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Access to 1,2,4-triazole-tethered potential CRBN ligands starting from α-diazo glutarimide and azlactones

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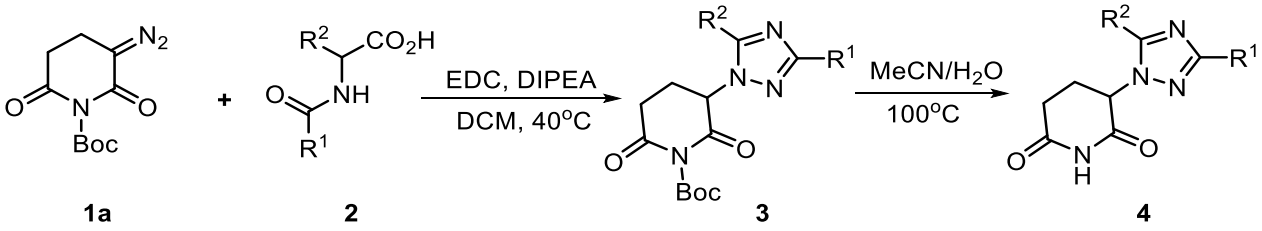
1. Experimental procedures and characterization data

General considerations. All reagents were used as purchased from commercial suppliers without further purification. Dichloromethane (DCM) was freshly distilled over P_2O_5. NMR spectra were recorded using Bruker Avance III spectrometer in $CDCl_3$, DMSO-d_6, Methanol-d_4 or Acetonitrile-d_3 (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; ^{19}F 376.50 MHz); chemical shifts are reported as parts per million (δ, ppm); the residual solvent peaks were used as internal standard: 7.26, 2.5, 3.31, 1.94 for ^{1}H and 77.16, 39.7, 49.0, 1.30 ppm for ^{13}C in $CDCl_3$, DMSO-d_6, Methanol-d_4 or Acetonitrile-d_3, respectively; multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet/doublets of doublets; coupling constants, *J*, are reported in Hz. Mass spectra were recorded using Bruker microTOF spectrometer (ionization by electrospray, positive ions detection). Analytical thin-layer chromatography was carried out on UV-254 silica gel plates using appropriate eluents. Compounds were visualized with short-wavelength UV light. Column chromatography was performed using silica gel Merk grade 60 (0.040−0.063 mm) 230−400 mesh. For gradient mode chromatography, a mixture of *n*-hexane/acetone or petroleum ether/acetone was used as eluent. *n*-Pentane or *n*-heptane can also be used instead of *n*-hexane as a non-polar phase.

Synthesis of starting materials

tert-Butyl 3-diazo-2,6-dioxopiperidine-1-carboxylate **1a** is a well-known and synthetically available compound. It was synthesized using a previously reported method[S1].

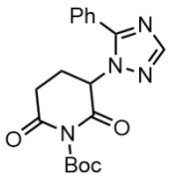
Synthesis of 1,2,4-Triazole Derivatives 4



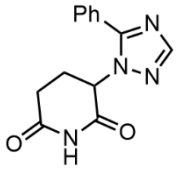
General procedure GP1 for the preparation of compounds 3a-3l and 4a-4l.

1st step: A solution or suspension of the corresponding *N*-acylated amino acid **2** (0.8 mmol, 2 equiv.) and EDC hydrochloride (0.9 mmol, 2.25 equiv.) in dry DCM (3 mL) was placed in a screw-cap, thick-walled vial and stirred at 40 °C using heating block. The diazo glutarimide **1a** (0.4 mmol, 1 equiv.) and DIPEA (0.4 mmol, 1 equiv.) were added sequentially. In most cases, gas evolution was observed upon the addition of DIPEA. The reaction mixture was then sealed and stirred at 40 °C for 6–20 hours. After complete conversion of the diazo reagent (controlled using TLC), the reaction mixture was cooled to room temperature (Caution: after the reaction has taken place, some excess pressure may remain in the closed reaction vessel — open it carefully!). Next, the resulting mixture was subjected to column chromatography on silica gel (eluting with petroleum ether/acetone) to obtain a pure target product **3**.

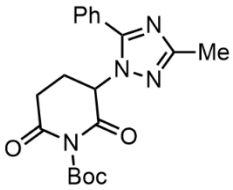
2st step: A solution of the corresponding *N*-Boc derivative of 1,2,4-triazole **3** (0.4 mmol) in wet MeCN (2.5 mL) was placed in a thick-walled tube with a screw-cap and stirred at 100 °C using heating block. After complete conversion of the initial *N*-Boc derivative of 1,2,4-triazole **3** (controlled by TLC), the reaction mixture was dried on a rotary evaporator to obtain a pure product **4**.



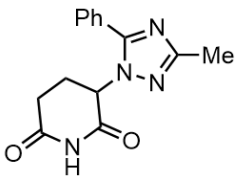
***tert*-Butyl 2,6-dioxo-3-(5-phenyl-1*H*-1,2,4-triazol-1-yl)piperidine-1-carboxylate (3a).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 131 mg (92%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (s, 1H), 7.67 – 7.58 (m, 2H), 7.58 – 7.49 (m, 3H), 5.15 (dd, *J* = 11.3, 5.3 Hz, 1H), 3.12 – 3.01 (m, 1H), 2.97 – 2.82 (m, 1H), 2.78 – 2.66 (m, 1H), 2.37 – 2.25 (m, 1H), 1.57 (s, 9H) ppm.



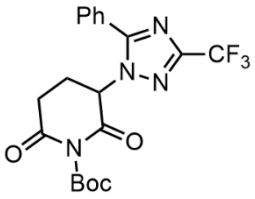
3-(5-Phenyl-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4a). Prepared according to GP1 (2st step). Yield: 83 mg (87%). Yellow amorphous solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.00 (s, 1H), 7.97 (s, 1H), 7.70 – 7.50 (m, 5H), 5.30 (dd, *J* = 11.9, 5.3 Hz, 1H), 2.88 – 2.64 (m, 3H), 2.33 (dd, *J* = 11.1, 5.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 172.7, 170.3, 152.2, 131.4, 130.0, 130.0, 129.0, 118.3, 58.8, 31.4, 25.2 ppm. HRMS (ESI), *m/z* calcd for $C_{13}H_{13}N_4O_2$ $[M+H]^+$ 257.1033 found 257.1035.



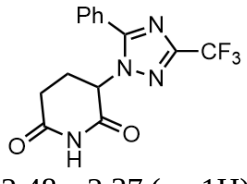
***tert*-Butyl 3-(3-methyl-5-phenyl-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3b).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (15% to 60% of acetone). Yield: 145 mg (98%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.57 (m, 2H), 7.56 – 7.46 (m, 3H), 5.06 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.05 (dt, *J* = 17.5, 4.2 Hz, 1H), 2.94 – 2.81 (m, 1H), 2.70 (ddd, *J* = 17.6, 12.7, 5.1 Hz, 1H), 2.43 (s, 3H), 2.34 – 2.24 (m, 1H), 1.56 (s, 9H) ppm.



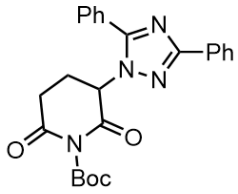
3-(3-Methyl-5-phenyl-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4b). Prepared according to GP1 (2st step). Yield: 60 mg (100%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 7.69 – 7.60 (m, 2H), 7.59 – 7.51 (m, 3H), 5.41 (dd, *J* = 11.6, 5.2 Hz, 1H), 2.91 – 2.76 (m, 1H), 2.72 – 2.56 (m, 2H), 2.30 (s, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 170.5, 159.7, 156.7, 130.6, 129.4, 129.2, 128.1, 57.6, 30.9, 24.6, 14.2 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{15}N_4O_2$ $[M+H]^+$ 271.1190 found 271.1184.



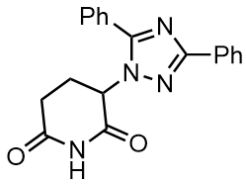
***tert*-Butyl 2,6-dioxo-3-(5-phenyl-3-(trifluoromethyl)-1*H*-1,2,4-triazol-1-yl)piperidine-1-carboxylate (3c).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (10% to 60% of acetone). Yield: 164 mg (96%). Yellow amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.63 (m, 2H), 7.63 – 7.51 (m, 3H), 5.19 (dd, *J* = 11.7, 5.2 Hz, 1H), 3.10 – 2.90 (m, 2H), 2.80 – 2.67 (m, 1H), 2.41 – 2.30 (m, 1H), 1.58 (s, 9H) ppm.



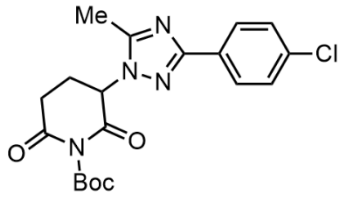
3-(5-Phenyl-3-(trifluoromethyl)-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4c). Prepared according to GP1 (2st step). Yield: 56 mg (100%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 (s, 1H), 7.77 – 7.70 (m, 2H), 7.69 – 7.56 (m, 3H), 5.69 (dd, *J* = 12.2, 5.2 Hz, 1H), 2.93 – 2.79 (m, 1H), 2.77 – 2.59 (m, 2H), 2.48 – 2.37 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.9, 169.9, 158.9, 152.2 (q, ^2J = 38.9 Hz), 131.6, 129.6, 129.6, 126.4, 121.1 (q, $^1J_{C\text{-}F}$ = 269.8 Hz), 59.0, 30.8, 24.2 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ -64.11 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{12}F_3N_4O_2$ $[M+H]^+$ 325.0907 found 325.0905.



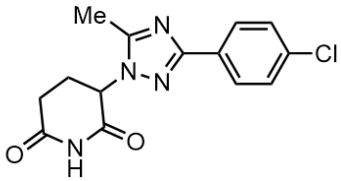
***tert*-Butyl 3-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3d).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (15% to 60% of acetone). Yield: 158 mg (91%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.10 (m, 2H), 7.76 – 7.67 (m, 2H), 7.60 – 7.51 (m, 3H), 7.48 – 7.38 (m, 3H), 5.15 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.12 (dt, *J* = 17.6, 4.5 Hz, 1H), 3.05 – 2.91 (m, 1H), 2.74 (ddd, *J* = 17.3, 12.0, 5.2 Hz, 1H), 2.37 (dt, *J* = 13.7, 4.9 Hz, 1H), 1.58 (s, 9H) ppm.



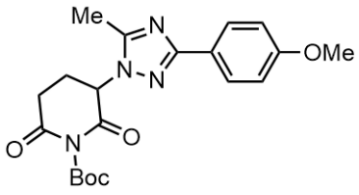
3-(3,5-Diphenyl-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4d). Prepared according to GP1 (2st step). Yield: 59 mg (100%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.12 – 8.01 (m, 2H), 7.82 – 7.69 (m, 2H), 7.66 – 7.55 (m, 3H), 7.54 – 7.40 (m, 3H), 5.55 (dd, *J* = 11.6, 5.3 Hz, 1H), 2.96 – 2.74 (m, 2H), 2.72 – 2.62 (m, 1H), 2.45 – 2.34 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 170.5, 160.8, 157.6, 131.1, 130.9, 129.9, 129.5, 129.4, 129.3, 127.9, 126.4, 58.1, 30.9, 24.6 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{17}N_4O_2$ $[M+H]^+$ 333.1346 found 333.1342.



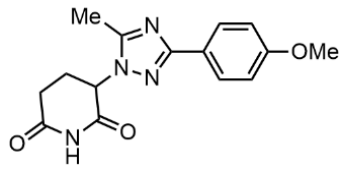
***tert*-Butyl 3-(3-(4-chlorophenyl)-5-methyl-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3e).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (10% to 60% of acetone). Yield: 145 mg (90%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 5.00 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.15 (dt, *J* = 17.5, 4.2 Hz, 1H), 3.02 – 2.77 (m, 2H), 2.55 (s, 3H), 2.51 – 2.41 (m, 1H), 1.55 (s, 9H) ppm.



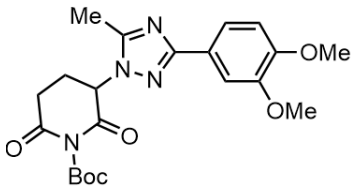
3-(3-(4-Chlorophenyl)-5-methyl-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4e). Prepared according to GP1 (2st step). Yield: 62 mg (100%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 7.96 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 5.56 (dd, *J* = 12.1, 5.1 Hz, 1H), 2.90 – 2.60 (m, 3H), 2.46 (s, 3H), 2.37 – 2.25 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.0, 170.1, 159.2, 155.8, 134.1, 130.3, 129.3, 127.8, 57.3, 31.2, 23.9, 12.1 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{14}ClN_4O_2$ $[M+H]^+$ 305.0800 found 305.0793.



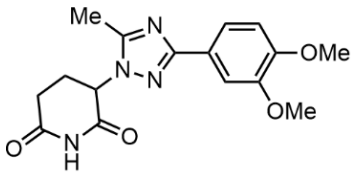
***tert*-Butyl 3-(3-(4-methoxyphenyl)-5-methyl-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3f).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 57 mg (57%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.96 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.84 (s, 3H), 3.22 – 3.11 (m, 1H), 3.02 – 2.89 (m, 1H), 2.89 – 2.77 (m, 1H), 2.54 (s, 3H), 2.51 – 2.41 (m, 1H), 1.56 (s, 9H) ppm.



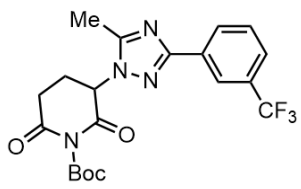
3-(3-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4f). Prepared according to GP1 (2st step). Yield: 44 mg (100%). Gray amorphous solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.87 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.24 – 5.11 (m, 1H), 3.83 (s, 3H), 2.89 – 2.72 (m, 3H), 2.45 (s, 3H), 2.39 (td, *J* = 5.3, 4.7, 2.6 Hz, 1H) ppm. ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 172.8, 170.1, 161.5, 161.4, 156.1, 128.3, 124.9, 114.9, 58.0, 56.0, 31.5, 24.6, 12.1 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{17}N_4O_3$ $[M+H]^+$ 301.1295 found 301.1298.



