ELECTRONIC SUPPORTING INFORMATION

Rapid Synthesis of Pomalidomide-Conjugates for the Development of Protein Degrader Libraries

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General Experimental

All chemical reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. “Dri-Solv” EMD Millipore grade DMF was used. A KD Scientific KDS-210 syringe pump was used for dropwise additions of reagents. Triturations were performed using a VWR model 75T ultrasonic cleaner. Solvents were removed in vacuo using either a Buchi R-300 Rotavapor (equipped with an I-300 Pro Interface, B-300 Base Heating Bath, Welch 2037B-01 DryFast pump, and VWR AD15R-40-V11B Circulating Bath), a Biotage V-10 evaporator, or a Kugelrohr short path distillation apparatus. Reactions were monitored by thin-layer chromatography carried out on Merck glass silica gel plates (60F254) using UV light as a visualizing agent and iodine and/or phosphomolybdic acid stain as developing agents. Manual flash chromatography was performed using Silicycle SiliaFlash F60 silica gel (particle size 0.040−0.063 mm, 230−400 mesh) as well as for automated flash chromatography. Solvents for silica gel chromatography were used as supplied by Sigma-Aldrich. Automated flash chromatography was performed on a Biotage Isolera instrument, equipped with a UV detector and Biotage Dalton mass detector. Chromatograms were recorded at 254 and 280 nm. High-resolution mass spectra (HRMS) and low-resolution mass spectra were obtained using Agilent 6520 Accurate-Mass QTOF LC/MS or Bruker MALDITOF Autoflex III and GenTech 5890 series II SSQ 7000 instruments, respectively. Optimization experiments were performed using an analytical high-performance liquid chromatography (HPLC) on an Agilent 1260 Infinity LC equipped with an Agilent 1260 autosampler, an Agilent 1260 multi-wavelength UV detector, and an Agilent 1260 automated fraction collector with a Poroshell 120 EC-C18 4.6 × 50 mm^2 2.7 μm column coupled with a Poroshell 120 EC-C18 4.6 × 5 mm^2 2.7 μm ultra-high performance liquid chromatography guard column. Experiments were run with a flow rate of 1.5 mL/min. Solvents (H2O, acetonitrile, and isopropanol) containing 0.1% trifluoroacetic acid (TFA) were used. The following gradient was used at 40 °C: method A: 5−95% MeCN in water, 0−20 min. Compound characterisation and purity were analysed by MS and nuclear magnetic resonance (NMR). ^{1}H NMR (400, 600 MHz)

and ^{13}C NMR (100, 151 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6 at 298K on Bruker Avance III 400 MHz (broadband fluorine observe probe), Bruker DRX 400 MHz (broadband observe (BBO) probe), Bruker Avance 400 MHz (BBO probe), or Bruker Avance III 600 MHz (BBO probe) spectrometers. Chemical shifts (δ) are reported in ppm relative to solvent signals (δ = 7.26 and 77.16 ppm for $CDCl_3$ / 2.50 and 39.52 for DMSO-d_6). Coupling constants (*J*) are quoted in Hz. Abbreviations used for multiplicity are as follows: s – singlet, d – doublet, t – triplet, q – quartet, br – broad, m – multiplet.

Experimental Procedures and Characterising Data for Compounds

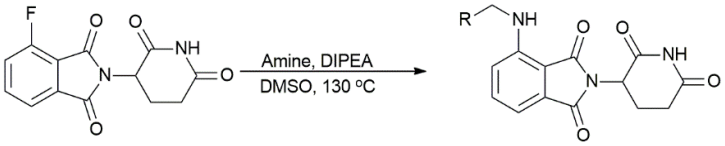
Procedure for solvent screen:

To a vial containing **1** (0.2 mmol, 1.0 eq) and either **4** or **5** (1.1-1.3 eq) with 1,3,5-trimethoxybenzene as an internal standard was added the desired solvent (1 mL) and DIPEA (3 eq). The reactions were heated to 90 °C for 16 hours, then cooled to room temperature and volatiles were removed. The residue was dissolved in DMSO-d_6 and ^1H NMR spectra were collected. Each sample was prepared in duplicate and the yields were averaged.

Procedure for temperature screen:

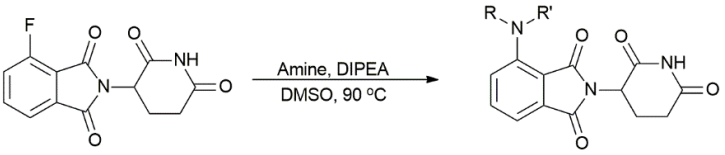
To a vial containing **1** (0.2 mmol, 1.0 eq) and either **4** or **5** (1.1-1.3 eq), optionally with $Ca(NO_3)_2$ (2 eq) and with 1,3,5-trimethoxybenzene as an internal standard was added DMSO-d_6 and DIPEA (3 eq). The reactions were heated the desired temperature for 16 hours, then cooled to room temperature and volatiles were removed. The remaining solution of DMSO-d_6 was filtered over a syringe filter and ^1H NMR spectra were collected. Each sample was prepared in duplicate and the yields were averaged.

General S_NAr Procedure for Primary Amines (GP1)



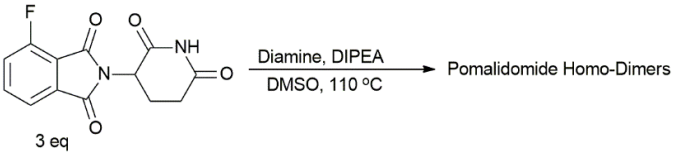
4-Fluorothalidomide (124 mg, 0.45 mmol, 1.0 equiv.), amine (0.50 mmol, 1.1 equiv.) and DIPEA (230 µL, 1.35 mmol, 3.0 equiv.) were dissolved in DMSO (1.0 mL, 0.2 M) and warmed to 130 °C for 16 hours. After this time, the solvent was removed by Kugelrohr distillation at 40 °C and 0.1 Torr. The residue was purified by flash column chromatography over silica gel, eluting with EtOAc:hexanes (20 – 100 %).

General S_NAr Procedure for Secondary Amines (GP2)



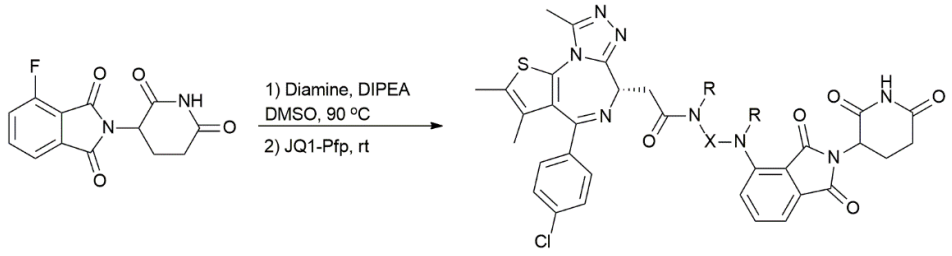
4-Fluorothalidomide (100 mg, 0.36 mmol, 1.0 equiv.), amine (0.40 mmol, 1.1 equiv.) and DIPEA (193 µL, 1.09 mmol, 3.0 equiv.) were dissolved in DMSO (1.8 mL, 0.2 M) and warmed to 130 °C for 16 hours. After this time, the solvent was removed by Kugelrohr distillation at 40 °C and 0.1 Torr. The residue was purified by flash column chromatography over silica gel, eluting with EtOAc:hexanes (20 – 100 %).

General Procedure for Pomalidomide Homo-Dimers (GP3)



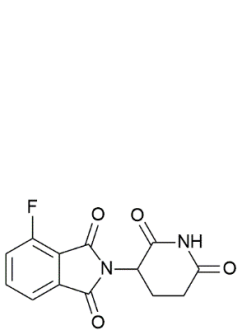
4-Fluorothalidomide (**GP3a**: 325 mg, 1.2 mmol, 3.0 equiv.; **GP3b**: 166 mg, 0.60 mmol, 3.0 equiv.), amine (**GP3a**: 0.40 mmol, 1.0 equiv.; **GP3b**:0.20 mmol, 1.0 equiv.) and DIPEA (**GP3a**: 230 µL, 1.5 mmol, 3.8 equiv.; **GP3b**: 105 µL, 0.6 mmol, 3.0 equiv.) were dissolved in DMSO (**GP3a**: 2.0 mL, 0.2 M; **GP3b**: 1.0 mL, 0.2 M) and warmed to 110 °C (**GP3a**) or 90 °C (**GP3b**) for 16 hours. After this time, the solvent was removed by Kugelrohr distillation at 40 °C and 0.1 Torr. The residue was purified by flash column chromatography over silica gel, eluting with MeOH:DCM (1 – 10%) and then by reverse phase flash chromatography with C_{18} functionalized silica gel (5 – 95%, MeCN in water).

General Procedure for One-Pot JQ1-Pomalidomide Conjugates (GP4)



4-Fluorothalidomide (28 mg, 0.10 mmol, 1.0 equiv.), amine (0.12 mmol, 1.2 equiv.) and DIPEA (53 µL, 0.3 mmol, 3.0 equiv.) were dissolved in DMSO (1.0 mL, 0.2 M) and warmed to 90 °C for 3.5 hours. After this time, the reaction was cooled to room temperature and compound **9** (1.1 eq) was added to the solution and stirred for 16 hours. The solvent was then removed by Kugelrohr distillation at 40 °C and 0.1 Torr. The residue was purified by flash column chromatography over silica gel, eluting with MeOH:DCM (1 – 10%) and then by reverse phase flash chromatography with C_{18} functionalized silica gel (5 – 95%, MeCN in water).

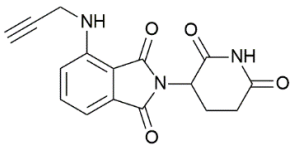
4-Fluorothalidomide **(1)** [1]



To a suspension of 4-fluoroisobenzofuran-1,3-dione (5.66 g, 34.1 mmol, 1.0 equiv.) and 3-aminopiperidine-2,6-dione (4.37 g, 34.1 mmol, 1.0 equiv.) in acetic acid (100 mL) was added sodium

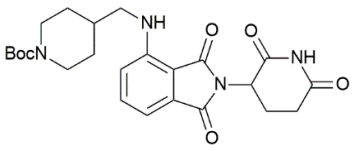
acetate (3.36 g, 40.9 mmol). The resulting mixture was heated to reflux overnight. After cooling to room temperature, the solvent was removed *in vacuo*, the resultant solid was suspended in water (50 mL) and filtered. The cake was washed with water (3 x 50 mL) and dried under suction for 1 hour. The cake was then dried under vacuum at 40 °C overnight to yield the compound **1** as an off-white solid (7.64 g, 27.7 mmol, 81%): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.15 (s, 1H), 7.96 (ddd, *J*=8.4, 7.3, 4.5, 1H), 7.80 (d, *J*=7.3, 1H), 7.75 (app. t, *J*=8.9, 1H), 5.17 (dd, *J*=12.8, 5.4, 1H), 2.95 – 2.85 (m, 1H), 2.69 – 2.53 (m, 2H), 2.11 – 2.04 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.7, 169.6, 166.1 (d, $J_{C\text{-}F}$ = 3.0), 163.9, 156.8 (d, $J_{C\text{-}F}$ = 262.3), 138.0 (d, $J_{C\text{-}F}$ = 8.1), 133.4, 123.0 (d, $J_{C\text{-}F}$ = 19.5), 120.0 (d, $J_{C\text{-}F}$ = 3.2), 117.0 (d, $J_{C\text{-}F}$ = 12.5), 49.1, 30.9, 21.8; HRMS (ESI) *m/z* calculated for $[C_{13}H_9FN_2O_4 + Na]^+$ = 299.0439, found 299.0438.

2-(2,6-dioxopiperidin-3-yl)-4-(prop-2-yn-1-ylamino)isoindoline-1,3-dione **(2a)**[2]



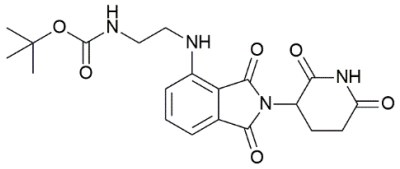
Following **GP1**: Compound **2a** was isolated as a yellow solid, (0.117 g, 0.38 mmol, 84%): R_f = 0.37 (EtOAc:hexanes 1:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.1 (s, 1H), 7.7 (dd, *J*=8.5, 7.1, 1H), 7.2 (d, *J*=8.5, 1H), 7.1 (d, *J*=7.1, 1H), 6.9 (t, *J*=6.2, 1H), 5.1 (dd, *J*=12.9, 5.4, 1H), 4.2 (dd, *J*=6.2, 2.5, 2H), 3.2 (t, *J*=2.3, 1H), 2.9 (ddd, *J*=17.3, 14.0, 5.4, 1H), 2.6 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.8, 170.0, 168.6, 167.2, 145.2, 136.1, 132.1, 118.0, 111.4, 110.3, 80.9, 73.8, 48.6, 31.5, 31.0, 22.1; HRMS (ESI) *m/z* calculated for $[C_{16}H_{12}N_3O_4 - H]^-$ = 310.0833, found 310.0827.

tert-butyl-4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)piperidine-1-carboxylate **(2b)**



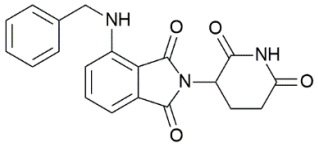
Following **GP1**: Compound **2b** was isolated as a yellow solid, (0.175g, 0.37 mmol, 83%): R_f = 0.23 (EtOAc:hexanes, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.82 (s, 1H), 7.44 (dd, *J*=8.5, 7.1, 1H), 7.04 (d, *J*=7.1, 1H), 6.84 (d, *J*=8.5, 1H), 6.33 (t, *J*=6.0, 1H), 4.90 (dd, *J*=12.2, 5.4, 1H), 4.10 (s, 2H), 3.13 (t, *J*=6.0, 2H), 2.85 – 2.57 (m, 5H), 2.11 – 2.01 (m, 1H), 1.75 – 1.72 (m, 3H), 1.42 (s, 9H), 1.21 – 1.09 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.6, 169.6, 168.7, 167.6, 154.8, 147.0, 136.2, 132.5, 116.6, 111.5, 110.0, 79.5, 48.9, 48.3, 36.3, 31.4, 30.0, 28.5, 22.8; HRMS (ESI) *m/z* calculated for $[C_{24}H_{30}N_4O_6 + Na]^+$ = 493.2058, found 493.2054.

***tert-butyl (2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)carbamate* (2c)[3]**



Following **GP1**: Compound **2c** was isolated as a yellow solid, (0.118 g, 0.28 mmol, 64%): R_f = 0.17 (EtOAc:hexanes, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.24 (s, 1H), 7.50 (dd, *J*=8.5, 7.1, 1H), 7.11 (d, *J*=7.1, 1H), 6.98 (d, *J*=8.6, 1H), 6.39 (t, *J*=6.1, 1H), 4.95 – 4.85 (m, 2H), 3.44 (q, *J*=6.1, 2H), 3.36 (q, *J*=6.1, 2H), 2.92 – 2.85 (m, 1H), 2.85 – 2.67 (m, 2H), 2.15 – 2.08 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.2, 169.5, 168.5, 167.7, 156.2, 147.0, 136.4, 132.6, 116.8, 112.0, 110.4, 79.9, 49.0, 42.7, 40.3, 31.6, 28.5, 22.9; HRMS (ESI) *m/z* calculated for $[C_{20}H_{23}N_4O_6\text{-}H]^-$ = 415.1623, found 415.1607.

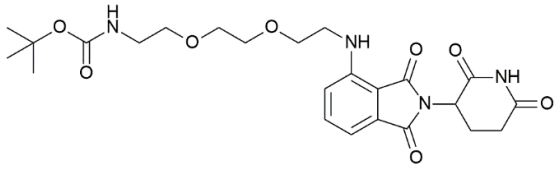
4-(benzylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2d)



Following **GP1**: Compound **2d** was isolated as a yellow solid, (0.104g, 0.29 mmol, 68%): R_f = 0.25 (EtOAc:hexanes, 1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.11 (s, 1H), 7.51 (dd, *J*=8.6, 7.1, 1H), 7.39 – 7.31 (m, 4H), 7.28 – 7.20 (m, 2H), 7.02 (d, *J*=7.0, 1H), 6.96 (d, *J*=8.6, 1H), 5.07 (dd, *J*=12.9, 5.5,

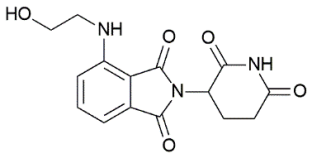
1H), 4.56 (d, *J*=6.3, 2H), 2.89 (ddd, *J*=17.0, 13.9, 5.5, 1H), 2.63 – 2.51 (m, 2H), 2.04 (dtd, *J*=12.8, 5.5, 2.3, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.8, 170.1, 168.7, 167.3, 146.1, 138.9, 136.1, 132.2, 128.5, 127.0, 126.9, 117.6, 110.7, 109.5, 48.6, 45.4, 31.0, 22.1; HRMS (ESI) *m/z* calculated for $[C_{20}H_{17}N_3O_4 + Na]^+$ = 386.1111, found 386.1117.

***tert-butyl(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl) carbamate* (2e)[4]**



Following **GP1**: Compound **2e** was isolated as a yellow solid, (0.203 g, 0.40 mmol, 92%): R_f = 0.58 (EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.78 (s, 1H), 7.46 (dd, *J*=8.5, 7.1, 1H), 7.07 (d, *J*=7.1, 1H), 6.89 (d, *J*=8.5, 1H), 6.49 (t, *J*=5.7, 1H), 5.07 (s, 0H), 4.94 – 4.85 (m, 1H), 3.70 (t, *J*=5.4, 2H), 3.65 – 3.59 (m, 4H), 3.54 (t, *J*=5.1, 2H), 3.45 (q, *J*=5.5, 2H), 3.29 (q, *J*=5.5, 2H), 2.86 – 2.67 (m, 3H), 2.11 – 2.07 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.5, 169.4, 168.7, 167.7, 156.1, 146.9, 136.1, 132.6, 116.8, 111.7, 110.4, 79.3, 70.8, 70.4, 70.2, 69.5, 49.0, 42.4, 40.5, 31.5, 28.5, 22.9; HRMS (ESI) *m/z* calculated for $[C_{24}H_{31}N_4O_8 - H]^-$ = 503.2147, found 503.2137.

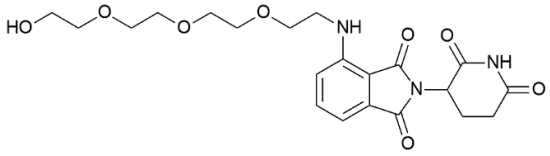
2-(2,6-dioxopiperidin-3-yl)-4-((2-hydroxyethyl)amino)isoindoline-1,3-dione (2f)



Following **GP1** : Compound **2f** was isolated as a yellow solid (0.061 g, 0.192 mmol, 43%): R_f = 0.57 (EtOAc); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (br s, 1H), 7.58 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.64 (t, *J* = 5.8 Hz, 1H), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.90 (t, *J* = 5.2 Hz, 1H), 3.59 (t, *J* = 5.4 Hz, 2H), 3.36 (q, *J* = 5.7 Hz, 2H), 2.88 (ddd, *J* = 17.0, 13.9, 5.4 Hz,

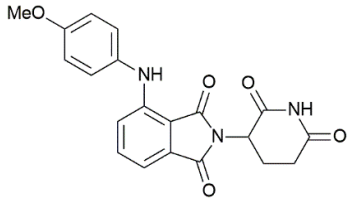
1H), 2.64 – 2.50 (m, 2H), 2.03 (dtd, J = 13.1, 5.3, 2.2 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.8, 170.1, 168.9, 167.3, 146.6, 136.2, 132.1, 117.4, 110.5, 109.2, 59.4, 48.5, 44.3, 31.0, 22.1; HRMS (ESI) *m/z* calculated for $[C_{15}H_{15}N_3O_5 + H]^+$ = 318.1084, found 318.1078.

2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl)amino)isoindoline-1,3-dione (2g)[5]



Following **GP1**: On a 1.0 mmol scale, compound **2g** was isolated as viscous yellow oil, (0.358 g, 0.80 mmol, 80%): R_f = 0.35 (5% MeOH in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.22 (br s, 1H), 7.39 (dd, J = 8.5, 7.1 Hz, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.42 (t, J = 5.7 Hz, 1H), 4.95 – 4.77 (m, 1H), 3.67 – 3.56 (m, 12H), 3.55 – 3.50 (m, 2H), 3.39 (q, J = 5.5 Hz, 2H), 3.05 (br s, 1H), 2.81 – 2.64 (m, 3H), 2.08 – 1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9, 169.2, 168.9, 167.6, 146.7, 135.9, 132.4, 116.7, 111.4, 110.1, 72.4, 70.5, 70.5, 70.4, 70.2, 69.4, 61.5, 48.8, 42.2, 31.3, 22.6; HRMS (MALDI) *m/z* calculated for $[C_{21}H_{27}N_3O_8 + H]^+$ = 472.1690, found 427.1692.

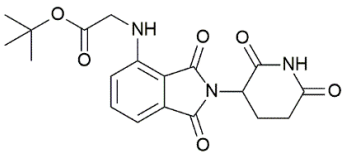
2-(2,6-dioxopiperidin-3-yl)-4-((4-methoxyphenyl)amino)isoindoline-1,3-dione (2h)



Following **GP1**: Compound **2h** was isolated as an orange solid, (0.109 g, 0.287 mmol, 64%): R_f = 0.45 (EtOAc:hexanes, 1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.12 (s, 1H), 8.24 (s, 1H), 7.55 (dd, J = 8.6, 7.1 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.15 (dd, J = 12.3, 7.8 Hz, 2H), 7.01 – 6.94 (m, 2H), 5.11 (dd, J = 12.7, 5.4 Hz, 1H), 3.77 (s, 3H), 2.91 (ddd, J = 16.7, 13.6, 5.4 Hz, 1H), 2.64 – 2.51 (m, 2H), 2.06 (ddd, J = 12.9, 5.8, 3.5 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 170.0, 168.4, 167.1, 156.6, 144.3,

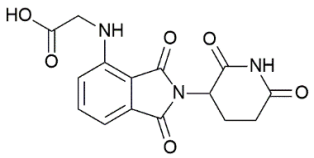
136.1, 132.3, 131.7, 125.3, 118.5, 114.7, 112.4, 110.6, 55.3, 48.7, 31.0, 22.1; HRMS (ESI) *m/z* calculated for $[C_{20}H_{17}N_3O_5 + H]^+$ = 380.1241, found 380.1234.

tert-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetate (2i)[6]



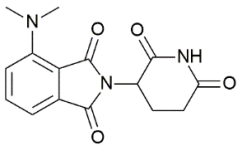
Following **GP1**: Compound **2i** was isolated as a yellow solid, (0.093 g, 0.24 mmol, 53%): R_f = 0.62 (EtOAc:hexanes, 1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.10 (br s, 1H), 7.58 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.85 (t, *J* = 6.1 Hz, 1H), 5.07 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.09 (d, *J* = 6.0 Hz, 2H), 2.89 (ddd, *J* = 17.0, 13.8, 5.4 Hz, 1H), 2.64 – 2.51 (m, 2H), 2.04 (dtd, *J* = 13.0, 5.4, 2.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 170.0, 169.2, 168.7, 167.2, 145.8, 136.1, 132.0, 117.7, 111.1, 109.8, 81.2, 48.6, 44.5, 31.0, 27.7, 22.1. ; HRMS (ESI) *m/z* calculated for $[C_{19}H_{21}N_3O_6 + Na]^+$ = 410.1323, found 410.1314.

2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetic acid (2j)[6]



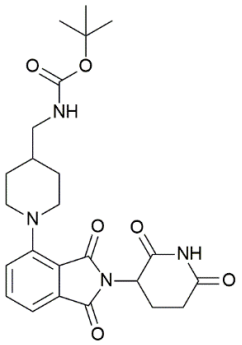
Following **GP1**: Compound **2j** was isolated as a yellow solid, (0.020 g, 0.060 mmol, 13%): R_f = 0.54 (1% AcOH in EtOAc); ^{1}H NMR (600 MHz, DMSO-d_6) δ =12.98 (br s, 1H), 11.10 (br s, 1H), 7.70 – 7.47 (m, 1H), 7.07 (d, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.85 (t, *J* = 5.9 Hz, 1H), 5.07 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.10 (d, *J* = 5.8 Hz, 2H), 2.89 (ddd, *J* = 17.0, 13.9, 5.5 Hz, 1H), 2.65 – 2.51 (m, 2H), 2.10 – 1.99 (m, 1H); 13C NMR (151 MHz, DMSO-d_6) δ = 172.8, 171.4, 170.0, 168.8, 167.2, 145.8, 136.1, 132.0, 117.7, 111.0, 109.6, 48.6, 43.8, 31.0, 22.1. HRMS (ESI) *m/z* calculated for $[C_{15}H_{13}N_3O_6 + Na]^+$ = 354.0697, found 354.0691.

Preparation of 4-(dimethylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (3)



To a solution of **1** (0.225 g, 0.81 mmol, 1.0 eq) in DMF (4 mL) was added DIPEA (0.70 mL, 4.0 mmol, 4.9 eq) and propargylamine (0.05 mL, 0.78 mmol, 1.0 eq). The solution was heated to 90 °C for 16 hours and then cooled to room temperature. Volatiles were removed by Kugelrohr distillation and the crude residue was adsorbed to silica gel and purified by silica gel flash chromatography (25 – 65% EtOAc in hexanes) to afford compound **2a** (0.087 g, 0.30 mmol, 37%) and compound **3** (0.079 g, 0.26 mmol, 32%) as yellow solids. Compound **3** was recrystallized from EtOAc and hexanes (1:1) to afford X-Ray quality crystals. R_f = 0.29 (EtOAc:hexanes, 1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.07 (s, 1H), 7.63 (dd, J = 8.6, 7.0 Hz, 1H), 7.31 – 7.18 (m, 2H), 5.08 (ddd, J = 12.7, 5.5, 1.7 Hz, 1H), 3.04 (s, 6H), 2.94 – 2.81 (m, 1H), 2.64 – 2.51 (m, 2H), 2.08 – 1.94 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.8, 170.0, 167.1, 166.3, 149.9, 135.2, 133.9, 122.6, 113.4, 113.0, 48.8, 42.9, 30.9, 22.1. HRMS (ESI) *m/z* calculated for $[C_{15}H_{15}N_3O_4 + H]^+$ = 302.1135, found 302.1136.

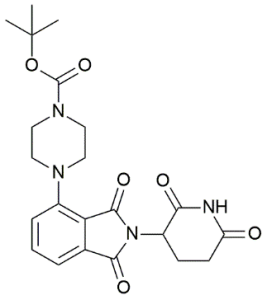
***tert-butyl ((1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperidin-4-yl)methyl)carbamate* (6a)**



Following **GP2**: Compound **6a** was isolated as a yellow solid, (0.156 g, 0.33 mmol, 92%): R_f = 0.29 (EtOAc:hexanes, 6:4); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.08 (s, 1H), 7.67 (dd, J=8.4, 7.2, 1H), 7.32 (s, 1H), 7.31 (s, 1H), 6.90 (t, J=5.9, 1H), 5.10 (dd, J=12.9, 5.4, 1H), 3.69 (d, J=11.6, 2H), 2.95 – 2.76 (m, 5H), 2.65 – 2.51 (m, 2H), 2.14 – 1.95 (m, 1H), 1.79 – 1.66 (m, 2H), 1.64 – 1.49 (m, 1H), 1.39

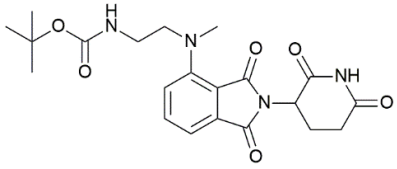
(s, 9H), 1.36 – 1.22 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.7, 170.0, 167.1, 166.3, 155.8, 150.1, 135.7, 133.6, 123.9, 116.3, 114.4, 77.4, 50.9, 48.8, 45.4, 35.8, 31.0, 29.6, 28.3, 22.1; HRMS (ESI) *m/z* calculated for $[C_{24}H_{30}N_4O_6 + H]^+$ = 471.2248, found 471.2238.

***tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperazine-1-carboxylate* (6b)**[3]



Following **GP2**: Compound **6b** was isolated as a yellow solid, (138 mg, 0.31 mmol, 86 %): R_f = 0.37 (EtOAc:hexanes, 6:4); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.1 (s, 1H), 7.71 (dd, *J*=8.4, 7.1, 1H), 7.39 (d, *J*=7.1, 1H), 7.37 – 7.31 (m, 1H), 5.12 (dd, *J*=12.9, 5.4, 1H), 3.57 – 3.45 (m, 4H), 3.32 – 3.17 (m, 4H), 2.94 – 2.85 (m, 1H), 2.64 – 2.53 (m, 2H), 2.09 – 1.99 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.2, 170.4, 167.4, 166.8, 154.3, 150.0, 136.3, 134.1, 124.3, 117.4, 115.7, 79.5, 50.9, 49.3, 31.4, 28.5, 22.5; HRMS (ESI) *m/z* calculated for $[C_{22}H_{26}N_4O_6 + H]^+$ = 443.1927, found 443.1925.

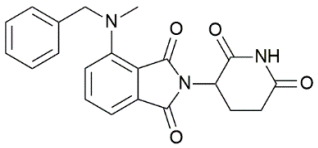
***tert-butyl (2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)(methyl)amino)ethyl)carbamate* (6c)**[4]



Following **GP2**: Compound **6c** was isolated as a yellow solid, (131 mg, 0.30 mmol, 84%): R_f = 0.30 (EtOAc:hexanes, 6:4); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.07 (s, 1H), 7.61 (dd, *J*=8.6, 7.0, 1H), 7.25 (d, *J*=8.6, 1H), 7.22 (d, *J*=7.0, 1H), 6.72 (t, *J*=5.8, 1H), 5.09 (dd, *J*=12.8, 5.4, 1H), 3.71 – 3.48 (m, 2H), 3.16 (q, *J*=6.3, 2H), 3.04 (s, 3H), 2.97 – 2.82 (m, 1H), 2.65 – 2.52 (m, 2H), 2.07 – 1.94 (m, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.2, 170.4, 167.6, 166.8, 155.9, 149.9, 135.5, 134.4,

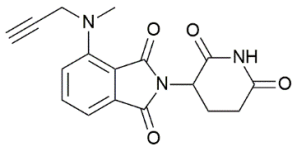
123.6, 113.7, 113.3, 78.0, 54.6, 49.2, 39.9, 38.1, 31.4, 28.6, 22.6; HRMS (ESI) *m/z* calculated for $[C_{21}H_{26}N_4O_6 + H]^+$ = 431.1935, found 431.1925.

4-(benzyl(methyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **(6d)**



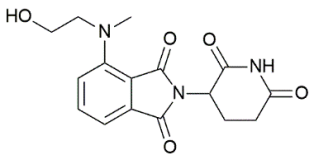
Following **GP2**: Compound **6d** was isolated as a yellow solid, (112 mg, 0.30 mmol, 82 %): R_f = 0.53 (EtOAc:hexanes, 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.93 (s, 1H), 7.48 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.37 – 7.20 (m, 6H), 7.08 (d, *J* = 8.5 Hz, 1H), 5.01 – 4.88 (m, 1H), 4.67 (s, 2H), 2.96 (s, 3H), 2.91 – 2.57 (m, 3H), 2.16 – 1.89 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.5, 168.7, 167.5, 166.8, 150.1, 137.5, 135.2, 134.5, 128.6, 127.7, 127.4, 123.3, 114.7, 114.4, 59.5, 49.2, 40.3, 31.4, 22.7; HRMS (ESI) *m/z* calculated for $[C_{21}H_{18}N_3O_4 + H]^+$ = 378.1448, found 378.1448.

2-(2,6-dioxopiperidin-3-yl)-4-(methyl(prop-2-yn-1-yl)amino)isoindoline-1,3-dione **(6e)**[4]



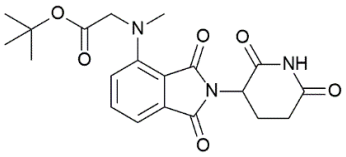
To a solution of **1** (100 mg, 0.36 mmol, 1.0 eq) in DMSO (1.8 mL) was added N-methylpropargylamine (34 μL, 0.40 mmol, 1.1 eq) and DIPEA (194 μL, 1.1 mmol, 3.0 eq). The resulting mixture was then stirred at room temperature for 16 hours, after which time volatiles were removed by Kugelrohr distillation at 40 °C and 0.1 Torr. The residue was then purified by flash column chromatography to afford **6e** as a yellow solid (72 mg, 0.22 mmol, 61%): R_f = 0.44 (EtOAc:hexane, 6:4); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.10 (s, 1H), 7.75 – 7.71 (m, 1H), 7.39 (s, 1H), 7.37 (s, 1H), 5.11 (dd, *J*=12.8, 5.4, 1H), 4.33 (d, *J*=2.4, 2H), 3.24 – 3.22 (m, 1H), 3.02 (s, 3H), 2.94 – 2.84 (m, 1H), 2.63 – 2.55 (m, 2H), 2.08 – 2.02 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.3, 170.5, 167.5, 166.9, 149.0, 136.0, 134.1, 124.7, 116.4, 115.3, 79.8, 76.3, 49.4, 44.7, 40.4, 31.4, 22.5; HRMS (ESI) *m/z* calculated for $[C_{17}H_{15}N_3O_4 + H]^+$ = 326.1134, found 326.1135.

2-(2,6-dioxopiperidin-3-yl)-4-((2-hydroxyethyl)(methyl)amino)isoindoline-1,3-dione (6f)



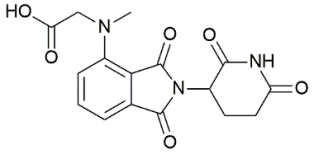
Following **GP2**: Compound **6f** was isolated as a yellow solid, (0.115 g, 0.35 mmol, 96%): R_f = 0.37 (EtOAc); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.07 (br s, 1H), 7.60 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 1H), 5.08 (dd, *J* = 12.7, 5.4 Hz, 1H), 4.62 (t, *J* = 5.1 Hz, 1H), 3.63 (q, *J* = 5.6 Hz, 2H), 3.60 – 3.54 (m, 2H), 3.06 (s, 3H), 2.88 (ddd, *J* = 16.9, 13.8, 5.5 Hz, 1H), 2.62 – 2.51 (m, 2H), 2.06 – 1.97 (m, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.8, 170.0, 167.1, 166.4, 149.6, 135.0, 133.9, 123.3, 113.0, 112.7, 58.7, 57.2, 48.7, 40.2, 31.0, 22.1. HRMS (ESI) *m/z* calculated for $[C_{16}H_{17}N_3O_5 + H]^+$ = 332.1241, found 332.1239.

tert-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)(methyl)amino)acetate (6g)



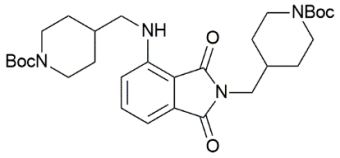
Following **GP2**: Compound **6g** was isolated as a yellow solid, (0.124 g, 0.31 mmol, 84%): R_f = 0.0.75 (EtOAc); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.08 (br s, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 2H), 5.08 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.42 – 4.28 (m, 2H), 3.05 (s, 3H), 2.88 (ddd, *J* = 16.9, 14.0, 5.4 Hz, 1H), 2.63 – 2.51 (m, 2H), 2.09 – 1.94 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 169.9, 169.1, 167.0, 166.6, 148.8, 135.2, 133.6, 123.3, 113.5, 113.2, 80.7, 57.2, 48.8, 30.9, 27.7, 22.0; HRMS (ESI) *m/z* calculated for $[C_{20}H_{23}N_3O_6 + H]^+$ = 402.1660, found 402.1663.

2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)(methyl)amino)acetic acid (6h)



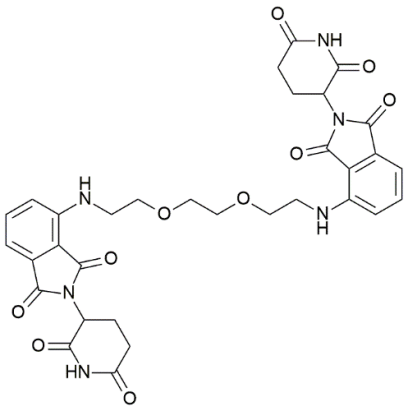
Following **GP2**: Compound **6h** was isolated as a yellow solid, (0.083 g, 0.24 mmol, 67%): R_f = 0.43 (1% AcOH in EtOAc); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 12.54 (br s, 1H), 11.07 (br s, 1H), 7.64 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.32 – 7.18 (m, 2H), 5.08 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.37 (s, 2H), 3.05 (s, 3H), 2.87 (ddd, *J* = 17.0, 13.9, 5.5 Hz, 1H), 2.63 – 2.52 (m, 1H), 2.06 – 1.95 (m, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.8, 171.5, 170.0, 167.0, 166.6, 148.9, 135.2, 133.7, 123.3, 113.4, 113.1, 56.5, 48.8, 40.5, 30.9, 22.0; HRMS (ESI) *m/z* calculated for $[C_{16}H_{15}N_3O_6 + H]^+$ = 346.1034, found 346.1027.

tert-butyl-4-(((2-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-1,3-dioxoisoindolin-4-yl)amino)methyl)piperidine-1-carboxylate (7)



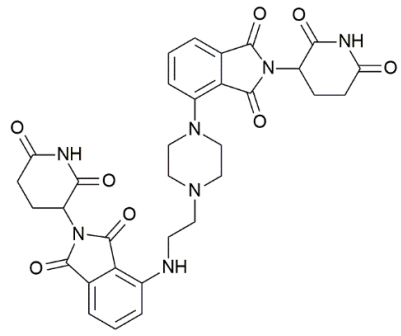
4-Fluorothalidomide (56.0 mg, 0.20 mmol, 1.0 equiv.), *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (136.8 mg, 0.64 mmol, 3.2 equiv.), 1,3,5-trimethoxybenzene (12.6 mg) as an internal standard, and DIPEA (0.105 μL, 0.60 mmol, 3.0 equiv.) were dissolved in DMSO-d_6 (1.0 mL) and warmed to 90 °C for 16 hours. After this time, an NMR yield was determined for **7** (0.074 mmol, 36%) and **2b** (0.028 mmol, 14%), and then the solvent was removed by Kugelrohr distillation at 40 °C and 0.1 Torr. The residue was purified by column chromatography over silica gel, eluting with EtOAc:hexanes (15 – 60 %) to give compounds **2b** (6 mg, 0.013 mmol, 6%) and **7** as a yellow-green solids (20 mg, 0.036 mmol, 18%): R_f = 0.57 (EtOAc:hexanes, 1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.52 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.58 (t, *J* = 6.3 Hz, 1H), 4.04 – 3.78 (m, 4H), 3.38 (d, *J* = 7.1 Hz, 2H), 3.20 (t, *J* = 6.5 Hz, 2H), 2.66 (s, 2H), 1.87 – 1.70 (m, 2H), 1.70 – 1.62 (m, 2H), 1.60 – 1.52 (m, 2H), 1.40 – 1.36 (m, 20H), 1.12 – 0.95 (m, 4H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 170.0, 168.1, 153.8, 153.8, 146.3, 135.8, 132.3, 116.9, 110.1, 109.3, 78.4, 47.1, 43.4, 42.7, 42.1, 35.4, 35.0, 29.4, 29.3, 28.1, 28.1; HRMS (ESI) *m/z* calculated for $[C_{30}H_{44}N_4O_6 + H]^+$ = 557.3340, found 557.3334.

***4,4'-(((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(azanediyl))bis(2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione)* (8a)**[7]



Following **GP3a**: Compound **8a** was isolated as a yellow solid, (38 mg, 0.058 mmol, 14%): R_f = 0.38 (EtOAc); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (s, 1H), 7.53 (dd, *J* = 8.6, 7.0 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.99 (d, *J* = 7.0 Hz, 1H), 6.58 (t, *J* = 5.8 Hz, 1H), 5.04 (dd, *J* = 12.9, 5.5 Hz, 1H), 3.64 (t, *J* = 5.4 Hz, 2H), 3.43 (q, *J* = 5.5 Hz, 2H), 2.87 (ddd, *J* = 16.9, 13.9, 5.4 Hz, 1H), 2.62 – 2.51 (m, 2H), 2.05 – 1.97 (m, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 170.0, 168.9, 167.2, 146.3, 136.1, 132.0, 117.3, 110.6, 109.2, 69.8, 68.9, 48.5, 41.6, 31.0, 22.1; HRMS (ESI) *m/z* calculated for $[C_{32}H_{32}N_6O_{10} + H]^+$ = 661.2253, found 661.2259.

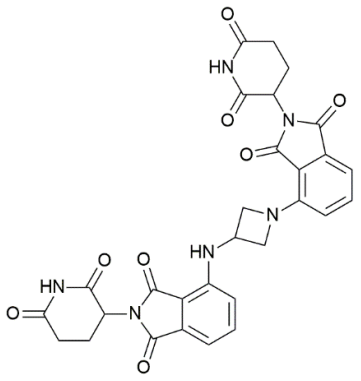
2-(2,6-dioxopiperidin-3-yl)-4-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)piperazin-1-yl)isoindoline-1,3-dione **(8b)**



Following **GP3a**: Compound **8b** was isolated as a yellow solid, (129 mg, 0.20 mmol, 49%): R_f=0.18 (EtOAc); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (s, 2H), 7.73 – 7.67 (m, 1H), 7.60 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.82 (d, *J* = 5.5 Hz, 1H), 5.13 – 5.02 (m, 2H), 3.43 (q, *J* = 5.9 Hz, 2H), 2.92 – 2.81 (m, 2H), 2.66 (q, *J* = 5.8, 4.7 Hz,

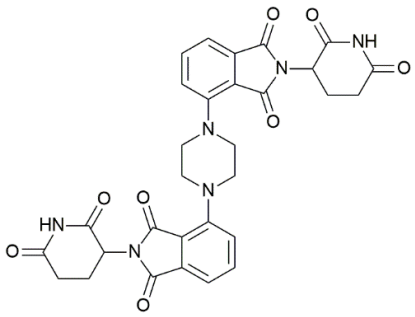
6H), 2.63 – 2.51 (m, 4H), 2.06 – 1.98 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 170.0, 169.9, 168.9, 167.3, 167.0, 166.3, 149.6, 146.3, 136.3, 135.8, 133.6, 132.1, 123.8, 117.5, 116.6, 114.8, 110.5, 109.2, 55.8, 52.3, 50.6, 48.8, 48.5, 38.6, 31.0, 30.9, 22.1, 22.0; HRMS (ESI) *m/z* calculated for $[C_{32}H_{31}N_7O_8 + H]^+$ = 642.2307, found 642.2319.

