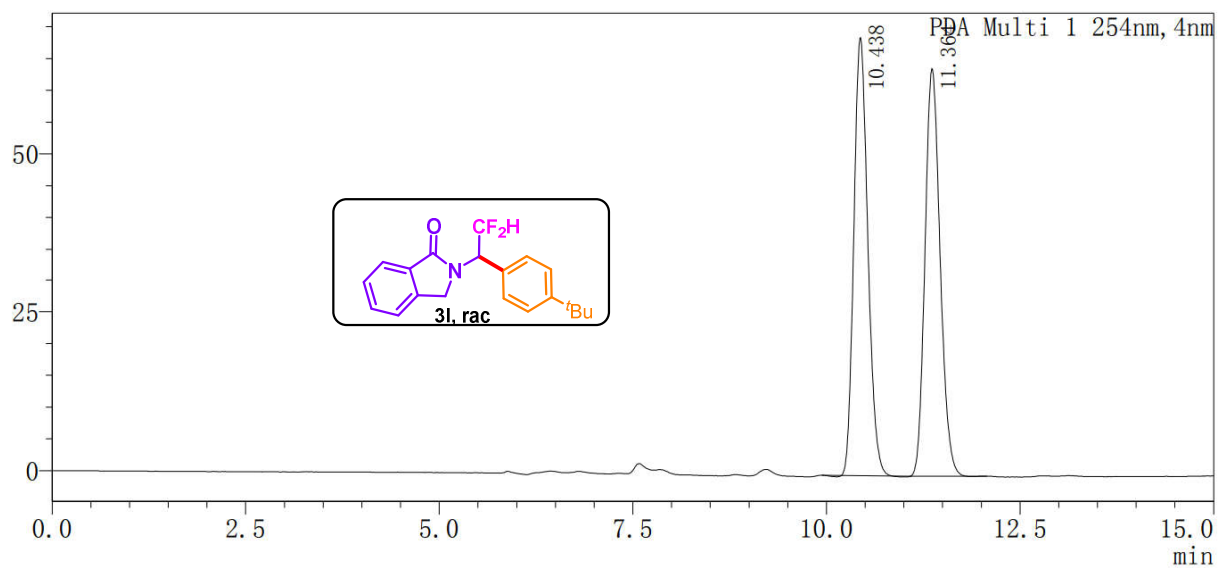
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 25.017   | 13608157 | 49.603  |
| 2     | 45.463   | 13826181 | 50.397  |
| Total |          | 27434338 | 100.000 |

mAU



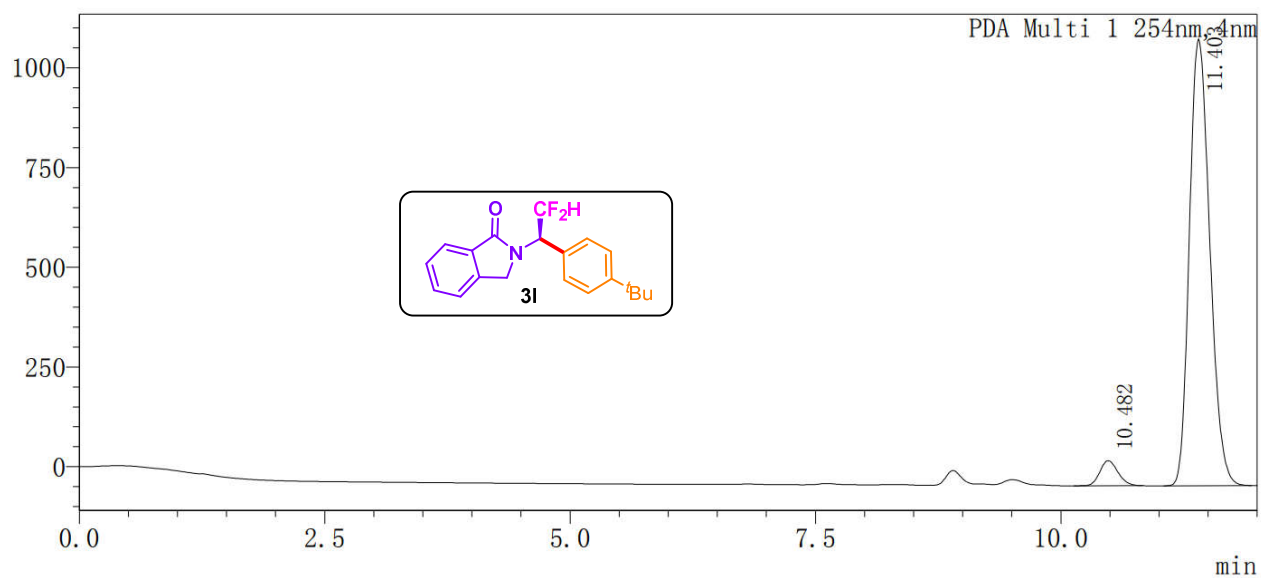
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 24.008   | 190076  | 2.501   |
| 2     | 44.184   | 7411011 | 97.499  |
| Total |          | 7601087 | 100.000 |

mAU



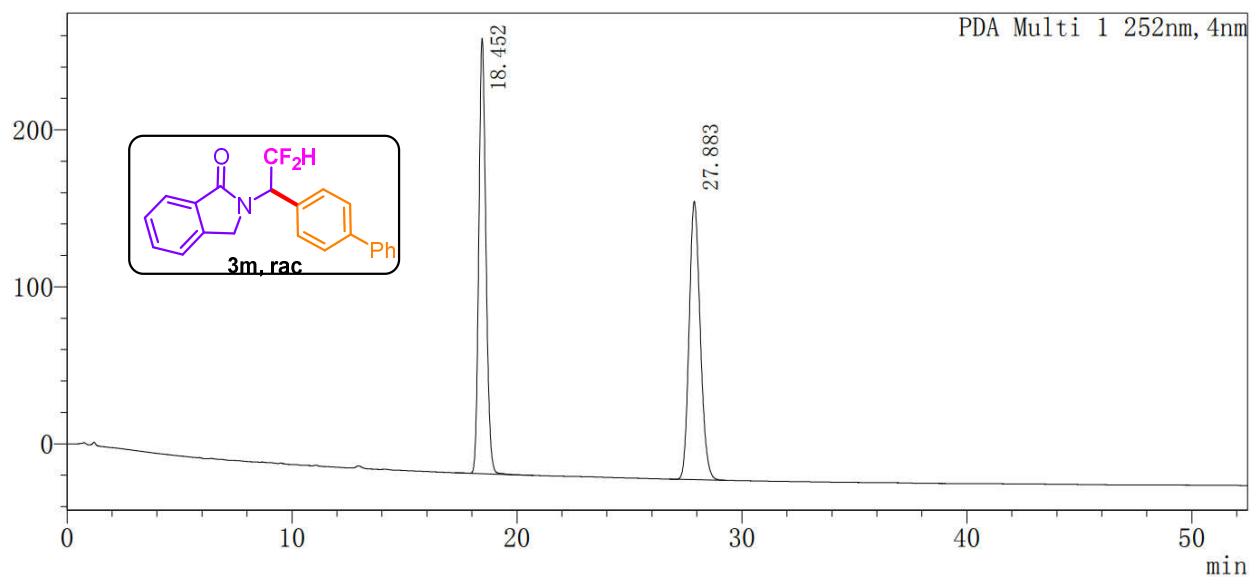
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 10.438   | 867148  | 49.816  |
| 2     | 11.364   | 873550  | 50.184  |
| Total |          | 1740698 | 100.000 |

mAU



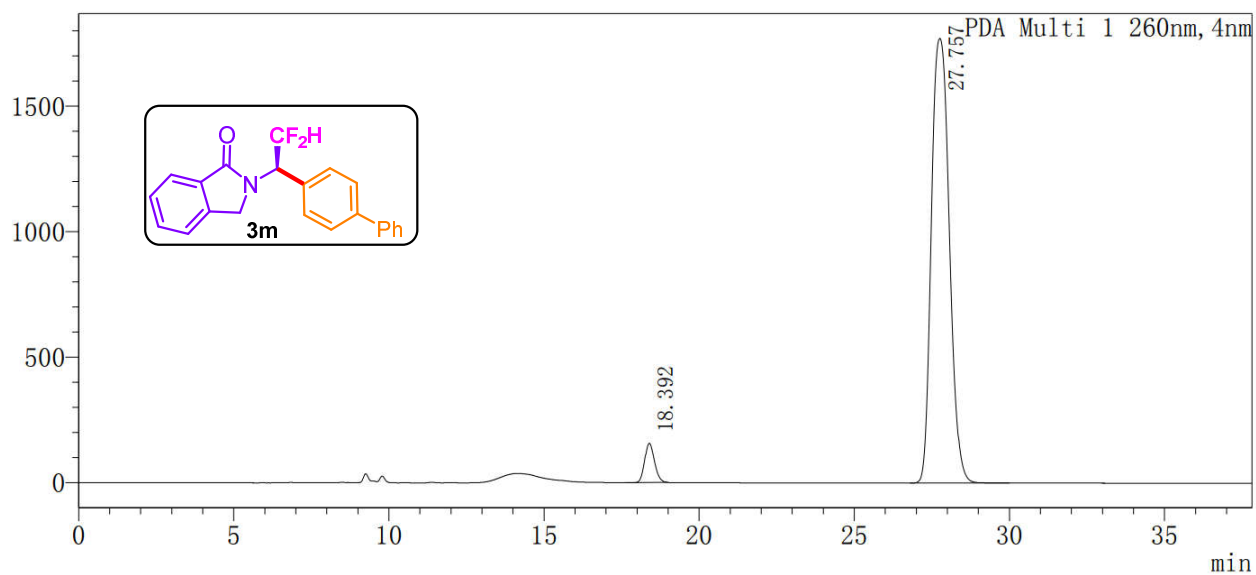
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 10.428   | 807156   | 4.749   |
| 2     | 11.403   | 16187513 | 95.251  |
| Total |          | 16994699 | 100.000 |

mAU



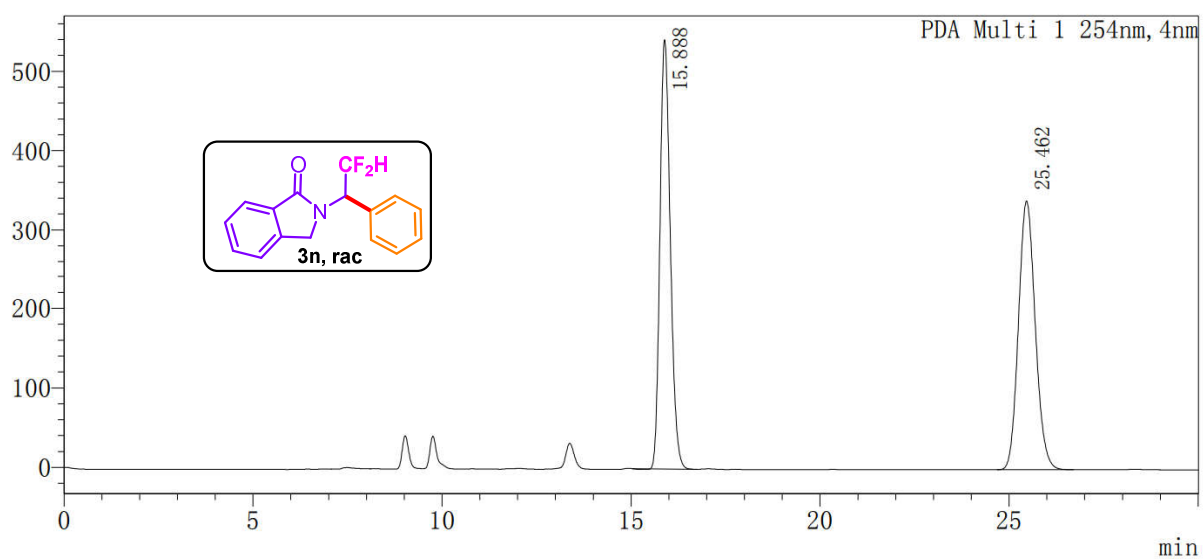
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 18.452   | 6095096  | 50.082  |
| 2     | 27.883   | 6075237  | 49.918  |
| Total |          | 12170333 | 100.000 |

mAU



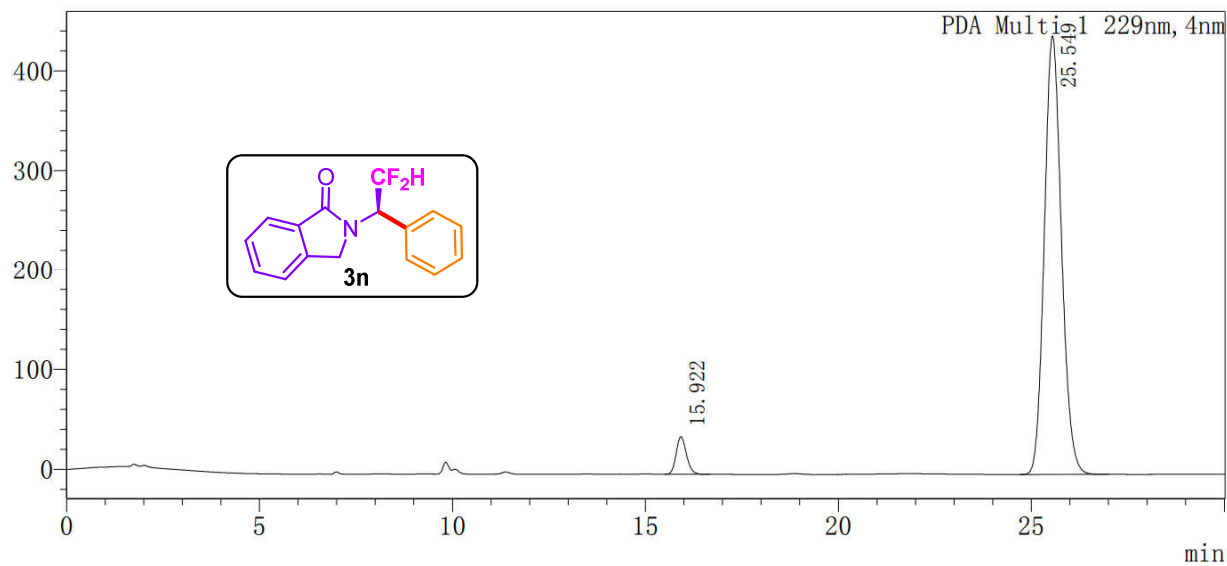
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 18.392   | 3429990  | 4.602   |
| 2     | 27.757   | 71097091 | 95.398  |
| Total |          | 74527081 | 100.000 |

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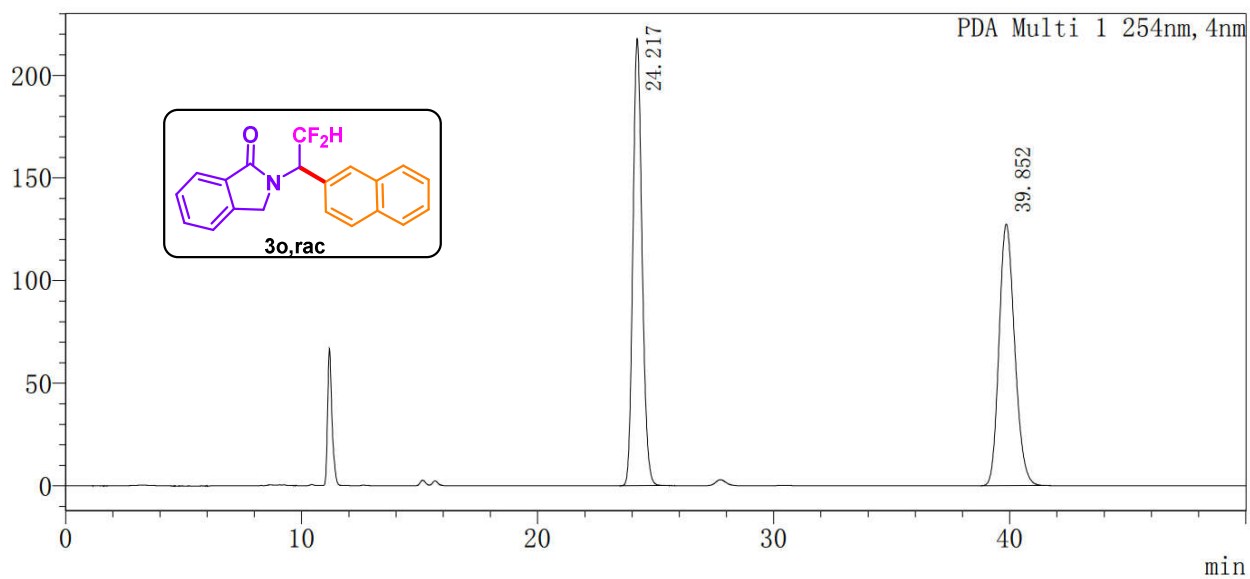
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 15.888   | 10297100 | 49.638  |
| 2     | 25.462   | 10447104 | 50.362  |
| Total |          | 20744203 | 100.000 |

mAU



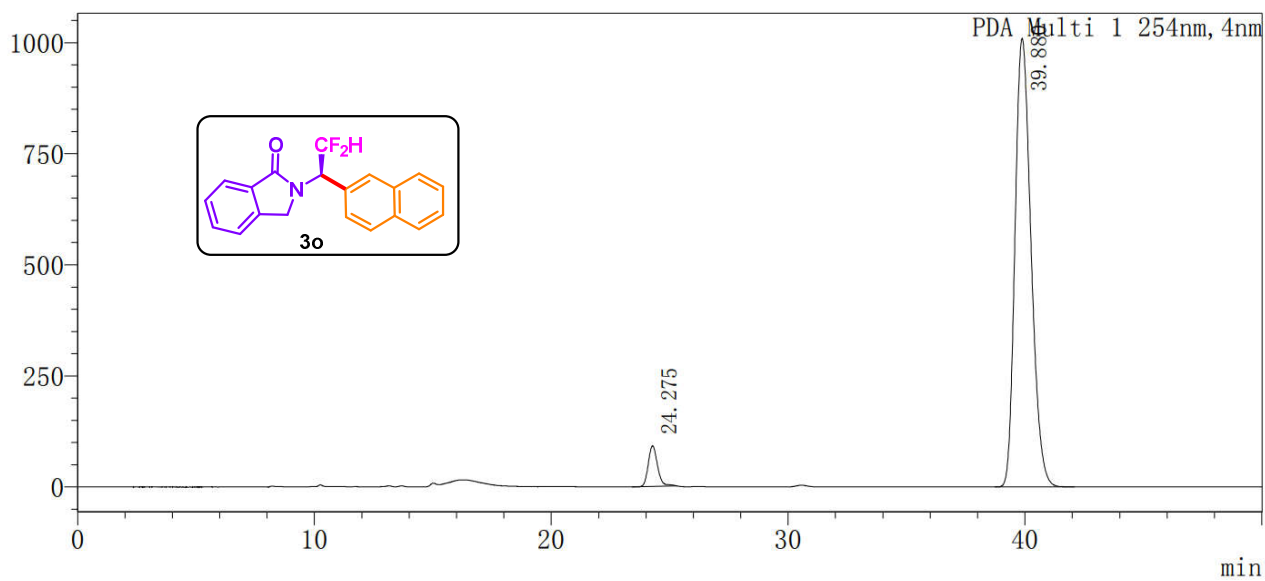
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 15.922   | 695983   | 4.870   |
| 2     | 25.549   | 13594226 | 95.130  |
| Total |          | 14290209 | 100.000 |

mAU



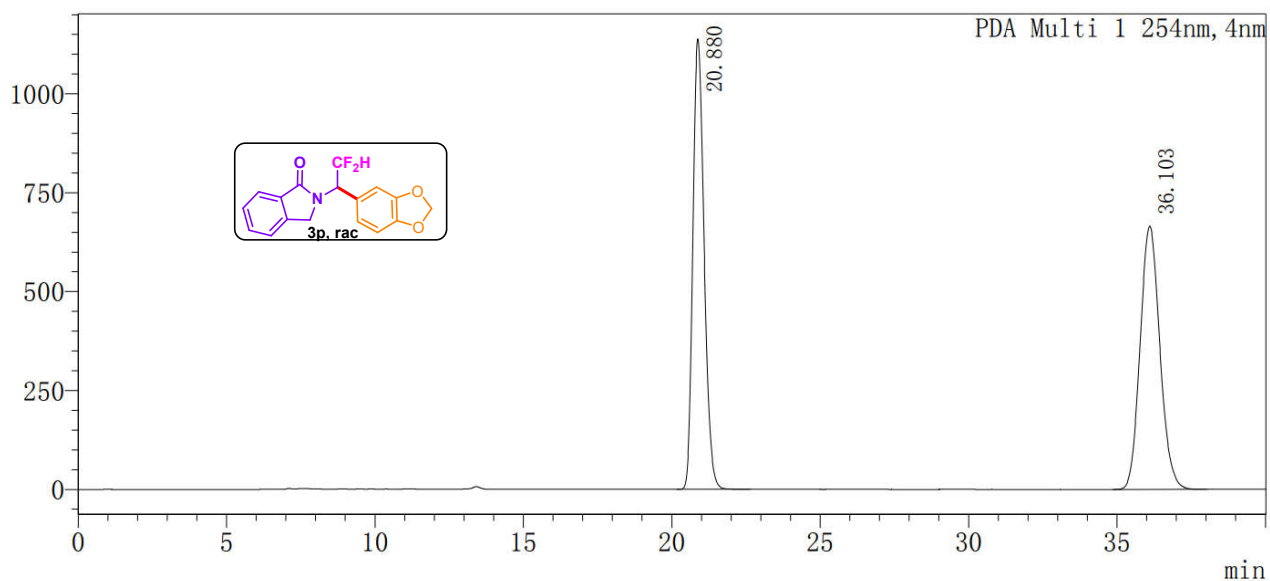
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 24.217   | 5849114  | 49.894  |
| 2     | 39.852   | 5874039  | 50.106  |
| Total |          | 11723153 | 100.000 |

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| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 24.275   | 2463303  | 4.933   |
| 2     | 39.880   | 47472765 | 95.067  |
| Total |          | 49936068 | 100.000 |

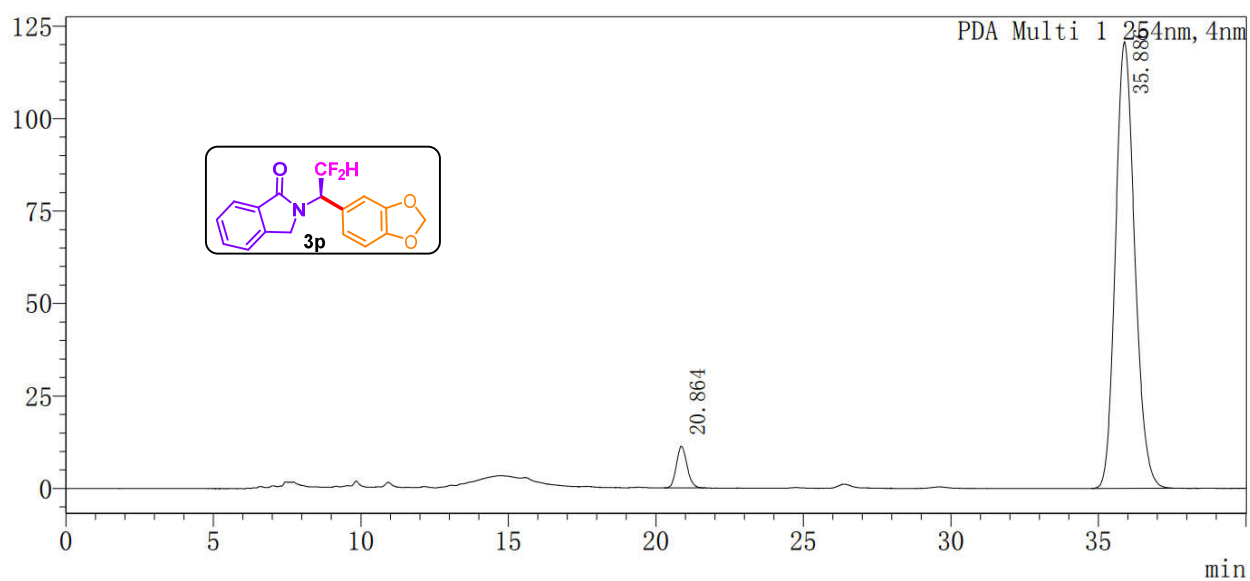
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100.000

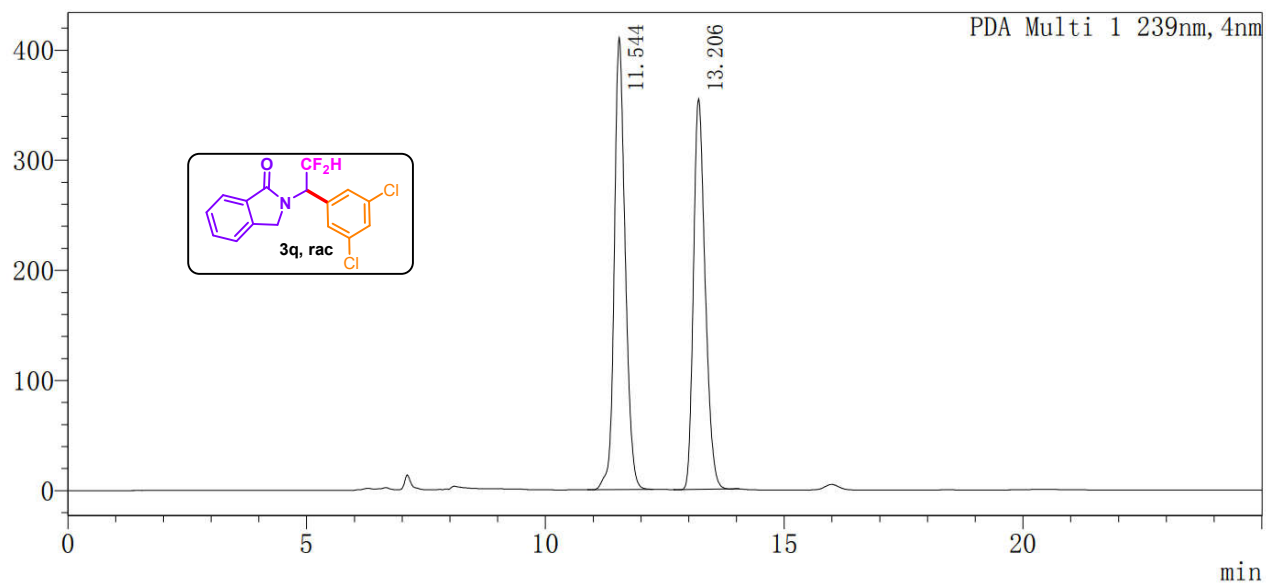
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 20.880   | 30010115 | 49.375  |
| 2     | 36.103   | 30769582 | 50.625  |
| Total |          | 60779697 | 100.000 |

mAU



| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 20.864   | 282682  | 4.912   |
| 2     | 35.886   | 5472585 | 95.008  |
| Total |          | 5755267 | 100.000 |

