Supporting Information
for

Trapping in situ generated CF_3-nitrile imines with maleimides under solvent-free mechanochemical conditions

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Content:

1. General information

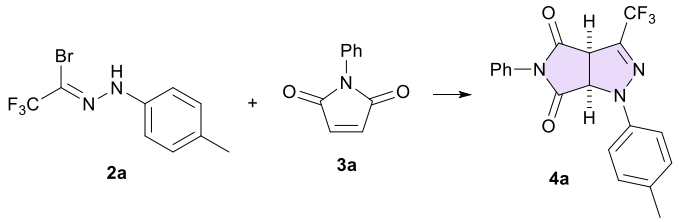
Experimental procedures:

Commercially available solvents and starting materials were 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. Mechanochemical transformations were performed with a Retsch Mixer Mill MM400. If not stated otherwise, products were purified by filtration through a short silica gel pad (FCC) or by standard column chromatography (CC), by using freshly distilled solvents as eluents or by recrystallization from appropriate solvents. Melting points were determined in capillaries with a MEL-TEMP II apparatus (Laboratory Devices), and are uncorrected. NMR spectra were measured on Bruker Avance III or Bruker AvanceNeo instruments (^{1}H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz); chemical shifts are reported 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] or to $CFCl_3$ (^{19}F NMR: δ = 0.00) used as external standard. For selected representative products additional 2D measurements (HMQC) were performed to deduce assignments and multiplicity of the signals in ^{13}C NMR spectra. 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. Combustion analyses were obtained with a Vario EL III (Elementar Analysensysteme GmbH) instrument.

Starting materials: The starting hydrazonoyl bromides **2** were prepared following the literature protocols, through condensation of commercially available fluoral hydrate (ca. 75% in H_2O) with the respective arylhydrazine (MeOH, closed ampoule, molecular sieves 4Å, 75 °C, overnight),[1] followed by bromination of the first formed hydrazone with solid NBS (dry DMF, rt, up to 3h).[2] The starting maleimides **3a**, **3b**, and **3d**-**3h** were prepared by treatment of maleic anhydride with two-fold excess of the respective amine, in hot glacial acetic acid, as reported in the literature.[3] Maleimides **3c**, **3i**, and **3j** were purchased and used as received.

2. Synthetic procedures and characterization data

2.1. Optimization of reaction conditions

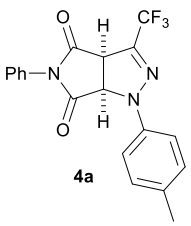


Entry	Deviation from standard conditions [a]	Conversion (%)
1	none	100
2	1.0 equiv. of **2a**	96
3	TEA instead of K_2CO_3	62 [b]
4	DABCO instead of K_2CO_3	54 [b]
5	KF instead of K_2CO_3	66 [b]
6	CsF instead of K_2CO_3	30 [b]
7	Na_2CO_3 instead of K_2CO_3	92
8	Cs_2CO_3 instead of K_2CO_3	61
9	5 mL jar with 3 x 3 mm balls	97
10	5 mL jar with 2 x 5 mm balls	98
11	THF, 60 °C, 24 h, excess K_2CO_3	90 [c]
12	THF, 30 °C, excess K_2CO_3	18 [c]

[a] Standard conditions: maleimide **3a** (173 mg, 1.0 mmol), bromide **2a** (209 mg, 1.1 mmol), K_2CO_3 (166 mg, 1.2 mmol), stainless jar and ball (1 x ø7 mm), r.t. → 30°C, 90 min; [b] Partial decomposition of starting bromide **2a**; [c] in solution.

2.2. General protocol for synthesis of pyrrolo[3,4-*c*]pyrazoles 4a-4q: Solid hydrazonoyl bromide **2** (1.1 mmol), solid maleimide **3** (1.0 mmol), and solid K_2CO_3 (1.2 mmol, 166 mg) were placed in a 5 mL stainless steel grinding jar with one stainless steel ball (7 mm diameter). The jar was closed and ball-milled at 22 Hz until the starting maleimide was fully consumed. Then, CH_2Cl_2 (10 mL) was added, the precipitate was filtered off, washed with CH_2Cl_2 (2 × 10 mL), and the solvent was removed in vacuo. The crude product **4** was purified by chromatography on silica or recrystallized.

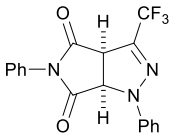
5-Phenyl-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4a**):



Reaction time 90 min; FCC (SiO_2, petroleum ether/DCM 1:1); colorless solid, 347 mg (93%); mp 169-170 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.80 (dq, *J* = 1.2, 11.5

Hz, 1H), 5.41 (d, *J* = 11.5 Hz, 1H), 7.16-7.19 (m, 2H), 7.29-7.31 (m, 2H), 7.42-7.50 (m, 5H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 20.8, 52.2, 66.4, 115.2, 120.2 (q, $^1J_{C\text{-}F}$ = 270.0 Hz), 126.3, 129.4, 129.5, 130.0, 131.0, 131.3 (q, $^2J_{C\text{-}F}$ = 39.8 Hz), 133.1, 140.3, 169.1, 170.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.6 (s, CF_3). IR (neat) ν 1722, 1514, 1498, 1379, 1320, 1193, 1122, 1077, 1040 cm^{-1}. (-)-ESI-MS (*m/z*): 372.1 (100, [M–H]$^-$). Anal. calcd for $C_{19}H_{14}F_3N_3O_2$ (373.3): C 61.13, H 3.78, N 11.26; found: C 61.13, H 3.77, N 11.24.

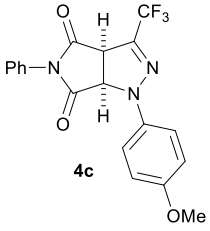
1,5-Diphenyl-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4b**):



4b

Reaction time 90 min; FCC (SiO_2, petroleum ether/DCM 1:1); light orange solid, 341 mg (95%); mp 195-196 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.84 (dq, *J* = 1.2, 11.5 Hz, 1H), 5.47 (d, *J* = 11.5 Hz, 1H), 7.09-7.12 (m, 1H), 7.30-7.32 (m, 2H), 7.37-7.40 (m, 2H), 7.42-7.45 (m, 1H), 7.48-7.51 (m, 2H), 7.56-7.58 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 52.2, 66.2, 115.2, 120.1 (q, $^1J_{C\text{-}F}$ = 270.1 Hz), 123.4, 126.3, 129.48, 129.51, 129.54, 131.0, 131.9 (q, $^2J_{C\text{-}F}$ = 39.7 Hz), 142.5, 168.9, 170.6. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.7 (s, CF_3). IR (neat) ν 1715, 1592, 1498, 1383, 1327, 1193, 1133, 1085, 1044 cm^{-1}. (-)-ESI-MS (*m/z*): 358.1 (100, [M–H]$^-$). Anal. calcd for $C_{18}H_{12}F_3N_3O_2$ (359.1): C 60.17, H 3.37, N 11.69; found: C 59.93, H 3.38, N 11.88.

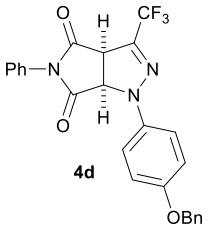
1-(4-Methoxyphenyl)-5-phenyl-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4c**):



4c

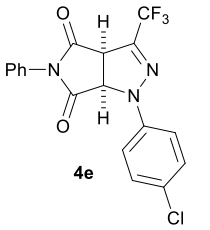
Reaction time 90 min; FCC (SiO_2, petroleum ether/DCM 1:1); orange solid, 358 mg (92%); mp 158-159 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.81 (dq, *J* = 1.2, 11.6 Hz, 1H), 5.36 (d, *J* = 11.6 Hz, 1H), 6.91-6.93 (m, 2H), 7.29-7.32 (m, 2H), 7.42-7.45 (m, 1H), 7.47-7.51 (m, 4H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 52.3, 55.7, 67.0, 114.8, 116.9, 120.2 (q, $^1J_{C\text{-}F}$ = 269.7 Hz), 126.3, 129.4, 129.5, 131.01, 131.04 (q, $^2J_{C\text{-}F}$ = 39.7 Hz), 136.5, 156.2, 169.1, 170.9. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.6 (s, CF_3). IR (neat) ν 1718, 1498, 1368, 1249, 1189, 1126, 1070, 1036 cm^{-1}. (+)-ESI-MS (*m/z*): 412.3 (100, [M+Na]$^+$). Anal. calcd for $C_{19}H_{14}F_3N_3O_3$ (389.1): C 58.62, H 3.62, N 10.79; found: C 58.42, H 3.70, N 10.85.

1-(4-Benzyloxyphenyl)-5-phenyl-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4d**):



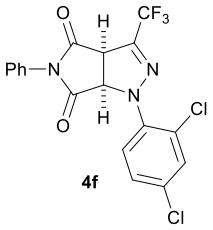
Reaction time 180 min; CC (SiO_2, petroleum ether/DCM 1:1); colorless solid, 386 mg (83%); mp 194-195 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.83 (dq, *J* = 1.2, 11.6 Hz, 1H), 5.06 (s, 2H), 5.38 (d, *J* = 11.6 Hz, 1H), 6.98-7.01 (m, 2H), 7.29-7.34 (m, 3H), 7.37-7.40 (m, 2H), 87.42-7.45 (m, 3H), 7.48-7.51 (m, 4H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 52.3, 67.0, 70.6, 115.9, 116.8, 120.2 (q, $^1J_{C\text{-}F}$ = 270.0 Hz), 126.3, 127.6, 128.2, 128.8, 129.45, 129.50, 131.0, 131.1 (q, $^2J_{C\text{-}F}$ = 39.8 Hz), 136.7, 137.0, 155.3, 169.1, 170.8. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.6 (s, CF_3). IR (neat) ν 1718, 1513, 1383, 1334, 1249, 1193, 1133, 1081, 1047 cm^{-1}. (+)-ESI-MS (*m/z*): 488.4 (100, $[M+Na]^+$), 466.3 (56, $[M+H]^+$). Anal. calcd for $C_{25}H_{18}F_3N_3O_3$ (465.1): C 64.52, H 3.90, N 9.03; found: C 64.46, H 3.88, N 9.04.

1-(4-Chlorophenyl)-5-Phenyl-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4e**):



Reaction time 6 h; CC (SiO_2, petroleum ether/DCM 1:1 gradient DCM); colorless solid, 322 mg (82%); mp 155-157 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.83 (dq, *J* = 1.2, 11.6 Hz, 1H), 5.41 (d, *J* = 11.6 Hz, 1H), 7.28-7.31 (m, 2H), 7.32-7.34 (m, 2H), 7.43-7.46 (m, 1H), 7.48-7.51 (m, 4H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 52.3, 66.1, 116.4, 120.0 (q, $^1J_{C\text{-}F}$ = 270.2 Hz), 126.3, 128.6, 129.49, 129.54, 129.6, 130.9, 132.5 (q, $^2J_{C\text{-}F}$ = 40.0 Hz), 141.0, 168.7, 170.5. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.8 (s, CF_3). IR (neat) ν 1718, 1595, 1495, 1387, 1312, 1189, 1126, 1040 cm^{-1}. (-)-ESI-MS (*m/z*): 392.0 (100, $[M–H]^–$). Anal. calcd for $C_{18}H_{11}ClF_3N_3O_2$ (393.0): C 54.91, H 2.82, N 10.67; found: C 54.80, H 3.01, N 10.61.

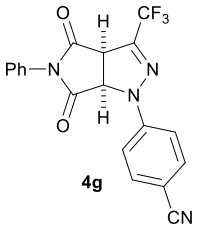
1-(2,4-Dichlorophenyl)-5-Phenyl-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4f**):



Reaction time 10 h; CC (SiO_2, petroleum ether/DCM 1:1 gradient DCM); colorless solid, 342 mg (80%); mp 159-160 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.10 (dq, *J* = 1.3, 10.9 Hz, 1H), 5.87 (d, *J* = 10.9 Hz, 1H), 7.22-7.24 (m, 2H), 7.42-7.51 (m, 5H), 7.73-7.75 (m, 1H). ^{13}C{1H}

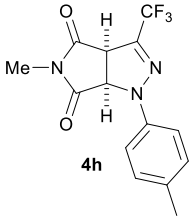
NMR (151 MHz, DMSO-d_6) δ 52.7, 65.6, 120.2 (q, $^1J_{C\text{-}F}$ = 270.0 Hz), 126.8, 127.1, 127.8, 128.3, 128.9, 129.1, 129.2, 131.1, 131.5, 134.5 (q, $^2J_{C\text{-}F}$ = 38.3 Hz), 138.3, 170.3, 170.7. ^{19}F NMR (565 MHz, DMSO-d_6): δ –62.7 (s, CF_3). IR (neat) ν 1718, 1480, 1379, 1301, 1189, 1133, 1074 cm^{-1}. (-)-ESI-MS (*m/z*): 427.9 (67), 427.0 (38), 425.9 (100, [M–H]$^-$). Anal. calcd for $C_{18}H_{10}Cl_2F_3N_3O_2$ (427.0): C 50.49, H 2.35, N 9.81; found: C 50.51, H 2.32, N 9.76.

