

**Highly mono-selective *ortho*-trifluoromethylation of benzamides via
8-aminoquinoline assisted Cu-promoted CH-activations**

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Supporting Information

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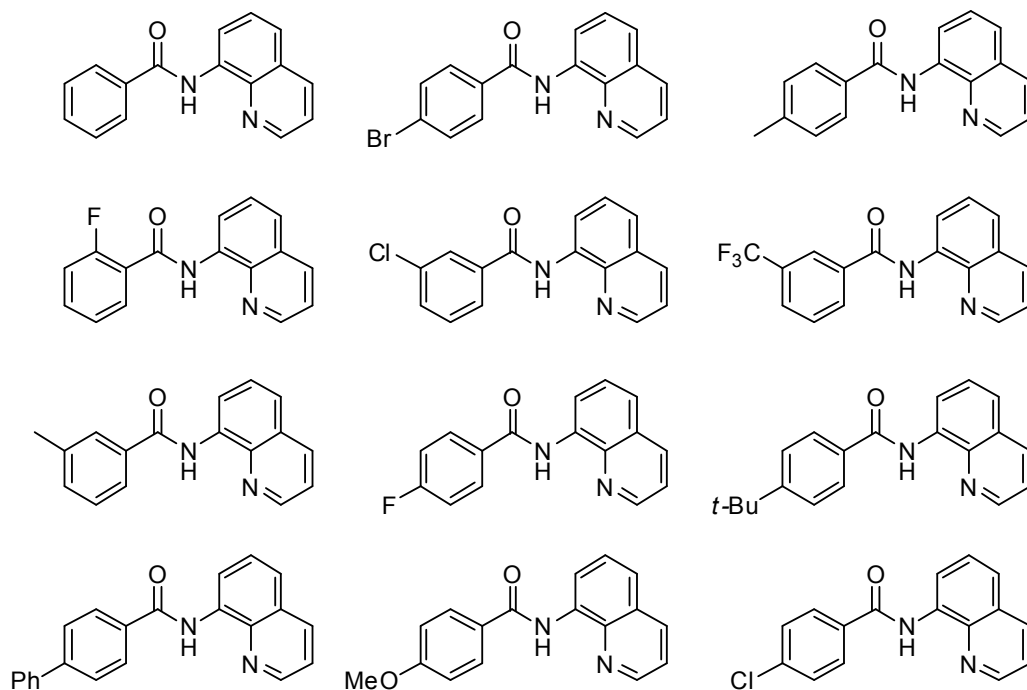
1. General information

^1H NMR, ^{13}C NMR and ^{19}F NMR were recorded in CDCl_3 at room temperature on the Varian INOVA-400 spectrometer (400 MHz, ^1H). The ^1H NMR chemical-shifts scale is based on internal TMS and ^{19}F NMR is referenced using fluorobenzene as a standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; qui, quintet; sxt, sextet. The coupling constants, J are reported in Hertz (Hz). High-resolution mass spectral (HRMS) analyses were carried out using a TOF MS instrument with an ESI source.

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Anhydrous CuBr was purchased from Alfa Aesar. All solvents were purified and dried according to standard methods prior to use. Products were purified by flash column chromatography on 200-300 mesh silica gel, SiO_2 .

2. Typical procedure for the preparation of benzamides

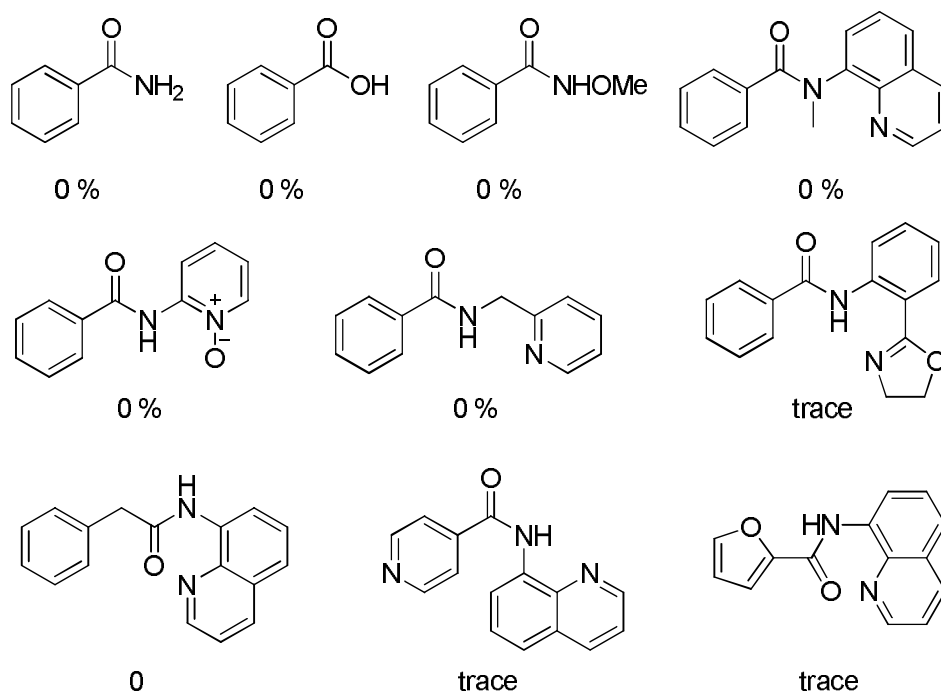
All benzamides were synthesized from the corresponding benzoic acids or benzoyl chlorides and 8-aminoquinoline. The deuterated amides were synthesized according to a literature method, spectral properties are consistent with literature values.¹ The following amides were synthesized according to literature procedures.²



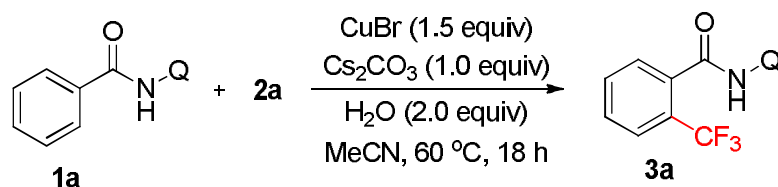
3. Copper-promoted C-H trifluoromethylation

3.1 Optimization of reaction conditions

Scheme S1 ineffective directing groups and substrates

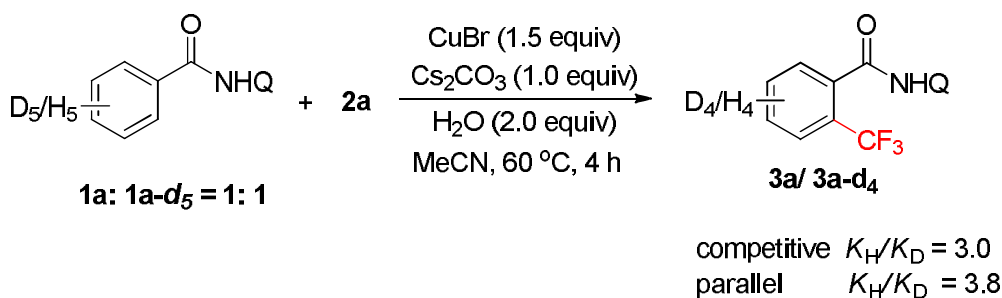


3.2 General procedure for copper-promoted C-H trifluoromethylation



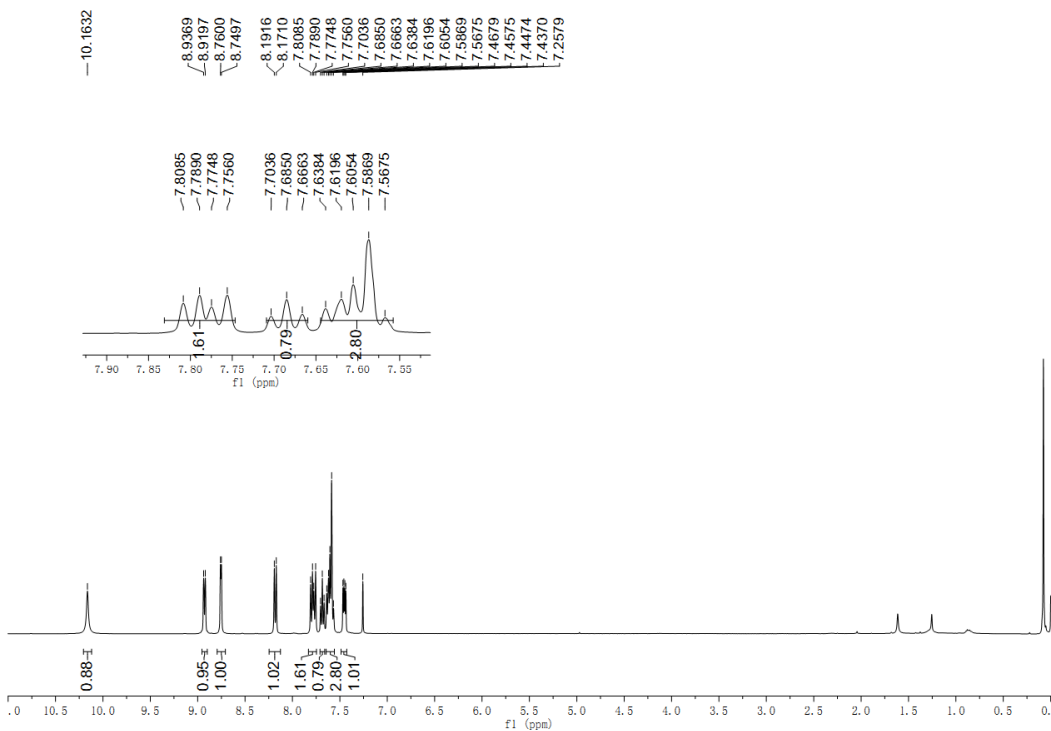
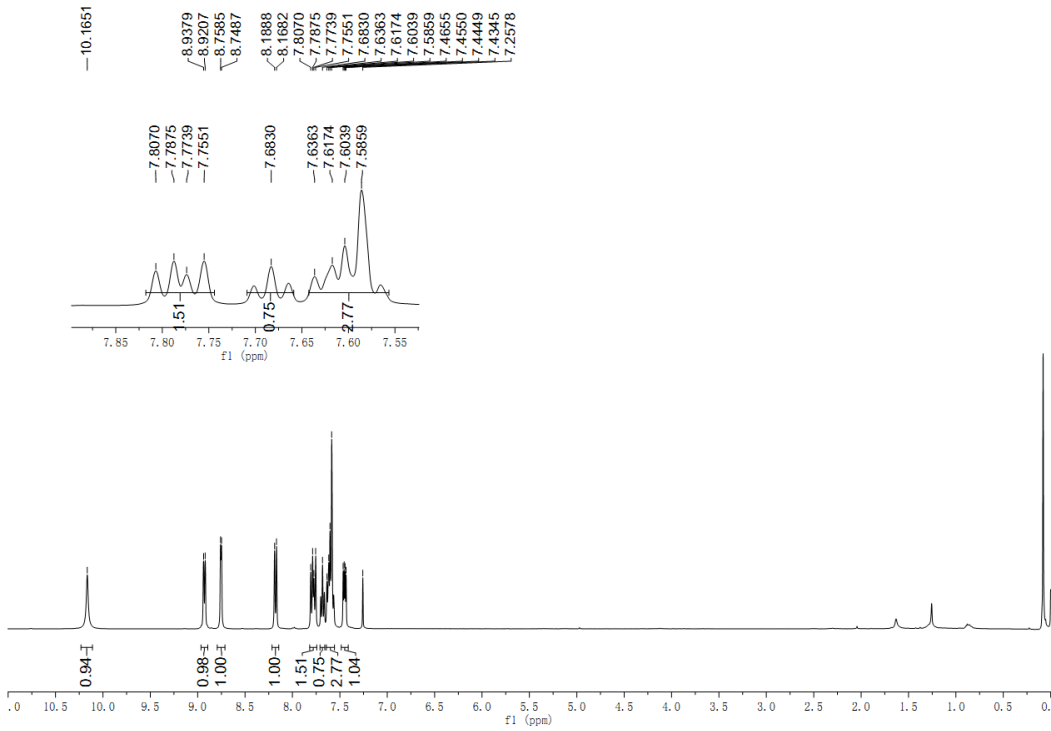
Benzamide **1a** (50 mg, 0.2 mmol), anhydrous CuBr (43 mg, 0.3 mmol), Cs₂CO₃ (65 mg, 0.2 mmol), H₂O (7 mg, 0.4 mmol), Togni reagent II **2a** (95 mg, 0.3 mmol) and anhydrous MeCN (1 mL) were added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed under air and stirred at 60 °C for 18 h. After the completion of the reaction, the solvent was evaporated under reduced pressure. The mixture was extracted with ethyl acetate, and the combined organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with petroleum ether/ethyl acetate eluent (10/1 to 15/1) gave the desired product **3a**.

3.3 Deuterium-labeling experiments

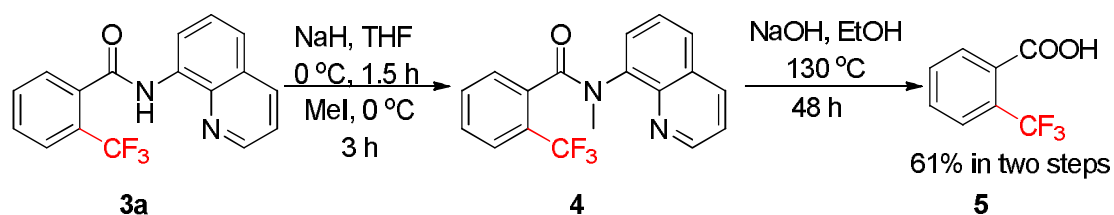


Intermolecular competition KIE Following general procedure: **1a** (50 mg, 0.2 mmol), **1a'**- d_5 (51 mg, 0.2 mmol), CuBr (86 mg, 0.6 mmol), Cs₂CO₃ (130 mg, 0.4 mmol), **2a** (190 mg, 0.6 mmol) and anhydrous MeCN (2 mL) were added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed under N₂ and stirred at 60 °C for 2 h. The product was separated by column chromatography to give the desired product less than 12 % yield. ¹H NMR (400 MHz, CDCl₃): δ 10.09 (s, 1H), 8.85 (d, *J* = 6.9 Hz, 1H), 8.67 (d, *J* = 3.9 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.72–7.68 (m, 1.54H), 7.62–7.60 (m, 0.77H), 7.56–7.51 (m, 2.78H), 7.37 (dd, *J* = 8.2, 4.2 Hz, 1H). The KIE value was calculated as $k_H/k_D = 3.0$.

Intermolecular parallel KIE Following general procedure: **1a** (50 mg, 0.2 mmol) or **1a'**- d_5 (51 mg, 0.2 mmol), CuBr (43 mg, 0.3 mmol), Cs₂CO₃ (65 mg, 0.2 mmol), **2a** (95 mg, 0.3 mmol) and anhydrous MeCN (1 mL) were added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed under N₂ and stirred at 60 °C for 2.5 h. The product was separated by column chromatography to give the desired product less than 17 % yield. ¹H NMR (400 MHz, CDCl₃): δ 10.09 (s, 1H), 8.85 (d, *J* = 6.9 Hz, 1H), 8.67 (d, *J* = 3.9 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.72–7.68 (m, 1.61H), 7.62–7.60 (m, 0.8H), 7.56–7.51 (m, 2.81H), 7.37 (dd, *J* = 8.2, 4.2 Hz, 1H). The KIE value was calculated as $k_H/k_D = 3.8$.



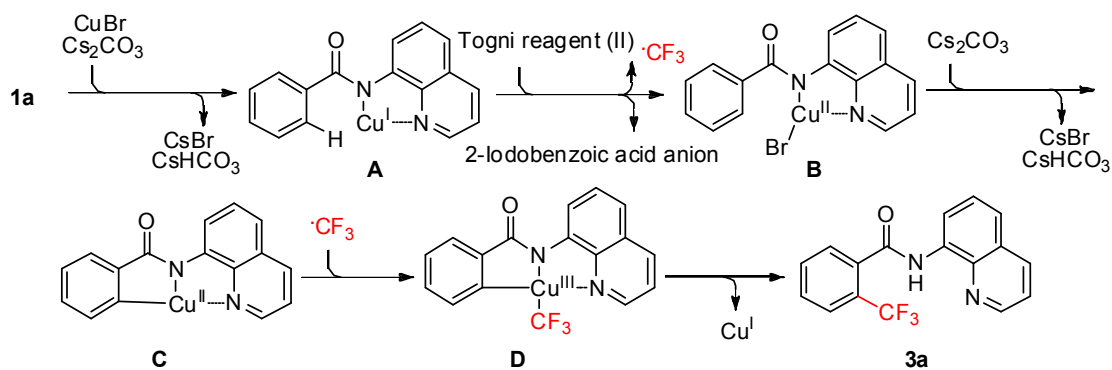
3.4 Removal of directing group



2-(trifluoromethyl)-N-(quinolin-8-yl)benzamide (3a) (316 mg, 1 mmol) was dissolved in anhydrous THF (10 mL) and the resulting solution was cooled to 0 °C. To this solution, NaH (80 mg, 2 mmol) was added in portions over 10 min. The resulting solution was allowed to stir for 1.5 h. MeI (710 mg, 5 mmol) was added dropwise over 5 min, and reaction mixture was stirred for additional 3 hours at 0 °C and stirred overnight at rt. After the reaction was quenched by addition water, the mixture was extracted with Et₂O, and the organic layer was dried by anhydrous Na₂SO₄. After remove the solvent, the residue was purified by column chromatography to give intermediate **4** as white solid (264 mg, 80%). Intermediate **4** (165 mg, 0.5 mmol) and NaOH (307 mg, 7.5 mmol) were dissolved in EtOH (5 ml). The resulting mixture was stirred at 130 °C for 48 hours. After that, reaction mixture was diluted with EtOAc (100 mL) and 1 N HCl (30mL) was added. Organic layer was washed with 1N HCl (5 x 20 mL), dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under vacuum affording pure product as a white solid (61% in two steps).

3.5 A Possible mechanism

Based on the reported literatures^{9f,20} and the evidence above, a plausible mechanism for the copper promoted trifluoromethylation of C-H bond of *N*-(quinolin-8-yl)benzamides is depicted in Scheme 4. Firstly, complex **A** is generated from **1a** and copper(I) bromide in the presence of base. Next the generated Cu(I)-complex **A** reacts with Togni reagent **2a** to form a Cu(II)-complex **B** and a trifluoromethyl radical. Alternatively, the sequence of these two steps can be reversed in order. Cu(II)-complex **B** next undergoes CH-activation to generate a aryl-Cu(II) complex **C** which subsequently reacts with trifluoromethyl radical to give a Cu(III)-complex **D**. Finally reductive elimination of Cu(III)-complex **D** affords the desired product **3a**.

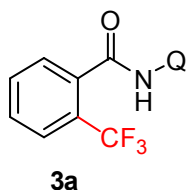


Scheme 4 A possible mechanism.

4. Characterization data of products

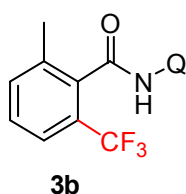
2-trifluoromethyl-N-(quinolin-8-yl)benzamide (3a)³

Compound 3a: 46 mg, 73% yield, white solid, mp: 103–105 °C (from ethyl acetate/petroleum ether = 12:1); $R_f = 0.51$ (petroleum ether/ethyl acetate = 8:1); ¹H NMR (400 MHz, CDCl₃): δ 10.07 (s, 1H), 8.83 (d, $J = 7.0$ Hz, 1H), 8.64 (d, $J = 4.0$ Hz, 1H), 8.05 (d, $J = 8.2$ Hz, 1H), 7.69–7.64 (m, 2H), 7.58–7.54 (m, 1H), 7.51–7.45 (m, 3H), 7.33 (dd, $J = 8.2, 4.2$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 165.9, 148.3, 138.4, 136.3, 136.1 (q, $J = 2.0$ Hz), 134.3, 132.1, 130.1, 128.4, 127.9, 127.6 (q, $J = 31.8$ Hz), 127.3, 126.6 (q, $J = 4.9$ Hz), 123.6 (q, $J = 272.0$ Hz), 122.2, 121.7, 116.8; ¹⁹F NMR (375 MHz, CDCl₃): δ -58.8; HRMS (ESI) calcd for C₁₇H₁₂F₃N₂O (M + H)⁺ 317.0902, found 317.0895.



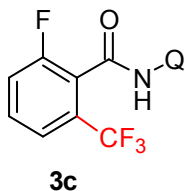
2-trifluoromethyl-6-methyl-N-(quinolin-8-yl)benzamide (3b)

Compound 3b: 50 mg, 75% yield, white solid, mp: 153–155 °C (from ethyl acetate/petroleum ether = 12:1); $R_f = 0.48$ (petroleum ether/ethyl acetate = 8:1); ¹H NMR (400 MHz, CDCl₃): δ 9.91 (s, 1H), 8.88 (d, $J = 7.0$ Hz, 1H), 8.66 (d, $J = 3.2$ Hz, 1H), 8.10 (d, $J = 8.2$ Hz, 1H), 7.55–7.49 (m, 3H), 7.40–7.36 (m, 3H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 165.8, 148.3, 138.4, 136.7, 136.3, 135.4 (q, $J = 2.0$ Hz), 134.1, 129.2, 128.0, 127.3 (q, $J = 31.3$ Hz), 125.2, 123.8 (q, $J = 272.2$ Hz), 123.7 (q, $J = 4.8$ Hz), 122.5, 122.3, 121.7, 117.0, 19.3; ¹⁹F NMR (375 MHz, CDCl₃): δ



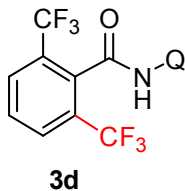
-58.9; HRMS (ESI) calcd for $C_{18}H_{14}F_3N_2O$ ($M + H$)⁺ 331.1058, found 331.1056.

2-fluoro-6-trifluoromethyl-*N*-(quinolin-8-yl)benzamide (**3c**)⁴



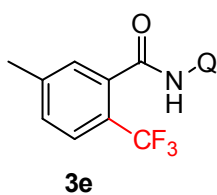
Compound 3c: 45 mg, 67% yield, white solid, mp: 167–169 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.54 (petroleum ether/ethyl acetate = 8:1); ¹H NMR (400 MHz, CDCl₃): δ 10.07 (s, 1H), 8.86 (dd, J = 5.9, 2.8 Hz, 1H), 8.69 (d, J = 3.9 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.54–7.52 (m, 4H), 7.40–7.35 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 160.5, 159.4 (d, J = 248.7 Hz), 148.4, 138.3, 136.4, 134.0, 131.4 (d, J = 8.5 Hz), 127.9, 127.4, 124.1 (q, J = 272.2 Hz), 122.5, 122.2 (q, J = 4.5 Hz), 121.8, 120.1, 119.9, 117.1; ¹⁹F NMR (375 MHz, CDCl₃): δ -59.2, -113.1; HRMS (ESI) calcd for $C_{17}H_{11}F_4N_2O$ ($M + H$)⁺ 335.0808, found 335.0805.

2, 6-ditrifluoromethyl-*N*-(quinolin-8-yl)benzamide (**3d**)



Compound 3d: 50 mg, 65% yield, white solid, mp: 177–179 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.60 (petroleum ether/ethyl acetate = 8:1); ¹H NMR (400 MHz, CDCl₃): δ 10.05 (s, 1H), 8.84–8.82 (m, 1H), 8.67 (d, J = 3.7 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 7.8 Hz, 2H), 7.70–7.66 (m, 1H), 7.54–7.53 (m, 2H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 162.3, 148.4, 138.4, 136.4, 134.1 (q, J = 2.1 Hz), 133.9, 130.1 (q, J = 5.2 Hz), 130.0, 129.3 (q, J = 31.8 Hz), 128.0, 127.4, 123.1 (q, J = 272.1 Hz), 122.6, 121.8, 117.1; ¹⁹F NMR (375 MHz, CDCl₃): δ -58.9; HRMS (ESI) calcd for $C_{18}H_{11}F_6N_2O$ ($M + H$)⁺ 385.0776, found 385.0776.

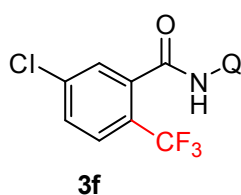
2-trifluoromethyl-5-methyl-*N*-(quinolin-8-yl)benzamide (**3e**)



Compound 3e: 50 mg, 76% yield, white solid, mp: 125–127 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.46 (petroleum ether/ethyl acetate = 8:1); ¹H NMR (400 MHz, CDCl₃): δ 10.05 (s, 1H), 8.84 (d, J = 7.0 Hz, 1H), 8.67 (d, J = 4.1 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.52–7.46 (m, 3H), 7.36 (dd, J = 8.2, 4.2 Hz, 1H), 7.31

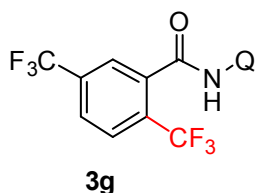
(d, $J = 8.0$ Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.1, 148.3, 142.8, 138.4, 136.3, 136.0 (q, $J = 2.0$ Hz), 134.4, 130.6, 129.1, 127.9, 127.4, 126.6 (q, $J = 4.9$ Hz), 124.8 (q, $J = 32.0$ Hz), 123.8 (q, $J = 272.0$ Hz), 122.2, 121.7, 116.9, 21.3; ^{19}F NMR (375 MHz, CDCl_3): δ -58.5; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 331.1058, found 331.1064.

