

Supporting Information

Assembly of trifluoromethylated fused tricyclic pyrazoles via cyclization of β -amino cyclic ketones

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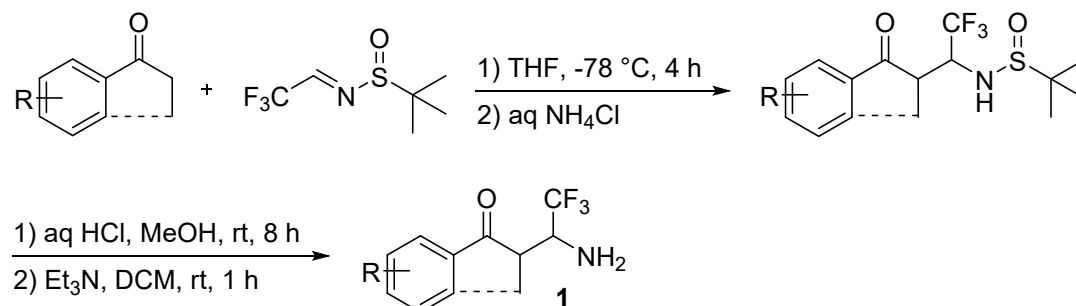
1. General information

All the commercial reagents including solvents were used directly without further purification.

Amines **1a-w** were synthesized according to the literature.¹ All the experiments were monitored by thin layer chromatography (TLC) with UV light. The TLC employed 0.25 mm silica gel coated on glass plates. Purification of products was carried out by silica gel 60 F-254 TLC plates of 20 cm × 20 cm and column chromatography with silica gel 60 (300-400 mesh). Melting points were recorded without correction on RY-1G of Tianjin Xintianguang instrument company. NMR spectra were recorded on Bruker 400 MHz and 600 MHz spectrometers. High resolution mass spectra (HRMS) were measured on Agilent 6210 ESI/TOF MS instrument. Molecular docking molecular docking was performed using the Autodock 4.2 software and the Lamarckian genetic algorithm. The crystal structure of KDR kinase (PDB ID: 1VR2) were obtained from the protein data bank (<http://www.rcsb.org/>). The PyMOL (The PyMOL Molecular Graphics System, Version 2.6, Schrodinger, LLC) package was used to produce molecular images.

1. C. Xie, H. Mei, L. Wu, V. A. Soloshonok, J. Han and Y. Pan, *RSC Adv.*, 2014, **4**, 4763.

2. General procedure for the synthesis of amine **1**

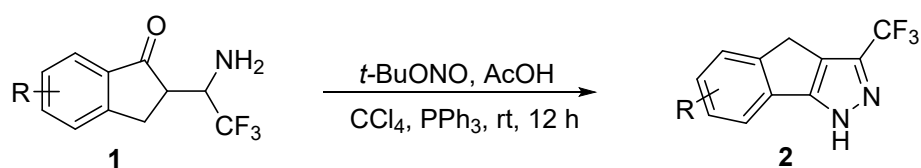


Into a vial was taken ketone (8.5 mmol, 1.7 equiv) and anhydrous THF (20.0 mL). The reaction vial was cooled to -78°C and LDA (2 M in THF, 4.68 mL) was added dropwise with stirring. After 40

min at $-78\text{ }^{\circ}\text{C}$, sulfinylimine (5.0 mmol) dissolved in anhydrous THF (5.0 mL) was added dropwise. Stirring was continued at $-78\text{ }^{\circ}\text{C}$ for 4 h, then the reaction was quenched with saturated NH_4Cl (10.0 mL), followed by H_2O (10.0 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc ($3 \times 15\text{ mL}$). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered and the solvent was removed to give the crude Mannich adduct, which was purified by the silica gel column (petroleum ether : EtOAc = 4 : 1).

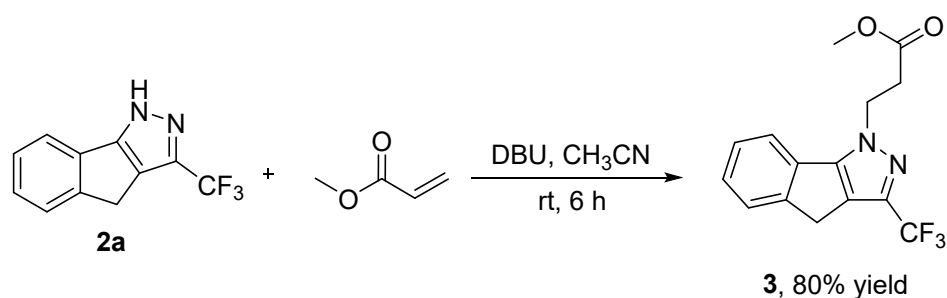
Mannich adduct (1.0 mmol) and MeOH (10 mL) were placed in a round-bottom flask and aq HCl (36%, 2 mL) was added. The reaction was stirred at rt for 8 h. Volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and Et_3N (30.0 mmol) was added. The mixture was stirred at room temperature for 1 h, then H_2O (10 mL) was added. The organic layer was taken, washed with H_2O ($3 \times 10\text{ mL}$), dried with anhydrous Na_2SO_4 , filtered and the solvent was removed to give the crude product **1**, which was purified by by the silica gel column (petroleum ether:EtOAc = 4 : 1).

3. General procedure for the cyclization reaction

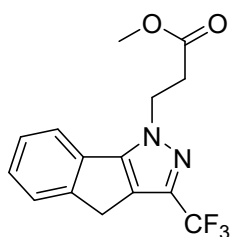


Amine **1** (0.2 mmol), PPh_3 (1.0 mmol), CH_3COOH (0.3 mmol) and CCl_4 (1 mL) were taken into a vial. The mixture was stirred at room temperature and $t\text{-BuONO}$ (0.5 mmol) dissolved in CCl_4 (1 mL) was added dropwise. After 12 h, solvent was removed in vacuum. The product **2** was purified by TLC plate of $20\text{ cm} \times 20\text{ cm}$ using petroleum ether/ethyl acetate (4:1, v/v) as eluent.

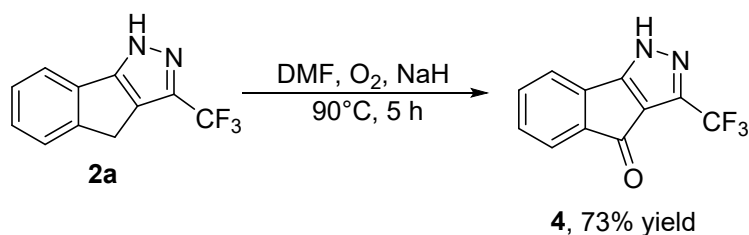
4. Procedure for the reactions from 2a to 3 and 4



The obtained **2a** (0.2 mmol), methyl acrylate (0.3 mmol) and DBU (0.1 mmol) were dissolved in CH_3CN (5 mL) at room temperature. After 6 h, the mixture was concentrated reduced pressure. The resulting residue was purified by TLC plate of 20 cm \times 20 cm using petroleum ether/ethyl acetate (6:1, v/v) as eluent, and the pure product was isolated in 80% yield.

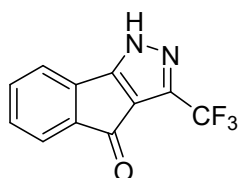


Compound **3**: 49.5 mg, 80% yield, white solid, mp 76-78 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.69-7.67 (m, 1H), 7.54-7.52 (m, 1H), 7.44-7.40 (m, 1H), 7.36-7.32 (m, 1H), 4.73-4.70 (m, 2H), 3.68 (s, 3H), 3.65 (s, 2H), 3.09-3.06 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.0, 150.2, 148.6, 136.8 (q, J = 38.6 Hz), 131.0, 127.1, 127.1, 126.4, 125.5 (d, J = 267.0 Hz), 124.4, 119.2, 52.0, 46.9, 34.3, 28.5. ^{19}F NMR (376 MHz, CDCl_3): δ = -61.6 (s, 3F). HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_2^+$ 311.1002, found 311.1007.



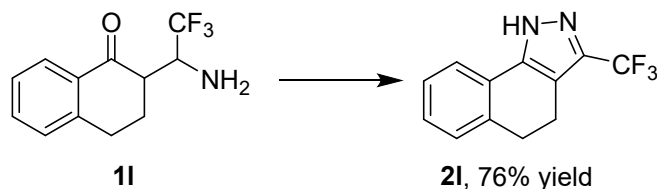
Under the atmosphere of oxygen, **2a** (0.2 mmol) and NaH (0.8 mmol) were dissolved in DMF (5

mL). The mixture was stirred at 90 °C for 8 h. The reaction was quenched with H₂O (20 mL). Then organic layer was taken and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous Na₂SO₄, filtered and the solvent was removed in vacuum. The resulting residue was purified by TLC plate of 20 cm × 20 cm using petroleum ether/ethyl acetate (4:1, v/v) as eluent, and the pure product was isolated in 73% yield.



Compound **4**: 34.5 mg, 73% yield, yellow solid, mp 221-223 °C. ¹H NMR (400 MHz, CD₃OD): δ = 7.54-7.48 (m, 2H), 7.39-7.35 (m, 2H). ¹³C NMR (100 MHz, CD₃OD): δ = 181.3, 160.4, 139.9, 133.6, 132.7, 130.2, 124.3, 124.2 (q, *J* = 267.2 Hz), 119.9, 118.6. ¹⁹F NMR (376 MHz, CD₃OD): δ = -63.8 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₁H₆F₃N₂O⁺ 239.0427, found 239.0436.

5. Large scale synthesis



Amine **11** (5.25 mmol), PPh₃ (30.00 mmol), CH₃COOH (9.00 mmol) and CCl₄ (30 mL) were taken into a flask. The mixture was stirred at room temperature and *t*-BuONO (15.00 mmol) dissolved in CCl₄ (15 mL) was added dropwise. After 12 h, solvent was removed in vacuum. The product **21** was purified by column chromatography using petroleum ether/ethyl acetate (5:1, v/v) as eluent, and the pure product was isolated in 0.95 g (76% yield).

6. Detection of reaction process by ^{19}F NMR

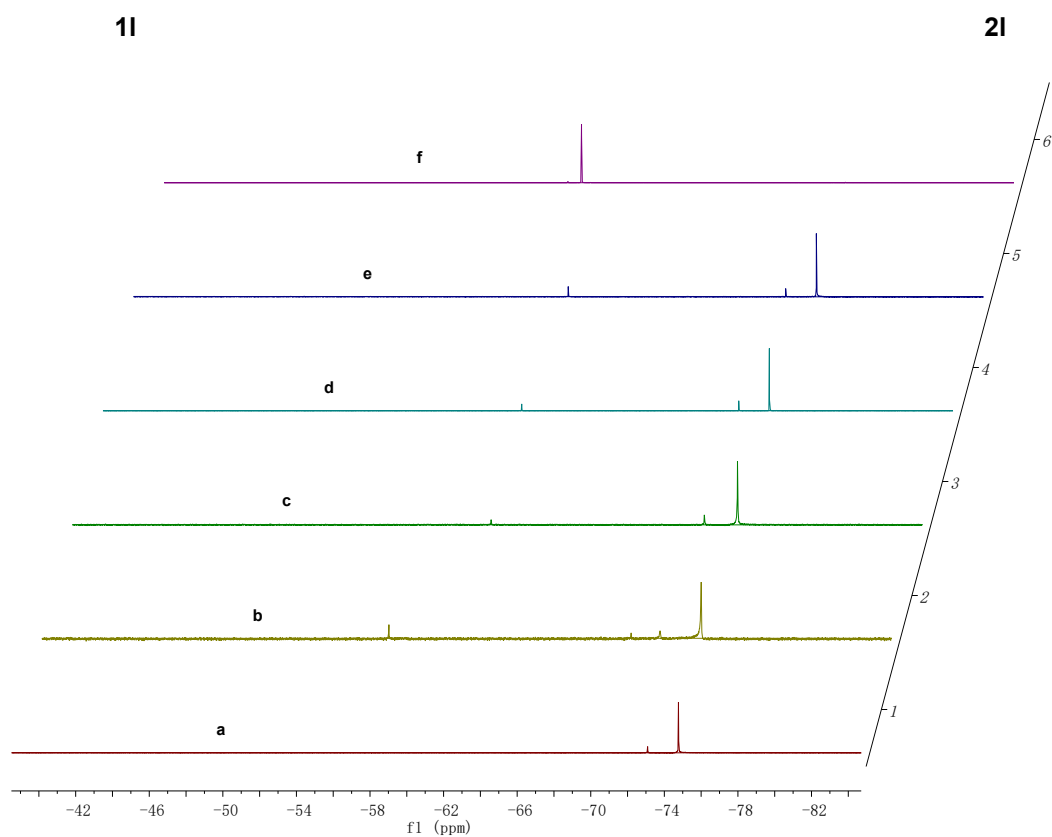
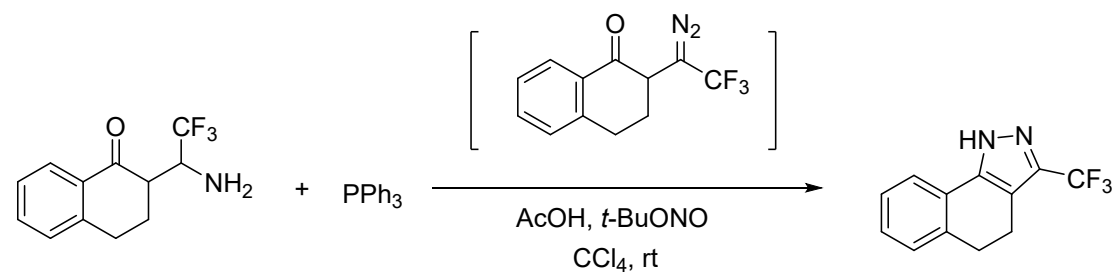
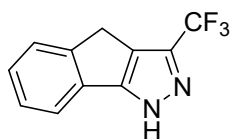


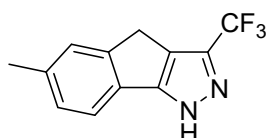
Figure S1. ^{19}F NMR study of the reaction process.

(a): Pure amine **11**. **(b):** Amine **11** (0.2 mmol), AcOH (0.3 mmol), CCl_4 (2 mL) were taken into a vial, followed by the addition of *t*-BuONO (0.5 mmol) dissolved in CCl_4 (1 mL) dropwise, and then stirred for 5 min. **(c):** The same procedure as **(b)** and after addition, followed by the addition of PPh_3 (1.0 mmol) dissolved in CCl_4 (1 mL) dropwise. **(d)-(e):** The same procedure as **(c)** and after addition, the reaction stirred for 10 min, 25 min respectively. **(f):** Pure product **21**.

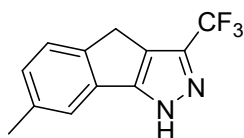
7. Characterization data of compounds 2, 3, 4



Compound **2a**: 30.9 mg, 70% yield, white solid, mp 167-168 °C. ¹H NMR (400 MHz, CD₃CN): δ = 11.94 (s, 1H), 7.67-7.58 (m, 1H), 7.56-7.46 (m, 1H), 7.42-7.26 (m, 2H), 3.61 (s, 2H). ¹³C NMR (100 MHz, CD₃CN): δ = 151.4, 148.6, 135.5 (d, *J* = 39.2 Hz), 131.0, 127.0, 127.0, 126.2, 126.0 (q, *J* = 265.7 Hz), 123.9, 119.6, 28.1. ¹⁹F NMR (376 MHz, CD₃CN): δ = -61.9 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₁H₈F₃N₂⁺ 225.0634, found 225.0645.

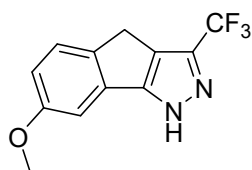


Compound **2b**: 28.8 mg, 60% yield, white solid, mp 192-193 °C. ¹H NMR (400 MHz, CD₃CN): δ = 11.82 (s, 1H), 7.54 (d, *J* = 7.72 Hz, 1H), 7.37 (s, 1H), 7.22 (d, *J* = 7.64 Hz, 1H), 3.64 (s, 2H), 2.41 (s, 3H). ¹³C NMR (100 MHz, CD₃CN): δ = 151.3, 149.0, 137.3, 131.8, 128.5, 127.7, 126.9, 126.0 (q, *J* = 265.9 Hz), 123.5, 119.3, 28.1, 20.6. ¹⁹F NMR (376 MHz, CD₃CN): δ = -61.9 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₂H₁₀F₃N₂⁺ 239.0791, found 239.0798.

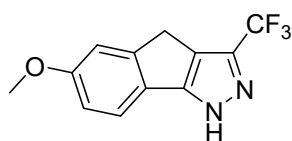


Compound **2c**: 24.8 mg, 52% yield, white solid, mp 184-185 °C. ¹H NMR (400 MHz, CD₃OD): δ = 7.43-7.34 (m, 2H), 7.13 (d, *J* = 7.72 Hz, 1H), 3.55 (s, 2H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CD₃OD): δ = 150.9, 145.6, 136.8, 136.3 (d, *J* = 37.1 Hz), 130.7, 127.7, 125.6, 123.6, 123.1 (d, *J* = 265.6 Hz), 119.5, 27.4, 20.0. ¹⁹F NMR (376 MHz, CD₃OD): δ = -63.0 (s, 3F). HRMS (ESI) *m/z*:

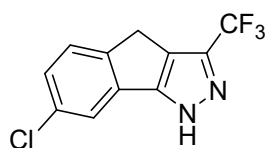
$[M+H]^+$ calcd for $C_{12}H_{10}F_3N_2^+$ 239.0791, found 239.0799.



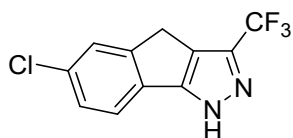
Compound **2d**: 33.0 mg, 65% yield, white solid, mp 144-146 °C. 1H NMR (400 MHz, CD_3OD): δ = 7.40 (d, J = 8.32 Hz, 1H), 7.13 (s, 1H), 6.88 (d, J = 8.36 Hz, 1H), 3.84 (s, 3H), 3.54 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ = 159.4, 150.8, 140.3, 136.3 (d, J = 38.1 Hz), 131.6, 126.4, 124.4, 123.1 (d, J = 265.8 Hz), 112.7, 104.6, 54.5, 27.1. ^{19}F NMR (376 MHz, CD_3OD): δ = -63.0 (s, 3F). HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{12}H_{10}F_3N_2O^+$ 255.0740, found 255.0748.



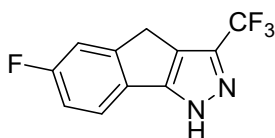
Compound **2e**: 31.6 mg, 62% yield, white solid, mp 178-180 °C. 1H NMR (400 MHz, CD_3OD): δ = 7.48 (d, J = 7.36 Hz, 1H), 7.11 (s, 1H), 6.92 (d, J = 8.24 Hz, 1H), 3.83 (s, 3H), 3.60 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ = 159.7, 150.8, 136.2 (d, J = 37.7 Hz), 125.8 (q, J = 266.7 Hz), 123.7, 122.3, 119.6, 112.5, 111.9, 54.5, 28.0. ^{19}F NMR (376 MHz, CD_3OD): δ = -63.0 (s, 3F). HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{12}H_{10}F_3N_2O^+$ 255.0740, found 255.0747.



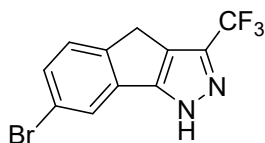
Compound **2f**: 28.4 mg, 55% yield, white solid, mp 193-195 °C. 1H NMR (400 MHz, CD_3OD): δ = 7.59 (s, 1H), 7.51 (d, J = 8.12 Hz, 1H), 7.33-7.28 (m, 1H), 3.66 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ = 160.4, 146.9, 134.8, 132.8, 128.0, 127.1, 126.7, 124.5, 122.6 (d, J = 268.2 Hz), 119.2, 27.5. ^{19}F NMR (376 MHz, CD_3SOCD_3): δ = -59.9 (s, 3F). HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{11}H_7ClF_3N_2^+$ 259.0244, found 259.0254.



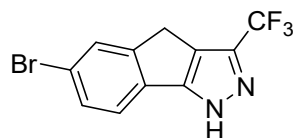
Compound **2g**: 24.4 mg, 47% yield, white solid, mp 203-205 °C. ^1H NMR (400 MHz, CD_3OD): δ = 7.59-7.52 (m, 2H), 7.39 (d, J = 8.12 Hz, 1H), 3.68 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ = 150.5, 149.8, 136.4, 132.7, 129.4, 127.0, 126.3, 123.6, 123.0 (d, J = 266.6 Hz), 119.9, 27.9. ^{19}F NMR (376 MHz, CD_3OD): δ = -63.0 (s, 3F). HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_7\text{ClF}_3\text{N}_2^+$ 259.0244, found 259.0251.



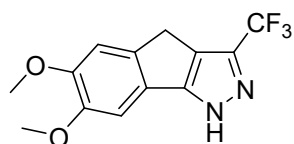
Compound **2h**: 19.6 mg, 40% yield, white solid, mp 188-190 °C. ^1H NMR (400 MHz, CD_3SOCD_3): δ = 13.9 (s, 1H), 7.63-7.60 (m, 1H), 7.46 (d, J = 9.16 Hz, 1H), 7.27-7.23 (m, 1H), 3.73 (s, 2H). ^{13}C NMR (100 MHz, CD_3SOCD_3): δ = 163.1, 160.6, 151.5 (d, J = 8.7 Hz), 149.9, 135.7 (d, J = 38.1 Hz), 127.7, 123.8, 123.7 (d, J = 266.1 Hz), 120.9 (d, J = 9.0 Hz), 114.7 (d, J = 23.2 Hz), 28.8. ^{19}F NMR (376 MHz, CD_3SOCD_3): δ = -59.9 (s, 3F), -114.8 (s, 1F). HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_7\text{F}_4\text{N}_2^+$ 243.0540, found 243.0541.



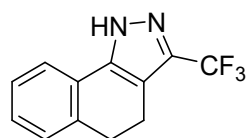
Compound **2i**: 25.3 mg, 42% yield, white solid, mp 213-215 °C. ^1H NMR (400 MHz, CD_3OD): δ = 7.69 (s, 1H), 7.42-7.35 (m, 2H), 3.58 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ = 147.3, 132.9, 129.6, 127.4, 124.3, 124.2, 122.8 (d, J = 265.9 Hz), 122.1, 120.5, 27.6. ^{19}F NMR (376 MHz, CD_3OD): δ = -62.9 (s, 3F). HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_7\text{BrF}_3\text{N}_2^+$ 302.9739, found 302.9008.



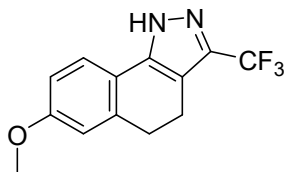
Compound **2j**: 18.4 mg, 30% yield, white solid, mp 215-217 °C. ¹H NMR (400 MHz, CD₃SOCD₃): δ = 14.0 (s, 1H), 7.78 (s, 1H), 7.61-7.54 (m, 2H), 3.74 (s, 2H). ¹³C NMR (100 MHz, CD₃SOCD₃): δ = 151.1, 149.8, 135.4, 130.5, 130.3, 129.9, 124.1, 123.6 (d, *J* = 261.3 Hz), 121.3, 120.4, 28.6. ¹⁹F NMR (376 MHz, CD₃SOCD₃): δ = -59.9 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₁H₇BrF₃N₂⁺ 302.9739, found 304.9734.



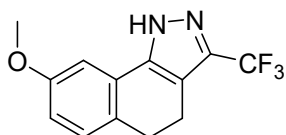
Compound **2k**: 34.8 mg, 61 % yield, white solid, mp 181-183 °C. ¹H NMR (400 MHz, CDCl₃): δ = 12.0 (s, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.62 (s, 2H). ¹³C NMR (100 MHz, CD₃SOCD₃): δ = 161.1, 151.2, 148.9, 148.7, 141.3, 123.7, 123.1, 121.1 (d, *J* = 262.3 Hz), 110.8, 103.5, 56.2, 56.1, 28.3. ¹⁹F NMR (376 MHz, CDCl₃): δ = -61.1 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₃H₁₂F₃N₂O₂⁺ 285.0845, found 285.0853.



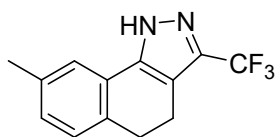
Compound **2l**: 43.7 mg, 92% yield, white solid, mp 147-149 °C. ¹H NMR (400 MHz, CDCl₃): δ = 13.31 (s, 1H), 7.42-7.40 (m, 1H), 7.27-7.21 (m, 3H), 2.80-2.77 (m, 2H), 2.63-2.59 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 141.1, 138.5, 136.0, 128.7, 128.5, 127.1, 125.7 (q, *J* = 267.7 Hz), 125.0, 121.7, 114.7, 28.7, 18.2. ¹⁹F NMR (376 MHz, CDCl₃): δ = -61.2 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₂H₁₀F₃N₂⁺ 239.0791, found 239.0795.



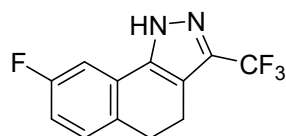
Compound **2m**: 50.9 mg, 95% yield, white solid, mp 152-153 °C. ¹H NMR (400 MHz, CDCl₃): δ = 12.97 (s, 1H), 7.37 (d, *J* = 8.32 Hz, 1H), 6.80 (s, 1H), 6.77 (d, *J* = 8.44 Hz, 1H), 3.84 (s, 3H), 2.83-2.79 (m, 2H), 2.67-2.64 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 159.9, 141.3, 138.0, 123.1, 120.4, 122.1 (d, *J* = 267.6 Hz), 118.3, 114.6, 113.4, 111.8, 55.3, 29.2, 18.3. ¹⁹F NMR (376 MHz, CDCl₃): δ = -61.2 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₃H₁₂F₃N₂O⁺ 269.0896, found 269.0905.



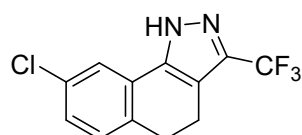
Compound **2n**: 50.9 mg, 95% yield, white solid, mp 150-152 °C. ¹H NMR (400 MHz, CDCl₃): δ = 13.3 (s, 1H), 7.17 (d, *J* = 8.36 Hz, 1H), 7.03 (s, 1H), 6.82 (d, *J* = 8.32 Hz, 1H), 3.70 (s, 3H), 2.82-2.79 (m, 2H), 2.73-2.70 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 158.7, 141.8, 138.1, 129.5, 128.0, 125.9, 125.6 (q, *J* = 267.6 Hz), 115.0, 114.9, 106.6, 55.1, 28.0, 18.5. ¹⁹F NMR (376 MHz, CDCl₃): δ = -61.3 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₃H₁₂F₃N₂O⁺ 269.0896, found 269.0903.



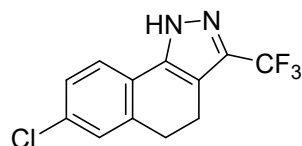
Compound **2o**: 45.5 mg, 90% yield, white solid, mp 147-149 °C. ¹H NMR (400 MHz, CDCl₃): δ = 13.1 (s, 1H), 7.25 (s, 1H), 7.15 (d, *J* = 7.64 Hz, 1H), 7.09 (d, *J* = 7.60 Hz, 1H), 2.78-2.75 (m, 2H), 2.67-2.63 (m, 2H), 2.32 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 141.2, 138.7, 136.8, 133.0, 129.4, 128.4, 124.9, 123.1 (d, *J* = 267.6 Hz), 122.3, 114.7, 28.3, 20.9, 18.4. ¹⁹F NMR (376 MHz, CDCl₃): δ = -61.1 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₃H₁₂F₃N₂⁺ 253.0947, found 253.0957.



Compound **2p**: 49.5 mg, 97% yield, white solid, mp 150-152 °C. ¹H NMR (400 MHz, CDCl₃): δ = 13.4 (s, 1H), 7.23-7.20 (m, 1H), 7.14 (d, *J* = 8.72 Hz, 1H), 6.97-6.93 (m, 1H), 2.84-2.80 (m, 2H), 2.72-2.68 (m, 2H). ¹³C NMR (150 MHz, CDCl₃): δ = 162.6 (d, *J* = 244.1 Hz), 141.1, 131.5 (d, *J* = 3.1 Hz), 130.0 (d, *J* = 7.8 Hz), 126.6 (d, *J* = 8.3 Hz), 124.1 (q, *J* = 267.8 Hz), 115.5 (d, *J* = 21.0 Hz), 115.2, 109.0, 108.8, 28.1, 18.3. ¹⁹F NMR (376 MHz, CDCl₃): δ = -61.1 (s, 3F), -114.5 (s, 1F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₂H₉F₄N₂⁺ 257.0696, found 257.0704.



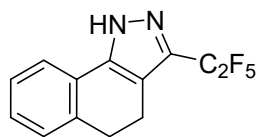
Compound **2q**: 50.3 mg, 92% yield, white solid, mp 172-174 °C. ¹H NMR (400 MHz, CDCl₃): δ = 12.9 (s, 1H), 7.42 (s, 1H), 7.24-7.19 (m, 2H), 2.90-2.87 (m, 2H), 2.82-2.78 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.9, 138.1, 134.3, 132.9, 129.9, 128.6, 126.7, 125.4 (q, *J* = 267.5 Hz), 121.8, 115.3, 28.4, 18.2. ¹⁹F NMR (376 MHz, CDCl₃): δ = -61.1 (s, 3F). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₂H₉ClF₃N₂⁺ 273.0401, found 273.0405.



