Supporting Information
for

Exercise in 1-aryl-3-CF_3-1*H*-pyrazoles: Regioselective synthesis of 4-/5-iodides and cross-coupling reactions

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Content:

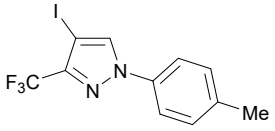
1. General information

Common solvents and starting materials were purchased and used as received. If not stated otherwise, reactions in solutions were carried out under inert atmosphere of argon, in flame-dried flasks; subsequent manipulations were conducted in air. Products were purified either by filtration through a short silica gel pad (FCC) or by standard column chromatography (CC), using freshly distilled solvents as eluents; selected solid materials were recrystallized from appropriate solvents. Melting points were determined in capillaries with a Stuart SMP30 apparatus with automatic temperature monitoring, and are uncorrected. NMR experiments were performed with a Bruker Avance III or with a Bruker AvanceNeo instruments (^{1}H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz); chemical shifts are given relative to solvent residual peaks [for $CDCl_3$: ^{1}H NMR: δ = 7.26, ^{13}C NMR: δ = 77.16; for DMSO-d_6: ^{1}H NMR: δ = 2.50, ^{13}C NMR: δ = 39.52][1] or to $CFCl_3$ (^{19}F NMR: δ = 0.00) used as external standard. The IR spectra were measured with an Agilent Cary 630 FTIR spectrometer, in neat. ESI-MS were performed with a Varian 500-MS LC Ion Trap; high resolution MS (ESI-TOF) measurements were taken with a Waters Synapt G2-Si mass spectrometer. Combustion analyses were performed with a Vario EL III (Elementar Analysensysteme GmbH) instrument. Starting nitrile imine precursors i.e. hydrazonoyl bromides **7a**-**7h** were prepared in analogy to general literature protocol,[2a] by NBS-mediated bromination of the respective fluoral arylhydrazones.[2b]

2. Synthetic procedures and characterization data

General Procedure A for synthesis of 4-iodopyrazoles **4a**-**4f**: A solution of 1-aryl-3-trifluoromethylpyrazole **3** (1.0 mmol), CAN (603 mg, 1.1 mmol), and elemental iodine (330 mg, 1.3 mmol) in MeCN (6 mL) was refluxed overnight. After solvent was removed in vacuo, the residue was dissolved in DCM (15 mL), the mixture was washed with sat. aq. $Na_2S_2O_3$ (5 mL), then with water (10 mL), and the organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product **4** was purified by filtration through a short silica gel pad (FCC) or by standard column chromatography (CC).

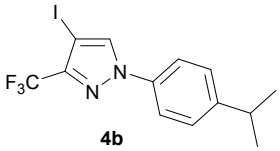
4-Iodo-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**4a**):



4a

FCC (SiO_2, hexane/DCM 3:2); yellow oil, 285 mg (81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.29-7.31 (m, 2H), 7.53-7.55 (m, 2H), 7.97 (s, 1H, 5-H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 21.1, 55.9 (q, $^{3}J_{C\text{-}F} \approx 1.6$ Hz), 119.7, 121.0 (q, $^{1}J_{C\text{-}F} = 270.2$ Hz), 130.3, 134.4, 136.7, 138.5, 144.9 (q, $^{2}J_{C\text{-}F} = 37.2$ Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.72 (s, CF_3). IR (neat) ν 1521, 1470, 1394, 1230, 1163, 1129, 1066, 992, 813 cm^{-1}. ESI-MS (*m/z*): 353.1 (100, $[M+H]^+$). Anal. calcd for $C_{11}H_8F_3IN_2$ (352.1): C 37.52, H 2.29, N 7.96; found: C 37.45, H 2.33, N 7.85.

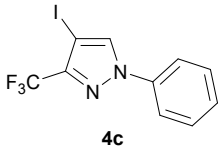
4-Iodo-1-(*p*-isopropylphenyl)-3-trifluoromethylpyrazole (**4b**):



4b

FCC (SiO_2, hexane/DCM 4:1); yellow oil, 285 mg (75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (d, J = 7.0 Hz, 6H), 2.97 (hept, J = 7.0 Hz, 1H), 7.32-7.34 (m, 2H), 7.54-7.56 (m, 2H), 7.96 (s, 1H, 5-H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 23.9, 33.8, 55.8 (br, C-4), 119.8, 121.0 (q, $^1J_{C\text{-}F}$ = 270.0 Hz), 127.7, 134.4, 136.8, 144.8 (q, $^2J_{C\text{-}F}$ = 37.3 Hz), 149.4. ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.58 (s, CF_3). IR (neat) ν 1525, 1502, 1476, 1394, 1230, 1163, 1129, 1051, 992, 835 cm^{-1}. ESI-MS (*m/z*): 381.2 (100, $[M+H]^+$). Anal. calcd for $C_{13}H_{12}F_3IN_2$ (380.1): C 41.07, H 3.18, N 7.37; found: C 41.19, H 3.18, N 7.36.

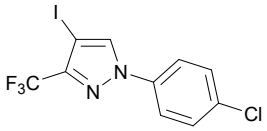
4-Iodo-1-phenyl-3-trifluoromethylpyrazole (**4c**):



4c

FCC (SiO_2, hexane); colorless oil, 297 mg (88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.40 (m, 1H), 7.47-7.50 (m, 2H), 7.64-7.66 (m, 2H), 8.00 (s, 1H, 5-H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 56.2 (q, $^3J_{C\text{-}F}$ ≈ 1.7 Hz), 119.8, 120.9 (q, $^1J_{C\text{-}F}$ = 270.2 Hz), 128.4, 129.8, 134.5, 138.9, 145.2 (q, $^2J_{C\text{-}F}$ = 37.1 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.78 (s, CF_3). IR (neat) ν 1599, 1476, 1394, 1230, 1163, 1126, 1066, 992, 757, 686 cm^{-1}. ESI-MS (*m/z*): 339.2 (100, $[M+H]^+$). Anal. calcd for $C_{10}H_6F_3IN_2$ (338.1): C 35.53, H 1.79, N 8.29; found: C 35.57, H 1.81, N 8.32.

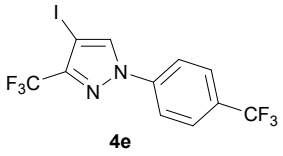
1-(*p*-Chlorophenyl)-4-iodo-3-trifluoromethylpyrazole (**4d**):



4d

FCC (SiO_2, hexane/DCM 4:1); pale yellow solid, 290 mg (78%); mp 60-62 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.46 (m, 2H), 7.58-7.61 (m, 2H), 7.97 (s, 1H, 5-H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 56.6 (q, $^3J_{C\text{-}F}$ ≈ 1.6 Hz), 120.7 (q, $^1J_{C\text{-}F}$ = 270.3 Hz), 120.9, 130.0, 134.1, 134.4, 137.3, 145.5 (q, $^2J_{C\text{-}F}$ = 37.4 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.86 (s, CF_3). IR (neat) ν 1476, 1387, 1230, 1156, 1111, 1059, 985, 958, 824 cm^{-1}. ESI-MS (*m/z*): 375.1 (38, $[M\{^{37}Cl\}+H]^+$), 373.1 (100, $[M\{^{35}Cl\}+H]^+$). Anal. calcd for $C_{10}H_5ClF_3IN_2$ (372.5): C 32.24, H 1.35, N 7.52; found: C 32.35, H 1.40, N 7.36.

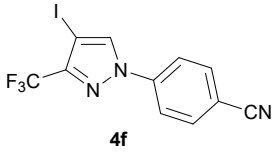
4-Iodo-1-(*p*-trifluoromethylphenyl)-3-trifluoromethylpyrazole (**4e**):



4e

FCC (SiO_2, hexane/DCM 9:1); colorless solid, 300 mg (74%); mp 62-63 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75-7.77 (m, 2H), 7.80-7.82 (m, 2H), 8.08 (s, 1H, 5-H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 57.2 (br, C-4), 119.6 (br), 120.7 (q, $^1J_{C\text{-}F}$ = 270.5 Hz, 3-CF_3), 123.7 (q, $^1J_{C\text{-}F}$ = 272.2 Hz), 127.2 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 130.3 (q, $^2J_{C\text{-}F}$ = 33.2 Hz), 134.5, 141.1, 146.0 (q, $^2J_{C\text{-}F}$ = 37.5 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.08, –62.59 (2s, 2CF_3). IR (neat) ν 1618, 1476, 1390, 1320, 1238, 1137, 1107, 1078, 1055, 992, 954, 842, 801 cm^{-1}. ESI-MS (*m/z*): 407.1 (100, $[M+H]^+$). Anal. calcd for $C_{11}H_5F_6IN_2$ (406.1): C 32.54, H 1.24, N 6.90; found: C 32.52, H 1.38, N 6.88.

4-(4-Iodo-3-trifluoromethylpyrazol-1-yl)benzonitrile (**4f**):

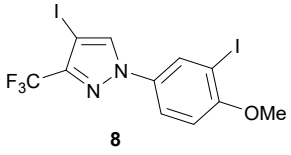


4f

FCC (SiO_2, hexane/DCM 1:1); colorless solid, 247 mg (68%); mp 149-151 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79-7.84 (m, 4H), 8.11 (s, 1H, 5-H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 57.8 (br, C-4), 111.9, 117.9, 119.7, 120.5 (q, $^1J_{C\text{-}F}$ = 270.6 Hz), 134.0, 134.5, 141.5, 146.4 (q, $^2J_{C\text{-}F}$ = 37.8 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.20 (s, CF_3). IR (neat) ν 2229, 1607, 1506, 1476, 1390, 1279, 1170, 1115, 1051, 947, 764, 741 cm^{-1}. (-)-ESI-MS (*m/z*): 361.8 (100, $[M–H]^–$). Anal. calcd for $C_{11}H_5F_3IN_3$ (363.1): C 36.39, H 1.39, N 11.57; found: C 36.49, H 1.36, N 11.52.

Attempted synthesis of **4h** by treatment of 1-(*p*-methoxyphenyl)-3-trifluoromethylpyrazole (**3h**) with I_2/CAN according to the General Procedure A provided a mixture of 4-iodopyrazole derivatives **8** and **9**, which were isolated by standard column chromatography (CC).

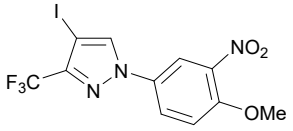
4-Iodo-1-(3-iodo-4-methoxyphenyl)-3-trifluoromethylpyrazole (**8**):



8

CC (SiO_2, hexane/DCM 7:3, first eluted); colorless solid, 148 mg (30%); mp 92-94 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.60 (dd, *J* = 2.7, 8.8 Hz, 1H), 7.91 (s, 1H, 5-H), 8.06 (d, *J* = 2.7 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 56.1 (q, $^3J_{C\text{-}F} \approx$ 1.5 Hz), 56.9, 86.3, 110.9, 120.8 (q, $^1J_{C\text{-}F}$ = 270.3 Hz), 121.2, 131.1, 133.2, 134.5, 145.1 (q, $^2J_{C\text{-}F}$ = 37.3 Hz), 158.3. ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.74 (s, CF_3). IR (neat) ν 1487, 1275, 1230, 1163, 1115, 1070, 1044, 988, 813 cm^{-1}. ESI-MS (*m/z*): 495.0 (100, $[M+H]^+$). Anal. calcd for $C_{11}H_7F_3I_2N_2O$ (494.0): C 26.75, H 1.43, N 5.67; found: C 26.76, H 1.65, N 5.41.

4-Iodo-1-(4-methoxy-3-nitrophenyl)-3-trifluoromethylpyrazole (**9**):



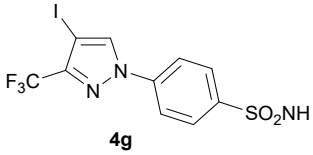
9

CC (SiO_2, hexane/DCM 7:3, second eluted); pale yellow solid, 193 mg (39%); mp 131-133 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.03 (s, 3H), 7.22 (d, J = 9.1 Hz, 1H), 7.90 (dd, J = 2.8, 9.1 Hz, 1H), 8.01 (s, 1H, 5-H), 8.16 (d, J = 2.8 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 56.6 (q, $^3J_{C\text{-}F}$ ≈ 1.4 Hz), 57.2, 114.9, 117.3, 120.6 (q, $^1J_{C\text{-}F}$ = 270.5 Hz), 125.3, 131.6, 134.4, 139.6, 145.7 (q, $^2J_{C\text{-}F}$ = 37.5 Hz), 152.6. ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.96 (s, CF_3). IR (neat) ν 1536, 1476, 1346, 1275, 1223, 1170, 1126, 1066, 992, 876, 816, 746 cm^{-1}. ESI-MS (*m/z*): 414.1 (100, $[M+H]^+$). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_8F_3IN_3O_3$ 413.9562, found 413.9572.

Competition experiment: A solution of **3a** (22.6 mg, 0.1 mmol), **3f** (23.7 mg, 0.1 mmol), CAN (27.4 mg, 0.05 mmol), and elemental iodine (12.7 mg, 0.05 mmol) in MeCN (1 mL) was refluxed overnight. After standard aqueous work-up according to General Procedure A the resulting mixture was analyzed by ^{1}H NMR spectroscopy, which evidenced the formation of the expected products **4a** and **4f** in ca. 10:1 ratio, along with unconsumed starting materials (conversion of **3a**: 79%; conversion of **3f**: 8%).

General Procedure B for synthesis of 4-iodopyrazoles **4g** and **4h**: To a solution of CF_3-pyrazole **3g** or **3h** (1.0 mmol) in glacial acetic acid (1 mL) was added a solution of NIS (338 mg, 1.5 mmol) in TFA (1 mL) and the resulting mixture was heated overnight at 80 °C. The solution was cooled to room temperature, diluted with DCM (60 mL), washed with sat. aq. $Na_2S_2O_3$ (2 x 5 mL), and then with sat. aq. $NaHCO_3$ (3 x 5 mL). The organic layer was separated, dried over Na_2SO_4, and solvents were removed in vacuo. The products were purified by column chromatography (CC).

4-(4-Iodo-3-trifluoromethylpyrazol-1-yl)-benzenosulfonamide (**4g**):

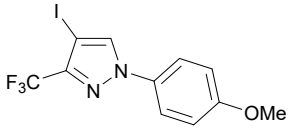


4g

CC (SiO_2, hexane/EtOAc 2:3); light yellow solid, 296 mg (71%); mp 166-168 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.48 (s_{br}, 2H, NH_2), 7.97-7.99 (m, 2H), 8.05-8.08 (m, 2H), 9.05 (s, 1H, 5-H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 59.7 (br), 119.4, 120.9 (q, $^1J_{C\text{-}F}$ = 270.0 Hz), 127.4, 136.7, 140.2, 143.2, 144.1 (q, $^2J_{C\text{-}F}$ = 36.4 Hz). ^{19}F NMR (565 MHz, DMSO-d_6): δ –60.72 (s, CF_3). IR (neat) ν 3340, 3247, 1592, 1477, 1387, 1331, 1234, 1156, 1118, 1096, 992, 910, 835 cm^{-1}. HRMS ((-)-ESI-TOF) *m/z*: $[M-H]^-$ calcd for $C_{10}H_7F_3IN_3O_2S$ 415.9177, found 415.9178.

Following the General Procedure B the reaction of **3h** (1.0 mmol) with NIS (1.5 mmol) in AcOH/TFA provided, after standard work-up, a ca. 4:1 mixture of 4-iodopyrazole **4h** and 3-iodo-4-methoxyphenyl-functionalized pyrazole **10** identified as major products, which were separated by standard column chromatography (CC).