2-(2,6-dioxopiperidin-3-yl)-4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)azetidin-1-yl)isoindoline-1,3-dione **(8c)**



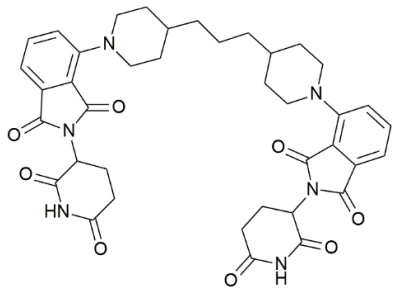
Following **GP3b**: Compound **8c** was isolated as an orange solid, (50 mg, 0.085 mmol, 43%): R_f = 0.51 (10% MeOH in DCM); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.10 (s, 1H), 11.07 (s, 1H), 7.64 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.59 (ddd, *J* = 8.4, 7.0, 2.3 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 2H), 7.05 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.95 (d, *J* = 5.6 Hz, 1H), 6.84 (dd, *J* = 8.6, 3.1 Hz, 1H), 5.11 – 5.02 (m, 2H), 4.64 (q, *J* = 10.4, 8.6 Hz, 3H), 4.13 (t, *J* = 9.4 Hz, 2H), 2.94 – 2.82 (m, 2H), 2.63 – 2.52 (m, 3H), 2.09 – 1.93 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.7, 172.7, 170.0, 169.9, 168.4, 167.1, 166.5, 147.8, 144.7, 136.4, 134.9, 133.2, 132.3, 120.2, 117.7, 112.0, 111.7, 110.5, 110.5, 60.9, 60.9, 48.6, 48.6, 42.6, 30.9, 22.1, 22.1; HRMS (ESI) *m/z* calculated for $[C_{29}H_{24}N_6O_8 + Na]^+$ = 607.1548, found 607.1547.

4,4'-(piperazine-1,4-diyl)bis(2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione) **(8d)**



Following **GP3b**: The reaction was purified by precipitating the reaction solution with the addition of water (2 mL), following by filtration to afford the precipitated compound **8d** as an orange solid, (101 mg, 0.17 mmol, 81%):; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.10 (s, 1H), 7.74 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.52 – 7.35 (m, 2H), 5.12 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.51 (s, 3H), 2.88 (ddd, *J* = 16.9, 13.9, 5.4 Hz, 1H), 2.63 – 2.52 (m, 2H), 2.11 – 1.98 (m, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 169.9, 167.0, 166.4, 149.5, 135.9, 133.6, 123.8, 116.7, 115.1, 50.4, 48.8, 30.9, 22.0; HRMS (EI) *m/z* calculated for $[C_{30}H_{26}N_6O_8]^+$ = 598.1812, found 598.1796.

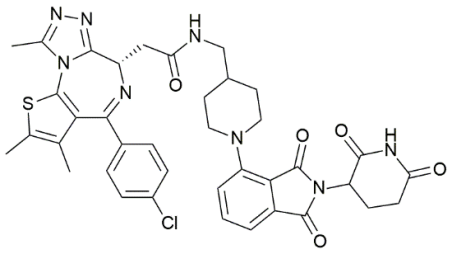
4,4'-(4,4'-(propane-1,3-diyl)bis(piperidine-4,1-diyl))bis(2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione) **(8e)**



Following **GP3b**: Compound **8a** was isolated as an orange solid, (97.6 mg, 1.35 mmol, 67 %): R_f = 0.59 (5% MeOH in DCM); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (s, 1H), 7.66 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.35 – 7.27 (m, 2H), 5.09 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.69 (dd, *J* = 9.0, 5.7 Hz, 2H), 2.95 – 2.76 (m, 3H), 2.64 – 2.50 (m, 2H), 2.08 – 1.96 (m, 1H), 1.83 – 1.70 (m, 2H), 1.52 – 1.20 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 170.0, 167.1, 166.2, 150.2, 135.7, 133.7, 123.8, 116.2, 114.3, 51.2,

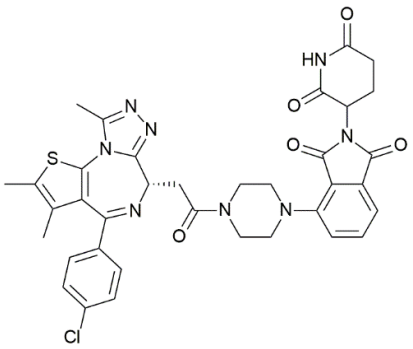
48.8, 36.2, 34.7, 32.0, 30.9, 23.1, 22.1; HRMS (ESI) *m/z* calculated for $[C_{39}H_{42}N_6O_8 + Na]^+$ = 745.2956, found 745.2938.

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-((1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperidin-4-yl)methyl)acetamide **(10a)**



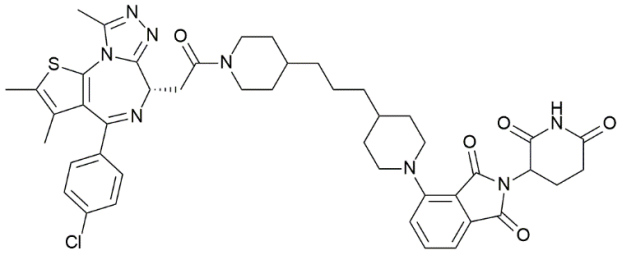
Following **GP4**: Compound **10a** was isolated as a yellow solid, (112 mg, 82 %): R_f = 0.30 (5% MeOH in DCMt); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.08 (s, 1H), 8.34 – 8.18 (m, 1H), 7.67 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.53 – 7.38 (m, 4H), 7.33 (dd, *J* = 7.8, 5.0 Hz, 2H), 5.08 (ddd, *J* = 13.0, 5.5, 2.3 Hz, 1H), 4.53 (ddd, *J* = 8.5, 5.6, 1.9 Hz, 1H), 3.78 – 3.61 (m, 2H), 3.31 – 3.00 (m, 4H), 2.95 – 2.77 (m, 3H), 2.65 – 2.51 (m, 5H), 2.40 (s, 3H), 2.14 – 1.96 (m, 1H), 1.80 (d, *J* = 11.4 Hz, 2H), 1.72 – 1.65 (m, 1H), 1.61 (s, 3H), 1.38 (t, *J* = 12.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.7, 169.9, 169.6, 167.1, 166.3, 163.0, 155.1, 150.1, 149.8, 136.7, 135.7, 135.2, 133.7, 132.2, 130.7, 130.1, 129.8, 129.6, 128.4, 123.9, 116.3, 114.4, 54.0, 50.7, 48.8, 44.0, 37.7, 35.5, 31.0, 29.7, 22.1, 14.0, 12.7, 11.3; HRMS (ESI) *m/z* calculated for $[C_{38}H_{37}ClN_8O_5S + H]^+$ = 753.2369, found 753.2360.

4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **(10b)**



Following **GP4**: Compound **10b** was isolated as a yellow solid, (36.3 mg, 0.050 mmol, 50 %): R_f = 0.28 (5% MeOH in DCM); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.10 (s, 1H), 7.75 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.46 – 7.44 (m, 2H), 7.40 (dd, *J* = 13.5, 7.7 Hz, 2H), 5.13 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.61 (dd, *J* = 7.2, 6.2 Hz, 1H), 3.88 (s, 2H), 3.70 (dd, *J* = 16.2, 7.1 Hz, 3H), 3.55 – 3.39 (m, 3H), 3.30 (d, *J* = 11.0 Hz, 3H), 2.96 – 2.80 (m, 1H), 2.63 – 2.56 (m, 4H), 2.42 (s, 3H), 2.09 – 2.01 (m, 1H), 1.64 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 169.9, 168.4, 167.0, 166.3, 162.9, 155.2, 149.7, 149.4, 136.7, 135.9, 135.2, 133.6, 132.2, 130.6, 130.1, 129.9, 129.6, 128.4, 123.9, 116.9, 115.2, 54.2, 50.8, 50.3, 48.8, 45.0, 41.2, 34.8, 30.9, 22.0, 14.0, 12.7, 11.3; HRMS (ESI) *m/z* calculated for $[C_{36}H_{33}ClN_8O_5S + Na]^+$ = 747.1875, found 747.1871.

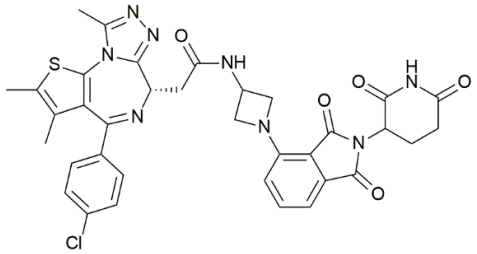
4-(4-(3-(1-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)propyl)piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **(10c)**



Following **GP4**: Compound **10c** was isolated as a yellow solid, (32.2 mg, 0.038 mmol, 37%): R_f = 0.60 (10% MeOH in $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (s, 1H), 7.68 – 7.65 (m, 1H), 7.50

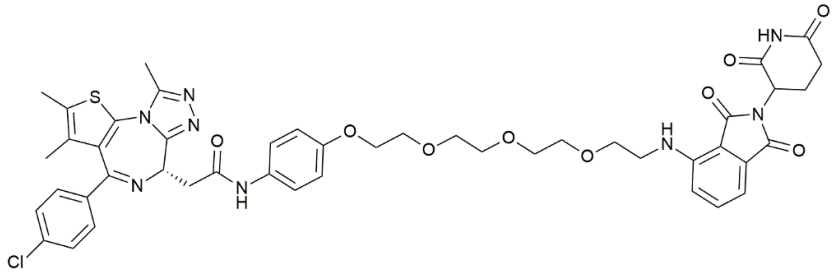
– 7.47 (m, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 8.1 Hz, 4H), 5.10 – 5.07 (m, 1H), 4.57 (dd, J = 7.4, 6.0 Hz, 1H), 4.36 (d, J = 12.6 Hz, 1H), 4.12 (d, J = 13.2 Hz, 1H), 3.69 (d, J = 11.6 Hz, 4H), 3.64 – 3.53 (m, 1H), 3.37 (dt, J = 16.1, 5.3 Hz, 1H), 3.10 (q, J = 11.4 Hz, 1H), 2.90 – 2.83 (m, 4H), 2.62 – 2.54 (m, 5H), 2.41 (s, 3H), 2.04 – 2.00 (m, 1H), 1.83 – 1.71 (m, 4H), 1.72 – 1.66 (m, 1H), 1.63 (d, J = 1.7 Hz, 3H), 1.58 – 1.31 (m, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.2, 170.4, 168.1, 167.5, 166.7, 163.3, 155.8, 150.6, 150.1, 137.3, 136.1, 135.6, 134.1, 132.6, 131.1, 130.6, 130.3, 130.1, 128.9, 124.3, 116.7, 114.8, 54.7, 51.7, 49.2, 45.8, 42.0, 36.7, 36.6, 35.8, 35.2, 35.1, 32.4, 31.4, 23.5, 22.5, 14.5, 13.1, 11.7. ; HRMS (ESI) *m/z* calculated for $[C_{45}H_{49}ClN_8O_5S + H]^+$ = 849.3308, found 849.3305.

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)azetidin-3-yl)acetamide **(10d)**



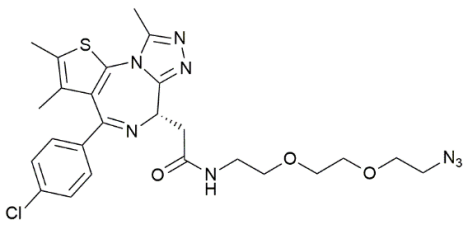
Following **GP4**: Compound **10d** was isolated as a yellow solid, (44.1 mg, 0.062 mmol, 62%): R_f = 0.36 (5% MeOH in DCM); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.08 (s, 1H), 8.98 (t, J = 6.1 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.52 – 7.36 (m, 4H), 7.20 – 7.13 (m, 1H), 6.86 (dd, J = 8.6, 0.8 Hz, 1H), 5.07 (dd, J = 12.7, 5.6 Hz, 1H), 4.64 – 4.39 (m, 4H), 4.08 (d, J = 38.3 Hz, 2H), 3.30 – 3.15 (m, 1H), 2.95 – 2.83 (m, 1H), 2.64 – 2.53 (m, 5H), 2.42 (s, 3H), 2.08 – 1.92 (m, 1H), 1.69 – 1.53 (m, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 169.9, 169.7, 167.1, 166.5, 163.1, 155.0, 149.8, 147.7, 136.7, 135.2, 135.0, 133.3, 132.3, 130.7, 130.1, 129.8, 129.5, 128.4, 120.1, 111.9, 110.3, 53.8, 53.8, 48.7, 40.4, 37.5, 31.0, 22.1, 14.0, 12.7, 11.3; HRMS (ESI) *m/z* calculated for $[C_{35}H_{31}ClN_8O_5S + H]^+$ = 711.1899, found 711.1890.

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide (10e, ARV-825)[8]



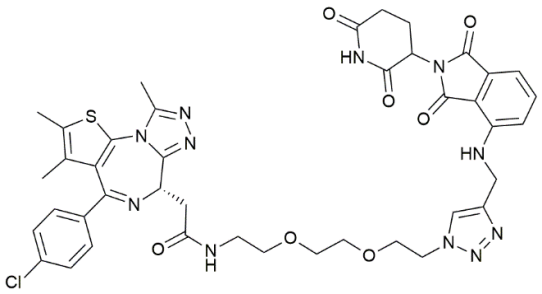
Following **GP4**: Compound **10e** (**ARV-825**) was isolated as a yellow solid (24.5 mg, 0.027 mmol, 25%): R_f = 0.26 (5% MeOH in DCM); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.08 (br s, 1H), 10.15 (br s, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.60 (t, *J* = 5.8 Hz, 1H), 5.05 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.59 (t, *J* = 7.1 Hz, 1H), 4.03 (t, *J* = 4.7 Hz, 2H), 3.72 – 3.68 (m, 2H), 3.62 (t, *J* = 5.5 Hz, 2H), 3.58 – 3.52 (m, 8H), 3.46 (t, *J* = 5.8 Hz, 4H), 2.87 (ddd, *J* = 17.3, 13.8, 5.5 Hz, 1H), 2.61 – 2.51 (m, 5H), 2.41 (s, 3H), 2.05 – 1.98 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 170.0, 168.9, 168.0, 167.2, 163.1, 155.0, 154.3, 149.8, 146.4, 136.7, 136.2, 135.2, 132.5, 132.3, 132.1, 130.7, 130.1, 129.8, 129.5, 128.4, 120.5, 117.4, 114.4, 110.6, 109.2, 69.9, 69.8, 69.8, 69.7, 68.9, 68.9, 67.2, 53.8, 48.5, 41.7, 38.5, 30.9, 22.1, 14.0, 12.7, 11.3; HRMS (ESI) *m/z* calculated for $[C_{46}H_{47}ClN_8O_9S + H]^+$ = 923.2948, found 923.2907.

(S)-N-(2-(2-(2-azidoethoxy)ethoxy)ethyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide (11)



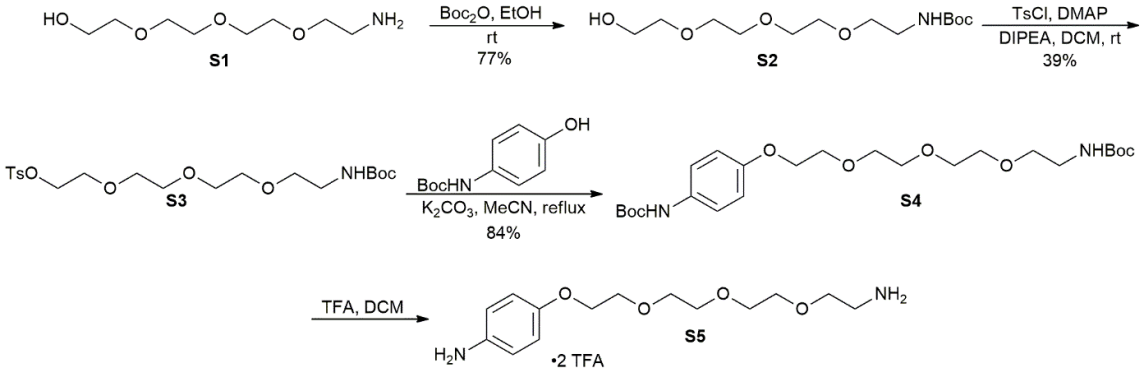
To a solution of **1** (64 mg, 0.113 mmol, 1.0 eq.) in DMF (3mL) was added DIPEA (0.10 mL, 74 mg, 0.57 mmol, 5.0 eq.) followed by a solution of Azide-PEG2-NH_2 (20 mg, 0.113 mmol, 1.0 eq.) in DMF (1 mL). After stirring for 1 h at room temperature the reaction mixture was concentrated *in vacuo* and the residue was redissolved in DMF (2.5 mL) and stirred with K_2CO_3 (60 mg) for 1 h. The salts were filtered up and the filtrate was concentrated *in vacuo*. The residue was subjected to flash column chromatography over silica gel, eluting with EtOAc, followed by MeOH in $CHCl_3$ (0 to 10% MeOH in $CHCl_3$) to furnish **11** as a colourless oil, (61 mg, 0.110 mmol, 96% yield): R_f = 0.17 (10% MeOH in$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.35 (m, 2H), 7.35 – 7.29 (m, 2H), 6.79 (t, *J* = 5.4 Hz, 1H), 4.63 (t, *J* = 7.0 Hz, 1H), 3.72 – 3.63 (m, 6H), 3.62 – 3.44 (m, 5H), 3.42 – 3.34 (m, 3H), 2.65 (s, 3H), 2.38 (s, 1H), 1.65 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.7, 164.0, 155.7, 149.9, 136.9, 136.7, 132.2, 131.0, 130.9, 130.6, 129.9, 128.8, 70.7, 70.5, 70.2, 69.9, 54.5, 50.8, 39.5, 39.3, 14.5, 13.2, 11.9; HRMS (ESI) *m/z* calculated for $[C_{25}H_{29}ClN_8O_3S + H]^+$ = 557.1845, found 557.1850.

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(2-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethyl)acetamide (12)



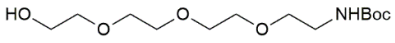
A solution of the corresponding S_NAr product prepared following **GP1** using **1** (33 mg, 0.12 mmol, 1.1 eq.), propargylamine (7.1 mg, 0.13 mmol, 1.2 eq.) and DIPEA (47 mg, 0.36 mmol, 3.3 eq) in DMSO (1 mL) was concentrated *in vacuo* and the residue was dissolved in THF (3 mL). This prepared solution was consequently treated with **11** (61 mg, 0.11 mmol, 1.0 eq.), water (0.15 mL), $CuSO_4x5H_2O$ (8 mg, 0.032 mmol, 0.30 eq.), sodium ascorbate (16 mg) and stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue was stirred in $CHCl_3$ (6 mL) for 15 min.

The solution was filtered and concentrated *in vacuo*. The crude residue was then purified by flash column chromatography over silica gel, eluting with MeOH:$CHCl_3$ (5 – 10%) which furnished **12** as a bright yellow oil, (64 mg, 0.074 mmol, 67%): R_f = 0.23 (5% MeOH in$CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (br s, 1H), 8.25 (td, *J* = 5.6, 2.4 Hz, 1H), 7.99 (br s, 1H), 7.55 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.45 – 7.39 (m, 2H), 7.17 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.06 (t, *J* = 6.1 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 5.05 (ddd, *J* = 12.9, 5.5, 2.2 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 2H), 4.55 – 4.45 (m, 3H), 3.79 (t, *J* = 5.2 Hz, 2H), 3.51 (dd, *J* = 5.8, 3.4 Hz, 2H), 3.47 (dd, *J* = 5.9, 3.6 Hz, 2H), 3.42 – 3.38 (m, 2H), 3.31 – 3.17 (m, 4H), 2.87 (ddd, *J* = 17.0, 13.9, 5.4 Hz, 1H), 2.63 – 2.51 (m, 5H), 2.38 (d, *J* = 4.0 Hz, 3H), 2.07 – 1.96 (m, 1H), 1.59 (d, *J* = 3.3 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.7, 170.0, 169.7, 168.7, 167.2, 163.0, 155.1, 149.7, 145.8, 144.3, 136.7, 136.0, 135.2, 132.2, 132.1, 130.6, 130.1, 129.8, 129.5, 128.4, 123.2, 117.6, 110.8, 109.6, 69.5, 69.4, 69.1, 68.7, 53.8, 49.3, 48.5, 38.6, 37.6, 37.5, 30.9, 22.1, 14.0, 12.6, 11.2; HRMS (ESI) *m/z* calculated for $[C_{41}H_{42}ClN_{11}O_7S + H]^+$ = 868.2751, found 868.2788.



Scheme S1. Synthesis of ARV-825 linker

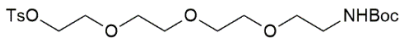
tert-butyl (2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl)carbamate (S1)



Following literature preparation,[9] a solution of 2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethanol (2.180 g, 11.3 mmol, 1.0 equiv.) in ethanol (20 mL) was added a solution of di-*tert*-butyl dicarbonate (3.013

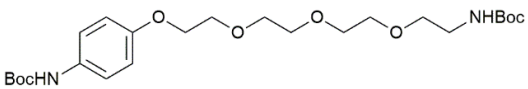
g, 13.8 mmol, 1.2 equiv.) in ethanol (10 mL). The solution was stirred for 16 hours and then the solvent was removed *in vacuo*. The residue was dissolved in DCM (150 mL) and washed with consecutively with 1N HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was then dried over anhydrous sodium sulphate and the solvent was removed *in vacuo*. The crude residue was then purified by flash column chromatography over silica gel, eluting with MeOH:DCM (0 – 5%) and dried overnight in a vacuum oven to afford **S1** as a yellow oil, (2.547 g, 8.7 mmol, 77%): R_f = 0.46 (5% MeOH in DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.65 (br s, 1H), 3.77 – 3.69 (m, 2H), 3.74 – 3.57 (m, 11H), 3.52 (dd, *J* = 5.5, 4.5 Hz, 2H), 3.31 (q, *J* = 5.3 Hz, 2H), 3.04 (br s, 1H), 1.43 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.3, 79.1, 72.8, 70.8, 70.7, 70.6, 70.5, 70.3, 61.9, 40.6, 28.6; HRMS (ESI) *m/z* calculated for $[C_{13}H_{27}NO_6 + H]^+$ = 294.1911, found 294.1922.

2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-yl 4-methylbenzenesulfonate (S2)



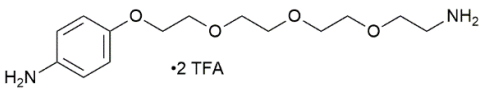
Following literature preparation,[9] to a solution of **S1** (2.524 g, 8.6 mmol, 1.0 equiv.) in DCM (75 mL) was added DIPEA (3.0 mL, 17.2 mmol, 2.0 equiv.), tosyl chloride (2.520 g, 13.2 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (105 mg, 0.86 mmol, 0.1 equiv.). The solution was stirred at room temperature for 16 hours and then volatiles were removed *in vacuo*. The crude residue was then purified by flash column chromatography eluting with EtOAc:hexanes (35 – 100%) and then dried in an vacuum oven overnight to afford **S2** as a viscous yellow oil (1.505 g, 3.4 mmol, 39%): R_f = 0.64 (5% MeOH in DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.83 – 7.74 (m, 2H), 7.39 – 7.28 (m, 2H), 4.20 – 4.11 (m, 2H), 3.70 – 3.65 (m, 2H), 3.62 – 3.55 (m, 8H), 3.52 (t, *J* = 5.2 Hz, 2H), 3.29 (q, *J* = 5.5 Hz, 2H), 2.44 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.1, 144.9, 133.2, 129.9, 128.1, 79.3, 70.9, 70.7, 70.7, 70.4, 70.3, 69.3, 68.8, 40.5, 28.6, 21.8.

tert-butyl (4-((2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-yl)oxy)phenyl)carbamate (S3)



To a solution of **S2** (0.402 g, 0.90 mmol, 1.0 equiv.) in MeCN (20 mL) was added potassium carbonate (0.400 g, 2.9 mmol, 3.2 equiv.) and N-boc-4-hydroxyaniline (0.225 g, 1.1 mmol, 1.2 equiv.) and the resultant mixture was refluxed for 16 hours. Once cooled to room temperature the volatiles were removed *in vacuo*. The crude residue was then adsorbed to silica gel and purified by flash column chromatography eluting with EtOAc:hexanes (25 – 100%) to afford **S3** as a yellow viscous oil (0.370 g, 0.76 mmol, 84%): R_f = 0.58 (100% EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.42 (br s, 1H), 5.00 (br s, 1H), 4.12 – 4.04 (m, 2H), 3.82 (t, *J* = 4.9 Hz, 2H), 3.71 (dd, *J* = 5.5, 3.8 Hz, 2H), 3.68 – 3.64 (m, 2H), 3.63 (dd, *J* = 5.8, 3.7 Hz, 2H), 3.60 (dd, *J* = 6.4, 3.3 Hz, 2H), 3.52 (t, *J* = 5.2 Hz, 2H), 3.28 (q, *J* = 5.4 Hz, 2H), 1.49 (s, 8H), 1.43 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.1, 155.0, 153.3, 131.9, 120.6, 115.2, 80.3, 79.3, 71.0, 70.8, 70.7, 70.4, 70.3, 69.9, 68.0, 40.5, 28.6, 28.5; HRMS (ESI) *m/z* calculated for $[C_{24}H_{40}N_2O_8 + H]^+$ = 485.2857, found 485.2855.

4-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethoxy)aniline trifluoroacetate (S4)



To a solution of **S3** (68 mg, 0.14 mmol, 1.0 equiv.) in DCM (2 mL) was added TFA (0.48 mL, 6.3 mmol, 45 equiv.) and the mixture was stirred at room temperature for 1 hour. Volatiles were then removed *in vacuo* to afford **S3** which was used immediately for the synthesis of **10e** without further purification.

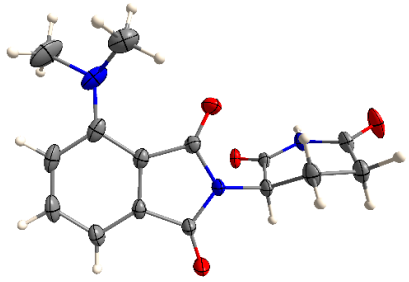


Figure S1. Crystal structure of 3.

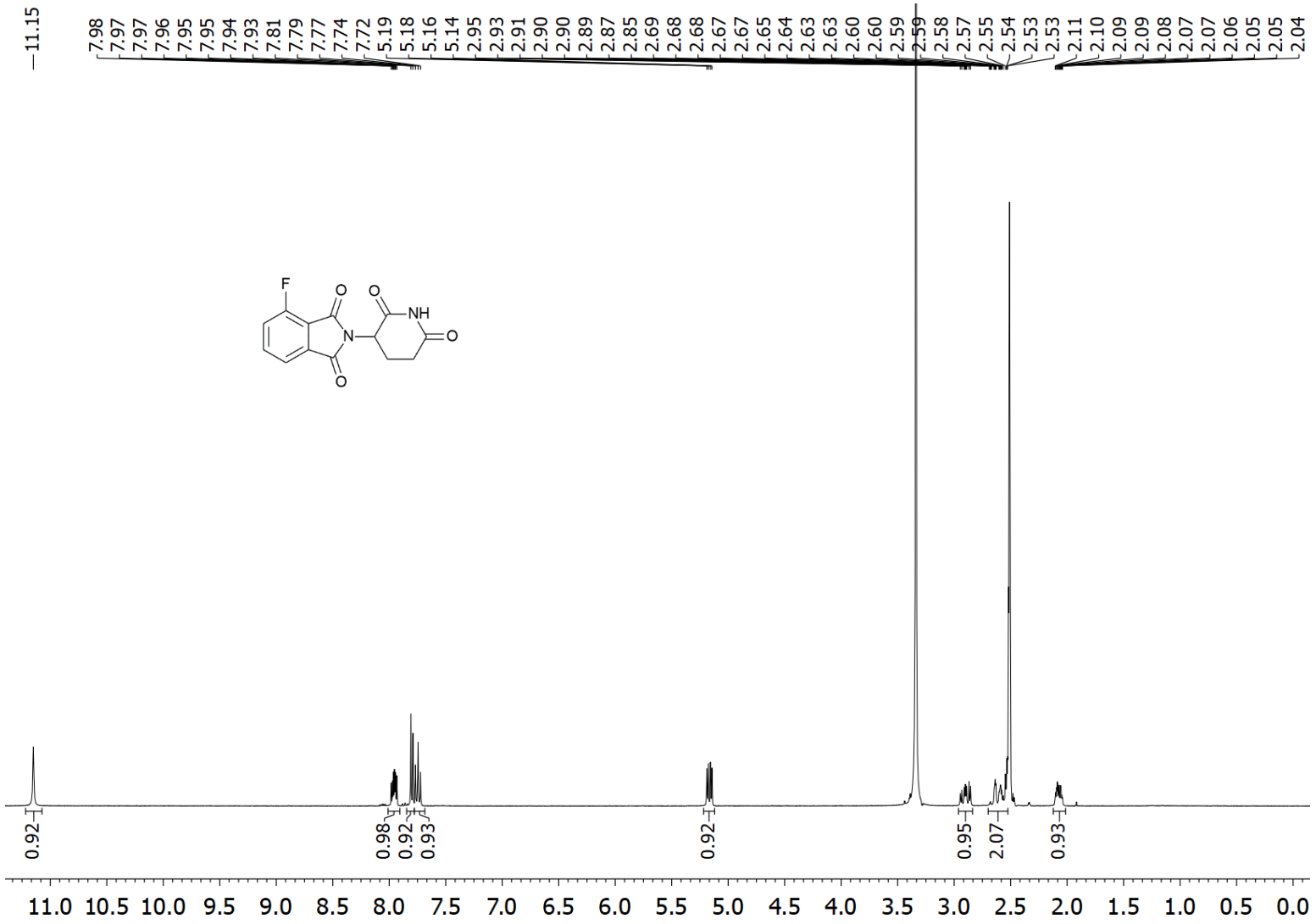
Table S1. Crystal data and structure refinement for 3.

Identification code	3
Moiety Formula	$C_{15}H_{15}N_3O_4 \bullet (C_4H_8O_2)_{0.377}(C_6H_{14})_{0.123}$
Empirical formula	$C_{17.25}H_{19.73}N_3O_{4.75}$
Formula weight	345.11
Temperature/K	173.0
Crystal system	triclinic
Space group	P-1
a/Å	7.2814(2)
b/Å	10.1224(2)
c/Å	12.1780(3)
α/°	92.523(2)
β/°	106.963(2)
γ/°	100.062(2)
Volume/Å^3	841.02(4)
Z	2
ρ_{calc}g/cm^3	1.363
μ/mm^{-1}	0.839
F(000)	364.5
Crystal size/mm^3	0.341 × 0.263 × 0.206
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.628 to 136.564
Index ranges	$-8 \le h \le 8$, $-12 \le k \le 12$, $-14 \le l \le 14$
Independent reflections	3077 [R_{int} = 0.0315, R_{sigma} = 0.0109]
Data/restraints/parameters	3077/286/323
Goodness-of-fit on F^2	1.068
Final R indexes [I>=2σ (I)]	R_1 = 0.0482, wR_2 = 0.1237
Final R indexes [all data]	R_1 = 0.0490, wR_2 = 0.1247
Largest diff. peak/hole / e Å^{-3}	0.31/-0.33

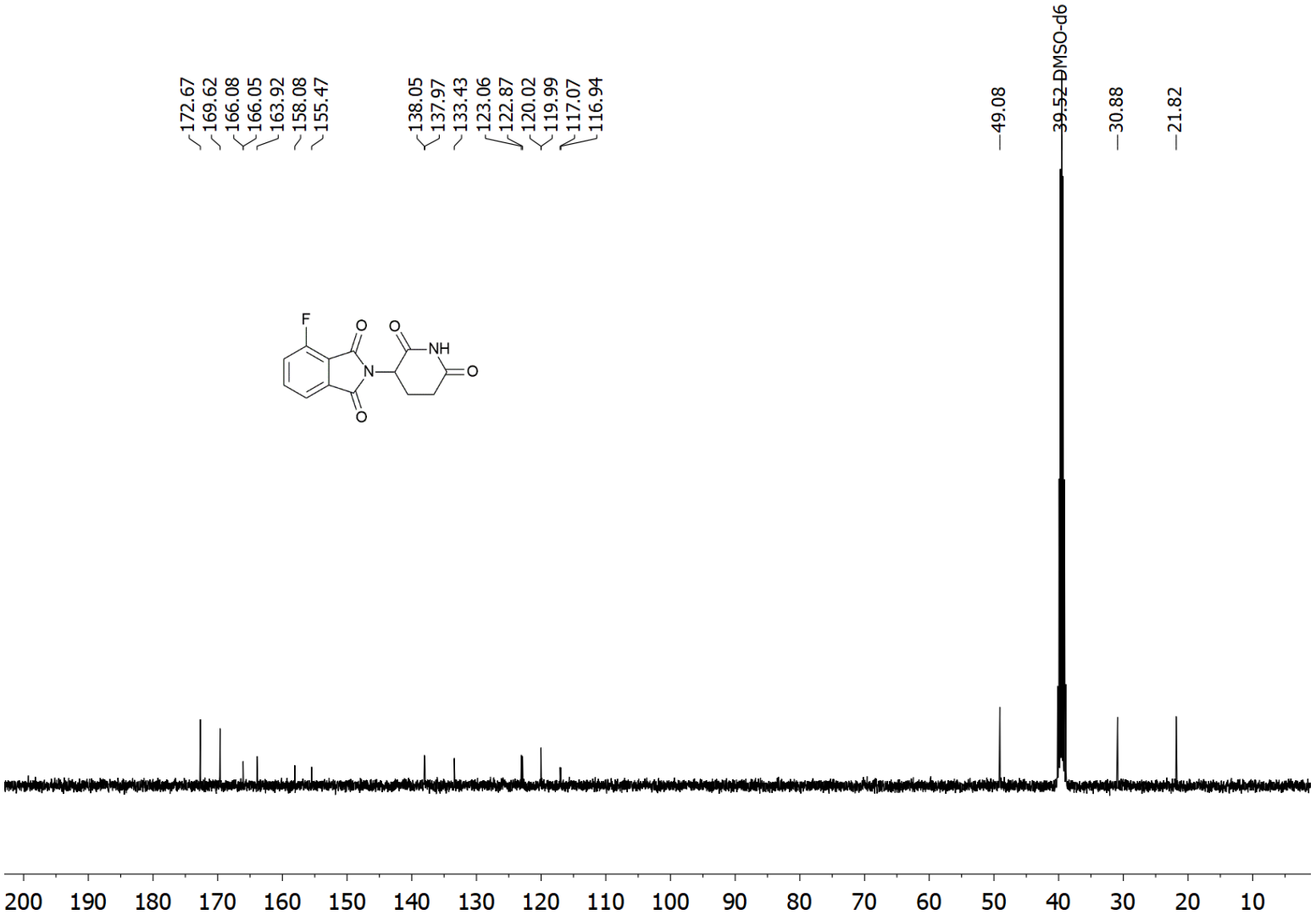
Single Crystal Data Collection, Solution, and Refinement

Single crystals of **3** were grown by slow evaporation. A suitable crystal was selected and mounted on a glass loop using Paratone. Diffraction experiments were performed on a Bruker Smart diffractometer equipped with an Incoatec Microfocus (graphite monochromated Cu Kα, λ = 1.54178 Å) and an APEX II CCD detector. The crystal was kept at 173 K during data collection. Diffractions spots were integrated and scaled with SAINT[10] and the space group was determined with XPREP.[11] In order to improve the completeness of the reflections collected, the crystal was remounted to a new position, missing reflections collected, and the resulting datasets were merged isotropically with XPREP.[11] Using Olex2,[12] the structure was solved with the ShelXT[13] structure solution program using Intrinsic Phasing and refined with the ShelXL[14] refinement package using Least Squares minimisation. During the refinement, it became evident that there were two overlapping and disordered species – likely hexane and diethyl ether. Several restraints were used on these solvent molecules to obtain a stable and chemically reasonable model, though they are likely disordered over additional sites.

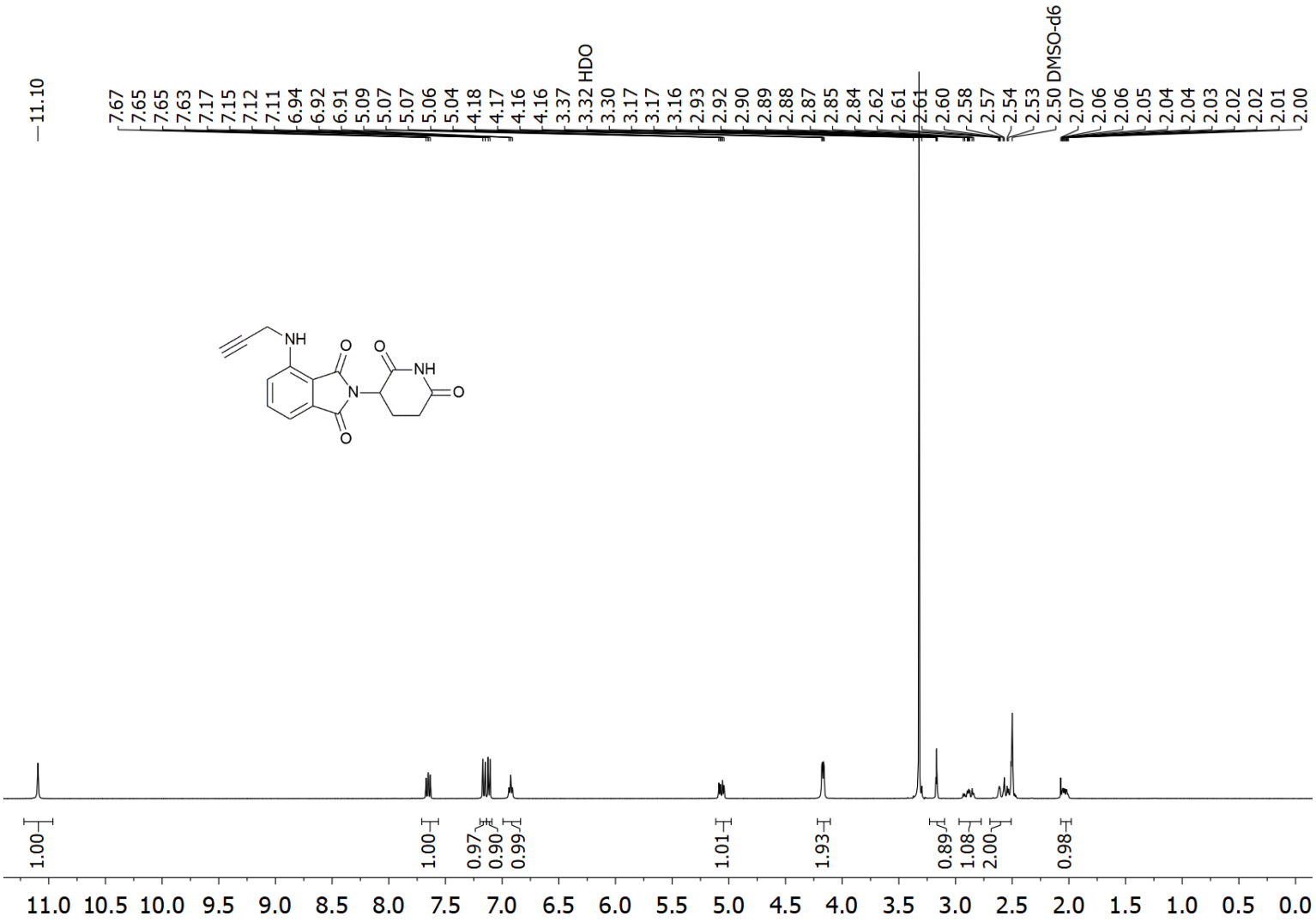
^{1}H NMR spectrum of 4-Fluorothalidomide (**1**) (400 MHz, DMSO-d_6)



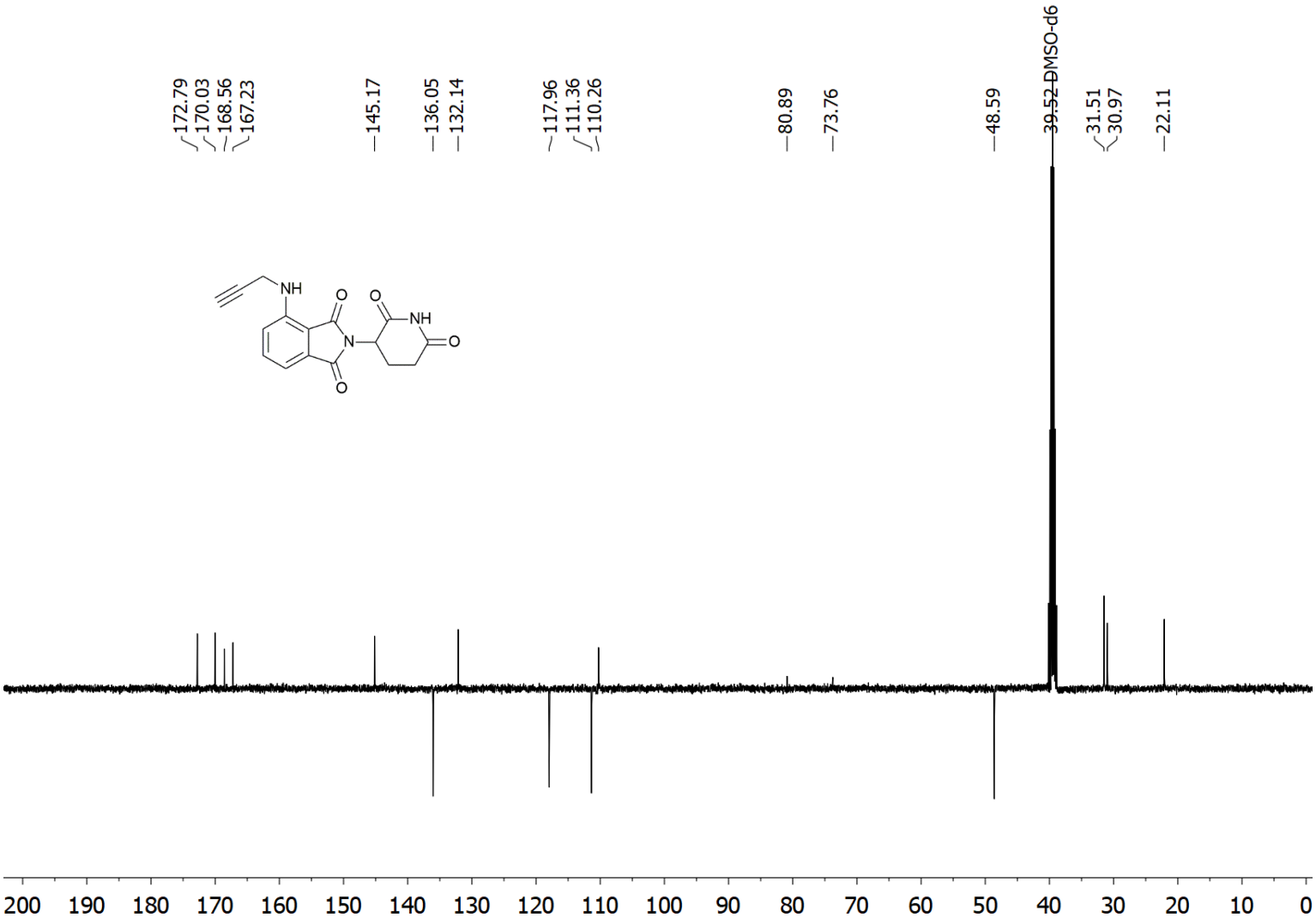
^{13}C NMR spectrum of 4-Fluorothalidomide (**1**) (100 MHz, DMSO-d_6)



