

Remote Selective Decarboxylative Difluoroarylmethylation of 8-Aminoquinolines under Transition Metal-Free Conditions

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1. General Information

Unless otherwise noted, all reagents and solvents were used directly as obtained commercially without further purification. Column chromatography was performed using silica gel (200-300 mesh size) with indicated solvents. Thin-layer chromatography (TLC) was conducted with silica gel GF254 precoated plates (0.25 mm) and visualized with UV light. All ^1H NMR spectra were recorded on 600 MHz spectrometers, and the data are reported in ppm using solvents as internal standards (CDCl_3 at 7.26 ppm, $\text{DMSO-}d_6$ at 2.50 ppm). All proton-decoupled ^{13}C NMR spectra were recorded at 151 MHz, and the data are reported in ppm using solvents as internal standards (CDCl_3 at 77.2 ppm, $\text{DMSO-}d_6$ at 39.5 ppm). HRMS analyses of the compounds were conducted on a Thermo Q Exactive mass spectrometer using electrospray ionization in the positive ion mode. All the compounds were solid, and melting points were measured on a micromelting point apparatus.

2. General Procedures

General Procedures for the Synthesis of 8-Aminoquinolines¹

A 100 mL two-necked round-bottom flask was equipped with magnetic stirbar and charged with 8-Aminoquinoline (10 mmol), *N,N*-dimethyl-4-aminopyridine (DMAP, 0.1 equiv, 0.12 g) dissolved in 15 mL anhydrous CH_2Cl_2 at 0 °C. Then acyl chloride (15.0 mmol) was added to the system dropwise under air. After the addition, the reaction was then warmed to room temperature, stirred for overnight and extracted three times using dilute hydrochloric acid (1.0 mol/L) and saturated sodium carbonate solution, the organic layer was dried over Na_2SO_4 , and the target product was obtained by flash column chromatography on silica gel using petroleum ether and ethyl acetate.

General procedure for the Synthesis α , α -difluoroarylacetic acids²

Activation of Cu powder:

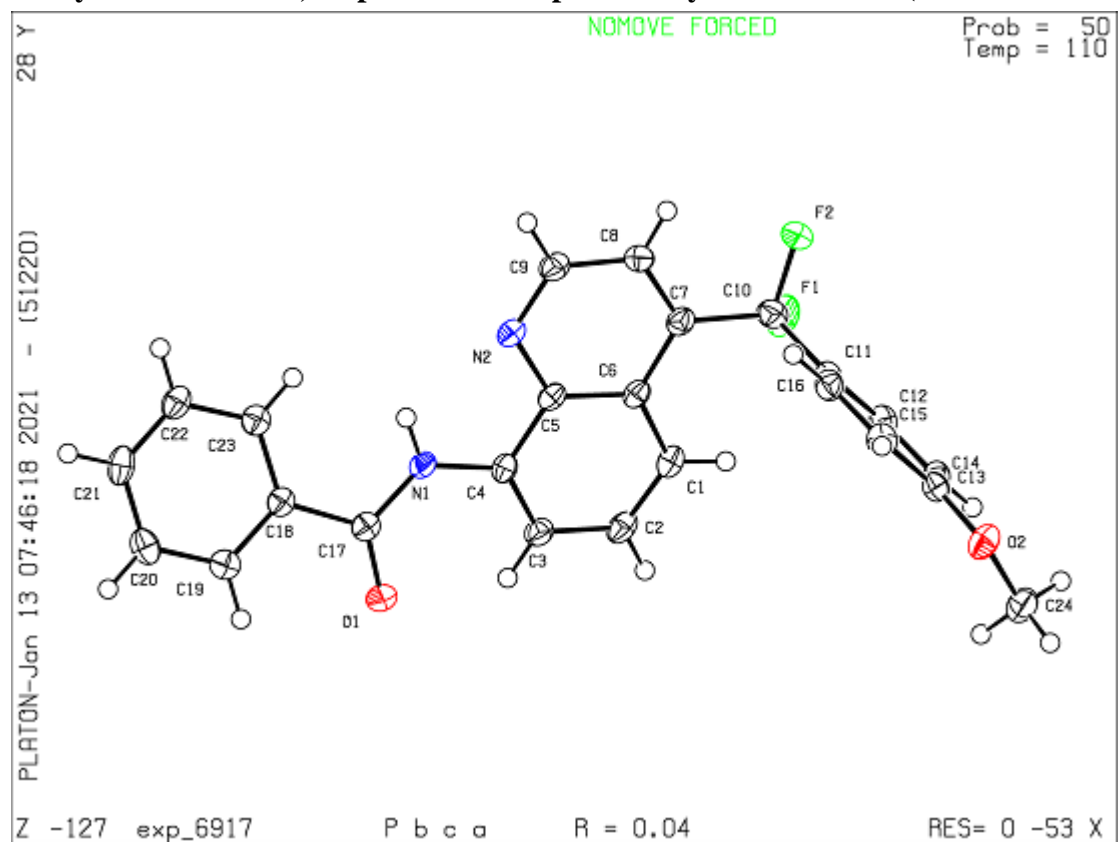
Copper powder (< 424 μm , 26 mmol) was stirred vigorously in diluted aq. HCl (1 M, 10 mL) for 10 min at room temperature and filtered. This procedure was repeated with water (10 mL), MeOH (10 mL) and acetone (10 mL), respectively. Finally, the copper powder was dried under vacuum for 15 min before use.

In a 50 mL round bottom flask under air the appropriate aryl iodide (10 mmol) and ethyl bromodifluoroacetate (1.3 mL, 10 mmol) were added to a suspension of Cu powder (1.7 g, 26 mmol) in DMSO (26 mL, 0.4 M). The reaction mixture was stirred at 60 °C for 12 h, after which time it was poured into water (50 mL), and extracted with EtOAc (2 \times 30 mL). Then, the combined organic layer was washed with water (3 \times 30 mL), dried over Na_2SO_4 and concentrated in vacuum. The product was used for next step without further purification.

In a 50 mL round bottom flask, product obtained by last step was added to a mixture of MeOH (30 mL) and 1 M K_2CO_3 aq. (30 mL) and stirred for 2 h at room temperature. The reaction was then poured into 3 M HCl aq. to acidify to pH 1, and the aqueous phase was extracted with EtOAc (2 \times 50 mL), washed with brine (2 \times 30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography with *n*-hexane/ EtOAc (5/1 to 3/1) to afford α , α -difluoroaromatic acids.

3. Crystal data of 3a

X-ray structure of 3a, ellipsoid contour probability levels is 50%. (CCDC No. 2055729)

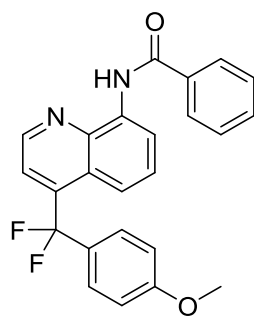


Compound	3a
Empirical formula	C ₂₄ H ₁₈ F ₂ N ₂ O ₂
Formula weight	404.40
Temperature/K	109.90(10)
Crystal system	orthorhombic
Space group	Pbca
a/Å	15.1154(4)
b/Å	8.6495(3)
c/Å	28.5881(9)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å ³	3737.6(2)
Z	8
ρ _{calc} / mg mm ⁻³	1.437

μ/mm^{-1}	0.106
F(000)	1680
Crystal size/ mm^3	0.34*0.33*0.15
2 θ range for data collection	6.1 to 52 °
Index ranges	-16 \leq h \leq 18, -10 \leq k \leq 6, -33 \leq l \leq 35
Reflections collected	10777
Independent reflections	3611[R(int) = 0.0461 (inf-0.9Å)]
Data/restraints/parameters	3611/0/272
Goodness-of-fit on F ²	1.045
Final R indexes [$I > 2\sigma(I)$ i.e. $F_o > 4\sigma(F_o)$]	R ₁ = 0.0431, wR ₂ = 0.0920
Final R indexes [all data]	R ₁ = 0.0611, wR ₂ = 0.1028
Largest diff. peak/hole / e Å ⁻³	0.197/-0.221
Flack Parameters	N
Completeness	0.9955

4. ¹H, ¹⁹F NMR, ¹³C NMR, and HRMS Data

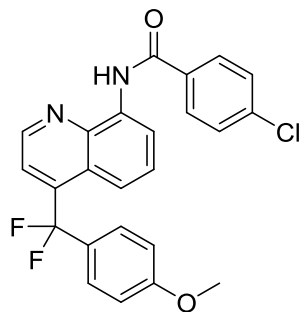
N-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)benzamide (3a).



White solid, M.p.:149-150oC;

¹H NMR (600 MHz, CDCl₃) δ 10.84 (s, 1H), 8.98 (d, J = 4.5 Hz, 1H), 8.93 (dd, J = 7.7, 1.2 Hz, 1H), 8.12-8.08 (m, 2H), 7.82 (d, J = 4.4 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.61-7.52 (m, 4H), 7.39 (d, J = 6 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -84.40. ¹³C NMR (151 MHz, CDCl₃) δ 165.55, 161.23, 147.30, 139.18, 135.00, 134.92, 131.96, 128.82, 128.38, 127.54 (t, J = 5.0 Hz), 127.36, 127.11, 124.38, 120.27, 119.62 (d, J = 2.8 Hz), 119.29 (t, J = 7.5 Hz), 117.17, 114.01, 113.65, 55.36. HRMS(ESI) calcd. for C₂₄H₁₈F₂N₂O₂ [M+H]⁺ 405.1409, found 405.1409.

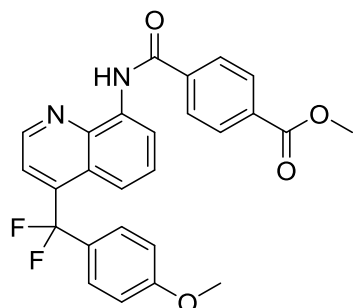
4-chloro-N-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)benzamide (3b)



White solid, M.p.: 156-157°C;

¹H NMR (600 MHz, CDCl₃) δ 10.80 (s, 1H), 8.97 (d, *J* = 4.5 Hz, 1H), 8.90 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.81 (d, *J* = 4.5 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 3H), 7.39 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.41. **¹³C NMR** (151 MHz, CDCl₃) δ 164.33, 161.23, 147.51, 142.05 (d, *J* = 24.1 Hz), 139.32, 138.25, 134.77, 133.43, 129.10, 128.73, 128.43, 128.26, 127.54 (t, *J* = 5.1 Hz), 124.31, 120.28, 119.77, 119.37 (t, *J* = 7.4 Hz), 116.84, 114.00, 55.36. **HRMS(ESI)** calcd. for C₂₄H₁₇ClF₂N₂O₂ [M+H]⁺ 439.1019, found 439.1015.

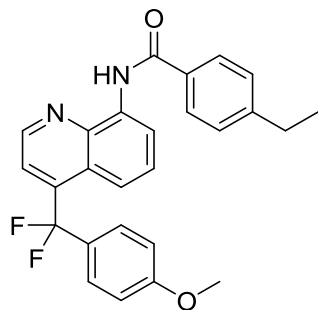
Methyl 4-((4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)carbamoyl)benzoate (3c)



White solid, M.p.: 142-143°C;

¹H NMR (600 MHz, CDCl₃) δ 10.87 (s, 1H), 8.97 (d, *J* = 4.4 Hz, 1H), 8.92 (d, *J* = 7.7 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 4.5 Hz, 1H), 7.64 (dd, *J* = 8.9, 1.5 Hz, 1H), 7.55-7.50 (m, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.98 (s, 3H), 3.82 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.41. **¹³C NMR** (151 MHz, CDCl₃) δ 166.27, 164.44, 161.22, 147.63, 141.87, 139.41, 138.87, 134.73, 133.07, 130.08, 128.43, 128.21, 127.54 (t, *J* = 5.1 Hz), 127.32, 124.29, 120.29, 119.91, 119.41 (t, *J* = 7.4 Hz), 116.81, 114.00, 55.36, 52.44. **HRMS(ESI)** calcd. for C₂₆H₂₀F₂N₂O₄ [M+H]⁺ 463.1464, found 463.1463.

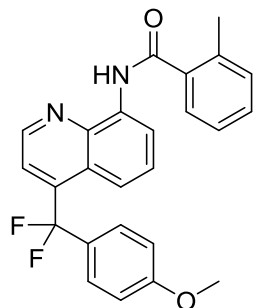
N-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)-4-ethylbenzamide (3d).



White solid, M.p.: 161-162°C;

¹H NMR (600 MHz, CDCl₃) δ 10.81 (s, 1H), 8.98 (d, *J* = 4.4 Hz, 1H), 8.92 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 2H), 7.83 (d, *J* = 4.2 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.54 (t, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.4, 3.9 Hz, 4H), 6.91 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 3H), 2.76 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.40. **¹³C NMR** (151 MHz, cdcl₃) δ 165.54 (s), 161.20 (s), 148.68 (s), 147.25 (s), 135.04 (s), 132.43 (s), 128.37 (s), 128.29 (s), 127.53 (t, *J* = 5.0 Hz), 127.46 (s), 124.36 (s), 119.55 – 119.37 (m), 119.23 (t, *J* = 7.7 Hz), 116.99 (s), 113.99 (s), 55.36 (s), 28.87 (s), 15.32 (s). **HRMS(ESI)** calcd. for C₂₆H₂₂F₂N₂O₂ [M+H]⁺ 433.1722, found 433.1719.

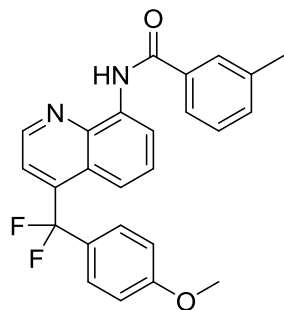
***N*-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)-2-methylbenzamide (3e).**



White solid, M.p.: 115-116°C;

¹H NMR (600 MHz, CDCl₃) δ 10.29 (s, 1H), 8.93 (d, *J* = 7.7 Hz, 1H), 8.88 (d, *J* = 4.4 Hz, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.68 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.61 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.54-7.50 (m, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.36-7.31 (m, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 2.60 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.42. **¹³C NMR** (151 MHz, CDCl₃) δ 168.15, 161.20, 147.45, 141.75, 139.26, 136.71, 136.56, 135.18, 131.41, 130.40, 128.50, 128.21, 127.54 (t, *J* = 5.1 Hz), 127.24, 126.04, 124.28, 120.29, 119.72 – 119.50 (m), 119.26 (t, *J* = 7.5 Hz), 116.65, 113.98, 55.36, 20.19. **HRMS(ESI)** calcd. for C₂₅H₂₀F₂N₂O₂ [M+H]⁺ 435.1515, found 435.1502.

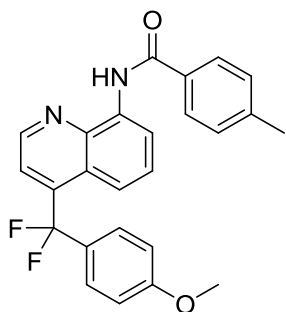
***N*-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)-3-methylbenzamide (3f)**



White solid, M.p.: 148-149°C;

¹H NMR (600 MHz, CDCl₃) δ 10.79 (s, 1H), 8.98 (d, *J* = 4.4 Hz, 1H), 8.93 (d, *J* = 7.6 Hz, 1H), 7.91-7.86 (m, 2H), 7.81 (d, *J* = 4.4 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.53 (t, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.42-7.38 (m, 3H), 6.91 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H), 2.49 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.39. **¹³C NMR** (151 MHz, CDCl₃) δ 165.72, 161.20, 147.36, 141.94, 139.30, 138.70, 135.04, 132.69, 128.65, 128.45, 128.31, 128.10, 127.54 (t, *J* = 5.0 Hz), 124.32, 124.27 (d, *J* = 14.3 Hz), 120.29, 120.29, 119.50, 119.26 (t, *J* = 7.4 Hz), 119.26 (t, *J* = 7.4 Hz), 116.92, 113.99, 55.35, 21.48. **HRMS(ESI)** calcd. for C₂₅H₂₀F₂N₂O₂ [M+H]⁺ 419.1566, found 419.1564.

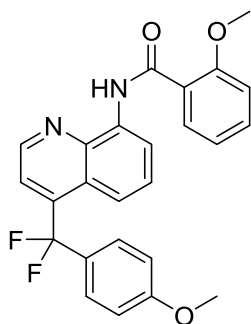
***N*-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)-4-methylbenzamide (3g).**



White solid, M.p.: 169-170°C;

¹H NMR (600 MHz, CDCl₃) δ 10.80 (s, 1H), 8.96 (d, *J* = 4.5 Hz, 1H), 8.93 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.00-7.97 (m, 2H), 7.79 (d, *J* = 4.4 Hz, 1H), 7.60 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.51 (dd, *J* = 8.7, 7.7 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.38-7.34 (m, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 2.46 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.39. **¹³C NMR** (151 MHz, CDCl₃) δ 165.45, 161.20, 147.41, 142.45, 141.78, 139.43, 135.15, 132.26, 129.49, 128.50, 128.29, 127.55 (t, *J* = 5.1 Hz), 127.31, 124.29, 120.32, 119.37, 119.26 (t, *J* = 7.5 Hz), 116.64, 113.98, 55.35, 21.54. **HRMS(ESI)** calcd. for C₂₅H₂₀F₂N₂O₂ [M+H]⁺ 419.1566, found 419.1562.

***N*-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)-2-methoxybenzamide (3h).**

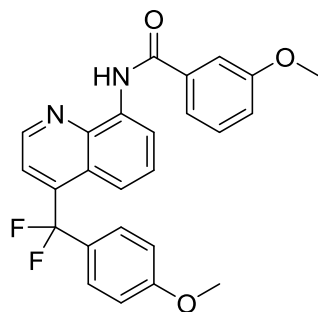


White solid, M.p.: 181-182°C;

¹H NMR (600 MHz, CDCl₃) δ 12.39 (s, 1H), 9.03 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.99 (d, *J* = 4.4 Hz, 1H), 8.34 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.79 (d, *J* = 4.4 Hz, 1H), 7.57 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.54-7.48 (m, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.17-7.13 (m, 1H), 7.10 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.92-6.88 (m, 2H), 4.22 (s, 3H), 3.81 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.32. **¹³C NMR** (151 MHz, CDCl₃) δ 163.63, 161.17, 157.72, 147.35, 141.52, 139.92, 136.21, 133.21, 132.41, 128.62, 128.40, 127.56 (t, *J* = 5.0 Hz),

124.35, 122.33, 121.35, 120.37, 119.24, 119.03 (t, $J = 7.6$ Hz), 117.46, 113.96, 111.62, 56.14, 55.35. **HRMS(ESI)** calcd. for $C_{25}H_{20}F_2N_2O_3$ $[M+H]^+$ 435.1515, found 435.1508.

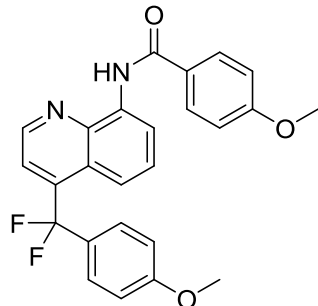
***N*-4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)-3-methoxybenzamide (3i).**



White solid, M.p.: 150-151°C;

1H NMR (600 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.98 (d, $J = 4.5$ Hz, 1H), 8.93 (d, $J = 7.7$ Hz, 1H), 7.92-7.86 (m, 2H), 7.82 (d, $J = 4.4$ Hz, 1H), 7.63 (d, $J = 8.7$ Hz, 1H), 7.54 (t, $J = 8.2$ Hz, 1H), 7.44 (t, $J = 7.5$ Hz, 1H), 7.42-7.38 (m, 3H), 6.91 (d, $J = 8.5$ Hz, 2H), 3.82 (s, 3H), 2.49 (s, 3H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -84.39. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.74, 161.22, 147.36, 141.98, 139.29, 138.71, 135.04, 132.70, 128.66, 128.46, 128.33, 128.11, 127.55 (t, $J = 5.1$ Hz), 124.24, 121.90, 120.30, 119.51, 119.27 (t, $J = 7.4$ Hz), 118.70, 116.97, 114.00, 55.36, 21.48. **HRMS(ESI)** calcd for $C_{25}H_{20}F_2N_2O_3$ $[M+H]^+$ 435.1515, found 435.1503.

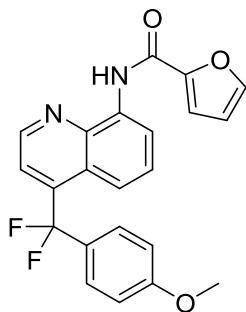
***N*-4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)-4-methoxybenzamide (3j).**



White solid, M.p.: 179-180°C;

1H NMR (600 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.96 (d, $J = 4.4$ Hz, 1H), 8.91 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.08- 8.04 (m, 2H), 7.78 (d, $J = 4.4$ Hz, 1H), 7.59 (dd, $J = 8.6, 1.5$ Hz, 1H), 7.52-7.48 (m, 1H), 7.39 (d, $J = 8.9$ Hz, 2H), 7.07-7.03 (m, 2H), 6.92-6.89 (m, 2H), 3.90 (s, 3H), 3.81 (s, 3H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -84.40. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.99, 162.59, 161.20, 147.37, 141.95, 141.77, 139.42, 135.23, 129.18, 128.69, 128.51, 128.31, 127.55 (t, $J = 5.1$ Hz), 127.36, 124.29, 120.32, 119.30, 116.53, 114.00 (d, $J = 5.8$ Hz), 55.48, 55.35. **HRMS(ESI)** calcd. For $C_{25}H_{20}F_2N_2O_3$ $[M+H]^+$ 435.1515, found 435.1561.

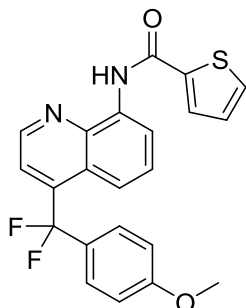
***N*-4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)furan-2-carboxamide (3k)**



White solid, M.p.: 150-151°C;

¹H NMR (600 MHz, CDCl₃) δ 10.68 (s, 1H), 8.97 (d, *J* = 4.4 Hz, 1H), 8.84 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.86 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.80 (d, *J* = 4.4 Hz, 1H), 7.62-7.59 (m, 2H), 7.52-7.48 (m, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.20 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.41. **¹³C NMR** (151 MHz, CDCl₃) δ 161.21, 159.98, 147.49, 141.85, 139.96, 139.13, 134.76, 131.03, 128.49 (d, *J* = 10.1 Hz), 128.27, 127.89, 127.54 (t, *J* = 5.1 Hz), 124.28, 121.89, 120.29, 119.63- 119.45 (m), 119.33 (t, *J* = 7.5 Hz), 116.70, 114.00, 55.36. **HRMS(ESI)** calcd. For C₂₂H₁₆F₂N₂O₃ [M+H]⁺ 395.1163, found 395.1161.

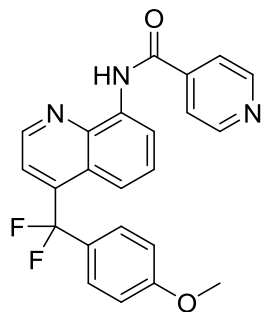
***N*-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)thiophene-2-carboxamide (3l).**



White solid, M.p.: 168-169°C;

¹H NMR (600 MHz, CDCl₃) δ 10.86 (s, 1H), 9.00 (d, *J* = 4.4 Hz, 1H), 8.87 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.79 (d, *J* = 4.5 Hz, 1H), 7.64 (d, *J* = 0.9 Hz, 1H), 7.61 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.50 (t, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 3.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.60 (dd, *J* = 3.4, 1.7 Hz, 1H), 3.82 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.40. **¹³C NMR** (151 MHz, CDCl₃) δ 161.20, 156.35, 148.29, 147.57, 144.57, 141.75, 139.28, 134.66, 128.48, 128.19, 127.55 (t, *J* = 5.0 Hz), 124.29, 120.32, 119.63 (d, *J* = 2.9 Hz), 119.33 (t, *J* = 7.4 Hz), 116.82, 115.25, 113.99, 112.48, 55.35. **HRMS(ESI)** calcd for C₂₂H₁₆F₂N₂O₂S [M+H]⁺ 411.0973, found 411.0964.

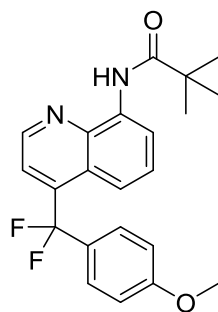
***N*-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)isonicotinamide (3m).**



White solid, M.p.: 173-174°C;

¹H NMR (600 MHz, CDCl₃) δ 10.92 (s, 1H), 8.97 (d, *J* = 4.4 Hz, 1H), 8.90 (t, *J* = 5.7 Hz, 3H), 7.97 (d, *J* = 6.2 Hz, 2H), 7.81 (d, *J* = 4.5 Hz, 1H), 7.68 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.53 (t, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.43. **¹³C NMR** (151 MHz, CDCl₃) δ 163.18, 161.23, 150.66, 147.75, 142.1, 141.98, 139.32, 134.27, 128.35, 128.15, 127.51 (t, *J* = 5.1 Hz), 124.28, 121.07, 120.33, 120.24, 119.51 (t, *J* = 7.3 Hz), 117.01, 114.01, 55.36. **HRMS(ESI)** calcd. for C₂₃H₁₇F₂N₃O₂ [M+H]⁺ 406.1362, found 406.1360.

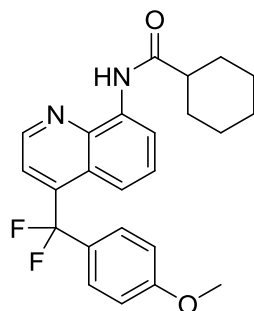
***N*-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)pivalamide (3n).**



White solid, M.p.: 155-156°C;

¹H NMR (600 MHz, CDCl₃) δ 10.34 (s, 1H), 8.93 (d, *J* = 4.4 Hz, 1H), 8.78 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.76 (d, *J* = 4.4 Hz, 1H), 7.54 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 1.43 (s, 9H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.43. **¹³C NMR** (151 MHz, CDCl₃) δ 177.22, 161.17, 147.38, 141.64, 139.45, 135.16, 128.54, 128.23, 127.53 (t, *J* = 5.1 Hz), 124.20 (d, *J* = 2.3 Hz), 121.90, 120.30, 119.25 – 118.97 (m), 116.33, 113.95, 55.34, 40.38, 27.71. **HRMS(ESI)** calcd. for C₂₂H₂₂F₂N₂O₂ [M+H]⁺ 385.1722, found 385.1721.

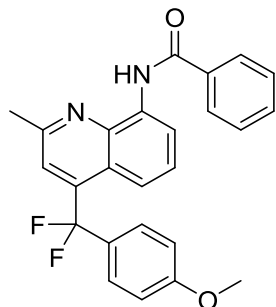
***N*-(4-(difluoro(4-methoxyphenyl)methyl)quinolin-8-yl)cyclohexanecarboxamide (3o)**



White solid, M.p.: 166-167°C;

¹H NMR (600 MHz, CDCl₃) δ 10.00 (s, 1H), 8.92 (d, *J* = 4.5 Hz, 1H), 8.79 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.77 (d, *J* = 4.5 Hz, 1H), 7.57-7.53 (m, 1H), 7.45 (t, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.50 (tt, *J* = 11.8, 3.5 Hz, 1H), 2.08 (dd, *J* = 13.7, 2.9 Hz, 2H), 1.88 (dt, *J* = 13.0, 3.5 Hz, 2H), 1.77 – 1.72 (m, 1H), 1.63 (qd, *J* = 12.4, 3.5 Hz, 2H), 1.40 (qt, *J* = 12.7, 3.4 Hz, 2H), 1.32 (tt, *J* = 12.5, 3.3 Hz, 1H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.42. **¹³C NMR** (151 MHz, CDCl₃) δ 174.87, 161.19, 147.19, 139.06, 135.07, 128.49, 128.27, 127.52 (t, *J* = 5.1 Hz), 124.23, 120.28, 119.18, 119.13, 119.08, 116.65, 113.97, 55.35, 46.90, 29.74, 25.77, 25.74. **HRMS(ESI)** calcd. for C₂₄H₂₄F₂N₂O₂ [M+H]⁺ 411.1879, found 411.1877.

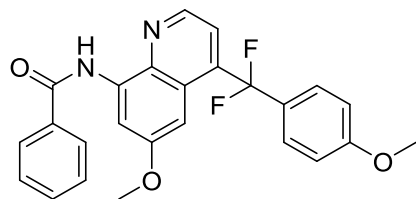
***N*-(4-(difluoro(4-methoxyphenyl)methyl)-2-methylquinolin-8-yl)benzamide (3p).**



White solid, M.p.: 151-152°C;

¹H NMR (600 MHz, CDCl₃) δ 10.92 (s, 1H), 8.87 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.11-8.08 (m, 2H), 7.68 (s, 1H), 7.62-7.53 (m, 4H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.87 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.37. **¹³C NMR** (151 MHz, CDCl₃) δ 165.36, 161.17, 156.58, 138.82, 135.20, 134.27, 131.84, 128.82, 128.52, 127.54 (t, *J* = 5.1 Hz), 127.28, 127.18, 122.53, 120.28, 120.10 (t, *J* = 7.5 Hz), 119.50, 117.03, 117.00, 113.96, 55.35, 25.47. **HRMS(ESI)** calcd. for C₂₅H₂₀F₂N₂O₂ [M+H]⁺ 419.1566, found 419.1564.

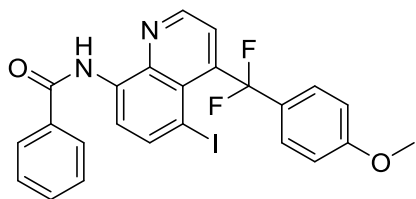
***N*-(4-(difluoro(4-methoxyphenyl)methyl)-6-methoxyquinolin-8-yl)benzamide (3q)**



White solid, M.p.: 122-123°C;

¹H NMR (600 MHz, CDCl₃) δ 10.80 (s, 1H), 8.78 (d, *J* = 4.5 Hz, 1H), 8.67 (d, *J* = 2.6 Hz, 1H), 8.11 – 8.06 (m, 2H), 7.75 (d, *J* = 4.5 Hz, 1H), 7.62-7.53 (m, 3H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 2.2 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H). **¹³C NMR** (151 MHz, CDCl₃) δ 160.66, 156.38, 154.01, 139.90, 135.35, 131.33, 131.13, 130.16, 127.22, 124.07, 122.74 (t, *J* = 5.1 Hz), 122.53, 120.64, 114.96 (t, *J* = 7.6 Hz), 109.20, 104.08, 94.00, 72.47, 72.25, 72.04, 50.68. **¹⁹F NMR** (565 MHz, CDCl₃) δ -85.95. **HRMS(ESI)** calcd. for C₂₅H₂₀F₂N₂O₃ [M+H]⁺ 435.1515, found 435.1517.

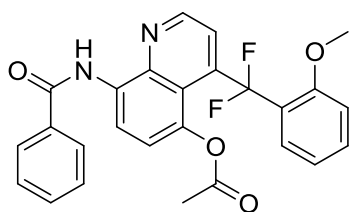
***N*-(4-(difluoro(4-methoxyphenyl)methyl)-5-iodoquinolin-8-yl)benzamide (3r)**



White solid, M.p.: 132-133°C;

¹H NMR (600 MHz, CDCl₃) δ 10.31 (s, 1H), 8.74 (d, J = 8.3 Hz, 1H), 8.56 (d, J = 8.7 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 7.4 Hz, 2H), 7.59 (dd, J = 14.5, 8.0 Hz, 3H), 7.51 (t, J = 7.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H). **¹³C NMR** (151 MHz, CDCl₃) δ 164.99, 160.89, 154.30, 142.56, 139.55, 137.79, 135.69, 134.25, 132.10, 129.68, 128.80, 128.08, 127.67 (t, J = 5.9 Hz), 127.10, 119.75, 118.47, 113.74, 88.84, 55.33. **¹⁹F NMR** (565 MHz, CDCl₃) δ -90.50. **HRMS(ESI)** calcd. for C₂₄H₁₇F₂IN₂O₂ [M+Na]⁺ 553.0195, found 553.0200.

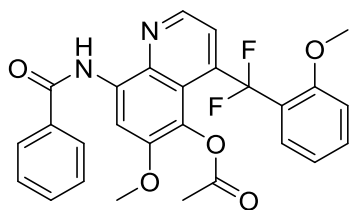
8-benzamido-4-(difluoro(2-methoxyphenyl)methyl)quinolin-5-yl acetate (3s)



White solid, M.p.: 154-155°C;

¹H NMR (600 MHz, CDCl₃) δ 10.87 (s, 1H), 9.05 (d, J = 8.6 Hz, 1H), 8.98 (d, J = 4.5 Hz, 1H), 8.09 (d, J = 6.9 Hz, 1H), 7.89 (d, J = 4.6 Hz, 1H), 7.63-7.55 (m, 3H), 7.29 (dd, J = 8.7, 4.5 Hz, 3H), 6.90 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 1.94 (s, 3H). **¹³C NMR** (151 MHz, CDCl₃) δ 169.71, 165.36, 161.14, 147.57, 140.00, 139.06, 134.98, 133.56, 131.98, 129.42, 128.84, 127.60 (t, J = 4.1 Hz), 127.28, 123.90, 121.74 (t, J = 10.2 Hz), 120.64, 116.84, 113.70, 55.36, 20.93. **¹⁹F NMR** (565 MHz, CDCl₃) δ -76.59. -90.45. **HRMS(ESI)** calcd. for C₂₆H₂₀F₂IN₂O₄ [M+H]⁺ 463.1464, found 463.1469.

8-benzamido-4-(difluoro(2-methoxyphenyl)methyl)-6-methoxyquinolin-5-yl acetate (3t)

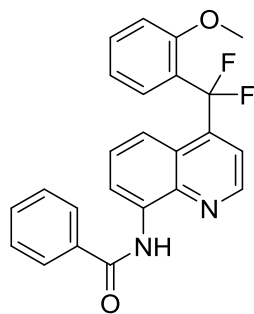


Yellow solid, M.p.: 186-187°C;

¹H NMR (600 MHz, CDCl₃) δ 10.99 (s, 1H), 9.09 (s, 1H), 8.77 (d, J = 4.5 Hz, 1H), 8.09 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 4.5 Hz, 1H), 7.62-7.55 (m, 3H), 7.45 (t, J = 7.9 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 11.2 Hz, 1H), 4.00 (s, 3H), 3.67 (s, 3H), 1.97 (s, 3H). **¹³C NMR** (151 MHz, CDCl₃) δ 169.72, 165.36, 161.15, 147.59, 140.03, 139.06, 134.99, 133.58, 132.32, 131.99, 128.85, 128.77, 127.61 (t, J = 4.2 Hz), 127.28, 127.08, 123.89, 121.74 (t, J = 8.8 Hz), 120.74, 119.28, 116.80,

116.58, 113.70, 55.37, 29.68, 20.93. ^{19}F NMR (565 MHz, CDCl_3) δ -93.54. HRMS(ESI) calcd. for $\text{C}_{27}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 493.1570, found 493.1575.

