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Synthesis of 3-(2,3,5,6-tetrafluoropyridinylthio)pyrazoles from 3-aminopyrazoles

Denis S. Koltun and Alexander D. Dilman

Content

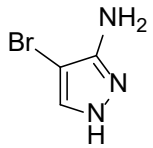
1. General information

Melting points were determined on a STUART Melting point SMP30 apparatus. NMR spectra were recorded on Bruker AM-300, DRX-500 or AV-600 spectrometers. High resolution mass spectra were recorded on a Bruker MicroTOF II instrument in positive ion mode (capillary voltage 4500 V) using electrospray ionisation (ESI) and methanol or acetonitrile as a solvent.

1.1. Starting materials

1*H*-Pyrazol-3-amine (**1a**), ethyl 3-amino-1*H*-pyrazole-4-carboxylate (**1b**), 4-chloro-1*H*-pyrazol-3-amine (**1c**) were obtained from commercial sources. Compound **1a** was dried in a vacuum desiccator over sulfuric acid. Compounds **1b** and **1c** were used without additional purification. 2,3,5,6-Tetrafluoropyridine-4-thiol,[S1] 1,2-bis(perfluoropyridin-4-yl)disulfane,[S1] pyrazoles **3a**[S2] and **3b**[S3] were prepared according to literature procedures.

Synthesis of 4-bromo-1*H*-pyrazol-3-amine (1d).

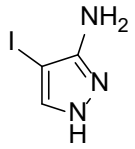


Aminopyrazole **1a** (2.5 g, 30 mmol) was dissolved in acetic acid (12 mL) and cooled to -5 °C. A solution of bromine (4.8 g, 30 mmol) in acetic acid (12 mL) was added dropwise over one hour. Then, chloroform (10 mL) was added leading to the formation of a precipitate, and the mixture was stirred for additional 20 minutes. The mixture was neutralized with a saturated $NaHCO_3$ solution to pH = 7. The precipitate was filtered, washed with water, and dried in air.

Yield of 40% (1.95 g). White solid. Mp = 132-134 ºC.

^{1}H NMR (500 MHz, DMSO-*d*$_6$, 353 K) δ 4.47, (br. s, 2H, N$\underline{H}_2$), 7.39 (s, 1H, C5$\underline{H}$), 11.65 (br. s, 1H, N$\underline{H}$). ^{13}C NMR (126 MHz, DMSO-*d*$_6$, 293 K) δ 79.34 (C4), 128.85 (C5H), 152.40 (C3). HRMS (ESI) calcd for $C_3H_5Br^{79}N_3$: 161.9661 [M+H$^+$], found: 161.9664.

Synthesis of 4-iodo-1*H*-pyrazol-3-amine (1e).



Aminopyrazole **1a** (2.5 g, 30 mmol) was dissolved in water (50 mL). Iodine (3.8 g, 15 mmol) and hydrogen peroxide (50% in water, 1 mL) were added at room temperature, and the mixture was stirred for 30 minutes. Solid Na_2SO_3 was added to the mixture until discoloration of the solution, which was accompanied by prepitation. The precipitate was filtered, washed with water, and dried in air.

Yield of 33% (1.04 g). Dark green solid. Mp = 147-150 °C (dec).

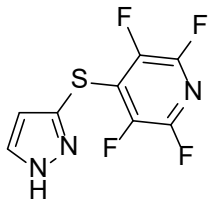
^{1}H NMR (500 MHz, DMSO-d_6, 353 K) δ 7.36 (s, 1H, C5H). ^{13}C NMR (126 MHz, DMSO-d_6, 353 K) δ 43.26 (C4), 136.52 (C5H), 152.95 (C3). HRMS (ESI) calcd for $C_3H_5IN_3$: 209.9523 [M+H$^+$], found: 209.9531.

2. Synthesis of SPyf-containing pyrazoles

2.1. Synthesis of compounds 2 (General procedure).

Aminopyrazole (for **2d,e** and **4a,b**, 0.3 mmol; for **2a,b,c**, 0.5 mmol) was dissolved in a mixture of water (2 mL) and MeCN (2 mL) and stirred at -5 °C (ice/NaCl bath). Concentrated aqueous hydrochloric acid (for **2d,e** and **4a,b**, 93 μL; for **2a,b,c**, 150 μL) was added, and the mixture was stirred at -5 °C for 5 minutes. Then, a solution of $NaNO_2$ (for **2d,e** and **4a,b**, 31.1 mg, 0.45 mmol; for **2a,b,c**, 51.8 mg, 0.75 mmol) in water (0.5 mL) was added dropwise, the color of the solution changed to dark yellow, and the mixture was stirred for 10 minutes at -5 °C. 2,3,5,6-Tetrafluoropyridine-4-thiol (for **2d,e** and **4a,b**, 73.3 mg, 0.4 mmol; for **2a,b,c**, 120 mg, 0.65 mmol) was added dropwise, partial discoloration of the solution was observed, and the mixture was stirred for 15 minutes. The cooling bath was removed, saturated K_2CO_3 solution (1 mL) was added to pH 10–11. The mixture was heated to 70 °C with stirring for 10 min. A change in the color of the solution to dark red was observed, and the product formation was controlled using TLC. The mixture was allowed to cool to room temperature. The mixture was extracted with EtOAc (3 × 20 mL), the combined organic phase was dried with $MgSO_4$, concentrated under vacuum, and the residue was purified by column chromatography.

4-(1*H*-Pyrazol-3-yl)thio-2,3,5,6-tetrafluoropyridine (2a).

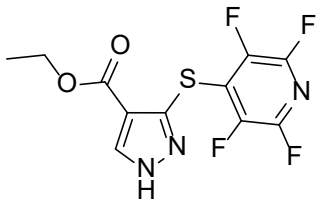


Chromatography: EtOAc/hexane = 1/3. Yield of 79% (98.5 mg).

White crystalline powder. Mp = 80-82 °C.

^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.63 (d, *J* = 2.4 Hz, 1H, C4H,), 7.7 (d, *J* = 2.4 Hz, 1H, C5H), 12.35 (br. s, 1H, NH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 111.35 (C4H), 129.57 (m, C3), 130.92 (C5H), 137.14 (C3-S-C), 139.67 – 142.01 (m, 2C-F), 142.25 – 144.48 (m, 2C-F). ^{19}F NMR (282 MHz, DMSO-d_6) δ -93.27 (m), -138.75 (m). HRMS (ESI): calcd for $C_8H_4F_4N_3S$ [M+H$^+$]: 250.0057; found 250.0051.

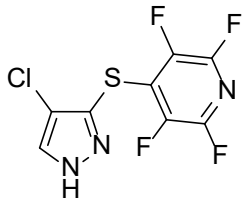
Ethyl 3-(perfluoropyridin-4-yl)thio-1*H*-pyrazole-4-carboxylate (2b).



Chromatography: EtOAc/hexane = 1/4. Yield of 64% (102.8 mg). Yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 4.25 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 8.47 (s, 1H, C5H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.13 (CH_3CH_2), 60.20 (CH_3CH_2), 111.79 (C4), 126.99 (C3), 134.60 (C5H), 136.03 (C3-S-C), 139.75 – 143.60 (m, 2C-F), 140.77 – 144.46 (m, 2C-F), 161.93 (C4-C=O). ^{19}F NMR (282 MHz, DMSO-d_6) δ -92.89 (m), -135.75 (m). HRMS (ESI): calcd for $C_{11}H_8F_4N_3O_2S$ [M+H$^+$]: 322.0268; found 322.0263.

4-(4-Chloro-1*H*-pyrazol-3-yl)thio-2,3,5,6-tetrafluoropyridine (2c).



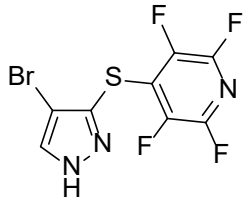
Chromatography: EtOAc/hexane = 1/3. Yield of 65% (91.4 mg).

White crystalline powder. Mp = 82-84 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H, C5H), 13.79 (br. s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 112.90 (C4), 129.00 (C5H), 130.89 (C3), 134.12 (C3-S-C), 138.56 – 142.43 (m, 2C-F),

140.87 – 144.55 (m, 2C-F). ^{19}F NMR (282 MHz, DMSO-d_6) δ -92.88 (m), -139.61 (m). HRMS (ESI): calcd for $C_8H_3Cl^{35}F_4N_3S$ [M+H$^+$]: 283.9667; found 283.9671.

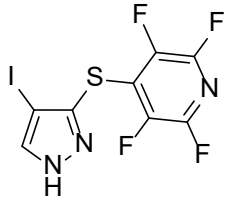
4-(4-Bromo-1*H*-pyrazol-3-yl)thio-2,3,5,6-tetrafluoropyridine (2d).



Chromatography: EtOAc/hexane = 1/3. Yield of 59% (58.1 mg). Brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H, C5H), 12.32 (br. s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.03 (C4), 128.07 (m, C3), 132.15 (C5H), 137.16 (C3-S-C), 138.95 – 142.87 (m, 2C-F), 141.63 – 145.35 (m, 2C-F). ^{19}F NMR (282 MHz, DMSO-d_6) δ -90.65 (m), -138.23 (m). HRMS (ESI): calcd for $C_8H_2Br^{79}F_4N_3SNa$ [M+Na$^+$]: 349.8981; found 349.8989.

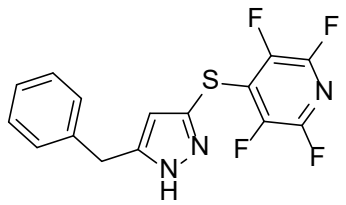
2,3,5,6-Tetrafluoro-4-[(4-iodo-1*H*-pyrazol-3-yl)thio]pyridine (2e).



Chromatography: EtOAc/hexane = 1/5. Yield of 53% (59.65 mg). Brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H, C5H), 12.39 (br. s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.20 (C4), 128.46 (m, C3), 136.93 (C5H), 138.91 – 142.84 (m, 2C-F), 140.89 (C3-S-C), 141.66 – 145.38 (m, 2C-F). ^{19}F NMR (282 MHz, DMSO-d_6) δ -90.69 (m), -138.03 (m). HRMS (ESI): calcd for $C_8H_3IF_4N_3S$ [M+H$^+$]: 375.9023; found 375.9018.

4-(5-Benzyl-1*H*-pyrazol-3-yl)thio-2,3,5,6-tetrafluoropyridine (4a).



Chromatography: EtOAc/hexane = 1/5. Yield of 40% (40.8 mg).

White crystalline powder. Mp = 70-72 °C.

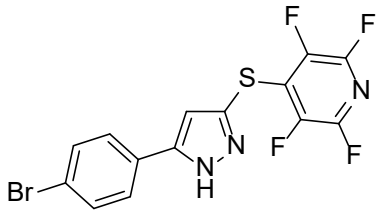
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 2H, Ph-CH_2), 6.32 (s, 1H, C4H), 7.29 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.14 (Ph-CH_2), 95.31 (C4H), 109.93 (C3), 127.18 (*p*-C$_{Ph}$), 128.58 (2 *o*-C$_{Ph}$),

128.88 (*i*-C$_{Ph}$), 128.94 (2 *m*-C$_{Ph}$), 136.62 (C5), 139.51 – 145.17 (m, 4C-F + C3-S-C). ^{19}F NMR (282 MHz, DMSO-d_6) δ -91.40 (m), -138.07 (m). HRMS (ESI): calcd for $C_{15}H_{10}F_4N_3S$ [M+H$^+$]: 340.0526; found 340.0520.

2.2. Synthesis of compounds 4b and 5.

5-(4-Bromophenyl)-1*H*-pyrazole-3-amine **3b** (0.3 mmol, 72.6 mg), 2,3,5,6-tetrafluoropyridine-4-thiol (0.4 mmol, 73.3 mg) and 1,2-bis(perfluoropyridin-4-yl)disulfane (0.15 mmol, 54.6 mg) were added to a test tube containing MeCN (1.5 mL) and a magnetic stir bar. *tert*-Butyl nitrite (0.6 mmol, 61.9 mg) was added, and the mixture was irradiated by blue LEDs (400 nm, 40 W) at room temperature for 2 h. The reaction mixture was extracted with EtOAc (3 × 10 mL), the combined organic phase was dried with $MgSO_4$, concentrated under vacuum. The residue was separated by column chromatography (EtOAc/hexane, from 1/3 to 1/2) affording 17.8 mg of compound **4b** (15%) and 36.4 mg (54%) of pyrazole **5**.

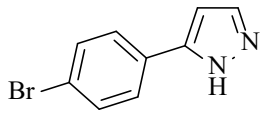
4-[5-(4-Bromophenyl)-1*H*-pyrazol-3-yl]thio-2,3,5,6-tetrafluoropyridine (4b).



White crystalline powder. Mp = 123-125 °C (dec.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 4H, 4H Ph), 7.89 (s, 1H, C4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.88 (C4H), 123.86 (C3), 128.66 (C5), 129.36 (2 *o*-C$_{Ph}$), 132.10 (2 *m*-C$_{Ph}$), 132.88 (*i*-C$_{Ph}$), 138.57 – 142.46 (m, 2CF), 140.66 (C3-S-C), 141.82 – 145.31 (m, 2CF), 149.82 (*p*-CBr). ^{19}F NMR (282 MHz, DMSO-d_6) δ -91.27 (m), -140.35 (m). HRMS (ESI): calcd for $C_{14}H_7Br^{79}F_4N_3S$ [M+H$^+$]: 403.9475; found 403.9470.

5-(4-Bromophenyl)-1*H*-pyrazole (5).[S4]



White solid. Mp = 105-107 °C (dec.).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61, (s, 1H, C4H), 7.60 (m, 5H, BrC_6H_4 + C5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 102.75 (C4H), 121.96 (C3H), 127.33 (C5H), 131.32, 131.84, 132.22, 148.99.

3. References

S1. M. O. Zubkov, M. D. Kosobokov, V. V. Levin and A. D. Dilman, *Org. Lett.*, 2022, **24**, 2354.

S2. P. Oakley, N. J. Press, C. Spanka and S. J. Watson, Patent WO 2009106539 A1, 2009.

S3. S.-F. Wang, Y. Yin, Y.-L. Zhang, S.-W. Mi, M.-Y. Zhao, P.-C. Lv, B.-Z. Wang and H.-L. Zhu, *Eur. J. Med. Chem.*, 2015, **93**, 291.

S4. F. Yi, W. Zhao, Z. Wang and X. Bi, *Org. Lett.*, 2019, **21**, 3158.

4. NMR spectra

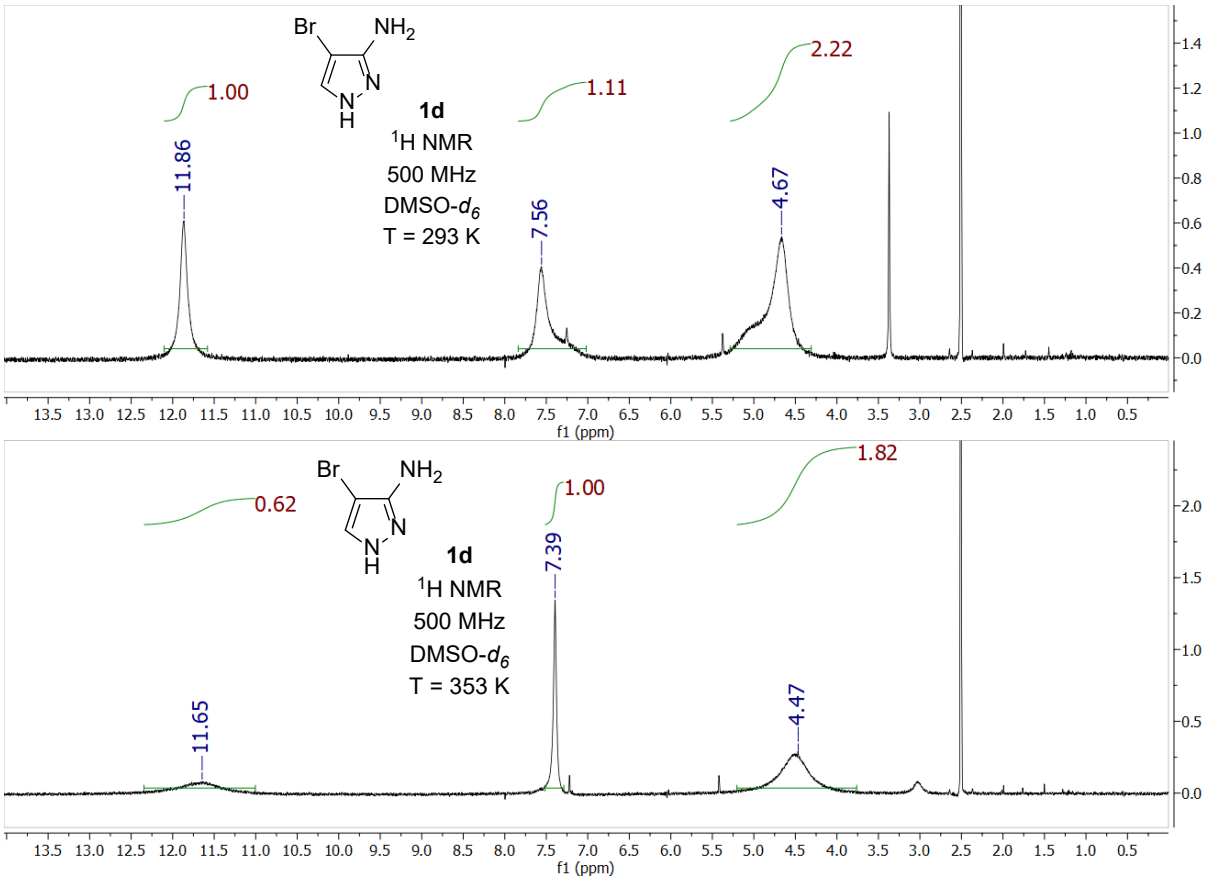


Figure S1. ^{1}H NMR of **1d** at 239 K (top) and 353 K (bottom) in DMSO-d_6.

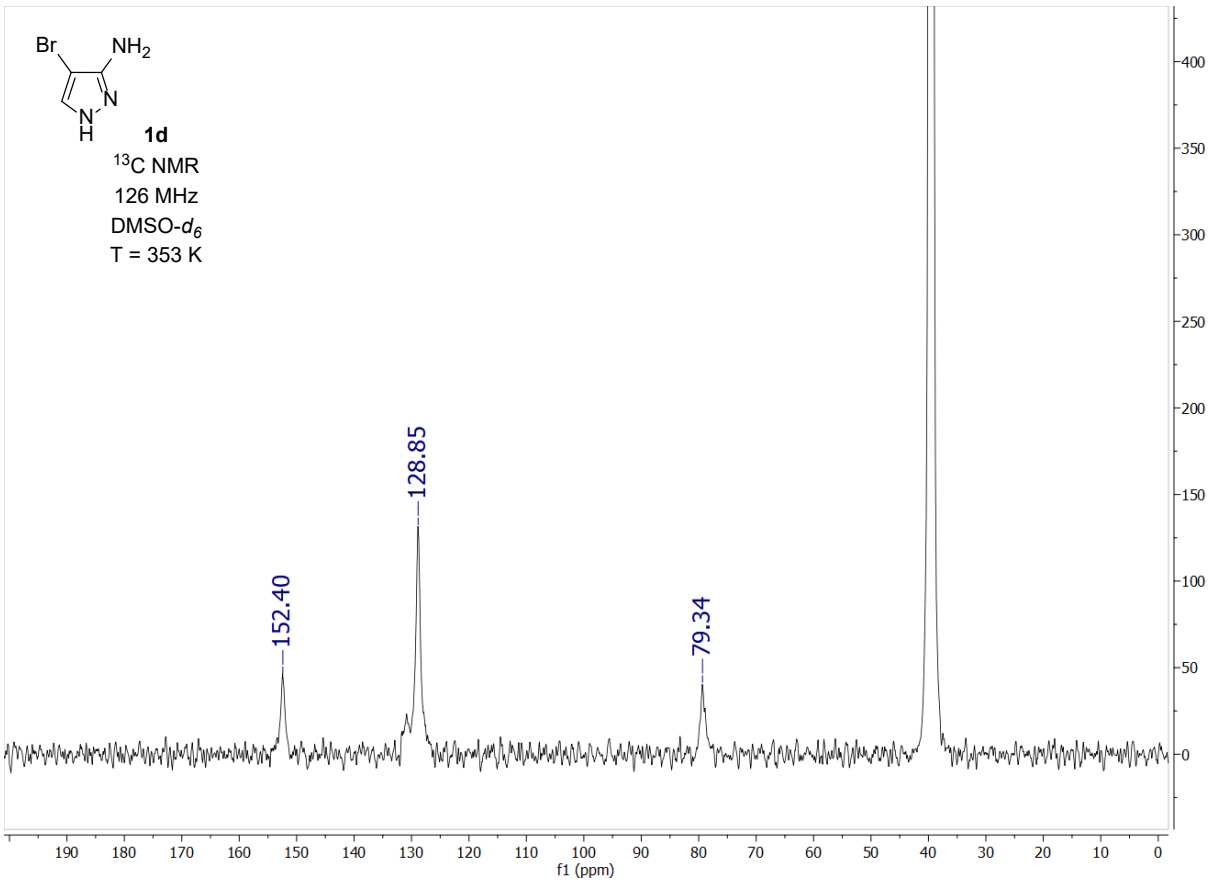


Figure S2. ^{13}C NMR of **1d** in DMSO-d_6.

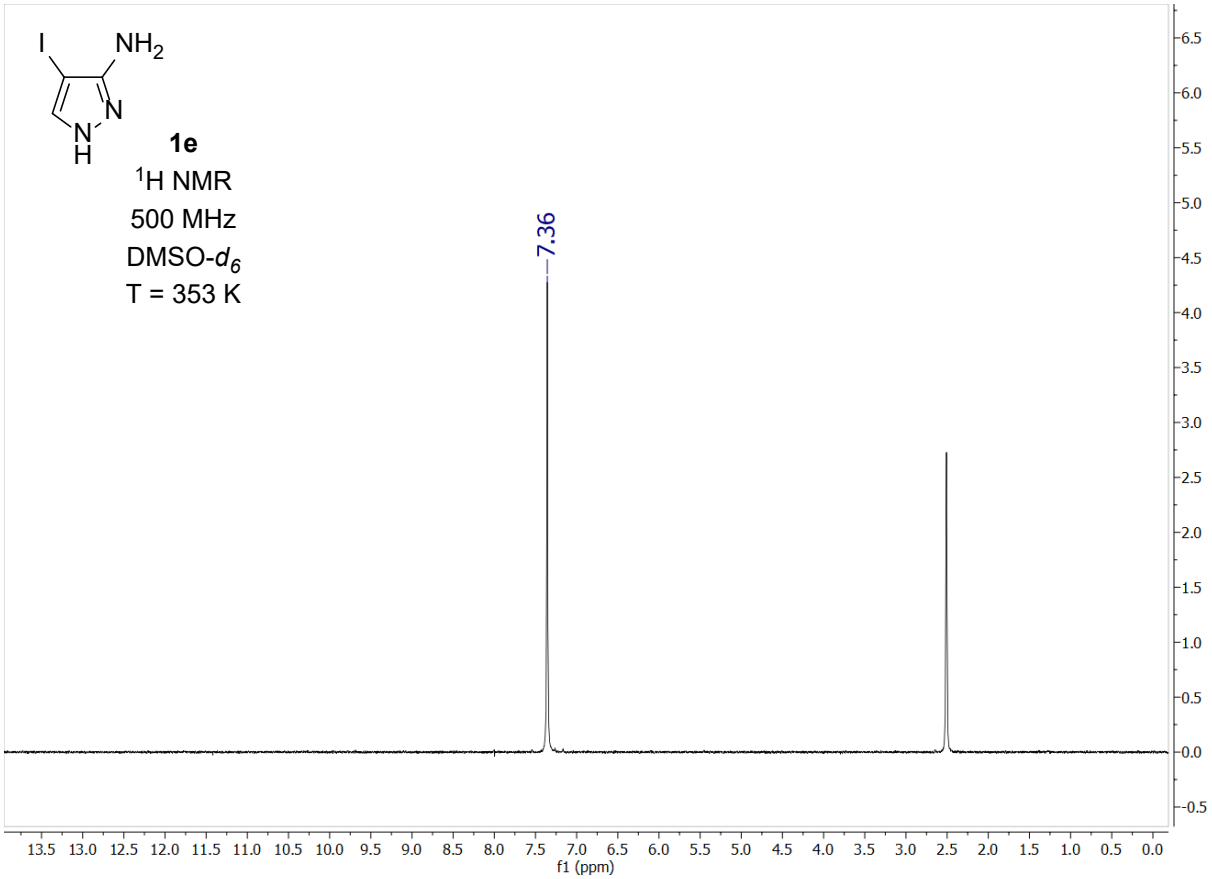


Figure S3. ^{1}H NMR of **1e** in DMSO-d_6 (353 K).