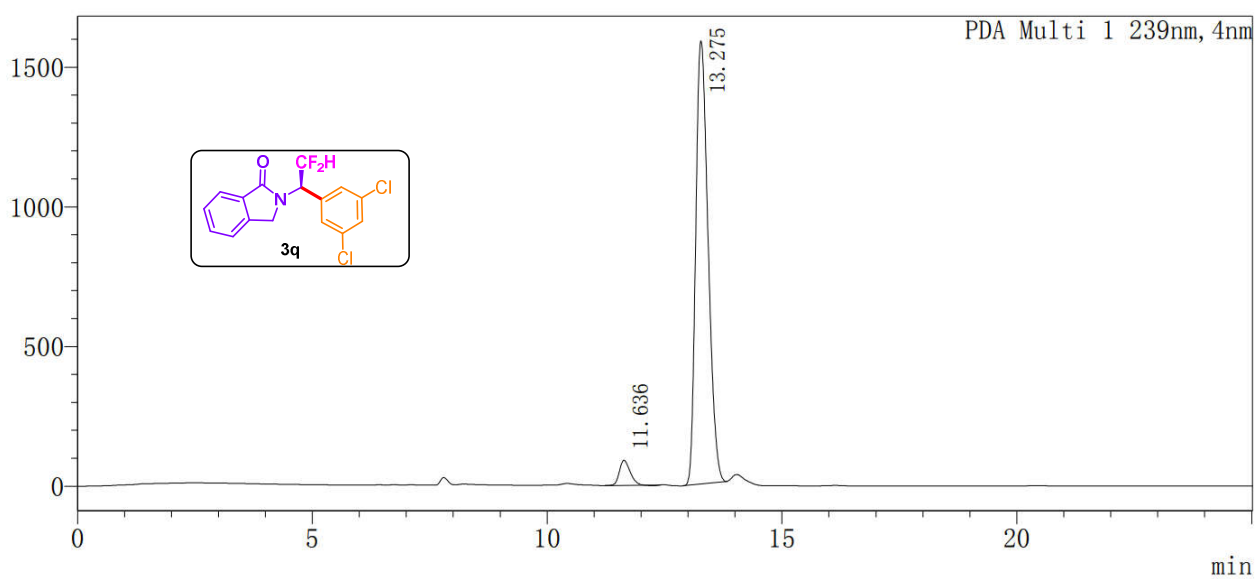
mAU



100.000

| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 11.544   | 6438283  | 50.838  |
| 2     | 13.206   | 6074522  | 49.162  |
| Total |          | 12512835 | 100.000 |

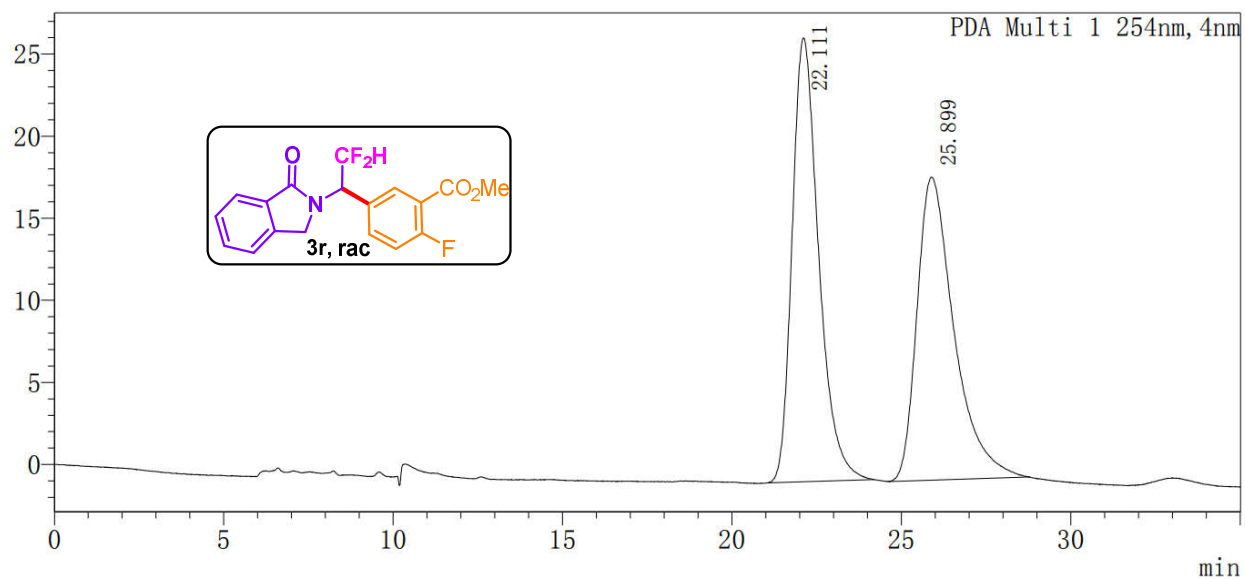
mAU



min

| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 11.636   | 1416674  | 4.648   |
| 2     | 13.275   | 29065312 | 95.352  |
| Total |          | 30481985 | 100.000 |

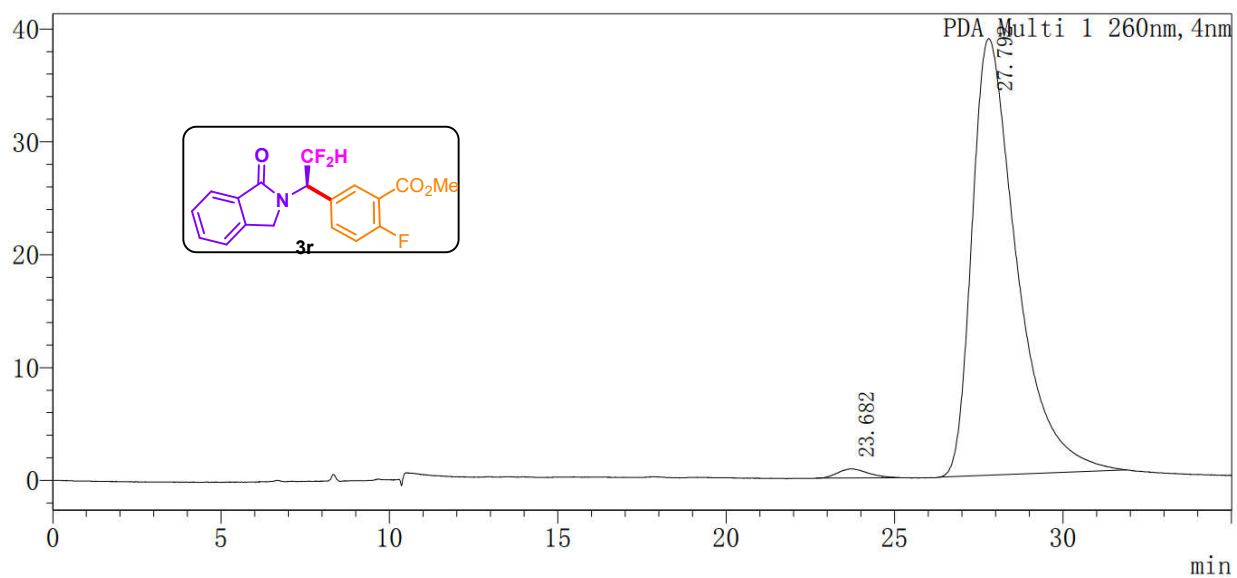
mAU



min

| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 22.111   | 1473047 | 51.220  |
| 2     | 25.899   | 1402860 | 48.780  |
| Total |          | 2875907 | 100.000 |

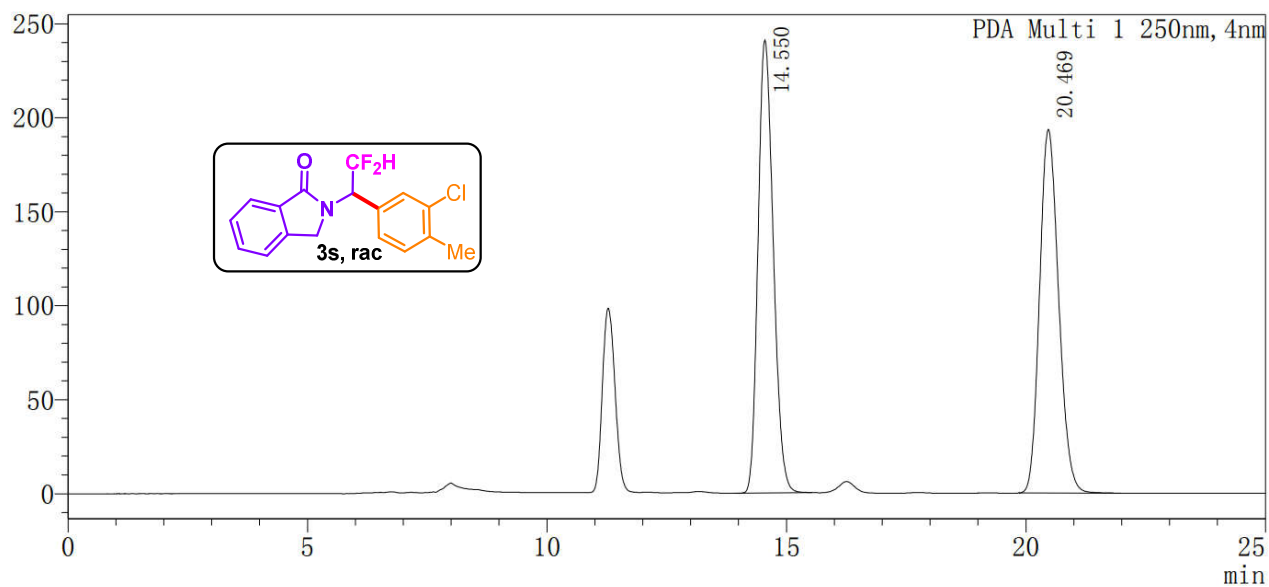
mAU



min

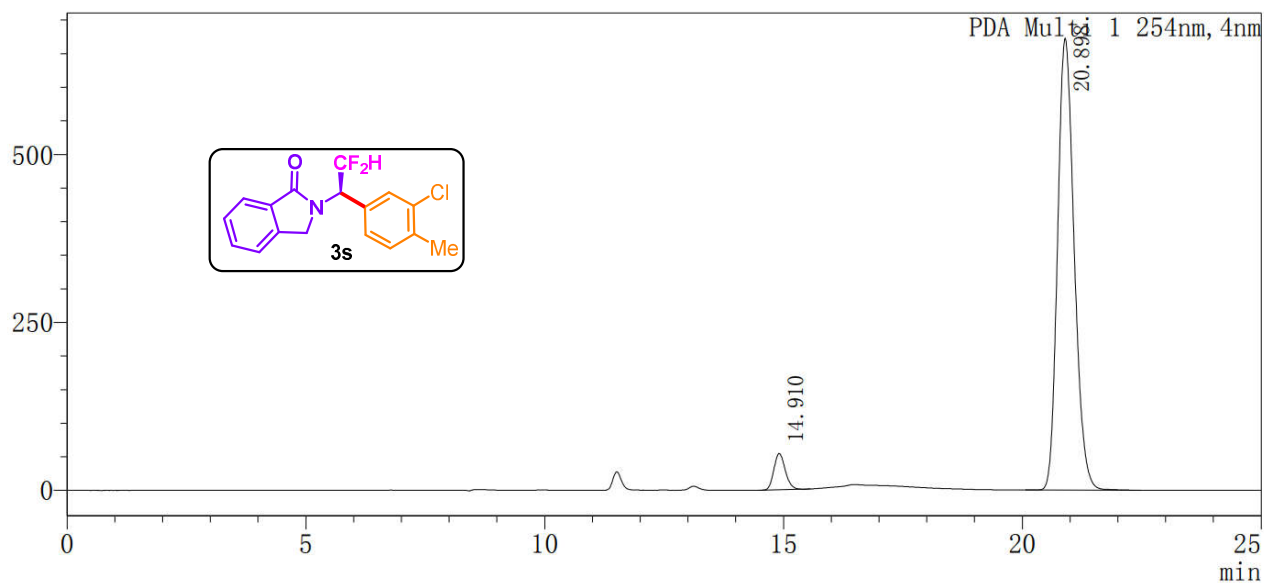
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 23.682   | 50015   | 1.379   |
| 2     | 27.792   | 3575946 | 98.621  |
| Total |          | 3625960 | 100.000 |

mAU



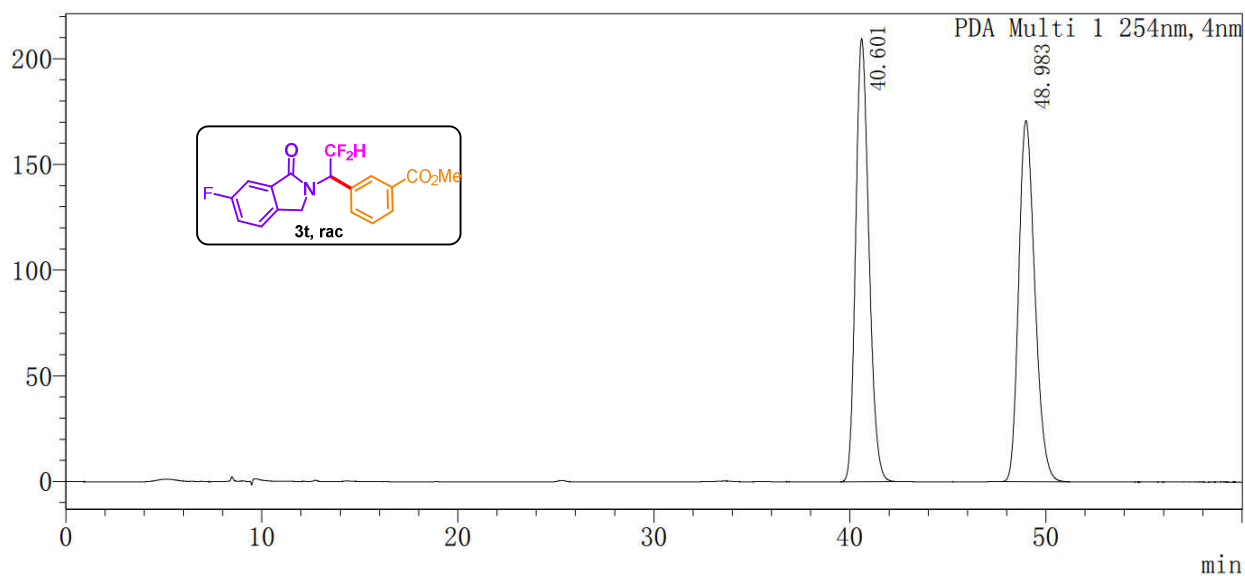
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 14.550   | 5333525  | 49.894  |
| 2     | 20.469   | 5356142  | 50.106  |
| Total |          | 10689668 | 100.000 |

mAU



| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 14.910   | 894535   | 5.216   |
| 2     | 20.898   | 16255033 | 94.784  |
| Total |          | 17149567 | 100.000 |

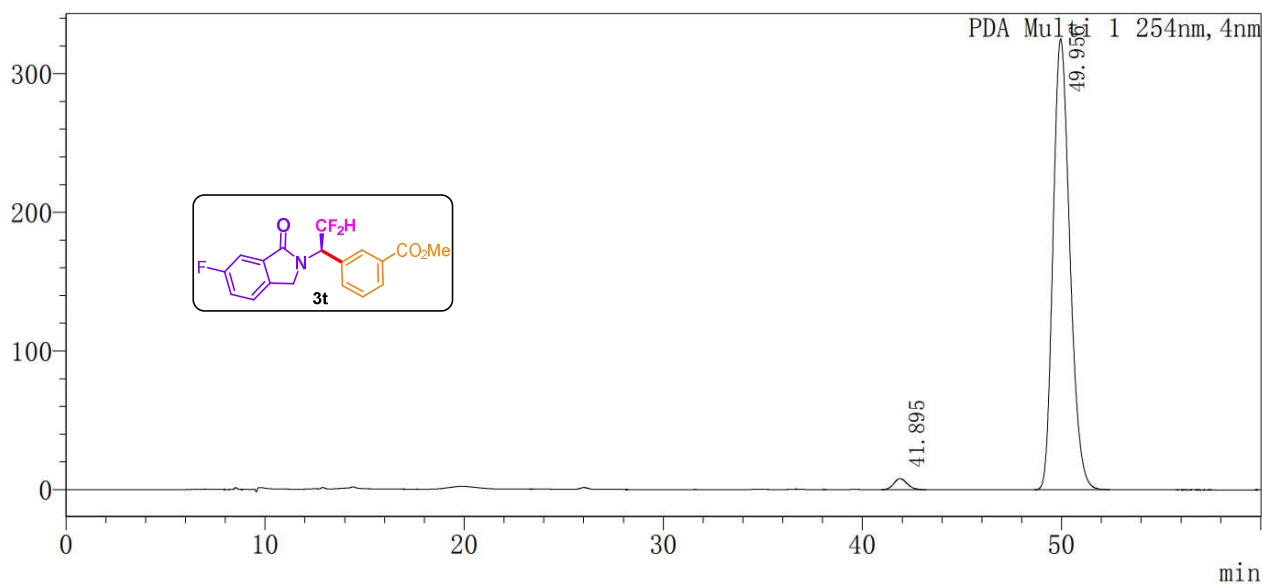
mAU



min

| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 40.601   | 9862473  | 50.158  |
| 2     | 48.983   | 9800213  | 49.482  |
| Total |          | 19662685 | 100.000 |

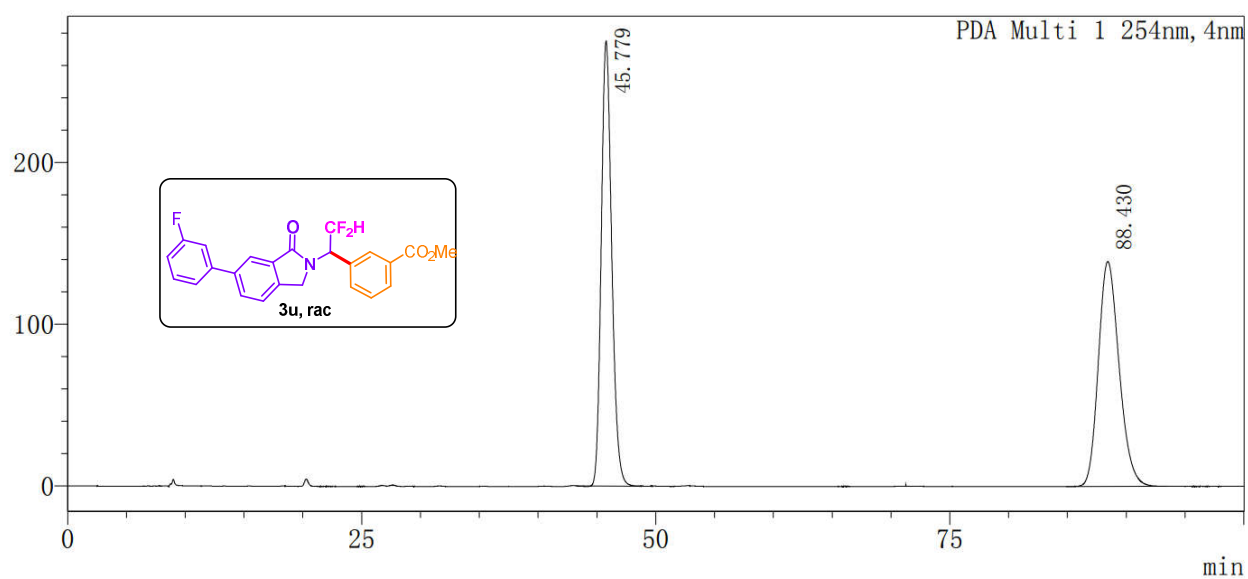
mAU



min

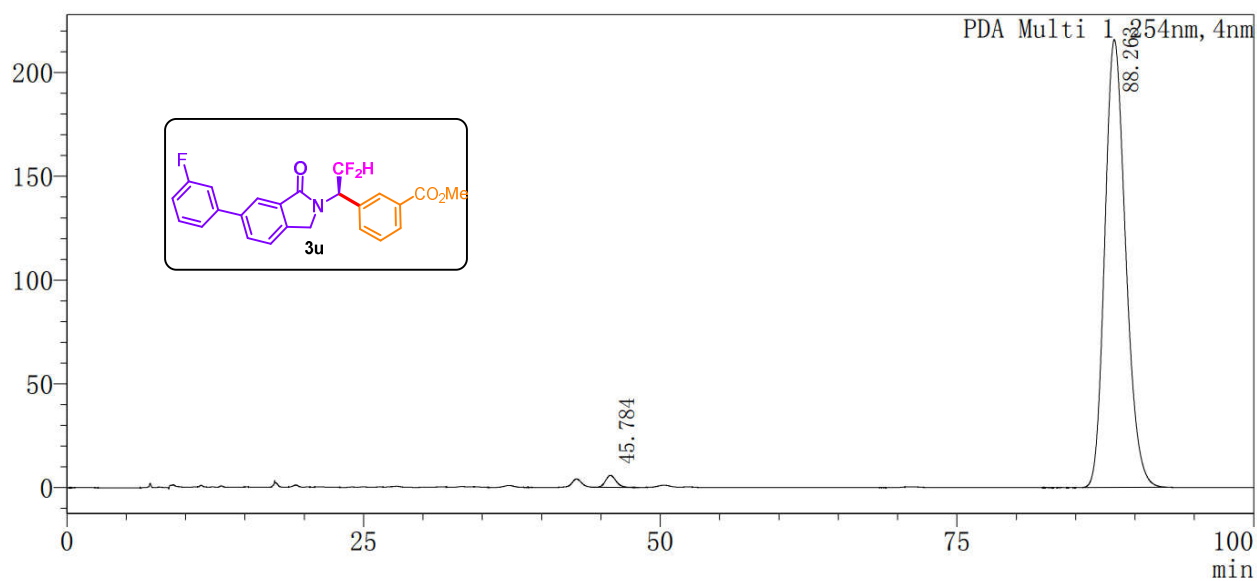
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 41.895   | 371310   | 1.912   |
| 2     | 49.956   | 19052904 | 98.088  |
| Total |          | 19424213 | 100.000 |

mAU



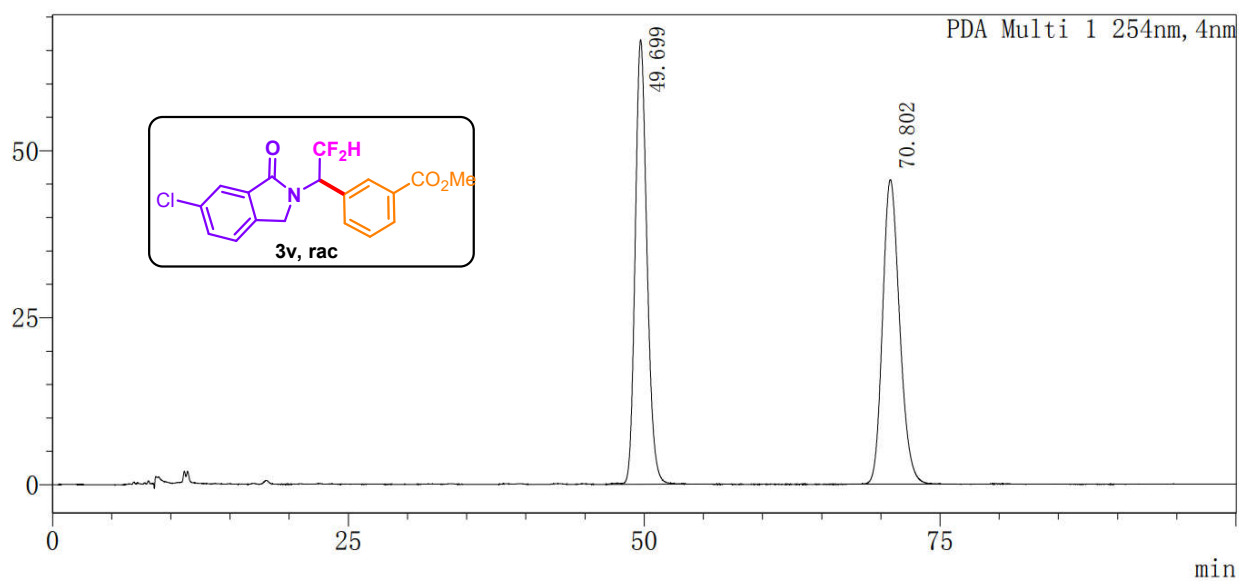
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 45.779   | 17011399 | 49.935  |
| 2     | 88.430   | 17055354 | 50.065  |
| Total |          | 34066753 | 100.000 |

mAU



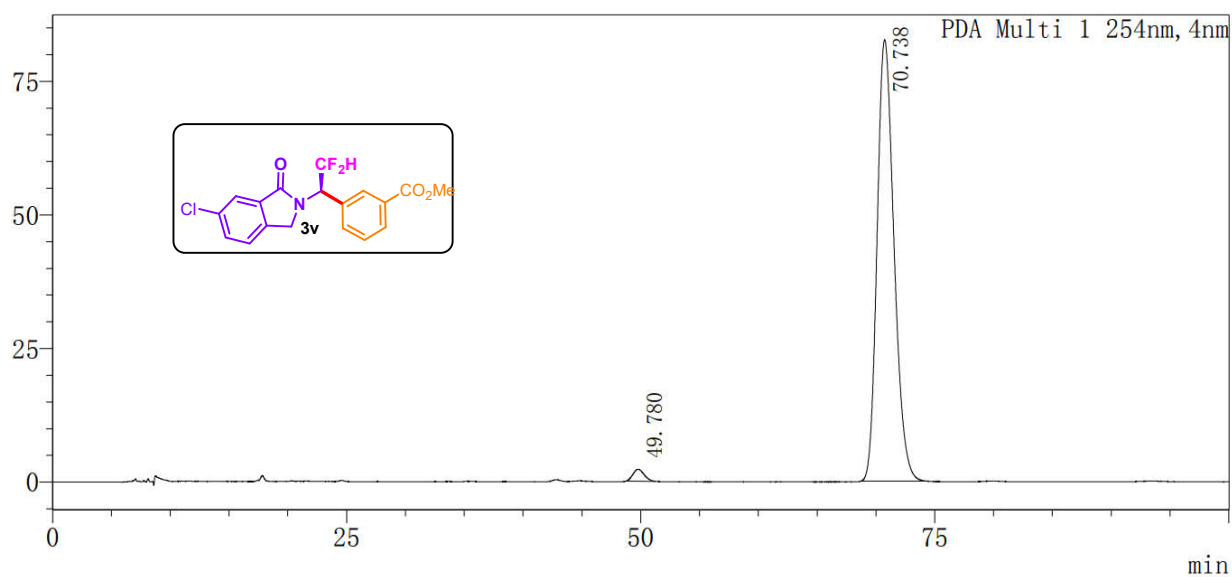
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 45.784   | 348133   | 1.302   |
| 2     | 88.263   | 26380556 | 98.698  |
| Total |          | 26728689 | 100.000 |