1-(4-Cyanophenyl)-5-Phenyl-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4g**):



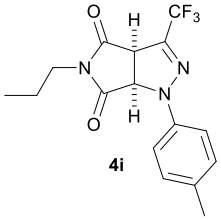
Reaction time 18 h; recrystallized from DCM; colorless solid, 330 mg (86%); mp 230-231 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.09 (dq, *J* = 1.4, 11.3 Hz, 1H), 5.86 (d, *J* = 11.3 Hz, 1H), 7.33-7.35 (m, 2H), 7.44-7.47 (m, 1H), 7.50-7.53 (m, 2H), 7.55-7.58 (m, 2H), 7.83-7.85 (m, 2H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 53.2, 65.6, 103.6, 114.7, 119.2, 120.1 (q, $^1J_{C\text{-}F}$ = 270.1 Hz), 127.1, 129.0, 129.1, 131.7, 133.7, 135.3 (q, $^2J_{C\text{-}F}$ = 38.6 Hz), 145.7, 169.7, 171.5. ^{19}F NMR (565 MHz, DMSO-d_6): δ –63.0 (s, CF_3). IR (neat) ν 2218, 1722, 1595, 1513, 1371, 1323, 1193, 1133, 1040 cm^{-1}. (-)-ESI-MS (*m/z*): 383.0 (100, [M–H]$^-$). Anal. calcd for $C_{19}H_{11}F_3N_4O_2$ (384.1): C 59.38, H 2.89, N 14.58; found: C 59.37, H 2.99, N 14.56.

5-Methyl-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4h**):



Reaction time 90 min; FCC (SiO_2, petroleum ether/EtOAc 3:1); pale yellow solid, 283 mg (91%); mp 140-141 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.10 (s, 3H), 4.67 (d_{br}, *J* ≈ 11.4 Hz, 1H), 5.28 (d, *J* = 11.4 Hz, 1H), 7.16-7.18 (m, 2H), 7.40-7.42 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 20.8, 26.0, 52.2, 66.4, 115.1, 120.2 (q, $^1J_{C\text{-}F}$ = 269.7 Hz), 130.0, 131.1 (q, $^2J_{C\text{-}F}$ = 39.7 Hz), 132.9, 140.3, 170.1, 171.1. ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.4 (s, CF_3). IR (neat) ν 1703, 1513, 1323, 1290, 1189, 1126, 1066 cm^{-1}. (-)-ESI-MS (*m/z*): 310.0 (100, [M–H]$^-$). Anal. calcd for $C_{14}H_{12}F_3N_3O_2$ (311.1): C 54.02, H 3.89, N 13.50; found: C 54.01, H 3.83, N 13.51.

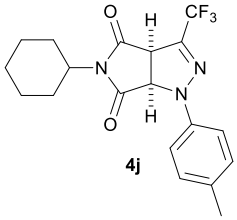
5-Propyl-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4i**):



4i

Reaction time 90 min; CC (SiO_2, petroleum ether/EtOAc 3:1); yellow solid, 270 mg (80%); mp 124-125 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3H), 1.60-1.66 (m, 2H), 2.33 (s, 3H), 3.56 (t, J = 7.3 Hz, 2H), 4.64 (dq, J = 1.3, 11.4 Hz, 1H), 5.26 (d, J = 11.4 Hz, 1H), 7.15-7.18 (m, 2H), 7.40-7.42 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 11.2, 20.8, 20.9, 41.6, 52.1, 66.4, 115.2, 120.2 (q, $^1J_{C\text{-}F}$ = 269.8 Hz), 130.0, 131.4 (q, $^2J_{C\text{-}F}$ = 39.7 Hz), 140.4, 170.1, 171.8. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.8 (s, CF_3). IR (neat) ν 1703, 1521, 1402, 1320, 1211, 1129, 1074, 1033 cm^{-1}. (-)-ESI-MS (*m/z*): 338.0 (100, $[M–H]^-$). Anal. calcd for $C_{16}H_{16}F_3N_3O_2$ (339.1): C 56.64, H 4.75, N 12.38; found: C 56.65, H 4.67, N 12.23.

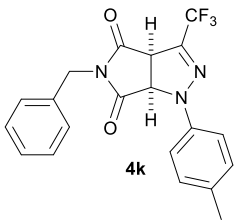
5-Cyclohexyl-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4j**):



4j

Reaction time 90 min; CC (SiO_2, petroleum ether/EtOAc 3:1); yellow solid, 318 mg (84%); mp 146-147 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16-1.35 (m, 3H), 1.59-1.68 (m, 3H), 1.82-1.87 (m, 2H), 2.07-2.17 (m, 2H), 2.32 (s, 3H), 3.99-4.04 (m, 1H), 4.64 (dq, J = 1.2, 11.3 Hz, 1H), 5.20 (d, J = 11.3 Hz, 1H), 7.15-7.18 (m, 2H), 7.39-7.42 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 20.8, 25.0, 25.9, 28.8, 51.9, 53.3, 66.0, 115.2, 120.3 (q, $^1J_{C\text{-}F}$ = 270.1 Hz), 130.0, 131.5 (q, $^2J_{C\text{-}F}$ = 39.6 Hz), 132.8, 140.4, 170.1, 171.9. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.8 (s, CF_3). IR (neat) ν 1707, 1521, 1368, 1320, 1185, 1133, 1080, 1033 cm^{-1}. (+)-ESI-MS (*m/z*): 402.4 (100, $[M+Na]^+$). Anal. calcd for $C_{19}H_{20}F_3N_3O_2$ (379.2): C 60.15, H 5.31, N 11.08; found: C 60.18, H 5.36, N 10.95.

5-Benzyl-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4k**)[4]:

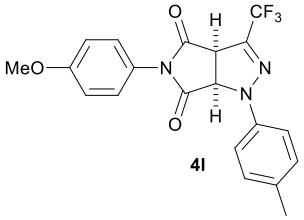


4k

Reaction time 90 min; FCC (SiO_2, petroleum ether/EtOAc 3:1); yellow solid, 344 mg (89%); mp 175-176 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.70 and 4.72 (AB system, J = 14.1 Hz, 2H), 4.63 (dq, J = 1.3, 11.4 Hz, 1H), 5.24 (d, J = 11.4 Hz, 1H), 7.14-7.17 (m, 2H), 7.29-7.34 (m, 3H), 7.36-7.41 (m, 4H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 20.8, 43.7, 52.2, 66.3, 115.1, 120.2 (q, $^1J_{C\text{-}F}$ = 269.8 Hz), 128.6, 129.0, 129.2, 130.0, 131.1 (q, $^2J_{C\text{-}F}$ = 39.7 Hz), 132.9, 134.6, 140.2,

169.8, 171.4. ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.4 (s, CF_3). IR (neat) ν 1707, 1513, 1390, 1312, 1223, 1178, 1118, 1040 cm^{-1}. (-)-ESI-MS (*m/z*): 385.9 (100, [M–H]$^-$). Anal. calcd for $C_{20}H_{16}F_3N_3O_2$ (387.1): C 62.01, H 4.16, N 10.85; found: C 62.02, H 3.99, N 10.85.

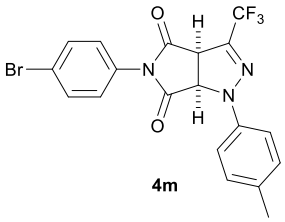
5-(4-Methoxyphenyl)-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4l**):



4l

Reaction time 90 min; FCC (SiO_2, petroleum ether/EtOAc 3:1); yellow solid, 362 mg (90%); mp 170-171 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.83 (s, 3H), 4.78 (dq, *J* = 1.3, 11.5 Hz, 1H), 5.39 (d, *J* = 11.5 Hz, 1H), 6.96-6.99 (m, 2H), 7.16-7.22 (m, 4H), 7.43-7.46 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 20.8, 52.1, 55.7, 66.4, 114.7, 115.2, 120.2 (q, $^1J_{C\text{-}F}$ = 269.9 Hz), 123.5, 127.6, 130.0, 131.4 (q, $^2J_{C\text{-}F}$ = 39.7 Hz), 133.0, 140.3, 160.1, 169.3, 170.9. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.7 (s, CF_3). IR (neat) ν 1713, 1513, 1387, 1327, 1252, 1189, 1122, 1085, 1021 cm^{-1}. (-)-ESI-MS (*m/z*): 402.1 (100, [M–H]$^-$). Anal. calcd for $C_{20}H_{16}F_3N_3O_3$ (403.1): C 59.55, H 4.00, N 10.42; found: C 59.38, H 4.11, N 10.47.

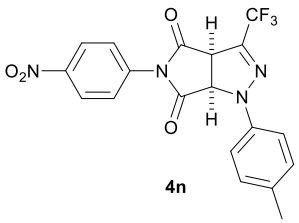
5-(4-Bromophenyl)-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4m**):



4m

Reaction time 90 min; FCC (SiO_2, petroleum ether/EtOAc 4:1); colourless solid, 383 mg (85%); mp 215-216 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.27 (s, 3H), 5.04 (dq, *J* = 1.4, 11.6 Hz, 1H), 5.67 (d, *J* = 11.6 Hz, 1H), 7.18-7.21 (m, 2H), 7.30-7.35 (m, 4H), 7.71-7.74 (m, 2H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 20.2, 52.9, 66.8, 114.5, 120.4 (q, $^1J_{C\text{-}F}$ = 269.5 Hz), 122.0, 129.2, 129.6, 131.1, 131.2, 131.6 (q, $^2J_{C\text{-}F}$ = 38.3 Hz), 132.1, 140.3, 170.0, 171.6. ^{19}F NMR (565 MHz, DMSO-d_6): δ –62.5 (s, CF_3). IR (neat) ν 1722, 1513, 1494, 1379, 1323, 1185, 1126, 1085, 1044 cm^{-1}. (-)-ESI-MS (*m/z*): 451.9 (100, [{^{81}Br}M–H]$^-$), 450.0 (91, [{^{79}Br}M–H]$^-$). Anal. calcd for $C_{19}H_{13}BrF_3N_3O_2$ (451.0): C 50.46, H 2.90, N 9.29; found: C 50.44, H 2.90, N 9.03.

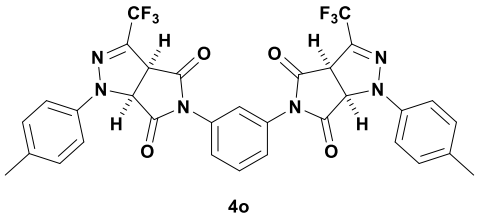
5-(4-Nitrophenyl)-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4n**):



4n

Reaction time 90 min; FCC (SiO_2, petroleum ether/EtOAc 1:1); yellow solid, 364 mg (87%); mp 175-177 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.27 (s, 3H), 5.08 (dq, J = 1.5, 11.7 Hz, 1H), 5.71 (d, J = 11.7 Hz, 1H), 7.19-7.21 (m, 2H), 7.34-7.37 (m, 2H), 7.66-7.69 (m, 2H), 8.37-8.40 (m, 2H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 20.2, 53.0, 66.8, 114.5, 120.4 (q, $^1J_{C\text{-}F}$ = 269.5 Hz), 124.3, 128.3, 129.6, 131.3, 131.5 (q, $^2J_{C\text{-}F}$ = 38.3 Hz), 137.4, 140.3, 147.1, 169.8, 171.4. ^{19}F NMR (565 MHz, DMSO-d_6): δ –63.6 (s, CF_3). IR (neat) ν 1722, 1525, 1517, 1375, 1346, 1323, 1230, 1178, 1133, 1081, 1044 cm^{-1}. (-)-ESI-MS (*m/z*): 417.1 (100, [M–H]$^-$). Anal. calcd for $C_{19}H_{13}F_3N_4O_4$ (418.1): C 54.55, H 3.13, N 13.39; found: C 54.35, H 3.01, N 13.15.

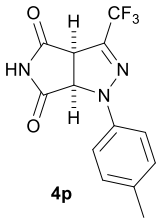
syn-1,3-bis[1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione-5-yl]phenylene (**4o**):



4o

Following the general protocol hydrazonoyl bromide **2a** (2.2 mmol), 1,3-phenylene bis-maleimide (**3i**, 1.0 mmol), and solid K_2CO_3 (2.4 mmol, 332 mg) was used. Reaction time 90 min; CC (SiO_2, petroleum ether/EtOAc 3:1); orange solid, 414 mg (62%); mp 156-158 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.26 (s, 6H), 5.04 (d_{br}, $J \approx$ 11.6 Hz, 2H), 5.67 (d_{br}, $J \approx$ 11.6 Hz, 2H), 7.17-7.20 (m, 4H), 7.32-7.35 (m, 4H), 7.39-7.41 (m, 1H), 7.43-7.45 (m, 2H), 7.64-7.68 (m, 1H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 20.3, 53.0, 66.8, 114.6, 120.5 (q, $^1J_{C\text{-}F}$ = 269.3 Hz), 126.0, 127.8, 129.7, 129.8, 131.5, 131.7 (q, $^2J_{C\text{-}F}$ = 38.3 Hz), 132.4, 140.4, 170.2, 171.8. ^{19}F NMR (565 MHz, DMSO-d_6): δ –62.4 (s, CF_3). IR (neat) ν 1722, 1513, 1364, 1320, 1223, 1182, 1118, 1074, 1044cm^{-1}. (-)-ESI-MS (*m/z*): 667.2 (100, [M–H]$^-$). Anal. calcd for $C_{32}H_{22}F_6N_6O_4$ (668.2): C 57.49, H 3.32, N 12.57; found: C 57.68, H 3.16, N 12.38. HPLC (Chiralcel-OD): R_t = 5.0 min (hexane:^{i}PrOH:MeOH 85:10:5, flow 0.7 mL); 5.5 min (hexane:^{i}PrOH:MeOH 89:10:1, flow 0.5 mL); R_t = 8.7 min (hexane:^{i}PrOH 90:10, flow 0.5 mL).

1-(*p*-Tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4p**):

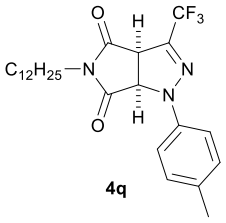


4p

Reaction time 90 min; CC (SiO_2, petroleum ether/EtOAc 1:1); pale yellow solid, 252 mg (85%); mp 174-175 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.68 (dq, J = 1.2, 11.4 Hz, 1H), 5.29 (d, J = 11.4 Hz, 1H), 7.15-7.18 (m, 2H), 7.37-7.39 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$)

δ 20.8, 53.4, 67.5, 115.1, 120.2 (q, $^{1}J_{C\text{-}F}$ = 270.0 Hz), 130.0, 131.1 (q, $^{2}J_{C\text{-}F}$ = 39.9 Hz), 133.0, 140.2, 169.9, 171.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.6 (s, CF_3). IR (neat) ν 3067, 1715, 1513, 1316, 1223, 1185, 1133, 1077, 1033 cm^{-1}. (-)-ESI-MS (*m/z*): 296.0 (100, [M–H]$^-$). Anal. calcd for $C_{13}H_{10}F_3N_3O_2$ (297.1): C 52.53, H 3.39, N 14.14; found: C 52.27, H 3.55, N 14.28.

One-pot telescopic synthesis of 5-dodecyl-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (4q): Hydrazonoyl halide **2a** (1.1 mmol, 309 mg, solid), maleimide (**3j**, 1.0 mmol, 97 mg, solid), and K_2CO_3 (1.1 mmol, 152 mg, solid) were placed in a 5 mL stainless steel grinding jar with one stainless steel ball (7 mm diameter). The jar was closed and the mixture was ball-milled at 22 Hz for 1.5h. Then, dodecyl bromide (2.0 mmol, 498 mg, liquid), K_2CO_3 (10 mmol, 1.38 g) and dry DMF (0.2 mL) were added and liquid assisted grinding (η = 0.35 µL/mg) was continued at 30 Hz for 5h. The resulting mixture was triturated with EtOAc (30 mL) and with aqueous solution of NH_4Cl (sat., 30 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), solvents were removed under reduced pressure, and the crude product was purified by standard column chromatography (SiO_2, petroleum ether/CH_2Cl_2 1:1) to give **4q** (386 mg, 83% overall yield) as colorless solid.



4q

Mp 70-71 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.21-1.32 (m, 18H), 1.58 (quint, *J* = 7.4 Hz, 2H), 2.33 (s, 3H), 3.57 (t, J = 7.4 Hz, 2H), 4.63 (dq, *J* = 1.3, 11.4 Hz, 1H), 5.25 (d, *J* = 11.4 Hz, 1H), 7.15-7.18 (m, 2H), 7.40-7.43 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 14.2, 20.8, 22.8, 26.7, 27.5, 29.1, 29.5, 29.6, 29.7*, 32.1, 40.1, 52.1, 66.3, 115.2, 120.2 (q, $^{1}J_{C\text{-}F}$ = 270.0 Hz), 130.0, 131.3 (q, $^{2}J_{C\text{-}F}$ = 39.8 Hz), 132.9, 140.4, 170.1, 171.8; *higher intensity. ^{19}F NMR (565 MHz, $CDCl_3$): δ –63.7 (s, CF_3). IR (neat) ν 2922, 2855, 1711, 1513, 1398, 1323, 1185, 1137 cm^{-1}. (-)-ESI-MS (*m/z*): 464.1 (100, [M–H]$^+$). Anal. calcd for $C_{25}H_{34}F_3N_3O_2$ (465.3): C 64.50, H 7.36, N 9.03; found: C 64.68, H 7.34, N 8.92.

Synthesis of pyrrolo[3,4-*c*]pyrazole 4q by alkylation of 4p in solution: To a solution of pyrrolo[3,4-*c*]pyrazole **4p** (0.5 mmol, 149 mg) and K_2CO_3 (1.5 mmol, 207 mg) in MeCN (5 mL), dodecyl bromide (0.6 mmol, 149 mg) in dry MeCN (1 mL) was added at room temperature. The reaction mixture was heated to 60 °C upon stirring for 16 h, then cooled to room temperature, diluted with water (20 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and solvents were removed under reduced pressure. The residue was purified by standard column chromatography (SiO_2, petroleum ether/CH_2Cl_2 1:1) to give **4q** (203 mg, 87 %) as a colorless solid.

3. Copies of NMR spectra

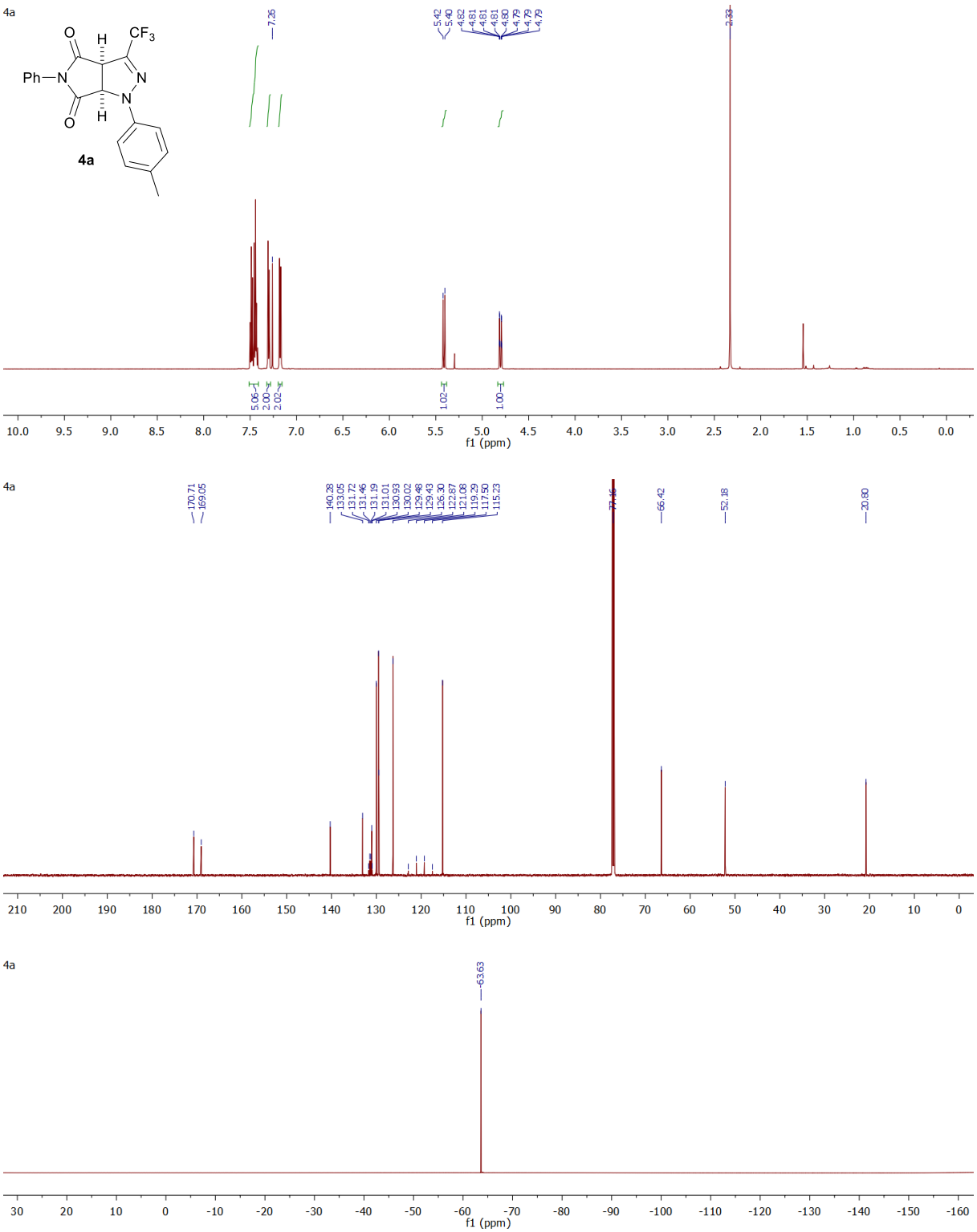


Fig S1. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4a**.

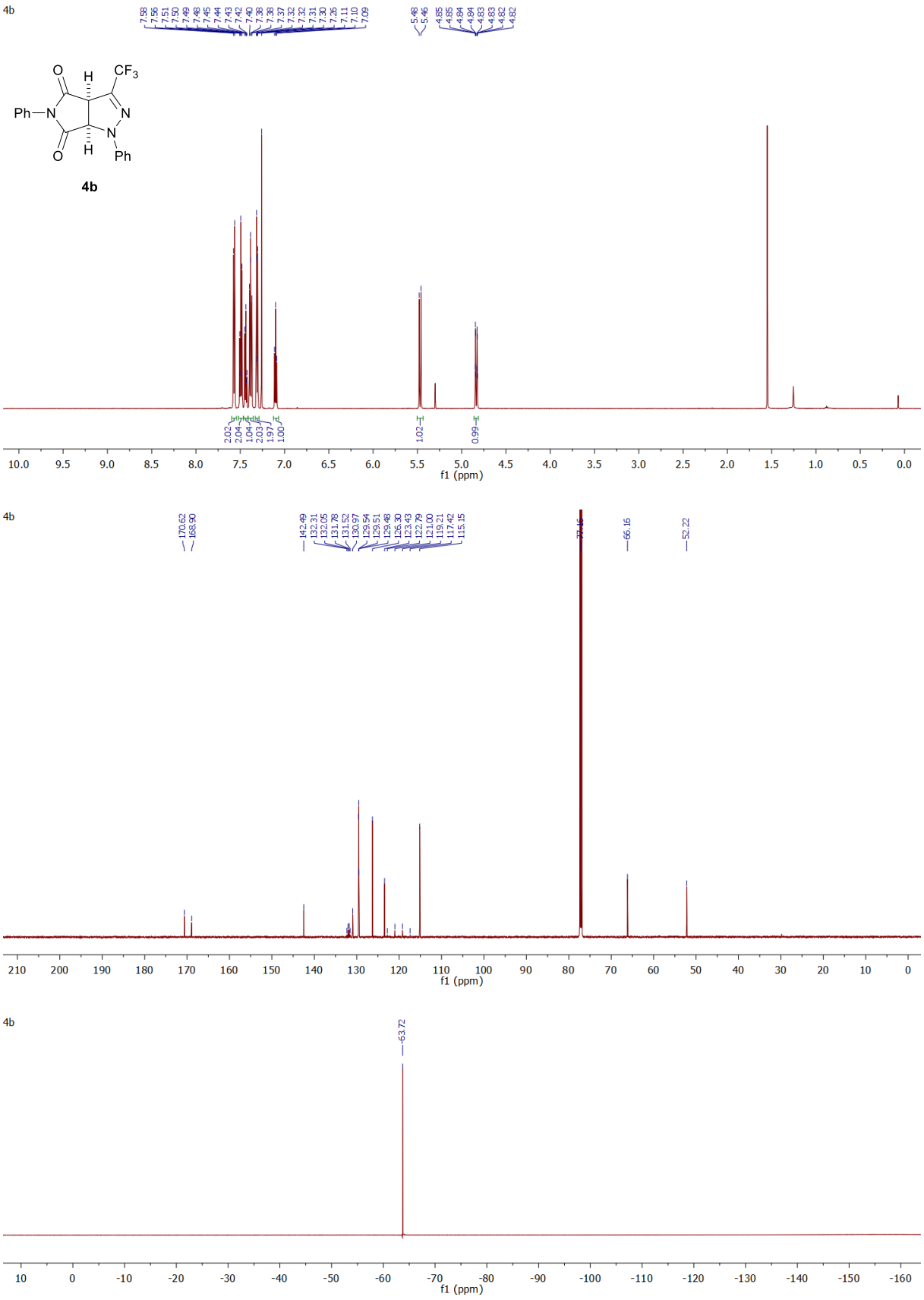


Fig S2. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4b**.

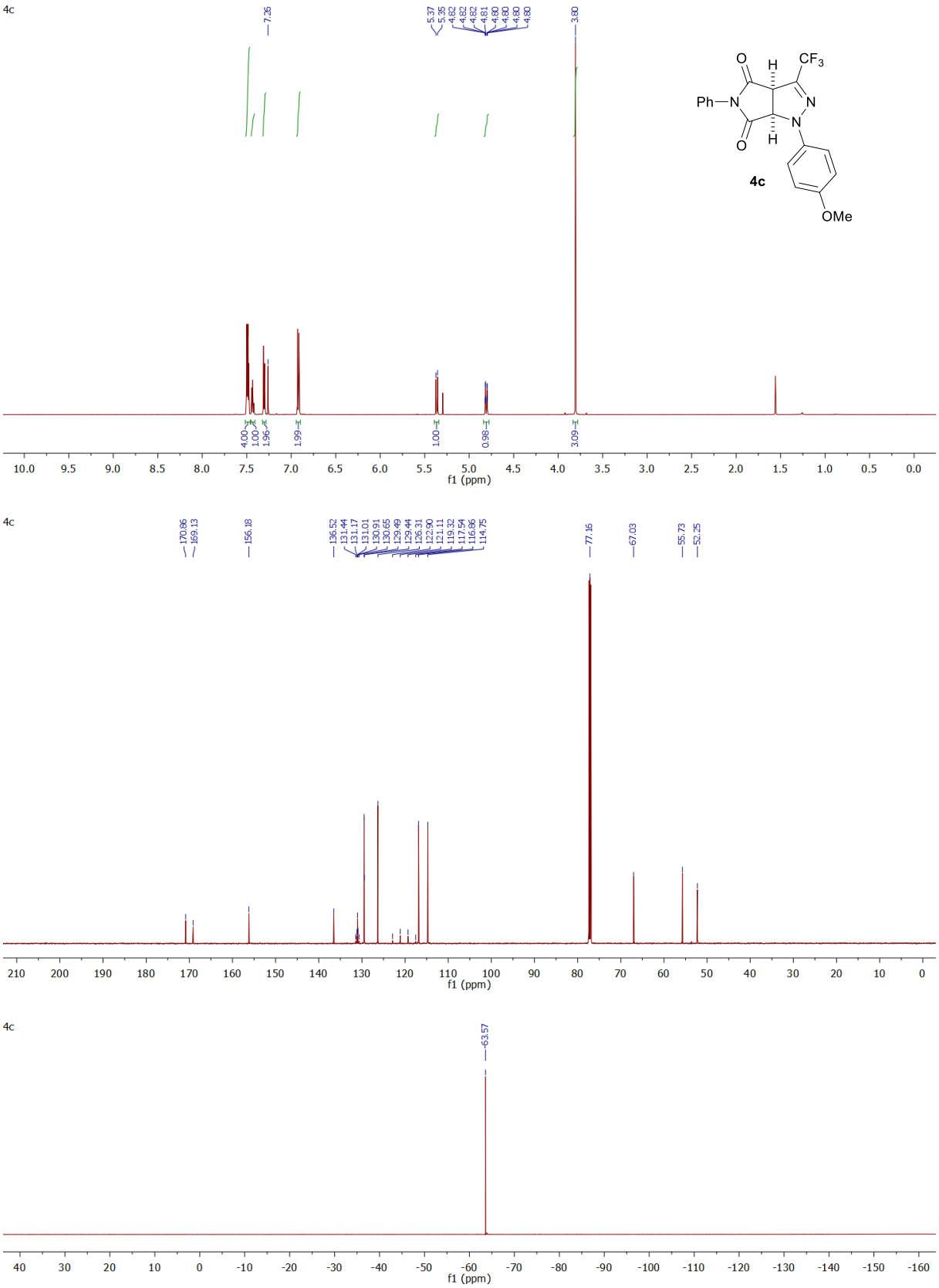


Fig S3. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4c**.

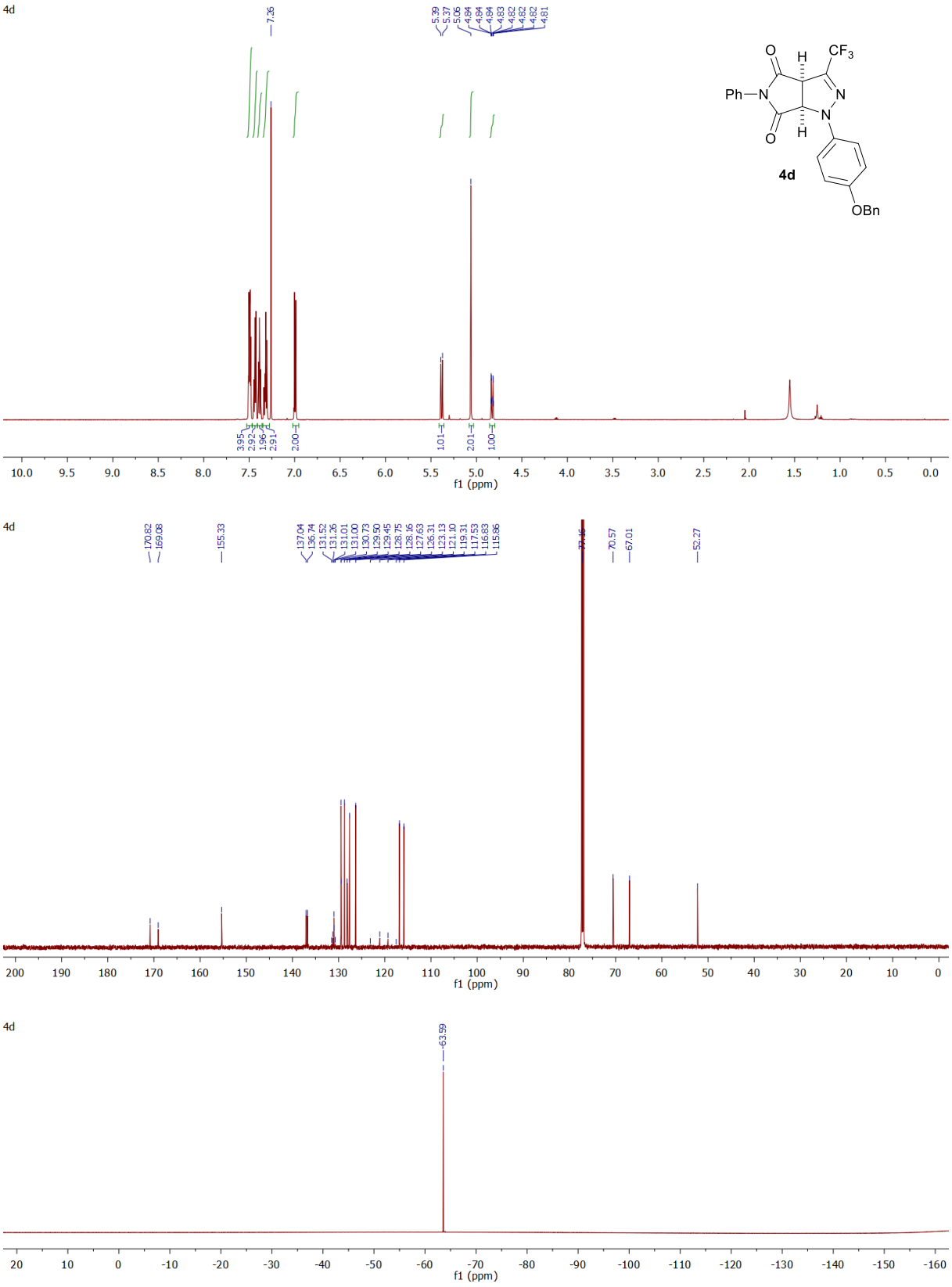


Fig S4. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4d**.

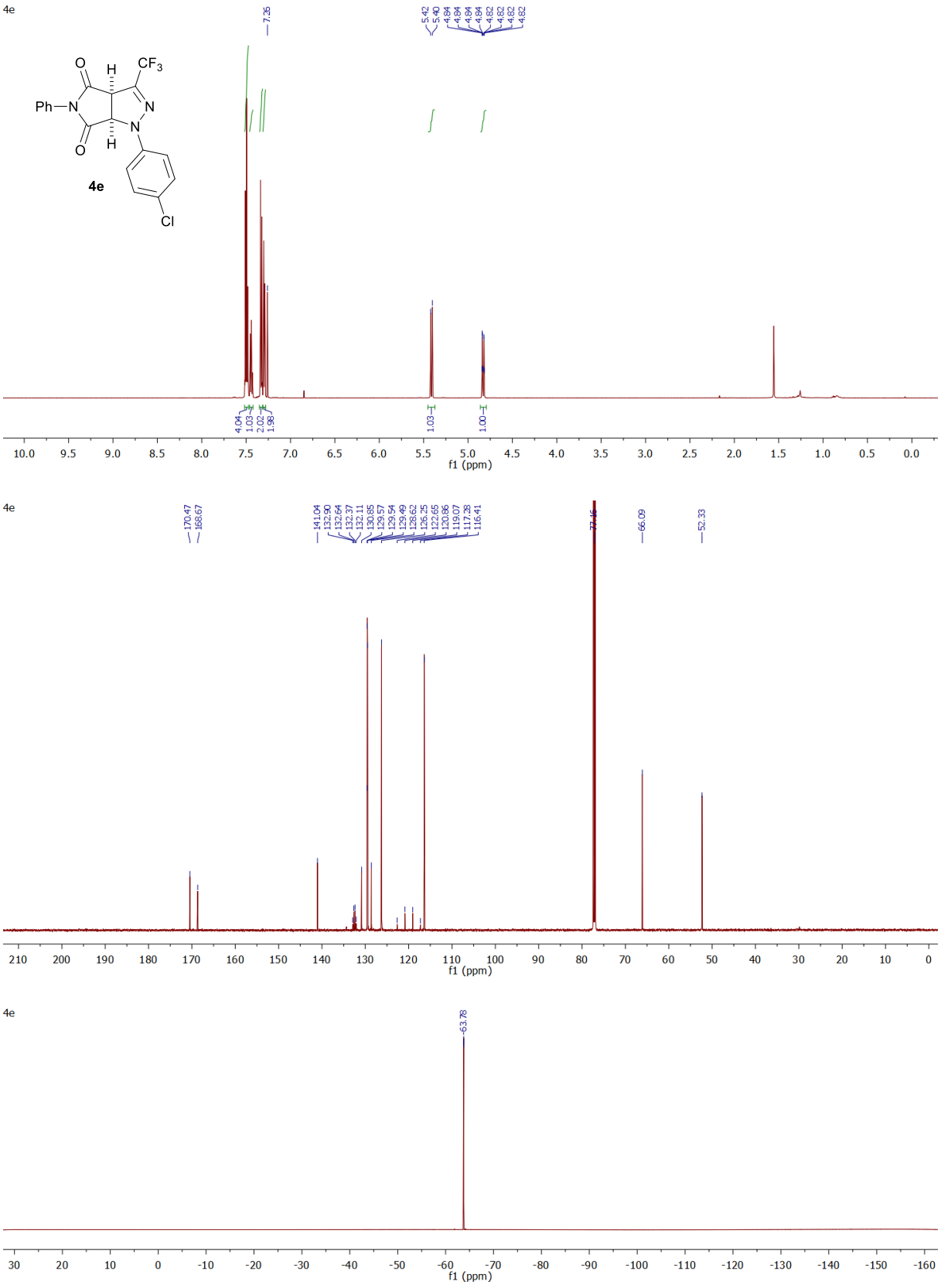


Fig S5. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4e**.

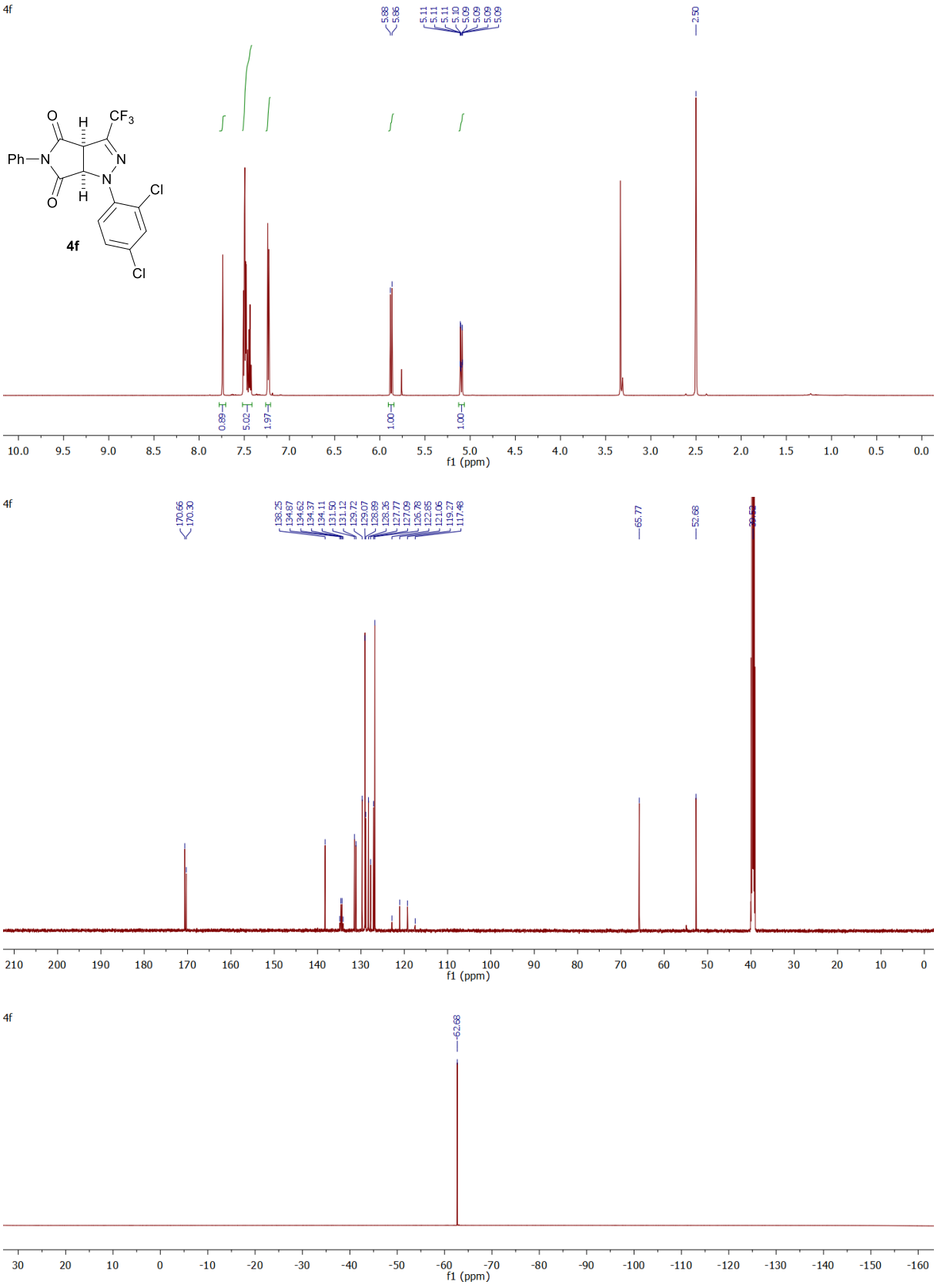


Fig S6. ^{1}H- (600 MHz), ^{13}C- (151 MHz) and ^{19}F NMR (565 MHz) spectra for compound **4f**, taken in DMSO-d_6.

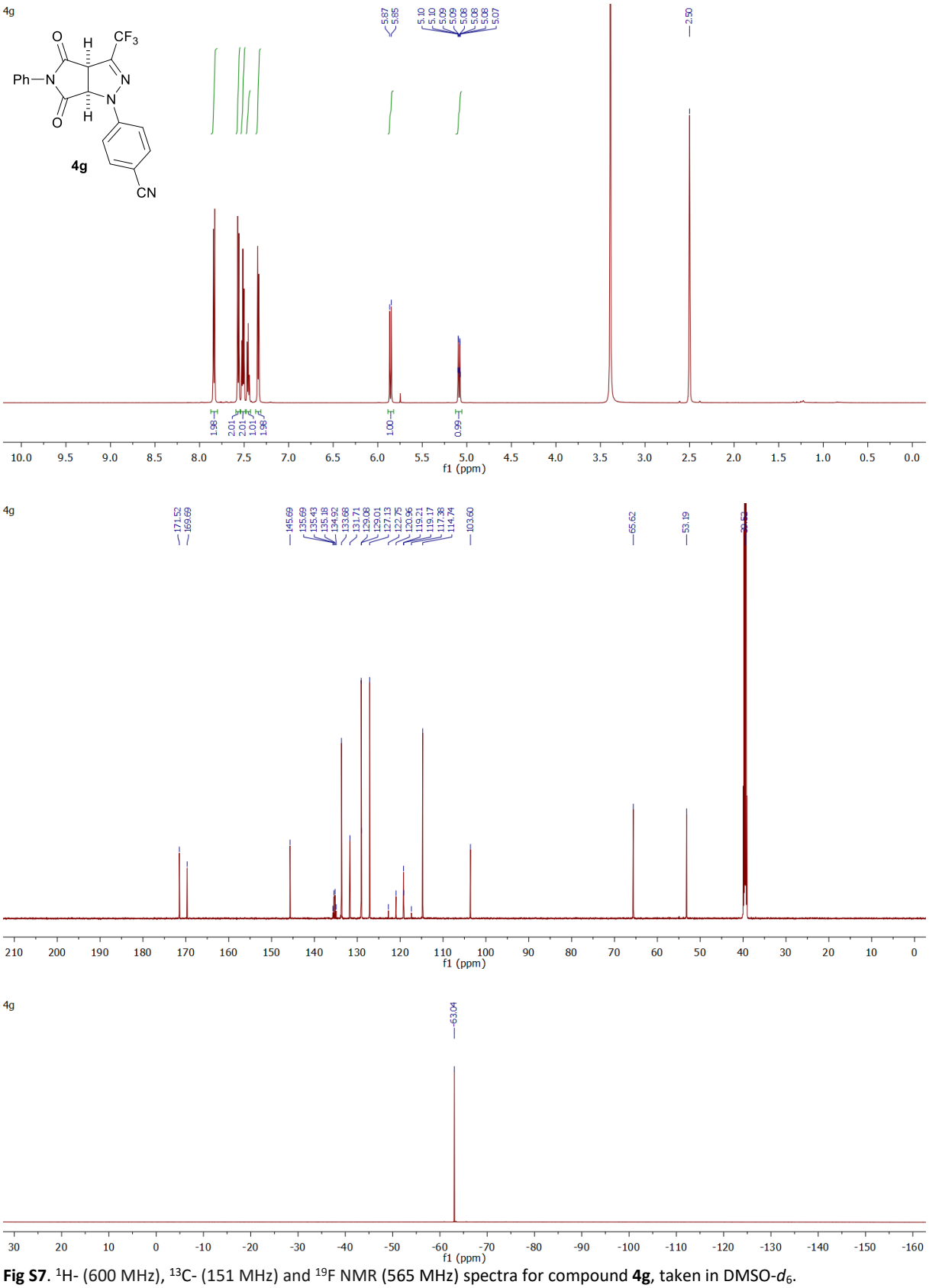


Fig S7. ^{1}H- (600 MHz), ^{13}C- (151 MHz) and ^{19}F NMR (565 MHz) spectra for compound **4g**, taken in DMSO-d_6.

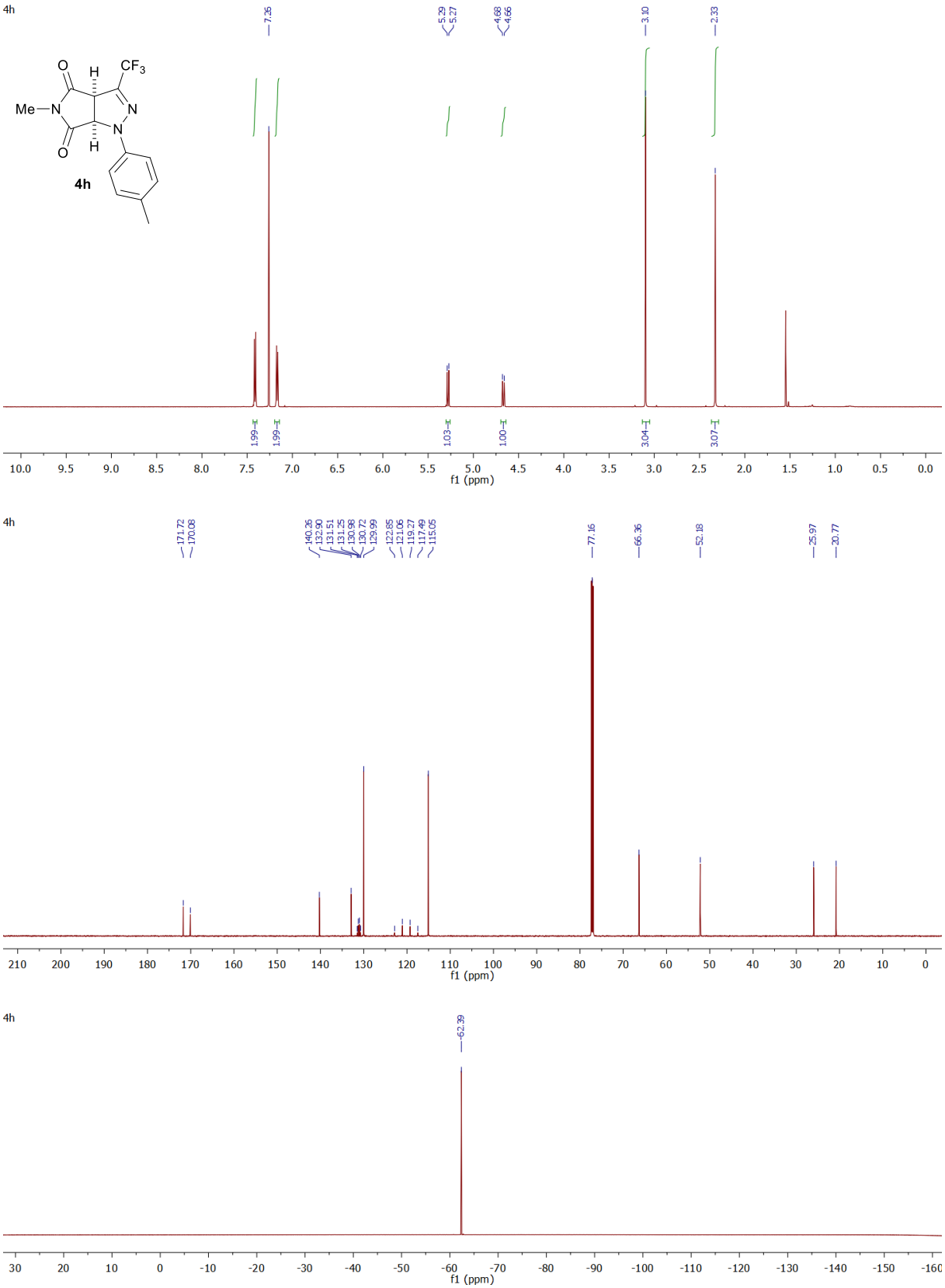


Fig S8. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4h**.

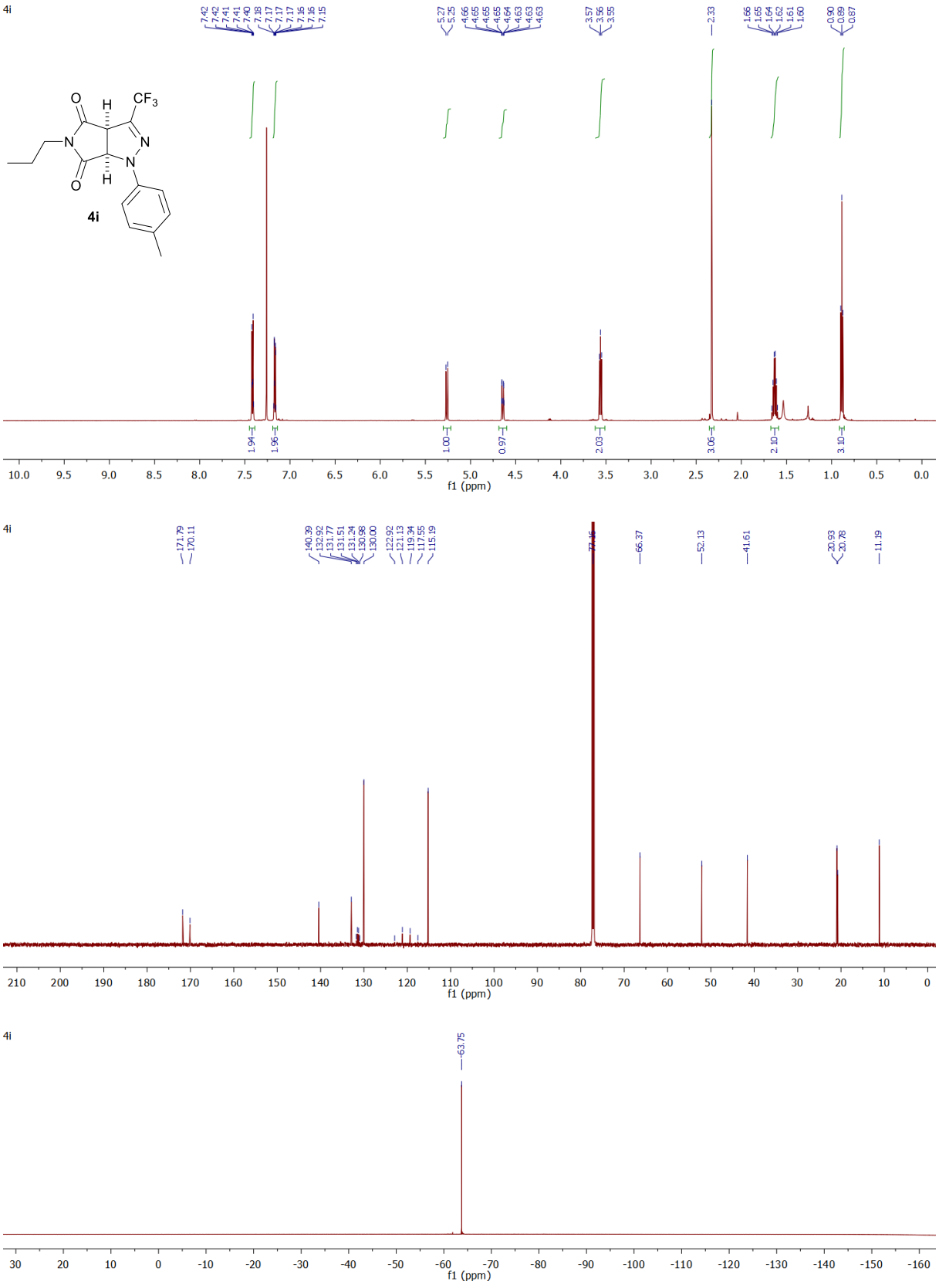


Fig S9. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4i**.

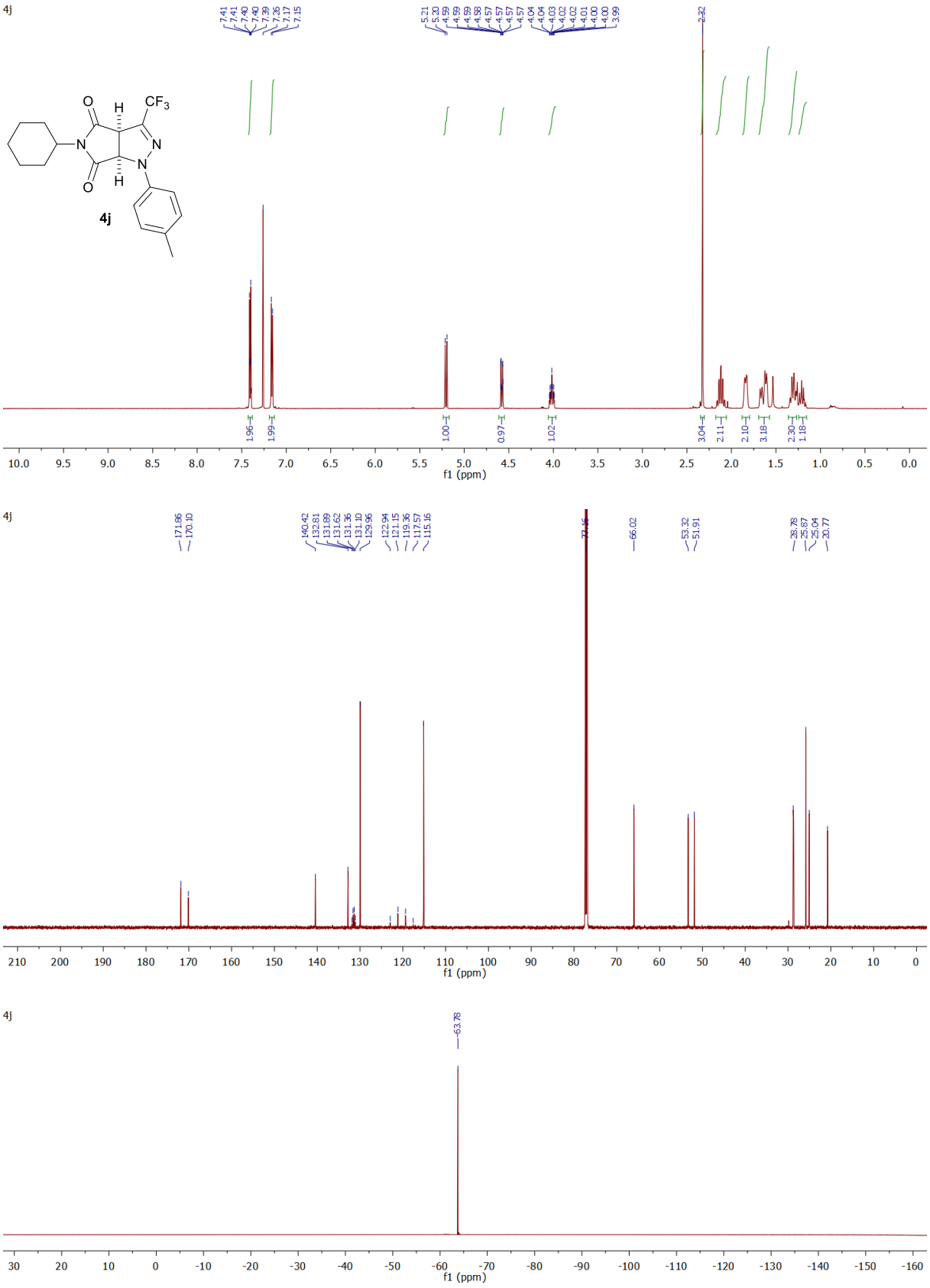


Fig S10. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4j**.

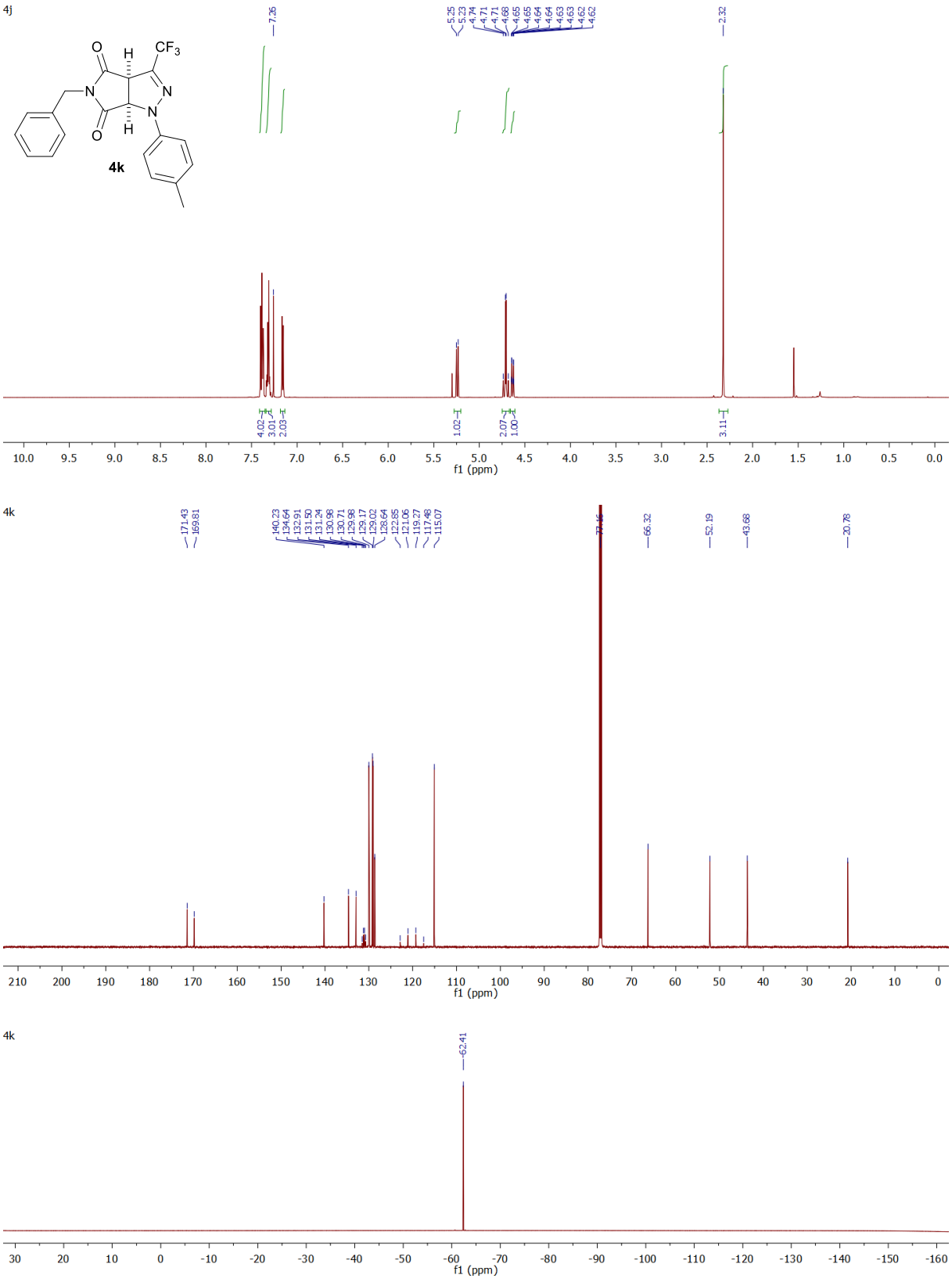


Fig S11. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4k**.

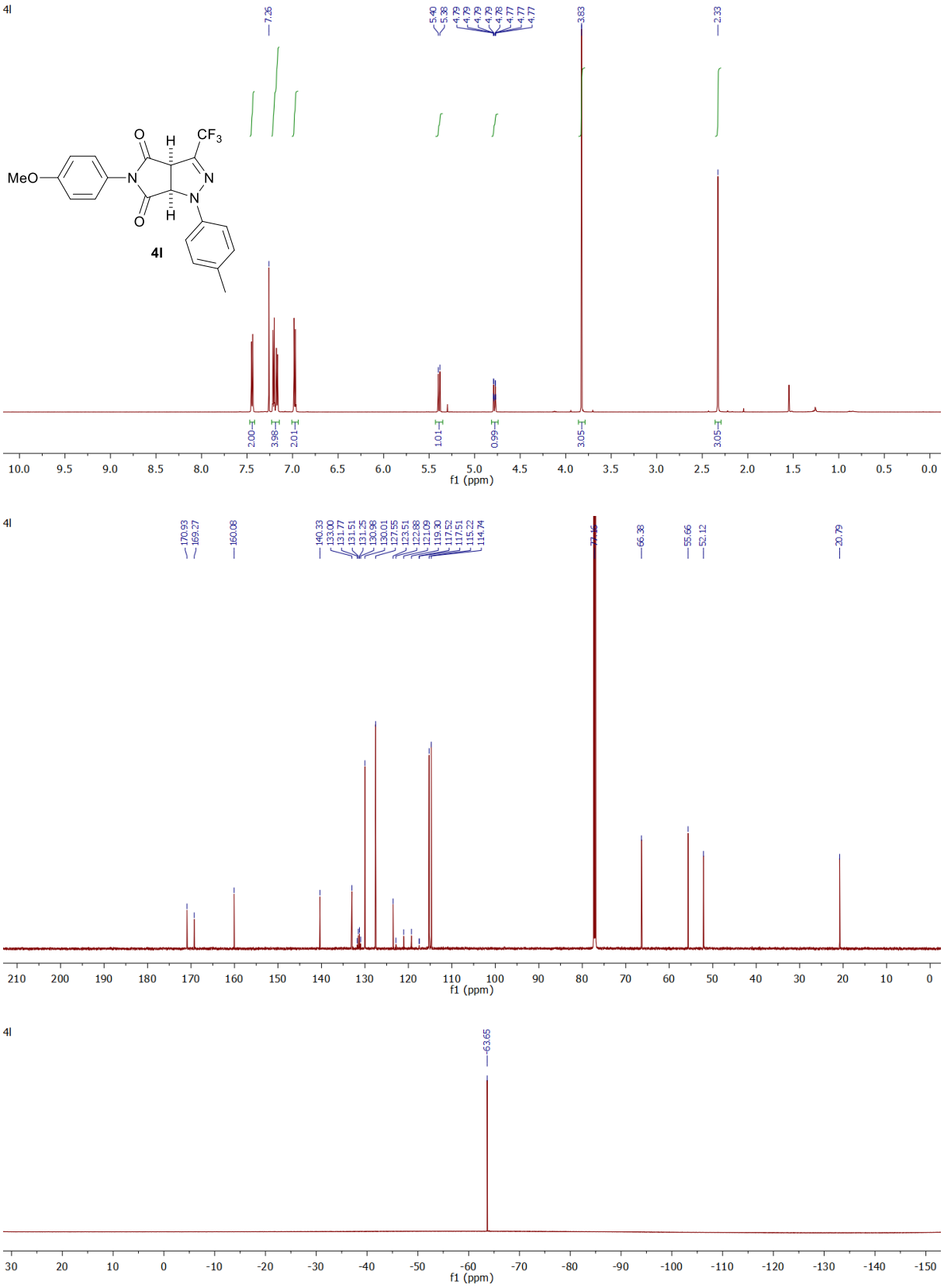


Fig S12. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4l**.