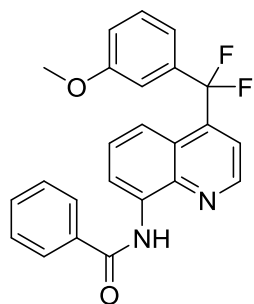
***N*-4-(difluoro(2-methoxyphenyl)methyl)quinolin-8-yl)benzamide (3u).**



White solid, M.p.: 159-160°C;

^1H NMR (600 MHz, CDCl_3) δ 10.85 (s, 1H), 8.93 (d, $J = 4.5$ Hz, 1H), 8.90 (dd, $J = 7.7, 1.1$ Hz, 1H), 8.10-8.07 (m, 2H), 7.83 (dd, $J = 7.6, 1.5$ Hz, 1H), 7.81 (d, $J = 4.5$ Hz, 1H), 7.72 (dd, $J = 8.7, 1.5$ Hz, 1H), 7.61-7.54 (m, 3H), 7.52-7.48 (m, 1H), 7.46 (td, $J = 7.9, 1.7$ Hz, 1H), 7.12 (t, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 3.52 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.73. ^{13}C NMR (151 MHz, CDCl_3) δ 165.43, 157.08, 147.23, 142.46, 139.36, 135.15, 134.94, 132.37 (d, $J = 1.9$ Hz), 131.87, 128.80, 127.88, 127.29, 127.15 (t, $J = 7.4$ Hz), 124.39, 124.14, 120.60, 119.84 (t, $J = 7.6$ Hz), 119.23, 118.99 (d, $J = 2.6$ Hz), 116.40, 112.25, 55.37. HRMS(ESI) calcd. for $\text{C}_{24}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 405.1409, found 405.1406.

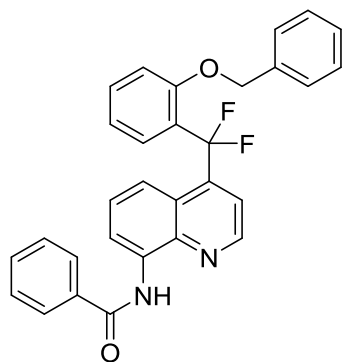
***N*-4-(difluoro(3-methoxyphenyl)methyl)quinolin-8-yl)benzamide (3v).**



White solid, M.p.: 181-182°C;

^1H NMR (600 MHz, CDCl_3) δ 10.83 (s, 1H), 8.97 (d, $J = 4.5$ Hz, 1H), 8.94 (d, $J = 7.7$ Hz, 1H), 8.09 (d, $J = 7.0$ Hz, 2H), 7.79 (d, $J = 4.4$ Hz, 1H), 7.65 (d, $J = 8.7$ Hz, 1H), 7.56 (ddd, $J = 22.0, 15.6, 7.7$ Hz, 4H), 7.32 (t, $J = 8.0$ Hz, 1H), 7.08 (s, 1H), 7.00 (t, $J = 7.8$ Hz, 2H), 3.81 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -86.51. ^{13}C NMR (151 MHz, CDCl_3) δ 165.46, 159.75, 147.43, 141.56, 139.41, 137.59, 135.07, 131.93, 129.90, 128.83, 128.37, 127.30, 124.20, 120.03, 119.37, 119.32, 119.27, 118.26 (t, $J = 5.4$ Hz), 116.79, 116.02, 111.71 (t, $J = 5.4$ Hz), 55.39. HRMS(ESI) calcd. for $\text{C}_{24}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 405.1409, found 405.1409.

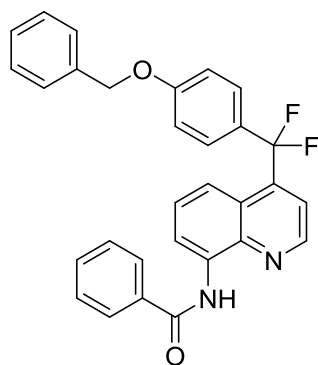
***N*-4-((2-(benzyloxy)phenyl)difluoromethyl)quinolin-8-yl)benzamide (3w).**



White solid, M.p.: 162-163°C;

¹H NMR (600 MHz, CDCl₃) δ 10.83 (s, 1H), 8.88 (d, *J* = 7.7 Hz, 1H), 8.57 (d, *J* = 4.6 Hz, 1H), 8.10 (d, *J* = 7.4 Hz, 2H), 7.96 – 7.94 (m, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 4.6 Hz, 1H), 7.61-7.55 (m, 3H), 7.46 (dt, *J* = 19.6, 7.9 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 7.26-7.24 (m, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.93 – 6.90 (m, 3H), 4.75 (s, 2H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -88.92. **¹³C NMR** (151 MHz, CDCl₃) δ 165.42, 155.99, 147.22, 142.24, 139.07, 135.47, 135.14, 134.88, 132.31, 131.88, 128.81, 128.39, 128.12, 127.78, 127.68, 127.31 (d, *J* = 1.6 Hz), 127.09 (t, *J* = 7.4 Hz), 124.58, 124.05, 120.75, 120.43, 120.04 (t, *J* = 7.8 Hz), 118.78, 116.36, 112.92, 70.25. **HRMS(ESI)** calcd. for C₃₀H₂₂F₂N₂O₂ [M+H]⁺ 481.1722, found 481.1716.

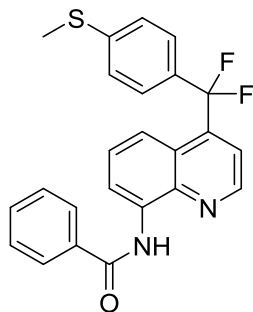
***N*-(4-((3-(benzyloxy)phenyl)difluoromethyl)quinolin-8-yl)benzamide (3x).**



White solid, M.p.: 152-153°C;

¹H NMR (600 MHz, CDCl₃) δ 10.83 (s, 1H), 8.97 (d, *J* = 4.5 Hz, 1H), 8.94 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.09 (dd, *J* = 6.9, 1.6 Hz, 2H), 7.80 (d, *J* = 4.5 Hz, 1H), 7.64-7.50 (m, 5H), 7.43-7.36 (m, 6H), 7.35-7.32 (m, 1H), 7.00-6.97 (m, 2H), 5.07 (s, 2H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.45. **¹³C NMR** (151 MHz, CDCl₃) δ 165.45, 160.41, 147.49, 141.73, 139.47, 136.29, 135.09 (d, *J* = 3.8 Hz), 131.93, 128.84, 128.74, 128.66, 128.56, 128.28, 128.20, 127.59 (t, *J* = 4.9 Hz), 127.48, 127.29, 124.28, 120.29, 119.51 (d, *J* = 2.9 Hz), 119.31 (t, *J* = 7.4 Hz), 116.66, 114.86, 70.13. **HRMS(ESI)** calcd. for C₃₀H₂₂F₂N₂O₂ [M+H]⁺ 481.1722, found 481.1718.

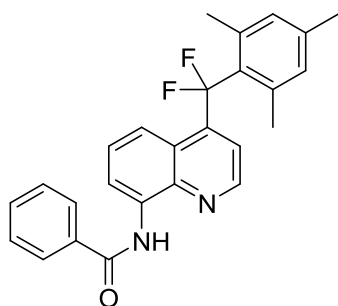
***N*-(4-(difluoro(4-(methylthio)phenyl)methyl)quinolin-8-yl)benzamide (3y).**



White solid, M.p.: 99-100°C;

¹H NMR (600 MHz, CDCl₃) δ 10.82 (s, 1H), 8.97 (d, *J* = 4.4 Hz, 1H), 8.94 (d, *J* = 7.7 Hz, 1H), 8.09 (d, *J* = 7.1 Hz, 2H), 7.79 (d, *J* = 4.5 Hz, 1H), 7.62-7.58 (m, 2H), 7.56 (t, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 2.48 (s, 3H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -85.78. **¹³C NMR** (151 MHz, CDCl₃) δ 165.45, 147.48, 142.44, 141.44, 139.46, 135.09 (d, *J* = 5.8 Hz), 134.16, 132.55, 131.94, 128.84, 128.38, 127.29, 126.32 (t, *J* = 5.2 Hz), 125.73, 124.17, 120.16, 119.37, 119.29 (d, *J* = 7.5 Hz), 116.72, 15.05. **HRMS(ESI)** calcd. for C₂₄H₁₈F₂N₂OS [M+H]⁺ 421.1181, found 421.1177.

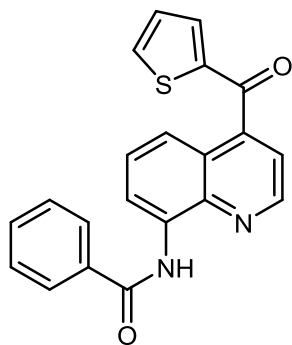
***N*-(4-(difluoro(mesityl)methyl)quinolin-8-yl)benzamide (3ab).**



White solid, M.p.: 199-200°C;

¹H NMR (600 MHz, CDCl₃) δ 10.83 (s, 1H), 9.02 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.77 (d, *J* = 4.5 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 8.12 – 8.08 (m, 2H), 7.73 (t, *J* = 8.3 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.09 (d, *J* = 4.4 Hz, 1H), 6.98 (s, 2H), 2.36 (s, 3H), 2.25 (t, *J* = 4.3 Hz, 6H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -77.18. **¹³C NMR** (151 MHz, CDCl₃) δ 165.44, 147.38, 141.83, 141.64, 139.83 (d, *J* = 9.3 Hz), 137.71 (t, *J* = 3.1 Hz), 135.12, 135.03, 131.89, 131.20, 129.12, 128.97, 128.81, 128.51, 127.31, 124.55 (d, *J* = 9.3 Hz), 120.42 (t, *J* = 5.5 Hz), 119.97 (t, *J* = 4.2 Hz), 117.07, 22.51 (t, *J* = 5.9 Hz), 20.84. **HRMS(ESI)** calcd. for C₂₆H₂₂F₂N₂O [M+H]⁺ 417.1733, found 417.1774.

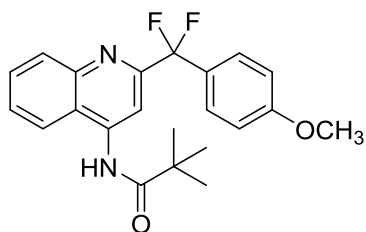
***N*-(4-(thiophene-2-carbonyl)quinolin-8-yl)benzamide (3ac).**



Yellow solid, M.p.: 172-173°C;

$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 10.80 (s, 1H), 9.00 (dd, $J = 7.7, 1.4$ Hz, 1H), 8.98 (d, $J = 4.3$ Hz, 1H), 8.12 (d, $J = 7.0$ Hz, 2H), 7.85 (d, $J = 4.9$ Hz, 1H), 7.69 (dd, $J = 8.6, 1.4$ Hz, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.62 (q, $J = 3.2$ Hz, 2H), 7.58 (q, $J = 7.2, 6.8$ Hz, 2H), 7.44 (d, $J = 3.9$ Hz, 1H), 7.15 (t, $J = 4.4$ Hz, 1H). $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 187.45, 177.29, 165.50, 147.33 (d, $J = 2.4$ Hz), 144.48, 143.77, 139.19, 136.42 (d, $J = 4.1$ Hz), 135.06, 134.93, 131.96, 128.85, 128.73, 128.57, 127.31, 124.53, 119.86, 119.16, 117.17. **HRMS(ESI)** calcd. for $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 359.0810, found 359.0852.

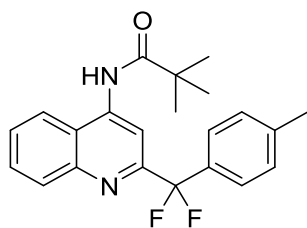
***N*-(2-(difluoro(4-methoxyphenyl)methyl)quinolin-4-yl)pivalamide (5a)**



White solid, M.p.: 195-196°C;

$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.71 (s, 1H), 8.26 (s, 1H), 8.22 (d, $J = 8.4$ Hz, 1H), 7.75 (ddd, $J = 8.4, 6.8, 1.3$ Hz, 1H), 7.72 (dd, $J = 8.5, 1.3$ Hz, 1H), 7.62 (dd, $J = 8.0, 6.2$ Hz, 3H), 6.90 (d, $J = 8.8$ Hz, 2H), 3.80 (s, 3H), 1.44 (s, 9H). $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ -94.11. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 176.93, 160.73, 156.68, 147.94, 141.49, 131.42, 129.84, 128.94, 127.46, 120.38, 119.60, 118.76, 118.27, 113.69, 107.21 (t, $J = 4.3$ Hz), 55.28, 40.60, 27.62. **HRMS(ESI)** calcd. for $\text{C}_{22}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 385.1722, found 385.1717.

***N*-(2-(difluoro(*p*-tolyl)methyl)quinolin-4-yl)pivalamide (5b)**

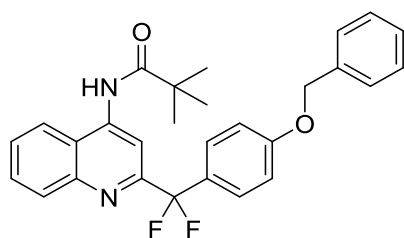


White solid, M.p.: 136-137°C;

$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.72 (s, 1H), 8.32 (s, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 7.76-7.72 (m, 2H), 7.62 (ddd, $J = 8.3, 6.7, 1.3$ Hz, 1H), 7.59 (d, $J = 8.2$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 2.34 (s, 3H), 1.45

(s, 9H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -95.50. **¹³C NMR** (151 MHz, CDCl₃) δ 176.96, 147.64, 140.00, 131.15, 130.00, 129.04, 127.53, 125.85, 125.81, 125.77, 119.58, 118.68, 118.37, 117.06, 107.17 (d, *J* = 4.4 Hz), 40.63, 27.61, 21.27. **HRMS(ESI)** calcd. for C₂₂H₂₂F₂N₂O [M+H]⁺ 369.1773, found 369.1769.

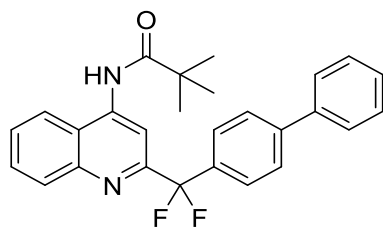
***N*-(2-((4-(benzyloxy)phenyl)difluoromethyl)quinolin-4-yl)pivalamide (5c)**



White solid, M.p.: 136-137°C;

¹H NMR (600 MHz, CDCl₃) δ 8.71 (s, 1H), 8.27 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.76 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.65-7.61 (m, 3H), 7.42 – 7.39 (m, 2H), 7.37 (td, *J* = 6.6, 6.1, 1.7 Hz, 2H), 7.33-7.30 (m, 1H), 6.99 – 6.96 (m, 2H), 5.06 (s, 2H), 1.44 (s, 9H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -94.18. **¹³C NMR** (151 MHz, CDCl₃) δ 176.93, 159.96, 147.86, 141.58, 136.58, 131.36, 129.90, 129.15, 128.60, 128.04, 127.54, 127.49 (d, *J* = 2.2 Hz), 127.45 (d, *J* = 4.8 Hz), 119.59, 118.70, 118.29, 114.59, 107.19, 70.01, 40.61, 27.62, 1.01. **HRMS(ESI)** calcd. for C₂₈H₂₆F₂N₂O₂ [M+H]⁺ 461.2035, found 461.2033

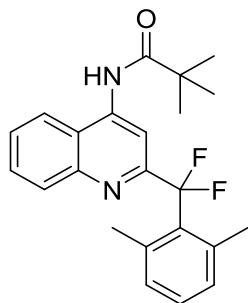
***N*-(2-([1,1'-biphenyl]-4-yl)difluoromethyl)quinolin-4-yl)pivalamide (5d)**



White solid, M.p.: 157-158°C;

¹H NMR (600 MHz, CDCl₃) δ 8.79 (d, *J* = 5.0 Hz, 1H), 8.39 – 8.19 (m, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.74 (dt, *J* = 21.4, 7.5 Hz, 2H), 7.67-7.60 (m, 3H), 7.58 – 7.55 (m, 2H), 7.45-7.40 (m, 2H), 7.38-7.33 (m, 1H), 1.46 (s, 9H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -95.52. **¹³C NMR** (151 MHz, CDCl₃) δ 176.99, 147.92, 142.82, 141.69, 140.32, 131.38, 129.95, 128.78 (d, *J* = 6.5 Hz), 127.68, 127.57 (d, *J* = 1.9 Hz), 127.19 (d, *J* = 4.3 Hz), 127.13, 126.67, 126.38, 125.54, 119.63, 118.33, 111.42, 107.10 (d, *J* = 4.1 Hz), 40.64, 27.63. **HRMS(ESI)** calcd. for C₂₇H₂₄F₂N₂O [M+H]⁺ 431.1929, found 431.1926.

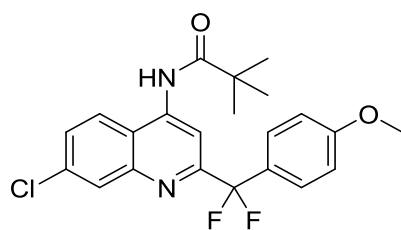
***N*-(2-((2,6-dimethylphenyl)difluoromethyl)quinolin-4-yl)pivalamide (5e)**



White solid, M.p.: 116-117°C;

¹H NMR (600 MHz, CDCl₃) δ 8.69 (s, 1H), 8.34 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.78-7.72 (m, 2H), 7.64 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 7.01 (s, 1H), 2.32 (d, *J* = 8.1 Hz, 6H), 1.45 (s, 9H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -92.09. **¹³C NMR** (151 MHz, CDCl₃) δ 176.86, 147.61, 141.59, 139.94, 136.48 (t, *J* = 2.9 Hz), 132.52, 131.38, 129.83, 127.55, 126.76 (t, *J* = 8.3 Hz), 126.22, 119.73, 118.39, 107.76 (t, *J* = 3.7 Hz), 40.60, 27.63, 21.10, 20.34 (t, *J* = 2.6 Hz). **HRMS(ESI)** calcd. for C₂₃H₂₄F₂N₂O [M+H]⁺ 383.193, found 383.1928.

***N*-(7-chloro-2-(difluoro(4-methoxyphenyl)methyl)quinolin-4-yl)pivalamide (5f)**



White solid, M.p.: 172-173°C;

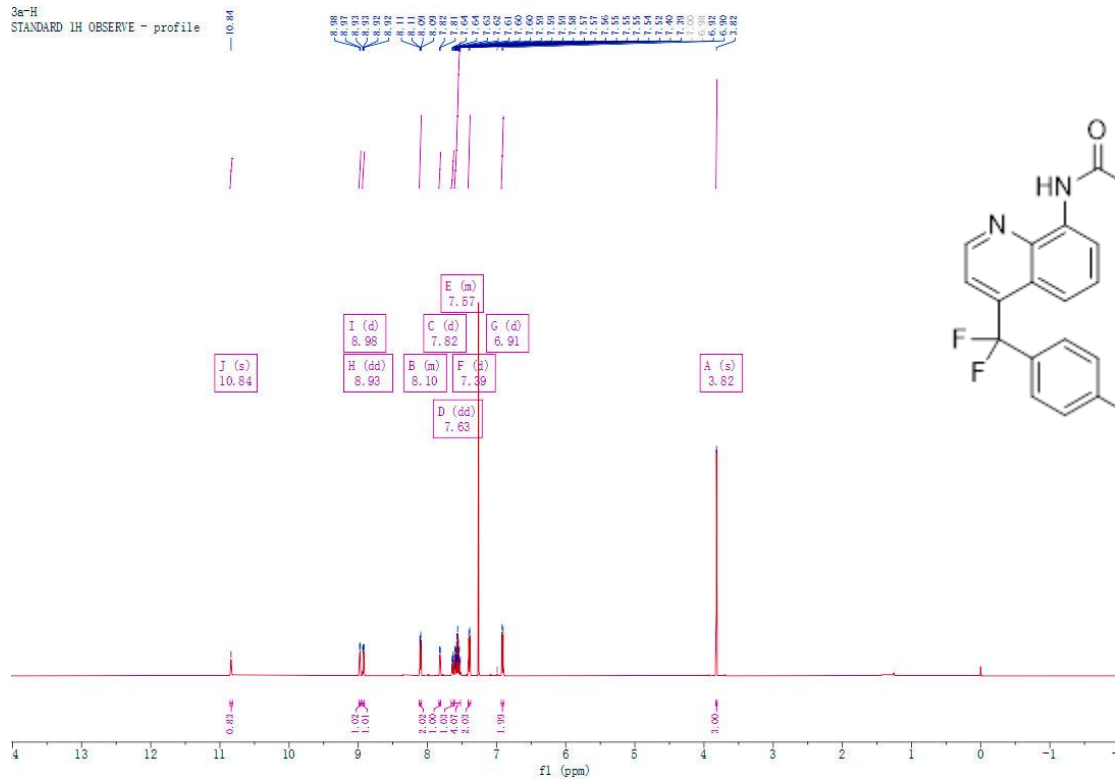
¹H NMR (600 MHz, CDCl₃) δ 8.68 (s, 1H), 8.26 (s, 1H), 8.22 (d, *J* = 2.1 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.63-7.59 (m, 2H), 7.55 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.93-6.89 (m, 2H), 3.80 (s, 3H), 1.45 (s, 9H). **¹⁹F NMR** (377 MHz, CDCl₃) δ -94.82. **¹³C NMR** (151 MHz, CDCl₃) δ 176.97, 160.81, 157.80, 148.29, 141.95, 136.07, 130.04, 128.55, 128.32, 127.41 (t, *J* = 5.7 Hz), 120.03, 118.55, 118.14, 113.74, 107.54 (t, *J* = 4.1 Hz), 55.29, 40.61, 27.59. **HRMS(ESI)** calcd. for C₂₂H₂₁ClF₂N₂O₂ [M+H]⁺ 419.1332, found 419.1328.

5. References

- [1] J. Li, Y. Wang, Y. Yu, R. -B. Wu, J. Weng, G. Lu, ACS Catal. **2017**, 7, 2661-2667.
- [2] S. Mizuta, I. S. R Stenhagen, M. L. O'Duill, J. R. Wolstenhulme, A. Kirjavainen, S. S. Forsback, M. Tredwell, G. Sandford, P. Moore, M. Huiban, S. Luthra, J. Passchier, O. Solin, V. Gouverneur, Organic letters. **2013**, 15 11, 2648-51.

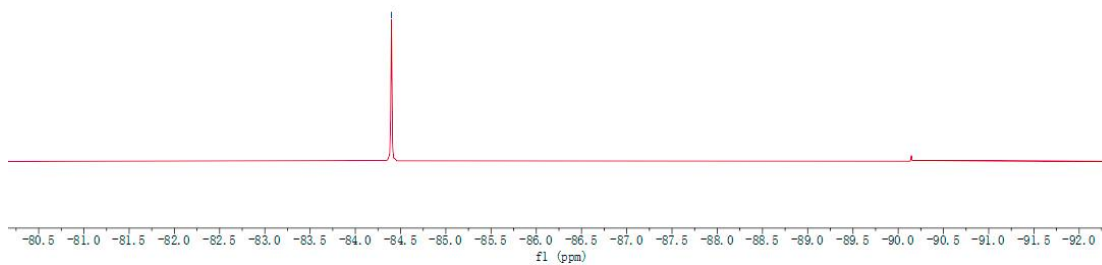
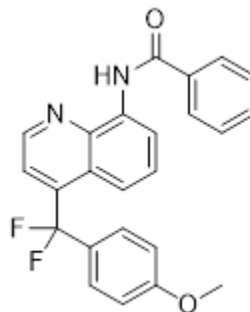
6. Copies of ^1H , ^{19}F and ^{13}C NMR Spectra

3a-H
STANDARD 1H OBSERVE - profile



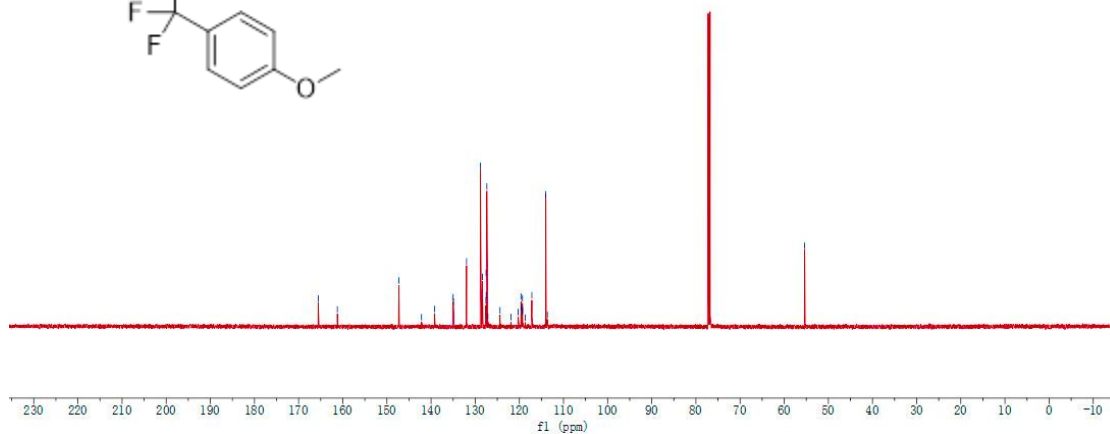
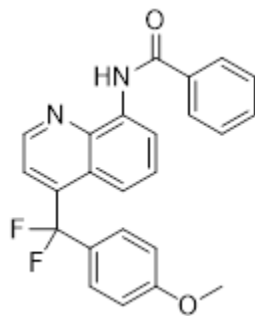
wangluyao-20210113.1.fid
3a in CDCl3, 19F

84.40

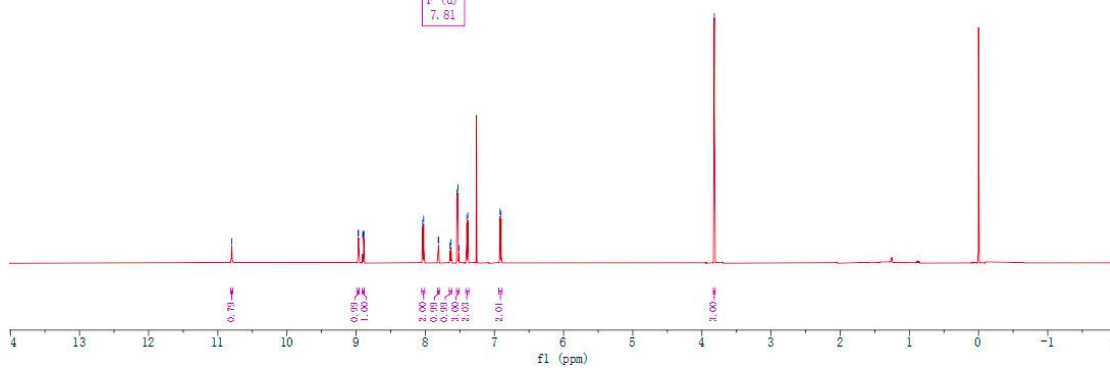
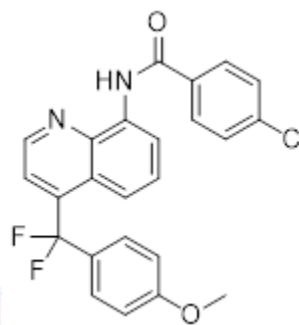
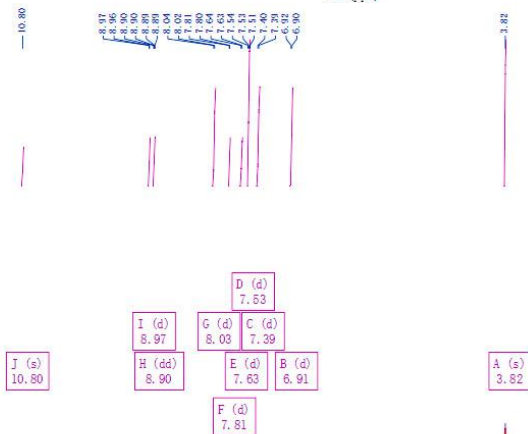


3a-C
STANDARD 1H OBSERVE - profile

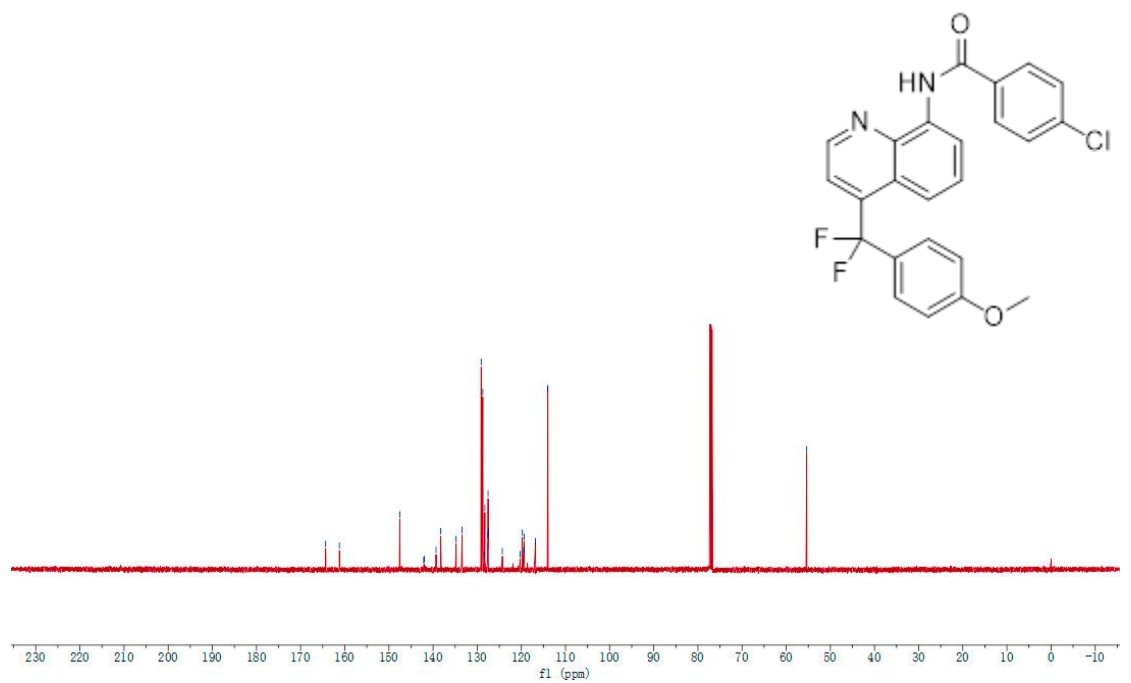
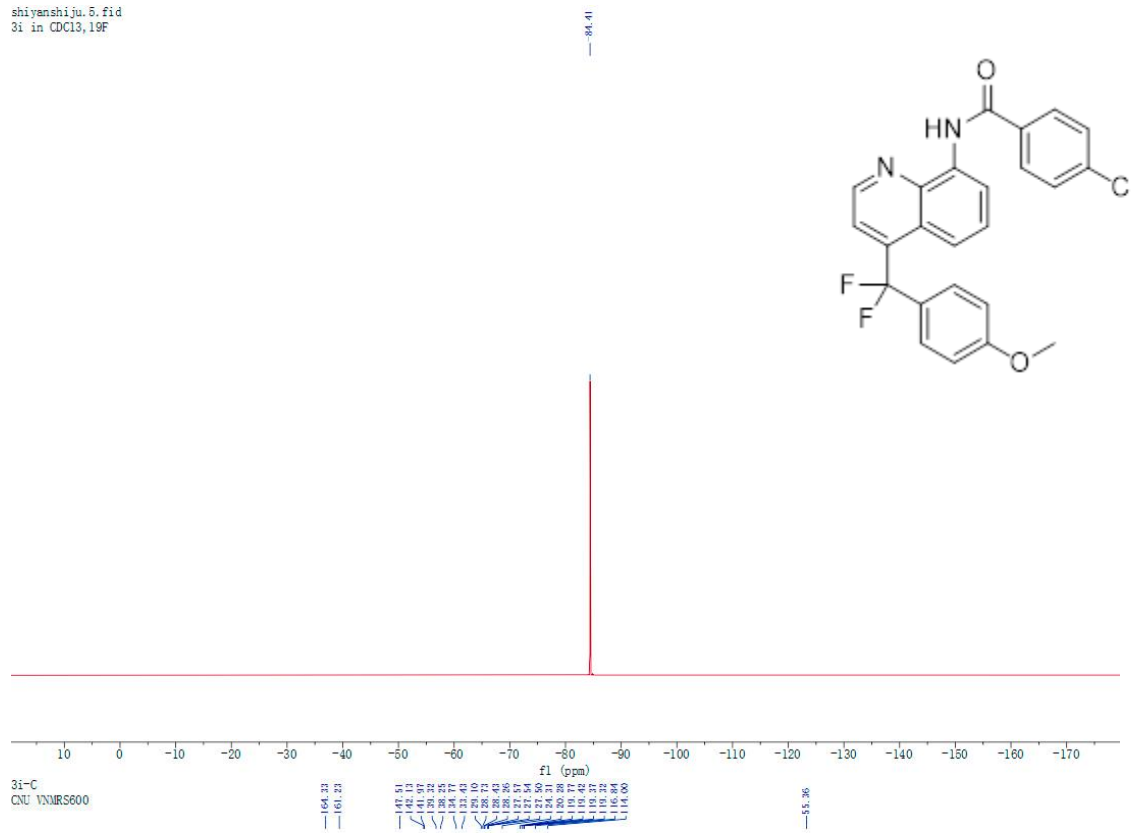
165.55
161.23
141.20
139.18
135.00
131.96
128.82
127.57
127.36
127.11
121.87
120.27
119.61
119.24
119.24
118.67
114.01
112.65
55.36