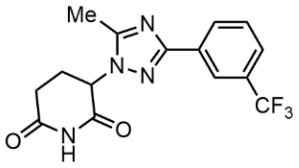
***tert*-Butyl 3-(3-(3,4-dimethoxyphenyl)-5-methyl-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3g).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (5% to 45% of acetone). Yield: 47 mg (47%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.00 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.13 – 3.04 (m, 1H), 3.02 – 2.88 (m, 1H), 2.87 – 2.76 (m, 1H), 2.51 (s, 3H), 2.46 – 2.37 (m, 1H), 1.53 (s, 9H) ppm.



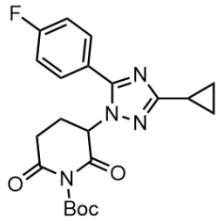
3-(3-(3,4-Dimethoxyphenyl)-5-methyl-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4g). Prepared according to GP1 (2st step). Yield: 41 mg (100%). White amorphous solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.60 – 7.55 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 5.49 – 5.42 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.92 – 2.82 (m, 3H), 2.54 (s, 3H), 2.45 – 2.38 (m, 1H) ppm. ^{13}C NMR (101 MHz, Methanol-d_4) δ 174.4, 170.9, 161.7, 156.8, 151.7, 150.5, 124.7, 120.4, 112.7, 110.8, 58.4, 56.4, 56.4, 31.7, 24.9, 11.6 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{19}N_4O_4$ $[M+H]^+$ 331.1401 found 331.1403.



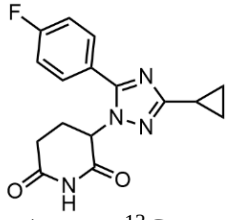
***tert*-Butyl 3-(5-methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3h).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 142 mg (81%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 2.1 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 5.01 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.23 – 3.10 (m, 1H), 3.08 – 2.94 (m, 1H), 2.92 – 2.79 (m, 1H), 2.57 (s, 3H), 2.54 – 2.43 (m, 1H), 1.56 (s, 9H) ppm.



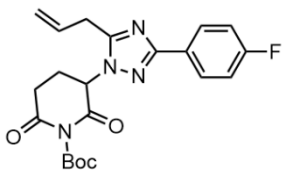
3-(5-Methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4h). Prepared according to GP1 (2st step). Yield: 105 mg (100%). White amorphous solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.01 (s, 1H), 8.31 – 8.22 (m, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.68 – 7.59 (m, 1H), 5.28 – 5.20 (m, 1H), 2.89 – 2.76 (m, 3H), 2.49 (s, 3H), 2.44 – 2.36 (m, 1H) ppm. ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 172.8, 170.0, 160.2, 156.9, 133.2, 131.4 (q, $^{2}J_{C\text{-}F}$ = 32.2 Hz), 130.7, 130.4, 126.5 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 125.3 (q, $^{1}J_{C\text{-}F}$ = 271.3 Hz), 123.3 (q, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 58.3, 31.5, 24.5, 12.2 ppm. ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -63.32 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{14}F_3N_4O_2$ $[M+H]^+$ 339.1063 found 339.1065.



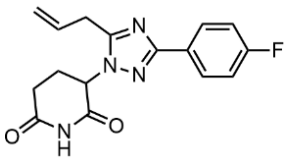
***tert*-Butyl 3-(3-cyclopropyl-5-(4-fluorophenyl)-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3i).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 139 mg (84%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.55 (m, 2H), 7.18 (t, *J* = 8.6 Hz, 2H), 4.94 (dd, *J* = 11.0, 5.3 Hz, 1H), 3.14 – 3.02 (m, 1H), 2.95 – 2.80 (m, 1H), 2.77 – 2.63 (m, 1H), 2.34 – 2.23 (m, 1H), 2.10 – 1.99 (m, 1H), 1.57 (s, 9H), 1.07 – 0.93 (m, 4H) ppm.



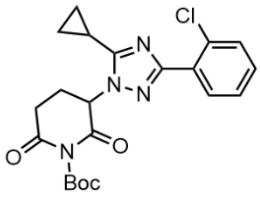
3-(3-Cyclopropyl-5-(4-fluorophenyl)-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4i). Prepared according to GP1 (2st step). Yield: 100 mg (100%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H), 7.71 – 7.61 (m, 2H), 7.36 (t, *J* = 8.9 Hz, 2H), 5.34 (dd, *J* = 11.6, 5.3 Hz, 1H), 2.87 – 2.73 (m, 1H), 2.71 – 2.57 (m, 2H), 2.34 – 2.22 (m, 1H), 2.04 – 1.94 (m, 1H), 0.98 – 0.89 (m, 2H), 0.89 – 0.79 (m, 2H) ppm. ^{13}C NMR (101 MHz, Methanol-d_4) δ 174.3, 171.1, 166.5, 165.6 (d, $^{1}J_{C\text{-}F}$ = 249.7 Hz), 157.6, 132.6 (d, $^{3}J_{C\text{-}F}$ = 8.9 Hz), 124.8 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 117.2 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz), 58.9, 31.4, 25.4, 9.6, 8.2 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.75 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{16}FN_4O_2$ $[M+H]^+$ 315.1252 found 315.1255.



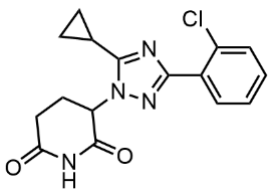
***tert*-Butyl 3-(5-allyl-3-(4-fluorophenyl)-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3j).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 75 mg (90%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 – 7.98 (m, 2H), 7.09 (t, *J* = 8.7 Hz, 2H), 6.11-5.92 (m, 1H), 5.31 – 5.14 (m, 2H), 5.01 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.82 – 3.70 (m, 1H), 3.68 – 3.54 (m, 1H), 3.21 – 3.09 (m, 1H), 3.01 – 2.87 (m, 1H), 2.87 – 2.74 (m, 1H), 2.48 – 2.34 (m, 1H), 1.56 (s, 9H) ppm.



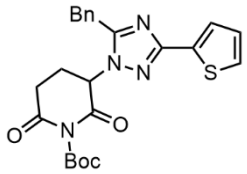
3-(5-Allyl-3-(4-fluorophenyl)-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4j). Prepared according to GP1 (2st step). Yield: 44 mg (88%). Beige amorphous solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.00 (s, 1H), 8.07 – 7.97 (m, 2H), 7.23 – 7.13 (m, 2H), 6.05 (ddt, *J* = 16.7, 10.2, 6.3 Hz, 1H), 5.27 – 5.15 (m, 3H), 3.65 – 3.57 (m, 2H), 2.86 – 2.74 (m, 3H), 2.42 – 2.30 (m, 1H) ppm. ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 172.8, 169.9, 164.3 (d, $^{1}J_{C\text{-}F}$ = 245.9 Hz), 161.0, 157.7, 133.4, 129.0 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 128.7 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 118.3, 116.5 (d, $^{2}J_{C\text{-}F}$ = 21.9 Hz), 58.0, 31.4, 30.9, 24.8 ppm. ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -114.14 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{16}FN_4O_2$ $[M+H]^+$ 315.1252 found 315.1254.



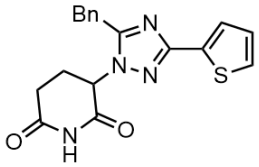
***tert*-Butyl 3-(3-(2-chlorophenyl)-5-cyclopropyl-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3k).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 79 mg (79%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.80 (m, 1H), 7.47 – 7.41 (m, 1H), 7.29 (dd, *J* = 5.9, 3.5 Hz, 2H), 5.28 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.28 – 3.15 (m, 1H), 3.00 – 2.79 (m, 2H), 2.58 – 2.46 (m, 1H), 1.95 – 1.84 (m, 1H), 1.56 (s, 9H), 1.37 – 1.30 (m, 1H), 1.22 – 1.06 (m, 3H) ppm.



3-(3-(2-Chlorophenyl)-5-cyclopropyl-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4k). Prepared according to GP1 (2st step). Yield: 40 mg (64%). Gray amorphous solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.67 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.46 – 7.32 (m, 2H), 5.71 (dd, *J* = 11.5, 5.3 Hz, 1H), 2.99 – 2.74 (m, 3H), 2.52 – 2.42 (m, 1H), 2.20 – 2.09 (m, 1H), 1.23 – 1.07 (m, 4H) ppm. ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 172.8, 169.9, 160.7, 159.7, 133.0, 132.2, 131.5, 131.2, 131.2, 127.9, 57.8, 31.4, 24.8, 8.9, 8.8, 6.9 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{16}ClN_4O_2$ $[M+H]^+$ 331.0956 found 331.0958.



***tert*-Butyl 3-(5-benzyl-3-(thiophen-2-yl)-1*H*-1,2,4-triazol-1-yl)-2,6-dioxopiperidine-1-carboxylate (3l).** Prepared according to GP1 (1st step); eluent – petroleum ether–acetone (10% to 60% of acetone). Yield: 163 mg (90%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.39 – 7.27 (m, 4H), 7.25 – 7.19 (m, 2H), 7.09 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.76 (dd, *J* = 10.9, 5.3 Hz, 1H), 4.47 (d, *J* = 16.4 Hz, 1H), 4.14 (d, *J* = 16.5 Hz, 1H), 3.01 – 2.89 (m, 1H), 2.70 – 2.58 (m, 1H), 2.56 – 2.45 (m, 1H), 2.05 – 1.93 (m, 1H), 1.56 (s, 9H) ppm.



3-(5-Benzyl-3-(thiophen-2-yl)-1*H*-1,2,4-triazol-1-yl)piperidine-2,6-dione (4l). Prepared according to GP1 (2st step). Yield: 69 mg (100%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 7.56 (ddd, *J* = 15.7, 4.3, 1.2 Hz, 2H), 7.38 – 7.29 (m, 4H), 7.29 – 7.20 (m, 1H), 7.12 (dd, *J* = 5.0, 3.6 Hz, 1H), 5.71 (dd, *J* = 12.3, 5.2 Hz, 1H), 4.26 (d, *J* = 15.9 Hz, 1H), 4.19 (d, *J* = 15.9 Hz, 1H), 2.86 – 2.55 (m, 3H), 2.24 – 2.10 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.9, 169.9, 157.6, 157.0, 136.8, 134.1, 129.2, 129.0, 128.4, 127.5, 127.2, 126.3, 57.2, 31.2, 31.1, 24.3 ppm. HRMS (ESI), *m/z* calcd for $C_{18}H_{17}N_4O_2S$ $[M+H]^+$ 353.1067 found 353.1073.

2. Crystallographic data for compounds 3i

X-ray Single Crystal analysis was performed on SuperNova, Single source at offset/far, HyPix3000 diffractometer. Crystal growth was performed by slow evaporation of solution in chloroform at room temperature. The crystal was kept at 100 K during data collection. Using Olex2[S2], the structure was solved with the SHELXT[S3] structure solution program using Dual Space and refined with the SHELXL[S4] refinement package using Least Squares minimization. Hydrogen atoms in all structures were placed in ideally calculated positions according to neutron diffraction statistical data[S5] and refined as colliding atoms with the parameters of relative isotropic displacement. The main data of crystallography and details of refinement are presented in **Table S1** in Supporting Information.

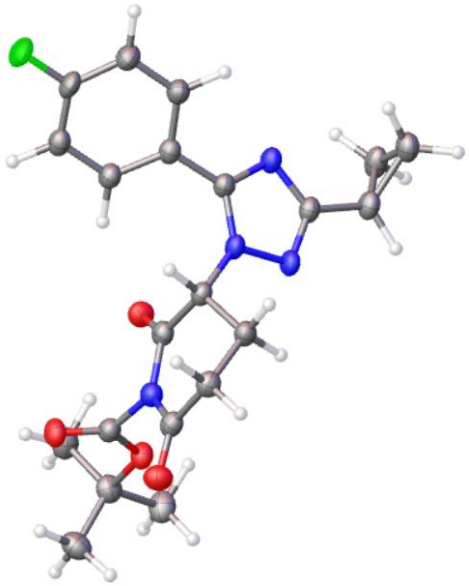


Figure S1. ORTEP representation of compound **3i** displaying thermal ellipsoids at 50%.

Table S1. Crystal data and structure refinement for **3i**	
Identification code	**3i**
Empirical Formula	$C_{22}H_{24}Cl_3FN_4O_4$
Formula weight	533.80
Temperature, K	100.(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.4718(5)
b/Å	8.8467(5)
c/Å	16.5267(6)
α/°	88.426(4)
β/°	81.433(4)
γ/°	81.602(4)
Volume/Å^3	1211.66(11)
Z	2
ρ_{calc}g/cm^3	1.463
μ/mm^{-1}	3.816
F(000)	552.0
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	5.408 to 141.346
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-20 \leq l \leq 20$
Reflections collected	11128
Independent reflections	4589 [R_{int} = 0.0532, R_{sigma} = 0.0470]
Data/restraints/parameters	4589/0/310
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0889, wR_2 = 0.2196
Final R indexes [all data]	R_1 = 0.0937, wR_2 = 0.2267
Largest diff. peak/hole / e Å^{-3}	1.89/-0.51
CCDC	**2531509**

3. Biological data

Cell culture

The human multiple myeloma cell line MM1.S was obtained from the ATCC. Peripheral blood mononuclear cells (PBMCs) were isolated from healthy donor blood by density-gradient centrifugation. MM1.S cells and PBMCs were maintained in RPMI-1640 medium (Gibco, UK) supplemented with 10% fetal bovine serum (FBS, Gibco, UK), penicillin (100 U mL^{-1}), streptomycin (100 μg mL^{-1}), and GlutaMax (2 mM, Gibco, UK). Cells were cultivated under a humidified atmosphere of 95% air and 5% CO_2 at 37 °C. Cell viability and density were determined by trypan blue exclusion before each experiment.

MTT assay

MM1.S cells and PBMCs were diluted with complete growth medium to 3.0×10^5 cells mL^{-1}, and aliquots (1.5×10^4 cells in 50 μL) were seeded into individual wells of white 96-well plates (Nunc, USA). Cells were treated in triplicate with the test compounds at a final concentration of 50 μM. Control wells received an equivalent volume of DMSO (Sigma, USA), with the final DMSO concentration not exceeding 0.1%. Plates were incubated for 72 h at 37 °C in a humidified atmosphere containing 5% CO_2. After incubation, 100 μL of CellTiter-Glo® One Solution reagent (Promega, USA) was added to each well according to the manufacturer's instructions. The plates were shaken for 10 min to ensure complete cell lysis and stabilization of the luminescent signal. Luminescence was measured using a GloMax® Multi+ microplate reader (Promega, USA). Cell viability was expressed as a percentage relative to the DMSO-treated control. Each compound was evaluated in three independent experiments. All stock solutions for biological evaluations were prepared via dissolving synthesized compounds in DMSO.

Table S2. Cytotoxicity of compounds **4** against human multiple myeloma cell line (MM1.S) and peripheral blood mononuclear cells (PBMC)

Compound	Cell viability, %		Compound	Cell viability, %	
	MM1.S	PBMC		MM1.S	PBMC
4a	56.0	67.1	**4g**	76.6	77.3
4b	75.2	69.0	**4h**	80.9	75.3
4c	90.1	75.4	**4i**	78.8	39.5
4d	83.0	70.6	**4j**	91.2	50.0
4e	79.8	66.2	**4k**	73.8	73.7
4f	82.6	76.1	**4l**	84.5	76.0

4. References

S1. G. Kantin, P. Golubev, A. Sapegin, A. Bunev, D. Dar'in, *Beilstein J. Org. Chem.* 2023, 19(1), 1841–1848. https://doi.org/10.3762/bjoc.19.136

S2. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. Howard, H. Puschmann, J. *App. Cryst.* 2009, 42, 339–341. https://doi.org/10.1107/s0108767309093283

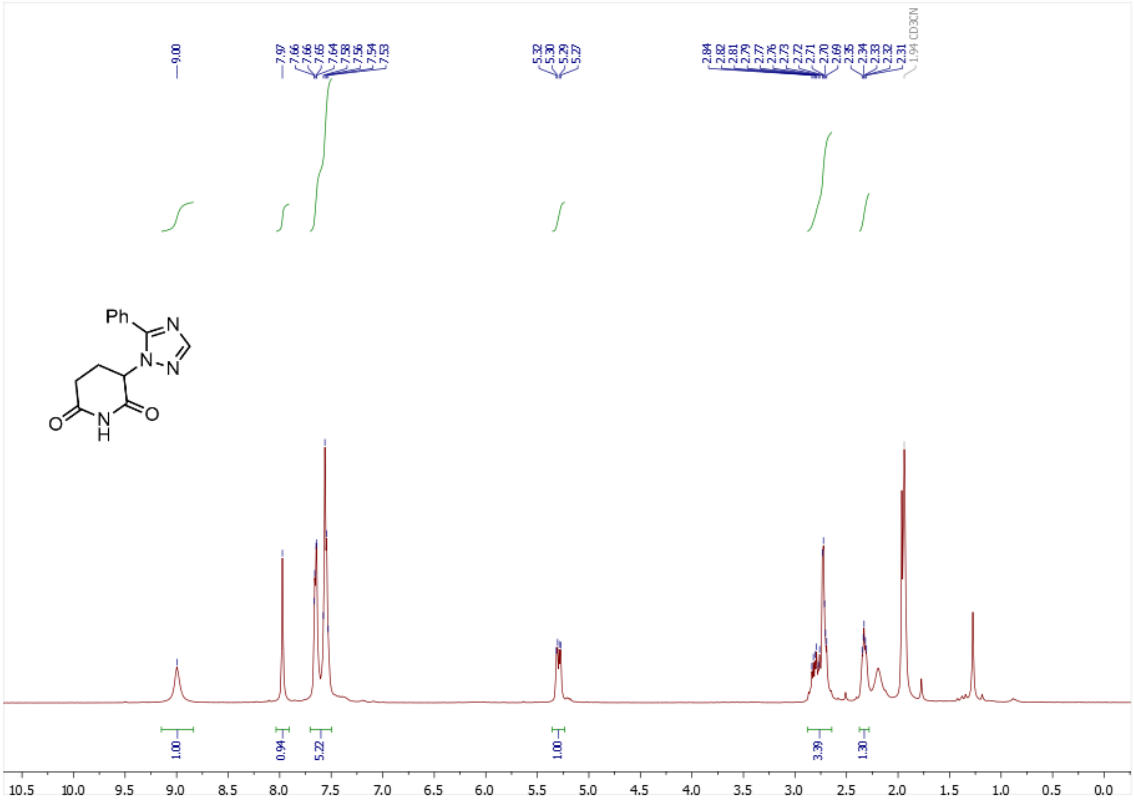
S3. G. M. Sheldrick, *Acta Cryst. Sec. A Found. Adv*. 2015, 71, 3–8. https://doi.org/10.1107/S2053273314026370

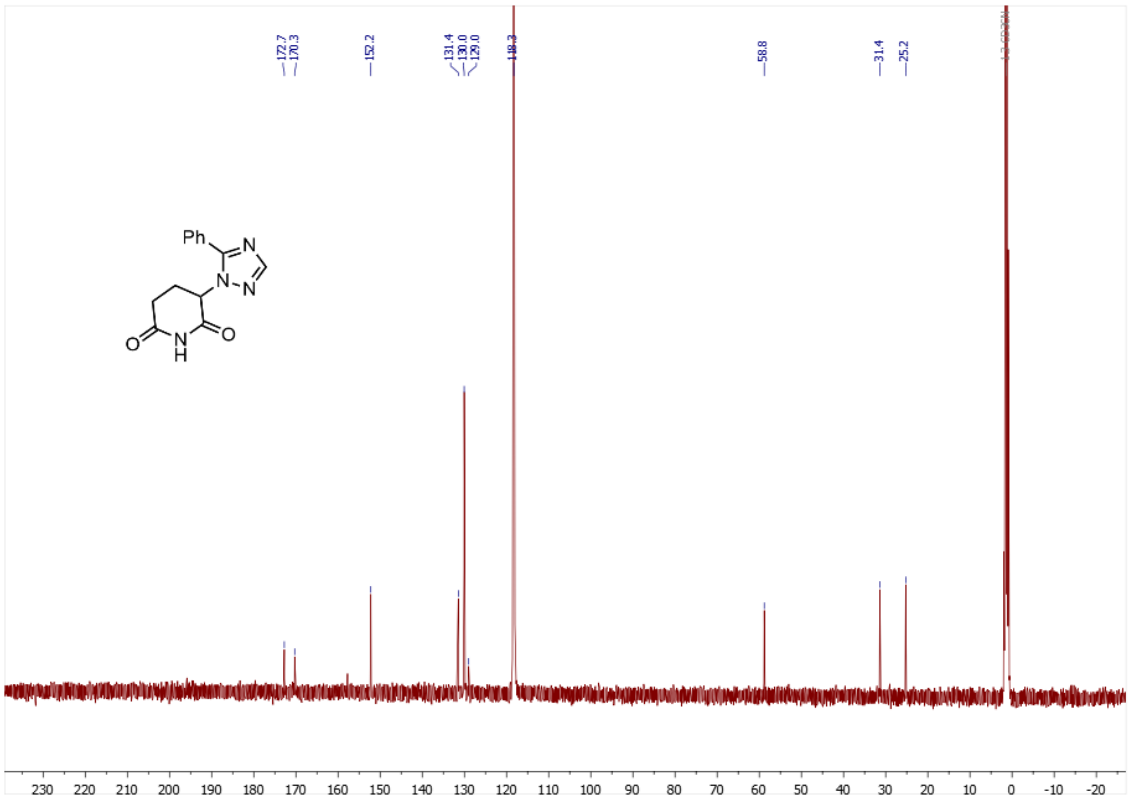
S4. G. M. Sheldrick, *Acta Cryst. Sec. C Struct. Chem*. 2015, 71, 3–8. https://doi.org/10.1107/S2053229614024218

S5. F. H. Allen, I. J. Bruno, *Acta Cryst. Sec. B Struct. Sci*. 2010, 66, 380–386. doi:10.1107/S0108768110012048

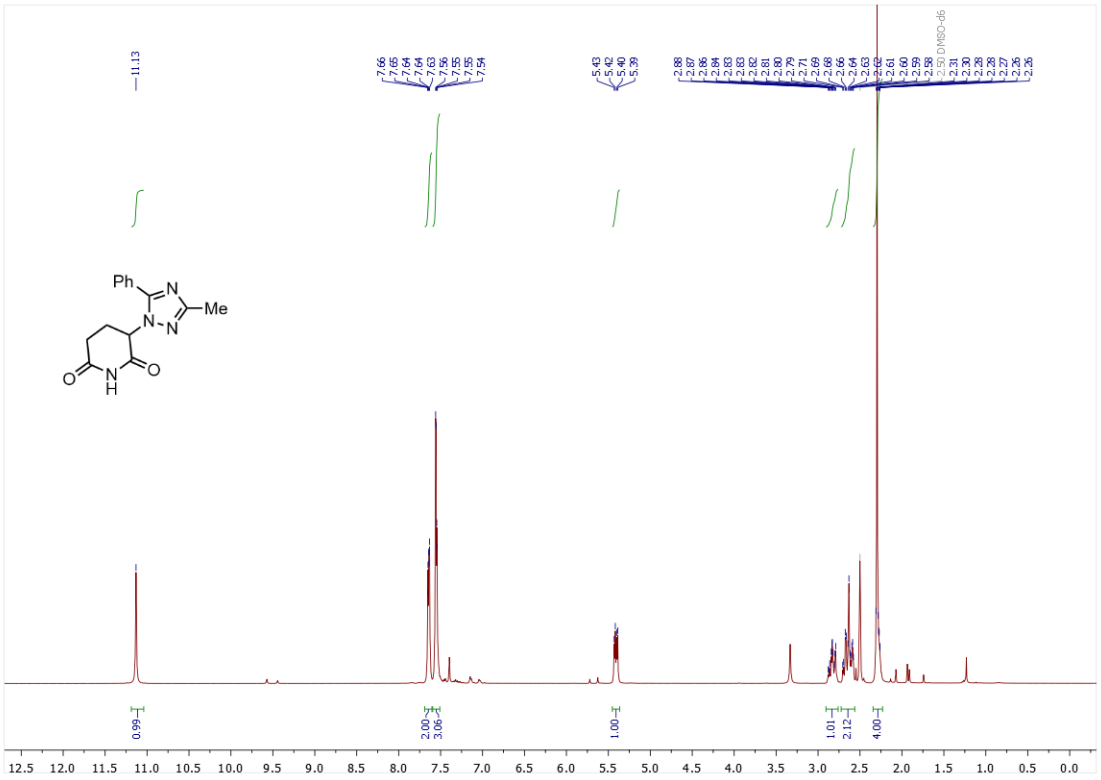
5. Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra

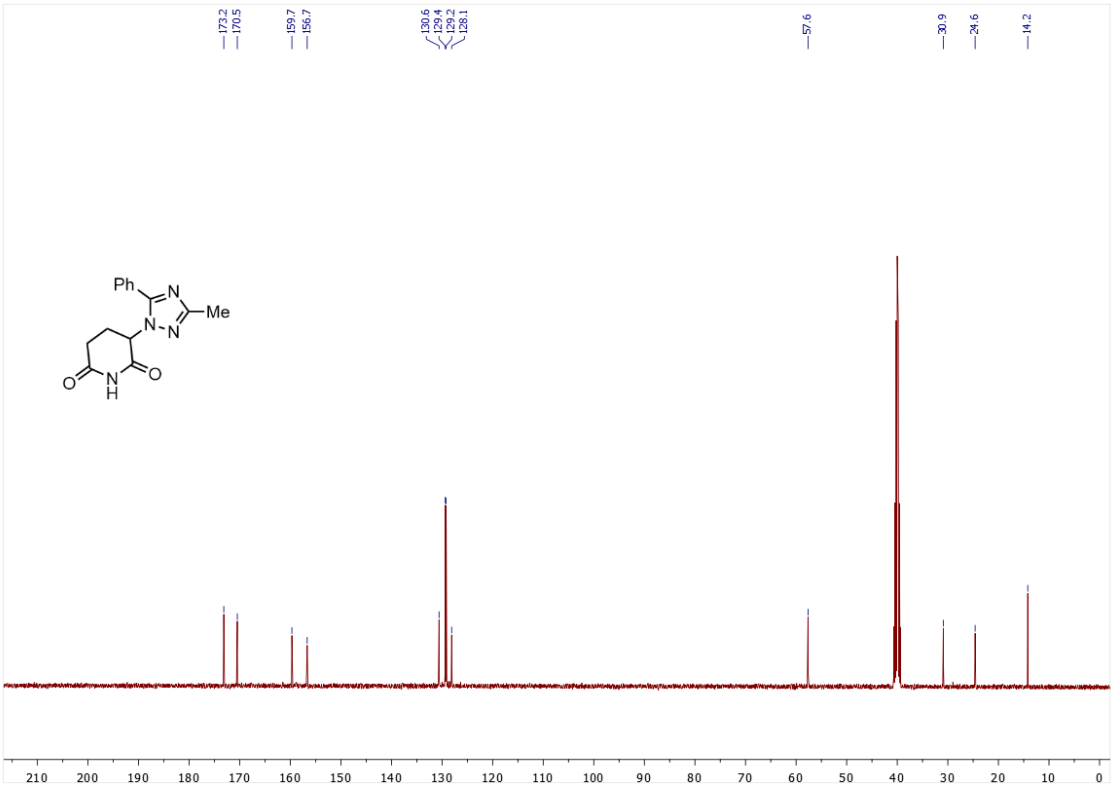
Copies of ^{1}H (400.13 MHz, Acetonitrile-d_3) and $^{13}C\{^{1}H\}$ (100.61 MHz, Acetonitrile-d_3) spectra of **4a**