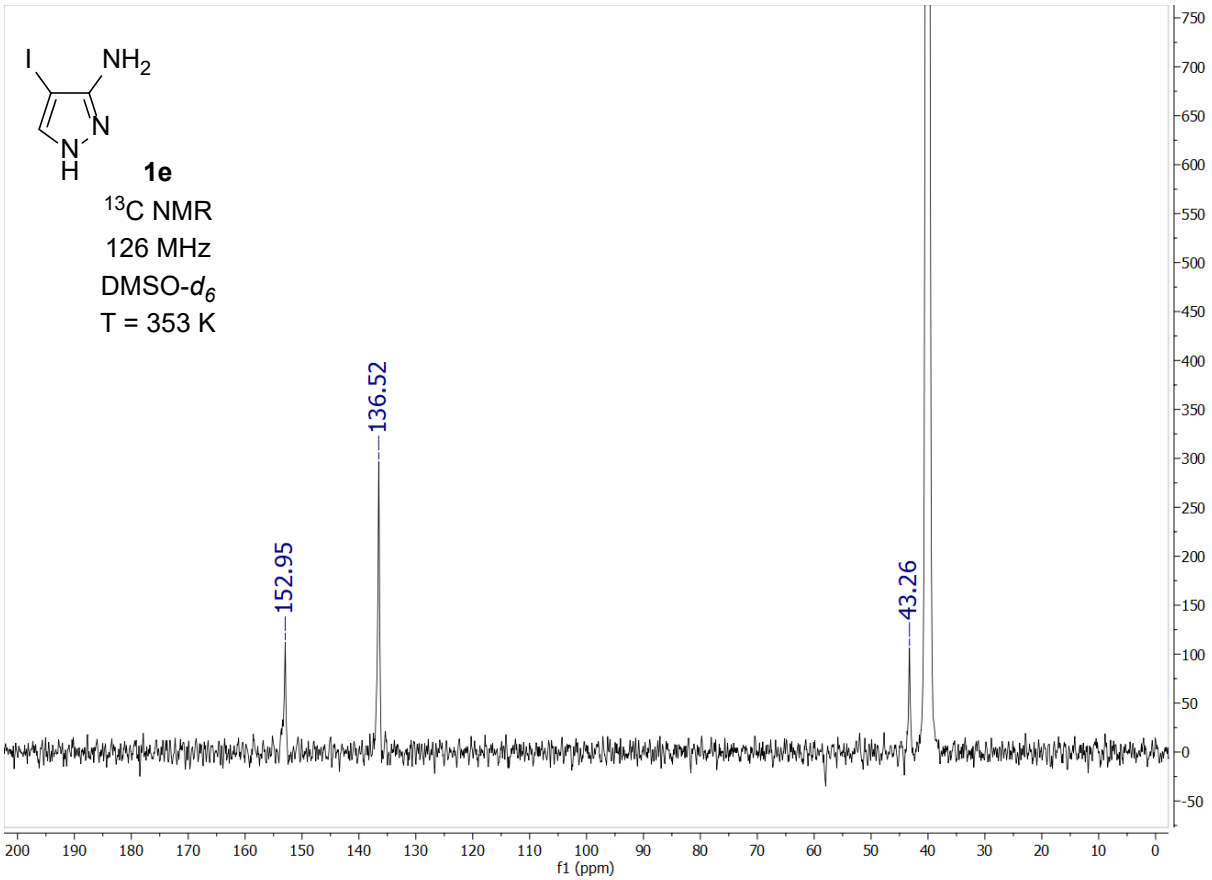


Figure S4. ^{13}C NMR of **1e** in DMSO-d_6 (353 K).

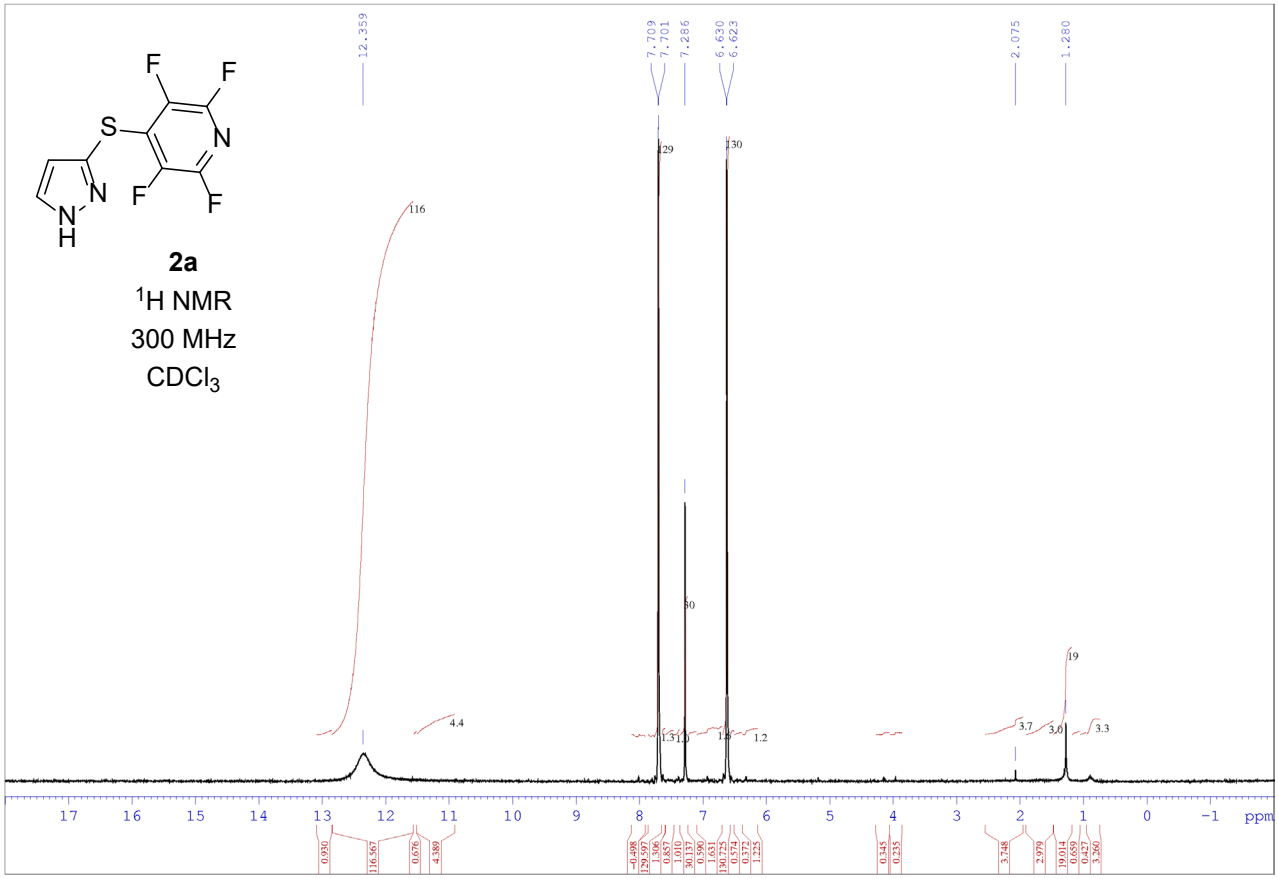


Figure S5. ^{1}H NMR of **2a** in $CDCl_3$.

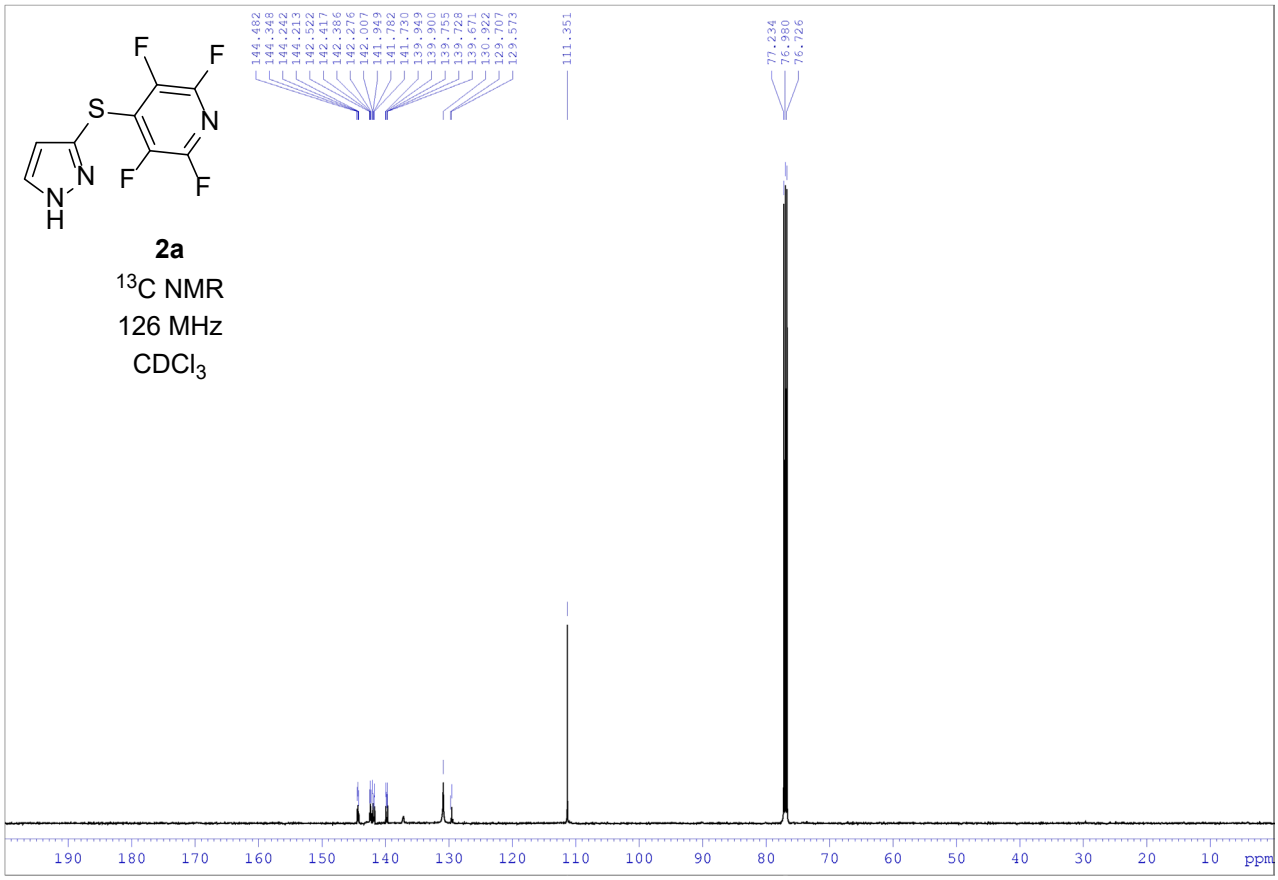


Figure S6. ^{13}C NMR of **2a** in $CDCl_3$.

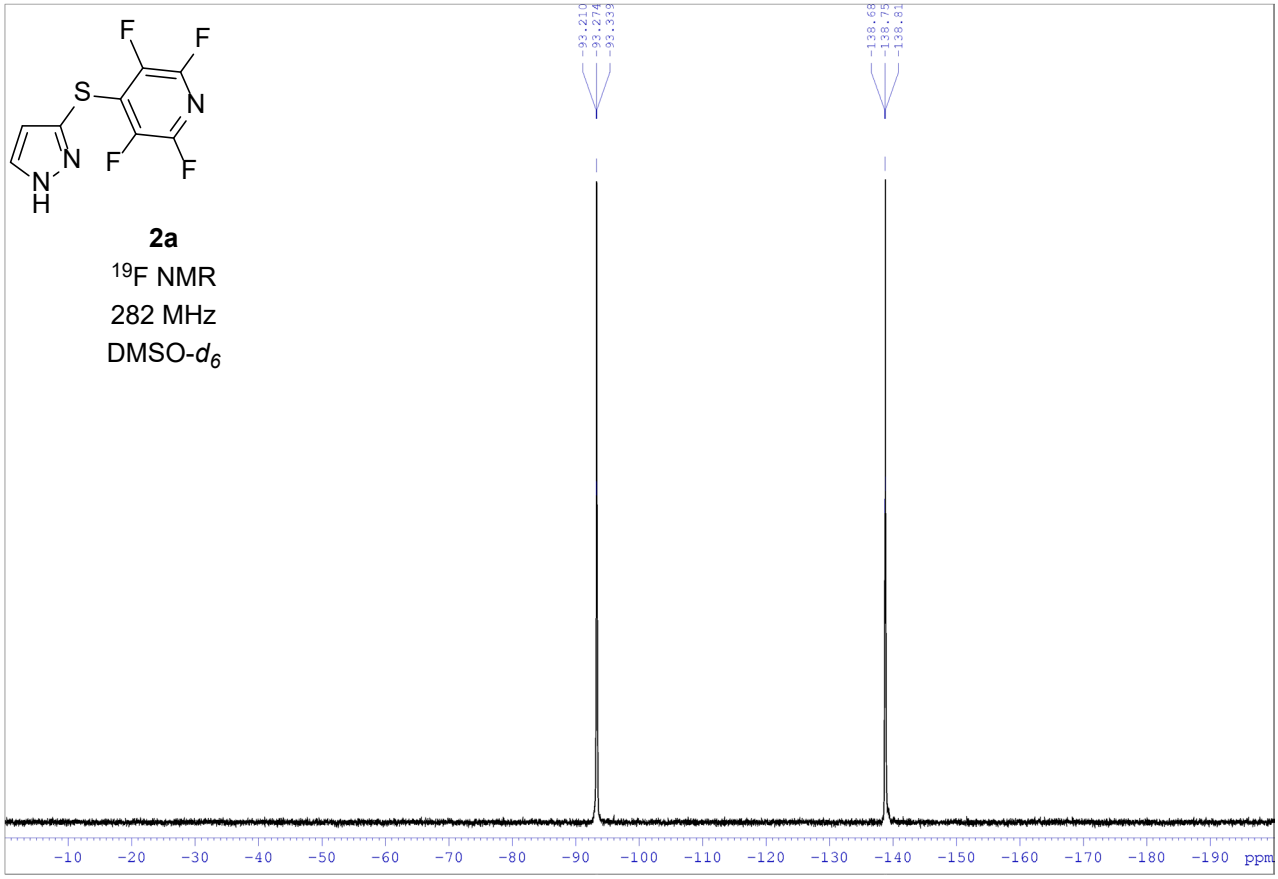


Figure S7. ^{19}F NMR of **2a** in DMSO-d_6.