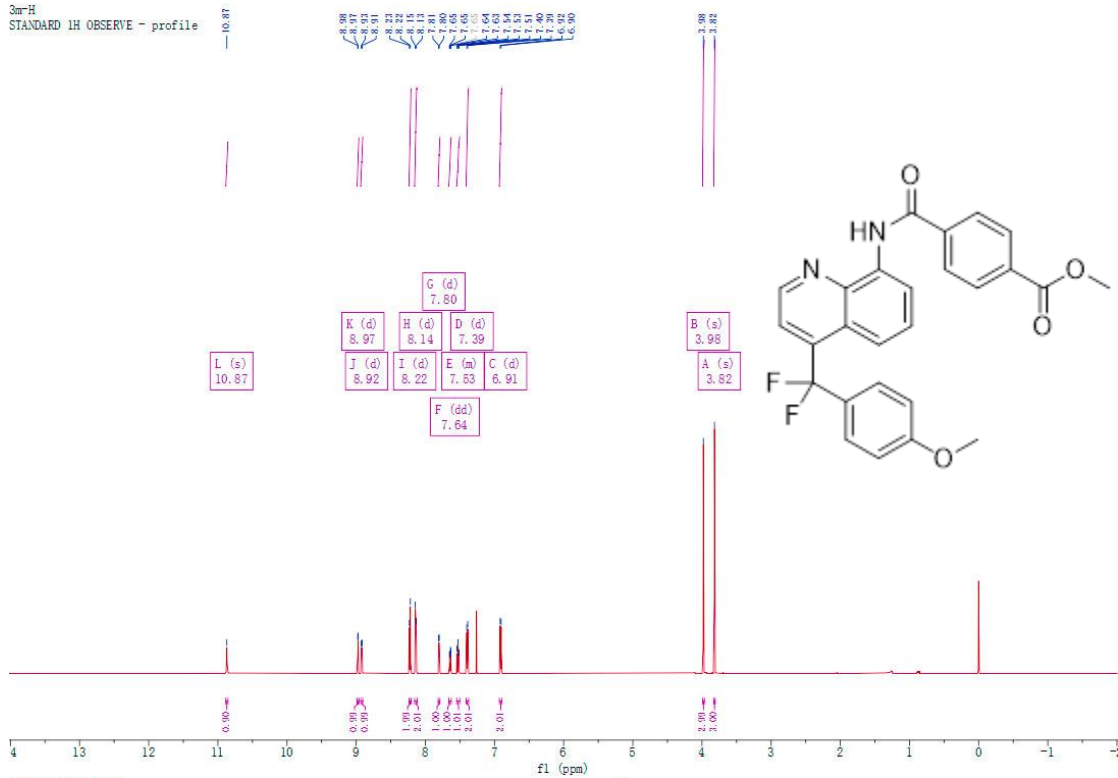
3i-H
CNU VNMR5600



shiyanshiju. 5.fid
3i in CDCl3, 19F

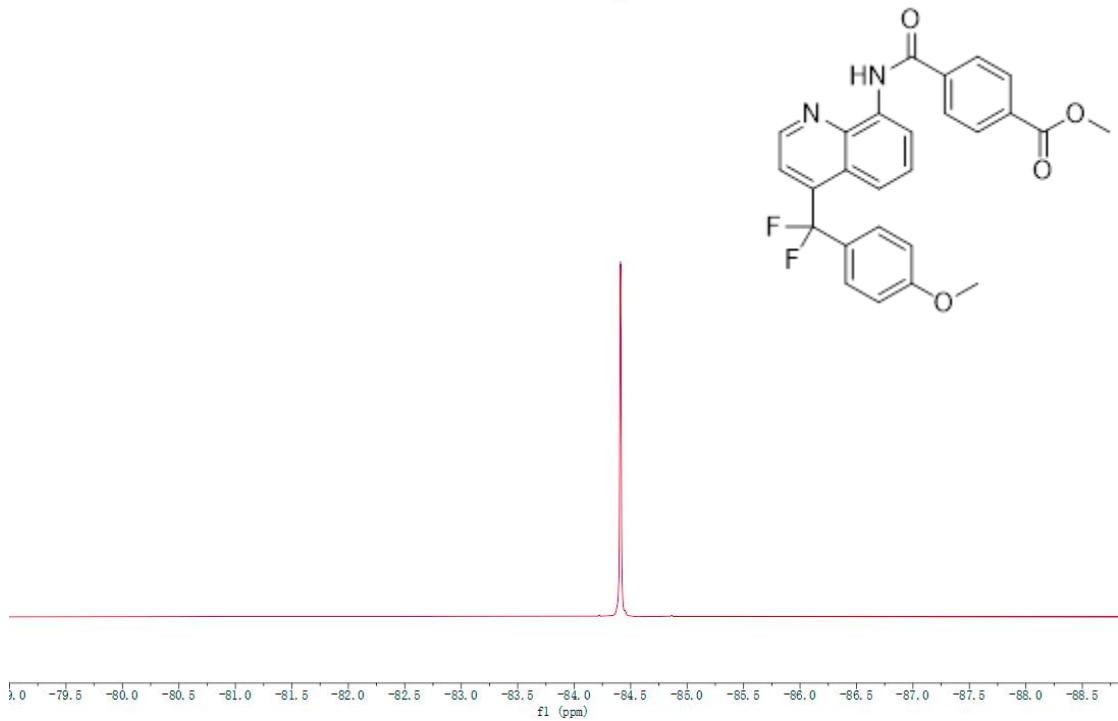


3m-H
STANDARD 1H OBSERVE - profile



shiyanshiju.7.fid
3m

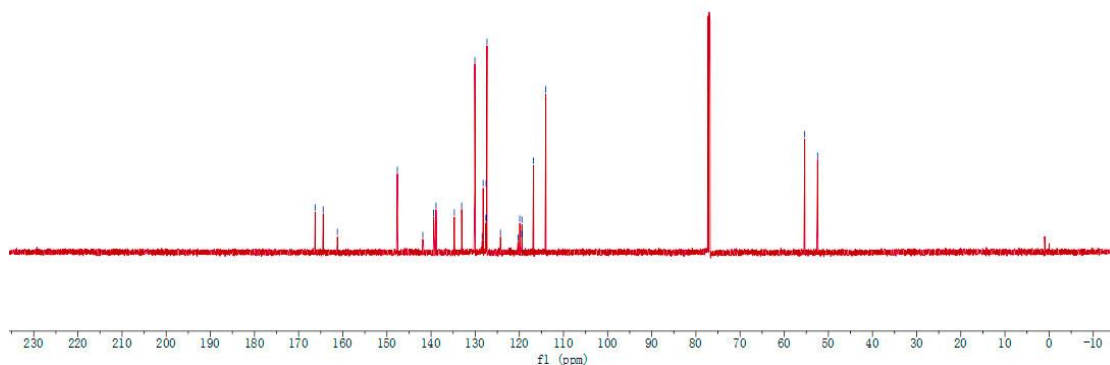
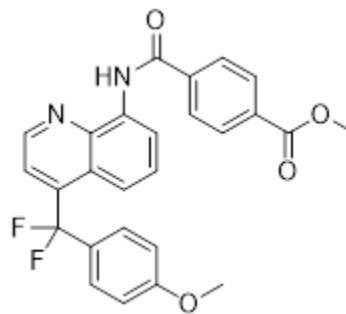
-84.41



3m-C
STANDARD 1H OBSERVE - profile

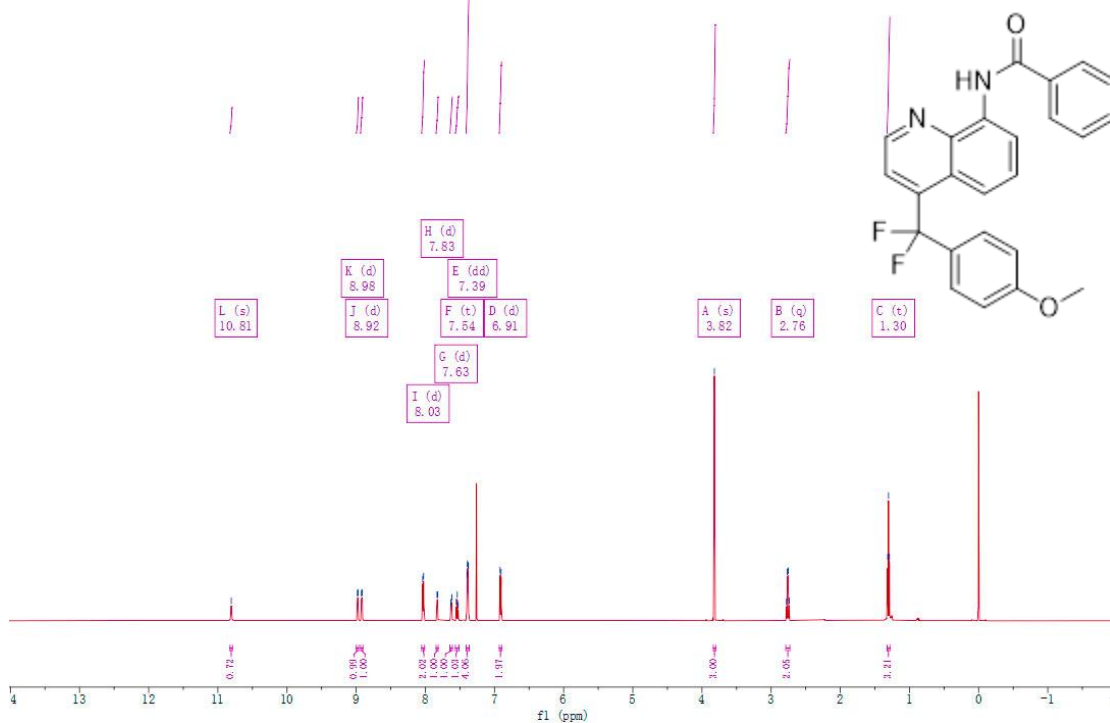
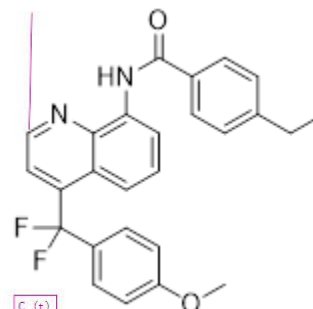
165.32
163.44
161.32
141.63
139.41
138.87
138.81
133.07
130.04
129.21
127.54
127.50
127.22
126.29
119.91
118.41
118.26
118.00

55.26
52.44

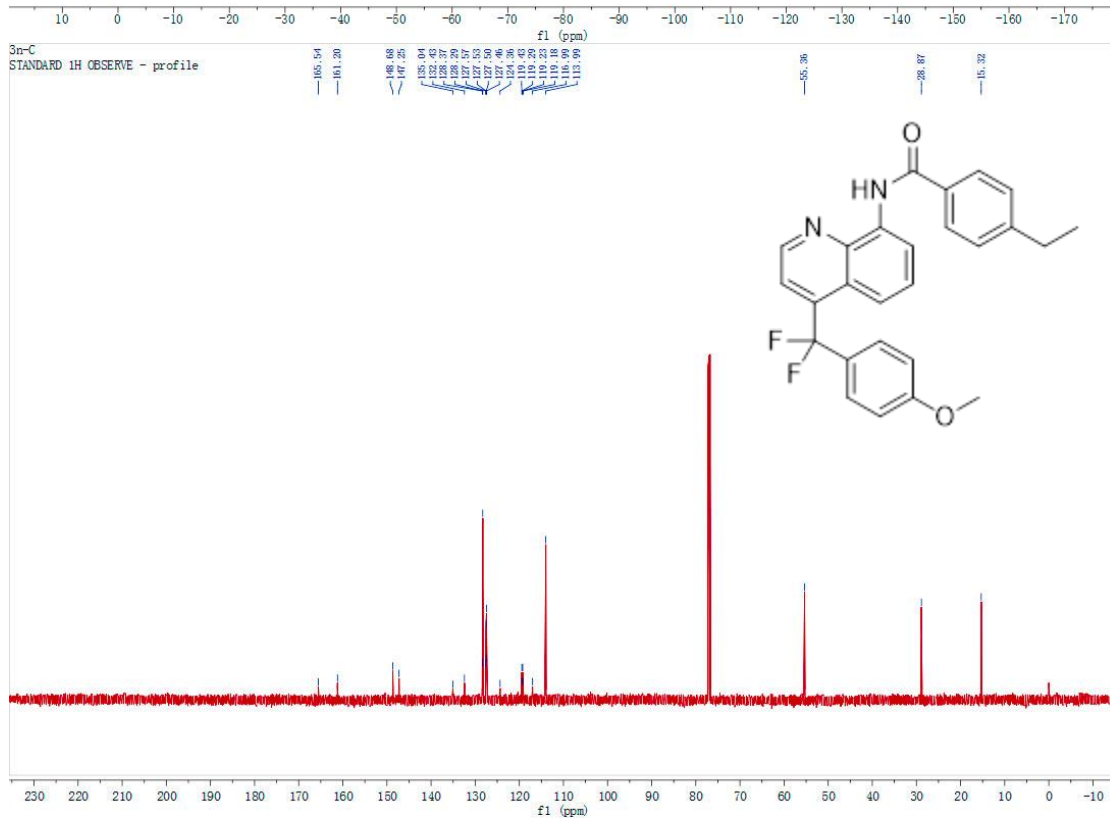
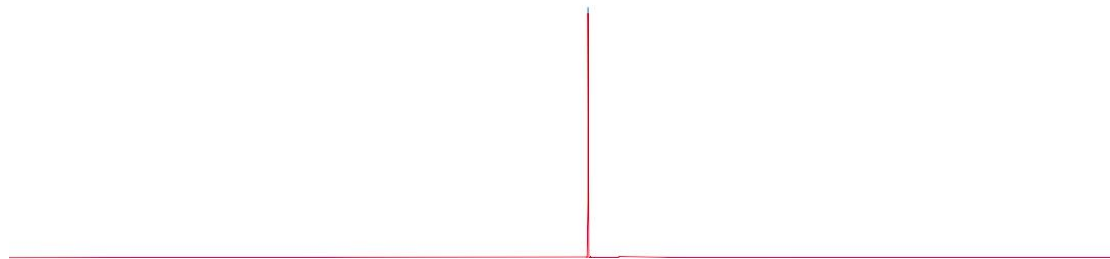
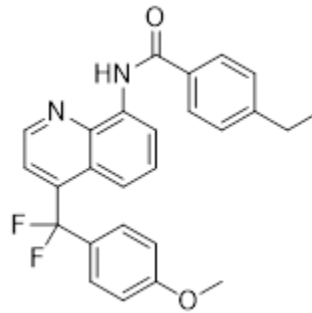


3m-H
STANDARD 1H OBSERVE - profile

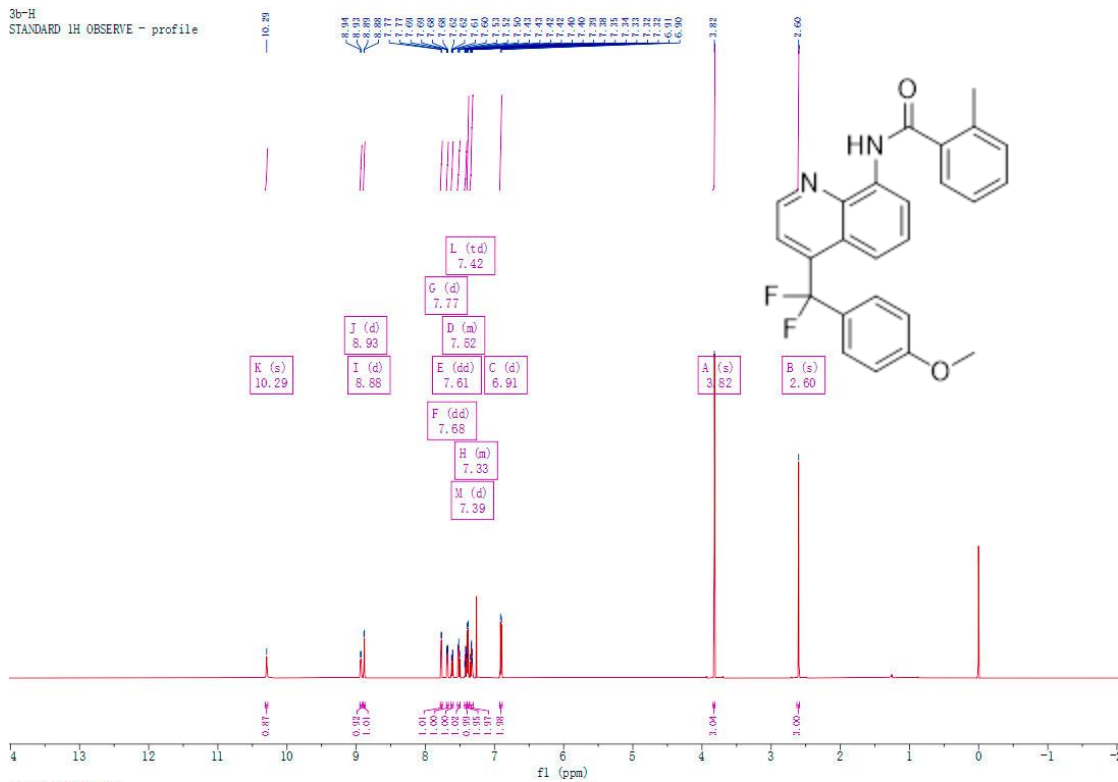
10.81
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8.92
8.91
8.82
8.63
8.54
8.40
8.39
8.38
8.30
3.82
2.76
1.30



-81.40



3b-H
STANDARD 1H OBSERVE - profile

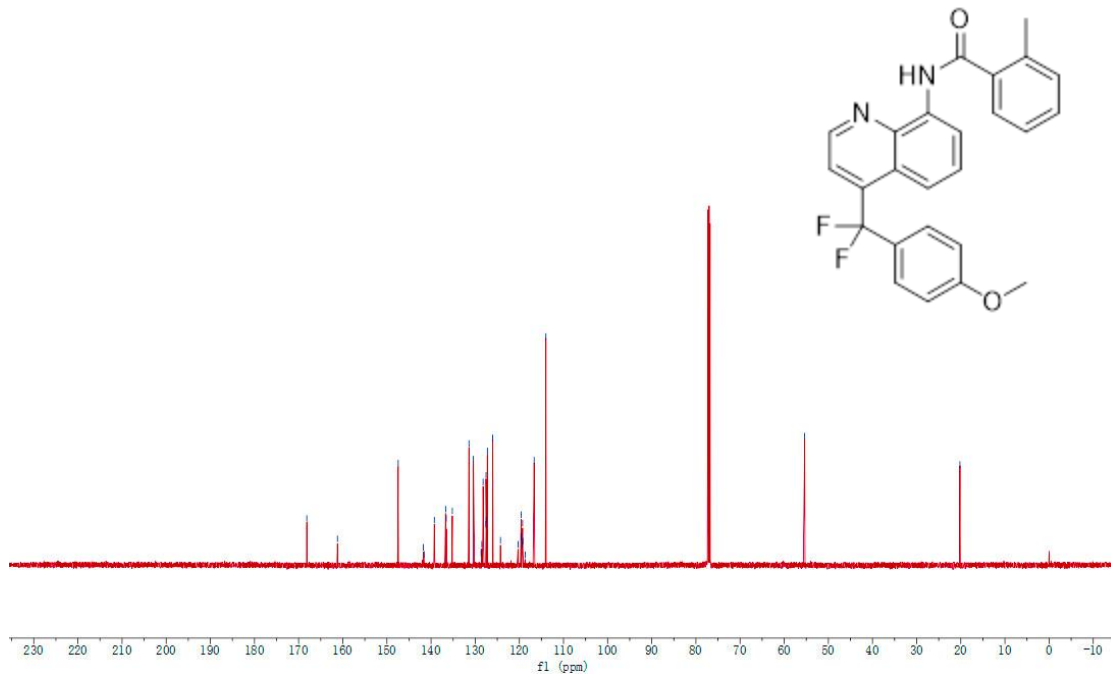


shiyanshiju.3.fid
3e



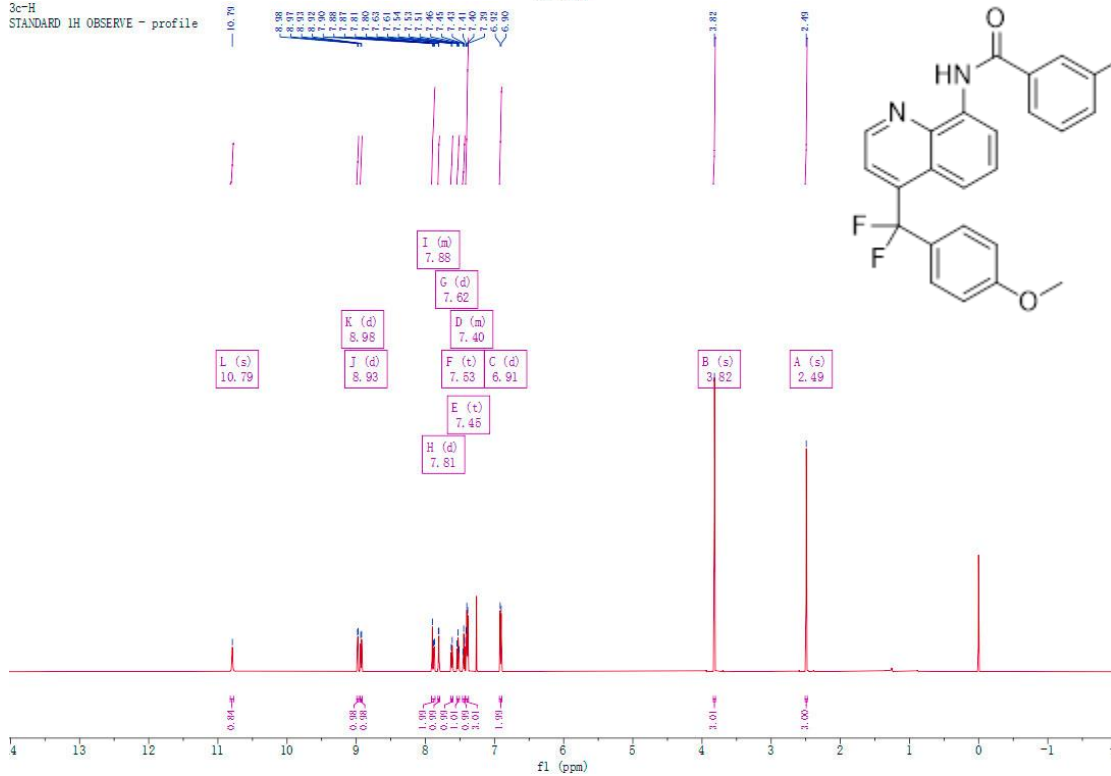
3b-C
STANDARD 1H OBSERVE - profile

168.15
161.20
147.45
141.57
139.29
136.56
135.18
130.40
128.68
128.21
127.58
127.24
124.28
120.29
119.59
119.21
116.65
113.98
55.26
20.19

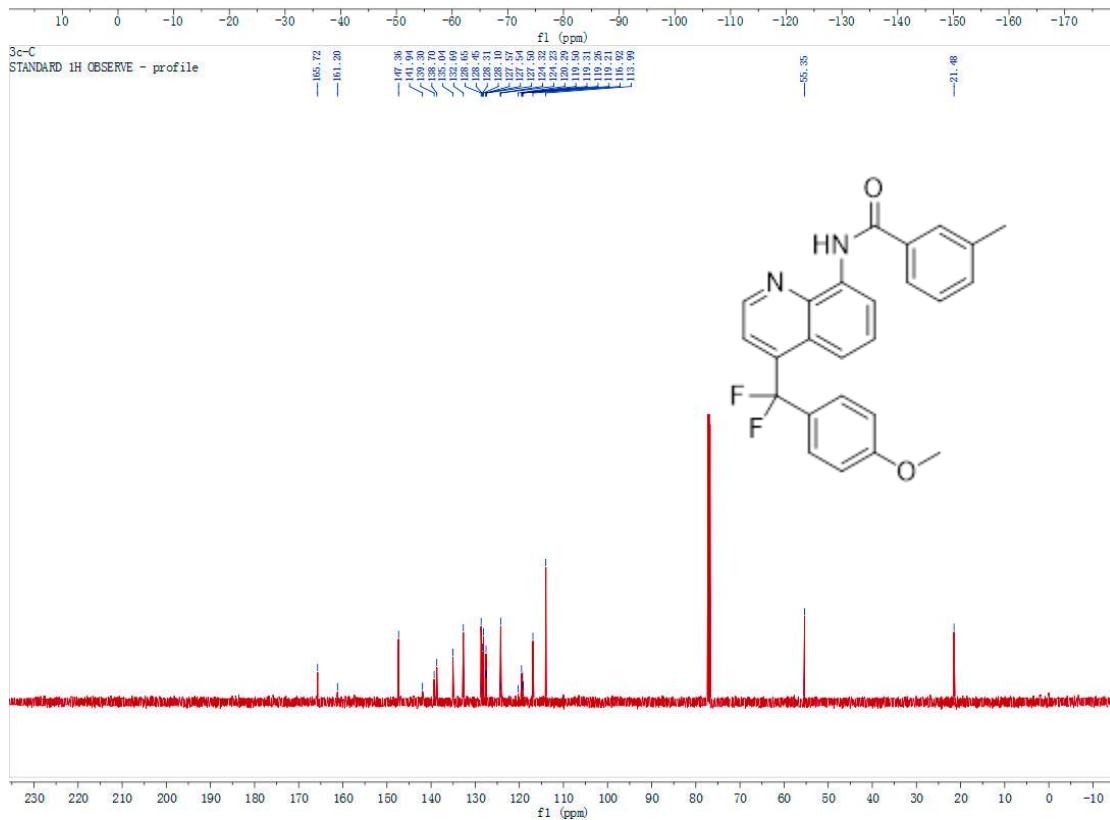
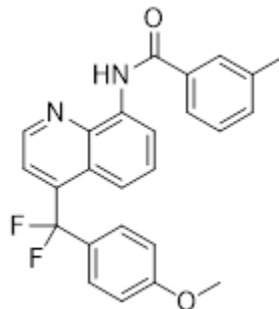


3b-H
STANDARD 1H OBSERVE - profile

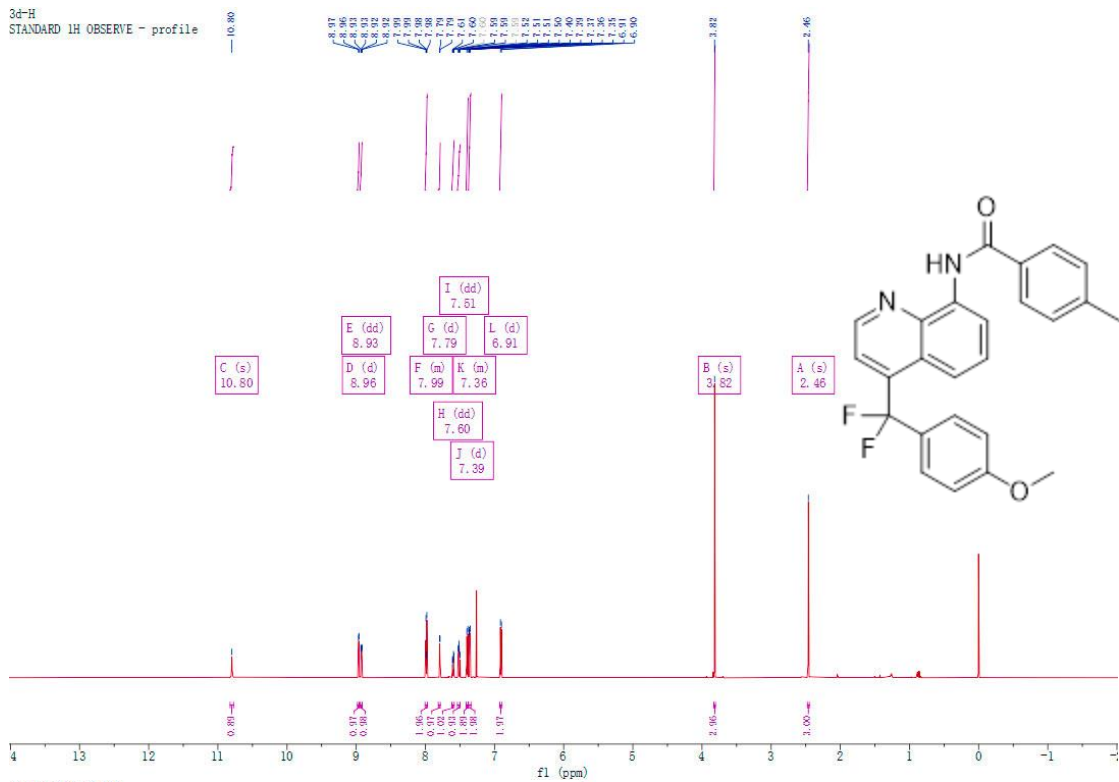
10.79
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8.80
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8.51
8.46
8.41
8.39
8.30
8.20
3.82
2.49



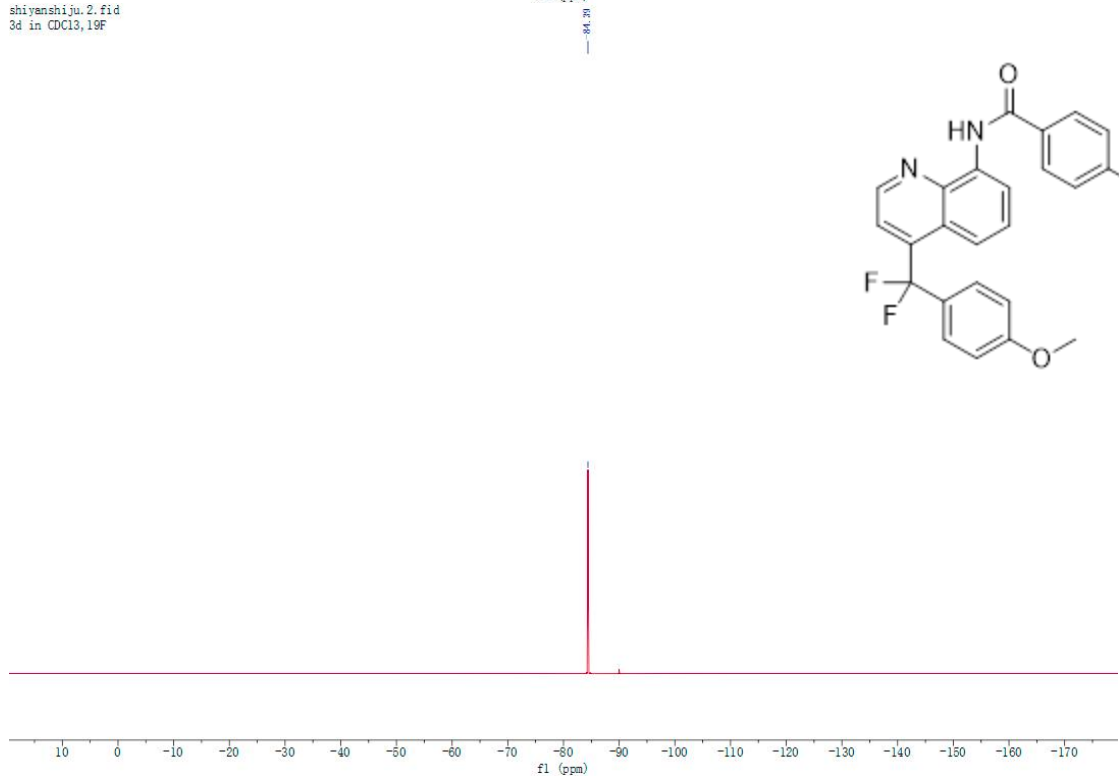
-81.29



3d-H
STANDARD 1H OBSERVE - profile



shiyanshiju.2.fid
3d in CDCl₃, 19F

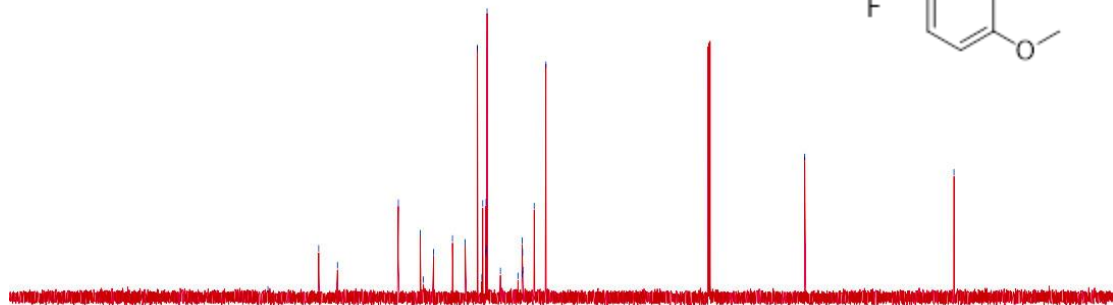
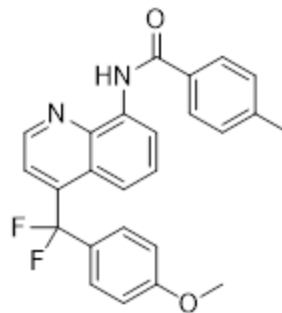


3d-C
STANDARD 1H OBSERVE - profile

16.95
165.45
161.30
147.41
144.78
139.43
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128.93
127.58
127.51
127.21
120.32
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119.21
112.98

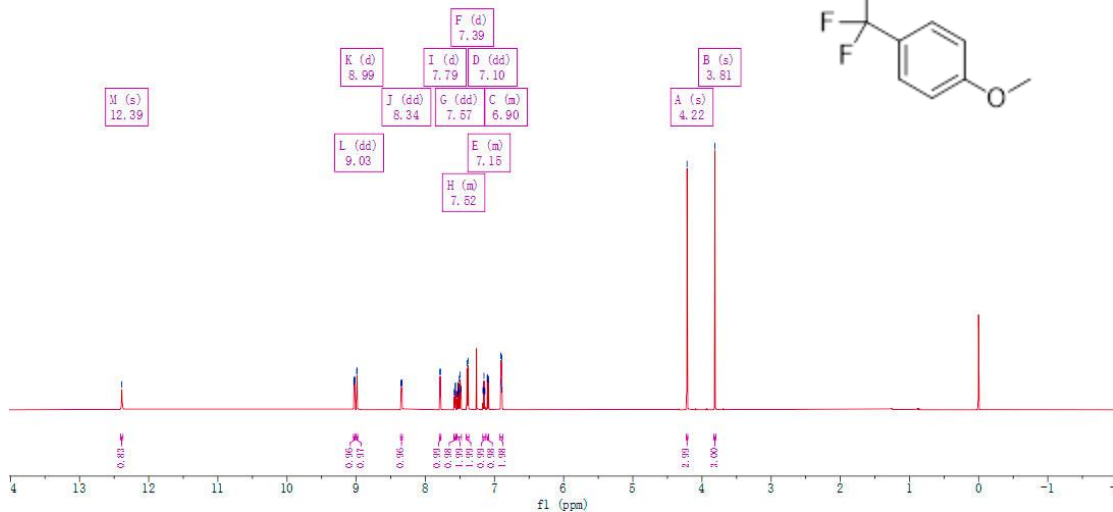
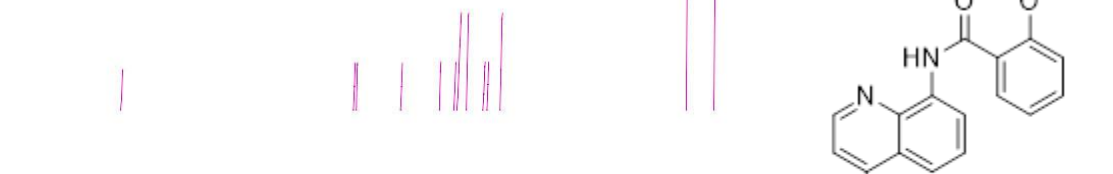
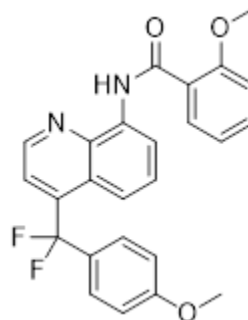
55.35