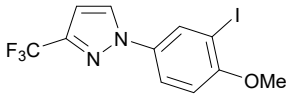
4-Iodo-1-(*p*-methoxyphenyl)-3-trifluoromethylpyrazole (**4h**):



4h

CC (SiO_2, hexane/EtOAc 9:1, first eluted); yellow oil, 133 mg (36%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.97-6.99 (m, 2H), 7.53-7.56 (m, 2H), 7.90 (s, 1H, 5-H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 55.6 (br, C-4), 55.8, 114.9, 121.0 (q, $^1J_{C\text{-}F}$ = 270.1 Hz), 121.6, 132.6, 134.6, 144.9 (q, $^2J_{C\text{-}F}$ = 37.2 Hz), 159.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ –61.71 (s, CF_3). IR (neat) ν 1521, 1502, 1476, 1230, 1163, 1126, 1066, 1029, 992, 831 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_9F_3IN_2O_2$ 368.9712, found 368.9712.

1-(3-Iodo-4-methoxyphenyl)-3-trifluoromethylpyrazole (**10**):

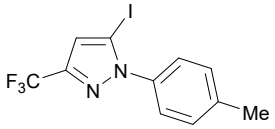


10

CC (SiO_2, hexane/EtOAc 9:1, second eluted); light orange oil, 37 mg (10%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 7.64 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.84 (m_c, 1H), 8.11 (d, *J* = 2.7 Hz, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 56.9, 86.2, 106.1 (q, $^3J_{C\text{-}F}$ = 2.2 Hz), 110.9, 121.3 (q, $^1J_{C\text{-}F}$ = 268.7 Hz), 128.5, 131.3, 133.9, 144.0 (q, $^2J_{C\text{-}F}$ = 38.5 Hz), 158.0. ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.06 (s, CF_3). IR (neat) ν 1495, 1383, 1275, 1167, 1129, 1051, 1018, 958, 805, 764 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_9F_3IN_2O$ 368.9712, found 368.9720.

General Procedure C for synthesis of 5-iodopyrazoles **5a**-**5h**: To a solution of 1-aryl-3-CF_3-pyrazole **3** (1.0 mmol) in dry THF (5 mL) was added dropwise *n*-BuLi (2.5M in hexane, 0.52 mL, 1.3 mmol) under vigorous stirring at –78 °C. After 10 min, a solution of iodine (356 mg, 1.4 mmol) in dry THF (3 mL) was added and the mixture was allowed to reach room temperature within 4h. The resulting was diluted with DCM (30 mL), washed with sat. aq. $Na_2S_2O_3$ (10 mL), then with water (5 mL), the organic layer was dried over Na_2SO_4, and the solvents were removed under reduced pressure. Crude product was isolated by filtration through a short silica gel pad (FCC).

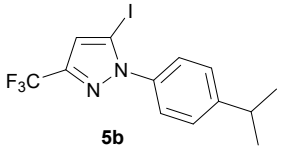
5-Iodo-1-(*p*-tolyl)-3-trifluoromethyl-1*H*-pyrazole (**5a**):



5a

FCC (SiO_2, hexane/DCM 1:1); light orange solid, 303 mg (86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.86 (s, 1H, 4-H), 7.30-7.31 (m, 2H), 7.38-7.40 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 21.3, 83.0, 115.1 (q, $^3J_{C\text{-}F}$ ≈ 2.1 Hz), 120.8 (q, $^1J_{C\text{-}F}$ = 269.3 Hz), 126.3, 129.7, 137.1, 139.9, 145.4 (q, $^2J_{C\text{-}F}$ = 38.8 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.39 (s, CF_3). IR (neat) ν 1506, 1457, 1368, 1230, 1167, 1118, 1085, 980, 965, 824, 801 cm^{-1}. ESI-MS (*m/z*): 353.1 (100, $[M+H]^+$). Anal. calcd for $C_{11}H_8F_3IN_2$ (352.1): C 37.52, H 2.29, N 7.96; found: C 37.62, H 2.31, N 7.77.

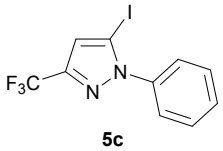
5-Iodo-1-(*p*-isopropylphenyl)-3-trifluoromethylpyrazole (**5b**):



5b

FCC (SiO_2, hexane/DCM 9:1); colorless oil, 296 mg (78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7.0 Hz, 6H), 3.00 (hept, *J* = 7.0 Hz, 1H), 6.87 (s, 1H, 4-H), 7.35-7.37 (m, 2H), 7.42-7.44 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 24.0, 34.1, 82.9, 115.2 (q, $^3J_{C\text{-}F}$ = 2.1 Hz, C-5), 120.8 (q, $^1J_{C\text{-}F}$ = 269.3 Hz), 126.4, 127.2, 137.3, 145.4 (q, $^2J_{C\text{-}F}$ = 38.9 Hz), 150.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.47 (s, CF_3). IR (neat) ν 1506, 1457, 1372, 1230, 1170, 1133, 1100, 980, 835 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}F_3IN_2$ 381.0076, found 381.0082.

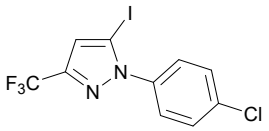
5-Iodo-1-phenyl-3-trifluoromethylpyrazole (**5c**):



5c

FCC (SiO_2, hexane/DCM 4:1); light orange oil, 284 mg (84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (s, 1H, 4-H) 7.47-7.54 (m, 5H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 82.9, 115.4 (q, $^3J_{C\text{-}F}$ ≈ 2.1 Hz), 120.7 (q, $^1J_{C\text{-}F}$ = 269.3 Hz), 126.5, 129.2, 129.7, 139.5, 145.6 (q, $^2J_{C\text{-}F}$ = 38.9 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.40 (s, CF_3). IR (neat) ν 1495, 1368, 1230, 1167, 1129, 1100, 980, 764, 696 cm^{-1}. ESI-MS (*m/z*): 339.2 (100, $[M+H]^+$). Anal. calcd for $C_{10}H_6F_3IN_2$ (338.1): C 35.53, H 1.79, N 8.29; found: C 35.44, H 1.77, N 8.30.

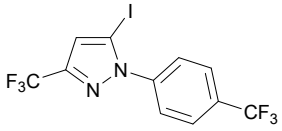
1-(*p*-Chlorophenyl)-5-iodo-3-trifluoromethylpyrazole (**5d**):



5d

FCC (SiO_2, hexane/DCM 9:1); light orange solid, 286 mg (77%); mp 120-121 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (s, 1H, 4-H), 7.47-7.51 (m, 4H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 82.8, 115.7 (q, $^3J_{C\text{-}F}$ = 2.2 Hz), 120.6 (q, $^1J_{C\text{-}F}$ = 269.3 Hz), 127.9, 129.5, 135.8, 138.0, 146.0 (q, $^2J_{C\text{-}F}$ = 39.1 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.66 (s, CF_3). IR (neat) ν 1487, 1364, 1226, 1178, 1126, 1088, 980, 828, 801, 738 cm^{-1}. ESI-MS (*m/z*): 375.0 (31, [M{^{37}Cl}+H]$^+$), 373.1 (100, [M{^{35}Cl}+H]$^+$). Anal. calcd for $C_{10}H_5ClF_3IN_2$ (372.5): C 32.24, H 1.35, N 7.52; found: C 32.37, H 1.61, N 7.54.

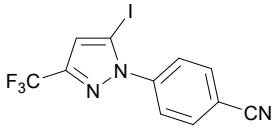
5-Iodo-1-(*p*-trifluoromethylphenyl)-3-trifluoromethylpyrazole (**5e**):



5e

FCC (SiO_2, hexane/DCM 9:1); orange solid, 349 mg (86%); mp 101-103 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.93 (s, 1H, 4-H), 7.70-7.73 (m, 2H), 7.78-7.81 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 82.3, 116.3 (q, $^3J_{C\text{-}F}$ = 2.1 Hz) 120.6 (q, $^1J_{C\text{-}F}$ = 269.5 Hz, 3-CF_3), 123.7 (q, $^1J_{C\text{-}F}$ = 272.5 Hz), 126.5 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 126.9, 131.7 (q, $^2J_{C\text{-}F}$ = 33.2 Hz), 142.2, 146.4 (q, $^2J_{C\text{-}F}$ = 39.2 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.73, –62.74 (2s, 2CF_3). IR (neat) ν 1618, 1513, 1398, 1364, 1323, 1230, 1156, 1103, 1066, 980, 846, 813, 701 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_6F_3IN_2$ 406.9480, found 406.9478. Anal. calcd for $C_{11}H_5F_6IN_2$ (406.1): C 32.54, H 1.24, N 6.90; found: C 32.56, H 1.46, N 7.05.

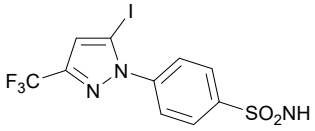
4-(5-Iodo-3-trifluoromethylpyrazol-1-yl)benzonitrile (**5f**):



5f

FCC (SiO_2, hexane/DCM 4:1) followed by recrystallization from hexane; light orange solid, 239 mg (66%); mp 116-117 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1H, 4-H), 7.74-7.76 (m, 2H), 7.82-7.84 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 82.0, 113.5, 116.7 (q, $^3J_{C\text{-}F}$ = 2.0 Hz), 117.8, 120.4 (q, $^1J_{C\text{-}F}$ = 269.5 Hz), 127.0, 133.2, 142.6, 146.7 (q, $^2J_{C\text{-}F}$ = 39.3 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.78 (s, CF_3). IR (neat) ν 2233, 1607, 1506, 1368, 1230, 1185, 1126, 1092, 980, 846, 813 cm^{-1}. ESI-MS (*m/z*): 364.0 (100, [M+H]$^+$). Anal. calcd for $C_{11}H_5F_3IN_3$ (363.1): C 36.39, H 1.39, N 11.57; found: C 36.24, H 1.55, N 11.71.

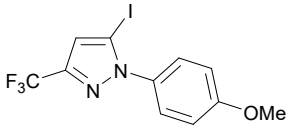
4-(5-Iodo-3-trifluoromethylpyrazol-1-yl)-benzenosulfonamide (**5g**)[3]: Following our previous report, 4/5-unsubstituted pyrazole **3g** (1.0 mmol) in a mixture of dry THF (5 mL) and TMEDA (0.45 mL) was reacted with excess *n*-BuLi (2.5M in hexane, 1.2 mL, 3.0 mmol), at -78 °C, and treated with a solution of I_2 (812 mg, 3.2 mmol) in dry THF to give after standard work-up (performed according to General Procedure C) crude product **5g** which was purified by column chromatography (CC).



5g

CC (SiO_2, hexane/EtOAc 3:1 gradient 3:2); colorless solid, 270 mg (65%); mp 165-167 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.34 (s, 1H, 4-H), 7.57 (s_{br}, 2H, NH_2), 7.82-7.85 (m, 2H), 8.00-8.04 (m, 2H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 89.0, 115.6 (br), 120.8 (q, $^1J_{C\text{-}F}$ = 269.2 Hz), 126.8, 127.2, 141.4, 144.3 (q, $^2J_{C\text{-}F}$ = 38.0 Hz), 144.9. ^{19}F NMR (565 MHz, DMSO-d_6): δ –61.08 (s, CF_3). NMR spectra of **5g** in full accordance to the literature data.[3]

5-Iodo-1-(*p*-methoxyphenyl)-3-trifluoromethylpyrazole (**5h**)[3]:

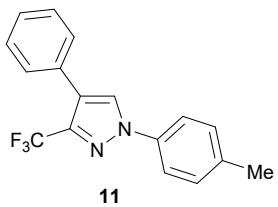


5h

CC (SiO_2, hexane/EtOAc 9:1); colorless solid, 327 mg (89%); mp 84-85 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.85 (s, 1H, 4-H), 6.98-7.01 (m, 2H), 7.39-7.42 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 55.7, 83.7, 114.3, 114.9 (q, $^3J_{C\text{-}F}$ = 2.1 Hz), 120.8 (q, $^1J_{C\text{-}F}$ = 269.2 Hz), 128.0, 132.6, 145.3 (q, $^2J_{C\text{-}F}$ = 38.9 Hz), 145.3. ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.50 (s, CF_3). NMR spectra of **5h** in full accordance to the literature data.[3]

Synthesis of diaryl 3-trifluoromethyl pyrazoles 11 and 12 through Suzuki-Myiaura cross-coupling: A solution of **4a** or **5a** (88 mg, 0.25 mmol), solid K_2CO_3 (138 mg, 1.0 mmol) and phenylboronic acid (46 mg, 0.38 mmol) in THF/H_2O (4:1 mixture, 10 mL) was degassed by a repeated procedure of freeze-pump-thaw, and $Pd(PPh_3)_4$ (87 mg, 30 mol% with respect to iodopyrazole) was added. The mixture was refluxed for 2 d, cooled to room temperature, diluted with H_2O (20 mL), and the resulting was extracted with DCM (3 x 5 mL). Combined organics were dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Crude product was purified by standard column chromatography (CC).

4-Phenyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**11**):

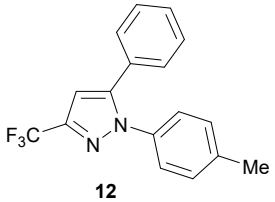


11

CC (SiO_2, hexane/DCM 9:1); colorless solid, 42 mg (56%); mp 69-71 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.28-7.31 (m, 2H), 7.36-7.39 (m, 1H), 7.42-7.44 (m, 2H),

7.47-7.50 (m, 2H), 7.61-7.63 (m, 2H), 7.96 (s, 1H, 5-H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 21.1, 119.8, 121.8 (q, $^1J_{C\text{-}F}$ = 269.7 Hz), 123.7 (br, C-4), 127.6, 128.0, 128.7, 128.8 (br, *ortho*-CH), 130.3, 130.5, 137.1, 137.9, 140.2 (q, $^2J_{C\text{-}F}$ = 36.7 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –59.40 (s, CF_3). IR (neat) ν 1521, 1476, 1402, 1293, 1223, 1156, 1118, 1070, 980, 816, 764, 693 cm^{-1}. ESI-MS (*m/z*): 303.3 (100, $[M+H]^+$). Anal. calcd for $C_{17}H_{13}F_3N_2$ (302.3): C 67.54, H 4.33, N 9.27; found: C 67.63, H 4.34, N 9.04.

5-Phenyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**12**):

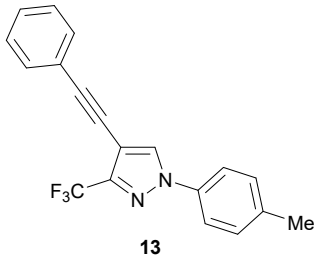


12

CC (SiO_2, hexane/DCM 9:1); colorless solid, 47 mg (62%); mp 83-85 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.74 (s, 1H, 4-H), 7.14-7.16 (m, 2H), 7.18-7.20 (m, 2H), 7.21-7.24 (m, 2H), 7.31-7.36 (m, 3H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 21.3, 105.5 (q, $^3J_{C\text{-}F}$ = 2.1 Hz), 121.5 (q, $^1J_{C\text{-}F}$ = 269.1 Hz), 125.5, 128.8, 128.9, 129.0, 129.5, 129.8, 137.0, 138.6, 143.1 (q, $^2J_{C\text{-}F}$ = 38.3 Hz), 144.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.15 (s, CF_3). IR (neat) ν 1506,1454, 1379, 1275, 1230, 1126, 1074, 969, 820, 764, 690 cm^{-1}. ESI-MS (*m/z*): 303.3 (100, $[M+H]^+$). Anal. calcd for $C_{17}H_{13}F_3N_2$ (302.3): C 67.54, H 4.33, N 9.27; found: C 67.57, H 4.51, N 9.31.

Synthesis of tri-substituted pyrazoles 13 and 14 through Sonogashira cross-coupling: A solution of iodopyrazole **4a** or **5a** (88 mg, 0.20 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02), and CuI (3.8 mg, 0.02 mmol) in a mixture of dry Et_3N (1.5 mL) and dry THF (2.0 mL) was degassed by a repeated procedure of freeze-pump-thaw. Meanwile, phenylacetylene (25.5 mg, 0.25 mmol) was dissolved in dry THF (2.0 mL) in a separate flask, under argon, and theresulting mixture was added dropwise to the first reaction flask. The mixture was heated at 80 °C for 24 h, cooled to room temperature, diluted with H_2O (10 mL), and extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, the solvents were removed in vacuo, and the resulting crude product was purified by column chromatography (CC).

4-Phenylethynyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**13**):

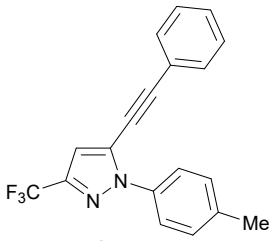


13

CC (SiO_2, hexane/DCM 4:1); colorless solid, 62 mg (95%); mp 104-106 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.27-7.30 (m, 2H), 7.34-7.38 (m, 3H), 7.52-7.55

(m, 2H), 7.56-7.58 (m, 2H), 8.07 (s, 1H, 5-H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 21.1, 77.1, 93.8, 104.2 (q, $^3J_{C\text{-}F}$ = 1.7 Hz), 119.9, 121.0 (q, $^1J_{C\text{-}F}$ = 270.2 Hz), 122.9, 128.5, 128.8, 130.3, 130.9, 131.7, 136.8, 138.4, 144.1 (q, $^2J_{C\text{-}F}$ = 37.1 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.00 (s, CF_3). IR (neat) ν 1521, 1484, 1405, 1305, 1230, 1170, 1118, 1055, 962, 816, 760, 690 cm^{-1}. ESI-MS (*m/z*): 327.3 (100, $[M+H]^+$). Anal. calcd for $C_{19}H_{13}F_3N_2$ (326.3): C 69.93, H 4.02, N 8.58; found: C 69.84, H 4.00, N 8.40.

5-Phenylethynyl-1-(*p*-tolyl)-3-trifluoromethylpyrazole (**14**):



14

CC (SiO_2, hexane/DCM 9:1); colorless solid, 60 mg (92%); mp 74-76 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.91 (s, 1H, 4-H), 7.30-7.32 (m, 2H), 7.35-7.41 (m, 3H), 7.44-7.46 (m, 2H), 7.69-7.72 (m, 2H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 21.3, 77.3, 97.4, 110.0 (q, $^3J_{C\text{-}F}$ = 2.2 Hz), 121.1 (q, $^1J_{C\text{-}F}$ = 269.0 Hz), 121.6, 123.9, 126.6, 128.7, 129.6, 129.7, 131.6, 136.9, 138.9, 143.0 (q, $^2J_{C\text{-}F}$ = 38.8 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.28 (s, CF_3). IR (neat) ν 1498, 1375, 1282, 1230, 1185, 1163, 1111, 1036, 973, 820, 753, 690 cm^{-1}. ESI-MS (*m/z*): 327.3 (100, $[M+H]^+$). Anal. calcd for $C_{19}H_{13}F_3N_2$ (326.3): C 69.93, H 4.02, N 8.58; found: C 70.01, H 4.15, N 8.52.

3. Copies of NMR spectra

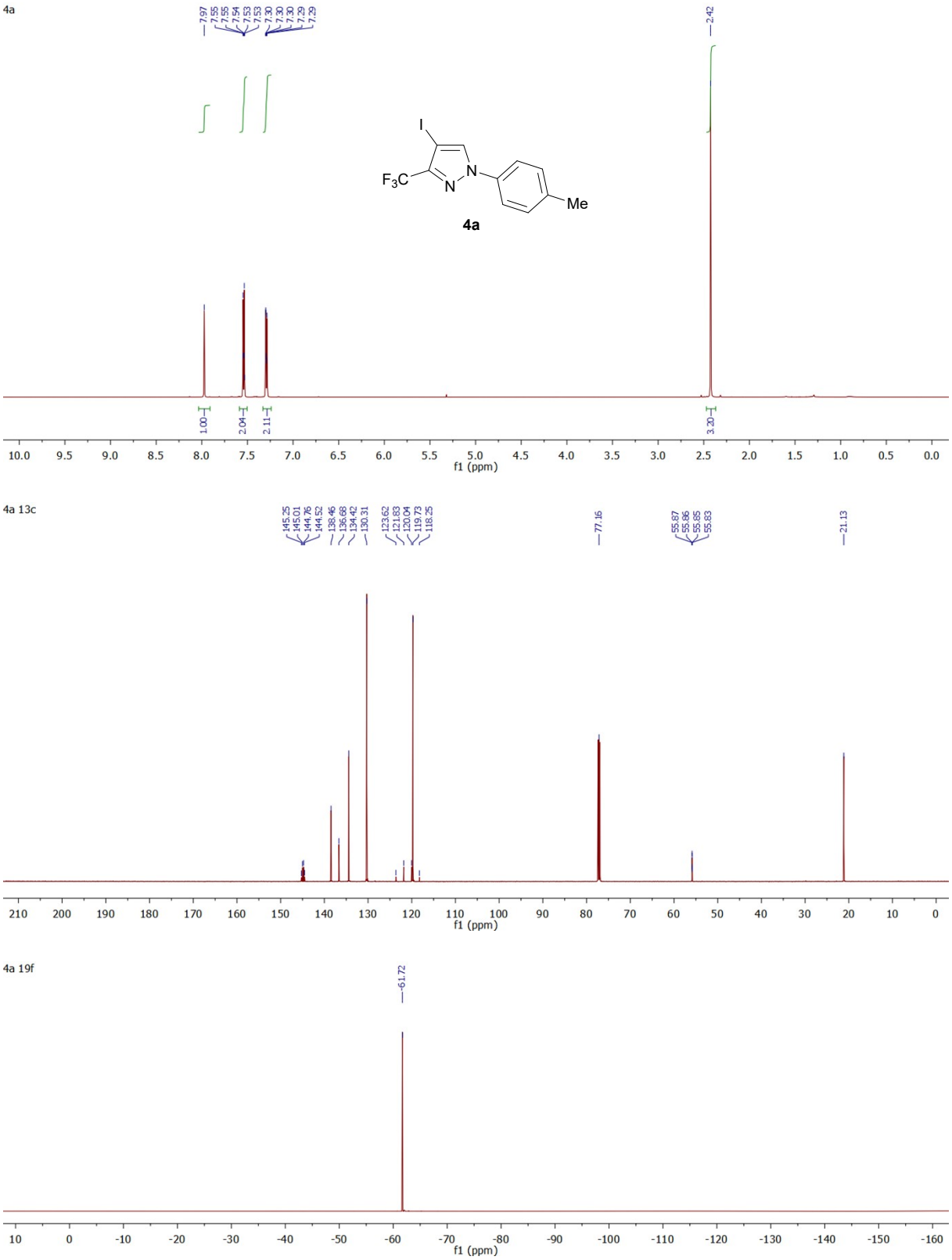


Fig S1. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4a**.

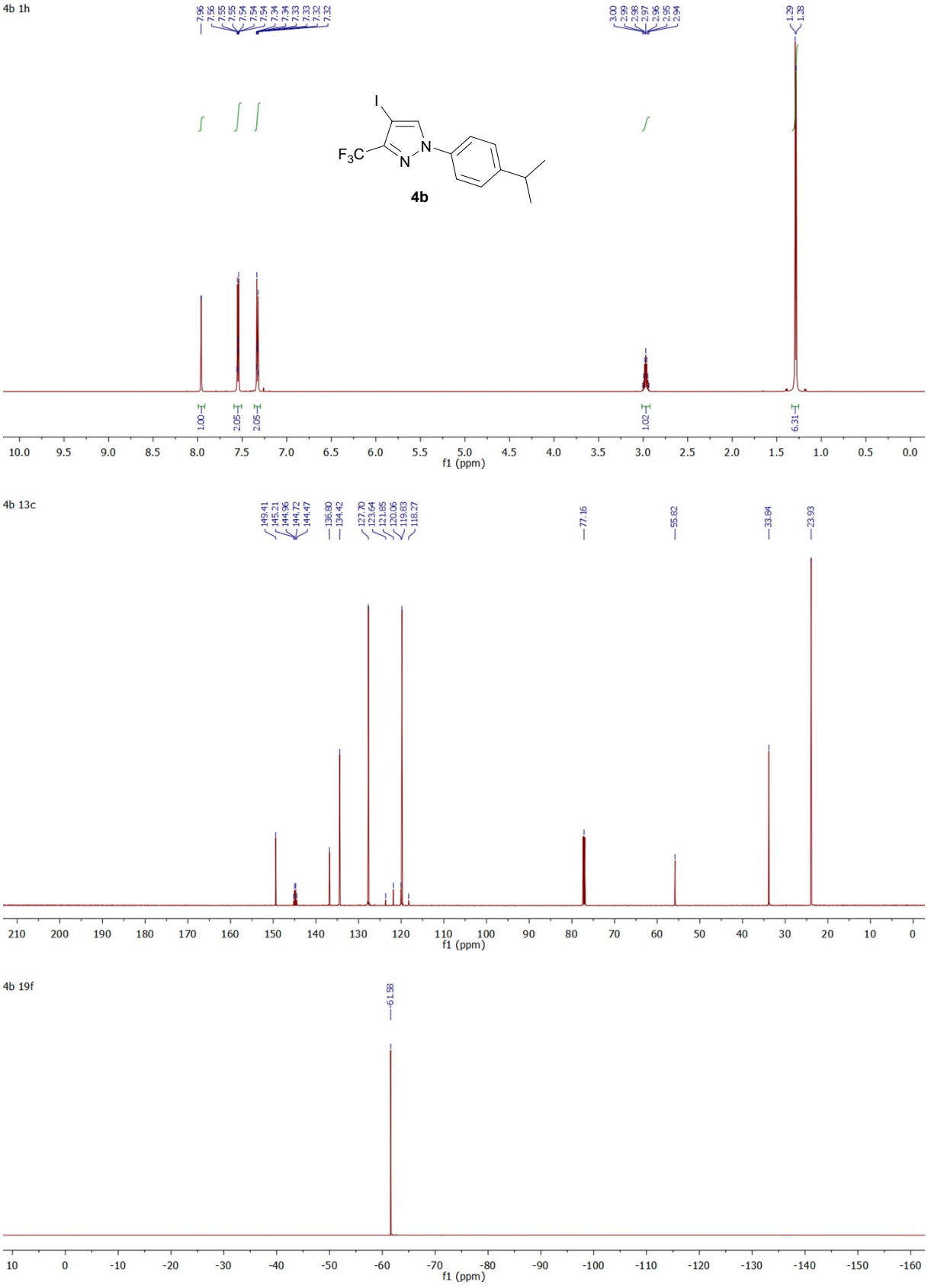


Fig S2. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4b**.

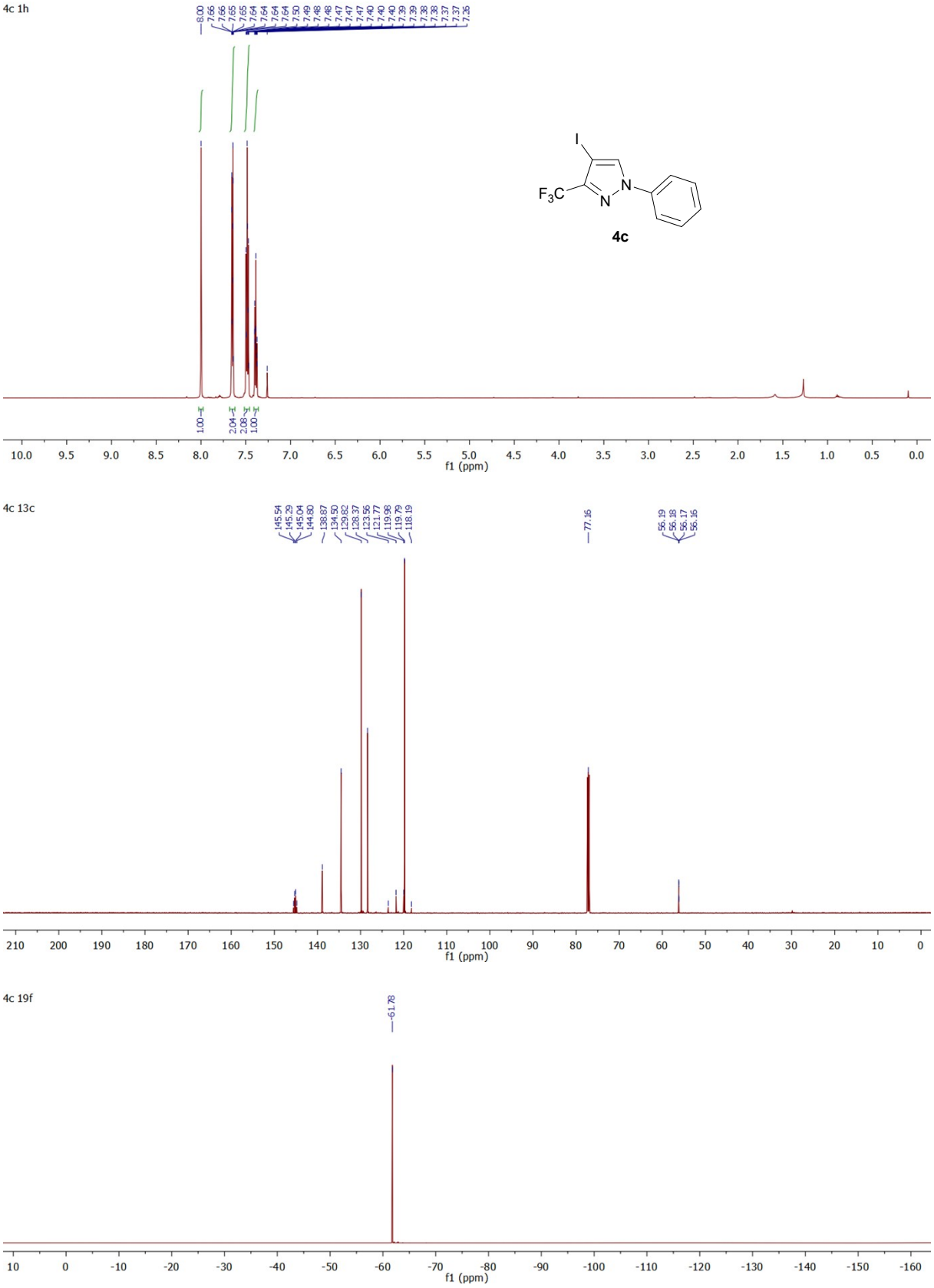


Fig S3. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4c**.