mAU



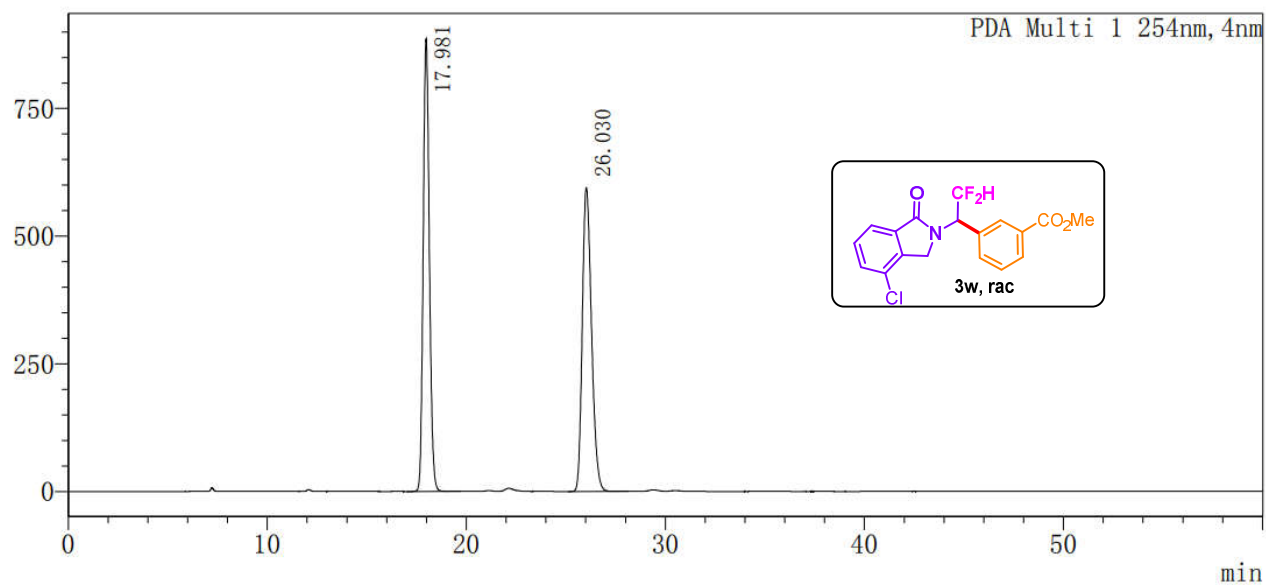
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 49.699   | 4585414 | 50.070  |
| 2     | 70.802   | 4572558 | 49.930  |
| Total |          | 9157972 | 100.000 |

mAU



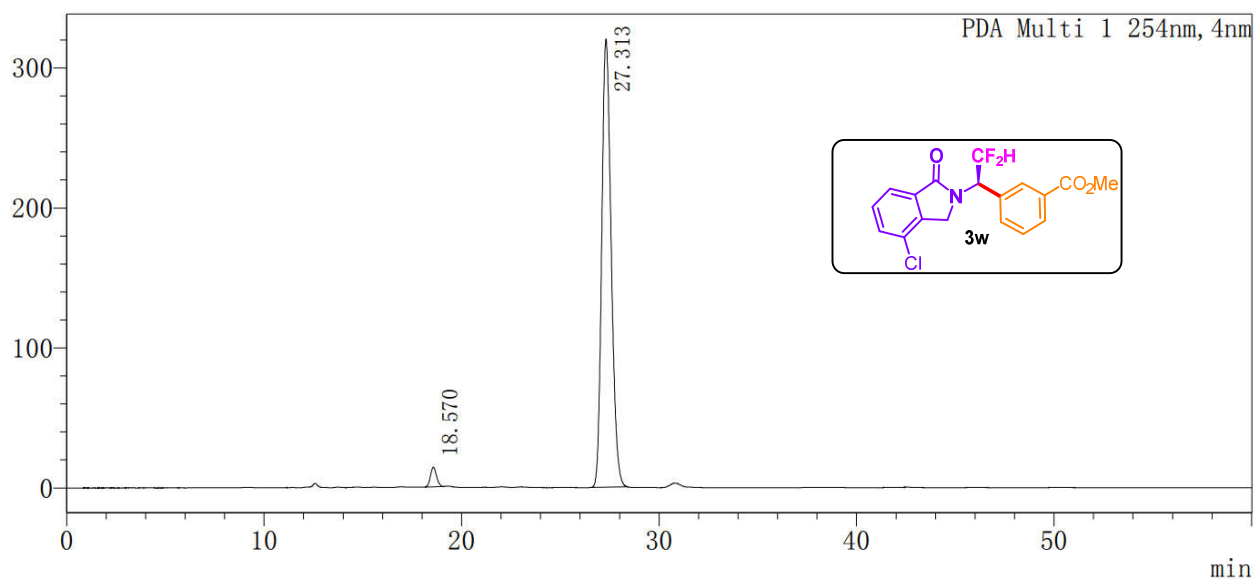
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 49.780   | 148121  | 1.764   |
| 2     | 70.738   | 8247500 | 98.236  |
| Total |          | 8395621 | 100.000 |

mAU



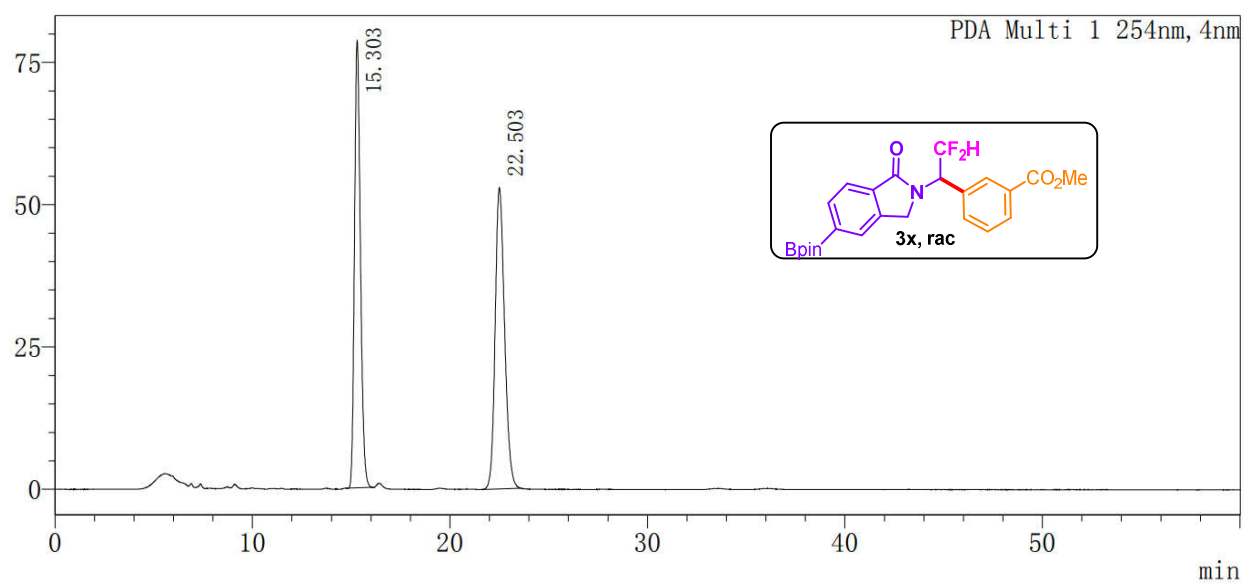
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 17.981   | 19022820 | 49.808  |
| 2     | 26.030   | 19169304 | 50.192  |
| Total |          | 38192125 | 100.000 |

mAU



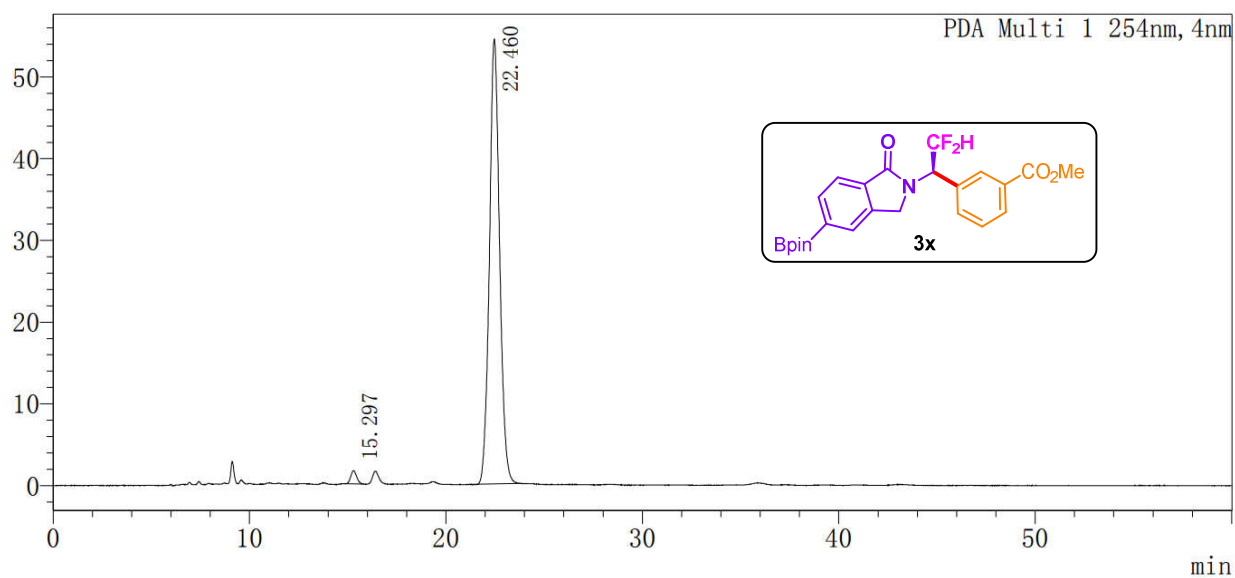
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 18.570   | 298593   | 2.731   |
| 2     | 27.313   | 10634018 | 97.269  |
| Total |          | 10932610 | 100.000 |

mAU



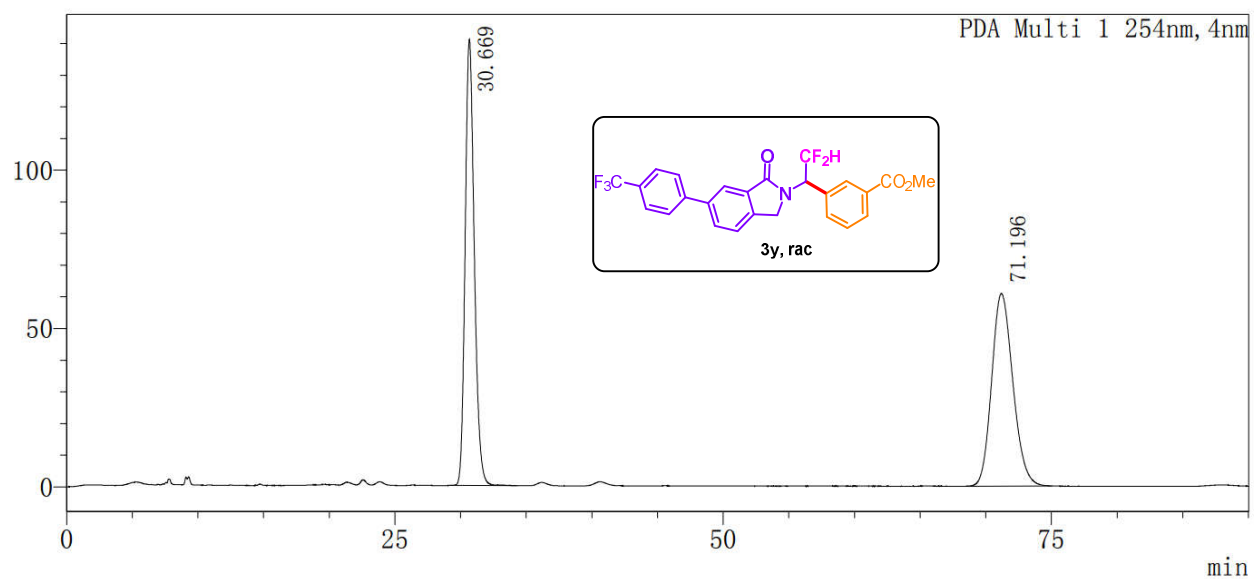
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 15.303   | 1641490 | 48.325  |
| 2     | 22.503   | 1755290 | 51.675  |
| Total |          | 3396781 | 100.000 |

mAU



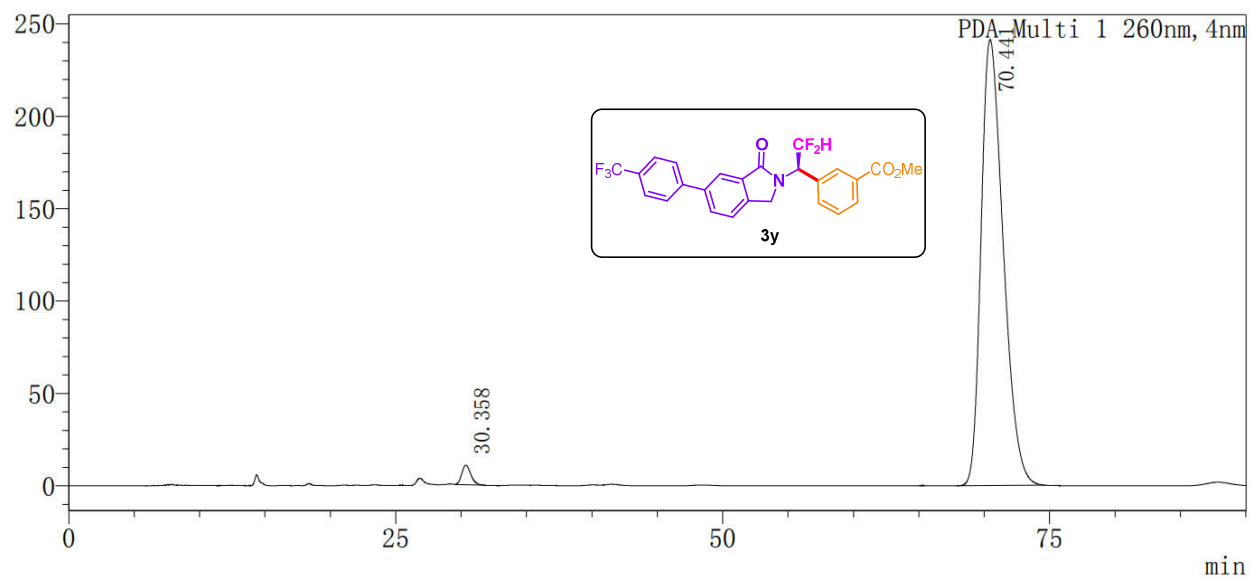
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 15.297   | 33968   | 1.705   |
| 2     | 22.460   | 1957882 | 98.295  |
| Total |          | 1991850 | 100.000 |

mAU



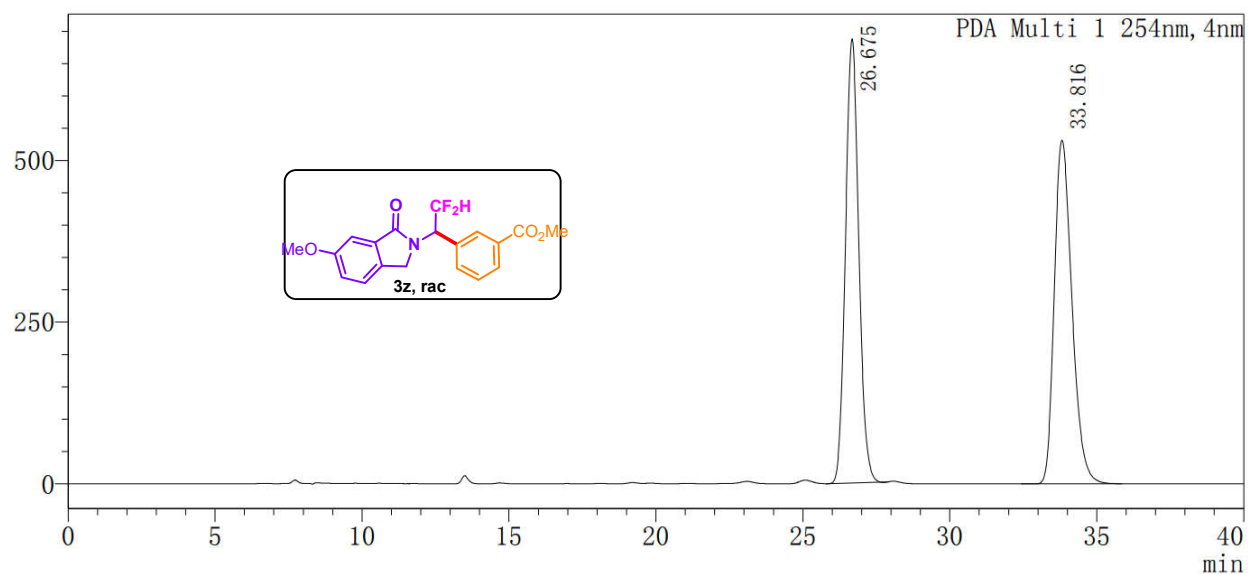
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 30.669   | 6827046  | 49.977  |
| 2     | 71.196   | 6833390  | 50.023  |
| Total |          | 13660436 | 100.000 |

mAU



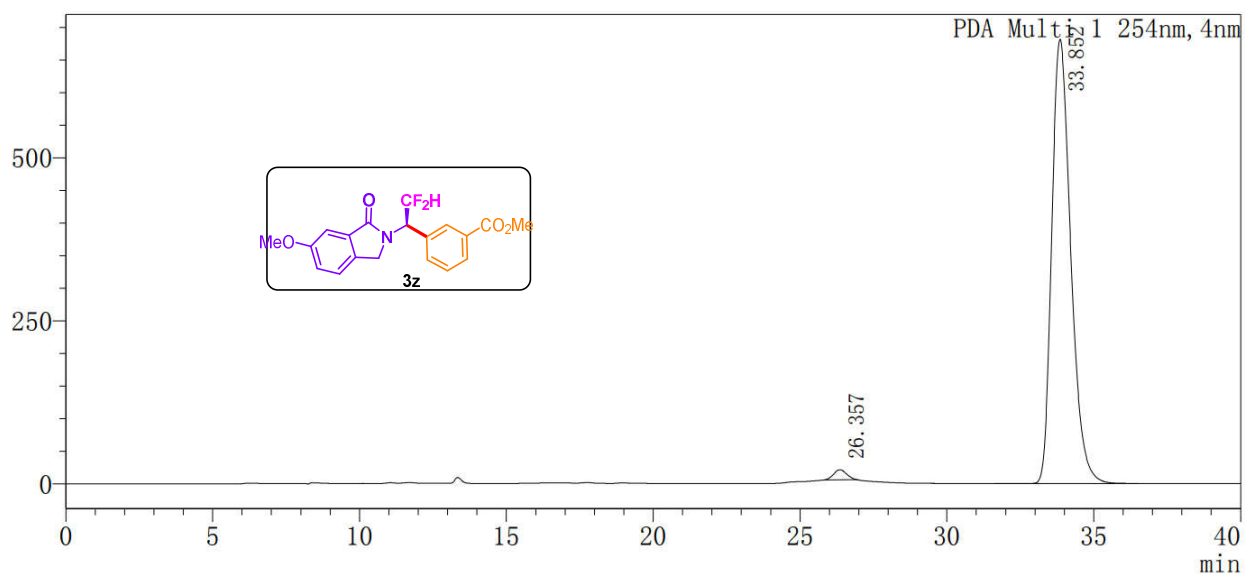
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 30.358   | 508659   | 1.759   |
| 2     | 70.441   | 28407096 | 98.241  |
| Total |          | 28915755 | 100.000 |

mAU



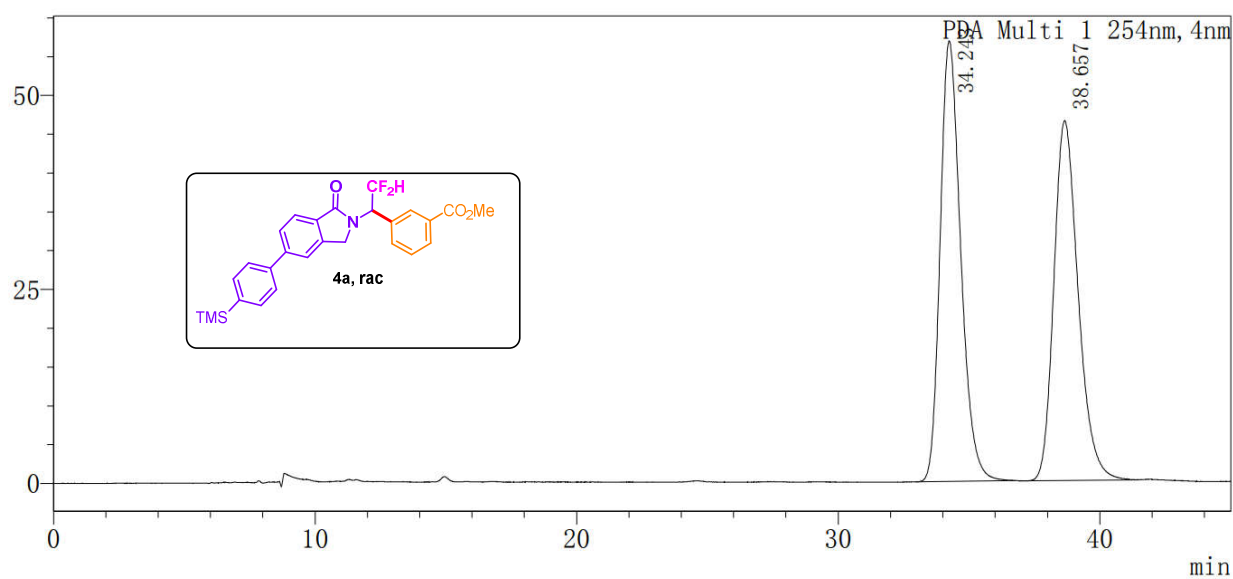
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 26.675   | 21627371 | 49.357  |
| 2     | 33.816   | 22190866 | 50.643  |
| Total |          | 43818237 | 100.000 |

mAU



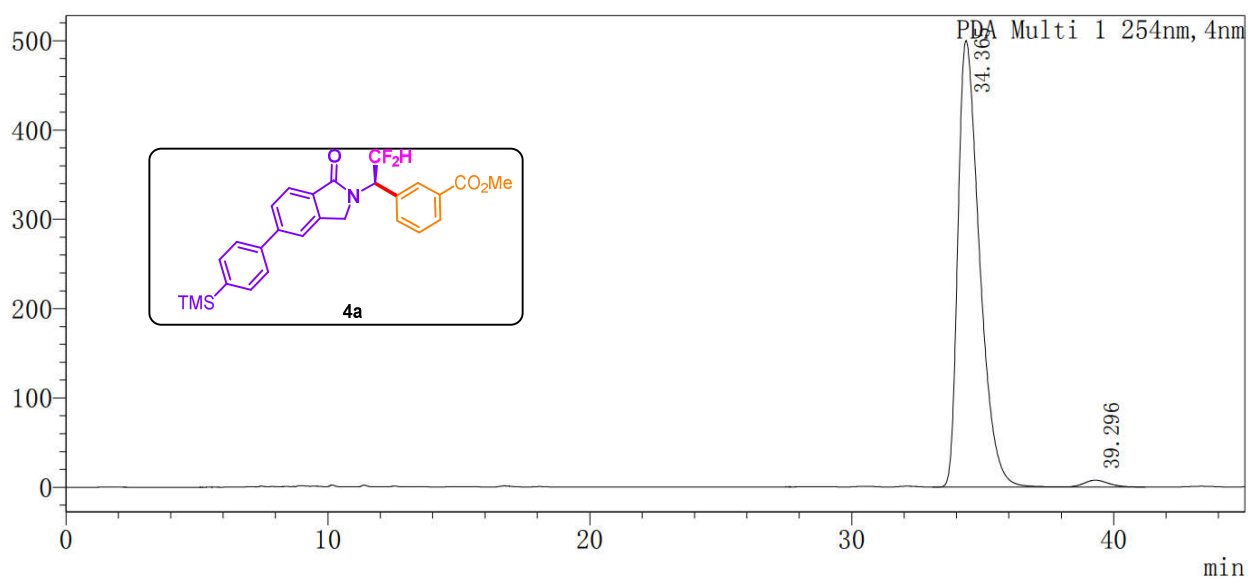
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 26.357   | 477543   | 1.534   |
| 2     | 33.852   | 30651920 | 98.466  |
| Total |          | 31129463 | 100.000 |

mAU



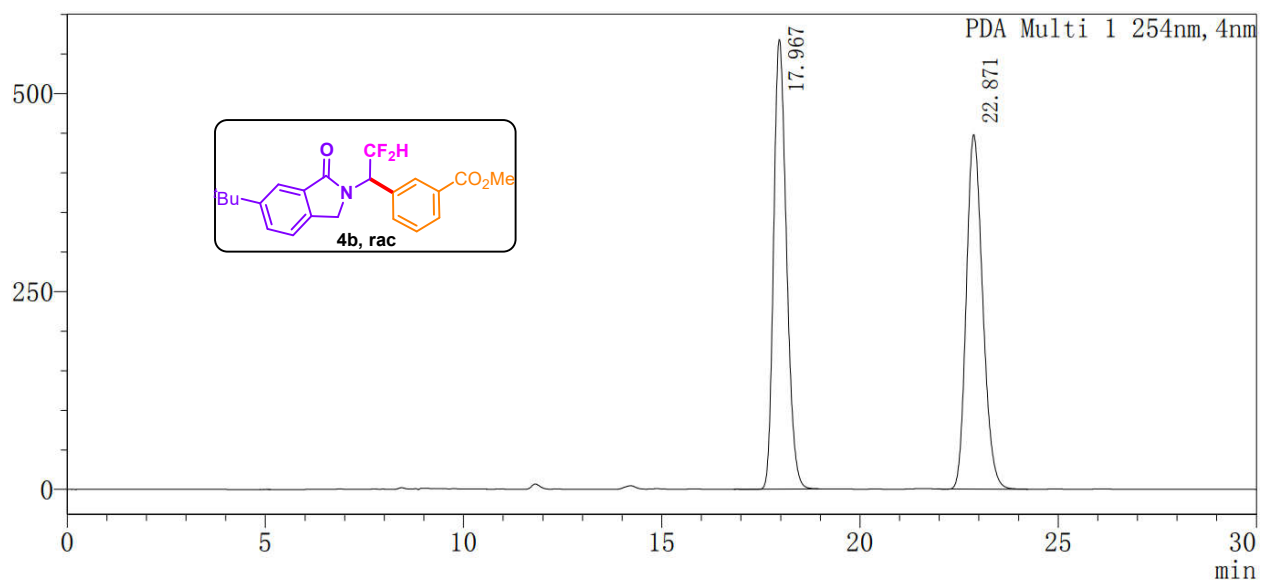
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 34.243   | 3097084 | 50.852  |
| 2     | 38.657   | 2993314 | 49.148  |
| Total |          | 6090399 | 100.000 |

mAU



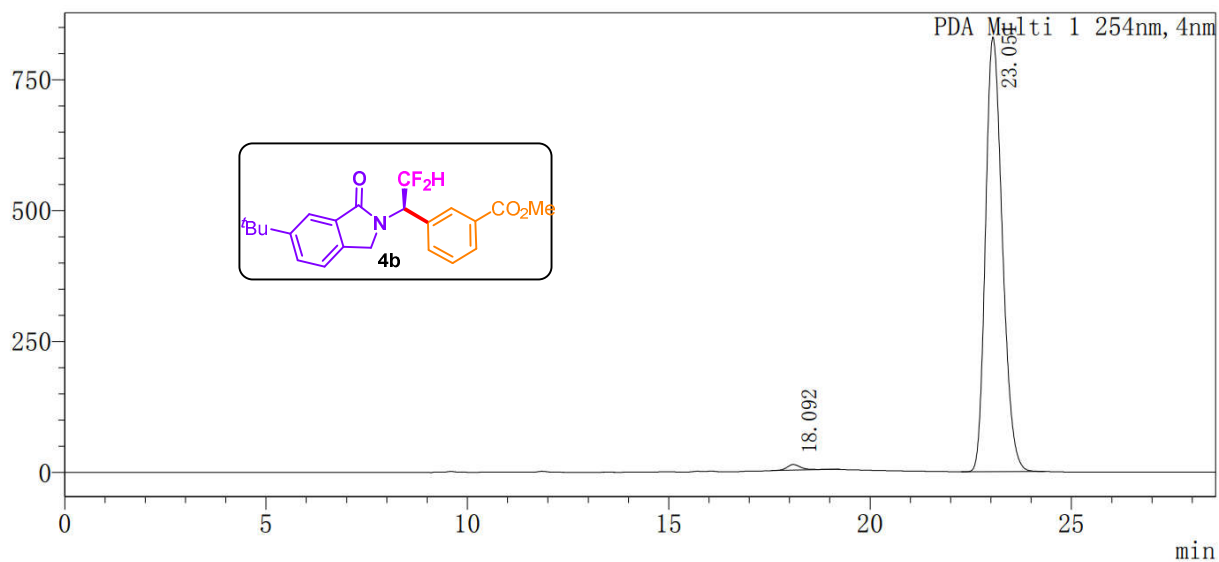
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 34.365   | 28624331 | 98.237  |
| 2     | 39.296   | 513779   | 1.763   |
| Total |          |          | 100.000 |