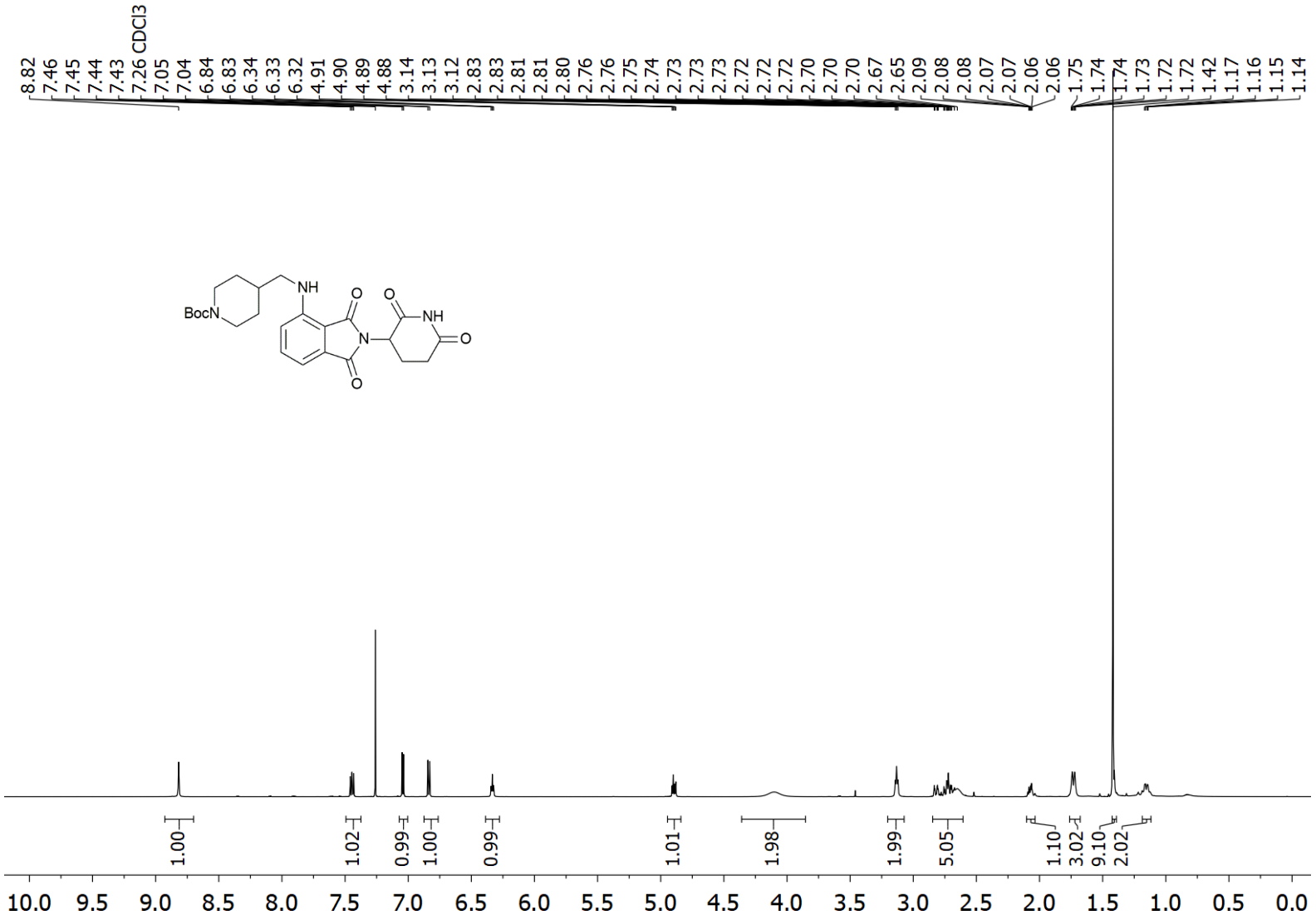
^{1}H NMR spectrum of **2a** (400 MHz, DMSO-d_6)



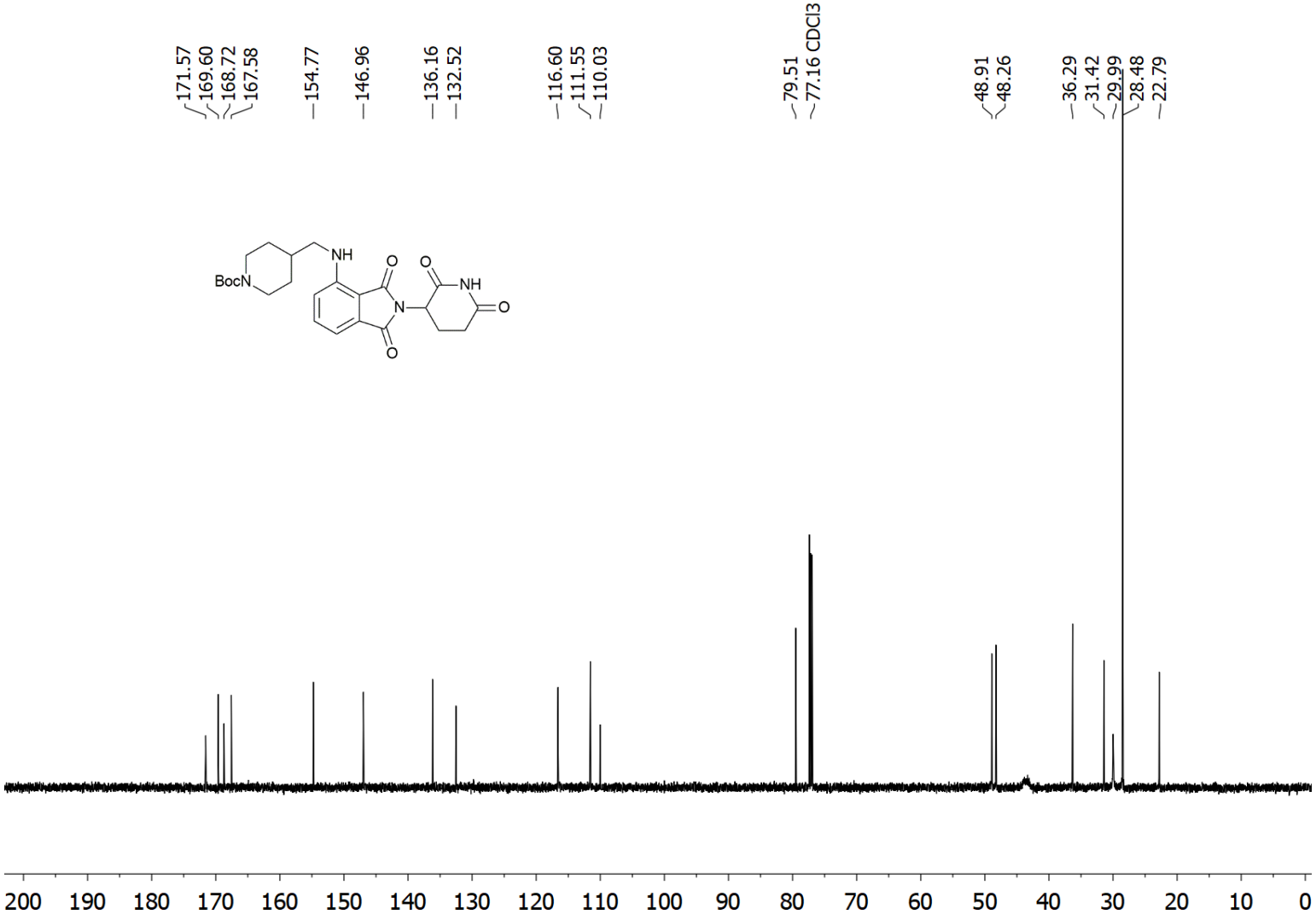
^{13}C DEPTQ NMR of **2a** (100 MHz, DMSO-d_6)



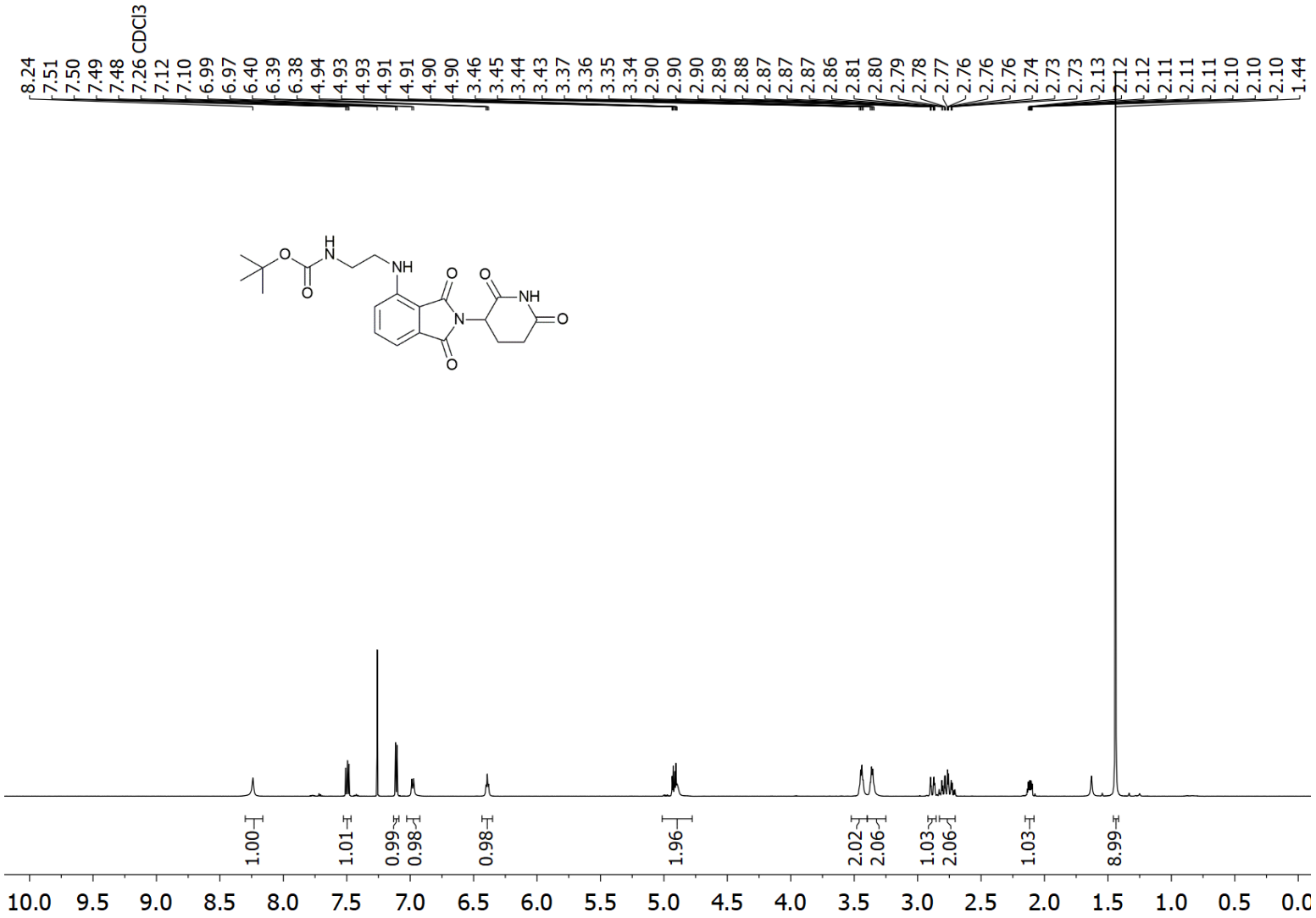
^{1}H NMR spectrum of **2b** (600 MHz, $CDCl_3$)



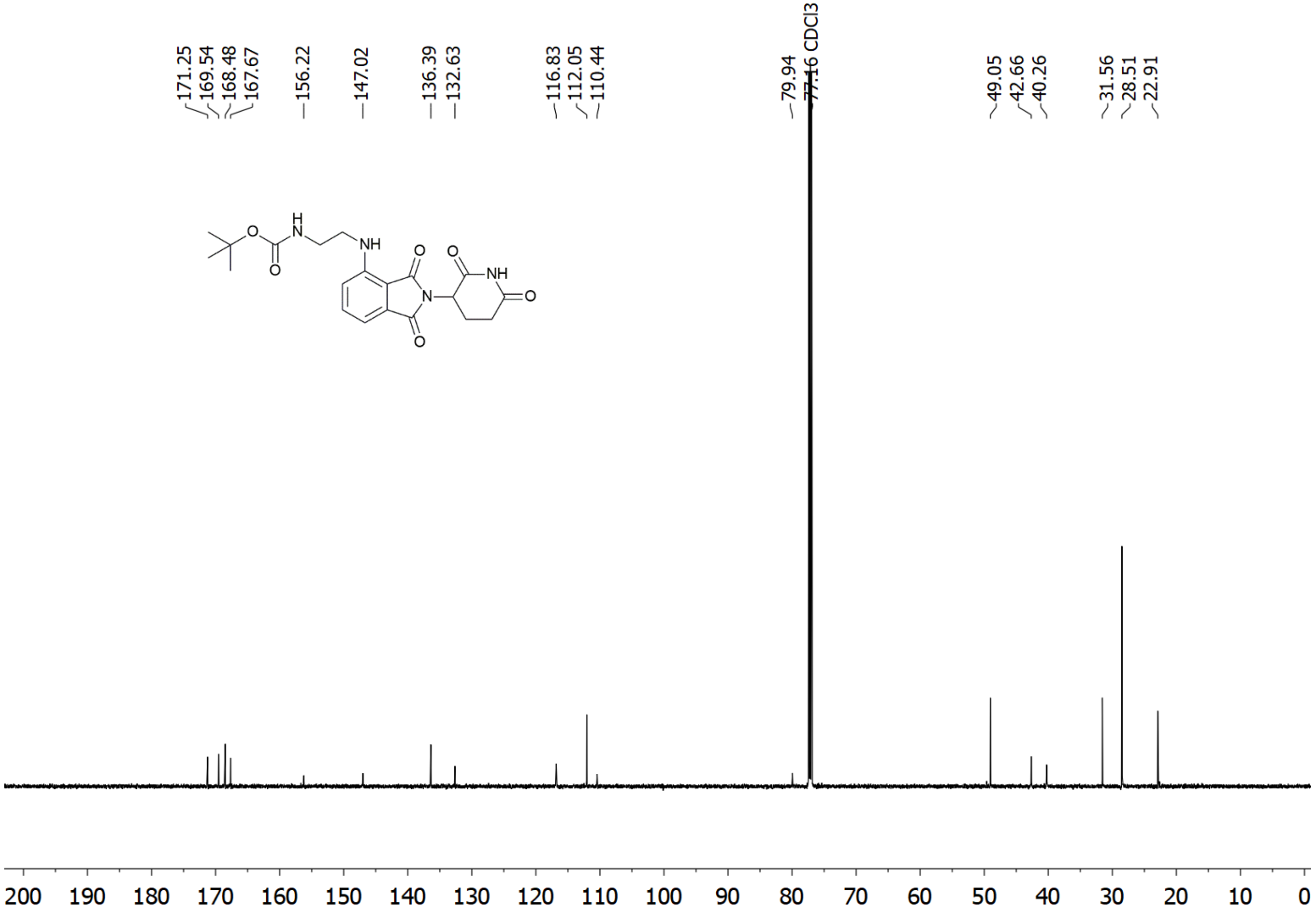
^{13}C NMR spectrum of **2b** (151 MHz, $CDCl_3$)



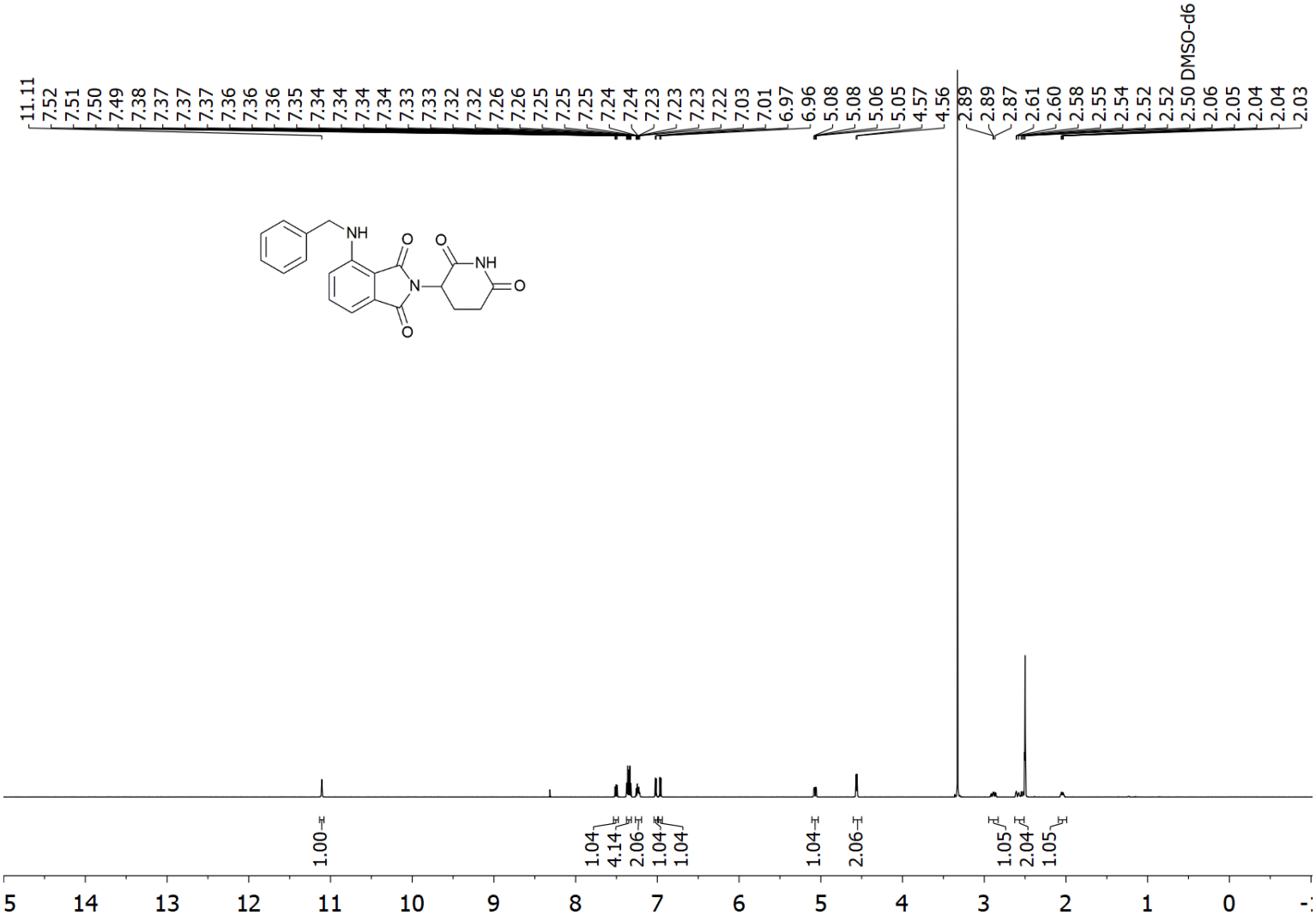
^{1}H NMR spectrum of **2c** (600 MHz, $CDCl_3$)



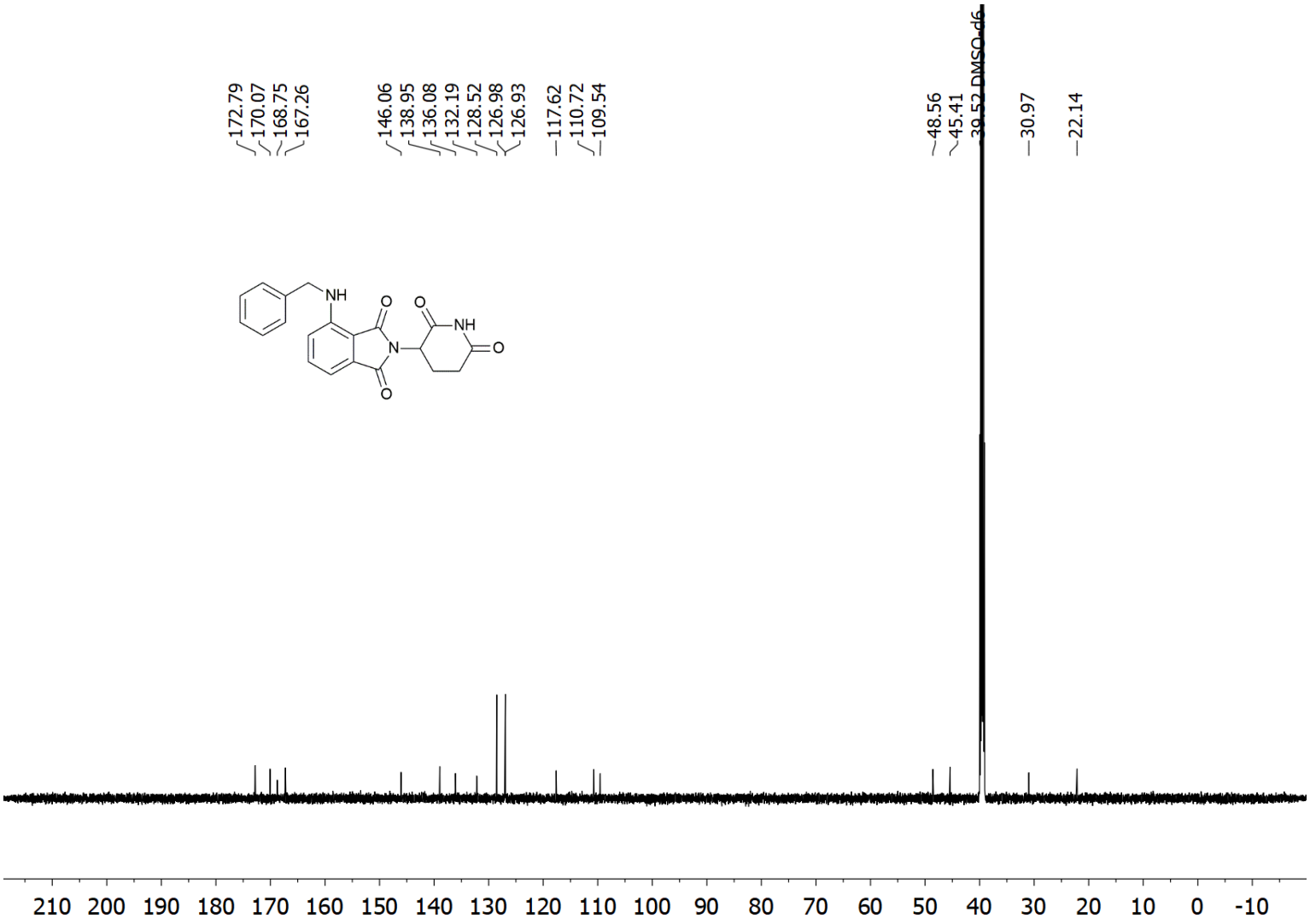
^{13}C NMR spectrum of **2c** (151 MHz, $CDCl_3$)



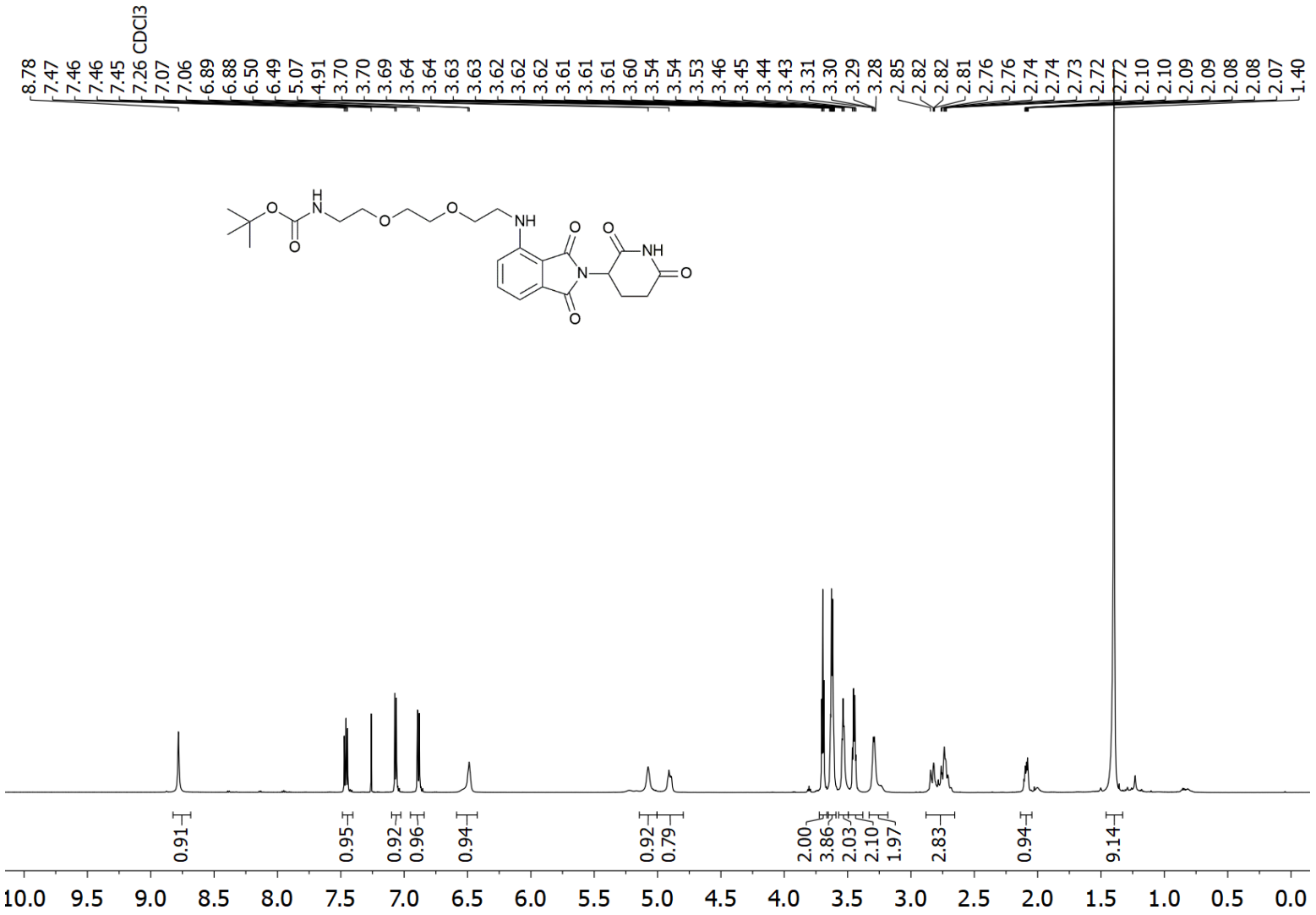
^{1}H NMR spectrum of **2d** (600 MHz, DMSO-d_6)



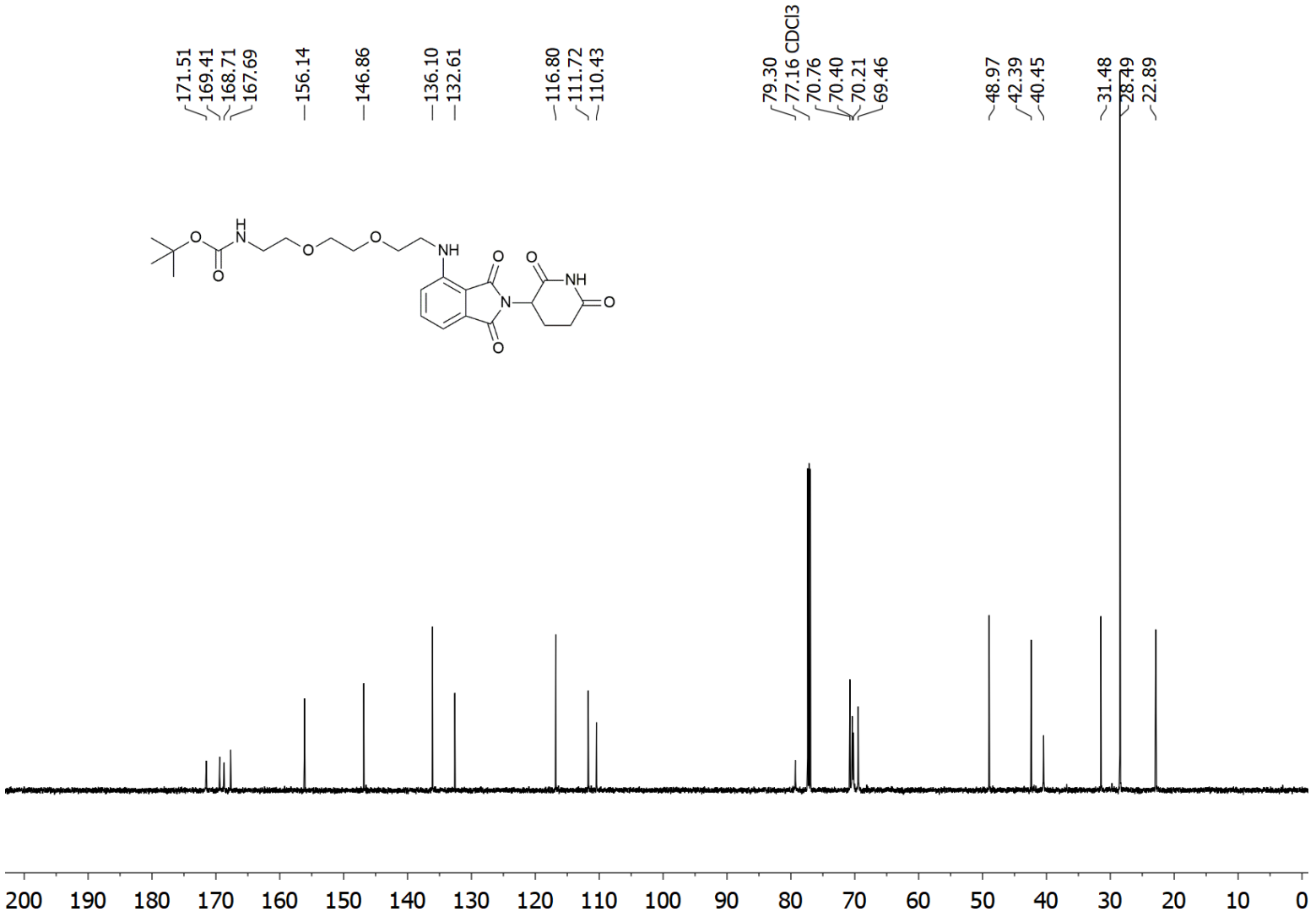
^{13}C NMR spectrum of **2d** (151 MHz, DMSO-d_6)



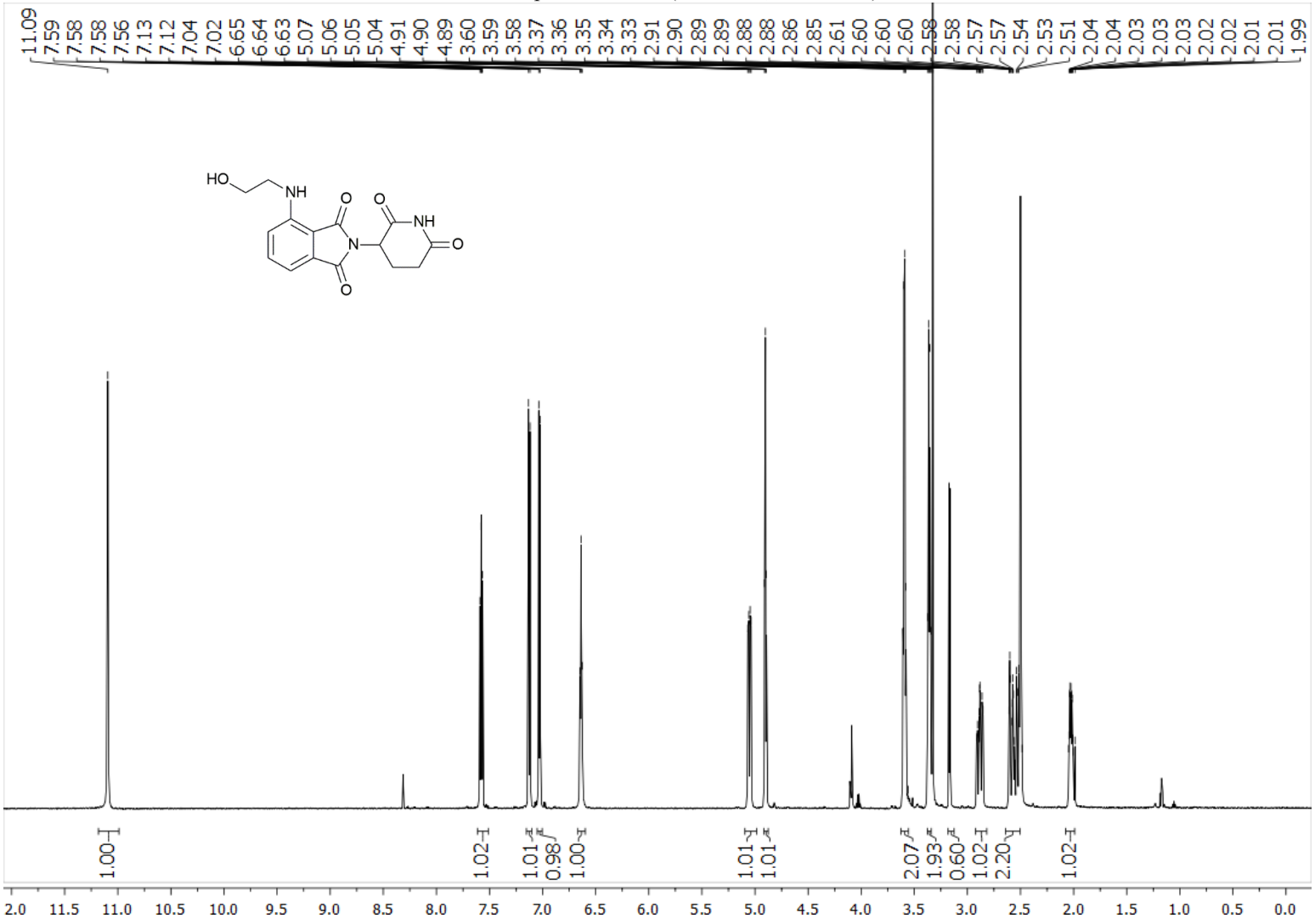
^{1}H NMR spectrum of **2e** (600 MHz, $CDCl_3$)



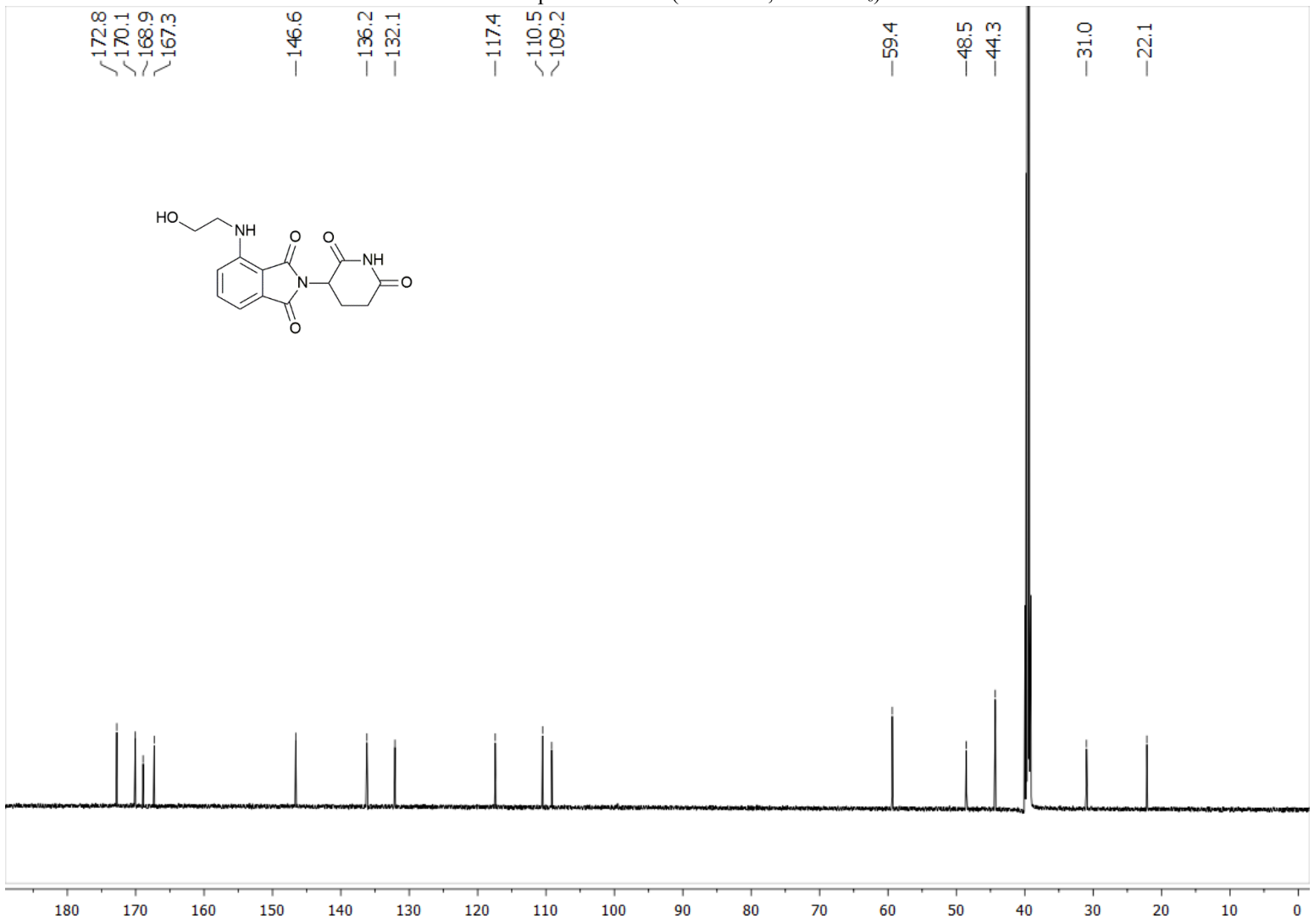
^{13}C NMR spectrum of **2e** (151 MHz, $CDCl_3$)



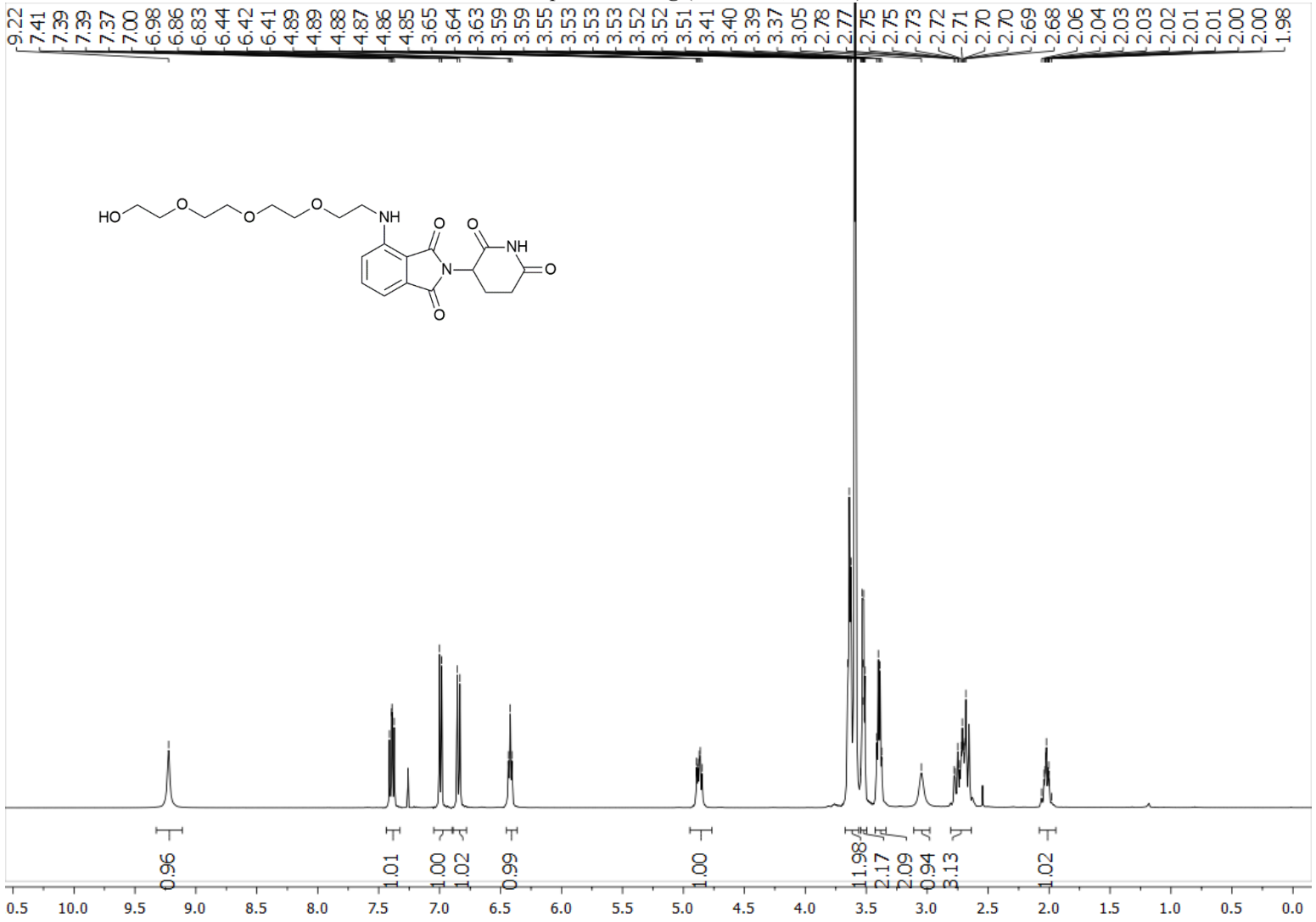
^{1}H NMR spectrum of **2f** (600 MHz, DMSO-d_6)