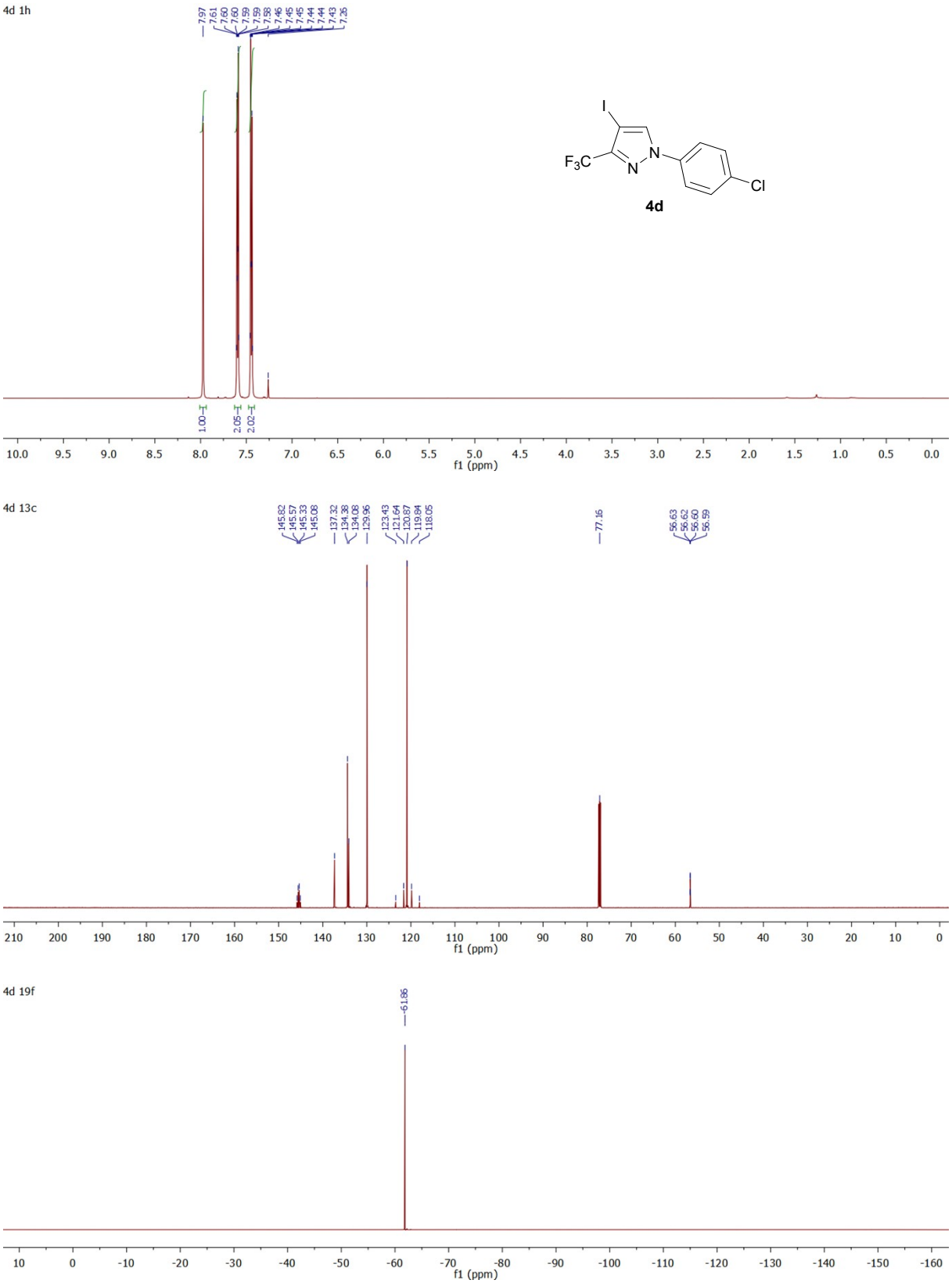


Fig S4. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4d**.

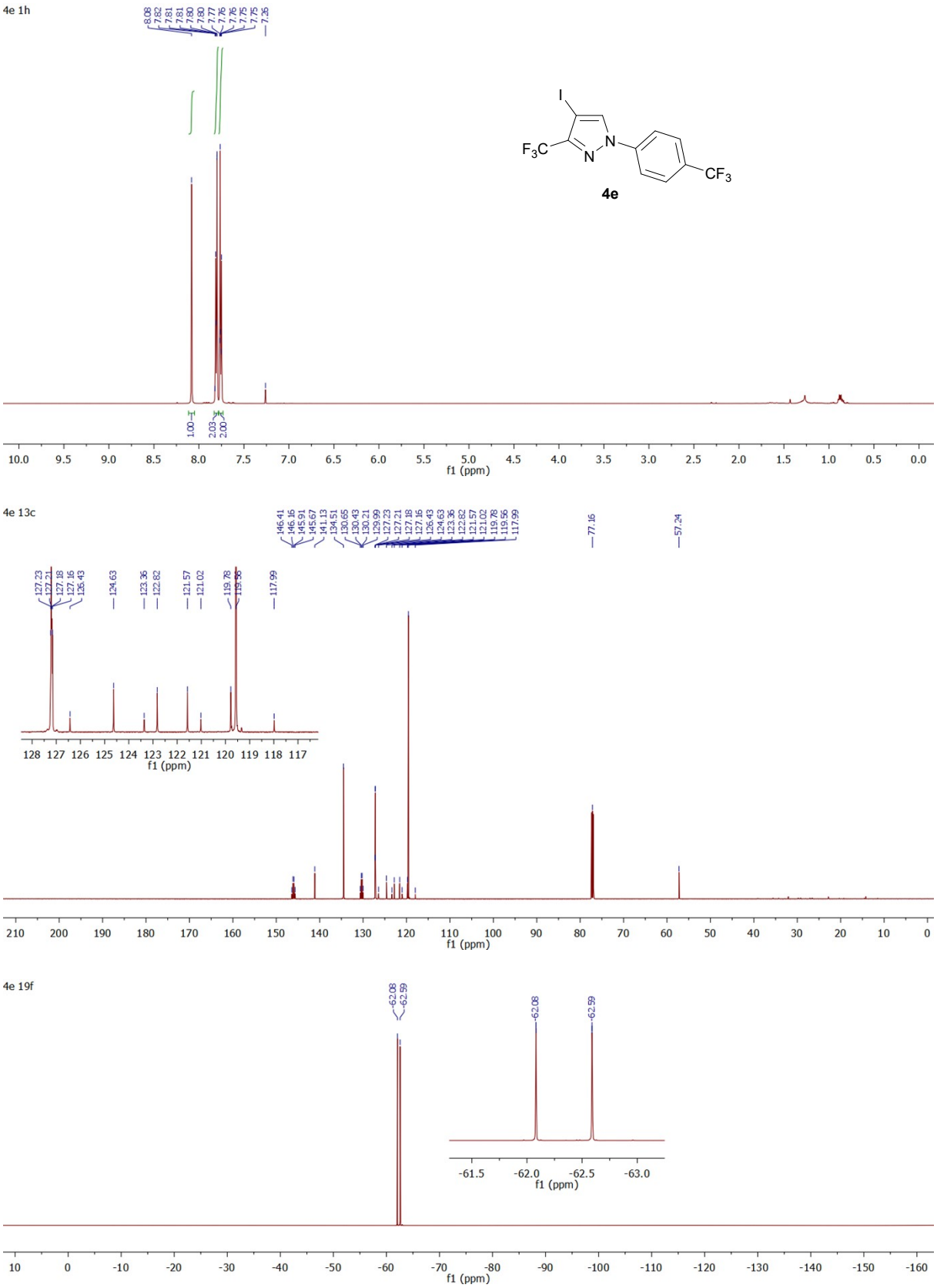


Fig S5. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4e**.

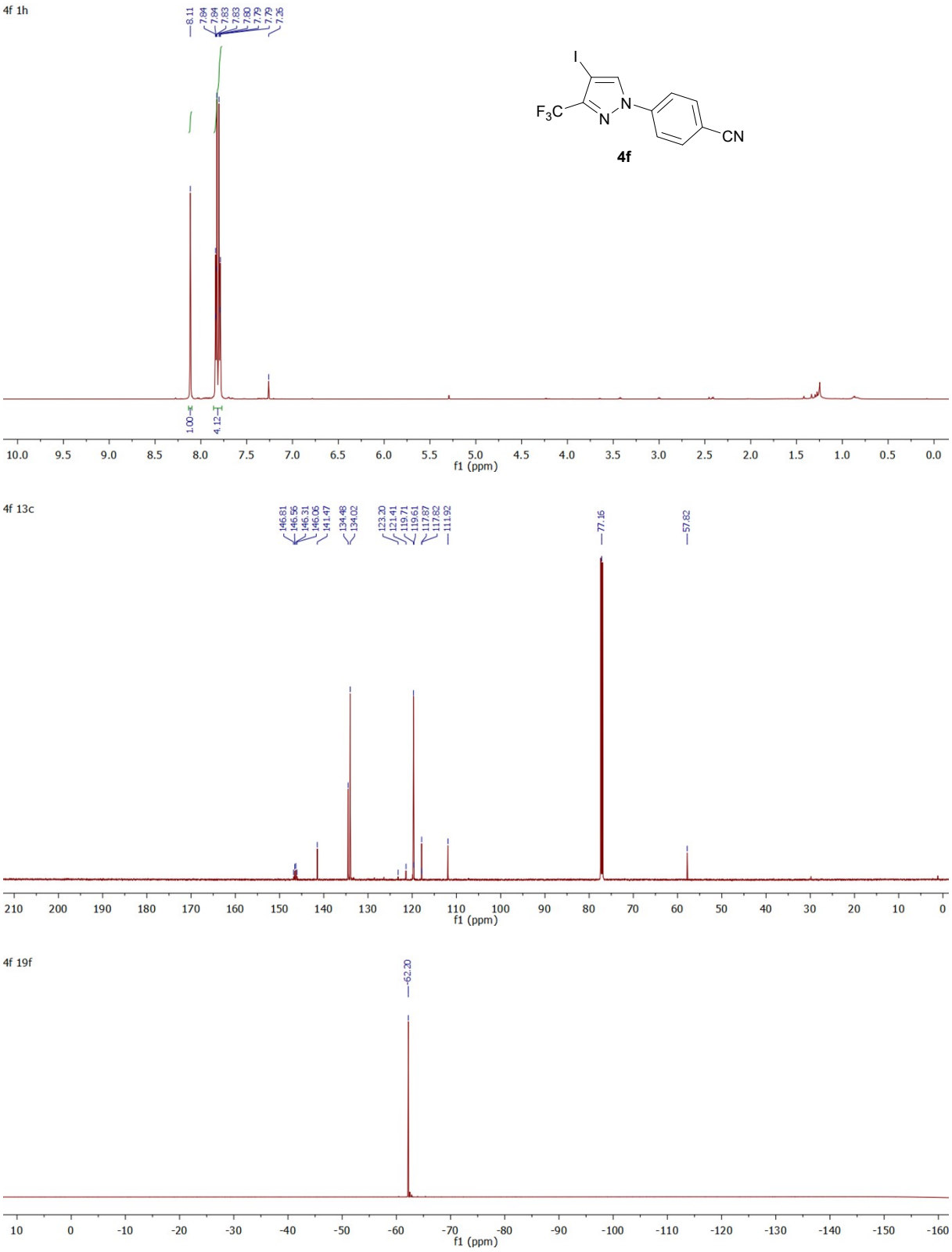


Fig S6. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4f**.

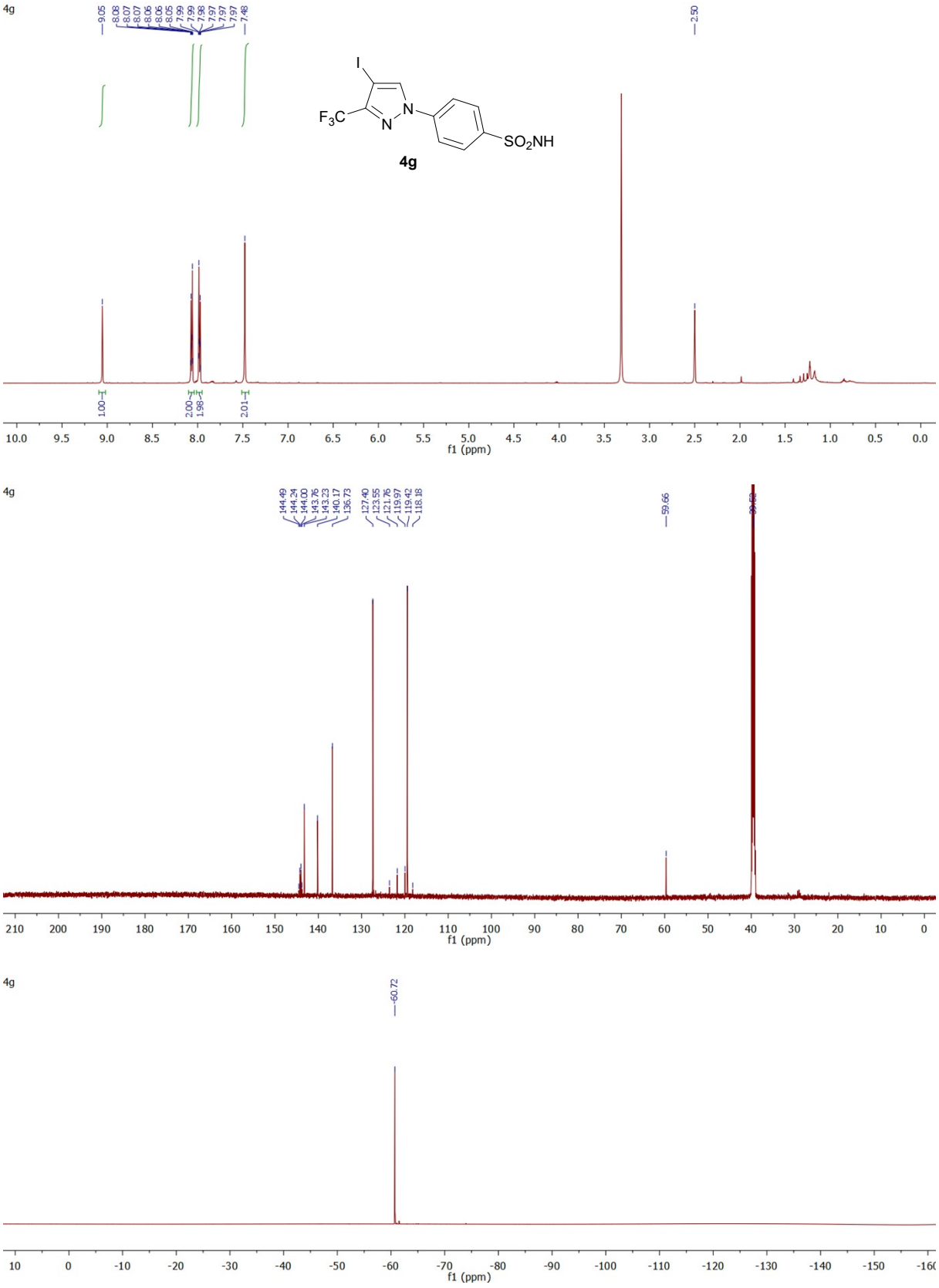


Fig S7. ^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz) and ^{19}F NMR (565 MHz) spectra for compound **4g**, taken in DMSO-d_6.