3-chloro-6-trifluoromethyl-*N*-(quinolin-8-yl)benzamide (3f)



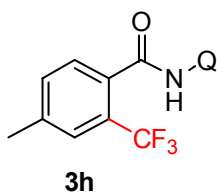
Compound 3f: 43 mg, 62% yield, white solid, mp: 137–139 °C (from ethyl acetate/petroleum ether = 12:1); $R_f = 0.58$ (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.09 (s, 1H), 8.82–8.80 (m, 1H), 8.71 (d, $J = 4.1$ Hz, 1H), 8.13 (d, $J = 8.3$ Hz, 1H), 7.67–7.65 (m, 2H), 7.54–7.51 (m, 3H), 7.40 (dd, $J = 8.2, 4.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.3, 148.4, 138.6, 138.4, 137.7 (q, $J = 2.1$ Hz), 136.4, 134.0, 130.3, 128.8, 128.2 (q, $J = 5.1$ Hz), 128.0, 127.4, 126.1 (q, $J = 32.4$ Hz), 123.3 (q, $J = 272.0$ Hz), 122.6, 121.8, 117.0; ^{19}F NMR (375 MHz, CDCl_3): δ -58.8; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{11}\text{ClF}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 351.0512, found 351.0514.

2,5-ditrifluoromethyl-*N*-(quinolin-8-yl)-benzamide (3g)



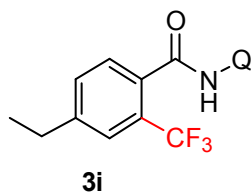
Compound 3g: 46 mg, 60% yield, white solid, mp: 116–118 °C (from ethyl acetate/petroleum ether = 12:1); $R_f = 0.62$ (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.14 (s, 1H), 8.82 (t, $J = 4.4$ Hz, 1H), 8.70 (d, $J = 3.7$ Hz, 1H), 8.13 (d, $J = 8.2$ Hz, 1H), 7.95 (s, 1H), 7.88–7.81 (m, 2H), 7.54 (d, $J = 4.5$ Hz, 2H), 7.40 (dd, $J = 8.3, 4.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.2, 148.5, 138.4, 137.0 (q, $J = 2.0$ Hz), 136.4, 134.4 (q, $J = 33.2$ Hz), 134.0, 130.9 (q, $J = 32.6$ Hz), 128.0, 127.5 (q, $J = 4.8$ Hz), 127.3, 127.0 (q, $J = 3.6$ Hz), 125.9 (q, $J = 3.6$ Hz), 122.9 (q, $J = 271.9$ Hz), 122.7 (q, $J = 271.8$ Hz), 122.7, 121.9, 117.1; ^{19}F NMR (375 MHz, CDCl_3): δ -59.4, -63.2; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{11}\text{F}_6\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 385.0776, found 385.0786.

2-trifluoromethyl-4-methyl-*N*-(quinolin-8-yl)benzamide (3h)



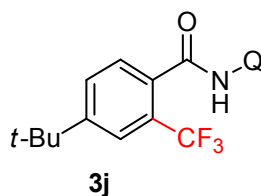
Compound 3h: 51 mg, 78% yield, white solid, mp: 120–122 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.45 (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.06 (s, 1H), 8.84 (d, J = 7.1 Hz, 1H), 8.66 (d, J = 3.8 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.52–7.46 (m, 3H), 7.38–7.33 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.1, 148.3, 140.6, 138.4, 136.3, 134.4, 133.4 (q, J = 2.0 Hz), 132.6, 128.5, 127.9, 127.6 (q, J = 31.8 Hz), 127.4, 127.2 (q, J = 4.8 Hz), 123.7 (q, J = 272.1 Hz), 122.1, 121.7, 116.8, 21.3; ^{19}F NMR (375 MHz, CDCl_3) δ -58.8; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 331.1058, found 331.1064.

2-trifluoromethyl-4-ethyl-*N*-(quinolin-8-yl)benzamide (3i)



Compound 3i: 52 mg, 76% yield, white solid, mp: 106–108 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.47 (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.07 (s, 1H), 8.84 (d, J = 7.1 Hz, 1H), 8.66 (d, J = 4.0 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.53–7.46 (m, 3H), 7.42–7.34 (m, 2H), 2.69 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.1, 148.3, 146.8, 138.4, 136.3, 134.4, 133.6 (q, J = 1.9 Hz), 131.4, 128.6, 127.9, 127.6 (q, J = 31.5 Hz), 127.4, 126.1 (q, J = 4.9 Hz), 123.7 (q, J = 272.2 Hz), 122.1, 121.7, 116.8, 28.7, 15.2; ^{19}F NMR (375 MHz, CDCl_3): δ -58.7; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 345.1215, found 345.1220.

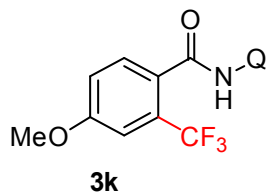
2-trifluoromethyl-4-(tert-butyl)-*N*-(quinolin-8-yl)benzamide (3j)



Compound 3j: 56 mg, 75% yield, white solid, mp: 166–168 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.53 (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.08 (s, 1H), 8.86 (d, J = 6.9 Hz, 1H), 8.68 (d, J = 4.0 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.71 (s, 1H), 7.64–7.60 (m, 2H), 7.55–7.49 (m, 2H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.2, 153.8, 148.3, 138.5, 136.4, 134.4, 133.4 (q, J = 1.9 Hz), 129.0, 128.5, 128.0, 127.4, 127.4 (q, J = 31.3 Hz), 123.8 (q, J = 272.0 Hz), 123.6 (q, J = 4.8 Hz), 122.1, 121.7,

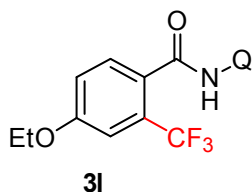
116.9, 35.1, 31.1; ^{19}F NMR (375 MHz, CDCl_3): δ -58.7; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 373.1528, found 373.1531.

4-methoxy-2-trifluoromethyl-4-(quinolin-8-ylcarbamoyl)benzoate (**3k**)



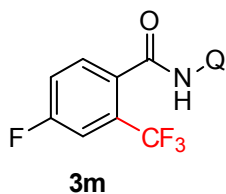
Compound 3k: 57 mg, 82% yield, white solid, mp: 122–124 °C (from ethyl acetate/petroleum ether = 10:1); R_f = 0.57 (petroleum ether/ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 10.07 (s, 1H), 8.83 (d, J = 7.0 Hz, 1H), 8.67 (d, J = 4.0 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.53–7.47 (m, 2H), 7.36 (dd, J = 8.2, 4.2 Hz, 1H), 7.20 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.8, 160.6, 148.3, 138.5, 136.3, 134.5, 130.4, 129.4 (q, J = 32.0 Hz), 128.5 (q, J = 1.9 Hz), 127.9, 127.4, 123.3 (q, J = 272.2 Hz), 122.1, 121.7, 116.7, 116.7, 112.7 (q, J = 5.2 Hz), 55.7; ^{19}F NMR (375 MHz, CDCl_3): δ -59.0; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 347.1007, found 347.1012.

4-ethoxy-2-trifluoromethyl-N-(quinolin-8-yl)benzamide (**3l**)



Compound 3l: 58 mg, 80% yield, white solid, mp: 115–117 °C (from ethyl acetate/petroleum ether = 10:1); R_f = 0.53 (petroleum ether/ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 10.15 (s, 1H), 8.91 (d, J = 7.0 Hz, 1H), 8.76 (d, J = 3.9 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.62–7.55 (m, 2H), 7.45 (dd, J = 8.2, 4.1 Hz, 1H), 7.28 (s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 4.13 (q, J = 6.9 Hz, 2H), 1.47 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.9, 160.0, 148.3, 138.5, 136.3, 134.5, 130.4, 129.3 (q, J = 31.9 Hz), 128.3 (q, J = 1.8 Hz), 128.0, 127.4, 123.4 (q, J = 272.1 Hz), 122.0, 121.7, 117.1, 116.8, 113.2 (q, J = 5.2 Hz), 64.1, 14.6; ^{19}F NMR (375 MHz, CDCl_3): δ -59.0; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 361.1164, found 361.1153.

4-fluoro-2-trifluoromethyl-N-(quinolin-8-yl)benzamide (**3m**)

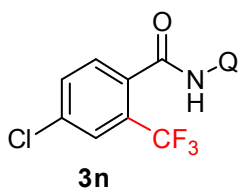


Compound 3m: 49 mg, 73% yield, white solid, mp: 122–124 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.48 (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.17 (s, 1H), 8.89 (dd, J =

6.2, 2.3 Hz, 1H), 8.76 (d, $J = 4.0$ Hz, 1H), 8.18 (d, $J = 8.2$ Hz, 1H), 7.80–7.77 (m, 1H), 7.62–7.57 (m, 2H), 7.51–7.44 (m, 2H), 7.39–7.35 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.8, 162.8 (d, $J = 251.0$ Hz), 148.4, 138.4, 136.4, 134.2, 132.5 (q, $J = 1.8$ Hz), 131.0 (d, $J = 8.3$ Hz), 130.1 (qd, $J = 33.0, 7.8$ Hz), 127.9, 127.3, 122.7 (qd, $J = 272.5, 2.5$ Hz), 122.4, 121.8, 119.1 (d, $J = 21.1$ Hz), 116.9, 114.5 (dq, $J = 25.0, 5.1$ Hz); ^{19}F NMR (375 MHz, CDCl_3): δ -59.3, -107.7; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{11}\text{F}_4\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 335.0808, found 335.0822.

4-chloro-2-trifluoromethyl-*N*-(quinolin-8-yl)benzamide (3n)

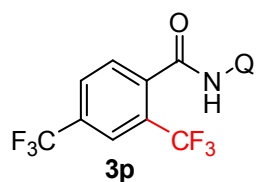
Compound 3n: 40 mg, 57% yield, white solid, mp: 111–113 °C (from ethyl acetate/petroleum ether = 12:1); $R_f = 0.46$ (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.17 (s, 1H), 8.90–8.88 (m, 1H), 8.76 (d, $J = 4.1$ Hz, 1H), 8.19 (d, $J = 8.3$ Hz, 1H), 7.79 (s, 1H), 7.73–7.71 (m, 1H), 7.67–7.65 (m, 1H), 7.60–7.59 (m, 2H), 7.47 (dd, $J = 8.2, 4.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.8, 148.4, 138.4, 136.4, 134.5 (q, $J = 1.9$ Hz), 134.1, 132.3, 130.1, 129.1 (q, $J = 33.5$ Hz), 128.7, 127.9, 127.4, 127.1 (q, $J = 5.1$ Hz), 122.8 (q, $J = 272.0$ Hz), 122.5, 121.8, 116.9; ^{19}F NMR (375 MHz, CDCl_3): δ -59.2; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{11}\text{ClF}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 351.0512, found 351.0528.



4-bromo-2-trifluoromethyl-*N*-(quinolin-8-yl)benzamide (3o)

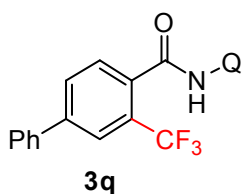
Compound 3o: 46 mg, 59% yield, white solid, mp: 110–112 °C (from ethyl acetate/petroleum ether = 12:1); $R_f = 0.44$ (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.16 (s, 1H), 8.90–8.87 (m, 1H), 8.76 (d, $J = 3.9$ Hz, 1H), 8.20 (d, $J = 8.2$ Hz, 1H), 7.97–7.94 (m, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 7.70–7.60 (m, 3H), 7.47 (dd, $J = 8.1, 4.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.8, 148.4, 138.4, 136.4, 135.3, 134.9 (q, $J = 1.8$ Hz), 134.1, 132.0, 130.2, 129.9 (q, $J = 5.1$ Hz), 129.4 (q, $J = 32.5$ Hz), 127.9, 127.4, 122.7 (q, $J = 271.9$ Hz), 122.5, 121.8, 117.0; ^{19}F NMR (375 MHz, CDCl_3): δ -59.2; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{11}\text{BrF}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 395.0007, found 395.0023.

2, 4-ditrifluoromethyl-*N*-(quinolin-8-yl)benzamide (3p)



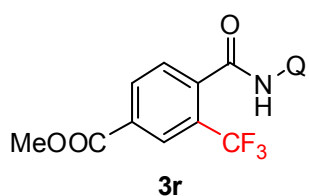
Compound 3p: 50 mg, 65% yield, white solid, mp: 120–122 °C (from ethyl acetate/petroleum ether = 12:1); $R_f = 0.71$ (petroleum ether/ethyl acetate = 8:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.22 (s, 1H), 8.91–8.89 (m, 1H), 8.77 (d, $J = 3.5$ Hz, 1H), 8.20 (d, $J = 8.2$ Hz, 1H), 8.03 (s, 1H), 7.96–7.88 (m, 2H), 7.61 (d, $J = 4.4$ Hz, 2H), 7.47 (dd, $J = 8.2, 4.1$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 164.2, 148.5, 138.4, 137.0, 136.4, 134.4 (q, $J = 33.5$ Hz), 133.9, 130.9 (q, $J = 32.4$ Hz), 127.9, 127.5 (q, $J = 4.9$ Hz), 127.3, 127.0 (q, $J = 3.6$ Hz), 125.8 (q, $J = 3.7$ Hz), 122.9 (q, $J = 272.8$ Hz), 122.8 (q, $J = 272.6$ Hz), 122.7, 121.9, 117.1; $^{19}\text{F NMR}$ (375 MHz, CDCl_3): δ -59.3, -63.2; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{11}\text{F}_6\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 385.0776, found 385.0793.

3-trifluoromethyl-*N*-(quinolin-8-yl)-[1, 1'-biphenyl]-4-carboxamide (3q)



Compound 3q: 48 mg, 62% yield, white solid, mp: 190–192 °C (from ethyl acetate/petroleum ether = 12:1); $R_f = 0.49$ (petroleum ether/ethyl acetate = 8:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.17 (s, 1H), 8.93–8.91 (m, 1H), 8.76 (d, $J = 3.8$ Hz, 1H), 8.21–8.17 (m, 3H), 7.67–7.62 (m, 4H), 7.57–7.45 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 162.3, 148.4, 143.5, 138.4, 137.6, 136.4, 134.0, 132.4, 129.9 (q, $J = 31.4$ Hz), 129.4, 129.3, 129.2, 128.4 (q, $J = 4.5$ Hz), 128.0, 127.4, 127.3, 123.1 (q, $J = 272.0$ Hz), 122.6, 121.8, 117.1; $^{19}\text{F NMR}$ (375 MHz, CDCl_3): δ -58.9; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{16}\text{F}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 393.1215, found 393.1210.

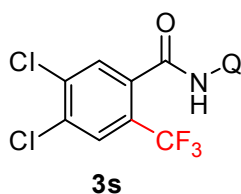
methyl 3-trifluoromethyl-4-(quinolin-8-ylcarbamoyl)benzoate (3r)



Compound 3r: 58 mg, 77% yield, white solid, mp: 147–149 °C (from ethyl acetate/petroleum ether = 10:1); $R_f = 0.35$ (petroleum ether/ethyl acetate = 8:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.20 (s, 1H), 8.91–8.89 (m, 1H), 8.76 (d, $J = 4.0$ Hz, 1H), 8.45 (s, 1H), 8.33 (d, $J = 7.9$ Hz, 1H), 8.19 (d, $J = 8.2$ Hz, 1H), 7.84 (d, $J = 7.9$ Hz, 1H), 7.63–7.60 (m, 2H), 7.46 (dd, $J = 8.2, 4.2$ Hz, 1H), 4.00 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 165.1, 164.9, 148.4, 139.7 (q, $J = 1.9$ Hz), 138.4, 136.4, 134.0, 133.2,

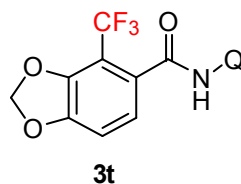
131.8, 128.9, 128.1 (q, $J = 32.6$ Hz), 128.0 (q, $J = 4.8$ Hz), 127.9, 127.2, 123.1 (q, $J = 272.4$ Hz), 122.6, 121.8, 117.1, 52.8; ^{19}F NMR (375 MHz, CDCl_3): δ -59.1; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 375.0957, found 375.0954.

4,5-dichloro-2-(trifluoromethyl)-*N*-(quinolin-8-yl)benzamide (3s)



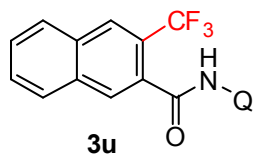
Compound 3s: 41 mg, 53% yield, white solid, mp: 163–165 °C (from ethyl acetate/petroleum ether = 10:1); $R_f = 0.67$ (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.18 (s, 1H), 8.87–8.85 (m, 1H), 8.78 (d, $J = 4.0$ Hz, 1H), 8.20 (d, $J = 8.2$ Hz, 1H), 7.88 (s, 1H), 7.86 (s, 1H), 7.61 (d, $J = 4.4$ Hz, 2H), 7.48 (dd, $J = 8.2, 4.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.3, 148.5, 138.4, 137.0, 136.4, 135.5 (q, $J = 1.8$ Hz), 134.9, 133.9, 130.8, 129.0 (q, $J = 5.1$ Hz), 128.0, 127.4 (q, $J = 33.2$ Hz), 127.3, 122.7, 122.5 (q, $J = 271.8$ Hz), 121.9, 117.1; ^{19}F NMR (375 MHz, CDCl_3) δ -59.1; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{10}\text{Cl}_2\text{F}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 385.0122, found 385.0123.

N-(quinolin-8-yl)-4-(trifluoromethyl)benzo[d][1,3]dioxole-5-carboxamide (3t)



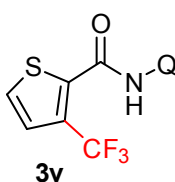
Compound 3t: 56 mg, 78% yield, white solid, mp: 108–110 °C (from ethyl acetate/petroleum ether = 10:1); $R_f = 0.40$ (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.12 (s, 1H), 8.87 (d, $J = 6.6$ Hz, 1H), 8.77 (d, $J = 3.5$ Hz, 1H), 8.18 (d, $J = 8.2$ Hz, 1H), 7.62–7.59 (m, 2H), 7.45 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.18 (d, $J = 5.4$ Hz, 2H), 6.12 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.4, 150.2, 148.9, 148.3, 138.5, 136.4, 134.3, 131.3 (q, $J = 2.4$ Hz), 128.0, 127.4, 123.4 (q, $J = 271.5$ Hz), 122.3, 121.9 (q, $J = 32.5$ Hz), 121.7, 117.0, 108.8, 106.9 (q, $J = 5.2$ Hz), 102.6; ^{19}F NMR (375 MHz, CDCl_3): δ -57.5; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{12}\text{F}_3\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 361.0800, found 361.0801. The regiochemistry of this compound is determined from the proton NMR based on the fact the singlet signal which is assigned to the hydrogen located on the benzene ring between the meta-substituent and the carbonyl group has disappeared.

3-trifluoromethyl-*N*-(quinolin-8-yl)-2-naphthamide (3u)



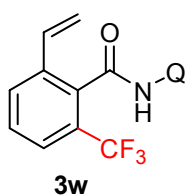
Compound 3u: 41 mg, 56% yield, white solid, mp: 187–189 °C (from ethyl acetate/petroleum ether = 10:1); R_f = 0.44 (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.31 (s, 1H), 8.98 (d, J = 7.1 Hz, 1H), 8.75 (d, J = 3.8 Hz, 1H), 8.32 (s, 1H), 8.27 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.01–7.98 (m, 2H), 7.70–7.68 (m, 2H), 7.65–7.58 (m, 2H), 7.46 (dd, J = 8.2, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.0, 148.3, 138.5, 136.4, 134.5, 133.7, 132.4 (q, J = 1.8 Hz), 132.4, 129.1, 128.9, 128.8, 128.5, 128.3, 128.0 (q, J = 5.6 Hz), 128.0, 127.5, 125.0 (q, J = 32.0 Hz), 122.2, 121.7, 123.8 (q, J = 271.6 Hz), 116.9; ^{19}F NMR (375 MHz, CDCl_3): δ -58.4; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{14}\text{F}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 367.1058, found 367.1062.

N-(quinolin-8-yl)-3-(trifluoromethyl)thiophene-2-carboxamide (3v)



Compound 3v: 30 mg, 47% yield, white solid, mp: 109–111 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.53 (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.60 (s, 1H), 8.87–8.83 (m, 2H), 8.20 (d, J = 8.3 Hz, 1H), 7.60–7.59 (m, 2H), 7.53 (d, J = 5.1 Hz, 1H), 7.49 (dd, J = 8.2, 4.1 Hz, 1H), 7.36 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.4, 148.5, 140.0 (q, J = 2.2 Hz), 138.6, 136.3, 134.2, 130.4 (q, J = 32.2 Hz), 128.1, 128.0, 127.3, 127.1 (q, J = 3.6 Hz), 122.5, 121.8, 121.7 (q, J = 272.6 Hz), 117.2; ^{19}F NMR (375 MHz, CDCl_3): δ -56.1; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{10}\text{F}_3\text{N}_2\text{OS}$ ($\text{M} + \text{H}$) $^+$ 323.0466, found 323.0459.

2-trifluoromethyl-6-vinyl-*N*-(quinolin-8-yl)benzamide (3w)

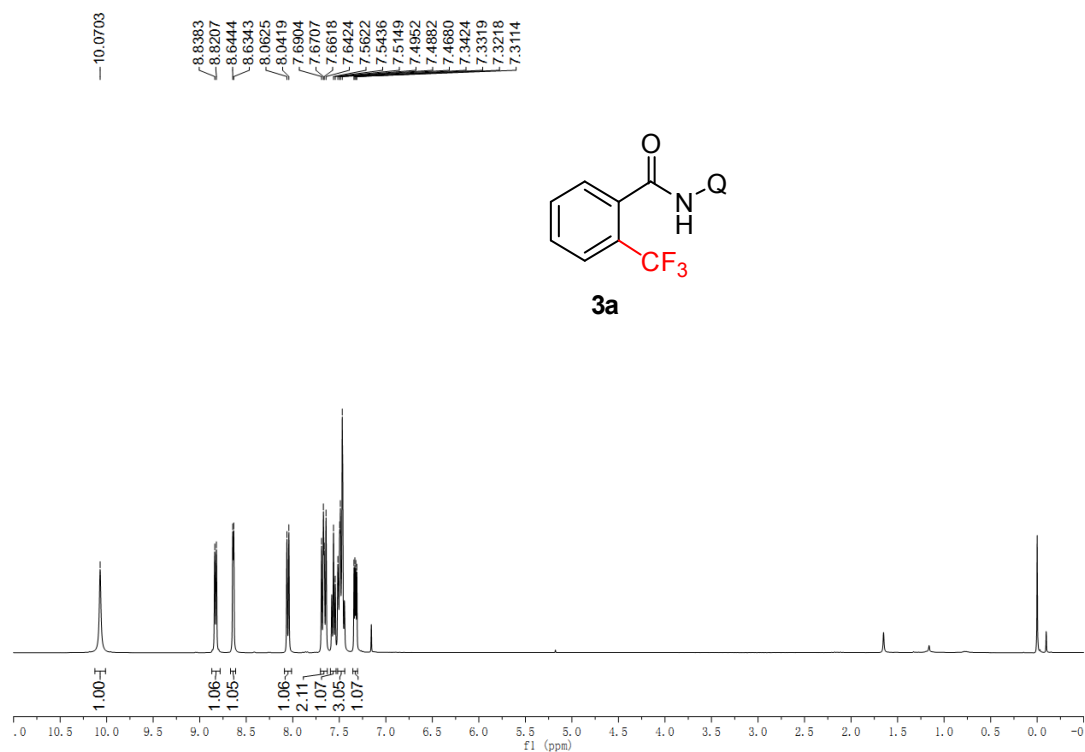


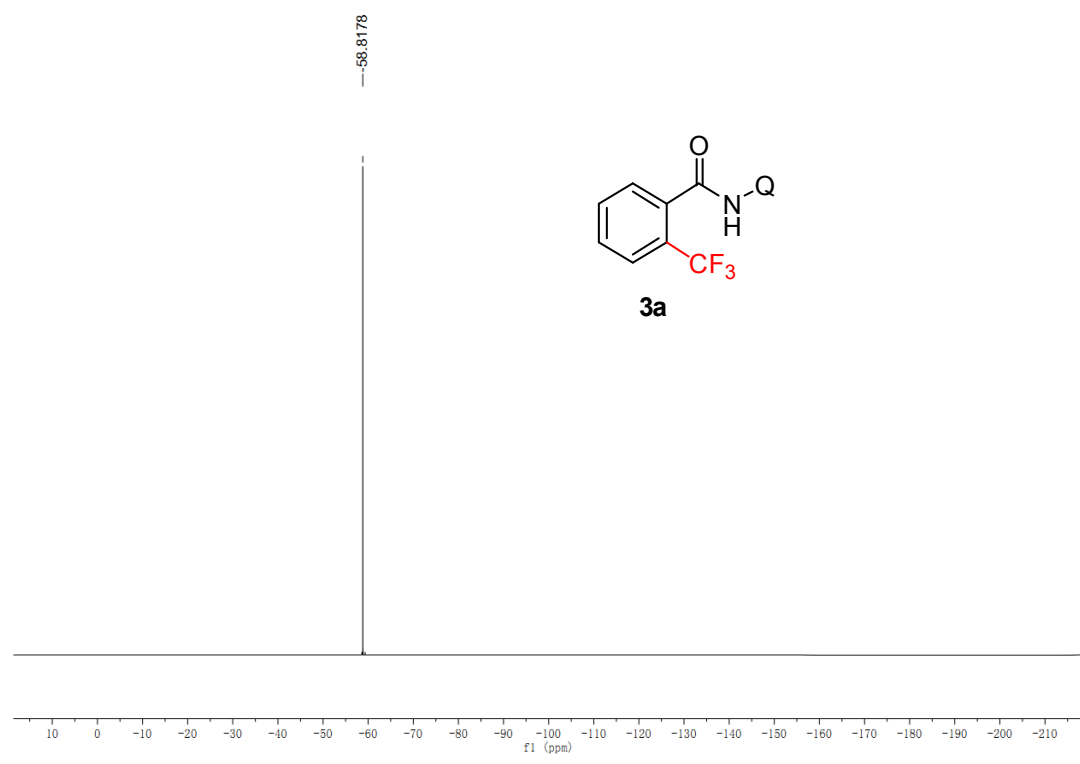
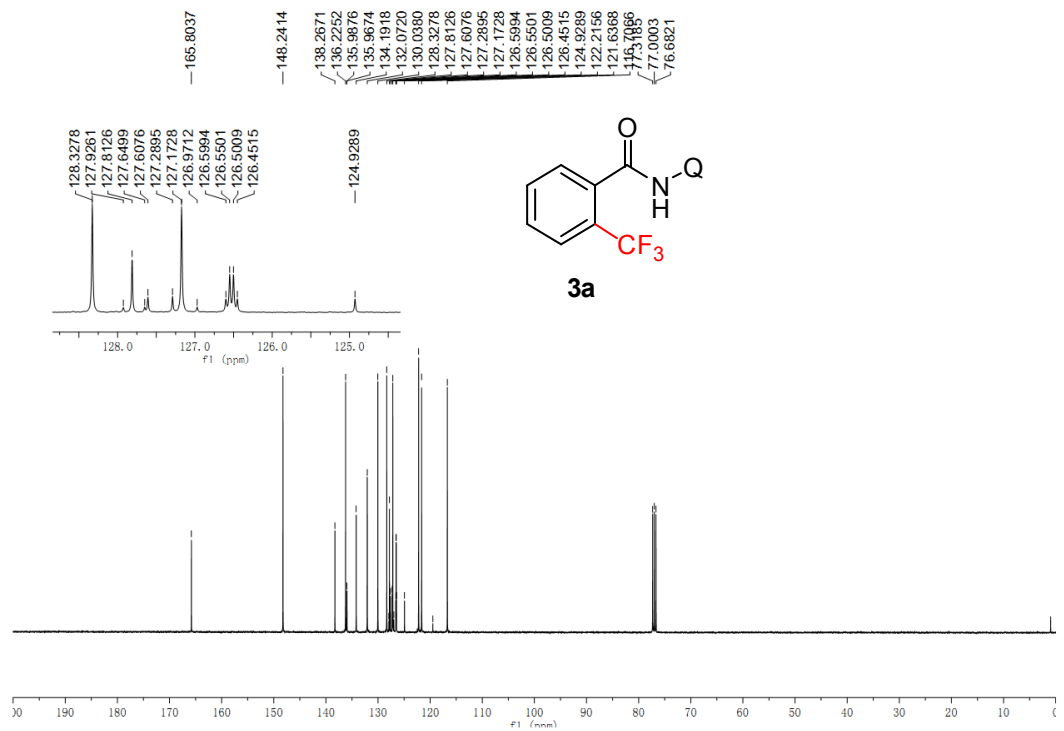
Compound 3w: 30 mg, 36% yield, white solid, mp: 121–123 °C (from ethyl acetate/petroleum ether = 12:1); R_f = 0.45 (petroleum ether/ethyl acetate = 8:1); ^1H NMR (400 MHz, CDCl_3): δ 10.03 (s, 1H), 8.97 (d, J = 6.8 Hz, 1H), 8.74 (d, J = 3.9 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.63–7.53 (m, 3H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 6.97 (dd, J = 17.2, 10.9 Hz, 1H), 5.85 (d, J = 17.3 Hz, 1H), 5.39 (d, J