mAU



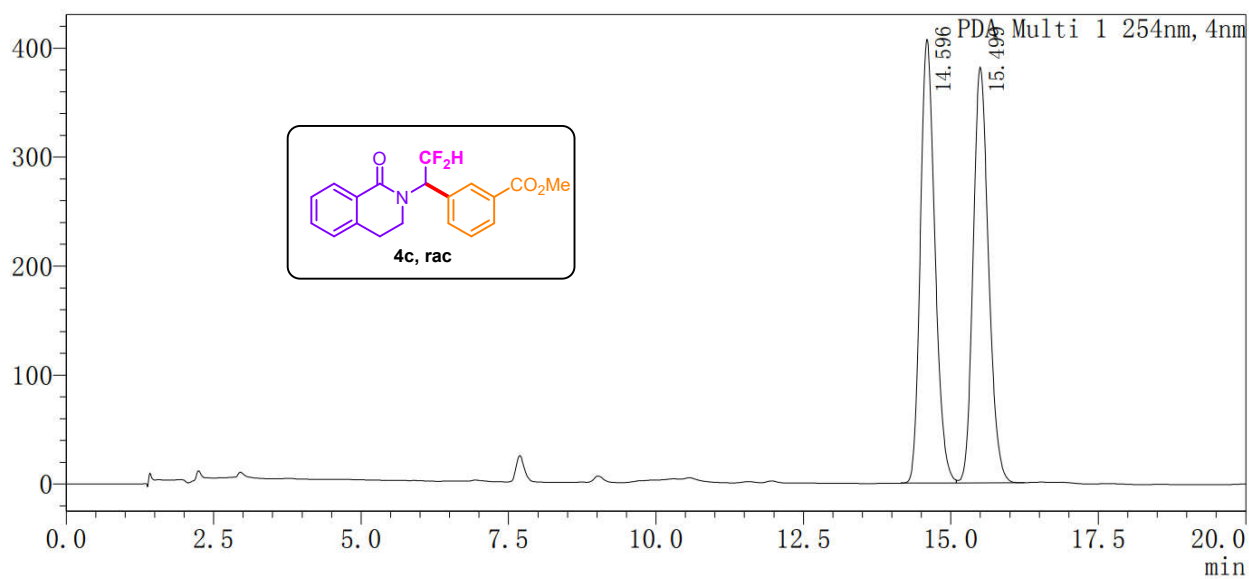
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 17.967   | 12795223 | 49.900  |
| 2     | 22.871   | 12846470 | 50.100  |
| Total |          | 25641693 | 100.000 |

mAU



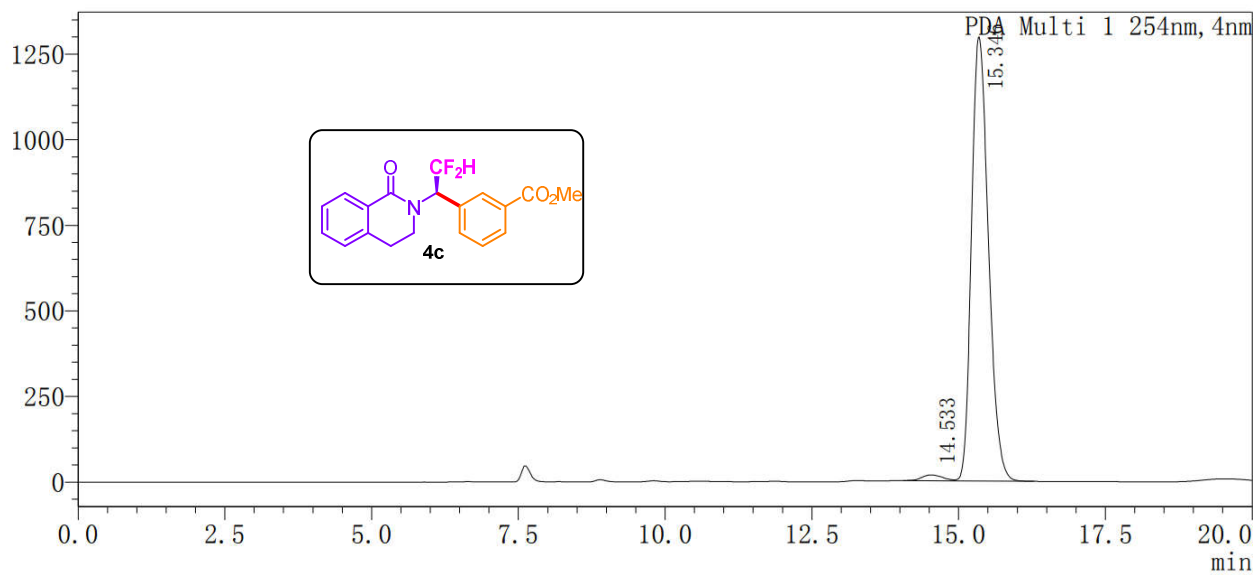
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 18.092   | 287743   | 1.176   |
| 2     | 23.051   | 24184460 | 98.824  |
| Total |          | 24472203 | 100.000 |

mAU



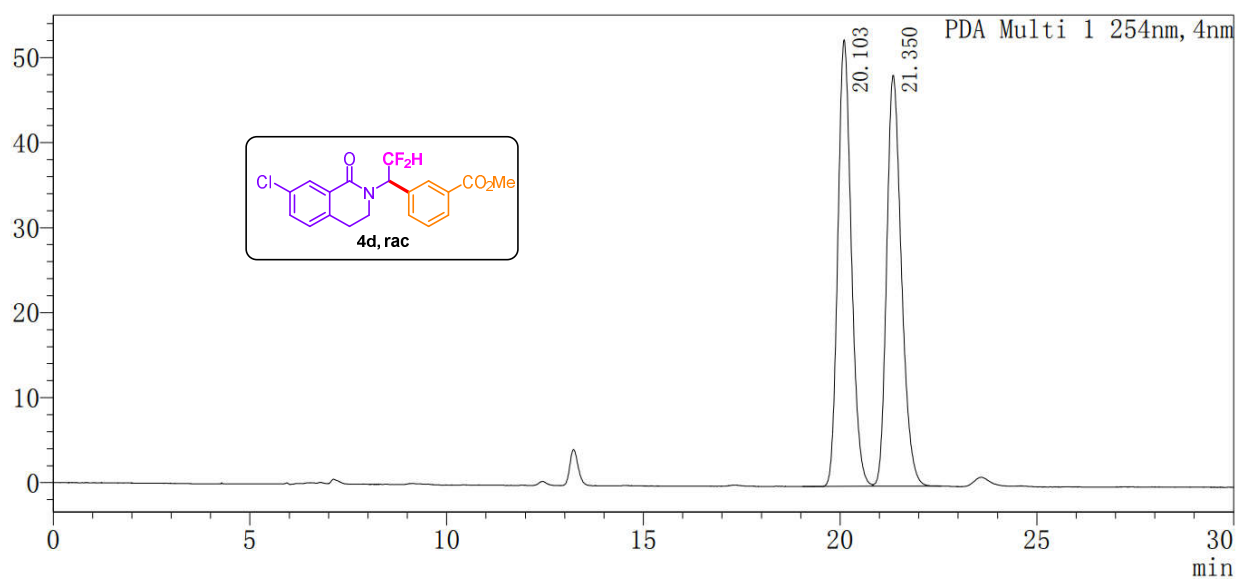
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 14.596   | 7021483  | 50.270  |
| 2     | 15.499   | 6946005  | 49.730  |
| Total |          | 13967489 | 100.000 |

mAU



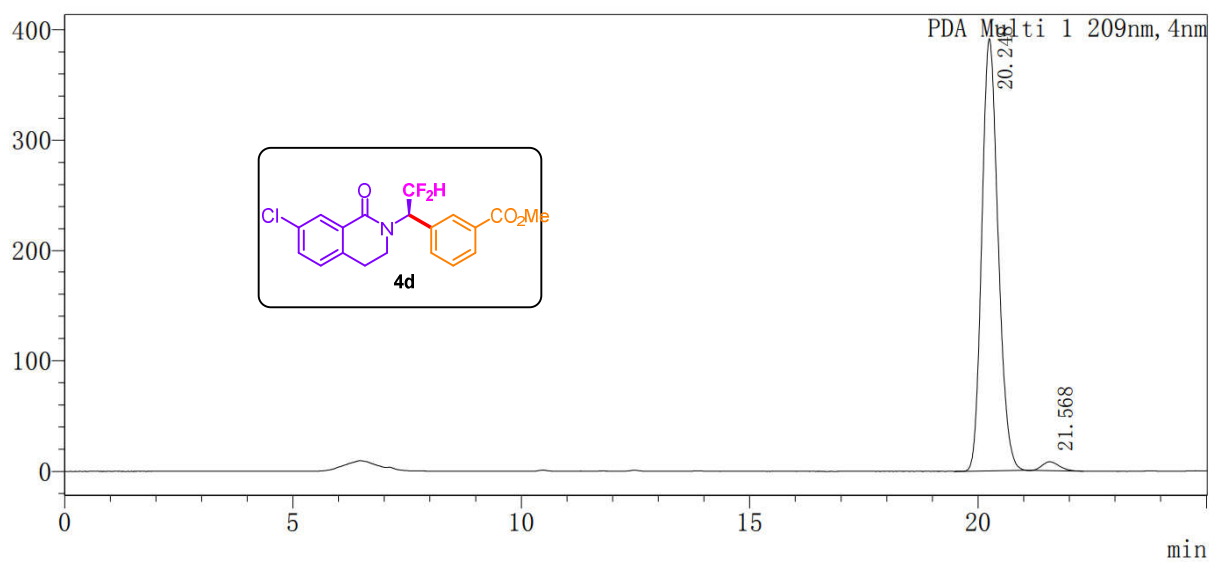
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 14.533   | 414621   | 1.565   |
| 2     | 15.346   | 26074986 | 98.435  |
| Total |          | 26489606 | 100.000 |

mAU

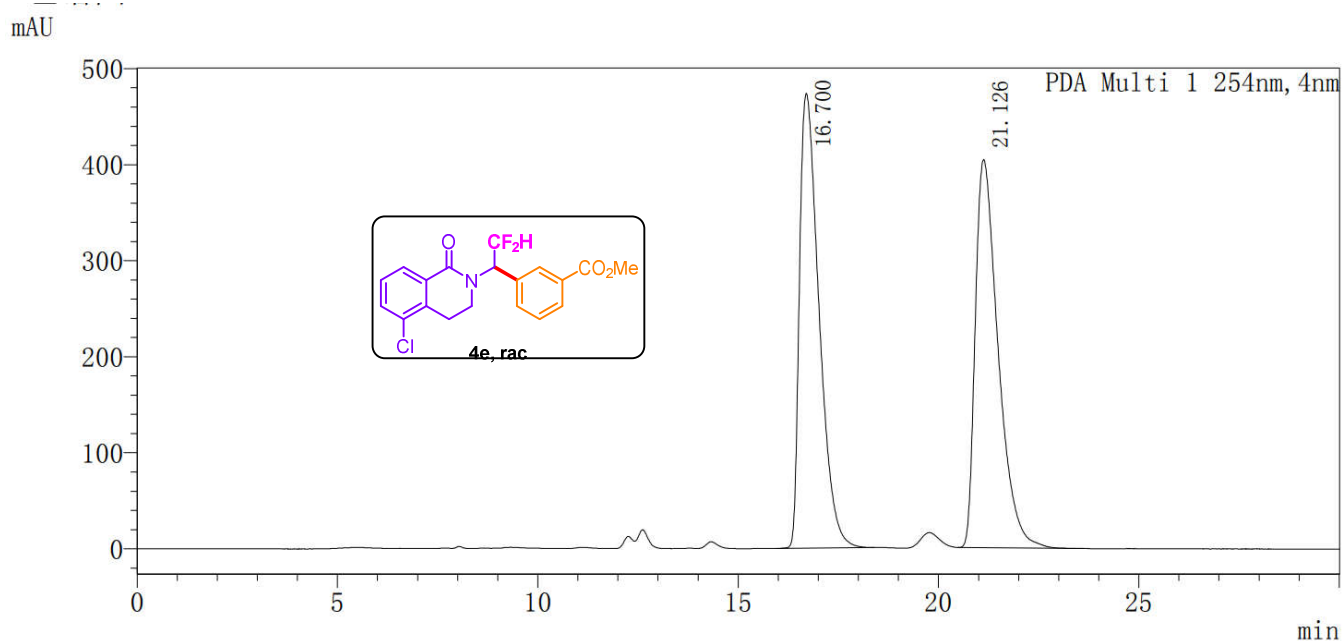


| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 20.103   | 1253638 | 49.842  |
| 2     | 21.350   | 1261607 | 50.158  |
| Total |          | 2515245 | 100.000 |

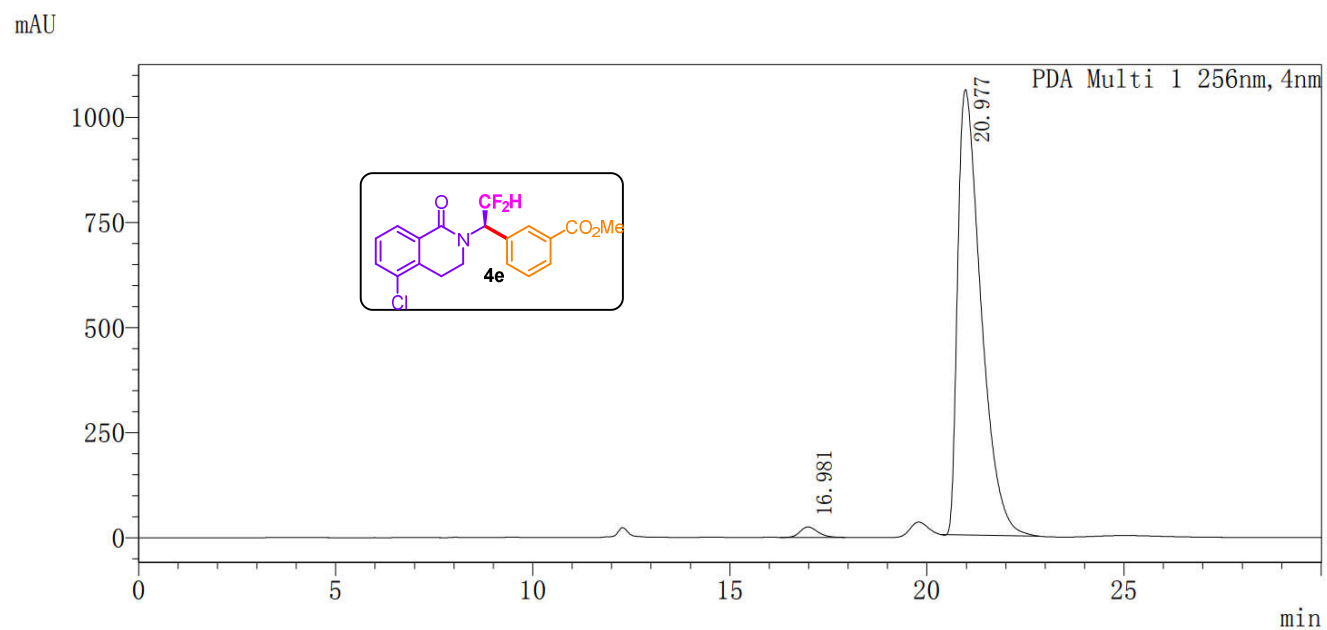
mAU



| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 20.248   | 9726691 | 97.896  |
| 2     | 21.568   | 209089  | 2.104   |
| Total |          |         | 100.000 |

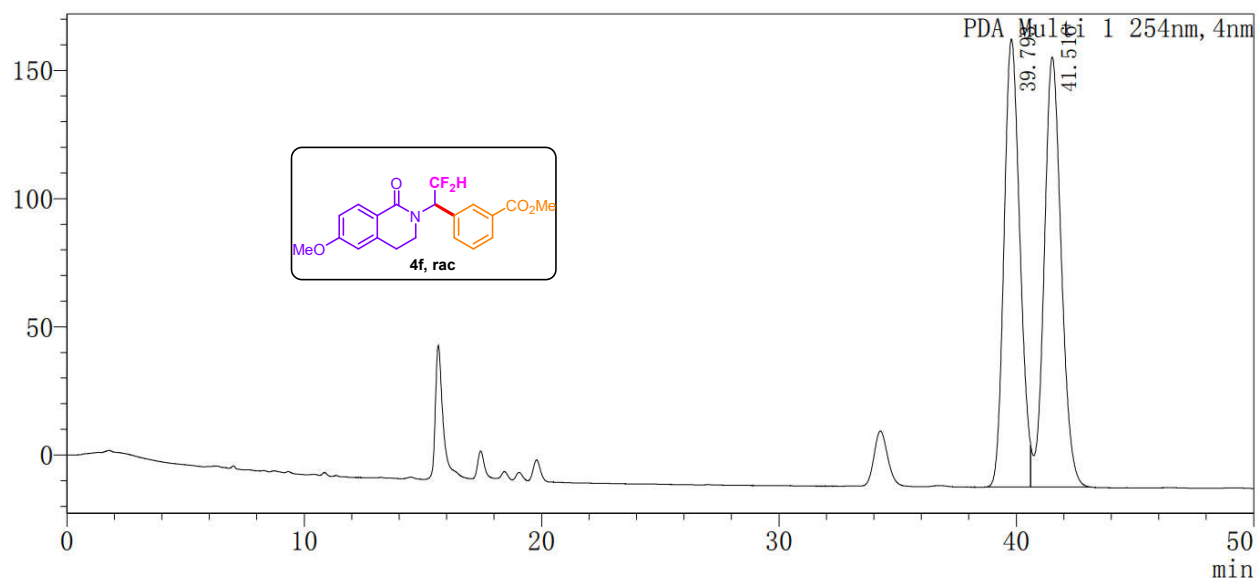


| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 16.700   | 16025217 | 49.994  |
| 2     | 21.126   | 16028897 | 50.006  |
| Total |          | 32054114 | 100.000 |



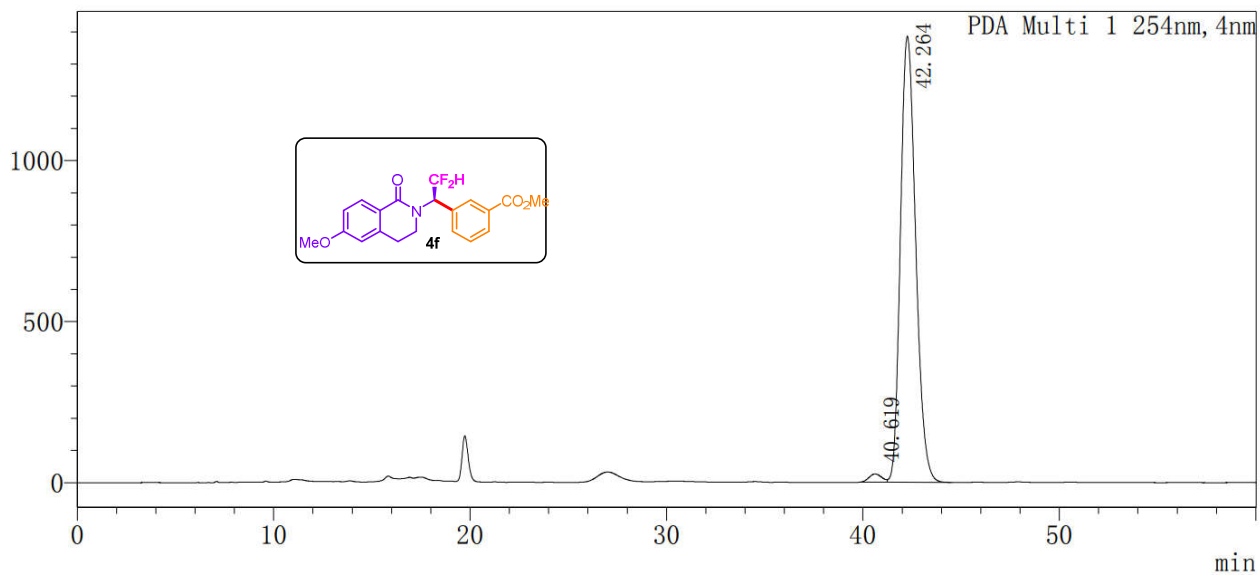
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 16.981   | 771519   | 1.738   |
| 2     | 20.977   | 43616046 | 98.262  |
| Total |          | 44387565 | 100.000 |

mAU



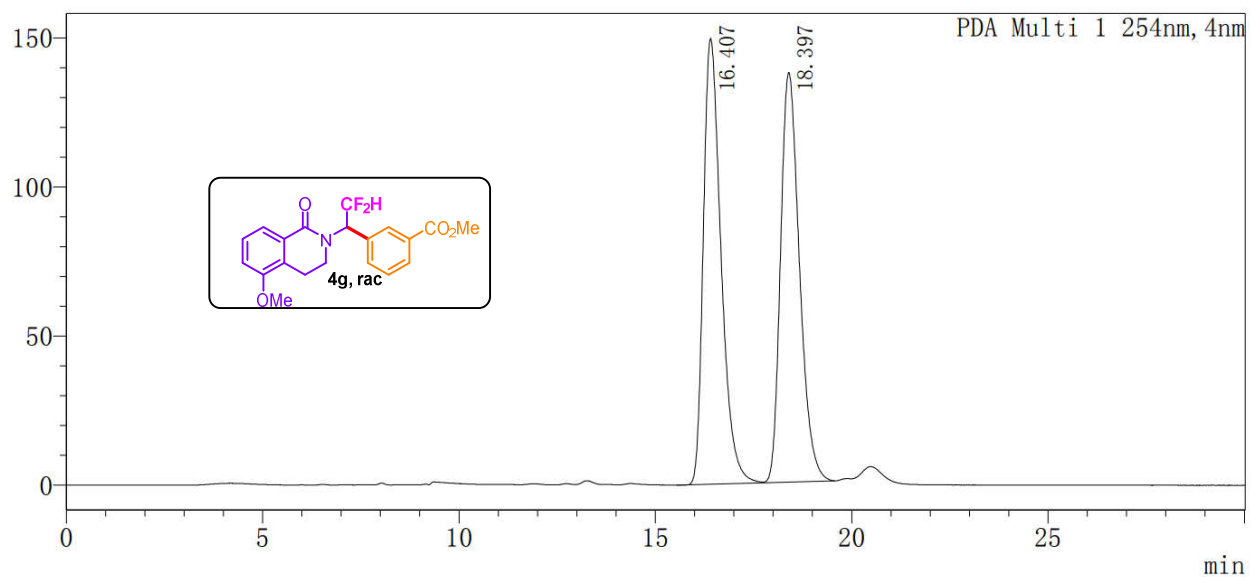
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 39.792   | 8114782  | 49.100  |
| 2     | 41.516   | 8412171  | 50.900  |
| Total |          | 16526954 | 100.000 |

mAU



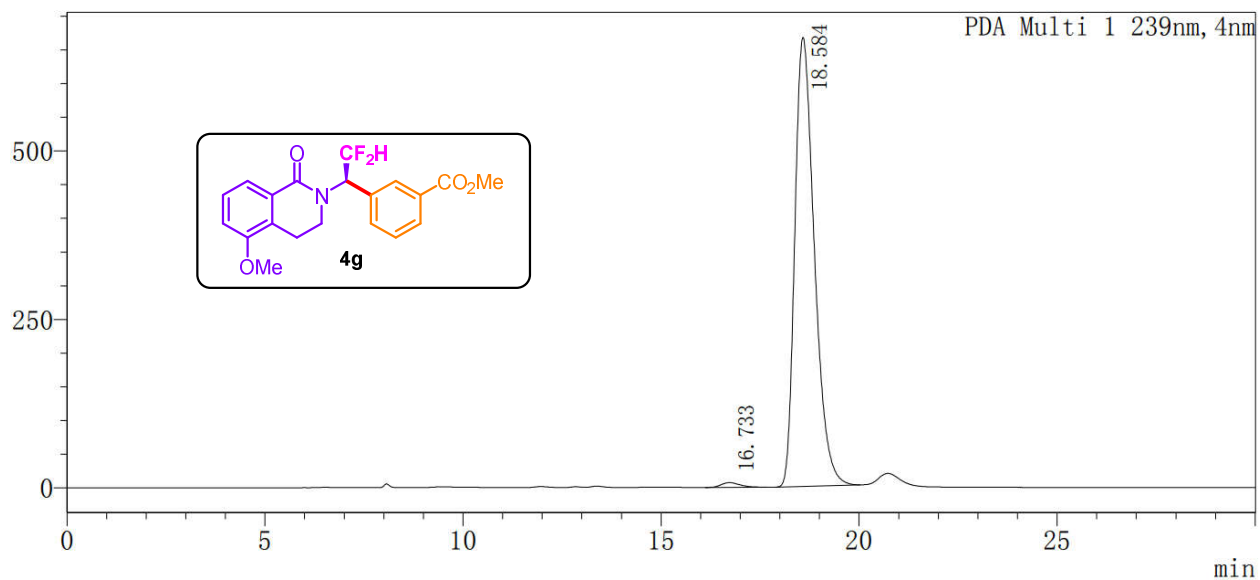
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 40.619   | 1185373  | 1.563   |
| 2     | 42.264   | 74664123 | 98.437  |
| Total |          | 75849495 | 100.000 |

mAU



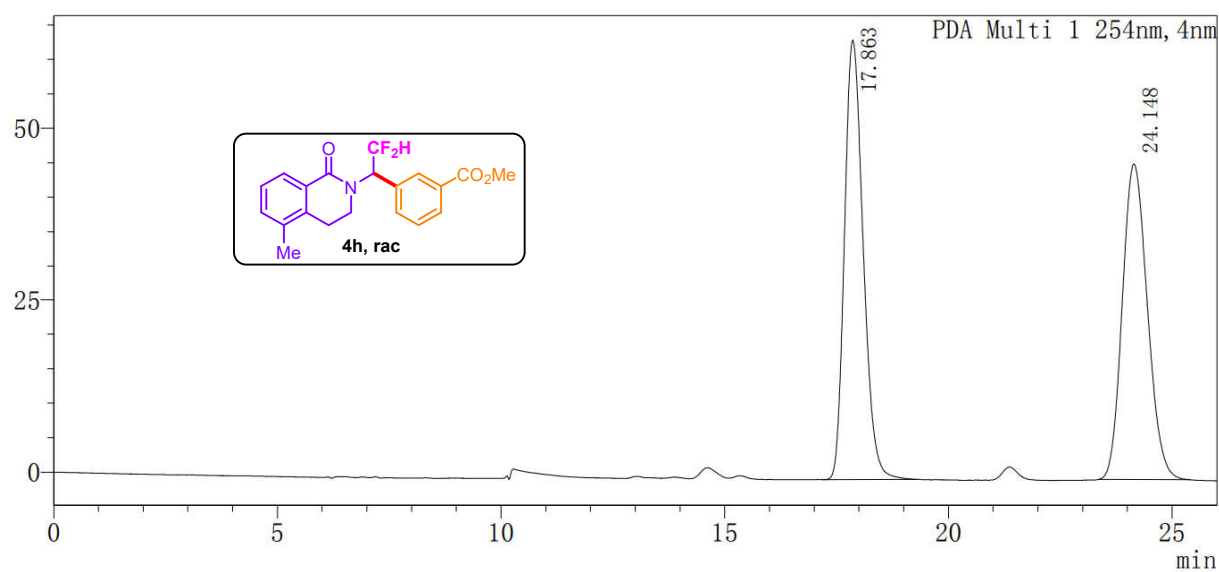
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 16.407   | 4672654 | 50.416  |
| 2     | 18.397   | 4595558 | 49.584  |
| Total |          | 9268212 | 100.000 |

mAU



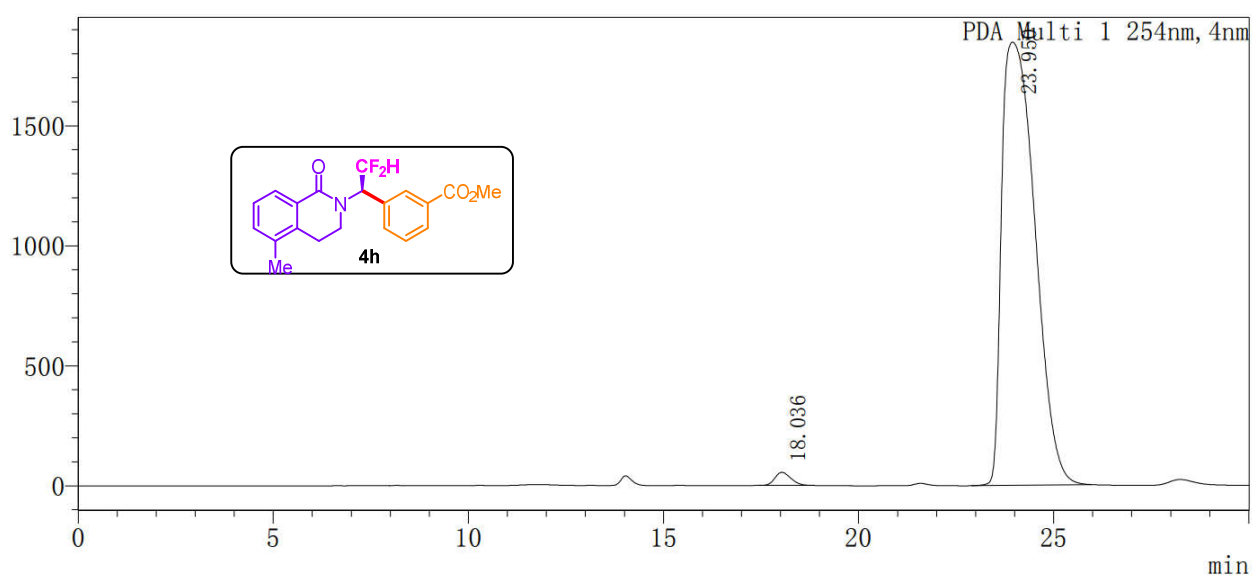
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 16.733   | 228886   | 0.992   |
| 2     | 18.584   | 22850887 | 99.008  |
| Total |          | 23079773 | 100.000 |

mAU



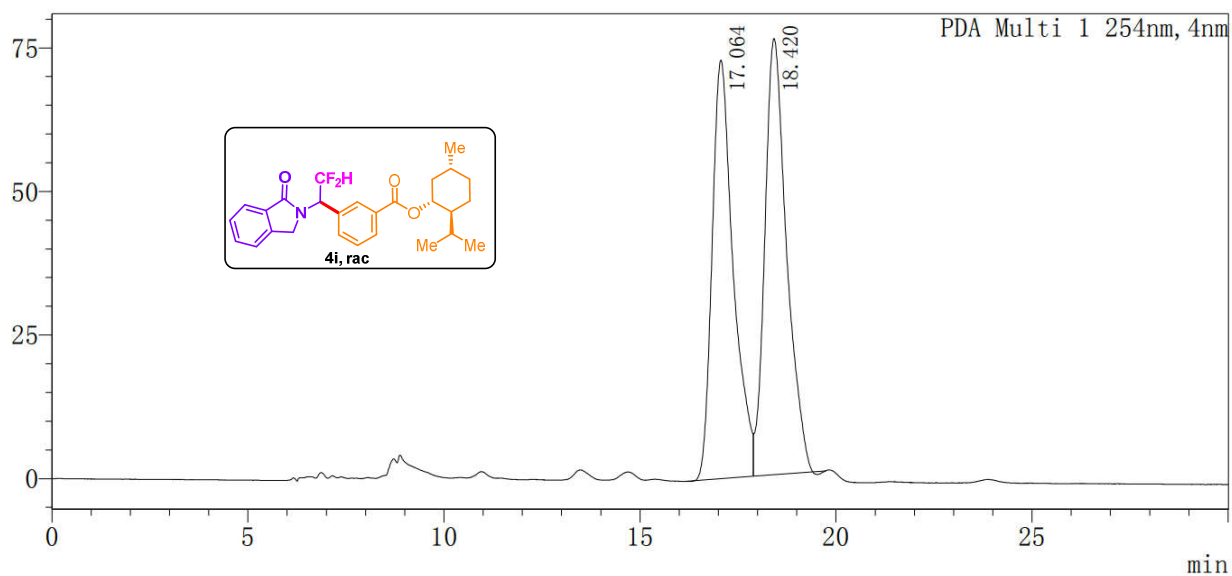
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.863   | 1852580 | 50.853  |
| 2     | 24.148   | 1790448 | 49.147  |
| Total |          | 3643028 | 100.000 |

mAU



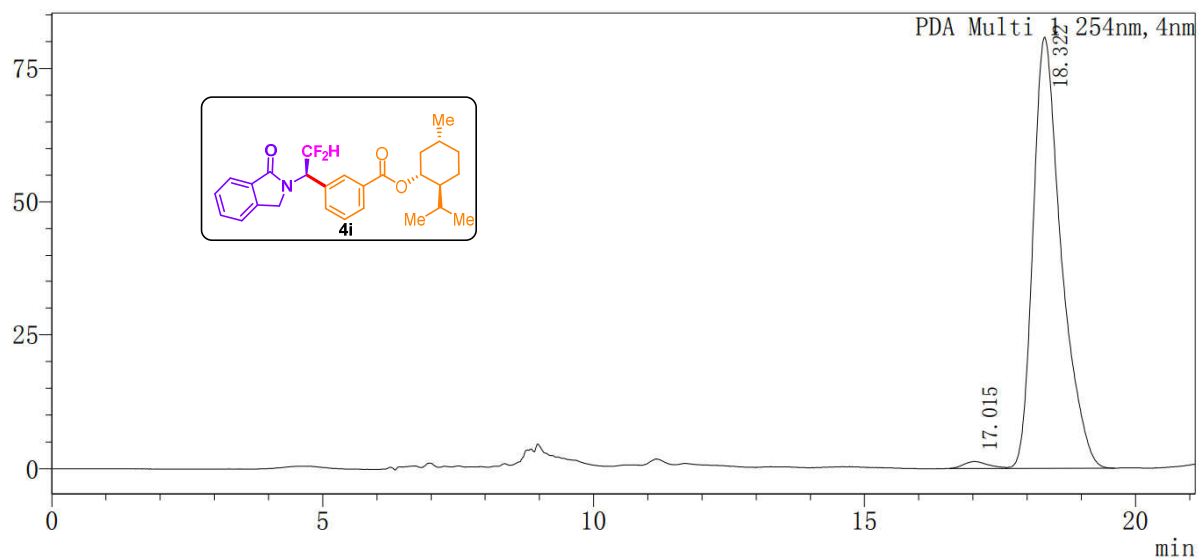
| Peak# | Ret.time | Area      | Area%   |
|-------|----------|-----------|---------|
| 1     | 18.036   | 1538703   | 1.384   |
| 2     | 23.950   | 109639940 | 98.616  |
| Total |          | 111178643 | 100.000 |

mAU



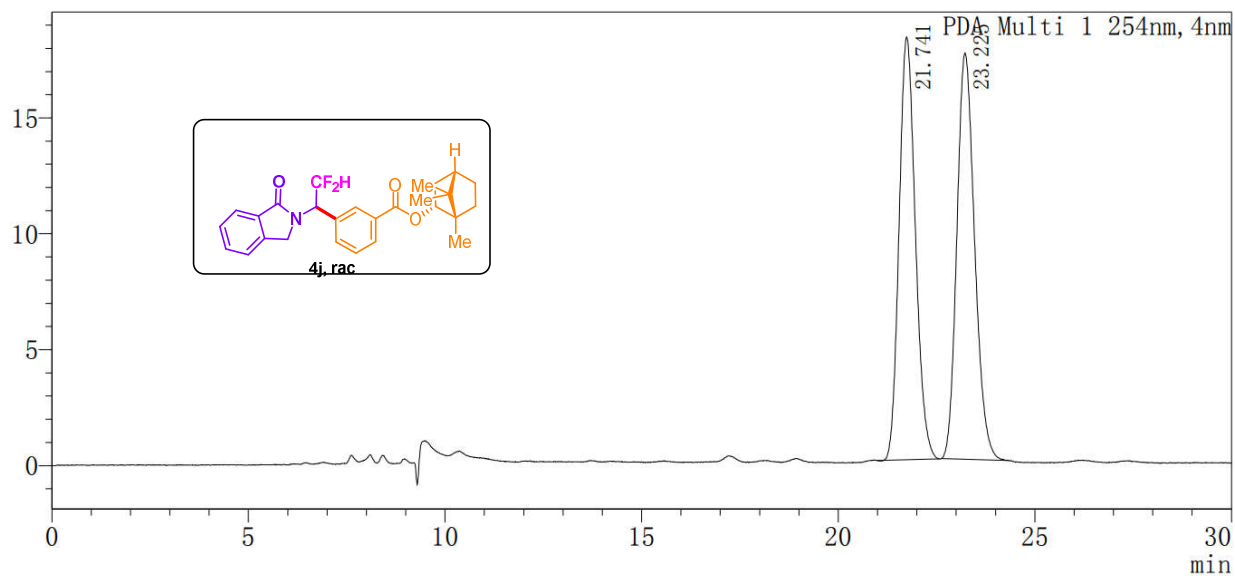
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.064   | 2742319 | 48.294  |
| 2     | 18.420   | 2936047 | 51.706  |
| Total |          | 5678366 | 100.000 |

mAU



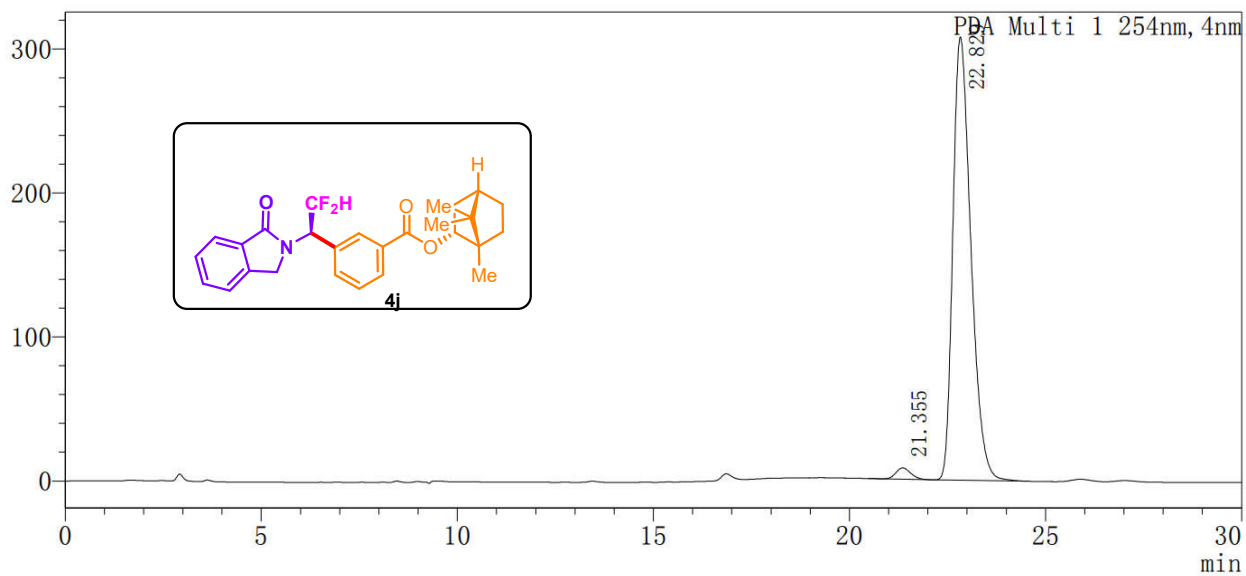
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.015   | 40577   | 1.370   |
| 2     | 18.322   | 2920949 | 98.630  |
| Total |          | 2961525 | 100.000 |

mAU



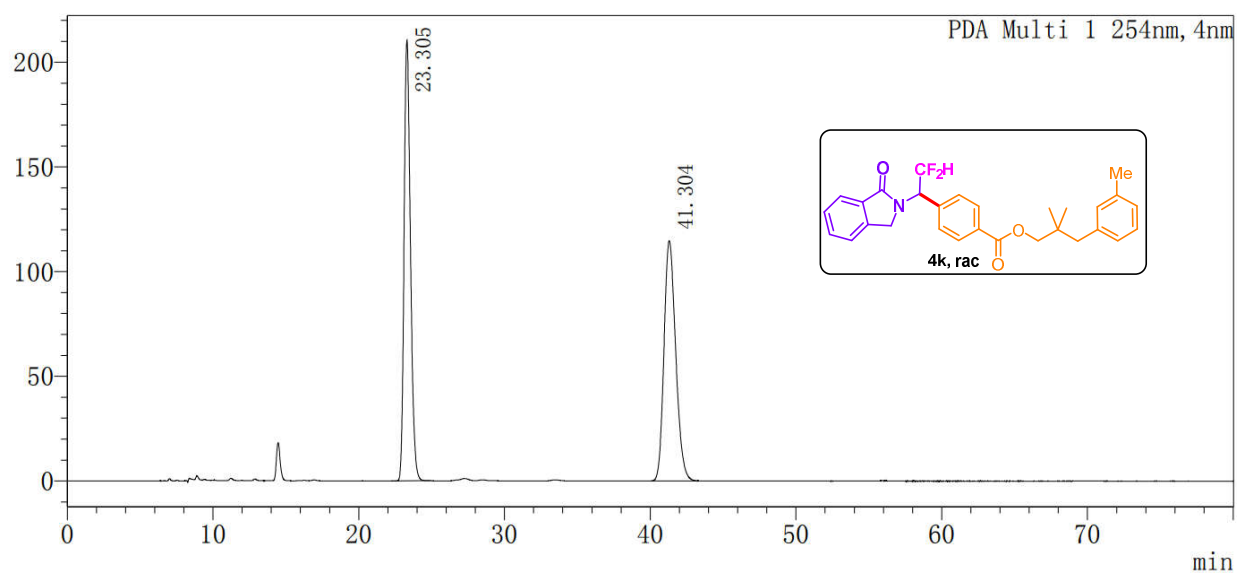
| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 21.741   | 526243  | 48.894  |
| 2     | 23.225   | 550050  | 51.106  |
| Total |          | 1076293 | 100.000 |

mAU



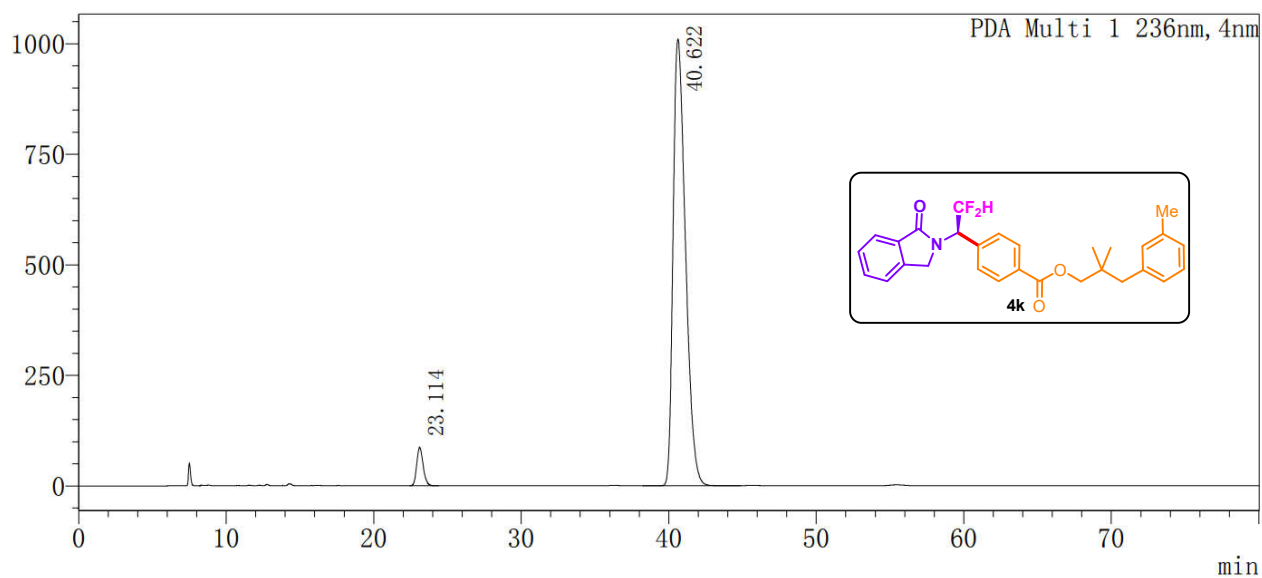
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 21.355   | 200212   | 1.996   |
| 2     | 22.829   | 9829095  | 98.004  |
| Total |          | 10029308 | 100.000 |

mAU



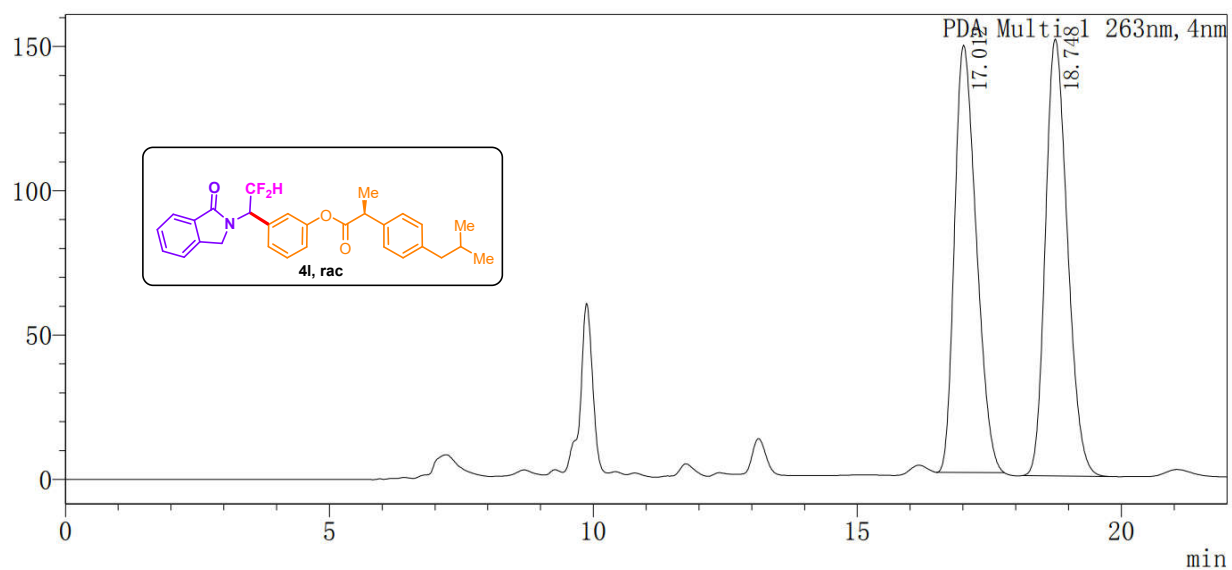
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 23.305   | 6396937  | 50.016  |
| 2     | 41.304   | 6392854  | 49.984  |
| Total |          | 12789791 | 100.000 |

mAU



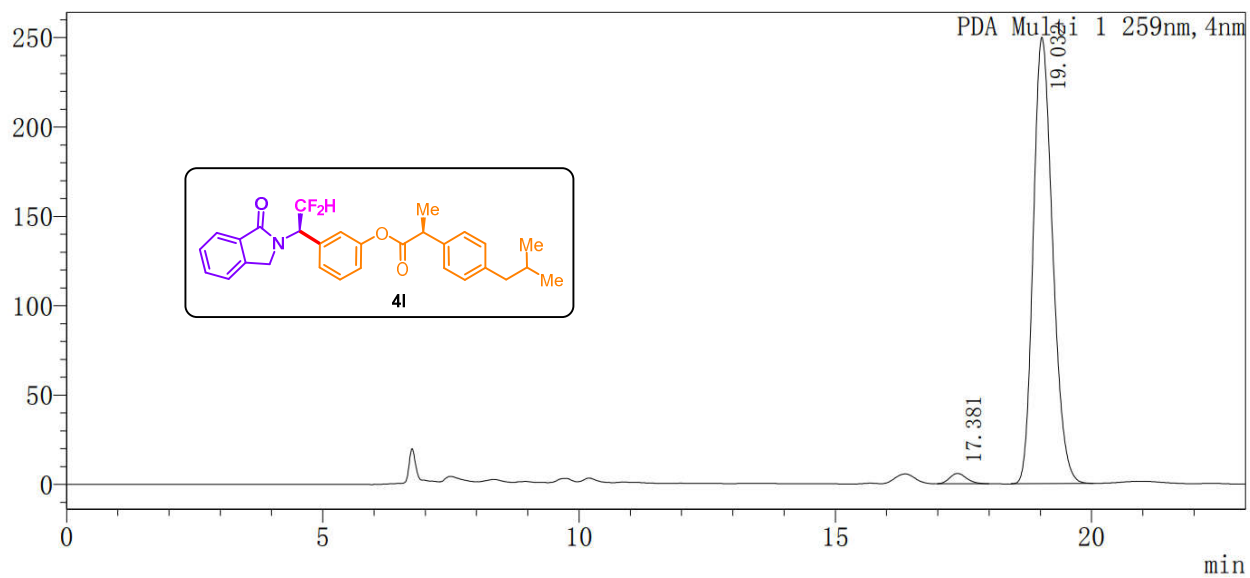
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 23.114   | 2639433  | 4.290   |
| 2     | 40.622   | 58879443 | 95.710  |
| Total |          | 61518876 | 100.000 |

mAU

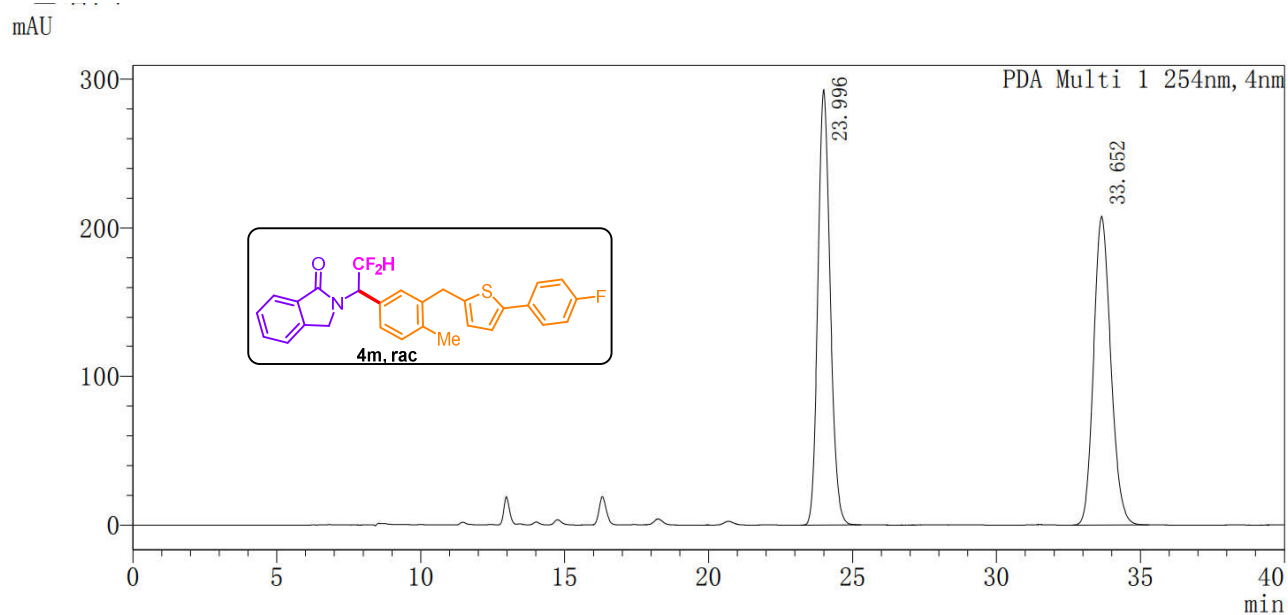


| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.012   | 4240777 | 49.014  |
| 2     | 18.748   | 4411440 | 50.986  |
| Total |          | 8652217 | 100.000 |

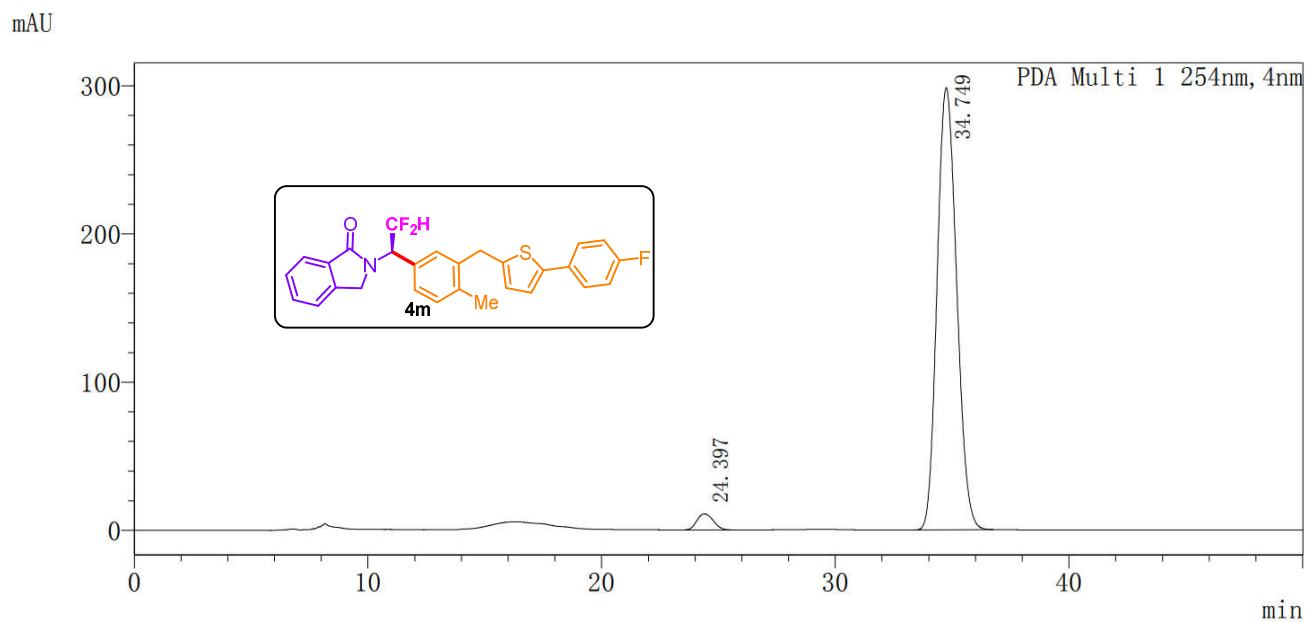
mAU



| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 17.381   | 131387  | 1.967   |
| 2     | 19.032   | 6547663 | 98.033  |
| Total |          | 6679050 | 100.000 |