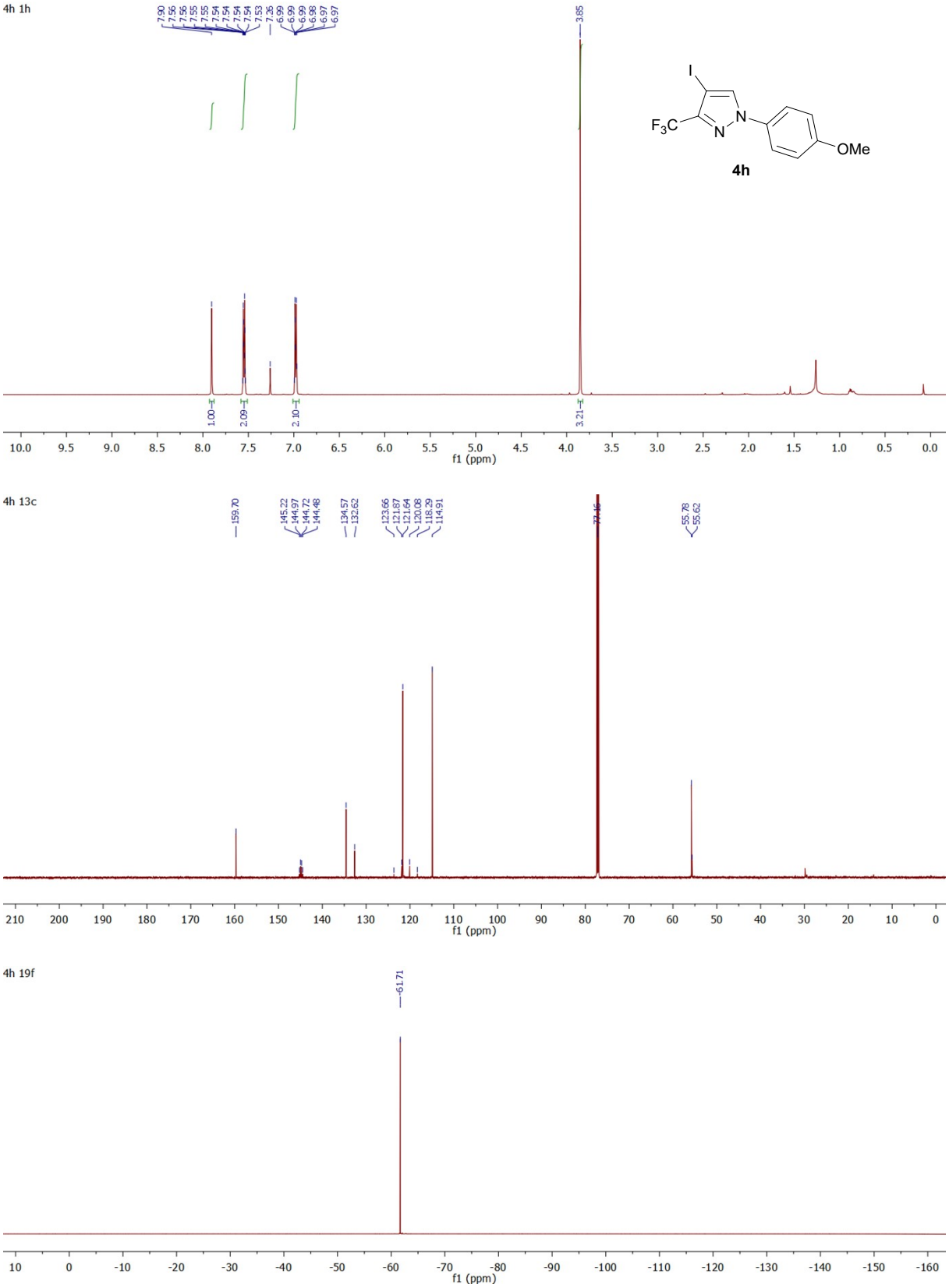


Fig S8. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4h**.

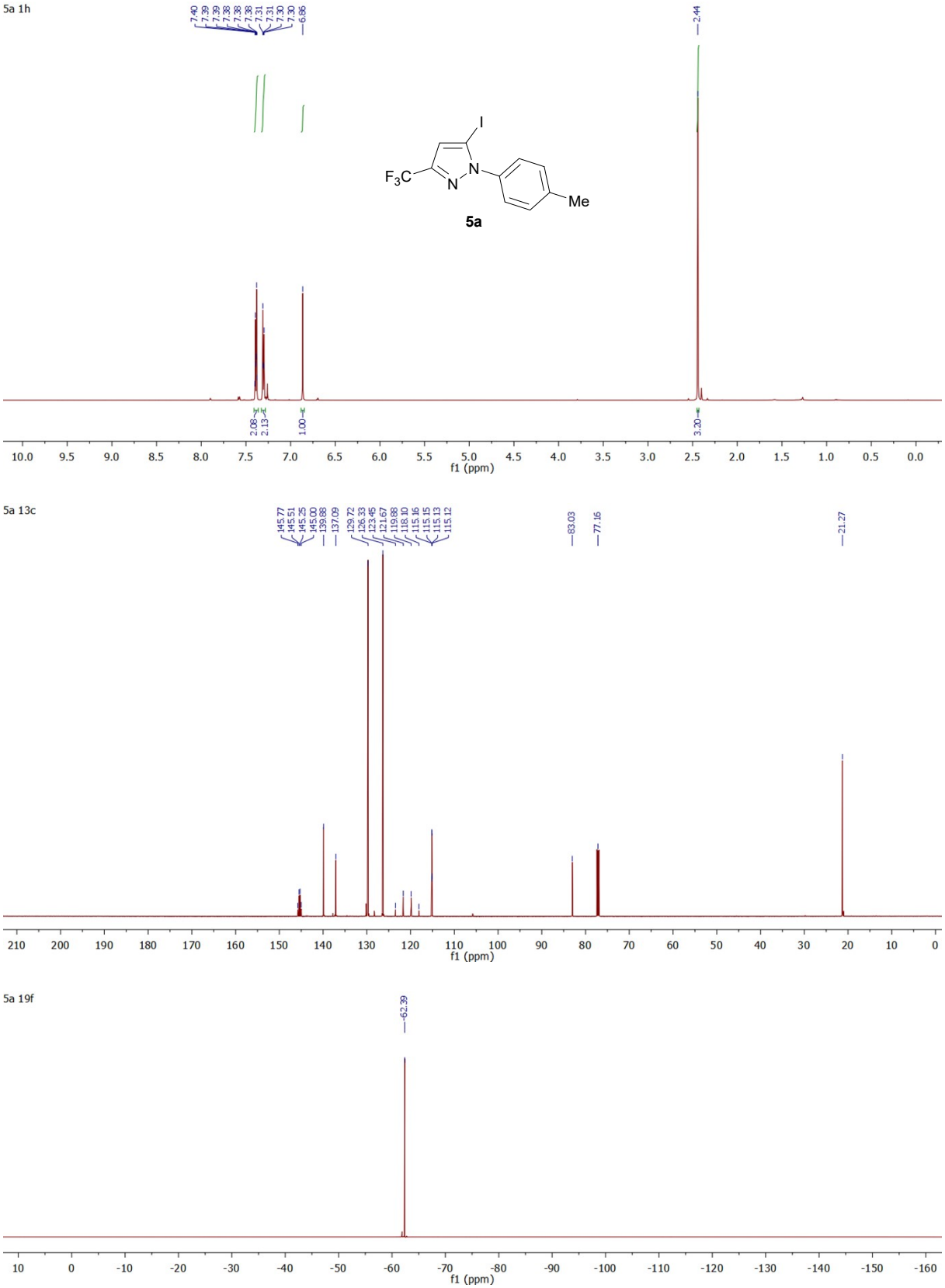


Fig S9. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **5a**.

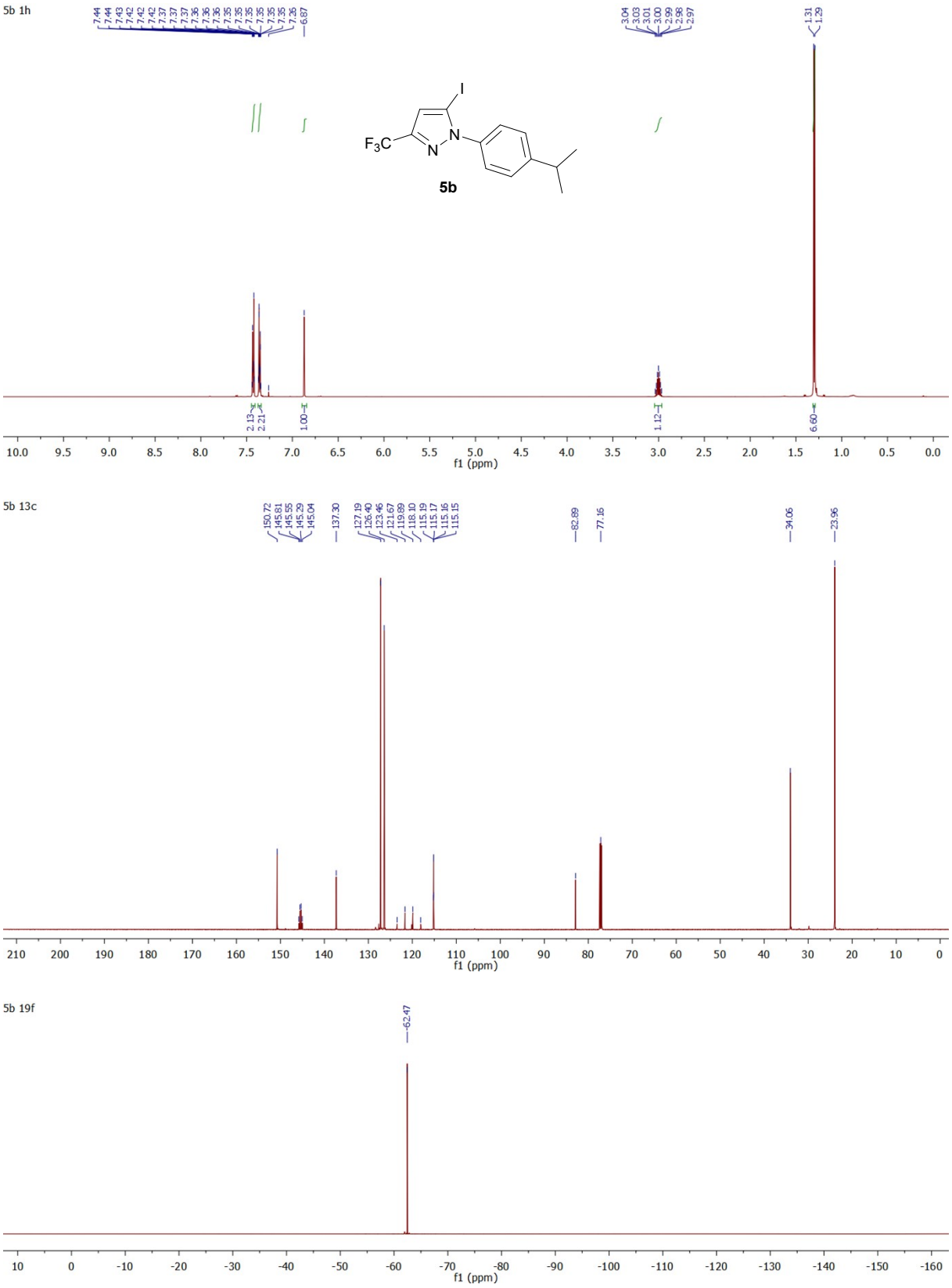


Fig S10. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **5b**.

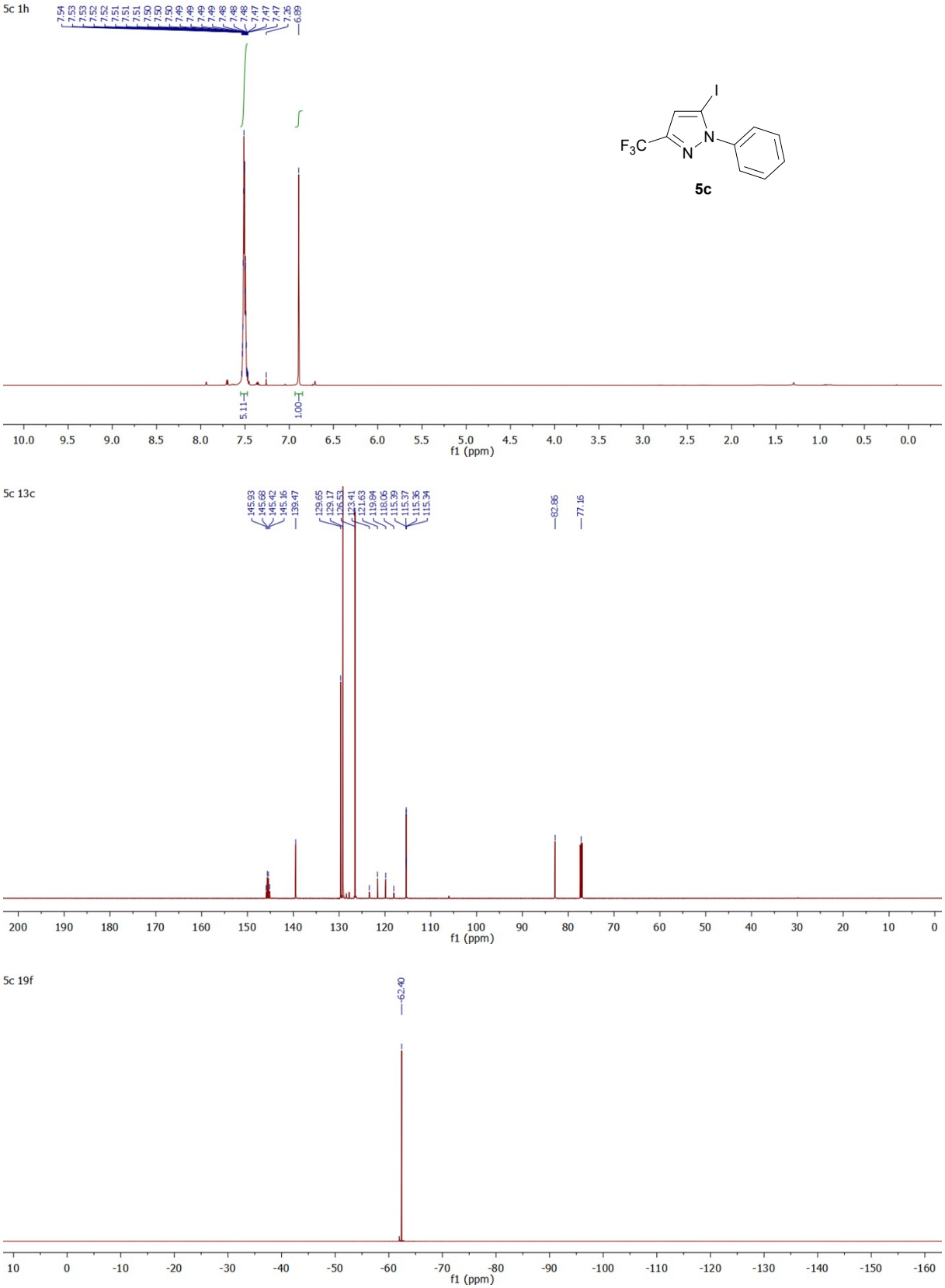


Fig S11. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **5c**.