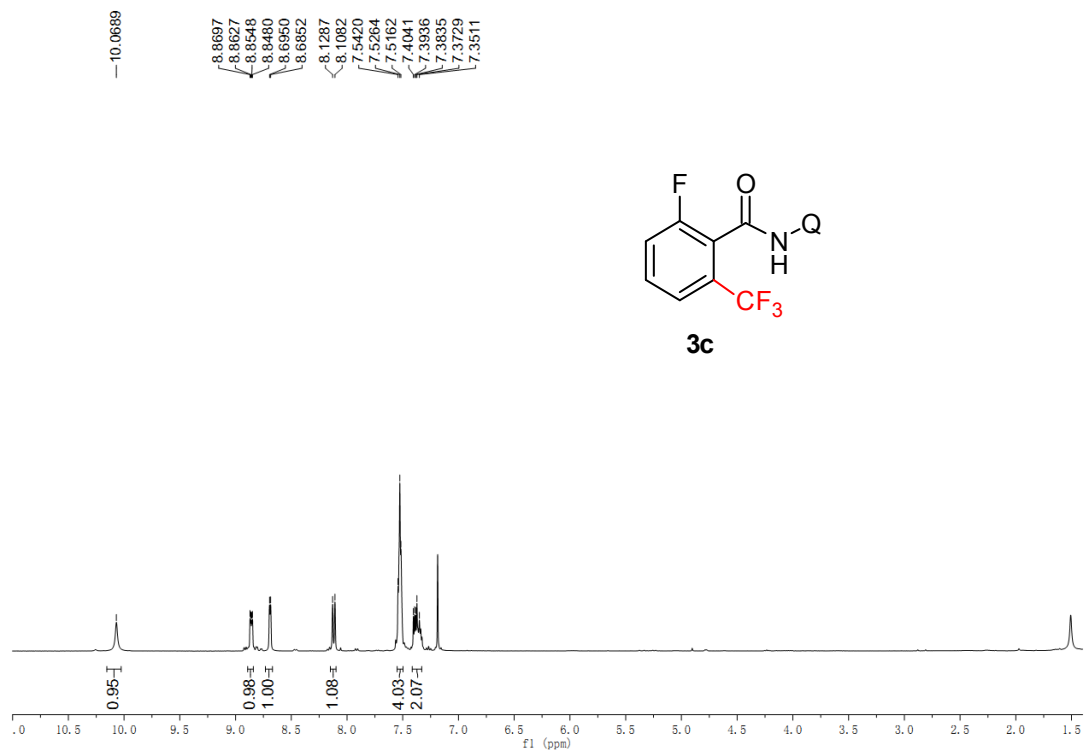
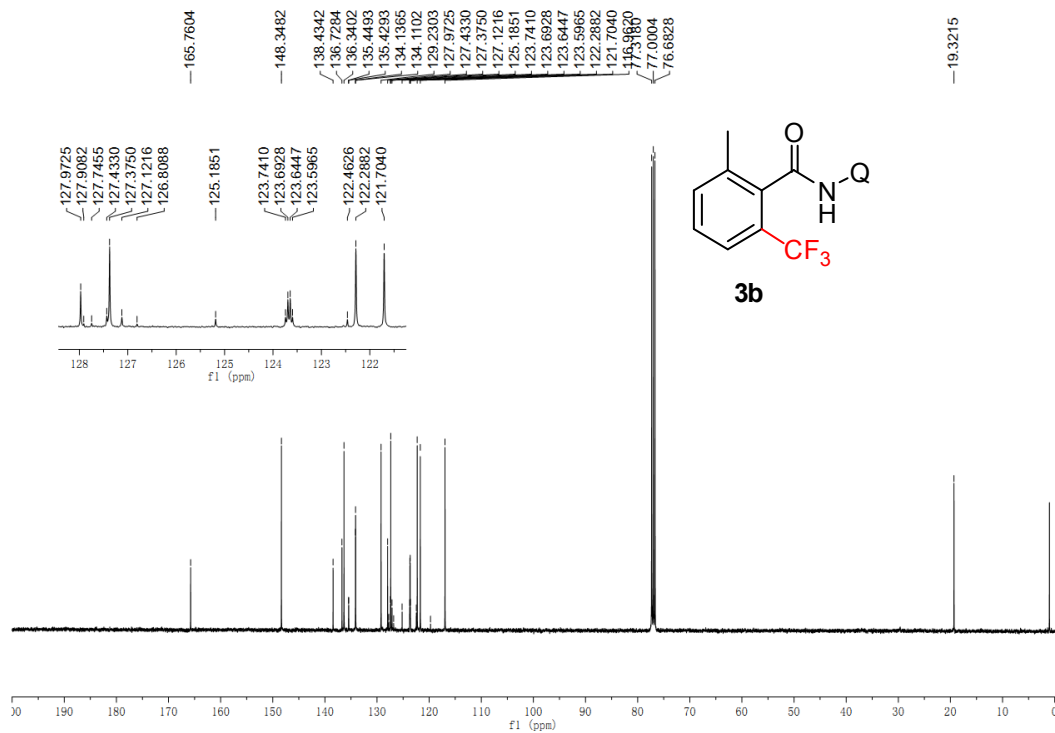
= 10.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.2, 148.4, 148.4, 138.5, 136.8, 136.3, 134.2, 132.7, 129.5, 129.5, 129.2, 128.0, 127.4, 125.5 (q, J = 4.1 Hz), 122.4, 121.7, 118.7, 117.0; ^{19}F NMR (375 MHz, CDCl_3): δ -59.0; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 343.1058, found 343.1063.

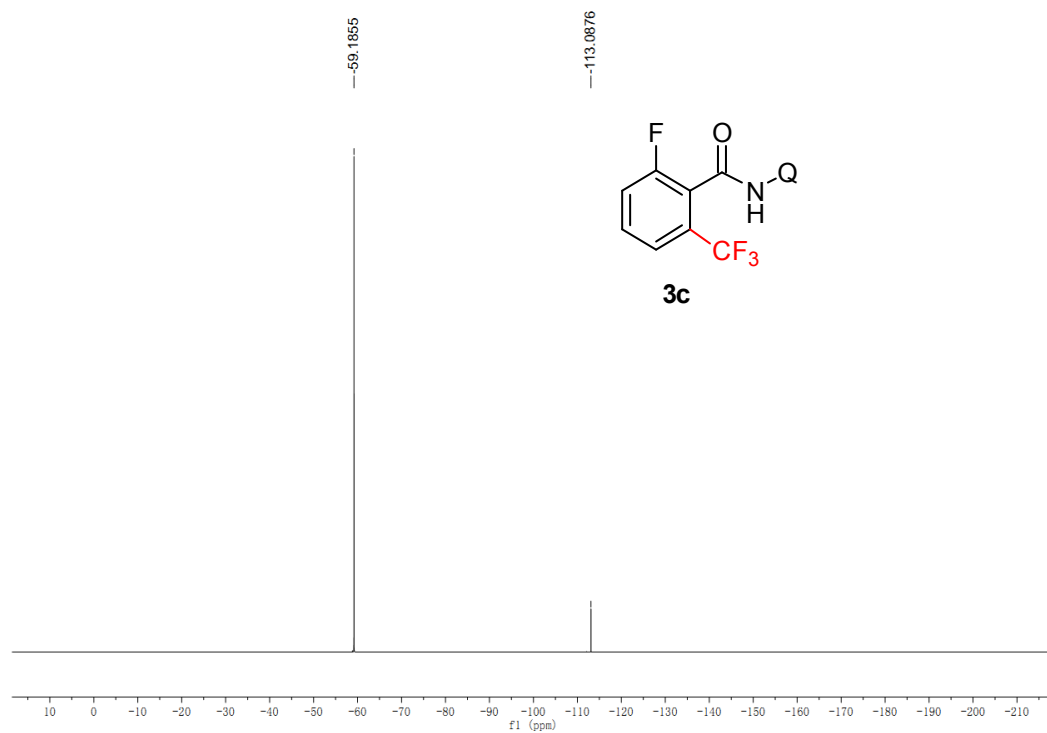
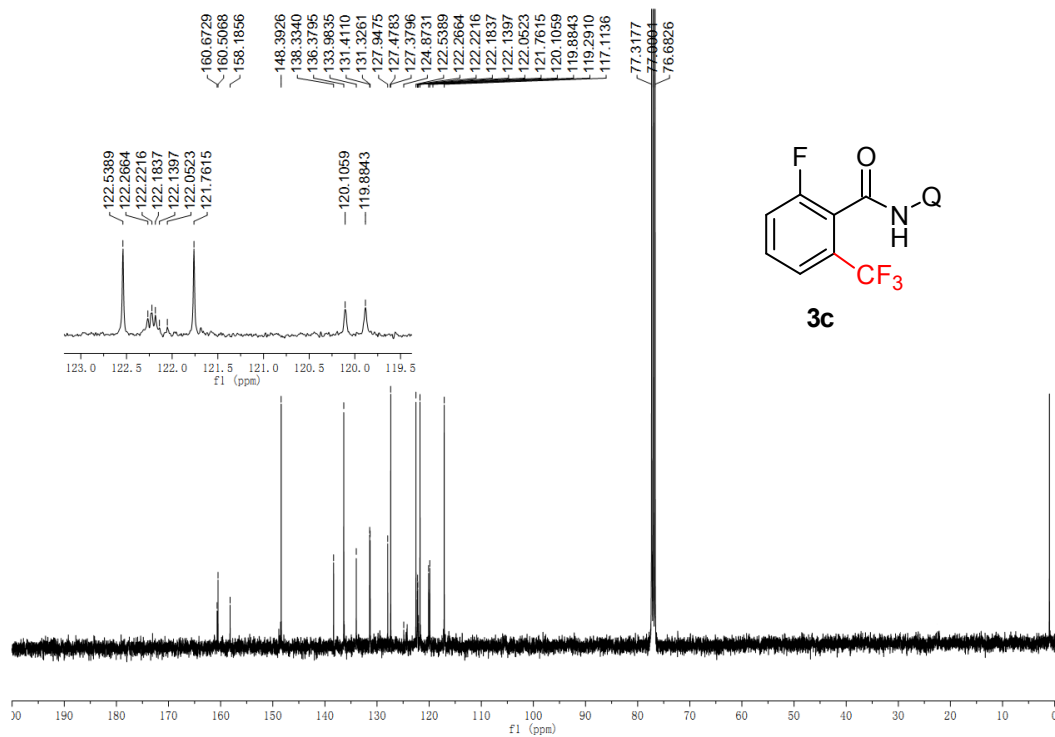
References

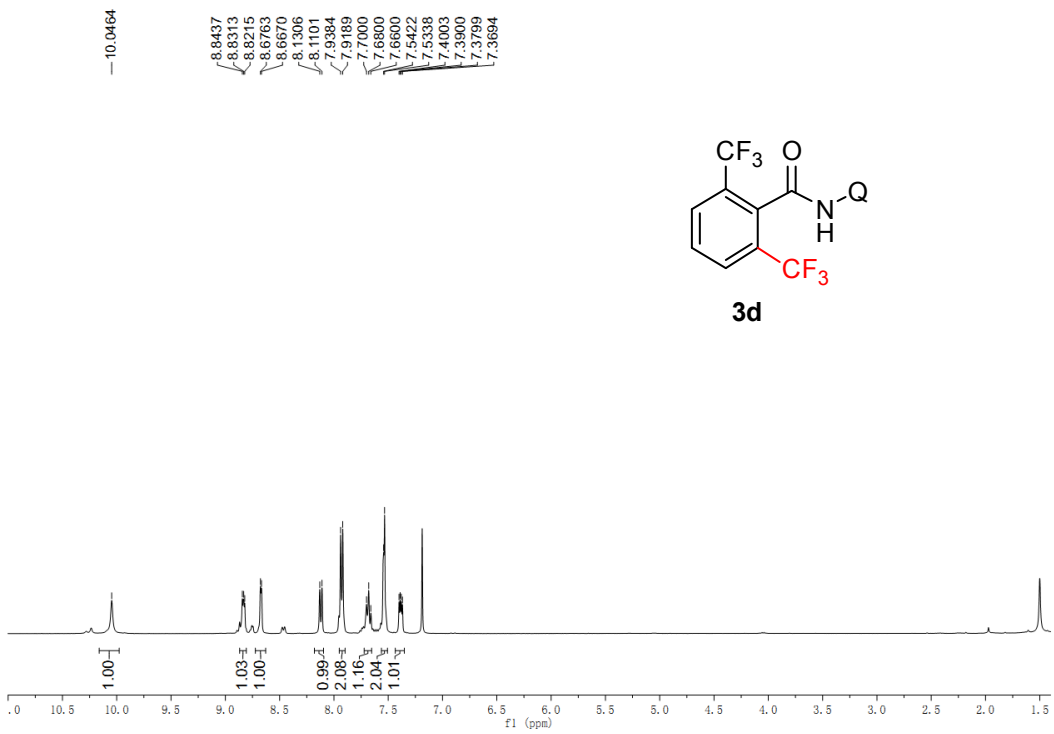
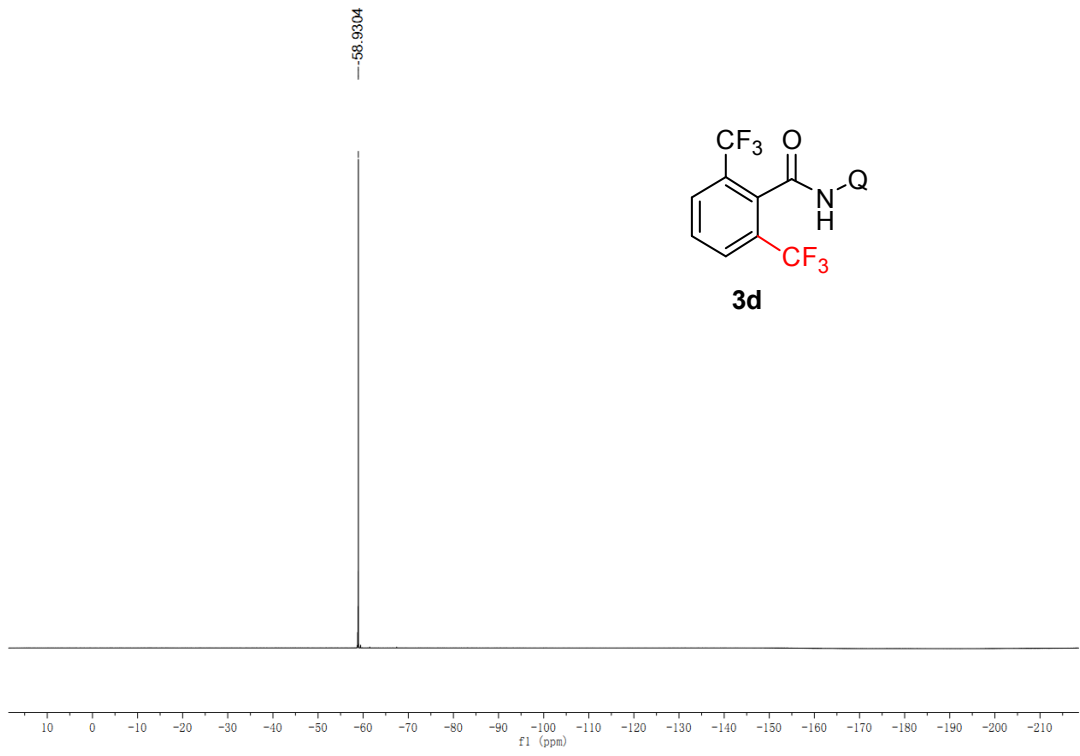
1. A. M. Suess, M. Z. Ertem, C. J. Cramer, S. S. Stahl., *J. Am. Chem. Soc.*, 2013, **135**, 9797.
2. (a) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237; (b) L. D. Tran, J. Roane, O. Daugulis, *Angew. Chem., Int. Ed.*, 2013, **52**, 6043; (c) J. Roane, O. Daugulis, *Org. Lett.*, 2013, **15**, 5842; (d) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.*, 2013, **52**, 4457.
3. D. Katayev, K. F. Pfister, T. Wendling, L. J. Gooßen, *Chem. Eur. J.*, 2014, **20**, 9902.
4. T. Truong, K. Klimovica, O. Daugulis, *J. Am. Chem. Soc.*, 2013, **135**, 9342.

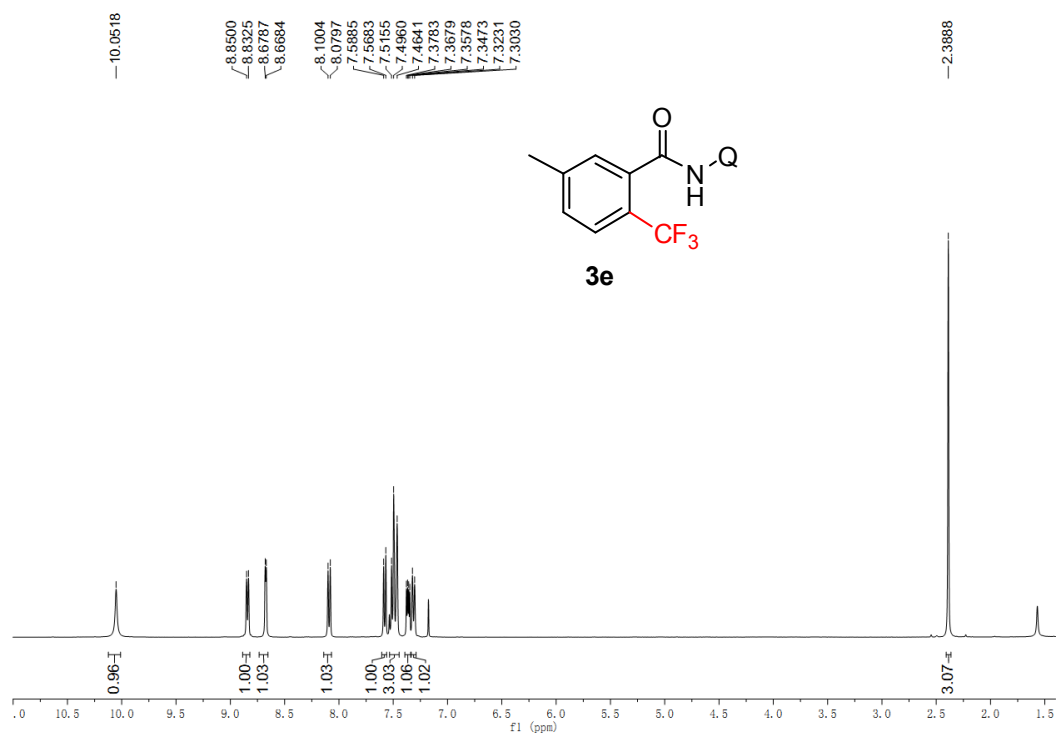
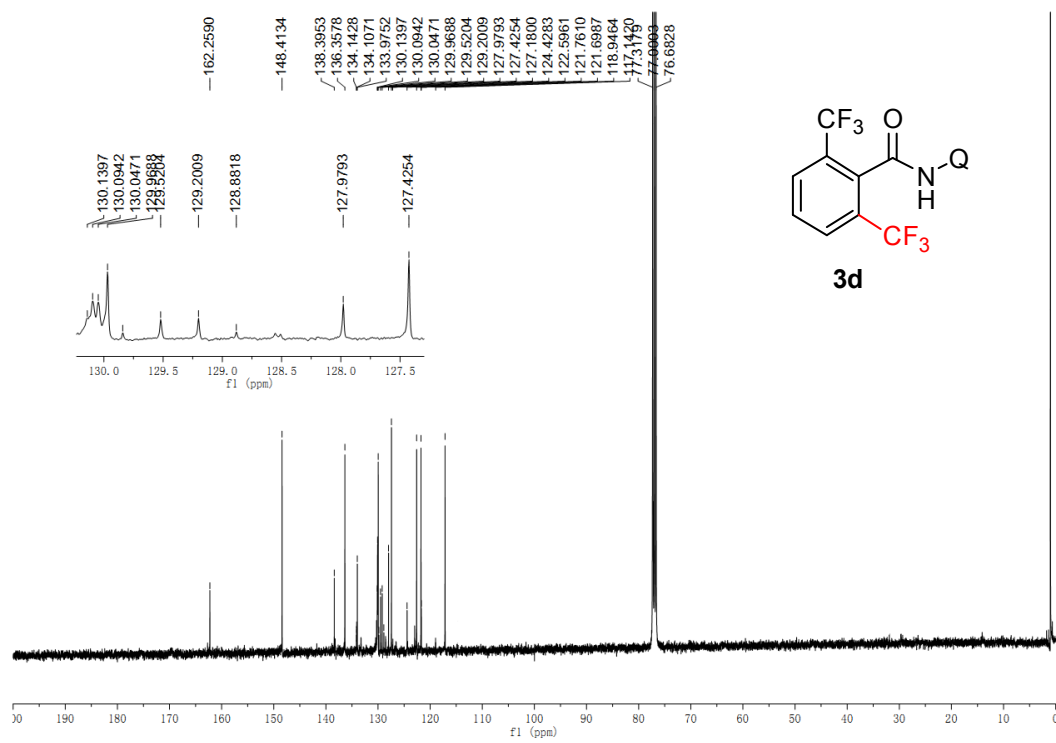