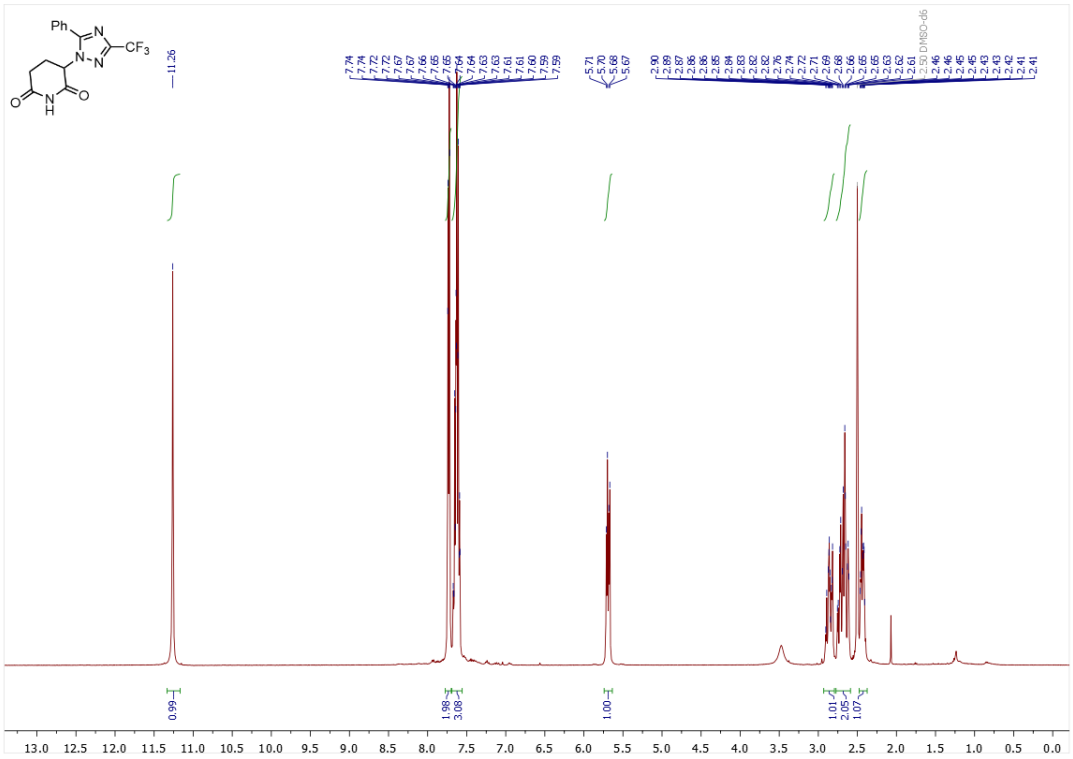


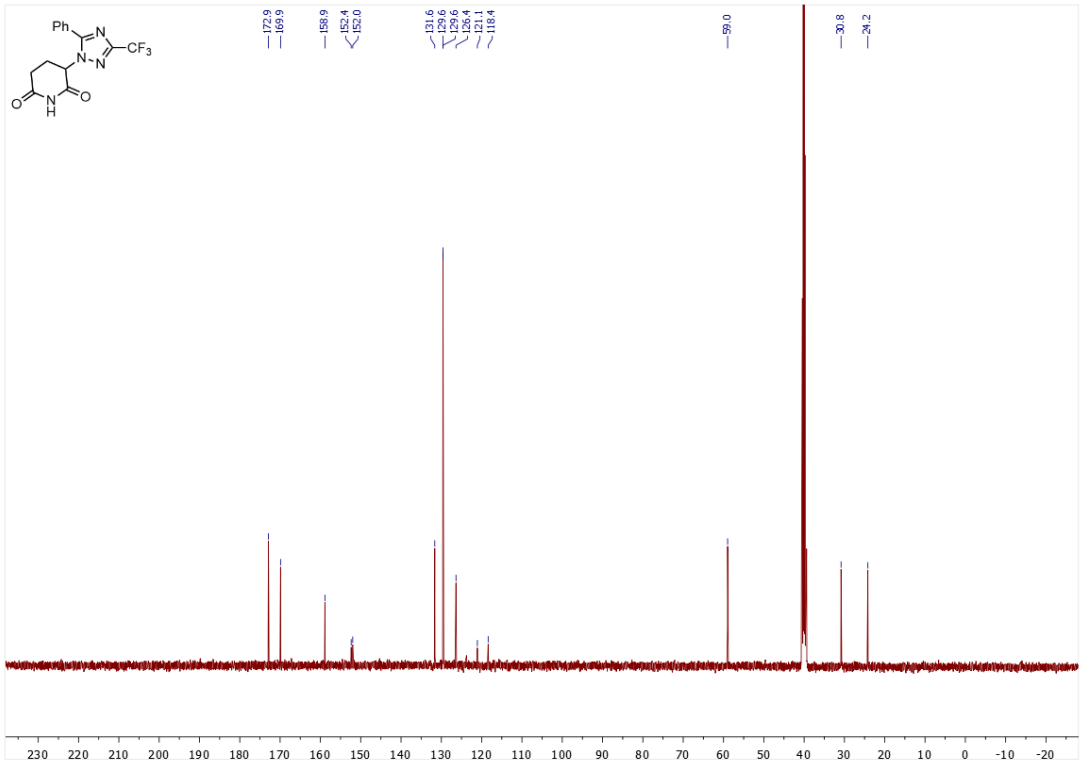
Copies of ^{1}H (400.13 MHz, DMSO-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, DMSO-d_6) spectra of **4b**

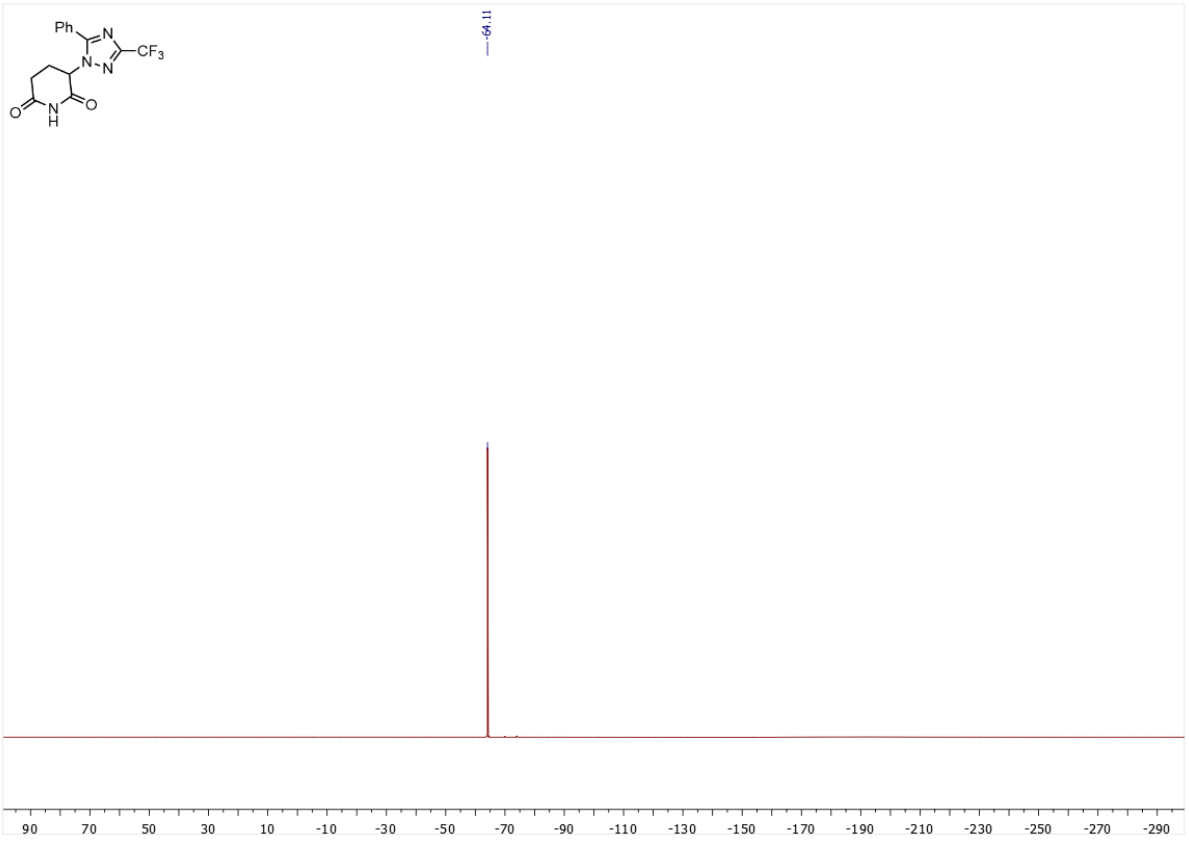




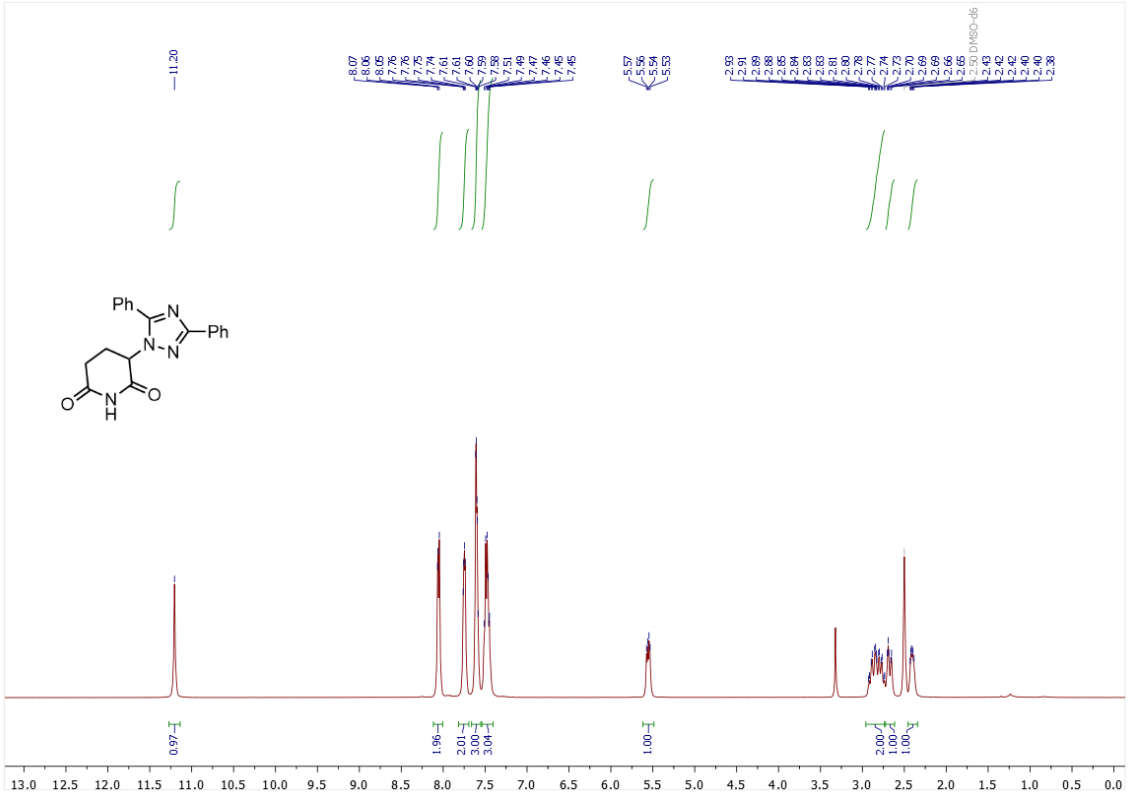
Copies of ^{1}H (400.13 MHz, DMSO-d_6), $^{13}C\{^{1}H\}$ (100.61 MHz, DMSO-d_6) and $^{19}F\{^{1}H\}$ (376.50 MHz, DMSO-d_6) spectra of **4c**

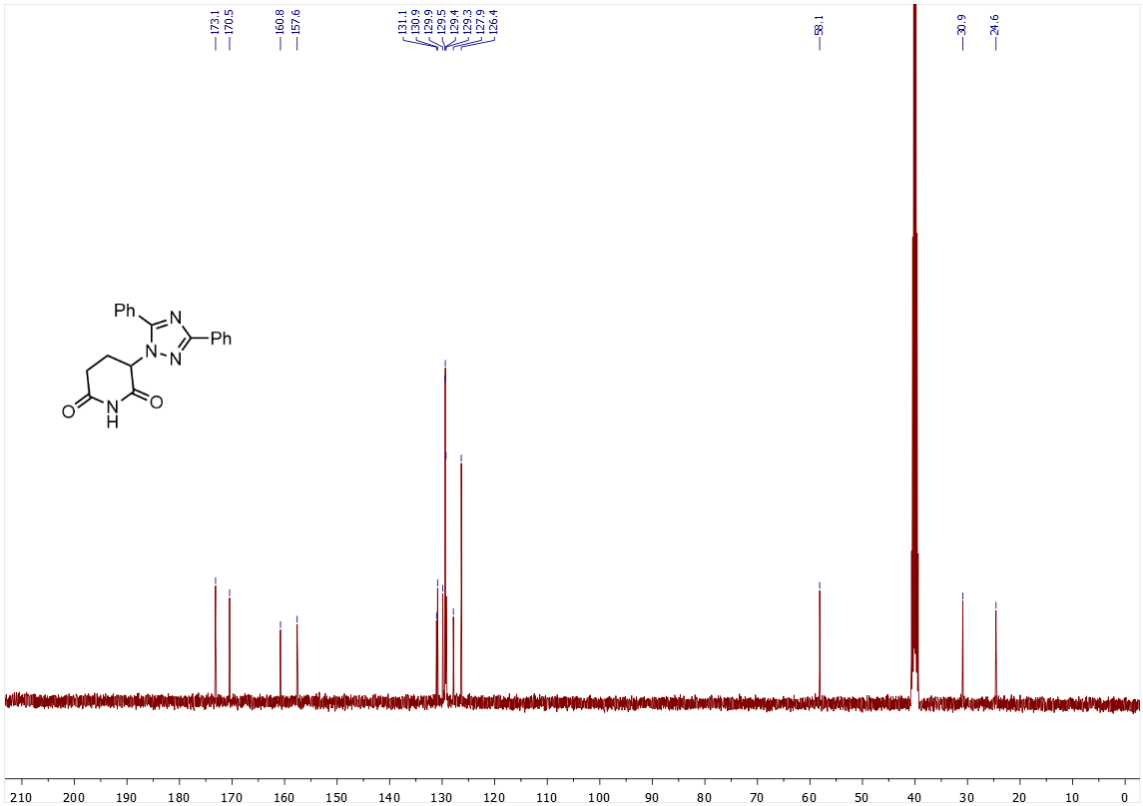




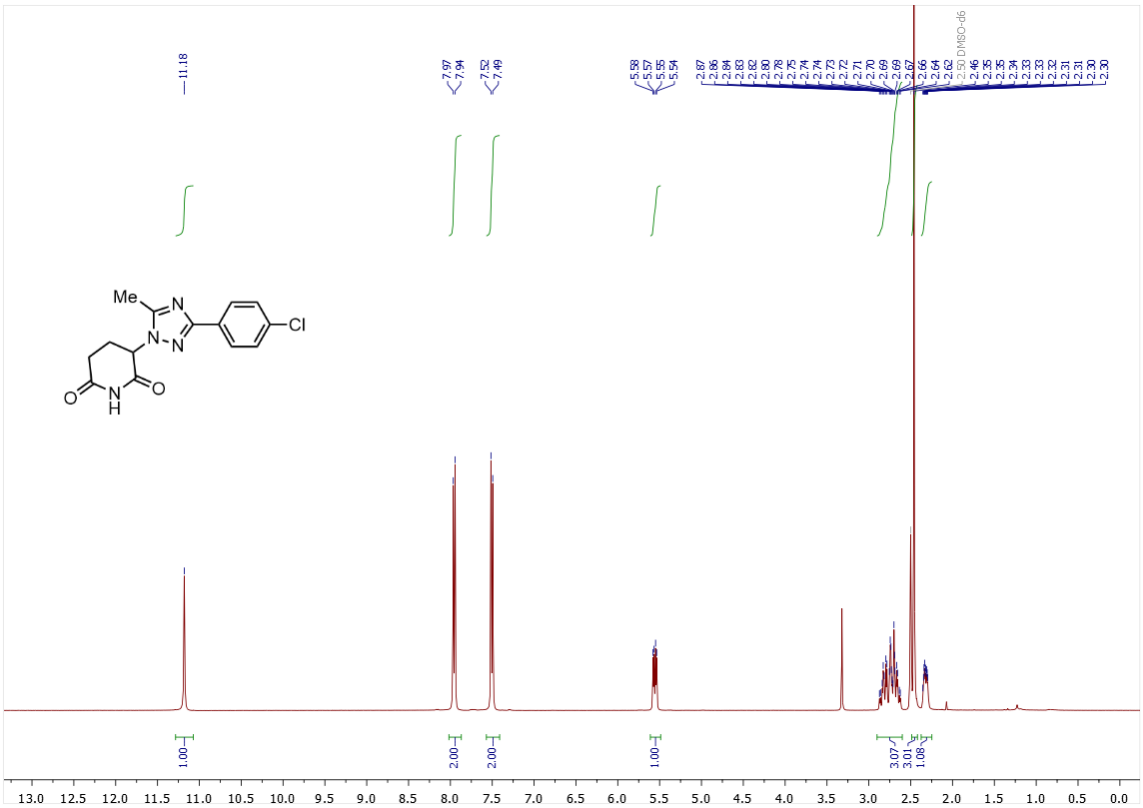

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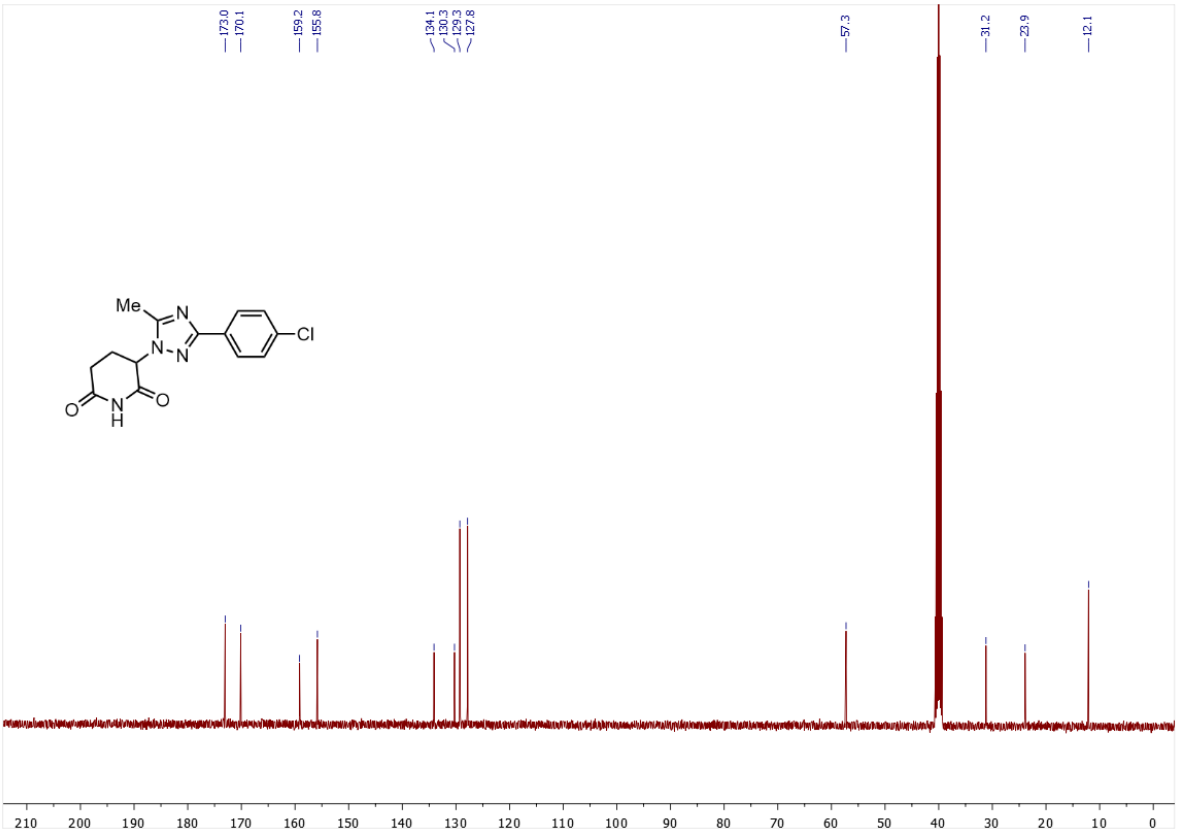
Copies of ^{1}H (400.13 MHz, DMSO-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, DMSO-d_6) spectra of **4d**



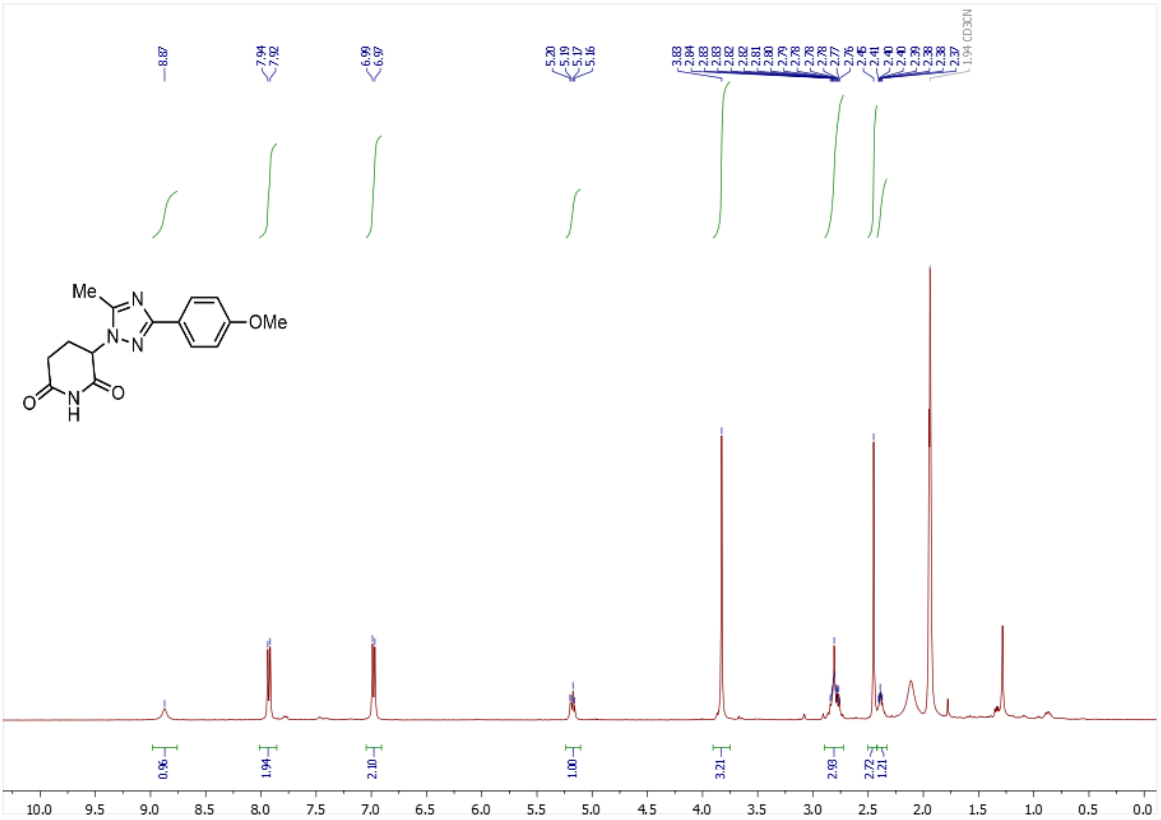


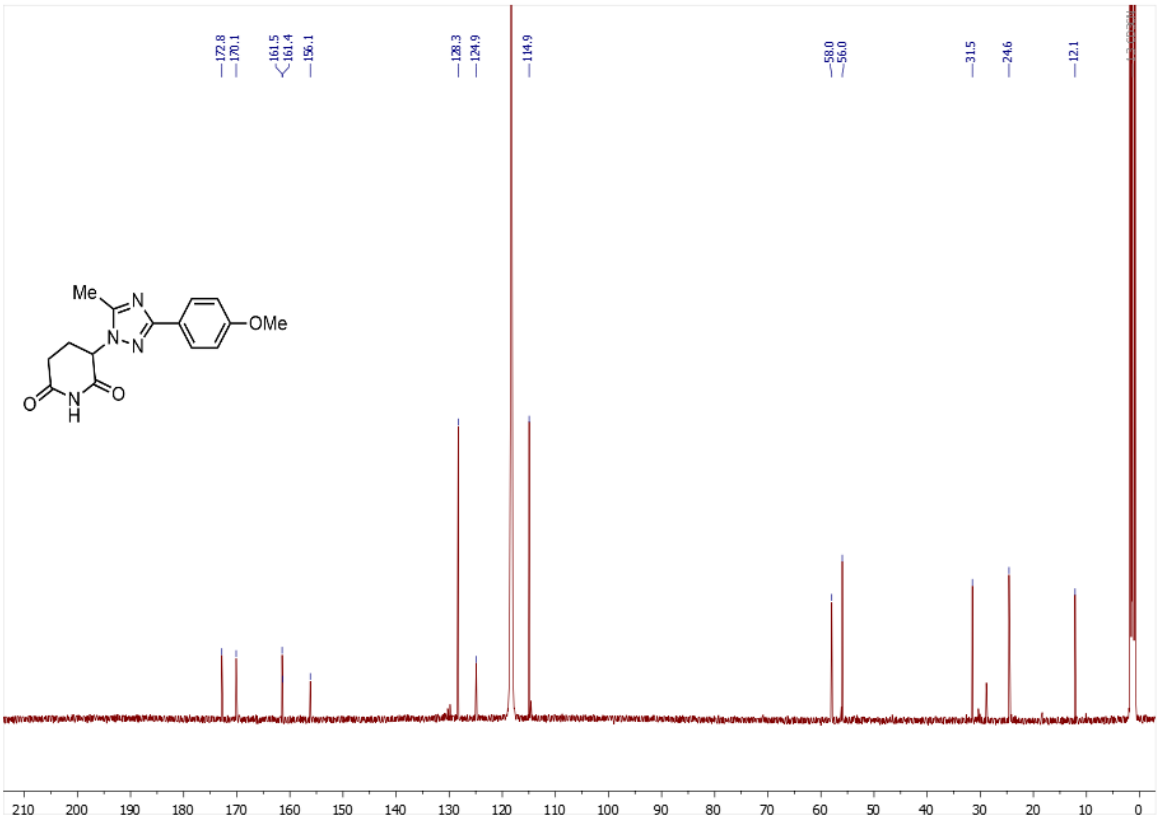
Copies of ^{1}H (400.13 MHz, DMSO-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, DMSO-d_6) spectra of **4e**