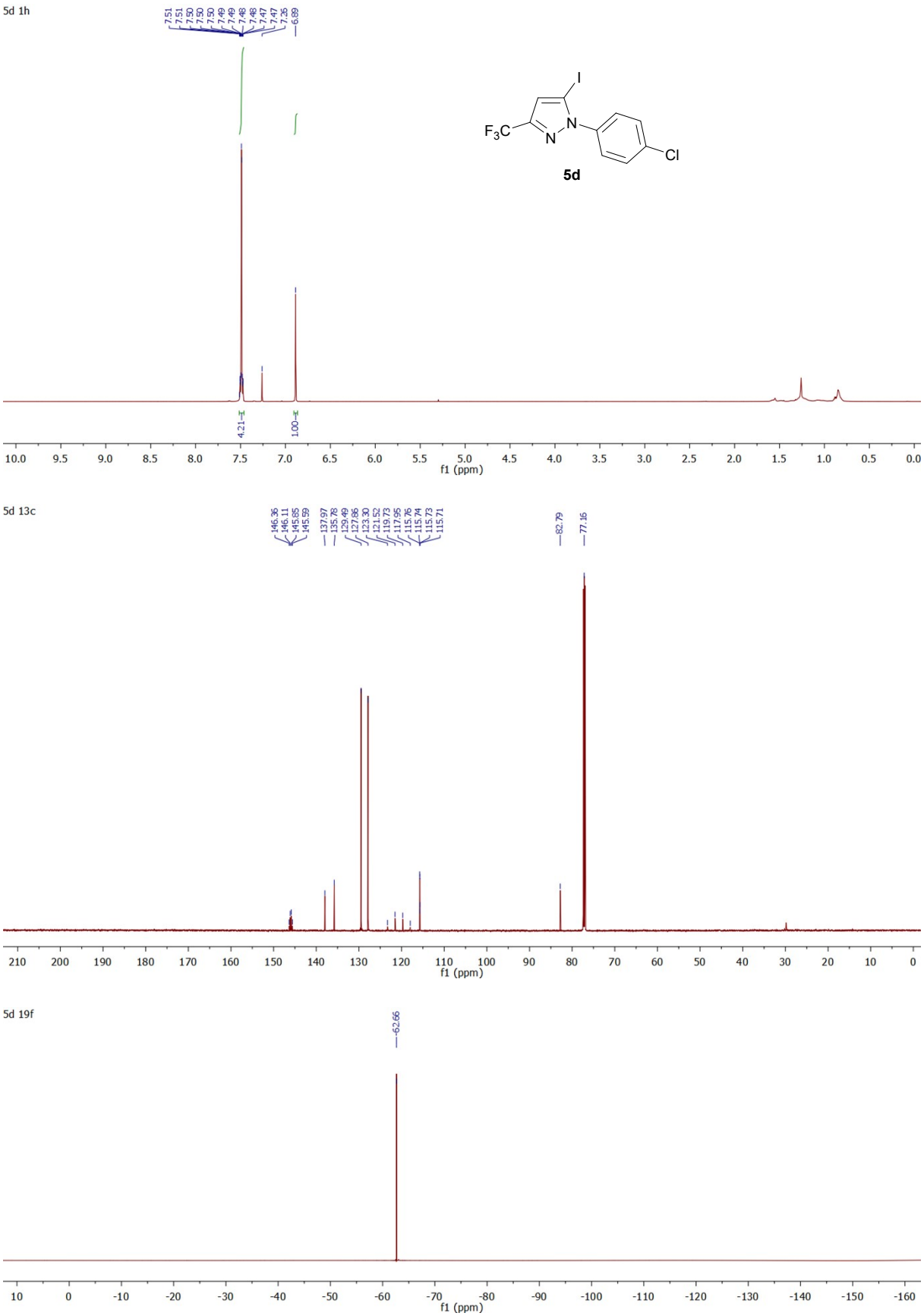


Fig S12. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **5d**.

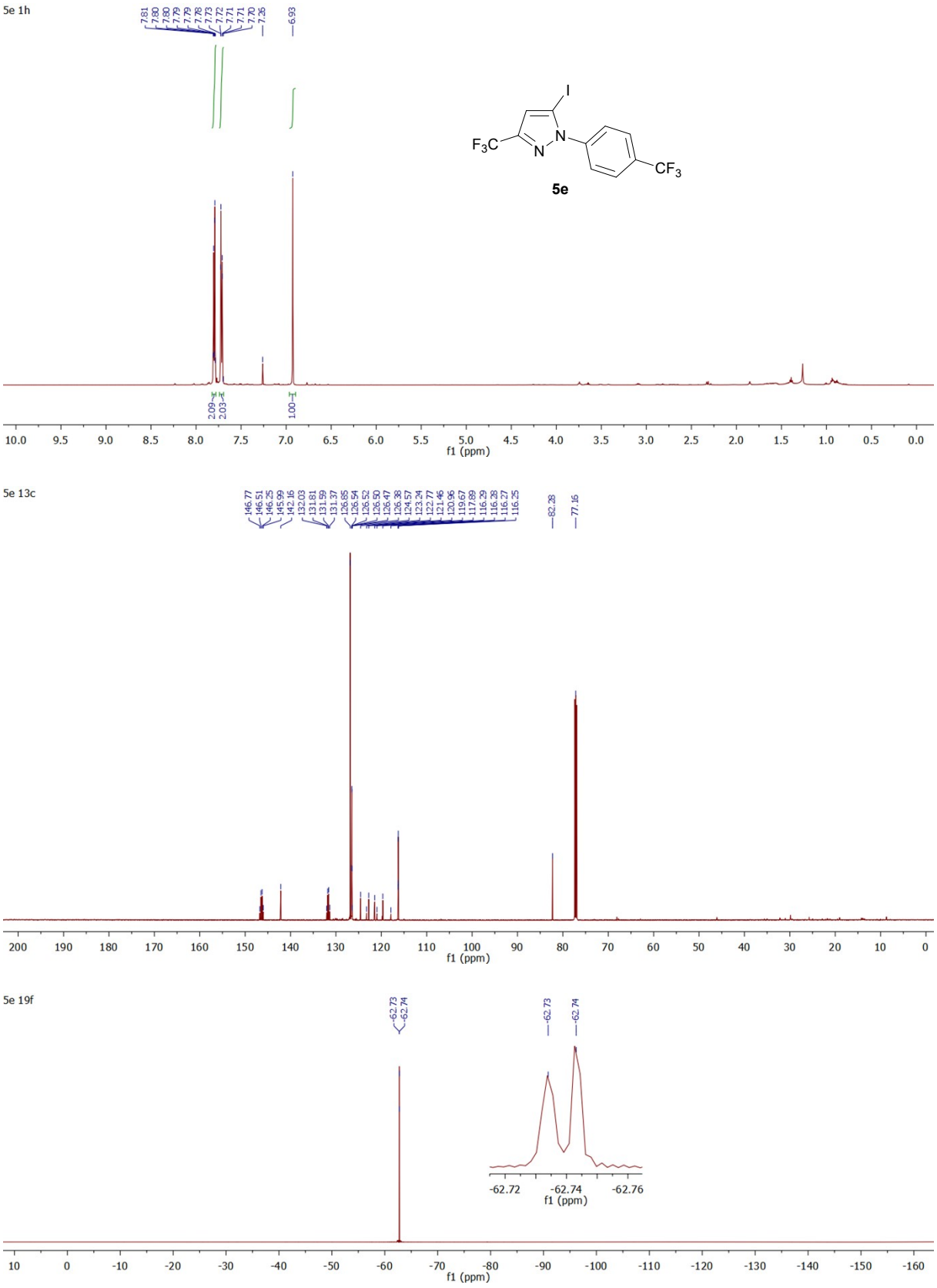


Fig S13. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **5e**.

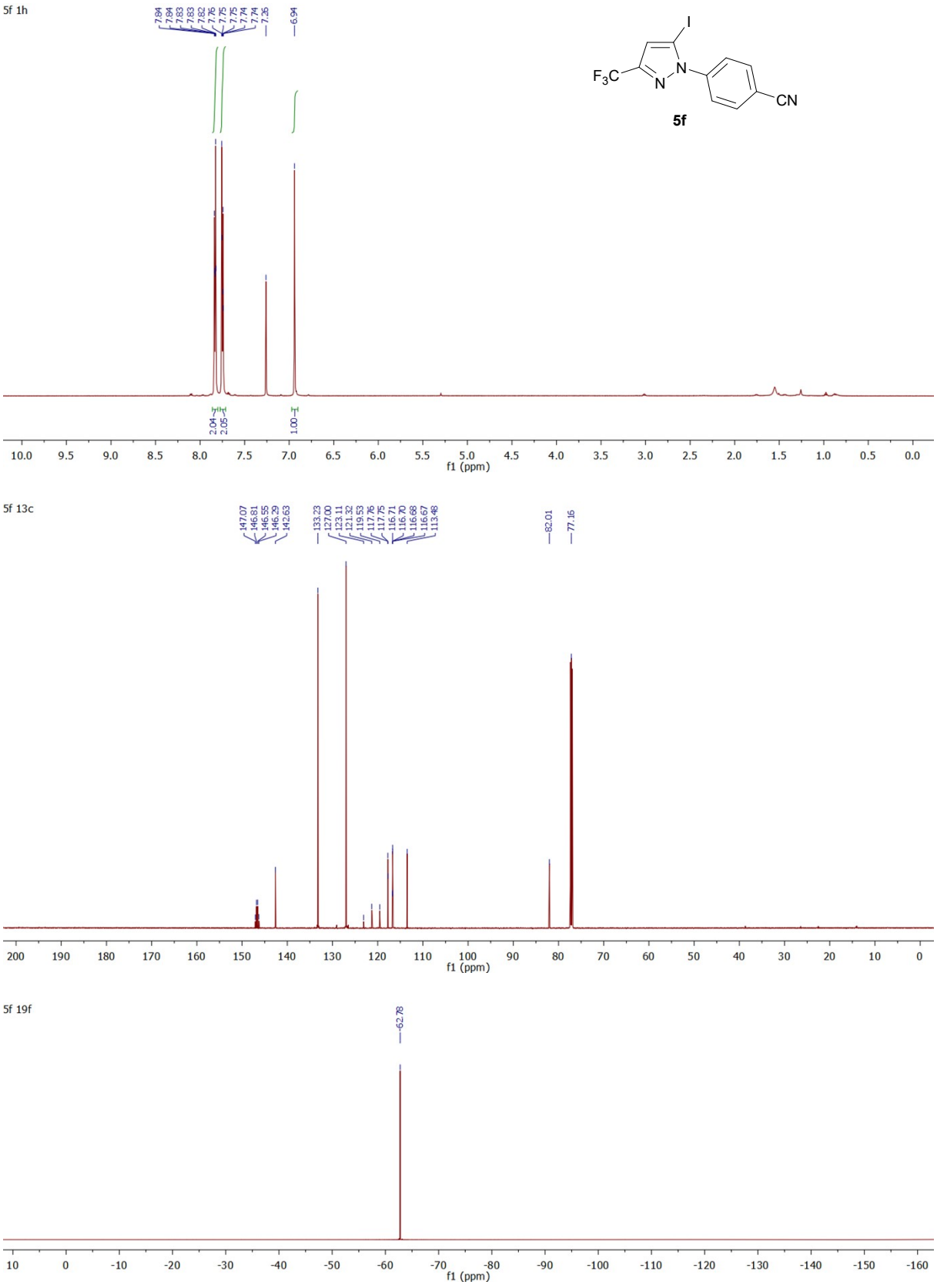


Fig S14. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **5f**.

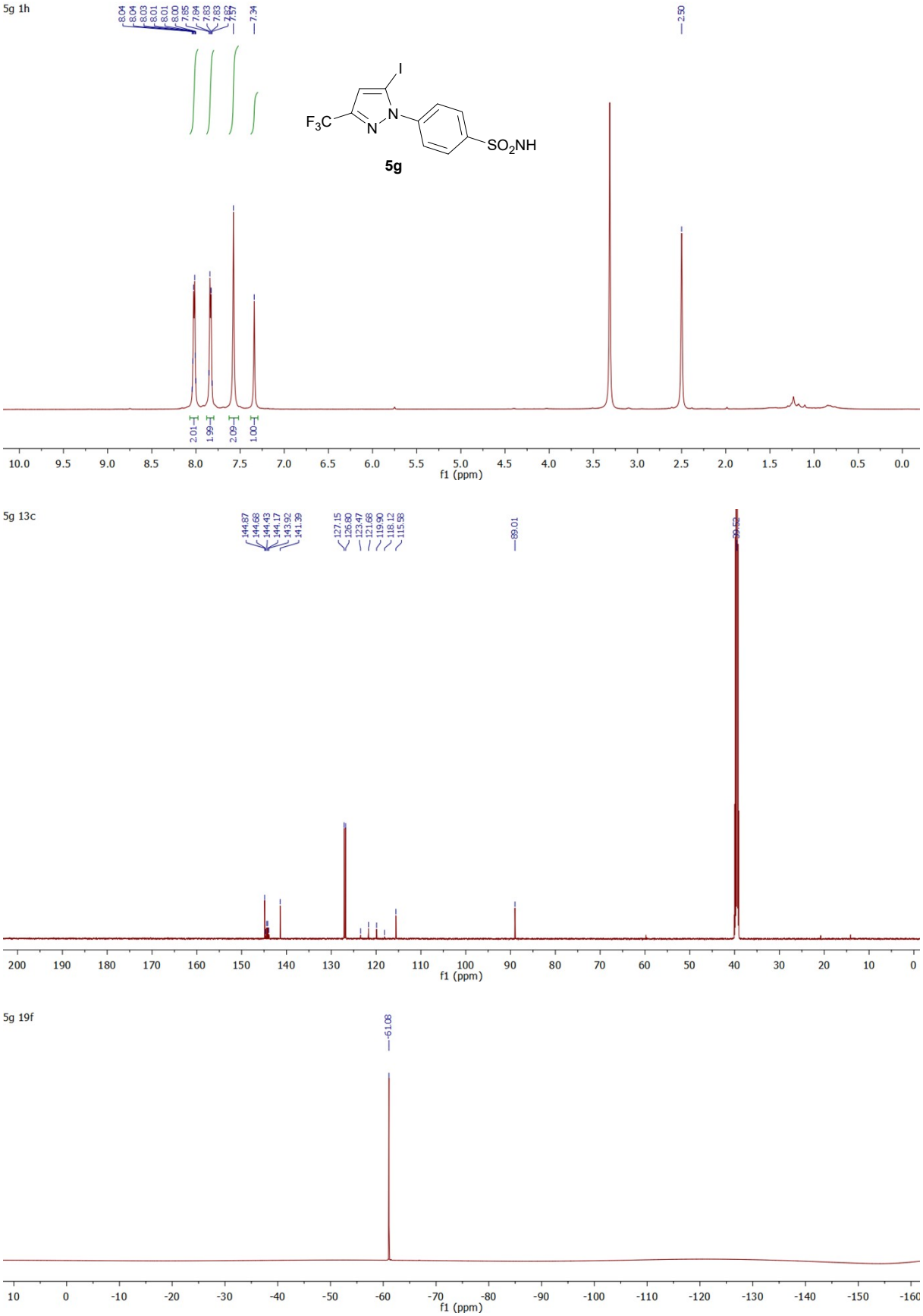


Fig S15. ^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz), and ^{19}F NMR (565 MHz) spectra for compound **5g**, taken in DMSO-d_6.

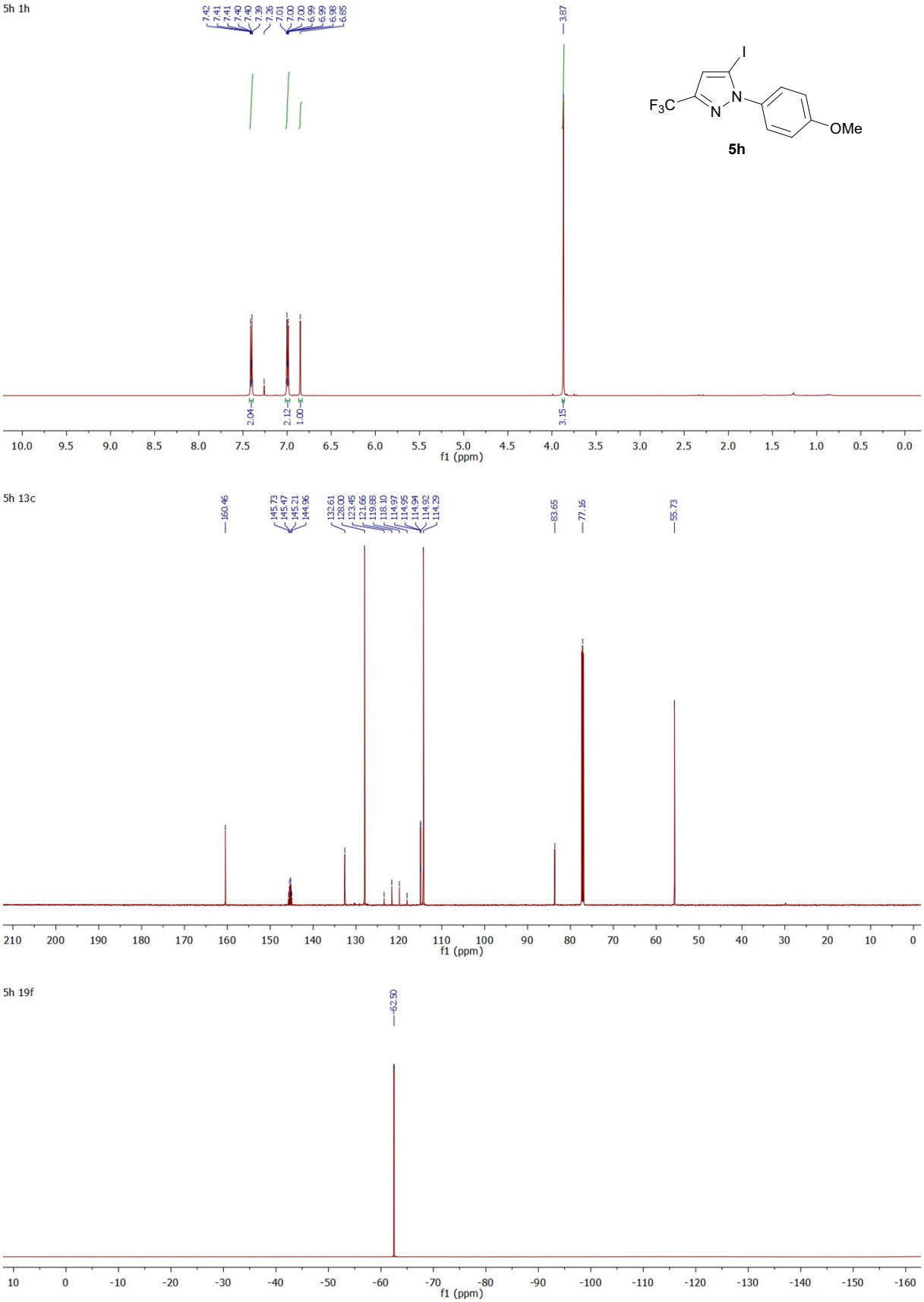


Fig S16. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **5h**.