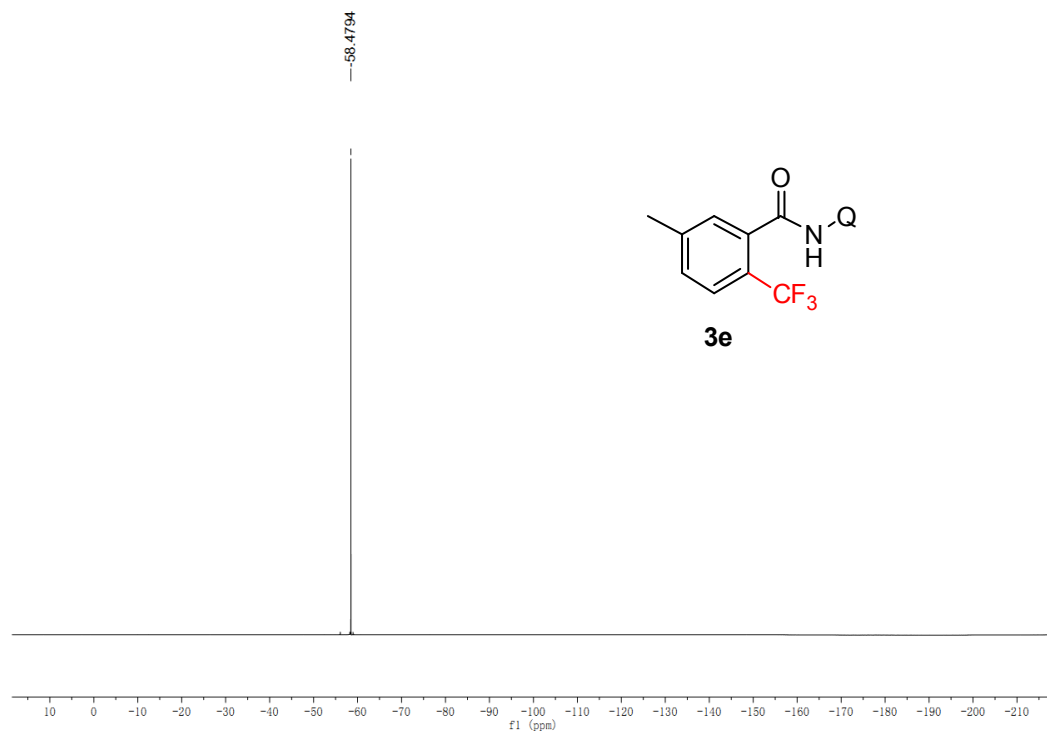
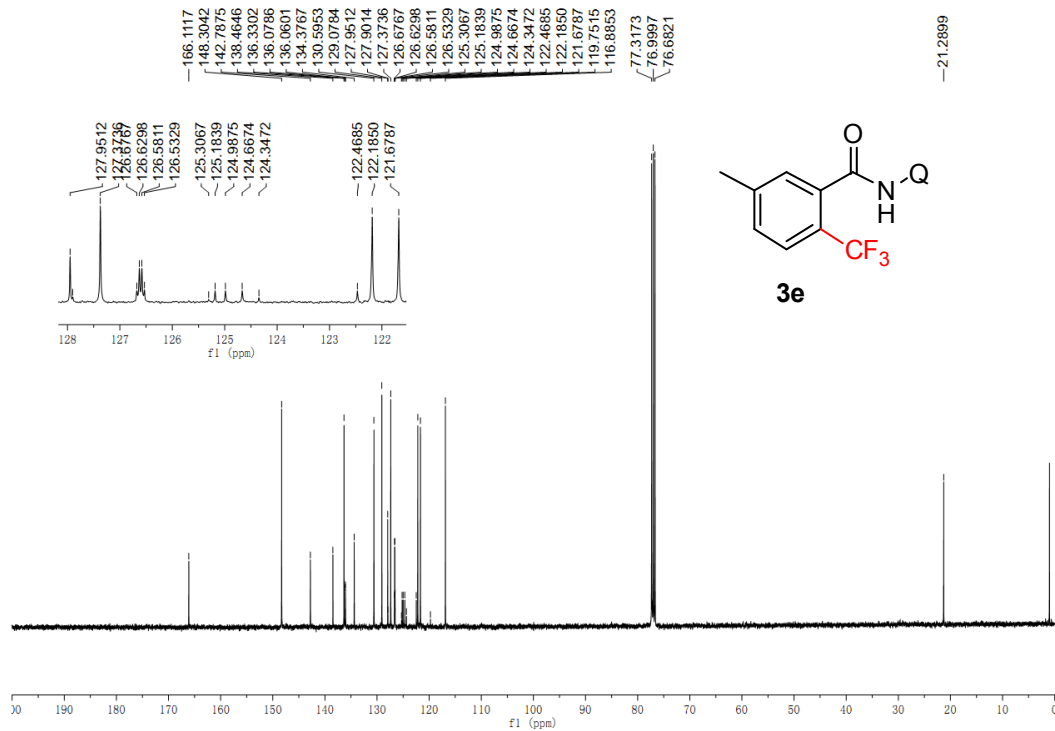


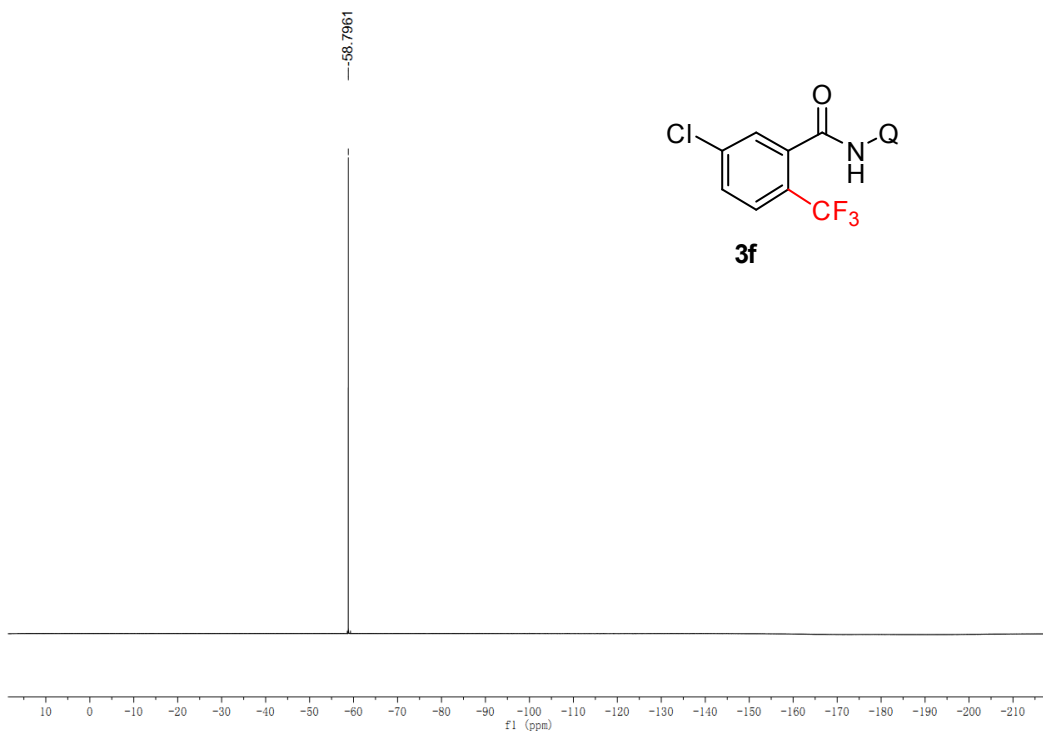


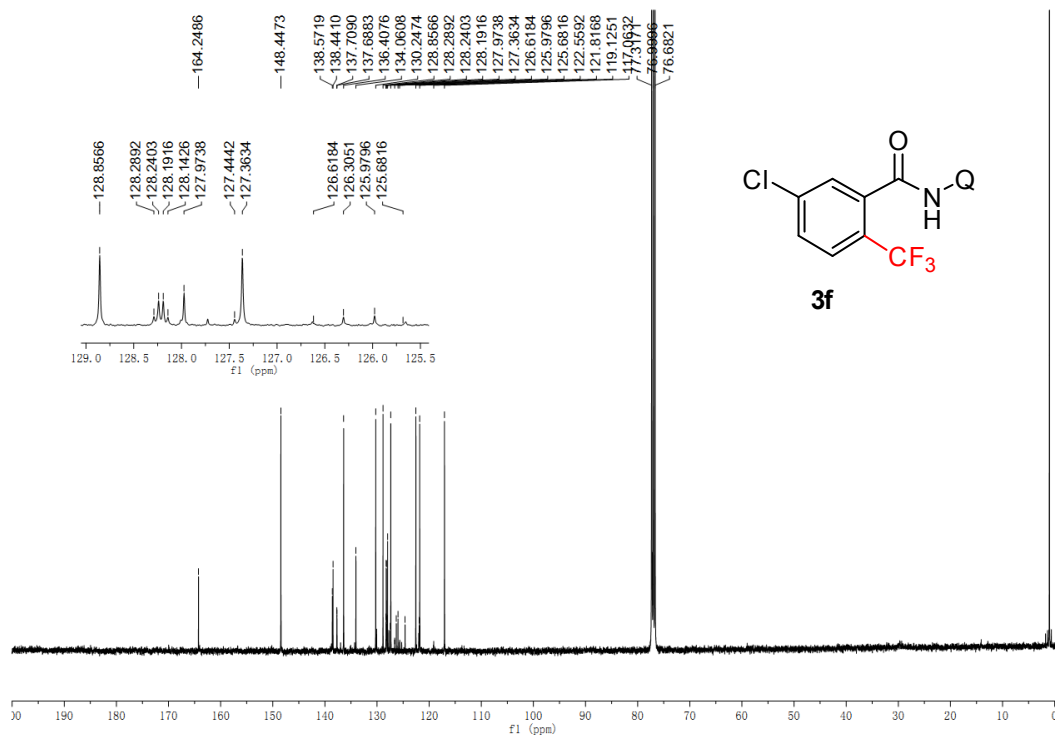
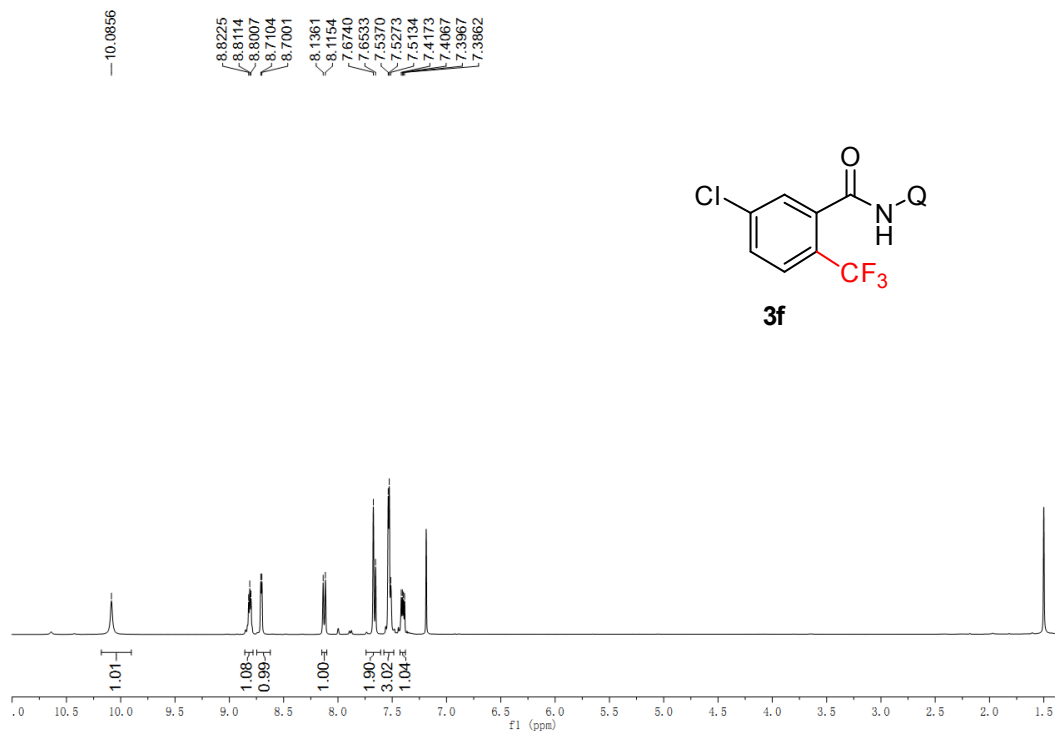


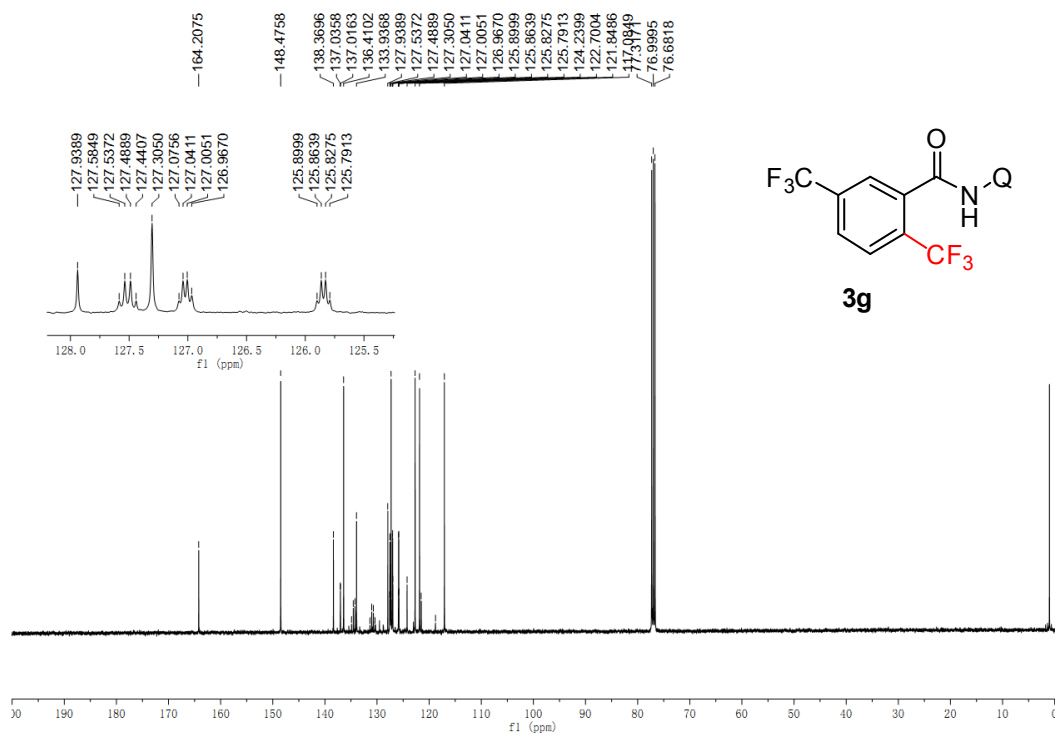
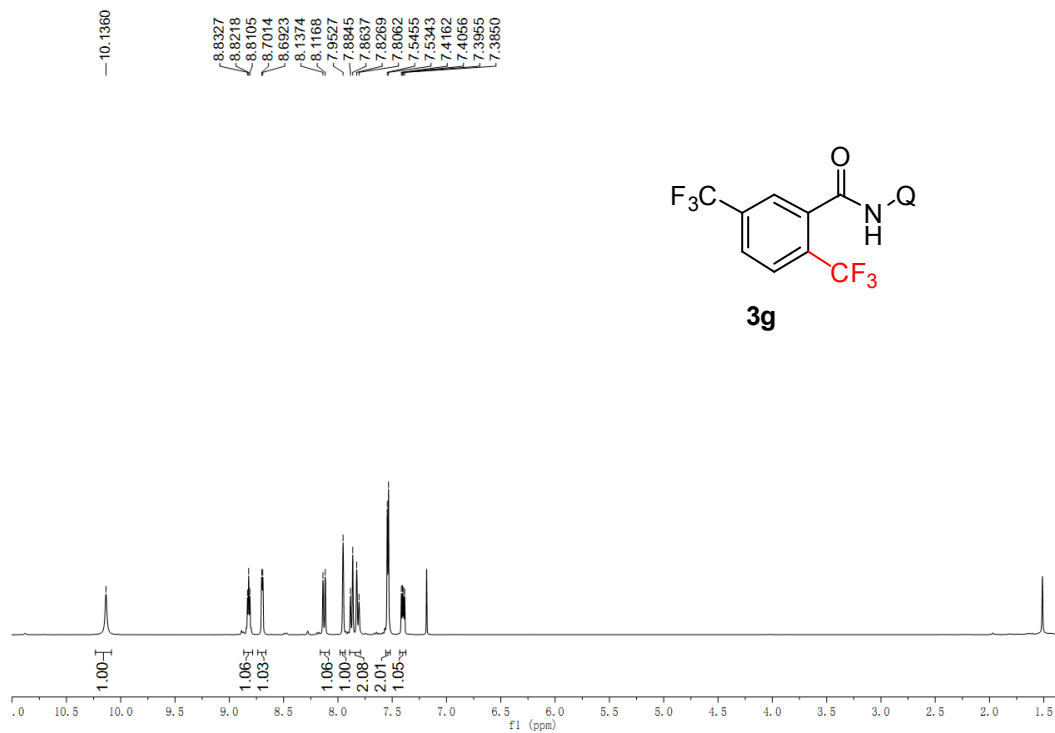


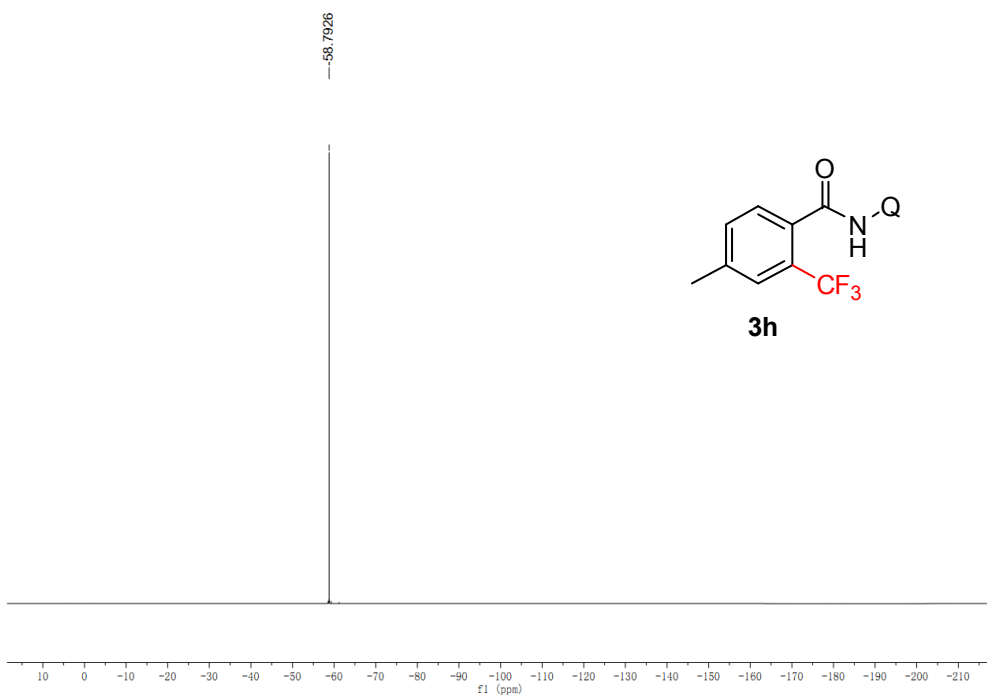
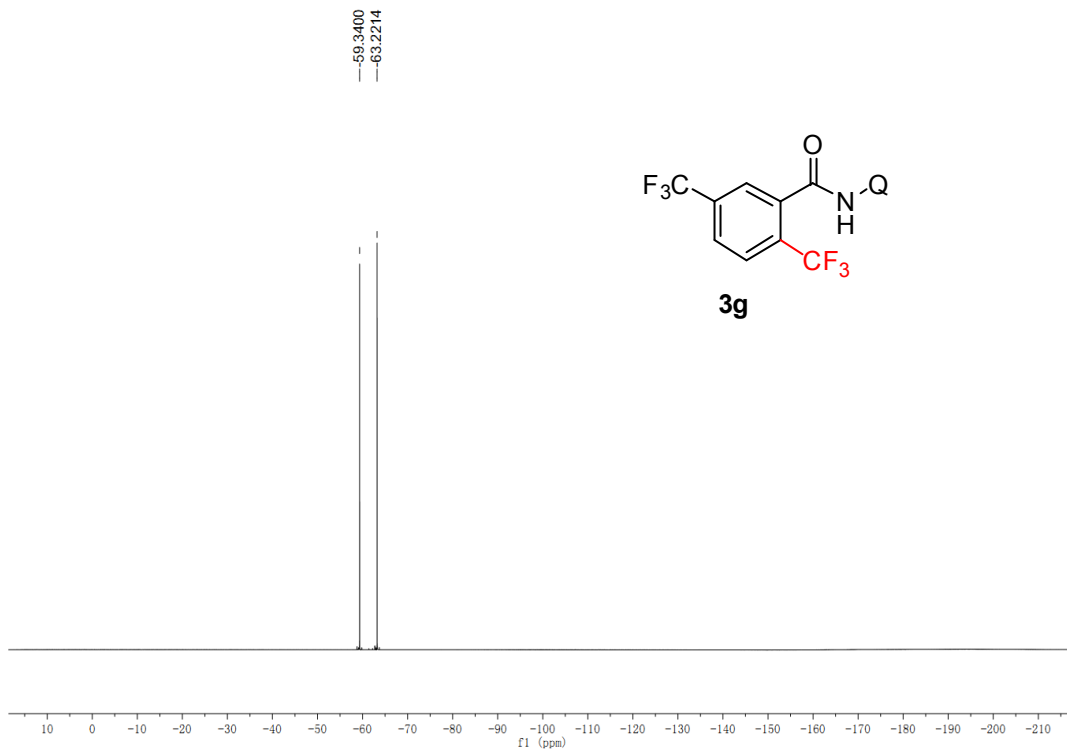


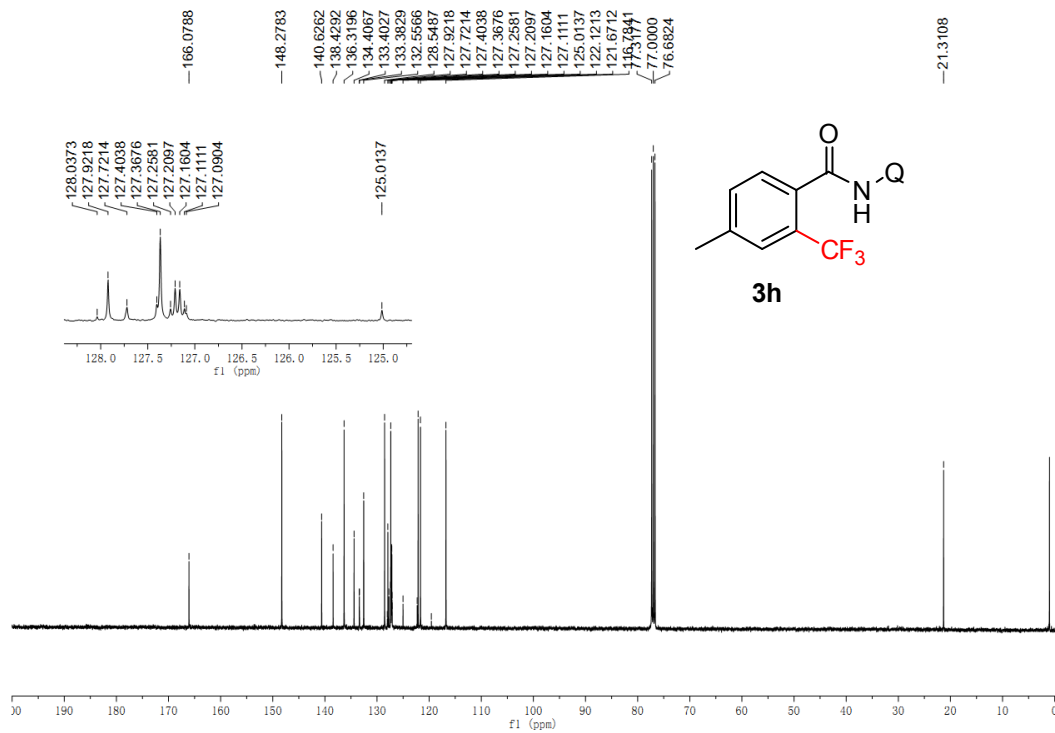
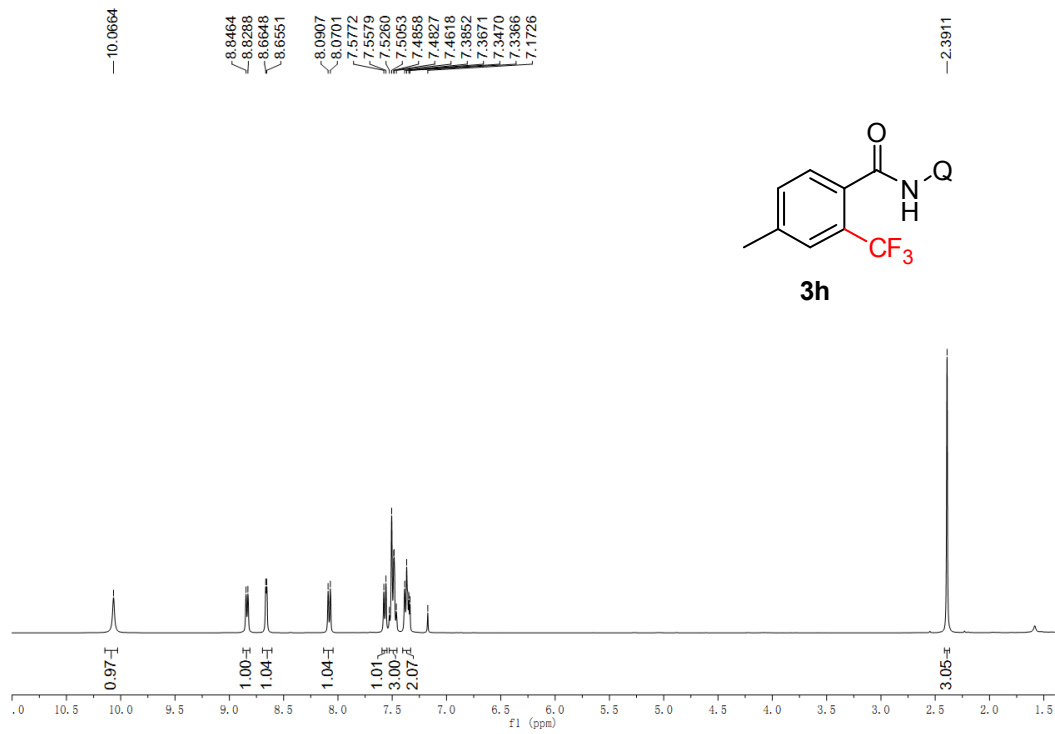