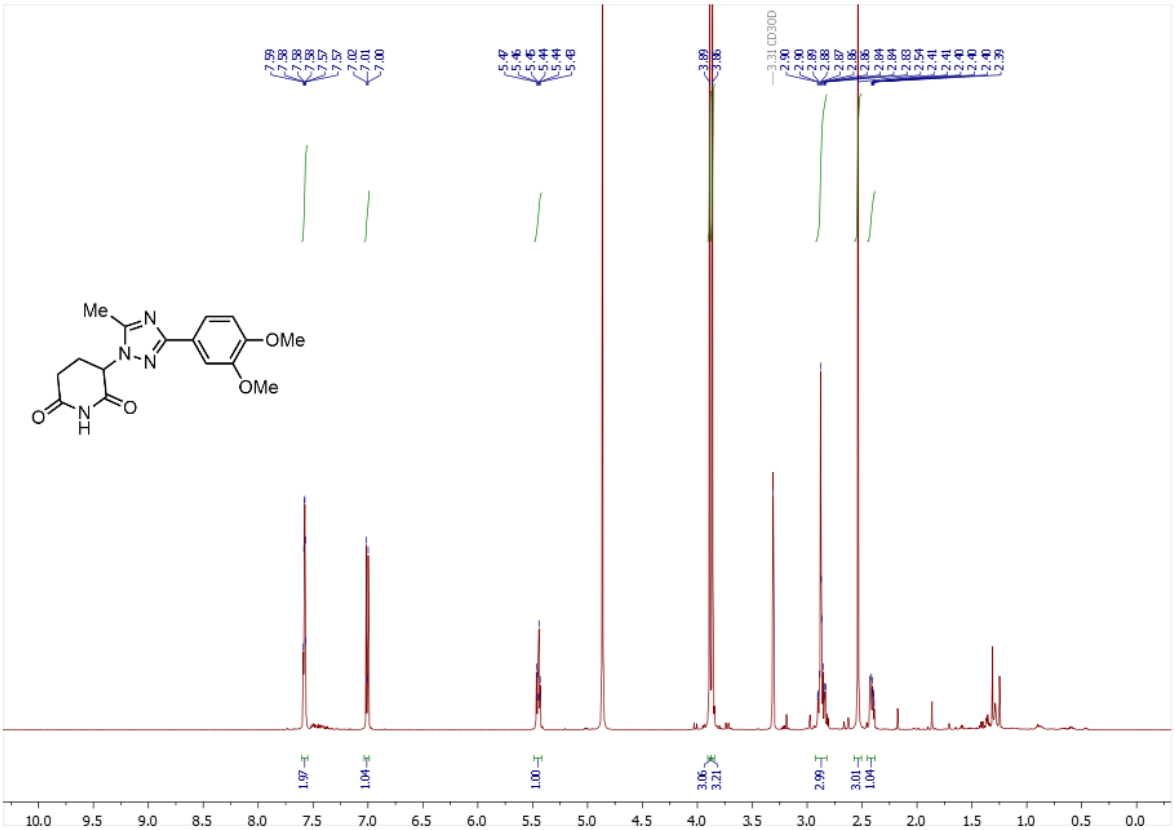


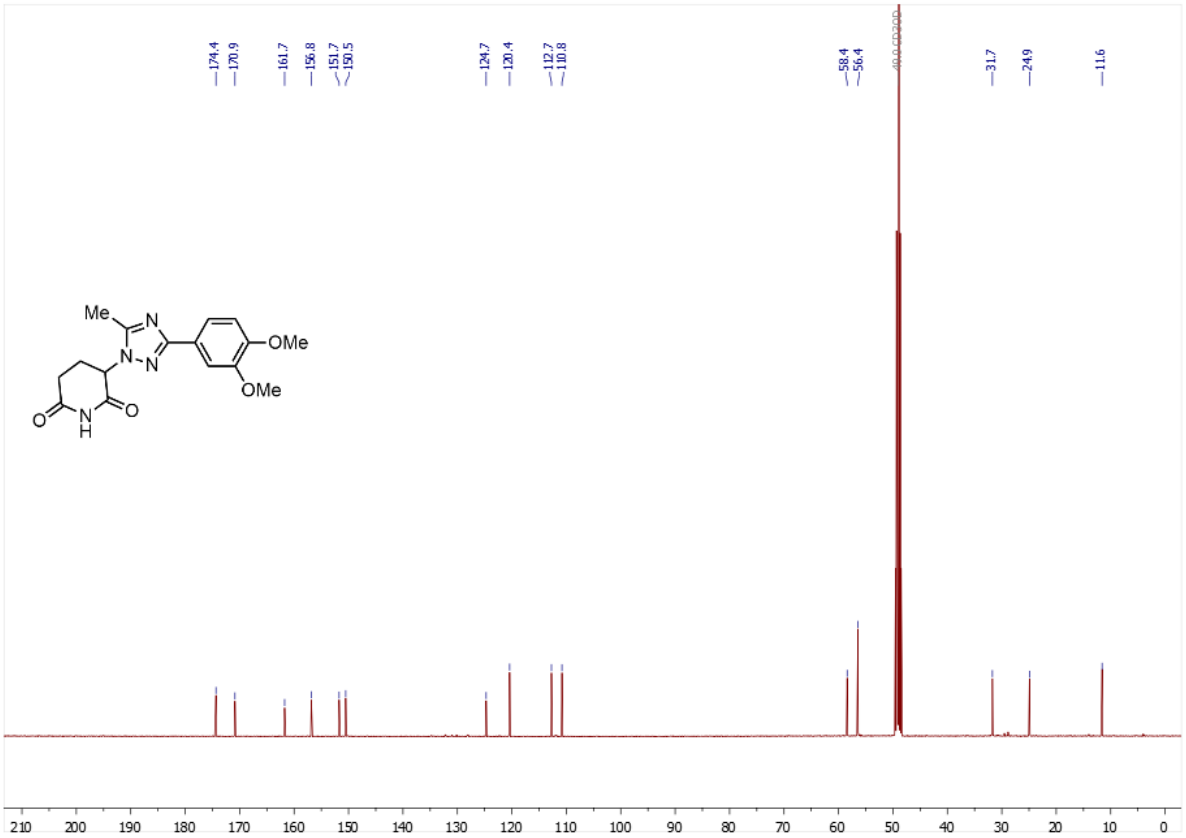
Copies of ^{1}H (400.13 MHz, Acetonitrile-d_3) and $^{13}C\{^{1}H\}$ (100.61 MHz, Acetonitrile-d_3) spectra of **4f**



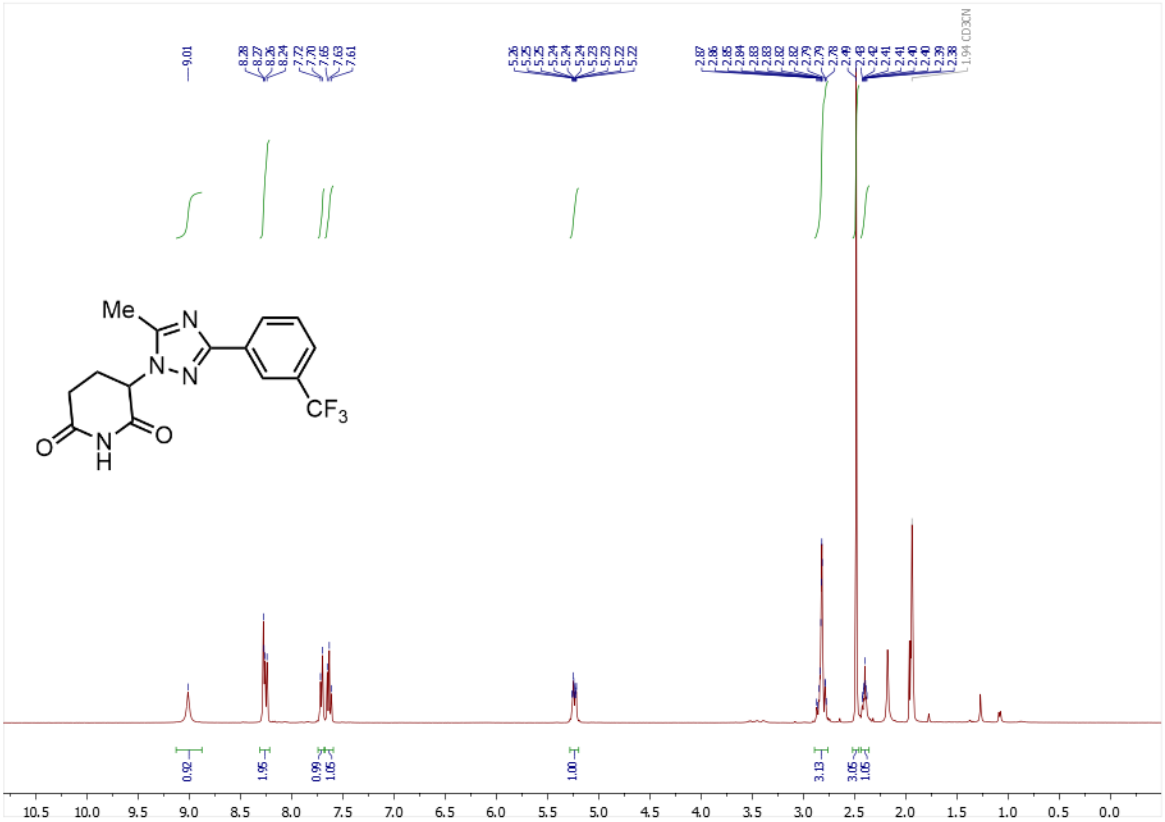


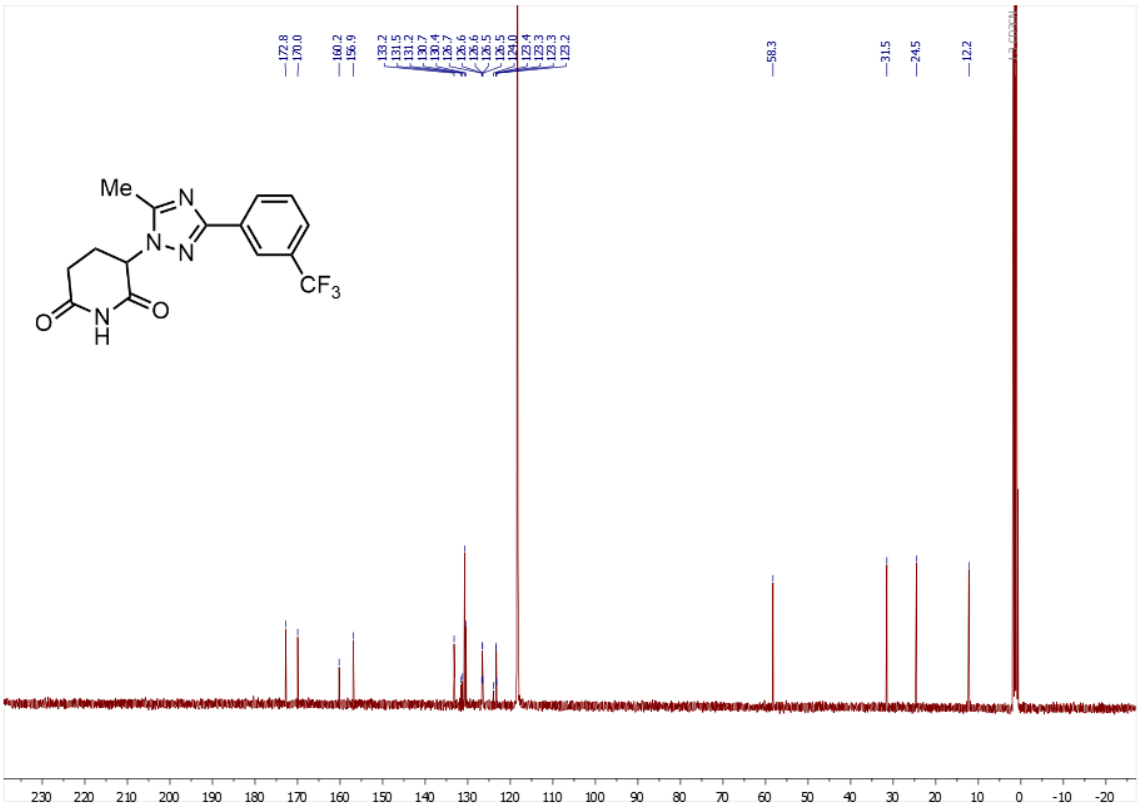
Copies of ^{1}H (400.13 MHz, Methanol-d_4) and $^{13}C\{^{1}H\}$ (100.61 MHz, Methanol-d_4) spectra of **4g**