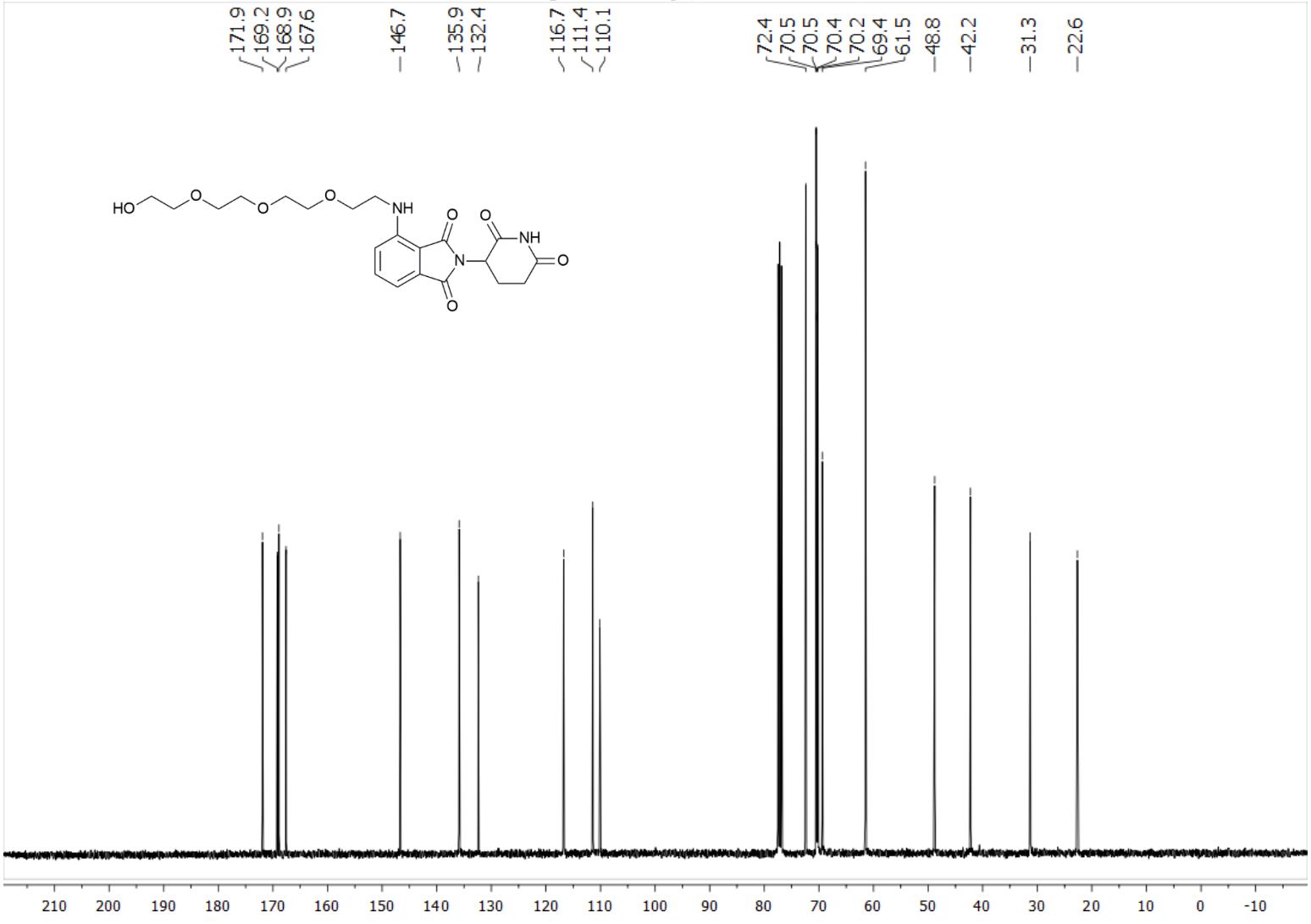
^{13}C NMR spectrum of **2f** (151 MHz, DMSO-d_6)



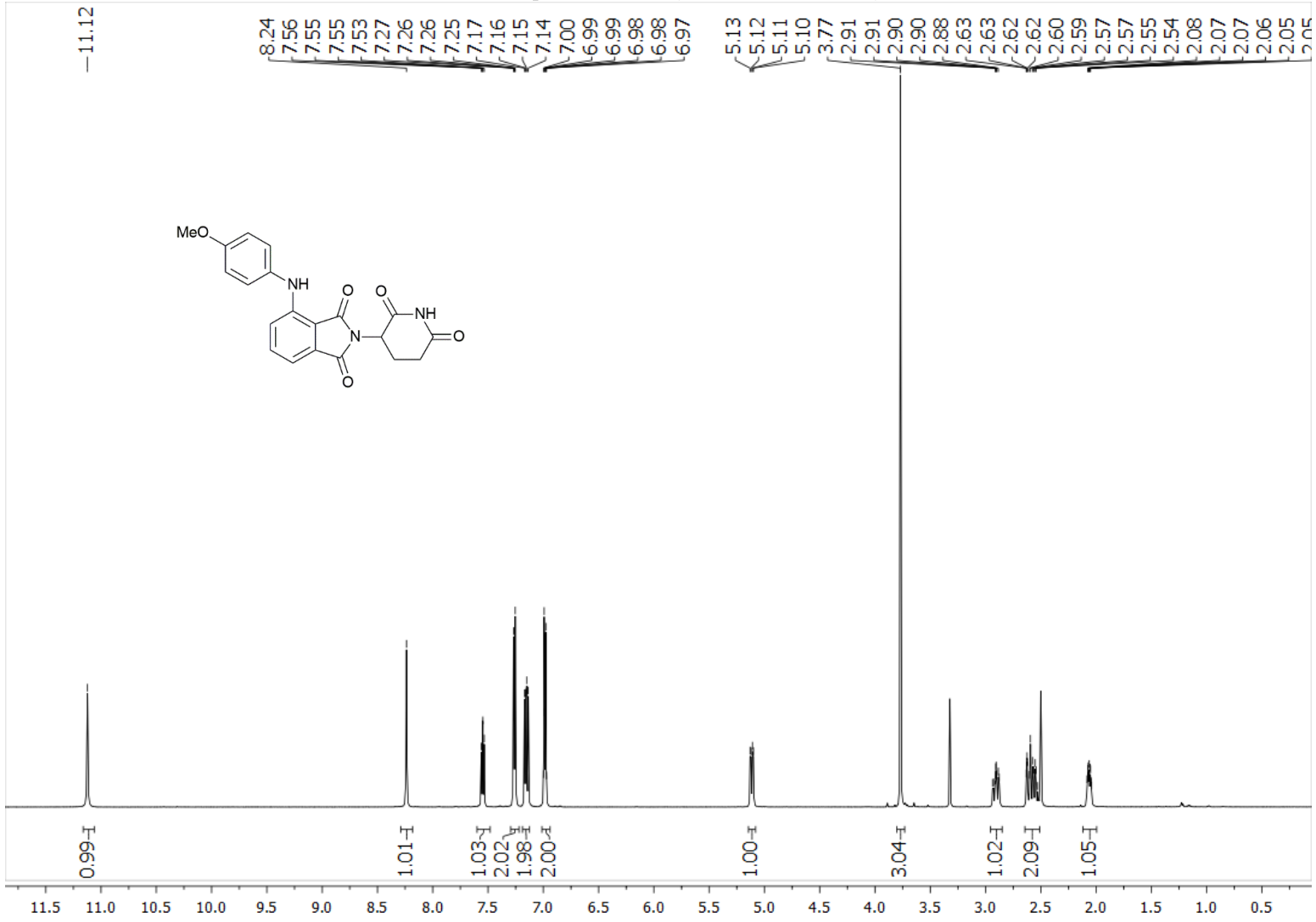
^{1}H NMR spectrum of **2g** (400 MHz, $CDCl_3$)



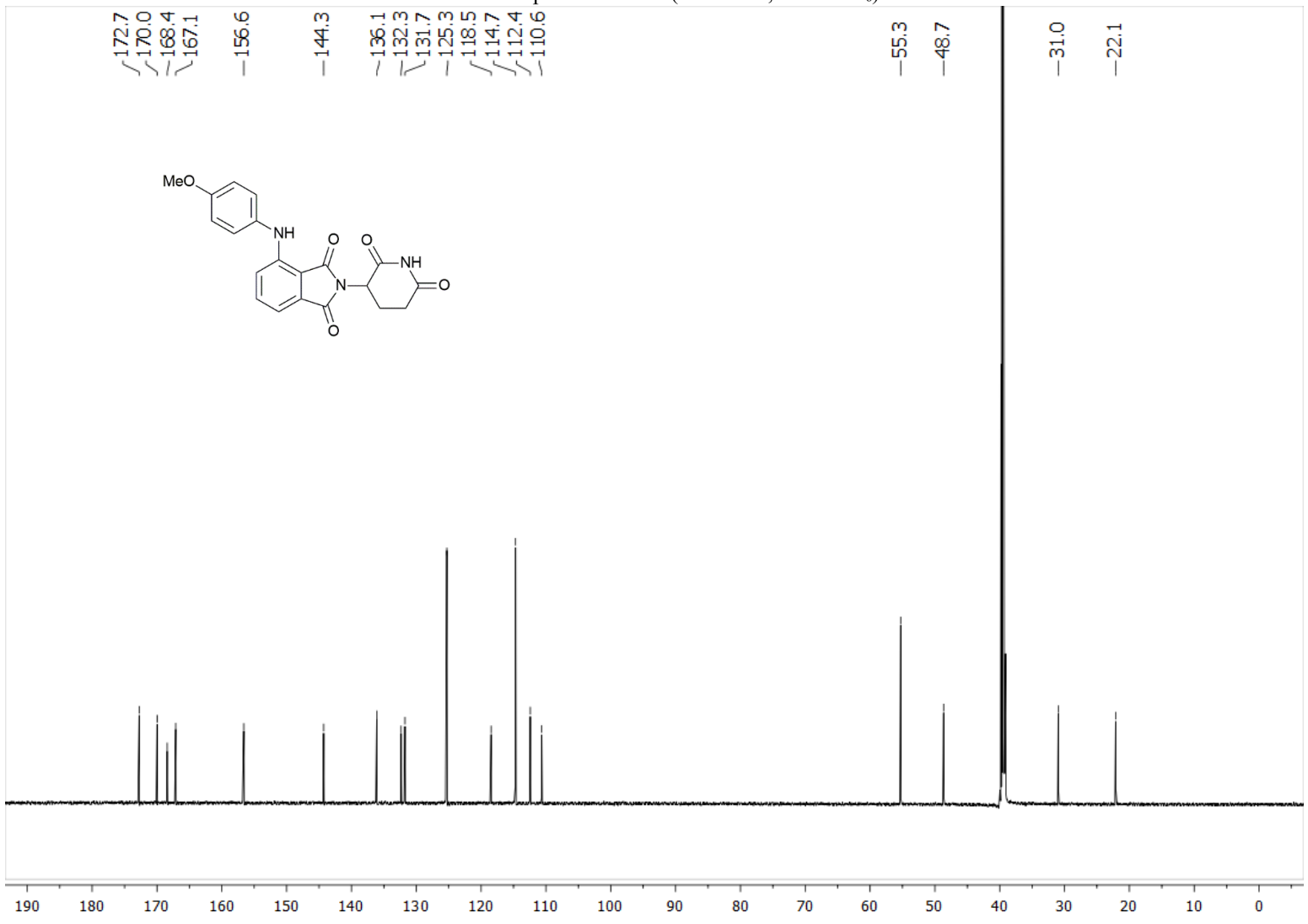
^{13}C NMR spectrum of **2g** (100 MHz, $CDCl_3$)



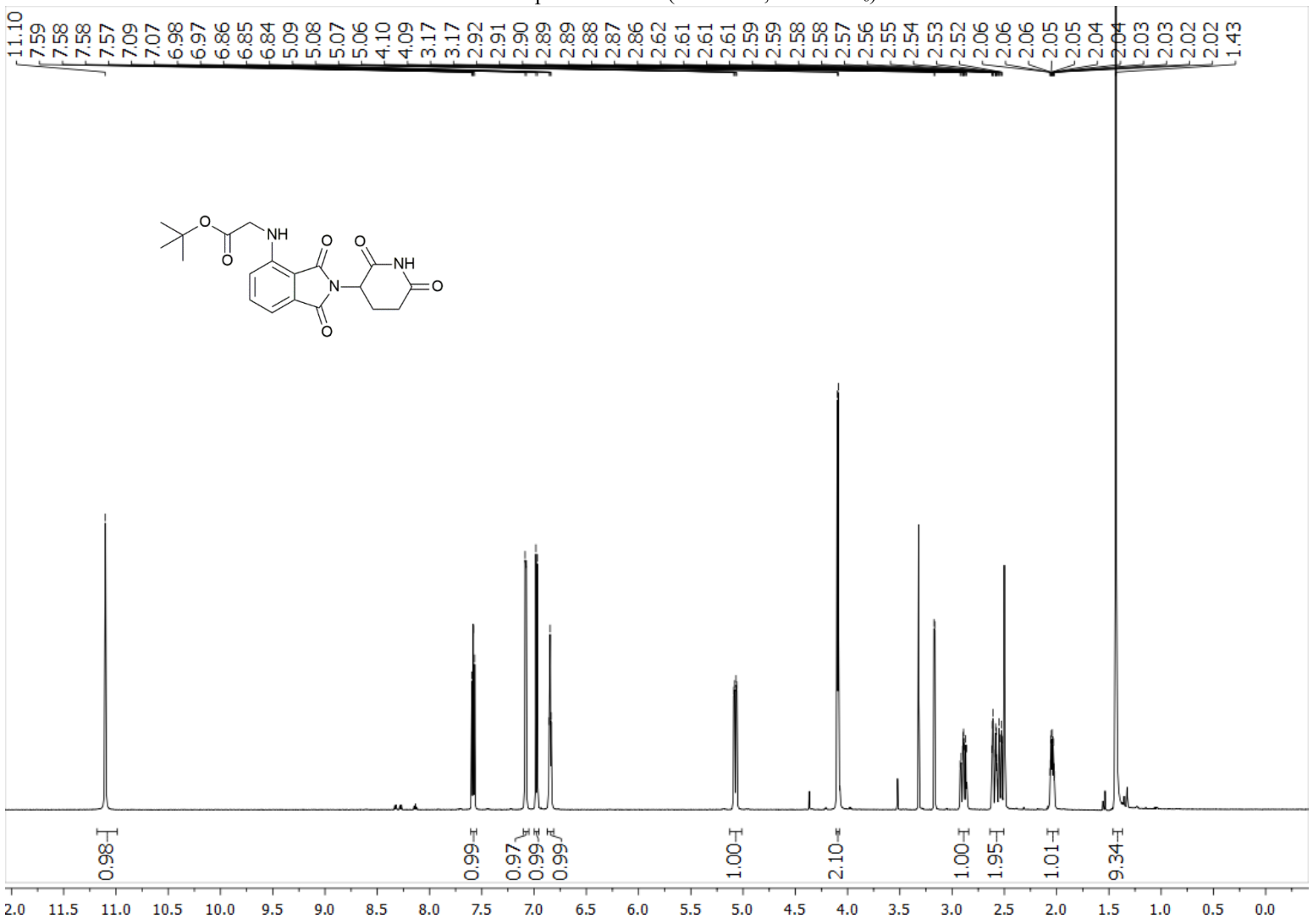
^{1}H NMR spectrum of **2h** (600 MHz, DMSO-d_6)



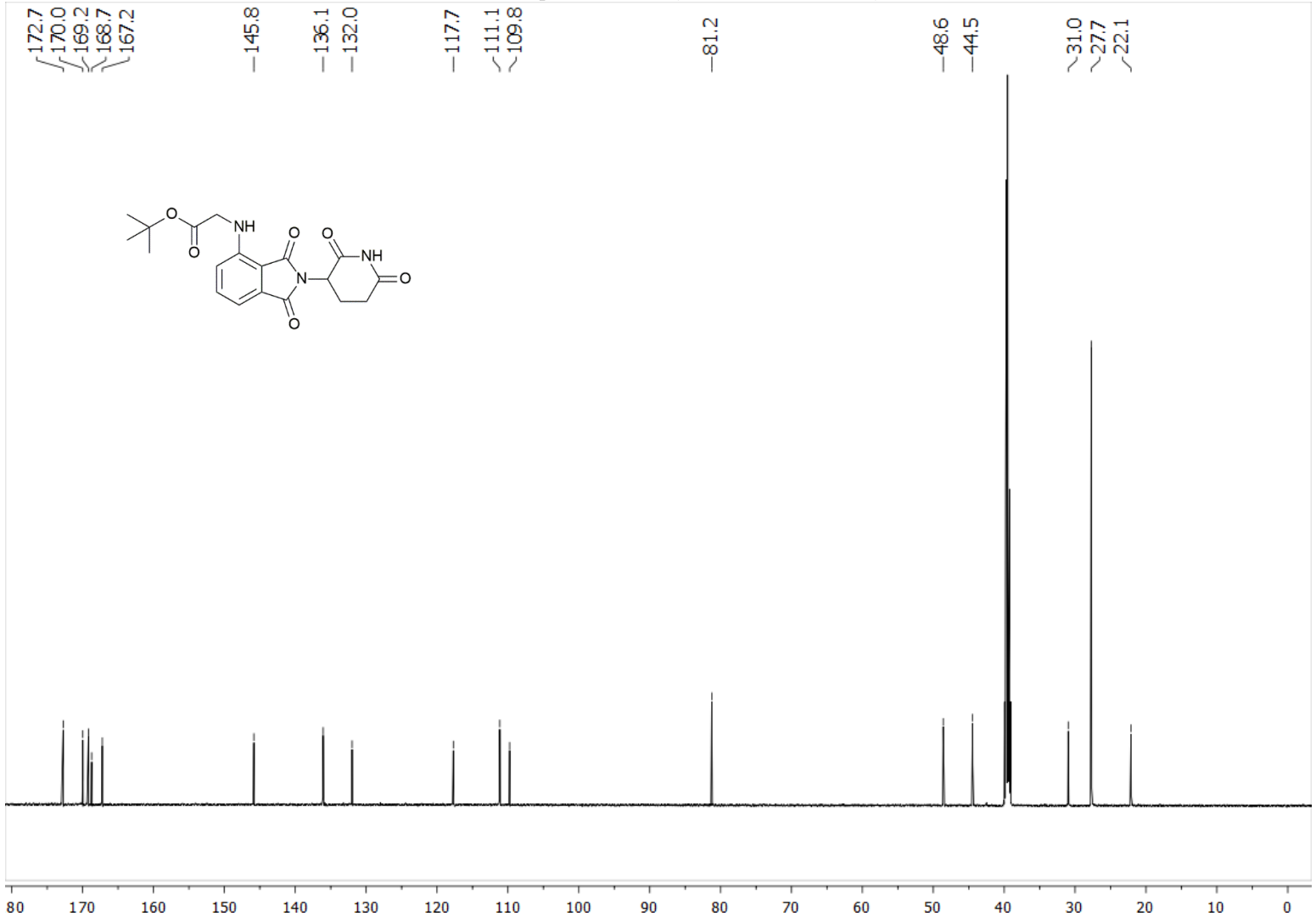
^{13}C NMR spectrum of **2h** (151 MHz, DMSO-d_6)



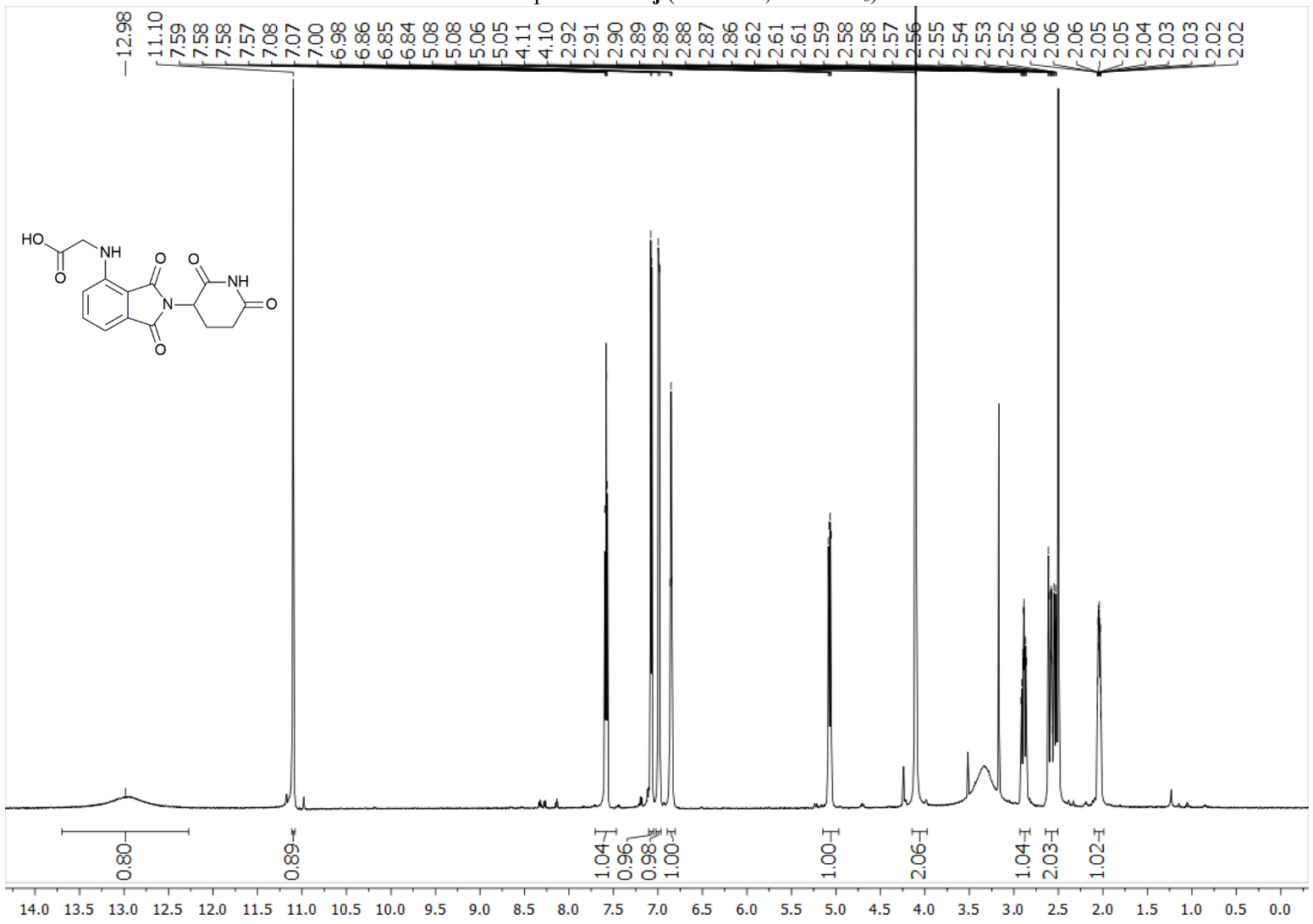
^{1}H NMR spectrum of **2i** (600 MHz, DMSO-d_6)



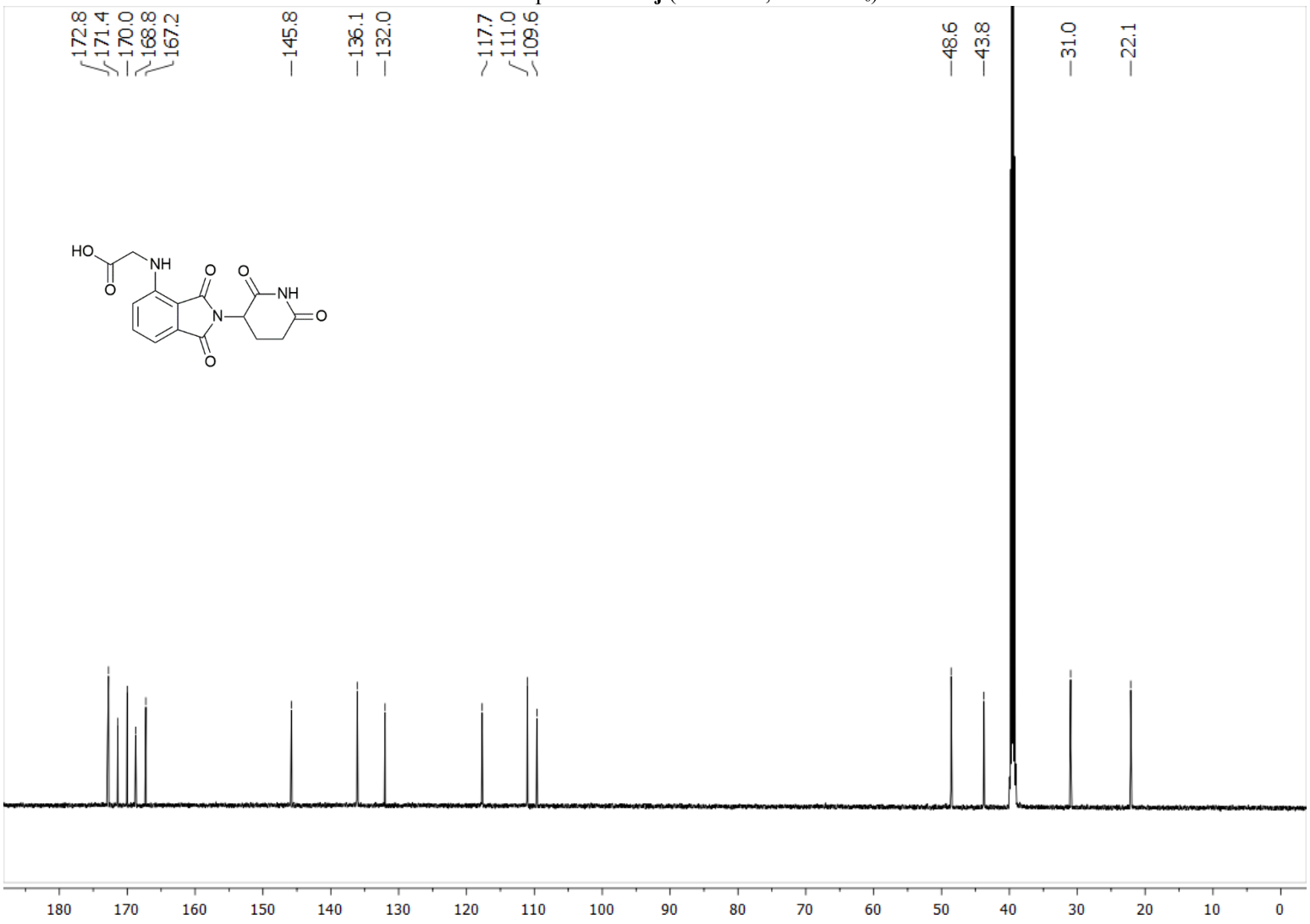
^{12}C NMR spectrum of **2i** (151 MHz, DMSO-d_6)



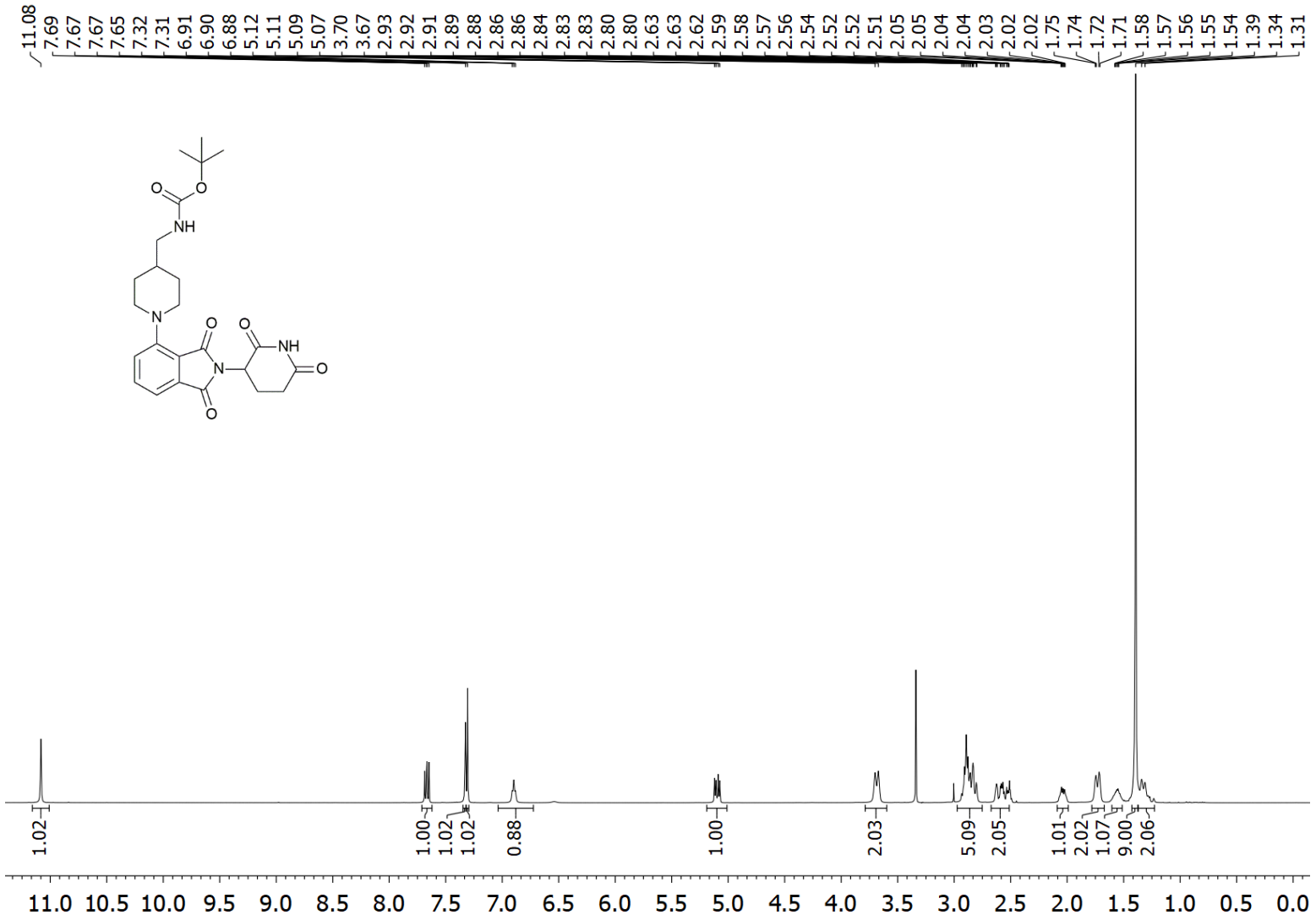
^{1}H NMR spectrum of **2j** (600 MHz, DMSO-d_6)



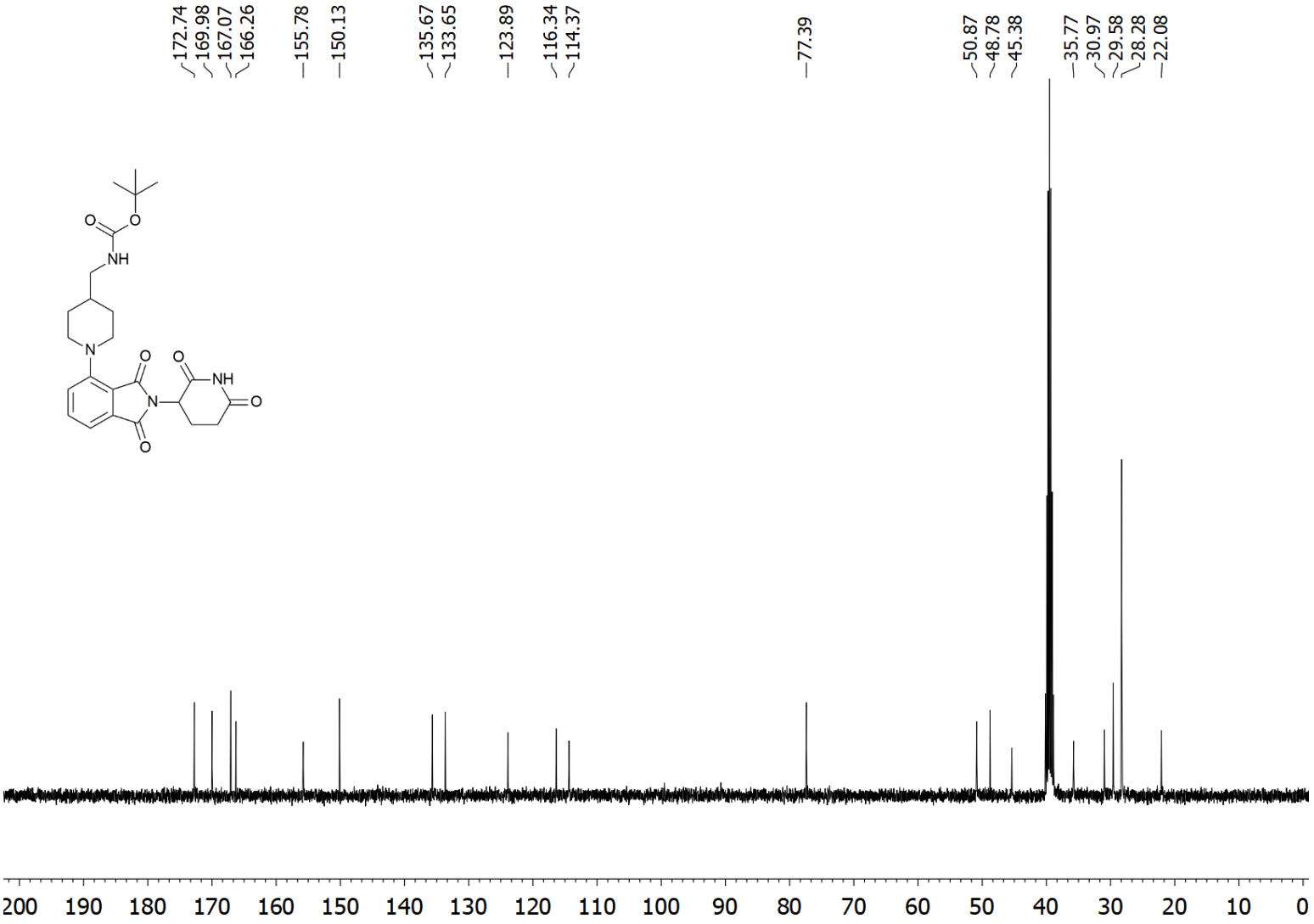
^{13}C NMR spectrum of **2j** (151 MHz, DMSO-d_6)



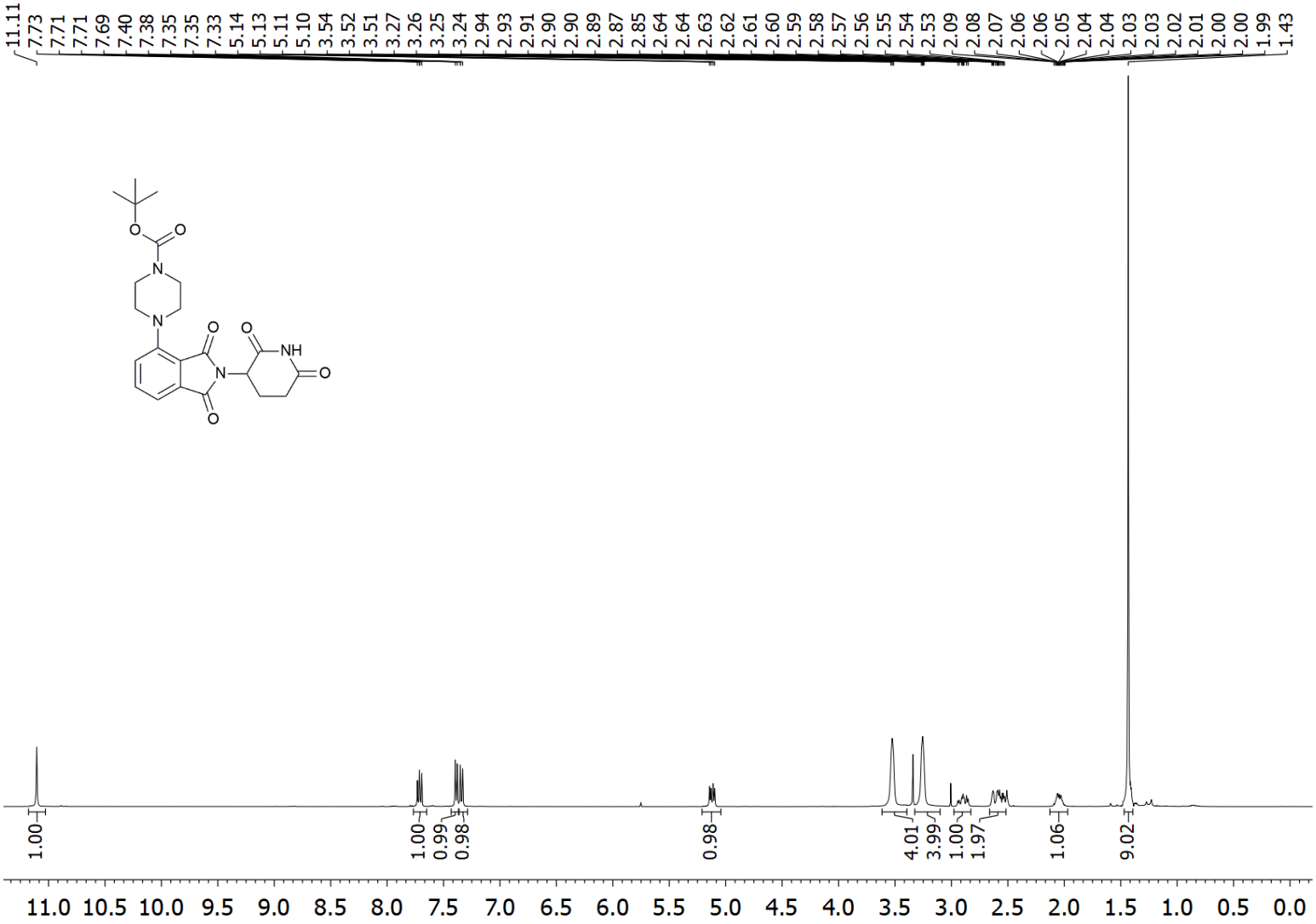
^{1}H NMR spectrum of **6a** (400 MHz, DMSO-d_6)



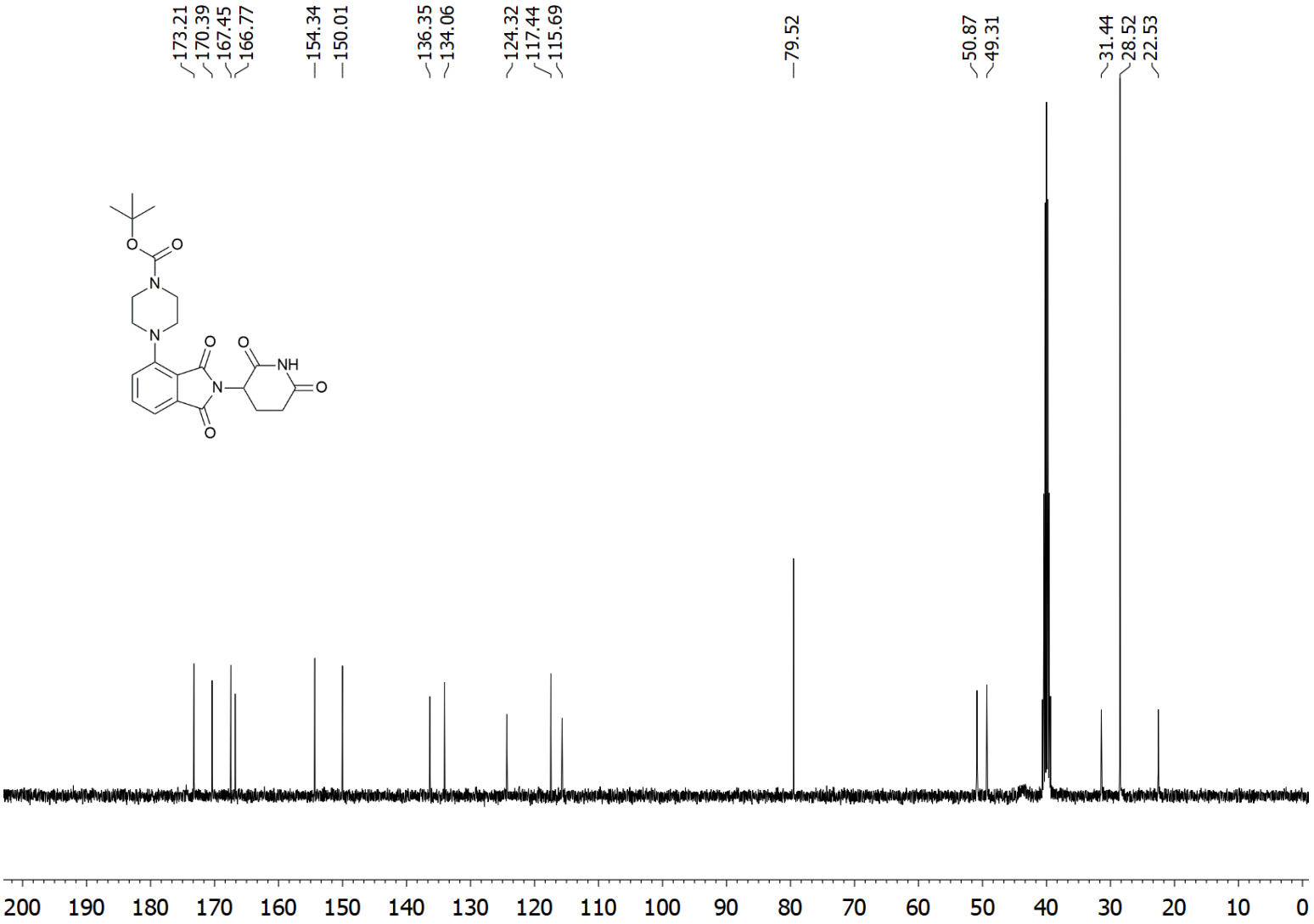
^{13}C NMR spectrum of **6a** (100 MHz, DMSO-d_6)



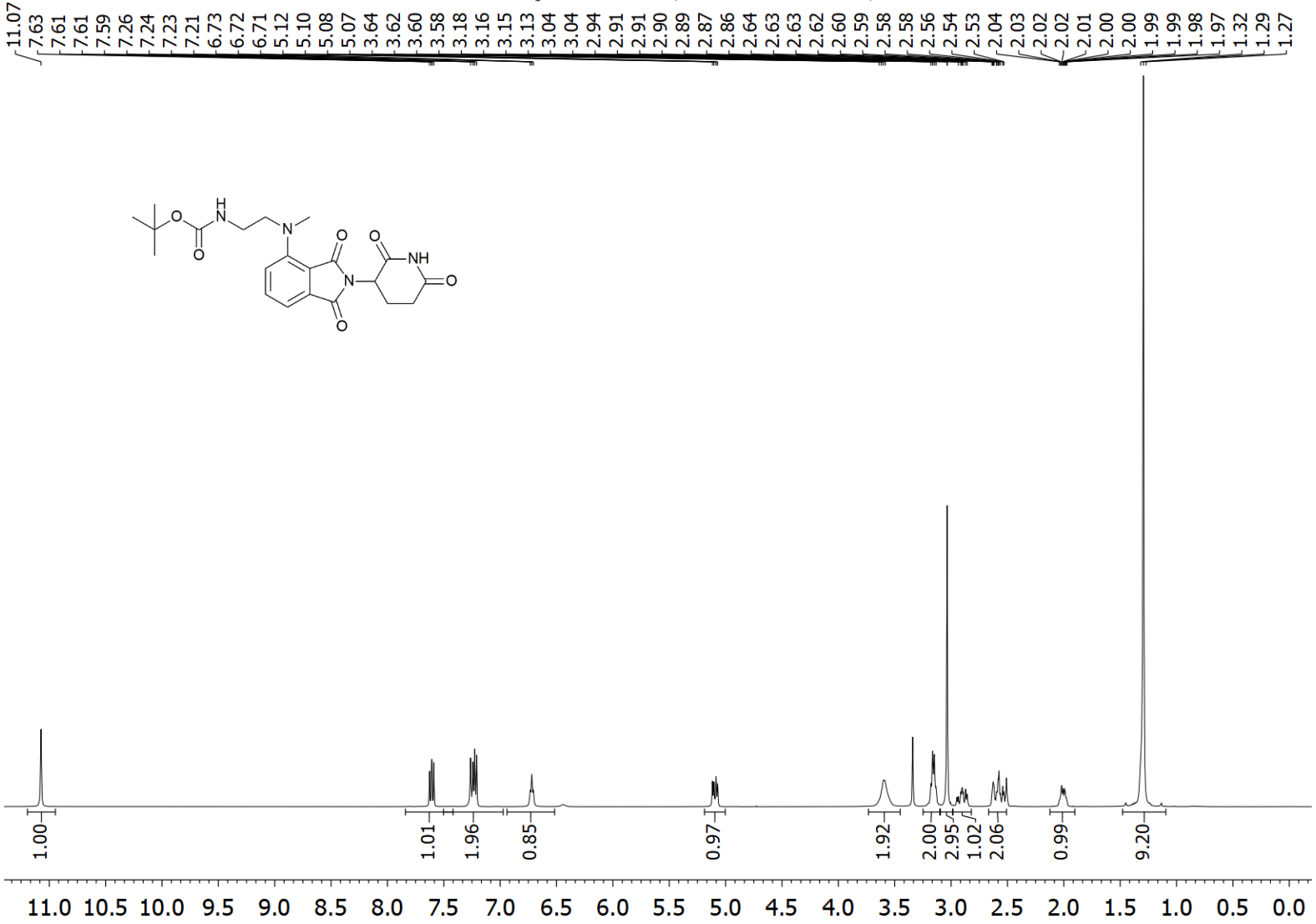
^{1}H NMR spectrum of **6b** (400 MHz, DMSO-d_6)



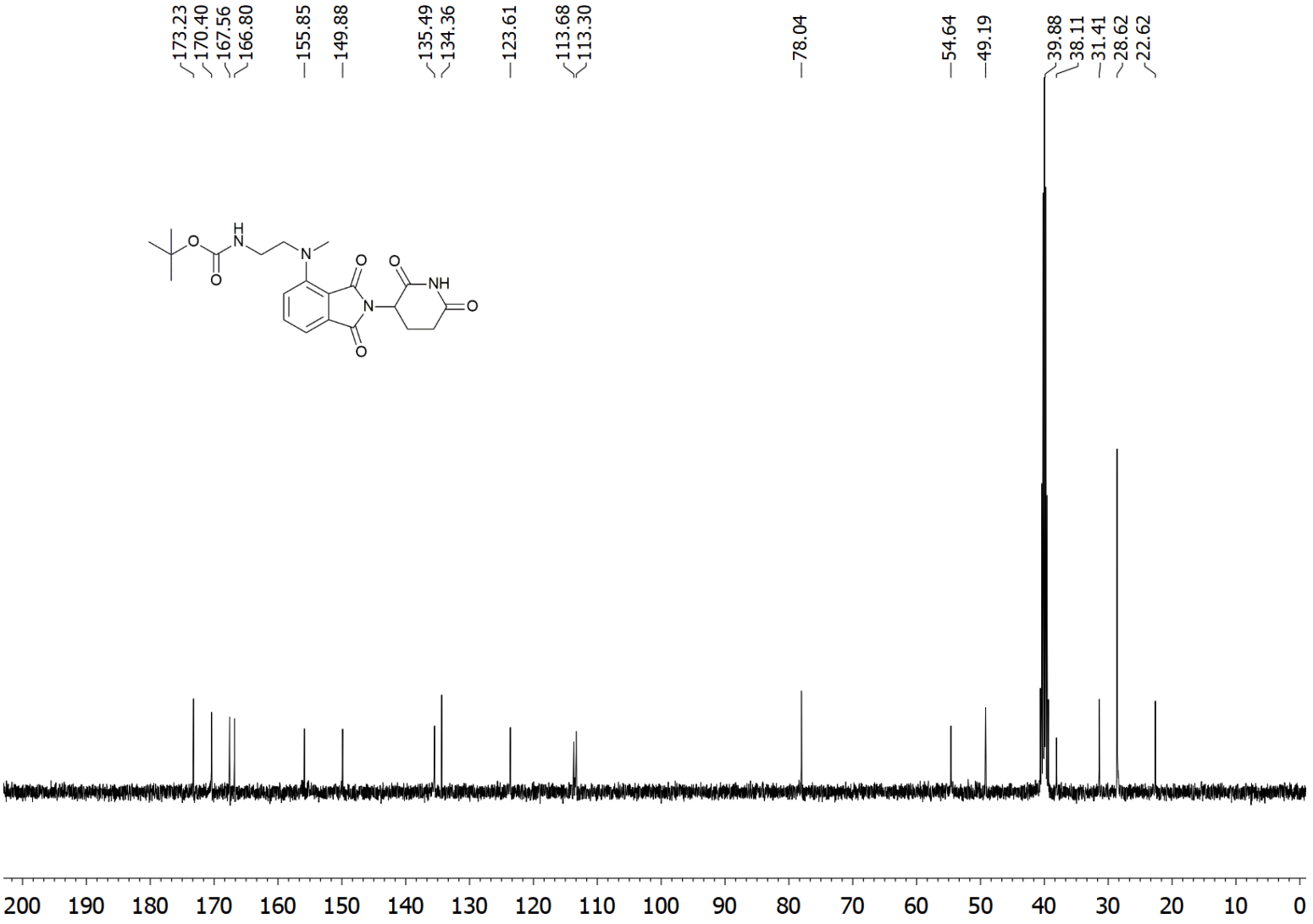
^{13}C NMR spectrum of **6b** (100 MHz, DMSO-d_6)



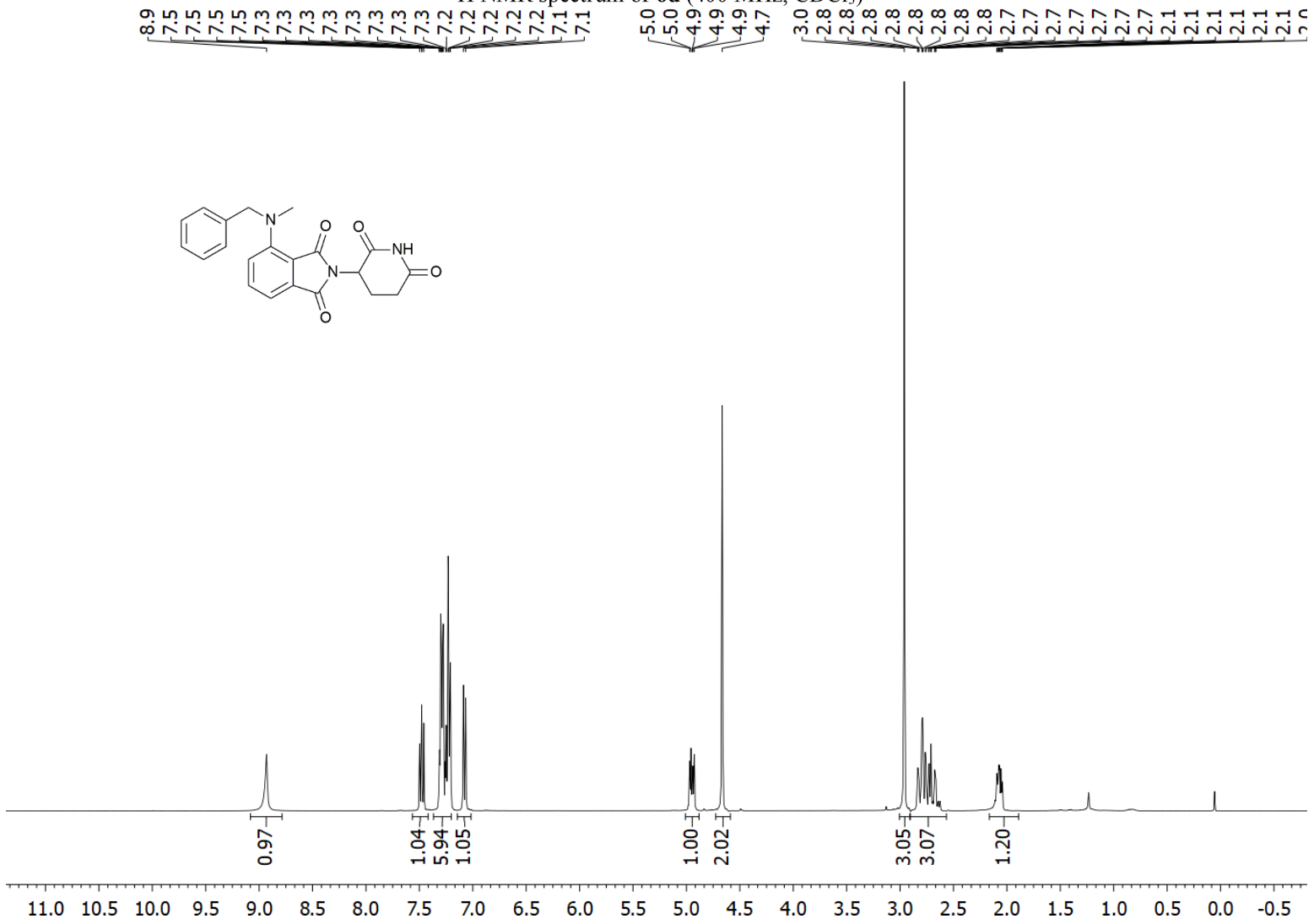
^{1}H NMR spectrum of **6c** (400 MHz, DMSO-d_6)



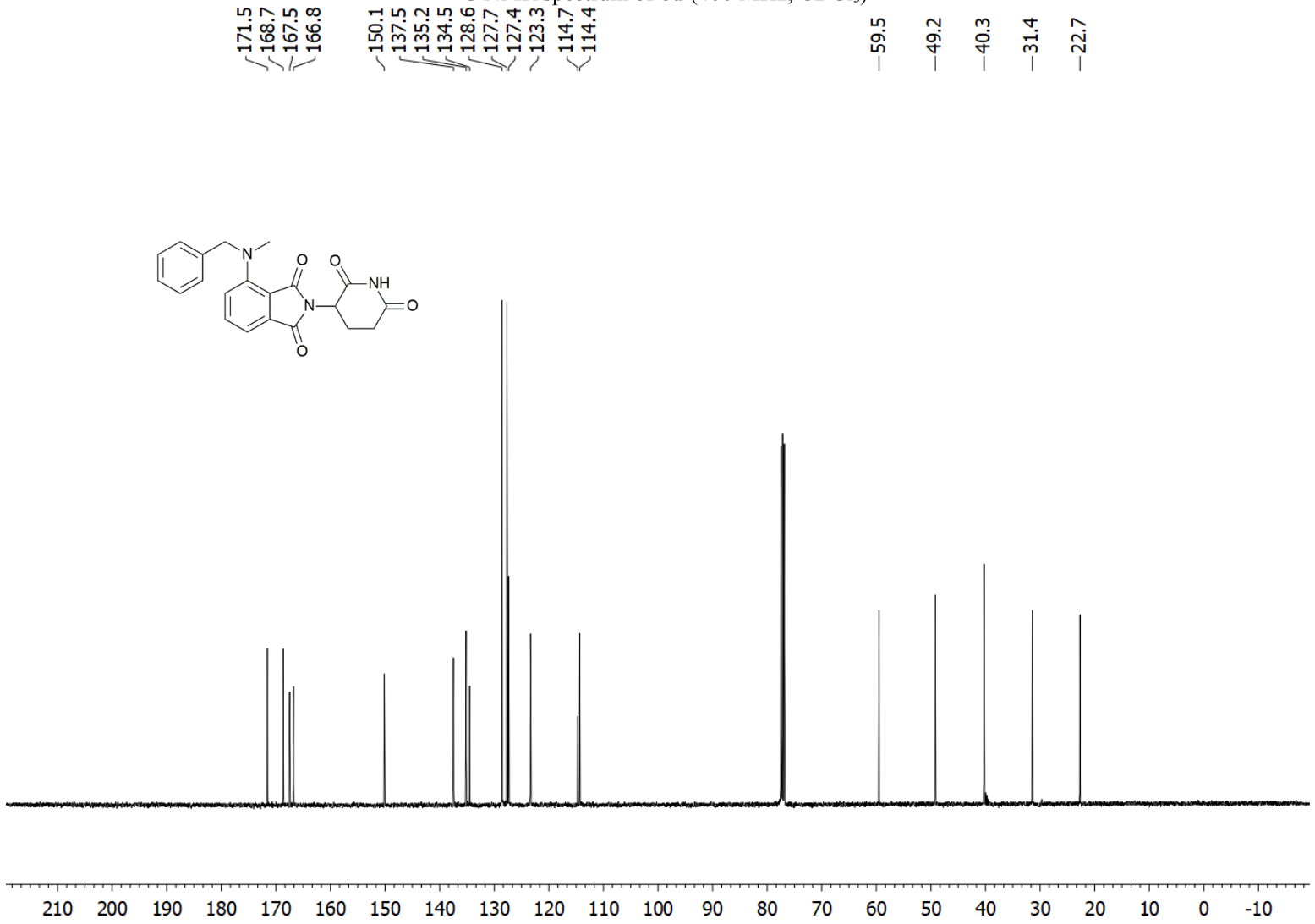
^{13}C NMR spectrum of **6c** (100 MHz, DMSO-d_6)



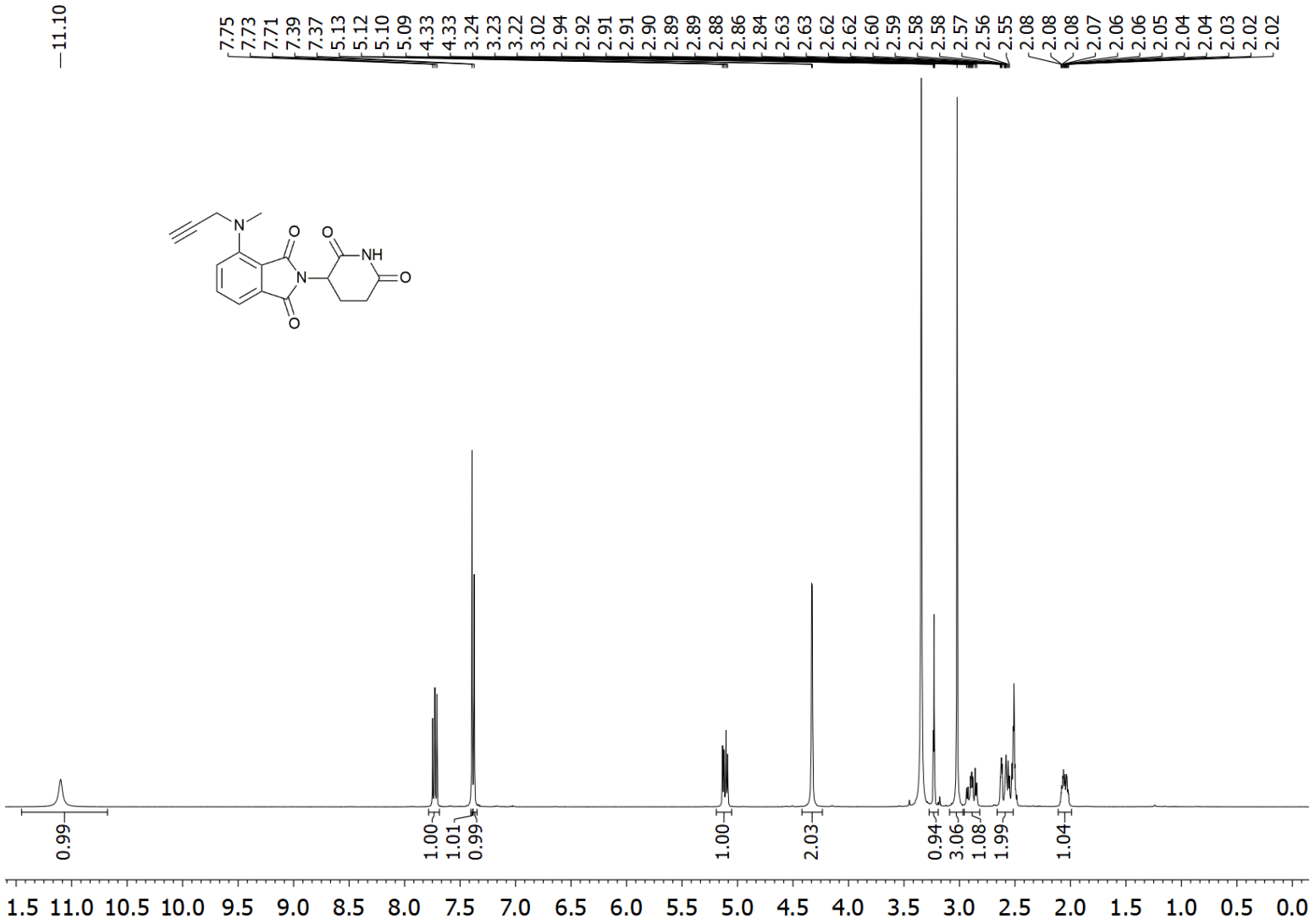
^{1}H NMR spectrum of **6d** (400 MHz, $CDCl_3$)



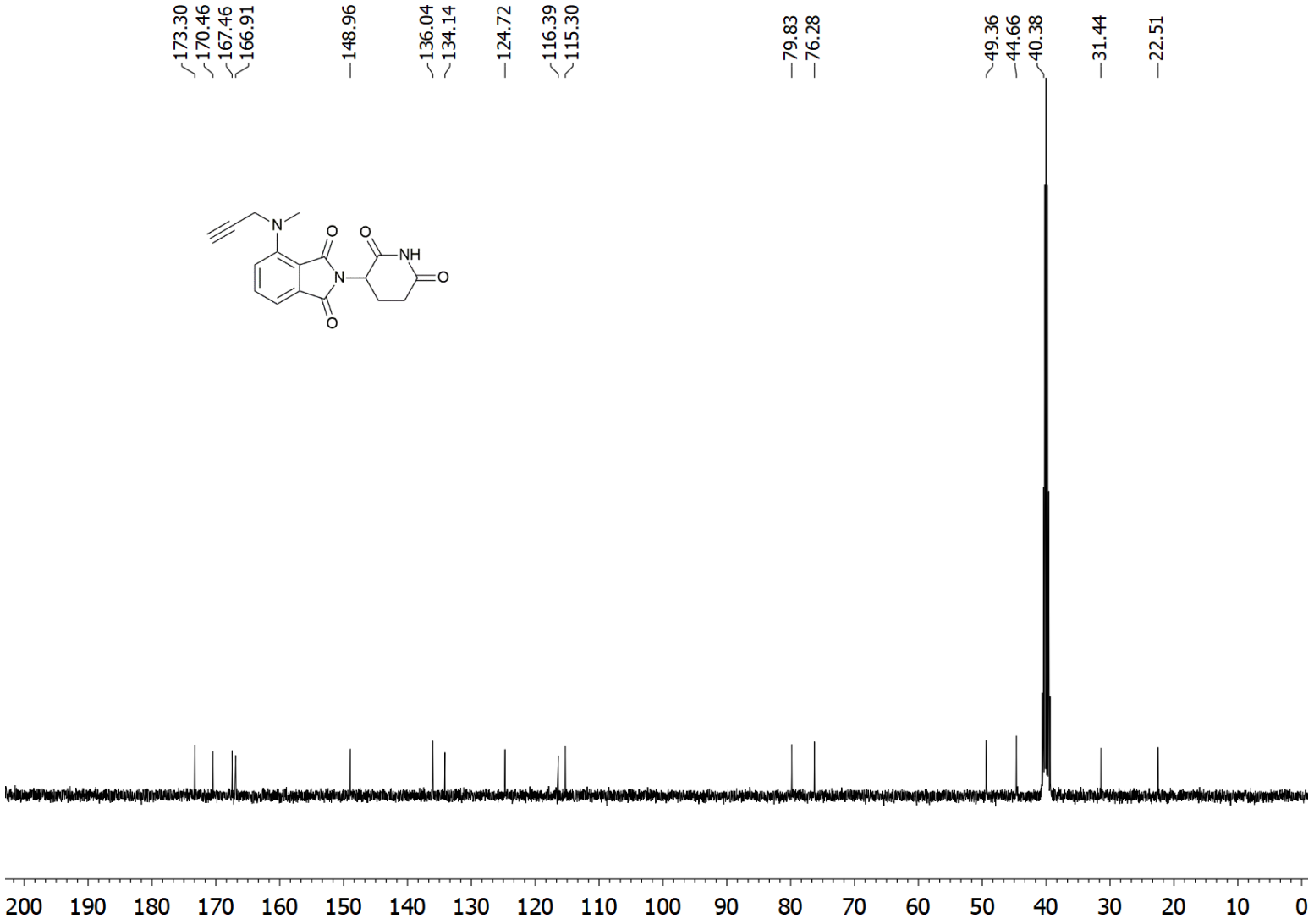
^{13}C NMR spectrum of **6d** (400 MHz, $CDCl_3$)



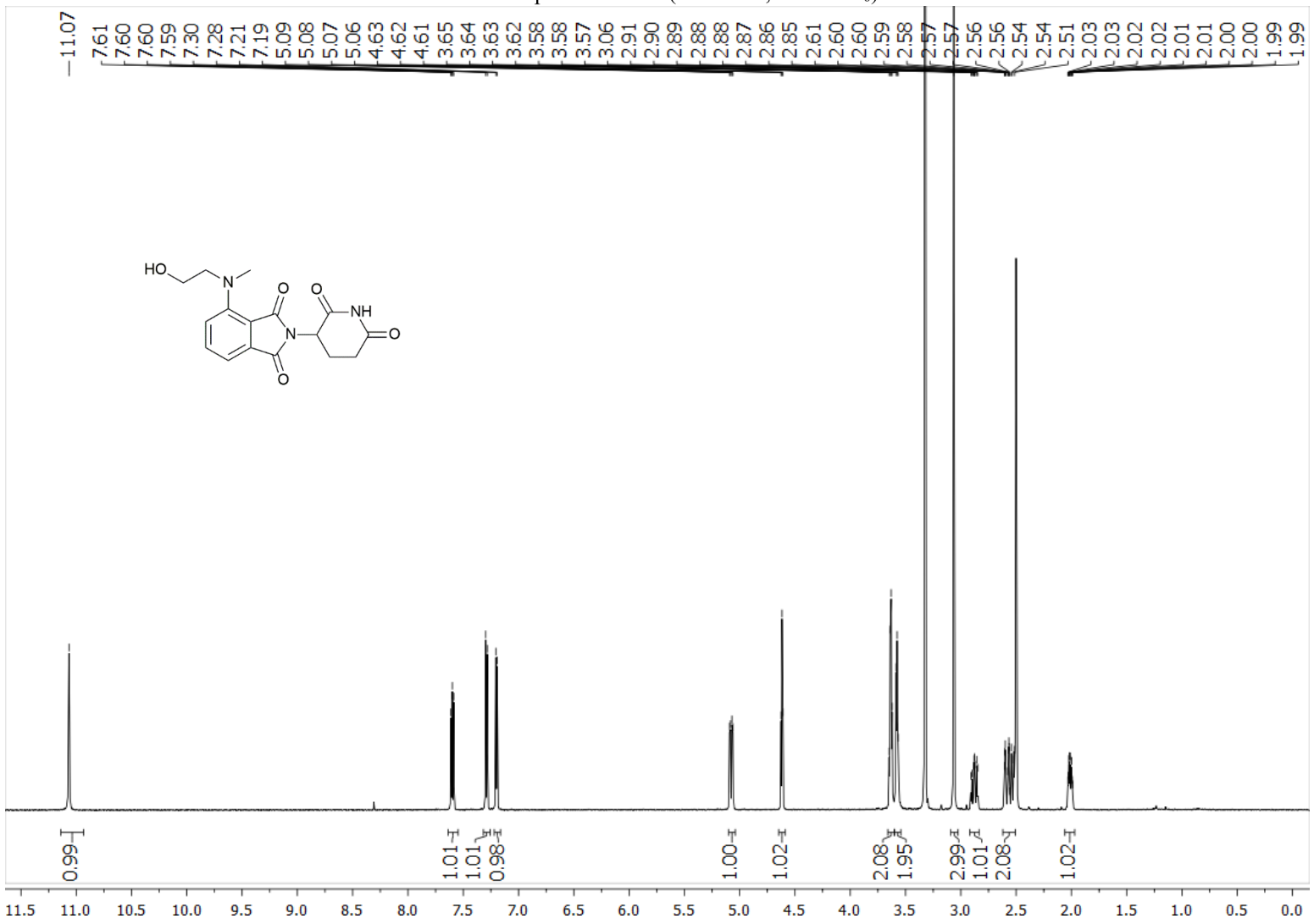
^{1}H NMR spectrum of **6e** (400 MHz, DMSO-d_6)



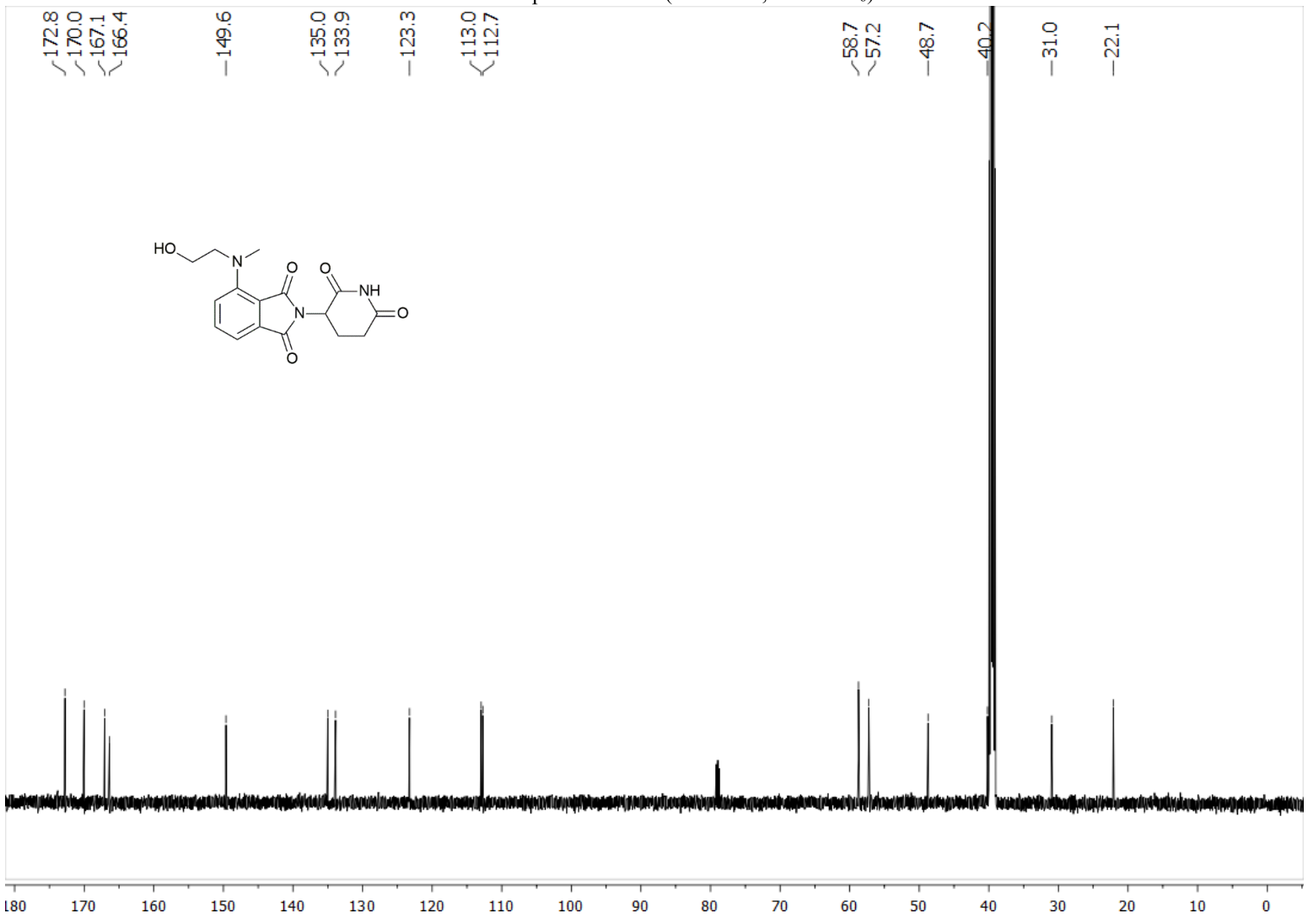
^{13}C NMR spectrum of **6e** (100 MHz, DMSO-d_6)



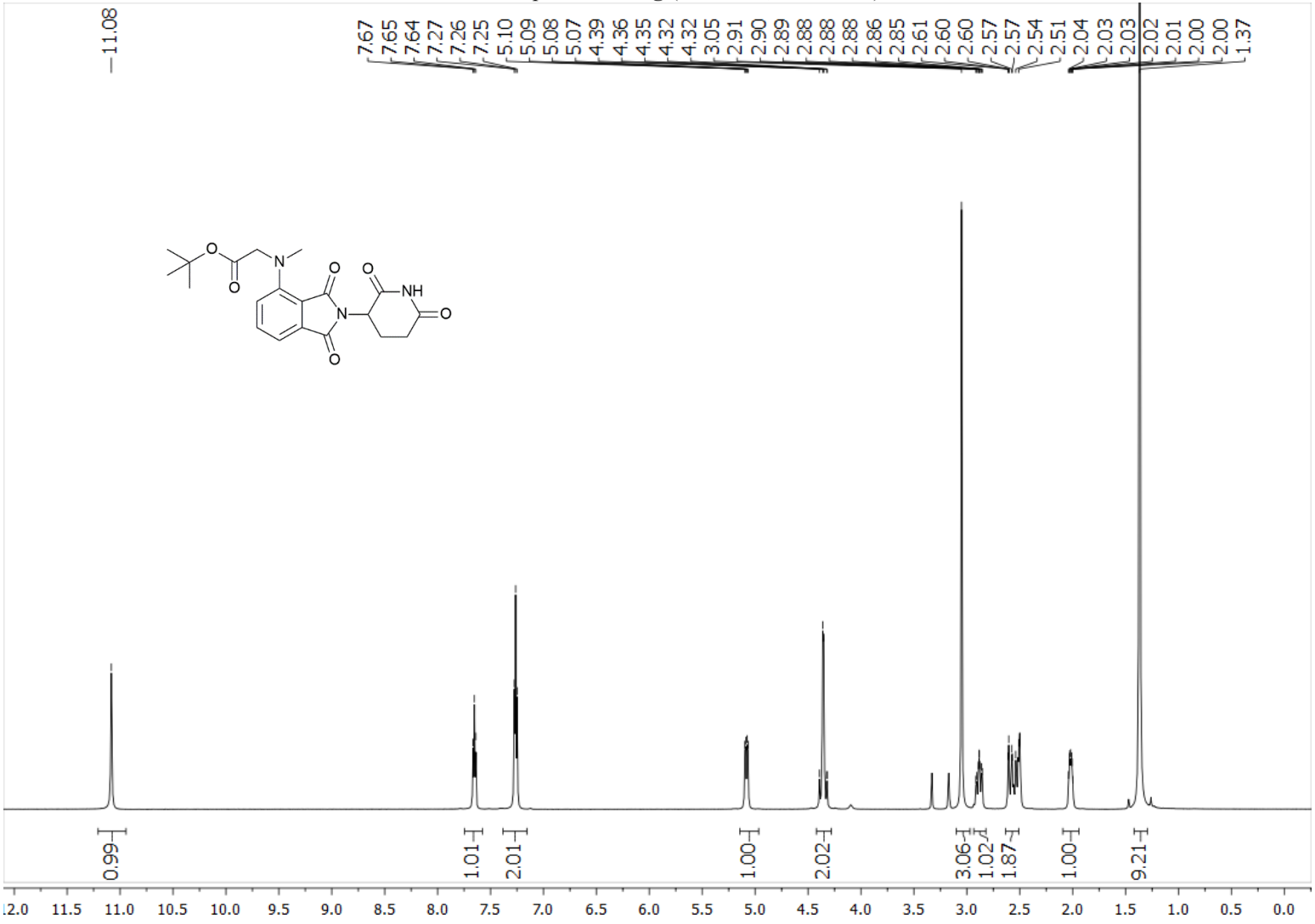
^{1}H NMR spectrum of **6f** (600 MHz, DMSO-d_6)



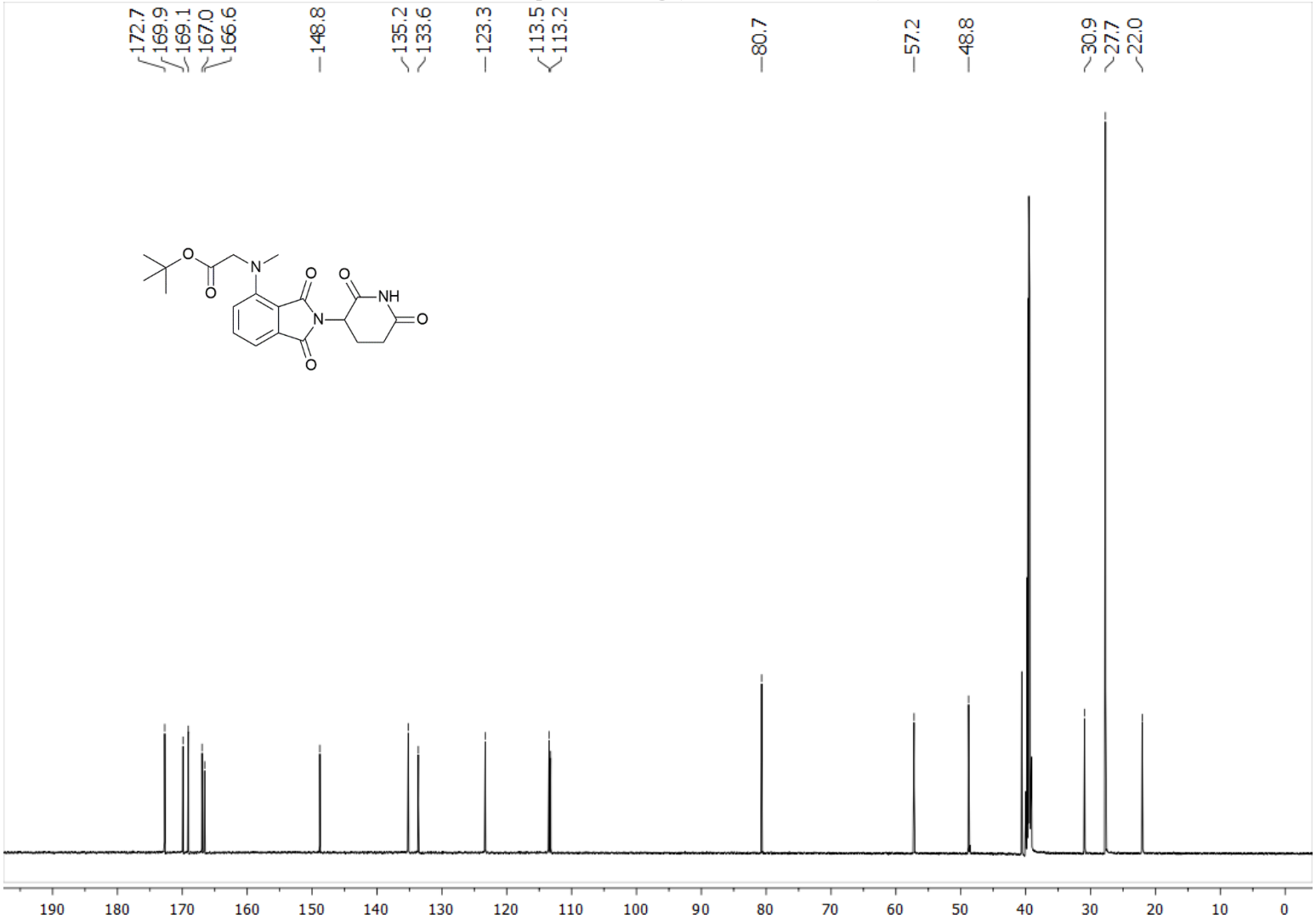
^{1}H NMR spectrum of **6f** (151 MHz, DMSO-d_6)



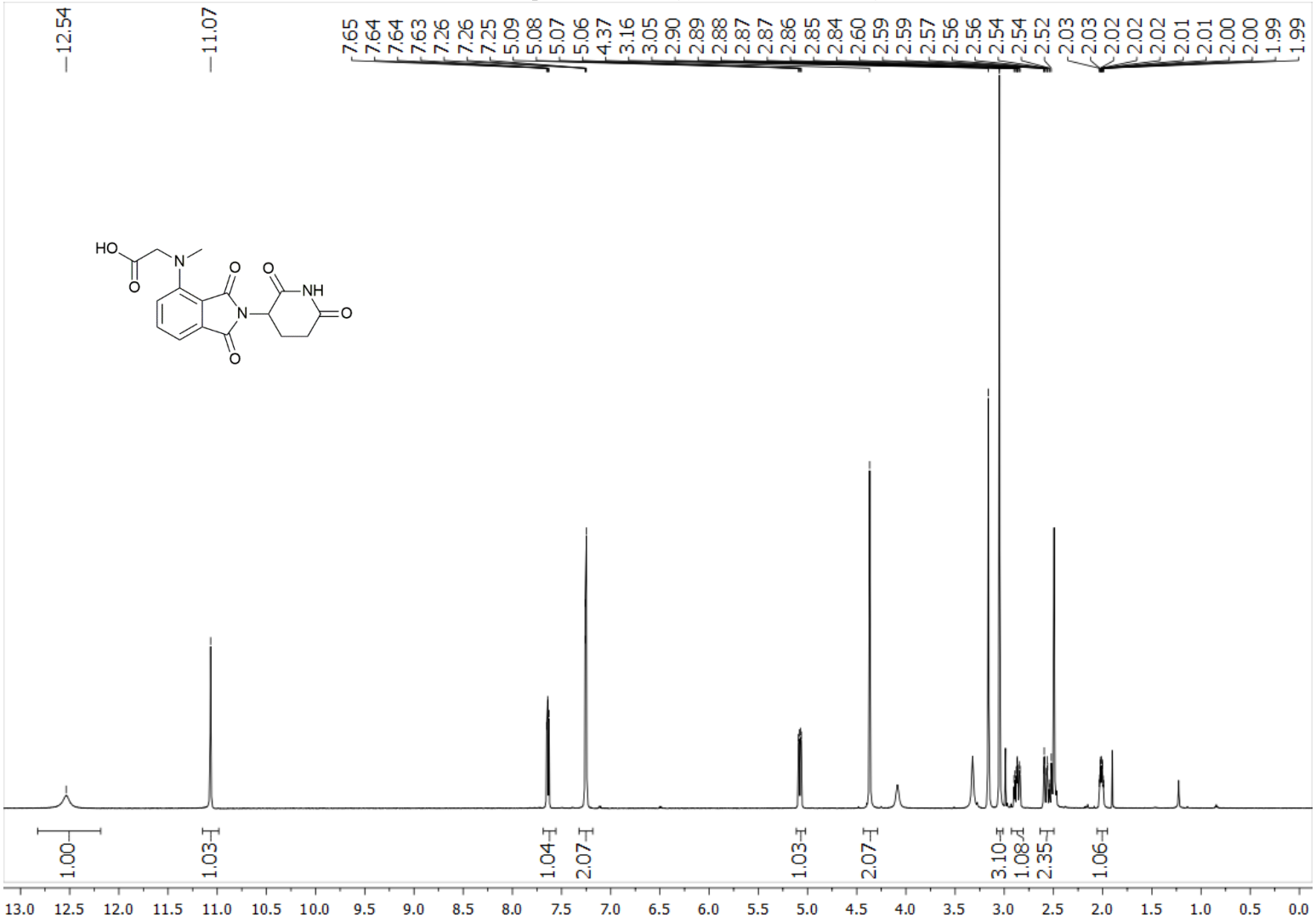
^{1}H NMR spectrum of **6g** (600 MHz, DMSO-d_6)



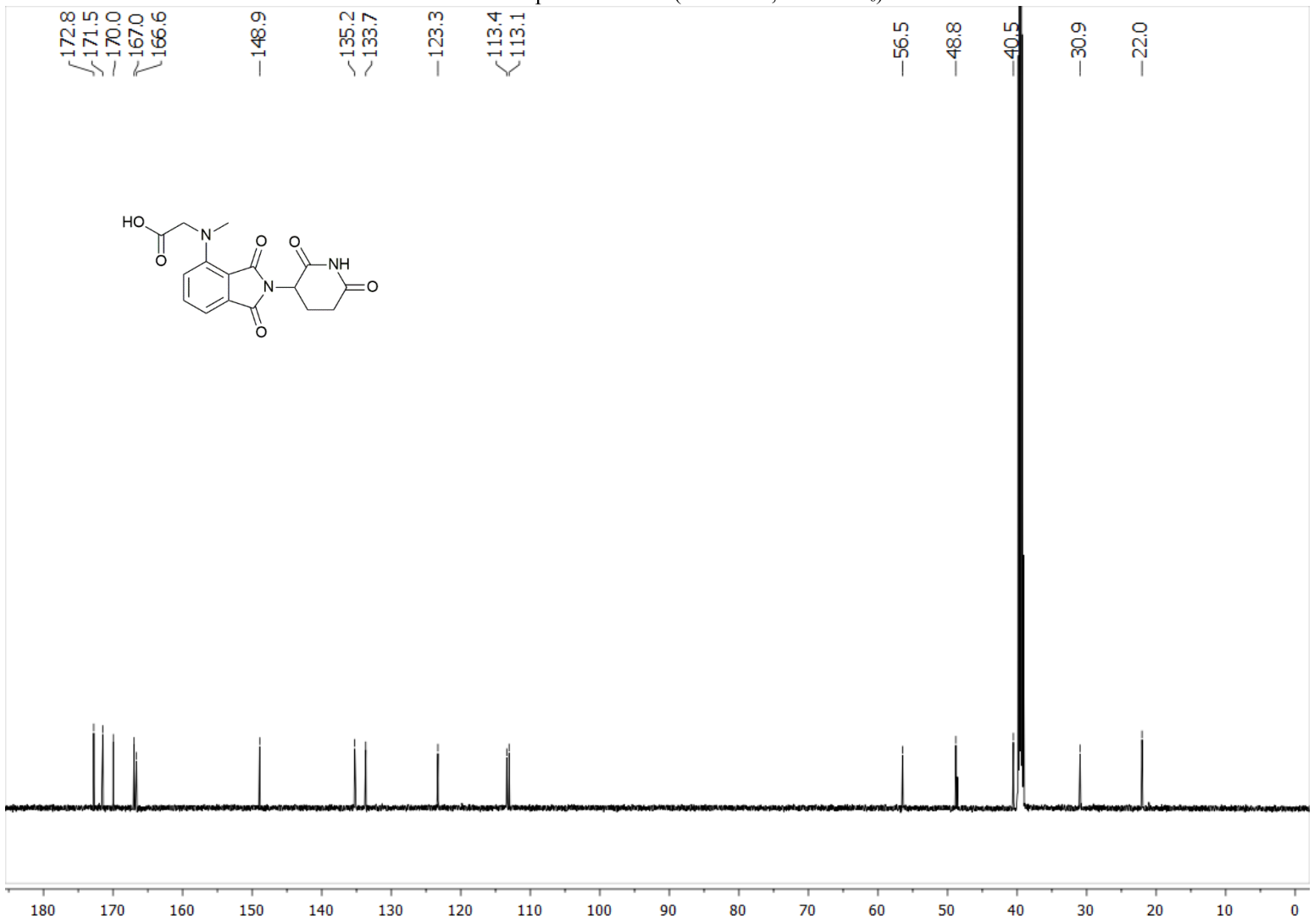
^{13}C NMR spectrum of **6g** (151 MHz, DMSO-d_6)



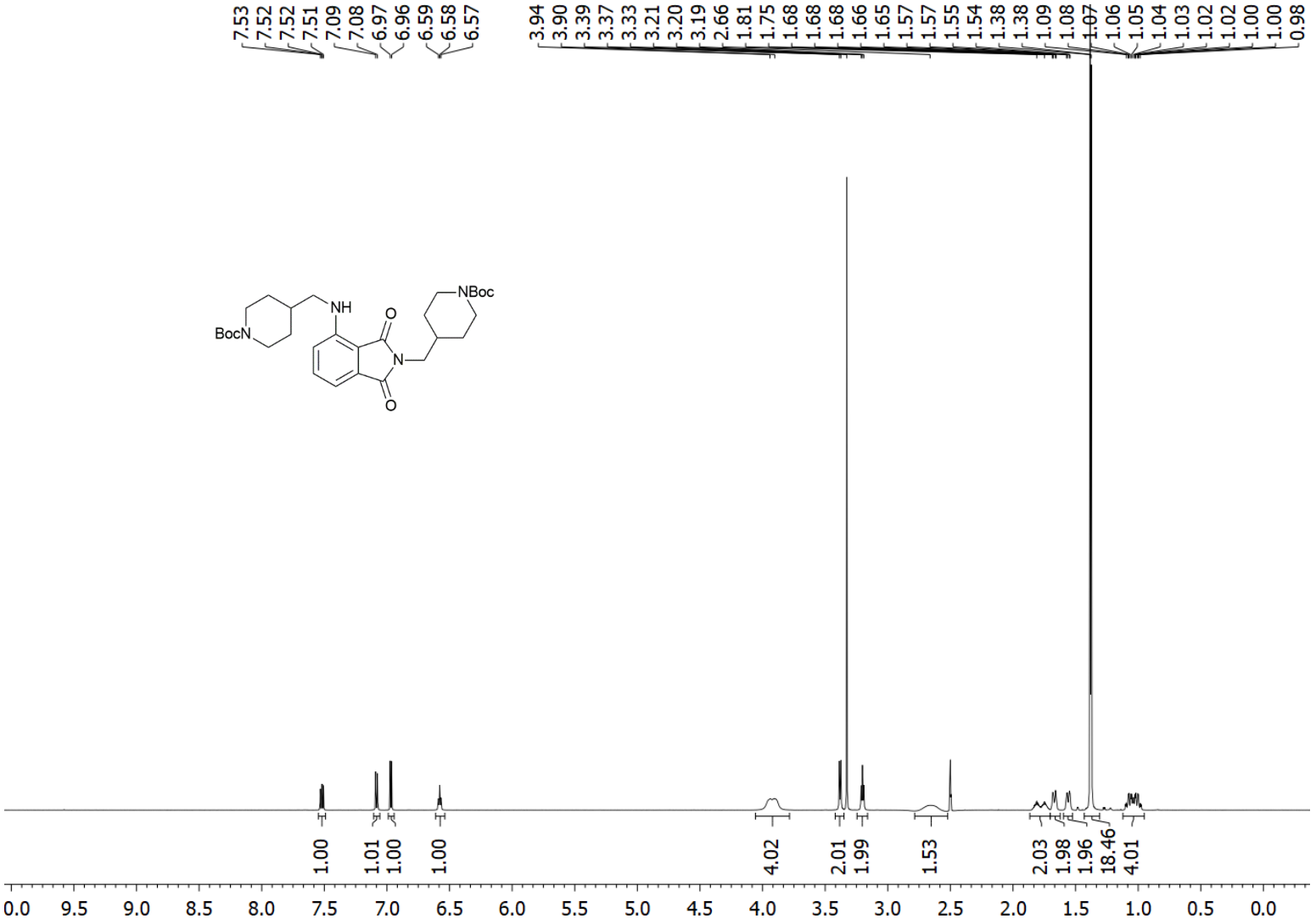
^{1}H NMR spectrum of **6h** (600 MHz, DMSO-d_6)



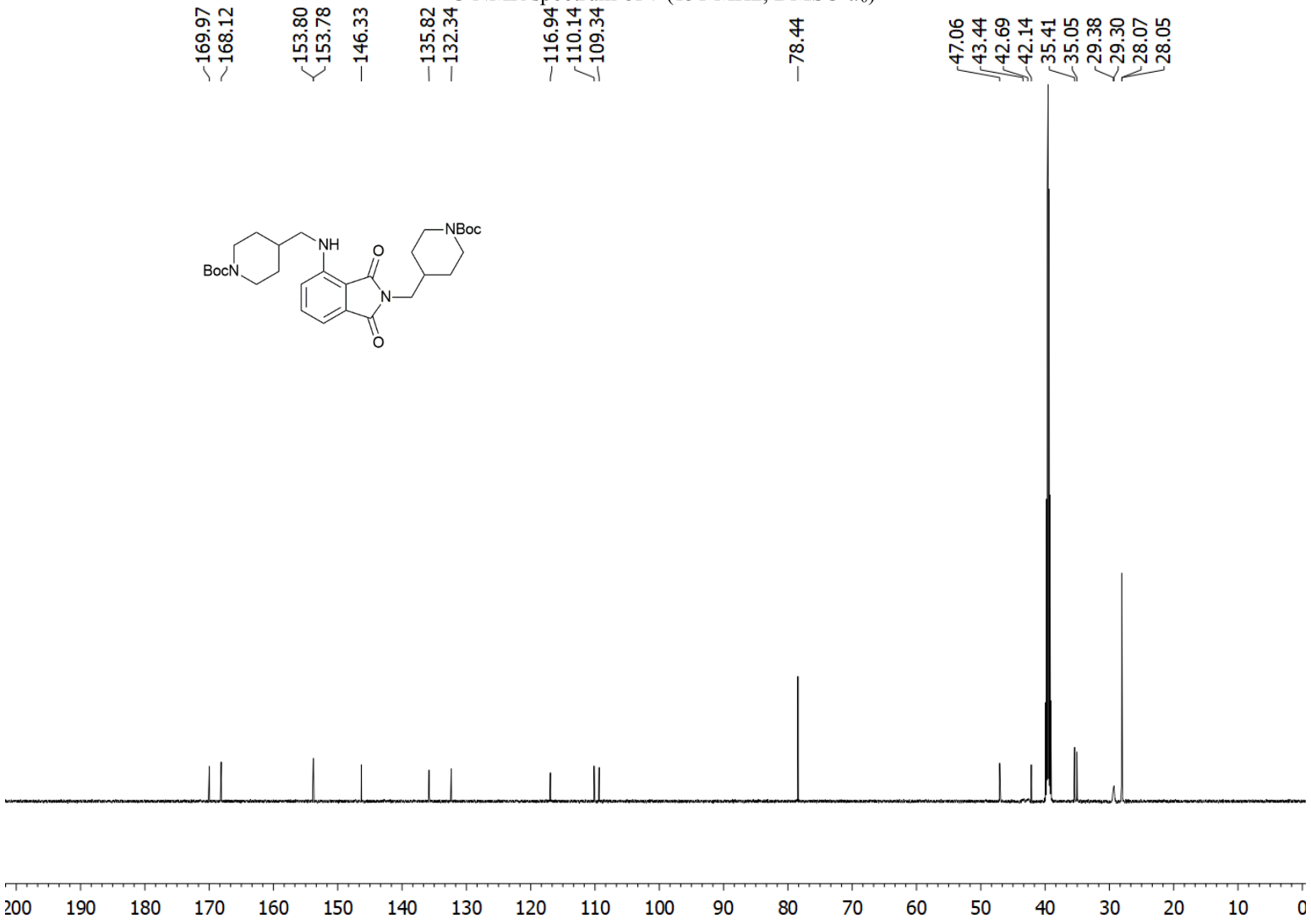
^{12}C NMR spectrum of **6h** (151 MHz, DMSO-d_6)



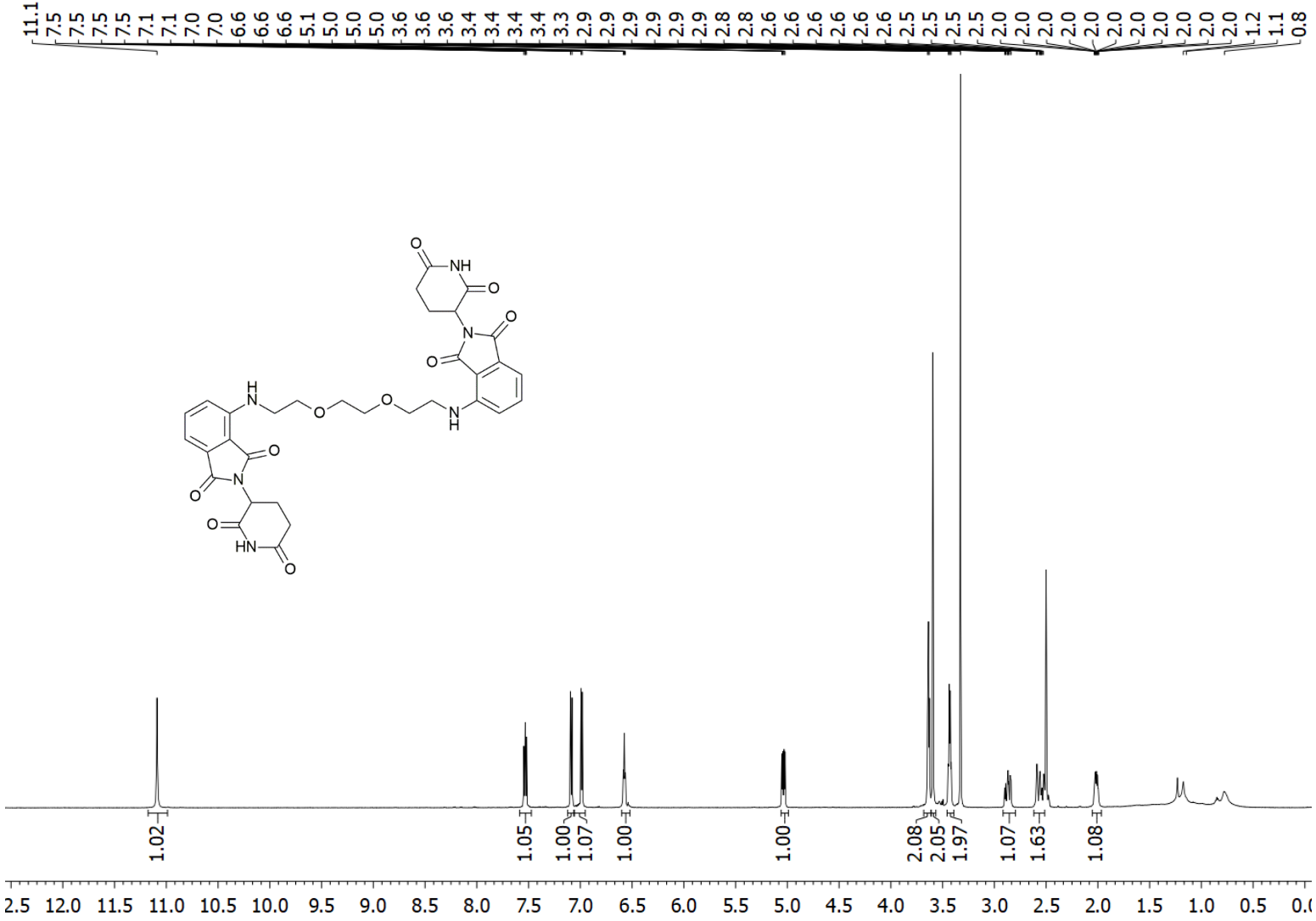
^{1}H NMR spectrum of **7** (600 MHz, DMSO-d_6)



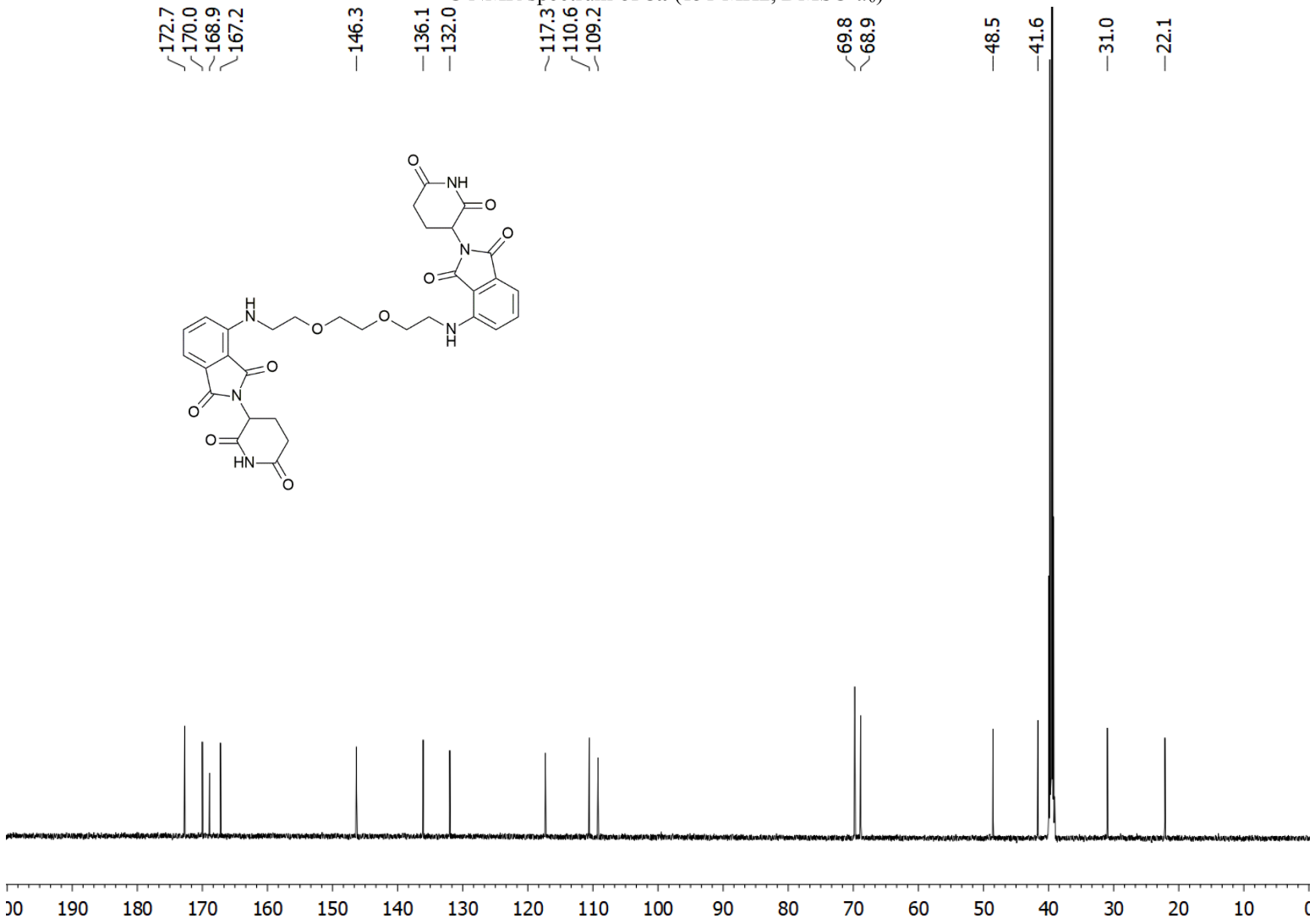
^{13}C NMR spectrum of **7** (151 MHz, DMSO-d_6)



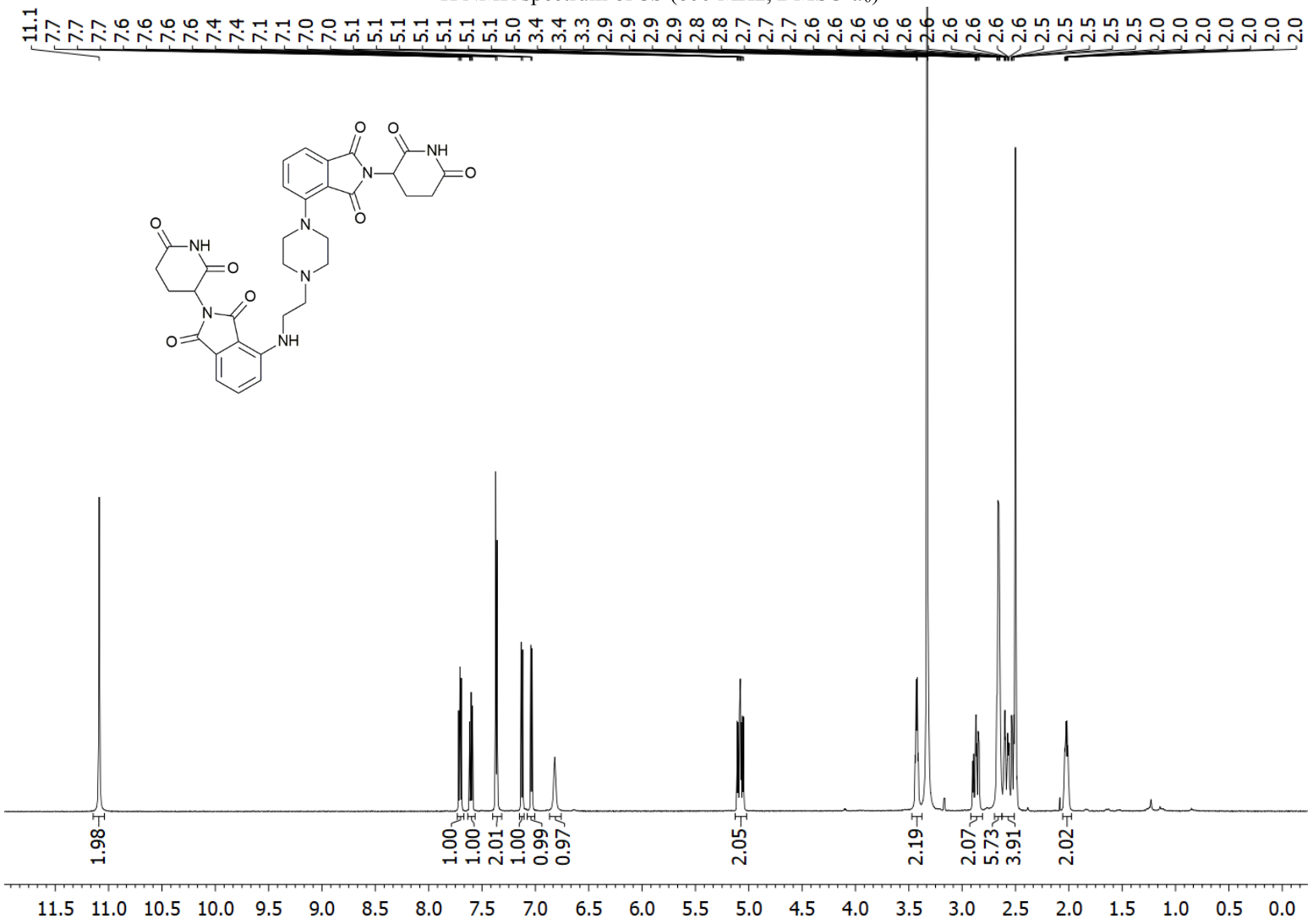
^{1}H NMR spectrum of **8a** (600 MHz, DMSO-d_6)



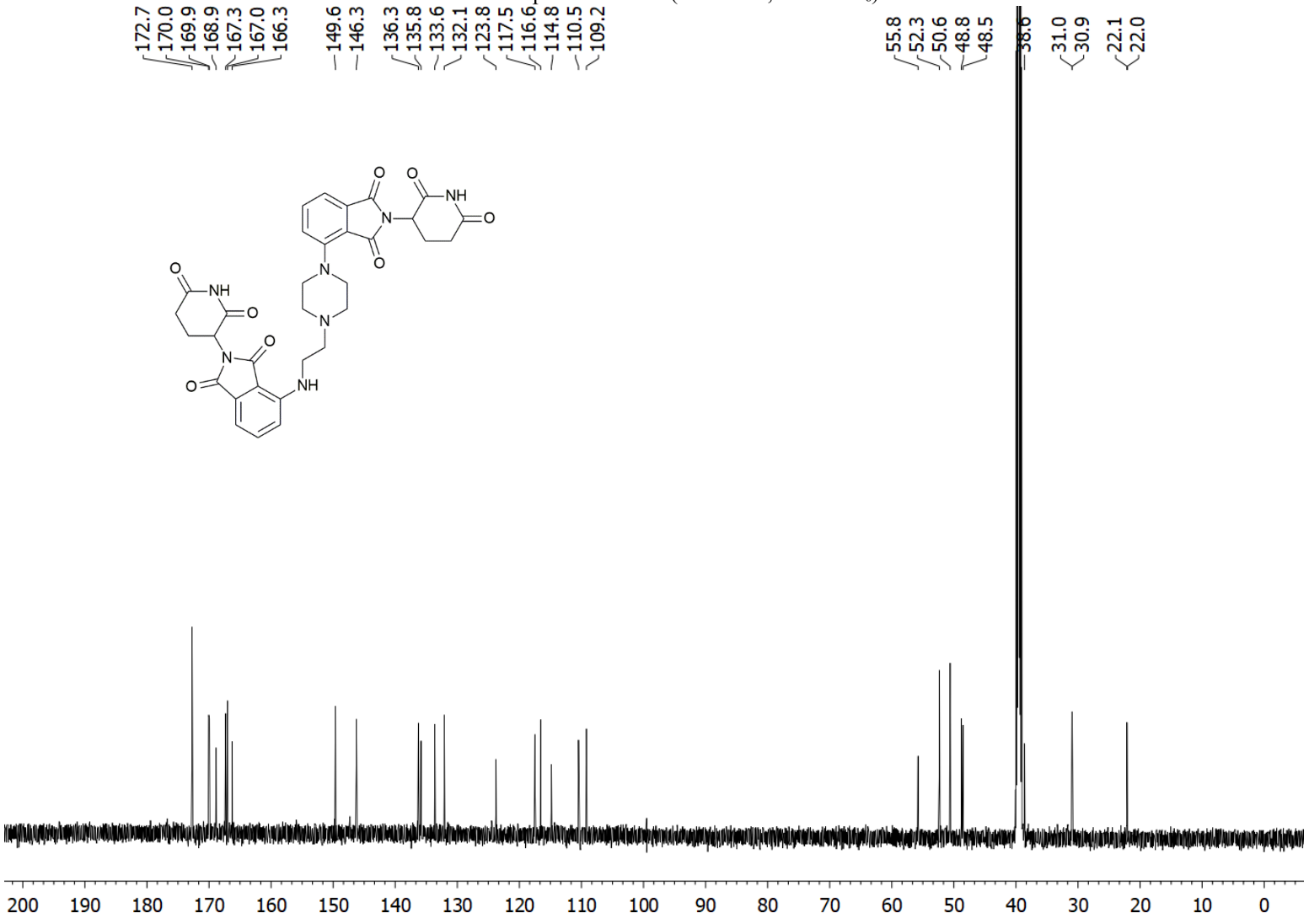
^{13}C NMR spectrum of **8a** (151 MHz, DMSO-d_6)



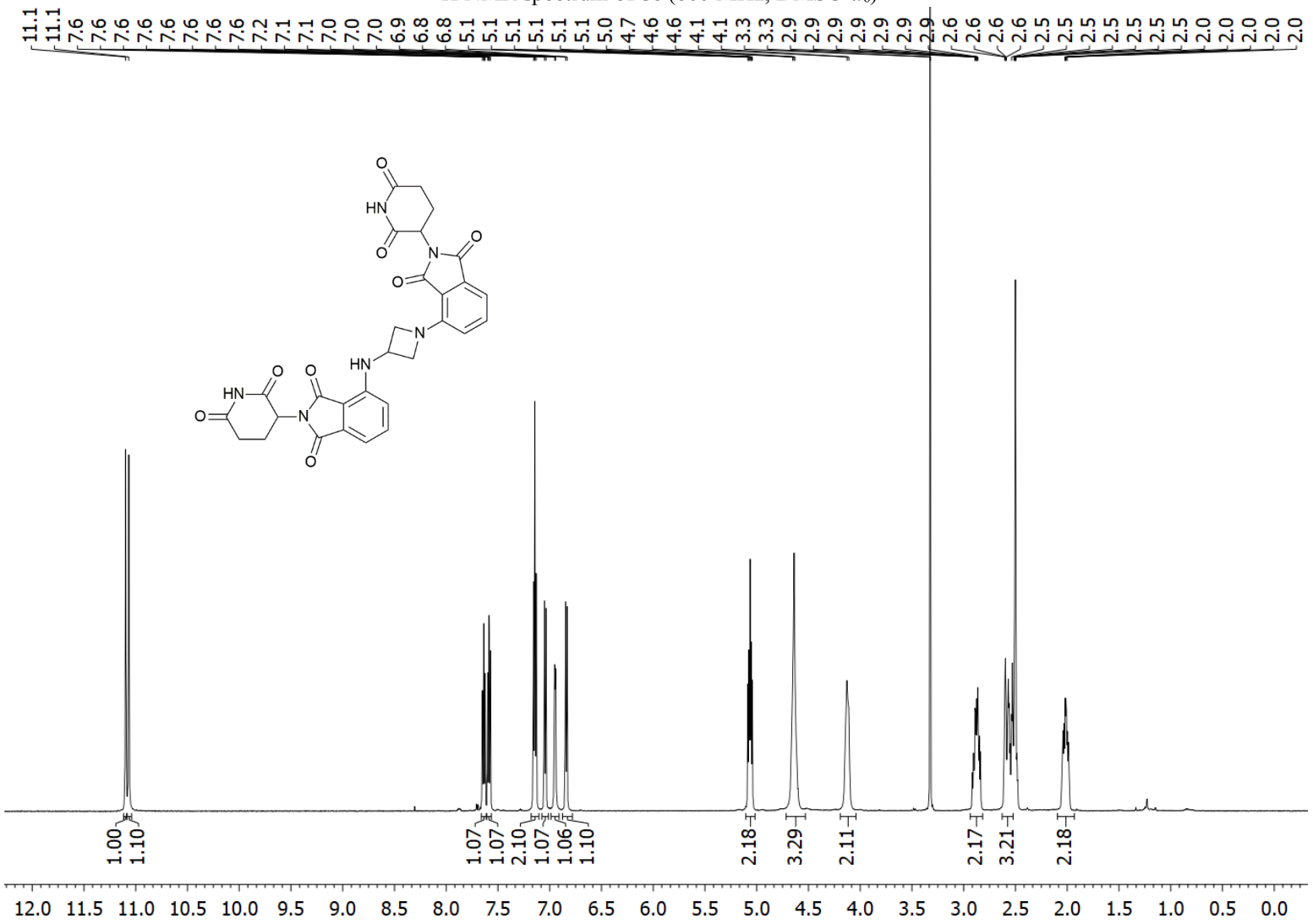
^{1}H NMR spectrum of **8b** (600 MHz, DMSO-d_6)



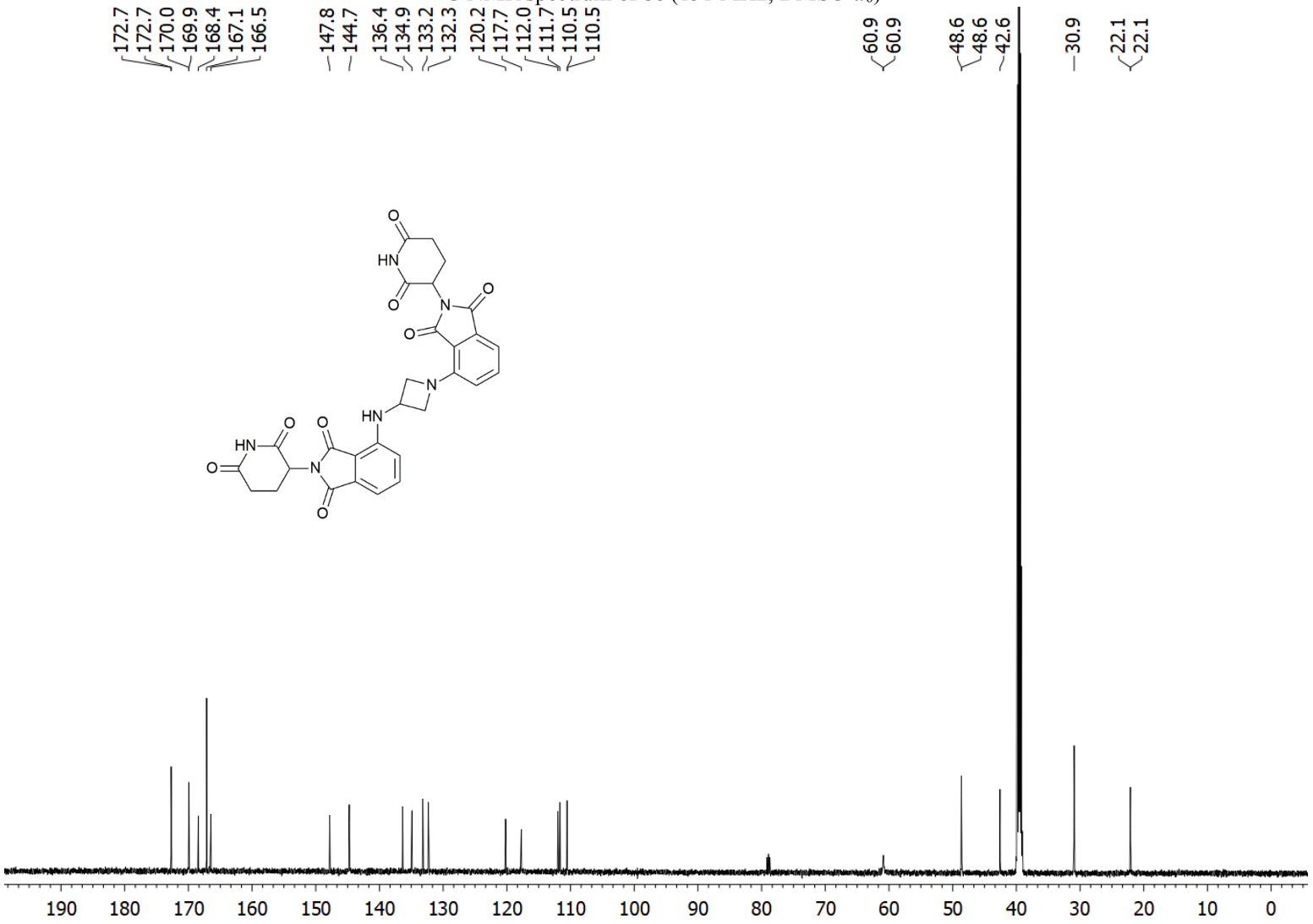
^{13}C NMR spectrum of **8b** (151 MHz, DMSO-d_6)



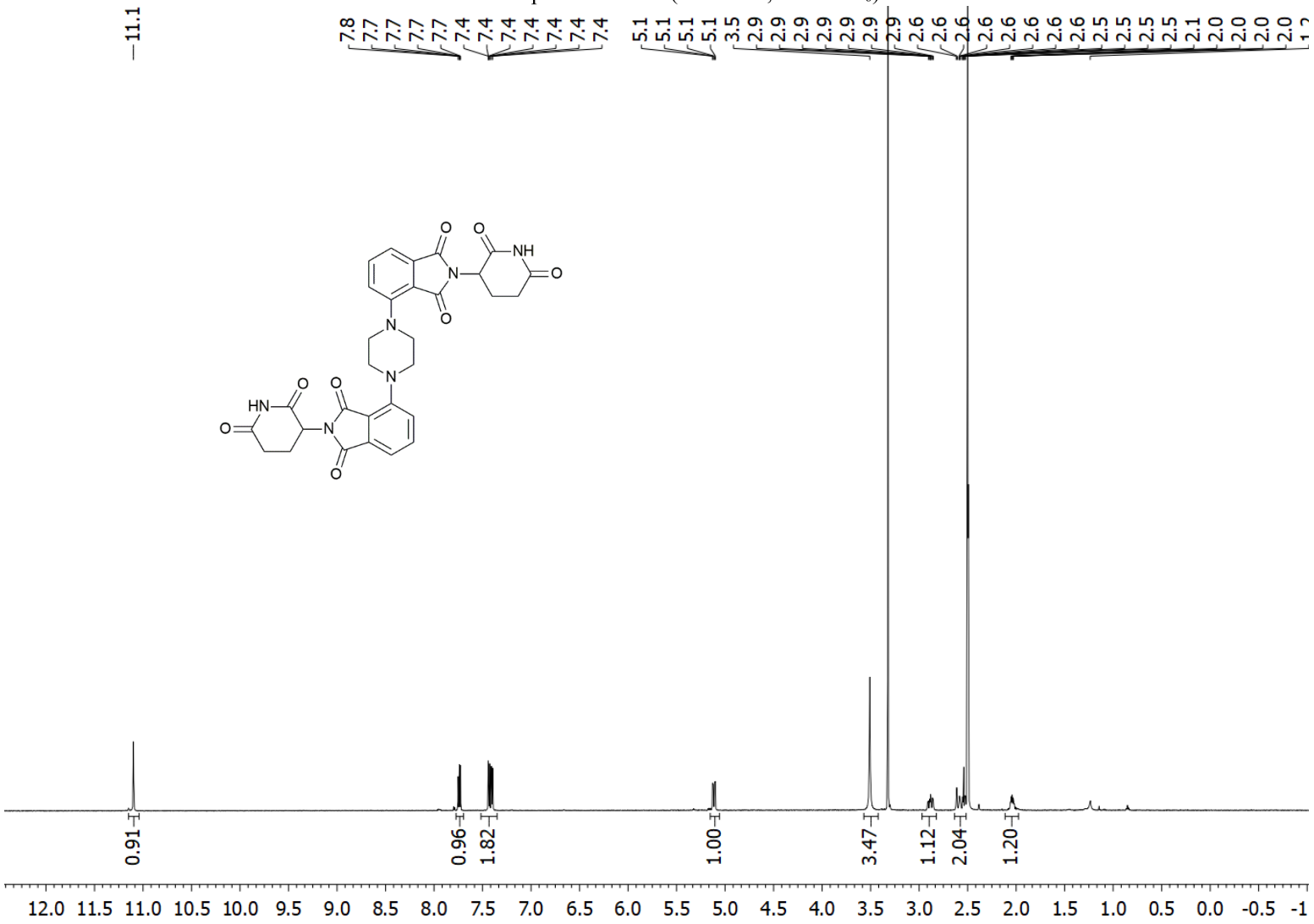
^{1}H NMR spectrum of **8c** (600 MHz, DMSO-d_6)



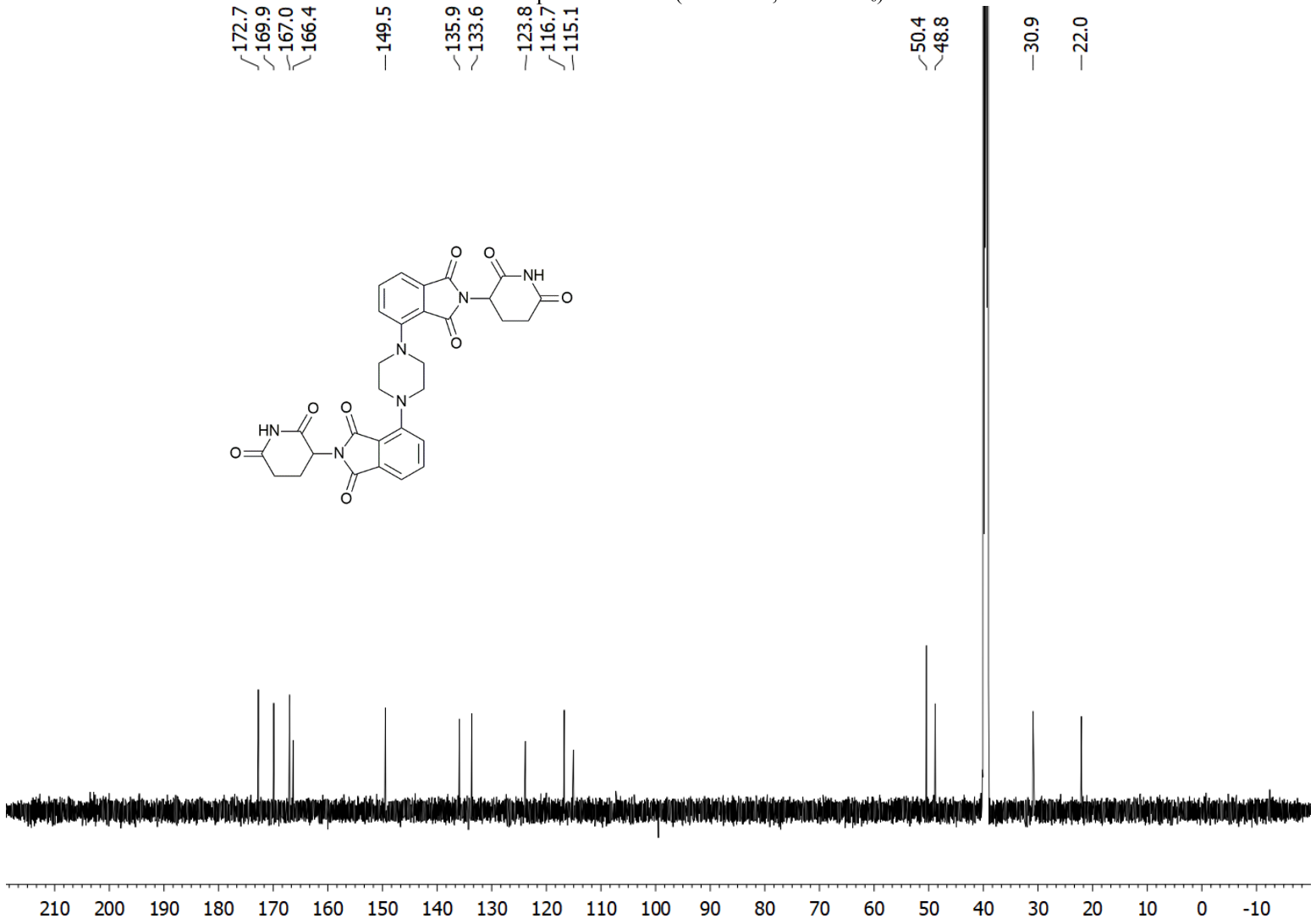
^{13}C NMR spectrum of **8c** (151 MHz, DMSO-d_6)



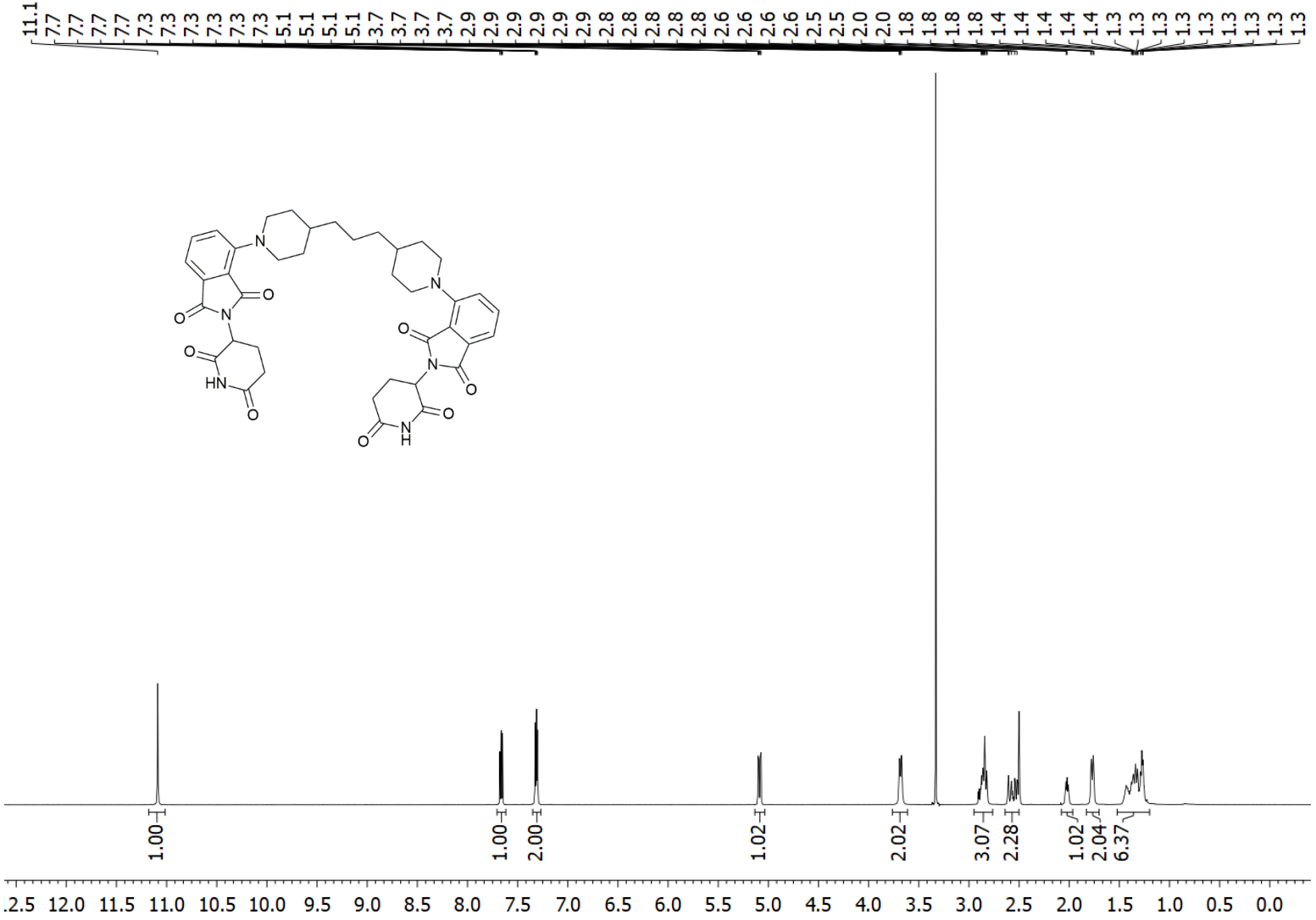
^{1}H NMR spectrum of **8d** (600 MHz, DMSO-d_6)



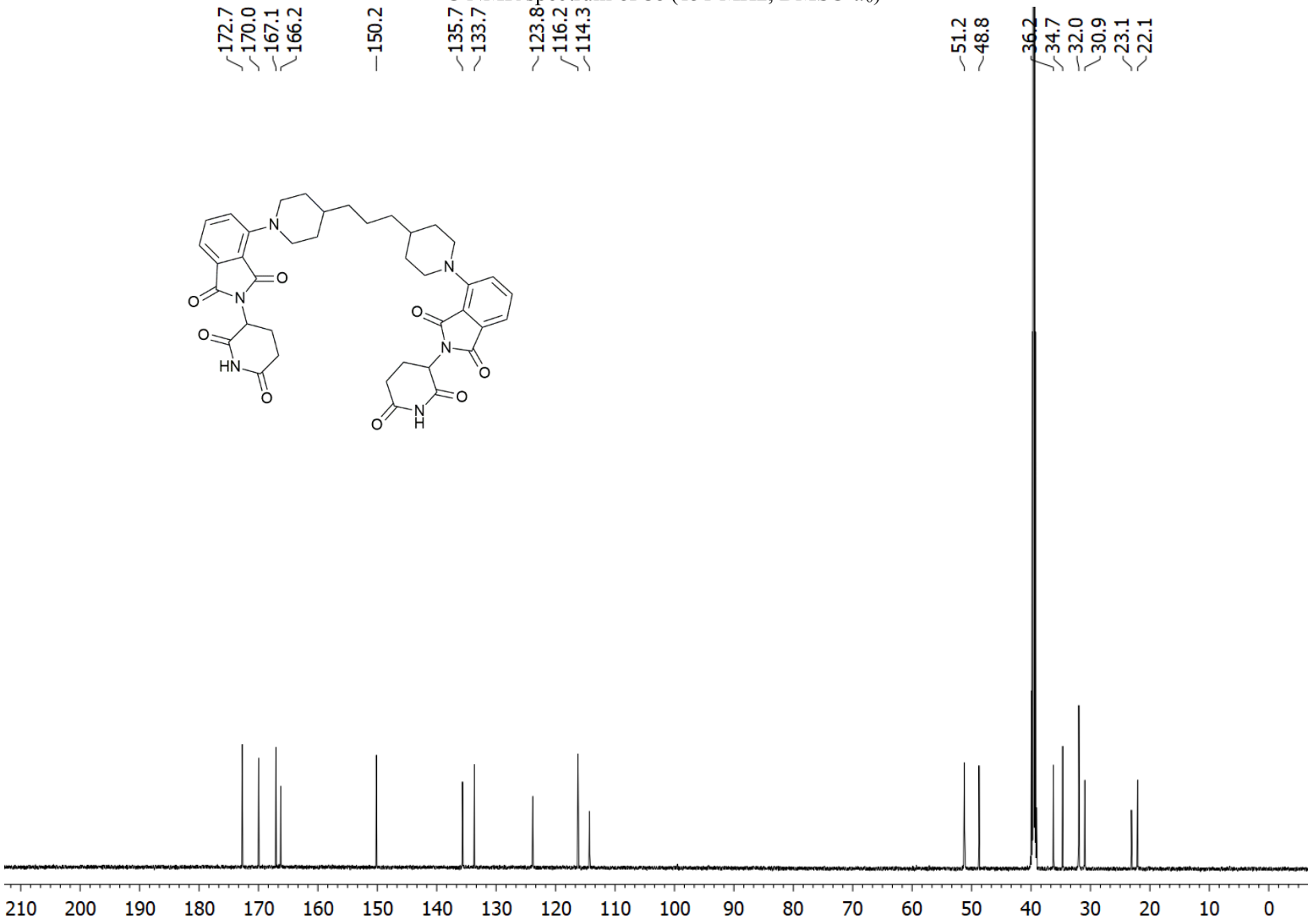
^{13}C NMR spectrum of **8d** (151 MHz, DMSO-d_6)



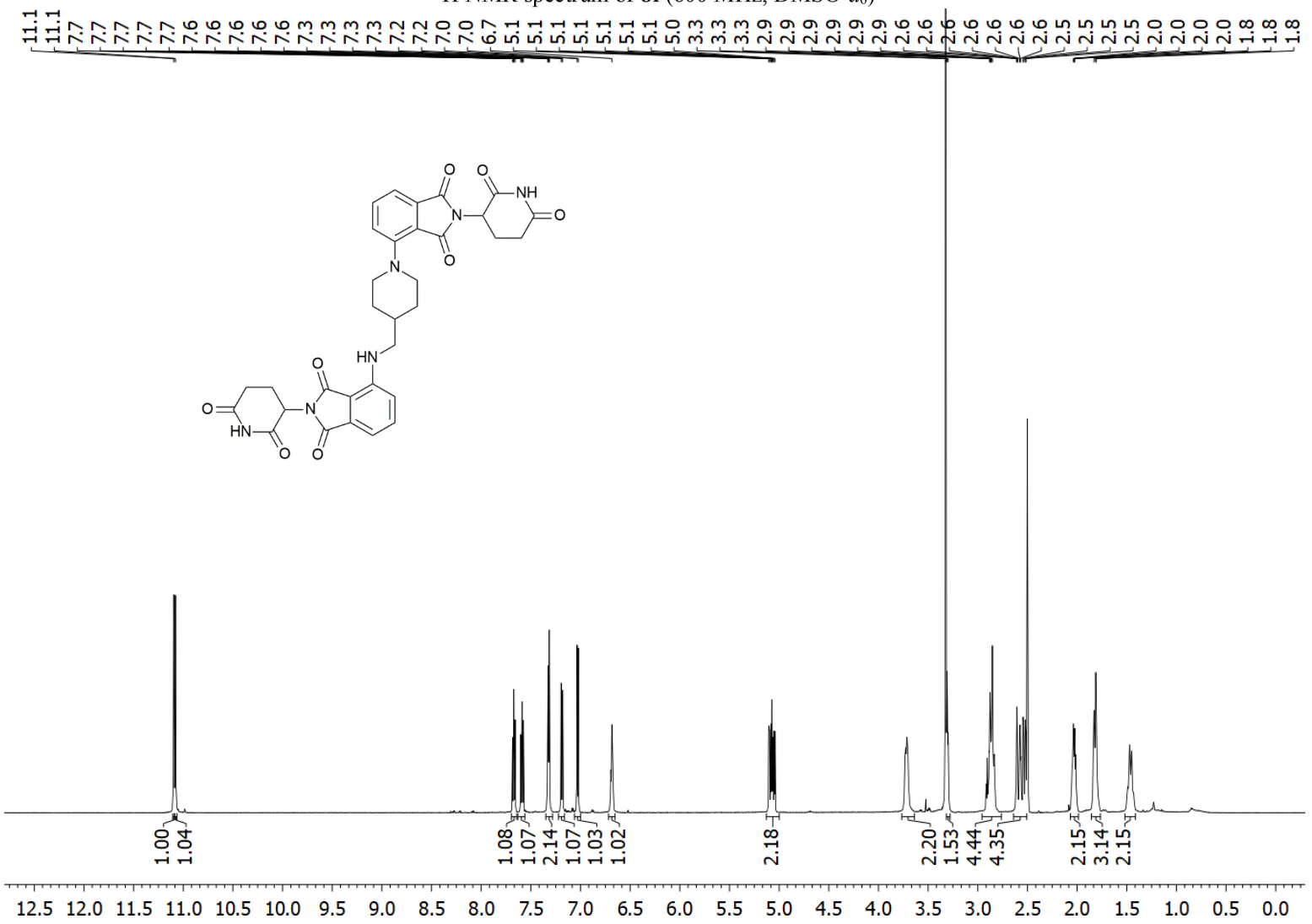
^{1}H NMR spectrum of **8e** (600 MHz, DMSO-d_6)



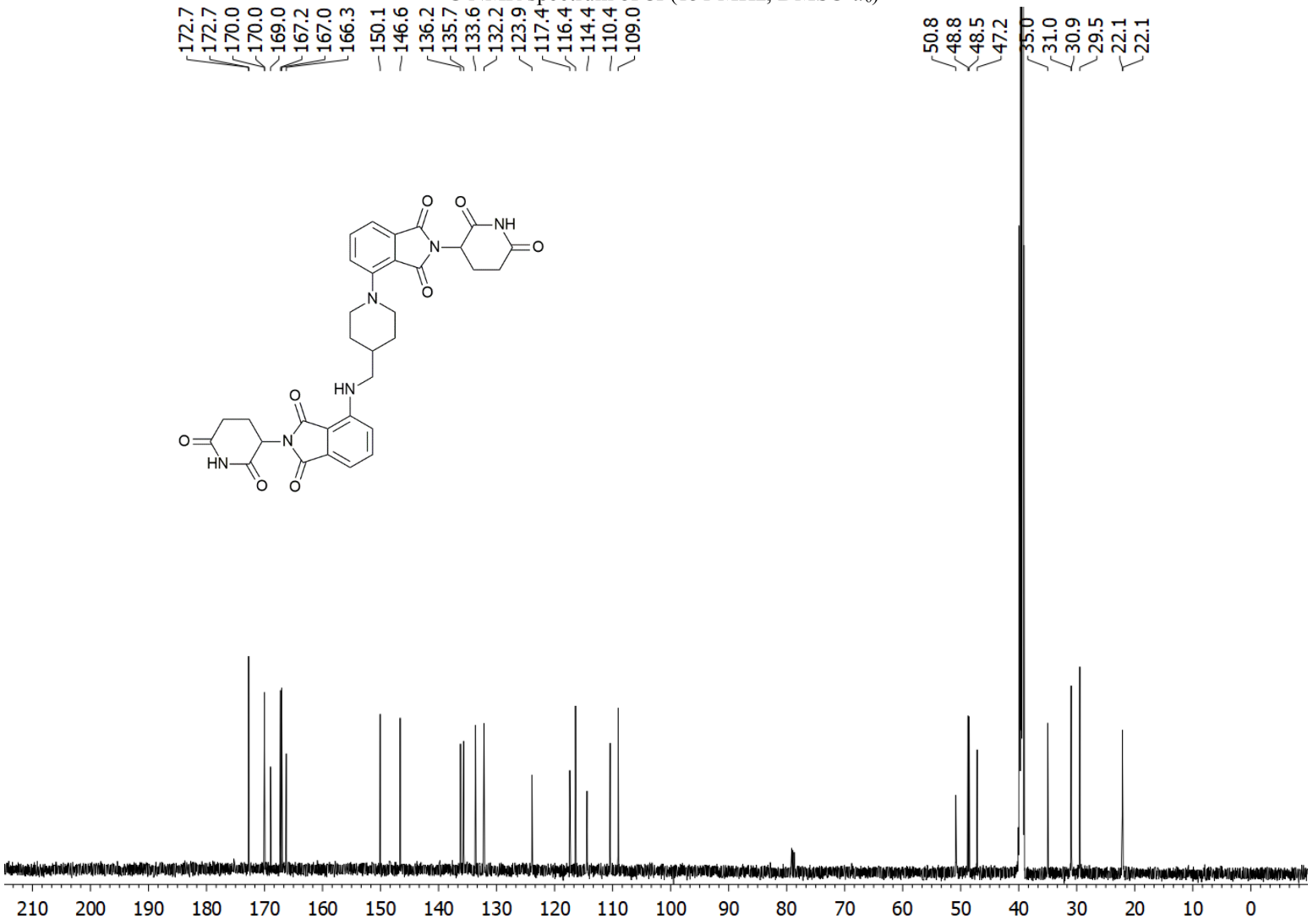
^{13}C NMR spectrum of **8e** (151 MHz, DMSO-d_6)



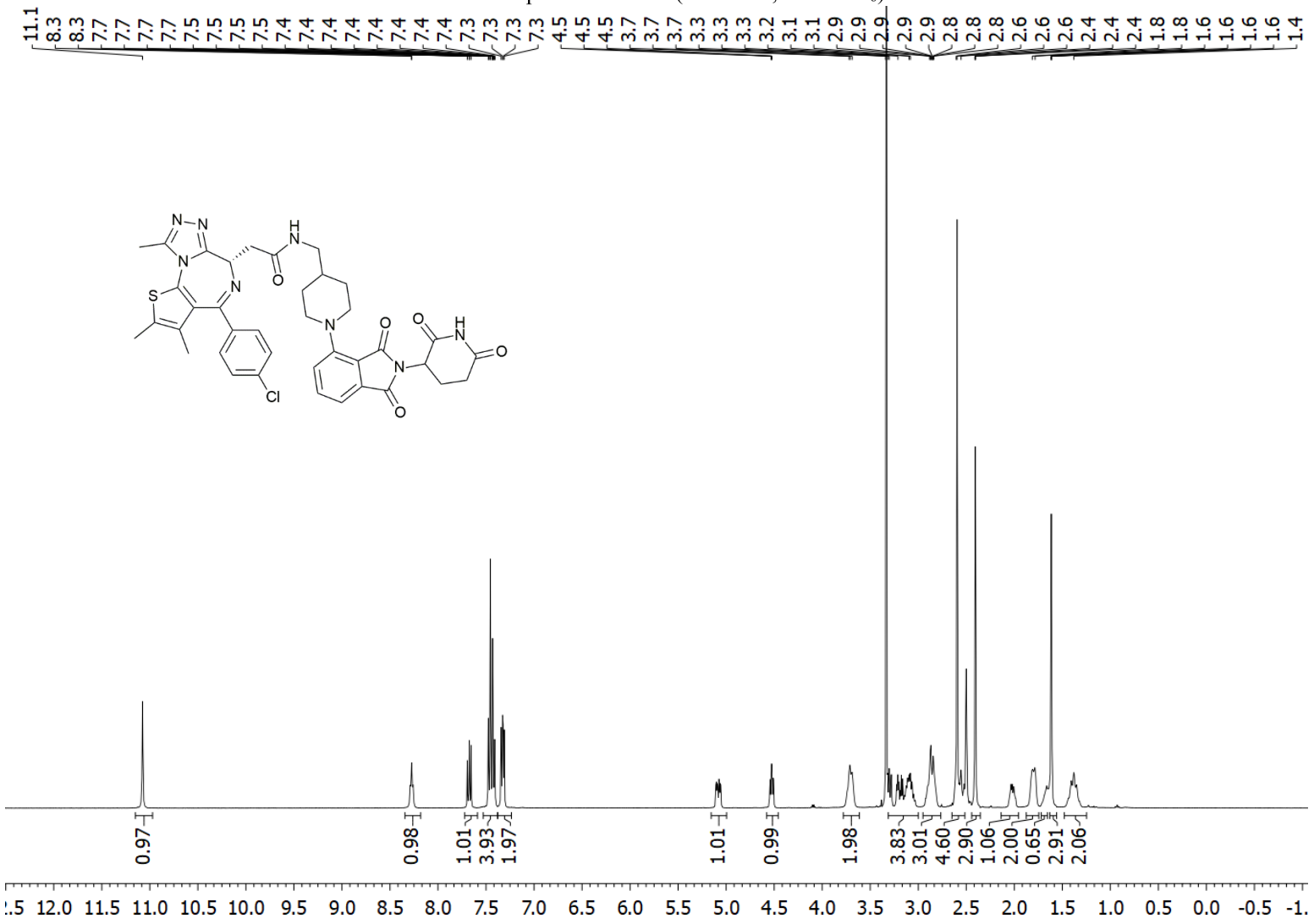
^{1}H NMR spectrum of **8f** (600 MHz, DMSO-d_6)



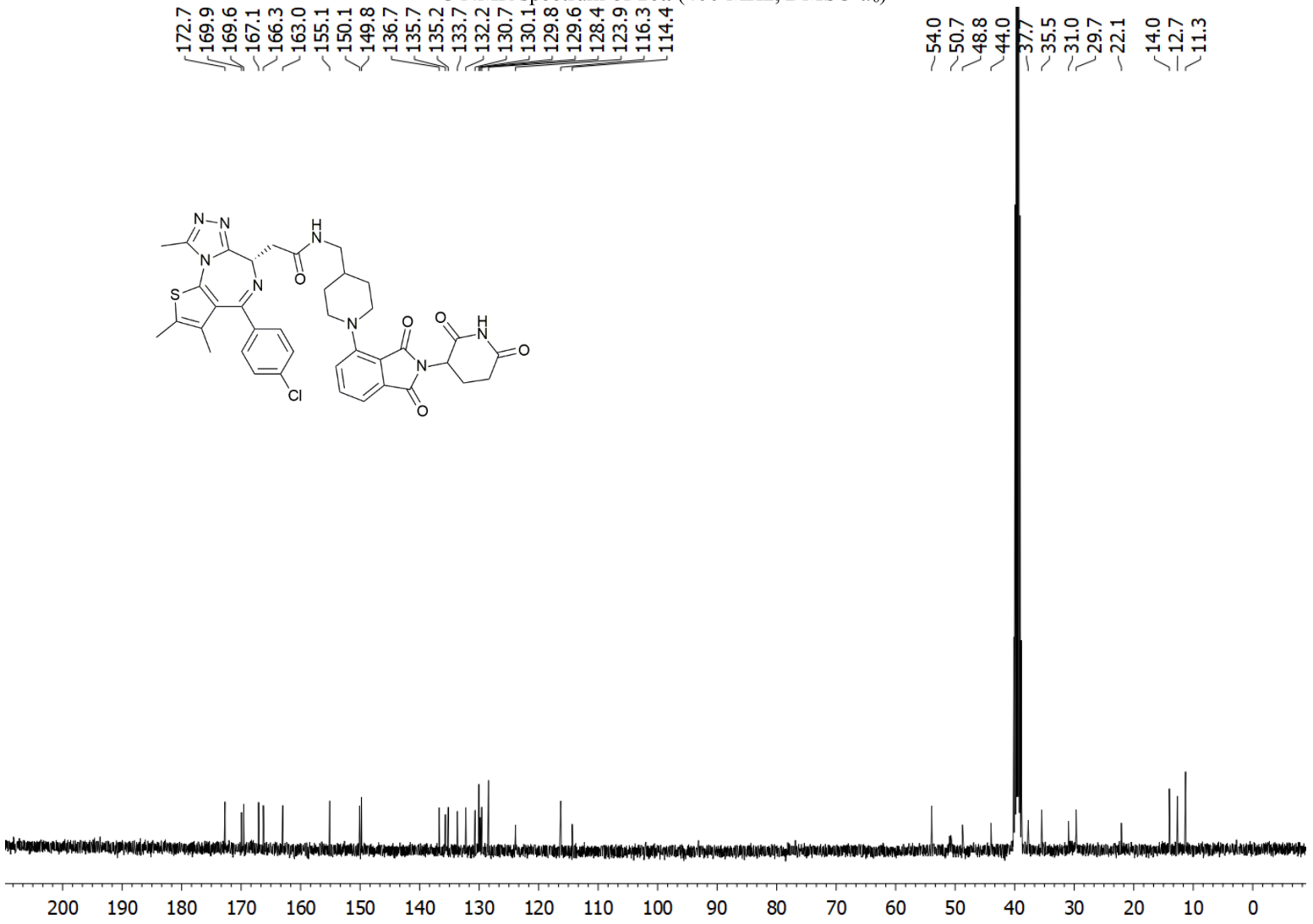
^{13}C NMR spectrum of **8f** (151 MHz, DMSO-d_6)



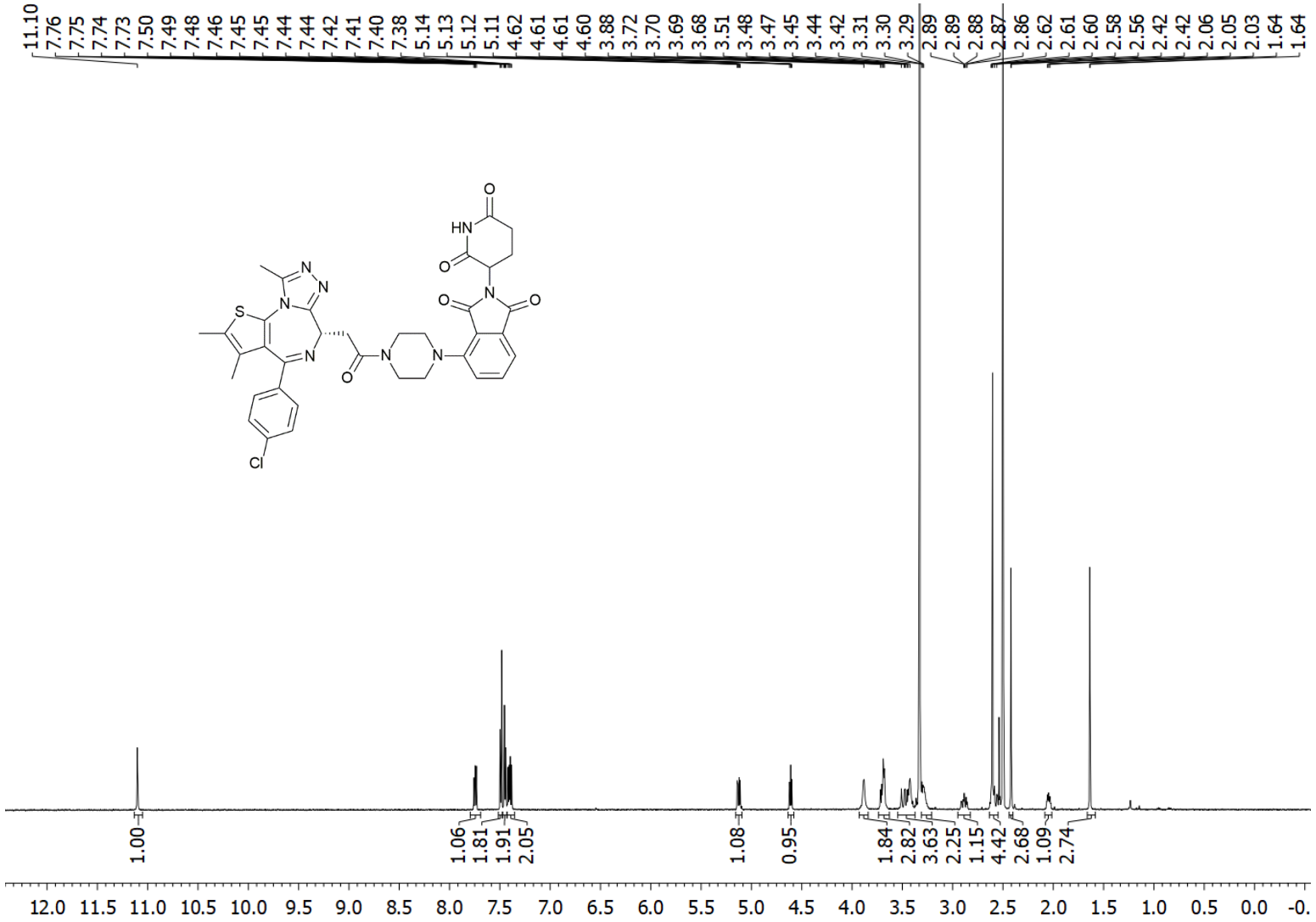
^{1}H NMR spectrum of **10a** (400 MHz, DMSO-d_6)



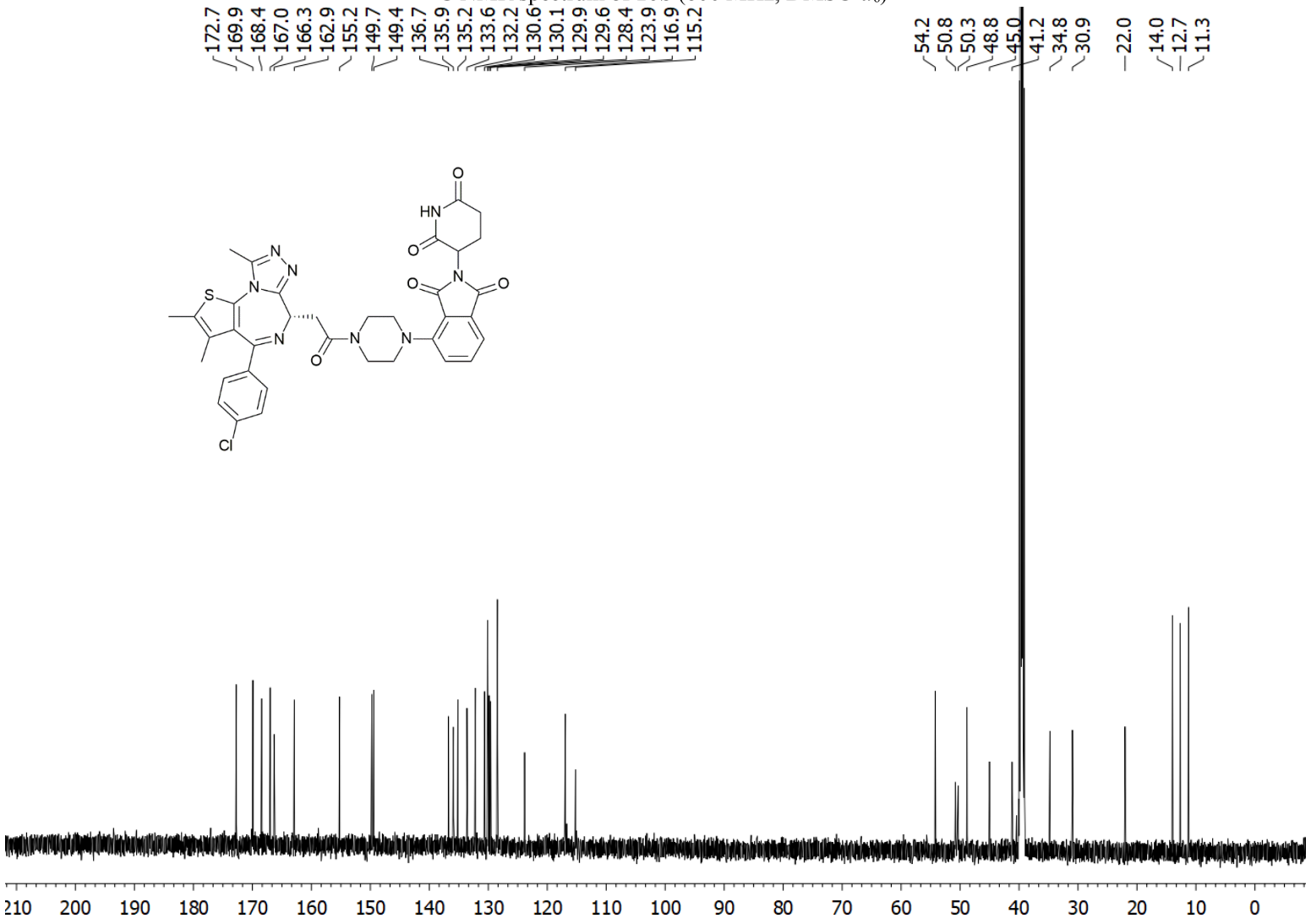
^{13}C NMR spectrum of **10a** (400 MHz, DMSO-d_6)



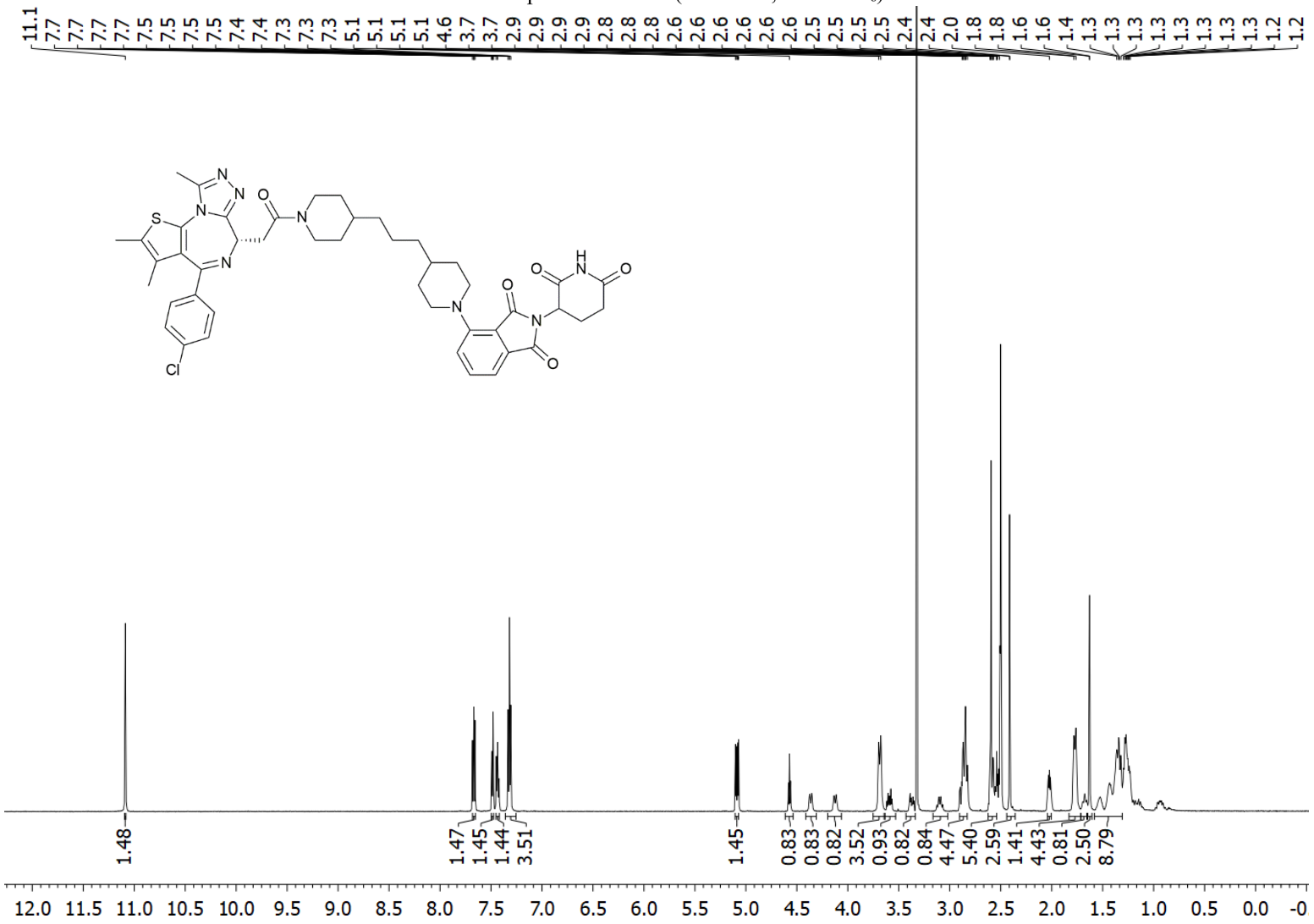
^{1}H NMR spectrum of **10b** (600 MHz, DMSO-d_6)



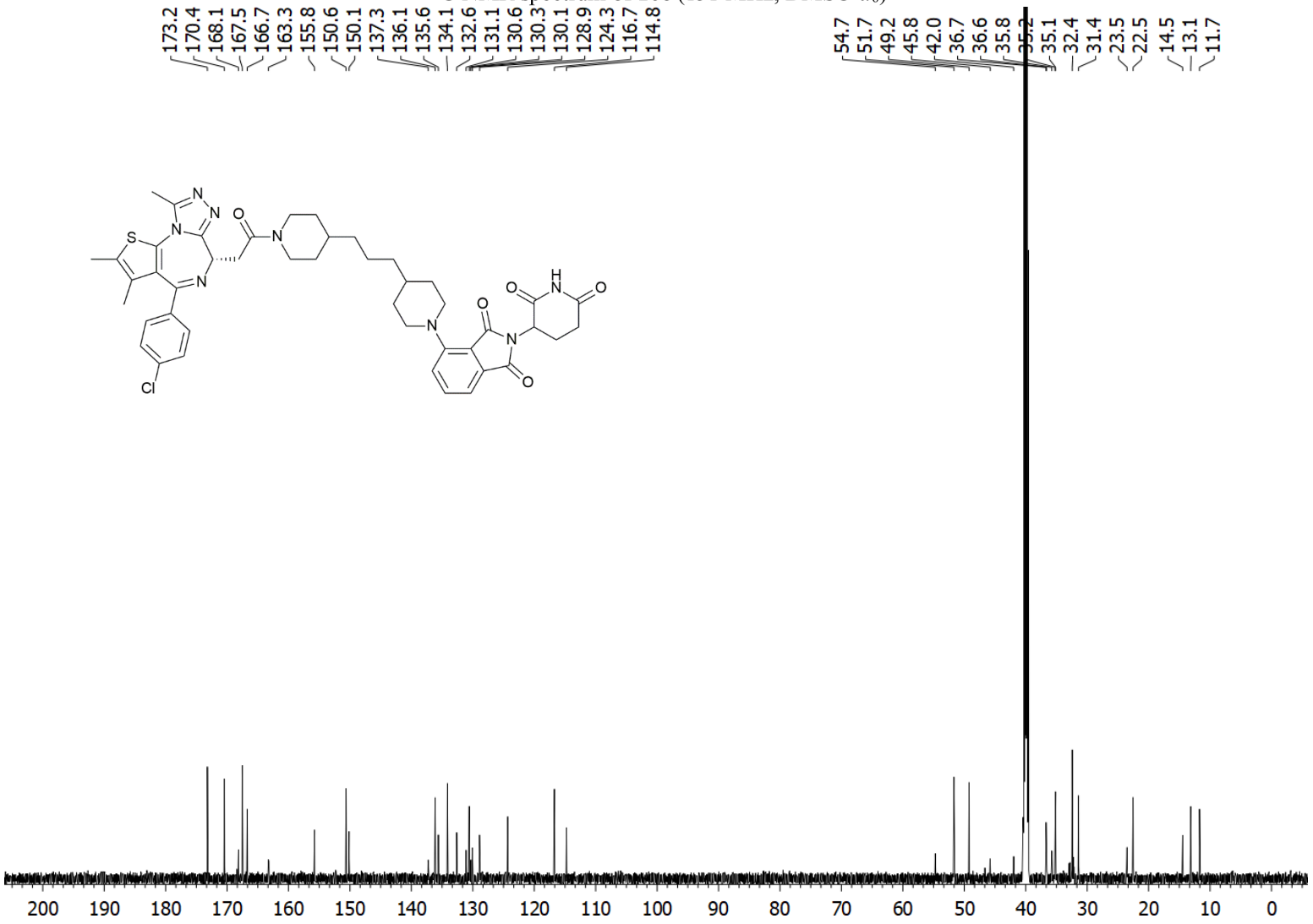
^{13}C NMR spectrum of **10b** (600 MHz, DMSO-d_6)



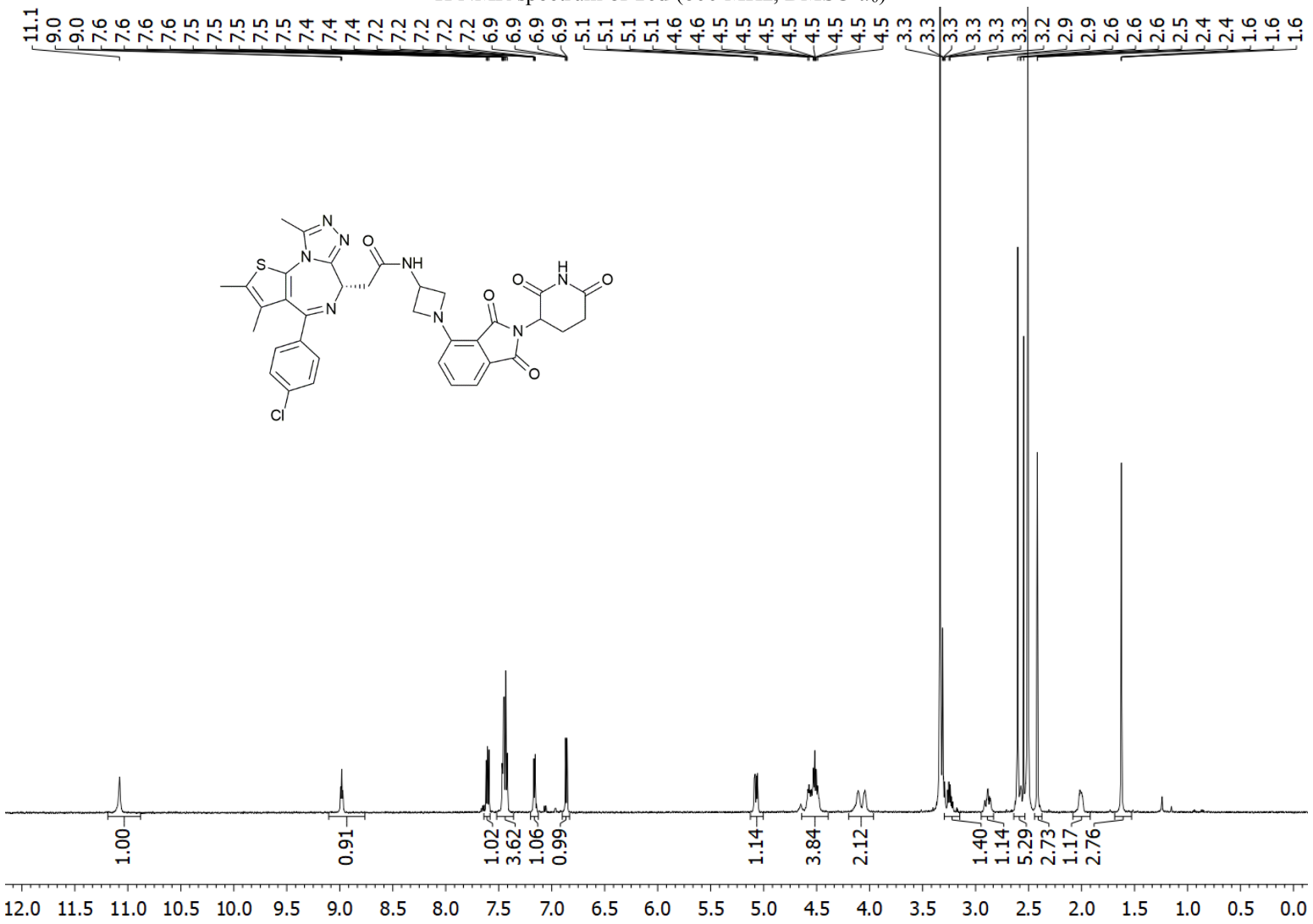
^{1}H NMR spectrum of **10c** (600 MHz, DMSO-d_6)



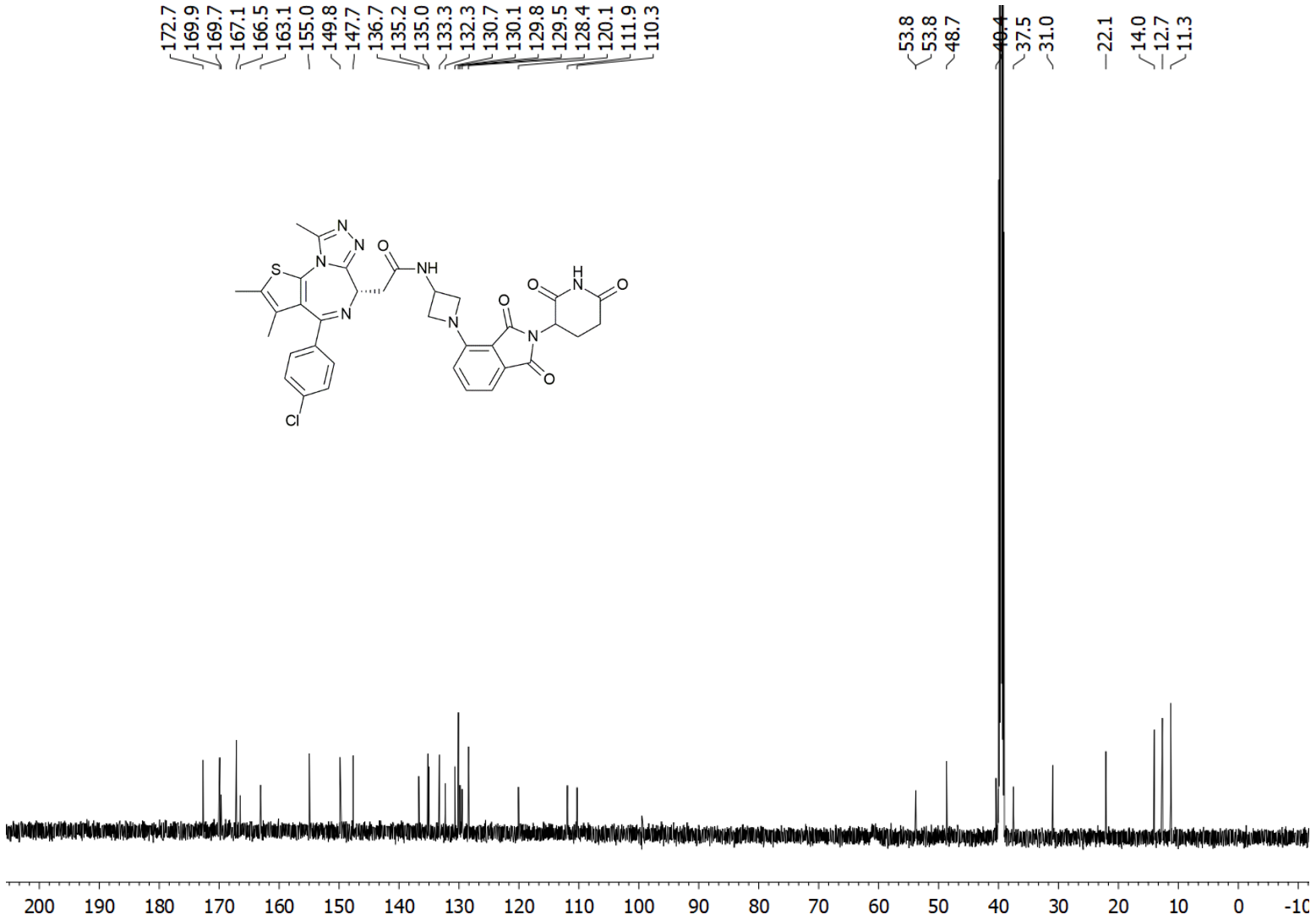
^{13}C NMR spectrum of **10c** (151 MHz, DMSO-d_6)



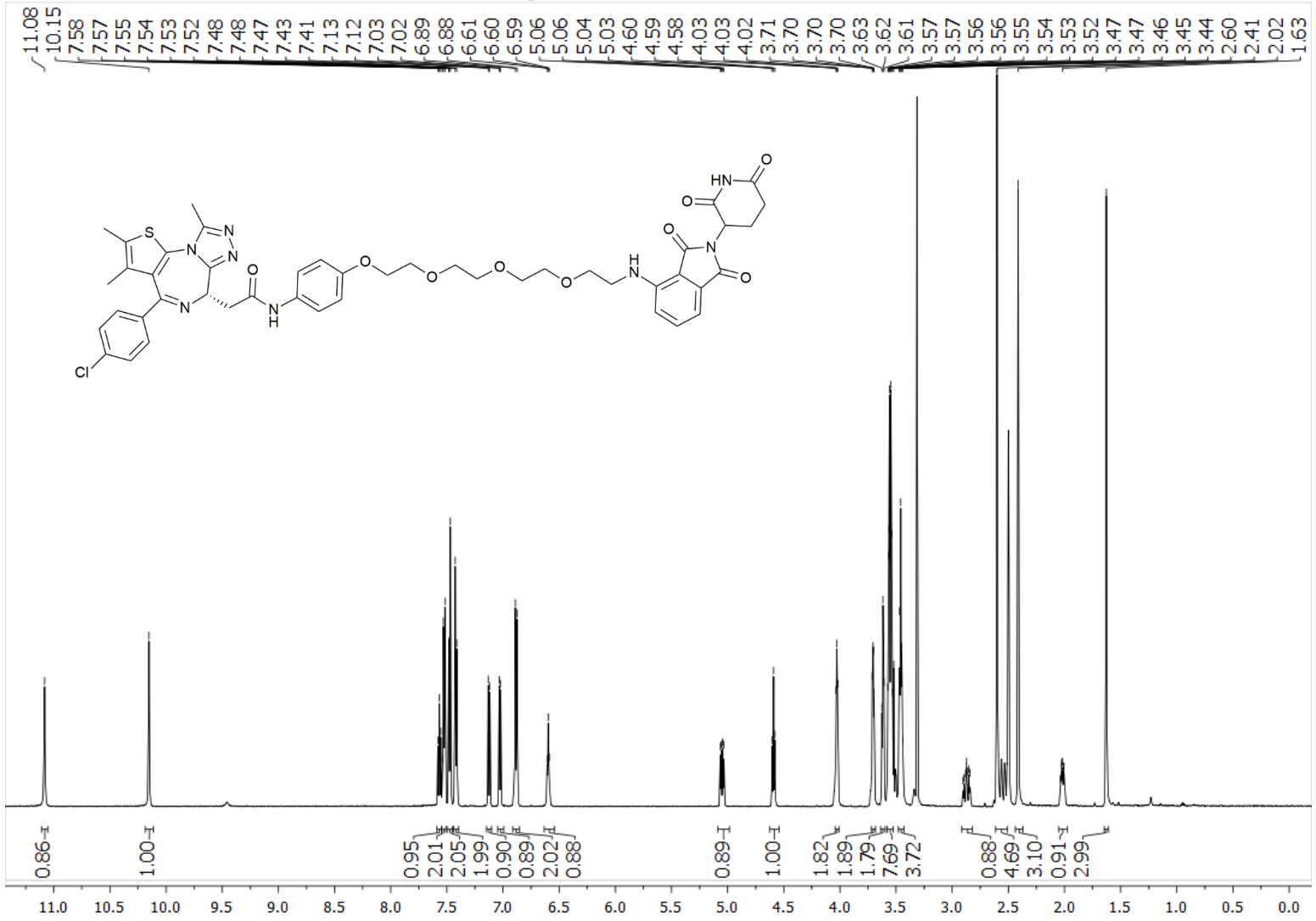
^{1}H NMR spectrum of **10d** (600 MHz, DMSO-d_6)