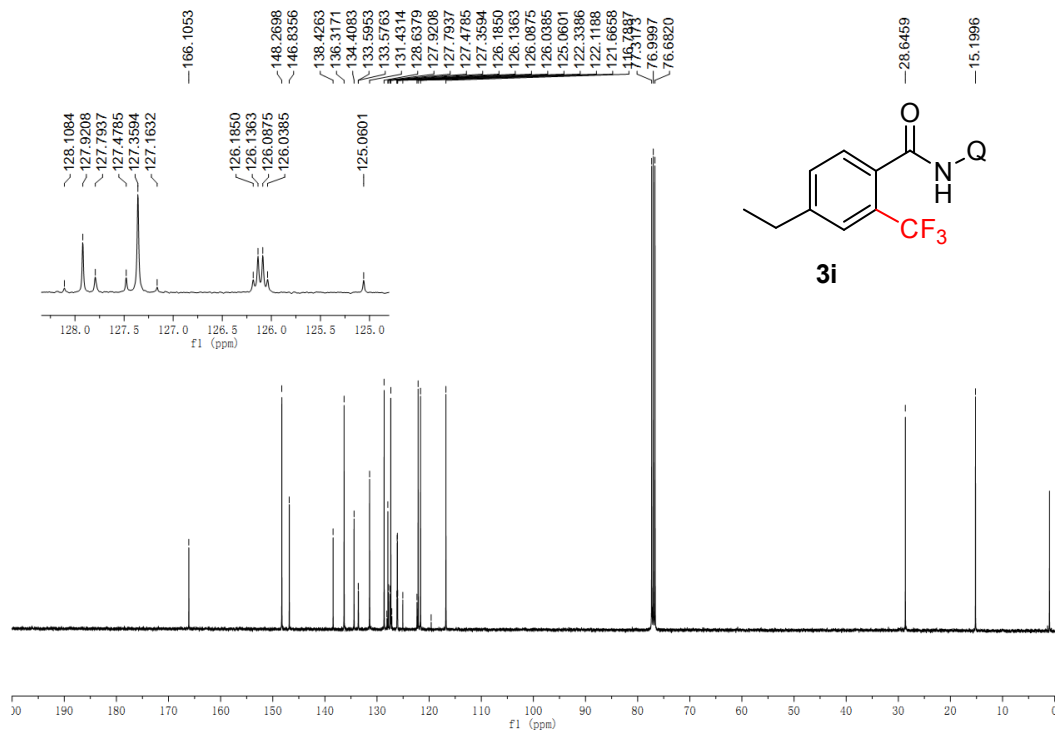
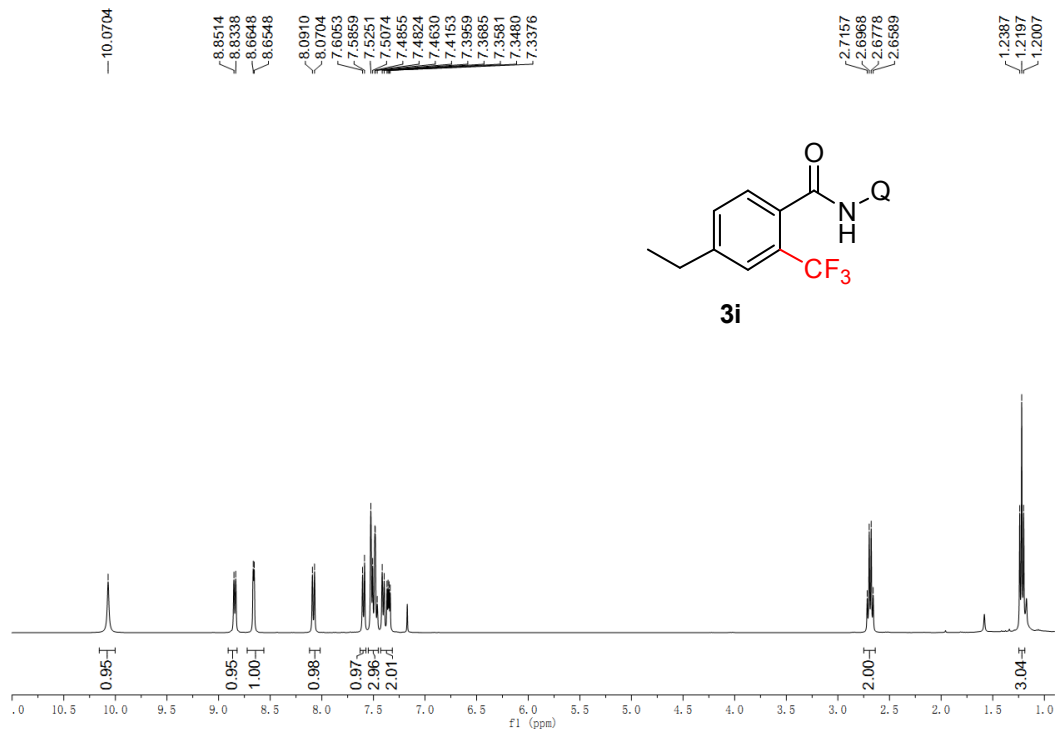


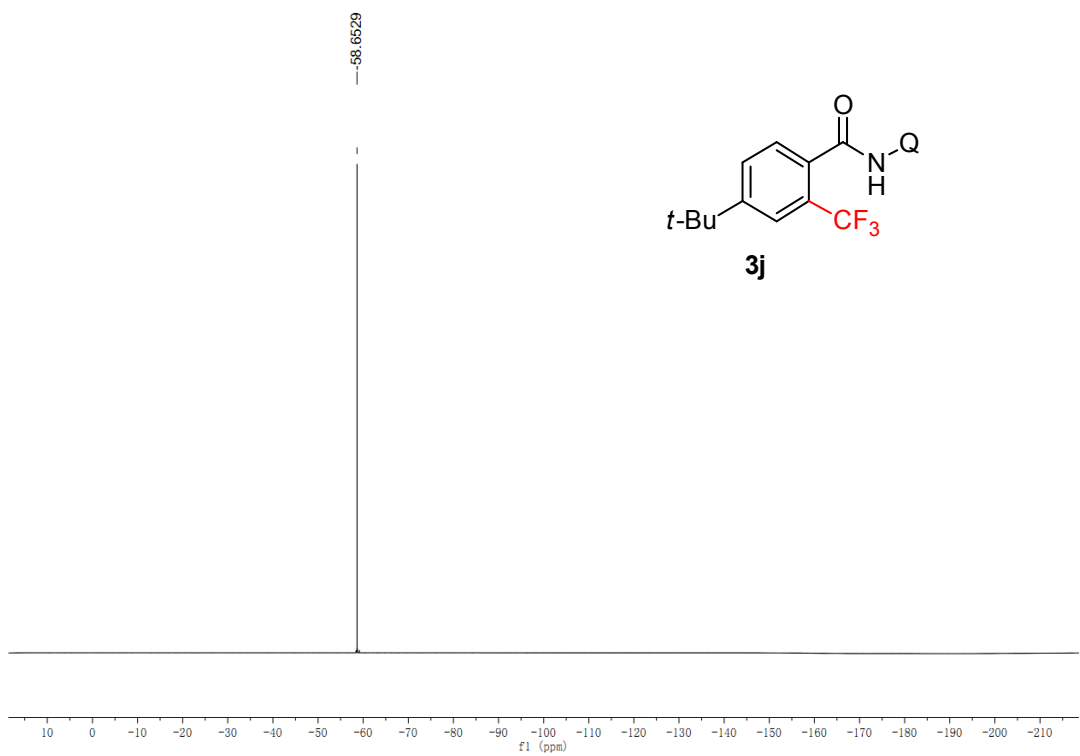
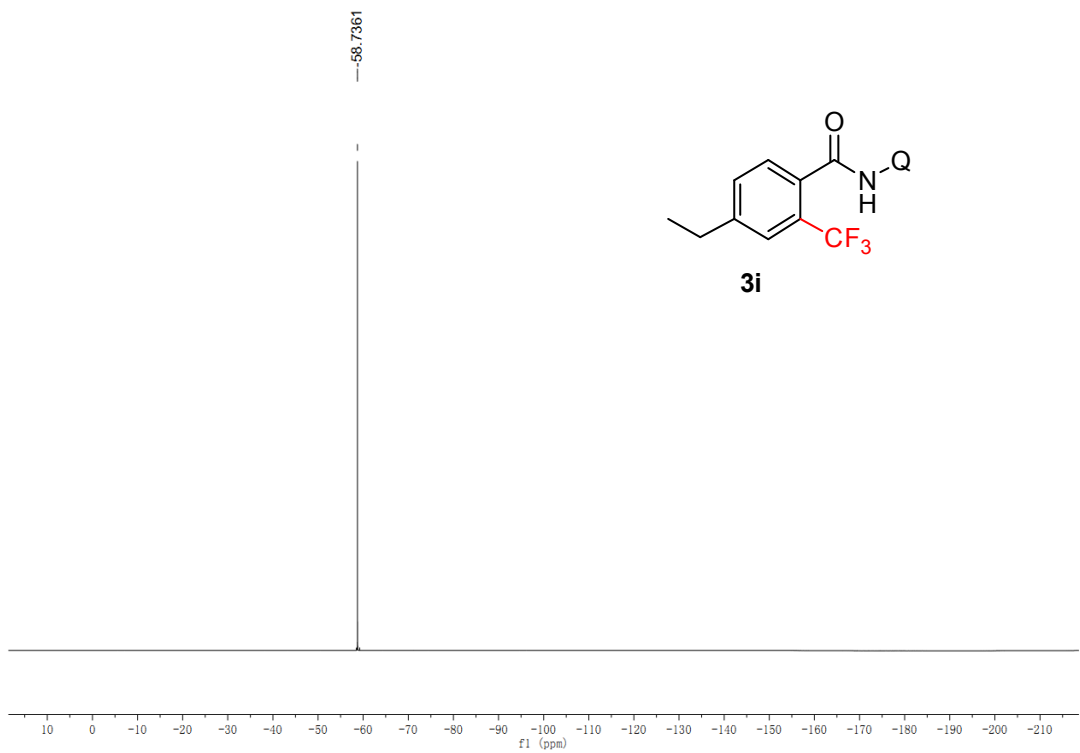


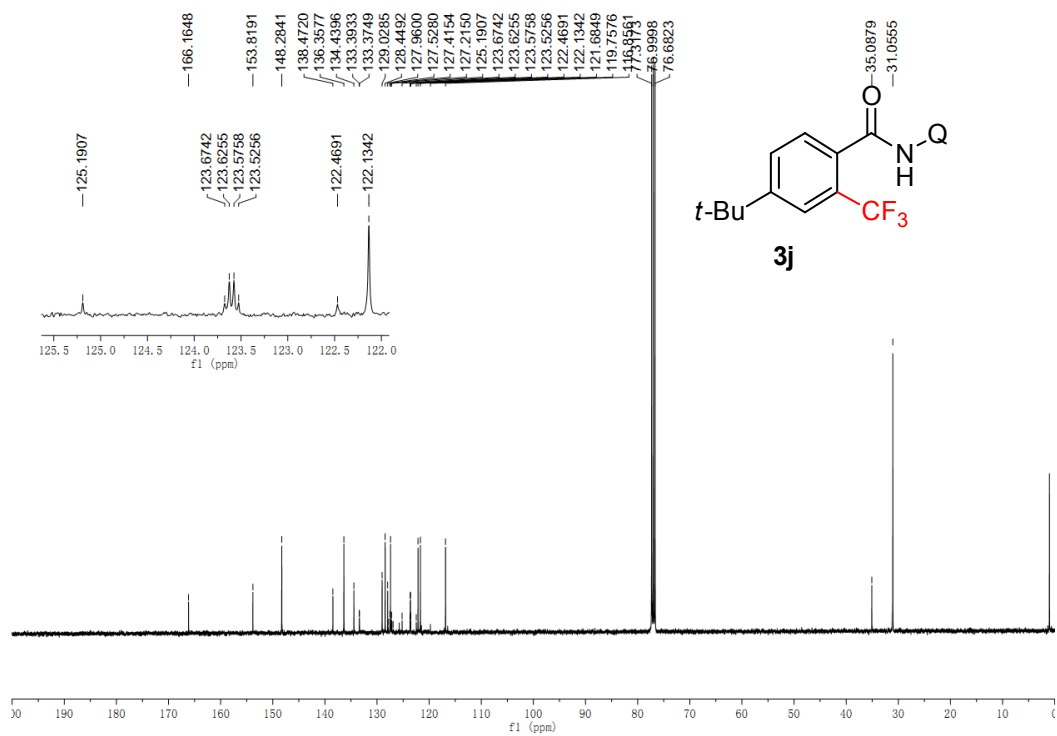
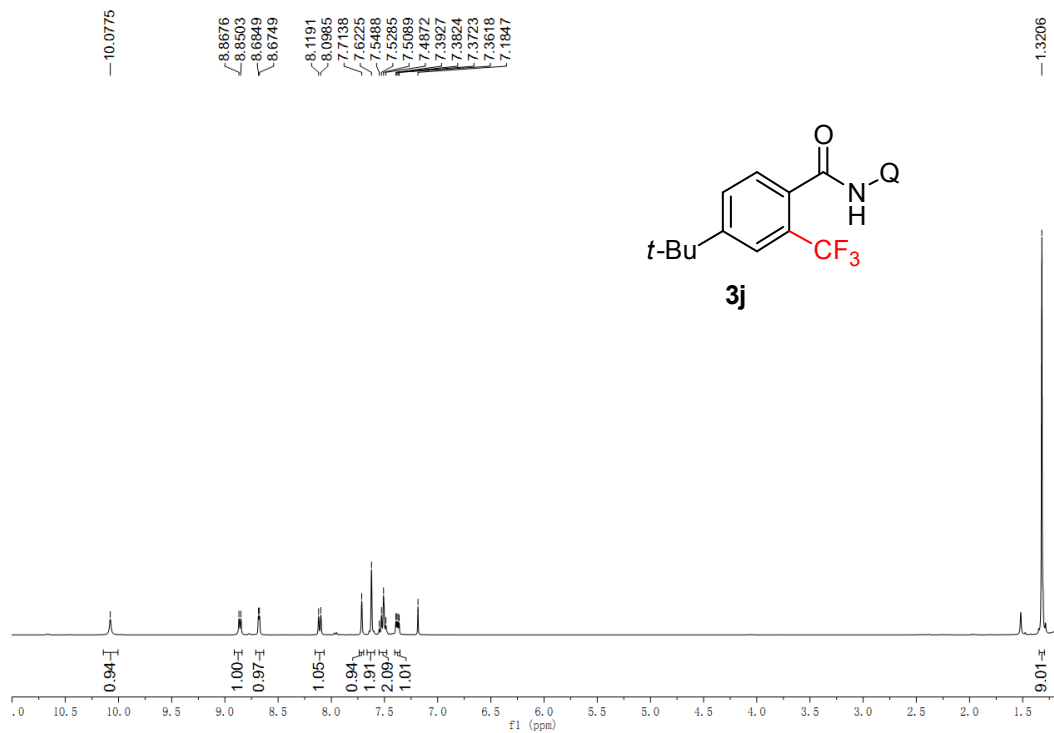


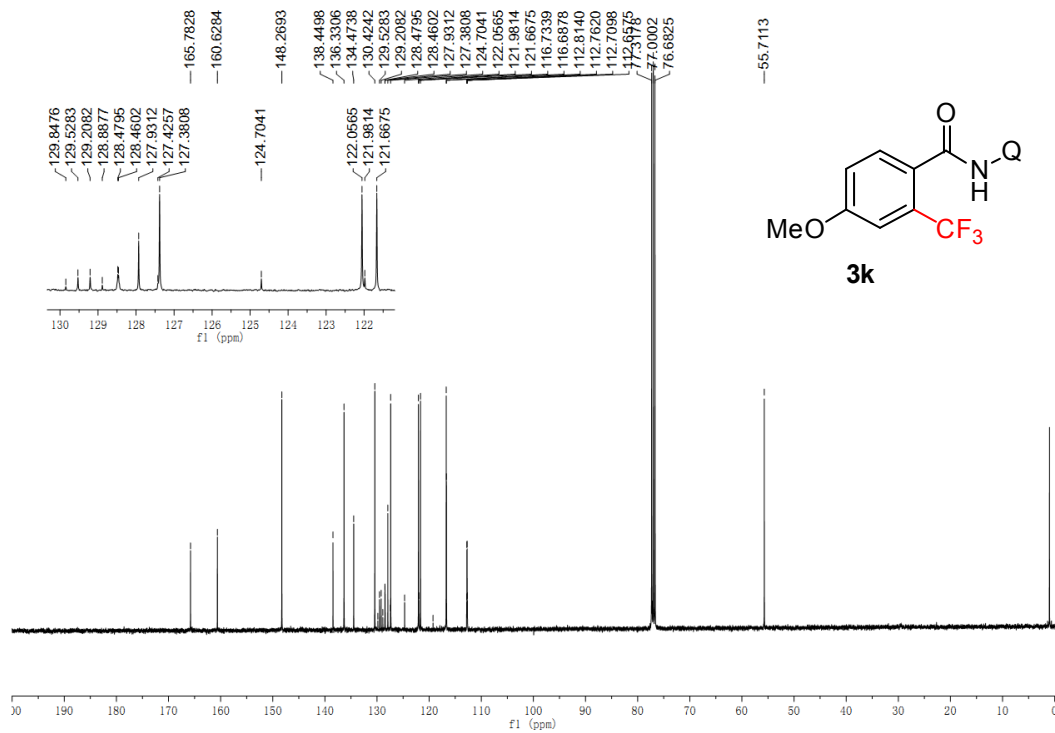
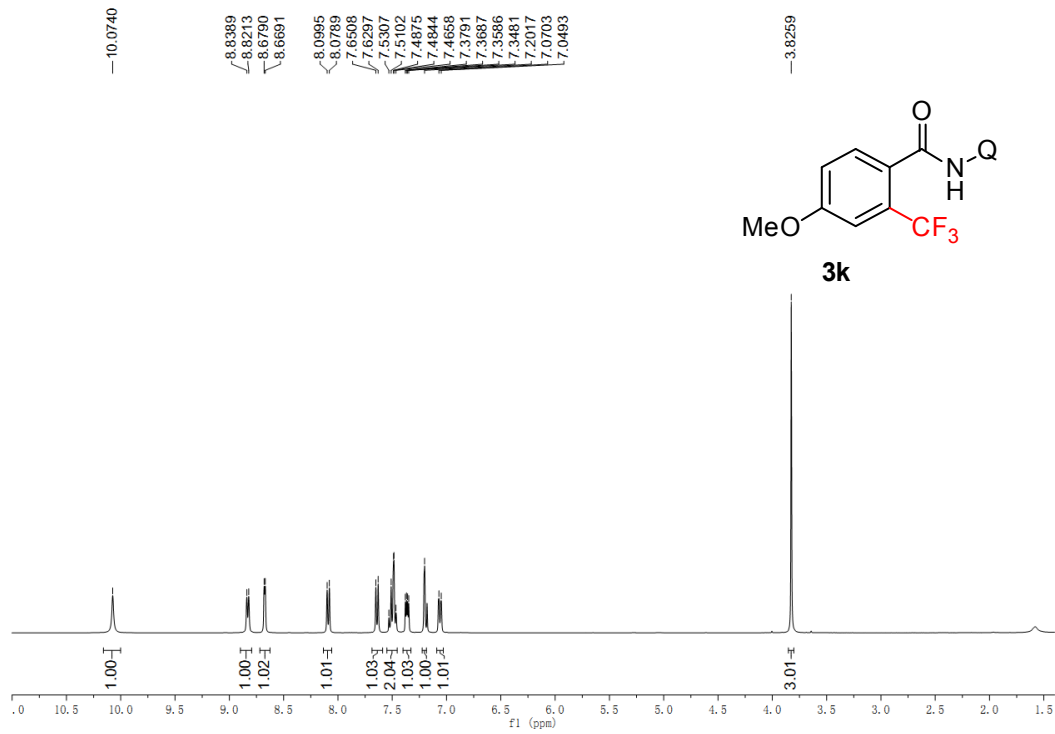


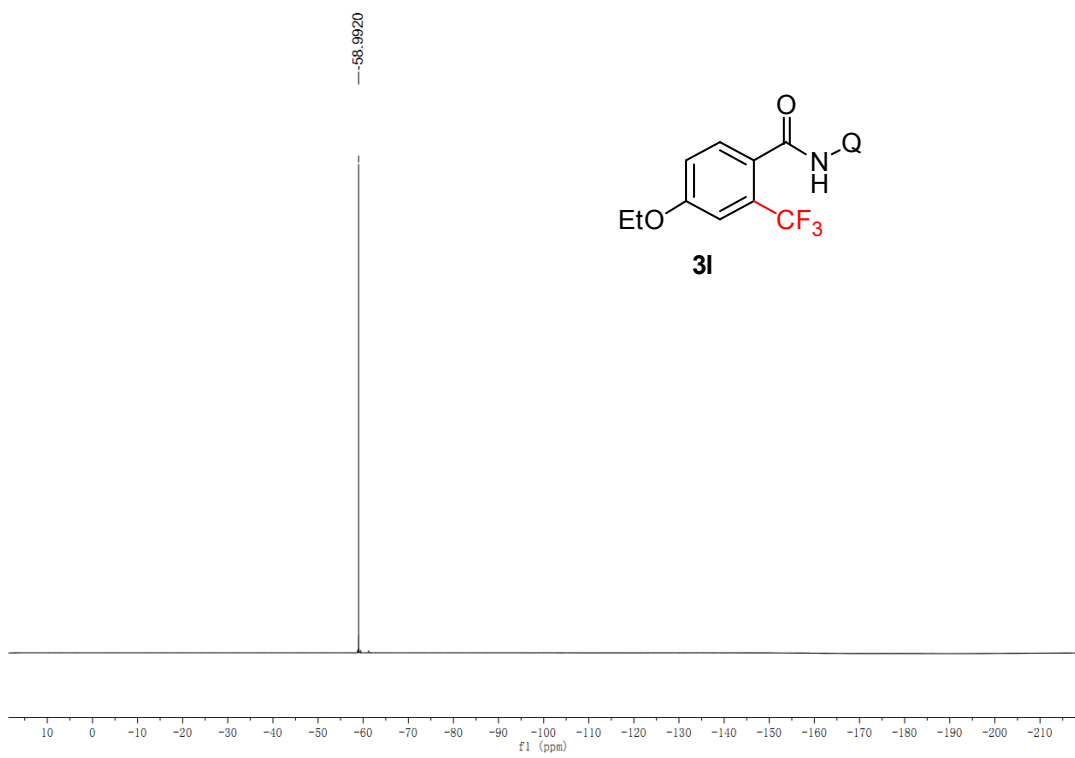
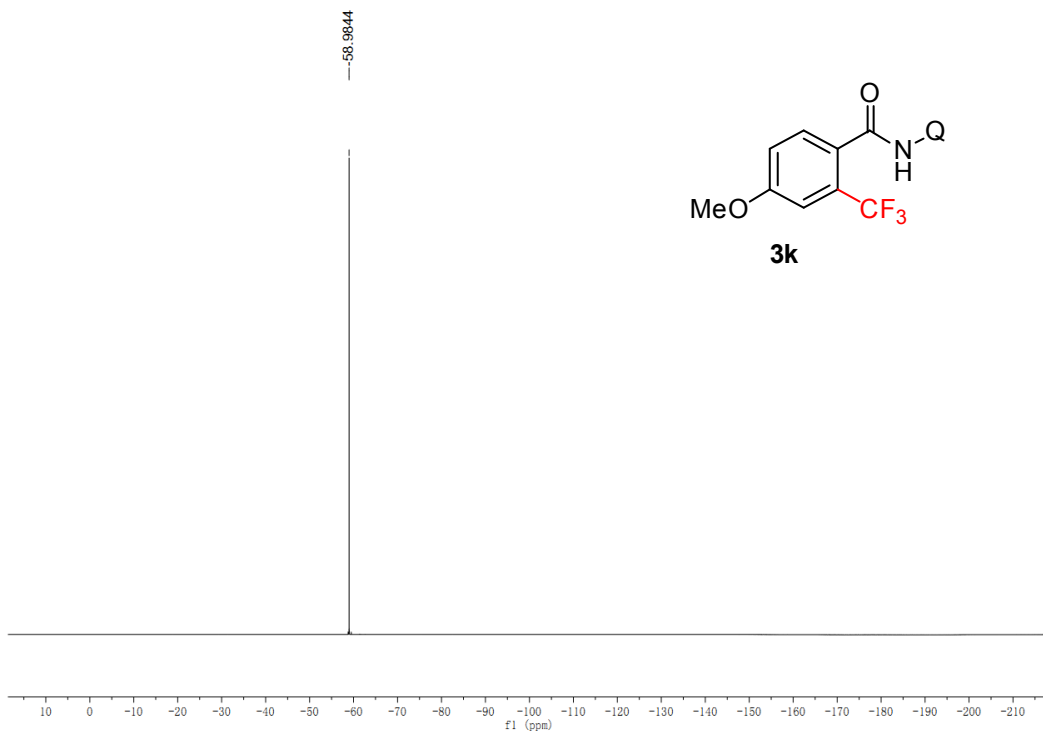