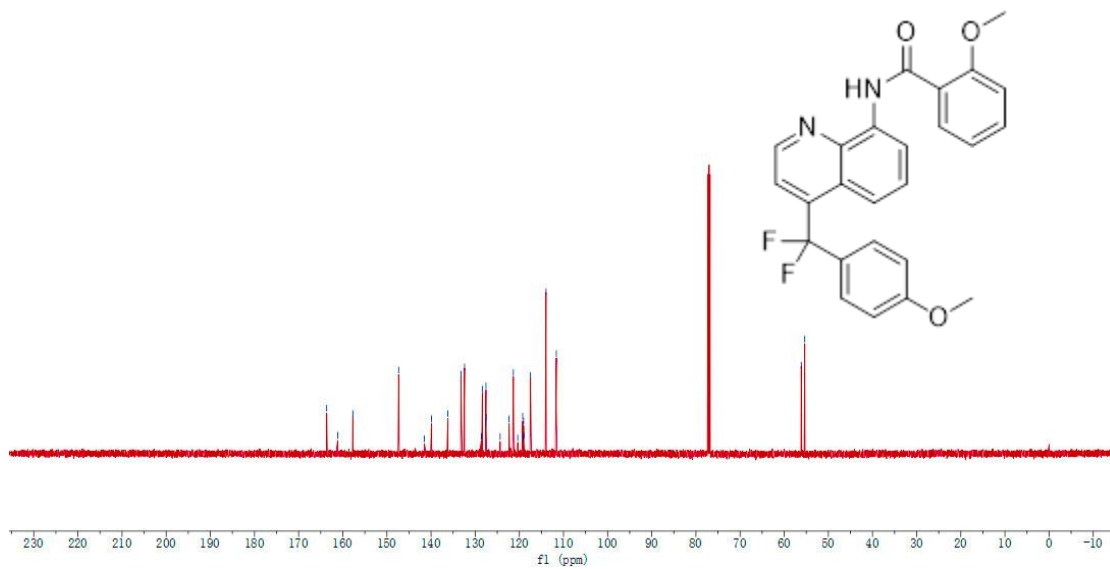
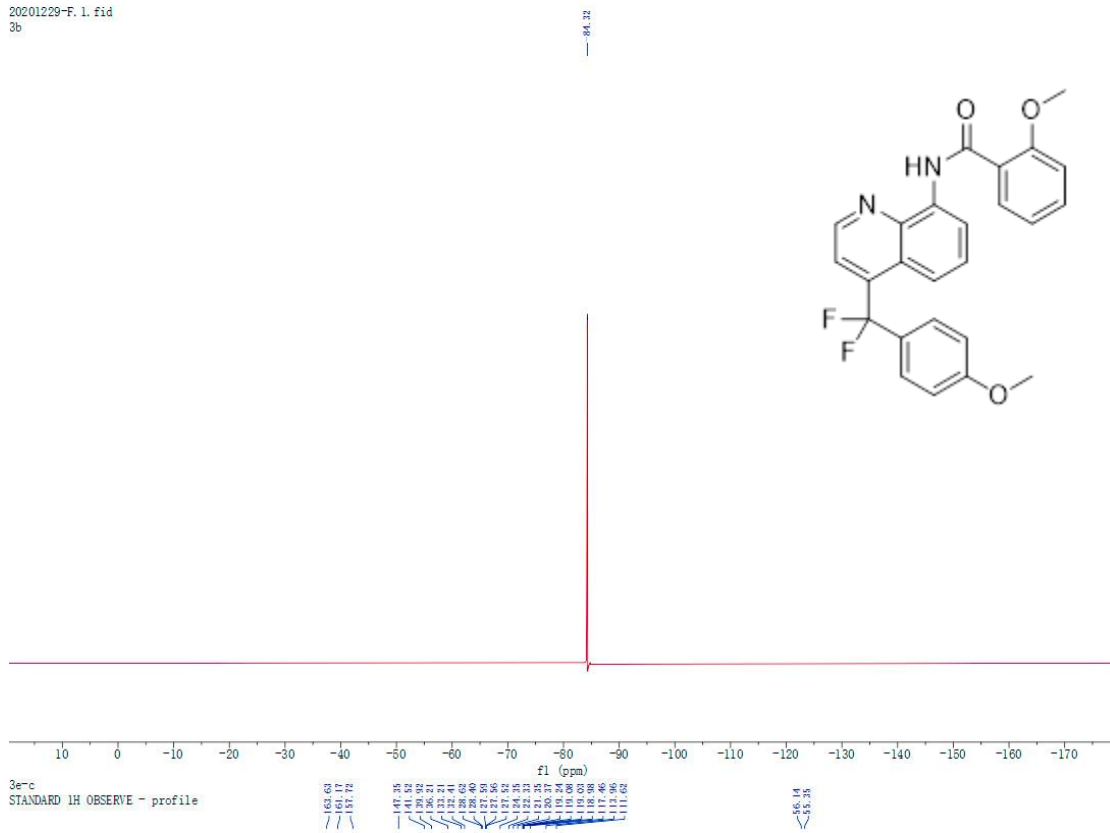
21.54



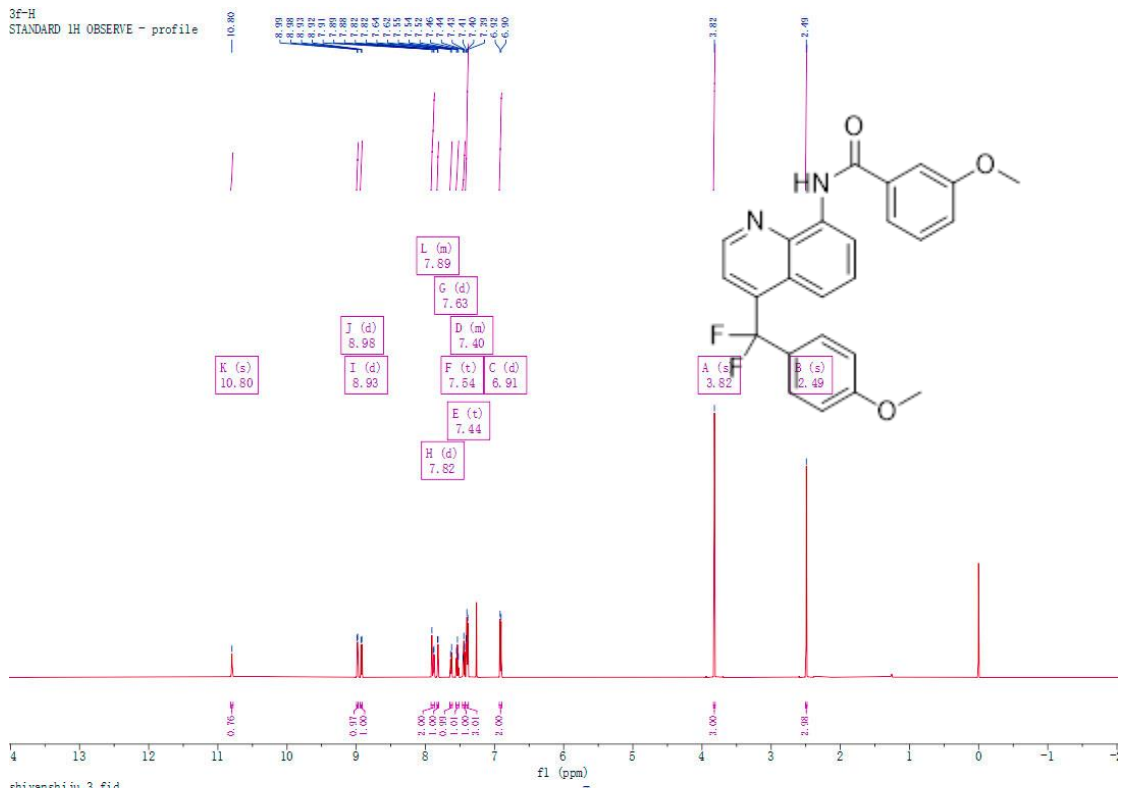
3d-H
STANDARD 1H OBSERVE - profile

8.99
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8.87
8.85
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8.81
8.79
8.77
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5.27
5.25
5.23
5.21
5.19
5.17
5.15
5.13
5.11
5.09
5.07
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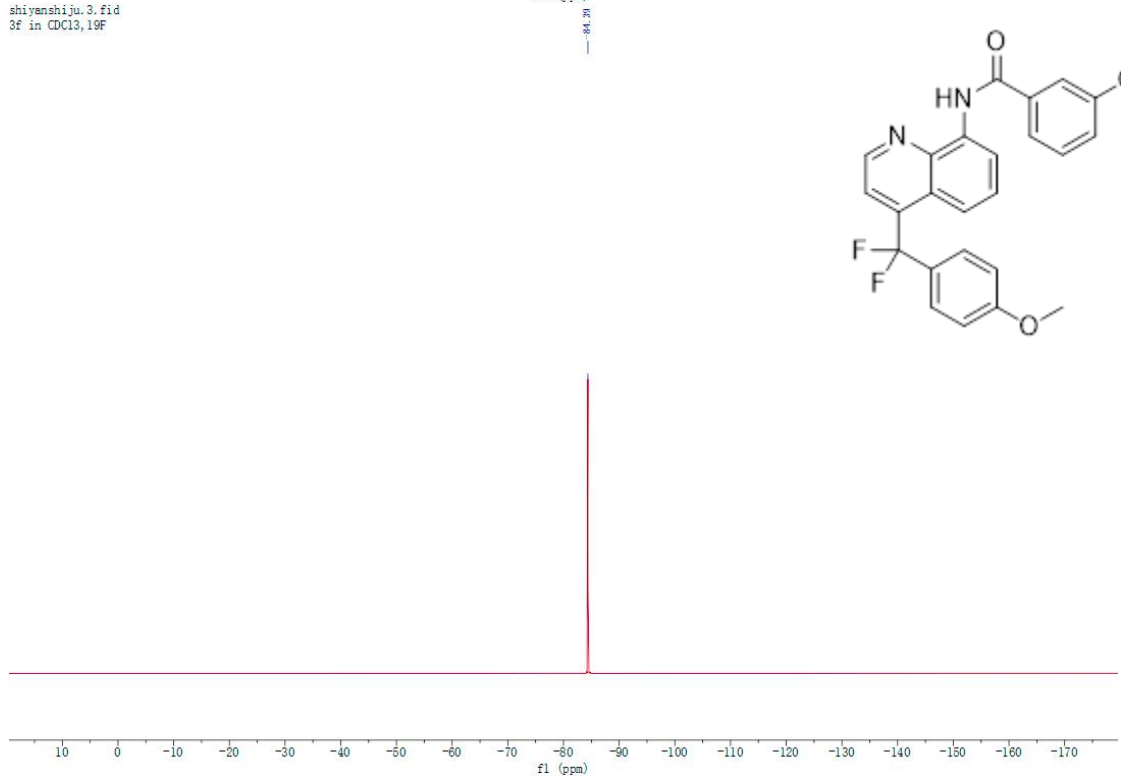




3F-H
STANDARD 1H OBSERVE - profile



shiyanshiju.3.fid
3f in CDCl3, 19F

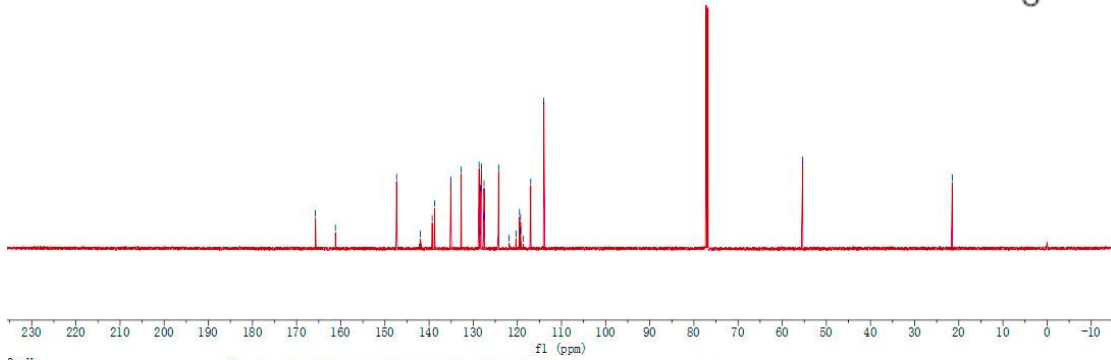
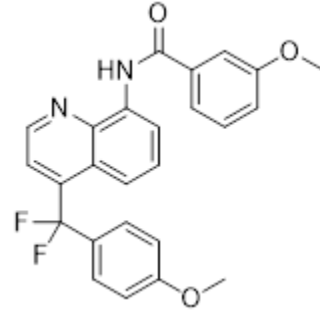


3F-C
STANDARD 1H OBSERVE - profile

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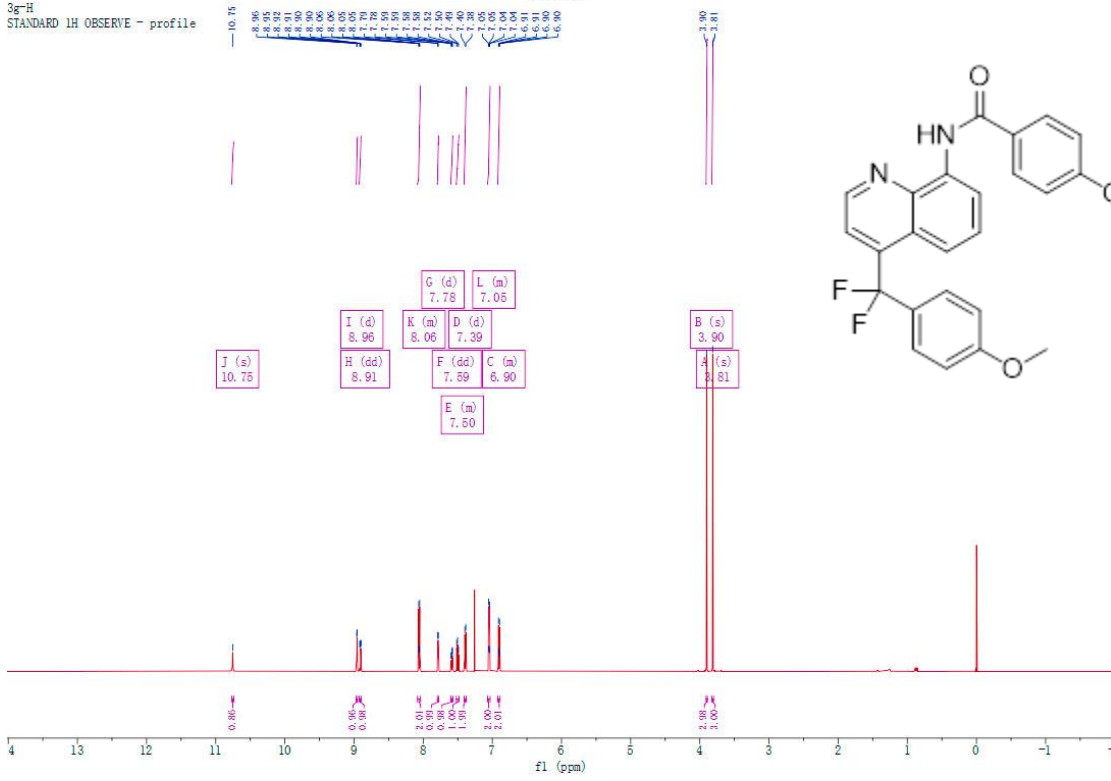
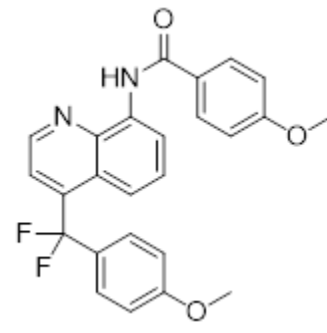
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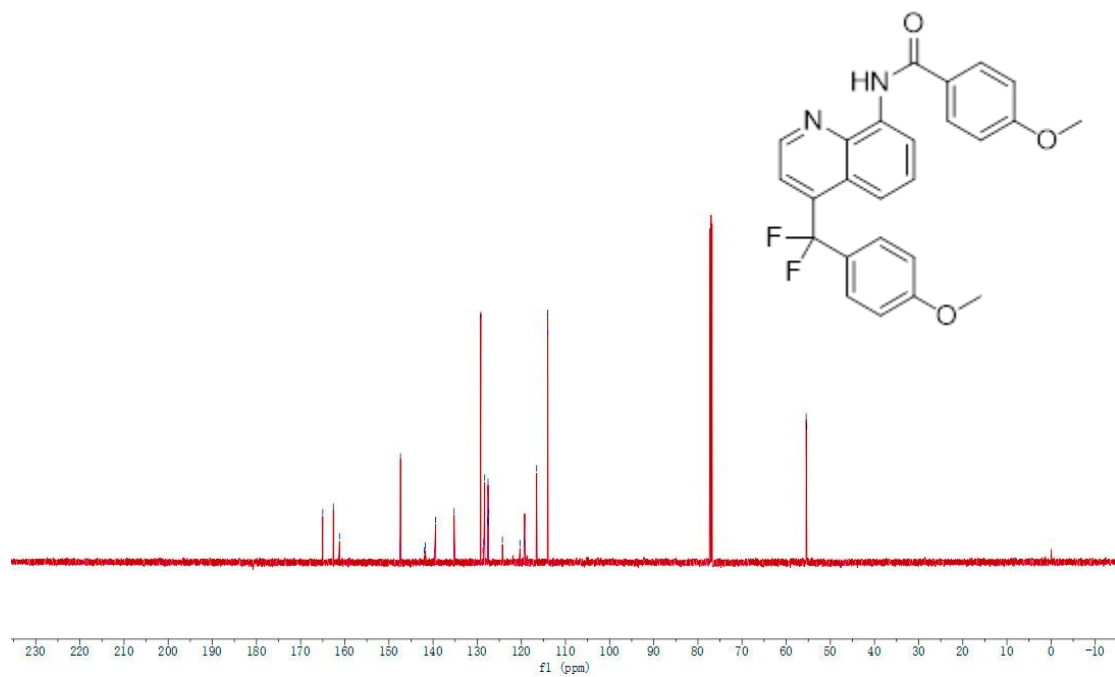
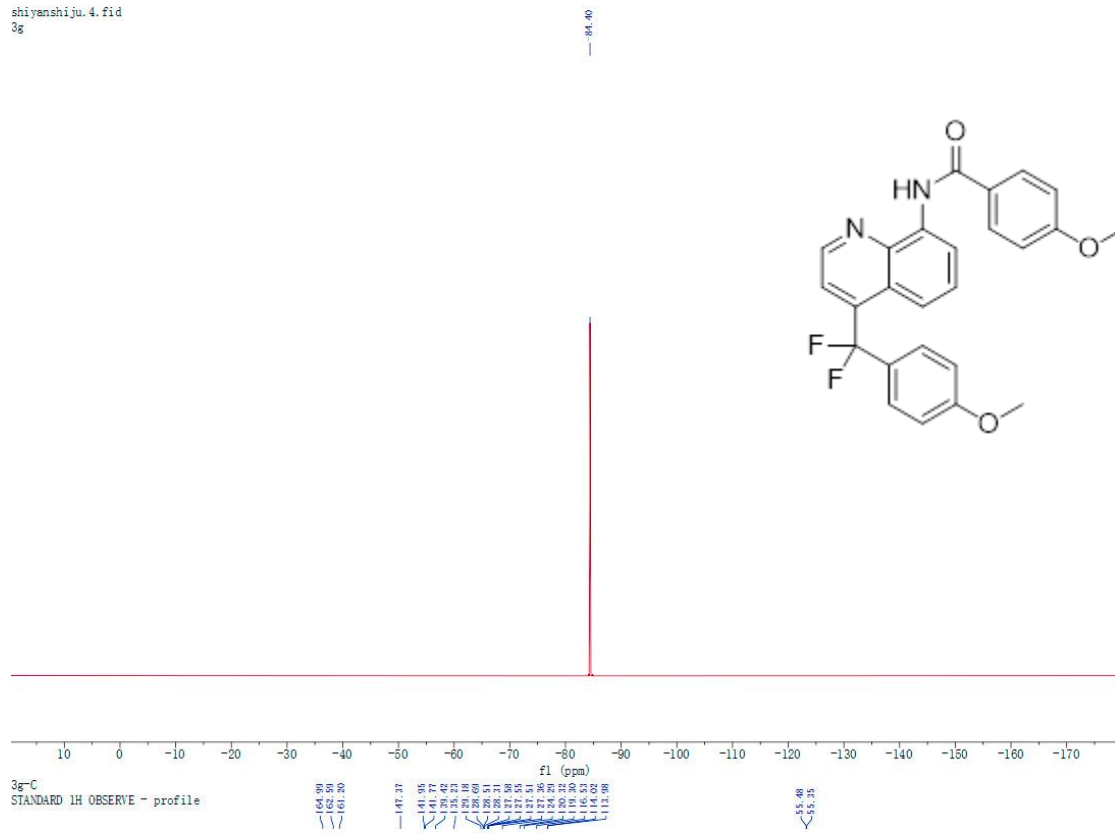


3g-H
STANDARD 1H OBSERVE - profile

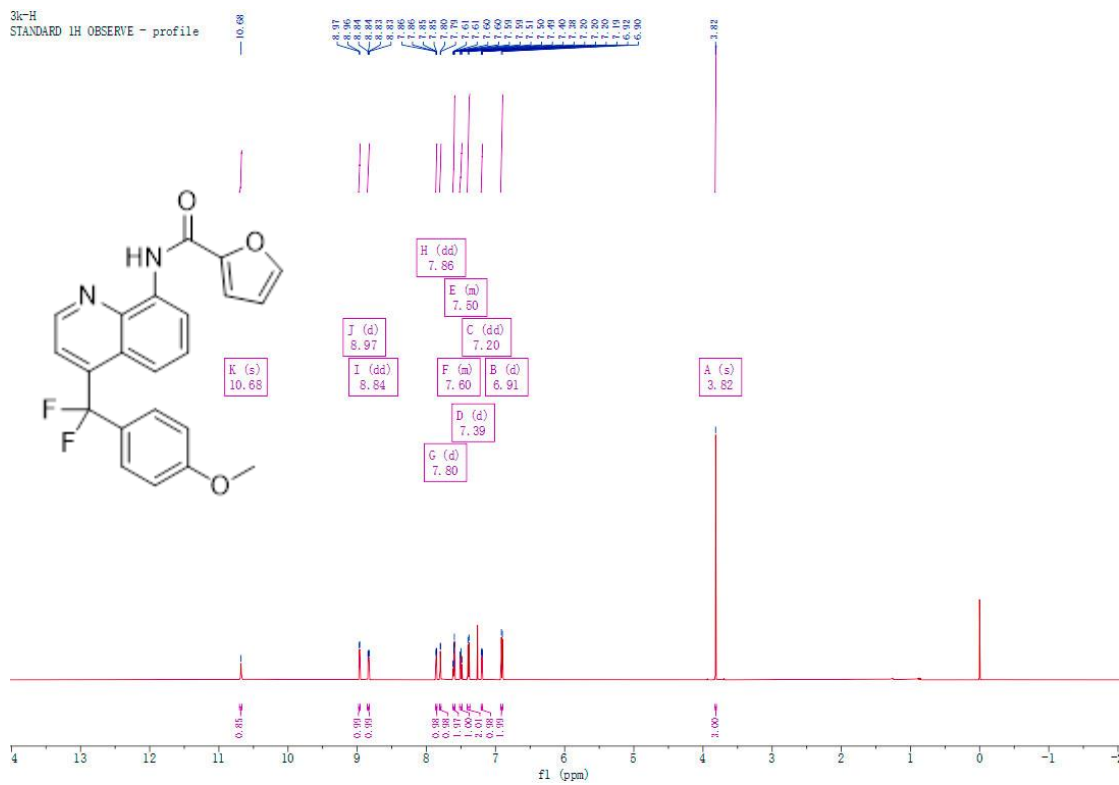
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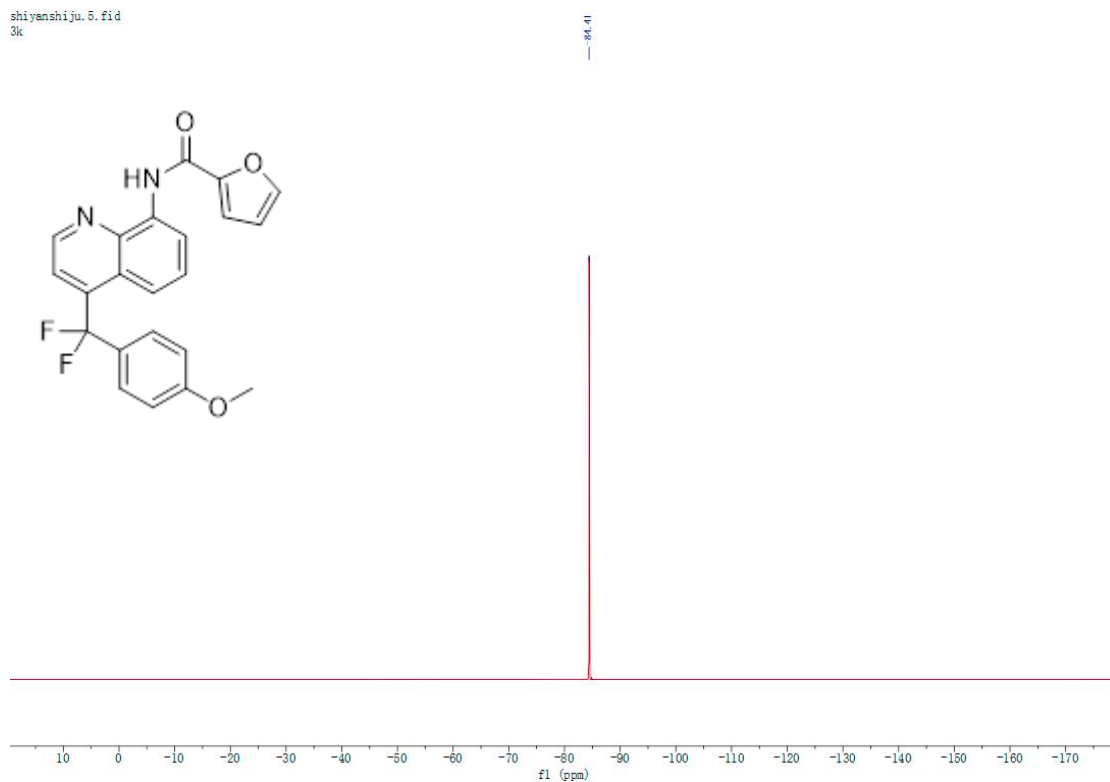
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3k-H
STANDARD 1H OBSERVE - profile



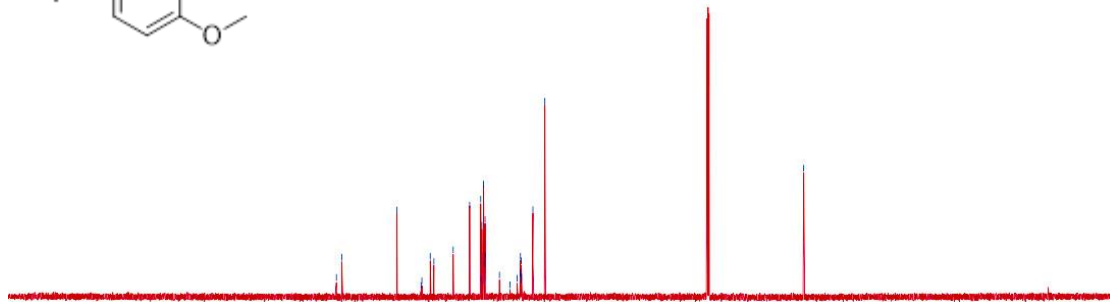
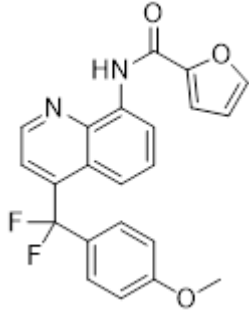
shiyanshiju.5.fid
3k



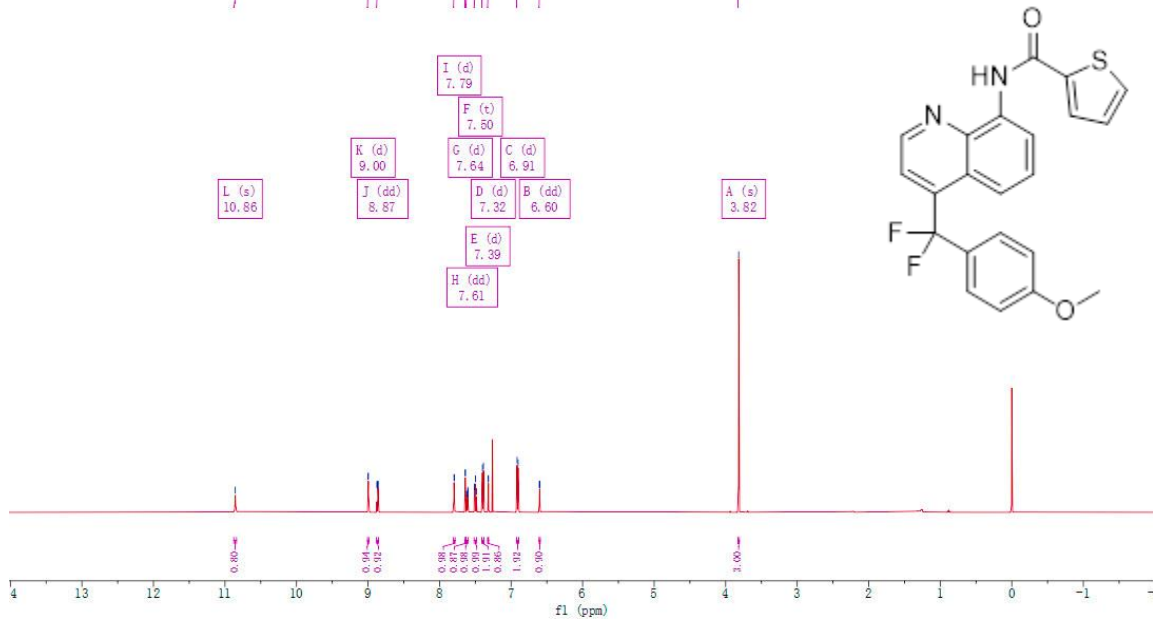
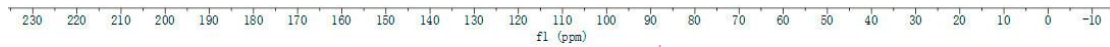
3k-C
STANDARD 1H OBSERVE - profile

151.78
142.80
141.85
139.82
134.76
133.82
128.45
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124.28
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119.23
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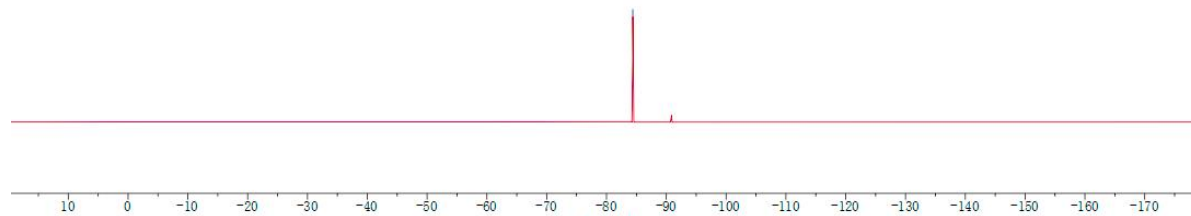
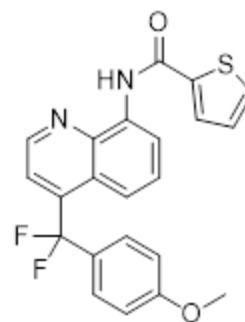


3j-H
GNU VNMR560



shiyanshiju.6.fid
3j in CDCl3,19F

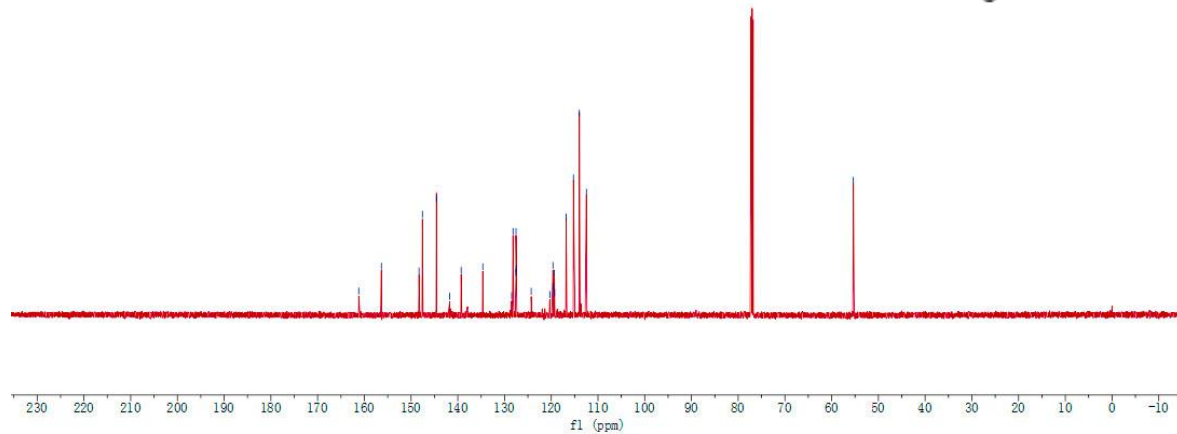
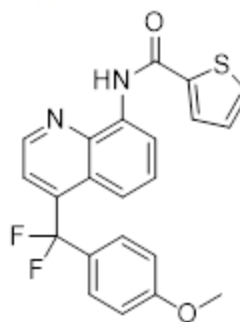
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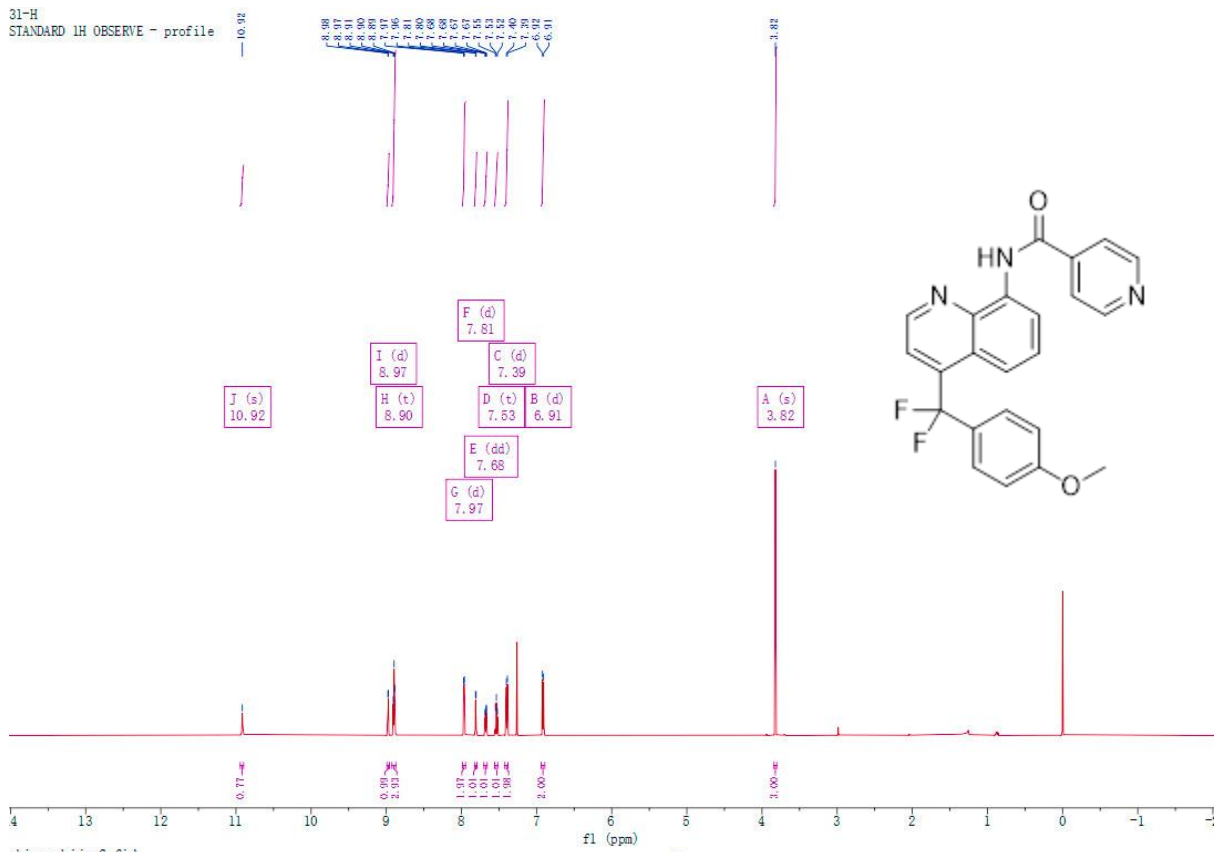
3J-c
GNU VNMR600