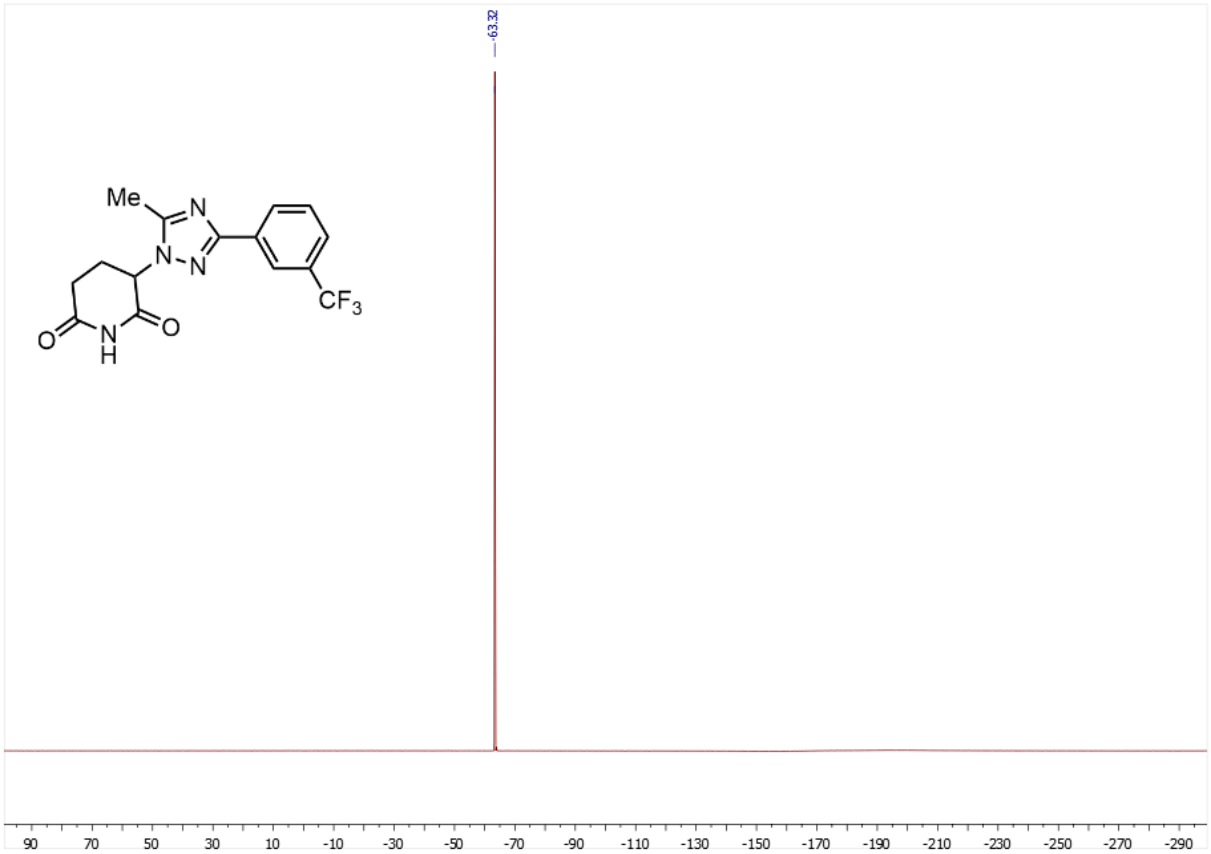




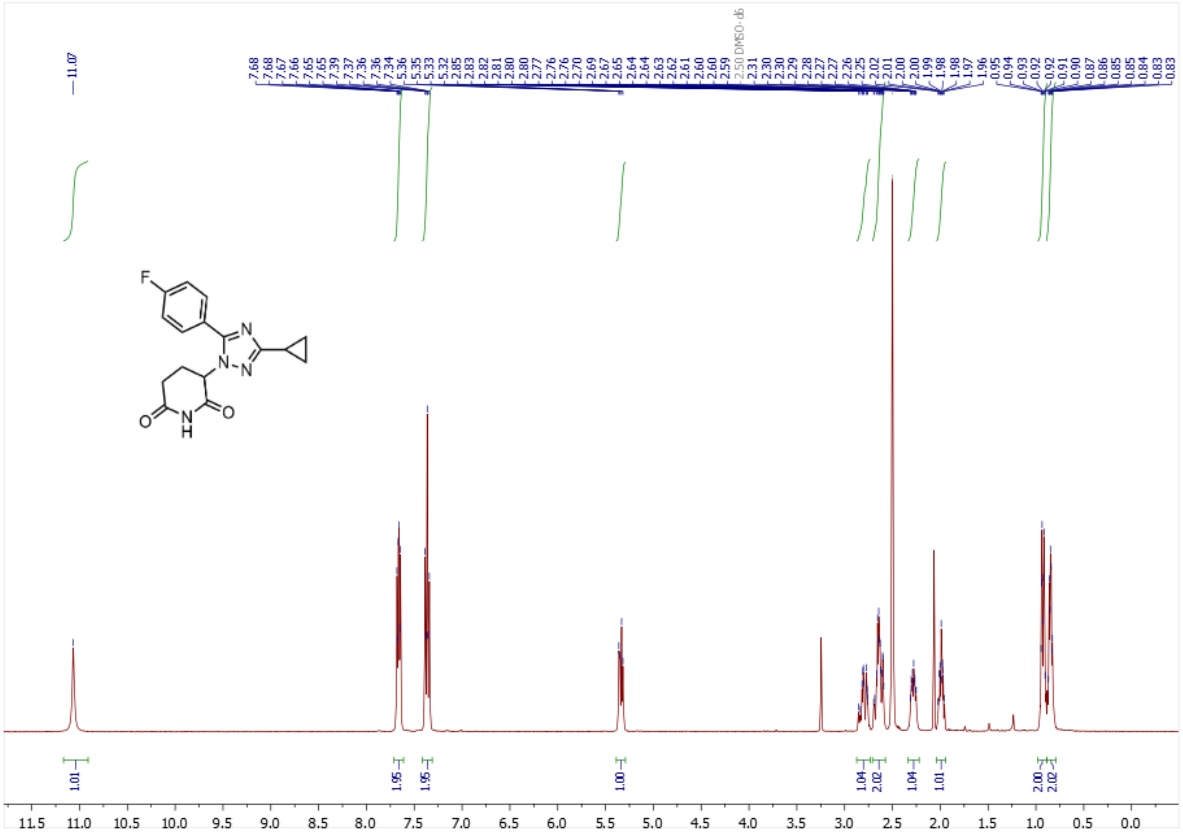
Copies of ^{1}H (400.13 MHz, Acetonitrile-d_3), $^{13}C\{^{1}H\}$ (100.61 MHz, Acetonitrile-d_3) and $^{19}F\{^{1}H\}$ (376.50 MHz, Acetonitrile-d_3) spectra of **4h**

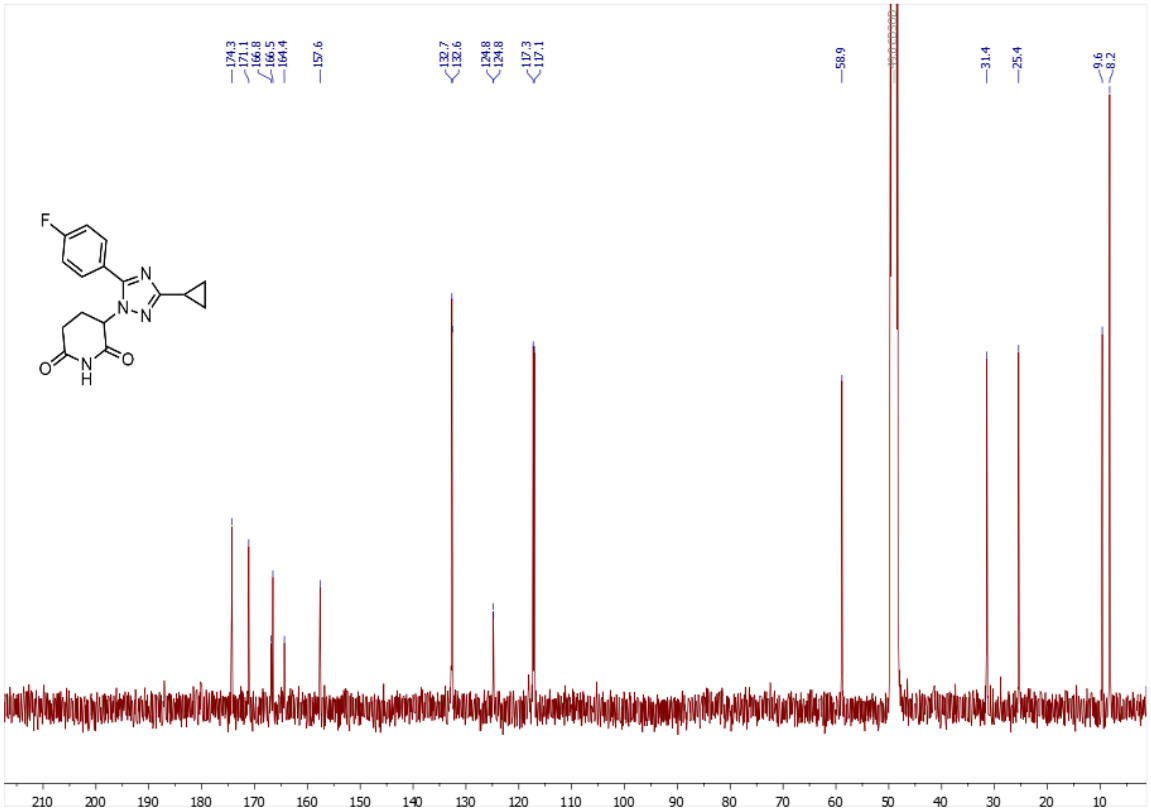


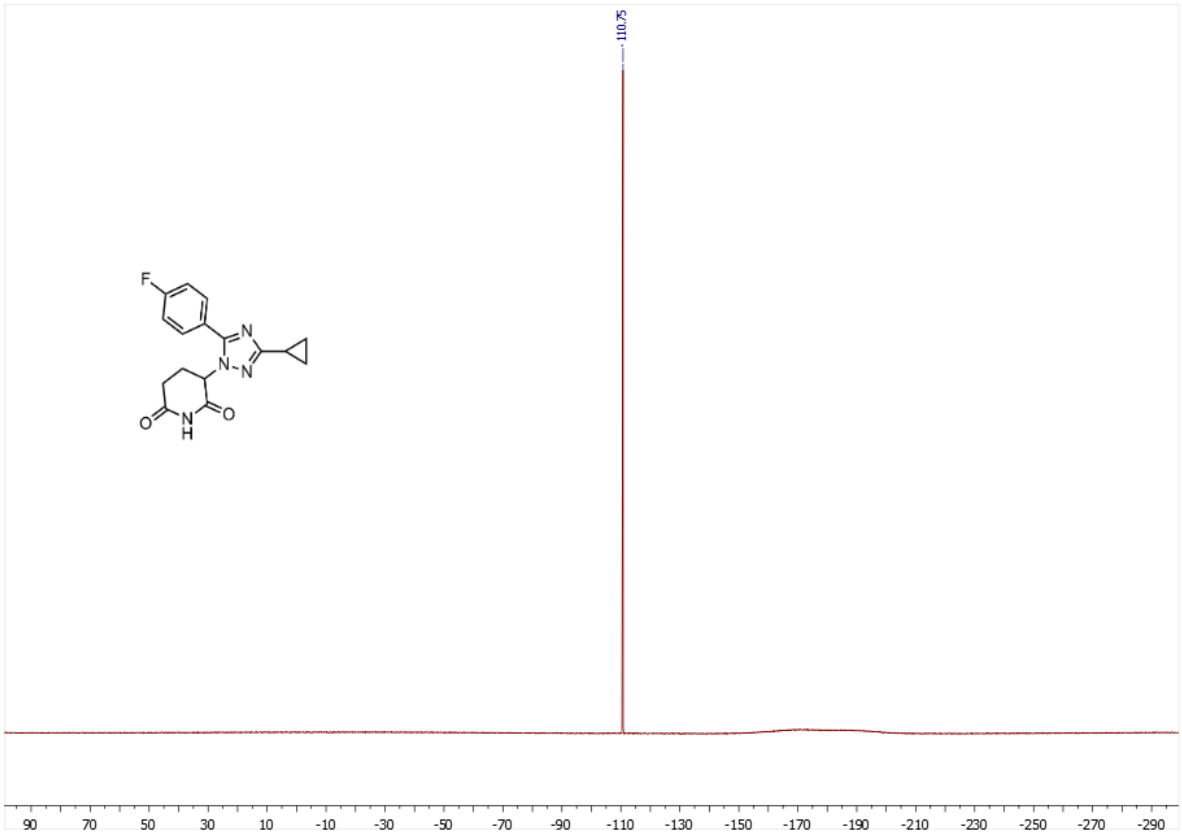



-63.32
Me
N
N
N
CF3
O
N
H
O
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
-290

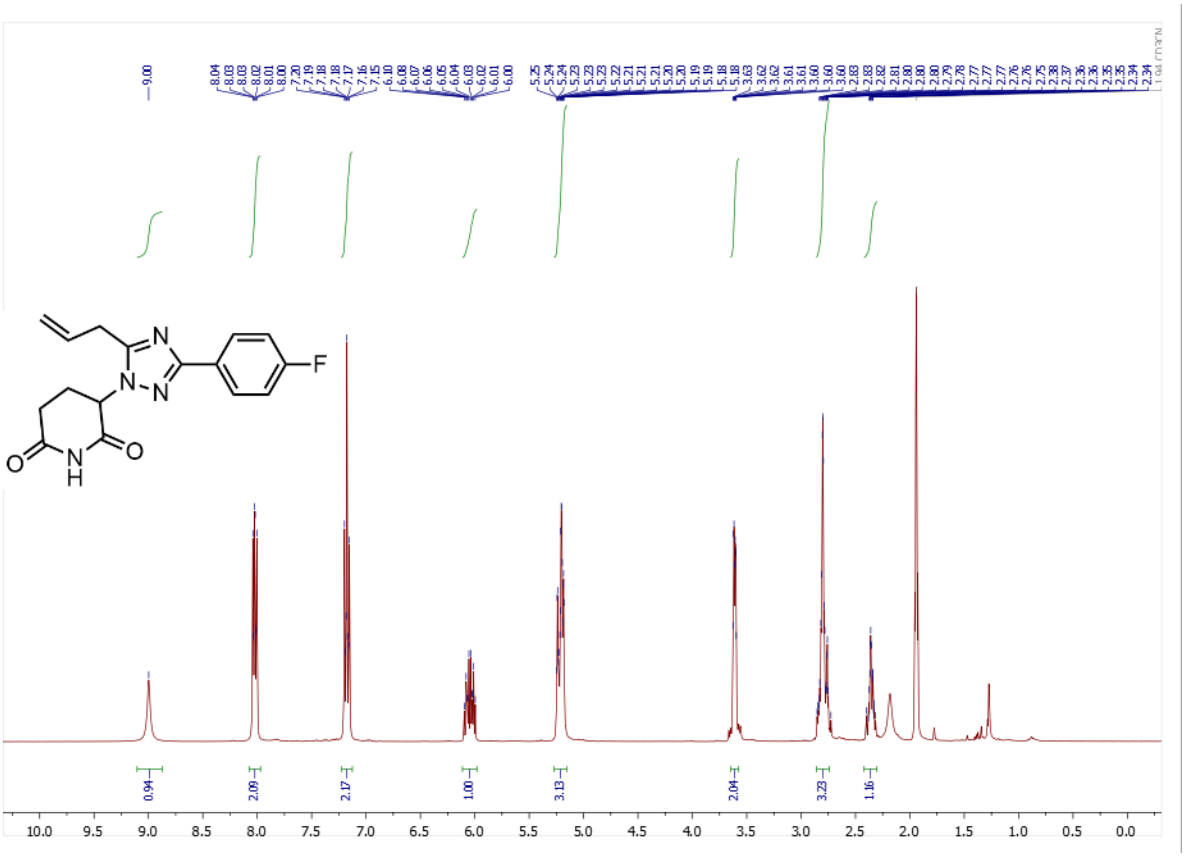
Copies of ^{1}H (400.13 MHz, DMSO-d_6), $^{13}C\{^{1}H\}$ (100.61 MHz, Methanol-d_4) and $^{19}F\{^{1}H\}$ (376.50 MHz, DMSO-d_6) spectra of **4i**