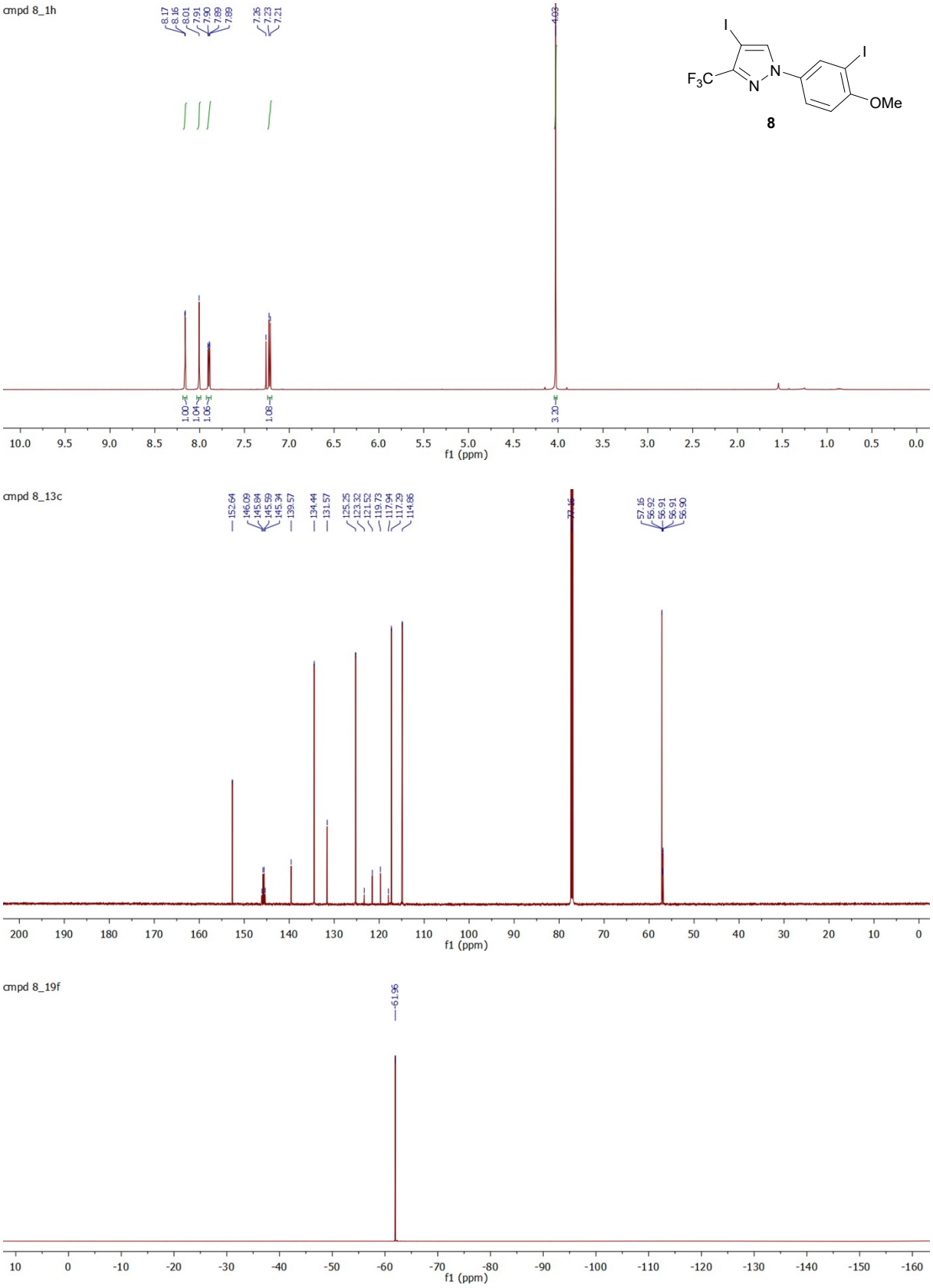


Fig S17. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **8**.

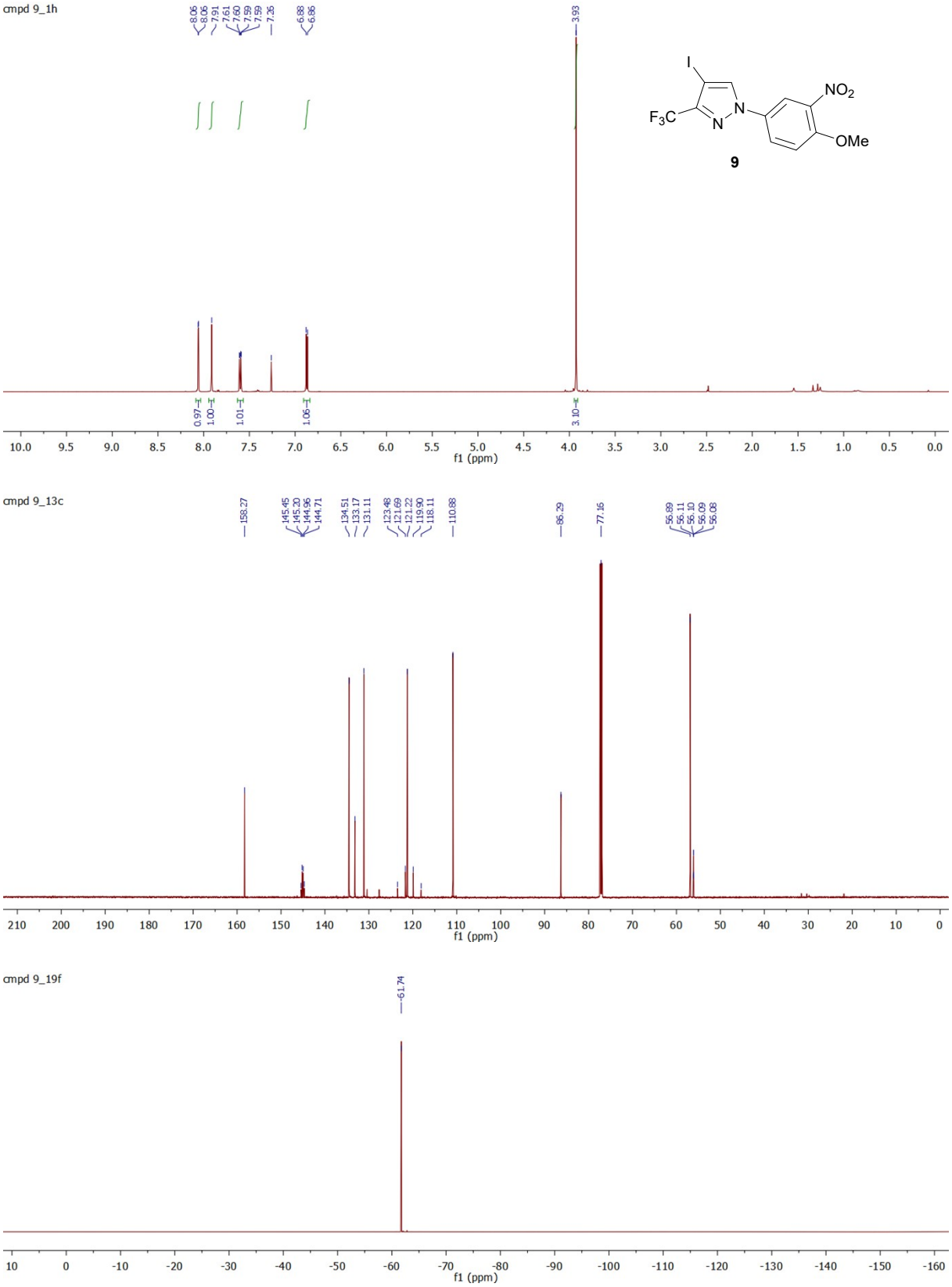


Fig S18. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **9**.

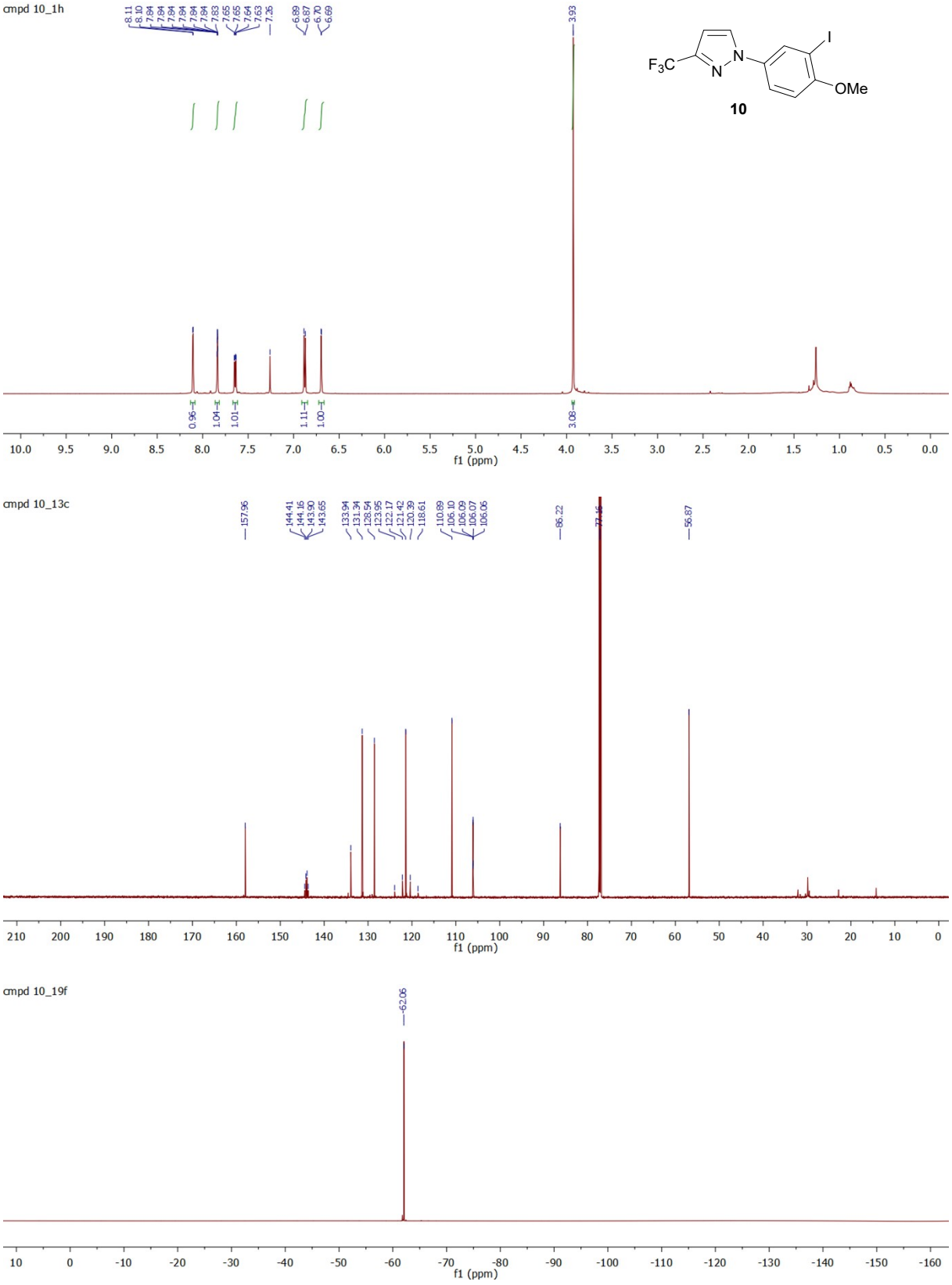


Fig S19. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **10**.