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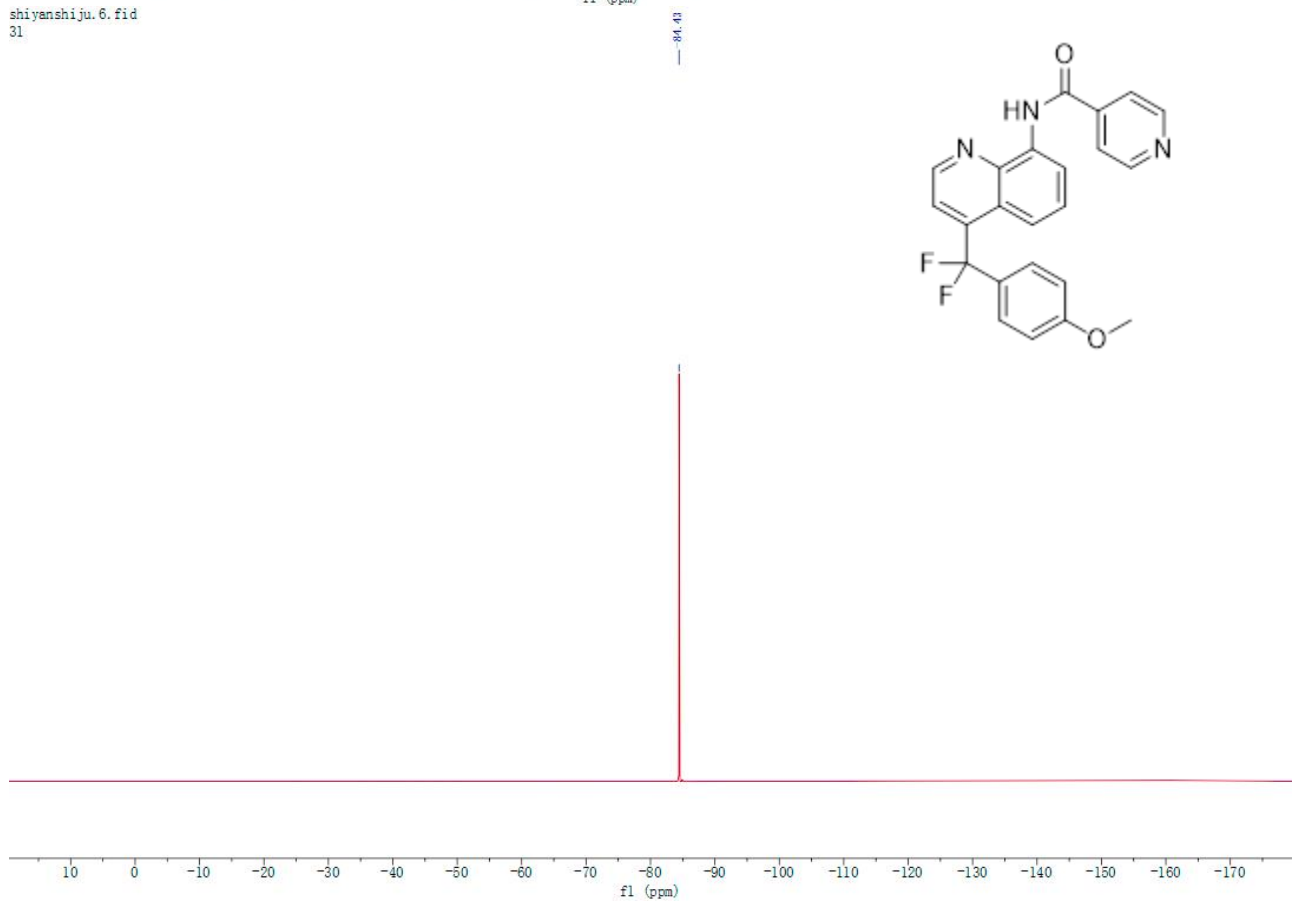
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31-H
STANDARD 1H OBSERVE - profile



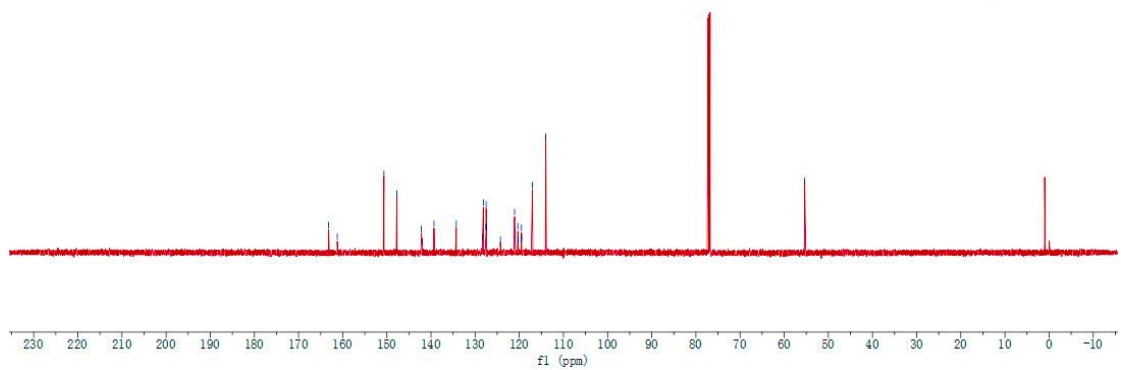
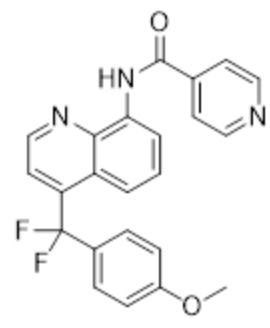
shiyanshiju.6.fid
31



3L-C
STANDARD 1H OBSERVE - profile

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128.15
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114.01

55.36

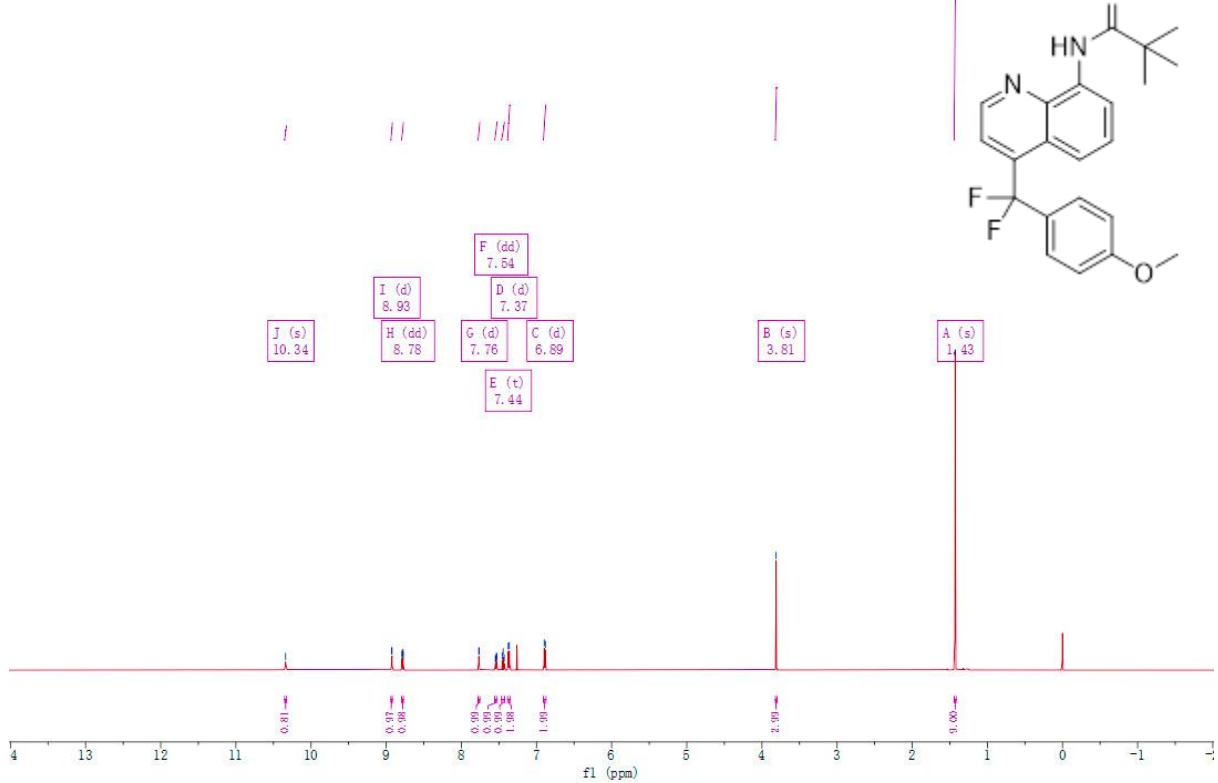
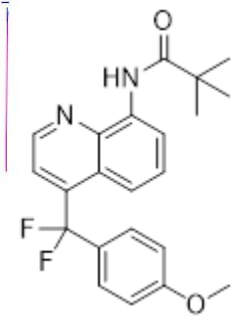


3s
GNU VNMR5600

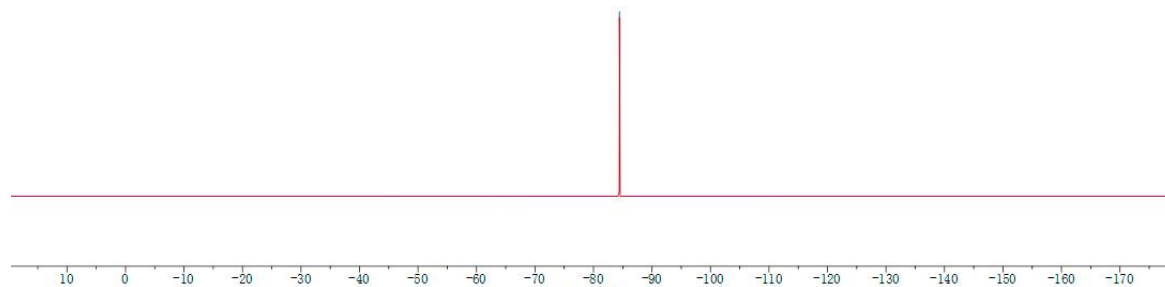
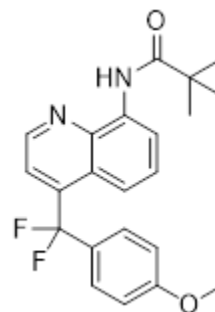
10.34
8.93
8.92
8.79
8.78
8.77
8.76
7.55
7.54
7.53
7.46
7.44
7.43
7.38
7.36
7.35
6.89
6.88

3.81

1.43

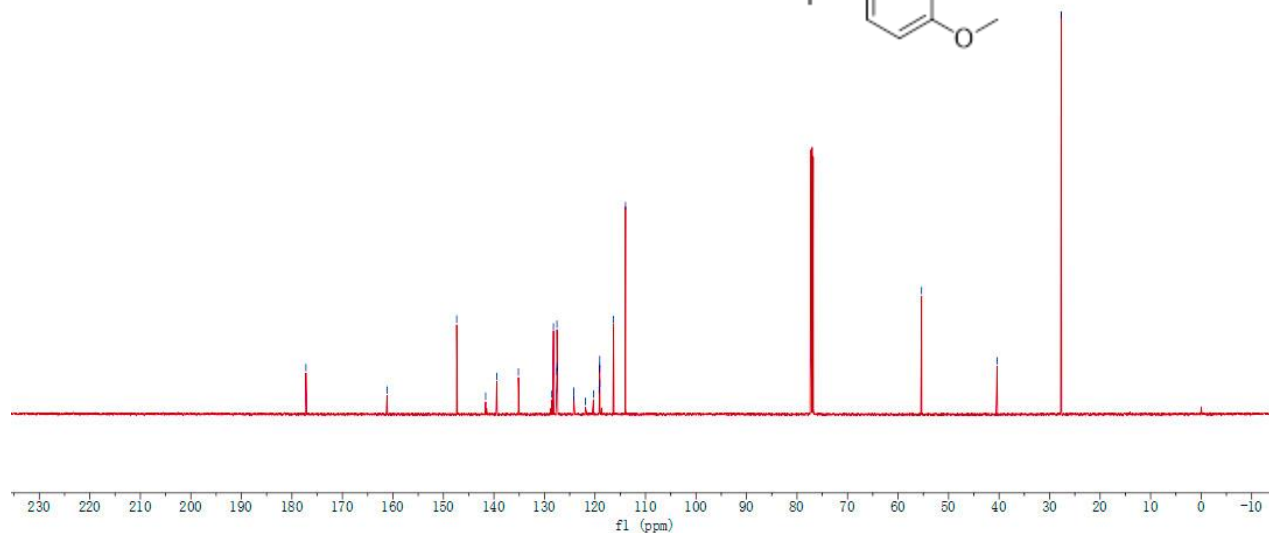
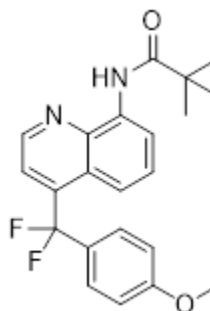


-96.43

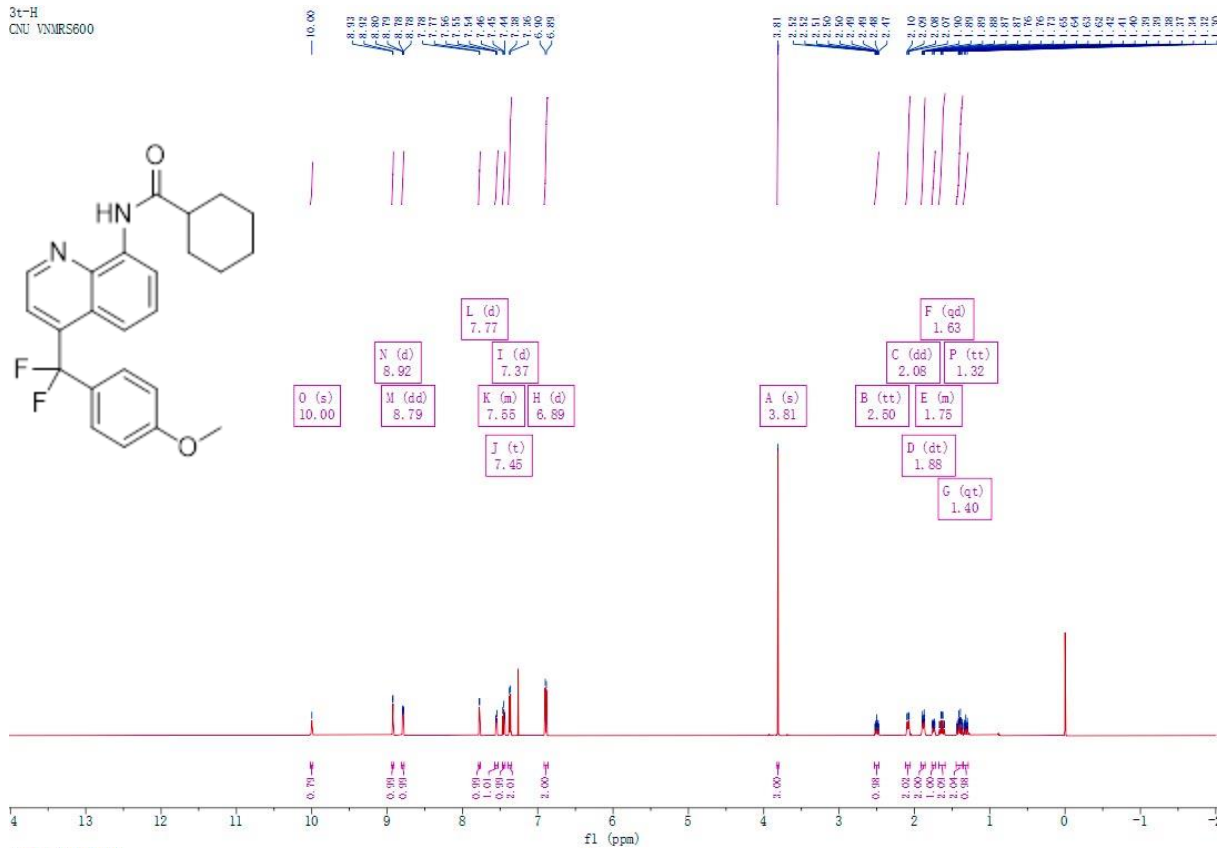
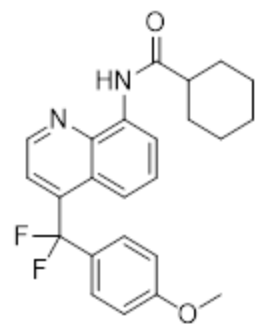


3s-C
CNU YNMRS600

177.22, 161.17, 147.28, 141.64, 139.45, 135.16, 132.51, 128.51, 127.56, 127.53, 127.49, 124.10, 121.90, 120.30, 119.17, 119.12, 119.07, 119.05, 119.03, 113.95, 55.34, 40.28, 27.71

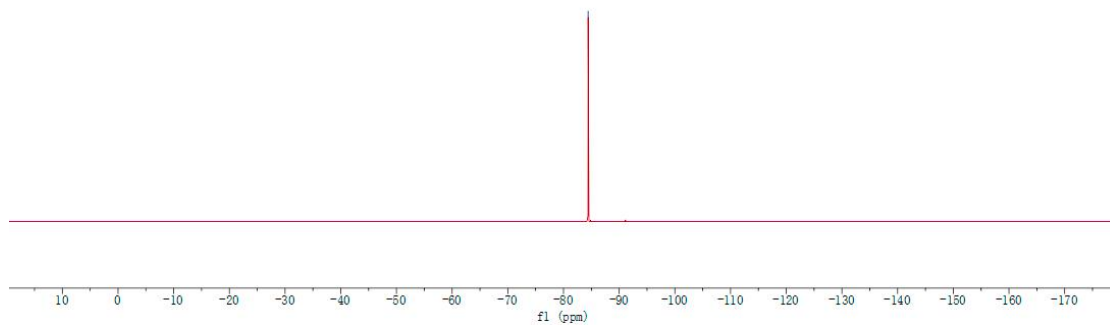
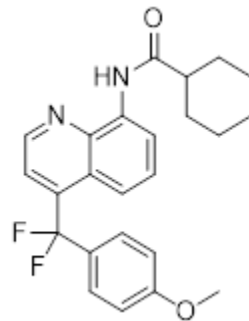


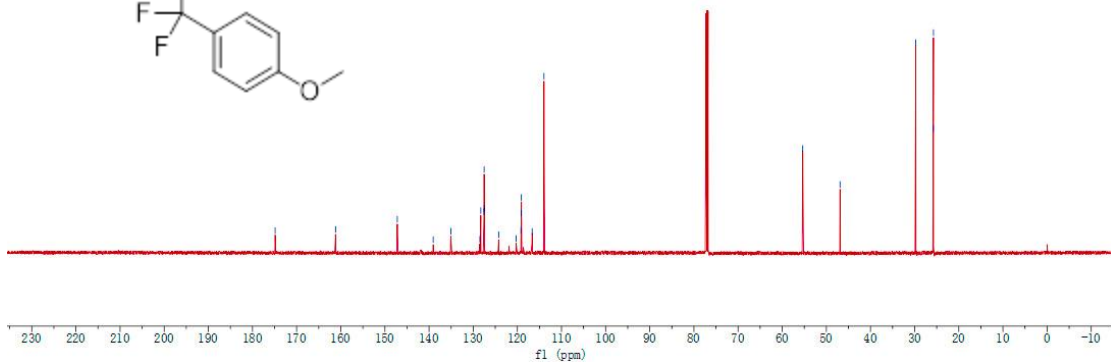
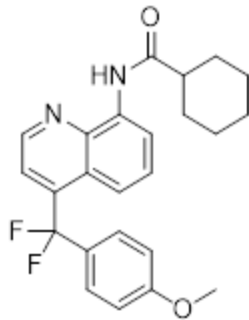
3t-H
CNV YNMRS600



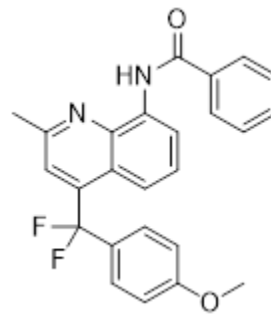
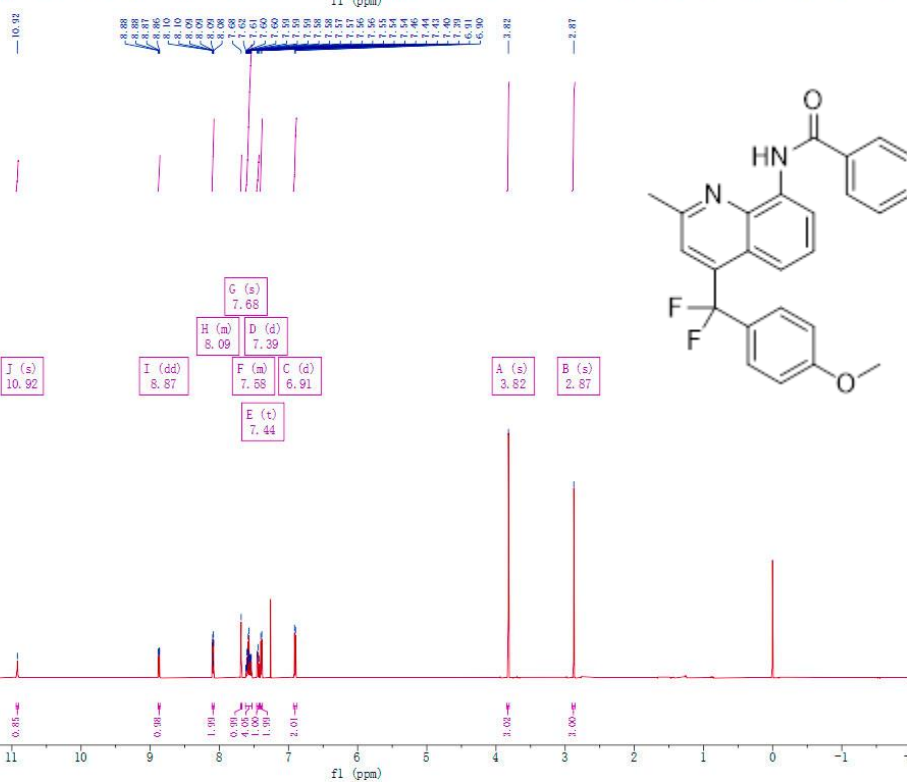
shiyanshiju_9.fid
3t in CDCl3, 19F

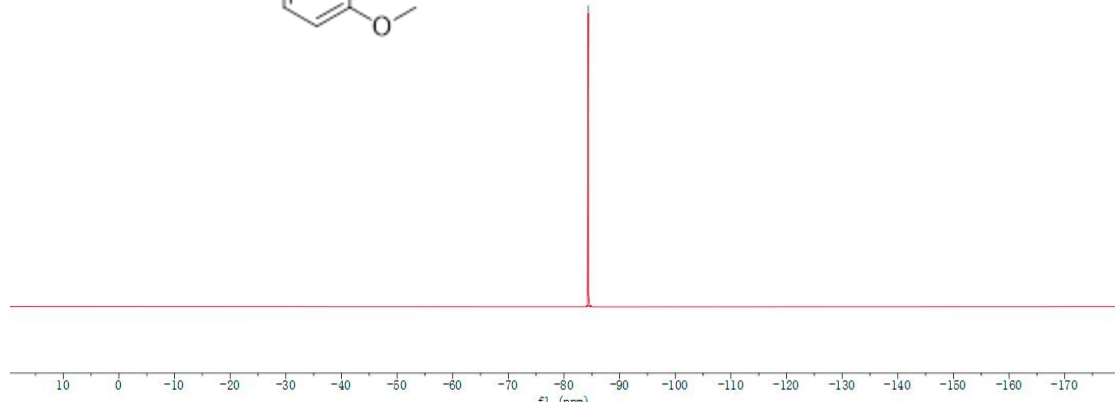
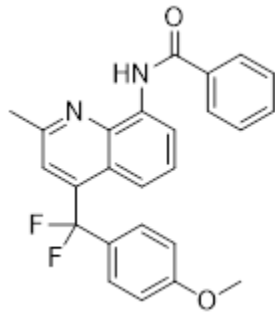
-84.4