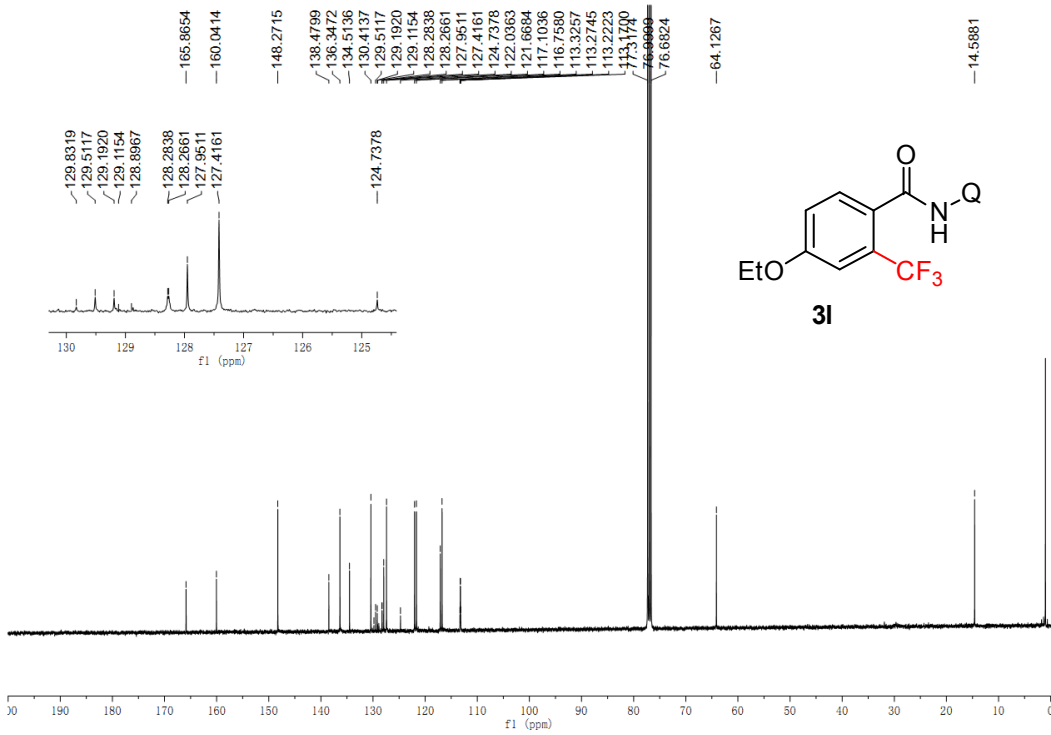
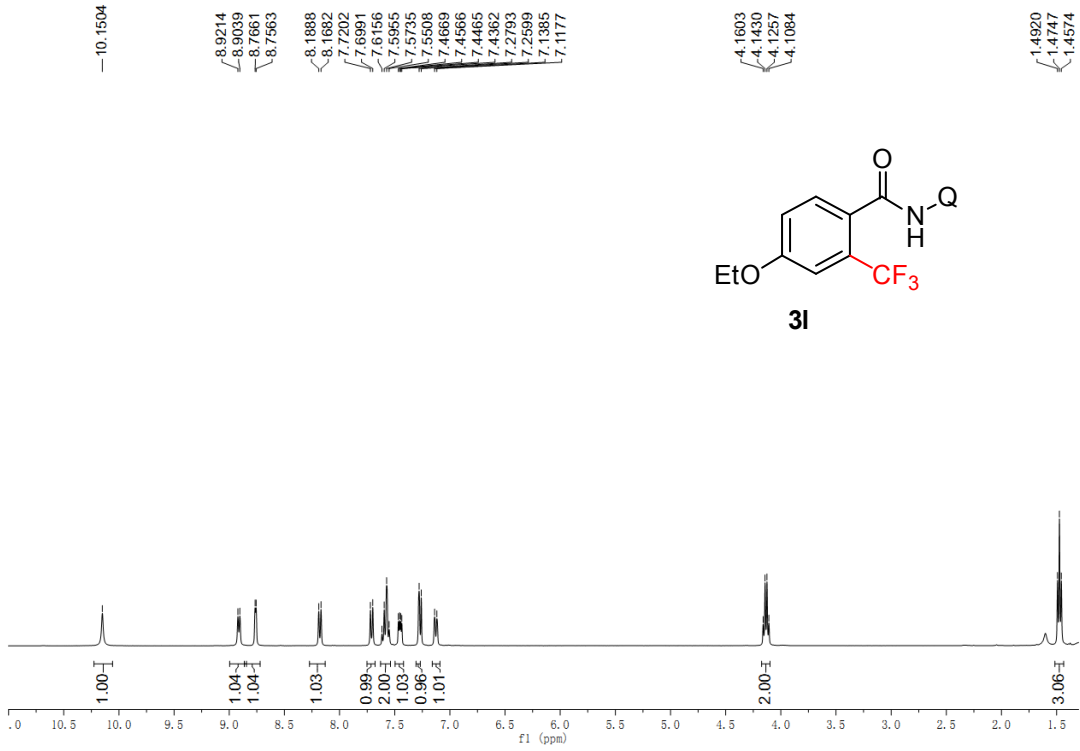


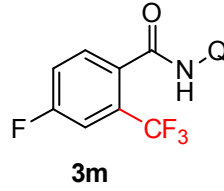
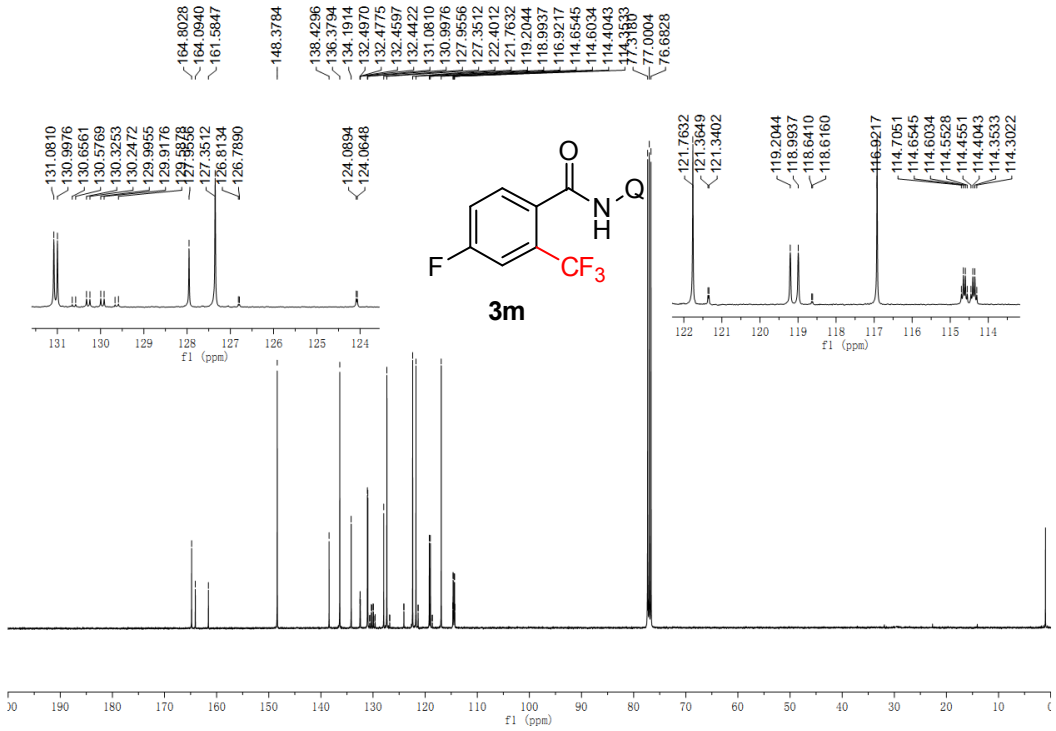
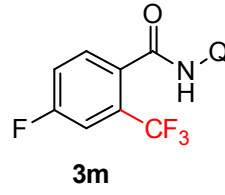
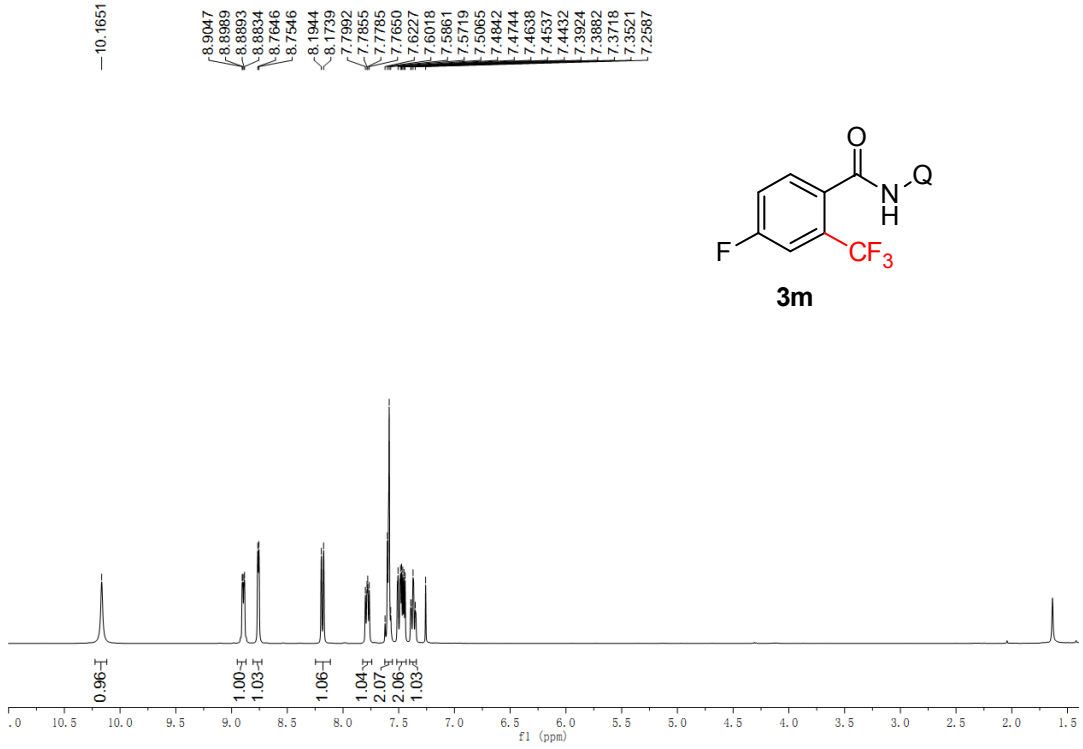


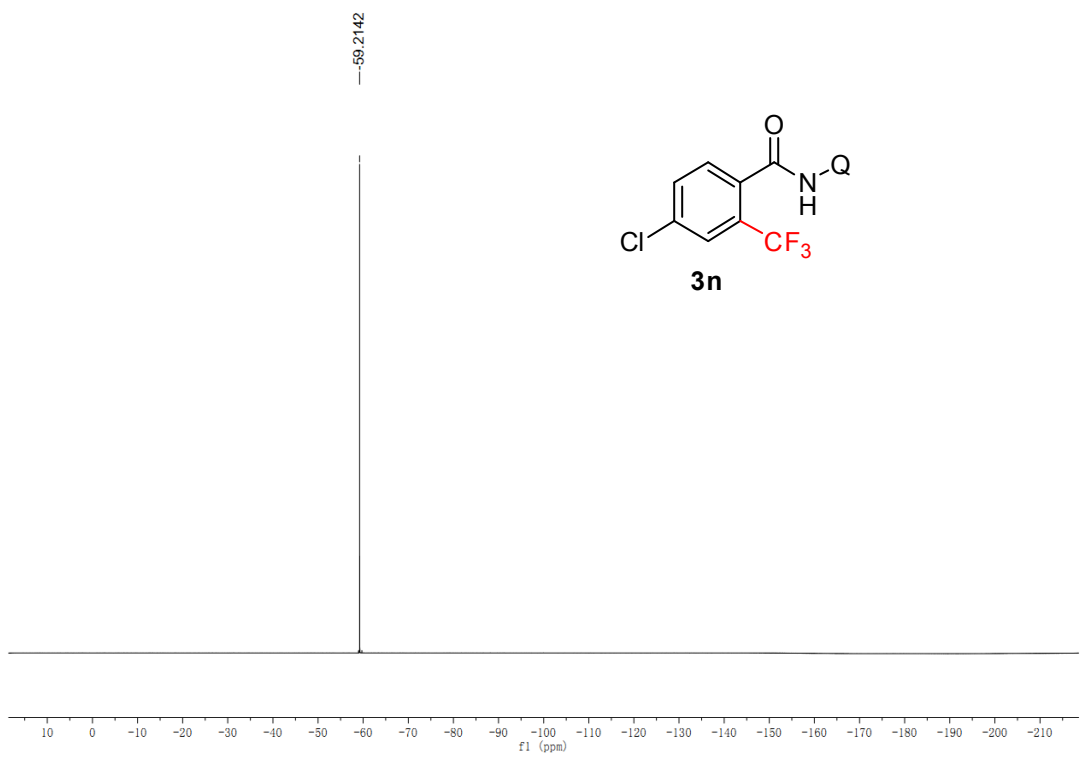
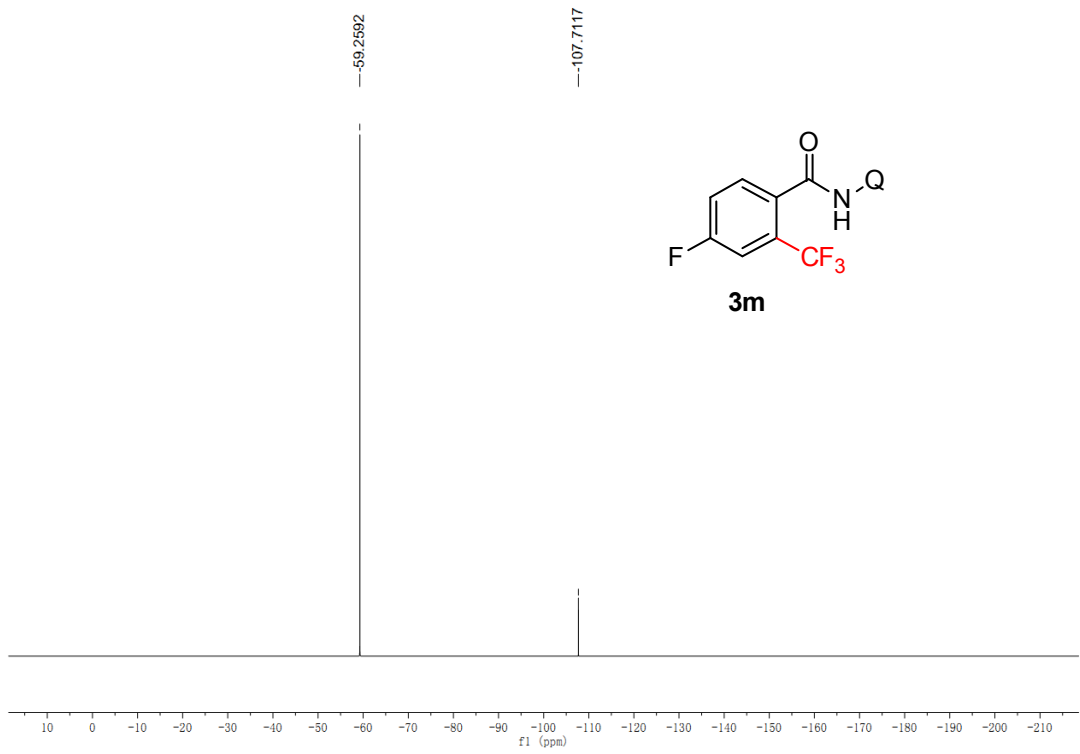


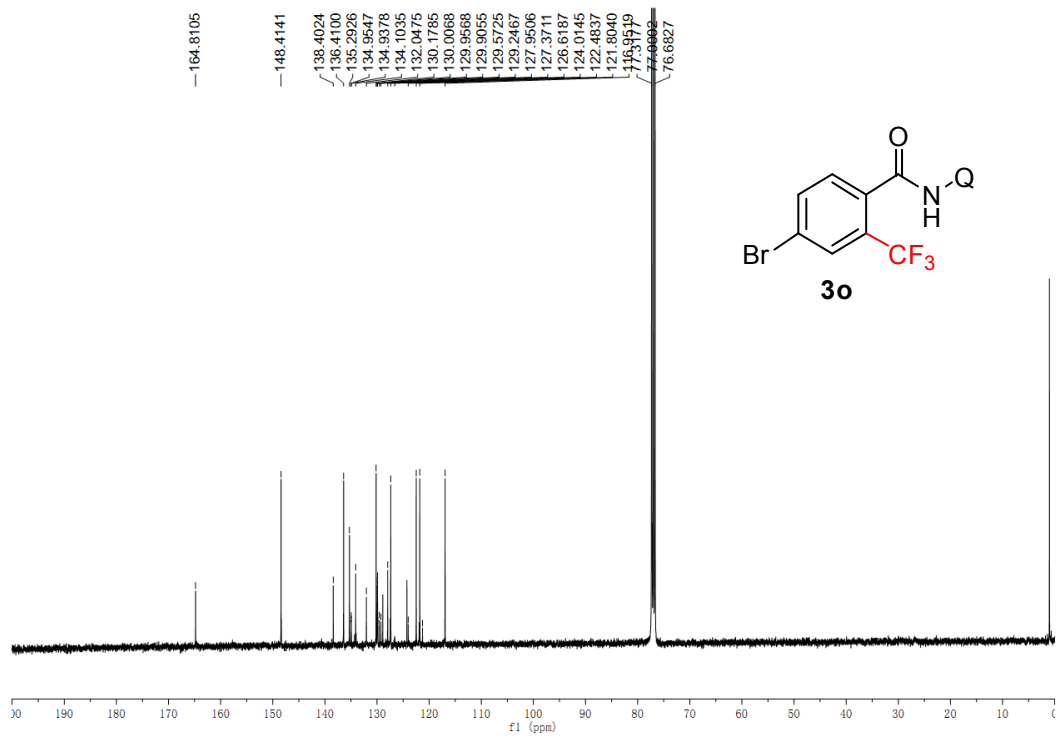
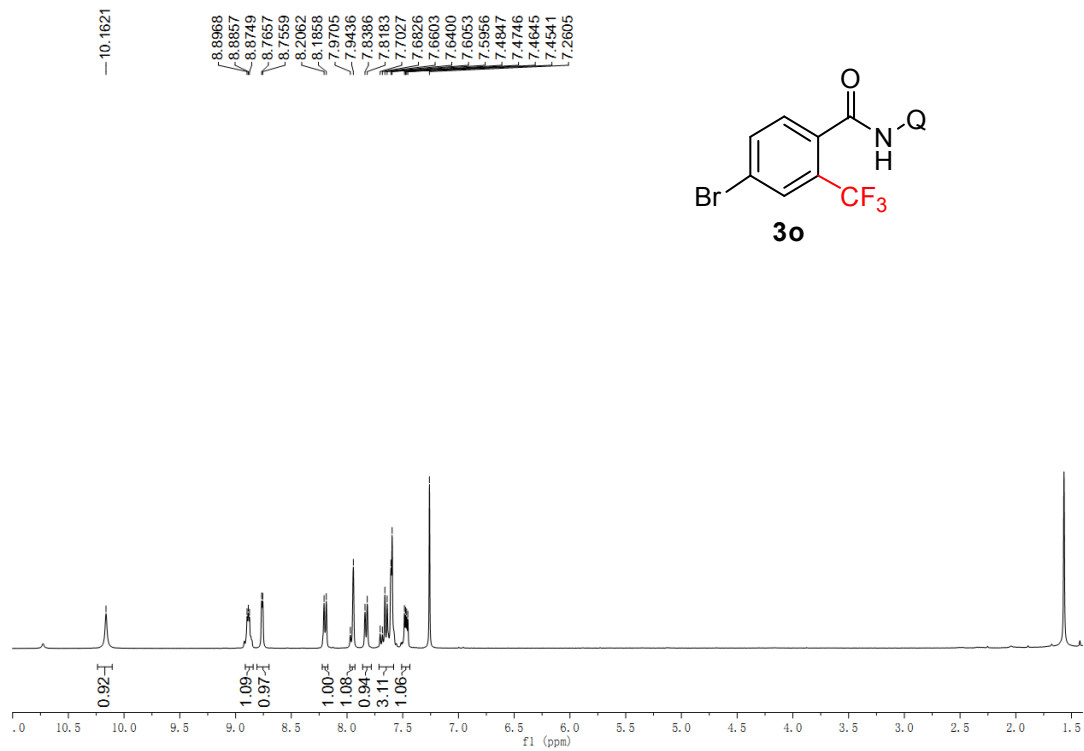


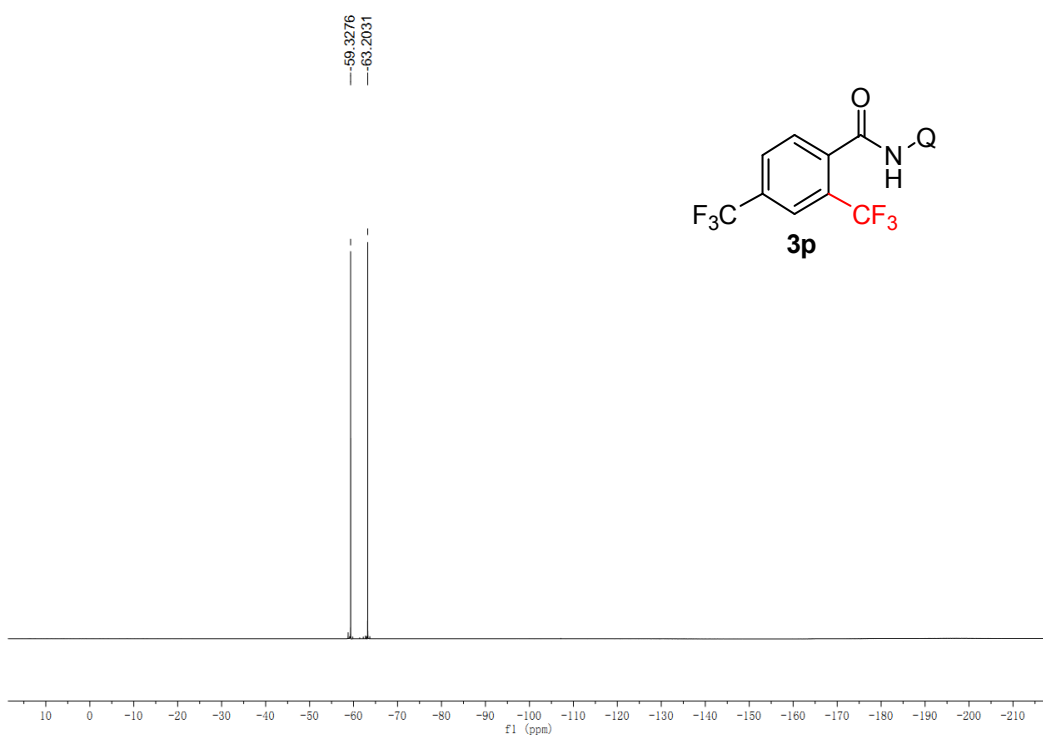
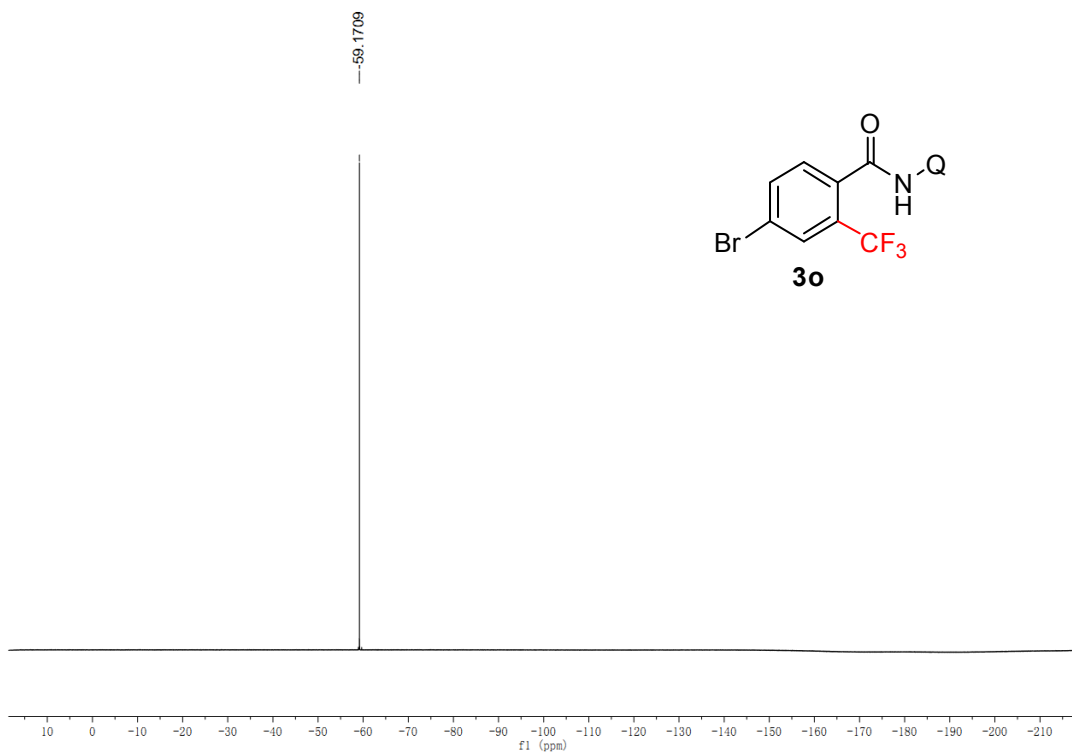