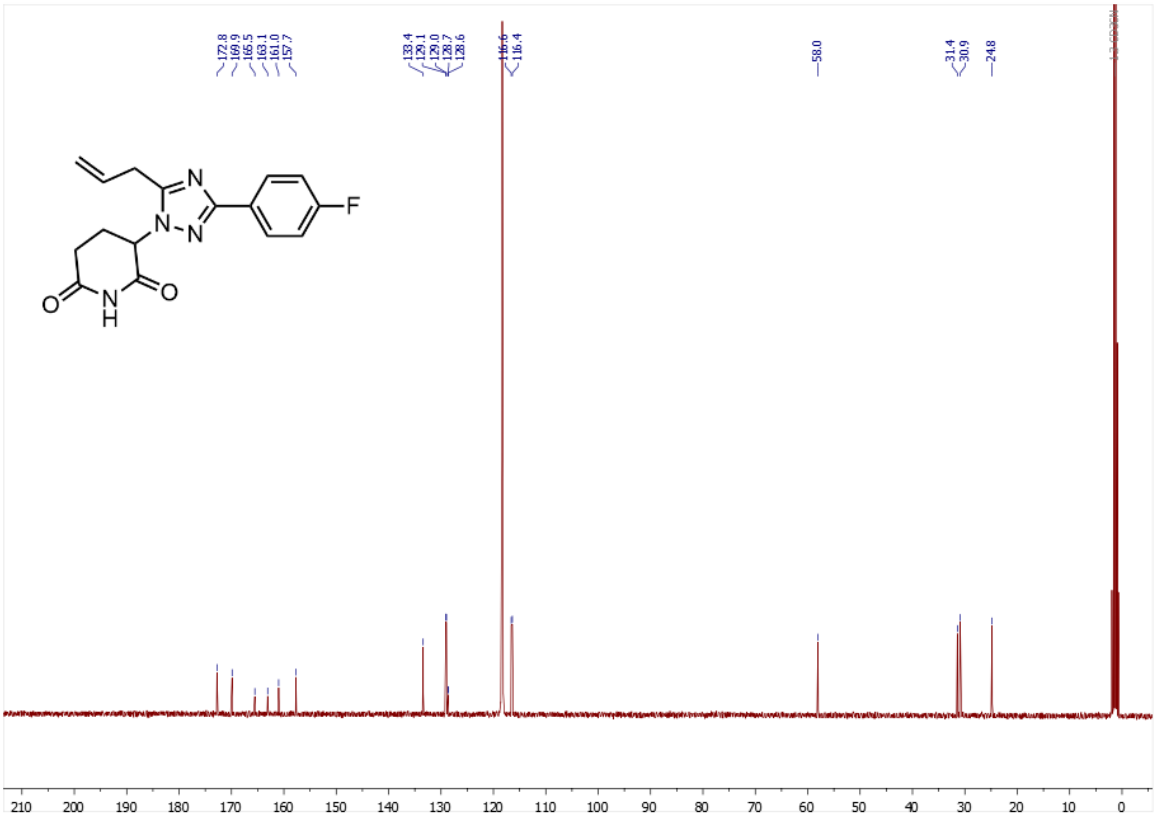


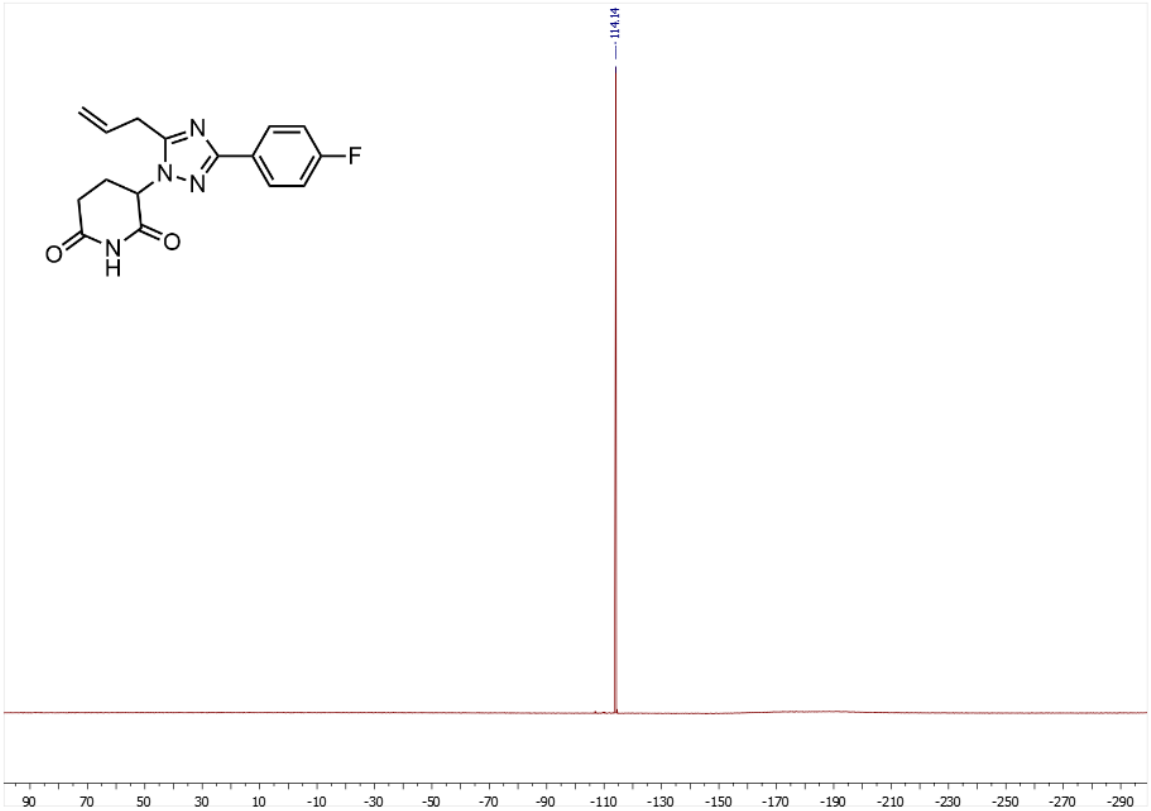



110.75
F
N
N
N
O
N
H
O
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
-290

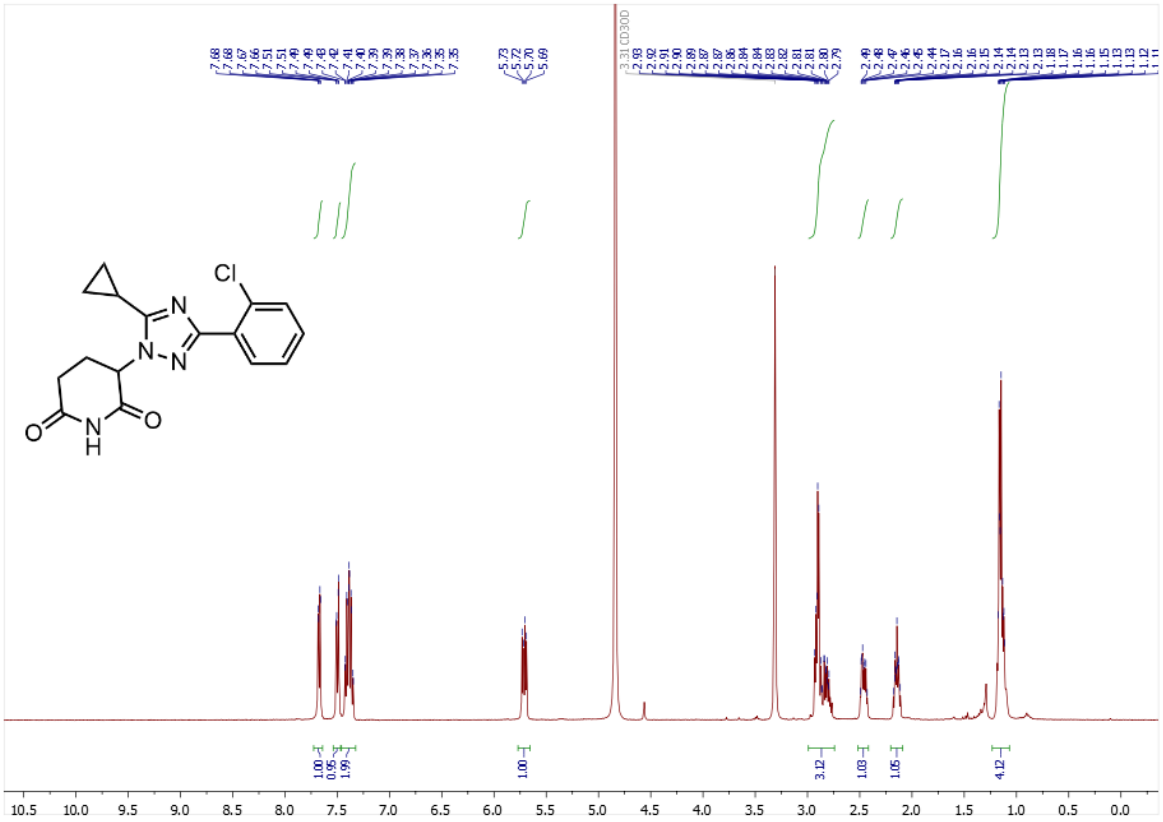
Copies of ^{1}H (400.13 MHz, Acetonitrile-d_3), $^{13}C\{^{1}H\}$ (100.61 MHz, Acetonitrile-d_3) and $^{19}F\{^{1}H\}$ (376.50 MHz, Acetonitrile-d_3) spectra of **4j**

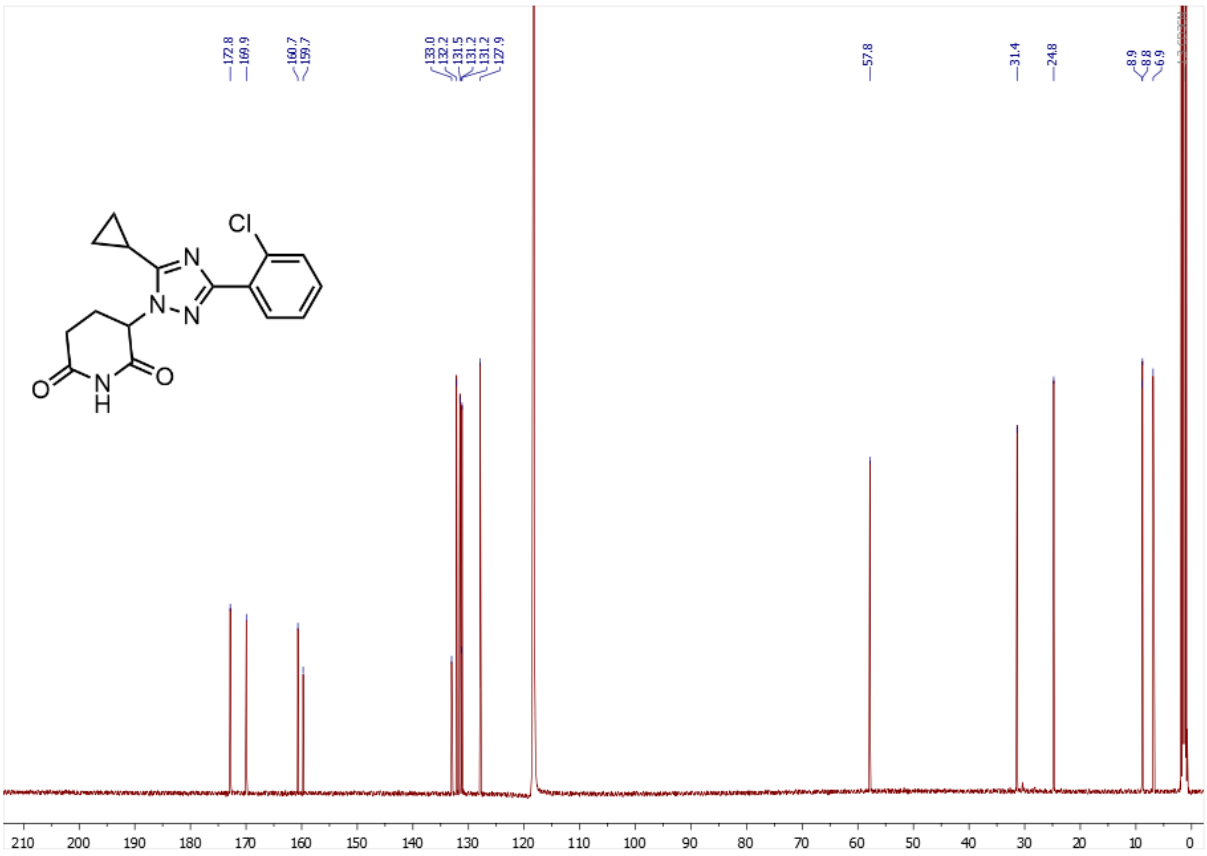





114.14
F
N
N
N
O
N
H
O
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
-290

Copies of ^{1}H (400.13 MHz, Methanol-d_4) and $^{13}C\{^{1}H\}$ (100.61 MHz, Methanol-d_4) spectra of **4k**





Copies of ^{1}H (400.13 MHz, DMSO-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, DMSO-d_6) spectra of **4l**