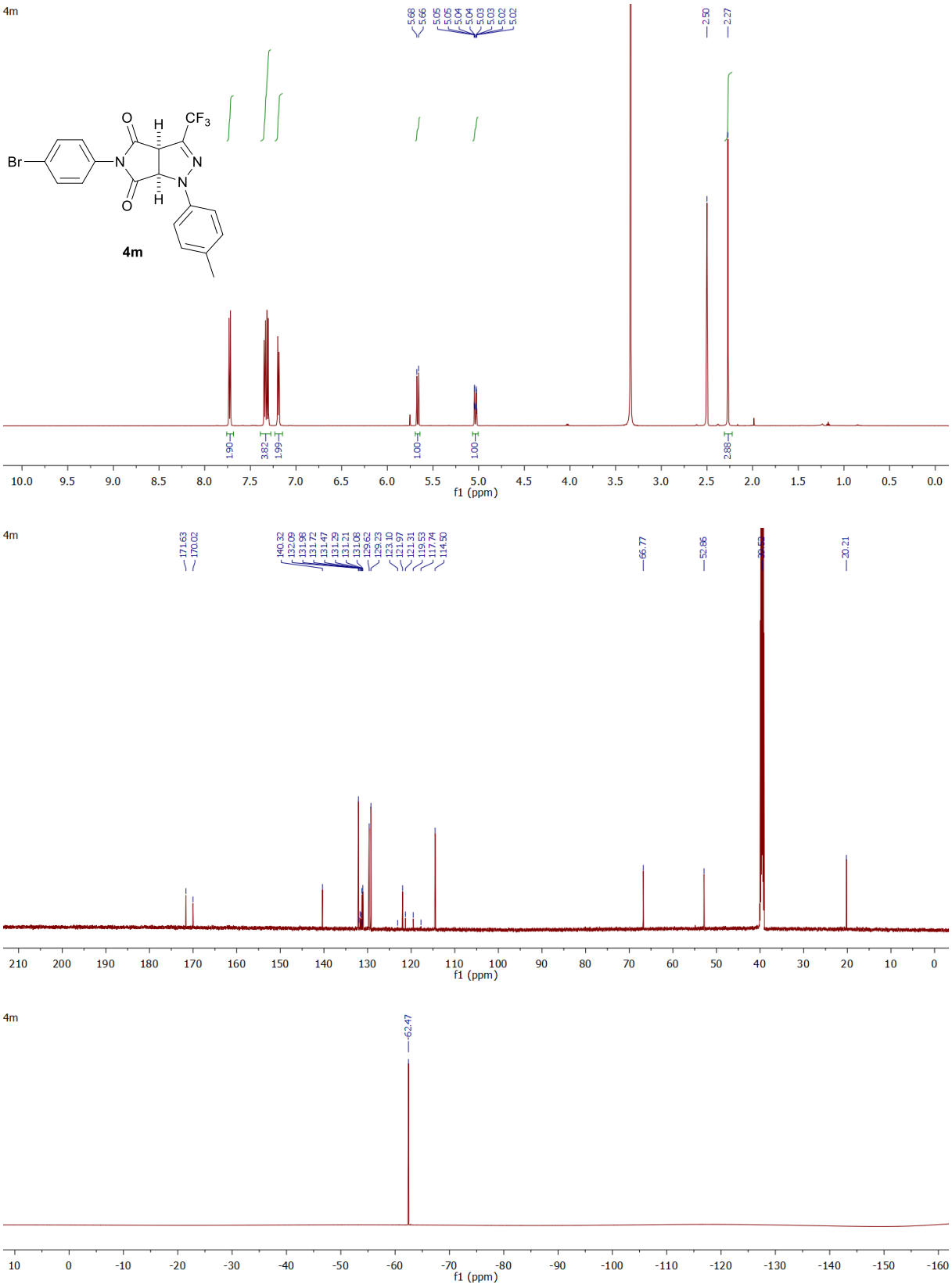


Fig S13. ^{1}H- (600 MHz), ^{13}C- (151 MHz) and ^{19}F NMR (565 MHz) spectra for compound **4m**, taken in DMSO-d_6.

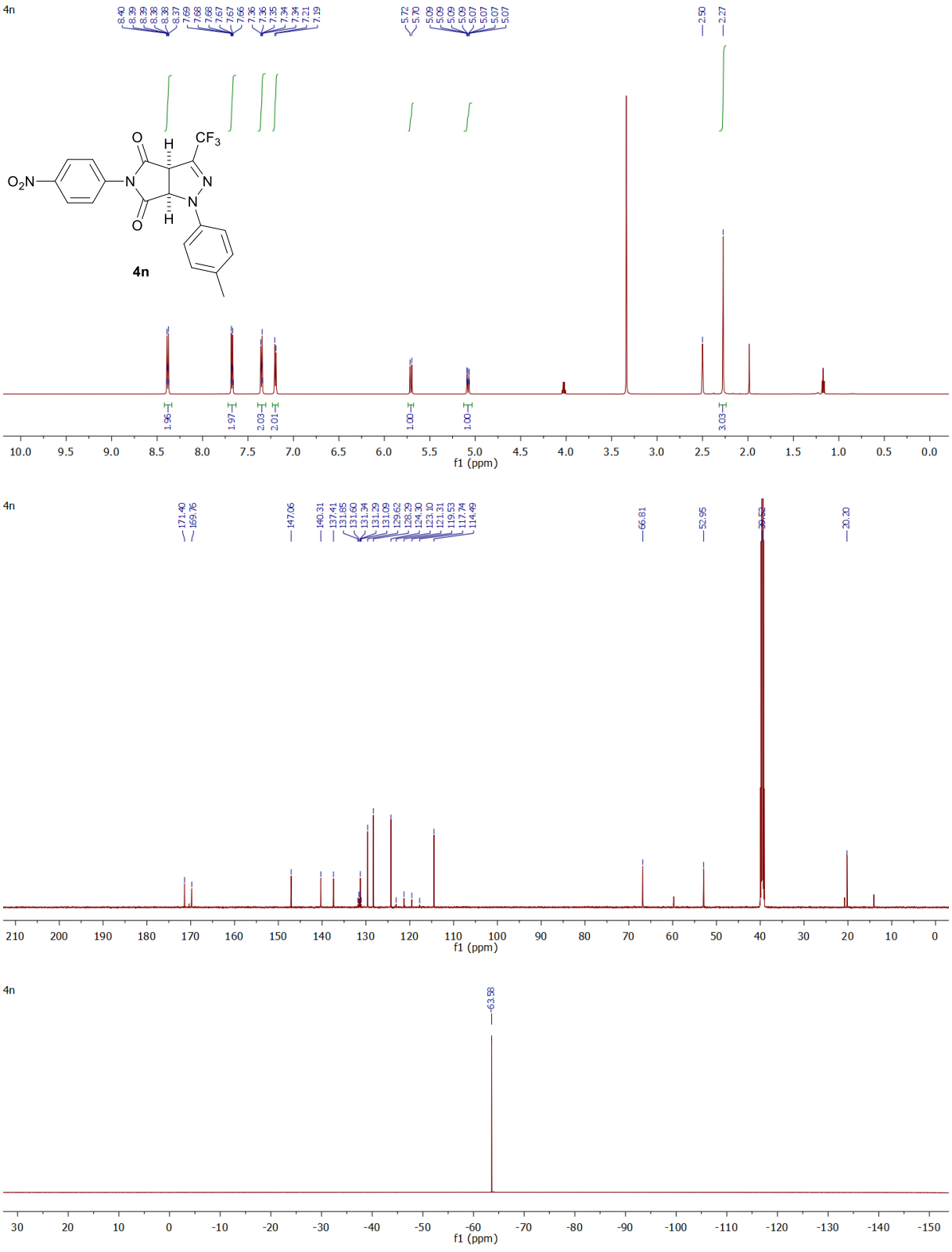


Fig S14. ^{1}H- (600 MHz), ^{13}C- (151 MHz) and ^{19}F NMR (565 MHz) spectra for compound **4n**, taken in DMSO-d_6; sample contaminated with small amounts of EtOAc.

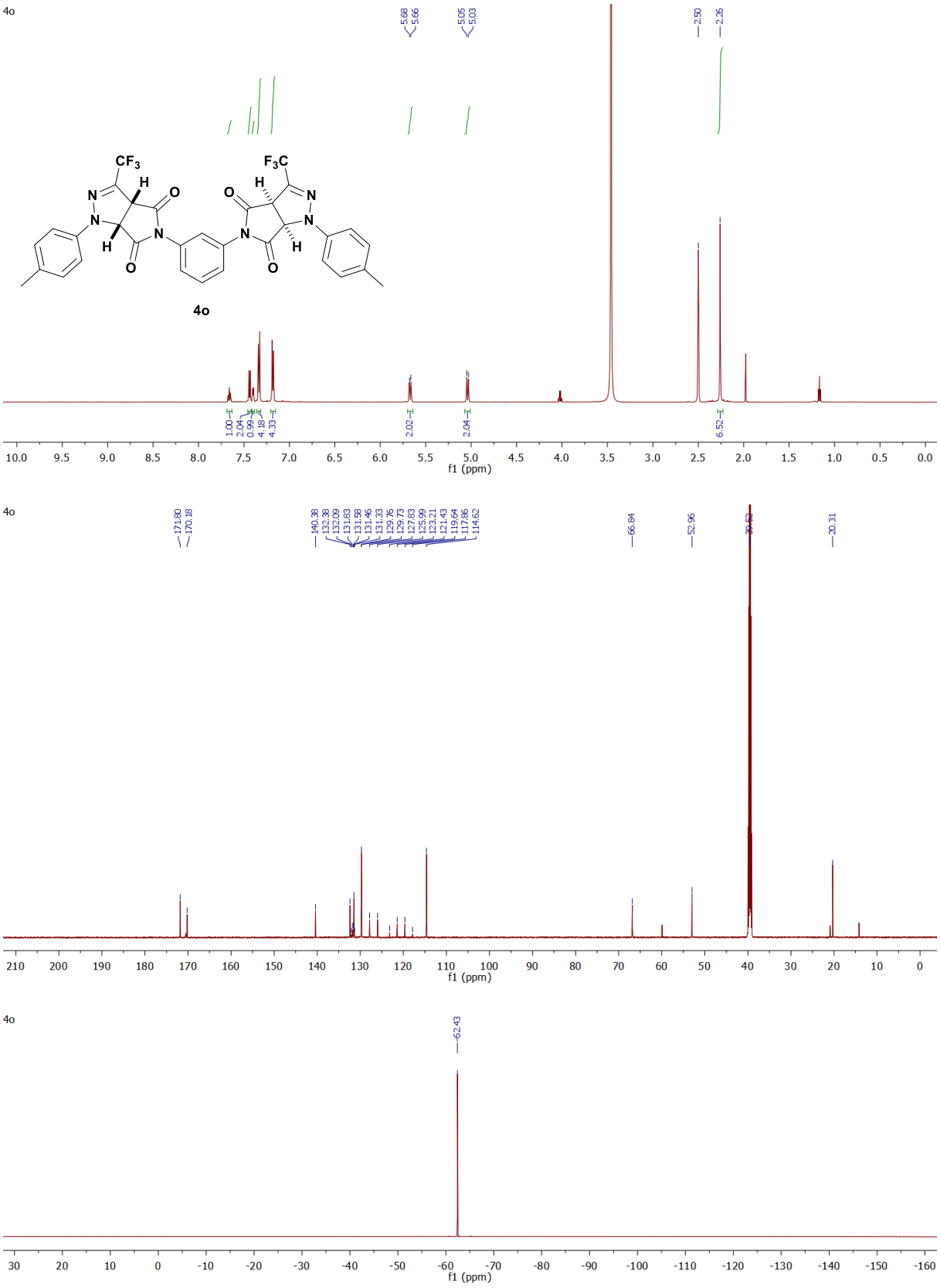


Fig S15. ^{1}H- (600 MHz), ^{13}C- (151 MHz) and ^{19}F NMR (565 MHz) spectra for compound **4o**, taken in DMSO-d_6; sample contaminated with small amounts of EtOAc.

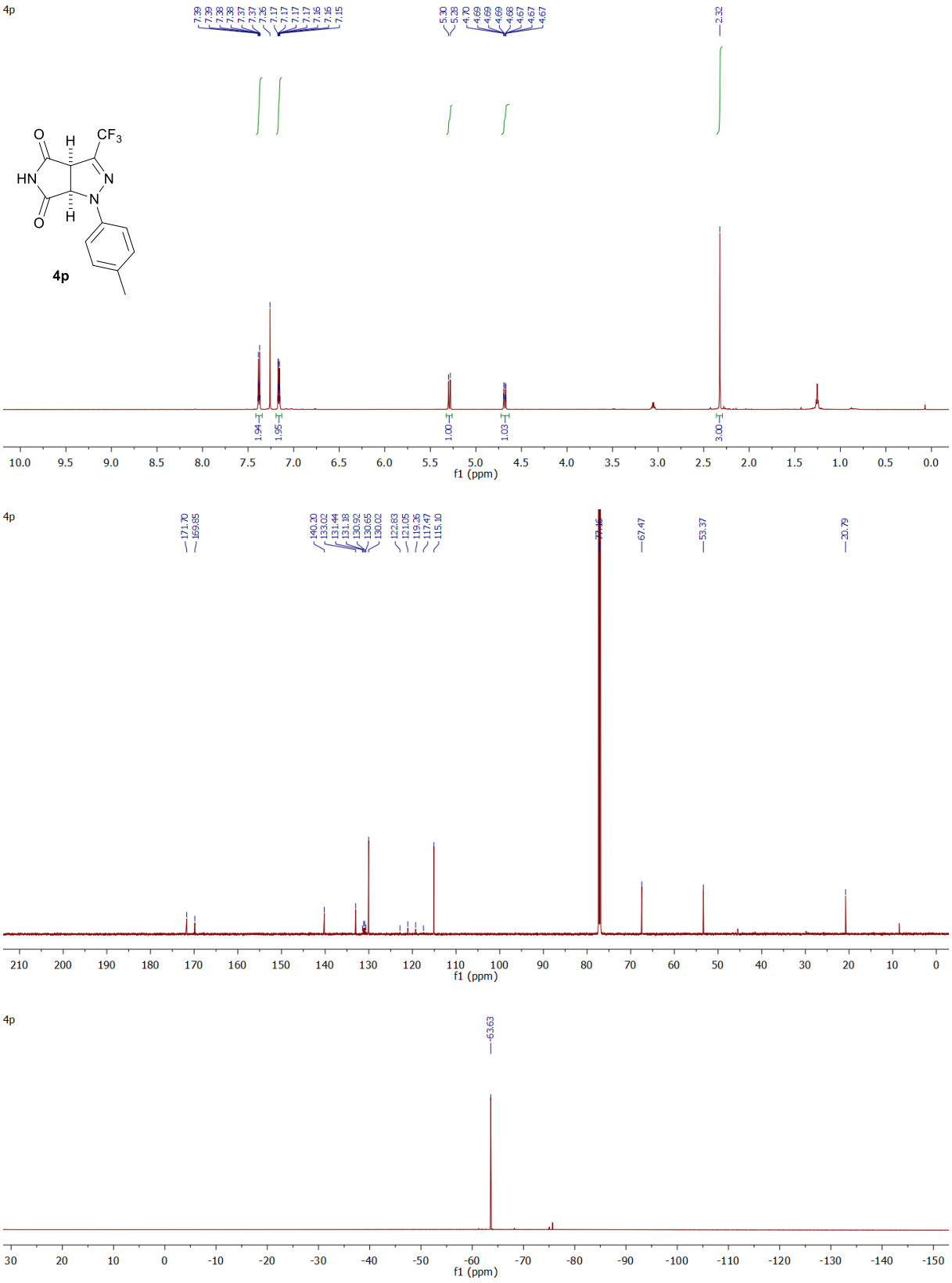


Fig S16. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4p**.