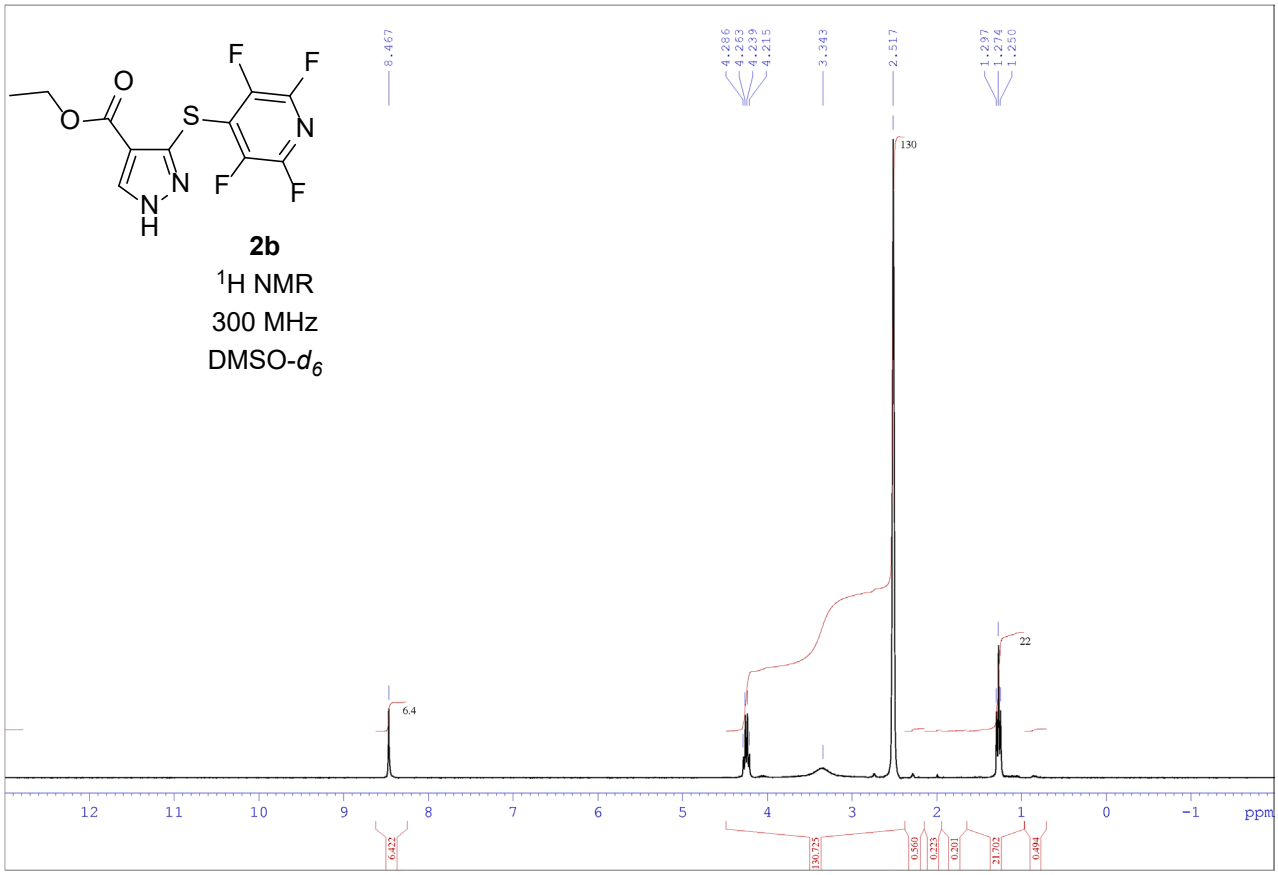


Figure S8. ^{1}H NMR of **2b** in DMSO-d_6.

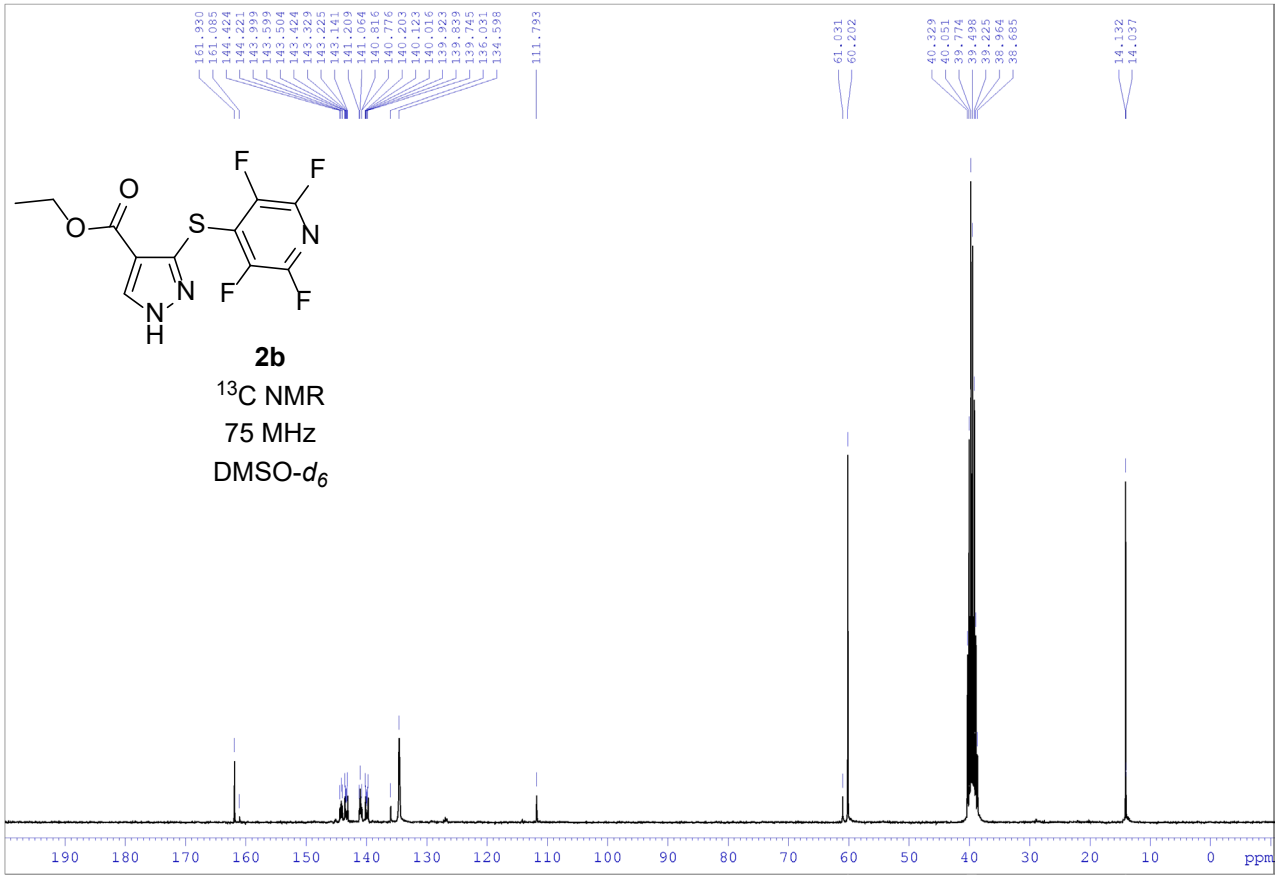


Figure S9. ^{13}C NMR of **2b** in DMSO-d_6.

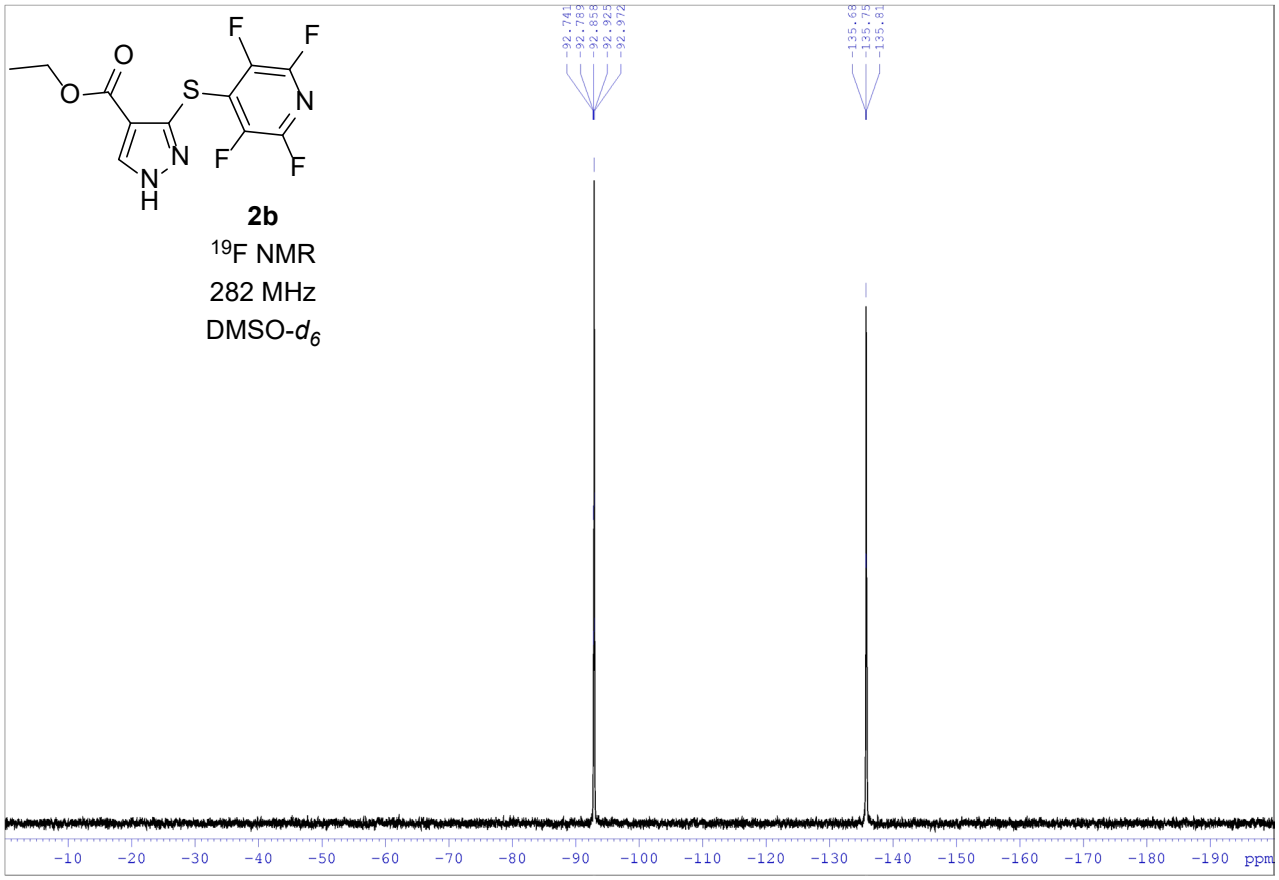


Figure S10. ^{19}F NMR of **2b** in DMSO-d_6.

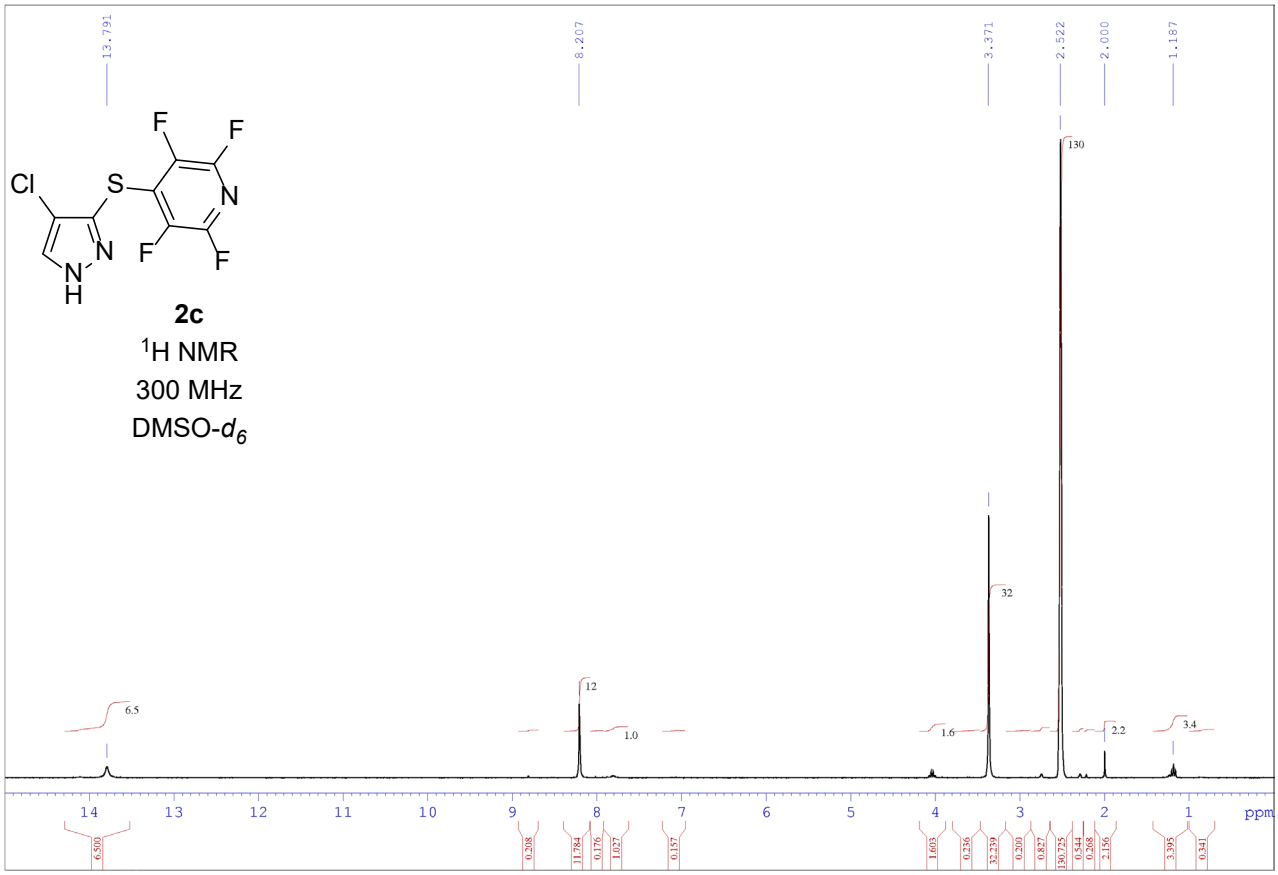


Figure S11. ^{1}H NMR of **2c** in DMSO-d_6.

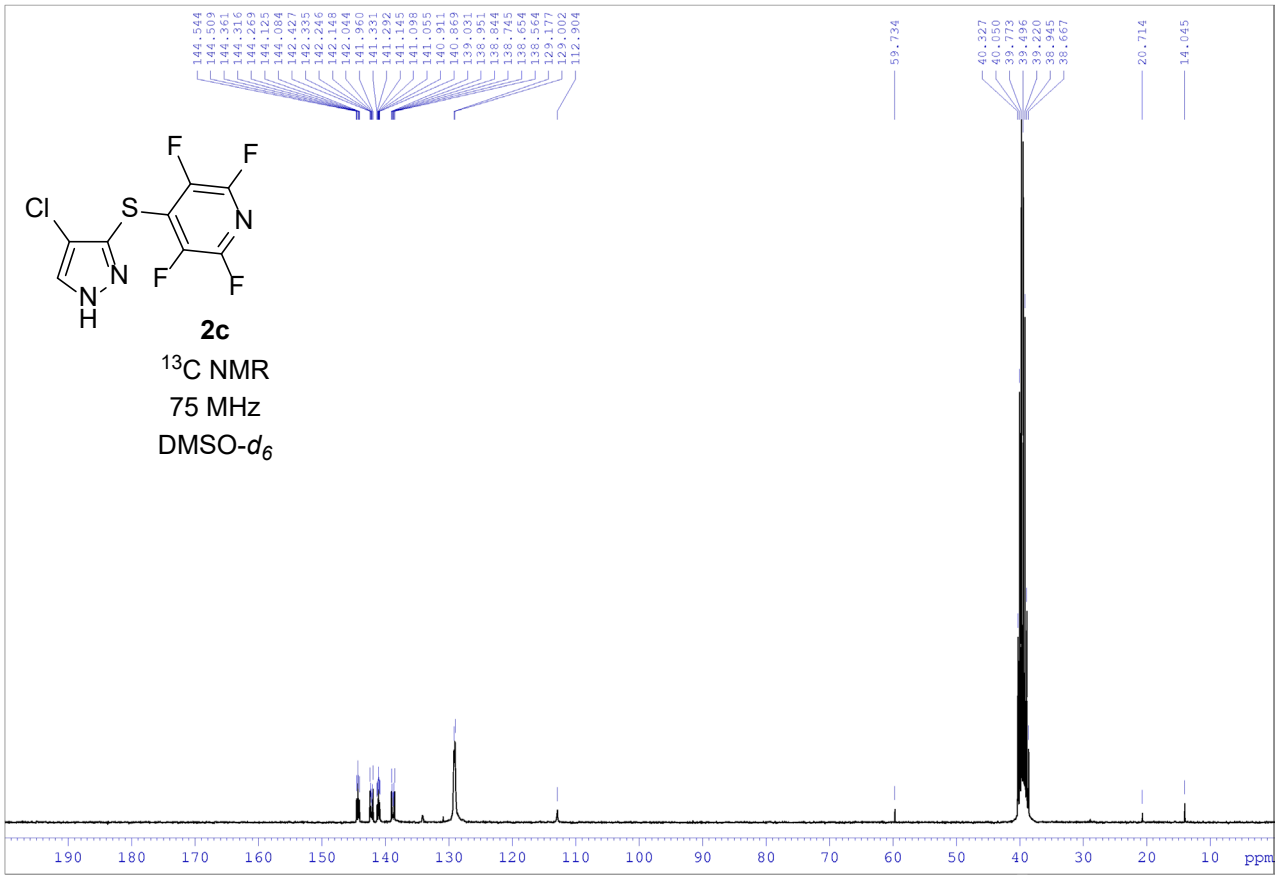


Figure S12. ^{13}C NMR of **2c** in DMSO-d_6.

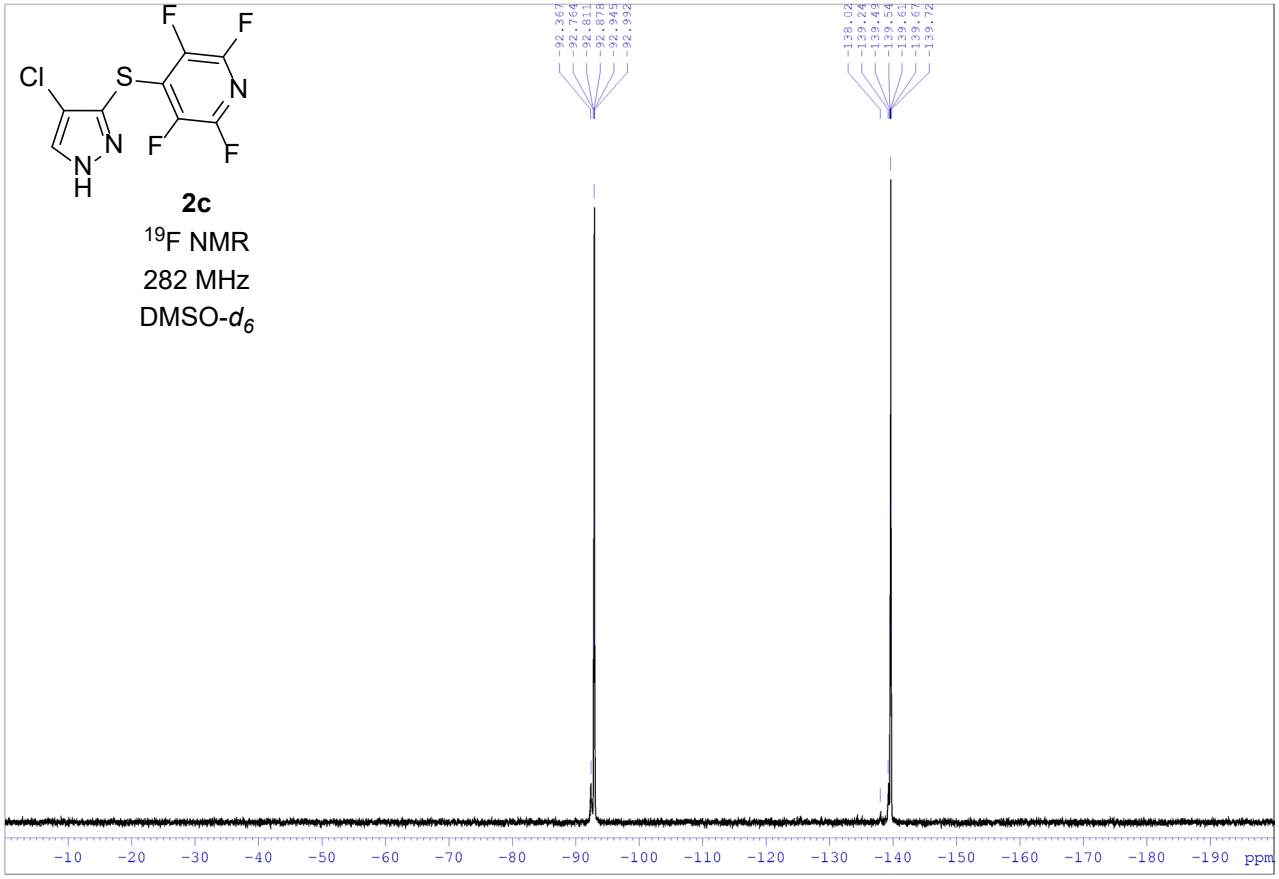


Figure S13. ^{19}F NMR of **2c** in DMSO-d_6.

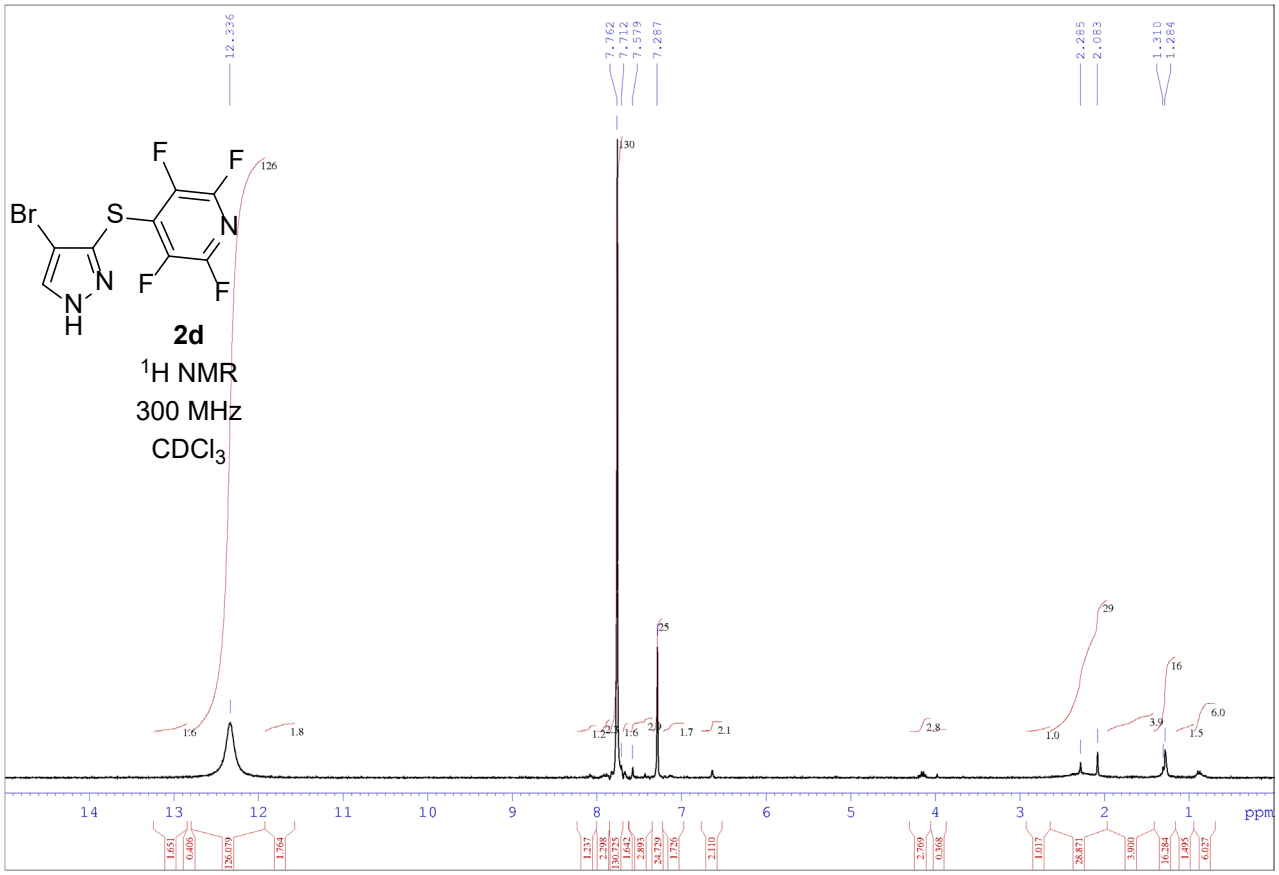


Figure S14. ^{1}H NMR of **2d** in $CDCl_3$.