Compound **2r**: 51.6 mg, 95% yield, white solid, mp 193-194 °C. ¹H NMR (400 MHz, CD₃CN): δ = 11.97 (s, 1H), 7.55 (d, *J* = 8.08 Hz, 1H), 7.36-7.31 (m, 2H), 2.99-2.95 (m, 2H), 2.86-2.82 (m, 2H). ¹³C NMR (100 MHz, CD₃CN): δ = 138.5, 133.4, 128.6, 126.9, 124.2, 123.5, 123.1, 120.9 (d, *J* =

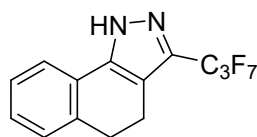
266.36 Hz), 114.8, 28.5, 18.0. ^{19}F NMR (376 MHz, CD_3CN): $\delta = -61.8$ (s, 3F). HRMS (ESI) m/z:

$[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_9\text{ClF}_3\text{N}_2^+$ 273.0401, found 273.0405.



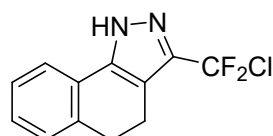
Compound **2s**: 37.1 mg, 64% yield, white solid, mp 162-164 °C. ^1H NMR (600 MHz, CDCl_3): $\delta = 12.6$ (s, 1H), 7.45-7.43 (m, 1H), 7.27-7.24 (m, 3H), 2.88-2.85 (m, 2H), 2.75-2.72 (m, 2H). ^{13}C NMR (150 MHz, CDCl_3): $\delta = 141.6, 136.9, 136.1, 128.8, 128.6, 127.1, 125.1, 121.5, 120.2-118.1$ (m), 116.4, 113.1-110.1 (m), 28.9, 18.6. ^{19}F NMR (376 MHz, CDCl_3): $\delta = -84.7$ (s, 3F), -113.7 (s, 2F).

HRMS (ESI) m/z: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{10}\text{F}_5\text{N}_2^+$ 289.0759, found 289.0766.



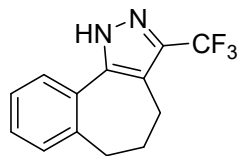
Compound **2t**: 55.1 mg, 82% yield, white solid, mp 157-158 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 13.2$ (s, 1H), 7.43-7.41 (m, 1H), 7.25-7.21 (m, 3H), 2.84-2.80 (m, 2H), 2.69-2.65 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 141.7, 136.0, 128.7, 128.5, 127.0, 125.1, 121.7, 116.6, 119.6-106.0$ (m), 28.8, 18.6. ^{19}F NMR (565 MHz, CDCl_3): $\delta = -80.4$ (s, 3F), -111.4 (s, 2F), -127.3 (s, 2F). HRMS

(ESI) m/z: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{10}\text{F}_7\text{N}_2^+$ 339.0727, found 339.0729.



Compound **2u**: 22.1 mg, 44% yield, white solid, mp 111-112 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.50-7.48$ (m, 1H), 7.28 (s, 3H), 2.97-2.94 (m, 2H), 2.86-2.83 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3):

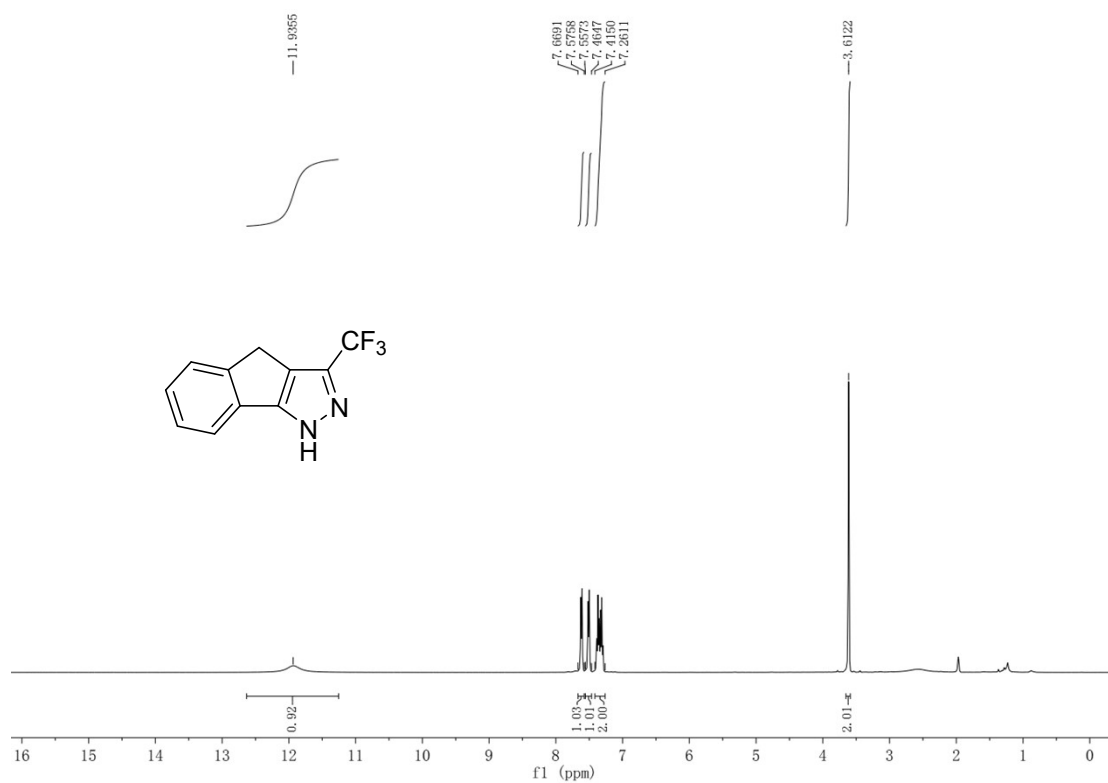
$\delta = 143.4$ (t, $J = 31.4$ Hz), 141.5, 136.1, 128.7, 128.6, 127.1, 126.1 (t, $J = 283.8$ Hz), 125.3, 121.7, 114.0, 28.9, 18.6. ^{19}F NMR (376 MHz, CDCl_3): $\delta = -47.0$ (s, 2F). HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{10}\text{ClF}_2\text{N}_2^+$ 255.0495, found 255.0503.



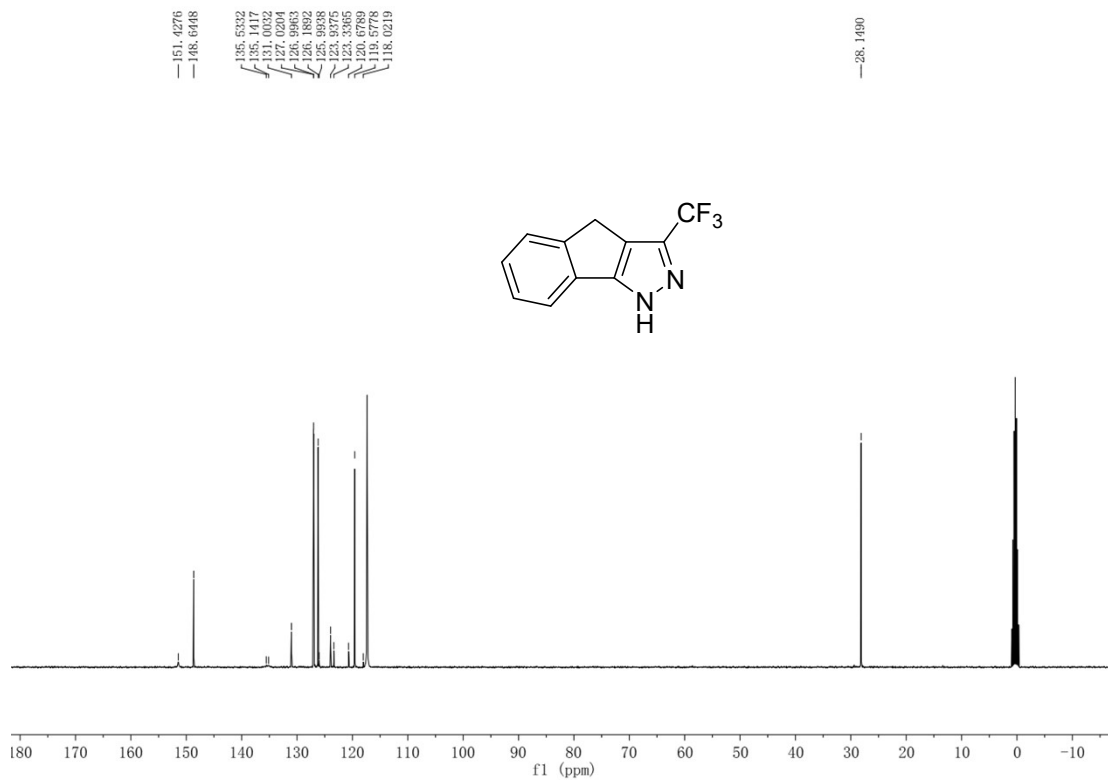
Compound **2w**: 48.8 mg, 97% yield, white solid, mp 164-165 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 12.5$ (s, 1H), 7.53-7.51 (m, 1H), 7.28-7.27 (m, 2H), 7.23-7.15 (m, 1H), 2.82-2.79 (m, 2H), 2.75-2.73 (m, 2H), 1.98-1.92 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 141.7$ (d, $J = 35.5$ Hz), 141.6, 140.9, 129.9, 128.6, 127.3, 126.8, 125.9 (d, $J = 267.9$ Hz), 125.4, 116.5, 34.8, 25.5, 24.2. ^{19}F NMR (565 MHz, CDCl_3): $\delta = -62.0$ (s, 3F). HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{12}\text{F}_3\text{N}_2^+$ 253.0947, found 253.0954.

8. ^1H , ^{13}C , ^{19}F NMR spectra for compounds 2, 3 and 4

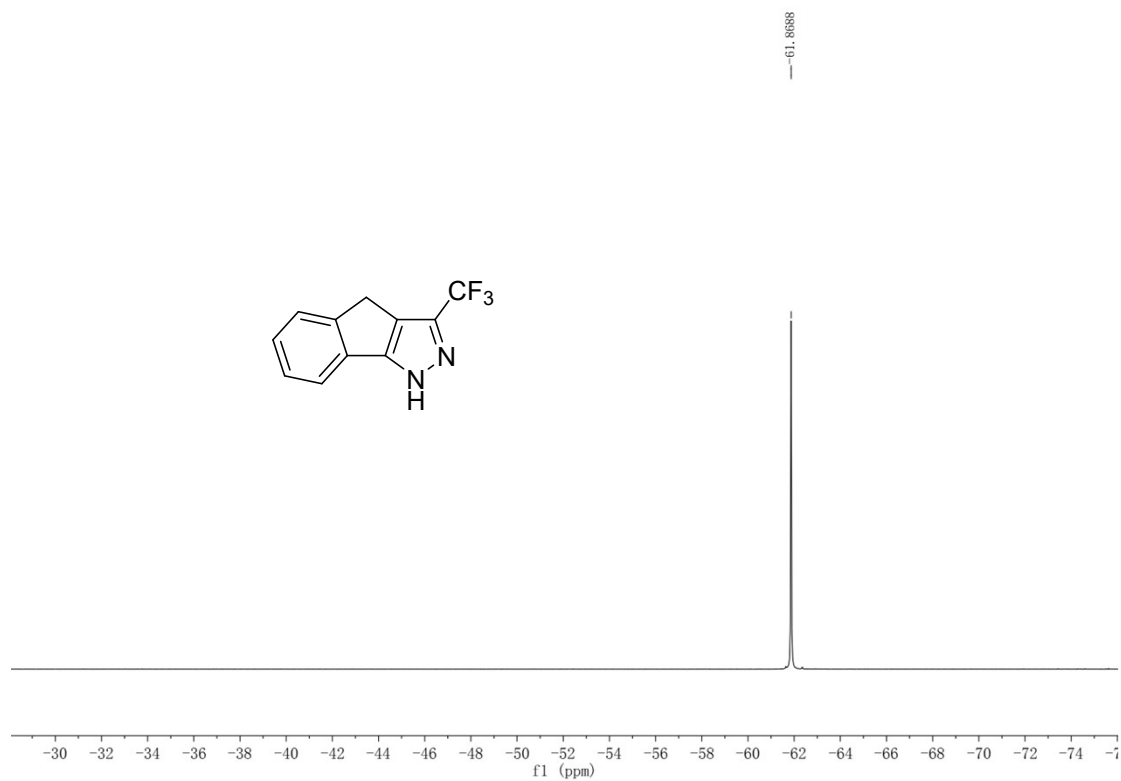
^1H NMR (400 MHz, CD_3CN) of **2a**:



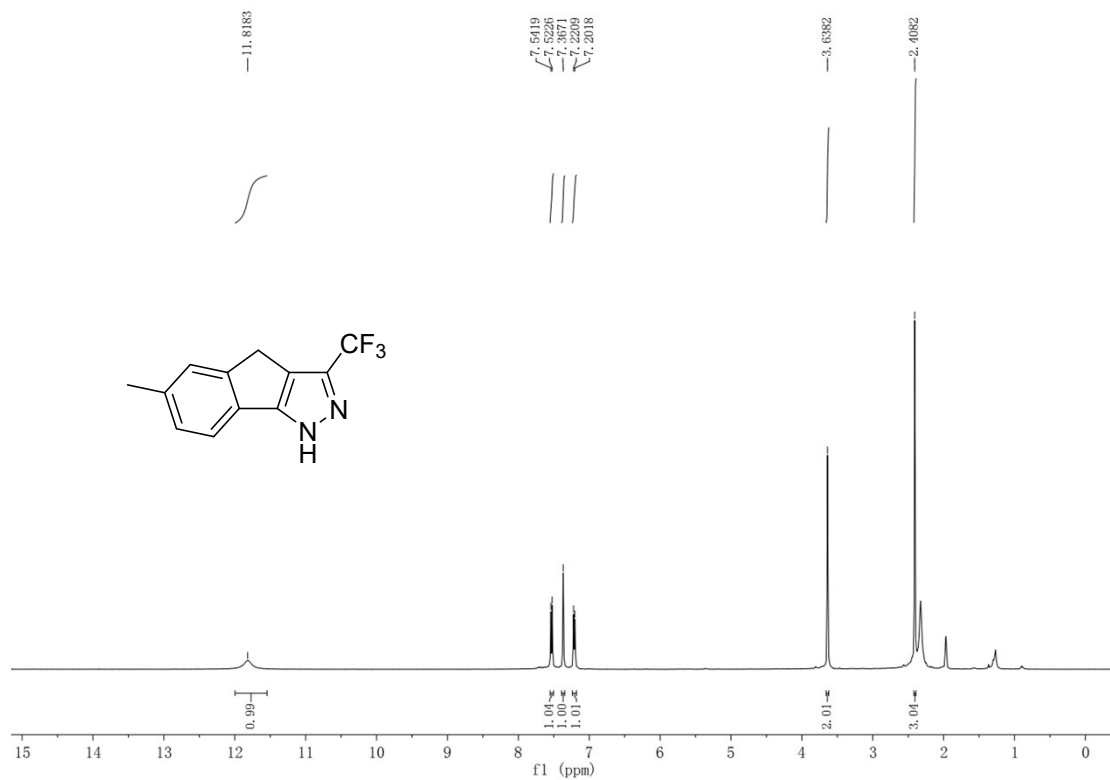
^{13}C NMR (100 MHz, CD_3CN) of **2a**:



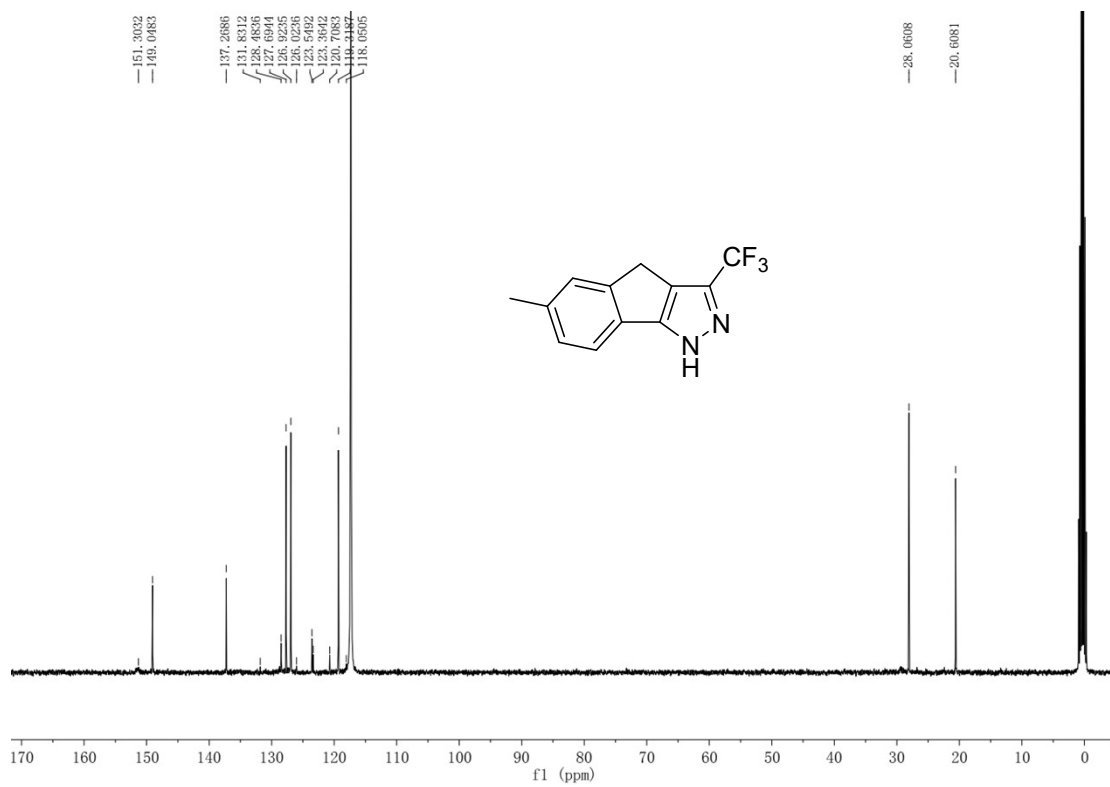
^{19}F NMR (376 MHz, CD_3CN) of **2a**:



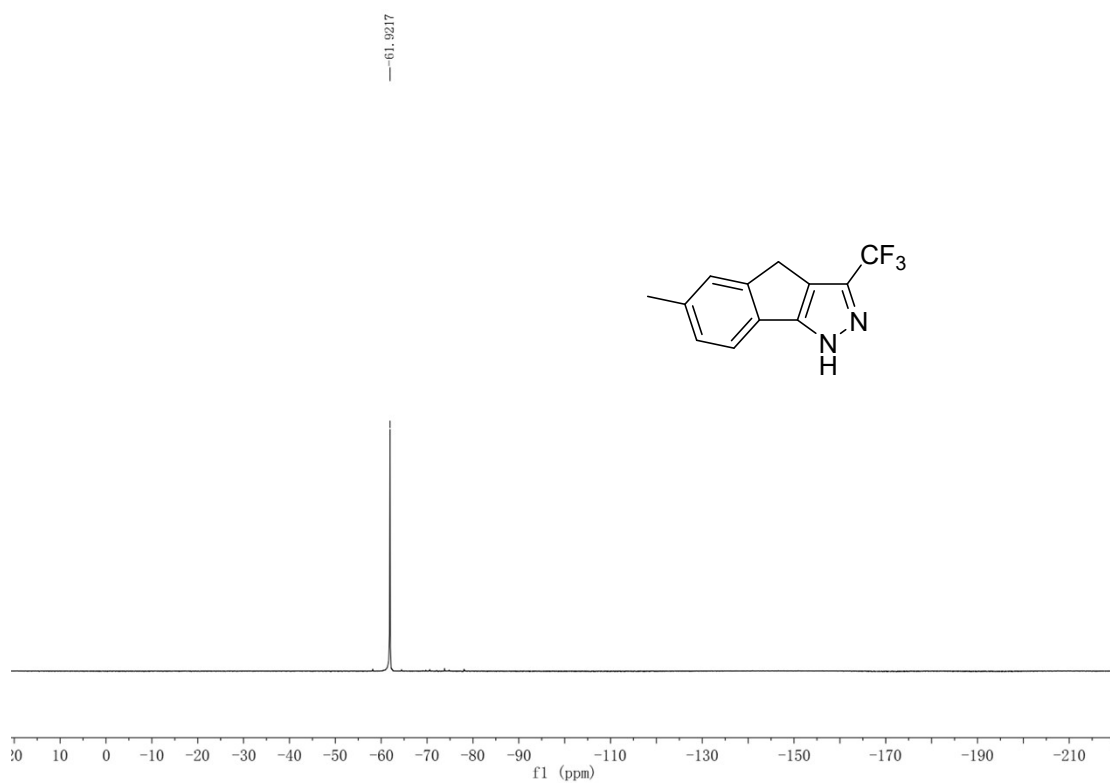
^1H NMR (400 MHz, CD_3CN) of **2b**:



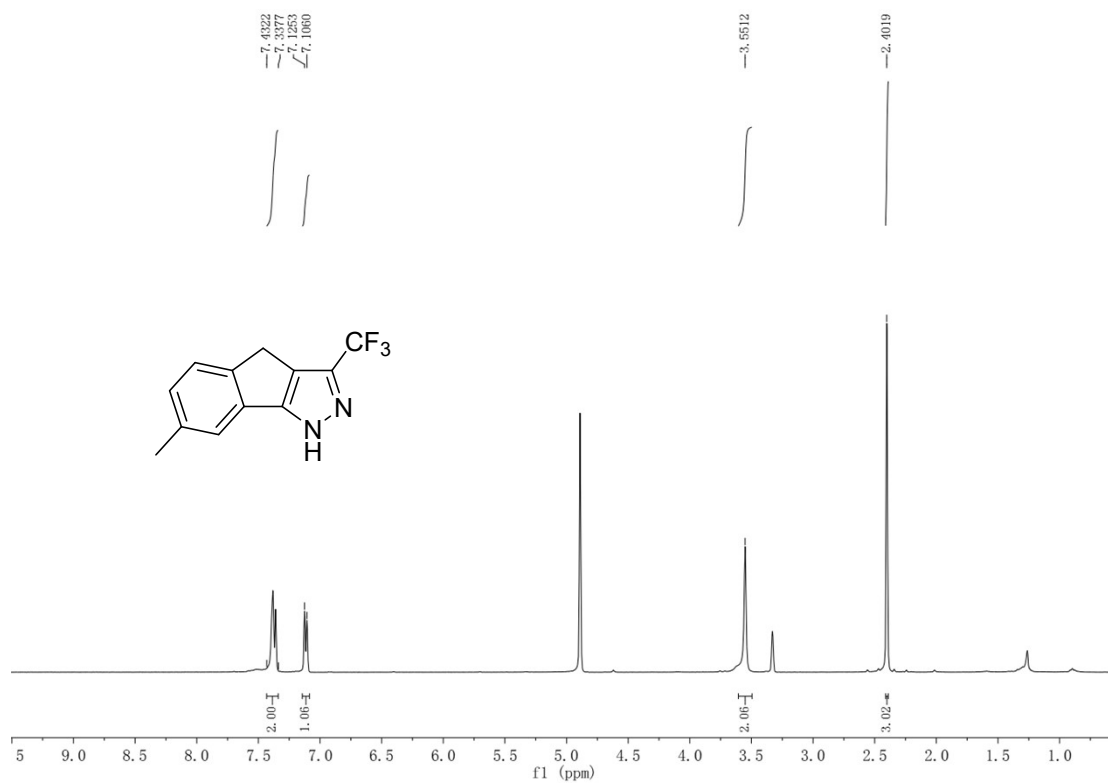
^{13}C NMR (100 MHz, CD_3CN) of **2b**:



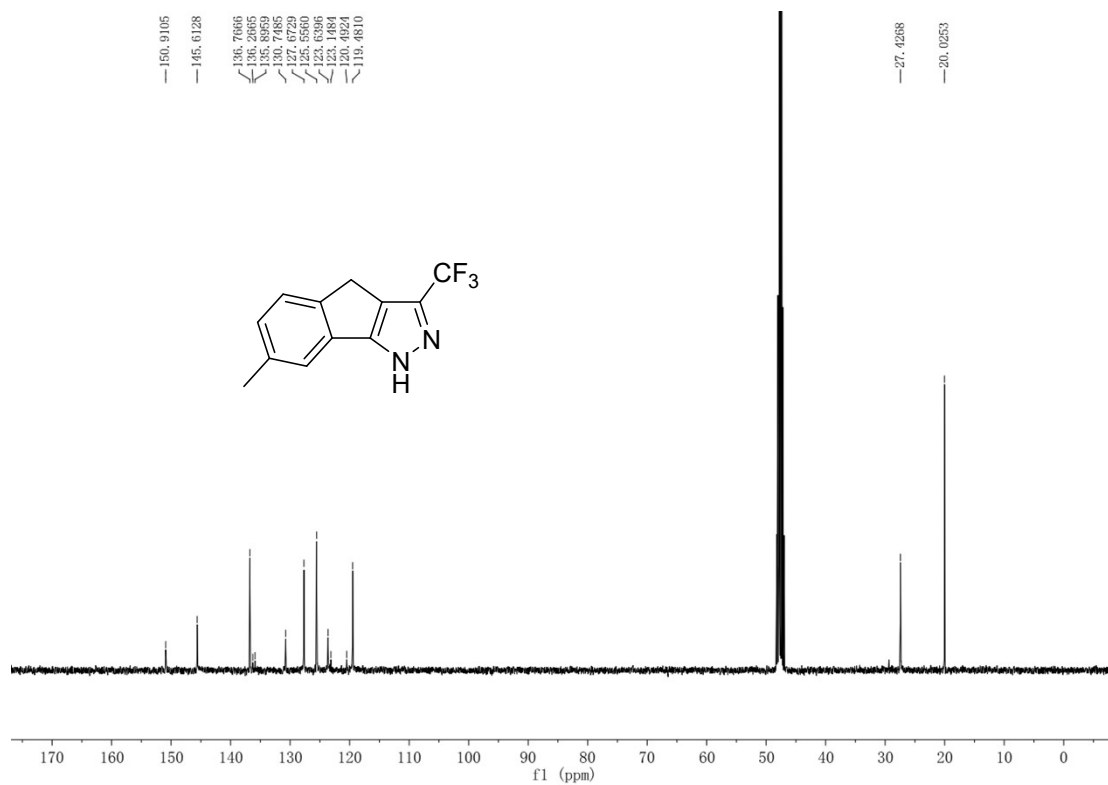
^{19}F NMR (376 MHz, CD_3CN) of **2b**:



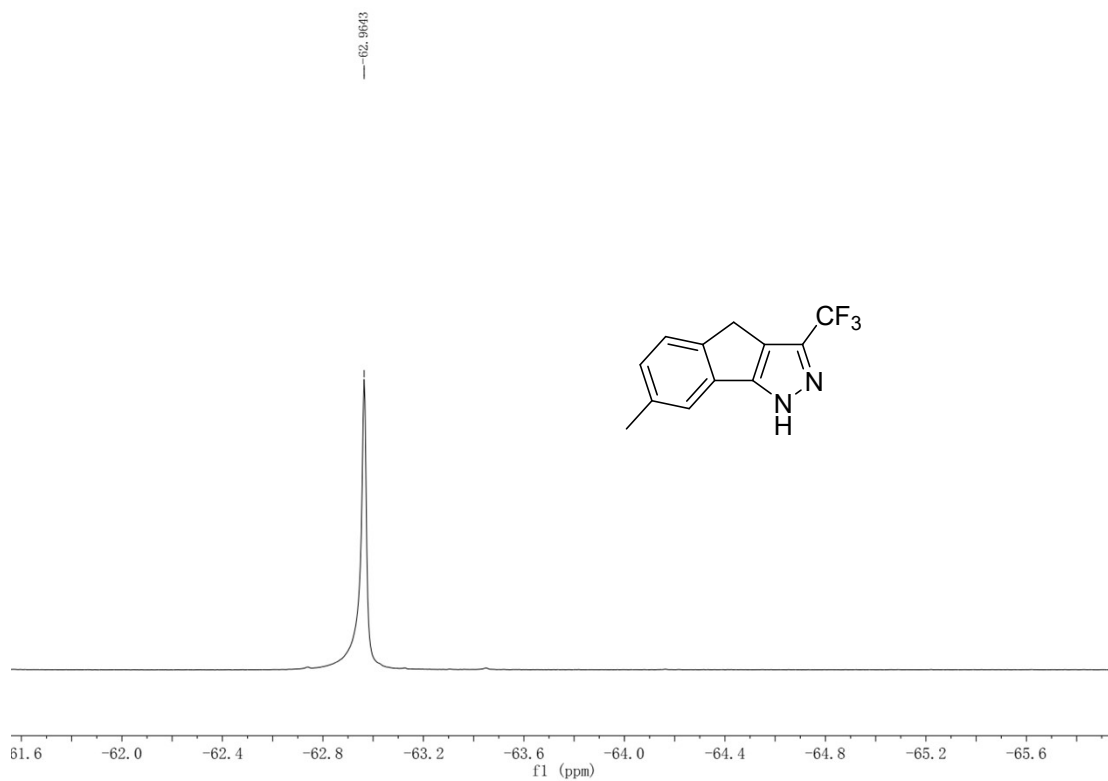
^1H NMR (400 MHz, CD_3OD) of **2c**:



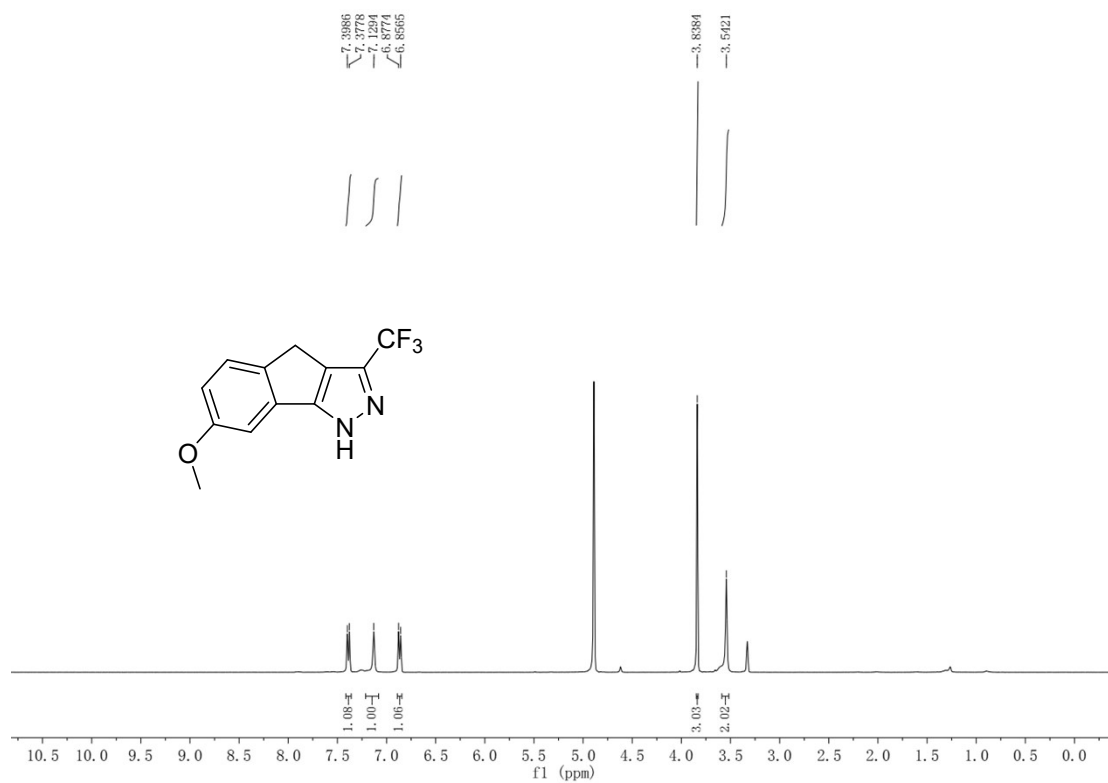
^{13}C NMR (100 MHz, CD_3OD) of **2c**:



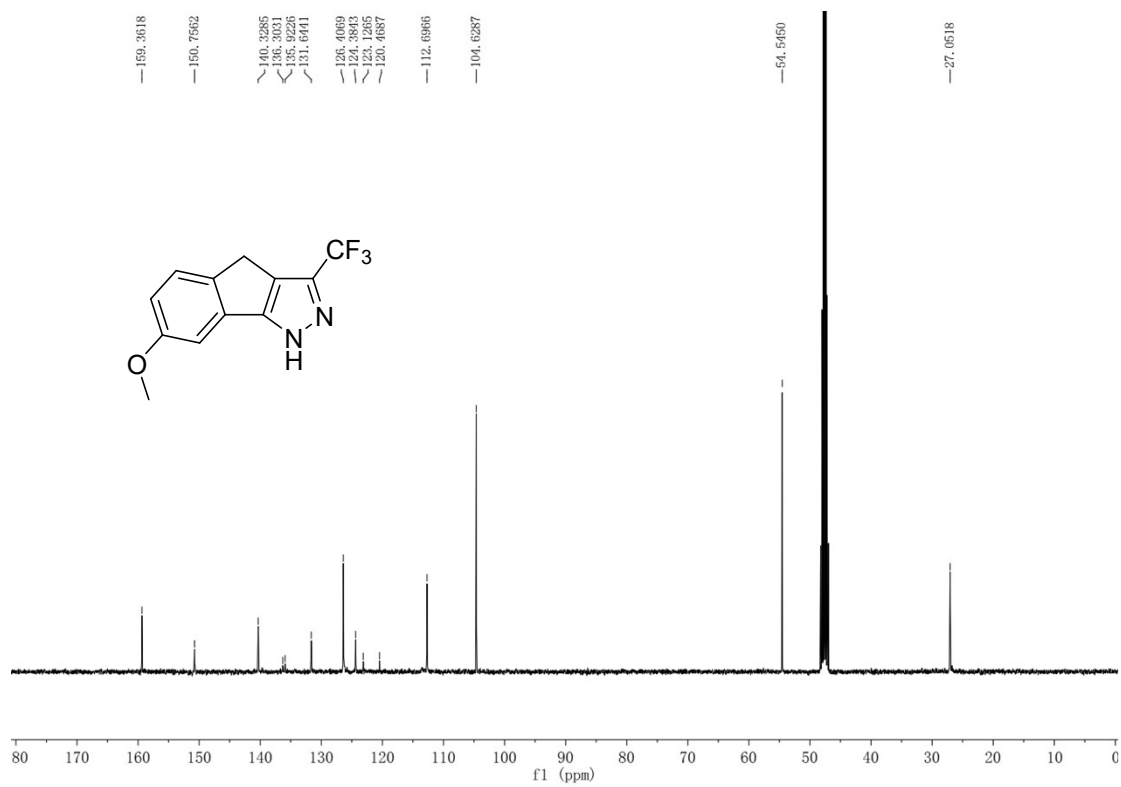
^{19}F NMR (376 MHz, CD_3OD) of **2c**:



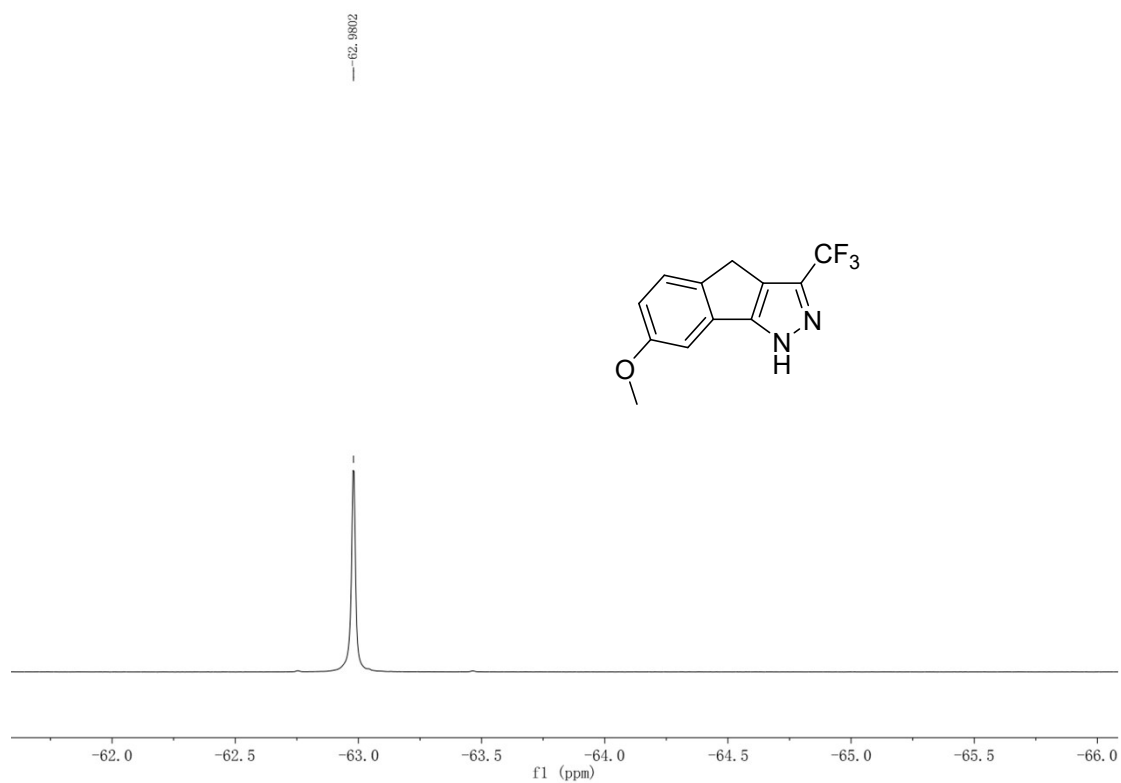
^1H NMR (400 MHz, CD_3OD) of **2d**:



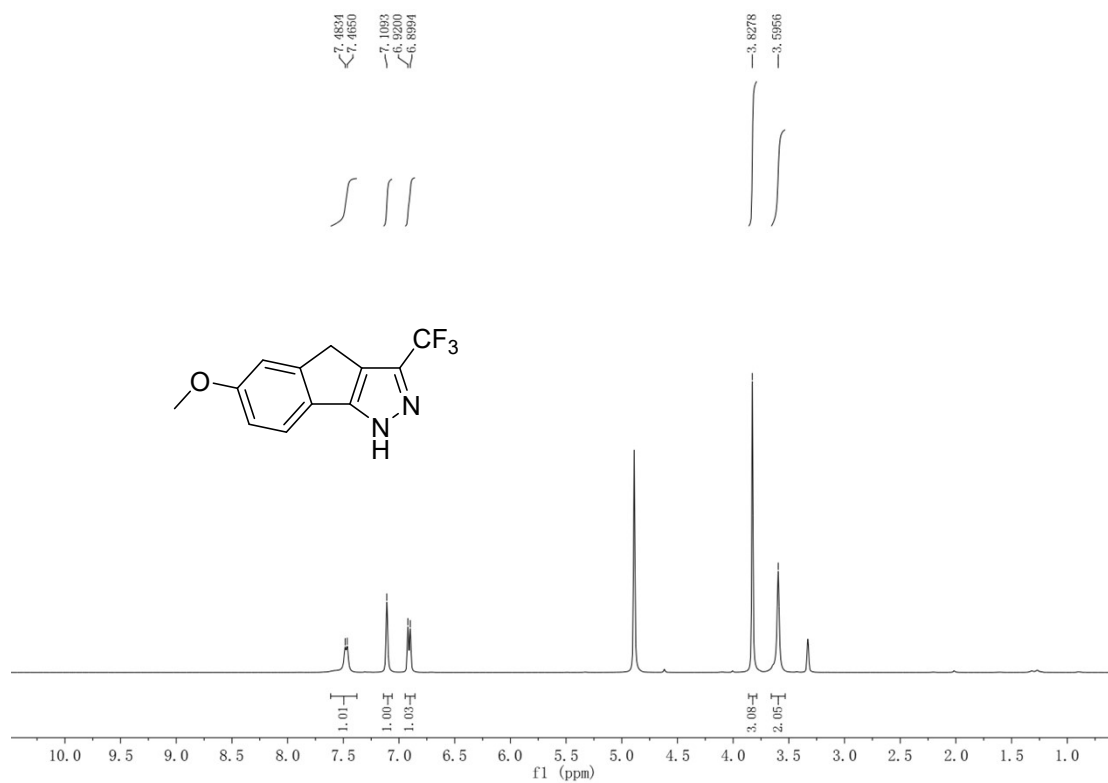
¹³C NMR (100 MHz, CD₃OD) of **2d**:



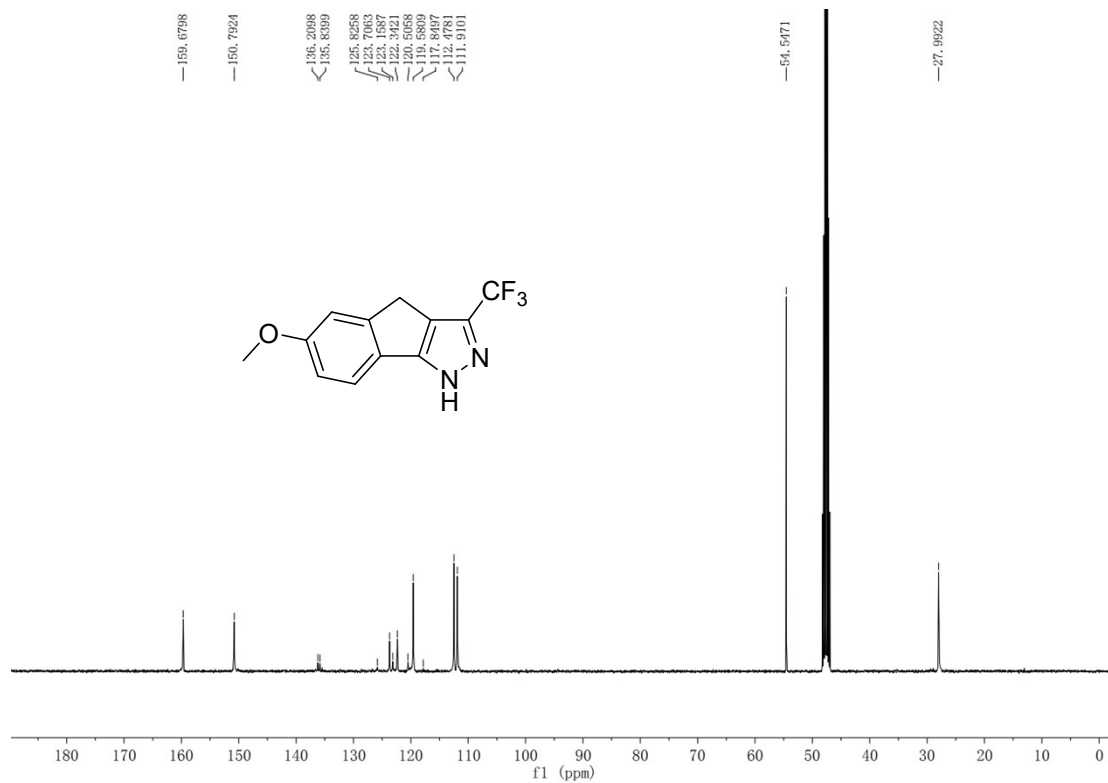
¹⁹F NMR (376 MHz, CD₃OD) of **2d**:



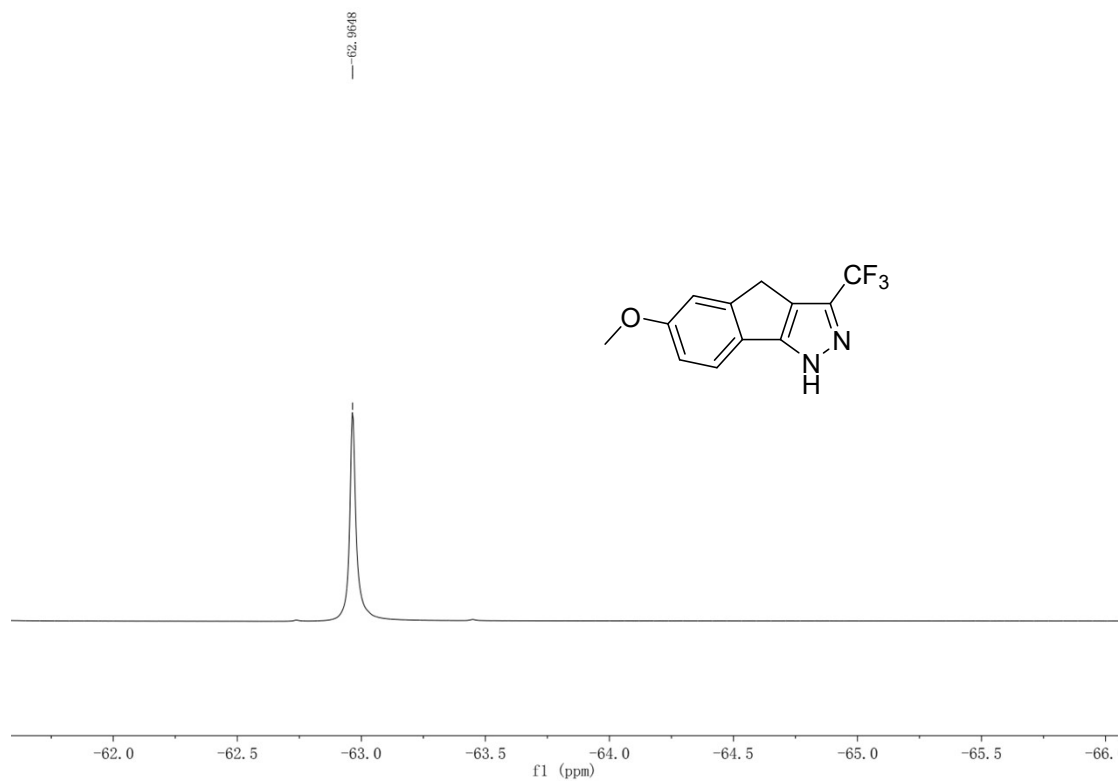
^1H NMR (400 MHz, CD_3OD) of **2e**:



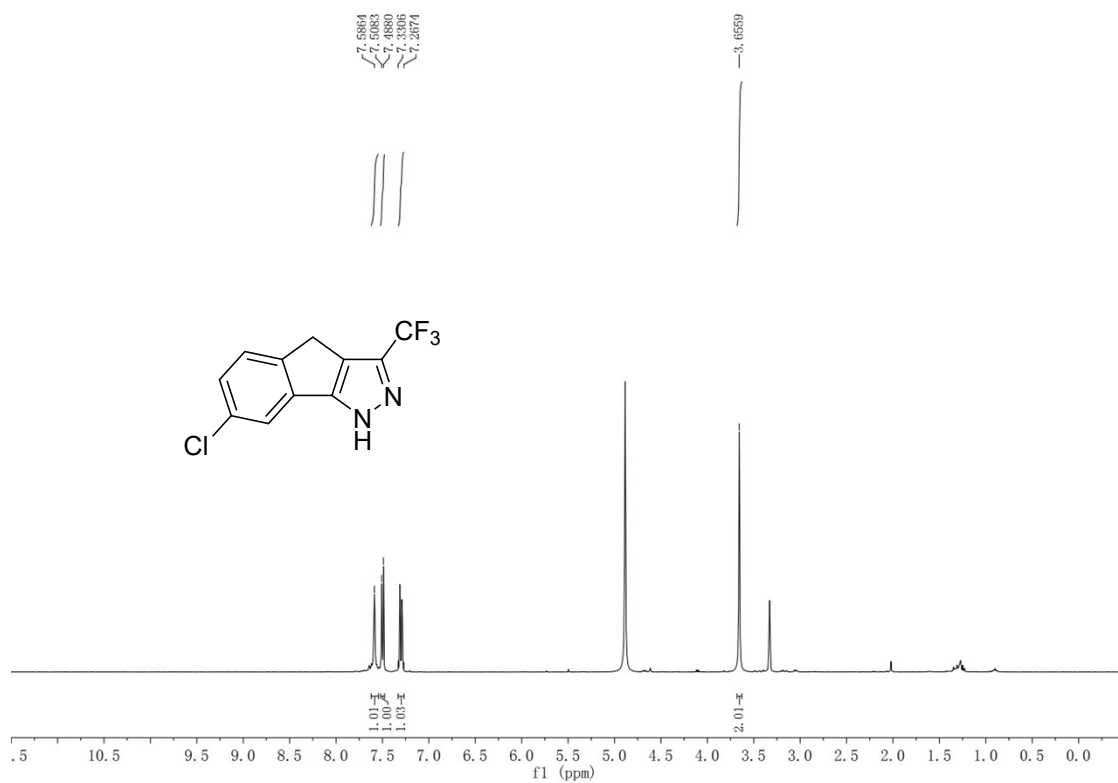
^{13}C NMR (100 MHz, CD_3OD) of **2e**:



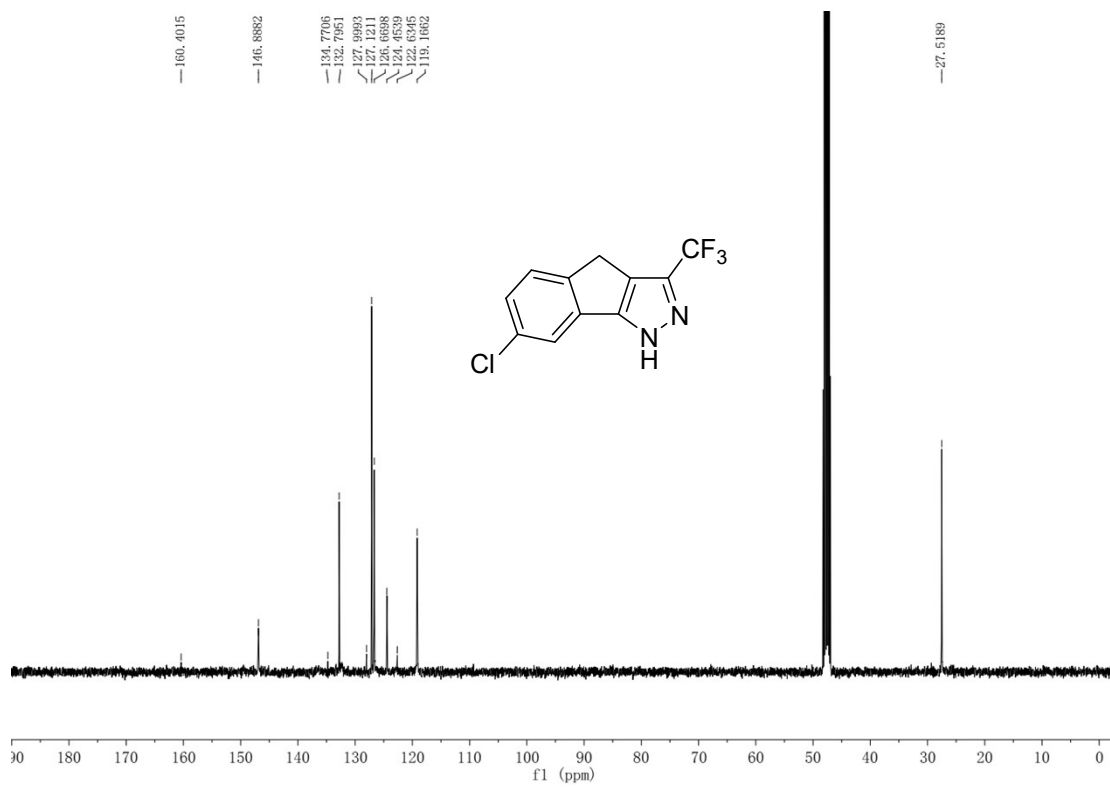
^{19}F NMR (376 MHz, CD_3OD) of **2e**:



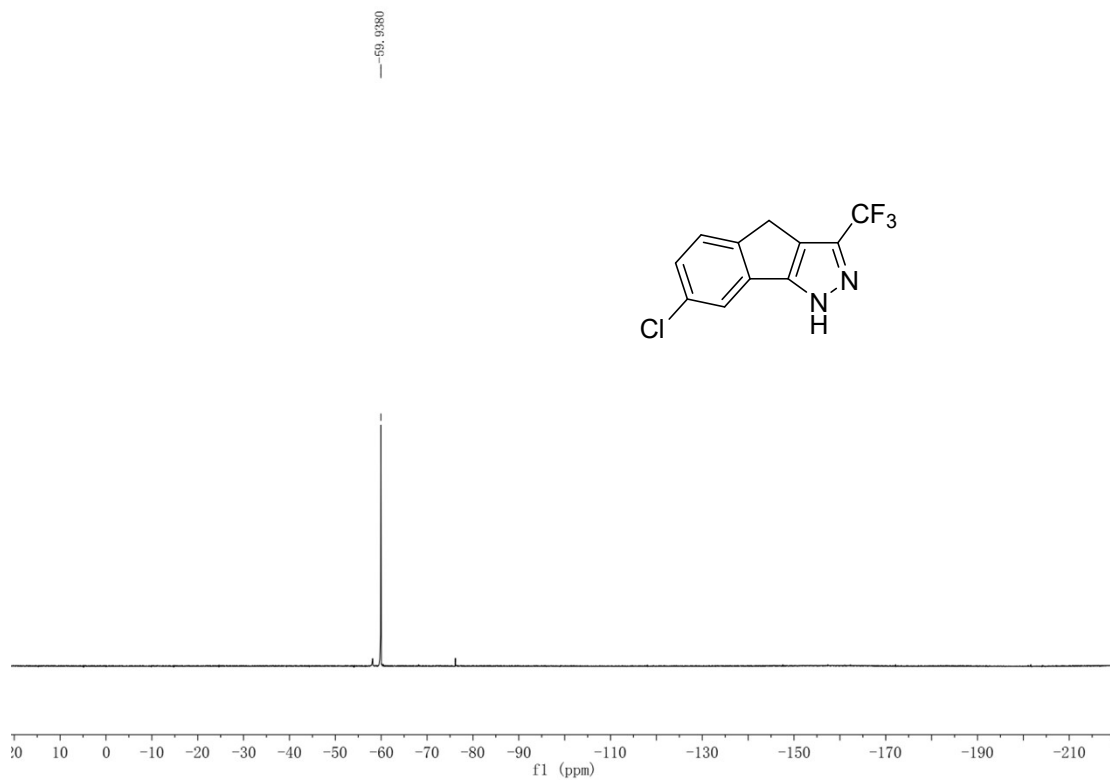
^1H NMR (400 MHz, CD_3OD) of **2f**:



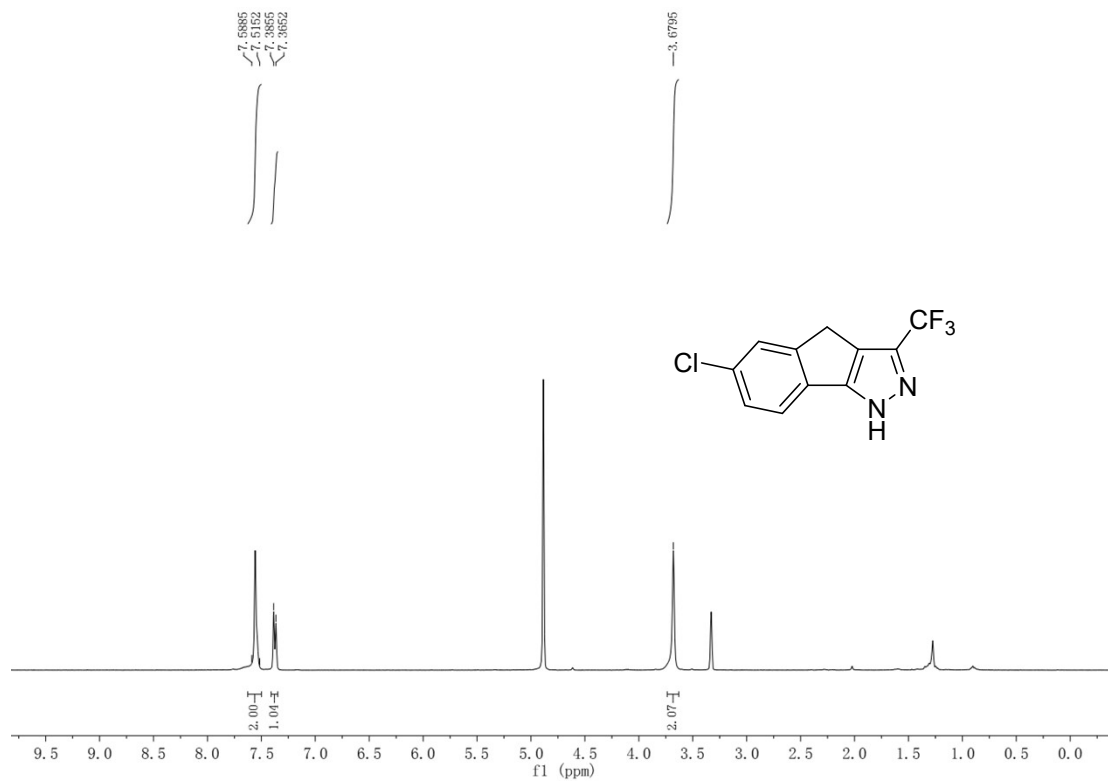
^{13}C NMR (100 MHz, CD_3OD) of **2f**:



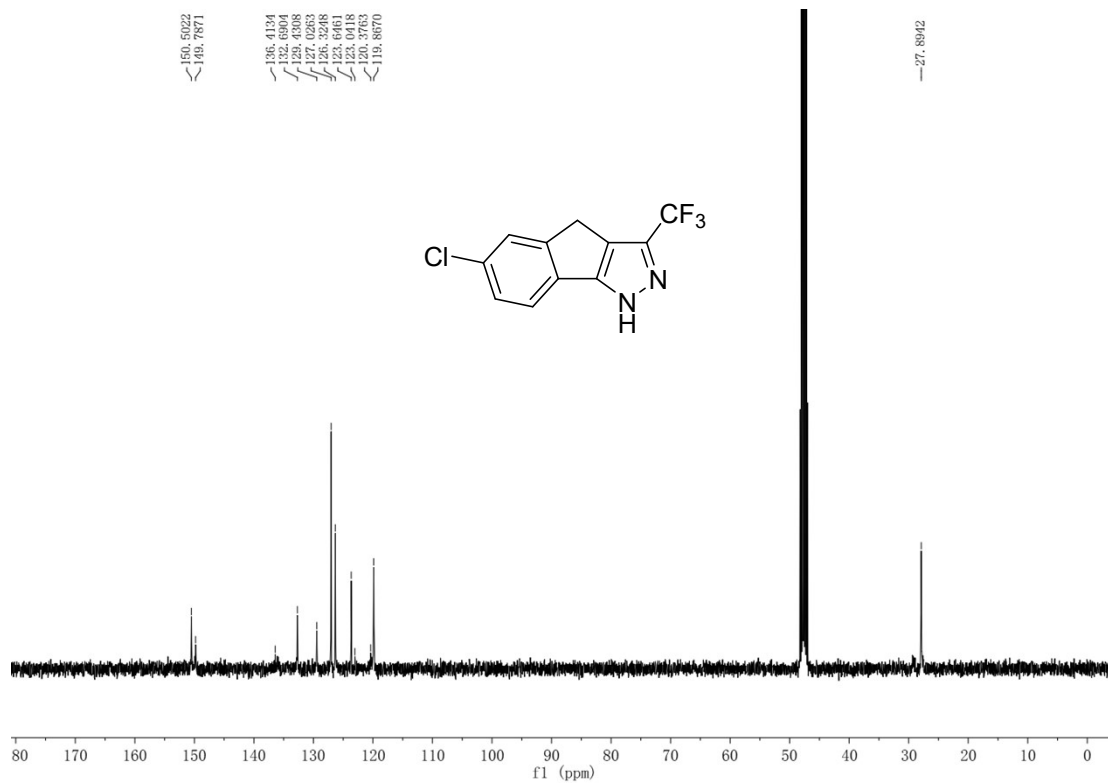
^{19}F NMR (376 MHz, CD_3SOCD_3) of **2f**:



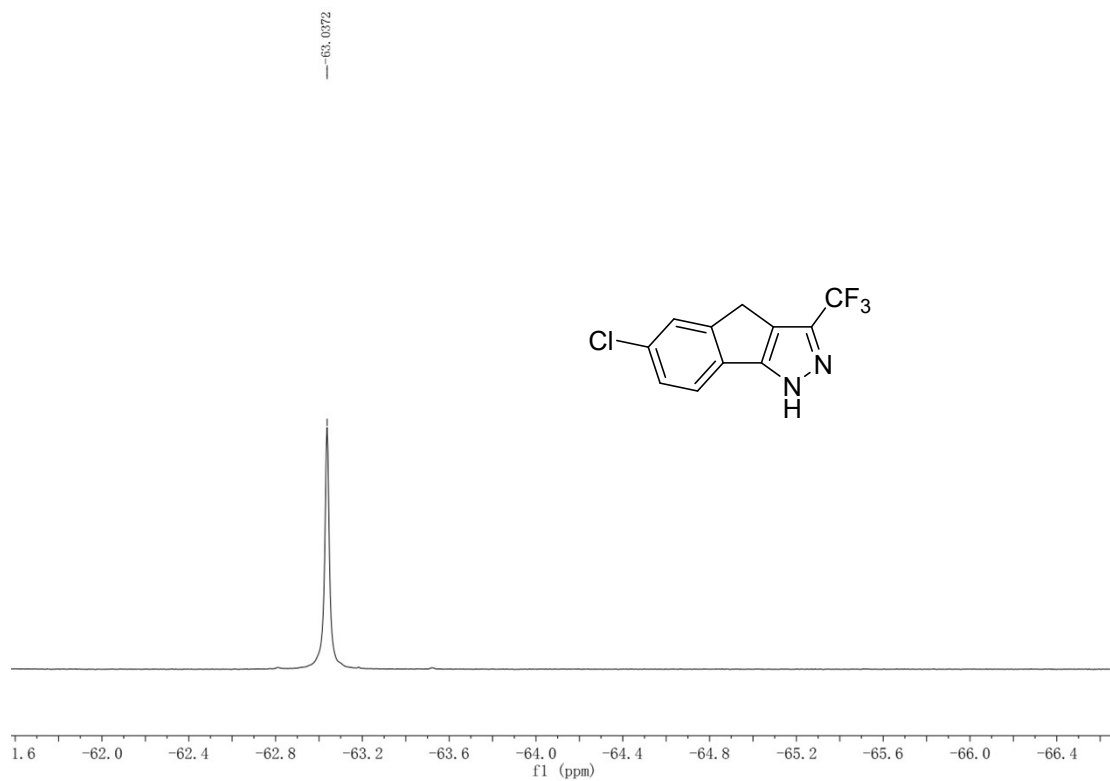
^1H NMR (400 MHz, CD_3OD) of **2g**:



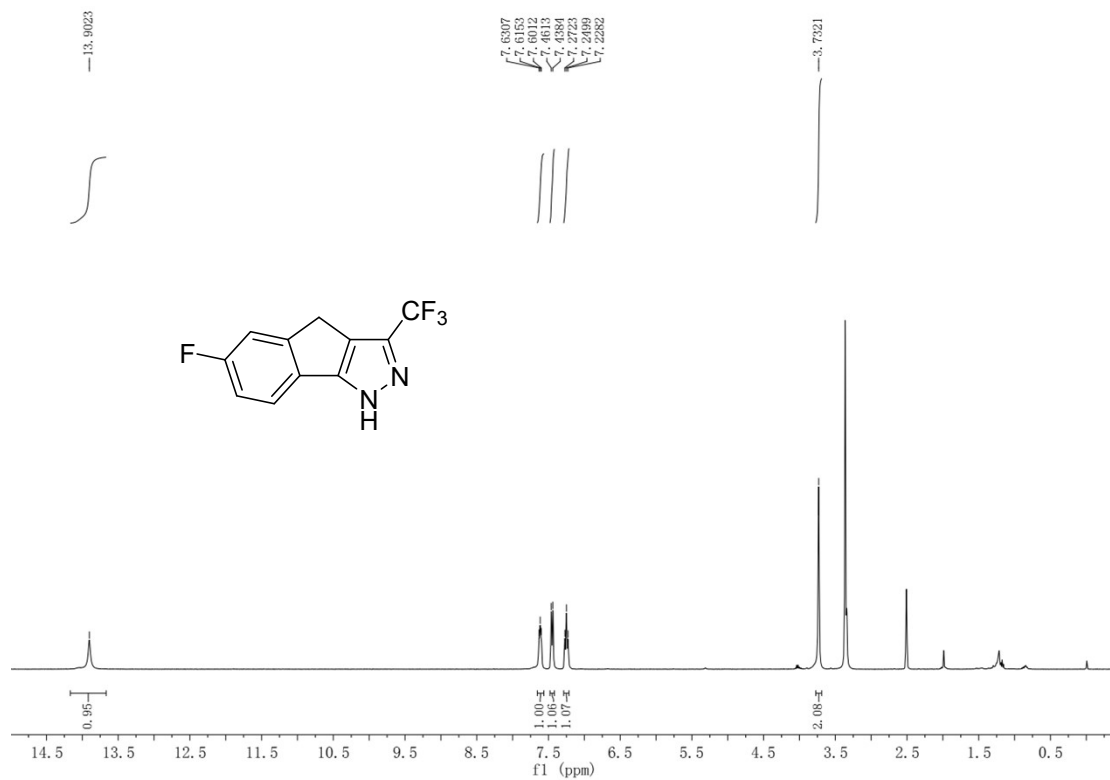
^{13}C NMR (100 MHz, CD_3OD) of **2g**:



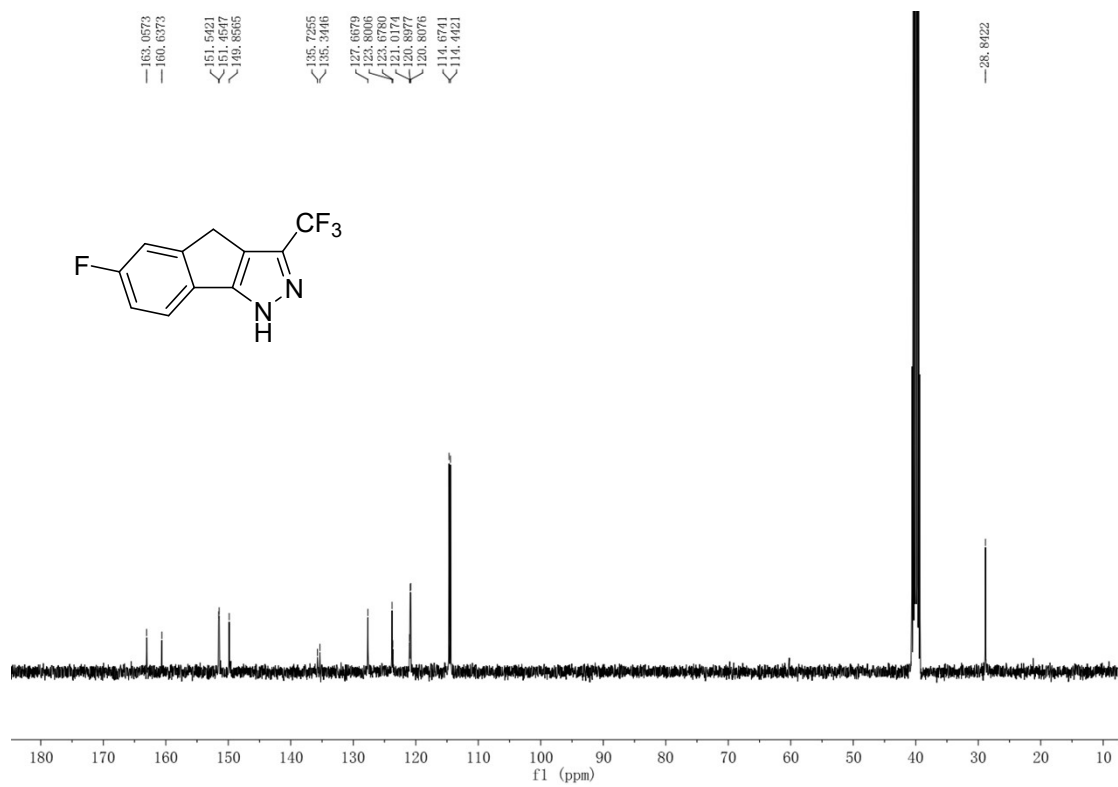
^{19}F NMR (376 MHz, CD_3OD) of **2g**:



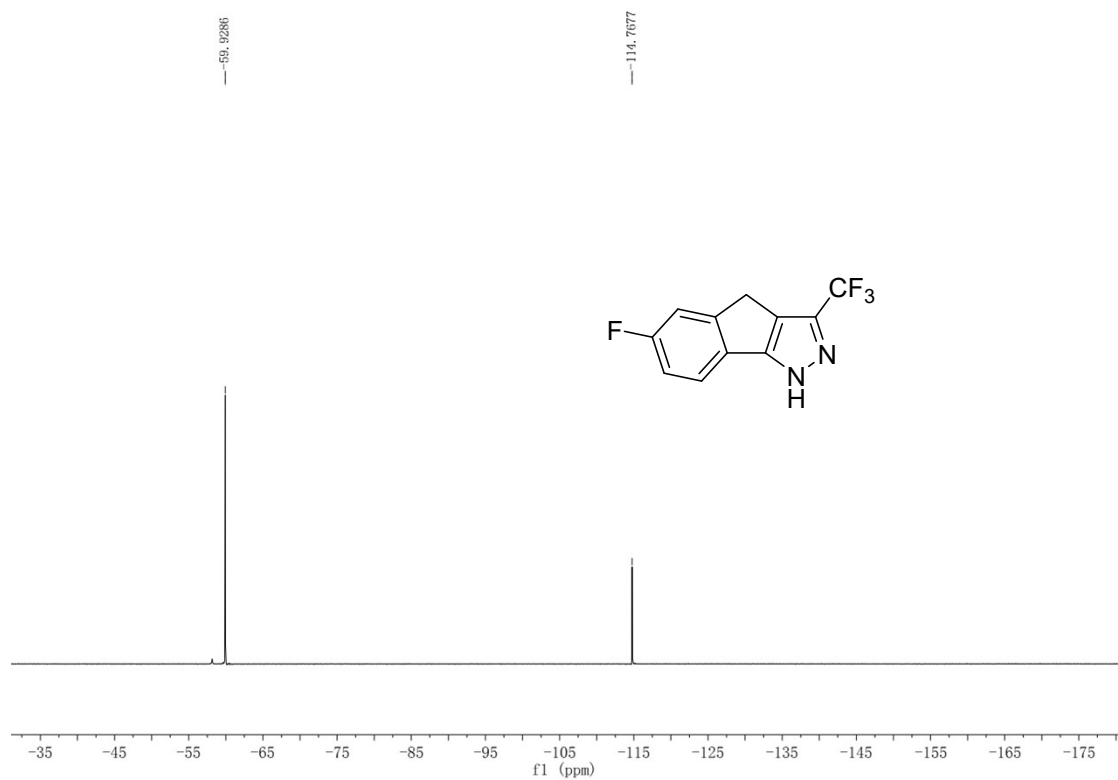
^1H NMR (400 MHz, CD_3SOCD_3) of **2h**:



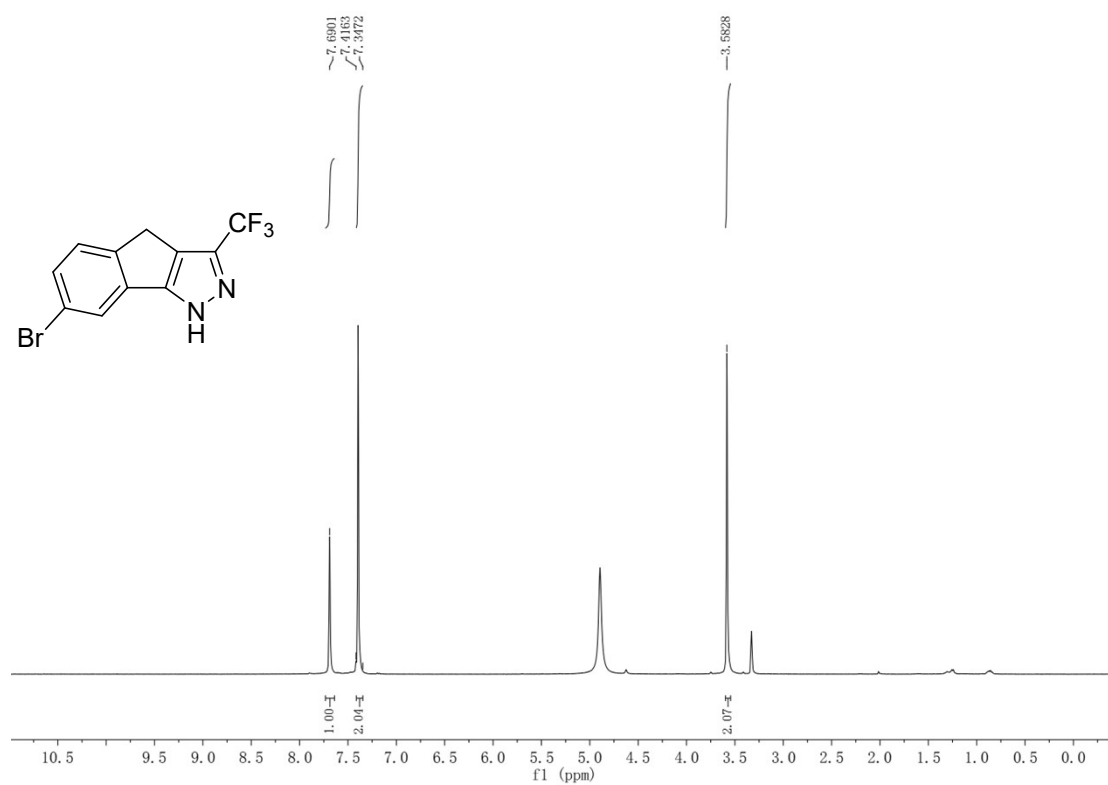
^{13}C NMR (100 MHz, CD_3SOCD_3) of **2h**:



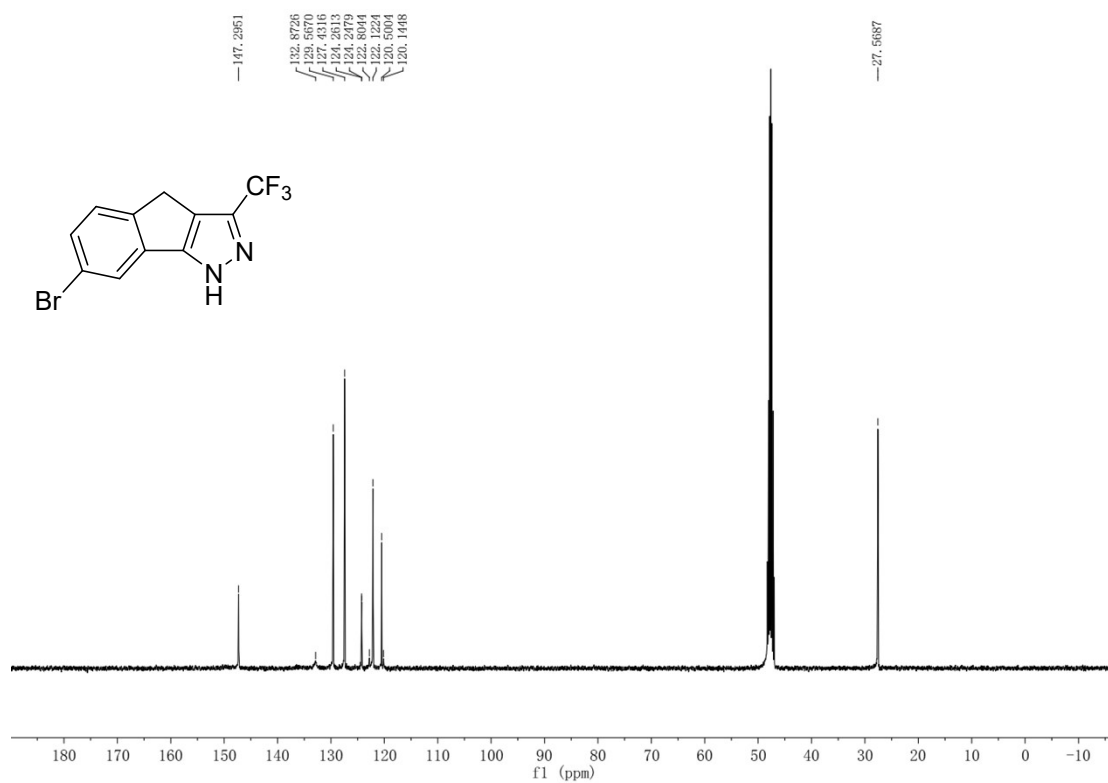
^{19}F NMR (376 MHz, CD_3SOCD_3) of **2h**:



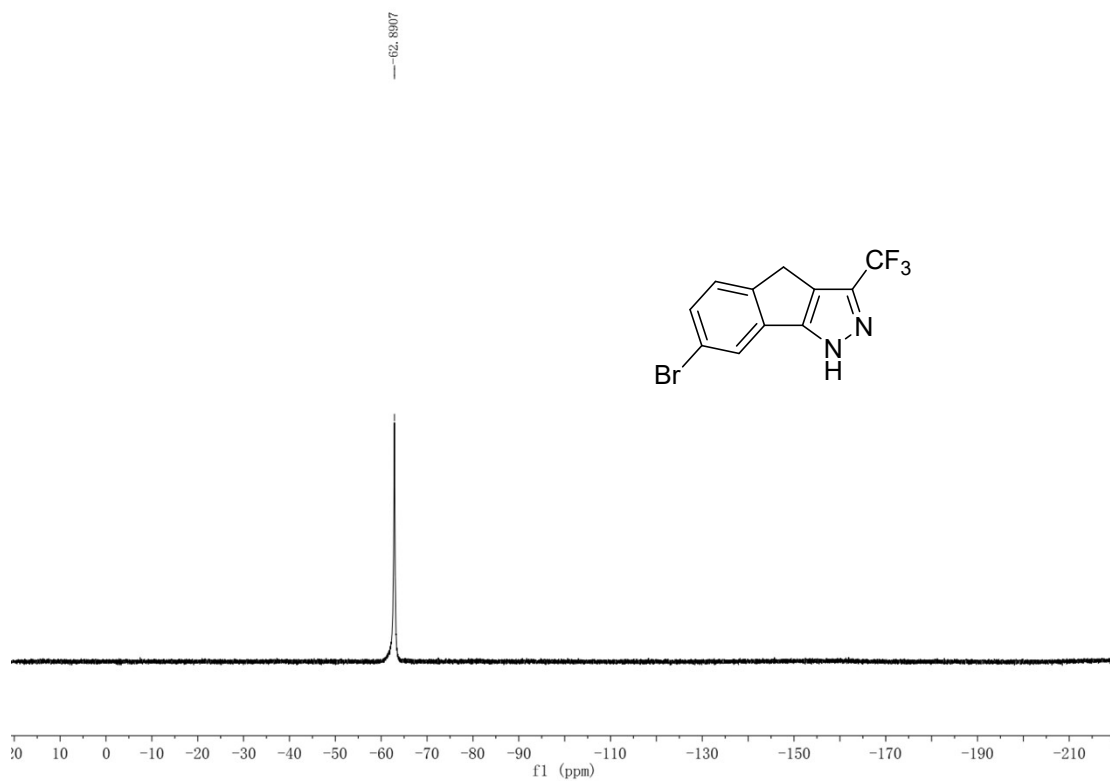
^1H NMR (400 MHz, CD_3OD) of **2i**:



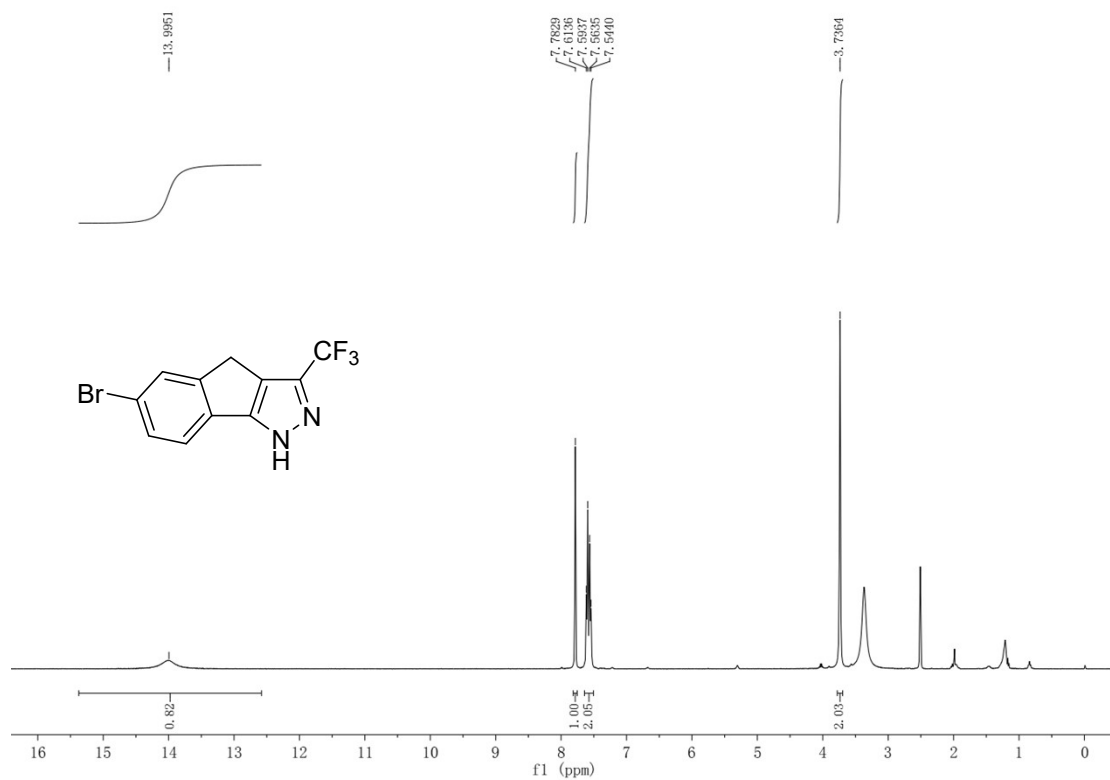
^{13}C NMR (100 MHz, CD_3OD) of **2i**:



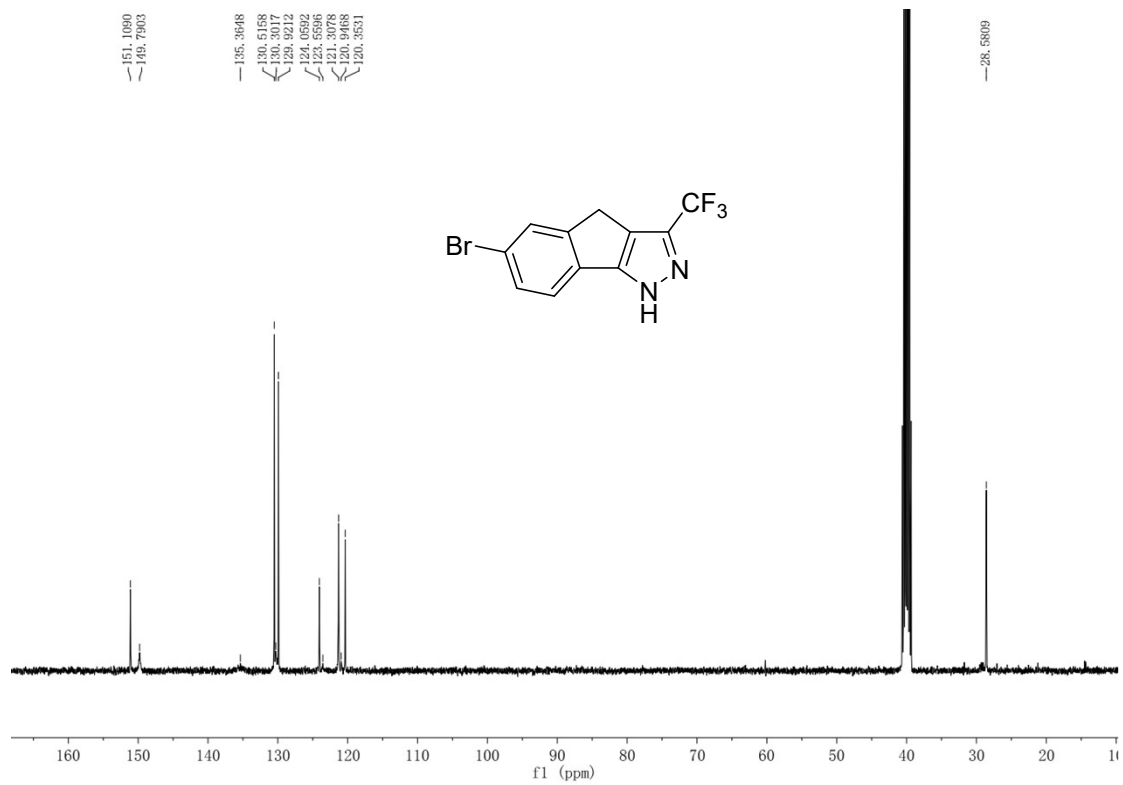
^{19}F NMR (376 MHz, CD_3OD) of **2i**:



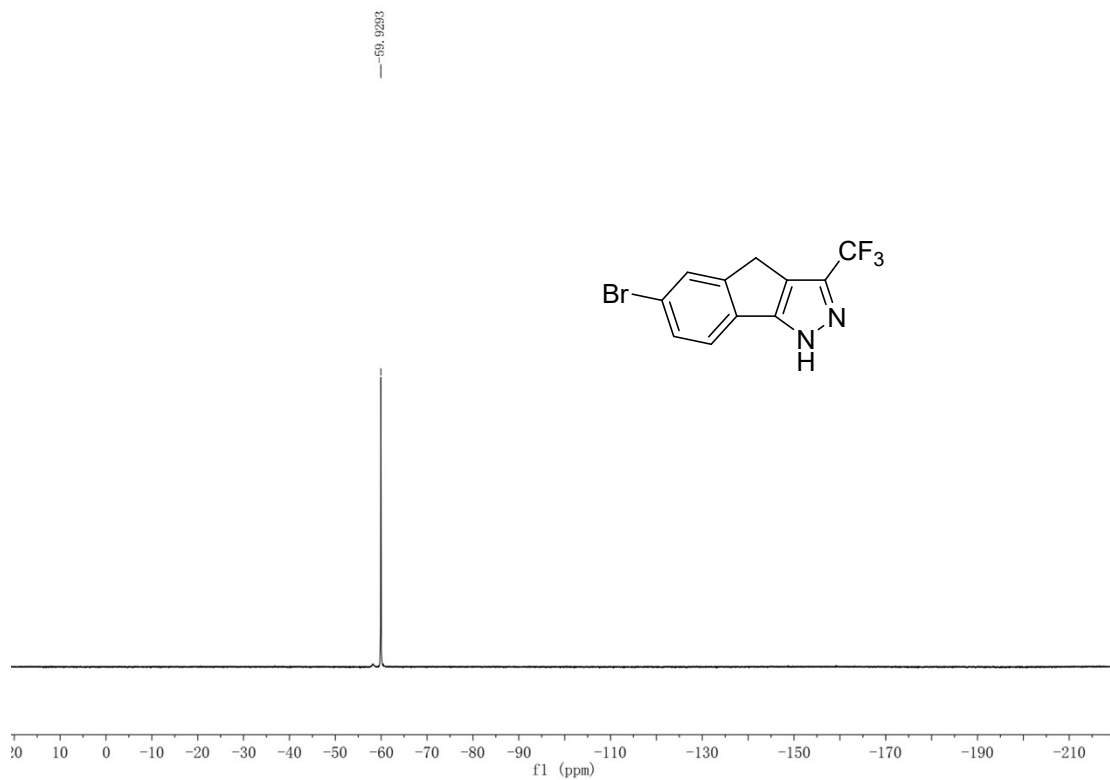
^1H NMR (400 MHz, CD_3SOCD_3) of **2j**:



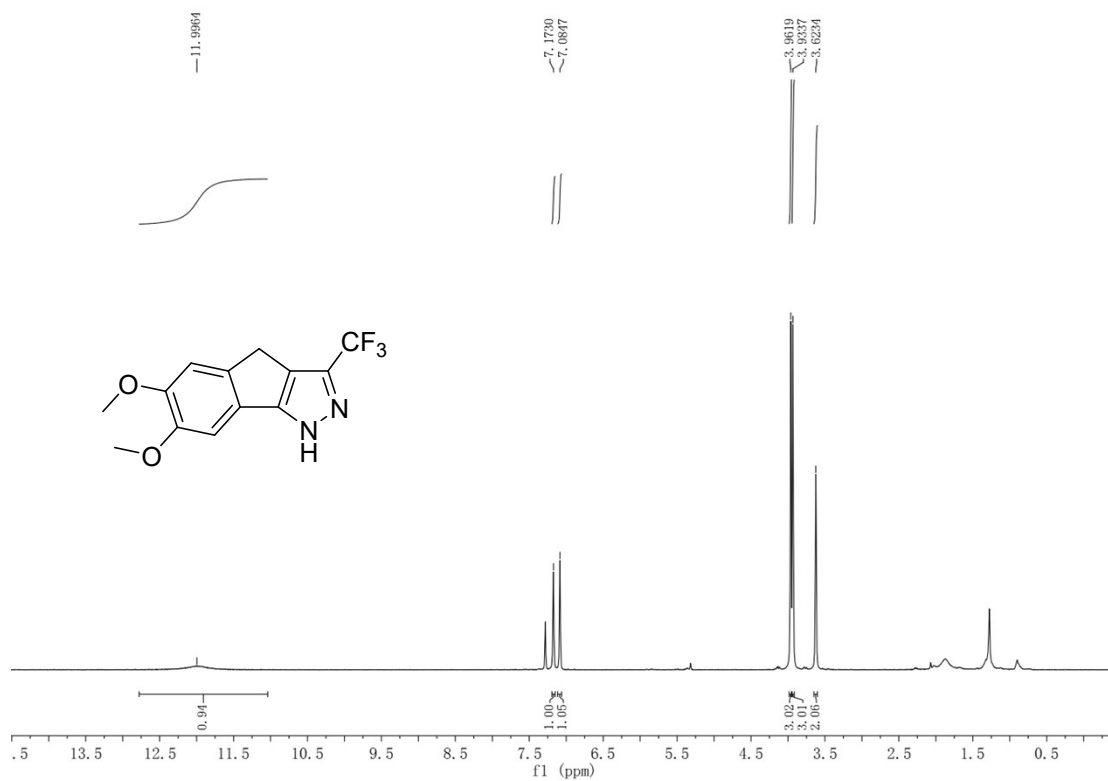
^{13}C NMR (100 MHz, CD_3SOCD_3) of **2j**:



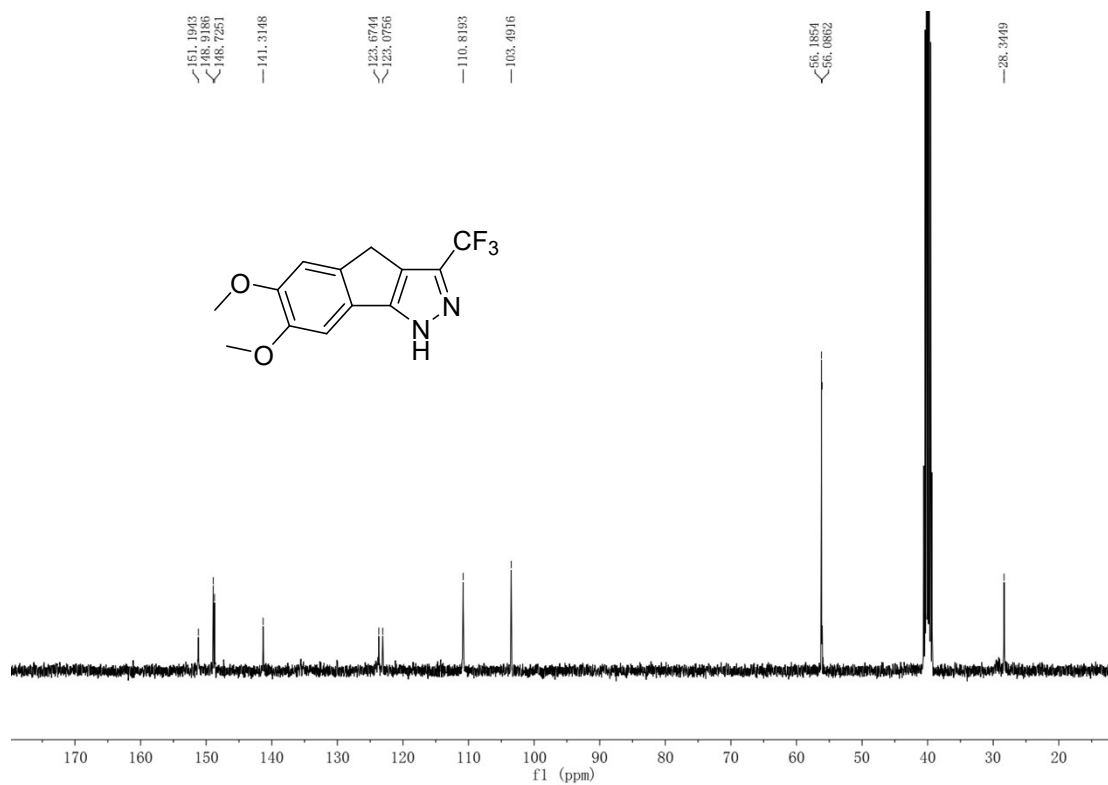
^{19}F NMR (376 MHz, CD_3SOCD_3) of **2j**:



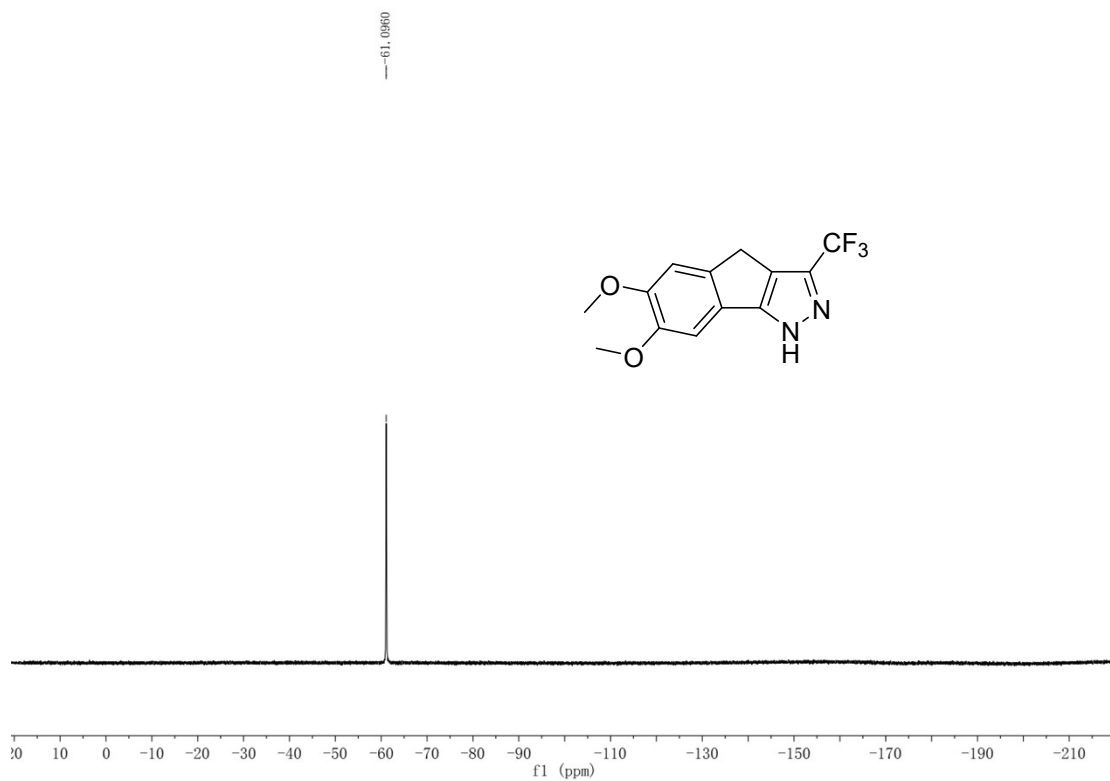
^1H NMR (400 MHz, CDCl_3) of **2k**:



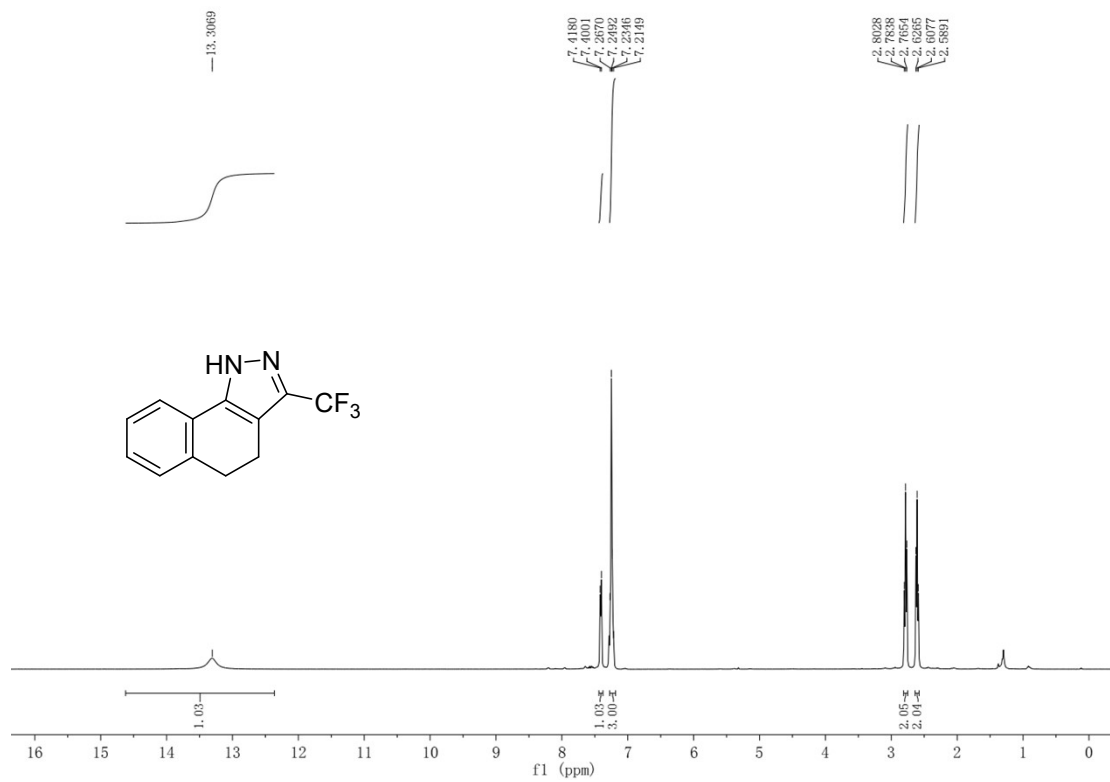
^{13}C NMR (100 MHz, CD_3SOCD_3) of **2k**:



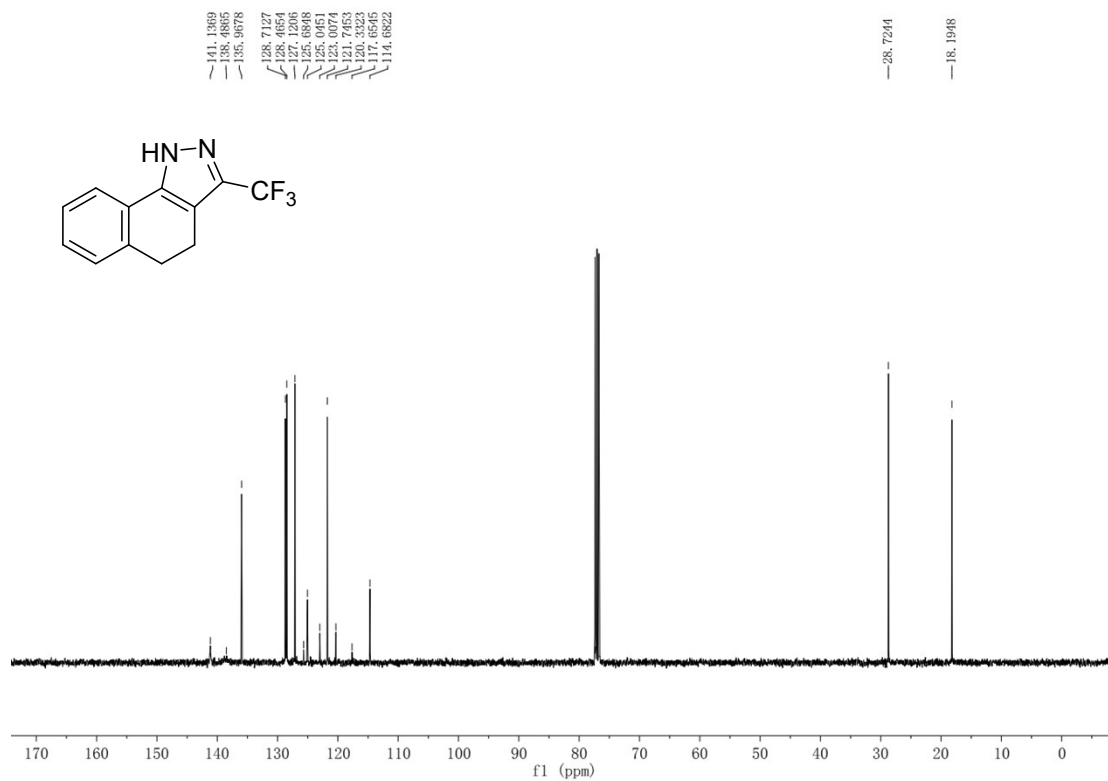
^{19}F NMR (376 MHz, CDCl_3) of **2k**:



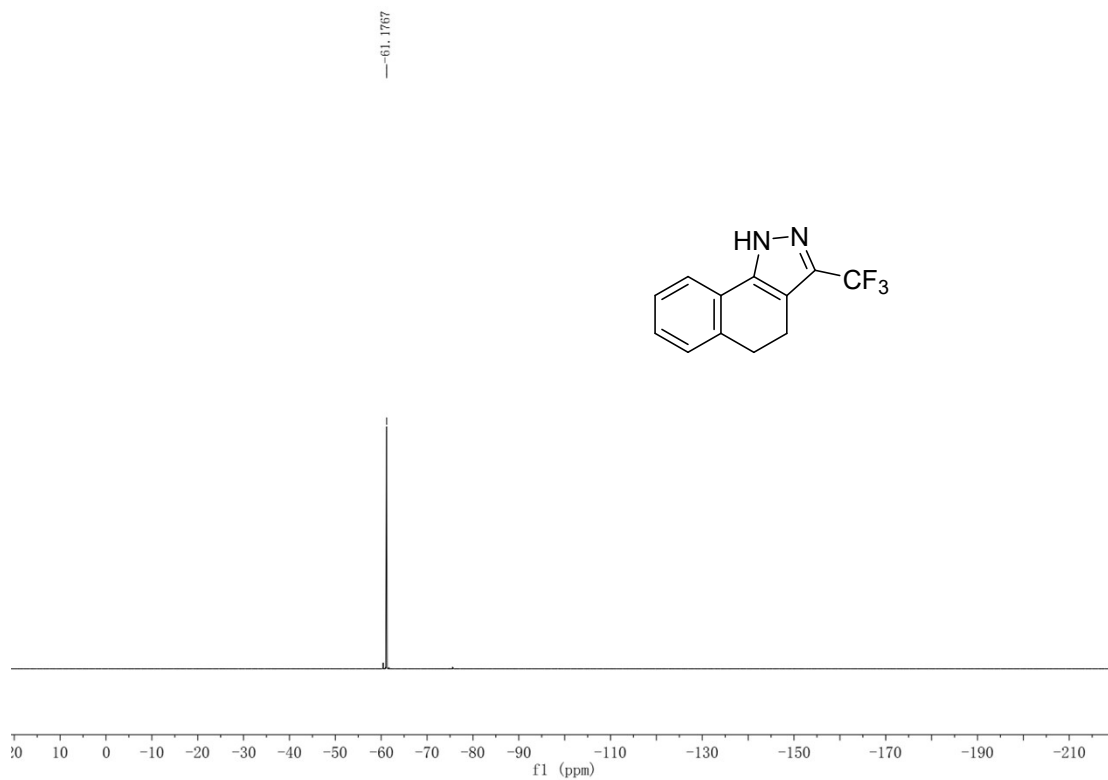
^1H NMR (400 MHz, CDCl_3) of **2l**:



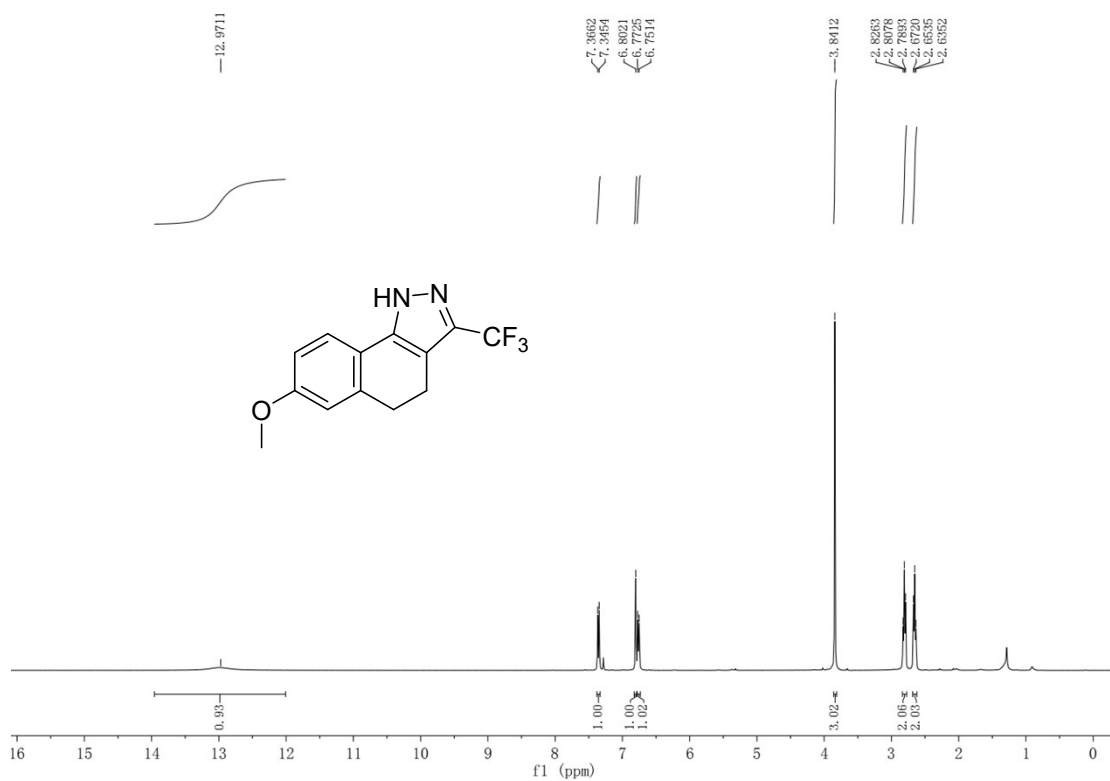
¹³C NMR (100 MHz, CDCl₃) of **21**:



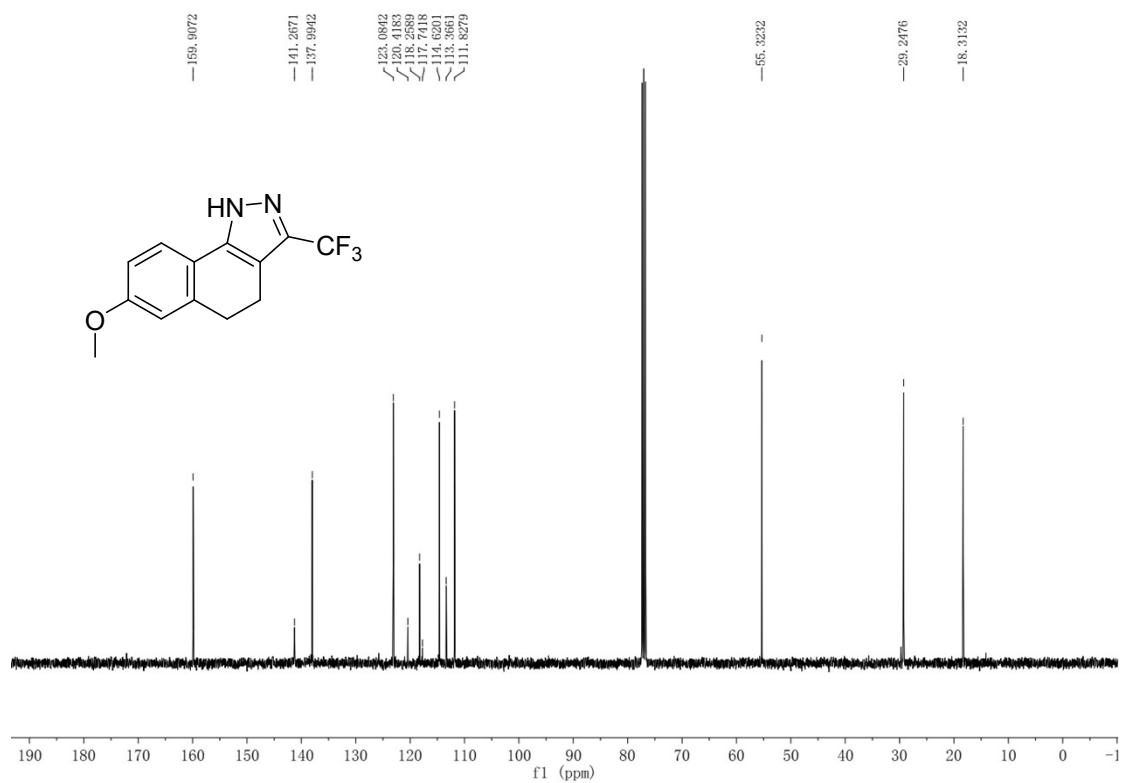
¹⁹F NMR (376 MHz, CDCl₃) of **21**:



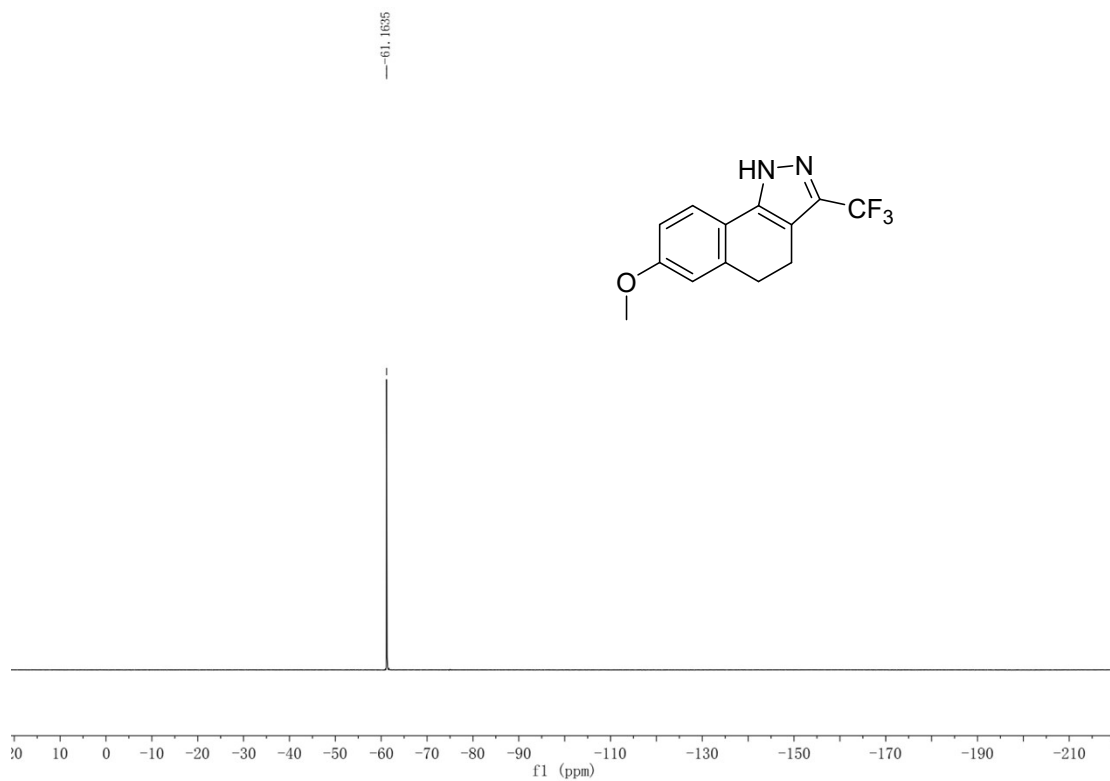
^1H NMR (400 MHz, CDCl_3) of **2m**:



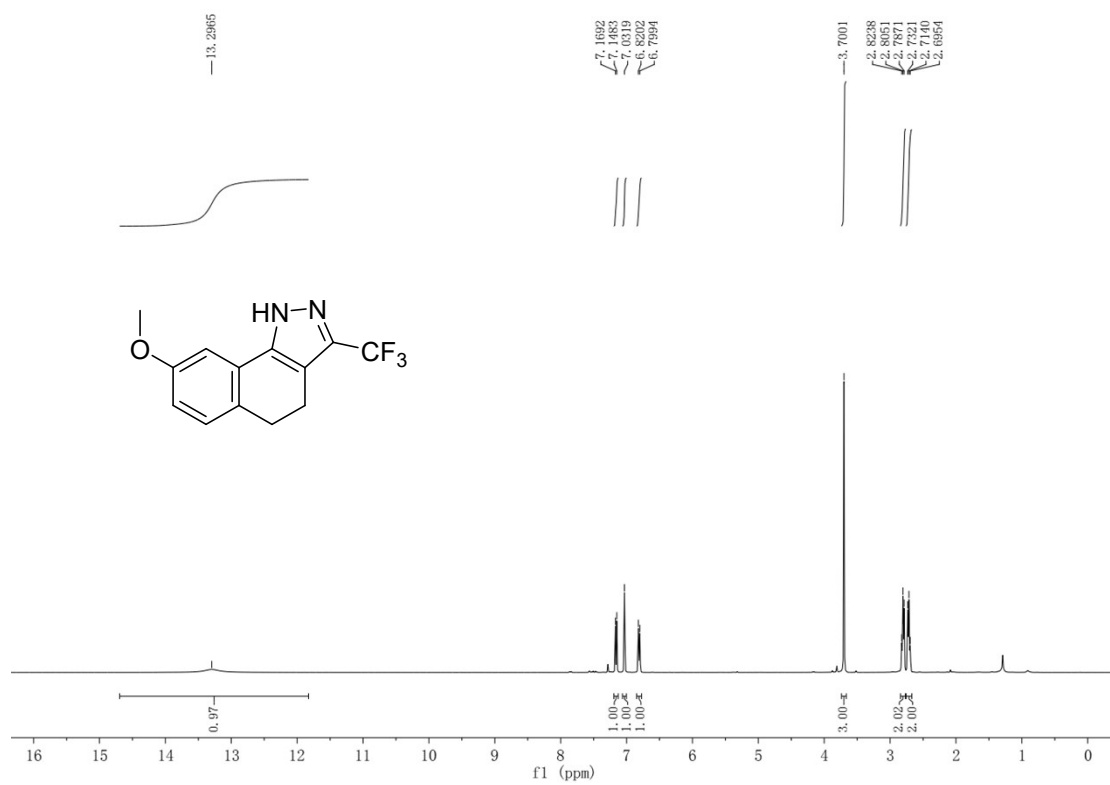
^{13}C NMR (100 MHz, CDCl_3) of **2m**:



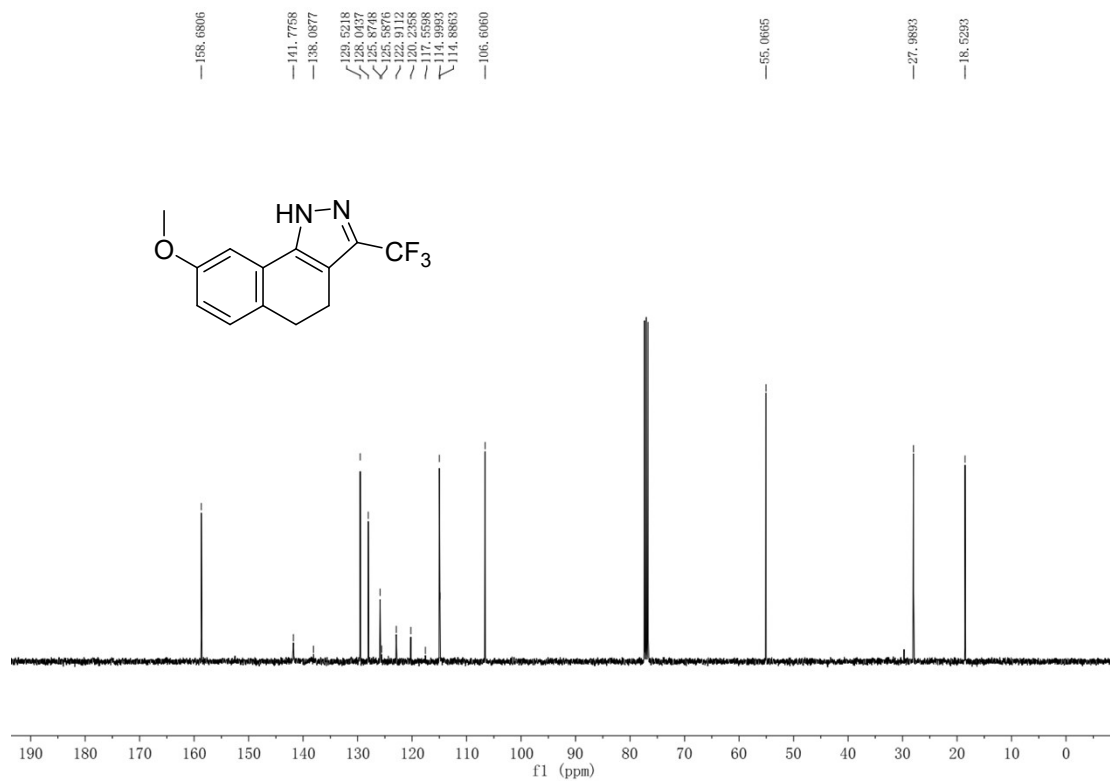
^{19}F NMR (376 MHz, CDCl_3) of **2m**:



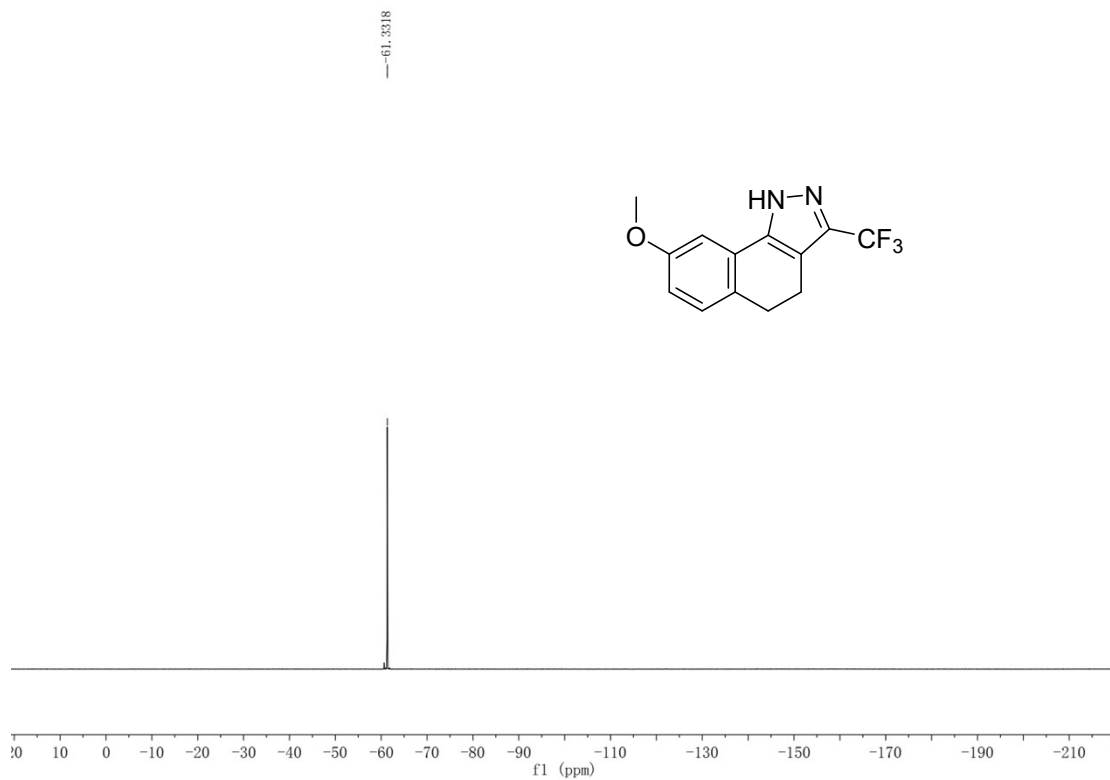
^1H NMR (400 MHz, CDCl_3) of **2n**:



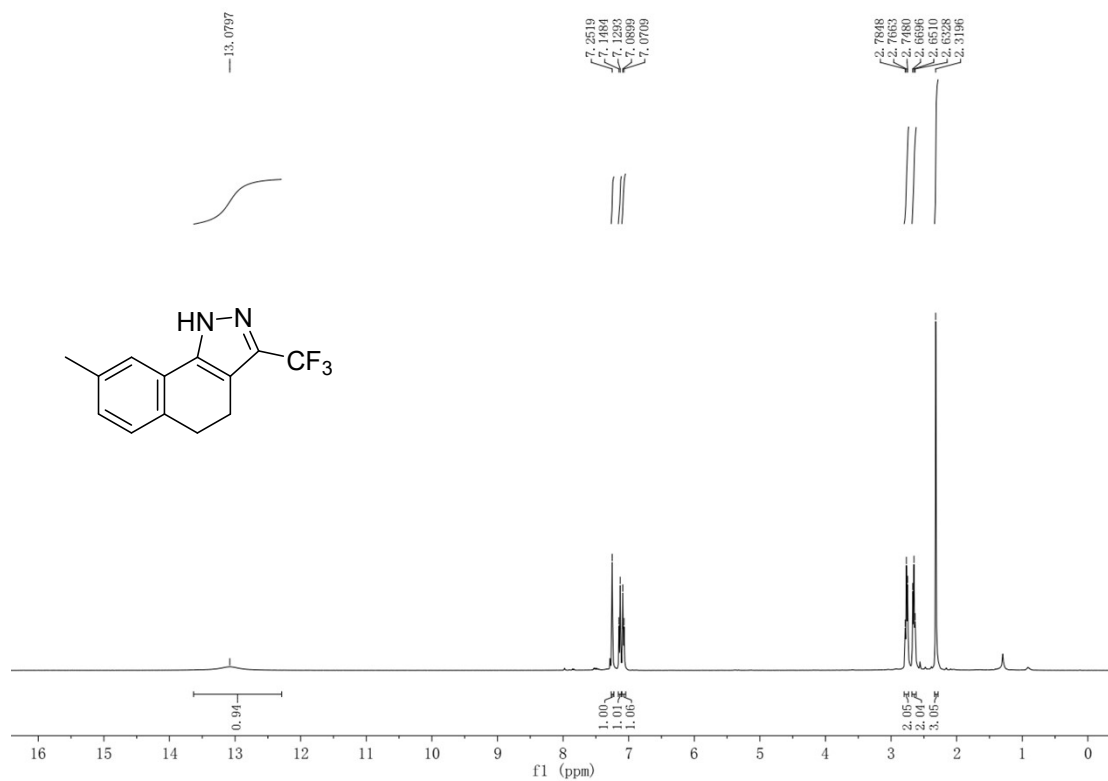
¹³C NMR (100 MHz, CDCl₃) of **2n**:



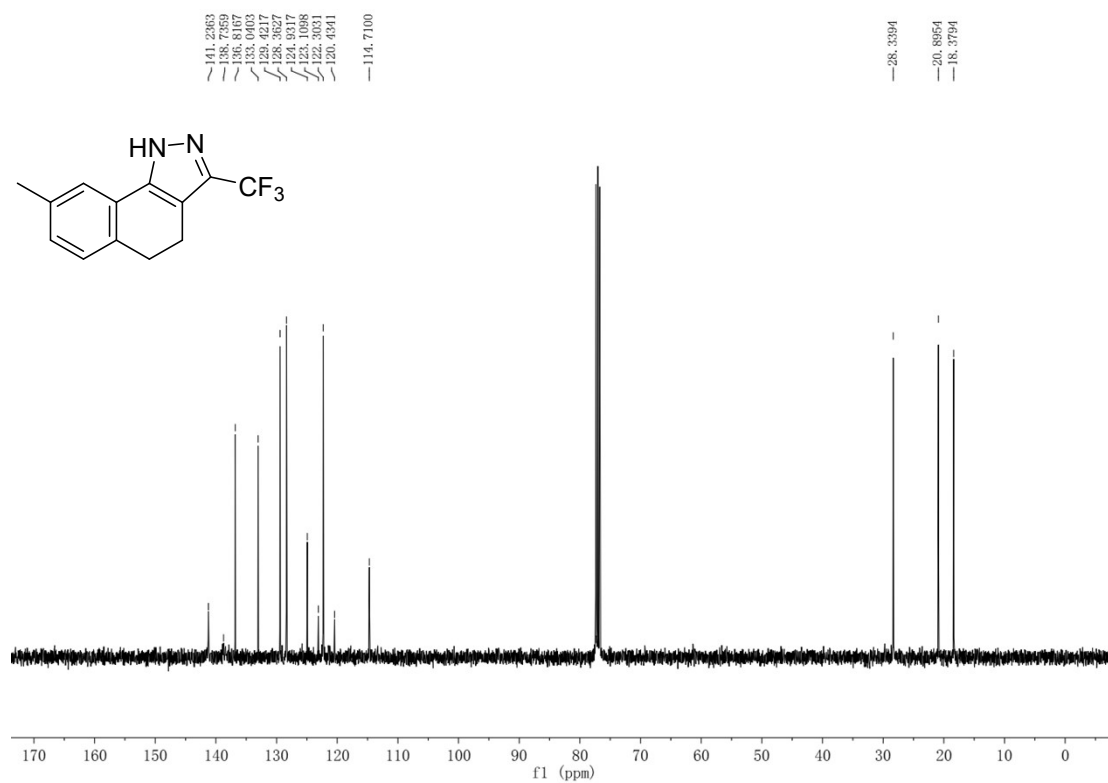
¹⁹F NMR (376 MHz, CDCl₃) of **2n**:



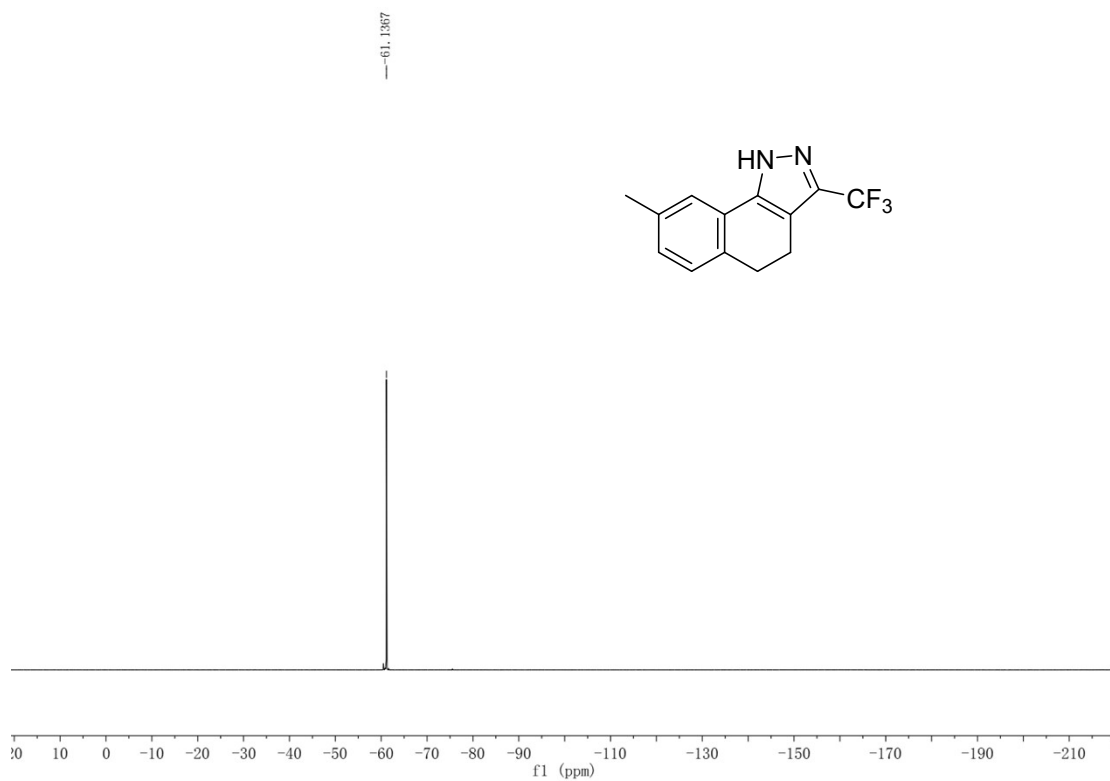
^1H NMR (400 MHz, CDCl_3) of **2o**:



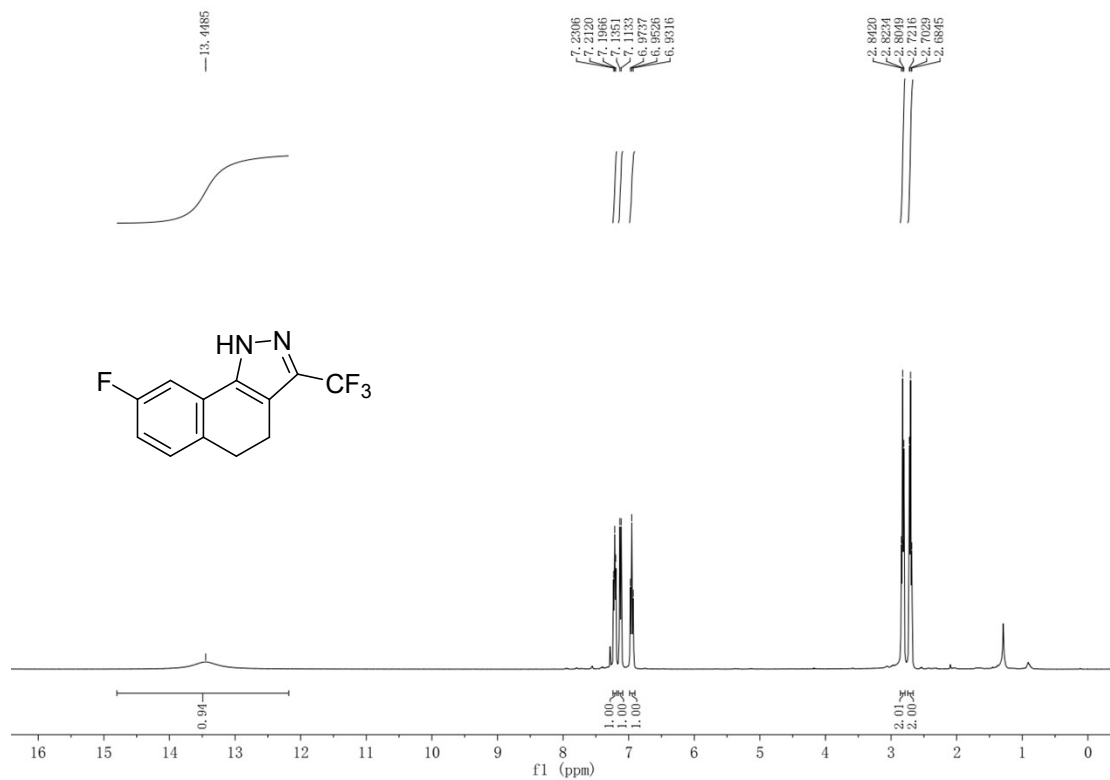
^{13}C NMR (100 MHz, CDCl_3) of **2o**:



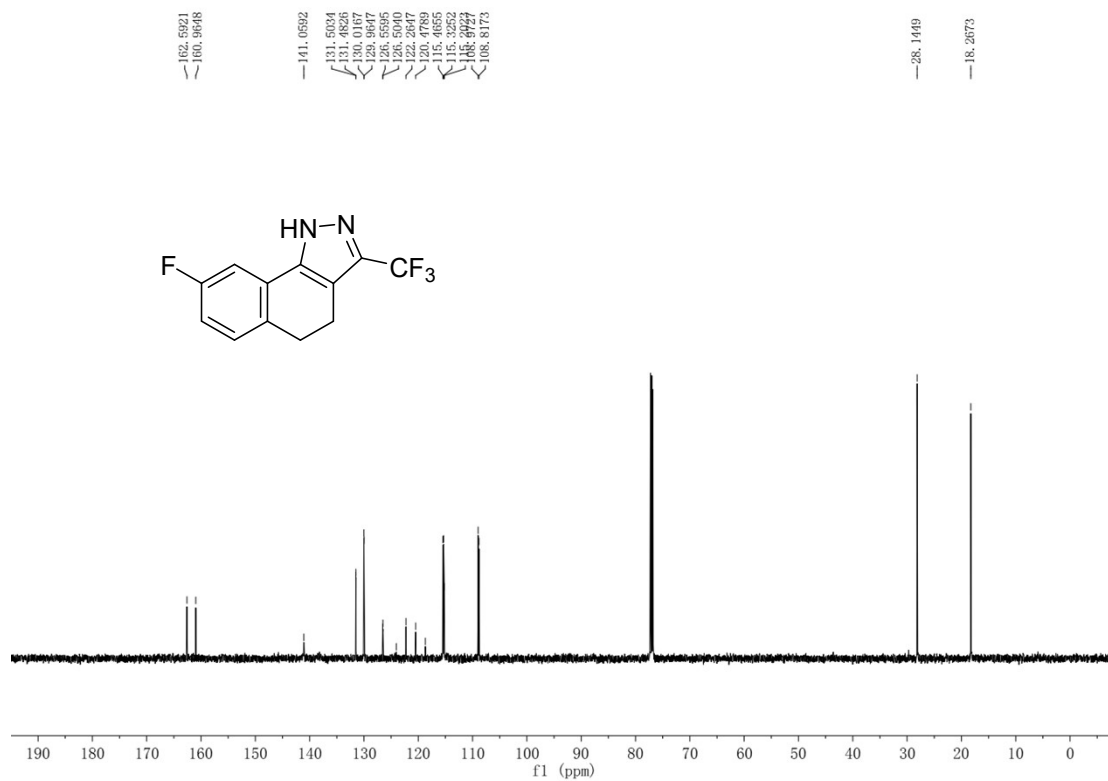
^{19}F NMR (376 MHz, CDCl_3) of **2o**:



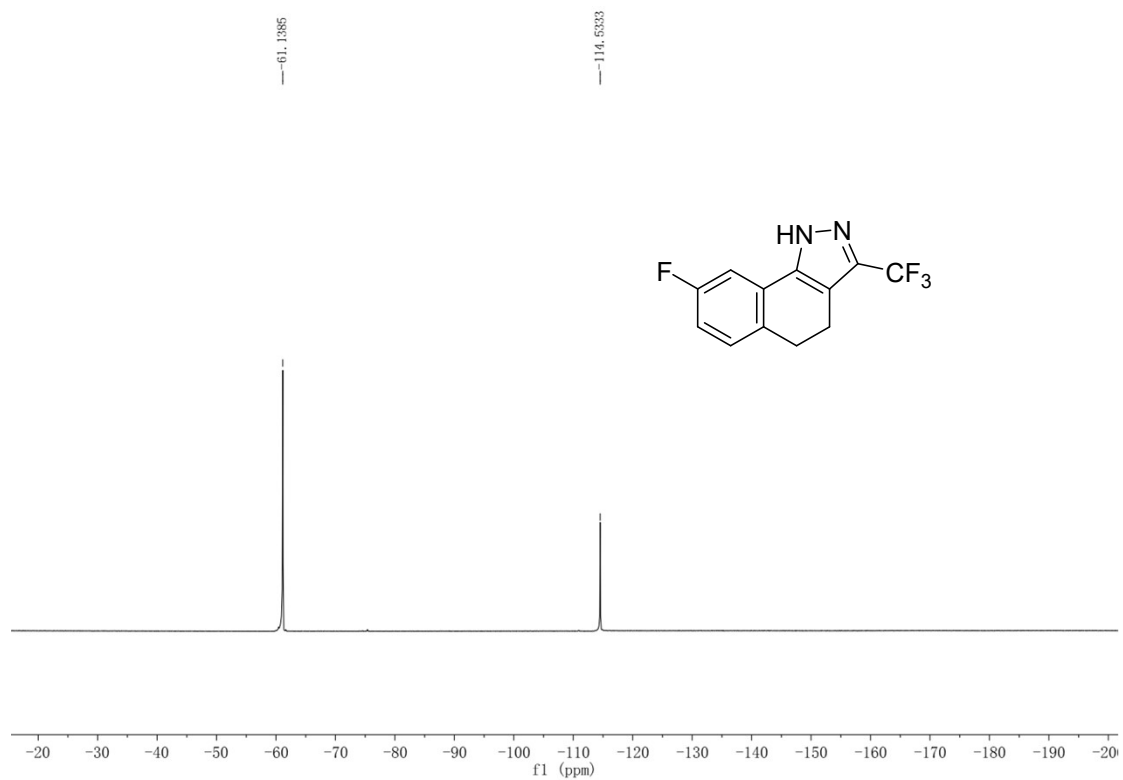
^1H NMR (400 MHz, CDCl_3) of **2p**:



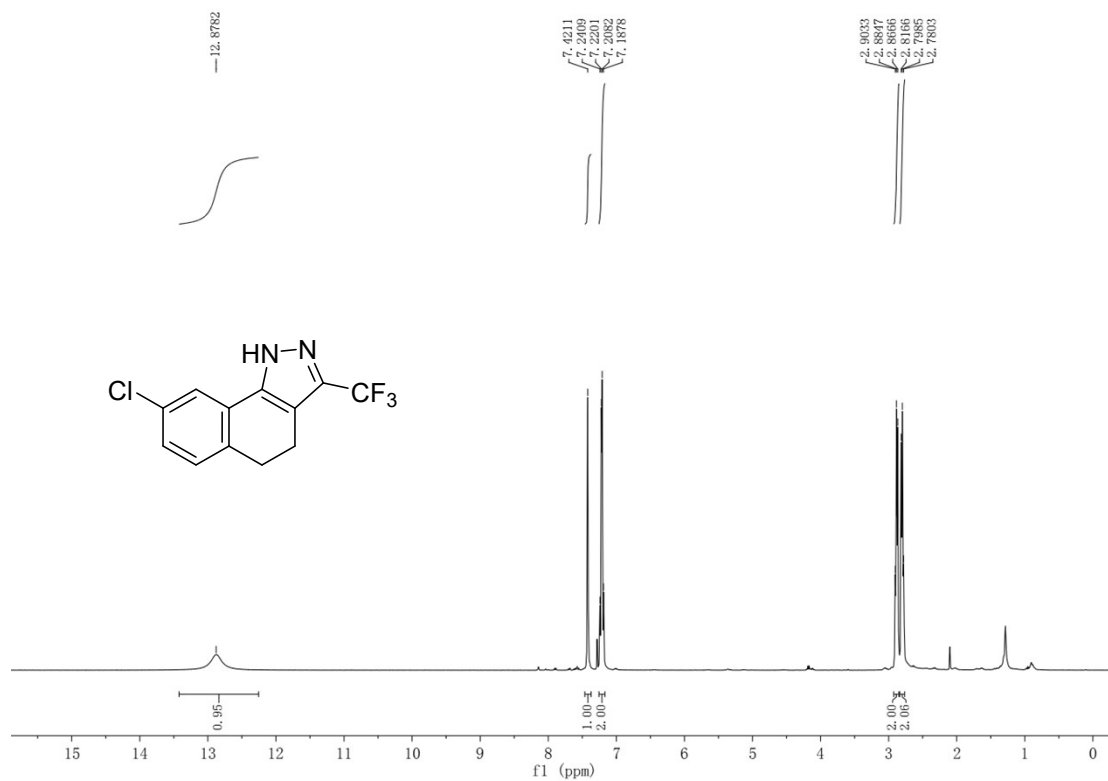
^{13}C NMR (150 MHz, CDCl_3) of **2p**:



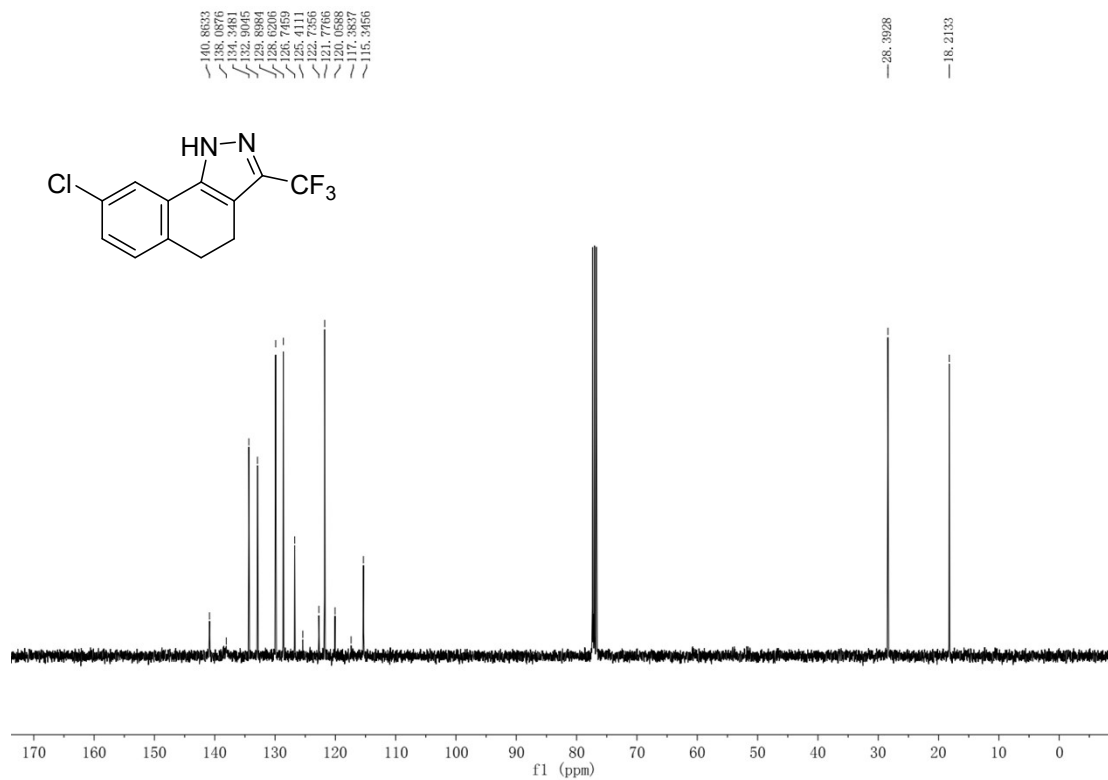
^{19}F NMR (376 MHz, CDCl_3) of **2p**:



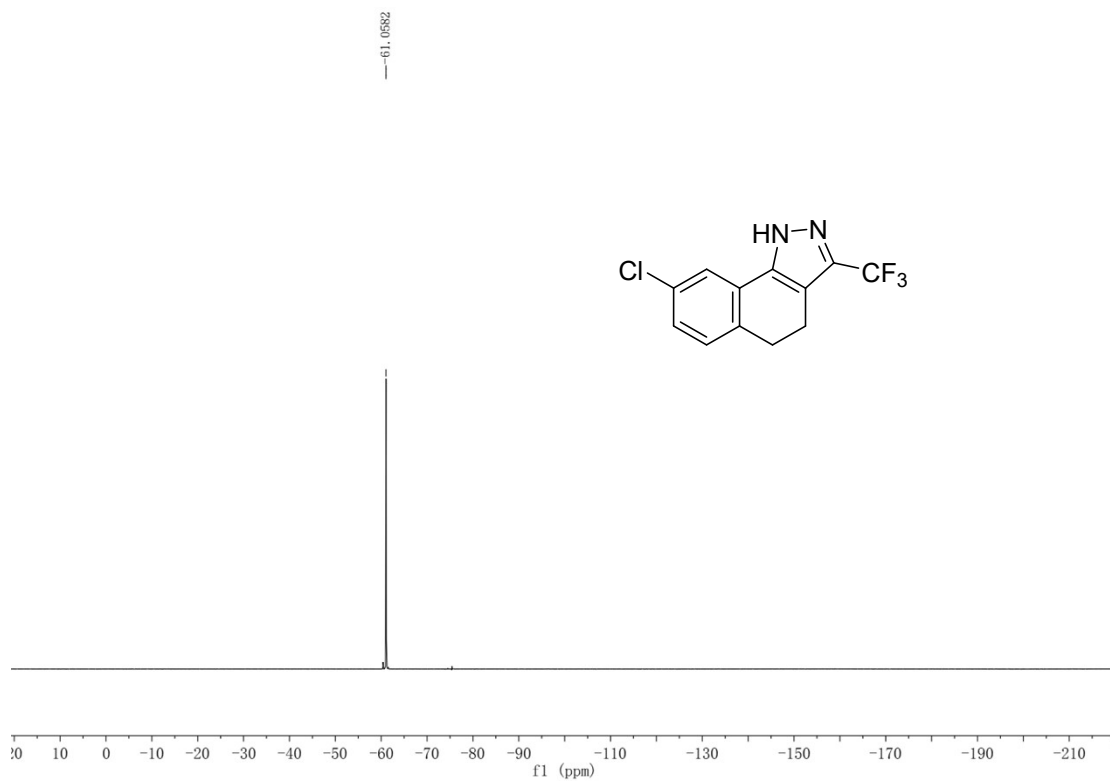
^1H NMR (400 MHz, CDCl_3) of **2q**:



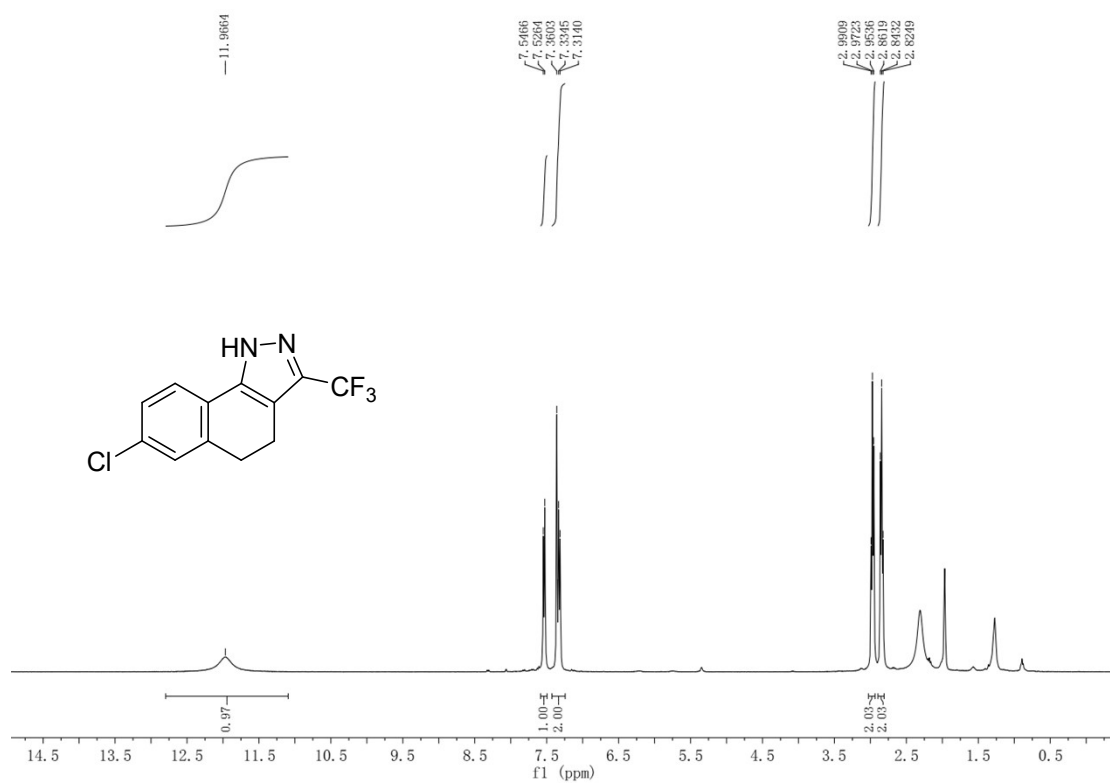
^{13}C NMR (100 MHz, CDCl_3) of **2q**:



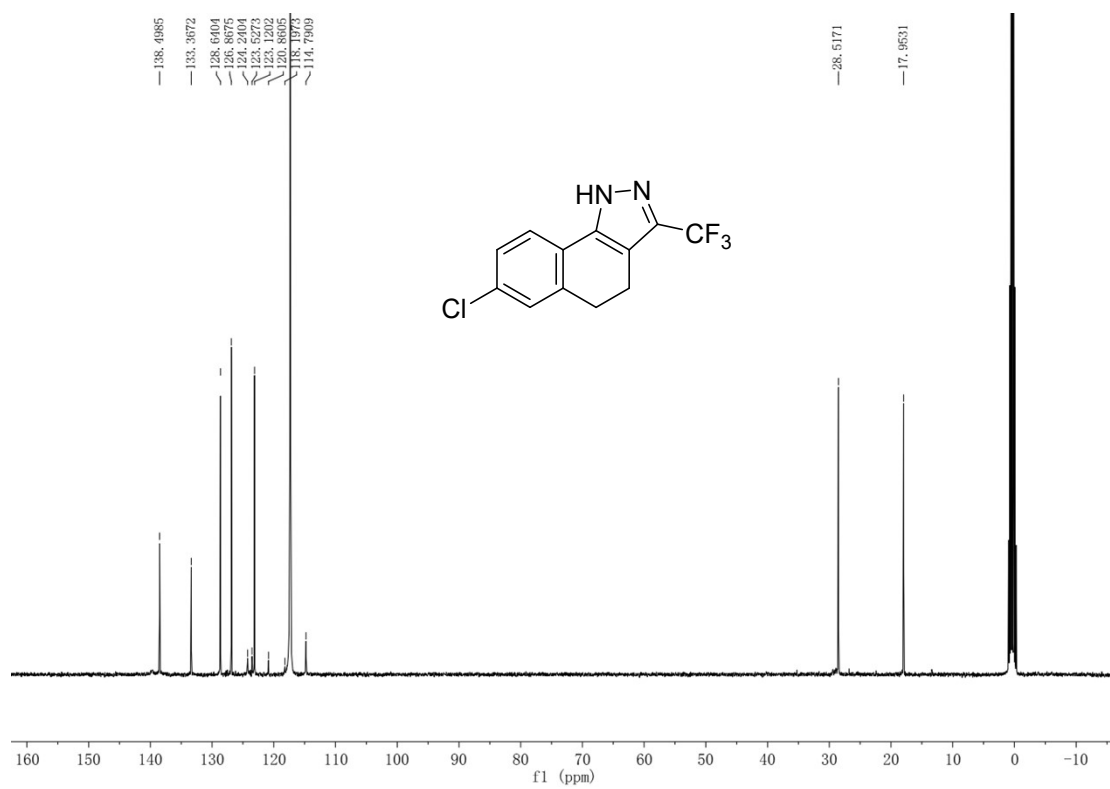
^{19}F NMR (376 MHz, CDCl_3) of **2q**:



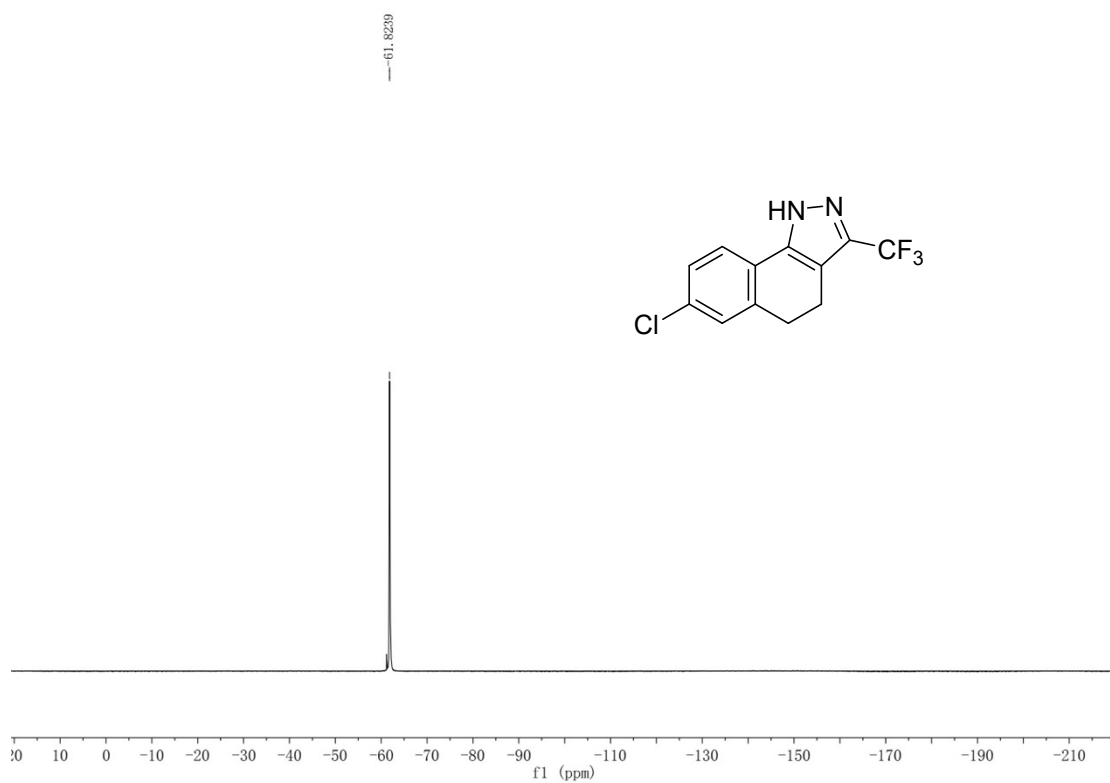
^1H NMR (400 MHz, CD_3CN) of **2r**:



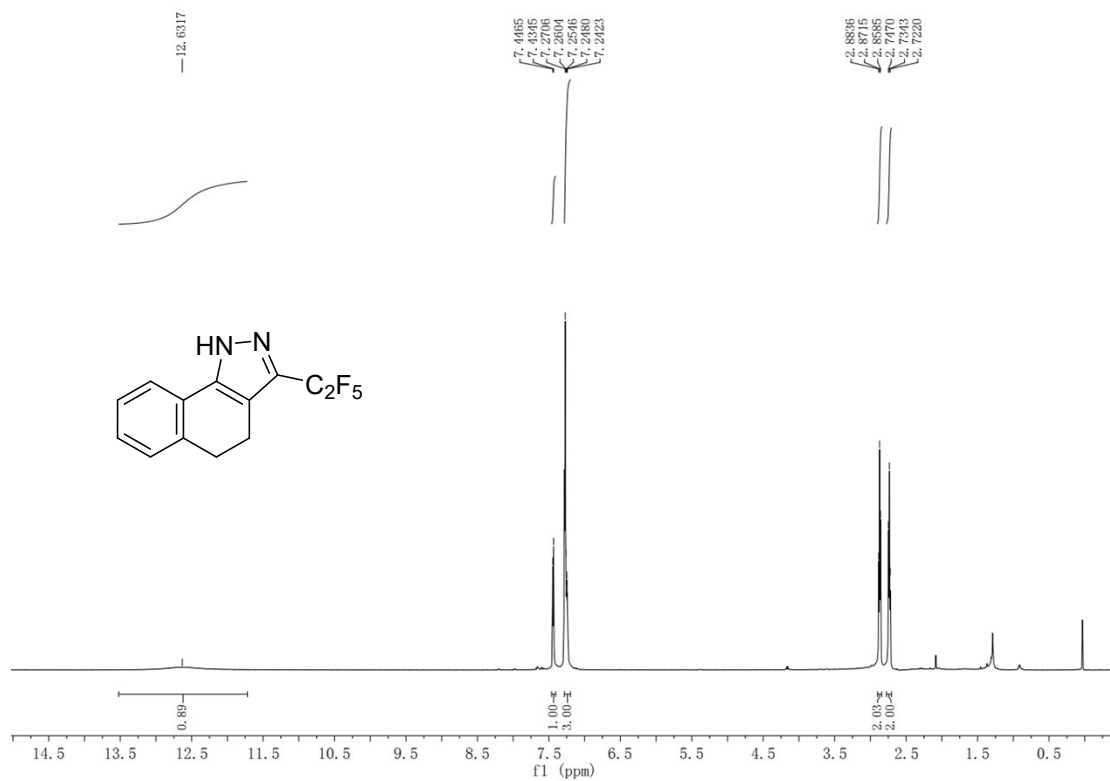
^{13}C NMR (100 MHz, CD_3CN) of **2r**:



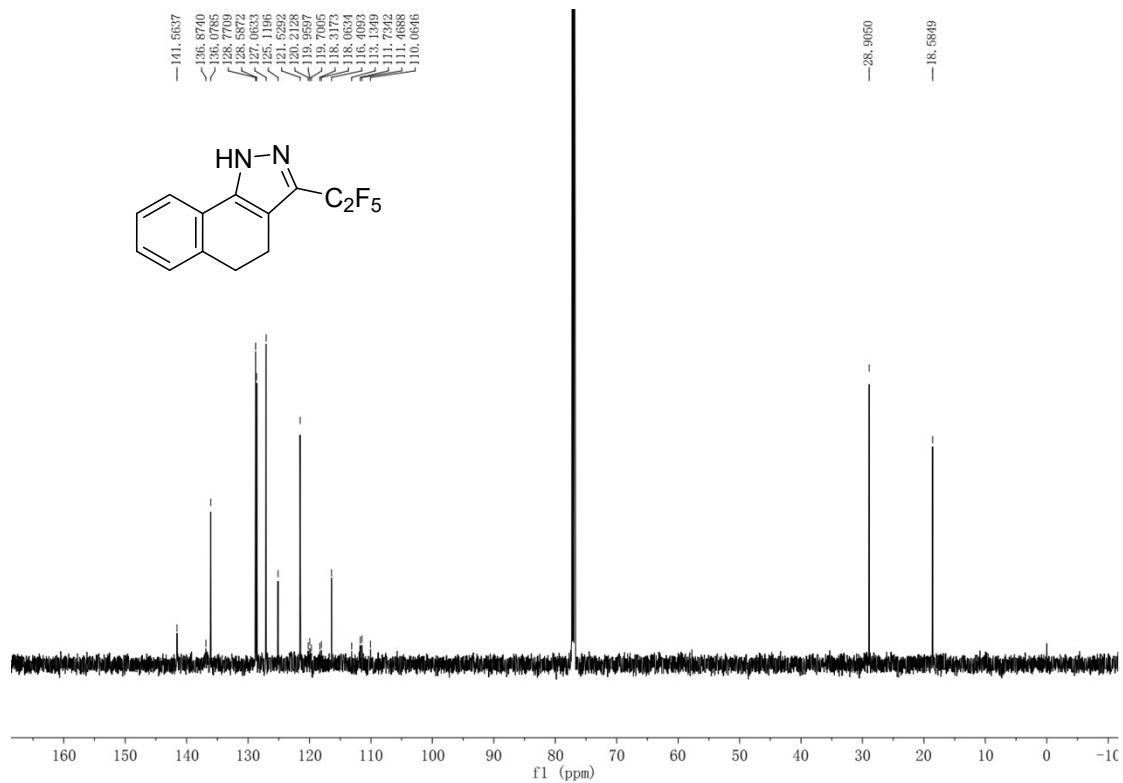
^{19}F NMR (376 MHz, CD_3CN) of **2r**:



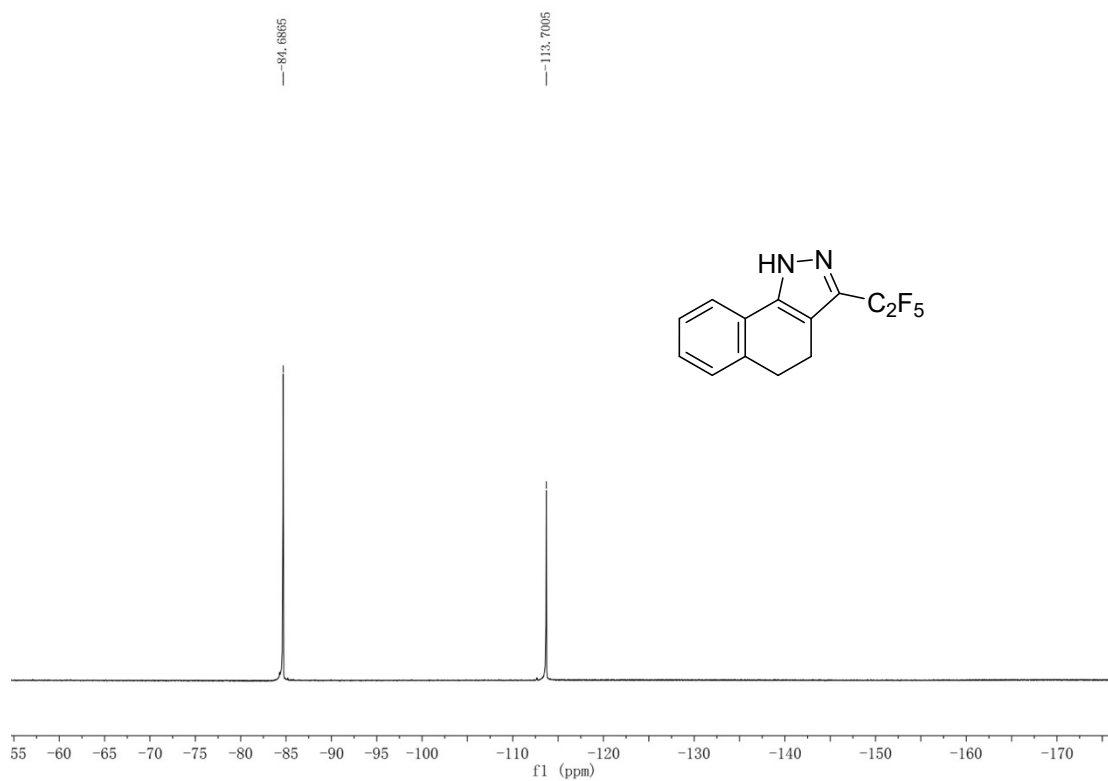
^1H NMR (600 MHz, CDCl_3) of **2s**:



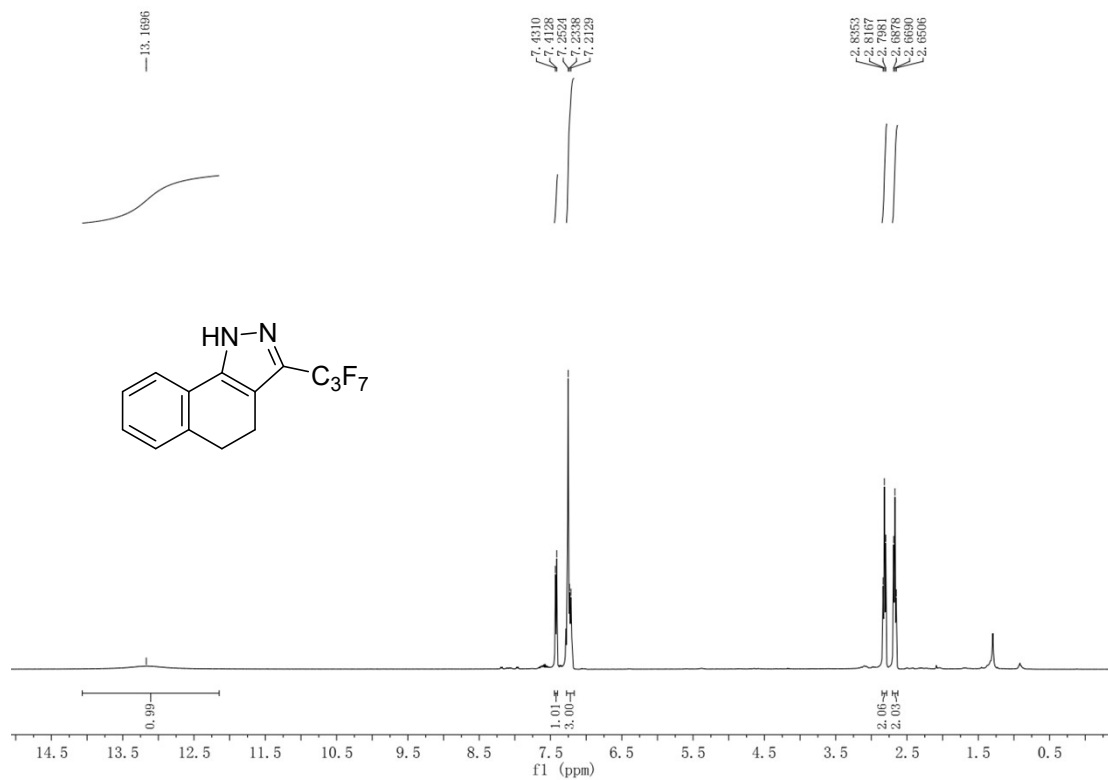
^{13}C NMR (150 MHz, CDCl_3) of **2s**:



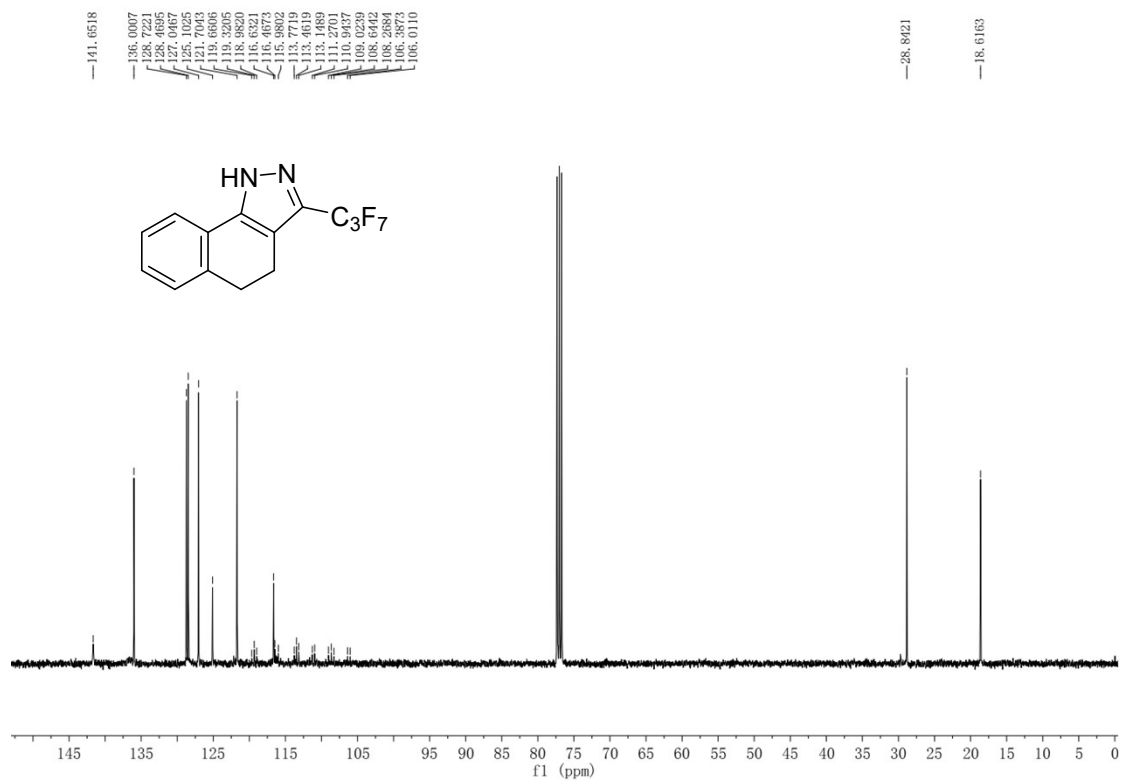
^{19}F NMR (376 MHz, CDCl_3) of **2s**:



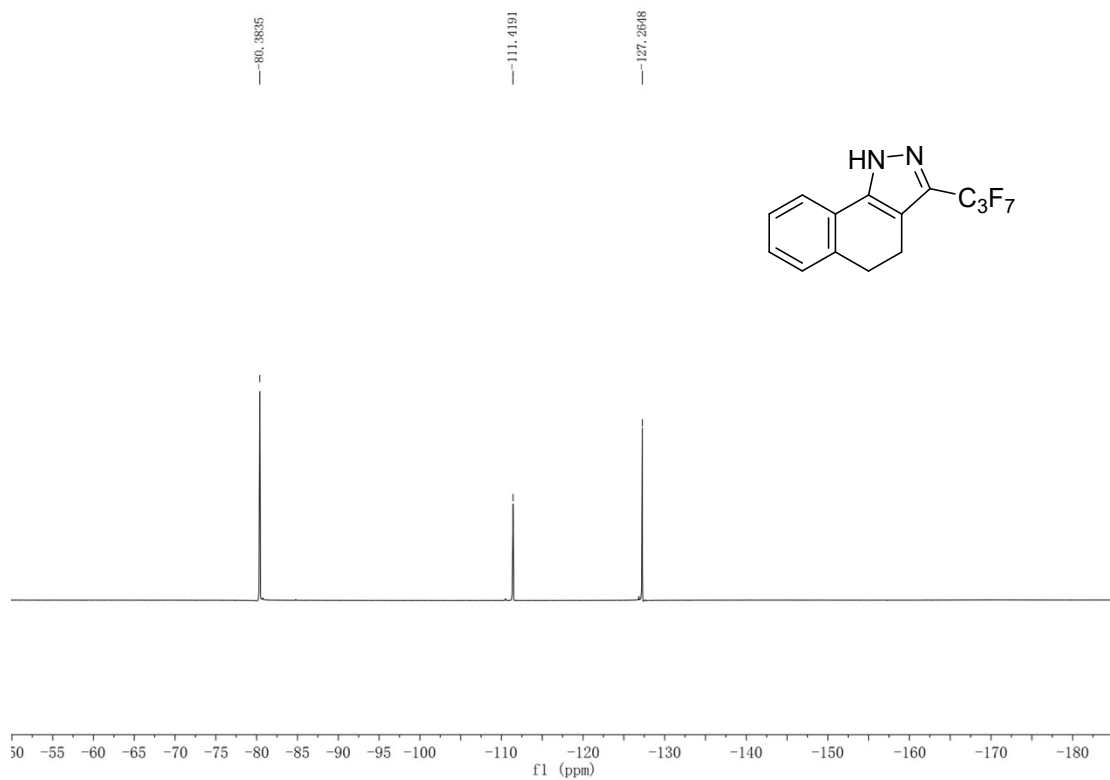
^1H NMR (400 MHz, CDCl_3) of **2t**:



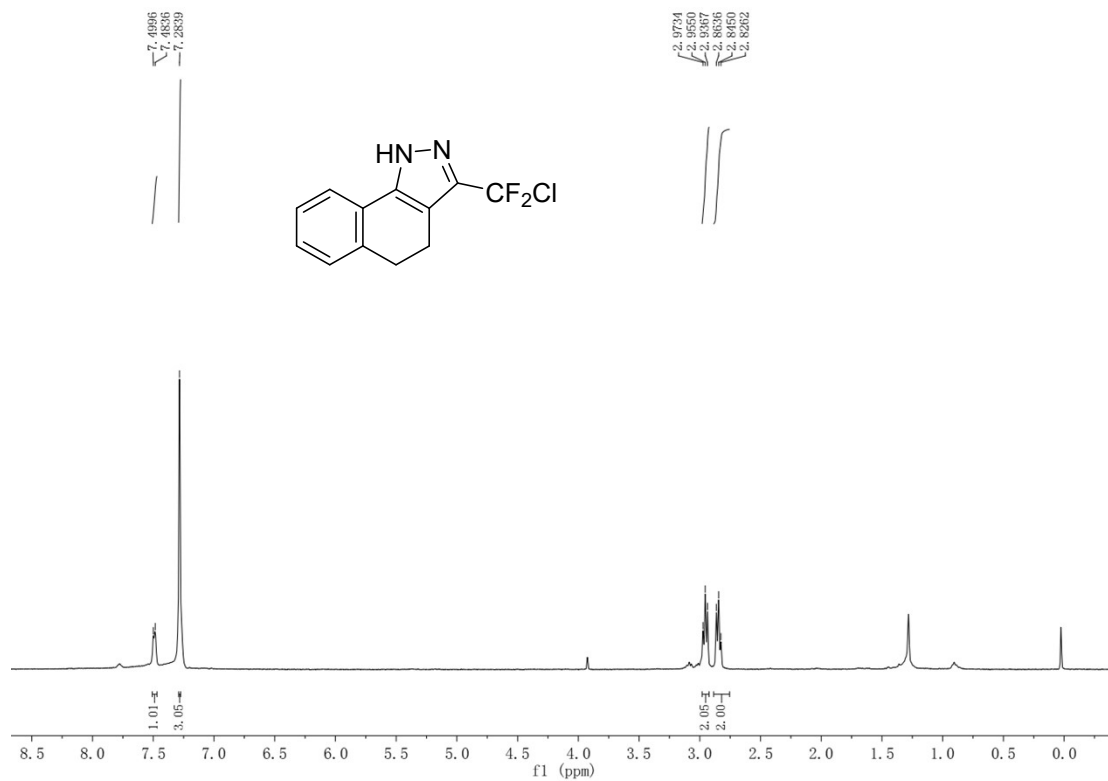
¹³C NMR (100 MHz, CDCl₃) of **2t**:



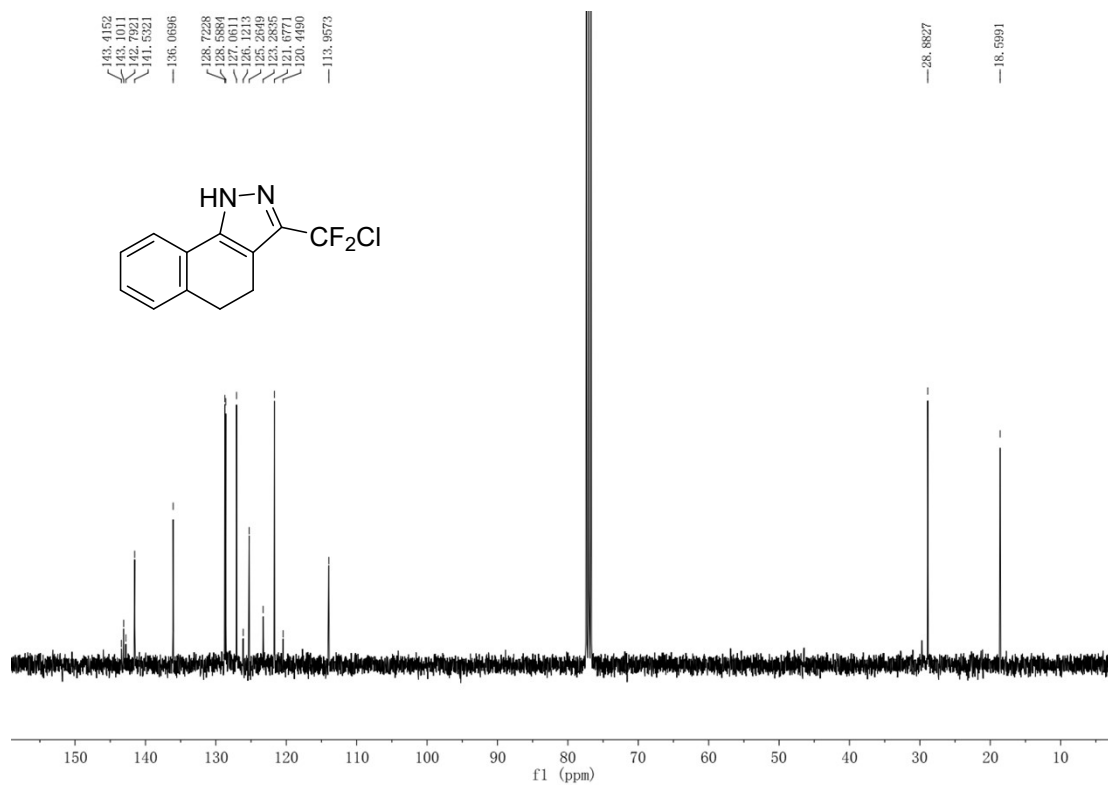
¹⁹F NMR (565 MHz, CDCl₃) of **2t**:



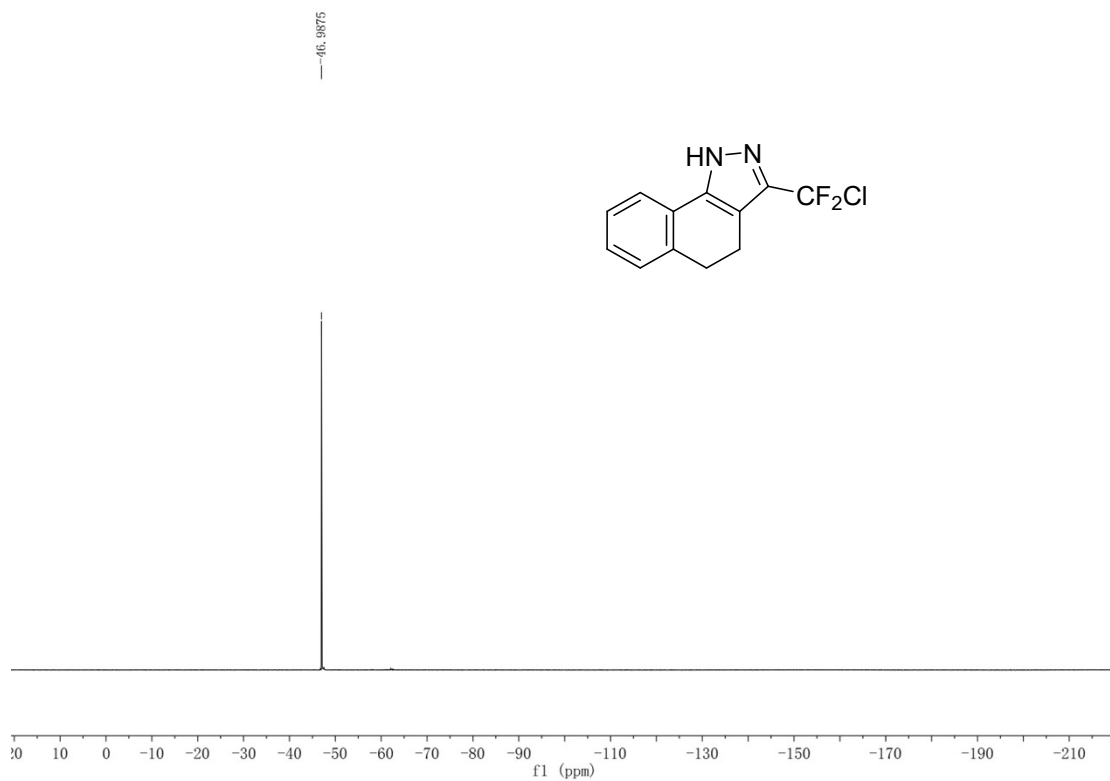
^1H NMR (400 MHz, CDCl_3) of **2u**:



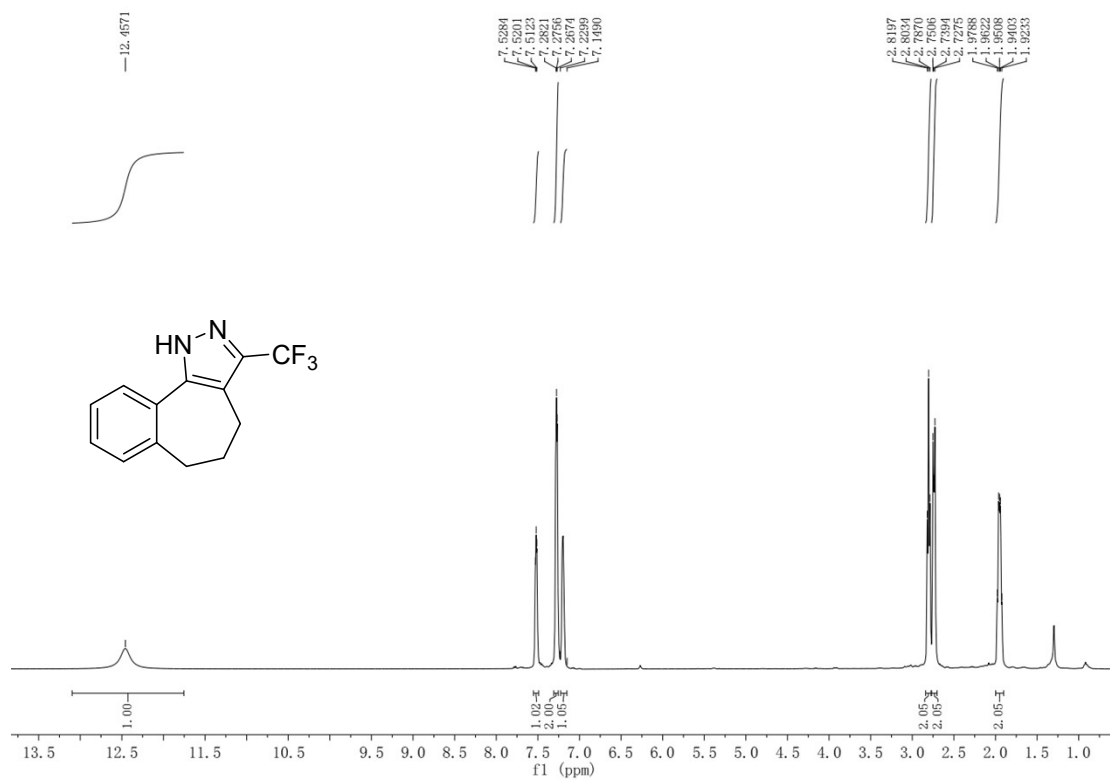
^{13}C NMR (100 MHz, CDCl_3) of **2u**:



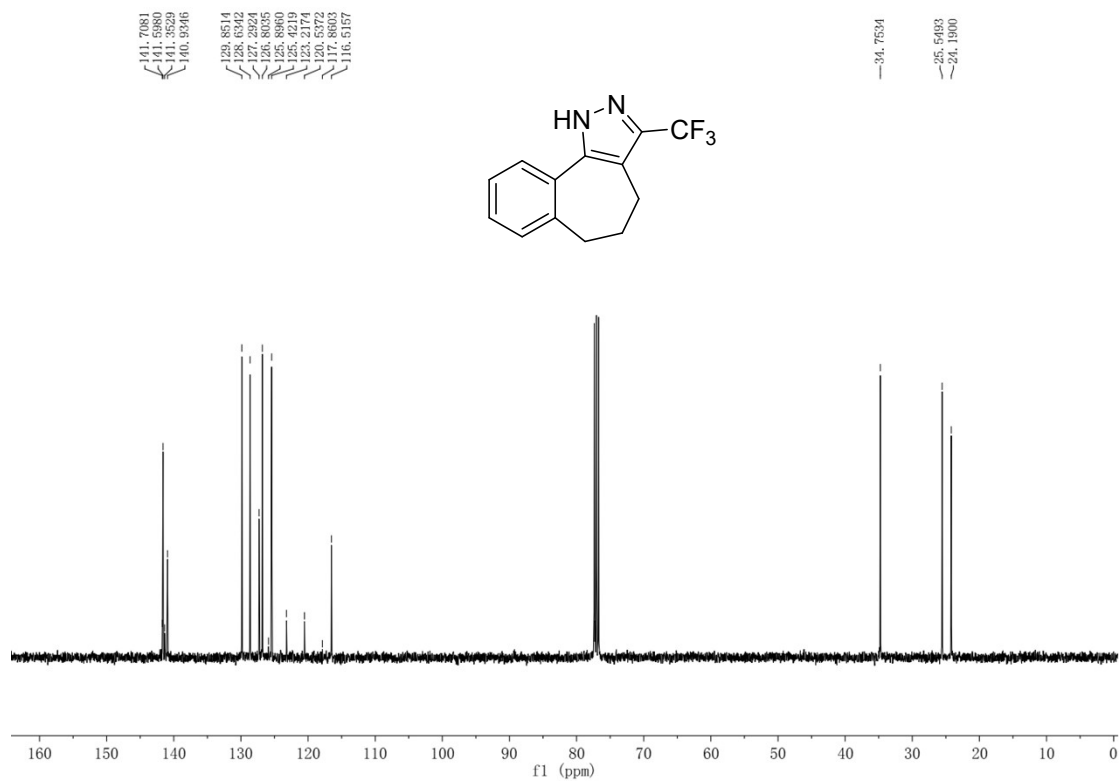
^{19}F NMR (376 MHz, CDCl_3) of **2u**:



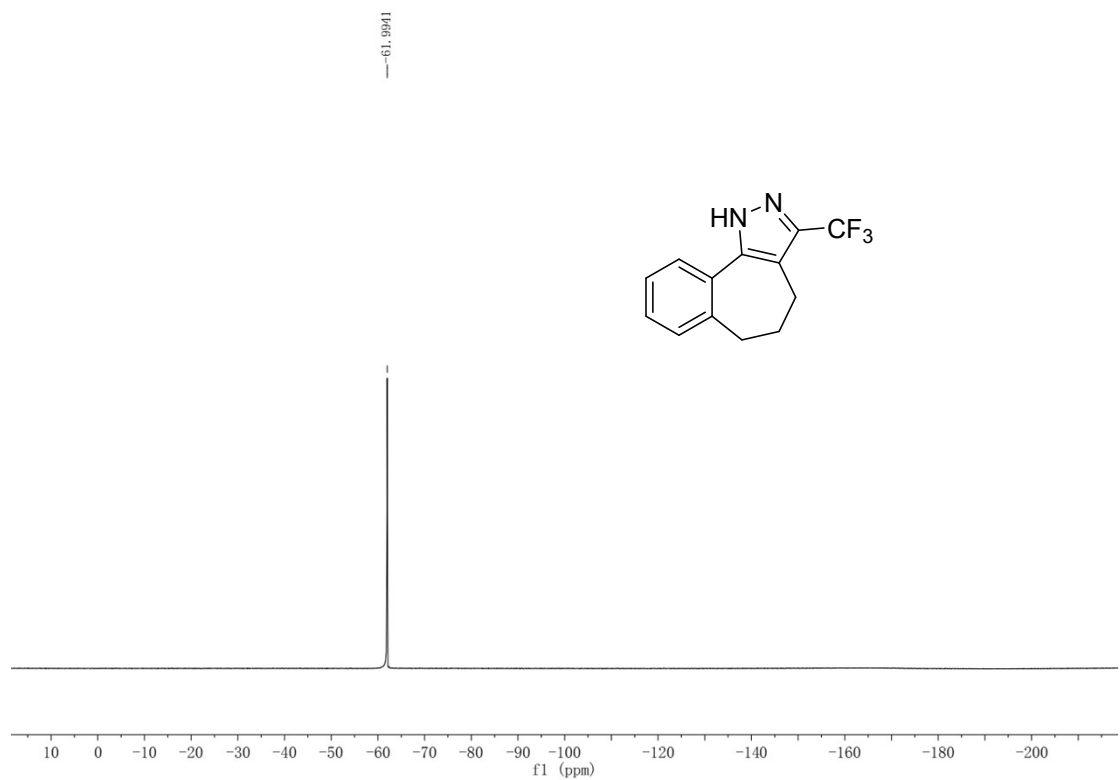
^1H NMR (400 MHz, CDCl_3) of **2w**:



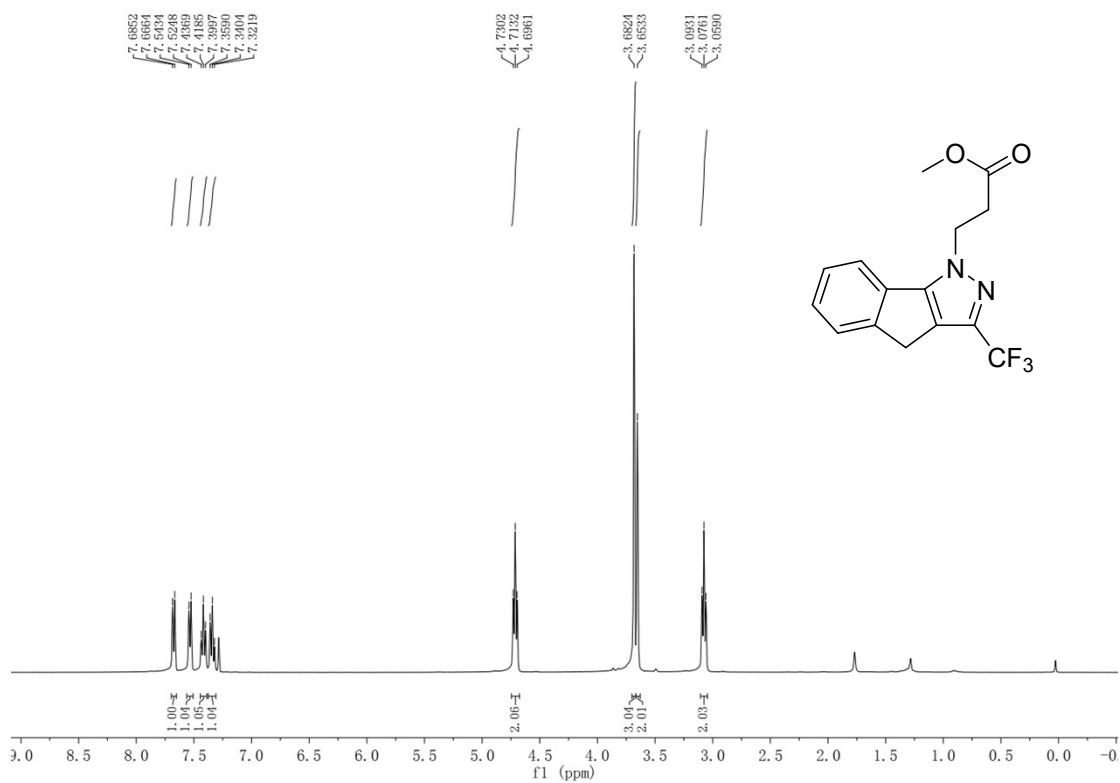
^{13}C NMR (100 MHz, CDCl_3) of **2w**:



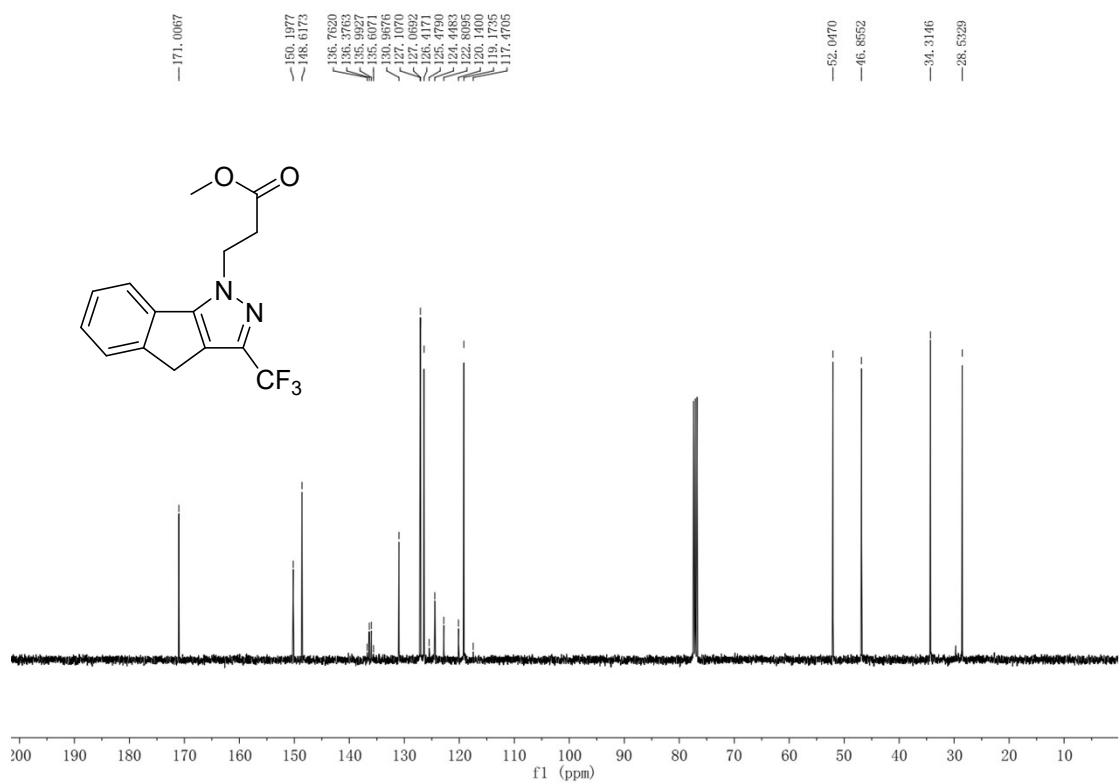
^{19}F NMR (565 MHz, CDCl_3) of **2w**:



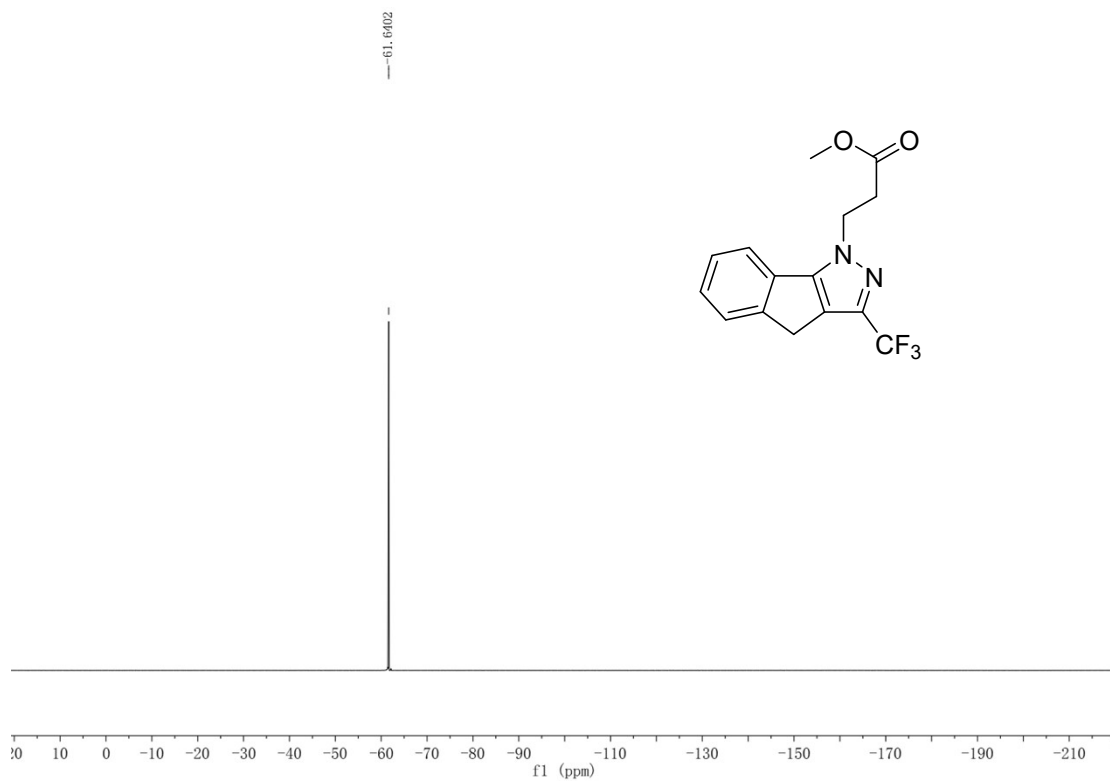
^1H NMR (400 MHz, CDCl_3) of **3**:



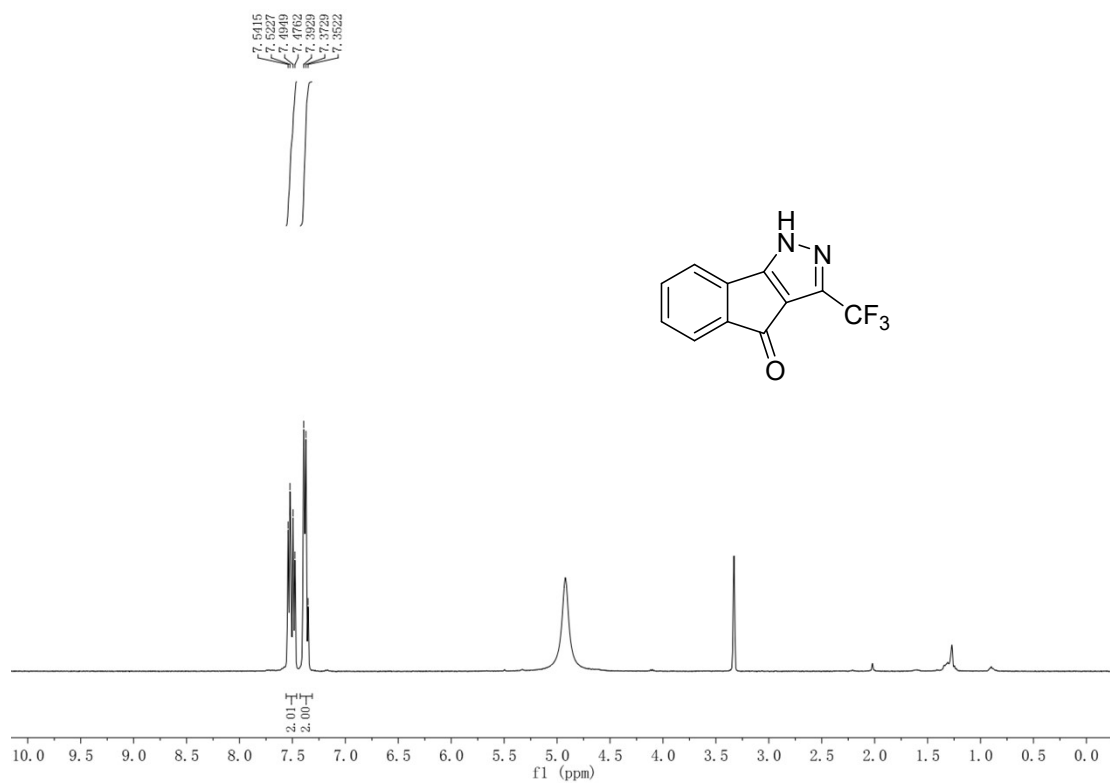
^{13}C NMR (100 MHz, CDCl_3) of **3**:



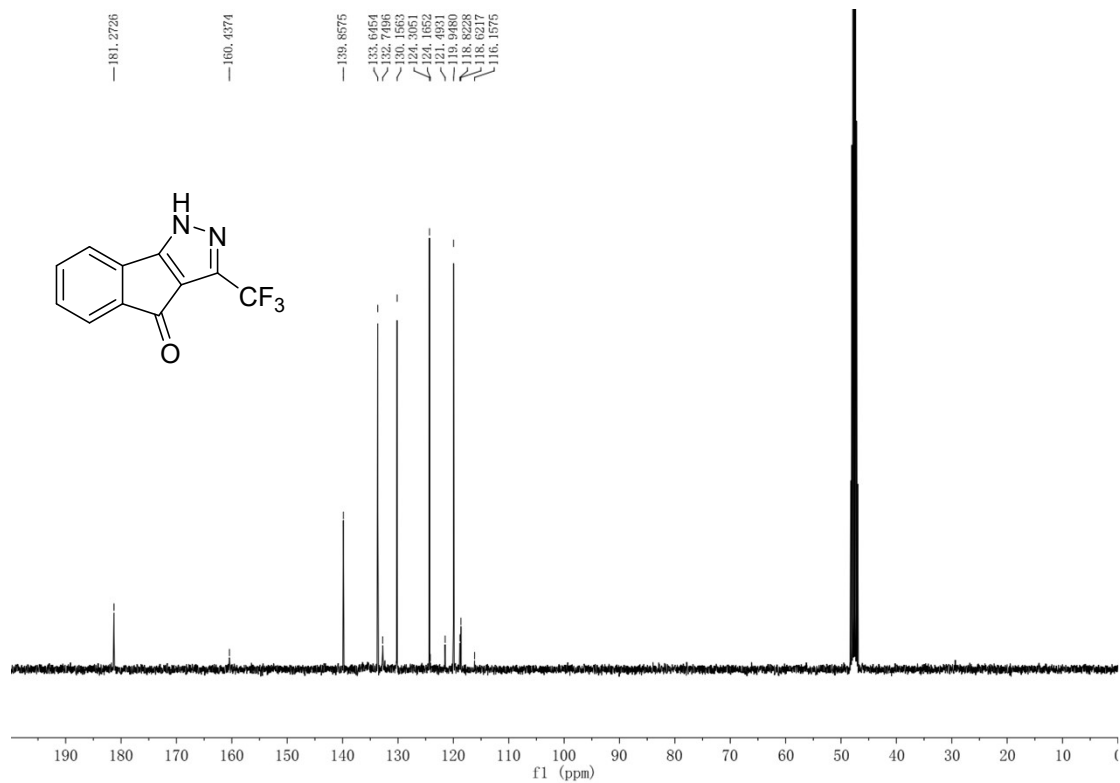
^{19}F NMR (376 MHz, CDCl_3) of **3**:



^1H NMR (400 MHz, CD_3OD) of **4**:



¹³C NMR (100 MHz, CD₃OD) of **4**:



¹⁹F NMR (376 MHz, CD₃OD) of **4**:

