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Synthesis of α-(azidomethyl)glutarimide and its application in construction of potential Cereblon ligands *via* the CuAAC reaction

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Table of contents

General information..... S2

Table S1. CRBN binding properties of the selected newly synthesized glutarimide derivatives. Pomalidamide used as a reference compound..... S3

General procedure for preparation of starting materials and their analytical data: S4

The synthesis of 1,4-disubstituted 1,2,3-triazoles 3. General procedure 1 ..... S6

The synthesis of 1,4-disubstituted 1,2,3-triazoles 4. General procedure 2 .... S13

References S18

Copies of ^{1}H and ^{13}C NMR spectra S18

General information

NMR spectra were acquired with 400 MHz Bruker Avance III spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in $CDCl_3$ or DMSO-d_6 and were referenced to residual solvent proton signals (δ_H = 7.26 and 2.50, respectively) and solvent carbon signals (δ_C = 77.16 and 39.52, respectively). Mass spectra were acquired with HRMS-ESI-qTOF spectrometer Nexera LCMS-9030 or MaXis II Bruker Daltonic GmbH (electrospray ionization mode, positive and negative ions detection). X-ray diffraction analysis was performed on an Agilent Technologies "Supernova" diffractometer using monochromatic X-ray radiation Cu Ka (λ = 1.54184) at a temperature of 100 K. Flash column chromatography on silica (Merck, 230-400 mesh) was performed with Ecom ECS58P instrument. TLC was performed on aluminium-backed pre-coated plates (0.25 mm) with silica gel 60 F254 with a suitable solvent system and was visualized using UV fluorescence.

Cell culture. Multiple myeloma cell line KMS-12-PE were purchased from the DSMZ. MM1.S, NALM-6 and WIL2-S cells were purchased from the ATCC. Cells were maintained in RPMI-1640 (Gibco, UK) supplemented with 10% fetal bovine serum (FBS, Gibco, UK), penicillin (100 UI mL^{-1}), streptomycin (100 μg mL^{-1}) and GlutaMax (2 mM, Gibco, UK). All cells line cultivation under a humidified atmosphere of 95% air/5% CO_2 at 37 °C. The number of viable cells was determined by trypan blue exclusion.

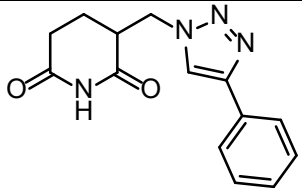
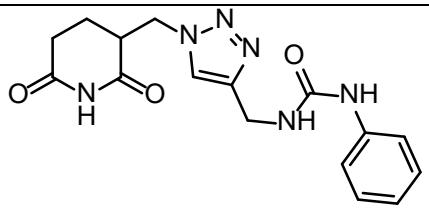
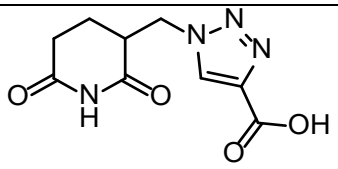
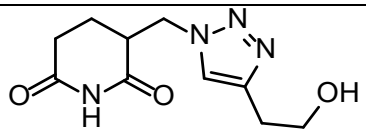
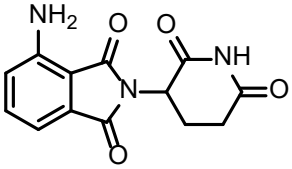
MTT assay. All examined cells were diluted with growth medium to a final concentration of 3.0×10^5 cells per mL. Aliquots of 15×10^3 cells in 50 μL were placed in individual wells of white 96-well multiplates (Nunc, USA). In triplicate wells, test compounds were added, initially starting at a concentration of 100 μM, then diluted to achieve a final concentration of 50 μM for testing. Dimethyl sulfoxide (DMSO, Sigma, USA) was used as a control at a final concentration of 0.1%. The plates were incubated for 72 hours at 37 °C in a 5% CO_2 atmosphere. Following incubation, 100 μL of CellTiter-Glo® One Solution (Promega, USA) was added to each well. The plates were then shaken for 10 minutes. Luminescence was measured using a GloMax Multi+ microplate reader (Promega, USA). Cytotoxicity of each compound was evaluated in three separate experiments.

Microscale Thermophoresis assay

For affinity measurements we used a previously described competitive MST assay[S1]. Compounds were dissolved in DMSO, diluted 1:1 in a 16-point dilution series and subsequently the complete series was diluted in H_2O. The resulting dilution series were mixed 1:1 with a protein reporter

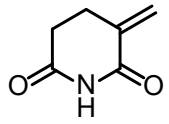
stock to final concentrations of 500 µM compound (highest concentration), 10 µM *h*TBD, 200 nM BODIPY-uracil and 0.5% DMSO. MST measurements were carried out with the Monolith NT.115, equipped with a Nano BLUE detector, at 20% excitation power, medium MST power and 25 °C. Resulting MST traces were evaluated at an MST on-time of 20 s. The corresponding normalized fluorescence counts of dublicates were baseline corrected (ΔF_{norm}) to the mean response of the lowest ligand concentration and analyzed using GraphPad Prism 9. IC_{50} values were obtained from a non-linear, 4 parameters fit of the Hill equation. The reported error corresponds to a symmetric 95% confidence interval of the IC_{50}. K_i values were calculated as reported previously[S2]. The lower 95% confidence interval was converted to a theoretical K_i. This theoretical K_i was subtracted from the K_i, resulting in the final error of the K_i.

Table S1. CRBN binding properties of the selected newly synthesized glutarimide derivatives. Pomalidamide used as a reference compound.

Compound	Structure	IC_{50} [µM]	Ki [µM]
3a		10.47 ± 1.07	2.04 ± 0.56
3h		13.88 ± 1.15	3.81 ± 0.60
3k		69.36 ± 22.86	32.67 ± 11.89
3o		39.21 ± 8.13	16.99 ± 4.23
Pomalidomide		13 ± 2.7	3.3 ± 1.4

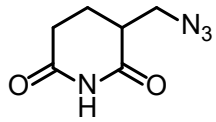
General procedure for preparation of starting materials and their analytical data:

3-Methylenepiperidine-2,6-dione (2)



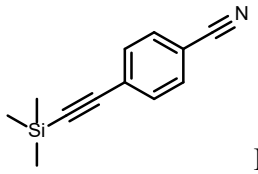
Preparation and NMR data in accordance with[S3].

3-(Azidomethyl)piperidine-2,6-dione (1)



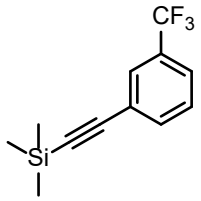
Azidotrimethylsilane (5.32 mL, 4.66 g, 40 mmol) was dissolved in dry dichloromethane (40 mL) followed by addition of acetic acid (2.32 mL; 3.49 g; 40 mmol). After stirring for 20 minutes, this mixture was transferred to another reaction vessel with stirred mixture of 3-methylenepiperidine-2,6-dione (1 g; 8 mmol) and triethylamine (226 µL; 164.1 mg; 1.6 mmol). After stirring for 12 hours at room temperature, the reaction mixture was concentrated *in vacuo*. The resulting product was purified by column chromatography on silica gel with a linear gradient (2-35%) of ethyl acetate in dichloromethane. Yield 1.19 g, 87 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 3.84 – 3.66 (m, 2H), 2.79 (dt, *J* = 17.7, 4.0 Hz, 1H), 2.71 – 2.47 (m, 2H), 2.12 (dtd, *J* = 13.8, 5.3, 3.2 Hz, 1H), 2.04 – 1.87 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 172.2, 50.8, 41.7, 31.5, 21.9. HRMS (ESI) m/z Calcd for $C_6H_8N_4O_2$ $[M+Na]^+$ 191.0539; Found 191.0530.

4-((Trimethylsilyl)ethynyl)benzonitrile (5a)



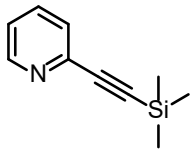
Preparation and NMR data in accordance with[S4].

Trimethyl((3-(trifluoromethyl)phenyl)ethynyl)silane (5b)



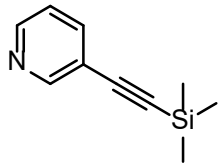
Preparation and NMR data in accordance with[S5].

2-((Trimethylsilyl)ethynyl)pyridine (5c)



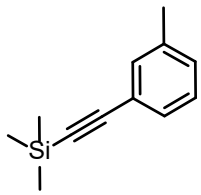
Preparation and NMR data in accordance with[S6].

3-((Trimethylsilyl)ethynyl)pyridine (5d)



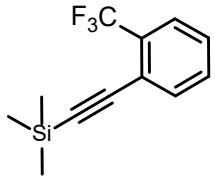
Preparation and NMR data in accordance with[S7].

Trimethyl(m-tolylethynyl)silane (5e)



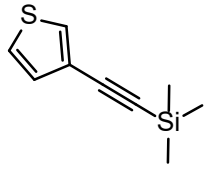
Preparation and NMR data in accordance with[S8].

Trimethyl((2-(trifluoromethyl)phenyl)ethynyl)silane (5f)



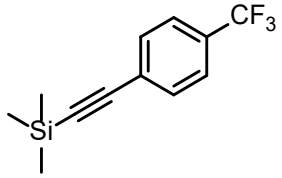
Preparation and NMR data in accordance with[S9].

Trimethyl(thiophen-3-ylethynyl)silane (5g)



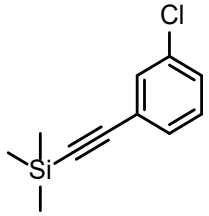
Preparation and NMR data in accordance with[S10].

Trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane (5h)



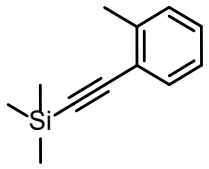
Preparation and NMR data in accordance with[S11].

((3-Chlorophenyl)ethynyl)trimethylsilane (5i)



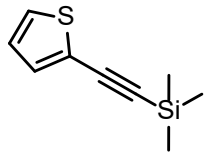
Preparation and NMR data in accordance with[S12].

Trimethyl(o-tolylethynyl)silane (5j)



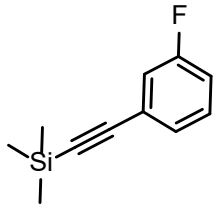
Preparation and NMR data in accordance with[S13].

Trimethyl(thiophen-2-ylethynyl)silane (5k)



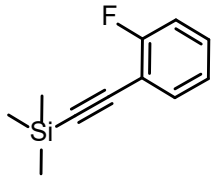
Preparation and NMR data in accordance with[S14].

((3-Fluorophenyl)ethynyl)trimethylsilane (5l)



Preparation and NMR[14] data in accordance with[S15].

((2-Fluorophenyl)ethynyl)trimethylsilane (5m)



Preparation and NMR data in accordance with[S16].

The synthesis of 1,4-disubstituted 1,2,3-triazoles 3. General procedure 1

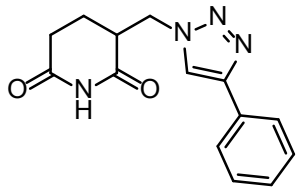
3-(Azidomethyl)piperidine-2,6-dione **1** (100 mg; 0.59 mmol) was dissolved in tetrahydrofuran (2 mL), then alkyne (0.59 mmol) and distilled water (1 mL) were added to the resulting mixture. A solution of sodium ascorbate (10% mol.; 11.78 mg; 0.059 mmol) and copper acetate (5% mol.; 5.95 mg; 0.003 mol) was prepared in 1 mL of distilled water and added to the stirred reaction mixture. The reaction mixture was left stirring at room temperature (30 °C) overnight.

Substances 3a-g. Tetrahydrofuran was removed under reduced pressure. The aqueous residue was diluted with sat. NaCl (7 mL) and extracted with CH_2Cl_2 (3×7 mL). The combined organic phase was washed with sat. NaCl (3×7 mL), dried over Na_2SO_4, filtered and concentrated. The resulting products were purified by column chromatography on silica gel using linear gradient of MeOH in DCM (5-15%).

Substances 3h-n. The reaction mixture was filtered and the resulting solid was dried *in vacuo*.

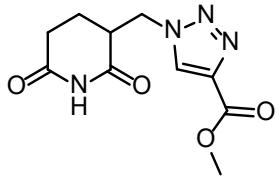
Substances 3o-q. A mixture of tetrahydrofuran and water was removed under reduced pressure. The resulting products were purified by column chromatography on silica gel using linear gradient of MeOH in DCM (5-15%).

3-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (3a)



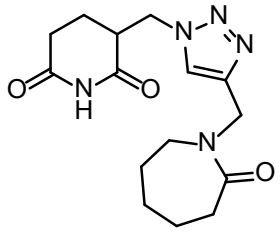
Yield 108 mg, 68%, white solid, mp = 199-201 °C. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 10.78 (s, 1H), 8.22 (s, 1H), 7.79 – 7.73 (m, 2H), 7.35 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.29 – 7.22 (m, 1H), 4.85 (dd, *J* = 14.1, 4.8 Hz, 1H), 4.65 (dd, *J* = 14.1, 7.0 Hz, 1H), 3.12 (ddt, *J* = 12.1, 7.0, 4.9 Hz, 1H), 2.56 – 2.47 (m, 2H), 1.88 (dq, *J* = 13.5, 4.5 Hz, 1H), 1.68 (tt, *J* = 13.2, 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 172.5, 172.3, 146.4, 130.2, 128.3, 127.4, 124.9, 121.3, 48.9, 41.4, 30.9, 21.2. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{14}H_{14}N_4O_2Na^+$ 293.1009; Found 293.0997

Methyl 1-((2,6-dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (3b)



Yield 93 mg, 62%, light brown solid, mp = 214-216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.72 (s, 1H), 4.88 (dd, *J* = 14.0, 5.2 Hz, 1H), 4.65 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.83 (s, 3H), 3.28 – 3.14 (m, 1H), 2.62 – 2.42 (m, 2H), 1.75 – 1.60 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 173.0, 160.6, 138.4, 129.9, 51.7, 49.3, 41.0, 30.8, 21.2. HRMS (ESI) m/z $[M-H]^-$ Calcd for $C_{10}H_{11}N_4O_4^-$ 251.0786; Found 251.0780

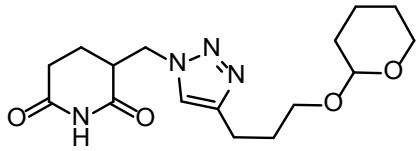
3-((4-((2-Oxoazepan-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (3c)



Yield 56 mg, 30%, white solid, mp = 190-195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.90 (s, 1H), 5.67 (s, 3H), 4.77 (dd, *J* = 14.0, 5.0 Hz, 1H), 4.57 (dd, *J* = 14.0, 7.3 Hz, 1H), 4.51 (s, 2H), 3.14 (dt, *J* = 12.4, 6.0 Hz, 1H), 2.65 – 2.28 (m, 3H), 1.68 – 1.46 (m, 6H), 1.40 (d, *J* = 6.0 Hz, 2H). δ ^{13}C NMR (101 MHz, DMSO-d_6) 174.4, 173.2, 173.1, 143.9,

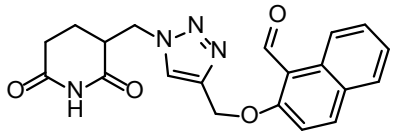
124.0, 48.9, 48.3, 42.0, 41.2, 36.3, 30.8, 29.1, 27.8, 22.8, 21.1. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{15}H_{22}N_5O_3Na^+$ 342.1537; Found 342.1527

3-((4-(3-((Tetrahydro-2H-pyran-2-yl)oxy)propyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (3d)



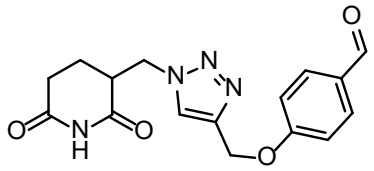
Yield 126 mg, 63%, light yellow solid, mp = 120-124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.40 (s, 1H), 4.81 (dd, J = 14.2, 4.6 Hz, 1H), 4.68 (dd, J = 14.2, 5.9 Hz, 1H), 4.57 (dd, J = 4.5, 2.8 Hz, 1H), 3.84 (ddd, J = 10.9, 7.5, 3.3 Hz, 1H), 3.75 (dtt, J = 10.6, 6.6, 3.0 Hz, 1H), 3.52 – 3.44 (m, 1H), 3.41 (dd, J = 9.8, 6.3 Hz, 1H), 2.99 (dq, J = 12.9, 5.1 Hz, 1H), 2.79 (td, J = 7.5, 2.6 Hz, 2H), 2.71 (dt, J = 18.4, 3.6 Hz, 1H), 2.54 (ddd, J = 18.1, 13.2, 5.5 Hz, 1H), 2.07 (dtd, J = 13.5, 5.2, 2.8 Hz, 1H), 1.95 (p, J = 7.0 Hz, 2H), 1.80 (dtd, J = 11.0, 7.8, 3.5 Hz, 1H), 1.75 – 1.62 (m, 2H), 1.57 (dt, J = 8.4, 4.4 Hz, 1H), 1.51 (qd, J = 7.5, 4.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.7, 173.6, 146.9, 123.1, 98.4, 66.3, 61.7, 49.2, 41.8, 31.3, 30.7, 29.5, 25.5, 22.2, 21.6, 19.6. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{16}H_{24}N_4O_4Na^+$ 359.1690; Found 359.1709

2-((1-((2,6-Dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (3e)



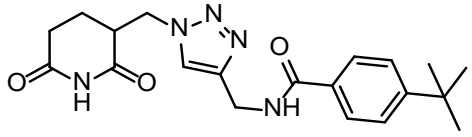
Yield 148 mg, 66%, light yellow solid, mp = 159-161 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 10.72 (s, 1H), 9.09 (d, J = 8.7 Hz, 1H), 8.29 (t, J = 5.2 Hz, 2H), 7.95 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 9.2 Hz, 1H), 7.64 (ddd, J = 8.5, 6.8, 1.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 5.53 (s, 2H), 4.83 (dd, J = 14.0, 4.9 Hz, 1H), 4.61 (dd, J = 14.1, 7.5 Hz, 1H), 3.22 – 3.10 (m, 1H), 2.58 – 2.37 (m, 2H), 1.63 (tq, J = 11.7, 5.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.3, 173.1, 173.0, 162.9, 142.1, 137.7, 130.5, 129.7, 128.5, 128.4, 125.5, 124.8, 123.9, 116.4, 115.5, 63.1, 49.0, 41.2, 30.8, 21.1. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{20}H_{18}N_4O_4Na^+$ 401.1220; Found 401.1212

4-((1-((2,6-Dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (3f)



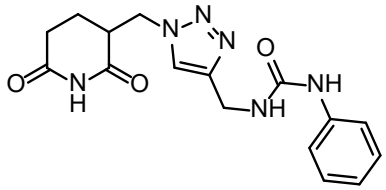
Yield 151 mg, 77%, light brown solid, mp = 169-172 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.85 (s, 1H), 9.88 (s, 1H), 8.24 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 5.28 (s, 2H), 4.83 (dd, *J* = 14.0, 4.9 Hz, 1H), 4.62 (dd, *J* = 14.1, 7.4 Hz, 1H), 3.18 (h, *J* = 5.1 Hz, 1H), 2.65 – 2.36 (m, 2H), 1.74 – 1.53 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 191.3, 173.2, 173.1, 162.9, 141.9, 131.7, 129.8, 125.6, 115.2, 61.4, 49.0, 40.1, 30.8, 21.2. HRMS (ESI) m/z [M+Na]$^+$ Calcd for $C_{16}H_{16}N_4O_4Na^+$ 351.1064; Found 351.1064

4-(tert-Butyl)-N-((1-((2,6-dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)benzamide (3g)



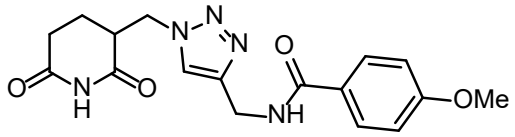
Yield 220 mg, 96%, white solid, mp = 135-140 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.83 (s, 1H), 8.93 (t, *J* = 5.8 Hz, 1H), 7.91 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 4.77 (dd, *J* = 14.0, 4.8 Hz, 1H), 4.56 (dd, *J* = 14.1, 7.5 Hz, 1H), 4.50 (d, *J* = 5.7 Hz, 2H), 3.14 (ddt, *J* = 12.5, 7.4, 5.2 Hz, 1H), 2.63 – 2.40 (m, 2H), 1.77 – 1.53 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.2, 173.1, 166.0, 154.1, 145.2, 131.3, 127.1, 125.0, 123.7, 48.8, 41.3, 34.8, 34.6, 30.9, 30.8, 21.2. HRMS (ESI) m/z [M+Na]$^+$ Calcd for $C_{20}H_{25}N_5O_3Na^+$ 406.1850; Found 406.1850

1-((1-((2,6-Dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-3-phenylurea (3h)



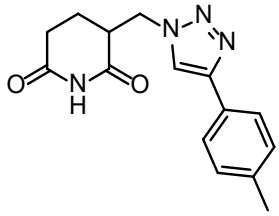
Yield 66 mg, 32%, white solid, mp = 176-180 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.83 (s, 1H), 8.53 (s, 1H), 7.92 (s, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 2H), 6.89 (t, *J* = 7.3 Hz, 1H), 6.56 (t, *J* = 5.8 Hz, 1H), 4.79 (dd, *J* = 14.1, 4.9 Hz, 1H), 4.58 (dd, *J* = 14.0, 7.5 Hz, 1H), 4.33 (d, *J* = 5.6 Hz, 2H), 3.15 (dq, *J* = 12.0, 5.6 Hz, 1H), 2.64 – 2.35 (m, 2H), 1.80 – 1.54 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.2, 173.1, 155.0, 145.5, 140.3, 128.6, 123.4, 121.1, 117.6, 48.8, 41.2, 34.8, 30.8, 21.2. HRMS (ESI) m/z [M+Na]$^+$ Calcd for $C_{16}H_{18}N_6O_3Na^+$ 365.1357; Found 365.1333

N-((1-((2,6-Dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxybenzamide (3i)



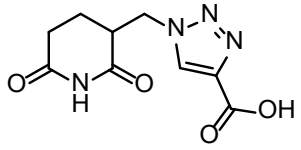
Yield 160 mg, 75%, white solid, mp = 209-213 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.83 (s, 1H), 8.85 (t, *J* = 5.8 Hz, 1H), 7.91 (s, 1H), 7.88 – 7.83 (m, 2H), 7.02 – 6.96 (m, 2H), 4.77 (dd, *J* = 14.1, 4.8 Hz, 1H), 4.56 (dd, *J* = 14.0, 7.5 Hz, 1H), 4.49 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 3.21 – 3.08 (m, 1H), 2.59 – 2.39 (m, 2H), 1.74 – 1.54 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 173.18, 173.12, 165.59, 161.60, 145.30, 129.10, 126.35, 123.75, 113.47, 55.33, 48.85, 41.28, 34.75, 30.85, 21.21. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{17}H_{19}N_5O_4Na^+$ 380.1329; Found 380.1318

3-((4-(p-Tolyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (3g)



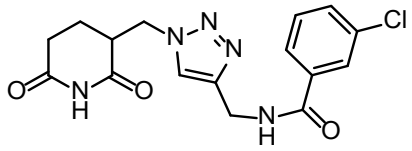
Yield 129 mg, 76%, light yellow solid, mp = 212-216 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.86 (s, 1H), 8.47 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 4.85 (dd, *J* = 14.0, 4.8 Hz, 1H), 4.61 (dd, *J* = 14.1, 7.7 Hz, 1H), 3.20 (dq, *J* = 12.1, 5.7 Hz, 1H), 2.68 – 2.39 (m, 2H), 2.32 (s, 3H), 1.74 (pt, *J* = 12.8, 6.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 173.2, 173.1, 146.3, 137.1, 129.4, 127.8, 125.0, 121.7, 49.1, 41.3, 30.8, 21.3, 20.8. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{17}N_4O_2^+$ 285.1346; Found 285.1346

1-((2,6-Dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (3k)



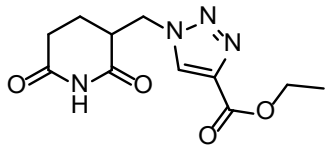
Yield 68 mg, 48%, white solid, mp = 235-240 °C. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-*d6*) δ 12.98 (s, 1H), 10.83 (s, 1H), 8.55 (s, 1H), 4.86 (dd, *J* = 14.0, 5.1 Hz, 1H), 4.64 (dd, *J* = 14.0, 7.4 Hz, 1H), 3.20 (dq, *J* = 12.2, 5.8 Hz, 1H), 2.66 – 2.31 (m, 2H), 1.86 – 1.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-*d6*) δ 172.8, 172.7, 161.5, 139.5, 129.4, 49.1, 41.1, 30.8, 21.1. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_9H_{10}N_4O_4Na^+$ 261.0594; Found 261.0586

3-Chloro-N-((1-((2,6-dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)benzamide (3l)



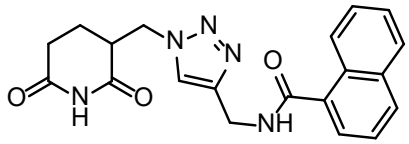
Yield 196 mg, 91%, light yellow solid, mp = 185-189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 9.14 (t, J = 5.8 Hz, 1H), 7.96 (s, 1H), 7.92 (s, 1H), 7.83 (dt, J = 7.8, 1.4 Hz, 1H), 7.60 (dt, J = 8.0, 1.5 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 4.78 (dd, J = 14.0, 4.8 Hz, 1H), 4.57 (dd, J = 14.1, 7.6 Hz, 1H), 4.51 (d, J = 5.7 Hz, 2H), 3.21 – 3.07 (m, 1H), 2.67 – 2.36 (m, 2H), 1.82 – 1.51 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 173.1, 164.7, 144.7, 136.1, 133.1, 131.1, 130.3, 127.1, 126.0, 123.8, 48.8, 41.2, 34.9, 30.8, 21.2. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{16}H_{16}ClN_5O_3Na^+$ 384.0834; Found 384.0815

Ethyl 1-((2,6-dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (3m)



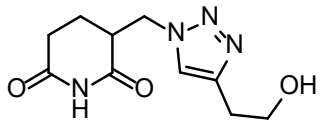
Yield 78 mg, 49%, white solid, mp = 197-200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.70 (s, 1H), 4.87 (dd, J = 14.0, 5.2 Hz, 1H), 4.65 (dd, J = 14.0, 7.4 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.28 – 3.16 (m, 1H), 2.64 – 2.36 (m, 2H), 1.77 – 1.60 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 173.0, 160.2, 138.7, 129.8, 60.5, 49.3, 41.0, 30.8, 21.2, 14.1. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{11}H_{14}N_4O_4Na^+$ 289.0907; Found 289.0897

N-((1-((2,6-Dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1-naphthamide (3n)



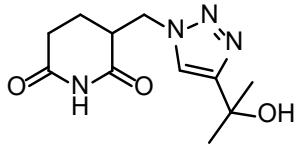
Yield 183 mg, 82%, white solid, mp = 210-214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 9.04 (t, J = 5.7 Hz, 1H), 8.25 – 8.16 (m, 1H), 8.04 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.62 (d, J = 6.9 Hz, 1H), 7.59 – 7.51 (m, 3H), 4.83 (dd, J = 13.9, 4.9 Hz, 1H), 4.68 – 4.60 (m, 1H), 4.58 (d, J = 6.1 Hz, 2H), 3.18 (dq, J = 11.5, 5.8 Hz, 1H), 2.62 – 2.40 (m, 2H), 1.67 (dtt, J = 25.4, 12.9, 6.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 173.0, 168.5, 134.4, 133.1, 129.8, 129.7, 128.1, 126.6, 126.1, 125.3, 125.2, 124.9, 123.7, 48.8, 41.3, 34.7, 30.8, 21.1. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{20}H_{19}N_5O_3Na^+$ 400.1380; Found 400.1375

3-((4-(2-Hydroxyethyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (3o)



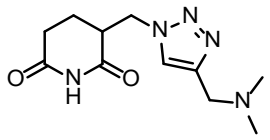
Yield 116 mg, 82%, white solid, mp = 113-118 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.83 (s, 1H), 7.81 (s, 1H), 4.75 (dd, *J* = 14.0, 4.7 Hz, 1H), 4.67 (t, *J* = 5.3 Hz, 1H), 4.54 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.62 (td, *J* = 6.9, 5.2 Hz, 2H), 3.12 (ddt, *J* = 12.6, 7.5, 5.1 Hz, 1H), 2.75 (t, *J* = 6.9 Hz, 2H), 2.63 – 2.35 (m, 2H), 1.81 – 1.49 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.2, 173.1, 144.4, 123.2, 60.3, 48.7, 41.3, 30.8, 29.1, 21.2. HRMS (ESI) m/z [M+Na]$^+$ Calcd for $C_{10}H_{14}N_4O_3Na^+$ 261.0958; Found 261.0954

3-((4-(2-Hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (3p)



Yield 74 mg, 49%, light yellow solid, mp = 151-154 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.84 (s, 1H), 7.82 (s, 1H), 5.09 (s, 1H), 4.76 (dd, *J* = 14.0, 4.7 Hz, 1H), 4.54 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.14 (ddt, *J* = 12.7, 7.6, 5.1 Hz, 1H), 2.67 – 2.32 (m, 2H), 1.77 – 1.53 (m, 2H), 1.44 (s, 6H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.2, 173.1, 155.8, 121.2, 67.0, 48.7, 41.3, 30.8, 30.7, 30.6, 21.2. HRMS (ESI) m/z [M+Na]$^+$ Calcd for $C_{11}H_{16}N_4O_3Na^+$ 275.1115; Found 275.1108

3-((4-(Dimethylaminomethyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (3q)



Yield 45 mg, 30%, yellow oil. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.55 (s, 1H), 7.86 (s, 1H), 4.78 (dd, *J* = 14.1, 5.0 Hz, 1H), 4.59 (dd, *J* = 14.1, 7.2 Hz, 1H), 3.16 (dq, *J* = 12.1, 5.6 Hz, 1H), 2.76 – 2.34 (m, 2H), 2.19 (s, 6H), 1.77 (dtd, *J* = 14.1, 5.3, 3.8 Hz, 1H), 1.64 (dtd, *J* = 13.5, 11.8, 5.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 172.5, 172.3, 152.1, 123.8, 48.6, 44.0, 41.0, 30.4, 20.9. HRMS (ESI) m/z [M+Na]$^+$ Calcd for $C_{11}H_{17}N_5ONa^+$ 274.1274; Found 274.1259

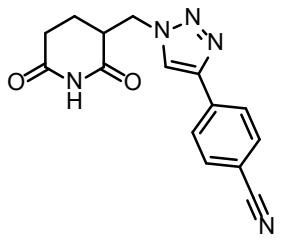
The synthesis of 1,4-disubstituted 1,2,3-triazoles 4. General procedure 2

TMS-protected alkyne **5a-m** (0.59 mmol) was dissolved in tetrahydrofuran (2 mL) and TBAF (186.6 mg; 0.71 mmol) was added to the resulting mixture. The reaction mixture was left stirred at room temperature for 20 minutes. Then it was transferred to a stirred mixture of 3-(azidomethyl)piperidine-2,6-dione **1** (100 mg; 0.59 mmol) and distilled water (1 mL). A solution of sodium ascorbate (10% mol.; 11.78 mg; 0.059 mmol) and copper acetate (5% mol.; 5.95 mg; 0.003 mol) was prepared in 1 mL of distilled water and added to the reaction mixture. The reaction mixture was left stirring at room temperature (30 °C) overnight.

Substances 4a-g. Tetrahydrofuran was removed under reduced pressure. The aqueous residue was diluted with sat. NaCl (7 mL) and extracted with CH_2Cl_2 (3×7 mL). The combined organic phase was washed with sat. NaCl (3×7 mL), dried over Na_2SO_4, filtered and concentrated. The resulting product was purified by column chromatography on silica gel with a linear gradient (15-50%) of acetone in hexane.

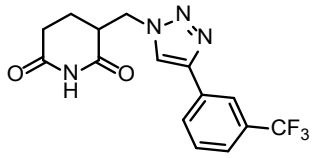
Substances 5h-m. The reaction mixture was filtered and the resulting solid was dried *in vacuo*.

4-(1-((2,6-Dioxopiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)benzonitrile (4a)



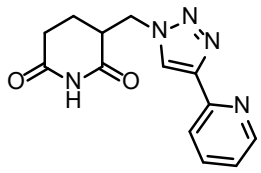
Yield 151 mg, 86%, brown solid, mp = 224-226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.74 (s, 1H), 8.06 – 8.01 (m, 2H), 7.95 – 7.88 (m, 2H), 4.89 (dd, J = 14.1, 4.9 Hz, 1H), 4.66 (dd, J = 14.1, 7.6 Hz, 1H), 3.26 – 3.16 (m, 1H), 2.63 – 2.42 (m, 2H), 1.86 – 1.66 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 173.0, 144.6, 135.1, 132.9, 125.7, 123.9, 118.8, 110.1, 49.4, 41.2, 30.9, 21.3. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{15}H_{13}N_5O_2Na^+$ 318.0961; Found 318.0955

3-((4-(3-(Trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4b)



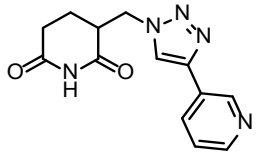
Yield 98 mg, 49%, white solid, mp = 149-152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.75 (s, 1H), 8.23 – 8.11 (m, 2H), 7.73 – 7.65 (m, 2H), 4.89 (dd, J = 14.1, 4.8 Hz, 1H), 4.65 (dd, J = 14.1, 7.6 Hz, 1H), 3.27 – 3.16 (m, 1H), 2.64 – 2.41 (m, 2H), 1.85 – 1.65 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 173.0, 144.8, 131.7, 130.1, 129.7 (q, J = 31.7 Hz), 128.9, 125.4 (q, J = 272.5 Hz), 124.3 (q, J = 3.9 Hz), 123.2, 121.4 (q, J = 4.0 Hz), 49.3, 41.3, 30.9, 21.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ -61.29. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{13}F_3N_4O_2^+$ 339.1063 Found 339.1054

3-((4-(Pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4c)



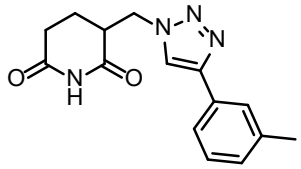
Yield 48 mg, 29%, white solid, mp = 206-211 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.65 – 8.57 (m, 1H), 8.55 (s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.89 (td, J = 7.7, 1.8 Hz, 1H), 7.34 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 4.89 (dd, J = 14.0, 5.0 Hz, 1H), 4.68 (dd, J = 14.0, 7.5 Hz, 1H), 3.24 (ddt, J = 10.8, 7.3, 3.7 Hz, 1H), 2.65 – 2.40 (m, 3H), 1.72 (ddq, J = 17.5, 12.4, 6.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 173.1, 149.8, 149.6, 147.2, 137.2, 124.0, 123.0, 119.3, 49.2, 41.2, 30.9, 21.2. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{13}H_{14}N_5O_2^+$ 272.1142; Found 272.1136

3-((4-(Pyridin-3-yl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4d)



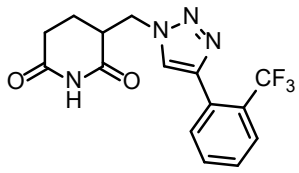
Yield 53 mg, 33%, white solid, mp = 146-148 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.67 (s, 1H), 8.23 (d, J = 7.7 Hz, 1H), 7.66 – 7.47 (m, 3H), 4.89 (dd, J = 14.0, 4.8 Hz, 1H), 4.66 (dd, J = 14.1, 7.6 Hz, 1H), 3.27 – 3.16 (m, 1H), 2.65 – 2.41 (m, 2H), 1.85 – 1.66 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 173.0, 132.1, 132.0, 131.5, 131.4, 128.8, 128.6, 123.0, 49.3, 41.3, 30.9, 21.3. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{13}H_{14}N_5O_2^+$ 272.1142; Found 272.1142

3-((4-(m-Tolyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4e)



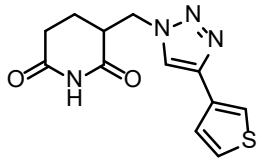
Yield 110 mg, 65%, white solid, mp = 159-164 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.50 (s, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 4.86 (dd, J = 14.0, 4.8 Hz, 1H), 4.62 (dd, J = 14.0, 7.7 Hz, 1H), 3.20 (ddt, J = 10.8, 7.4, 5.2 Hz, 1H), 2.63 – 2.42 (m, 2H), 2.35 (s, 3H), 1.83 – 1.63 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 173.1, 146.3, 138.0, 130.5, 128.7, 128.5, 125.7, 122.3, 122.1, 49.1, 41.3, 30.8, 21.3, 21.0. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{17}N_4O_2^+$ 285.1346; Found 285.1339

3-((4-(2-(Trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4f)



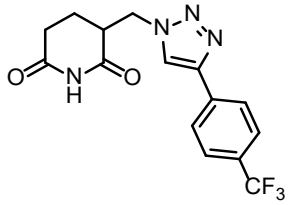
Yield 63 mg, 31%, white solid, mp = 157-160 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.28 (s, 1H), 7.89 – 7.83 (m, 1H), 7.83 – 7.73 (m, 2H), 7.63 (t, J = 7.5 Hz, 1H), 4.91 (dd, J = 14.0, 5.0 Hz, 1H), 4.71 (dd, J = 14.0, 7.4 Hz, 1H), 3.24 (ddt, J = 12.5, 7.4, 5.1 Hz, 1H), 2.65 – 2.43 (m, 2H), 1.81 – 1.58 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 173.1, 143.1, 132.6, 131.7, 129.4 (q, J = 2.0 Hz), 128.8, 126.4, 126.3 (q, J = 29.7 Hz), 124.8 (q, J = 4.1 Hz), 124.0 (q, J = 273.6 Hz), 49.1, 41.3, 30.8, 21.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ -57.34. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{15}H_{13}F_3N_4O_2Na^+$ 361.0883; Found 361.0888

3-((4-(Thiophen-3-yl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4g)



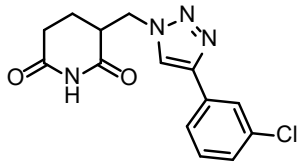
Yield 25 mg, 15%, yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.38 (s, 1H), 7.84 (dd, J = 3.0, 1.3 Hz, 1H), 7.64 (dd, J = 5.0, 3.0 Hz, 1H), 7.51 (dd, J = 5.0, 1.3 Hz, 1H), 4.84 (dd, J = 14.1, 4.8 Hz, 1H), 4.62 (dd, J = 14.1, 7.5 Hz, 1H), 3.19 (ddt, J = 12.4, 7.4, 5.1 Hz, 1H), 2.64 – 2.40 (m, 2H), 1.82 – 1.62 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 173.1, 142.8, 131.9, 127.1, 125.7, 121.9, 120.8, 49.1, 41.3, 30.9, 21.3. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{12}H_{12}N_4O_2S^+$ 277.0754; Found 277.0744

3-((4-(4-(Trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4h)



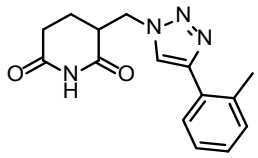
Yield 87 mg, 43%, white solid, mp = 210-212 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.71 (s, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 4.89 (dd, J = 14.1, 4.9 Hz, 1H), 4.66 (dd, J = 14.1, 7.6 Hz, 1H), 3.28 – 3.14 (m, 1H), 2.66 – 2.39 (m, 2H), 1.90 – 1.64 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 173.0, 144.8, 134.6, 128.0 (q, J = 31.6 Hz), 125.8 (q, J = 4.0 Hz), 125.6, 124.2 (q, J = 271.9 Hz), 123.5, 49.3, 41.3, 30.9, 21.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.99. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{14}FN_4O_2^+$ 339.1063; Found 339.1058

3-((4-(3-Chlorophenyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4i)



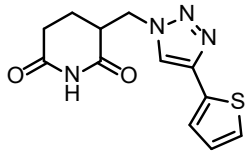
Yield 165 mg, 91%, brown solid, mp = 147-150 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.85 (s, 1H), 8.64 (s, 1H), 7.90 (t, *J* = 1.9 Hz, 1H), 7.82 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.44 – 7.32 (m, 1H), 4.87 (dd, *J* = 14.1, 4.8 Hz, 1H), 4.63 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.25 – 3.10 (m, 1H), 2.68 – 2.39 (m, *J* = 4.7, 3.9 Hz, 2H), 1.90 – 1.64 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.1, 173.0, 144.8, 133.6, 132.7, 130.8, 127.6, 124.7, 123.6, 123.0, 49.3, 41.3, 30.8, 21.3. HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{14}H_{14}ClN_4O_2^+$ 305.0800; Found 305.0806

3-((4-(o-Tolyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4j)



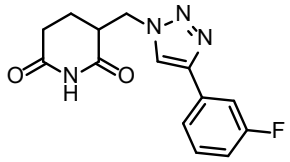
Yield 112 mg, 67%, white solid, mp = 167-170 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.87 (s, 1H), 8.36 (s, 1H), 7.81 – 7.65 (m, 1H), 7.27 (pd, *J* = 8.0, 3.7 Hz, 3H), 4.90 (dd, *J* = 14.0, 4.9 Hz, 1H), 4.65 (dd, *J* = 14.0, 7.7 Hz, 1H), 3.29 – 3.16 (m, 1H), 2.65 – 2.47 (m, 2H), 2.43 (s, 2H), 1.84 – 1.64 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.1, 173.1, 145.4, 134.8, 130.8, 129.9, 128.1, 127.7, 126.0, 124.1, 49.0, 41.3, 30.8, 21.3, 21.1. HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{15}H_{16}N_4O_2^+$ 285.1346; Found 285.1336

3-((4-(Thiophen-2-yl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4k)



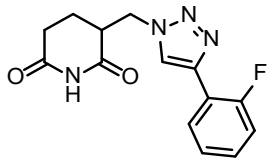
Yield 141 mg, 86%, brown solid, mp = 200-204 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.86 (s, 1H), 8.44 (s, 1H), 7.52 (d, *J* = 5.1 Hz, 1H), 7.43 (d, *J* = 3.6 Hz, 1H), 7.22 – 7.04 (m, 1H), 4.85 (dd, *J* = 14.0, 4.9 Hz, 1H), 4.62 (dd, *J* = 14.1, 7.5 Hz, 1H), 3.20 (dq, *J* = 12.1, 5.7 Hz, 1H), 2.68 – 2.36 (m, 2H), 1.73 (qq, *J* = 12.7, 5.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 173.1, 173.0, 141.6, 132.9, 127.8, 125.3, 124.0, 121.5, 49.2, 41.2, 30.9, 21.3. HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{12}H_{13}N_4O_2S^+$ 277.0754; Found 277.0746

3-((4-(3-Fluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4l)



Yield 137 mg, 80%, light brown solid, mp = 170-178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.62 (s, 1H), 7.73 – 7.66 (m, 1H), 7.65 (ddd, *J* = 10.4, 2.7, 1.5 Hz, 1H), 7.49 (td, *J* = 8.0, 6.1 Hz, 1H), 7.21 – 7.12 (m, 1H), 4.87 (dd, *J* = 14.1, 4.8 Hz, 1H), 4.64 (dd, *J* = 14.1, 7.6 Hz, 1H), 3.26 – 3.14 (m, 1H), 2.63 – 2.42 (m, 2H), 1.84 – 1.66 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 173.0, 162.5 (d, *J* = 243.1 Hz), 145.1 (d, *J* = 2.8 Hz), 133.0 (d, *J* = 8.7 Hz), 131.0 (d, *J* = 8.5 Hz), 122.9, 121.1 (d, *J* = 2.7 Hz), 114.5 (d, *J* = 21.1 Hz), 111.7 (d, *J* = 23.0 Hz), 49.3, 41.3, 30.9, 21.3.^{19}F NMR (376 MHz, DMSO-d_6) δ -112.72. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{14}FN_4O_2^+$ 289.1095; Found 289.1087

3-((4-(2-Fluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)piperidine-2,6-dione (4m)



Yield 82 mg, 48%, light brown solid, mp = 165-170 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.41 (d, *J* = 3.8 Hz, 1H), 8.13 (td, *J* = 7.6, 1.7 Hz, 1H), 7.47 – 7.37 (m, 1H), 7.37 – 7.28 (m, 2H), 4.91 (dd, *J* = 14.0, 5.0 Hz, 1H), 4.69 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.24 (ddt, *J* = 10.8, 7.5, 5.3 Hz, 1H), 2.64 – 2.40 (m, 2H), 1.82 – 1.59 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 173.1, 158.4 (d, *J* = 246.9 Hz), 139.6 (d, *J* = 2.5 Hz), 129.6 (d, *J* = 8.4 Hz), 127.2 (d, *J* = 3.6 Hz), 124.9 (d, *J* = 3.2 Hz), 124.6 (d, *J* = 11.5 Hz), 118.3 (d, *J* = 12.9 Hz), 116.0 (d, *J* = 21.3 Hz), 49.1, 41.2, 30.8, 21.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.63. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{14}FN_4O_2^+$ 289.1095; Found 289.1089

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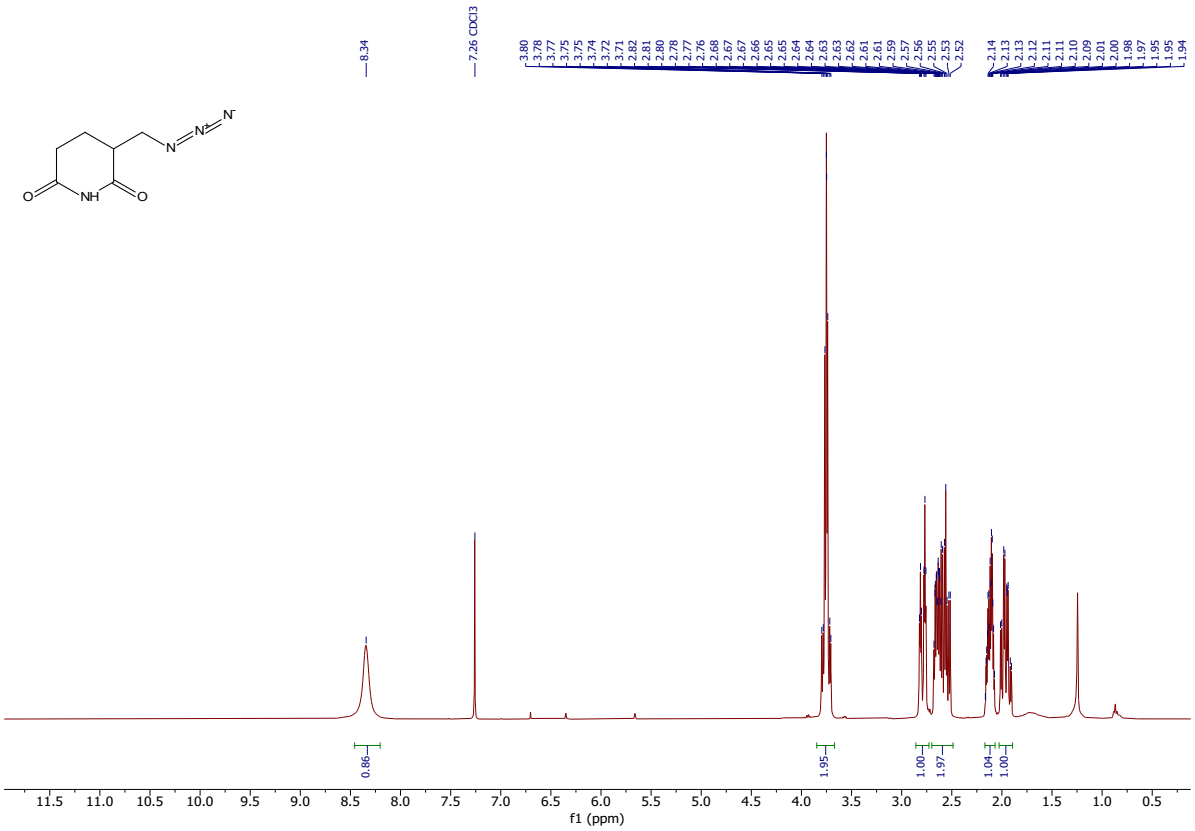
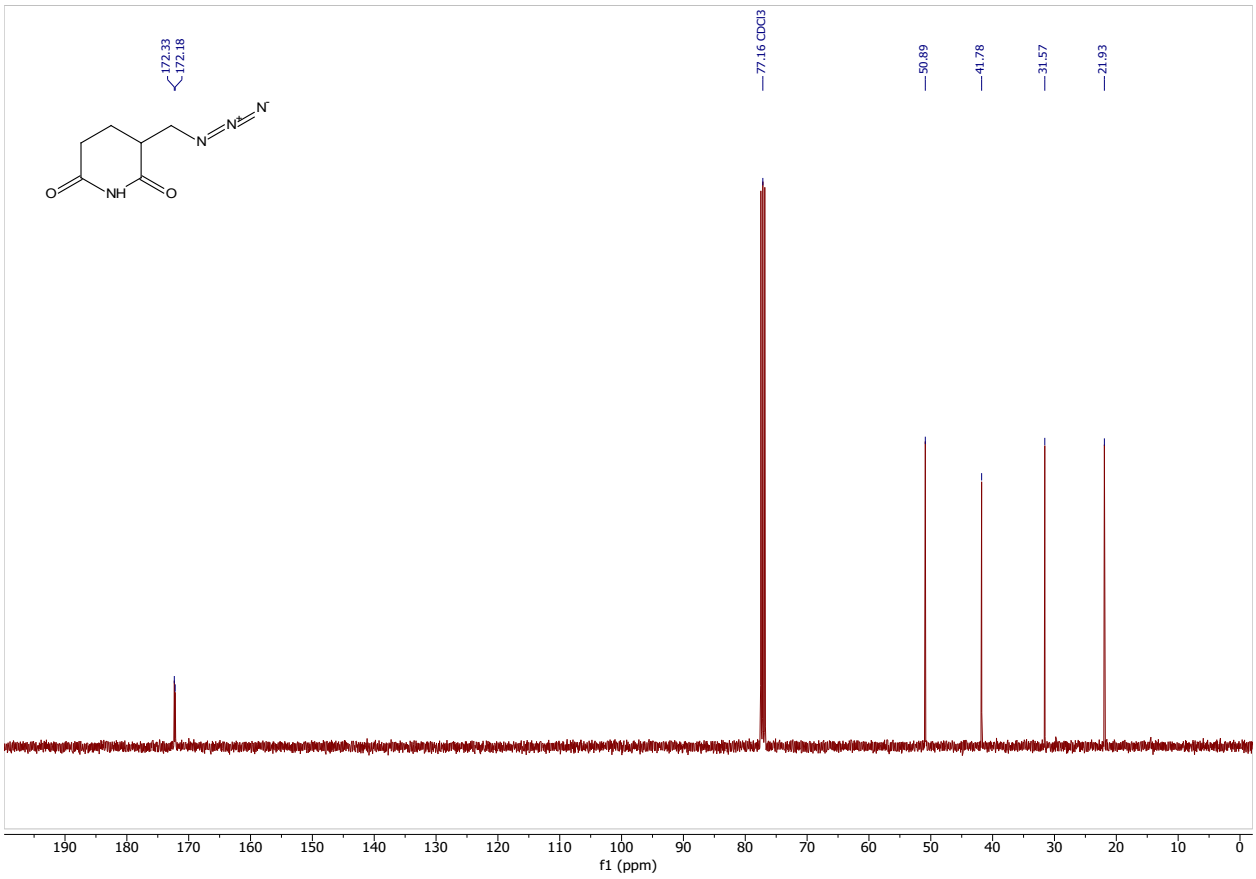
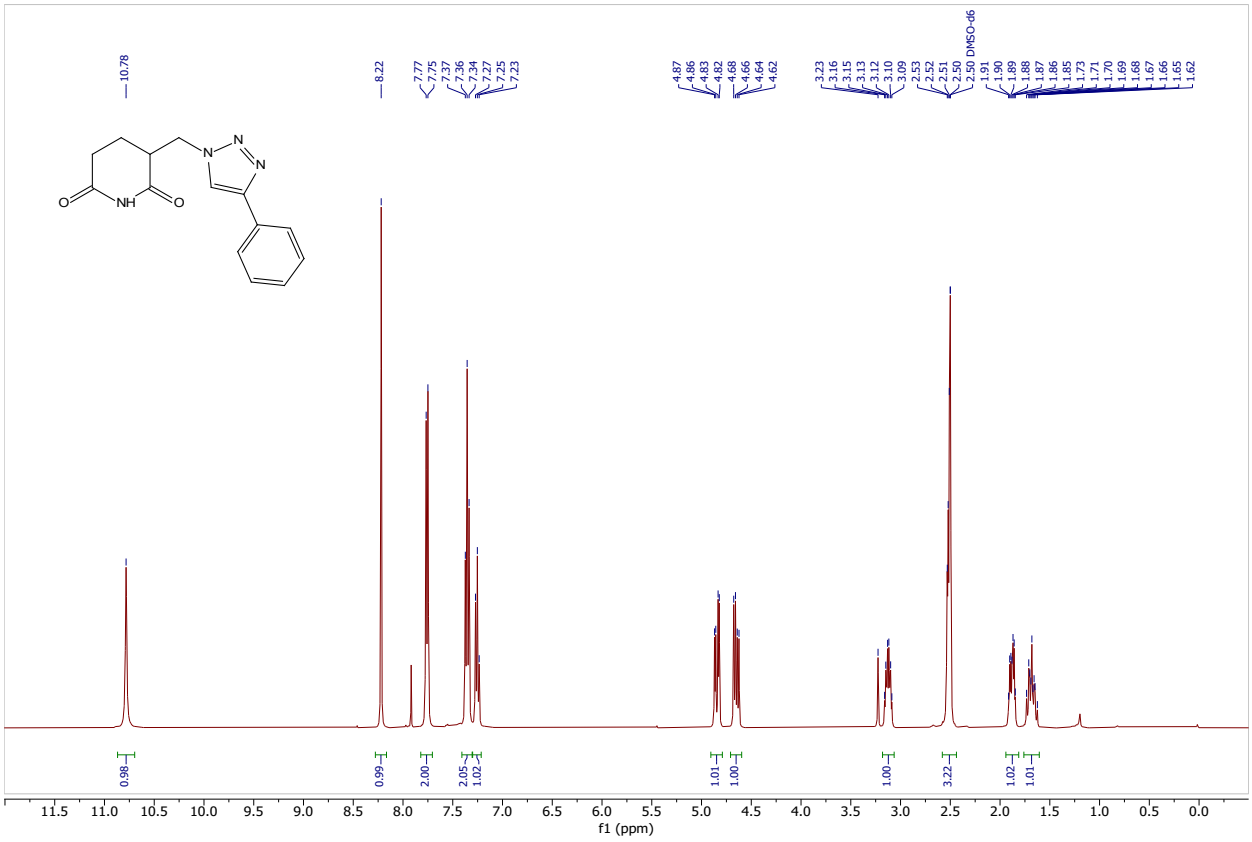
Copies of ^{1}H and ^{13}C NMR spectra

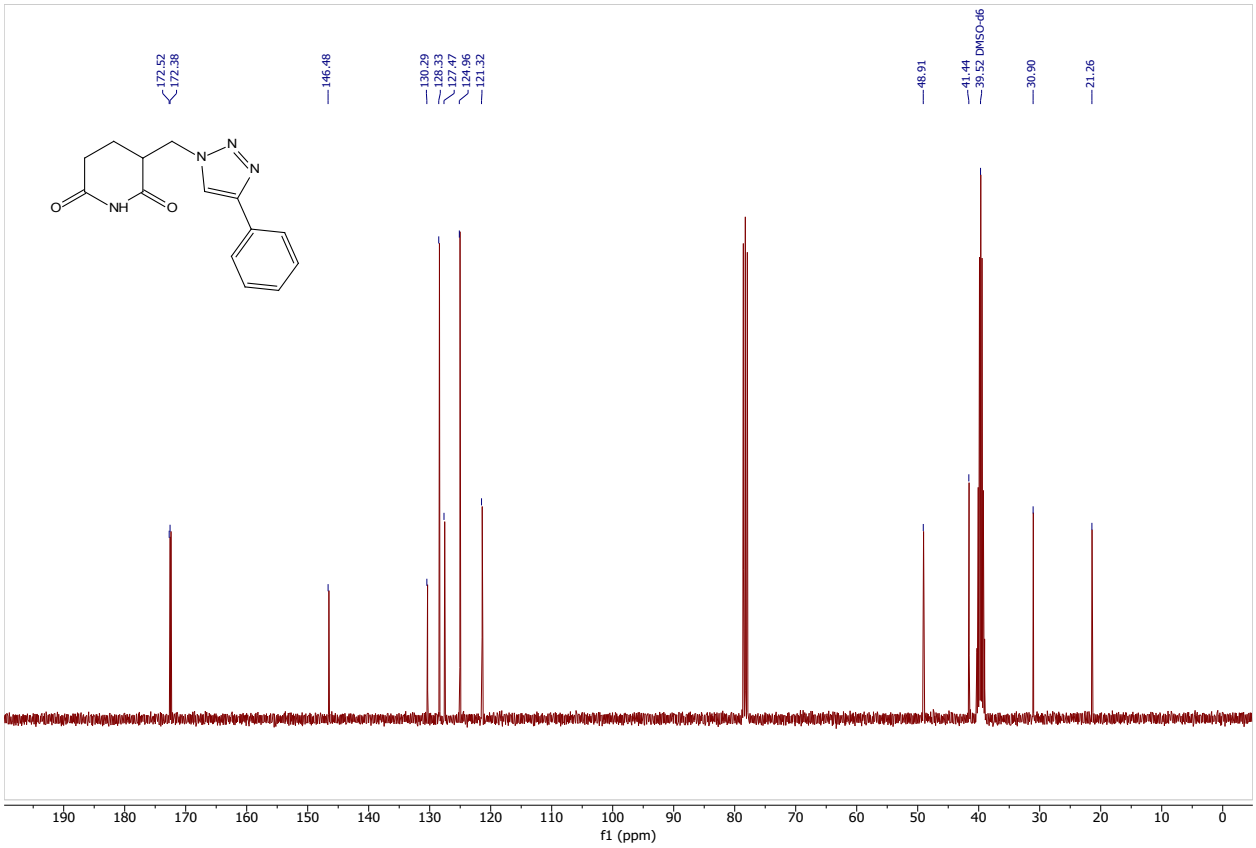
^{1}H and ^{13}C NMR spectra of compound ***1***



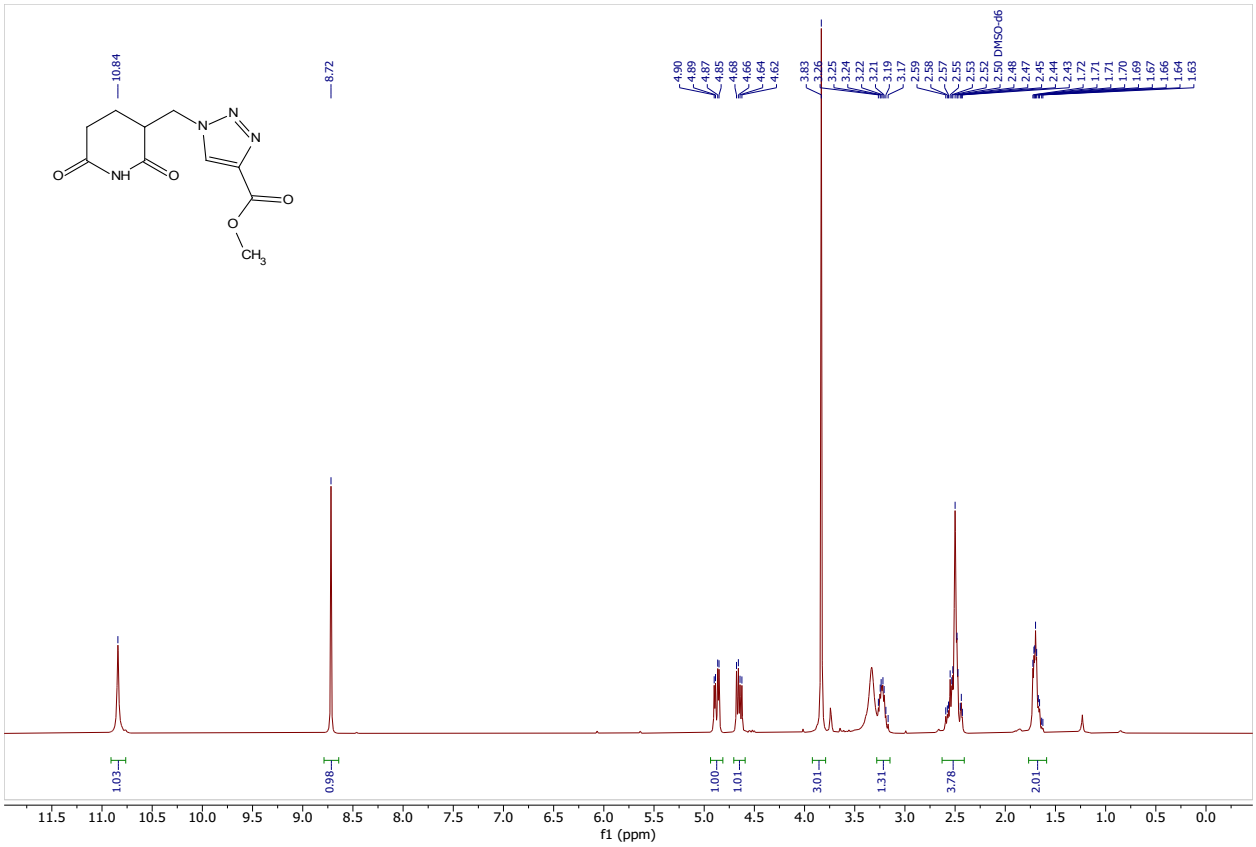


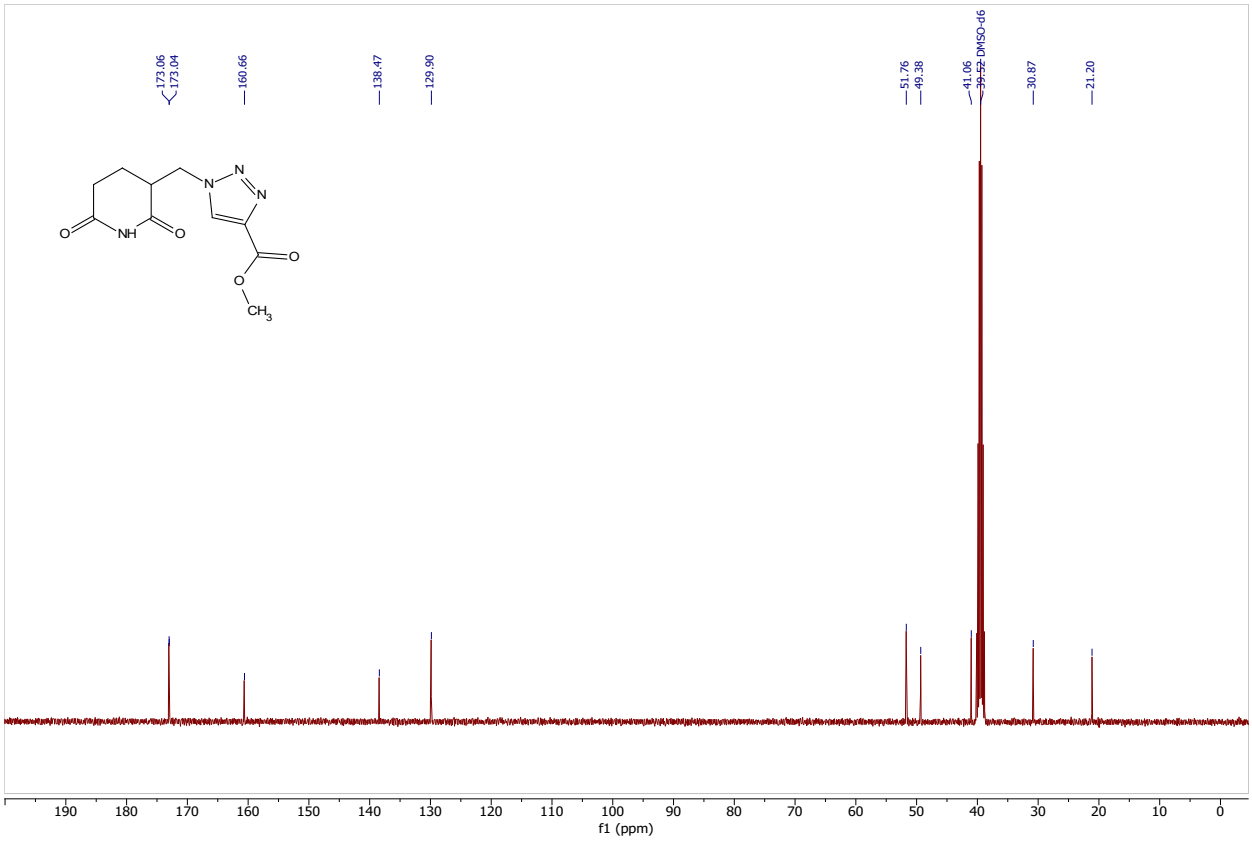
^{1}H and ^{13}C NMR spectra of compound ***3a***



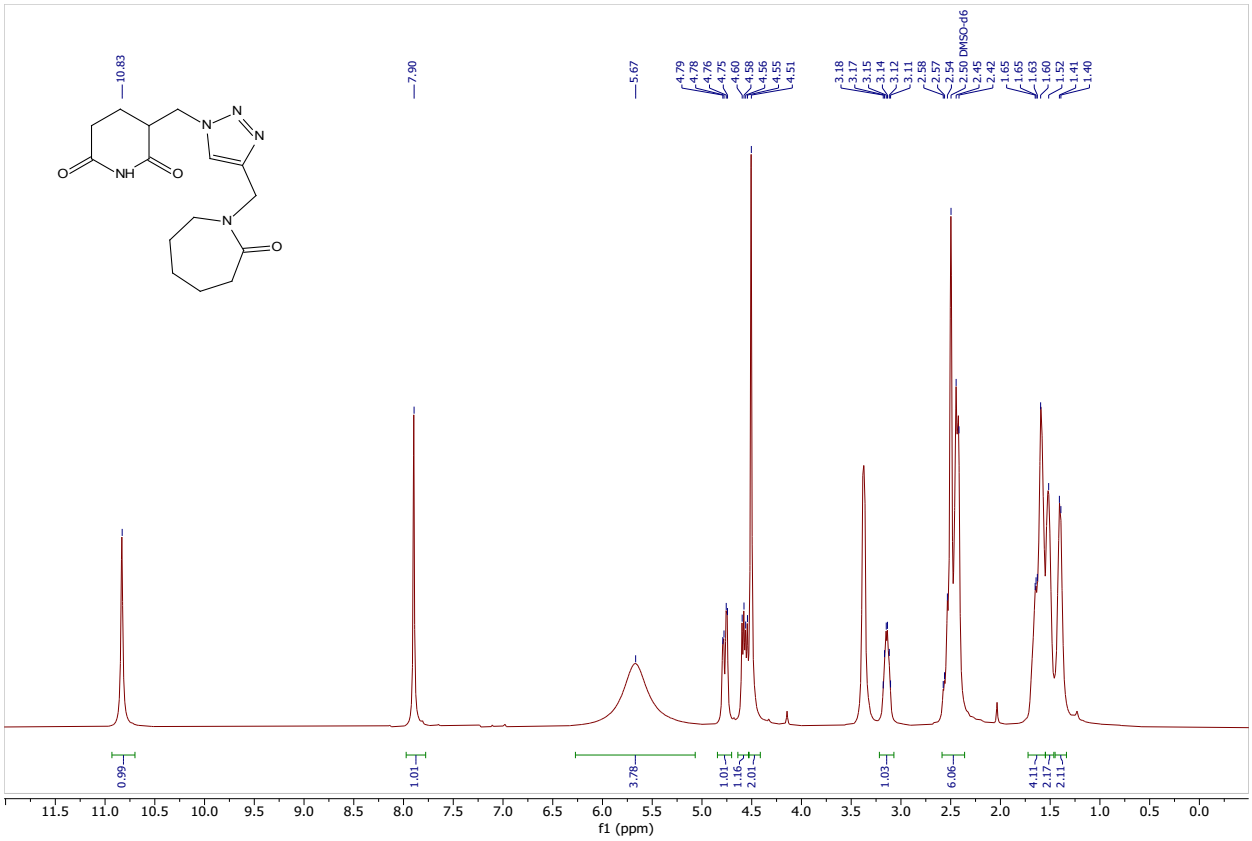


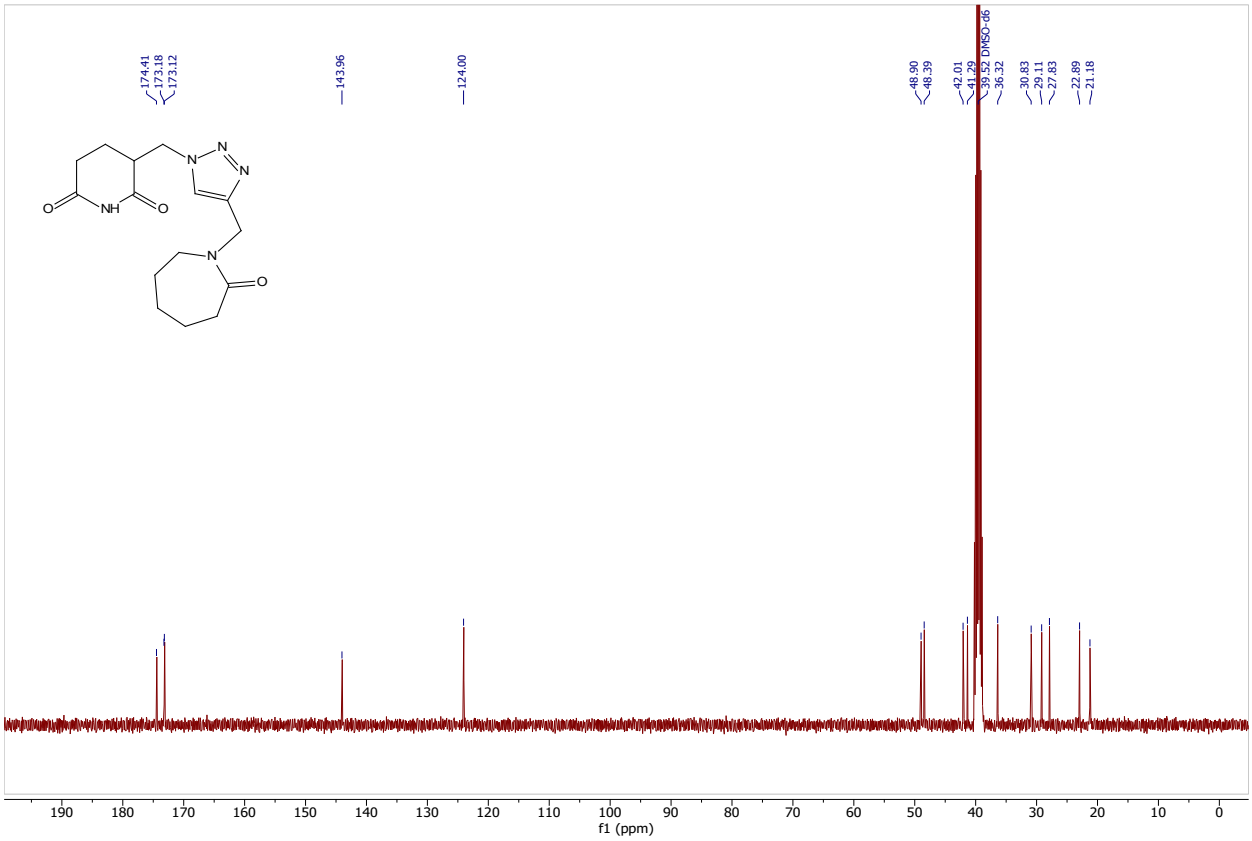
^{1}H and ^{13}C NMR spectra of compound ***3b***



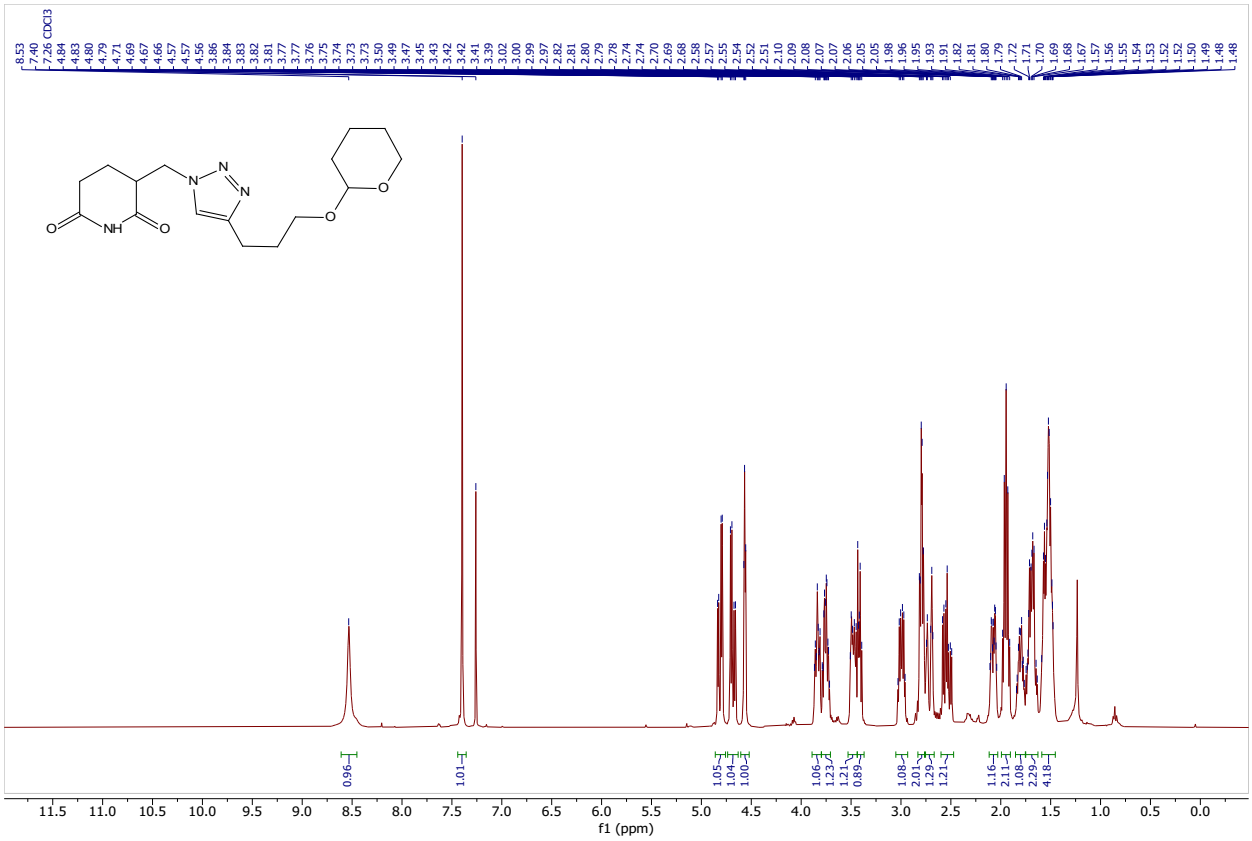


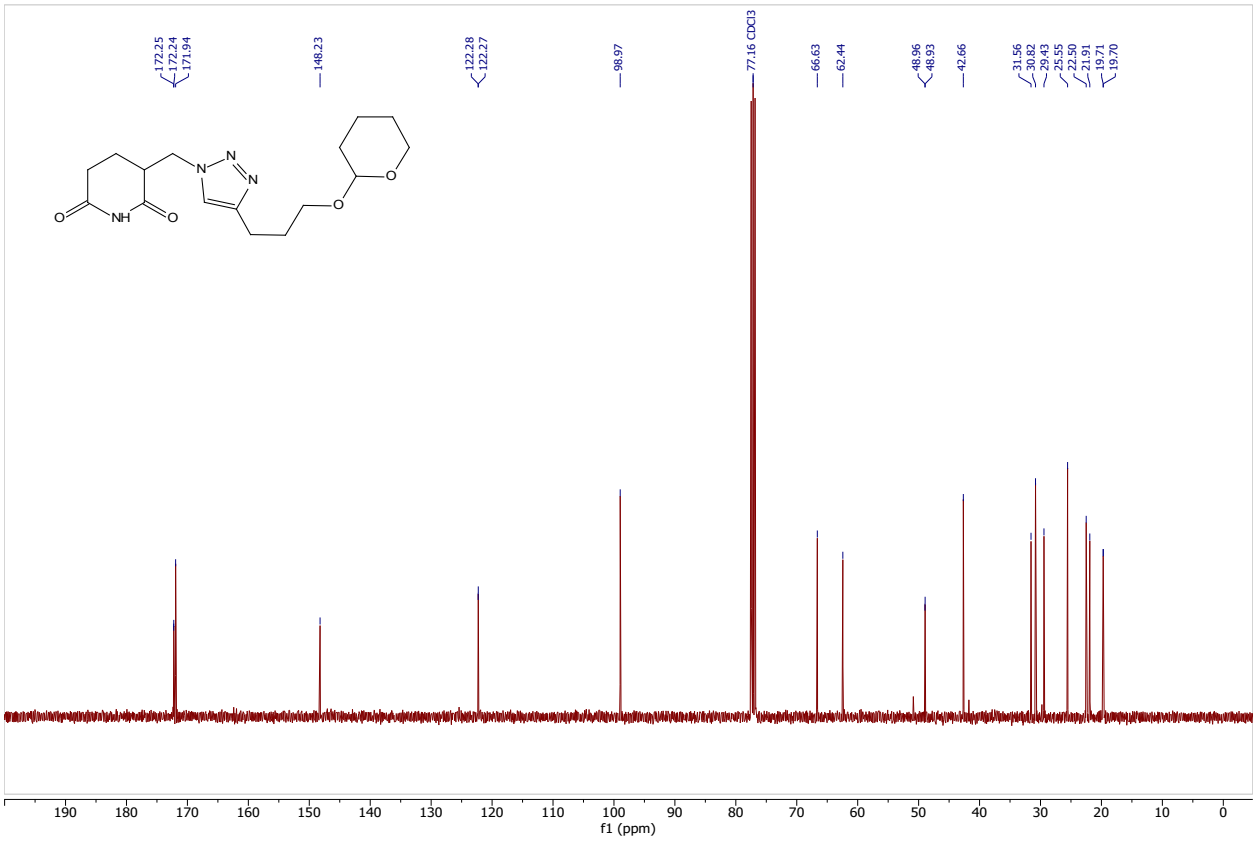
^{1}H and ^{13}C NMR spectra of compound ***3c***



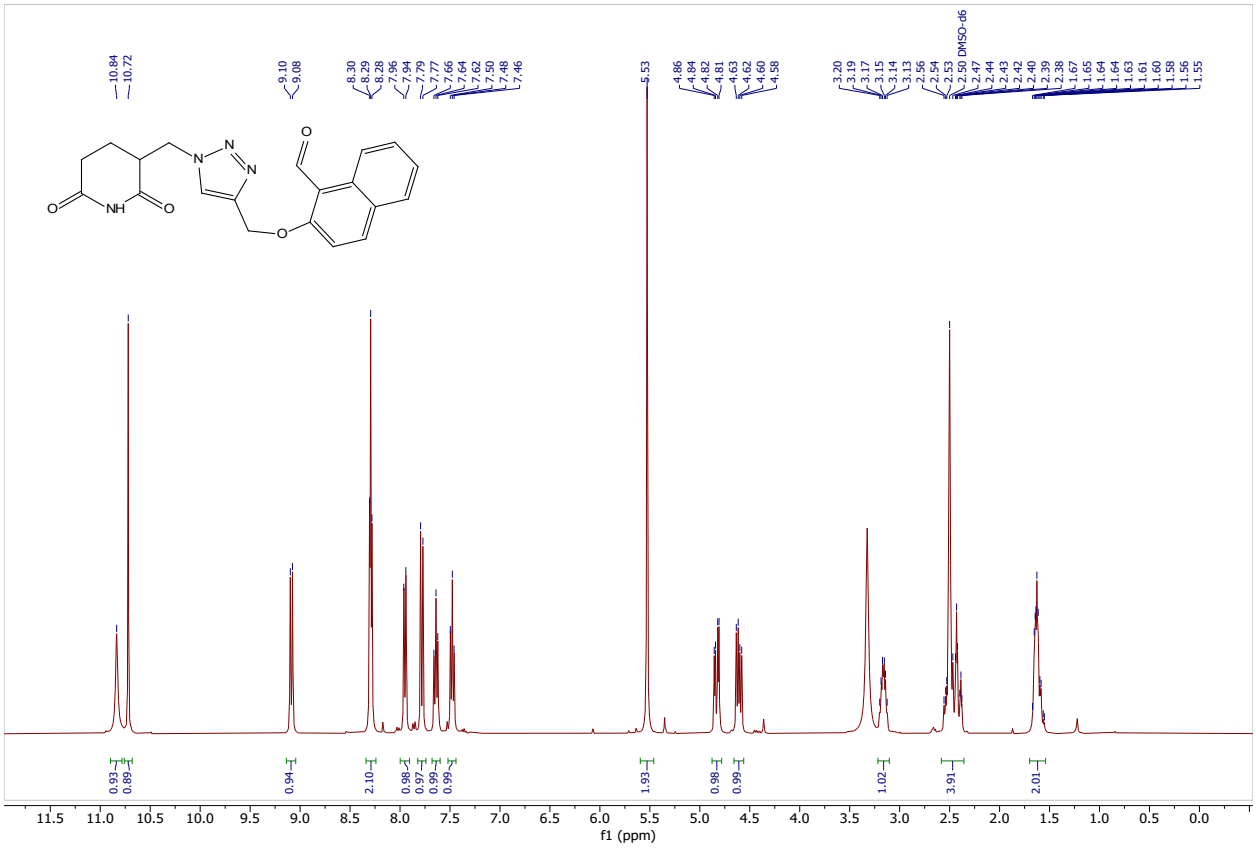


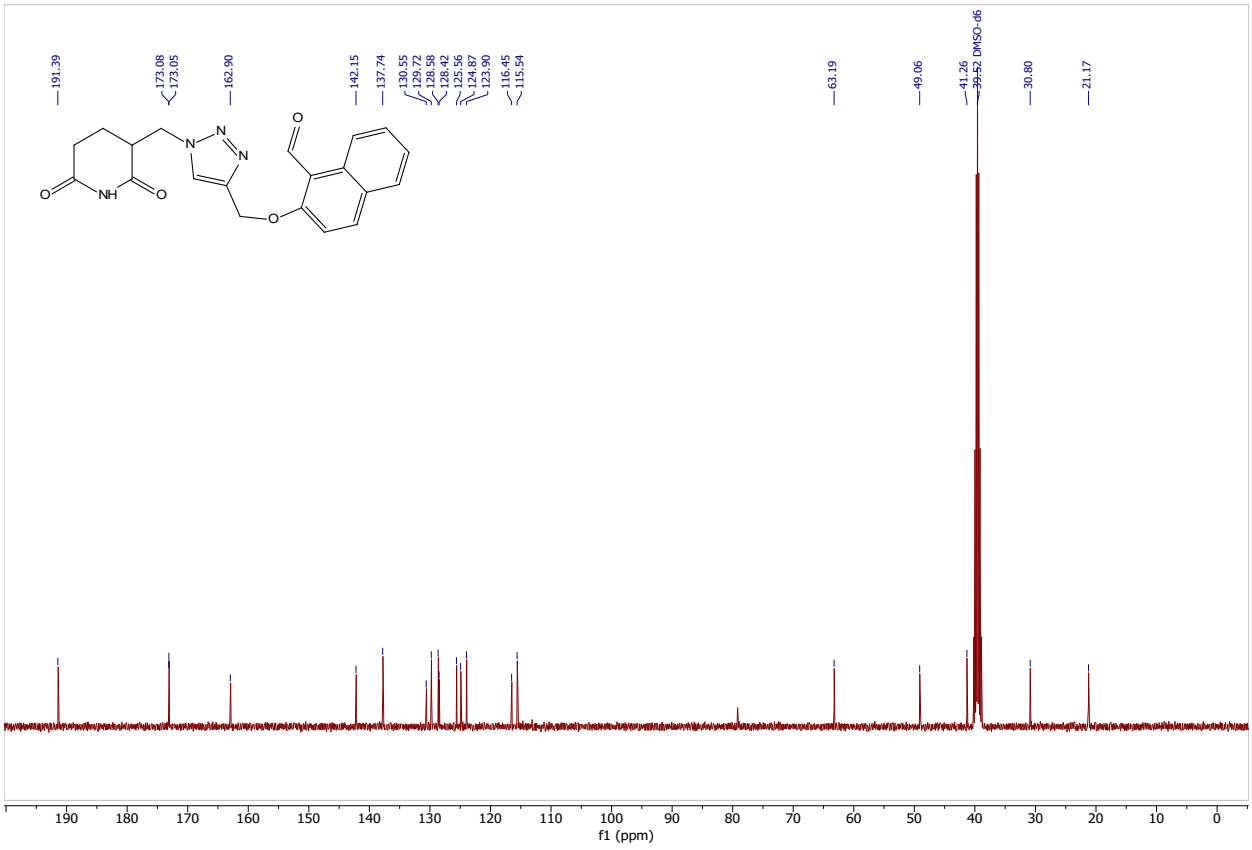
^{1}H and ^{13}C NMR spectra of compound ***3d***



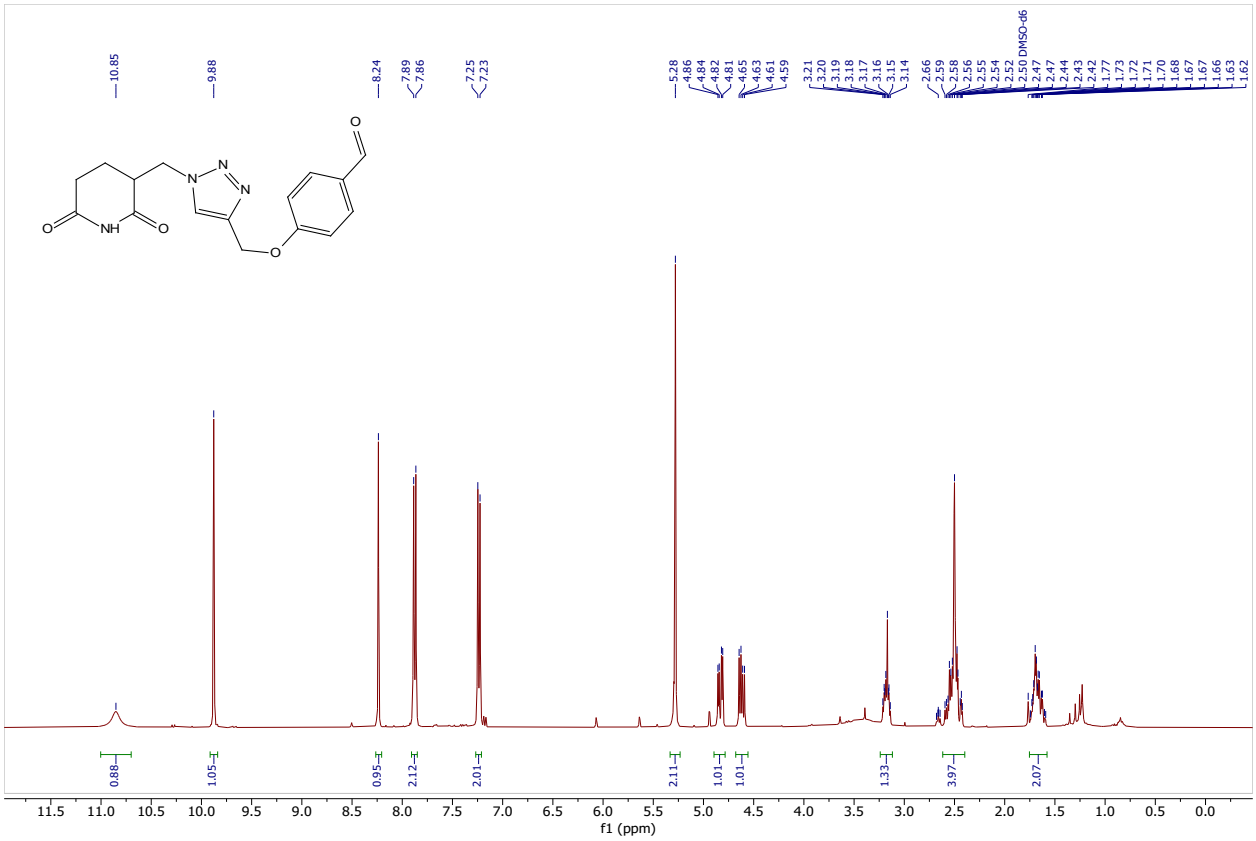


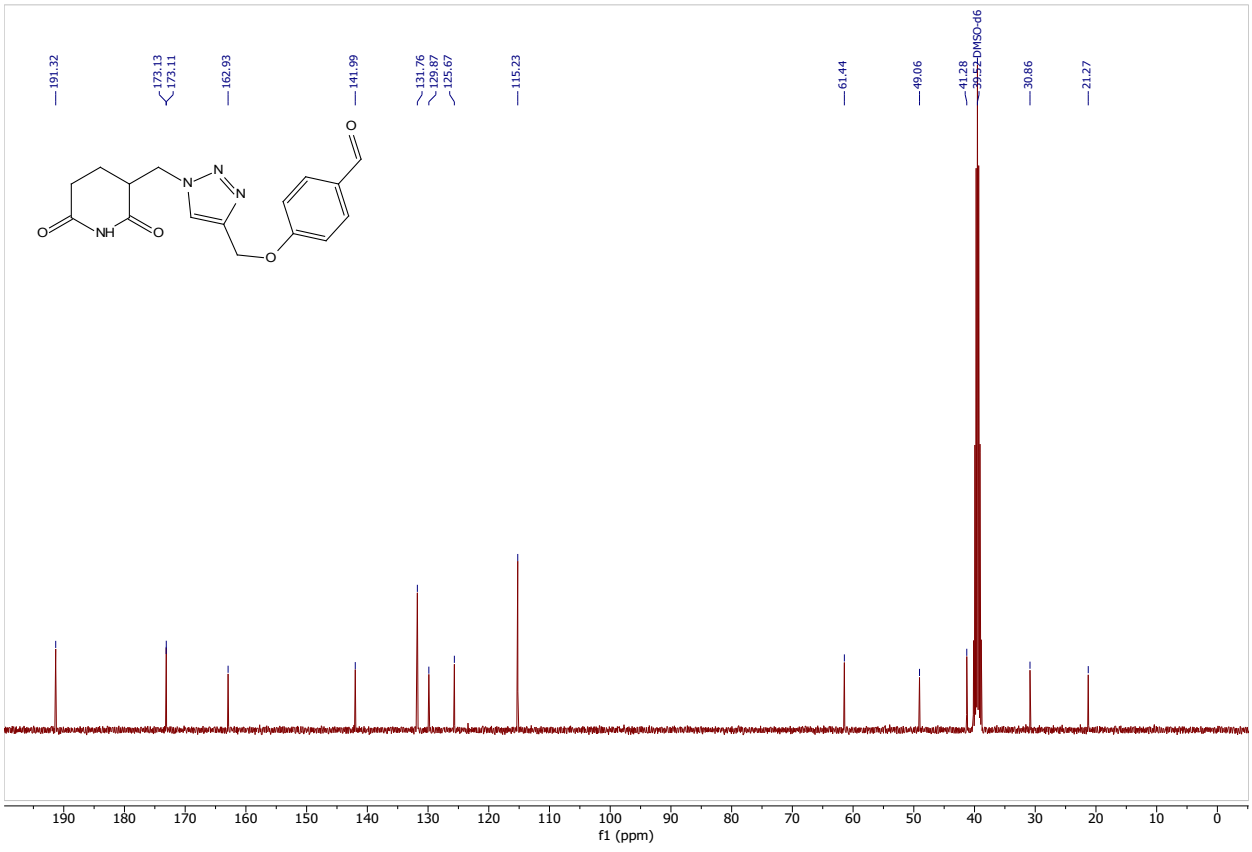
^{1}H and ^{13}C NMR spectra of compound ***3e***



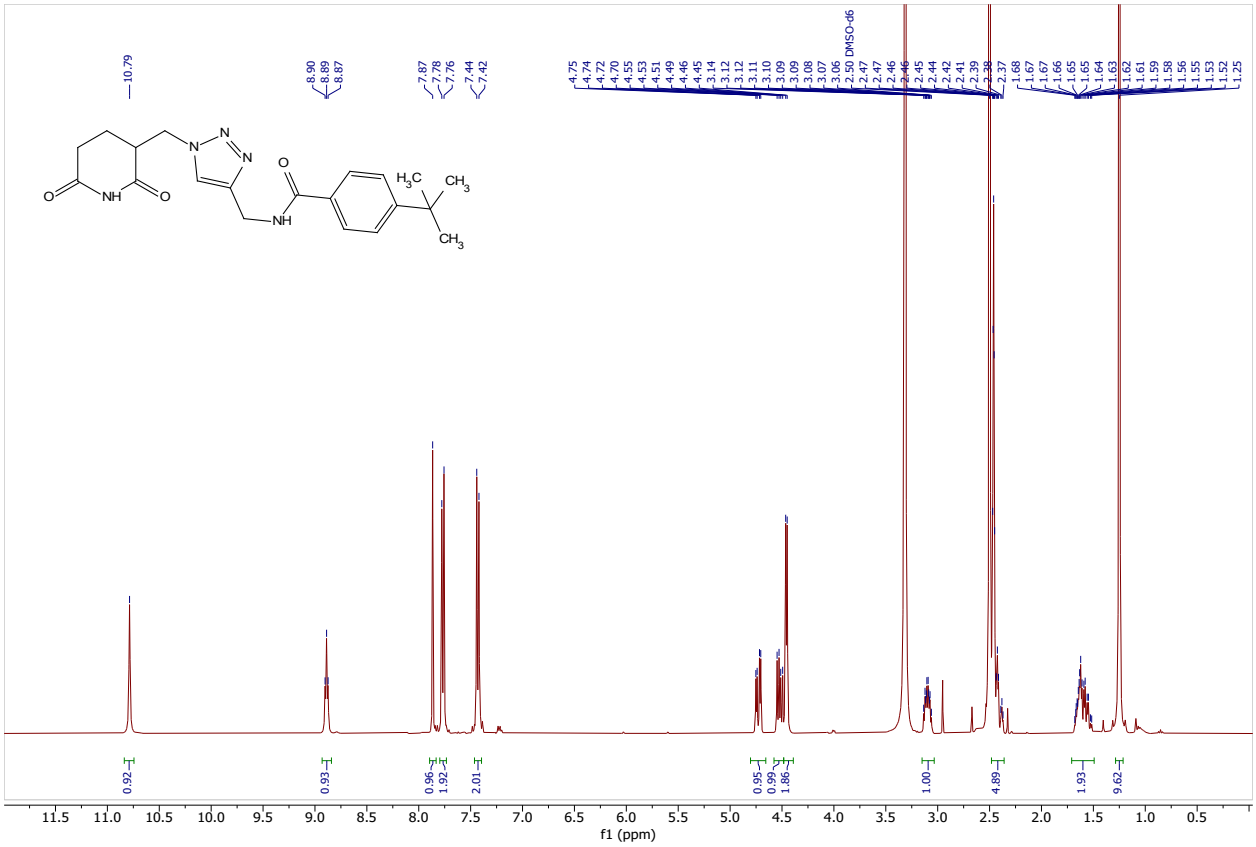


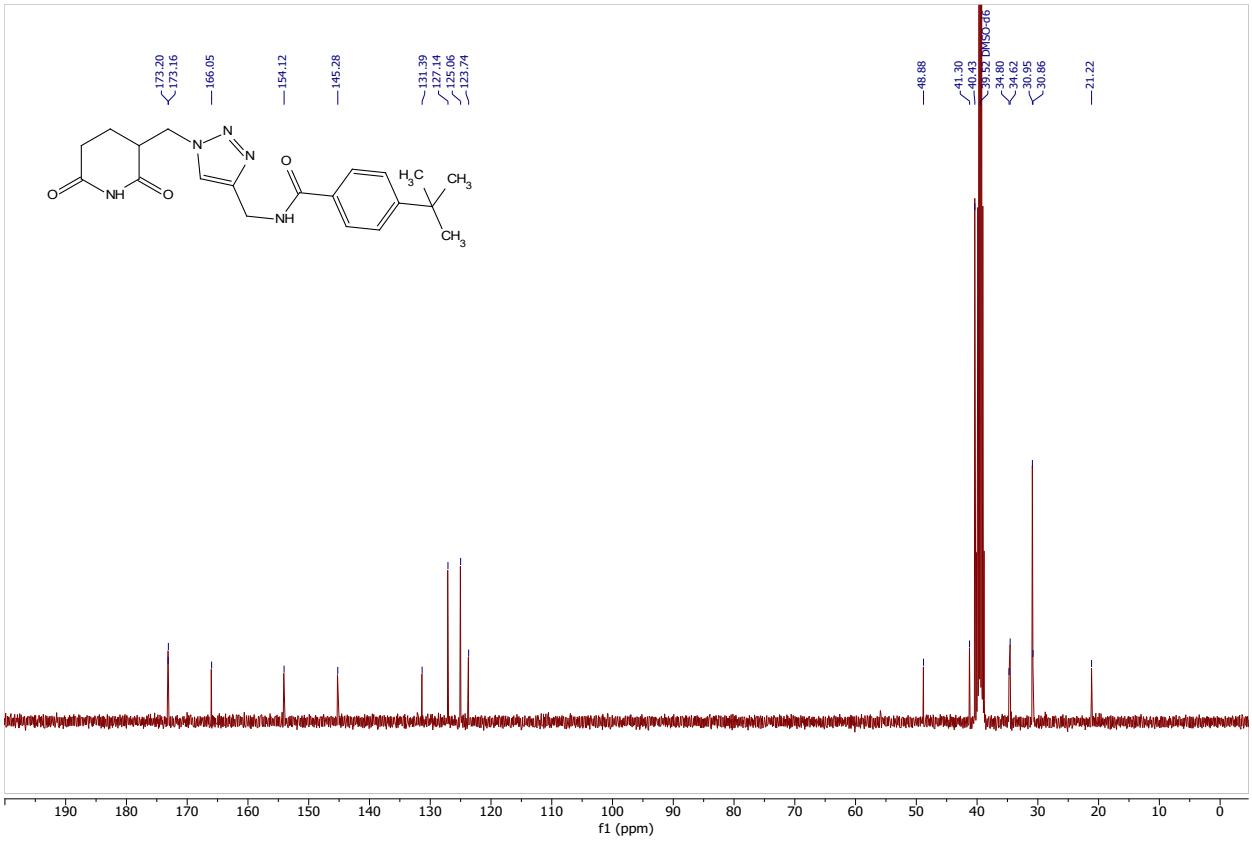
^{1}H and ^{13}C NMR spectra of compound ***3f***



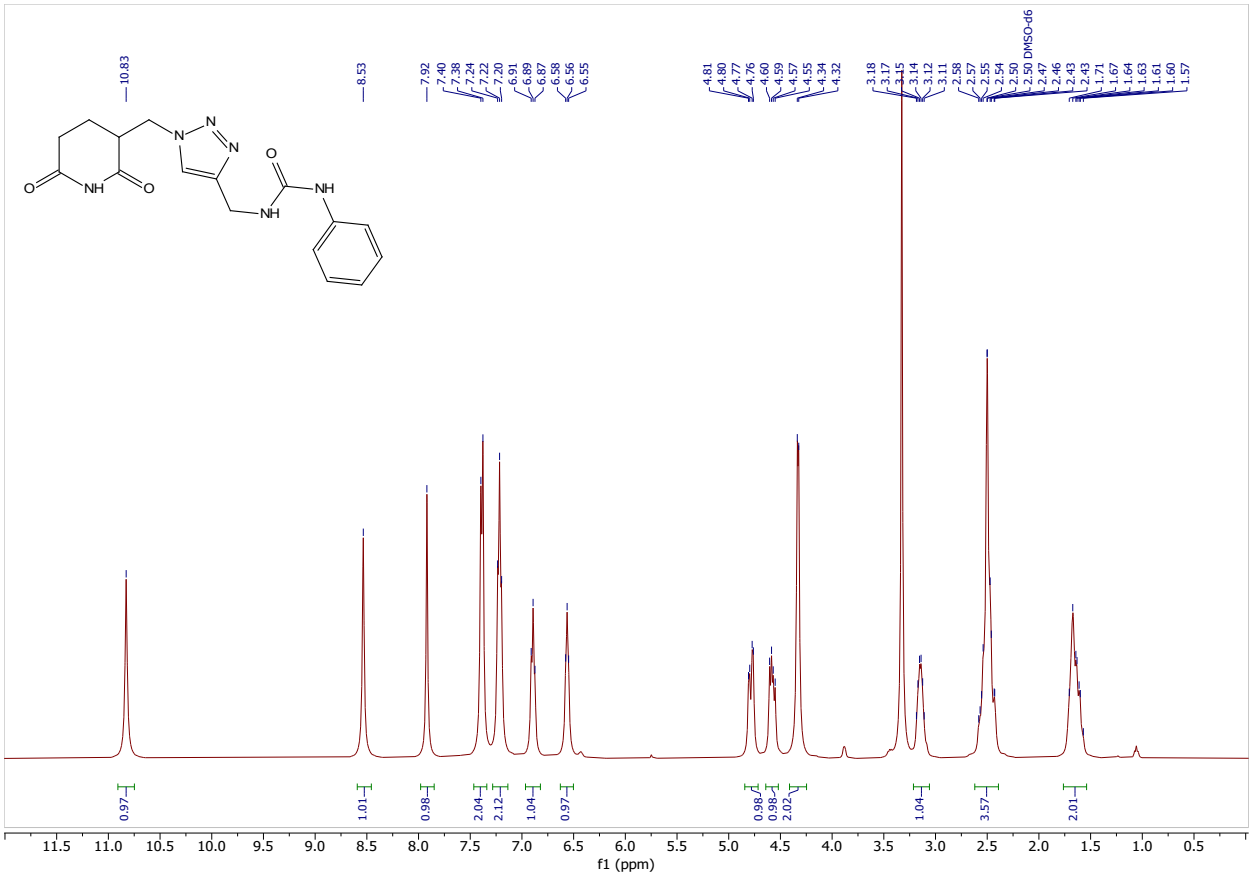


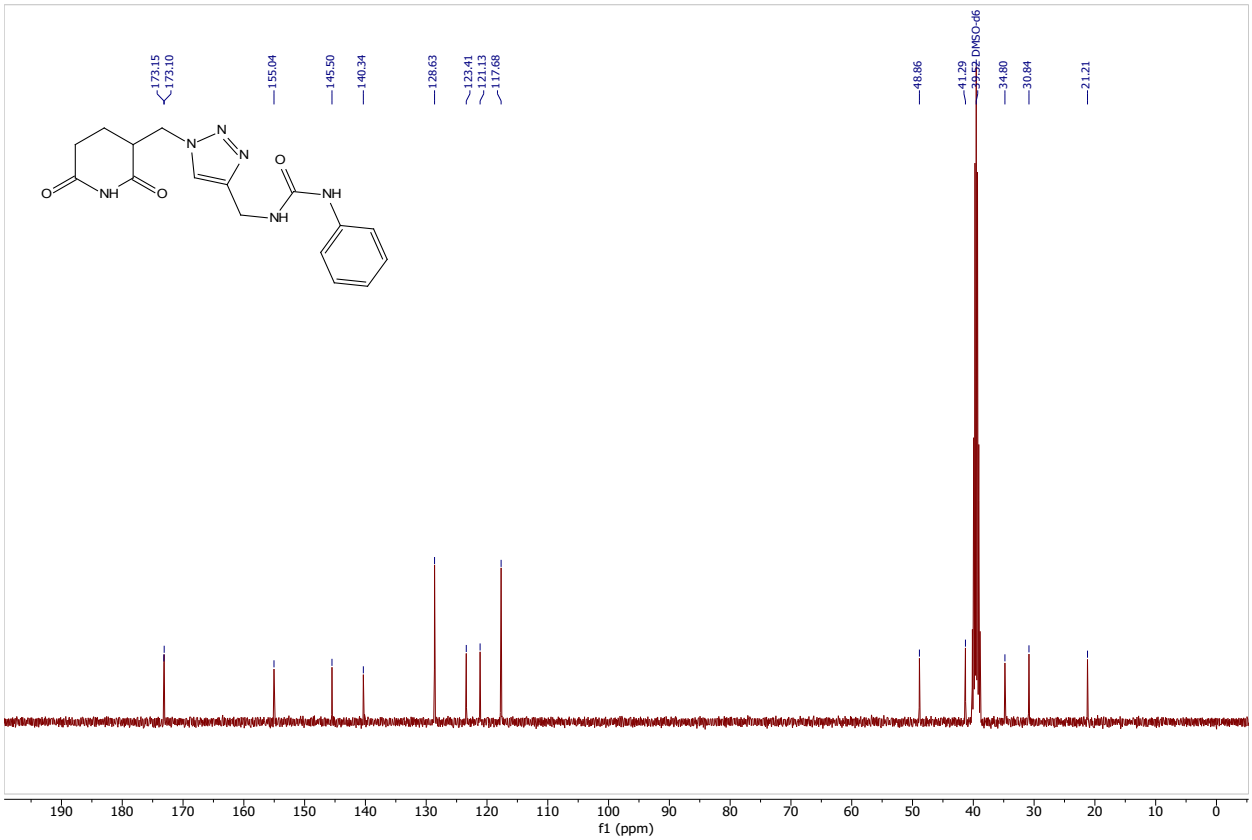
^{1}H and ^{13}C NMR spectra of compound ***3g***



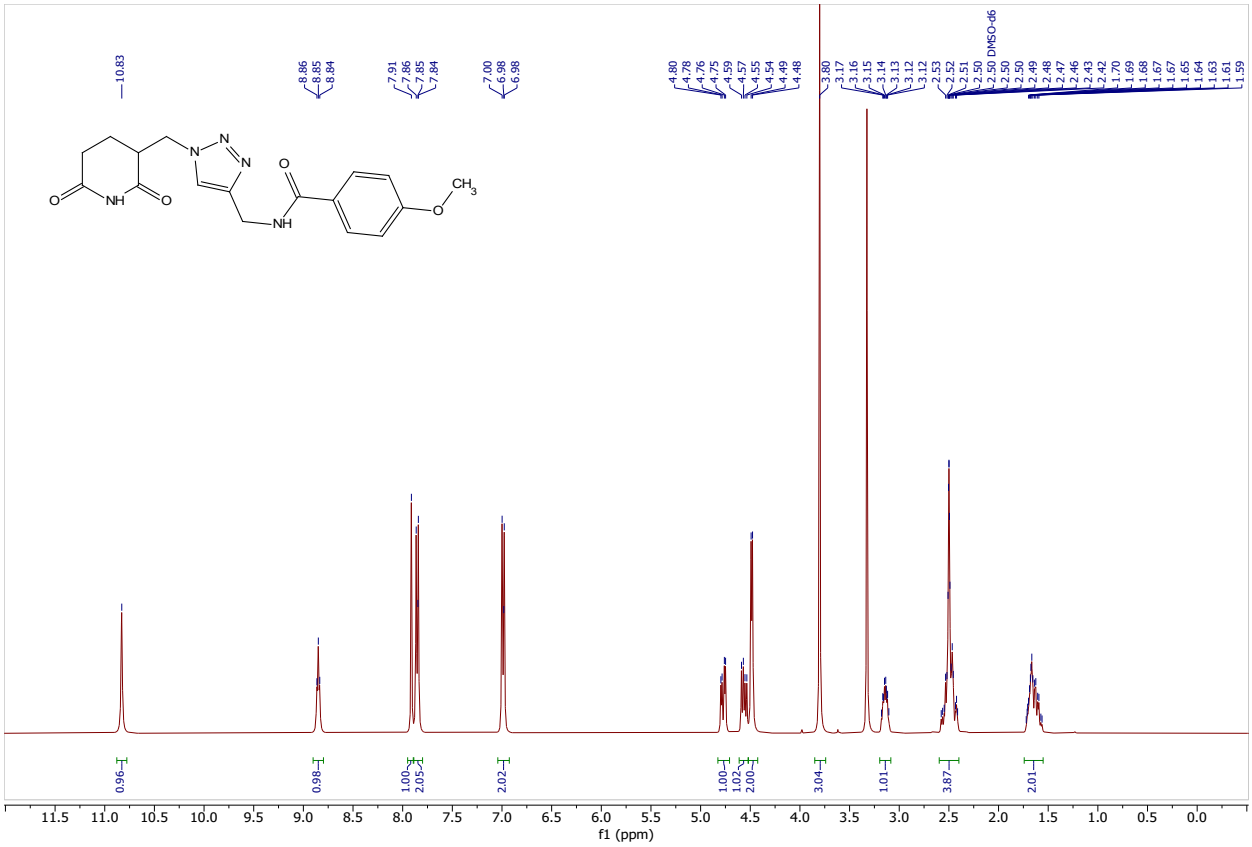


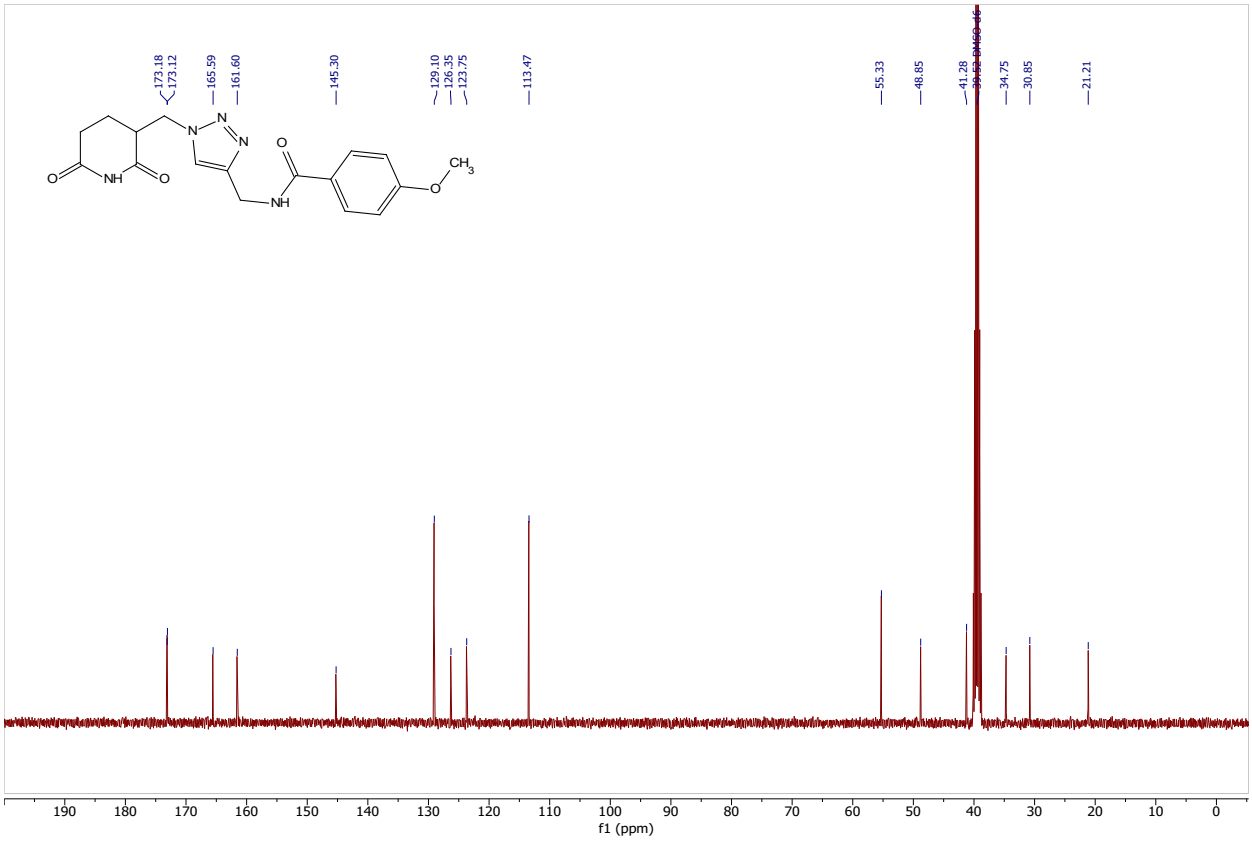
^{1}H and ^{13}C NMR spectra of compound ***3h***



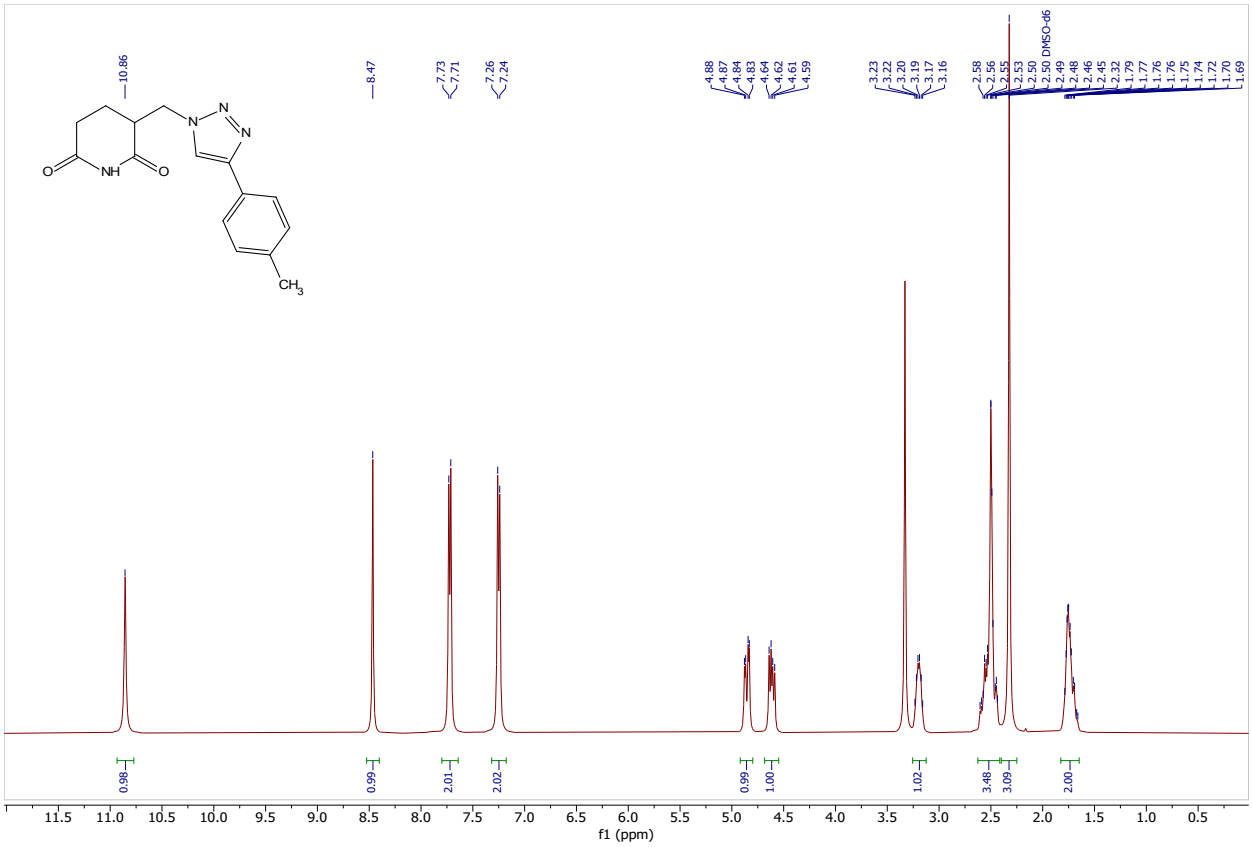


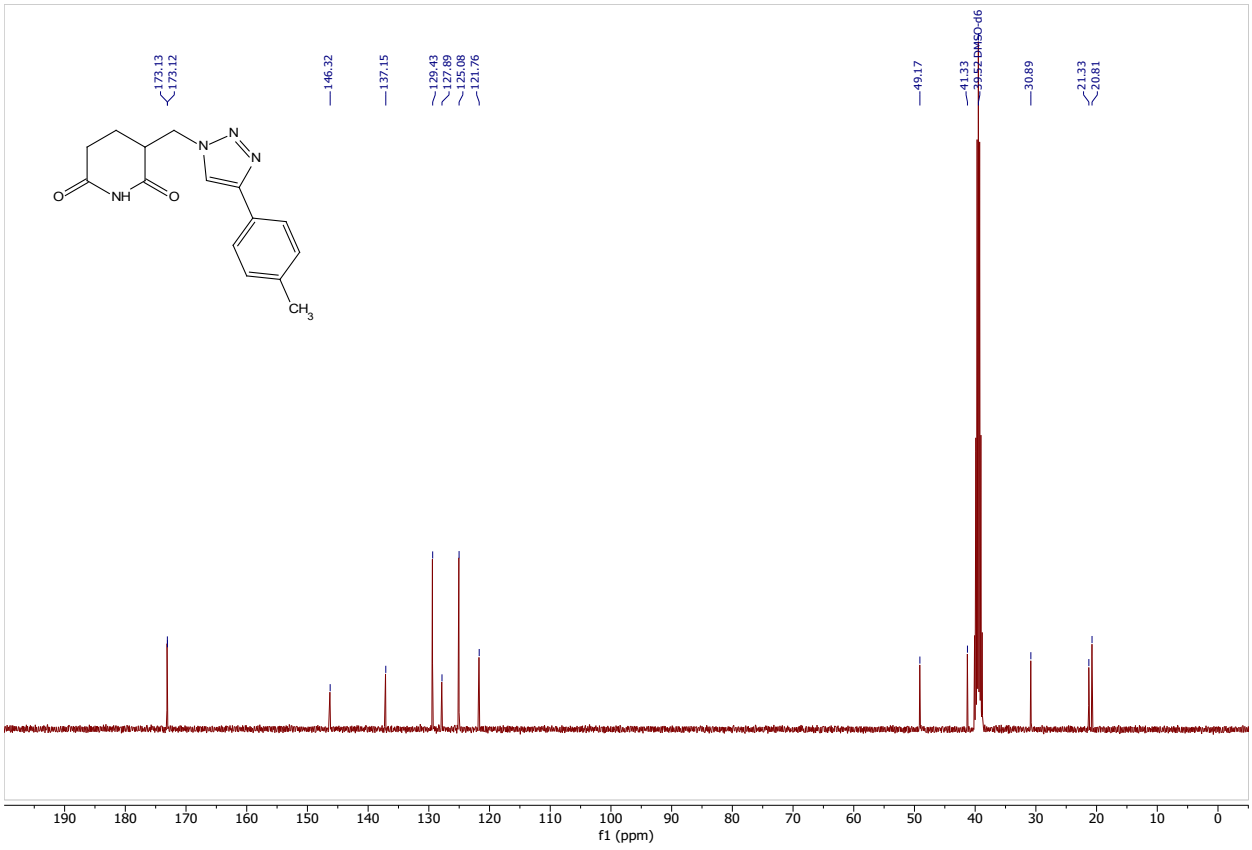
^{1}H and ^{13}C NMR spectra of compound ***3i***



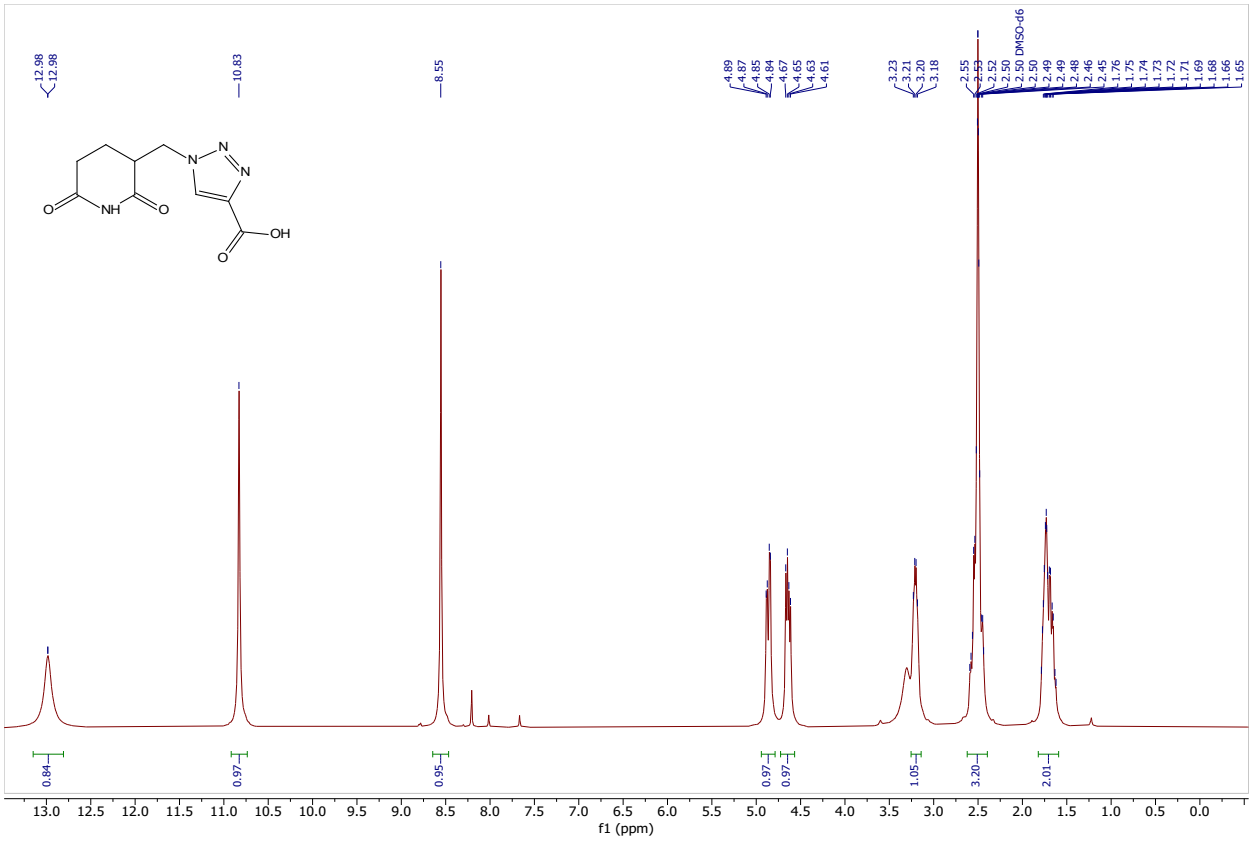


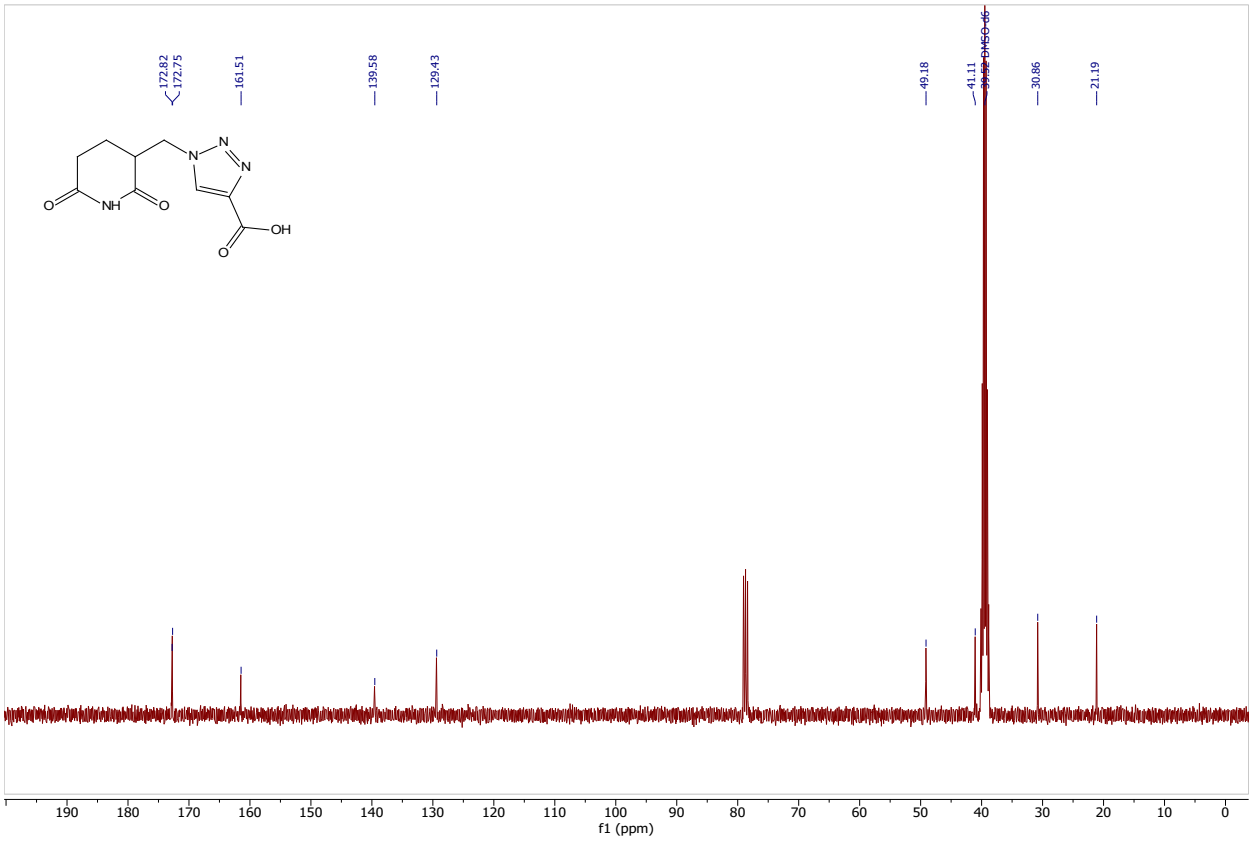
^{1}H and ^{13}C NMR spectra of compound ***3j***



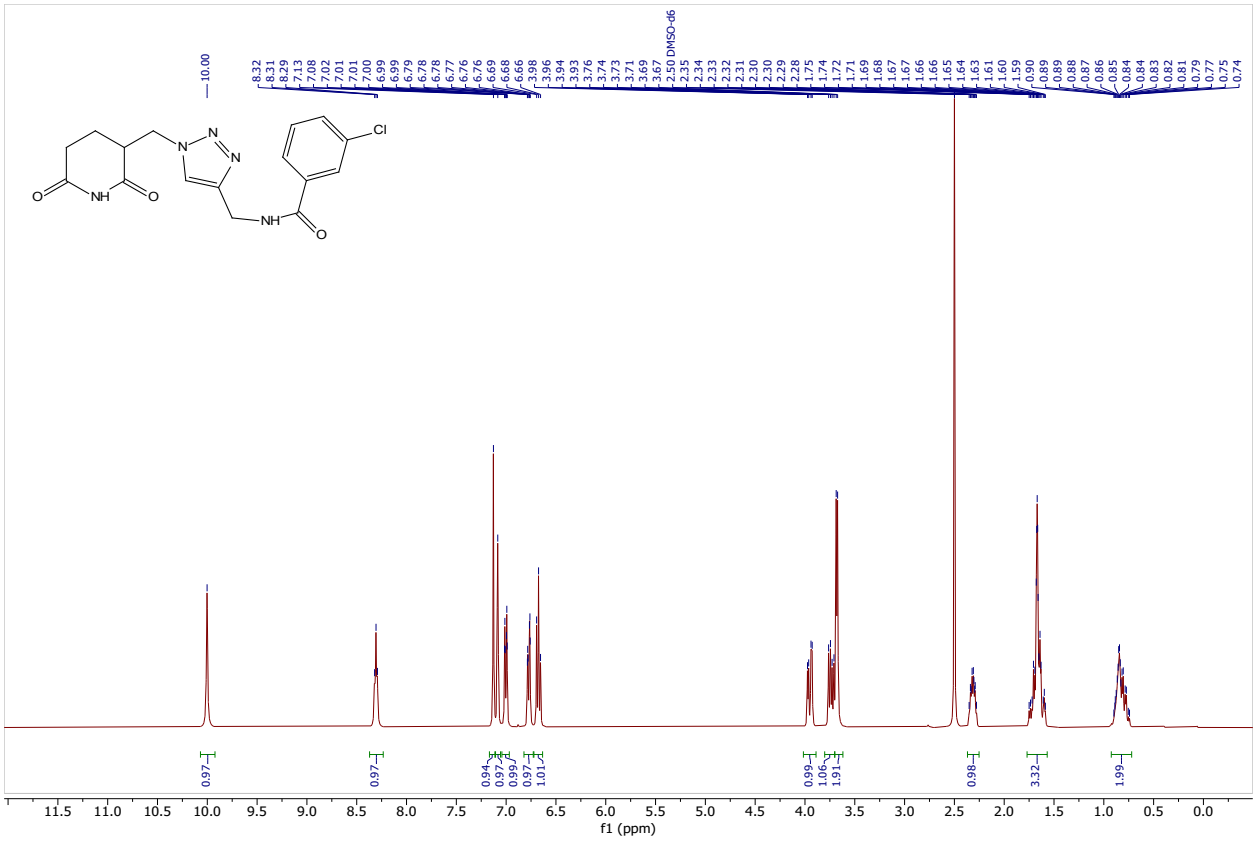


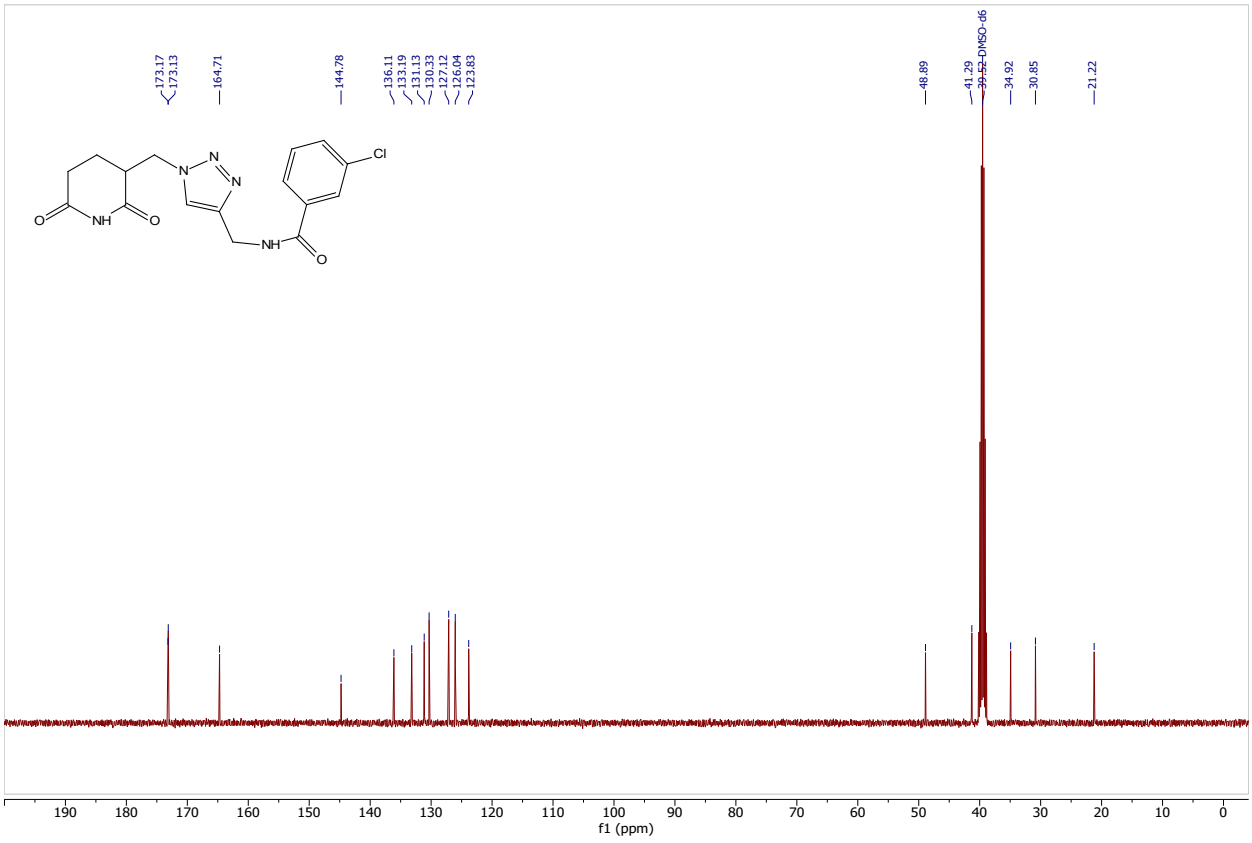
^{1}H and ^{13}C NMR spectra of compound ***3k***



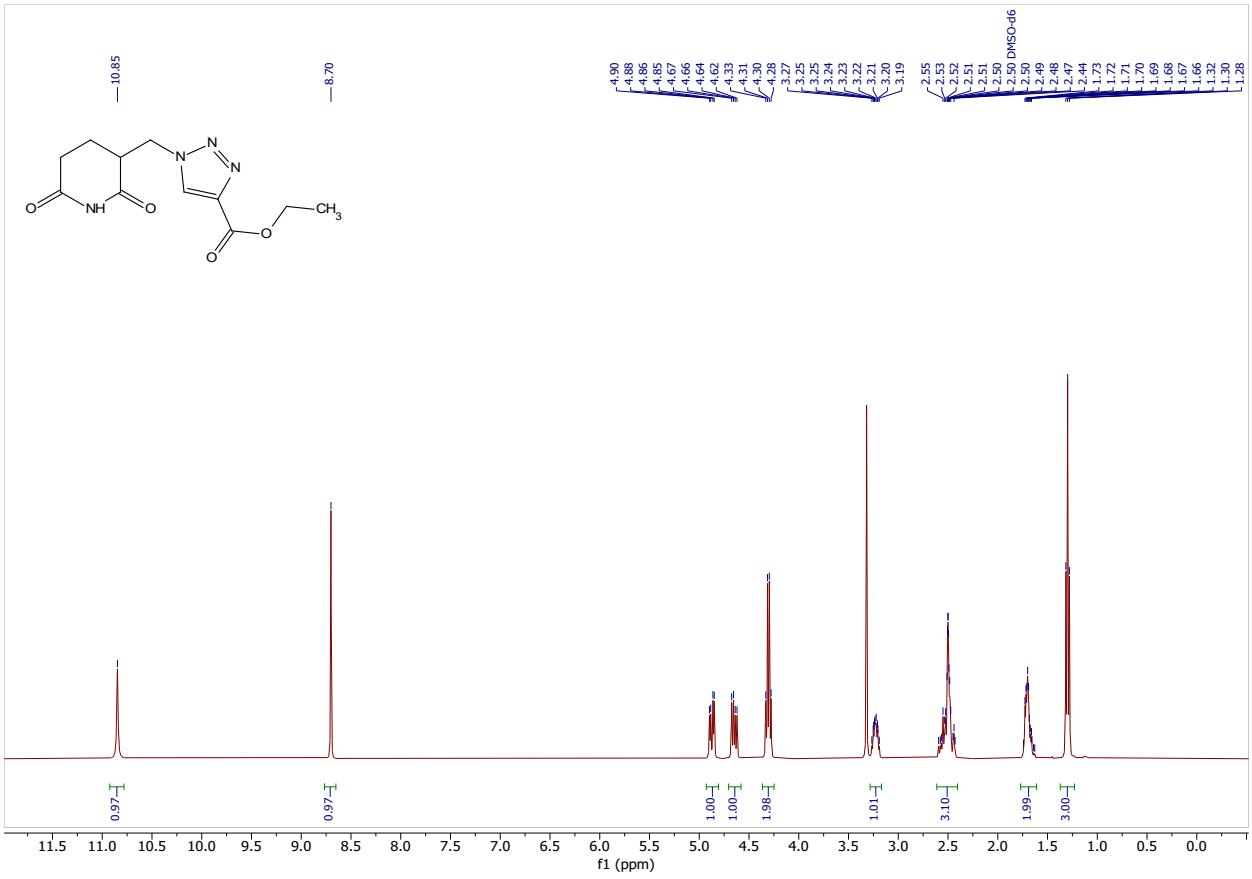


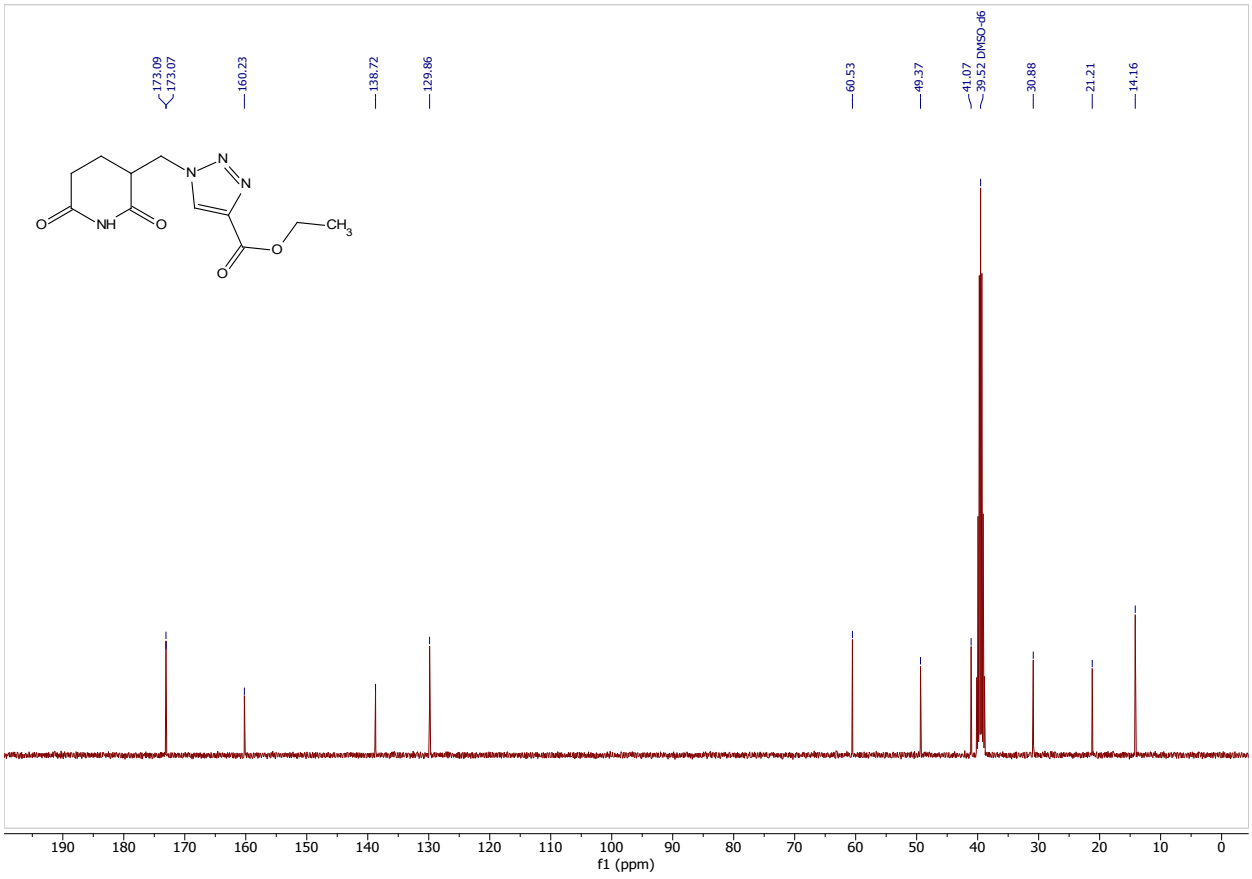
^{1}H and ^{13}C NMR spectra of compound ***3l***



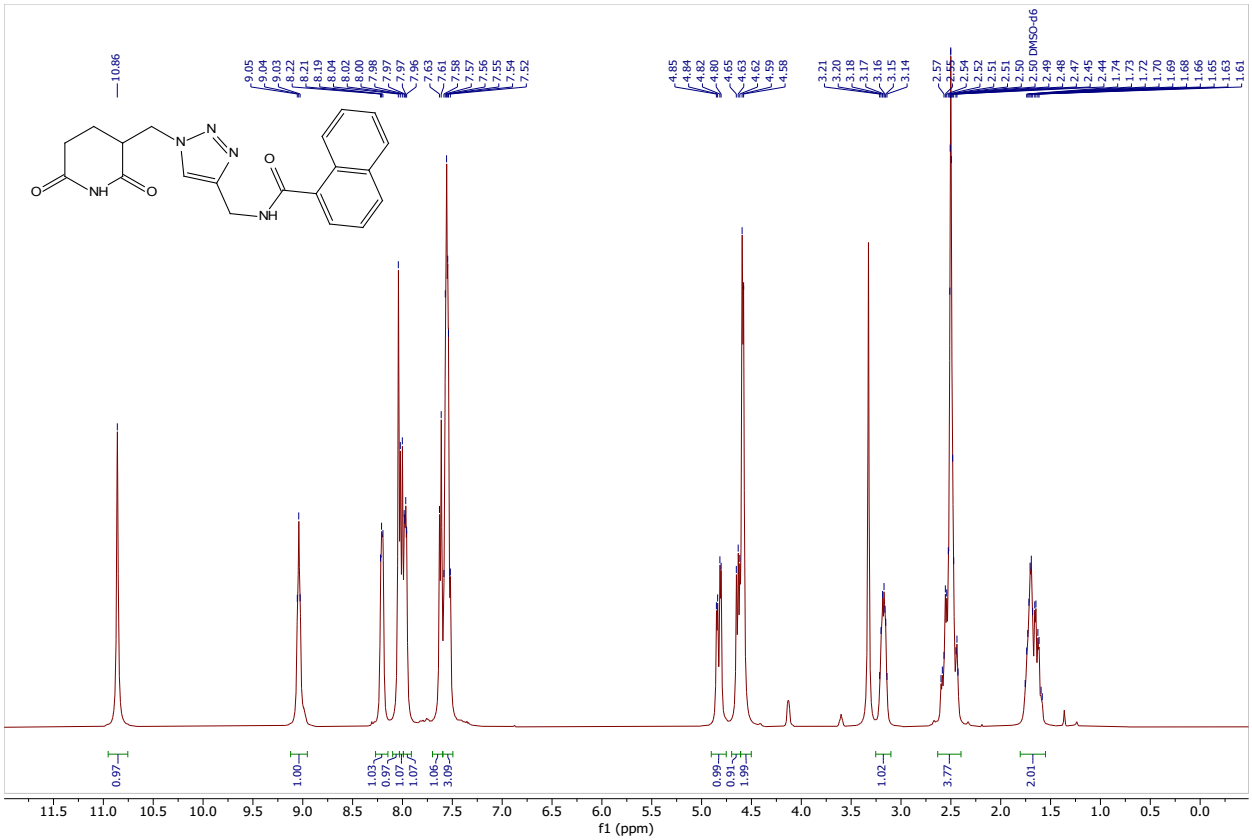


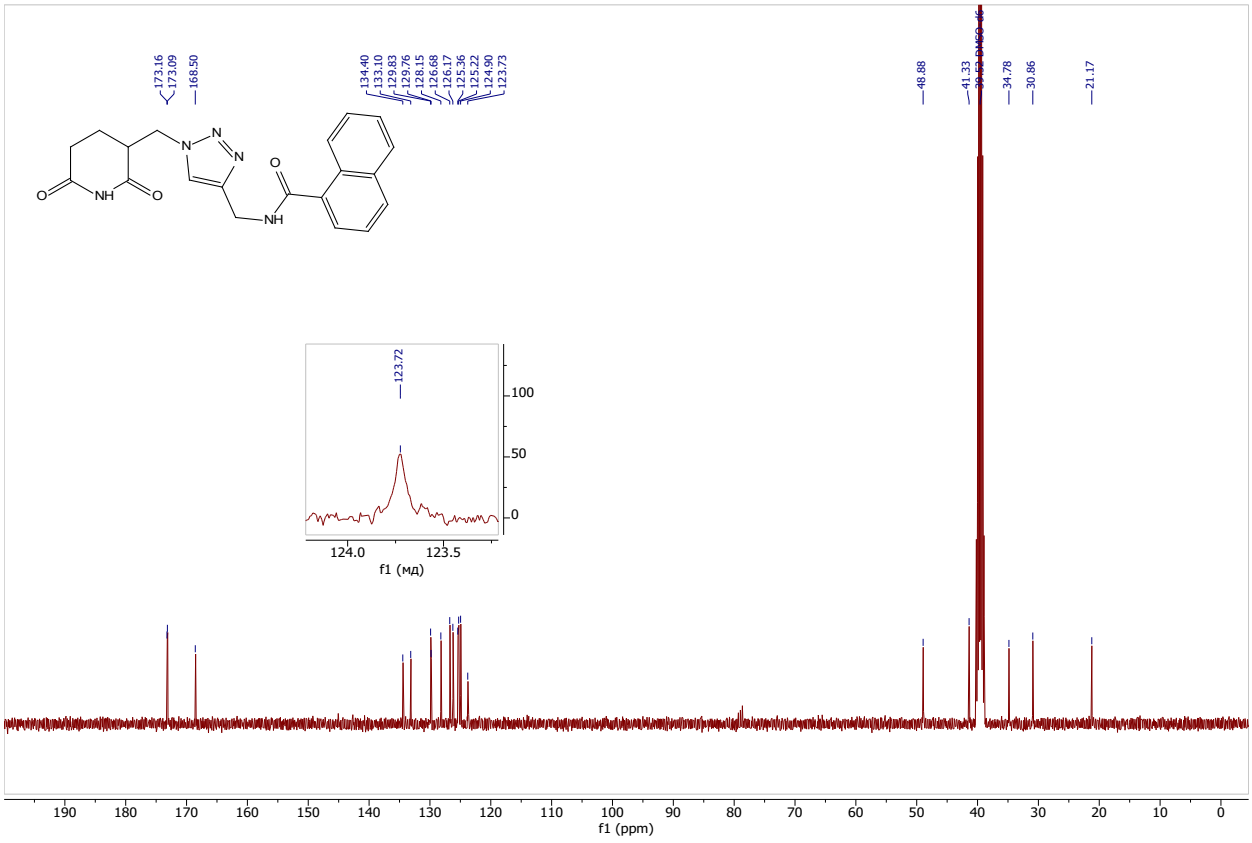
^{1}H and ^{13}C NMR spectra of compound ***3m***



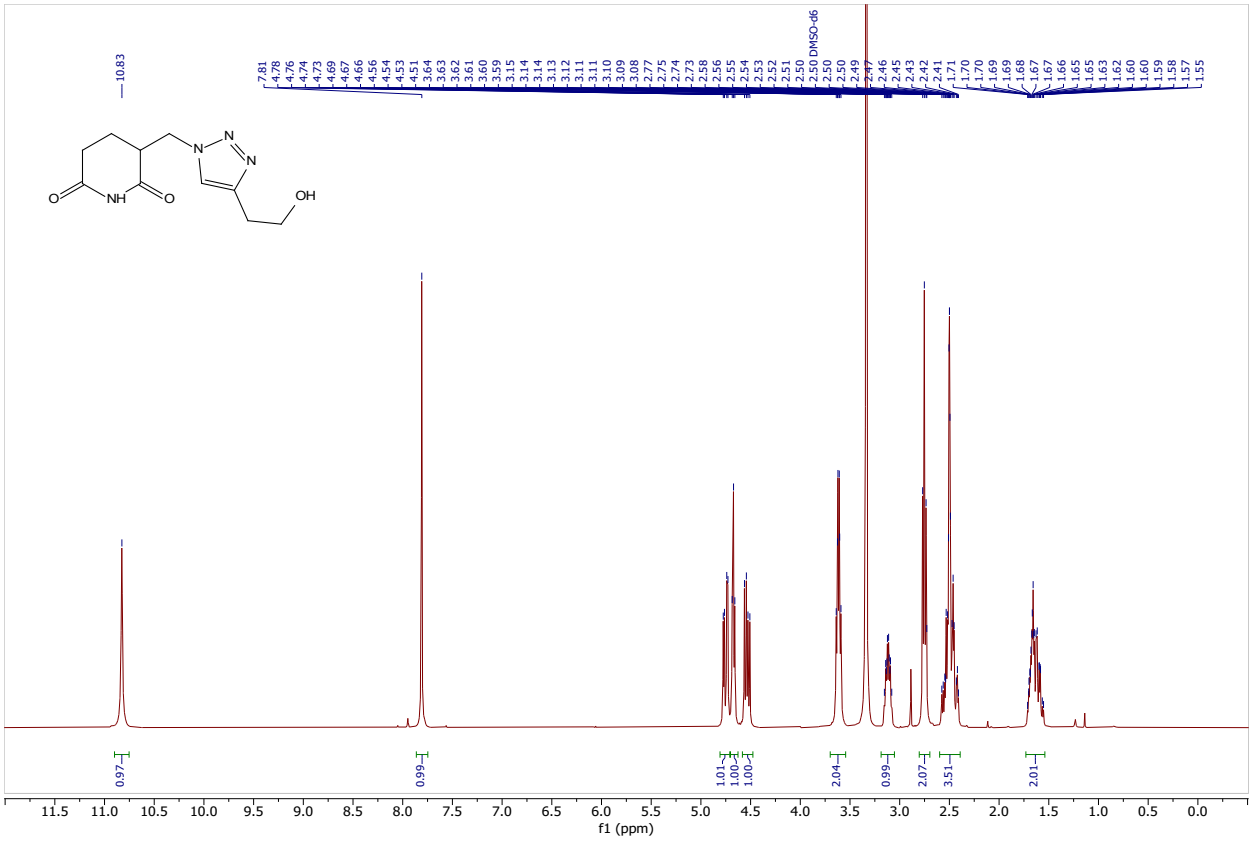


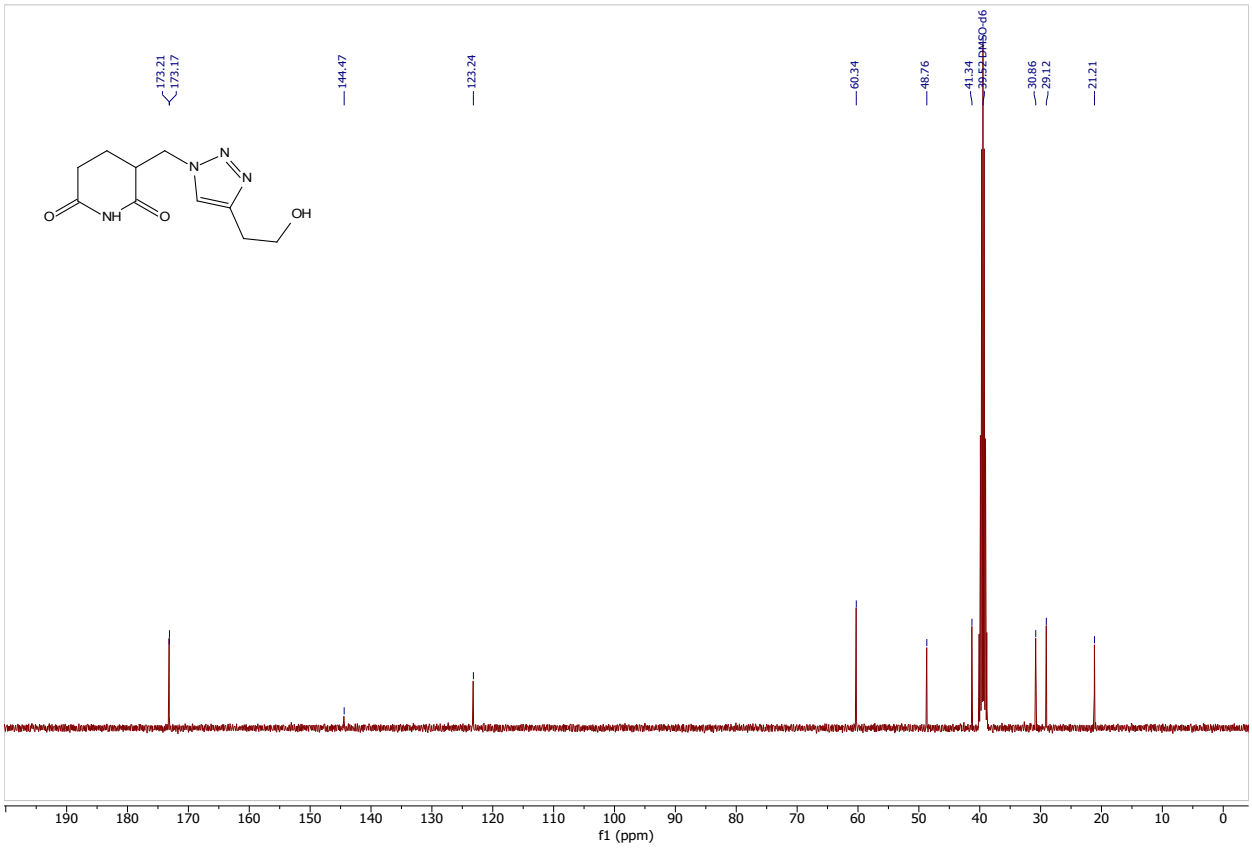
^{1}H and ^{13}C NMR spectra of compound ***3n***



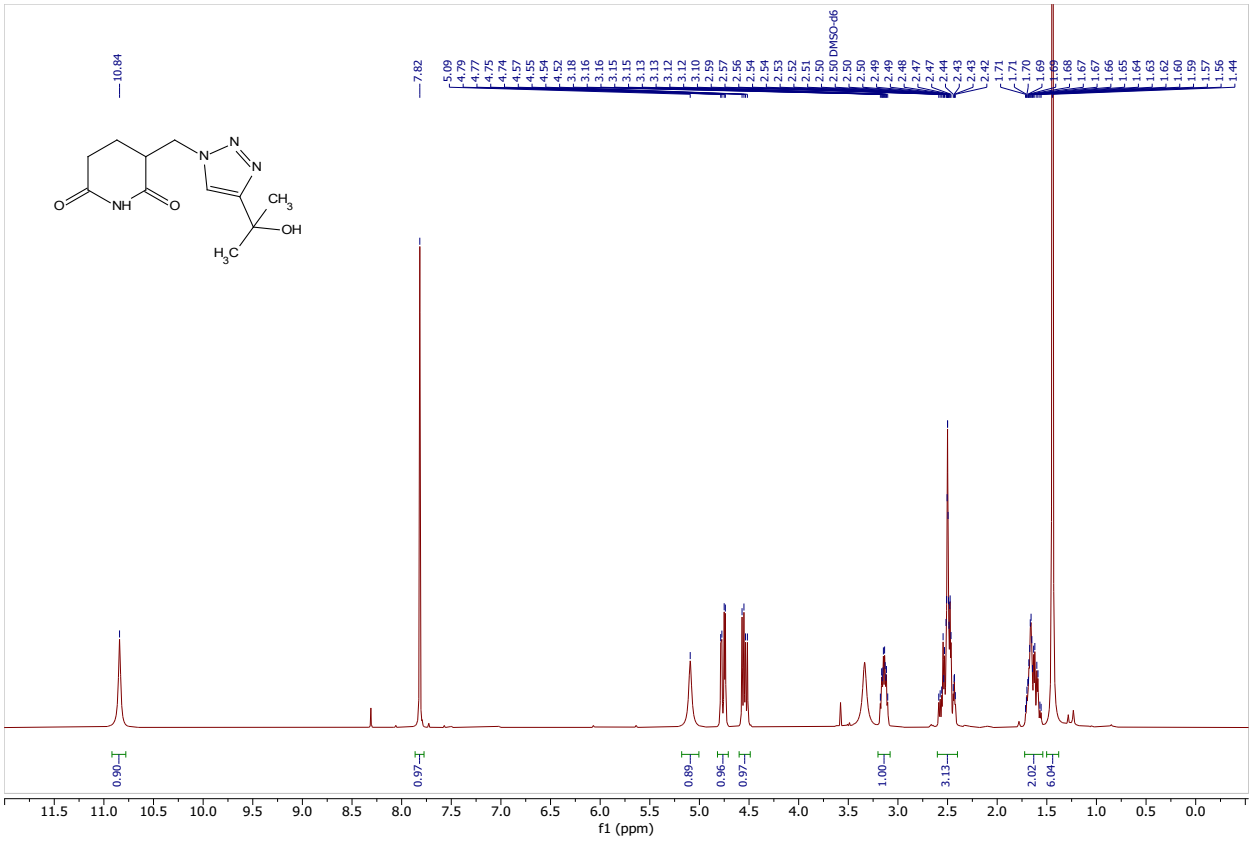


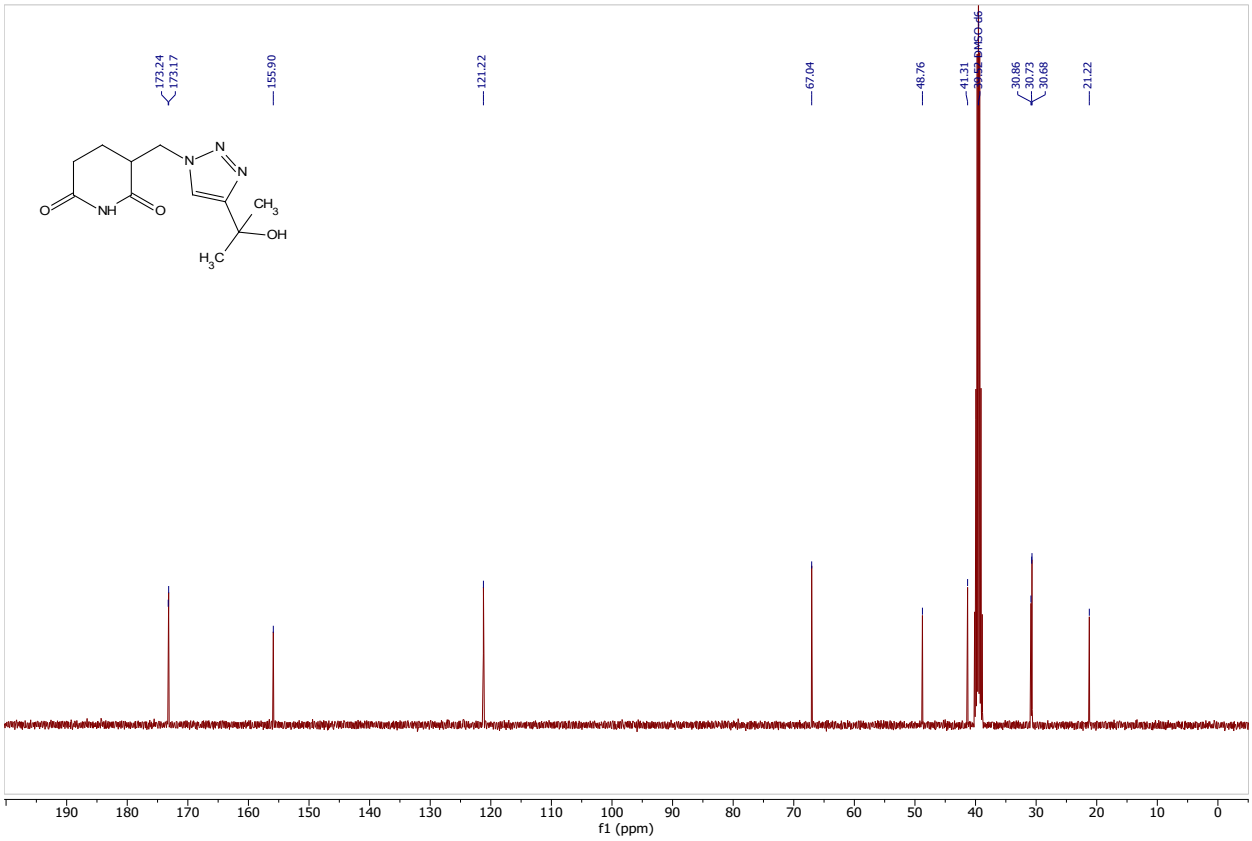
^{1}H and ^{13}C NMR spectra of compound ***3o***



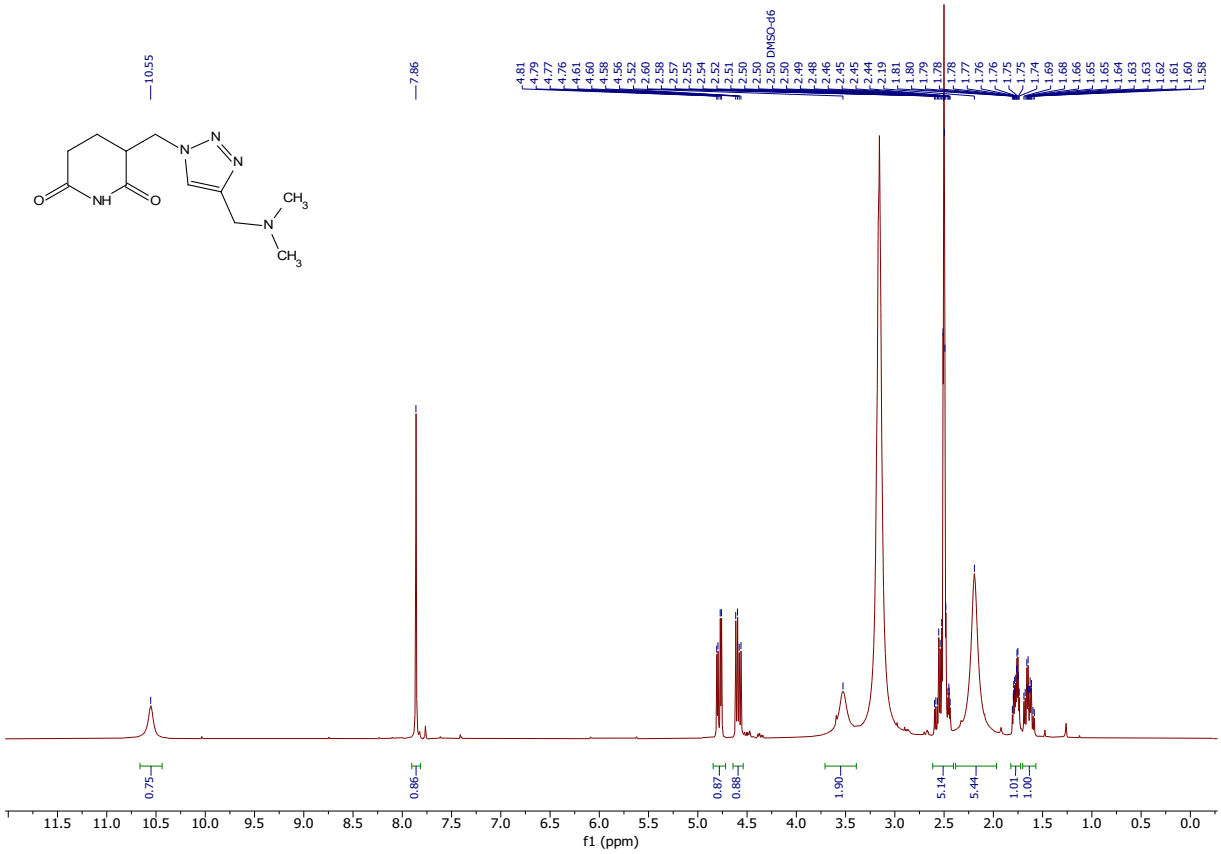


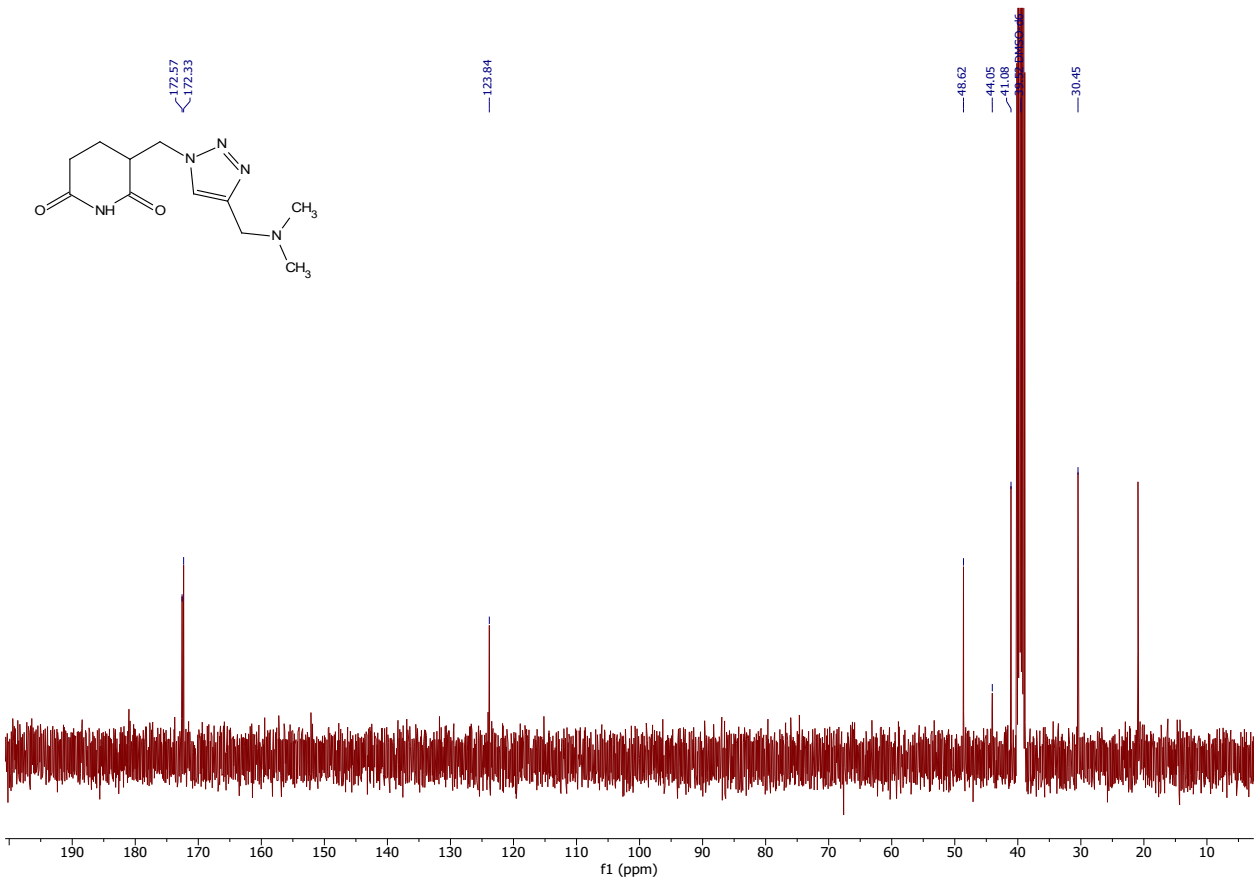
^{1}H and ^{13}C NMR spectra of compound ***3p***



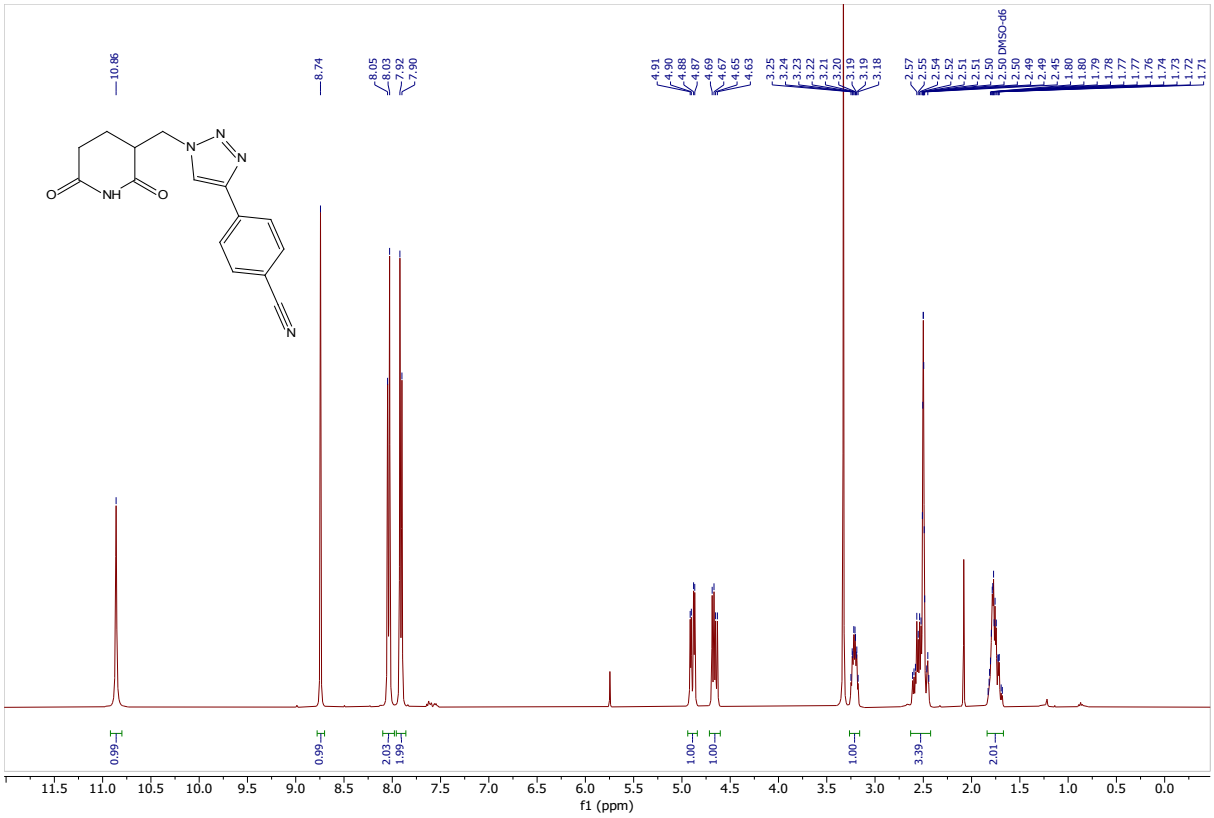


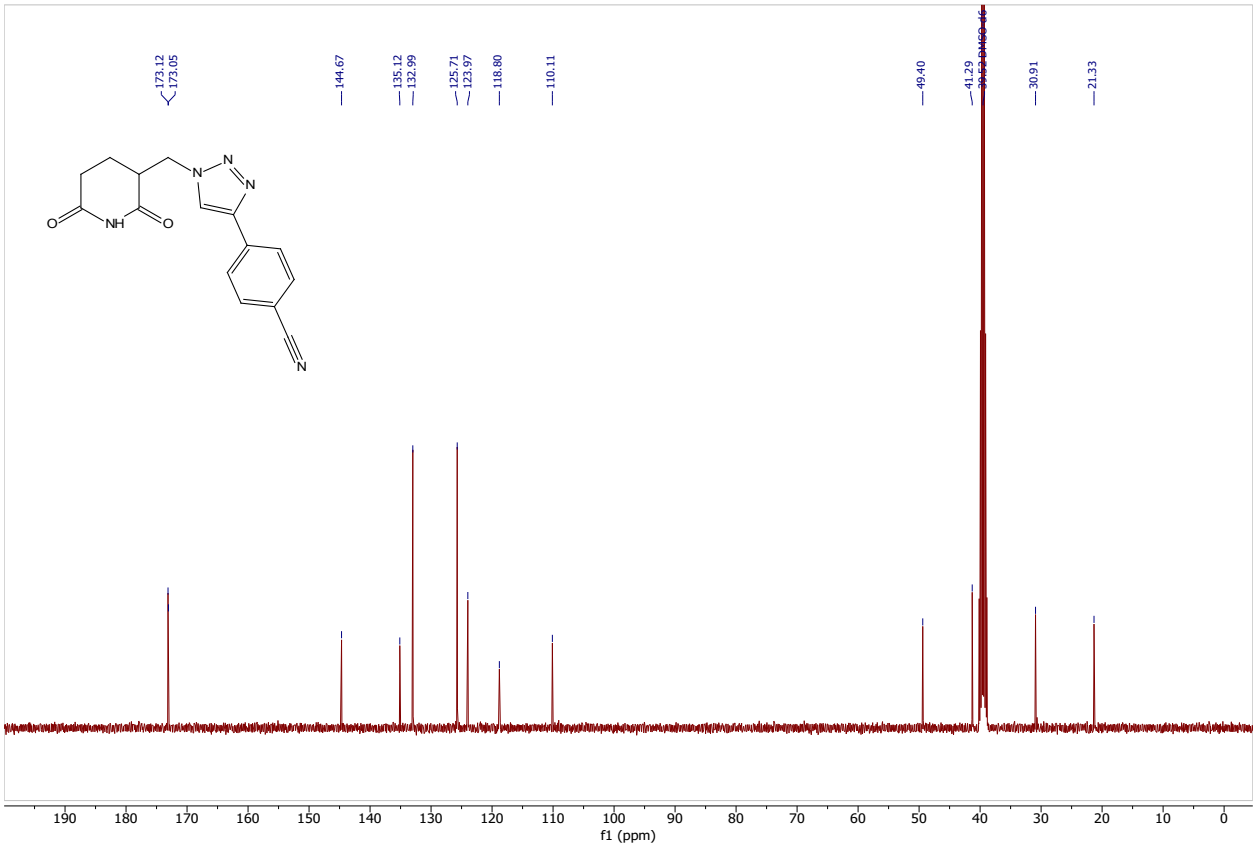
^{1}H and ^{13}C NMR spectra of compound ***3q***



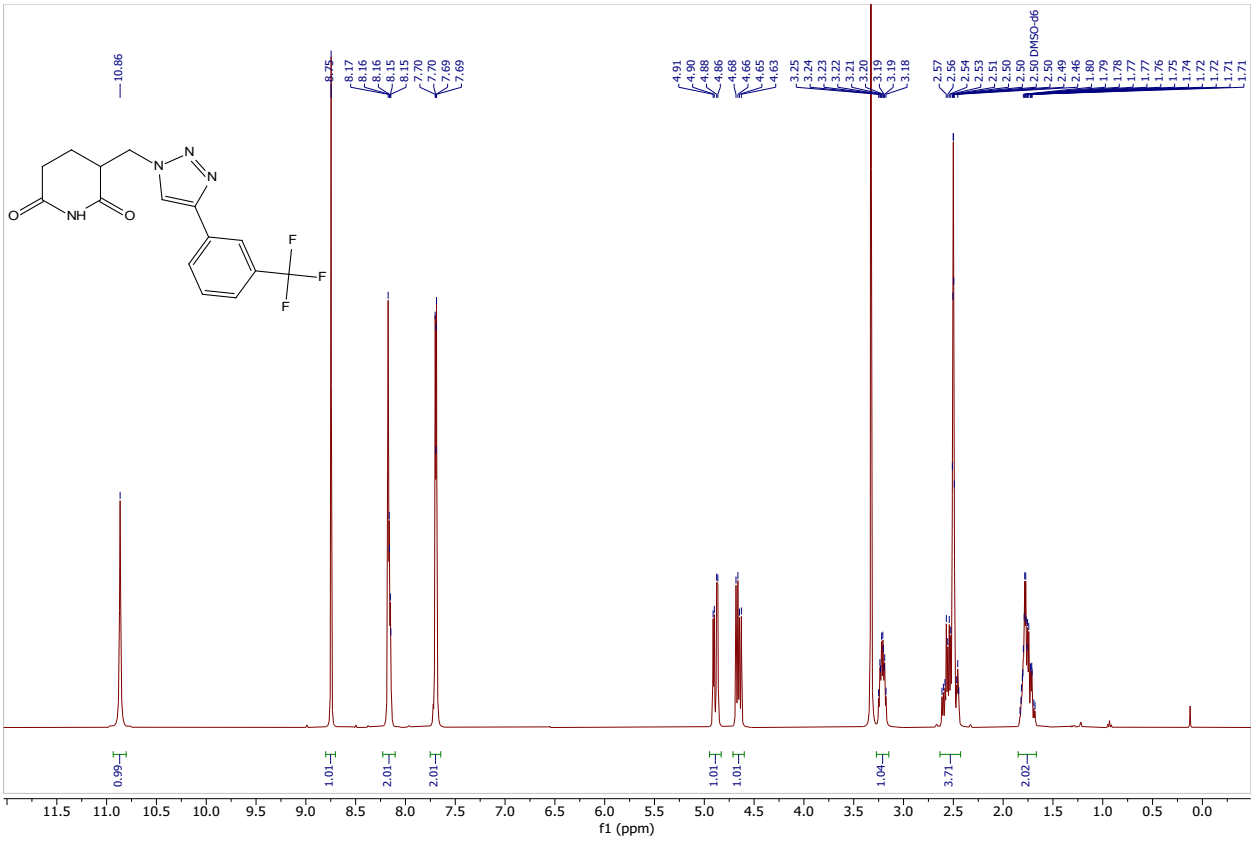


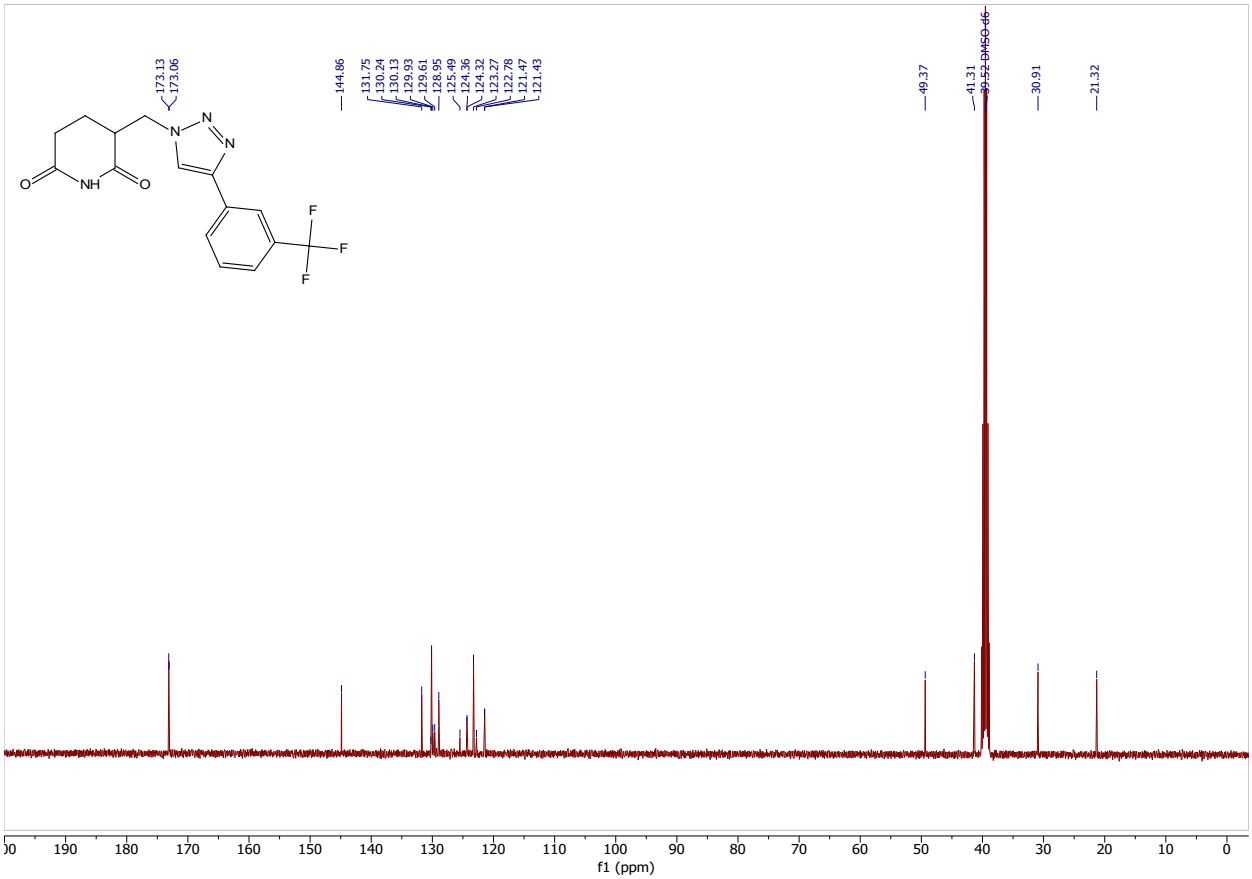
^{1}H and ^{13}C NMR spectra of compound ***4a***

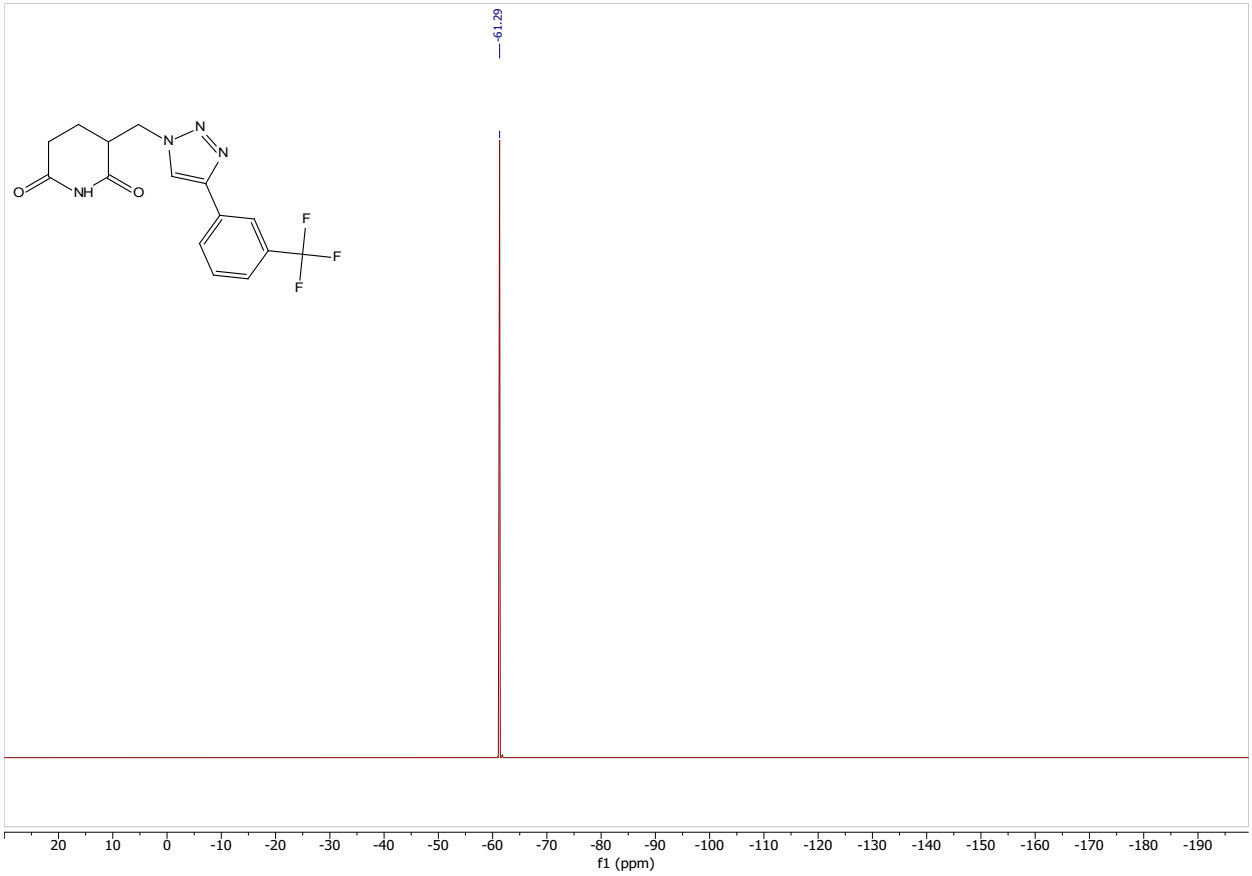




^{1}H, ^{13}C and ^{19}F NMR spectra of compound ***4b***






-61.29
O
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O
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N
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F
F
F
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10
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-10
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-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
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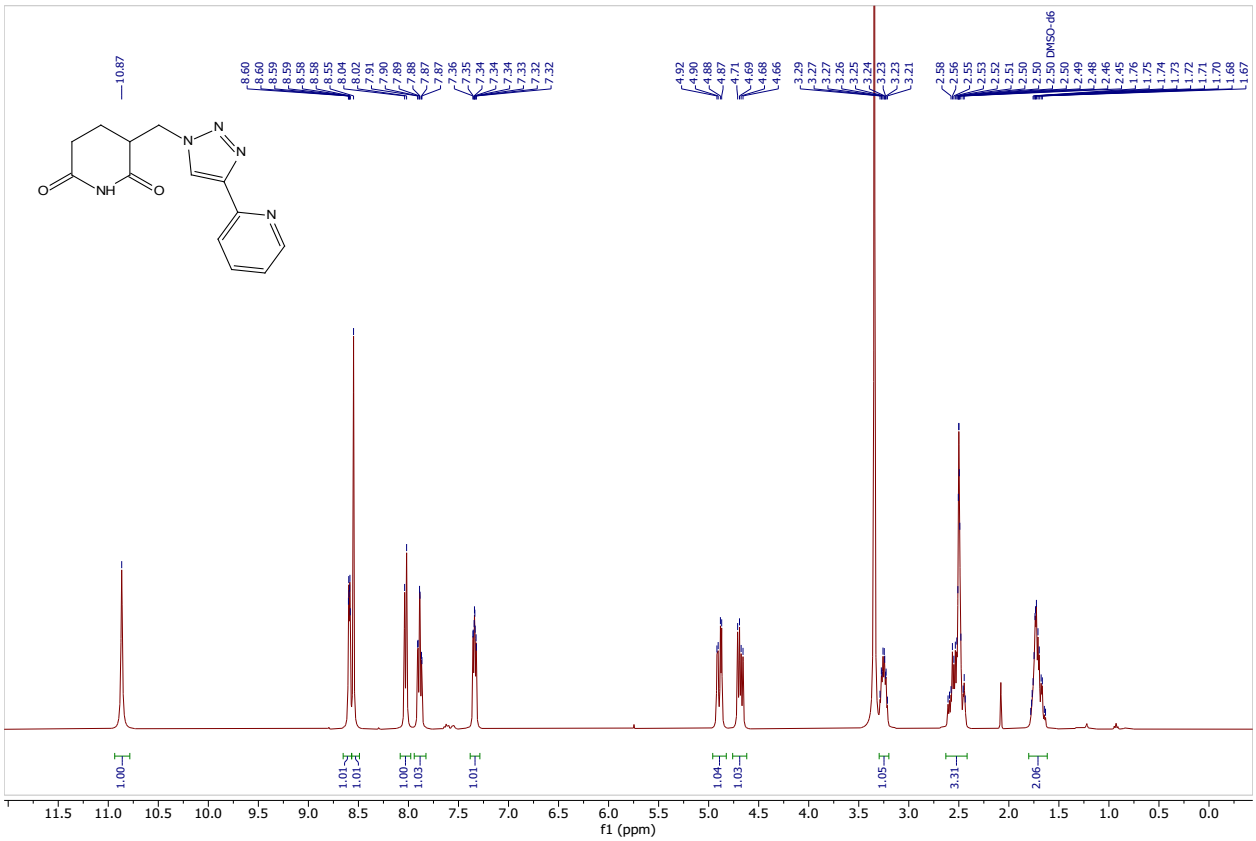
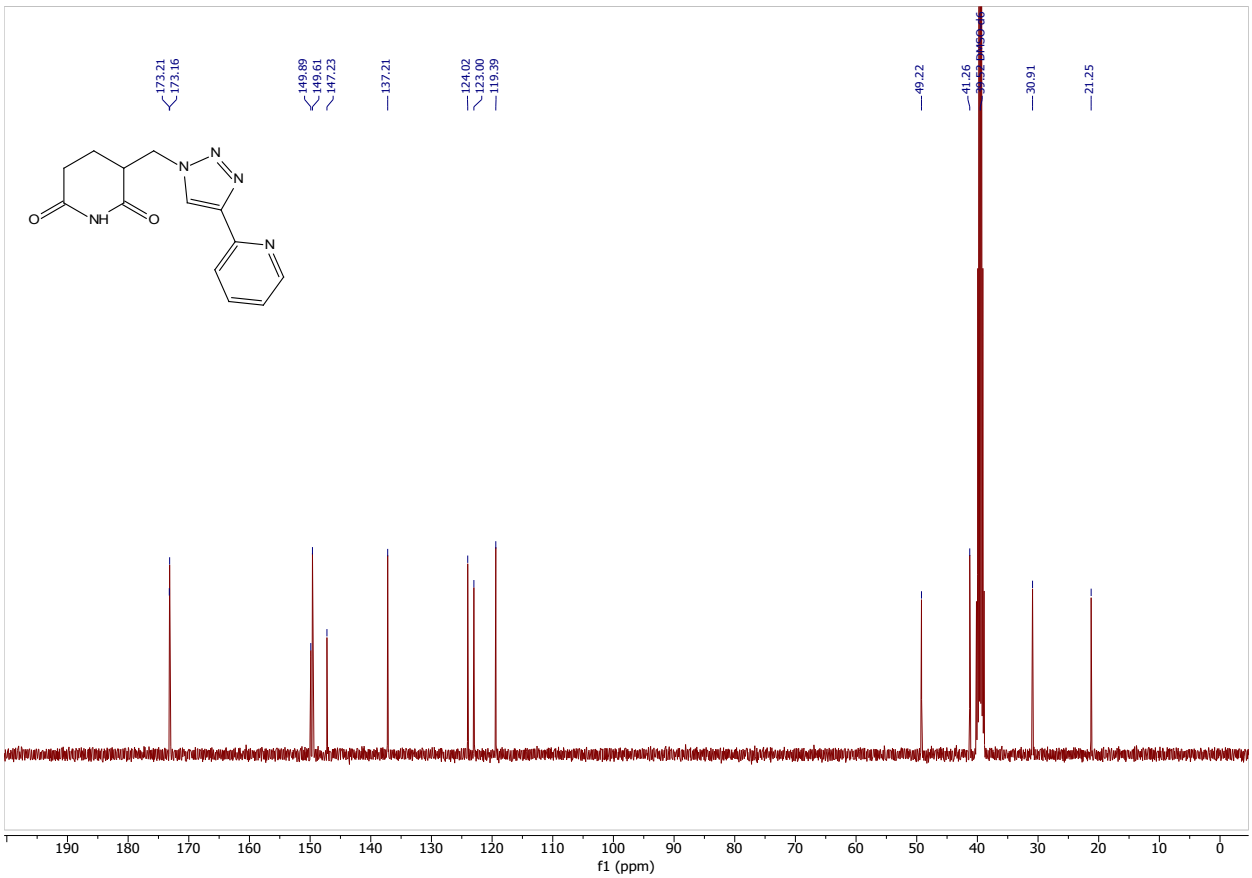
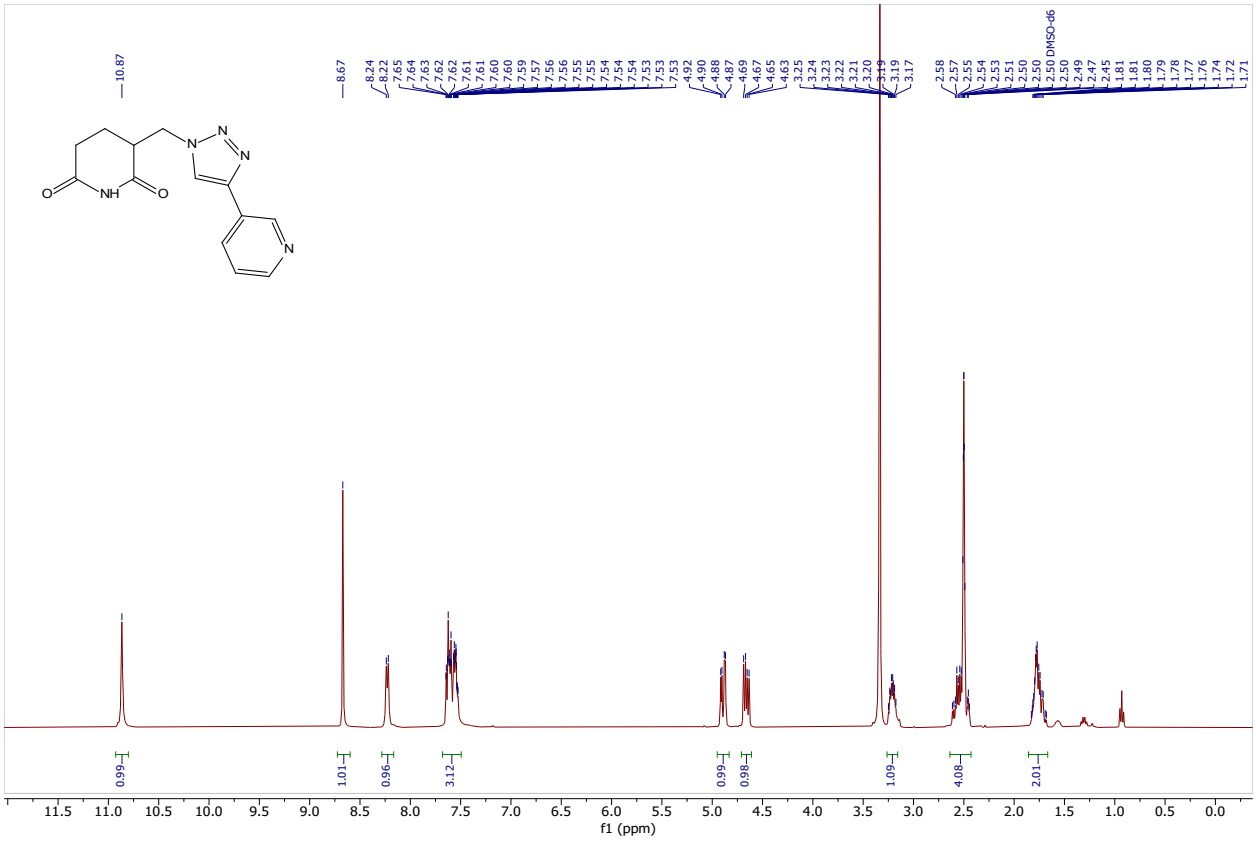
-140
-150
-160
-170
-180
-190
f1 (ppm)

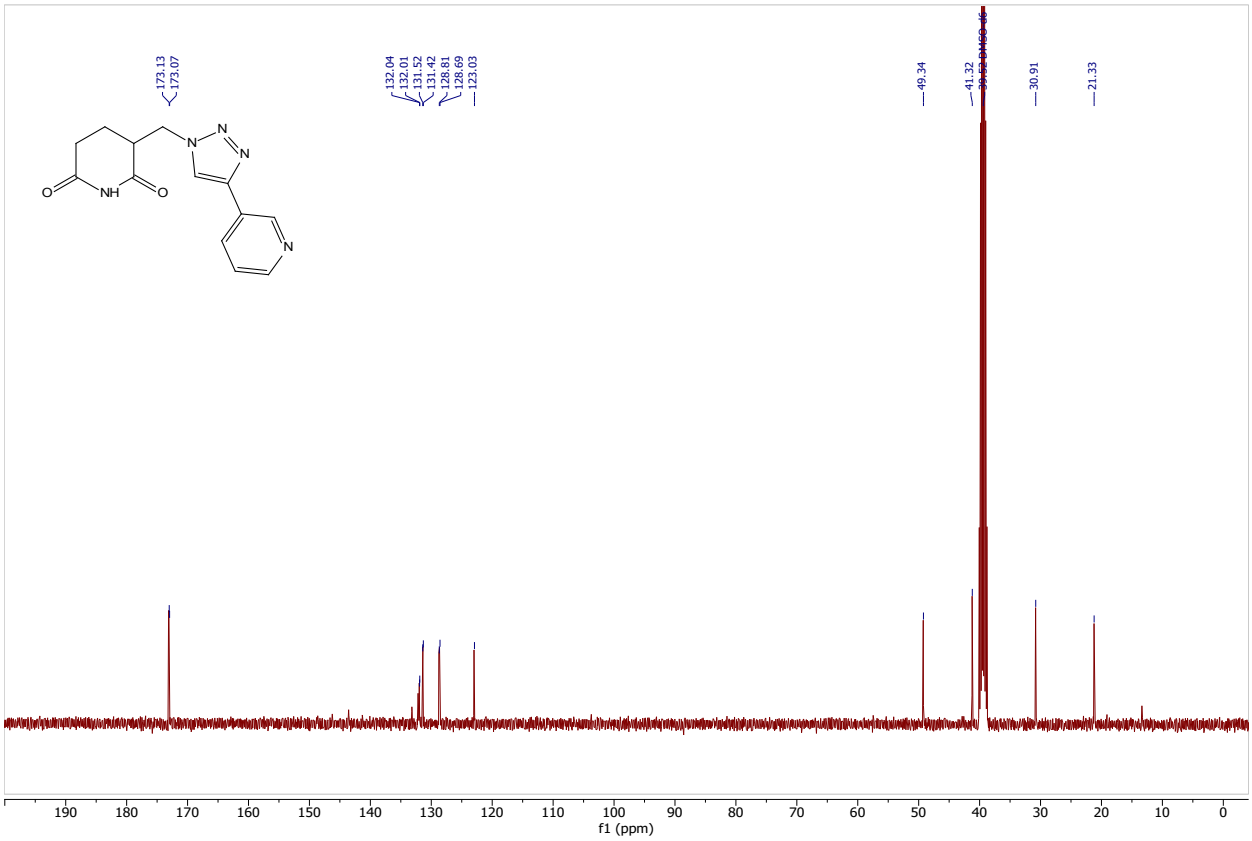
^{1}H and ^{13}C NMR spectra of compound ***4c***



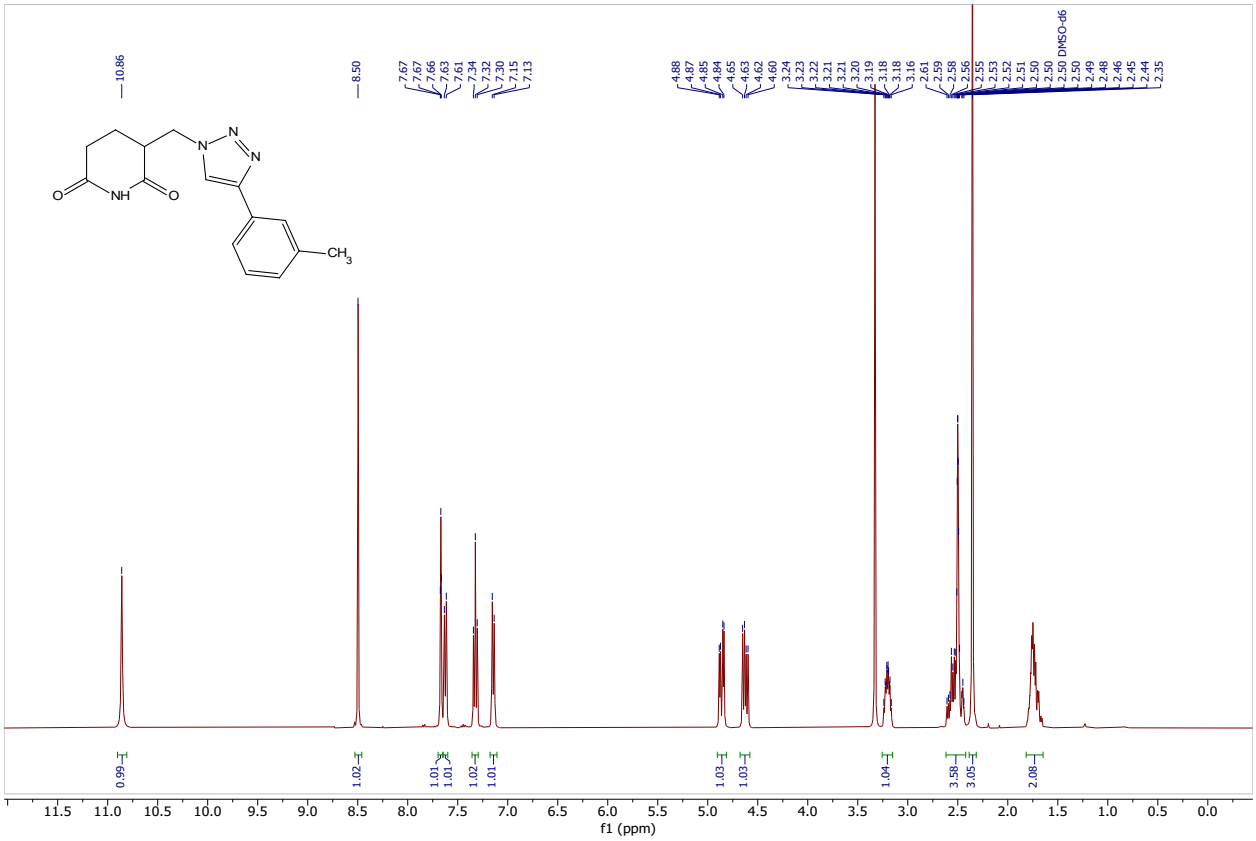


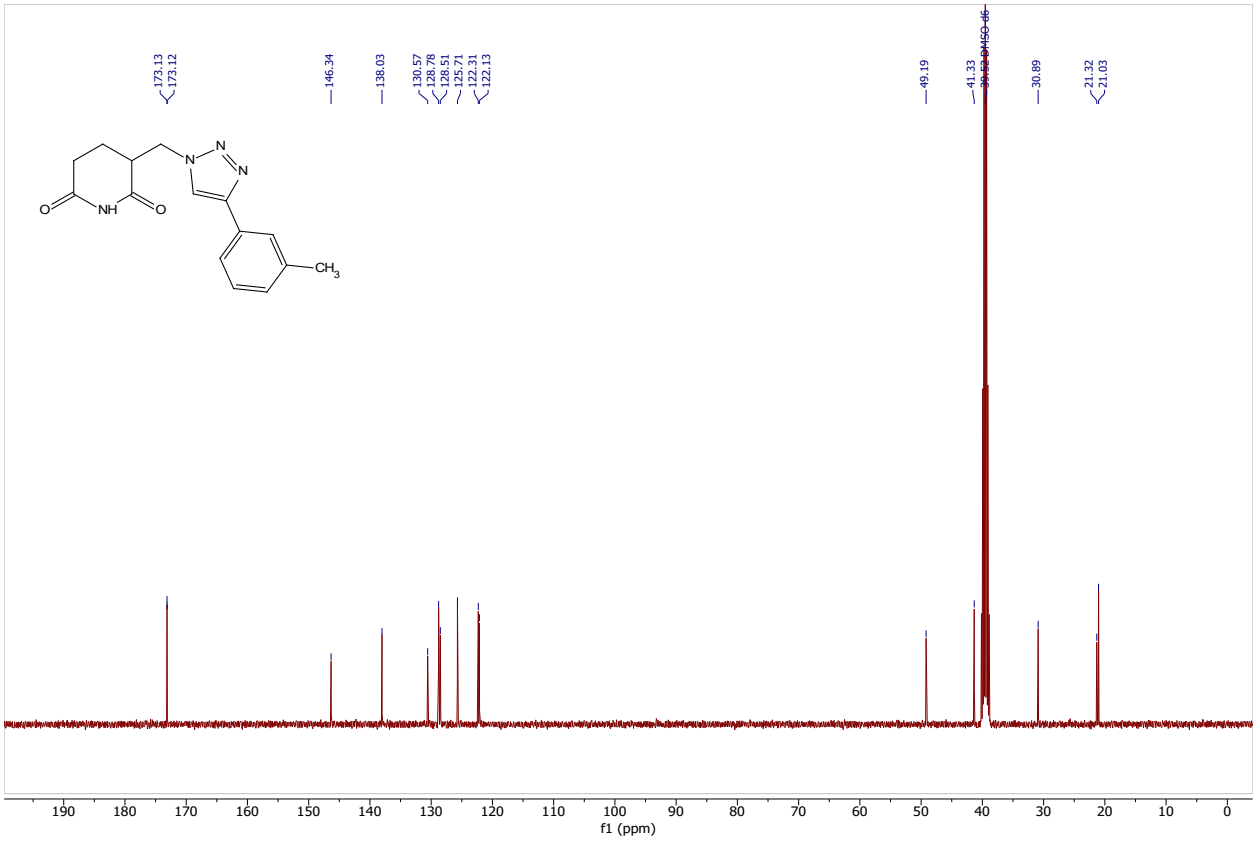
^{1}H and ^{13}C NMR spectra of compound ***4d***



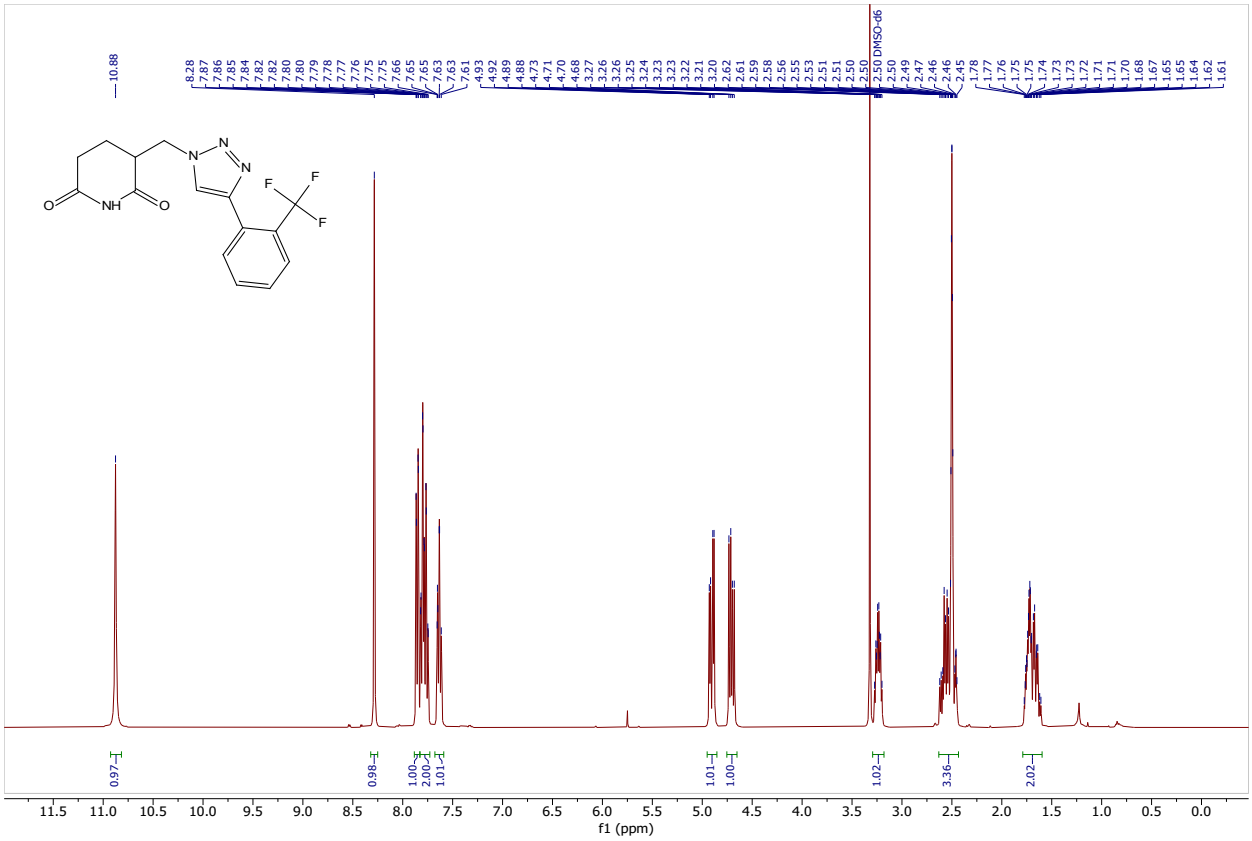


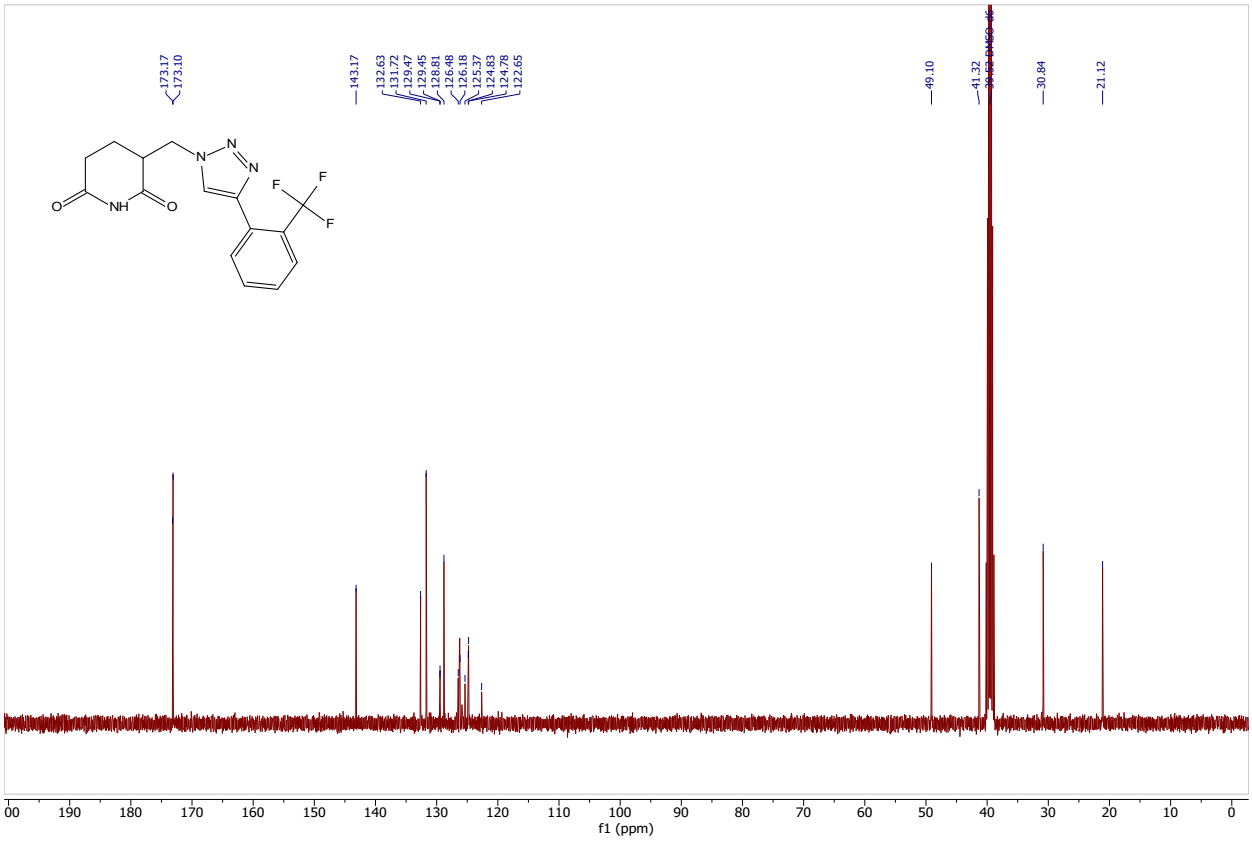
^{1}H and ^{13}C NMR spectra of compound ***4e***

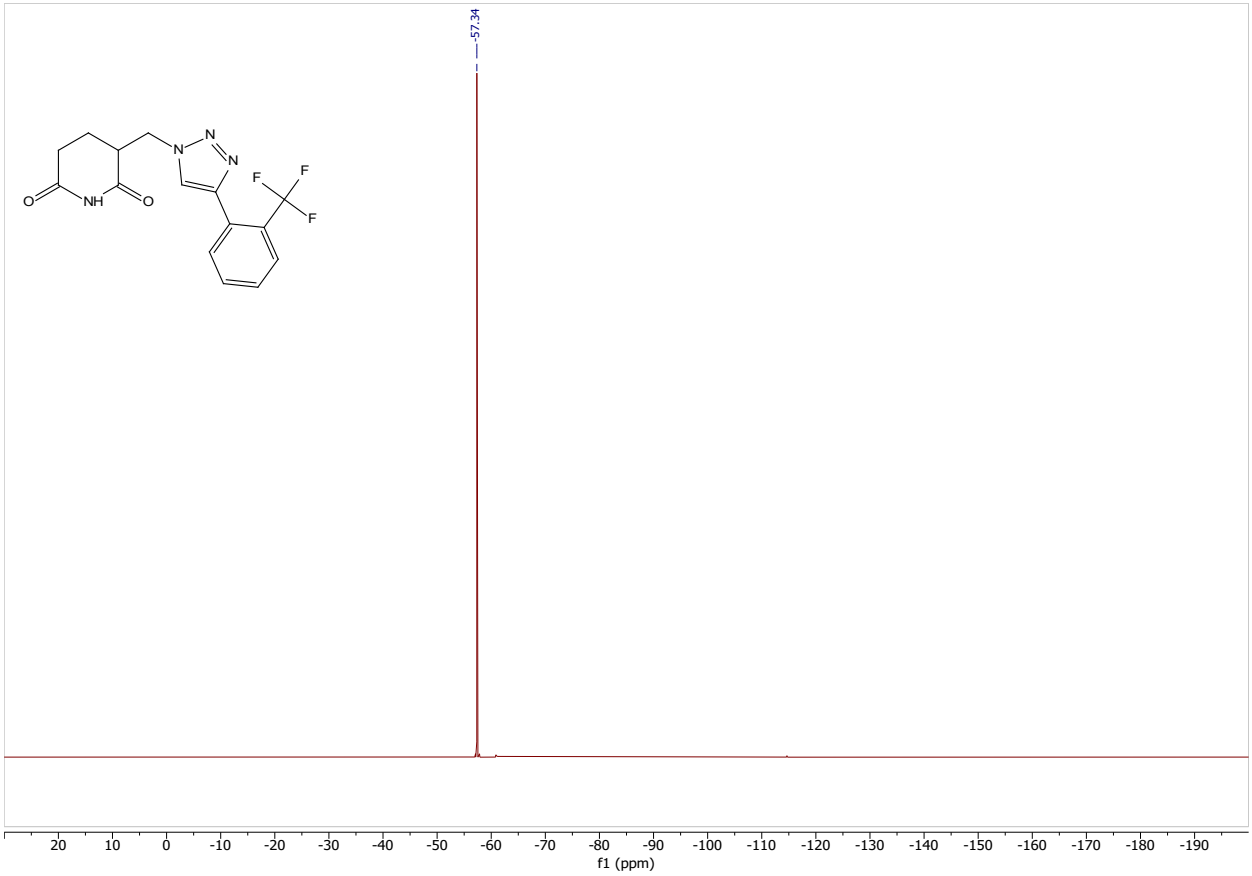




^{1}H, ^{13}C and ^{19}F NMR spectra of compound ***4f***






-57.34
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-50
-60
-70
-80
-90
-100
-110
-120
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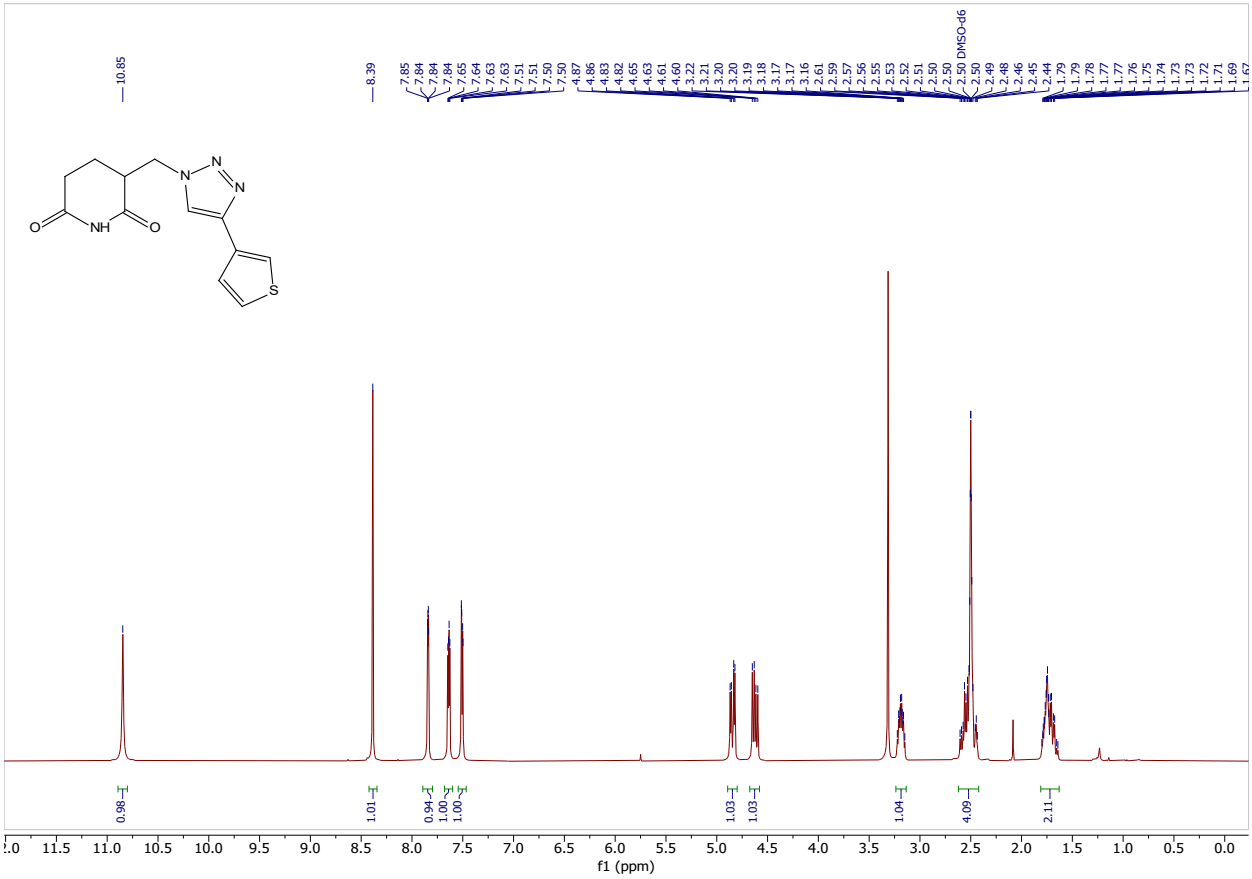
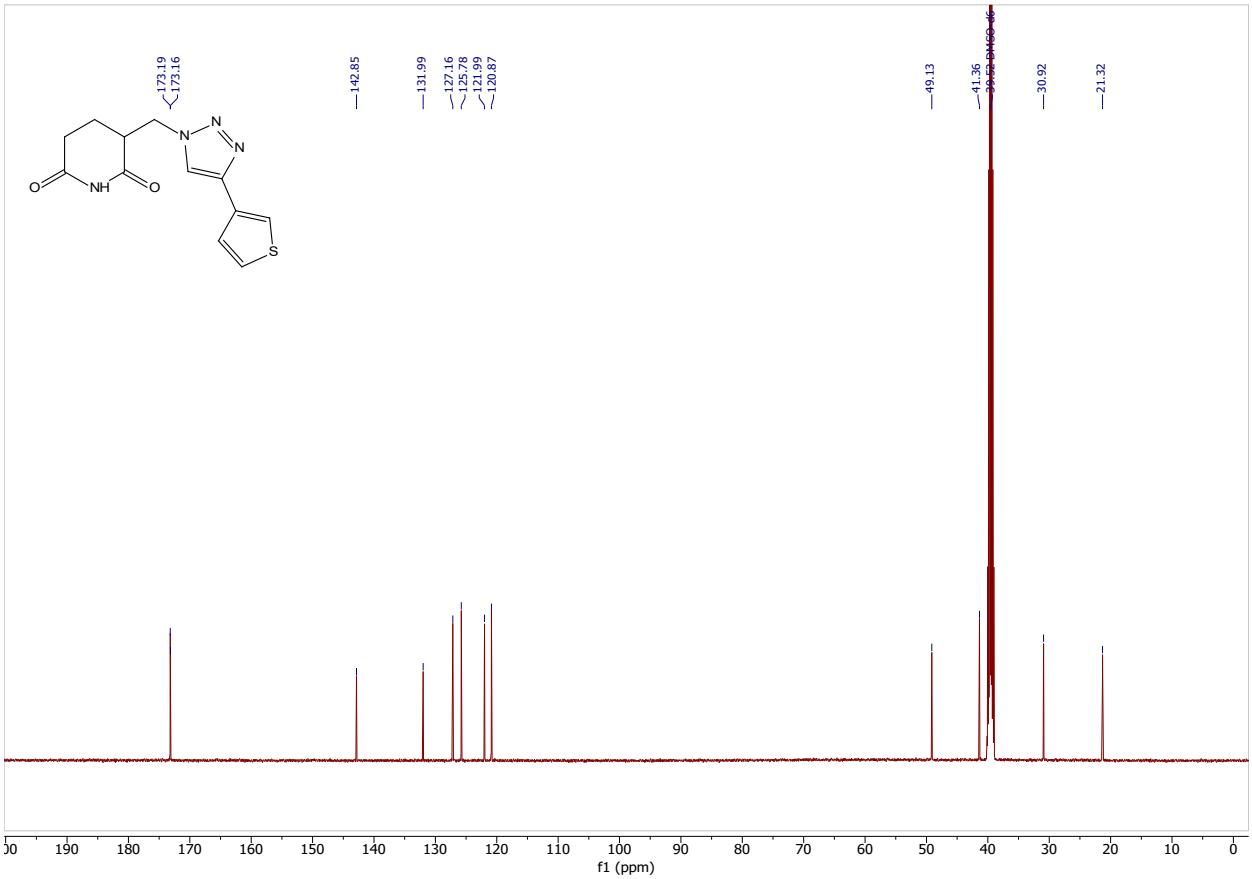
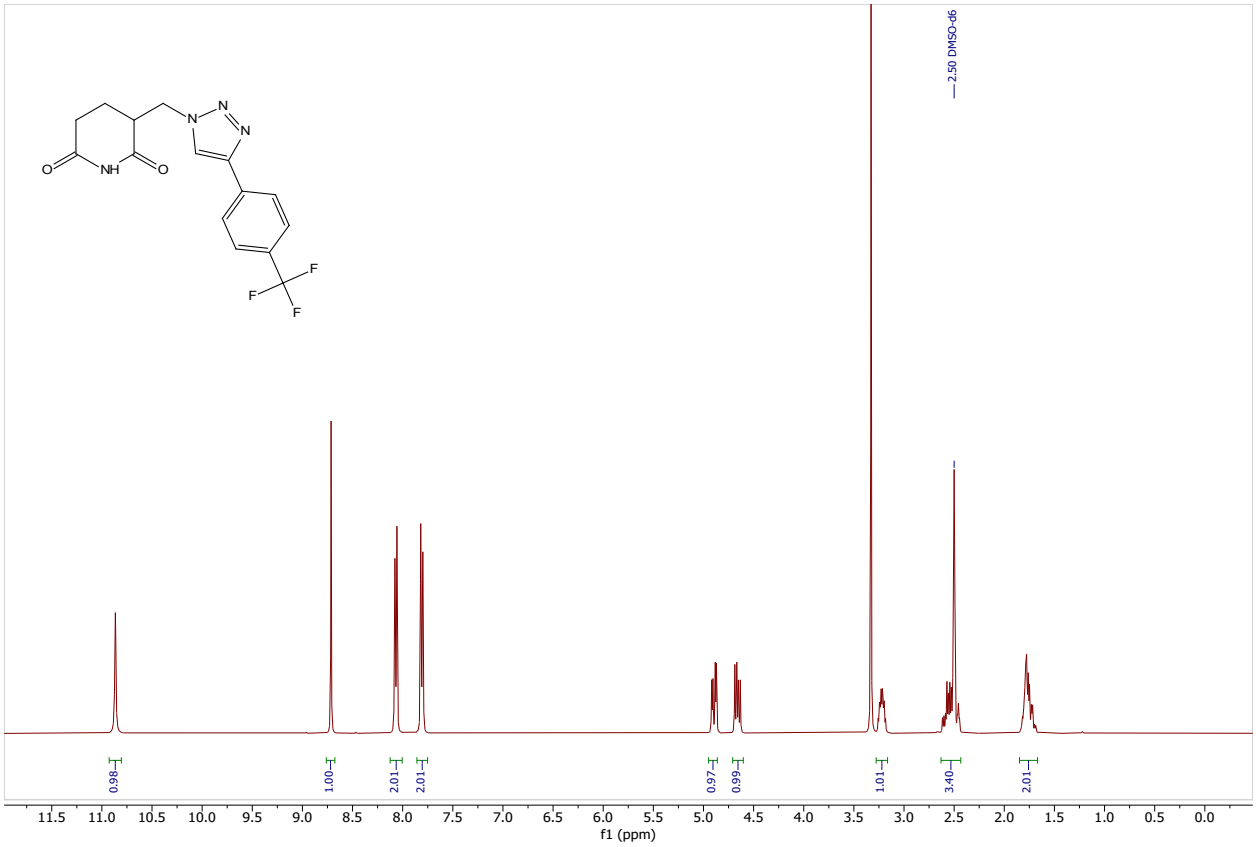
-140
-150
-160
-170
-180
-190
f1 (ppm)

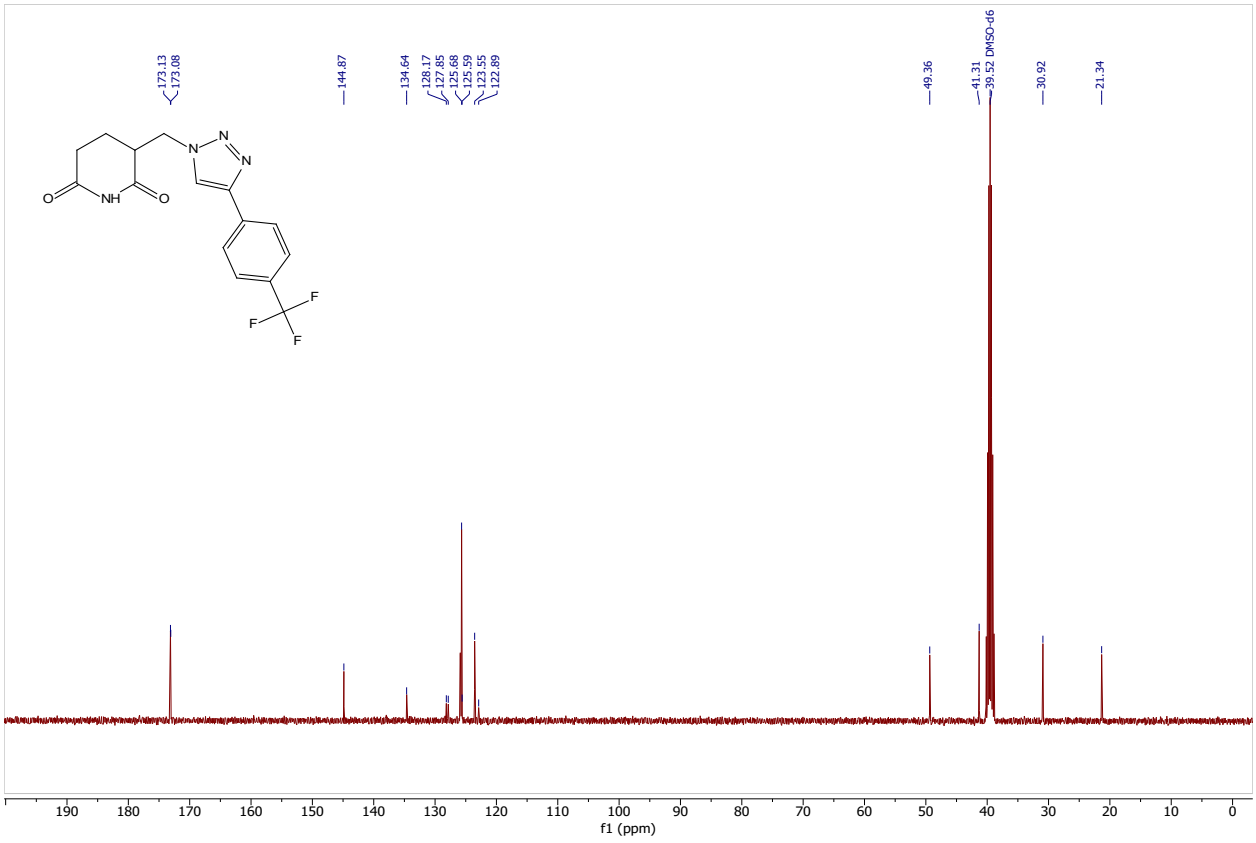
^{1}H and ^{13}C NMR spectra of compound ***4g***

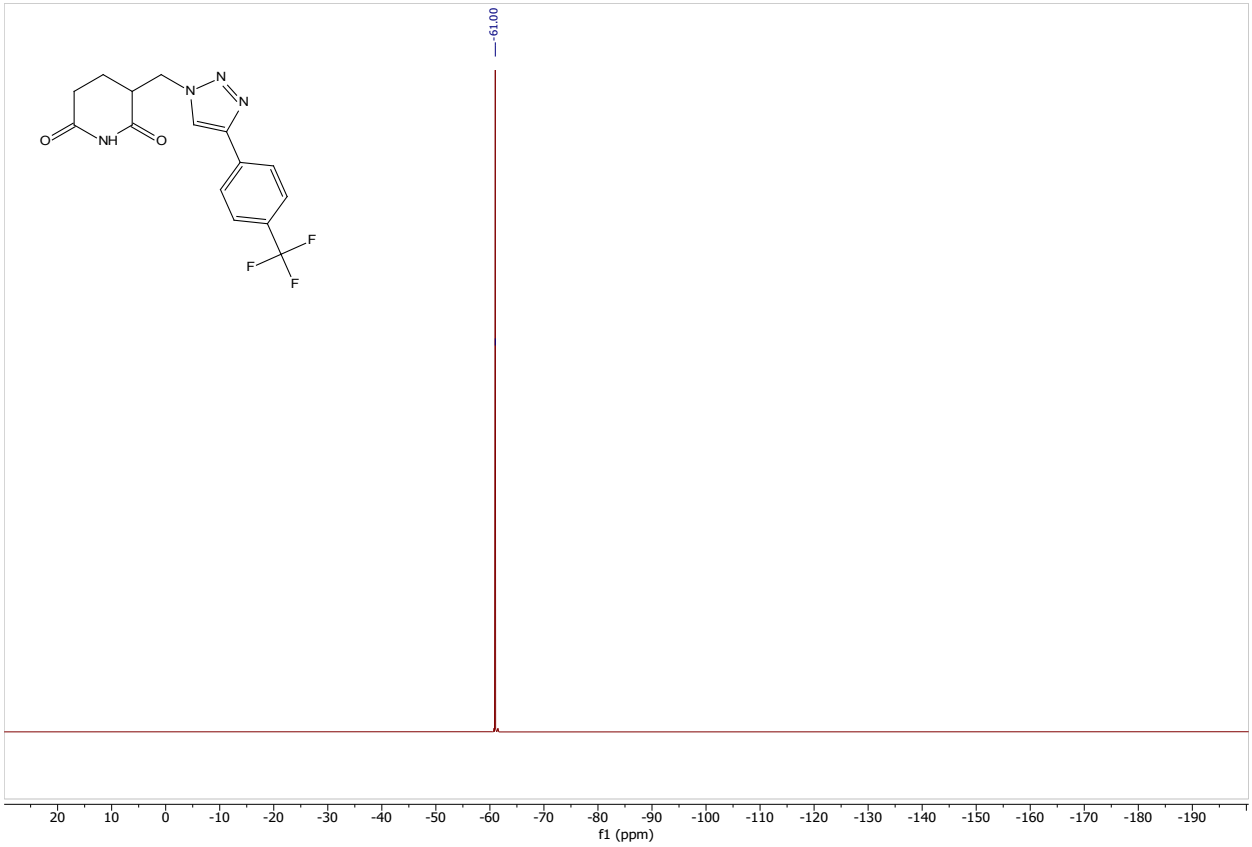




^{1}H, ^{13}C and ^{19}F NMR spectra of compound ***4h***






-61.00
O
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N
N
F
F
F
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10
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-30
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-50
-60
-70
-80
-90
-100
-110
-120
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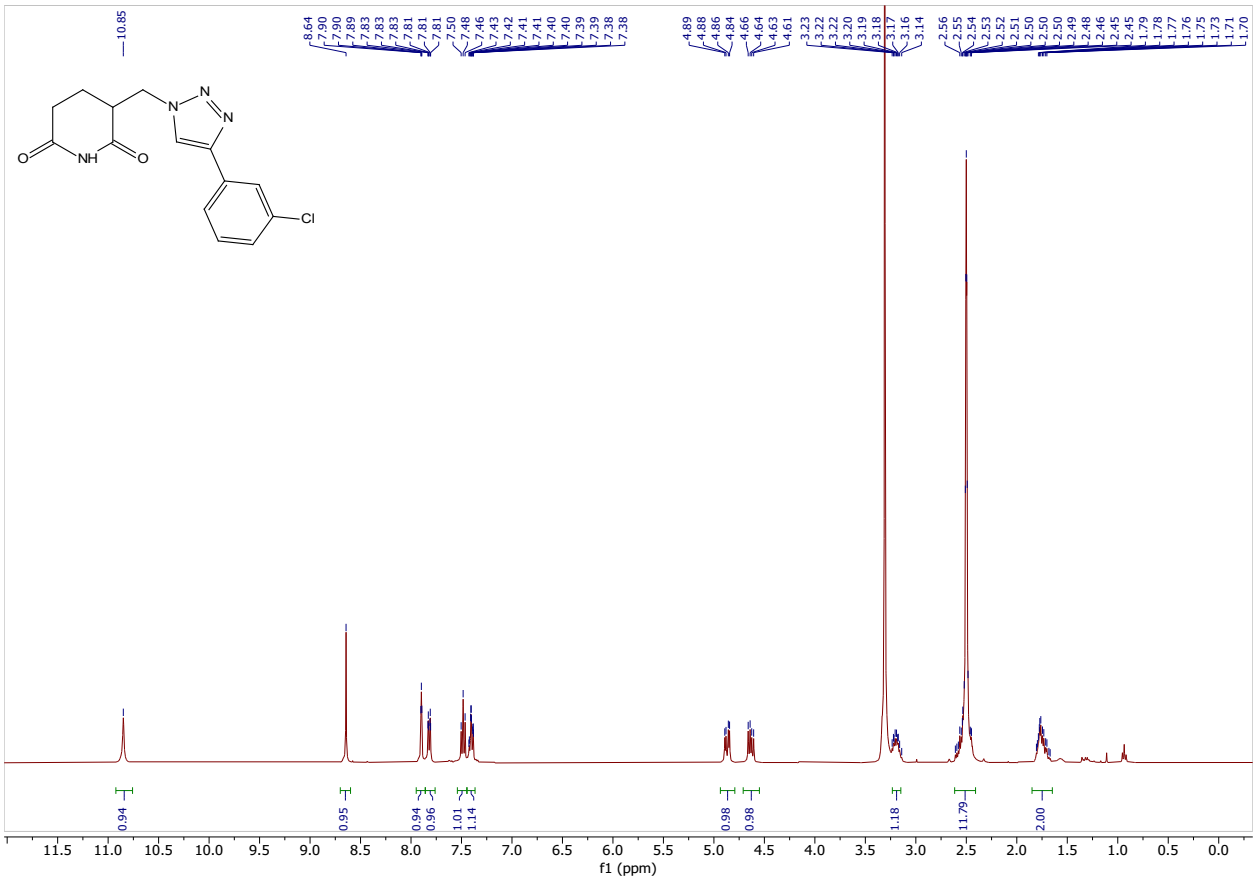
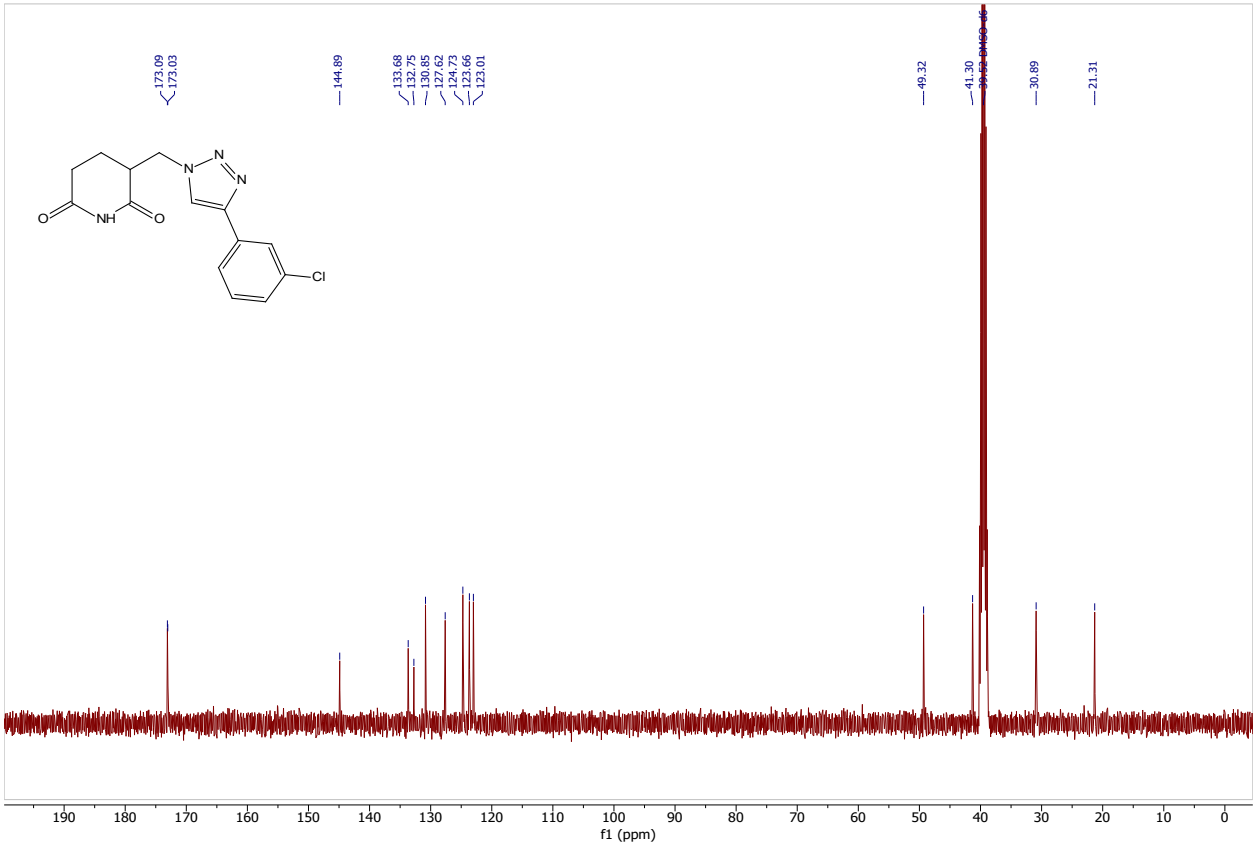
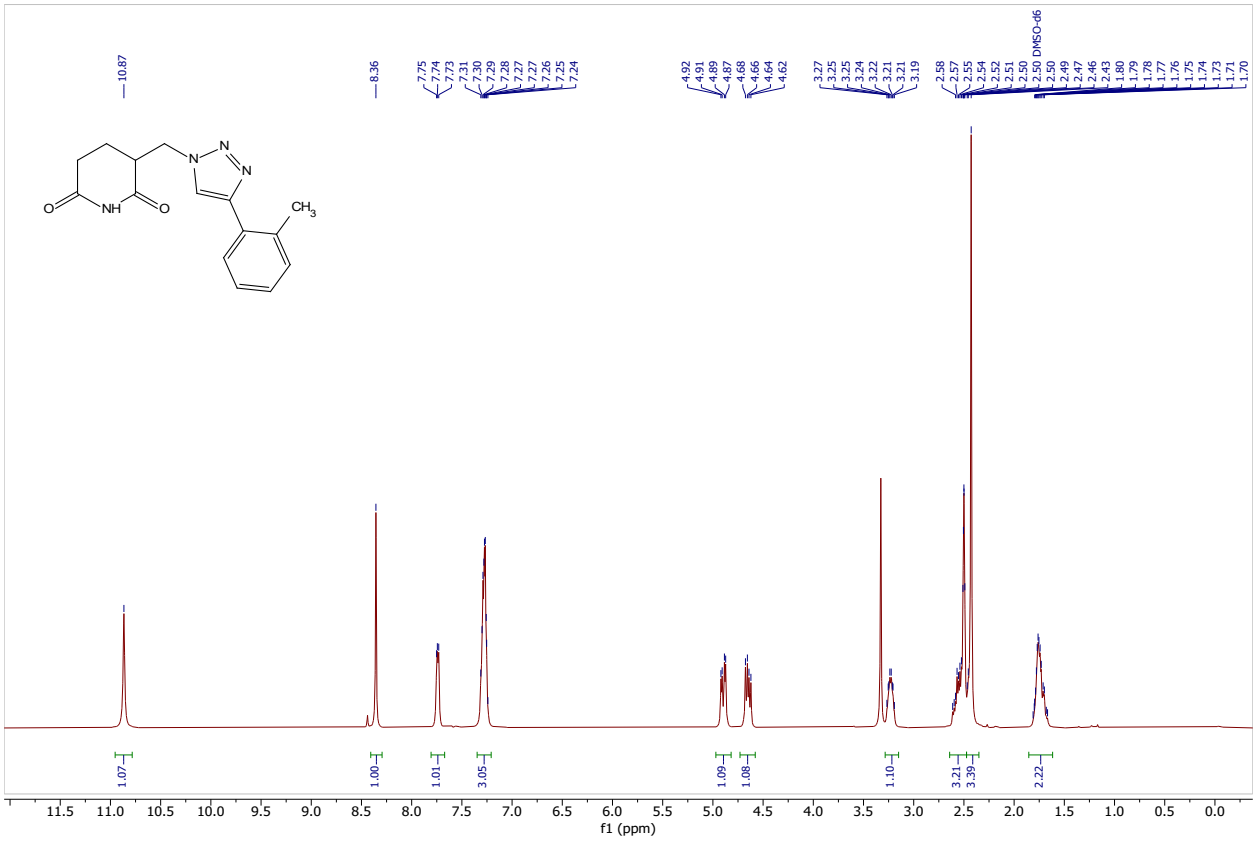
-140
-150
-160
-170
-180
-190
f1 (ppm)

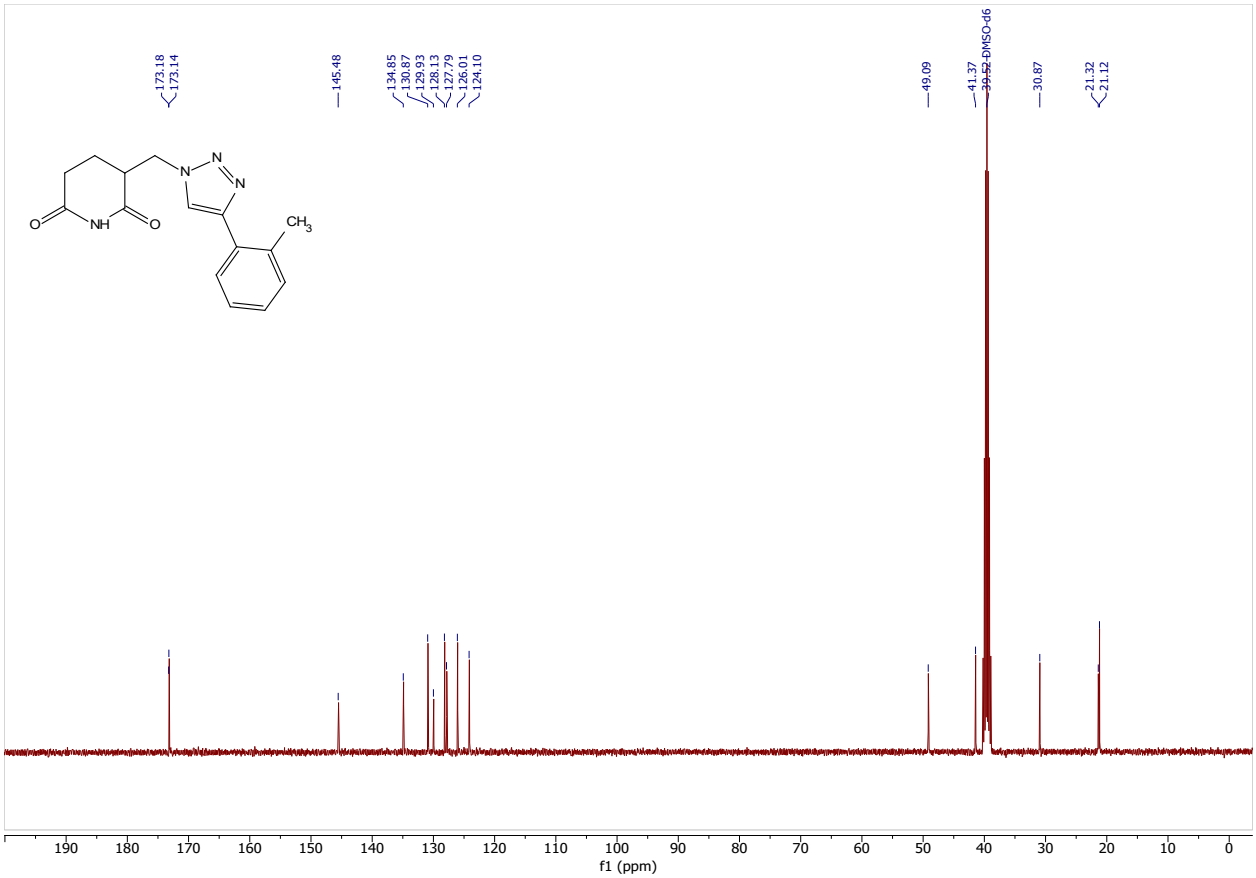
^{1}H and ^{13}C NMR spectra of compound ***4i***



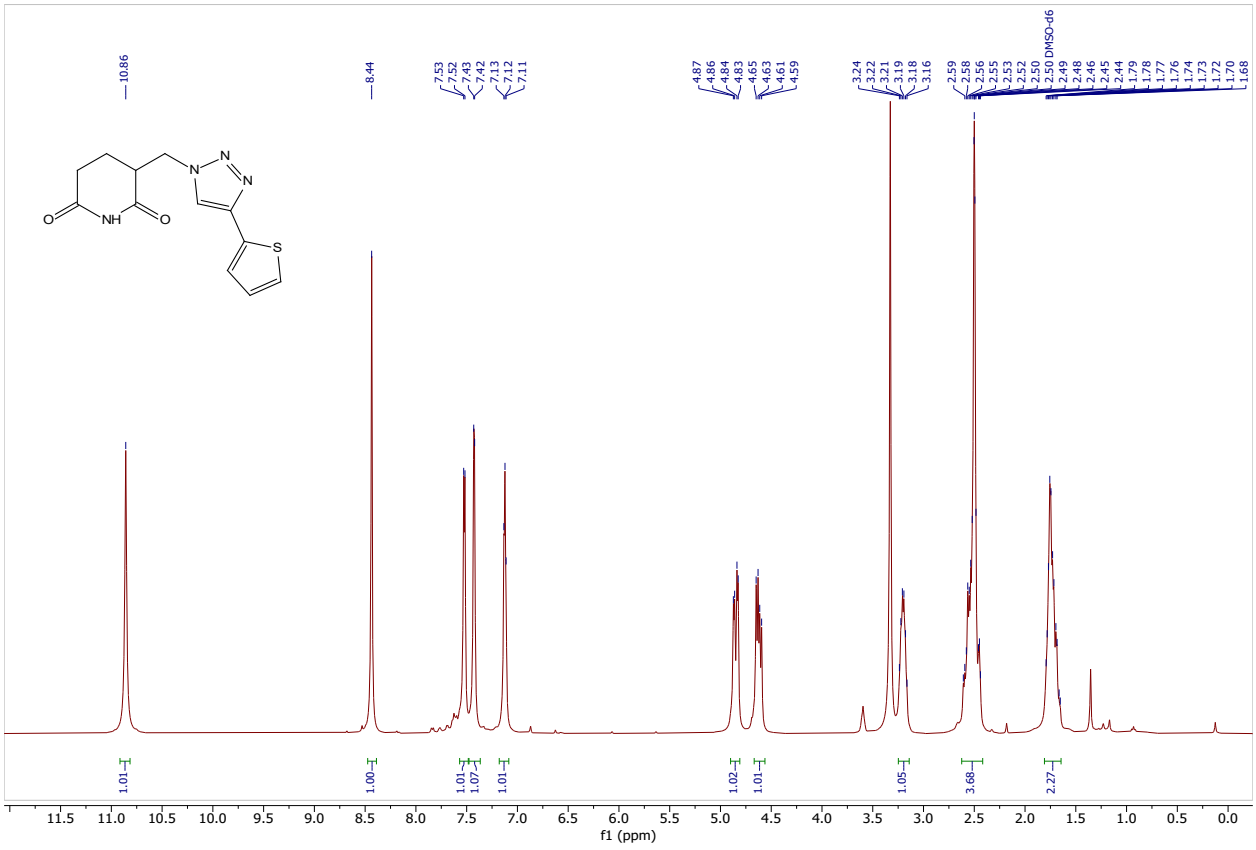


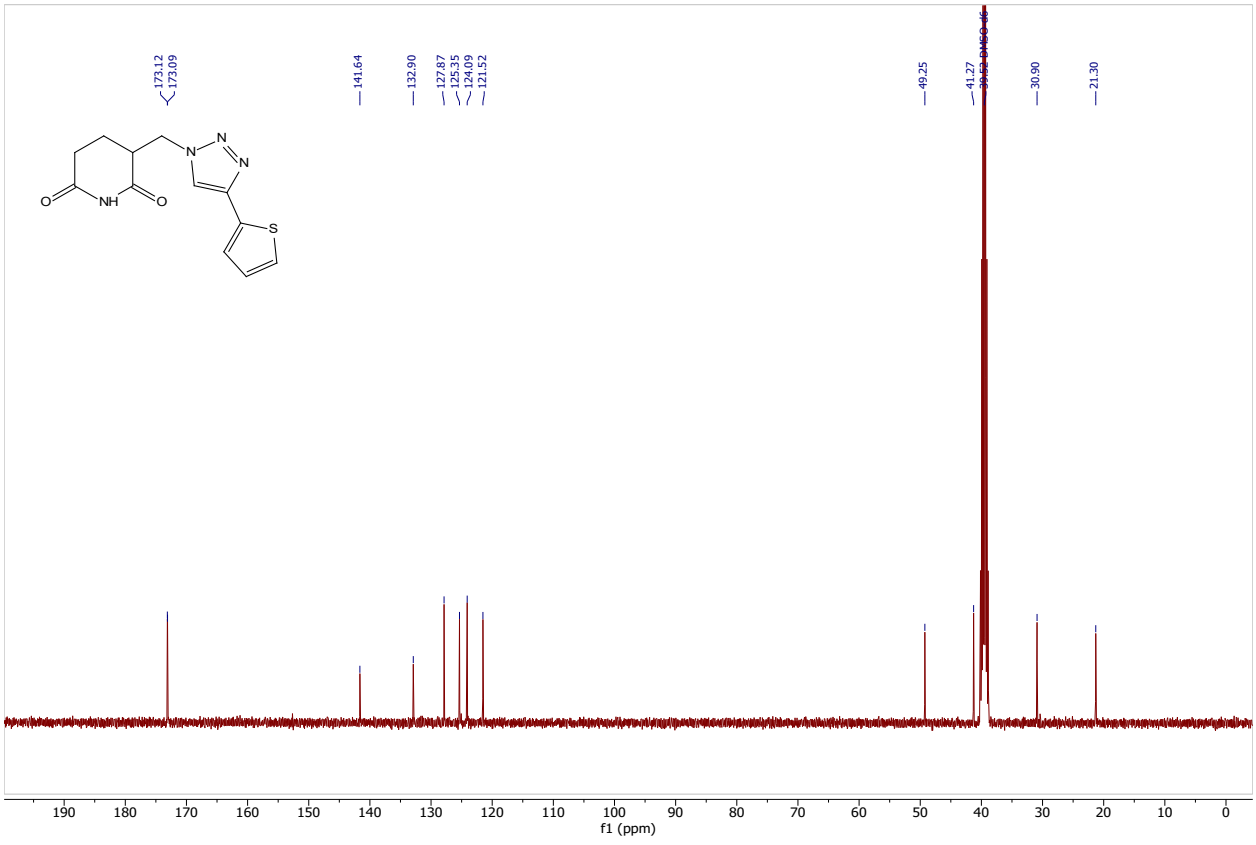
^{1}H and ^{13}C NMR spectra of compound ***4j***



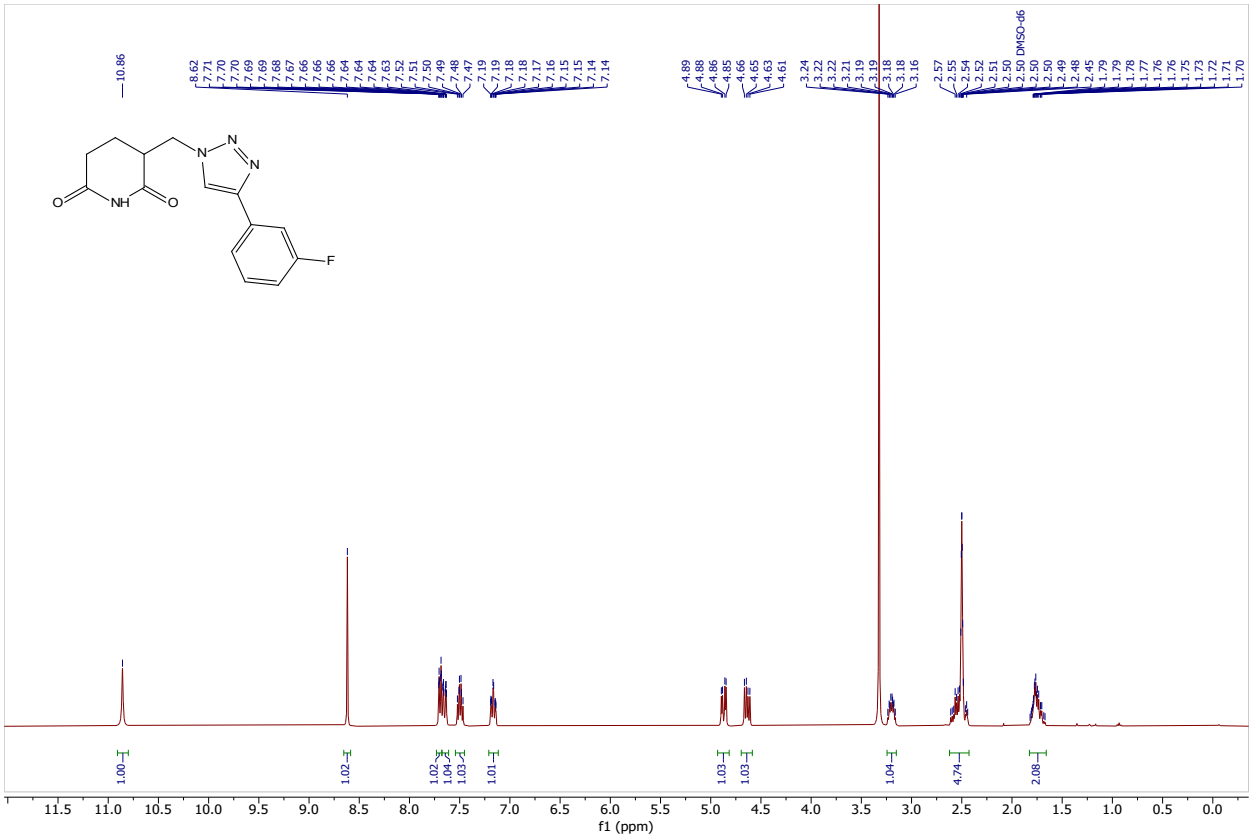


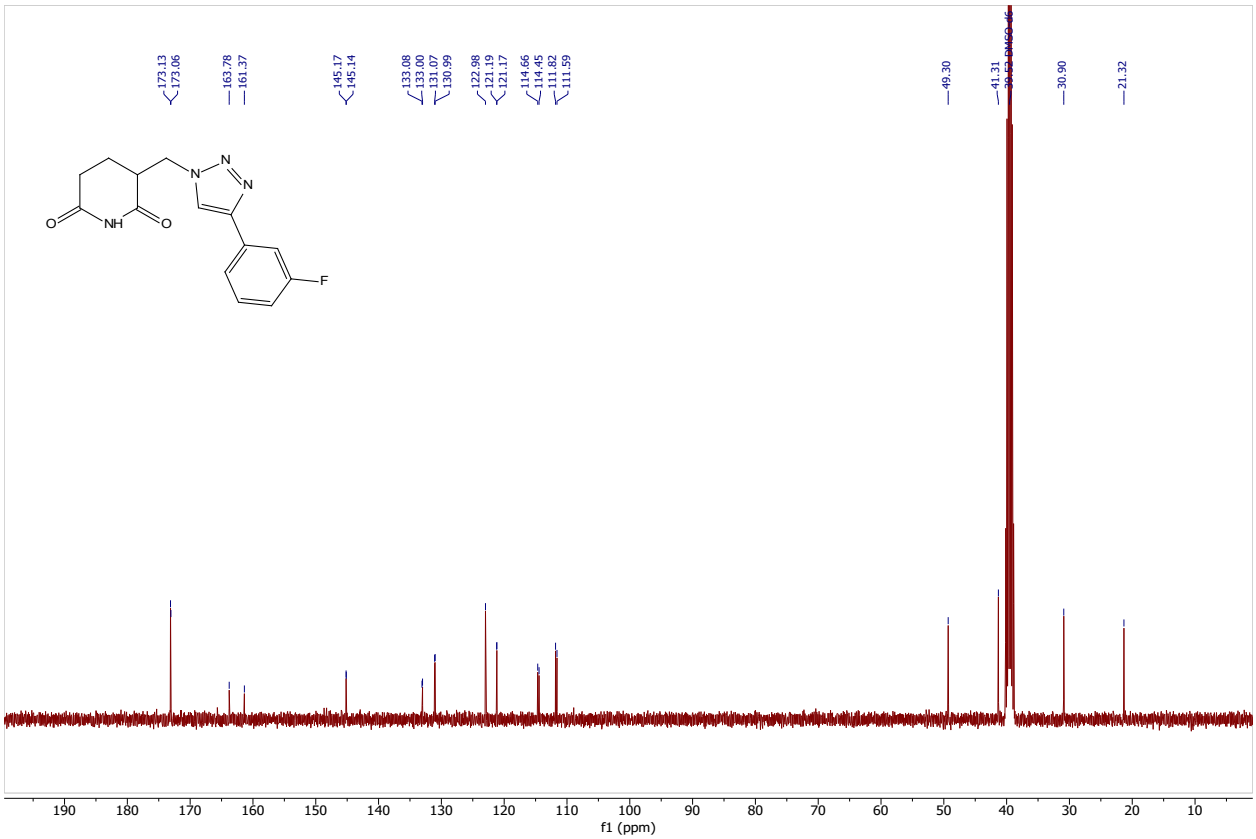
^{1}H and ^{13}C NMR spectra of compound ***4k***

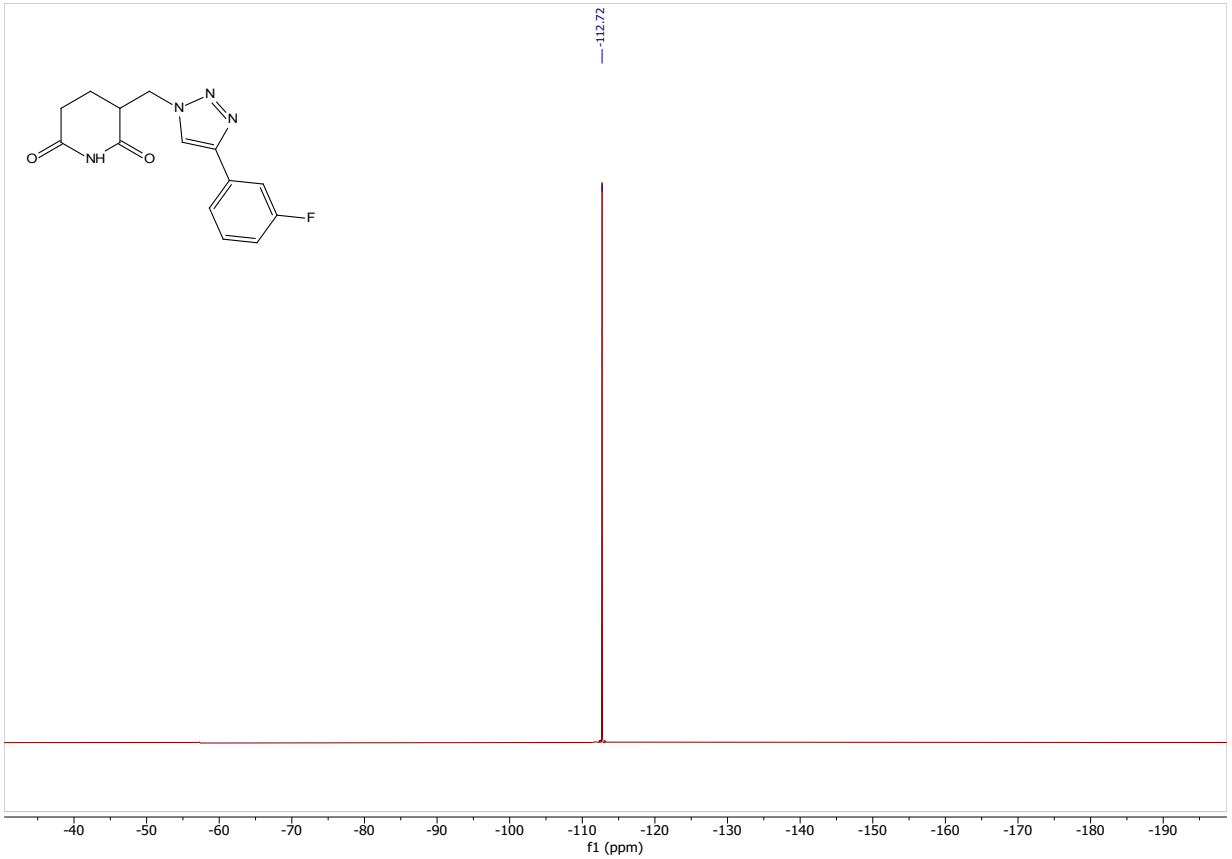




^{1}H, ^{13}C and ^{19}F NMR spectra of compound ***4l***






-112.72
O
NH
O
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N
N
F
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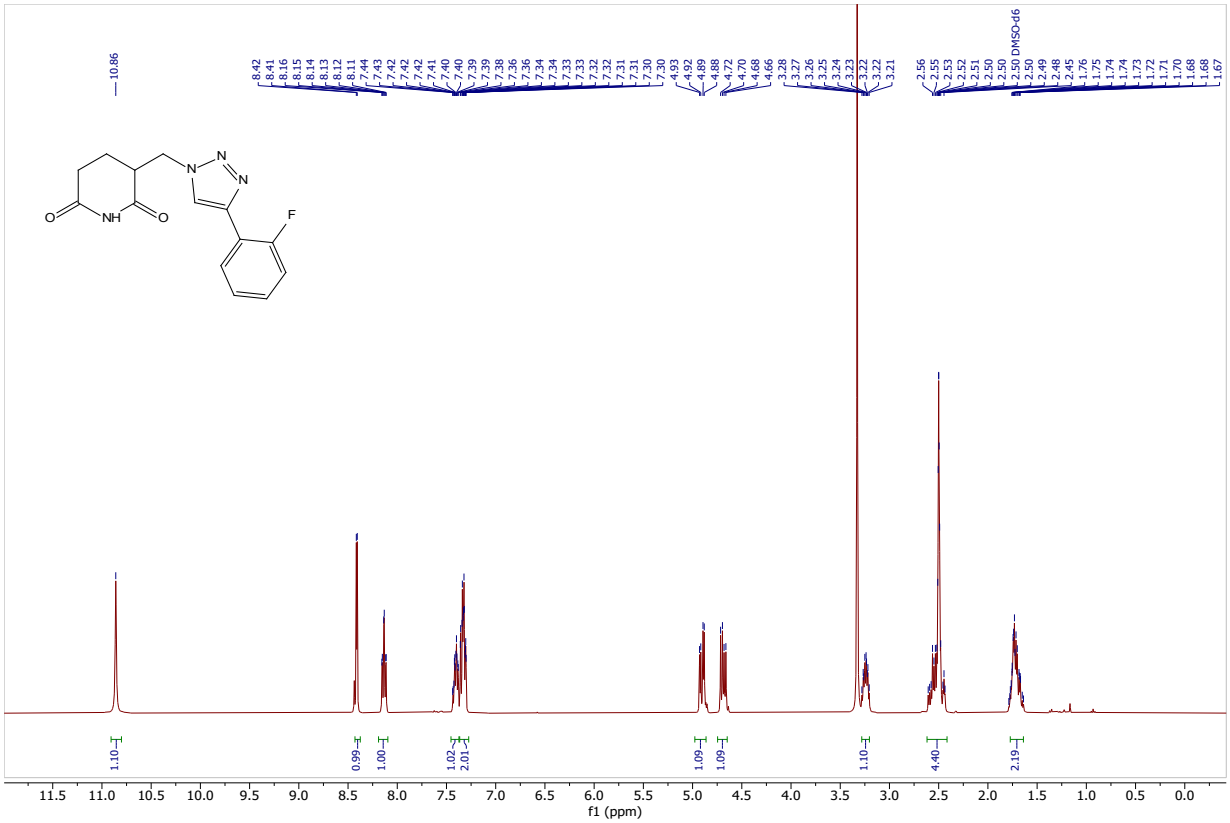
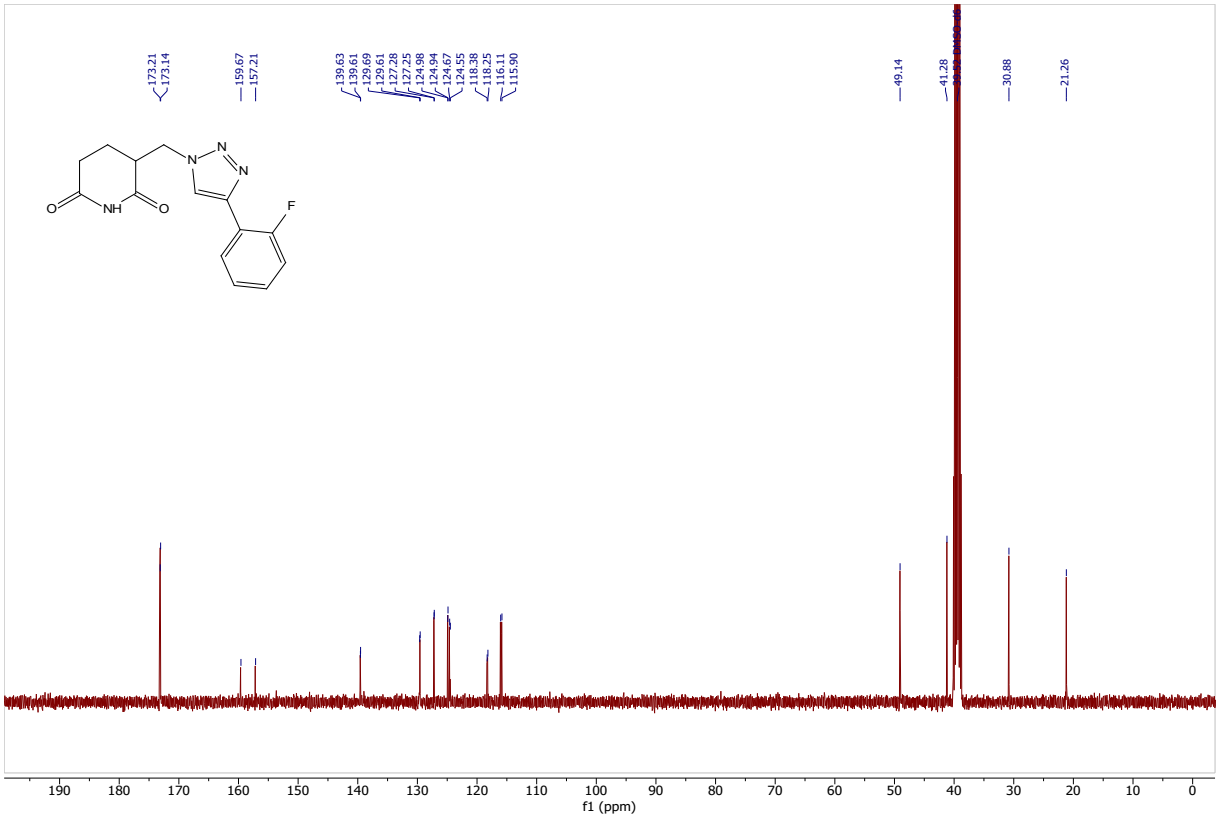
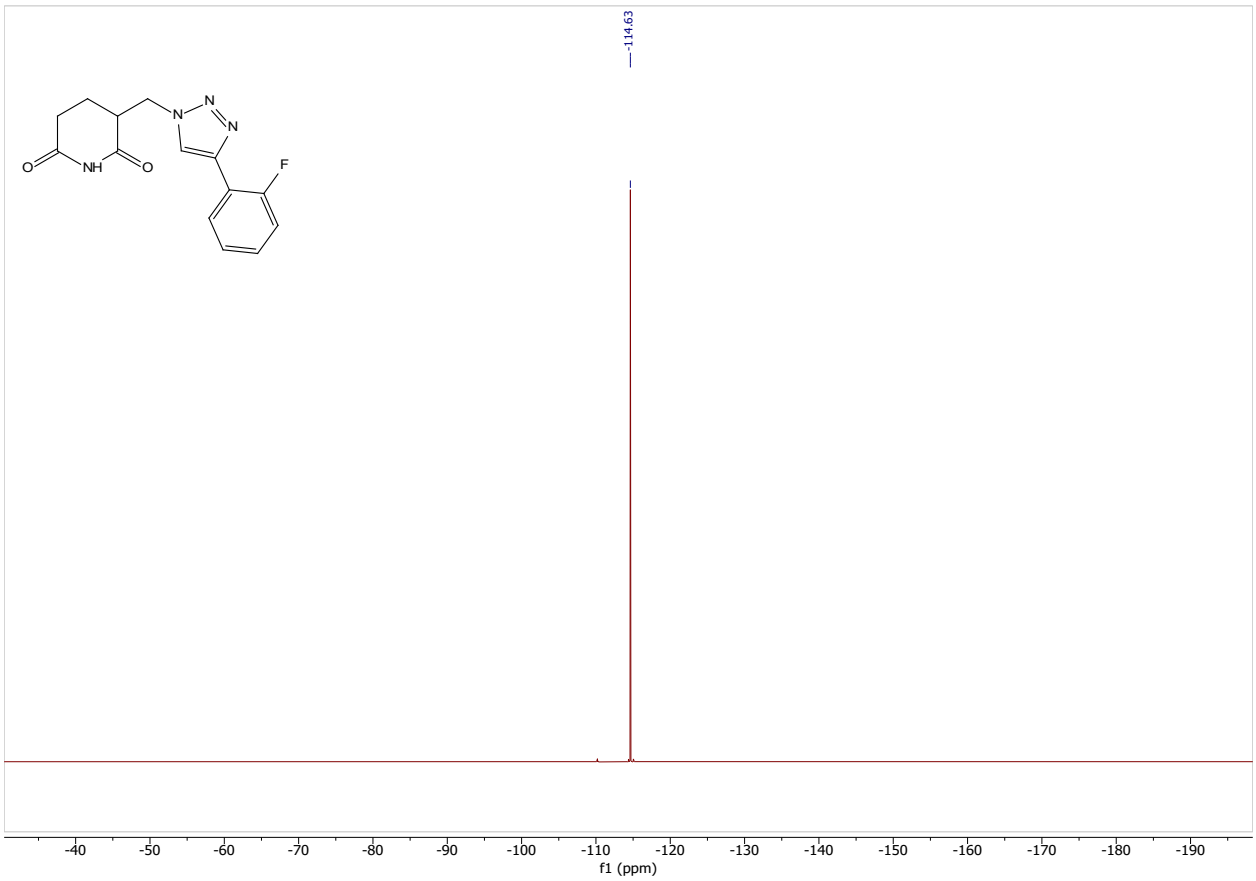
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

^{1}H, ^{13}C and ^{19}F NMR spectra of compound ***4m***






-114.63
O
NH
O
N
N
N
F
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)