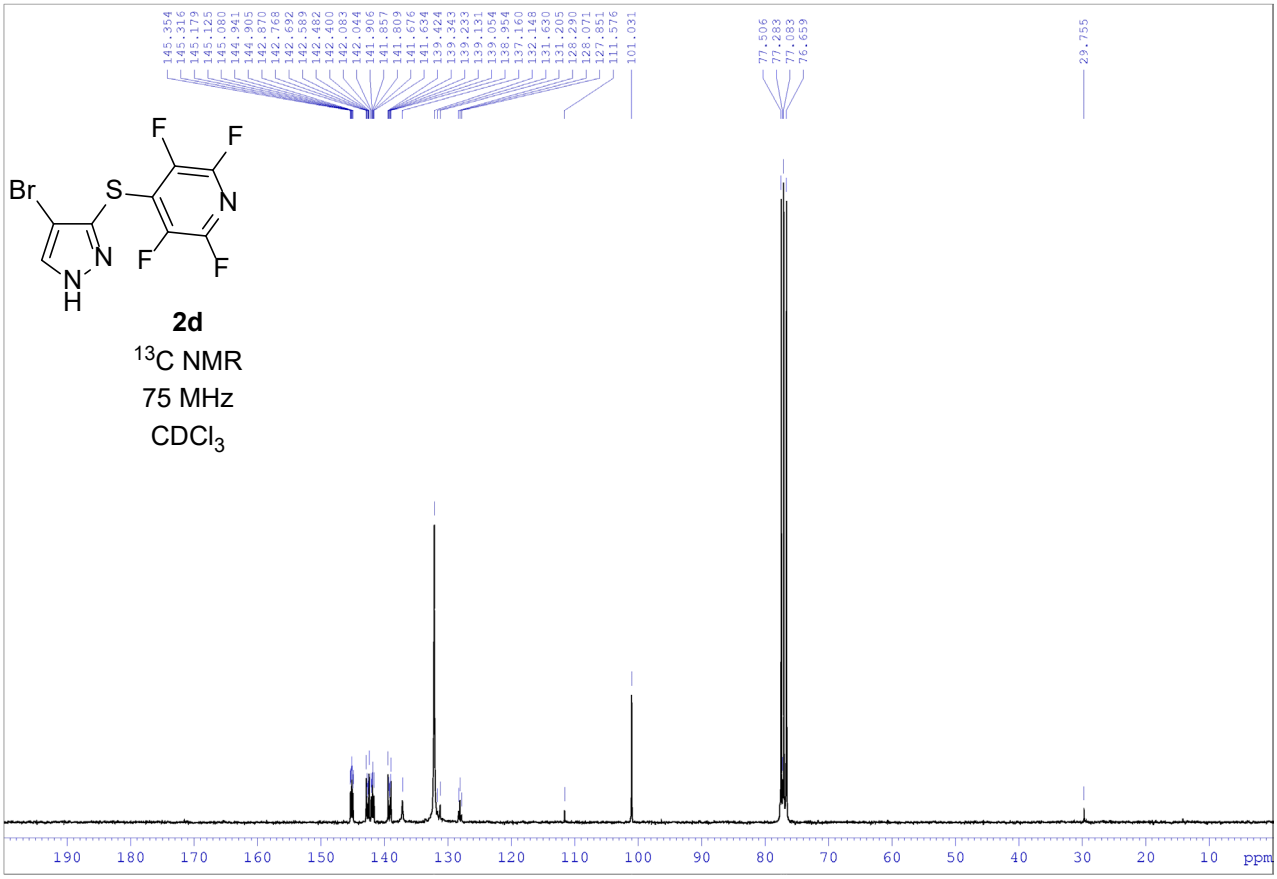


Figure S15. ^{13}C NMR of **2d** in $CDCl_3$.

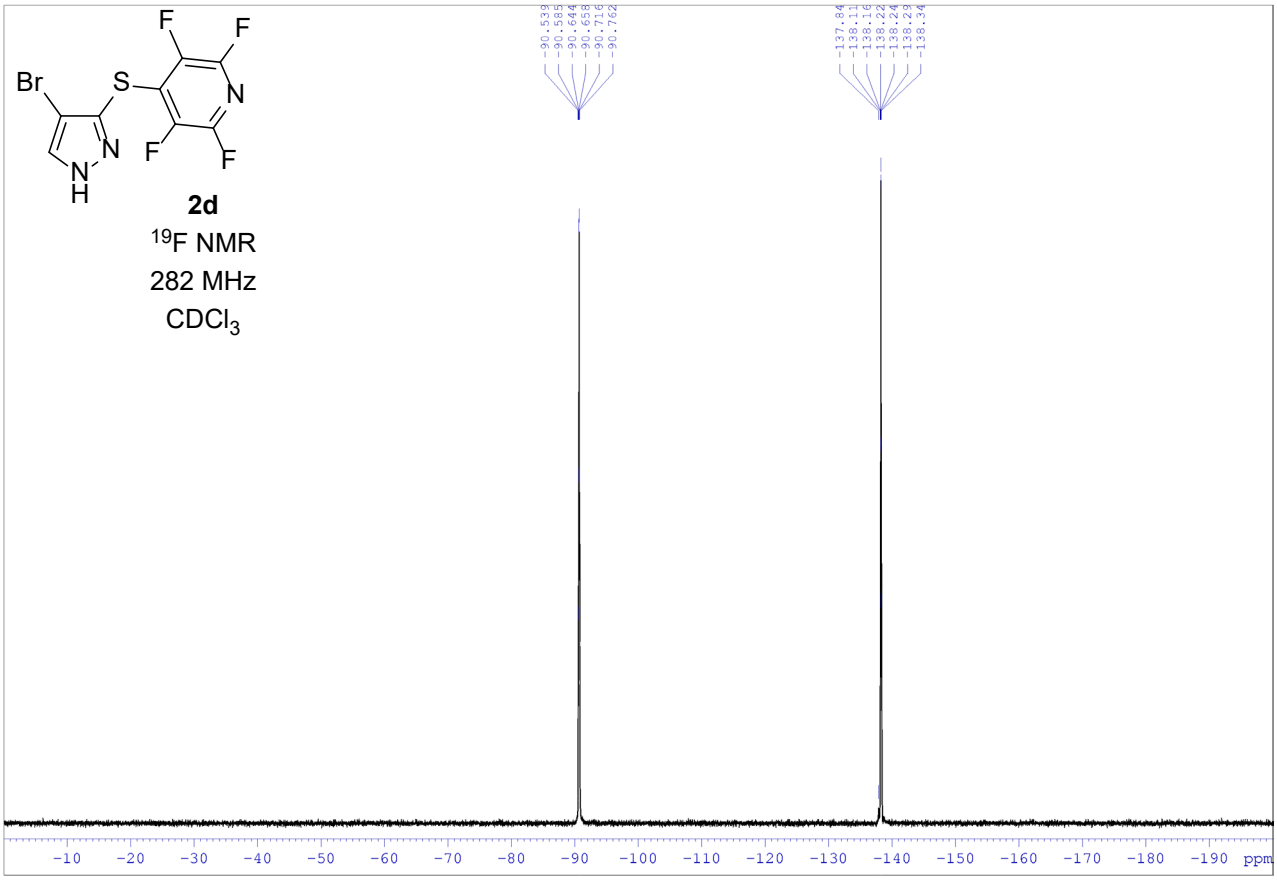


Figure S16. ^{19}F NMR of **2d** in $CDCl_3$.

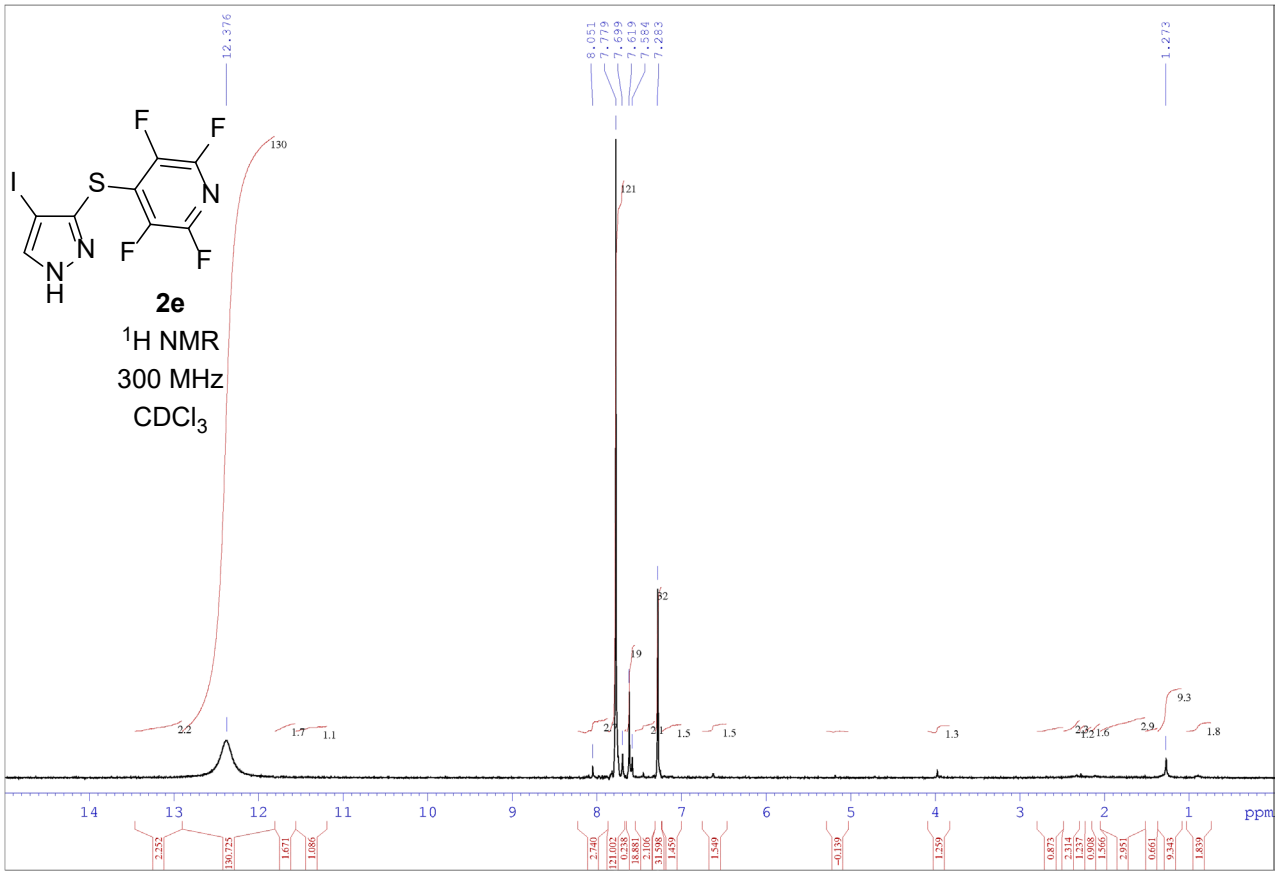


Figure S17. ^{1}H NMR of **2e** in $CDCl_3$.

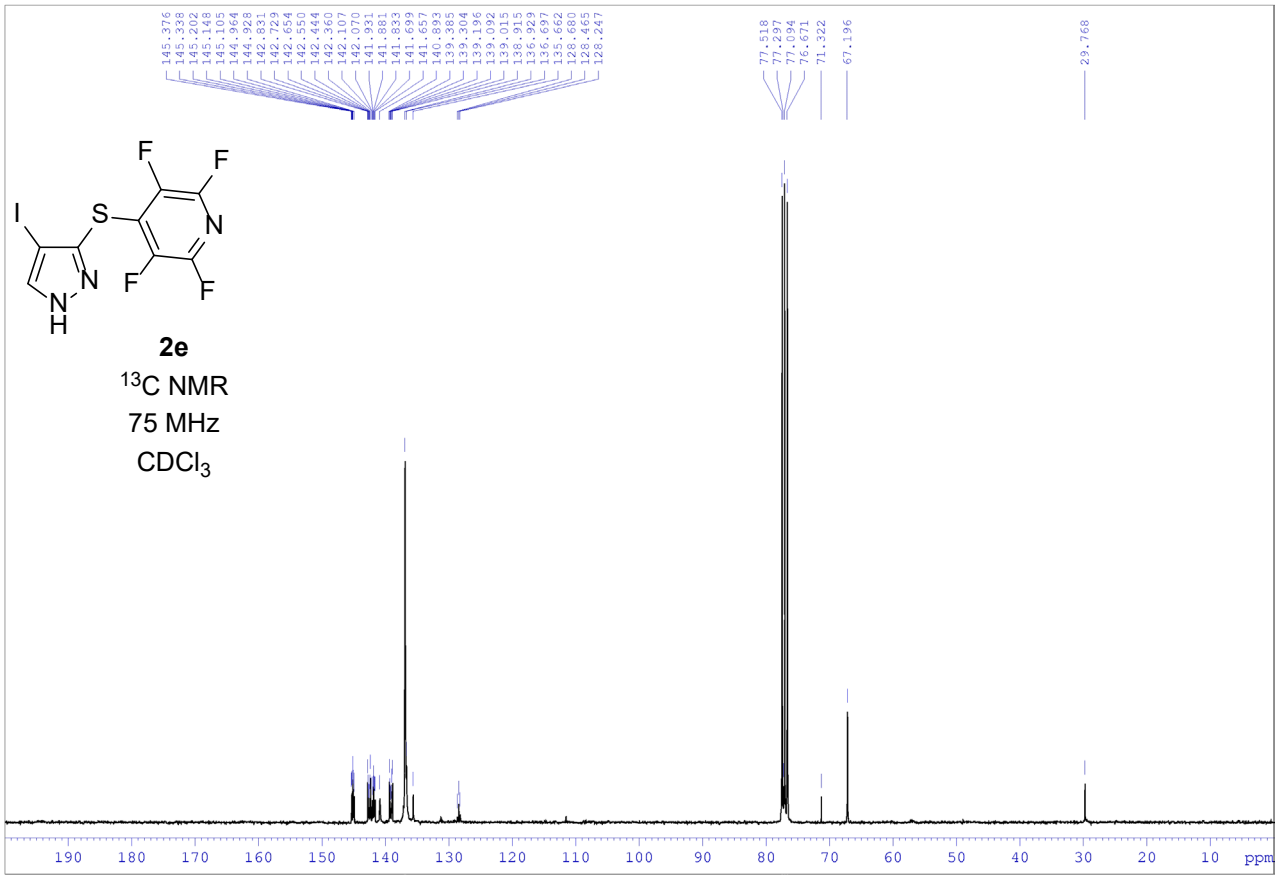


Figure S18. ^{13}C NMR of **2e** in $CDCl_3$.