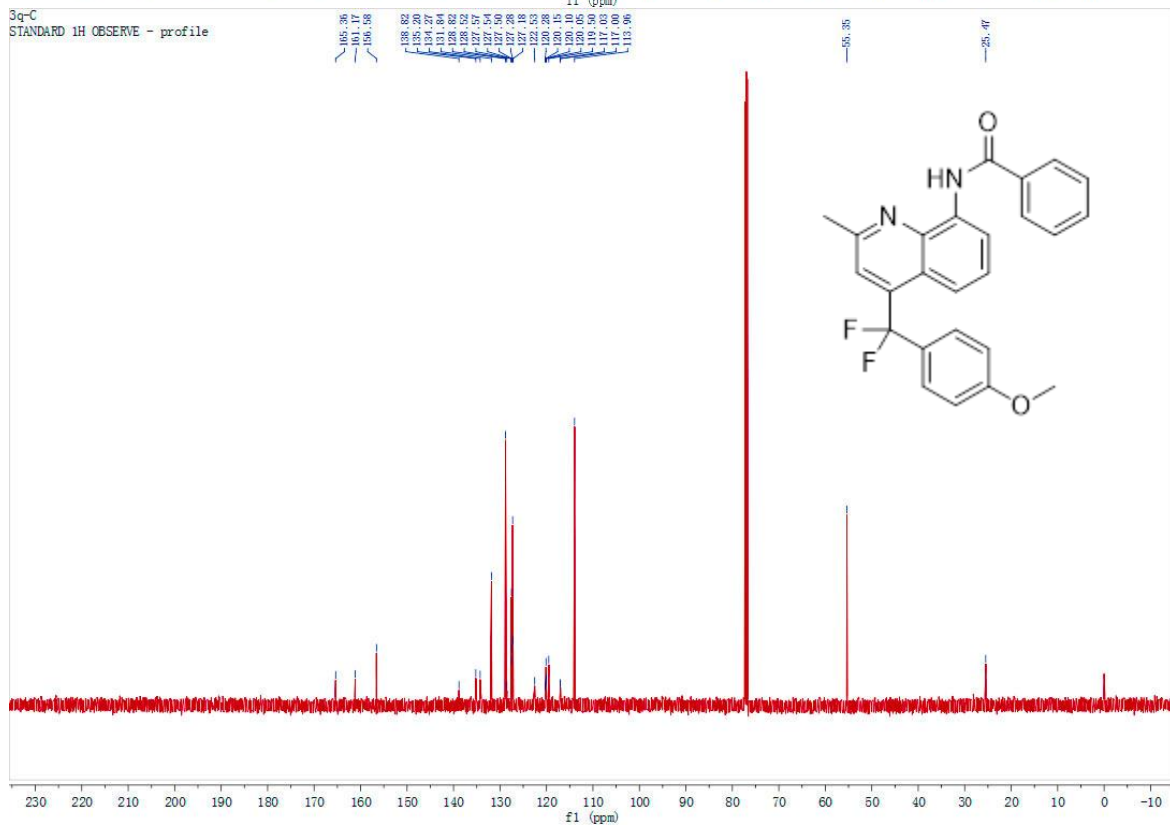


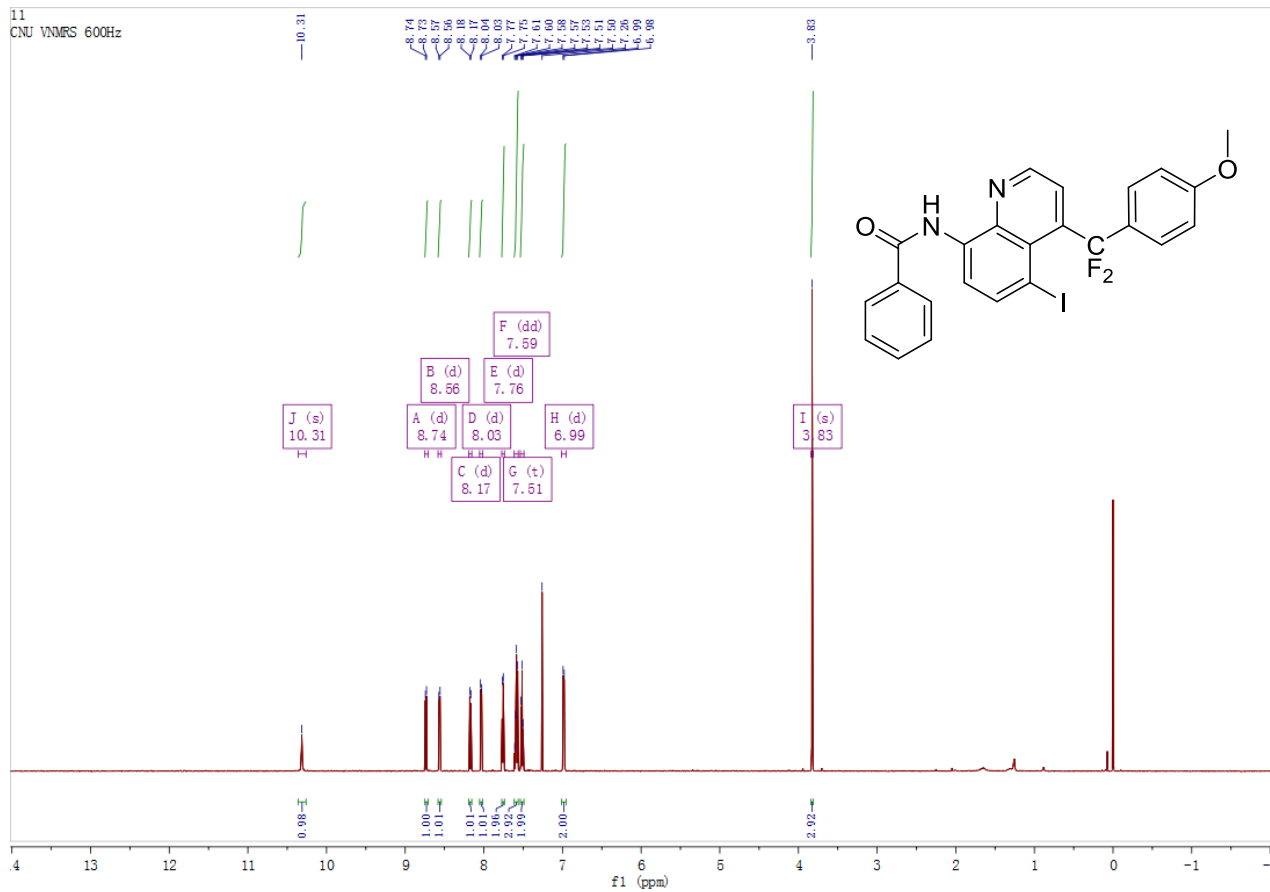
3q-H
STANDARD 1H OBSERVE - profile



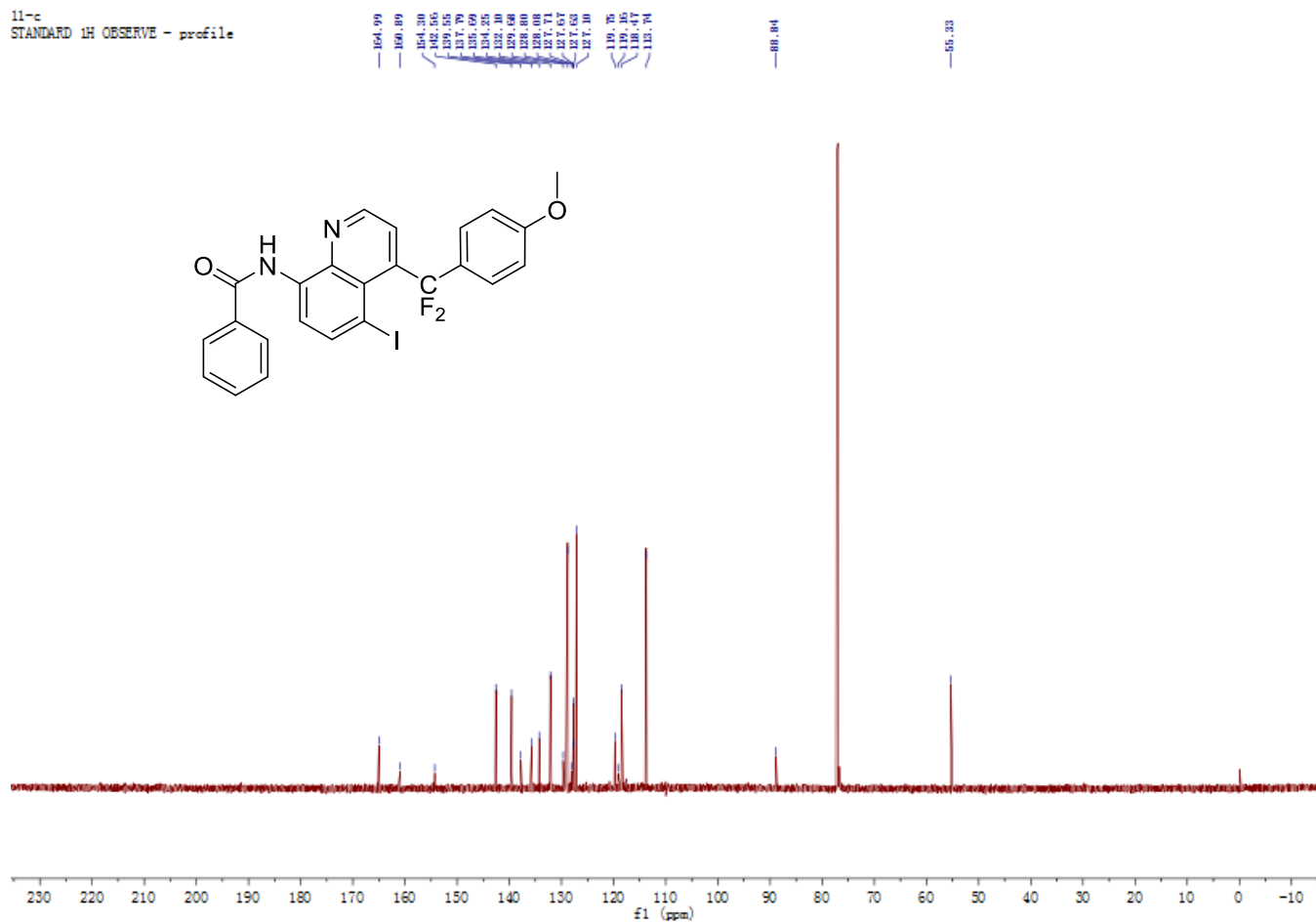


3q-C
STANDARD 1H OBSERVE - profile

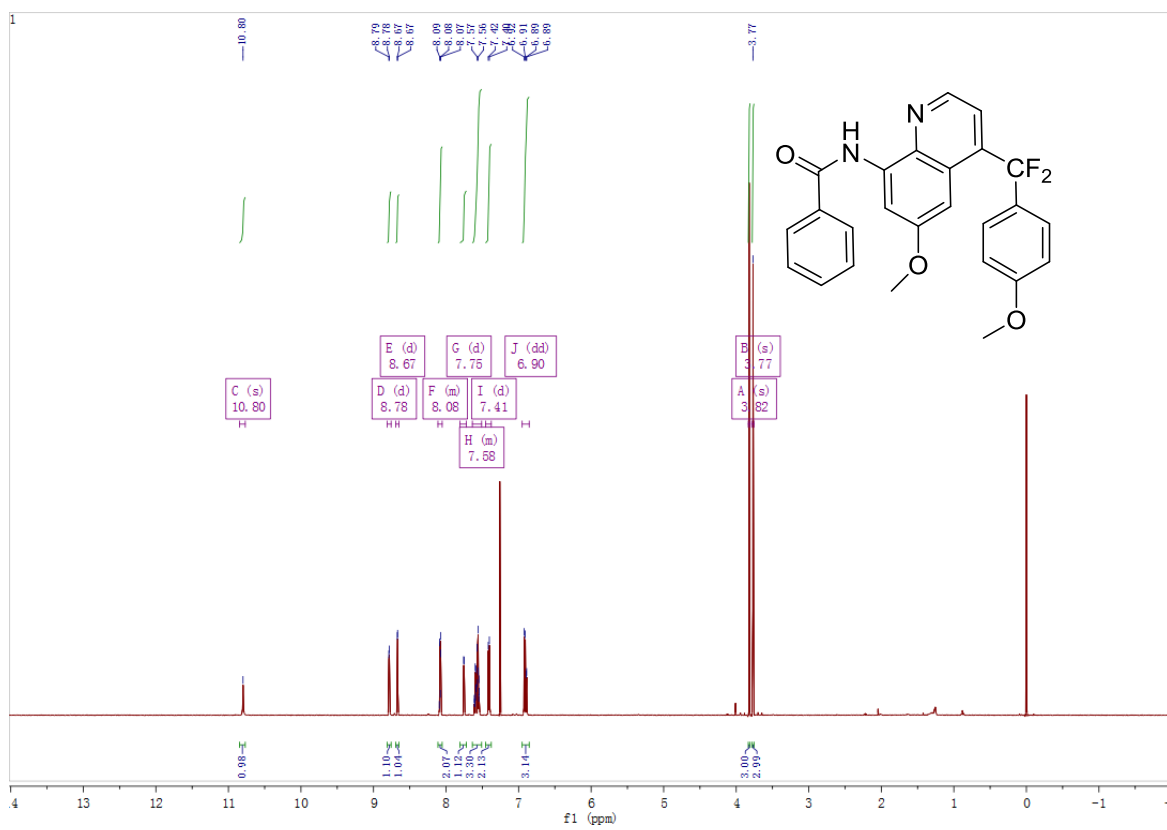
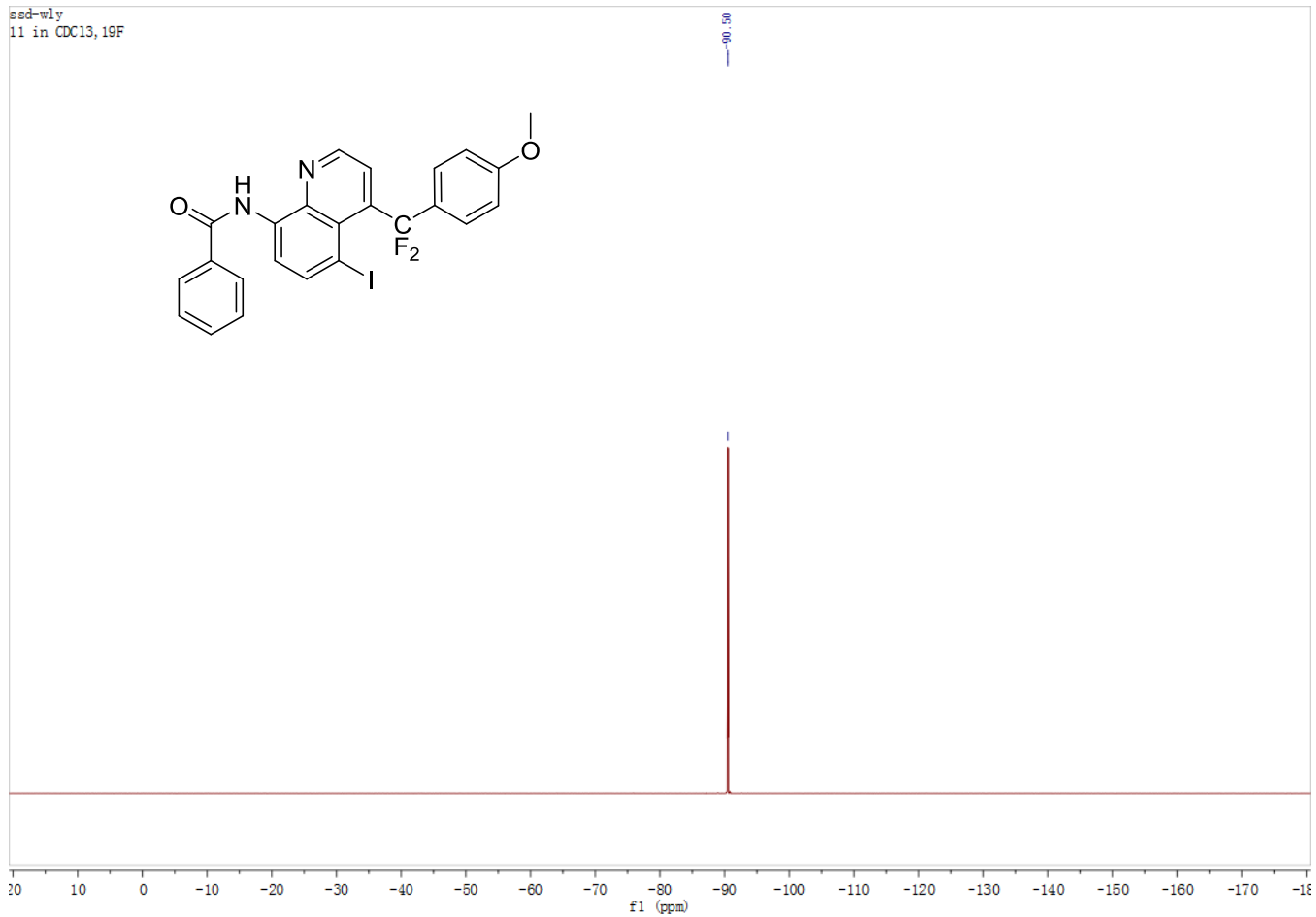




11-c
STANDARD 1H OBSERVE - profile

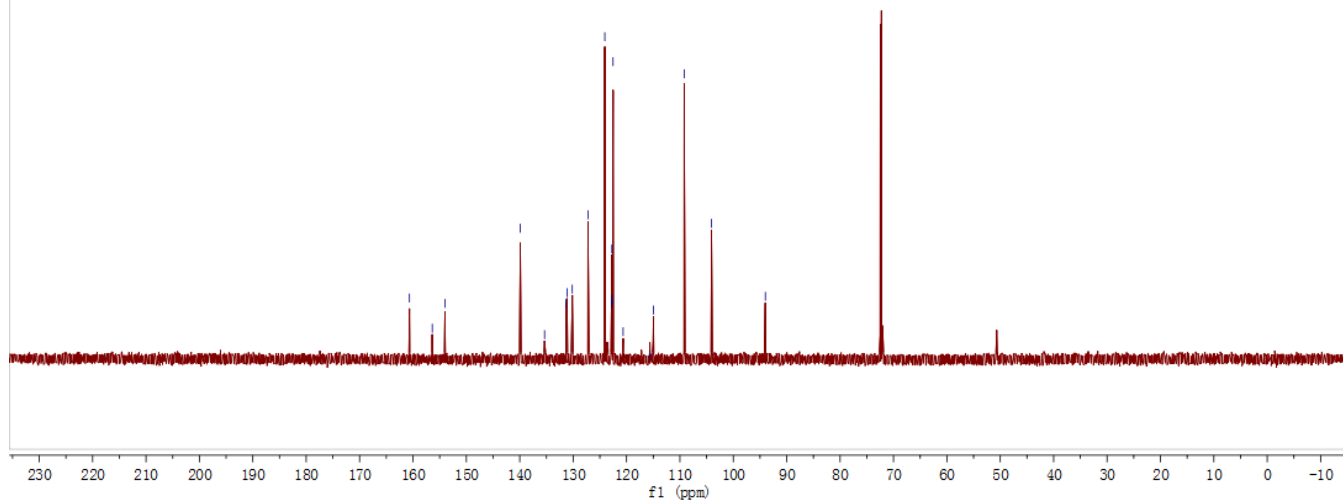
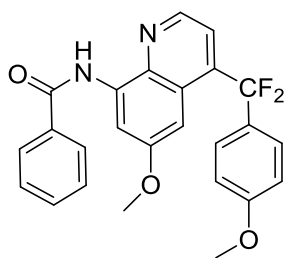


ssd-wly
11 in CDCl3, 19F

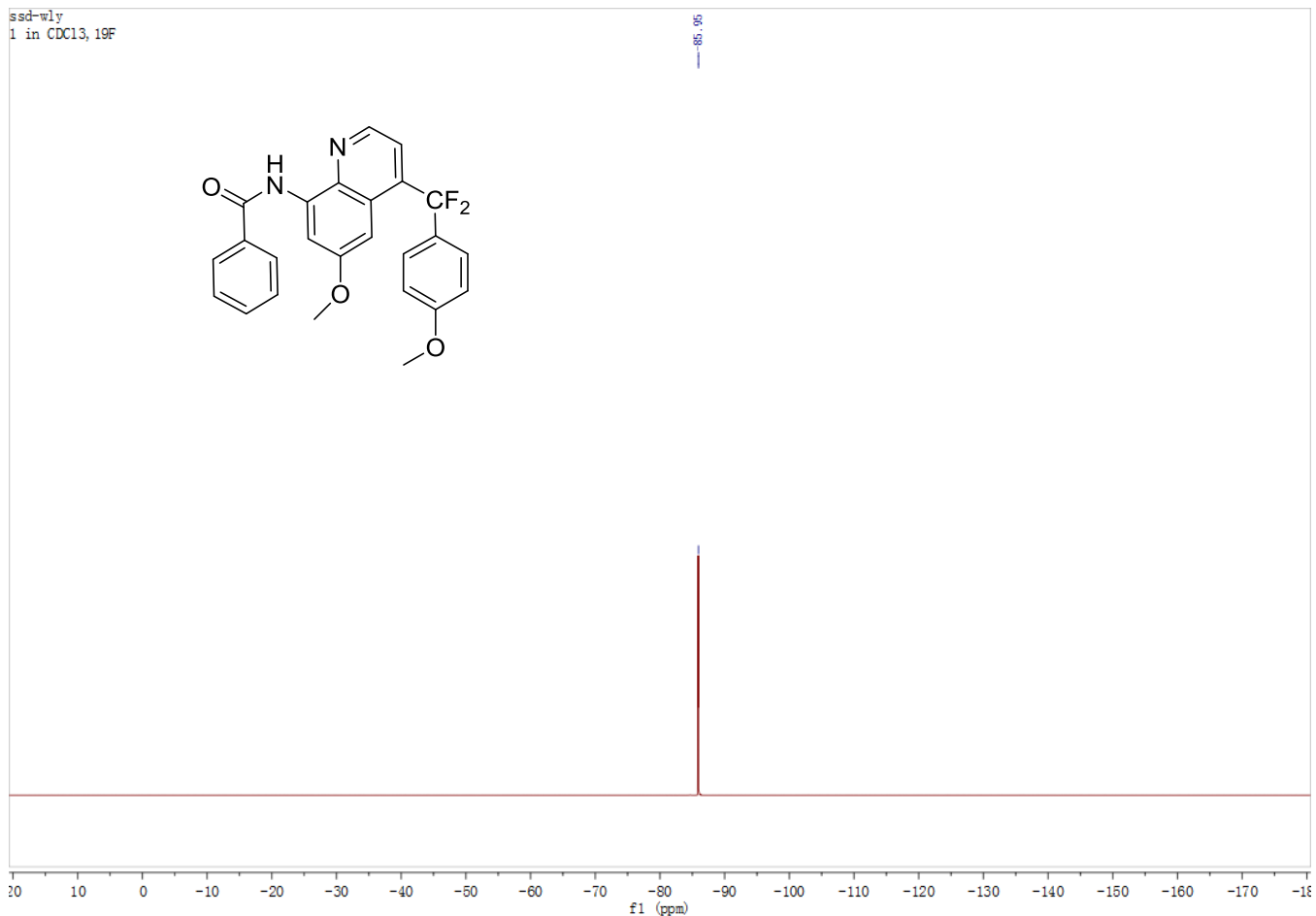


1-c
STANDARD 1H OBSERVE - profile

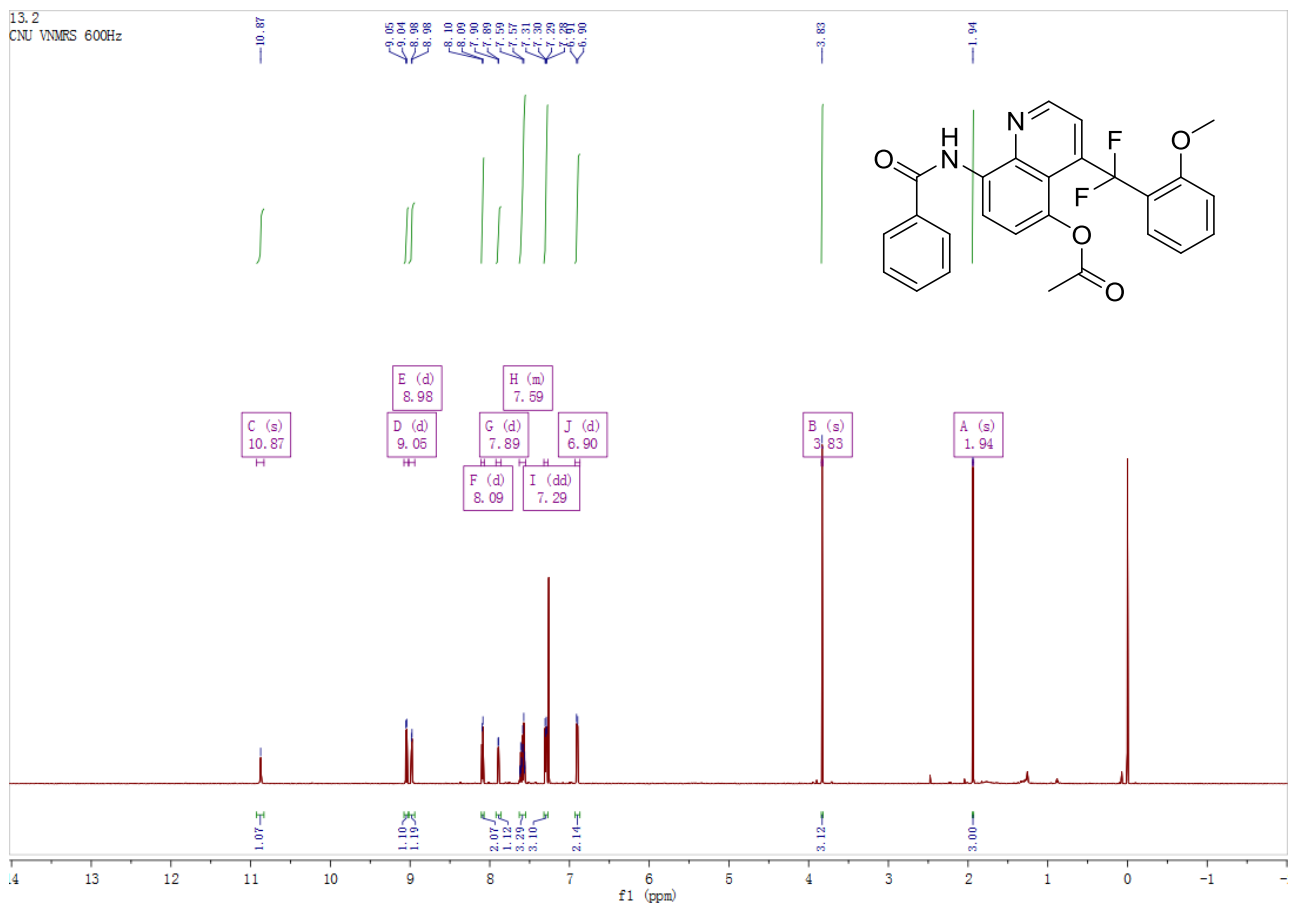
160.66
156.38
154.01
139.90
136.35
131.33
131.13
129.22
129.07
122.78
122.75
122.71
122.64
116.60
114.96
109.20
104.08
94.00



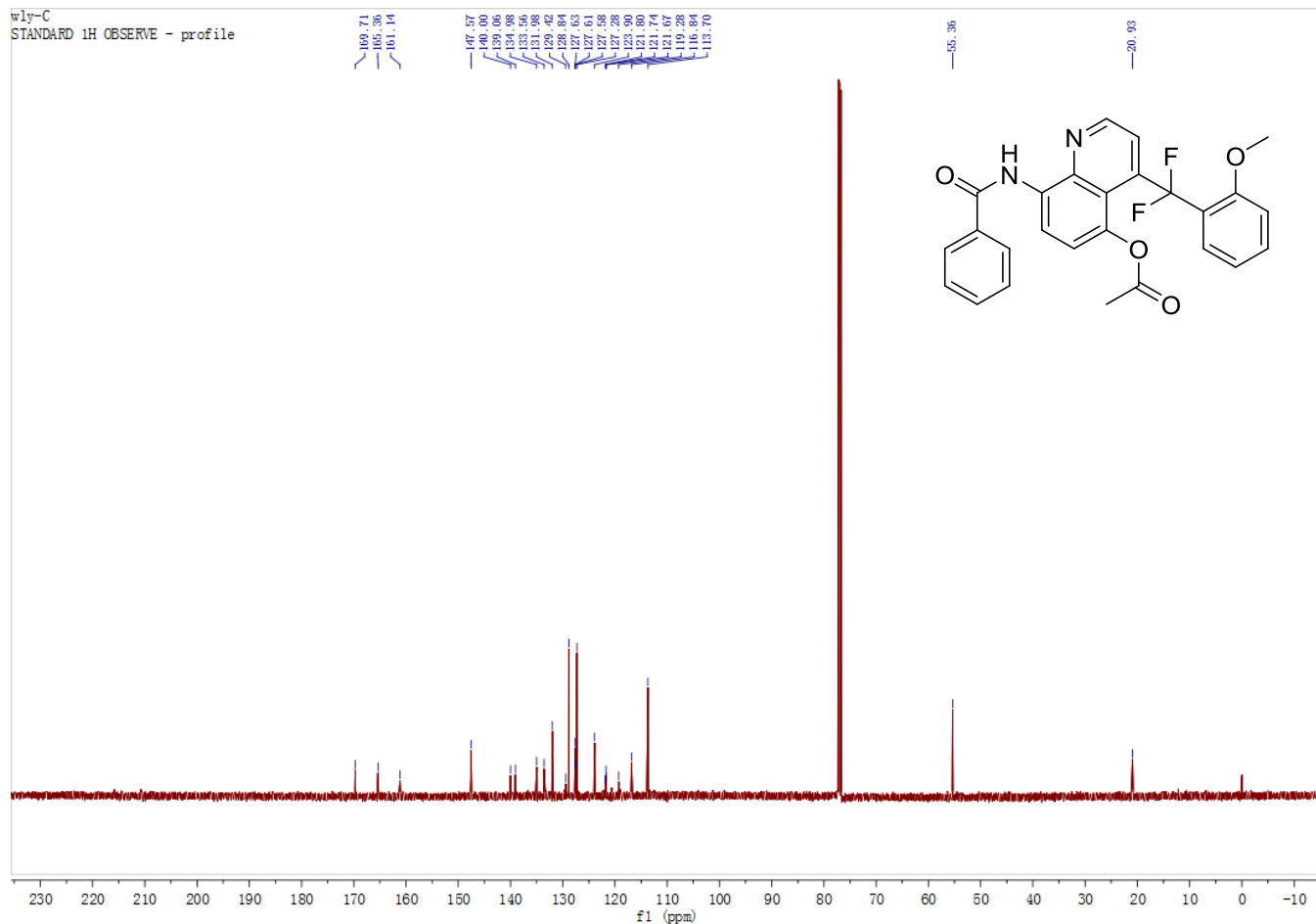
ssd-wly
1 in CDCl3, 19F



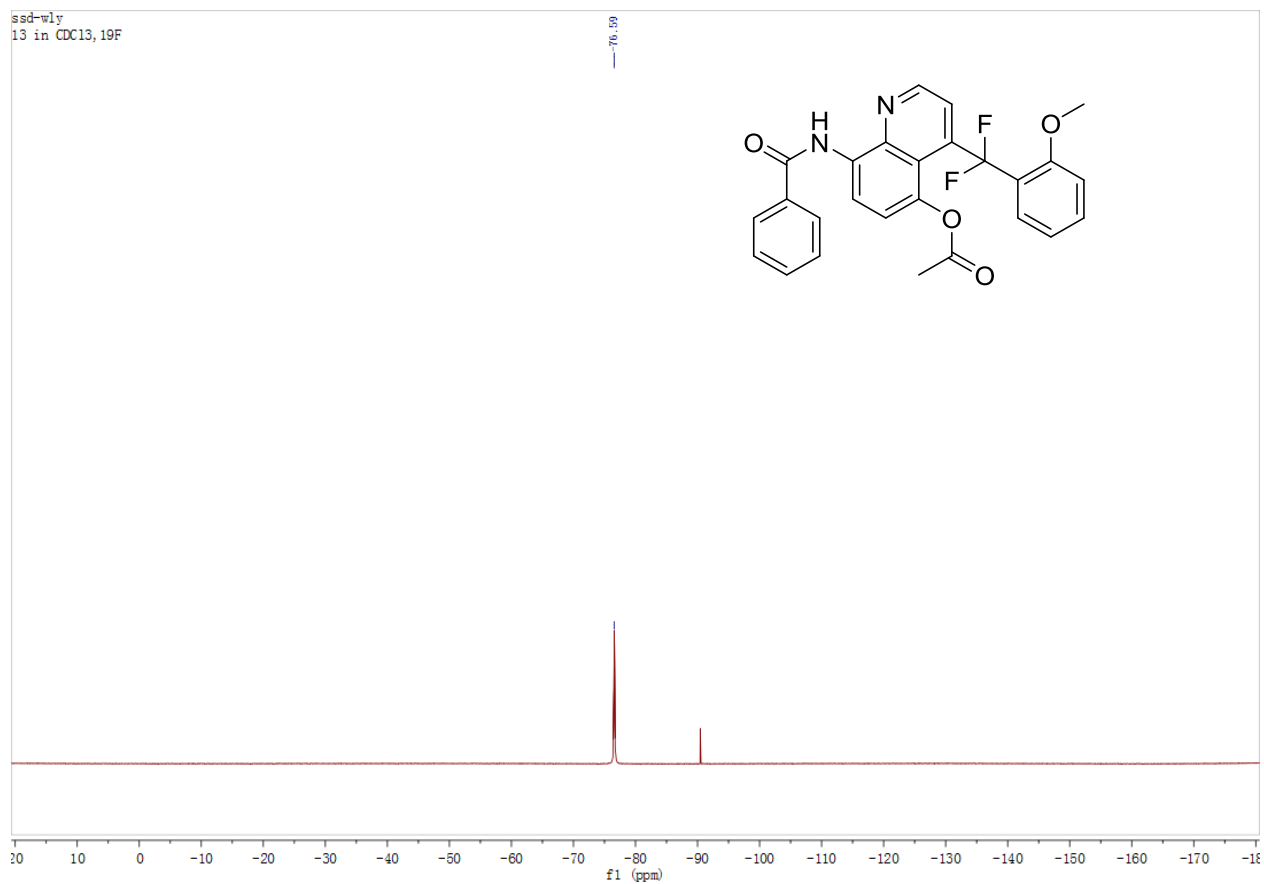
13.2
CNU VNMR5 600Hz



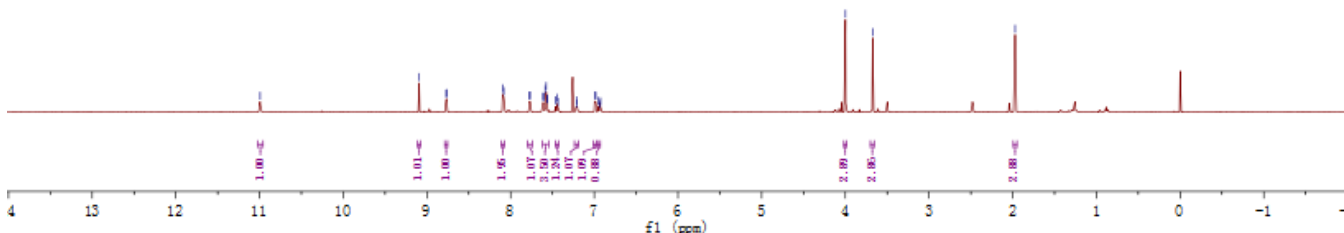
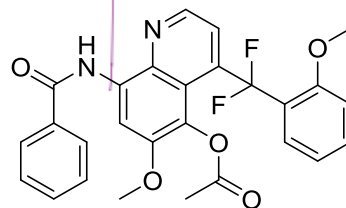
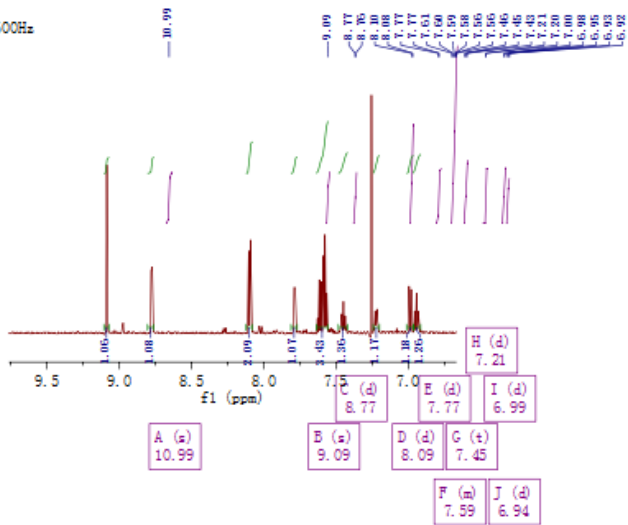
wly-C
STANDARD 1H OBSERVE - profile



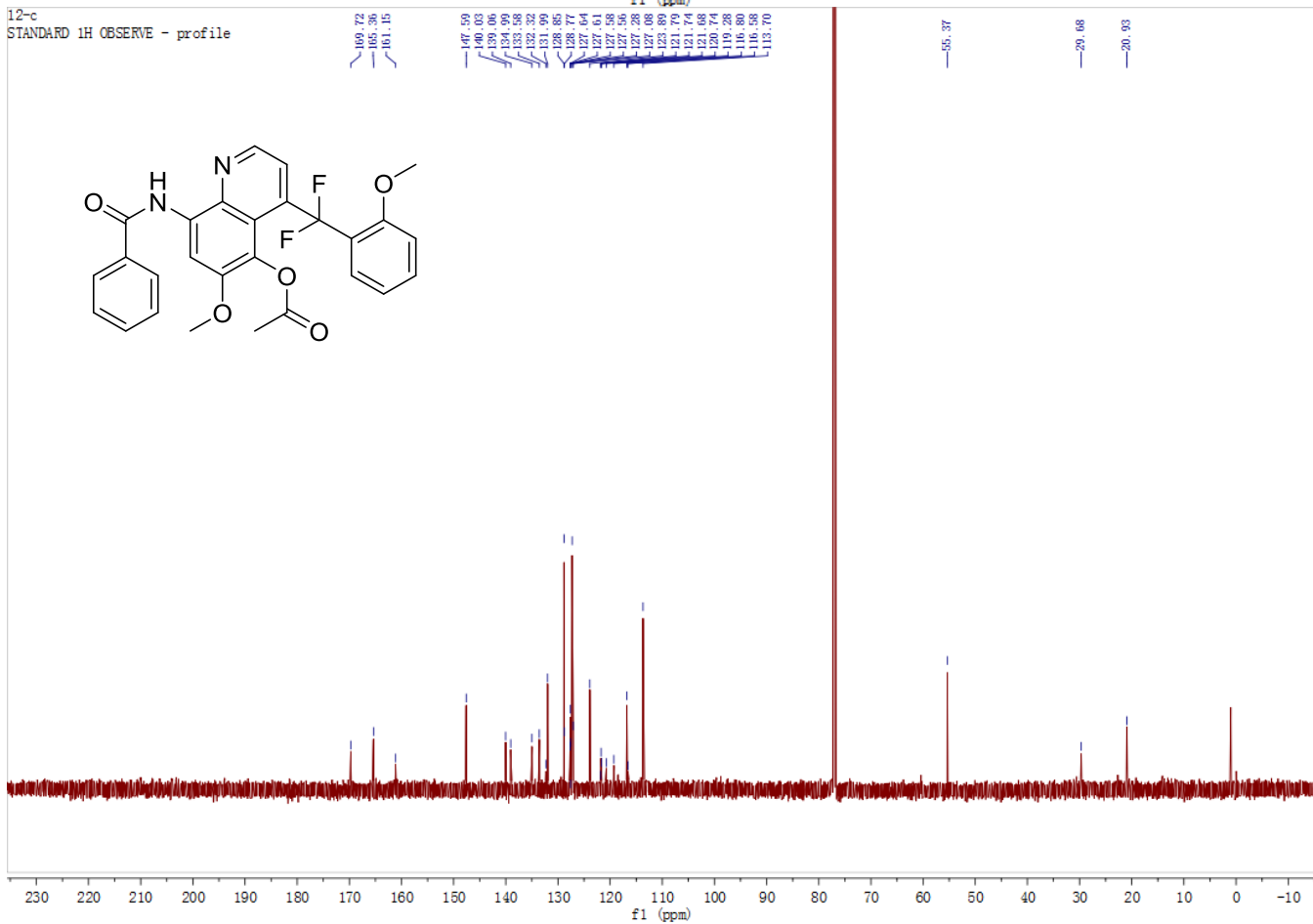
ssd-wly
13 in CDCl3, 19F



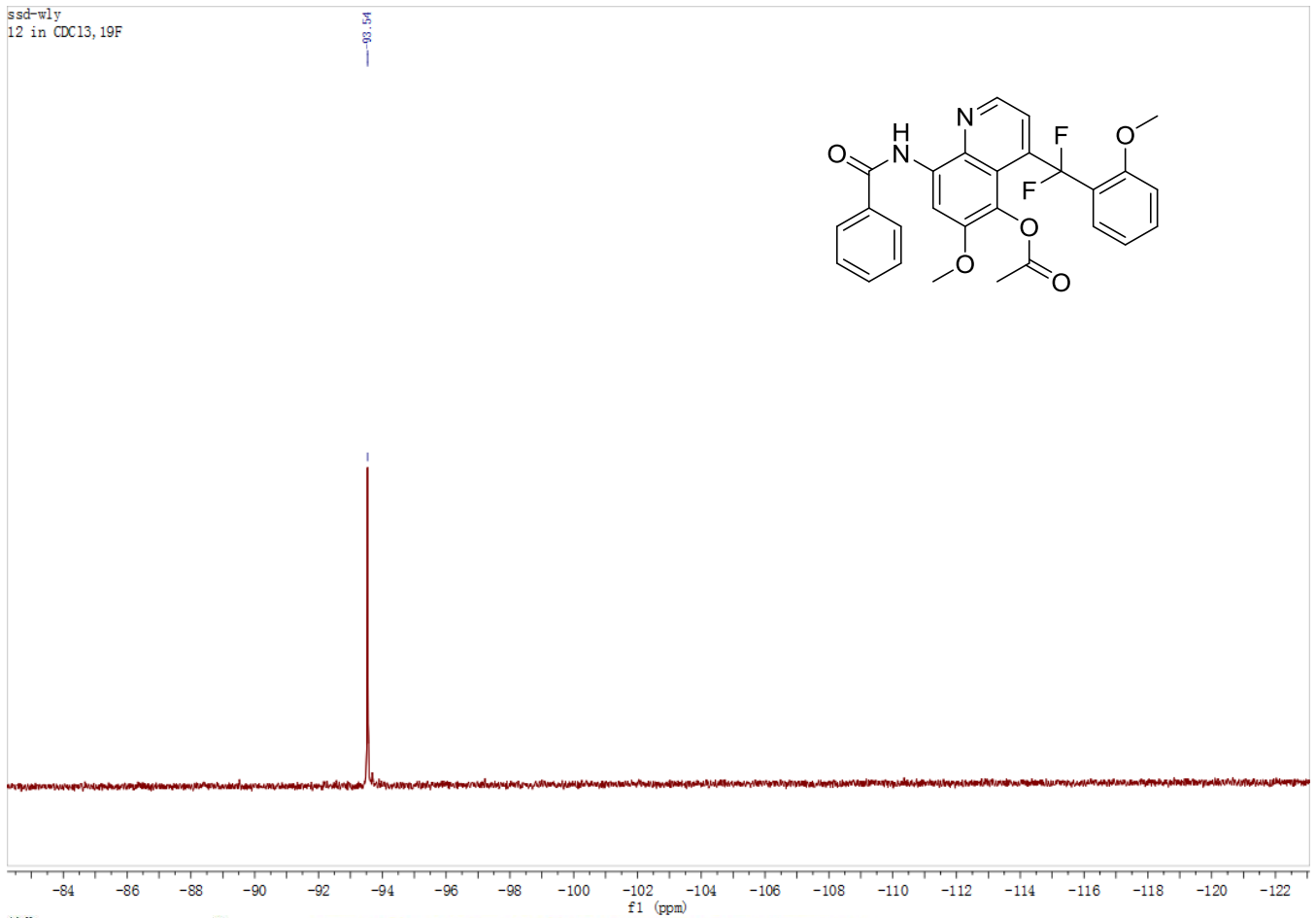
12
CNH NMR 600Hz



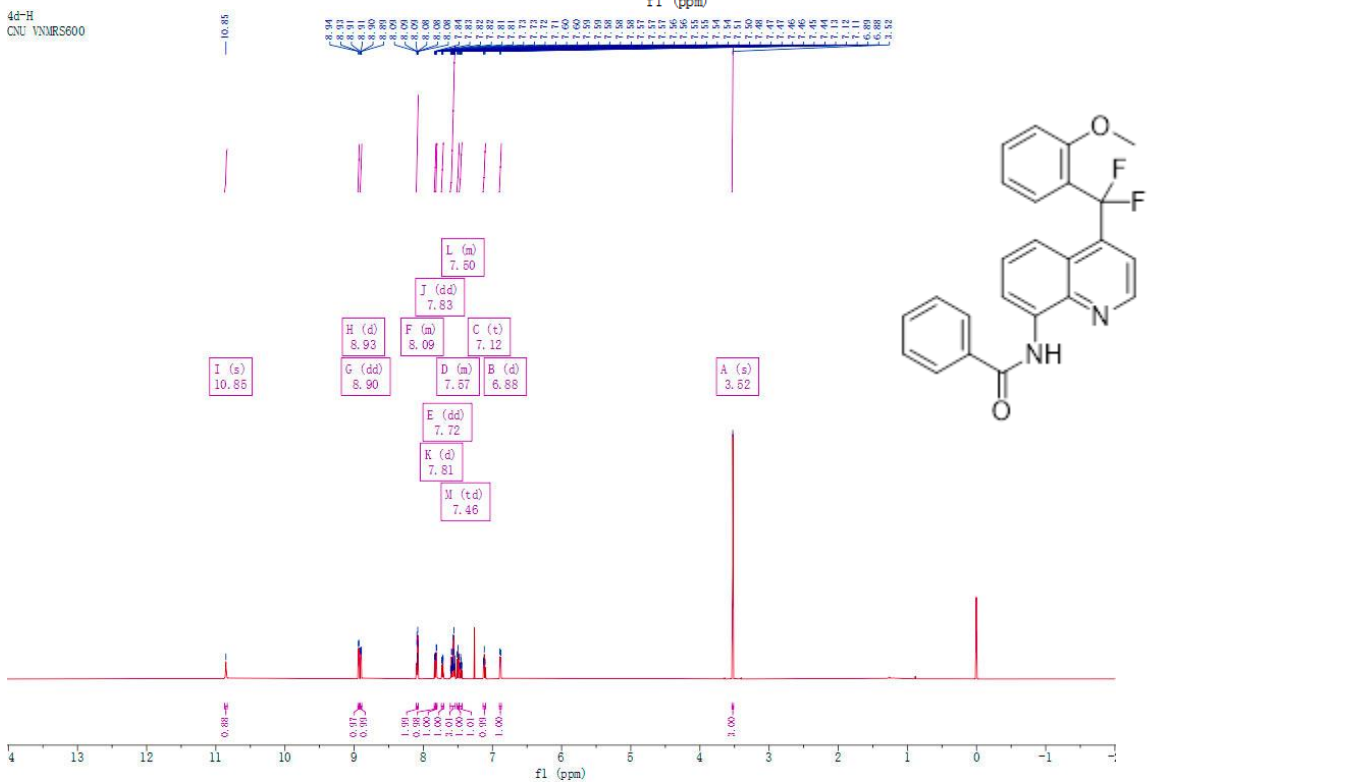
12-c
STANDARD 1H OBSERVE - profile

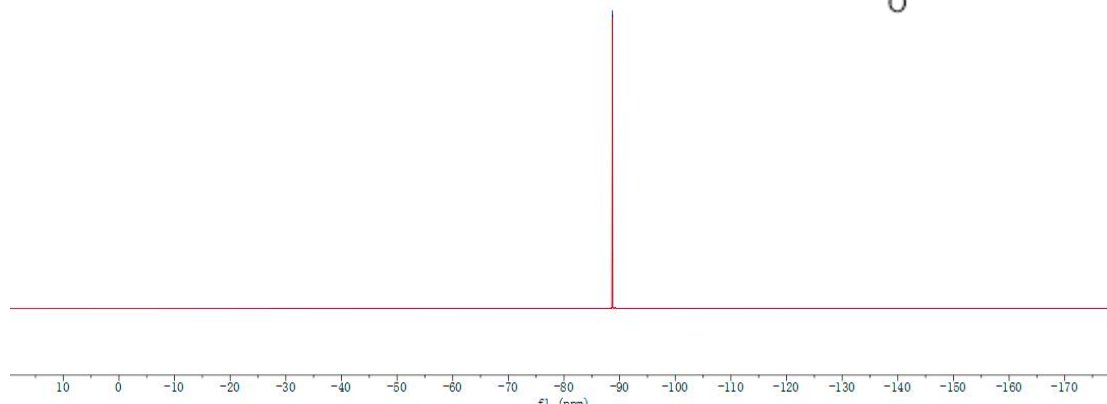
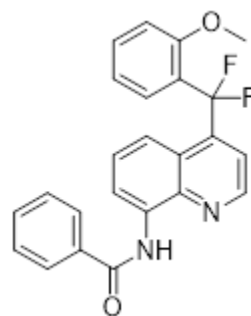