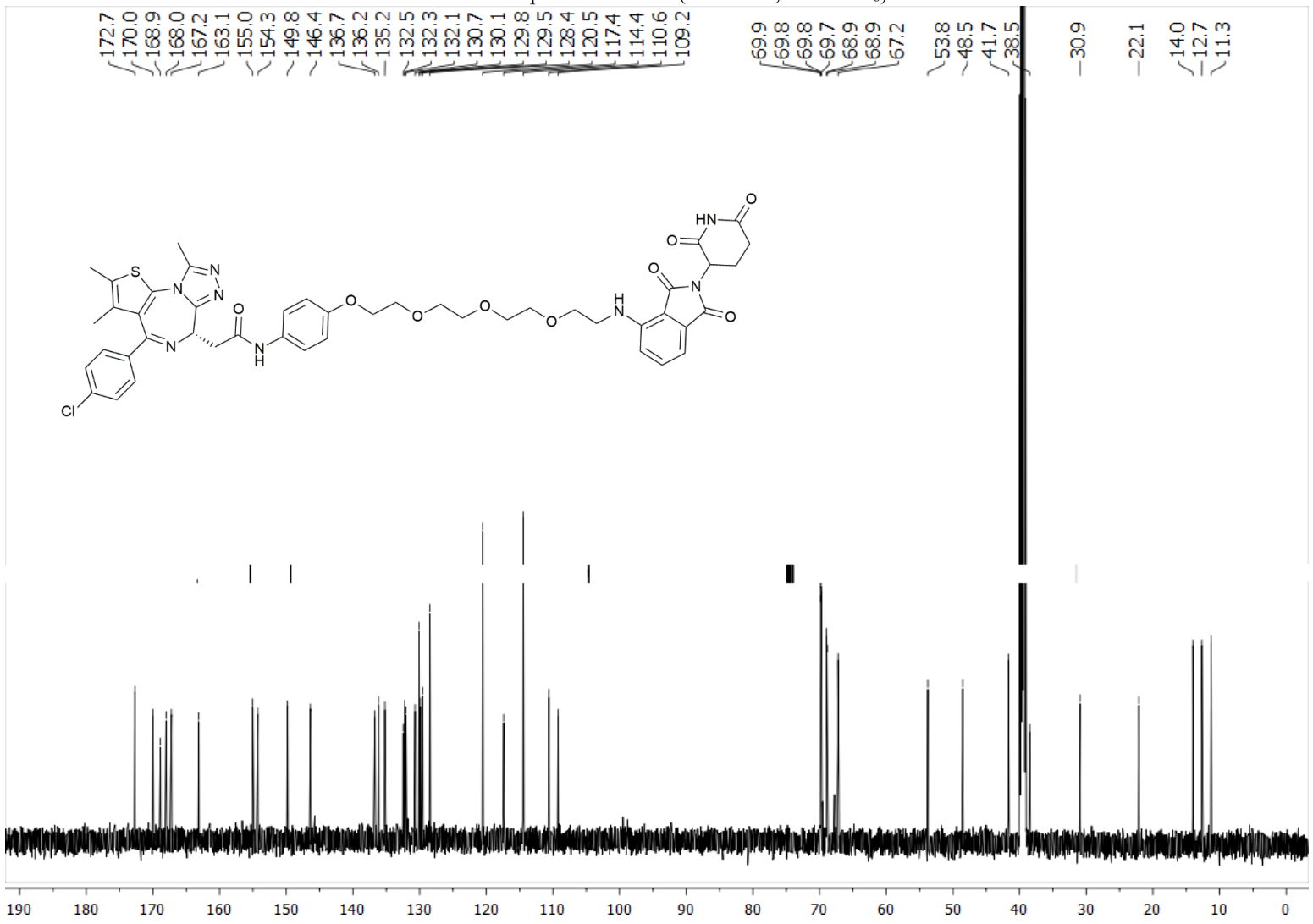
^{13}C NMR spectrum of **10d** (600 MHz, DMSO-d_6)



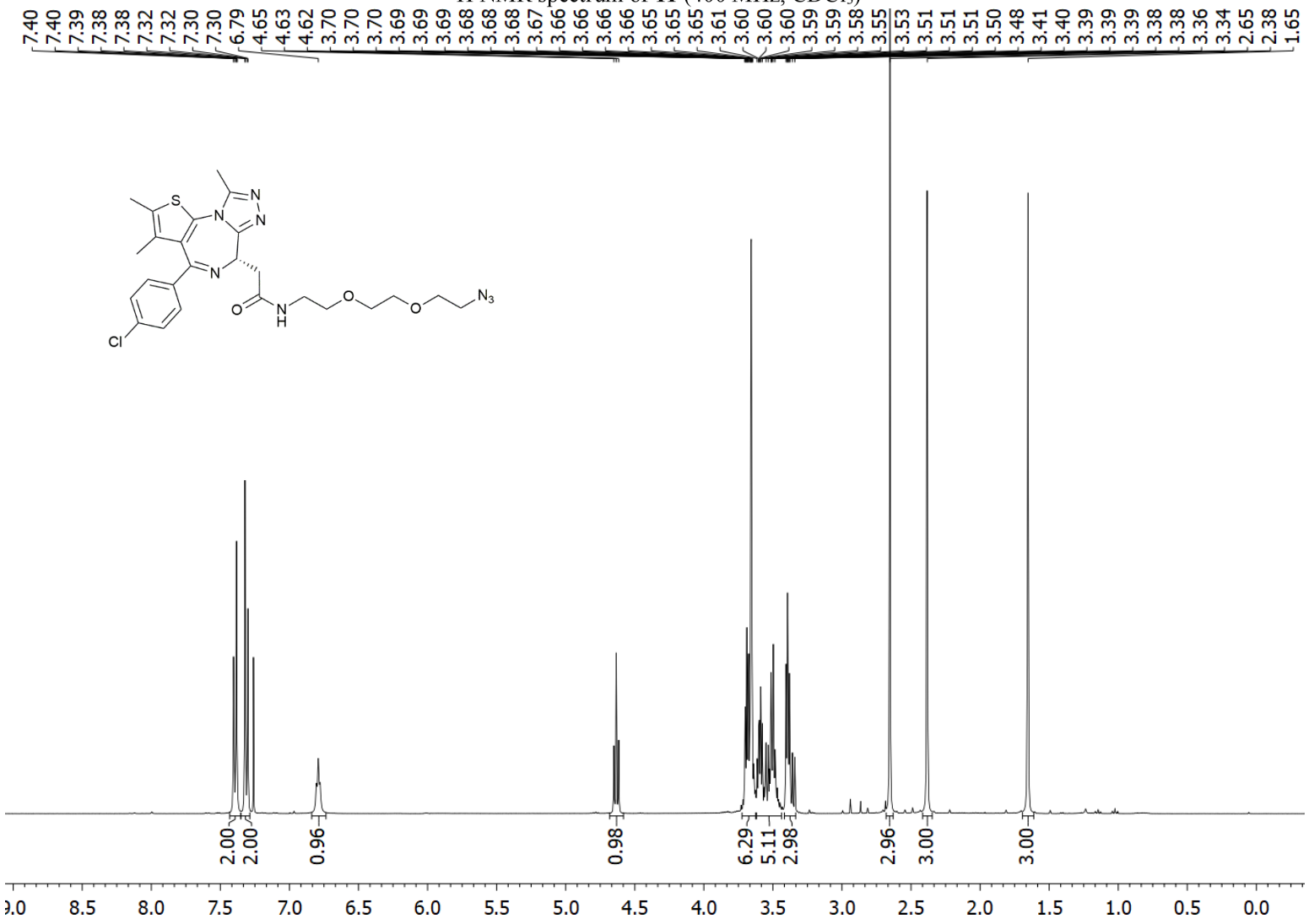
^{1}H NMR spectrum of **10e** (600 MHz, DMSO-d_6)



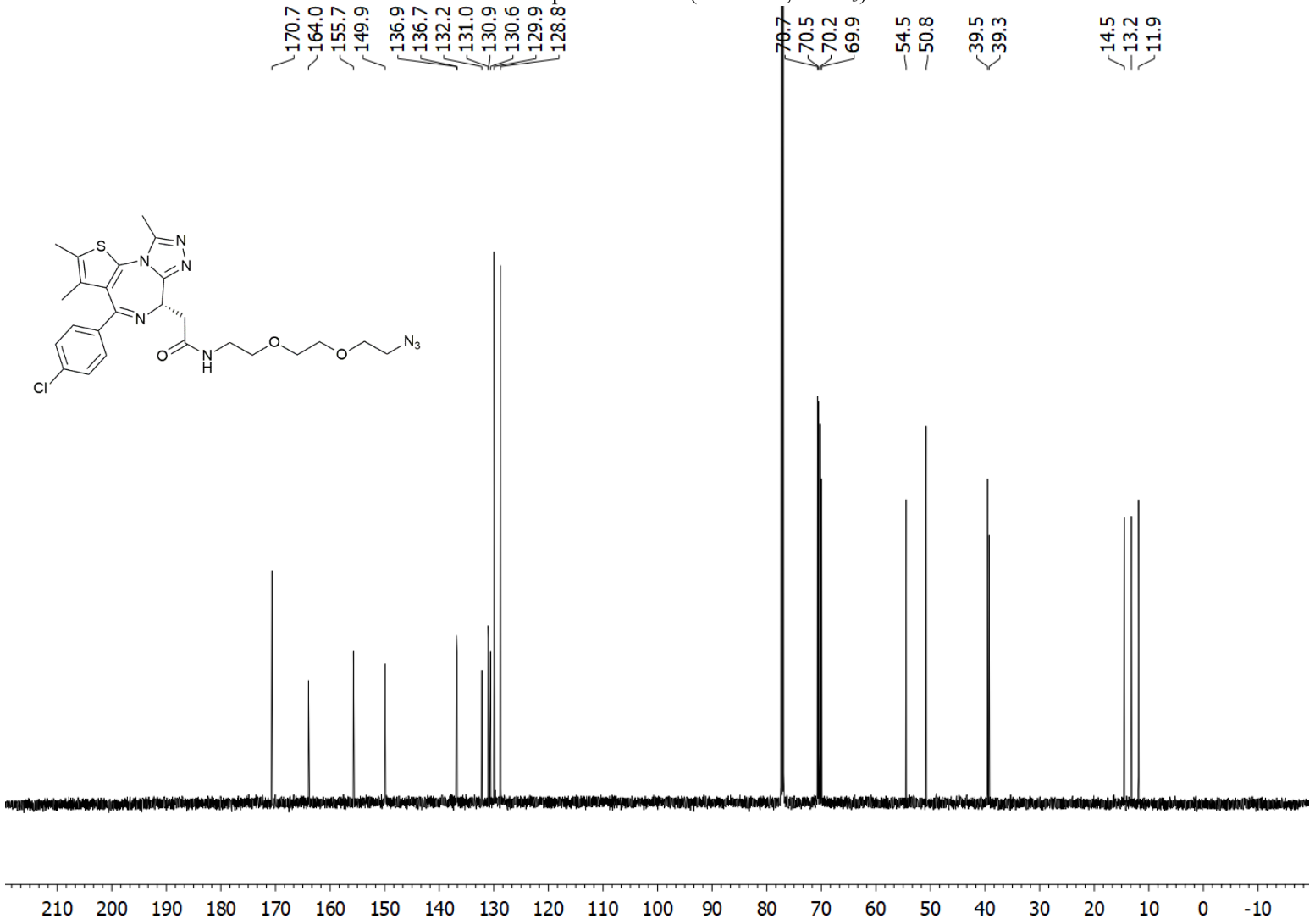
^{12}C NMR spectrum of **10e** (151 MHz, DMSO-d_6)



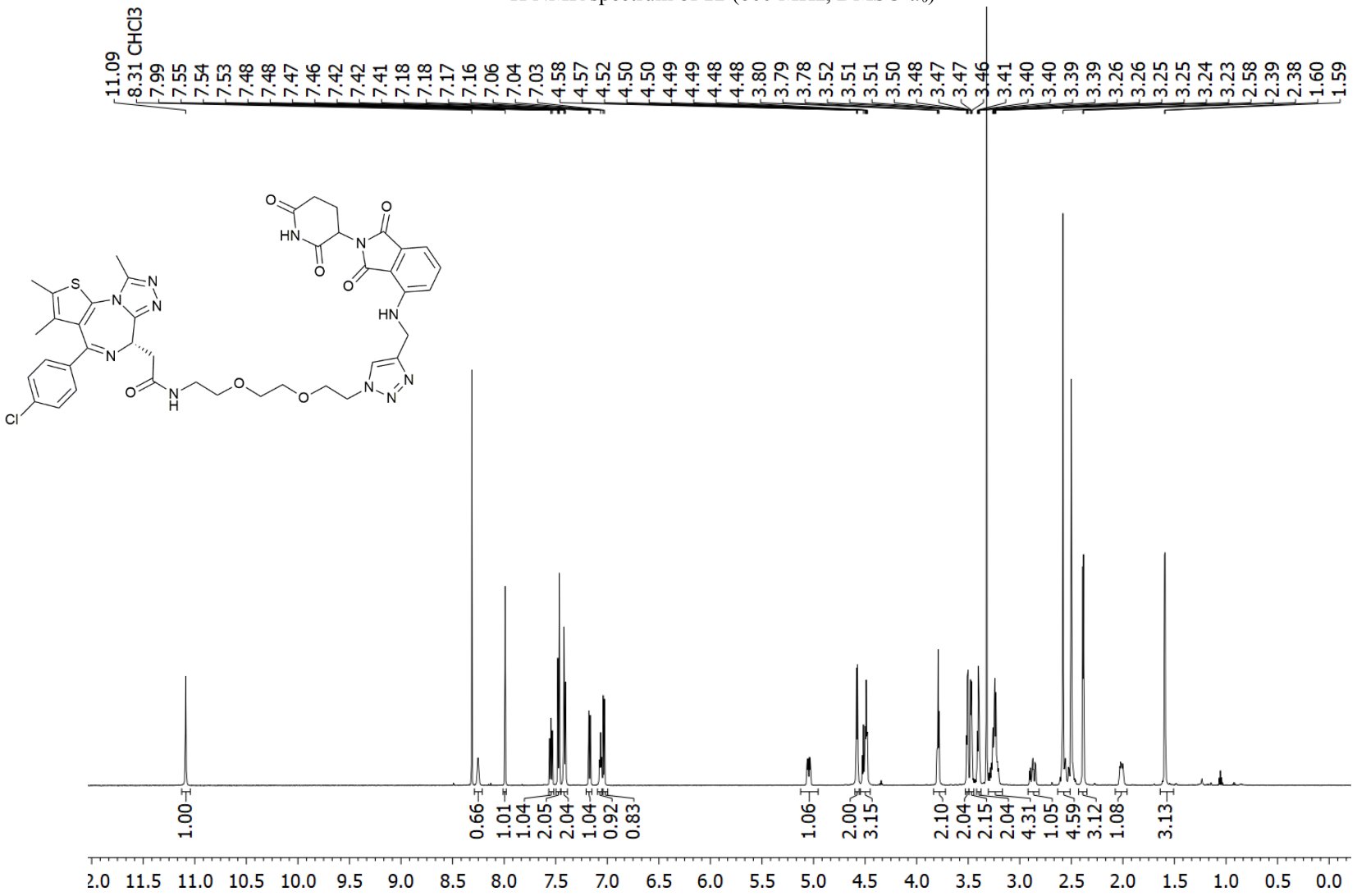
^{1}H NMR spectrum of **11** (400 MHz, $CDCl_3$)



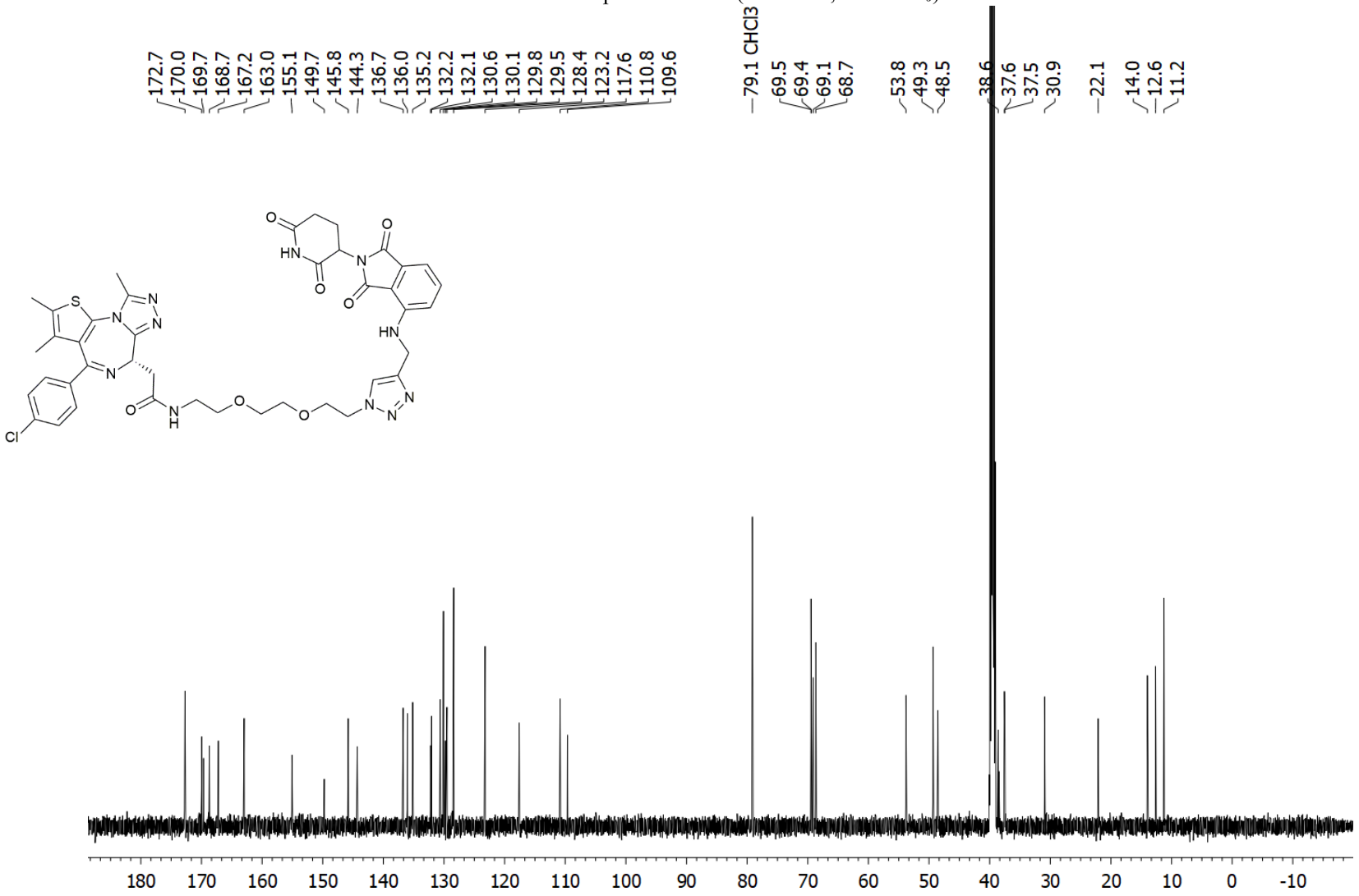
^{13}C NMR spectrum of **11** (100 MHz, $CDCl_3$)



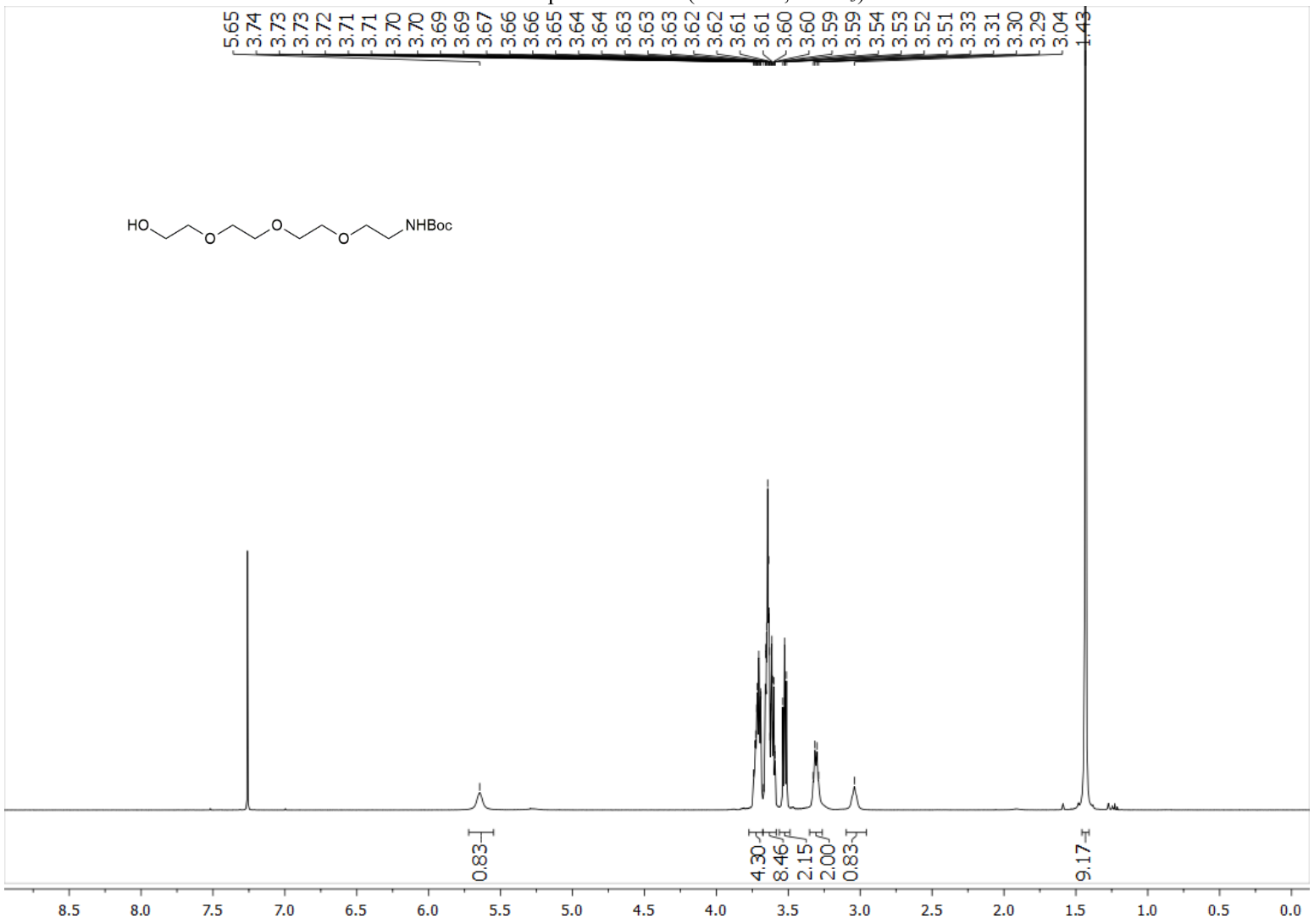
^{1}H NMR spectrum of **12** (600 MHz, DMSO-d_6)



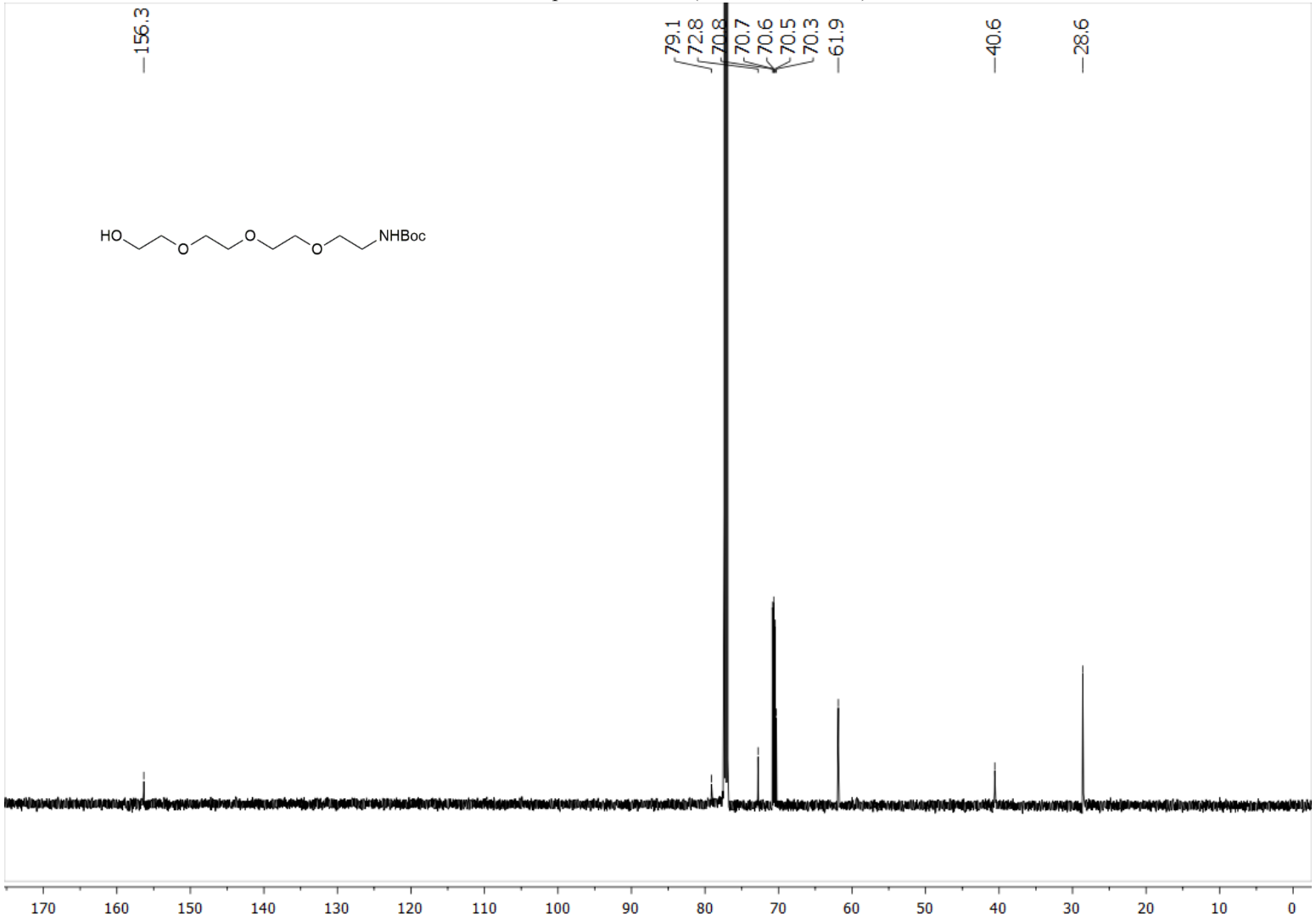
^{13}C NMR spectrum of **12** (151 MHz, DMSO-d_6)



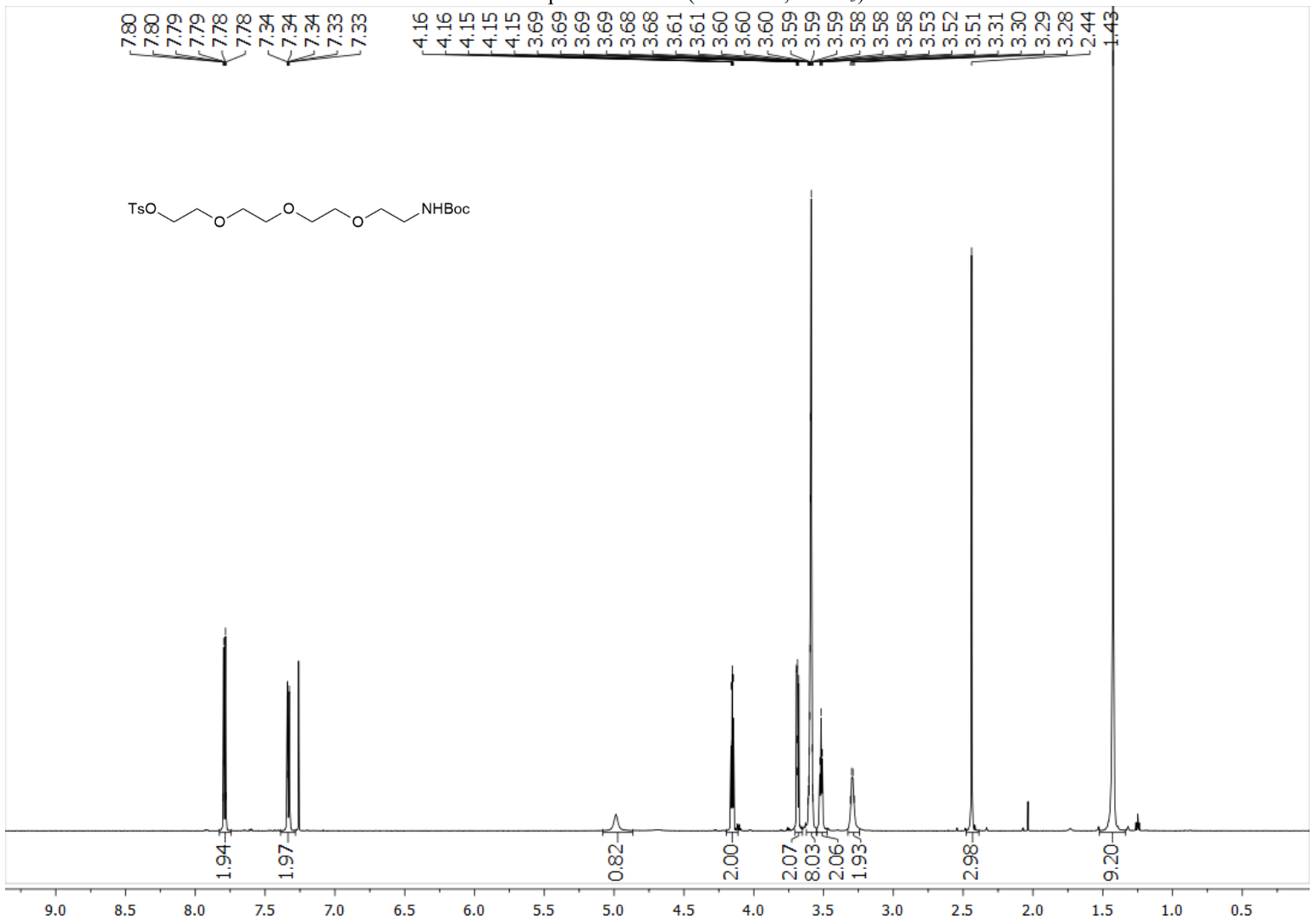
^{1}H NMR spectrum of **S1** (400 MHz, $CDCl_3$)



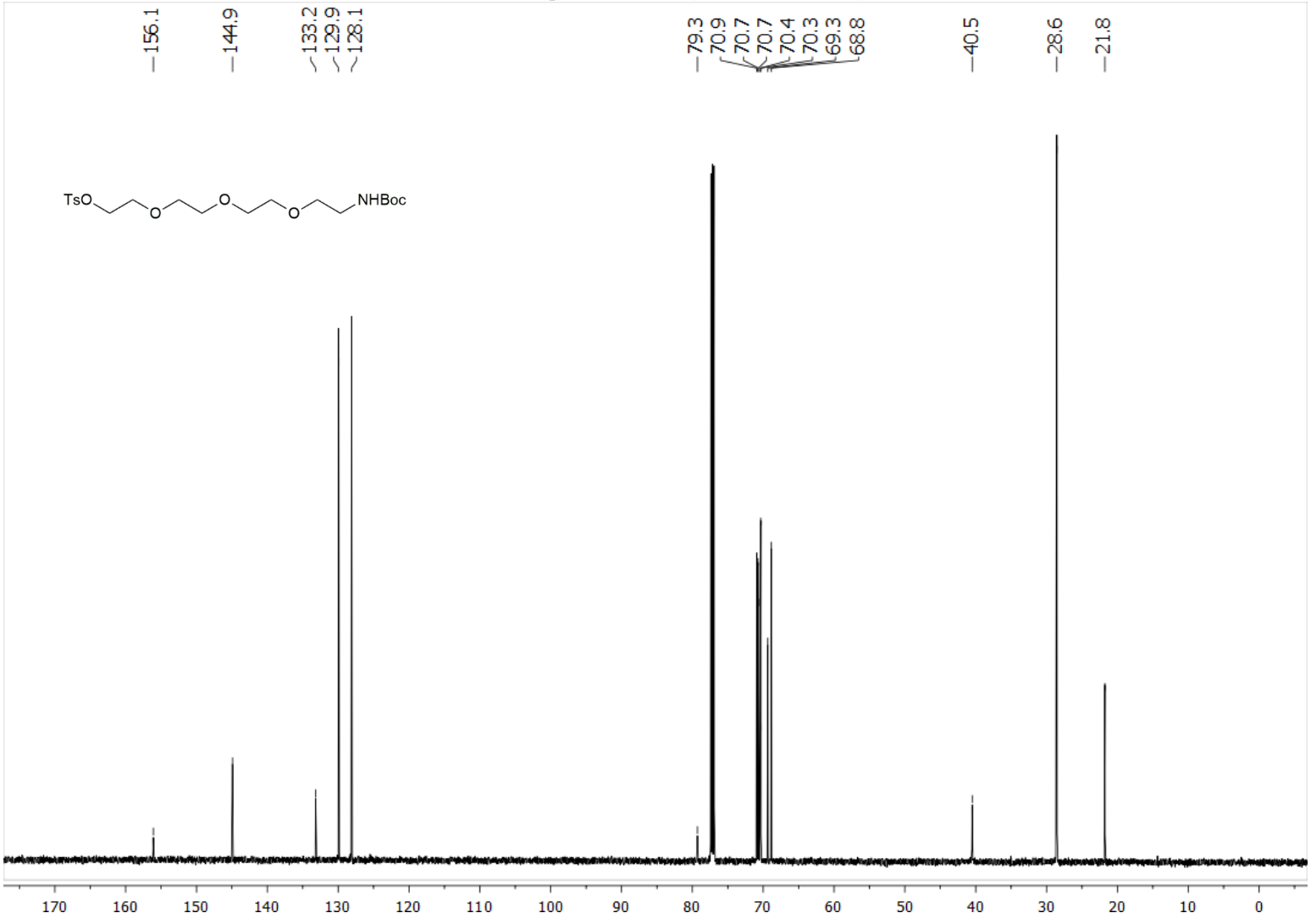
^{13}C NMR spectrum of **S1** (151 MHz, $CDCl_3$)



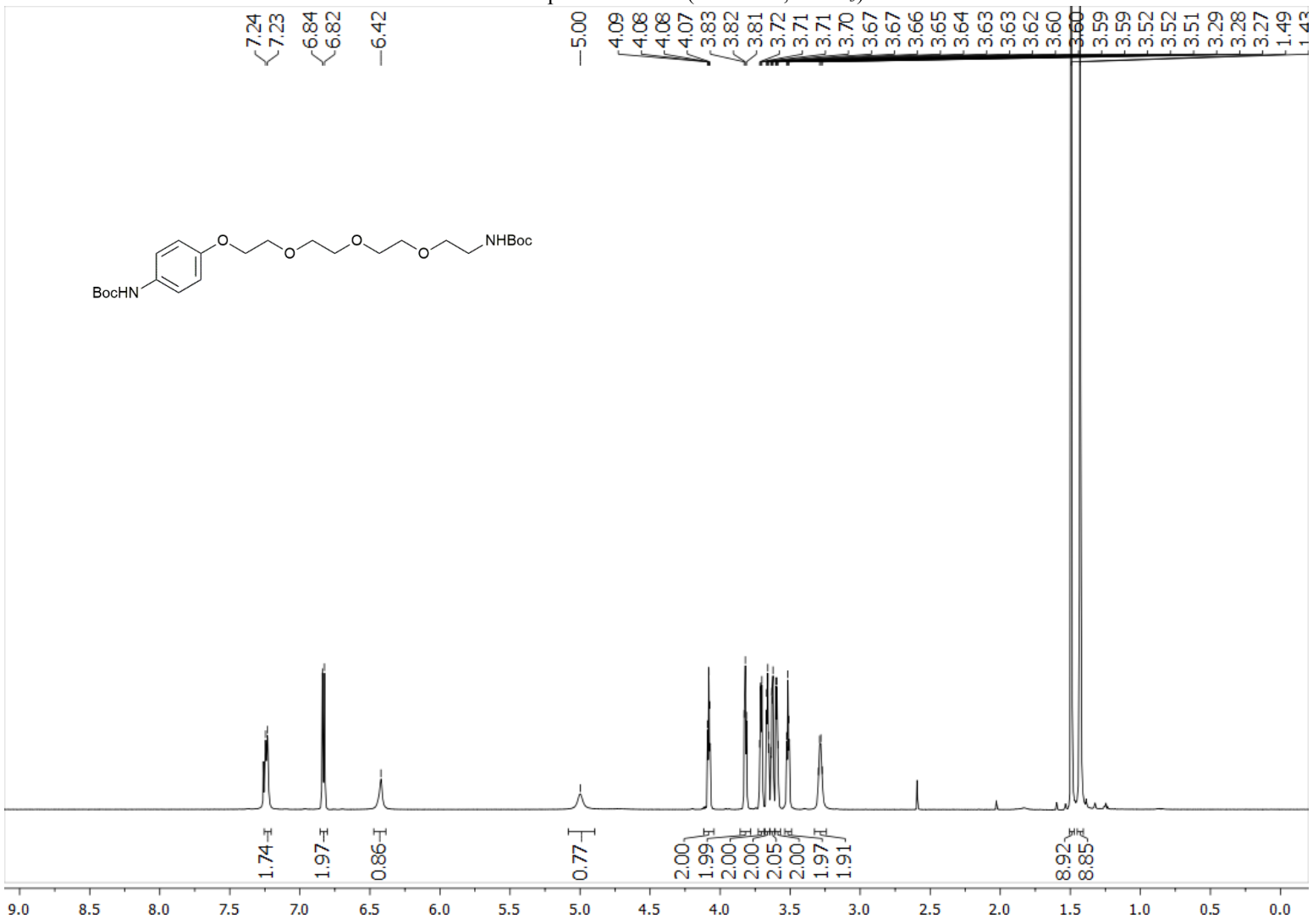
^{1}H NMR spectrum of **S2** (600 MHz, $CDCl_3$)



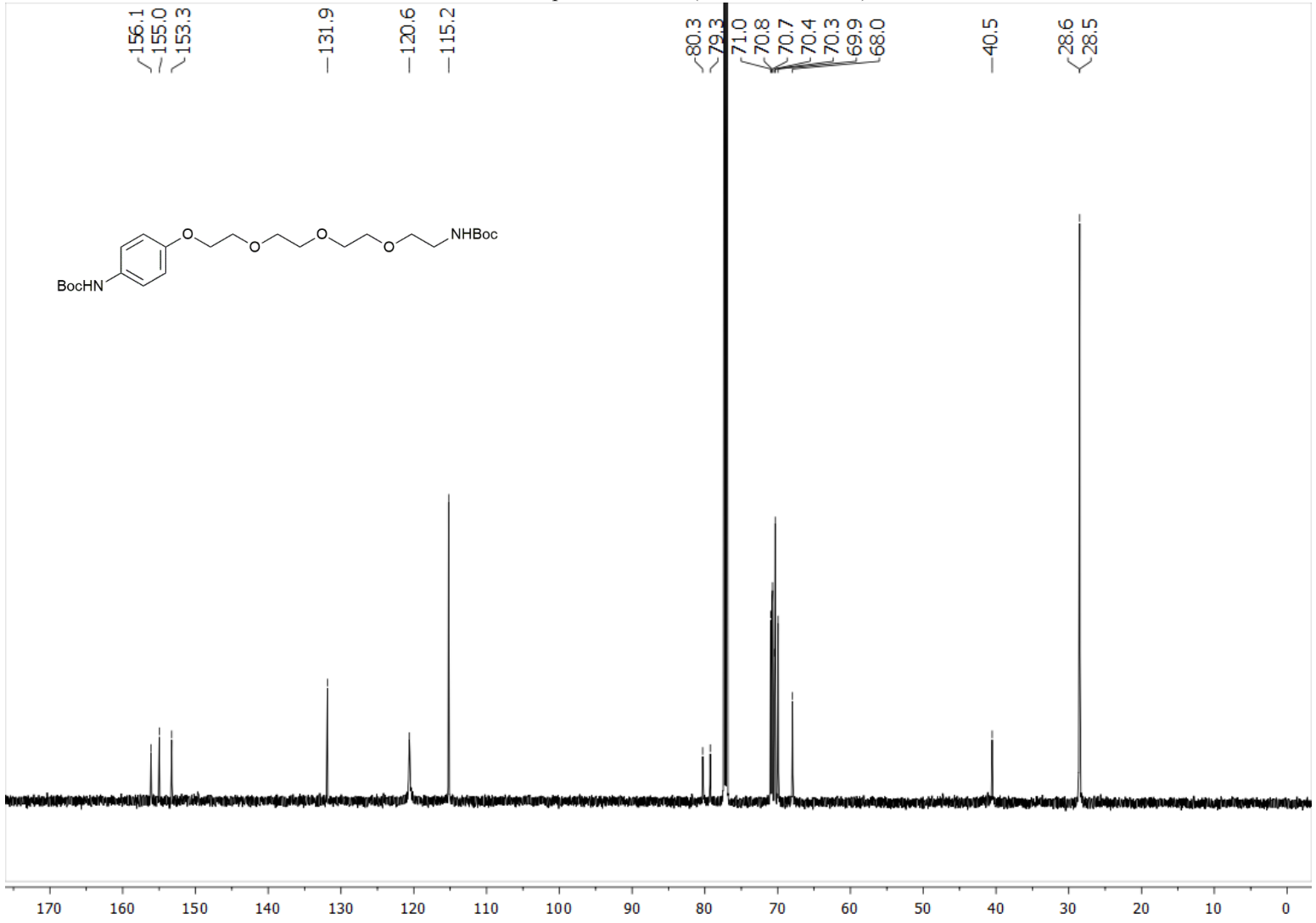
^{13}C NMR spectrum of **S2** (151 MHz, $CDCl_3$)



^{1}H NMR spectrum of **S3** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **S3** (151 MHz, $CDCl_3$)



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