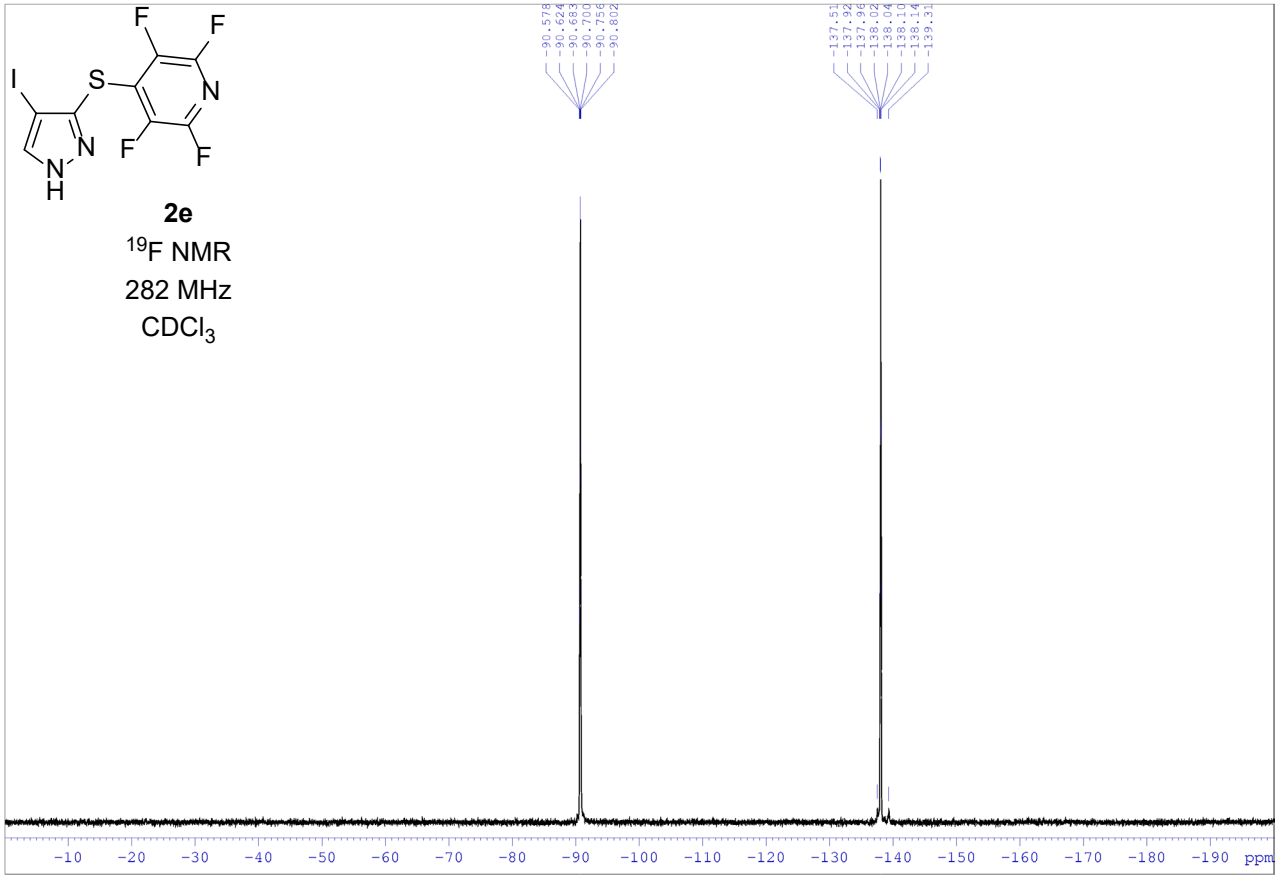


Figure S19. ^{19}F NMR of **2e** in $CDCl_3$.

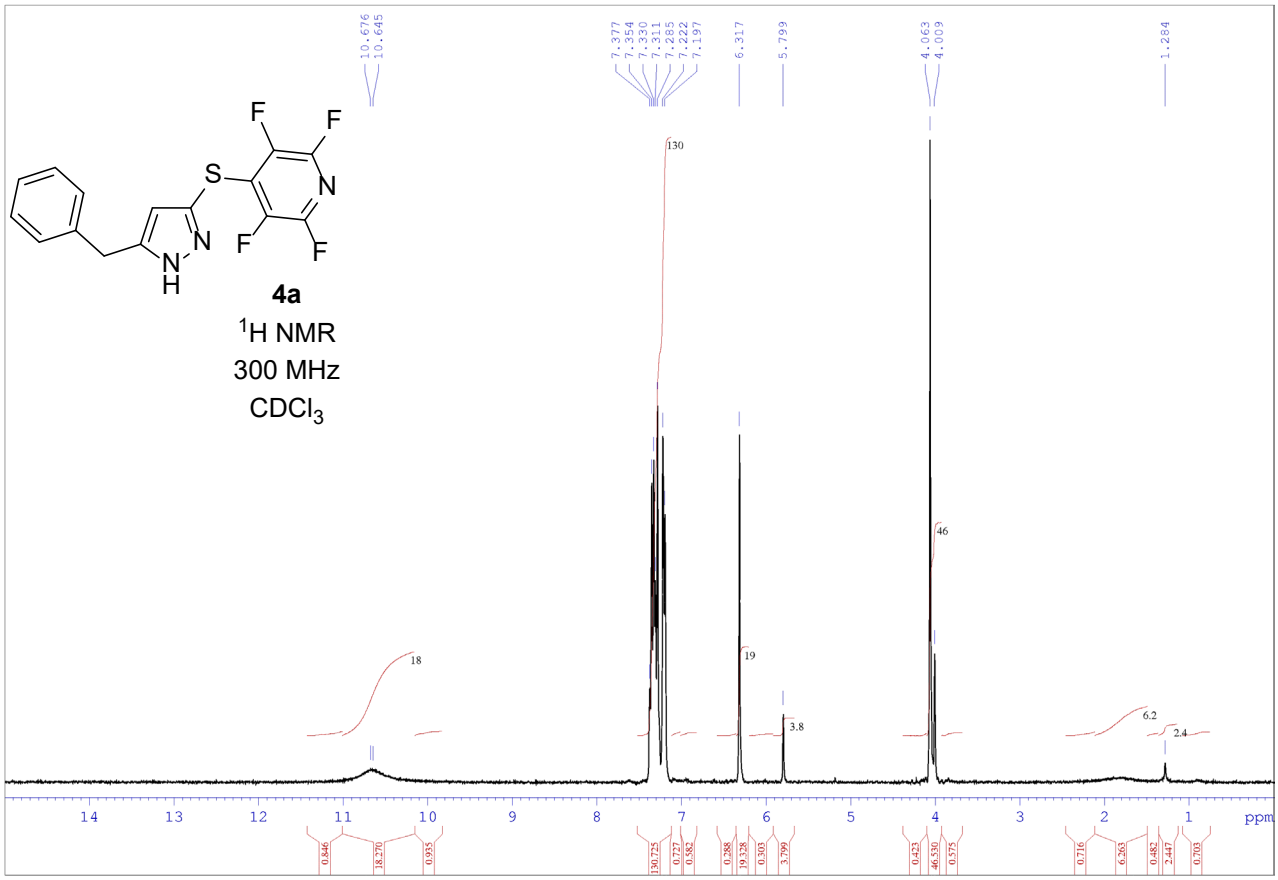


Figure S20. ^{1}H NMR of **4a** in $CDCl_3$.

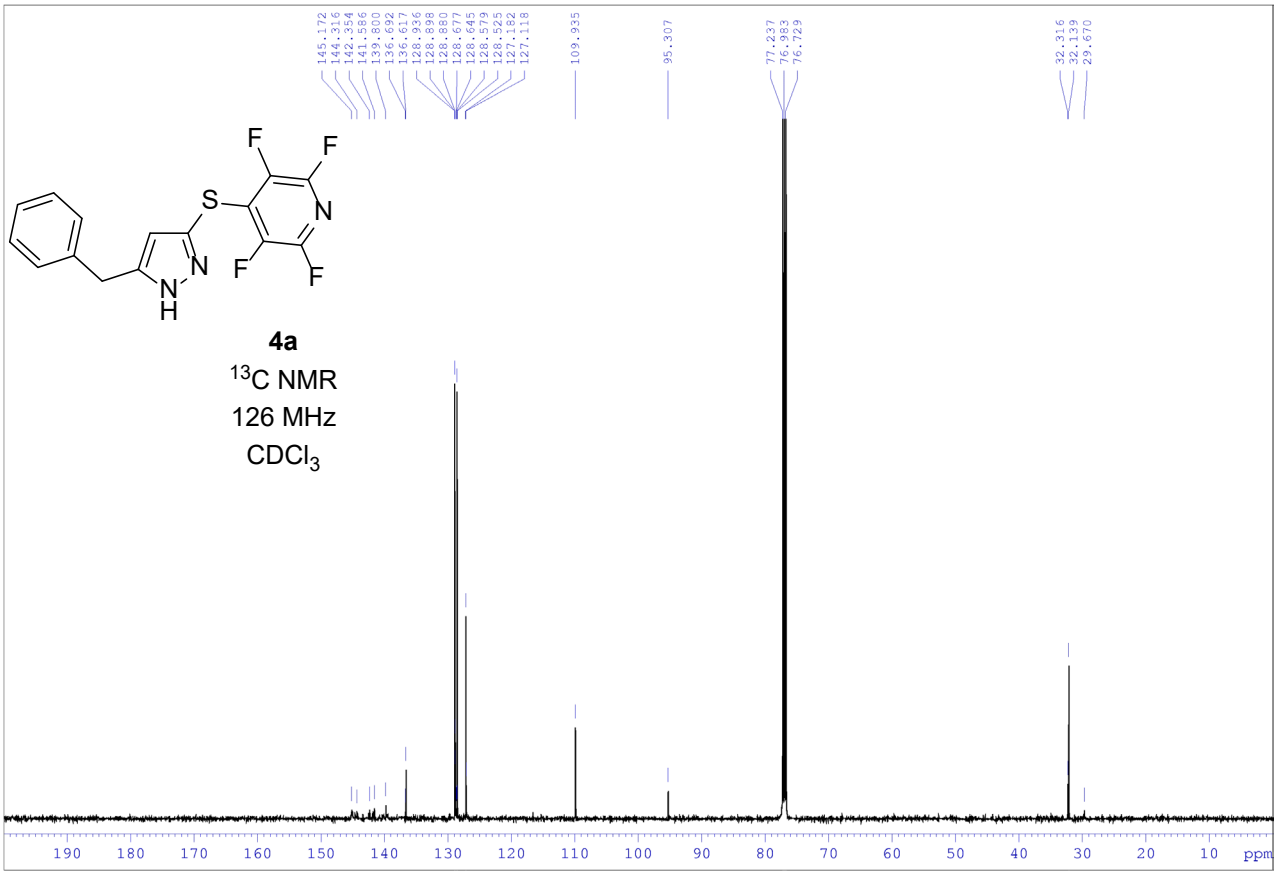


Figure S21. ^{13}C NMR of **4a** in $CDCl_3$.