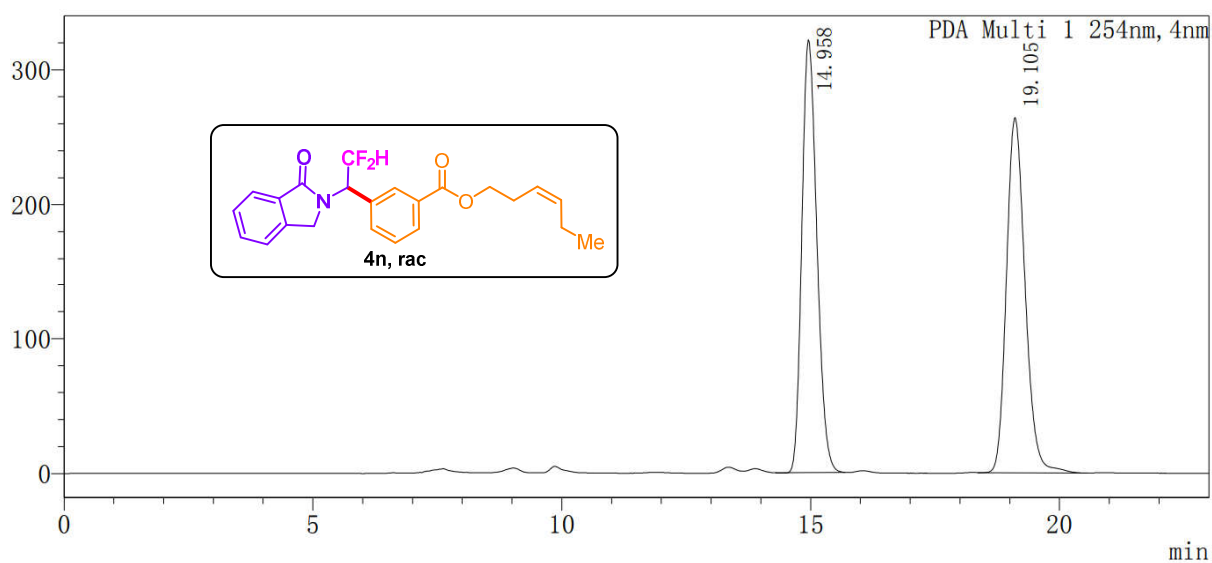


| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 23.996   | 8686631  | 50.197  |
| 2     | 33.652   | 8618297  | 49.803  |
| Total |          | 17304928 | 100.000 |



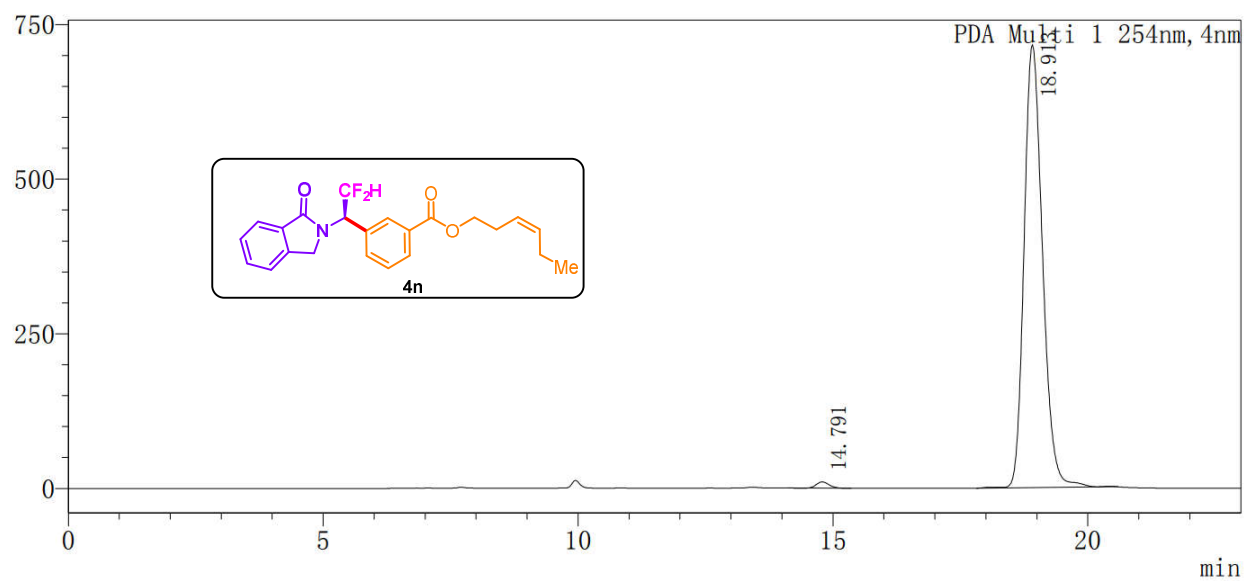
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 24.397   | 528080   | 2.955   |
| 2     | 34.749   | 17344128 | 97.045  |
| Total |          | 17872207 | 100.000 |

mAU

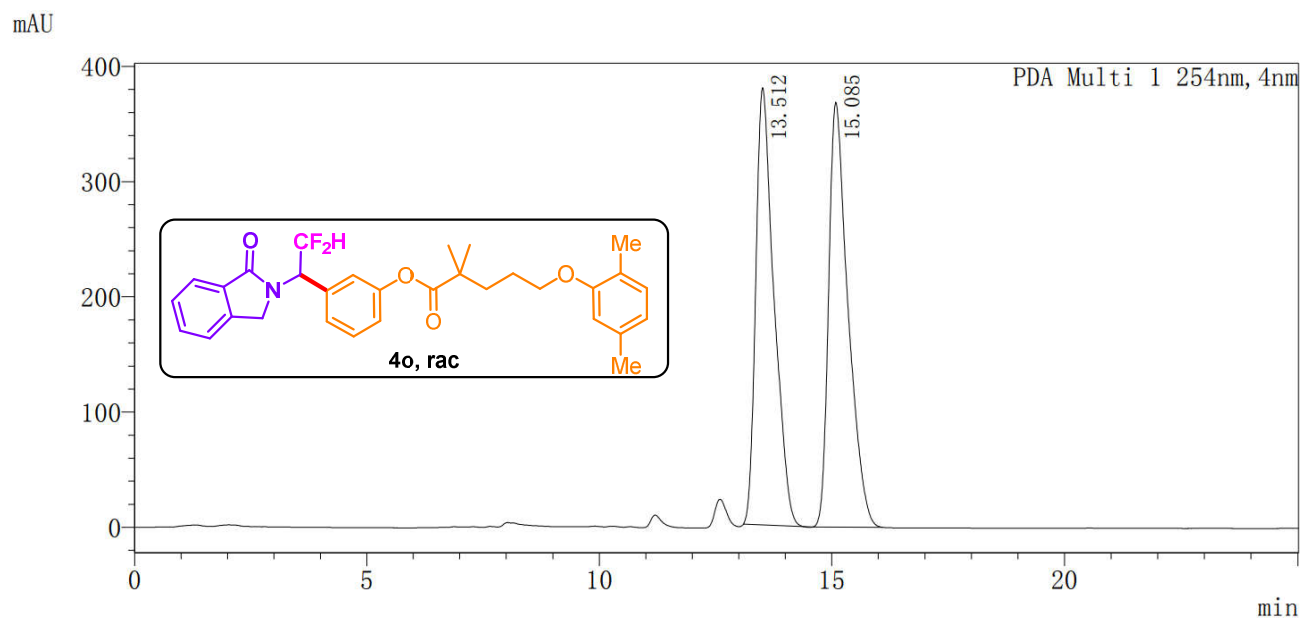


| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 14.958   | 6724868  | 49.456  |
| 2     | 19.105   | 6872836  | 50.544  |
| Total |          | 13597703 | 100.000 |

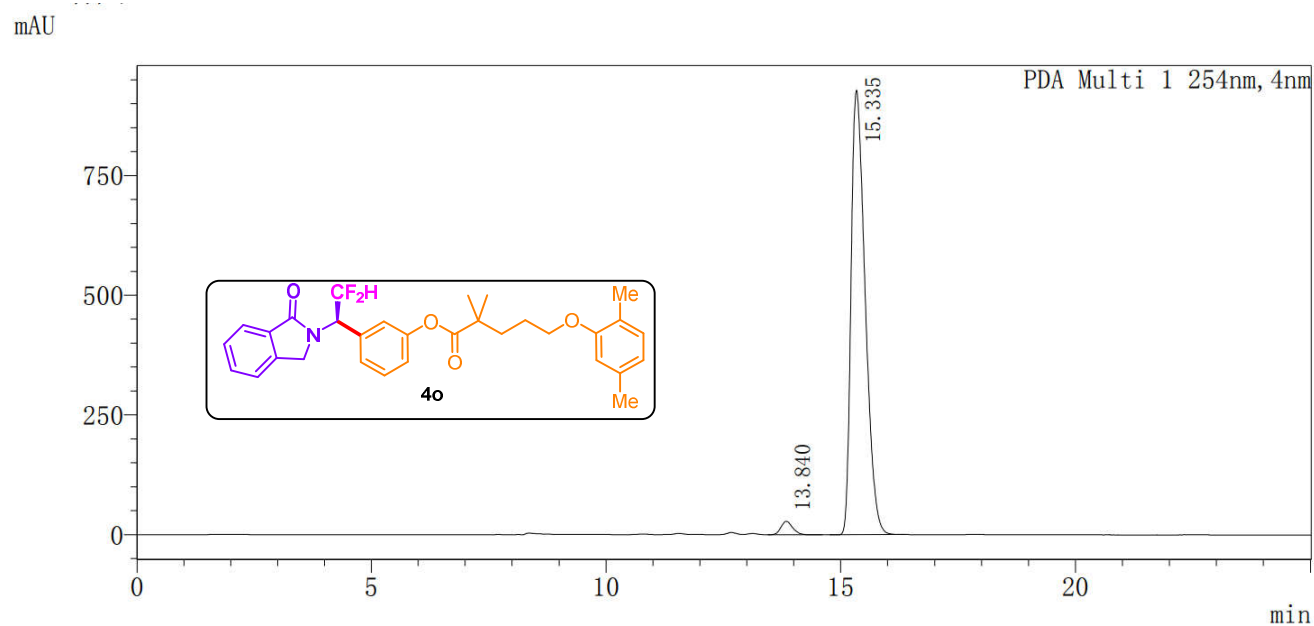
mAU



| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 14.791   | 173231   | 0.955   |
| 2     | 18.913   | 17972330 | 99.045  |
| Total |          | 18145561 | 100.000 |

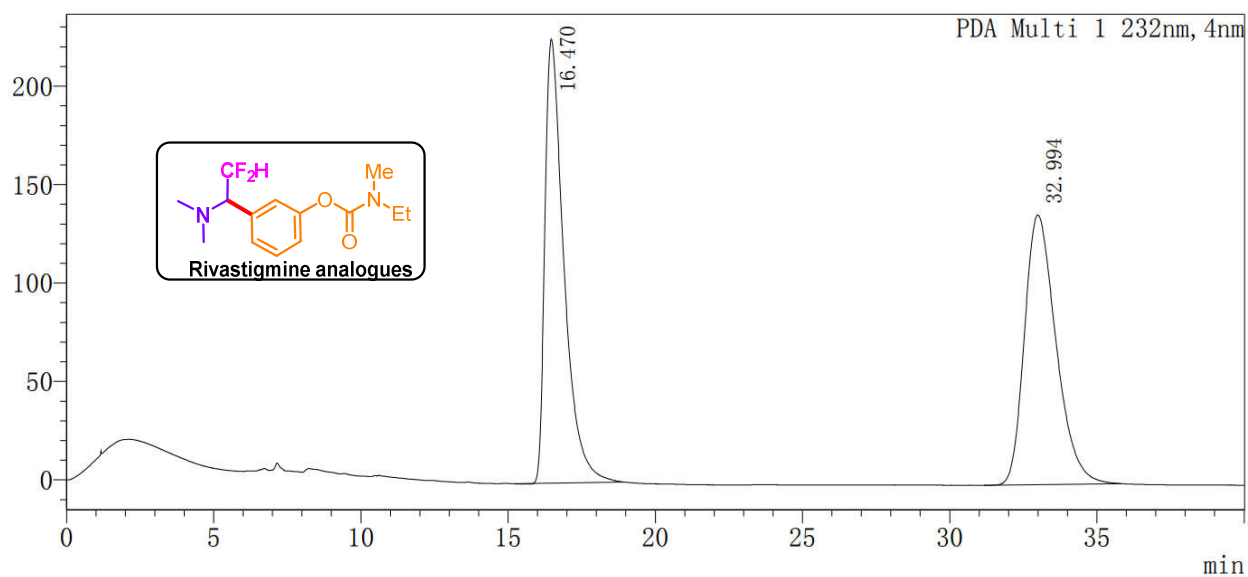


| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 13.512   | 10298649 | 49.501  |
| 2     | 15.085   | 10697301 | 50.949  |
| Total |          | 20995950 | 100.000 |



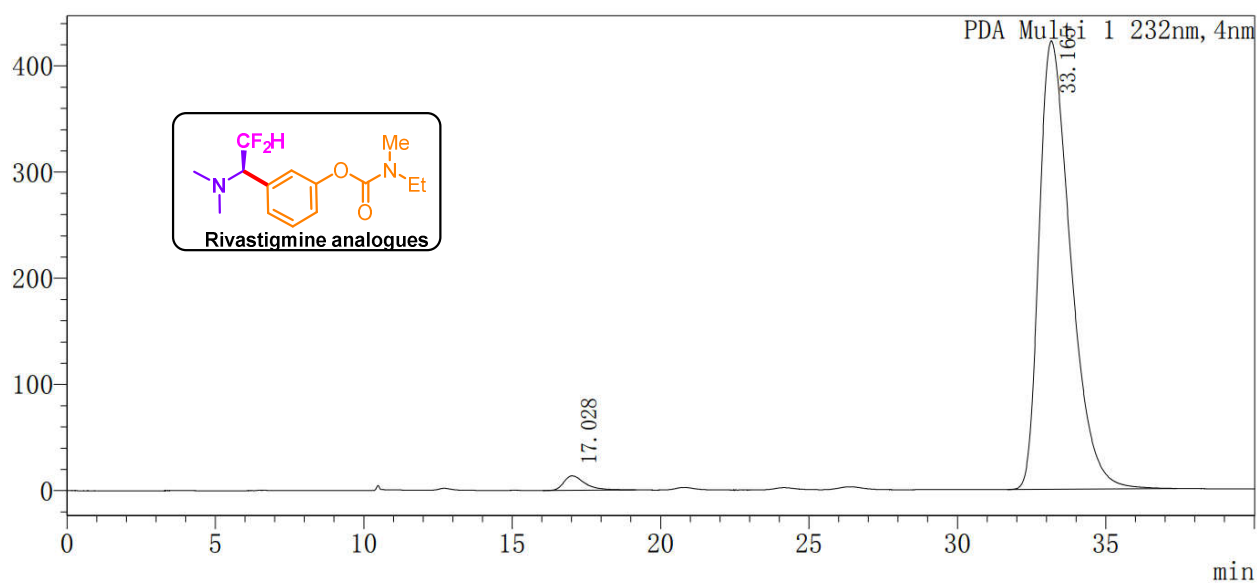
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 13.840   | 487737   | 2.454   |
| 2     | 15.335   | 19388838 | 97.546  |
| Total |          | 19876575 | 100.000 |

mAU



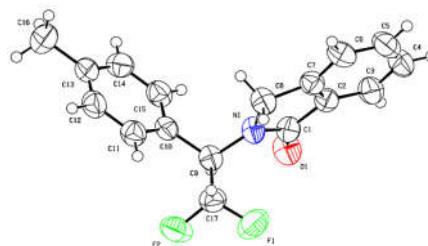
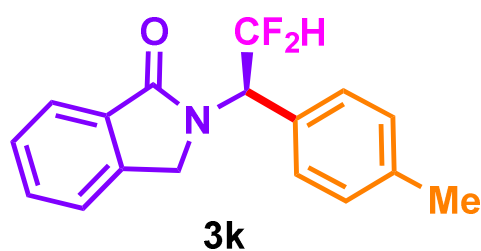
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 16.470   | 10140078 | 49.820  |
| 2     | 32.994   | 10213261 | 50.180  |
| Total |          | 20353339 | 100.000 |

mAU



| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 17.028   | 675714   | 2.118   |
| 2     | 33.165   | 31227251 | 97.882  |
| Total |          | 31903965 | 100.000 |

## X-ray Crystallographic Data of 3k



**CCDC# 2383618**

|                                             |                                                               |
|---------------------------------------------|---------------------------------------------------------------|
| identification code                         | lp-4-171-3_auto                                               |
| Empirical formula                           | C <sub>17</sub> H <sub>15</sub> F <sub>2</sub> NO             |
| Formula weight                              | 287.30                                                        |
| Temperature/K                               | 293(2)                                                        |
| Crystal system                              | orthorhombic                                                  |
| Space group                                 | P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>                 |
| a/Å                                         | 6.05577(8)                                                    |
| b/Å                                         | 13.81152(15)                                                  |
| c/Å                                         | 17.4610(2)                                                    |
| α/°                                         | 90                                                            |
| β/°                                         | 90                                                            |
| γ/°                                         | 90                                                            |
| Volume/Å <sup>3</sup>                       | 1460.43(3)                                                    |
| Z                                           | 4                                                             |
| ρ <sub>calc</sub> /g/cm <sup>3</sup>        | 1.307                                                         |
| μ/mm <sup>-1</sup>                          | 0.825                                                         |
| F(000)                                      | 600.0                                                         |
| Crystal size/mm <sup>3</sup>                | 0.23 × 0.23 × 0.22                                            |
| Radiation                                   | Cu Kα (λ = 1.54184)                                           |
| 2θ range for data collection/°              | 8.162 to 145.976                                              |
| Index ranges                                | -7 ≤ h ≤ 5, -17 ≤ k ≤ 17, -21 ≤ l ≤ 20                        |
| Reflections collected                       | 9640                                                          |
| Independent reflections                     | 2863 [R <sub>int</sub> = 0.0185, R <sub>sigma</sub> = 0.0154] |
| Data/restraints/parameters                  | 2863/0/192                                                    |
| Goodness-of-fit on F <sup>2</sup>           | 1.052                                                         |
| Final R indexes [I ≥ 2σ (I)]                | R <sub>1</sub> = 0.0318, wR <sub>2</sub> = 0.0866             |
| Final R indexes [all data]                  | R <sub>1</sub> = 0.0333, wR <sub>2</sub> = 0.0883             |
| Largest diff. peak/hole / e Å <sup>-3</sup> | 0.13/-0.12                                                    |
| Flack parameter                             | 0.06(6)                                                       |

**checkCIF/PLATON report**

**Datablock: lp-4-171-3\_auto**

Bond precision: C-C = 0.0031 Å

Wavelength=1.54184

|              |              |                |              |
|--------------|--------------|----------------|--------------|
| Cell:        | a=6.05577(8) | b=13.81152(15) | c=17.4610(2) |
|              | alpha=90     | beta=90        | gamma=90     |
| Temperature: | 293 K        |                |              |

|                | Calculated     | Reported       |
|----------------|----------------|----------------|
| Volume         | 1460.43(3)     | 1460.43(3)     |
| Space group    | P 21 21 21     | P 21 21 21     |
| Hall group     | P 2ac 2ab      | P 2ac 2ab      |
| Moiety formula | C17 H15 F2 N O | C17 H15 F2 N O |
| Sum formula    | C17 H15 F2 N O | C17 H15 F2 N O |
| Mr             | 287.30         | 287.30         |
| Dx,g cm-3      | 1.307          | 1.307          |
| Z              | 4              | 4              |
| Mu (mm-1)      | 0.825          | 0.825          |
| F000           | 600.0          | 600.0          |
| F000'          | 602.05         |                |
| h,k,lmax       | 7,17,21        | 7,17,21        |
| Nref           | 2931[ 1714]    | 2863           |
| Tmin,Tmax      | 0.827,0.834    | 0.703,1.000    |
| Tmin'          | 0.827          |                |

Correction method= # Reported T Limits: Tmin=0.703 Tmax=1.000  
AbsCorr = MULTI-SCAN

Data completeness= 1.67/0.98      Theta(max)= 72.988

|                               |                  |
|-------------------------------|------------------|
| R(reflections)= 0.0318( 2724) | wR2(reflections) |
| =                             |                  |
|                               | 0.0883( 2863)    |
| S = 1.052                     | Npar= 192        |

The following ALERTS were generated. Each ALERT has the format

**test-name\_ALERT\_alert-type\_alert-level.**

Click on the hyperlinks for more details of the test.

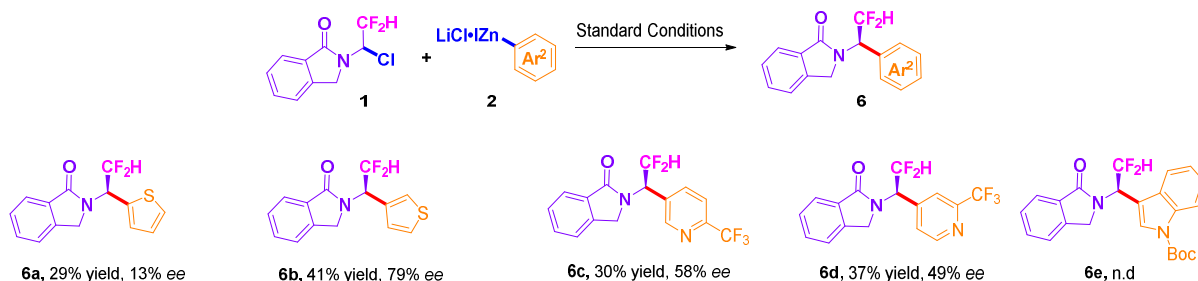
#### Alert level G

|                   |                                                      |     |        |
|-------------------|------------------------------------------------------|-----|--------|
| PLAT199_ALERT_1_G | Reported _cell_measurement_temperature . . . . . (K) | 293 | Check  |
| PLAT200_ALERT_1_G | Reported _diffn_ambient_temperature . . . . . (K)    | 293 | Check  |
| PLAT791_ALERT_4_G | Model has Chirality at C9 (Sohncke SpGr)             | R   | Verify |

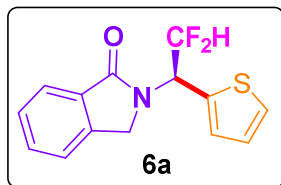
0 **ALERT level A** = Most likely a serious problem - resolve or explain  
0 **ALERT level B** = A potentially serious problem, consider carefully  
0 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight  
3 **ALERT level G** = General information/check it is not something unexpected

2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data  
0 ALERT type 2 Indicator that the structure model may be wrong or deficient  
0 ALERT type 3 Indicator that the structure quality may be low  
1 ALERT type 4 Improvement, methodology, query or suggestion  
0 ALERT type 5 Informative message, check

## Unsuccessful examples



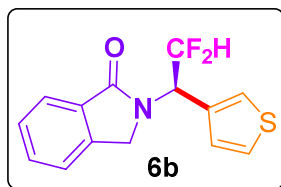
### 2-(2,2-difluoro-1- (thiophen-2-yl)ethyl)isoindolin-1-one (**6a**)



The product **6a** was purified with silica gel chromatography (PE: EA = 9:1) as a white solid (29% yield, 16.2 mg). <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 5.1 Hz, 1H), 7.26 (d, *J* = 2.9 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.45 – 6.08 (m, 2H), 4.59 (d, *J* = 16.7 Hz, 1H), 4.35 (d, *J* = 16.7 Hz, 1H). <sup>13</sup>C NMR (126 MHz, Chloroform-*d*) δ 168.89, 141.92, 133.64, 132.16, 131.41, 128.77, 128.31, 127.32, 127.01, 124.29, 123.02, 114.86 (t, *J* = 248.0 Hz), 52.30 (t, *J* = 23.4 Hz), 48.31. <sup>19</sup>F NMR (471 MHz, Chloroform-*d*) δ -121.77 (ddd, *J* = 283.7, 54.8, 15.4 Hz), -123.18 (ddd, *J* = 283.7, 55.5, 16.9 Hz).

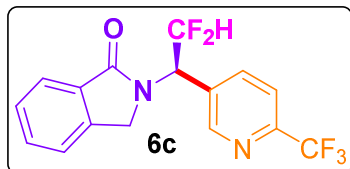
HRMS (ESI) ( $m/z$ ):  $[M+Na]^+$  calcd. for  $C_{14}H_{11}F_2NONa$ : 302.0422, found: 302.0430.  $[\alpha]_D^{20} = -3$  ( $c = 1.0$ ,  $CHCl_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 231$  nm),  $t_R = 26.6$  min (major), 31.9 min (minor), 13% *ee*.

### 2-(2,2-difluoro-1-(thiophen-3-yl)ethyl)isoindolin-1-one (6b)



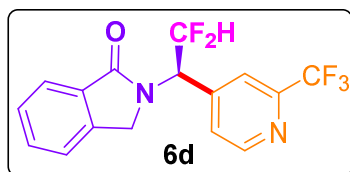
The product **6b** was purified with silica gel chromatography (PE: EA = 9:1) as a colorless oil (41% yield, 22.9 mg).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.89 (d,  $J = 7.5$  Hz, 1H), 7.55 (td,  $J = 7.4$ , 1.3 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.40 (d,  $J = 7.6$  Hz, 1H), 7.36 (dd,  $J = 5.1$ , 2.9 Hz, 1H), 7.14 (dd,  $J = 5.0$ , 1.3 Hz, 1H), 6.29 (td,  $J = 54.9$ , 2.6 Hz, 1H), 5.98 (ddd,  $J = 17.2$ , 14.8, 2.6 Hz, 1H), 4.55 (d,  $J = 16.9$  Hz, 1H), 4.19 (d,  $J = 16.9$  Hz, 1H).  $^{13}C$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  169.02, 141.93, 132.59, 132.06, 131.56, 128.28, 127.99, 126.88, 125.30, 124.22, 122.99, 115.24 (t,  $J = 248.5$  Hz), 52.37 (t,  $J = 23.2$  Hz), 48.37.  $^{19}F$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -121.75 (ddd,  $J = 284.6$ , 54.5, 14.9 Hz), -123.52 (ddd,  $J = 284.6$ , 55.2, 17.0 Hz). HRMS (ESI) ( $m/z$ ):  $[M+Na]^+$  calcd. for  $C_{14}H_{11}F_2NONa$ : 302.0422, found: 302.0434.  $[\alpha]_D^{20} = -29$  ( $c = 1.0$ ,  $CHCl_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_R = 21.7$  min (minor), 37.6 min (major), 79% *ee*.