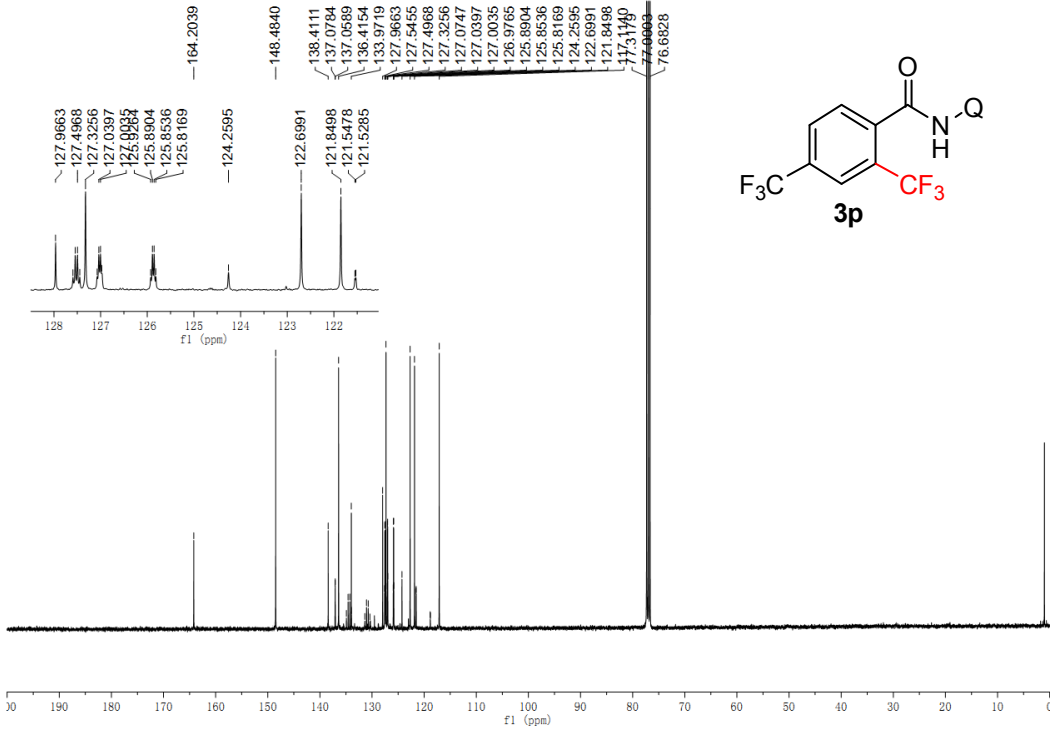
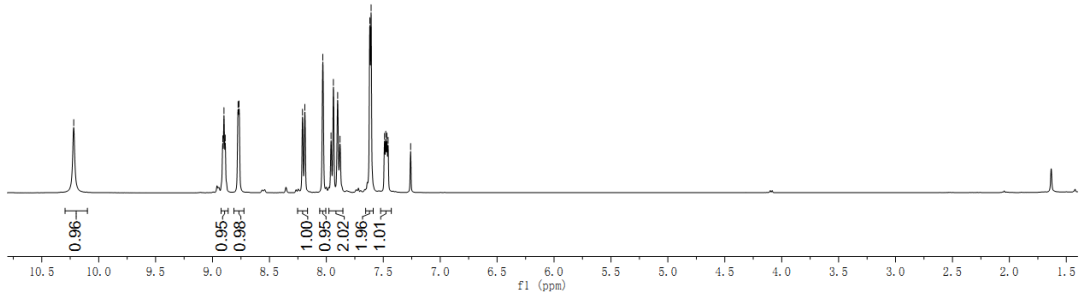
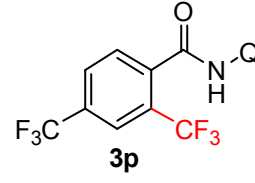






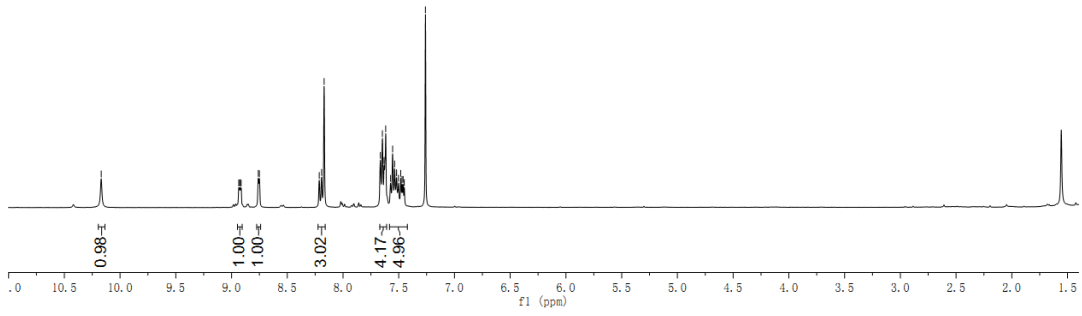
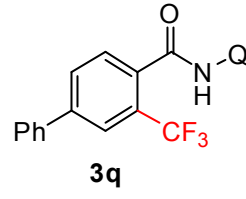
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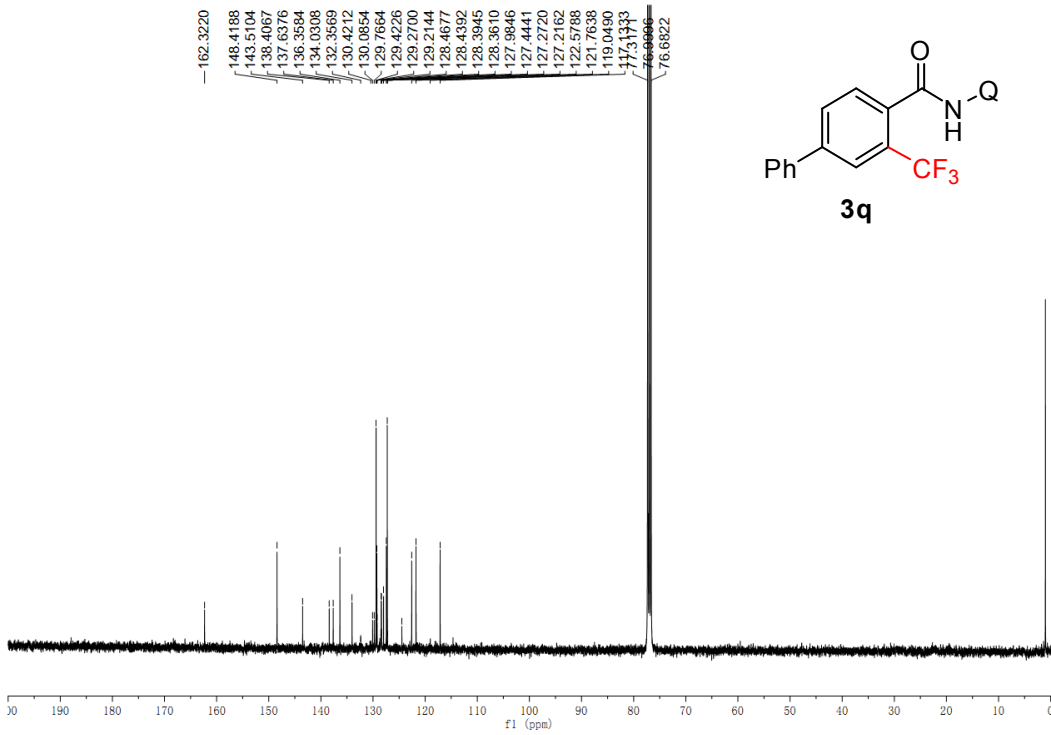
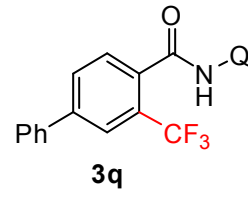


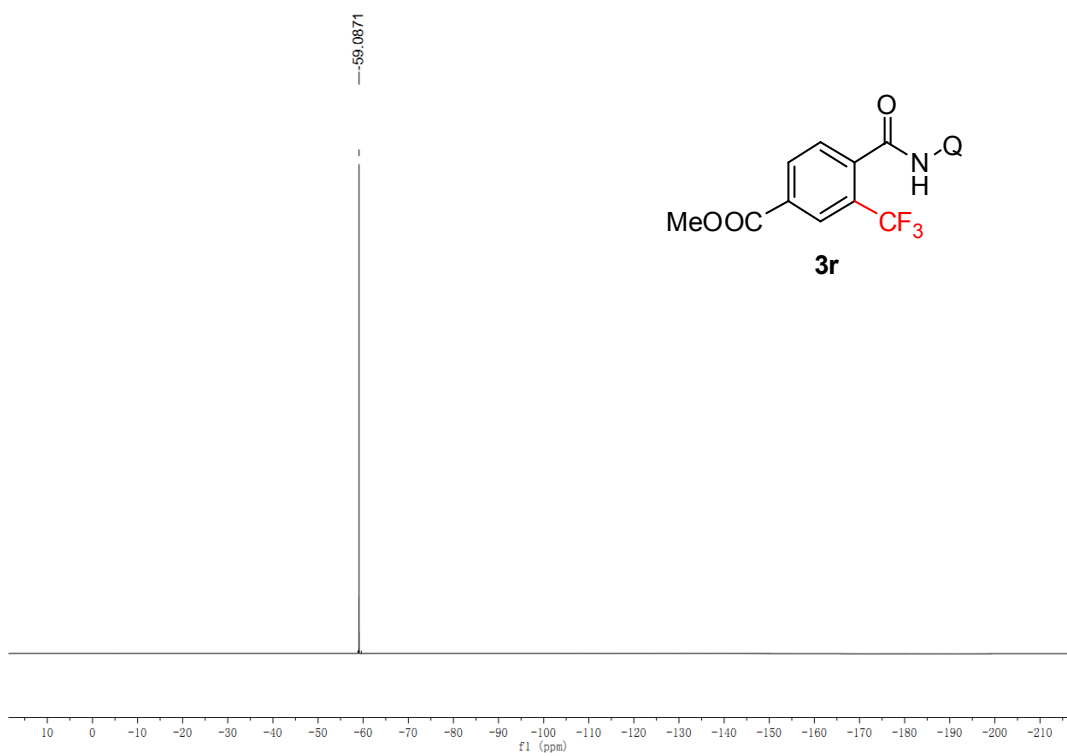
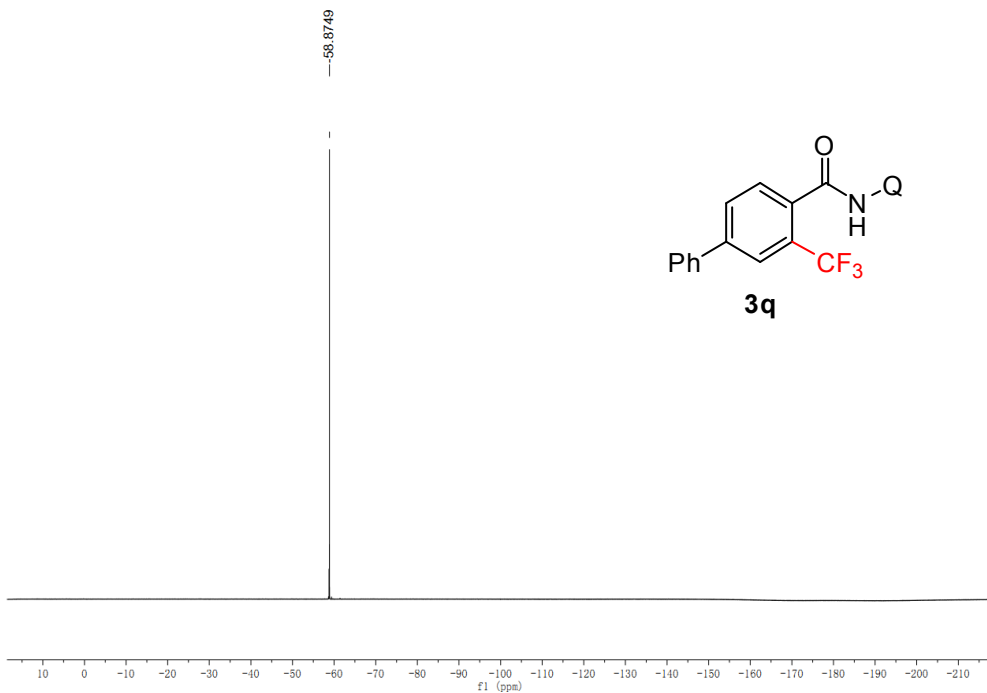
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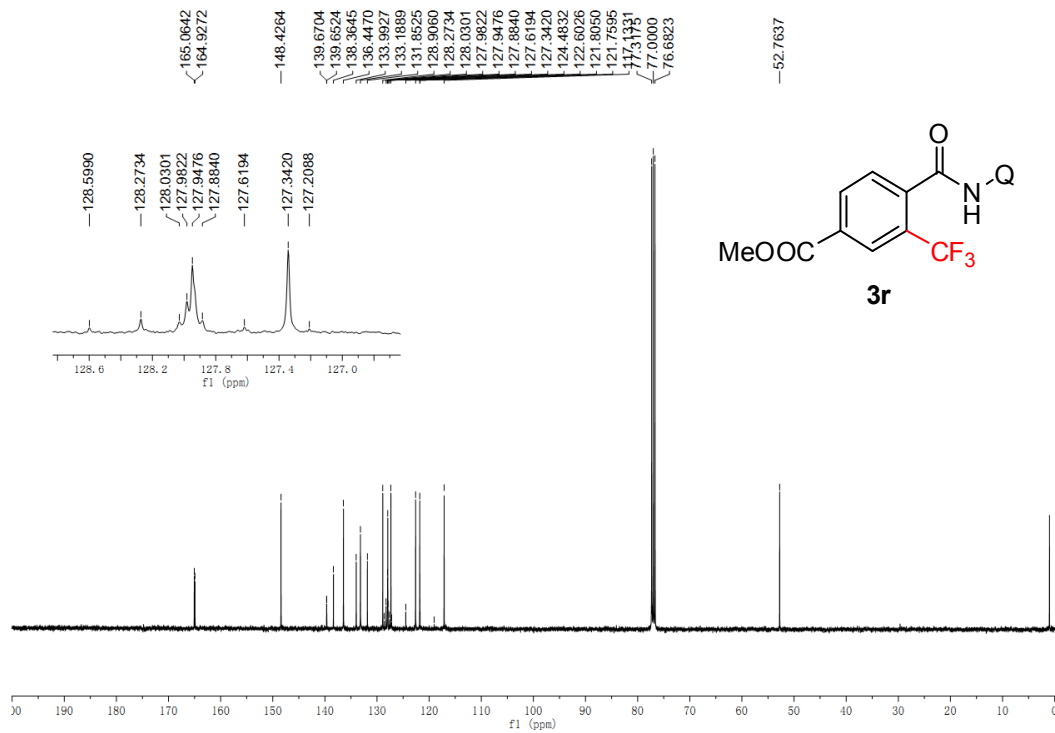
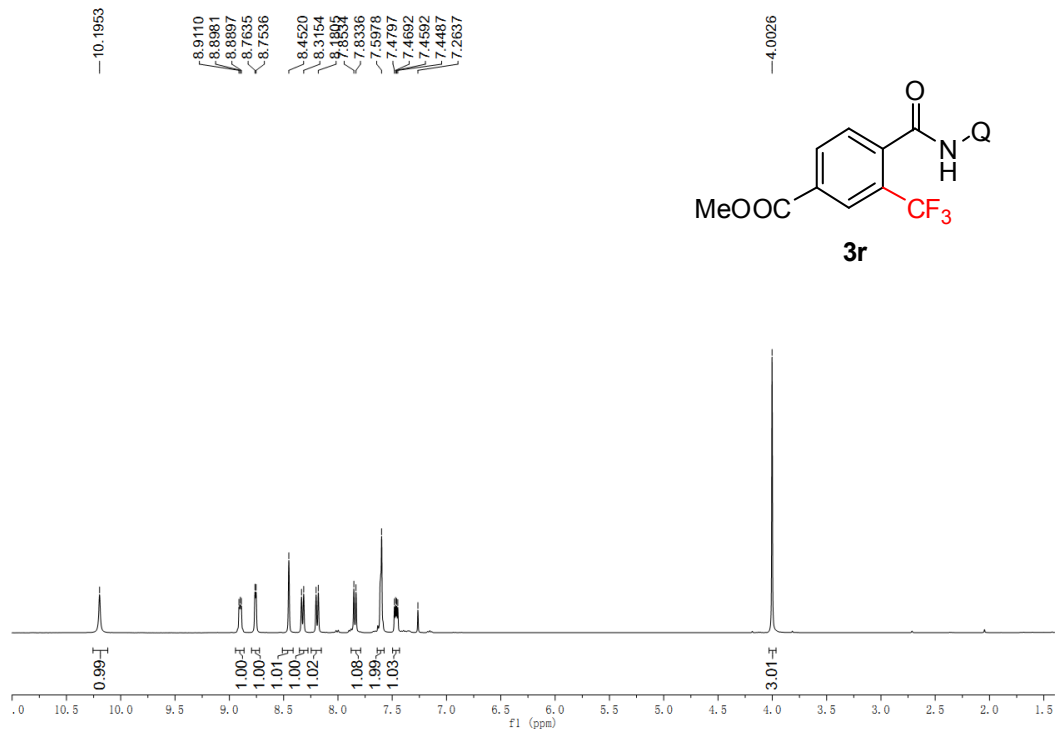
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7.6314
7.6170
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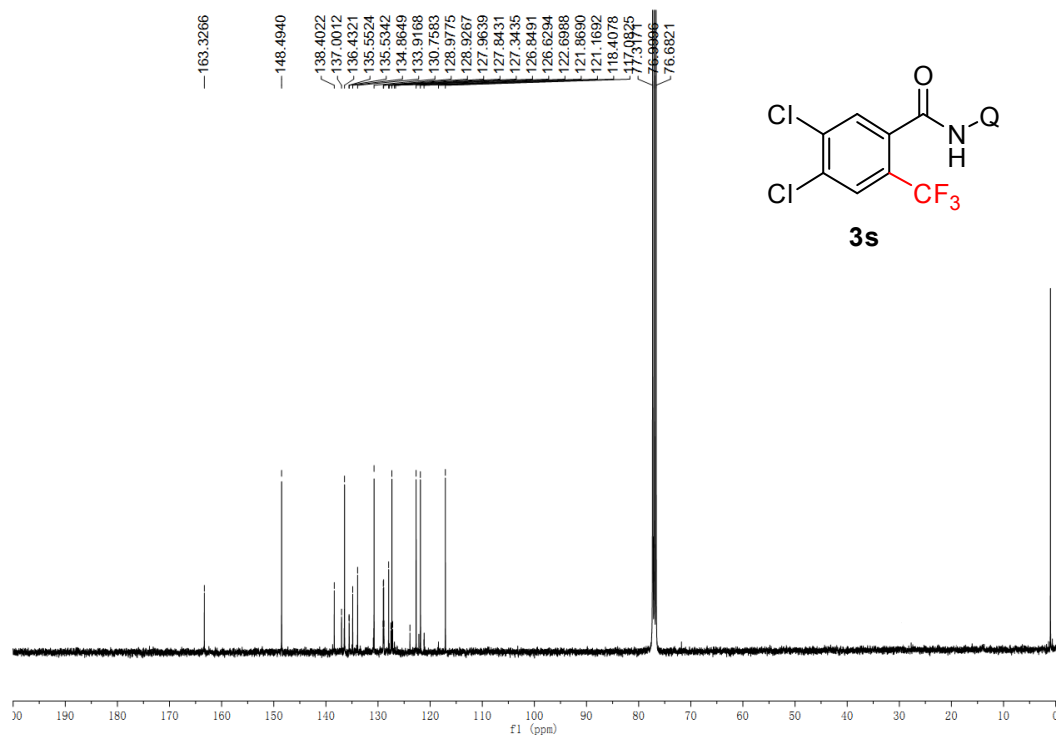
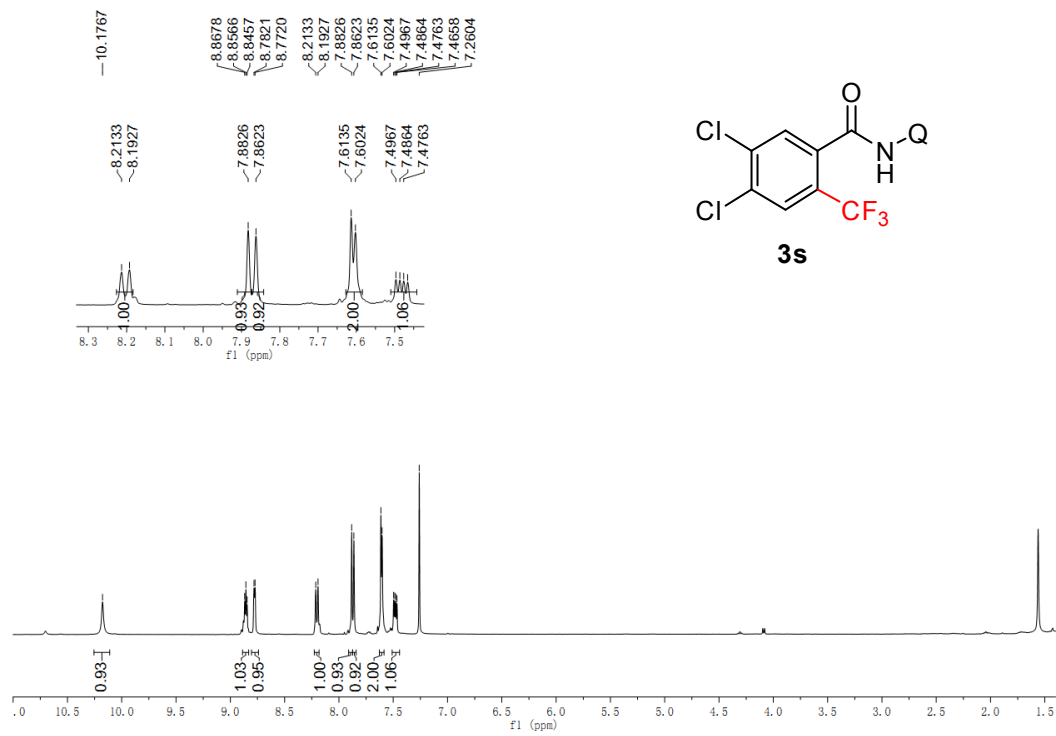


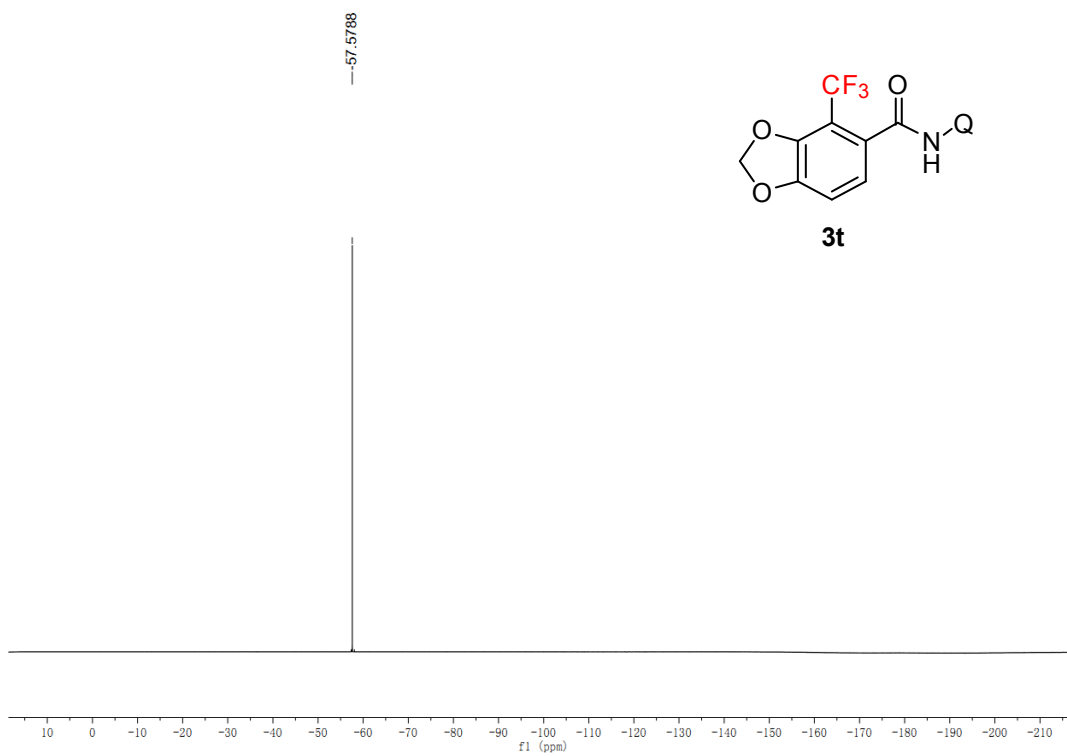
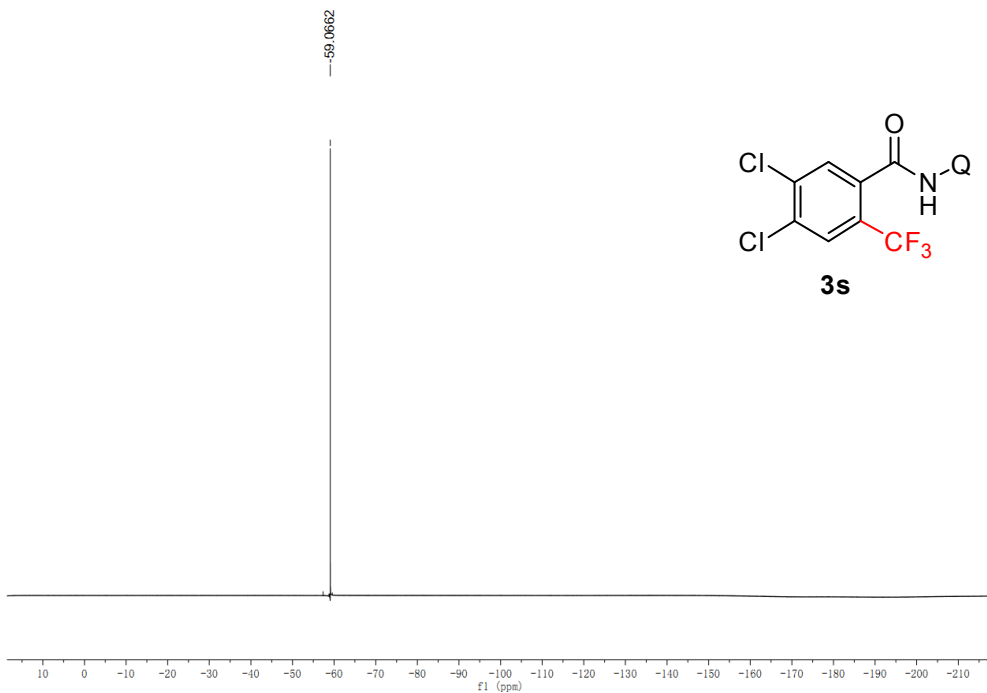
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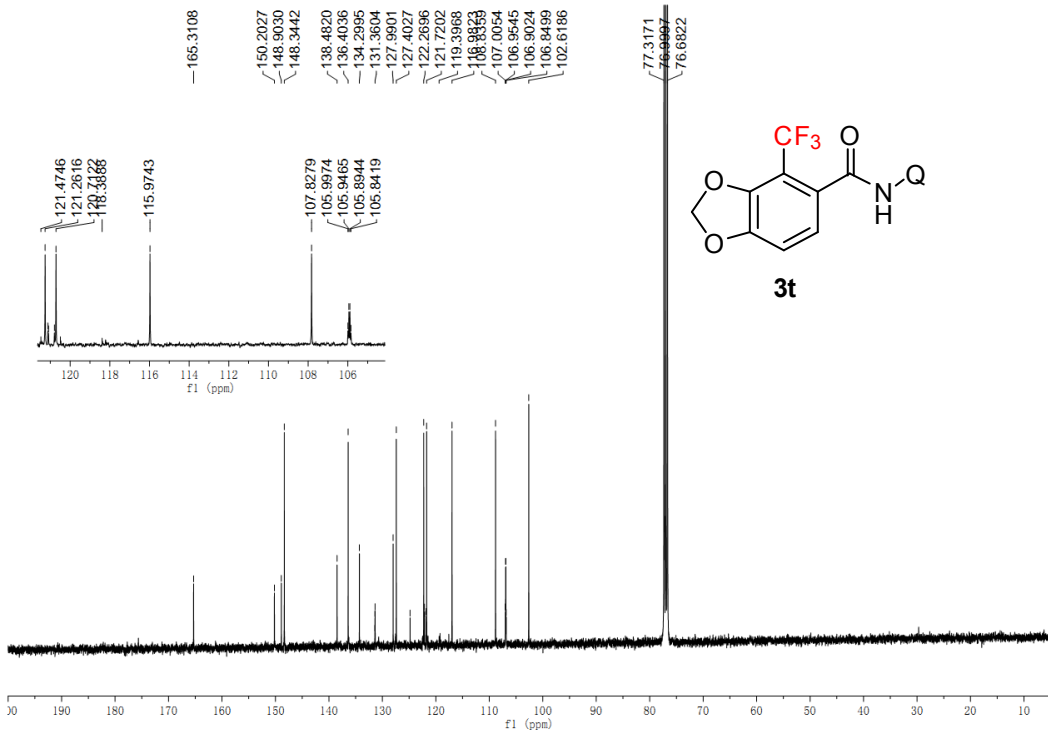
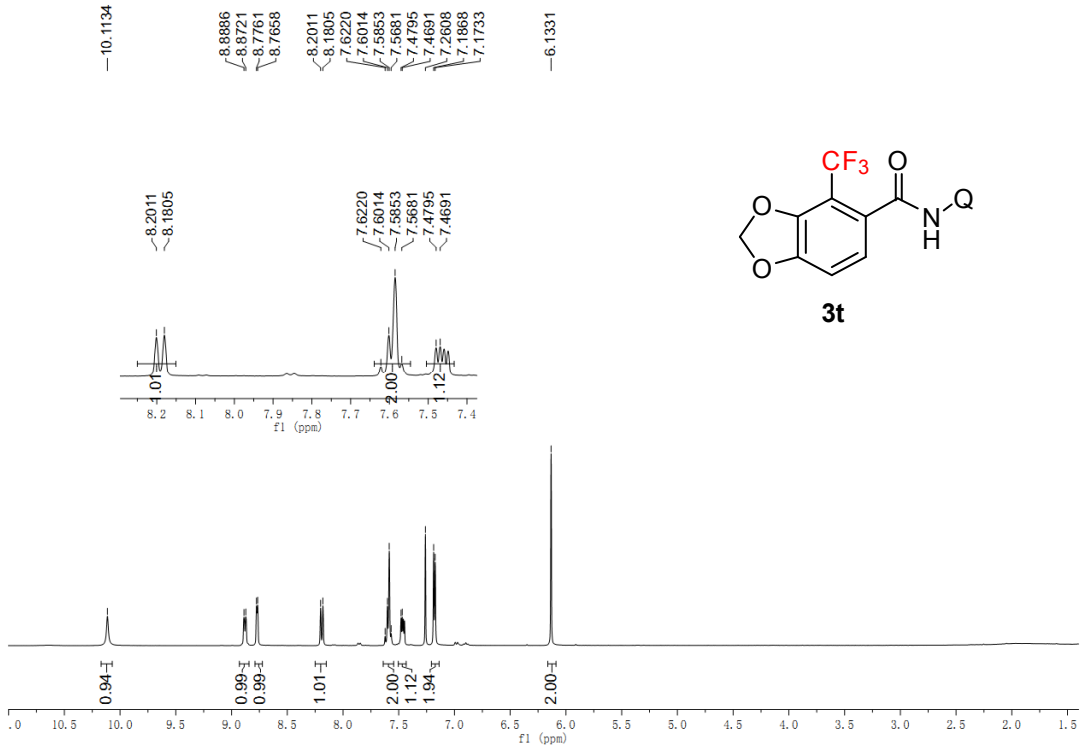


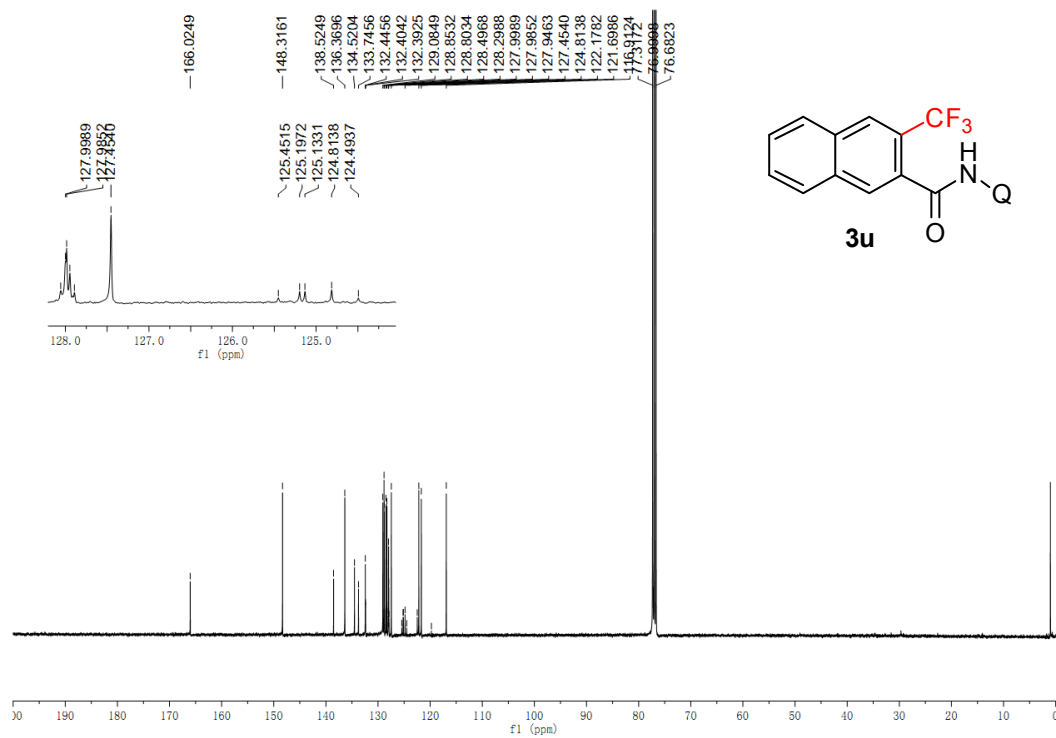
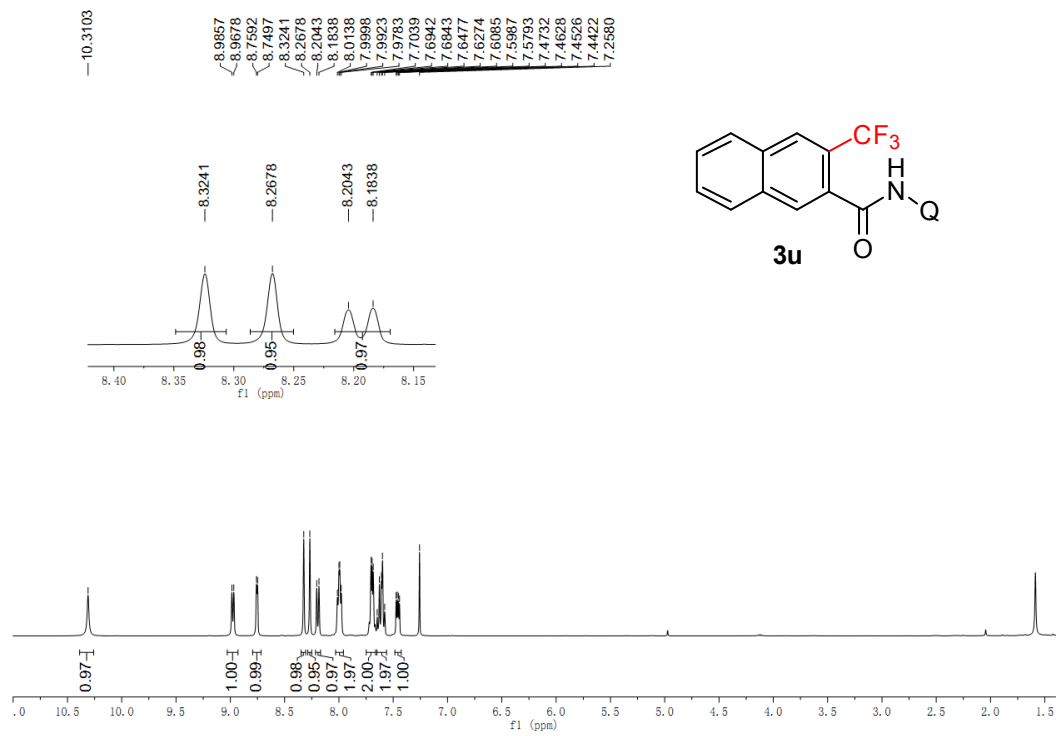


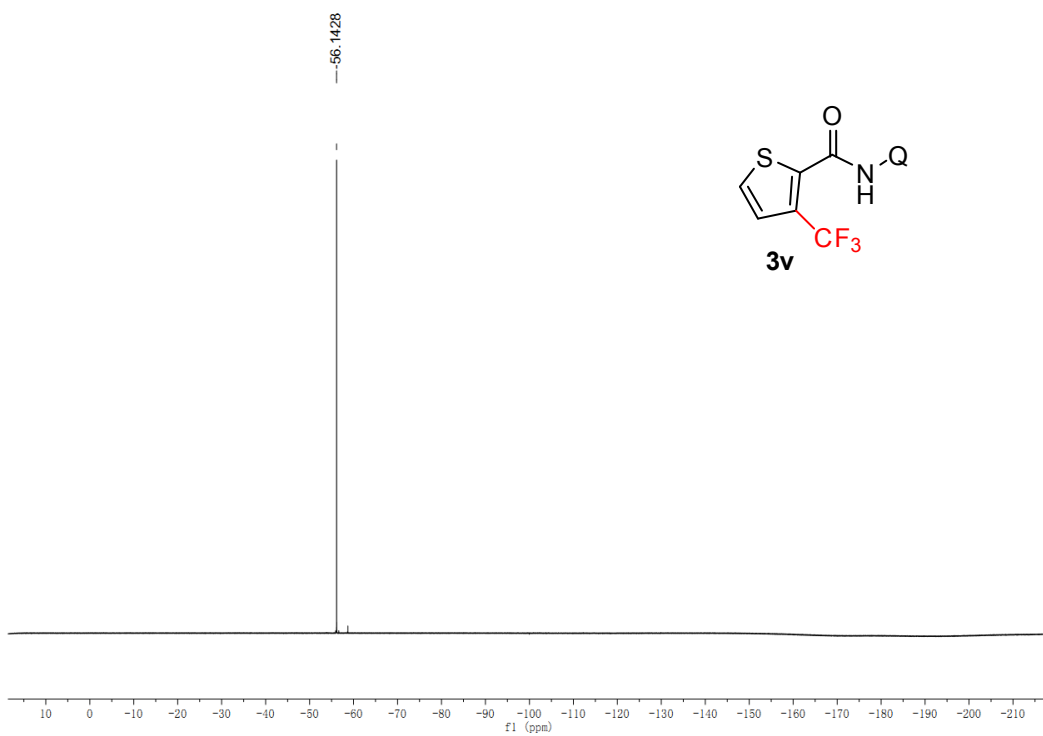
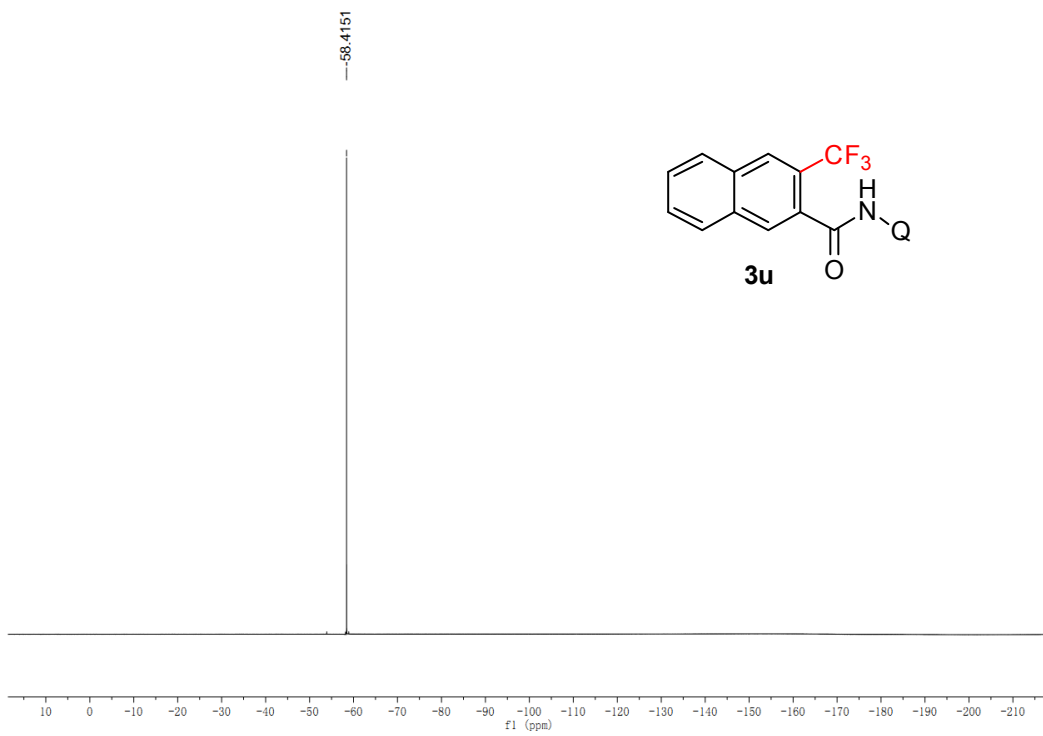






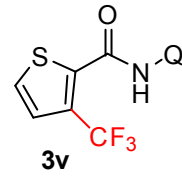
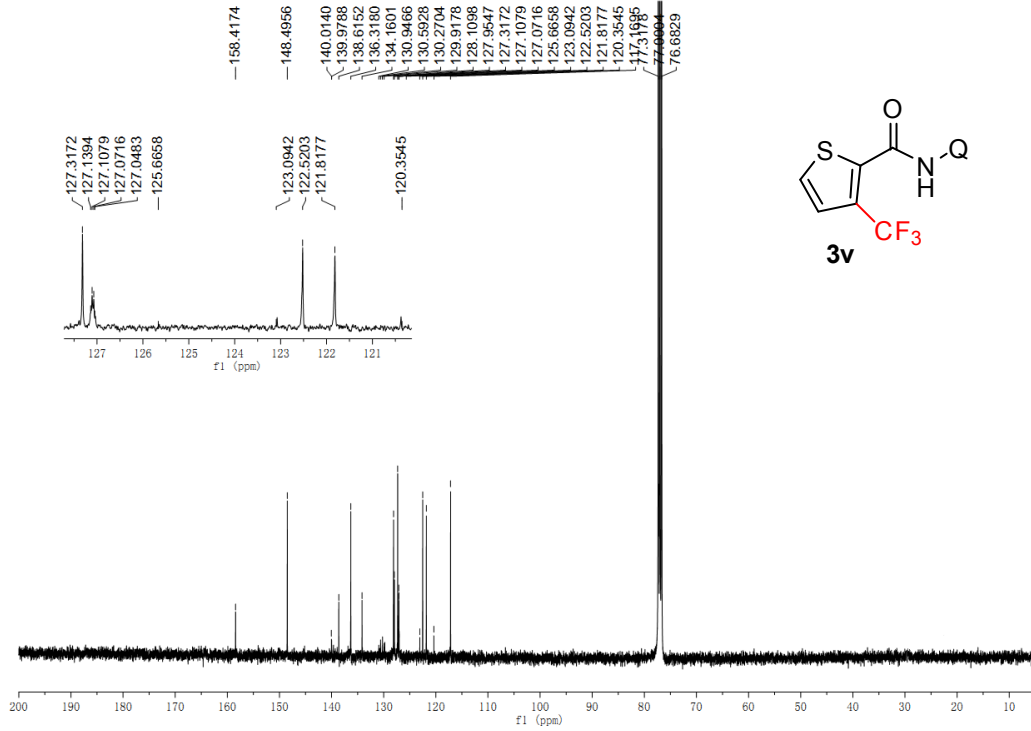
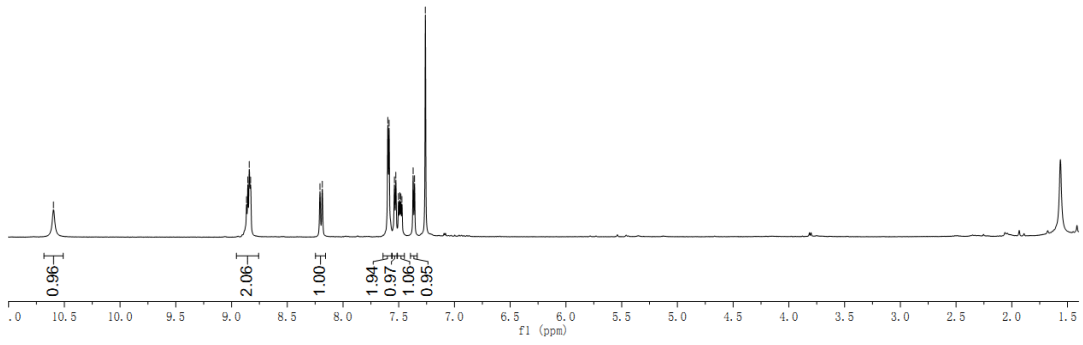
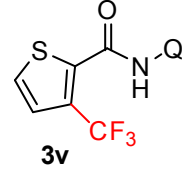


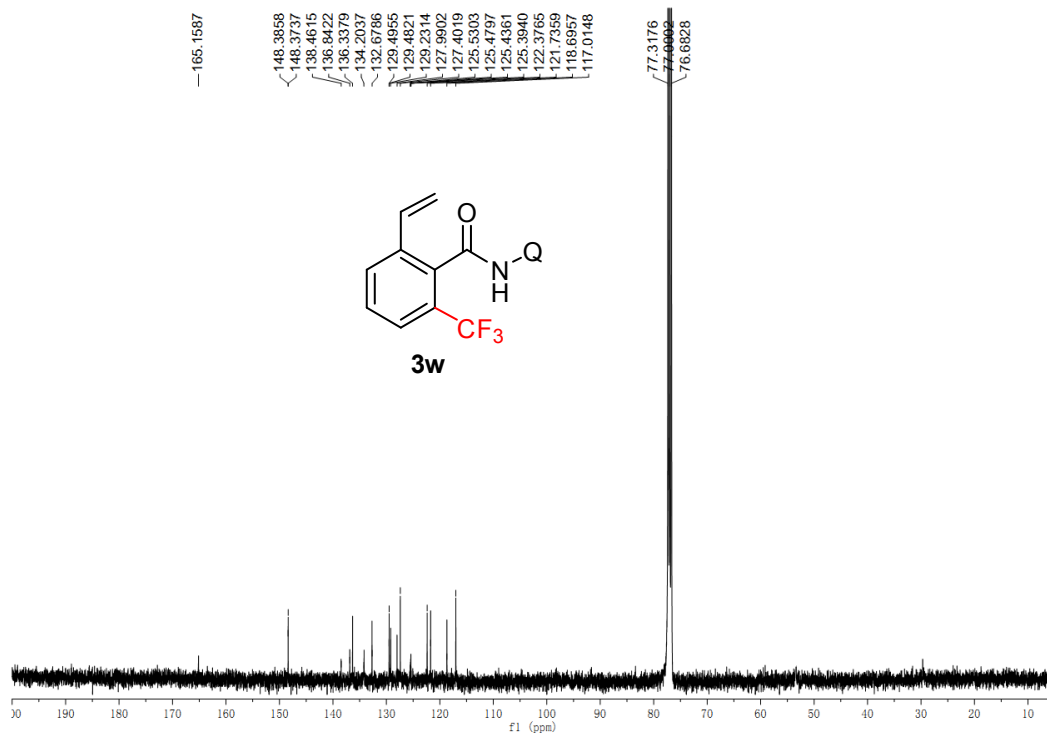
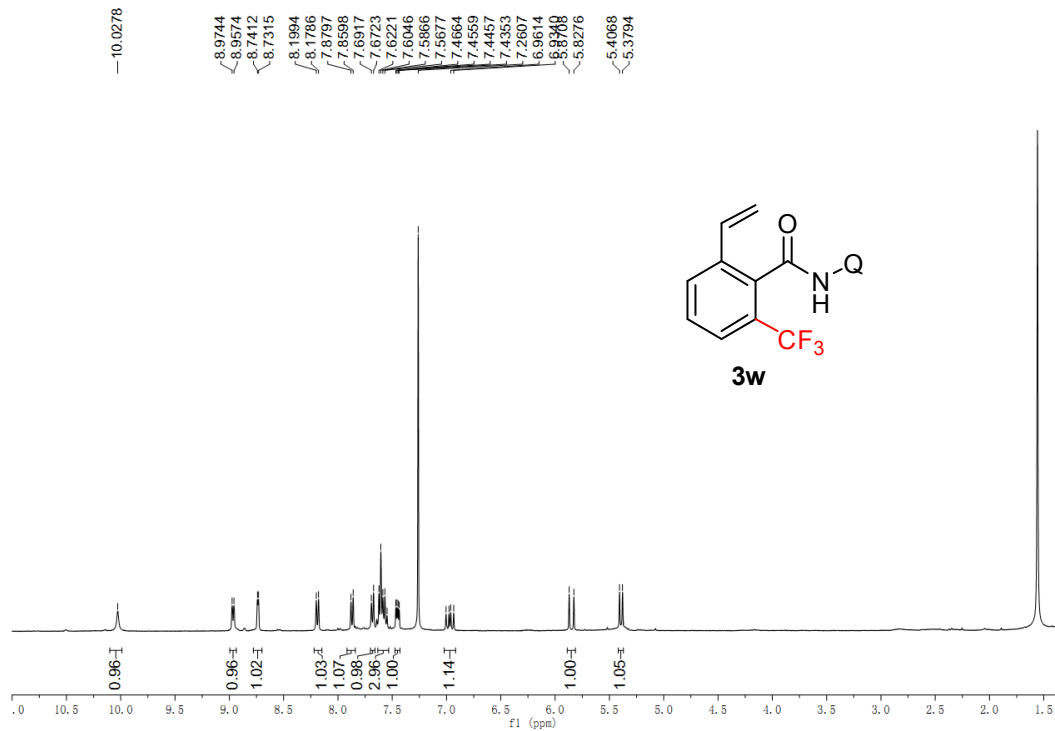




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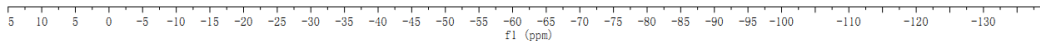
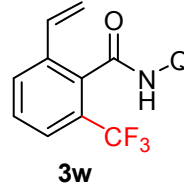
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7.4916
7.4813
7.4711
7.3713
7.3694
7.2611





¹⁹F NMR (376 MHz, CDCl₃) δ -59.03.

-59.0343



5. HRMS Spectra of TEMPO-CF₃

AB SCIEX

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225.134049118 (Mass/RT/Isotope/Library/Formula) ✓✓✓✓▲