ssd-wly
12 in CDCl3, 19F



4d-H
GNU VNMR600

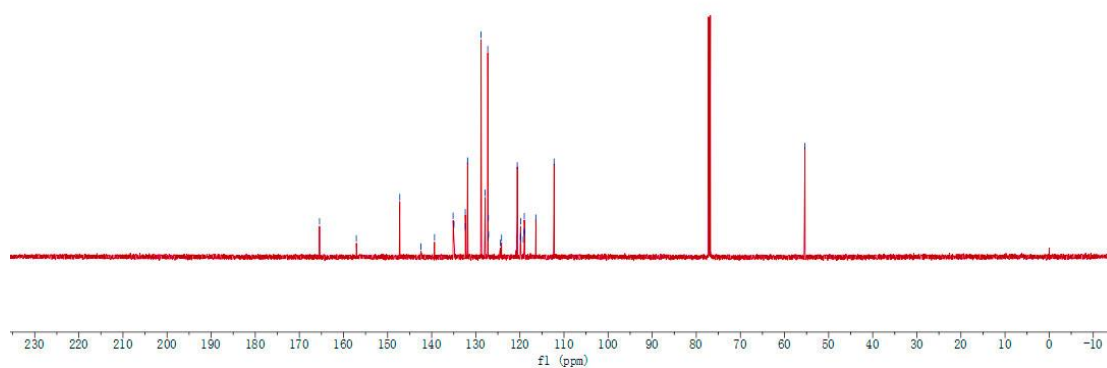
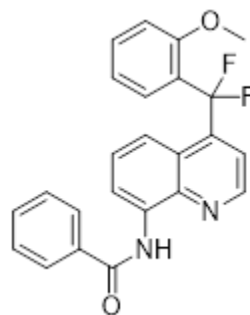




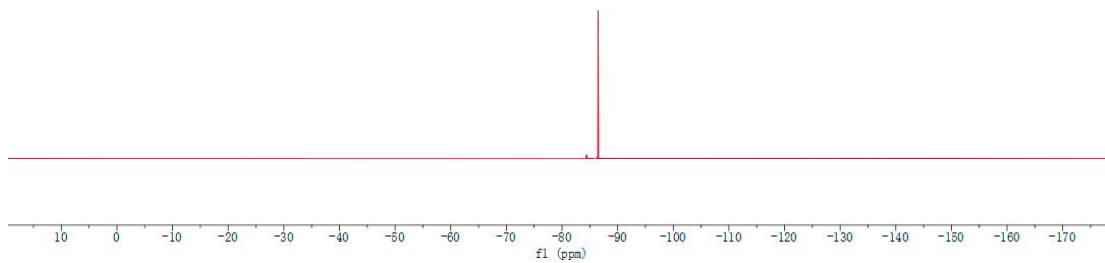
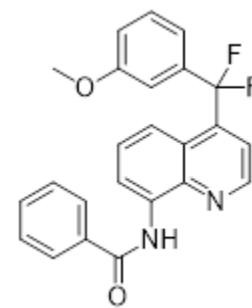
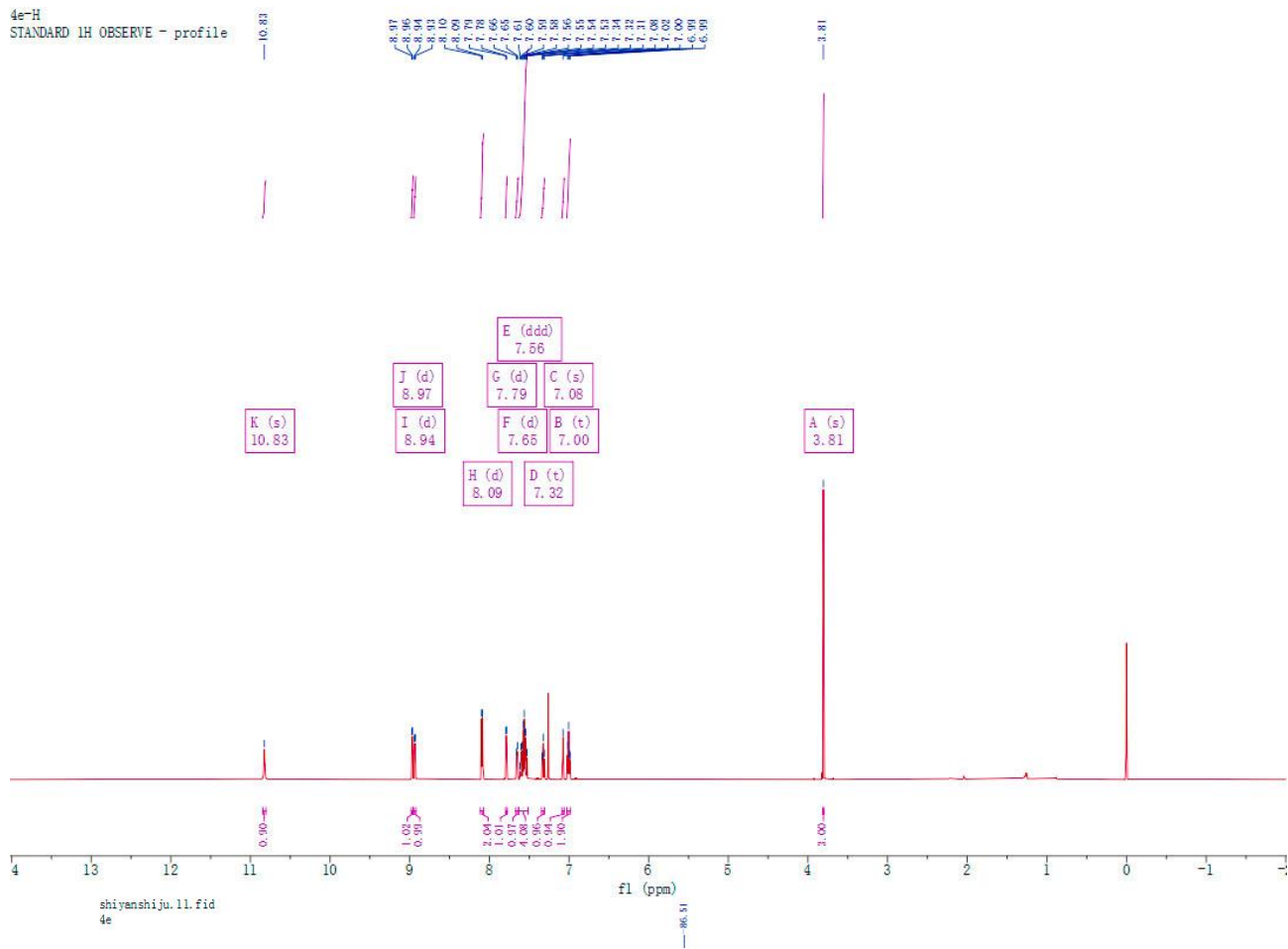
4d-C
CNU VNMR5600

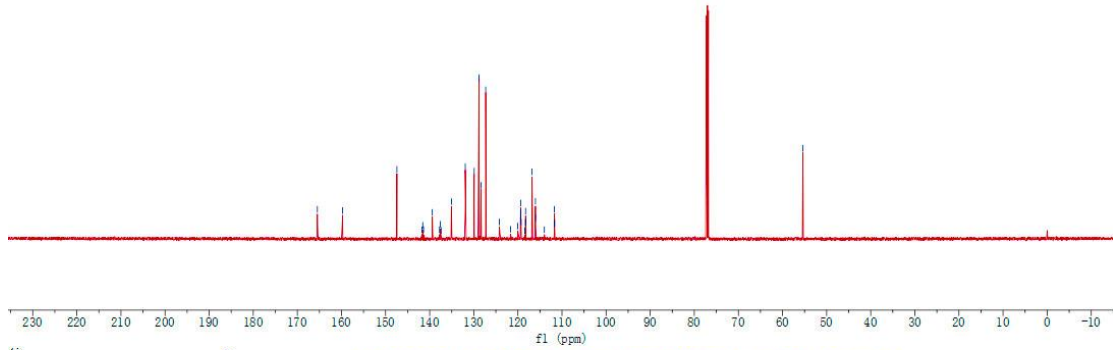
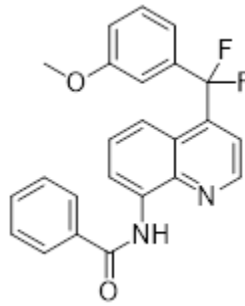
165.43
157.08
147.23
146.96
135.15
134.54
134.54
132.37
131.87
131.87
127.88
127.29
127.15
127.10
124.14
120.69
119.84
119.79
119.11
119.02
119.02
116.90
112.25

— 55.37

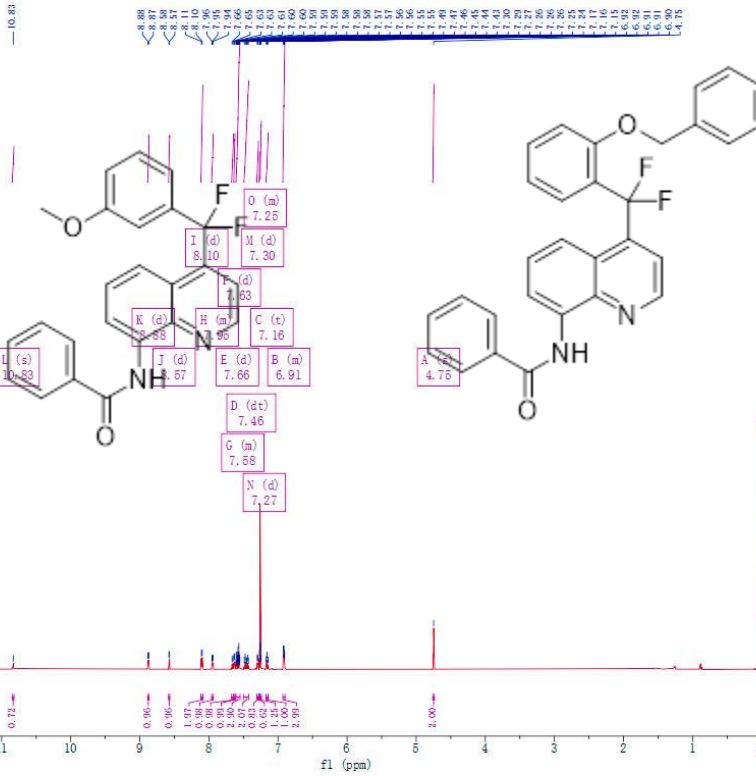


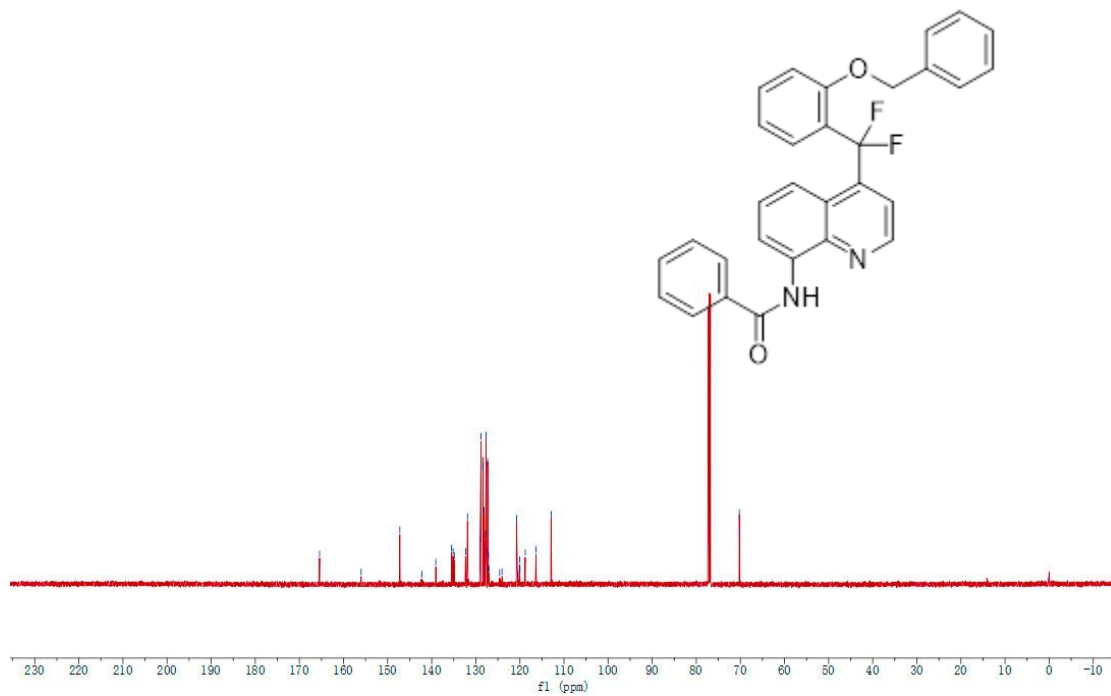
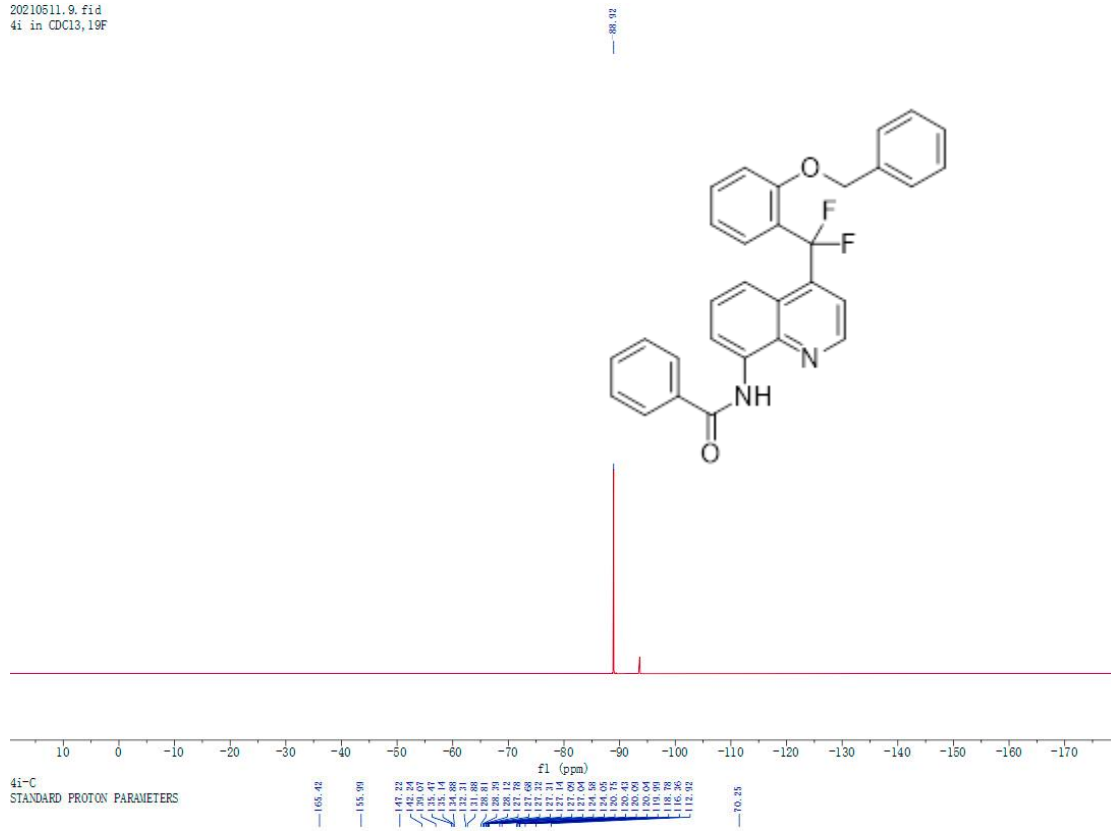
4e-H
STANDARD 1H OBSERVE - profile



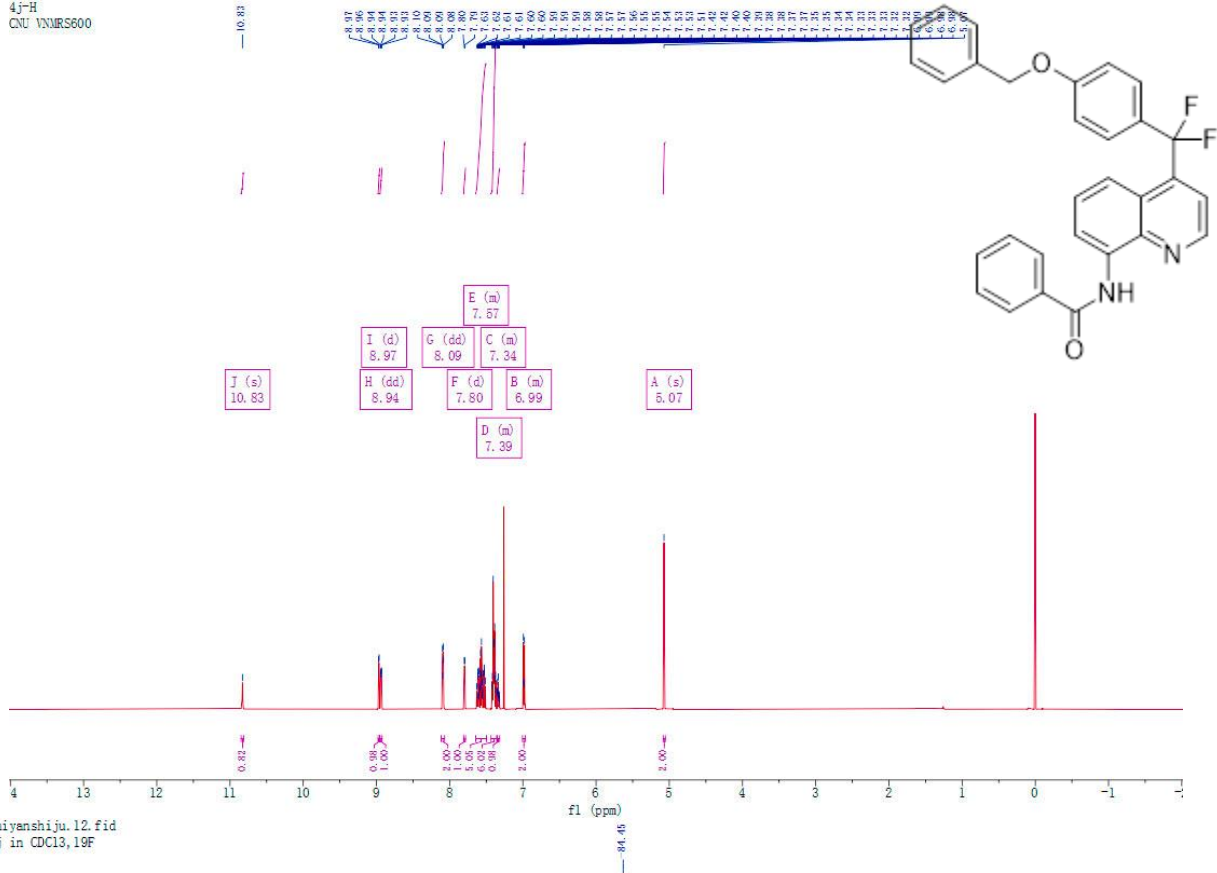


4f
STANDARD PROTON PARAMETERS

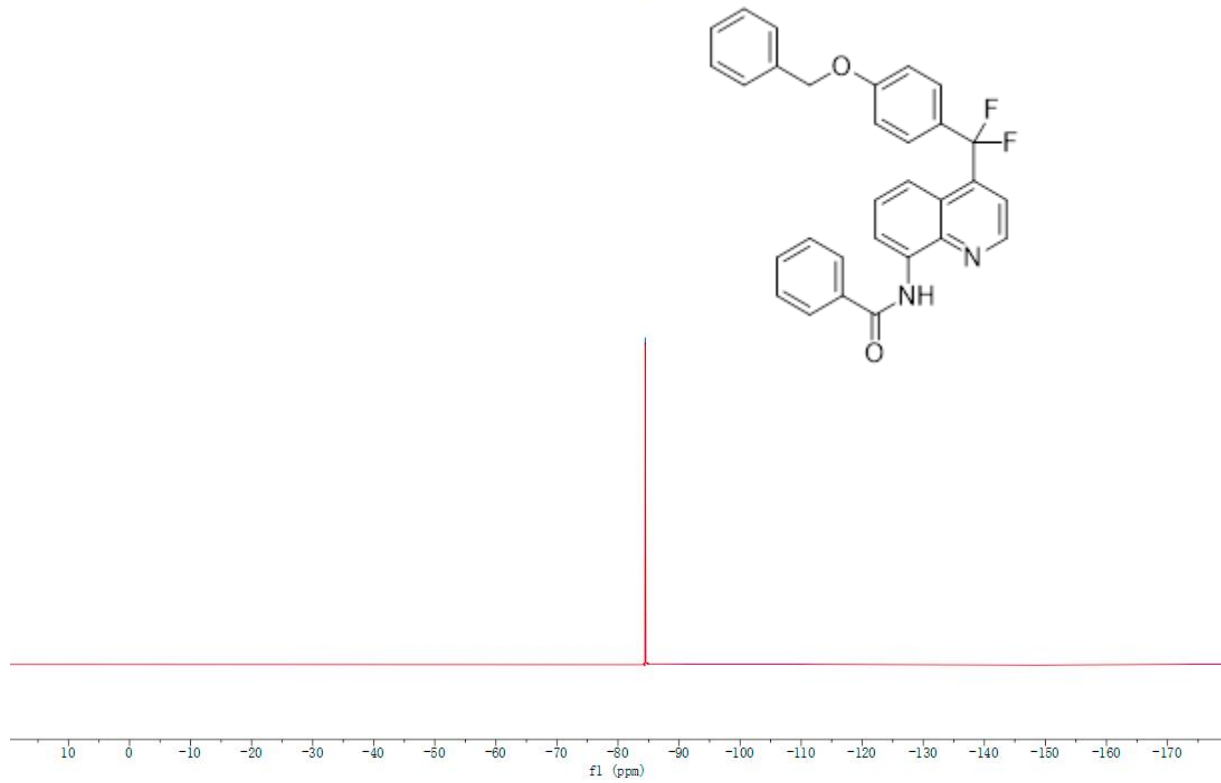




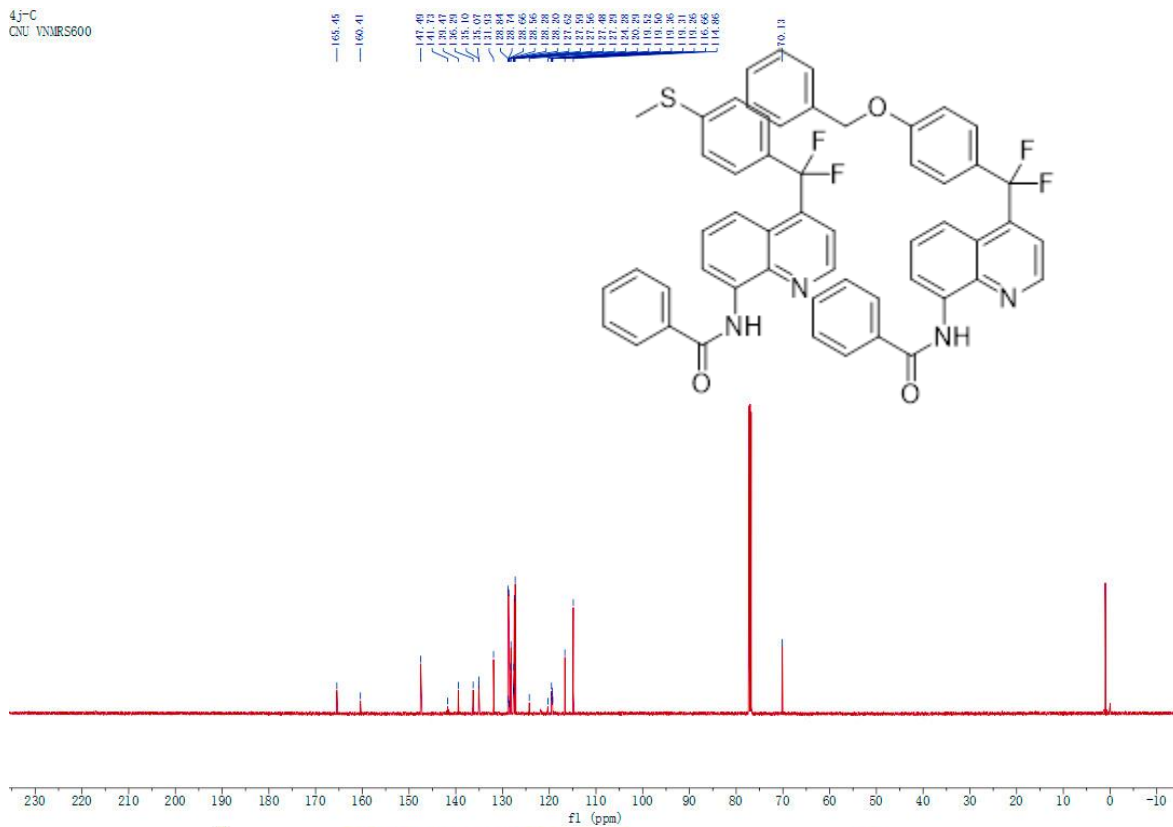
4j-H
CNV VNMR600



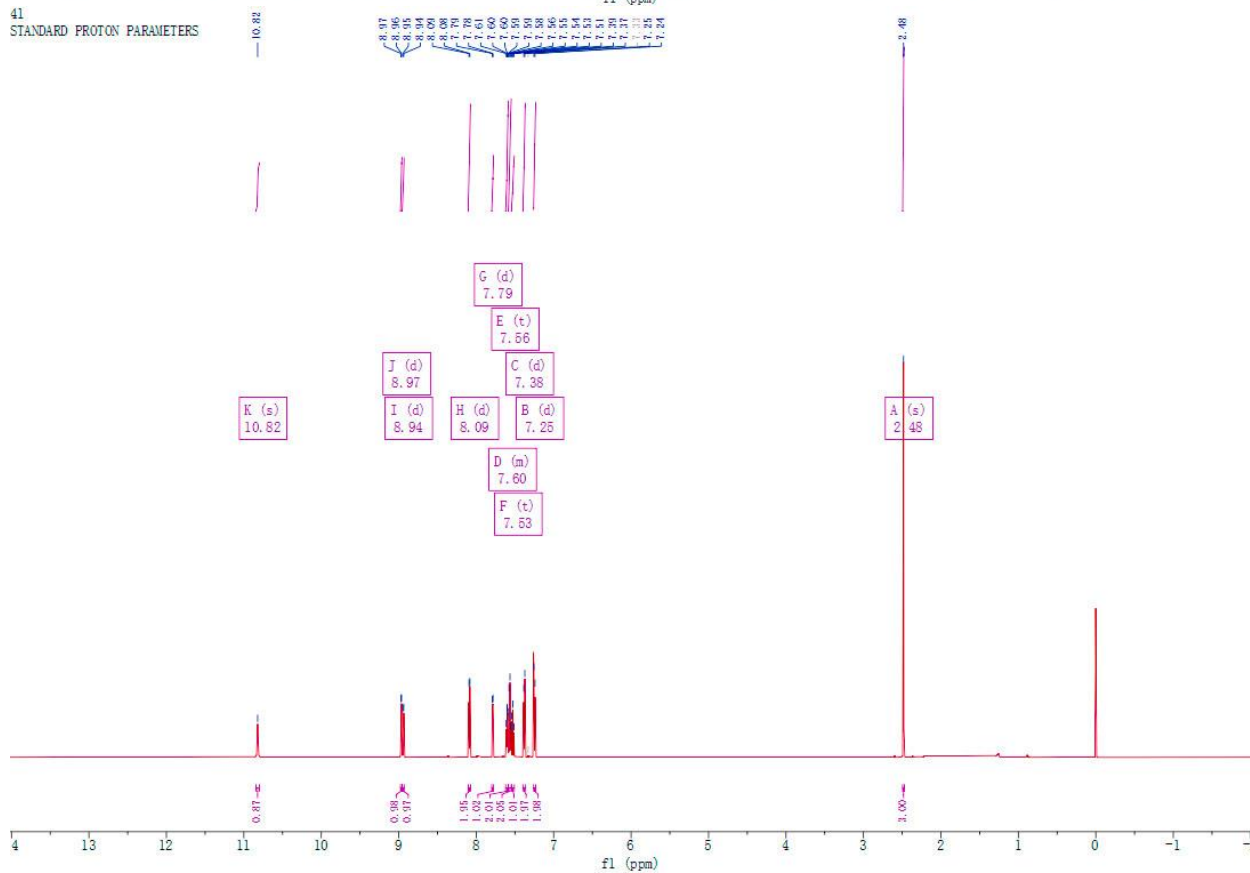
shiyanshiju.12.fid
4j in CDCl3,19F

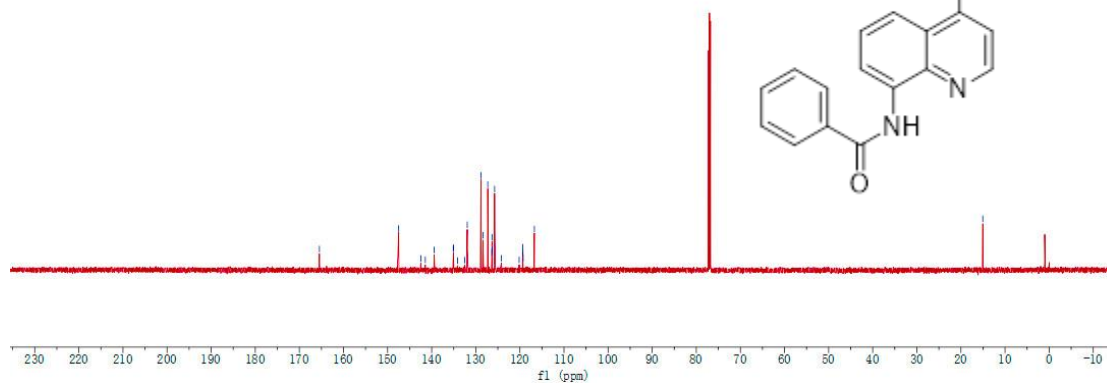
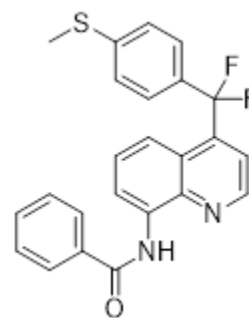
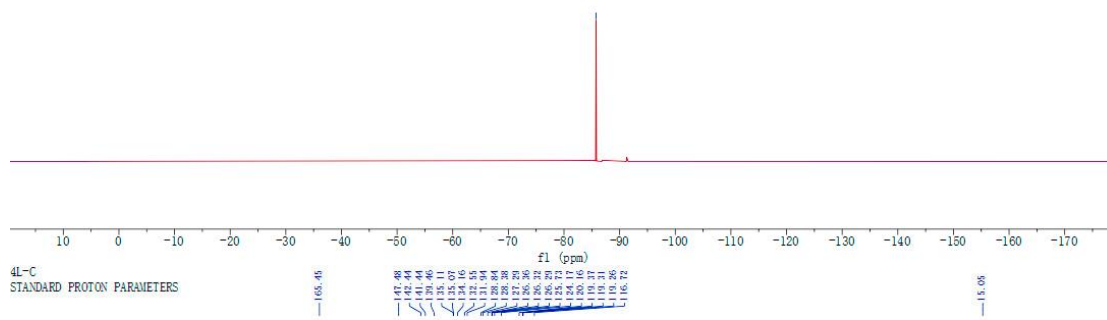
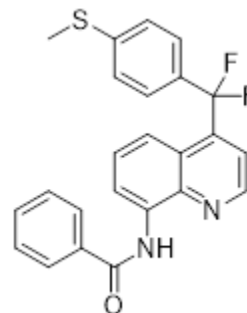