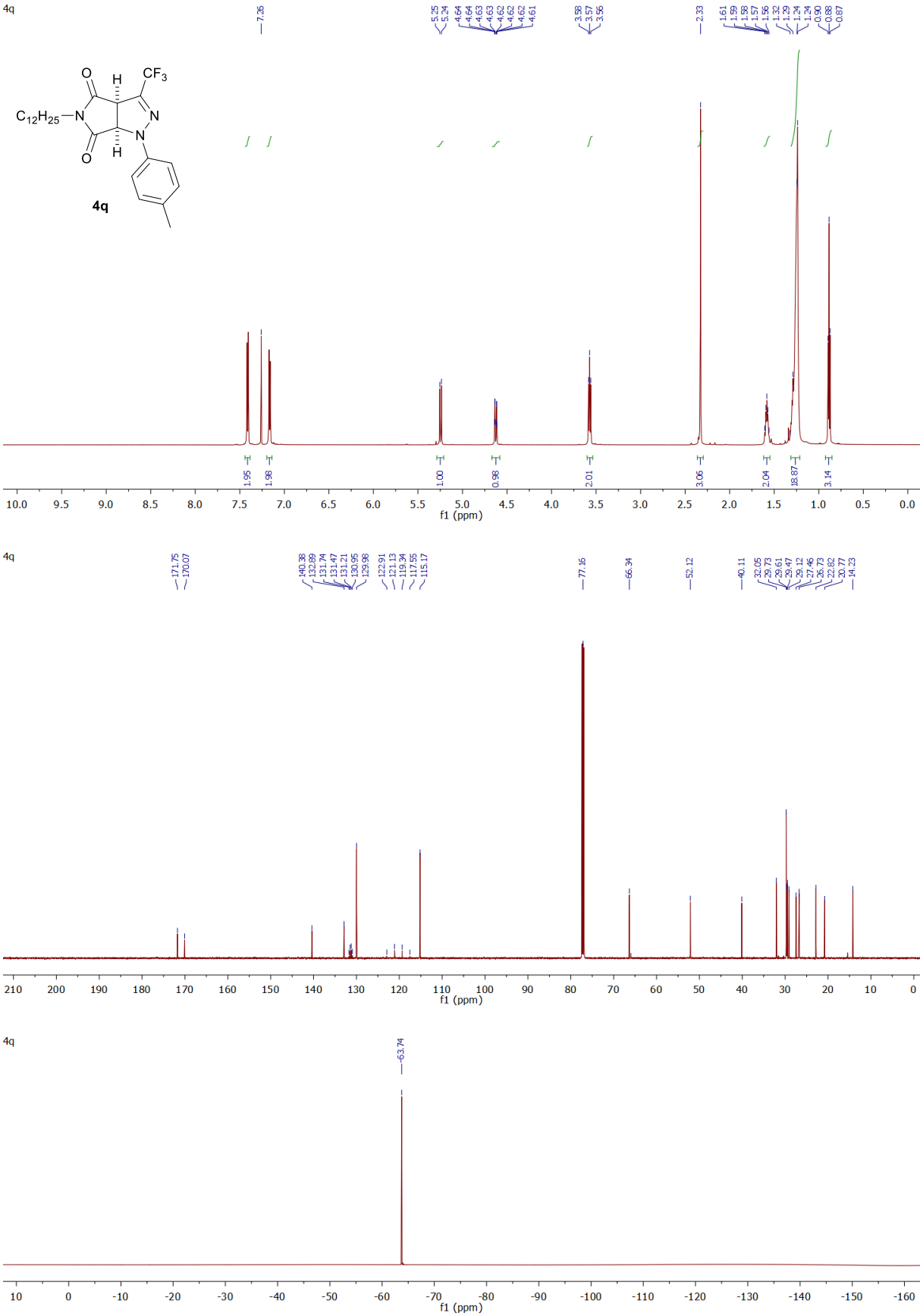


Fig S17. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4q**.

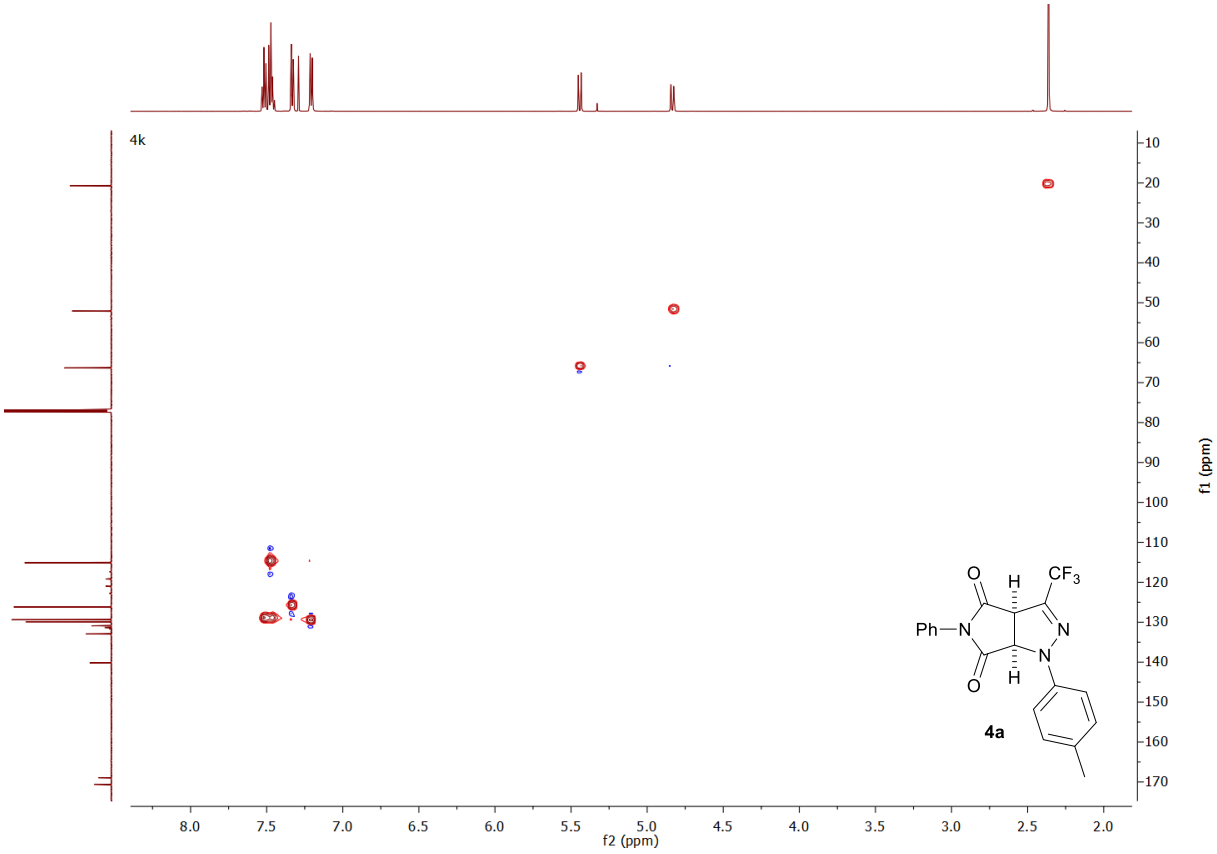


Fig S18. HMQC of **4a** ($CDCl_3$).

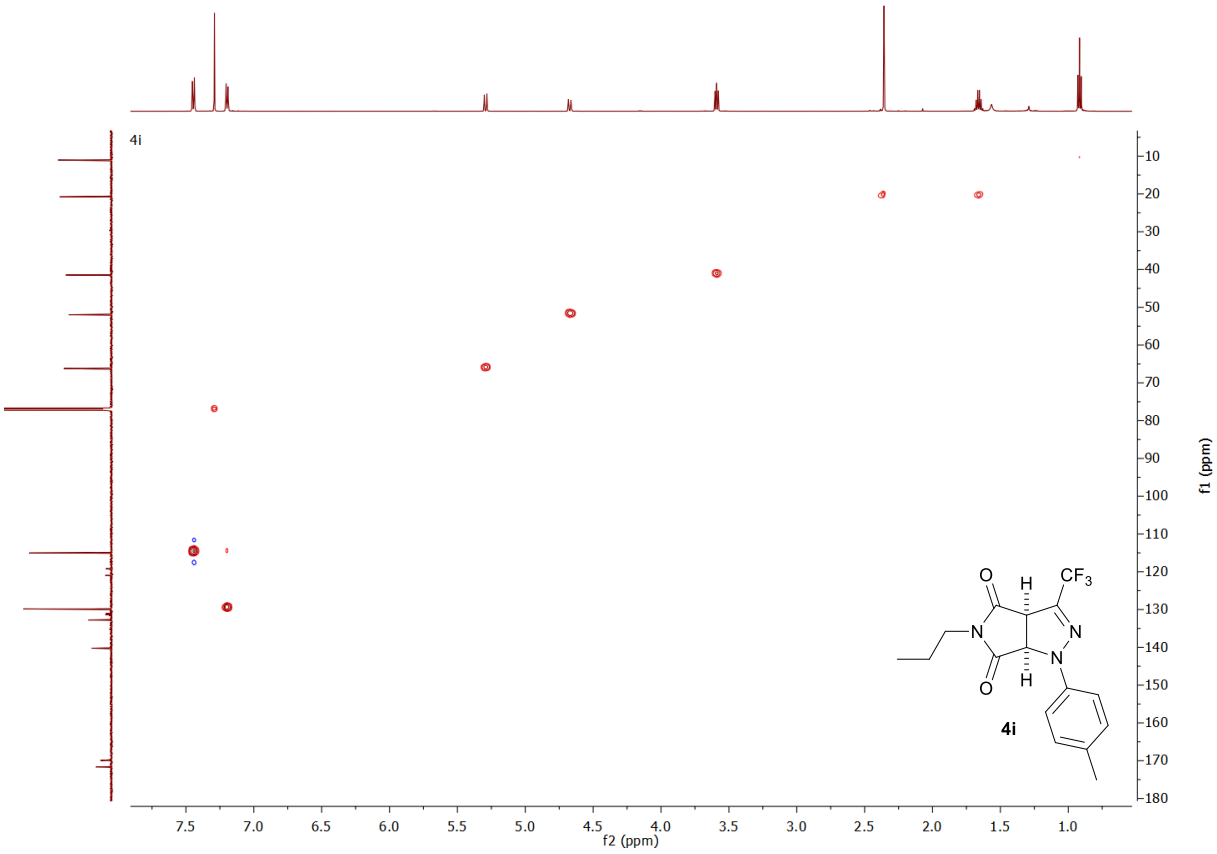


Fig S19. HMQC of **4i** ($CDCl_3$).

5. References

1. A. Wojciechowska, M. Jasiński, P. Kaszyński, *Tetrahedron* **2015**, *71*, 2349.
2. G. Mlostoń, K. Urbaniak, G. Utecht, D. Lentz, M. Jasiński, *J. Fluorine Chem.* **2016**, *192*, 147.
3. (a) L. Xiao, X.-G. Liu, M.-Z. Bao, J.-L. Song, S.-Y. Chen, Y.-C. Zheng, Y.-Z. Liu, S.-S. Zhang, *Org. Lett.* **2023**, *25*, 5185; (b) C. S. Santos, R. R. Mattioli, J. S. Baptista, V. H. Menezes da Silva, D. L. Browne, J. C. Pastre, *Green Chem.* **2023**, *25*, 5059; (c) L. Huang, J. Zhao, *Chem. Commun.* **2013**, *49*, 2751.
4. Y. Feng, B. Chang, Y. Ren, F. Zhao, K.-H. Wang, J. Wang, D. Huang, X. Lv and Y. Hu, *Tetrahedron* **2023**, *136*, 133353