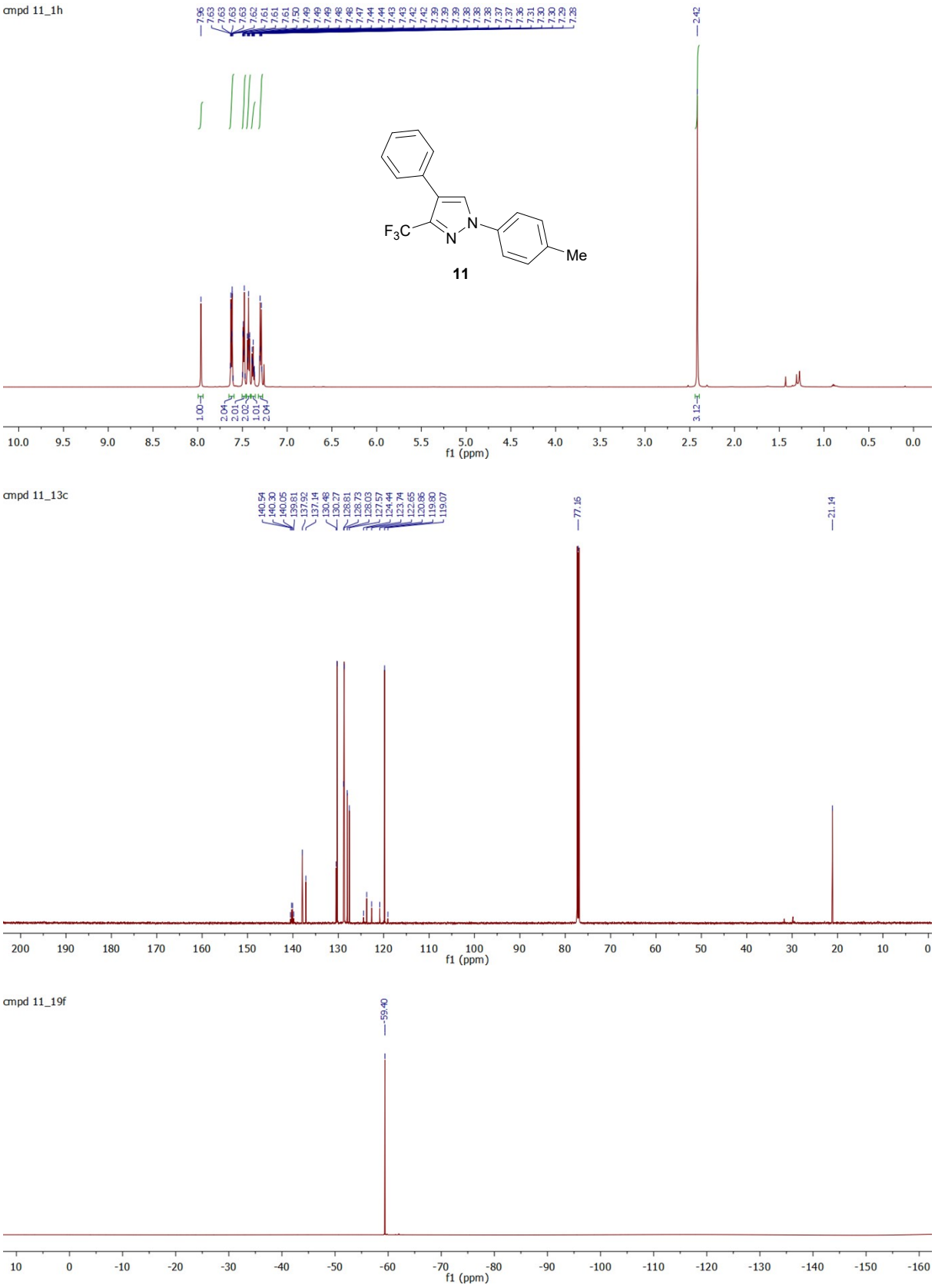
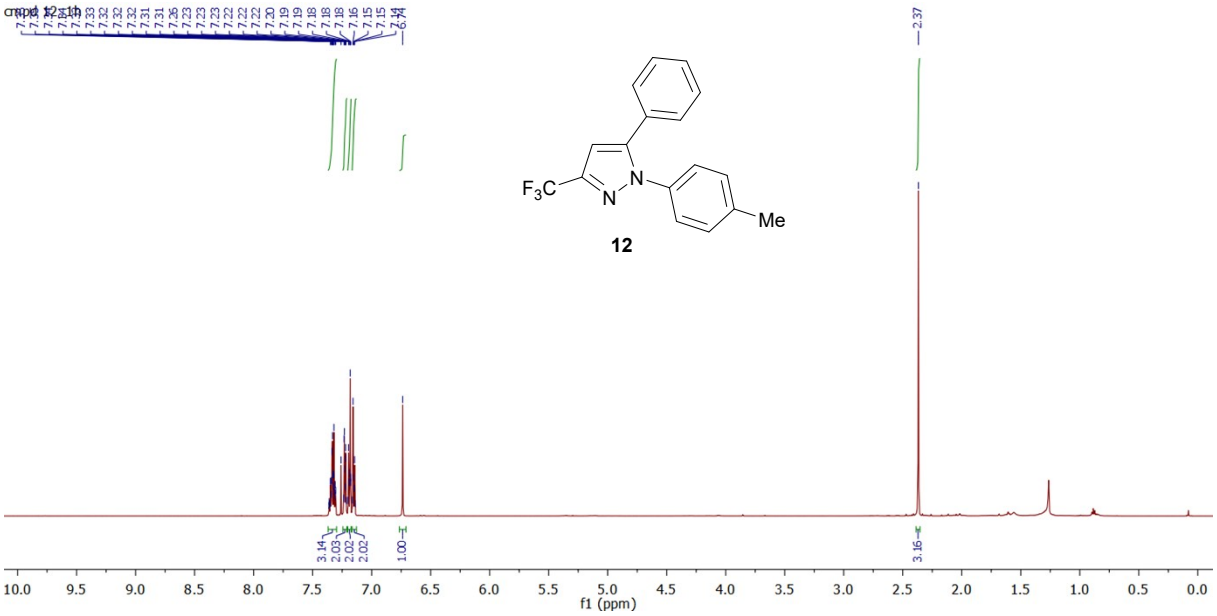
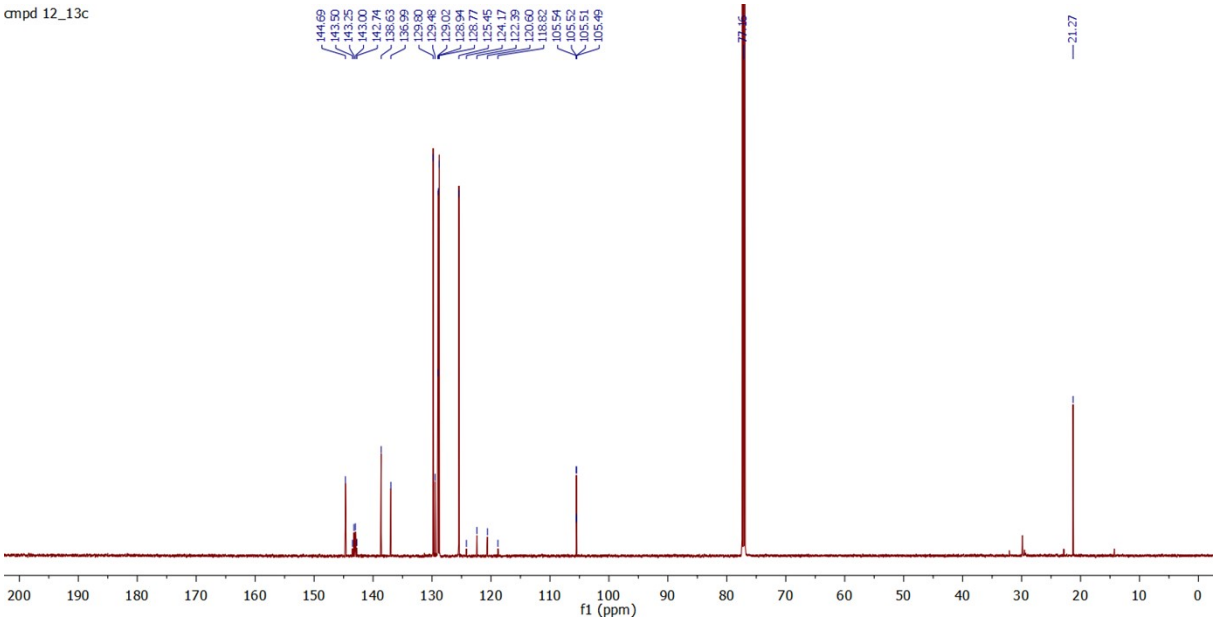


Fig S20. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **11**.





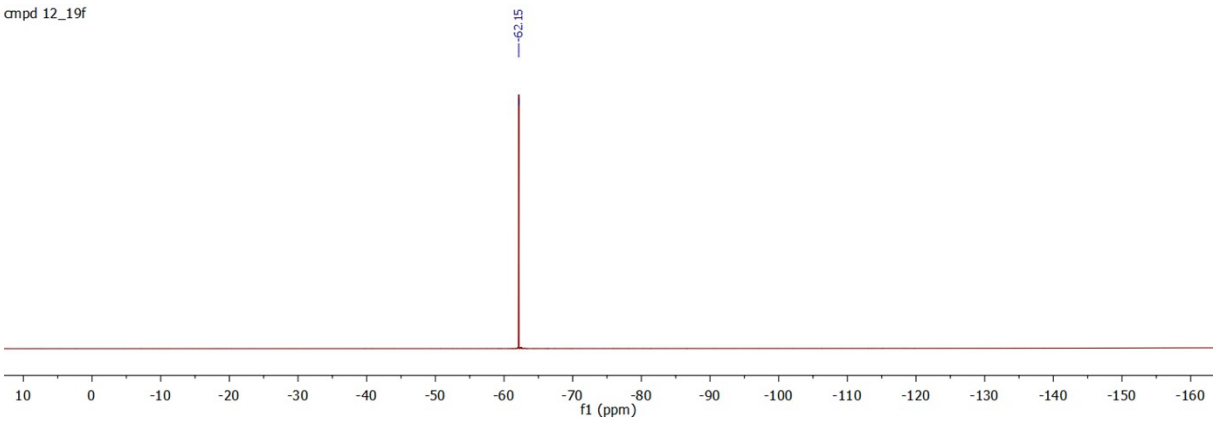


Fig S21. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **12**.

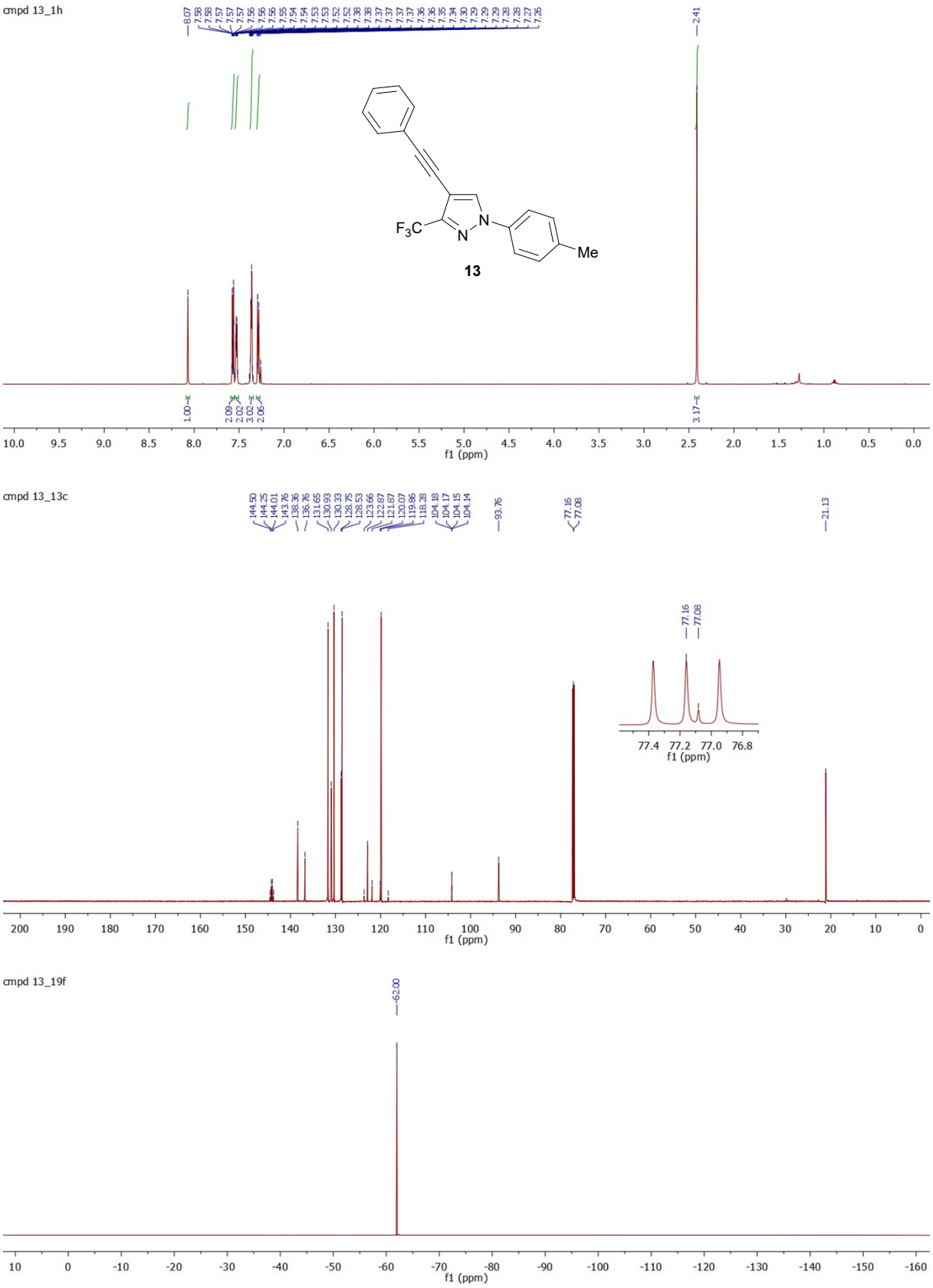


Fig S22. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **13**.

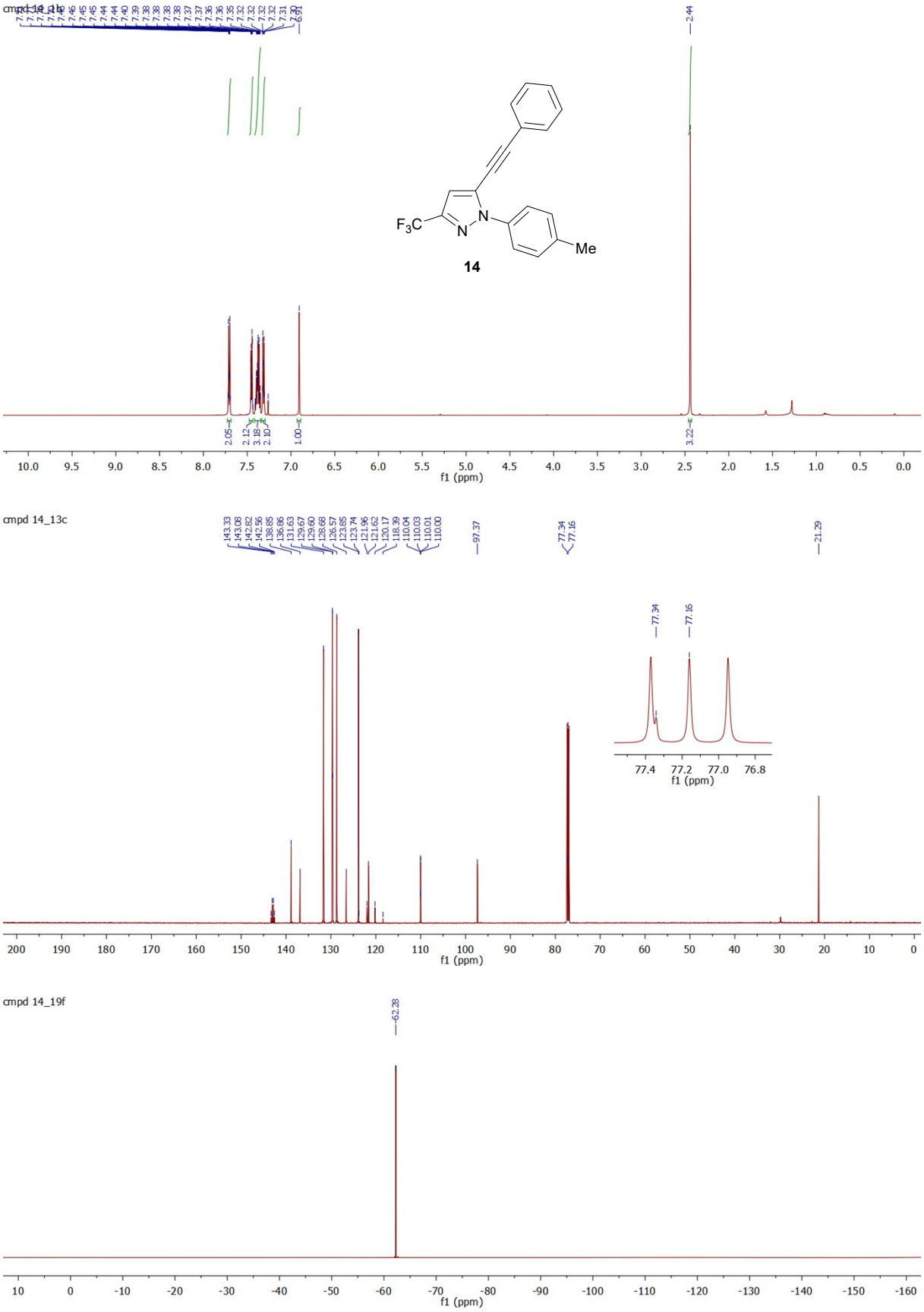


Fig S23. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **14**.

5. References

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