4J-C
CNV VNMR5000

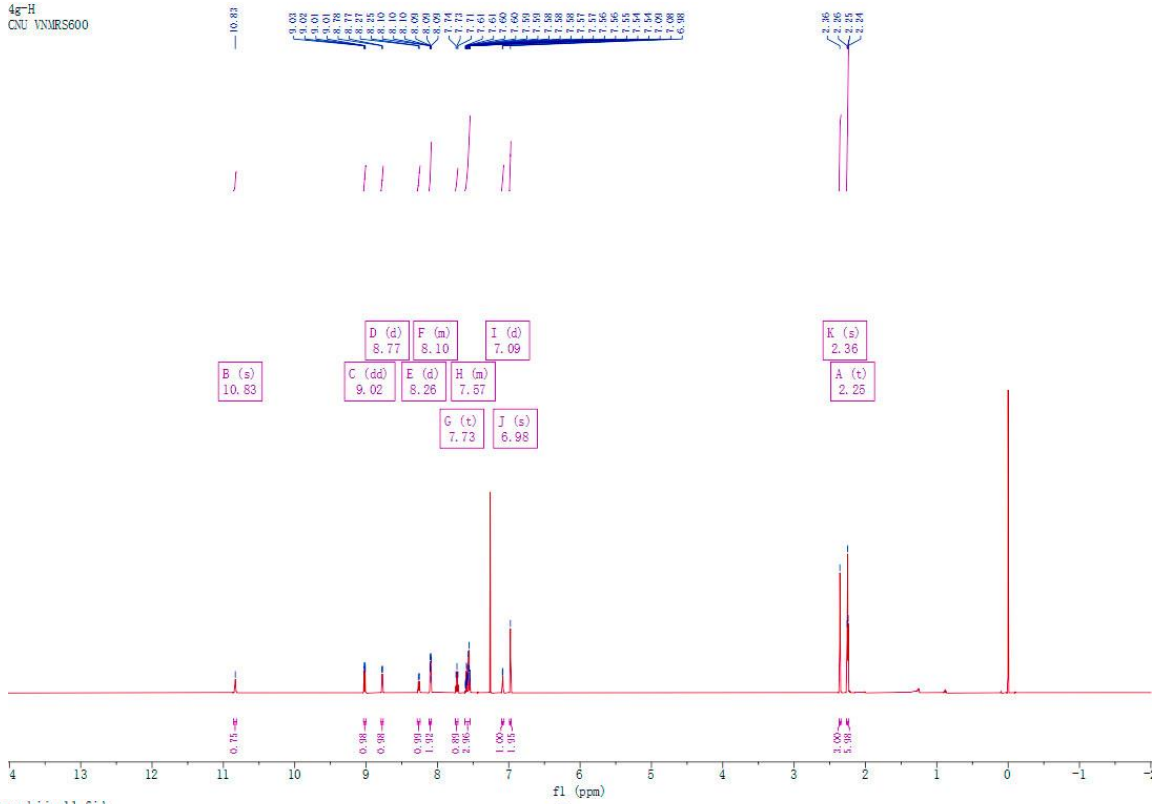


41
STANDARD PROTON PARAMETERS





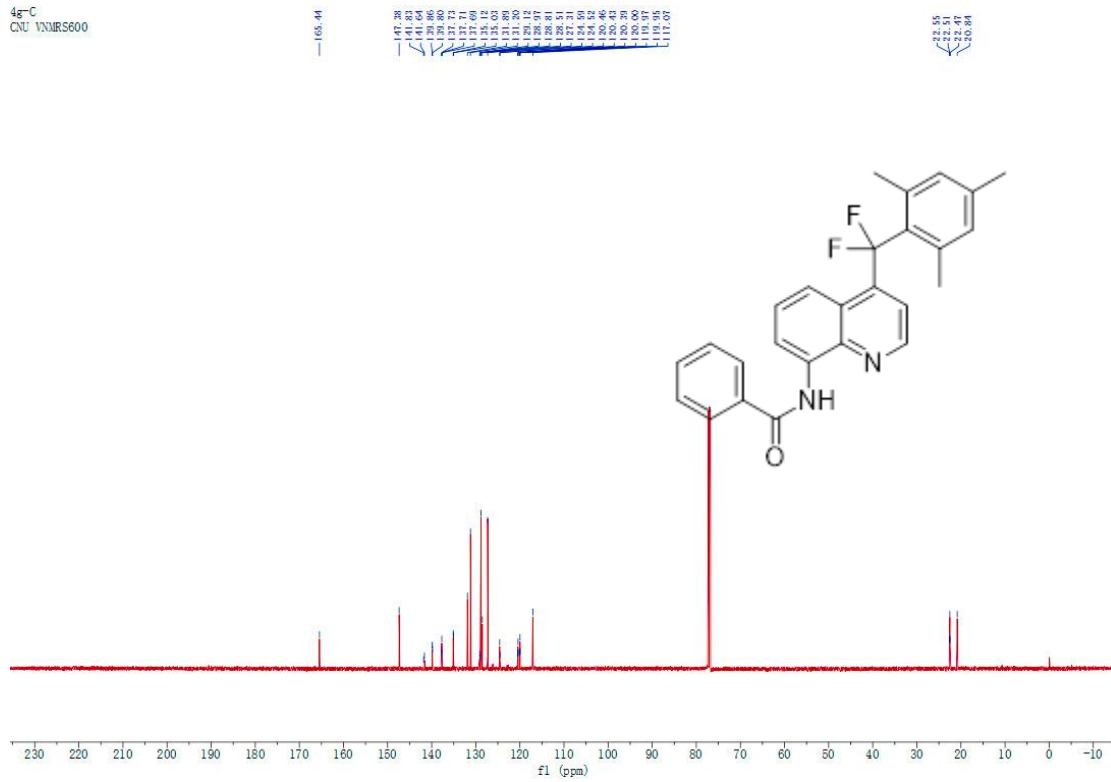
4g-H
CNV NMR5600



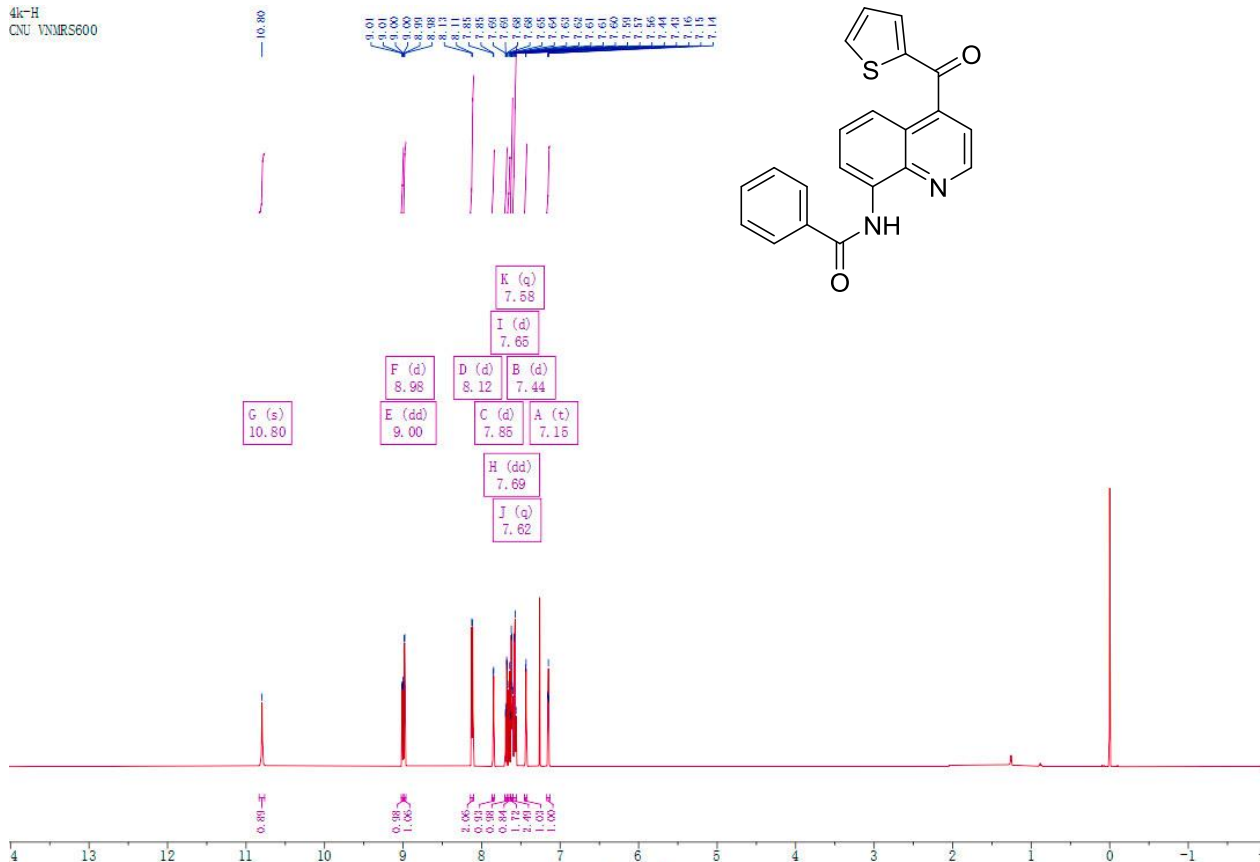
shiyanshiju.11.fid
4g in CDCl₃, 19F



4g-C
CNV VNMR5600

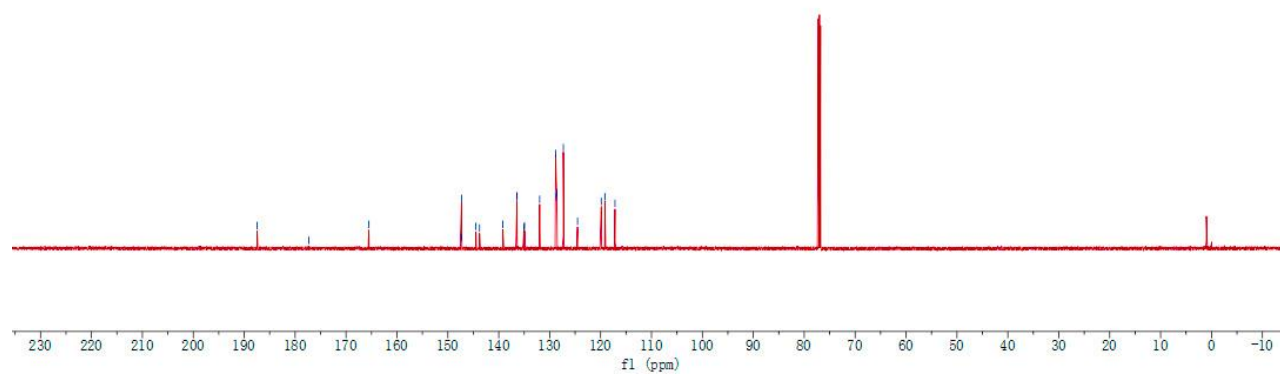
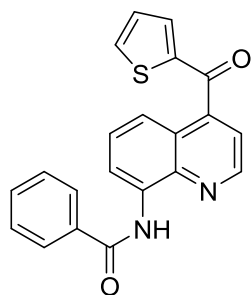


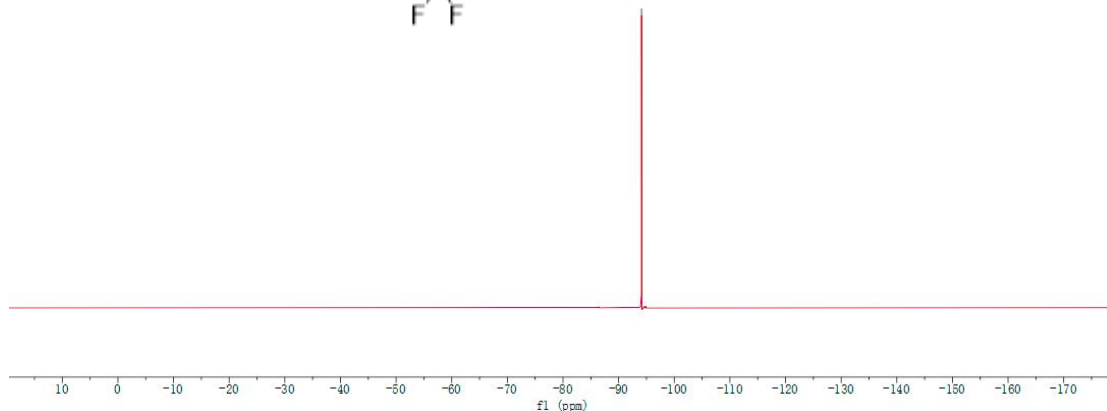
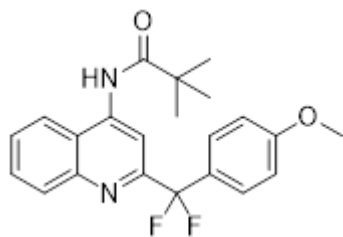
4k-H
CNV VNMR5600



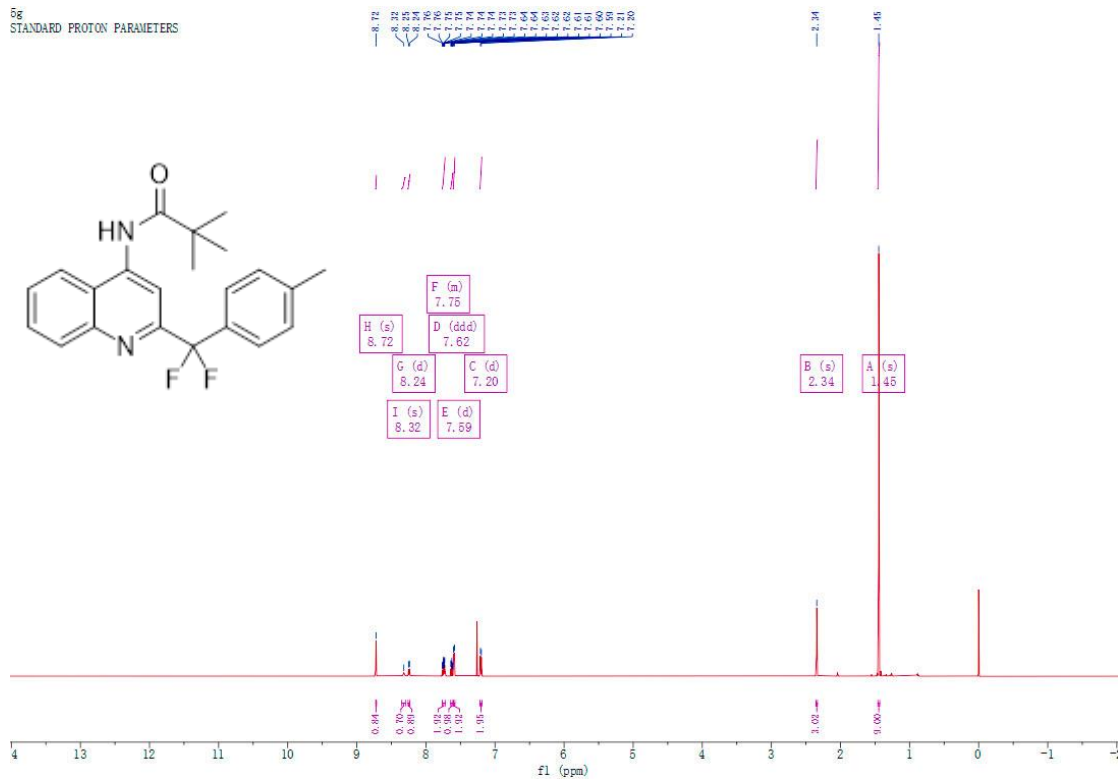
4k-C
CNU VMRS600

187.45
177.29
165.90
147.34
144.48
143.77
139.19
138.74
136.41
135.06
134.93
131.96
131.82
128.73
128.57
127.31
127.21
119.86
117.17





5a
STANDARD PROTON PARAMETERS



^{63}C
STANDARD PROTON PARAMETERS

116.96

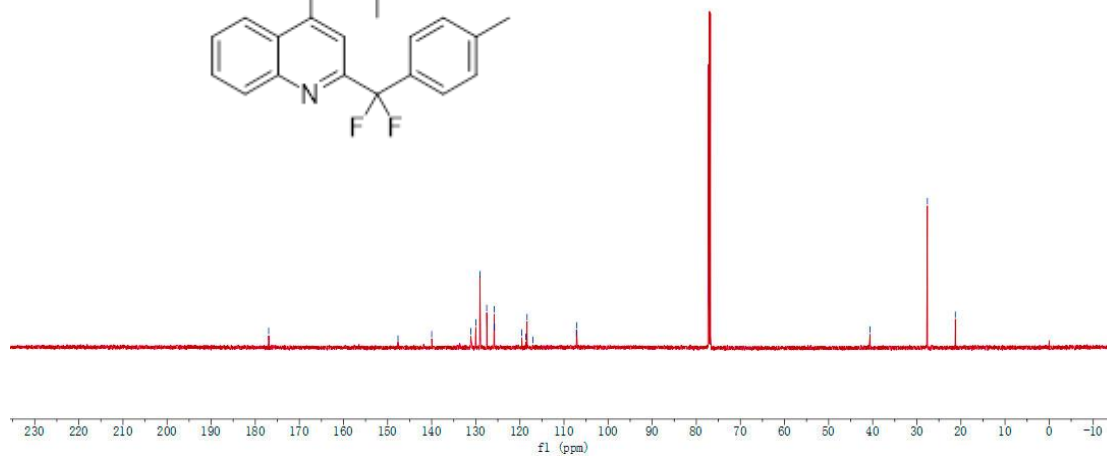
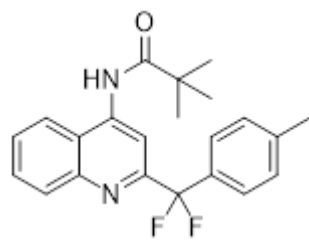
147.64

140.00
130.00
129.04
127.04
125.85
123.81
119.58
118.09
117.06
107.18
107.15

40.03

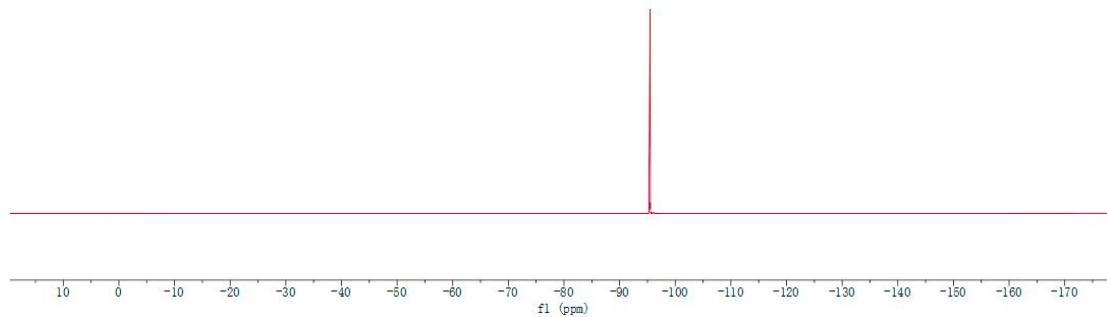
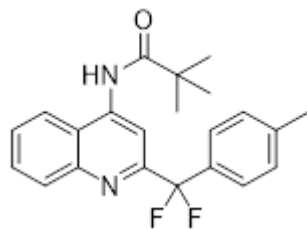
27.61

21.27



20210511.13.fid
6j in CDCl₃,19F

95.90



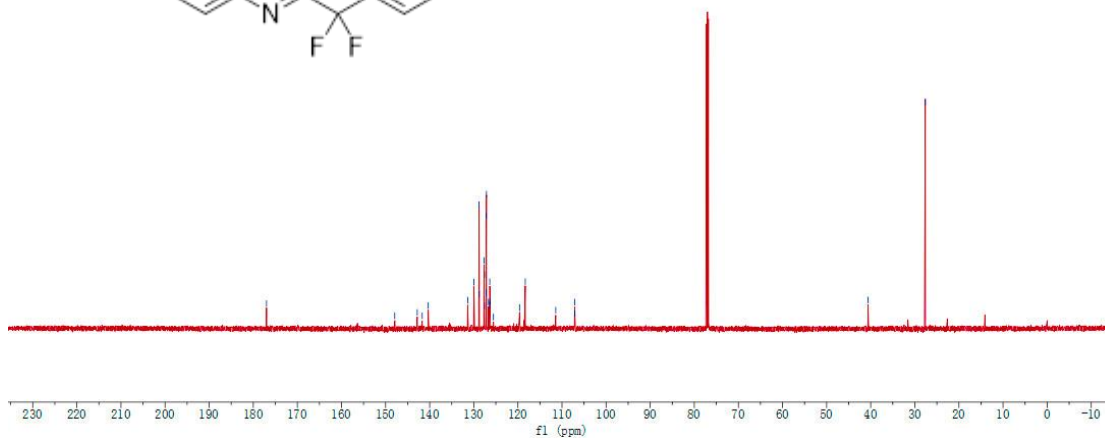
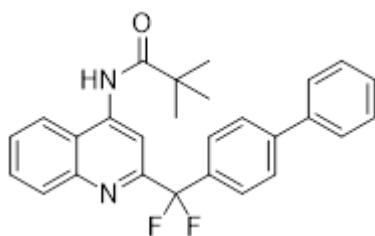
5R-C
STANDARD PROTON PARAMETERS

116.99

147.32
142.82
140.57
131.38
129.95
128.76
127.58
127.56
127.51
127.13
126.67
126.38
125.24
119.63
118.23
117.12
107.09

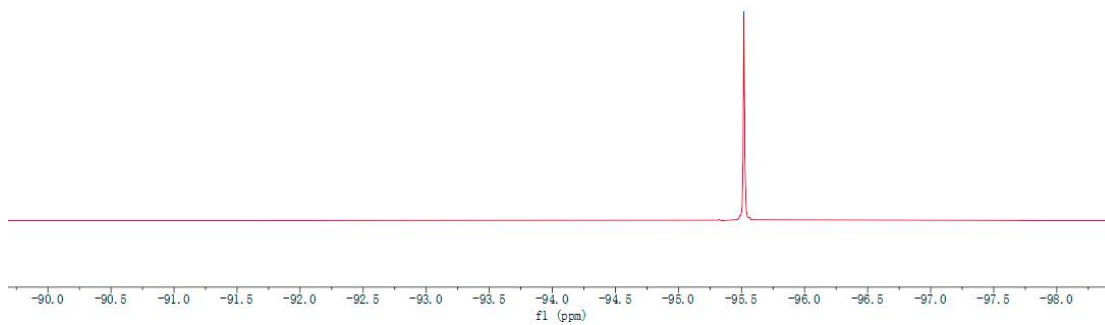
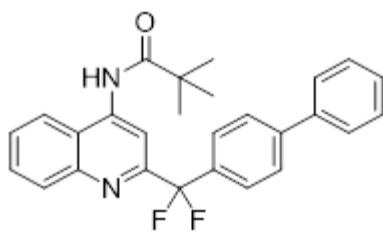
40.64

27.63

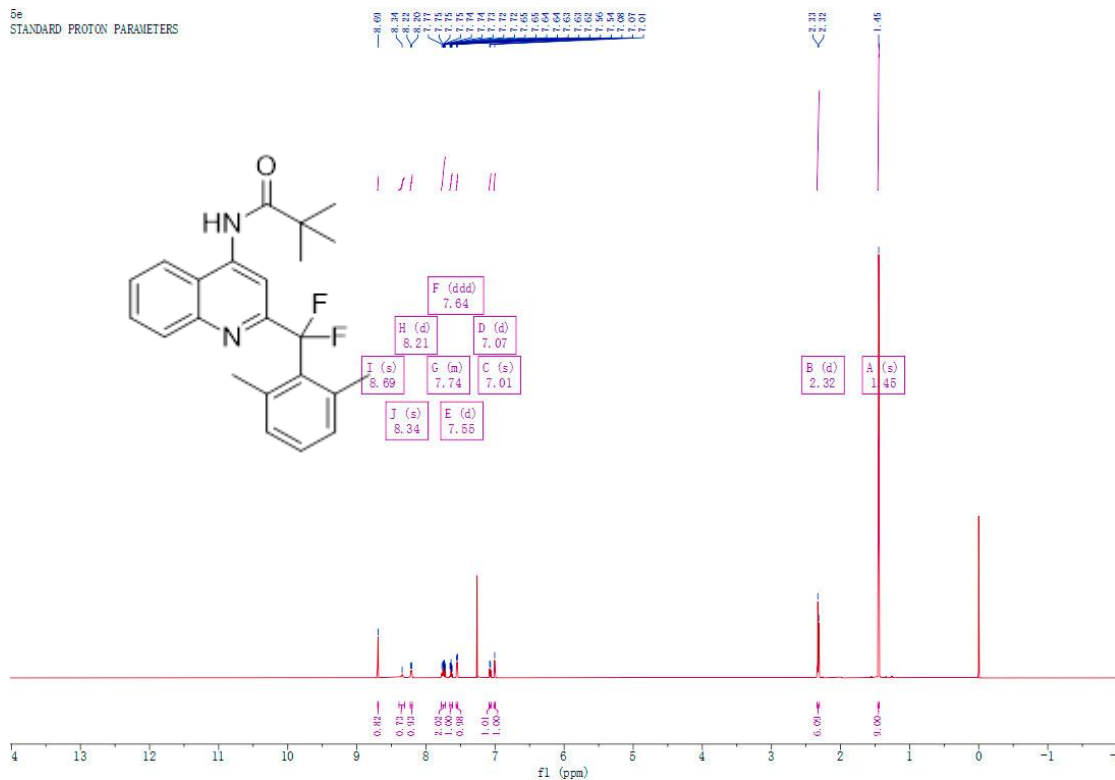


20210611.3.fid
5r in CDCl3,19F

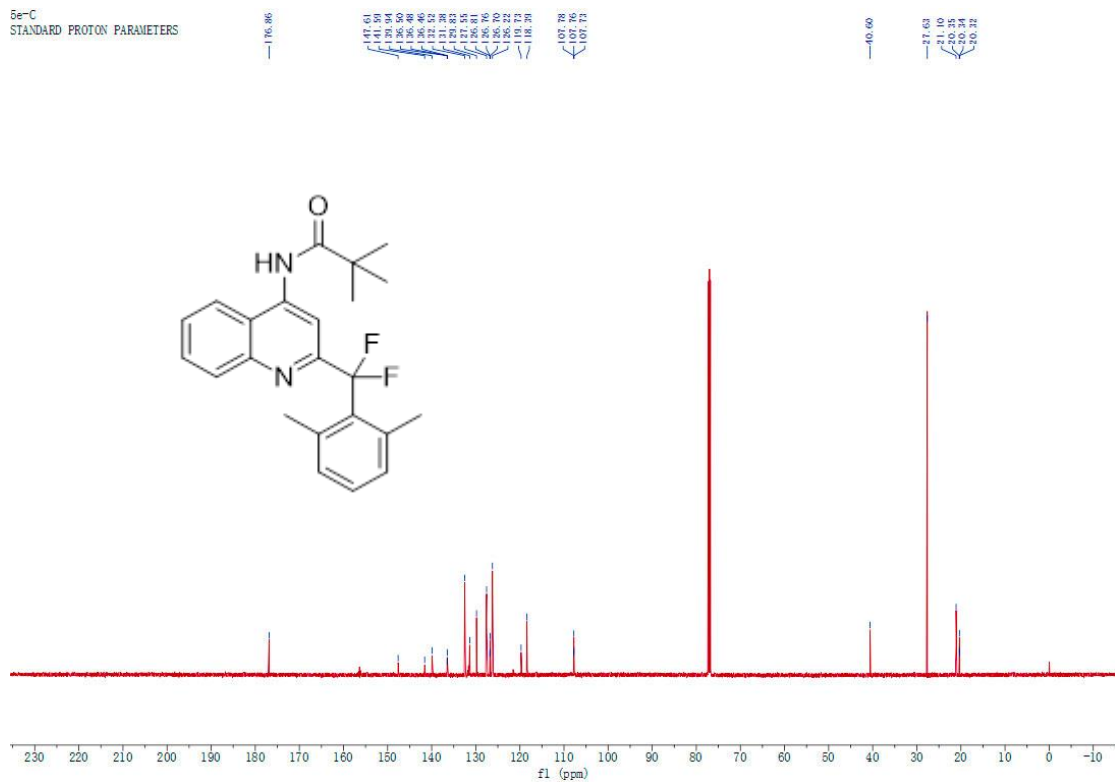
95.32

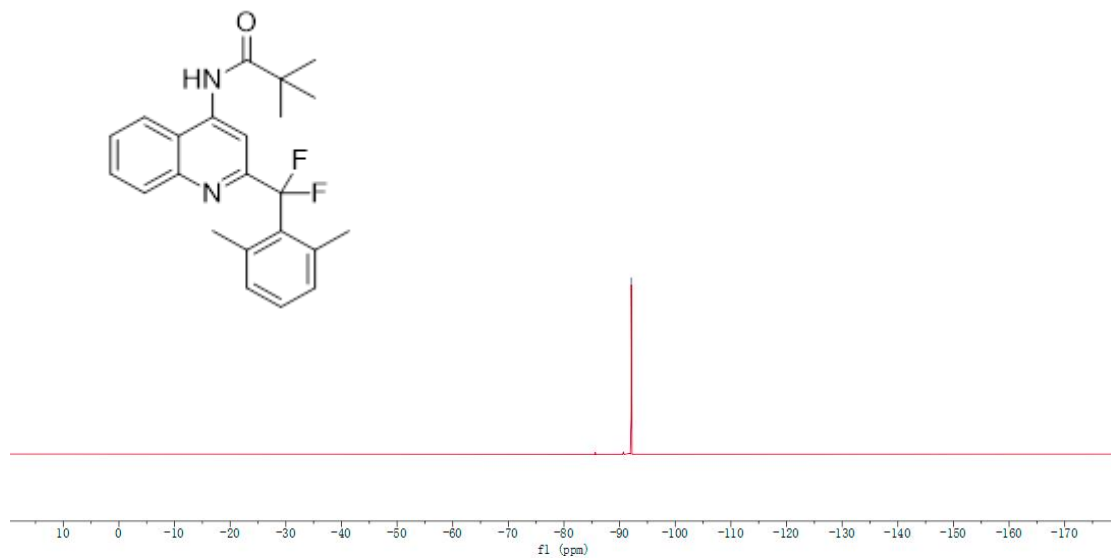


5e
STANDARD PROTON PARAMETERS

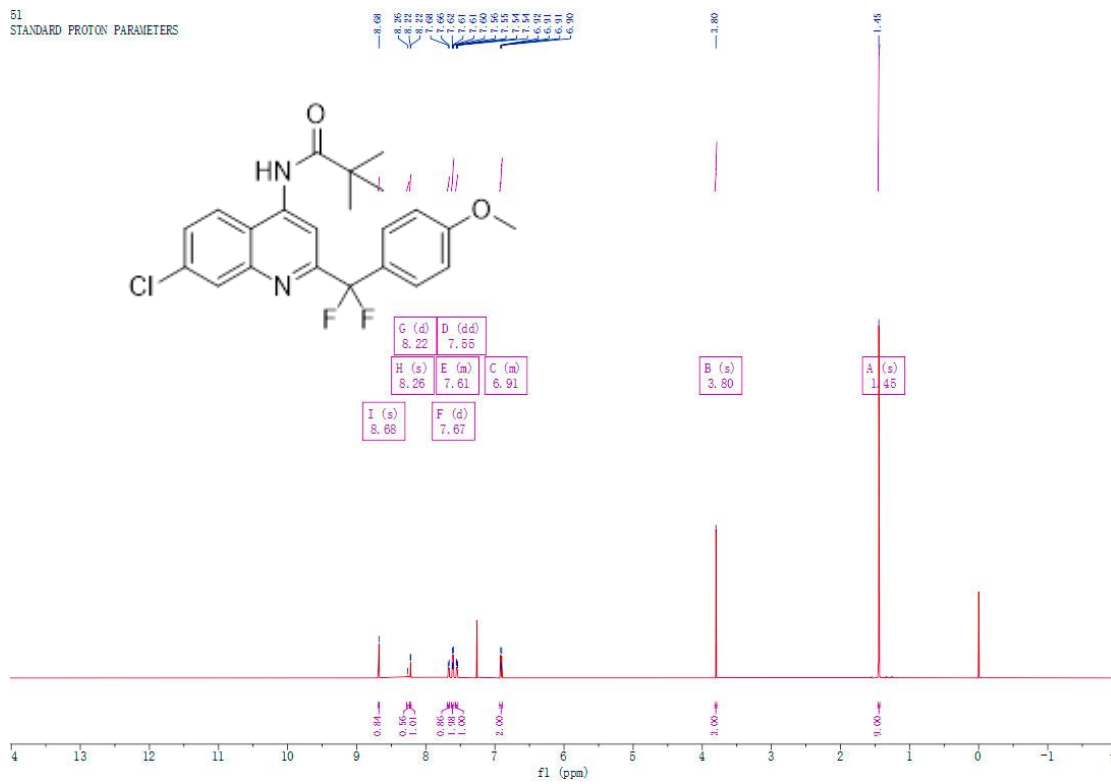


5e-C
STANDARD PROTON PARAMETERS



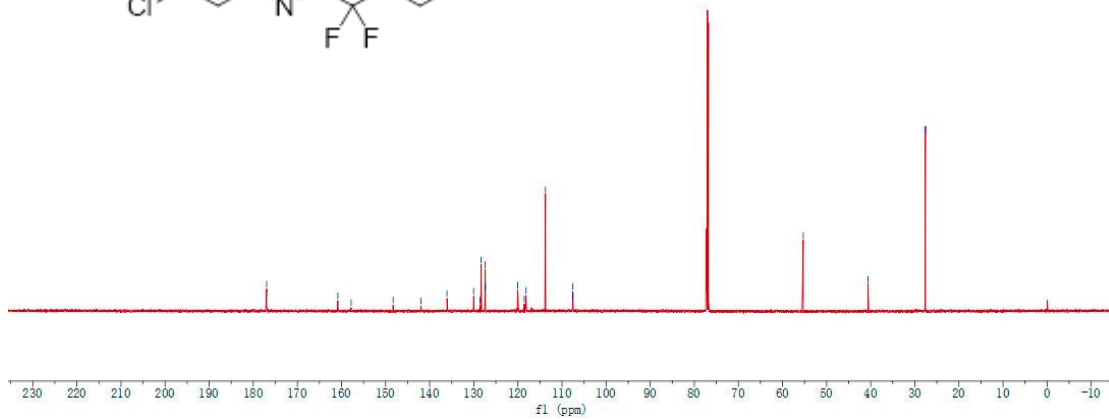
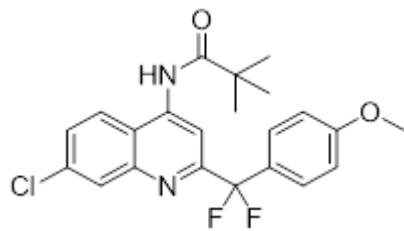


61
STANDARD PROTON PARAMETERS



SL-C
STANDARD 1H OBSERVE - profile

116.97
160.81
157.80
148.29
141.05
136.07
130.04
128.53
127.44
127.41
125.11
120.03
118.55
118.14
117.14
107.54
107.01
55.29
40.61
27.99



20210611.15.fid
51 in CDCl3,19F

94.41