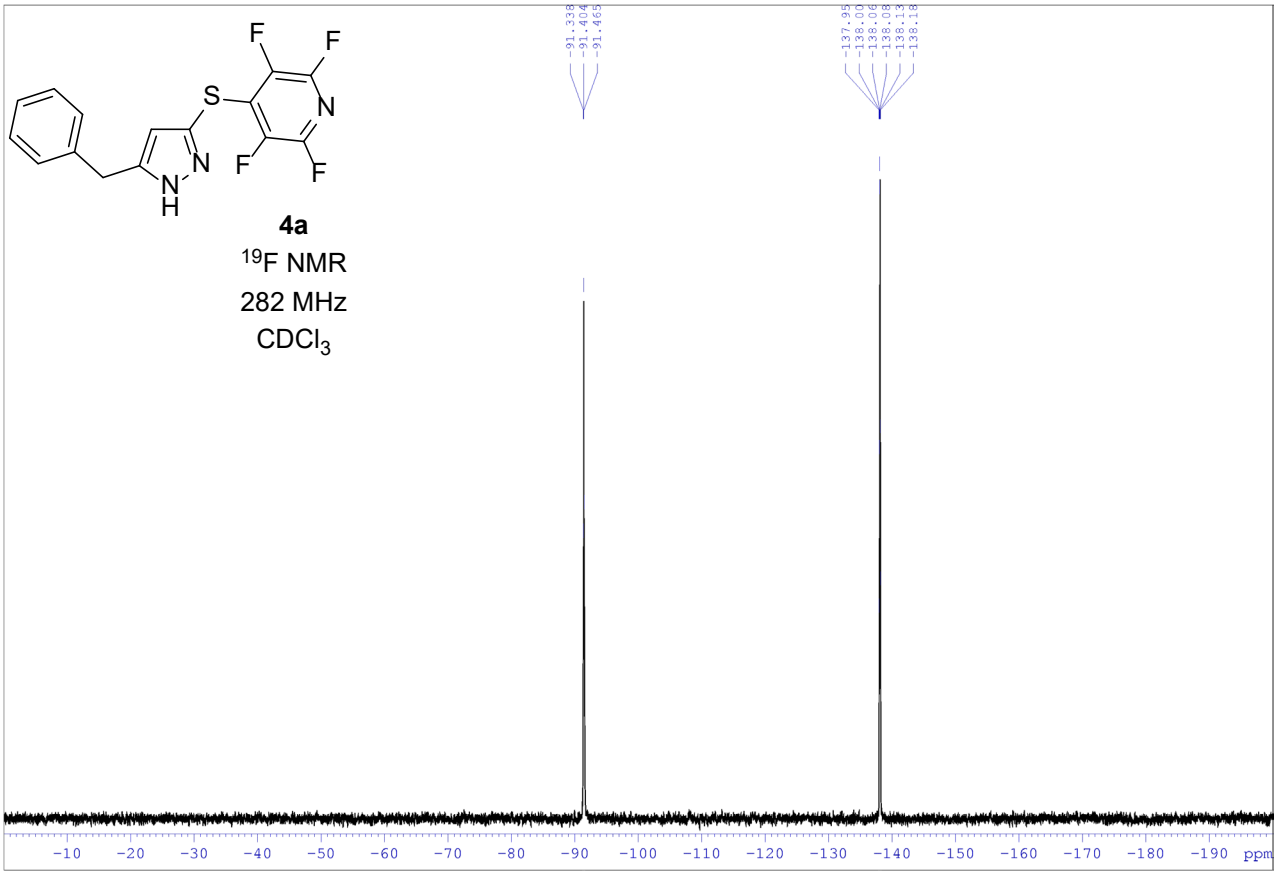


Figure S22. ^{19}F NMR of **4a** in $CDCl_3$.

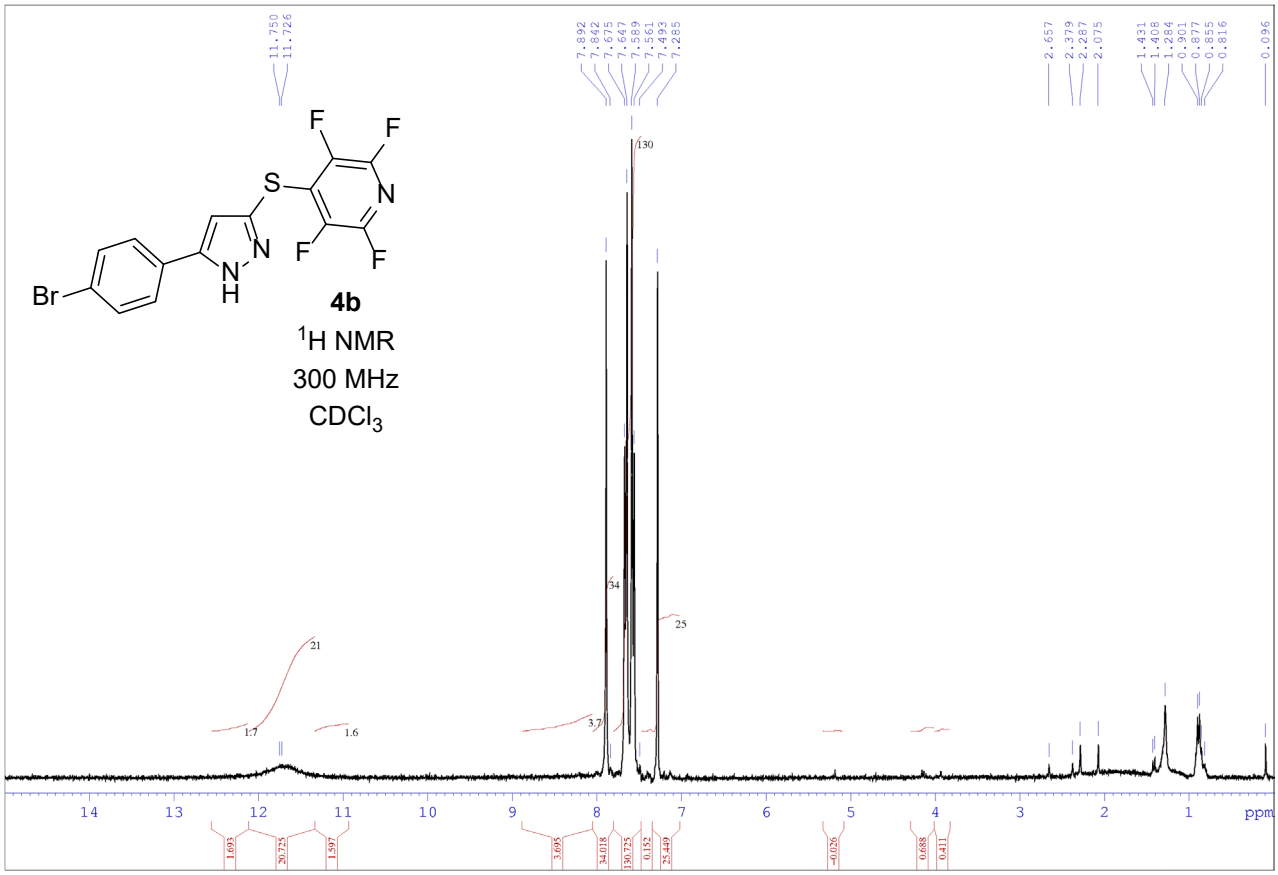


Figure S23. ^{1}H NMR of **4b** in $CDCl_3$.

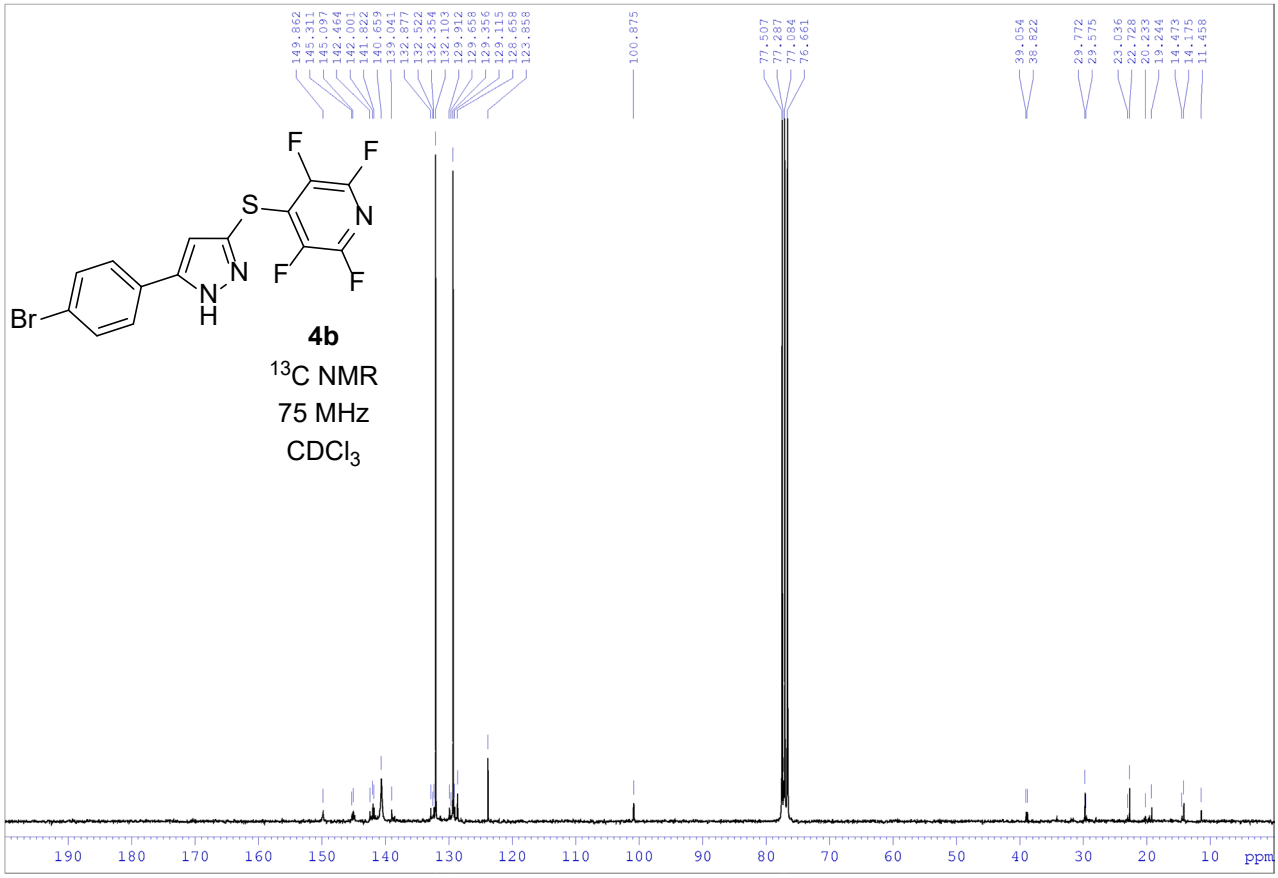


Figure S24. ^{13}C NMR of **4b** in $CDCl_3$.

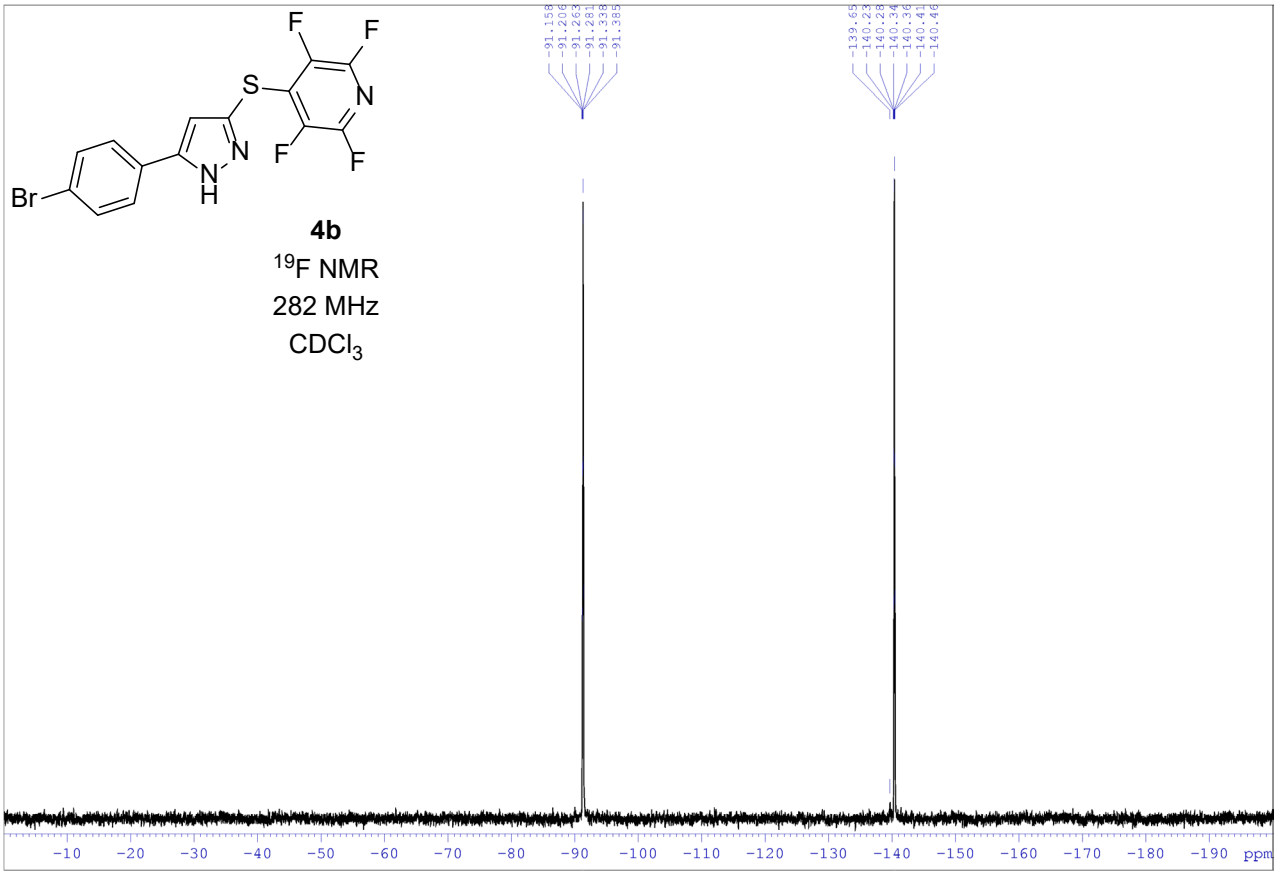


Figure S25. ^{19}F NMR of **4b** in $CDCl_3$