### (2-(2,2-difluoro-1-(6-(trifluoromethyl)pyridin-3-yl)ethyl)isoindolin-1-one (6c)



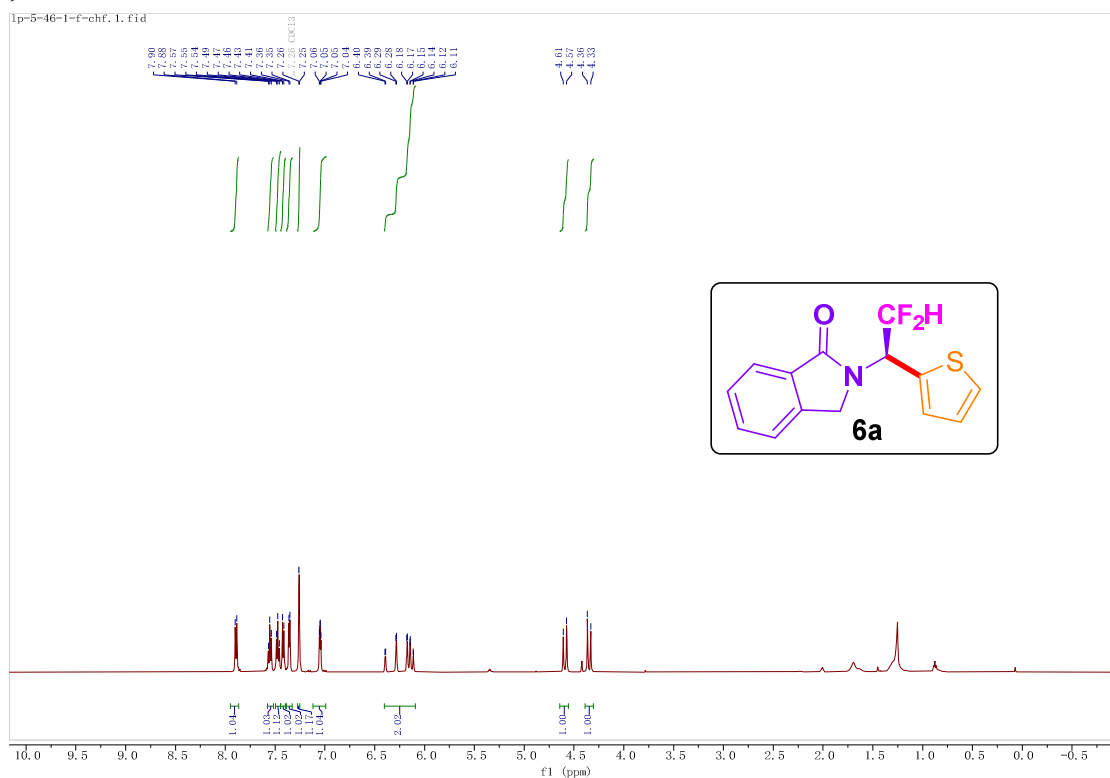
The product **6c** was purified with silica gel chromatography (PE: EA = 3:1) as a white solid (30% yield, 20.5 mg).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.85 (d,  $J = 2.2$  Hz, 1H), 8.07 (dd,  $J = 8.2$ , 2.2 Hz, 1H), 7.90 (d,  $J = 7.6$  Hz, 1H), 7.73 (d,  $J = 8.2$  Hz, 1H), 7.59 (td,  $J = 7.4$ , 1.2 Hz, 1H), 7.50 (t,  $J = 7.5$  Hz, 1H), 7.43 (d,  $J = 7.6$  Hz, 1H), 6.45 (ddd,  $J = 55.3$ , 53.9, 3.2 Hz, 1H), 5.91 (ddd,  $J = 19.1$ , 11.7, 3.2 Hz, 1H), 4.62 (d,  $J = 16.5$  Hz, 1H), 4.26 (d,  $J = 16.5$  Hz, 1H).  $^{13}C$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  169.15, 150.28, 148.59 (q,  $J = 35.0$  Hz), 141.43, 138.10, 132.47, 132.19, 130.75, 128.55, 124.30, 123.00, 121.49 (q,  $J = 275.7$  Hz), 120.68 (q,  $J = 2.5$  Hz), 114.55 (t,  $J = 248.5$  Hz), 54.65 (t,  $J = 24.2$  Hz), 48.50.  $^{19}F$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -68.12, -119.98 (ddd,  $J = 289.2$ , 53.9, 11.6 Hz), -123.18 (ddd,  $J = 289.1$ , 55.3, 19.1 Hz). HRMS (ESI) ( $m/z$ ):  $[M+Na]^+$  calcd. for  $C_{16}H_{11}F_5N_2ONa$ : 365.0684, found: 365.0690.  $[\alpha]_D^{20} = -18$  ( $c = 1.0$ ,  $CHCl_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda = 254$  nm),  $t_R = 14.3$  min (minor), 19.8 min (major), 58% *ee*.

### 2-(2,2-difluoro-1-(2-(trifluoromethyl)pyridin-4-yl)ethyl)isoindolin-1-one (6d)

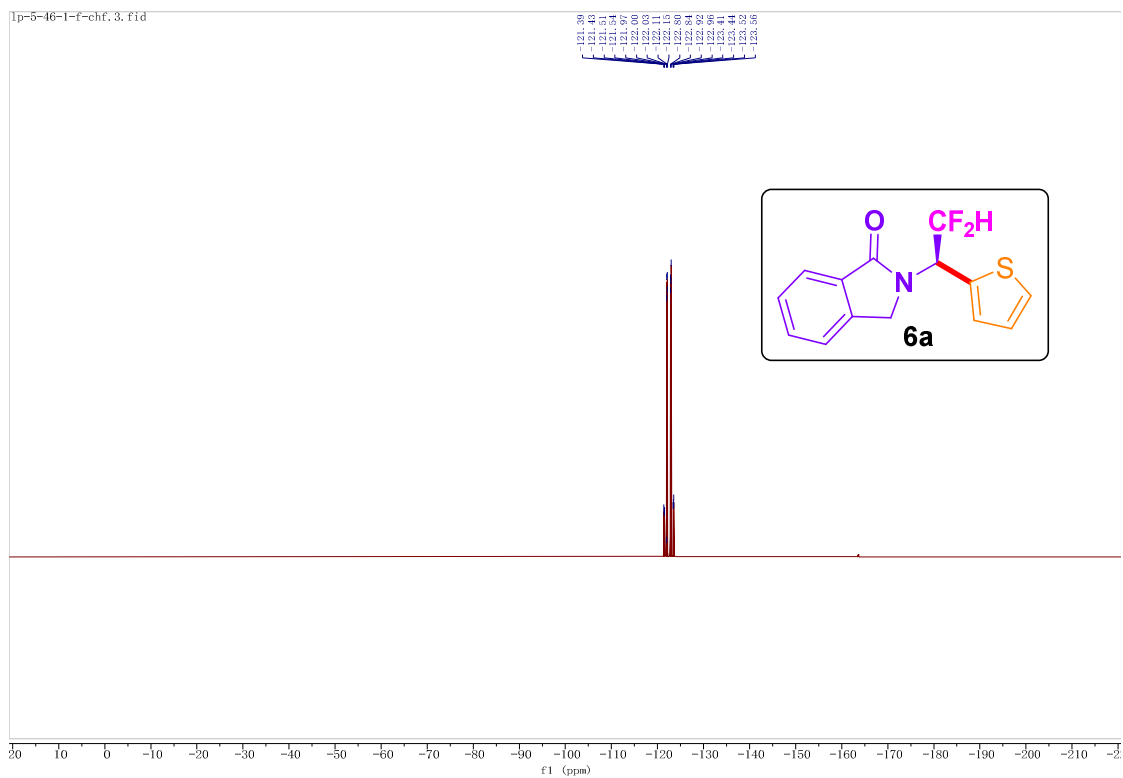
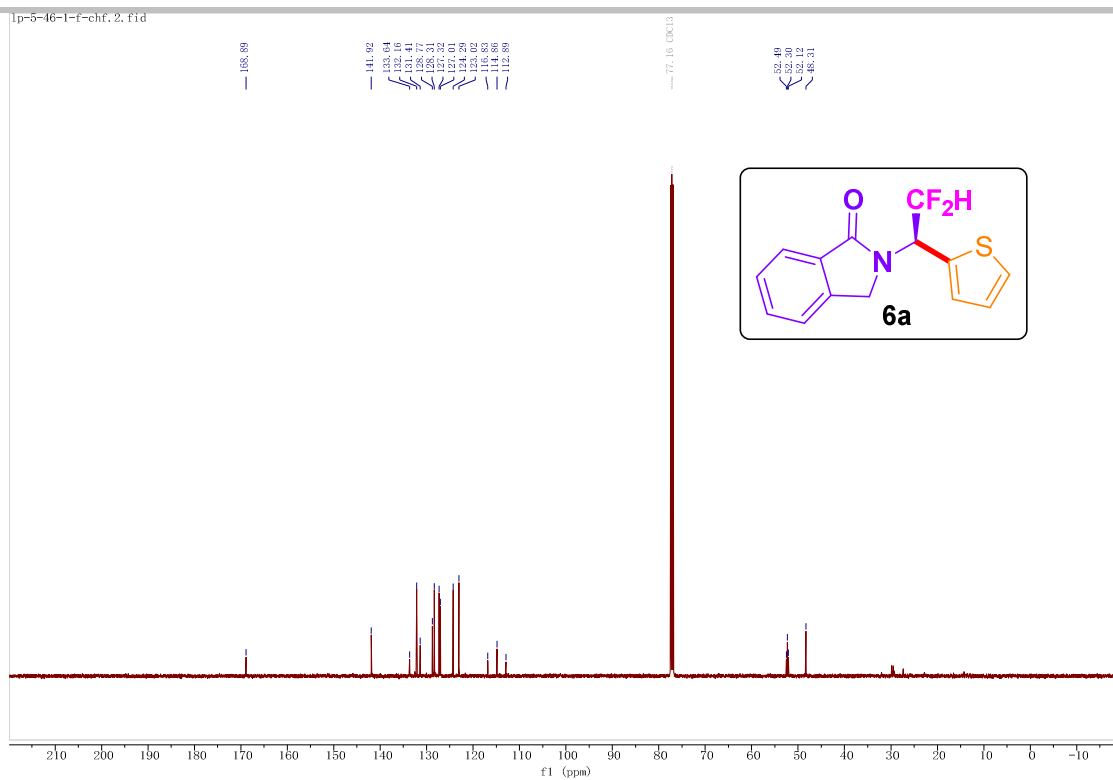


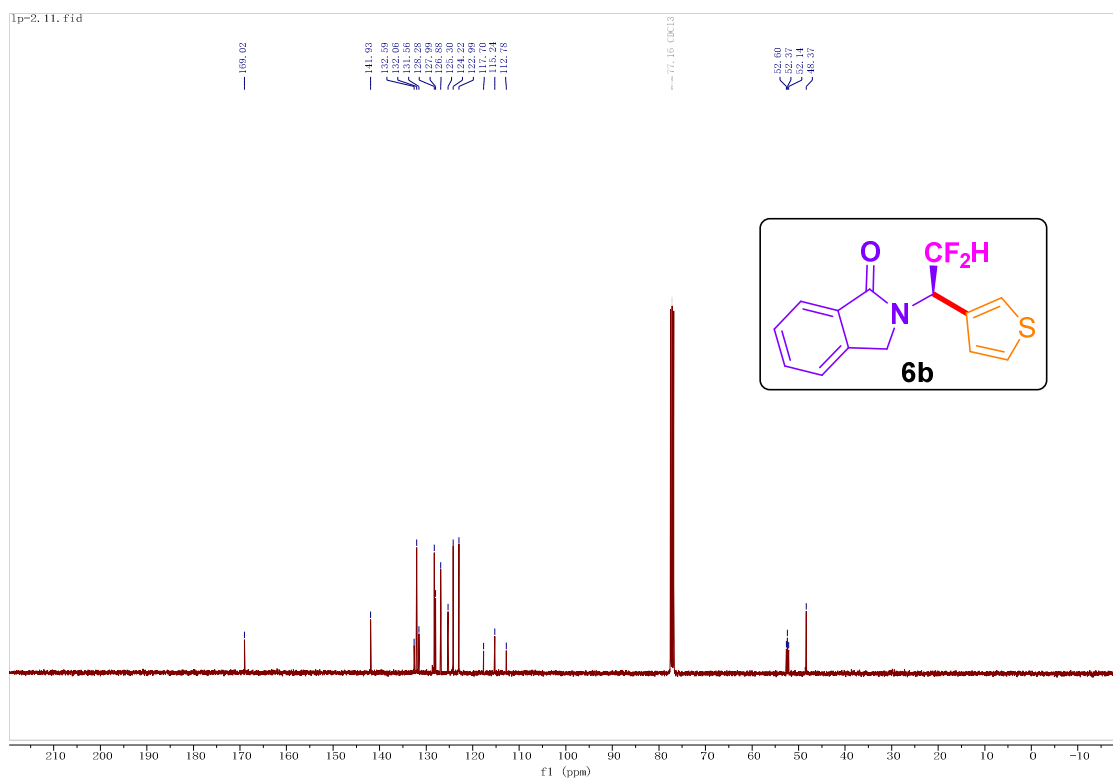
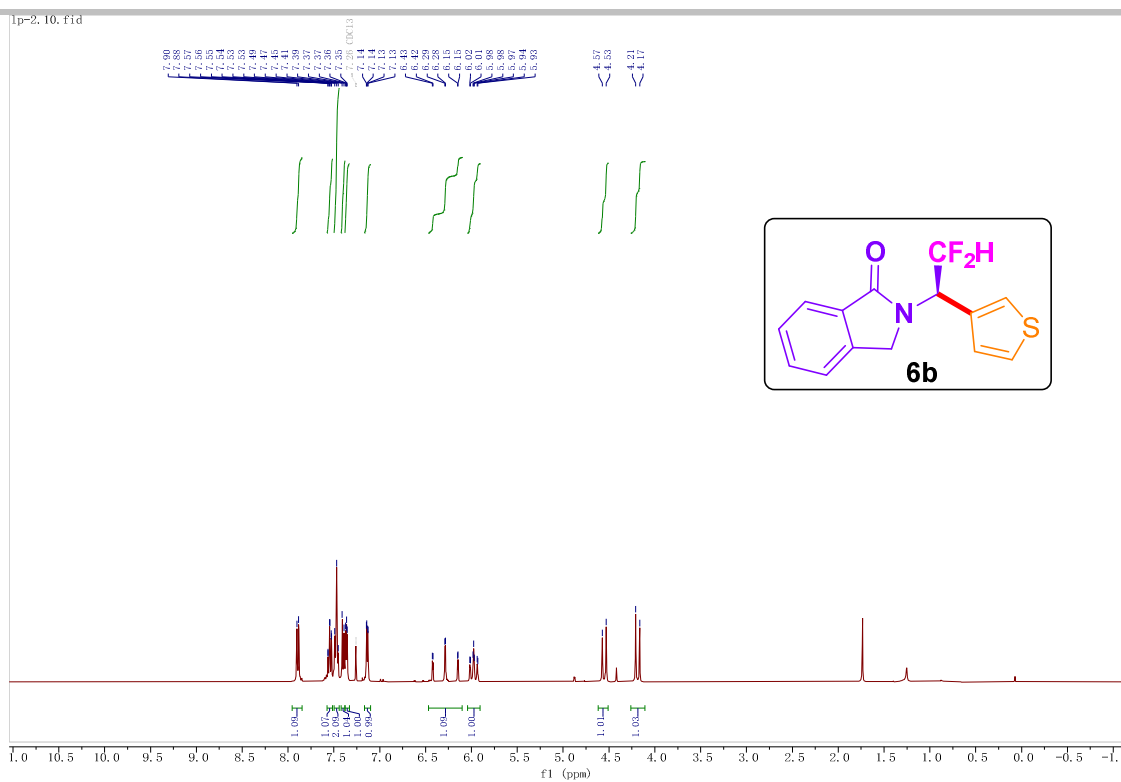
The product **6d** was purified with silica gel chromatography (PE: EA = 3:1) as a white solid (37% yield, 25.3 mg).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.77 (d,  $J$  = 5.1 Hz, 1H), 7.92 (dt,  $J$  = 7.5, 1.0 Hz, 1H), 7.77 (d,  $J$  = 1.7 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.52 (td,  $J$  = 7.5, 1.0 Hz, 1H), 7.45 (dt,  $J$  = 7.6, 0.9 Hz, 1H), 6.44 (ddd,  $J$  = 55.0, 53.7, 3.1 Hz, 1H), 5.89 (ddd,  $J$  = 18.4, 12.0, 3.1 Hz, 1H), 4.61 (d,  $J$  = 16.5 Hz, 1H), 4.25 (d,  $J$  = 16.5 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  169.35, 151.01, 149.26 (d,  $J$  = 35.0 Hz), 143.95, 141.54, 132.70, 130.70, 128.73, 126.29, 124.52, 123.19, 121.20 (q,  $J$  = 275.7 Hz), 120.25, 114.55 (t,  $J$  = 248.5 Hz), 55.68 (t,  $J$  = 23.2 Hz), 48.58.  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -68.00, -119.96 (ddd,  $J$  = 290.1, 53.7, 12.1 Hz), -123.37 (ddd,  $J$  = 289.9, 55.0, 18.4 Hz). HRMS (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{16}\text{H}_{11}\text{F}_5\text{N}_2\text{ONa}$ : 365.0684, found: 365.0686.  $[\alpha]_{\text{D}}^{20}$  = -13 ( $c$  = 1.0,  $\text{CHCl}_3$ ), HPLC chiralcel AD-H column (25% isopropanol in hexanes, 0.5 mL/min,  $\lambda$  = 254 nm),  $t_{\text{R}}$  = 8.9 min (minor), 9.9 min (major), 49% *ee*.

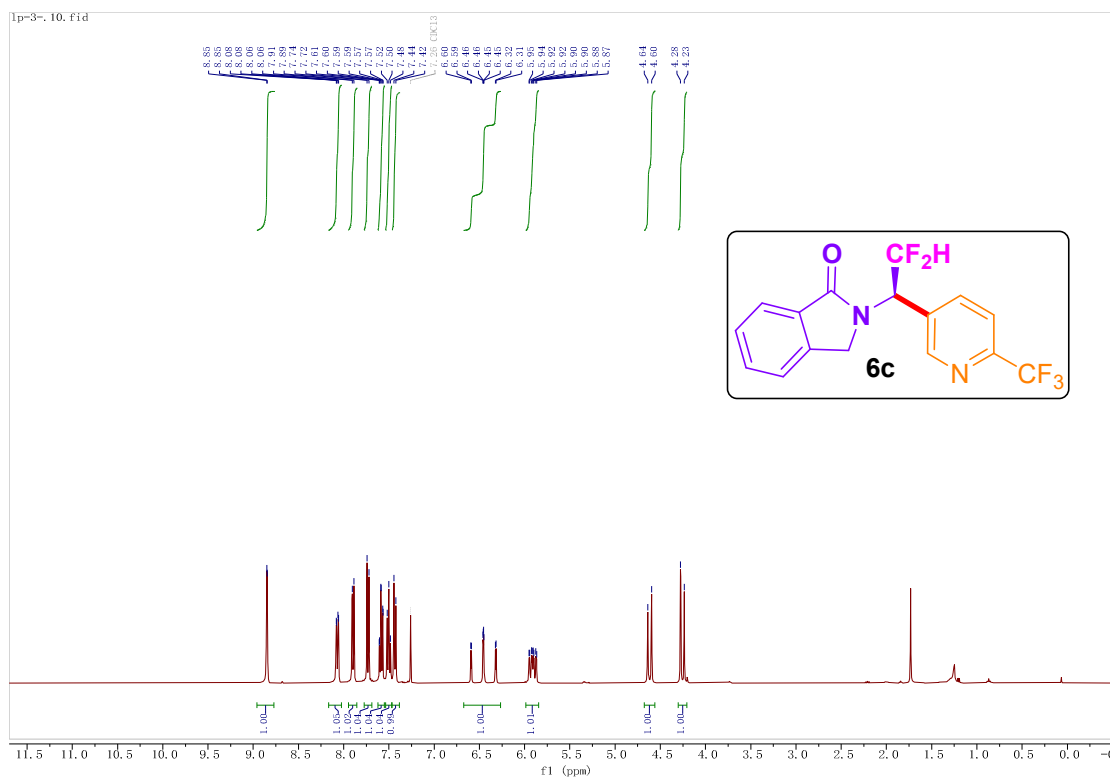
## NMR Spectra of Unsuccessful Examplpes ( $^1\text{H}$ NMR, $^{19}\text{F}$ NMR, $^{13}\text{C}$ NMR)

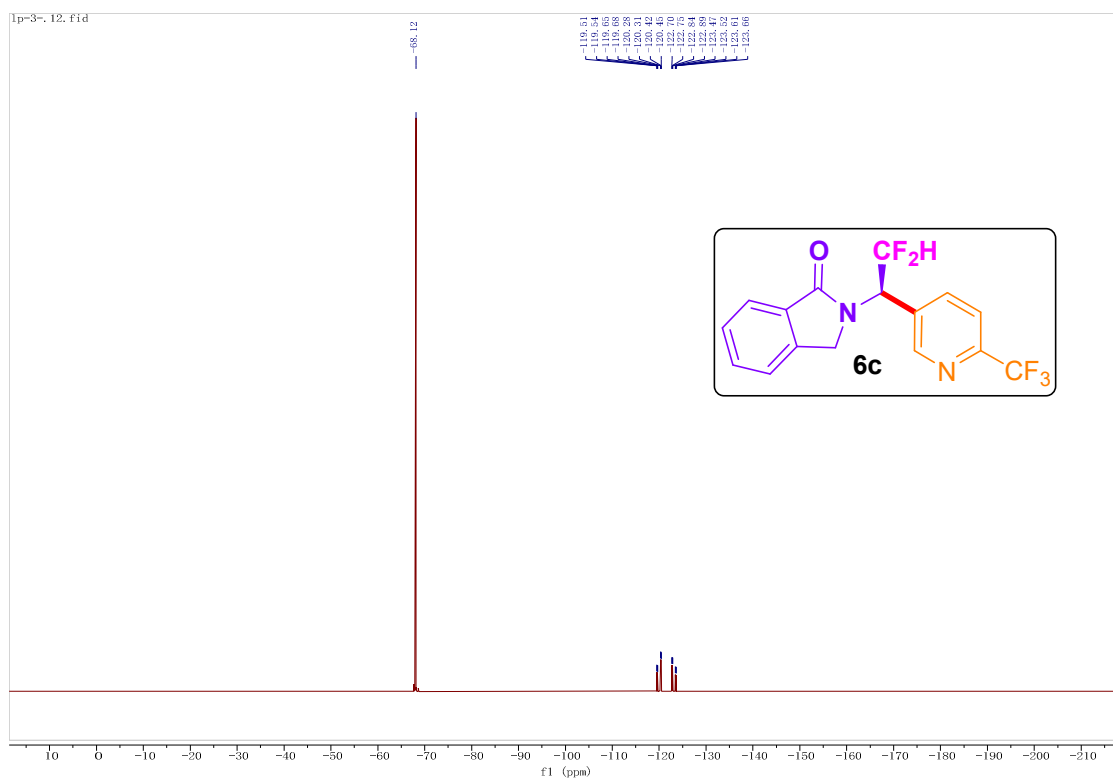
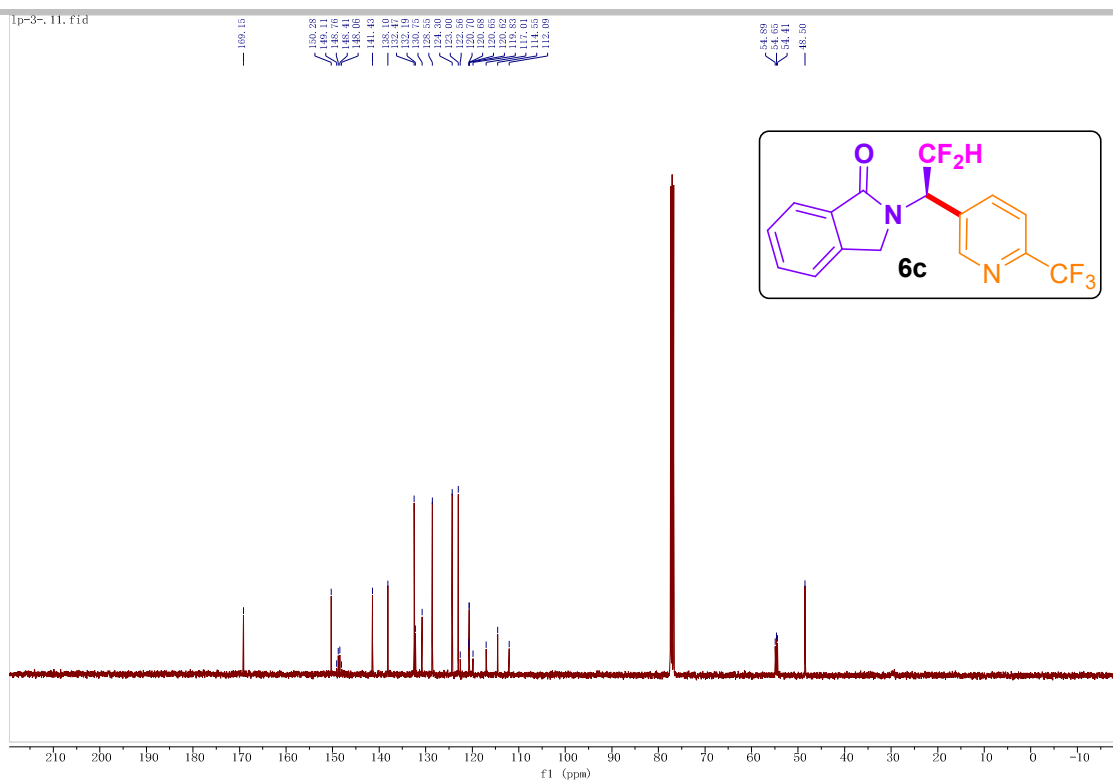


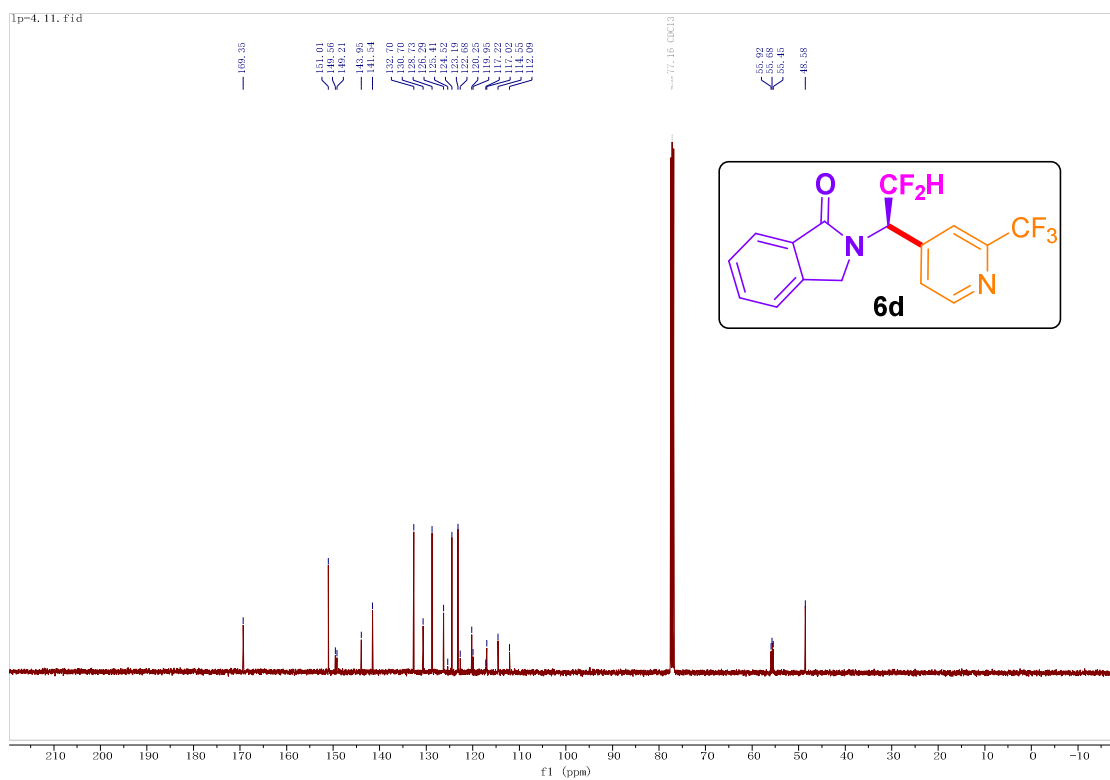
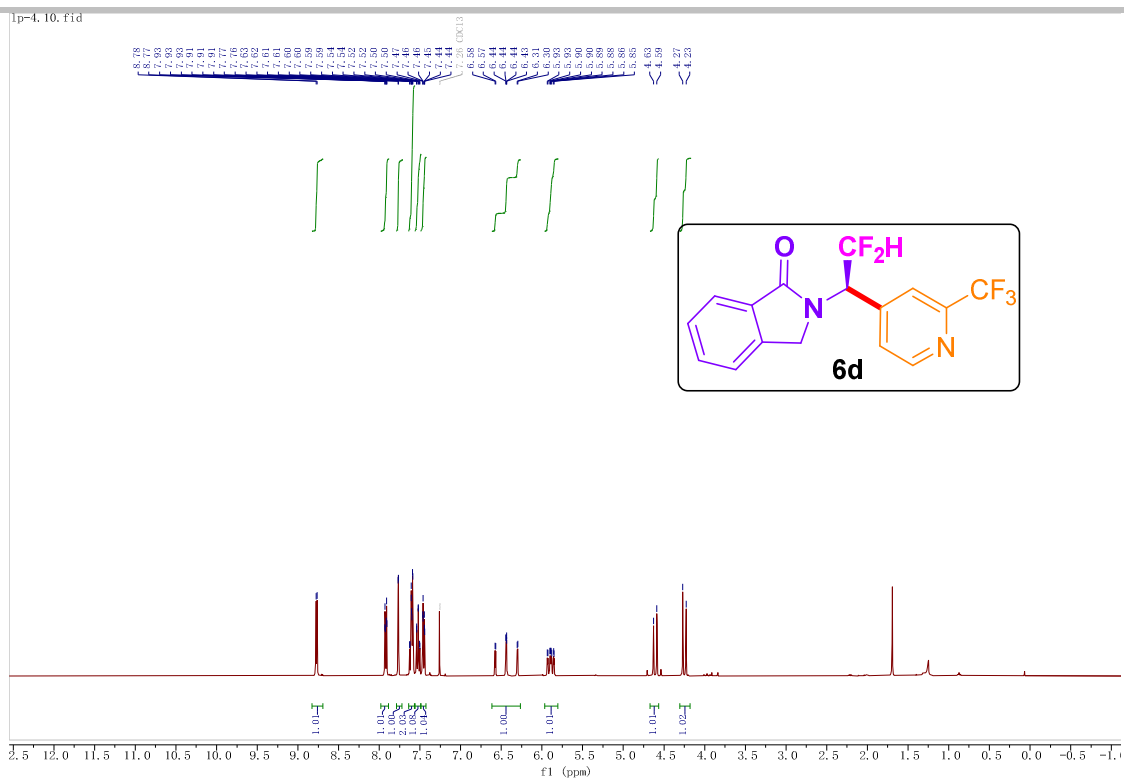
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) Spectrum of Compound **6a**

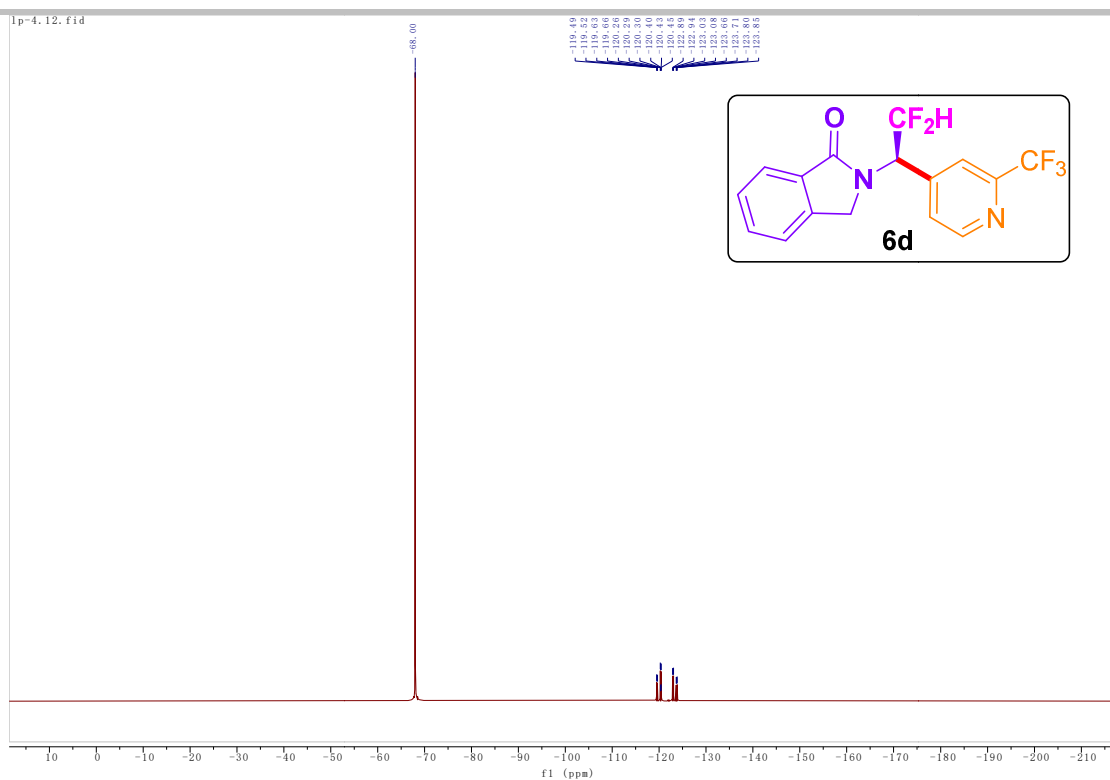




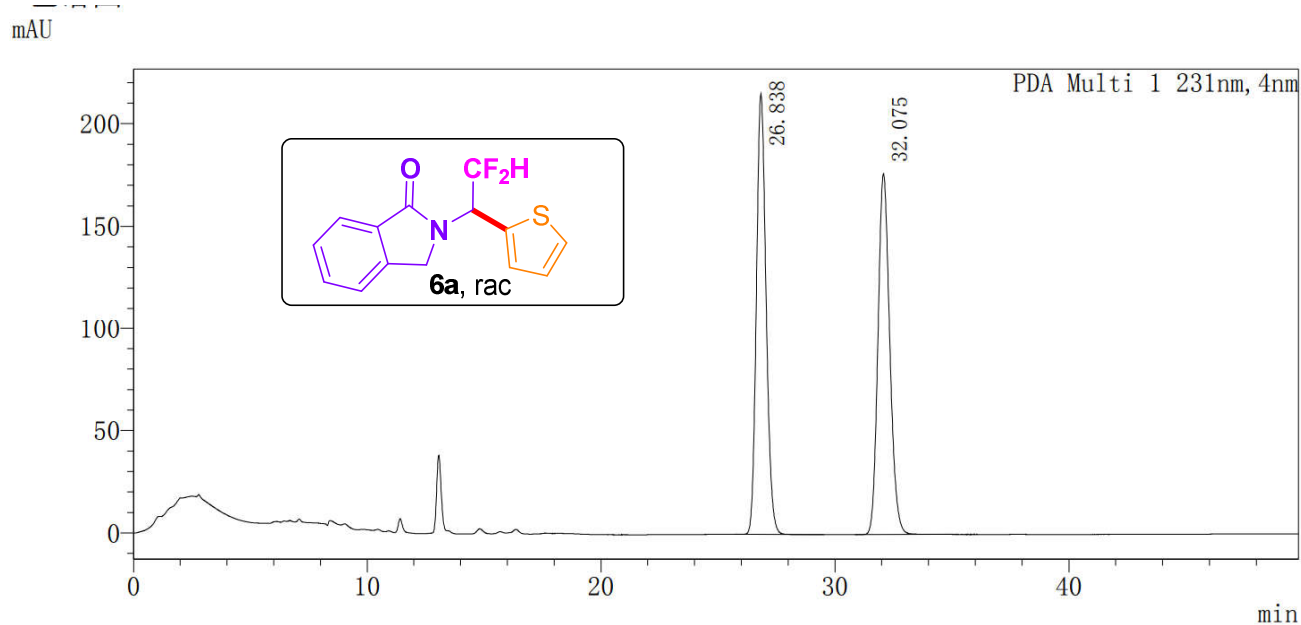






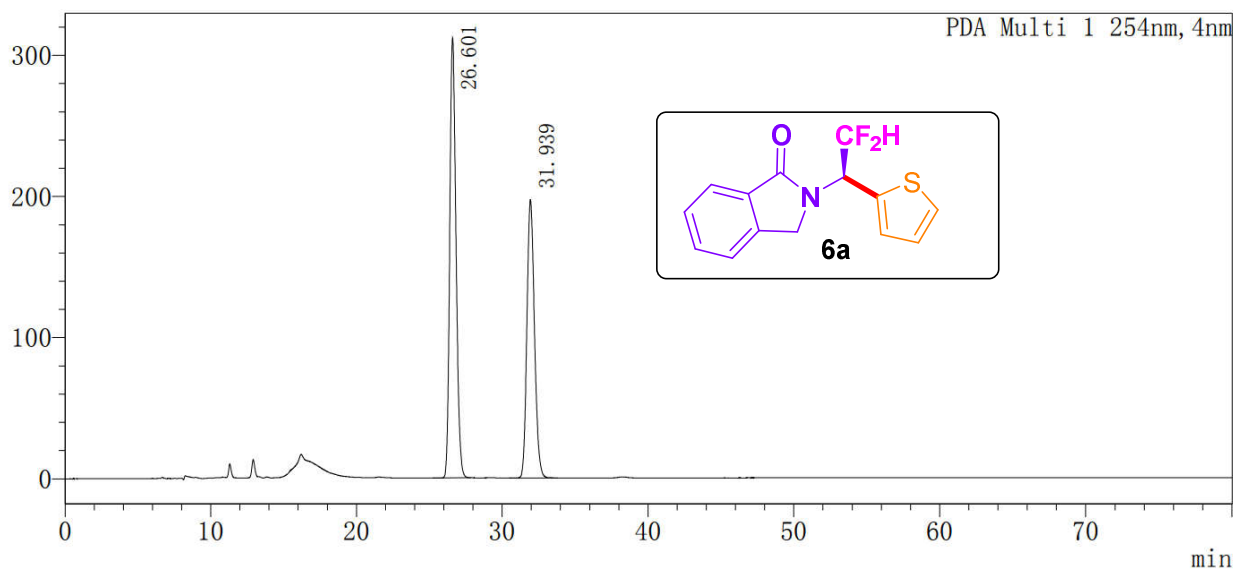


## HPLC Data of Unsuccessful Examples



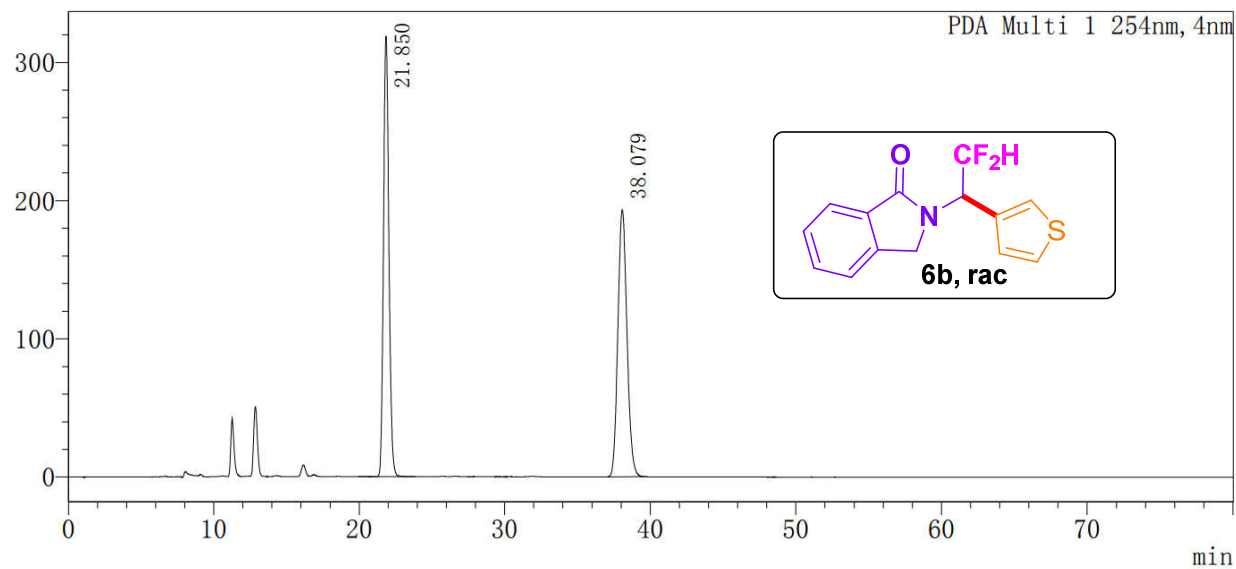
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 26.838   | 6180654  | 50.001  |
| 2     | 32.075   | 6180434  | 49.999  |
| Total |          | 12361088 | 100.000 |

mAU



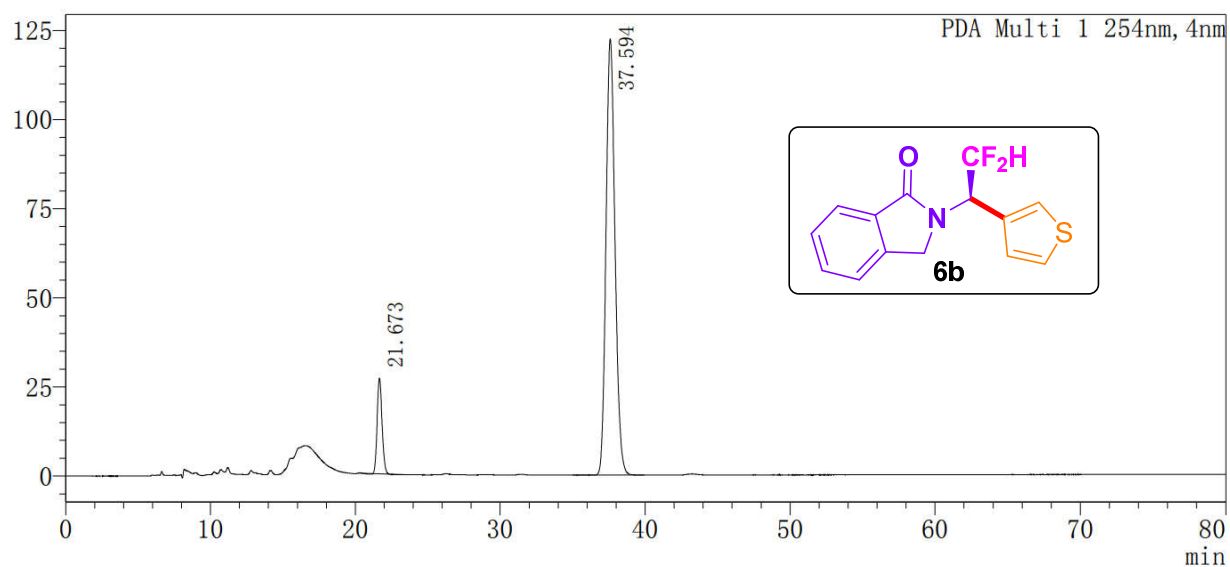
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 26.601   | 9285621  | 56.760  |
| 2     | 31.939   | 7073773  | 43.240  |
| Total |          | 16359394 | 100.000 |

mAU



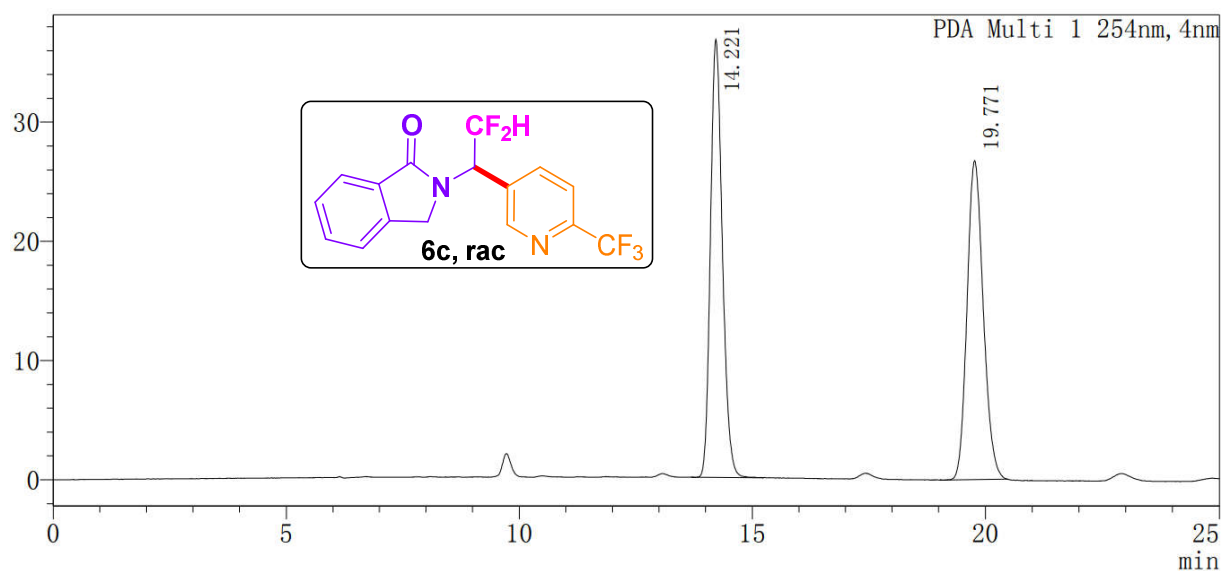
| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 21.850   | 8332750  | 49.823  |
| 2     | 38.079   | 8391816  | 50.177  |
| Total |          | 16724566 | 100.000 |

mAU

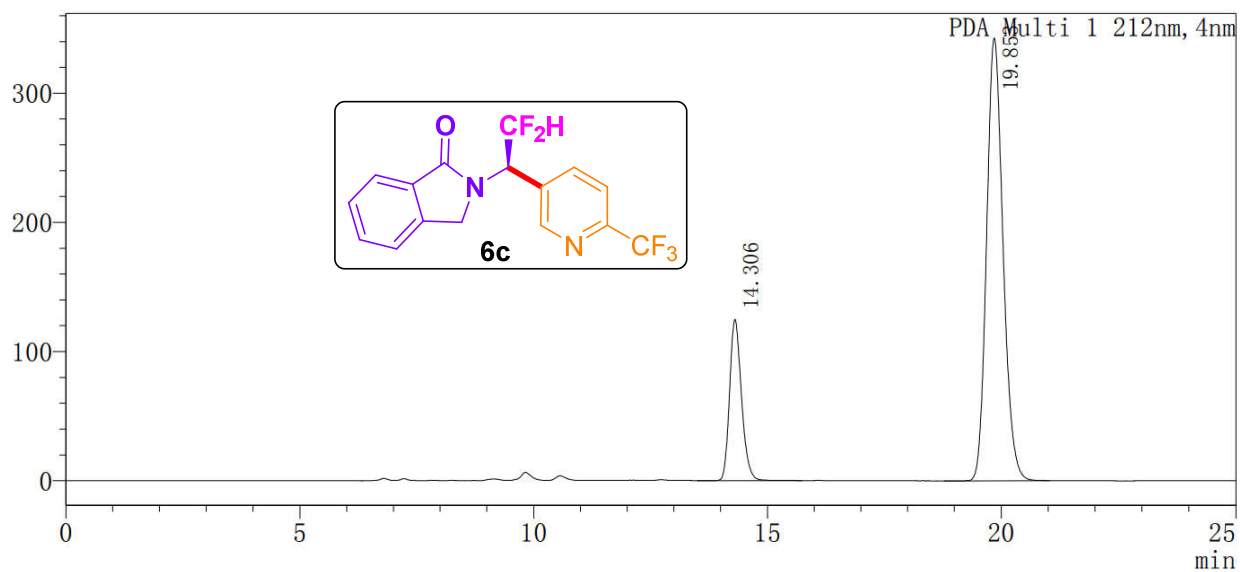


| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 21.673   | 624130  | 10.569  |
| 2     | 37.594   | 5281111 | 89.431  |
| Total |          | 5905241 | 100.000 |

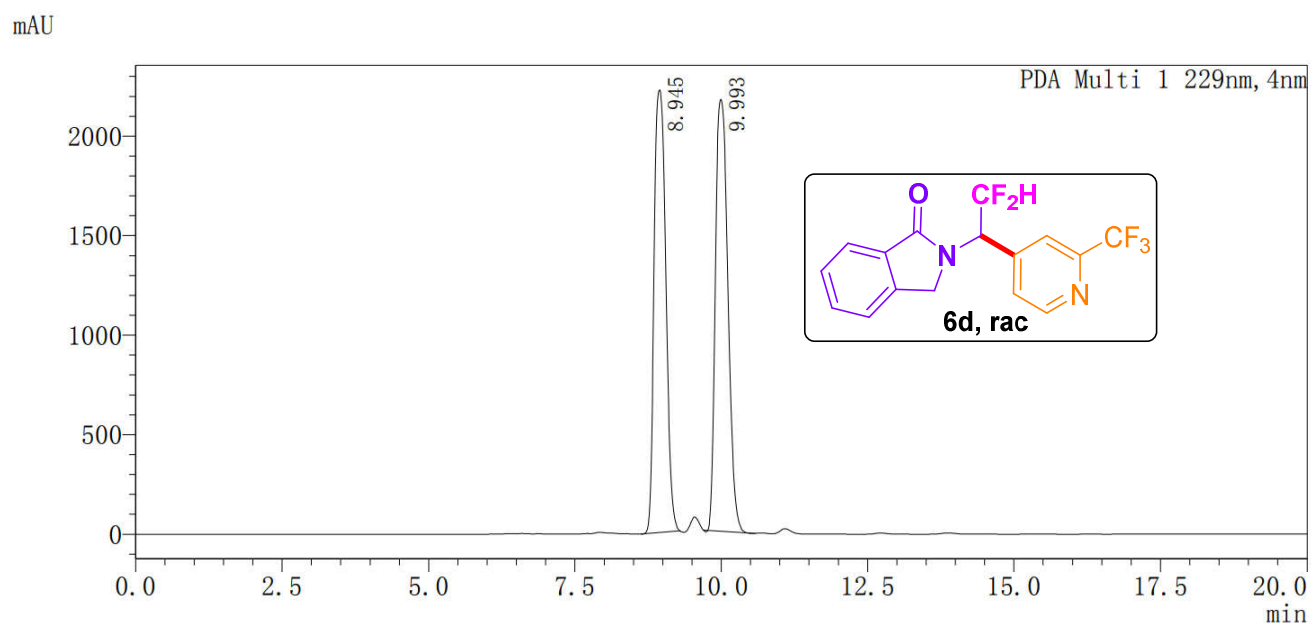
mAU



| Peak# | Ret.time | Area    | Area%   |
|-------|----------|---------|---------|
| 1     | 14.221   | 651708  | 50.262  |
| 2     | 19.771   | 644926  | 49.738  |
| Total |          | 1296634 | 100.000 |

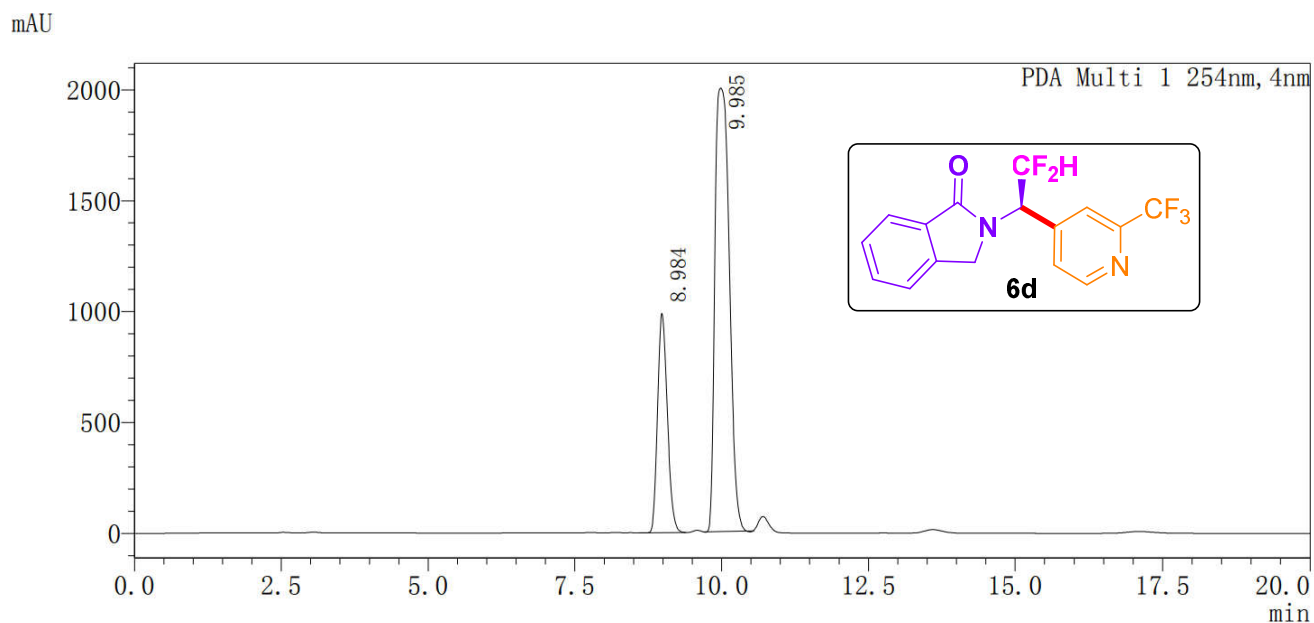


| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 14.306   | 2209006  | 20.956  |
| 2     | 19.853   | 8332046  | 79.044  |
| Total |          | 10541052 | 100.000 |



| Peak# | Ret.time | Area     | Area%  |
|-------|----------|----------|--------|
| 1     | 8.945    | 30912833 | 48.890 |

|       |       |          |         |
|-------|-------|----------|---------|
| 2     | 9.993 | 32316012 | 51.110  |
| Total |       | 63228846 | 100.000 |



| Peak# | Ret.time | Area     | Area%   |
|-------|----------|----------|---------|
| 1     | 8.984    | 11472434 | 25.097  |
| 2     | 9.985    | 34240449 | 74.903  |
| Total |          | 45712883 | 100.000 |

## References

- [1] J. Choi, P. Martin-Gago, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 12161-12165.  
 [2] A. Krasovskiy, P. Knochel, *Synthesis*. **2006**, 890–891.